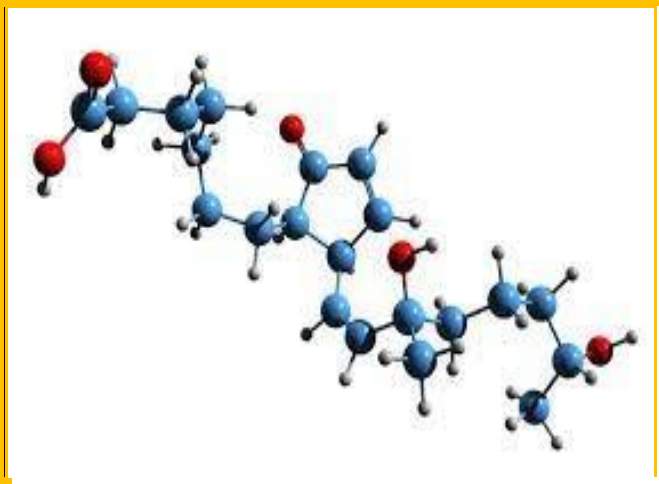
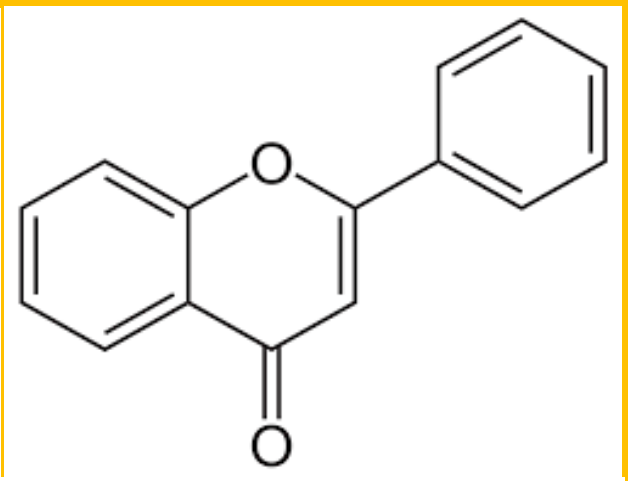
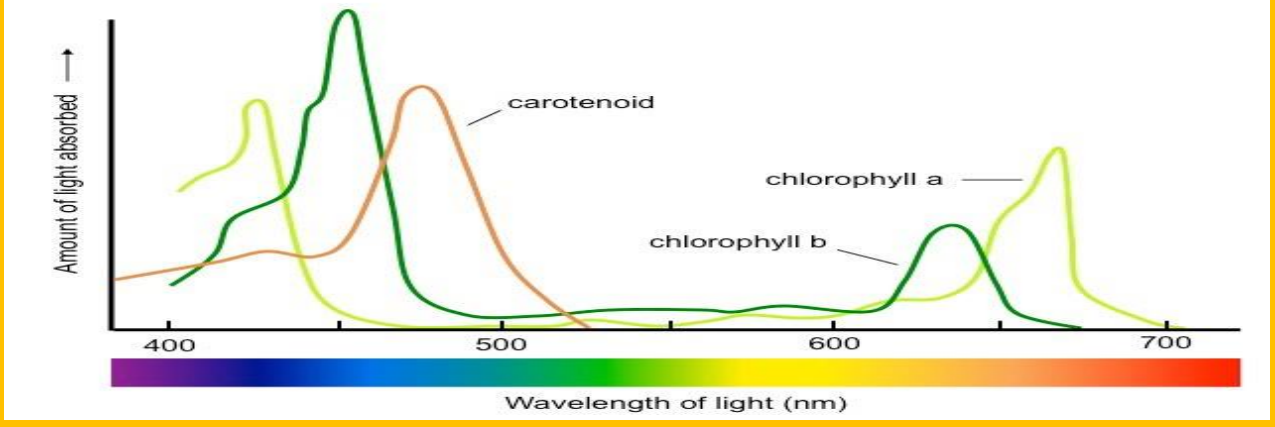
MSCCH-607
M.SC IV SEMESTER
CHEMISTRY OF NATURAL PRODUCTS & HETEROCYCLIC COMPOUNDS ((ELECTIVE)







SCHOOL OF SCIENCES
DEPARTMENT OF CHEMISTRY
UTTARAKHAND OPEN UNIVERSITY,HALDWANI (NAINITAL)

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SCHOOL OF SCIENCES

DEPARTMENT OF CHEMISTRY

UTTARAKHAND OPEN UNIVERSITY

Phone No. 05946-261122, 261123

Toll free No. 18001804025

Fax No. 05946-264232,

E. mail info@uou.ac.in htpp://uou.ac.

Expert Committee

Prof. B.S.Saraswat
Department of Chemistry
Indira Gandhi National Open University
MaidanGarhi, New Delhi

Prof. A.K. Pant
Department of Chemistry
G.B.Pant Agriculture, University
Pantnagar

Prof. A. B. Melkani
Department of Chemistry
DSB Campus,
Kumaun University, Nainital

Prof. Diwan S Rawat
Department of Chemistry
Delhi University
Delhi

Dr. HemantKandpal
Assistant Professor
School of Health Science
Uttarakhand Open University, HaldwaniUttarakhand Open University,

Dr. Charu C. Pant
Academic Consultant
Department of Chemistry

Board of Studies

Prof. A.B. Melkani
Department of Chemistry
DSB Campus, Kumaun University
Nainital

Prof. G.C. Shah
Department of Chemistry
SSJ Campus, Kumaun University
Nainital

Prof. R.D.Kaushik
Department of Chemistry
GurukulKangriVishwavidyalaya
Haridwar

Prof. P.D.Pant
Director I/C, School of Sciences
Uttarakhand Open University
Haldwani

Dr. Shalini Singh
Assistant Professor
Department of Chemistry
School of Sciences
Uttarakhand Open University, Haldwani

Dr. Charu C. Pant
Academic Consultant
Department of Chemistry
School of Science
Uttarakhand Open University, Haldwani

Programme Coordinator

Dr. Shalini Singh
Assistant Professor
Department of Chemistry
Uttarakhand Open University,
Haldwani

Unit Written By	Unit No.

1.Dr.Shalini Singh **01,02**
Assistant Professor
Department of Chemistry
Uttarakhand Open University, Haldwani

2. Dr Vinod Kumar **03**
Assistant Professor
Department of Chemistry
Uttarakhand Open University, Haldwani

3.Dr. Ruchi Pandy **04,05**
Assistant Professor
Department of Chemistry
Uttarakhand Open University, Haldwani

4. Dr.Balam singh Bisht **06**
Assistant Professor (Organic Chemistry)
Department of Chemistry
Government P.G. Collage ,Berinag

5. Dr.Drshan Kamboj **07, 08**
Assistant Professor
Department of Chemistry
Government P.G. Collage ,Dharwad

Course Editor

Dr.Shalini Singh
Assistant Professor
Department of Chemistry
Uttarakhand Open University, Haldwani

Dr.Ruchi Pandey
Assistant Professor
Department of Chemistry
Uttarakhand Open University, Haldwani

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Block I: Chemistry of Natural Product

UNIT:1 TERPENOIDS

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1.1 OBJECTIVE

1. To describe classification and isolation of terpenoids.
2. To explain nomenclarure.
3. To illustrate general method of structural determination
4. Introduction, synthesis and biosynthesis of Menthol, Santonin and β-Carotene
5. Stereochemistry of Menthol, Santonin and β-Carotene.

1.2 INTRODUCTION

The terpenoids, also known as isoprenoid, are a large and diverse class of naturally occurring organic chemicals derived from the 5- carbon compound isoprene, and isoprene polymers.

Initially the term terpene was used to describe a mixture of isomeric hydrocarbons of the molecular formula $C_{10}H_{16}$ mainly occurs in the terpentine and many essential oils obtained from certain plants and trees. At that time, the oxygenated derivatives like alcohols, aldehydes, ketones etc. were called camphors. Later, both the terms terpenes and camphors were jointly called as terpenoids. Thus, in modern term we can define it as follows:

"Terpenoids includes hydrocarbons of plant origin of the general formula $(C_5H_8)_n$ as well as their oxygenated, hydrogenated and dehydrogenated derivatives."

The term terpene is inappropriate to use for those hydrocarbons which include compounds such as alcohol, aldehydes, ketones etc. because the suffix "ene" signifies only unsaturated hydrocarbons. So, it is better to use term terpenoid than terpene. The tendency of using term terpen is restricted to the hydrocarbons, $C_{10}H_{16}$. On the other hand, terpenoids represent the hydrocarbons as well as oxygenated derivatives.

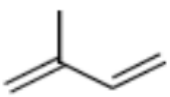
Thus, all terpenes are terpenoids but vice versa is not true.

Terpenoids are naturally occurring compounds. There occurrence is most widespread. The majority of terpenoids occurs in plants, a few of them have also been reported from other sources. They are volatile and fragrant component of plants, isolated by steam distillation, solvent extraction etc. These components are called the essential oils. These have been used in perfumery from the earliest times.

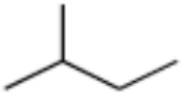
1.3 NOMENCLATURE

1.3.1 Isoprene rule:

In 1887, Wallach defined isoprene rule as follows:
"The skeleton structure of all naturally occurring terpenoids are constituted of isoprene units".
The empirical formula of almost all the naturally occurring terpenoids is C_5H_8. The basic molecular formula of terpenes are multiplies of $(C_5H_8)_n$, where n is the number of linked isoprene units.



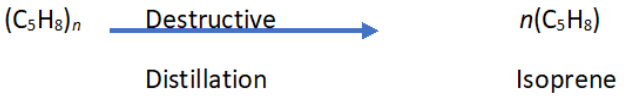
Isoprene



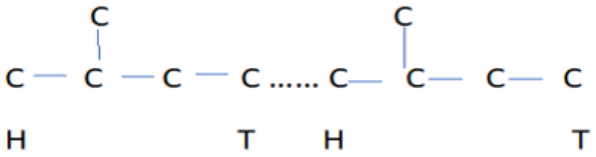
Isoprene Unit

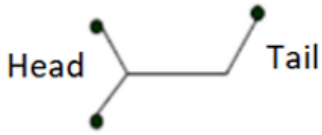
All the terpenoids gives isoprene as one of the products on the thermal decomposition.

Example- Rubber which is a polyterpenoid on destructive distillation yields isoprene as one of its products.



In 1925 Ingold proposed special isoprene rule. According to this rule, the isoprene units in terpenoid are linked in a head to tail fashion.





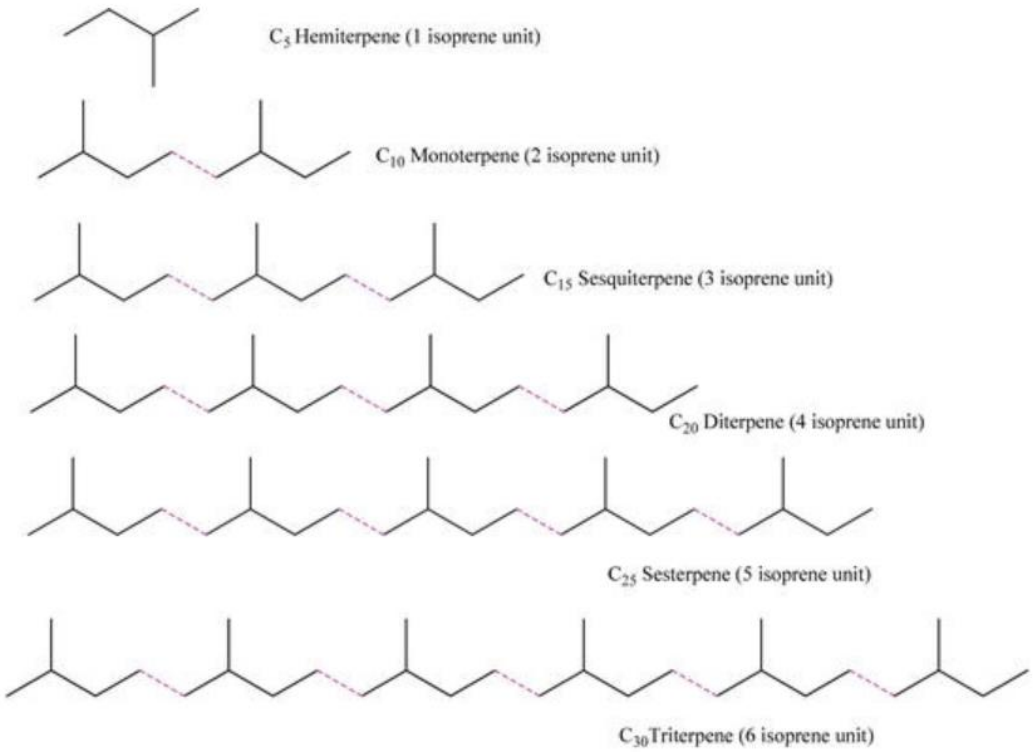
1.4 CLASSIFICATION OF TERPENOIDS

The general formula of terpenoids is $(C_5H_8)_n$ and the value of n is used as basis of classification.

	Class	No. of Isoprene units $(C_5H_8)_n$	Molecular formula	Examples
1	Hemiterpene or Isoprene	1	C_5H_8	
2	Monoterpene or Terpene	2	$C_{10}H_{16}$	p-cymene,camphore, pinane, carane
3	Sesquiterpenes	3	$C_{15}H_{24}$	Famesol, Zinziberene, Cadinene
4	Diterpenes	4	$C_{20}H_{32}$	Phytol, Vitamin A

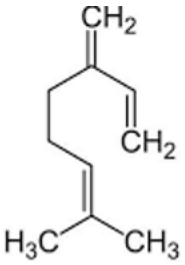
5	Triterpenes	6	$C_{30}H_{48}$	Pardinol B, E & F Cyclocariols A, B & H Polyporenic acid B
6	Tetraterpenes or Carotenoids	8	$C_{40}H_{64}$	B-carotene, Astazanthin
7	Polyterpenes or Rubber	n	$(C_5H_8)_n$	Rubber

The sesterterpenoid have been discovered recently. The first example of this class called solanesol, an acyclic unsaturated alcohol. Apart from the hydrocarbons in each class given in table, oxygenated compounds like alcohols, aldehydes, ketones are also known.

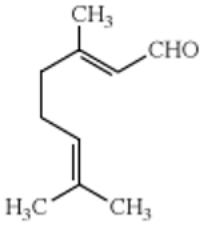


Each class of terpenoids has been further subdivided into subclasses according to the number of rings present in the molecule.

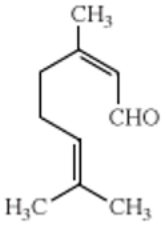
(i) Acyclic terpenoids- These contain an open-chain structure.



myrcene

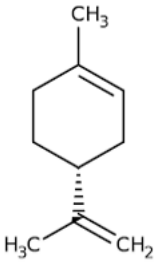


geranial
(citral a)

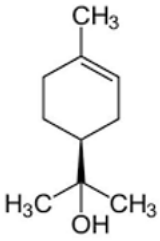


neral
(citral b)

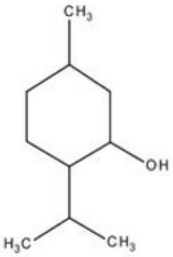
(ii) Monocyclic terpenoids- These have one rind in the molecule.



Limonene

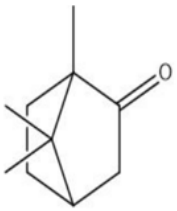


alpha- Terpineol

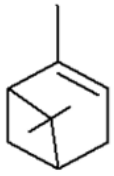


Menthol

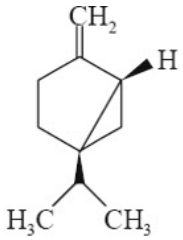
(iii) Bicyclic terpenoids- These have two rings in the molecule.



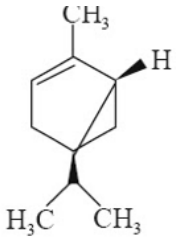
Camphore



α- pinene

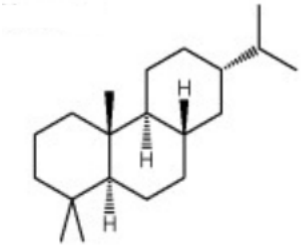


Sabinene

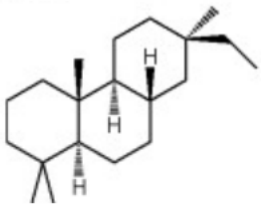


α-Thujane

(iv) Tricyclic terpenoids- These contain three rings in the molecule.

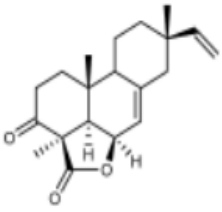


Abeitane

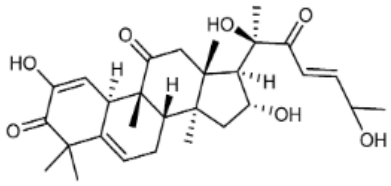


Pimarane

(v) Tetracyclic terpenoids- These contain four rings in the molecule.



Momilactone A



Cucurbitacin I

1.5 ISOLATION OF TERPENOIDS

Terpenoids are widely occurs in nature due to which they could not be isolated and separated by a general method.The common source of mono and sesqui-terpenoids is essential oil and therefore their isolation has been generalized. Isolation is carried out in two steps as follows:

(i) Isolation of essential oils

(ii) Separation of terpenoids from essential oils

Isolation of essential oils

(a) Expression Method- In this method plant material is cut into the small pieces. These pieces are then crushed to get the juice which is screened to remove the larger particles. After screening, the juice is centrifuged in a high-speed centrifugal machine where one-half of the oil extracted and the rest half of the essential oil remains with the residue. From residue, inferior quality of the oil is obtained by distillation. This method is used to extract citrus, lemon, and grass oils. This method is very less common.

(b) Steam distillation method- This is most widely used method. This is carried out by passing dry steam through the plant material where the steam volatile compounds are volatilized, condensed, and collected in receivers. In this technique the plant material is supported on a

screen, or a perforated grid placed at some distance above the bottom of the still. Distillation is carried out with low pressure steam which replaces the volatile compounds from the intact plant material. Distillate collected in receiver further extracted by using pure organic volatile solvents like light petroleum and the solvent is then removed by distillation under reduced pressure. Steam distillation have few demerits:

(i) Some essential oils undergo decomposition during steam distillation

(ii) Some constituents of the essential oils, e.g., esters, undergo decomposition. esters are responsible for the odour and fragrance of the oil, there decomposition during distillation may result perfume of inferior quality.

(c) Extraction by means of Volatile solvents-This method is widely used in perfume industry. This method is generally used for the plants which give low yield of oil due to the decomposition of essential oils. In such case, the plant material is directly treated with light petrol at 50^0C, the oil is taken up by the solvent along with soluble colouring materials. The essential oils from this extract are separated by removing the solvent by distillation under reduced pressure.

(d) Adsorption in purified fats or enfleurage method- This is very old technique of extracting the aromatic oils from flowers, it is widely employed in France. By this method the yield of the essential oil is generally higher. This method is used to extract a large number of essential oils like lily, rose, jasmine, lilac, gardenia etc. In this method, fat is warmed to 50^0C on glass plates and then flowers were placed on the fat and left for several days to release their oils. Then, the old flowers are replaced by fresh one and this process is repeated several times until the fat on the plate is completely saturated with the aromatic oils of the flowers. The saturated fat then digested with ethyl alcohol where all the oils present in the fat dissolved in alcohol. Some quantity of fat also dissolves in alcohol which can be separated by cooling the alcohol extract to 20^0C when the fat separates out. The alcoholic distillate is then finally fractionally distilled under reduced pressure to remove the solvent. Recently, coconut charcoal is used in place of fat due to its greater stability and higher adsorptive capacity.

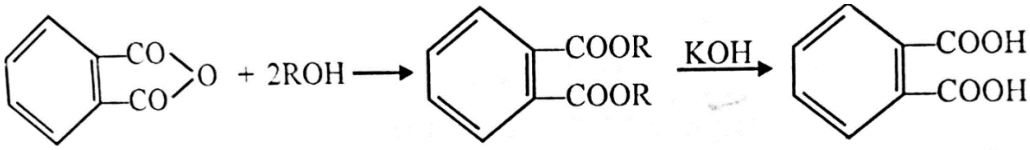
1.6 SEPARATION OF TERPENOIDS FROM ESSENTIAL OILS

The essential oils isolated from plants contain several terpenoids and these are separated by various physical and chemical methods.

1.6.1 Chemical method:

(i) In 1877, Tilden discovered that when essential oil containing terpenoid hydrocarbons are treated with nitrosyl chloride in chloroform, crystalline adduct having shar melting points are obtained. The adduct are separated and decomposed into their corresponding hydrocarbons.

(ii) The essential oils containing terpenoid alcohols are separated by their reaction with phthalic anhydride to form diester where, the primary alcohol react readily, secondary alcohol less readily and tertiary do not react at all. The diester are extracted with sodium bicarbonate and then decomposed by alkali to the parent terpenoid alcohols.



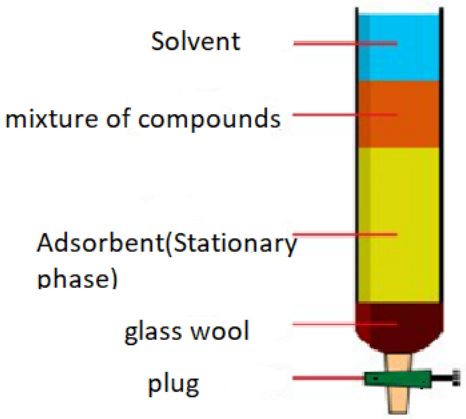
(iii) Essential oil containing terpenoid aldehyde and ketones are separated by reacting with the common carbonyl reagents like $NaHSO_3$, 2,4-dinitrophenylhydrazine, phenylhydrazine, semicarbazide, etc. After separation these are decomposed ti regenerate terpenoid aldehydes and ketones.

1.6.2. Physical method:

(i) Fractional distillation methods- Fractional distillation is one of the methods to separate terpenoids from essential oils. The terpenoid- hydrocarbons distil over first followed by the oxygenated derivatives. Distillation of the residue under reduced pressure yields the sesquiterpenoids and these are separated by fractional distillation. Many terpenes are sensitive to heat and atmospheric oxygen, in this case the fractional distillation has to be carried out under reduced pressure and in the presence of an inert gas. Some terpenoids are more volatile, so especially designed stills and efficient condensing system are used to minimize the loss of more volatile compounds.

(ii) Chromatography- Various chromatographic methods has been used for isolation and separation of terpenoids. The most common are adsorption chromatography, vapour phase chromatography, partition chromatography, counter-current separation method, gas chromatography.

In adsorption chromatography, the essential oil is allowed to flow through a specific adsorbent packed in a column. The different type of terpenoids are adsorbed at different places on the adsorbent which depends on their affinity to the adsorbent. Different chromatogramsare formed in the column, these chromatograms are eluted by different solvent system to get different elutes (each elute is having terpenoid of single group). Each elute is further subjected to adsorption chromatography separately to separate different terpenoids.



1.7 GENERAL METHODS OF STRUCTURAL DETERMINATION OF TERPENOIDS

The methods used for the determination of structure of terpenoids have been grouped into five classes:

1. Analytical methods
2. Synthetical methods
3. Physical methods
4. Knowledge of a molecular rearrangement
5. Synthesis

1.7.1 Analytical Method

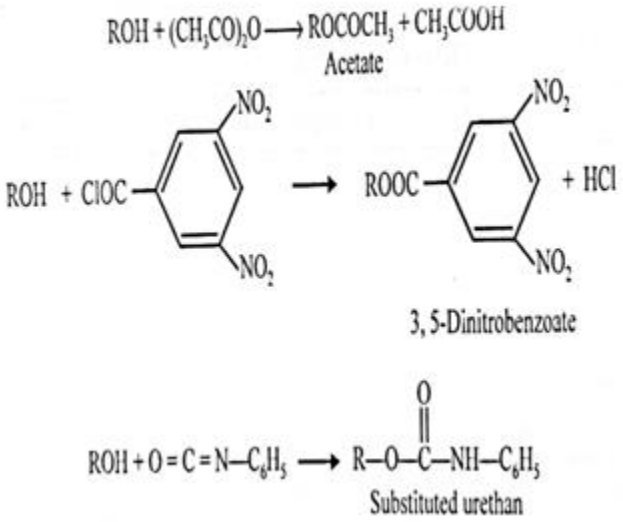
(a) Molecular formula- Molecular formula of pure terpenoid is determined by qualitative and quantitative analysis and by means of mass spectroscopy. Specific optical rotation is measured if the terpenoid is optically active.

(b) Nature of the oxygen atom- Generally hydroxy, aldehyde, keto or carboxylic groups are found in the terpenoids. Functional groups like $-OCH_3$, $-CONH_2$, $-NO_2$ etc. have not been reported in the terpenoids.

Identification of various groups can be done by following methods-

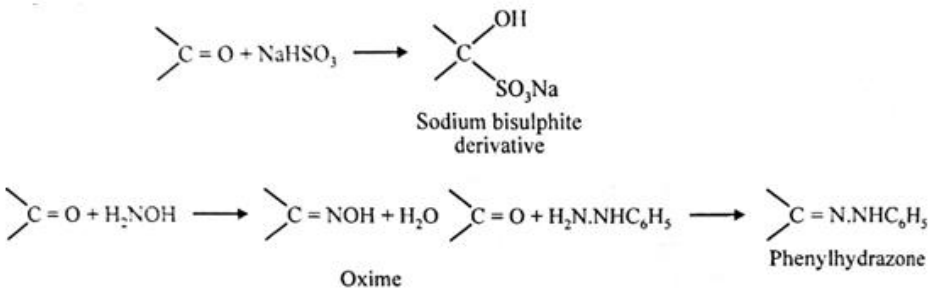
(i) Hydroxy group- Terpenoid hydroxy groups can be detected as follows:

- with acetic anhydride these form crystalline acetates.
- with 3,5- dinitrobenzoyl these form benzoates.
- with phenylisocynate this form substituted urethans.

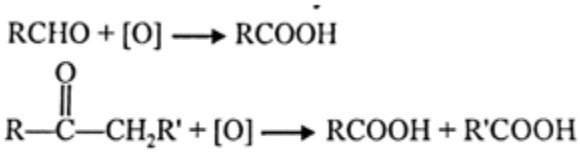


Further information regarding nature of hydroxy group (1^0,2^0,3^0) revealed by the rate of esterification.
Rate of esterification for alcohols is Primary alcohol> Secondary alcohol> tertiary alcohol.

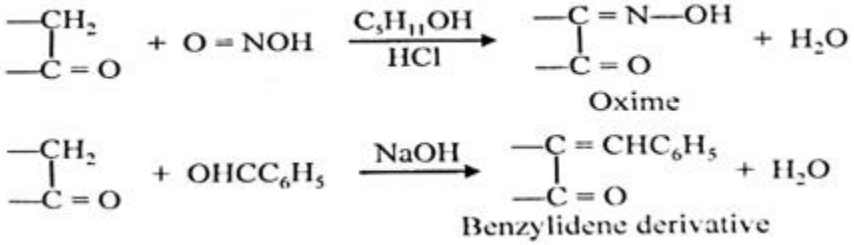
(ii) Carbonyl Group- If a terpenoid contains a carbonyl group it forms crystalline addition products like bisulphite derivative, oxime and phenylhydrazone.



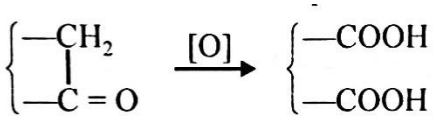
Aldehyde or keto groups can be ascertained by oxidation. On oxidation aldehydes yields monocarboxylic acid without loss of carbon atom whereas the ketone yields a mixture of lesser number of carbon atoms.

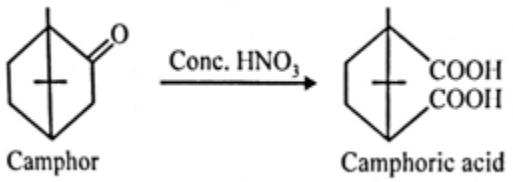


Terpenoids having -CH_2CO- groups forms oximes with nitrous acid and benzylidene derivatives with benzaldehyde in the presence of alkali.

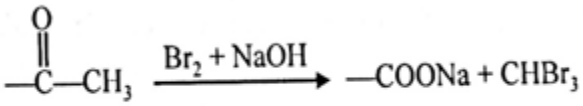


If -CH_2CO- group is present in ring, the terpenoid will form a dicarboxylic acid without any loss of carbon atom.





-$COCH_3$ group in terpenoids can be detected by Haloform reaction, e.g.



(iii) Carboxyl group- Terpenoid containing carboxylic group are soluble in ammonia and gives effervescence with sodium bicarbonate. Number of carboxylic groups is estimated by titration against standard alkali. Attachment of carboxylic group to a primary, secondary or tertiary carbon can be known by determination of rates of esterification of the acid which are in the following order:

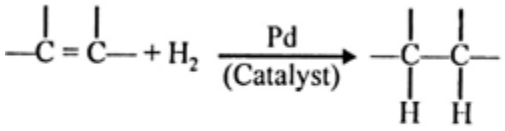
Tertiary < Secondary< Primary

Tertiary carboxylic groups are very difficult to esterify, and such acids do not form halogen substituted derivatives which shows the characteristics of acids having α-hydrogen atoms.

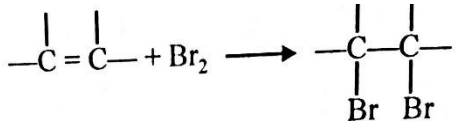
(iv) C-alkyl groups(C-methyl, isopropylidene and isopropenyl)-The terpenoid containing C-alkyl groups is detected and estimated by the oxidation with chromic acid. For e.g., all the C-methyl groups on oxidation with chromic acid are converted into CH_3COOH molecules (Kuhn-Roth method) with is estimated volumetrically.

(c)Unsaturation- The presence of number of olefinic double bonds in terpenoids have been determined by the formation of addition products with following reagents:

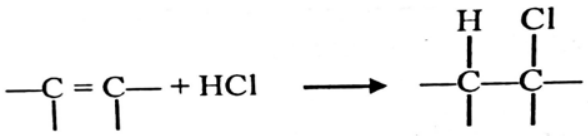
(i) Addition product with halogen- Terpenoids containing olefinic linkages hydrogenated in the presence of a catalyst and formsan addition compound called hydro compound. From the amount of hydrogen consumed the extent of unsaturation in a terpenoid can be calculated.



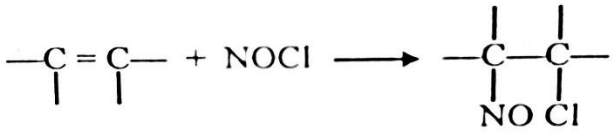
(ii)Addition product with halogens- Terpenoids containing olefinic linkages form addition compounds with halogens. The number of halogens used gives the amount of unsaturation.



(iii)Addition with halogen acids (HCl, HBr)- Halogenation of terpenoids takes place by dissolving in it in a suitable solvent followed by passing the halogen acid gas. Addition of the halogen acid takes place according to Markownikoff's rule.

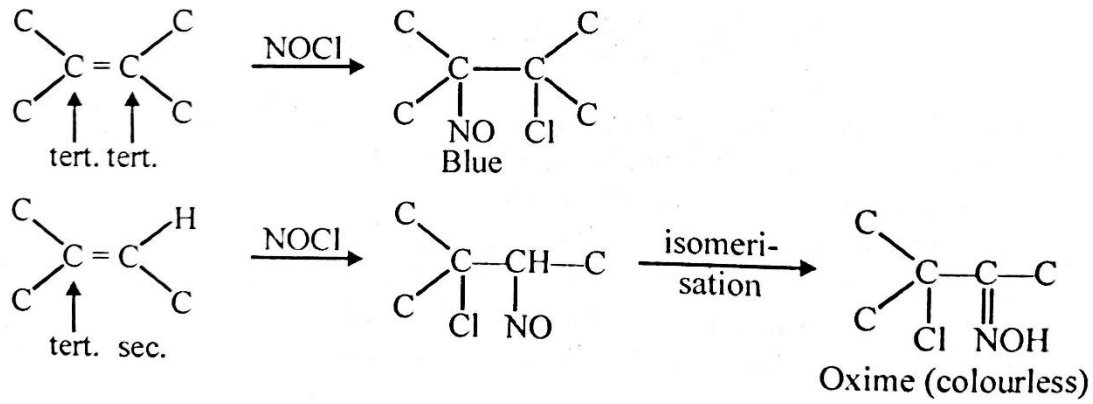


(iv)Addition with nitrosyl chloride (Tilden's reagent) -Nitrosyl chloride form addition compound with terpenoid containing olefinic double bonds which has very sharp melting point.

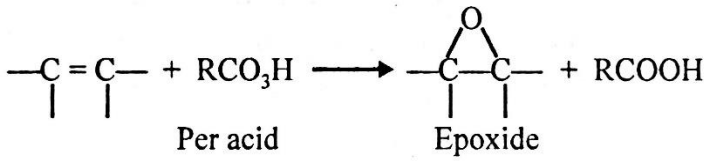


Addition of nitrosyl chloride also gives an idea about the nature of the carbon atoms having double bonds in terpenoids.If thetwo-carbon atom joined by olefinic linkage are tertiary in nature, then

blue coloured nitrosyl chloride is obtained. While, if one of the carbon atoms joined to double bond is tertiary and the other is secondary a colourless nitrosyl chloride is obtained.



(v) With peracid- Terpenoids containing olefinic double bonds form epoxides with peracids. Excess of peracid is treated with a known amount of terpenoid, the unused amount of acid is determined volumetrically. From the amount of peracid used, the number of olefinic double bonds can be determined.



(d)Number of rings- Table 1 gives relation between general formula of compound and type of compounds

Table 1

General formula of the compound	Type of compound
C_nH_{2n+2}	Acyclic
C_nH_{2n}	Monocyclic
C_nH_{2n-2}	Bicyclic
C_nH_{2n-4}	Tricyclic
C_nH_{2n-6}	Tetracyclic

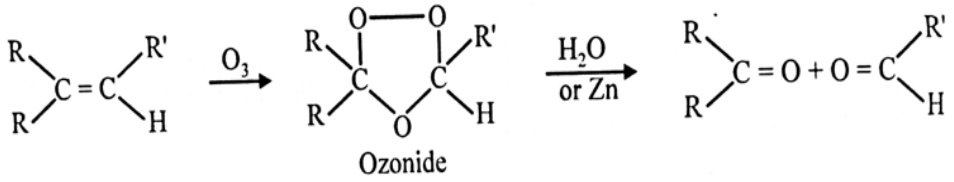
Example- Citral, Molecular formula- $C_{10}H_{16}O$ contains two double bonds and one oxygen atom as carbonyl group. So, the molecular formula of the parent hydrocarbon would be:

$C_{10}H_{16}O \equiv C_{10}H_{16}+4H$(for two double bond) + 2H (for carbonyl oxygen) $\equiv C_{10}H_{22}$

The molecular formula $C_{10}H_{22}$ corresponds to C_nH_{2n+2}, the general formula of acyclic compounds. Thus, citral must be acyclic.

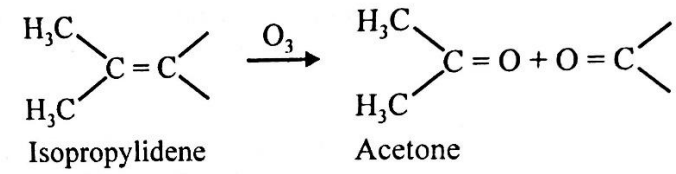
(e)Oxidative degradation product-The next step to know the structure of a terpenoid is to degrade it to small fragments. Oxidates is one the popular method to degrade the terpenoids.

(i) Oxidation with ozone-Ozone reacts with terpenoid olefinic linkage to form ozonide which further on hydrolysis or catalytic reduction yields the corresponding carbonyl compounds.



Ozonide

If isopropylidene group is present in a terpenoid on ozonolysis it yields acetone and formaldehyde which shows presence of terminal double bond.

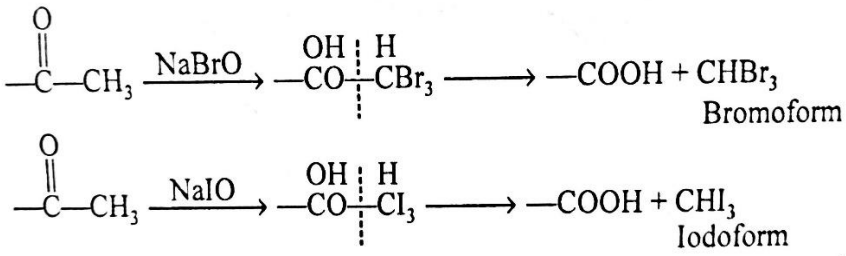


Isopropylidene Acetone

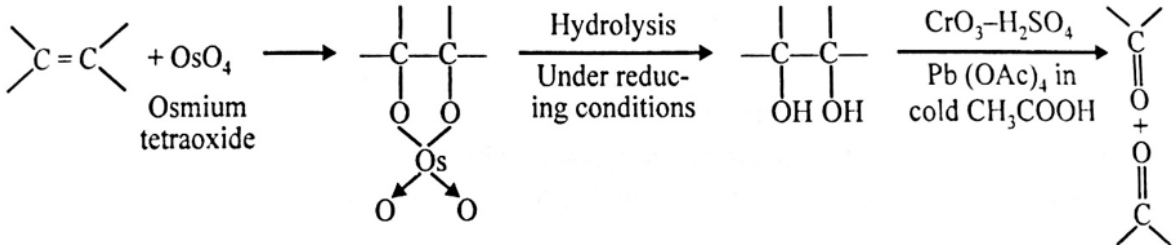
$>C = CH_2 \xrightarrow{O_3} >C = O + HCHO$

Terminal double bond

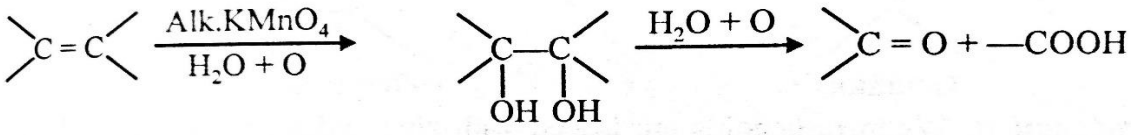
(ii) Oxidation with sodium hypohalite- Reaction of hypohalite (NaBrO or NaIO) used for the removal of one carbon atom as bromoform or iodoform from the methyl ketone group present in terpenoids. This reaction is known as haloform reaction.



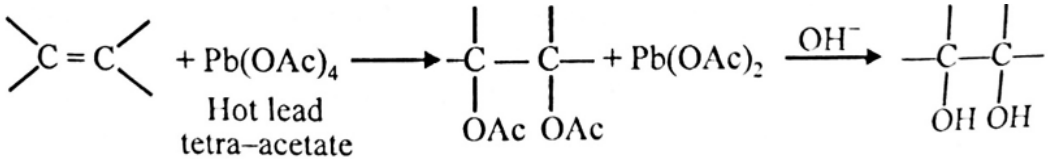
(iii) Oxidation with osmium tetra oxide- 1,2- glycols will be obtained which on further gives identified products.



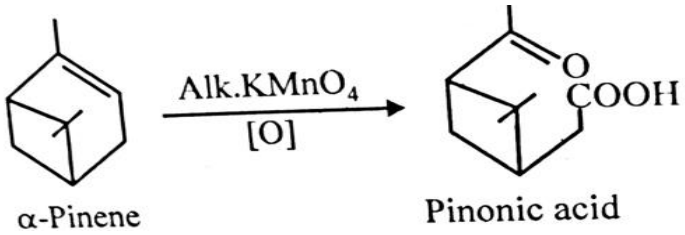
(iv) Oxidation with alkaline $KMnO_4$ – Gives 1,2- glycols.



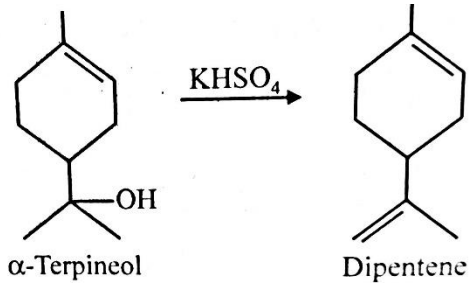
(v) Oxidation with lead tetra- acetate-

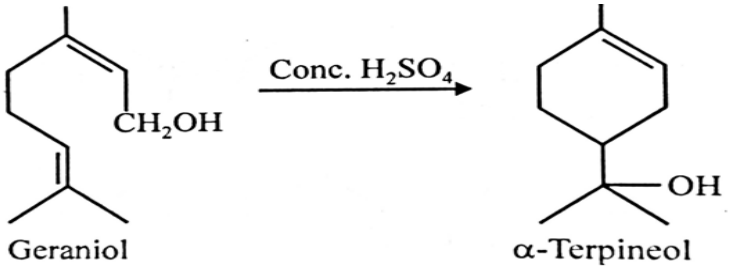


If double bonds are present in the ring, then on oxidation keto acids or dicarboxylic acids are obtained without the loss of carbon atoms.



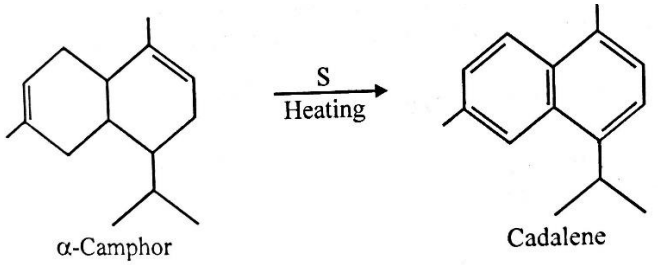
(vi) When terpenoids containing the alcoholic and ketonic groups are heated with dehydrating reagents like P_2O_5, $KHSO_4$, and conc. H_2SO_4, these lose a molecule of water and are converted into simple aromatic compounds.



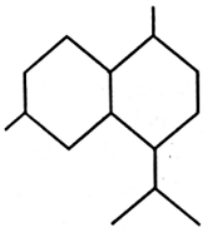


(vii) When terpenoids reacts with Zn, I_2, Br_2, S, Se, Pd etc., they are converted into aromatic compounds of known structure.

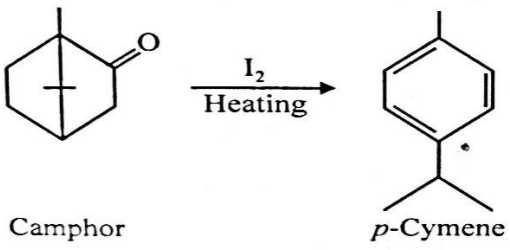
Example: 1



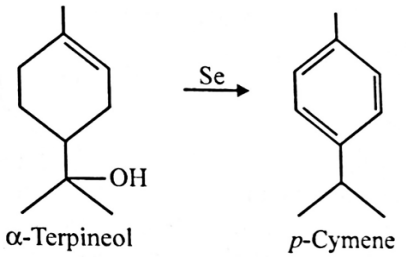
Carbon skeleton of cadinene is:



Example: 2



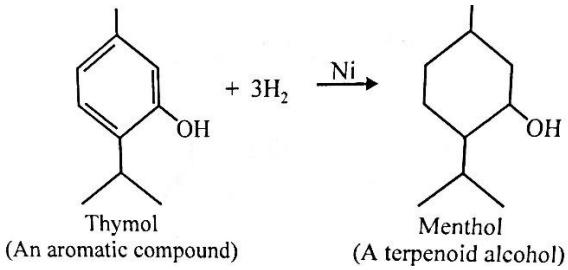
Example: 3



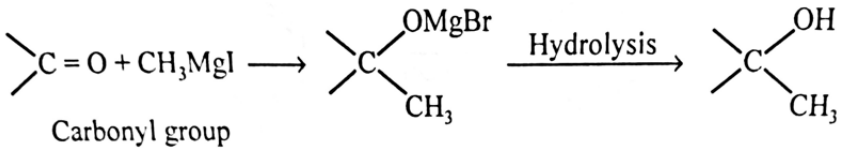
1.7.2 . Synthetical methods-

(i) Catalytical hydrogenation- Synthetic terpenoids are possibly obtained , when aromatic compounds are hydrogenated catalytically under suitable condition.

e.g. Thymol by catalytic hydrogenation can prepare a terpenoid menthol.

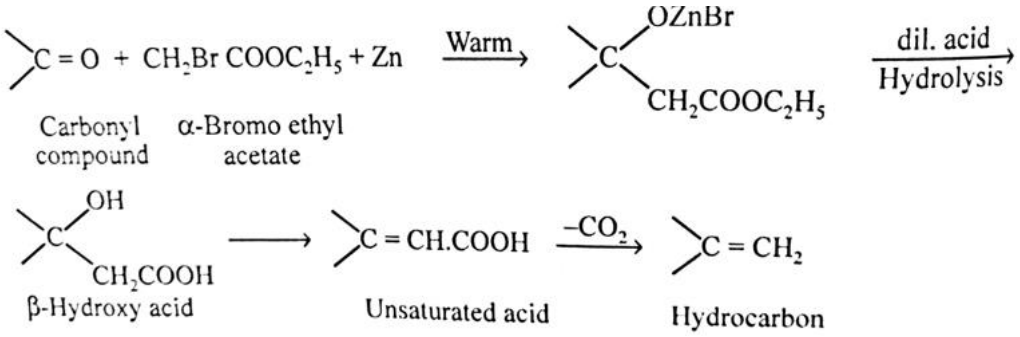


(ii)Grignard Reaction- Methyl or isopropyl groups can be introduced into a compound having carbonyl group by Grignard reagent.



A-terpineol is a naturally occurring terpenoid tertiary alcohol. It can be prepared by direct application of Grignard reagent.

iii) Reformatsky reaction-I this reaction firstly α-halogen substituted ester is treated with carbonyl compound in the presence of Zn to form a β-hydroxy ester. Then the β-hydroxy ester treated with dilute acid yield β-hydroxy acid which further converted into an unsaturated acid or a hydrocarbon.



1.7.3 Physical method-

The various method used to explicate the structure of terpenoids are as follows:

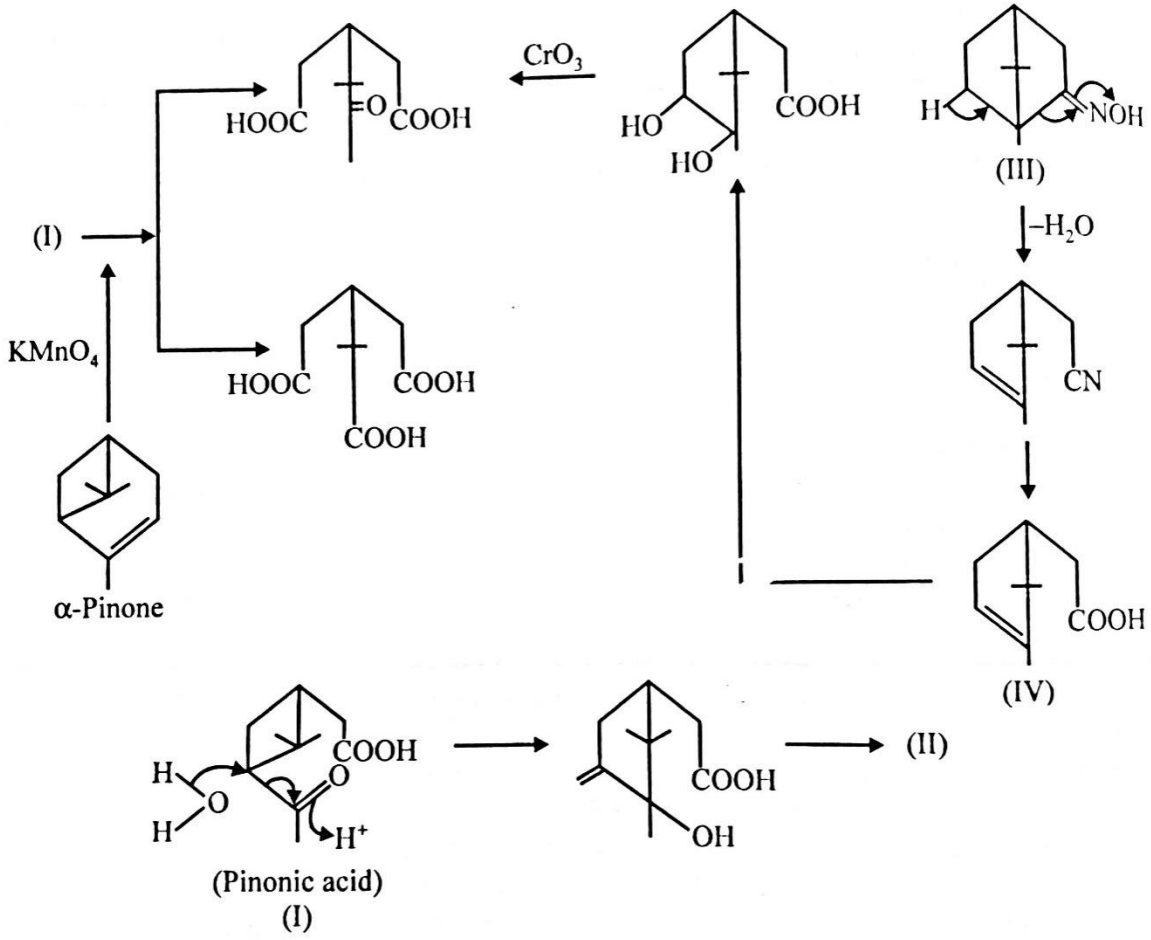
(a) Ultraviolet spectroscopy- This spectroscopy is used to detect the conjugation in terpenoids.
Some important λ_{max} values reported in terpenoids identification:

	λ_{max}
acyclic dienes	217-228nm
Heteroannular diene	230-240nm
Homoannular diene	256-265nm
α,β- unsaturated carbonyl system	220-250nm
Isolated double bond	175-200nm

(b) Infrared spectroscopy- IR spectroscopy is used to know the functional group basically. In terpenoid spectroscopy it is used to detect the presence of hydroxyl group, oxo group, α,β- unsaturated carbonyl system etc. IR spectroscopy can distinguish between heteronuclear dienes and unsubstituted α,β- unsaturated ketones and cis and trans isomers.
(c) NMR spectroscopy- This technique is used to detect the double bonds, to determine the nature of end group and the number of rings present. It also revels the orientation of methyl group in relative position of double bond.
(d) Mass spectroscopy- This technique is widely used to determine the molecular weight, molecular formula, the nature of various functional groups and the relative position of double bonds.
(e) X-ray analysis- This technique is used for elucidating structure and stereochemistry of terpenoids.
(f) Optical rotation- ORD studies are used to determine absolute configurations.

1.7.4 Knowledge of a molecular rearrangement-

Molecular rearrangement during some degradative work gives an idea about the structure of the molecule. For example- When α-pinene is oxidized with permanganate, it gives piononic acid (I) as one of the products. On oxidation with chromic acid pinonic acid degraded to isoketocamphonic acid (II). Camphor oxime (III) on acid-catalysed dehydration and hydrolysis yields α-campholenic acid (IV). During the oxidation of pinonic acid, a rearrangement, subsequent to protonation of carbonyl group has been involved. Thus, this work clearly indicates the relationship of camphor with α-pinene and gives some idea about the structure of the later.

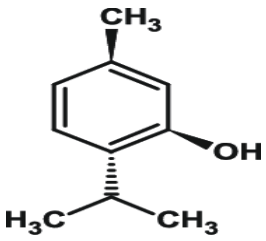


1.7.5 Synthesis:

Proposed structure of terpenoid is finally confirmed by synthesis. In terpenoid chemistry many of the synthesis are ambiguousand, in such cases, analytical evidenceis used in conjugation with the synthesis.

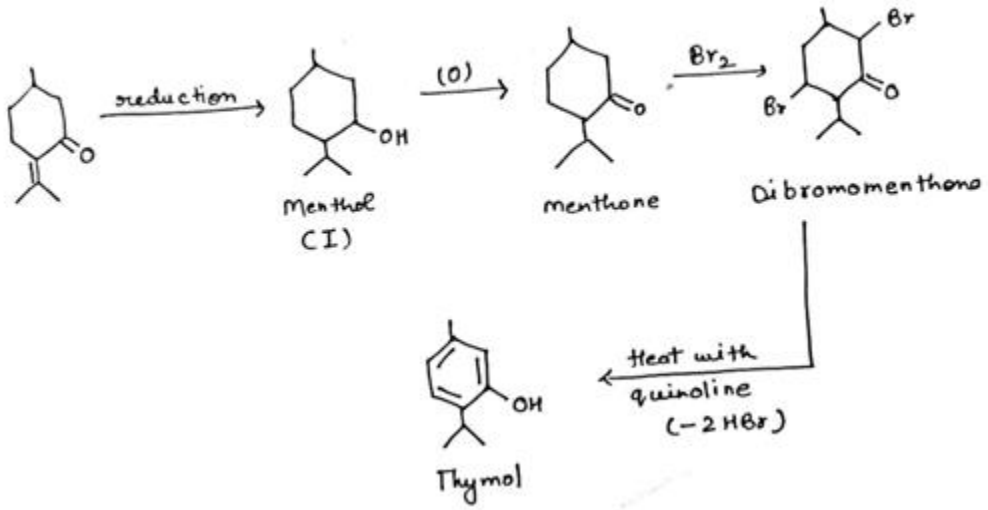
1.8 MENTHOL

Menthol is also called peppermint camphor.It is a terpene alcohol with a strong minty, cooling odour and taste. It is obtained from peppermint oil.Menthol is an optically active compound.Only levorotatory form i.e., (-) menthol or *l*-menthol is naturally occurring form of menthol. It is a saturated compound having m.p. 43^0C. Menthol is used in ointments; cough drops and nasal inhalers. It is also used as flavouring in food, cosmetics, and perfumes.

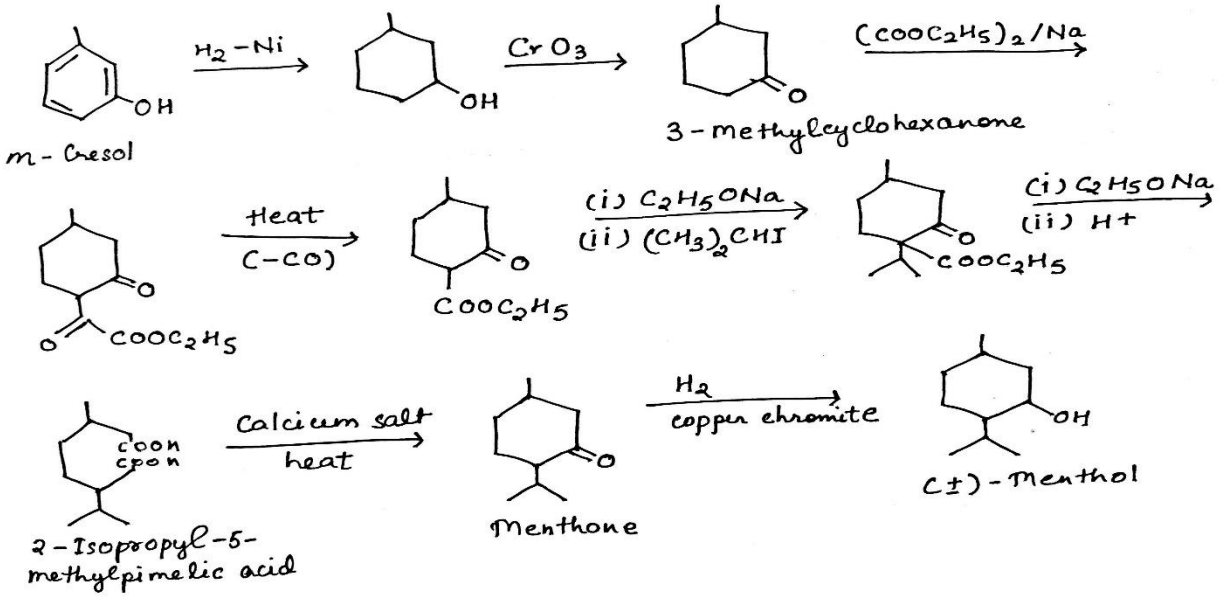


1.8.1 Constitution of Menthol

1. Molecular formula- $C_{10}H_{20}O$
2. Menthol forms esters with acids- It indicates the presence of alcoholic group in it.
   Oxidation of menthol yields a ketone, menthone- It indicates that the hydroxy group in menthol is secondary in nature.
3. On dehydration followed by dehydrogenation, menthol yield *p*-cymene – This indicates presence of *p*-cymene skeleton (*i.e.*,*p*-menthane skeleton) in the compound.
4. Oxidation product of menthone is menthol, the structure of menthol should be I. This can be further confirmed by the fact that reduction of pulegone gives menthol and structure of pulegone is known. So, the structure of menthol could be I.Further structure I explains all its reactions as given below.

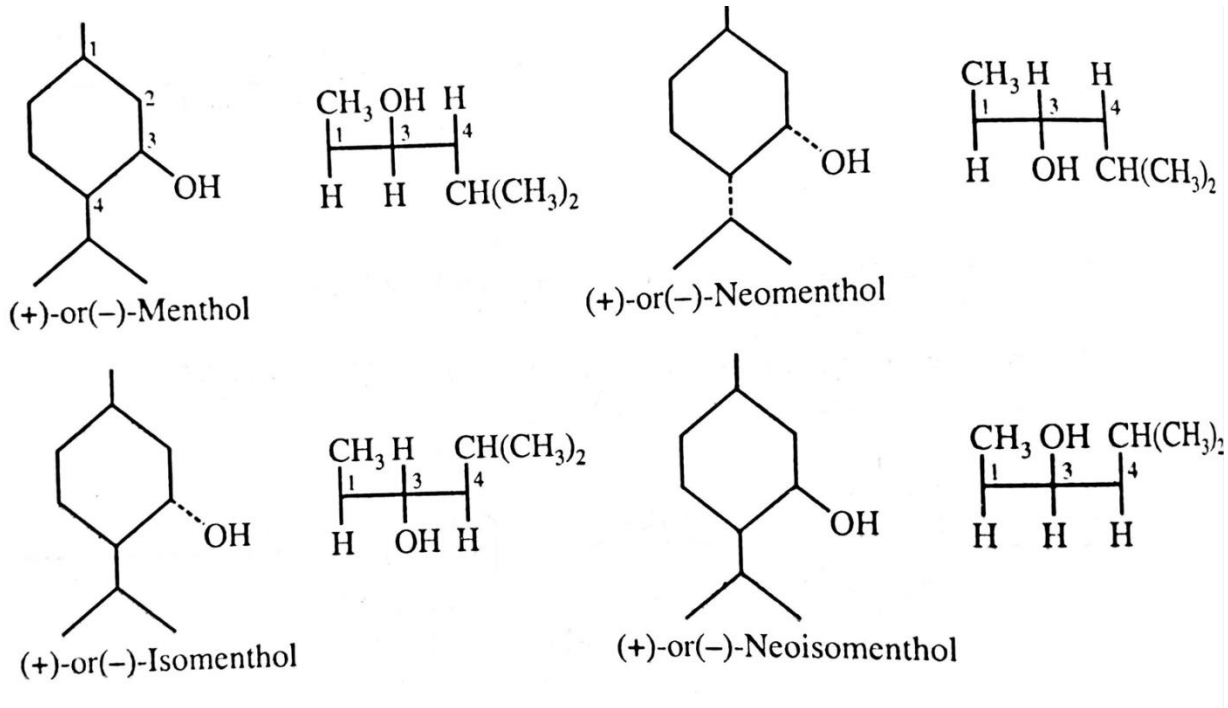


5. Synthesis:Structure of menthol have been confirmed by synthesis given by Kotz and Hese from *m*-cresol.



1.8.2 Stereochemistry of Menthol

Menthol has three chiral centers at position C_1,C_3 and C_4. Thus its eight ($=2^3$) optically active forms (four racemic modifications) are possible theoretically, which all are known.



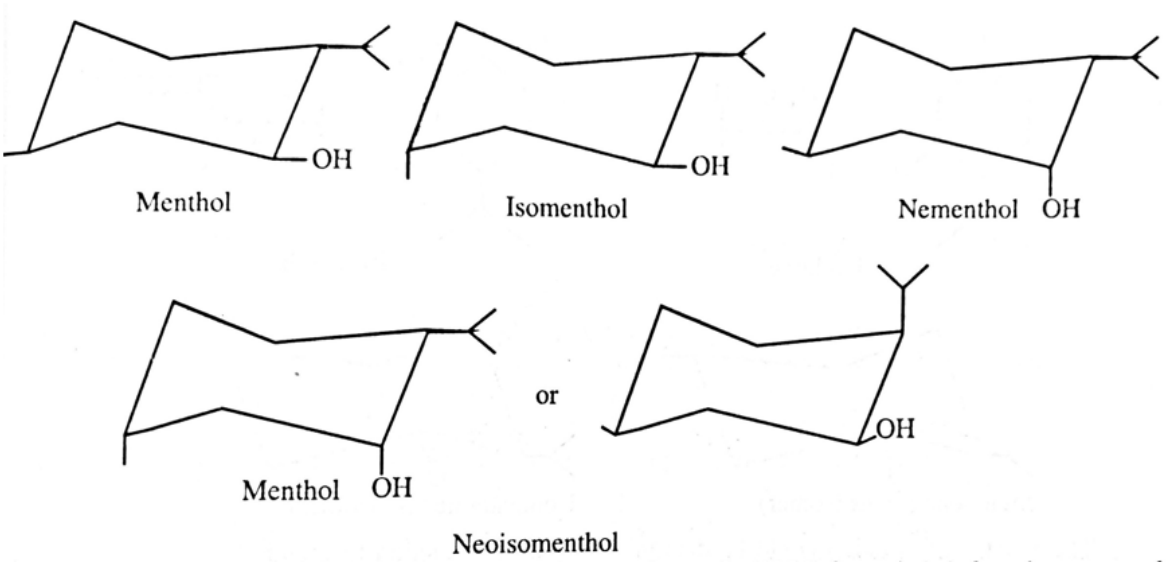
The horizontal lines in the above enantiomorphs, representing the plane of the cyclohexane ring.

The main form of menthol occurring in nature is (-)-menthol belongs to the L-series. The conformations of enantiomorphs of menthol have been confirmed by the postulates, given by Eliel as follows:

(i) The esterification of an equatorial group takes place more readily than axial group.
(ii) The esterification proceeds via the conformation of the molecule in which the reactive hydroxyl group occupies equatorial position.
(iii) The rate difference may be due to spending the energy which becomes necessary to place the other substituents, if necessary, into the axial conformation.

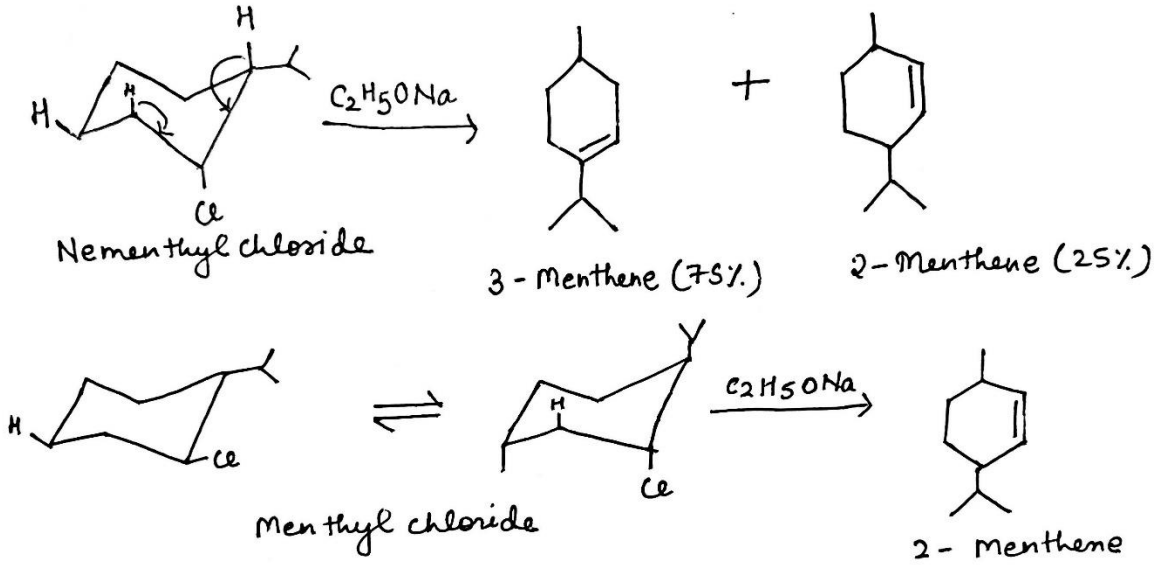
So, on the basis of above postulates the order of the rates of esterification of menthol would be:

Menthol > Isomenthol > Neoisomenthol > Neomenthol



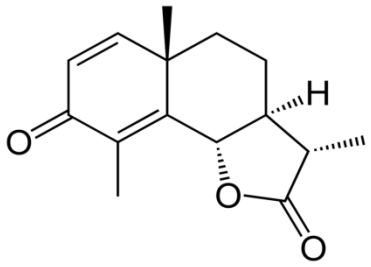
Configuration of Menthol assigned by Eliel

The rate of E_2 elimination of neomenthyl chloride has been found 200 times faster than the menthyl chloride. In neomenthyl chloride, chlorine atom is in axial position while in menthyl chloride it is at equotorial position. Further, neomenthyl chloride has two axial hydrogen, produces both menthene-2 and menthene-3 while menthyl chloride has only one axial hydrogen produces ony menthene-2.



1.9 SANTONIN

Santonin is a drug extracted from various species of *Artemesia* which is widely used in medicine as an anthelmintic. The unopened flower heads of *Artemisia maritima* var. *stechmanniana* are the source of santonica. Others claim that the derived species is *A. cina* or *A. chamaemelifolia*.



Santonin

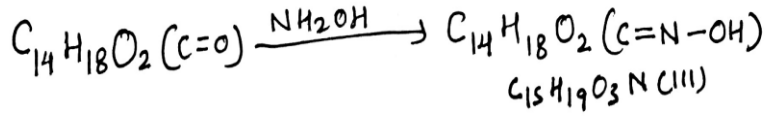
1.9.1 Constitution of Santonin

1. The molecule has the chemical formula $C_{15}H_{18}O_3$ as established by elemental analysis and molecular weight determination.

2.The compound's molecular formula reveals that it is a sesquiterpenoid.

3.Nature of three oxygen atoms:

(a)When combined with hydroxylamine, santonin produces monoxime (III).Formation of monoxime shows that one of the oxygen is present in the form of carbonyl group.



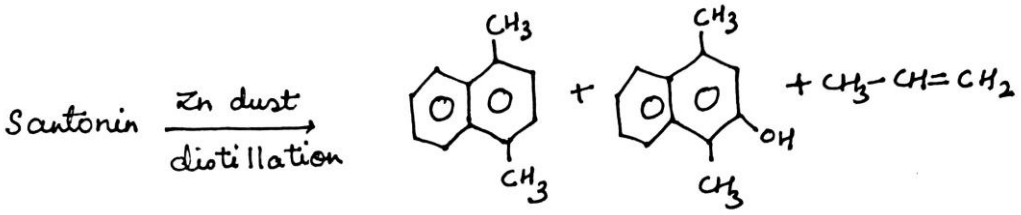
The UV spectrum of santonin reveals that the carbonyl group is present as an α,β-unsaturated ketone.

(b) Santonin is a neutral compound. It does not give positive test for hydroxyl group and carboxylic group. With sodium hydroxide it forms the sodium salt of hydroxyl acid, Santoninic acid (II), it shows that santonin is a lactone. The IR spectra of Santoninic acid reveal that it is a γ-lactone.

4. Number of double bonds: On catalytic reduction of Santonin, tetrahydro santonin(IV) is produced. This shows that santonin has two double bonds.

5.Nature of skeleton:

(a) Zn dust distillation of Santonin gives a mixture of 1,4-dimethyl naphthalene and 1,4-dimethyl naphthol which shows the presence of naphthalene skeleton in it.

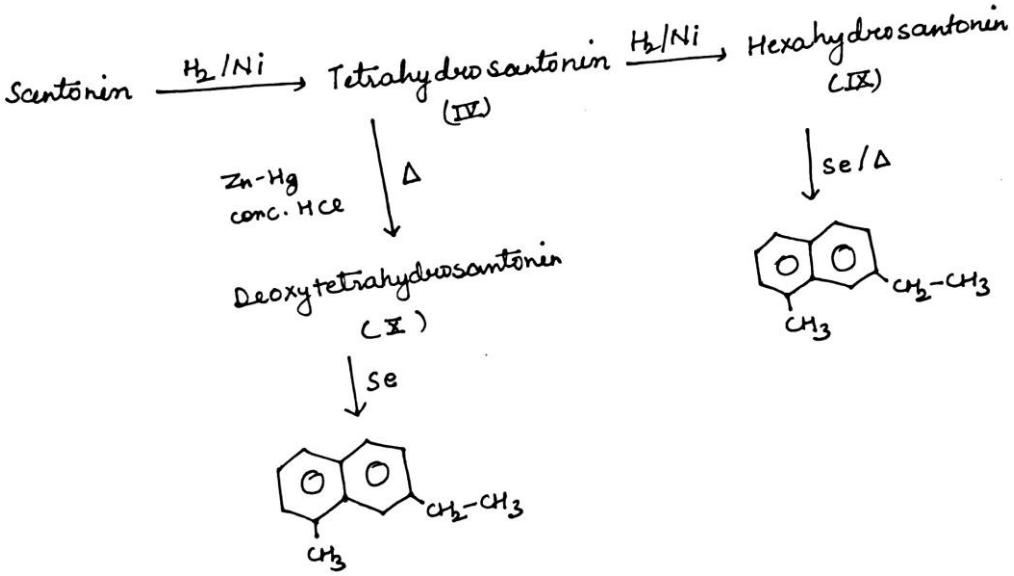


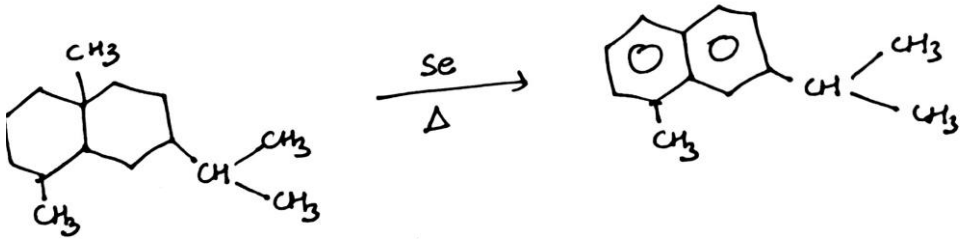
(b) Santonin oxime (III) on reduction with Zn/H2SO4 gives santoamine (V) which on further reduction with nitrous acid affords hyposantonin (VI). On oxidation with I2/CH3COOH hyposantonin gives santinic acid (VII). Santininc acid gives 7-ethyl-1methyl naphthalene when treated with $Ba(OH)_2$. Santininc acid also gives dihydrosantinic acid (VIII) when

treated with ethanolic HCl. Dihydrosantinic acid gives 7-ethyl-1-methyl naphthalene when treated with Ba(OH)2.

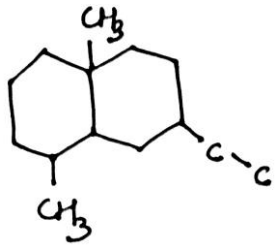
(c) Catalyticreduction of terahydrosantonin (VI) gives hexahydro derivative (IX). Clemmension reduction of tetrahydrosantonin yields deoxyterahydrosantonin (X). Hexa hydrosantonin and deoxytetrahydrasantonin on dehydrogenation with selenium gives 7-ehyl-1-methyl naphthalene.

Formation of 7-ehyl-1-methyl naphthalene shows that santonin have the eudesmane skeleton. Eudesmane is a bicyclic sesquiterpene which on dehydrogenation with selenium gives 7-isopropyl-1-methyl naphthalene. All sesquiterpenoid having eudesman skeleton gives 7-alkyl-1-methyl naphthalene on dehydrogenation with S or Se.

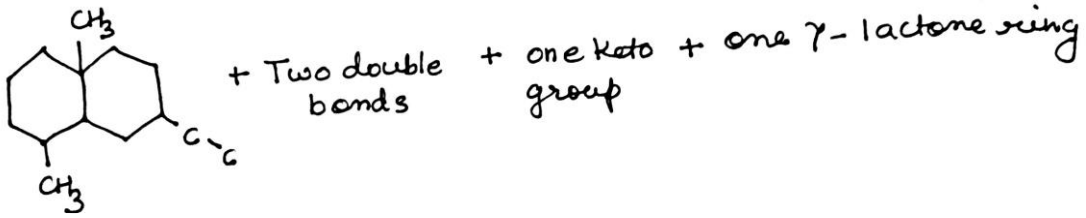




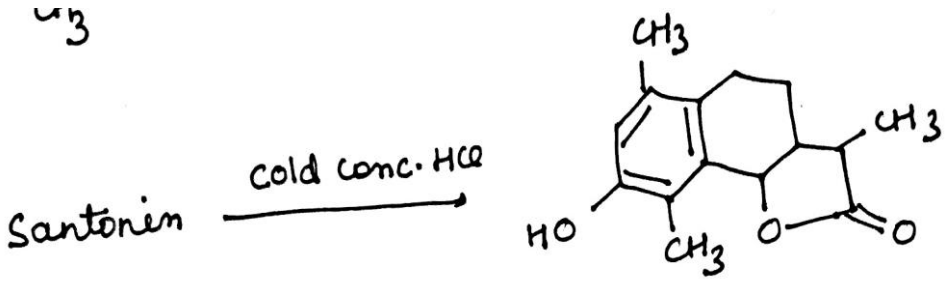
On the basis of above results the santonin should have following skeleton:



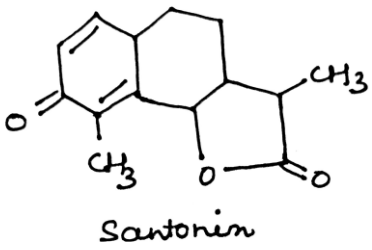
Thus, the partial structure of santonin can be drawn as follows:



1.Santonin when treated with cold concentrated hydrochloric acid it gives desmotroposantonin which is an aromatic compound formed by Dienone-phenol rearrangement of santonin.Desmotroposantonin has known structure which is confirmed by its synthesis.

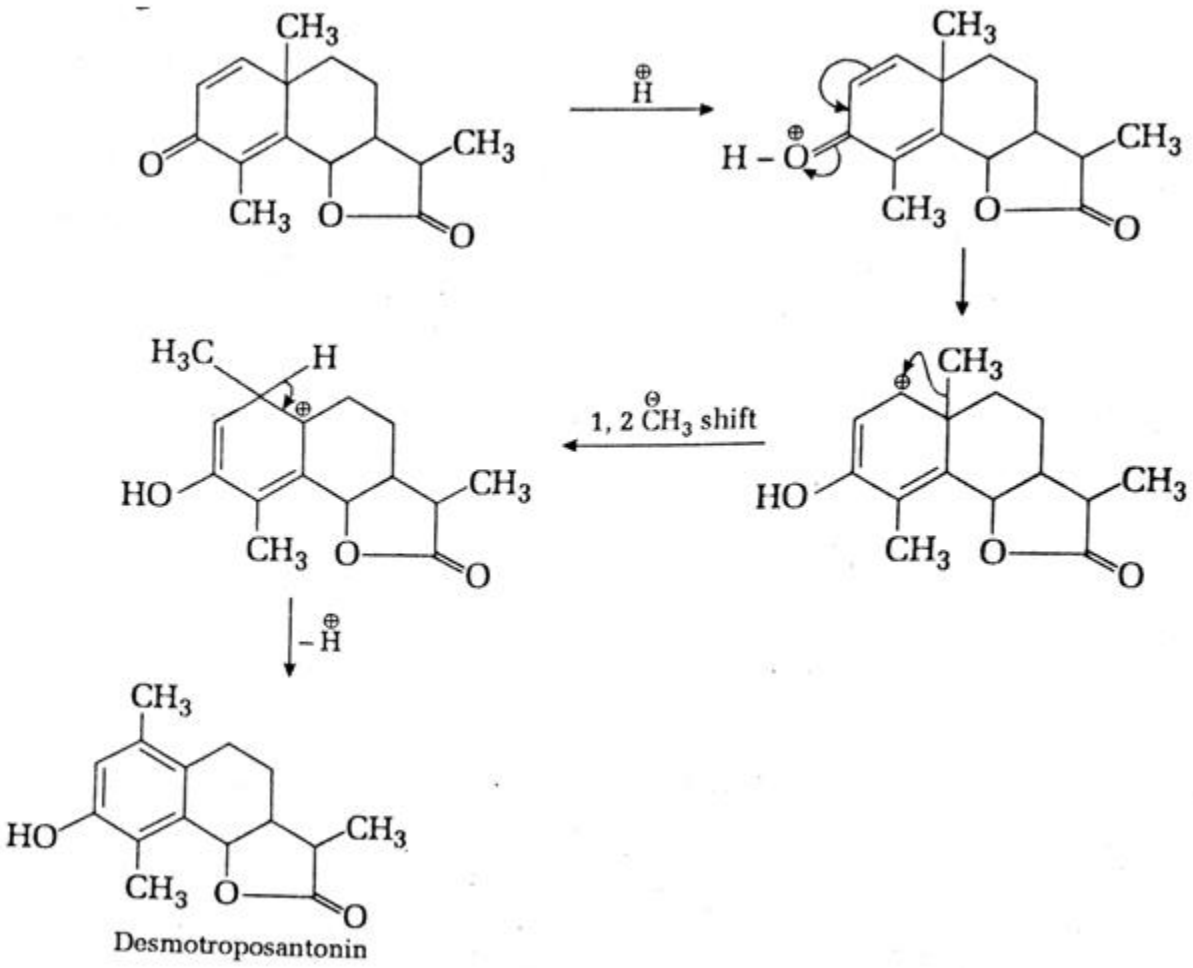


Rearrangement of santonin into desmotroposantonin can only be explain if santonin has the following structure.

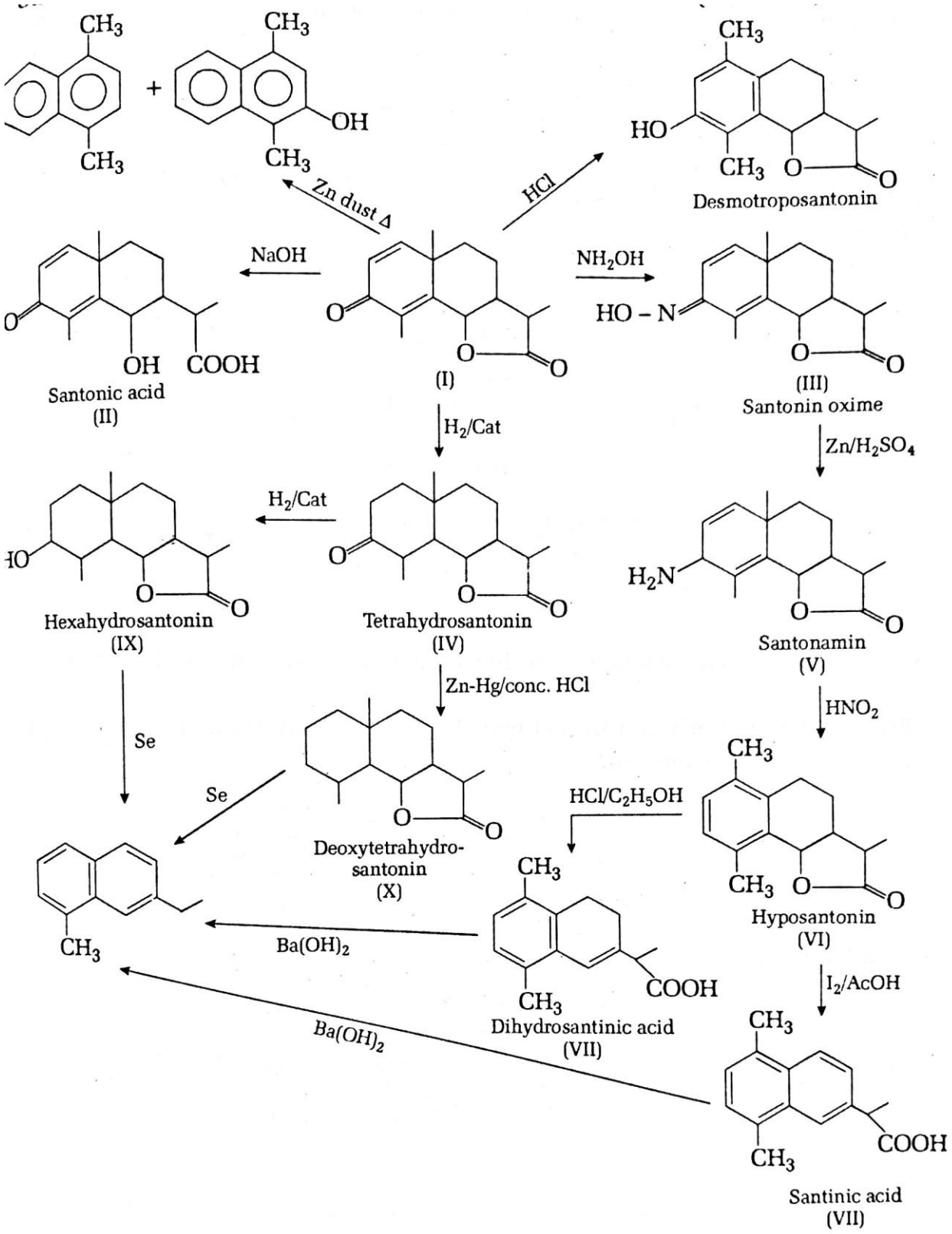


Santonin

Rearrangement of santonin into desmotroposantonin

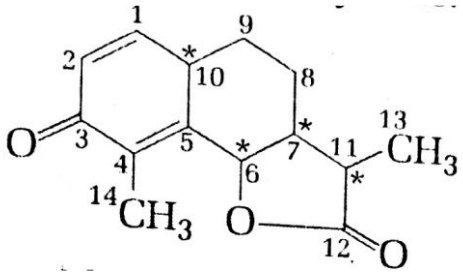


Structure of Santonin explains all the reactions of santonin.



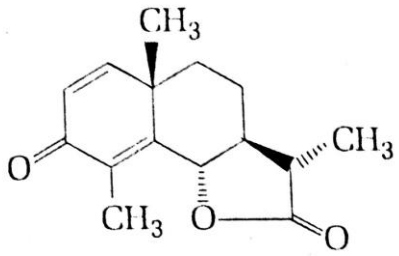
1.9.2 Stereochemistry of Santonin

The four chiral centres of santonin are denoted by stars.

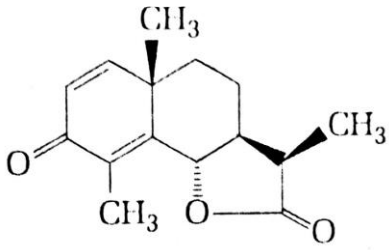


Thus, eight recemates with the santonin structure are feasible. Out of these racemates α and β santonins occurs in nature.

