CHEMISTRY

Physical Chemistry
Inorganic Chemistry
Organic Chemistry

Blocks - 9 - 13

Dr. B.R. AMBEDKAR OPEN UNIVERSITY
HYDERABAD
1996

CONTENTS

PART - C ORGANIC CHEMISTRY

BLOCK - 9

NITROGEN COMPOUNDS

Organic compounds that contain the element nitrogen are nitrogen compounds. There are different types of nitrogen compounds. Some of them are Cyanides, Isocyanides, Amines, Amides, Nitrocompounds, Nitrites, Nitrates, oximes and Acid hydrazides. Several of the above compounds are considered as the derivatives of ammonia. Amines are organic bases.

UNIT - 19 ALKYL CYANIDES AND ISOCYANIDES

Contents

19.1 AIMS AND OBJECTIVES

To familiarise the student with the structure, nomenclature and reactions of alkyl cyanides and isocyanides.

Once the study and comprehension of the contents of this unit are over you must be able to:

- name cyanides and isocyanides
- describe the methods of preparation of cyanides and isocyanides
- explain the chemical properties exhibited by cyanides and isocyanides.

19.2 NOMENCLATURE

The general formula of cyanides is RCN. R amy be an alkyl or aryl group. Alkyl or aryl cyanides are named by adding the suffix cyanide to the name of alkyl or aryl group. Cyanides may also be named as nitriles. In this method of nomenclature of the compounds, the names are based on the acids which would be formed upon hydrolysis. For instance methyl cyanide (CH_3CN) on hydrolysis gives acetic acid. Therefore the compound is also named as acetonitrile. Similarly C_6H_5CN is phenyl cyanide or benzonitrile. CH_3CH_2 NC ethyl cyanide, is also named as propionitrile.

Alkyl isocyanides or isonitriles are isomers of cyanides or nitriles. These are also called carbylamines. While naming these compounds as isocyanide or as isonitirle, their isomeric nature with cyanides or nitrile is indicated. CH_3CN is isomeric with methyl cyanide or acetonitrile (CH_3CN). Therefore it is named as methyl isocyanide or methyl isonitrile. C_6H_5NC is phenyl isocyanide or phenyl isonitrile.

19.3 PREPARATION OF CYANIDES AND ISOCYANIDES

1. **From alkyl halides:** Nucleophilic substitution of a halide ion in an alkyl halide with cyanide ion results in the formation of cyanide and isocyanide. In this reaction alkali metal cyanide or silver cyanide may be used. Either end of the cyanide ion ($:C\equiv N:$) may participate in the nucleophilic attack in reaction with alkyl halides giving a mixture of alkyl cyanides and isocyanides.

When potassium or sodium cyanide reacts with alkyl halides alkyl cyanides are the major products. If silver cyanide is used in the reaction, isocyanide is the major product.

$$R\text{-}X + KCN \rightarrow \underset{\text{Major product}}{RCN} + KX$$

Example:

$$\underset{\substack{\text{Methyl}\\\text{bromide}}}{CH_3Br} + KCN \rightarrow \underset{\substack{\text{Methyl}\\\text{cyanide}}}{CH_3CN} + KBr$$

$$RX + AgCN \rightarrow \underset{\text{Major product}}{RNC} + AgX$$

Example:

$$\underset{\substack{\text{Methyl}\\\text{chloride}}}{CH_3Cl} + AgCN \rightarrow \underset{\substack{\text{Methyl}\\\text{isocynaide}}}{CH_3NC} + AgCl$$

This method can not be employed for the preparation of aryl cyanides, as aryl halides are inert towards nucleophilic substituion.

2. Dehydration of amides and aldoximes: Ddehydration of amides or aldoximes furnish nitriles. This method is applicable for the preparation of alkyl and aryl cyanides. For dehydration P_2O_5 or $SOCl_3$ or benzene sulphonyl chloride are used. In the dehydration of aldoximes acetic anhydride is used.

$$RCONH_2 \xrightarrow{\text{D.A.}} RCN \text{ (D.A. = Dehydrating agent)}$$

$$RCH=NOH \xrightarrow{(CH_3CO)_2O} RCN + H_2O$$

Example:

$$\underset{\substack{\text{Acetamide}}}{CH_3ONH_2} \xrightarrow{P_2O_5} \underset{\substack{\text{Methyl cyanide}}}{CH_3CN} + H_2O$$

$$\underset{\substack{\text{Acetaldomixe}}}{CH_3CH=NOH} \xrightarrow{(CH_3CO)_2O} CH_3CN + H_2O$$

$$\underset{\substack{\text{Benzaldomixe}}}{C_6H_5CH=NOH} \xrightarrow{(CH_3CO)_2O} \underset{\substack{\text{Benzonitrile}}}{C_6H_5CN} + H_2O$$

3. Carbylamine reaction: Carbylamine reaction or isocyanide reaction is convenient method for preparation of isocyanides. In this an aliphatic or aromatic primary amine is reacted with chloroform in the presence of alkali. This infact is a test for primary amine.

$$RNH_2 + CHCl_3 + NaOH \rightarrow RNC + 3\,NaCl + 3\,H_2O$$

Example:

$$CH_3NH_2 + CHCl_3 + 3\,NaOH \rightarrow CH_3NC + 3NaCl + 3H_2O$$

$$C_6H_5NH_2 + CHCl_3\ 3NaOH \rightarrow C_6H_5NC + 3NaCl + 3H_2O$$

Check your Progress - 1

How do you identify primary amines?

.....

.....

.....

.....

19.4 PHYSICAL PROPERTIES

Alkyl cyanides have pleasant smell whereas isocyanides possess very offensive odours. Cyanides are less toxic than isocyanides. Alkyl cyanides are higher boiling liquids. Alkyl isocyanides, on the contrary are gases or volatile liquids.

19.5 CHEMICAL REACTIONS

1. Hydrolysis: In the hydrolysis of cyanides ammonia is liberated and carboxylic acids formed. Whereas isocyanides yield amines and formic acid.

$$RCN + 2H_2O \xrightarrow[H_3O \text{ or } OH]{\oplus \quad \ominus} RCOOH + NH_3$$

$$CH_3CN + 2H_2O \xrightarrow[H_3O \text{ or } OH]{\oplus \quad \ominus} CH_3COOH + NH_3$$

$$RNC + 2H_2O \xrightarrow[H_3O \text{ or } OH]{\oplus \quad \ominus} RNH_2 + HCOOH$$

$$CH_3NC + 2H_2O \xrightarrow[H_3O \text{ or } OH]{\oplus \quad \ominus} CH_3NH_2 + HCOOH$$

Methylamine

Check your progress - 2

What is the difference in the hydrolysis products of cyanides and isocyanides?

.....

.....

.....

.....

2. Reduction: Reduction of alkyl cyanides furnishes a primary amine, on the other hand reduction of an isocyanide yields secondary amine.

$$RCN \xrightarrow{R.A.} RCH_2NH_2$$ (R.A. = Reducing agent = $LiAlH_4$ or Na + alcohol or H_2/Catalyst)

$$RNC \xrightarrow{R.A.} \underset{\text{Secondary amine}}{RNHCH_3}$$

Example

$$\underset{\text{Ethyl cyanide}}{CH_3CH_2CN} \xrightarrow{R.A.} \underset{\text{n-propyl amine}}{CH_3\,CH_2\,CH_2NH_2}$$

$$\underset{\text{Methyl iso cyanide}}{CH_3NC} \xrightarrow{R.A.} \underset{\text{Dimethyl amine}}{CH_3NHCH_3}$$

3. Oxidation of iso cyanides: Isocyanides are oxidised to isocyanates. Mild oxidising agents like HgO are effective in this reacation.

$$\overset{\oplus}{R}N \equiv \overset{\ominus}{C} + HgO \rightarrow \underset{\text{Alkyl isocyanate}}{R\text{-}N = C = O} + Hg$$

Example

$$\underset{\text{Methyl iso-cyanide}}{CH_3NC} + HgO \rightarrow \underset{\text{Methyl isocyanate}}{CH_3\text{-}N = C = O} + Hg$$

4. Reaction wtih Grignard reagents: Addition of grignard reagents to nitriles followed by hydrolysis yield ketones.

$$R\text{-}C \equiv N + RMgX \rightarrow R\text{-}\underset{\displaystyle R}{\underset{|}{C}} = NMgX \xrightarrow{\overset{\oplus}{H_3O}} (R)_2\,C \equiv O$$

Example:

$$\underset{\text{Methyl cyanide}}{CH_3C{\equiv}N} + \underset{\text{Ethyl magnesium bromide}}{CH_3CH_2\,MgBr} \rightarrow CH_3\text{-}\underset{\displaystyle CH_2CH_3}{\underset{|}{C}} = NMgBr \xrightarrow{\overset{\oplus}{H_3O}} \underset{\text{Methyl ethyl ketone}}{CH_3\text{-}\underset{\displaystyle CH_2CH_3}{\underset{|}{C}} = O}$$

19.6 SUMMARY

Cyanides and isocyanides are nitrogen compounds. They are prepared in the laboratories by a) dehydration of aldoximes and primarily amines b) carbylamine reaction c) the treatment of alkyl halides with KCN or AgCN. The chemical properties of these compounds are presented in this unit under the headings hydrolysis, reduction, oxidation and grignard addition.

19.7 MODEL EXMAINATION QUESTIONS

I Answer the following in 10 lines

1. Give any two methods for the preparation of methyl cyanide and methyl isocyanide.

2. What reagents and conditions could be used for the following conversions? Write equations?

   a) CH_3Br to CH_3CN b) CH_3CN to CH_3COCH_3
   b) CH_3CN to CH_3COOH d) CH_3CN to $CH_3CH_2NH_2$

3. How are the following transformations effected? Write equations?

   a) CH_3NC to CH_3NCO b) CH_3NC to CH_3NH_2
   c) CH_3NC to CH_3NHCH_3 d) CN_3NH_2 to CH_3NC

II Answer each of the followin g in 30 lines.

1. How are nitriles and isonitriles prepared? How are they distinguished? Illustrate with suitable examples and equations?

19.8 MODEL ANSWERS TO CHECK YOUR PROGRESS

1. Primary amines on heating with chloroform and sodium hydroxide form isocyanides of bad offensive odour.

2. On hydrolysis cyanides form corboxylic acids and ammonia where as isocyanides form primary amines and formic acid.

Author: Dr. T. Sundara Ramayya

UNIT - 20 NITRO COMPOUNDS AND ALKYL NITRITES

Contents

20.1 AIMS AND OBJECTIVES

To familarise the student with nomenclature, structures preparations and reactions of nitro compounds and alkyl nitrites

Once you complete the study and ocmprehension of the subject matter of this unit you must be able to:

- name nitro-compounds and alkyl nitrites
- describe various laboratory methods of preparation of both aliphatic and aromatic nitrocompounds and alkyl nitrites.
- explain the chemical properties of nitrocompounds particularly the reduction of nitro-benzene in different media.

20.2 INTRODUCTION

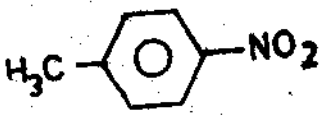
In nitro compounds a nitro group -N $\rightarrow$ O is linked through its nitrogen atom to a carbon atom. Accordingly we have nitroalkanes and nitro aromatic compounds.

Nitromethane, CH_3NO_2 is a nitroalkane.

Nitrobenzene, $C_6H_5NO_2$ is a nitro aromatic compound

20.3 NOMENCLATURE

The nitro compounds are named by adding the prefix nitro - to the name of the hydrocarbon from which the nitro compound is obtained. The compound $CH_3CH_2NO_2$ is derived by replacement of hydrogen atom in ethane. Therefore it is named as nitroethane. Similarly $CH_3CH(NO_2)CH_3$ is 2 - nitorpropane and



is p-nitrotolunee

20.4 NITROALKANES

The nitroalkanes are classified as primary, secondary and tertiary, depending on nature of carbon on which nitro group is present. If in a compound, the nitro group is linked to a primary carbon (carbon carrying at least two hydrogens), it is a primary nitro alkane, $CH_3CH_2CH_2NO_2$ 1-nitro butane is a primary nitro alkane. In secondary and tertiary nitro compounds, the carbon atom to which the nitrogen is linked carries one hydrogen and no hydrogens respectively. $CH_3CH_2CH(NO_2)CH_3$, 2- nitro butane is a secondary nitro alkane. $(CH_3)_3CNO_2$, 2-nitro-2, methyl-propane, is a tertiary nitro alkane.

20.5 METHODS OF PREPARATION

1. **By direct nitration of alkanes:** Vapour phase nitration of alkanes with nitric acid yields nitro alkanes.

$$RH + HNO_3 \xrightarrow{400^0} RNO_2 + H_2O$$

$$CH_4 + HNO_3 \xrightarrow{400_0} CH_3NO_2 + H_2O$$

In the nitration of alkanes, the order of reactivity is tertiary carbon > secondary carbon > primary carbon. The draw back of this method of synthesis of nitroalkanes is the formation of many fission products besides mononitro alkanes. For example, 2-methyl butane on vapour phase nitration yields the following proudcts.

$$\underset{\text{2-Methyl butane}}{CH_3CH(CH_3)CH_2CH_3} \xrightarrow[400^0]{HNO_3} O_2NCH_2CH(CH_3)CH_2CH_3 + CH_3CH(CH_3)CH_2CH_2NO_2 +$$

$$(CH_3)_2C(NO_2)CH_2CH_3 + (CH_3)_2CHCH(NO_2)CH_3 + CH_3NO_2 + CH_3CH_2NO_2 + CH_3CH_2CH_2NO_2 \text{ etc.}$$

2. Primary and secondary nitroalkanes are prepared by the action of KNO_2 or $NaNO_2$ on the respective alkyl iodides or bromides in dimethyl formamide or dimethyl sulfoxide.

$$RBr + KNO_2 \rightarrow RNO_2 + KBr$$

Example

$$CH_3Br + KNO_2 \rightarrow CH_3NO_2 + KBr$$

Alkyl nitrite is always obtained as the side product in this reaction.

3. Tertiary nitroalkanes are prepared by permanganate oxidation of amines in which NH_2 is bonded to tertiary carbon.

$$R_3CNH_2 \xrightarrow{KMnO_4} R_3CNO_2$$

Example:

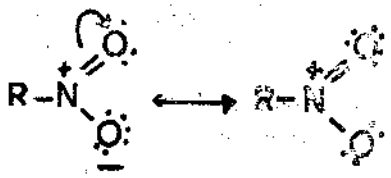
$$(CH_3)_3CNH_2 \xrightarrow{KMnO_4} (CH_3)_3CNO_2$$

tert. Butyl amine → 2-Nitro-2-methyl propane

20.6 PHYSICAL PROPERTIES

Because of the formal charges associated with nitro group, nitro alkanes are highly polar compounds. They have high boiling points. Nitro methane is about 10% soluble in water, and the higher members are insoluble.

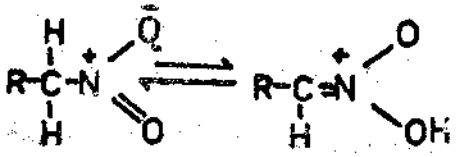
The nitro group is a resonance hybrid of two equivalent structures. The two nitrogen-oxygen bond distances in a nitro compound are identical and equal to 1.21A°.



20.7 CHEMICAL REACTIONS

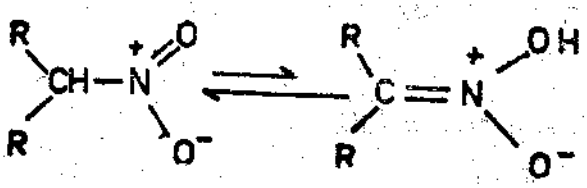
1. **Tautomerism and salt formation:** Primary and secondary nitro alkanes exhibit tautomerism. They exist as an equilibrium mixture of nitro and aci forms.

Primary nitro compound



Nitro form Aci form

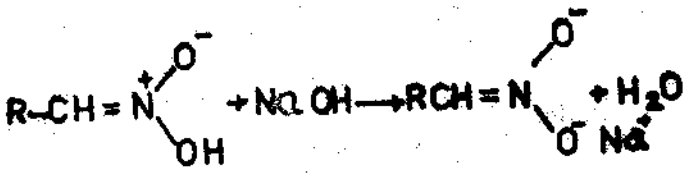
Secondary nitro compound



Nitro form Aci form

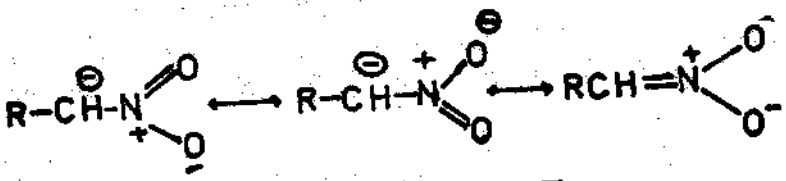
The aci form of a nitro alkane is a weak acid. Therefore primary and secondary nitro alkanes form salts with strong bases and are soluble in alkalies.

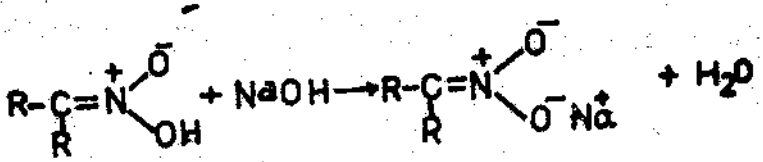
Primary Nitro Compound



Aci form Sodium salt of aci form

The anion of aci form of a nitroalkane is a resonance hybrid of three structures.





Secondary nitro Compound (aci form) Sodium salt of aci form

In tertiary nitro alkanes, the carbon linked to nitro group does not carry any hydrogens. Therefore they cannot exhibit tautomerism. Therefore they are insoluble in bases.

Check your progress - 1

What are pseudoacids?

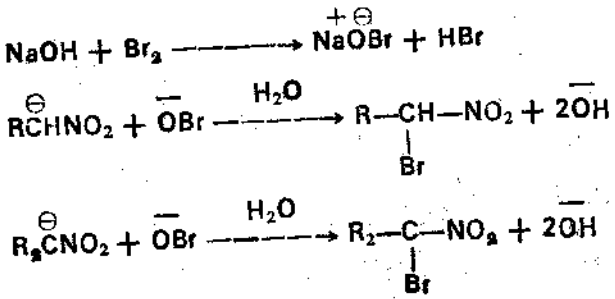
.....

.....

.....

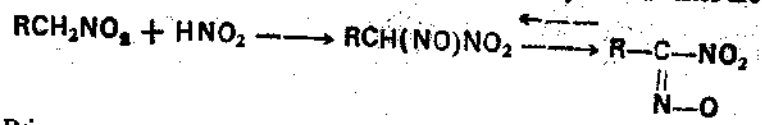
.....

2. Bromination: Primary and secondary nitro alkanes undergo bromination in alkaline solution at - α position.

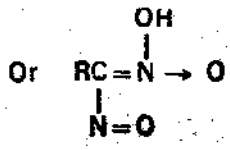


Tertiary nitro alkanes do not undergo bromination.

3. **Reaction with nitrous acid:** Primary and secondary nitro compounds give α -nitroso derivatives with nitrous acid. The nitroso products form primary and secondary nitro alkanes are blue in colour.



Primary nitro alkane — C-Nitroso-derivative — Nitrolic acid



$$R_2CHNO_2 + HNO_2 \rightarrow R_2C(NO)NO_2$$

Secondary nitro alkane

$$R_3CNO_2 + HNO_2 \rightarrow \text{No reaction}$$

Tert. nitro alkane

The nitroso derivatives of primary nitro alkanes still contain one acidic hydrogen atom. They exist as an equilibrium mixture of C-nitroso derivative and nitrolic acid. Therefore nitroso derivatives of primary nitro alkanes are soluble in NaOH giving a red solution. The nitroso derivative of secondary nitro alkane does not contain an acidic hydrogen and is insoluble in NaOH. The nitroso derivative of a primary nitro alkane is blue in colour and gives a red solution with NaOH, where as the nitroso derivative of secondary nitro alkane does not change its colour on treatment with sodium hydroxide. The tertitary nitro alkanes do not react with sodium hydroxide. The tertiary nitro alkanes do not react with nitrous acid and remain colourless. Hence this reaction is often referred to as red, blue and white reaction.

Check your progress-2

What happens if a primary nitrocompound is nitrosated and added to NaOH solution?

.....

.....

.....

.....

4. **Reduction of nitro alkanes:** Primary, secondary and nitro alkanes on reduction give primary amines.

$$RNO_2 + 3H_2 \rightarrow RNH_2 + 2H_2O \quad (R.A. = LiAlH_4;\ Zn\ HCl;\ Sn.\ HCl)$$

$$CH_3NO_2 + 3H_2 \rightarrow CH_3NH_2 + 2H_2O$$

$$(CH_3)_3CNO_2 + 3H_2 \xrightarrow{LiAlH_4} (CH_3)_3CNH_2 + 2H_2O$$

5. **Hydrolysis:** Acid catalysed hydrolysis of primary nitro alkanes yield carboxylic acids and salts of hydroxylamine.

$$RCH_2NO_2 + HCl + H_2O \rightarrow RCOOH + NH_2OH.HCl$$

Example:

$$CH_3CH_2NO_2 + HCl + H_2O \rightarrow CH_3COOH + NH_2OH.HCl$$

Nitroethane — Acetic acid

6. **Nef's reaction:** The salts of primary and secondary nitro alaknes are hydrolysed in H_2SO_4 to give aldehydes and ketones respectively.

$$2RCH=\bar{N}O_2\overset{+}{N}a + 2H_2SO_4 \xrightarrow{0^{\circ}C}$$

$$2RCHO + 2NaHSO_4 + 2H_2O + N_2O$$

Ex: $2CH_3CH=\bar{N}O_2\overset{+}{N}a + 2H_2SO_4 \xrightarrow{0^{\circ}}$

$$2CH_3CHO + 2NaHSO_4 + 2H_2O + N_2O$$

$$2R_2C=\bar{N}O_2\overset{+}{N}a + 2H_2SO_4 \xrightarrow{0^{\circ}}$$

$$2R_2CO + 2NaHSO_4 + 2H_2O + N_2O$$

Ex: $2(CH_3)_2C=\bar{N}O_2\overset{+}{N}a + 2H_2SO_4 \xrightarrow{0^{\circ}}$

$$2(CH_3)_2CO + 2NaHSO_4 + 2H_2O + N_2O$$

7. **Condensation with aldehydes and ketones:** Primary and secondary nitro compounds under the influence of a basic catalyst such as sodium ethoxide, undergo condensation reactions with carbonyl compounds (aldehydes and ketones). This reaction is analogous to aldol condensation and involves the nucleophilic attack of a carbanion on the carbonyl carbon of the aldehydes and ketones.

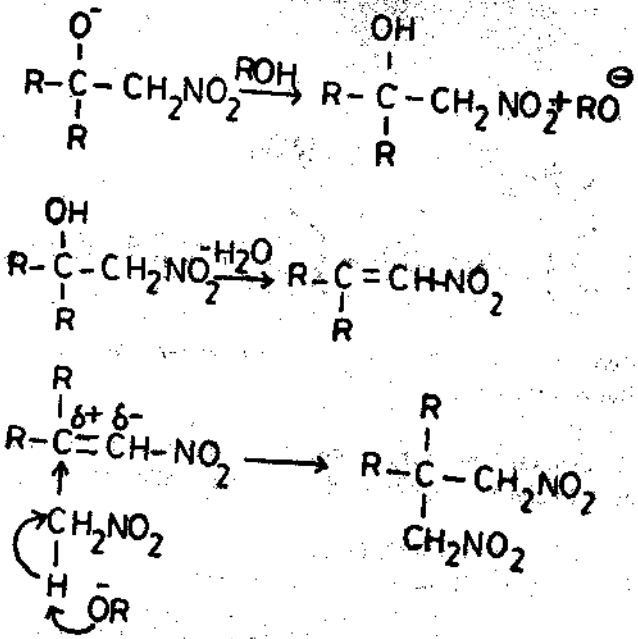
This is a Michael condensation which is a base catalysed addition of activated CH group to -α, β unsaturated nitro,carbonyl and cyanide compounds.

$$CH_2NO_2 \rightleftharpoons \overset{\ominus}{C}H_2NO_2 + EtOH$$

$$EtO^{\ominus} + H\text{-}CH_2NO_2 \rightleftharpoons EtOH + {}^{\ominus}CH_2NO_2$$

$$R\text{-}\overset{+}{C}\overset{\delta-}{=}O + {}^{\ominus}CH_2NO_2 \longrightarrow R\text{-}\underset{R}{\overset{O^-}{C}}\text{-}CH_2NO_2$$

$$O_2NH_2C^{\ominus}$$



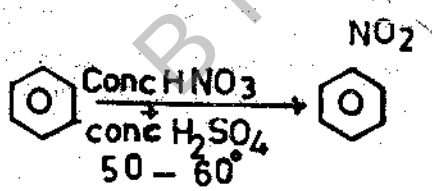
20.8 AROMATIC NITRO COMPOUNDS

In these compounds a nitro group is directly linked to benzene ring. Nitro-benzene is an important member of this group of compounds.

20.9 METHODS OF PREPARATION

1) **Nitration of aromatic hydrocarbons:** Aromatic hydrocarbons are nitrated to give nitro compounds. The nitrating agent commonly used is nitration mixture (conc.H_2SO_4 and conc. HNO_3 in a 1:1 volume ratio). The nitration of benzene at 50-60° gives nitro benzene.

$$ArH + O_2NOH \xrightarrow{\text{Conc. } H_2SO_4} ArNO_2 + H_2O$$



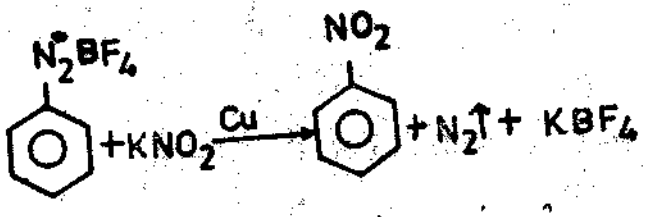
Nitro benzene

2. Replacement of diazonium groups: Aryl diazonium fluoro borates on treatment wth potassium nitrite in the presence of coppper, yield nitro aromatic compounds.

$$ArN_2X + HBF_4 \rightarrow \underset{\text{Aryl diazonium fluoroboate}}{ArN_2BF_4} + HX$$

$$ArN_2BF + NO_2 \dashrightarrow ArNO_2 + BF_4^- + N_2$$

Thus benzene diazonium fluoroborate gives nitrobenzene

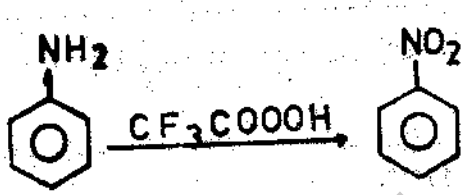


Benzene diazonium fluoroborate **nitrobenzene**

3. Oxidation of aromatic primary amines: Aromatic primary amines can be oxidised by trifluoroperacetic acid to give corresponding aromatic nitro compounds.

$$ArNH_2 \xrightarrow{CF_3COOOH} Ar\,NO_2$$

Aniline is oxidised by trifuuoroperacetic acid to give nitrobenzene. Trifluoroperacetic acid is obtained from trirluoroacetic anhydride and hydrogen peroxide.

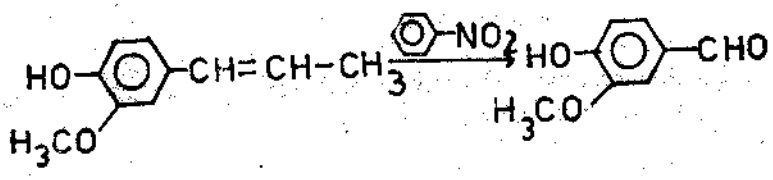


20.10 PHYSICAL PROPERTIES

Nitro aromatic hydrocarbons are polar substances. Nitrobenzene is a high boiling liquid (B.P. 208°). It is insoluble in water.

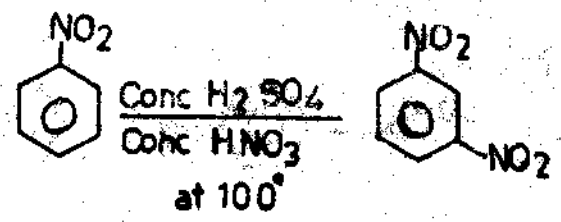
20.11 CHEMICAL REACTIONS

1. Oxidising property: Aromatic nitro compounds are mild oxidizing agents. Nitrobenzene is used as an oxidizing agent in the commercial synthesis of vanillin from isoeugenol.



Isoeugenol **Vanillin**

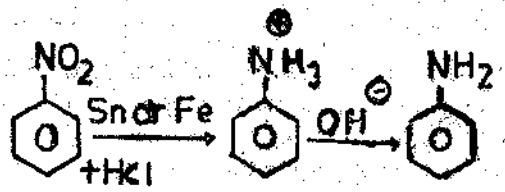
2. Electrophilic substitution Reaction: Nitro ($-NO_2$) group is a meta directing group. It deactivates the benzene ring towards electrophilic substitution. Nitrobenzene, for instance does not undergo Friedel - Crafts reaction. It undergoes further nitration less readily than benzene. At 100° it undergoes nitration giving meta dinitrobenzene.



Nitrobenzene **m-Dinitrobenzene**

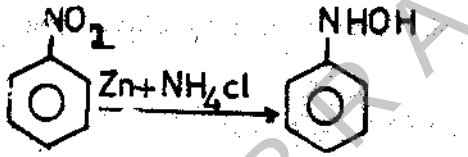
3. **Reduction:** Aromatic nitro compounds are reduced by a variety of reducing agents. The products of reduction depend upon the nature of the reducing agent. Nitrobenzene for instance is reduced under different reaction conditions to give following results.

a) **Acid medium:** Reduction of nitorbenzene by metal and acid gives aniline.



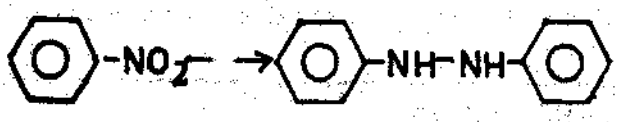
Aniline

b) **Neutral medium:** By using zinc and aqueous NH_4Cl, phenylhydroxyl amine is obtained from nitrobenzene.



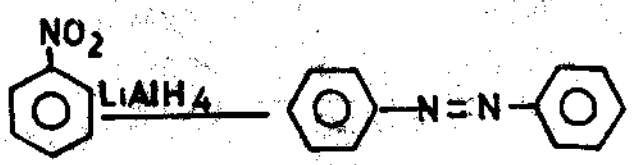
Phenylhydroxylamine

c) **Strong basic medium:** Reduction of nitrobenzene using zinc and NaOH yields hydrazobenzene.

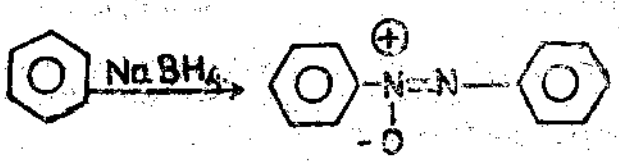


Hydrazobenzene

d) **Reduction with complex metal hydrides:** Reduction of nitrobenzene by Lithium aluminium hydride and sodium borohydride gives azo benzene and azoxybenzene respectively.



Azobenzene



Azoxybenzene

20.12 USES OF NITRO COMPOUNDS

The principal uses of nitro alkanes have been as solvents in plastic industry. They are useful as intermediates in the synthesis of pesticides, emulsifying agents, explosives and pharmaceuticals. CCl_3NO_2 chloropicrin is a powerful lachrymator and has been used in the tear bombs. Trinitrotoluene (TNT) and picric acid (Trinitrophenol) are powerful explosives.

20.13 ALKYLNITRITES

Alkylnitrites , RON=O are isomeric with nitroalkanes.In these compounds the nitrogen atom is linked to a carbon atom through an oxygen atom. These may be considered as esters of alcohols with nitrous acid. They are named by adding the suffix nitrite the name of alkyl group present in the compound. CH_3ONO_2 is methyl nitrate, (CH_3) CHON = O, is isopropyl nitrite.

1. Alkylnitrites are prepared by adding hydrochloric acid or sulphuric acid to an aqueous solution of sodium nitrite and alcohol.

$$NANO_2 + HCl \rightarrow NaCl + HNO_2$$

$$ROH + HNO_2 \rightarrow RON = O + H_2O$$

$$CH_3CH_2OH + HON = O \rightarrow \underset{\text{Ethyl nitrite}}{CH_3CH_2ON = O} + H_2O$$

2. Alkylnitrites are always obtained along with nitroalkanes in the reaction of alkyl halides with metal nitrites. Separation of alkyl nitrites from nitroalkanes is easy because of higher boiling points of the latter.

20.14 CHEMICAL REACTIONS

On hydrolysis alkylnitrites give alcohol and nitrous acid.

$$R\text{--}O\,NO + H_2O \rightarrow ROH + HNO_2$$
$$C_2H_5\text{-}\,O\text{-}NO + H_2O \rightarrow C_2H_5OH + HNO_2$$

20.15 SUMMARY

Aliphatic nitrocompounds are prepared by a) nitration of alkanes b) reaction of alkyl halides with nitrite salt and c) oxidation of amines 1° and 2° nitrocompounds exhibit tautomerism and they are acidic substances. They undergo - nitrosation and on reduction form amines. Salts of 1° and 2° nitrocompounds on hydrolysis give aldehydes and ketones respectively. Michael condensation is the addition of an active CH to C = C which is linked to a - m group. Aronatic nitrocompounds are prepared by a) nitration b) treatment of diazonium salts with a nitratie salt and c) oxidation of amines. These compounds undergo reduction into different substances in different media and different reagents.

20.16 MODEL EXAMINATION QUESTIONS

I Answer each of the following in 10 lines each.

1. Which of the following are soluble in sodium hydroxide? Give the reasons.

   a) 2-Nitro-2-methyl propane b) 2-Nitro propane
   c) 1-Nitro propane d) Nitrobenzene

2. Illustrate by equations the products formed for the reaction of

   a) HNO_2 b) Mixture of NaOH and Br_2 below 5°c on
   i) 1-Nitropropane ii) 2-Nitropropane iii) 2-Nitro - 2 -methylpropane

3. How are the following transformations effected in a single step? Give the conditions.

   a) Aniline to nitrobenzene b) Nitrobenzene to aniline
   c) Nitrobenzene to m-dinitrobenzene d) Nitrobenzene to phenylhydroxylamine
   e) 2-Nitropropane to isopropylamine.

4. How are the following conversions effected? Give equations.

   a) 2-Nitro propane to acetone b) Nitrobenzene to azoxybenzene
   c) Nitroethane to acetaldehyde d) p-Nitro toluene to p-toluidine

II Answer each of the following in 30 lines

1. Compound A (C_4H_9Br) reacts with potassium nitrite to give B ($C_4H_9O_2N$). Bis soluble in NaOH. B reacts with nitrous acid to give C($C_4H_8O_3N$). B on reduction gives D ($C_4H_{11}N$) which is soluble in dil. HCl. B when boiled with dil. HCl gives E ($C_4H_8O_2$) and hydroxylamine hydrochloride. E is soluble in NaOH solution. Write the structures of the compounds A,B,C,D and E, and explain the reactions involved in the above transformations.

2. How is nitrobenzene prepared? Give conditions and reagents required to convert nitrobenzene to m-dinitrobenzene. What are the products obtianed when nitro benzene is reduced under different conditions.

20.17 MODEL ANSWERS TO CHECK YOUR PROGRESS

1. Primary and secondary nitrocompounds which slowly dissolve in aqueous alkali are called pseudo acids.

2. A primary nitrocompound on nitrosation forms blue coloured α -nitroso derivative and becomes red on adding to alkali solution.

20.18 Glossary

1. **Michael addition:** Compounds containing reactive methylene groups (like HCH_2NO_2) add to -α, β - unsaturated compounds (like $CH_3CH = CHNO_2$) in presence of base catalyst.

$$CH_3CH = CHNO_2 + H - CH_2NO_2 \xrightarrow{\overset{\ominus}{OH}} CH_3 - \underset{CH_2NO_2}{CH} - CH_2NO_2$$

2. **Nef reaction:** The sodium salts of the primary and secondary nitro alkanes on treatment with sulphuric acid at O^0 C give aldehydes and ketones respectively.

$$RCH = NO_2Na + H_2SO_4 \xrightarrow{O^0 c} RCHO + 1/2\, N_2O\uparrow + NaHSO_4 + HOH$$

$$R_2C = NO_2Na + H_2SO_4 \xrightarrow{O^0} R_2C = O + 1/2\ N_2O + NaHSO_4 + HOH$$

Author: Dr. T. Sundera Ramaiah

UNIT - 21 AMINES

Contents

21.1 AIMS AND OBJECTIVES

To familiarise the student with the nomenclature, structures and the reactions of amines

After an intensive study and understanding of various aspects presented in this unit you must be able to:

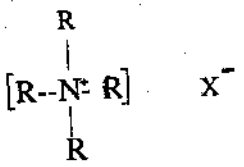
- name different types of amines
- give and describe the methods of preparation of aromatic and aliphatic amines
- compare the basic strenghts of different amines
- separate a mixture of 1°, 2° & 3° amines.
- describe the chemical properties of amines

21.2 INTRODUCTION

Amines may be considered as alkyl or aryl derivatives of ammonia. One or more hydrogen atoms in ammonia may be substituted by either alkyl or aryl groups. Amines are classified as primary, secondary and tertiary amines depending on the number of hydrogen atoms available on the nitrogen atom. If there are two hydrogen atoms on the nitrogen atom of the amine it is called a primary amine and if one hydrogen is present on the nitrogen the amine is a secondry amine. There are no hydrogen atoms on the nitrogen of tertiary amines.

NH_3	Ammonia	
RNH_2	Primary	R may be alkyl or aryl group
R_2NH	Secondary amine	
R_3N	Tertiary amine	

Quaternary ammonium salts are tetra alkyl or tetra aryl ammonium salts. In these the nitrogen is positively charged. These resemble ammonium salts in their structures.



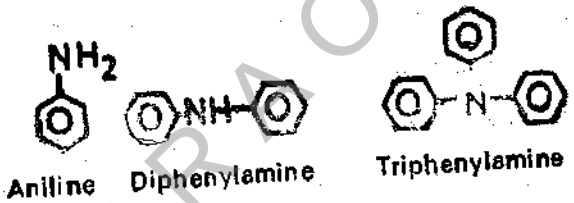
A quaternary ammonium salt

21.3 NOMENCLATURE

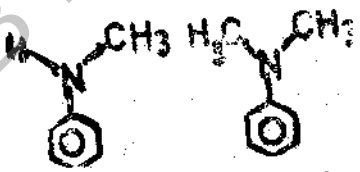
The common names of amines are derived by adding the suffix amine to the name(s) of the alkyl group (s) attached to the nitrogen atom of the amine. In the IUPAC system, amines are named as amino derivatives of a hydrocarbon.

Structure	Common name	IUPAC Name
CH_3NH_2	Methly amine	Amino methane
$CH_3CH_2CH_2NH_2$	propyl amine	Amino propane
$CH_3NHCH_2CH_2CH_2CH_3$	Methyl butyl amine	N-Methylamino butane
$CH_3CH_2CH(CH_3)-N(C_2H_5)-CH_3$	Methyl ethyl butyl amine	2(N-Methyl ethyl amino) butane

Some aromatic amines



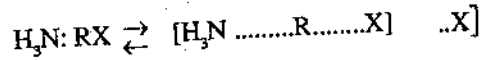
Aniline Diphenylamine Triphenylamine



N-Methyl aniline N-N-Dimethyl aniline

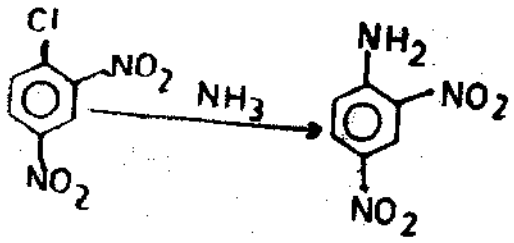
21.4 METHODS OF PREPARATION

1. **Alkylation of ammonia with alkyl halides:** Alkyl halides react with ammonia to give alkylamines.
This is a nucleophilic displacement reaction in which halide is displaced.



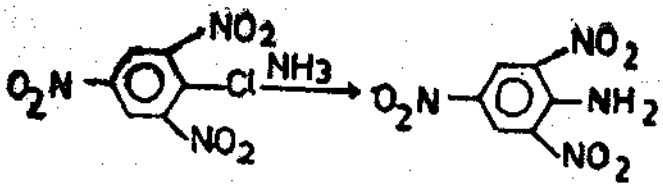
$$\oplus \quad \ominus \quad NH_3$$
$$RNH_3\ X \longrightarrow RNH_2 + NH_4X$$

Chlorobenzene, an aryl halide, does not react with ammonia under these conditions. Only activated aryl halides (containing electron with drawing groups at ortho and para positions) undergo reaction with ammonia. For instance, 2,4-dinitro chloro benzene and picryl chloride (2,4,6-trinitro-1 chlorobenzene) readily react with ammonia to give 2,4 dinitro aniline and picramide (2,4,6 - trinitro aniline) respectively.



2,4 -Dinitro-chlorobenzene

2,4- Dinitroaniline



Picryl chloride

2,4,6 - Trinitro aniline

A primary amine can react with excess of the alkyl halide to form the secondary amine and finally the tertiary amine. The tertiary amine in turn may react with one more molecule of alkyl halide to give quaternary ammonium salt.

$$RNH_2 + RX \rightarrow \underset{\text{Secondary amine}}{R_2NH} \quad (-HX)$$

$$R_2NH + RX \rightarrow \underset{\text{Tertiary amine}}{R_3N} \quad (-HX)$$

$$R_3N + RX \rightarrow \underset{\text{Quaternary ammonium salt}}{R_4\overset{\oplus}{N}X^{\ominus}}$$

In general in the reaction of an alkyl halide with ammonia, a mixture of primary, secondary and tertiary amines is formed. It is difficult in the laboratory to separate such a mixture.

Alkylation of ammonia using alcohols also yield amines. For exmaple, methylamines are preapred commercially by the reaction of ammonia with methanol in the presence of alumina catalyst.

$$\underset{\text{Excess}}{CH_3OH + NH_3} \xrightarrow[450^{\circ}]{Al_2O_3} CH_3NH_2 + (CH_3)_2NH + (CH_3)_3N$$

2. **Reduction of nitro compounds:** Nitro alkanes and aromatic nitro compounds undergo reduction to give primary amines, catalytic hydrogenation or reduction with metal and acid is convenient. Lithium aluminium hydride is used for the reduction of nitro alkanes.

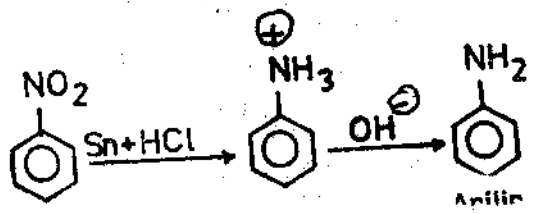
$$RNO_2 \xrightarrow{R.A} \underset{\text{Primary amine}}{RNH_2}$$

(R.A. = Metal+ HCl or $LiAlH_4$ Or Cat/H_2)

$$ArNO_2 \xrightarrow{R.A.} ArNH_2 \quad (R.A. = \text{Metal + HCl or } Cat/H_2)$$

Reduction of nitromethane and nitrobenzene for example yield methyl amine and aniline respectively.

$$CH_3NO_2 \xrightarrow{LiAlH_4} CH_3NH_2$$



Anilinium ion Aniline

3. Reduction of cyanides, isocyanides and amides: Nitriles and primary amides on reduction give primary amines, whereas isonitriles on reduction yield secondary amines containing a N-methyl group. On the other hand secondary and tertiary amides are reduced by lithium aluminium hydride to give secondary and tertiary amines respectively.

$$RCN \xrightarrow{R.A.} RCH_2NH_2 \quad (R.A. = Cat/H_2 \text{ or } LiAlH_4)$$
Primary amine

$$CH_3CN \xrightarrow{R.A.} CH_3CH_2NH_2$$
Methyl cyanide — Ethyl amine

$$RNC \xrightarrow{R.A.} R\,NHCH_3$$
Secondary amine

$$CH_3NC \xrightarrow{R.A.} CH_3\,NHCH_3$$
Methyl isocyanide — Dimethyl amine

$$ROCNH_2 \xrightarrow{LiAlH_4} R\,CH_2NH_2$$
Primary amide — Primary amine

$$CH_3CONH_2 \xrightarrow{LiAlH_4} CH_3\,CH_2NH_2$$
Acetamide — Ethylamine

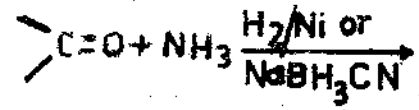
$$ROCNHR \xrightarrow{LiAlH_4} R\,CH_2NHR$$
Secondary amide — Secondary amine

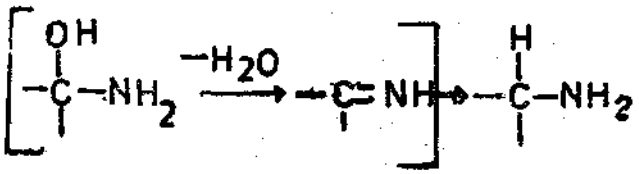
$$CH_3CONHCH_3 \xrightarrow{LiAlH_4} CH_3\,CH_2NHCH_3$$
N-Mehtyl Acetamide — Methyl ethyl amine

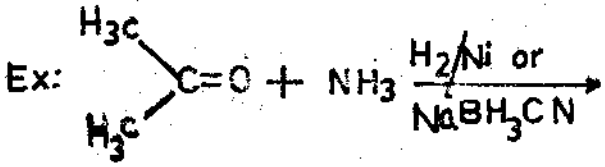
$$RCONR_2 \xrightarrow{LiAlH_4} R\,CH_2NR_2$$
Tertiary amide — Tertiary amine

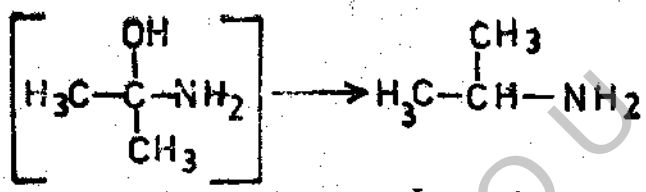
$$CH_3CON(CH_3)_2 \xrightarrow{LiAlH_4} CH_3\,CH_2N(CH_3)_2$$
N- Dimethyl Acetamide — Dimethyl ethyl amine

4. Reductive amination of carbonyl compounds: Both aliphatic and aromatic carbonyl compounds can be converted into amines by reductive amination. Reductive amination of aldehydes and ketones is carried out by using ammonia or primary and secondary amines under catalytic hydrogenation conditions. In place of catalyst and hydrogen, sodium cynohydridoborate may also be used. When ammonia is used in reductive amination, primary amine is the proudct. Secondary and tertiary amines are obtained by using primary and secondary amines respectively.

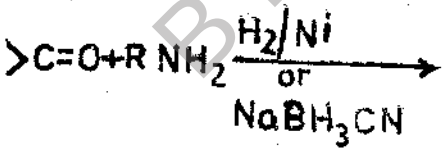


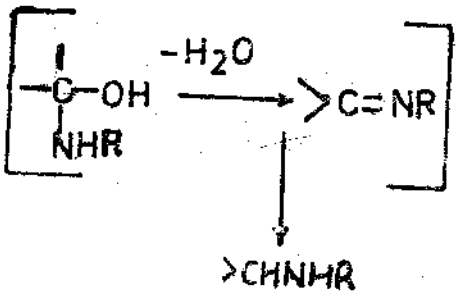




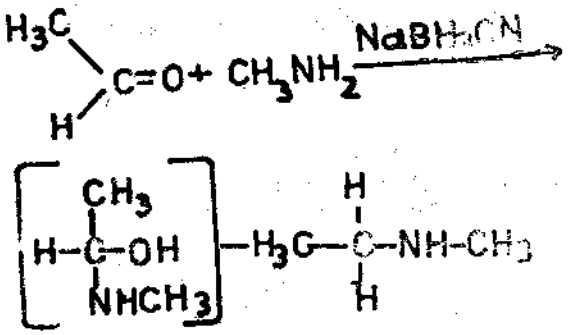


Isopropylamine
Primary amine

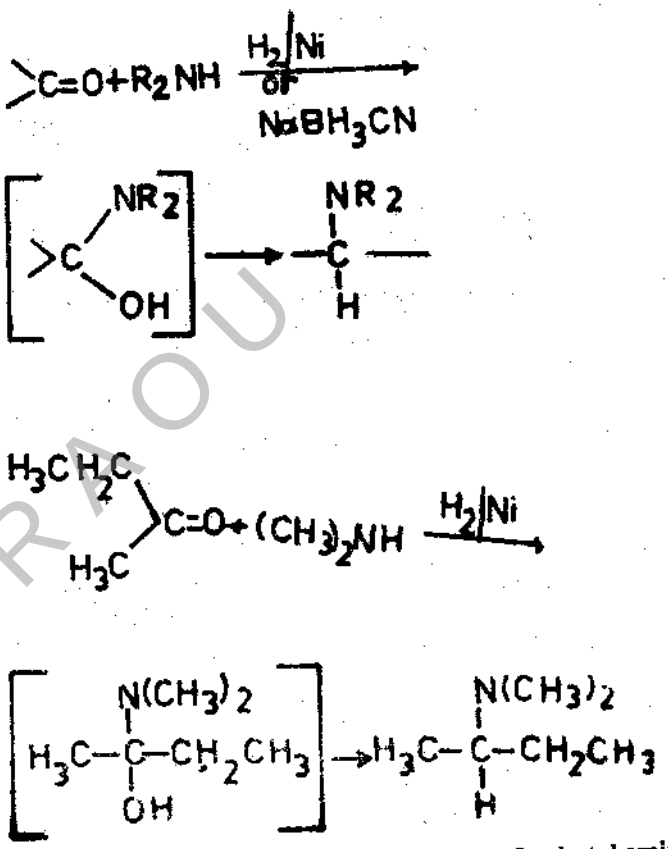




Secondary amine



Methyl ethyl amine
(Secondary amine)



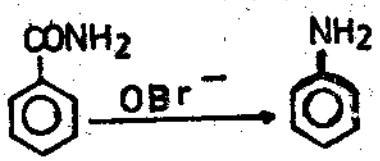
N,N-Dimethyl-N-Sec-butyl amine
(Tertiary amine)

5. Hofmann degradation of amides: Both aromatic and aliphatic primaryamides on treatment with Br_2 +NaOH give good yield of primary amines. Methyl amine and aniline are obtained from acetamide and benzamide respectaively.

$$RCONH_2 \xrightarrow{\ominus OBr} RNH_2$$

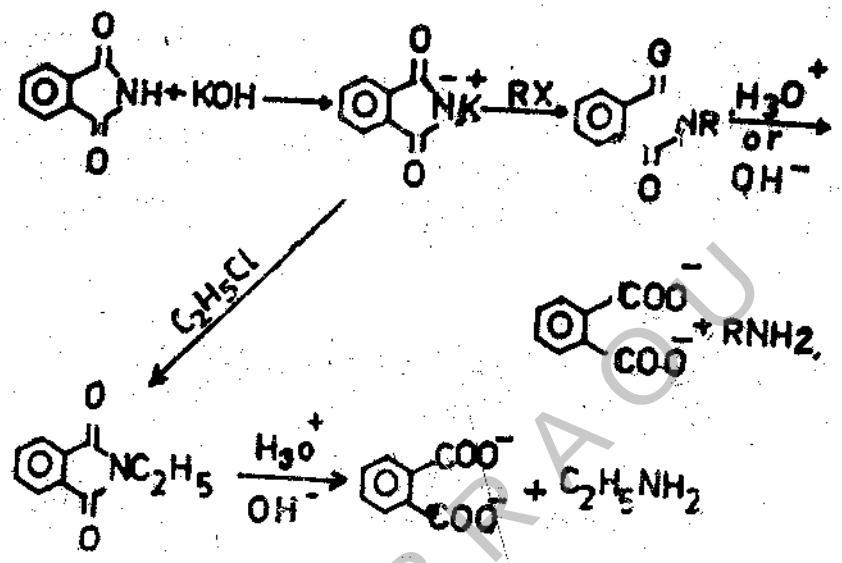
$$ArCONH_2 \xrightarrow{OBr^-} ArNH_2$$

$$CH_3CONH_2 \xrightarrow{OBr^-} CH_3NH_2$$



Benzamide **Aniline**

6. Gabriel phthalimide synthesis: In this method potassium salt of phthalimide is alkylated to give N-Alkyl phthalimides. N-Alkyl phthalimides on hydrolysis yield primary amines.



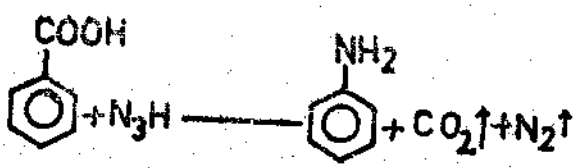
N-Ethyl Phthalimide **Ethylamine**

7. Schmidt reaction: Carboxylic acids can be directly converted into primary amines by the action of hydrozoic acid. Acetic acid and benzoic acid furnish methyl amine and aniline.

$$RCOOH + N_3H \longrightarrow RNH_2 + CO_2 \uparrow + N_2 \uparrow$$

$$CH_3COOH + N_3H \longrightarrow CH_3NH_2 + CO_2 \uparrow + N_2 \uparrow$$

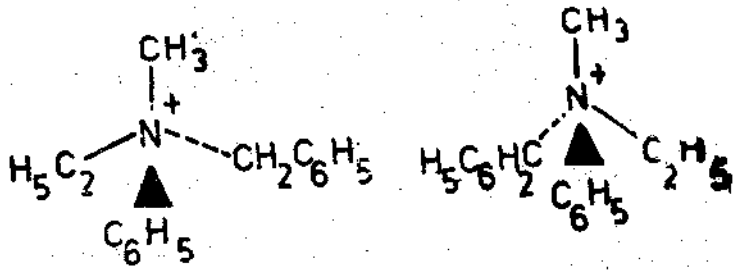
Example:



21.5 PHYSICAL PROPERTIES

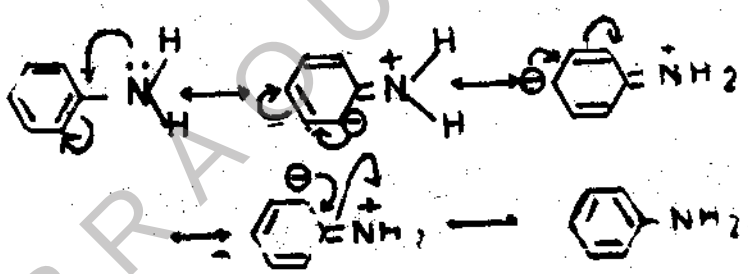
Aliphatic amines are either gases or low boiling liquids, whereas armotic amines are high boiling liquids. Aliphatic amines are more water soluble than aromatic amines.

1. **Optical isomerism of quaternary ammonium salts:** Quaternary ammonium salts, in which nitrogen atom of the amine is bonded to four different groups exhibit optical isomerism.



Enantiomers (non-superimposable mirror images)

2. **Basic strength:** Alkylamines are more basic than ammonia, this is due to increase in the electron density on the nitrogen by the electron-donating inductive effect (+ I effect of the alkyl groups. The expected order of basicity is $R_3N > R_2NH > RNH_2 > NH_3$. But due to solvation of the conjugate acid of the amines and steric hindarance in the amine, following is the order of basic strength of amines in aqueous solution $R_2NH > RNH_2 > R_3N > NH_3$. The electron pair on the nitrogen atom of aromatic amine is involved in + M effect. Therefore the aromatic amines are less basic than ammonia.



In general, amines with electron with-drawing groups attached to nitrogen atom are less basic than amines carrying electron donating groups on the nitrogen atom.

Check your progress - 1

Why the basic strength of methyl amine is more over that of ammonia?

.....

.....

.....

.....

21.6 CHEMICAL REACTIONS

1. **Salt formation:** Amines being basic, react with acids to form salts.

$$RNH_2 + HCL \rightarrow \overset{\oplus}{R}NH_3\,\overset{\ominus}{Cl}$$

Primary amine

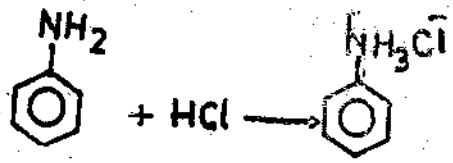
Example:

$$CH_3NH_2 + HCl \rightarrow \overset{\oplus}{C}H_3NH_3\,\overset{\ominus}{Cl}$$

Methyl amine — Mehtyl amine hydrochliride

$$ArNH_2 + HCl \text{--------} \overset{\oplus}{Ar}NH_3\,\overset{\ominus}{Cl}$$

Example:



Aniline **Aniline hydrochloride**

$$R_2NH + HCL \rightarrow \overset{\oplus}{R}_2NH_2\,\overset{\ominus}{Cl}$$

Secondary amine

Example:

$$(CH_3)_2NH + HCl \rightarrow (CH_3)_2\overset{\oplus}{N}H_2\,\overset{\ominus}{Cl}$$

dimethyl amine

$$R_3N + HCl \rightarrow \overset{\oplus}{R}_3NH\,\overset{\ominus}{Cl}$$

Tertiaryl amine

Example:

$$(CH_3)_3N + HCl \rightarrow (CH_3)_3\overset{\oplus}{N}H\,\overset{\ominus}{Cl}$$

Trimethyl amine

2. **N-Alkylation:** Amines are alkylated by reaction with alkyl halides. The end products of alkylation of amines are quaternary ammonium salts.

$$RNH_2 + RX \rightarrow R_2NH + HX$$

Primary amine — Secondary amine

$$R_2NH + RX \rightarrow R_3N + HX$$

Secondary amine — Tertairy amine

$$R_3N + RX \rightarrow \underset{\text{Quaternary salt}}{R_4\overset{\oplus}{N}X^{\ominus}}$$

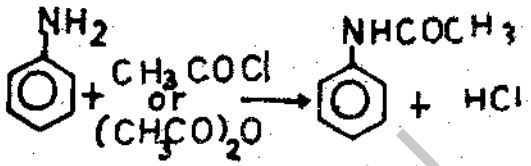
$$RNH_2 \xrightarrow{RX} RNHR \xrightarrow{RX} RNR_2 \xrightarrow{RX} R_4\overset{\oplus}{N}X^{\ominus}$$

Primary amine	Secondary amine	Tertiary amine	Quatemary salt

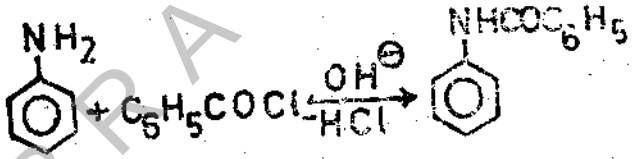
3. N-Acylation: Acylation of primary and secondary amines yields N-substituted amides. Acid chlorides, acid anhydrides and sulhhponic acid chlorides are used as acylating agents. Acylation of primary amines yields a secondary amide whereas that of a secondry amine give a tertiary amide.

$$RNH_2 + RCOCl \text{ or } (RCO)_2O \rightarrow \underset{\text{N-substituted amide}}{RCONHR}$$

Example:



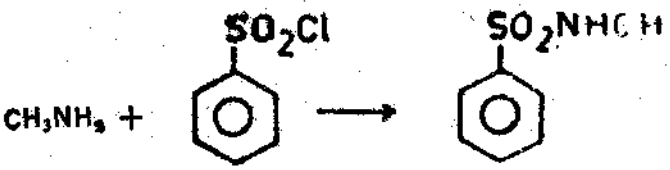
Anline — Acetanilide (N-phenyl acetamide)



Benzoyl — Benzanilide

$$RNH_2 + ArSO_2Cl \rightarrow ArSO_2NHR$$

- Arene sulphony Chloride — N-substituted sulphonamide



Methyl amine — Benzene sulphonyl chloride — N-Methyl Benzene sulphonamide

$$R_2N + RCOCl \text{ or } (R'CO)_2O \rightarrow RCONR_2$$

Example:

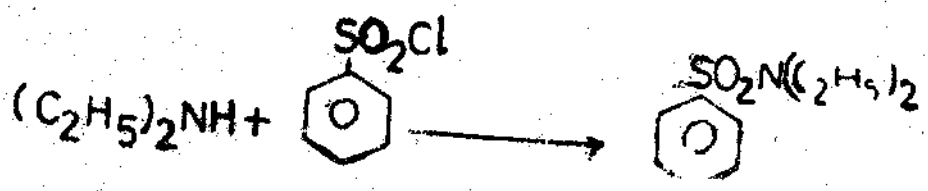
$(CH_3)_2NH + CH_3COCl \longrightarrow CH_3CON(CH_3)_2 + HCl$

Dimethyl amine — N, N--Dimethyl acetamide

$R_2NH + ArSO_2Cl \longrightarrow ArSO_2NR_2 + HCl$

N, N-Disubstituted arene sulphonamide

Example:



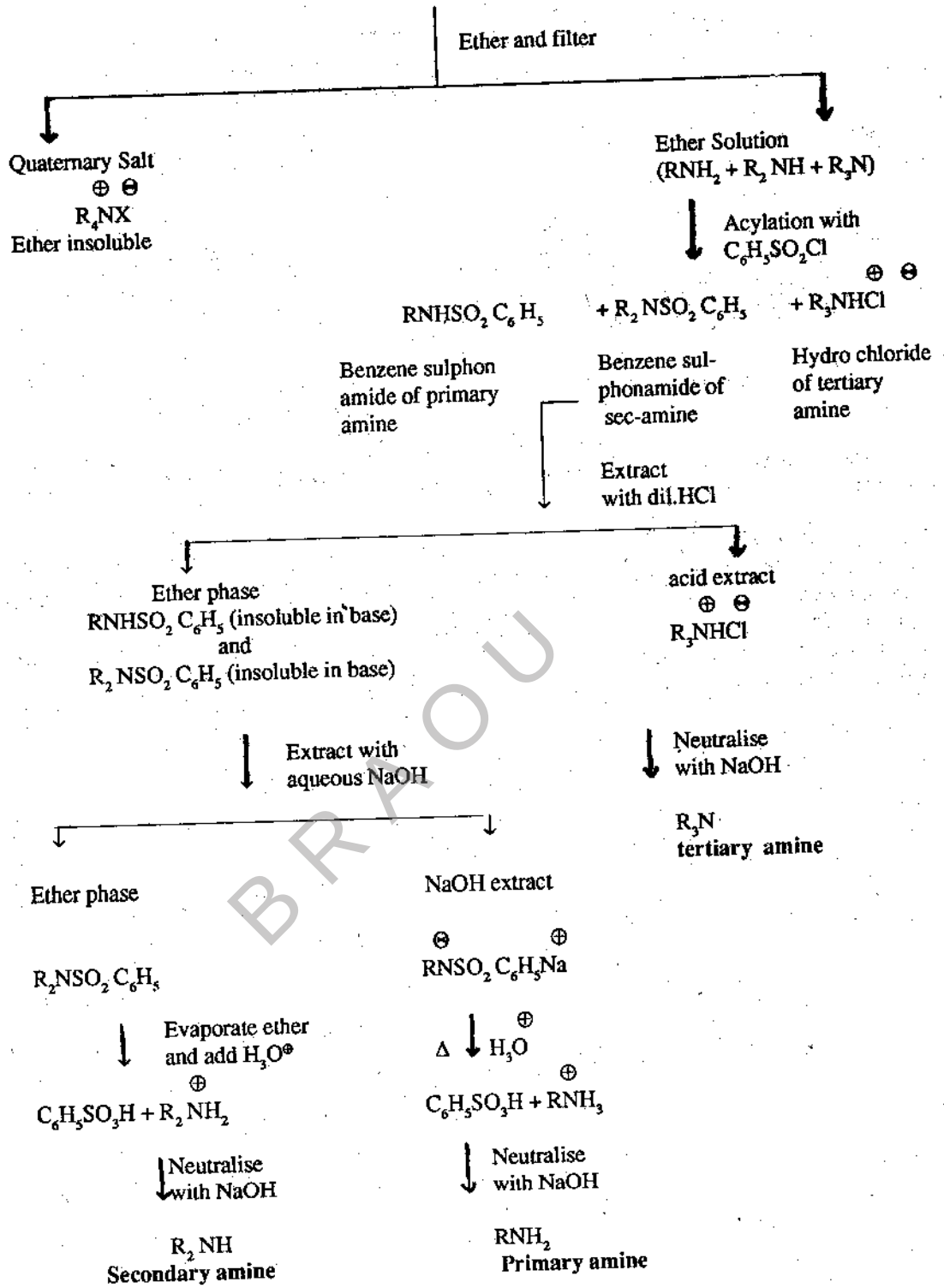
Dimethyl amine — **N, N--Dimethyl benzene Sulphonamide**

Acylation of amines using aromatic acid chlorides in the presence of alkali is some times referred to as **Schotten-Baumann reaction.**

Hinsberg method of separation of amines: Acylation of amines with benzene sulphonyl chloride forms the basis of Hinsberg's method of separation of amines. quaternary ammonium salts are insoluble in ether whereas primary, secondary and tertiary amines soluble in ether. Tertiary amines can not form benzene sulphonamides but form only water soluble salts. Primary amines and secondary amines form benzene sulphonamide derivatives. Benzene sulphonamides of primary amines are acidic and therefore soluble in alkali, whereas those of secondary amines are insoluble in alkali.

Following is the outline of the procedure for the separation of amines.

Mixture of Primary, secondary and tertiary amines and quaternanry ammomium salts



4. Reaction with HNO_2 : Primary secondary and tertiary amines cna be differentiated by the action of nitrous acid.

Action of HNO_2 on primary amines at low temperature is known as diazotisation reaction. Aliphatic primary amines give unstable diazonium salts which decompose giving alcohols. Aromatic primary amines on the other hand give stable diazonium salts. In these compounds the diazonium groups replaced by other groups. Therefore diazonium salts are useful in the preparation of many classes of aromatic organic compounds.

$$RNH_2 \xrightarrow[\text{below } 5^oC]{NaNO_2 + HCl} \underset{\text{(Unstable)}}{R\overset{\oplus}{N}\ \overset{\ominus}{Cl}} \longrightarrow R^{\oplus} + N_2 \uparrow + \overset{\ominus}{Cl}$$

$$R^{\oplus} + H_2O \longrightarrow ROH + H^{\oplus}$$

$$Ar\,NH_2 \xrightarrow[\text{below } 5^oC]{NaNO_2 + HCl} Ar\overset{\oplus}{N}\ \overset{\ominus}{Cl}$$

$$Ar\overset{\oplus}{N} \equiv N \longleftrightarrow Ar{-}N{=}\overset{\oplus}{N}$$

Diazonium ion

Aliphatic or aromatic secondary amines react with nitrous acid to give - N- nitroso amines.

$$R_2NH + HNO_2 \longrightarrow R_2N{-}N{=}O$$

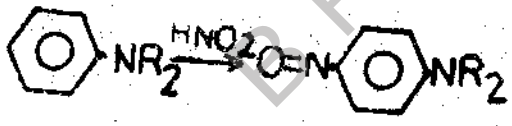
$$ArNHR + HNO_2 \longrightarrow Ar{-}\underset{\displaystyle R}{\underset{|}{N}}{-}N{=}O$$

} N—Nitrosoamines

Aliphatic tertiary amines react with nitrous acid to yield a salt.

$$R_3N + HNO_2 \longrightarrow R_3N\,HNO_2$$

But aromatic tertiary amines on rection with nitrous acid form p - nitroso derivatives.



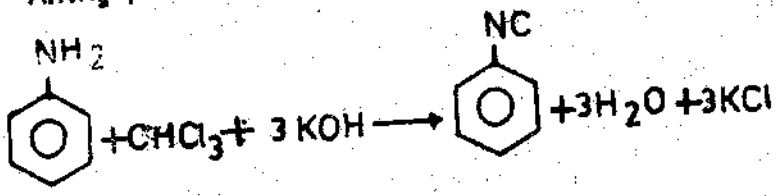
5. Carbylamine reaction: Both aliphatic and aromatic primary amines on heating with chloroform in the presence of alcoholic potassium hydroxide produce isocyanides. The isocyanides are volatile substances with extremely unpleasant smell. Formation of isocyanides serves as a test for primary amines.

$$RNH_2 + CHCl_3 + 3KOH \longrightarrow RNC + 3H_2O + 3KCl$$

Example :

$$\underset{\text{Methyl amine}}{CH_3NH_2} + CHCl_3 + 3KOH \longrightarrow \underset{\text{Methyl isocyanide}}{CH_3NC} + 3H_2O + 3KCl$$

$$ArNH_2 + CHCl_3 + 3KOH \longrightarrow ArNC + 3H_2O + 3KCl$$



Aniline **Phenyl isocyanide**

Check your progress - 2

How do you differentiate a primary amine from a secondary amine?

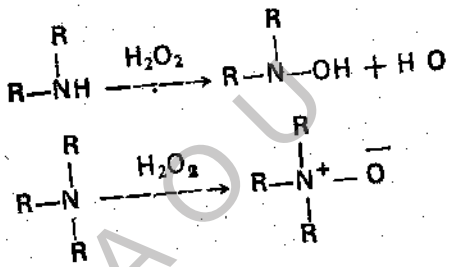
.....

.....

.....

.....

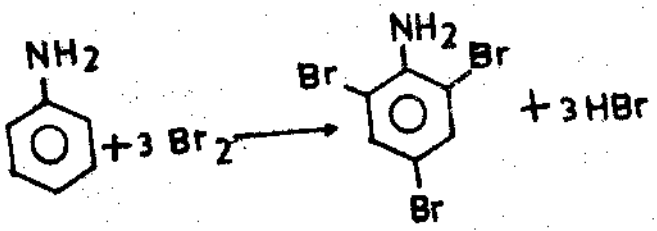
6. Oxidation of amines: Primary amines on oxidation with H_2O_2 give a mixture of products, secondary amines give the N-hydroxylation products and tertiary amines give N-oxides.



21.7 SPECIAL REACTIONS OF AROMATIC AMINES

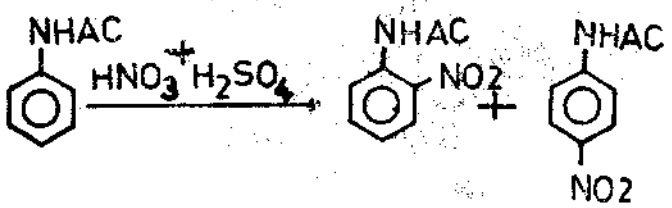
Following are some other reactions characteristic of aromatic amines.

1. Electrophilic subbstitution reactions: The amino group is ortho, para directing group. It activates the benzene ring towards electrophilic substitution. Like phenol, aniline for instance undergoes bromination to give tribromoaniline.

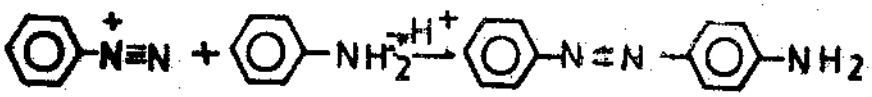


tribromoamiline

s are nitrated directly. N-Acetyl derivatives of amines are normally used. Acetanilide on
s a mixture of o-and p-nitro acetanilides.

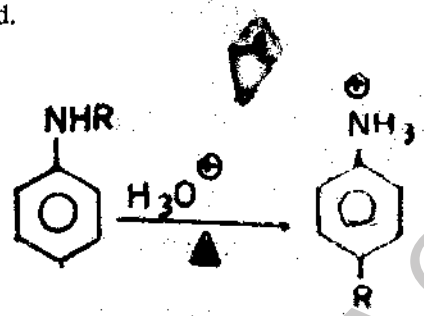


Amines couple with diazonium salts to give azo dyes. Reaction of aniline with benzene diazonium-chloride in mild acidic medium gives amino azobenzene.



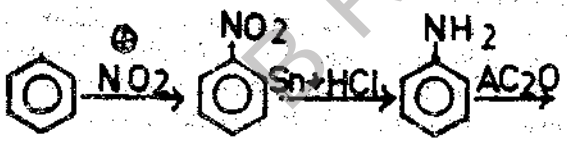
Amino azo benzene

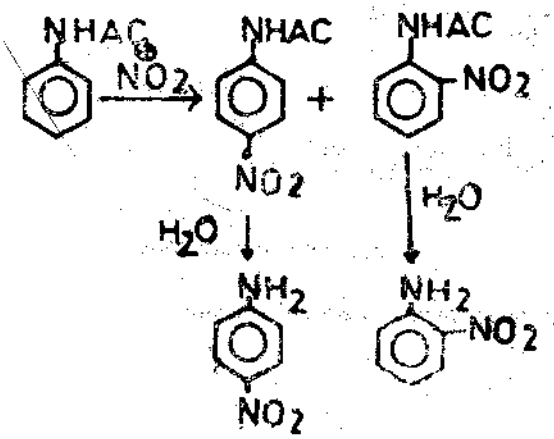
II. Hofmann rearrangement: N-Alkylated anilines on heating with strong acids undergo a rearrangement. The alkyl substituent migrates to the para position. The substituent will migrate to ortho position if the para position is blocked.



Preparation of Nitro anilines (o,p and m) from benzene

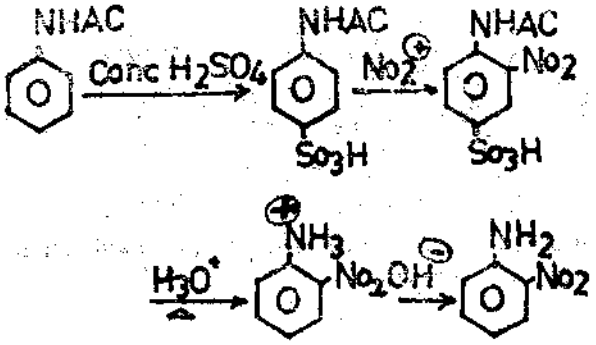
a) o-and p-Nitro anilines





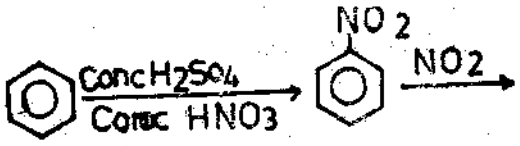
p-nitro aniline **o-nitroaniline**

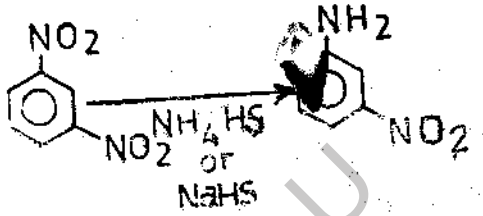
b) o - Nitro aniline



O-Nitroaniline

c) m-Nitro aniline

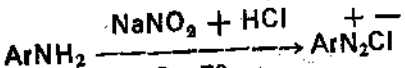


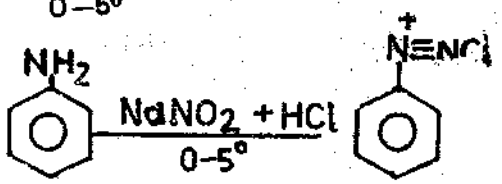


m-Dinitrobenzene

21.8 ARYL DIAZONIUM SALTS

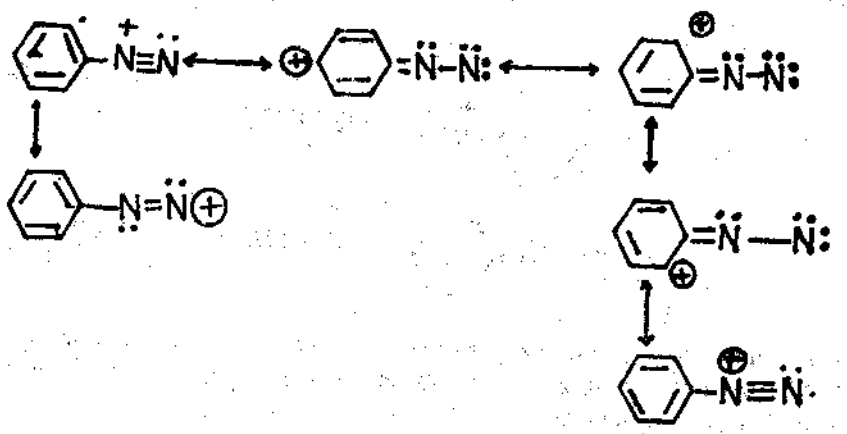
Treatment of aromatic primary amines with nitrous acid is called diazotisation. Diazotisation of aromatic amines results in the formation of aryl diazonium salts. To a solution or suspension of aromatic primary amine in strong mineral acid, an aqueous solution of sodium nitrite is added below 5^0, when a solution of aryl diazonium salt is obtained. Aryl diazonium salt is obtained. Aryl diazonium salts are generally not isolated from the solution. They are explosive substances.





Phenyldiazomium chloride

Phenyl diazonium ion is a resonance hybrid of several structures.



21.9 REACTIONS

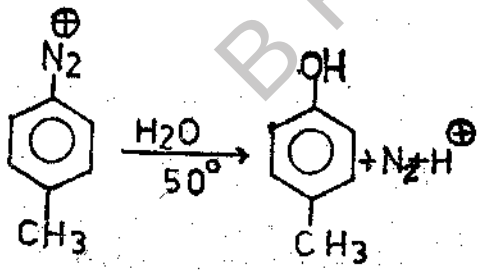
Aryldiazonium salts are reactive substances. The diazonium group can be replaced by a variety of groups. Diazomium salts are thus useful in the preparation of various aromatic compounds by nucleophilic displacement of the diazonium group.

1. Replacement of diazomium nitrogen

a) Replacement by - OH: By warming an aqueous solution of diazonium salt, the diazonium group is replaced by-OH group and phenol is obtained.

$$ArN_2^{\oplus} \xrightarrow[H_2O]{50\text{–}80^{\circ}} ArOH$$

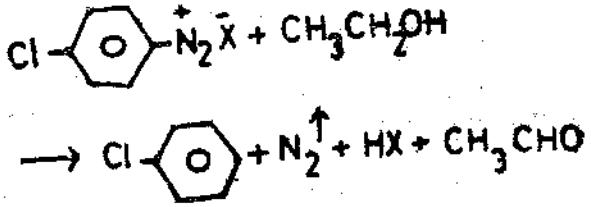
p-Cresol is obtained from p-toluene diazonium salts



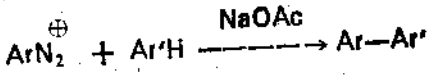
b) Replacement by H: Replacement of amino group of primary amine by hydrogen, through diazonium salt is known as deamination. The diazo group can be replaced by H by the action of hypophosphorous acid on diazonium salts. The same result is obtained by warming solution of diazonium salt with alcohol.

$$ArN_2^{\oplus} \xrightarrow[0\text{–}5^{\circ}]{H_3PO_2} ArH$$

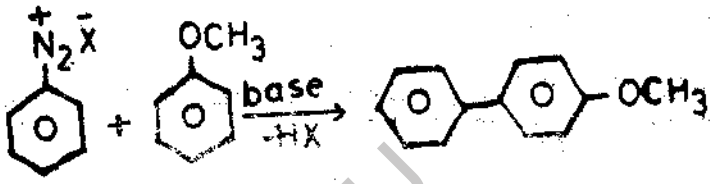
$$ArN_2^{\oplus}X^{\ominus} + CH_3CH_2OH \longrightarrow ArH + N_2\uparrow + HX + CH_3CHO$$



c) **Replacement by aryl group: Preparation of Biphenyls:** Bipheyls are formed by the reaction between an aryl diazonium salt and aromatic compound in the presence of a base. Aromatic compounds carrying ring activating group undergo this reaction readily.



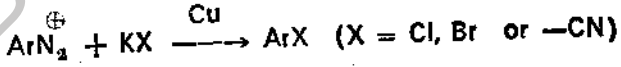
For exmaple: p-methoxy biphenyl is obtained by the reaction of anisole with phenyl diazonium salt.

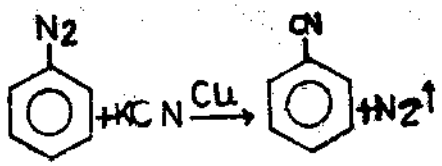


Anisole

d) **Displacement by -- Cl, Br, -- I and - CN**

i) **Gattermann reaction:** In this the aryl diazonium salt is reacted with potassium chloride, bromide or cyanide in the presence of copper powder, when the diazonium group is replaced by the anion of the potassium salt.

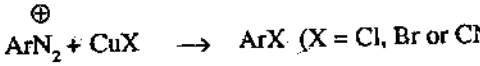


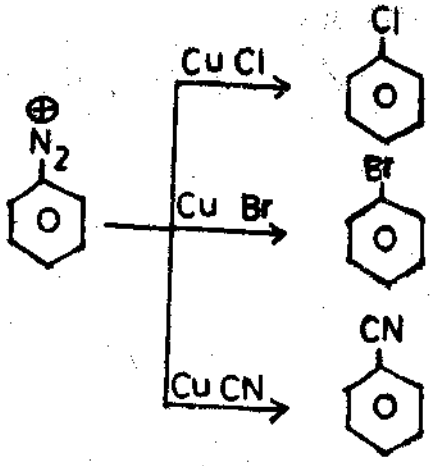


Benzonitrile

For the displacement of diazonium group by iodine, the catalyst, Cu is not required.

ii) **Sandmeyer's reaction:** Preparation of aryl halide or cyanide by the action of cuprous salts, CuX (X = Cl, Br or CN), on diazonium salts is known as Sandmeyer reaction.



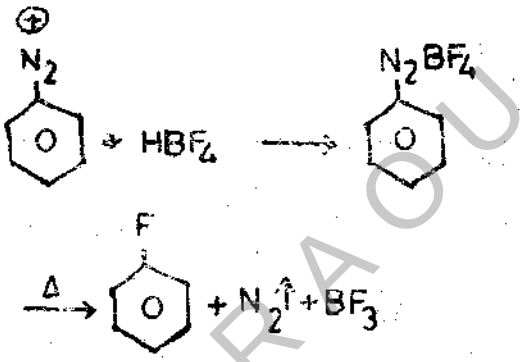


e) Replacement by F : Sheimann reaction:

Diazonium salts are first converted into diazonium flroroborate by the action of fluoroboric acid (HBF_4). Diazonium fluoroborate on heating decomposes to give aryl fluoride.

$$ArN_2^{\oplus} + HBF_4 \longrightarrow ArN_2BF_4 \xrightarrow{\Delta} ArF + N_2\uparrow + BF_3$$

Aryldiazonium fluoroborate

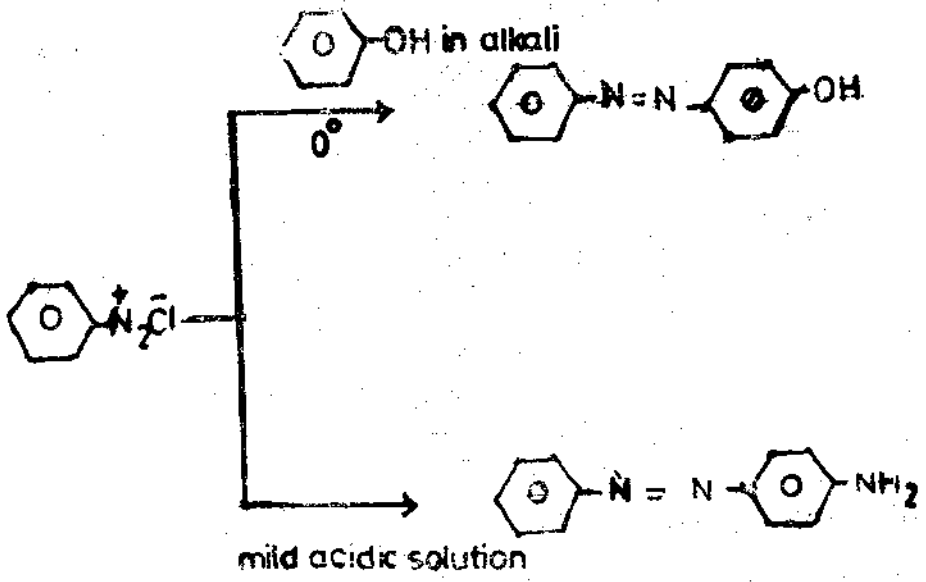


f) Replacement by - NO_2 group: Diazo group in aryl diazonium fluoroborates can be replaced by NO_2 group by the action of $NaNO_2$ in the presence of Cu powder.

$$ArN_2BF_4 \xrightarrow[Cu]{NaNO_2} ArNO_2 + N_2\uparrow + BF_4^{\ominus}$$

2. Coupling reactions: The diazonium ion is a weak electrophile and can couple only with aromatic compounds containing very strong electron releasing groups like - OH and amino groups. Phenols and amines couple with aryl diazonium salts to give dyes.

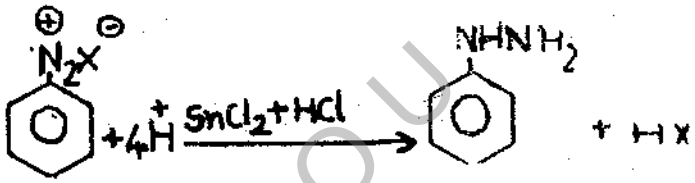
Amines couple in mild acidic solution, whereas phenols in mild alkaline solution.



Amines couple in mild acidic solution, whereas phenols in mild alkaline solution.

3. **Reduciton:** Reduciton of aryl diazonium salts with $SnCl_2$ in HCl give aryl hydrazines. Phenyl hydrazine is obtained by the reduction of phenyl diazonium salts.

$$ArN_2X + 2H_2 \xrightarrow{SnCl_2 + HCl} ArNHNH_2 + HX$$



Phenylhydrazine

21.10 SUMMARY

Amines are organic bases. There are different methods of their preparation. They are a) alkylation of ammonia b) reduction of different nitrogen compounds c) reductive amination of carbonyl compounds d) Hofman degradation e) Gabriel phthalimide f) schmidt reaction. Amines form salts with mineral acids. They undergo alkylation and acylation. A mixture of 1°, 2° and 3° amines can be separated by Hinsberg's method. Primary amines undergo carbylamine test. Aromatic primary amines undergo diazotisation and form azodyes. They also undergo different replacement reactions.

21.11 MODEL EXAMINATION QUESTIONS

I Answer each of the following in 10 lines

1. Write the structures of the following compounds and arrange them in the increasing order of basicity. Give reasons

   (i) (a) Ammonia (b) aniline (c) Methyl amine (d) Dimethyl amine

   (ii) (a) Aniline (b) p-Toluidine (c) o-Nitro aniline (d) m-Nitroaniline

   (iii) (a) Aniline (b) p-chloro aniline (c) p-Nitro aniline

PREFACE

This course deals with the topics in Physical, Inorganic and Organic Chemistry inlcuded in the syllabus for the Third Year of B.Sc Course offered by the Andhra Pradesh Open University. The syllabus is for the sake of convenience divided into Blocks, each of which comprises a number of Units. Each Block generally covers a specific area of the subject. The units are prepared by specialists in accordance with a format so designed as to enable the student read and understand them without much difficutly. Each unit begins with a statement of its aims and objectives and has at its end Model examination questions intended to test the students comprehension of its subject matter. Generally technical terms with which the student may not be familiar are given at the end of each unit under the head Glossary or Appendix wherever necessary.

In part-A dealing with physical Chemistry, it is attempted to explain the important aspects of thermodynamics, Electrochemistry, Chemical Kinetics, Surface Chemistry and Phase Rule. It is hoped that this part will help the student to acquire the necessarry knowledge in these areas.

In part-B delaing with Inorganic Chemistry efforts are made to describe the necessary aspects of the topics on crystal structure, Chemistry of d-block elements and general principles of metallurgy. These topics will enable the students to understand the salient features of the crystal structure, properties and the metallurgy of metals with special reference to transition metals.