The absolute configuration of α and β- santonins are as follows:



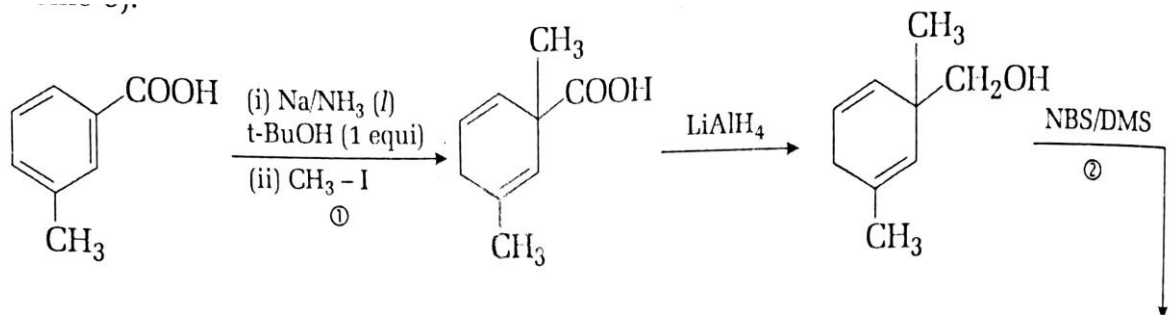
(–) 6α, 11βH-3-oxo-1, 4-endesmadiene-12, 6-olid
(α-Santonin)

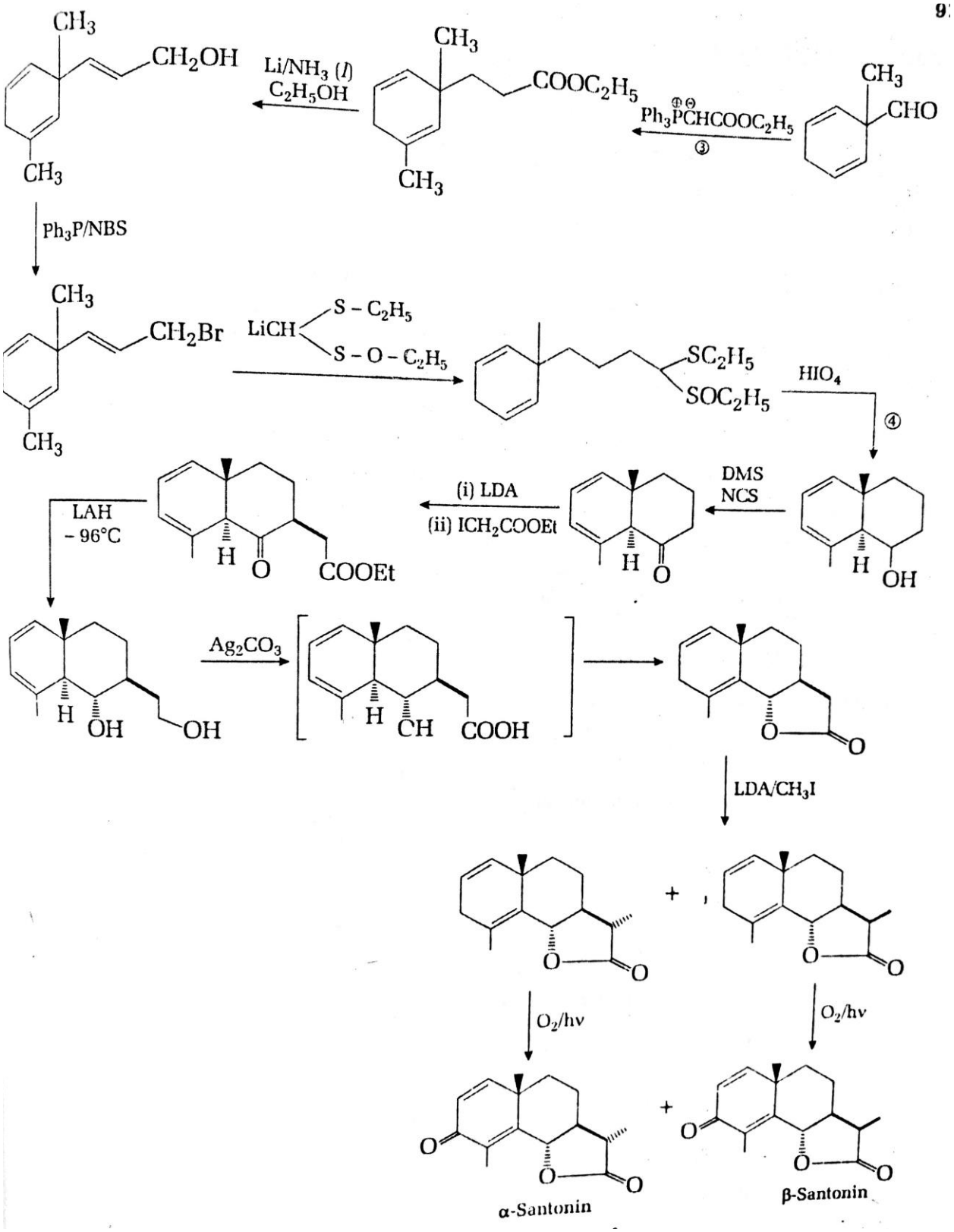


(–) 6α, 11αH-3-oxo-1, 4-endesmadiene-12, 6-olid
(β-santonin)

α and β- santonins are epimer at C-11 position. α -santonin has (S) configuration at C-11 and β-santonin has (R) configuration.

Synthesis of Santonin.

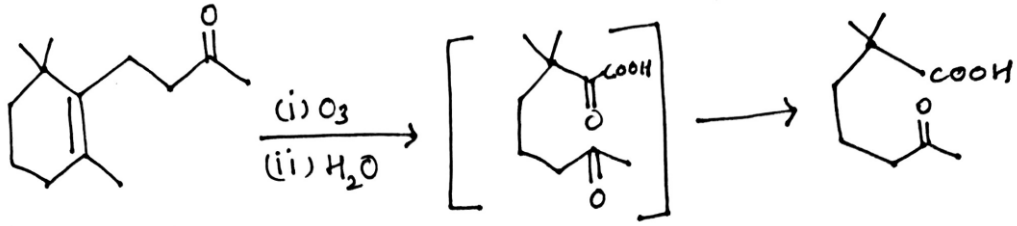



CH3
CH2OH
Li/NH3 (l)
C2H5OH
CH3
COOC2H5
CH3
Ph3PCHCOOC2H5
③
CH3
CHO
Ph3P/NBS
CH3
CH2Br
CH3
LiCH
S – C2H5
S – O – C2H5
SC2H5
SOC2H5
HIO4
④
LAH
– 96°C
H
O
COOEt
(i) LDA
(ii) ICH2COOEt
H
O
DMS
NCS
H
OH
H
OH
OH
Ag2CO3
H
CH
COOH
O
O
LDA/CH3I
O
O
O
O
O2/hv
O2/hv
O
O
O
O
α-Santonin
O
O
O
O
β-Santonin

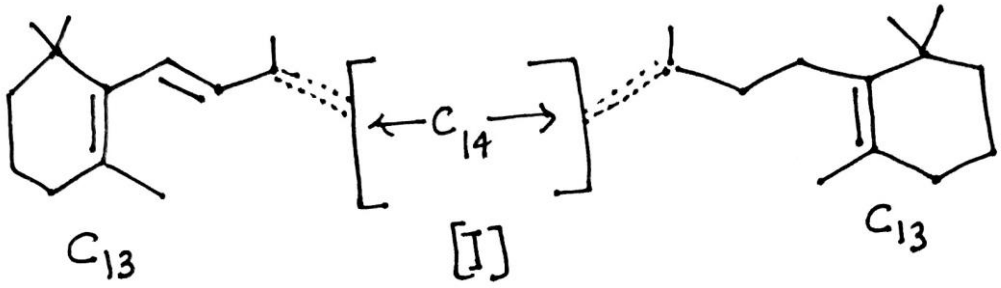
1.10 β *– CAROTENE:*

1.10.1 Constitution of Santonin

1. The molecular formula of β- carotene is $C_{40}H_{56}$.
2. β- carotene on catalytic hydrogenation gives perhydrocarotene, $C_{40}H_{78}$. This shows that β-carotene contains eleven double bonds. The chemical formula of perhydrocarotene, corresponds to C_nH_{2n-2}, indicates that -carotene has two rings.
3. A Diels- Alder adduct is formed when one mole of β- carotene reacts with five moles of maleic anhydride. This adduct formation shows that the ten double bonds in β- carotene are conjugated double bonds.
4. β- carotene easily oxidizes in the presence of oxygen, with the appearance of violet colour. This color is the characteristic of β-ionone which shows that β-ionone unit is present in β-carotene. Benzene solution of β- carotene on oxidation with cold aqueous potassium permanganate gives β-ionone.
   On ozonolysis β-ionone gives geronic acid as one of the products.



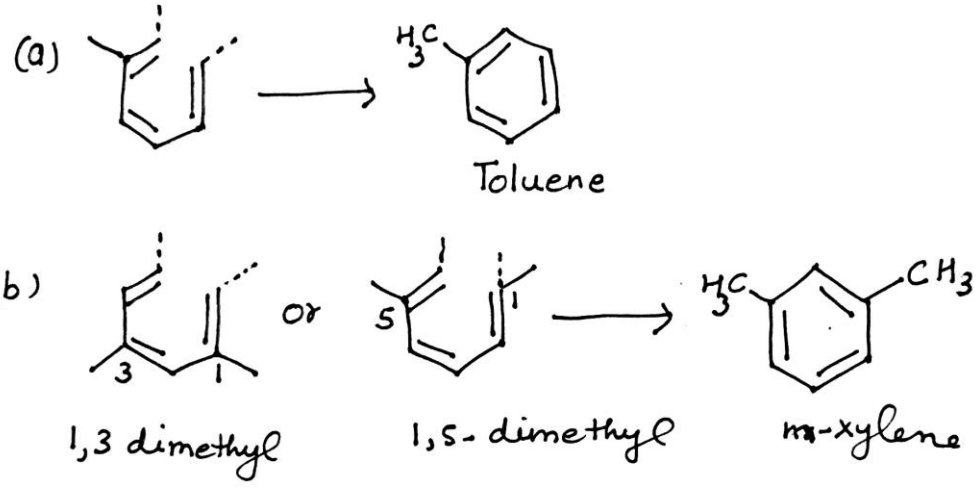
   On ozonolysis one mole of β- carotene gives two mole of geronic acid. This reaction indicates that β- carotene contains two β-ionone residues.
   Thus partial structure of β- carotene can be drawn as follows:



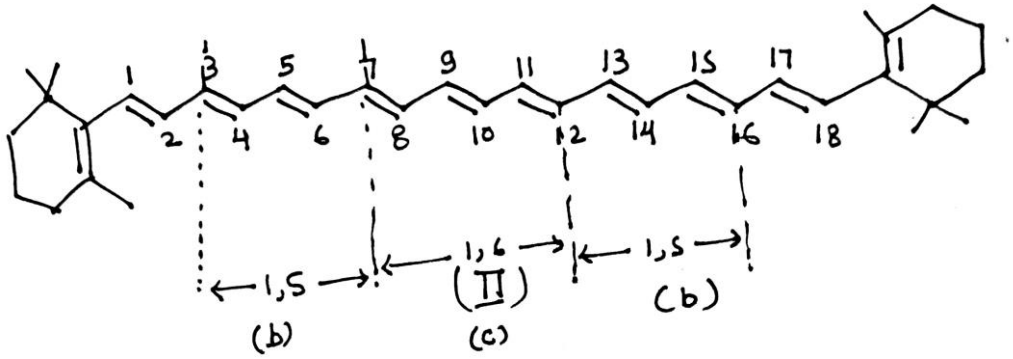
   β- carotene forms a Diels-Alder adduct with 5 moles of maleic anhydride which confirms the presence of conjugation at central portion i.e. C14.
5. Kuhn- Roth methyl side-chain determination- one mole of β- carotene on oxidation with chromic acid gives 5.4 moles of acetic acid. This indicates that there are six

–C(CH3)=CH- groups in the β- carotene. Formation of six moles of acetic acid accounts for two –C(CH3)=CH- groups on the two β-ionone rings and remaining four from the central parts between the two β-ionone rings.

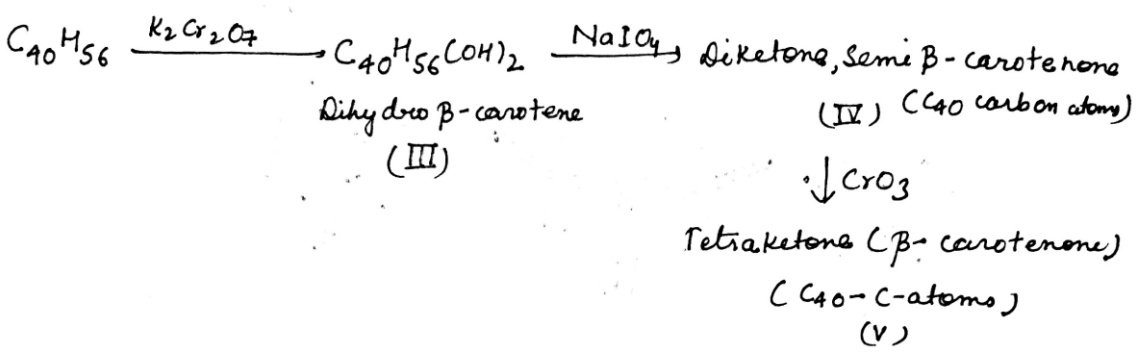
6. Structure of C14 portion of β- carotene:
   On distillation β- carotene gives toluene, *m*-xylene and 2, 6-dimethyl naphthalene.
   the formation of these products can be explained by the cyclisation of fragments of the conjugated chain without taking into consideration the beta ionone moiety in the partial symmetrical structure (I) for β- carotene.



The following symmetrical structure (II) of β- carotene would satisfy the requirements of a, b and c.



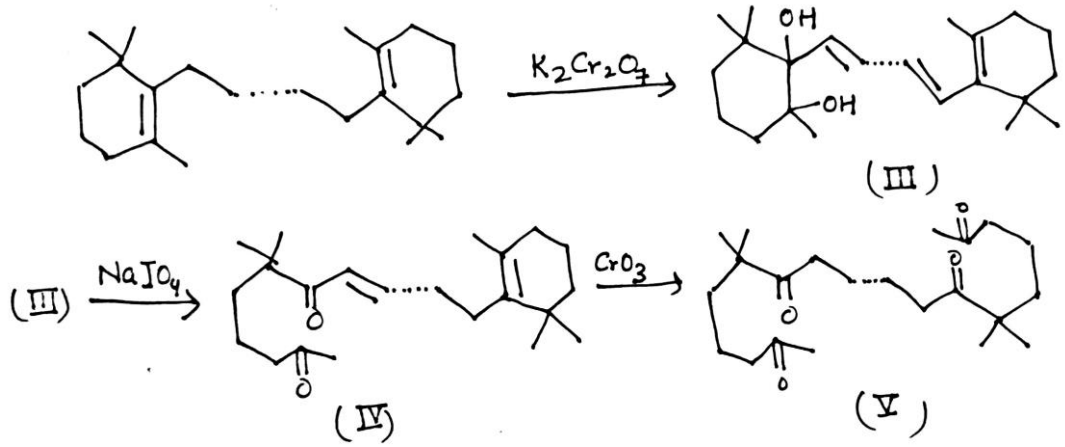
7. Symmetrical structure of β- carotene: It is supported by the following oxidative degradation:



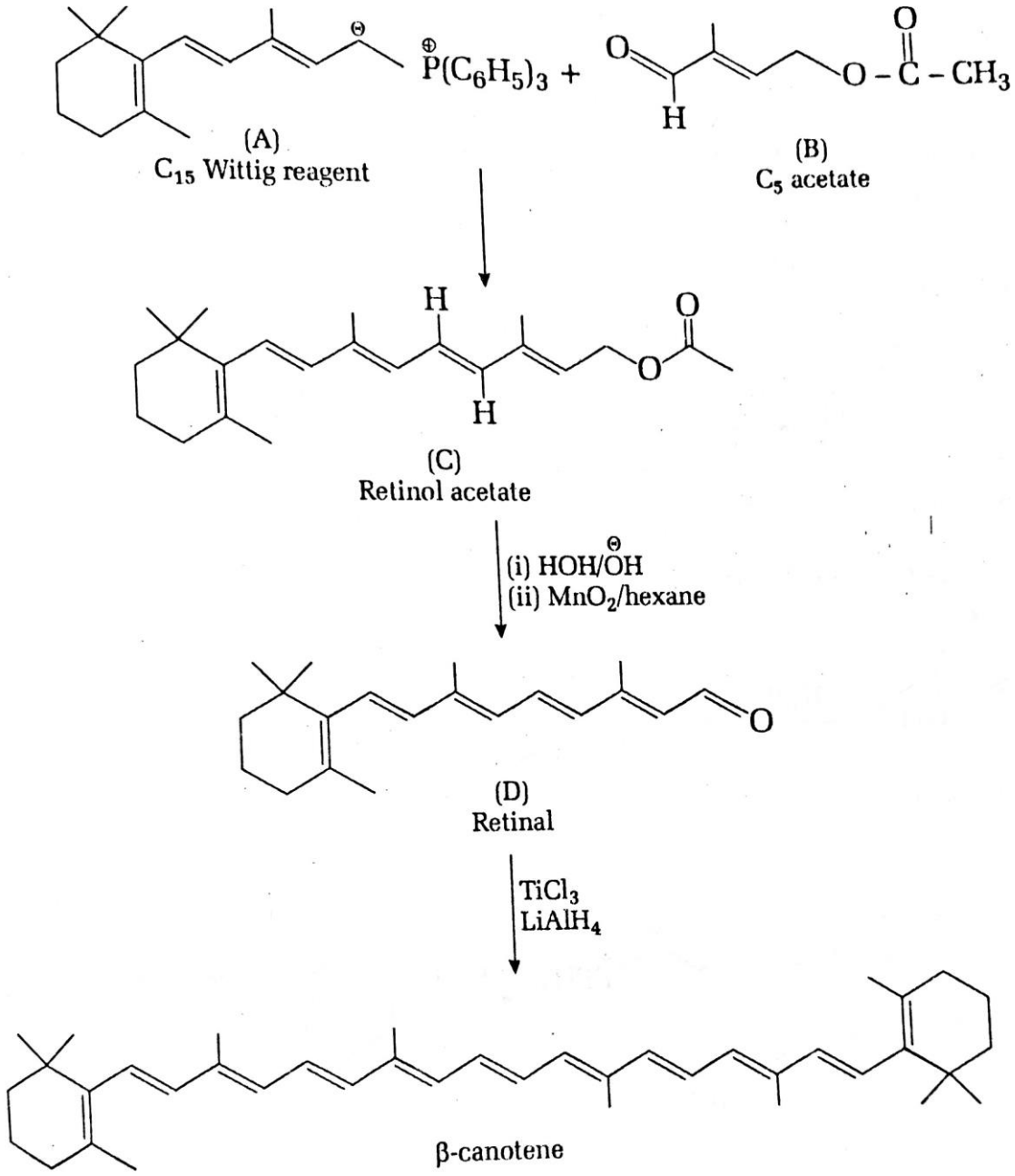
The number of carbon atoms in β- carotene, dihydroxy- β- carotene (III) and semi- β- carotenone (IV) is same which indicates that one of the double bond of β-ionone ring has been oxidized.

Oxidation of semi- β- carotenone (IV) with chromium trioxide form a tetraketon having 40 carbon atoms. This shows opening of second β-ionone ring of β- carotene.

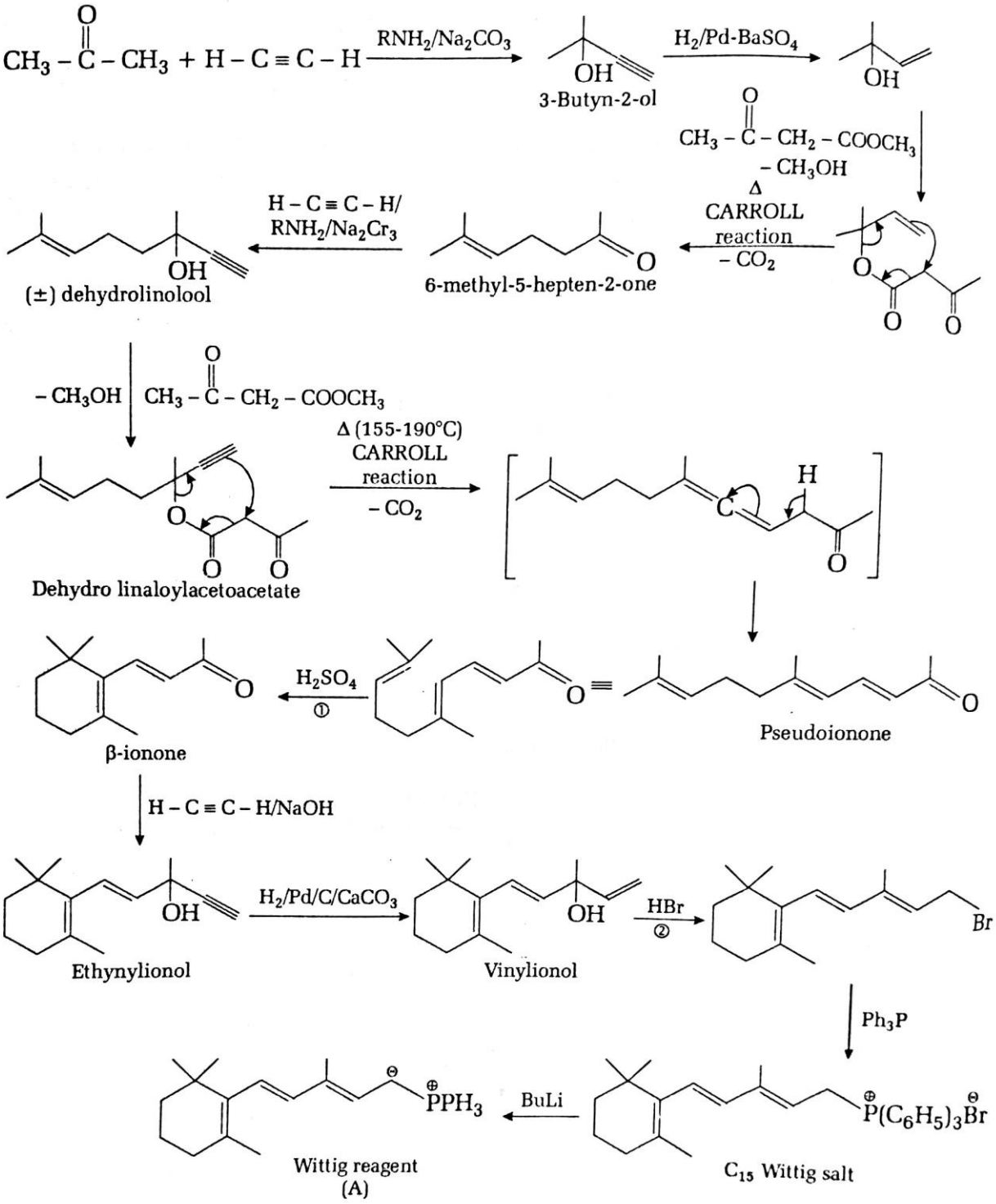
The oxidation product of this reaction are dihydroxy- β- carotene and semi carotene only. These experimental results show that β- carotene has symmetrical structure. Therefore the oxidation may be formulated as follows:



8. Structure of β- carotene has been finally confirmed by its synthesis: β- carotene is synthesized from C15 Wittig reagent (A) and C5 acetate (B). Reaction of these two gives retinol acetate (C), which on hydrolysis gives retinol. Retinol on futher oxidation with MnO2 gives retinal (D). An intermolecular McMurry deoxygenative coupling of retinal finally gives β- carotene.


P(C6H5)3 +
O – C – CH3
(A)
C15 Wittig reagent
(B)
C5 acetate
(C)
Retinol acetate
(i) HOH/OH
(ii) MnO2/hexane
(D)
Retinal
TiCl3
LiAlH4
β-canotene

C_{15} Wittig reagent is prepared as follows :



1.11 SUMMARY:

The terpenoids, also known as isoprenoid, are a large and diverse class of naturally occurring organic chemicals derived from the 5- carbon compound isoprene, and isoprene polymers. All the terpenoids gives isoprene as one of the products on the thermal decomposition. The general formula of terpenoids is $(C_5H_8)_n$.

The essential oils isolated from plants contain several terpenoids and these are separated by various physical and chemical methods. Menthol is terpenoid also called peppermint camphor. It is obtained from peppermint oil.Menthol is an optically active compound. It is used in ointments; cough drops and nasal inhalers. Menthol has three chiral centers at position C_1,C_3 and C_4. Thus its eight ($=2^3$) optically active forms (four racemic modifications) are possible theoretically, which all are known. Santonin is a terpenoid extracted from various species of *Artemesia* which is widely used in medicine as an anthelmintic. The molecule has the chemical formula $C_{15}H_{18}O_3$. β- carotene is terpenoid compound with molecular formula $C_{40}H_{56}$.Terepenoids are widely used in medicines, food and flavors.

1.12 TERMINAL QUESTIONS

1. What are terpenoids? Classify them on the basis of their isoprene units.
2. What is Isoprene rule?
3. Write about Isolation methods of terpenoids.
4. Write short note on the separation of terpenoids from essential oils.
5. Give the general methods of structural determination of terpenoids.
6. Give structural determination of the Menthol.
7. Write note on the synthesis and stereochemistry of snatonin.
8. Give structural determination of the β- carotene.

1.13 REFERENCES

1. G R Chatwal, *Organic chemistry of natural products*. Vol.-2 , Himalaya Publishing House.
2. Singh J, Ali S M, Singh J, *Natural Product Chemistry.* A Pragati Edition.

UNIT:2ALKALOIDS

Content:

2.1 Objectives

2.2 Introduction

2.3 Occurrence of alkaloids

2.4 Function of alkaloids

2.5 Properties of alkaloids

2.6 Medicinal use of alkaloids

2.7 Nomenclature of alkaloids

2.8 Classification of alkaloids

2.9 Isolation of alkaloids

2.10 General method of structure elucidation

2.11 Morphine

2.12 Reserpine

2.13 Summary

2.14 Terminal questions

2.15 References

2.1 OBJECTIVES

1. To describe classification and isolation of alkaloids.
2. To explain nomenclature.
3. To explain properties and medicinal use of alkaloids.
4. To illustrate general method of structural determination.
5. Introduction, synthesis of Morphine.
6. Introduction, synthesis of reserpine.

2.2 INTRODUCTION

Definition:

In 1819 W. Meissner firstly introduced the term "*alkaloids"*. According to him, "*Alkaloids were basic nitrogen containing compounds isolated from plant*."

In 1880 Konigs defined alkaloids as follows:"*Alkaloids are naturally occurring organic bases which contain a pyridine ring"*

Above definition was again modified by Ladenburg. "*According to him Alkaloids are natural plant compounds that have a basic character and contain at least one nitrogen atom in a heterocyclic ring."*

Again, the above definition is not complete because it excludes many synthetic compounds and many compounds obtained from animal source.

With the discovery of more alkaloids two more characteristics were identified. These characteristics are:

(i) Complex molecular structure

(ii) Significant pharmacological activity

So, Alkaloids were further defined as:*"basic nitrogenous plant products, mostly optically active and possessing nitrogen heterocycles as their structural units, with a pronounced physiological action."*

The above definition must be taken in consideration carefully because some compounds which are alkaloids do not limit to this definition, while other compounds which are not alkaloid limitto this definition. Forexample:

(i) *Colchicine*- It is considered as an alkaloid even though it is not heterocyclic and hardly basic. It is pharmacologically active and is of restricted botanical distribution.

(ii) *Thiamine*- Even though it is heterocyclic nitrogenous base, it is not considered as an alkaloid because it is universally distributed in living matter.

(iii) The heterocyclic rings of compounds like *ephedrine, hordenine, betaines, choline, muscarine, stachydrine* and *tryptamine* do not contain nitrogen, yet they are classified as an alkaloid or protoalkaloids.

(iv) Naturally occurring open chain bases like *cholines, amino acids* and *phenylethylamine* have marked physiological activity, even then they are not placed in the class of alkaloids.

(v) A compound like *caffeine* which fully satisfies the definition of alkaloids is not included in alkaloids.

(vi) *Piperine* is considered as an alkaloid despite of being having no basic nature and any physiological activity.

So, from the above discussion it could be concluded that it is difficult to define alkaloids due to great diversity and complexity, in the chemical structure of alkaloids.

2.3 OCCURRENCE OF ALKALOIDS

About 20,000 alkaloids are known, most being isolated from plants. They are found in abundance in higher plants families (particularly dicotyledons) but less frequently in lower plants and fungi. Alkaloids have also been found in microorganism, marine organisms such as algae, dinoflagellate and terrestrial animals such as insects, salamanders and toads. Alkaloids occurs in following forms:
(1) Free bases- e.g., narceine, nicotine etc.

(2) Salts with organic acids-Due to basic nature of alkaloids they form salts with organic acids like acetic, oxalic, citric, malic, lactic, tartaric, tannic, aconitic acids etc.

(3) Glycosidal form- Some alkaloids also occur as glycoside of sugar like glucose, rhamnose and galactose e.g., alkaloids of *Solanum* and *Veratrum* group.

(4) As amides of organic acids– e.g., piperine

(5) As ester of organic acids- e.g., atropine, cocaine

(6) Salts of the same acid-e.g, cinchona alkaloids with quininic acid, aconite alkaloids with aconitic acid and opium alkaloids with neconic acid.

Season, age and plant location are the factors which affects the concentration of alkaloids in plants. Closely related alkaloids generally occur together in the same plant. Similarities in structure have been found in different genera of the same family. For example, hyoscyamine is recorded in seven different genera of the family *Solanaceae*. It is investigated that simple alkaloids are often found in different plants whereas the complex alkaloids in one species or genus of a family.

2.4 FUNCTION OF ALKALOIDS

The purpose of existence of alkaloids in plant i.e. their functions in plants is not clearly understood. There are various views by different authorities, such as they are of no importance and may be regarded as byproducts of plant metabolism. They may act as reservoirs for protein synthesis. They may be used as reserve substance to supply nitrogen. They may act as protective substances against the animal or insect attacks. Like hormones, they may function as plant stimulants or regulators in activities like growth, metabolism and reproduction. Or they may function as detoxicating agents by methylating, condensing, and cyclizing the compounds whose accumulation might otherwise cause damage to the plant.

It is observed that about 85 t0 95 percent plants perform their normal activities without involving alkaloids. Thus, significant function of the alkaloids within the plants still under investigation.

2.5 PROPERTIES OF ALKALOIDS

Alkaloids are generally crystalline in nature but few amorphous alkaloids (e.g., emetine) and liquid alkaloids (e.g., coniine and nicotine)are also found. Most of the alkaloids are colourless some are coloured for e.g., Colchicineberberine is yellow. Betanidine is orange while the salts of

sanguinarine is copper red in colour.The free bases (i.e. alkaloids themselves) are insoluble in water but soluble in most of the organic solvents. Caffeine, ephedrine, codeine, colchicine, pilocarpine is exceptionally soluble in water and morphine, theobromine and theophylline are soluble in organic solvents.

Most of the alkaloids are levorotatory (optically active), although a few are dextrorotatory (e.g. coniine), while a few are even optically inactive, viz. papaverine. Generally, the alkaloids are bitter in taste and have pronounced physiological activity.

2.6 MEDICINAL USE OF ALKALOIDS

Alkaloids are used as anti-inflammatory, anticancer, analgesic, anesthetic, antimicrobial, antifungal etc. activities. Morphine is an important Alkaloid that is also used to relieve pain. It has also a disadvantage as it is an addictive drug.

Methyl ether is the derivative of morphine possesses an excellent analgesic activity and is known as relatively non-addictive. These alkaloids also act as respiratory and cardiac stimulants.

Tubocurarine is an alkaloid that is the ingredient of poison curare. It is also used in surgery as a muscle relaxant. Chemotherapeutic agents Alkaloids vincristine and vinblastine are used in the treatment of many cancer types. An alkaloid present in Erythroxylum coca, which is a potent local anesthetic is Cocaine.

Ergonovine is an alkaloid made from fungus Claviceps Purpurea. The Ephedra derived ephedrine is used as a vessel constrictor along with the Ergonovine. Ephedrine is also used in bronchial asthma. It is also used to relieve the discomfort of hay fever and sinusitis.

Quinine is also a powerful antimalarial agent. However, it can be replaced by synthetic drugs. It is very effective and less toxic. Quinidine is another alkaloid of Cinchona species. It has numerous medical applications in the treatment of irregular rhythms of the heartbeat which is also known as arrhythmias.

Colchicine is also an alkaloid of the Liliaceae family. It is known for the ages to treat acute gout attacks. Lobeline is another alkaloid. It is isolated from the Lobelia inflata. Which has multiple action mechanisms.

2.7 NOMENCLATURE OF ALKALOIDS

There is no defined nomenclature is designed for alkaloids due to complexity of its molecular structure. Though various methods are used to name alkaloids are as follows:

(i) Plants from which they are obtained- e.g., *papaverive*from *Papaver Someniferum* and *berberine* from *Berberis Vulgaris L*.

(ii) According to their physiological action- e.g., morphine- (Ger, morphine-God of dreams), narcotine(Greek-*narkoo*- to be numb), emetine (Greek- *emetikos*- to vomit).

(iii) After the name of discoverer- e.g., *pelletierine group* (Discoverer- P.J. Pelletier)

(iv) Minor alkaloids have been named by adding one prefix or suffix to the name of principal alkaloids. E.g., cinchona series.

(v) Prefixes such as *epi, iso, neo, pseudo* etc. have been used to designate isomeric or slightly modified structures.

(vi) The prefix *nor* is used to denote the structure which do not have a methyl group attached to the nitrogen atom.

2.8 CLASSIFICATION OF ALKALOIDS

Alkaloids can be classified as follows:

i)Based on their taxonomy: Alkaloids can be classified based on their biological source from which they are obtained. These may be described as *solanaceous* or *Papilionaceous* families without giving reference to the type of alkaloid present. Because both families contain several types of alkaloids so, it is not justified to classify them this way.

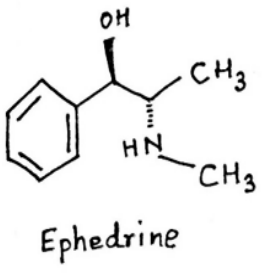
ii) Based on their pharmacological action:Alkaloids are known for their wide range of pharmacological activity like adrenergic, antibiotics, poisons, stimulants, diuretics, astringents, anti-inflammatory, anti-hypertensives, anti-mydriatics, analgesics, anti-gout, expectorant, emetic, anti-spasmodic and many others.Sometimes, structurally diverse molecules may show similar pharmacological actions while in few cases the activity might be identical for specific structure. So, it is very difficult to classify them on the sole basis of

pharmacological action.

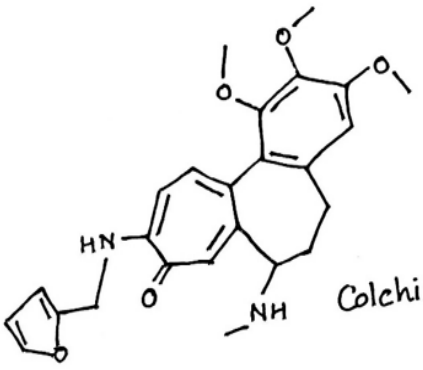
iii)Based on their biosynthesis: It is based on the type of starting material or precursor or building block compounds used by the plants to synthesize the complex structure. For e.g., number of complex indole alkaloids are known which are derived from amino acid tryptophan and mevalonic acid (Ergot and Cinchona alkaloids). Morphine, papaverine, narcotine, tubocurarine and colchicine have been derived from phenylalanine tyrosine bases. The disadvantage of this method is that it not always easy to set a relationship of alkaloids to each other and to their precursors.

iv) Alkaloids are broadly classified into two classes depending upon whether the nitrogen is a part of a ring or not.

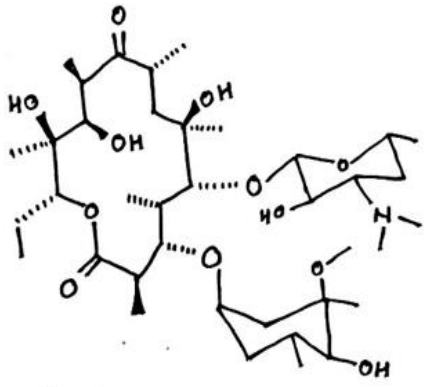
(a)Non-heterocyclic alkaloid or Atypical alkaloid- These alkaloids have nitrogen atoms which is not a part of any ring system. These are also known as protoalkaloids. E.g., ephedrine, colchicine, erythromycin, and taxol etc.



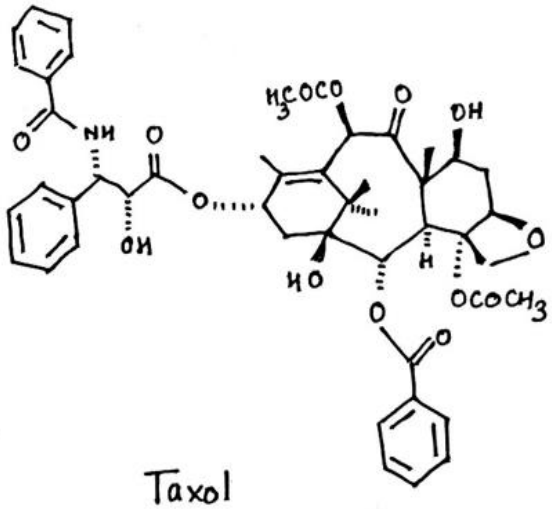
Ephedrine



Colchicine



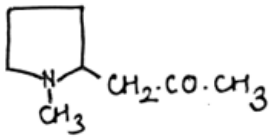
Erythromycin



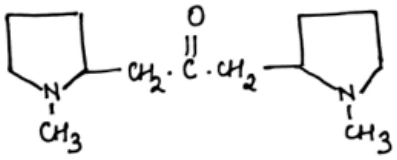
Taxol

(b)Heterocyclic alkaloids or Typical alkaloids:These alkaloids have nitrogen as part of their heterocyclic ring. They are of following types:

(i)Pyrollidine alkaloids:E.g., Hygrine,Cuscohygrine

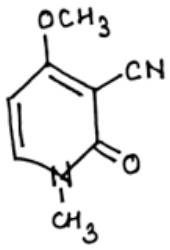


Hygrine

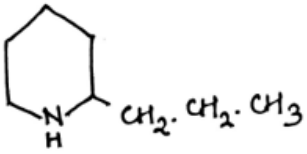


Cuscohygrine

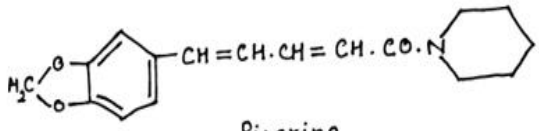
(ii)Pyridine or piperidine alkaloids: Example: Ricinine, coniine, piperine, pelletierine,isopelletierine,pseudopelletierine



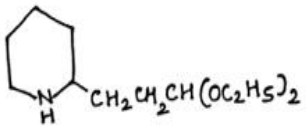
Ricinine



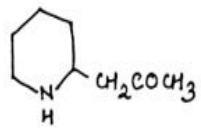
Coniine



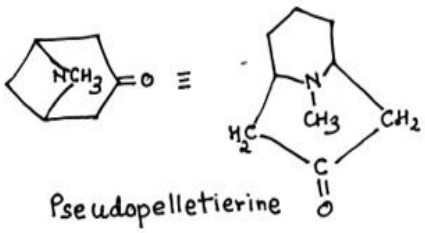
Piperine



Pelletierine acetal

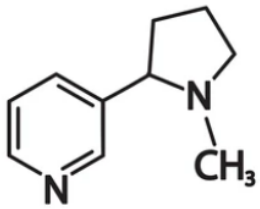


Isopelletierine

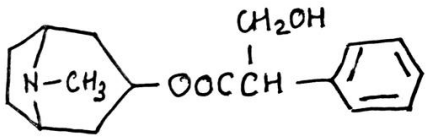


Pseudopelletierine

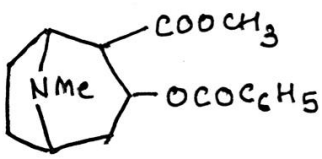
(iii)Pyridine-pyrrolidine alkaloids: E.g., Nicotine



(iv)Tropane alkaloids: E.g., Atropine, cocaine

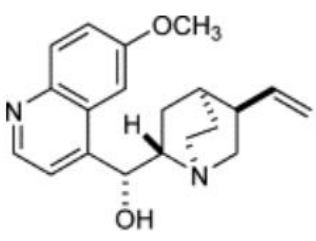


Atropine

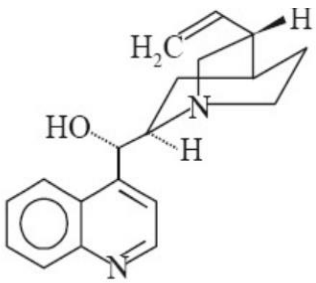


Cocaine

(v)Quinoline alkaloids: Quinine, cinchonine

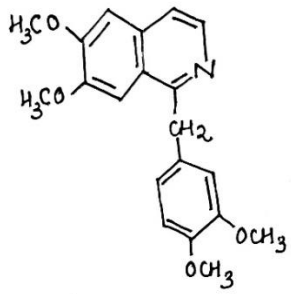


Quinine

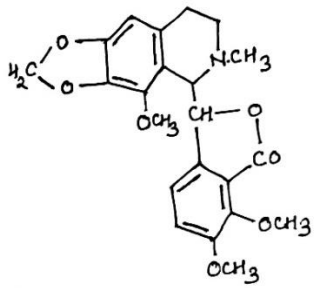


Cinchonine

(vi)Isoquinoline alkaloids: Papaverine,Narcotine, berberine, emetine

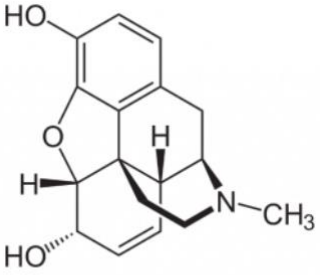


Papaverine



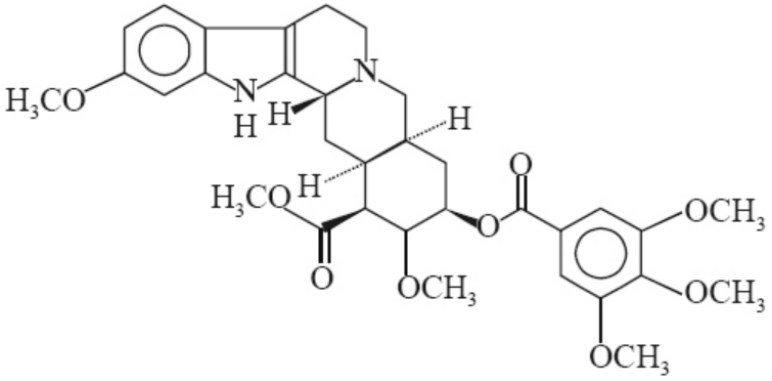
Narcotine

(vii)Phenanthrene alkaloids: morphine



Morphine

(viii)Indole alkaloids: reserpine



Reserpine

2.9 ISOLATION OF ALKALOIDS

Extraction and purification of alkaloid is a tedious process because alkaloids obtained from plants is a complex mixture of alkaloids along with presence of other compounds like glycosides, organic acids etc. So, these complex mixtures make the process harder to separate these compounds individually.

Some of the isolation principle for alkaloids are as follows:

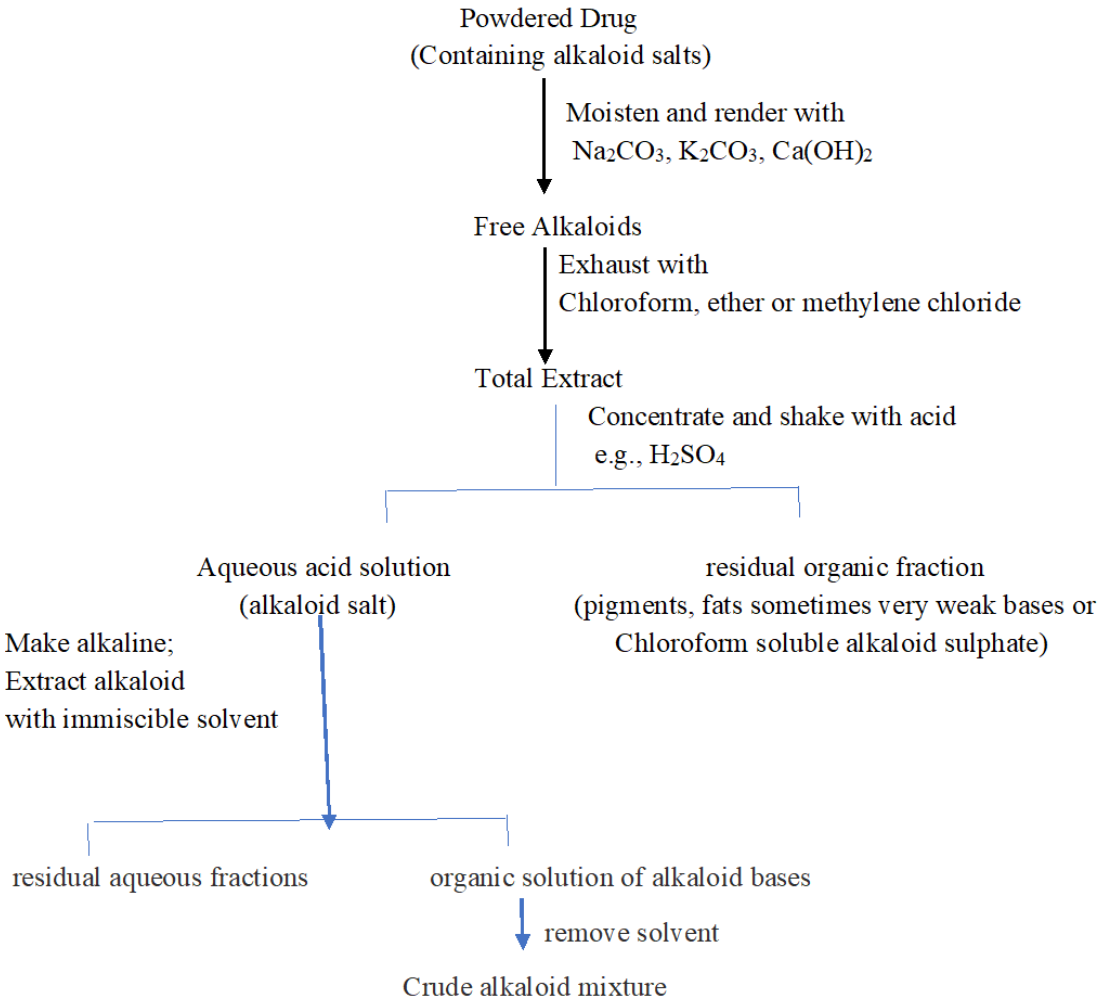
(i) Detection of alkaloids: Firstly,various reagents are used to detect the presence of alkaloids in plants, these are known as alkaloidal reagents. Some of the alkaloidal reagents are Mayer's reagent (potassium mercuric iodide), Dragendorff's reagent (potassium bismuth iodide), Wegner's reagent (iodine dissolved in potassium iodide), Hager's reagent (saturated solution of picric acid in water), chloroplatinic (H_2PtCl_6), chloroauric ($HAuCl_4$), phosphotungustic and molybdic acids, Marquis reagent, nitric acid etc. The precipitates of these reagent have characteristic colours used for detection of alkaloid in small amounts.

(ii) Separation of alkaloids from plant material:The general method of extraction of alkaloids from the plant source depends upon the purpose and scale of operation and also on the quantum and bulk of the raw material to be employed in the process.

(iii) Final step involves the separation and purification of individual alkaloids from the crude extract.

For isolation of small quantity of alkaloids, one can use chromatography method, which is good for research purpose.For large scale production following three methods can be used:

Method 1: This method is use water immiscible solvents such as chloroform, ether and methylene chloride for extraction.



Method 2- Inthis method powdered drug is treated with water- miscible solvents like methanol, ethanol or isopropanol and obtained extract is subjected to the same process as in method 1.

Method 3- This method uses acidulated water or alcohol for the extraction of powdered drug. Pigments and other unwanted materials are removed from the initial extract by shaking with chloroform or another suitable reagent. Further aqueous fraction is treated with excess of alkali to precipitate out the free alkaloids. Then free alkaloids are separated by filtration or with an immiscible solvent.

2.10 GENERAL METHOD OF STRUCTURE ELUCIDATION

(i)Molecular formula-Empirical formula of pure specimen is determined by combustion

analysis. Further its molecular weight is determined by the Rast procedure to establish its molecular formula. Double bond equivalent's is calculated to know the number of double bonds, triple bonds and ring in the molecular formula.A double bond and ring in a moleculeremove 2 H atoms relative to the corresponding saturated aliphatic hydrocarbons and is said to be a site of unsaturation (or degree of unsaturation). A triple bond removes 4 H atoms and constitutes 2 sites of unsaturation. For example: hexene(C_6H_{12}) has 2 H atoms less than hexane(C_6H_{14}) this difference is Double bond equivalents. For complex formula like $C_aH_bN_cO_d$the double bond equivalent is calculated as follows:

$$a-b/2 + c/2 + 1$$

For e.g., The DEB for Hygrine, molecular formula- $C_8H_{15}NO$ is

8- 15/2 + ½ + 1 = 2

Experimentally, hygrine was found to have only one carbonyl group, none of any other unsaturation. Thus, hygrine must be monocyclic.

(ii)Functional group analysis: If the alkaloid is available in good amount functional groups can be identified by using classical technique of organic analysis. The other popular method is infrared spectroscopy used to identify the functional groups.

(iii)Functional nature of oxygen:Various oxygen containing alkaloids are known. Oxygen in alkaloids may be present like Phenolic or alcoholic(-OH), methoxy (-OCH_3), acetoxyl (-$OCOCH_3$),benzoxyl(-$OCOC_6H_5$), carbonylgroups (>C=O) or lactone rings. These functional group can be analysedas follows:

(a) Hydroxyl Group: Alkaloid having hydroxyl group form acetate on treatment with acetic anhydride or acetal chloride and benzoate on treatment with benzyol chloride with NaOH.

$$R-OH + (CH_3CO)_2O \longrightarrow ROOCCH_3 + CH_3COOH$$

$$R-OH + CH_3COCl \longrightarrow ROOCCH_3 + HCl$$

$$R-OH + C_6H_5COCl \longrightarrow ROOCC_6H_5 + HCl$$

In this method number of hydroxyl groups is determined by acetylating the alkaloid then by treating acetyl derivative with a known volume of NaOH.

$$R\text{-}OH \xrightarrow{CH_3COCl} R\text{-}OCOCH_3 \xrightarrow{NaOH} R\text{-}OH + CH_3COONa$$

The excess of alkali is estimated by titration with a standard solution of HCl acid. The number of acetyl or hydroxyl groups can be calculated from the volume of alkali used for hydrolysis. Above test with acetic anhydride or acetal chloride andbenzoate are also given by the primary amines if present in alkaloids yield acetal and benzoyl derivatives. Further the number of hydroxyl group is determined by acetylation or Zerewitnoff's method. Here, the hydroxyl group can be detected by treatment with methylmagnesium iodide.

$$-OH + MeMgI \longrightarrow -O\text{-}MgI + CH_4$$
$$>N\text{-}H + MeMgI \longrightarrow >N\text{-}MgI + CH_4$$

By the estimation of CH_4 volumetrically, number of -OH and >NH can be identified.

(b)Phenolic hydroxyl group or alcoholic hydroxylic group: If alkaloid is phenolic, it can be confirmed by performing following tests:

(i) It is soluble in sodium hydroxide
(ii) It is reprecipitate by carbon dioxide and
(iii) It gives coloration (purple) with ferric chloride.

If the alkaloid does not give any positive result to the above tests of phenol, the hydroxyl group may be considered as an alcoholic. Further alcoholic alkaloids can be confirmed by dehydrating agents like sulphuric acid or phosphorus acid as alcoholic groups are readily dehydrated by them.

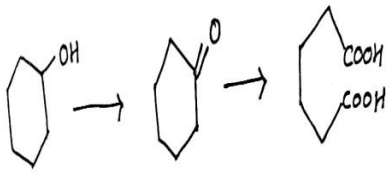
Nature of alcoholic group i.e., primary, secondary or tertiary is determined as follows:

Primary alcoholic group ($-CH_2OH$) on oxidation yields first aldehyde then acid having same number of carbon atoms as the parent alcohol.

$$-CH_2OH \longrightarrow -CHO \longrightarrow -COOH$$

On oxidation, secondary alcohol first yields ketone having the same number of carbon atoms and then acid having the lesser number of carbon atoms. If the secondary alcoholic group is attached to cyclic carbon atom, then the compound gets oxidized to open chain dicarboxylic acid having the same number of carbon atoms.

$>CHOH \longrightarrow >C=O \longrightarrow$ acids with lesser number of carbon atom



Oxidation of tertiary alcohol takes place under drastic conditions. On oxidation it gives ketone and acid having lesser number of carbon atoms.

(c)Carboxylic groups:If alkaloids have carboxylic group, they form ester with alcohol. They are also soluble in aqueous sodium carbonate or ammonia. The number of carboxylic groups in an alkaloid may be determined volumetrically by titration against a standard barium hydroxide solution using phenolphthalein as an indicator or gravimetrically by silver salt method.

(d)Oxo group: Oxo group in an alkaloid on reaction with hydroxylamine, semicarbazide or phenylhydrazine forms corresponding oximes, semicarbazone and phenylhydrazone respectively.

$$>C=O + H_2NOH \longrightarrow >C=N\text{-}OH + H_2O$$

Oxime

$$>C=O + H_2N.NHCONH_2 \longrightarrow >C=N.NHCONH_2 + H_2O$$

Semicarbazone

$$>C=O + H_2N.NHC_6H_5 \longrightarrow >C=N.NHC_6H_5 + H_2O$$

Phenylhydrazone

Distinction between aldehyde and ketone can be done on the basis of oxidation and reduction reactions.

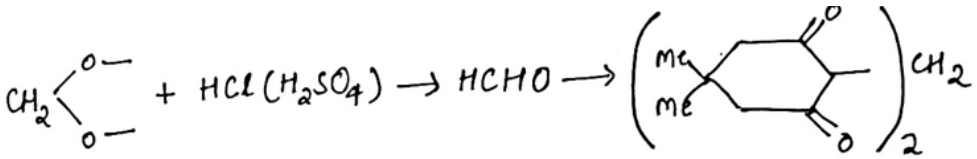
(e)Methoxy group($-OCH_3$) :This group can be determined by Zeisel determination.In this

method, a known wight of alkaloid is heated with hydriodic acid (HI) at its boiling point (126^0C). Thereafter all the methoxy groups are converted into methyl iodide which is treated with ethanolic silver nitrate which gives silver iodide as precipitate. Further the precipitate of is filtered, dried and weighed. From the weighed silver iodide, the number of methoxy groups can be calculated as follows:

$$\text{-O-Me + HI} \xrightarrow{126^0\text{C}} \text{-OH} + \text{MgI} \xrightarrow{AgNO_3} \text{AgI (ppt)}$$

Estimated gravimetrically

(f)Methylenedioxyl group (-OCH_2OO-): Alkaloid containing this group forms formaldehyde when heated with hydrochloric acid or sulphuric acid.The number ofMethylenedioxyl group can be confirmed by converting formaldehyde obtained into dimedone derivative which can be estimated gravimetrically.



(Dimedone derivative)

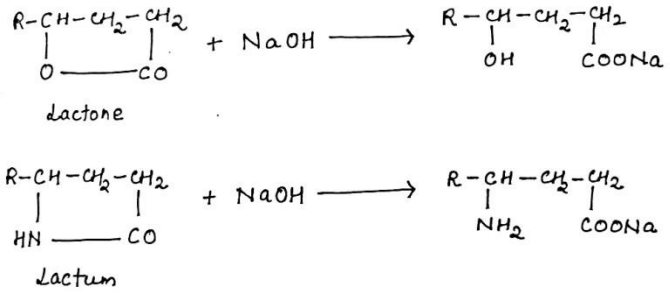
(g)Ester, Amide, Lactone, and Lactumgroups: The products of alkali and acid hydrolysis of these groups are used to detect and estimate them.

$$\text{-CONH}_2 + \text{NaOH} \xrightarrow{\text{Heating}} \text{-COONa} + NH_3$$

Amide

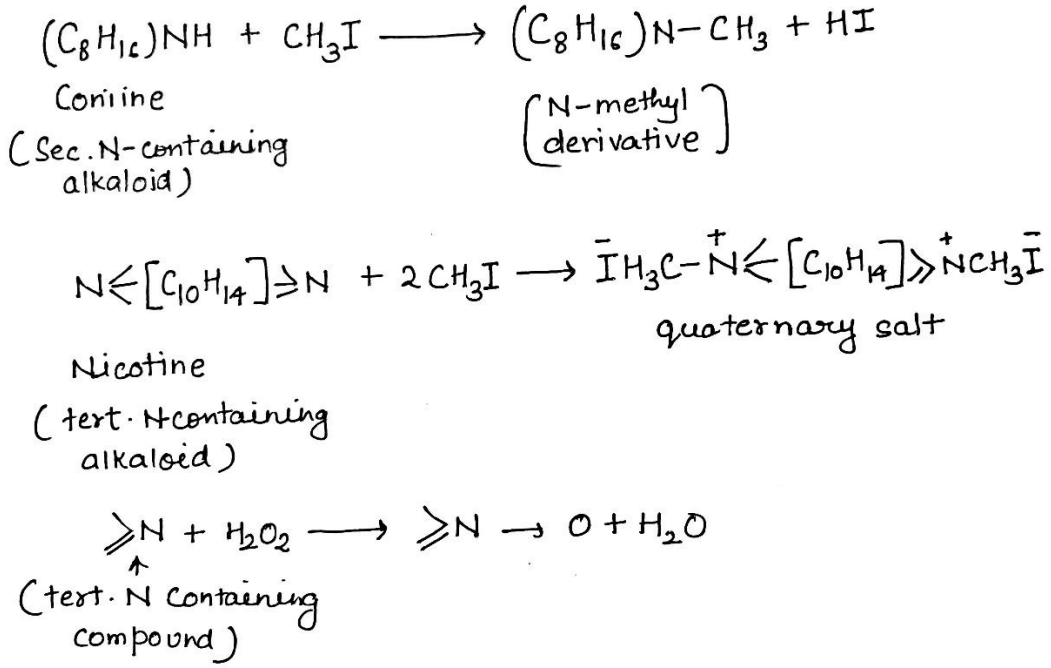
$$\text{-COOR} + \text{NaOH} \xrightarrow{\text{Heating}} \text{-COONa} + \text{ROH}$$

Ester



(h)Nature of Nitrogen: In most of the cases the nitrogen in alkaloids is present as a part of a heterocyclic ring except in phenylamine type of alkaloids where it is in the form of a primary amino ($-NH_2$) group. Therefore, alkaloid nitrogen in heterocyclic ring must be present either in secondary or tertiary form.

(i)Presence of secondary and tertiary Nitrogen:If secondary nitrogen is present in an alkaloid,on reaction with one mole of methyl iodide it forms N-methyl derivative. Tertiary nitrogen containing alkaloids forms crystalline quaternary salt with one mole of methyl iodide and it can also be detected by treating it with 30 percent hydrogen peroxide where tertiary nitrogen is oxidized to amine oxide.



(ii)The nature and number of alkyl groups which are attached to nitrogen may be identified by distilling with aqueous potassium hydroxide. If one, two or three methyl groups are attached to the nitrogen atom they form methyl amine, dimethyl amine or trimethyl amine respectively; the formation of ammonia shows the presence of an amino group.

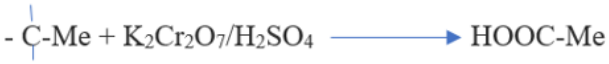
(iii)The presence of N-methyl group is often detected by distillation of alkaloid with soda-lime when methyl amine is obtained.

(iv)To detect and estimate the number of methyl groups attached to N-atom Herzig-Meyer's method is used. In this method N-methyl amine containing alkaloid is treated with hydriodic acid at 150-300^{0}C forms methyl iodide which is further treated with silver nitrate solution where methyl iodide converted to silver iodide. This so formed silver iodide estimated gravimetrically.

(Estimated gravimetrically)

(v)Amide linkage if present can be identified by hydrolysis followed by the characterization of acid and amine moieties.

(j)Estimation of C-methyl group: It is estimated by Kuhn- Roth oxidation. In this reaction the acetic acid formed being distilled off and distillate titrated against standard base.

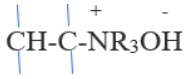


Estimated titrimetrically

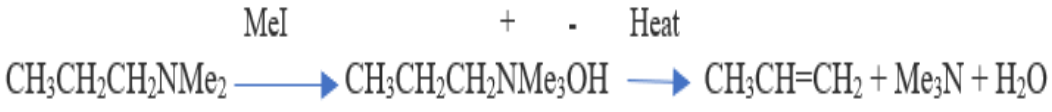
(k)Degradation of alkaloids:Degradation of alkaloids is employed to know about the structural system which incorporates the substituent groups.

The methods used are as follows:

(a) Hofmann exhaustive methylation method: When this method is applied on alkaloids the heterocyclic rings are opened with the elimination of nitrogen. From the nature of the remaining carbon skeleton, the nature of the heterocyclic ring can be identified.

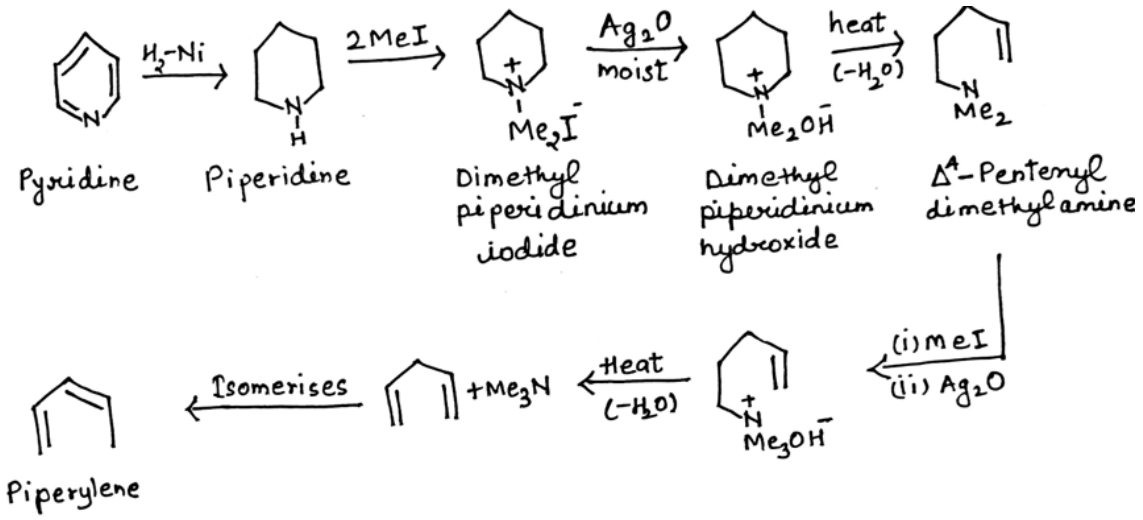
When the compound contains the structural unit like 

, it eliminates a trialkylamine on pyrolysis at 200^{0}C or above to yield an olefin.



Quaternary ammonium Hydroxide

The above rection follow E_2 mechanism, where the β-hydrogen, and quaternary nitrogen group are present in trans- antiparallel configuration. If the nitrogen atom is a part of a cyclic structure, two or three such cycles are required to liberate the nitrogen and get the remaining carbon skeleton. This method is applicable for the system like piperidine, it fails with compounds like pyridine. Pyridine needs to convert into piperidene for the further degradation.



Isoquinolenecannot be degraded by this method because there is no β- hydrogen is available with respect to nitrogen.

Hordenine methyl ether and laudanosine are the other examples which can be degraded by this method.

Hoffmann's exhaustive methylation fails with following:

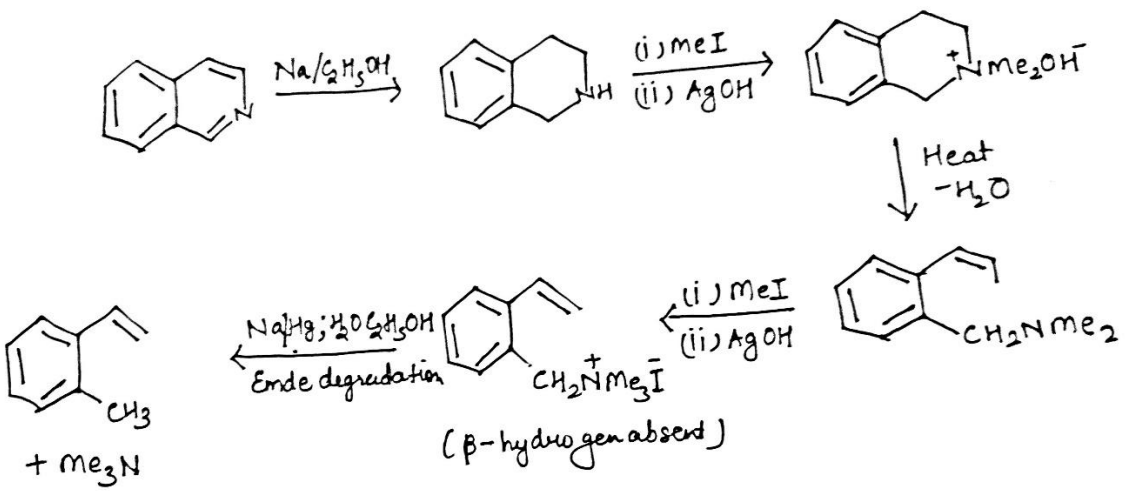
(i)With unsaturated heterocyclic rings

(ii)When there is no β- hydrogen atom

(iii)With tetrahydroquiniline

(b)Emde's Degradation:Emde's method is used when there is no β- hydrogen is available in an alkaloid. The final step of this reaction involves reductive cleavage of quaternary ammonium salts either with sodium amalgam or sodium in liquid ammonia or by catalytic hydrogenation.

Example: Degradation of isoquinolene:



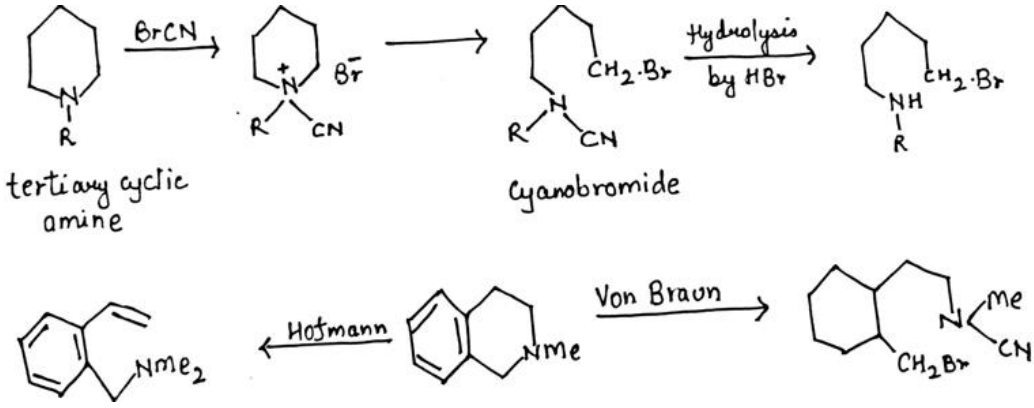
(c) Von Braun's Method:This method is of two types.

1.The first method is for tertiary amine which contains at least one alkyl substituent. It is treated with cyanogen bromide which separate of an alkyl-nitrogen bond to give an alkyl halide and a substituted cyanamide.

$$R_3N + CN\text{-}Br \longrightarrow R\text{-}Br + R_2N\text{-}CN$$

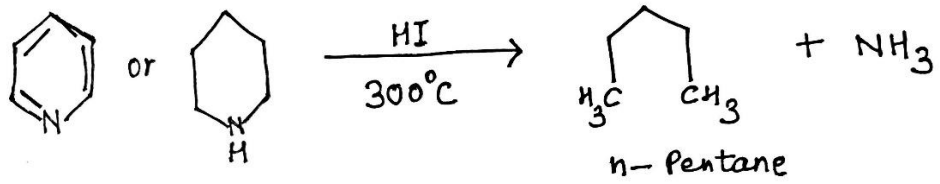
If amine is unsymmetrically substituted, it yields the alkyl halide derived from the smallest alkyl substituent.

$$Et_2NMe + CN\text{-}Br \longrightarrow MeBr + Et_2N\text{-}CN$$



2.The second Von Braun's method is used for secondary cyclic amine. The secondary cyclic amine for example piperidine on treatment with bezoylchloride in presense of NaOH forms N- benzoylpiperidine (benzoyl derivative) which further on treatment with phosphorus halide (such as PBr_5) followed by distillation under reduced pressure forms 1,5-Dibromopentane with the elimination of benzonitrile.

(d)Reductive degradation and zinc dust distillation- Ring opening may be done by heating with hydrocloric acid at 300^0C . e.g.,



Zinc dust distillation is also used to know about the carbon framework of the alkaloid molecule. It produces simple fragments, and also brings about dehydrogenation or removal of oxygen if present. For e.g.

$$C_8H_{17}N \xrightarrow[\text{Heating}]{\text{Zn dust}} \underset{\text{Conyrine}}{C_6H_5CH_2CH_2CH_3} + 6[H]$$

As conyrine is formed by loss of six hydrogen atoms, it means that coniine must contain a piperidine ring.

(e)Alkali fusion-This method is used to break down the complex alkaloid molecules into simpler fragments. For exampleAdrenaline on fusion with sodium potassium hydroxide yield protocatechuic acid.

Papaverine on fusion with alkali yields an isoquinoline derivative showes that it must contain an isoquinoline.

(f)Oxidation- This method is very useful to know about the expected structure of alkaloid. There are number of oxidizing agent which are as follows:

For mild oxidation - hydrogen peroxide, iodine in ethanolic solution, alkaline potassium ferricyanide.

For medium oxidation- acid or alkaline potassium permanganate, chromium trioxide in acetic acid.

For vigorous oxidation- potassium dichromate- sulphuric acid, chromium trioxide-sulphuric acid, concentrated nitric acid or manganese dixide- sulphuric acid.

Above classification is not fixed because the strength of an oxodizing agent depends to some extent on the nature of the alkaloid which is being oxidised.

(g)Dehydrogenation- Various catalyst are used in the dehydrogenation process such as sulphur, selenium or palladium etc. This process break the compound into relatively simple products which can be used to identify the gross skeleton of the alkaloid. During dehydrogenation, elimination of peripheral groups such as hydroxyl and C-methy takes place.

(h)Synthesis- The final confirmation of the structure can be done by its synthesis only.

(i)Physical method-Structure of alkaloids can be identified by the modern instrumental techniques. The most important instrumental techniques are:UV spectroscopy, Infra-red spectroscopy, Nuclear magnetic resonance spectroscopy, mass spectrometry, Optical rotatory dispersion and circular dichroism, conformational analysis and X-ray diffraction.

Ultraviolet spectrospopy is used to know about the particular chromophoric system present in alkaloids such as benzene, pyridine, indole, quinoline etc. These have specific absorption maxima and extinction coefficients. So, data observed for new alkaloids may compared with already existed data to know about the system in new compound.

Infrared spectroscopy is used to identify the type of functional group present in the unknown alkaloid.

Nuclear magnatic resonance spectroscopy is used for the identification and quantitative estimation of the substituents like O-methyl, N-methyl, O,O-methylenedioxy, C-methyland phenolic groups present in the alkaloid.

Mass spectromerty is used to know about the molecular weight, emperical formula and the molecular structure by comparing the fragmentation pattern with the analogous system.

Optical rotatory dispersion and circular dichroism is mainly used for elucidation of the sterochemistry of optical active alkaloids.

Conformational analysis is used to investigate the stereochemistry as well as physical properties and chemical reactivity of alkaloids.

X-ray diffraction is a popular method which is used to know about the exact structure of the molecule, including bond angle, bond leangth, absolute configuration of the molecule

2.11 MORPHINE

Morphine is one of the oldest drugs to be known. In opium it is present about 10-25 percent along with other substances like fats, proteins, carbohydrates, mineral salts etc. Codein and thebaine are closely related to morphine commonly known as morphine alkaloids. They all contains phenanthrene nucleus and are widely used asanalgesic agents.

Morphine is colourless prismatic substance. Its melting point is 247^0C. It is laevorotatory in nature having a specific rotation of -131^0. Morphine is soluble in alcohol and alkali solution and less soluble in water, ether and chloroform.

Chloride of morphine are used in medicine. Diacetyl derivative of morphine also known as heroin is also used.

Constitution

The constitution of morphine is confirmed as follows :

1.Molecular formula- This has been found $C_{17}H_{19}O_3N$.

2.Nature of the nitrogen atom-Formation of quaternary salt of morphine with methyl iodide shows the presence of tertiary nitrogen atom in it. This was further confirmed by Hofmann degradation of codeine derivative which also confims the presence of nitrogen atom in ring.>N-CH_3 group in morphine was confirmed by Herzig-Meyer method.

3.Nature of oxygen atoms-

(i)Presence of hydroxyl group- On acetylation or benzoylation morphine produces diacetyl or benzoyl derivative, which indicates presence of two hydroxyl groups.

$$C_{17}H_{17}ON(OH)_2 \xrightarrow[2CH_3COCl]{\text{acetylation}} \underset{\text{Diacetyl morphine}}{C_{17}H_{17}ON(OCOCH_3)_2} + 2HCl$$

$$C_{17}H_{17}ON(OH)_2 \xrightarrow[2C_6H_5COCl]{\text{benzoylation}} \underset{\text{Dibenzoyl morphine}}{C_{17}H_{17}ON(OCOCH_3)_2} + 2HCl$$

(ii)Nature of hydroxyl groups- Morphine gives purple coloure with ferric chloride. With aqueous sodium hydroxide solution it forms monosodium salt which is reconverted into morphine by passing CO_2 through it. All these experiments shows that one of the two hydroxyl groups is phenolic in nature.

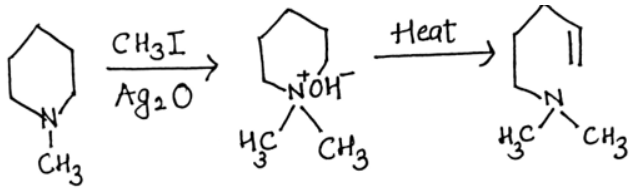
Morphine forms monohalogen derivative with halogen acids. In this reaction hydroxyl group is replaced by a halogen acid. This reaction is charecteristic of alcohols. So the second hydroxyl group is alcoholic in nature.

(iii)The third oxygen atom in morphine is considered as in an ether linkage due to its unreactive nature. It was further confirmed by degradation of morphine.

4.Presence of ethylenic bond-Codein(methylated morphine) takes up one hydrogen molecule when reduced catalytically in the presence of palladium, suggesting that both coedine and morphine contain one ethylenic link.

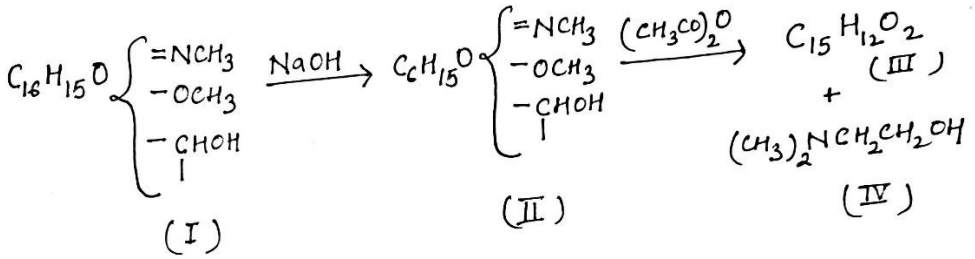
5.Presence of benzene nucleus-A mono-bromo derivative of morphine is produced when it is brominated, along with evolution of hydrogen bromide. This indicates that morphine has a benzene nucleus.

6.Presence of a cyclic tertiary base system-When codeine on exhaustive methylation produced α-codeimethine, which has a formula that has one more CH_2 than codeine and the nitrogen atom remains intact.If codeine has an acyclic tertiary amine system, the resulting product will have fewer carbon atoms and will also lose nitrogen. Presence of tertiary cyclic base system in codeine can be explained by following reaction.

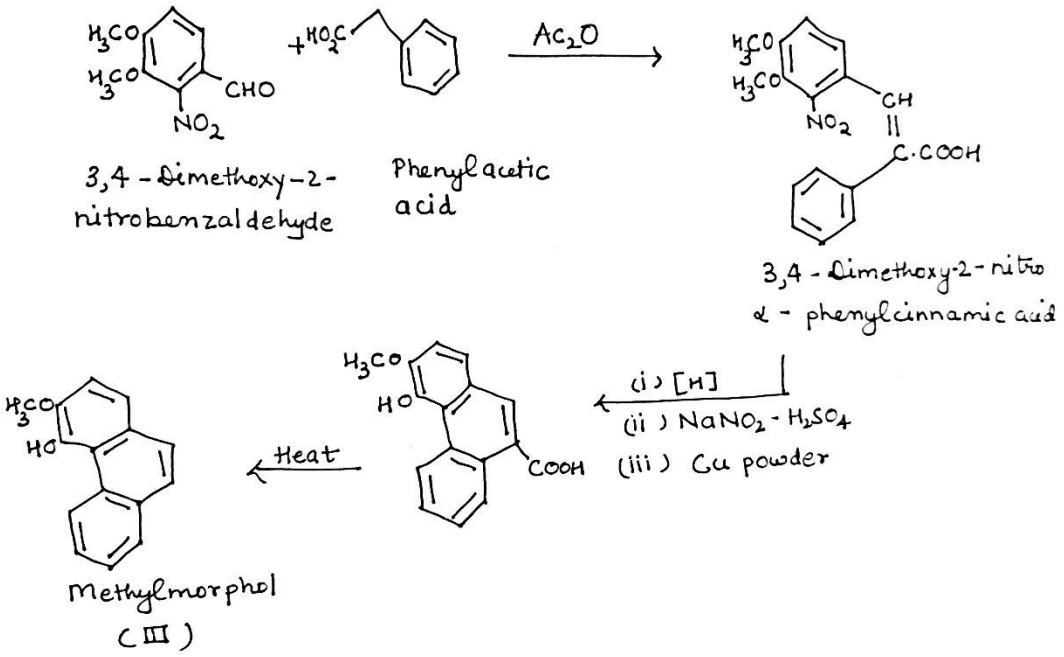


7.Presence of phenanthrene-When morphine is treated with zinc dust, it gives phenanthrene and number od bases, shows that morphine may contain a phenanthrene nucleus. As further evidence consider the follwing.

Codeine(methylated morphine) on treatment with methyl iodide, gives codeine methiodide (I), which on reaction with sodium hydroxide solution, yield α-methylmorphimethine (II). Compound (II) on further teatment with acetic anhydride yields a mixture of methyl morphol (III) and ethanoldimethylamine (IV).



Structure of methylmorphol (III) can be determined as follows: On heating compound (III) with hydrochloric acid at 180^0C under pressure, morphol or dihydroxyphenanthrene is obtained. Presence of two hydroxyl group in same ring was investigated by the oxidation of diacetylmorphol which produces diacetylphenanthraquinone, indicatind that position 9 and 10 are free which on further oxidation with permagnate yields phthalic acid.Additionally, both of these hydroxyl groups in morphol are in the ortho position because protocatechuic acid is produced when morphine is fused with alkali. Pschorr *et al.* synthesized methylmorphol and showed it to be 4-hydroxy-3-methoxyphenanthrene. Synthesis is as follows:



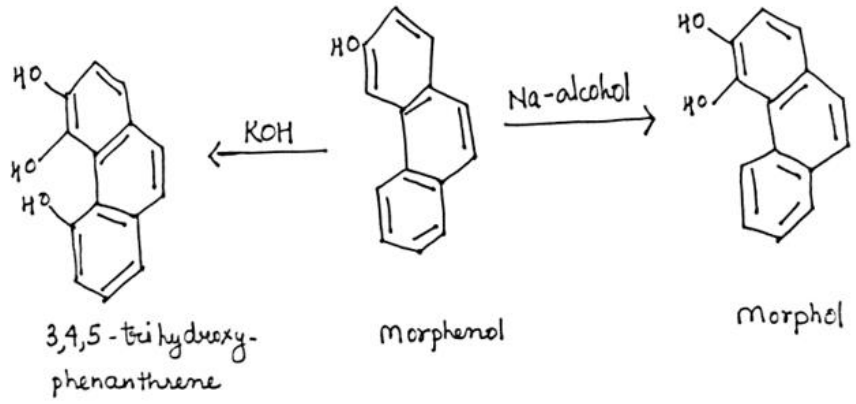
Presence of >N-CH_3 group- Codine(methylated morphine) includes a >NCH_3 group, as shown by the synthesis of dimethylaminoethanol(II) from α-methylmorphimethine(II). This was further supported by the data showing that when codein is subjected to Von Braun degradation, one nitrogen atom is added but three hydrogen atoms are lost.The conversion of >NCH_3 into NCN is a simple way to interpret these findings, and it follows that codeine and moephine both include an N-methyl group.

8.Position of three oxygen atoms- The position of two oxygen atoms can be determined by elucidating the structure of morphenol.

When heated with water, β-methylmorphimethine produces trimethylamine, ethylene, and methylmorphenol. Morphenol, is produced when hydrochloric acid demethylates methylmorphenol. It has one phenolic hydroxyl group and an inert oxygen atom. When morphenol is fused with potassium hydroxide, it yields 3,4,5- trihydroxyphenanthrene.

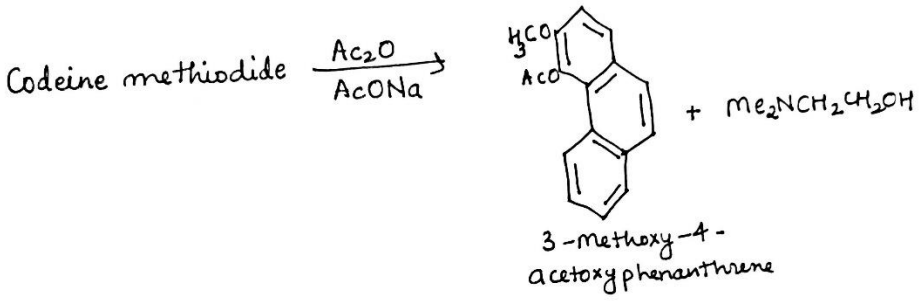
The synthesis of the later molecule, which was discovered to be similar to the end product produced by methylating the trihydroxyphenanthrene obtained from morphenon, validated the structure of the later compound. Also, morphenol when reduced with sodium and ethanol yields morphol.

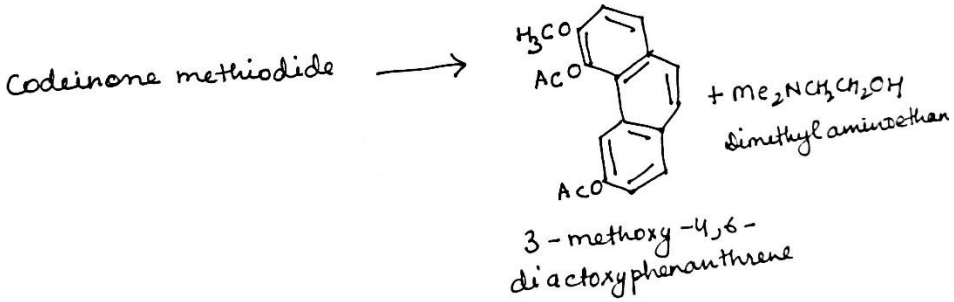
Alltheaboveresultscanbeexplainedifthemorphenolhasstructure(V)containingetherbondsatthe4,5positionsofthephenanthrenenucleus.



The position of two of the three oxygen atoms in morphine—one at C_3 and the other in the ether linkage between C_4 and C_5 of the phenanthrene nucleus—is determined by the structure of morphenol and its production from codeine. The position of third oxygen atom has been shown to be at C_6 as follows:

Codeine methiodide and codeinone methiodide on heating separatly with a mixture of Ac2O-AcONa gives 3-methoxy-4-acetoxyphenanthrene and 3-methoxy-4,6-diacetoxyphenanthrene respectively.The latter has an additional acetoxy group in position 6, whereas in the former, the secondary alcoholic group is lost as a water molecule during dehydrogenation to the aromatic product, whereas in the latter, the ketonic group enolizes during the route to the aromatic product, and as a result, it appears as an acetoxy group in the final product.



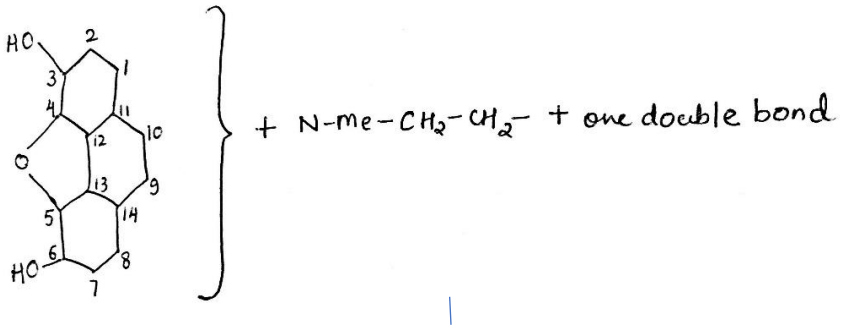


The hydroxy group(i.e., third oxygen atom) in the 6 position must therefore be produced from the oxygen of the keto group in codeine.

Thus, the position of all the three oxygen atoms in morphine have been well establishedat C3 (phenolic), between C4 and C5 (ether linkage) and at C6 of the phenanthrene nucleus.

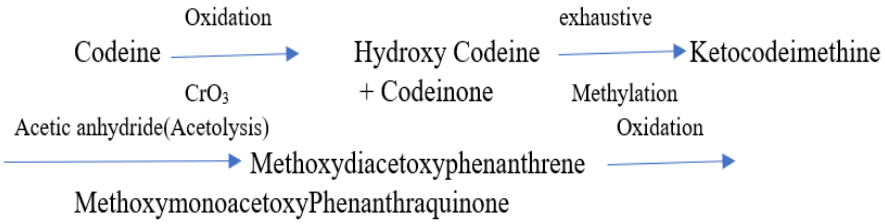
1.Structure of Morphine

(i)Morphine generates monoderivatives with bromine and monosodium salt with sodium hydroxide, as previously mentioned, showing that it includes one benzenoid structure. Further, ethylene is produced as one of the byproducts of the thorough methylation of dimethylaminoethanol and codeimethines. Both these products favour that a $-CH_2-CH_2-CMe$ chain must be present in morphine. Also, a double bond and a tertiary nitrogen atom are present in it. On the basis of all the above facts, the partial structure of morphine may be drawn as followes:



(ii)Position of linkage of the $-CH_2-CH_2-NMe$ chain-

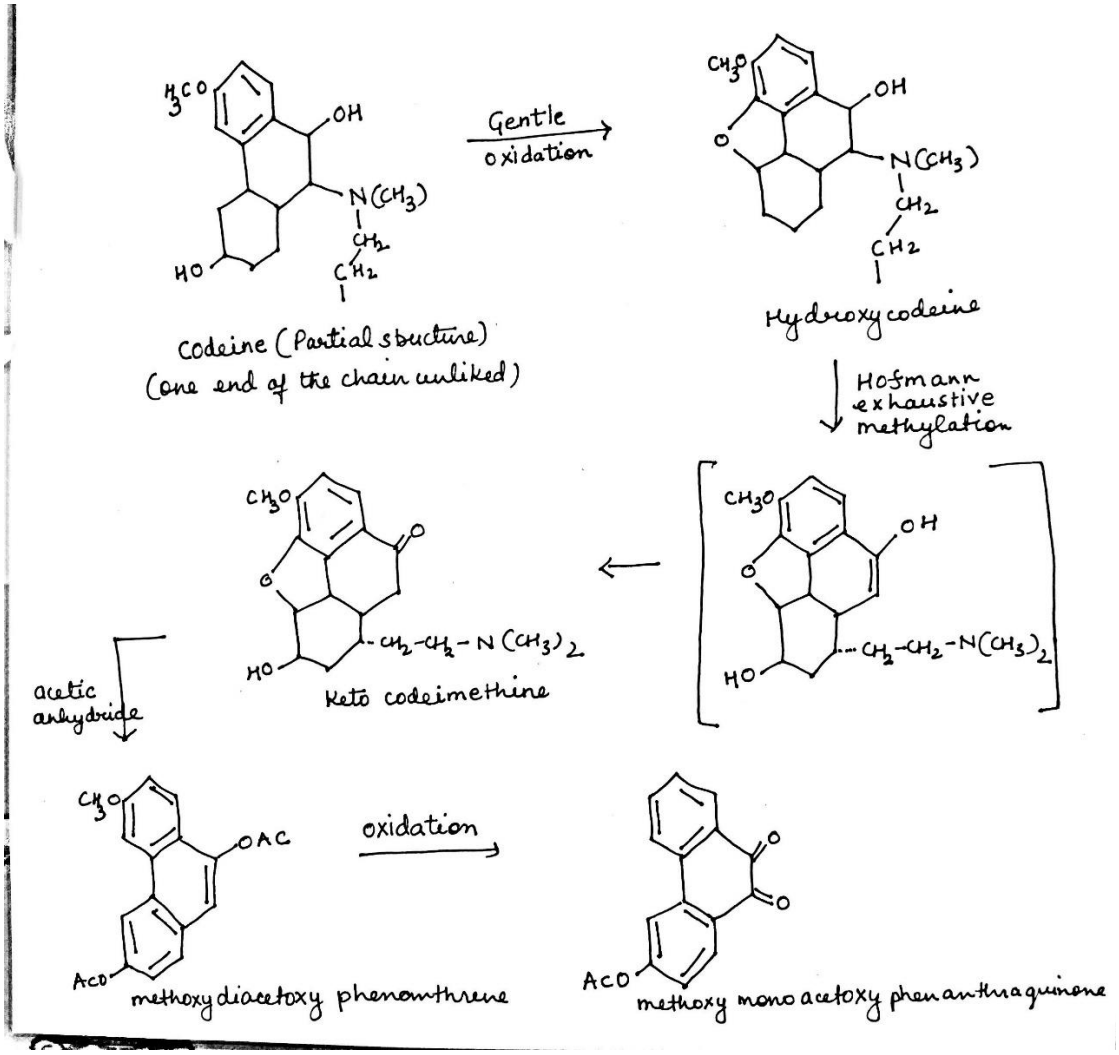
This can be explained by taking the following reaction scheme :



Methoxydiacetoxyphenanthrene is oxidised to methoxymonoacetoxyphenanthrene, which results in the loss of an acetyl group. This shows that one of the acetoxy groups in the former compounds must be present, and it must be either C9 or C10. On the basis of steric consideration, the attachment at C9 is most probable.

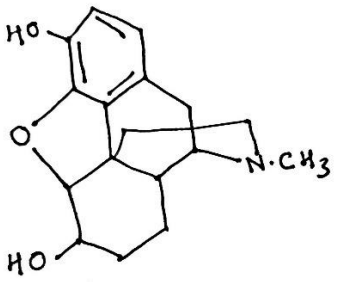
Since the Hofmann exhaustive methylation transforms the new hydroxyl group of hydroxycodeine into a keto group, a double bond must be created between C9 and C10 during the fission of the nitrogen ring, hence the nitrogen must be connected at either C9 or C10. The exact point of linkage of nitrogen at C9 has been established after the synthesis of morphine.

All the reactions mentioned above can be explained, if the partial structure of codeine is drawn as follows:



We have seen that the side chain having nitrogen atom is always eliminated during the aromatization of the phenanthrene nucleus.Gulland and Robinson(1923) claim that unless the ethamine chain is displaced, the synthesis of the phenanthrene derivative is structurally not possible. But it has been already shown that the nitrogen end of the side chain is linked to C9. Therefore, the carbon end of the side chain must be located at an angular position so that its extrusion from that position should take place during aromatization. Among the two possible positions C13 and C14 , the former is selected because this structure can only be used to explain the rearrangement of thebaine to thebenine.

Based on the above facts the partial structure of morphine can be written as:

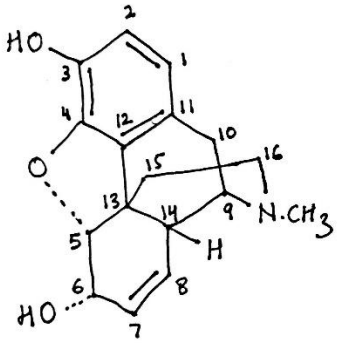


Partial structure of morphine

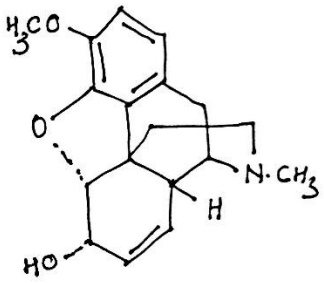
(i)Position of the double bond-

On treatment with PCl_5 codeine, yields α-chlorocodide which on hydrolysis with acetic acid solution yields a mixture of codeine, isocodeine, pseudocodeine and allopseudocodeine. The first two yield the same ketone on oxidation, shows that they differ in the configuration of the hydroxyl group on C_6. The remaining two also yield the same ketone pseudecodeinone on oxidation, showing that these two also differ in the configuration and position of the -OH group at C_6 which is at C_8. These changes can be explained if the double bond is in between C_7 and C_8.

Based on the above facts, the structure of morphine and Codeine is as follows:



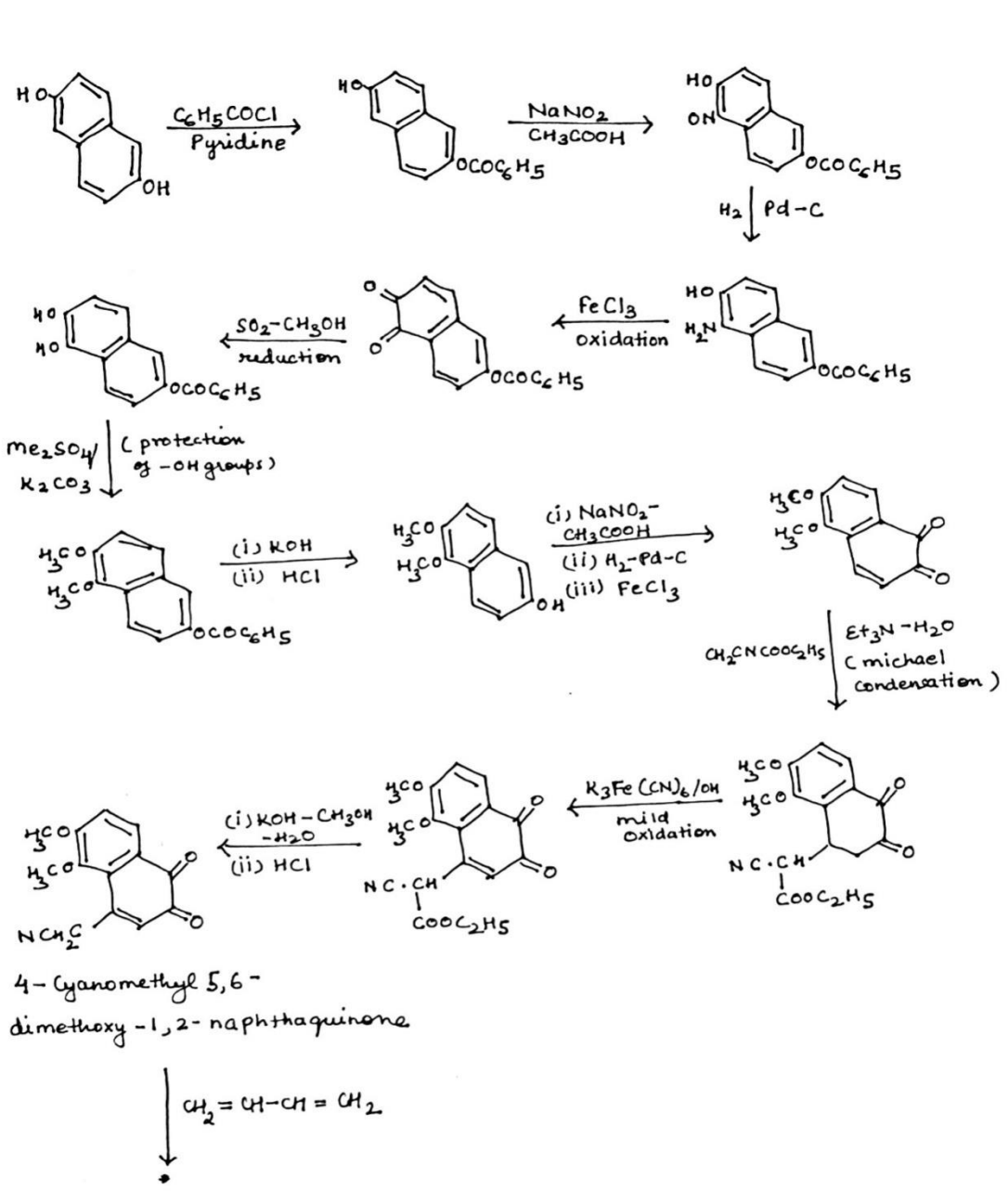
Morphine

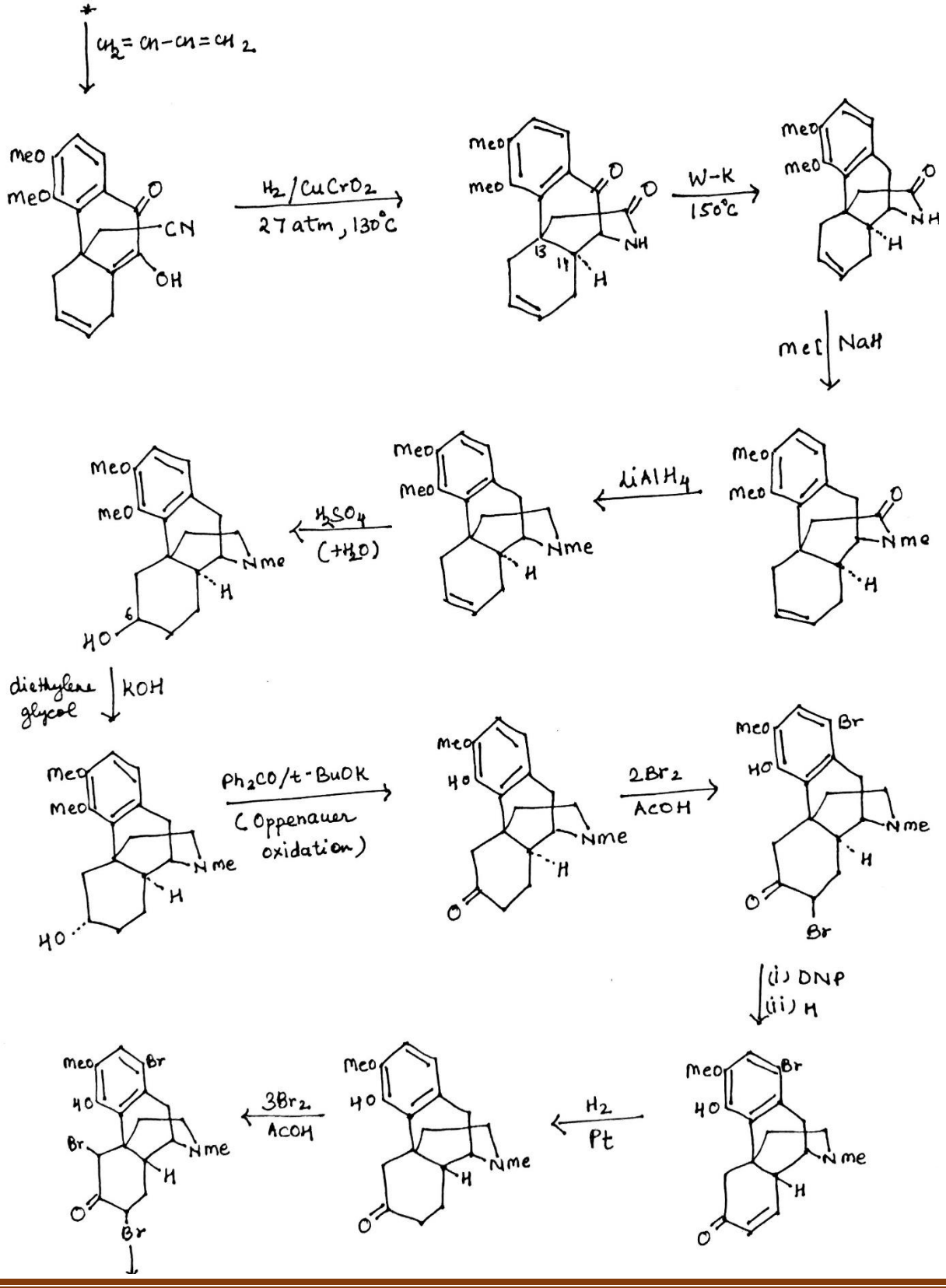


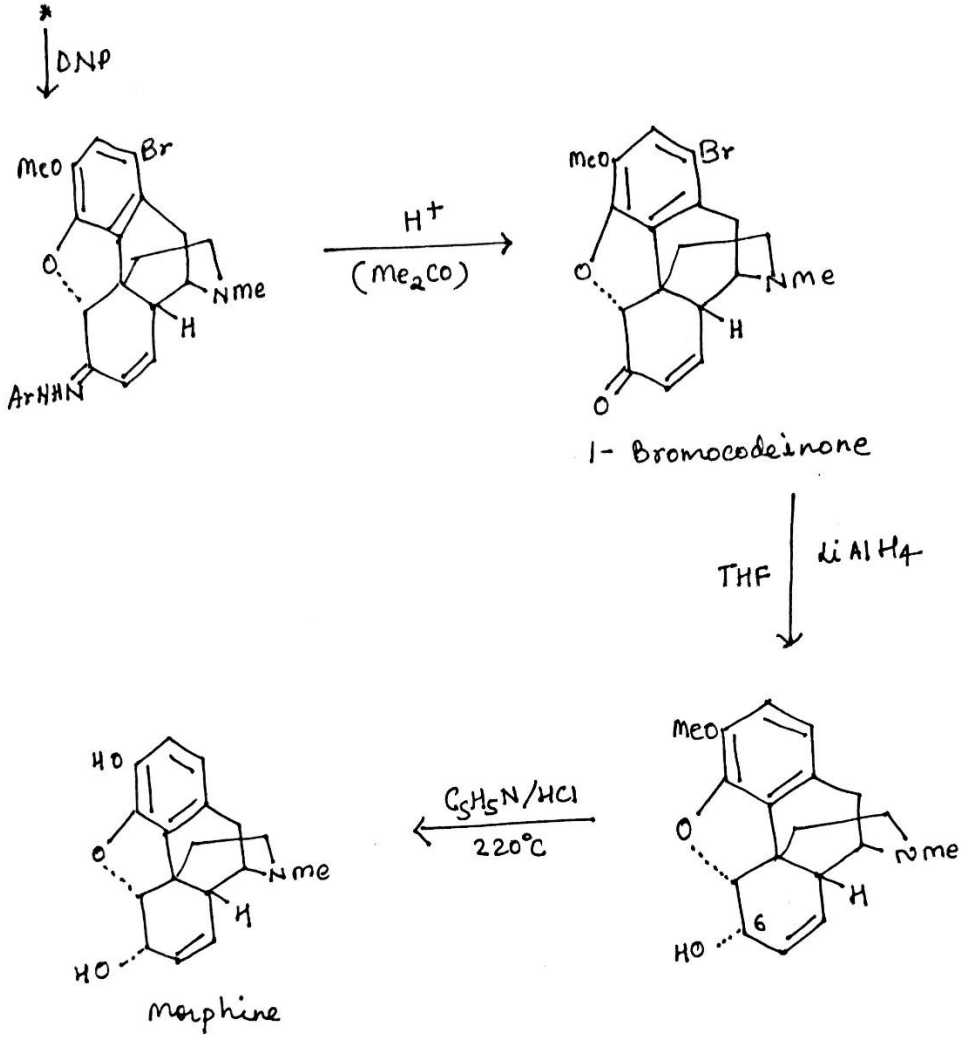
Codeine

10.Synthesis of Morphine:

Gates's synthesis :


C6H5COCl
Pyridine
NaNO2
CH3COOH
H2 | Pd-C
FeCl3
oxidation
SO2-CH3OH
reduction
Me2SO4/
K2CO3
(protection of -OH groups)
(i) KOH
(ii) HCl
(i) NaNO2-
CH3COOH
(ii) H2-Pd-C
(iii) FeCl3
CH2CNCOOC2H5
Et3N -H2O
(michael condensation)
K3Fe(CN)6/OH
mild oxidation
(i) KOH - CH3OH
-H2O
(ii) HCl
4- Cyanomethyl 5,6-
dimethoxy -1,2- naphthaquinone
CH2 = CH-CH = CH2


$CH_2=CH-CH=CH_2$
MeO
MeO
CN
OH
$H_2/CuCrO_2$
27 atm, 130°C
NH
W-K
150°C
MeI / NaH
N-Me
$LiAlH_4$
H_2SO_4
$(+H_2O)$
HO
diethylene glycol
KOH
$Ph_2CO/t\text{-}BuOK$
(Oppenauer oxidation)
$2Br_2$
AcOH
Br
(i) DNP
(ii) H
H_2
Pt
$3Br_2$
AcOH

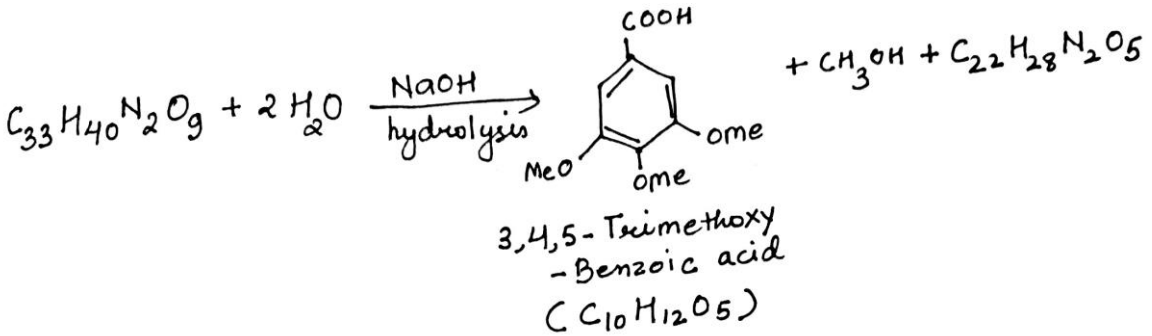

DNP
MeO
Br
O
NMe
H
ArNHN
H+
(Me2CO)
1- Bromocodeinone
THF
LiAlH4
MeO
HO
C5H5N/HCl
220°C
6
Morphine

2.11 RESERPINE

It is an alkaloid found in Rauwolfia serpentina and R. vomitoria roots. Reserpine prevents norepinephrine from entering storage vesicles, which depletes serotonin and other neurotransmitters like catecholamines from both central and peripheral axon terminals. Although it has been utilized as a research tool, antipsychotic, and antihypertensive, its undesirable effects prevent it from being used clinically.

Constitution

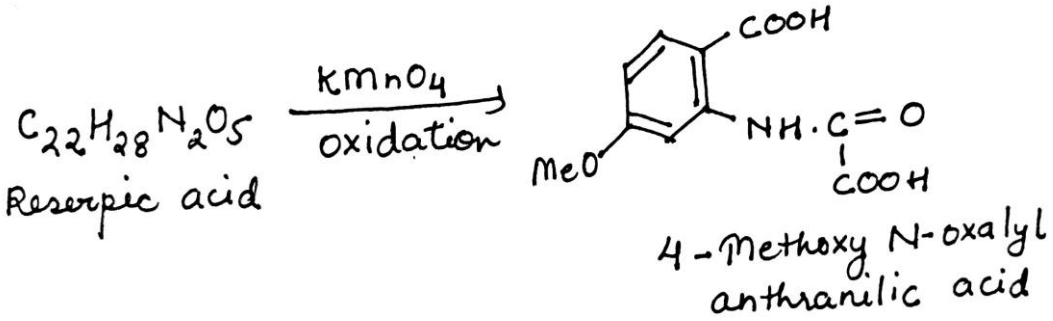
1. Molecular formula- Qualitative and quantitative analysis suggested the molecular formula of reserpine i.e $C_{33}H_{40}N_2O_9$.
2. Presence of five methoxy groups- Heating reserpine with hydrogen iodide at its boiling point (126^0C), gives five moles of methyl iodide, which shows the presence of five methoxy groups in reserpine. This method is known as Zeisel's method.
3. Nature of nitrogen atom- Given that reserpine is a weak base, it suggests that the ring structure should contain both nitrogen atoms. Reserpine also produces a monoacetyl derivative, proving that one of the nitrogen atoms is present as an >NH group despite the fact that it has no hydroxy groups. This has been further confirmed by the IR spectral analysis which revels the presence of an indole nucleus. With methyl iodide reserpine forms a methiodide, this indicate that the second nitrogen atom must be in tertiary state.
4. Hydrolysis- On hydrolysis with alkali solution, reserpine yields a mixture of methyl alcohol, 3,4,5-trimethoxy benzoic acid and another acid A corresponding to the composition $C_{22}H_{23}N_2O_5$ reserpic acid. As reserpine does not contain –COOH or –OH groups, the introduction of the two carboxylic acidic groups (one in 3,4,5-trimethoxy benzoic acid and another in reserpic acid) and two alcoholic groups (one on methyl alcohol and another in reserpic acid) in its hydrolysis products shows that reserpine is a diester. In order to determine the structure of reserpine, one must know the structure of reserpic acid which can be elucidated as follows:



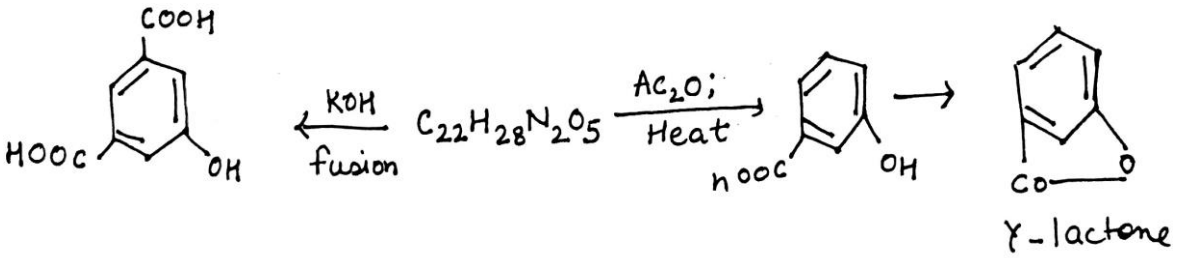
5. Structure of reserpic acid-
   (a) Molecular formula- The molecular formula has been found to be $C_{22}H_{23}N_2O_5$.
   (b) Presence of one carboxy group- Presence of one carboxylic group in reserpic acid can be determined by silver salt method.
   (c) Presence of one –OH group-Reserpic acid contains a secondary alcoholic group it was determined by oxidation . On oxidation reserpic acid yields ketone.
   (d) Presence of two methoxy groups- By Zeisel's method, it is shown that reserpic acid contains two methoxy groups.
   (e) Nature of two N atoms- In reserpic acid two nitrogen atoms are present in hertrocyclic rings, one in the form of a secondary amino group while other in the form of tertiary amino group.
   On the basis of above point a to e, reserpic acid may be written as.
   $C_{19}H_{20}N_2$ with two –OCH3, one –OH, -COOH

   (f) Reduction of reserpic acid- On reduction with $LiAlH_4$ reserpic acid yields alcohol which has two $–OCH_3$, one –OH and one $–CH_2OH$ groups. Thus, the structure may contain: $C_{19}H_{20}N_2$ (Reserpic alcohol) with two $–OCH_3$, one –OH, $-CH_2OH$

   (g) Oxidation of reserpic acid- Oxidation of reserpic acid with potassium permagnate yields 4-methoxy N-oxalyl anthraanilic acid. This confirms the presence of one indole nucleus in reserpic acid. It also shows that one of the methoxy groups is present in meta position to >NH group.



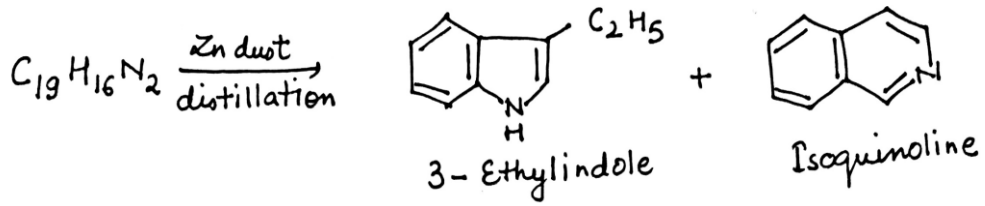
   (h) Fusion with KOH- Reserpic acid on fusion with potash, yields 5-hydroxyphthalic acid. Now since one of the acidic groups of isophthalic acid must be the carboxy group of reserpic acid itself, it means that the hydroxyl and carboxylic groups in reserpic acid must be present in the meta position to each other. This can be further confirmed by the reaction of reserpic acid with acetic anhydride with yields a γ-lactone.



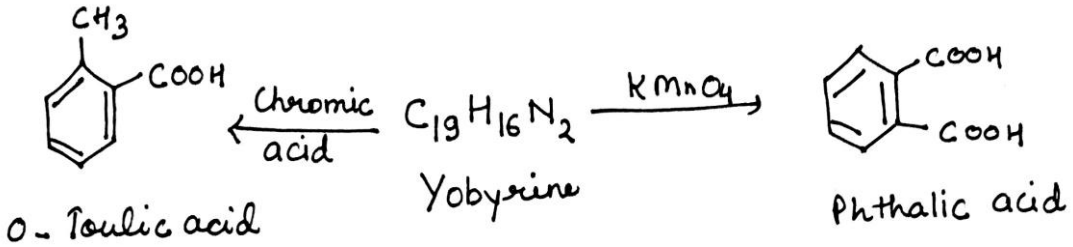
(i) Dehydrogenation- Dehydrogenation of methyl reserpate with selenium yields a hydrocarbon with molecular formula $C_{19}H_{16}N_2$. This hydrocarbon is also obtained by the dehydrogenation of yohimbine with selenium and was therefore named as yobyrine. Structure determination of yobyrine is essential to elucidation of the final structure of the reserpine.

Structure of the hydrocarbon yobyrine

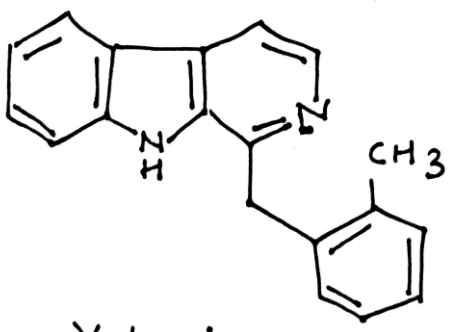
1. When distilled with zinc dust, yobyrine yields 3-ethyl indole and isoquinoline.



2. Oxidation of yobyrine with permagnate, gives phthalic acid. With chromic acid it gives *o*-toulic acid.

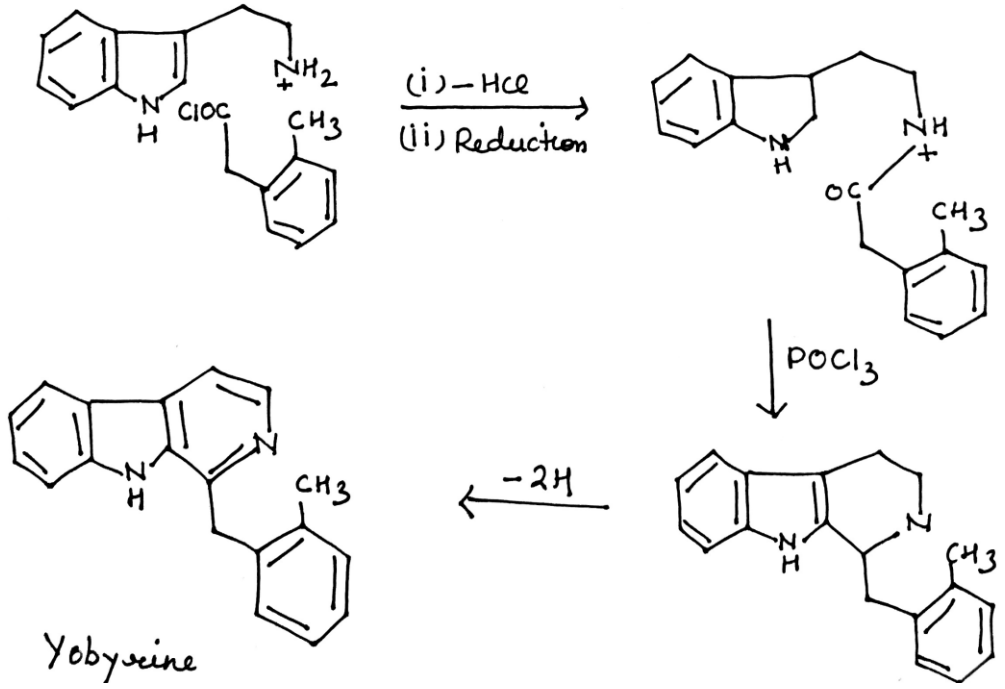


3. With aldehydes yobyrine gives condensation products. It suggest the presence of a pyridine ring with a-CH_2-substituent adjacent to the nitrogen.
On the basis of the aforementioned facts, the following structure for yobyrine has been proposed.



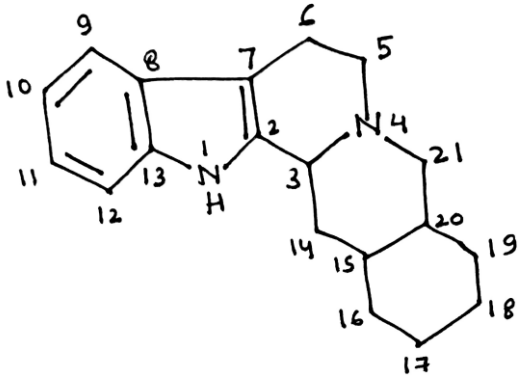
Yobyrine

The structure of yobyrine has been confirmed by its synthesis.

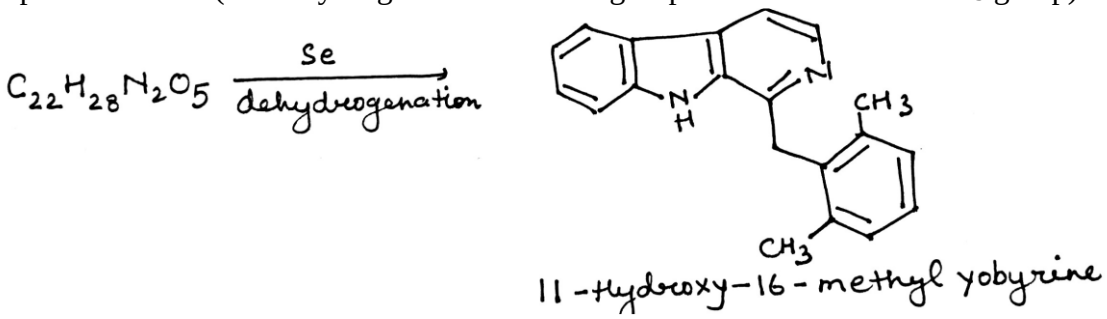


Yobyrine

(j) Since reserpic acid is the precursor of yobyrine, reserpic acid may have the skeleton structure in the following way.

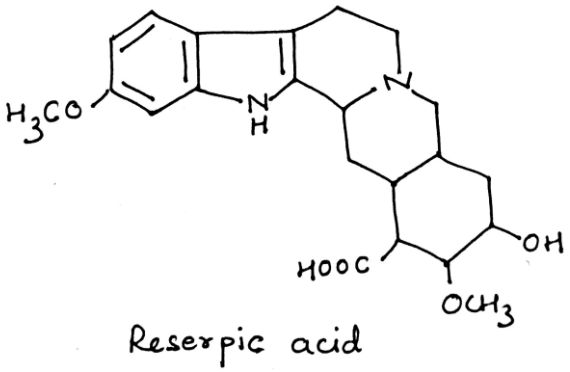


(k) According to the point (5) (g), one of the mrthoxy group is present in the *m*-position to the >NH group of indole, i.e., on C-11.On dehydrogenation with selenium reserpic acid yields 11-hydroxy-16-methyl yobyrine. This may be only formed when a –COOH group is present on C16(On dehydrogenation –COOH group is converted into $–CH_3$ group).

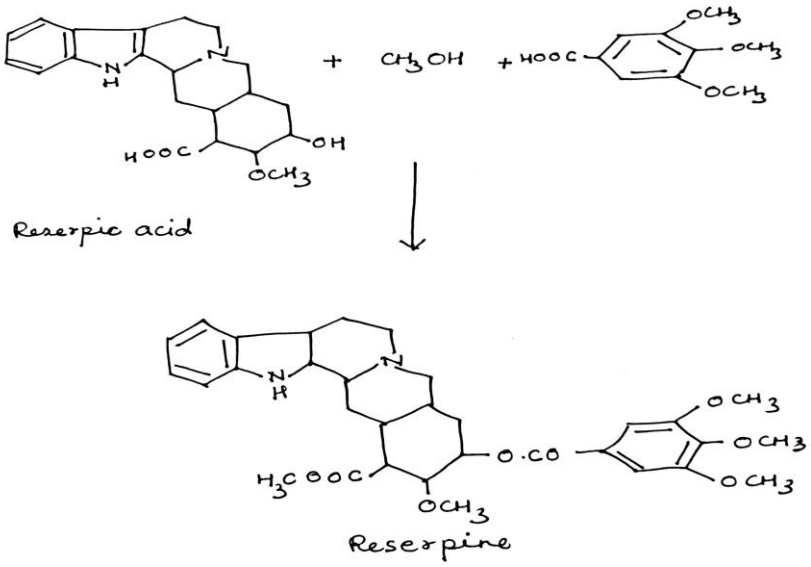


From the point (5) (h) –COOH and –OH groups are *m*-position to each other but –COOH is present at C_{16}. So,-OH group must be present at C_{18}. From purely biogenetic reasons, the second methoxyl group has been assigned position 17.

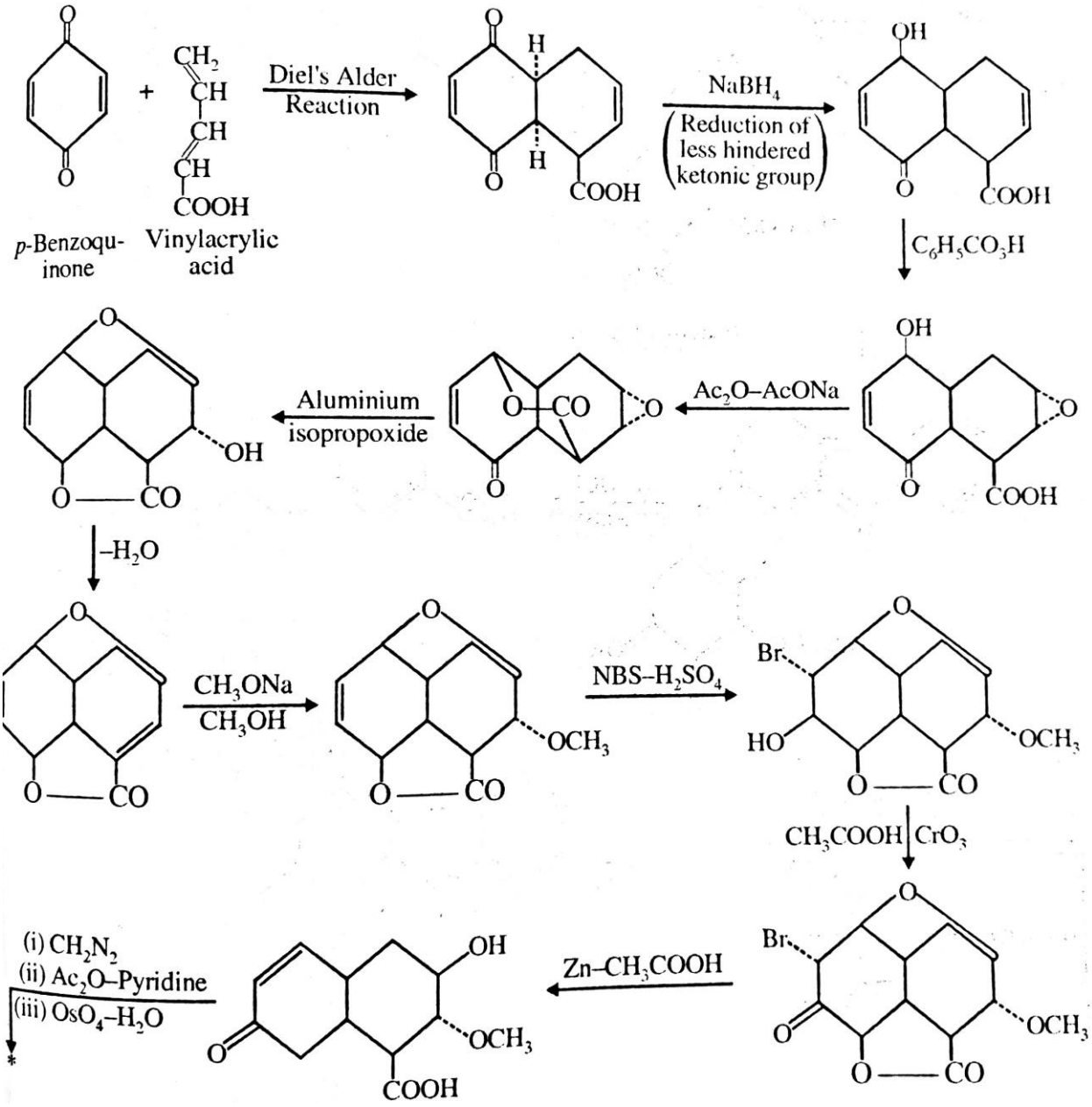
On the basis of the above points, the structure of reserpic acid may be written as follows:

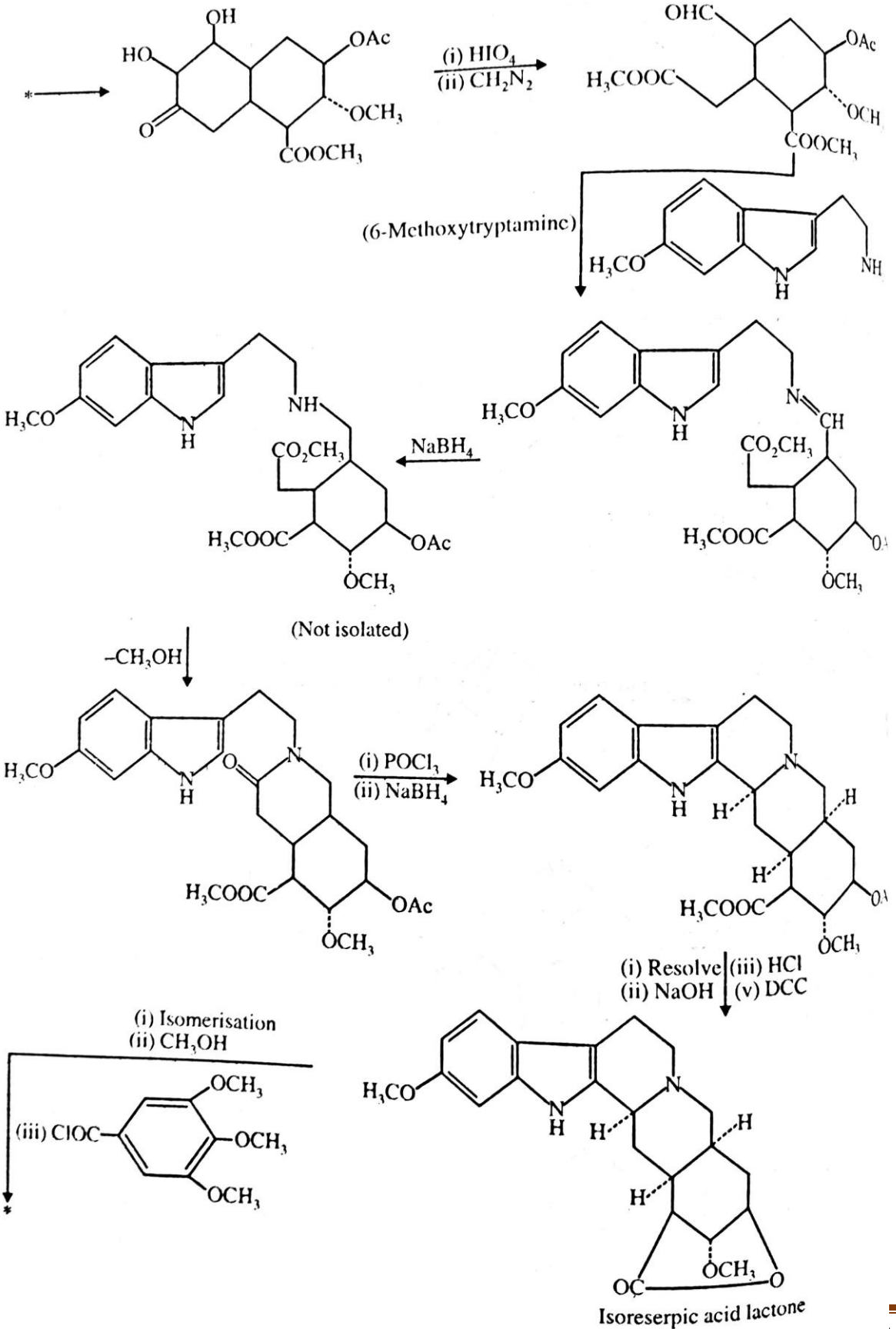


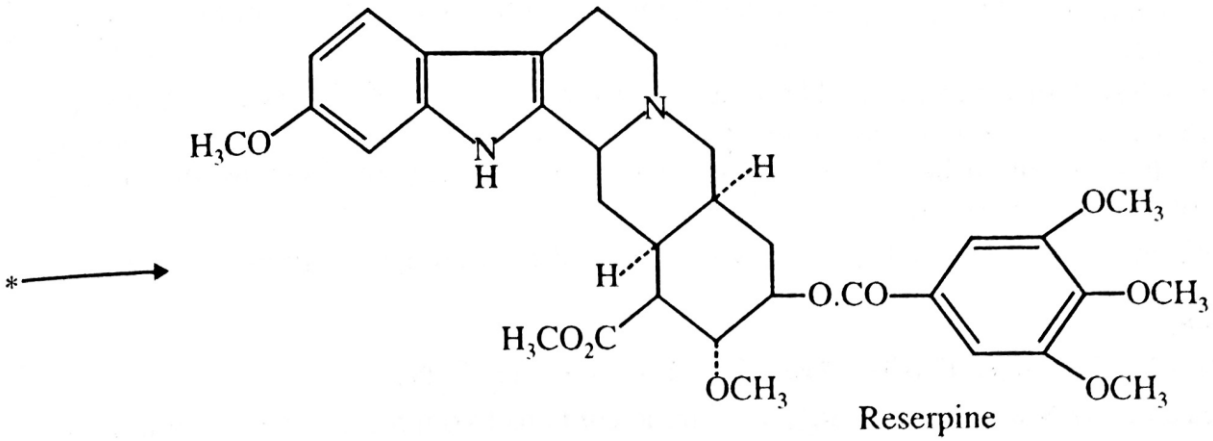
6.Structure of reserpine: Reserpine is a diester of reserpic acid. Its structure may be written as follows:


+ CH3OH + HOOC
OCH3
OCH3
OCH3
HOOC
OH
OCH3
Reserpic acid
O.CO
H3COOC
OCH3
Reserpine

6. Synthesis of reserpine:

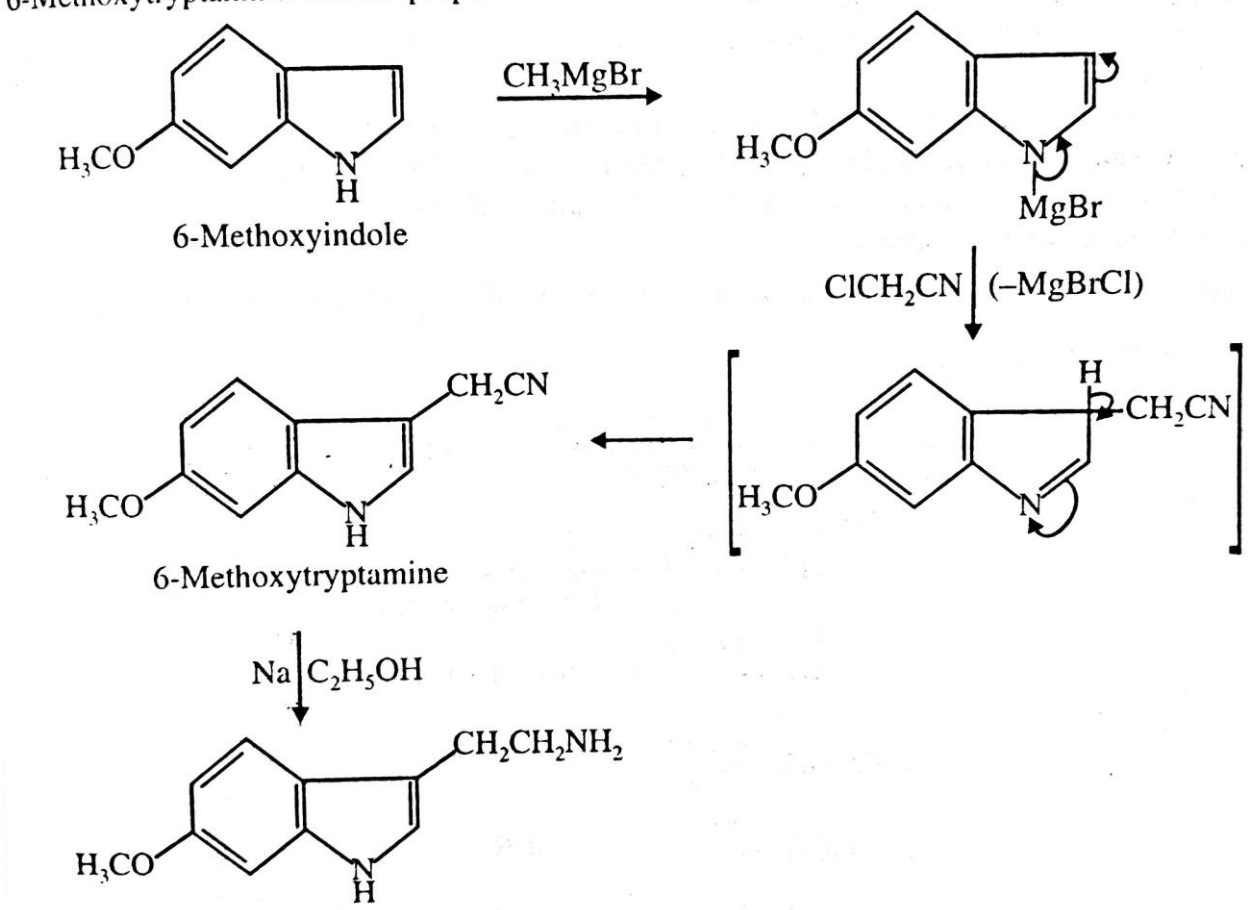



OH
HO
OAc
OCH3
O
COOCH3
(i) HIO4
(ii) CH2N2
OHC
H3COOC
OAc
OCH3
COOCH3
(6-Methoxytryptamine)
H3CO
NH
N
H
N
CH
CO2CH3
H3COOC
OAc
OCH3
NaBH4
(Not isolated)
–CH3OH
(i) POCl3
(ii) NaBH4
H
(i) Resolve
(ii) NaOH
(iii) HCl
(v) DCC
(i) Isomerisation
(ii) CH3OH
(iii) ClOC
Isoreserpic acid lactone



Reserpine

6-Methoxytryptamine can be prepared from 6-methoxyindole in the following way.



2.13 SUMMARY

There are 20,000 or more known alkaloids, the majority of which were isolated from plants. They are more prevalent in higher plant groups, especially dicotyledons, but less common in lower plant and fungal families. There are various views by different authorities, such as they are of no importance and may be regarded as byproducts of plant metabolism. They may act as reservoirs for protein synthesis. They may be used as reserve substance to supply nitrogen. Alkaloids have a number of therapeutic uses, including those for anti-inflammatory, anti-cancer, analgesic, and anesthetic properties. A significant alkaloid used to treat pain is morphine. Extraction and purification of alkaloid is a tedious process because alkaloids obtained from plants is a complex mixture of alkaloids along with presence of other compounds like glycosides, organic acids etc. One of the first known medications is morphine. Along with other compounds including lipids, proteins, carbohydrates, mineral salts, etc., it makes up roughly 10–25 percent of opium. The morphine alkaloids, codein and thebaine, are closely linked to morphine. Roots of Rauwolfia serpentina and R. vomitoria contain the alkaloid reserpine. Reserpine blocks the entry of norepinephrine into storage vesicles, causing serotonin and other neurotransmitters like catecholamines to be depleted from both central and peripheral axon terminals.

2.14 TERMINAL QUESTIONS

1. What are alkaloids? Classify them.

3. Write about Isolation methods of alkaloids.

4. Write short note on the isolation of alkaloids.

5. Give the general methods of structural determination of terpenoids.

6. Give structural determination of the Morphine.

7. Give structural determination of the reserpine.

2.15 REFERENCES

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UNIT -3: STEROIDS

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3.1 Introduction

3.1.1 Classification of steroids

3.1.2 Synthetic steroids

3.2 Objective

3.3 Structure and nomenclature of steroids

3.4 Stereochemistry of steroid

3.5 Diel's hydrocarbon

3.6 Cholesterol

3.6.1 Structure of cholesterol

3.6.2 Synthesis of cholesterol

3.6.3 Biosynthesis of cholesterol

3.7 Testosterone

3.7.1 Testosterone Structure and stereochemistry

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3.8.1 Structure of estrone (Oestrone)

3.8.2 Synthesis of estrone (Oestrone)

3.8.3 Biosynthesis of estrone (Oestrone)

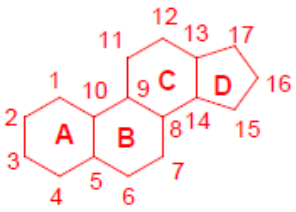
3.9 Summary

3.10 Terminal questions

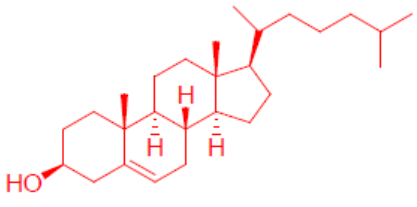
3.11 References and bibliography

3.1 INTRODUCTION:

Steroids are the class of naturally occurring organic compounds with tetracyclic system (four rings) system composed of three six membered rings and one five membered ring arranged in a specific molecular configuration. Methyl groups are normally present at C-10 and C-13. An alkyl side chain may also be present at C-17. Sterols are steroids carrying a hydroxyl group at C-3 and most of the skeleton of cholestane. Additional carbon atoms may be present in the side chain. Steroids exhibit two principal biological functions such as important components of cell membranes which alter membrane fluidity and as signaling molecules.



Steroid Ring



Cholesterol

Hundreds of steroids can be found in animals, plants, and fungi. They are also called corticosteroids which can act as inflammatory medicines. In animals, the most abundant member of steroid is cholesterol, which is the precursor of all other steroids. Steroid hormones are involved in the functioning of the control of metabolism, development of sex characters, inflammation, functions related to the immune system, and salt-water balance. Cholesterol is also precursor for the synthesis of the bile acids. For example, the bile acid, cholic acid synthesized in liver, stored in gallbladder and secreted into the small intestine, where it acts as an emulsifying agent so that fats and oils can be digested by water-soluble enzymes.

3.1.1 Classification of steroids

The steroids are classified depending on the functions and structure. Steroids can be broadly classified into five groups: glucocorticoids, mineralocorticoids, androgens, estrogents, and progestins.

- Glucocorticoids are involved in metabolism of glucose, proteins and fatty acids. Cortisone is an example for this type of steroid. Cortisone is used as anti-inflammatory agent to treat arthritis.
- Mineralocorticoids are responsible for the increased reabsorption of Na^+, Cl^- and HCO_3^- ions by the kidneys that can lead to an increase in the blood pressure. Aldosteron is an example of a mineralocorticoid.
- Antrogens are male sex hormones. They are responsible for the development of male secondary sex characteristics during puberty. Testosterone is an example of androgens.
- Estrone and estradiol are female sex hormones known as estrogens. They are responsible for the development of female secondary characteristics and secreted by the ovaries. Estrogens also regulate the menstrual cycle.
- Progesterone is the hormone that is essential for the maintenance of preganancy. It also prevents ovulation during pregnancy.

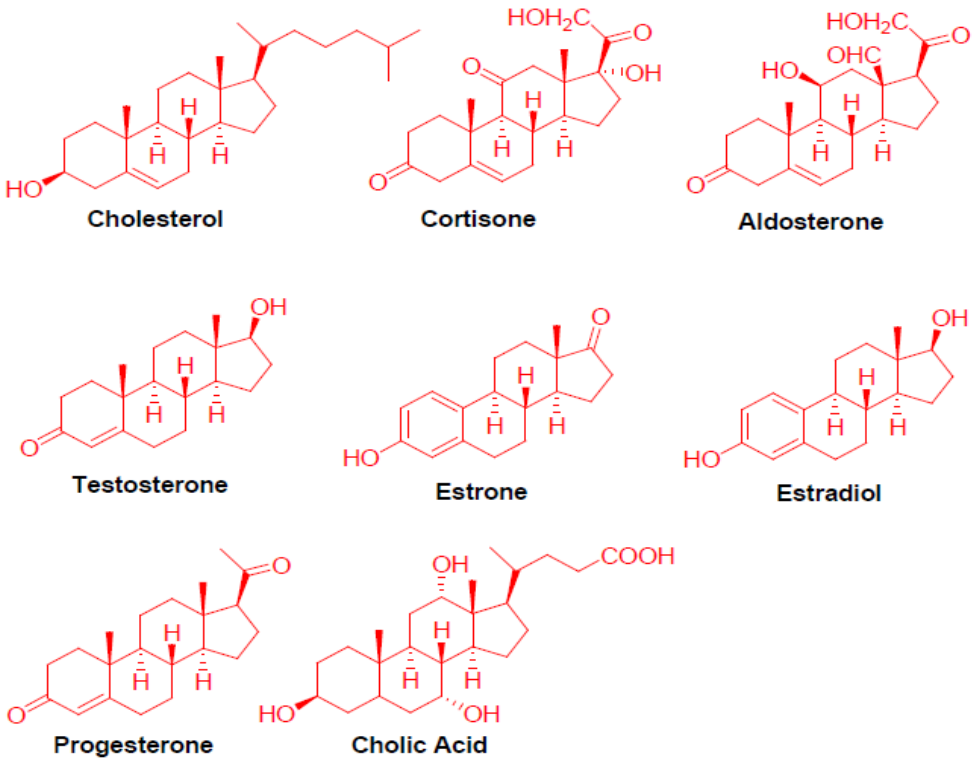


Fig. 3.1 Examples of Steroids

3.1.2 Synthetic steroids

- The potent physiological properties of naturally occurring steroids have led to the development of synthetic steroids. For examples, stanozolol and dianbol are drugs developed in this way exhibit the same muscle-building effect as testosterone.
- Some of the synthetic steroids have been found to be more potent than natural steroids. For examples, norethindrone is better than progesterone in arresting ovulation, while RU 486 terminates preganancy within the first nine weeks of gestation. These oral contraceptives have structures similar to that of progesterone.

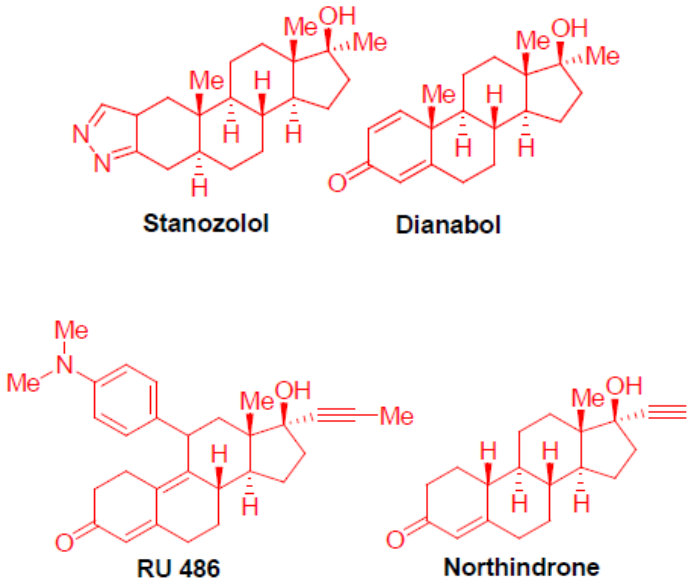


Fig. 3.2 Examples of Synthetic Steroids

3.2 OBJECTIVE:

After completing this section, learners should be able to

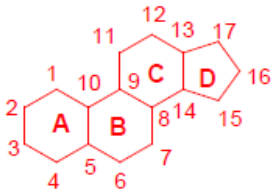
- Draw the tetracyclic ring system on which the structure of all steroids is based.
- Sketch the stereochemical conformation of a steroid, given an adequate wedge and dash structure, and determine whether the ring substituents in such a compound occupy axial or equatorial positions.

- The main aim of this unit is to introduce the learners to the basic structure, nomenclature and functions of steroids.
- To understand the biosynthesis of steroids.
- To learn about cholesterol‟s structure, precursor and its role in biomolecules.
- To learn about various sex hormones
- How do cholesterol, estrone and testosterone synthesize.

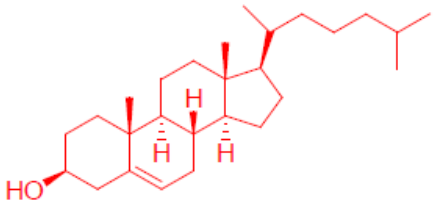
3.3 STRUCTURE AND NOMENCLATURE OF STEROIDS:

As per IUPAC system steroids have a common basic ring structures, three-fused cyclohexane rings, together the phenanthrene part, fused to a cyclopentane ring system, known as cyclopentaphenanthrene (Fig. 3.3). Three six-member cyclohexane rings (rings A, B and C) and one five-member cyclopentane ring (the D ring). These fused rings can be *trans* fused or *cis* fused. In steroids, the B, C and D rings are always *trans* fused. In most naturally occurring steroids, rings A and B are also *trans* fused. Different steroids vary in the functional groups attached to these rings.

The substituents designated by R are often alkyl groups, but may also have functionality. The R group at the A: B ring fusion is most commonly methyl or hydrogen, that at the C:D fusion is usually methyl. Many steroids have methyl groups at C-10 and C-13 positions. These are called angular methyl groups. Steroids may also have a side chain attached to C-17, and is usually larger than methyl. The most common locations of functional groups are C-3, C-4, C-7, C-11, C-12 & C-17. Many steroids have an alcoholic hydroxyl attached to the ring system, and are known as sterols. The most common sterol is cholesterol. All steroids possess at least 17 carbons and vary by the functional groups attached to this four ring. Almost all steroids are named as derivatives of their fundamental ring (Cyclopentanoperhydrophenanthrene ring**)** systems.



Steroid ring

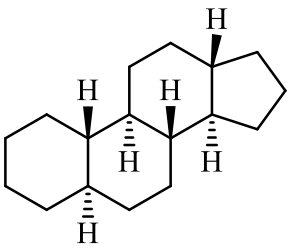


Cholesterol

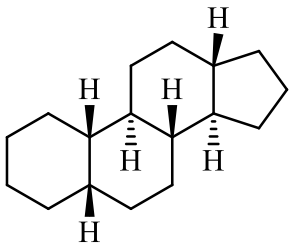
Fig. 3.3 Cyclopentanoperhydrophenanthrene ring in steroid

- Solid line indicates groups above the plane of the nucleus (β-configuration) and dotted line denote groups below the plane (α- configuration).
- The configuration of the hydrogen (-H) at C-5 position is always indicate in the name.
- Compounds with 5-α cholestane belong to the 'allo series' while compounds derived from the 5-β- cholestane belongs to the 'normal series'.
- If the double bond is not between sequence numbered carbon, in that case both carbons are indicated in the name.
- The symbol δ(delta) is used to indicate C=C bond in steroids.
- When a methyl group is missing from the side chain, these are not indicated by the prefix 'nor' with the number of the carbon atom which is disappear.

Gonane: The parent tetracyclic hydrocarbon without methyl groups at C-10 and C-13 and without a side chain at C-17 is named gonane (C =17) (Fig. 3.4). For example 5 (α or β) gonane.



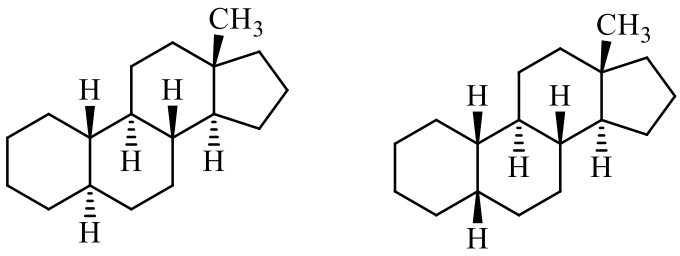
5α-Gonane



5β-Gonane

Fig. 3.4 Structure of Gonane

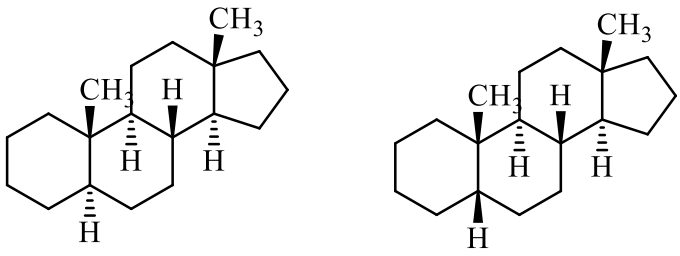
Estrane: The hydrocarbon with a methyl group at C-13 but without a methyl group at C-10 and without a side chain at C-17 is named as estrane (C =18) (Fig. 3.5). For example 5 (α or β) estrane



5α-Estrane 5β-Estrane

Fig. 3.5 Structure of Estrane

Androstane: The hydrocarbon with methyl groups at C-10 and C-13 but without a side chain at C-17 is named as androstane (C =19) (Fig. 3.6). For example 5 (α or β) androstane



5α-Androstane 5β-Androstane

Fig. 3.6 Structure of Androstane

Pregnane: The hydrocarbon with methyl groups at C-10 and C-13, with a side chain at C-17 upto C-21 containing is named Pregnane (C=21) (Fig. 3.7). It is a parent hydrocarbon for two series of steroids stemming from 5α-pregnane and 5β-pregnane.

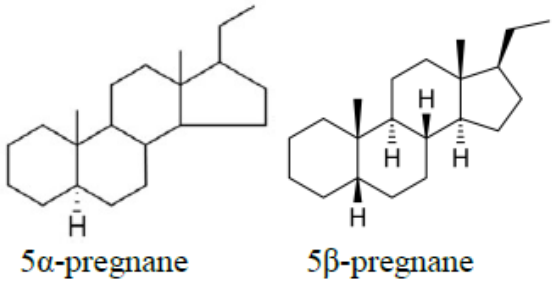


Fig. 3.7 Structure of Pregnane

Cholane & Cholestane: The hydrocarbon with methyl groups at C-10 and C-13, with a side chain at C-17 upto Carbon chain 24 is named Cholane and upto Carbon chain 27 named Cholestane (Fig. 3.8).

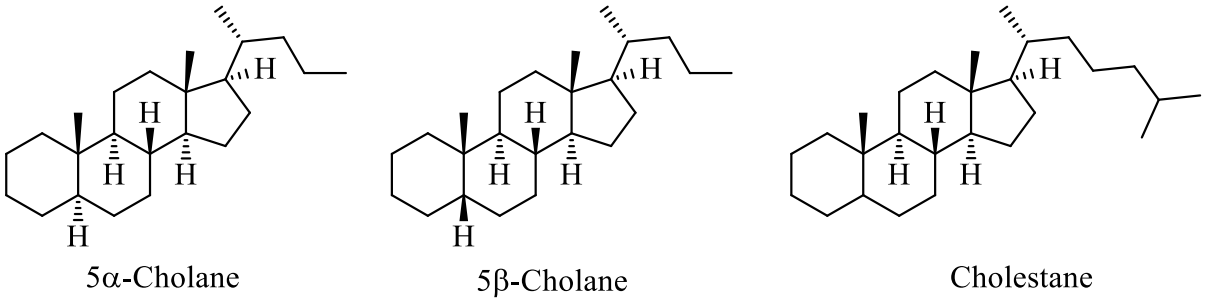


Fig. 3.8 Structure of Cholane & Cholestane

3.4 STEREOCHEMISTRY OF STEROID:

- There are six asymmetric carbon atoms/ chiral centres 5,8,9,10,13,14 in the nucleus, therefore 64 optically active forms are Possible (Fig. 3.9). The absolute stereochemistry of a steroid is defined by the parent name for some chiral centres α,β, R or S for other centres. When the configuration at one or more centres is not known, this is indicated by the Greek letter ξ (xi).

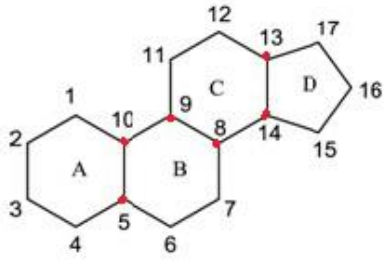


Fig. 3.9 Structure of steroids with assymmetric centre/ chiral centre

- Cholestane, androstane and pregnane exist in two conformations such as chair form and boat form. Chair form is more stable then boat form due to less angle strength, therefore all cyclohexane ring in steroid nucleus exist in the chair form (Fig. 3.10).

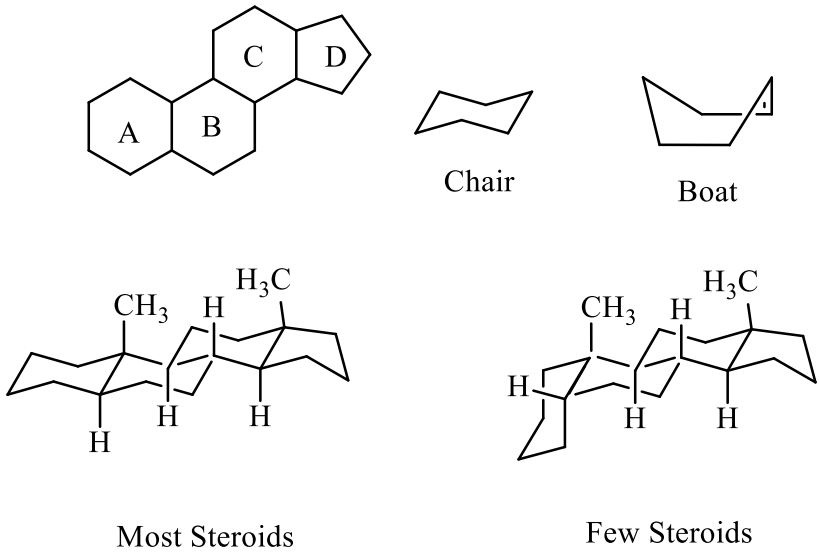


Fig. 3.10 Conformations of steroids

- If the atom or group attached to the ring depicted as orientation above the plane named β (beta) and if the attached group below the plane termed as α (alpha). Bond to atoms or gropus/ substituent laying below the plane α (alpha) represented as broken line (------) and bond to atoms or gropus lying above the plane β (beta) represented as solid line/thikened line (—). Bonds toatoms or groups whose configuration is not known are denoted by wavy lines (~~). Thus the absolute stereochemistry of the molecule and any substituent is shown with solid bond (β configuration) and dotted bond (α-configuration) (Fig. 3.11).

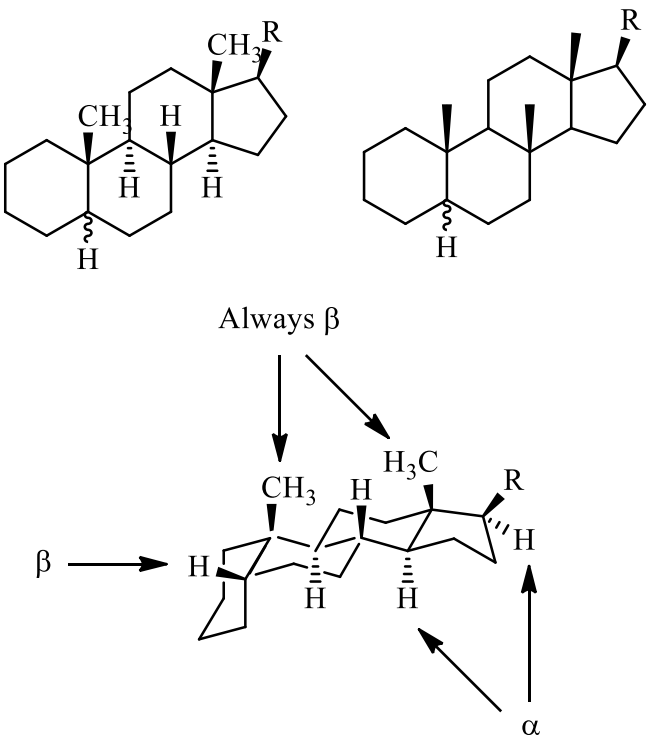
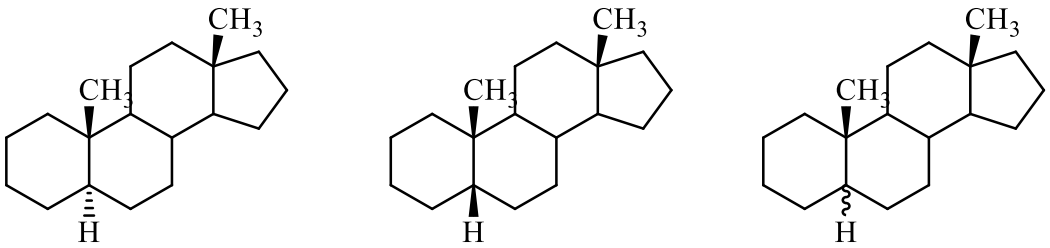


Fig. 3.11 Configuration of steroids

- Steroid name implies that atoms or groups attached at the bridgehead positions 8, 9, 10, 13 and 14 are oriented as shown in Fig. 3.11 (i.e. 8β,9α,l0β,l3β,14α), and a side chain attached at position 17 is assumed is always assumed to be β-configuration. The configuration of hydrogen (or a substituent) at the bridgehead position 5 is always to be designated by adding α, β or ξ after the numeral 5 (Fig. 3.12). The stereochemistry of substituents attached to the tetracyclic system A-D is stated by adding α, β or ξ after the respective numerals denoting their position.
- The term *cis* and *trans* are sometimes used to indicate the backbone stereochemistry between the rings. Example; 5-α- steroid are A/B Trans and 5-β- steroids are A/B Cis. If A/B fusion *cis* and *trans* both position possible or position is unknown, it is indicated by waving lines/bonds (Fig. 3.12).



5α-Steroid
A/B trans

5β-Steroid
A/B cis

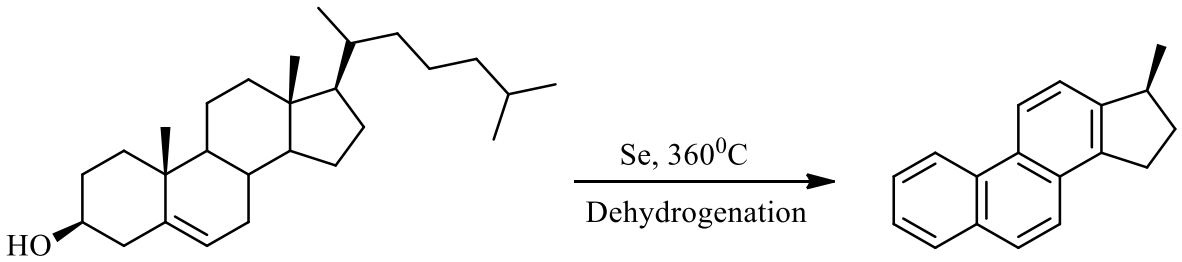
Fig. 3.12 Structure of 5α and 5β steroid and cis, trans steroid

- The stereochemistry of double bonds in the side chain should be indicated using the E,Z convention.

3.5 DIEL'S HYDROCARBON:

In 1934 Otto Paul Hermann Diels synthesized hydrocarbon by the chemical dehydrogenation of polynuclear compounds (cholesterol). The structure of obtained hydrocarbon, $C_{18}H_{16}$, m.p. 127^0C, by Se-dehydrogenation of cholesterol was determined, and the compound is known as Diels hydrocarbon (Fig. 3.13).

This method was applied by Diels to other steroids; many of them produced the same carbon scaffold Diels hydrocarbon. Its structure gave a vital clue to the structures of steroids; all of them contain four rings (methylcyclopentanoperhydrophenanthrene) and thus this skeletal pattern as derived by Diels has become the identifying feature of the steroids.



Cholesterol
($C_{27}H_{46}O$)

Diel's Hydrocarbon
($C_{18}H_{16}$)

Fig. 3.13 Structure of Diels Hydrocarbon

3.6 CHOLESTEROL:

Cholesterol is a tetracyclic alcohol and a type of sterol (steroids have an alcoholic hydroxyl attached to the ring system, and are known as sterols). Added to the sterol frame with the alcohol group at position 3 are 2 methyl groups at carbon positions 10 and 13 and a 2-isooctyl group at position 17. The molecule is unsaturated at position 5,6 with an alkene group. Cholesterol has 8 asymmetric centers, thus 256 stereoisomers are possible. However, in nature only one exists. Cholesterol is an important component of cell membranes and related to heart disease (Fig.3.14)

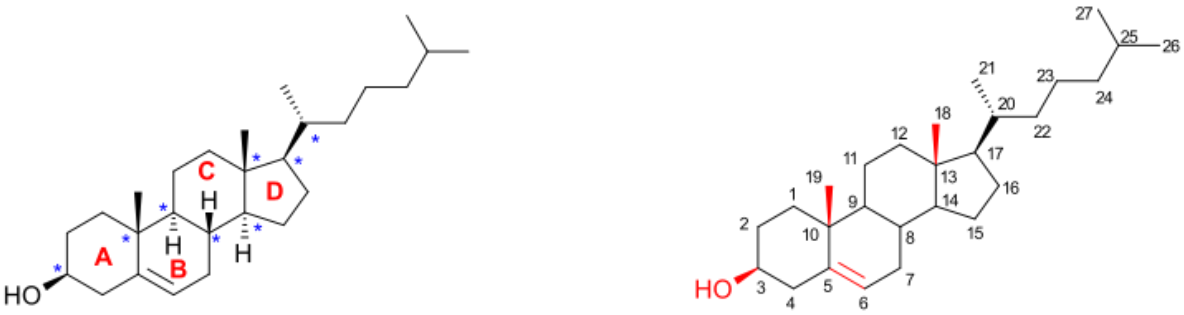


Fig. 3.14 Structure of Cholesterol with chiral centre

3.6.1 Structure of cholesterol :

Cholesterol is white crystalline soild with molecular formula $C_{27}H_{46}O$ having melying point149^{o}C. It is optically active and levorotatory in the nature. The structure consist four ring, hydroxyl group, double bond, methyl group and side chain. Hence the structure can be explained under the following points (Fig. 3.15):

(a) Structure of nucleus (ring)

(b) Nature and position of hydroxyl group

(c) Position of double bond

(d) Nature and position of side chain

(e) Position of the two angular methyl groups

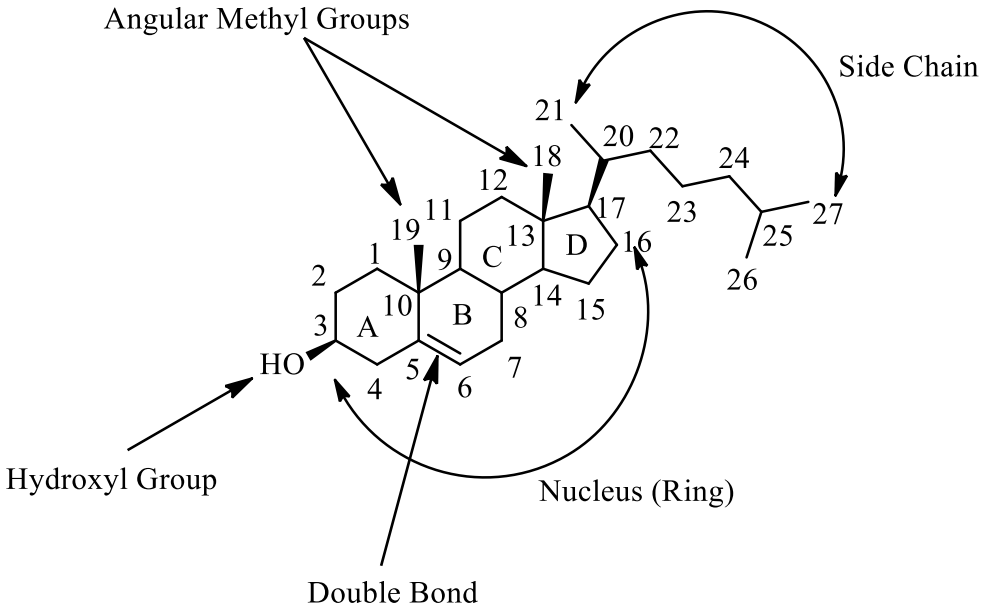


Fig. 3.15 Complete structure of cholesterol

(a) Structure of nucleus (ring)

Cholesterol contain cyclopentenophenanthrene nucleus (tetracyclic ring). It is confirmed by the formation of Diels hydrocarbon by Se-dehydrogenated at 360°C of cholesterol. The formation of dicaroxylic acid, tricarboxylic acid and cyclic anhydride from the cholesterol indicat that the cholesterol contained three six memberd ring and one five memberd ring (Fig. 3.16).

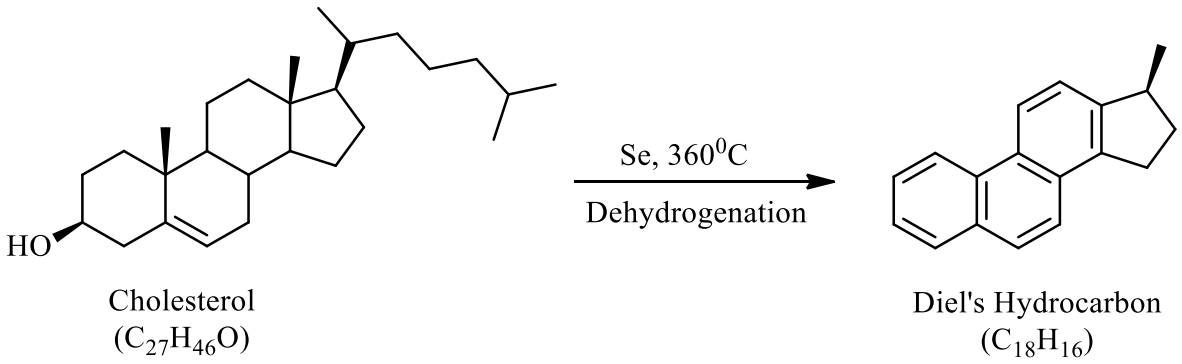


Fig. 3.16 Structure of nucleus in cholesterol

(b) Nature and position of hydroxyl group

When the cholesterol catalytically reduced followed by the oxidation with chromic acid give the cholestanone. Cholestanone upon the oxidation with nitric acid prodiced dicarboxylic acid and upon the pyrolysis gives the Ketone. This indicated that the hydroxyl group present at ring A and secondary in the natutre. When the cholestanone is treated with methyl magnesium iodide followed by the selenium dehydrogenation gives 3,7-dimethylcyclopentenophenanthrene this indicat that hydroxy group present at position C-3 (Fig 3.17).

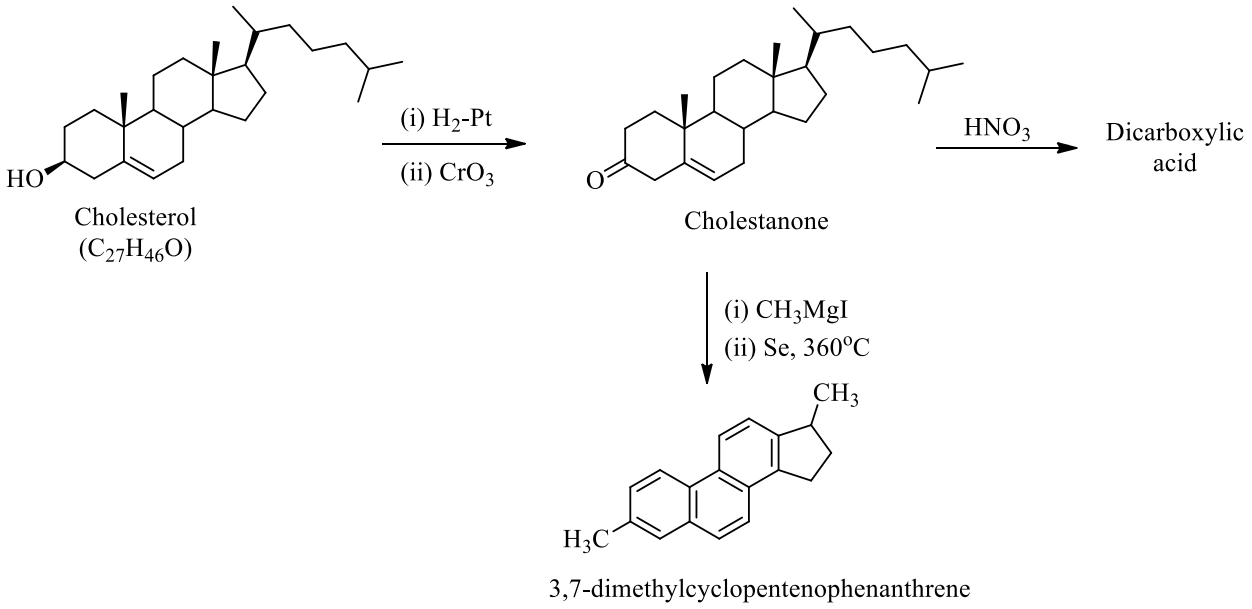


Fig. 3.17 Nature and position of hydroxyl group in cholesterol

(c) Position of double bond

The position of the double bond can be confirmed by the reaction in which cholesterol gives the cholestanetriol upon hydroxylation. The obtained cholestanetriol oxidised with chromic acid followed by zinc acetate to gives diketone viz. hydroxycholestanedione and cholestanedione. Cholestanedione further oxidised into tetracarboxylic acid with chromic acid and gives the pyridazine derivative when treated with hydrazine. The above reaction showed that the double bond present at ring B between C-5 and C-6 of cholesterol and at γ-position with repect to hydroxyl group present at C-3 of ring A (Fig. 3.18).