Part-C (Blocks 9-13 separate book) dealing with Organic Chemistry expalins chemistry of Nitrogen compounds, Alicyclic and Hetorocycilic compounds; Carbohydrates-to the needed extent. The organic functional group analysis included at the end gives the student some knowledge to identify functional groups of carbon compounds.

The University hopes that this course material will help the student to get acquainted with fairly advanced aspects of chemistry.

$CH_3CH_2NH_2$ (b) $CH_2(Cl)CH_2NH_2$ (c) $CH_3CH(Cl)NH_2$ (d) $CHCl(Cl)CNH$

(v) CH_3NH_2 (b) $(CH_3)_3CNH_2$ (c) $CH_3CH_2NH_2$ (d) $(CH_3)_2CHNH_2$

2. How is ethylamine obtained starting from the following compounds? Give equations.

(a) Ethyl bromide (b) Propionamide (c) Nitroethane (d) Acetonitrile

3. How are the compounds in the following pairs are differentiated from one another?

(a) Ethylamine and diethylamine (b) Aniline and N-methylaniline (c) p-Toluidine and N, N - dimethyl p-toluidine (d) Aniline and ethylamine (e) Trimethyl amine, N,N - dimethy laniline

4. How do the following compounds react with benzene sulphonylchloride? Give structures of the products and indicate the solubility in alkali.

(a) Aniline (b) N-Methylaniline (c) Triethylamine

5. write equations for the synthesis of aniline by the following reactions. Give the names of starting materials and detailed reaction conditions in each case.

II Answer each of the following in 30 lines

1. How is aniline prepared from benzene? How does it react with the following reagents?

(a) Acetic anhydride (b) $CHCl_3$ and alcoholic KOH
(c) Benzene sulphonylchoride (d) Bromine . (e) $NaNO_2$ + dil. HCl at O-5° C

2. How is benzene diazonium chloride prepared? How are the following compounds prepared fromit? give equations.

(a) Fluorobenzene (b) Benzene (c) Biphenyl (d) Benzonitrile
(e) phenol (f) Nitro-benzene (g) Phenylhydrazine

3. How are the following converstions brought about? write equations.

(a) Aniline to p-nitro aniline (b) Aniline to o-nitro aniline (c) N-Methyl aniline to p-toluidine (d) Aniline to benzanilide (e) Aniline to benzonitrile

4. Write the structure sof all possible isomers for the compound with molecular formula C_8H_9N. Give their names.

5. An organic compound A (C_8H_9NO) when heated with dil. HCl gave "B" ($C_8H_8O_2$). B gave "C" (C_7H_9N) on treatment with hydrozoic acid. A also gave 'C' by reaction with bromine in the presence of sodium hyroxide. 'C' on treatment with nitrous acid followed by warming the aqueous solution gave p-cresol. Give the structures of A,B and C and explain the reaction involved in the above mentioned transformations.

21.12 MODEL ANSWERS TO CHECK YOUR PROGRESS

1. Methyl amine is a stronger base over ammonia due to the + I effect of methyl group in the former.

2. Based on carbyl amine test. a primary amine on heating with $CHCl_3$ and NaOH forms carbylamine which possesses bad smell.

21.13 GLOSSARY

1. **Carbylamine reaction:** Primary amines (both aliphatic and aromatic) react with chloroform in the presence of alcholic KOH solution to give isocyanides.

$$RNH_2 + CHCl_3 + 3KOH \rightarrow RNC + 3\ KCl + 3\ H_2O$$

2. **Deamination:** Removal of an amino group of an aromatic primary amine is known as deamination reaction. The aromatic primary amine is converted into aryl diazonium salt and the diazonium salt is treated with hypophosphorous acid or ethanol when the diazonium group is replaced by H.

3. **Hinsberg reaction:** This is a method used for the separation of primary, secondary and tertiary amines. The principle involved is the reaction of benzene sulphonyl chloride with amines and the nature of the resulting sulphonamides.

4. **Gattermann reaction:** The diazonium group in an aromatic diazonium salt can be replaced by X (X = Cl, Br, or CN) by the action of potassium halide or cyanide in the presence of copper powder. The catalyst is not needed if X = I.

$$Ar\text{-}\overset{\oplus}{N_2} + KX\ Cl \rightarrow ArX + \overset{\oplus}{K} + N_2\uparrow$$

5. **Sandmeyer's reaction:** The diazo group in an aromatic diazonium salt can be replaced by X (X=Cl, Br or CN) by treatment with the corresoponding cuprous salt (CuX)

$$Ar\ \overset{\oplus}{N_2} + CuX \rightarrow ArX + N_2\uparrow + \overset{\oplus}{Cu}$$

6. **Schiemann reaction:** Aryl diazonium fluoroborates on heating decompose to give fluoroborates.

$$Ar\ N_2\ BF_4 + CuX \xrightarrow{\Delta} ArX + N_2\uparrow + BF_3$$

Author: Dr. T. Sundara Ramaiah

UNIT - 22 AMINO ACIDS & PROTEIMS

Contents

22.1 AIMS AND OBJECTIVES

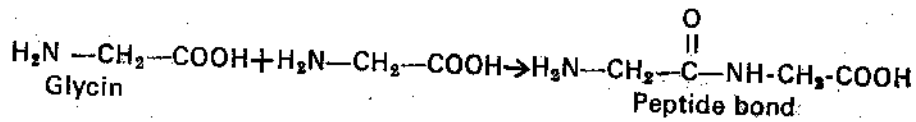
To explain the structure, synthesis and chemistry of amino acids, and to introduce the concept of peptide bond and nature of proteins.

After completing the reading and understanding of the contents of the unit you must be able to:

- describe the names, structures and classifiction of amino acids
- describe different methods of preparation of α - amino acids
- explain the properties of amino acids due to $-NH_2$, -COOH and both the groups

22.2 INTRODUCTION

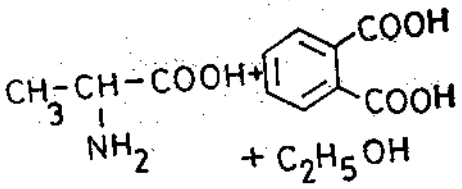
Amino acids are an important class of organic compounds which have two functional groups - an amino (NH_2) group and a carboxyl (COOH) group - in their structure. They are the building blocks from which proteins are constructed. Proteins are biopolymers which function as structural materials. They play an important role in biological conversion of chemical energy to mechanical energy. They catalyse and direct the chemical reactions necessary for the growth and maintenance of the living matter. Two molecules of amino acids form an amide bond. Such a linkage is called a peptide bond, and the resulting compounds are called peptides. For example, two molecules of glycine-an amino acid, form a peptide called glycylglycine. Glycylglycine is a dipeptide.



A tripeptide is derived from three amino acid molecules, a tetrapeptide from four, and so on. As more amino acid units are added, a polymer of high molecular weight is obtained. Such polymers are called polypeptides. Proteins are special types of polypeptides with molecular weights ranging from 6000 to more than 1,000, 000.

22.3 OCCURRENCE, STRUCTURE AND NOMENCLATURE OF AMINO ACIDS

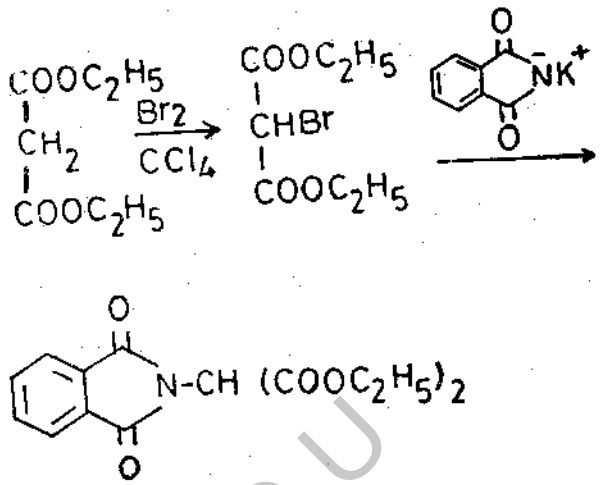
Well over 100 amino acids have been isolated to-date from natural sources, and identified. The great majority of these naturally occuring amino acids are α - amino acids. In these compounds, the amino



4

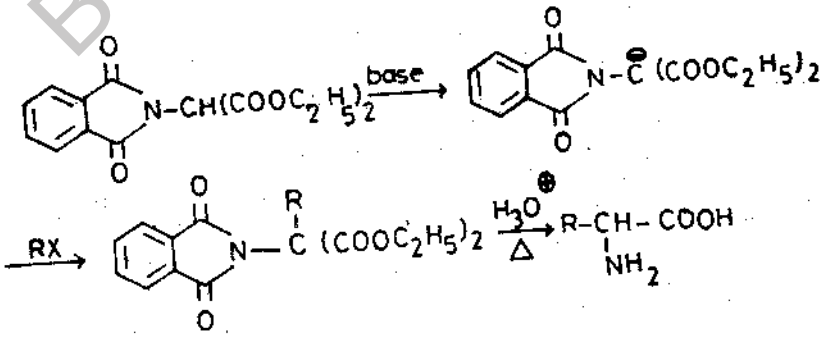
1. Pthalimide 2. Potassium pthalimidate 3. Ethyl-α-bromo propionate 4. Alanine

3. **From malonic ester:** Mon obromo derivative of diethyl malonate reacts with potassium salt of phthalimide to give N-phthalimido malonic ester.

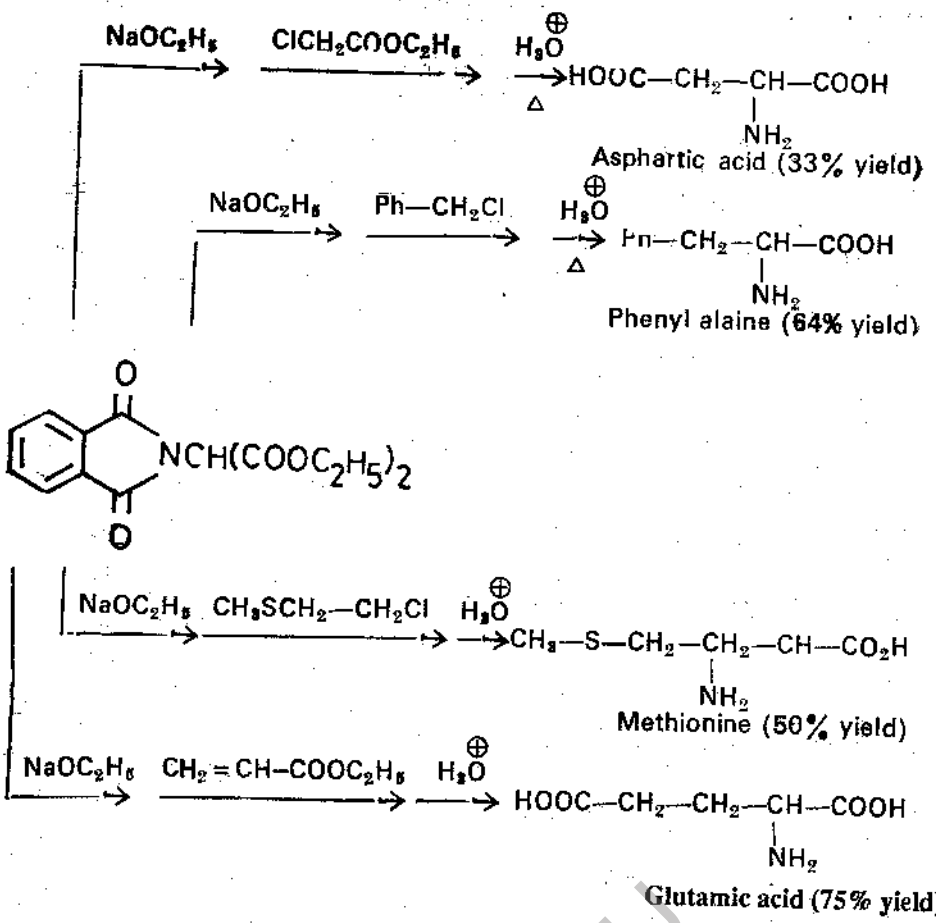


N-pthalimido malonic ester

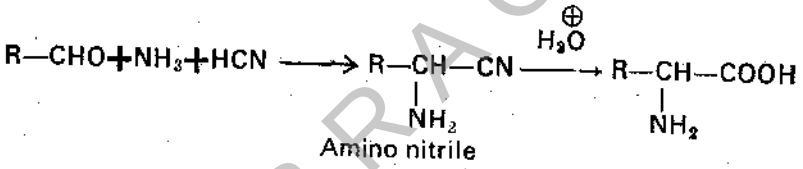
The ester may be alkylated by a variety of alkyl halides. Vigorous acid hydrolysis of the resulting compound causes hydrolysis of both ester group and phthalimido group, and decarboxylation of the amino dicarboxylic acid.



This method is essentially a variation of malonic ester synthesis and is a useful general method for the synthesis of α- amino acids in good yields. Some examples of the synthesis of amino acids using this method are given below:



4. Strecker's synthesis: In this method, an aldehyde is converted to an α- amino nitrile by action of hydrogen cyanide and ammonia. The amino nitrile is hydrolysed by mineral acids to give α- amino acids.

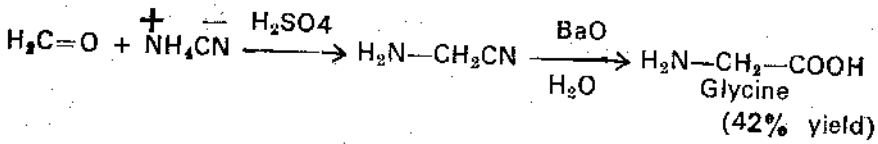


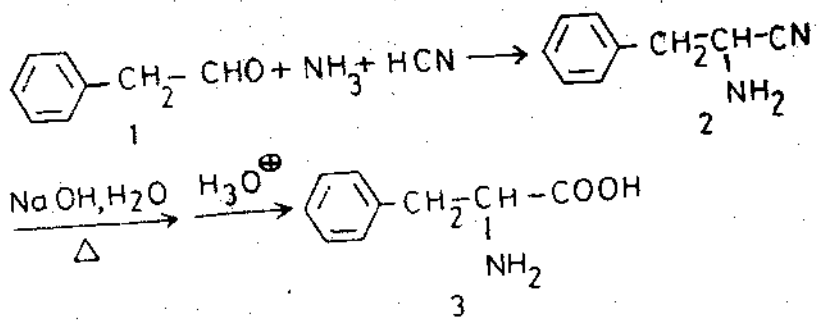
The formation of α - amino nitrile involves condensation of the aldehyde and ammonia, and addition of HCN to the resulting imine.

$$R\text{--}CHO + NH_3 \rightarrow \underset{\text{Imine}}{R\text{--}CH = NH} + H_2O$$

$$R\text{--}CH = NH + HCN \rightarrow R\text{--}\underset{\underset{NH_2}{|}}{CH}\text{ -- }CN$$

For example, glycine can be obtained from formaldehyde, and phenyl alanine from phenyl acetaldeyde, (74% yield)





1. Phenyl acetaldehyde 2. α -- Amino -β - Phenyl propionitrile 3. Phenyl alanine.

The methods described above are of general applicability for the synthesis of simpler amino acids. Some of the amino acids with more complicated structures must be prepared by other methods, which ar4e beyond the scope of the present lesson. The synthetic amino acids are racemic, therefore must be resolved into optically active components for the synthesis of peptides.

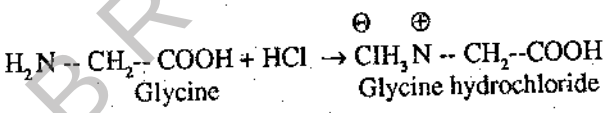
22.5 PHYSICAL PROPERTIES OF AMINO ACIDS

Amino acids are colourless crystalline compounds. They are soluble in water, but sparingly soluble in organic solvents. the melting points of amino acids are generally high, and most amino acids decompose instead of melting . Amino acids show both acidic and basic properties. In the solid phase, the I.r. spectra of amino acids show absorption bands at 3130-3000cm-1 (due to $^{\oplus}NH3$), 1600-1500 cm-1 (due to $COO^{\ominus}$) and 1300-880 cm-1. Except phenylalanine, tyrosine and tryptophan, other amino acids are trasparent above 250 nm, in the U.V. region.

22.6 CHEMICAL PROPERTIES OF AMINO ACIDS

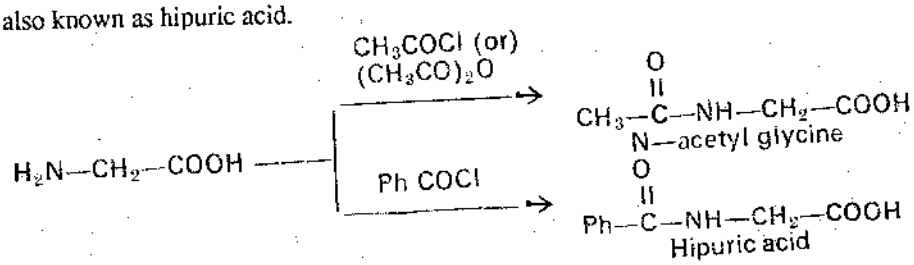
1. Reactions due to the amino group

a) The amino acids form salts with strong mineral acids like hydrochloric acid. These salts are sparingly soluble in water, and the free acid may be liberated by the addition of organic bases like pyridine.



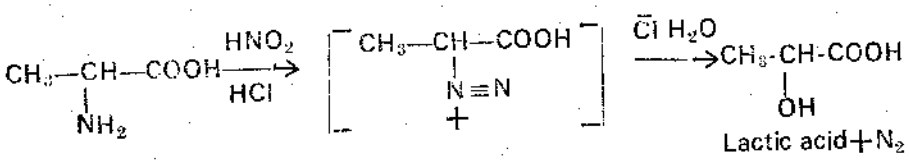
Glycine — Glycine hydrochloride

b) α - Amino acids may be acetylated by reaction with acetyl chloride or acetic anhydride. When benzoyl chloride is used, the corresponding benzoyl derivative is formed. Benzoyl derivative of glycine is also known as hipuric acid.



N—acetyl glycine — Hipuric acid

c) Nitrous acid liberates nitrogen from α - amino acids. This reaction is the basis of **'Von-Slyke method'** for the estimation of amino acids.



Unstable diazonium salt — Lactic acid + N_2

d) Nitrosyl Chloride (or bromide) reacts with amino acids to form chloro (or bromo) acids.

$$\underset{\text{Glycine}}{H_2N\text{--}CH_2\text{--}COOH} + NOCl \rightarrow \underset{\text{Chloroacetic acid}}{Cl\text{--}CH_2\text{--}COOH} + N_2 + H_2O$$

e) When heated wtih hydroiodic acid at 200°C, the amino group in amino acids is eliminated with the formation of a fatty acid.

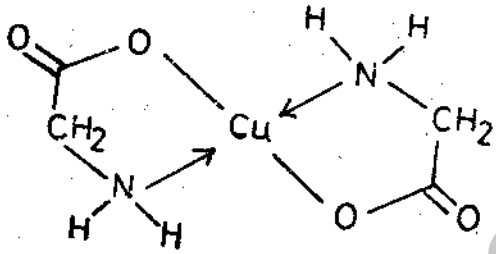
$$Ph\text{--}\underset{\displaystyle NH_2}{\underset{|}{CH}}\text{--}COOH \xrightarrow[\Delta]{HI} Ph\text{--}CH_2\text{--}CH_2\text{--}COOH$$

β - Phenyl Propionic acid

II. Reactions due to carboxylic group

a) Amino acids form salts with heavy metals. For example, a copper salt of glycine (deep blue needles) is formed by heating copper oxide with an aqueous solution of glycine.

$$2\ H_2N\text{-}CH_2\text{-}COOH + CuO \xrightarrow{H_2O}$$



b) α - Amino acids react with alcohols in the presence of hydrogen chloride. The free ester may be isolated by the neutralisation of the ester hydrochloride with sodium carbonate.

$$H_2N\text{--}CH_2\text{--}COOH + C_2H_5OH + HCl \longrightarrow Cl\,H_3N\text{--}CH_2\text{--}COOC_2H_5 + H_2O$$

$$\xrightarrow{Na_2CO_3} \underset{\text{Ethyl ester of glycine}}{H_2N\text{--}CH_2\text{--}COOC_2H_5}$$

c) Amino acids undergo reduction with lithium aluminum hydride ($LiAlH_4$) to give β - amino alcohols. Thus glycine is converted into β - amino ethanol.

$$H_2N\text{--}CH_2\text{-}COOH \xrightarrow{LiAlH_4} \underset{\text{β- Amino ethanol}}{H_2N\text{--}CH_2\text{--}CH_2OH}$$

d) Amino acids react with phosphorus pentachloride (PCl_5) to give acid chloride hydrochlorides.

$$\underset{\displaystyle NH_2}{\underset{|}{CH_3\text{--}CH}}\text{--}COOH + PCl_5 \rightarrow \underset{\text{Alanine acid chloride hydrochloride}}{\underset{\displaystyle \oplus NH_3\,\overset{\Theta}{Cl}}{\underset{|}{CH_3\text{--}CH}}\text{--}COCl} + POCl_3$$

Alanine

e) When an amino acid is heated in the presence of dry barium oxide, decarboxylation occurs to give alkyl amines.

$$R\text{--}\underset{\displaystyle NH_2}{\underset{|}{CH}}\text{--}COOH \xrightarrow[-CO_2]{BaO,\ \Delta} R\text{--}CH_2\text{--}NH_2$$

III Reactions due to both amino and carboxyl groups

a) The high melting points, and the large dipole moment values of amino acids, their solubility in water and insolubility in most of the organic solvents suggest that the amino acid exist as "Zwitter ions". The formation of these inner salts may be visualised as due to intramolecular neutralisation of the basic amino group and the acidic carboxyl group. X-ray analysis supports this view.

$$R\text{--}\underset{\displaystyle NH_2}{\underset{|}{CH}}\text{--}COOH \rightarrow R\text{--}\underset{\displaystyle \oplus NH_3}{\underset{|}{CH}}\text{--}COO$$

Zwitter ion

In aqueous medium, the dipolar ion may be in equilibrium with its conjugate base (CB), formed by loss of a proton, and conjugate acid (CA), formed by gain of a proton.

$$\underset{\text{Conjugate acid (CA)}}{R\text{--}\underset{\displaystyle \oplus NH_3}{\underset{|}{CH}}\text{--}COOH} \underset{+H\oplus}{\overset{-H^{\oplus}}{\rightleftharpoons}} \underset{\text{Dipolar ion (DA)}}{R\text{--}\underset{\displaystyle \oplus NH_3}{\underset{|}{CH}}\text{--}COO^{-}} \underset{+H\oplus}{\overset{-H^{\oplus}}{\rightleftharpoons}} \underset{\text{Conjugate base (CB)}}{R\text{--}\underset{\displaystyle NH_2}{\underset{|}{CH}}\text{--}COO^{-}}$$

The position of this equilibrium depends upon the p^H of the solution. In acidic solution, the conjugate acid predominates, and in alkaline solution, the conjugate base predominates. For each amino acid, there is a particular p^H at which the concentration of the dipolar ion is a maximum. Since the net charge is zero, the dipolar ion is electrically neutral, and consequently, in this condition, the amino acid does not migrate when placed in an electric field. This p^H at which migration does not occur, is called the "isoelectric point" (or isoionic point) of the amino acids. This point represents the p^H at which the solubility of the amino acid in non-polar solvents is at a maximum. The isoelectric point of any amino acid can be calculated by the formula.

$$K_1 = \frac{[H^+]\ [\overset{\oplus}{H_3}N\ CH_2COO^{\ominus}]}{[\overset{\oplus}{H_3}N\ CH_2\overset{\ominus}{COO}]}$$

$$K_2 = \frac{[H_+]\ [H_2N\ CH_2\ \overset{\ominus}{COO}]}{[\overset{\oplus}{H_3}N\ CH_2\ \overset{\ominus}{COO}]}$$

$\therefore$ Isoelectric point of the amino acid (pHi) = $pk_1 + pk_2$

For glycine $pk_1 = 2.35$, $pk_2 = 9.78$

$\therefore$ pHi = 2.35 + 9.78 = 6.06

When the amino acid contains two amino or two carboxyl groups, there are several possibilities for the structure of the dipolar ion at the isoelectric point. In all the α-amino acids, it is the ionisation of the α - carboxyl group that is involved, but the amino group could also be the terminal one.

$$HOOC\text{--}(CH_2)_2\text{--}\underset{\displaystyle \oplus NH_3}{\underset{|}{CH}}\text{--}\overset{\ominus}{COO}$$

glutamic acid

$$H2N\text{--}(CH_2)_4\text{--}\underset{\displaystyle NH_2}{\underset{|}{CH_2}}\text{--}\overset{\ominus}{COO}$$

Lysine

Check your progress - 1

What is isoelectric point?

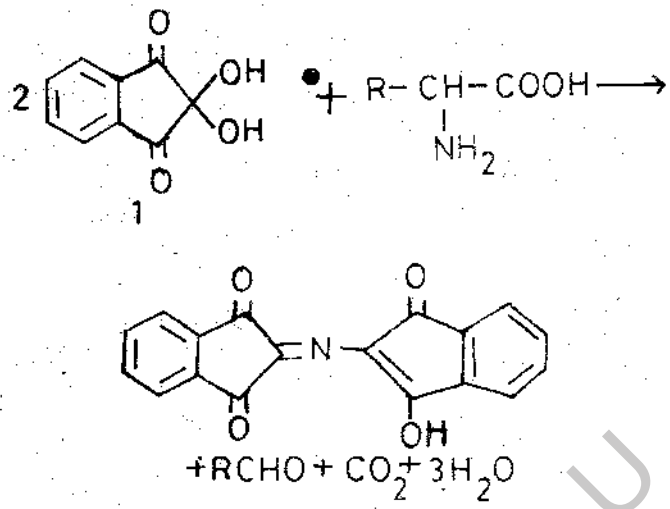
.....

.....

.....

.....

b) Ninhydrin reaction: When an aqueous solution of an amino acid is treated with triketohydrindene hydrate (ninhydrin) a violet colour is produced.



1. Ninhydrin

The violet cloured solutions show an absorption maximum at 570 nm in th U.V. region, and the intensity of the absorption is proportional to the amount of α - amino acid present. Ninhydrin is thus an important reagent in the identification and estimation of α-amino acids.

22.7 PEPTIDES - STRUCTURE AND NOMENCLATURE

We have seen that -amino acids contain both amino and carboxylic groups. It is possible that the amino group of one molecule and the carboxyl group of another molecule can undergo condensation reaction to form an amide linkage. The resulting compound is known as a dipeptide. The dipeptide can further react with a third molecule of amino acid to give a tripeptide, and so on.

Check your progress - 2

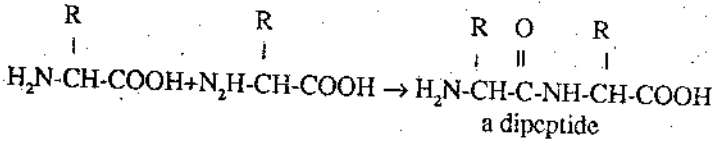
What do you mean by a dipeptide?

.....

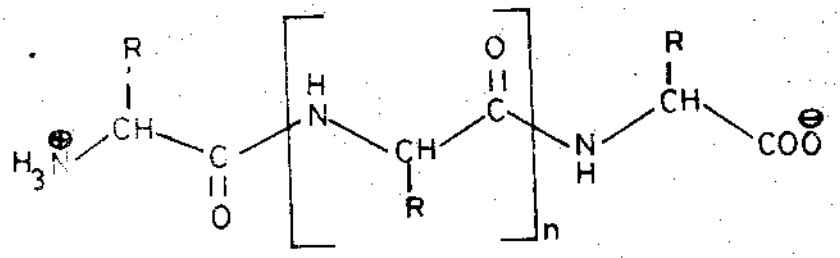
.....

.....

.....

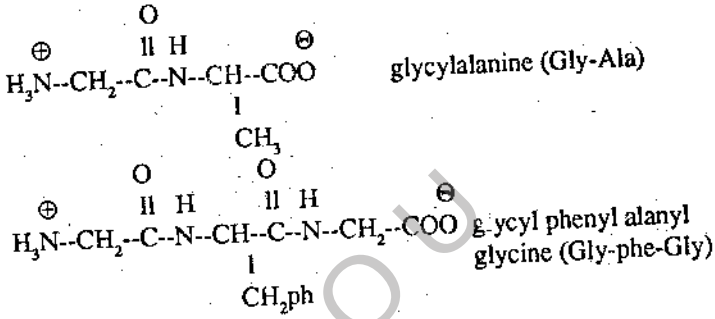


Peptides or polypeptides, are thus polymeric compounds containing 2 to about 50 individual amino acid units. The individual amino acids are linked through an amide bond, knwon as peptide bond. A linear polypeptide will conti a free-NH_3 group (the $\overset{\oplus}{N}$-terminal unit) and a free-COO--group (the -terminal unit).



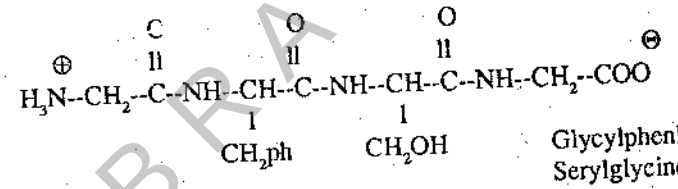
N-Tern nal amino acid C-Terminal amino acid

By convention, structures are always written with the N-terminal unit on the left, and the C-terminal unit on the right. They are named by prefixing the N-terminal amino acid followed by other amino acids. While writing these structures, usually abbreviations for amino acids are used.



glycylalanine (Gly-Ala)

glycyl phenyl alanyl glycine (Gly-phe-Gly)



Glycylphenlalanyl Serylglycine (Gly-phe-ser-Gly)

Like the simpler amino acids, peptides are amphoteric compounds. since they also contain a free amino group and a free carboxyl group. They exist as zwitterions. Like amino acids, peptides also have isoelectric points, the P^H at which the peptide is least soluble in aqueous solution.

22.8 SUMMARY

α - Amino acids are the building blocks of proteins. They are prepared in the laboratories by a) amination of α - haloacids b) Gabriel pthalimide synthesis c) Phthalimidomalonic ester synthesis d) strecker synthesis. α - Amino acids are colorless crystalline substances with high melting points and boiling points. They are amphoteric substances.α - Amino acids exist as zwitter ions. Isoelectric point of an amino acid is the p^H of a solution in which it does not migrate to any electrode on electrolysis. They exhibit the propeties of amines, carboxylic acids and also some additional properties due to the presence of both $-NH_2$ and -COOH groups with in the molecules.

22.9 MODEL EXAMINATION QUESTIONS

I Answer each of the following in 10 lines.

1. What are amino acids? Describe any three mehods of their synthesis.
2. Discuss the chemical properties of amino acids due to the amino group.
3. Discuss the chemical properties of amino acids due to the carboxyl group.
4. Discuss the properties of amino acids due to the presence of both amino and carboxyl groups.
5. What are peptides? Write the structures and names of all the possible tripeptides formed from glycine, alanine and serine.

II Answer each of the following in 30 lines

1. Discuss the synthetic methods available for amino acids.
2. Discuss the physical and chemical properties of amino acids.
3. List the names and structures of essential amino acids and discuss one synthesis for each.
4. What are peptides? Discuss briefly their structure and nomenclature?
5. List the names and structures of naturally occurring amino acids.

22.10 MODEL ANSWERS TO CHECK YOUR PROGRESS

1. It is the p^H of a solution in which an amino acid does not migrate to any electrode electrolysis.
2. Carboxyl group of an amino acid can react with the amino group of the other forming an amide bond. This amide bond is called peptide bond and the resulting product is a dipeptide.

Author: Dr. P.S.N. Reddy

UNIT 23 ALICYCLIC COMPOUNDS

Contents

23.1 AIMS AND OBJECTIVES

To familiarise the student with the nomenclature, preparations, properties of cyclo-alkanes and conformations of cyclohexane.

After a thorough study and understanding of the contents of this unit, you are expected to:

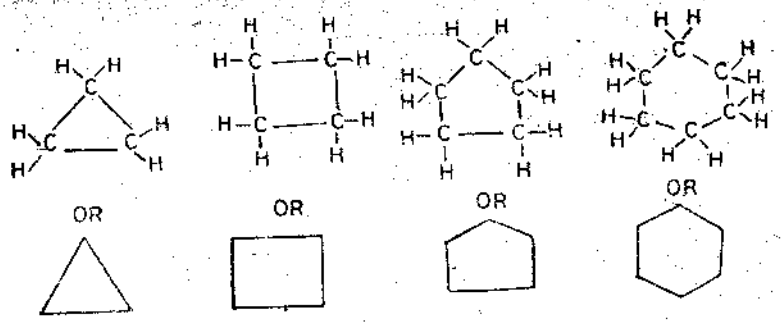
- be able to name different alicyclic compounds
- describe the classification and different methods of preparation of cycloalkanes
- explain the reactivity of cycloalknes
- give an account of the conformations of cyclohexane.

23.2 INTRODUCTION

Alicyclic compounds are **cyclic aliphatic compounds**. These are also known as **cycloaliphatic compounds.** In these compounds rings consist of carbon atoms. These rings may contain three, four, five, six or more number of carbon atoms. Alicyclic hydrocarbons like aliphatic hydrocarbons may be further classified into cycloalkanes, cycloalkenes and cycloalkynes. The general formula of cycloalkanes is $C_n H_{2n}$. Where 'n' is the number of carbon atmos.

23.3 NOMENCLATURE

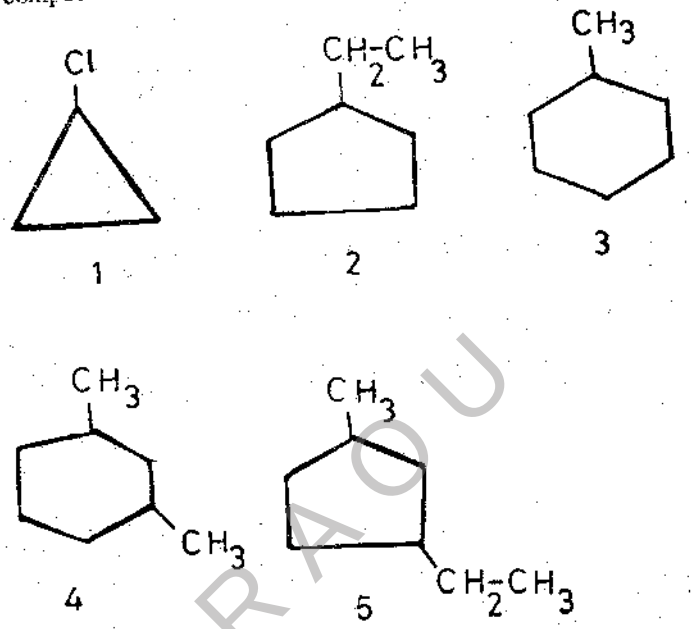
In the nomenclature of alicyclic compounds the prefix 'cyclo' is used. The name also indicates the number of carbon atoms in the ring, and number, position and nature of the functional groups, if any present in the molecule. Unsubstituted cycloalkanes containing three, four, five, and six carbon atoms are named as cyclopropane, cyclobutane, cyclopentane and cyclohexane respectively. The structure of these compounds are given below.



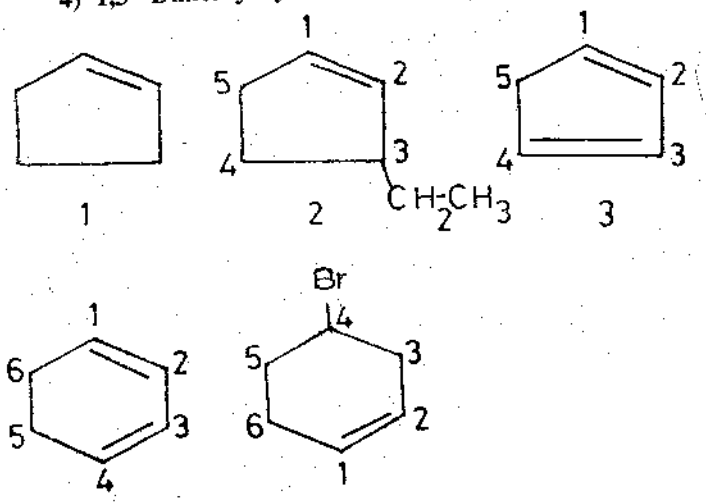
Cyclopropane **Cyclobutane** **Cyclopentane** **Cyclohexane**

The following examples illustrate the nomenclature of alicyclic compounds.

Alicyclic compounds are classified according to the size of the ring as follows:



1) chloro cyclopropane 2) Elhyl cyclopentane 3) Methyl cyclohexane
4) 1,3 - Dimethyl cyclohexane 5) 3 - Ethyl-methyl cyclopentane



1) Cyclopentene 2) 3-Ethyl cyclopentene 3) 1,3 - Cyclopentadiene
4) 1,3 - Cyclohexadiene 5) 4-Bromo cyclohexene.

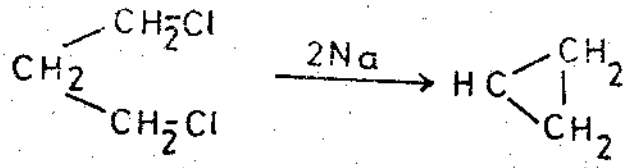
Alicyclic compounds are classified according to size of the ring as follows:

Small rings - Rings containing 3 and 4 carbons
Regular rings - Rings containing 5,6 and 7, carbons
Medium rings - Rings containing 8 to 11 carbons
Large rings - Rings containing 12 or more carbons

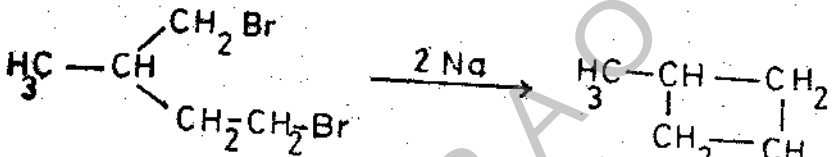
23.4 METHOD OF PREPARATION OF CYCLOALKANES

Many methods are available for the preparation of cycloalkanes. The choice of the method depends upon the number of carbon atoms in the ring. Some of the very common methods used for the synthesis of cycloalkanes are given below.

i) **Freund method:** This reaction is also known as internal Wurtz reaction. Preparation of cycloalkanes by the action of sodium metal on dihaloalkanes is knwon as Freund reaction. Use of zinc in place of sodium has been found to improve the yield of products. This method is quite valuable for the synthesis of small size rings i.e. cyclopropanes and cyclobutanes. For example Freunds reaction of 1,3 dichloro propane and 1,4 dibromo 2- methyl butane yields cyclopropane and methyl cyclobutane respectively.

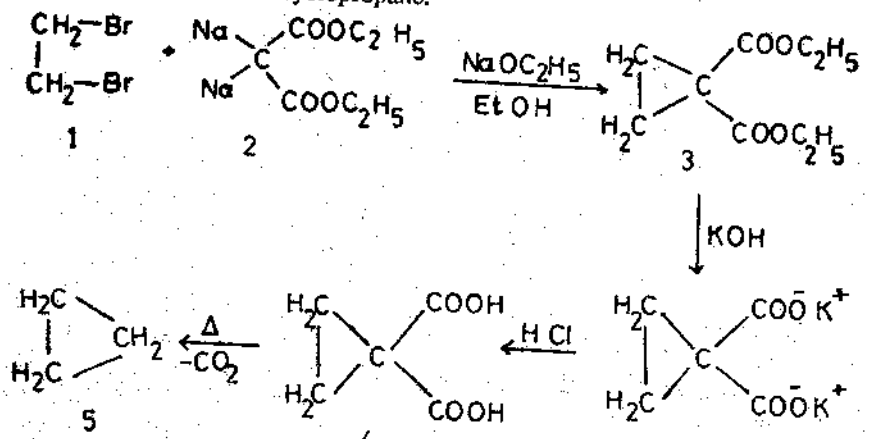


1, 3-Dichloropropane — Cyclopropane

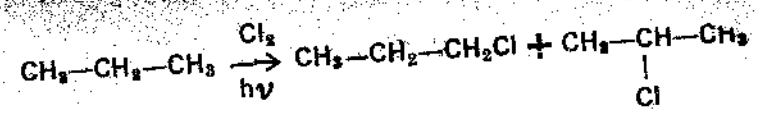


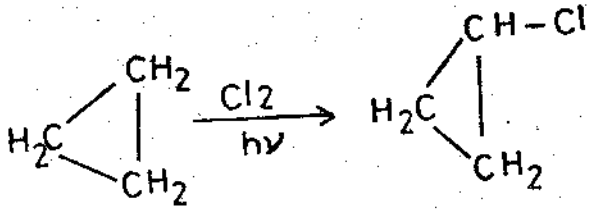
1,4 - Dibromo - 2- methyl butane — Methyl cyclobutane

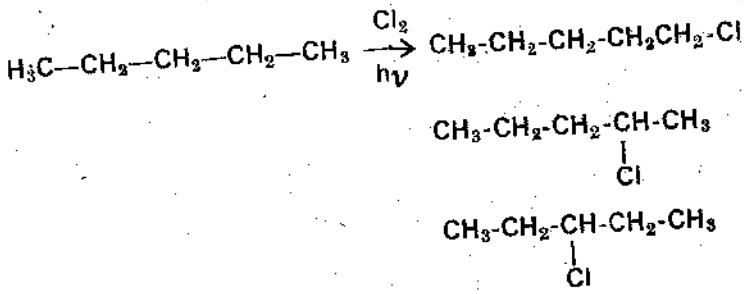
ii) **Perkin's method:** When malonic ester reacts with dihaloalkanes in the presence of sodium ethoxide, derivatives of cycloalkanes are obtained. Reaction of ethylene dibromide with malonic ester in the presence of sodium ethoxide gives 1, 1 - dicarbethoxy cyclopropane. This may be hydrolysed to give the corresponding dicarboxylic acid. Cyclopropane-1, 1-dicarboxylic acid on decarboxylation furnishes cyclopropane.

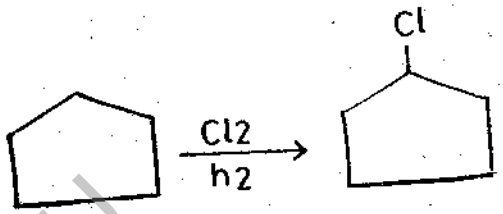


1) Ethylenedibromide 2) Sodiomalonic ester 3) 1,1-dicarbethoxy cyclopropane
4) Cyclopropane 1,1 - dicarboxylic acid 5) cyclopropane

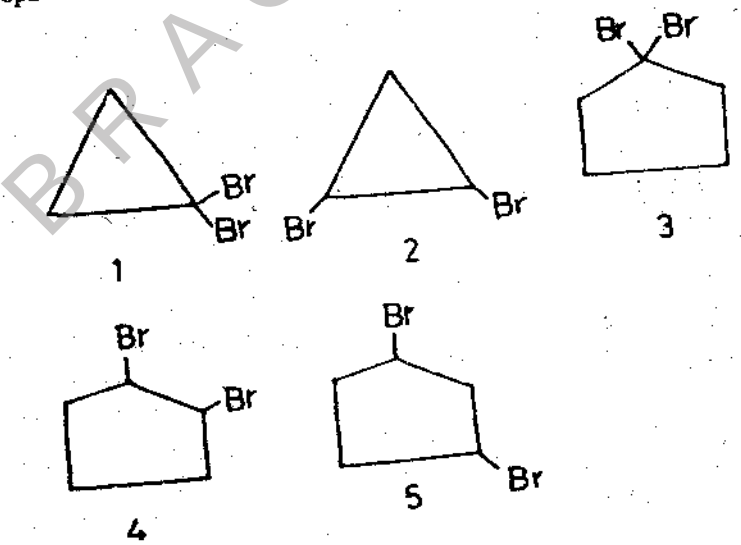








On the other hand isomeric disubstituted cycloalkanes are possible. Following are the isomeric dibromocyclopropanes and dibromocyclopentanes.

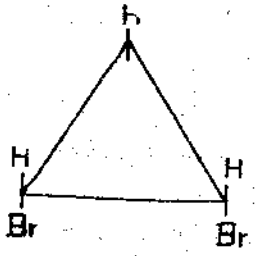


1) 1,1 Dibromo cyclopropane 2) 1,2 - Dibromocyclopropane 3) 1,1 - dibromocyclopentane 4) 1,2 - Dibromocyclopentane 5) 1,3 Dibromocyclopentane

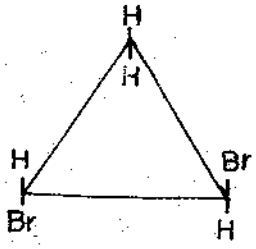
This disubstituted cycloalkanes exhibit three types of isomerism.

1. Position isomerism: Isomers which differ from each other with respect to the position of a reference atom or group are known as position isomers. For ex: 1,1-; 1,2-; 1,3-dibromo cyclopentanes as position isomers.

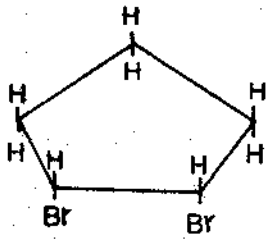
2. Cis-Trans isomerism: In a 1,2 - dibromocycloalkane, the two bromine atoms may be on the same side or on opposite sides of the ring. The isomer with the two bromine atoms on the same side is knwon as cis-isomer and the other isomer with the two bromine atoms on the opposite sides is known as trans-isomer. Following are the cis-trans isomers of 1,2 - dibromo propane and 1,2 - dibromo cyclopentane.



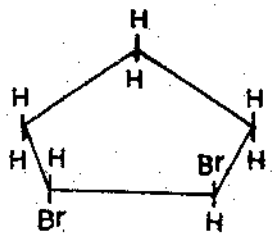
Cis-1,2 - dibromo cyclopropane



Trans-1,2-dibromo cyclopropane



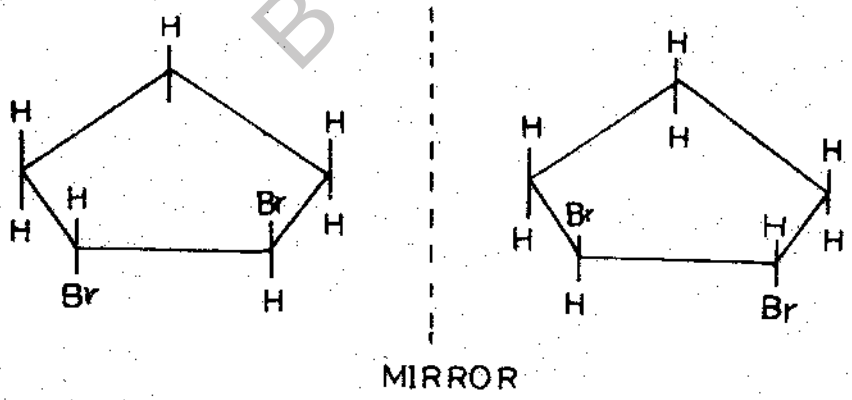
Cis-1,2 - dibromo cyclopentane



Trans-1,2-dibromo cyclopentane

Cis-trans isomerism is also exhibited by 1,3 - disubstituted cyclopentanes.

3. Optical isomerism: Certain disubstituted cycloalkanes, when suitably substituted exhibit optical isomerism. Trans 1,2-dibromo cyclopentane, for example is not symmetric. When there is no plane of symmetry in a molecule two non-superimposable isomeric structures, bearing mirror-image relationship, are possible. One of these isomers rotating the plane polarized light to the right is called the dextro rotatory isomer. The other isomer rotating the plane polarized light to left is called the levo rotatory isomer.

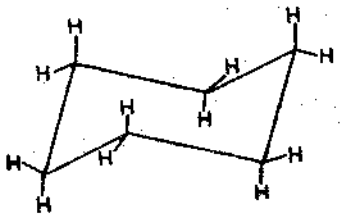


non-superimposable mirror images of trans - 1,2 dibromocyclopentane

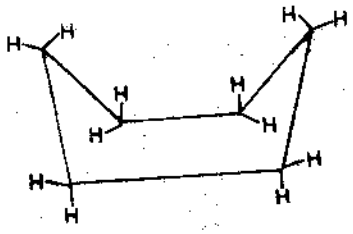
On the other hand, cis-1,2-dibromocyclopentane possesses a plane of symmetry. A plane bisecting C_1-C_2 bond and passing through C_4 bisects the molecule into two identical halves. Therefore a symmetric molecule like cis-1,2-dibromocyclopentane is optically inactive.

iii) In cyclohexane the ring may be present in two conformations - Chair and Boat conformation. In these conformations the C-C-C bond angles are 109°28'.

iv) The chair and boat conformations of cyclohexane are free from bond angle strain.



Chair Conformation of Cyclohexane



Boat-Conformation of Cyclohexane

Sachse's proposal was initially discounted on the ground that cyclohexane has been obtained only in one form. In 1918 **Mohr** revived the idea and pointed out that inteconversions of boat, and chair forms can be accomplished in the models by rotation at C-C single bonds, without distorting the normal tetrahedral angles. Thus the two possible forms of cyclohexane may be so closely equivalent in energy content to be indistinguishable. It was **Huckel** who later obtained two steric forms of decalin viz. *cis* and *trans* decalins.

Check your progress - 2

Why chair form of cyclohexane is more stable over boat form?

.....

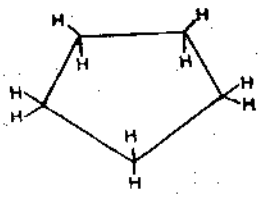
.....

.....

.....

(i) Conformations of cyclopentane

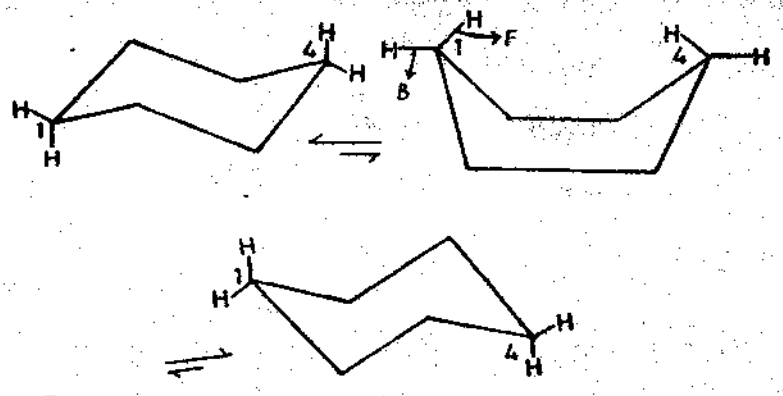
In puckered conformation of cyclopentane, four carbon atoms of the ring are coplanar and the fifth is pushed slightly out of plane. The puckered conformation is taken up in turn by all the ring carbons, thus making them all equivalent. An examination of the model of cyclopentane reveals that the hydrogen atoms present on any two adjacent carbon atoms which are coplanar are eclipsed. Thus there is a repulsion between the adjacent hydrogen atoms. This strain is due to repulsion between the adjacent hydrogen atoms. This strain ... repulsion between the adjacent hydrogen atoms is called **Pitzer strain**



Envelope form of cclopentane

(ii) Conformations of Cyuclohexane

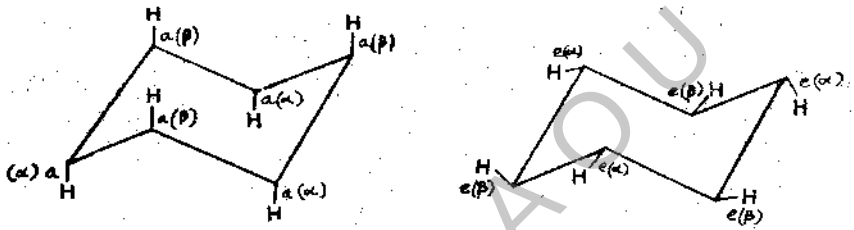
In the chair conformation of cyclohexane all the CH_2 groups are in the staggered conformation. In this conformation there is no Pitzer strain and no bond angle strain. By a twist about C-C bonds a chair of cyclohexane is converted into another chair form through a boat form.



F = Flag pole hydrogen B = Bow spirit hydrogen

In boat form cyclohexane the hydrogen atoms present on C_1 and C_4 are called *flag pole hydrogens* and bow *spirit hydrogens*. The flag-pole hydrogens are very close to each other. As a result, a sort of repulsion operates between the two flag pole hydrogen atoms present on C_1 and C_4. The flag pole-flag pole hydrogen repulsion makes boat conformation unstable relative to chair conformation by about 6 K. Cal/mole. Therefore at ordinary temperatures cyclohexane exists, entirely in the chair conformation.

In the chair conformation of cyclohexane two types of C-H bonds are present. The six C-H bonds which are oriented perpendicular to the average plane of the cyclohexane ring are known as axial bonds and are designated as 'a'. The other six C-H bonds which radiate from the ring making an angle of 109°.5' to the average plane of the ring are known as **equatorial bonds** and are denoted as 'e'. The axial and equatorial bonds are further classified as α - and β - bonds depending upon whether these bonds are directed below or above the average plane of ring respectively.



a = axial e = equatorial

23.9 SUMMARY

Alicyclic compounds are carbocyclic compounds which exhibit the properties of aliphatic compounds. Cycloalkanes can be prepared by a) Freund reaction b) Perkin reaction c) Pyrolysis of dicarboxylic acid salts d) Dieckmann condensation and e) acyloin condensation. Alkanes and cyclokanes are similar in their chemical reactivity. Cyclopropane and cyclobutane undergo ring opening additions in order to get rid of bond angle strain. Sachse and Mohr proposed bond angle strain free puckered conformations to cyclohexane. They are chair form and boat form. Chair form is more stable over boat form due to the repulsion between flagpole hydrogens and between bow sprit hydrogens of the latter conformer.

23.10 MODEL EXAMINATION QUESTIONS

I **Answer each of the following in 10 lines**

1. Explain how cyclopropane differs from ethene in its reactions with (a) cold dilute KMn_4, (b) HI (c) Bromine (d) Hydrogen/catalyst.
2. Write notes on Baeyer's strain theory
3. Write notes on Sachese-Mohr theory.

II **Answer each of the following in 30 lines**

1. Discuss the general methods of preparation of alicyclic compounds.

2. Discuss the merits and demerits of Baeyer's strain theory.

3. Explain the reasons for stability of cyclohexane.

23.11 MODEL ANSWERS TO CHECK YOUR PROGRESS

1. Cyclopropane and cyclobutane undergo ring opening reactions in order to get rid of their bond angle strain.

2. Chair form is more stable over boat form due to the following two types of strain in the latter. a) repulsion between flagpole hydrogens b) eclipsed strain between bowspirit hydrogens.

Author: Dr. P. N. sharma

UNIT 24 HETEROCYCLIC COMPOUNDS

Contents

24.1 AIMS AND OBJECTIVES

To outline the importance, synthesis and reactivity of five membered heterocyclic systems containing one heteroatom viz. pyrrole, furan and thiophene.

After a detailed study and understanding of contents of this unit, you are expected to:

- define heterocyclic compounds
- to realise the importance of five membered heterocyclic systems containing one heteroatom pyrrole, furan and thiophene
- give an account of the methods of synthesis of pyrrole, furan, thiophene and their derivatives
- describe the aromatic character, reactivity and orientation in electrophilic substitution reactions of pyrrole, furan and thiophene.

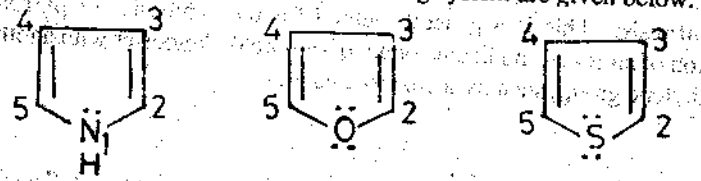
24.2 INTRODUCTION

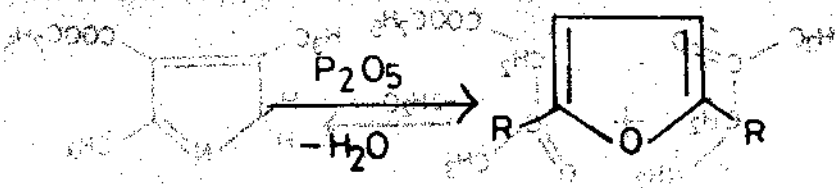
Heterocyclic compounds are cyclic compounds with one or more heteroatoms in the ring. Atoms of elements other than carbon and hydrogen are called heteroatoms. The most common heteroatoms are nitrogen, sulphur and oxygen. According to this definition one may be tempted to consider compounds like ethylene oxide, succinic anhydride etc., as heterocyclic. But as they are easily converted into openchain derivatives these are not generally considered as heterocyclic compounds. Heterocyclic compounds may be aromatic or non-aromatic. They are classified on the basis of the size of the ring and the number of heteroatoms in the ring.

Heterocyclic compounds are very widely distributed in nature, and they are essential to life in various ways. They are present in most of the members of vitamin 'B' complex, in alkaloids, antibiotics, chlorophyll, haemoglobin, plant pigments, drugs, enzymes etc.

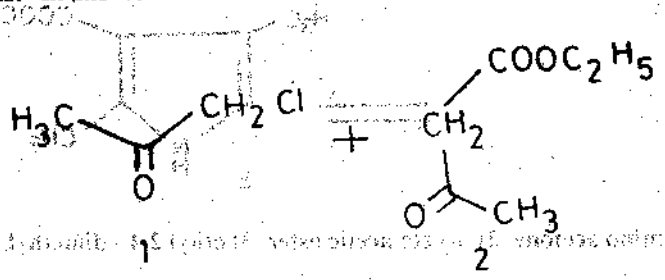
24.3 FIVE MEMBERED RINGS CONTAINING ONE HETEROATOM

Pyrrole, furan, thiophene are the important members of the five membered aromatic heterocyclic compounds containing one heteroatom. Pyrrole ring system is present in chlorophyl and haemoglobin. The formulae of these compounds and numbering of the ring system are given below.

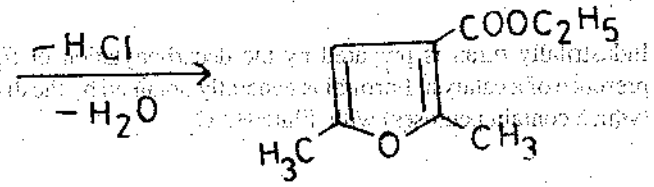




iv) **Feist - Banary Synthesis:** In this reaction an α - chloroketone is condensed with β - keto ester in pyridine solution.



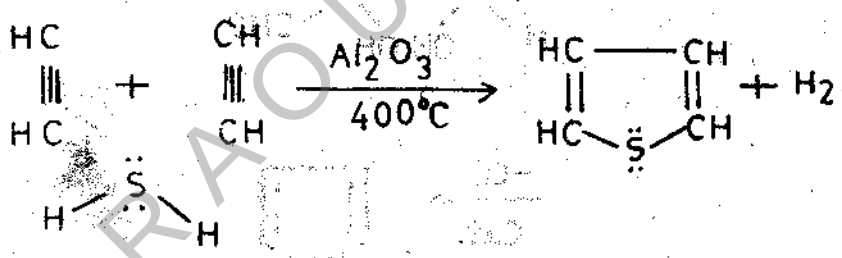
1 2



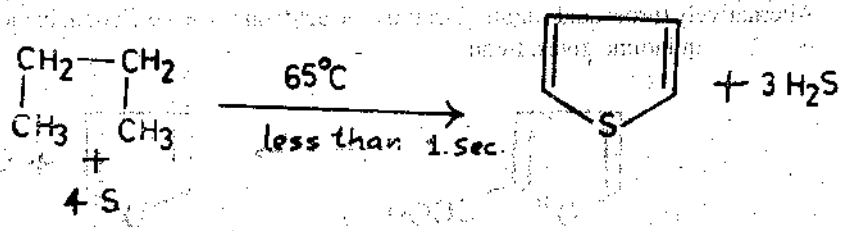
1. Chloroacetone 2. Ethyl acetoacetate

c) **Synthesis of thiophene:** Thiophene can be prepared by the following methods.

i) **Passing a mixture of acetylene and hydrogen sulphide over alumina at 400°C**

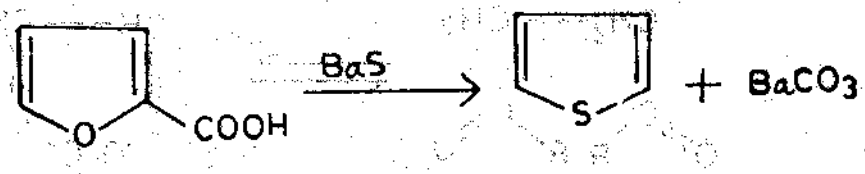


ii) **Thiophene is commercially obtained by the direct reaction between sulphur and n-butane in the vapour phase.**

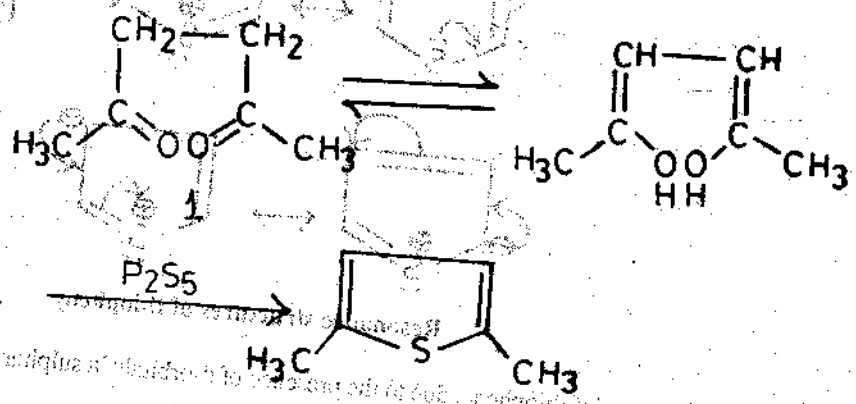


In this reaction butadiene may be used in place of n-butane.

iii) **Furoic acid, on distillation with barium sulphide, yields thi ophene**



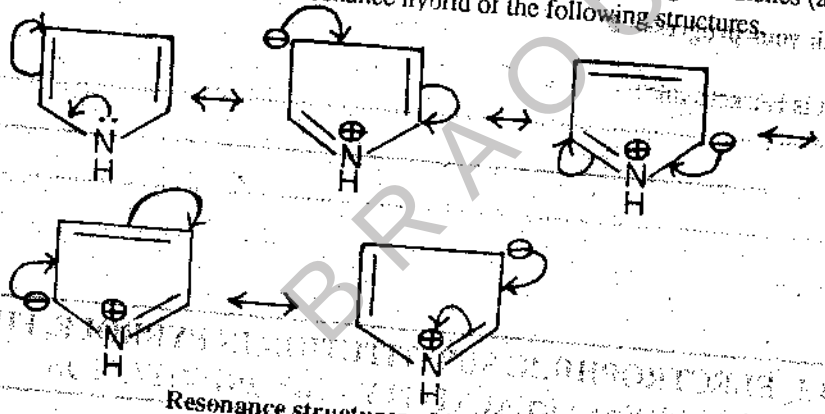
iv) **Paal-Knorr-Synthesis: Thiophene derivatives are prepared by heating 1,4 - dicarbonyl compounds with phosphorus pentasulphide.**



1. Acetonyl acetone

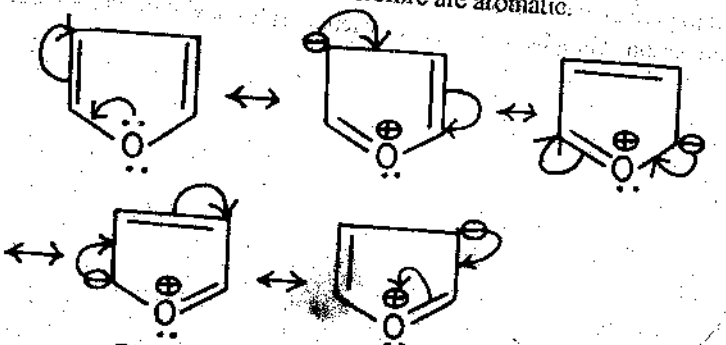
24.4 PROPERTIES OF PYRROLE, FURAN AND THIOPHENE

These heterocycles and their derivatives are aromatic compounds. They commonly undergo electrophilic substitution reactions viz. nitration, suphonation, halogenation, Friedel-Craft's acylation, and even the Reimer - Tiemann reaction and coupling with diazonium salts. Heats of combustion indicate resonance stabilisation to the extent of 22-28 K. cals/mole. Their resonance energies are somewhat less than that of benzene (36 K-Cals/mole) but much greater than the acyclic conjugated dienes (about 3 K. Cals / mole) Pyrole can be considered as a resonance hybrid of the following structures.

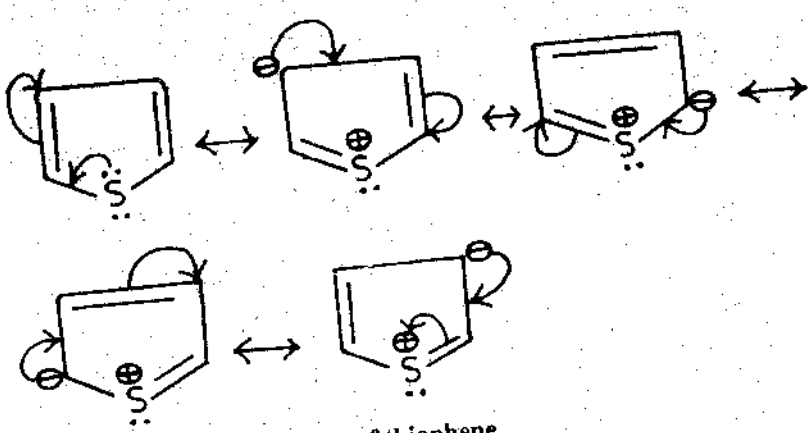


Resonance structures of Pyrrole

These structures are derived by the +M effect of the heteroatom. A positive charge is creacted on the hetero atom and a negtive charge on the carbon atoms of the ring. These resonance structures indicate that inspite of the presence of NH-function pyrrole is acidic. Four π- electrons (of the two double bonds) and the lone pair of electrons on the hetero atom constitue the aromatic sextet. Accordong to the Huckel's rule these are $4n + 2\ \pi$ - electron systems (n=1), and therefore are aromatic.



Resonance structures of Furan



Resonance structures of thiophene

In the case of thiophene, due to the presence of d-orbitals in sulphur, an extra resonance structure is possible

In all the resonance structures given above the ring carbons are electron surplus. Therefore pyrrole, furan and thiophene are considered π - electron surplus heterocycles. They undergo electrophilic substitution reactions.

Check your progress - 2

What is Huckel's rule?

.....

.....

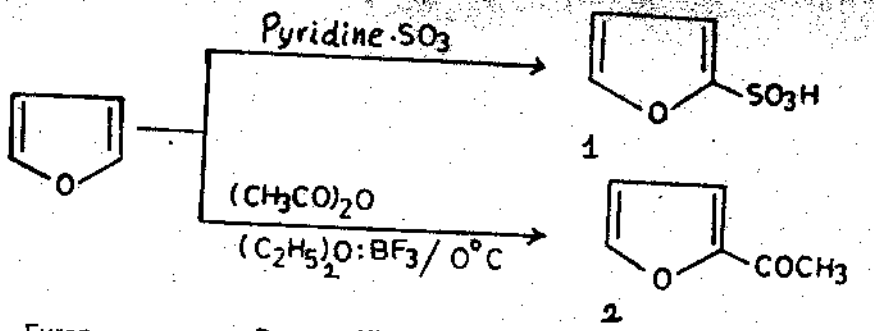
.....

.....

24.5 ELECTROPHILIC SUBSTITUTION IN PYRROLE, FURAN AND THIOPHENE: REACTIVITY AND ORIENTATION

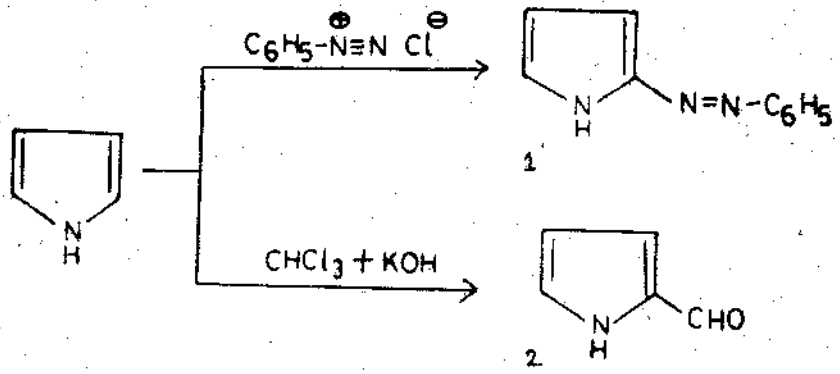
These five-membered heterocycles are much more reactive than benzene in electophilic substitution reactions. Substitution generally occurs in α - position (2-position)

Furan can be sulphonated by pyridine - SO_3 reagent to give furan - 2- sulphonic acid. It can be acetylated to give 2-acetyl furan. Pyrrole can couple with aryl diazonium salts and can undergo Reimer-Tiemann reaction. Thiophene undergoes friedel-craft's acylation in 2-position.

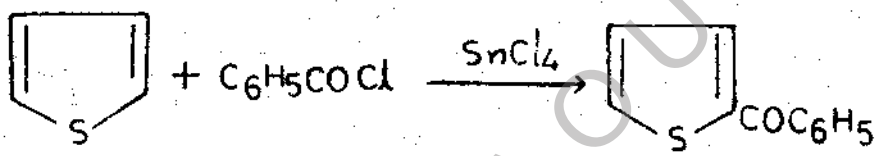


Furan — Boron trifluoride etherate

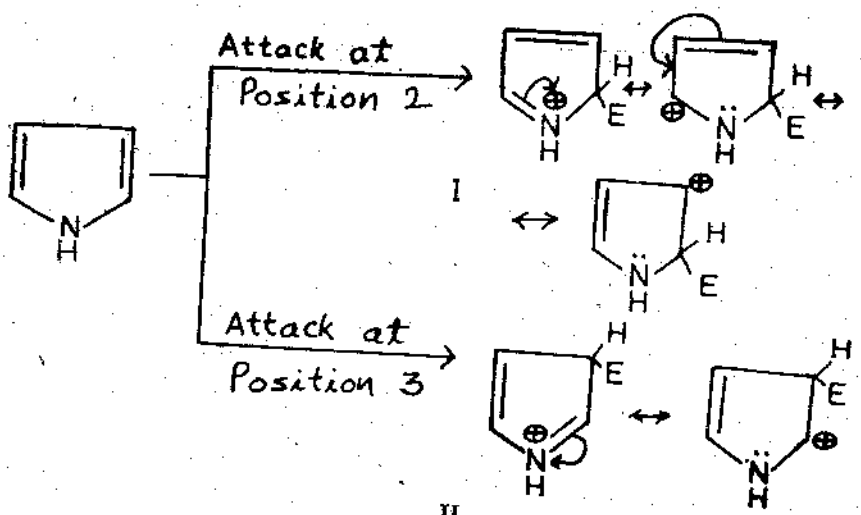
1. Furan-2-sulphonic acid
2. 2-Acetyl Furan



1. 2-(Phenylazo) Pyrrole
2. 2-Pyrrole carboxaldehyde



We can account for the orientation of electrophilic substitution in these compounds. The key step is the attack by the electrophile at α- or β - position to give cationic intermediates. Attack at position - 2 yields a stable carbonium ion which is a resonance hybrid of ;three structures. On the otherhand, electrophilic attack at position-3 leads to a less stable intermediate which is a resonance hybrid of only two structures. Thus, in these heteroaromatic compounds electrophilic substitution preferably leads to α - substitution.



I = more stable resonance structures II = Less stable resonance structures

UNIT 25 CARBOHYDRATES - (MONOSACCHARIDES)

Contents

25.1 AIMS AND OBJECTIVES

To explain the salient features of various classes of carbohydrates, and to discuss the reactions and structure of aldoses and ketoses.

After a thorough study and understanding this unit, you must be able to:

- classify, name and elucidate the structures of monosaccharides
- describe the structure of glucose and general reactions of monosaccharides
- lengthen and degrade the carbon chain of aldoses
- account for the cyclic structures and ring size of glucose.

25.2 INTRODUCTION

Plants prepare (+) -glucose by a process called Photosynthesis. Thousands of (+) - glucose molecules formed in this way combine to form cellulose. Cellulose is the important constituent of supporting frame work of plant. Several (+) - glucose molecules can be combined in somewhat different way to form starch. Starch is the reserve food of plants stored mainly in the seeds. when consumed by the animals, starch break down into (+) -glucose units. (+) - Glucose is supplied through the blood stream to the tissues, where it releases energy by undergoing oxidation to carbondioxide and water. Excess of (+) -glucose is stored in the liver in the form of glycogen. Some of the (+) - glucose is converted into fats and some react with nitrogen cotaining compounds to form aminoacids, which in turn combine to form the proteins in the animal body.

(+) - Glucose, cellulose and glycogen all belong to the class of organic compounds called carbohydrates. Thus carbohydrates are the ultimate source of our food. Our clothes are derived from cellulose eg., cotton, rayon cellulose acetate. Paper, is an important cellulose material. Thus carbonhydrates play a very vital role in our daily life.

25.3 DEFINITION

Carbodydrates are ploy hydroxyaldehydes or ketones, or substances that yield these on hydrolysis. These generally conform to the general formula $C_n (H_2O))_x$ - hence the name carbohydrates (hydrates of carbon).

(+) -glucose

oxylic acid is deviod of the properties

$\longrightarrow$ $C_6H_{12}O_7$ or $C_6H_{11}O_6COOH$

The monocarboxylic acid

erefore in glucose the carbonyl group is in the form of an aldehydic function $(C_6H_{11}O_5)CHO$

Oxidation of the above monocarboxylic monocarboxylic acid with nitric acid yields a dicarboxylic acid containing 6 carbon atoms.

$$(C_5H_{11}O_5)\,COOH \xrightarrow[(O)]{HNO_3} C_6H_{10}O_8 \text{ or } C_4H_8O_4(COOH)_2$$

The dicarboxylic acid

Glucose therefore contains a primary alcoholic group. In the dicarboxylic acid one of the carboxyl groups is obtained by the oxidation of - CHO group and the other by the oxidation of - CH_2OH group.

$$HOH_2C - (C_4H_8O_4) - CHO \xrightarrow{\text{Conc. } HNO_3} HOOC-C_4H_8O_4 - COOH$$

The dicarboxylic acid

6. (+) - Glucose reacts with acetic anhydride to give a penta acetate and liberates 5 moles of acetic acid. This shows that there are five hydroxyl groups in the glucose molecule.

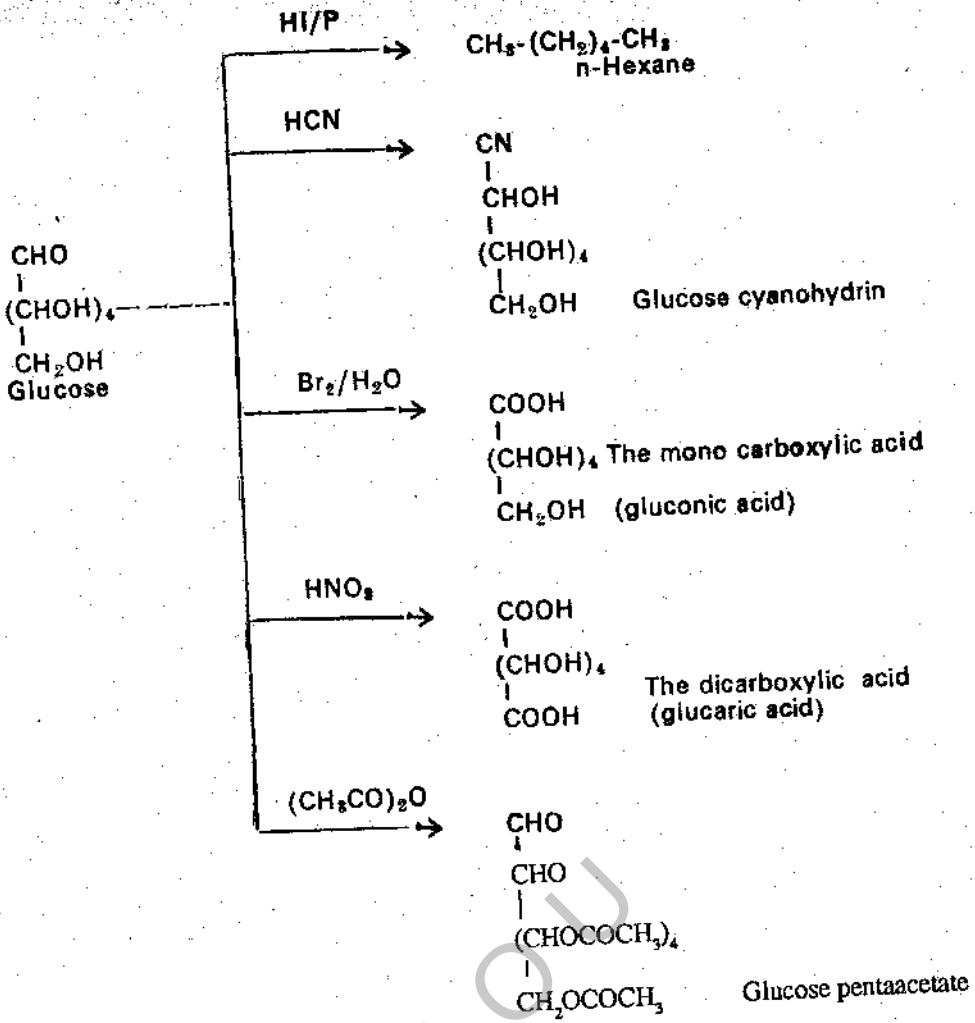
$$C_6H_7O(OH)_5 + 5(CH_3CO)_2O \rightarrow C_6H_7O(O\text{-}C\text{-}CH_3)_5 + 5CH_3COOH$$

Glucose — Glucose penta acetate

Thus glucose is a pentahydroxyaldose and in the molecule of glucose there are four secondary alcoholic groups, a primary alcoholic group and an aldehydic group.

$$HOH_2C - (CHOH)_4 - CHO$$

All the above reactions of glucose can be explained starting with pentahydroxyaldehyde structure.



II. A Ketohexose

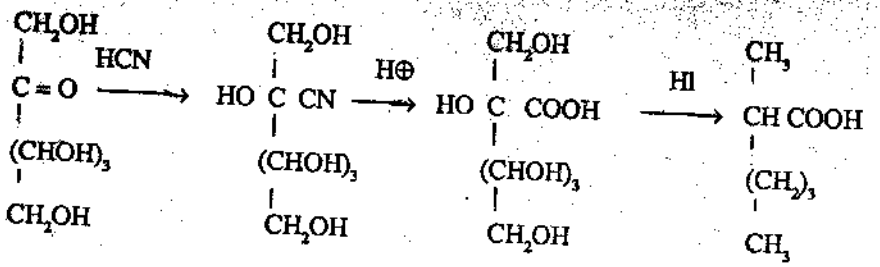
(-) -Fructose reacts with hydrogen cyanide to give a cynohydrin. This reaction indicates the presence of a carbonyl group.

$$(C_5H_{12}O_5)\,C=O \xrightarrow{HCN} (C_5H_{12}O_5)\,C(OH)CN$$

Fructose → Fructose cyanonydrin

2. Fructose forms a pentaacetate, on reaction with acetic anhydride. This indicates the presence of five hydroxyl groups.

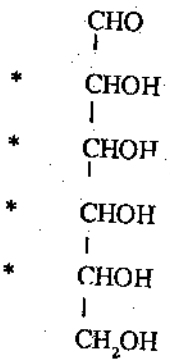
3. The cynohydrin (formed from fructose and HCN) on hydrolysis with mineral acids gives a hydroxy acid. The hydroxy acid is reduced by hydrogen iodide to give - methyl caproic acid. In this reaction the carboxyl group in the product i.e, - methyl caproic acid is obtianed from cyanohydrin function. The point of linkage of - COOH group in - methyl caproic acid indicates the position of carbonyl group in fructose. The carbonyl group in fructose is thus in 2-position of a straight chain containing of six carbon atoms. Therefore the carbonyl group is in the form of ketonic group and fructose is a pentahydroxyketone i.e, a ketohexose.



Fructose | Fructose cyanohydrin | Hexahydroxy carboxylic acid | α - Methyl caproic acid

III Stereoisomers of (+) -Glocose

(+) -Glocose is an aldohexose and contains four asymmetric carbons. Therefore sixteen stereoisomers ($2^n = 2^4 = 16$) i.e. eight pairs of enantiomeric structures are possible for the structure.

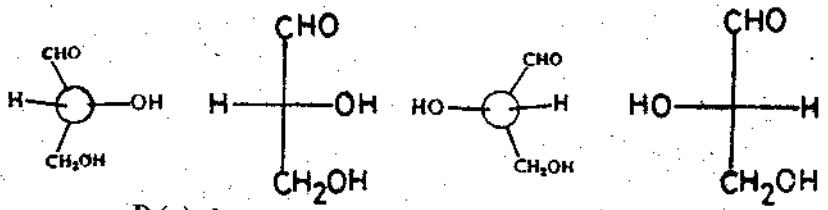


* indicates the asymmetric carbon atom.

All these sixteen isomers are known. Glucose, mannose, galactose are some of these.

25.6 CONFIGURATION OF (+) - GLUCOSE

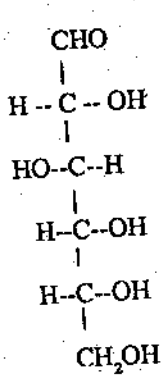
(+) - Glucose can have any one of 16 possible configurations. The question is, which configuration it has. **Emil Fischer** completed his work on the configuration of (+) - glucose and other aldohexoses in 1901. For this outstanding piece of work he was awarded Nobel Prize in 1902. Glyceraldehyde, CH_2OH-*CHOH-CHO, has one asymmetric carbon atom and may exist as dextro and levo forms. Fischer arbitrarily assigned D-configuration to dextro rotatory glyceraldehyde i.e, dextro isomer of glyceraldehyde has D-configuration, and whereas levotatory isomer has L-configuration. Later work, supported the configurations assigned by Fischer (+) and (-) -glyceraldehydes.



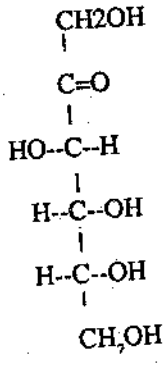
D (+) glyceraldehyde **L (-) - glyceraldehyde**

Fischer assigned configurations to (+) -glucose and other sugars, taking (+) -glyderaldehyde as reference. According to Fischer and Haworth, sugars with -OH group on the rightside in the fifth position or on carbon atom fifth from the top (C-5) in the Fischer projection formulae, are called D-Sugars. Thus (+) -glucose and (-) fructose are D-Sugars.

Fischer assigned following configurations to (+) - glucose and (-) -fructose.



D (+) - Glucose



D(-) - Fructose

25.7 SOME GENERAL REACTIONS OF CARBOHYDRATES

1. Molisch test:

To a mixture of alcoholic α - napthol and an aqueous solution of carbohydrate, addition of conc. H_2SO_4 from the sides of the test tube, develops two layers with a red to violet ring at the junciton. Thisis known as Moisch test-a characteristic qualitative test for carbohydrates.

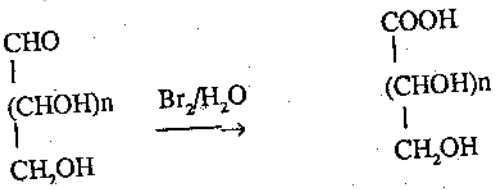
2. Oxidation:

a) Reduction of Tollens' and Fehling's reagents:

All monosaccharides (aldoses and ketoses) are α - hydroxy carbonyl compounds. They reduce Tollens' reagent and fehling's reagents. These tests are characteristic ofα - hydroxy carbonyl compounds. This test is not useful to differentiate between aldoses and ketoses. Further, aldoses and ketoses undergo decomposition and isomerisation in the akaline medium employed in these tests.

b) Oxidation with bromine water

This reaction is useful to differentiate aldoses from ketoses. Bromine-water oxidises only aldoses but not ketoses.

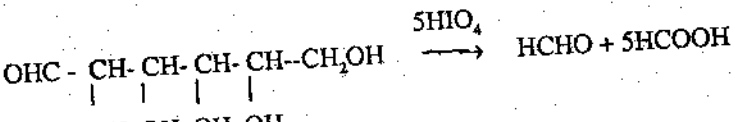


An aldose

An aldonic acid

c) Periodic acid oxidation

Periodic acid cleaves the carbon-carbon bonds in vicinal diols and α - hydroxy aldehydes and ketones. An aldohexose consumes five moles of HIO_4.

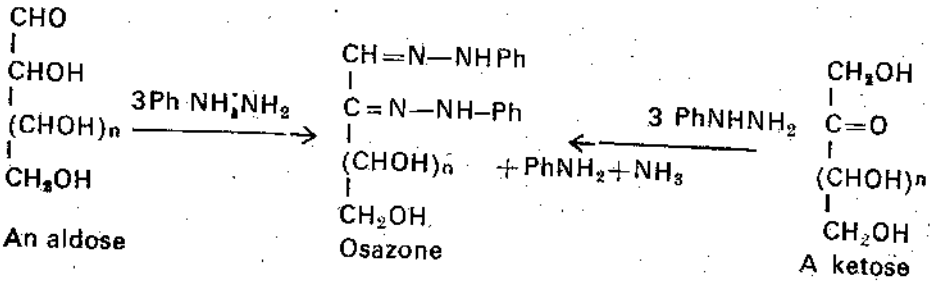


A pentahydroxy aldchyde
(An aldohexose)

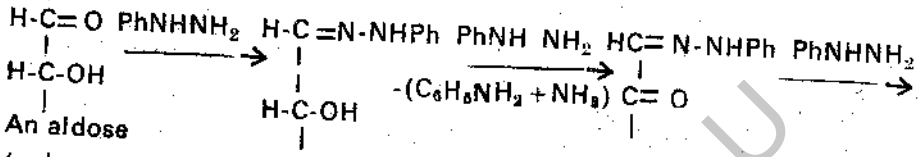
In this reaction five moles of formic acid and one mole of formaldehyde are formed. a-CHO group adjacent to hydroxyl-bearing carbon is oxidised to give formic acid. Similarly a hydroxyl bearing carbon, flanked on either side by hydroxyl-bearing carbons is also oxidised to give formic acid. A primary alcoholic group with an adjacent hydroxyl-bearing carbon is oxidised to give formaldehyde.

3. Osazone formation and epimers

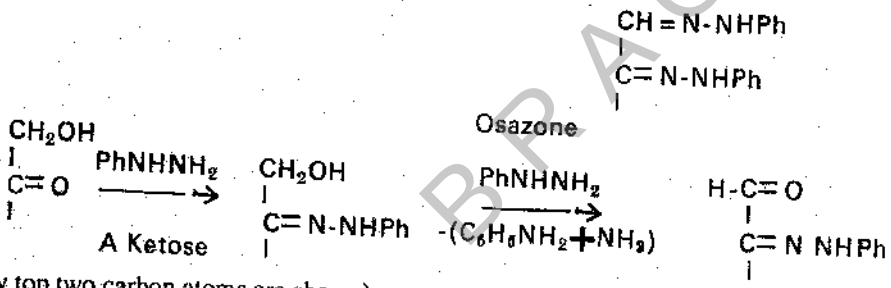
Both aldoses and ketoses contain - hydroxycarbonyl function. They react with phenlyhydrazine to give osazones. Three moles of phenylhydrazine are consumed and one molecule each of aniline and ammonia are liberated.