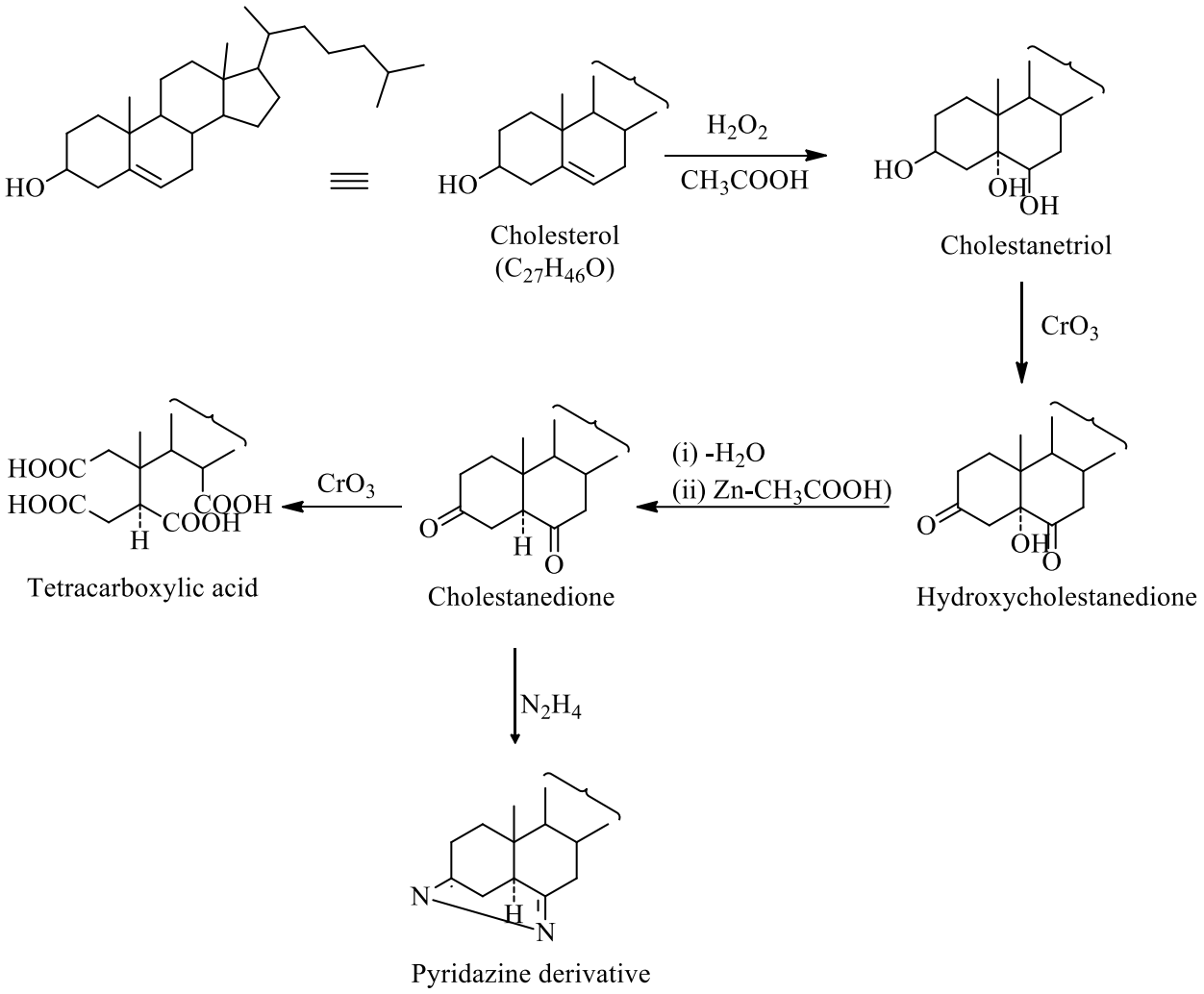


Fig. 3.18 Position of double bond in cholesterol

(d) Nature and position of side chain

The nature and position of side chain in the structure of the cholesterol was confirmed by the accylation and oxidation reaction of cholesterol. Cholesteryl acetate was produced from the accylation of cholesterol and this accetylated product further oxidised by chromium trioxide gives steam volatile ketone (isohexyl methyl ketone) and non steam volatile acetate of hydroxy ketone. The formation of isohexyl methyl ketone confirmed that the side chain attached with the carbon of keto group. Hence the side chain attached at C-17 in the cholesterol structure (Fig. 3.19).

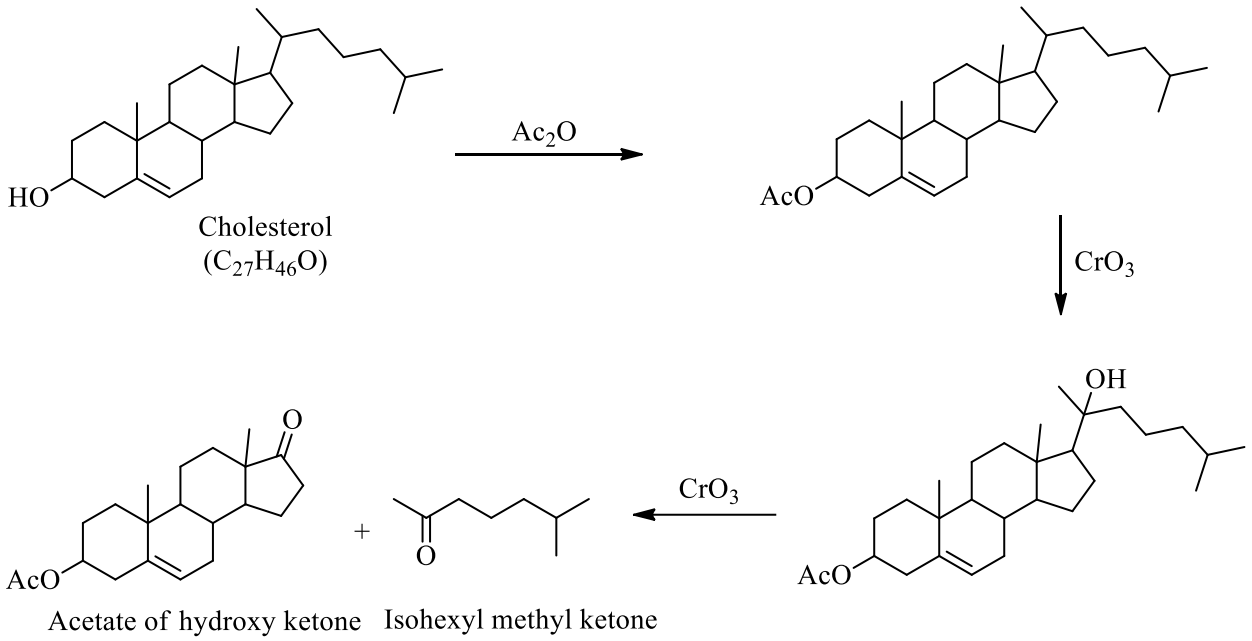


Fig. 3.19 Position and nature of side chain in cholesterol

(e) Position of the two angular methyl groups

The complete structure of cholesterol was dived into two parts, first part cyclopentenophenanthrene nucleus having total 17 carbons and second part side chain having total 8 carbons. The cholesterol contains total 27 carbon atom it means two remaining carbon atom present in the form of two angular methyl group. These two methyl group confirmed from the following reaction:

(i) When the cholesterol was heated with copper ooxide at 290°C gives cholestenone which further upon oxidation with permagnate gives keto acid. The obtained keto acide reduced by Clemention reduction followed by the Barbier-Wieland degradation to gives the acid. In the obtained acid carboxyl group attached to a tertiary carbon atom. Hence alkyl group present at position C-10 (Fig. 3.20).

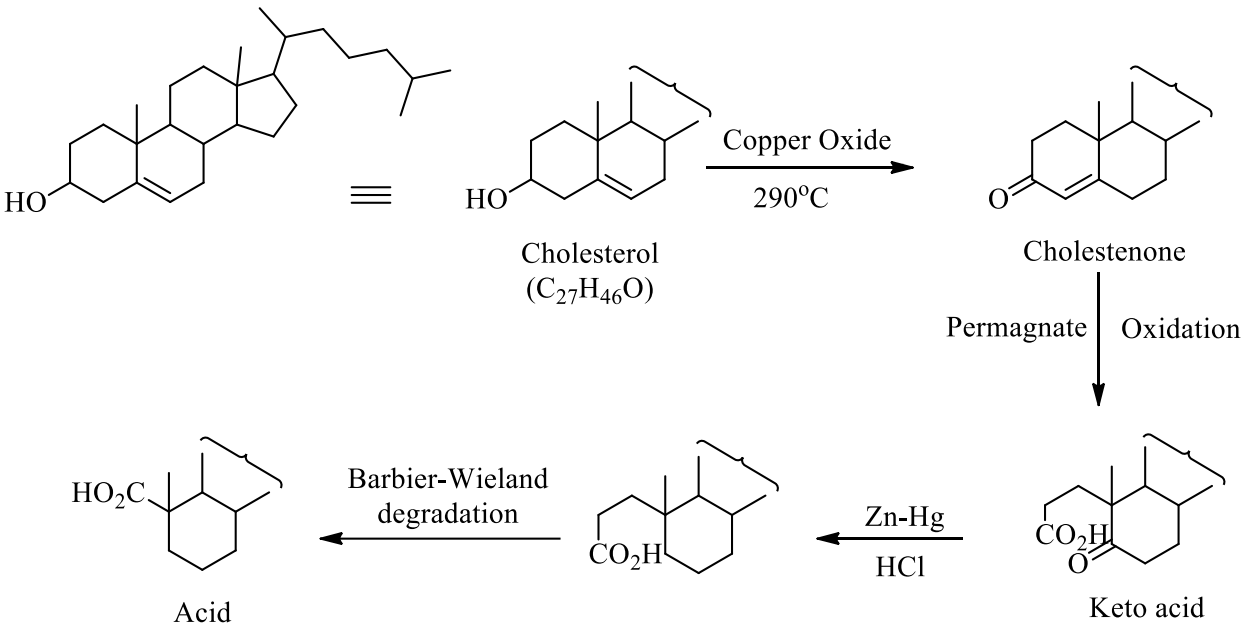


Fig. 3.20 Position of methyl group at C-10 in cholesterol

(ii) Cholesterol upon the Se-dehydrogenation gives Diel's hydrocarbon and chrysene. In the Se-dehydrogenation the methyl group enters into five memberd ring to form six memberd rings to produced chrysene. Hence the methyl group present at C-13 (Fig.3.21).

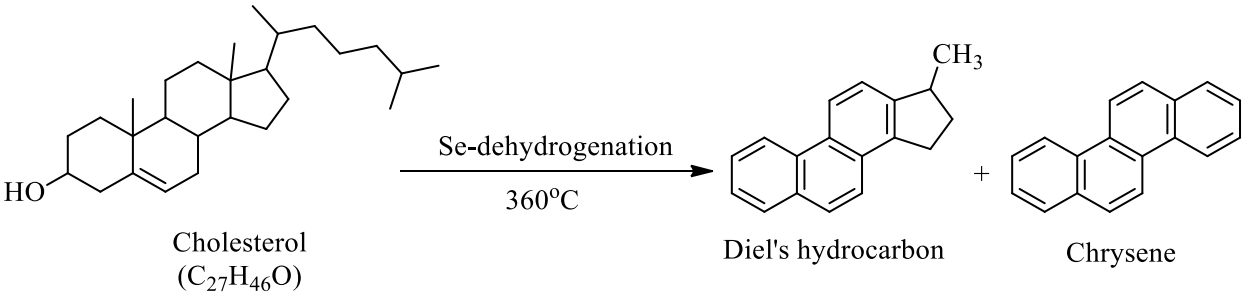


Fig. 3.21 Position of methyl group at C-13 in cholesterol

3.6.2 Synthesis of cholesterol

Cholesterol is synthesized in the following steps:

(i) The starting material in the synthesis of cholesterol is 4-methoxy-2,5-toluquinone (I). The compound (I) on the condensation with butadiene (II) in the presence of acid gives product trans-isomer compund (III). The obtained compound (III) reduced with lithium almunium hydride (LiAlH4) in the presence of aqueous acid to give hydrated compound (IV).

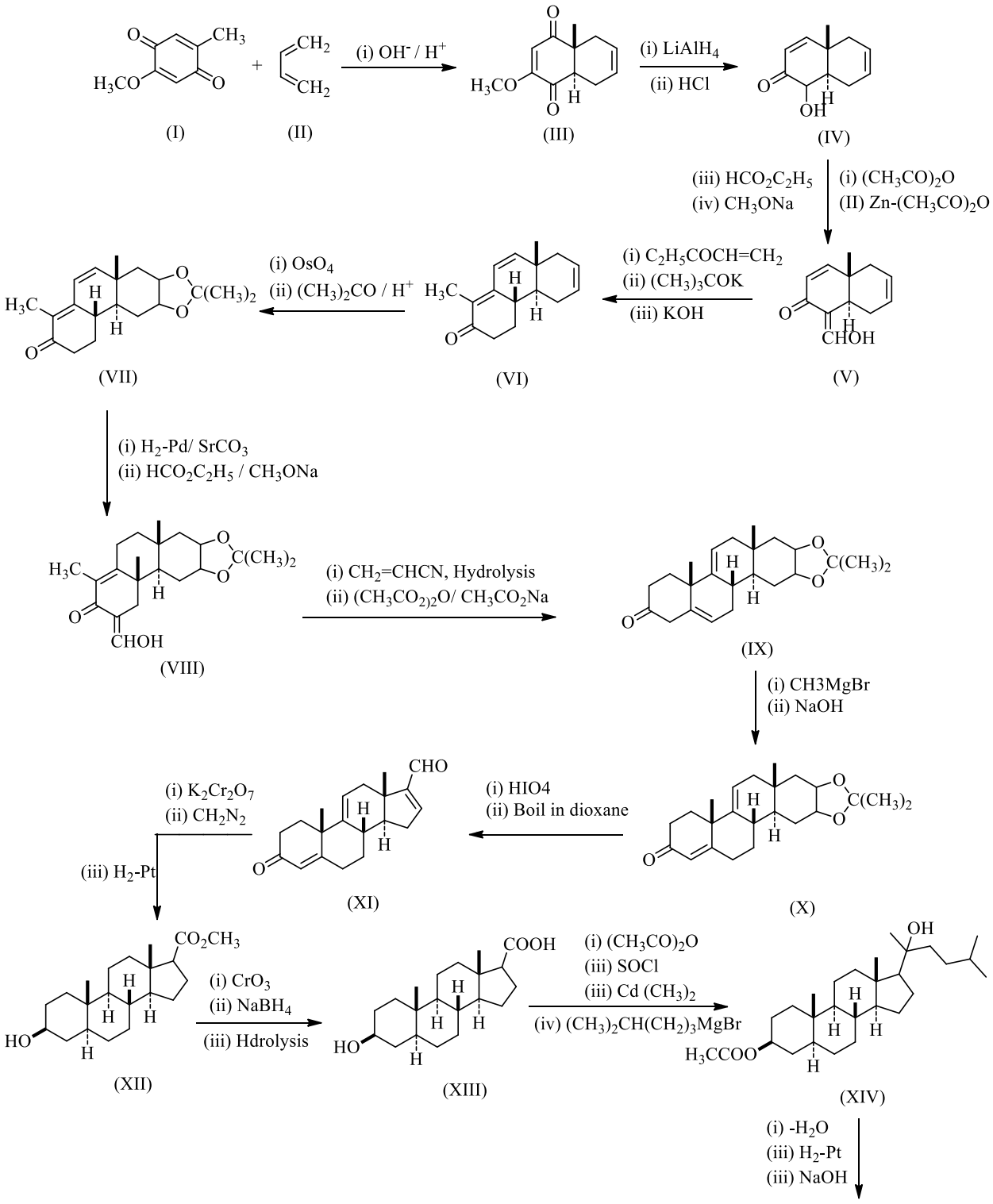
(ii) The obtained compound (IV) acetylated with acetic anhydride in the presence of zinc acetic anhydride followed by the Claisen condensation in the presence of ethyl formate and sodium methoxide to give compound (V). This compound (V) undergoes Michael condensation in the presence of potassium t-butoxide and cyclised with KOH in dioxan to produced compound (VI).

(iii) The product (VI) treated with osmium tetraoxide to gives cis-glycol followed by the reaction with acetone in the presence of copper sulphate to gives compound (VII). The reduction of compound (VII) with H_2-Pd/$SrCO_3$ and condensation with sodium methoxide gives the product (VIII).

(iv) The product (VIII) treated with methylaniline and condensation reaction with vinyl cinide followed by hydrolysis gives the product (IX). This compound treated with methylmagnesium bromide followed by ring closer with alkali to form compound (X) which upon oxidation with periodic acid in dioxan give the product (XI).

(v) Compound (XI) oxidised with $K_2Cr_2O_7$ followed by the treatment with diazomethane and catalytic reduction with H_2-Pt to gives the compound (XII). The obtained compound further oxidised with CrO_3 and reduced with $NaBH_4$ and upon hydrolysis gives the product (XIII). The compound (XIII) now acetylated and treated with thionylchoride and dimethyl cadmium followed by the reaction with isohexyl magnesium bromide to produce compound (XIV).

(vi) Compound (XIV) upon dehydration and catalytic hydrogenation gives the cholestanol (XV). The obtained cholestanol now oxidised and reduced wthe several reagent to produced compound (XVI) and then final product cholesterol (XVII) obtained. The complete reaction involved in the synthesis of choleterol was represented in the Fig. 3.22.


(I)
(II)
(i) OH⁻ / H⁺
(III)
(i) LiAlH4
(ii) HCl
(IV)
(iii) HCO2C2H5
(iv) CH3ONa
(i) (CH3CO)2O
(II) Zn-(CH3CO)2O
(V)
(i) C2H5COCH=CH2
(ii) (CH3)3COK
(iii) KOH
(VI)
(i) OsO4
(ii) (CH3)2CO / H+
(VII)
(i) H2-Pd/ SrCO3
(ii) HCO2C2H5 / CH3ONa
(VIII)
(i) CH2=CHCN, Hydrolysis
(ii) (CH3CO2)2O/ CH3CO2Na
(IX)
(i) CH3MgBr
(ii) NaOH
(X)
(i) HIO4
(ii) Boil in dioxane
(XI)
(i) K2Cr2O7
(ii) CH2N2
(iii) H2-Pt
(XII)
(i) CrO3
(ii) NaBH4
(iii) Hdrolysis
(XIII)
(i) (CH3CO)2O
(iii) SOCl
(iii) Cd (CH3)2
(iv) (CH3)2CH(CH2)3MgBr
(XIV)
(i) -H2O
(iii) H2-Pt
(iii) NaOH

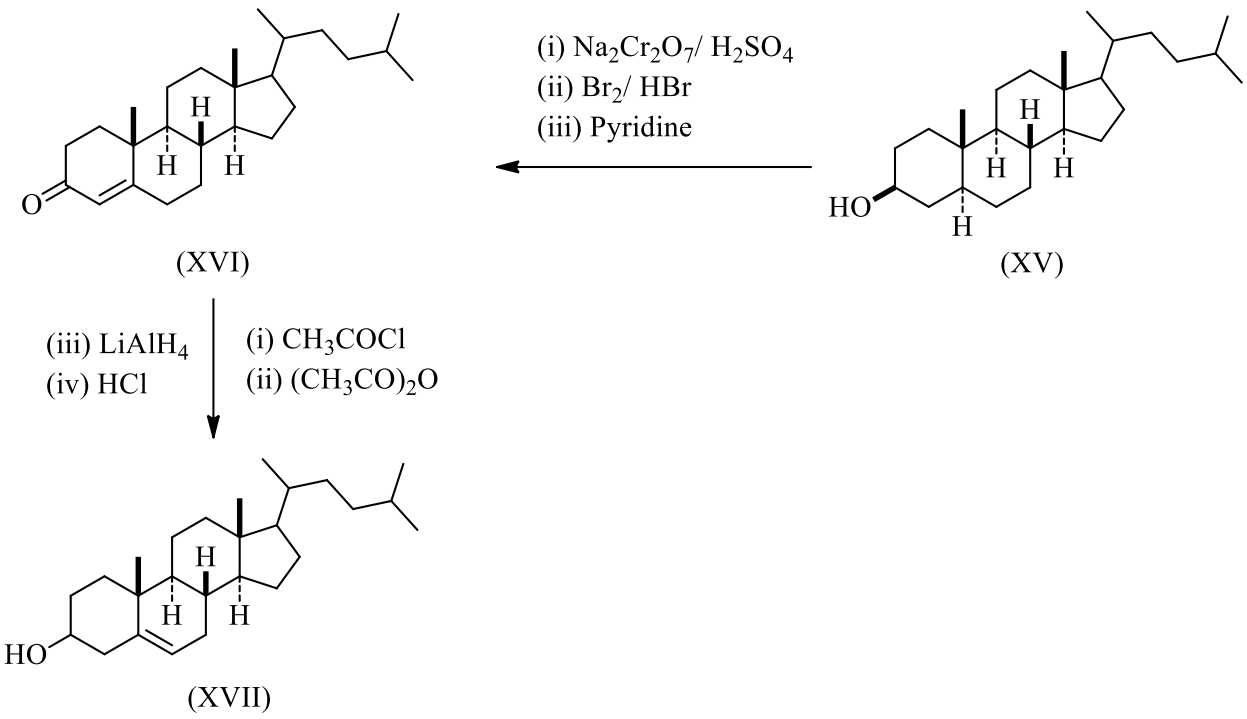


Fig. 3.22 Synthesis of cholesterol

3.6.3 Biosynthesis of cholesterol

Cholesterol is synthesized from acetyl-CoA in the following steps:

(i) Biosynthesis of cholesterol is believed to start with labelled acetic acid. Acetic acid which acts as active acetate combines with coenzyme-A to form active acetate, which rearranges to aceto acetyl CoA. Thus In the first step, two molecules of acetyl-CoA upon the action of thiolase reversibly forms acetoacetyl-CoA.

(ii) Acetoacetyl-CoA combines with one molecule of active acetate to form hyroxymethylglutarate having R configuration. It is then reduced by NADPH to mevaldic acid, which is further reduced to mevalonic acid.

(iii) Mevalonic acid contains six carbon atoms, one carbon is lost by phosphorylation process to yield isoprene unit. Two phosphorylation of mevalonic acid followed by loss of molecule of carbon dioxide (decarboxylated) and water to form 3-methylbutyl-3-enyl(isopentyl) pyrophosphate (A) which isomerises to 3-methylbut-2-enyl(β,β dimethylallyl) pyrophosphate

(B). Thus mevalonate/ mevalonic acid is phosphorylated from ATP to form the 5-carbon (C-5) isoprene units or isoprenoids, namely isopentyl pyrophosphate, which can isomerize or interconvert to dimethylallyl pyrophosphate.

(iv) Two isopentenyl pyrophosphate units condense, forming a C-10 compound, geranyl pyrophosphate, which reacts with another C-5 unit to form a C-15 compound, farnesyl pyrophosphate.

(v) Two farnesyl pyrophosphate molecules undergo tail to tail union to give squalene via NADPH.

(vi) Squalene is formed from two C-15 units and then oxidized and multicyclization intiated by epoxide cleavage to give protosterol carbonium ion two undergo two methyl shifts to give lanosterol.

(vii) Lanosterol is converted to cholesterol in a series of steps. In which methyl group at C-14 is first oxidized to hydroxymethyl and then to carboxyl group followed by decarboxylation to give 14-desmethyl lanosterol. Removal of 4,4-gem dimethyl group proceed through oxidation to hydroxymethyl and then to carboxyl group which decarboxylate to give zymosterol. Isomerization of double bond from 8,9 to 7,8 and then to 5,6 followed by reduction of double bond at C-24 and C-25 gives cholesterol.

(viii) The overall representation and biosynthesis of steroids (cholesterol) was mentioned in the fig.3.23 and 3.24.

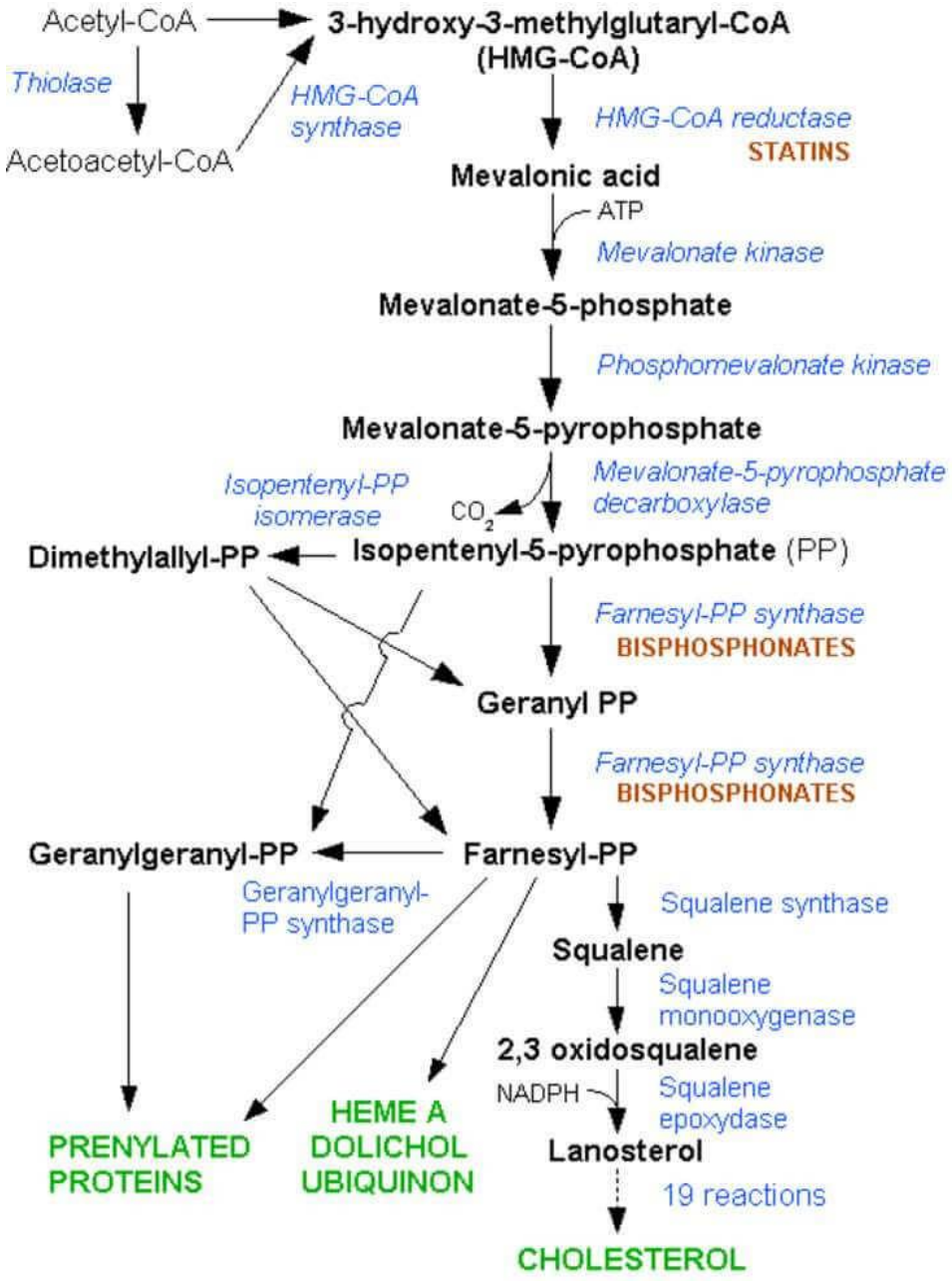


Fig. 3.23 Graphical representation of biosynthesis of cholesterol

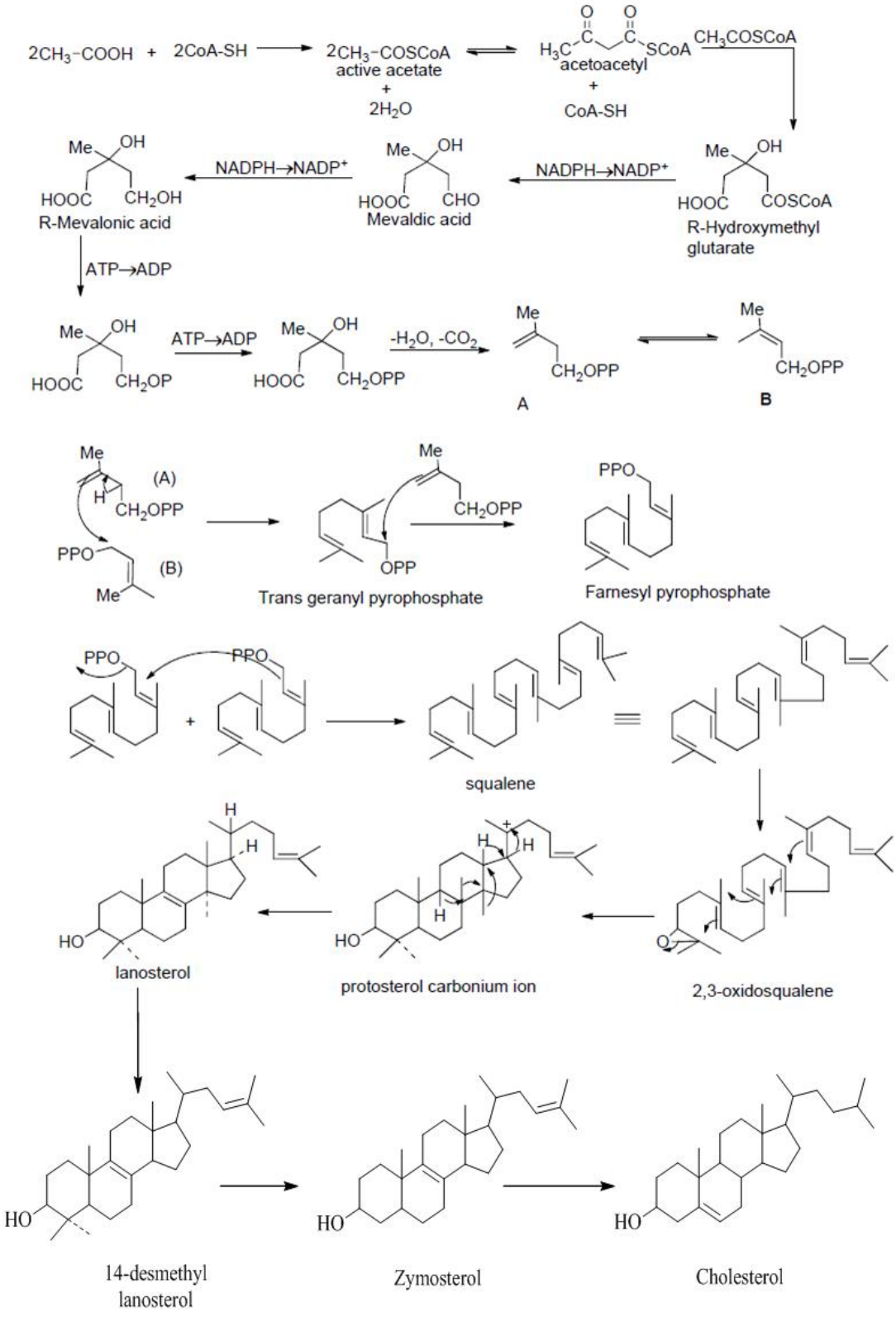


Fig. 3.24 Biosynthesis of cholesterol

3.7 TESTOSTERONE :

Testosterone is the major male reproductive hormone secreted by Leydig cells of testis. In male humans, testosterone plays a key role in the development of male reproductive tissues such as testes and prostate, as well as promoting secondary sexual characteristics such as increased muscle and bone mass, and the growth of body hair. Chemically it is a 19 carbon steroid hormone (androstane) and its IUPAC name is 17β-Hydroxyandrost-4-en-3-one (Fig. 3.25).

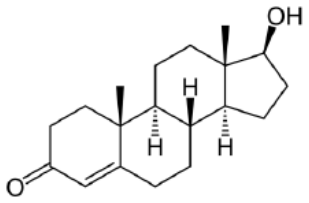
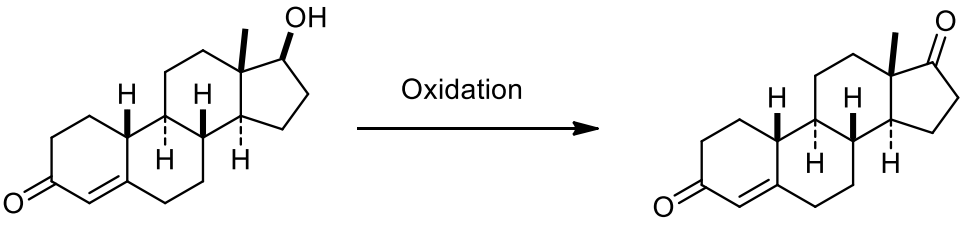


Fig. 3.25 Structure of testosterone

3.7.1 Testosterone structure and stereochemistry

Testosterone is an androstanoid with molecular formula $C_{19}H_{28}O_2$. The experimental data sugessted that testosterone have tetracyclic hydrocarbon which contain one double bond, one ketonic group and a secondary alcohol. When the compound treated with alkali data reveals that it contains α,β-unsaturated ketone which showe the UV absorption band at (λ_{max}=240nm). The diketone (androst-4-ene-3,17-dione) was obtained from the oxidation of testosterone. Which suggested that testosterone contains 17-beta-hydroxy and 3-oxo groups, as well as C-4,C-5 unsaturation (Fig. 3.25).



The stereochemistry of the tesrosterone was established by the preparation of the testosterone from cholesterol. The hydroxyl group present at C-17 is conformed as β-type by the molecular rotation measurments.

3.7.2 Synthesis of testosterone

Testosterone from cholesterol was synthesised by the method given by Ruzicka and Butenandt. Cholesterol on acetylation, bromination followed by oxidation yields dehydroepiandrosterone. Acetylation followed by selective hydrogenation reduces the C-17 carbonyl group. Benzoylation followed by selective hydrolysis and oppenauer oxidation yields testosterone (Fig. 3.26).

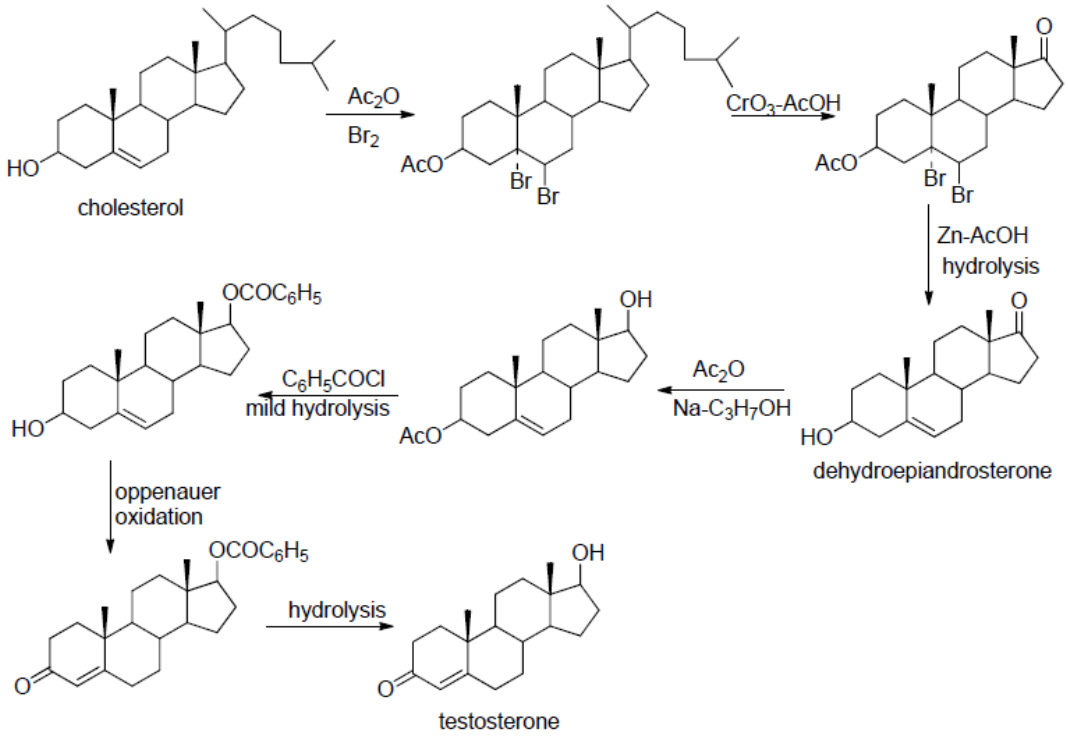


Fig. 3.26 Synthesis of testosterone

3.7.3 Biosynthesis of testosterone

The first step in the biosynthesis involves the oxidative cleavage of the side-chain of cholesterol by cholesterol side-chain cleavage enzyme (cytochrome P-450), a mitochondrial cytochrome P-450 oxidase with the loss of six carbon atoms to give pregnenolone. In the next step, two additional

carbon atoms are removed by the CYP17A1 (17α-hydroxylase/17,20-lyase) enzyme in the endoplasmic reticulum to yield a variety of C-19 steroids. In addition, the 3β-hydroxyl group is oxidized by 3β-hydroxysteroid dehydrogenase to produce androstenedione. In the final and rate limiting step, the C-17 keto group androstenedione is reduced by 17β-hydroxysteroid dehydrogenase to yield testosterone (Fig. 3.27).

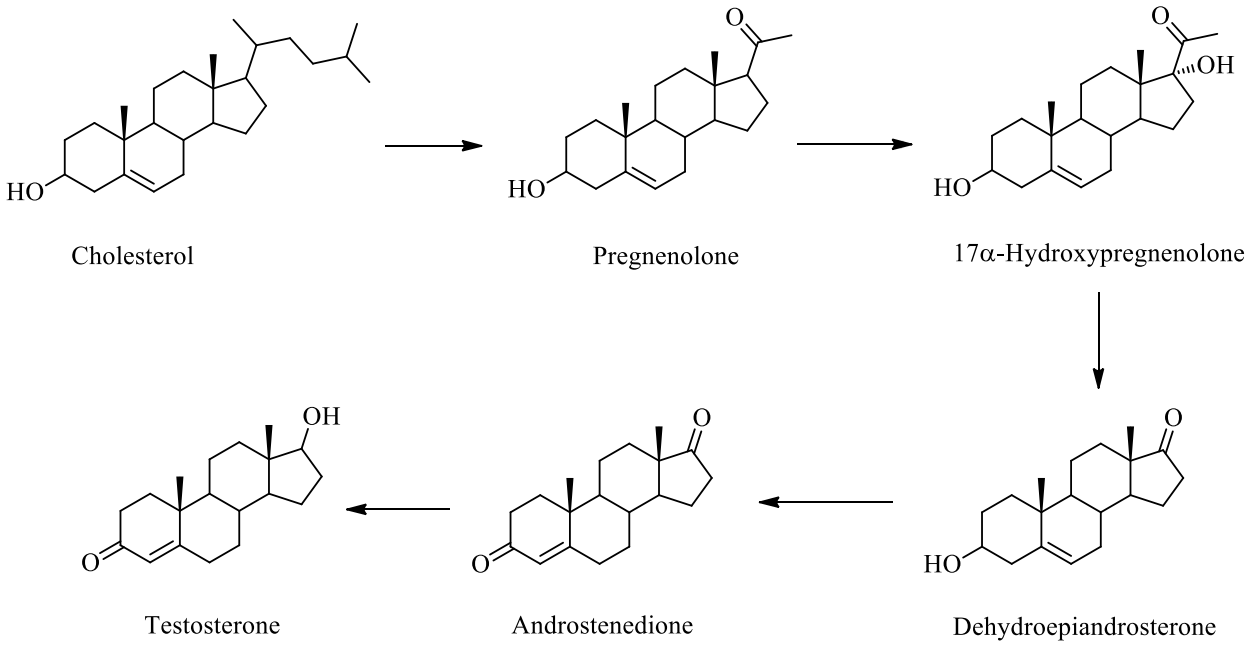


Fig. 3.27 Biosynthesis of testosterone

3.8 ESTRONE (OESTRONE):

Estrone is female sex hormones known as estrogens. They are responsible for the development of female secondary characteristics and secreted by the ovaries.Estrone was characterised by the absence of CH_3 group at C-10 and by aromatic nature of ring A, making the OH group phenolic (Fig. 3.28).

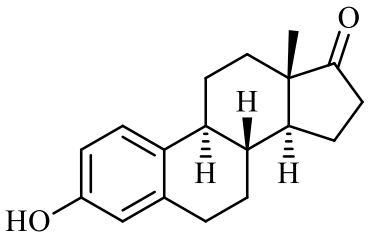


Fig. 3.28 Structure of estrone

3.8.1 Structure of estrone (Oestrone)

Estrone exists in the rhombic and monoclinic crystaline form with molecular formula $C_{18}H_{22}O_2$. The structure of estrone explains on the baisis of following points:

(a) Presence of steroid nucleus

(b) Presence of double bond and benzenoid ring

(c) Nature and position of phenolic-OH group

(d) Nature and position of keto group

(a) Presence of steroid nucleus

When the estrone treated with zinc dust it produced chrysene, showing that estrone related to steroid and contain the steroid nucleus. On the other hand Double bond equivalent of estrone is 8 which indicate that one unit is for keto group, three units for the three double bonds and four for the rings. Thus estrone is tetracyclic in nature.

(b) Presence of double bond and benzenoid ring

On catalytic hydrogenation estrone absorbs four moles of hydrogen forming Octahydroestrone $C_{18}H_{30}O_2$. This compound contains two hydroxyl groups. One mole of hydrogen was used for converting keto to secondary hydroxyl group while three mole of hydrogen are use for saturation of three double bond. If the three double bonds are in one ring i.e benzenoid ring is present then only the phenolic group can be accounted. The presence of benzene ring was confirmed by UV which showed λmax at 280 nm.

(c) Nature and position of phenolic-OH group

On reaction with acetic anhydride, estrone forms mono acetate. Indicating the presence of one hydroxyl group. This hydroxyl group was found to be phenolic in nature as estrone forms coloured complex with $FeCl_3$ and it also couples with diazonium salt in alkaline medium.

When monomethyl ether of estrone is subjected to Wolf-Kishner reduction it yields a product, which on distillation with selenium yields 7-methoxy 1,2-cyclopentenophenanthrene. Formation of 7-methoxy 1,2-cyclopentenophenanthrene suggests that estrone contains a steroid nucleus and

hydroxyl group (Phenolic –OH) is present at position 3, which is in ring A. Thus ring A is aromatic (Fig 3.29).

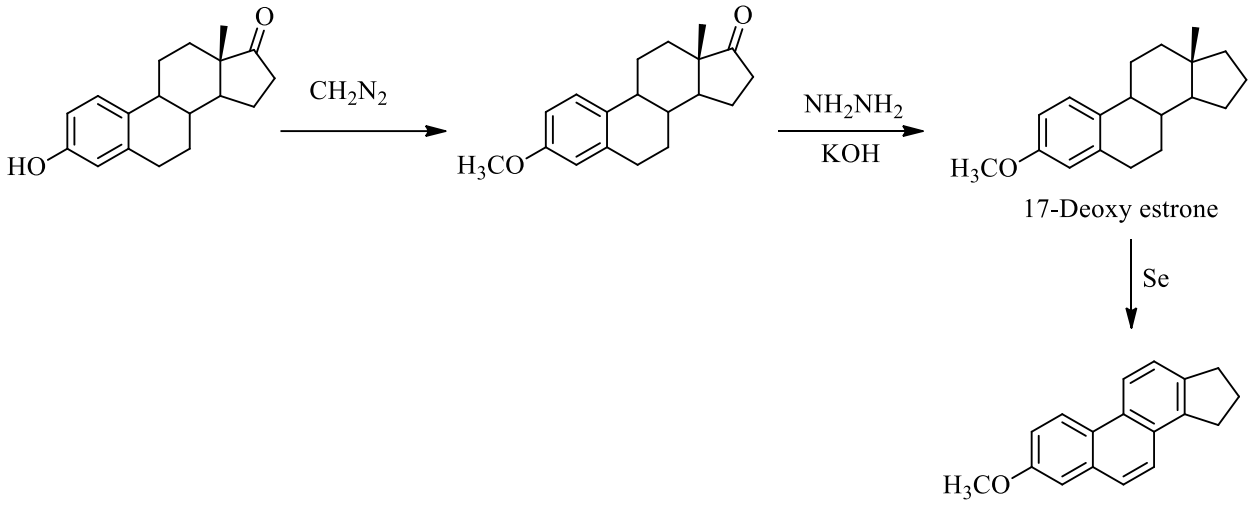


Fig. 3.29 Position and nature of phenolic-OH in estrone

(d) Nature and position of keto group

On reaction with 2,4,DNP and hydroxylamine, estrone forms 2,4-dinitrophenyl hydrazone and oxime respectively. Indicating the presence of one oxygen as carbonyl group. This carbonyl group was found to be ketonic as it gives silver mirror test with silver nitrate.

When monomethyl ether of estrone is condensed with methyl magnesium iodide it forms tertiary alcohol (II) which on dehydration with potassium hydrogen sulphate gives an ethylenic compound (lll), which is catalytically reduced to compound (IV). Compound (IV) on distillation with selenium yields 7-methoxy,3,3' dimethyl-1,2- cyclopentenophenanthrene. Position 7 and 3' in terms of steroid structure are 3 and 17. Thus hydroxyl group is present at C-3 and keto group at C-17 (Fig. 3.30).

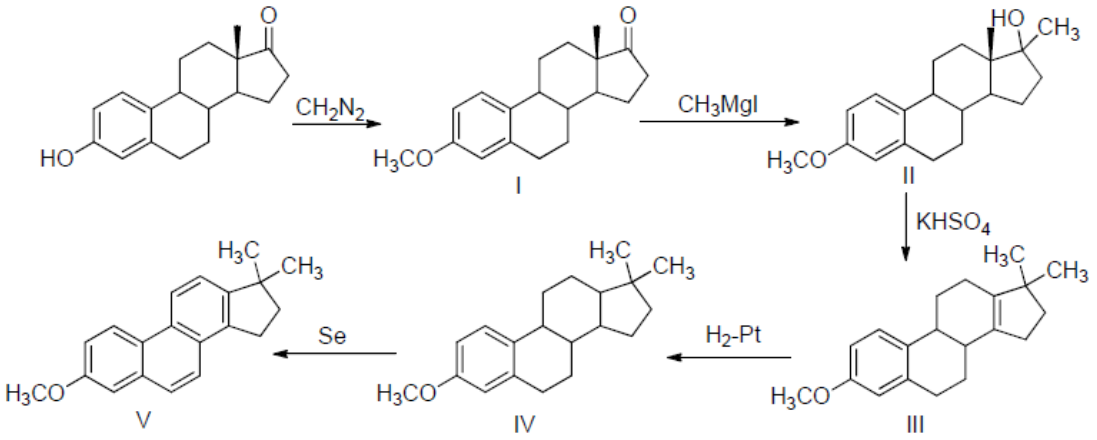


Fig. 3.30 Position and nature of ketonic group in estrone

3.8.2 Synthesis of estrone (Oestrone)

Estrone synthesised by the Johnson method as given below (Fig. 3.31).

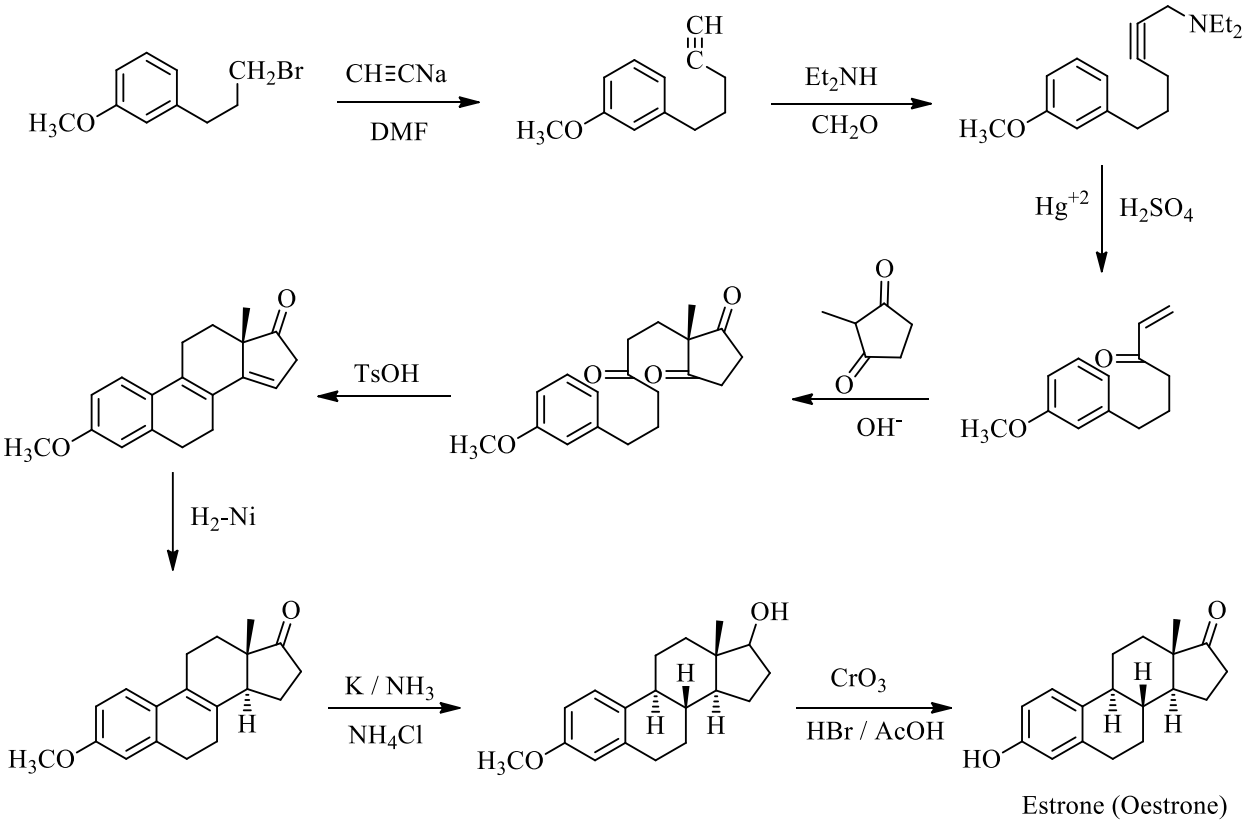


Fig. 3.31 Synthesis of estrone

3.8.3 Biosynthesis of estrone (Oestrone)

The first step in the biosynthesis involves the oxidative cleavage of the side-chain of cholesterol by cholesterol side-chain cleavage enzyme (cytochrome P-450), a mitochondrial cytochrome P-450 oxidase with the loss of six carbon atoms to give pregnenolone. In the next step, two additional carbon atoms are removed by the CYP17A1 (17α-hydroxylase/17,20-lyase) enzyme in the endoplasmic reticulum to yield a variety of C-19 steroids. In addition, the 3β-hydroxyl group is oxidized by 3β-hydroxysteroid dehydrogenase to produce androstenedione. In the final and rate limiting step, the C-17 keto group androstenedione is reduced by 17β-hydroxysteroid dehydrogenase to yield testosterone (Fig. 3.32).

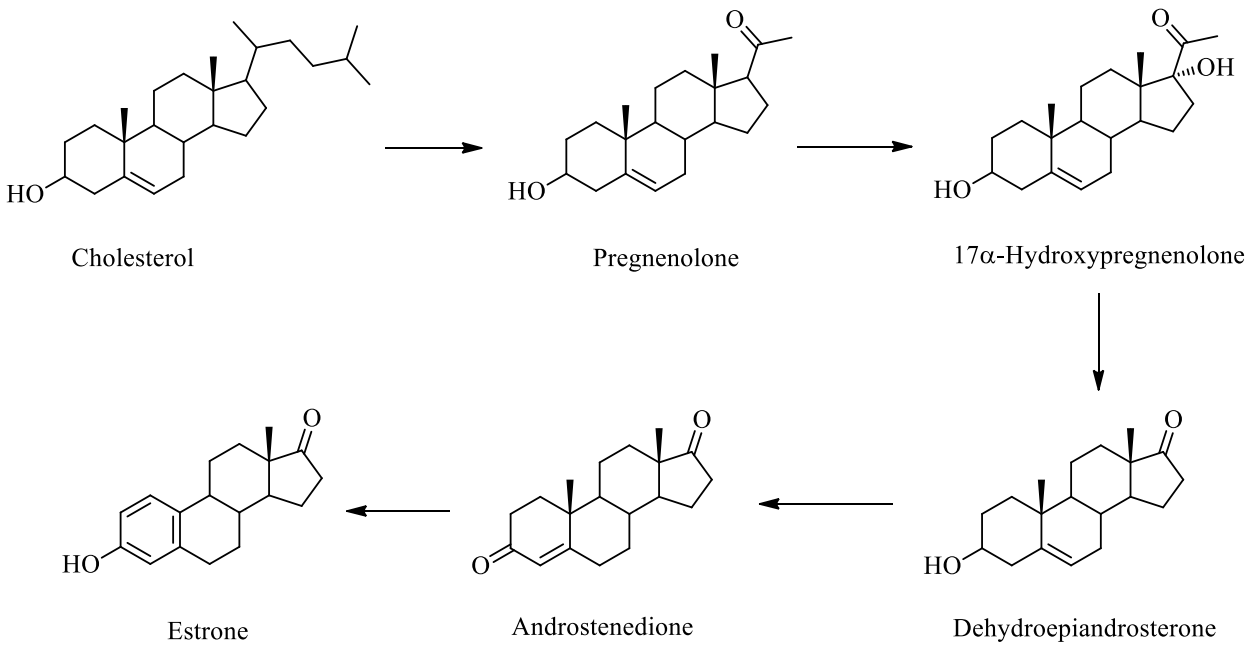


Fig. 3.32 Biosynthesis of estrone

3.9 SUMMARY:

- Steroids can be broadly classified into five groups: glucocorticoids, mineralocorticoids, androgens, estrogents, and progestins.

- Cholesterol has 8 asymmetric centers, thus 256 stereoisomers are possible. However, in nature only one exists. Cholesterol is an important component of cell membranes and related to heart disease.
- Precurssor for the biosynthesis of steroids (cholesterol) is aceto acetyl CoA.
- Antrogens are male sex hormones. They are responsible for the development of male secondary sex characteristics during puberty. Testosterone is an example of androgens.
- Estrone and estradiol are female sex hormones known as estrogens. They are responsible for the development of female secondary characteristics and secreted by the ovaries. Estrogens also regulate the menstrual cycle.

3.10 TERMINAL QUESTIONS:

Q.1 Discuss the structure of cholesterol.

Q. 2 Write the biosynthesis of steroid with givinn the example of cholesterol.

Q.3 Write the synthesis of testosterone from the cholesterol.

Q.4 Discuss the structure of estrone and testosterone.

Q.5 Write in details of cholesterol synthesis.

Q.6 Write short note on Diel's hydrocarbon.

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UNIT :4 PLANT PIGMENT / PORPHYRINS

CONTENTS:

4.1 Objectives`

4.2 Introduction

4.3 Occurrence and extraction of plant pigments

4.4 Classification of plant pigments

4.5 Chemical characterization and functions of anthocyanins, flavonoids, Xanthophylls and porphyrins

4.6 Chemistry and structure of cyanins, flavones, flavonol, quercetin

4.7 Biosynthesis of flavonoids: acetate and shikimic acid pathway

4.8 Structure and synthesis of porphyrin skeleton

4.9 Haemin and chlorophyll

4.10 Summary

4.11 Terminal questions

4.11.1 Fill in the blanks

4.11.2 True and false type questions

4.11.3 Long answer type questions

4.12 References and further studies

4.1 OBJECTIVES :

Pigments are present in all living matter and provide attractive colors In this unit you will learn about :

- Exttraction and Classification of plant pigments
- Chemical characterization and functions of anthocyanins, flavonoids, Xanthophylls and porphyrins
- Chemistry and structure of cyanins, flavones, flavonol, quercetin
- Biosynthesis of flavonoids: acetate and shikimic acid pathway
- Structure and synthesis of porphyrin skeleton
- Structure and synthesis of Haemin and chlorophyll

4.2 INTRODUCTION

Plant pigments, the impeccable natural source of color, display enormous potential to substitute many of the synthetic colorants. Chlorophylls, carotenoids, anthocyanins, and betalains are the extensive classes of natural colors contributing comprehensive color shades to foods. There are good perspectives for the inclusion of plant pigments in the food industry. Pigments cause the natural spectacular color of plants. Red-yellow betalains, green chlorophylls, red-purple anthocyanins, and yellow-orange carotenoids are the most common pigments found in vegetables and fruits. Apart from their coloring properties, these plant pigments exhibit potential health-promoting functions .

Pigments produce the colors that we observe at each step of our lives, because pigments are present in each one of the organism in the world and plants are the principal producers.They are in leaves fruits , vegetables, and flowers also they present in skin eyes, and other animals structures, and in bacteria and fungi . Natural and synthetic pigments are used in medicines, food, clothes furniture, cosmetics,and in other products. However, natural pigments have important functions other than the imparted beauty, such as the following: we could not ` have photosynthesis or probably life all over the world without chlorophylls and carotenoids.

4.3 OCCURRENCE AND EXTRACTION OF PLANT PIGMENTS :

Plant pigments are mostly the coloring substances found either in cell sap (as water-soluble forms, or in the plastids (water-insoluble forms). Normally, the plastidial pigments (double-membrane organelles)are responsible for photosynthesis while cell sap pigments are responsible for coloration of floral parts and various plant organs. Isolation of cell sap pigments are very simple, which can be done by boiling water or by alcohol. On the other hand, plastidial pigments are isolated by solvent extraction method using acetone, petroleum ether, methanol, chloroform, alcohol etc.Their are some important methods to extraction of plant pigments depents upon the nature of plant source.

First method:

This method used to isolation of anthocyanins.After drying plant petals then powdered, extracted with alcoholic HCl, anthocyanins converted into corresponding chloride.Than after:

a)Ether is added in chloride solution to precipitate the pigments.The crude pigments dissolved in minimum amount of HCl and then repracipitated by ether.Then precipitated pigment recrystallised from alcohol.

b)To the chloride solution, dichloropicric acid is added ,precipitate out dichloropicrate , which is then converted into soluble chloride.

c) To the chloride solution,anthocyanins are precipitated as lead salt which are than decomposed into anthocyanins by H_2S and the pigments is extracted with a suitable solvent.

Anthocyanins obtained as above further isolated and separated by column chromatography ,and using of cellulose powder, silica gel as a ion exchange resins. Anthocyanins are coloured , so its produce a series of bands on the column.However better procedure for identifying of Anthocyanins is paper chromatography.

Second Method:

a)This method mainly used to extraction flavons/ flavonols. In general, organic solvents (methanol, ethanol, acetonitrile, petroleum ether, acetone), water, and mixtures of these solvents are used for the removal of flavonoids from plant matrices, such as herbs, industrial residues, stems or plant seeds.
In which water extract is diluted and treated with lead acetate to precipitate tannin impurities as a lead salts. After filtration in filtrate flavones is present as associated form.After filtration, filtrate diluted with water and acidified with HCl precipitated a suger free flavones / flavonols. Precipitation with lead acetate is very old method of isolation of flavones and in this method obtained flavonoid is flavonoid phenols anf may be co-precipitate other compounds.

Third method:

Silica gel chromatography is the main method to isolate / identify flavonoids. It is applied to isolate low/ medium polar constituents. Reversed phase silica gel is commonly used to isolated flavonoid glycosides.

Fourth method:

In Polyamide chromatography, Polyamide is a good adsorbent to isolate flavonoids.

The adsorption strength hinges on hydrogen bonding associated between polyamide and flavonoids, which depends on the number and positions of –OH group in the molecules of flavonoids.

Fifth method:

An efficient method for separating chlorophyll a from spinach leaves by column chromatography and solvent extraction techniques has been developed. The purity and identity of the chlorophyll a have been confirmed by UV-Vis, IR and mass spectrometry. In this procedure, Fresh spinach leaves were first separated from the mid-ribs and washed with cold water. They were then frozen for storage. The freeze-dried spinach leaves (100 g) were crushed and extracted with four 50 mL portions of 80% aqueous acetone. The combined extracts (200 mL) were concentrated to about 50 mL and washed with petroleum ether (60-80 °C). The aqueous acetone layer, which contained mostly carotenes and other acetone-soluble plant constituents, was discarded. The petroleum ether layer was washed with aqueous methanol (60:40 v/v). The petroleum ether layer was analyzed by UV-Vis and IR spectroscopy. The petroleum ether layer containing the chlorophyll a was chromatographed on a silica gel column. The column was eluted with petroleum ether and with 0.5% n-propanol in petroleum ether to give the chlorophyll a.

4.4 CLASSIFICATION OF PLANT PIGMENTS :

Defination:

"A Pigments are chemical compounds that absorb light in the wavelength range of the visible region. Produced color is due to a molecule-specific structure (chromophore); this structure captures the energy and the excitation of an electron from an external orbital to a higher orbital is produced; the nonabsorbed energy is reflected and/or refracted to be captured by the eye, and generated neural impulses are transmitted to the brain where they could be interpreted as a color."
They are colored material and completely or nearly insoluble in water. In contrast, dyes are typically soluble, at least at some stage in their use. Generally dyes are often organic compounds whereas pigments are often inorganic compounds.

Classification : Pigments are mainly classified as follows**:**

1. By Their Origin : By their origin pigments are mainly classified natural, synthetic/ Inorganic. Natural pigments are colored substance derived from natural sources such as plants, animals, insects, fungi, and microorganisms , while synthetic pigments are obtained from laboratories. Natural and synthetic pigments are organic compounds, but Inorganic pigments can be found in nature or reproduced by synthesis.

2. By the Chemical Structure of the Chromophore :

On the basis of chemical structure of the chromophore pigments can be classified as:

a) **Chromophores with conjugated systems:** Carotenoids, anthocyanins, betalains, caramel, synthetic pigments, and lakes.
b) **Metal-coordinated porphyrins**: Myoglobin, chlorophyll, and their derivatives.

3. As Food Additive : By considering the pigments as food additives, their classification by the

FDA is :

a) Certifiable : These are manmade and subdivided as synthetic pigments and lakes.

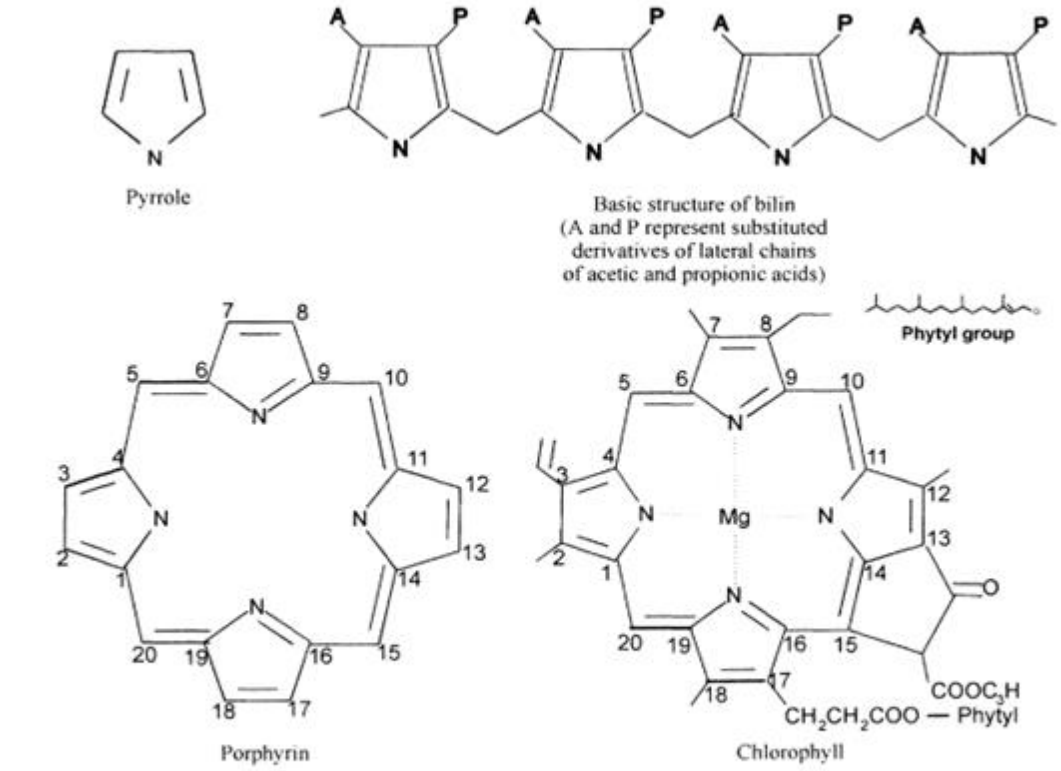
b) Exempt from certification : These pigments derived from natural sources such as vegetables, minerals, or animals, and manmade counterparts of natural derivatives.

4. By the Structural Characteristics of the Natural Pigments :

Natural pigments can be classified by their structural characteristics as:

a) **Tetrapyrrole derivatives**: Chlorophylls and heme colors.
b) **Isoprenoid derivatives:** Carotenoids and iridoids.
c) **N-heterocyclic compounds:** Purines, pterins, flavins, phenazines, phenoxazines, and betalains.
d) **Benzopyran derivatives(oxygenated heterocyclic compounds):** Anthocyanins and other flavonoid pigments.
e) **Quinones**: Benzoquinone, naphthoquinone, anthraquinone.
f) **Melanins**

a) **Tetrapyrrole derivatives**: In tetraoyrrole derivatives pyrrole rings in linear or cyclic arrays. **Figure 4.1** shows some common structures of tetrapyrrole derivatives. Phytochrome is very common in algae (Rhodophyta, Cryptophyta), and bilin in this basic structure (lineal array). In the cyclic compounds, we can mention the heme group (the porphyrin ring is bonded to an iron atom); this group is present in hemoglobin and myoglobin, present in animals, and also in cytochromes, peroxidases, catalases, and vitamin B_{12} as a prosthetic group, all of them with a wide distribution. However, chlorophylls constitute the most important subgroup of pigments within the tetrapyrrole derivatives.



Basic structure of porphyrinic pigments (pyrrol) and of some porphyrinic pigments with biological importance.

Figure 4.1

b) Isoprenoid Derivative : Isoprenoids, also called terpenoids, represent a natural compounds, they are found in all kingdoms where they carry out multiple functions (hormones, pigments, phytoalexns). On the bases of abundance and structure, two subgroups of compounds are considered pigments: quinones and carotenoids. However, in addition, and only recently, iridoids is a third group of plant isoprenoid compounds that have acquired some relevance.In relation to iridoids, these are found in about 70 families (Capriofilaceae, Rubiaceae, Cornaceae, among others) grouped in some 13 orders. Saffron (Crocus sativus L.) and cape jasmine fruit (Gardenia jasminoids Ellis) are the best-known iridoid-containing plants, but their colors are more importantly influenced by carotenoids.

c) N-Heterocyclic Compounds : Hetrocyclic compounds possess a cyclic structure with two or more different kinds of atoms in the ring. In organic heterocyclic compounds at leasr on carbon atom , all atoms other than carbon are considered as hetro

atoms.some hetrocyclic compounds are as follows;

i)Purines : As a nucleotides, purines are found in two macromolecules : in DNA (deoxyribonucleic acid) and RNA (ribonucleic acid) . Free purines have been found in animals Like : golden and silvery fish.

ii) Pterins : Most of the natural pteridins have an amino group at C-2 and an hydroxyl group at C-4. Also, 2,4-dihydroxipteridins have been described as important components in the flavin biosynthesis. Pterins are responsible for color insome insects, in vertebrate eyes, human urine, and bacteria .

iii) Flavins : In these compounds a pteridin and a benzene ring are condensed. Riboflavin is the main compound of this group, and it is synthesized in all live cells of microorganisms and plants. Riboflavin is found in a wide range of leafy vegetables,milk, meat, and fish.

iv) Phenazines : Phenazines comprise a large group of nitrogen-containing heterocyclic compounds that differ in their chemical and physical properties based on the type and position of functional groups present. Bacteria are the only known source of natural phenazines.

v) Phenoxazine : The structure of phenoxazine consists of an oxazine fused to two benzene rings. It occurs as the central core of a number of naturally occurring chemical compounds such as dactinomycin and litmus. The dyes Nile blue and Nile red are also based on a phenoxazine core. They are found in fungi and insects.

vi) Betalains : Betalains are unique nitrogen-containing pigments found exclusively in families of the Caryophyllales order and some higher order fungi, where they replace anthocyanin pigments. Betalains, consisting of betacyanins and betaxanthins are generally used as color additives in food.**(Figure 4.2)**

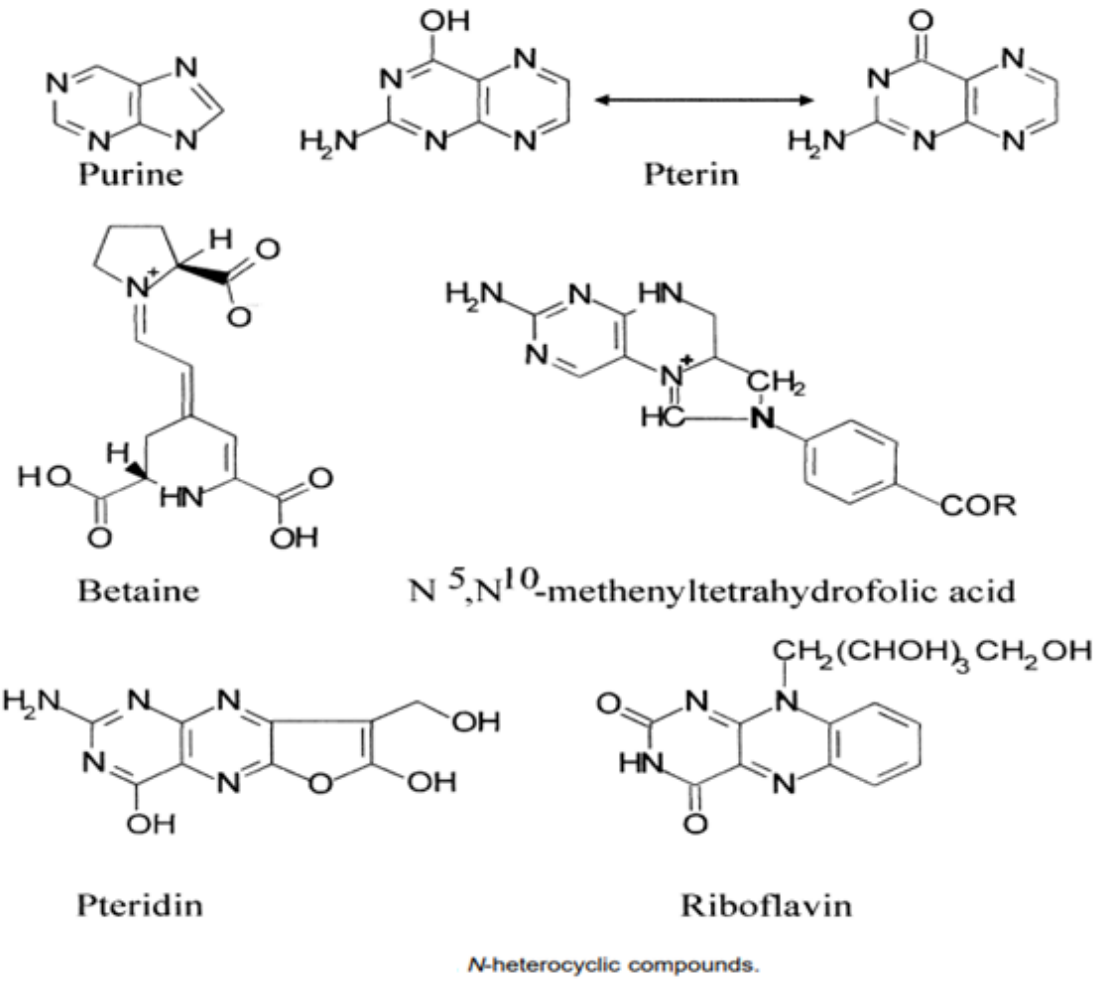


Figure 4.2

c) **Benzopyran Derivatives :** These are phenolic compounds with two aromatic rings bonded by a C_3 unit (central pyran ring) and divided in 13 classes based on the oxidation state of the pyran ring and on the characteristic color: anthocyanins, aurons, chalcones, yellow flavonols, flavones, uncolored flavonols, flavanones, dihydroflavonols, dihydrochalcones, leucoanthocyanidins, catechins, flavans, and isoflavonoids. **Figure 4.3** shows some flavonoid structures. Each type of flavonoid can be modified by hydroxylation, methylation, acylation, and glycosylation to obtain a great natural diversity of compounds. Flavonoids are water soluble and show a wide distribution in vascular plants. In the flavonoids, the anthocyanins are the most important pigments; they produce colors from orange to blue in petals, fruits, leaves, and roots . Flavonoids also contribute to the yellow color of flowers, where they are present with carotenoids or alone in 15% of the plant species. Flavones and flavanones are found free or glycosylated in leaves of angiosperms. Flavanones are

especially common in Rosaceae, Rutaceae, legumes and Compositae. Dihydrochalcones are found mainly hydroxylated in apple and in some species of Rosaceae, Ericaceae, Fagaceae, legumes, and Salicaceae. Leucoanthocyanidins (flavan 3,4-diols) are widely distributed in plants, and they have been isolated from wood and peel of trees (particularly Acacia) and methylated, and C-alkylated leucoanthocyanidins have been identified in a variety of sources and flavans are found mainly in leaves. Catechins and epicatechins are among the commonest flavonoids known, sharing a distribution almost as widespread as quercetin in the Dicotyledoneae. Many flavans are lipid soluble and appear to be leaf-surface constituents. Isoflavonoids have the B ring in C-3 instead of C-2, and many natural products are in this group: isoflavones, rotenoids, pterocarps, and coumestans and Isoflavones are the most common in legumes.

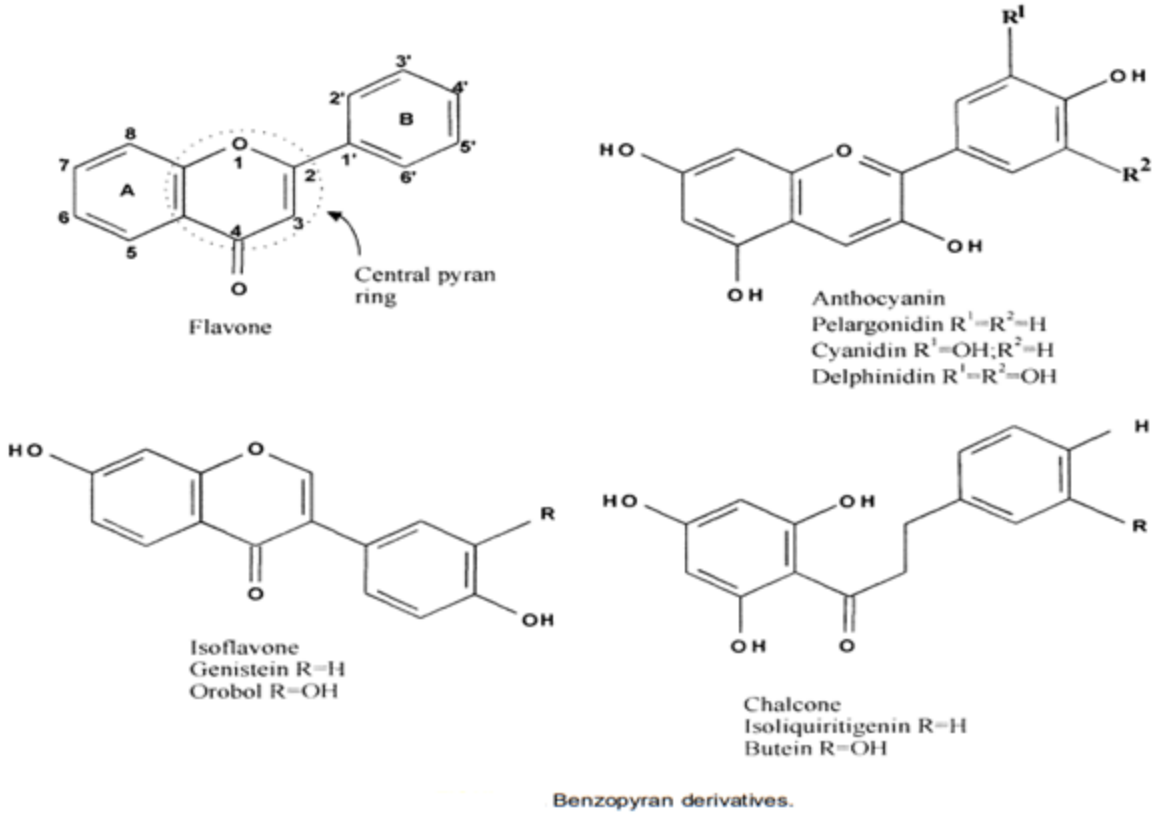


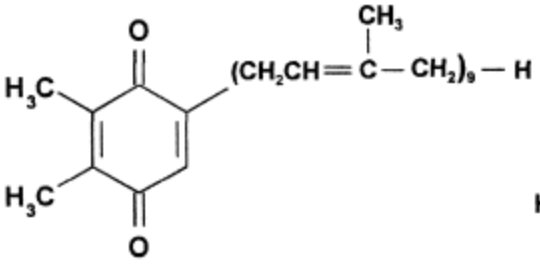
Figure 4.3

e) Quinone : Quinones have a great number of coloring compounds (**Figure 4.4**). They are more widely distributed than other natural pigments (with the exception of carotenoids and melanins). The basic structure consists of a desaturated cyclic ketone that is derived from an aromatic monocyclic or polycyclic compound. Quinones can be divided by their structure as benzoquinones, naphthoquinones, anthraquinones, and miscellaneous quinones; moreover, dibenzoquinones, dianthraquinones, and dinaphthoquinones have been reported. The variability in the kind and structure of substituents conduce to large number of quinones. Quinones are found in plants:

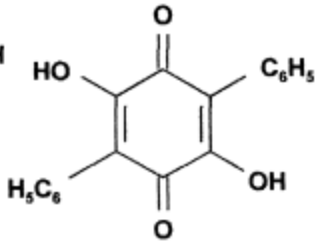
plastoquinones are found in chloroplasts of higher plants and algae; ubiquinones are ubiquitous in living organisms; menaquinones are found in bacteria; naphthoquinones in animals; and anthraquinones in fungi, lichens, flowering plants, and insects. In general, quinones produce yellow, red, or brown colorations, but quinone salts show purple, blue, or green colors.

A

1,4-Benzoquinone

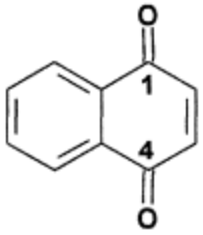


Plastoquinone

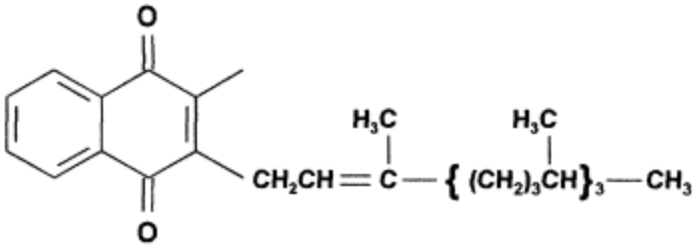


Polyporic acid

B



1,4-Naphthoquinone



Vitamin K

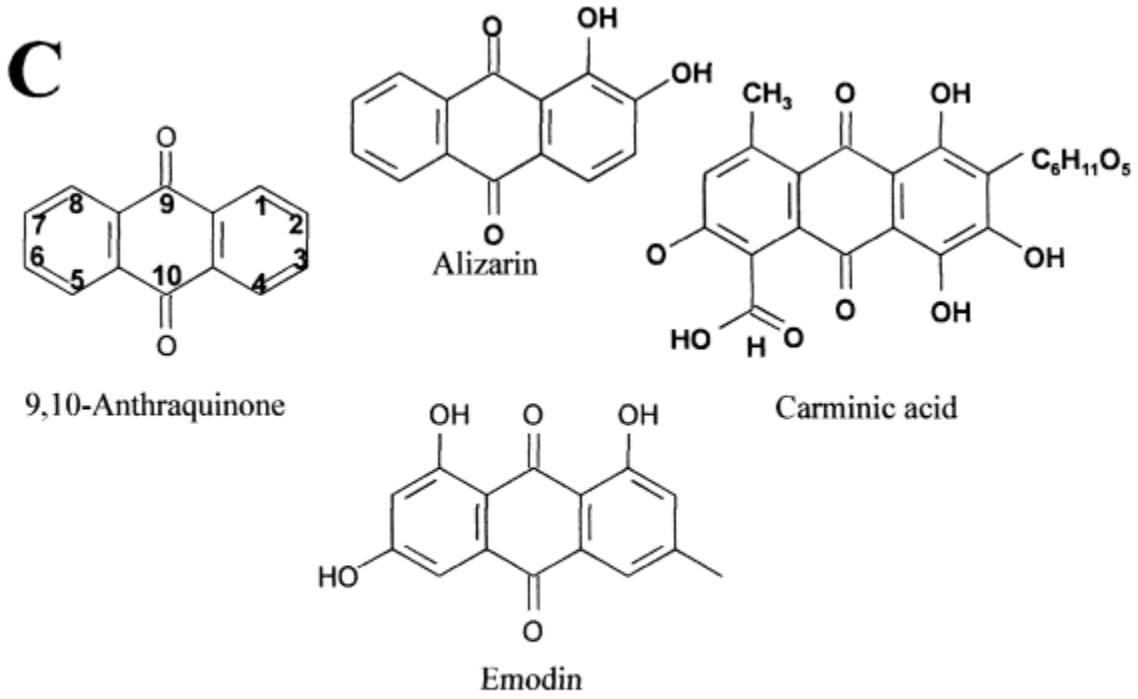
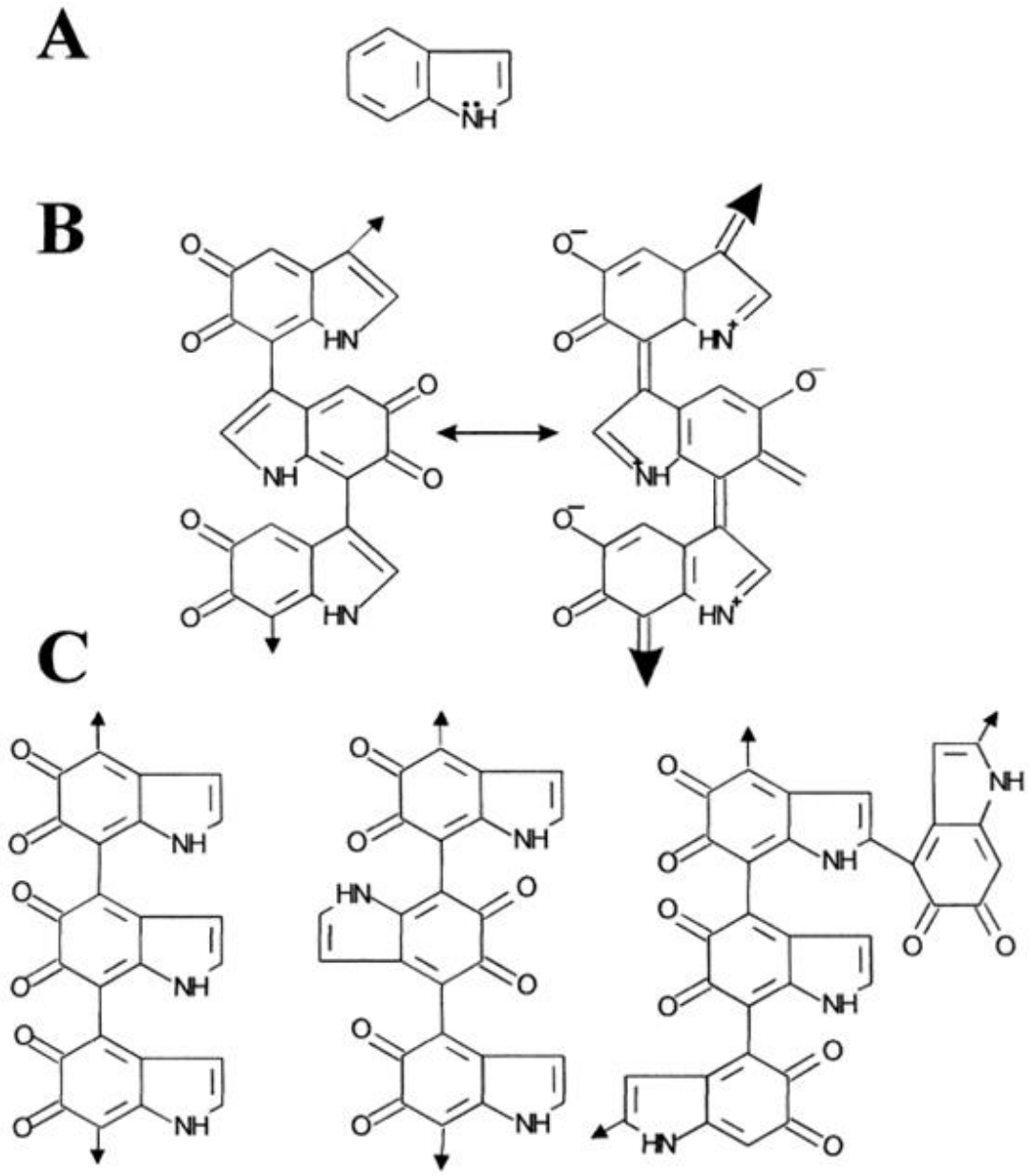


Figure 4.4

f. Melanins : Melanins are nitrogenous polymeric compounds whose monomer is the indole ring (**Figure 4.5).** Melanins are not homopolymers but present a mixture of macromolecules. These are responsible of many of the black, gray, and brown colorations of animals, plants, and microorganisms. Eumelanins are widely distributed in vertebrate and invertebrate animals. Phaemelanins are macromolecules of mammals and birds. Allomelanins have been described in seeds, spores, and fungi, and esclorotins in arthropods.