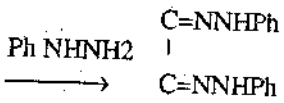
First mole of phenyl hydrazine reacts with the carbonyl group. The second mole oxidises the alcholic group to carbonyl group while itself getting reduced to aniline. The carbonyl group thus generated condenses with the third mole of the reagent.



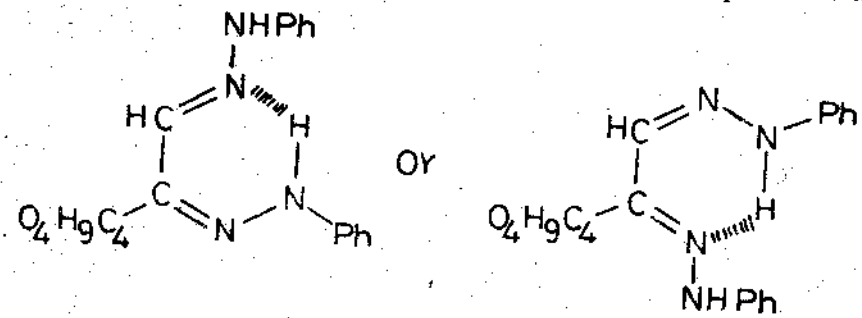
(only top two carbon atoms are shown).



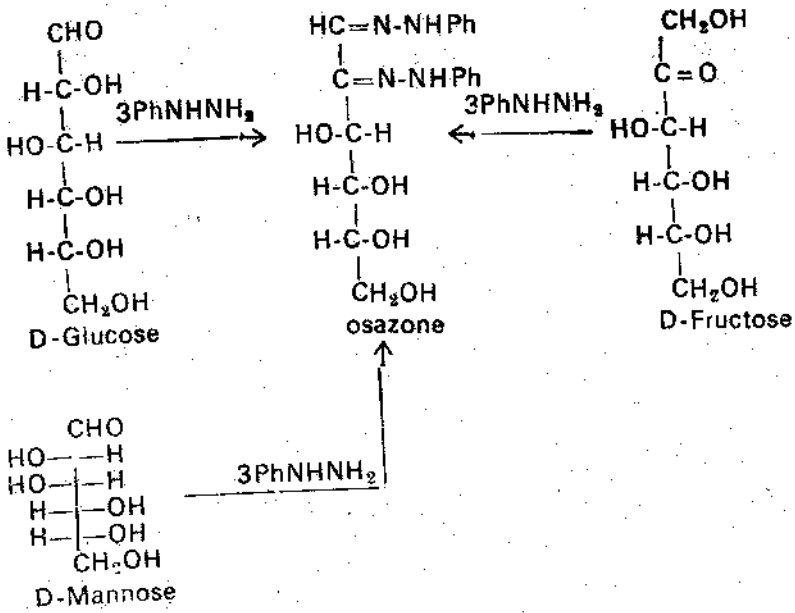
(only top two carbon atoms are shown)



Once the osazene is formed it is stabilised by chelation which prevents further reaction.



Osazone formation is not only useful in the identification of carbonhydrates but also in the determinatin of their configurations. For example, the two diastereomeric aldohexoses, D-glucose and D-mannose, yield the same osazone. Osazone formation destroys the configuration about C-2 of an aldose. Further aldohexose and kethohexose with same configuration about C-3 to C-5 for instance D-glucose and D-fructose, give a osazone.



Check your progress - 1

Why glucose, mannose and fructose form the same osazone?

.....

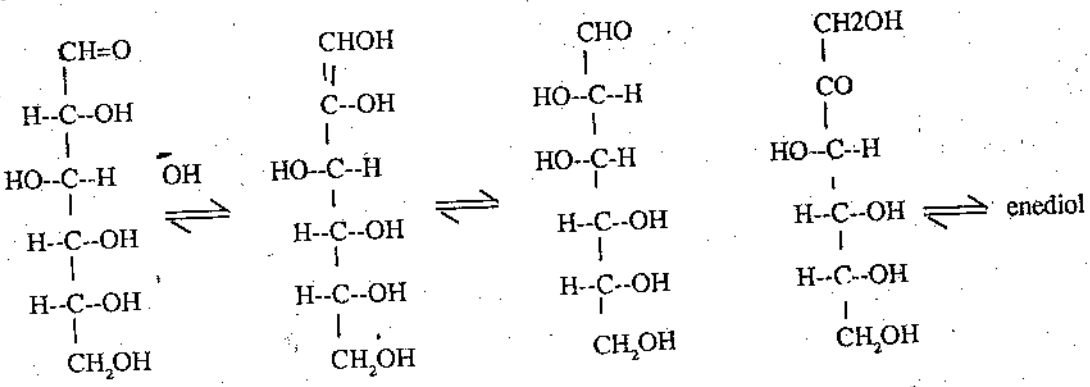
.....

.....

.....

4. Action of alkali (Lobry de Bruyn and van Ekenstein transformation)

D-Glucose, for instance, on reaction with dilute solutins of weak bases eg. dil, calcium hydroxide yield an equilibrium mixture of D-glucose D-mannose and D-fructose. D-Glucose first tautomerises to an enediol which can give three carbonyl forms (ketoforms) via., D-glucose, D-mannose and D-fructose.



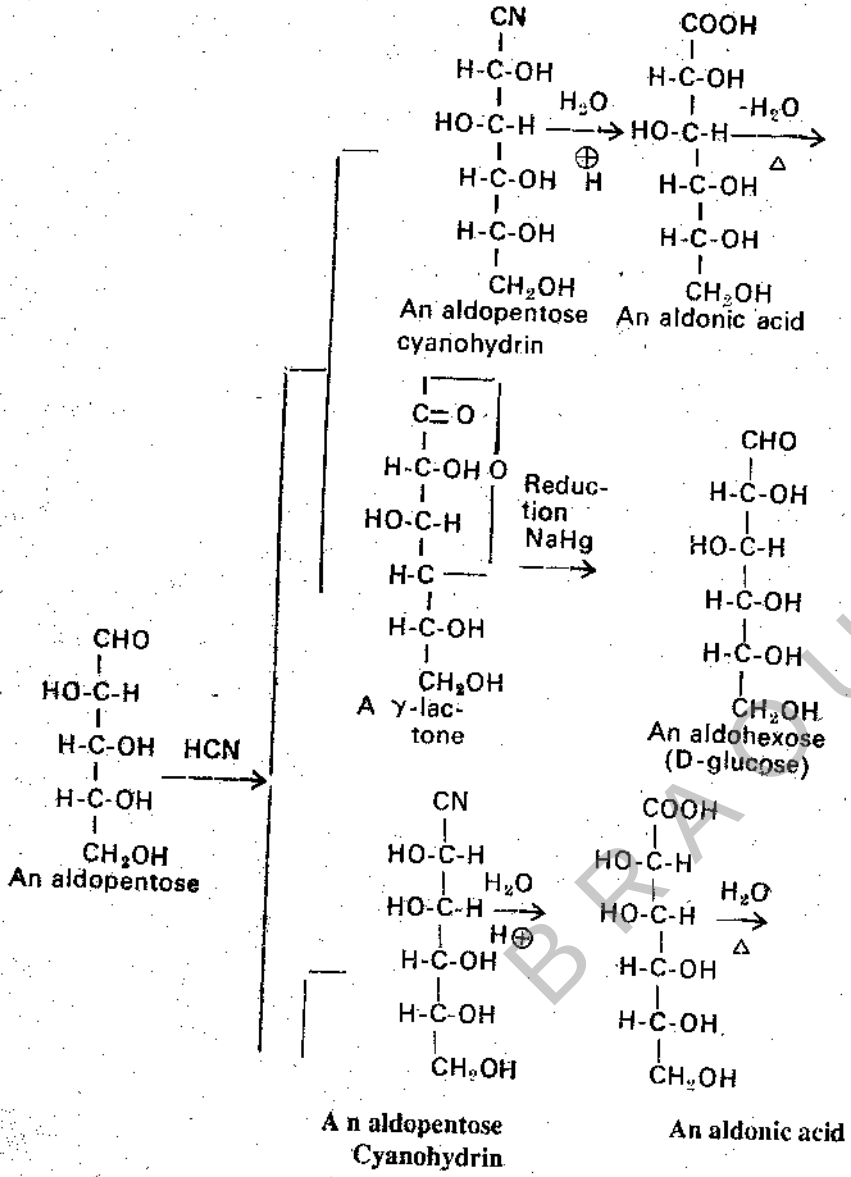
D (+) - glucose enediol D (-) mannose D (-) -fructose

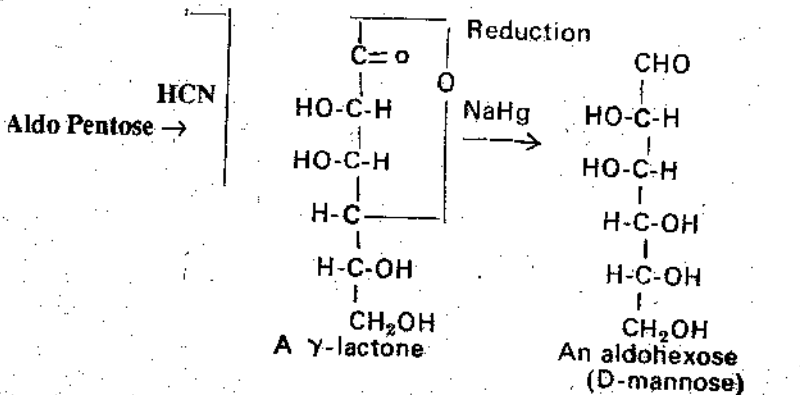
A strong solution of alkali on the otherhand breaks the molecule into a mixture of formaldehyde and hydroxyacetaldehyde and other lower sugars.

5. Lengthening the carbon chain in aldoses

The Kiliani Fischer Synthesis: This reaction is useful in the synthesis of higher members of aldoses and also in the determination of their configuration.

Following equations illustrate the synthesis of two epimeric aldohexoses from aldopentose.

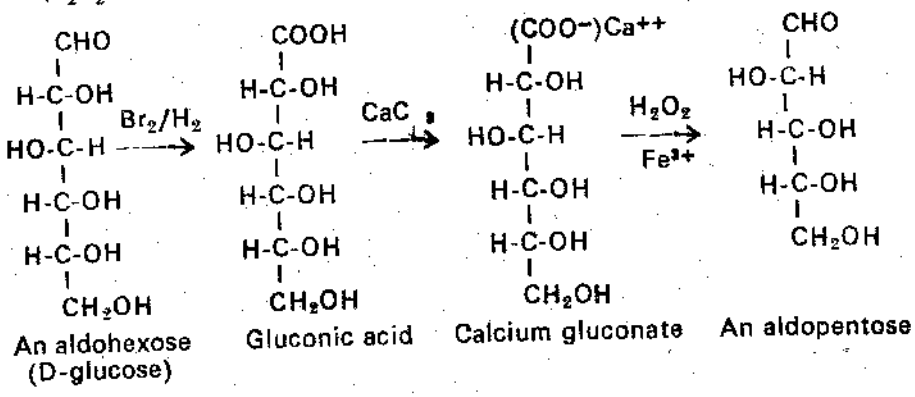




The aldopentose is converted into a mixture of two cyanohydrins. The cyanohydrin mixture is hydrolysed to the corresponding carboxylic acids. These carboxylic acids are separated and converted separately into γ - lactones. The γ - lactones on reduction give aldohexoses.

6. Shortening the carbon chain of aldoses:

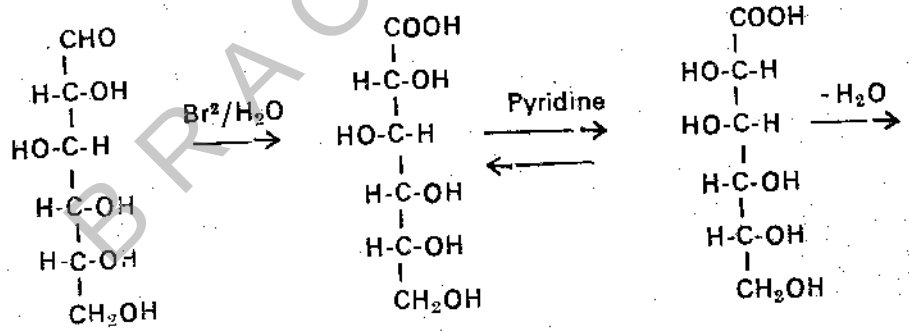
Ruff's degradation: An aldohexose can be converted into an aldopentose by Ruff's degradation. The aldohexose is oxidised to aldonic acid by bromine-water. Oxidation of the calcium salt of the aldonic acid with Fenton's reagent (H_2O_2/Ferric salts) yields an aldose with one carbon atom less.



An aldohexose (D-glucose) | Gluconic acid | Calcium gluconate | An aldopentose

7. Conversion of an aldose into its epimer (epimerisation)

Aldoses which differ only in the orientation of -OH group at α - carbon atom are called epimers. Interconversion of epimers is known as epimerisation. The aldose is oxidised to its acid by Br_2/H_2O, the aldonic acid is epimerised by treatment with pyridine to give an equilibrium mixture. Two epimers are separated by fractional crystallisation and the appropriate isomer is converted into a γ - lactone and then reduced by sodium amalgum to give epimeric aldose.



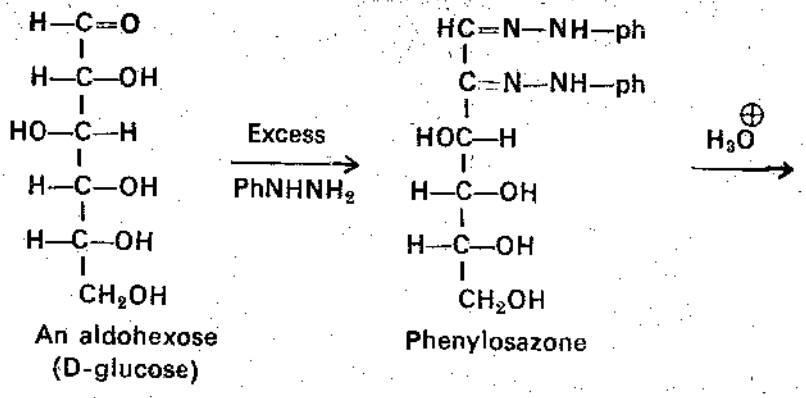
An aldohexose (D-glucose)

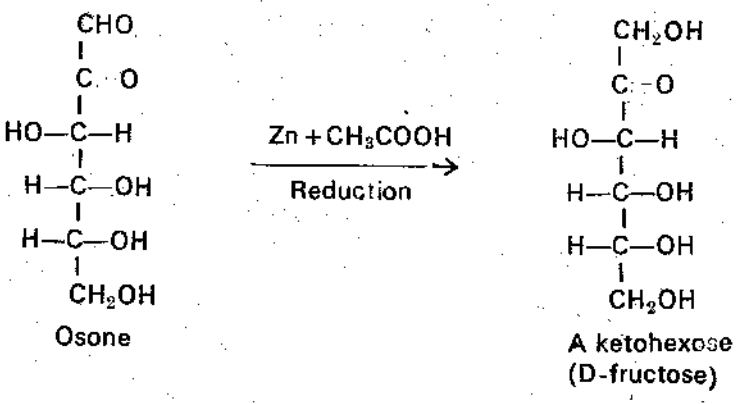
Epimeric aldonic acids (This can give D-glucose through γ-lactone)

8. Interconversions

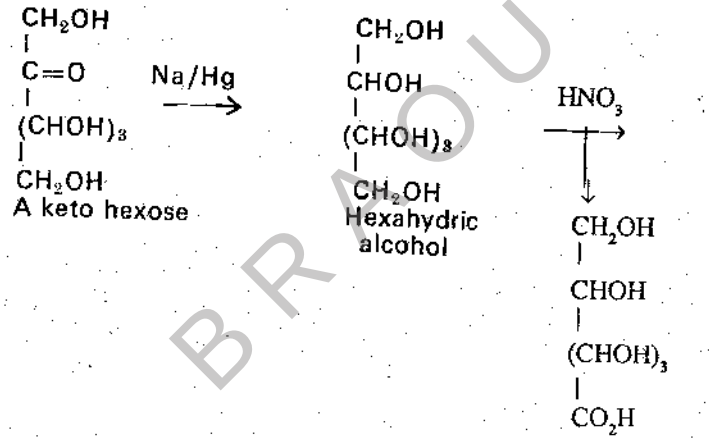
a) Aldohexose (glucose) to ketohexose (fructose)

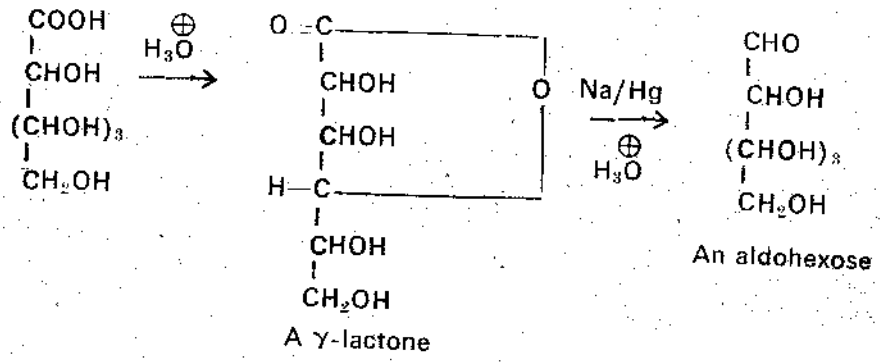
An aldohexose is first converted into phenylosazone. The phenylosazone is hydrolysed to Osone, which is reduced by zinc and acetic acid to give the ketohexose. Zinc in glacial acetic acid medium reduces aldehydic group in perference to keto group.





b) A ketose to an aldose





The keto hexose is reduced by Na/Hg to give a hexahydric alcohol. The hexahydric alcohol is oxidised by nitric acid to a monocarboxylic acid (only one of the wo terminal - CH_2OH groups being oxidised. This mono carboxylic acid is converted into γ - lactone. Reduction of the γ - lactone by sodium amalgum in acid medium gives the aldohexose. In the absence of acid medium, the reduction may go up to alcohol stage.

25.8 CYCLIC STRUCTURE OF D (+) -GLUCOSE

Open chain structure of D (+) -glucose cannot explain a number of reactions.

i) D(+)-glucose does not undergo certain reactions of aldehydes

D(+) - glucose reduces Tollens' and Fehling's reagents, but it gives a negative test with Schiff's reagent and does not form sodium bisulphite addition compound.

ii) Mutarotation

Glucose when recrystallised from water melts at 146°C. Its aqueous solution shows specific rotation of + 112° and upon standing this value gradually changes to a constant value of + 52°. A sample of glucose recrystallised from pyridine melts at 150°C. Its aqueous solutions show a specific rotation of + 19°, which steadily increases to a constant value of + 52°. The change of optical rotation of a compound with time is called mutarotation. The glucose with higher positive rotation (+ 112°) is called α - D (+) - glucose , and the one with lower positive rotation (+19°) is called β-D (+) -glucose.

Check your progress -2

What is mutarotation?

.....

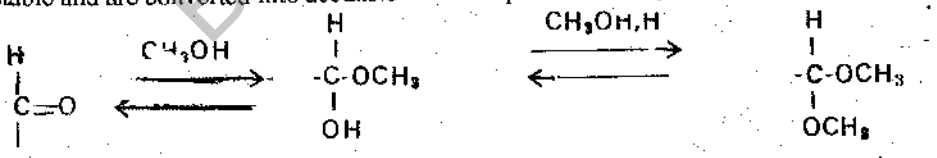
.....

.....

.....

iii) D (+) -Glucose forms two isomeric methyl-D-glucosides

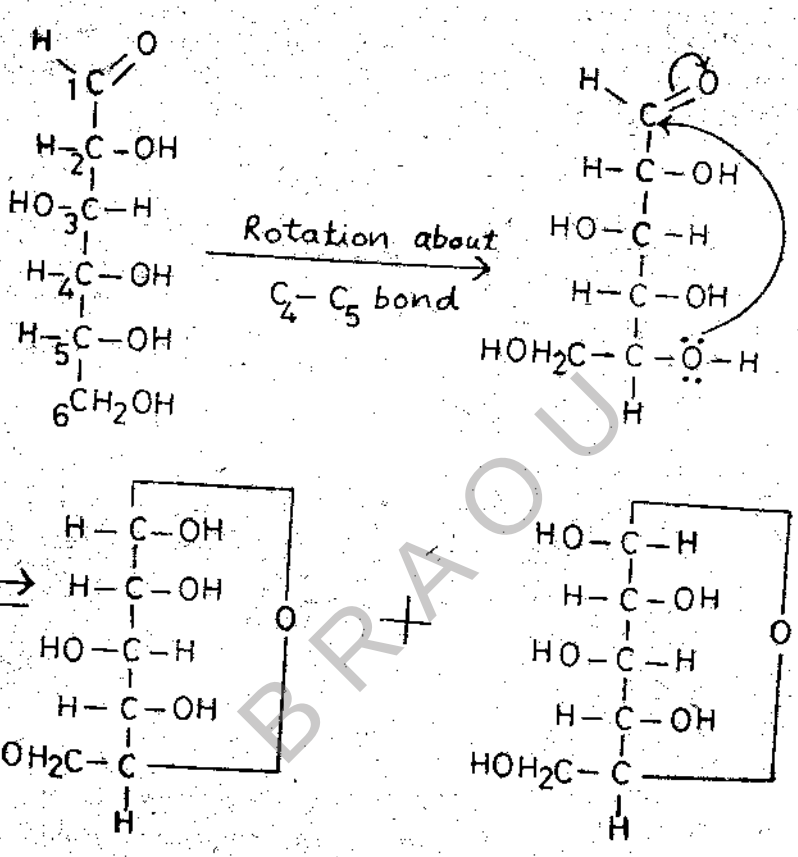
We know that aldehydes react with alcohols in the presence of dry HCl to form acetals. The aldehyde on dissolving in alcohol forms an equilibrium mixture of aldehyde and hemiacetal. Hemiacetals are unstable and are converted into acetals only in the presence of dry HCl and excess of alcohol.



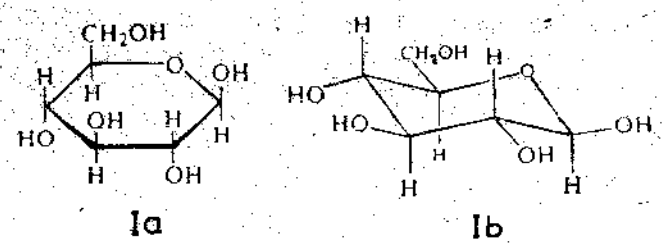
D(+) -Glucose when treated with methyl alcohol and dry HCl forms methyl D-glucoside. Methyl-D-glucoside contains only one methyl group but still resembles regular acetals in properties. It is quite stable and does not revert to glucose and methanol. Further, two isomeric methyl-D-glucosides are formed in the reaction of D-glucose with methanol in the presnce of dry HCl. These are called methyl α - D-glucoside and methyl β-D-glucoside. These glucosides do not exhibit mutarotation and do not reduce Tollens' or Fehling's reagent.

All these observations suggest a cyclic structure for glucose. A cyclic structure for glucose may be obtained by intramolecular hemiacetal formation between the aldehydic group and C_5-OH (hydroxy group on δ - carbon) of glucose. The configuration of D-glucose is given in the following Fischer projection. In this the -OH group on C-5 is above the plane and therefore can not interacat with the carbonyl carbon. For the formation of hemiacetal between - OH group (on C-5) and the carbonyl group of glucose, rotation about

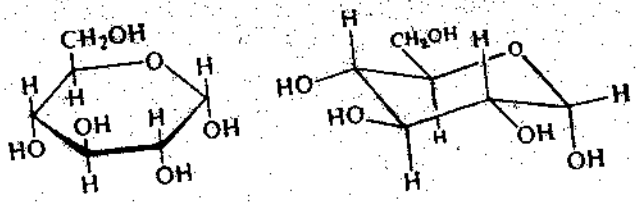
C_4-C_5 bond is required. This brings the two interacting groups in favourable orientation i.e, in the same plane. Intramolecular hemiacetal formation between the crbonyl carbon and -OH group on C leads to two six membered structures called pyranose structures. They are called D-glucopyranoses. These differ only in the orientatin of -OH group on the newly created asymmetric centre (C-1). The pyranose structure in which the -OH group on C-1 is to the right is called β - D-gluco-pyranose, and the other one is called α -D-glucopyranose. These vertieal oxide ring structures may also be written in the form of **Haworth structures**. The vertical structure is tilted in such a way that the ring is in a plane perpendicular to that of paper and ring oxygen is in the upper right hand corner of the ring. The groups oriented on the right side in vertical oxide structure become oriented below the plane or become alpha, in the Haworth structure, and vice versa. The thick lines indicate that the carbon framework is closer to the observer. Thus α - D -glucopyranose and β -D-glucopyranose differ in the configuration about C-I. In the former the -OH on C-1 Carbon is known as anomeric carbon. D (+) -Glucose exists mainly as an equilibrium mixture of α - and β - D-Glucopyranoses, with a very small quantity as pentahydroxy aldose. Mutarotation of d-glucose is due to the conversion of one pyranose form into another, through the open chain form.



α-D-Glucopyranose β-D-Glucopyranose



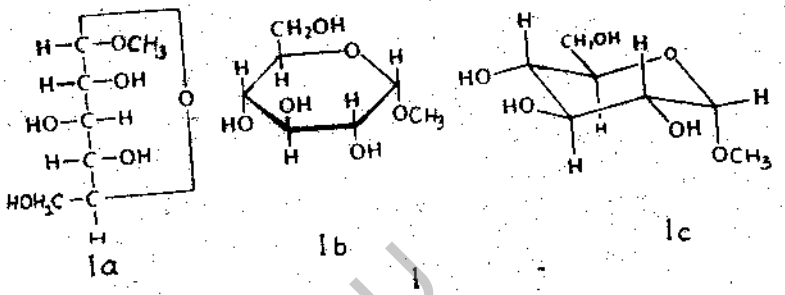
Ia Ib



IIa IIb

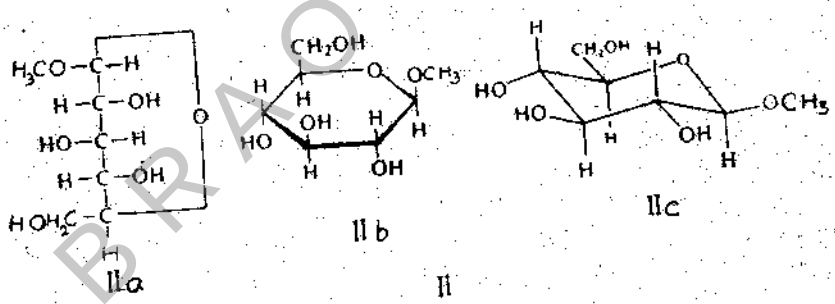
Ia = β - D - Glucopyranose (Haworth structure)
Ib = β - D - Glucopyranose (Conformational structure)
IIa = α - D - Glucopyranose(Haworth structure)
IIb = α- D - Glucopyranose(conformational structure)

More meaningful conformtional structures may be written for α - D - gluco pyranose andβ - D - glucopyranose. These structures clearly reveal the axial and equatorial orientation of the substituents. Following are the vertical oxide structures, Haworth structures and conformational structures for methyl α - and methyl β - D - glucopyranosides.



Ia Ib Ic

I



IIa IIb IIc

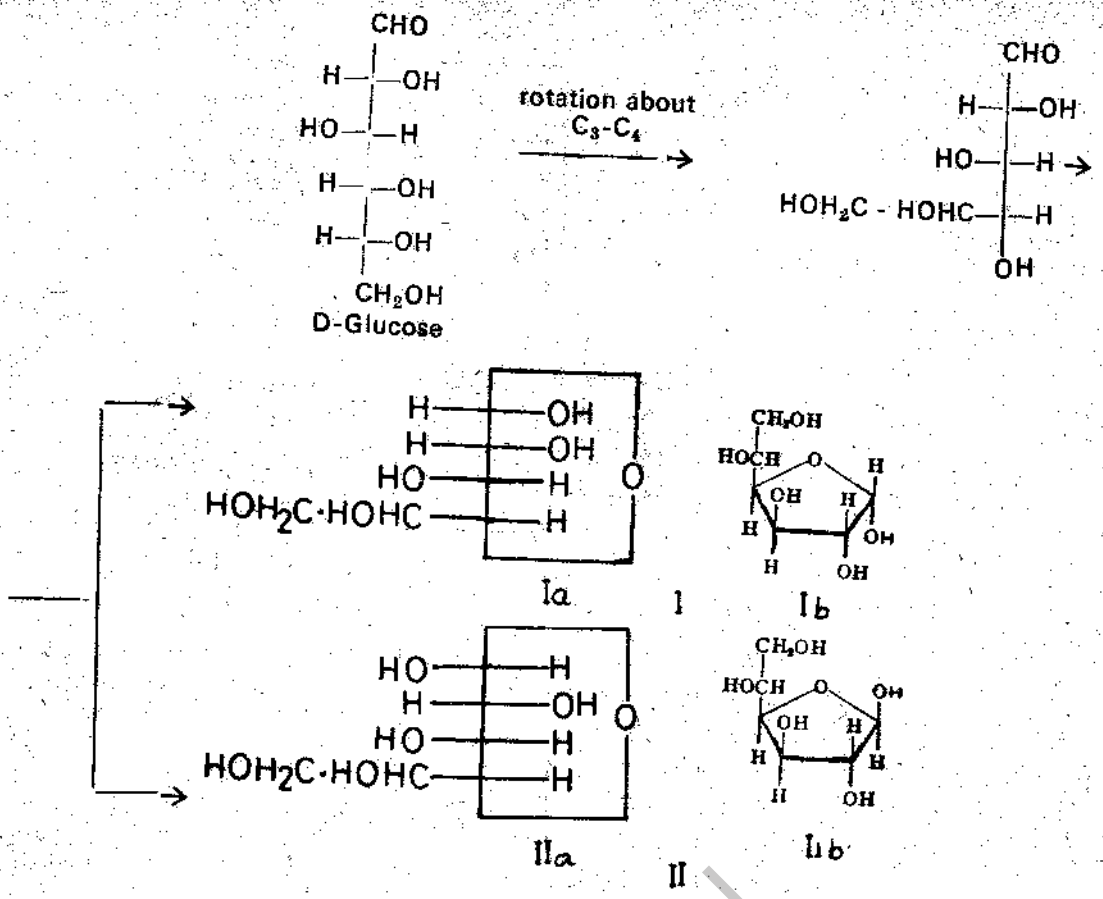
II

I. Methyl - α - D-glucopyranoside.
II. Methyl - β - D-glucopyranoside.

Ia = vertical oxide structure
Ib = Haworth structure
Ic = Conformational structure

IIa = Vertical oxide structure
IIb = Haworth structure
IIc = Conformational structure

It can be seen that due to orientation of all bulky groups in equatorial conformation. β - D - glucopyranose is sterically more stable than the - D - glucopyranose. Therefore the equilibrium mixture contains relatively larger amount of β - isomer. Glucose and other aldohexoses may also be expected to be present as 5-membered rings. i.e, as furanoses. Following are the steps involved in arriving at the furanose structures for D-glucose.

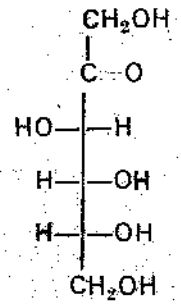


I = α - D - Glucofuranose
II = β - D - Glucofuranose

Ia = Vertical oxide stucture
Ib = Haworth structure

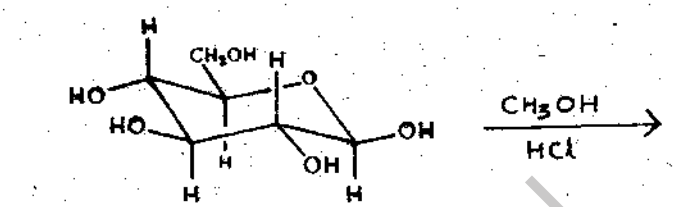
IIa = Vertical oxide structure
IIb = Haworth structure

Similarly pyranose and furanose structures are possible for a ketohexose eg: D-fructose.

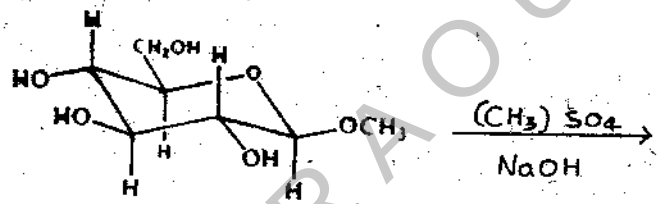


D-Fructose
(Acyclic structure)

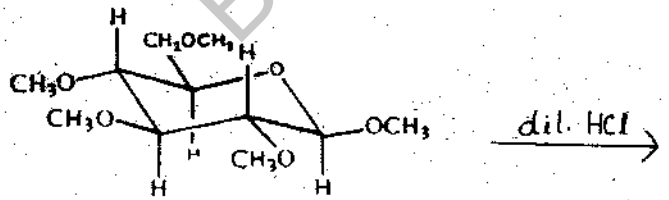
on either side of the hydroxyl bearing carbon will occur to give a mixture of dicarboxylic acids. If the α and β -D-glucoses were in pyranose form, the tetra-O-methyl -D-glucose will have a free-OH group on C-5. Detemination of ring size becomes a matter of finding out which carbon carried a free-OH group. When methyl - β - D - glucoside, for instance, is treated with methylsulphate and sodium hydroxide and the product is hydrolysed by dilute hydrochloric acid, a mixture of α - β - tetra - O - methyl - D - glucoses is obtained. In addition to these there exists a little of open-chain form. This open-chain tetra - O - methyl - D - glucose, and α and β - tetra - O - methyl - D - glucoses contain an aldehydic group and four - OCH_3 groups. They also contain a free or unmethylated - OH group on the carbon initially involved in the hemiacetal formation. If the α- and β -D-glucose were in pyronose form there should be a free-OH group on C-5 in the tetra - O - methyl - D- glucose. Oxidation of 2,3,4,6 -tetra -O-methyl-D-glucose should yield a mixture of trimethoxy glutaric acid (five carbon containing acid) and a dimethtoxy succinic acid (four carbon containing acid). The formation of dicarboxylic acids containing 4 and 5 carbon atoms on nitric acid oxidation of α- and β- tetra - O - methyl -D-glucoses indicates that there is a freee hydroxyl group on C-5, and the oxidation of carbon chain has occured on the either side of hydroxyl containing carbon. If α - and β - D - glucoses were present as 5- membered rings i.e, furanoses, a mixture of dicarboxylic acids containing 3 and 4 carbon atoms in the carbon chain (dimethoxy malonic acid and dimethoxy succinic acid respectively) should have been obtained. Actually on oxidation of α and β - tetra - O- methyl-D-glucose with conc. HNO_3, a mixture of dimethoxy succinic acid and trimethoxy glutaric acid is obtained indicating the D-glucose is present in pyranose form.



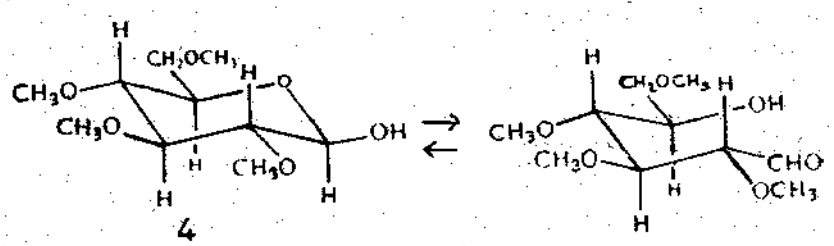
1



2



3

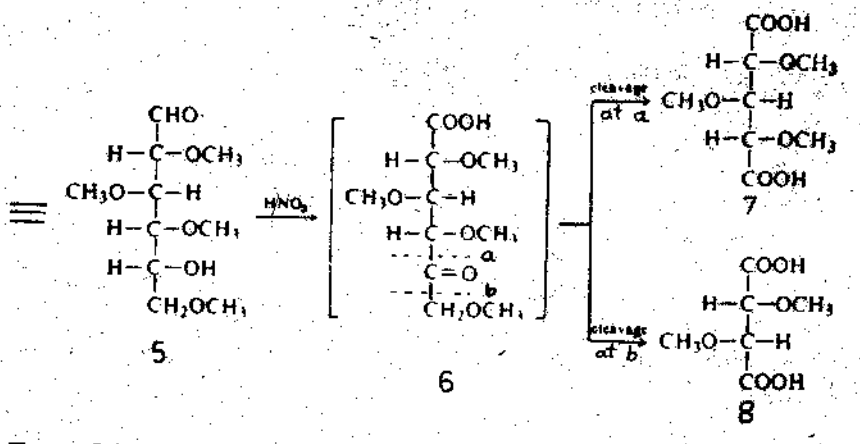


4 5

1).β D - Glucose 2). Methyl - β - D- glucose

3). Methyl – β - 2,3,4, 6 - tetra - O - methyl - D - glucoside

4). 2,3,4,6 - Tetra - O - methyl β- D - glucose



5) 2,3,4,6 - Tetra - O - methyl - D - glucose (open chain form)
6) Keto acid
7) Trimethoxy glutaric acid
8) Dimethoxy succinic acid.

25.10 SUMMARY

Carbohydrates are natural products. They are optically active polyhydroxy aldehydes or ketones or those substances which on hydrolysis give the above. Carbohydrates are classified in two ways based on their nature and hydrolysis. Structures of monosaccharides can be established based on their simple reactions. The reactions of monosaccharides, their interconversions, epimerisation, extension of carbon skeleton and degradation are presented in the form of their chemical properties in the unit. Variation of specific rotation of reducing sugars in aqueous solution with time is called mutarotation. In order to account for all the chemical properties of glucose, cyclic structures were proposed to it. Free glucose and fructose exist as pyranoses.

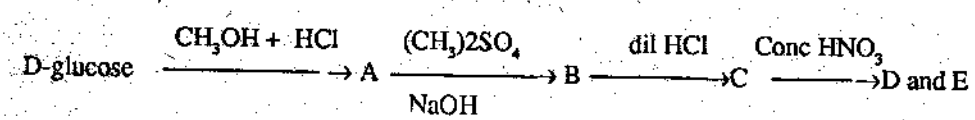
25.11 MODEL EXAMINATION QUESTIONS

I Answer each of the following in 10 lines

1. Write the open chain structure of D-glucose and its C-2 epimer. Write the open structure of the ketohexose which gives the same osazone as D-glucose.

2. Write the open chain structure and vertical oxide structure, Haworth and conformational formulae of α - D-glucopyranose and methyl β- D- glucopyranoside.

3. Write the structures of A to E obtained in the following reactions. write conformational structures whereever necessary



4. Define the following

i) Empimers ii) Anomers iii) D-Sugars

II Answer each of the following in 30 lines

1. Formulate the following conversion with suitale examples

i)	An aldohexose	→	A kethoxose
ii)	A ketohexose	→	An aldohexose
iii)	An aldohexose	→	An aldopentose
iv)	An aldopentose	→	An aldohexose

2. How are carbohydrates classified? How is the structure of an aldohexose established?

3. Discuss the experimental evidence in favour of the cyclic structure for D-glucose. How is the ring size determined.

4. Write notes on.

a) Mutarotation.
b) Lobry de Bruyn van Ekenstein rearrangement
c) Oxidation of aldohexoses.
d) Kiliani sysnthesis

25.12 MODEL ANSWERS TO CHECK YOUR PROGRESS

1. Glucose, fructose and mannose form the same osazone due to their identical configuration at C-3, C-4 and C-5.

2. Change of specific rotation of sugars in aqueous solution with time is called mutarotation. It is the characteristic property of reducing sugars.

Author: Dr. P.S.N. Reddy

UNIT 26 CARBOHYDRATES - DISACCARIDES AND POLYSACCHARIDES

Contents

26.1 AIMS AND OBJECTIVES

To introduce the salient sructural featrues of some common disaccharides and the general methods of their structural elucidation. To give an elementary idea of occurence, structure and utility of common poly-saccharides viz. cellulose and starch.

After a detailed study and understanding of the contents of this unit you must be able to:

- describe the mode of linkage of monosaccharide units in reducing and nonreducing disaccharides.
- elucidate the structures of some typical disaccharides - sucrose, maltose,cellobiose and lactose
- give the structure and utility of cellulose and its derivatives among polysaccharides
- present the structure of starch - α - amylose and β- amylose

26.2 INTRODUCTION

Disaccharides are made up of two monosaccharide units.Disaccharides on hydroloysis yield two molecules of monosaccharides. For example, sucrose, cellobiose and lactose are all disaccharides. Onhydrolysis, a molecule of each of these yields two molecules of monosaccharides. Sucrose on hydrolysis gives one molecule each of - D - glucose and-D-fructose. Both maltose and cellobiose on hydrolysis yield two molecules of -D-glucose. Thus, maltose and cellobiose are derived by two different combinations of two-D-glucose units. Lactose, on the otherhand, yields one molecule each of -D-glucose and-D-galactose.

$C_{12}H_{22}O_{11} + H_2O \rightarrow C_6H_{12}O_6 + C_6H_{12}O_6$
Sucrose — D-Glucose D-Fructose

$C_{12}H_{22}O_{11} + H_2O \rightarrow 2C_6H_{12}O_6$
Maltose — D-Glucose

$C_{12}H_{22}O_{11} + H_2O \rightarrow 2C_6H_{12}O_6$
Cellobiose — D-Glucose

$C_{12}H_{22}O_{11} + H_2O \rightarrow C_6H_{12}O_6 + C_6H_{12}O_6$
Lactose — D-Glucose Galactose

A monosaccharide unit, D-glucose, for instance, may theoretically combine with another monosaccharide unit by eliminating a molecule of water to give a disaccharide.

$2C_6H_{12}O_6 \rightarrow C_{12}H_{22}O_{11} + H_2O$
D-Glucose — A disaccharide

If the two monosaccharide units are linked through their anomeric carbons, the resulting disaccharide is called a non-reducing sugar. A non-reducing disaccharide does not exhibit mutarotation. Sucrose is a non-reducing disaccharide. On the other hand, in reducing disaccharides the hydroxyl group on the anomeric carbon of atleast one monosaccharide unitis free. Cellobiose, maltose and lactose are all reducing sugars. In disaccharide formation the hyroxyl group on anomeric carbon of a monosaccharide unit with the hydrogen of the -OH present on the anomeric carbon or some other carbon of the second monosaccharide unit is lost as water. Thus, disaccharides may be considered as acetals of two monosaccharides.

26.3 SOME TYPICAL DISACCHARIDES

A. Sucrose: Sucrose is usually obtianed from sugar cane. Therefore it is also known as **cane sugar.** A brief account of the structure elucidation of sucrose is given below.

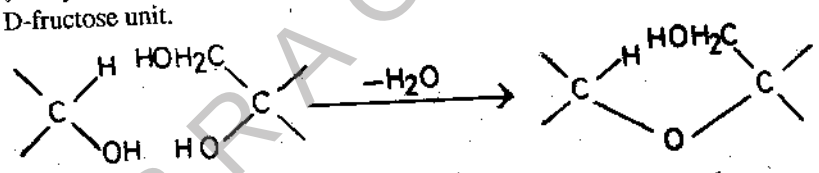
1) The molecular formula of sucrose is $C_{12}H_{22}O_{11}$. It does not reduce Tollens' reagent or Fehling's reagent. It does not exhibit mutarotation and does not form osazone. These properties suggest that there is no free carbonyl (aldehydic or ketonic) group in sucrose.

2) Hydrolysis of sucrose by dilute aqueous acids yields D-glucose and D-fructose in equal amounts.

$$C_{12}H_{22}O_{11} + H_2O \xrightarrow{\oplus H_3O} C_6H_{12}O_6 + C_6H_{12}O_6$$

Sucrose D-Glucose D-Fructose

Thus, sucrose is a disaccharide. In sucrose, D-glucose and D-fructose units are linked through their anomeric hydroxyl groups. *Maltase* - an enzyme specific for cleavage of α - glucoside linkage also hydrolyses sucrose. The mutarotation of D-glucose, produced on hydrolysis, is in a downward direction. In otherwords, on hydrolysis of sucrose, D-glucose is liberated first. Therefore D-glucose is linked by its α - bond to a D-fructose unit.



Anomeric carbon of D-glucose

Anomeric carbon of D-fructose

Linkage between D-glucose & d-fructose in sucrose

3) Complete methylation of sucrose followed by mild hydrolysis gives a mixture of 2,3,4,6 - tetra - O - methyl - D- glucopyanose and 1,3,4,6-tetra - O - methyl-D-fructofuranose.

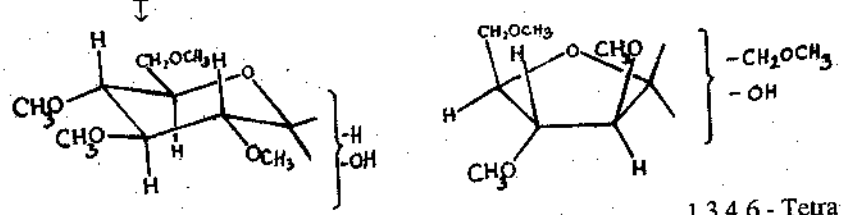
Sucorse

$(CH_3)_2SO_4$ + NaOH

↓

Octa-O-methyl sucrose

dil. HCl

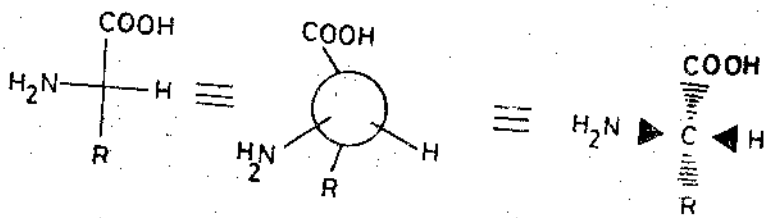


2,3,4,6-Tetra-O-methyl D-glucopysanose (mixture of two anomers)

1,3,4,6 - Tetra - O-methyl D-fructofuranose (mixture of two anomers)

In addition to the carboxyl group and the amino group on the alpha carbon, some amino acids contain another carboxyl group (eg.aspartic acid, glutamic acid) and these are called **acidic amino acids.** Some contain a second basic group which may be an amino (eg. lysine), a guanidino (eg. arginine) or the imidazole ring (eg. histidine). These are called **basic amino acids.**

With the exception of glycine, in all other amino acids the α -carbon is asymmetric (attached to four different groups) and hence all amino acids except glycine are **chiral molecules** i.e. exhibit optical isomerism. All the naturally occurring amino acids have L-configuration at the asymmetric carbon. However, the α - amino acids with L-configuration may be either dextro rotatory or levorotatory.

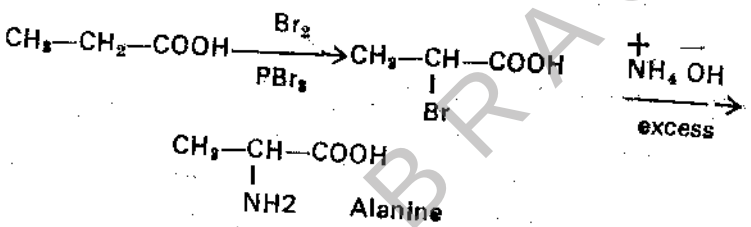


L. amino acids

22.4 SYNTHESIS OF α - AMINO ACIDS

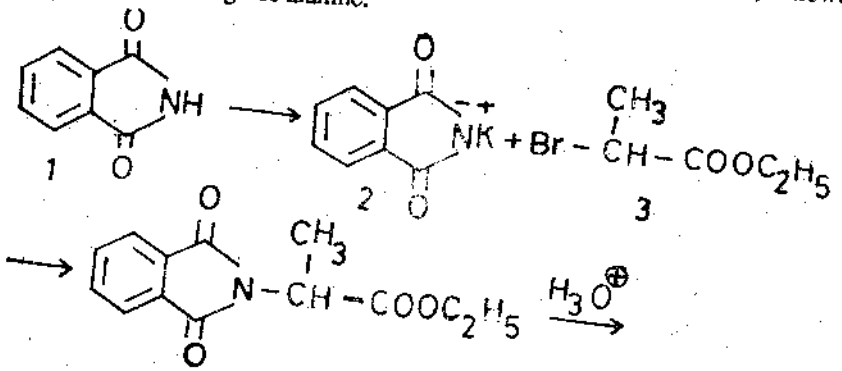
Many of the amino acids can be obtained from protein hydrolysate, but it is more convenient to obtain them by synthesis. Thus all of the racemic amino acids are synthetic and are prepared commecially. Several general methods are known for the synthesis of α -amino acids. A suitable method can be chosen keeping in view the availability of starting materials and the type of amino acid required.

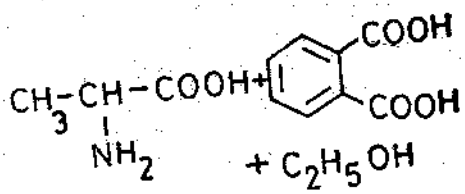
1. Amination of -halo acids: α- Halo acids are easily prepared by direct halgenation of the corresponding acids (Hell-Volhard-Zelinsky reaction). Direct amination of α-halo acids using excess of ammonium hydroxide results in the formation of amino acids. Thus, α -bromopropionic acid on reaction with excess of ammonium hydrdoxide gives alanine.



If ammonia is not used in excess, formation of secondary and tertiary amines is a possible side reaction which will reduce the yield of the amino acid.

2. Gabriel's Phthalimide synthesis: α -Amino acids are synthesised by the reaction of α-bromo derivatives of an ester with potassium phthalimidate. This is known as the 'Gabriel's phthalimide synthesis'. For example, the reaction of ethyl-α-bromopropionate with potassium phthalimidate, followed by hydrolysis of the resulting compound gives alanine.

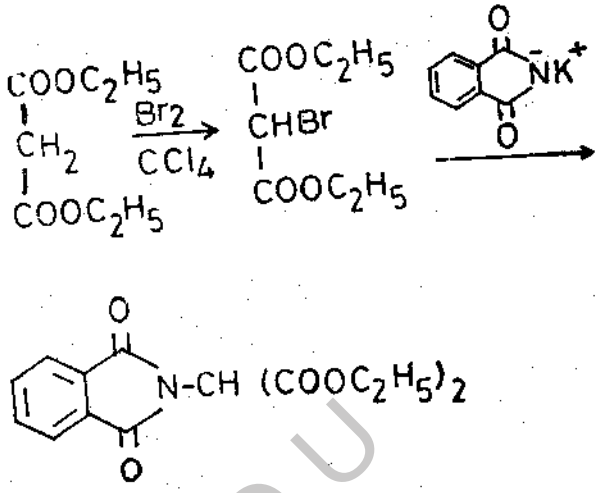




4

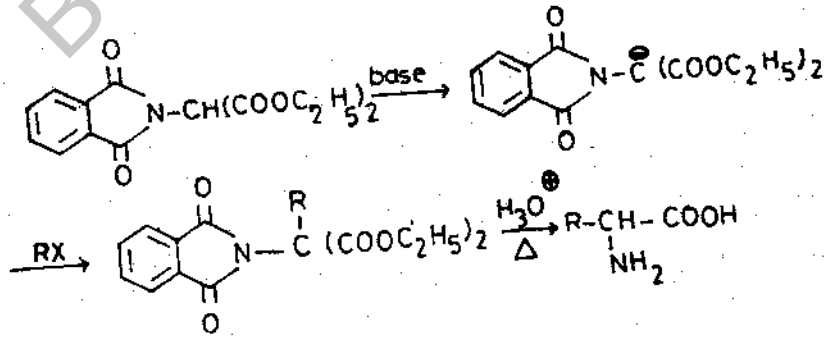
1. Pthalimide 2. Potassium pthalimidate 3. Ethyl-α-bromo propionate 4. Alanine

3. **From malonic ester:** Mon obromo derivative of diethyl malonate reacts with potassium salt of phthalimide to give N-phthalimido malonic ester.



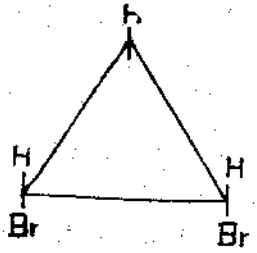
N-pthalimido malonic ester

The ester may be alkylated by a variety of alkyl halides. Vigorous acid hydrolysis of the resulting compound causes hydrolysis of both ester group and phthalimido group, and decarboxylation of the amino dicarboxylic acid.

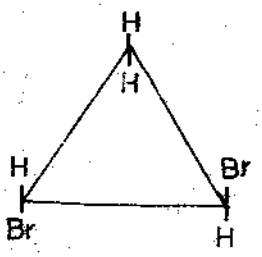


This method is essentially a variation of malonic ester synthesis and is a useful general method for the synthesis of α- amino acids in good yields. Some examples of the synthesis of amino acids using this method are given below:

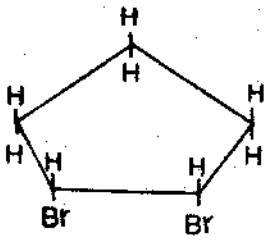
2. Cis-Trans isomerism: In a 1,2 - dibromocycloalkane, the two bromine atoms may be on the same side or on opposite sides of the ring. The isomer with the two bromine atoms on the same side is knwon as cis-isomer and the other isomer with the two bromine atoms on the opposite sides is known as trans-isomer. Following are the cis-trans isomers of 1,2 - dibromo propane and 1,2 - dibromo cyclopentane.



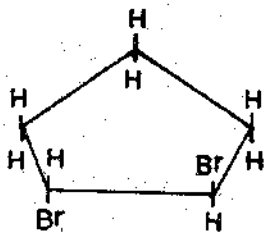
Cis-1,2 - dibromo cyclopropane



Trans-1,2-dibromo cyclopropane



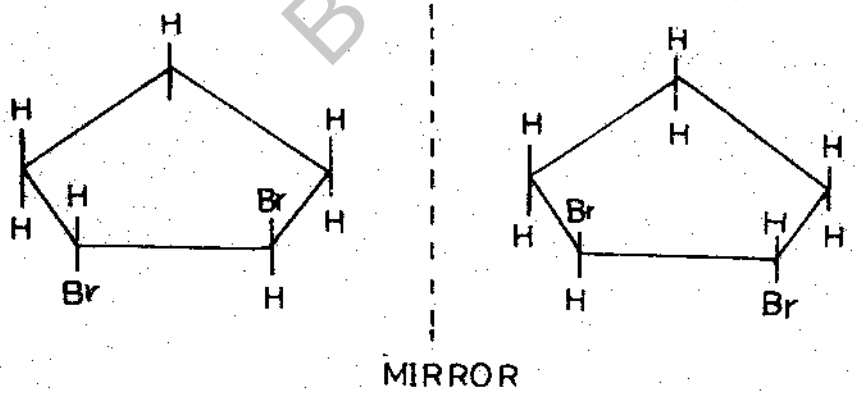
Cis-1,2 - dibromo cyclopentane



Trans-1,2-dibromo cyclopentane

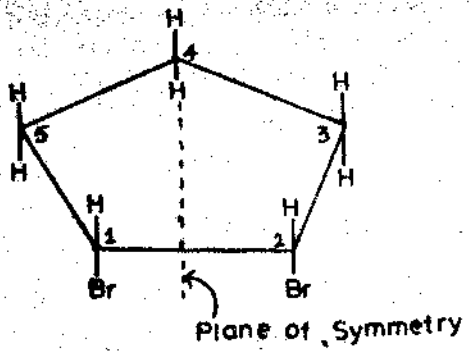
Cis-trans isomerism is also exhibited by 1,3 - disubstituted cyclopentanes.

3. Optical isomerism: Certain disubstituted cycloalkanes, when suitably substituted exhibit optical isomerism. Trans 1,2-dibromo cyclopentane, for example is not symmetric. When there is no plane of symmetry in a molecule two non-superimposable isomeric structures, bearing mirror-image relationship, are possible. One of these isomers rotating the plane polarized light to the right is called the dextro rotatory isomer. The other isomer rotating the plane polarized light to left is called the levo rotatory isomer.

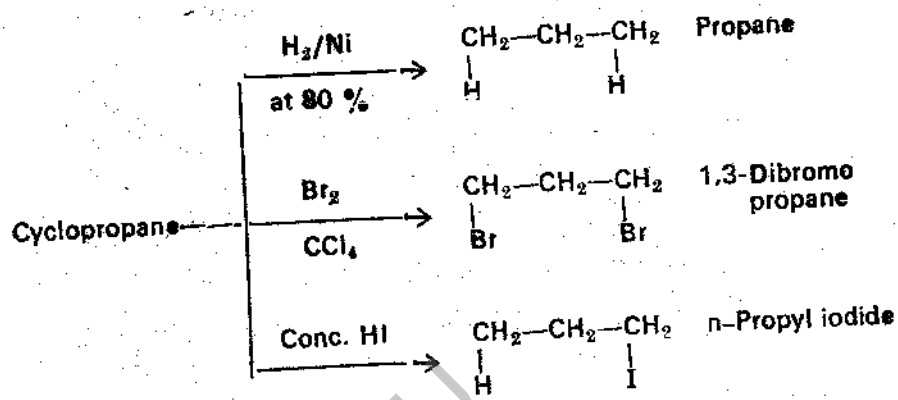


non-superimposable mirror images of trans - 1,2 dibromocyclopentane

On the other hand, cis-1,2-dibromocyclopentane possesses a plane of symmetry. A plane bisecting C_1-C_2 bond and passing through C_4 bisects the molecule into two identical halves. Therefore a symmetric molecule like cis-1,2-dibromocyclopentane is optically inactive.



B. addition reactions: Besides the free-radical substitution reactions that are characteristic of cycloalkanes, small ring compounds like cyclopropanes and cychlobutanes undergo certain addition reactions. During these addition reactions the cyclic structure is opened up giving aliphatic compounds.



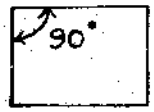
Cyclobutane also undergoes addition reactions but only at high temperatures. Alicyclic compounds containing five carbons onwards do not undergo these addition reactions.

23.7 BAEYER STRAIN THEORY

In 1885 **Adolf Von Baeyer** proposed a theory to account for (1) the reactivity of cyclopropane and cyclobutane in addition reactions and (2) the difficulty in the preparation of macrocyclic rings. This is known as Baeyer strain theory. In alkanes or paraffins the carbon atoms form four covalent bonds with other atoms and the angle between any pair of bonds is $109^0\ 28^1$. Baeyer assumed that all cycloalkanes are planar. Based on this the C-C bond angle in cyclopropane would be 60^0. Similarly in cyclobutane the bond angle would be 90^0. Thus the carbon-carbon bonds in cyclopropane and cyclobutane are bent inward from its normal bond angle of $109^0\ 28'$. This deviation of C-C-C bond angle ($49^0\ 28'$ in cyclopropane and $19^0 28'$ in cyclobutae) is responsible for strain in cyclopropane and cyclobutane molecules. Therefore these molecules undergo addition reaction and relieve their bond angle strain by ring opening. Baeyer calculated the magnitude of the deviation of bond angles in ethylene and various cycloakanes from normal tetrahedral angle, and on that basis calculated angles of distortion in these molecules.

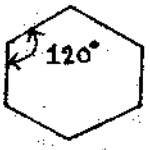
Molecule	Deviation of bond-angle	Angle of Strain
$CH_2=CH_2$	$\frac{109^\circ 28' - 0^\circ}{2}$	$54^\circ 44'$

$\frac{109^\circ 28' - 60^\circ}{2}$ $24^\circ 44'$ (inward)

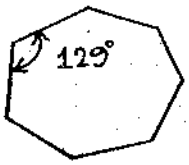


$\frac{109^\circ 28' - 90^\circ}{2}$ $9^\circ 44'$ (inward)

$\frac{109^\circ 28' - 108^\circ}{2}$ $0^\circ 44'$ (inward)



$\frac{109^\circ 28' - 120^\circ}{2}$ $-5^\circ 16'$ (outward)



$\frac{109^\circ 28' - 129^\circ}{2}$ $-9^\circ 46'$ (outward)

The angle strain in ethylene thus accounts for the high reactivity of ethylene in addition reactions. The angle strain in cyclopropane is greater than that in cyclobutane. Therefore cyclopropane undergoes addition reactions more readily than cyclobutane. cyclopentane is virtually free of bond angle strain. According to Baeyer cyclohexane should have a small strain and cycloheptane should have as much strain as cyclobutane. Higher cycloalkanes, should be associated with more angle strain. This should explain the difficulty encountered then in the preparation of alicyclic compounds containing large rings. However, it is found that cyclohexane and cycloheptane are as stable as cyclopentane, and later by adopting suitable methods it was possible to prepare macrocyclic compounds.

progress - 1

opane and cyclobutane undergo ring opening reactions?

.....

.....

.....

E-MOHR THEORY

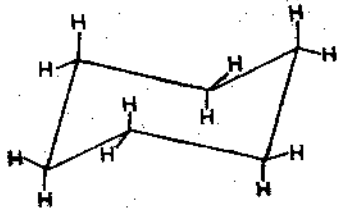
xplanation for the above discrepancies in Baeyer theory. He suggested that:

essentially planar with respect to the carbon atoms.

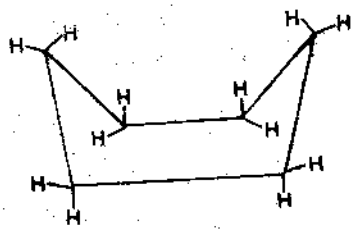
atoms are not planar but have puckered or non-planar

iii) In cyclohexane the ring may be present in two conformations - Chair and Boat conformation. In these conformations the C-C-C bond angles are 109°28'.

iv) The chair and boat conformations of cyclohexane are free from bond angle strain.



Chair Conformation of Cyclohexane



Boat-Conformation of Cyclohexane

Sachse's proposal was initially discounted on the ground that cyclohexane has been obtained only in one form. In 1918 **Mohr** revived the idea and pointed out that inteconversions of boat, and chair forms can be accomplished in the models by rotation at C-C single bonds, without distorting the normal tetrahedral angles. Thus the two possible forms of cyclohexane may be so closely equivalent in energy content to be indistinguishable. It was **Huckel** who later obtained two steric forms of decalin viz. *cis* and *trans* decalins.

Check your progress - 2

Why chair form of cyclohexane is more stable over boat form?

.....

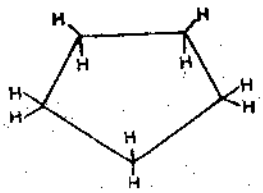
.....

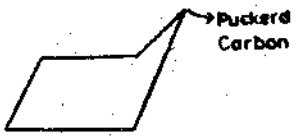
.....

.....

(i) Conformations of cyclopentane

In puckered conformation of cyclopentane, four carbon atoms of the ring are coplanar and the is pushed slightly out of plane. The puckered conformation is taken up in turn by all the ring carbons making them all equivalent. An examination of the model of cyclopentane reveals that the hydrogen present on any two adjacent carbon atoms which are coplanar are eclipsed. Thus there is a re between the adjacent hydrogen atoms. This strain is due to repulsion between the adjacent hy atoms. This strain ... repulsion between the adjacent hydrogen atoms is called **Pitzer st**





Envelope form of cclopentane

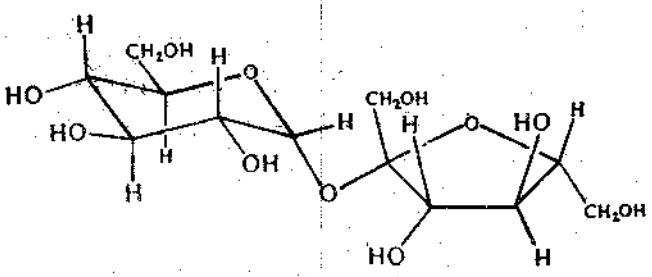
(ii) Conformations of Cyuclohexane

In the chair conformation of cyclohexane all the CH_2 groups are in ... this conformation there is no Pitzer strain and no bond angle str... of cyclohexane is converted into another chair form through a ...

Invertase, an enzyme specific for the hydrolysis of β - fructoside linkages in sugars also hydrolyses sucrose.

$$C_{12}H_{22}O_{11} + H_2O \xrightarrow{\text{Invertase}} \underset{\text{D-Glucose}}{C_6H_{12}O_6} + \underset{\text{D-Fructose}}{C_6H_{12}O_6}$$

In sucrose, therefore, D-fructose is linked to -D-glucose, through its β - bond. All the reactions mentioned above suggest that sucrose is α - D- glucopyranosyl β - D- fructofuranoside or β - D- fructofuranosyl - D- glucopyranoside.



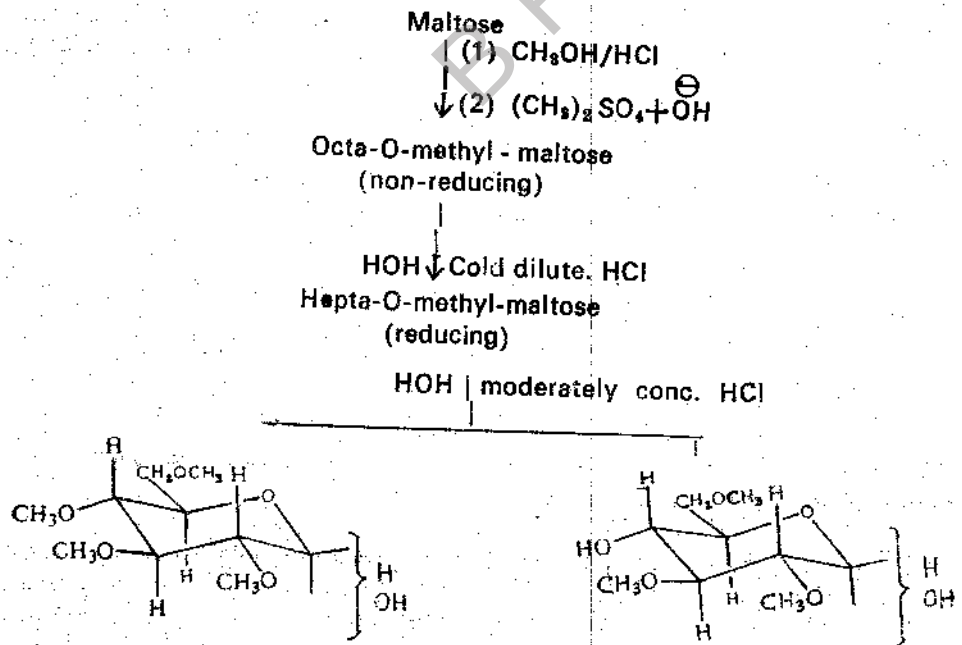
Sucrose

In the formula of sucrose, D-fructo furanose ring is shown inverted upside down i.e, anomeric carbon is shown to left. This has been down to allow glycoside linkage involving the hydroxyl group on the anomeric carbon of D-glucopyranose ring and the hydroxyl group on anomeric carbon of D-fructofuranose ring. The structure of sucrose has also been confirmed by periodic acid oxidation studies and synthesis. The synthesis of sucrose (R.U. Lemieux and G. Huber, 1953) has been described as the "Mount everest of organic chemistry".

Sucrose is dextrorotatory, whereas a solution of the product of hydrolysis of sucrose (containing equimolar amounts of D-glucose and D-fructose) is levorotatory. Due to this the mixture of sugars obtianed on hydroloysis of sucrose is called invert sugar.

B. Maltose: It is obtianed by partial hydrolysis of starch. Its molecular formula is $C_{12}H_{22}O_{11}$. Hydrolysis of maltose with dilute meneral acids yields two moles of D-glucose. Maltose is a reducing sugar, exhibits mutarotation and forms an osazone. Maltose is hydrolysed by the enzyme *maltase*. Therefore, the non-reducing D-glucose moiety in maltose is linked by α - bond.

Complete methylation of maltose followed by hydrolysis of resulting octa-O-methyl-maltose yields a mixture of 2,3,4,6 - tetra-O-methyl -D - glucopyranose and 2,3,6-tri-O-methyl- D- glucopyranose.



2,3,4,6 - Tetra - O - methyl - D-glucopyranose (two anomers)

2,3,6 - Tri - O - methyl - D-glucosepyranose (two anomers)

ii) **Cellophane:** When viscose is extruded on to rollers in an acid medium, thin films of cellophane are obtained. Cellophane is a useful packing material.

b) Cellulose dinitrate (proxylin)

i) Cellulose dinitrate is insoluble in ether and alcohol but soluble in 1:1 mixture of ether and water. The solution is called collodion. When this is spread on a wound and the solvent allowed to evaporate, a transparent, protective film resembling skin is produced. For this reason pyroxylin is nicknamed as new skin.

ii) **Celluloid:** When a mixture of collodion and camphor is heated, a gelatin is obtained which thickens to a plastic. This plastic is called celluloid.

Cellulose trinitrate is called gun cotton, and is used as a propellant.

c) Cellulose acetate

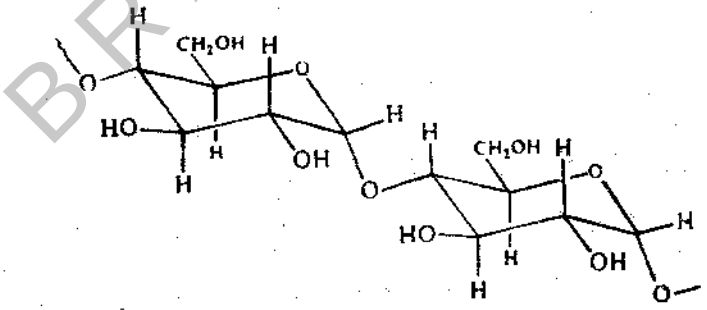
It is used in the preparation of safety glass and acetate rayon.

i) Safety glass is obtained by passing a solution of cellulose acetate in acetone between two layers of glass. This prevents the glass pieces from flying apart when shattered.

ii) **Acetate rayon:** When cellulose acetate solution is forced out of a spinneret, fine filaments of cellulose acetate are obtained. These fibres are called *acetate rayon.*

C. **Starch:**

The molecular formula fo starch is $(C_6H_{10}O_5)n$. Hydrolysis of starch gives D-glucose in quantitative yield. Methylation of starch produces a trimethyl derivative. This on hydrolysis produces 2,3,6-tri-O-mehtyl-D-glucose as the main product. Starch is hydrolysed by the enzyme *diastase* to give maltose. Thus maltose units are present in starch. i.e, several D-glucopyranose units are linked through 1,4,positions by α-linkages.



A segment of starch molecule

Viscosity measurments show that starch has highly branched structure. Starch can be separated into two fractions, α-amylose and β -amylose. When butanol is added to a hot colloidal solution of starch in water and the mixture is allowed to cool to room temparature α-amylose is precipitated. β-Amylose or amylopectin is obtained by the addition of methanol to the mother liquors. - Amylose is soluble in water and gives a blue colour with iodine. β- Amylose is insoluble in water gives a violet colour with iodine. Both the amyloses are polymers and their molecular weight depends upon the method of preparation and the starch used.

Check your progress - 2

What is the structural difference of starch and cellulose?

.....

.....

.....

.....

26.5 SUMMARY

Disaccharides are the sugars which on hydrolysis give two moles of monosaccharides. The methods of structural determination of the disaccharides sucrose, maltose, cellobiose and lactose are presented in the unit. Starch and cellulose are polysaccharides. Their ultimate hydrolysis product is glucose. Cellulose in the linear polymer of glucose with 1,4-β-linkages. On partial hydrolysis it gives cellobiose. Starch has a water soluble fraction amylose a linear polymer of glucose with 1,4-α-linkages and a water insoluble fraction amylopectin a branched high polymer of glucose with 1,4 and 1,6 - α–linkages. starch on partial hydrolysis gives maltose.

26.6 MODLE EXAMINATION QUESTIONS

I **Answer each of the following in 10 lines**

1. How is starch separated into two fractions?

2 Give the name of enzyme (s) that hydrolyse the following.
a) sucrose b) maltose c) cellobiose d) lactose e) starch f) cellulose

3. What happens when sucrose is successively treated with the following reagents? Write equations.

II **Answer each of the following in 30 lines**

1. a) Write the structures of segments of cellulose and starch. Account for the difference in their properties.

   b) give a brief account of some useful derivatives of cellulose.

2. What are disaccharides? Outline the experiments that led to the structural elucidation of sucrose.

3. What are polysacchrides? Outline the experiments that helped in the elucidation of structure of starch and cellulose.

26.7 MODEL ANSWERS TO CHECK YOUR PROGRESS

1. Both maltose and cellobiose are the disaccharides of glucose. The former has α-1, 4-linkage and the latter β-1,4-linkage.

2. Cellulose is the linear polymer of glucose with β-linkages. Starch has low molecular weight linear polymer of glucose, amylose with α-1,4-linkages and high molecular weight branched polymer amylopectin with α-1, 4and 1,6 - linkages.

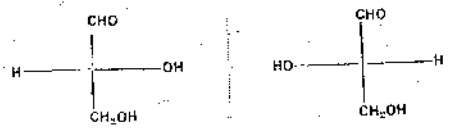
Author: Dr. P.S.N. Reddy

BLOCK 12

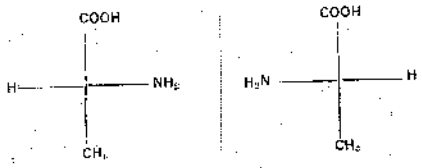
OPTICAL ACTIVITY

Optical isomerism is a branch of stereoisomerism. Those organic compounds which can rotate the plane of vibration of polarised light when it is passed through them are called optically active substances. Nicol prisms have the capacity to transform ordinary light into plane polarised light. Ordinary light has planes of vibration in all directions with in 360°, whereas polarised light has only one plane of vibration. Optical activity of organic substances is measured with an instrument called polarimeter. A number of natural products eg. alkaloids, sugars, terpenoids and steroids are optically active. Organic compounds of definite configuration and optical rotation are biologically active. D (+) glucose is assimilated by living beings and not L(-) glucose.

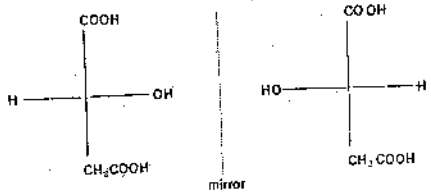
Fisher projection formulae of the enantiomers of glyceraldehyde (OHC-CH(OH-)CH_2OH), alanine (HOOC-CH(NH_2)-CH_3) and malic acid (HOOC-CH(OH)-CH_2COOH), each containing one asymmetric carbon atom are given below.



Enantiomers of glyceraldehyde

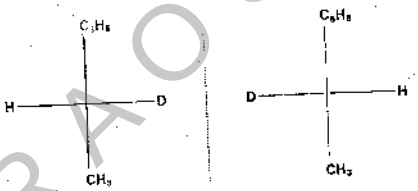


Enantiomers of alanine



Enantiomers of malic acid

The isotopes, such as H and D, are different enough to permit detectable optical isomerism. Thus, α-D-ethyl benzene, CH_3-CH-(D)-C_6H_5, exhibits enantiomerism.



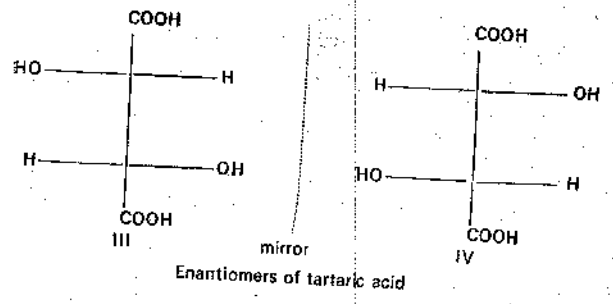
Enantiomers of α -D-ethyl benzene

27.5 MOLECULES CONTAINING TWO ASYMMETRIC CARBON ATOMS

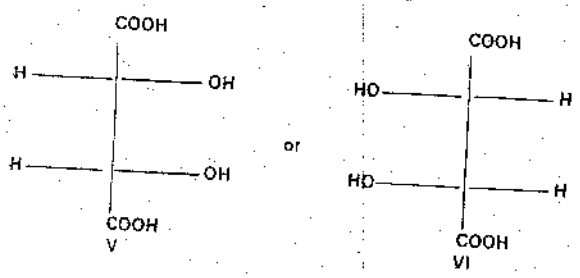
Natural products such as carbohydrates, alkaloids etc.contain two or more asymmetric carbon atoms. When molecules contain two asymmetric carbons, both the asymmetric carbons may be attached to identical groups or they may be attached to different groups. accordingly molecules containing two asymmetric carbons may be divided into molecules containing two similar asymmetric carbon atoms, and moelcules containing two dissimilar asymmetric carbon atoms.

27.6 MOLECULES WITH TWO SIMILAR ASYMMETRIC CARBON ATOMS

In tartaric acid, HOOC-C (OH)-CH (OH) COOH each asymmetric carbon is linked to the same four groups i.e, -H, OH, COOH and -CH (OH) COOH groups. Thus tartaric acid is an example of compounds with two similar asymmetric carbon atoms. In the case of tartaric acid, in all, these isomers are possible- two enantiomers (dextro and levorotatory tartaric acids) are optically active and the third one (mesotartaric acid) is optically inactive. The Fisher projection formulae of enantiomers of tartaric acid and mesotartaric acid are given below.

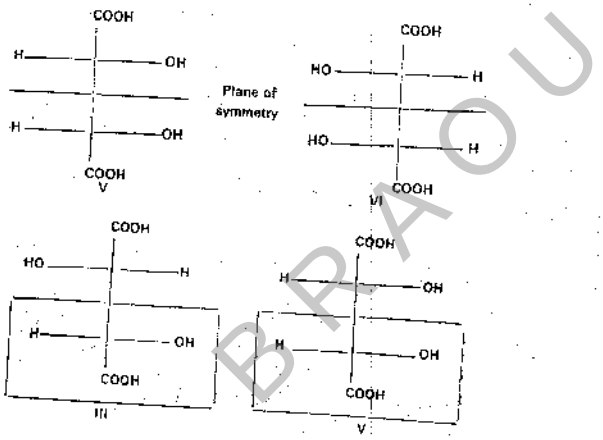


Enantiomers of tartaric acid

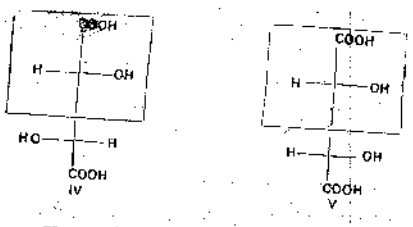


Mesotartaric acid

Structure V and VI bear mirror image relationship but they are superimposable. It can be seen that by rotation of structure V in the paper plane by 1800 structure VI results, and vice versa. Thus V and VI represent one and the same stereoisomer i.e., meso isomer of tartaric acid. The molecule has plane of symmetry, bisecting the bond between the asymmetric carbon atoms. One half of the moelcule is mirror image of the othe half. Such molecules cannot exhibit optical activity and are called **meso compounds**. Meso compounds, unlike racemic mixtures cannot be resolved.



In structures III and V the configurations (the arrongements of groups) about the bottom asymmetric carbon atoms are identical whereas those at the top asymmetric carbon atoms bear mirror image relationship.



On the other hand, structures IV and V have identical configuration at the top asymmetric carbons, whereas those at the bottom asymmetric carbons bear mirror image relationship. Structures such as III and V, with configuration partly identical and partly bearing mirror image relationship, are called **diastereoisomers** or **diastereomers**. III is diastereoisomeric with V. Similarly IV is diastereomeric with V.

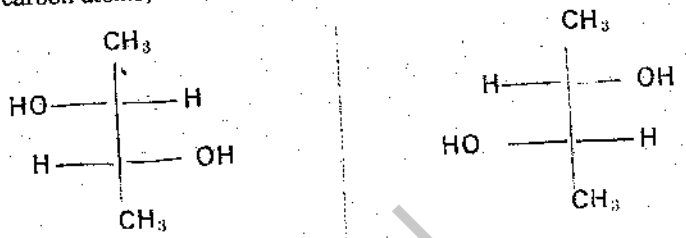
III and IV enantiomers whereas III and IV are diastereoisomers of V. In other words, stereoisomers that are not enantiomeric are called diastereoisomers. Diastereoisomers have substantially different chemical and physical properties.

Physical properties of tartaric acids

Tartaric acid	in H_2O	M.P.C°	Density	Solubility g/100 ml at 25° H_2O
1. Dextrorotatory	+ 11.98	170	1.760	147
2. Levorotatory	- 11.98	170	1.760	147
3. Racemic	-	205	1.788	25
4. Meso	--	140	1.66	120

Racemic acid has higher melting point and lower solubility than either of its constituents.

Butane-2,3 - diol, $CH_3CH(OH)$--$CH(OH)$-CH_3, is another example of compounds containing two similar asymmetric carbon atoms, Here also, a pair of enantiomers and a mesoisomer are possible.



mirror

Enantiomers of butane-2,3-diol

Mesoisomer of butane 2,3-diol

Check your progress - 2

What are diastereomers?

.....

.....

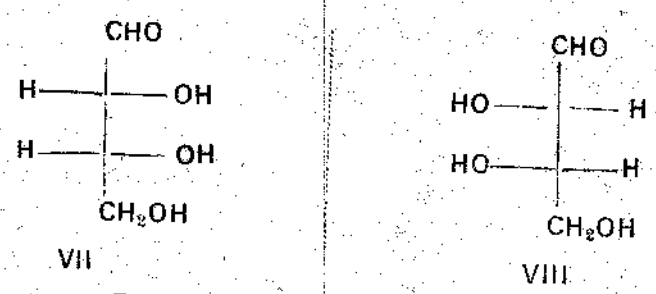
.....

.....

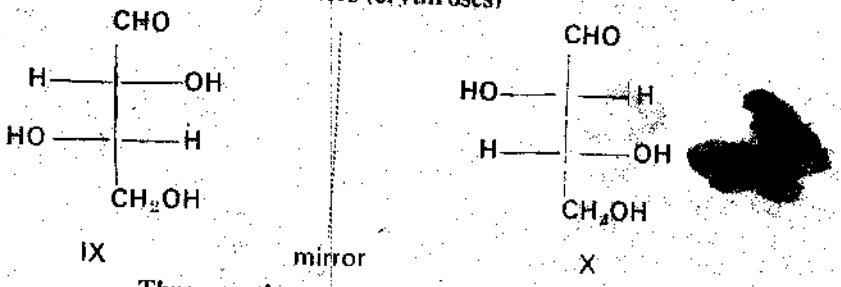
27.7 MOLECULES WITH TWO DISSIMILAR ASYMMETRIC CARBON ATOMS

For molecules with two or more dissimilar asymmetric carbon atoms the number of stereoisomers will be 2^n (where n = number of asymmetric carbon atoms). Thus for aldotetrose CH_2OH-CHOH-CHOH-CHO (containing two dissimilar asymmetric carbon atoms) four stereoisomers are possible. These four

stereoisomers constitute two pairs of enantiomers. The projection formulae of four stereoisomers of aldotetrose are given below.

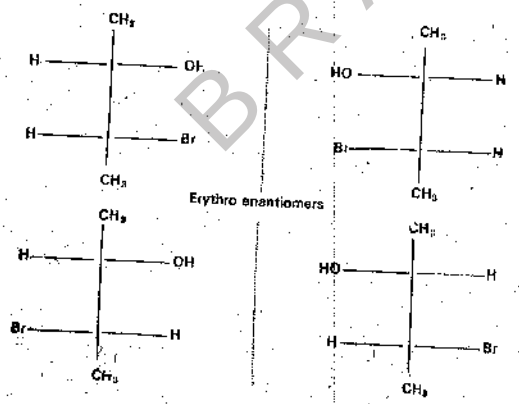


Erythro enantiomers (erythroses)



Threo enatiomers (threoses)
optical isomers of aldotetrose

In the Fischer projection formulae VII and VIII, two pairs of similar groups (two OH groups and two H's) are on the same side. Such optical isomers are called **erythro isomers**. Thus, VII and VIII represent enantioners of erythrose. One of these is dextrorotatory and the other is levorotatory. In structures IX and X, the two hydroxyl groups are on different side (and also the hydrogens). Such optical isomers are called **threo isomers**. Structures IX and X represent enantiomers of threose. It may be seen that VII and VIII are diastereomers of either IX or X. Similarly IX and X are diastereomeric with either VII or VIII. Mesomers are not possible for compounds containing two or more dissimilar asymmetric crabon atoms. 3-Bromo-2-butanol CH_3 CHOH-CHBr-CH_3 is another example a molecule containing tow asymmetric carbon atoms. the structures of the four active isomers are given below.



threo enantiomers
optical isomers of 3-bromo - 2- butanol

27.8 RACEMIC MIXTURES

A mixture of equal amounts of dextro and levo isomers is called racemic mixture. A racemic mixture is optically inactive. This is duc to cancellation of the optical rotatory power of dextrorotatory molecules by equal number of levorotatory molecules present in the mixture. The process of obtaining a racemic mixture is called racemisation.

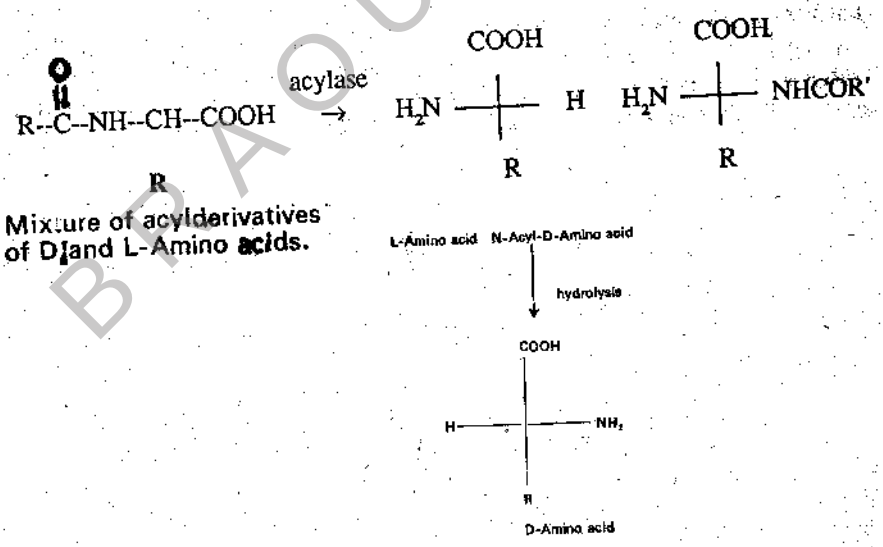
Resolution of racemic mixtures

A racemic mixture can be separated to give the two enantiomers in the pure state. This process is called resolution of a racemic mixture. Some of the important methods of resolution of racemic mixtures are given below.

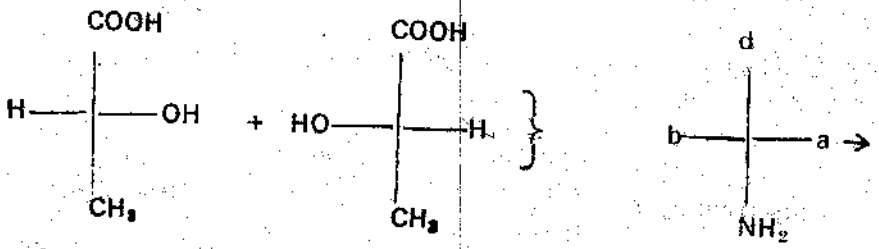
a) **Mechanical method:** The first resolution by mechanical method was carried out by **Louis Pasteur** in 1848. By allowing a dilute solution of racemic sodium ammonium tartarate to crystallise slowly below 28°C crystals of two different shapes were obtained. These crystals were mirror images of each other. Pasteur separated two types of crystals by hand. He found the two batches of crystals were identical except that they rotated the plane of polarised light to the same extent but in opposite direction. This method of separation is tedious and cannot be applied to all types of racemic mixtures because (i) all compounds do not crystallise into readily distinguishable crystals, (ii) the separation is very slow and (iii) cannot be applied to liquid substances.

b) **[redacted]chemical method:** This method depends on the ability of living organisms to destory or me[redacted]ore rapidly one enantiomer. Pasteur found that d-ammonium tartarate is destroyed more rapidly than the l-isomer by ***Penicillium glaucum***. Similarly it was observed by **Emil Fischer** that D-glucose Appendix-III can be fermented by yeast while L-glucose is unaffected. The success of this method therefore depends on the availability of an organism that can destroy one of the enantiomers. Another disadvantage of this method is that only one of the enantiomers is recovered and the other is destroyed.

A very useful application of this technique is in the separation of racemic mixtures of amino acids. In this method a racemic mixture of amino acids is acylated. The racemic mixture of N-acyl amino acids so obtained is subjected to hydrolysis in the presence of an enzyme, ***acylase or amidase***. This enzyme selectively hydrolyses acyl derivative of L-amino acid, and the N-acyl D-amino acid is unaffected. The hydrolysed L-amino acid is easily seperated from the acylated D-amino acid. Hydrolysis of the latter yields pure D-amino acid.

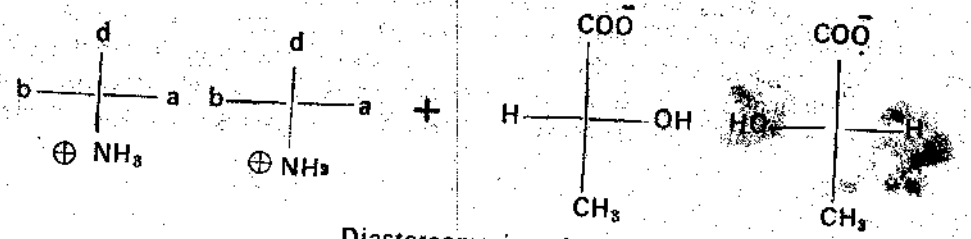


c) **Diastereoisomer fractionation method:** This is a chemical method and finds widest utilization. For instance, a racemic mixture of lactic acid reacts with an optically pure amine (either d-or l-isomer) to form a mixture of salts. These two salts are not enantiomers but are diastereoisomers. They have different physical properties including solubilities. They may, therefore, be separated by fractional crystallisation. After separation, the salts may be neutralised by the addition of mineral acid to give optically pure lactic acids. In a similar way a racemic mixture of an organic base can be resolved by using either 'd' or 'l' tartaric acid. The diastereomeric salts can be separated and neutralised to give optically pure bases.

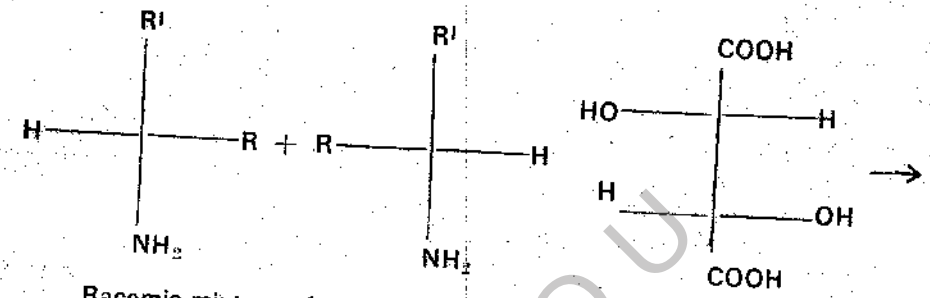


Racemic mixture of lactic acid

An enantiomer of an amine

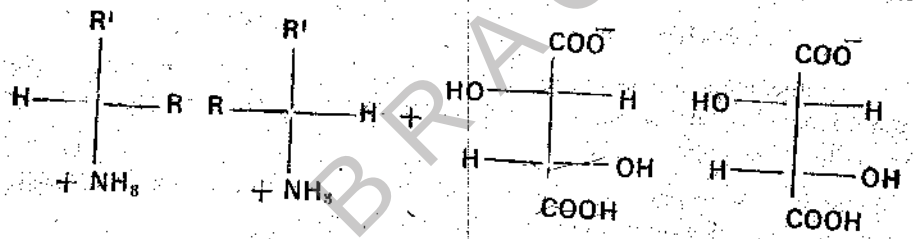


Diastereomeric salts



Racemic mixture of an amine

An enantiomer of tartaric acid



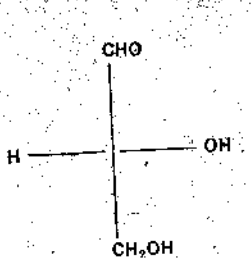
Diastereomeric salts

In the resolution of a racemic mixture of alcohols, solid diastereoisomeric esters are obtained by reaction with an optically pure organic acid. Separation of the diastereoisomeric esters by fractional crystallisation followed by hydrolysis gives pure enantiomers of the alcohol.

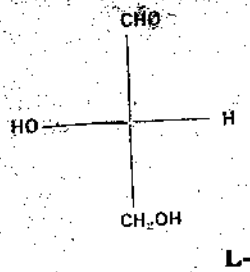
27.9 CONFIGURATION

The term configuration is used to denote the arrangement of the atoms or groups in space around the asymmetric carbon atom. Different notations are used for indicating the configuration of organic molecules.

a) D and L configurations: Fischer and Rosanoff used D and L notations to indicate the configuration of the two enantiomers of glyceraldehyde. Fischer projection formulae are widely used to show the configuration of optical isomers. The Fischer projection formulae of the enantiomers of glyceraldehyde are given below.

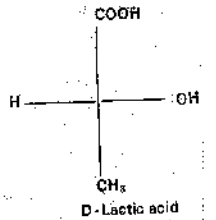


D-Glyceraldehyde

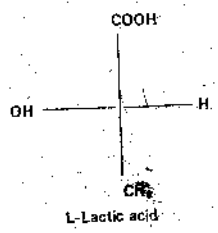


L-Glyceraldehyde

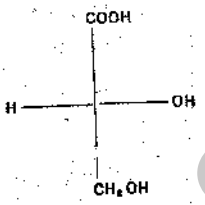
In both the structures H and OH are on the horizontal axis, one of the structures in which the OH group is to the right represents glyceraldehyde of D-configuration (D-glyceraldehyde). The other in which the OH group is to the left is the configurational formula of L-glyceraldehyde. The notation D and L simply indicate the configurations of H and OH groups in the two enantiomers in a correct Fischer projection formula. The configurational formulae do not tell us whether an enantiomer is dextrorotatory or levorotatory. All acyclic molecules in which the configuration at the bottom asymmetric centre is similar to that of D-glyceraldehyde and L-glyceraldehyde are assigned D and L configuration respectively.



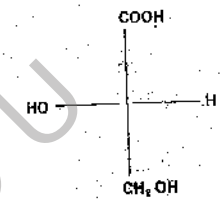
D-Lactic acid



L-Lactic acid



D-Glyceric acid

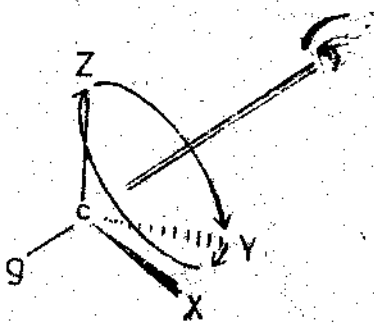


L-Glyceric acid

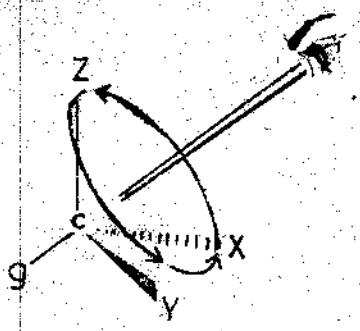
The configuration only at a single asymmetric centre is indicated according to D, L - notation. Therefore this notation is not satisfactory for molecules containing multiple asymmetric centres. Also this notation is difficult to apply to cyclic molecules.

b) R and S configuraions: This method enabnles us to indicate configuration at each asymmetric centre in molecules which contain several asymmetric atoms.

For assigning R and S configuraion at an asymmetric centre, the groups attached to the asymmetric carbon are arranged in priority sequence \based on the sequence rules (Appendix - IV). Let us assume that the asymmetric carbon is linked to four groups, X, Y, g and Z, and the decreasing order of priority of these groups is Z, Y, X, g i.e, g is the least priority group. Then the arrangement of groups at the asymmetric carbon is viewed from the side, remote from the least priority group. Then the arrangement of groups at the asymmtric carbon is viewed from the side, remote from the least priority group, when the other three groups become arranged in the form of a steering wheel model.. If the arrangement of the groups Z, Y and X on this steering wheel model is clockwise, the asymmetric carbon is assigned R configuration (R=*rectus*, in latin for right). If the arrangement of Z, Y and X is anticlockwise, the asymmetric carbon is assigned S configuration (S=*sinister*, in latin for left.



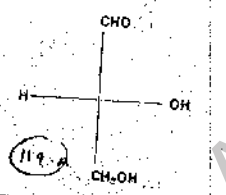
Clockwise sequence
(R-configuration)



Anticlockwise sequence
(S-configuration)

It is quite convenient to assign R,S configuration using moleuclar models. To assign the configuration about an asymmetric carbon atom in a projection formula, in terms of R andS notation, first fix the priority of the groups. Then draw another convenient Fischer projection formula,by making an even number of exchange of pairs' of groups in the original projection formula, such that the least priority group is at the bottom of the vertical axis. It must be remembered that even number of exchange of pairs of groups in a model or a Fischer projection formula does not alter the configuration. The clockwise or anticlockwise arrangement of the other three groups can be directly read from the new Fischer projection formula.

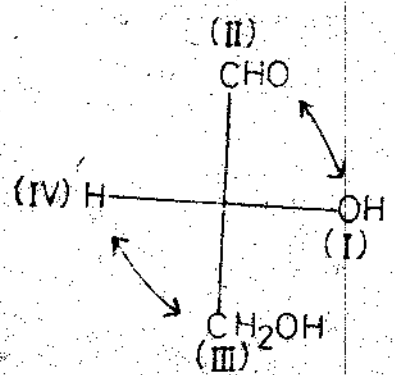
As an example let us assign configuration in terms of R and S, to D-glyceraldehyde.



D-Glyceraldehyde

The order of priority, of groups on the basis of sequence rules is $OH > CHO > CH_2OH > H$

Thus, OH group is of first priority, CHO of second priority. CH_2OH of third priority and H is of least priority.

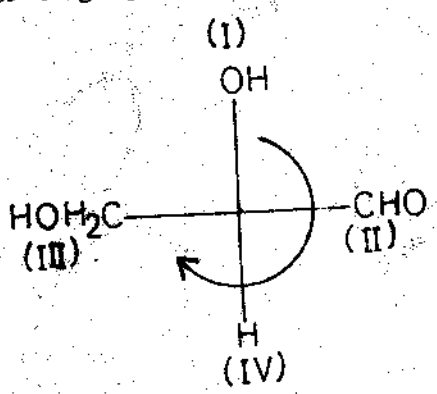


D-Glyceraldehyde

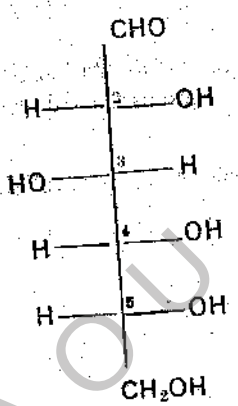
(Here $H \leftarrow\rightarrow CH_2OH$ means exchange of H with CH_2OH group and vice versa)

Now make an even number of exchanges of pairs of groups; so as to bring H (least priority group) at the bottom of the vertical axis.

By making two oxchanges of pair of groups (OH exchanging the position of CHO group and H exchanging the position of CH OH group) we get a projection formula.



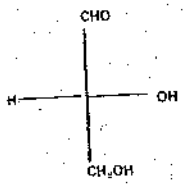
In the projection formula the arrangement of highest priority group (OH group), second priority group (CHO group) and the third priority group (CH_2OH group) is clockwise. Therefore, the configuration of D-glyceraldehyde is R. In a similar way the configuration, at each asymmetric carbon in D-glucose can be worked out in stages.



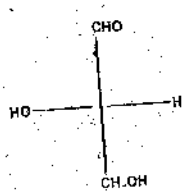
D-Glucose
(2R, 3S, 4R, 5R-Aldohexose)

27.10 DETERMINATION OF ABSOLUTE CONFIGURATION

The projection formulae of D-and L-glyceraldehydes are given below:



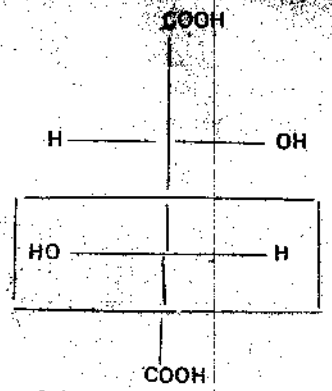
D-Glyceraldehyde



L-Glyceraldehyde

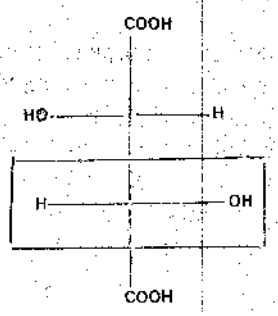
One of these is (+) glyceraldehyde and the other (-) glyceraldehyde. It is difficult to say, from the formulae, which one is the dextro isomer and which one is levo isomer. Finding out answer to this question constitutes determination of absolute configuration.

By X-ray diffraction analysis, Bijovet (1951) determined the absolute configuration of (+) tartaric acid. It was shown to have L-configuration. This constitutes the first and direct determination of absolute configuration.



L(+) - Tartaric acid

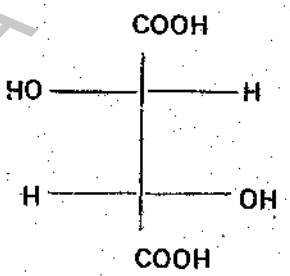
Therefore (-) - tartaric acid must have D-configuration



D (-) - Tartaric acid

Absolute configuration of other compounds has been detremined indirectly. In this, the configuration of a compound is determined by chemically relating it to a compound of known configuration. This method of determination of configuration is known as chemical correlation method. (+) -glyceraldehyd has been chemically related to D-(-) tartaric acid whose absolute configuration is already knwon. (+) glyceraldehyde is thus shown to have D-configuration (Appendix-V)

(+) - glyceraldehyde → → →



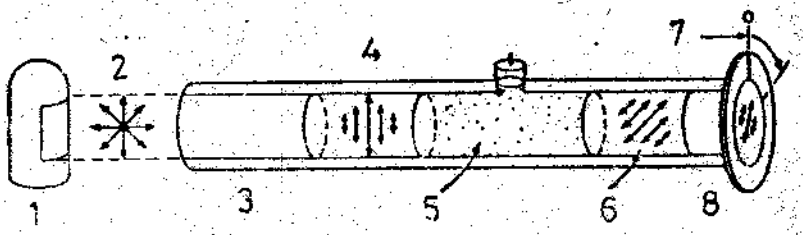
D-(-)-Tartaric acid

Appendix-1

a) Plane polarised light: A beam of ordinary light consists of two components viz. electric field and magnetic field, in mutually perpendicular planes. Further, a beam of ordinary light consists of rays of different wavelength vibrating in many different planes. The light of a single wavelength, obtained either from a special light source such as sodium lamp or by using filters, is called monochromatic light. The monochromatic light still consists of waves vibrating in many planes at right angels to the direction of propagation, However, the light emerging from a Nicol prism differs from the normal light in beig polarised light. The Nicol prism permits passage of only those light waves vibrating in a specific single plane. Nicol prism used in polarimeter for obtaining plane polarised light is prepared by bisecting a crystal of calcite (Iceland spar), $CaCO_3$, along one of its natural axes and by cementing the two halves with Canada balsam.

b) Polarimeter: The rotation of the plane polarised light is measured in a polarimeter. It consists of a light source (sodium lamp), two Nicol prisms, and a tube to hold the solution of the optically active

compound. These are arranged such that light passess through the first prism (polarizer) and then through the tube and the second prism (analyzer) and finally reaches the observer. First the polarizer and analyzer are set at an angle at which, with the tube empty, maximum intensity of light is seen through the analyzer.



Schematic diagram of a polarimeter

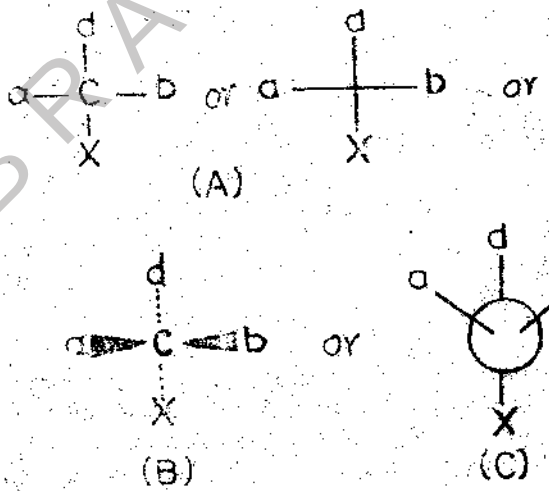
1. Light source 2. Normal light beam 3. Polarizer 4. Polarized light beam 5. Solution of optically active compound 6. Plane of polarisation rotated 7. Angle of rotation 8. Analyzer.

When the analyzer is at right angles to this normal postion, the intensity of light will be minimum. Again adjust the postion of the analyzer to maximum light and fill the tube with the solution of the sample under investigation. If the substance does not affect the plane polarized light i.e, optically inactive, the intensity of light reaching the analyzer will be maximum. On the other hand if the substance rotates the plane polarised light i.e, opticaly active, the analyzer has to be rotated either clockwise (right) or anticlockwise (left) to see the maximum light again. The direction (clockwise or anti-clockwise) of rotation and the angle through which the analyzer has been turned is called angle of rotation.

Appendix II

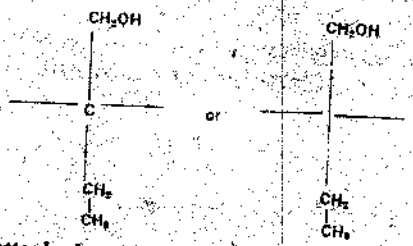
Fischer projectin formulae

While writing the correct Fischer projection formulae of an organic compound the longest chain of carbon atoms is shown on the vertical axis with the more oxidised carbon on the top. The other two groups about the asymmetric carbon become arranged on the horizontal axis. The groups on the vertical axis are considered to be below the paper plane and those on the horizontal axis are above the paper plane.

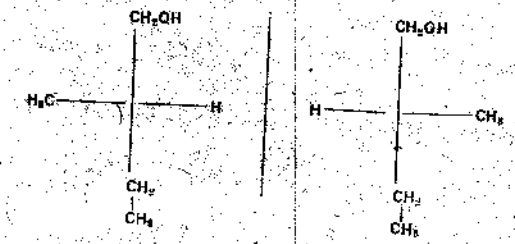


Projection formulae of a molecule in which an asymmetric carbon is linked to four groups (a,b,d, and x), (A); Fischer projection formulae: The groups 'a' and 'b' are above the plane of the paper while 'd' and 'x' are below the paper plane. (The Groups 'd' and 'x' together with asymmetric carbon atom constitute the longest chain of carbon atoms, and 'd' being the more oxidised group (B). Thick lines indicate the bonds above the plane and dotted lines indicate the bonds below the plane (C) The circle represents the asymmetric carbon atom. The lines extending into the circle represent the bonds above the plane and the lines that just touch the circle represent the bonds below the paper plane.

In the Fischer projection formulae of 2-methyl-1-butanol $HOCH_2$-CH (CH_3) - CH_2CH_3 the longest chain of carbon atoms (Containing four atoms) is shown on the vertical axis with the more oxidised carbon (carbon attached to - OH group) on the top.



The other two groups attached to the asymmetric carbon (H and CH_3) can be arranged in two ways on the horizontal axis. In one arrangement the hydrogen is to the right and in the other it is to the left.



Fischer projection formulae of enantiomers of 2-methyl-1-butanol.

Appendix III

Sign of rotation and configuration

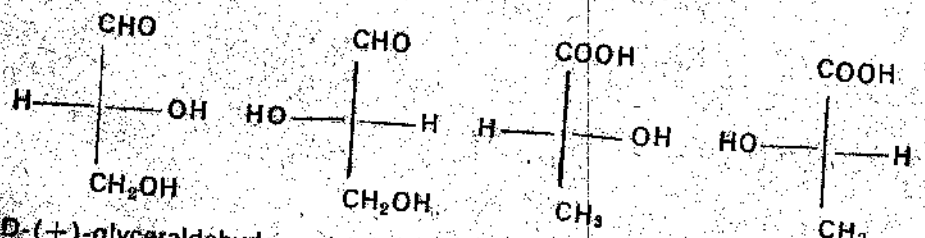
The sign of optical rotation and configuration are two different aspects of an optical isomer. The letters d and l indicate the dextrorotatory and levorotatory isomers. The same meaning is conveyed by (+) and (-) rotation. These rotations do not tell anything about configuration.

On the other hand the capital letters, D or L, indicate only configuration of an optical isomer an d do not convey any information about the sign of their optical rotation.

A complete discription of both the sign of optical rotation and the configuratin of an optical isomer is sometimes given in the prefix part of the name. For eg. D, d - or D-(+) -glyceraldehyde indicates that dextrorotatory glyceraldehyde has d-configuration. The prefix - d-(+) is generally used in preference to D, d to avoid the confusion arising by use of a capital letter (D) and small letter (d). Similarly L-(-) glyceraldehyde is levorotatory glyceraldehyde with L-configuration. (Capital letters, D and L, indicate configuration whereas small letters d and l or the signs, (+) and (-), indicate direction of rotation).

It is wrong to assume that all dextrorotatory isomers have D-configuration and levorotatory isomers have L-configuration. For instance (-) -lactic acid has D-configuration and (+) -lactic acid has L-configuration. They are therefore described as D-(-) lactic acid and L-(+) lactic acid respectively.

The sign of optical rotation of a compound is determined by polarimetry and just cannot be predicted from its projection formulae.



Appendix IV

Sequence rules for R and S configuration

1) The priority of the groups attached to the asymmetric carbon is fixed based on the atomic weight of the α - atom i.e, atom of the group that is directly linked to the asymmetric carbon.

Order of priority: -I > - Br > - Cl > -SH - > F > -OR > -N - R -> C - R (R, R, R)

2) If two groups have the same -atom, consider the atomic weights of atoms etc for assigning priority.

Order of priority: -O-OR > -O-N-R-> O- CH_3 . O-H > O -F

3) Is topic atoms of higher mass number precede those of lower mass number

Order of priority : -T > -D > H and $-\overset{14}{C}H_3 > -\overset{13}{C}H_3 > -CH_3$

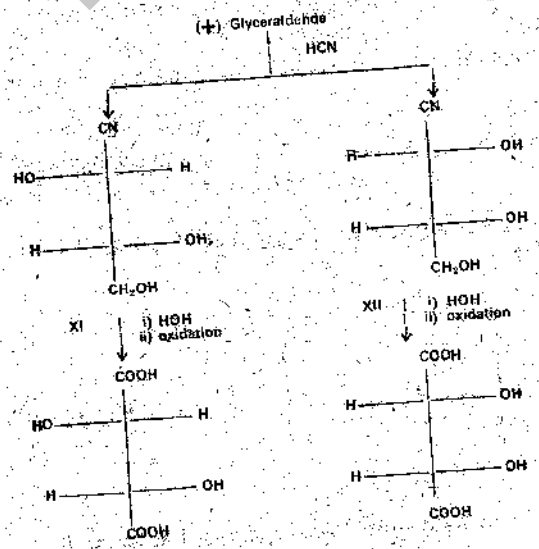
4) When a multiple bond is present, substitute an equal number of atoms. For eg. the aldehyde group - C=O is considered a s C-O-wh

assigning priority. Thus C-O has higher priority over - C-H

5) C is groups precede isomeric trans groups, and R groups precede isomeric groups.

Appendix V

Chemical correlation of the absolute configuration of (+) -glyceraldehyde.



(+) -Glyceraldehyde on reaction with HCN gave a mixture of cyanohydrins. Hydrolysis of cyanohydrins followed by oxidation gave a mixture of (-) -tartaric acid (already shown to have D-configuration) and mesotartaric acid. From this we can write the configurations of cyanohydrins as XI and XII. Since XI and XII are obtained from (+) -glyceraldehyde, the latter should have D-configuration.

27.11 SUMMARY

Ordinary light has planes of vibration in all directions but polarised light has only one plane of vibration. Optical isomers rotate the plane of vibration of polarised light to the left or right. Compounds containing asymmetric carbon atoms may or may not exhibit optical isomerism. But compounds without any symmetry elements possess non-superimposable mirror images and they will definitely exhibit optical activity. Such compounds may not contain asymmetric carbon atoms. Equimolar mixture of two optical isomers is called racemic mixture. Separation of optical isomers from racemic mixtures is resolution. Among the different methods of resolution diastereoisomeric method is the method of wide application. Orientation of OH group on bottom asymmetric carbon atom is indicated in Fischer projection formula by D (right side) and L (left side) notation. It is possible to indicate the configuration at asymmetric carbon atoms by R,S - configurational nomenclature.

27.12 MODEL EXAMINATION QUESTIONS

I Answer each of the following in 5 lines

1. Explain the following with suitable examples
   a) erythroisomers b) threoisomers c) diastereomers

2. Write appropriate formulae for (i) d-glyceraldehyde and ii) L-tartaric acid and assign R and S configuration at each asymmetric centre in these molecules.

II Answer each of the following in 30 lines

1. What is plane polarised light? expalin the functions of various components in a polarimeter.

2. Illustrate with suitable examples the difference between optical isomers of compounds containing (a) two similar asymmetric carbon atoms and (b) two dissimilar asymmetric carbon atoms.

3) What is configuration? Explain the different configurational notations in vogue.

4) What is a racemic mixture? Outline the different methods of resolution of racemic mixtures.

5) What is absolute configuration? Illustrate the different methods of determination of absolute configuration.

27.13 MODEL ANSWERS TO CHECK YOUR PROGRESS

1. A carbon atom with four different atoms or groups is called an asymmetric carbon.

2. Non-enantiomeric stereoisomers are called diastereomers. They possess identical structure in some part of their molecules and mirror image relation in the other.

Author: Dr. P.S.N. Reddy

BLOCK - 13

ORGANIC ANALYSIS

The methods of structure determination of organic compounds have undergone revolutionary changes in the last few decades. Now a days physical methods are preferred over chemical methods due to a number of advantages in the former. It is necessary to find whether an organic compound is pure or not before its analysis. M.P; mixed M.P; B.P. and T.L.C. are the methods of judging the purity. If necessary they can be purified by a) recrystallisation b) distillation c) sublimation d) steam distillation and e) column chromatography. The steps invoved in the analysis of an organic compound are elemental detection, their estimation, molecular formula and finally molecular structure determination. Now a days spectroscopic methods of structure determination are in wide application. These are I R., U V, N MR, and mass spectroscopic methods.

UNIT 28 ORGANIC FUNCTIONAL GROUP ANALYSIS

Contents

28.1 AIMS AND OBJECTIVES

To outline the steps involved in the structure determination of organic compounds by chemical methods.

After a thorough study and understanding of the contents of this unit, you must be able to:

- know the evaluation methods of purity of organic compounds.
- describe the detection of elements in organic compounds - Lassaigne test.
- realise the importance of the estimation of carbon, hydrogen, nitrogen, halogens and sulphur in organic compounds.
- determine and understand the relation between empirical formulae and molecular formulae.
- give the detection methods of functional group in organic compounds.

28.2 INTRODUCTION

One of the aims of an organic chemist is to purify and establish the structure of unknown organic compounds. The structure determination of an organic compound involves several stages such as evaluation of its purity, detection and estimation of elements, molecular weight determination and functional group analysis.

28.3 EVALUATION OF PURITY

The most important criterion of the purity of an organic compound is sharp melting or boiling point. For pure organic compounds, the gap between the temperatures at which they begin to melt or boil and at which the boiling or melting is complete is less than two degrees. In the case of impure compounds this gap is more.

Solid organic compounds are generally purified by recrystallisation. Solids that sublime can be purified by sublimation. In special cases chroamatographic methods may be employed for purification. Pure organic solids have well defined crystalline shape. Liquid samples are purified by fractional distillation. Steam volatile compounds are purified by steam distillation.

28.4 DETECTION OF ELEMENTS

Carbon is essentially present in all organic compounds. Most of the organic compounds contain hydrogen, and in some oxygen, sulphure, nitrogen and/or halogens may be present. Usually, the presence

of carbon, hydrogen and oxygen in organic compounds is not tested. The presence of oxygen may be inferred by the funcitonal gorup tests.

i) **Lassaigne test:** Lassaigne test is performed to detect the presence of nitrogen, sulphur and halogens in organic compounds. On heating an organic compound with sodium metal, the nitrogen along with the carbon, present in the compound, is converted into sodium cyanide (Na CN), whereas sulphur and halogens are converted into sodium sulphide (Na_2S) and sodium halides (NaX) respectively. In Lassaigne test, an organic compound is fused with sufficient quantity of sodium metal in an ignition tube, plunged into water, taken in a mortor, finely ground and filtered. The filtrate should be clear and colourless. This filtrate is called sodium fusion extract. The fusion extract is then tested for the presence of sodium cyanide, sodium sulphide and sodium halides.

$$Na + C + N \rightarrow NaCN$$
$$2\,Na + S \rightarrow Na_2S$$
$$Na + X \rightarrow NaX \text{ (Sodium halide)}$$

ii) **Test for nitrogen:** The fusion extract is boiled for few minutes with excess of ferrous sulphate and then acidified with dilute sulphuric acid. After the addition of ferrous sulphate if a bluish green precipitate is not obtained, few drops of sodium hydroxide are added. During heating, oxidation of some of Fe^{++} ions to Fe^{+++} ions occurs. Formation of a prussian blue precipitate or colour, due to ferric ferro cyanide, indicates the presence of nitrogen in the given compound. Following equations explain the test.

$$FeSO_4 + 2\,NaOH \rightarrow Fe(OH)_2 + Na_2SO_4$$

$$Fe(OH)_2 + 6\,NaCN \rightarrow \underset{\text{(Sodium ferrocyanide)}}{Na_4[Fe(CN)_6]} + 2\,NaOH$$

$$3Na_4[Fe(CN)_6] + 2\,Fe_2(SO4)_3 \rightarrow \underset{\text{Ferric Ferrocyanide}}{Fe_4[Fe(CN)_6]_3} + 3\,Na_2SO_4$$

iii) **Tests for sulphur:** (a) A black precipitate of lead sulphide (PbS) is formed by the addition of acetic acid and a solution of lead acetate to the sodium fusion extract.

$$Na_2S + (CH_3COO)_2Pb \rightarrow PbS\downarrow + 2\,CH_3COO\,Na$$

b) Another test for sulphur is to add one or two drops of freshly prepared dilute solution of sodium nitropursside. Appearance of a violet or pink colour is a positive test for sulphide ion in the extract, and therefore for the presence of sulphur in the organic compound.

$$Na_2S + Na_2[Fe(NO)(CN)_5] \rightarrow Na_4[Fe\,CON - SNa(CN)_5]$$

iv) **Test for halogens:** The fusion extract is strongly heated with conc. nitric acid to destroy sodium cyanide which interferes with the test for sodium halides. Then the presence of halides in the fusion solution i.e, halogens in the given compound, is tested by the addition of silver nitrate solution. Formation of a white, pale yellow or yellow precipitate indicates the presence of chlorine, bromine or iodine respectively in the compound.

$$Na\,X + Ag\,NO_3 \rightarrow Ag\,X\downarrow + Na\,NO_3$$

28.5 ESTIMATION OF ELEMENTS

Carbon, hydrogen, nitrogen, sulphur and halogens in organic compounds are estimated by different methods.

i) **Estimation of carbon and hydrogen:** When an organic compound is strongly heated with dry cupric oxide, the carbon and hydrogen are converted into carbon dioxide and water respectively. This is the principle underlying **Liebig and Gay-Lussac methods** for the estimation of carbon and hydrogen respectively. A known weight of the compound (W/gm) is subjected to combustion at about 700-8000 in the presence of coper oxide. The products of combustion (CO_2 and H_2O) are swept, by a stream of dry nitrogen gas, into weighed absorption tubes containing dry KOH and $CaCl_2$ respectively. The increase in the weights of absorption tubes containing potassium hydroxide and calcium chloride corresponds to the amounts of carbondioxide (X gm) and water (Y gm) respectively formed in the combustion of the compound.

$$C + 2\,CuO \rightarrow CO_2 + 2\,Cu$$
$$2\,H + CuO \rightarrow H_2O + Cu$$

From the weights of carbondioxide and water formed in the combustion, the percentage of carbon and hydrogen in the given compound are calculated as follows.

$$\% \text{ Carbon} = \frac{12}{44} \times \frac{X}{W} \times 100$$

$$\% \text{ Hydrogen} = \frac{2}{18} \times \frac{Y}{W} \times 100$$

When X = Weight of Water formed
Y = Weight of Carbondioxide formed

ii) **Estimation of nitrogen:** There are two methods for the estimation of nitrogen.

(a) **Dumas method:** In this method, a weighed amount of the organic compound containing nitrogen is mixed with dry copperoxide and heated in an atmosphere of carbondioxide. The nitrogen gas thus produced is collected and measured in a nitrometer. From the volume of nitrogen evolved at STP, the percentage of nitrogen is calculated:

weight of the compound = W gm
Volume of nitrogne collected in nitrometer at T°(Absolute) and P_{mm} pressure = V ml

$$\text{Volume of nitrogen at STP (V0 ml)} = \frac{P \times V}{T} \times \frac{273}{760}$$

$$\therefore \text{wt of nitrogen} = \frac{28}{22400} \times V_0 \text{ gm}$$

$$\therefore \% \text{ Nitro gen} = \frac{28}{22400} \times \frac{V_0}{w} \times 100$$

b) **Kjeldahl's Method:** The estimation of nitrogen is generally carried out in the laboratary by this method. A known weight of the sample (x gm) is digested with excess of concentrated sulphuric acid in the presence of a catalyst (a mixture of copper sulphate, selenium and potassium sulphate). During digestion, the nitrogen present in the compound is converted into ammonium sulphate. To this excess of sodium hydroxide is added and steam distilled. The liberated ammonia is absorbed in known excess of standard sulphuric acid solution. The remaining sulphuric acid is back titrated against a standard sodium hydroxide solution. The percentage of nitrogen is calculated as follows.

Weight of the nitrogen containing compound = W gm
Volume of O.1 N a_2SO_4 in which ammonia is absorbed = 'x' ml

volume of O.1 N NaOH required to titrate = 'V' ml
sulphuric acid remaining.

$\therefore$ Volume of O.1 N H_2SO_4 used for nuetralisation
of liberated ammonia = (x-V) ml

$\therefore$ Ammonia liberated is equivalent to (x-V) ml of O. 1N NH_3 solution 1000 of 0.1 N NH_3 solution = 17 gm of NH_3 = 14 gm of nitrogen

$$\therefore \text{(x-v) ml of o.IN NH3 solution} = \frac{x-v}{1000} \times \frac{14}{10} \text{ g of nitrogen}$$

$$\therefore \% \text{ Nitrogen} = \frac{(x-v)}{1000} \times \frac{14}{10} \times \frac{100}{W} = \frac{(x-v)}{100} \times \frac{14}{W}$$

iii) Estimation of halogens: Halogens are estimated by Carius method. A known weight of the organic substance is heated with fuming nitric acid and silver nitrate solution in a sealed tube. The halogen is converted into silver halide. The precipitate of silver halide is filtered, washed while on filter, dried and weighed. The percentage of chlorine, for instance, is calculated as follows:

Weight of the sample = W gm.
Weight of silver chloride = W_1 gm.
Molecular weight of AgCl = 108 + 35.5 = 143.5
143.5 gm of AgCl contains 35.5 g of chlorine

$$\text{w1 gm of AgCl containing} = \frac{35.5}{143.5} \times w_1 \text{ gm of chlorine}$$

$$\therefore \% \text{ chlorine} = \frac{35.5 \times w_1}{143.5} \times \frac{100}{w}$$

iv) Estimation of sulphur: Sulphur present in a compound is converted into a soluble sulphate by oxidation with a mixture of sodium peroxide and sodium carbonate. The soluble sulphate is then converted into barium sulphate by adding a solution of barium chloride. The precipitate of barium sulphate is filtered, washed, dried and weighed. From the weight of $BaSO_4$ obtained (x gm) from a known weight (w gm) of the organic compound the percentage of sulphur is calculated.

$$\% \text{ S} = \frac{32}{233.4} \times \frac{x}{W} \times 100$$

The oxygen in an organic compound is not experimentally determinated directly. The percentage of oxygen in a compound is obtained indirectly. If the total of the percentages of C, H, N, S, and halogens in a compound is significantly less than 100, the difference is generally taken as the percentage of oxygen. For instance, in a compound containing C, H and O only with 76.6% C, 6.27% H, % oxygen would be 100- (76.6 + 6.27) = 17.13.

Check your progress - 1

How the percentage of amount of oxygen of organic compounds is determined?

.....

.....

28.6 CALCULATION OF EMPIRICAL FORMULA

Empirical formula of a compound is the simplest ratio of atoms of different elements present in the compound, obtained experimentally. Molecular formula, on the other hand, represents the number of atoms of different elements present in a molecule of a compound. Themolecular formula of acetic acid CH_3COOH for example, is $C_2H_4O_2$. But its empirical formula is CH_2O. In some cases molecular formula and empirical formula are one and the same. For instance, CH_3Cl represents empirical formula and as well as molecular formula of methyl chloride. From composition of the compound, its empirical formula may be deduced. Following are the steps in the determination of empirical formula.

(a) Divide the percentage of different elements in the organic compound by the atomic weights of the respective elements. This gives relative number of atoms of the elements in the compound.

(b) Divide the relative number of atoms of different elements with the smallest relative number. The values so obtained are rounded off to nearest whole numbers. These numbers represent the simplest ratio of the atoms of the elements in the compound or the empirical formula of the compound.

Following example illustrates the steps:

Example - 1

An organic compound contains 76.6% C, 6.27% H, and 17.13% oxygen. Calculate the empirical formula of the compound.

Element	% composition	Relative number of atoms	Simplestratio of atoms
C	76.6	$\frac{76.6}{12} = 6.38$	$\frac{6.38}{1.07} = 5.96 = 6$
H	6.27	$\frac{6.27}{1} = 6.27$	$\frac{6.27}{1.07} = 5.86 = 6$
O	17.13	$\frac{17.13}{16} = 1.07$	$\frac{1.07}{1.07} = 1 = 1$

∴ The empirical formula is C_6H_6O

Molecular formula

Molecular formula of a compound is a simple multiple of empirical formula

Molecular formula = n (Empirical formula)

OR

Molecular formula weight or Molecular weight = n (Empirical formula weight)

Where n is an integer

The value of 'n' may be obtained by dividing the molecular weight of the compound with empirical formula weight.

$$n = \frac{\text{Molecular weight}}{\text{Empirical formula weight}}$$

With the knowledge of empirical formula (and therefore empirical formula weight) and the value of 'n' the molecular formula can be determined. Following example illustrates the point.

The empirical formula of a compound is C_6H_6O. Its molecular weight is 91.8 Calculate its molecular formula.

Example- 2

Empirical formula = C_6H_6O

Empirical formula weight = $(12 \times 2 + 1 \times 6 + 16 \times 1) = 24 + 6 + 16 = 46$

$$n = \frac{\text{Molecular weight}}{\text{Empirical formula weight}} \qquad \frac{91.8}{46} = 1.99 \text{ or } 2$$

Molecular formula = n (Empirical formula) = n $(C_6H_6O) = C_4H_{12}O_2$

Various methods are available for the determination of molecular weights of compounds. Depending upon the nature of the compound Victor Meyer's method, Cryoscopic (depression of freezing point) or ebullioscopic method (elevation of boiling point) may be employed (see Course-2 of chemistry). In the case of acids and bases, the equivalent weight may be determined, and multiplied with basicity or acidity to give the molecular weight. The molecular weight of acids and bases may also be determined by silver salt method and chloroplatinic salt method respectively.

28.7 FUNCTIONAL GROUP ANALYSIS

Functional groups in organic compounds are detected by chemical reactions. In all these reactions formation of a precipitate, appearance of a colour or discharge of colour is observed. Following are some characteristic chemical tests for different functional groups.

(i) Tests for carbonyl compounds:

2,4-Dinitro phynyl hydrazone formation: All aldehydes and ketones respond postively to this reaction. To 2,4-dinitrophenyl hydrazine reagent (5 ml) add 1 or 2 drops of the substance. If a yellow red precipitate is formed within 5 minutes, the test is positive. For a solid compound, its solution in ethanol or dioxan is used. If it is a liquid, it can be added directly.

(a) Tollens' test: To a solution of silver nitrate (2ml) ammonical aq. sodium hydroxide solution is added drop by drop with shaking, in a clean test tube, until the precipitate of silver oxide formed just dissolves. This is calledTollens' reagent. To this add 3 to 4 crystals or drops of the compound and if necessary heat on steam bath for 5 minutes. If a black precipitate or silver mirror is formed the test is positive. this test differentiates aldehydes from ketones. With the former the test is postive. Hydroxy ketones, such as fructose, also give positive test.

(b) Fehling's test: To a solution of 0.2 gm of the compound in water or dioxan, Fehling's reagent is added and the mixture is heated on steam bath. If a red ppt. is formed the test is positive. This test differentiates aliphatic aldehydes from aromatic aldehydes. the former gives postiive test.

(ii) Test for phenols

To 0.1 gm. of the compound in methyl alcohol (1 ml) 2 drops of methanolic ferric chloride, are added . Phenols exhibit a vivid colour change.

Phenols are soluble in strong alkali (NaOH) but insoluble in $NaHCO_3$ solution. Phenols react readily with bromine-water and thus discharge the colour of bromine, with evolution of HBr.

(iii) Test for carboxylic acids

Carboxylic acids are strong enough to react with a solution of sodium bicarbonate and evolve carbon dioxide i.e, effervescence is observed.

(iv) Test for alcohols

Alcohols change the colour of Ceric nitrate reagent from yellow to red. To a small quantity of compound in water or in dioxan add 0.5 ml. of the reagent, shake and note the colour.

Alcohols react with sodium metal and evolve hydrogen. rimary, secondary and tertiary alcohols may be differentiated by **Lucas test.**

(v) Test for amines

(a) **Primary amines:** Both aliphatic and aromatic primary amines give postive carbyl amine test. To a small quantity of the substance, few drops of chloroform and alcoholic KOH solution, are added and the solution warm gently. If an offensive odour due to formation of isocyanide is observed, the test is positive.

(b) **Secondary amines:** Both aliphatic and aromatic secondary amines undergo Liebermann's nitroso reaction. To the amine (0.1 gm) a solution of sodium nitrite in water is added dropwise with cooling. Separate the resulting yellow oily substance(N-Nitroso derivative). The yellow oil is mixed with a drop of phenol and conc. sulphuric acid, when a red colour is obtained. The colour changes to green on making the solution alkaline.

(c) Aromatic tertiary amines on diazotisation give C-nitroso dervatives as green solids. Primary, secondary and tertiary amines can be separated and differentiated by Hinsberg's test.

(vi) Test for nitro compounds

All nitro compounds give positive Baker-Mullikan test. To 0.1 gm. of the compound, ammonium chloride (0.5 gm) and zinc dust (0.5 gm) and water (5 ml). are added. Boil the mixture for few minutes and filter into a test tube containing Tollens' reagent. If a black ppt or silver mirror is formed the test is positive.

(vii) Test for amides

Primary amides on strong heating with sodium hydroxide evolve ammonia. To 0.1 gm of the compound 1 or 2 pellets of NaOH are added and heated strongly. If ammonia is evolved, the test is positive.

(viii) Tests for carbohydrates

(a) **Molisch test:** To 0.1 gm. of the compound add 5ml. of water and 2 drops of a strong solution of α-naphthol in alcohol, are added first and then 5 ml. of conc. H_2SO_4 are added down the side of the test tube. A red ring is formed at the junction of the two layers. This is a general test for carbohydrates.

(b) Carbohydrates (mono and disaccharides) are soluble in water, but insoluble in ether.

(c) All reduing sugars give positive test with tollens' and Fehlings reagents.

ix) test for unsaturation

Unsaturated compounds discharge the colour of bromine solutions or the pink colour of Bayer's reagent.

(a) **Bromine in carbon tetrachloride:** Few crystals or drops of the compound are dissolved in 2 ml. of carbon tetracloride, to this a 5% of bromine in carbon tetrachloride is added drop by drop. If the colour of bromine solution is discharged without evolution of HBr the test is positive.

(b) **Baeyer's test:** 2-3crystals or drops of the compound are dissolved in water or alcohol (2 ml) and add a 2% aq. solutin of $KMnO_4$ drop by drop. If the pink colour of the reagent is discharged the test is positive.

The structure determination of a complex organic compound, isolated from plant or animal source also requires chemical degradation of the molecule into smaller molecules. Identification of these smaller molecules considerably helps in understanding the structure of the complex molecule. The structure assigned to the compound is finally confirmed by its synthesis by unambiguous methods starting from smaller molecules of known structure, and establishing the identity of synthetic sample with the compound isolated from the natural source.

28.8 SUMMARY

In this unit the methods of evaluation of purity of organic compounds, detection and estimation of different elements of organic compounds are presented. There are no direct methods of detection and estimation of oxygen. Extra elements are detected by Lass aigne's method. Nitrogen can be estimated by either Dumas method or kjeldahl's method. Sulphur and halogens are estimated by Carius method. Empirical formula and molecular formula are related . E. form. x n = Mol. form.

Functinal groups of organic ompounds are identified by different chemical and physical tests. In adition to the above the synthesis of the organic compound isolated in the laboratory finally proves the structure proposed.

28.9 MODEL EXAMINATION QUESTIONS

I Answer each of the following in 10 lines

1. How are the presence of nitrogen and halogens in an organic compound tested, using its soidum fusion extract?
2. outline the Dumas method for the estimation of nitrogen.
3. How are halogens and sulphur in an organic compound estimated?
4. How is empirical formula of a compound determined?

II Answer each of the following in 30 lines

1. Analysis of an organic substance (A) containing C, H and O only, gave the following results: 0.2115 gm of the substance gave 0.4655 gm CO_2 and 0.2533 gm H_2O. Its vapour density was found to have 29.7. The compound reacted with sodium metal liberating hydrogen. The compound on oxidation gave compound (B) which gives positive Iodofrom test. What are A andB?
2. An organic compound contains 78.6% C, 8.42% H and 13.06% N. Its molecular weight was found to be 106.8. The compound gives positive carbylamine test. What possible structural formulae may be assigned to the organic compound?

28.10 MODEL ANSWERS TO CHECK YOUR PROGRESS

1. The percentage amount of oxygen is calculated by the substraction of the sum of the percentages of all other elements from 100.
2. Ammoniacal solution of silver nitrate with little alkali is called Tollen's reagent. Its formula is $(Ag(NH_3)_2]^+ + OH^-$.

Author: Dr. P.S.N. Reddy

UNIT 29 ORGANIC STRUCTURAL DETERMINATION

Contents

29.1 AIMS AND OBJECTIVES

To outline the principle and applications of ultraviolet and infrared spectroscopy in the structure determination of organic compounds.

Once you complete the study and understanding of the contents of this unit, youmust be able to:

- remember different types of electromagnetic radiation, their wavelength and frequency
- realise the importance of absorption spectroscopy in structure determination

(i) **U.V. spectroscopy:** Electronic transitions, chromophores and auxochromes, conjugated systems.

(ii) **Infrared spectroscopy:** Molecular vibrations, infrared absorption frequencies.

29.2 INTRODUCTION

Spectroscopy has become the most widely used tool in chemistry today. It has been used in the elucidation of structure of complex organic and inorganic ompounds. Spectroscopy deals with the interaction of electromagnetic radiation with matter.

29.3 ELECTROMAGNETIC RADIATION

Electromagnetic radiation is a form of energy. Visible light is an example of radiation which occupies only a small region in the spectrum of electromagnetic radiation. You have learnt in Course-2 that electromagnetic radiation may be regarded as electric waves moving through space in a wave like motion. A wave of electromagnetic radiation can be described by its wavelength.

Following are the wavelength ranges of different regions of electromagnetic radiation:

Radiation	Wavelength
X-rays	0.1 - 100 m μ
Vacuum ultraviolet light	100 to 100 mμ
Visible light	400 to 800 mμ
Near infrared light	0.8 μ - 2.5 μ
Infrared light	2.5 μ - 25 μ
Microwave region	> 25 μ

29.4 ABSORPTION SPECTROSCOPY

Absroption of radiation causes certain changes in the molecules. The exact nature of the change depends on the wavelength of radiation absorbed. Absorption of U.V. and visible radiation by organic molecules causes electronic excitation i.e, an electron form bonding or nonbonding orbital is promoted to antibonding orbital. Infrared radiation, on the other hand, influences the vibrational and rotational states of covalent molecules.

An absorption spectrum is obtained by placing the compound (in the suitable state) between the spectrometer and the source of appropriate radiation viz. I.R. or U.V. - visible light. The spectrometer analyses the relative intensities of incident and transmitted lights at different wavelengths. Plot of these absorbed light (or transmitted light) versus wavelength is called an absorption spectrum. The ultraviolet and infrared spectra are extremely useful in the structure elucidation of organic compound. The former are useful in understanding the nature of multiple bonds or conjugation in the molecules. The latter, however, give valuable information about the functional groups.

29.5 ULTRAVIOLET SPECTROSCOPY

The absorption of light in the U.V. and visible range excities the valence electrons in the molecules. The electrons in a molecule will be present in bonding orbitals (σ and π orbitals), non-bonding orbitals (n-orbitals) and probably also in antibonding orbitals [σ^* (singma starred) and π^* (pi starred) orbitals]. By absorption of U.V. - visible radiation of appropriate wavelength, an electron from σ, π or n molecular orbital is promoted to an empty σ^* or π^* molecular orbital. You have already learnt in Course-2, that the diffrent electronic transitions that can be envisaged in a molecule are ,$\sigma - \sigma^*$, $\pi - \pi^*$ and $n - \sigma^*$. The energy required to bring about the transition. $\sigma - \sigma^* > \pi - \pi^* > n - \sigma^*$.

SOME TYPICAL APPLICATIONS

In ethane $\sigma - \sigma^*$ transition (of C-C σ bond) occurs at 154 m μi.e, in the vacuum U.V. region. Similarly in ethylene the $\pi - \pi^*$ transition (of C=C double bond) occurs at 180 m μ. Therefore we say that saturated molecules and simple olefins of not absorb in the regular U.V and visible region and therefore are colorless. Two transitions, $\pi - \pi^*$ and $n - \pi^*$ are possible in formaldehyde which has a pi bond and nonbonding electrons. These occur at 185 m μ and 270 m μ respectively. The absorption at 185 m μ resutls in a strong band whereas that at 270 m μ is responsible for a weak band.

H_3C-CH_3	$H_2C=CH_2$	$H-C=O$ | H
Ethane	Ethylene	Formaldehyde
$\sigma - \sigma^*$ transition	$\pi - \pi^*$ transition	$\pi - \pi^*$ transition (λ = 185 mμ)
(λ=154 mμ)	(λ= 180mμ	$n\pi^*$ transition (λ = 270 mμ)

Chhromophores

Multiple bonds, such as C=C andC=O , which are responsible for $\pi - \pi^*$ or n transition are called chromophores. Multiple bonds such as, C=N,N=N, C=S and N=O are examples of other chromophores. These chromophores in simple molecules absorb at different wavelengths and explain the colour of compsounds.

Chromophore	Compound	λ (mμ)	Colour of the compound
C=C	$CH_2=CH_2$	180	colourless
C=N	$(H_3C)_3C-CH=N-C(CH_3)_3$	250	colourless
C=O	$(CH_3)_2C=O$	280	colourless
N=N	$CH_3N=N-CH_3$	347	Pale yellow
C=S	$(CH_3)_2C=S$	400	light yellow
N=O	$CH_3-CH_2-CH_2-N=O$	665	blue green

Check your progress - 1

What do you mean by a chromophore?

.....

.....

.....

.....

Auxochromes

Functional groups that do not absorb in the U.V. visible region (above 200 m) but (when attached to a chrmophoric system) influence the absorption of chromophores are called auxochromes. Auxochromes cause a shift in the absorption to longer wavelength (bathochromic shift) and increase the intensity of the absorption peak. Common auxochromic groups are hydroxy, amino, mercapto groups (and their derivatives) and halogens, Pi bonds are not present in these groups. But they all contain nonbonding electrons.

Conjugated systems

Two or more chromophores may be present in molecules. When these groups are directly linked by a single bond a conjugated system results. In ia conjugated diene two sets of doubly bonded carbons are directly linked by a single bond: > C = C - C= C (conjugated diene).

Different conjugated systems result when a carbon-carbon double bond is directly linked by a single bond to other chromophores. Due to conjugation, electron excitation in these systmes occurs readily i.e, absorb radiation of longer wavelength. In butadiene $\pi - \pi^*$ occurs at 217 m. The presence of conugated multiple bonds in moelcules leads to bathochromic shift. The wavelength of radiation absrobed by some of the simple conjugated systems given below:

Chromophore	Compound	λ (m μ)
C=C-C=C	1,3 Butadiene	217
C=C-C=C	Vinylacetylene	219 and 228
C=C-C=C	Crotonaldehyde	218 and 320
C=C-C=N-	N-n-butyl cortanaldimine	219
C=C-NO_2	1-Nitro-1-propene	229 and 235
O=C-C=O	glyoxal	195 and 463

Benezene absorbs at 203 mμ but in conjugated systems like aniline (230 mμ) and benzophenone (252mμ) the absorption shifts to longer wavelengh (Fig 29.1)

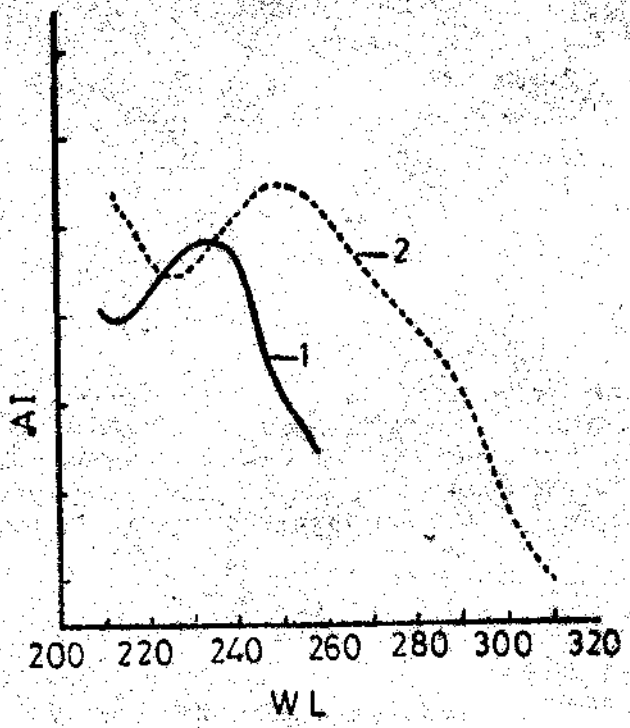
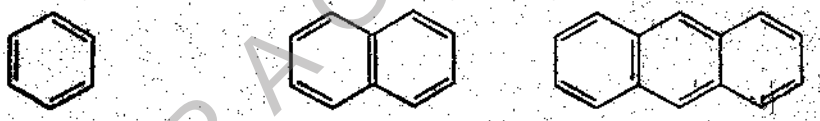


Fig 29.1 U.V. spectra of 1) Aniline and 2) benzophenone
Al= Abrooption Intensity WL = wave lengnth

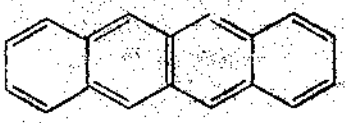
The colour of polynuclear aromatic compounds increases with the increase in the number of benzene rings. This is due to the presence of extended conjugation in the molecules.



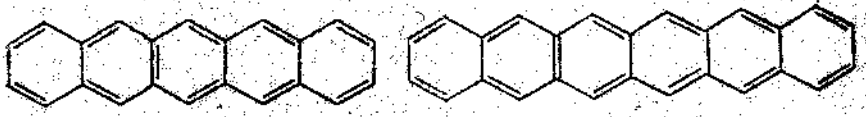
Benzene
λmax 203 m
(colourless)

Napthalene
λmax 314 m
(colourless)

Anthracene
λmax 380 m
(buff colour)



Napthacene λ max 480 mμ (yellow)



Pentacene, λmax 580 mμ
(blue)

Hexacene, λmax 600 mμ
(green)

If two or more chromophoric groups, ina molecule, are separated by two or more single bonds, an isolated unsaturated system results. Penta-14-diene is an isolated diene.

CH_2=CH-CH_2-CH=CH_2
(Penta-14 -diene

The effect of two isolated chromophores on the intensity of absorption band of the molecule is additive, but does not significantly influence the wavelength of absorption.

Ultraviolet spectra, do not provide information about individual bonds (functional groups); rather they are characteristic of multiple bonds. They reflect the extent of conjugation of multiple bonds, and other structural features such as steric hindrance and hydrogen bonding which influence conjugation.

Check your progress-2

What do you mean by a bathochromatic shift?

.....

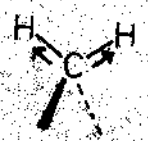
.....

.....

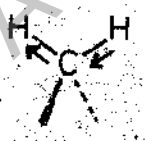
.....

29.6 INFRARED SPECTROSCOPY

Infrared spectroscopy is another spectroscopic technique used in the analysis of organic compounds. A molecule resembles a system of balls of varying masses corresponding to the atoms and springs of varying strengths corresponding to chemical bonds of a molecule. The number of vibrations in a molecule increases with increasing number of atoms. The number of vibrations possible in linear and non-linear molecules containing 'n' atoms are 3n-5 and 3n-6 respectively. For example the number of vibrations in CO_2 is 4 (3 x 3-5) and the number of vibrations in H_2O is 3(3 x 3-6). The molecule vibrations are broadly classified into two types viz. stretching vibrations and bending (or deformtion) vibrations. In stretching vibration of a bond the distance between two atoms increases and decreases but the atoms remain in the same bond axis. Stretching vibrations are further classified as symmetric and asymmetric stretching vibrations.



a



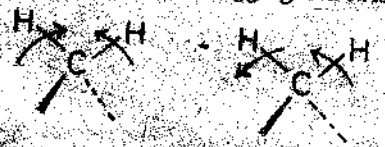
b

a. **Symmetric stretching vibration (the bond distance increses in both the C-H bonds) as shown by the arrow head)**

b. **Asymmetric stretching vibration (the bond distance in one C-H bond increases and in the other it decreases)**

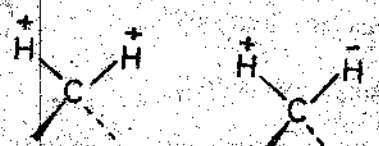
Stretching vibrations

In bending vibrations the position of the atoms changes relative to the original bond axis. Bending vibrations are differentiated into inplane bending vibrations (scissoringand rocking) and out-of-plane bending vibrations (wagging and twisting)



I a I b

I



II a II b

II

I. **In-plane bending vibrations**
I. **a. Scissoring. I. b. Rocking**

II. **Out-of-plane bending vibrations**
II **a. wagging II. b. Twisting.**

Bending vibrations

The sign + and - represent the vibration above and below the plane of paper.

Infrared spectrum of compound is a plot of the relative intensity of the light transmitted by the compound at different frequencies (or wavelenghts) of radiation in the I.R. range. Only vibrations that cause change in the dipolemoment of a molecule result in the absorption of charactreistic frequencies of I.R. radiation and also transmit characteristic frequencies. The frequencies ofstretching vibrations increase with increasing bond strength. The force constants of the bonds increase from the single bond to triple bond i.e, the strengh of the bonds : C-N>C=N>C-N. Accordingly the absorption frequencies of these bonds are about 2250 cm^{-1}, 1650 cm^{-1}, respectively. The frequency of absorption of a bond also increases with decreasing atomic masses. The stretching frequencies of the C-Br (500-600 cm^{-1}), C-Cl (600-800cm^{-1}) and C-F (1000-1400 cm^{-1}) bonds, O-H (3570cm^{-1}) and O-D (2630 cm^{-1}) bonds illustrate this point.

From the spectra of a large number of organic compounds chemists assigned frequency ranges for different bonds. Some of the vlaues are given below:

Bond type	Frequency range (cm-1)
H-Csp^3	2850-2960
H-Csp^2	3010-3040
H-Csp	3250-3300
C=C	1620-1680
C-C	2100-2260
C-N	2215-2260
C-O	1060-1270
C-F	1000-1400
C-Cl	600-800
C-Br	500-600
O-H	3590-3650
N-H	3300-3500
S-H	2500-2600

Bending vibrations generally require less energy and occur at longer wavelength (lower wave number) than stretching vibrations of the same bond. Absorption peaks resulting from the stretching vibrations are usually most intense peaks in the spectrum. Many of the absroption bands cannot be assigned acurately. But those that can be assigned provide valuable information about the structure of a molecule.

29.7 CHARACTERISTIC INFRARED ABSOPTION FREQUENCIES OF FUNCTIONAL GROUPS

Some of the functional groups whose absorptions can be easily interpreted are given below. If a spectrum does not contain a peak at the frequency assigned to a certain functional group, the molecule does not contain that funcitonal group.

a) Carbonyl compounds

A peak due to absroption by carbonyl group is expected in these compounds. The frequency of stretching vibration varies with the nature of the carbonyl compound.

Aldehyes and ketones

Aliphatic carbonyl compounds	1720-1740 cm^{-1}.
Carbonyl group in cyclohexanone	1715 cm^{-1}.
Aromatic carbonyl compounds and α, β-- unsaturated aliphatic carbonyl compounds	1670-1690cm^{-1}
Carbonyl group involved in hydrogen bond	1600-1640 cm^{-1}

Saturated cyclic ketones

4 membered = 1775 cm^{-1}
5 membered = 1740-1750 cm^{-1}
6 membered and higher = 1705 - 1725cm^{-1}

The carbonyl compounds are best identified by IR spectra. The strong band due to C=O stretching appeatrs at about 1700 cm^{-1}. It is one of the most useful bands. Typical IR spectra of an aliphatic aldehyde (n-butyraldehyde) and an aromatic ketone (acetophenone) are presented in Figures 29.2 and 29.3.

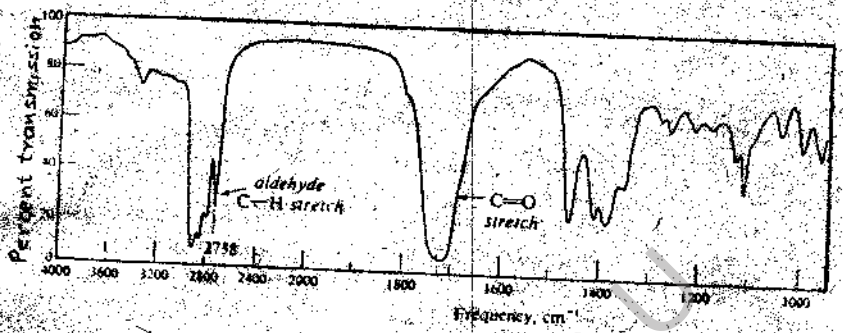


Fig. 29.2 IR spectrum of n-Butyraldehyde

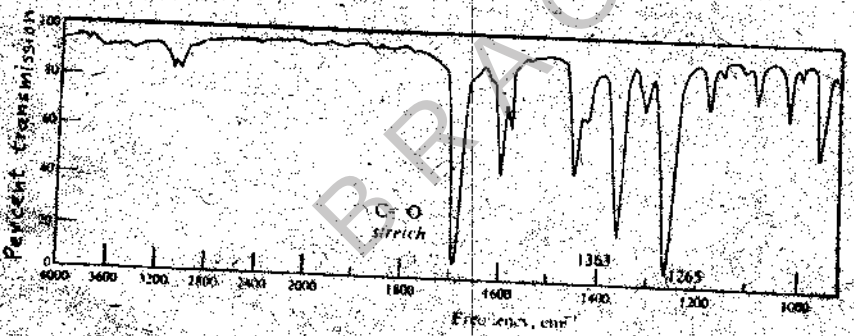


Fig. 29.3 IR spectrum of Acetophenone

b) Esters

saturated acyclic esters = 1735-1750 cm^{-1}.
saturated cyclic esters
5 membered (β - lactones) = 1820cm^{-1}
6 membered (γ - lactones) = 1760-1780cm^{-1}
7 membered (lactones) = 1735-1750 cm^{-1}
larger rings

Esters (-COOR) are distinguished from acids (-COOH) by the absence of band due to -OH group. They are also differentiated from ketones (C=O) by two strong C-O stretching bands in the region 1050-1300 cm^{-1}. The exact position of the bands depends on the structure of the ester. Typical IR spectrum of methyl acetate is presented below.

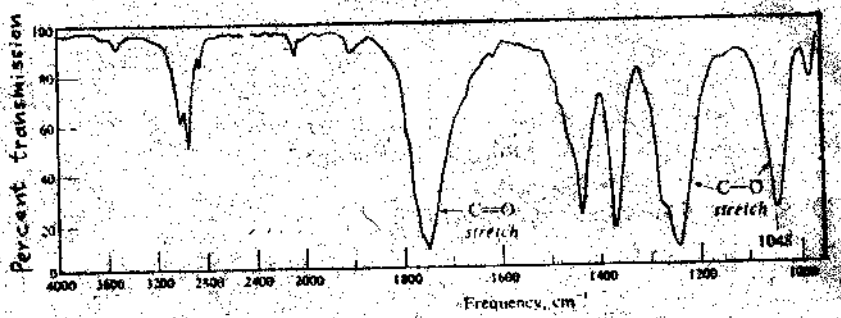


Fig. 29.4 IR spectrum of Methyl acetate

C) Alcohols and phenols

In these compounds absorption by OH group results in a peak. The stretching vibrations of the hydroxy groups in different compounds are given below:

i) Alcohols

Monomolecular-unassociated alcohols	= 3590-3650 cm^{-1}
Intermolecularly hydrogen bonded OH group (changes on dilution)	= 3450-3550 cm^{-1}
Intramolecularly hydrogen bonded -OH group (no change on dilution)	= 3450-3570 cm^{-1}

The most significant feature is a strong broad band in 3200-3600 cm-1 region due to O-H stretching. Another strong broad band due to C-O stretching appears in the 1000-1200 cm^{-1} region. The exact value depends on the nature of alcohol. Typical IR spectra of an aliphatic alcohol (Sec-butyl alcohol) and an aromatic alcohol (benzyl alcohol) are presented in figures 29.5 and 29.6.

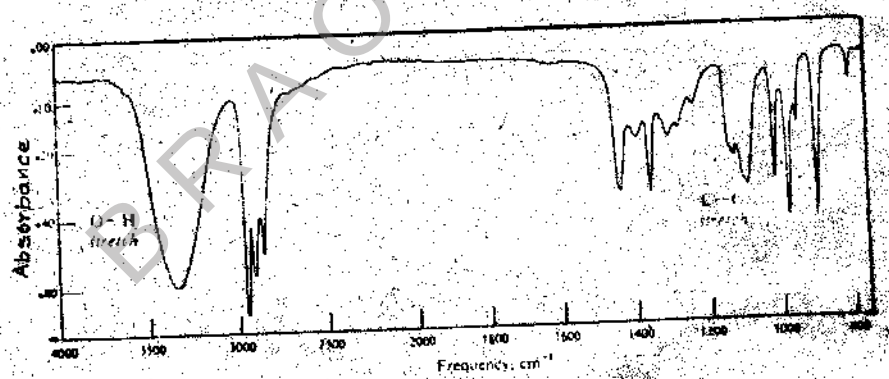


Fig. 29.5 IR spectrum of Sec-bytyl alcohol

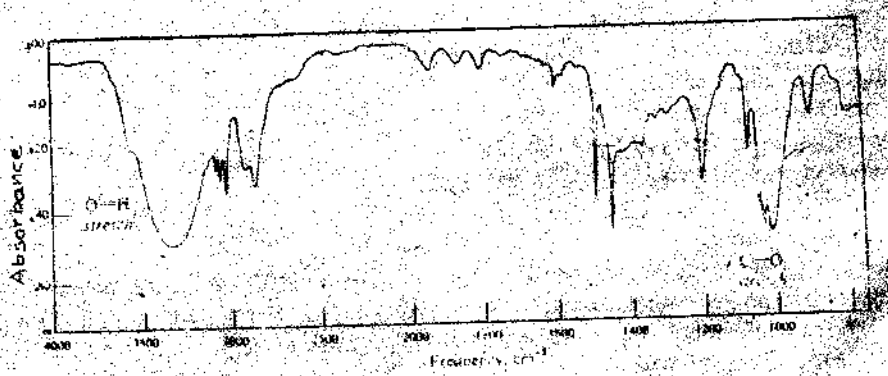


Fig. 29.6 IR spectrum of benzyl alcohol

ii) **Phenols**

Monomolecular phenols	~	36.. ' cm^{-1}
Intermolecularly associated phenols	~	3610 cm^{-1}
Intramolecularly associated phenols	~	3100 cm^{-1}.

Phenols also show the bands like alcohols. But the C-O stretching appears at higher frequencies. The spectrum of a typical phenol (p-Cresol) is shown in Figure 29.7. Phenols show peak at about 1230 cm^{1} while alcohols show at 1050 - 1200 cm^{-1}.

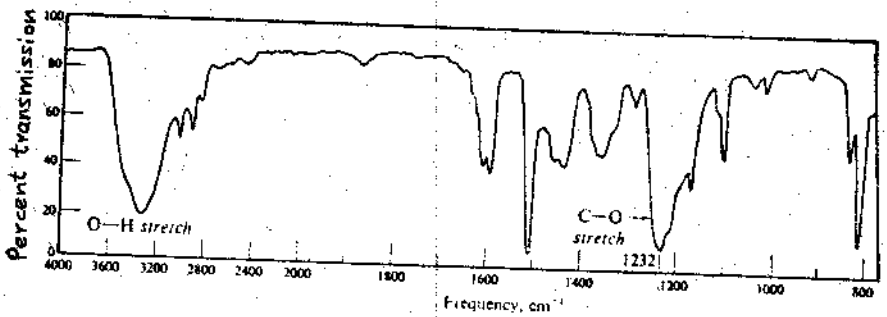


Fig. 29.7 IR spectrum of p - Cresol

d) **Carboxylic acids**

The stretching vibrations of carbonyl and hydroxy groups in these compounds occur at 1700-1725 cm^{-1} and 3520 cm^{-1} respectively.

It is obvious that -COOH group is made up of both C=O group and -OH group. The IR spectrum reflects both these structural units. For hydrogen bonded (dimeric) acids, O-H stretching band (broad) occurs at 2500-3000cm^{-1}. Acids show C-O stretching band at about 1250 $cm^{-1}$and OH bending near 1400 cm^{-1} and 920 cm-1 (broad). Spectra of typical acids propionic acid and o-toluic acid are presented in Figures 29.8 and 29.9.

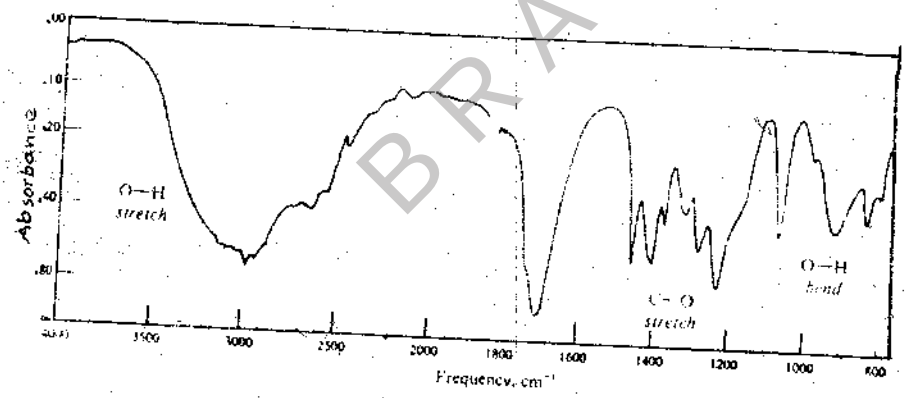


Fig. 29.8 IR spectrum of Propanic acid

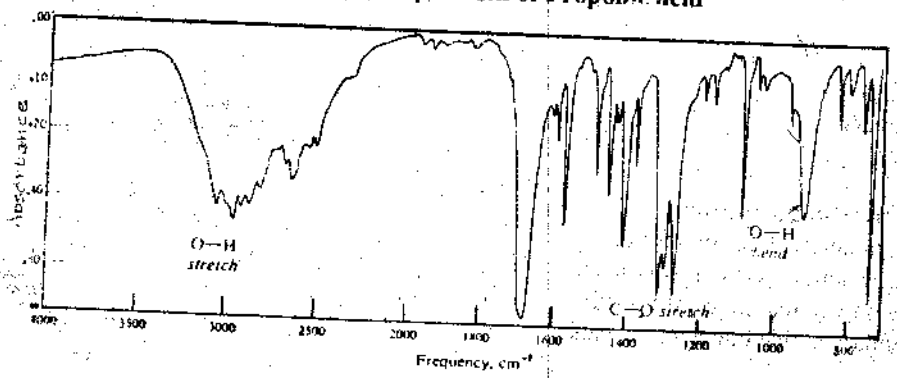


Fig. 29.9 IR spectrum of 0-toluic acid

e) **Amines**

Folowing are the stretching vibrations in amines due to N-H funciton:

Primary amine, free (two bands)	3400 cm-1 and 3500 cm^{-1}
Secondary amine (free one band)	3310 - 3500 cm^{-1}.

Amines exhibit bands whose position and number depend on the class to which the amine belongs. -NH stretching bands as mentioned above and NH bending bands at 650-900 cm^{-1} (broad) and at 1560-1650 cm^{-1}

Besides these CN stretching at 1030-1230 cm^{-1} (weak) for aliphatic compounds and two at 1180-1360cm^{-1} (strong) for aromatic compounds.

Spectra of typical compounds; isobutylamine and N-methyl aniline are presented in figures 29. 10 and 29.11.

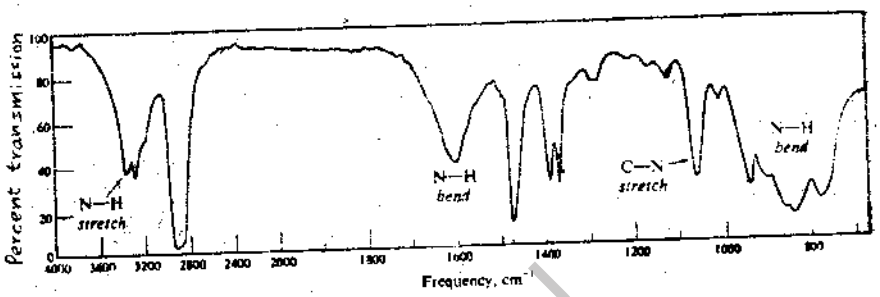


Fig. 29.10 IR spectrum of isobutyl amine

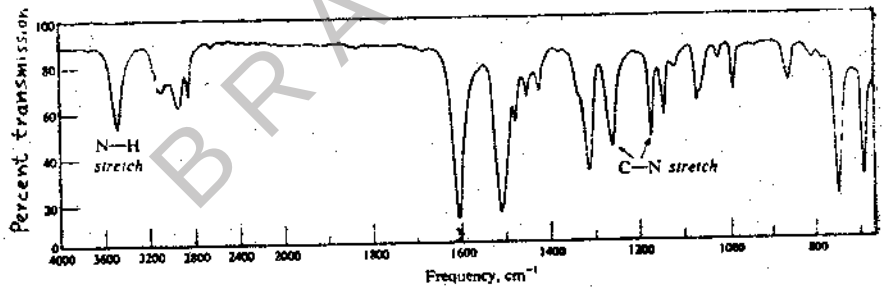


Fig. 29.11 IR spectrum of N-methyl aniline

f) **Amides**

(i)	**Carbonyl Stretching vibrations**	
	Primary	1650 cm^{-1}
	Secondary	1630-1680cm^{-1}
	Tertiary	1630-1670cm^{-1}
ii)	**NH stretching vibrations**	
	Primary amine, free (two bands)	3400 cm^{-1} and 3500 cm^{-1}
	Primary amide, bonded (two bands)	3180 cm^{-1} and 3350 cm^{-1}
	Secondary amide, free (one band)	3430 cm^{-1}
	Secondary amide bonded (one band)	3140 - 3320 cm^{-1}.

Amides (-CO NH_2) show absoption due to N-H stretching in the region 3050-3550 cm^{-1} besides C=O band. N-H bending band occurs in the region 1600-1640cm^{-1}. Typical spectra of benzamide is shown in Figure 29.12.

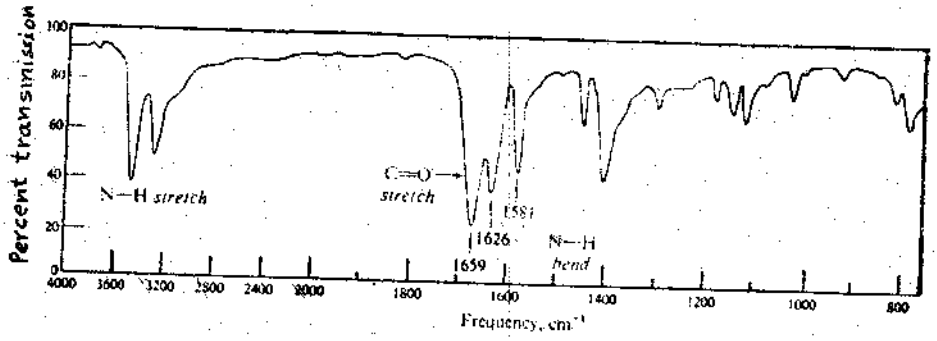


Fig. 29.12 IR spectrum of benzamide

g) Azides

These absorb at 2120-2160 cm-1

h) Nitro compounds

The nitro group in nitro aromatic compounds give two strong peaks at 1300-1370 cm^{-1} and 1500-1570 cm^{-1}. In aliphatic nitrocompounds these peaks are observed at 1370-1380 cm^{-1} and 1550-1570 cm^{-1}. These are four absroption bands in the region 1430-1670 cm^{-1} that are particularly diagnostic of aromatic structure. The absence of absorption in this region is fair assurance that the compound is not aromatic.

The region of infrared spectrum, 910-1430 cm (μ 7-11) is particularly rich in absorption bands and is characteristic of a compound. This region of spectrum is called the finger print region. Although similar molecules show very similar spectra in the region 1430-4000 cm^{-1}, but they will have different spectral characteristics in the finger print region. Perhaps the most powerful function of IR spectroscopy is establishing conclusively the identity of two samples that have identical spectra when determined in the same medium.

29.8 SUMMARY

Spectroscopy is the study of interaction of electromagnetic radiation with the matter. It is an important method of structure determination.

Based on wavelength electromagnetic radiation is classified into different types. Absorption spectrum of a compound is a plot or graph between Io/It and wavelength or wave number. Absorption of U.V.radiation by organic molecules usually causes $n\text{-}\pi^*$ and $\pi\text{-}\pi^*$ electron transitions. Functional groups which undergo these transitions are called chromophores. Those groups without π - bonds that affect the absorption bands of chromophores are called auxochromes. Shift of absorption to longer wavelength region is called bathochromic shift and the opposite shift is hypsochromic shift. Based on U.V. spectroscopy the type of conjugation in organic compounds can be determined.

By the absorption of infrared radiation usually the frequencies of stretching and bending vibrations of bonds get increased. Based on the postions of absorption bands in the infrared spectrum of a compound it is possible to detect its functional groups. In the infrared spectrum the region 910-1430 cm^{-1} is called finger print region which is characteristic of every compound. Two samples indicate the same compound if they possess superimposable infrared spectra.

Dr. B.R. AMBEDKAR OPEN UNIVERSITY
Faculty of Science
(Under Graduation Programme)
III YEAR
CHEMISTRY COURSE - III

Assignment - 3

N.B:-

1. Do not copy the answer directly from any of the books
2. As far as possible try to answer the questions independently in your own words.
3. If it is necessary to quote from any source give the correct reference.
4. Use your own fullscape pages for writing the assignment.
5. Leave sufficient margins for the comments of dthe evaluator.
6. Completion of this assignment normally should not take more than two hours time.

SECTION - A

I Answer the following in 30 lines

1. Describe theree methods for the preparation of primary aminos. How does aniline react with the following:-
   a) Acetic anhydride b) Benzoylchloride

2. Discuss the open chain structure of glucose.

3. Describe Paal-Knorr pyrrole synthesis. Why pyrrole exhibits acidic properties.

SECTION - B

II Answer the following in 10 lines

1. What is racemmic mixture? Give any two examples.

2. Define and explain the following :
   i) Zuitter ion
   ii) Isoelectric Point.

3. What are apimers and enantiomers? Give an example for each.

Dr. B.R. AMBEDKAR OPEN UNIVERSITY
Faculty of Science
B.Sc. III Year (3 YDC) Examination
Model Question Paper

CHEMISTRY COURSE - III

Time: 3 hours

Max. Marks : 75
Min. Marks: 27

SECTION - A

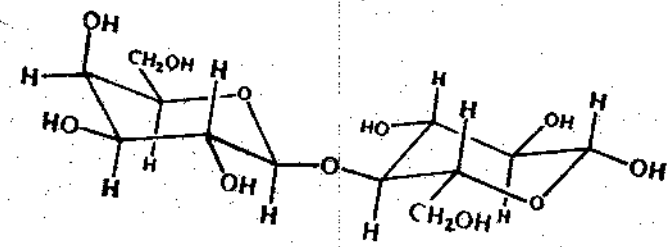
Note: Answer any three of the following :-
Each question carries 15 Marks.
Answer the following in about 30 lines

1. Explain the terms Rate Constant), order land molecularity of a reaction. Derive an expression for the rate constant of a first order reaction.
2. Describe the structural isomerism in co-ordination compounds.
3. Give the composition of two important ores of Silver. Describe the method of extraction of Silver from one of the ores.
4. Discuss Debye-Huckel theory of strong electrolytes.
5. Discuss the merits and demerits of Bayer's strain theory.
6. Discuss the cyclic structure of D-glucose.

SECTION - B

Note: Answer any five of the following :-
Each Question carries 6 marks.
Answer the following in about 10 lines.

7. Give the different forms in which the first law of thermodynamics can be expressed.
8. Discuss the magnetic properties of transition metals.
9. Explain the effective atomic number concept proposed by Sidgwick.
10. Explain the valence bond theory of metallic bond.
11. Explain the terms Roasting, Calcination and Smelting.
12. Write the phenomenon of Keto-Enol tantomenism with a suitable exmaple.
13. What are amino acids? Describe any three methods of their synthesis.
14. Write a note on gold number.
15. Write the resonance structures of Furan.
16. What are ligands? Give their classification.

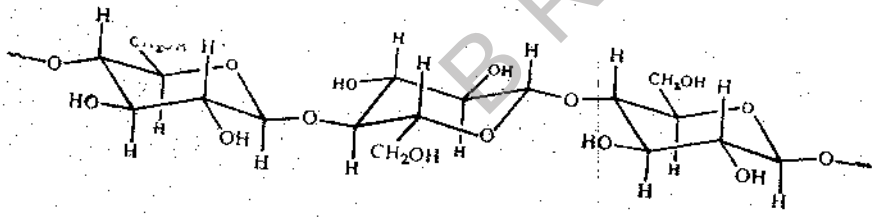


Lactose
(β-anomer)

26.4 POLYSACCHARIDES

Polysaccharides are high polymers of the monosaccharides. Some of the polymers, eg. starch, are useful as structural materials in plants. Starch and glycogen serve as reserve food in plants and animals respectively. The composition of cellulose and starch corresponds to the formula $(C_6H_{10}O_5)n$. The polysaccharide, chitin, is the structural material in lower animals, eg. shells of crustaceans. Thus, polysaccharides are biopolymers.

A) Cellulose: The molecular formula of cellulose is $(C_6H_{10}O_5)n$. It is most widely distributed polysaccharide. Regardless of the source, cellulose has same constitution, only its fine structure varies. The molecular weight of cellulose ranges between 200,000 - 800,000 (n=1300 to 5000). Acid hydrolysis of cellulose gives a qunatitative yield of D-glucose. Therefore cellulose is homoglucan. complete methylation, acetylation or nitration of cellulose results in a trisubtitution product. Thus, in each D-glucose unit of cellulose there are three free hydroxyl groups. Fully methylated cellulose on hydrolysis yields 2,3,6 tri-O-methyl-D-glucose. Therefore in D-glucose units in cellulose free hydroxyl groups are present in 2,3 and 6-postions, and the hydroxyl groups in 1,4 and 5-positions must be involved in some sort of linkages. when cellulose is subjected to acetolysis (simultaneous acetylation and hydrolysis by using a mixture of acetic anhydride and conc. sulphuric acid), cellobioseoctaacetate is formed. From this it follows that, in cellulose, D-glucose units are present in pyranose from (-OH group on C-5 is involved in ring formation) and D-glucose units are linked by - linkages to give the polymer. The polymer chain is formed by joining D-glucose units through -OH group on C-1 of one unit and the -OH group on C-4 of the other unit, and so on.



A Segment of cellulose molecule

Cellulose forms fibres. The molecule in all likelihood may be linear. X-Ray analysis supports the linear nature of the molecule. Long chains of cellulose segments are held together by hydrogen bonding. Cellulose, therefore, produces strong fibres with great rigidity and no flexibility.

B. Uses of cellulose and its derivatives

a) Cellulose

i) **Viscose rayon:** Treatment of a solution of cellulose in sodium hydroxide with carbon disulphide gives a viscous colloidal solution of cellulose xanthate. This is called viscose. When viscose is forced through a spinneret (a tube closed at one end with tiny orifices) into an acid solution, cellulose fibres are formed. These are called rayon and are used to produce textiles. Rayon is regenerated cellulose.

ii) **Cellophane:** When viscose is extruded on to rollers in an acid medium, thin films of cellophane are obtained. Cellophane is a useful packing material.

b) ***Cellulose dinitrate (proxylin)***

i) Cellulose dinitrate is insoluble in ether and alcohol but soluble in 1:1 mixture of ether and water. The solution is called collodion. When this is spread on a wound and the solvent allowed to evaporate, a transparent, protective film resembling skin is produced. For this reason pyroxylin is nicknamed as new skin.

ii) **Celluloid:** When a mixture of collodion and camphor is heated, a gelatin is obtained which thickens to a plastic. This plastic is called celluloid.

Cellulose trinitrate is called gun cotton, and is used as a propellant.

c) ***Cellulose acetate***

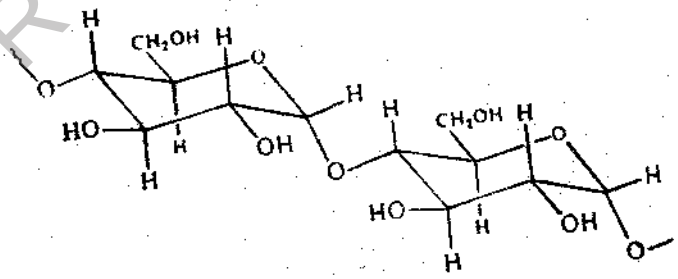
It is used in the preparation of safety glass and acetate rayon.

i) Safety glass is obtained by passing a solution of cellulose acetate in acetone between two layers of glass. This prevents the glass pieces from flying apart when shattered.

ii) **Acetate rayon:** When cellulose acetate solution is forced out of a spinneret, fine filaments of cellulose acetate are obtained. These fibres are called *acetate rayon*.