Melanin-related structures and some properites. (A) Basic structure (indolic ring). (B) Resonance structures that are probaly involved in the process of color. (C) Some of the suggested forms of indolic polymerization to form melanins. The arrows show the points and sense of polymerization.

Figure 4.5

4.5CHEMICAL CHARACTERIZATION AND FUNCTIONS OF ANTHOCYANINS, FLAVONOIDS, XANTHOPHYLLS AND PORPHYRINS :

A) Anthocyanins

i) Introduction: Anthocyanins are part of the plant-derived flavonoid compounds and are responsible for colours ranging from pale pink to red to purple and deep blue. They are present in a wide range of plant tissues, principally flowers and fruit, but also storage organs, roots, tubers and stems. Within the plant kingdom they are almost universally present in higher plants, with the exception of the betalain producers, and are also present in lower plants such as algae, liverworts, mosses and ferns.Chemically , anthocyanins are glycosides and their aglycons i.e, the suger free pigments are known as anthocyanidins.Furthermore the various anthocyanins were shown to possess the same carbon skeleton and differed only in the nature of substituent group.In all the anthocyanins and anthocyanidins the fundamental nucleus is benzopyrylium chloride whereas the parent compound is 2- phenylbenzopyrylium chloride or flavylium chloride. Anthocyanins have been considered to be derivatives of 3,5,7- trihydroxyflavylium chloride.(**Figure 4.6)**

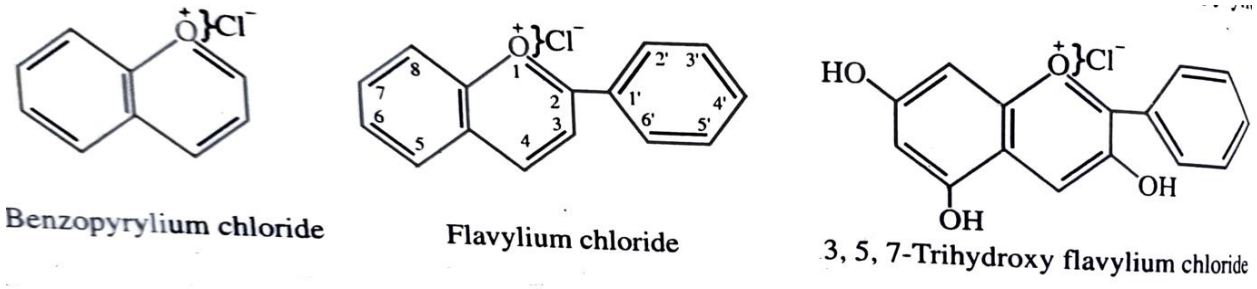


Figure 4.6

The various anthocyanins and anthocyanidine differ in the number , nature and position of other methoxy group($-OCH_3$) ,Hydroxy group (-OH) and sugar residue.

ii) Properties of Anthocyanins: The various properties of anthocyanins are as follows :

- The anthocyanins are water soluble pigments belonging to the phenolic group.
- It is amphoteric in nature.
- The color and stability of these pigments are influenced by pH, light, temperature, and structure.
- In acidic condition, anthocyanins appear as red but turn blue when the pH increases.
- A typical UV-Vis spectrum of an anthocyanin shows two basic clusters of absorbance, the first one at a wavelength region of **260–280 nm (UV region) and the other one at 490–550 nm (visible region)**.

- In **490–550 nm** region band actual value depend upon the number of the methoxy group($–OCH_3$) ,Hydroxy group (-OH) groups.However ,if these are fixed , the value of band depends on pH and solvent.

iii) Functions of Anthocyanins : The exact functions of anthocyanins in plants are not known with certainty. However assumed that some following functions in plants given below:

- In photosynthetic tissues (such as leaves and sometimes stems), anthocyanin have been shown to act as a "**sunscreen**", protecting cells from high-light damage by absorbing blue-green light, thereby protecting the tissues from photo-inhibition, or high-light stress.
- Anthocyanins may cause an increase in osmotic pressure of the cell sap.
- In flowers, bright reds and purples due to anthocyanin pigments help attract pollinators.
- In addition to their role as light-attenuators, anthocyanins also act as powerful antioxidants**.**
- The anthocyanins may act as light filters and thus hinder the decomposition of chlorophyll against strong light.
- In respiration and photosynthesis , anthocyanins are expected to play some vital role.

B) Flavonoids

i) Introduction: The term Flavonoids is derived from Latin word " Flavus" meaning yellow so large no of flavonoids are yellow in color.Flavonoids, a group of natural substances with variable phenolic structures, are found in fruits, vegetables, grains, bark, roots, stems, flowers, tea and wine. These natural products are well known for their beneficial effects on health and efforts are being made to isolate the ingredients so called flavonoids**.**

Flavonoids are an important class of natural products; particularly, they belong to a class of plant secondary metabolites having a polyphenolic structure, widely found in fruits, vegetables and certain beverages. Flavonoids can be subdivided into different subgroups depending on the carbon of the C ring on which the B ring is attached and the degree of unsaturation and oxidation of the C ring (**Figure 4.7**). Flavonoids in which the B ring is linked in position 3 of the C ring are called isoflavones. Those in which the B ring is linked in position 4 are called neoflavonoids, while those in which the B ring is linked in position 2 can be further subdivided into several subgroups on the basis of the structural features of the C ring.

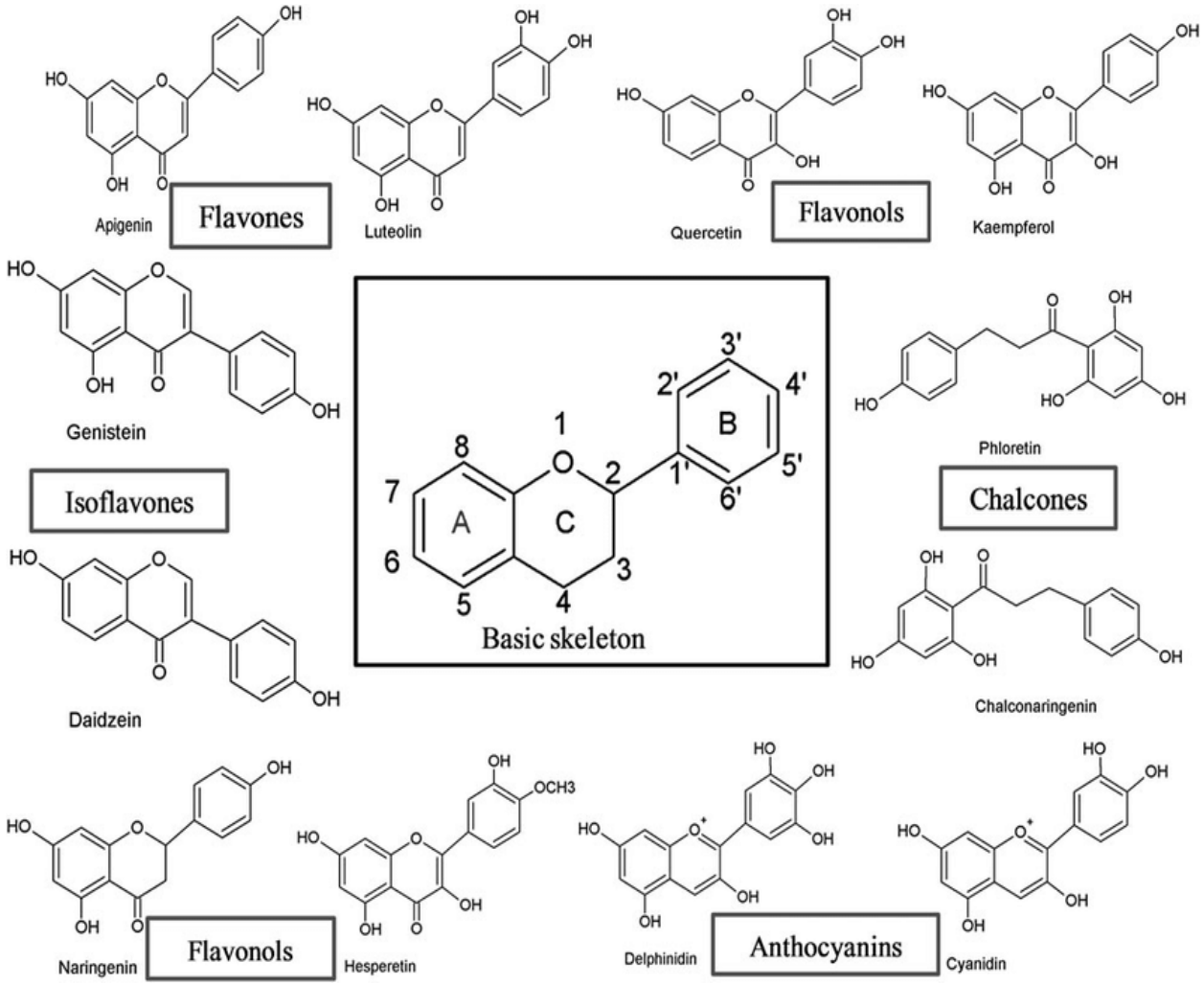


Figure 4.7 : Basic skeleton stricture of Flavonoids and their classes

ii) Properties of Flavonoids: Some important properties of flavonoids are :

- Flavonoids are crystalline compounds.
- These are bitter in taste and odorless compounds.
- These are responsible for yellow , red, blue in color of flower, fruits, seeds, leaves, bark etc.
- Flavonoids are alcohol ,water soluble but insoluble in organic solvents like ether, chloroform etc.
- They are also known as vitamin P,because they have nutritional values like other vitamins.
- In flavonoids major absorption bands: Band I (320–385 nm) represents the B ring absorption, while Band II (250–285 nm) corresponds to the A ring absorption.

iii) Functions of Flavonoids: Flavonoids possess many biochemical properties,the functions of flavonoids are given below:

- In plant , flavonoids have synthesized in particular sites and are responsible for the colour and aroma of flowers, and in fruits to attract pollinators and consequently fruit dispersion to help in seed and spore germination and the growth and development of seedlings.
- Flavonoids protect plants from different biotic and abiotic stresses and act as unique UV filters.
- Flavonoids are structurally diverse secondary metabolites in plants, with a multitude of functions.
- They may also act as chemical messengers, physiological regulators, and cell cycle inhibitors.
- In higher plants, they are involved in UV filtration, symbiotic nitrogen fixation, and floral pigmentation. They may also act as chemical messengers, physiological regulators, and cell cycle inhibitors.

C) Xanthophylls

i) Introduction: Xanthophylls are yellow pigments that are one of the important divisions of the carotenoid group. The word xanthophylls is made up of the Greek word xanthos, meaning yellow, and phyllon, meaning leaf. **xanthophyll .**As both are carotenoids, xanthophylls and carotenes are similar in structure, but xanthophylls contain oxygen atoms while carotenes are *purely hydrocarbons*, which do not contain oxygen. Their content of oxygen causes xanthophylls to be more polar (in molecular structure) than carotenes, and causes their separation from carotenes in many types of chromatography. Xanthophylls present their oxygen either as hydroxyl groups and/or as hydrogen atoms substituted by oxygen atoms when acting as a bridge to form epoxides.**(Figure 4.8)**

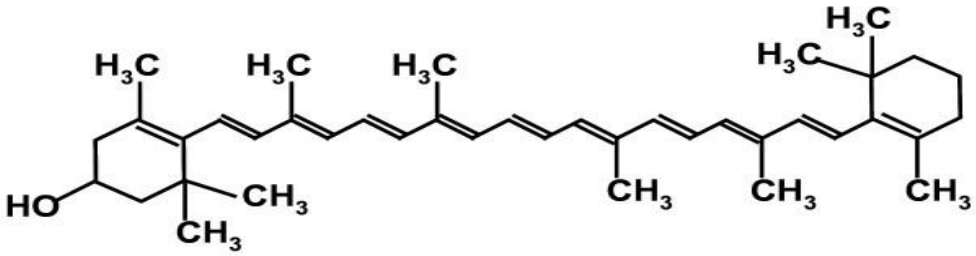


Figure 4.8: The chemical structure of crptoxanthin Xanthophylls typically present oxygen as a hydroxyl group.

ii) Properties of Xanthophylls: The various properties of xanthophylls are given below:

- Xanthophylls have properties similar to lipids, being **insoluble in water.**

- Xanthophylls are light-harvesting protein complexes found in many vascular plants and algae.
- Xanthophylls are pigment molecules found inside the photosynthesis complex that shield photosynthetic organisms from the harmful effects of light.

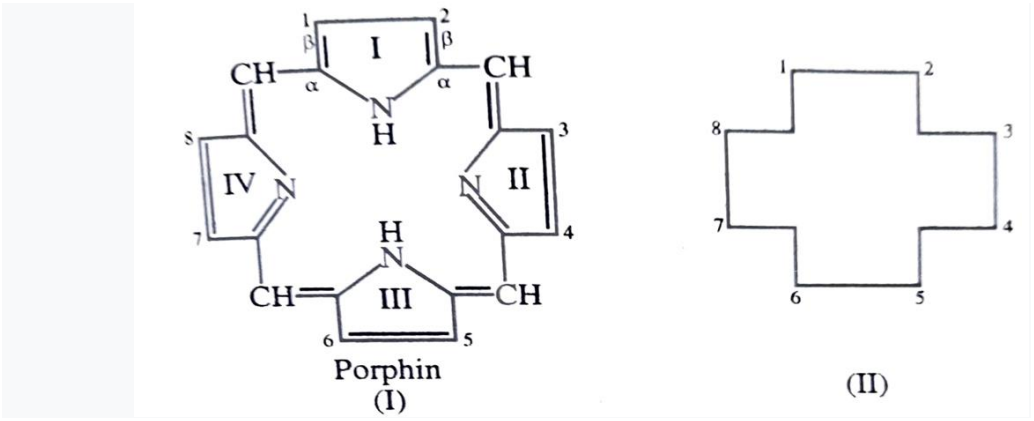
iii) Functions of Xanthophyll: Xanthophylls are light-harvesting pigments that can also serve as structural entities within the light harvesting complex and compounds that protect photosynthetic creatures from the potentially damaging effects of light.

- **Light-harvesting:** The accessory pigments xanthophylls operate as a photosynthetic light-harvesting compound in algae and vascular plants.
- **Dissipation of energy as heat:** Xanthophyll assists in photoprotection, or the protection of the photosynthetic system from photo-oxidative degradation in the presence of excessive light, by dissipating energy.

D) Porphyrins

i) Introduction : The name "porphyrin" derives from the Greek word meaning ***purple***
Porphyrins are a group of heterocyclic macrocycle organic compounds, composed of four modified pyrrole subunits interconnected at their α carbon atoms via methine bridges (=CH−). The parent of porphyrins is porphine, a rare chemical compound of exclusively theoretical interest. Substituted porphines are called porphyrins.With a total of 26 π-electrons, of which 18 π-electrons form a planar, continuous cycle, the porphyrin ring structure is often described as aromatic. One result of the large conjugated system is that porphyrins typically absorb strongly in the visible region of the electromagnetic spectrum, i.e. they are deeply colored.Porphyrins are derivatives of porphins formed by replacement of hydrogen atoms of the pyrrole ring, situated at the outer rim with some other groups of atoms**.**

ii)Representation: The structure of porphin may be represented as I.This may be written as (II) by Fisher.



In structure I the carbon atoms forming the methane bridge are labelled as **α,β,γ, and δ** and hydrogen atom attached to these methane group known as meso hydrogen. In structure I pyrrole rings are represented as I, II,III, and IV respectively.

In **Figure 4.9** is the alternative method of IUPAC naming.The alternative structure **Figure 4.9** has confirmed by X- rays analysis shown below:

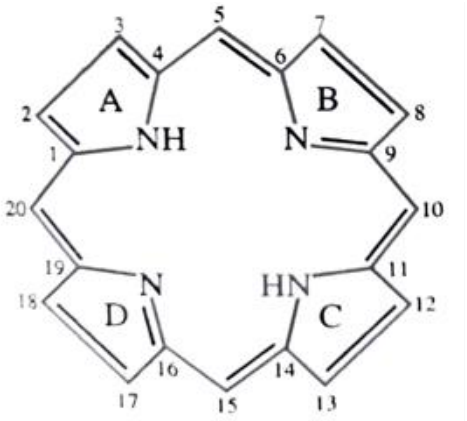


Figure 4.9

Similarly in above structure (**Figure4.9)**, Pyrrole rings represented as A,B,C,D and methine bridges are labelled as 1,2,3and 4.

iii) Properties of Porphyrins: These are as follows:

- Porphyrins are crystalline deep coloured substance
- The colour of porphyrines depends upon the some factors like: PH value ,Nature of the solvent, concentration of the solvent etc.
- It have the tendency to form metallic complex with copper, iron, magnesium, zinc etc, and these complex derivatives used as a respiratory pigments, photosynthestic pigments, and catalysts.
- As porphyrins are absorbed differently on various absorbents, their separation and purification can be done by adsorption chromatography.
- Some functional group like OH, COOH, COOR etc can be identified by IR spectra of porphyrins.
- The visible spectra of porphyrin monocation are recorded they consist of four visible bands at ~625nm (I) , ~570nm (II), ~530nm (III), and ~625nm (IV) (**Figure 4.10)** are obtained.The

spectra also exhibit one more band in 400nm which is known as the Soret band(I,II).It is the characteristic band of all conjugated tetrapyrroles.

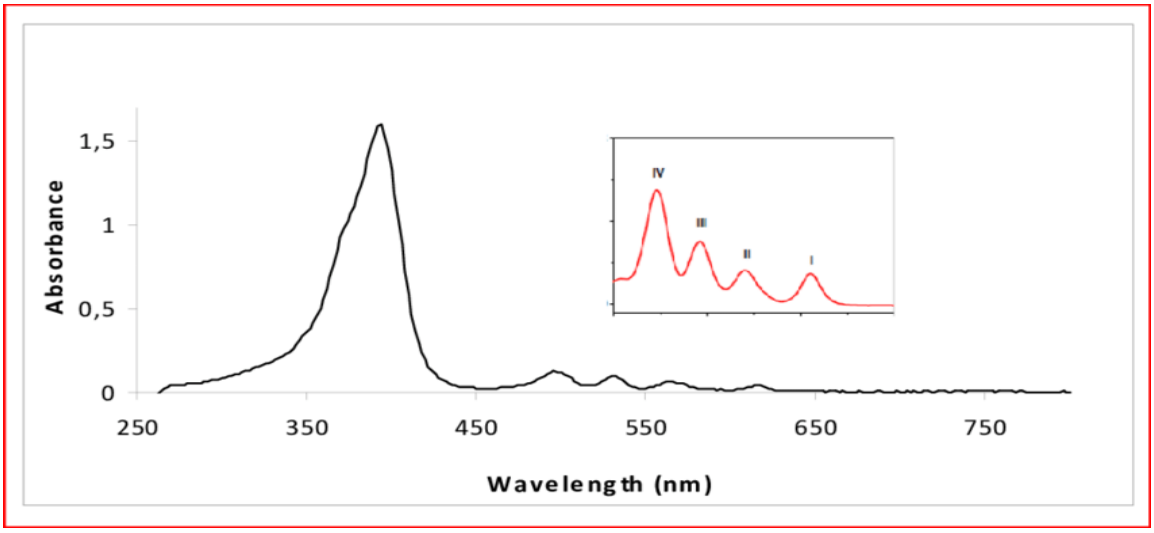


Figure:4.10

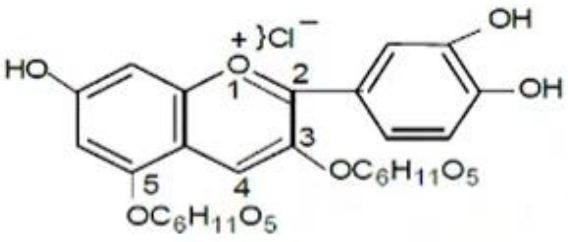
iv) Functions of Porphyrins: Porphyrins main functions are :

- Natural porphyrins include the red-colored heme present in hemoglobin, which is responsible for blood oxygen transport, and the chlorophylls in some bacteria and in plants which are utilized for photosynthesis.
- The role of porphyrins in electron transport appears to be as handmaidens to the redox properties of iron ions.
- Porphyrins are best known for their use in medical applications, in particular as photosensitizers in photodynamic therapy.

4.6 CHEMISTRY AND STRUCTURE OF CYANINS, FLAVONES, FLAVONOL, QUERCETIN

A. CYANINS :

i)Introduction: ***Cyanin*** belonging to the group of ***anthocyanins***, are among the most widespread pigments occurring in red roses and and blue cornflowers.It is red, blue, or violet pigments, all of which are glycosidic in nature and its isolated as cyanin chloride.



Cyanin Chloride

ii) General methods for the Elucidation of Structure of Cyanins Chloride: The structure of cyanin chloride elucidated on the basis of following analytical and synthetic evidences:

1.By analytical data and molecular weight determination , the molecular formula of cyanin chloride is $C_{27}H_{31}ClO_{16}$.

2.Hydrolysis : On hydrolysis of cyanin chloride with HCl gives two molecules of D-glucose and one molecules of cyanidine chloride.

$$C_{27}H_{31}ClO_{16} + 2\,H_2O \xrightarrow{HCl} \underset{\text{Cyanidin chloride}}{C_{15}H_{11}ClO_6} + 2\,\underset{\text{D-Glucose}}{C_6H_{12}O_6}$$

The hydrolytic products indicates that cyanin chloride is a diglucoside of cyanidine chloride. The structure of cyanidine chloride which give a complete structure of cyanin:

3) Structure of cyanidine chloride:

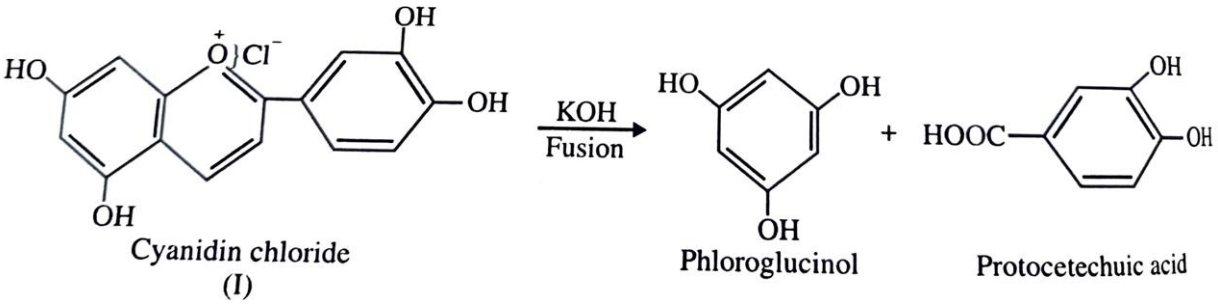
a) From the analytical data, molecular weight determination, the molecular formula of cyanidine chloride is $C_{15}H_{11}ClO_6$.

b)When cyanidine chloride dissolved in aqueous solution of NaOH ,this shown that cyanidine chloride contains five –OH (Hydroxy group).

$$C_{15}H_6ClO(OH)_5 + 5(CH_3CO)_2O \xrightarrow{CH_3COONa} \underset{\text{Penta acetyl derivative of cyanidin chloride}}{C_{15}H_6ClO(O.COCH_3)_5} + 5CH_3COOH$$

- By analysis of Zeisel's method shown that cyanidine chloride does not contain any $-OCH_3$ group (methoxy group).

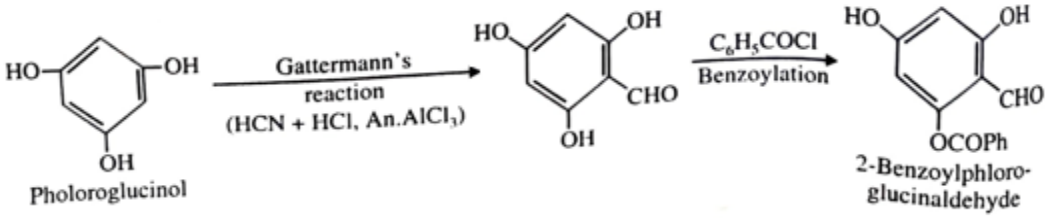
c) When cyanidine chloride fused with KOH solution, it yield phloroglucinol and protocatechuic acid (3,4-dihydroxy benzoic acid). The formation of these products indicates that structure I is the correct structure of cyanidine chloride.



Cyanidin chloride (I) — Phloroglucinol — Protocetechuic acid

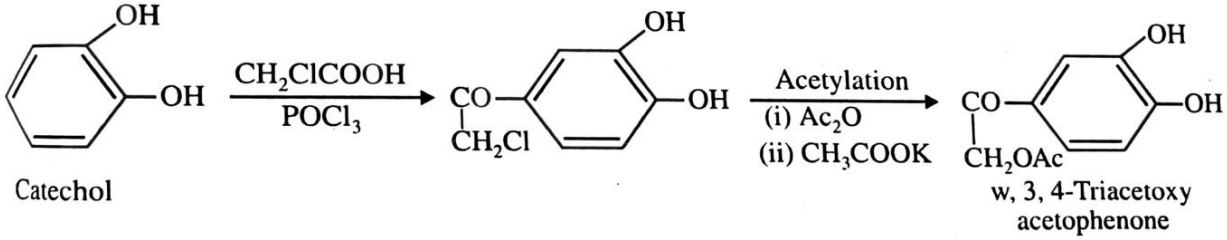
d) The structure of cyanidine chloride (I) has been confirmed by its synthesis. The various step of synthesis are as follows:

- Synthesis of 2- Benzoylphloroglucinaldehyde.



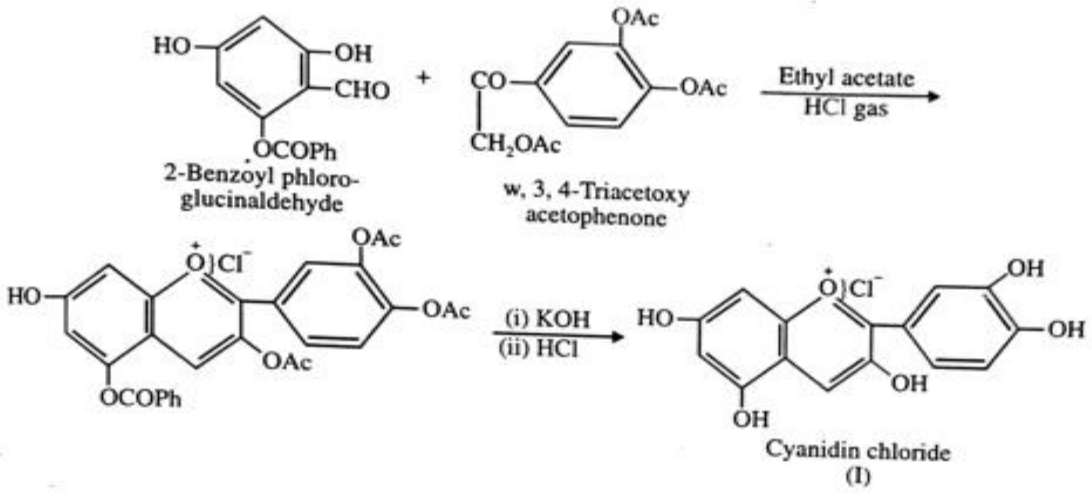
Pholoroglucinol — 2-Benzoylphloro-glucinaldehyde

- Synthesis of ω,3,4-Triacetoxyacetophenone .



Catechol — w, 3, 4-Triacetoxy acetophenone

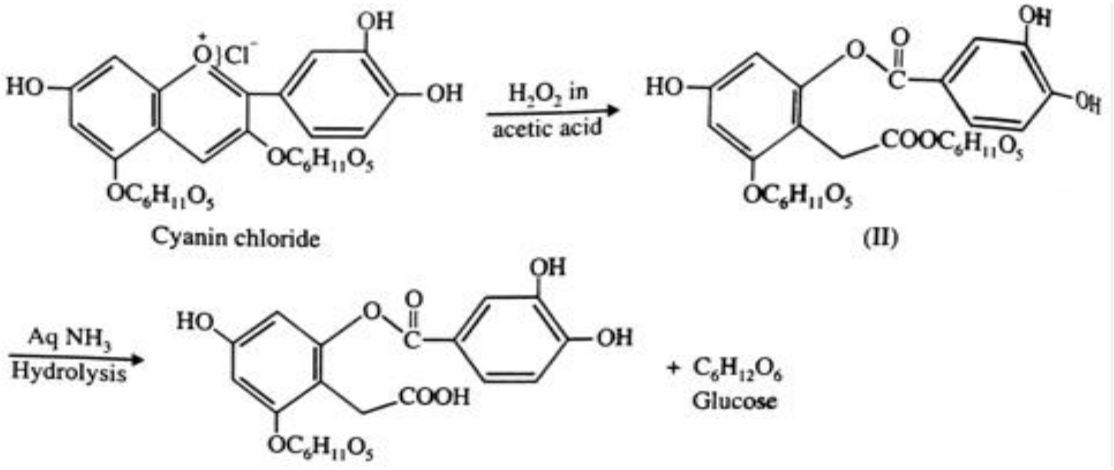
- Compound 1 and 2 converted into cyanidine chloride (I) as follows:



4)Position of glucose units in cyanin molecules:

a) Position of one glucose units:

- Cyanidine chloride when treated with 15% H_2O_2 in acetic acid,which opens the hetrocyclic ring by breaking C_2-C_3bond, without removing sugar residue.
- Latter compound when ,treated with ammonia,undergoes hydrolysis give one molecules of glucose.This reaction shown that cyanin has one glucose unit at 3- position.
- If the glucose residue is present in compound (II) in 5- or 7- position then this glucose is removed only by heating with dilute HCl.

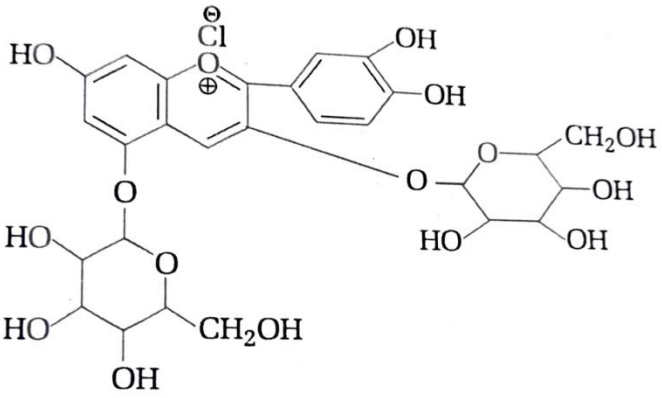


b)Position of second glucose units:

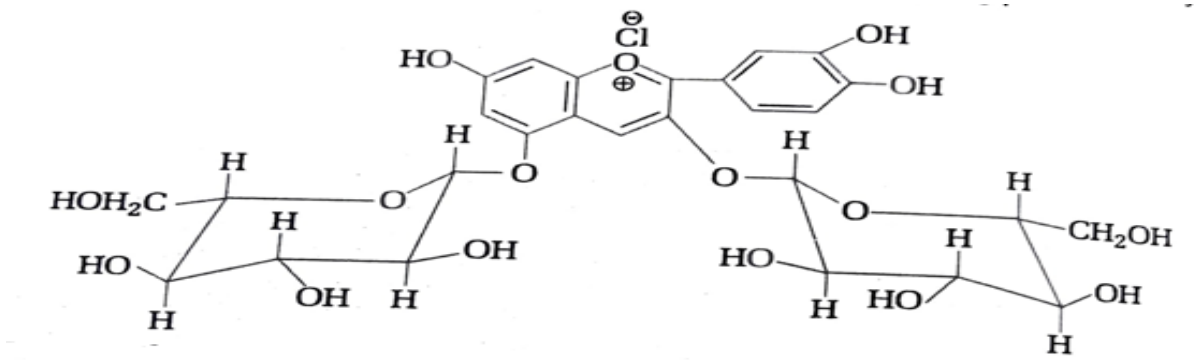
- When cyanin chloride is methylated , yields tri methyl derivative.

- The methylated product hydrolysis first with HCl, heating with $Ba(OH)_2$, yields methyl phloroglucinol and veratric acid(3,4,5-trimethoxybenzic acid).
- The two free hydroxyl groups in monomethyl phloroglucinol reveal the position of sugar residue indicates that other glucose residue is present in position-5.

Thus structure of cyanin chloride is as follows:

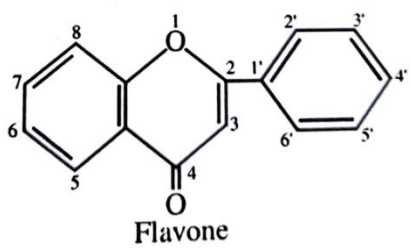


5)Cyanin chloride is hydrolysed by β-glucosidase. This shown that in cyanin chloride have β glucosidic linkage. Thus final structure of cyanine chloride as follows:



B.FLAVONES:

i) Introduction: Flavones are colorless or yellow compounds made from naringenin flavanone by addition of a double bond to the C-ring between C-2 and C-3. Also, flavones are structurally very similar to flavonols and differ only in the absence of hydroxylation at the 3-position on the C-ring.These are also known as anthoxanthins.In most of the flavones , position 5 and 7 are hydroxylated and also one or more of positions 3,4,5, are also hydroxylated. Further , position 3′ and 5′ are often methylated whereas position 5,7, and 4′ are usually unmethylated.



Flavone

ii)Proerties: The properties of flavones are as follows:

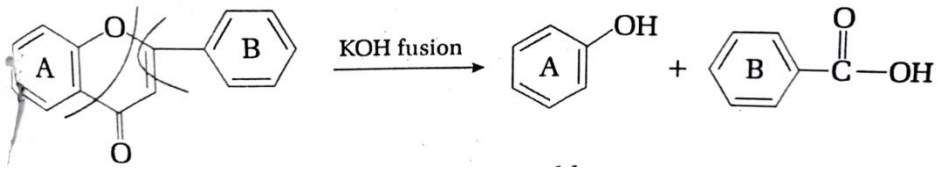
- Yellow solids.
- With ferric chloride, flavones give either a dull green /red brown colour.
- Flavones are soluble in water, ethanol and dilute acid.
- Flavones exhibit two absorption bands, Band 1, 330-350 nm and Band 2, 250-270 nm. Thus , it becomes possible to distinguish flavones from the anthocyanins on the basis of absorption bands and also by colour reactions.
- In presence of water flavones form oxonium salts,which is very unstable.
- In acidic medium flavones are usually more highly coloured than the bases.

iii)General methods for the Elucidation of Structure of Flavones: The structure of flavone can be determined as follows:

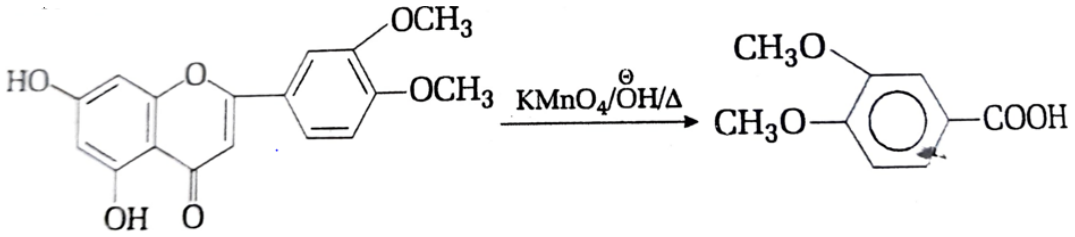
1) $C_{15}H_{10}O_2$ Molecular formula of flavone has been determined on the basis of analytical data and molecular weight determination.

2) When acetylated , flavone does not yield any acetyl derivative , indicating the absence of any –OH (Hydroxyl group).

3) When flavone fused with KOH,it yield Phenol and benzoic acid. This indicates the position of –OH (hydroxyl) and $–OCH_3$(methoxy) group in ring A and ring B.

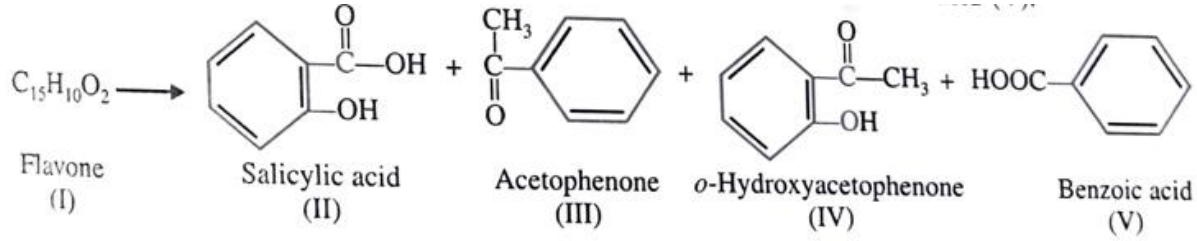


4)On oxidation with $KMnO_4$ ring B converts into benzoic acid /substituted benzoic acid.

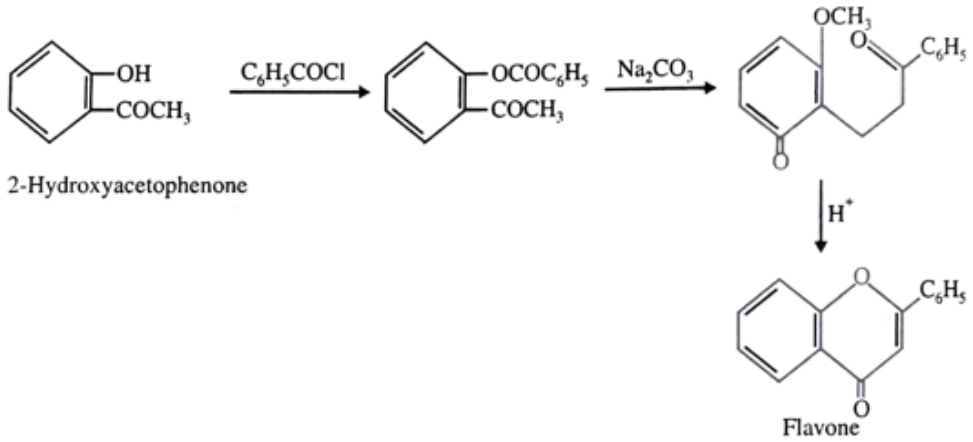


Product 3,4- dimethoxy benzoic acid is due to the presence of methoxy group at position -3′ and 4′ in the given flavone.

4)Flavone (I) boiled with alcoholic solution of KOH , yield four different products i.e Salicylic acid (substituted salicylic acid) (II),Acetophenone (III), o-Hydroxyacetophenone (IV) and Benzoic acid (V).

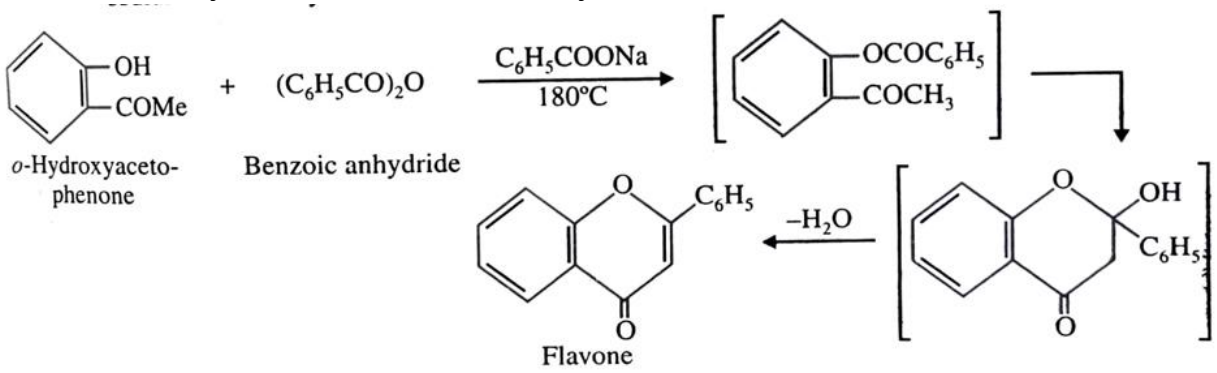


The formation of these products , which produce in the pairs (II) and (III) and pairs (IV) and(V) can be explained on the basis of opening of the pyrone ring of flavones (I) productes o-Hydroxydibenzoylmethane (IA) which then undergoes scission in two ways, and produce two pairs of products.

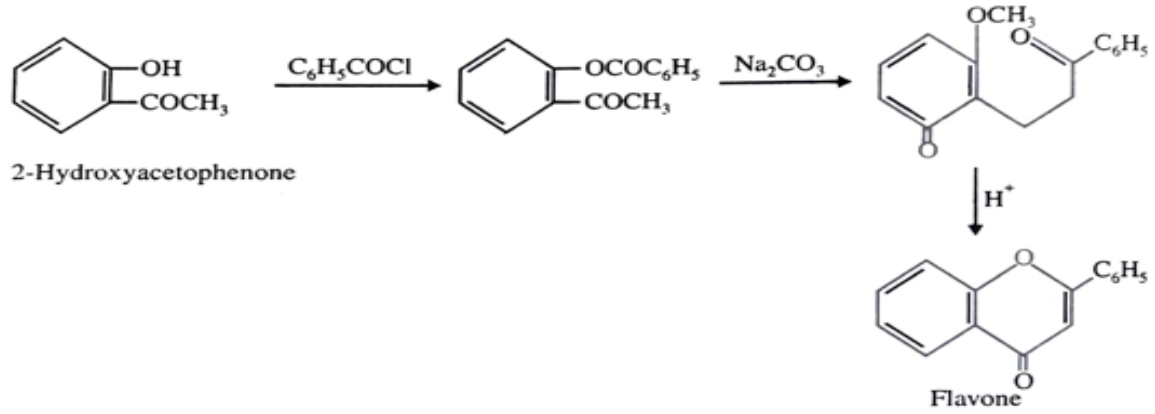


4) Finally the structure of flavones has been confirmed by its various synthesis. Some method of synthesis are given below:

a)Robinson's synthesis (1924): This synthesis is a reversal of the formation of (IV) and (V) .In this method flavone obtained in one step by heating of o-Hydroxyacetophenone at 180^0 with benzoic anhydride and sodium benzoate yield flavone.



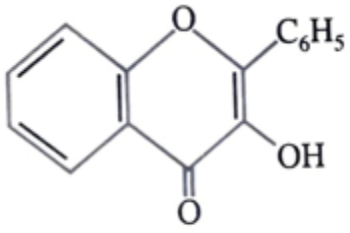
b)The Baker –Venkataram Synthesis: In this method, first step O-benzoyloxy aceto phenone was synthesized from reaction of O-hydroxy aceto phenone with benzoyl chloride in the presence of pyridine. In the second step O-benzoyloxy aceto phenone is heated with glycerol at 260^0 C for two hrs which leads to the formation of flvone.



C.FLAVONOLS (3-Hydroxy flavone)

i)Introduction : Flavanonols, also called dihydroflavonols or catechins, are the **3-hydroxy derivatives of flavanones**. They are a highly diversified and multi substituted subgroup. Flavonols exist in many colors varying from white to yellow, and they are closely related in structure to the flavones; they only differ in having a hydroxyl group at 3-position on the C-ring .The 3-hydroxyl group can link a sugar, that is, it can be glycosylated.Like many other flavonoids, most of them is found in fruit and vegetables, and in plant-derived foods, in glycosylated

form.



Flavonol

ii) Properties : The general properties of flavonol (3-Hydroxy flavone) given below:

- Flavonols are the most abundant yellow colorants.
- Flavonols can easily chelate with meal cations due to the presence of neighboring hydroxyl–keto functional groups.
- Flavonols shown characteristic band at 350-390nm and 150- 270 nm in ultraviolet spectrum.

iii) General methods for the Elucidation of Structure of Flavonols(3-Hydroxy flavone) :

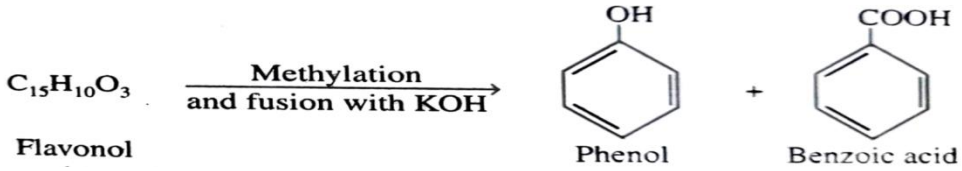
The structure of flavonol can be elucidated on the basis of following facts:

1)On the basis of analytical data and molecular weight determination,the molecular formula of flavonol is $C_{15}H_{10}O_3$.

2)When flavonol is acetylated yield monoacetyl derivative, indicated that it contains on –OH group(Hydroxy group)

$$\underset{\text{Flavonol}}{C_{15}H_9O_2(OH)} + CH_3COCl \longrightarrow \underset{\text{Monoacetyl derivative of flavonol}}{C_{15}H_9O_2(OCOCH_3)} + HCl$$

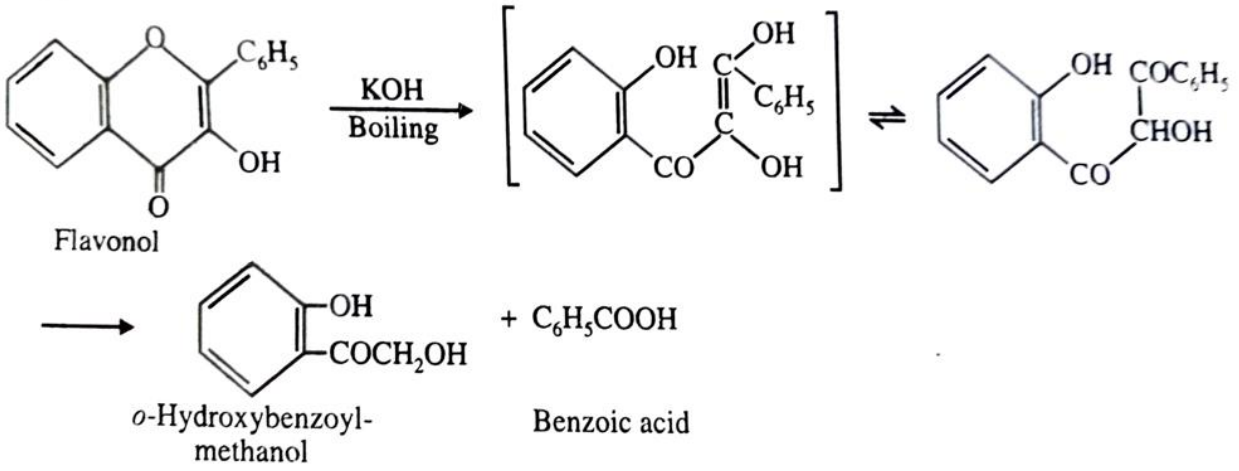
3)Flavonol is methylated and fused with KOH ,to produce phenol and benzoic acid as a product indicated that,methoxy group must be present at C_3 which must have been lost in KOH fusion.



Flavonol Phenol Benzoic acid

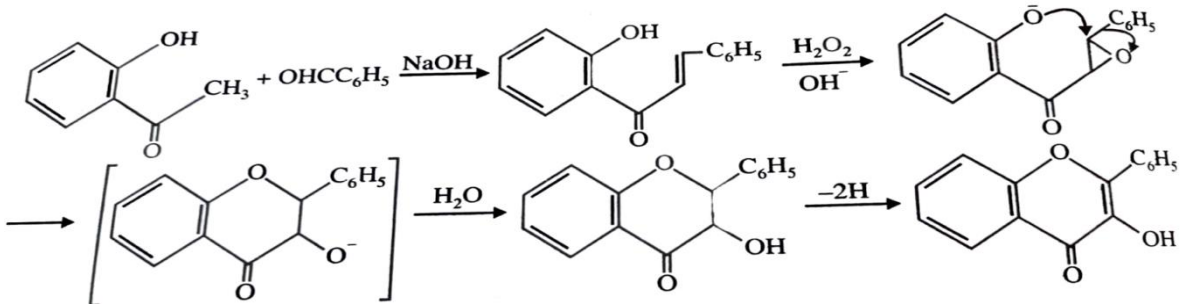
4)With ethanolic solution of KOH flavonol yield a mixture of o- hydroxybenzoylmethanol

and benzoic acid.Both products reveals that in flavonol C3 contains –OH group (Hydroxy group).Hence flavonol must be 3-hydroxyflavone (3-hydroxy-2-phenyl-γ-chromone).



5)Synthesis: The structure of flavonol has been confirmed by its synthesis:

Algar-Flynn Oyamada's Synthesis: In this synthesis 2-hydroxychalcone the interaction of 2-hydeoxy acetophenone with benzaldehyde in the presence of alkali like NaOH , then further treated with H_2O_2 first converted into3-hyderoxyflavanone and then final product flavonol obtained.



D. Quercetin

i) Introduction:Quercetin is a plant flavonol fromthe flavonoid groupof polyphenols.Quercetin extensively found in all type testy red , green and purple- pigmented plants, for example,blueberries, apple, onions, grapes, rasphberry, cherries and citrus fruits.It is widely distributed pigments and occurs as rhamnoside (quercitrin) in the bark of Quercus tinctoria. The name quercetin (3,3',4',5,7-pentahydroxyflavone**) (Figure 4. 11)** comes from the Latin

word "Quercetum"which means Oak Forest, belongs to the class called flavonols.

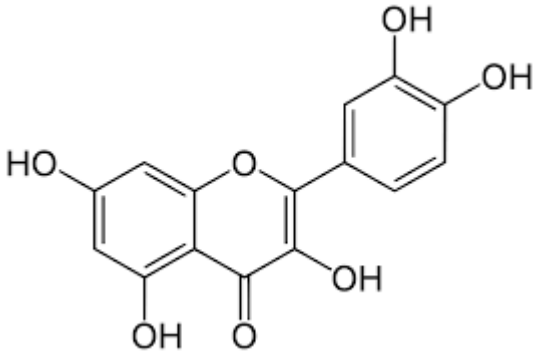


Figure 4.11

ii) Proerties : Some properties of quercetin are given below:

- It is yellow colored pigments.
- Quercetin soluble in hot water, alcohol and lipids and is insoluble in cold water.
- In the UV–visible range of **240–500 nm**, quercetin has two main absorption bands: band A (240–280 nm) and band B (340–440 nm).
- The most common quercetin glycosides have a sugar group at the 3-poistion, such as quercetin-3-*O*-β-glucoside (**Figure 4.12**) . It is these glycosylated structures that are most common in nature, not the aglycone, or parent compound.

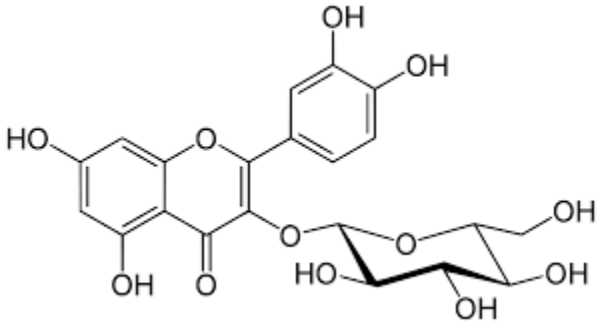


Figure 4.12

iii)General methods for the Elucidation of Structure of Quercetin (3,3',4',5,7-pentahydroxyflavone): The structure of quercetin has been elucidated on the basis of following synthetical and analytical facts:

1)From analytical data and molecular weight determination the molecular formula of Quercitrin has been found to be $C_{21}H_{20}O_{11}$.

2)Hydrolysis: On hydrolysis with HCl,quercitrin gives one molecules of quercetin and one molecules of rhamnose.This reaction indicates that quercitrin is mono glycoside of quercetin.

$$C_{21}H_{20}O_{11} + H_2O \xrightarrow{HCl} \underset{\text{Quercetin}}{C_{15}H_{10}O_7} + \underset{\text{Rhamnose}}{CH_3(CHOH)_4CHO}$$

3)Structure of quercetin:

a)From the analytical data , molecular weight determination the molecular formula of quercetin is $C_{15}H_{10}O_7$.

b) Presence of Hydroxyl group: With acetylation quercetin forms penta-acetyl derivatives, indicating the presence of five –OH group (Hydroxy group).

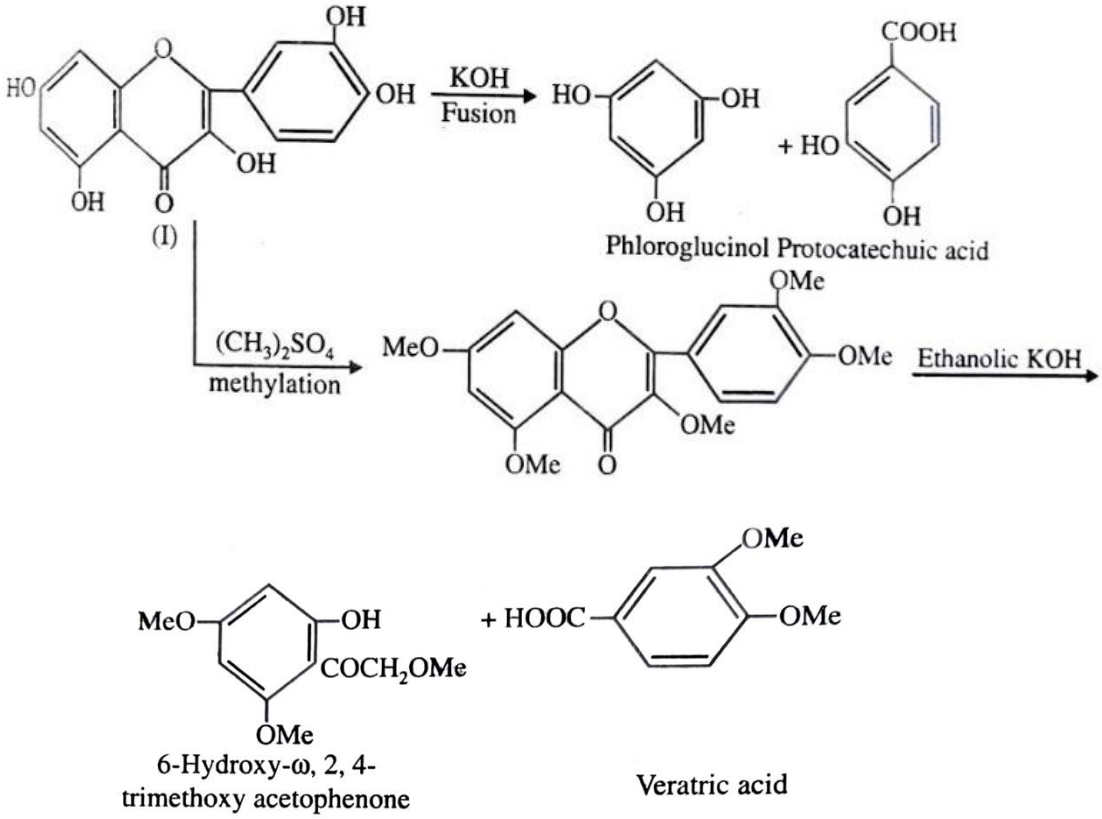
$$\text{Quercetin} \xrightarrow{(CH_3CO)_2O/CH_3COONa} \textit{Pentaacetyl quercetin}$$

c) Further analysis of quercetin by Zeisel's method shown the absence of methoxy groups.

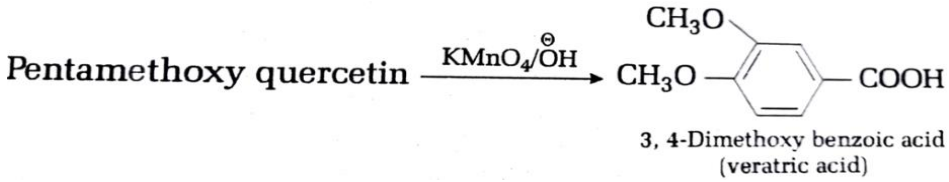
d) Acetylation and permethylation shows that quercetin contain five –OH groups (Hydroxy group) and one hydroxyl group is present at 3- position.

e)Position of (-OH)Hydroxy group:

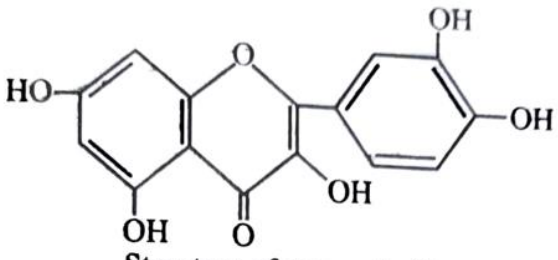
- When quercetin fused with KOH gives phloroglucinol and protocatechuic acid.
- When penta- methyl quercetin boiled with ethanolic solution of KOH , yield a mixture of 2,4-trimethoxyacetophenone (II) and 3,4-dimethoxy benzoic acid(veratric acid)-(III).



Both of above product shown that ring B has two hydroxyl group at position-3′ and 4.′



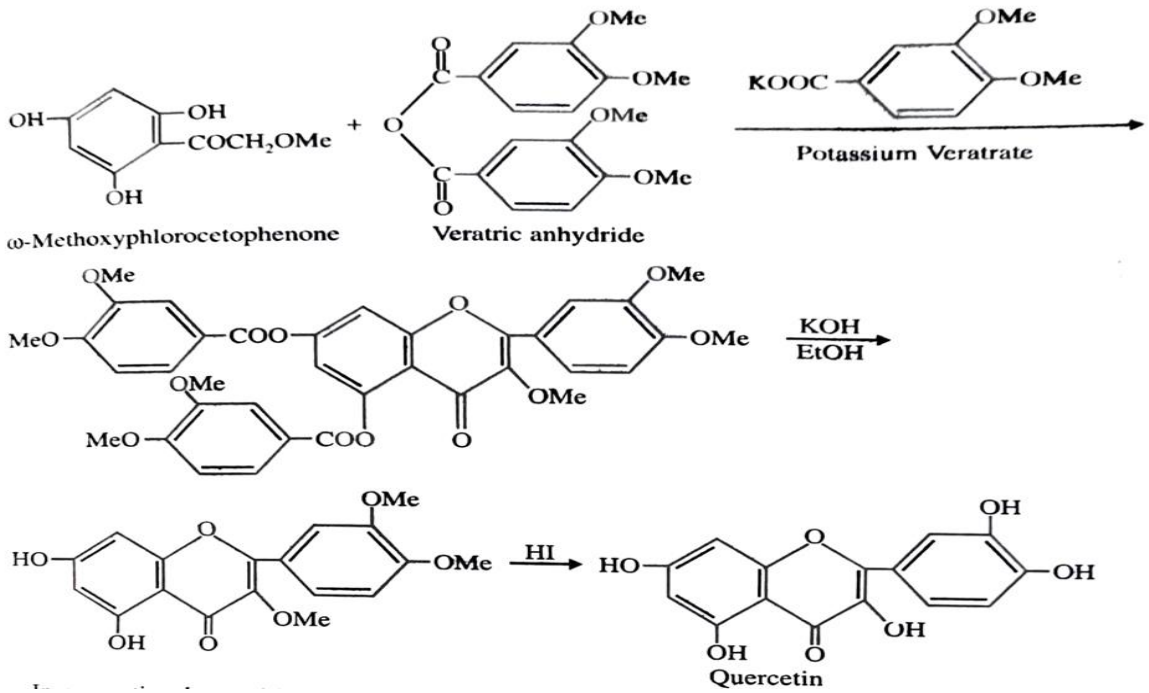
- The formation of phloroglucinol indicates that ring-A of quercetin contain two hydroxyl group :one at 5 and other at 7 positions.
- Above facts indicating that quercetin is 5,7,3′,4′- tetrahydroxyflavonol /3,5,7,3′,4′-pentahydroxyflavone(I).So, the above fact accepted the correct structure of quercetin is below:



Structure of quercetin (I)

4)Synthesis: All the forgoing reactions can be explain on the basis of structure(I) of quercetin as follows:

Robinson synthesis : In this method ω-methoxyphloroacetophenone condensed with veratric anhydride in the presence of potassium salt of veratric acid (3,4-dimethoxy benzoic acid), quercetin is obtained.



In quercetin , the position of the rhamnose has been proved to be 3. **(Herzing *et al*. 1912)**.

4.7 BIOSYNTHESIS OF FLAVONOIDS: ACETATE AND SHIKIMIC ACID PATHWAY

Introduction: The biosynthesis of flavonoids has long been the focus of intense research in plant biology. Flavonoids are derived from the phenylpropanoid metabolic pathway, and its have a basic structure. The flavonoida are constituted by 15 carbon atoms, which are arranged in C_6-C_3-C_6 backbone skeleton rings, in which ring Aand ring B are linked by three carbon ring C. The skeleton of ring represented in **Figure 4.13**

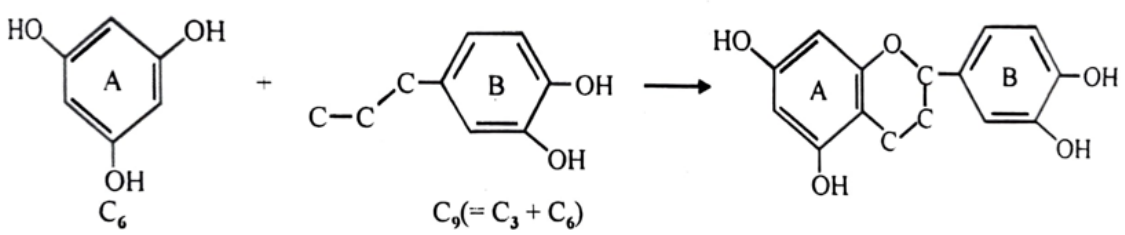


Figure 4.13

- One part having six carbon atoms, which from the ring A, while the other part having nine carbon atoms known as phenylpropanoid moiety.
- It is well established that the biogenesis of ring A take place via acetate or polyketide route, while that of ring B take place via the shikimate pathway.
- According to Robinson,The C_{15} skeleton of flavonoids is considered to be composed of two parts C_6 and C_9 .

Acetate or Polyketide Pathway: Ring A

- Malonate is a precursor of fatty acids.It act as the precursor of C_6 Polyketide.
- The actual mechanism for the formation of ring –A is, however , still unknown .Now it is supposed that the CoA derivatives of all acids reacts with each other by head to tail condensation
- Acetyl CoA is probably first converted to malonyl CoA as in the case of Biosynthesis of fatty acids.
- Three molecules of malonyl CoA condensed with each other to give polyketide.
- The route followed by acetate pathway is shown as follows in **Figure 4.14**

Shikimate Pathway: Ring B

The condensation of phosphoenol pyruvate (PFP) with D- erythrose -4-phosphate catalyzed by the enzyme 3- deoxy- D-arabino-heptulosonic acid-7-phosphate synthase(DHAP synthase) produce 3-deoxy-D-arabino-heptulosonate-7-phosphate. **Figure 4.14**

- The enzyme,3-dehydroquinate dehydratase is able to catalyze the dehydration to introduce a double bond between C-4 and C-5 to afford 3- dehydroshikimate.
- Reversible reduction of C-3 carbon group catalyzed by shikimate dehydrogenase occurs to yield the shikimate.
- Shikimate by the action of enzyme shikimate kinase converted to shikimate -3-monophosphate.

- Produce product on condensation with phosphoenol pyruvate (PEP) catalyzed by enzyme yield 5- enolpyruvyl-3-phospho-shikimate.
- In final step of shikimate pathway involves dehydration to introduce a second double bond in the six membered ring to yield chorismate.

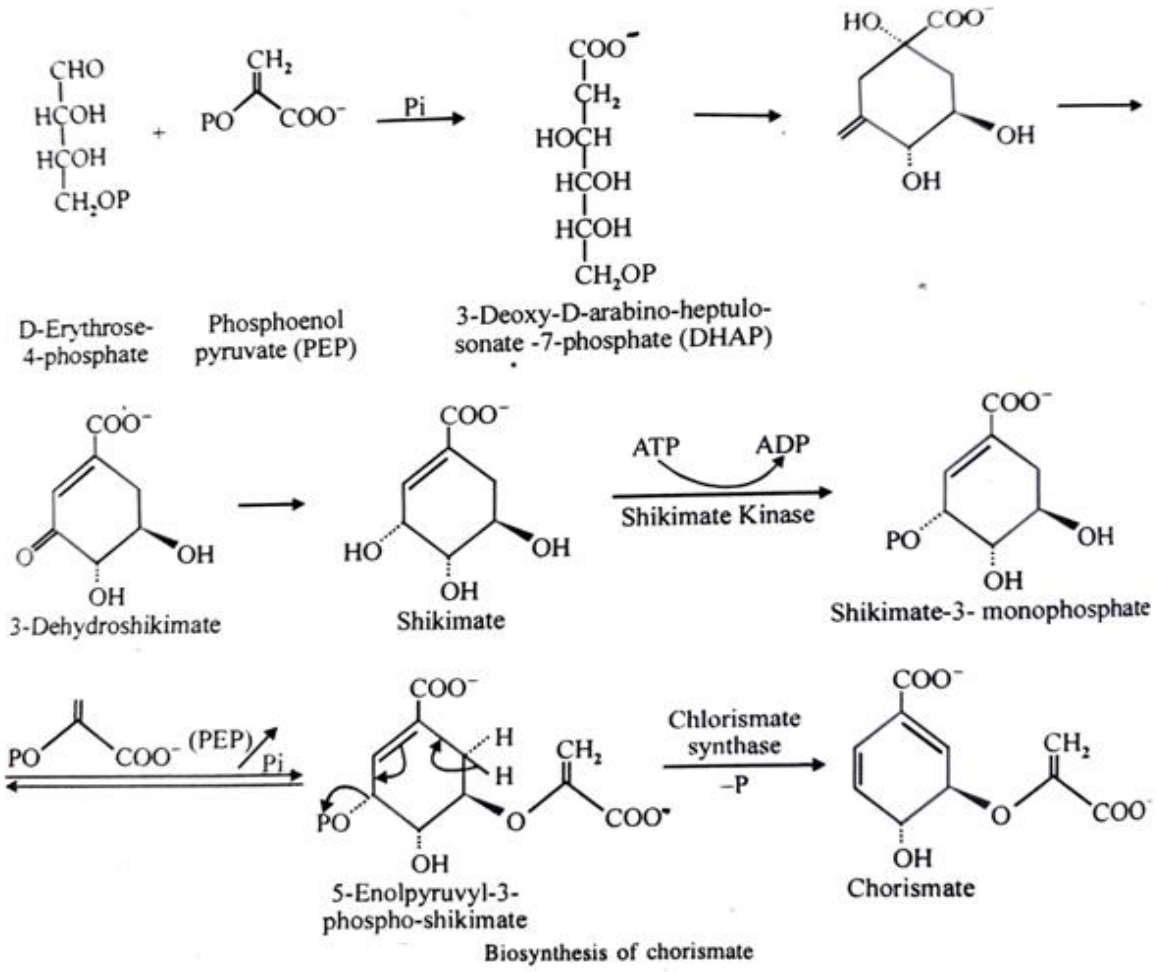


Figure 4.14

Phenyl propanoid Moiety:

- By a pericyclic reaction , the enzyme chorismate mutase would catalyse and converted chorismate to prephenate.This is called unimolecular intermolecular rearrangement.
- Prephenate by the catalytic action of prephenate-dehydratase converted into Phenylpyruvate.

- Phenylpyruvate catalyzed by aromatic amino acid gives rise to phenylalanine. In this trans-amination glutamate behave as a donor of amino group.
- The enzymatic deamination of phenylalanine catalyzed by L-phenylalanine ammonialyase (PAL) take place stereospecifically with the loss of NH_2 and pro-S-hydrogen from the L-amino acid to produce trans-cinnamate, which is the phenyl propanoid moiety, (C_6- C_3), the precursor of ring B in flavonoids.
- Hydroxylation at C-2 and C-4 of trans cinnamic acid form p-coumaric acid and 2,4-dihydroxycinnamic acid.
- 2,4- dihydroxycinnamic acid glycosylated to produce 2-glycosyl-4-hydroxycinnamic acid, which on cyclization affords the coumarin , umbelliferone.
- Phenolic compounds like saffrole, p-coumaric acid , eugenol, and vanillin get formed through this biosynthetic pathway.

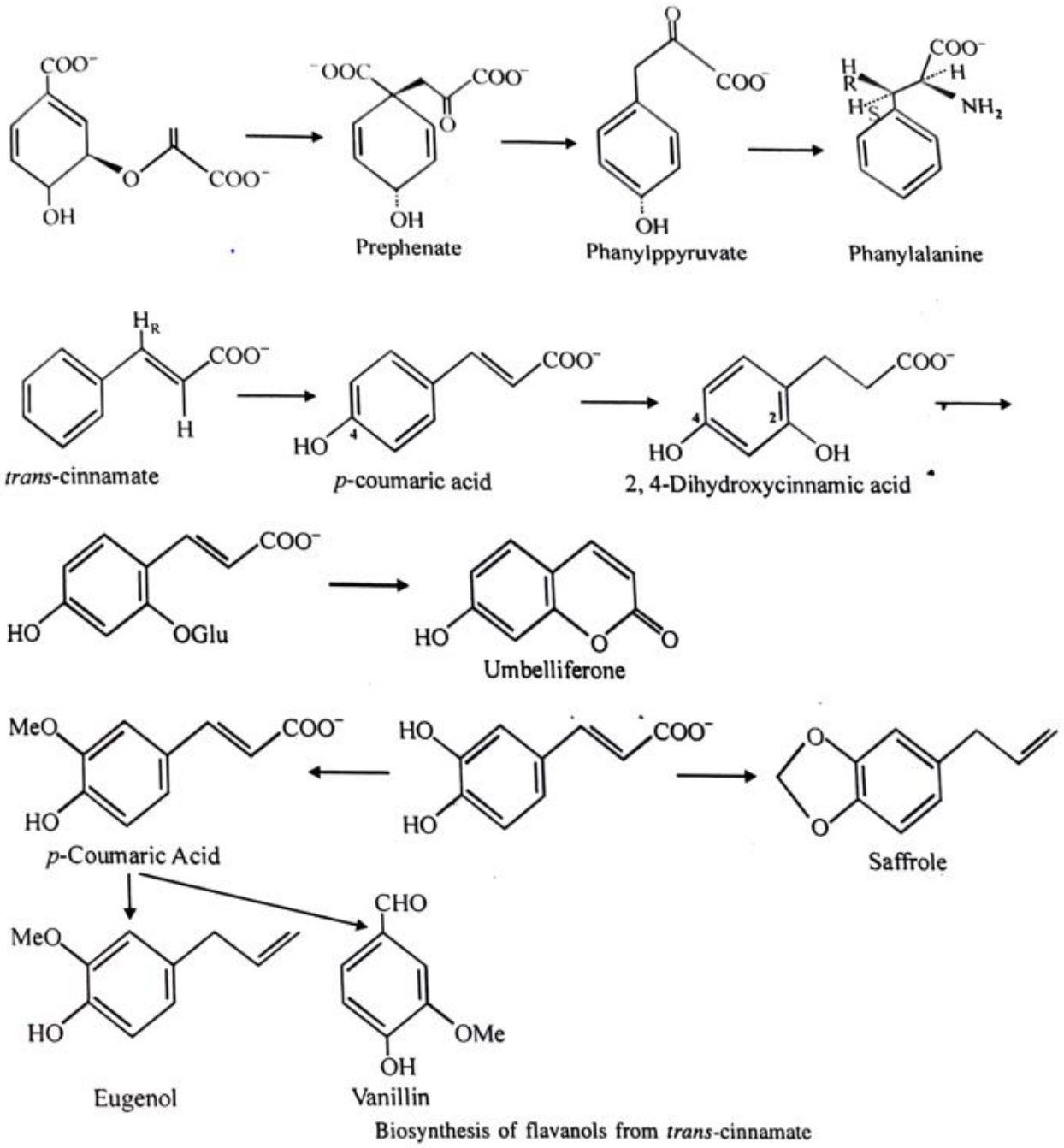


Figure 4.15

Role of shikimic acid pathway:

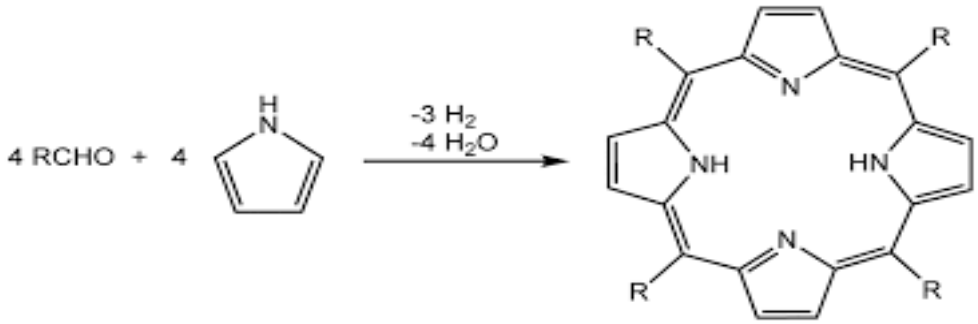
1) Shikimic acid is the starting point in the biosynthesis of many phenolic cpmpounds.
2) Shikimic acid pathway also involved in the biosynthesis of other compounds like indole, indole derivatives,and aromatic amino acid derivatives, many alkaloids and other metabolic metabolites.

3) Shikimic acid pathway the biosynthesis of phenypropanoids are used to produce flavonoids, coumarins, lignin and tannins.

4.9STRUCTURE AND SYNTHESIS OF PORPHYRIN SKELETON

Porphyrins are a group of heterocyclic macrocycle organic compounds, composed of four modified pyrrole subunits interconnected at their α carbon atoms via methine bridges (=CH−). The parent of porphyrins is porphine and substituted porphines are called porphyrins.

(i) Laboratory synthesis: A common synthesis for porphyrins is the **Rothemund reaction**, first reported in 1936, which is also the basis for more recent methods described by Adler and Longo.The general scheme is a condensation and oxidation process starting with pyrrole and an aldehyde.

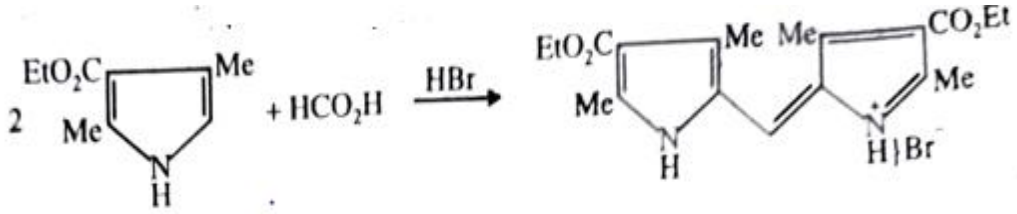


(ii)Synthesis of porphyrin skeleton: Porphyrin synthesis involve in two steps:

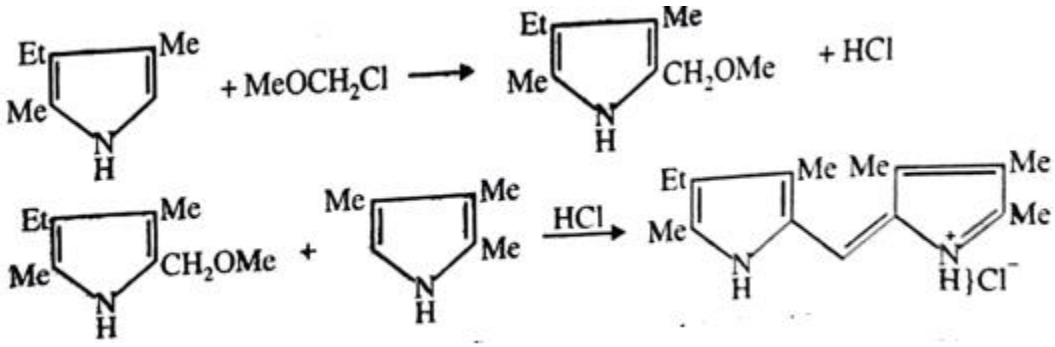
Step First :

1)Synthesis of dipyrrylmethenes: It is synthesized from the pyrrole units by the following methods:

First method: Dipyrrylmethenes prepared by the coupling of pyrroles having 5- position as vacant by means of formic acid in presence of HBr.(Fischer *et al.*)



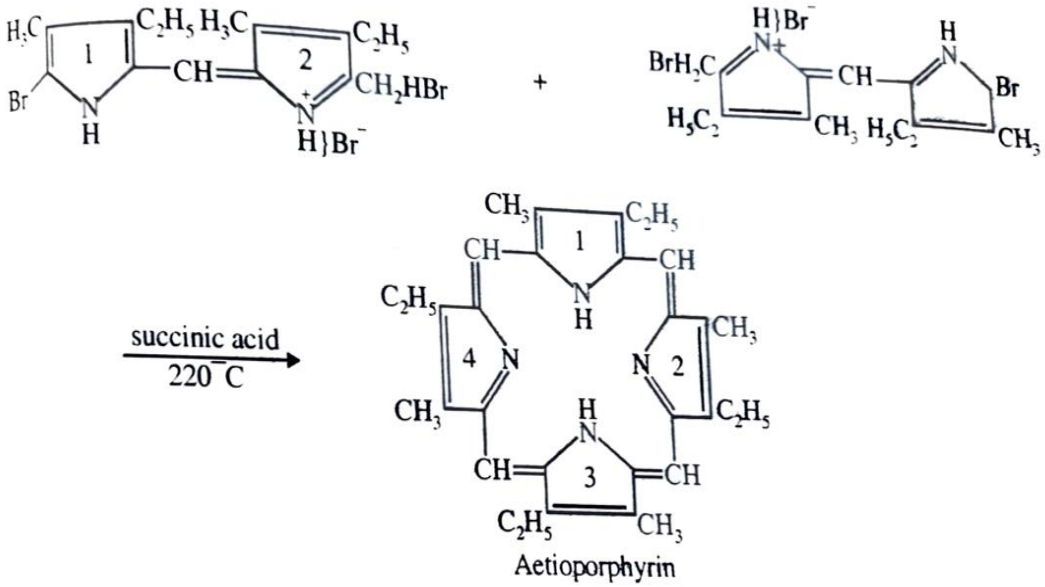
I) Fischer *et al* gave another method for preparing of dipyrrymethenes.



Step Second :

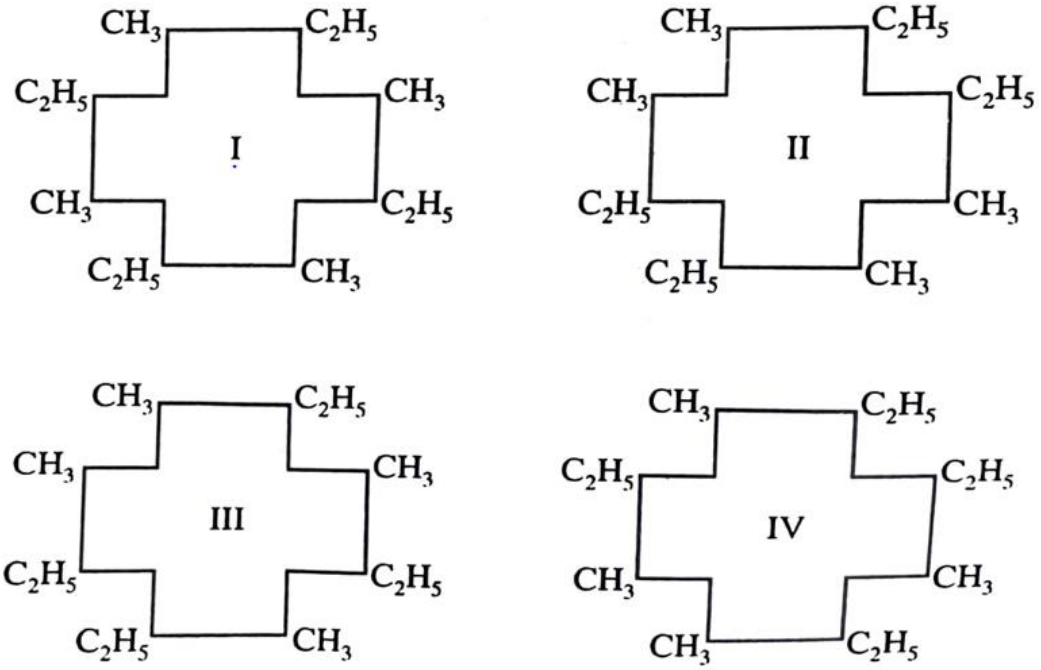
2)Condensation of dipyrrymethenes to porphyrins:

- Condensation between the hydrobromides of two 5-bromo-5′ methyldipyrrylmethenes.
- Condensation between the hydrobromides of 5,5′- dibromo and 5,5′-dimethyl dipyrrylmethene
- The condensation were done by heating with succinic acid at 220^0C.



Aetioporphyrin

(iii)Isomerism in Porphyrins; The simplest and common porphyrin is aetioporphyrin (tetramethyl-tetraethylporphin) ,which can exist in four different forms are given below:



Four position isomers of aetioporphyrin

4.9HAEMIN AND CHLOROPHYLL

A.Haemoglobin: **Hemoglobin** from the Greek word *haima* 'blood' + Latin *globus* 'ball, sphere' in abbreviated **Hb** or **Hgb**, is the iron-containing oxygen-transport metalloprotein present in red blood cells (erythrocytes) of almost all vertebrates (the exception being the fish family Channichthyidae)as well as the tissues of some invertebrates.Hemoglobin is made of two parts proteins called globin 94% and nonprotein part called haem 6%.

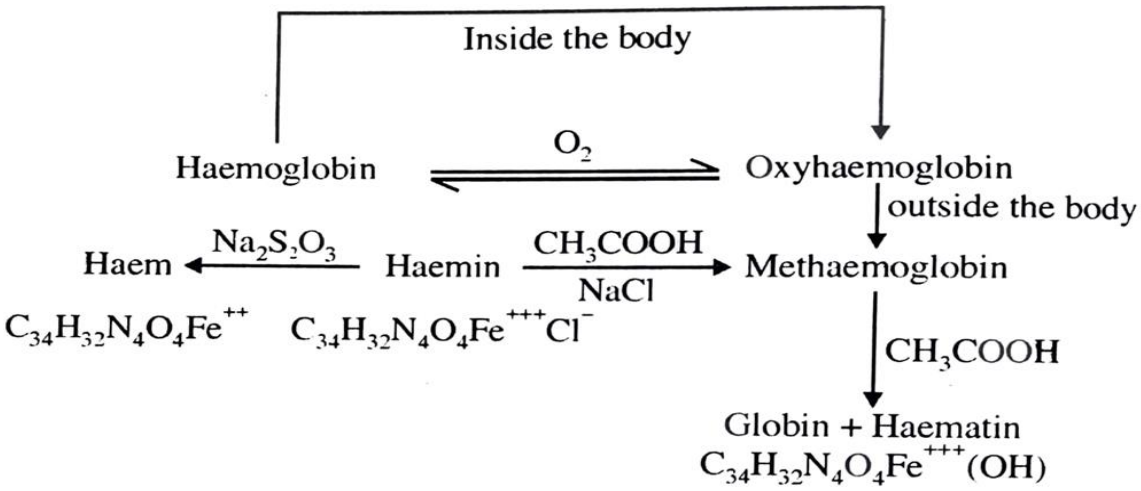
Haem is a prosthetic group that consists of iron ion contained in the center of a larg hetrocyclic ring called porphyrin.Haem is an iron-orotoporphyrin complex which is of two types:

a) In haem,when iron atom in ferrous state known as ferrous protoporphyrin,ferroprotoporphyrin, protohaem /haem , and it is a electrically neutal molecules.
b) In haem, when iron atom in ferric state known as ferric protoporphyrin or haemin , and it is a positively charge molecules.