C. Starch:

The molecular formula fo starch is $(C_6H_{10}O_5)n$. Hydrolysis of starch gives D-glucose in quantitative yield. Methylation of starch produces a trimethyl derivative. This on hydrolysis produces 2,3,6-tri-O-mehtyl-D-glucose as the main product. Starch is hydrolysed by the enzyme *diastase* to give maltose. Thus maltose units are present in starch. i.e, several D-glucopyranose units are linked through 1,4,positions by α-linkages.



A segment of starch molecule

Viscosity measurments show that starch has highly branched structure. Starch can be separated into two fractions, α-amylose and β -amylose. When butanol is added to a hot colloidal solution of starch in water and the mixture is allowed to cool to room temparature α-amylose is precipitated. β-Amylose or amylopectin is obtained by the addition of methanol to the mother liquors. - Amylose is soluble in water and gives a blue colour with iodine. β- Amylose is insoluble in water gives a violet colour with iodine. Both the amyloses are polymers and their molecular weight depends upon the method of preparation and the starch used.

UNIT 27 OPTICAL ACTIVITY

Contents

27.1 AIMS AND OBJECTIVES

To explain about plane polarised light, optically active compounds, racemisation, resolution, absolute configuration and R, S-configurational nomenclature of organic compounds.

After a detailed study and understanding of the contents of this unit, you are supposed to:

describe optical activity, plane polarized light and polarimeter.

explain enantiomers and their characteristics.

find out the number and the type of optical isomers of organic compounds containing (i) one asymmetric carbon (ii) two similar asymmetric carbon stoms and (iii) two dissimilar asymmetric carbon atoms.

know racemisation and the methods of resolution of racemic mixtures

realise the importance of D, L. and R,S notations. and the determination of absolute configuration

27.2 INTRODUCTION

Isomers are the compounds of the same molecular formula that differ in properties. The particular kind of isomers that are different from each other only in the way the atoms are oriented in space are called stereoisomers. Stercoisomers that can rotate the plane of vibration of polarised light are optical isomers. Optical isomers differ in their biological activity, sign of optical rotation and reactivity with other optically active compounds.

27.3 OPTICAL ACTIVITY

When plane polarised light is passed through a solution of an optically active substance, it emerges from the solution in a different plane (Appendix -I). The ability of a compound to rotate the plane polarised light is known as pitcal activity.

Substances that rotate the plane polarised light to the right are called dextrorotatory (d), and those rotating the plane polarised light to the left are called levorotatory (l). The angle of rotation is dependent on concentration of the solution, temperture, solvent used, the wavelength of the light used and the length of the light of the light path through the solution.

The specific rotation of a substance, $[\alpha]^{t}_{\lambda} = \frac{\alpha}{l \times c}$

Where α = measured rotation in degrees,

l = length of the polarimeter tube in decimeters

c = concentration in grams per ml. of the solution (for neat liquids 'c' is replaced by the density of liquid, g/ml)

t = temperature

λ = wavelength of light used

The temperature, solvent and the wavelength of light should also be indicated while reporting specific rotation. Thus specific rotation is defined as the rotation produced by a solution containing one gram/ml of a substance in a 1 decimeter long tube. For eg. $[\alpha]^{25^0}_{D} = -66$ means that the compound is laevorotatory and its specific rotation at 25° using sodium vapour lamp (589.3 nm) as the light source is-66°.

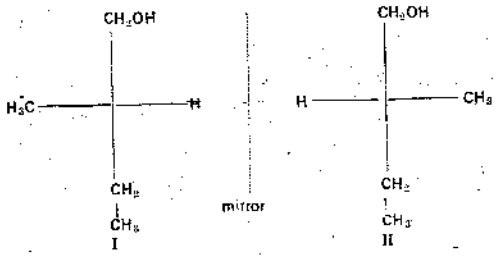
Sometimes molecular rotation [M] is used in preference to specific rotation.

The molecular rotation is the product of specific rotation and the molecular weight.

$$[M]^{t}_{\lambda} = \frac{[\alpha]^{t}_{\lambda} \times M}{100}$$ M --Mol.wt. of the compound

vant Hoff and **Le Bel** related the phenomenon of optical activity of organic compounds to the presence of an asymmetric carbon. A tetrahedral carbon atom linked to four different groups is called an asymmetric carbon. Now it is known that some compounds without an asymmetric carbon can also exhibit optical activity. Further certain stereoisomers of compounds containing two or more asymmetric carbon atoms have been found to be optically inactive. Now it is accepted that the necessary and sufficient condition for a compound to exhibit optical activity is that it should exist as two non-superimposable structures with mirror image relationship.

For instance, 2-methyl-1-butanol $HOH_2C\text{-}CH(CH_3)\text{-}CH_2\text{-}CH_3$- contains an asymmetric carbon (marked with asterisk). It is linked to four different groups viz. CH_2OH,H,CH_3 and CH_2CH_3.Two stereoisomers of 2-methyl-1-butanol are possible. The Fischer projection formulae (Appendix -II) of the two stereoisomers are given below.



Enantiomers of 2-methyl-1-butanol

Inspection of the molecular models indicate that neither molecule is identical to the other (the two molecules will not fit into the same mold), and that when either molecule is placed before a mirror, its reflection is identical to the other isomer. In other words I and II are two nonsuperimposable structures with mirror image relationship. Only chiral molecules exist as two nonsuperimposable structures with mirror image relationship. Therefore, molecules of 2-methyl-1-butanol are called chiral molecules. The structures I and II are called enantiomers or optical antipodes of 2 - methyl - 1- butanol. One of these two

structures represents dextrorotatory isomer of 2-methyl-1-butanol and the other levorotatory isomer. It is important to note here that from the structures one cannot and should not predict which of these is dextrorotatory and which one is levorotatory. Enantiomers have the same physical and chemical properties. they only differ in their behaviour towards plane polarized light. Even their specific rotation is exactly equal. They only differ in the direction of rotation. Following are some important physical properties of the enantiomers of 2-methyl-1-butanol.

Physical property	d' or (+)-2-methyl-1-butanol	l' or (-)-2-methyl-1-butanol
Specific rotation	+ 5.90	-5.90
B. P	128.9°C	128.9° C
Density	0.8193	0.8193

Thus enantiomes rotate the plane polarized light by equal magnitude but in opposite driection. A mixture of equal amounts of two enantiomers is called a racemic mixture. A racemic mixture is optically inactive, but can be resolved by suitable methods.

Asymmetric molecules may contain one or more asymmetric carbons in the structure.

Check your progress - 1

What do you mean by an asymmetric carbon atom?

.....

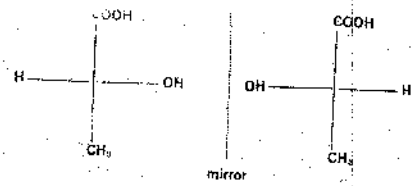
.....

.....

.....

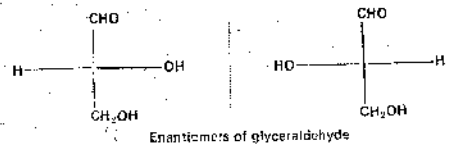
27.4 MOLECULES CONTAINING ONE ASYMMETRIC CARBON ATOM

2-methyl-1-butanol is an example of a compound with one asymmetric carbon atom. We have seen such compounds exist as dextrorotatory and levorotatory isomers. These isomers are also known as enantiomers or optical antipodes. This is the general observation with all compounds containing one asymmetric carbon atom. A well known example of this type of compounds is lactic acid, CH_3CHOH-COOH (α - hydroxy propionic acid). Lactic acid produced in the living muscle (sacrolactic acid) is dextrorotatory whereas the lactic acid formed by fermentation of lactose (souring ofmilk) is levorotatory.

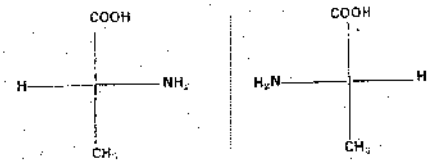


Enantiomers of lactic acid

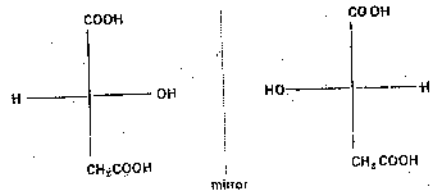
Fisher projection formulae of the enantiomers of glyceraldehyde (OHC-CH(OH-)CH_2OH), alanine (HOOC-CH(NH_2)-CH_3) and malic acid (HOOC-CH(OH)-CH_2COOH), each containing one asymmetric carbon atom are given below.



Enantiomers of glyceraldehyde

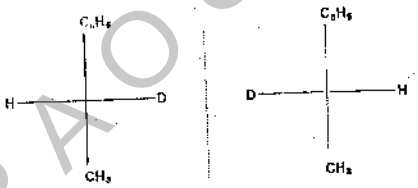


Enantiomers of alanine



Enantiomers of malic acid

The isotopes, such as H and D, are different enough to permit detectable optical isomerism. Thus, α-D-ethyl benzene, CH_3-CH-(D)-C_6H_5, exhibits enantiomerism.



Enantiomers of α -D-ethyl benzene

27.5 MOLECULES CONTAINING TWO ASYMMETRIC CARBON ATOMS

Natural products such as carbohydrates, alkaloids etc.contain two or more asymmetric carbon atoms. When molecules contain two asymmetric carbons, both the asymmetric carbons may be attached to identical groups or they may be attached to different groups. accordingly molecules containing two asymmetric carbons may be divided into molecules containing two similar asymmetric carbon atoms, and moelcules containing two dissimilar asymmetric carbon atoms.

27.6 MOLECULES WITH TWO SIMILAR ASYMMETRIC CARBON ATOMS

In tartaric acid, HOOC-C (OH)-CH (OH) COOH each asymmetric carbon is linked to the same four groups i.e, -H, OH, COOH and -CH (OH) COOH groups. Thus tartaric acid is an example of compounds with two similar asymmetric carbon atoms. In the case of tartaric acid, in all, these isomers are possible- two enantiomers (dextro and levorotatory tartaric acids) are optically active and the third one (mesotartaric acid) is optically inactive. The Fisher projection formulae of enantiomers of tartaric acid and mesotartaric acid are given below.

BOOKS SUGGESTED FOR FURTHER READING

1. Organic Chemistry

2. Organic Chemistry -- R.T. Morrison and R.N. Boyd.

3. Text Book of Organic Chemistry -- Llyod N. Ferguson

4. Modern Organic Chemistry -- Norman and Waddington

5. Organic Chemistry -- Fieser and Fieser

6. Applications of Absorption Spectroscopy of Organic Compounds -- John. R. Dyer.

7. A Text Book of practical Organic Chemistry -- A.I. Vogal.

Dr. B.R. AMBEDKAR OPEN UNIVERSITY
Faculty of Science
(Under Graduation Programme)
III YEAR
CHEMISTRY COURSE - III

Assignment - 3

N.B:-

1. Do not copy the answer directly from any of the books
2. As far as possible try to answer the questions independently in your own words.
3. If it is necessary to quote from any source give the correct reference.
4. Use your own fullscape pages for writing the assignment.
5. Leave sufficient margins for the comments of dthe evaluator.
6. Completion of this assignment normally should not take more than two hours time.

SECTION - A

I **Answer the following in 30 lines**

1. Describe theree methods for the preparation of primary aminos. How does aniline react with the following:-
   a) Acetic anhydride b) Benzoylchloride
2. Discuss the open chain structure of glucose.
3. Describe Paal-Knorr pyrrole synthesis. Why pyrrole exhibits acidic properties.

SECTION - B

II **Answer the following in 10 lines**

1. What is racemmic mixture? Give any two examples.
2. Define and explain the following :
   i) Zuitter ion
   ii) Isoelectric Point.
3. What are apimers and enantiomers? Give an example for each.

CHEMISTRY

Agrochemicals
&
Drugs

BLOCKS : 1 - 5

Dr B.R. AMBEDKAR OPEN UNIVERSITY
HYDERABAD
1992

COURSE TEAM

Prof. K. Rama Reddy (Chairman)
Dr. G.V. Subramanyam (Editor)
Prof. S. Brahmaji Rao
Prof. P.S. Rao
Pro. A.S.R. Anjaneyulu
Prof. D. Bhaskar Reddy
Dr. S.G. Peeran
Dr. R. Venkateswarulu
Dr. K. Ramasubba Reddy
Dr. T. Sundara Ramaiah
Smt. C. Sesharatnam
Mr. V. Santhosh Reddy (Academic Assistant)
Mr. Chandra (Artist-cum-Designer)
Mr. M. Ramesh (Jr. Artist-Cover page designer)

Course Co-Ordinator

Dr. G. Ramachandraiah

Dr B.R. Ambedkar Open University, Hyderabad.

This text forms part of an Open University Course. The complete syllabus for the course appears at the end of the text.

Further information on Open University Courses may be obtained from the Director (Academic), Dr B.R. Ambedkar Open University, Hyderabad, A.P.

Printed at : *ART WAVES*, Offset Printers, Malakpet, Hyderabad - 500 036.
Phone No. 44323.

PREFACE

This course deals with the topics in Agrochemicals (Part-A) and Drugs (Part-B) which is a part of organic chemistry included in the syllabus for the third year of B.Sc. course offered by the Dr. B.R. Ambedkar Open University. The syllabus is for the sake of convenience divided into units, each of which comprises a number of lessons. Each unit generally covers a specific area of the subject. The lessons are prepared by specialists in accordance with a format so designed as to enable the student read and understand them without much difficulty. Each lesson begins with a statement of its objective followed by a synopsis and has at its end assignment intended to test the students comprehension of its subject matter. Generally technical terms with which the student may not be familiar are given at the end of each unit under the head Glossary or Appendix whenever necessary.

In part-A dealing with Agrochemicals it is attempted to explain the important aspects of Plant Nutrients, Plant disease control chemicals and plant growth hormones, environmental effects of Agrochemicals and Pesticide formulation. It is hoped that this part will help the student to acquire necessary knowledge in these areas.

In part-B dealing with Drugs, efforts are made to describe the necessary aspects of the topics on Drugs from Plants, Microbes and Synthetic drugs with special reference to Analgesics, Antimalarials, Antibacterials and Antibiotics. We have also dealt with Hormones and Vitamins in this part. These topics will enable the student to understand the chemistry and the applications of some important drugs.

The University hopes that this course material will help the student to get acquainted with fairly advanced aspects in chemistry of Agrochemicals and chemistry of Drugs.

CONTENTS

PART-A : AGROCHEMICALS

PART - B : DRUGS

Part - A

AGROCHEMICALS

BLOCK - 1 : PLANT NUTRIENTS

Most of the plants manufacture their food material in photosynthesis. Human beings and animals depend on plants for their food material. For the manufacture of food material, plants absorb some elements from the soil in the combined state called plant nutrients. It is well established that most of the elements required by the plants are also essential from human beings and animals. Food or fodder obtained from soil which is deficient of the nutrients may lead to malnutrition. Therefore the required plant nutrients are to be added to the field in the form of natural or synthetic manures.

UNIT-1 : HISTORICAL ASPECTS OF PLANT NUTRIENTS

Contents

1.1 AIMS AND OBJECTIVES

To introduce the importance of fertilisers plant disease control chemicals, the processes of manufacture of some important fertilisers and the usefulness of the micronutrients to the plants.

After a thorough study and understanding of the various aspects of fertilisers presented in this unit, you are supposed to:

- remember the historical aspects of the plant nutrients,
- know the classification of fertilisers based on their action on the soil and also their sources,
- realise the importance of the industrial manufacture of urea, ammonium sulphate, super phosphate and potassium sulphate,
- bear in mind the importance of the micro nutrients in plants.

1.2 INTRODUCTION

Human beings and animals depend on plants for their sustenance. Plants like animals need food for growth and development. The food needed by plants consists of some chemical elements in a combined form. These are called the plant nutrients. Most of the elements needed by the plants are also essential for human beings and animals. Because the humans have to depend on the plants for obtaining the essential elements, it is necessary to see that the plants receive these elements. If the food or fodder obtained from the plants, grown in soils deficient in some of these nutrients is consumed by humans and animals, malnutrition and retarded growth could occur.

1.3 HISTORICAL ASPECTS OF PLANT NUTRIENTS

Use of manures such as farm yard manure, green manures, night soil, bones etc., for improvement of the crop yield is as old as the agricultural practice by man. The ancient man practised it by experience and observation. Later, an attempt was made to understand the scientific principles underlying the plant growth by the use of various chemicals. A rationalisation of farming and soil management had thus emerged. With the advent of the chemical research as applied to the agricultural sciences, there was a rapid development in the understanding of the plant growth substances and the mineral nutrients.

Theodore de Saussure and Jean Baptiste Boussingault are two prominent scientists of the 19th century to demonstrate the need of mineral nutrients for the growth of plants It was shown that the source of nitrogen for plants was the soil. Justus Von Leibig who is considered as the father of agricultural chemistry showed in 1840 that plants obtain the elements calcium, potassium, sulphur and phosphorus was the carbon source for the plants. Leibig showed the essential nature of potassium in plant nutrition and suggested that the depleted soil fertility has to be restored by the addition of some minerals to obtain a good second crop. Superphosphate was introduced as a fertiliser by John B Lawes in 1840.

Gris showed that the plant disease called Chlorosis could be rectified by the use of iron salts. Necessity of other plant micronutrients was recognised by several researchers over a period of about one hundred years.

1.4 ESSENTIAL PLANT NUTRIENTS

Plants need 16 elements for their growth.. They are carbon, hydrogen, oxygen, potassium, phosphorus , nitrogen, calcium, magnesium, sulphur, zinc, boron, copper, manganese, molybdenum, chlorine and iron. Of these, carbon, hydrogen and oxygen are called natural nutrients because these are derived from air and water. Nitrogen, phosphorus and potassium consumed by the plants in large quantities, are considered as primary nutrients or macro nutrients. Calcium, magnesium and sulphur are called the secondary nutrients. Other elements needed only in minute quantities are classified as micronutrients.

1.5 CLASSIFICATION OF FERTILIZERS

On repeated cultivation, the soil is depleted of the plant nutrients and it becomes less productive. This deficiency must be made up through addition of certain elements in order to improve the subsequent crop. These additives are called fertilizers. The fertilizers supplement the elements removed by the plants from the soil, and maintain the pH of the soil at 7 to 8 to facilitate the optimum growth of the plants.

Fertilisers are classified as follows on the basis of their action on the soil.

1.5.1 DIRECT FERTILISERS

Fertilisers that are directly absorbed by the plants from the soil eg., Nitrates, super phosphate and ammonium salts.

1.5.2 INDIRECT FERTILIZERS

Substances that help fertilisation by keeping an optimum pH of the soil for plant growth. eg., Limebarn yard.

1.5.3 COMPLETE FERTILIZERS

Fertilizers which provide all the essential nutrients such as nitrogen, phosphorus etc., eg., Guano.

1.5.4 INCOMPLETE FERTILIZERS

Substances which contain only one of two of the required elements. eg., Ammonium phosphate and potassium nitrate.

1.5.5 MIXED FERTILIZERS

These are prepared by mixing the appropriate quantities of ammonium salts, potassium salts and phosphate etc.

1.6 FERTILIZER SOURCES

Fertilizers are of two different types depending on their sources :
A) Natural Organic and Inorganic fertilizers and (b) Artificial fertilizers :

A) **Natural Organic Fertilizers :** The natural fertilizers consist of plant matter obtained from the oil cakes of cotton seed; linseed and castor seeds, farm yard manure composed of the dung of cows, buffaloes and sheep. Animal matter such as powdered dry fish, dried blood from slaughter houses as well as guano consisting of birds excretions, fish bones and fish refuge form other important natural fertilizers.

Natural Inorganic Fertilizers : Chile salt peter ($NaNO_3$), Rock phosphates, wood ash containing about 5 percent of potash form important natural inorganic fertilizers.

B) **Artificial Fertilizers :** Based on the essential element supplied by them, these are divided into 3 categories.

1. Nitrogenous fertilizers consisting of the nitrates of sodium, calcium, ammonium and potassium, urea, ammonium sulphate and calcium cyanamide.

2. Phosphatic fertilizers exemplified by the phosphate rock, normal super phosphates, triple super phosphate, mono and diammonium phosphates and calcium meta phosphate.

3. *Potash fertilizers :* The important potash fertilizers are potassium nitrate (KNO_3), Potassium chloride (KCl) and potassium sulphate (K_2SO_4).

Check Your Progress - I
What are fertilizers?

.....

.....

.....

.....

1.7 MANUFACTURE OF UREA

Urea (NH_2CONH_2), a white crystalline hydroscopic solid melting at 132°C with about 45 percent of nitrogen, is one of the best fertilizers. As urea is highly soluble in water, it is readily available for absorption by the plants. Urea has a tendency to hydrolyse and lose ammonia. It is manufactured by reacting liquid CO_2 and liquid ammonia in a silver lined special vessel to get ammonium carbamate.

Iron : Iron is a constituent of several porphyrin compounds. It occurs in cytochromes which are known to play an important role in oxidative phosphorylation during respiratory electron transport and photophosphorylation during photosynthesis. Ferredoxin, an iron containing protein helps reduction of carbondioxide, atmospheric nitrogen and sulphate. The root nodules of leguminous plants contain a haemoglobin like protein containing iron. Iron is well known for its catalytic role in enzyme activity. Succinic dehydrogenase, sulphite oxidase, cytochrome oxidase, catalase and peroxidase are some of the important enzymes which contain iron. Iron is directly or indirectly involved in all the major metabolic processes of plants. It plays a direct role in the photosynthesis in which atmospheric carbondioxide is transformed into complex organic substances. It also plays an important role in oxidative phosphorylation and nitrogen fixation. Deficiency of iron in plants results in the disintegration of chloroplasts and a decrease in reducing sugars and organic acids.

1.16 MODEL ANSWERS TO CHECK YOUR PROGRESS

1. Synthetic or natural substances that are added to the field to maintain the soil fertility are called fertilizers.

2. The elements which are required for plants in very small quantities are called micronutrients.

Author : Prof. P.S. Rao.

BLOCK - 2 : PLANT DISEASE CONTROL CHEMICALS

In agriculture crops in fest disease due to the attack of bacteria, viruses and fungi. Insects, birds and rodents destroy the crops. Some unwanted plants called weeds also decrease the crop yield. In order to avoid the above crop loss and also the decrease of crop yield a number of chemicals are used in agriculture called pesticides. They destroy selectively the pest causing organising without much loss to the host plant, animals and human beings. During the application of these chemicals one has to be quite aware of the environmental pollution and health hazards that result due to the misuse of them. In our country pesticides have come into application in agriculture as a part of green revolution which resulted in the tremendous increase of the yield of food grains.

UNIT-2 : BRIEF SURVEY OF PLANT DISEASE CONTROL CHEMICALS

Contents

2.1 AIMS AND OBJECTIVES

This unit is mainly aimed to appreciate various chemical methods that are used to protect field crops, vegetables, fruits etc., from the attack of insects, fungi, weeds, rats and other destructive organisms and also to create an awareness of the environmental pollution and the probable health-hazards as a result of misuse of the chemicals that are used for the above purposes.

Once you completely study and understand the contents of the unit, you are expected to :

define and classify pesticides
give an account of inorganic and organic insecticides like halogen containing, organophosphate and carbamate insecticides,
describe the biodegradability of pesticides.
narrate the insecticidal properties of plant origin insecticides pyrethrins, rotenoids and nicotine
discuss about the importance of fungicides, herbicides and rodenticides in agriculture
account for the role of plant growth regulating hormones, insect sterilants, insect repellants and Luvenile hormones in agriculture.

2.2 INTRODUCTION

It is well known that the rats and birds are enemies of the farmers while harvesting the crops and storing the paddy. Similarly fungi, white ants, worms, insects, cockroaches and moths etc., destroy the food stuffs, paper and clothes etc., in the houses and therefore, certain chemicals such as napthalene balls, D.D.T. and gammexane are used to prevent such destruction.

While growing vegetables, fruits, the commercial crops such as tobacco, cotton and chillies and also the field crops such as paddy, wheat and sugar cane, plants infest certain diseases caused by the attack of the microorganisms such as bacteria, virus and fungi and insects such as grass hoppers, stem borers, plant lice, caterpillars and beetles. In agricultural fields, along with the crops certain unwanted plants known as weeds or herbs also grow, consuming most of the fertilizers and water and reduce the yields of the crops.

Thus, right from the cultivation and harvesting to storage, the menace of living organisms is so great that well over one third of the agricultural products grown by humans are consumed or destroyed.

In order to meet the growing needs of food requirements of the world population, new techniques in the field of agriculture are introduced along with the use of synthetic fertilizers and plant growth hormones etc., to increase the food production, To combat the agriculturalist, certain chemicals of both synthetic and natural origin are used and they are known as pesticides. The pesticides destroy selectively the harmful organisms such as fungi, insects, birds and rats etc., and also weed out the unwanted plants, without causing much damage to the host plants and human beings. A great care must be exercised while using the pesticides, so that the biological ecosystem and the environment are not disturbed. For instance, D.D.T., which was once proved to be a potent insecticide, is now banned in the western world. This insecticide was found to damage the biological processes of the chicken and certain other birds. As a result of this, the birds were unable to deposit calcium in their egg shells.

2.3 CLASSIFICATION OF PESTICIDES

Agricultural pests are of different types. Some of them are micro-organisms such as virus, bacteria and fungi. Some are insects and worms, with a not so well-developed body. Some organisms are with a well-built body system. Based upon the type of pests, pesticides such as birds and rats are classified as insecticides, fungicides, weedicides or herbicides and rodenticides etc. Usually, the pesticides are used for spraying after being mixed with water or a suitable solvent or directly as dusty powders or as pressurised sprays of aerosols. The pesticides are inhaled or swallowed by insects or absorbed through the skin of the insects and cause toxic effects to the insects. In case of fungicides and herbicides, the toxic chemicals are absorbed through the cell membrane of the fungi or weeds. Thus the pesticides may interfere with enzymatic or other biological activities of the pests and arrest the growth of the agricultural pests. Usually one pesticide may be active against one type of pest. Some times one pesticide may be useful to eradicate one or more types of pests. Further, all the living organisms have a characteristic property of adaptability by selection to environmental changes including foreign chemicals. Therefore, agricultural pests also develop resistance in due course of time to a particular type of pesticide. In such cases, a new type of pesticide or a combination of pesticides has been found useful. The various pesticides have different levels of toxicity ranging from slightly toxic to extremely toxic. While using the pesticides, the toxicity level should be tolerable to the host plants, humans and other mammals.

2.4 INSECTICIDES

The Insecticides are the chemicals used to kill insects which are harmful to field crops, vegetables and fruits etc. Among the insect pests, they vary greatly in their habit, habitat and nature of feeding etc. Some insects attack a number of unrelated plants, while others attack some related plant species. Some insects live in the soil and feed on the underground part of the plant. Others live on the plant parts above the ground and feed on the foliage of tender stems and twigs. Some insects bore inside the leaves, stems or fruits and suck the cell sap. Further, some insects have soft-bodies, while others have hard-bodies. Therefore, specific insecticides would be effective in each case depending upon the type of feeding, habit or the body type of the insects.

Based upon the chemical nature, insecticides are classified into inorganic and organic insecticides. Among organic insecticides, there are certain natural compounds derived from plant products. But, mostly synthetic organic insecticides are in common use, as a result of availability of cheaper and highly specific compounds.

2.4.1 INORGANIC INSECTICIDES

Relatively, a few inorganic compounds, the metallic salts of arsenic, flourine, sulphur and phosphorous, are used as insecticides and fungicides. For example, lead arsenate ($Pb\ HAsO_4$) and calcium arsenate $\left[Ca_3(AsO_4)_2\right]$ were frequently used as insecticides in apple orchards, cotton fields and potato crops.

Calcium polysulphide ($Ca S_x$, x = 4.5) is used in the preparation of many pesticides which are used for controlling pests in soil, mites and insects. Because of the poisonous character of the arsenic and other inorganic insecticides to man and other mammals, they are replaced by organic insecticides.

2.4.2 ORGANIC INSECTICIDES

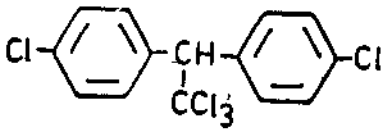
a) Synthetic Organic Insecticides : There are several synthetic organic compounds that are used as insecticides. Based upon the chemical nature of the groups present in the insecticides, they are classified into (i) halogenated organic insecticides, (ii) organophosphate insecticides and (iii) carbamate insecticides.

(i) Halogenated Organic Insecticides

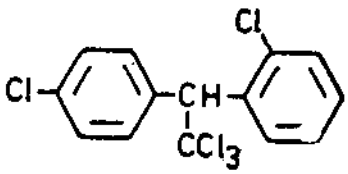
D D T and BHC are chlorinated hydrocarbons which exhibit broad insecticidal properties.

D D T (Dichloro Diphenyl Trichloroethane)

D D T can exist in a number of isomers, depending upon the ortho, meta and para positions of the chloro-groups on the benzene rings. The para-para isomer (1a) is the most potent insecticide, the ortho-para isomer (1b) has very little insecticidal potency. The systematic name of the para isomer of D D T is 1, 1-bis-(p-chlorophenyl) - 2,2,2 - trichloro-ethane.



(1a)

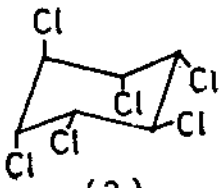


(1b)

D D T was first synthesised by Zeigler in Germany in 1874 and its insecticidal properties were discovered by Paul Muller in Switzerland in 1939. Currently, the chemical has been almost eliminated from the use in the Western World for the following reasons. Many insects developed resistance to D D T The residue of D D T and the degradation products of D D T were found stored in the animal fats. Further it was reported to cause like diseases in the mice and rats.

BHC (Gammexane or Lindane)

BHC (2), benzene hexachloride or 666 (from the molecular formula $C_6H_6Cl_6$) also exists in several isomers. But the insecticidal properties of the compound is due to its γ-isomer and hence the name, gammexane (2). It is also known as lindane, after van der Linden who established the existance of the first four isomers.



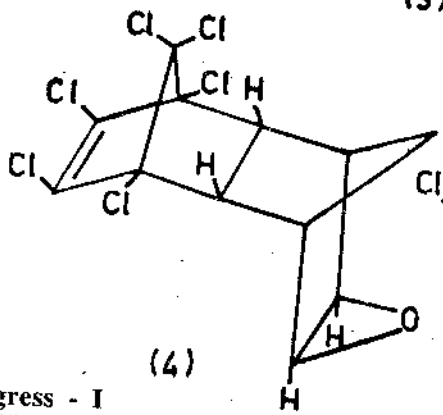
(2)

Endrin (4) and endosulphan (5) etc., are the insecticides belonging to cyclopentadiene (3) group. They are highly chlorinated insecticides and very toxic to animal life, particularly to fish. Further, they are not easily 'biodegradable'.

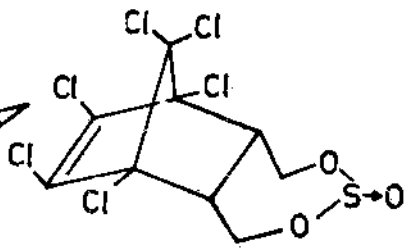
'Biodegradability' is the property of any synthetic chemical such as a pesticide or a detergent to undergo decomposition, to harmless artefacts in nature. The decomposition of pesticide into smaller and harmless molecules is brought about by naturally occurring micro organisms such as bacteria. Sometimes they may be decomposed by natural processes such as hydrolysis by moisture in the atmosphere, or photolysis by sunlight or metabolism by the host plant.

If the pesticide is not biodegradable, its residues will persist or continue to be present in the food products, in the soil and in the environment. Thus the persistance of aldrin and other organochlorine insecticides has been observed in sandy soils upto 40% even after 14 years. The persistance of pesticides in the environment causes pollution problems, and thereby health hazards to the human beings and mammals.

(3)



(4)



(5)

Check Your Progress - I

What is biodegradability?

.....

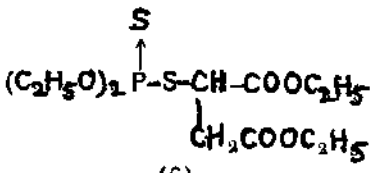
.....

.....

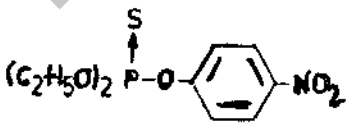
.....

(ii) Organophosphate Insecticides

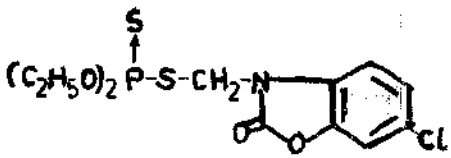
Malathion (6), parathion (7), phosalene (8), mevinophos (9) and monocrotophos (10) are some of the coimmonly used organophosphate insecticides.



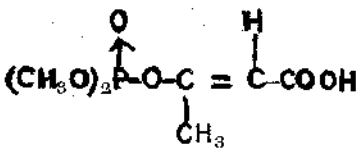
(6)



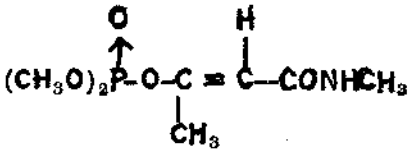
(7)



(8)



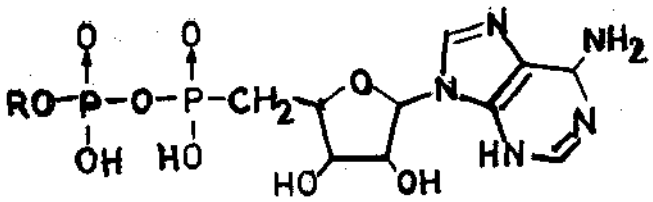
(9)



(10)

The phosphate esters play an important role in many biological processes. For example, ADP (adenosine diphosphate) (11), and ATP (adenosine triphosphate) (12), are present in muscle tissues of animals. They involve in the energy storage and energy releasing processes of metabolic activities.

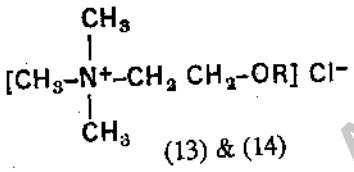
Similarly, acetyl choline (14) is a chemical present in the nerve cells in a bound state. Stimulation of nerve cells releases the acetyl choline, which in turn stimulates the neighbouring nerve cells to release once again the acetyl choline. Thus the impulses in the nerve cells are transmitted by the release of acetyl choline. When once the impulse is transmitted, the acetyl choline will be deactivated. This deactivation is carried out by an enzyme acetyl cholinesterase (or cholinesterase) by hydrolysing acetyl choline to choline (13). Acetyl choline exerts an exceptionally strong physiological effect. When it is administered into the body of an animal, it causes the contraction of muscles, convulsions and intensive peristalis. Therefore, the inactivation of the enzyme acetyl cholinesterase, say be the use of insecticides, amounts to the excess release of acetyl choline in the tissues of insects and leads to the death of insects. The organophosphate insecticides phosphorylate the active site of the enzyme acetyl cholinesterase and inactivate its enzymatic action.



(11) & (12)

(11) Adenosine diphosphate (ADP) R = H

(12) Adenosine triphosphate (ATP) R = —P(=O)(OH)—OH

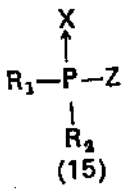


(13) & (14)

(13) Choline chloride R = H

(14) Acetyl choline chloride R = $COCH_3$

Generally the structure of an insecticide (15) of phosphorus esters will have lower alkyl, alkoxy, alkylthio or alkylamino groups. One of the groups can readily be hydrolysed and the resulting phosphorus moiety is utilised for phosphorylating the enzyme cholinesterase. Thus many of the organophosphate insecticides are highly toxic to mammals as well.

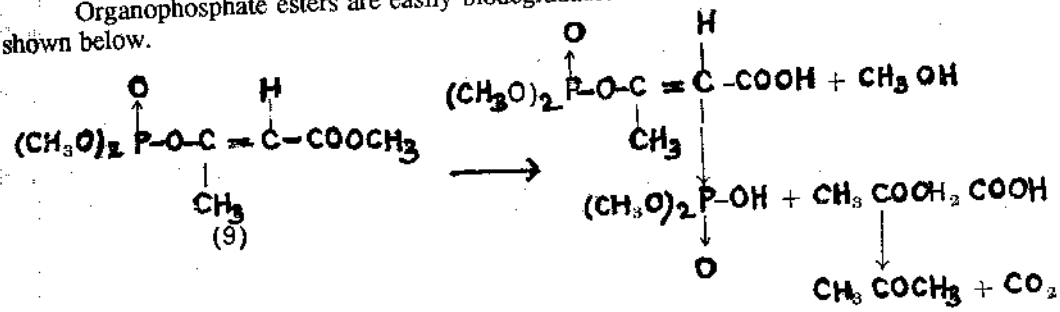


(15)

X = O or S

Z = hydrolysable group

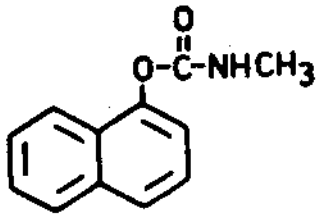
Organophosphate esters are easily biodegradable. For instance, mevinophos (9) is degraded as shown below.



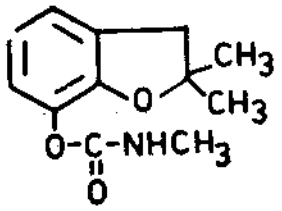
(9)

(iii) Carbamate Insecticides

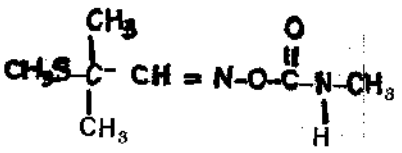
Another important class of Compounds used as insecticides is carbamates. The carbomate esters also owe their insecticidal properties to anti-cholinesterase activity. Carbaryl (16), carbofuran (17), aldicarb (18) etc., are some of the commonly used carbamate insecticides. The insecticide, isoproturon (19) is related to urea.



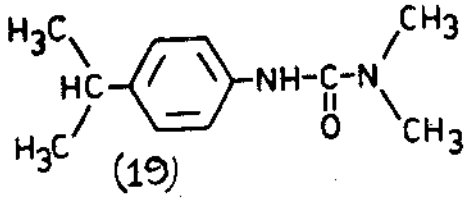
(16)



(17)



(18)

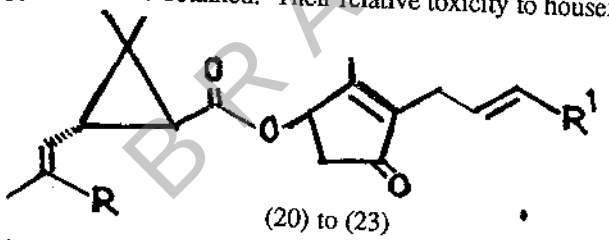


(19)

b) Insecticides of Plant Origin

Pyrethrins

Pyrethrins are esters of cyclopropane carboxylic acids and cyclopentyl alcohols. There are four types, pyrethrin I (20), pyrethrin II (21), cinerin I (22) and cinerin II (23). When the flower heads of the plant **Chrysanthemum cinerariaefolium** are extracted with an organic solvent such as petroleum ether or kerosine, pyrethrins are obtained. Their relative toxicity to houseflies is 100 : 23 : 71 : 18.



(20) to (23)

(20)	Pyrethrin I	$R = CH_3$, $R' = -CH = CH_2$
(21)	Pyrethrin II	$R = -COOCH_3$, $R' = -CH = CH_2$
(22)	Cinerin I	$R = R' = -CH_3$
(23)	Cinerin II	$R = -COOCH_3$, $R' = CH_3$

Pyrethrin has proved to be an excellent insecticide for protection against mosquitos and other insects. It is effective at a very low dosage Pyrethrin does not harm wild life, including birds, fish etc. and also domestic and pet animals. It is easily biodegradable and also labile to sunlight. Hence it has no problem of persistance.

Rotenone

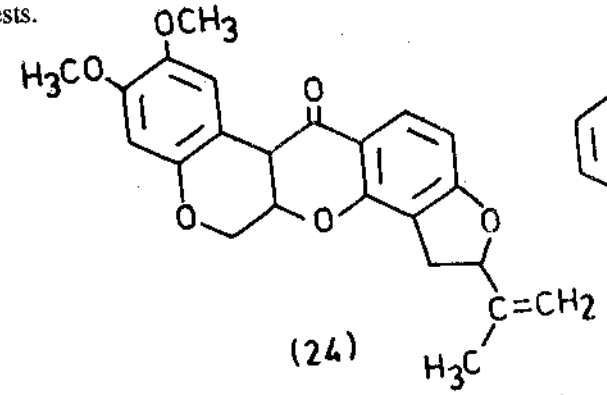
Rotenoids are a class of compounds which are present in several tropical and subtropical plants. They are used as insecticides. Rotenone (24) is one such active principle and commercially extracted from the roots of a plant Derris Elliptica cultivated in Malaya. This is non-toxic to humans, but highly toxic to fish and certain insects.

Nicotine

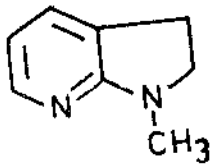
Nicotine (25) is an important alkaloid present in the tobacco plant, Nicotiana Tobacum. Nicotine solutions are used against leaf hopers and other insects.

2.5 FUNGICIDES

Fungicides are the chemicals used to control plant diseases caused by fungi. Next to the insect pests, attack of fungi on various field crops, vegetables and fruits is the biggest problem related to agricultural pests.

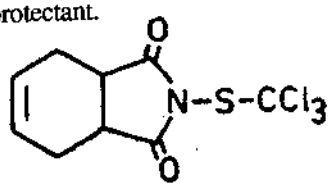


(24)

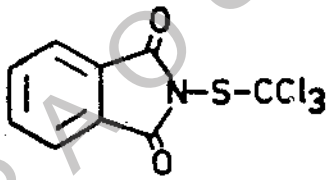


(25)

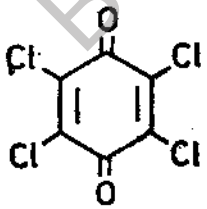
Certain copper salts, particularly a mixture of copper sulphate and hydrated lime dissolved in water (Bordeaux mixture) is used safely to control many fungal diseases of the ornamental plants, vegetables and fruits. Captan (26), folpet (27) and chloranil (28) are commonly used fungicides. Folpet (27) is the perchloromethyl mercaptan derivative of ophthalic acid and captan (26) is that of tetrahydrophthalic acid. Both of them have low toxicity towards mommals and a wide range of fungicidal activity. They are used on fruit crops, grapes, tomatoes, and seed dressings. Chloranil (28) appears to be a very good seed protectant.



(26)



(27)



(28)

2.6 HERBICIDES OF WEEDICIDES

Herbicides or weedicides are the chemicals useful for preventing the growth of unwanted plants or herbs (weeds), either in the field crops or ornamental plants. The problem of weeds in irrigation canals, farm ponds and in aquatic lands is also acute. This has to be tackled with greater efficiency in order to protect the biological ecosystem and the level of the ground water-table. There are different types of herbicides. Based upon their mode of application, they are classified as pre-emergence and post-emergence herbicides. A pre-emergence herbicide, for example, atrazine (29), is applied before the weed germinates from the seed. Such chemical should be applied at the time of crop seeding. A post-emergence herbicide is one that exhibits its activity by killing the weeds from seeding stage onwards. Paraquat dimethyl sulphate (30) is used as a post-emergence herbicide. Monuran (31) is used as a soil sterilant in regions of moderate rain falls and used citrus gardens.

Hormones are certain chemicals secreted in the insects, animals and mammals from the ductless glands. They are useful in various metabolic activities. For example, ecdysone (43), a juvenile hormone if present in excess, it interferes with the normal life cycle of insects and prevents the insects from reaching mature adult stage.

There are other biological methods also developed to control the problem of pests. For example, certain bacterium is cultured and used to infect at the larval stage of certain insects. Similarly, weeds can also be eradicated by using certain type of insects or bugs.

2.10 SUMMARY

In this unit you have learnt about:

i. The classification of pesticides into different types based on the nature of the pest causing organisms.

ii. The inorganic insecticides lead arsenate, calcium arsenate and organic insecticides DDT, BHC, endrin, endosulphan, parathion, malathion, monocrotophos, carboryl and carbofuran.

iii. The insecticides of plant origin prepared for their own protection. They are pyrethrins, rotenoids and nicotine.

iv. The importance of fungicides, herbicides and also rodenticides.

v. The role of plant growth regulators in agriculture.

vi. The importance of sex attractants of insects called pheromones and furemile hormones in agriculture.

2.11 GLOSSARY

1. **Biodegradability :** This is the property of a synthetic chemical to undergo decomposition into simpler harmless compounds by the action of micro-organisms or sun light etc.
2. **Enzymes :** Enzymes are chemicals secreted in the body which are used to catalyse the metabolic reactions.
3. **Fungicides:** Fungicides are chemicals used to kill fungi.
4. **Herbicides:** Herbicides are chemicals used to kill unwanted plants such as herbs or weeds.
5. **Hormones:** Hormones are chemicals secreted by ductless glands in animals which are useful to regulate various physiological activities.
6. **Insecticides:** Insecticides are chemicals used to kill insects.
7. **Insect attractants:** They are naturally occurring pheromones or synthetic compounds used to attract insects for trapping or to destroy them.
8. **Insect repellents:** They are the chemicals by the smell of which, insects are repelled.
9. **Insect sterilants:** They are chemicals used to make the insects sterile.
10. **Persistance:** : It is the property of a pesticide without undergoing biodegradation or decomposition by a natural process.

11. **Pesticides:** Pesticides are chemicals used to kill various agricultural pests such as, insects, fungi, weeds, rodents, etc.

12. **Pesticide Residues:** They are the chemicals related to pesticides, such as degradation products or metabolites or pesticides found in food products and are toxic for human beings and animals.

13. **Pheromones:** Pheromones are chemicals emitted by insects to use them as insect signalling agents.

14. **Plant growth regulators:**They are the chemicals, which are used to activate or decrease the enzymatic activities in the metabolism of plants.

15. **Rodenticides:** Rodenticides are chemicals used to kill rats and other rodents.

16. **Soil sterilant:** It is a type of pesticide used to destroy the pests such as bacteria or fungi present in the soil.

17. **Toxicity:** Toxicity is the poisonous character of certain chemicals (toxins) which are released by microorganisms into the host plants or animals. The term 'toxicity' is also used in general to indicate poisonous character of a pesticide or a drug.

2.12 MODEL EXAMINATION QUESTIONS

I. **Answer each of the following in 10 lines.**

1. Define the terms pesticide, insecticide , fungicide, herbicide and rodenticide.
2. Give few examples of organophosphate insecticides.
3. Give an example of a rodenticide and explain how does it act on rodents.
4. What are fungicides? Give their names and chemical structures.

II. **Answer each of the following in 30 lines.**

1. Write a note on synthetic organic insecticides.
2. Explain the insecticides of plant origin.
3. How are pesticides divided into different categories? Define them and give two examples for each of the category.

2.13 MODEL ANSWERS TO CHECK YOUR PROGRESS

1. The property of synthetic chemicals like pesticides and detergents to undergo decomposition in organisms into harmless substances is called biodegradability.

2. The chemicals secreted by some insects which function as signalling agents are called pheromones.

Author : Dr. R. Venkateshwarulu

(b) *Calcium arsenate (2) :* It is formed by heating a mixture of calcium hydroxide and arsenic acid. The commercial calcium arsenate is a mixture of basic calcium arsenates and calcium hydroxide.

$$6Ca(OH)_2 + 4H_3AsO_4 \longrightarrow 2Ca_3(AsO_4)_2 + 12H_2O$$

(2)

(c) *Paris green (3) :* It is a double salt of copper acetate and copper arsenate (3), formed by boiling a mixture of cupric acetate and arsenic acid in acetic acid medium.

$$4(CH_3COO)_2Cu + 2H_3AsO_4 \longrightarrow Cu(AsO_4)_2\,Cu(CH_3COO)_2 + 6CH_3COOH$$

(3)

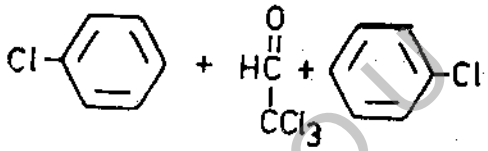
These arsenates are effective against potato beetle and for the codling moth.

ii) ORGANIC CHEMICALS :

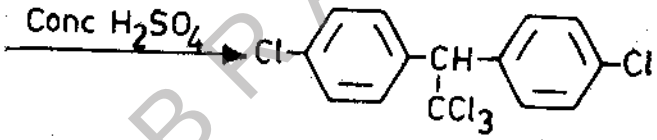
(A) **Halogenated compounds :** Chlorinated insecticides like D D T (4), BHC (8), endrin etc. have been banned in many parts of the world because of their low biodegradability. They enter the human body through food chain and cause health hazards.

(a) D D T -Dichloro Diphenyl Trichloroethane (4)

Paul Muller was awarded Nobel prize for the discovery of insecticidal properties of DDT (1,1-bis (p-chlorophenyl) 2,2,2-trichloroethane DDT (4) is prepared by condensation of chloral (5) and mono-chlorobenzene (6) by agitating with three times their combined weights of strong sulphuric acid.



(6) (5) (6)

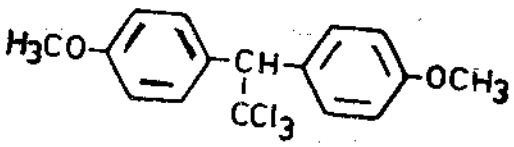


(4)

DDT is the major product in this condensation but not the sole product. As would be expected, in addition to the desired para-para-compound (DDT), small quantities of ortho-para and ortho-ortho compounds are also formed. Commercial DDT is a mixture of all the above three forms. DDT (4) has a wide spectrum of activity against different families of insects.

It is effective against insects on the pea crop. It has a specific effect against jassides, coccinellids and a few species of cutworms. DDT (4) is very slow in its reaction unlike pyrethrem and thiocyanates which can immobilize insects in a few seconds.

The p,p-methoxy analogue of DDT is called methoxychlor (7). The method of preparation of methoxichlor is similar to that of DDT (4). Anisole is used instead of chlorobenzene for the condensation.

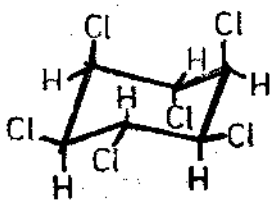


(7)

Use of DDT (4) for keeping the cow houses free from flies is now suspended as significant amounts of DDT residues were detected in the milk of the cows. Methoxychlor (7) is used for this purpose as it is degraded in the body.

(b) *BHC Benzene hexachloride (8)*

It is prepared by photochlorination of benzene. Benzene hexachloride (1,2,3,4,5,6 - hexachloro cyclo hexane) is obtained as a mixture of seven isomeric forms α, β, γ, δ, E, η and φ. Only γ-isomer has insectidal activity and is obtained in 13% yield. The γ-isomer has a, a, a e, e, e confirmation.



(8)

The γ-isomer is commercially known as lindane or gammaxane. It is specific against most of the external feeders and repeated applications can give a certain amount of relief against tissue borers.

Check Your Progress - II

What is gammaxane?

.....

.....

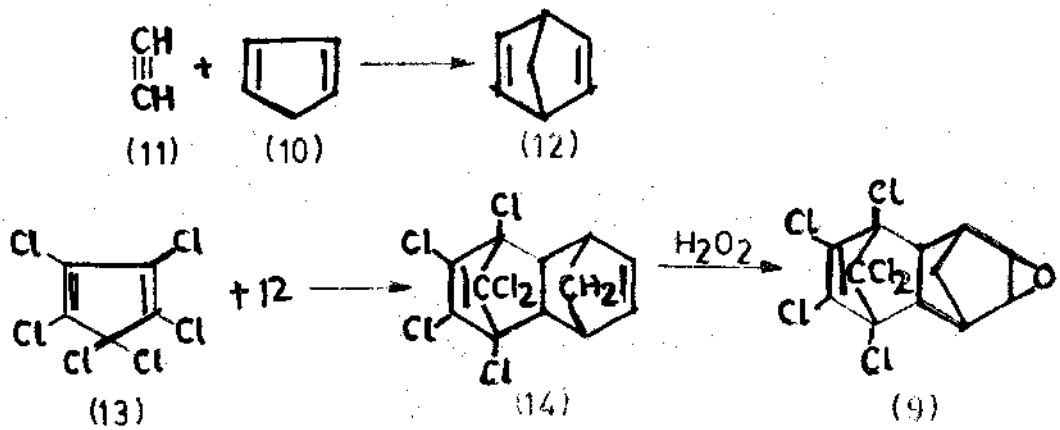
.....

.....

.....

(c) *Dieldrin (9)*

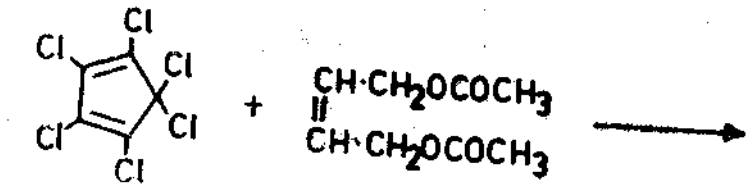
Diels-Alder reaction of cyclopentadiene (10) and acetylene (11) gives dicycloheptadiene (12) which is again subjected to Diels-Alder reaction with hexa chloro penta diene (13) to give aldrin (14). Epoxidation of aldrin (14) with hydrogen peroxide gives dieldrin (9).



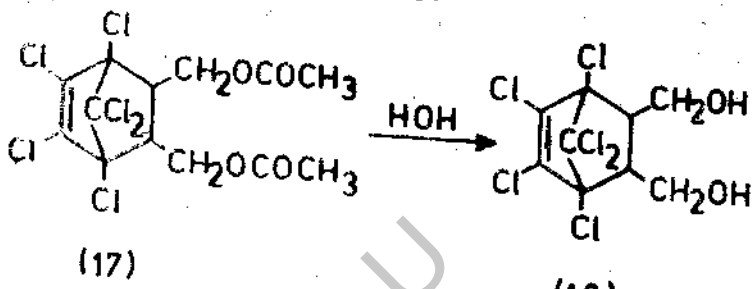
The stereo isomer of dieldrin is known commercially as endrin, which is prepared by epoxidation of isodrin. Isodrin is a stereoisomer of aldrin (14). Dieldrin is effective against sweet potato, weevil, boll worms etc. It is also a good soil insecticide. Aldrin is especially useful for the control of gross hoppers, ants and also used as a soil insecticide.

(d) *Endo sulphan (15)*

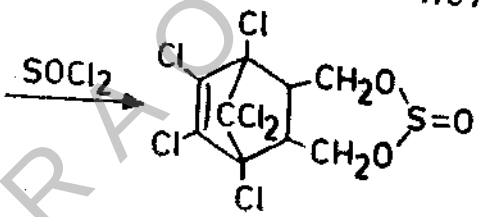
Synthesis of endosulphan or thiodan (15) consists of Diels-Alder reaction between hexa- chloro-pentadiene (13) and 1,4-diacetoxy-2-butene (16) to give bicycloadduct (17) which is hydrolysed to a diol (18). Treatment of the diol (18) with thionyl chloride leads to endosulphan (15). This compound is useful for controlling aphids, caterpillars, plant bugs and borers.



(13) (16)



(17) (18)



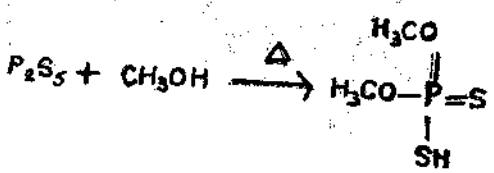
(15)

B. ORGANOPHOSPHOROUS COMPOUNDS

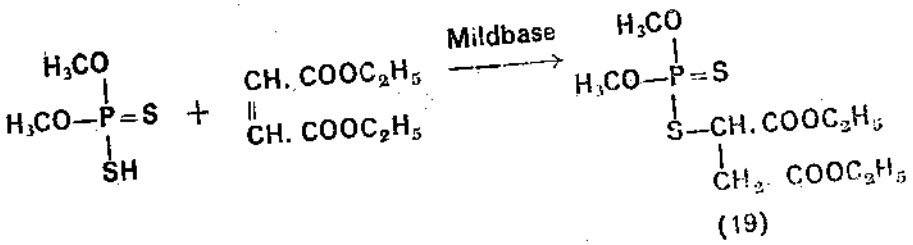
Organophosphorous compounds have high insecticidal activity and wide spectrum of action.

i) *Malathion (19)*

It is the most widely used organophosphorous insecticide with low mammalian toxicity. It is fairly rapidly biodegraded and is used for mosquito control. Malathion (19) is prepared by the addition of dimethyl-dithiophosphoric acid (20) to diethylmaleate (21). The dimethyl dithio phosphoric acid (20) used in this synthesis is prepared by heating a mixture of phosphorous pentasulphide and methanol.



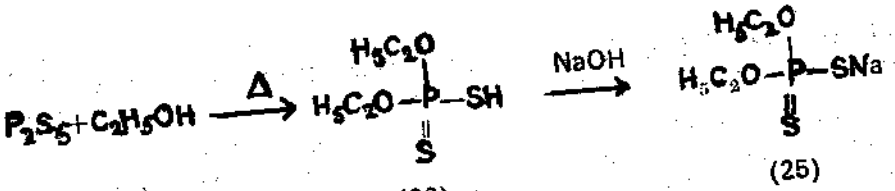
(20)

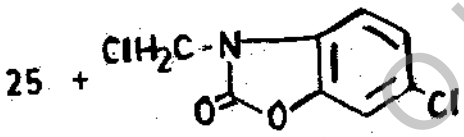


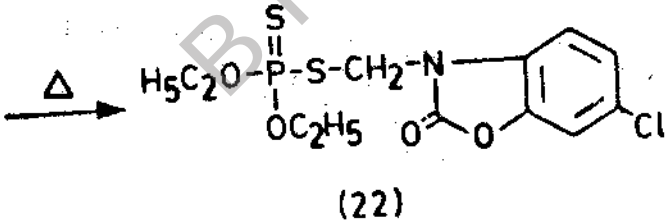
It is useful in the control of aphids, jassids, thrips, caterpillars and white flies.

ii) *Phosolone or Zolone* (22)

Phosolone (22) is prepared by heating a mixture of sodium salt of diethyl-dithio-phosphoric acid (25) and 6-chloro-N-chloromethyl-3-benzoxazolone (24). Diethyl-dithiophosphoric acid (23) is prepared by the action of ethanol on phosphorous-pentasulphide.

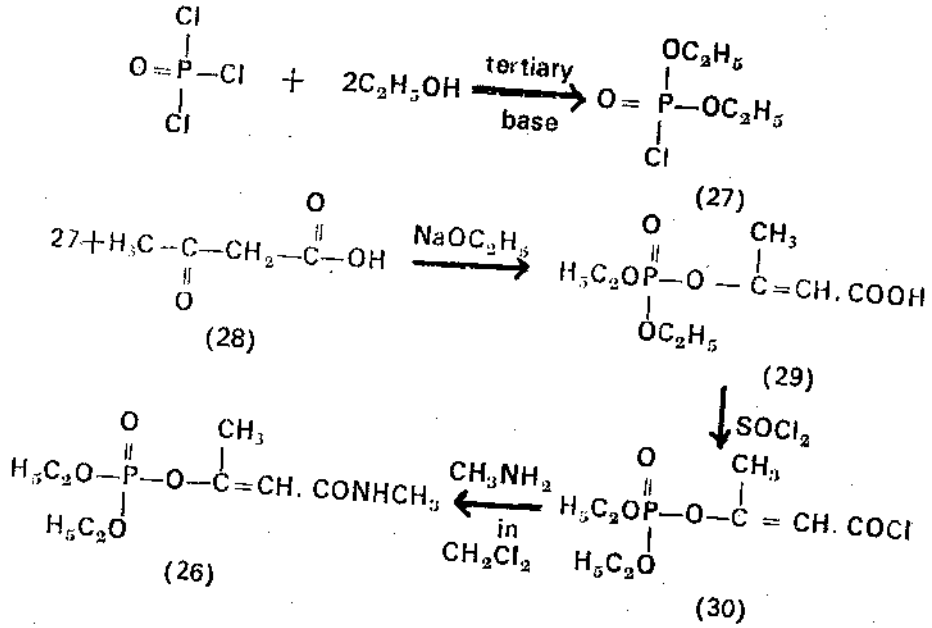






iii) Monocrotophos (26)

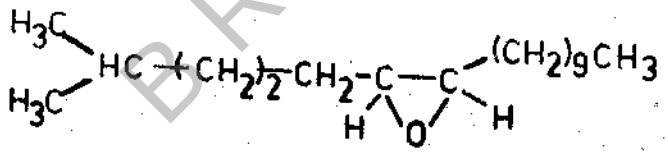
Reaction between diethyl-chloro-phosphate (27) and β-ketobutyric acid (28) in presence of sodium ethoxide gives the acid (29) which is converted into acyl chloride (30). Treatment of the acid chloride with methylamine gives monocrotophos (26). Diethyl-chlorophosphate used in this reaction is obtained by the action of phosphorous oxychloride and ethanol in presence of a tertiary base.



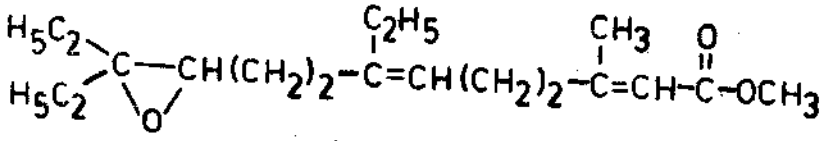
3.5 PHEROMONES AND JEVUNILE HORMONES

Chemical agents are useful to control the insect population but most of the synthetic insecticides have certain drawbacks such as (i) development of resistance by insects and making them ineffective with time (ii) toxicity to humans and other living species due to nonbiodegradability.

Recently, sex hormones, called pheromones, which regulate the growth cycles of insects, have been utilised for the insect control. Pheromones are the chemicals that are naturally excluded by some female insects to attract their males and are effective in very small concentrations. Dispalure (31) is one such hormone which is used against gypsy moth. Cecropia moth juvenile hormone (32) is an example of a hormone which disrupts the growth cycles of moths.



(31)



(32)

3.6 SUMMARY

The main points you have studies in this unit are :

i. The classifications of insecticides based on their action on insects and their nature.

ii. The industrial preparations of lead arsenate, calcium arsenate, endosulphan, malathion, parathion, phosolone and monocrotophos.

iii. The sex hormones of insects called pheromones and also the the juvenile hormones that are used in modern agriculture to control the insect pests.

3.7 GLOSSARY

1. *Acaricides :* Chemicals used to kill mites or arcachinids.
2. *Adjuvants :* Materials which act as wetting or spreading agents.
3. *Algaecides :* Materials which control or prevent plant diseases caused by algae.
4. *Diels-Alder reaction :* 1,4-Addition of a dienophile (ethylenic compounds activated by electron withdrawing groups) to a conjugated diene to give cyclic compounds.
5. *Fungicides :* Materials which control or prevent plant diseases caused by fungi.
6. *Fumigants :* Gaseous state insecticides.
7. *Herbicides :* Materials which kill certain types of plants (weeds) without injuring the desirable plants.
8. *Nematicides:* Substances which control nematodes.
9. *Rodenticides :* Substances which kill rats, mice and other rodents without causing danger to domestic animals and man.

3.8 MODEL EXAMINATION QUESTIONS

I. **Answer each of the following in 10 lines.**

1. Outline the synthesis of DDT and BHC

II. **Answer each of the following in 30 lines.**

1. Outline the synthesis of any one of the following.
   (a) Monocrotophos (b) Malathion (c) Phosolone (d) Dieldrin (e) Endosulphan.

3.9 MODEL ANSWERS TO CHECK YOUR PROGRESS

1. Those insecticides which on application in the field are absorbed by the plants rendering the plants tissue toxic to insects which feed on them.

2. Benzene hexachloride (BHC) has a number of geometrical isomers. But only γ-isomer has insecticidal property. This isomer is called gammaxane or lindane.

UNIT-4 : FUNGICIDES

Contents

4.1 AIMS AND OBJECTIVES

To introduce a brief account of fungicides in general and to consider the chemistry of a few organic and inorganic fungicides.

After the completion of the study and comprehension of this unit, you must be able to:

* describe the classification of fungicides into different types.
* explain the mode of fungicidal action.
* give an account of the methods of application of fungicides.
* give the industrial methods of synthesis of captan and chloranil.
* describe the preparation of mercury fungicides $HgCl_2$, Hg_2Cl_2 and HgO.

4.2 INTRODUCTION

Fungicides are chemicals that inhibit or prevent fungus reproductions without killing the organisms. Fungicides are used in agriculture to control plant diseases and reduce crop losses and prevent decay of manufactured or natural materials.

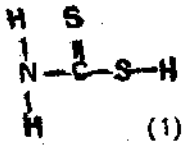
4.3 INORGANIC AND ORGANIC FUNGICIDES

4.3.1 INORGANIC FUNGICIDES

Inorganic fungicides such as bordeaux mixture and sulphur are in use even today. Bordeaux mixture is made by mixing a solution of copper sulphate with a suspension of lime (calcium hydroxide). Another group of inorganic fungicides includes mercury compounds.

4.3.2 ORGANIC FUNGICIDES

The first organic chemical used as a fungicide was dithio-carbamate, discovered in 1934. Some of the most useful organic fungicides are derivatives of dithiocarbamic acid (1).



(1)

Examples are ferbam and ziram, the iron and zinc salts of dimethyl-dithiocarbamic acid and nabam, maneb, and maneb, the sodium, zinc and manganese salts of ethylene bis (dithiocarbamic acid) (2).

$$\begin{array}{l} CH_2.\,NH.\,CS.\,SH \\ | \\ CH_2.\,NH.\,CS.\,SH \end{array}$$

(2)

Other representative fungicides which are widely used are captan, chlorothanil, chloranil, dichlone etc.

4.4 FORMULATION

The success of fungicide often depends on the manner in which these compounds are applied. They are applied as wettable powders, dusts or emulsions. Raw fungicide must be pulverised to unform particles of the most effective size. They must be mixed with wetting agents or dissolved in solvents. The wetting agents or solvents should not degrade the fungicide or injure the plant.

4.5 FOLIAGE FUNGICIDES

This type of fungicide is applied to parts of the plants above the ground usually to prevent disease rather than cure it. Fungicides applied to foliage fall into two groups. Those used against fungi, the mycelium of which is exposed on the surface of the leaf, for example powdery mildrews.

In general these fungicides kill fungi by direct contact. But a large number of fungi causing foliar diseases live within the plant tissue. So they are inaccessible to the chemicals applied on the surface. Against such fungi the primary object is protection of the foliage from infection. Such fungicides are protective (known as protective fingicides) and should be applied at a time prior to the arrival of the fungal spores. Otherwise the leaves would be infected. However, if application is too late and the plant was infected, it is still possible in certain cases to apply a fungicide which will kill the infected tissues. Such a compound is usually called an eradiction fungicide.

Foliage fungicide must adhere to the foliage despite weathering. They also must be sufficiently stable chemically and resist degradation by water, oxygen, carbon dioxide and sun light.

Check Your Progress - 1

What do you mean by an eradicant fungicide?

.....

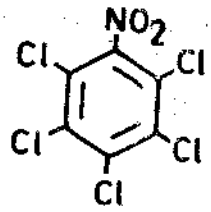
.....

.....

.....

4.6 SEED AND SOIL TREATMENTS

Seeds and seedlings are protected against fungi in the soil by treating the seeds and the soil with fungicide. Seed treating materials must be safe for seeds and resists degradation by soil and soil microorganisms. Some soil fungicides are safe to use on living plants. An example is pentachloro nitrobenzene (3) which can be drenched around seedlings of cruciferous crops and lettuce to protect them against root-rotling fungi. Other soil fungicides such as formaldehyde (HCHO), chloropicrin ($CCl_3.NO_2$) and methyl isothiocyanate (CH_3NCS) are injurious to seeds and living plants. If these volatile compounds are used before planting, they have a chance to kill the soil fungi and then escape from the soil.



(3)

Check Your Progress - 2

What do you mean by seed treatment.

.....

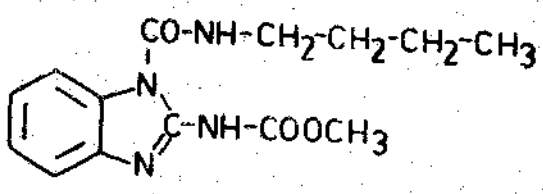
.....

.....

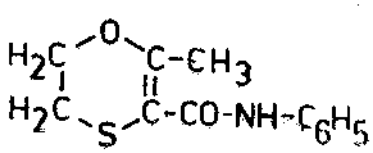
.....

4.7 SYSTEMATIC FUNGICIDES

Systematic fungicides are compounds that permeate plants to protect new growth or to eliminate infections that have already occured. Since the advent of benomyl (4) and of carboxin (5) other effective fungicides like captan (6) have become available.



(4)



(5)

4.8 FUNGICIDAL ACTION

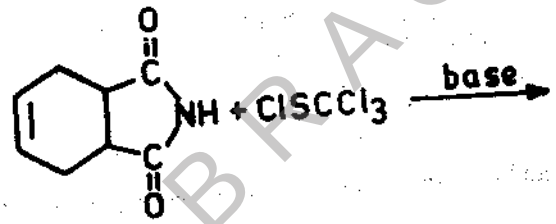
The nature of fungicidal action varies with different compounds. Some alter the permeability and structure of the membranes within the fungus cells. Some interfere with the normal utilization of metabolites by the fungus cell. Other fungicides block or impair cell respiration of the fungus. Many fungicides act as direct toxicants, causing accumulation or production of toxic substances. The effectiveness of a fungicide may be modified by several factors, including light, humidity and temperature.

4.9 APPLICATION METHODS

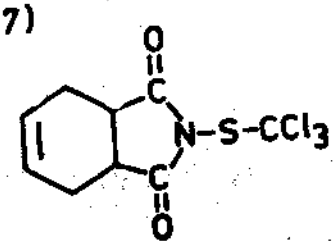
Dusters and sprayers are used to apply foliage fungicide. Conventional sprayers apply 2800-4700 litres/hectare at pressures upto 600 psi. This equipment ensures uniform and adequate coverage of the fungicide. Recent developments in spray equipment are the mist blower and low-pressure, low volume sprayer. The mist blower uses an air blast to spray droplets onto foliage. Mist blowers are useful for applying fungicides to trees but are less satisfactory for application to row crops. The low-pressure low-volume sprayers are light weight machines that apply about 300 liters of concentrated spray liquid per acre at a pressure of about 100 psi. These have been successfully used to protect tomatoes and potatoes against diseases caused by fungi. The most recent refinement of this method is ultra low-volume (ULV) spraying, which employs special spinning cage micronizers. Growers can protect certain crops by applying as little as 2-8 litres of spray liquid per acre. Fungicides are also applied from air crafts.

4.10 CAPTAN

Captan is the trade name of the protective fungicide, N-trichloro-methylthio-1-cyclohexene-1,2-dicarboximide (6) widely used foliage protection since 1949. It is prepared by reacting tetra hydrophthalimide (7) with trichloromethyl-sulphonylchloride (CCl_3SCl) under basic conditions.



(7)



(6)

7. Tetrahydrophthalimide 6. Captan

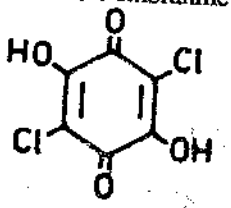
Captan has a pungent odour and is non-volatile, and insoluble in water. It is useful for treatment of the soil or seed to control damping off diseases. Captan is also used as an effective germicide in soaps and for protection of leather against microbial deterioration.

Captan is quite harmless to warm-blooded animals but harmful to fish. Contamination of ponds, water ways and ditches must be avoided with this chemical.

Chloranil was evaluated as a systemic fungicide as it persists very poorly on foliage. Because of this chloranil is used primarily as a seed protectant and has limited utility. It has been used against must of barley and sorghum, bunt of wheat, damping off and seed rot of beans, cabbage, cotton and peas.

Chloranil residue vanishes from foliage due to solublization and loss through hydrolysis photochemical decomposition and sublimation.

Chloranil is hydrolysed to the water soluble chloranilic acid (16) which is lost from the foilage.



(16)

Photochemical instability of chloranil is due to photolysis to the corresponding hydroquinone, and subsequent dimerization.

As chloranil sublimes above 75°F, it disappears from the foilage on hot days.

4.12 MERCURY FUNGICIDES

Inorganic and organic compounds of mercury are highly fungitoxic. They have been used extensively in plant protection especially for seed treatment against seed-borne diseases. The inorganic compounds of mercury were also found to possess bactericidal properties. However due to their persistance in the soil and on the plant surface and toxicity to animal life the use of mercury fungicides is being discouraged. The possibility of phyto toxicity has restricted their use as foliar sprays.

The inorganic compounds of mercury such as mercuric chloride and mercurous chloride are used for seed treatment. Sometimes solutions of the above compounds are used for soil drenching to eradicate the soil-borne pathogens. However due to residual toxicity this treatment is not considered safe. In fruit orchades, wounds on stem and branches are disinfected with mercuric chloride solution.

The organic compounds of mercury are more commonly used, for seed treatment. They have both eradicant as well as protective action.

(i) Mercurous chloride (Hg_2Cl_2)

a. Mercurous chloride is precipitated on addition of chloride ions to a mercury salt.

$$[Hg_2]^{2+} + 2Cl^- \longrightarrow Hg_2Cl_2 \text{ (White)}$$

b. Mercurous chloride is also prepared by heating a mixture of mercuric chloride and mercury.

$$HgCl_2 + Hg \longrightarrow Hg_2Cl_2 \downarrow$$

Mercurous chloride is long used both as an insecticide and as a fungicide for the treatment of turf disease and against club root of brassicas and white rot of onion.

(ii) Mercuric chloride ($HgCl_2$) or corrosive sublmate

a. Mercuric chloride is prepared by heating a solid mixture of the mercuric sulphate and common salt.

$$HgSO_4 + 2NaCl \xrightarrow{\text{heat}} HgCl_2 \downarrow + Na_2SO_4$$

b. A solution of the salt is prepared by adding hydrochloric acid to mercuric oxide.

Mercuric chloride is used at 1 : 1000 dilution for seed treatment. The solution is sometimes used for soil drenching to eradicate soil-borne pathogens. It is also used as a wood preservative.

iii). Mercuric Oxide HgO

Mercuric oxide like some other mercuric compounds is dimorphous. It occurs in yellow and red forms. These two forms differ from each other only in the particle size.

The yellow form is precipitated on addition of alkali to a solution of a mercury (II) salt.

$$Hg^{2+} + 2OH^{-} \longrightarrow \underset{\text{(Yellow)}}{HgO\downarrow} + H_2O$$

The red form is obtained when mercury is heated in air almost to the boiling point.

$$2Hg + \underset{\text{(air)}}{O_2} \longrightarrow 2HgO$$

Mercuric oxide is used as a protective seal on bank injuries and pruning cuts.

4.13 SUMMARY

The main points you have covered in this unit are :

1. Classification of fungicides based on their application into foliage, systemic, seed and soil treatment fungicides.
2. Formulation and the methods of fungicidal action.
3. The methods of application of fungicides i.e., wettable powders, dusts and emulsions.
4. The methods of industrial preparations of organic fungicides captan and chloranil.
5. The methods of preparations of inorganic fungicides $HgCl_2$, Hg_2Cl_2 and HgO.

4.14 MODEL EXAMINATION QUESTIONS

I. **Answer each of the following in 10 lines.**

1. Write short note on the following.
   a) Foliage fungicides b) Fungicidal action c) Mercury fungicides

II. **Answer each of the following in 30 lines.**

1. Discuss the chemistry of Captan.
2. How is chloranil prepared and what are its uses?

4.15 MODEL ANSWERS TO CHECK YOUR PROGRESS

1. A fungicide applied on an infected crop to remove the fungal disease is called as eradicant fungicide.
2. In order to prevent the attack of fungal infections on agriculture crops, fair before harvesting the seedlings are treated with fungicides to destroy the spores of infecting fungi. This process is called seed treatment.

UNIT-5 : HERBICIDES AND RODENTICIDES

Contents

5.1 AIMS AND OBJECTIVES

To describe in brief the meaning, structure and action of few important herbicides and rodenticides. After a thorough study and understanding of this unit, the important points to be remembered are:

* an account of weedicides and the methods of weed control.
* the methods of application of herbicides.
* the chemical classification of weedicides.
* the structures of the common weedicides 2,4-D, monuran and isoproturon.
* an account of the common rodenticides warfarin, zinc phosphide and aluminium phosphide.
* the structure of warfarin and the methods of application of rodenticides.

5.2 INTRODUCTION

Weeds are unwanted plants in agriculture fields. The chemicals used to prevent the germination of the seeds of weeds or kill weeds are called weedicids. These are also called herbicides. They offer competition in crops for water, nutrients and sun light, thereby reduce the crop yield. Thousands of tonnes of food grains are lost due to rodents menace both in the fields and in the store houses chemicals used to kill these rodents are called rodenticides. Usually a rodenticide is mixed with the food material of the rodents called bait and applied to kill the rodents.

5.3 HERBICIDES

In nature, certain plants, the seeds of which are not by man, come up at all times and under all conditions of soil, water and climate. These plants, generally called 'weeds', grow where they are not wanted and particularly when man is attempting to grow something else. Therefore we can define a 'Weed' as an unwanted useless plant or as a plant growing where it is not desired or a plant growing at a time when it is not desired. Jethnotull (1731) was the first person to use the word 'weed' in this sense. For example 'wheat' is a weed in maize fields. Similarly a mustard plant is a weed in oat fields. Prickly pear growing in deserts is not a weed in desert areas but it becomes an agressive weed in nondesert areas.

Weeds reduce crop yields on account of their competition with crop for water, soil nutrients and light. Certain weeds reduce crop growth by releasing inhibitors or poisonous substances into the soil. Therefore weeds increase the cost of labour, make harvesting difficult and reduce the quality and

marketability of agricultural commodities. Some weeds are poisonous to human beings and live stock too. They also harbour insect, fungal and viral organisms.

Therefore there is an absolute need to prevent or control weeds. One of the important methods employed for the purpose is to use chemicals to kill the weeds. A chemical employed to destroy or to kill the weeds is called herbicide.

Classification of weeds :

Weeds are classified, in one type of classification, on the basis of the time required for the completion of the life cycle and the mode of reproduction. The weeds are classified in this type as annuals, biennials and perennials.

Annuals live and produce their seeds in a single growing season. But biennials require two years to complete the reproductive cycle. Perennials live indefinitely. The annuals and biennials multiplicate through seed. But perennials are propagated not only by seeds but also often vegetatively through underground structures such as rhizomes, bulbs and tubers.

5.4 METHODS OF WEED CONTROL

Weed seeds germinate earlier, the seedlings grow faster, flower earlier and mature ahead of crops. Weed menance is generally tackles in two ways, 1) preventive methods and 2) control methods.

Preventive methods consist in using crop seeds not contaminated with weed seeds, using manure, free from weed seeds, and using irrigation water not laden with weed seeds.

Control methods involve mechanical, cultural, biological and chemical measures.

Chemical methods of weed control occupy an important place these days. Chemical weed control can be adopted quite in time, and in situations where the other methods of control fail. The chemical methods of control is easier, less time consuming and less costly.

These chemicals used in this method are called weed killers. Chemical weed control in crops thus makes use of chemicals known as weed killers and increases the yields and ensure efficient utilization of plant protection measures such as insecticidal and fungicidal sprays.

What are Herbicides?

A herbicide is any chemical that kills or inhibits the growth of unwanted plants or weeds.

Selective herbicides remove certain weeds from certain crops. Non-selective herbicides remove a wide range of vegetation although plants differ in their susceptibilities to any special chemical.

The application of any herbicide is effected through foliage or soil treatment. The foilage application consists of treatments made to the leaves of growing plants usually as sprays. Soil treatments are made to the soil before emergence of the crop (Pre emergence) or after the emergence of the crop (Post emergence). In this soil treatment, incorporation of chemical into the soil is essential for obtaining results.

Besides the two popular treatments namely foliage treatment and soil treatment, some times aquatic treatment is also adopted. A number of chemicals are used for control of submerged aquatic weeds. In this control the chemicals are dissolved or emulsified in water in canals, ditches, ponds and lakes.

Check Your Progress - 1

What do you mean by a pre emergent weedicide?

.....

.....

.....

.....

5.5 CHEMICAL CLASSIFICATION OF HERBICIDES

Often herbicides have certain similarities in their structural formulae. Most of them are homologues and analogues of a basic structure. Herbicides belonging to one chemical family tend to have similar modes of action on plants and behaviour in soil. Some important types of compounds employed as herbicides are presented below.

a) Substituted Benzenes

Trichlorobenzenes

Methyl benzenes (Xylenes)

b) Substituted phenols

Nitrosubstituted phenols (Dinosam)

Chloro substituted phenols (PCP)

c) Phenoxy acids

2,4-dichloro phenoxy acetic acid

d) Symmetrical triazines

Atrazine, chlorazine

Prometone

e) Substituted triazoles

Amitrole

f) Substituted pyrimidines

Picloram

g) Substituted ureas

Buturon, Diuron, Isoproturon

h) Substituted amides and anilides

Bensulide, Butachlor

i) Anilines and Toluidines

Benofin, Dibutalin

j) Chlorates and Borates

Ammonium borate

Sodium chlorate

k) Arsenicals

Sodium arsenate

l) Cyanamides

Calcium cyanamide

m) Thiocyanates

Ammonium thiocyanate

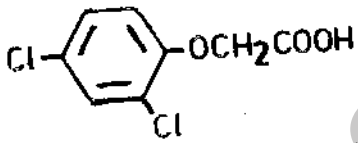
Some widely known and popularly used herbicides belonging to the important categories mentioned above are

i) 2, 4-Dichloro phenoxy acetic acid (2,4-D)
ii) 3- (4-Chlorophenyl)-1, 1-dimethyl urea (Monuron)
iii) 3- (4-isopropyl phenyl)-1, 1-dymethyl urea (isoproturon)
iv) Calcium cyanamide
v) Ammonium sulphamate

Some important properties of these herbicides are presented briefly in the following paragraphs.

i) 2,4-Dichlorophenoxy acetic acid

This is popularly known as 2, 4-D. The chemical structure is



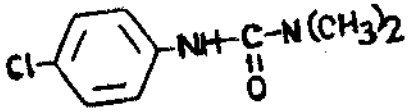
The molecular formula is $C_8H_6Cl_2O_3$ and the molecular weight is 221.4. It is obtained as colourless crystals, melting at 140°C. It is stable upto 50°C for at least 2 years. It is soluble in water upto 0.06 g./100g. at 20°. It is more soluble in organic liquids.

It is selective herbicide and translocatable with properties of a growth promotor. It is useful in postemergence control of annual and perennial broad leaf weeds, in cereals, sugarcane and grass seed crops. Ester formulation are generally used on turf and grassland. It is very important to avoid spray drift. A large drop size should be used during the application. It can be used as a solution or as wettable powder. It can be mixed with other herbicides such as aminotriazole and administered. the compound undergoes degradation in soil and plants to form 2,4-dichloro phenol. Duration of residual activity in soil is about 6 weeks at 1 Kg/ha. As the compound reacts with skin, eyes and respiratory tract of human beings, it is essential to avoid continuous exposure.

No specific antidote is known for this compound. Symptomatic treatment is to induce vomitting. Liver protection therapy and control of circulation are suggested.

ii) 3- (4-Chlorophenyl) 1-1-dimethyl urea (Monuron)

The chemical structure of the compound is

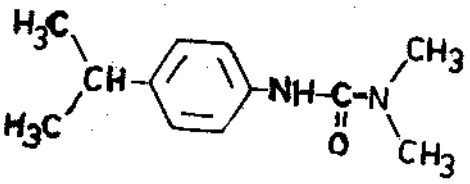


It is chlorophenyl derivative of 1, 1-dimethyl urea.

The IUPAC name of the compound is 3- (4-chlorophenyl)-1, 1-dimethyl urea. It is commonly known as Monuron. Its trade name is Monurex. The molecular formula and the molecular weight are $C_9H_{11}ClN_2O$ and 198.66 respectively. It is available as colourless crystals with a melting point of 174-175°C. It is quite stable in neutral media at normal temperatures but is hydrolysed slowly by acids and alkalis. It is quite soluble in water, the solubility being 230 mg/l. at 25°C. It is a root herbicide and acts through the inhibition of photosynthesis. It functions through the total preemergence control of weeds in noncropped areas. It is used as a selective herbicide in asparagus, cotton, and sugar beet. Monuron could be formulated as wettable powder. It has good comparability with other powder herbicides. In soils and plants, demethylation of the terminal nitrogen atom and simultaneous ring hydroxylation occur. This results in the formation of 3-(2-hydroxy-4-chlorophenyl) urea as the degradation product. Since the herbicide irritates eyes and the skin, contact is to be avoided. No antidote is known. Hence only symptomtic treatment is to be administered.

iii) 3- (4-isopropyl phenyl)-1, 1-dimethyl urea (Isoproturon)

The chemical structure of the compound is



It is seen from the structure that the compound is a derivative of urea. Its trade names are Arelon, Graminon and Tolkan. The molecular formula and molecular weight are $C_{12}H_{18}N_2O$ and 206.29 respectively. It is usually available as colourless crystals melting at 151-153°C. It is highly stable to light and acids. It is soluble in water to the extent of 70 mg/l. at 20°C. It is readily soluble in common organic solvents.

It is absorbed via roots and leaves. It is a selective pre and post emergence herbicide. It is highly useful in the pre and post emergence control of blackgrass, bent grass, wild oats and the broad lead weeds in winter wheat.

Its formulation types include suspension concentrate and wettable powder. It possesses wide compatability with other herbicides.

It undergoes enzymic and microbial demethylation at the nitrogen. The phenyl urea is hydrolysed to 4-isopropyl aniline. The herbicides should be kept out of the reach of children and away from food stuffs. No specific antidote is known for the compound.

iv. Calcium Cyanamide

This can be classified under inorganic herbicides. Its formula is $CaCN_2$. Structurally the compound is represented as

$$Ca = N—C \equiv N$$

The common name of the herbicide is calcium cyanamide and the trade name is cyanamide or Alzodef. The molecular weight of the compound is 80.11. It is generally available as a grey powder and always contains calcium carbide as an impurity. It melts at 1200°C. It is highly stable under dry storage conditions. But it decomposes under moist conditions and in the presence of acids, to calcium hydrogen cyanamide. It is insoluble in water as well as in organic solvents. It acts as a foliant and pre and post emergence herbicide. It possesses secondary fungicidal action. It is used in the preplant treatment of tobacco plant beds and turf seed beds. Chlorophyll of the most plants is sensitive to this compound especially in humid conditions. It is administered as granules. It mixes very well with fertilizers. It is taken into plants and permantively degraded. Skin and eyes must be protected from the compound and no specific antidote is known.

Ammonium Sulphamate

The compound is known by its trade name Ammate, or Amcide. Its molecular formula and molecular weight are $H_6N_2O_3S$ and 114.13 respectively. The chemical formula of the compound is $NH_4SO_3NH_2$. The compound is obtained as colourless odourless, hygroscopic crystals melting at 125 - 130°C (Decomposes at 160°C).

It is very stable under storage conditions and corrosive to metals. The compound is readily soluble in water. It functions as herbicide by rapid absorption via leaves and surfaces in wood. But it causes leaf damage. It is used for nonselective herbicidal control of weeds on noncropped or fallow land or on land to be planted or in forestry. It also controls poison ivy in fruit orchards. It is highly compatable with other water soluble herbicides or wettable powders. It is microbially decomposed in soil within 6-8 weeks. The sprayers are to be washed thoroughly after use and one should not inhale spray mists. The is no specific antidote.

5.6 RODENTICIDES

A great menace is caused to agricultural commodities both in the fields and in the store houses by rats. It is estimated that every year thousands of tonnes of food grains are lost due to this rat menace. It is therefore very essential that the rat population both in the fields and store houses is to be effectively controlled. It is found by experience that many chemicals can be used for this purpose. Those chemicals which kill rats, when the later eat the chemicals, are known as rodenticides. These chemicals are usually mixed with food taken by the rats. The food used for such purposes is called 'bait. The bait is placed in the small holes made in the fields or store houses. The few commonly used rodenticides are

i. Warfarin
ii. Zinc-Phosphide
iii. Aluminium Phosphide

The physical characteristics and the mode of application and action of these rodenticides are described in brief in the following paragraphs.

Check Your Progress - 2

What do you mean by bait?

.....

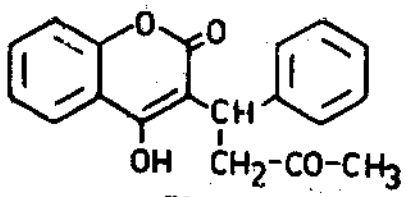
.....

.....

.....

Warfarin

It is sold in the market by various names such as coumfane, Zoo-coumarin etc. The chemical name of the compound is 4-hydroxy-3- (3-oxo-1-phenyl butyl) coumarin. It is a derivative of coumarin, an organic compound generally present in the plants. The chemical structure of the compound is



Warfarin

The molecular formula and the molecular weight are $C_{19}H_{16}O_4$ and 308.22 respectively. It is obtained as colourless crystals melting at 161-162°C. It is highly stable and resists even the action of acids. It is noncorrosive. It is practically insoluble in water (1.7 mg/100 ml. at 20°C). It is moderately soluble in methanol and ethanol. It dissolves readily in aqueous alkalis forming sodium salts. It kills the rats through inhibition of blood coagulation. It blocks prothrombin formation. It is used to control brown rats and house mice. It is administered along with the bait or as a concentrate. It is compatable with other rodenticides. It is less dangerous to humans and domestic animals. It is degraded or metabolised in to hydroxy coumarin. The prepared bait should not be laid indiscriminately and not used within 2-3 meters of the stores. In mills, the bait should be used only in rooms adjoining the storage area. The bait or the chemical must be kept away from food, food stuffs, children and domestic animals. It is essential to avoid contact with skin, eyes and mouth. The chemical must be stored away from heat and flame.

Vitamin K_1 (oral or intravenous) combined with blood transfusions functions as an antidote for the substance.

ii) Zinc Phosphide

This is an inorganic chemical, widely used as a rodenticide. The chemical formula is Zn_3P_2. It is an amorphous greyblack powder with a garlic-like odour. It melts at temperatures higher than 420°C and has a molecular weight of 258. It is stable under dry conditions but decomposes slowly in moist air. It reacts violently with acids with the formation of highly toxic and inflammable phosphine. It is practically insoluble in water and alcohol. It is used as a bait rodenticide for the control of rats, mice, ground squirrels and house mice.

In the event of incorrect or careless storage, there is a danger of explosion and fire hazard through the evolution of phosphine. Care must be taken to keep the chemical away from children, domestic animals, food and food stuffs. No specific antidote is known. Emptying the stomach and administration of medicinal charcoal and oxygen help to a large extent.

Since it is very harmful to human beings and domestic animals, this has to be used only in special and by trained people.

iii) Aluminium Phosphide

This chemical is almost similar in action and other properties to zinc phosphide. But this is less toxic and dangerous than zinc phosphide. Its chemical formula is Al P. It is obtained as a gray powder with characteristic odour. It reacts with acids and liberates poisonous gases. It is used to kill or control of field rats, mice, and house mice.

5.7 SUMMARY

The main points you have studied in this unit are:

1. the methods of weed control.
2. the classification of weedicides based on molecular structure.

3. some important properties of herbicides 2,4-D, monuron, isoproturon, calcium cyanamide and ammonium sulphamate.

4. some physical characteristics, mode of application and the action of the rodenticides warfarin, zinc phosphide and aluminium phosphide.

5.8 MODEL EXAMINATION QUESTIONS

I. **Answer each of the following in 10 lines.**

1. Discuss in brief the meaning of a 'weed' and describe its harmful actions.
2. How are herbicides classified?
3. Discuss how rodenticides are applied and describe their mode of action.

II. **Answer each of the following in 30 lines.**

1. Describe in detail the meaning of a herbicide and describe the action and structure of three important herbicides.
2. Discuss the meaning of a rodenticide and describe the action and structure of two rodenticides.

5.9 MODEL ANSWERS TO CHECK YOUR PROGRESS

1. A weedicide with which the soil of the field is to be treated to prevent the germentation of the seeds of the weeds before the emergence of the crop is called a preemergent weedicide.

2. The food material of rodents which will be mixed with a rodenticide to prevent the rodent menace in agriculture is called the bait.

Author : Mrs. C. Sesharatnam

BLOCK - 3 : PLANT GROWTH HORMONES, ENVIRONMENTAL EFFECTS OF AGROCHEMICALS AND PESTICIDE FORMULATION

Organic compounds that play a major role in the plant growth are plant growth hormones. Some of them promote growth by cell elongationand others byincreasing the cell division. Ethylene is responsible for fruit repending. There are some hormones that inhibit the plant growths called plant growth inhibitors. By a systematic co-ordinated application of these hormones in modern agriculture, it is possible to promote proper growth of the crops and achieve high yields.

Most of the people in our country depend on agriculture for their livelyhood. By the use of high yielding crop varieties, fertilizers and pesticides the agriculture produce has been tremendously increased in the last twenty five years. This increase is called green revolution. There are different methods of the application of pesticides called pecticide formulation. Repeated application of agrochemicals in the fields is leading to environmental pollution. Therefore in order to avoid this we have to encourage farmers to use such agrochemicals that do not persist long and get biodegraded in a short time after their application.

Chlorine : Many chlorine containing organic substances have been found to be the metabolites of many micro organisms. However, no such compounds have been obtained from higher plants. Chlorine is shown to play an important part in oxygen evolution during the primary photo-synthetic processes. Deficiency of chlorine leads to the wilting of the leaf blade tips.

Cobalt : Many micro organisms need cobalt for their growth and metabolism. Cobalt plays an important role during the fixation of elemental nitrogen by the rhizobia of the leguminous and non-leguminous plants. It is a structural component of vitamin-B_{12} (Cyano cobalamine) which is essential for the formation of intermediates needed for nitrogen fixation. Besides, cobalt plays a catalytic role by activating the enzymes.

1.13 SUMMARY

The main points you have learnt in the unit are,

(i). The historical aspects and the importance of fertilizer in agriculture.

(ii). Classification of plant nutrients into macro and micro types.

(iii). Classification of fertilisers based on their action on the soil into direct, indirect, complete, incomplete and mixed fertilisers. Fertilisers are also classified on the basis of their sources into two types. They are natural and synthetic fertilizers.

(iv). The industrial manufacture of urea, ammonium sulphate, super phosphate and potassium sulphate.

(v). The importance of micronutrients in plants. These nutrients are Cu, Zn, Fe, Cl and Co.

1.14 GLOSSARY

1. **Enzymes :** Proteins made in the protoplasm of cells that catalyse or speed up the reactions in them.
2. **Fixation of Nitrogen:** Conversion of the elemental nitrogen from the atmosphere into organic compounds containing nitrogen.
3. **Nutrient :** A substance having food value, or able to be used by plants to make food.

1.15 MODEL EXAMINATION QUESTIONS

I. **Answer each of the following in 10 lines.**

1. What is a fertilizer? Give the classification of the fertilizers.
2. How is urea manufactured? What makes urea a good fertilizer?
3. How is super phosphate manufactured?
4. Give the method of manufacture of ammonium sulphate by the Gypsum process.

II. **Answer each of the following in 30 lines.**

1. What are the important functions of nitrogen in plants?
2. List the micronutrients essential for plant growth.
3. Discuss the role of zinc and iron as micronutrients for plants.

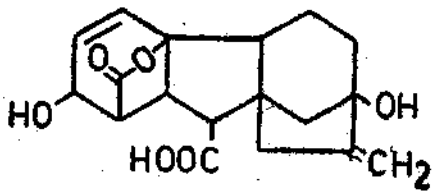
Iron : Iron is a constituent of several porphyrin compounds. It occurs in cytochromes which are known to play an important role in oxidative phosphorylation during respiratory electron transport and photophosphorylation during photosynthesis. Ferredoxin, an iron containing protein helps reduction of carbondioxide, atmospheric nitrogen and sulphate. The root nodules of leguminous plants contain a haemoglobin like protein containing iron. Iron is well known for its catalytic role in enzyme activity. Succinic dehydrogenase, sulphite oxidase, cytochrome oxidase, catalase and peroxidase are some of the important enzymes which contain iron. Iron is directly or indirectly involved in all the major metabolic processes of plants. It plays a direct role in the photosynthesis in which atmospheric carbondioxide is transformed into complex organic substances. It also plays an important role in oxidative phosphorylation and nitrogen fixation. Deficiency of iron in plants results in the disintegration of chloroplasts and a decrease in reducing sugars and organic acids.

1.16 MODEL ANSWERS TO CHECK YOUR PROGRESS

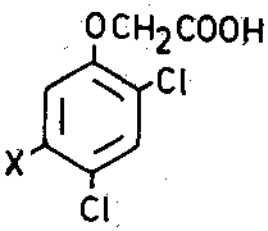
1. Synthetic or natural substances that are added to the field to maintain the soil fertility are called fertilizers.

2. The elements which are required for plants in very small quantities are called micronutrients.

Author : Prof. P.S. Rao.



(37)

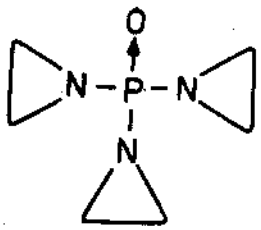


X = H (38)
X = Cl (39)

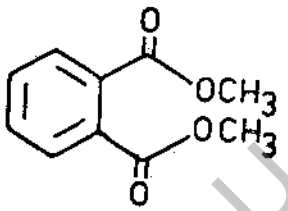
2.9 PHEROMONES (SEX ATTRACTANTS) AND HORMONES

In recent years more modern methods and chemicals are used in agriculture mainly to protect crops, vegetables, fruits and food grains from the agricultural pests. Some of them are insect sterilants, insect repellents, insect sex attractants (pheromones) and juvenile hormones.

When APO or tepa (triaziridyl phosphine oxide) (40), is used as a sterilant for male insects, the insects become sterile and their progony is not developed. DMP (dimethyl phthalate) (41) is used as insect repellent, to repel from infecting the crops.

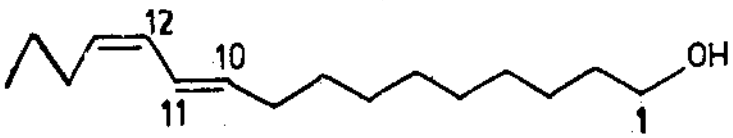


(40)



(41)

There are some chemicals secreted from the body of certain insects during certain periods to use as insect signalling agents. For example, at the time of mating, some chemicals are released by insects. By the smell of these chemicals, insects of opposite sex are attracted to participate in their courtship. Such cnemicals are known as pheromones (insect signal agents). Bombykol (42) (1-hydroxy-trans 1-cis-12-hexadecadiene) secreted from the abdominal cells of the silkworm moth acts as sex attractant. Usually sex pheromones are used to attract male or female insects from a distance and then they can be trapped or made sterile by using chemical sterilants.



(42)

Check Your Progress - 2

What are Pheromones?

.....

.....

.....

.....

Hormones are certain chemicals secreted in the insects, animals and mammals from the ductless glands. They are useful in various metabolic activities. For example, ecdysone (43), a juvenile hormone if present in excess, it interferes with the normal life cycle of insects and prevents the insects from reaching mature adult stage.

There are other biological methods also developed to control the problem of pests. For example, certain bacterium is cultured and used to infect at the larval stage of certain insects. Similarly, weeds can also be eradicated by using certain type of insects or bugs.

2.10 SUMMARY

In this unit you have learnt about:

i. The classification of pesticides into different types based on the nature of the pest causing organisms.

ii. The inorganic insecticides lead arsenate, calcium arsenate and organic insecticides DDT, BHC, endrin, endosulphan, parathion, malathion, monocrotophos, carboryl and carbofuran.

iii. The insecticides of plant origin prepared for their own protection. They are pyrethrins, rotenoids and nicotine.

iv. The importance of fungicides, herbicides and also rodenticides.

v. The role of plant growth regulators in agriculture.

vi. The importance of sex attractants of insects called pheromones and furemile hormones in agriculture.

2.11 GLOSSARY

1. **Biodegradability :** This is the property of a synthetic chemical to undergo decomposition into simpler harmless compounds by the action of micro-organisms or sun light etc.

2. **Enzymes :** Enzymes are chemicals secreted in the body which are used to catalyse the metabolic reactions.

3. **Fungicides:** Fungicides are chemicals used to kill fungi.

4. **Herbicides:** Herbicides are chemicals used to kill unwanted plants such as herbs or weeds.

5. **Hormones:** Hormones are chemicals secreted by ductless glands in animals which are useful to regulate various physiological activities.

6. **Insecticides:** Insecticides are chemicals used to kill insects.

7. **Insect attractants:** They are naturally occurring pheromones or synthetic compounds used to attract insects for trapping or to destroy them.

8. **Insect repellents:** They are the chemicals by the smell of which, insects are repelled.

9. **Insect sterilants:** They are chemicals used to make the insects sterile.

10. **Persistance:** : It is the property of a pesticide without undergoing biodegradation or decomposition by a natural process.

UNIT-6 : ORGANIC PLANT GROWTH HORMONES

Contents

6.1 AIMS AND OBJECTIVES

To introduce the organic plant growth hormones dealing briefly with their importance in the regulation of plant growth, and their isolation.

Once you complete the study and comprehension of the contents of the unit, you are expected to

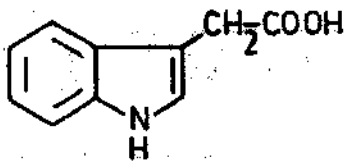
* know that there are four types of plant growth hormones auxins, gibberellins, cytokinins and ethylene.
* realise that some hormones elongate the plant cells and others promote cell division and ripen the fruits.
* remember the structures and hormonal activity of indole acetic acid, gibberellic acid, 6-furfuryl-amino purine, diphenyl urea, sorbitol and ethylene.
* know that abscissic acid, naringenin, vanilic acid and azelaic acid are some plant growth inhibitors.

6.2 INTRODUCTION

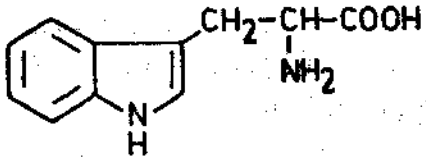
The organic compounds that are produced in very small quantities but play a decisive role in plant growth are called plant growth hormones. Four major types of plant growth hormones are found to exist in plants. They are i) auxins ii) gibberellins iii) cytokinins and iv) ethylene. The auxins and gibberellins mainly promote growth by causing cell elongation while cytokinins stimulate cell division. Ethylene plays an important role in plant growth development and ripening of fruits. A delicate balance of these hormones besides other factors is needed for proper control of growth and morphogenesis of plants.

6.3 AUXINS

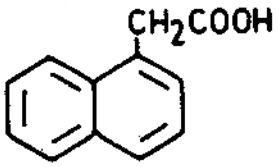
It was recognised that leaf tips produce some special substance which control plant growth. This was termed as auxin and was identified as indole acetic acid IAA (1), Tryptophan (2) was considered as the biogenetic precursor of IAA. After the recognition of IAA as growth regulating substance several substances with auxin activity were synthesised such as indole-3-aceto nitrile, indole 3-propionic acid, naphthalene acetic acid (3). 2, 4-dichloro phynoxy acetic acid (4) and 2,4,5-trichloro phynoxy acids are widely used as selective herbicides.



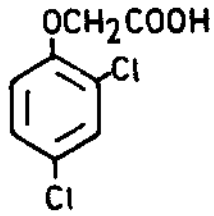
(1)



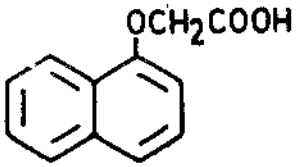
(2)



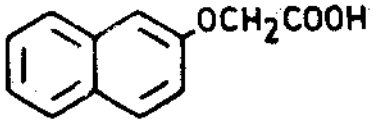
(3)



(4)



(5)



(6)

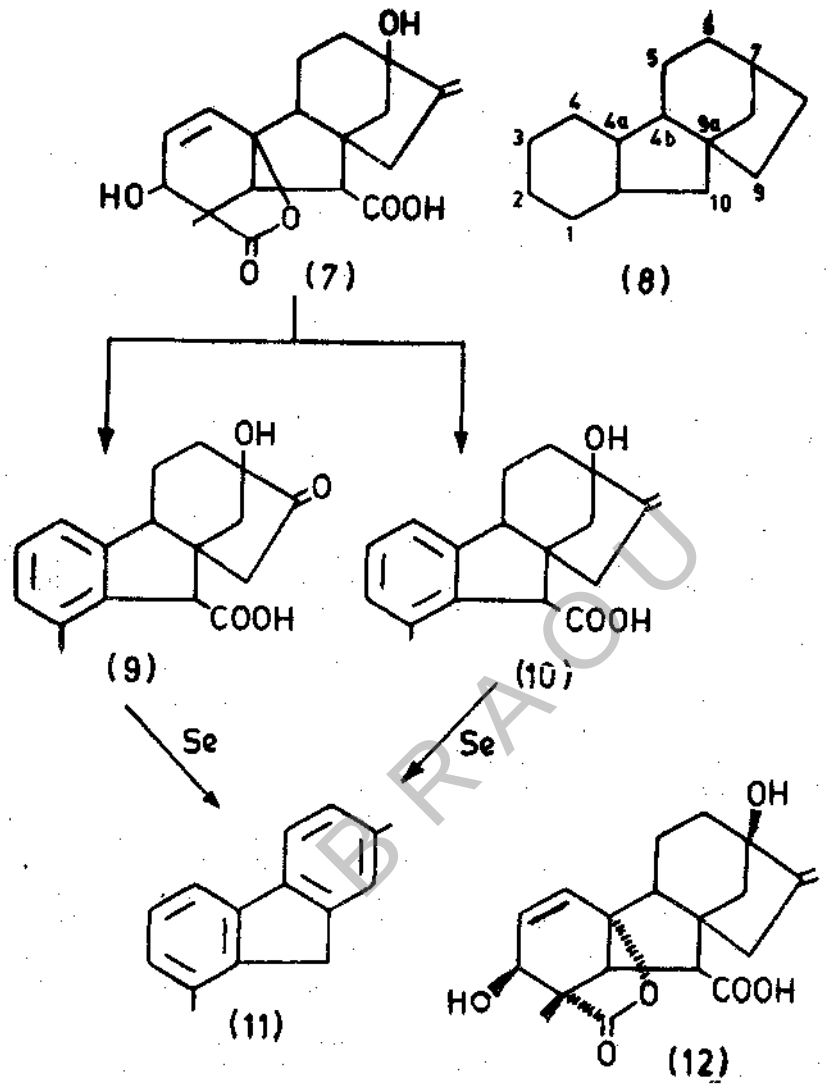
6.4 GIBBERELLINS

A group of closely related compounds called gibberellins form the most important plant hormones. The researches of the Japanese scientists (Sawada, 1912; Krosawa, 1929 and Yabuta, 1935) led to the discovery that the fungus, Gibberella fugifuroi was responsible for the bakanae disease of rice. The disease is characterised by unusual elongation of seedling. They also discovered that the same fungus which infects rice plants could also stimulate the growth of rice seedlings. The active principle of the fungus was called 'Gibberellin' after the name of the fungus was called 'Gibberellin' after the name of the fungus. Mitchell and Angel (1950) later showed the culture filtrate of the same fungus stimulates bean seedlings. The pure substance isolated from the fungus (Cross, 1954) was named as Gibberellin; acid (7). The chemical structure of this was established by Cross and his co-workers in 1961.

All naturally occurring compounds which possess a gibbane skeleton (8) with required biological properties are given the generic name Gibberellins. They have also been designated as GA_1, GA_2 and so on. Infact, GA_3 is gibberellic acid. A large group of gibberellins have been discovered during the last three decades. There are some naturally occurring substances whose chemical structures have not been established but still show similar biological properties as Gibberellins and are termed "Gibberelline like substances".

i) **Gibberellins - Occurrence and Isolation :** Gibberellin and gibberellin like substances have been found to occur in all flora starting from bacteria, fungii, algae, ferns to higher plants. They have been shown to play a decisive role in all the phases of plant growth and development from germination of seeds to senescence. They may be in the form of free gibberellins or bound to glucose. Only three gibberellins were extracted from the fungus, Gibberellus fugikuoi. The material is first extracted with methanol or n-butanol. The compounds are isolated and purified by using chromatographic methods and counter current distribution methods.

ii) **Chemical Structure :** The gibberellins are isopropenoid in nature and belong to a class of compounds called the diterpenes, with 20 carbon atoms, composed of four isoprene units. Some of them possess only 19 carbons. All of them contain the basic structure (8) called 'gibbane' and consist of a tetracyclic system with four carbocyclic rings fused together. The numbering of the system is represented in the figure.



Check Your Progress - 1

What are gibberellins?

.....

.....

.....

.....

6.5 CYTOKININS

In tissue culture experiments it was discovered in addition to indole acetic acid, another substance was needed for sustained growth of the callus tissue. This substance named as Kinetin was identified as 6 furfurylamino purine (13). In plants Kinetin is never found as such although other related adenine derivatives are found. They also induce cell division and are collectively called cytokinins. A few other substances like diphenyl urea (14), sorbitol (15), myo-and scylloinositols (16, 17) are recognised as cell division hormones.

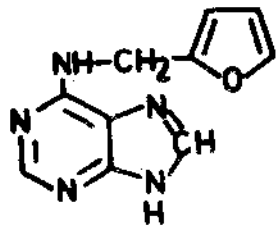
6.6 ETHYLENE

Ethylene is an important hormone having a role in plant growth, development and ripening of fruits. It was first found to be abundant in bananas even before ethylene was discovered it was found that ripening fruits give off a volatile substance which accelerates the ripening of other fruits stored nearby. In fact, many of the activities which were hitherto attributed to auxins are attributed to ethylene activity alone or in combination with auxin.

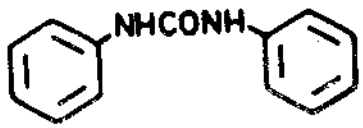
In addition to hormones several vitamins have also been used to promote plant growth.

6.7 PLANT GROWTH INHIBITORS

In addition to growth hormones plants produce some growth inhibitors also. Three types of inhibitors have been recognised based on their physiological functions. These are i) dormancy inhibitors, such as abscissic acid ABA; (18), a sesquiterpene derivative and naringenin (19) a flavanone pigment ii) Germination inhibitors such as coumarin (20), salicylic acid, vanilic acid (21) and ferulic acid (22) and azelaic acid, COOH. $(CH_2)_7$.COOH and iii) Extension growth inhibitors such as coumarin and chelidonic acid (23), a γ-pyrone dicarboxylic acid. Several synthetic plant growth inhibitors such as α– and β–naphthoxy acetic acids (5, 6) and 2, 4, 6-trichlorophenoxy acetic acids have been in use.

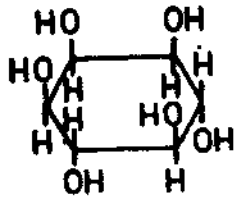


(13)

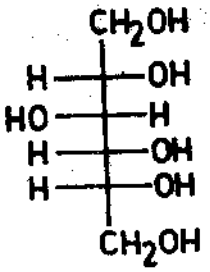


(14)

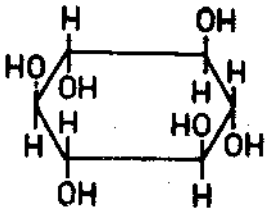
13. 6-furfusylamins Purine 14. Diphenylurea



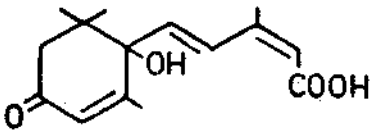
(16)



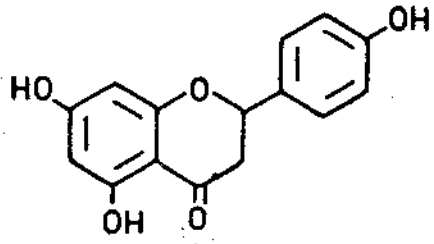
(15)



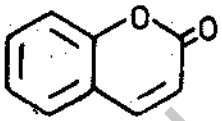
(17)



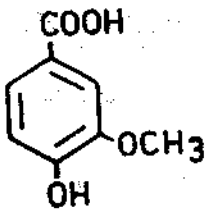
(18)



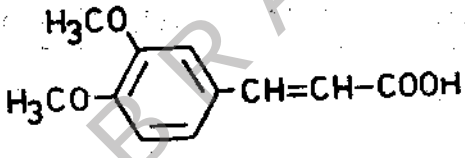
(19)



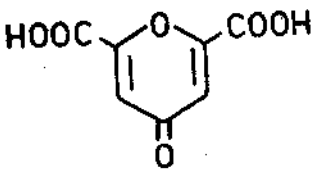
(20)



(21)



(22)



(23)

15. Sorbitol 16. myoinositol
17. Scylloinositol 18. abscissic acid (ABA) 19. Naringenin
20. Coumarin 21. Vanilic acid 22. Ferulic acid
23. Khelidonic acid.

Check Your Progress - 2

What are plant growth inhibitors?

.....

.....

.....

.....

6.8 SUMMARY

The main points you have studied in this unit are :

1. The role of hormones in plants and their types.
2. The representative members of auxins, gibberellins, cytokinins and ethylene.
3. Plant growth inhibitors that supress the growth of plants at different stages.

6.9 MODEL EXAMINATION QUESTIONS

I. **Answer each of the following in 10 lines.**

1. Write a short note on the role of plant growth hormones.
2. Write down the structure of gibberellic acid, and indicate its key reactions and products.

II. **Answer each of the following in 30 lines.**

1. Write a concise account on the plant growth hormones.

6.10 MODEL ANSWERS TO CHECK YOUR PROGRESS

1. Naturally occuring biologically active organic compounds containing the gibbane skeleton are called gibberellins.

2. Hormones of plant origin or synthetic that inhibit the growth of plants are called plant growth inhibitors.

Author : Prof. A.S.R. Anjaneyulu

UNIT-7 : EFFECTS OF AGROCHEMICALS ON THE ENVIRONMENT

Contents

7.1 AIMS AND OBJECTIVES

To introduce the impact of use of several agrochemicals, such as inorganic and organic fertilisers, plant growth regulators, insecticides on the environment and to highlight on the importance of biodegradable pesticides.

Once you study and understand the contents of this unit, you are expected to :

* realise the toxic effects of the persistant pesticides and their degraded products.
* find out the environmental effects of pesticides.
* recognise the importance of the limits of pecticidal residues.
* realise the importance of biodegradable pesticides in the modern agriculture.

7.2 INTRODUCTION

India is an agricultural country. There has been increasing use of inorganic and organic fertilisers for bringing out higher crop production along with denser spacing methods for cultivating more plants per unit area. This led to increased agricultural produce fittingly termed as "green revolution". As a result, more and more pest control methods need to be employed necessitating increasing use of modern synthetic pesticides (insecticides, fungicides, herbicides etc.

7.3 PESTICIDE RESIDUES AND THEIR PERSISTENCE

Most of these substances are toxic and persist in the environment for varying periods, and in some cases for a few years. The duration of retention of a pesticide preparation in the environment usually is called persistence. The persistence of a chemical depends both on physical and chemical properties like volatility, hydrolytic stability, resistance to the action of soil microorganisms and to oxidation by air stability to light. In some cases they biodegrade into totally harmless substances but in a few other cases the biodegraded products are more toxic than the parent compounds.

The following table gives some of the insecticides and their persistence after use:

Examples	Persistent nature	Duration of activity
Malathion, Parathion, Methyl Parathion, Carbaryl	Non-persistent	1 - 12 weeks
DDT, BHC, Aldrin, Endrin, Chlordane, Heptachlor	Persistent	2 - 5 years
Phenyl mercury acetate arsenate of lead	Permanent	Degraded to permanent residues

Check Your Progress - 1

What do you mean by pesticidal persistence?

.....

.....

.....

.....

7.4 ENVIRONMENTAL EFFECTS

For successful use of pesticides in agriculture it is necessary that in addition to their high biocidal activity for various pests, the preparations should be sufficiently safe in both production and use for man, domestic animals, useful plants and beneficial insects and microorganisms. After specific periods, plants that have been treated with any pesticide must contain only safe residual amounts of the compound. Indiscriminate and excessive use of pesticides and other substances have led to wide-spread detection of pesticide residues and their biodegraded products in various food products, drinking water and air. The live stock, the human beings, the aquatic flora and fauna are affected by the toxic effects of these substances resulting in serious health hazards and ecological imbalance.

i) **Pest-Natural enemy equilibrium :** The first impact of the use of pesticides on environment will be reflected on the equilibrium existing between the insect pests and their parasites or predators. In the rice fields, spiders are natural enemies of the insects, rice stem borers. Extensive use of BHC for the control of rice-stem borers affect the spider population through their feeding on contaminated prey. It was observed that the leaf and plant hoppers decreased immediately after application of either parathion or BHC but their populations restored to original levels after three or five weeks. This rapid build up of the insects after application of the insecticides was found to be due to the destruction of the spider population which feed on both the adults and larve of the insects. Successful application of any pesticide must supress more effectively the green leaf hopper population without affecting their natural control agents.

ii) **Impact on Non-target species :** Together with the target pest, several non-target insects are also reduced. Extensive use of insecticides in rice fields are often subject to criticism as they also reduce aquatic beneficial insects such as spiders, dargon flies and fireflies.

iii) **Impact on Aquatic organisms :** The soil generally acts as a reservoir for pesticides from which they degrade or gradually spread to other environments eg. water and air. Pesticides such as BHC and parathion and in particular, the water soluble compounds such as the sodium salt of PCC used in the rice fields are translocated to the nearby lakes, irrigation canals and ultimately to rivers. Accumulation of these in greater concentration were found to kill and affect the fish and shell fish.

iv) **Hazards to wild life :** Rats are a menace on the rice fields as well as to the stored grains and food products. Several rodenticides have been in use. These highly toxic substances may indirectly affect the canine wild life which eat the dead rats killed by the poisons. The death of swallo's and sparrows were reported in the fields sprayed by parathion and fenithion to treat the rice hoppers.

v) **Contamination of foods and the human body :** Pesticide residues come to stay on and in food commodities to varying proportion. Consumption of the food stuffs contaminated beyond tolerance levels may cause acute or chronic health hazards to live stock and human beings. High levels of BHC isomers have been detected in the milk of cattle which were fed on rice straw and dressed grains with residual pesticides. The pesticide residues may be accumulated in the animals in their livers. These in turn have affect on the human beings who depend on them for their food.

7.5 LIMITS OF PESTICIDE RESIDUE

Several physicochemical techniques have been developed to estimate the pesticide residues. Various standards such as lethal dose, tolerance level, accepted daily intake have been fixed up. The required laws have been enforced to stick to these standards. Lethal dose (LD_{50}) is the amount expressed in mg/kg/body weight required to kill 50% of the test animals. Accepted daily intake (ADI) of a substance is expressed in mg/kg of body weight/day which can be consumed during an entire life with no harm. Tolerance level of a pesticide residue is its maximum concentration that is permitted in or on a food stuff. Different levels are specified at various stages of harvesting, storage, marketing and preparation of the food upto the final point of consumption.

7.6 BIO-DEGRADABLE PESTICIDES

Most of the chloroorganic insecticides and pesticides like DDT, BHC, aldrin and endrin are very resistant to the degradation by microbes and persist in nature for varying periods. It might be for the reason that they have chemical structures which do not exist in nature. On the other hand, the several organophosphorous insecticides undergo a very rapid hydrolysis in the environment giving ultimately phosphoric acids with no problem of building up residues. However, they are some times converted to more toxic substances by environment for example, parathion is readily oxidised by atmospheric oxygen or enzymatically to a derivative that is four times as toxic as parathion itself.

Check Your Progress - 2

Give some examples for pesticides that persist for a long time.

.....

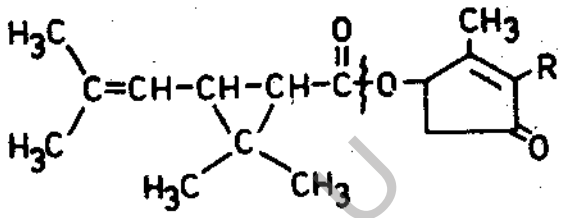
.....

.....

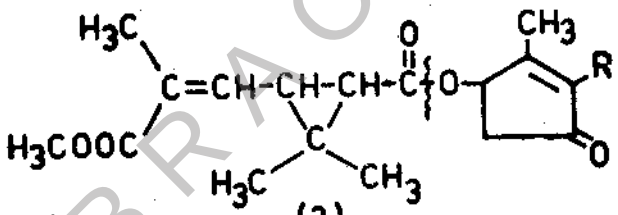
.....

Pollution free pesticides should be stable chemically but sensitive to photolysis and degradation by micro-organisms. It is supposed that the naturally occurring compounds or their derivatives are amenable to microbial degradation and may not pose environmental problems. For this reason, interest in the use of natural insecticides and pesticides e.g., pyrethrins and cinerins from chrysanthemum flowers, the rotenoids derived from the plant species Derris, Lonchocarpus and Tephrosia, nicotine from the tobacco waste and the oil and the seed powder of neem has been revived and increased many fold. For instance, the powder of dried chrysanthemum (pyrethrum) flowers has been in use for many centuries to control harmful insects. The structures of the active ingredients Pyrethrin I (1a) Cinerin I (1b) and Pyrethrin II (2a) and Cinerin II (2b) were established. These are primarily esters of a Chrysanthemic acid, cyclypropane carboxylic acid (3a) or its derivative (3b) and an alcohol (4), a substituted cyclopentenone derivative (4a or 4b). They are readily hydrolysed by alkalies and are rapidly inactivated used in the food industry. Most of the mosquito coils in the control of mosquito do contain pyrethroids. Several synthetic pyrethroids have been prepared in an effort to increase their insecticidal activity and reduce mammalian toxicity over the natural ones, as well as to reduce the cost of the latter. Two of these are bioresmethrin (5) and permethrin (6) which are closely related to pyrethrin and found to be 50 times as active as pyrethrin and much less toxic. Another biodegradable chloroorganic insecticide in use is fenvalerate (7), α-cyano-3-phenoxy benzyl α- (4-chloro-phenyl-isovalerate which is an ester of α- (4-chlorophenyl) isovaleric acid and m-phenoxy-α-cyano benzylalcohol.

More modern methods of pest and insect control insect pheromones, insect repellants and antifeedants.



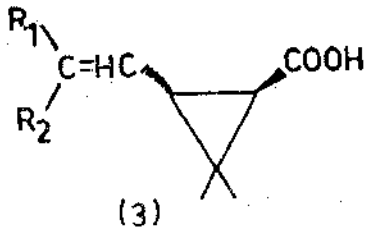
(1)



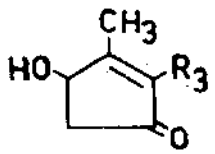
(2)

a) R = $-CH_2-CH=CH-CH_3$

b) R = $-CH_2-CH=CH-CH=CH_2$



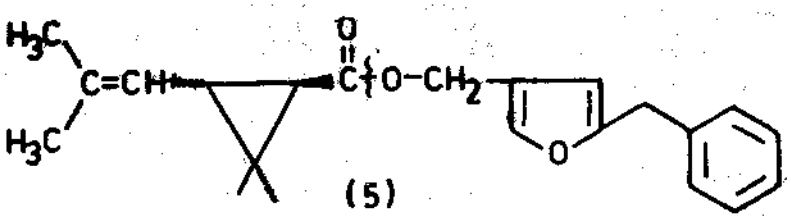
(3)



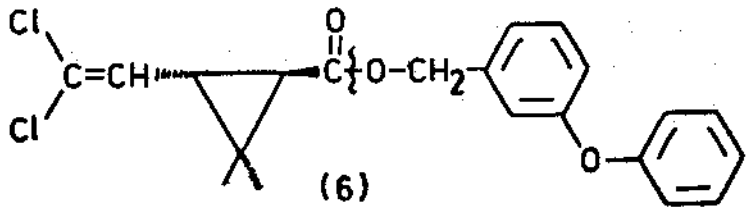
(4)

a) $R_1=R_2=CH_3$ a) $R_3=-CH_2-CH=CH-CH_3$

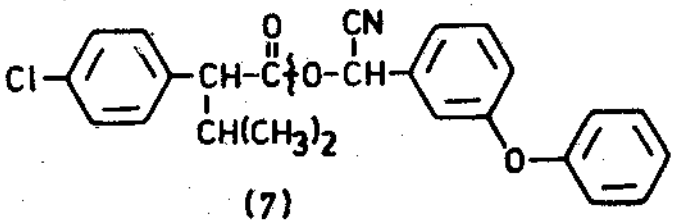
b) $R_1=CH_3$, $R_2=COOCH_3$ b) $R_3=-CH_2-CH=CH-CH=CH_2$



(5)



(6)



(7)

5. Bioresmethrin 6. Permethrin 7. Fenvalerate

7.7 SUMMARY

In this unit you have studied about :

i. The persistence of pesticides in agriculturel

ii. The toxic effects of the pesticides and their degraded products on the environment i.e., live stock, human beings, the aquatic flora and fauna which result in serious health hazzards and ecological imbalance.

iii. The pecticidal standards lethal dose, tolerence level and the accepted daily intake.

iv. The biodegradation of pecticides, a property that minimises the environmental pollution due to pecticides application in agriculture.

7.8 MODEL EXAMINATION QUESTIONS

I **Answer each of the following in 10 lines.**

1. Write a short note on the pesticide residues and their persistence.

II. **Answer each of the following in 30 lines.**

1. Write a concise account on the pesticidal residues and their effect on environmental pollution.

7.9 MODEL ANSWERS TO CHECK YOUR PROGRI

1. Pesticidal persistence is the duration of the retention of the pecticide after into application in the agriculture field.

2. They are DDT, BHC, endrin and aldrin.

UNIT-8 : PESTICIDE FORMULATIONS

Contents

8.1 AIMS AND OBJECTIVES

To introduce the student to the various formulations of pesticides used in agriculture.

Once you complete the study and comprehension of this contents of the unit, you are expected to :

* realise the importance of the pesticide formulation i.e., the methods that bring the pesticides into the direct contact of the pests.
* know the prominent methods of pesticide formulation dusts, wettable powders, solution concentrates, emulsifiable oils, aerosols and sustained release formulations.
* find out the advantages and disadvantages involved in different methods of pecticide formulation.

8.2 INTRODUCTION

The success of pesticides to control harmful insects, mites, micro-organisms and weeds depends to a large extent on its formulation i.e., its preparation, and the conditions under which the chemical compound is brought into contact with the pests. As the chemical compounds vary in their nature a large number of formulations suitable for their practical use are necessary. Several hundreds of different formulations are being use are necessary. Several hundreds of different formulations are being employed. The most important types of formulations are the following.

1. Dusts
2. Wettable powders
3. Solution concentrates
4. Emulsifiable oils
5. Aerosols
6. Sustained release formulations

8.3 DUSTS

The insecticides are used as dusts or powders. The active ingredient is mixed with an inert diluent and pulverised to a particle size of 3-30 μ. In the grinding process, the pesticide particles are not only distributed evenly among the particles of the diluent but give an effective coating on them. An efficient dust is therefore, formed by grinding the pesticide and the diluent together rather than mixing these two after grinding.

Pesticides with a well formed crystalline structure having high friability and low plasticity grind well and give good dusts. The grinding is made in either a ball mill or an air-jet mill. For the best preparation of a pesticide, it is necessary that, it should not form lumps either during preparation or storage. A suitable diluent in the proper proportion is essential to prevent lumping. For example, pure DDT which melts above 106°C is easily ground and needs only 5 - 10% of kaolin as diluent. But a technical grade DDT contains oily impurities, and forms coarse aggregates and sticks to the walls of the mills and requires 25% of kaolin as diluent. Dusts from liquid organic compounds can be easily made by mixing the active constituent with the diluent.

The best diluents for most of the preparations used in dusting plants are hydrophobic minerals of the talc and pyrophyllite type, which have a lamellar structure and adhere well to the plant foliage. It is necessary that the diluent is chemically inert which otherwise may catalyze the decomposition of pesticides or effect their photochemical stability. For example, alkaline diluents cannot be used in the production of dusts from esters, as they are hydrolysed. The use of kaolin, clay and bentonite which are hydrophilic easily cake in highly humid conditions. In such cases, hydrophobic compounds such as calciumsitreate, mineral oils are added to increase the retention of powder formulation on plant.

Check Your Progress - 1

What do you mean by a diluent in the preparation of dusts?

.....

.....

.....

.....

8.4 WETTABLE POWDERS

Formulations in the form of powder which on dilution with water yield stable suspensions are called wettable powders. Suspensions are usually more effective than dusts. The same dosage of pesticides is more effective when sprayed on plants and other surfaces than dusted. The particles of a suspension adhere well to surfaces, do not penetrate and can be washed off.

The wettable powders need the following requirements.

1) They must be reasonably stable in storage and should not form cake.
2) They must be capable of forming suspensions rapidly, and take longer time for settling of solid particles.
3) They must spread easily over the surface of sprayed objects and retain on the sprayed surfaces for longer time.

The effectiveness of a wettable powder depends on the dispersion of the active ingredient which should contain not less than 80% of its particles with a size below 3µ. Wettable powders differ in their method of preparation. The active ingredient, is generally used in combination with a diluent, a surface active agent, and an auxiliary material. Special stickers are also, sometimes, added to them to increase their retention power.

The following table gives typical formulations of wettable powders containing 90 per cent DDT.

Ingredients	Composition (%)			
	A	B	C	D
DDT	90	90	90	90
Diluent	7	6	7.5	6.5
Emulsifier	3	3	-	-
Auxiliary material	-	1	-	1
Film forming material	-	-	2	2
Wetting agent	-	-	0.5	0.5

Effective formulations are made by using pure insecticides without impurities and a diluent with low density and large sorbtive capacity. As diluents special kinds of silica gels, hydrated aluminium oxide, calcium silicate are used. With a poor quality diluent, a surface active agent is added which increases the sorbtive capacity of the surface.

A variety of detergents is also used in the preparation of wettable powders. These are alkylaryl ethers of polyethylene glycol poly-propylene glycol and sulfonates of alkali metals.

As auxiliary materials, sodium salts of sulfonic acids, obtained by sulfonation of petroleum products and lignin are used. Sometimes, film forming materials such as carboxymethyl cellulose, polymers of unsaturated alcohols, gelatin, animal glues, caseinates and salts of resin acids are used.

The wettable products are produced by grinding the active insecticide with the diluent and the other ingredients, in a colloidal mill, in an air-jet mill or in a good ball mill. Pesticides obtained from aqueous solutions by precipitation can be used without milling. In this case, the precipitated and washed pesticide is mixed with the other ingredients and dried in a spray dryer. Pesticides such as copper oxychloride, ziram, cuprous oxide are made this way. Wettable powders usually contain 70-80% ingredient, 2-3% OP-7, 2-3% sulfite waste liquor and 5% carbomethoxy cellulose. Compositions of a few pesticide wettable powders are given the following table :

Ingredients	Composition (Weight %)			
	DDT	BHC	Ester sulfonate	Dichloral urea
Pesticide	30 - 50	50 - 80	50 - 80	80
Kaolin	45.5 - 67.5	14 - 47	16.5 - 47.5	15 - 16
Sulfite waste liquor	1.5 - 2.5	1 - 2	1.5 - 2	-
OP-7	1 - 2	2 - 4	1 - 1.5	4 - 5

8.5 SOLUTION CONCENTRATES

Pesticides are used in the form of solutions either in water or organic solvents depending upon their solubility. The salts of organic acids with different bases and some organophosphorous insecticides are used as aqueous solutions. Disinfection of seeds with aqueous solutions of formalin and organic

mercuric compounds is widely used. This method is particularly efficient and more economical than dry disinfection. For example, 15 gms. of Hg is applied for a ton of wheat seed for disinfecting it from Granosan, while aqaeous solution of ethyl-mercury phosphate containing only 3 gms. of Hg per ton gives same effect. However, wet disinfection of seed is not used. Pesticides which quickly penetrate into plant are often applied in the form of aqueous solutions.

Solutions of pesticides in organic solvents are also widely used as sprays. The most frequently used solvents are the petroleum hydrocarbons, kerosene, mineral oils, diesel fuel and white spirit. To increase the solubility of the pesticide in the normal inexpensive solvent, some intermediate solvents which have greater solubility are added. Some of these are cyclohexanone, methyl cyclo hexanones, mesityl oxide, tetrahydrafuran, thiophene, methylethyl ketone, dimethyl carbamate, alkyl-acetates, xylenes, chlorobenzene and other aliphatic halogenated hydrocarbons like carbon tetra chloride, methylene chloride, dichloro ethane and trichloro and tetrachloro ethylenes.

In choosing a solvent for pesticide or a mixture of pesticides, besides the solubility, other properties of the solvents such as phytocidal effect, flammability and toxicity for man and domestic animals, ignition temperatures are also to be considered.

8.6 EMULSIFIABLE OILS

Some pesticides, particularly many liquid pesticides are suitable for formulation as emulsifiable oils or concentrates. Emulsifiable oil on dilution with water gives stable emulsion suitable for spraying plants and surfaces.

The emulsive concentrates are prepared by one of the following methods :

1) An aqueous solution of the pesticide in a water-immiscible solvent is made by means of colloid mill. Pesticides that the stable to the action of water are suitable for this preparation. Oil emulsions of DDT, benzene hexachloride, anthracene oil are used. The concentrated emulsions are stabilised by the addition of sulfite waste liquor.

2) The emulsifiable concentrates of pesticides are made in miscible oils which on mixing with water give stable emulsions. These normally consists of a pesticide, solvent and an emulsifier. As solvents hydrocarbons or their halogenated derivatives, esters, various petroleum products, coaltar oils and many other compounds are used. Calcium sulfonates, ethers of polyethylene and polypropylene glycols, monoesters of sorbitol and mannitol with higher fatty acids, various soaps, salts of naphthenic acids are used as oils.

Check Your Progress - 2

What type of pesticides are suitable for formulation as emulsifiable oils?

.....

.....

.....

.....

8.7 AEROSOLS

The application of pesticides in the form of aerosols is increasingly used in recent times. These are made by the following methods.

1. The pesticide is burnt which on combustion sublimes and forms smokes or clouds poisonous to insects.

2. Spraying solutions of pesticides in readily volatile solvents.

3. By mechanical atomisation of solutions of pesticides.

The best method of producing aerosols is to impregnate the pesticide with paper or other combustible porous materials. Besides the pesticide, the combustible smoke forming compositions usually contain a combustible substance, filter, and an oxidising agent. Nitrates, nitrites, chlorates, chromates etc. are used as oxidising agents. Fillers include Kaolin, infusorial earth etc. saw dust, waste products from cellulose manufacture carbon, bitumen are used to maintain the necessary temperature.

8.8 SUSTAINED RELEASE FORMULATIONS

It may be necessary sometimes to use the pesticide in the form of sustained formulation. Extremely toxic systemic insecticides are made in the form of gelatin capsules at the factory and placed in the soil. The geletin gradually breaks down in the soil and the insecticide enters the soil water and is absorbed by the plant roots. This process eliminates the contact of harmful pesticides by the workers.

8.9 SUMMARY

The main points you have studied in this unit are :

1. The importance of the pesticide formulation to be adopted to control the pest of a crop.

2. The prominent methods of pesticide formulation dusts, wettable powders, solution concentrates, emulsifiable oils, aerosols and sustained release formulations.

3. The different roles played by diluents, emulsifiers, auxillary materials, film forming materials and wetting agents.

8.10 MODEL EXAMINATION QUESTIONS

I. **Answer each of the following in 10 lines.**

1. Write a short account on pesticide formulations as emulsifiable oils.
2. Write short notes on aerosols.

II. **Answer each of the following in 30 lines.**

1. Write a concise account on the important pesticide formulations.

8.11 MODEL ANSWERS TO CHECK YOUR PROGRESS

1. A pesticide to be applied as a dust may form lumps during storage or preparation. To avoid this lumping a suitable chemical is to be added as a diluent in required proportion.

2. Liquid pesticides are suitable for formulation as emulsifiable oils.

Author : Prof. A.S.R. Anjaneyulu

Part - B

DRUGS

UNIT-9 : BRIEF HISTORY OF MEDICINAL PLANTS, MICROBIAL PRODUCTS AND SYNTHETIC DRUGS

Contents

9.1 AIMS AND OBJECTIVES

To familiarise the student with a brief history of the origin of drugs of natural and synthetic origin.

After the complete study and understanding of the contents of this unit, you are expected to :

* know a preliminary account of the knowledge of the medicinal plants.
* find out the emergence of Meteria Medica and Pharmacopea in the ancient medicine.
* give an account of chemotherapy and synthetic drugs. The importance of these in the modern medicine.
* describe the antibiotic age which enriched the scope of chemotherapy.

9.2 INTRODUCTION

The drugs used today in medicine are either obtained from nature or synthesised in a laboratory. The first, which are called the natural drugs are obtained from plants, animals, or mineral kingdom. Drugs from microorganisms are the latest addition known as antibiotics.

The history of medicinal plant is as old as the history of mankind. In the early periods, the primitive man went in search of food,eating at random, plants or parts of plants like tubers, fruits, leaves etc. If no harmful effects were found by eating such part of the plant, he considered it as edible and used it as food. If by eating other actions were found, it was considered inedible and tried to use it as a drug according to the action. For example, if it caused diarrohea, it was used as a purgative; if vomiting, it was used as an emetic and if poisonous and fatal, he used it as arrow poison. The knowledge of medicinal plants obtained by this trial and error was passed from one generation to the other.

9.3 KNOWLEDGE OF MEDICINAL PLANTS

The knowledge of medicinal plants in India is very old and medicinal properties of plants are described in Rigveda and Adharvaveda (3,500 - 1,500 B.C.) from which Ayurveda, (knowledge of life) is developed. The Charak Sanhita dealing mostly with plants and Susrut samhita dealing with surgery are the well known ancient treatises in Ayurveda. The antileprotic action of the chaulmoogra fruit,

the efficacy of amla fruit as a tonic, the use of Rauwolfia serpentina, as a hypotensive drug, the bark of Saraca indica (Ashoka) as uterine tonic, the dried roots and stems of Withania somnifere (Aswangandha) as sedative were known to ancient Indians.

The oldest records of medicinal plants were also found in other oriental civilizations as in China and Mediterranean civilizations of Greek, Roman, Hebrew and Egyptian. The Chinese Emperor-scholar Shen Nung (2735 BC) compiled a book of herbs. The antifebrile effects of Ch'ang Shang, which has been now shown to contain antimalarial alkaloids was discovered by him. Similarly, he recorded the drug "Ma Huang" for its diaphoretic and stimulatory effect from which ephedrine was isolated as the active alkaloid by Nagai, nearly 5000 years later. The ipecacuahna root which was used for the treatment of dysentery and diarrhoea contains the alkaloid, emetine, which even today is an important drug for amebiasis. The "Ebers Papyrus" dated about 1500 B.C. and found in mummies gives a collection of drugs prevalent at that time.

9.4 DEVELOPMENT OF MATERIA MEDICA AND PHARMACOPEA

Hippocrates (460 - 370 B.C.), the Greek Scientist was considered as the father of medicine in the Western World. He recommended the use of metallic salts. Aristotle (384-32 B.C.), a student of Plato and Philosopher is known for his writings on animal kingdom and Theophrastus (370-287 B.C.), a student of Aristotle wrote about plant kingdom. Dioscordides, a physician living in the first century A.D. described medicinal plants, some of which like Belladona, Ergot, Opium, Colchicum are used even today. The Roman naturalist Galenus (131-200 A.D.) devised methods of preparation of plant and animal drugs known as "galenicals". He contended that herbal mixtures could provide all the essential elements of health and that proper herb mixtures could be used to relieve all the human ailments. His impressions influenced the middle age civilizations, though superstitiously sometimes, for nearly fifteen centuries. The beginnings of a "materia medica", the necessity to maintain and assay the "purity" of drugs and an intimation of "dosage levels" find beginnings in his work.

Many new drugs of botanical and mineral origin came into use and several materia medicas and Pharmacopeias were compiled in the 16th century in various countries. The active principles of ancient herbal drugs were extracted, purified and the physiological actions of these pure drugs were quantitatively estimated. Thus classification of botanical drugs on the basis of their biological functions made its beginning in the 18th century. Terms like antispasmodic, antiseptic, cathartic and emetic found their use. Efforts were initiated by organic chemists to unravel the structures of organic compounds and to synthesize them in the laboratory during the later part of nineteenth century.

9.5 CHEMOTHERAPY AND SYNTHETIC DRUGS

The history of Chemotherapy falls into three phases i) the early period of empricism upto the discovery of salvarsan by Ehrlich and Hata in 1905; ii) the period upto 1935 when Domagk introduced prontosil and iii) the modern period of sulphonamides and antibiotics. Simultaneous with the isolations of pure drugs from the long known natural sources, drugs synthesised in the laboratory started coming up in the late 19th century. Early syntheses were of acetanilide and salicylic acid (Kolbe 1818-1894), antipyrine (Knorn, 1883), aspirin (Dresser, 1899) and barbital (Emil Fishcher and Mering, 1903). The first hormone, adrenaline (Stolz, 1904) and the local anaesthetics, procaine and beryocaine (Einhorn, 1901-1904).

The ideas of Louis Pasteur (1822-1895) that diseases were caused by pathogenic parasites led to the age of "Chemotherapy" or healing with chemicals. Early foundations of Chemotherapy were laid by Paul Ehrlich (1854-1915). Dreaming on his initial success on dye intermediates, Ehrlich was wondering whether it would be possible to evolve a drug which on administration selectively attacks the parasitic organisms that cause the specific disease, ii) to evolve a drug that works as a "magic bullet" attacking the parasite along and not the host tissue and iii) to evolve a drug that should exercise maximum effect to bring out "Therepia Magna Sterilans" in destroying all the parasitic invaders in one single massive dosage. These ideas stimulated further developments in the field of chemotherapy and the therapeutic dreams of Ehrlich have been realised.

The research activity shifted to cooperative efforts of groups of scientists and Industrial laboratories rather than individuals. Barger and Dale in 1909 made fundamental studies on the effect of chemical structure in the series of sympathomimetic amines. The discovery from Ehrlich's laboratories in the successful use of antispirochetal arsenical 4-arsonephenyl urea (carbarsone) was found to be effective in amebiasis and some organomercurials as diuretics. Ehrilich assigned values to the synthetic compounds referred to as therapeutic index which indicates the ratio of maximum tolerable dose to minimum curative dose. The made laborious search for synthetic compounds to meet the above requirements. This led to a knowledge of the relation between chemical structure and biological effect. The organic arsenical "Erlich's 606" developed by him indicates that it was made after 606 modifications in the chemical structure. The first 40 years of this century have seen the synthesis and development of drugs like the trypanocidal drug, suramin, the modern antimalarjals, like chloroquine, primaquine, amidoquine etc; some antihistaminic drugs in use, the antibacterial sulphonamide drugs, surface active ammonium antiseptics, antituberculous thiosemicarbazones.

Synthetic chemotherapeutic agents were found to be very effective against diseases of protozoal and spirochetal origin. They did not make much head way against bactericidal infection and use of bacteriocidal and bacteriostatic drugs against systemic bacterial infections followed later. The discovery by Domagk in 1932 that the red dye, 2,4-diaminoazobenzene-4-sulphonamide (Prontosil) could cure the dangerous systemic Gram positive bacterial infections in animals and humans created tremendous interest in this area. After the active constituent of this dyestuff was recognised as sulphanilamide, several thousands of compounds having P-aminobenzene sulphonamide structure were prepared and tested. Of course, only a few of them were accepted in medicine.

Woods and Fildes observe in 1940 that the bacteriostatic action of sulphonamide drugs is antagonised completely by P-aminobenzoic acid. This led to the idea that a drug should interfere with the biological synthesis or utilization of a recognised cell metabolite. The successful use of this antimetabolite theory resulted in the development of P-amino-salicylic acid isoniazid as antituberculous drugs.

Check Your Progress - 1

What is chemotherapy?

.....

.....

.....

.....

9.6 ANTIBIOTIC AGE

The discovery of antibiotics became the greatest boon to the mankind and enlarged the field of chemotherapy. An antibiotic is a metabolic product obtained from one living micro-organism and is harmful to the other living organisms even in very small amounts. Although they are of recent origin and development, in reality, they were known for centuries. The Chinese were aware of the curative properties of moulded curd of soya beans in boils and carbuncles. Fungus grown on shoes was said to be used as medicine in remote villages in India. It was again, Louis Pasteur who recognised the curative potentialities of some germs in the middle of the last century. He remarked "among lower beings, even more than among higher animals and plants, life destroys life". Such mutual antagonism in microorganisms is the basis of antibiotic chemotherapy.

The discovery of the first antibiotic, penicillin, was quite accidentally made by Fleming in 1928. He observed that a culture plate on which he planted the microorganism Staphylococcus did not show enough growth as it should. It was found that an invisible sporebearing fungus from air had settled on the plate earlier, grew rapidly and secreted a chemical substance which killed or prevented the growth of Straphylococci. The spore-bearing mould was identified as Penicillium notatum and the chemical substance it produced as penicillin.

Fleming mentioned that the crude penicillium filterate from P.notatum might be useful as a topical antiseptic. In 1930 Raistrick and his colleagues made unsuccessful attempts to isolate and purify the antibacterial agent present in the culture fluid of P. notatum. Fleming's suggestion received little attention until 1940 when Florey and Chain re-examined the above filtrates and isolated a water soluble powder of much higher antibacterial properties and lower toxicity than the known synthetic chemotherapeutic agents. The powder was found to be a mixture of several compounds called penicillins which were separated and their structures established. Penicillin was manufactured in large scale by novel methods of fermentation and extraction techniques. The discovery of penicillins came as a boon to the making, particularly to the wounded soldiers of the second world war in saving their lives, in alleviating paid from severe injuries and in avoiding otherwise necessary amputations. This was the beginning of the antibiotic era.

Check Your Progress - 2

What are antibiotics?

.....

.....

.....

.....

An immense amount of planned research beginning with the preliminary screening of thousands of microorganisms and their metabolic products followed which resulted in the isolation of several important antibiotics. Some of these are the streptomycin (Waksman, 1944) a powerful tuberculostat, from Streptomyces griseus, Chloramphenicol (Burckholder, 1947) an effective antityphoid drug, from S. Venezuelae, the broad spectrum antibiotics, chlortetracycline (Duggar, 1948) from S. aureofacieus, oxytetracycline (Finlay, Keefer, 1950) from S. rimosus and tetracycline. The other useful antibiotics obtained from cultures of streptomyces are erythromycin (Mc. Guire, 1952) from S. erythreus, neomycin (Waksman, 1949) from S. fradiae.

9.7 SUMMARY

The main points you have studied in this unit are :

i. a general account of the medicinal plants and ayurveda.
ii. the development of Malaria Medica and Pharmascopea.
iii. the meaning of chemotherapy and its utility in medicine.
iv. a general account of the antibiotics and their application in modern medicine.

9.8 MODEL EXAMINATION QUESTIONS

I. **Answer each of the following in 10 lines.**

1. Give a short account on the important contributions of Erlich.
2. Write a short note on the contribution of Chinese Emperor Shen Nung to medicinal plant.
3. Trace the early recordings of medicinal plant in Indian civilization.

II. **Answer the following in 30 lines.**

1. Give a brief historical account of the medicinal plant.

9.9 MODEL ANSWERS TO CHECK YOUR PROGRESS

1. Chemotherapy is the curing of diseases by using chemical substances as medicines.
2. Antibiotics are the metabolic products of microorganisms that are harmful to other micro organisms even in very small quantities.

9.10 GLOSSARY

1. *Protozoa :* Microscopic acellular organisms ranging from plant like forms to members that feed and behave like animals.
2. *Spirochetes:* Long spirally twisted unicellular bacteria surrounded by flexible wall.
3. *Gram positive and Gram negative bacteria :* These are unicellular microorganisms surrounded by a rigid, complex polysaccharide-protein cell wall. Bacteria can be divided arbitrary into two classes. Gram-positive bacteria are those that stain blue with Gram's reagent (crystal violet and iodine) and Gram-negative bacteria are those that do not retain these reagents but may be counterstained with safranin or similar reagents.

Author : Prof. A.S.R. Anjaneyulu

UNIT-10 : CLASSIFICATION OF DRUGS BASED ON PHARMACOLOGICAL ACTIVITY AND STRUCTURE - ACTIVITY RELATIONSHIP

Contents

10.1 AIMS AND OBJECTIVES

To introduce the student to the classification of drugs based on their pharmocological activity, to highlight the structure-activity relationship and to familiarise him with the mode of administration of the drug.

After the completion of the study of this unit, you are expected to :

* be able to classify drugs based on their pharmacological activity.
* be aware of the molecular structures of drugs and their relation with the medicinal activity.
* be well versed with the methods of administration of drugs.

10.2 INTRODUCTION

Drugs are obtained either by synthetic methods or extracted from plants. All such drugs are classified on the basis of their pharmacological action. Structure and medicinal activity relationship of some drugs was established and a lot is to be explored. The method of administration of drugs depends on many factors.

10.3 CLASSIFICATION OF DRUGS BASED ON PHARMACOLOGICAL ACTIVITY

The activity principles of ancient herbal drugs were being extracted, purified and their physiological actions quantitatively estimated. Thus classification of natural drugs on the basis of their biological functions made its beginning in the eighteenth century. Terms like antispasmodic, antiseptic, cathartic and emetic were used in the medical lectures of the Scottish Physician, William Cullen (1712-1790). The advent of synthetic drugs beginning with this century, has seen in particular, enormous increase in the number of drugs being used. To put the predictions about biological activity or therapeutical usefulness of drugs on experimental basis, the medicinal chemist has studied experimental biology. pharmacology, and biochemical mechanism of action of drugs in the animal and human organism. Systematic studies in Pharmacology have made available the mode of action of drugs on the various physiological mechanisms in the body, the mechanism of their therapeutic action, their acute and chronic toxicity and their biochemical fate and elimination.

The pharmacological activity of a drug allows a rational basis of classification. They are thus classified as analgesics, drugs which give relief from pain; antimalarials which act against malarial parasite, antibacterials, drugs which either kill or reduce the growth of harmful bacteria, anesthetics, drugs which produce anesthesia, insensitive to pain, hypnotics, sedatives and tranquilisers which act on the central nervous system and produce sedation and sleep etc.

Check Your Progress - 1

What are hypnotics?

.....

.....

.....

.....

10.4 STRUCTURE ACTIVITY RELATIONSHIP

In the nineteenth century several pure drugs were isolated from the long known sources of botanical origin. Most of the earlier discovered drugs were alkaloids such as morphine, atropine and quinine. The organic chemists developed methods of unraveling the structures of organic compounds. The pharmacological tests gave some ideas about their physiological properties, such as therapeutical usefulness, poisonous and toxic activity. Certain structural units found in some biologically active compounds were also found in other substances having similar properties. The ideas of structure and its relationship to activity thus found their beginning in the early period of this century.

Barger and Dale in 1909 made a fundamental study of the effect of chemical structure in the series of sympathomimetic amines upon their physiological action. Based on certain relationships of structure and pharmacological activity, the organic chemist prepares numerous compounds with the hope that they might have specific therapeutic use. The millions of organic compounds thus made must undergo a thorough process of pharmacological screening and clinical evaluation, first on animals and finally on human beings. Only a very small percentage of them reach the status of a drug and come into the market. The development of a few potent synthetic drugs and some antibacterial sulphonamide drugs has been a result of such large scale synthesis and pharmacological screening of compounds in the early part of this century.

The modification of the structure of a drug has become the new line of approach to produce new drugs. The hope in doing such exercises is to produce a better drug by reducing the toxicity and side effects of the original unit and make improvements etc. in its solubility, volatility etc. The drug activity may be either a) structurally specific or b) structurally non-specific. Structurally specific activity appears to be dependent on the interaction of the drug with a cellular acceptor. At times even a minor change in the chemical structure may bring in serious physiological effects. On the other hand, structurally non specific action appears due to accumulation of drug in vitally important part of a cell with lipid characteristics. Specific absorption to a cellular receptor is apparently not very important in the latter case.

The activity of research that led from the isolation of cocaine from the leaves of coca Erythroxylon coca to the discovery of local anesthetics provides a classic example of molecular dissection approach to drug design and synthesis on one hand and structure activity relationship on the other. It was Wohler who discovered that a dilute solution of the alkaloid cocaine (1) produced local deadening of pain and this led its use as a local anaesthetic in opthalmic surgery.

Even before the correct structure of cocaine was established, a chance discovery was made that simple ethyl ester of P-amino benzoic acid showed local anaesthetic activity. The simple drug,

benzocaine (2) thus introduced in 1903 is still in use. Procaine (3), an ester of p-amino benzoic acid with N,N-diethyl amino ethanol is a prototype of cocaine with basic similarities in their structure and accepted as a good local anaesthetic. Numerous compounds were synthesised with all the possible structural variations of the two distinct components, the acid part and the ethanolamine part. These studies led to some of the points regarding structure and activity relationship in anaesthetics. There are :

1) the aromatic ring of the acid can be substituted.

2) the amino group is also not essential and it can be an ether like ethoxy group.

3) the aliphatic basic nitrogen of the side chain lacks no structural demand. The n-alkyl may vary in its structure, the nitrogen may become part of a ring as in pyridocaine (4).

4) incorporation of extensive branching in the side chain similarly does not decrease the pharmacological activity.

5) the basic ester grouping was also not found necessary as the amide, procainamide (5) still showed anaesthetic activity. This drug was in fact proved to have a direct depresent effect on Cardiac ventricular muscle also.

6) It was also found that the structure can be modified by reversing the amide to anilide with aromatic amine and aliphatic acid.

The low structural requirements found for local anaesthetic activity does not find in other drugs.

10.5 MODE OF ADMINISTRATION OF THE DRUG

Physical properties of a drug play an important role in its administration, absorption to complementary receptor in the body and its final excretion from the body. Since water is the solvent found in the transport system of living organisms the water solubility is an important factor for any drug. The solubility of a substance in water or in fats and oils determines the course of administration of a drug. Compounds which are not excreted from the body rapidly will accumulate in the body fats. Prolonged storage of a drug and its slow liberation might be advantageous in some cases for example, the effective amoebicide, biallylamicol, is rapidly concentrated in body fat and slowly released during an year or more. By its slow liberation it will be in continuous contact with the amoebae for long periods. Similarly in hormonal therapy, fat soluble steriodal drugs are often used with their slow release and prolonged action. The injections of aqueous solutions such as penicillins are rapidly distributed throughout the organism and eliminated also rapidly from kidneys. The injections are thus to be repeated at regular intervals to maintain therapeutically effective blood levels.

Check Your Progress - 2
What type of drugs show prolonged action in patients?

.....

.....

.....

.....

The drugs are administered in the form of solutions, syrups and emulsions, tablets, powders, ointments or lotions. The drug in the appropriate form is selected to suit the desired mode of-action. For local action as on skin, eye, ear the drug is applied at the site of action in the form of powder, ointment, drop, lotion, gargle, lozenge etc. For systemic action the drugs are administered in several modes. They may be administered orally in the form of powders, tablets, mixtures or capsules, where the drug is absorbed through the alimentary canal and gastro intestinal tract. Parenteral route is used through subcutaneous, intramuscular or intravenous injections if the drug is likely to be destroyed or not absorbed from alimentary tract or when a drug is irritant in gastrointestinal tract or when an immediate action is required or in treating an unconscious patient. By intravenous route accurate amount of drug can be put in systemic circulation with quick action. So, over dose by this route is hazardous and cannot be withdrawn. By intramuscular mode the drug is absorbed rapidly as the muscles offer a greater surface area and vascularity. It is less hazardous than the intravenous route. In some cases sublingual administration of the drug is used. By this method the tablet is placed under the tongue where it is rapidly absorbed through oral mucous membrane. This method becomes advantageous when the drug is likely to be destroyed in the gastrointestinal tract. Besides those methods mentioned above some drugs need to be administered at special sites such as cardiac muscle, bone etc.

10.6 SUMMARY

The main points you have studied in this unit are :

i. the classification of drugs based on their pharmacological activity.

ii. the structure and medicinal activity of drugs.

iii. the methods of administration of drugs.

10.7 MODEL EXAMINATION QUESTIONS

I. **Answer each of the following in 10 line**

1. Procaine forms the prototype of Cocaine. How do you justify the statement?
2. What are the advantages and disadvantages in the administration of a drug by intravenous method?

II. **Answer each of the following in 30 lines.**

1. Write a concise account on the structure-activity relationship.
2. Write a brief account on how the drugs are administered.

10.8 MODEL ANSWERS TO CHECK YOUR PROGRESS

1. These are the drugs which act on the central nervous system and induce sleep.

2. Fat soluble drugs, due to their accumulation in the body fat and subsequent release slowly, exhibit prolonged action in patients.

Author : Prof. A.S.R. Anjaneyulu

BLOCK - 5 : DRUGS FROM PLANTS, MICROBES AND SYNTHETIC DRUGS

Plants synthesise many chemicals for different purposes. Many of them offer protection to their parental plants. Some of those chemicals are used as drugs. But as a result of chemotherapy now a day's synthetic drugs have wide application. In Ayurveda mostly plant materials are used as drugs whereas in Allopathy synthetic drugs are popular. An effective method of controlling the diseases in their total eradication than curing them after their attack. In this direction immunisation plays an important role. Eventhough so many drugs have come into application, new diseases are making their appearance. Almost there are no drugs to cure them. e.g., cancer and AIDS.

UNIT-11 : ANALGESICS

Contents

11.1 AIMS AND OBJECTIVES

To introduce the student to the topic of analgesics and to outline the methods of preparation and use of few analgesics.

Once you completely study and understand the contents of the unit, you are expected to be well versed with :

* an account of analgesics and antipyreties.
* the classification of the analgesics into narcotic and non-narcotic analgesics.
* the industrial preparations of antipyrine, aspirin, paracetimol, oxyphenbutajone, pethidine and ibuprofen.

11.2 INTRODUCTION

Analgesics are defined as drugs that relieve pain. Analgesics selectively reduce or abolish pain without disturbing consciousness. Analgesics are usually divided into two classes. They are narcotic analgesics and non-narcotic analgesics.

11.2.1 NARCOTIC ANALGESICS

Narcotic analgesics are also know as strong analgesics. They relieve severe pain by acting mainly on the central nervous system. The oldest and the best narcotic analgesics are opium alkaloids. The most active alkaloid of opium group is morphine. Narcotic analgesics provide relief from cough and supress respiration. If these drugs are taken for longer periods, one needs larger and larger doses to obtain the desired effects. If the intake of the drug is stopped, very disagreable withdrawal effects like severe pain, seating, salvation, hyperventilation, restlessness and confusion are observed. Thus the narcotic analgesics are all potentially addictive.

Check Your Progress - 1

What do you mean by drug withdrawal effects?

.....

.....

.....

.....

.....

11.2.2 NON-NARCOTIC ANALGESICS

These are mild analgesics and relieve minor pains such as head ache by acting through peripheral mechanisms. The non-narcotic analgesics are antipyretic and antiinflammatory. Narcotic analgesics have neither of these properties.

11.2.3 ANTIPYRETICS

Antipyretics are agents used to lower the body temperature during fever. The antipyretic drugs affect the hypothalamic centres which in turn activate the dilation of the peripheral blood vessels and increases the rate of respiration. This causes the body to lose heat and subsequently lowers the body temperature. Antipyretics have no effect on the normal body temperature.

Antipyretics do not affect the infectious cause of fever. Therefore, they have been replaced by sulpha drugs, antibiotics and antimalarials which reduce fever and also attack the organisms causing infection.

The most commonly used analgesics and antipyretics are acetyl-salicylic acid (Aspirin), pyrazolone and aniline derivatives. The first pyrazolone derivative used was antipyrine. Later phenylbutazone and oxyphenylbutazone were introduced. Aniline derivatives include acetanilide, phenacetin and paracetamol. The other analgesics are pethidine and ibuprofen.

Check Your Progress - 2
What are antipyretics?

.....

.....

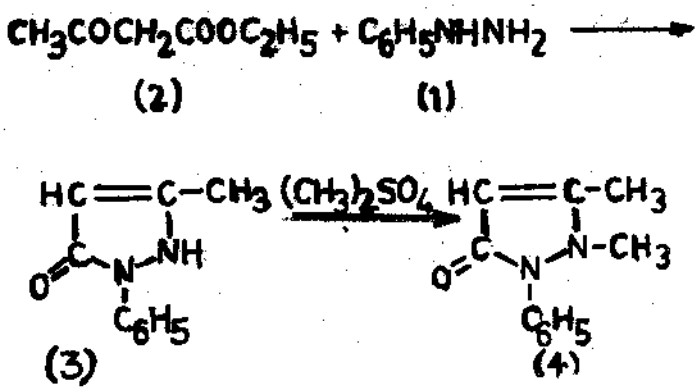
.....

.....

11.3 ANTIPYRINE (PHENAZONE OR SEDATINE)

2,3-Dimethyl-1-phenyl-5-pyrazolone or antipyrine was introduced in the year 1884 as an antipyretic. Since the discovery of its analgesic properties, it has been used mainly to relieve pain (analgesic).

Antipyrine was first made by Knorr in 1884 and this method is still used. In this method phenylhydrazine (1) is condensed with ethyl acetoacetate (2) to furnish 3-Methyl-1-phenyl pyrazolone (3) which is methylated to yield antipyrine (4).

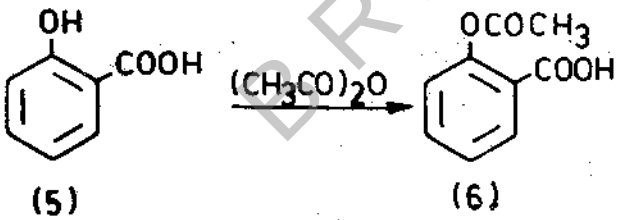


Antipyrine is a potent analgesic and anti-inflammatory agent. Because it is associated with a high incidence of blood abnormalities, particularly agranuclocytosis (break down of certain white blood cells), this drug is now seldom used.

11.4 ASPIRIN

Although acetyl salicylic acid was discovered by Gilm in 1859, Dreser introduced it as a drug under the trade name (Aspirin in 1899. It is one of the drugs most widely used to reduce fevers (antipyretic) and to relieve pain (analgesic). It reduces fever by increasing the blood flow to the surface of the body, there by promoting sweating and heat loss. Once it was thought that aspirin acted directly on the brain, but now most authorities believe that it alters the blood flow or waler balance, thereby reducing painful swelling and throbing. However aspirin is effective only for relieving low intensity pain, such as headache, or pain originating in muscles or joints, such as rheumatism. It is not effective for pains originating in internal organs.

Aspirin (6) may be prepared by acetylating salicylic acid (5) with acetic anhydride in the presence of catalytic amount of sulphuric acid.



Aspirin is a white crystalline powder, odourless and slightly bitter in taste.

Some individuals show severe sensitivity after ingestion of aspirin, resulting in decrease in circulation of the blood and breathing difficulty.

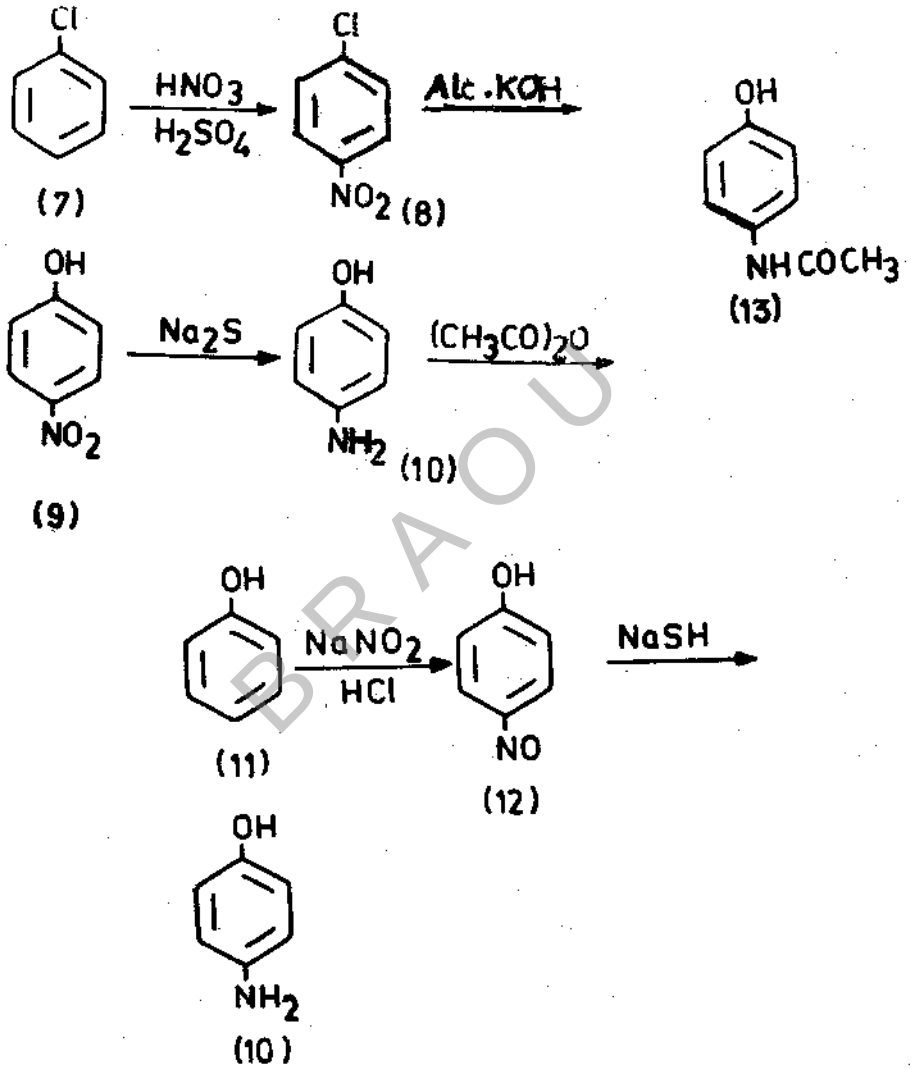
The symptoms of mild aspirin poisoning are burning pains in the mouth, throat and abdomen, difficulty in breathing, lethargy, vomiting, ringing in the ears and dizziness. More severe poisoning leads to delirium fever, sweating, incoordination, coma, convulsions, cyanosis (blueness of the skin), failure of kidneys and respiratory function and death.

Concentrated solutions of aspirin and other salicylates can dissolve the tissues. High doses of aspirin cause bleeding ulcers through attack of the stomach wall.

11.5 PARACETAMOL (ACETAMINOPHEN)

In the year 1949, it was discovered that both phenacetin and acetanilide are converted in the body to paracetamol. This led to the introduction of this compound as a replacement for phenacetin. Paracetamol, the acetyl derivative of p-aminophenol, is the most commonly used antipyretic.

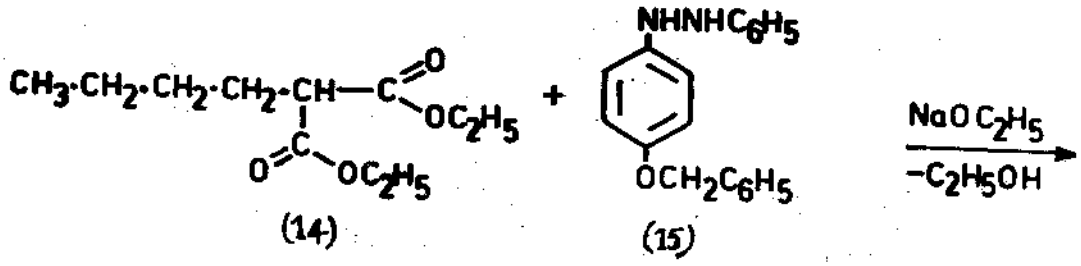
Paracetamol is prepared starting from chlorobenzene. Chloro-benzene (7) is nitrated to obtain p-chloro nitrobenzene (8) which is converted to p-nitrophenol (9) by heating with alcoholic potassium hydroxide. p-Nitrophenol is reduced to p-aminophenol (10) with sodium sulphide. Alternatively, nitrosation of phenol (11) give p-nitrosophenol (12), which is reduced with sodium hydrosulphide to yield p-amino-phenol (10). p-Aminophenol is acetylated with acetic anhydride to form paracetamol (13).

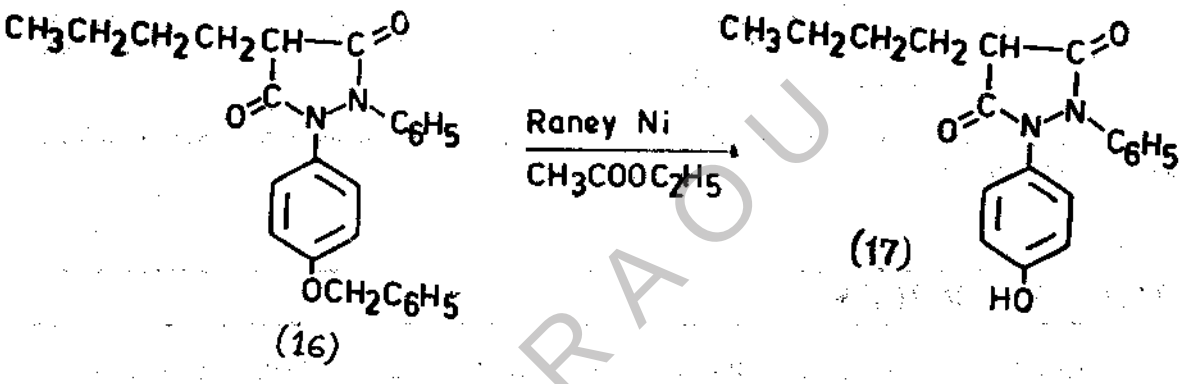


Paracetamol is an analgesic and antipyretic with low antiinflammatory activity. In contrast to phenacetin and acetanilide, paracetamol causes little or no methemoglobinemia (a disease in which the blood pigment haemoglobin is unable to function in respiration, after prolonged use). Heavy dosage of paracetamol may damage the liver and kidneys.

11.6 OXYPHENBUTAZONE-(1-p-HYDROXYPHENYL-2-PHENYL-4-BUTYL- 3,5-DIOXOPYRAZOLIDINE)

Structural modifications of pyrazolone analgesics (Eg. antipyrine) has resulted in the introduction of oxyphenbutazone. n-Butyl malonic ester (14), is condensed with 1-p-benzyloxyphenyl-2-phenyl hydrazine (15) in the presence of sodium ethoxide to yield 1-p-benzyloxy-phenyl-2-phenyl-4-butyl-3, 5-dioxopyrazolidine (16) which on treatment with Raney nickel gives oxyphenbutazone (17).



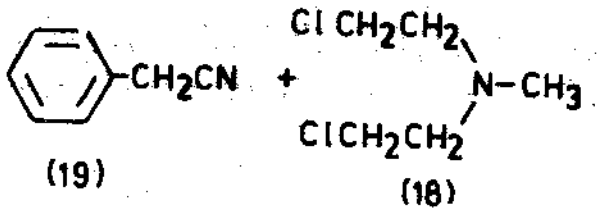


Although, oxyphenbutazone was used as an effective drug for gout, rheumatic fever, arthrit is for several years, it is being discontinued due to some toxic side effects.

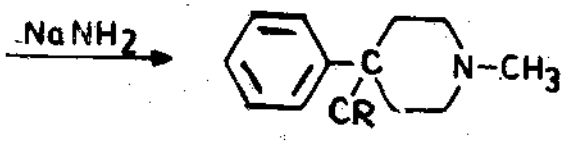
11.7 PETHIDINE

It is known by several names like meperidine, demerol, dolantol, dolantin or isonipecaine. Pethidine was introduced in 1939. The compound exhibited marked analgesic properties.

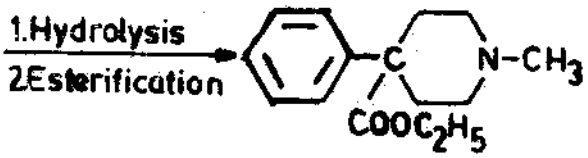
Methyl bis (2-chloro ethyl) amine (18) is condensed with benzyl-cyanamide (19) in the presence of sodamide. The resulting nitrile (20) is hydrolysed and esterified to yield pethidine (21).



(19) (18)



(20)



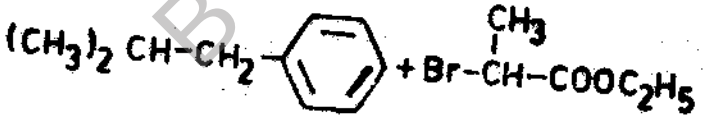
(21)

As bis chloroethylamine (18) is highly lachrymatory, alternative synthesis involving alkylation of benzyl cyanide with 2-chloroethyl vinyl ether is developed. Alkylation of benzyl cyanide with 2-chloro ethyl vinyl ether (22) followed by hydrolysis gives an intermediate (23), which on treatment with phosphorous pentachloride and methylamine forms nitrile (20). The nitrile on hydrolysis followed by esterification yields pethidine (21).

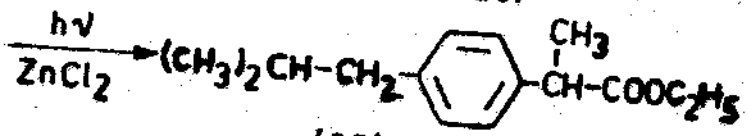
Pethidine has been used to lessen the severity of withdrawal symptoms of the morphine addicts, although pethidine itself might cause addiction.

11.8 IBUPROFEN

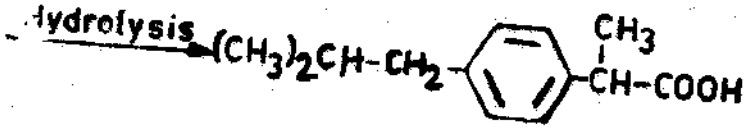
Ibuprofen or 2- (4-isobutylphenyl)-propionic acid is widely used as an antiinflammatory agent.



(25) (26)



(27)



(24)

Isobutylbenzene (25) is subjected to photochemical reaction with ethyl α-bromopropionate (26) in the presence of zinc chloride. This reaction results in the formation of an ester (27) which on hydrolysis gives ibuprofen (24).

Synthesis of Ibuprofen starts with Friedel-Crafts reaction on Isobutyl benzene (25) with acetic anhydride to form p-isobutyl acetophenone (28). Condensation of the acetophenone (28) with iso chloro-acetate in the presence of sodium ethoxide gives a cyclic ether (29). Treatment of the cyclic ether with aqueous sodium hydroxide gives an aldehyde, (30) which on oxidation leads to ibuprofen.

Ibuprofen is as effective as aspirin in smaller doses and is tolerated by patients who suffer from dyspepsia.