A proteinic part of globin has four polypeptide chains and in humans the chains are called α-chains and β-chains. In a normal adult human two α- chains with 141 amino acids and two β-cahins with 146 amino acids.

In human body haemoglobin haemoglobin combined with oxygen forming unstable oxyhaemoglobin.This unstable compound loses oxygen when it reaches various parts of the organism.In this way haemoglobin carries oxygen from the organs of respiration to the tissues of the body.

When oxyhaemoglobin is present outside the organism, it is changed into stable compound called methaemoglobin , it is further treated with acetic acid gives globin and as well as brownish –red pigment haematin ($C_{34}H_{32}N_4O_4Fe^{+3}$) OH^- .However if methaemoglobin is treated with acetic acid with NaCl ,it gets hydrolysed yield Haemin and Globin.

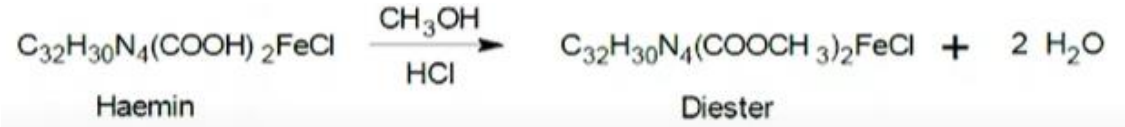


Iron free and and iron containing compounds are called porphyrins and haems respectively.

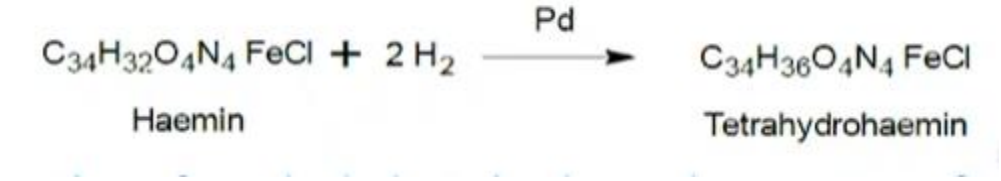
Constitution of Haemin: The constitution of haemin by employing various degradation reactions and finally confirmed by its synthesis.

1)The molecular formula of haemin has been found to be $C_{34}H_{32}N_4O_4FeCl$.

2)**Presence of two –COOH group:**When haemin treated with methanol and HCl (MeOH/HCl) diester is obtained. This indicate that haemin contains two carboxylic groups (-COOH).

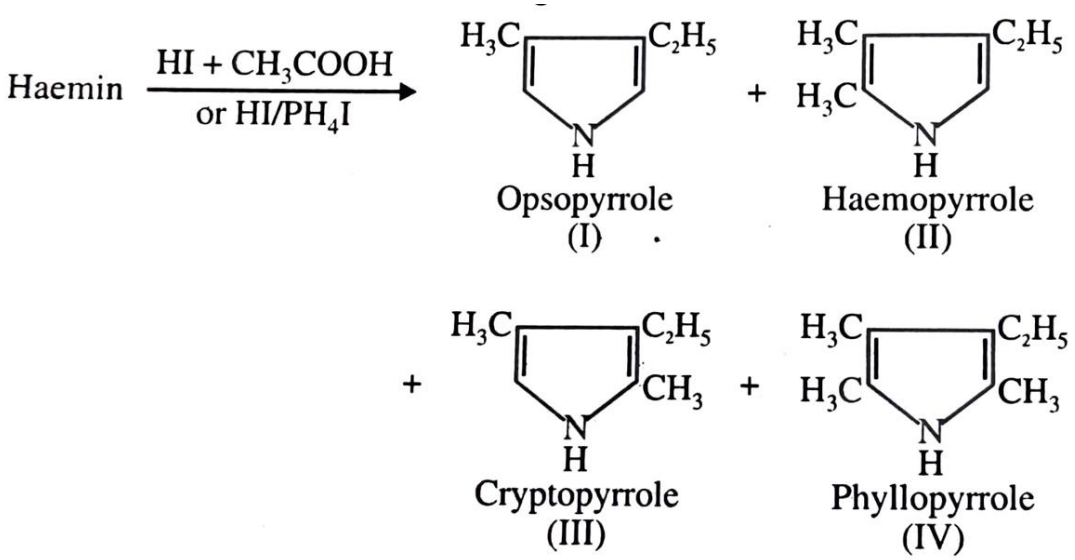


3)**Presence of two double bonds:**Catalytic hydrogenation of haemin with H2 / Pd catalyst gives tetrahydrohaemin.This reaction shown the presence of two double bonds in haemin.



4)**Presence of four pyrrole units:**

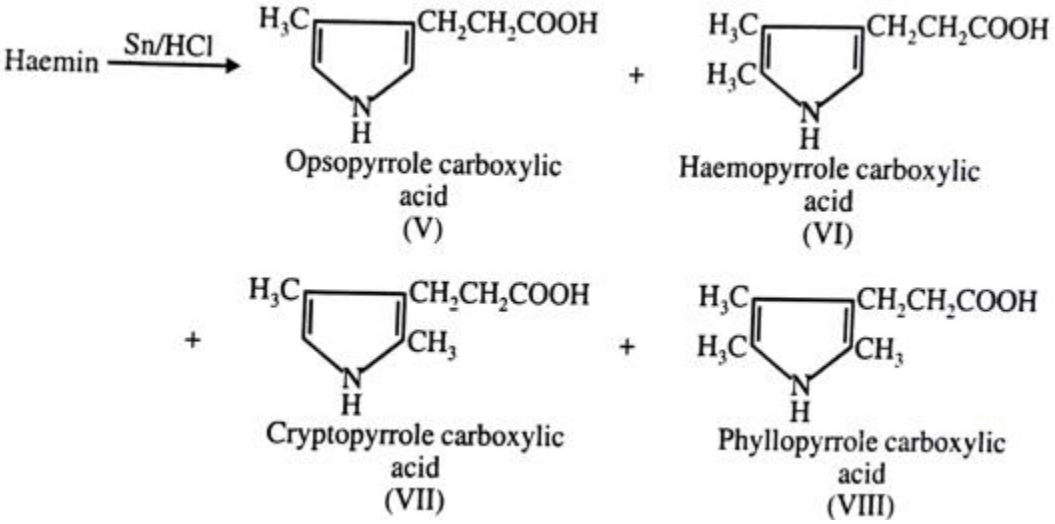
a)**Reductive degradation :** On vigorous reduction with HI and acetic acid / HI and phosphorium iodide ,haemin gives four substituted pyrrole derivatives.Structure of four pyrrole derivatives has been confirmed by their synthesis.



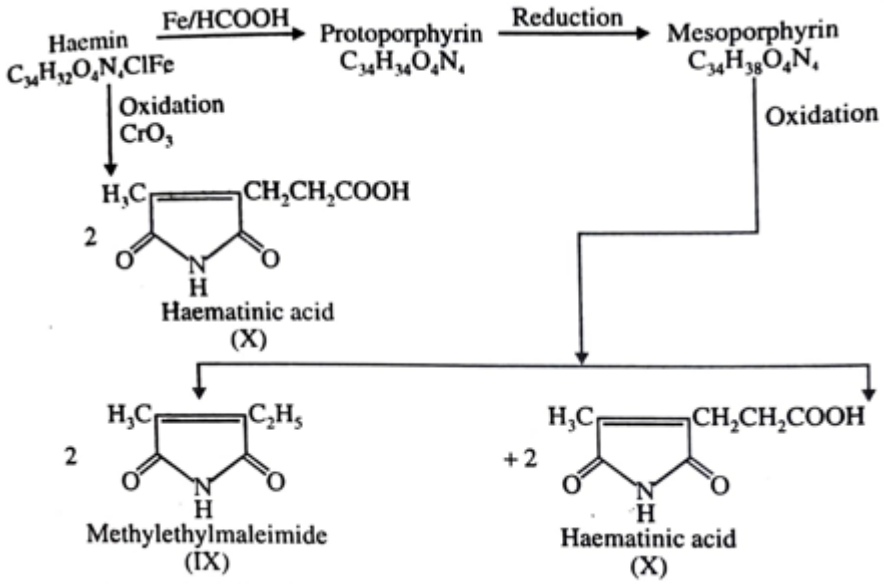
Above reaction shown that haemin molecule contain four nitrogen atom with four pyrrole nuclei having group in β- position.

b)**Reductive degradation with Sn / HCl :**Haemin on reduction with tin and hydrochloric acid(Sn/HCl) gives four pyrrole substituted carboxylic acid(V to VIII) corresponding to four pyrroles (I to IV).

These product also confirmed that haemin nuclei having methyl group in β- position.



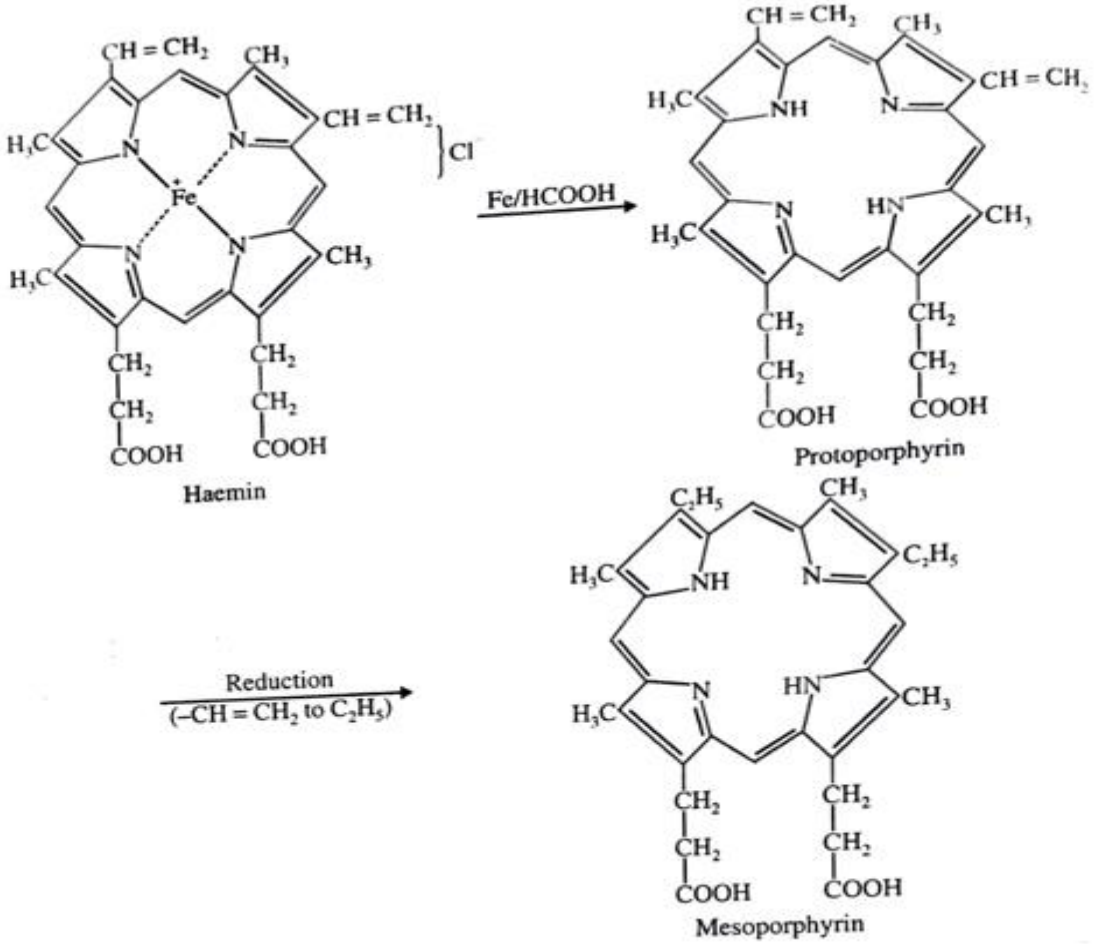
5**)Reduction with zinc dust:** Haemin on reduction with zinc dust with formic acid gives protoporphyrin$C_{34}H_{34}O_4N_4$,which on further reduction gives mesoporphyrin($C_{34}H_{38}O_4N_4$) Oxidation of mesoporphyrin produce two molecules of methylethylmaleimide and two molecules of haematinic acid.If direct oxidation is done with chromic acid produce only two molecules of haematinic acid.



Above product suggests that the pyrrole nuclei are linked through the α- position.Further, the formation of methyl group join at α- position in compoundes II,III,IV,V,VI,VII,and VIII .

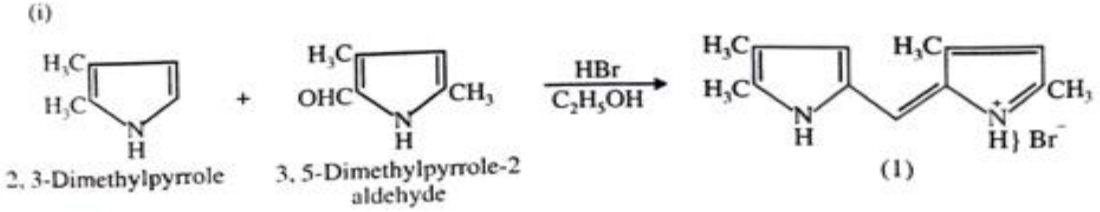
6)**Position of substituents in four pyrrole nuclei :**Mesoporphyrin on decarboxylation gives aetioporphyrin which was identified as tetraethyltetramethylporphyrin.This compound cn exist in four different isomers.Therefore, the aetioporphyrin obtained from haemin could not be identified.

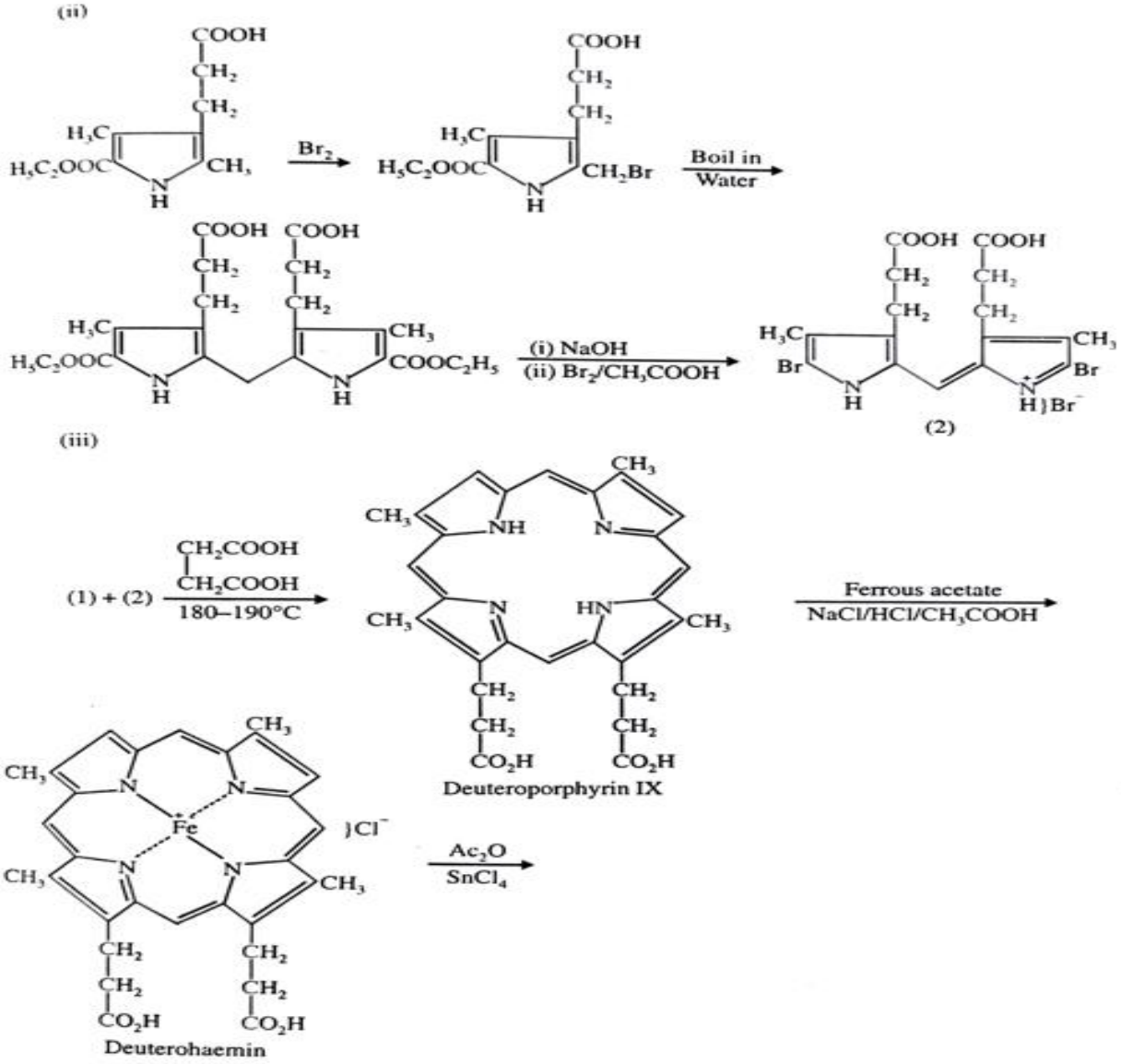
As mesoporphyrin is derived by the reduction (-CH=CH_2 to $-C_2H_5$) of protoporphyrin and latter is obtained from haemin by removal of iron atom.Thus the structure of protoporphyrin and haemin written as follows:

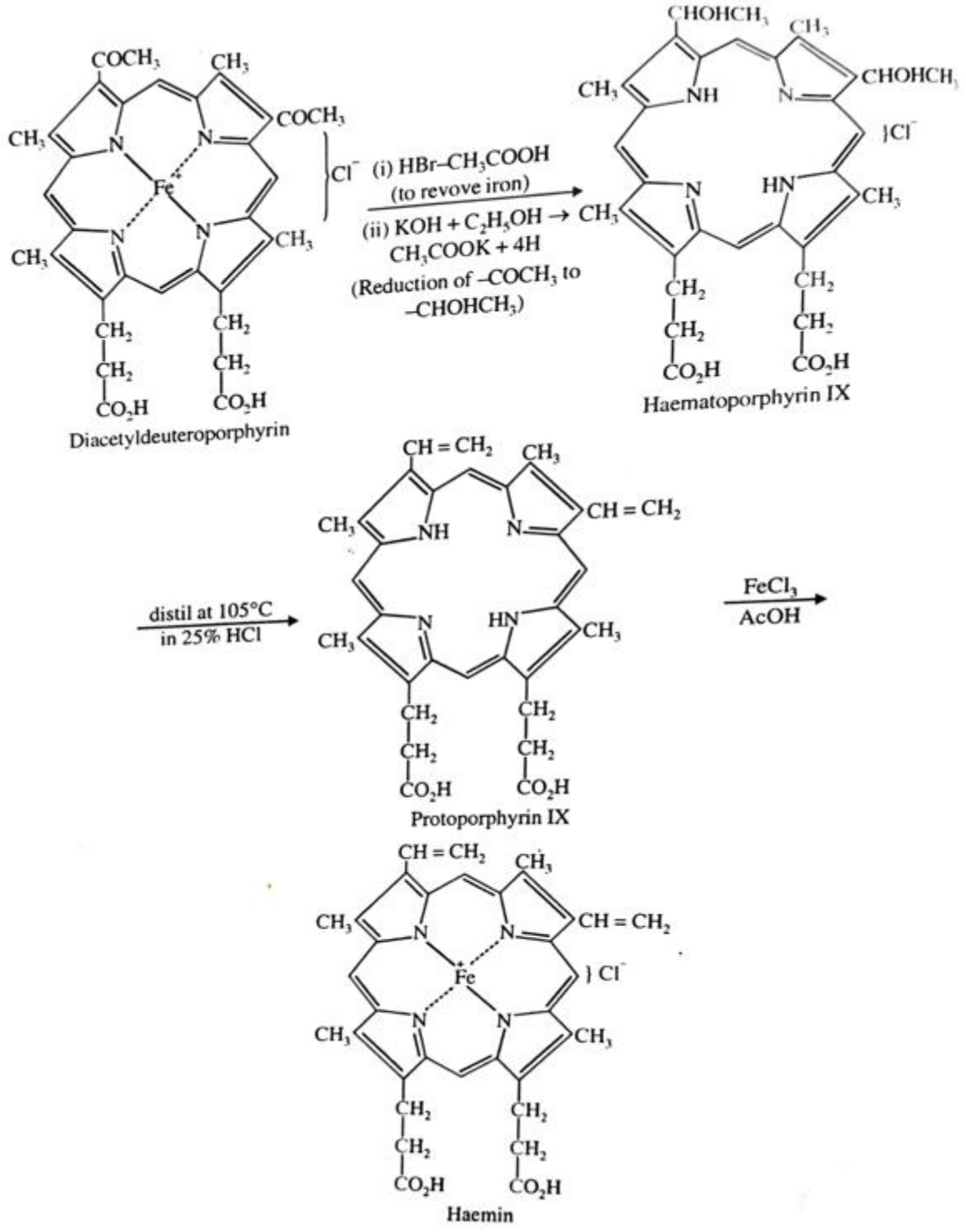


7)**Synthesis of haemin:** Finally the structure of haemin confirmed by its synthesis. Synthesis of haemin involves the following steps:

(i)




(ii)
Br2
Boil in Water
(i) NaOH
(ii) Br2/CH3COOH
(2)
(iii)
(1) + (2)
CH2COOH
CH2COOH
180–190°C
Ferrous acetate
NaCl/HCl/CH3COOH
Deuteroporphyrin IX
Ac2O
SnCl4
Deuterohaemin



B. Chlorophyll:

(i) Introduction: Chlorophylls are ubiquitous pigments in the plant kingdom that play a key role in photosynthesis, a vital function for life on Earth. These pigments involved in photosynthesis,

process by which light energy is converted to chemical energy through the synthesis of organic compounds. It absorbs energy from light; this energy is then used to convert carbon dioxide to carbohydrates.

There are five forms of chlorophylls found in plants and photosynthetic organism, but in plant kingdom only two major forms are commonly found, that is, chlorophylls *a* and *b*. The difference between these chlorophylls is chemical compound at position 7.

The molecular formula of Chlorophyll *a* is $C_{55}H_{72}N_4O_5Mg$, composed of $–CH_3$ while chlorophyll *b* $C_{55}H_{70}N_4O_6Mg$,is composed of –CHO. The difference in chemical composition leads to the difference in color; chlorophyll *a* exhibits blue-green, while chlorophyll *b* appears yellow-green color but both gives green solution in organic solvents.These two forms of chlorophyll coexist in plants in an approximate ratio of 3:1 with chlorophyll *a* being predominant.chlorophyll *a* exhibits characteristic maxima at 380,418,428,510,and 700nm whereas chlorophyll-b exhibits characteristic maxima at 428,464, and 675nm.

Chlorophylls are commonly found oil-soluble pigments responsible for the green color of plants.The basic structure of chlorophyll is a ring made up of four pyrroles, a tetrapyrrole, which is also known as porphyrin. This cyclic tetrapyrrole, like the heme group of globins and cytochromes is biosynthetically derived from protoporphyrin. The Mg^{++} present in the center of the porphyrin is bound with N atoms by covalent and coordinate bondings. **Figure:4.16**

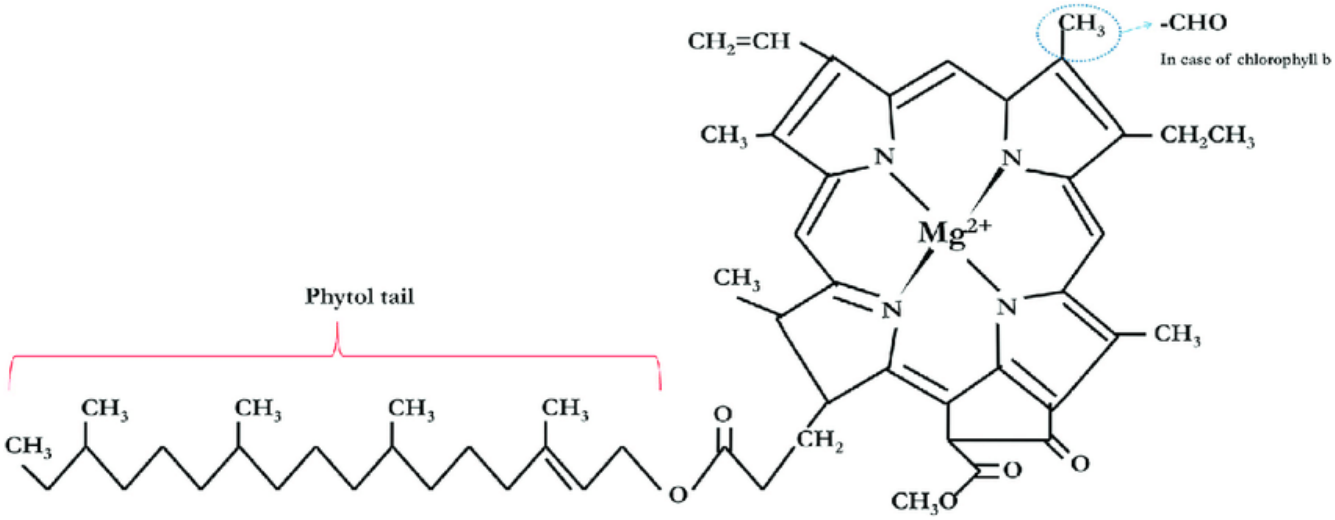
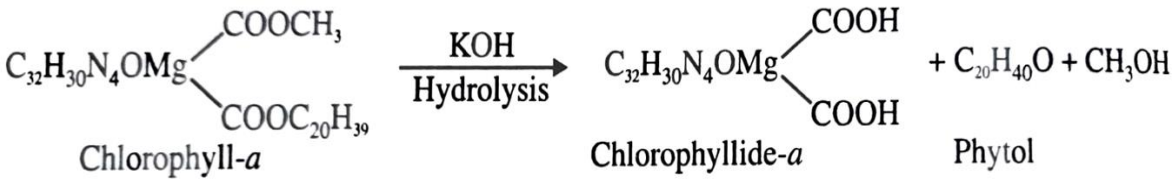


Figure: 4.16

ii) Constitution of chlorophyll-a : Constitution of chlorophyll-a have been ascertained on the basis of following facts:

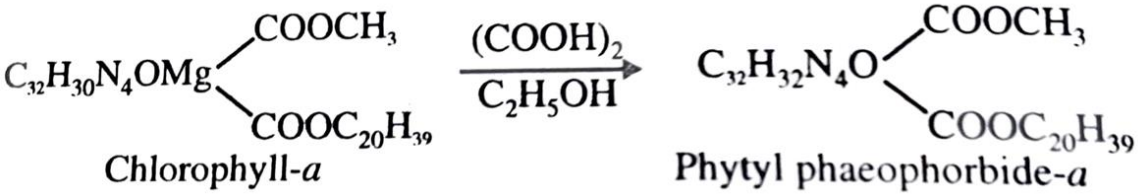
1) **Molecular formula:** The molecular formula chlorophyll-a of has been found to be $C_{55}H_{72}N_4O_5Mg$.

2) **Presence of diester group:** Hydrolysis of chlorophyll-a with cold dilute KOH solution, produce one molecules of chlorophyllide-a (I) , one molecules of phytol, and one molecules of methanol.This reaction shown that chlorophyll-a is a diester.



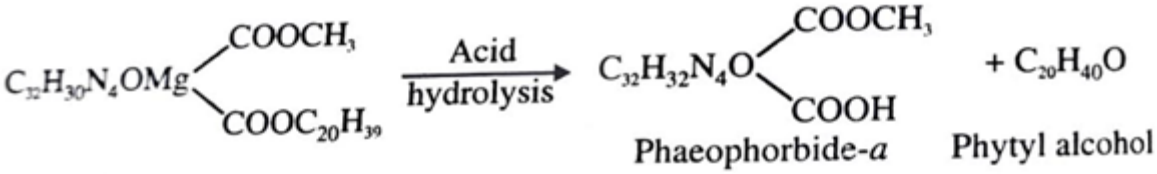
Chlorophyll-*a* Chlorophyllide-*a* Phytol

3)**Presence of phytyl group: a)** When chlorophyll-a heated with etanolic solution of oxalic acid , the magnesium atom is replaced by two hydrogen atoms to produce phytyl phaeophorbide-a.



Chlorophyll-*a* Phytyl phaeophorbide-*a*

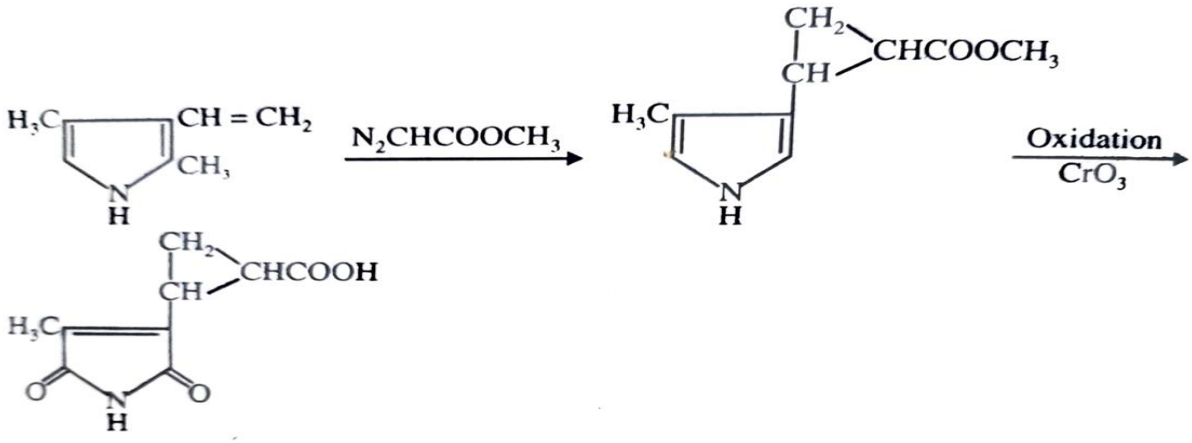
b) If it is hydrolysed with mineral acid, we get phaeophorbide-a.



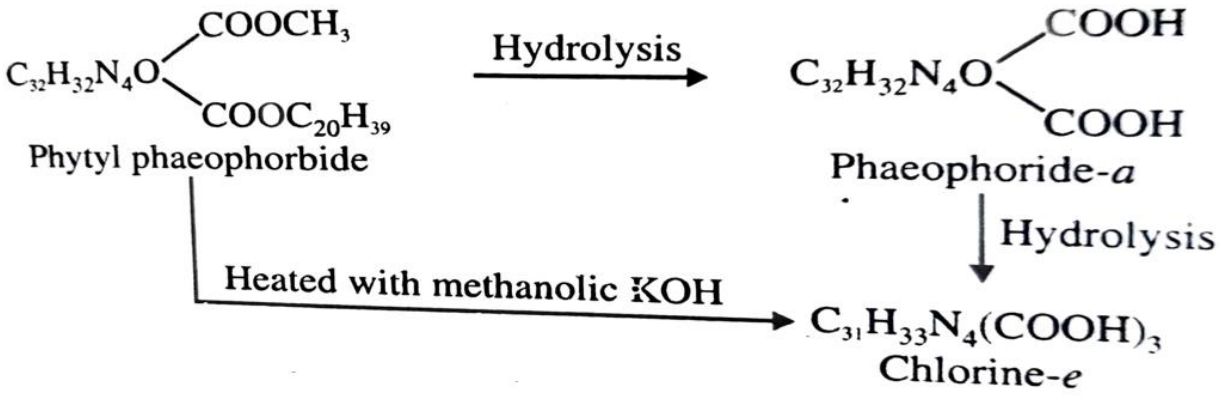
Phaeophorbide-*a* Phytyl alcohol

Both hydrolytic reaction shown that in chlorophyll-a ,has been presence of phytyl group .

4)**Presence of vinyl group:** Phaeophorbide-a,treated with diazoacetic ester gives cyclopropane derivative, which further oxidized with chromic acid CrO_3, yield methyl maleimide cyclopropyl carboxylic acid.This is the characterstic reaction of porphyrin.Which shown the double bond/ vinyl group has been confirmed in chlorophyll-a.

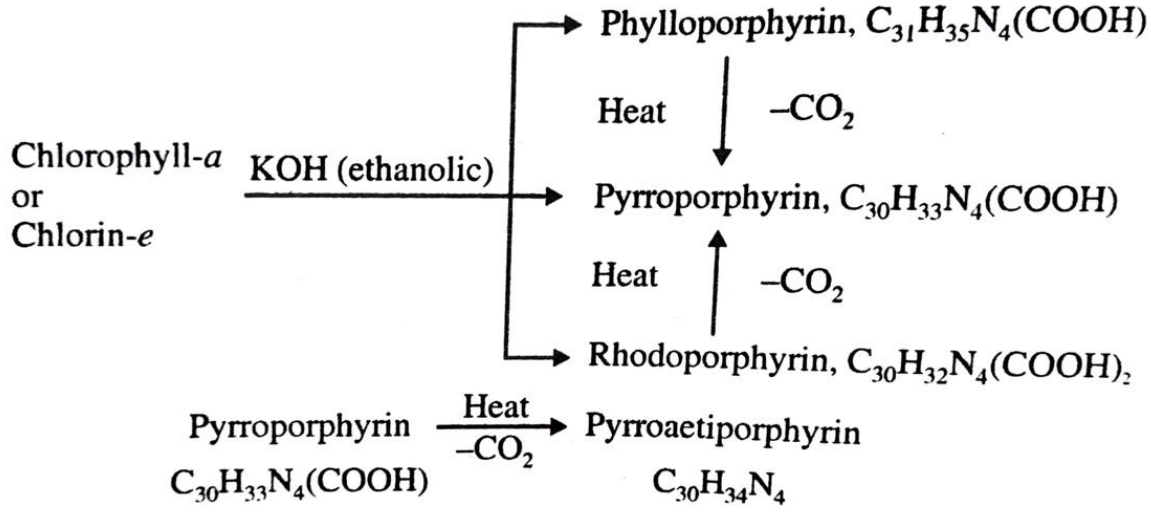


5)**Nature of the porphyrin nucleus: a)**Phytyl phaeophorbide –a heated with methanolic KOH, yield chlorine-e (trimethyl ester $C_{31}H_{33}N_4(COOH)_3$),on the other hand hydrolysis of chlorophyllide –a , similarly formed chlorine-e.



This shown that chlorphyllide-a must contain some group which give rise to third -COOH carboxyl group.Such group either a lacton / cyclic ketone because no carbon atoms lost during hydrolysis.

b)Chlorophyll-a/ chlorine-e on heating with ethanolic solution of KOH , it undergoes degradation produce various porphyrins repectivaly:Pyrroporphyrin ($C_{30}H_{33}N_4(COOH)$ Rhodoporphyrin($C_{30}H_{32}N_4(COOH)_2$,and Phylloporphyrin($C_{31}H_{35}N_4(COOH)$ .By heating with sodium ethoxide (C_2H_5ONa), causing loss of $–CH_2$ latter by CO_2, Rhodoporphyrin,Phylloporphyrin can be converted into Pyrroporphyrin.



From the above discussion, it shown that structure skeleton ,chlorine-e contains two carboxylic group in **Figure 4.17,** but chlorine-e contains three carboxyl groups **Figure 4.18.**In structure (**Figure 4.18)** explains the formation of a methylene group at the γ-carbon atom.

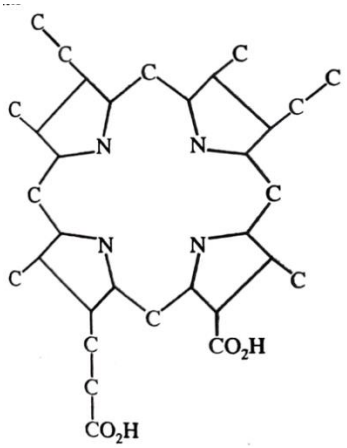


Figure 4.17

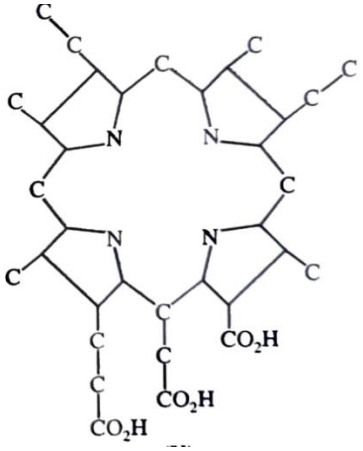


Figure 4.18

6)Position of vinyl group: When reduced catalytically , phaeophorbide-a yield dihydro-derivative in which keto group remains intact. This reaction reveals that phaeophorbide-a contains readily reducible double bond. From oxidation of phaeophorbide-a and dihydrophaeophorbide-a follows that, vinyl group is present in the former on position-2.

Structure of chlorophyll –b: The structure of chlorophyll-b has been elucidated in the same manner as that for chlorophyll-a . The presence of an aldehyde group(-CHO) has been done by the formation of dioxime from methyl phaeophorbide-b and its position has been ascertained on the

basis of conversion of trimethyl ester rhodin-e into a compound, 3-dimethyldoxophylloerythrin of known structure.

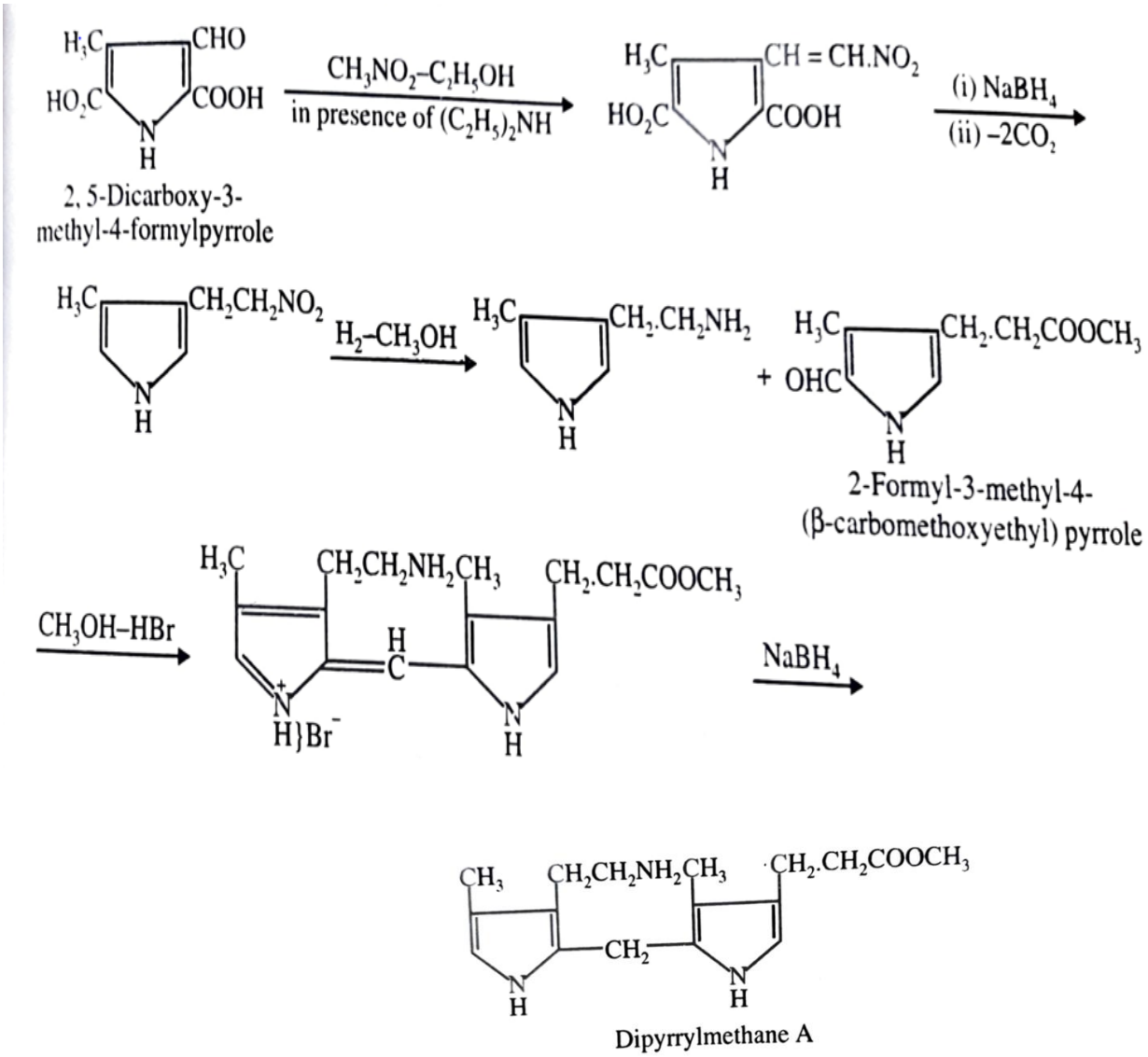
Synthesis of chlorophyll : Chlorophyll –a can be prepared as follows:It can be divided into two part:

i) a)Synthesis of dipyrrylmethane A

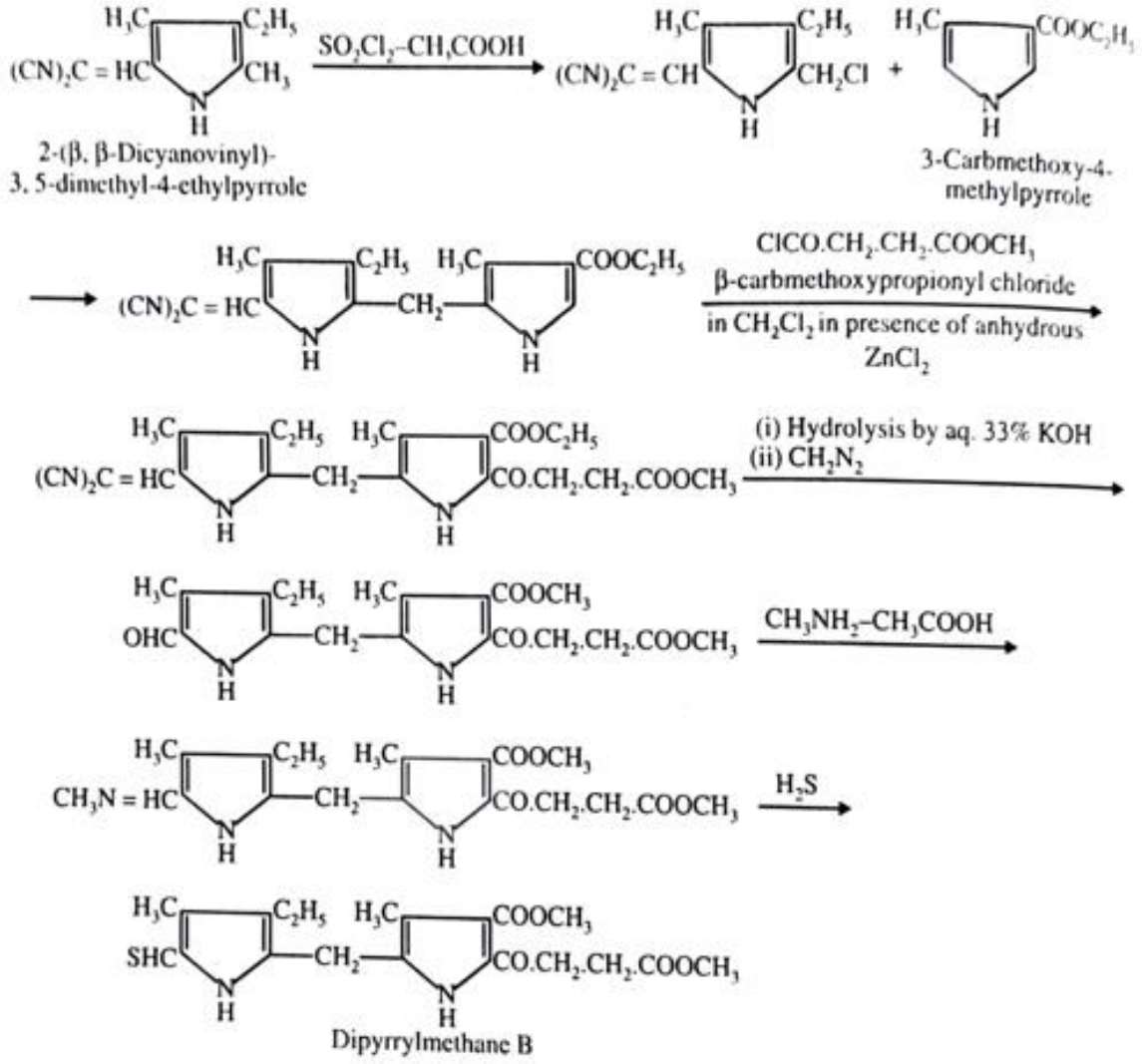
b)Synthesis of dipyrrylmethane B

ii)Condensation of A and B dipyrrylmethanes to yield chlorophyll.

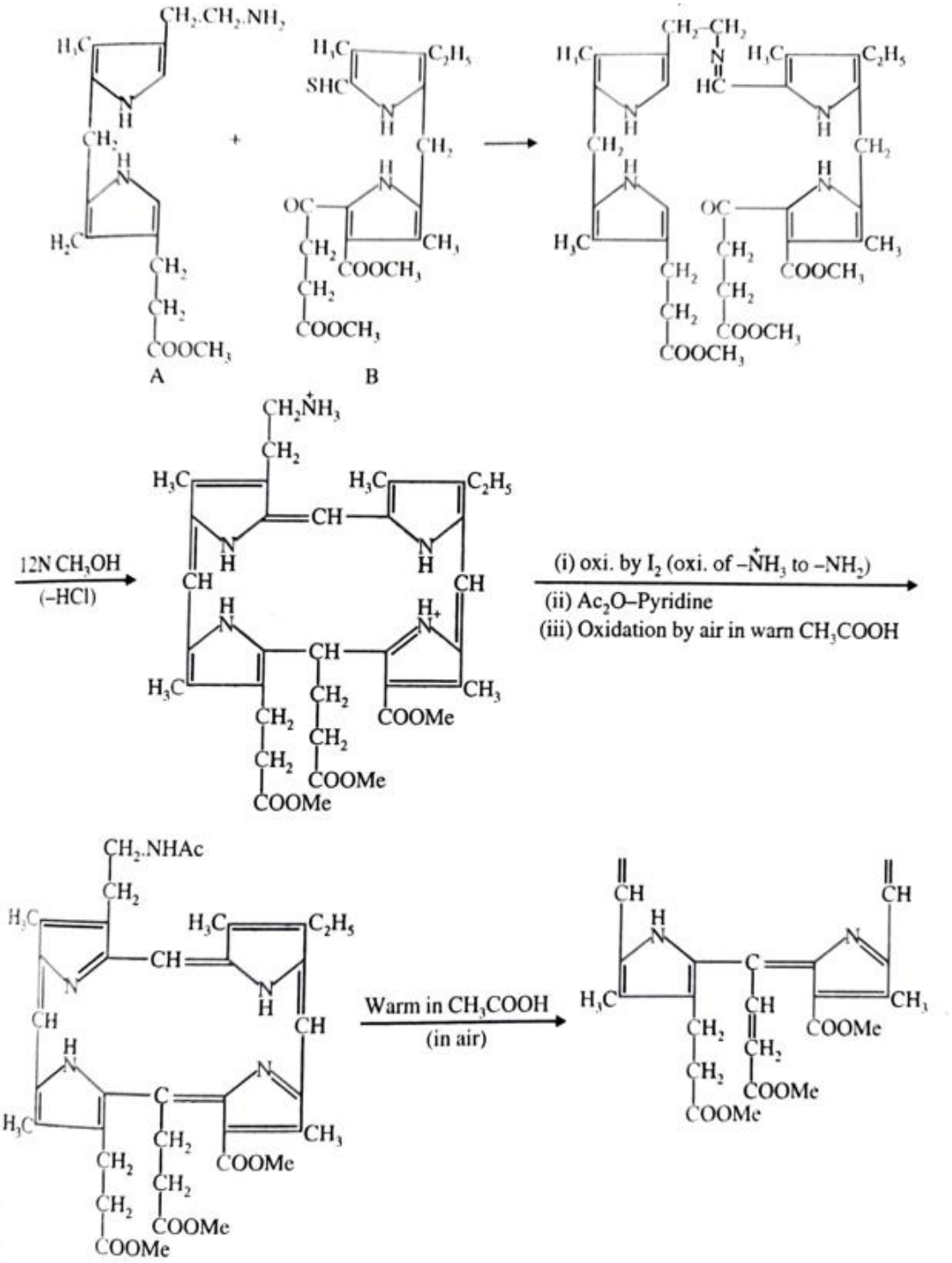
i) a)Synthesis of dipyrrylmethane A

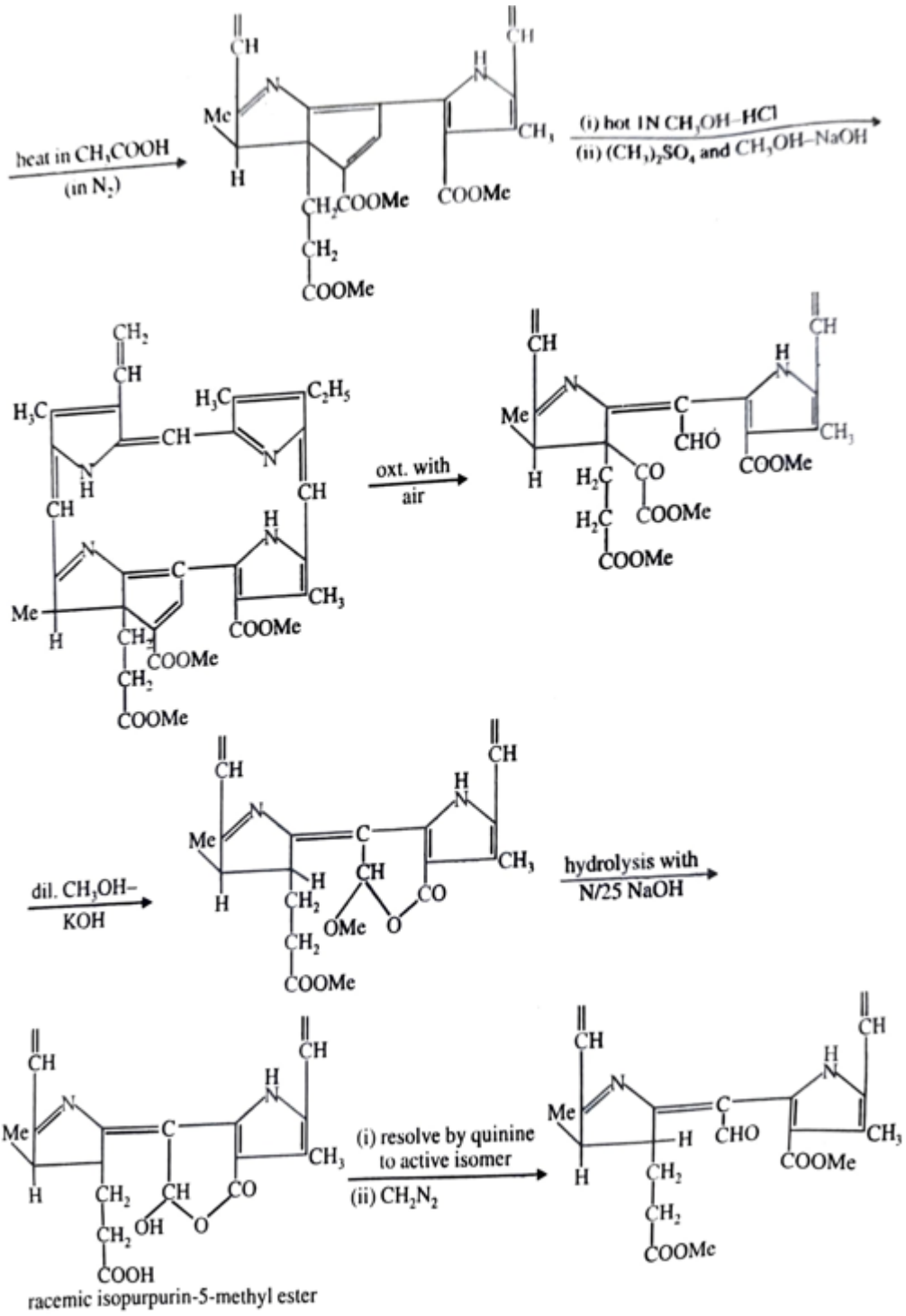


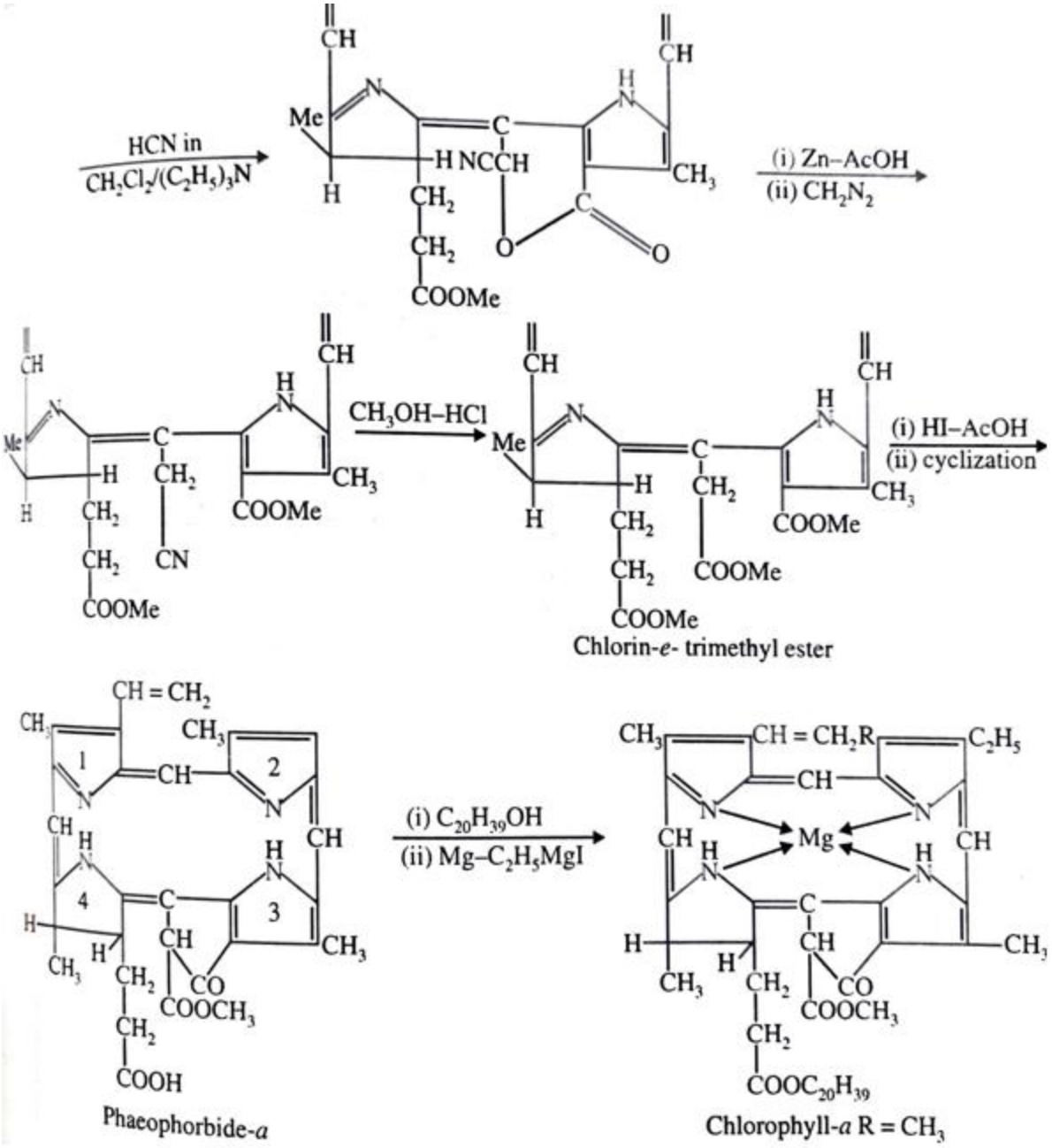
b)Synthesis of dipyrrylmethane B



ii)Condensation of A and B dipyrrylmethanes to yield chlorophyll.


A
B
12N CH3OH
(–HCl)
(i) oxi. by I2 (oxi. of –NH3+ to –NH2)
(ii) Ac2O–Pyridine
(iii) Oxidation by air in warn CH3COOH
Warm in CH3COOH
(in air)


heat in CH_3COOH
(in N_2)
(i) hot 1N CH_3OH–HCl
(ii) $(CH_3)_2SO_4$ and CH_3OH–NaOH
oxt. with air
dil. CH_3OH–KOH
hydrolysis with N/25 NaOH
(i) resolve by quinine to active isomer
(ii) CH_2N_2
racemic isopurpurin-5-methyl ester



4.10 Summary:

This chapter provides concise details about the occurrence and extraction, classification of plant pigments.Chemical characteristic ,structure and functions of some selective pigments.

Biosynthesis of flavonoids with Acetate and Shikimic acid pathway.In this unit we learned about the,structure and synthesis of porphyrin skeleton. We also learn the, preparation and structure determination of haemin and chlorophyll.

4.11 Terminal questions

4.11.1 Fill in the blanks:

1) Dyes are often **……** compounds whereas pigments are often **…….** compounds.
2) Xanthophylls have properties similar to lipids, being …… in water.
3) In porphyrins , pyrrole subunits interconnected at their α carbon atoms via **……..**
4) Haem is a **……**group that consists of iron ion contained in the center of a larg hetrocyclic ring.
5) Anthocyanins is **……** in nature.
6) In adult human two α- chains with …… amino acids

4.11.2 True and false questions:

1) The structure of phenoxazine consists of an oxazine fused to two benzene rings.
2) The molecular formula of flavonol is $C_{15}H_9O_3$.
3) Flavonoids are water insoluble and show a wide distribution in vascular plants.
4) Most of the natural pteridins have an amino group at C-2 and an hydroxyl group at C-4.
5) Most common quercetin glycosides have a sugar group at the 2-poistion.
6) Hemoglobin is made of two parts proteins called globin 96% and nonprotein part called haem 4%.

4.11.3Long answer type questions:

1) What are pigments? Give the various classification of pigments?
2) Define the acetate and shikimic acid pathway for biosynthesis of flavonoids?
3) What are chlorophyll-a and –b ? What is the structural difference betwwn chlorophyll-a and –b? Give the synthesis of chlorophyll-a?
4) Explain chemical characteristics and functions of anthocyanins and xanthophylls?
5) What products are obtained when given compounds are fused with KOH?
   i) Quercetin ii) Cyanidin iii) Flavonol

6) Explain the general methods for the Elucidation of Structure of Flavones?

7) Give synthesis of haemin.

8)Give one method of synthesis for each of the following:

i) Cyanidine chloride (I) ii) flavone

iii) Quercetin iv) flavonol

Answers: 4.11.1

1) organic ,Inorganic 2) Insoluble 3) methine bridges 4) prosthetic

5) amphoteric 6) 141

Answers: 4.11.2

1) True 2)False 3) False 4)True 5) False 6) False

4.12References and further studies:

1)Organic Chemistry , Vol. 2, Sterochemistry and the chemistry of natural products, by I.L.Finar.

Critical Reviews in Food Science and Nutrition, 40(3):173–289 (2000)

2)Natural Pigments: Carotenoids, Anthocyanins, and Betalains — Characteristics, Biosynthesis Processing, and Stability F. Delgado-Vargas,A. R. Jiménez, and O. Paredes-López

3)Natural Product, Chemistry,Jagdamba Singh, UGC Curriculum M.Sc.final: Elective paper VIII Page no : 276-336, 337-370

4)Organic Chemistry of natural products Vol-II ,Gurdeep R. Chatwal, page no:2.1-2.110, 13.1- 13.5

5)Isolation of chlorophyll a from spinach leaves, E.D. Dikio and D.A. Isabirye* Department of Chemistry, North-West University, South Africa , Bull. Chem. Soc. Ethiop. 2008, 22(2),Page no. 301- 304.

6)Isolation and structure identification of flavonoids, Weisheng Feng , Zhiyou Hao and Meng Li, DOI: 10.5772/67810

7) Chemical Society of Ethiopia communication isolation of chlorophyll a from spinach leaves E.D. Dikio and D.A. Isabirye* Department of Chemistry, North-West University, Private Bag X2046, Mmabatho 2735, South Africa ,Bull. Chem. Soc. Ethiop. 2008, 22(2), 301-304. ISSN 1011-3924 Printed in Ethiopia 2008.

UNIT 5 : PROSTAGLANDINS/ PYRETHROIDS AND ROTENONES:

CONTENTS:

5.1 Objectives`

5.2 Introduction

5.3 Occurrence of Prostaglandins

5.4 Nomenclature and Classification of Prostaglandins

5.5 Biogenesis and physiological effects

5.5.1. Meaning of Biogenesis

5.5.2. Metabolism

5.5.3 Physiological effects of Prostaglandins

5.6 Structure Elucidation of PGE_1

5.7 Synthesis of PGE_2 and $PGE_{2\alpha}$.

5.8 Synthesis and reactions of Pyrethroids and Rotenones

5.8.1. Introduction of pyrethroids

5.8.2. Classification of Pyrethroids

5.8.3. Physical properties of Pyrethrins I and Pyrethrins II

5.8.4. Synthesis of pyrethrin I

5.8.5. Synthesis of some pyrethroids

5.8.6. Introduction of Rotenone

5.8.7. Synthesis of Rotenone

5.8.8. Reaction of Rotenone

5.9 Summary

5.10 Terminal questions

5.10.1 Fill in the blanks

5.10.2 True and false type questions

5.10.3 Long answer type questions

5.11 References and further studies

Note: In structure elucidation, emphasis is to be laid on the use of spectral parameters, wherever possible**.**

5.1 OBJECTIVES :

Prostaglandins are hormone-like substances that affect several bodily functions, including inflammation, pain and uterine contractions. In this unit you will learn about :

- Occurrence ,Nomenclature and Classification of Prostaglandins
- Biogenesis and physiological effects of Prostaglandins
- Synthesis of PGE_2 and $PGE_{2\alpha}$.
- Some selective methods of Synthesis and reactions of Pyrethroids and Rotenones and its uses.

5.2 INTRODUCTION:

Prostaglandins were discovered in human semen in 1935 by the Swedish physiologist Ulf von Euler, who named them, thinking that they were secreted by the prostate gland, later realized that Prostaglandins, are synthesized in almost all the tissues (exception erythrocytes).

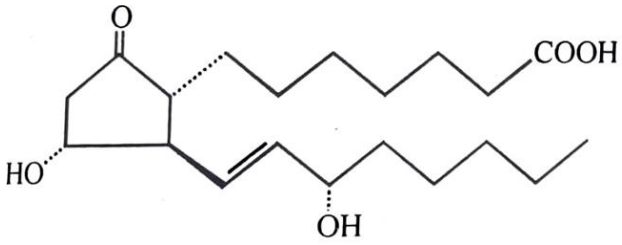
The first total syntheses of prostaglandin $F_{2\alpha}$ and prostaglandin E_2 were reported by E. J. Corey in 1969, an achievement for which he was awarded the Japan Prize in 1989.

In 1971, it was determined that aspirin-like drugs could inhibit the synthesis of prostaglandins. The biochemists Sune K. Bergström, Bengt I. Samuelsson and John R. Vane jointly received the 1982 Nobel Prize in Physiology or Medicine for their research on prostaglandins.

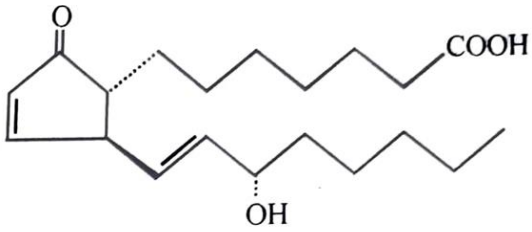
Prostaglandins are produced on demand in numerous parts of the body as mediators of inflammation, immune response, and muscle constriction and relaxation, as well as metabolic activities.

Every prostaglandin contains 20 carbon atoms, including a 5-carbon ring.In 5- carbon ring with two side chains is having generally a β- ketone /an enone / two hydroxyfunctionalities.In side

chains having one, two or three double bonds. An α- hydroxyl group at C-15 is present in all bioactive prostaglandins.The structures of prostaglandin E_1 and prostaglandin A_2 are as follows:



Prostaglandin E_1



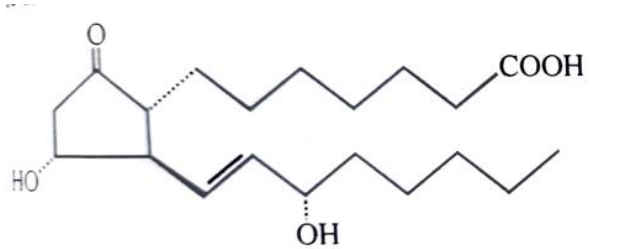
Prostaglandin A_2

5.3 OCCURRENCE OF PROSTAGLANDINS:

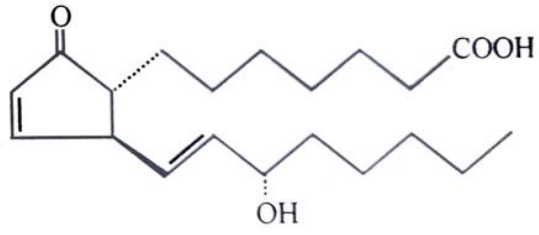
Prostaglandins have been found in almost every tissue in humans and other animals. On the basis of recent study, in sheep vesicular gland was having large amounts of Prostaglandins and were found to exist in various tissues like : lungs, brain, thymus, kidney, pancreas etc.In recent study the richest source of Prostaglandins is the human seminal plasma which is having upto 50- 60 mg /ml and other derivatives have been isolated from soft coral , *Plexaura homomalla.*

5.4 NOMENCLATURE AND CLASSIFICATION OF PROSTAGLANDINS :

In defining the various structures, prostanoids are best considered as derivatives of a C_{20} saturated fatty acid, prostanoic acid, which does not itself occur in nature. A key feature of prostaglandins is a five-membered ring encompassing carbons 8 to 12 , as illustrated below:

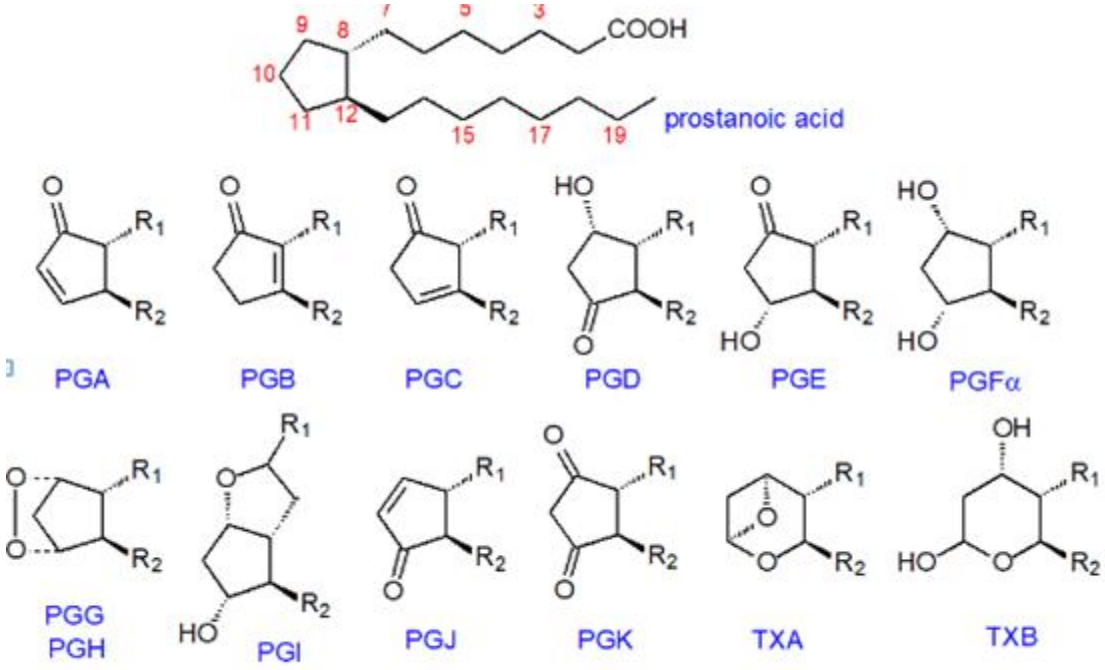


Prostaglandin E_1



Prostaglandin A_2

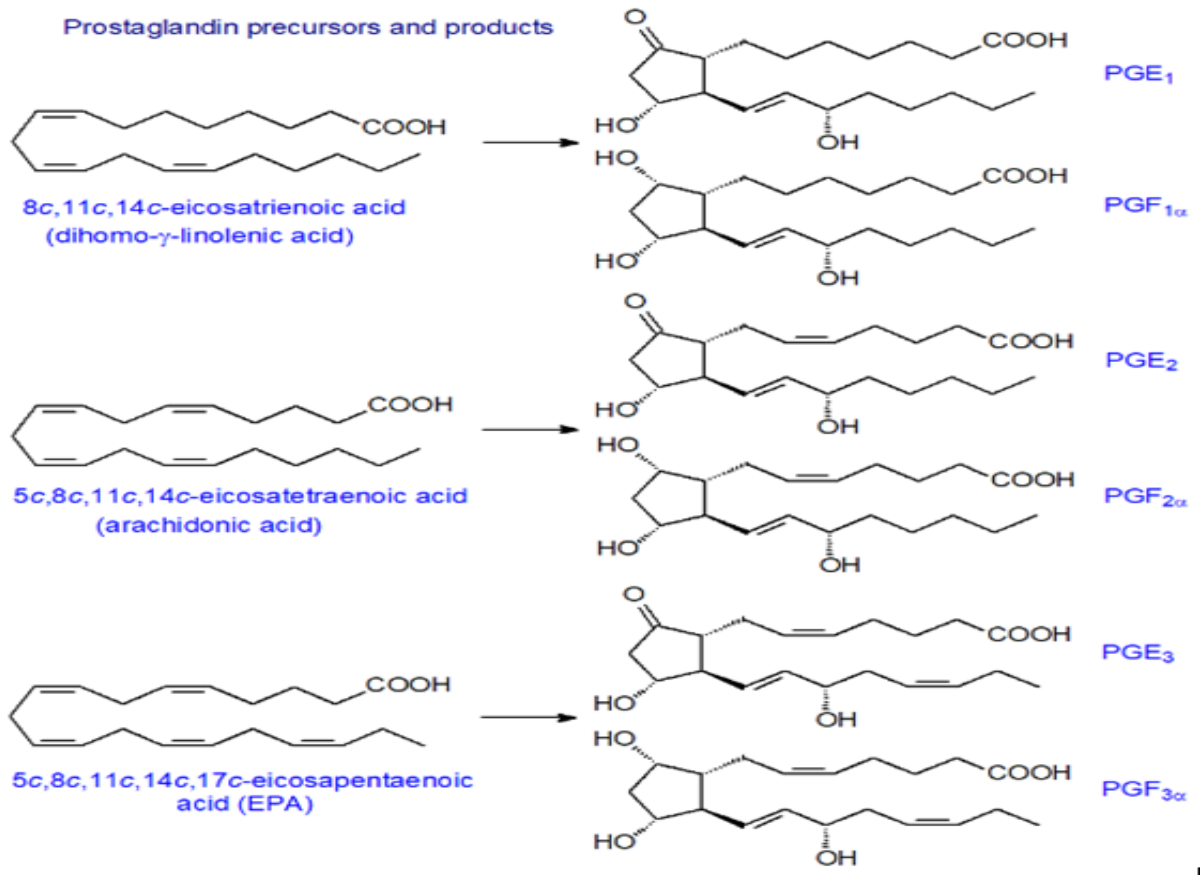
In the approved nomenclature, each prostaglandin is named using the prefix 'PG' followed by a letter A to K depending on the nature and position of the substituent's on the ring.On the basis of this, prostaglandins are classified into several families PGA, PGB, PGC, PGD, PGE, PGF,and PGH.



Prostanoids: prostaglandins (PG), prostacyclins (PGI) and thromboxanes (TX)

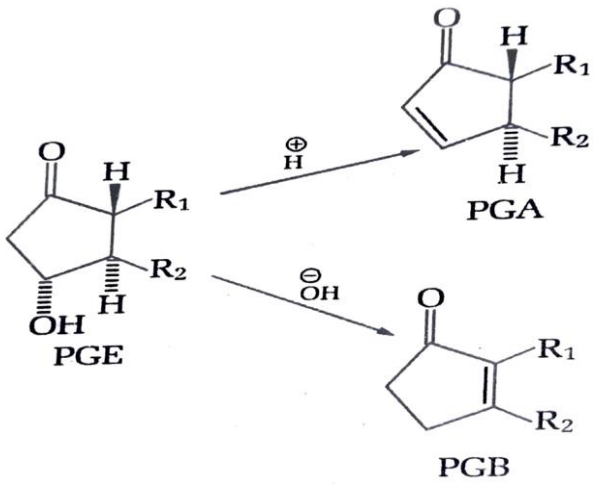
The five membered rings of PGA's , PGB's and PGC's contain a carbonyl group and double bond the position of double bond determines whether a prostaglandin is a PGA's , PGB's and PGC's. Constant features of all prostaglandins are a hydroxyl group of the *S*-configuration on carbon 15 and a *trans*-double bond at carbon 13 of the alkyl substituent (R_2). PGA to PGE and PGJ are distinguished by a keto group in various positions on the ring, together with the presence or absence of double bonds or hydroxyl groups in various positions in the ring. PGF has two hydroxyl groups, while PGK has two keto substituents on the ring. PGG and PGH are bicyclic endoperoxides, while an oxygen bridge between carbons 6 and 9 distinguishes prostacyclin (PGI).

To define prostaglandins further, a numerical subscript (1 to 3) is used to denote the total number of double bonds in the alkyl substituents, and a Greek subscript (α or β) is used with prostaglandins of the PGF series to describe the stereochemistry of the hydroxyl group on carbon 9. The number of double bonds depends on the nature of the fatty acid precursor. This is illustrated for prostaglandins PGE and PGF_α of the 1, 2 and 3 series below :



The compounds with greater solubility in ether are known as PGE while the compound with greater solubility in phosphate (fosfate in Swedish) buffers is PGFs.

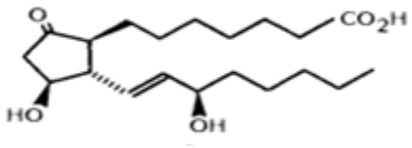
The Latters A and B in PGA and PGB refer to prostaglandins resulting from the treatment of PGE with acid and base respectively.



Six prostaglandins of E series and the F series (E_1 , E_2, E_3, $F_{1\alpha}$, $F_{2\alpha}$, and $F_{3\alpha}$) are known as primary prostaglandins.

Format for structural Presentation of prostaglandins : Prostaglandin structures , as written correspond to the absolute configuration of prostaglandin from mammalian sources. Therefore, the structures are presented in a consistent format with the carboxy side chain extending to the upper right hand side(R.H.S) with the omega-alkyl side chain extending to the lower right hand side of the cyclopentane nucleus. Solid / Wedge – shaped line indicate substituent's with a β-configuration(extending above the plane of the paper), dotted or broken lines indicate substituent's with an α- configuration (extending below the plane of the paper), and a wavy or straight line indicates either unknown , unspecified or mixture of two configuration.

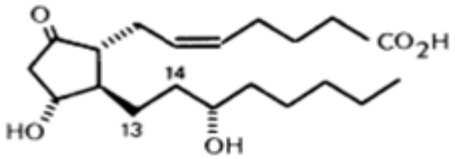
In all the chiral centers of a natural prostaglandin are reversed, the molecules is an enantiomer and is designated with the prfix *ent*.The structure is written in the usual format with the two side chains extending to the right. For example:



***ent*-pprostaglandin E_1**

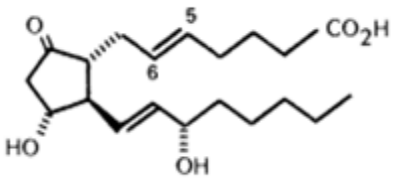
Selected Examples of Prostaglandin Nomenclature: The following examples of prostaglandin nomenclature have been given below:

- Saturation of Carbon-Carbon Double Bonds. — A numbered prefix [e.g., 13,14-dihydro, is used to denote reduced carbon-carbon double bonds. Products arising from reduction of the 10,11-double bond of A prostaglandins are normally referred to as 11-deoxy E prostaglandins.



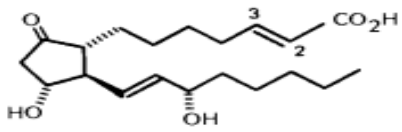
13,14- dihydroprostaglandin E_2

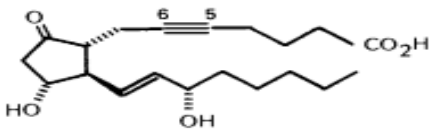
- Existing Unsaturation. — Changes in cis-trans isomerization in a parent molecule are denoted by a prefix followed by its locant (e.g., trans-5 or cis-13); see below. The letters Z (for cis) and E (for trans) may also be used .



***trans*-5- prostaglandin E_2**

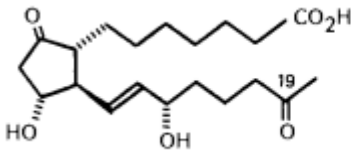
- New Unsaturation. — For new unsaturation a numbered prefix giving its location and configuration is used (e.g., 2,3-trans-didehydro, 5,6-didehydro); see below:

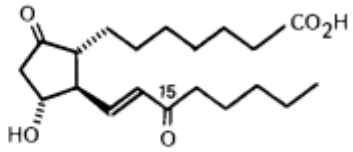




2,3-trans-didehydroprostaglandin E_1 **5,6-didehydroprostaglandin E2**

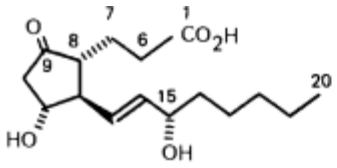
- Introduction of Carbonyl Groups. — A numbered-oxo prefix (e.g., 19-oxo) is used to denote replacement of a méthylène group with a carbonyl; see below example . A carbonyl group derived from oxidation of an alcohol group is denoted by a numbered-dehydro prefix.



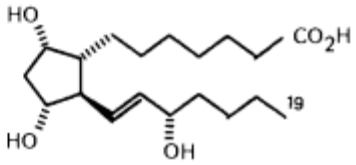


19-oxoprostaglandin E-1 **15-dehydroprostaglandin E_1**

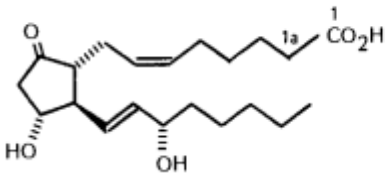
- Changing the Length of Side Chains. — Structural variants of prostaglandins which are homologs or analogs of prostanoic acid are designated as nor- or homo-prostanoic acid derivatives. The letters a and ω may be added to signify whether the C-1 or C-20 end of the molecule is involved, or the méthylène group or groups involved may be identified by a locant or locants, with the appropriate nor or homo prefix. Nelson has suggested that new méthylène groups be listed as la-homo, la,1b-dihomo, etc., so as to avoid altering the parent prostaglandin numbering system. Lengthening of the omega chain is handled by indicating the group added to C-20; see examples:



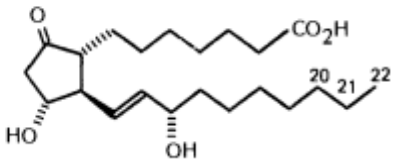
2,3,4,5-tetranorprostaglandin E_1



20-norprostaglandin $F_{1\alpha}$

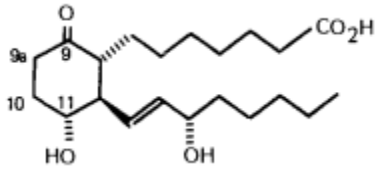


1a-homoprostaglandin E_2

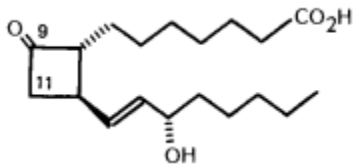


20-ethylprostaglandin E_1

- Change in Ring Size. — A decrease in size of the five-membered ring is indicated by a numbered-nor prefix, while an increase is indicated with a numbered-homo prefix; see examples:



9a-homoprostaglandin E_1



10-nor-11-deoxyprostaglandin E_1

5.5 BIOGENESIS AND PHYSIOLOGICAL EFFECTS OF PROSTAGLANDINS :

5.5.1. Meaning of Biogenesis :

Meaning of Biogenesis Biogenesis, is the production of new living organisms.Conceptually biogenesis sometimes attributed to Louis Pasteur and encompasses the belief that complex living things come only from other living things, by means of reproduction. For Example:Biogenesis is any process by which life forms produce other life forms.

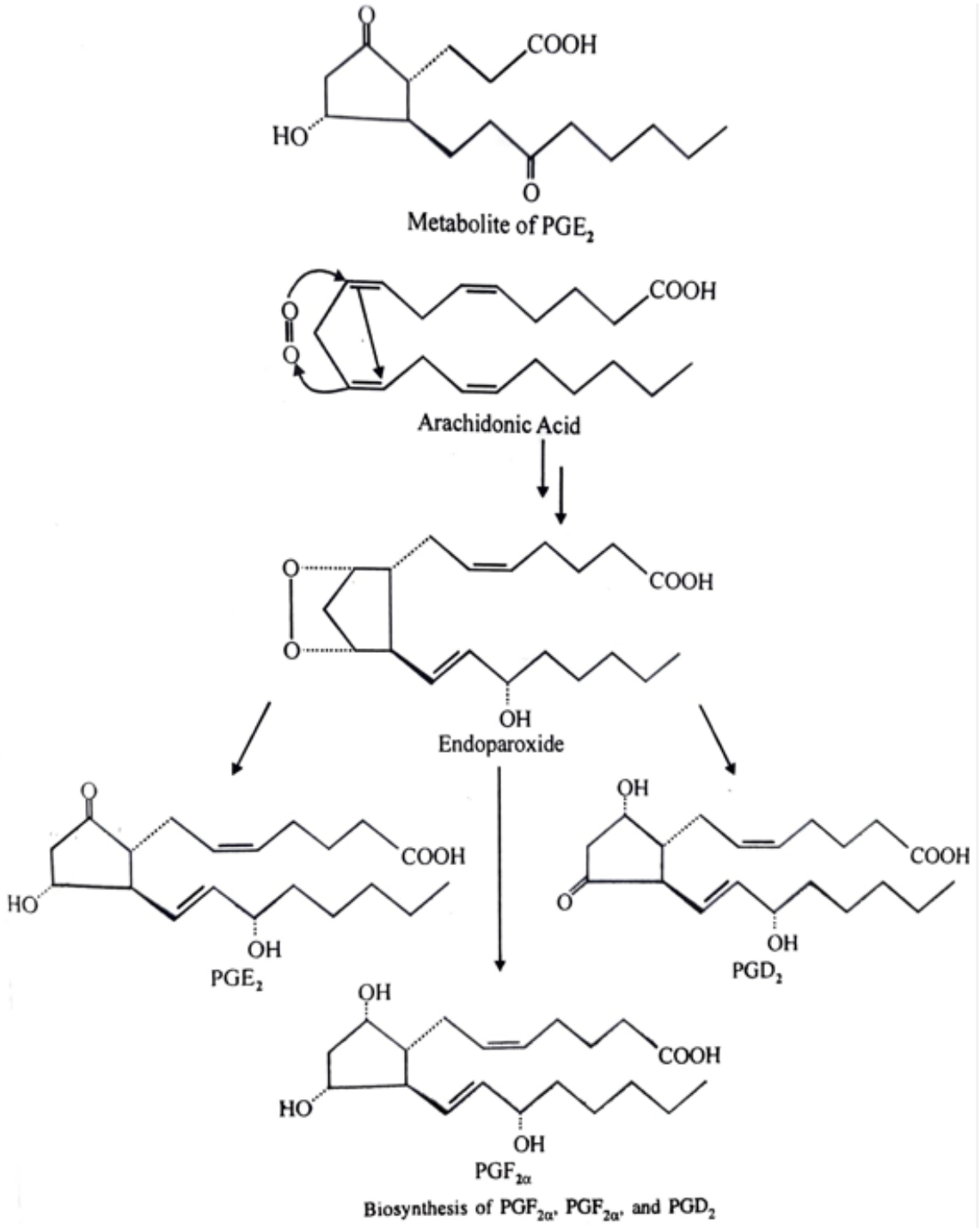
A microsomal enzyme system called *Prostaglandin synthetase* is widely distributed in mammalian tissues. This enzyme brings about the biosynthesis of prostaglandins from essential fatty acids such as arachidonic acid cascade.The prostaglandins are not stored in tissues but are biosynthesized and released on demand by physiological stimuli.