11.9 SUMMARY

You have studied the following in this unit.

i. A general account of analgesics and antipyretics.

ii. The classification of analgesics into two types i.e. narcotic and non-narcotic analgesics.

iii. The industrial methods of synthesis of antipyrine, aspirin, p-acetamol, oxyphenbutazone, pethidine and ibuprofen.

11.10 MODEL EXAMINATION QUESTIONS

I. **Answer each of the following in 10 lines.**

1. Write a note on antipyretics.
2. Give the synthesis of antipyrine.
3. Describe the various steps involved in the preparation of paracetamol from chlorobenzene.
4. How is oxyphenbutazone prepared?
5. What are the withdrawal effects of the narcotic analgesics?

II. **Answer each of the following in 30 lines.**

1. Describe important methods of preparing pethidine.
2. Outline the synthesis of ibuprofen.

11.11 MODEL ANSWERS TO CHECK YOUR PROGRESS

1. The after effects of the addictive drugs i.e., severe pain, sweating, salvation, hyperventilation, restlessness and confusion are called the drug withdrawal effects.

2. Antipyraties are the drugs which reduce the body temperature during fever. They do not have any effect on the normal body temperature.

Author : Dr. Syed Ghouse Peeran

UNIT-12 : HYPNOTICS, SEDATIVES AND TRANQUILISERS

Contents

12.1 AIMS AND OBJECTIVES

To introduce the student to the terms hypnotics, sedatives, tranquilisers and barbiturates, their uses and abuses.

After the completion of this study of the unit, you must be able to :

* descri e the sedatives and hypnotics.
* give the structures of some barbiturates and the synthesis of barbital.
* remember some tranquilizers and describe the synthesis of diazepam

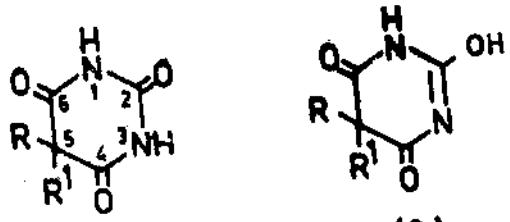
12.2 INTRODUCTION

There are a number of drugs that affect the nervous system. Some of them relieve tension, some have quitening effect and others induce sleep.

12.3 SEDATIVES AND HYPNOTICS

Sedatives are Organic substances which induce a quieting effect followed by relaxation and rest. They usually do not induce sleep. These are generally used for reducing excitement. On the other hand, hypnotics induce sleep where the sleeplessness is due to pain or itching. Usually both sedative and hypnotic properties are exhibited by the same drug. A small dose of the drug may act as a sedative while in a larger dose, the same drug may act as a hypnotic. Sedatives are used in conditions of neurosis and hypertension and other heart troubles. Use of hypnotic drugs depends on the type of sleeplessness. Sedative and hypnotic agents are frequently used in psychiatry and also for preanesthetic medication. Prolonged use of these drugs results in habituation and dependence.

Sedatives and hypnotics can be grouped under three heads : i) barbiturates, ii) non-barbiturates and iii) minor tranquilisers.



(1) $R = R^1 = H$ (2)

Check Your Progress - 1

Differentiate sedatives from hypnotics?

.....

.....

.....

.....

12.4 BARBITURATES

Barbiturates, the most frequently used sedative-hypnotic drugs, are the derivatives of barbituric acid (1). This is the cyclic ureide, malonyl urea which can exist as a keto form (1) or an enol form (2).

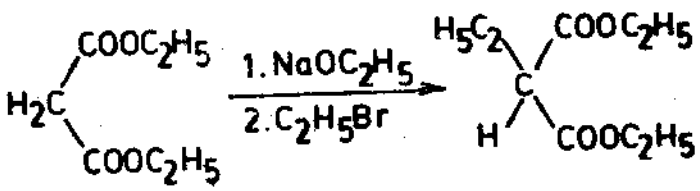
Unsubstituted barbituric acid does not possess any hypnotic properties. Substitution at 5 in the barbituric acid by alkyl groups imparts sedative-hypnotic properties to the compound. The duration of their physiological effect depends on the substitution pattern. Some important barbiturates are given in table-12.1. These are classified on the basis of the duration of their action.

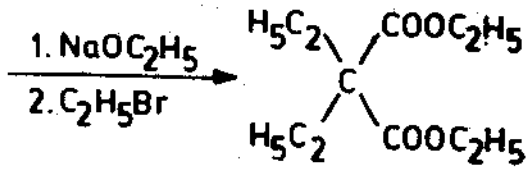
Barbituric acid derivative are widely used where sleep is needed-under conditions of anxiety, tension associated with hypertension. Barbiturates are also used as anticonvulsant drugs. Some of them are also used as anaesthetics for surgical operations of short duration.

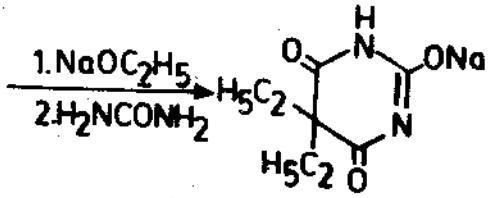
Barbiturates have adverse effects on alcoholics and patients with respiratory difficulties. Barbiturates lead to addiction in some patients.

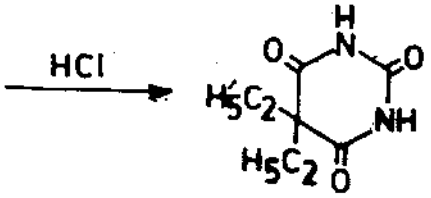
12.5 PREPARATION OF BARBITAL (5,5-DIETHYL BARBITURIC ACID) (3) :

Barbital, one of the long acting Barbiturates is prepared starting from malonic ester. Dialkylation of malonic ester is carried out in two stages introducing one alkyl group at a time. Condensation of diethyl malonic ester with urea yields Barbital.









(3)

12.6 TRANQUILIZERS

Tranquilizers are substances which relieve anxiety and tension without producing sedation. Benzodiazepines diazepam (4), Chloro-diazepoxide (5) and oxazepam (6) belong to this category.

Check Your Progress - 2
What are tranquilizers?

.....

.....

.....

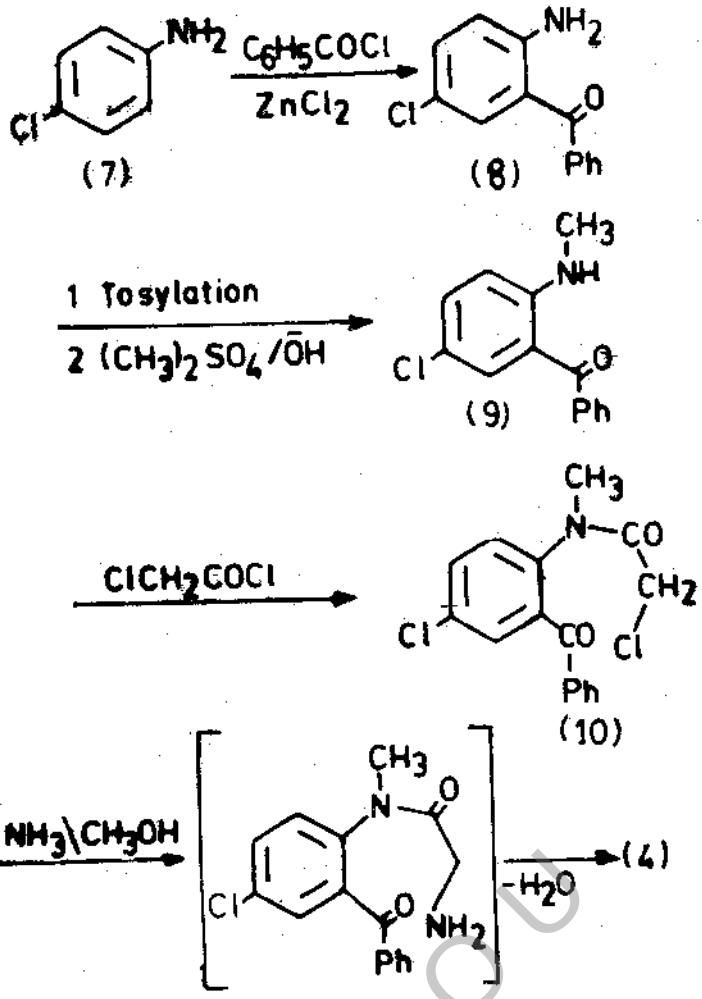
.....

12.7 DIAZEPAM

Diazepam (7-Chloro 1,3-dihydro-1-methyl-5-phenyl-2H-1, 4-benzodiazepin-2-one) (4) is prepared as follows: p-chloroaniline (7) is treated with benzoyl chloride using zinc chloride as the condensing agent to get 2-benzoyl 4-chloro aniline (8). Tosylation of (8) followed by treatment with dimethyl sulphate under alkaline conditions yields 2-(methylamino)-5-chloro benzophenone (9). This on treatment with chloro acetyl chloride gives the chloroketone (10) which on reaction with methanolic ammonia gives diazepam (4).

Diazepam, a colourless and odourless crystalline compound melting at 131°C, is readily soluble in chloroform and ethanol but very sparingly soluble in water.

Diazepam is particularly useful in relief of tension and anxiety caused on alcohol withdrawal. It is also used as an adjunct in the therapy of skeletal muscle spasms and convulsive disorders.



12.8 SUMMARY

The main points you have studied in this unit are :

i. a general account of sedatives and hypnotics.

ii. structures of some barbiturates and the synthesis of barbital.

iii. an account of tranquilizers and the synthesis of diazepam.

12.9 MODEL EXAMINATION QUESTIONS

I. **Answer each of the following in 10 lines.**

1 Give the synthesis of Amobarbital.

2. Name four important barbiturates?

II. **Answer the following in 30 lines.**

1. Outline the synthesis of diazepam.

12.10 MODEL ANSWERS TO CHECK YOUR PROGRESS

1. Sedatives are the drugs that induce quietness followed by relaxation and rest. Hypnotics induce sleep. Same drug in a smaller dose can be a sedative, in a larger dose a hypnotic.

2. Tranquilizers are the drugs that relieve the individual from anxiety and tension without producing any sedation.

Author : Prof. P.S. Rao

UNIT-13 : ANTIMALARIALS

Contents

13.1 AIMS AND OBJECTIVES

To give brief outline of malarial disease and to familiarise the drugs available for this disease and their synthesis.

Once you go through the contents of this unit, you are expected to,

* know a general account of malaria and the natural antimalarials used in the earlier days.
* be able to give a general account and synthesis of the antimalarials of 8-aminoquinolines, 4-aminoquinolines, acridine derivatives and biguanide derivative series.

13.2 INTRODUCTION

Malaria is one of the most widespread infectious diseases and a major problem in several tropical countries. The disease is a protozo an infection caused by four protozoan organisms of the genus *Plasmodium* viz. *P. falciparum*, *P.vivax*, *P.malariae* and *P.ovale*. Parasites of these species reproduce a sexually in the red blood cells (RBC) and other cells of the human body and sexually in the mosquito. when an infected mosquito bites a human being, sporozoites are injected into the human body. The sporozoites develop into a mature tissue called merozoites in the liver. During this primary development stage (8-12 days), symptoms of the disease will not appear. The infected cells rupture and release merozoites into the blood stream. The young merozoites called trophozoites penetrate into the red blood cells and multiply until red blood cells rupture liberating merozoites. The perpetual production and release of a sexual forms of parasite are responsible for the malaria. The secondary tissue forms are believed to be responsible for relapse of malaria. Some of the daughter merozoites of the red blood cells which cannot be reproduced asexually are called gametocytes. When a mosquito bites a human being, the gametocytes enter the insect where they are converted into sporozoites and set further stage of infection. In P.falciparum infection relapses do not occur as the secondary tissue forms are not present in this parasite.

Check Your Progress - 1

How mosquitos spread malaria?

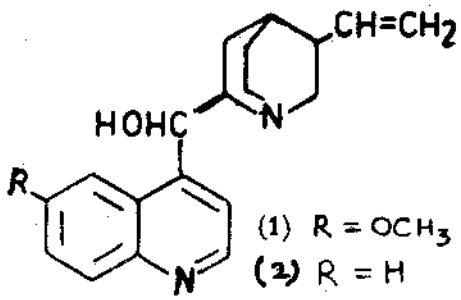
.....

.....

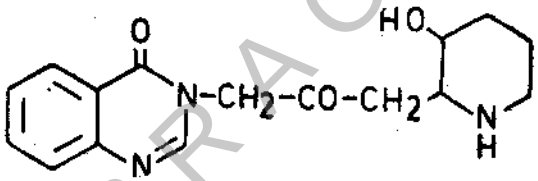
Immunity, developed by persons living in malarial regions for generations, makes malarial attacks less severe and more susceptible to chemotherapeutic treatment. Infection due to *P.falciparum* produces malaria of malignant nature and immunity factors also do not help.

Natural Antimalarials :

Cinchona bark in various forms was used as a remedy for malaria in ancient times. The medicinal value of the Cinchona bark was found to be due to the presence of quinoline group of alkaloids, quinine (1), cinchonine (2) etc.



In Chinese medicine, the root of Dichroa febrifuga was used an antimalarial for centuries. The antimalarial activity of the root is due to the presence of the active principle, febrifugine (3).



(3)

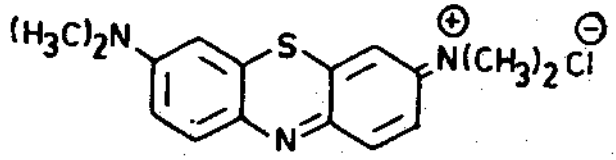
Quinine is again prominence, because of its effectiveness, against, P.falciparaum strains resistant to chloroquine. Quinine (1) brings clinical cure in both P.vivax a dn P.falciparum.

Check Your Progress - 2
How cinchona back is able to function as an antimalarial?

13.4 SYNTHETIC ANTIMALARIALS

13.4.1 8-AMINOQUINOLINES

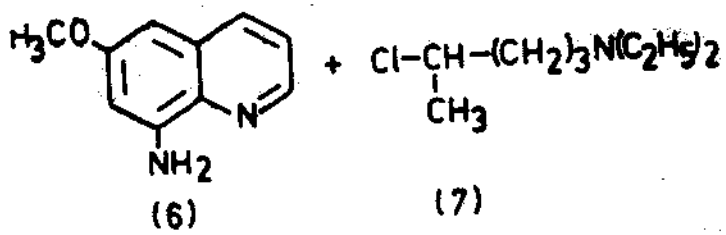
Shortage of quinine in World War I necessitated search for synthetic substitutes. The observation of Gultam and Ehrlich, that methylene blue (4) had some chemotherapeutic value against malaria had led to the synthesis of aminoquinolines. The first drug of this group is pamaquin (5).



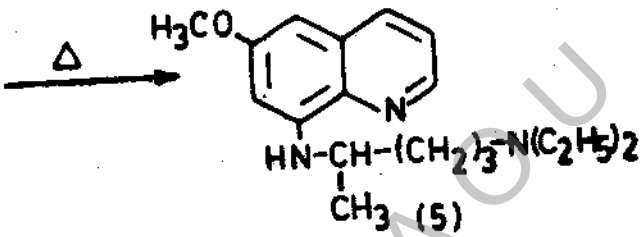
8-Aminoquinolines are highly active against *P. vivax* and *P. falciparam* and gametocytes of all the four plasmodia species that infect man. The major draw back of 8-aminoquinolines for therapeutic utility is their toxicity. The toxic symptoms include anorexia, nausea, cyanosis, epigastric distress, abdominal pain and cramps, chestpain and weakness.

1. Synthesis of Pamaquin (Plasmoquin) (5)

Pamaquin (5) is prepared by condensation of 8-amino-6-methoxy quinoline (6) with 4-chloro-N, N-diethylpentylamine (7).

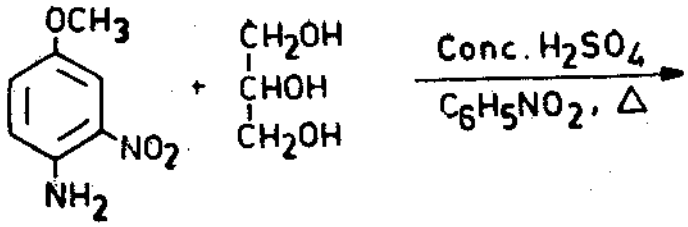


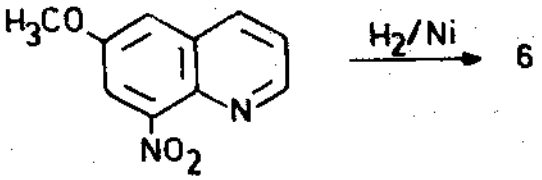
(6) (7)



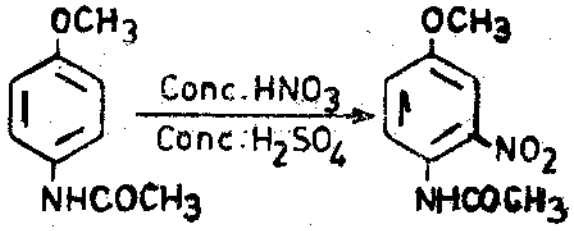
2. Synthesis of 8-amino-6-methoxy quinoline (6)

8-Amino-6-methoxy quinoline (6) is prepared through reaction of 4-amino-3-nitro anisole (8) with glycerol in the presence of sulphuric acid and nitrobenzene (Skraup synthesis) followed by reduction of the resulting product (9). 4-Amino-3-nitro-anisole (8) is obtained by nitration of N-acetyl-p-anisidine (10) and subsequent hydrolysis of the intermediate, 4-N-acetyl-3-nitro anisole (11).

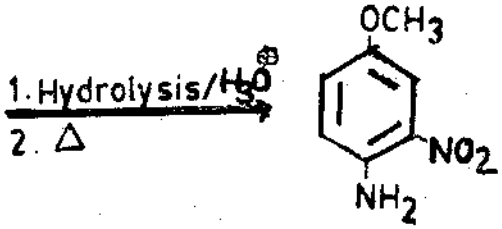




(9)



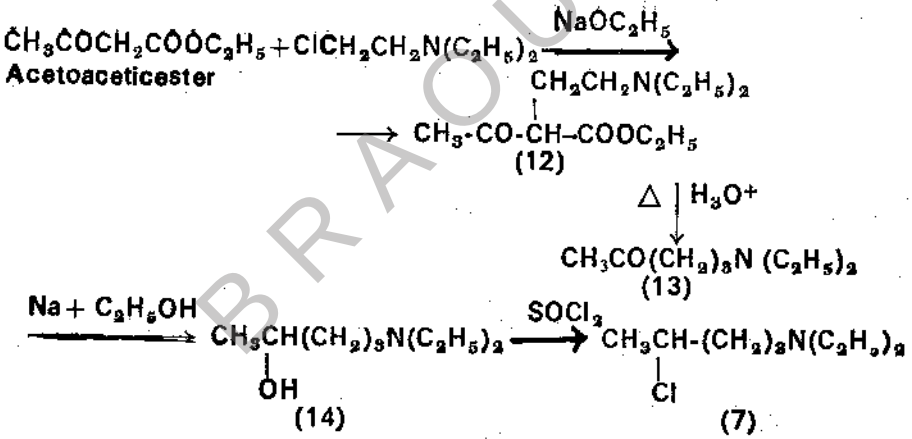
(10) (11)



(8)

3. Synthesis of 4-chloro-N, N-diethyl pentylamine (7)

Treatment of monosodium derivative of acetoacetic ester with 2-chloro-1-N, N-diethylaminoethane followed by ketonic hydrolysis of the product (12) with dilute sulphuric acid gives 5-N, N-diethylamo-2-pentanone (13). This on reduction with sodium and ethanol gives alcohol (14), which on treatment with $SOCl_2$ results in the formation of (7).



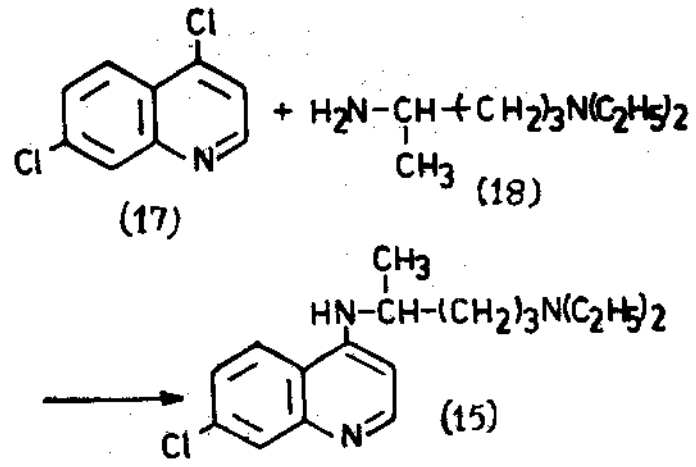
13.4.2 4-AMINOQUINOLINES

The presence of quinoline nucleus in antimalarial drugs prompted syntheses of this group of compounds. The most prominent amongst these are chloroquin (15) and amodiaquin (16).

4-Aminoquinolines act against the asexual blood forms of all species of *Plasmodia* that cause human malaria. Their toxicity is very low, but therapeutic doses may cause mild and transient headache, visual and gastrointestinal disturbances.

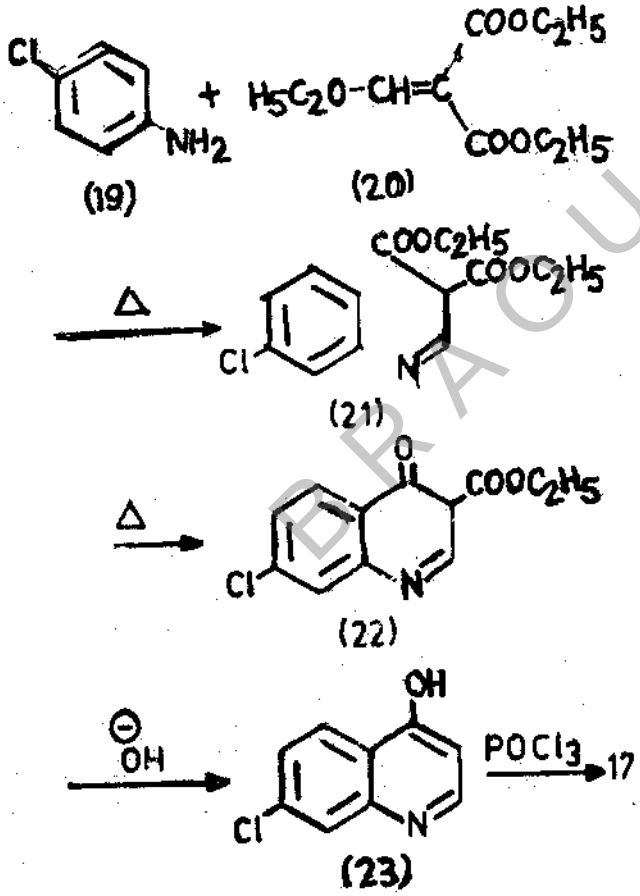
1. Synthesis of chloroquin (15)

Chloroquin (15) is prepared by condensation of 4,7-dichloroquinoline (17) with 4-N, N-diethyl amino-1-methylbutyl amine (18) (Novaldiamine).

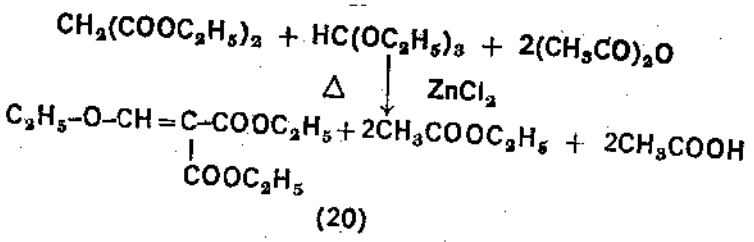


2. Synthesis of 4,7-dichloroquinoline (17)

Condensation of m-chloroaniline (19) with ethoxymethylene malonate (20) followed by cyclisation of the product (21) by heating in dowtherm (a high boiling solvent) yields the ester (22). Hydrolysis of the ester (22) gives 7-chloro-4-quinolinol (23), which on treatment with phosphorous oxychloride furnishes 4, 7-dichloroquinoline (17).



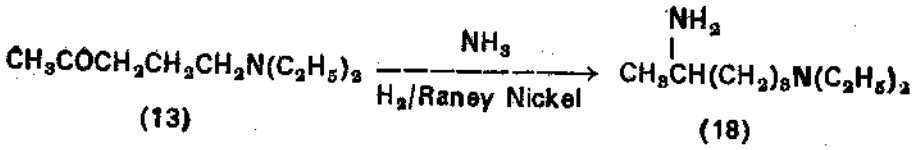
Ethoxymethylene malonate is obtained by heating a mixture of malonic ester, ethylorthoformate and acetic anhydride in presence of fused zinc chloride.



(20)

3. Synthesis of 4-N, N-diethylamino-1-methyl-butylamine (18) (Novaldiamine)

Reductive amination of 5-N, N-diethylamino-2-pentanone (13) gives novaldiamine (18).



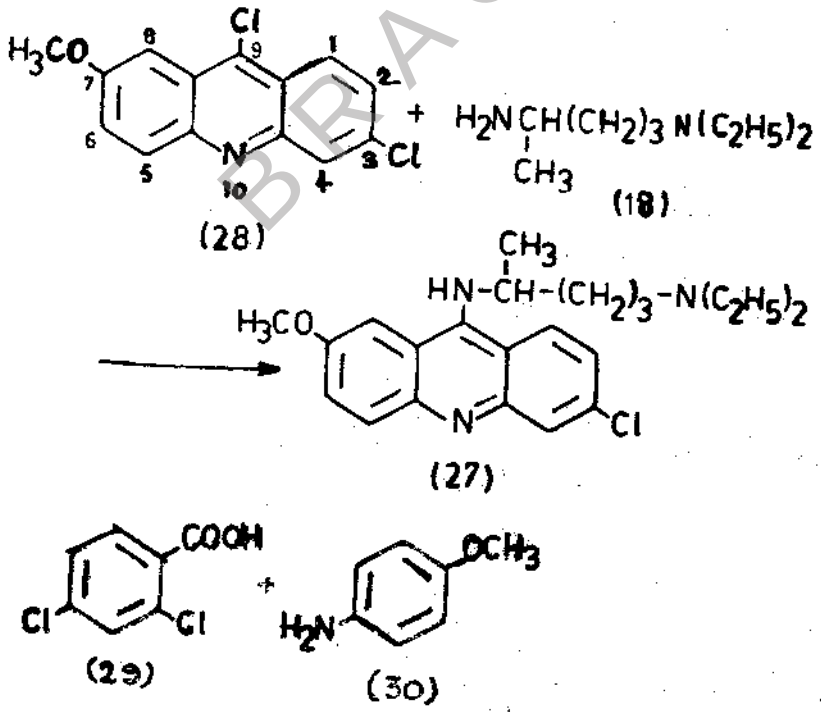
(13) (18)

13.4.3 ACRIDINE DERIVATIVES

The most prominent drug belonging to this group is Mepacrine (Atebrin, Quinacrine) (27). It is prepared by condensation of 3, 9-dichloro-7-methoxy acridine (28) with 4-N, N-diethyl amino methyl butyl amine (Novaldiamine) (18).

Synthesis of 3, 9-dichloro-7-methoxyacridine (28)

Condensation of 2,4-dichloro benzoic acid (29) and p-anisidine (30) gives 5-chloro-4,-methoxy diphenyl amine-2-carboxylic acid (31) which on ring closure followed by chlorination of the product with $POCl_3$ yield 3,9-dichloro-7-methoxy acridine (28).

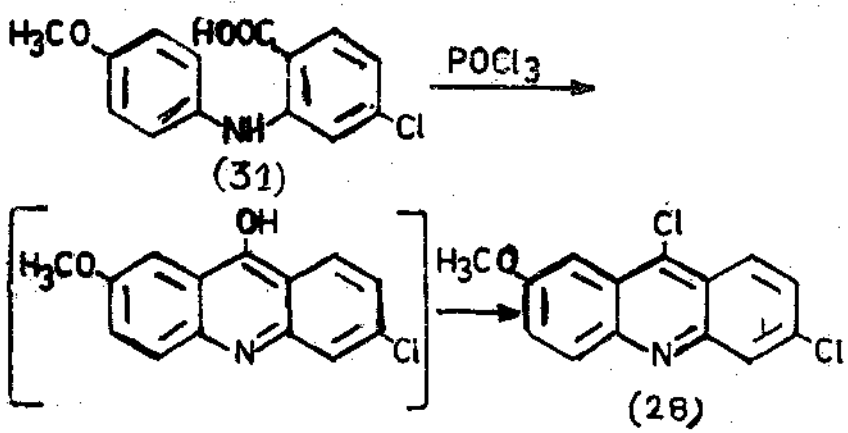


(28) (18) (27)

(29) (30)

BLOCK - 4 : HISTORICAL ASPECTS AND CLASSIFICATION OF DRUGS

Ancient man used to cure his diseases by unsystematic methods. He was using the materials of plant, animal and mineral origin which he had learnt from trial and error methods. Subsequently the emergence of chemotherapy developed medicine systematically in a short time. Paul Ehrlich and Domagk initiated this development. Collective efforts of the researchers all over the world led to the determination of the structure activity relationship and consequently a number of synthetic drugs were prepared. An ideal drug should be stable at room temperature, dissolve in water, be able to be administered orally, have no side effects, be able to cure many diseases, go to all the cells of the body and be available at a cheaper rate. But no drug has all the above qualities. Subsequent discovery of antibiotics was a boon to mankind. Pencillin is the first antibiotic discovered by Alexander Fleming in 1828 A.D. Later on a number of antibiotics were discovered which led to the antibiotic age.

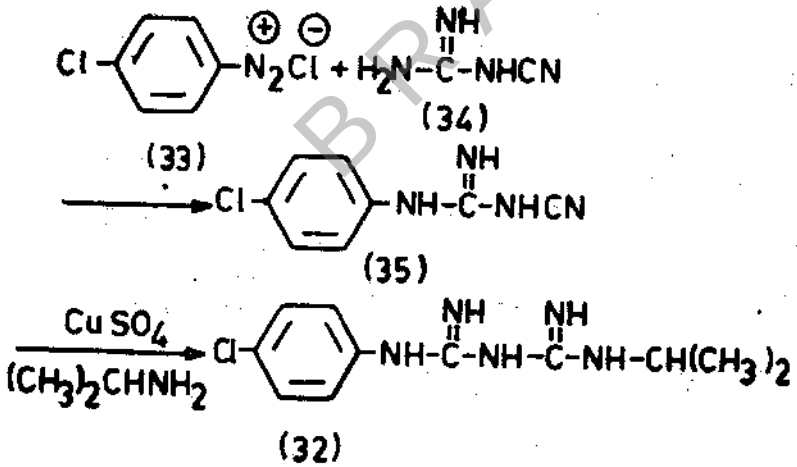


Mepacrine (27) has almost been superceded by other antimalarials because of its bitter taste and side effects such as producing yellow colour to the skin and eyes, nausea etc.

13.4.4 BIGUANIDE DERIVATIVES

Paludrin (32) (chloroguanide or Proguanil) is a highly active antimalarial, prepared by coupling p-chlorobenzene diazonium chloride (33) with cyanoguanidine (34) and then treating the product (35) with isopropylamine in the presence of copper sulphate.

Other antimalarials include pyrimidine derivatives like pyrimethamine, sulphonamides like sulphadoxin, sulphomethoxines etc.



13.5 SUMMARY

You have learnt the following in this unit.

i. The tropical disease malaria and the microorganisms responsible for this disease.

ii. The antimalarial nature of the alkaloids of cinchona bark.

iii. The methods of synthesis of the antimalarials of the series 8-amino-quinolines, 4-aminoquinolines, acridine derivatives and biguanide derivatives.

13.6 MODEL EXAMINATION QUESTIONS

I. **Answer each of the following in 10 lines.**

1. Outline the synthesis of any one of the following antimalarials.
   (a) Pamaquin (b) Chloroquin (c) Mepacrine (d) Paludrin.

2. How do you prepare 6-methoxy quinoline by skraup synthesis?

II. **Answer each of the following in 30 lines.**

1. Write a brief account of how malaria is induced in human beings. Name some important antimalarials of natural and synthetic origin. Give synthesis of any one antimalarial drug.

13.7 MODEL ANSWERS TO CHECK YOUR PROGRESS

1. Mosquitos receive gametocytes when they bite malaria patients. These develop into sporozoits in them which are in turn transfered into healthy individuals by the mosquito bite and thereby the disease is spread by the mosquitos.

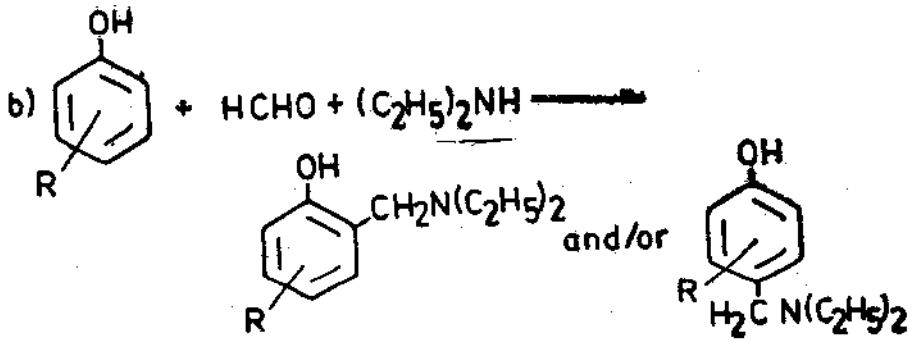
2. Due to the presence of the alkaloids quinone and cinchonine, cinchona bark exhibits the antimalarial property.

13.8 GLOSSARY

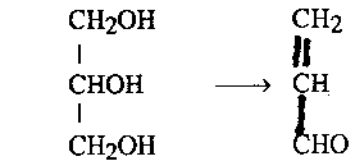
1. *Dowtherm :* It is an eutectic mixture containing 26.5% of diphenyl and 73.5% of diphenyl ether, boiling at 258°.

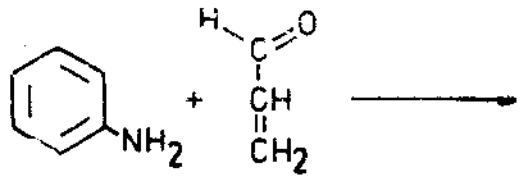
2. *Mannich reaction :* Reaction of active methylene compounds (eg. carbonyl compounds with α-hydrogens) or phenols with formaldehyde and ammonia or primary or secondary amine to afford β-amino carbonyl compounds or substituted amino derivatives of phenols.

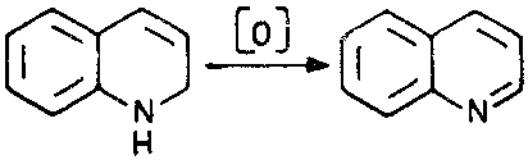
a) $CH_3COCH_3 + HCHO + (C_2H_5)_2NH \longrightarrow CH_3COCH_2N(C_2H_5)_2$

b) 

3. *Skraup synthesis :* This is a general method used for the synthesis of quinoline and its derivatives. It consists of heating a mixture of primary aromatic amine with at least one free ortho position, with glycerol, conc. sulphuric acid, nitrobenzene and ferrous sulphate. The first step is conversion of glycerol to acraldehyde, which then undergoes nucleophilic addition with the amine to give dihydroquinoline which is oxidised to quinoline by nitrobenzene. Violent nature of this reaction is supressed in the presence of ferric sulphate.







4. *Sporozoite :* The male and female parasite forms unite to form a fertilised ovum (Oocyst). The mature Oocyst divides into a numerous small nuclei. Each nucleus gets surrounded by a little cytoplasm. This is known as sporozoite.

Authors : Prof. D. Bhaskar Reddy

Dr. T. Sundararamaiah

UNIT-14 : ANTIBACTERIALS

Contents

14.1 AIMS AND OBJECTIVES

To enable you to understand the term antibacterials and also to differentiate them from the other drugs such as antibiotics etc.

After a thorough study of this unit, you must be able to :

* describe the discovery of Prontocil, the advantage and disadvantages of sulpha drugs over antibiotics as antibacterials
* present the structure and activity relationship of sulpha drugs.
* give the methods of synthesis of sulpha drugs sulphadiazine, sulphamethoxazole and trimethoprim.

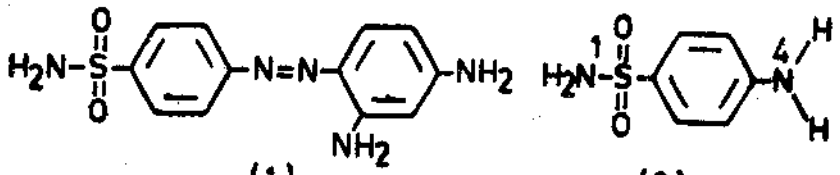
14.2 INTRODUCTION

Antibacterials are the chemicals used for the treatment of certain diseases caused by bacterial infections. For example , sulphanilamide and its related compounds known as 'Sulpha drugs' are used in the treatment of bacillary dysentery, pneumonia, and many other bacterial infections. There are also other chemicals produced by microorganisms, such as penicillins, tetracyclines etc., which are used to combat bacterial infections. They are known as antibiotics. As antibacterials, the sulpha drugs have certain advantages and disadvantages over antibiotics. Emergence of resistant bacteria and hypersensitization to the host are some of the problems met with the sulpha drugs. But they are effective in drug action, inexpensive, quite safe and free of superinfection problems of the antibiotics. Therefore, they are continued as antibacterials since more than four decades.

14.3 THE SULPHA DRUGS

Domagk (1934) discovered that a red dye prontosil (2,4-diamino-azobenzene-4-sulphonamide) (1) had a curative effect against bacterial infections in animals and in man. Later, a research team at the Pasteur Institute in Paris established that the curative effect of the dye stuff was due to sulphanilamide (2), which could be readily formed from the dye. This led to the discovery of several sulpha drugs. The prefix 'sulpha' is used to designate the group 'sulphanilamide'.

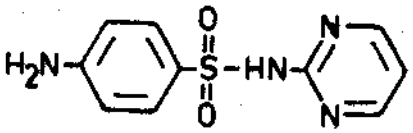
Check Your Progress - 1
What is Prontocil?



(1)

(2)

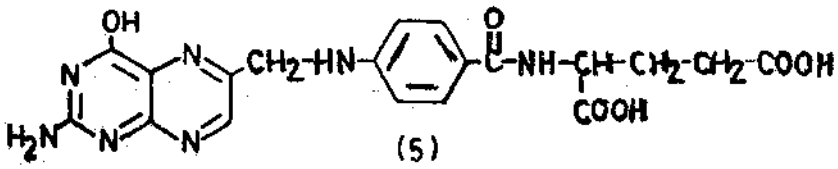
(3)



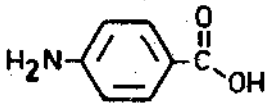
(4)

The sulphanilamide (p-aminobenzene sulphonamide) (2) and its derivatives have great antibacterials activity. Sulphonamide itself is active against infections caused by Streptococci, Gonococci and Pneumcocci. The greatest danger with sulphonamides is the crystal formation of acetylated sulphonamide in the kidney. Therefore, more soluble sulphonamide drugs are now developed. These derivatives have substituents on the nitrogen atom of the sulphonamido group and also the amino group. Substituents on the amide group of sulphanilamide are called N^1-substituents and substituents of the amino group are called N^4-substituents. For example, in sulphadiazine (4), pyrimidine (3) nucleus is present on sulphamido nitrogen atom.

Solubility of the sulphonamides, their protein binding nature, the pathway of metabolism, and mechanism, of elimination determine the toxicity, half-life period and effectiveness of the sulphonamide drugs. The sulpha drugs prevent the synthesis of folic acid (5) from p-aminobenzoic acid (6) in bacteria. Folic acid is a growth factor for bacteria. The depression of folic acid metabolism to a lesser degree in bacteria than in human beings, is responsible for the antibacterial activity of the sulpha drugs.



(5)



Check Your Progress - 2
How sulpha drugs function as antibacterials?

.....

.....

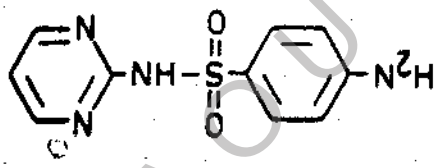
.....

.....

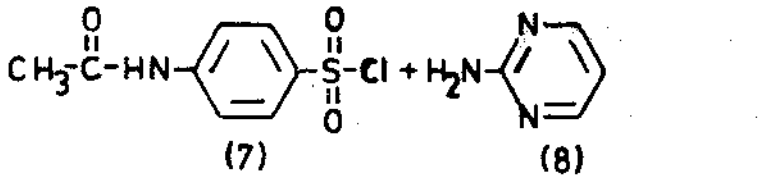
Some of the antibacterials other than antibiotics, such as sulphadiazine, sulphamethoxazole and trimethoprim and their syntheses are described below.

14.4 SULPHADIAZINE

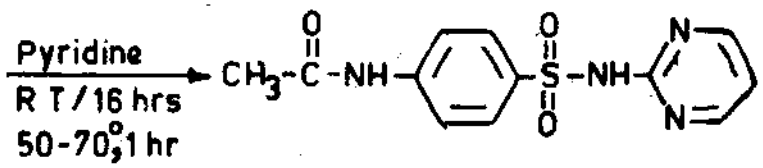
The chemical name of sulphadiazine (4) is 4-amino-N-2-pyrimidinyl benzene-sulphonamide, with molecular formula $C_{10}H_{10}N_4O_2S$. It is a crystalline compound, m.p. 252-6°C, used as an antibacterial against infections caused by several bacteria, such as *Bacillus, Clostridium Streptococcus, Gonococcus, Plague* etc.

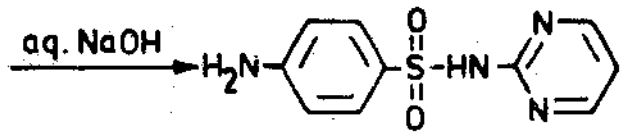


Sulphadiazine (4) can be prepared by the condensation of p-acetyl amino benzene sulphonyl chloride and 2-amino pyrimidine (8) followed by hydrolysis. The intermediate p-acetyl aminobenzene sulphonyl chloride (7) is synthesised by the sulphonation reaction between acetanilide (9) and chlorosulphonic acid (10).



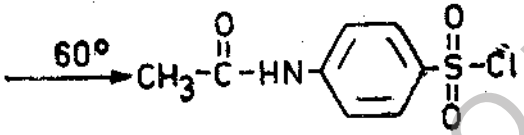
(7) (8)





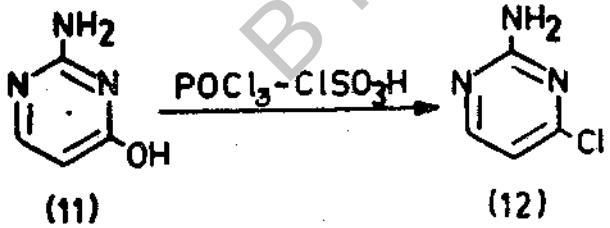
(4)

(9) (10)

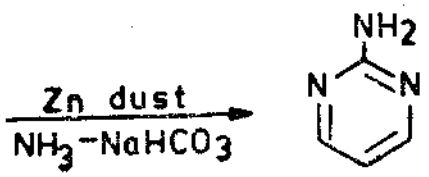


(7)

2-Aminopyrimide (8) can be prepared by treating isocystasine (11) with $POCl_3$-$ClSO_3H$ to get 2-amino-6-chloro pyrimidine (12) which is then subjected to catalytic reductive dechlorination.



(11) (12)

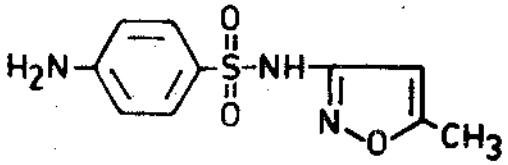


(8)

In general pyramidine derivatives can be prepared by the condensation of a 1,3-dicarbonyl compound or a potential 1,3-dicarbonyl compound and an amidine derivative in presence of a base. For example, isocystasine (11) may be prepared from glyoxalicester and guanidine in presence of a base

14.5 SULPHAMETHOXAZOLE

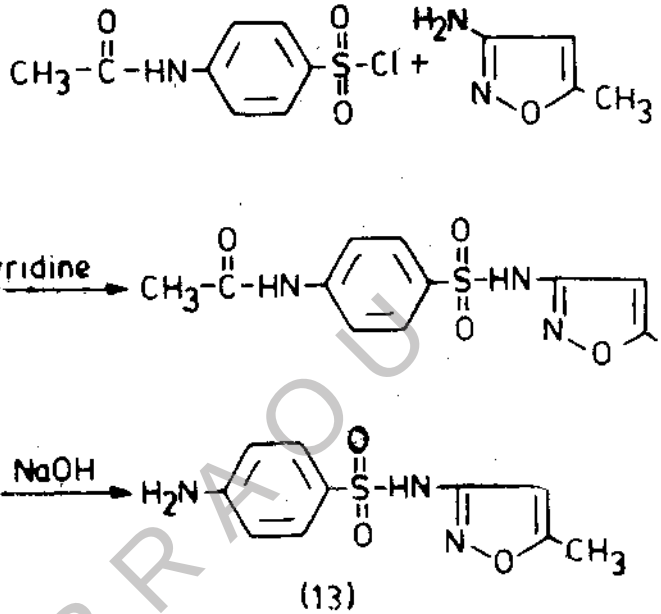
The chemical name of sulphamethoxazole (13) is 4-amino-N-5-methyl-3-isoxazolyl) benzene sulponamide, with molecular formula $C_{10}H_{11}N_3O_3S$. It is a crystalline powder m.p. 170-3°C, and used as an antibacterial, especially in chronic urinary tract infections.



(13)

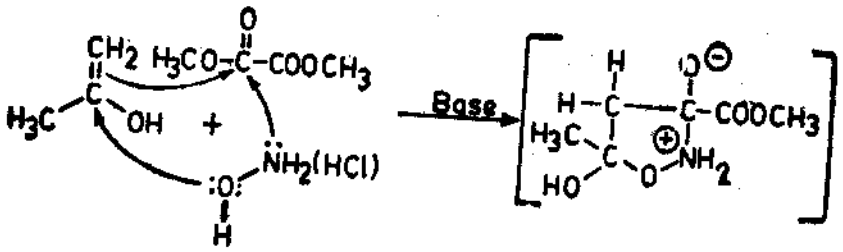
Sulphamethoxazole (13) can be synthesised by the condensation of 3-amino-5-methyl isoxazole (14) and p-acetyl aminobenzene sulphonyl chloride (7) in pyridine and then followed by hydrolysis.

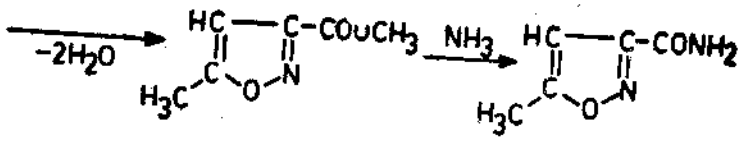
(7) (14)



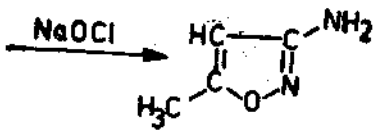
(13)

The intermediate 3-amino-5-methyl isoxazole (14) can be prepared by the reaction of dimethyl oxalate (15), acetone (16) and hydroxylamine hydrochloride (17). The resulting methyl 5-methyl isoxazole-3-carboxylate (18) is treated with ammonia to obtain the corresponding amide (19). Thus, the 5-methyl isoxazole-3-carboxamide (19) is subjected to Hofmann reaction by treating it with sodium hypochlorite to get the required intermediate (14). The mechanism of the reaction is uncertain but the sequence may be given as follows.





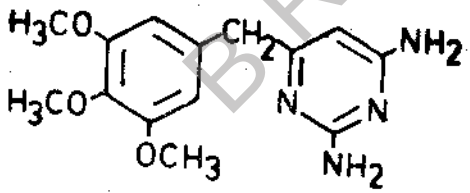
(18) (19)



(14)

14.6 TRIMETHOPRIM

The chemical name of trimethoprim is 5-[(3,4,5)-trimethoxy phenyl methyl] 2,4-pyrimidine diamine (20). It is a bitter crystalline compound m.p. 199-203oC, with molecular formula, $C_{14}H_{18}N_4O_3$. This belongs to 2,4-diamino pyrimide type of heterocyclic compound, having antimalarial and antibacterial activity.



(20)

Drug combination of trimethoprim and sulphamethoxazole (1:4) is used in the formulation of bactrim and septran. It is very effective in the treatment of chronic bronchits and other respiratory tract infections and chronic urinary tract infections. The components of the combination drug act sequentially interfering with the metabolism of folic acid in the microorganisms. Further, the drug reduces also the development of bacterial resistance.

Trimethoprim (20) can be prepared by the condensation of 3,4,5-trimethoxy benzaldehyde (24) with the intermediate morpholinopropionitrile (23) as shown in the scheme-1. Addition of morpholine (21) to acrylonitrile (22) produces morpholino propionitrile (23). The intermediate condenses with trimethoxy benzaldehyde (24) in presence of NaOMe (25) and aniline (26) to yield 2-(3,4,5-trimethoxy benzyl-3-anilinoprop-3-enyl nitrite (27). This will react with guanidine nitrate (28) to produce trimethoprim (20).

UNIT-15 : ANTIBIOTICS

Contents

15.1 AIMS AND OBJECTIVES

To introduce the student to a brief account of the antibiotics, the mode of the preparation of some important antibiotics, their structures and applications.

After a thorough study of this unit, you must be able to :

* define and give a brief account of discovery and general characteristics of antibiotics.
* present the mode of action and the bacterial resistance of antibiotics.
* describe the production, isolation, structure and applications of penicillins, streptomycin, chloramphenicol and tetracyclines.

15.2 INTRODUCTION

15.2.1 HISTORICAL

The development of antibiotic drugs is one of the major advances in chemotherapy. The introduction of the antibiotic has not only influenced the practice of medicine, but are finding applications in animal nutrition, agriculture and food processing industries. Diseases thought to be incurable a century ago have been treated successfully with antibiotics. This is true of disease of childhood, pneumonia, dysentery, typhoid, and typhus fevers, plague and cholera, tuberculosis and other infectious diseases caused by bacteria, fungi and protozoa.

Prior to 1939 a small group of drugs like antitoxins, antisera and vaccine preparations provided a limited degree of control over systemic microbial infections. The value of these preparations was largely prophylactic. They were of little use once the infection was established in the host. The drugs, active against bacterial infections in the blood stream, were not available till sulphonamide drugs were introduced.

In 1938, Florey, Chain and their colleagues were investigating the chemotherapeutic potentialities of the enzyme lysozyme. This enzyme has the property of lysing bacteria in vitro. However, this substance gave disappointing results in vivo. Therefore Florey and Chain decided to examine a substance called penicillin, isolated by Sir Alexander Fleming from a mould culture (Penicillium notatum) in 1929, and found it has the property of lysing bacteria. The discovery of other antibiotics now in use has been the result of an immense amount of planned research. It began with the preliminary screening of thousands of microorganisms and their metabolic products. As a result more than 20 antibiotics are known so far. Some important antibiotics and the year of their discovery is shown below.

Antibiotic	**Year of discovery**
Penicillins	1929
Streptomycin	1944
Chloramphenicol	1947
Chloratetracycline	1948
Oxytetracycline	1950
Tetracycline	1953

15.2.2 DEFINITION AND CHARACTERISTICS OF ANTIBIOTICS

During 1942, Waksman defined antibiotic as a chemical substance, produced by micro-organisms that interfered with the growth and multiplication of other organisms. But there is increasing tendency to expand the definition to cover all the microbial substances derived from microbes as well as from plants and animal tissues. As the synthesis of antibiotics like penicillin, chloramphenicol, tetracyclines and several other antibiotics have been developed in the laboratory, the above definition seems not to be satisfactory. Yet the original definition is retained, because majority of the antibiotics are produced by micro-organisms.

Antibiotics vary greatly in their chemical structure. They comprise of carbohydrates, polypeptides polyketides etc.,

The antimicrobial action of antibiotic is selective. Some organisms are affected by antibiotics and others are not affected at all or only to a limited degree. Each antibiotic is characterised by a specific range of activity against different organisms. Some have a broad spectrum. They are active against various bacteria belonging to both gram-positive and gram-negative bacteria. Others have narrow spectrum. They are active largely upon members of a specific group of microbes, such as gram-positive bacteria or gram-negative bacteria, acid fast bacteria or yeast like organisms.

Check Your Progress - 1

What do you mean by broad spectrum antibiotics?

.....

.....

.....

.....

15.2.3 MODE OF ACTION AND BACTERIAL RESISTANCE

Antibiotics are largely bacteriostatic agents. They inhibit the growth of sensitive organisms without destroying them. Some also have marked bactericidal or bacteriolytic properties. They act upon bacteria by interfering with their capacity to absorb and assimilate nutrients and to synthesize cell substances. They also affect various enzyme systems and bacterial cell division.

Many bacteria adapt themselves to the effect of antibiotics upon continued contact with them, leading to the development of resistance. There are two possible explanations for the development of bacterial resistance; either there is a spontaneous mutation of the bacterial culture or there is a gradual killing of the sensitive cells within a culture by the antibiotic and the remaining cells develop into a new strain.

The degree to which resistance develops varies with each antibiotic. Fortunately a culture of an organism that has become resistant to one antibiotic still may remain sensitive to others. In order to prevent the development of resistance, combination of antibiotics, such as penicillins and streptomycin often are used. Antibiotics also may be combined with synthetic compounds as in the treatment of tuberculosis.

Check Your Progress - 2
What is bacterial resistance?

.....

.....

.....

.....

15.3 PENICILLINS

In 1929 Fleming found that a micro-organism, known as Penicillium notatum inhibits the growth and multiplication of certain bacteria. This observation of antibiosis (anti means against and bio means life) of Penicillium notatum led Florey and his colleagues to discover the medical potentialities of the organism. They suggested that the biological activity of the organism is due to the presence of a group of organic compounds, named as penicillins.

15.3.1 PRODUCTION AND ISOLATION

Penicillins are produced commercially by the fermentation process. Various culture methods have been developed for the production of penicillins on a large scale. One such method is submerged culture method.

The composition of the medium in this process is 2% crude lactose, 4-5% corn steep liquor, small amount of citric acid and calcium carbonate. The containers are long horizontal drums provided with means of rotation, heating and cooling. The medium is inoculated with the mould and the fermentation is carried on for two or three days. During this period the temperature is maintained at 24°C. Under these conditions, Penicillium notatum grows in bulk and the concentration (0.1 mg. to 0.2 mg/cc) of penicillin is obtained. It has been observed that the additions of zinc as a catalyst increases the yield of penicillin by 0.2-0.3 mg/cc.

After fermentation, the contents are cooled rapidly and mycelium is separated by filtration. Now the clear solution (filtrate) containing penicillin is protected from contamination. Aseptic handling, chilling and addition of an antiseptic is essential at this stage. The cooled filtrate is acidified with phosphoric acid and the pH is maintained at 2-3. Penicillin can be extracted from the aqueous solution with various organic solvents immiscible with water such as ether and chloroform.

Penicillin is not stable in solution, particularly when present as free acid. Therefore organic layer containing penicillin is immediately treated with sodium bicarbonate solution. In bicarbonate solution penicillin is present as sodium salt. The bicarbonate solution is then cooled to -10°C and is evaporated under high vacuum. As the great part of penicillin produced is intended for administration by injection the final sample must be non-toxic, sterilized and free from pyrogens. To achieve these conditions the concentrated solution of purified penicillin salt is allowed to run through asbestos. This absorbs micro organisms and pyrogens. Finally it is biologically standardised before putting for sale. The activity of penicillins is expressed in oxford units. The smallest amount of penicillin which, when dissolved in 50 cc of meat extract broth completely inhibits the growth of Staphyloccus aurens, invitro, has been called one oxford unit. The number of oxford unit corresponds to 1 mg. of the pure sodium penicillins is listed below.

Name	Oxford unit in 1 mg. of pure sodium salt
Benzylpenicillin	1,667
p-Hydroxy benzyl penisillin	900
n-Amyl penicillin	1,500
2-pentenyl penicillin	1,600
n-Heptylpenicillin	2,300

15.3.2 VARIOUS PENICILLINS

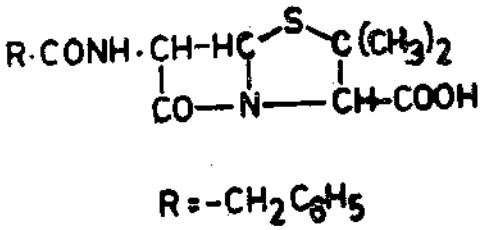
The material obtained by fermentation method is a mixture of several penicillins. They can be represented by the molecular formula $C_9H_{11}O_4N_2SR$. They have a very similar properties. All penicillins have a common nucleus but differ in the nature of side chain R. They are named by using prefixes indicating the nature of side chain R. Some penicillins are listed below.

Chemical name	Other names	Side chain R
Pent-2-enylpenicillin	Penicillin-F	$-CH_2CH = CHCH_2CH_3$
Benzyl penicillin	Penicillin-G	$-CH_2C_6H_5$
n-Amyl penicillin	Dihydro-F-Penicillin	$-(CH_2)_4\ CH_3$
n-Heptyl Penicillin	Penicillin-K	$-(CH_2)_6\ CH_3$
Phenoxymethyl Penicillin	Penicillin-V	$-CH_2OC_6H_5$
p-Hydroxybenzyl Penicillin	Penicillin-X	$-CH_2C_6H_4OH$ (1:4)

Commercial preparation of penicillin will contain one or more of the above penicillins in various proportions. The type of penicillin that will be formed in a particular fermentation depends upon the mould strain and the culture method employed. It has been found that the addition of various compounds to the culture medium increases the yield of penicillins. For example the addition of phenylacetic acid, phenylacetamide and phenylethylamine etc. (i.e., compounds containing a benzyl group $C_6H_5CH_2$—) to the culture medium increases the total yield of penicillins and also the proportion of benzylpenicillin. Similarly the addition of compounds containing p-hydroxy benzyl group to the culture medium increases the proportion of p-hydroxybenzyl penicillin. On the other hand the addition of various compounds to the culture medium, a number of 'unnatural' penicillins have been prepared.

15.3.3 STRUCTURE AND APPLICATIONS

All penicillins are monocarboxylic acids. Among all the penicillins benzyl penicillin has been investigated in detail. Both physical and chemical methods have been used to derive the structure of benzylpenicillin. It is shown to contain a β-lactam structure and can be represented by the structure.



$R = -CH_2C_6H_5$

(1)

For the commercial production of benzyl penicillin, fermentation method is employed as it is superior over the synthetic methods.

Penicillin is very effective against gram-positive bacteria, but not against other micro-organisms. Hence it is called a narrow spectrum antibiotic. Broad spectrum antibiotics like chloramphenicol and tetracyclins are effective against a wide variety of organisms.

Penicillin has proved to be very effective for the treatment of pneumonia, diphtheria, scarlet fever, child birth fever, rehumatic fever, wound infections, gonorrhea, syphilis and many other diseases.

Although penicillin is least toxic of all the antibacterial drugs, allergic effects are common when it is given for a long period for the treatment of asthma and eczema.

15.4 STREPTOMYCIN

Streptomycin was discovered by Waksman in 1944 and structure elucidated in 1948. Streptomycin was isolated from the cultures of Streptomyces griseus.

15.4.1 PRODUCTION AND ISOLATION

For the manufacture of streptomycin, surface culture method was first employed but it is soon replaced by submerged culture method as in penicillin. In addition to other constituents the culture medium must contain protein materials such as soyabean meal and cotton-seed meal for better growth of the organism. The culture medium is inoculated with the organism Streptomyces griseus and maintained at 25°C for three days. During the process an antifoaming agent is added to the medium and sterile aeration is employed. In the early stages of growth, Streptomyces griseus is susceptible for attach by a virus-like agent called actinophage. Therefore, maintenance of sterility is essential for the process. During the fermentation, the reaction medium changes from acidic to basic state. The point of highest alkalinity, i.e., pH 8.2 to 8.6, corresponds to the highest streptomycin production. The yield of streptomycin can be increased by irradiating the culture solution by X-rays or ultraviolet light.

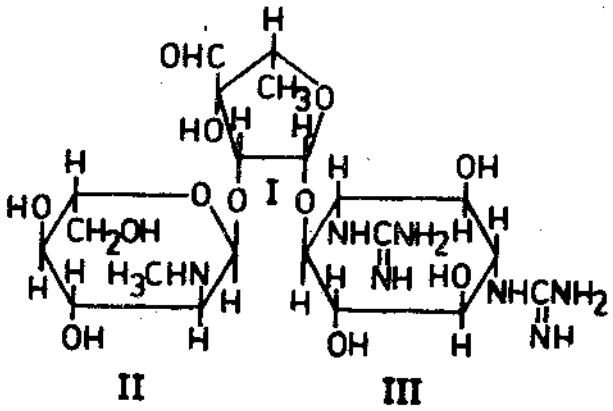
After fermentation, the mycelium and other waste products are separated by filtration. Streptomycin is recovered from the filtrate either by absorption on charcoal or on base exchange resins and elution with dilute aqueous or ethanolic mineral acid. Pure form of streptomycin is obtained as sulphate or a crystalline double salt of calcium chloride.

Since streptomycin is administered by injection, the final sample must be sterilized and free from impurities. For this the purified crystalline salt of streptomycin is redissolved to get 25% solution which is freed from impurities, passed through seiltz filter and freeze dried.

15.4.2 PROPERTIES AND STRUCTURE

Streptomycin is a colourless solid. It is a strong base. It is soluble in water and is leavo-rotatory.

The molecule of streptomycin (2) is built up of three units namely streptose (I), N-methyl-L-glucosamine (II), and streptidine (III) as shown below.



(2)

Unit I and II, together is known as streptobiosamine. The streptose unit is neither isolated from the degradation products of streptomycin nor synthesized. Its structure is derived from reactions of streptomycin. The other units namely streptidine and N-methyl-L-glucosamine have been isolated. Their structures are elucidated and confirmed by synthesis.

15.4.3 APPLICATIONS

Streptomycin is active against gram-negative bacteria. This observation was highly encouraging since penicillins and sulphonamide drugs are chiefly effective against gram-positive bacteria.

Streptomycin is specially employed for the treatment of tuberculosis. It has also been used in the treatment of babonic plague and influenzal meningitis caused by *Haemophilus influenzea*. Among the side effects, it causes irreversible deafness.

15.5 CHLORAMPHENICOL

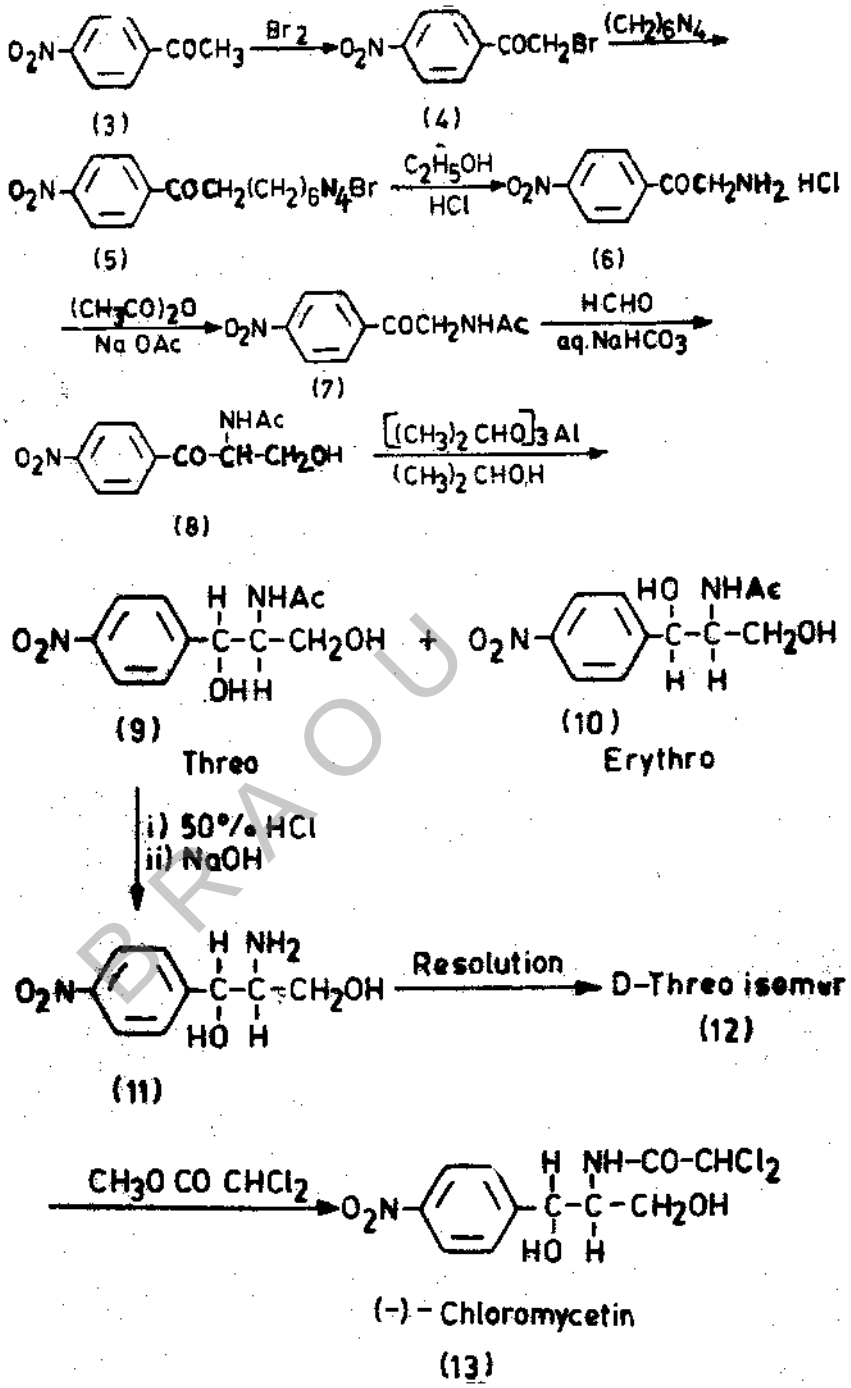
Chloramphenicol was isolated independently by the research groups of Ehrich and Carter. The trade name of chloramphenicol is chloromycetin. Chloramphenicol is produced by an organism called *Streptomyces venezuelae*. This type of actinomycetes are obtained from the soil samples near Venezuela.

This is the simplest antibiotic for which practical synthesis have been devised. It was originally prepared by fermentation process.

15.5.1 SYNTHESIS OF CHLORAMPHENICOL

Bromination of p-nitroacetophenone (3) gives p-nitrobromoacetophenone (4), which on reaction with hexamethylenetetramine yields the complex (5). The complex is hydrolysed to p-nitro-amino-aceto-phenone hydrochloride (6) by means of concentrated hydrochloric acid. The amino group is next acetylated with acetic anhydride to give p-nitroacetamido-acetophenone (7) which on treatment with

formaldehyde undergoes hydroxymethylation and forms p-nitro-(1-acetamide-2-hydroxy) propiophenone (8). This is subjected to a Meerwein-Pondorf-Verley reduction to give racemic threo-2-acetamido-1-p-nitrophenylpropane-1,3-diol (9). It is contaminated with a small amount of the erythro isomer (10). The amine (11) is resolved with optically active, D-camphorsulphonic acid to the threo isomer (12) which on reaction with methyl dichloroacetate yields chloramphenicol (13).



D-(--)-threo-2-Dichloro acetamido-1-p-nitrophenyl propane-1,3-dicl.

Chloramphenicol, a colourless neutral solid, is bitter in taste. It is taken orally, in the form of capsules and solution.

15.5.2 APPLICATIONS

Chloramphenicol is active against a variety of pathogenic organisms as those causing typhoid fever, bacillary dysentery, urinary tract infection, respiratory infection, ocular and otic infection meningitis and rickettsial infection.

15.6 TETRACYCLINES

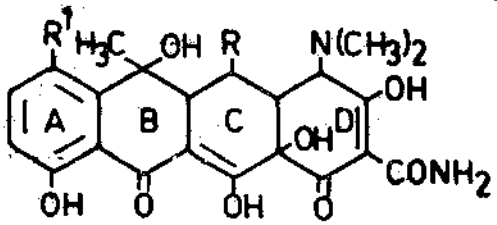
The tetracycline group of antibiotics includes chlortetracycline, oxytetracycline and tetracycline. All these antibiotics contain hydronapthacene skeleton as a characteristic structural unit. Tetracycline antibiotics are yellow in colour. They are amphoteric substances and form salts with both acids and bases. They also form complexes with metals such as aluminium, magnesium, calcium or iron. The acid salts are readily soluble in water.

Chlortetracycline is the first of these group of antibiotics discovered by Duggar in 1948. It is produced by an organism known as Streptomyces aureofaciens. This name was given to this organism because it produced a golden yellow pigment. Hence it is also known as aureomycin. Another antibiotic very similar in biological activity to chlorotetracycline is oxytetracycline. Oxytetracycline was isolated in 1950 by Finlay as a result of a systematic survey of soil samples from all over the world. It is produced by an organism known as Streptomyces remosus. The trade name of oxytetracycline is terramycin. Terramycin derives its name from the Latin word Terra for 'soil'. Of the three antibiotics tetracycline has the simplest structure, but was infact discovered last. Tetracycline was prepared from chlortetracycline by replacing the halogen with hydrogen in a simple catalytic hydrogenation.

15.6.1 PRODUCTION AND STRUCTURE

For the production of these antibiotics submerged culture method similar to those used for the production of penicillins and streptomycin was used.

All the three antibiotics contain the hydronapthacene skeleton. The structure of these antibiotics (14) has been elucidated by alkaline, acid and reductive degradative studies. Chlortetracycline differs from oxytetracycline in having a chlorine atom on the ring D of the hydronaphthacene skeleton and in lacking the second hydroxyl group on the B ring. The third member of the group, tetracycline has hydrogen in place of chlorine in chlortetracycline. The structure of the three antibiotics is represented as shown below.



(14)

Chlortetracycline	:	R = H, R' = Cl
Oxytetracycline	:	R = OH, R' = H
Tetracycline	:	R = H, R' = H

Tetracyclines are broad spectrum antibiotics of great therapeutic value and low toxicities.

15.7 SUMMARY

You have learnt the following in this unit.

i. Definition, a brief account and general characteristics of antibiotics.

ii. The method of action of antibiotics on bacteria and bacterial resistance against antibiotics.

iii. The description of production, isolation, structure and applications of penicillins, streptomycin, chloramphenicol and tetracyclines.

15.8 MODEL EXAMINATION QUESTIONS

I. **Answer each of the following in 10 lines.**

1. Write the different natural penicillins and give their common names.
2. Give the structural formula of terramycin.
3. Give the structural formula of streptomycin.

II. **Answer each of the following in 30 lines.**

1. How is penicillin produced on a large scale and isolated?
2. Describe the synthesis of chloramphenicol.
3. Give an account of the production and isolation of streptomycin.

15.9 MODEL ANSWERS TO CHECK YOUR PROGRESS

1. Those antibiotics which are active against different disease causing bacteria i.e., gram +ve and gram -ve bacteria are called broad spectrum antibiotics..
   eg. : tetracyclines.

2. Due to the continuous use of a drug against a particular disease, the concerned disease causing bacteria develops tolerence against the drug, called bacterial resistance and the drug becomes less effective. In such cases, combination of drugs will be effective in curing the diseases.

15.10 GLOSSARY

1. In vitro	:	Outside the body
2. In vivo	:	Inside the body
3. Gram positive and Gram negative bacteria	:	These are bacteria classified according to their reaction to a differential strain known as Gram-strain.
4. Bactericidal	:	Bacteria killing
5. Bacteriolytic	:	Bacteria dissolving
6. Mycelium	:	A waster product formed during the growth of micro-organisms.
7. Pyrogens	:	Fever producing organisms.
8. Corn steep liquor	:	Water used for steeping maize in maize starch production.

UNIT-16 : ANTIDIABETICS

Contents

16.1 AIMS AND OBJECTIVES

To introduce the students to the pancreatic hormone, insulin and the consequences of its deficiency, to make them understand the usefulness of insulin treatment and more generally the use of oral hypoglycemic drugs namely chlorpropamide and tolbutamide.

After a thorough study of this unit, you must be able to :

* describe the role of pancreatic hormone insulin in the utilisation of glucose.
* give an account and synthesis of oral hypoglycemic drugs chlorpropar. and tolbutamide.

16.2 INTRODUCTION

Pancreas is one of the important parts of the gastro intestinal tract. It consists of glandular tissue which secretes several digestive enzymes. There is a region in the pancreas consisting of some special cells called the islets of the Langerhans. It has two types of cells, the alpha and the beta cells. The beta cells secrete the hormone insulin while the alpha cells produce a factor known as glucagon.

In the body, glucose is either used as a fuel for production of energy or is converted into glycogen, which is a less soluble polymer of glucose. In either case insulin is needed. When the supply of insulin is inadequate, a disease known as Diabetes mellitus results. The concentration of glucose in the body fluids increases and when the blood glucose level exceeds a certain point, the glucose is excreted through kidneys. The condition in which excess glucose is present in the blood is called hyperglycemia. The amount of glucose excreted through urine depends on the severity of the disease. This condition is called glycosuria. Continued glycosuria results in the depression of the functions of the brain, muscle and other tissues. If not treated promptly, several other complications may arise leading to coma followed by death.

Administration of insulin or insulin preparations at regular intervals in the desired doses would control this disease. Fall in the blood sugar level is called hypoglycemala and the chemical substance which perform this function are called the hypoglycemic agents. Insulin is the ideal natural hypoglycemic agent. It is extracted from the pancreas of the beef, sheep, whale or pig and is a polypeptide. (See Unit - 20). Several insulin preparations are in use. They differ principally from each other in their solubility and duration of action. Insulin is usually administered subcutaneously. It can not be administered orally because it gets degraded by the enzymes present in the gastrointestinal tract.

Check Your Progress - 1

Differentiate hyperglycemia from hypoglycemia?

.....

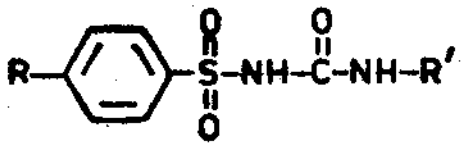
.....

.....

.....

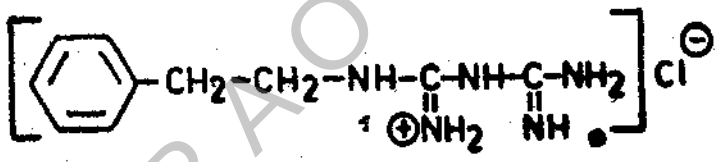
16.3 ORAL HYPOGLYCEMIC DRUGS

Besides insulin, several other substances were also shown to possess hypoglycemic activity. Several of these compounds belong to the class of benzene sulphonyl ureas represented by the general formula (I), Chlorpropamide belong to this group of compounds.



(1)

The other hypoglycemic compounds belong to the formamidinyl amino ureas of the biguanide group. Phenformin hydrochloride (2) belongs to this class.



(2)

Check Your Progress - 2
What are hypoglycemic drugs?

.....

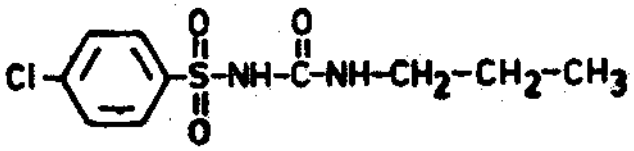
.....

.....

.....

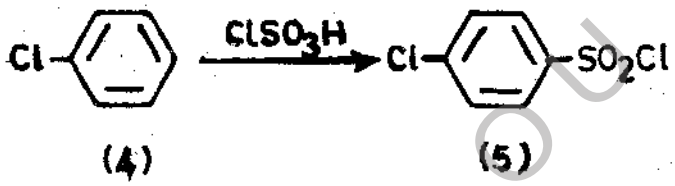
16.4 CHLORPROPAMIDE

4-Chloro-N-[(Propylaminocarbonyl)] benzene sulphonamide. It causes the release of insulin from the beta cells of the islets of the Langerhans. It is useful in the treatment of mild, uncomplicated cases of diabetes mellitus.

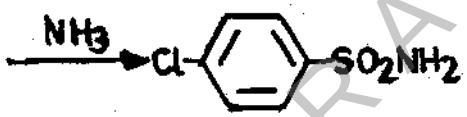


(3)

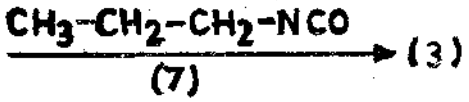
Synthesis : Treatment of Chlorobenzene (4) with chlorosulphonic acid gives p-chlorobenzene sulphonyl chloride (5). Treatment of the chloride (5) with ammonia yields p-chlorobenzene sulphonamide (6). Reaction of the sulphonamide (6) and propyl isocyanate (7) yields chlorpropamide (3) Chlorpropamide (3) is a white crystalline powder melting at 125-129°C. It is insoluble in water but soluble in alcohol



(4) (5)

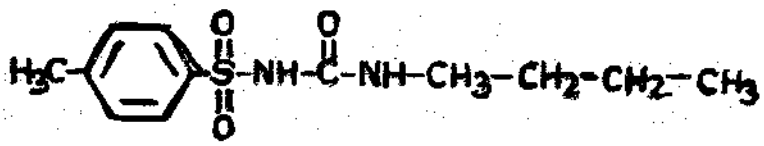


(6)



16.5 TOLBUTAMIDE

[N-(butylamino carbonyl)] 4-methyl benzene sulphonamide.



Check Your Progress - 2
What are the main symptoms of dysentery?

.....

.....

.....

.....

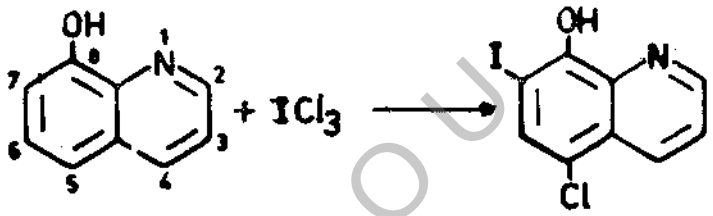
17.3 ANTIDYSENTERY AGENTS

The following drugs are in use in the treatment of dysentery.

a) Iodochlorhydroxyquin
b) Metronidazole
c) Tinidazole

a) Iodochlorhydroxyquin

One of the earlier drugs used in the amoebic infections is iodochlorhydroxyquin (5-chloro-7-iodo-8-quinolino). It is a quinoline derivative synthesised from halogenation of 8-hydroxyquinoline with iodine trichloride.

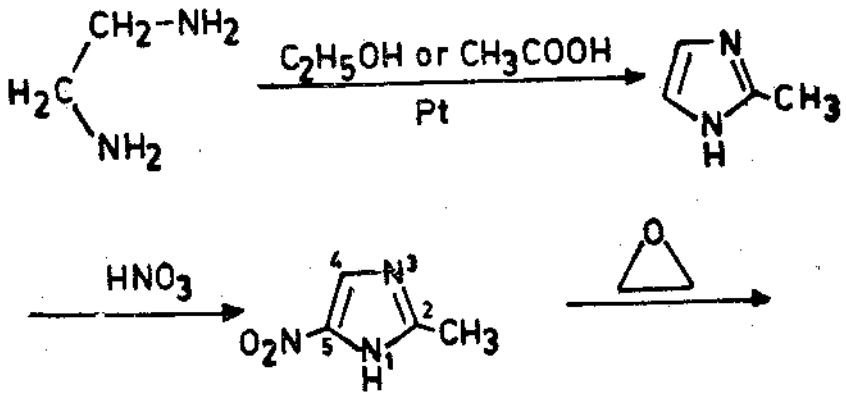


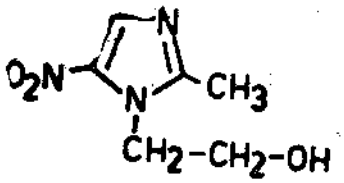
8–Hydroxyquinoline Iodo–chlorhydroxyquin.

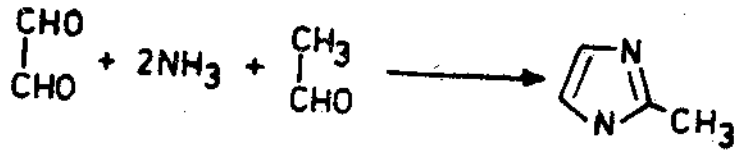
This drug is being removed from the market as it is known to damage the optical nerves.

b) Metronidazole

Nitration of the 2-methylimidazole gives 2-methyl-5-nitro imidazole, which on treatment with ethylene oxide yields metronidazole. The starting material, 2-methyl-imidazole, is prepared by the reaction of ethylene diamine with acetic acid or ethanol in the presence of platinum catalysts or from condensation of glyoxal, acetaldehyde and ammonia.

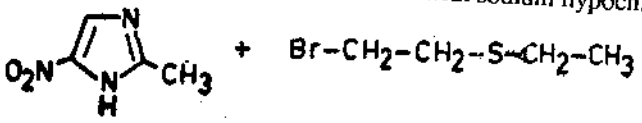


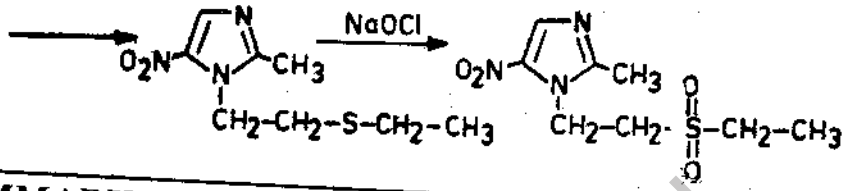




c) **Tinidazole : [1-(2-Ethylsulfonyl) ethyl-2-methyl-5-nitroimidazole]**

Alkylation of 2-methyl-5-nitroimidazole with β-bromoethyl sulphide gives ethyl [2-(2-methyl-5-nitro-1-imidazole] ethyl sulphide, which on oxidation with sodium hypochlorite yields tinidazole.





17.4 SUMMARY

You have studied the following in this unit

1. The root cause of dysentery, its methods of spreading, symptoms and its methods of curing.
2. The methods of synthesis of antidysentery agents iodochlorhydroxyquin, mitronidazole and tinidazole

17.5 MODEL EXAMINATION QUESTIONS

I. **Answer the following in 10 lines.**

1. How do you synthesize metronidazole from 2-methyl imidazole?

II. **Answer each of the following in 30 lines.**

1. Starting from 2-methyl-5-nitro imidazole, write the steps involved in the synthesis of tinidazole?
2. Write a brief note on antidysentery agents.

17.6 MODEL ANSWERS TO CHECK YOUR PROGRESS

1. It spreads through oral route and contaminated food. Excreta of infected individuals is the source of the disease and flies are the mechanical carriers.
2. The symptoms are dehydration of the body with the result of loss of water and salts particularly potassium leakness and if it is prolonged it may lead to death.

UNIT-18 : ANTIALLERGIC AGENTS

Contents

18.1 AIMS AND OBJECTIVES

To introduce the student to the nature of allergic reactions and disease, chemical mediators released in allergic reaction and some important antiallergic drugs.

Once you complete the study of the contents of this unit, you are expected to :

* define allergens, antibodies and chemical mediators.
* explain the role of antiallergic agents.
* give the methods of synthesis of antiallergents ephedrene and chlorpheniramine maleate.

18.2 INTRODUCTION

Body does not tolerate the interaction of some foreign materials called allergens. In order to counter and destroy allergens, body secretes some chemicals which actually produce the allergic symptoms. The materials used to block the above chemical mediators are called antiallergic agents.

18.3 NATURE OF ALLERGY AND CHEMICAL MEDIATORS

Allergy can be defined as a condition in which the body develops sensitivity to foreign material resulting in tissue injury. The foreign materials, known to contain allergens, include pollens, moulds, animal dander, insecticides, certain food materials and drugs. The allergens are macromolecules like proteins, polysaccharides, lipids or small molecules, which are also termed as antigens or immunogens. In response to the attack by an antigen, the body stimulates its defence mechanism and produces antibodies. The antibodies are proteins which interact with antigens. The interaction initiates a chain of events resulting in the rupture of the cell walls, which leads to the release of many chemicals known as chemical mediators. Some of the mediators are histamine and serotonin. Histamine is the most important of the mediator implicated in producing allergic symptoms such as asthma, contact dermatitis, hay fever etc.

Check Your Progress - 1

What are allergens?

.....

.....

.....

.....

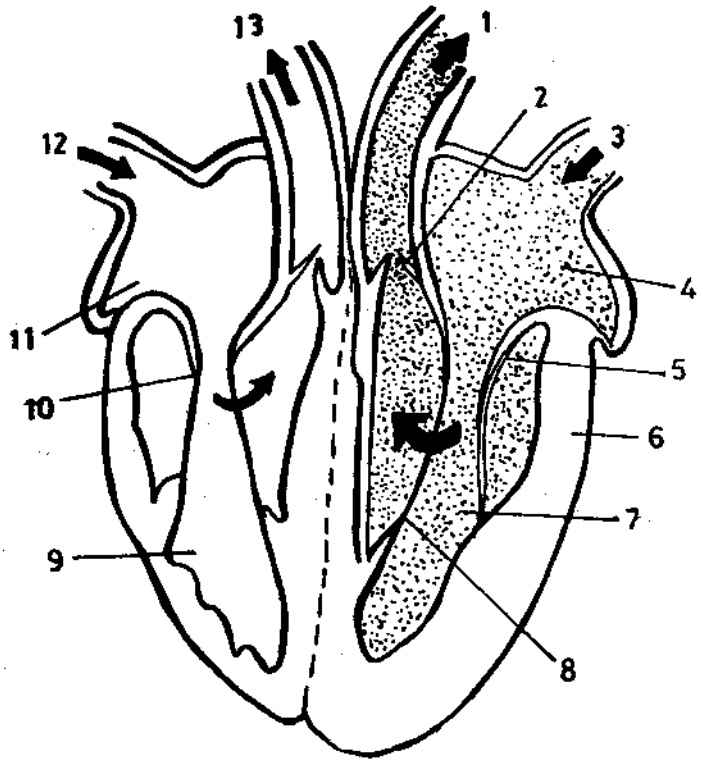


Fig. 19.1 Heart (Longitudinal Section)

1. Aorta (To head and body)
2. Semilumininar Valve
3. Pulmonary Vein (from lungs)
4. Left atium
5. Bicuspid Valve
6. Muscle
7. Left Ventricle
8. Tendon supporting Valve
9. Right Ventricle
10. Tricuspid Valve
11. Right atrium
12. Vena Cava (From head and body)
13. Pulmonary artery to lungs

If the coronary artery becomes obstructed by an internal blood clot, there is a reduction of the blood flow. The heart muscle is thus deprived of oxygen thereby affecting the ventricular contraction. This condition is called the coronary thrombosis and is often fatal. This is the familiar heart-attack.

Check Your Progress - 1

What is coronary thrombosis or heart attack?

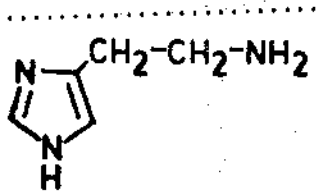
.....

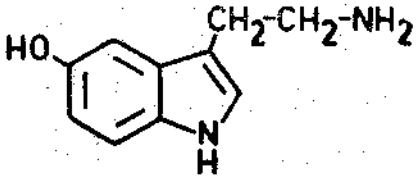
.....

.....

.....

There is another condition known as arteriosclerosis. This arises because of the deposition of fatty matter on the inner lining of the arteries resulting in a decrease in their internal diameter. This restricts the blood flow and consequently the disease.