Arachidonic acid is the precursor of PGE_2 and $PGF_{2\alpha}$ .This acid stored as a phospholipid in tissues. On demand by physiological stimuli, phospholipase A activated which

liberates the free arachidonic acid. The acid is acted upon by prostaglandin synthetase. The key intermediate is cyclic endoperoxide which gets converted to prostaglandins such as PGE_2,$PGF_{2\alpha}$ and PGD_2 .

5.5.2. Metabolism:

The prostaglandins get rapidly inactivated by enzymatic reactions, thereby limiting their activity. The two major enzymatic reactions involve oxidation of the C-15 allylic hydroxyl group by 15-hydroxygenase,followed by reduction of the 13,14 –double bond by Δ^{13} reductase. Subsequently β and ω oxidations may also take place. One of the human urinary metabolites has been shown below:



5.5.3Physiological effects of Prostaglandins:

Prostaglandins are not stored in cells. Their release is immediately preceded by synthesis and its some physiological role are:

i)Prostaglandins can Activate or inhibit (prevent) platelet buildup for blood clot formation.

ii)They control lipid and carbohydrate metabolism.

iii)Prostaglandins serve as a treatment of hypertension.

iv)Prostaglandins are natural mediators of inflammation reactions, since they inhabit Prostaglandins synthesis.

v)Prostaglandins (E_1,E_2 and A) inhibits acid secretion, and it is used for the treatment of gastric and peptic ulcers.

vi) Prostaglandin E_2 , used for treatment of impaired renal blood flow.

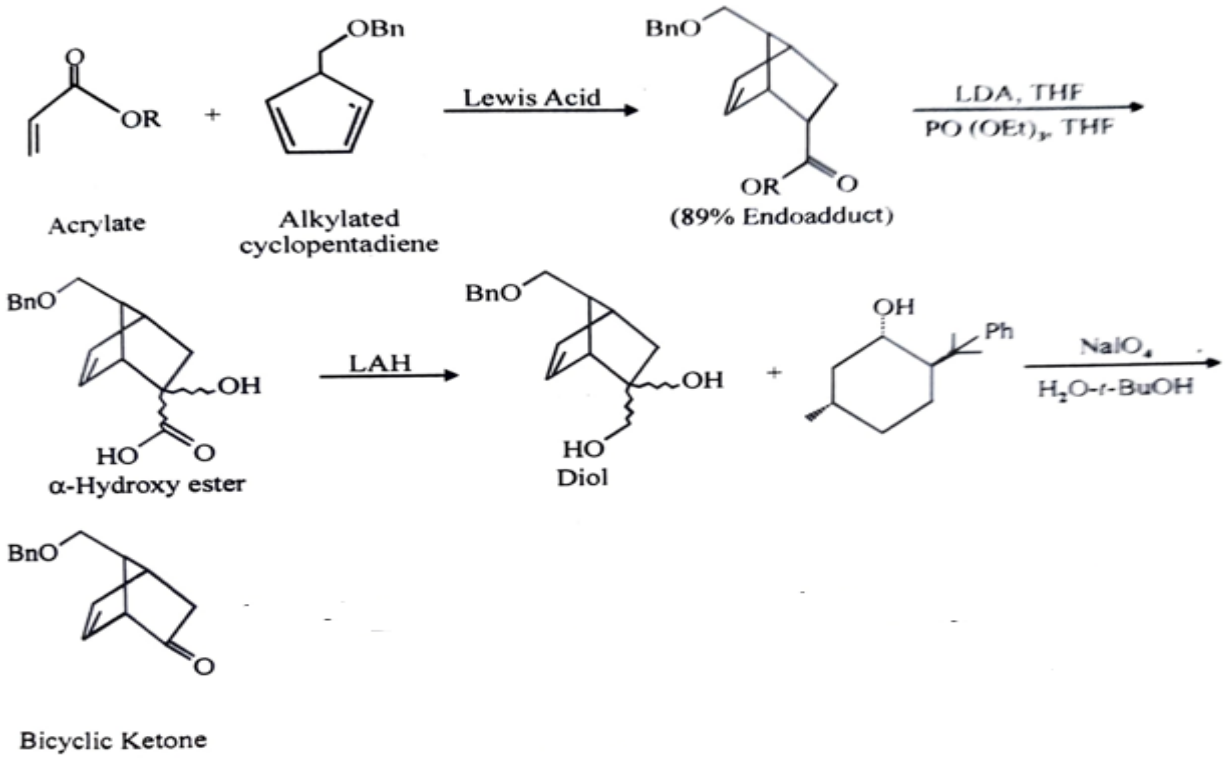
vii) Prostaglandin F2α stimulates uterine.It is used for induction of labor and medical termination of pregnancy.

viii)The therapentic effect of anti-inflammatory , analgestic, and antipyretic drug is ascribed to the inhibition of prostaglandin biosynthesis by these drug. For example: Aspirin prevents the functioning of arachidonic acid cascade.

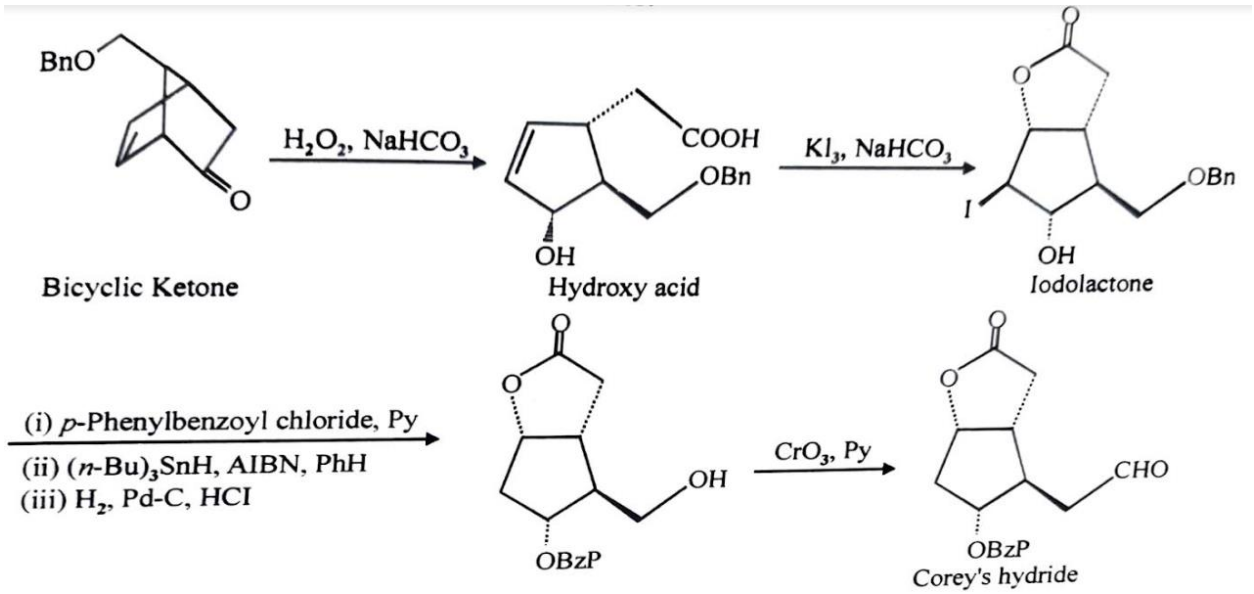
5.6 SYNTHESIS OF PGE_2 AND $PGE_{2\alpha}$:

These synthesis worked out by corey and his co workers in 1969 by involving bicycle(2,2,1) heptanes' intermediate. These syntheses are stereo specific.

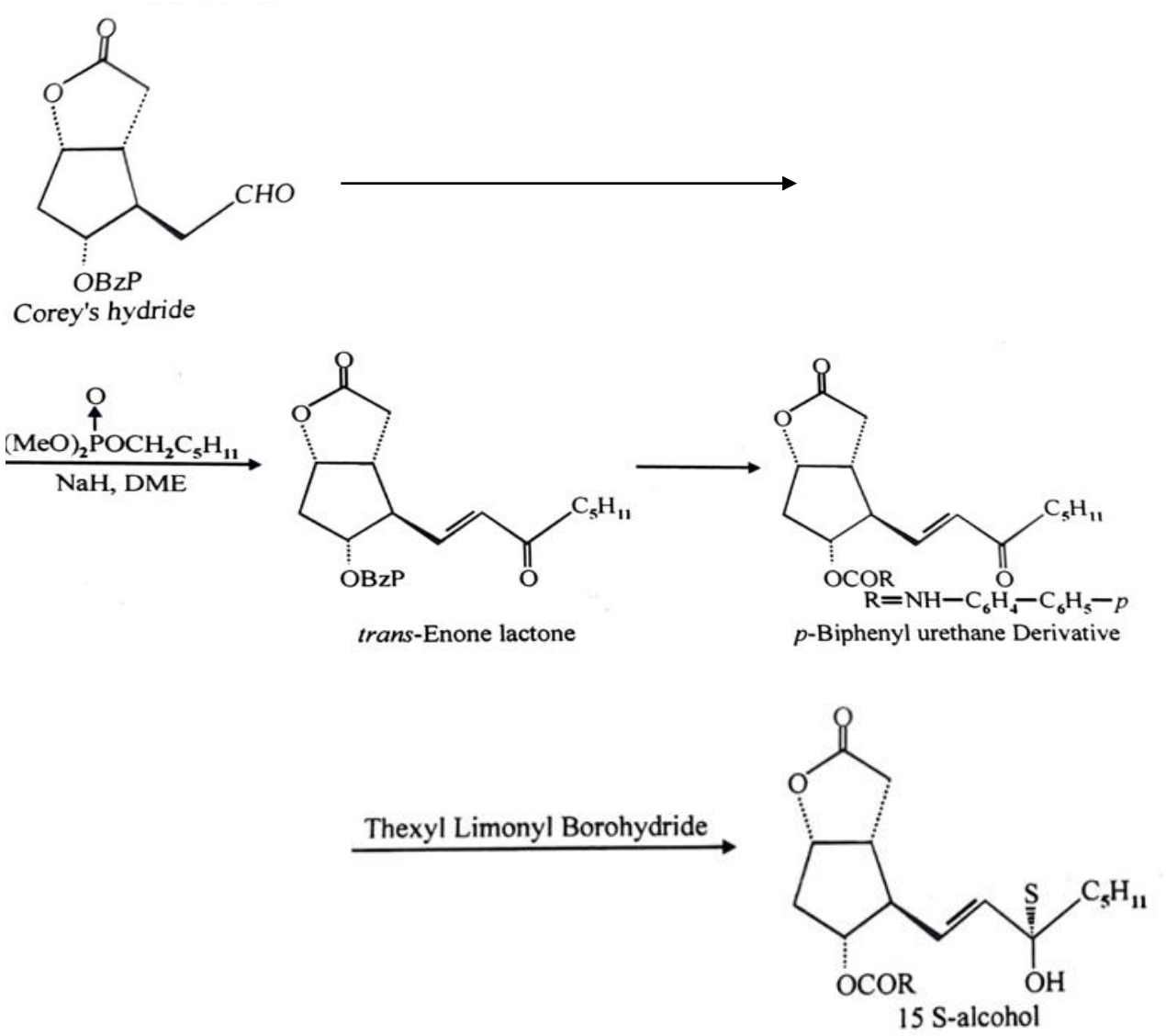
In first step lewis acid catalysed asymmetric Diels-Alder reaction of optically acrylate and cyclopentadiene to yield the endo adduct.This enolate of endo adduct is added to an oxygenated solution of tetrahydrofuran having triethyl phosphate to yield α- hydroxyl ester which on reduction with lithium aluminium hydride (LAH) yields diol along with the regeneration of the chiral catalyst.The reaction of diol with sodium periodate yield the optically active bicyclic ketone .



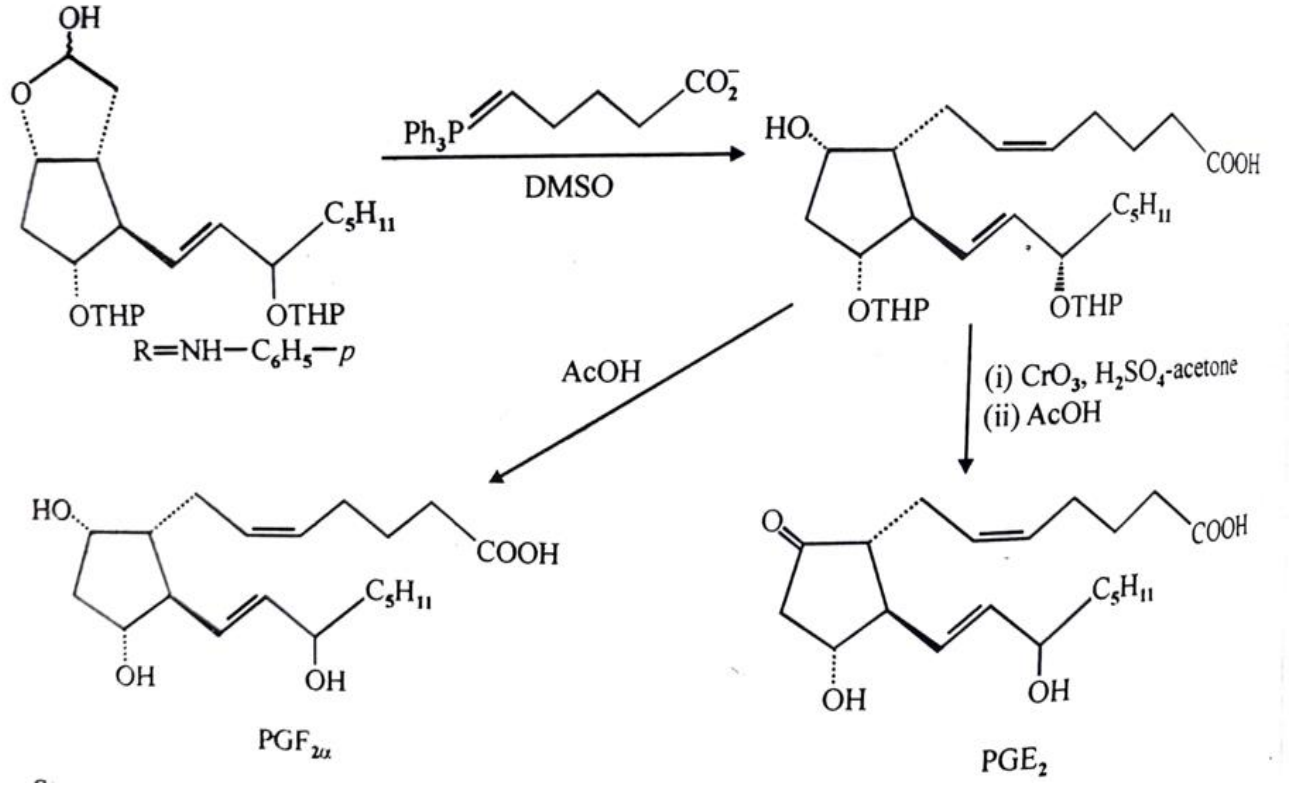
Bicyclic ketone an oxidation followed by saponification yields the hydroxyl acid. This acid on treatment with aqueous potassium tri-iodiate yield optically active isolactone which is having the same optical rotation as the materials by resolution of recemic hydroxyl acid with amphetamine.The optically active iodolactone is esterified with p-benzoyl chloride followed by deiodination with tri-n-butyltin hydride and cleavage of the benzyl ether with H_2 / Pd yield the alcohol which is oxidized with Collin's reagent to give the optically active Corey's aldehyde.



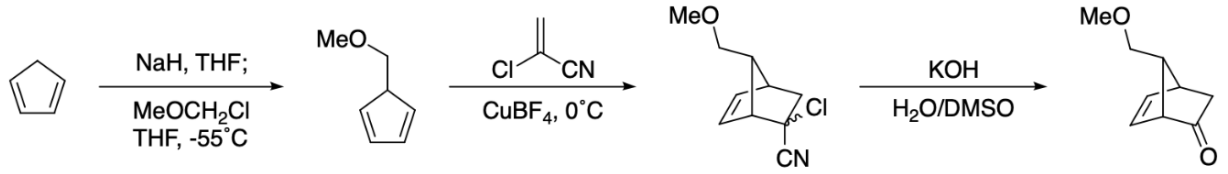
The reaction of Corey's aldehyde with dimethyl-2-oxoheptyl-phosphonate in the presence of sodium hydride and dimethoxy ethane yield the trans- enone lactone which on conversion to p-biphenyl urethane derivative followed by asymmetric reduction with thexyl limonyl borohydride yield the 15-S-alcohol as the major product.

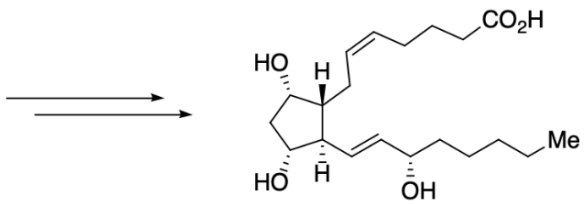


Removal of the p-biphenylurethane from 15S-alcohol by hydrolysis with aqueous lithium hydroxide yield the diol which is protected as the tetrahydroperanyl ether. The lactone is reduced to lactol by reaction with DIBAL. Witting condensation of lactol with 5- triphenylphosphonium pentanoic acid and sodium methylsulfiny methide yield the hydroxyl acid.Deprotection of the hydroxyl acid with acetic acid yield $PGF_{2\alpha}$ .On the other hand the oxidation followed by hydrolysis yield PGE_2.



- The original synthesis of prostaglandins F2α and E2 is shown below. It involves a Diels–Alder reaction which establishes the relative stereochemistry of three contiguous stereocenters on the prostaglandin cyclopentane core.



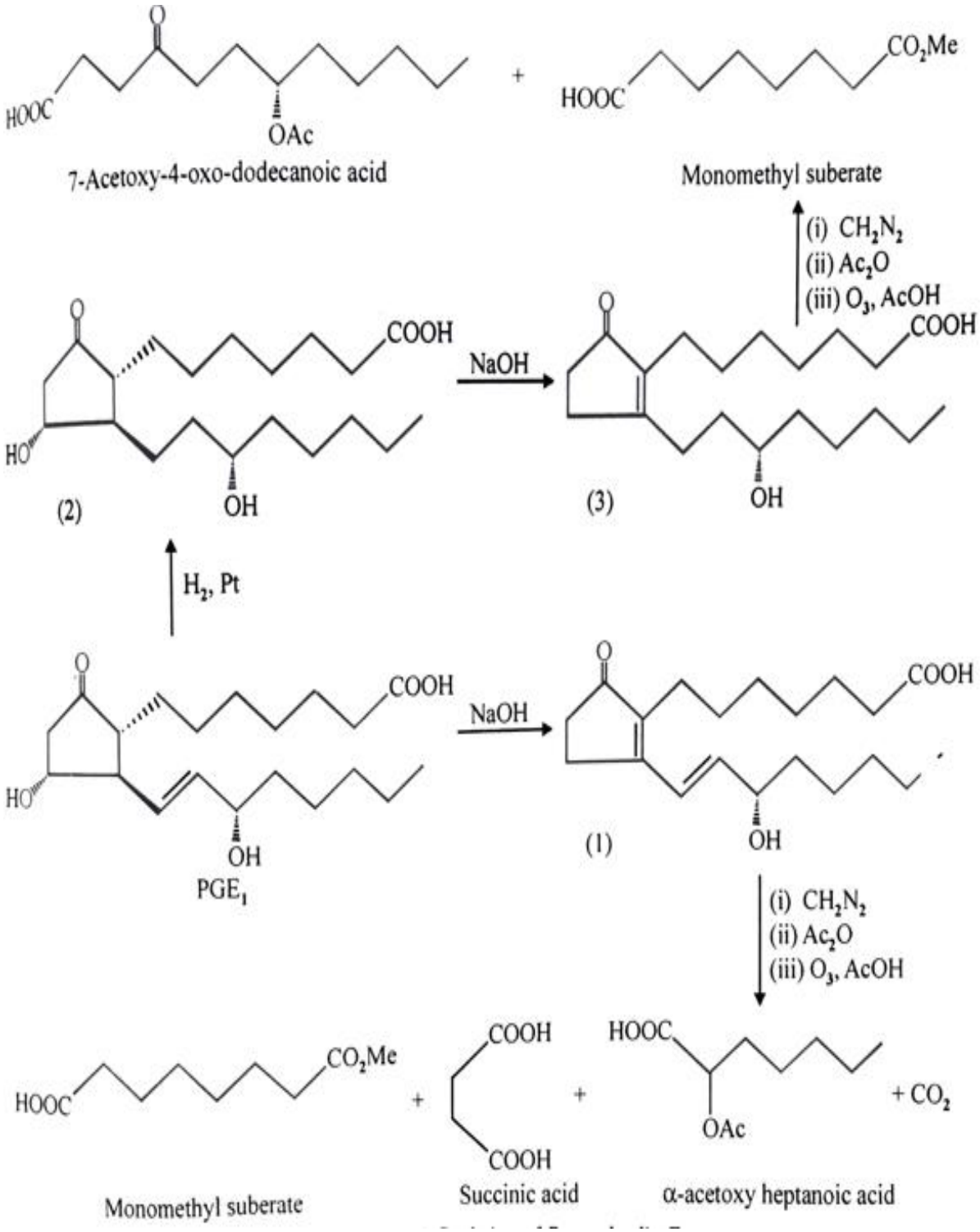


Prostaglandin $F_{2\alpha}$

5.7 STRUCTURE ELUCIDATION OF PROSTAGLANDINS:

The understanding of prostaglandins grew in the 1960s and '70s with the pioneering research of Swedish biochemists Sune K. Bergström and Bengt Ingemar Samuelsson and British biochemist Sir John Robert Vane. The threesome shared the Nobel Prize for Physiology or Medicine in 1982 for their isolation, identification, and analysis of numerous prostaglandins.The structure was finally confirmed by X- rays diffraction techniques . Following is brief account of the structure elucidation of PGE_1:

- The prostaglandins are made up of unsaturated fatty acids , straight-chain,polyunsaturated fatty acid precursor arachidonic acid.
- On the basis of I R spectra(1740 cm^{-1}) ,that contain a cyclopentane (5-carbon) ring and are derived from the 20-carbon.
- The PGE_1 did not show any UV absorption in the 210-225 mμ region , it shown that double bond was non-conjugated.
- On reduction in neutral medium the trans configuration of the double bond was found by disappearance of the IR band at 970 cm^{-1}.
- On hydrogenation , PGE_1 gave the dihydro derivative (2) , which on treatment with NaOH gave compound (3). Ozonolysis of compound (3) produce monomethyl suberate and 7-acetoxy-4-oxo-dodecanoic acid. This shown that 20 carbon atom in PGE_1.
- Ozonolysis of product (1), product monomethyl suberate, succinic acid and α-acetoxyheptanoic acid. It accounted for nineteen carbon atoms of , PGE_1.
- The ozonolysis product α-acetoxyheptanoic acid revealed that -OH group is secondary, and it is present in the side chain.
- Ozonolysis of product (1) isolated monomethyl suberate revealed that ,carboxyl side chain is attached to the carbonyl group.
- Ozonolysis of product (1), product succinic acid revealed that , in cyclopentane ring two vicinal methyl group were present.This also suggested that 3, carbon atom bearing the two side chains and the keto group must be adjacent.
- Final confirmation of all products and structure of PGE_1 was done on the basis of mass spectrometry , gass chromatography and X- rays diffraction studies.


HOOC
OAc
7-Acetoxy-4-oxo-dodecanoic acid
+
HOOC
CO2Me
Monomethyl suberate
(i) CH2N2
(ii) Ac2O
(iii) O3, AcOH
COOH
NaOH
HO
OH
(2)
(3)
H2, Pt
PGE1
(1)
HOOC
CO2Me
Monomethyl suberate
Succinic acid
α-acetoxy heptanoic acid
+ CO2

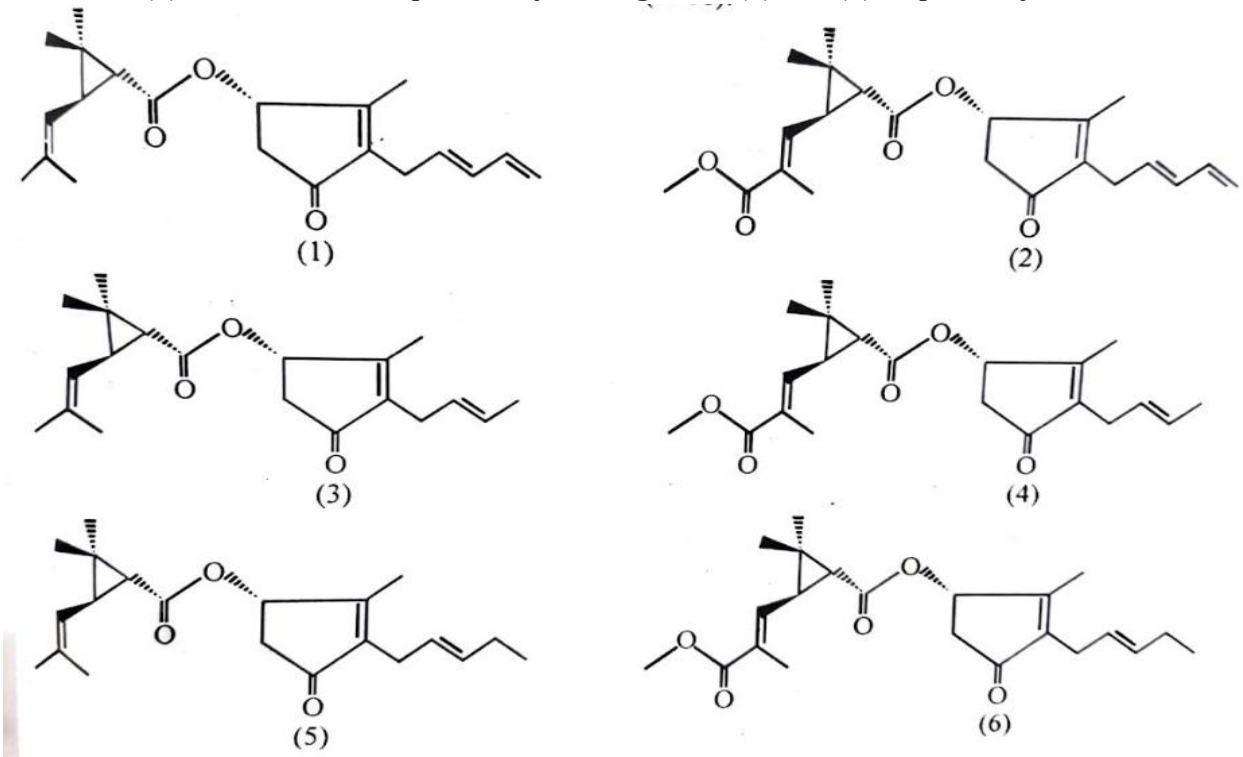
5.8 SYNTHESIS AND REACTIONS OF PYRETHROIDS AND ROTENONES :

5.8.1.Introduction of pyrethroids :

A pyrethroid is an organic compound similar to the natural pyrethrum, these are also called natural pyrethroid or pyrethrins.Which are produced by the flowers of pyrethrums (*Chrysanthemum cinerariaefolium* and *C. coccineum*). Pyrethroids are used as commercial and household insecticides. In household concentrations pyrethroids are generally harmless to humans and are toxic to aquatic organisms, especially fish.Pyrethroids are synthetic ester derived from pyrethrins, engineered for insect death, knockdown effect, and synthetic modification make these compounds more toxic to organisms , less degradable in environment.

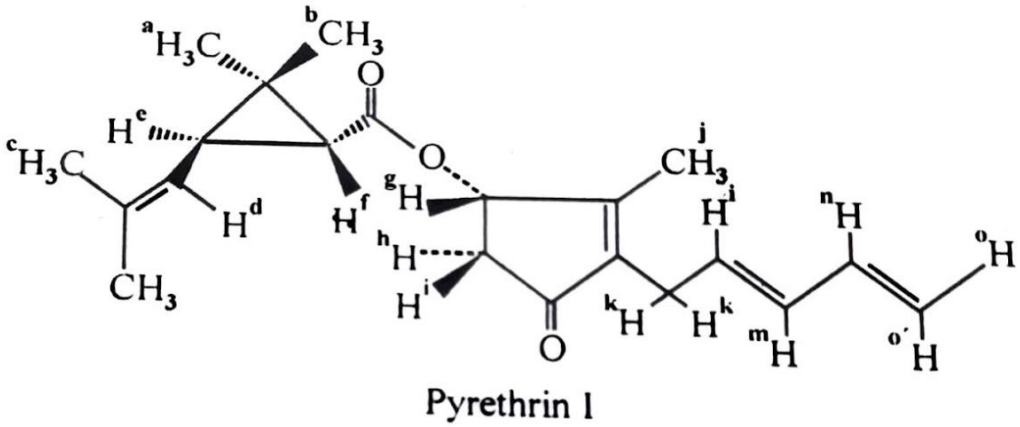
5.8.2.Classification of Pyrethroids:

Pyrethroids, which comprise a diverse range of structures, have historically been classified into two broad groups (Pyrethrin I and Pyrethrin II) on the basis of structure and ,their biological responses. The active constituents of pyrethrum are pyrethrin I (1) ,which is the (+)-3- penta-1, 3-dienyl-2-methyl-4-oxo-cyclopent-2-en-1-yl ester of (+)-(1R,3R) (E)-chrysanthemic acid, pyerthrin II (2), which is the(+)-3-Penta-1,3-dienyl-2-methyl-4-oxo-cyclopent-2-en-1-ylester of (+)-(1R,3R)-(E)-pyrethric acid, cinerin I(3) and cinerin II (4) , the 3-but-enyl analogues and Jasmolin I (5) and Jasmilin II (6) , which are the 3-pent-2-enyl analogues of (1) and (2) respectively.



The pyrethroids (1-6) are optically active, their absolute configuration are 1R,3R,4′ R. The double bond in the alcoholic part has Z, while that in the carbonic acid part has E-configuration.

The structure of Pyrethrin I and Pyrethrin II was ascertained on the basis of spectral data is given below:



Pyrethrin I

The toxicity of pyrethroid is low in memmals, this is because carboxylesterases occur in abundance in mammalian tissues.

5.8.3.Physical properties of Pyrethrins I and Pyrethrins II :

Pyrethrins I :

i)The molecular formula of Pyrethrin I is $C_{21}H_{28}O_3$ with molecular mass 328.4.

ii) The boiling point of Pyrethrin I, 170°C at 0.1 mmHg with decomposition.

iii)It λ^{EtOH}_{max} in its UV spectrum is 225mμ.

Pyrethrins II :

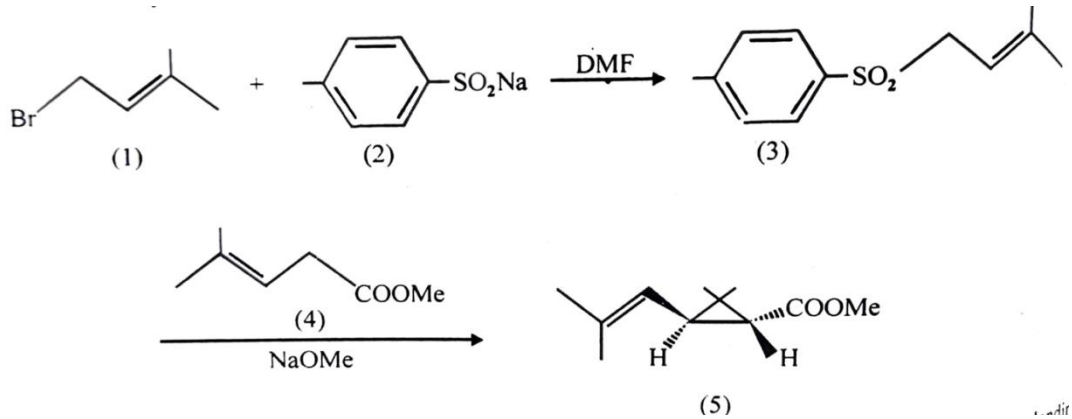
i)The molecular formula of Pyrethrin II is $C_{22}H_{28}O_3$ with molecular mass373.4.

ii) The boiling point of Pyrethrin II is 200°C at 0.1 mmHg with decomposition.

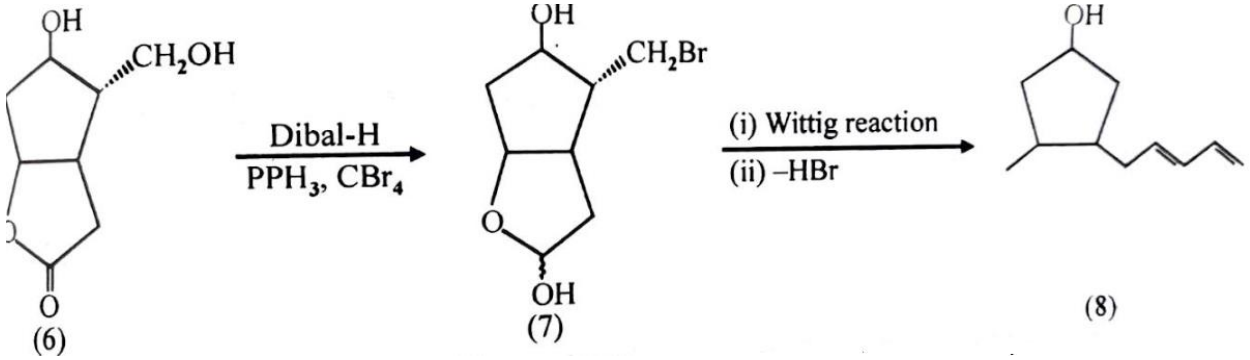
iii) It λ^{EtOH}_{max} in its UV spectrum is 229 mμ.

5.8.4.Synthesis of pyrethrin I: Synthesis of pyrethrin I involves in three steps:

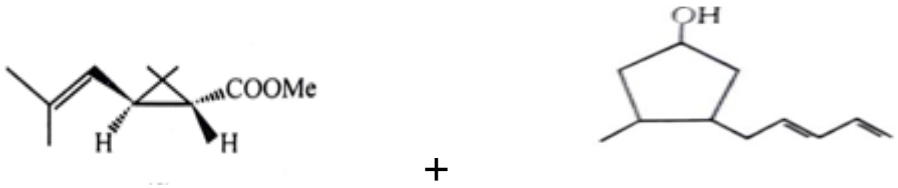
i) In first step condensation of 1-bromo-3-methyl -2-butene(1) with sodium p-toluenesulfinate(2) yield the allylsulfone (3). Then allylsulfone (3) is base catalyse addition with 3-methyl-2-butenoic acid methyl ester by 1,3-elimination produce trans-chrysanthemic acid methyl ester.

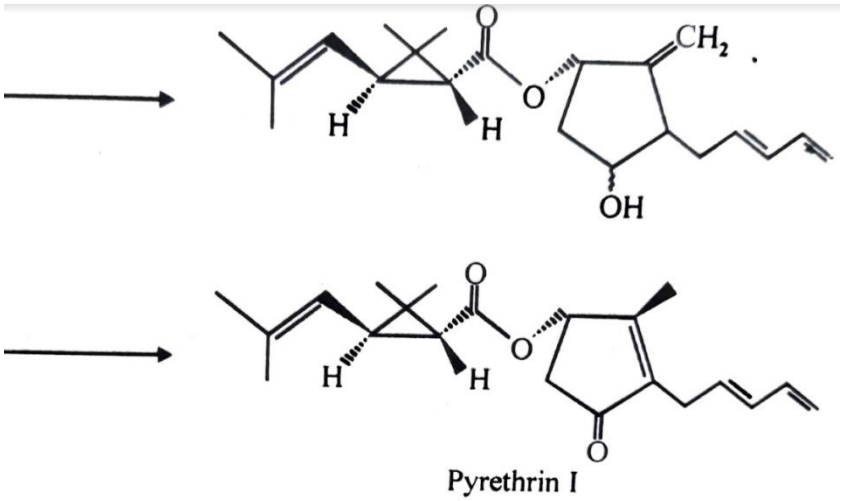


ii) In second step lactol is reduce with DIBALH yield bromo compound (7). These bromo compound by witting reaction followed by dehydrobromination yield the required alcohol(8).



iii) In this step condensation of trans-chrysanthemic acid methyl ester with alcohol followed by oxidation of the hydroxyl group and isomerisation of the exo-methylene group to enone yield pyrethrin I.

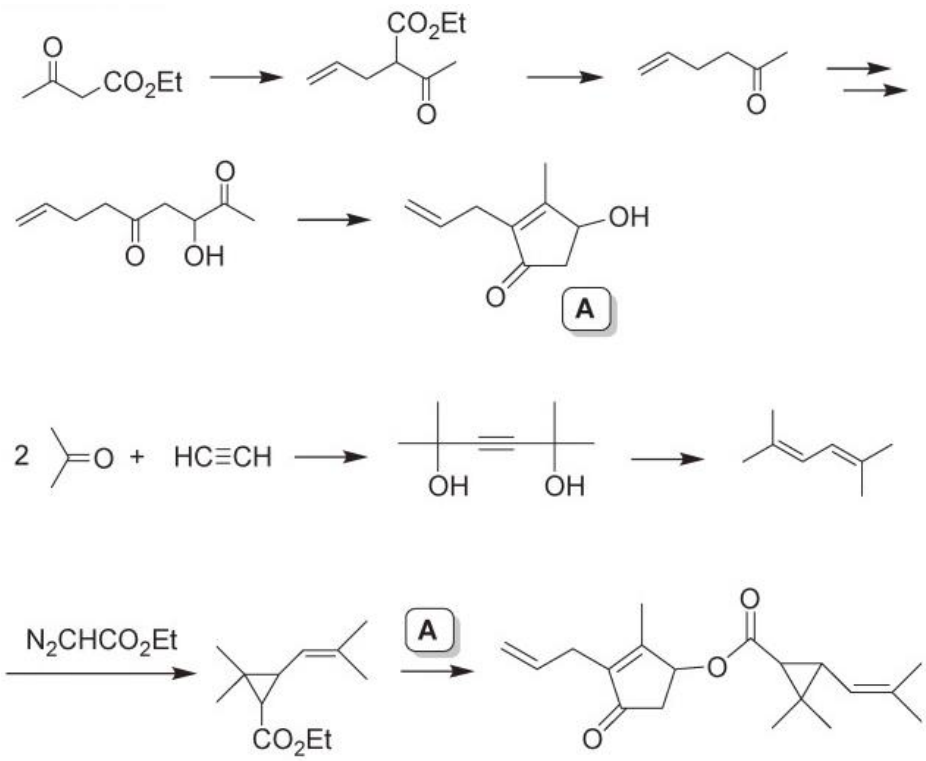




Pyrethrin I

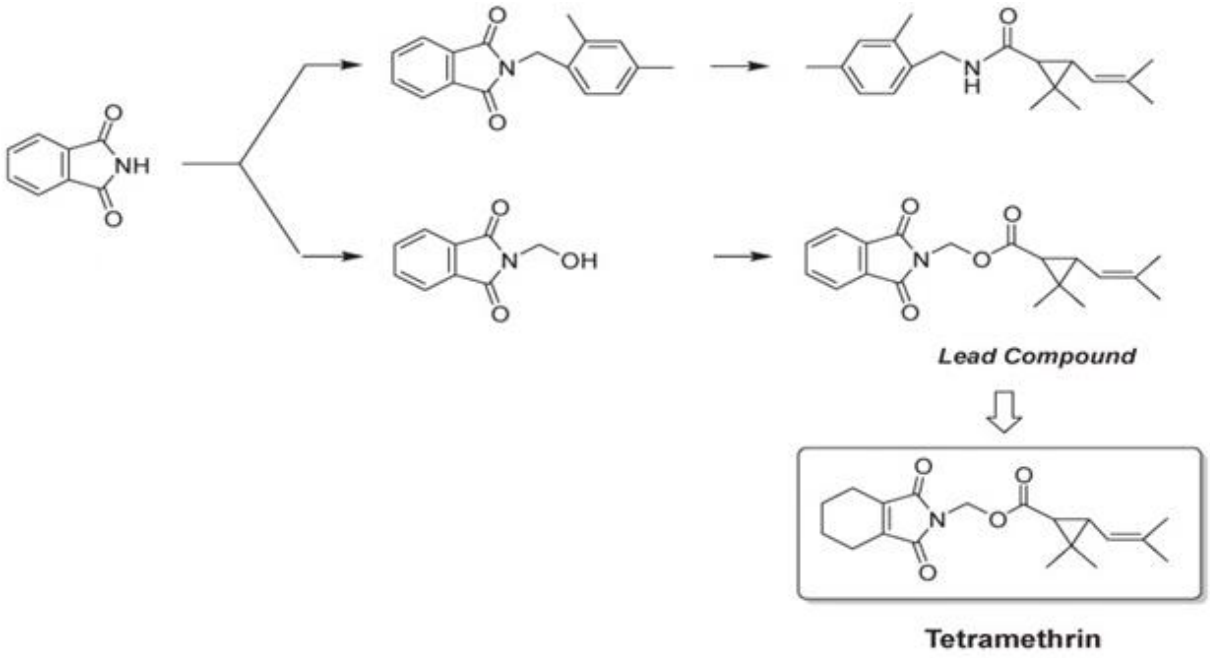
5.8.5.Synthesis of some pyrethroids:

1.The first pyrethroid, allethrin was discovered by Schechter and LaForge in 1949.
The **allethrins** are a group of related synthetic compounds used in insecticides. They are classified as pyrethroids, i.e. synthetic versions of pyrethrin, a chemical with insecticidal properties found naturally in *Chrysanthemum* flowers.



They are commonly used in ultra-low volume sprays for outdoor mosquito control, and in many household insecticides such as RAID, as well as mosquito coils.

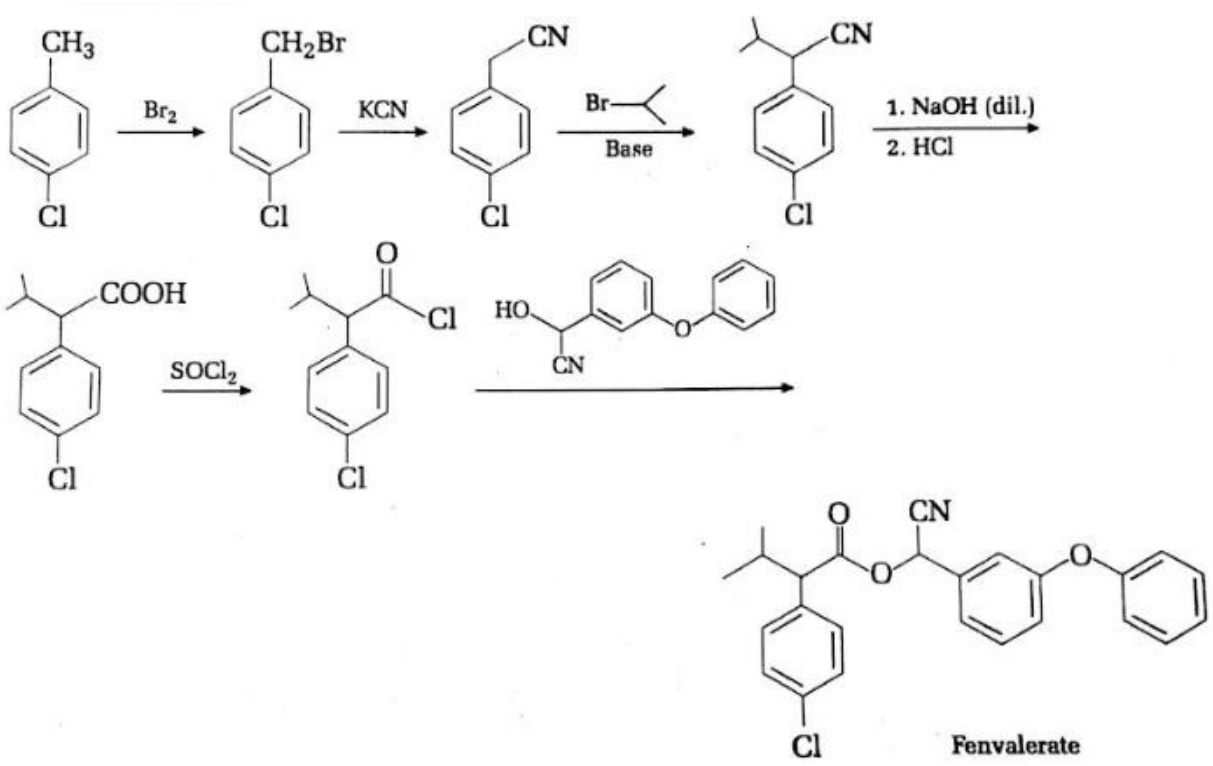
2) **Tetramethrin:** It is a potent synthetic insecticide in the pyrethroid family.



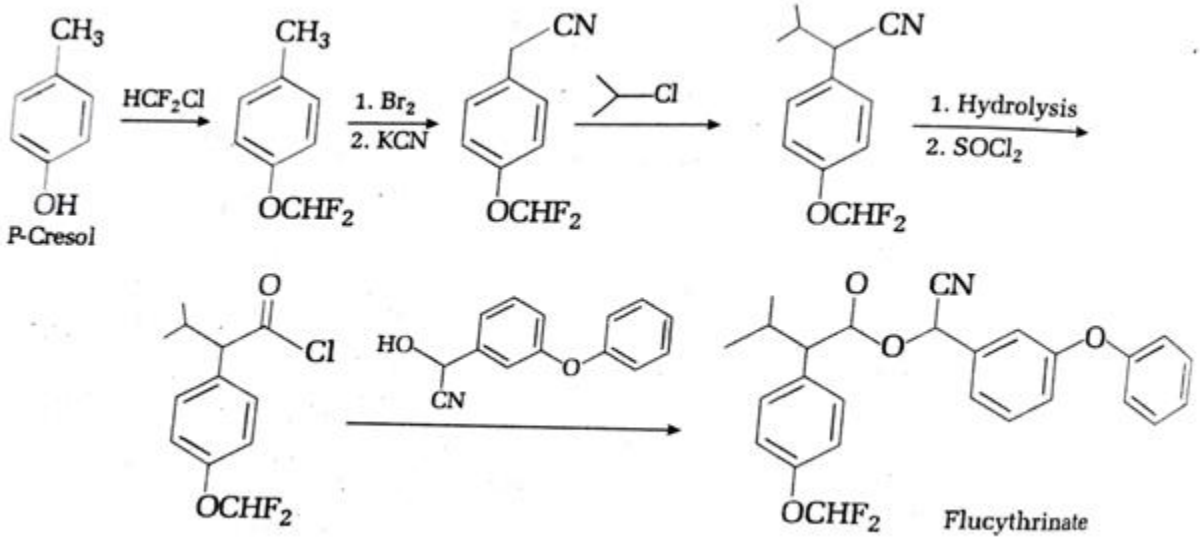
Tetramethrin

3)Synthesis of some other pyrethroids which are not derivatives of cyclopropanecarboxylic ester can be achieved as follows:

a) Fenvalerate: Fenvalerate is a synthetic pyrethroid insecticide. Its IUPAC name is,(RS)-alpha-Cyano-3-phenoxybenzyl (RS)-2-(4-chlorophenyl)-3-methylbutyrate .It is a mixture of four optical isomers which have different insecticidal activities. Fenvalerate is an insecticide of moderate mammalian toxicity. In laboratory animals, central nervous system toxicity is observed following acute or short-term exposure.



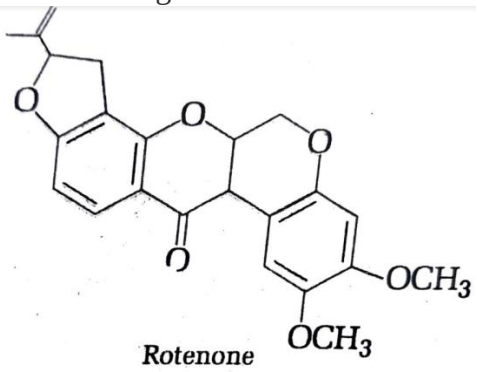
b)Flucythrinate: The chemical name of flucythrinate **is,(**RS)-alpha-cyano-3-phenoxybenzyl- (S)-2-[4-(difluoromethoxy)phenyl]-3-methylbutyrate. Flucythrinate is extremely toxic to fish, which die when exposed to concentrations above 10 ug/l. Marine mammals and sea birds are much more tolerant to the compound, as the are only affected after consumption of several grams per kilogram of body weight. Flucythrinate has a low water solubility and a high tendency to adsorb to organic matter and suspended particles.



ROTENONE:

5.8.6. Introduction:

Rotenone is one of the oldest naturally occurring ketonic compounds, derived from the roots of *Lonchocarpus* species . Rotenone is the trivial name of the main chemical component of certain plants of the "*Derris*," "*Lonchocarpus*," "*Tephrosia*" and "*Mundulea*" species. It has a molecular formula of $C_{23}H_{22}O_6$ and a molecular weight 394.42. Its chemical structure is shown in Figure



Rotenone

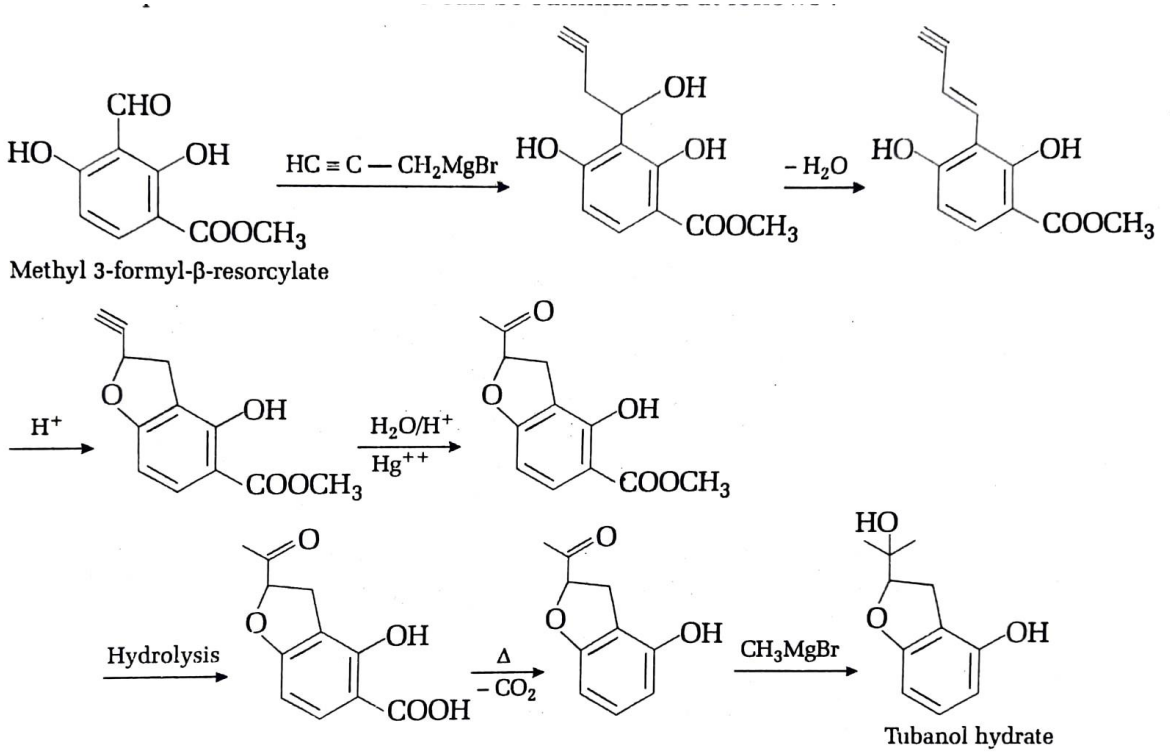
The formula consist of three characteristic systems,a central dihydro-γ- pyrone combined on the one hand with a dihydrobenzopyran and on the other with a dihydrobenzofurane systems.The characteristic of the on or other of three systems and are aupported by analogies with other compounds containing same system.

It is a commonly used pesticide and is also used in lakes and reservoirs to kill fish that are perceived as pests. In general, rotenone is an excellent organic pesticide used in home gardens for insect control, for lice and ticks on pets, and fish eradications as part of water body management.

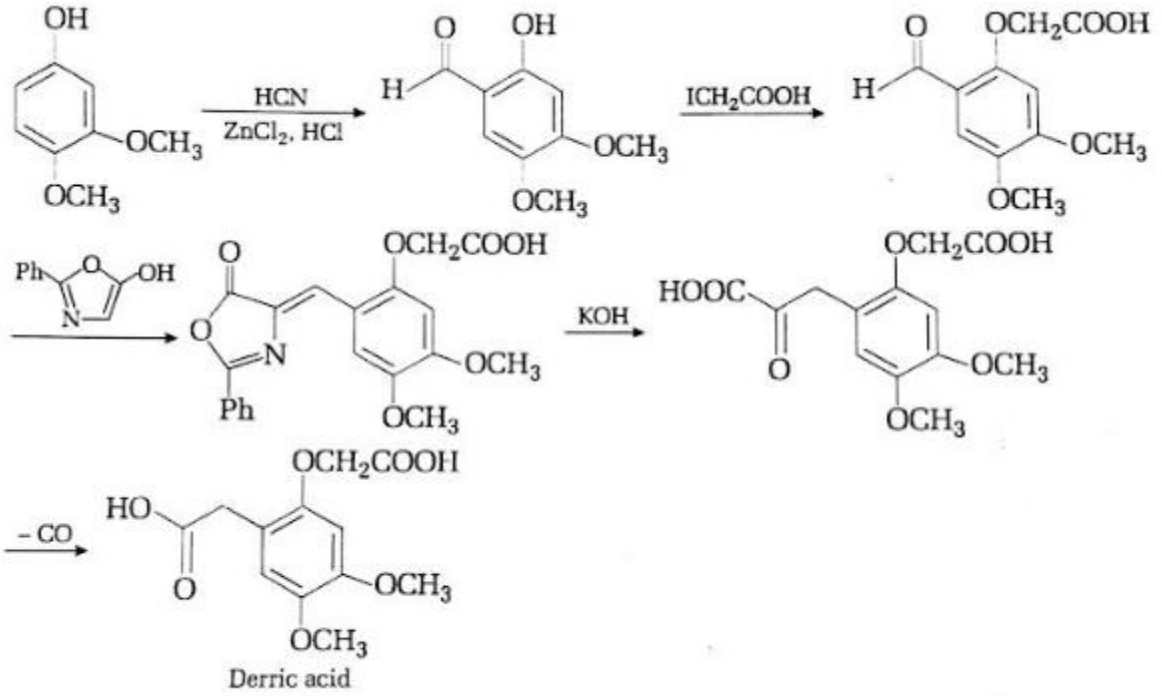
5.8.7. Synthesis of Rotenone:

1) Method First:

a) In this method at first prepare Tubanol hydrate. Synthesis of tubanol was difficult and involved a number of steps. Using methyl 3- formyl –β-resorcylate as the starting material,tubanol obtained in following steps:

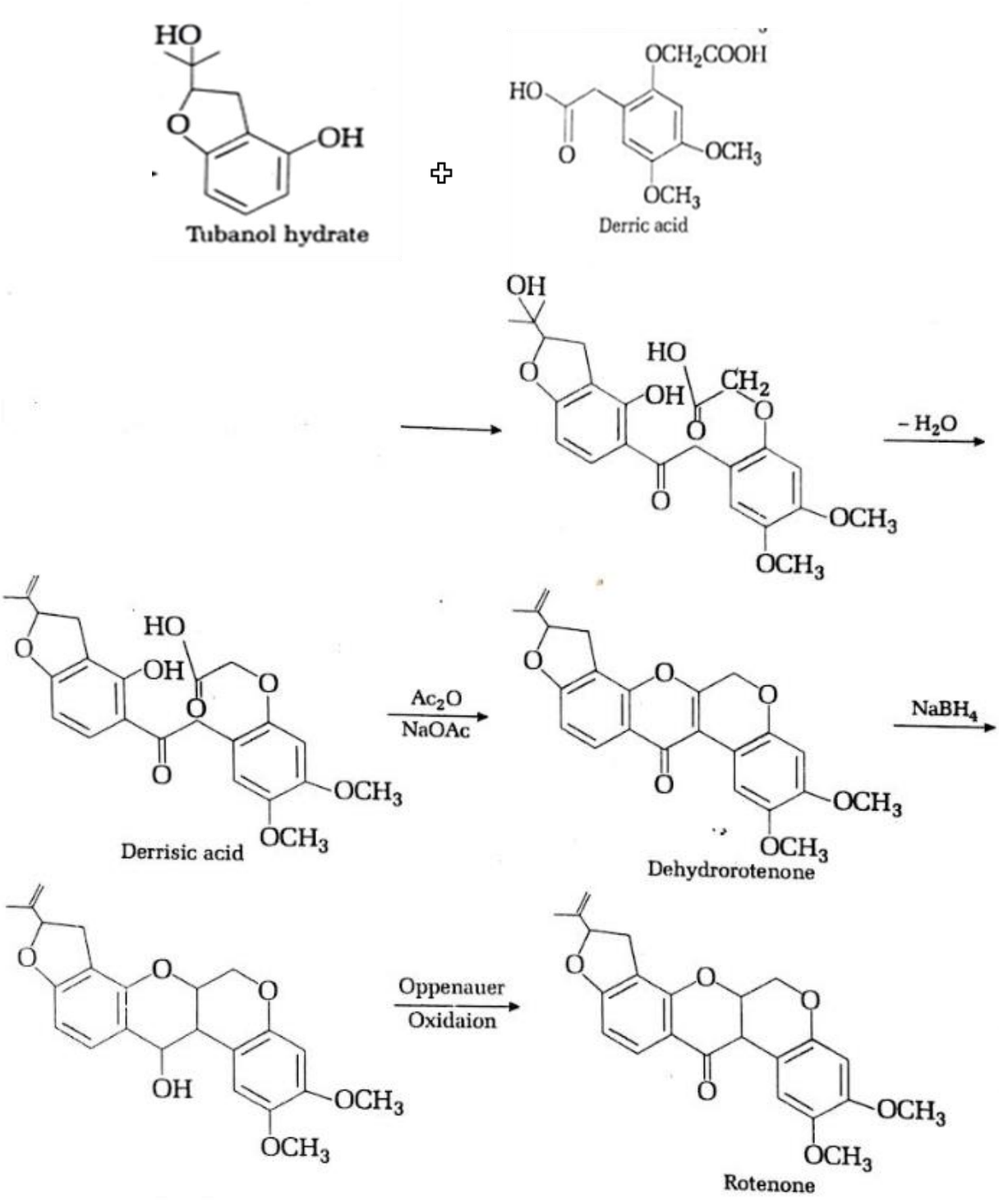


b)In second step 3,4dimethoxyphenol is starting material, and derric acid was synthesized from it.All these reactions can be summarized as follows:

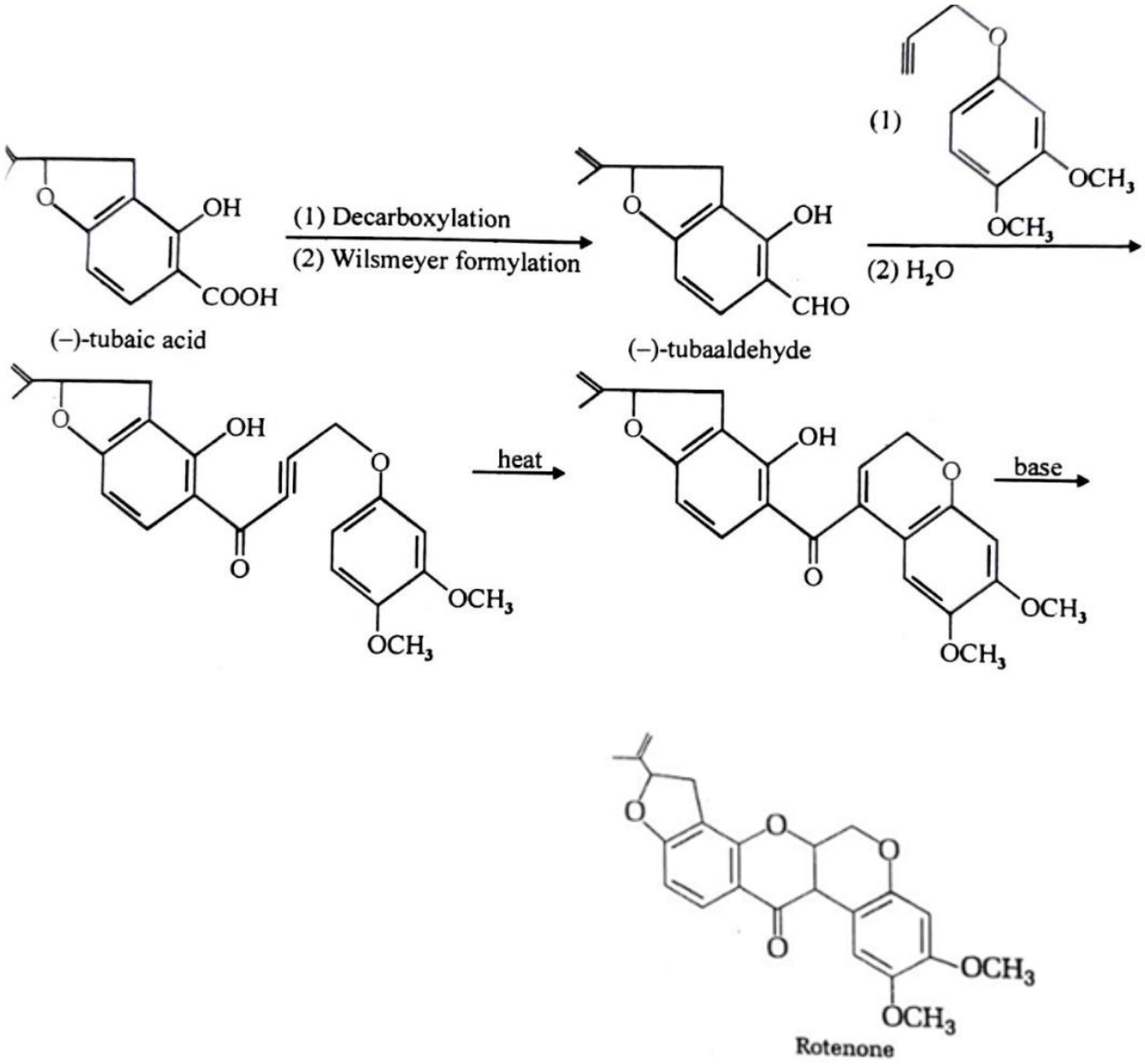


Derric acid

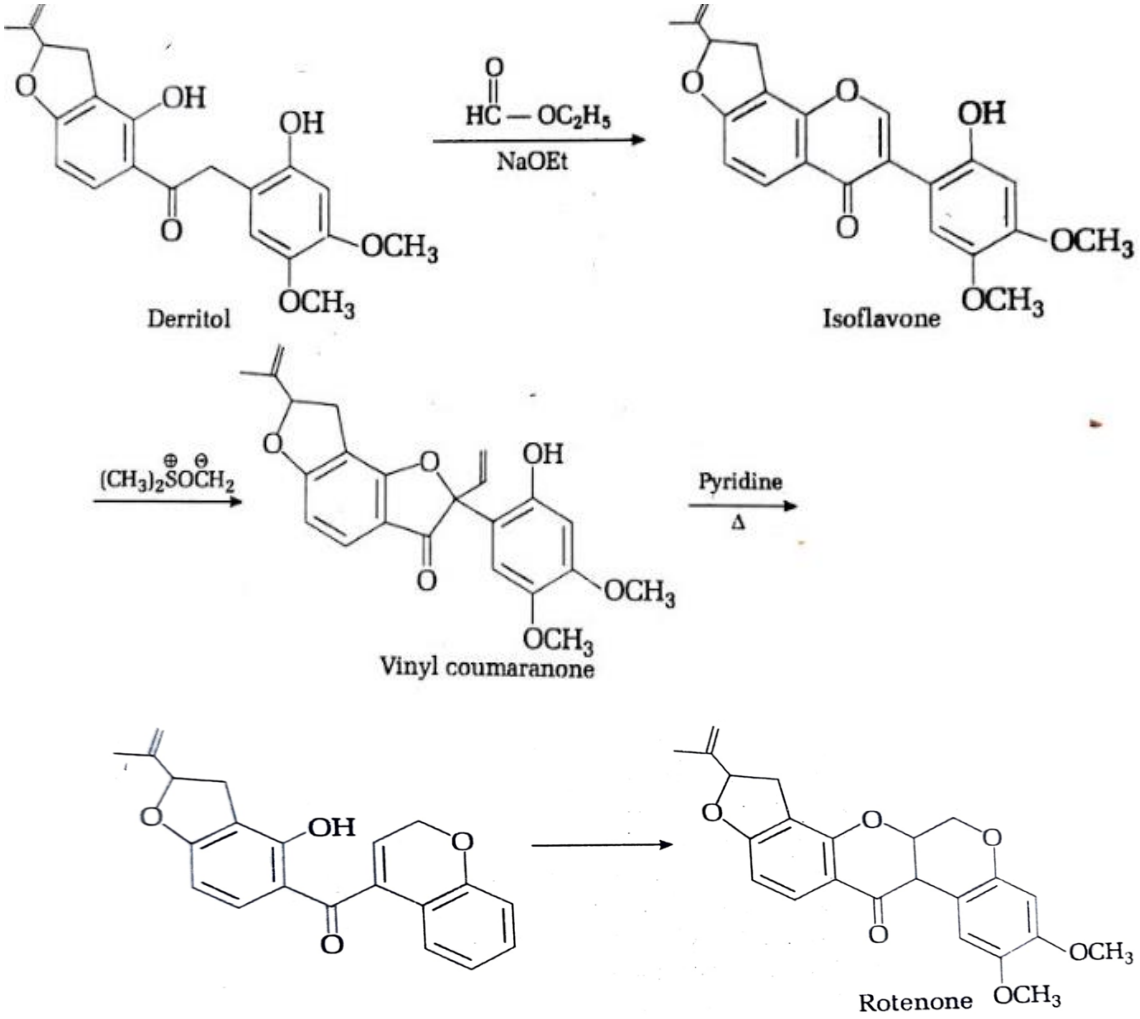
c)In this step final combination of tubanol hydrate with Derric acid in various step gives final product i.e. Rotenone.


HO
O
OH
Tubanol hydrate
OCH2COOH
HO
O
OCH3
OCH3
Derric acid
OH
HO
OH
CH2
O
O
O
OCH3
OCH3
– H2O
HO
OH
O
O
O
OCH3
OCH3
Derrisic acid
Ac2O
NaOAc
O
O
O
OCH3
OCH3
Dehydrorotenone
NaBH4
O
O
O
OH
OCH3
OCH3
Oppenauer
Oxidaion
O
O
O
O
OCH3
OCH3
Rotenone

Method Second: Another synthesis route for rotenone was developed by Sasaki and Yamashita (1979) from (-) tubaic acid.

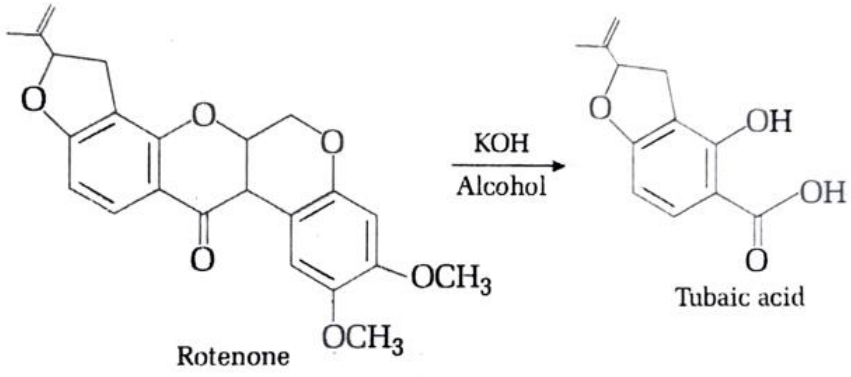


Method Third: Another approach to the synthesis of rotenone involves reaction of 2′-hydroxyisoflavone with dimethyl sulphoxonium methylide to afford vinyl coumaranone which , when heated in pyridine gives rotenone skeleton via a dehydrorotenol intermediate. Derritol can be converted to isoflavone by reaction with ethyl formate in the presence of a base.



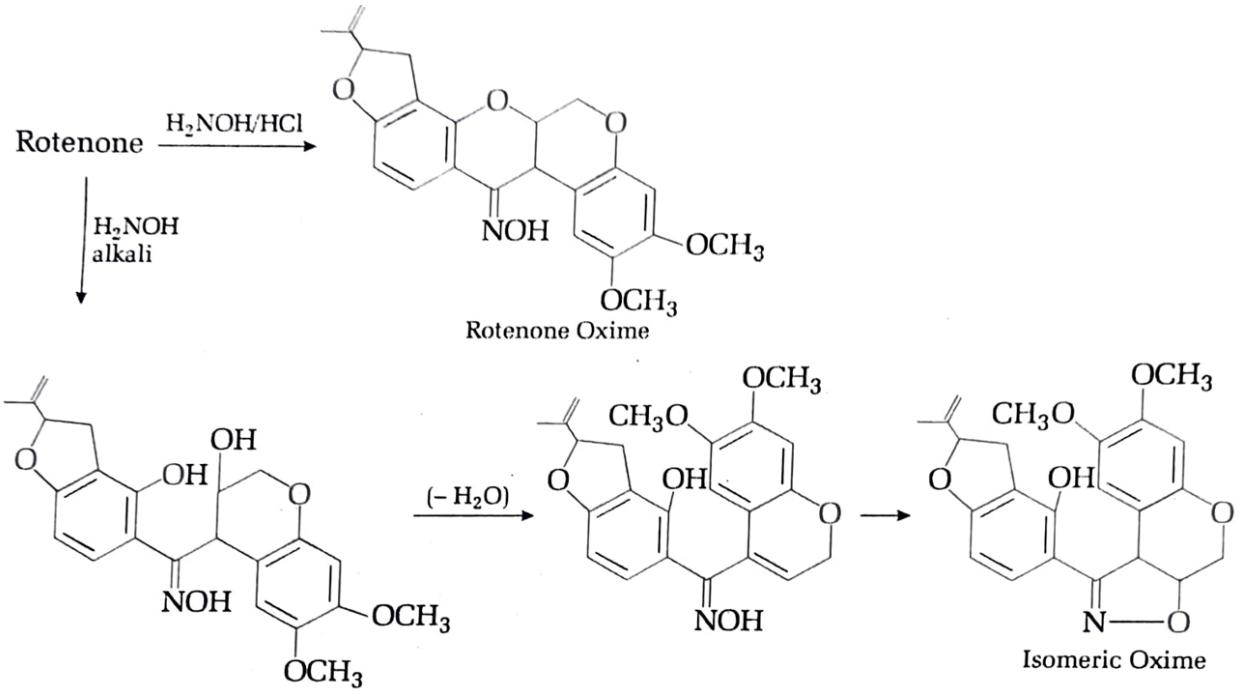
5.8.8.Reaction of Rotenone:

1)Retenone is cleaved by alcoholic alkali like KOH give an tubacic acid, and rotenone derivatives yield corresponding tubaic acid derivatives which could also be prepared from tubaic acid.

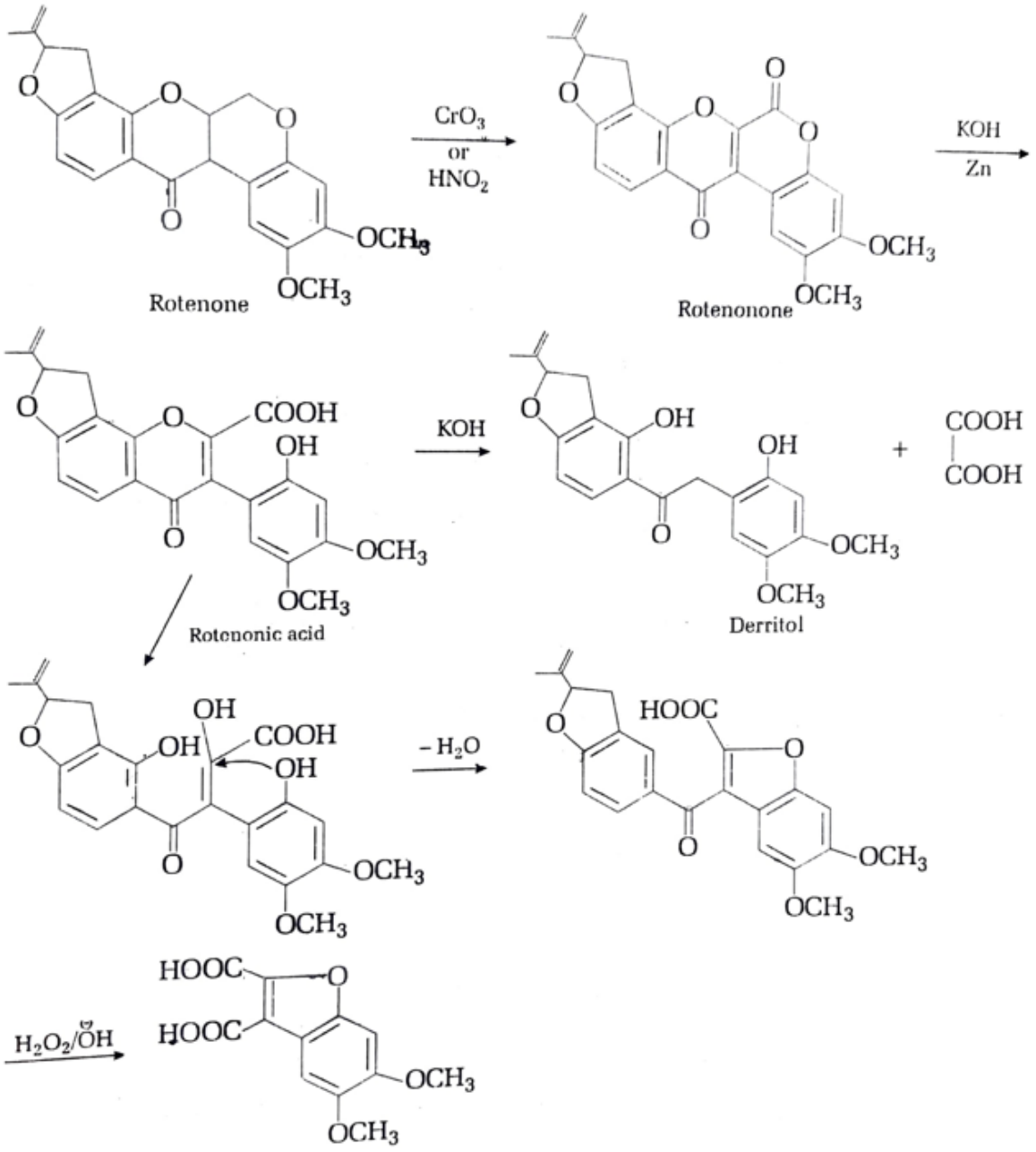


2)Rotenone and its derivatives from oximes and hydrazone derivatives with hydroxylamine and hydrazine

,respectively.In acidic medium it form normal derivatives but in alkali medium rotenone form isomeric phenolic oxime.



3)When rotenone is oxidized with chromium trioxide/ nitrous acid produce rotenonone (derivative of lactone), which on further treated with zinc dust and alkali gives rotenonic acid and another carboxylic acid , which on further oxidation with H_2O_2 / OH gives carboxylic acid derivatives.



Uses of Rotenone: Rotenone used as a:

- Rotenone has historically been used by indigenous peoples to catch fish. Typically , rotenone-containing plants in the fabaceaefamily of legumes are crushed and introduced into a body of water, and as rotenone interferes with cellular respiration, the affected fish rise to the surface in an attempt to gulp air, where they are more easily caught.
- Rotenone is used as a pesticide , insecticide ,and as a nonselective pesticide.

- It kill potato beetles,cucumber beetles,flea beetles,cabbage warm,raspberry beetles,as well as most other arthropods.It repedly biodegrades under warm condition so harmful residues are minimum.A light dusting on the leaves of plants will control insects for several days.
- Rotenone also used in powdered form to treat scabies and head lice on humans and parasitic mites on chickens, livestock , and pet animals.
- Commercialized it is used as cube, tuba or derris , in single preparation or in synergistic combination with other insecticides.

5.9 SUMMARY:

Prostaglandins are a group of endogenously produced compounds that play essential roles in regulating human physiology. Synthetically derived prostaglandins can be used to modulate numerous processes in the body. Similarly Pyrethroids are synthetic insecticides, which are used for the controlling insect pests in agriculture, public health, and animal health. In this unit we learn about ,basic knowledge of Prostaglandins , Occurrence ,Nomenclature and Classification, Biogenesis and physiological effects of Prostaglandins . Here we explain the synthesis of PGE2 ,PGE2α synthesis and explained the some selective reactions of Pyrethroids , Rotenones .

5.10 TERMINAL QUESTIONS:

5.10.1. Fill in the blanks :

1) Every prostaglandin contains …….. atoms, including a 5-carbon ring.

2) Pyrethrin a chemical with insecticidal properties found naturally ..... flowers.

3) Rotenone is one of the oldest naturally occurring ……. compounds.

4) Physiological Prostaglandins control …… and …….. metabolism.

5) The boiling point of Pyrethrin I, …….. at 0.1 mmHg with decomposition.

6) The Latters A and B in PGA and PGB refer to prostaglandins resulting from the treatment of PGE …… with respectively.

5.10.2. True and false type questions :

1) Prostaglandins are not stored in cells.

2) The five membered rings of PGA's , PGB's and PGC's contain a carbonyl group.

3) Prostaglandins is the human seminal plasma which is having upto 50- 600 mg /ml.

4) The molecular formula of Pyrethrin II is $C_{20}H_{22}O_{10}$.

5) Derritol can be converted to isoflavone by reaction with ethyl formate in the presence of a base.

5.10.3 Long answer type questions:

1)Define the term pyrethroides?What are the physiological properties of these compounds? Give synthesis of atleast twp pyrethroids.

2)What are rotenones?Give synthesis , properties ,and uses of rotenones.

3)How the following conversion can be performed?

i) Tubaic acid ---------- Rotenone

ii) Isoflavone --------- Rotenone

4) What are prostaglandins? Give their classification.

5) Give the Corey's synthesis of PGE_2 and $PGE_{2\alpha}$.

6) Define biogenesis and physiological effects of prostaglandins?

ANSWERS:

5.10.1. 1) 20 carbon 2) Chrysanthemum 3) Ketonic

4) lipid ,carbohydrate 5) 170°C 6) acid and base

5.10.2. 1) True 2) False 3) False 4)False 5)True

5.11 REFERENCES AND FURTHER STUDIES:

1. Organic Chemistry of natural products Vol-II ,Gurdeep R. Chatwal, page no:12.1-12.15, 14.1-14.10.

2. Natural Product, Chemistry,Jagdamba Singh, UGC Curriculum M.Sc.final: Elective paper VIII Page no : 276-336, 337-370.

3. Prostaglandin E1Wikipedia https://en.wikipedia.org › wiki › Prostaglandin_E1

4. Rotenone R.C. Gupta, in Encyclopedia of Toxicology (Third Edition), 2014.

Block -2

UNIT 6: NOMENCLATURE OF HETEROCYLIC COMPOUNDS

CONTENTS:

6.1 Objective

6.2 Introduction

6.3 Nomenclature

- 6.3.1 Common Nomenclature
- 6.3.2 Trivial Names
- 6.3.3 Replacement method of nomenclature
- 6.3.4 Hantzsch-Widman Nomenclature
- 6.3.5 Hantzsch-Widman Rules For Partially Unsaturated Heterocycles

6.4 Nomenclature of fused system

6.5 Tautomerism in heterocyclic compounds

6.6 Strain

6.7 Types of strain

- 6.7.1 Bond angle strain
- 6.7.2 Steric strain
- 6.7.3 Torsional strain

6.8 Conformation of six membered heterocycle

6.9 Barrier to ring inversion

6.10 Pyramidal inversion at nitrogen

6.11 1,3 Diaxial Interaction

6.12 Summary

6.13 Reference

6.14 Terminal question

6.1OBJECTIVES:

The objective of this unit, you will be able to learn-

- What are the heterocyclic compounds.
- Classification of heterocyclic compounds.
- Nomenclature of heterocyclic compounds.
- Tautomerism in heterocyclic compounds.
- Types of strain in heterocyclic compounds.
- Stereochemistry of heterocyclic compounds.

6.2 INTRODUCTION:

Heterocyclic compounds are the "Cyclic compounds having as ring members atoms of at least two different elements, e.g. quinoline, 1,2-thiazole, bicyclo[3.3.1]tetrasiloxane". Usually they are indicated as counterparts of carbocyclic compounds, which have only ring atoms from the same element. Another classical reference book, the Encyclopaedia Britannica, describes a heterocyclic compound, also called a heterocycle, as: Any of a class of organic compounds whose molecules contain one or more rings of atoms with at least one atom (the heteroatom) being an element other than carbon, most frequently oxygen, nitrogen, or sulfur. Although heterocyclic compounds may be inorganic, most contain within the ring structure at least one atom of carbon, and one or more elements such as sulfur, oxygen, or nitrogen. Since non-carbons are usually considered to have replaced carbon atoms, they are called heteroatoms. The structures may consist of either aromatic or non-aromatic rings. Heterocyclic chemistry is the branch of chemistry dealing with the synthesis, properties, and applications of heterocycles.

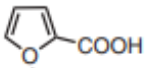
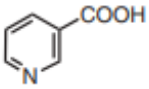
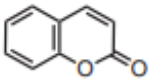
6.3 NOMENCLATURE:

There are three systems for naming heterocylic compounds:

1. The common nomenclature: which convey little or no structuralinformation but it still widely used.

2. The replacement method.
3. The Hantzsch-Widman (IUPAC or Systematic) method which in contrast is designed so that one may deduce from it the structure of the compound.

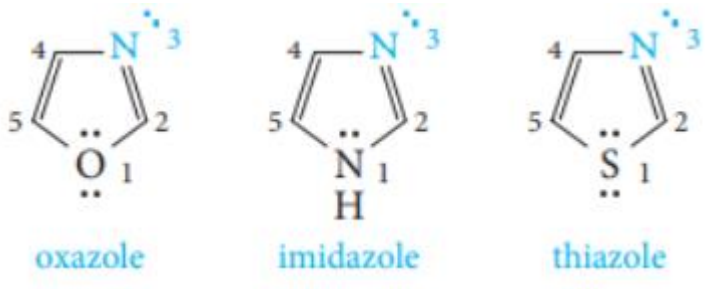
Many organic compounds, including heterocyclic compounds, have a trivial name. This usually originates from the compounds occurrence, its first preparation, or its special properties.

Structure	Trivial name	Systematic name (IUPAC)
	ethylene oxide	oxirane
	pyromucic acid	furan-2-carboxylic acid
	pyridine	pyridine (instead of azine)
	nicotinic acid	pyridine-3-carboxylic acid
	coumarin	2*H*-chromen-2-one

6.3.1 Common Nomenclature :

1) Each compound is given the corresponding trivial name (which should be memorized). This usually originates from the compounds occurrence, its first preparation or its special properties.

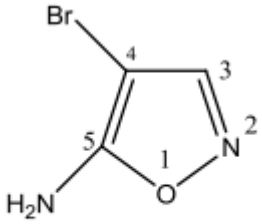
2) If there is more than one heteroatom of the same type numbering starts at the saturated one, e.g. imidazole.



3) If there is more than one type of the heteroatoms, the ring is numbered starting at the heteroatom of the higher priority (O>S>N) and it continues in the direction to give the other

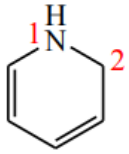
heteroatoms the lower numbers as possible.

4) If substituents are present, their position should be identified by the number of the atoms bearing them and then they should be listed in alphabetical order.