Histamine
2-(4-imidazolyl) ethylamine

Serotonin
5-Hydroxy-3-(2-amino ethyl)–indole

Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg
Bradykinin

Anti-allergic agents that block some of the actions of histamine are called antihistamines.

18.4 ASTHMA

One of the most common allergic disorders is asthma, characterised by difficulty in breathing, wheezing and tightness in the chest. During breathing, the air has to enter the lungs through small holes in the chest called bronchioles. When the allergen enters the lungs from the air, allergic reaction develops which result in swelling of the muscles containing bronchioles. Consequently the bronchioles become smaller and smaller and obstruct free flow of air in the lungs. Asthma is aggrevated by secondary factors like change of temperature, humidity, exposure to noxious fumes (chemicals, paints, waxes etc.), emotional stress and some physiological changes in women like puberty, menstruation, pregnancy and menopause.

Check Your Progress - 2
Why breathing is difficult for asthma patients?

.....

.....

.....

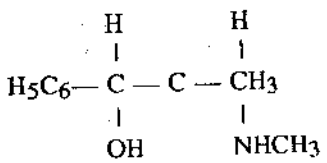
.....

18.5 ANTIALLERGIC AGENTS

As it is difficult to prevent the allergens from the environment, drug treatment is necessary to relieve the allergic patient. Some of the drugs used in the treatment of allergy are :

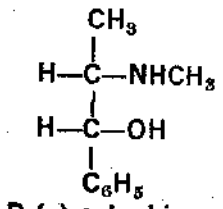
a) Ephedrine
b) Salbutamol
c) Chlorpheniramine maleate

a) D(—) Ephedrine : (1-phenyl-2-methylamino-1-propanol)

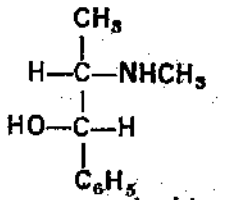


D(—) Ephedrine is an alkaloid present in the genus *Ephedra*. It is one of the most important constituents of the Chinese drug, Ma Haung, used in the treatment of bronchial asthma and hayfever.

Four different stereoisomers are possible for ephedrine as two asymmetric centres are present.



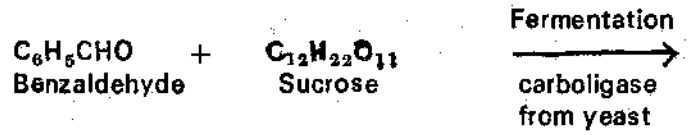
D (–) ephedrine (naturally occurring)

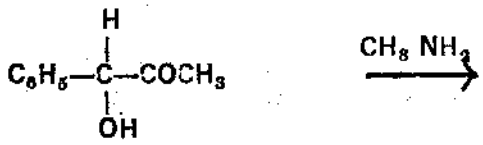


L (+) Ψ-ephedrine

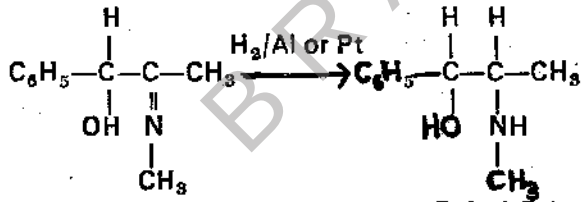
The (+) Ψ-ephedrine also occurs in nature and possesses the pharmacological property. The Ψ-isomer could be substantially converted to (—) ephedrine by boiling with dil. hydrochloric aicd.

Synthesis : Sugar is fermented through the action of enzyme carboligase of yeast in the presence of benzaldehyde to obtain (—) phenyl-acetylcarbinol. Phenylacetylcarbinol is reacted with methylamine and the product is reduced catalytically by means of activated aluminium or platinum to obtain ephedrine.





Phenylacetyl Carbinol



D (—) Ephedrin

b) Salbutamol

Salbutamol is an antiasthmatic drug belonging to the ethanolamine group.

c) Chlorpheniramine maleate

2,1 p-Chloroacetophenone condensed with formaldehyde and dimethylamine to obtain ketoamine (13) (Mannich reaction). Subsequent reaction of the Amine (13) with pyridyl lithium followed by acid treatment of the product (14) and hydrogenation with Raney Nickel gives chlorpheniramine.

Chlorpheniramine maleate is prepared by treating chloropheniramine with maleic acid or anhydride.

18.6 SUMMARY

You have studied the following in this unit

1. Definitions and explanation of allergens, antibodies, chemical mediators and antiallergy agents.
2. The method of prevention of allergy by antiallergy agents.
3. The methods of synthesis of antiallergents ephedrine and chlorpheniramine maleate.

18.7 MODEL EXAMINATION QUESTIONS

I. **Answer each of the following in 10 lines.**

1. What are the stereoisomers possible for ephedrine?
2. What is allergy? Mention three diseases associated with allergy?

II. **Answer the following in 30 lines.**

1. Write the steps involved in the synthesis of chlorpheniramine.

18.8 MODEL ANSWERS TO CHECK YOUR PROGRESS

1. Those foreign materials against which the body develops sensitivity resulting in tissue injury are called allergens.
   eg : **Pollen, moulds,** insecticides etc.
2. When the allergens enter the lungs, the muscles of the branchioles swell and become patients free flow of air is obstructed and breathing becomes difficult.

18.9 GLOSSARY

1. Tissue : Aggregate of similar cells
2. Mould : Flubby growth on the food matter
3. Dander : A form of dandruff
4. Dermatitis : A skin disease
5. Hayfever : Irritation of the throat, nose etc. with headache

Author : Dr. K. Rama Subba Reddy

UNIT-19 : CARDIOVASCULAR DRUGS AND CNS STIMULANTS

Contents

19.1 AIMS AND OBJECTIVES

To introduce the student to the drugs that affect the heart and blood vessels; the nature of the Central Nervous System (CNS) in controlling and co-ordinating the body and the chemical agents used in the stimulation of the Central Nervous System.

After a thorough study of this unit, you myst be able to :

* describe the cardiovascular diseases which are connected to heart and blood vessels.
* give an account of the role of heart and blood vessels in the body functions and increase of blood pressure, hypertension.
* present the methods of synthesis of propranol and methyl DOPA.
* remember an account of CNS stimulants.
* describe the synthesis of caffeine.

19.2 CARDIOVASCULAR DRUGS

19.2.1 INTRODUCTION

The disease associated with heart and the blood vessels are called cardiovascular diseases. The drugs that are used directly or indirectly to bring about cardiovascular actions are called the cardiovascular drugs. For example, drugs which bring about an increase or decrease (hypertensive drugs) in blood pressure, stimulate the heart or the coronary dilators come under this category.

a) *The Heart :* The heart is a muscular blood pumping organ situated in the thorax. It consists of four chambers (Fig. 18.1). The upper chambers are called the atria and are relatively thin walled. They receive the blood from the veins. The lower chambers are called the ventricles. Oxygenated blood from the lungs enters the left atrium through the pulmonary vein vena cava. The atria have openings into their corresponding ventricles through large apertures with non-return valves. The ventricles are thick walled and muscular. The walls of the left ventricles are 3 to 4 times thicker than those of the right ventricle. This is so because it has to pump the blood all round the body through the aorta. The right ventricle pumps blood to the lungs through the pulmonary artery. The muscle of the atria and the ventricles is supplied with oxygenated blood from the coronary artery. This branches out from aorta.

Check Your Progress - 2
What is artesclerosis?

.....

.....

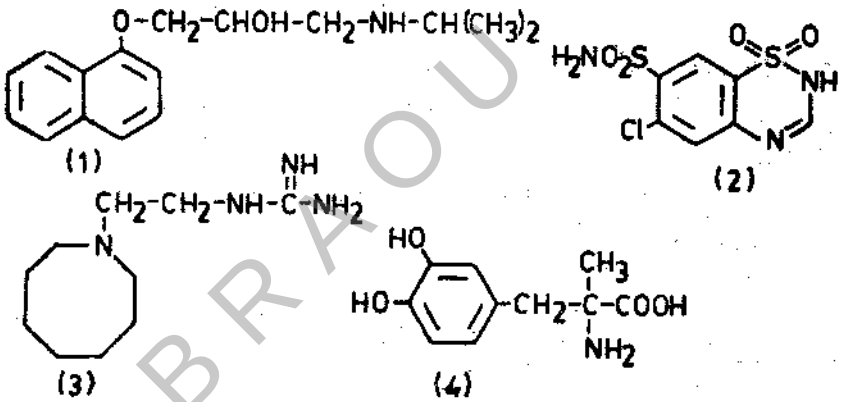
.....

.....

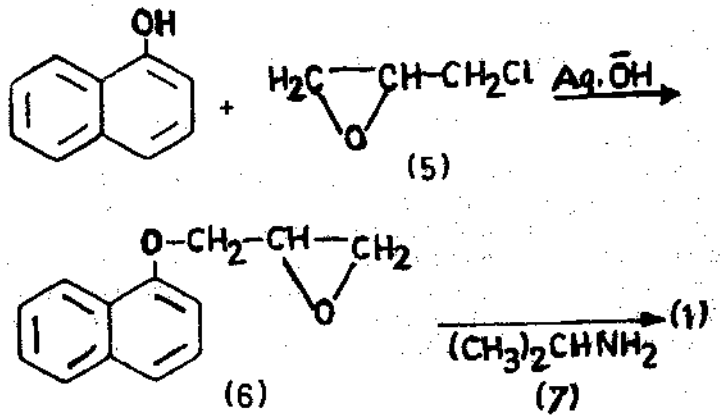
b) *Blood Pressure :* The heart has to maintain a relatively high blood pressure in the circulatory system. This is because the atmospheric pressure compresses the tissues and consequently the flow of blood is affected. This must be overcome. The blood pressure varies with (a) the region of the circulatory system i.e., the artery or vein. (b) the phase of the heart beat (diastole or cystole) and (c) the physiological condition of the body. The pressure in the arteries during cystole is usually around 120 mm of Hg and the pressure during diastole is about 75 mm of Hg. However both of them vary with age from one person to another. The blood pressure is regulated by the reflex nervous mechanism of the heart. An increase in the blood pressure is called hypertension.

19.2.2 DRUGS

Antihypertensive drugs are used in the treatment of hypertension. Propranolol (1) and chlorothiazide (2) are used to treat moderate hypertension. More severe hypertension is generally treated with guanethidine (3) or methyl DOPA (4) in combination with a diuretic.

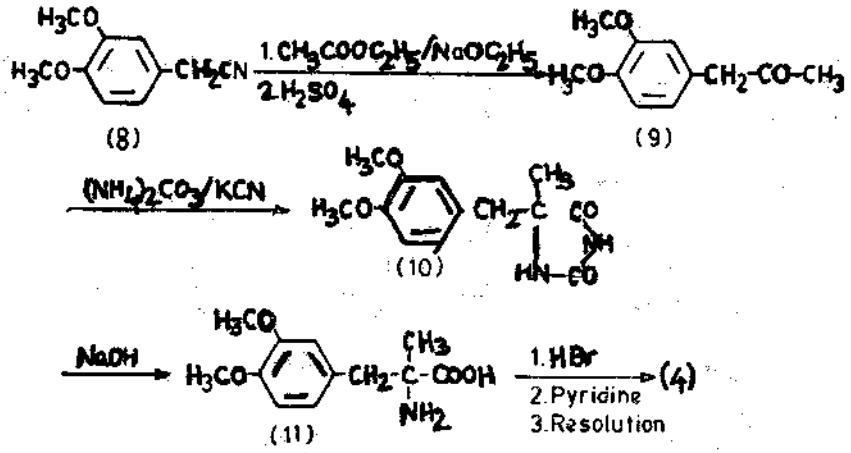


(a) Propranolol (1) : Propranolol (1) is 1-(Isopropylamino)-3-(1-napthyloxy)-2-propanol. Treatment of α-naphthol with epichloro hydrin (5) yields the glycidic ether (6) which on reaction with isopropylamine (7) yields propranolol (1).



Propranolol (1) is a colourless, crystalline compound melting at 161°C. It has a bitter taste. It dissolves in water and alcohol but is slightly soluble in chloroform.

(b) Methyl DOPA (4) : The laevo rotatory enantiomer of methyl DOPA is physiologically active. It is prepared by the following route 3, 4-dimethoxy benzyl cyanide (8) is condensed with ethyl acetate using sodium ethoxide followed by acid hydrolysis to yield 3,4-dimethoxy benzyl methyl ketone (9). Reaction of the ketone (9) with ammonium carbonate and potassium cyanide (Hydantoin synthesis) gives the substituted hydantoin (10) which on alkaline hydrolysis leads to the acid (11). Demethylation of the acid (11) followed by resolution using α-methyl benzylamine gives (—) Methyl DOPA (4).



Methyl DOPA is a colourless, microcrystalline compound melting above 290°C. It is sparingly soluble in water and alcohol.

Vertigo, nausea, headache and diarrhoea are some of the side effects encountered with the use of Methyl DOPA as an antihypertensive drug.

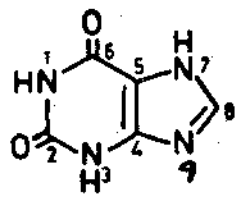
19.3 CNS STIMULANTS

19.3.1 INTRODUCTION

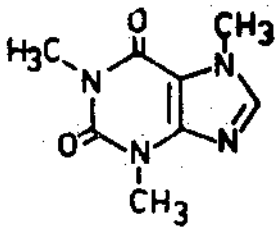
Human body is an extremely complicated structure made of some 5,000 billion cells. In order to enable this large structure to survive hazards of its environment, individual cells have become specialised in various functions. The Central Nervous System (CNS) serves to integrate and co-ordinate the activities of various part of the body. The CNS is composed by the brain and the spinal cord. The drugs which enhance the CNS activity are called CNS stimulants. They are employed in the treatment of mental depression. The word 'analeptics' is used to substances which act directly and stimulate the respiratory centre in the medulla of the brain.

They are used to increase the rate of respiration in a depression caused by carbon dioxide accumulation in the body.

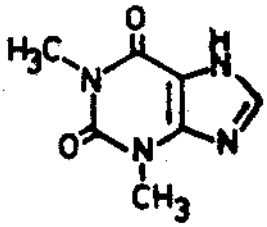
Earlier naturally occuring alkaloids such as strychnine were used as CNS stimulants. Currently methyl derivatives of xanthine, (12) like caffeine, (13) theophylline (14) are commonly used. Caffeine is more active and widely used alkaloid in the world. In the usual doses of 60-200 mg, caffeine may lessen fateigue and increase mental alertness. It stimulates the respiratory centre and therefore used as analeptic also. Caffeine is used in conjunction with aspirin in various headache remedies.



(12)



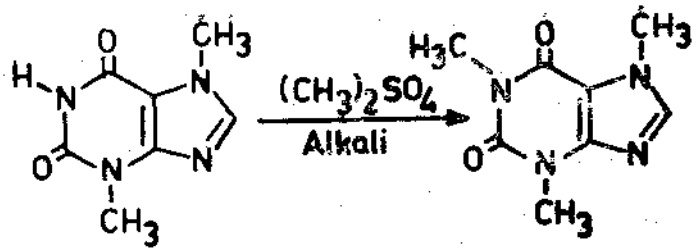
(13)



(14)

19.3.2 CAFFEINE

Caffeine (13) is found in coffee and tea to the extent of 1-5%. Theobromine, (15) an alkaloid obtained from Cocoa husks, is methylated by dimethyl sulphate and sodium hydroxide to yield caffeine.

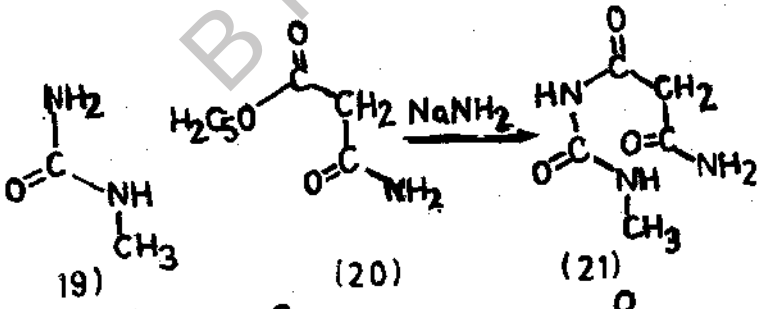


(15) (13)

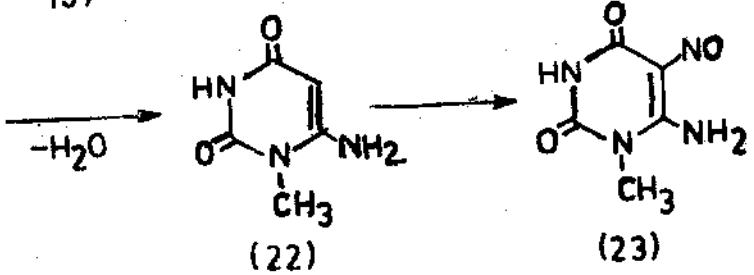
It is interesting to note that theobromine is almost devoid of stimulating activity. It appears that 1-methyl group on the xanthine nucleus is essential for CNS stimulant activity.

Modified Traube's method

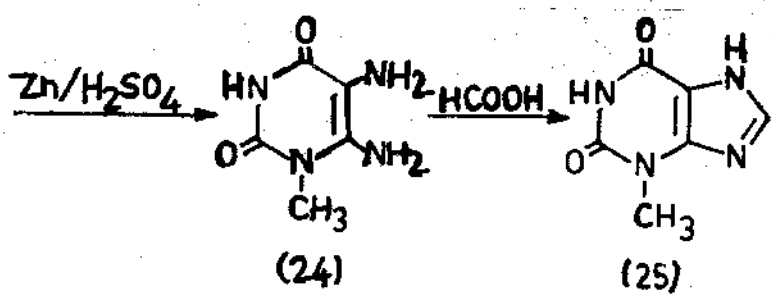
Methyl urea (19) is condensed with ethyl carboxamido-acetate (20) in the presence of a base like sodamide to yield a diamide (21), which undergoes cyclisation t pyrimidone derivative (22). Reaction of Nitrous acid on (22) yields a nitroso compound (23) which is reduced to the diamine (24). Condensation with formic acid converts the diamine into 3-methyl-xanthine (25), which on methylation with dimethyl sulphate and alkali gives rise to Caffeine. This method, developed originally by Traube, is used for commercial production.



19) (20) (21)



(22) (23)



$(CH_3)_2SO_4$ / Alkali → Caffeine

19.4 SUMMARY

You have studied the following in this unit.

1. Cardiovascular diseases blood pressure and heart attack.
2. The functions of the heart and blood vessels in the body.
3. The methods of synthesis of cardiovascular drugs propronolol and methyl DOPA.
4. An account of CNS stimulants and the synthesis of caffeine.

19.5 MODEL EXAMINATION QUESTIONS

I. **Answer each of the following in 10 lines.**

1. How is propronolol synthesised?
2. Write some natural sources of caffeines. How is theobromine converted into caffeine?

II. **Answer each of the following in 30 lines.**

1. Write the various steps involved in the manufacture of caffeine from methyl urea?
2. (i) What are the various xanthine derivatives used as CNS Stimulants?
   (ii) How do you synthesise Methyl Dopa from 3, 4 dimethoxy benzyl cyanide?

19.6 MODEL ANSWERS TO CHECK YOUR PROGRESS

1. If the artery which supplies blood to the heart muscles called caronary artery gets closed partly or completely by blood dot or some other obstacle like fat deposit, oxygen supply will be cut off affecting the ventricular contraction expansion. This condition is called caronary thrombosis or heart attack.

2. This is a vascular disease in which the fatty material deposits on the internal walks of the arteries. Thereby it restricts the blood flow and consequently leads to blood pressure and heart attack.

Author : Dr. K. Rama Subba Reddy

UNIT-20 : ANTILEPROTIC AGENTS

Contents

20.1 AIMS AND OBJECTIVES

To introduce the student to the nature of leprosy and drugs used for the treatment of leprosy.

After a thorough study of this unit, you must be in a position to:

* give a general account of leprosy.
* describe the methods of synthesis of Dapsone and Clofajimine.

20.2 INTRODUCTION

Leprosy or Hansen's disease is one of the man's oldest afflictions. Mycobacterium leproe, responsible for human leprosy is difficulty accessible to chemotherapeutic agents as the bacteria are encapsulated with lipoid sheath which is hard to penetrate. The disease provides a remarkable example of adaption of an infectious organism to a host. The organism is transmitted from one victim to another without any appearance of recognisable symptoms. Even when the disease is advanced, the person is often unaware of its presence, because the early lesions are painless. Though leprosy is a communicable disease it has a very low attack rate even in the heavily infected communities. Children are more susceptible to this disease. Much of the leprosy seen in adults is the result of exposure in the childhood.

Check Your Progress - 1

Why it is difficult to cure leprosy by using antibacterials?

.....

.....

.....

.....

20.3 ANTILEPROTIC AGENTS

Chaulmoogra oil, an oldest remedy for leprosy is obtained from the plant species Hydnocarpus kurzii. It is an yellow or brownish yellow liquid applied externally on the skin. The synthetic antileprotic agents are dapsone and clofazimine. Therapy with these agents requires treatment for several months.

Check Your Progress - 2
What are antileprotic agents?

.....

.....

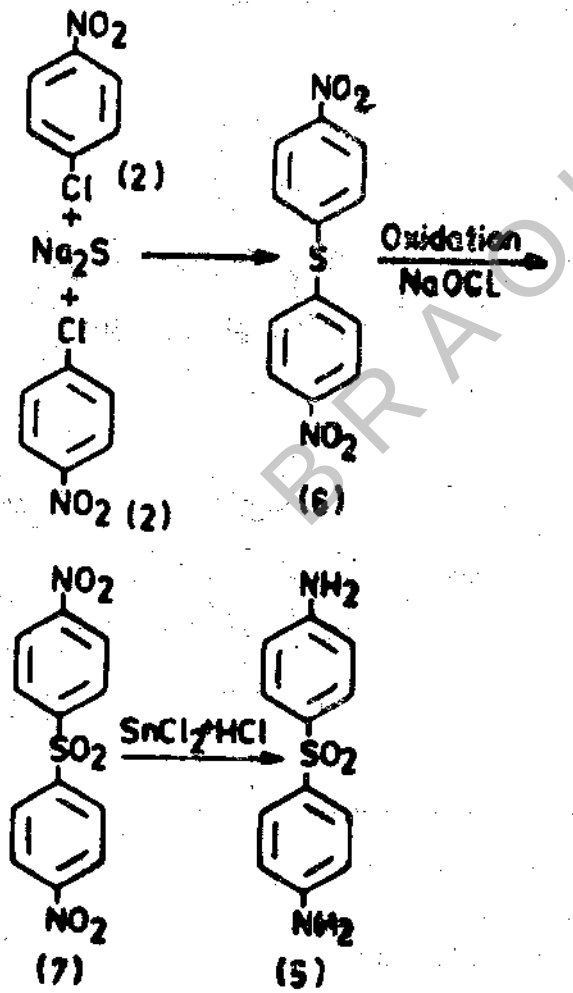
.....

.....

20.3.1 DAPSONE

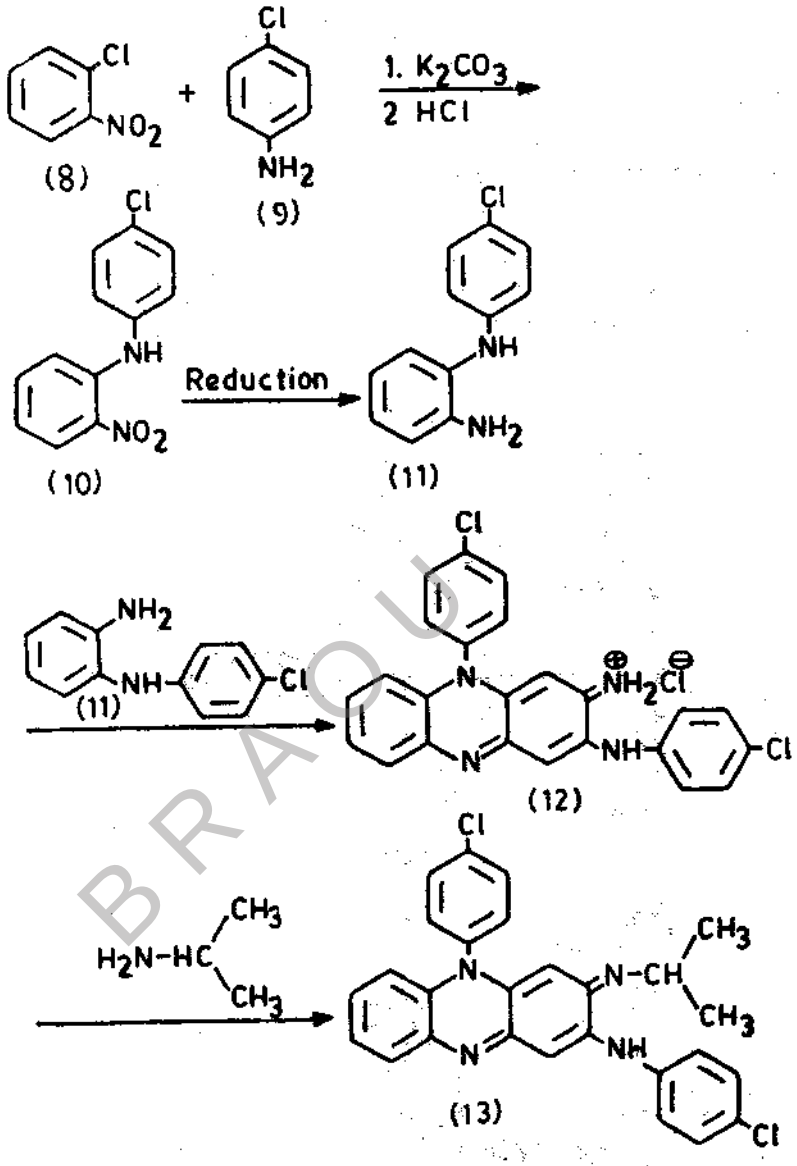
Dapsone is bis (4-aminophenyl)-sulphone. It is a light yellow crystalline solid sparingly soluble in water.

Reaction of two molecules of p-cnloronitrobenzene (2) and sodium sulphide leads to bis-(p-nitrophenyl)-sulphide (6), which is oxidised with sodium hypochlorite to the sulphone (7). Reduction of nitro groups with stannous chloride and hydrochloric acid yields dapsone (5).



20.3.2 CLOFAZIMINE

Clofazimine is a recent drug used in the treatment of leprosy. Reaction of o-nitrochlorobenzene (8) with p-chloroaniline (9), in the presence of potassium carbonate furnishes the nitroaniline (10), which on reduction leads to N-(p-chlorophenyl)-o-phenylene diamine (11). Condensation of two moles of the diamine (11) under oxidative influence of ferric chloride affords phenazine derivative (12). Treatment of the phenazine (12) with isopropyl amine completes the synthesis to yield clofazimine (13).



20.4 SUMMARY

You have studied the following in this unit

1. A general account of the bacterial infection leprosy.
2. The methods of synthesis of antileprotic agents Dapsone and Clofazimine.

20.5 MODEL EXAMINATION QUESTIONS

I. **Answer the following in 10 lines.**

1. Write various steps involved in the synthesis of clofazimine.
2. Sulphone derivatives are used as leprostatic agents. What are the derivatives and how they are synthesised?

II. **Answer the following in 30 lines.**

1. Write a brief note on Antileprotic Agents.

20.6 MODEL ANSWERS TO CHECK YOUR PROGRESS

1. It is so because the infecting bacteria Mycobacteria Leproe gets encapsulised with a lipid sheath which is hard to penetrate for antibacterials or antibiotics.
2. The drugs with which the patients are treated for months together for leprosy cure are called antileprotic agents.

UNIT-21 : ANTHELMINTICS

Contents

21.1 AIMS AND OBJECTIVES

To acquaint the student with the disease helminthiasis, nature and causes of the infection and some common drugs used for the treatment.

After the completion of the study and comprehension of the contents of the unit, you are expected to

* give a general account of helminthiasis.
* describe the synthesis of the antihelmintic, mebendazole.
* give an account of filariasis.
* present the method of synthesis of an antifilarial diethyl carbamazine citrate.

21.2 INTRODUCTION

Helminthiasis is a worm infection involving parasitization with cestodes (tape worms), nematodes (round worms) and trematodes (flukes). The infection is more prevalent in areas where there is poor sanitation, poor family hygine, crowded living conditions and malnutrition. The infection might last the entire life of a man, as the worms are severely parasitic. In addition, these diseases present serious economic problems to the animal industry, wherein every class of domestic animal is vulnerable to a large number of parasitic worm infections. About one third of human race suffers from helminth disease of which large number are multiple infections. Though the infection is usually associated with tropical regions, the disease is also present in the cold countries.

Check Your Progress - 1
In which type of localities helminthiasis is very common?

.....

.....

.....

.....

The majority of helminth infections are caused by contact with infected animals, ground contaminated by human and animal excrement, infected food and water. The filarial worms require arthropod vectors, such as blood sucking mosquitoes, which transmit the parasite from one host to another. The worms depend upon the host for permanent existence. Worms and their eggs or larva must have some method of gaining access to the body of the host. Helminth eff or larve may not produce immediate infection. Depending upon the type of worms, a period ranging from a few hours to months is necessary before the symptoms show up. Sudden onset of edema of the upper eyelids is one of the early characteristic signs. This may be followed by subconjuctival and retinal haemorrhage, pain and photophobia. Other systems include muscle soreness and pain, thirst, profuse sweating, fever, chills, weakness. Before preventive measures are taken to arrest parasitic infections knowledge about nature of the worm is essential.

21.3 ANTHELMINTICS

The anthelmintics are the drugs used in the treatment of helminthiasis. They are toxic compounds acting directly on the parasite. They act against intestinal helminths, kill, sterilize or paralyse the worms so that they lose hold on the intestinal mucosa.

Check Your Progress - 2
What are anthelmintics?

.....

.....

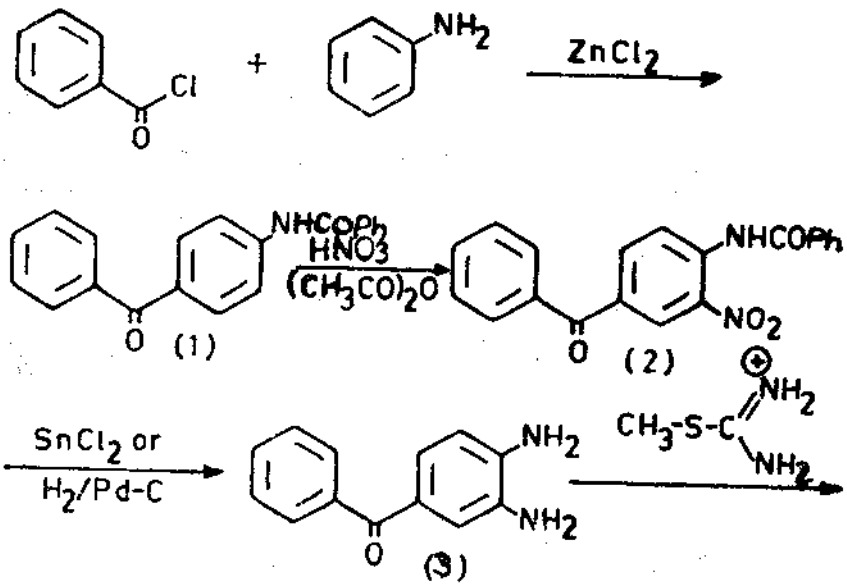
.....

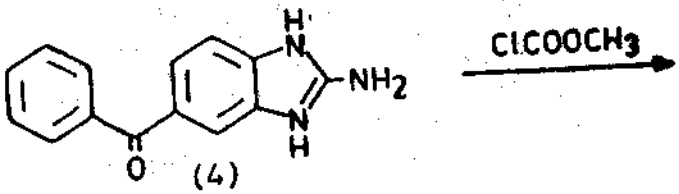
.....

Mebendazole :

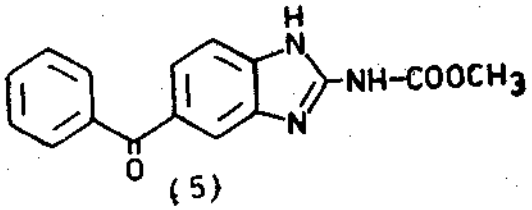
It is a broad spectrum anthelmintic, especially useful in the treatment of human whipworm infections. The drug is also effective against many other nematodes and cestodes as well. Mebendazole probably acts by irreversibly blocking glucose uptake by nematodes in colon.

Synthesis : Aniline is heated with benzoyl chloride in presence of zinc chloride to obtain the benzoyl derivative (1). Nitration of (1) yields 4-benzoyl-2-nitro-aniline (2). Reduction of (2) with either $SnCl_2$ or Pd/C yields an orthophenylene diamine (3), which undergoes condensation with S-methyl thiourea to give rise to 2-amino-5-benzoyl benzimidazole (4). Finally mebendazole (5) is obtained by reaction of (4) with methyl-chloroformate.





(4)

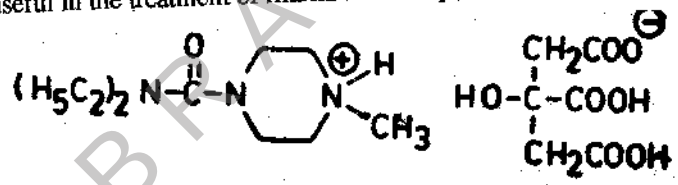


(5)

21.4 ANTIFILARIALS

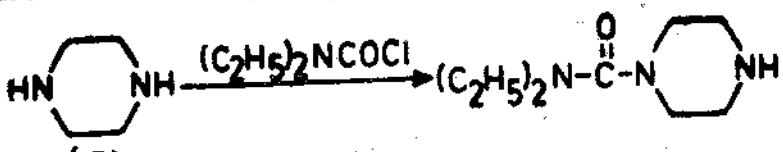
Several round worms live in soil and water. They cause diseases to the plants and animals. Some of them are known to cause disease in humans also. One such disease is filariasis caused in humans by various species of filarial worms, especially Wuchereria bancrofti. The larvae (called the microfilariae) inhabit certain species of mosquitoes and enter the human body when the mosquito bites a man. It inhabits the lymphatic vessel and makes its appearance in great numbers during night time. The worm causes inflammation and thickening of the tissues. In some cases overgrowth of the affected tissues results in severe deformation, a condition known as elephantiasis. The mosquito host may be any species belonging to the Aedes, Culex, Mansonia or Anopheles groups. Therefore, checking the growth of the mosquitoes is obviously an important measure for controlling the disease. Drugs which are capable of ridding the body of the parasitic worms are called anthelmintic drugs. Several classes of compounds are used as anthelmintics. Among them are the chlorinated hydrocarbons, phenols and their derivatives, dyes, piperazines and their derivatives, antimalarial compounds, various heterocyclic systems, alkaloids and related natural products.

Diethyl carbamazine citrate : N,N-Diethyl-4-methyl-1-piperazine carboxamide dihydrogen citrate (6), is useful in the treatment of filariasis and tropical eosinophilia.

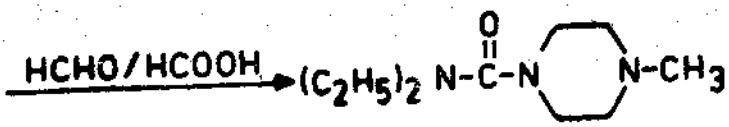


(6)

Piperazine (7) is acylated with diethyl carbamoyl chloride followed by methylation at 4N-position with formaldehyde and formic acid. The purified compound is treated with an equimolecular quantity of citric acid.



(7)



Diethylcarbamazine citrate, a colourless, crystalline compound with a m.p. 136-141°C, hygroscopic and is highly soluble in water. It is very effective in clearing the Wuchereria bancrofti infection.

21.5 SUMMARY

You have studied the following in this unit.

1. General features of the infection helminthiasis.
2. Synthesis of anthelmintic, mebendazole.
3. An account of the filariasis and the synthesis of antifilarial diethyl carbomazine citrate.

21.6 MODEL EXAMINATION QUESTIONS

I. **Answer each of the following in 10 lines.**

1. What is helminthiasis? What are its symptoms and causes?
2. Write briefly how mebendazole is manufactured?

II. **Answer the following in 30 lines.**

1. Write a brief account on anthelmintics.

21.7 MODEL ANSWERS TO CHECK YOUR PROGRESS

1. This infection is more prevalent in areas of poor sanitation, poor family hygine, crowded living conditions and malnutrition.
2. The drugs used to cure helminthiasis are called anthelmintics.

21.8 GLOSSARY

1. Parasite	:	An organism that lives in or on another organism and derives substance from it without rendering it any service in return.
2. Infection	:	To introduce pathogenic (producing disease) organism into.
3. Conjunctival	:	Related to front portion of the eye.
4. Retina	:	Sensitive layer of the eye.
5. Haemorrhage	:	Discharge of blood from the blood vessels.
6. Photophobia	:	Shrinking from light.

Author : Dr. K. Rama Subba Reddy

UNIT-22 : HORMONES

Contents

22.1 AIMS AND OBJECTIVES

To introduce the student to the ductless glands in the body and to their secretions namely the hormones; to make them appreciate the variety in the chemical nature of the hormones and their physiological function.

Once you complete the study of the contents of this unit, you must be able to :

* describe the endocrine glands, their position in the body and the hormones secreted by them.
* give the metabolic role of thyroxine and its synthesis.
* present the role of sex hormones secreted by reproductive organs.
* elucidate the structure of oestrone.
* describe the role of the hormones of pituitory gland.
* give an account of adrenal glands and their hormones.
* realise the physiological role of insulin secreted by islets of langerhan of pancreas.

22.2 INTRODUCTION

Many of the metabolic processes in the body are regulated by the secretion of chemicals from some special glands. These glands are called the ductless glands or endocrine glands. As their name indicates, they do not have any ducts or openings and the secretions from them are directly introduced into the blood stream as the blood passes through the glands. These chemicals which are secreted in the endocrine glands are called 'hormones' meaning 'chemical messengers'. They are thus circulated throughout the body. When they reach the appropriate part of the body, they cause certain effects to take place. The hormones control longterm changes such as rate of growth, rate of activity and sexual maturity. The hormones, when they pass through the liver they are converted into inactive compounds and are excreted through the kidneys. The duration of the hormonal activity is thus regulated by the liver. The position of some of the important endocrine glands in the body are shown in Fig. 22.1 Table 22.1 gives a list of the major endocrine glands and their secretions.

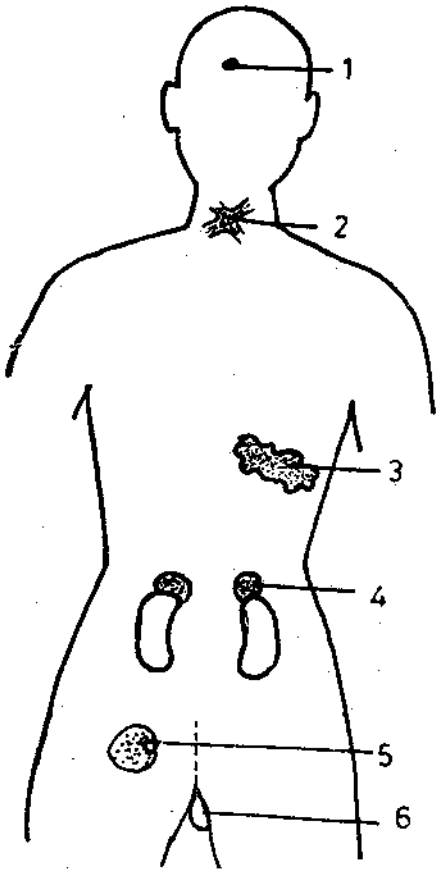
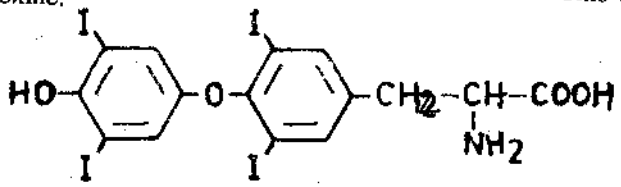


Fig. 21.1

1. Pituitary gland
2. Thyroid gland
3. Pancreas
4. Adrenal gland
5. Ovary
6. Testis

22.3 THYROID

The thyroid gland is situated in the throat, in front of the wind pipe. It is the largest of the endocrine glands and weighs about 30 gms., in man. It produces thyroxine, an iodine containing hormone. In young animals the hormone controls the rate of growth and development. Thus thyroxine brings about metamorphosis in tadpoles. In adult humans, thyroxine influences the rate of chemical activity, particularly respiration. Too little of thyroid activity leads to over-weight and sluggishness and too much causes thinness and over activity. Enlargement of the thyroid is known as goitre. Deficiency of thyroxine in infants causes a mental deficiency called cretinism. This can be controlled by the administration of thyroxine.



(7)

When thyroxine is treated with nitrous acid, a yellow colour deepened. When cooled and rendered alkaline with ammonia, it gave a red colour. This colour reaction is characteristic of phenols with iodine atoms in both ortho positions.

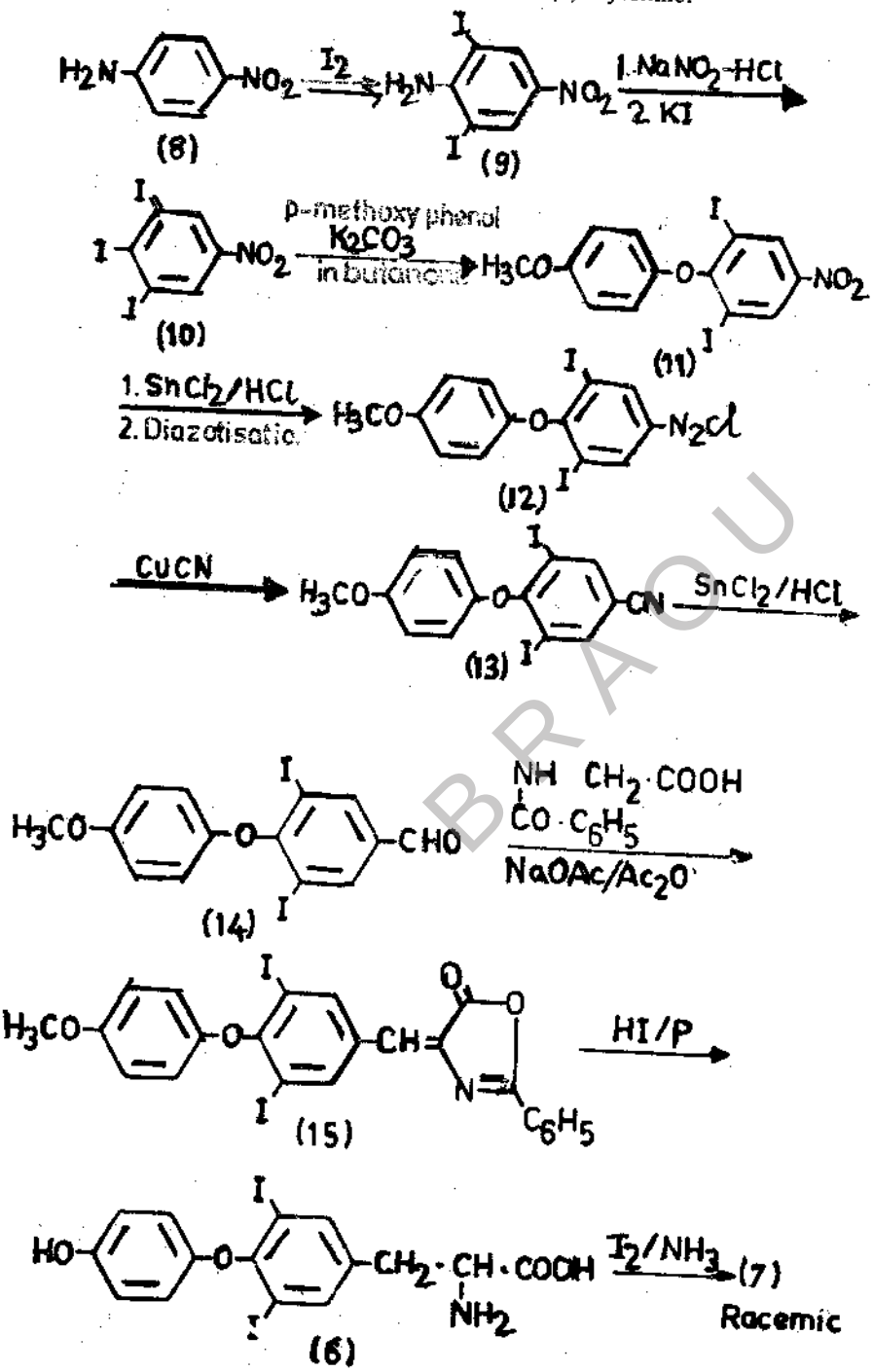
Table 22.1 MAJOR ENDOCRINE GLANDS : THEIR SECRETIONS AND FUNCTIONS

S. No.	Endocrine glands	Hormones elaborated	Their physiological functions
1.	Pituitary	Prolactin	Milk secretion
		Growth hormone	General growth and metabolism
		ACTH	Formation and secretion of adrenal cortical steroids
		Oxytocin	Uterine contraction
		Vasopressin	Blood pressure
2.	Thyroid	Thyroxine	Metabolic rate and oxygen consumption
3.	Pancreas	Insulin	Carbohydrate and protein metabolism
4.	**Adrenals :**		
	i) Cortex	Adrenal cortical steroids	Metabolism of electrolytes
	ii) Medulla	Adrenaline	Blood pressure
5.	**Reproductive organs :**		
	i) Ovary	Oestrone	Maturation, Accessory
		Oestradiol	Sex organ growth
	ii) Testis	Testosterone	Maturation and function of sex organ growth

Synthesis of thyroxine

A number of methods are available for the synthesis of thyroxine. The following synthesis is due to Harrington and his co-workers.

p-Nitroaniline (8) was iodinated with iodine to get the di-iodo derivative (9) which was subjected to a Sandmayer reaction yielding 3,4,5-triiodonitrobenzene (10). Treatment of this compound with p-methoxy phenol and potassium carbonate in butanone gives the diiodo derivative (11). Reduction of the nitro group followed by diazotisation and treatment with cuprous cyanide furnishes the nitrile (13). Stephen reduction of the nitrile yields the aldehyde (14) which was converted into the azlactone (15). Reduction of the lactone (15) with hydrogen iodine and red phosphorous gives diiodo (±) thyronine which on treatment with iodine in concentrated ammonia yields (±) thyroxine.

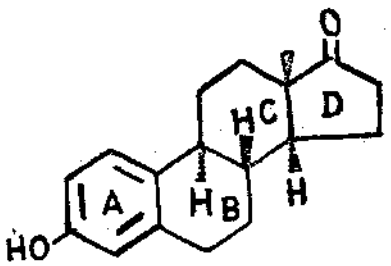


Resolution of the racemic product leads to the naturally occuring thyroxine belonging to the L-series.

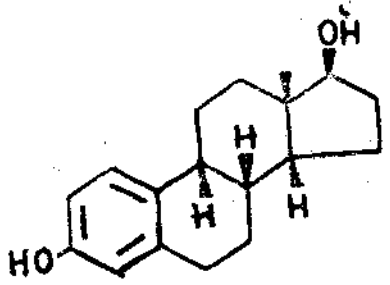
22.4 REPRODUCTIVE ORGANS

The ovary produces several hormones. These are called the Oestrogens. Of these, Oestrone (16) and Oestradiol - 17β (17) are most potent. The oestrogens control the female secondary sex characteristics at puberty. They cause the lining of the uterus to thicken just before an ovum is released. In some mammals oestradiol puts the female 'on heat' to get ready to mate with the male. Progesterone (18) is another hormone which supports the pregnancy. If pregnancy does not occur, its secretion ceases after a few days.

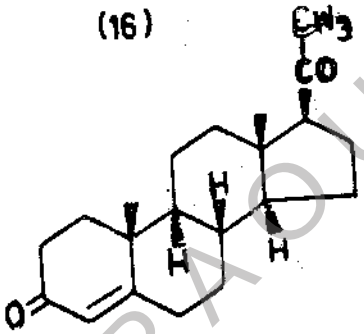
Testosterone (19) is the male sex hormone produced by the testis. It promotes the development of the masculine secondary sex characteristics.



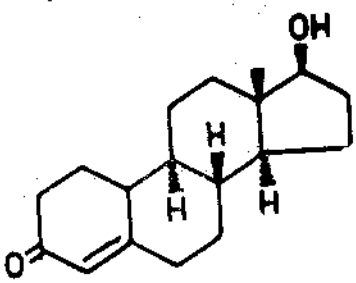
(16)



(17)



(18)



(19)

Check Your Progress - 1
What is the role of testosterone?

.....

.....

.....

.....

.....

22.5 OESTRONE

Butenandt and Doisy isolated oestrone independently in 1926 from the urine of pregnant women. Oestrone is optically active and is dextro rotatory, it melts at 259°C. It has a molecular formula $C_{18}H_{22}O_2$. It contains a phenolic hydroxyl and a ketonic function. Catalytic hydrogenation of the

14.8 MODEL EXAMINATION QUESTIONS

I. **Answer each of the following in 10 lines.**

1. Explain the terms 'antibacterials' and 'antibiotics'. Give examples for each of them.
2. What are the probable products that are obtained by the hydrolysis of folic acid?
3. Compare the reactions of the active groups of p-aminobenzoic acid and p-aminobenzene sulphonamide towards an acid and base (organic reagents).
4. Write the chemical reactions involved in the synthesis of sulphadiazine.
5. In the synthesis of sulphadiazine, p-acetyl amino benzene sulphonyl chloride is used instead of p-amino benzene sulphonyl chloride. Explain the reactivities of the two reagents.
6. Desing a synthetic scheme for the preparation of isocystasine.
7. Give the synthesis of trimethoprim.

II. **Answer the following in 30 lines.**

1. How is sulphamethoxazole synthesised? Also indicate the preparation of intermediate chemicals .
2. Give the chemical structures of antibacterial agents you have studies.

14.9 MODEL ANSWERS TO CHECK YOUR PROGRESS

1. Prontocil is a red dye discovered by Domagk that it cures bacterial infections in animals and man.
2. Sulpha drugs function as antibacterials by preventing the synthesis of folic acid, a growth factor in bacteria, from para amino benzoic acid (PABA). Therefore sulpha drugs are bacteriostatic and not bacteriocidal.

14.10 GLOSSARY

Antibiotics : Antibiotics are chemicals produced by microorganisms, that can inhibit the growth of other microorganisms or even destroy them.

Antibacterials (or Antimicrobial drugs) : Antibacterials are chemicals that can inhibit the growth or destroy the bacteria that cause infections to human beings.

Bacteria : These are unicellular microorganisms surrounded by a rigid, complex polysaccharide-protein cell wall. Bacteria can be divided arbitrarily into two classes. Gram-positive bacteria are those that stain blue with Gram's reagent (crystal violet and iodine) and Gramnegative bacteria are those that do not retain these reagents but may be countersigned with safranin or similar reagents.

Rosenmund reduction : The reduction of acid chlorides to aldehydes by poisoned palladium on barium sulphate catalysts.

Author : Dr. R. Venkateswarlu

UNIT-15 : ANTIBIOTICS

Contents

15.1 AIMS AND OBJECTIVES

To introduce the student to a brief account of the antibiotics, the mode of the preparation of some important antibiotics, their structures and applications.

After a thorough study of this unit, you must be able to :

* define and give a brief account of discovery and general characteristics of antibiotics.
* present the mode of action and the bacterial resistance of antibiotics.
* describe the production, isolation, structure and applications of penicillins, streptomycin, chloramphenicol and tetracyclines.

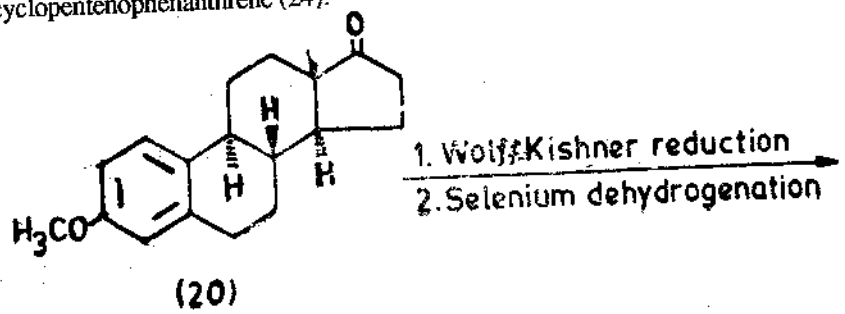
15.2 INTRODUCTION

15.2.1 HISTORICAL

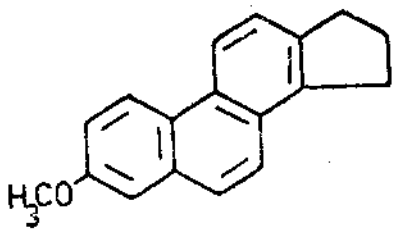
The development of antibiotic drugs is one of the major advances in chemotherapy. The introduction of the antibiotic has not only influenced the practice of medicine, but are finding applications in animal nutrition, agriculture and food processing industries. Diseases thought to be incurable a century ago have been treated successfully with antibiotics. This is true of disease of childhood, pneumonia, dysentery, typhoid, and typhus fevers, plague and cholera, tuberculosis and other infectious diseases caused by bacteria, fungi and protozoa.

compound gives an octahydro derivatives containing two hydroxyl groups. The presence of a phenolic hydroxyl indicates a benzene ring in the molecule. Wolff-Kishner reduction of oestrone methyl ether (20) followed by selenium dehydrogenation yields 7-methoxy 1,2-cyclo pentenophenanthrene (21).

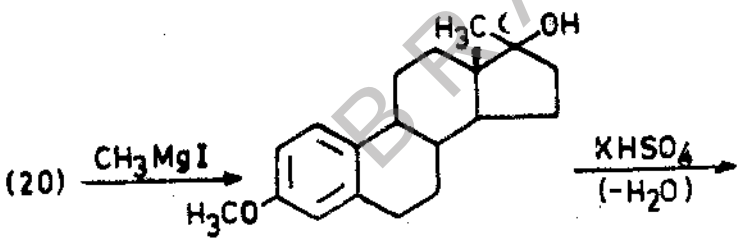
Thus the position of the phenolic hydroxyl was fixed in ring-A. Oestrone was thus shown to be a steroid in nature. The position of the ketone functions was shown by the following sequence of reactions. Oestrone methyl ether (20) was treated with methyl magnesium iodide to yield the carbinol (21) which on dehydration with potassium hydrogen sulphate gave the dehydration product (22) which underwent a rearrangement during dehydration. Catalytic reduction of the cyclopentane (22) yielded the cyclopentane (23) which on selenium dehydrogenation gave 7-methoxy 3,3-dimethyl 1,2-cyclopentenophenanthrene (24).



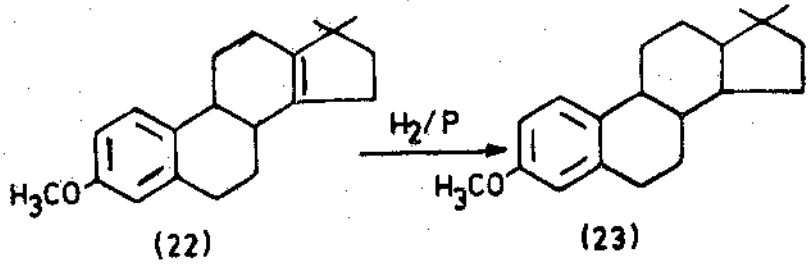
(20)



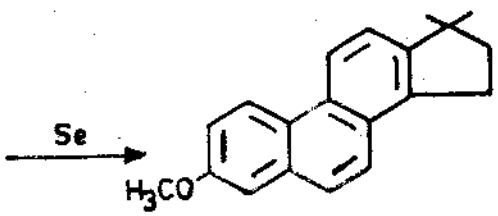
(21)



(21)



(22) (23)



(24)

The molecule of beef insulin is made up of 777 atoms, the molecular formula being $C_{254}H_{277}N_{65}O_{75}S_6$. The insulin molecule belongs to the category of peptides where the building units are the amino acids attached through a peptide bond. The total number of amino acids present in insulin molecule is 51. Of the 24 natural L-amino acids, 17 amino acids are present in insulin.

Insulin contained two chains, the A chain with 21 amino acids and the B chain with 30 amino acids. Chain A was shown to have a disulphide bridge and is linked to the B chain by two disulphide bonds. The structure assigned to human insulin is shown in Fig. 21.2. Human and sheep insulins were synthesized. Sanger was awarded the Nobel prize in chemistry for his remarkable work on insulin.

22.10 SUMMARY

You have learnt the following in this unit.

1. The positions of endocrine glands in the body and hormones secreted by them.
2. The metabolic role played by thyroxine and its chemical synthesis.
3. The role of the sex hormones secreted by reproductive organs and elucidation of the structure of oestrone.
4. The role of pituitary gland hormones in the body.
5. An account of adrenal gland hormones and their role in the body.
6. The role of insulin secreted by islets of langerhans of pancreas.

22.11 MODEL EXAMINATION QUESTIONS

I. **Answer each of the following in 10 lines.**

1. What are hormones? Explain their importance in human body.
2. What are endocrine glands? Name any two of them and the hormones secreted by them.
3. Write the physiological role of :
   a) Thyroxine b) Oestrone c) Insulin and d) Oxytocin

II. **Answer each of the following in 30 lines.**

1. Write a brief account of the peptide hormone, Insulin.
2. Outline the total synthesis of (±) Thyroxine.
3. Write a note on sex hormones.

22.12 MODEL ANSWERS TO CHECK YOUR PROGRESS

1. Testosterone is the male sex hormone produced by testes. It is responsible for the development of the masculine secondary sex characteristics.
2. Glucose is not effectively utilised by the body and it results in a disease called diabetes.

22.13 GLOSSARY

1. The bold lines and the broken lines in the steroidal structures indicate whether the functional groups are above (β) or below (α) the average plane of the molecule.

2. The following abbreviations are used for the α-amino acids.

Ala	: Alanine	Arg	: Arginine
Asn	: Aspargine	Cy-S-S-Cy	: Cystine
Glu	: Glutamic acid	Gln	: Glutamine
Gly	: Glycine	His	: Histidine
Ileu	: Isoleucine	Leu	: Leucine
Lys	: Lysine	Phe	: Phenyl alanine
Pro	: Proline	Ser	: Serine
Thr	: Thronine	Tyr	: Tyrosine
Val	: Valine		

3. Peptide bond : The carboxylic group of one α-amino acid is combined with the α-amino group of another α-amino acid (i.e., —CO—NH—).

4. ACTH : Adreno cortico trophic hormone.

Author : Prof. P.S. Rao

UNIT-23 : VITAMINS

Contents

23.1 AIMS AND OBJECTIVES

To introduce to the student the value of food, the importance of Vitamins in the food, the Chemistry of the Vitamins and the deficiency diseases.

Once you complete the study of this unit, you must be able to :

* give a general account of vitamins, their sources and deficiency diseases.
* remember the structures of vitamins A, B_1, B_2, B_6, C pantothenic acid, folic acid, biotin and α-tocopherol.
* describe the methods of synthesis of vitamin A and C.

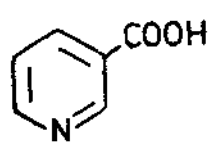
23.2 INTRODUCTION

The food is useful for energy, growth and replacement. The food is broken down in cells during respiraton. Energy is thus provided for the vital functions of the body. It helps the formation of protoplasm and thus contributes to the growth of the cells and tissues. It helps to replace the cells that die. It also contributes to the repair of the damaged body tissues and wounds. These requirements are met with by the so called 'body builders'. They are proteins, fats and carbohydrates, the chemical materials with food value. In addition, the diet must contain water, mineral salts and vitamins to make it balanced. These are needed for the proper functioning of the bodily activities. Proteins are used for body building and replacement. Carbohydrates and fats are the main sources of energy. The mineral salts are mainly used for maintaining the osmotic concentration of the blood.

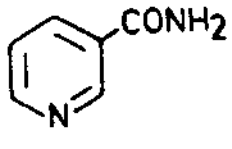
23.3 THE VITAMINS

Vitamins are complex chemical compounds. They do not have any energy value but they are essential for the normal chemical activities of the body. They are needed in small quantities. Deficiency of a vitamin leads to some symptoms of a disease. The disease can be cured by the inclusion of the necessary vitamin in the diet. Thus unlike hormones which are produced in the body itself, the vitamins must be supplied from an outside source. Sources of some important vitamins together with the diseases and the symptoms caused by lack of them are given in Table-23.1

Nicotinic acid (34) and nicotinamide (35) are the human pellagra preventing factor.



(34)

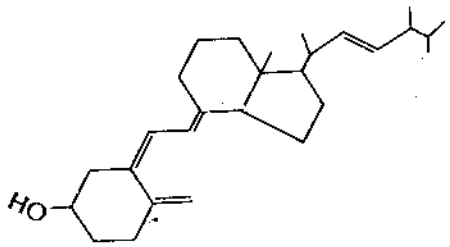


(35)

Vitamin B_{12} (Cyanocobalamine) is the antipernicious anaemia factor. It was isolated from the liver extract. It is a very complex molecule. Other members of the B-complex group of vitamins include para amino benzoic acid, myo inositol, choline, carnitine and lipoic acid.

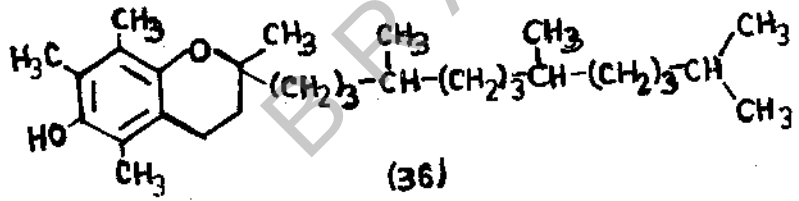
Vitamin D

Vitamin D group has four vitamin D_1, D_2, D_3 and D_4. They control calcium and phosphate metabolism in the body. They are necessary for bone formation. Their deficiency leads to a disease called rickets. Abnormal bone formation, soft bones with swollen ends are the symptoms of this disease. Cod liver oil, creams and egg yolk are rich in vitamin D. Natural fat present below the skin changes into vitamin D on irradiation to sun light. The structure of vitamin D_2 is given below.



Structure of vitamin D_2

Eight compounds, collectively called the tocopherols form the vitamin E group. Of these the α-tocopherol (36) is the most potent as the antisterility factor. It occurs in the wheat germ oil.



(36)

Vitamins K_1 (37) and K_2 form the vitamin K group of vitamins which are anti haemorragic. They occur in the leafy vegetables like spinach, alfalfa and carrots.

About 15 vitamins have been recognised and they are shown to act as catalysts in some essential chemical changes taking place in the body. Each vitamin influences a number of vital processes. For examples some of the B group vitamins act as hydrogen acceptors during respiration.

The vitamins are broadly classified based on their solubility characteristics as the fat soluble and water soluble vitamins. Vitamins A, E, D and K are the fat soluble while vitamins of the B group and vitamin-C belong to the water soluble group.

23.4 VITAMIN - A GROUP

Vitamin A, also called axerophthol or retinol, is present in food stuffs from animal sources. The liver fats of various grass fed animals are very rich sources of this vitamin. Fresh green vegetables such as cabbage, lettuce, green peas, carrots are also good sources of the vitamin. Deficiency of vitamin A leads to a reduced resistance to diseases and night blindness. A disease called xerophthalmia where the corneas of the eyes become dry also results from its deficiency.

a) *Isolation* : The liver oils of the fishes are chosen for the isolation of this vitamin. The oil is saponified. The unsaponifiable matter contains vitamins A and D along with other sterols. The mixture is dissolved in methyl alcohol and chilled to -60°C. The sterols crystallise out leaving vitamin A in the mother liquor. Further, purification of the vitamin is effected by chromatographic techniques or by fractional distillation under very high vacuum.

Pure vitamin A melts at 64°C. It is insoluble in water but readily dissolves in organic solvents. With antimony trichloride in chloroform solution, it gives a bright blue colour with an absorption maximum at 620 nm. This is called the Carri-Price reaction with conc. H_2SO_4 it produces a violet colour. The vitamin is destroyed by aerial oxidation.

Check Your Progress - 1
What is retinol? What are its sources?

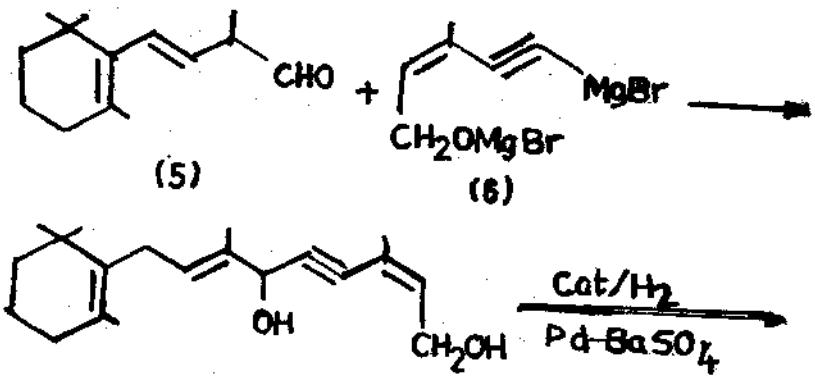
.....

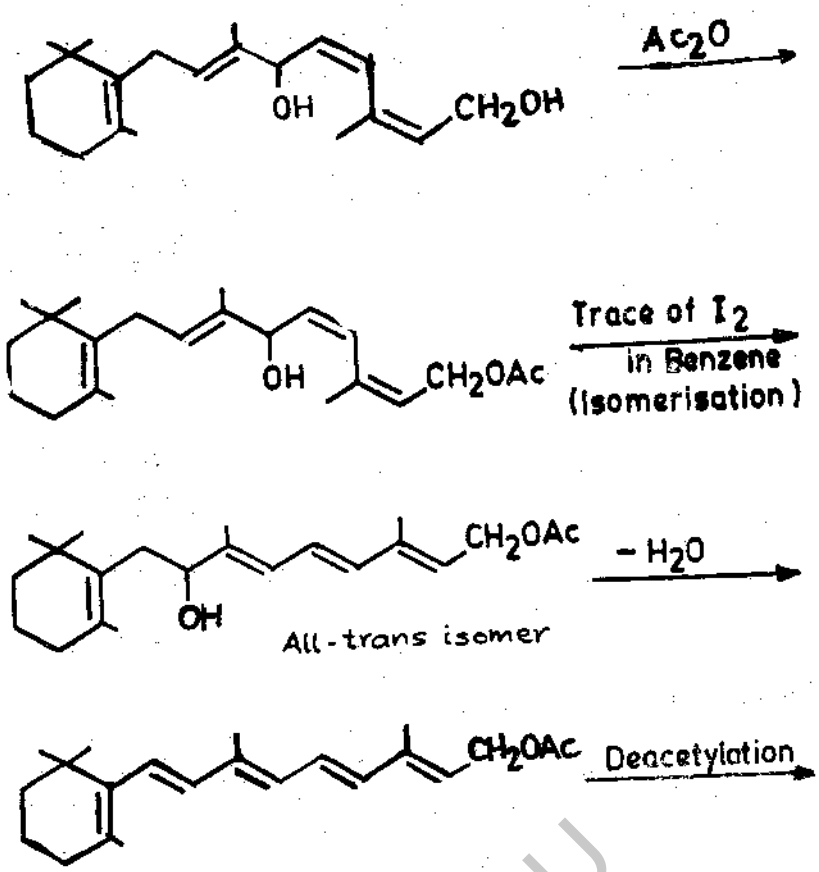
.....

.....

.....

b) *Synthesis* : The structure assigned to vitamin-A was confirmed by several syntheses. The following method, described by Isler and his co-workers is adopted for the commercial production of vitamin A. The intermediates (5) and (6), prepared respectively from β- ionone and methyl vinyl ketone were coupled and converted to vitamin A (4).





23.5 VITAMIN - B GROUP

About 9 vitamins are included under the vitamin B group of compounds. These are water soluble and take part in reversible oxidation reduction reactions and form part of various co-enzymes. The B group vitamins are universally required by all organisms from the unicellular protozoa to the animals and plants.

1. Vitamin - B_1 (Thiamine or Anuerine)

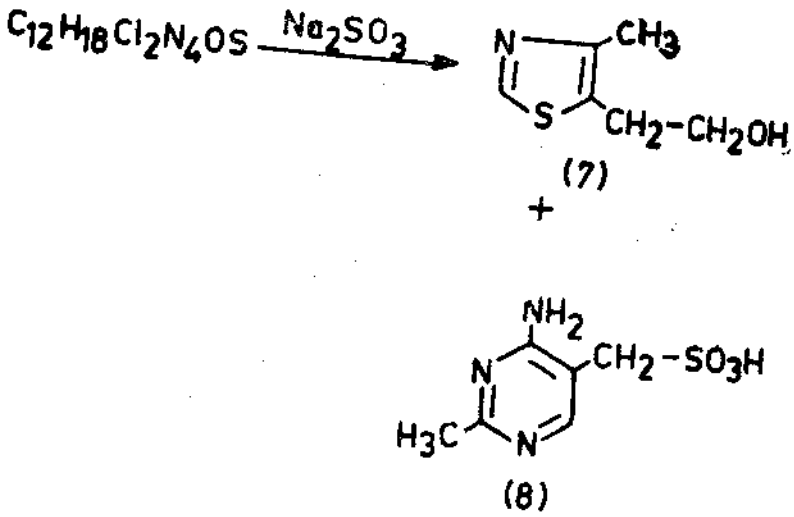
Loss of appetite, Beri-Beri are the common deficiency symptoms of this vitamin. People eating the polished rice usually suffer from the deficiency of this vitamin because the vitamin is lost during the rice polishing. The deficiency can be rectified by using hand pounded and par boiled rice. It occurs widely in nature. The richest sources are rice polishings, yeast, eggs and liver as well as green leafy vegetables.

Isolation : Rice polishings are first extracted with acidified water at pH 4.5. The aqueous solution containing the vitamin is treated with Fuller's earth into which the vitamin is adsorbed. The Fuller's earth adsorbate is treated with a solution of quinine sulphate when quinine displaces the vitamin. After removal of excess of quinine by neutralisation, the vitamin is precipitated with silver nitrate at pH 7.5. The decomposition of the silver salt regenerates the vitamin. Final purification of the vitamin is effected as thiamine chloride hydrochloride by crystallisation from alcohol. Thiamine chloride hydrochloride hemihydrate melts at 248-250°C. It is soluble in water and alcohol and is fairly stable to heat.

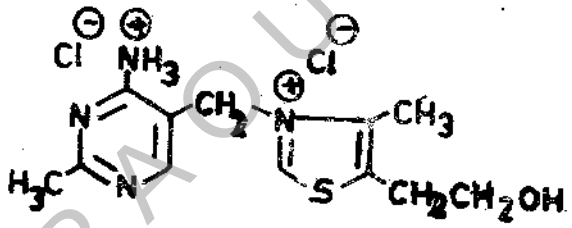
Structure : The structure determination of thiamine is based on the following data.

i) Thiamine chloride hydrochloride has a molecular formula $C_{12}H_{18}Cl_2N_4OS$.

ii) It quantitatively breaks into two components a thiazolidine component, C_6H_9NOS and a pyrimidine component $C_6H_9N_3O_3S$ when treated with sodium sulphite solution saturated with SO_2 at room temperature.



Considering the fission of the vitamin with sodium sulphite to give the fragments (7) and (8) it was suggested that the pyrimidine unit was attached through the CH_2 at position 5 to the nitrogen atom of the thiazole ring. This would account for the formation of chloride hydrochloride of thiamine. The chloride hydrochloride of thiamine would thus be (9).



(9)

2. Vitamin - B_6 (Pyridoxine)

This vitamin is widely distributed in plants and animals. Molasses, yeast and rice polishings are good sources of vitamin-B_6. The deficiency of this vitamin causes dermatitis in rats.

a) *Isolation* : The vitamin was isolated from rice polishings. Extraction of the polishings was done with water at pH 7.5. The extract acidified, concentrated and the residue was adsorbed on Fuller's earth at pH 2 to remove the impurities. The vitamin was eluted with baryta. It was recovered from the baryta solution and purified as its hydrochloride by crystallisation from absolute ethanol.

Pyridoxine melts at 159°C. It is soluble in water.

It gives a blood red colouration with ferrous sulphate suggesting that it has a carboxyl group in the 2-position of the pyridine nucleus. Thus the partial formula of the product would be

23.6 VITAMIN - C (ASCORBIC ACID)

This vitamin is also known as 'antiscorbutic factor'. Scurvy is the sailors' disease in the days of sail. The main symptoms of the disease are weakness in joints and spongy gums. It responds quickly to treatment with ascorbic acid.

a) *Occurence* : Vitamin C occurs in fresh vegetables like spinach, cauliflower and cabbage and fruits such as lemons, tomatoes and pine apple.

b) *Isolation* : The vitamin was originally isolated in quantity from the Hungarian Paprikas by Szent-Gyorgyi. Now a days all the vitamin C is produced on a commercial scale by synthetic methods.

Pure ascorbic acid is colourless, crystalline solid, m.p. 192°C, $[\alpha]D + 24°$.

.....

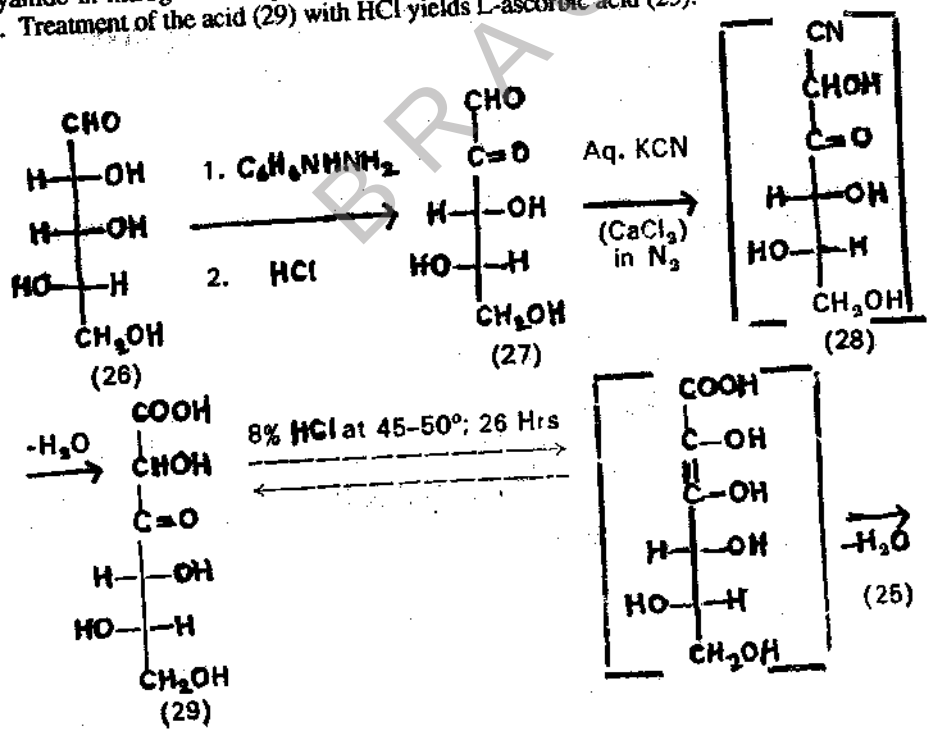
.....

.....

.....

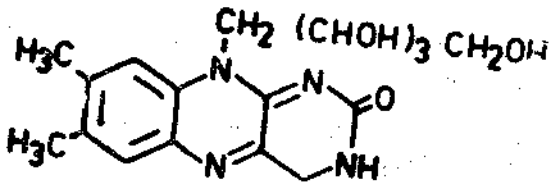
.....

c) *Synthesis* : Ascorbic acid is now synthesised by several methods. The following method is one of the earliest by Haworth and Hirst. L-Lyxose (26) on treatment with phenylhydrazine forms an osazone which on hydrolysis with hydrochloric acid gives L-xylosone (27). Treatment of (27) with aqueous potassium cyanide in nitrogen atmosphere yields pseudoascorbic acid (29) via the intermediate β-keto cyanide (28). Treatment of the acid (29) with HCl yields L-ascorbic acid (25).



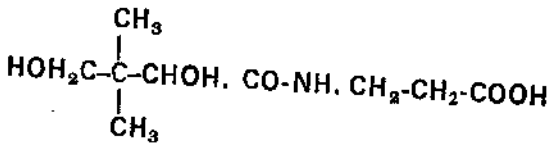
23.7 OTHER VITAMINS

The other important vitamins among the B complex group are :
Vitamin B_2 (Riboflavin, lactoflavin) (30) which occurs in yeast, green vegetables, milk and meat.



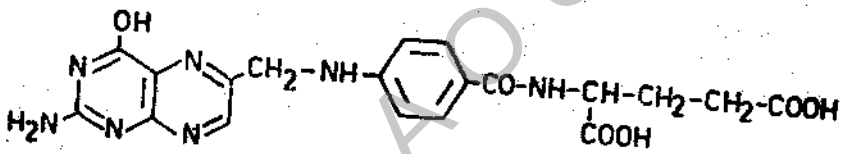
(30)

Pantothenic acid (31) a chick antidermatitis factor, occurs in liver, kidney and yeast.



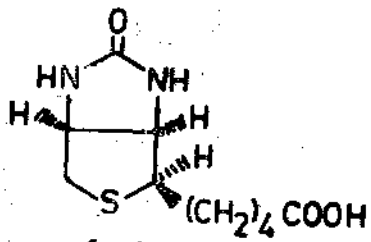
(31)

Folic acid (32) is a growth factor for many microorganisms and has been shown to have the structure.



(32)

It occurs in yeast, spinach etc. Biotin (Vitamin H) (33) is important for the growth of the animals. It occurs in yeast, egg yolk and liver.



(33)

23.8 SUMMARY

You have studied the following in this unit.

1. A general account of vitamins. The food material which contains the vitamins and the vitamin deficiency diseases.
2. The molecular structures of vitamins A, B, B_2, B_6, C, pantothenic acid, folic acid, biotin and α-tocophenol.
3. The methods of synthesis of vitamins A and C.

23.9 MODEL EXAMINATION QUESTIONS

I. **Answer each of the following in 10 lines.**

1. Write down the structure of Vitamin-B_1. How is it synthesized?
2. How is the structurs of B_1 is determined?

II. **Answer each of the following in 30 lines.**

1. Outline the structure elucidation of pyridoxin.
2. Outline the synthesis of ascorbicacid.
3. Give a brief account of riboflavin, folic acid, biotin and vitamin-K_1.

23.10 MODEL ANSWERS TO CHECK YOUR PROGRESS

1. Vitamin - A is called retinol. Its sources are liver fats of grass fed animals and flesh green vegetables such as cabbage, green peas, lettuce and carrots.
2. Deficiency of vitamin-C leads to the decrease of disease resistance, weakness in joints and spongy gums. Finally it results in a disease called scurvy.

23.11 GLOSSARY

Coenzymes : Enzymes usually have active sites in them constructed by functional groups which are non-proteinous in character. Such non-proteinous organic molecules are called coenzymes. They could be separated from the enzymes by physical methods.

Author : Prof. P.S. Rao

REFERENCE BOOKS

1. Manures and Fertilisers - by K.S. Yawalkar, J.P. Agarwal and S. Bokde

2. Industrial Chemistry - by B.K. Sharma

3. Chemicals for Pest Control - by G.S. Hartley and T.F. West

4. Riegel's Hand book of Industrial Chemistry - by James A. Kent

5. Pesticide Residues in Food and Biological Residues - by C.R. Krishnamurthy

6. The Use and Significance of Pesticides in the Environment - by E.L. Mc Ewen and G.R. Stephenson

7. A Note Book of Agricultural Facts and Figures - published by Department of Agriculture, Madras

8. Plant Growth Substances Vol. I Chemistry & Physiology - by L.J. Audus

9. Organic Chemistry Vol. I and II - by I.L. Finar

10. Pesticides - by S.K. Majumdar

11. Chemical Process Industries - by R. Norris Shreve and Joseph A. Brink, Jr.

Dr. B.R. AMBEDKAR OPEN UNIVERSITY

(Undergraduate programme)

Third Year Chemistry Syllabus

COURSE-IV : AGROCHEMICALS AND DRUGS

PART-A : AGROCHEMICALS

BLOCK-1 : PLANT NUTRIENTS

Unit-1 : Historical Aspects of Plant Nutrients

BLOCK-2 : PLANT DISEASE CONTROL CHEMICALS

Unit-2 : Brief Survey of Plant Disease Control Chemicals

Unit-3 : Insecticides

Unit-4 : Fungicides

Unit-5 : Herbicides and Rodenticides

BLOCK-3 : PLANT GROWTH HORMONES, ENVIRONMENTAL EFFECTS OF AGROCHEMICALS AND PESTICIDE FORMULATION

Unit-6 : Plant Growth Hormones

Unit-7 : Effects of Agrochemicals on the Environment

Unit-8 : Pesticide Formulations

PART - B : DRUGS

Dr B.R. AMBEDKAR OPEN UNIVERSITY
FACULTY OF SCIENCE
(Undergraduate Programme)
III YEAR
CHEMISTRY COURSE - IV

Section - A

Note : Answer only **three** of the following.
Each question carries 15 marks.
Answer the following in 30 lines.

1. What are Pesticides and Herbicides? Discuss the use and structures of any four of each of them.
2. What is meant by Allergy. Metnion reasons for the same. Discuss the preparation and structures of any three anti alergic agents.
3. Explain the terms "Cardio-Vascular drugs" and "CNS Stimmulants". Give examples and strucutres of any two of them.
4. What are endocrine glands? Name any four of them. What are the harmones secreted by them.
5. Name any three vitamines. Give their structures and uses what defieciences are caused by their absence?
6. What are fertilizers. How are synthetic fertilizers clarifies? Give the preparation of any two inorganic fertilizers.

Section - B

Note : Answer any five of the following.
Each question carries 6 marks.
Answer the following in about 10 lines

7. Give the preparation of any synthetic insecticide.
8. Name any rodenticide, give its chemical formulae and uses.
9. What is a Weedicide? Give its uses.
10. Give the names and chemical formulas of two plant growth harmones.
11. Explain the difference between a sedative and an Analgesic. Give one example for each.
12. What are the drugs used to control diabetics? Give the chemical structures.
13. What is meant by pharmacological activity of a drug.
14. Name two antipyretics and give their chemical structures.
15. Give the synthesis of any one antimalarial.
16. Name any two antibiotics and give their uses.

Dr B.R. AMBEDKAR OPEN UNIVERSITY
FACULTY OF SCIENCE
(Undergraduate Programme)
III YEAR
CHEMISTRY COURSE - IV
Assignment - III

N.B. :

1. Do not copy the answers directly from any of the books.
2. As far as possible try to answer questions independently in your own words.
3. If it is necessary to quote from any source, give the correct reference.
4. Use your own pages for writing the assignment.
5. Leave sufficient margins for the comments of the evaluator.
6. Completion of this assignment should not take more than two hours time.

SECTION - A

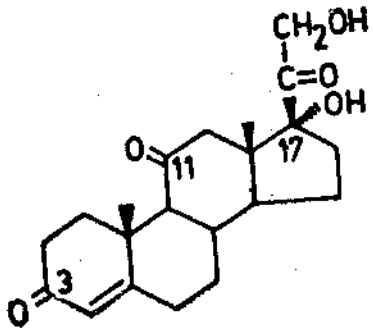
Answer the following in 30 lines.

1. What are cardio vascular drugs and CNS stimmulants. Give examples.
2. Explain the terms 'Endo Crime Glands' and 'Harmones'. Give an account of harmones secreted by different endocrine glands.
3. What are the functions of Vitamins? Give a detailed of the vitamins and their need.

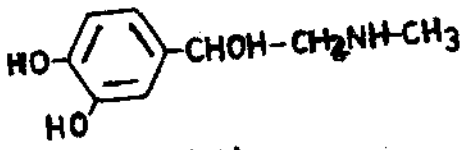
SECTION - B

Answer the following in 10 lines.

1. Give the structural formulas of terramycin and chloromphenicol.
2. What is helminthiasis and what are its symptoms and causes?
3. Write the structures of methyl dopa and pyridoxine.



(26)



(27)

22.9 PANCREAS

This is a leaf like gland attache to the small intestine. It contains cells that secrete digestive juices. A second type of cells called the b-cells of the islets of the Langerhans control the use of sugar in the body. The hormone responsible for this is insulin. It determines the amounts of sugar to be converted into glycogen and to be oxidised for energy. Insulin accelerates the conversion of blood sugar into glycogen in the liver, promotes the uptake of glucose from the blood by the body cells and increases the protein synthesis in some cells. The improper production of sufficient insulin leads to diabetes. The blood glucose level of a diabetic is not effectively regulated.

Check Your Progress - 2

What happens if the pancreas does not secrete sufficient amount of insulin?

.....

.....

.....

.....

Isolation of insulin : Insulin is commercially prepared from the pancreas of ox and the pig. The fresh glands are minced at a low temperature and soaked in acidified aqueous alcohol. The extract is separated by centrifugation and made alkaline with ammonia (pH 8). It is filtered and the filtrate reacidified and evaporated in vacuum. The separated fat is filtered reacidified and evaporated in vacuum. The separated fat is filtered off. The filtrate is treated with 25 percent sodium chloride solution when insulin separates out. Purification of insulin is effected by precipitating it at its isoelectric point at pH 5. The zinc salt of the hormone may be obtained in a crystalline form.

Crystalline insulin melts with decomposition at 233°C. It is optically active and leaevo rotatory. It is soluble in acids and alkalies but sparingly soluble in most other solvents.

Structure of Insulin : The structure of insulin was investigated by Sanger and co-workers for 10 years and finally solved in 1954. It is the simplest protein which can be obtained in a pure form. Chemically different insulines elaborated by Ox, Pig, Fish, humans differ from one another in their composition, but they show similar action.

The molecule of beef insulin is made up of 777 atoms, the molecular formula being $C_{254}H_{277}N_{65}O_{75}S_6$. The insulin molecule belongs to the category of peptides where the building units are the amino acids attached through a peptide bond. The total number of amino acids present in insulin molecule is 51. Of the 24 natural L-amino acids, 17 amino acids are present in insulin.

Insulin contained two chains, the A chain with 21 amino acids and the B chain with 30 amino acids. Chain A was shown to have a disulphide bridge and is linked to the B chain by two disulphide bonds. The structure assigned to human insulin is shown in Fig. 21.2. Human and sheep insulins were synthesized. Sanger was awarded the Nobel prize in chemistry for his remarkable work on insulin.

22.10 SUMMARY

You have learnt the following in this unit.

1. The positions of endocrine glands in the body and hormones secreted by them.
2. The metabolic role played by thyroxine and its chemical synthesis.
3. The role of the sex hormones secreted by reproductive organs and elucidation of the structure of oestrone.
4. The role of pituitary gland hormones in the body.
5. An account of adrenal gland hormones and their role in the body.
6. The role of insulin secreted by islets of langerhans of pancreas.

22.11 MODEL EXAMINATION QUESTIONS

I. **Answer each of the following in 10 lines.**

1. What are hormones? Explain their importance in human body.
2. What are endocrine glands? Name any two of them and the hormones secreted by them.
3. Write the physiological role of :
   a) Thyroxine b) Oestrone c) Insulin and d) Oxytocin

II. **Answer each of the following in 30 lines.**

1. Write a brief account of the peptide hormone, Insulin.
2. Outline the total synthesis of (±) Thyroxine.
3. Write a note on sex hormones.

22.12 MODEL ANSWERS TO CHECK YOUR PROGRESS

1. Testosterone is the male sex hormone produced by testes. It is responsible for the development of the masculine secondary sex characteristics.
2. Glucose is not effectively utilised by the body and it results in a disease called diabetes.