5-Amino-4-bromoisoxazole

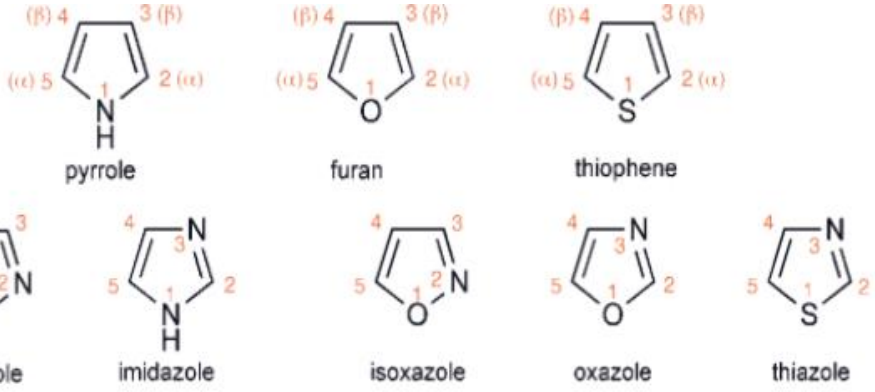
5) The words dihydro , or trihydro, or tetrahydro are used if two or three or four atoms are saturated. These words are preceded by numbers indicate the position of saturated atoms as low as possible and followed by the corresponding fully unsaturated trivial name.



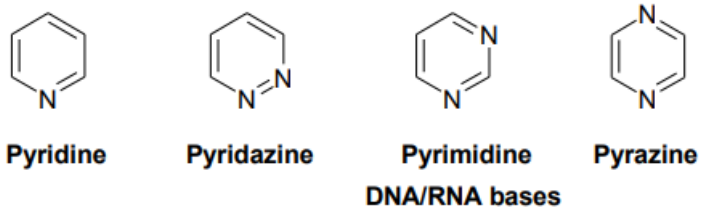
1,2-Dihydro-pyridine

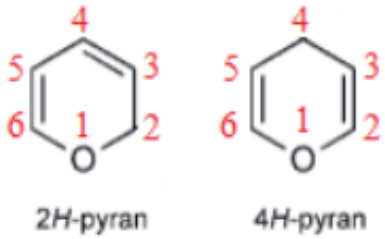
6.3.2 Trivial Names :

1. **Five -Membered heterocycles with one or two heteroatoms**

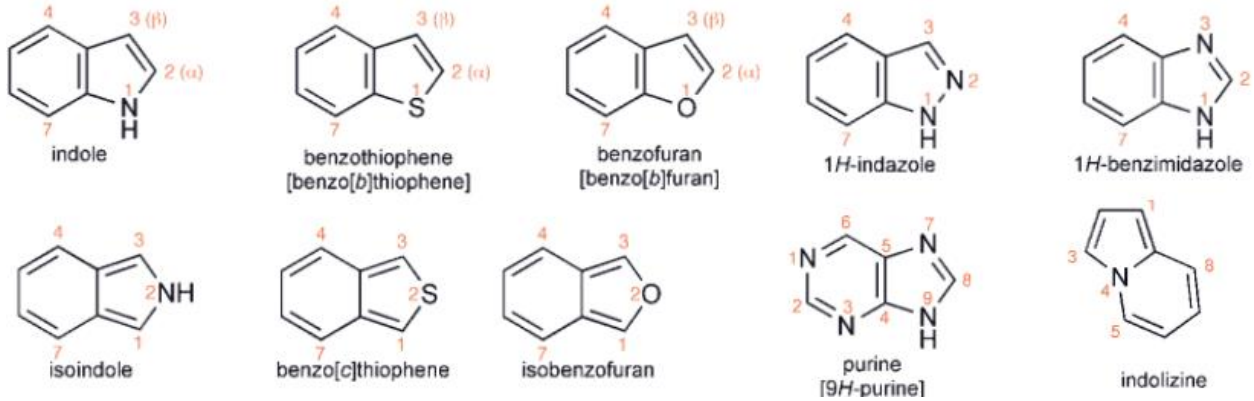


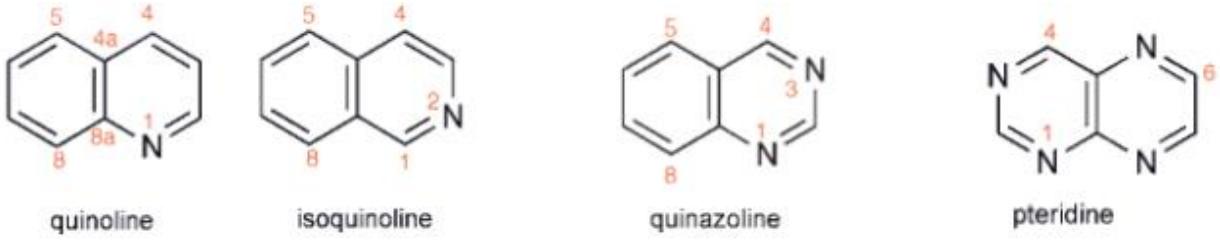
2. Six -Membered heterocycles with one or two heteroatoms



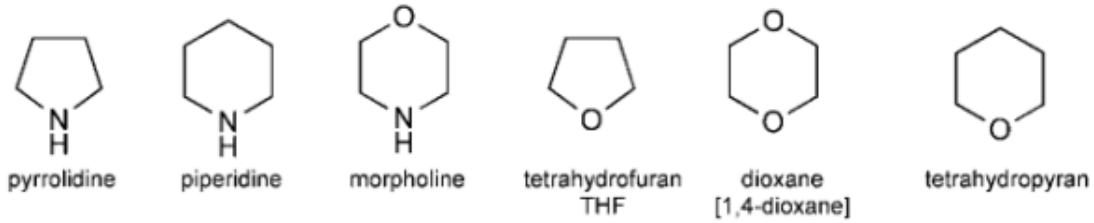


3. Fused heterocycles





4. Saturated Heterocycles

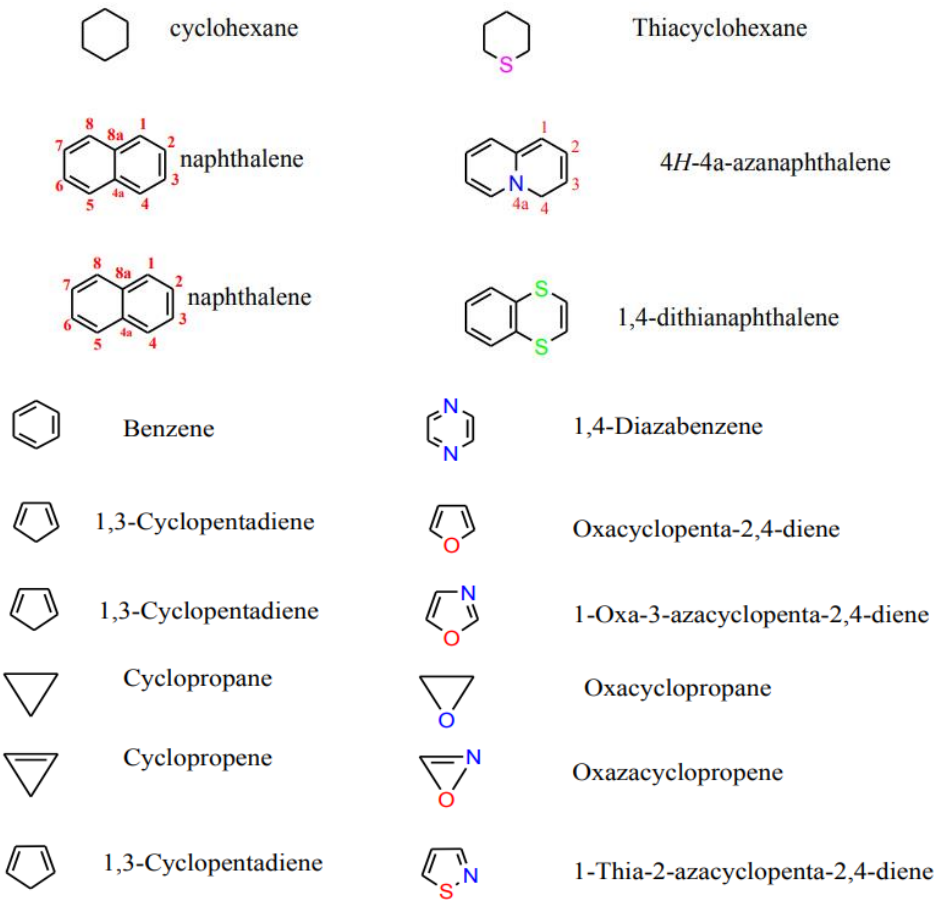


6.3.3 Replacement Method of Nomenclature:

In replacement nomenclature, the heterocycle's name is composed of the corresponding carbocycle's name and an elemental prefix for the heteroatom introduced (if more than one heteroatom is present they should be listed according to the priority order shown in table (1). According to this nomenclature, tetrahydrofuran, for instance, is called oxacyclopentane.

Atom	Prefix
O	oxa
Se	selena
S	thia
N	aza
P	phospha

Common Examples of Replacement Nomenclature



6.3.4 Hantzsch-Widman Nomenclature:

Hantzsch-Widman nomenclature is named after the German chemists Arthur Hantzsch and Oskar Widman, who proposed similar methods for the systematic naming of heterocyclic compounds in 1887 and 1888 respectively.

According to this system three to ten-membered rings are named by combining the appropriate prefix (or prefixes) that denotes the type and position of the heteroatom present in the ring with suffix that determines both the ring size (depending on the total number of atoms in the ring) and the degree of unsaturation (note that fully saturated and fully unsaturated have certain rules for nomenclature while partially unsaturation will be indicated in certain ways).

In addition, the suffixes distinguish between nitrogen-containing heterocycles and heterocycles that do not contain nitrogen

IUPAC name = locants +Prefix + suffix

Hantzsch-Widman rules for fully saturated and fully unsaturated heterocycles

1. Identify the hetroatom present in the ring and choose from (table 1 on slide 9) the corresponding prefix (e.g. thia for sulfur, aza for nitrogen and oxa for oxygen).
2. The position of a single heteroatom control the numbering in a monocyclic compound. The heteroatom is always assigned position 1 and if substituents present are then counted around the ring in a manner so as to take the lowest possible numbers.
3. A multiplicative prefix (di, tri, ect.) and locants are used when two or more similar heteroatoms contained in the ring(two nitrogen indicated by diaza) and the numbering preferably commenced at a saturated rather than an unsaturated atom, as depicted in the following example: 1,3-diazole
4. If more than one type of hetroatoms present in the ring the name will include more than one prefix with locants to indicate the relative position of the heteroatoms.
   a. Atom prefixes have a strict order of priority (preference) in which they are to be listed. For example,''Oxa''(for oxygen) always comes before ''aza'' (for nitrogen) in a name (see table 1).
   b. When combining the prefixes (e.g. oxa and aza) two vowels may end up together, therefore the vowel on the end of the first part should be omitted (oxaza).
   c. The numbering is started from the heteroatom of the highest priority in such a way so as to give the smallest possible numbers to the other heteroatoms in the ring (the substituents are irrelevant).
5. Choose the appropriate suffix from (table 2a) depending on the ring size.
6. The endings indicate the size and degree of unsaturation of the ring (table 2b).

Table-2a

Ring size	Suffix
3	ir
4	et

5	ol
6	in
7	ep
8	oc
9	on
10	ec

Table-2b

Ring size	With Nitrogen		Without Nitrogen	
	Unsaturated	**Saturated**	**Unsaturated**	**Saturated**
3	irine	iridine	irene	irane
4	ete	etidine	ete	etane
5	ole	olidine	ole	olane
6	ine	a	in	inane
7	epine	a	epin	epane
8	ocine	a	ocin	ocane
9	onine	a	onin	onane
10	ecine	a	ecin	ecane

a means use the prefix perhydro followed by the fully unsaturated name

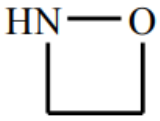
7.Combine the prefix (s) and suffix together and drop the first vowel if two vowels came together.

Example:

1.

- This ring contains (N): Prefix is aza.
- The ring is 3-membered and fully saturated: suffix is iridine.
- By combining the prefix and suffix, two vowels ended up together (azairidine), therefore the vowel on the end of the first part should be dropped.
- This gives the correct name: **Aziridine.**

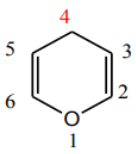
2.



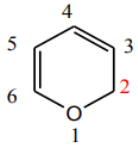
- This ring contains (O and N) (O has higher priority than (N) and by starting numbering the ring at (O): Prefix is 1,2-Oxaaza, but the first vowel must be omitted to give: 1,2-Oxaza.
- The ring is 4-membered and fully saturated: suffix is etidine.
- By combining the prefix and suffix, two vowels ended up together (1,2-oaxazaetidine), therefore the vowel on the end of the first part should be dropped.
- This gives the correct name:**1,2-oxazetidine**

6.3.5 Hantzsch-Widman Rules For Partially Unsaturated Heterocycles :

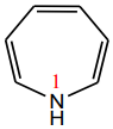
1.The position of nitrogen or carbon atoms which bear extra hydrogen atoms must be indicated by numbers and italic capital H (e.g. 1H, 2H, etc.) followed by the name of maximally unsaturated ring.



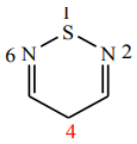
4*H*-Oxin



2*H*-Oxin



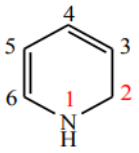
1*H*-Azepine



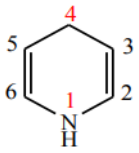
4*H*-1,2,6-Thiadiazine

2.The words dihydro, or trihydro, or tetrahydro are used if two or three or four atoms are

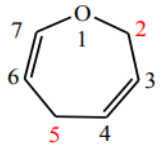
saturated. These words are preceded by numbers indicate the position of saturated atoms as low as possible and followed by the corresponding fully unsaturated Hantzsch-Widman name.



1,2-Dihydroazine



1,4-Dihydroazine



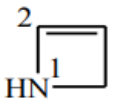
2,5-Dihydrooxepin

3.Alternatively, the partially unsaturated 4 and 5 rings (i.e. rings contain one double bond) are given special Hantzsch-Widman suffixes as in table 3 and the double bond is specified as Δ^1 , Δ^2 , Δ^3 , etc.. Which indicates 1 and 2 ; 2 and 3; 3 and 4 atoms respectively have a double bond.

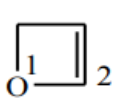
Name : Δ^x + Prefix + special suffix (x= locant of the double bond)

Table 3

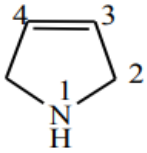
Ring size	With N	Without N
4	etine	etene
5	oline	olene



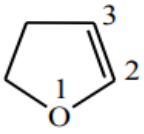
Δ^2 -Azetine
2-Azetine



Δ^2 -Oxetene
2-Oxetene



Δ^3 -Azoline
3-Azoline

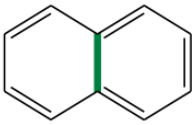


Δ^2-Oxolene
2-Oxolene

6.4 NOMENCLATURE OF FUSED SYSTEMS:

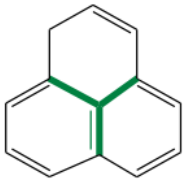
Fusion: This term is used to describe the process of joining two separate rings with the maximum number of non-cumulative double bonds via two atoms and one common bond.

• Ortho-fused rings: are those rings that have only two common atoms and one bond, example; Naphthalene



Naphthalene

Ortho-and peri-fused rings: are those found in a polycyclic compound with a ring that is ortho-fused to different sides of two other rings that are themselves ortho-fused together (i.e. there are three common atoms between the first ring and the other two), example; 1H-phenalene is considered as being composed of three benzene rings, each is ortho-peri-fused to the other two.



1*H*-Phenalene

Polycyclic compounds incorporating one heterocyclic ring or fused heterocylic system fused to benzene are known benzoheterocycles.

• Also bicyclic compounds with two fused heterocyclic rings are well known.

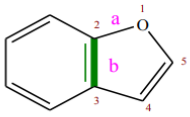
• Both types can be named according to certain rules.

A. Nomenclature of benzofused compounds:

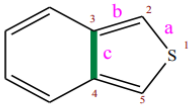
1. A benzene ring fused to a heteromonocycle of five or more members or a heterobicylcle is named by prefixing the word benzo to a letter indicating the position of fusion in square brackets by the name of heterocyclic ring (common or IUPAC or modified replacement name).

Name = Benzo [letter] name of heterocyclic ring.

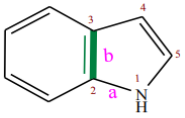
2. For designating the position of fusion, the peripheral bonds of the heterocyclic ring are consecutively assigned alphabetical letters staring with the 1,2-bond as a side and the labeling is continued around the ring to give the common bond the lowest order. Examples:



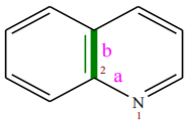
Benzo[*b*]furan



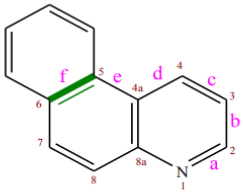
Benzo[*c*]thiophene



Benzo[*b*]pyrrole
Indole



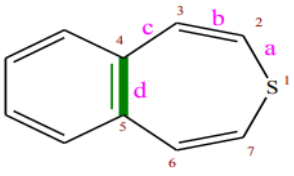
Benzo[*b*]pyidine
Qunioline



Benzo[*f*]qunioline

There is An exception to the two ring systems in which a benzene ring is fused to a hetero ring (which doesn't have a known common name) may be named by prefixing numbers indicating the positions of the hetero atoms to benzo followed by the name of the heterocyclic component.

• Numbering is assigned according to priority order of the hetero atoms i.e. O < S < N



Benzo[*d*]thiepine

B. Nomenclature of fused heterocylic compounds:

1. Naming a fused heterocyclic systems composed of two monoheterocyclic units or benzoheterocycles (e.g. chromene) fused with another hetrocycle ring is based upon considering one system as the parent (base) and the second is considered as substituent.

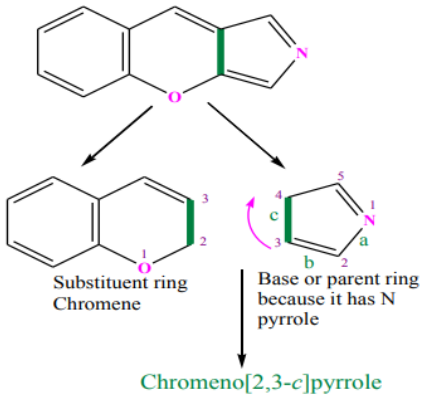
Name : name of minor ring [number, number-letter] name of major ring

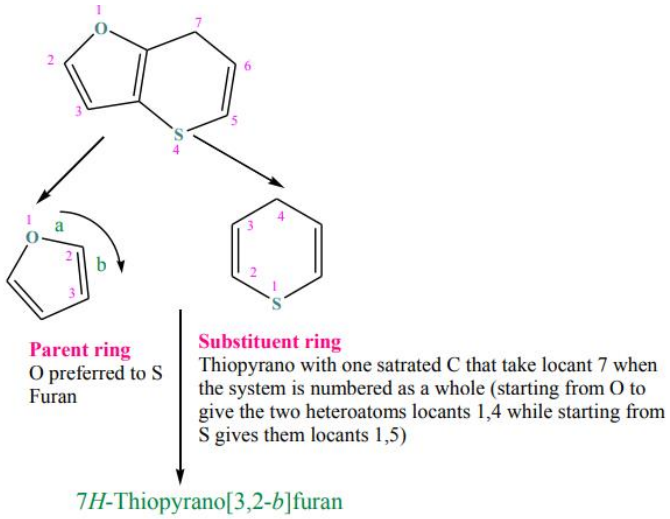
2. The name of the minor ring is derived by writing a contracted prefix for the substituent ring present. In an attached component prefix the terminal ‘e’ is changed to ‘o’ with exception of:

Furo	From Furan
Imidazo	From Imidazole
Thieno	From Thiophene
pyrido	From Pyridine
Pyrimido	From Pyrimidine
Quino	From Quinoline
Isoquino	From Isoquinoline

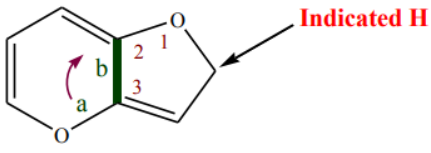
3. The numbers indicate which atoms in the minor ring are common to the major ring (fusion sites in minor ring).
4. The order of the numbers indicates which atom of the minor ring is encountered closest to atom 1 in the major numbering system
5. The letter defines the position of attachment of the minor ring to the major ring (fusion sites in base component).
6. Finally a suffix indicate the name of the base ring is written.
7. The numbering system for the whole fused system is not the same as the numbers in the square brackets (i.e. there are three numbering systems; one for minor ring, one for major ring and the third is for the system as a whole).
8. Priority order of component ring systems: Selection of a parent component or attached component is based on the following rules which are applied in order:

Rule 1: A heterocyclic ring containing the heteroatom occuring earlist in the order N, F, Cl, Br, I, O, S, Se,.. (i.e. ring containing N preferred to the rings does not contain N or containing O, or S)



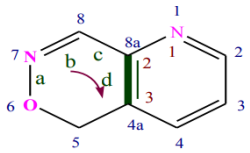


Rule 2: A heterocyclic component containing the largest possible individual ring



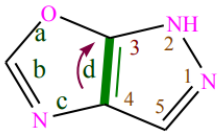
Numbering the whole system is started from O in furan ring to give the two heteroatoms locants 1,4 while starting from O in pyran ring gives them locants 1,5, thus the indicated H takes locant 2

Rule 3: A heterocyclic component containing the greater number of hetroatoms of any kind

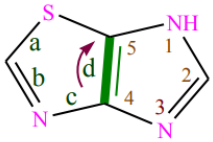


5*H*-Pyrido[2,3-*d*][1,2]oxazine
(Oxazine preferred to pyridine)

Rule 4: A heterocyclic component containing the greater variety of hetroatoms

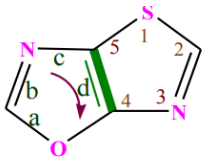


1*H*-Pyrazolo[4,3-*d*][1,3]oxazole
(O & N preferred to N only)



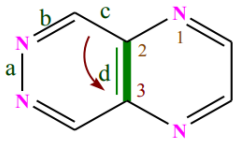
1*H*-Imidazo[4,5-*d*][1,3]thiazole

Rule 5: A heterocyclic component containing the greater number of heteroatoms most preferred when considered in order F, Cl, Br, I, O, S, Se, Te, N, P, As, Sb, Bi, Si, Ge, Sn Pb, B, Hg



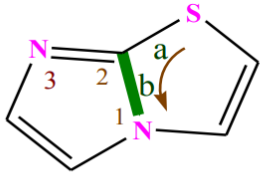
[1,3]Thiazolo[5,4-*d*][1,3]oxazole
(N & O preferred to N & S)

Rule 6: A heterocyclic component with the lower locants for heteroatoms



Pyrazino[2,3-*d*]pyridazine
(pyridazine [2N-1,2] preferred to pyrazine [2N-1,4]

Rule 7: If a position of fusion is occupied by a heteroatom the name of the component rings to be used are so chosen as both to contain the heteroatom.

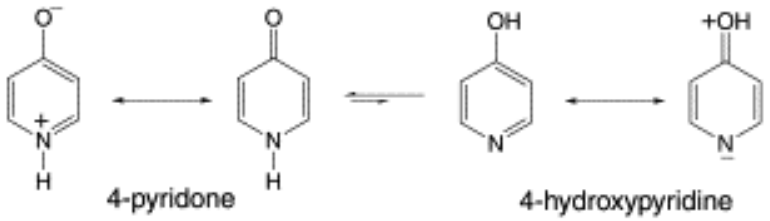


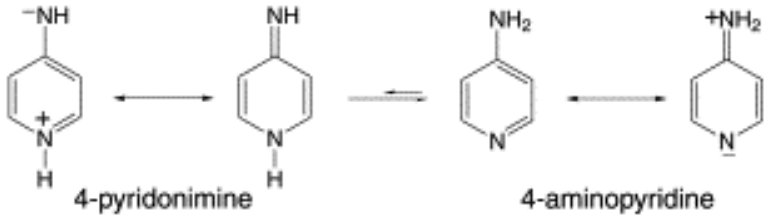
Imidazo[2,1-*b*][1,3]thiazole

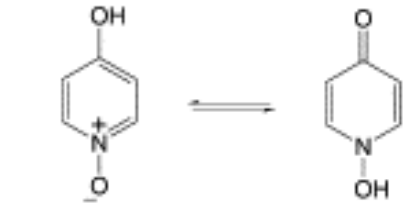
6.5TAUTOMERISM IN HETEROCYCLIC COMPOUNDS:

Tautomerism is very important in heterocyclic chemistry and many different types are known. Heteroolefinic compounds show tautomerism similar to their acyclic analogs. The azoles show annular tautomerism of the type exemplified next. Hydroxyamino, mercapto, and methyl substituents are capable of tautomerism when attached to a heterocyclic ring containing a pyridine-like nitrogen atom. This type of tautomerism is found in the pyridines. Pyridones predominate strongly over their tautomeric forms, the 2- and 4-hydroxypyridines. For the nitrogen analogs, the reverse is true, 2- and 4-aminopyridines being favored over the pyridonimine forms. This difference can be rationalized by considering the mesomerism of the alternative forms. The charge-separated form of 4-pyridone, being aromatic, is greatly preferred over the nonaromatic, charge-separated form of 4-hydroxypyridine. In the case of 4-aminopyridine, the charge-separated version of the imino form affords little stabilization, despite being aromatic, because nitrogen accommodates a negative charge.

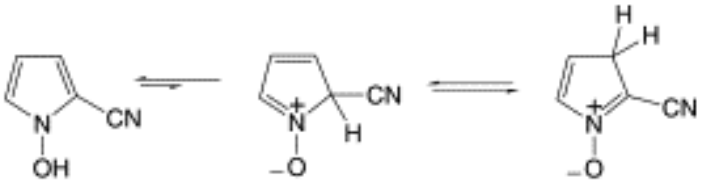
Following are the different examples of Tautomerism in Heterocyclic compounds







tautomerism of 4-hydroxypyridine 1-oxide



tautomerism of 1-hydroxy-2-cyanopyrrole

tautomerism of 2,3-dihydroxyheterocycles
(X = O, NH, S)

6.6 STRAIN:

Strain is defined as the distortion of bond lengths and bond angles from their ideal values. When a bond length or bond angle is distorted, potential energy is stored in the molecule. This potential energy that is stored in the molecule is referred to as the strain energy. Alternatively, strain can be thought about as the distortion of a molecule due to the three dimensional bonding requirements of atom. A molecule experiences strain when its chemical structure undergoes some stress which raises its internal energy in comparison to a strain-free reference compound. The internal energy of a molecule consists of all the energy stored within it. A strained molecule has an additional amount of internal energy which an unstrained molecule does not. This extra internal energy or strain energy, can be likened to a compressed spring. Much like a compressed spring must be held in place to prevent release of its potential energy, a molecule can be held in an energetically

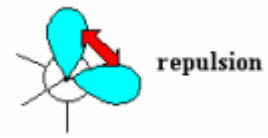
unfavourable conformation by the bonds within that molecule. Without the bonds holding the conformation in place, the strain energy would be released. Ring Strain: Ring strain is a type of instability that exists when bonds in a molecule form angles that are abnormal. It is most commonly discussed for small rings, such as cyclopropanes and cyclobutanes where the C-C-C angles deviate substantially from the idealized values of approximately 109°. According to Baeyer Strain theory, the stability of cyclic compounds (i.e., those of which the molecular structure includes one or more rings) depends on the amount by which the angles between the chemical bonds deviate from the value. The destabilization of a cyclic structure compared to a related non-cyclic structure, mainly due to angle and torsional strain. This extra energy is released when the ring is broken.

6.7TYPES OF RING STRAIN:

There are three classes of strain: Bond Angle Strain, Steric Strain or Van der Waals strain and Torsional Strain.

6.7.1. Bond angle strain :

The deviation of bond angle from the normal value of the tetrahedral angle (109°28') causes strain within the ring which, in turn, brings instability to the ring. The deviation in bond angle is caused by the electrostatic repulsion of the electrons in the bonds. The energy required to deviate the bond angle from the normal value is known as bond angle strain.



The deviation or distortion in the bond angle (α) can be calculated from:

$$\alpha = \frac{1}{2}\ (109°28' - \text{actual bond angle})$$

or in the generalized form it can be represented as:

$$\alpha = \frac{1}{2}\left[109°28' - \frac{2\,(n-2)}{2} \times 90\right]$$

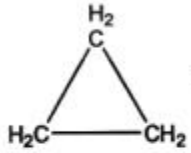
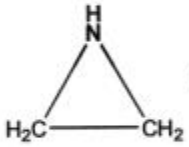
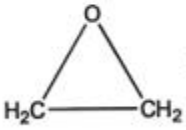
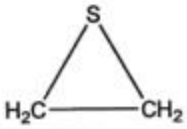
Where n is the number of members in the rings.

The deviation of bond angles is maximum in the three-membered rings and decreases with increasing ring size (minimum with five-membered rings). Bond angle strain is particularly significant in the small rings (three-and four-membered), while less significant or negligible in the five-and six-membered rings.

Bond Angle Strain In Small Ring Heterocycles

The replacement of a $–CH_2$ group in the small ring cycloalkanes by a heteroatom leads to the saturated small ring heterocycles and causes changes in the structural parameters. The carbon-heteroatom bond distances are often appreciably different from the carbon-carbon bond distance. Thus, carbon-oxygen bond (1.436A0) and carbonnitrogen bond (1.475A) are shorter than the carbon-carbon bond (1.54A0). The variation in the bond angles is less important for oxygen and nitrogen, but C-S-C bond angle is substantially different. In the small ring heterocycles (three-and four-membered), bond angle strain is large and the ring strain is mostly due to the bond angle deviation. The ring strain in three-and four-membered heterocycles is approximately of the same magnitude and depends on the nature of the heteroatom than on the size of the ring (cyclopropane=115 kJ/mol; cyclobutane=112 kJ/mol). The introduction of un-saturation in the small ring heterocycles further increases angle strain. Some molecular dimensions in the saturated three-membered rings with their strain energies are summarized in following Table:

Table: Molecular dimensions of saturated three-membered rings and their strain energies

Compound	Cyclic compound			Acyclic analog		Strain
	C–C (Å)	C–X (Å)	C–X–C	C–C (Å)	C–X (Å)	kJ/mol
	1.510	1.510	60°	1.54	–	115
	1.481	1.475	60°	1.54	1.470	113
	1.472	1.436	61°	1.54	1.430	114
	1.49	1.820	48.5°	1.54	1.810	83

Consequences Of Bond Angle Strain:

Bond angle strain in small ring heterocycles accounts for their chemical reactivity and, therefore, small ring heterocycles undergo ring opening reactions more readily than the normal rings. The effect of bond angle strain can be visualized well in their structures.

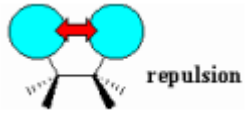
Bond angle strain of three membered heterocyclic compounds renders the molecule unstable and highly reactive due to the large amount of potential energy stored in the molecule. Three membered heterocyclic compounds, when burned, releases substantially more energy than when aliphatic counterpart is burned. The higher heat of combustion of three membered heterocyclic compounds is due to the angle strain.

Four membered heterocyclic compounds have less angle strain than three membered heterocyclic compounds (only 19.5°). It is also believed to have some bent-bond character associated with the carbon-carbon bonds. The molecule exists in a non-planar conformation in order to minimize hydrogen-hydrogen eclipsing strain. The medium-size rings (7 to 12 ring atoms) are relatively free

of angle strain and can easily take a variety of spatial arrangements. They are not large enough to avoid all non-bonded interactions between atoms.

6.7.2.Steric Strain:

Steric strain results from the electron-electron repulsion of atoms (or groups of atoms) that is too close together. It is also known as Van der Waals strain or repulsion. Steric strain stores potential energy in a molecule by forcing repelling groups together. Destabilization due to the repulsion between the electron clouds of atoms or groups. This occurs when atoms or groups are too close to each other due to the electrostatic repulsion of the electrons.



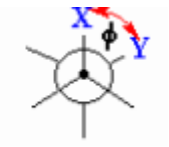
An example of a molecule that exerts steric strain is discussed below.

Example: 1, 3-diaxial repulsions of cyclohexane.

Cyclohexane in its chair conformation has equatorial and axial positions. In substituted cyclohexanes, such as methylcyclohexane, the substituent will encounter steric repulsions when it is in the axial position. These steric repulsions are termed 1,3-diaxial repulsions because they involve axially oriented groups in the 1 and 3 positions.

The close approaches of the methyl group (1) and the two axially upward hydrogens (2) when the methyl group is axial. It is these steric repulsions that cause the axial conformation of methyl cyclohexane to be higher in energy than the equatorial conformation. This conformation of the molecule is referred to as the s–cis conformation. In this conformation, the hydrogens (labeled 1 and 3 in the diagram below) are in close proximity. Therefore, they have steric repulsions. Because of steric repulsion, the preferred conformation of 1, 3-butadiene is the s-trans form. It shows the s-trans conformation in which the repelling hydrogen (1 and 3) are far apart. Third type of strain is called torsional strain.

6.7.3 Torsional Strain



Torsional strain is the resistance to bond twisting. In cyclic molecules, it is also called Pitzer strain. It occurs when atoms separated by three bonds are placed in an eclipsed conformation instead of the more stable staggered conformation. It occurs due to repulsion between pairs of bonds caused by the electrostatic repulsion of the electrons in the bonds. It occurs when atoms separated by three bonds are placed in an eclipsed conformation or staggered conformation. Angle between C-X and C-Y bonds in X-C-C-Y system. Also known as a dihedral angle. The barrier of rotation between staggered conformations of ethane is approximately 2.9 kcal/mol. It was initially believed that the barrier to rotation was due to steric interactions between vicinal hydrogens, but the Van der Waals radius of hydrogen is too small for this to be the case. Recent research has shown that the staggered conformation may be more stable due to a hyperconjugative effect. Rotation away from the staggered conformation interrupts this stabilizing force. More complex molecules, such as butane, have more than one possible staggered conformation. The anti conformation of butane is approximately 0.9 kcal/mol (3.8 kJ/mol) more stable than the gauche conformation. Both of these staggered conformations are much more stable than the eclipsed conformations. Instead of a hyperconjugative effect, such as that in ethane, the strain energy in butane is due to both steric interactions between methyl groups and angle strain caused by these interactions. In the conformation of butane, the torsional strain is minimized because the biggest groups are farthest apart from one another. Now let's analyze the torsional strain when the conformation is gauche. Notice that in the gauche conformation, the methyl groups are very close together. The following diagram shows butane in the eclipsed conformation. The eclipsed conformation has a very high energy because of the high amount of torsional strain because the methyl groups are in close proximity.

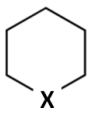
Consequences Of Torsional Strain:

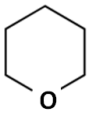
Bond Angle and Torsional Strain in Small Ring Heterocycles: Cyclohexane is considered a benchmark in determining ring strain in cycloalkanes and it is commonly accepted that there is little to no strain energy. In comparison, smaller cycloalkanes are much higher in energy due to increased strain. Cyclopropane is analogous to a triangle and thus has bond angles of 60°, much lower than the preferred 109.5° of a sp3 hybridized carbon. Furthermore, the hydrogens in cyclopropane are eclipsed. Cyclobutane experiences similar strain, with bond angles of approximately 88° (it isn't completely planar) and eclipsed hydrogens. The strain energy of cyclopropane and cyclobutane are 27.5 and 26.3 kcal/mol, respectively. Cyclopentane experiences much less strain mainly due to

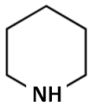
torsional strain from eclipsed hydrogens and have a strain energy of 6.2 kcal/mol. Three-membered heterocyclic compounds display a higher reactivity in comparison to the corresponding open-chain compounds. The higher reactivity arises from the noticeably strong ring strain. The strong ring strain can be attributed to two causes. Three-membered ring's geometry causes particularly small bond angles in the ring. In cyclopropane, for instance, each carbon is connected to four other atoms, namely two carbons and two hydrogens. Therefore, from an energetical point of view, sp3 hybridization and thus, a tetrahedral arrangement of the four atoms surrounding each carbon would be the most suitable for each ring carbon. In this case, the carbon-carbon bond angles in the ring would amount to 109.5°. However, due to the three-membered ring's geometry, each bond angle in the ring actually only amounts to 60°. As a result, the carbons are not precisely sp3 -hybridized. If this would be the case, the cyclopropane ring would not exist, as the orbital overlappings would be too small to allow the formation of stable carbon-carbon bonds. The orbitals are rather deformed in comparison to sp3 orbitals (banana bonds). On the other hand, as a result of the three-membered ring's geometry and the strongly restricted rotation of the ring bonds, the hydrogens of cyclopropane are forced into an eclipsed conformation. That is, the torsion angle of the hydrogens at adjacent carbons is nearly 0°. In the corresponding open-chain compound, bond rotation is hardly restricted. Thus, the open-chain compound can easily attain a staggered conformation. The eclipsed conformation that resulted in the three-membered ring causes additional steric interactions, which destabilize the ring. This destabilizing effect is known as torsional strain. The strength of torsional strain depends on the size, or steric demand, and on the number of substituents. Cyclopropane's torsional strain, for instance, is stronger than that of ethylene oxide (oxirane, 1,2-epoxyethane), as cyclopropane contains six hydrogens, while ethylene oxide possesses only four hydrogens.

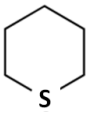
6.8 CONFORMATIONS OF SIX-MEMBERED HETEROCYCLES:

The difference in the ring of cyclohexane and **six-membered heterocycles** is carbon and hetero-atoms. The replacement of carbon with hetero-atom from cyclohexane ring results six-membered heterocycles which can alter the structural parameters and conformational characteristics of the ring because of the greater electronic interactions due to lone pair of electrons on hetero-atom. Like cyclohexane rings, six- membered heterocycles are characterized by the presence of various non-planar conformations: ***chair, boat*** and ***twist boat conformations.***









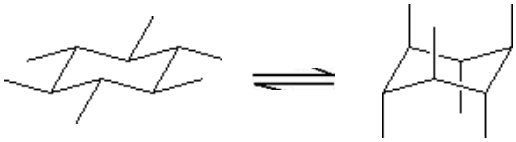
Six-membered heterocycles (X = NH or P or Si or O, *etc.*) **Tetrahydropyran Piperidine Thiane**

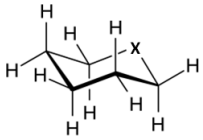
Like cyclohexane rings, **chair conformation** of six-membered heterocycles is more stable than ***boat*** and ***twist conformations*** because of its lowest energy. In chair conformation, the bonds/bond and lone pairs are equally axial and equatorial, i.e., out of total twelve bonds and lone pairs, six are axial and six are equatorial and each atom (carbon or hetero-atom) has one axial and one equatorial bond or lone pair. The chair conformation exits in two isomeric forms, ***axial*** and **equatorial conformations**.

Axial conformation **Equatorial conformation**

Conformations in six-membered Heterocycles (X = NH or P or Si or O, *etc.*)

In cyclohexane rings, there are six axial and six equatorial bonds while in six-membered





heterocycles one or two axial or equatorial bonds are replaced by lone pair of electrons (except with Si hetero-atom).

Axial bonds **Equatorial bonds** **Axial and equatorial bonds in tetrahydropyran (X = Hetero-atoms) Chair conformation in cyclohexane ring**

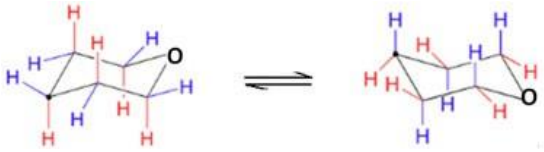
The hetero-atom and their lone pair of electrons distort the bond lengths and bond angles in conformational geometry from their analogs of cyclohexane ring. The axial-equatorial equilibria are however strongly affected by the replacement of a methylene by O or NH. For example the chair conformation of tetrahydropyran and piperidine are expected to be slightly more puckered

than that of cyclohexane ring. This is due to shorter C-O (1.43 A^o) and C-N (1.47 A^o) bonds than the C-C bond (1.54 A^o) length. On the other hand, the chair conformation of thiane is expected to be slightly less puckered than that of cyclohexane ring due to longer C-S (1.82 A^o) bond than the C-C bond. The normal valence angles are somewhat smaller than tetrahedral at oxygen and nitrogen and significantly so for sulphur, for which the normal C-S-C angle is about 100 A^0.

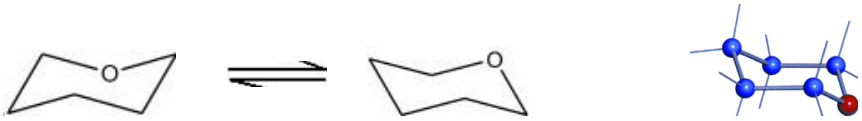
Examples:

(i) Tetrahydropyran:

The axial form of **tetrahydropyran** has been found to be the more stable than equatorial. Of the two lone pairs, one can be axial and one equatorial in both conformations. This is due to energy barrier the ring flipping.



Chair conformations in tetrahydropyran

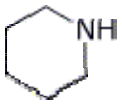


Axial form of tetrahydropyran

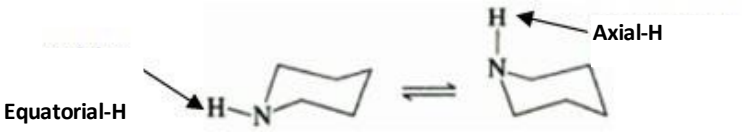
The energy barrier the ring flipping of **tetrahydropyran** is about 10 kcal/mol and the free energy of activation for ring inversion was calculated to be 42.4 kJ mol^{-1} (at 212 K). This value is quite similar to cyclohexane (43.1 kJ mol^{-1}) but lower than that of **piperidine** (46.2 kJ mol^{-1}).

(ii) Piperidine:

The hydrogen attached to nitrogen in **piperidine** can be either axial or equatorial and both chair conformations are approximately equal in stability.



Piperidine also prefers a chair conformation, similar to cyclohexane. Unlike cyclohexane, **piperidine** has two distinguishable chair conformations: one with the N–H bond in an axial position and the other in an equatorial position. The equatorial conformation was found to be more stable by 0.72 kcal/mol in the gas phase. In non-polar solvents, a range between 0.2 and 0.6 kcal/mol has been estimated, but in polar solvents the axial form may be more stable.



Chair conformations in piperidine

The two conformations interconvert rapidly through nitrogen inversion. The estimated free energy activation barrier for this process is 6.1 kcal/mol, which is substantially lower than the

10.4 kcal/mol for ring inversion. In the case of *N*-methylpiperidine, the equatorial conformation is preferred by 3.16 kcal/mol, which is much larger than the preference in methylcyclohexane,

1.74 kcal/mol.

Conformational Free Energy:

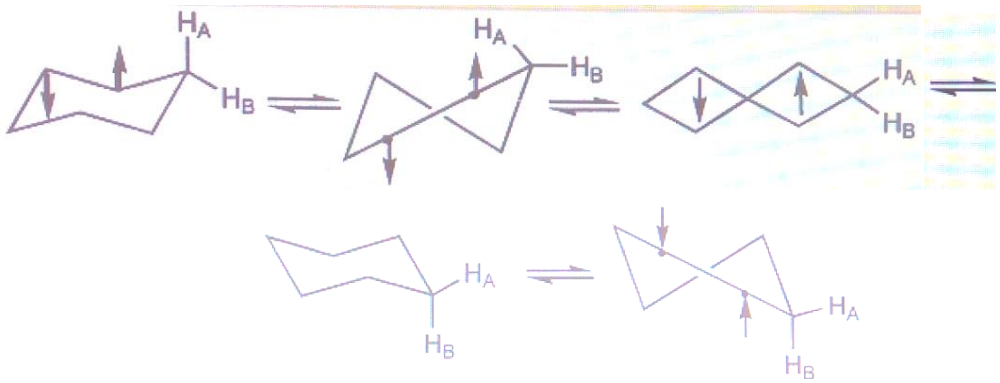
Conformational free energy (ΔG^0) provides valuable information on the relative stability of the conformers. The direct integration of resonance from both inter-convertible conformers in slow exchange NMR-spectrum gives equilibrium constant K_c, from which ΔG^0 can be calculated:

$$\Delta G^0 = -RT \ln K_c$$

ΔG^0 is usually negative and represents the free energy difference between equatorial and axial conformers.

6.9BARRIER TO RING INVERSION:

Six axial and six equatorial hydrogens of cyclohexane are not same. At low temperature, the rate of the ring inversion is decreased with the non-equilent hydrogens and the ring inversion is accompanied with the interchange of 1,3,5 and 2,4,6-carbon planes leading to the inverted chair conformation. Bond angle deformation in the chair form is accompanied by the increased torsional energy and leads to the transition state (boat form) with high energy (42-43 kJ/mol). The transition state is then changed into twist-boat conformation which without angle strain but with some torsional strain and corresponds to the energy of 23kJ/mol. The twist-boat conformation is converted to the inverted chair conformation.



Ring Inversion in cyclohexane

Similarly in six-membered heterocycles the process of chair-chair ring inversion coverts the ring to its mirror and interchanges the axial or equatorial nature of all the substituent. The barrier to ring inversion can be determined by examining NMR-spectrum as a function of temperature.

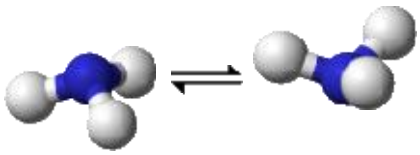
Ring Inversion in six-membered heterocycles (X = hetero-atom)

The transition state of chair-chair ring is generally considered to be the half chair conformation in which four ring atoms are coplanar. Six-membered heterocycles with one hetero-atom have the choice of three such conformations depending on the energy barriers. The increased energy barrier in the transition state is attributed to the increased torsional interaction and the bond angle strain. The torsional energy barrier of C-X bond (X = hetero-atom) is different from the C-C bond. Therefore, the energy of ring inversion in six-membered heterocycles will be different from that in cyclohexane ring. The barriers to ring inversion depend directly on the magnitude of the carbon-heteroatom torsional strain.

6.10.PYRAMIDAL INVERSION AT NITROGEN :

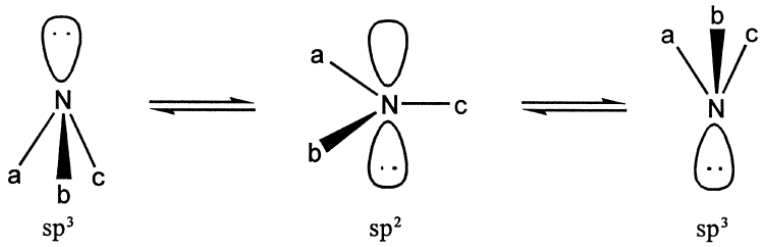
Pyramidal inversion is a property of nitrogen which distinguishes it from the tetravalent carbon. It occurs when the lone pair on nitrogen oscillates from one side of the plane of the three atoms attached to it to the other side of that plane. The substituents and hydrogen attached to nitrogen invert like an umbrella.

Lone pair is constantly moving from one side of the nitrogen atom to the other side and it goes through a transition state. The ammonia inter-conversion is rapid at room temperature. Two factors contribute to the rapidity of the inversion: a low energy barrier (24.2 kJ/mol) and a narrow width of the barrier itself, which allows for frequent quantum tunnelling.



Nitrogen inversion in ammonia

In amine, hydrogens and the substituents are in one planar and the lone pair is in a p orbital.



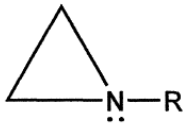
Pyramidal inversion in unstrained acyclic compound

The rate of atomic inversion is affected by the size of the ring in which nitrogen is inserted and the substituent(s) attached to nitrogen. But when nitrogen atom is involved in three-membered ring i.e. aziridine, the conformational changes arise mainly from the pyramidal inversion of nitrogen because the aziridine ring is planar and rigid. The pyramidal inversion in aziridine is reduced because of much higher energy barrier in aziridine (ΔG^* = 72.0 kJ/mol) as compared to the energy barrier in acyclic unstrained compounds which have very low energy barrier (NH_3 = 24-25 kJ/mol and $(CH_3)_3N$ = 34.4 kJ/mol). The relatively high energy barrier in aziridine is attributed to the highly strained transition state involving sp2-hybrldized nitrogen (for which nonnal valence angle is 120°) constrained to the angle of approximately 60°.

The energy barrier to pyramidal inversion in aziridines depends on the nature of the substituent attached to the nitrogen atom:

(i) Electron delocalizing substituents on small ring nitrogen lower the inversion barrier by lowering the energy of the transitonal 'flat' geometry in which three substituents of nitrogen are in the same plane (with acyl, aryl or carboalkoxy-energy barrier reduced).

(ii) The substituents bearing unshared electron pairs (NH_2, CI, OCR_3) increase the energy barrier considerably and the enantiomers can be isolated. The increased energy barrier is probably due to the unfavourable lone pair-lone pair interactions in the planar transition state.



6	R = C_2H_5	81.0 kJ/mol.
7	R = $C(CH_3)_3$	71.0 kJ/mol.
8	R = C_6H_5	49.0 kJ/mol.
9	R = $CON(CH_3)_2$	41.0 kJ/mol.
10	R = $COOCH_3$	30.0 kJ/mol.
11	R = NH_2, Cl, OCH_3	90.0 kJ/mol.

Energy barriers to N-inversion in different substituted aziridines

(iii) Sterle effect destabilizes pyramidal fonn and lowers the energy barrier.

(iv) The solvents which stabilize ground state confonner through the hydrogen bonding or by solvation raise the energy barrier. There are two circumstances in which a nitrogen atom cannot invert and therefore might be a stereocenter.

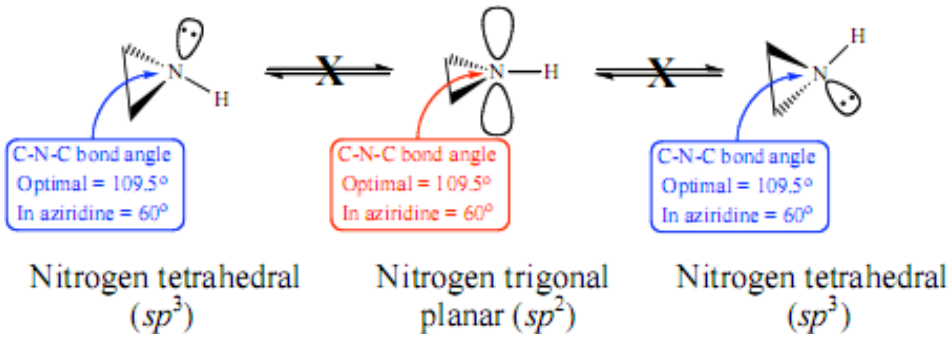
When the amine nitrogen is not part of a ring, this bond angle change is easily accommodated. However, if the nitrogen atom is part of a three-membered ring (called an aziridine) or a four-membered ring (called an azetidine) inversion is significantly retarded by strain.

Aziridine Azetidine Pyrrolidine Piperidine

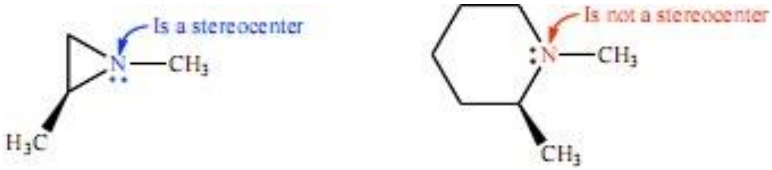
Strain prevents nitrogen inversion. *Nitrogen inversion occurs.*

For example in an aziridine, before inversion the nitrogen atom already experiences significant angle strain (109.5^0 optimal tetrahedral C–N–C bond angle versus the 60^0 actual bond angle in

the ring). The strain is at its worst when in the planar intermediate structure: 120^0 optimal trigonal planar C–N–C bond angles versus 60^o actual bond angle in the ring). The increase in strain makes it too difficult for the inversion to occur and the aziridine nitrogen atom can be a stereocenter.

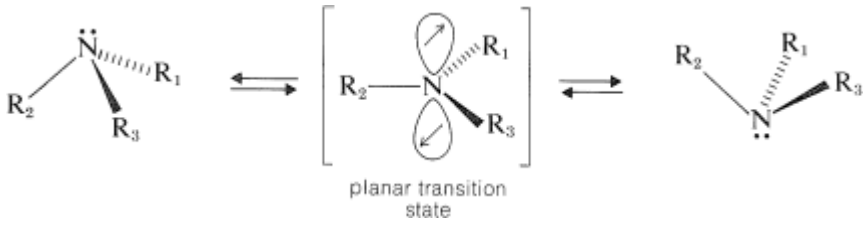


The situation is similar (although somewhat less severe) in an azetidine. In larger rings, such as a pyrrolidine ring or a piperidine ring, the strain increase required for inversion is less. Inversion can occur, and these nitrogens are not stereocenters.

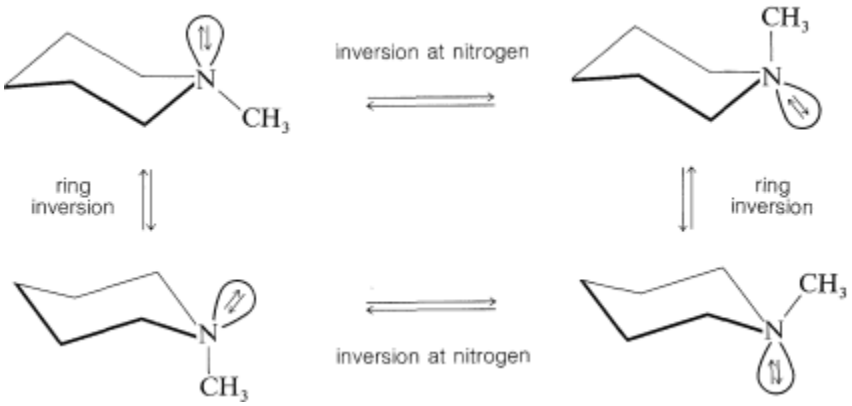


Aziridine and azetidine rings are not the only cases in which strain may prevent nitrogen inversion. Evaluate each case individually, and make a judgment call. For example, quinuclidine is a case in which the nitrogen atom is in a six-membered ring, but cannot invert due to the impossible geometry that would result.

The resolution of an acyclic chiral amine into its separate enantiomers has not been achieved yet, and it appears that the enantiomers are very rapidly interconverted by an inversion process involving a planar transition state:

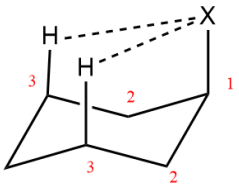


The stereochemistry of azacyclohexanes is complicated by the fact that there is a conformational change in the ring as well as inversion at the pyramidal nitrogen. Therefore it is difficult to say whether the axial- equatorial equilibrium of, for example, 1-methylazacyclohexane is achieved by ring inversion, or by nitrogen inversion, or both:



6.11. 1, 3-DIAXIAL INTERACTION:

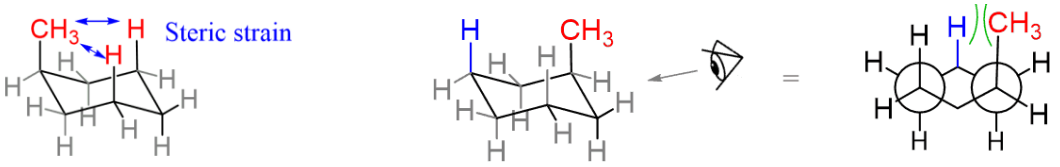
1,**3-diaxial interaction** is the syn-axial **interaction** (the steric interactions), usually repulsive, between paired electrons that occur between axial substituents in the axial chair form of six-membered homocycles (cyclohexane and their derivatives) and heterocycles.



(X = axial substituent)

1,3 Diaxial Interactions In Six Membered Homocycles :

1,3-Diaxial interactions are steric interactions between an axial substituent located on carbon atom **1** of a cyclohexane ring and the hydrogen atoms (or other substituents) located on carbon atoms **3** and **5**. For example, in the axial form of methylcyclohexane, the methyl group is above or below the planar cyclohexane ring. This is referred to as the **axial** position. The methyl group then interacts with the other two hydrogens also in the axial positions and facing the same direction. The molecular orbitals of these groups interfere with one another, making this conformation high in energy and unfavorable.



1,3-Diaxial interaction in methylcyclohexane

1,3 Diaxial Interactions In Six Membered Hetrocycles :

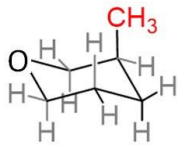
1,3-diaxial interaction in are increased in six membered hetrocycles due to shorter bond length than in cyclohexane ring. It is due to increased puchering of chair conformation in six membered hetrocycles. For example the shorter bond length causes larger **1,3-diaxial interaction** in 2-methyl tetrahydropyran and 2-methyl-1,3-dioxane than in methylcyclohexane.

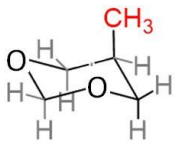
2-Methyl tetrahydropyran 2-methyl-1,3-dioxane

1,3-diaxial interactions

However, 1,3-diaxial interactions are considerably reduced when hydrogen is replaced by a

lone pair of electrons. It is due to smaller size of lone pair than hydrogen. For example **1,3-diaxial interaction** in 3- methyl tetrahydropyran is smaller than 2-methyl tetrahydropyran. Similarly, **1,3-diaxial interaction** in 5- methyl-1,3-dioxane is smaller than 2-methyl-1,3-dioxane.





3-Methyl tetrahydropyran **5-methyl-1,3-dioxane**

1,3-diaxial interactions

6.12 SUMMARY:

By going through this unit you must have achieved the objectives laid down at the start of the unit. As we know the heterocyclic compounds are the important category of chemical compounds found in living and non living systems. It is necessary to identify the structure, function and reactivity in order to decide the role and functioning of heterocyclic compounds. Present unit which discuss thoroughly the introductory concept and nomenclature of heterocyclic compounds will help you to gain the basic knowledge.

6.13 REFERENCES :

1. "Heterocyclic Chemistry" (3rd Edition) by Thomas. L. Gilchrist, Prentice Hall Publication, ISBN 978-0-5822-7843-1.

2. "Organic Chemistry" Vol. 1 by I L Finar, Published by Pearson Education; ISBN 10: 8177585428.

6.14TERMINAL QUESTIONS :

Short Answer Type Questions:

1. Write a note on strain bond angle in small ring heterocycles.

2. Write a note on Hantzns MCH-Widman system.
3. Describe aromaticity in heterocyclic compounds.
4. Discuss tautomerism in heterocyclic compounds.
5. What are the concequences of bond angle strain in small ring heterocycles.

Long Answer Type Questions :

1. Write down the systematic nomenclature of heterocyclic compounds.
2. Discuss the classification of six member heterocycle.
3. Describe barrier to ring inversion and pyramidal inversion.
4. Explain conformation of six membered heterocyclic compounds.

UNIT 7: HETEROCYCLIC SYNTHESIS

CONTENTS:

7.1 Introduction

7.2 Objective

7.3 Three membered heterocycles

7.4 Aziridines

7.4.1Methods of Preparation

7.4.2 Physical Properties

7.4.3 Chemical Reactions

7.5. Oxiranes

7.5.1Methods of Preparation

7.5.2 Physical Properties

7.5.3 Chemical Reactions

7.6. Thiiranes

7.6.1Methods of Preparation

7.6.2 Physical Properties

7.6.3 Chemical Reactions

7.7. Azetidines

7.7.1Methods of Preparation

7.7.2 Physical Properties

7.7.3 Chemical Reactions

7.8. Oxetanes

7.8.1 Methods of Preparation

7.8.2 Physical Properties

7.8.3 Chemical Reactions

7.9 Thietanes

7.9.1 Methods of Preparation

7.9.2 Physical Properties

7.9.3 Chemical Reactions

7.10. Benzo-fused five-membered heterocycles with one heteroatom

7.10.1 General

7.10.2 Reactivity

7.10.3 Orientation

7.11.Benzopyrroles (Indoles)

7.11.1 General

7.11.2 Synthesis

7.11.3 Structure

7.11.4Reactions

7.12. Benzofurans

7.12.1General

7.12.2 Synthesis

7.12.3Structure

7.12.4Reactions

7.13 Benzothiophenes

7.13.1General

7.13.2 Synthesis

7.13.3Structure

7.13.4Reaction

7.14 Summary

7.15 References

7.16. Terminal questions

7.1 INTRODUCTION

The properties of three-membered heterocycles are mostly a result of the high angle strain. The resultant ring strain is responsible forhigh chemical reactivity these compounds. Ring opening leads to the formation of acyclic products.

7.2.OBJECTIVE

The study of hetrocyclic compounds is of great interest in the theoretical as well aspractical point of view. Heterocyclic compounds occur in nature as well asnon-naturally occurring compounds. Knowledge of hetrocyclic chemistry is very usefulin biosynthesis and metabolism of drugs.

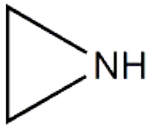
The study of benzo fused hetrocyclic compounds is of great interestbecause most of these compounds are medicinally and commercially very important. These compounds widely present in plants and animals and play important role in their biochemistry. Knowledge of benzo fused hetrocyclic compoundswill be helpful for students to understand biosynthesis and metabolism of drug.

7.3.THREE MEMBERED HETEROCYCLES

Simple examples of three membered heterocycles are aziridine, oxirane and thirane containing nitrogen, oxygen and sulphur as the hetero atoms,respectively.

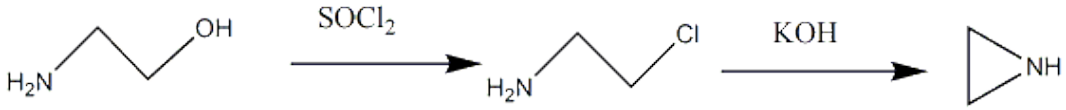
7.4AZIRIDINES

Aziridine is also known as ethylene imine. The plane in which the N-atom, itsnonbonding electron pair and the N-H bond are situated is perpendicular to the plane of
the aziridine ring.

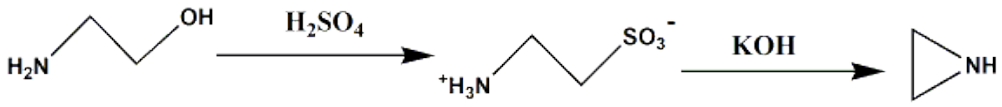


7.4.1 Methods of Preparation

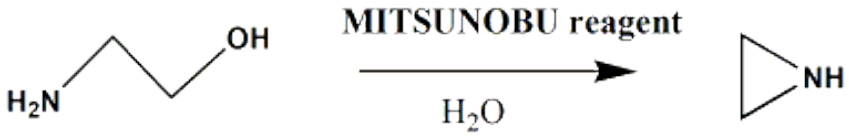
(i) Cyclization of β-substituted amines (Gabriel Method):β-Amino alcohols react with thionyl chloride to give chloramines. This on treatment with alkali getcyclized to produce aziridines.



(ii) Sulfate esterswhen treated with alkali also form aziridines.Sulfate estersobtained by the reaction of amino alcohols and sulfuric acid.

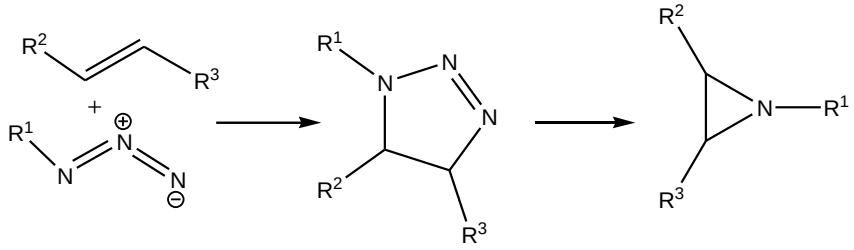


(iii)



MITSUNOBU reagent = Triphenylphosphine and diethyl azodicarboxylate

(iv)Thermal or photochemical reaction of azides with alkenes: Phenyl azide reacts with alkenes to produce 4,5-dihydro-l,2,3-triazoles (1,3-dipolar cycloaddition) which are thermally or photochemically converted into aziridines through loss of nitrogen:

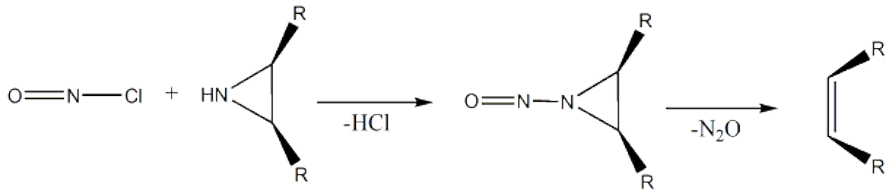


7.4.2 Physical Properties

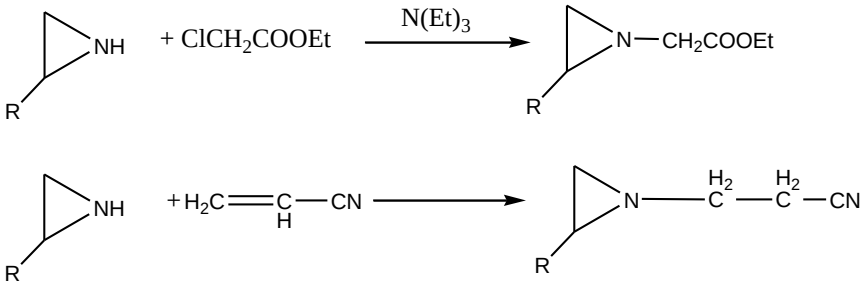
Aziridine is a colourless**,** water-soluble, poisonous liquid which have 57°C boiling point.

7.4.3 Chemical Reactions

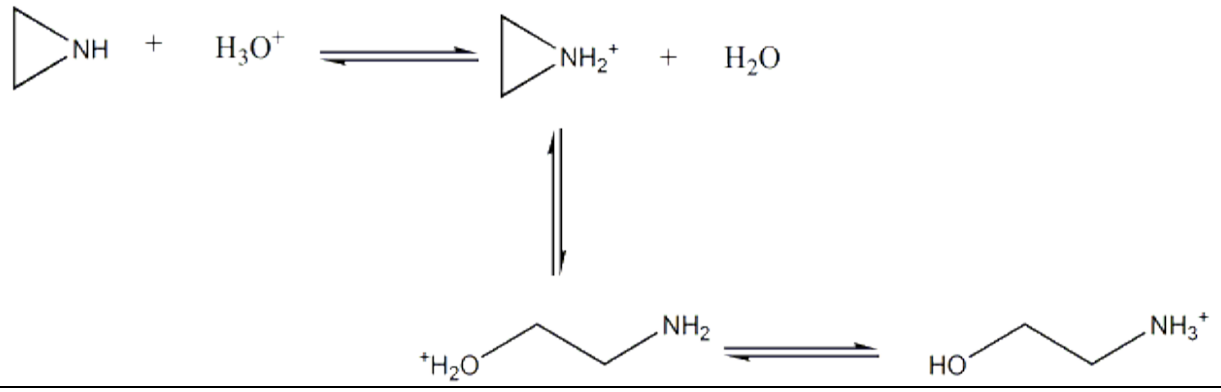
(i) Deamination to alkenes: Aziridine on treatment with nitrosyl chloride gives N-nitrosoaziridine.



(ii)Reactions with electrophilic reagents: Electrophilic substitution will take place at nitrogen by alpha haloesters or alkenes.

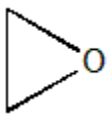


(iii) Ring opening reaction of aziridines: The ring-opening of the aziridines is catalysed especially and effectively by acids. The acid catalysedhydrolysis gives amino alcohols.



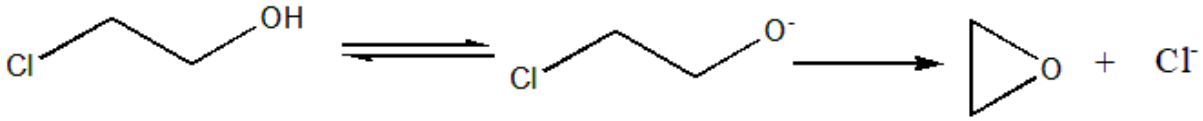
7.5 OXIRANES

Oxiranes are also known as epoxides.Ethylene oxide is an organic compound with the formula C_2H_4O. It is a cyclic ether and the simplest epoxide.It's a three-membered ring consisting of one oxygen atom and two carbon atoms. It is important as an intermediate in the petrochemical industry.Ethylene oxide is isomeric with acetaldehyde and with vinyl alcohol.

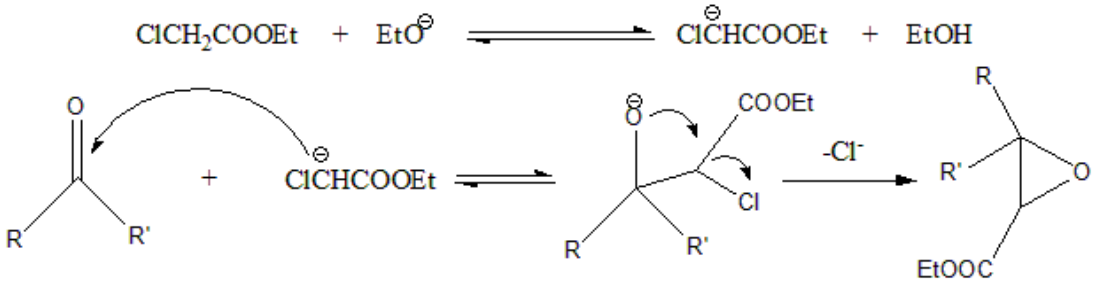


7.5.1 Methods of Preparation: On industrial scale it is produced by direct air oxidation of ethene in the presence of a silver catalyst.

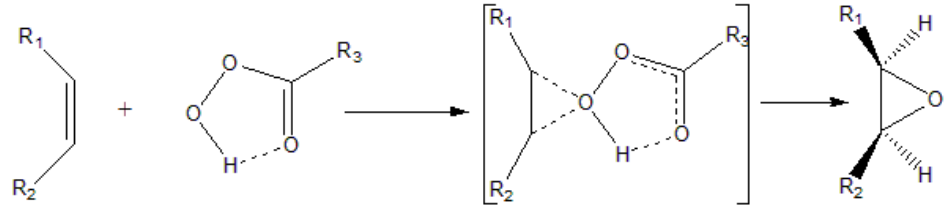
(i) Cyclodehydrohalogenation of β-halo alcohols: The reaction of β-halo alcohols with alcoholic KOH leads to produce oxiranes.



(ii) Darzens reaction: α-Halo esters on treatment with carbonyl compounds in the presence of sodium ethoxide produces 2-(ethoxycarbonyl) oxiranes.



(iii) Epoxidation of alkenes: Peroxyacids react with alkenes to give oxiranes. This reaction is a stereospecific reaction i.e. cis-alkene give cis- oxiranes and trans-alkene give transoxiranes.



Peroxyacidsmay be peroxybenzoic acid, *m*-chloroperoxybenzoic acid ormonoperoxyphthalic.

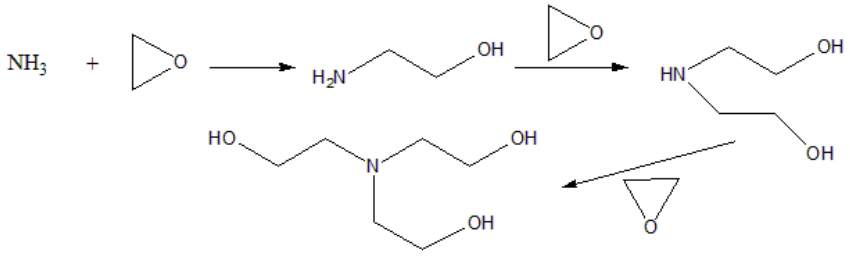
7.5.2 Physical Properties

Oxirane iscolourless,water-soluble,b.p. 10.5°C,extremely poisonousand flammable gas with a faintly sweet odour.

7.5.3 Chemical Reactions

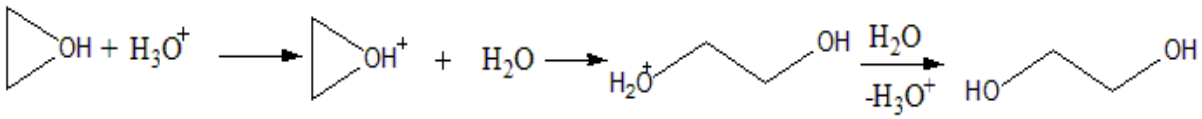
It is a strained ring, so it easily participates in a number of addition reactions that results in ring-opening reactions.

(i) Ring-opening by nucleophiles: (a) When nucleophiles like ammonia or amines react with oxiranes, ring of oxiranes open to produce amino alcohols.

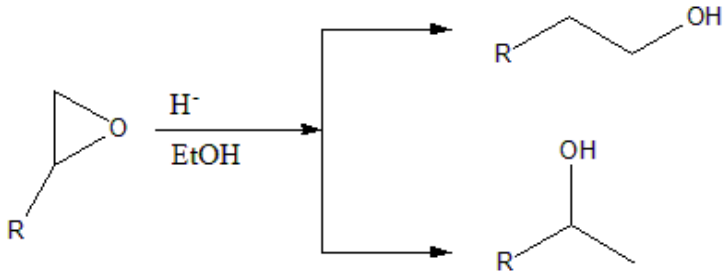


triethanolamine

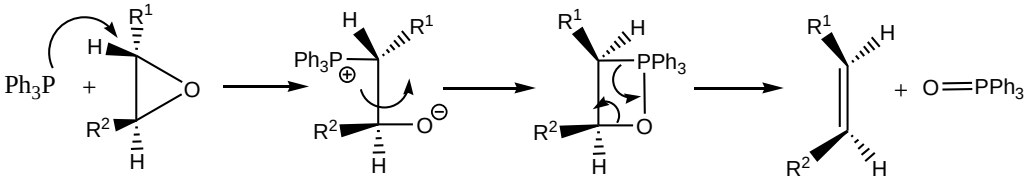
(b) The ring-opening of the oxiranes is catalysed by acids. The acid-catalysed hydrolysis gives 1,2-diols.



(c)Ring opening by hydride ion: Oxiranes are reduced by sodium borohydride to give alcohols. This reaction is a ring-opening by the nucleophilic hydride ion.

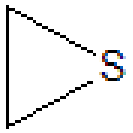


(ii) **Deoxygenation to olefins:** A number of reagents deoxygenate oxiranes to produce olefins. For instance, a transoxiraneyields a *z*-olefin on treatment with triphenylphosphane at 200°C.



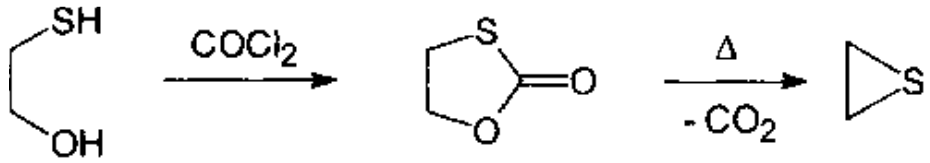
7.6 THIIRANES

Thiirane, more commonly known as ethylene sulfide, is the cyclic chemical compound with the formula C_2H_4S.Sulfur containing three membered saturated heterocycles are thiiranes. This compound is also known as thiacyclopropanes orepisulfides. Thiiranes is the smallest sulfur-containing heterocycle and the simplest episulfide.



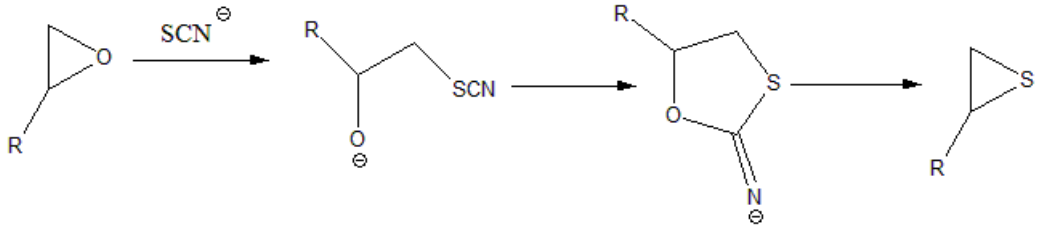
7.6.1 Methods of Preparation

(i) cyclization of β substituted thioles: The product obtained by the reaction of β-hydroxythiol and phosgene when heated it produces thiirane.



(ii) From Oxiranes

This is the most widely used method. In this reaction oxirane is treated with thiocyanate ion.The obtained product on heating produces thiirane and cyanate ion.



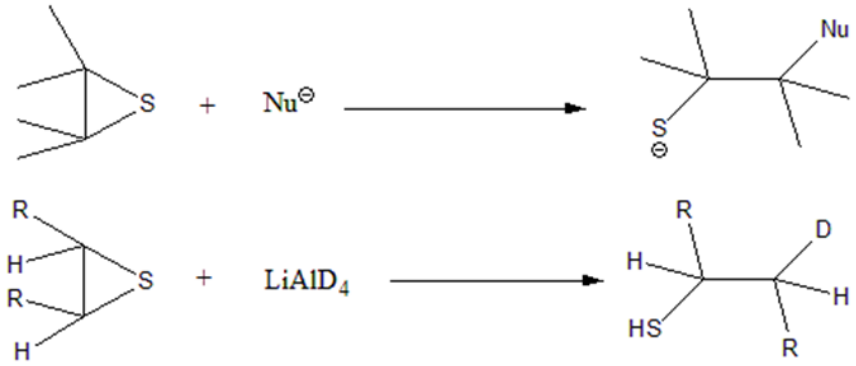
7.6.2 Physical Properties

Like other organosulfur compounds, these compounds have a highly unpleasant odour. It is colourless liquid, sparingly soluble in water and its boiling point is 55°C.

7.6.3 Chemical Reactions

(i) Nucleophilic Ring Opening Reactions

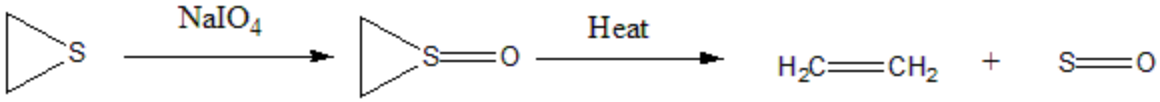
These reactions are stereospecific, so there is inversion of configuration at the site of attack. In this reaction incoming nucleophiles attack from opposite side of the heteroatom (sulfur atom).



In asymmetrically substituted thiiranes, the nucleophilic attacks at the lesssubstituted carbon atom from the opposite side of the heteroatom.

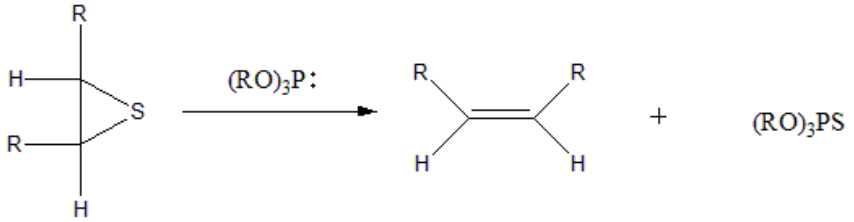
(ii) Oxidation

Thiiranes are oxidized by sodium periodate or peroxy acids and thiirane oxides is obtained which decompose at higher temperature into alkenes and sulfur monoxide.



(iii) Desulfurization to alkenes

The reaction of thiiranes with tertiary phosphines, thiirane gives the corresponding alkenes.



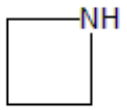
Four membered heterocycles

Four membered heterocycles are the analogues of cyclobutene. These are derived by replacing a $–CH_2$ group by a heteroatom (N, O or S). The four membered saturated heterocycles

having any one of nitrogen,oxygen and sulphur atoms are known as azitidines, oxetanes and thietanes, respectively.

7.7AZETIDINES

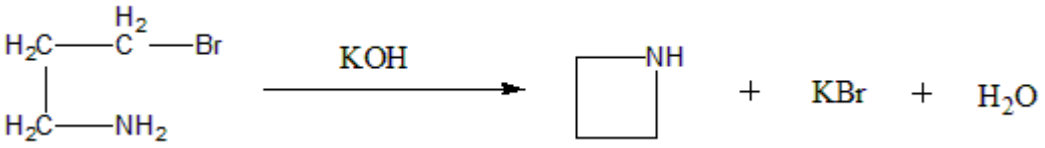
Azetidines are thermally stable and also these are less reactive than aziridines. Reactionsof azetidines are almost similar to secondary alkylamines. The azetidine is (*p*K*a*value of 11.29) more basic than aziridine *(p*K*a* = 7.98) and even more than dimethylamine *(pKa* = 10.73).



7.7.1 Methods of Preparation

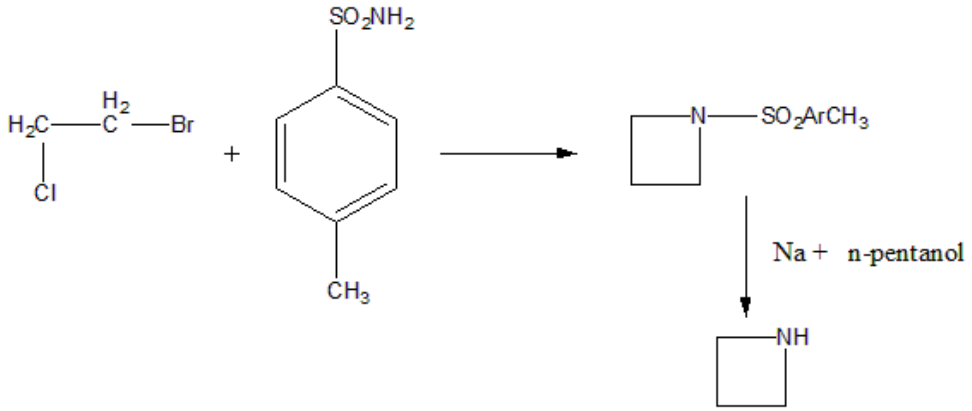
(i) Intramolecular Cyclization

3-Halogen substituted amines are dehydrohalogenated by bases and gives azetidines.



(ii) Action of *p*-toluenesulfonamide and bases on 1,3-dihaloalkanes

Azetidinesare prepared by the cycloaddition of trimethylene chlorobromide with *p*-toluenesulfonamide. The obtained product is further reduced by sodium and *n*-pentanol to give azetidines.



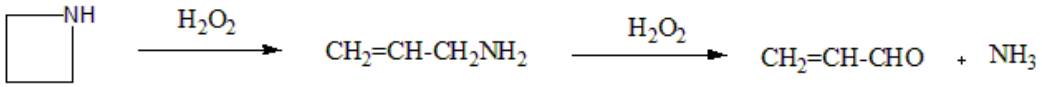
7.7.2 Physical Properties

Azetidine is awatermiscible,colourless liquid of boiling point 61.5°C and it have smell like ammonia.

7.7.3 Chemical Reactions

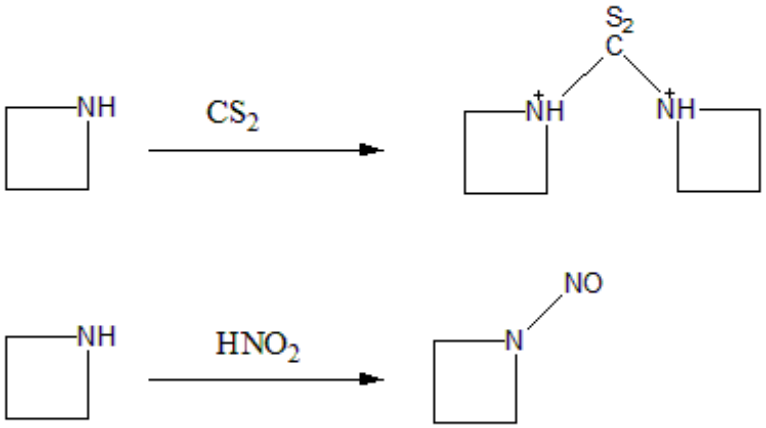
(i) Nucleophilic ring opening

Azitidines show lesser degree of reactivity towards nucleophilic ring opening reactions than aziridines.Azitidines are quite resistant for bases and nucleophiles. However,H_2O_2 cleaves the ring and gives acrolein and ammonia.



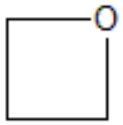
(ii) Fictionalization at nitrogen

Azitidineare similar secondary aliphatic amines, so both these shows similar reactions. Azitidine reacts with carbon disulfideto give a salt and with nitrous acid it reacts to gives N-nitrosoazetidine.



7.8 OXETANES

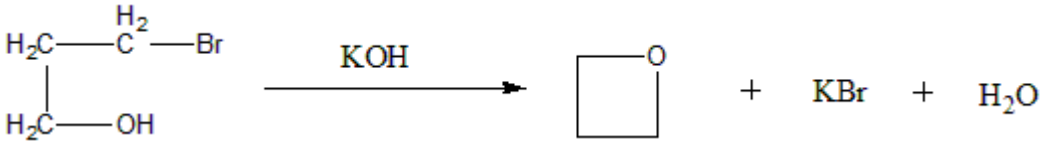
These are also known as oxacyclobutanes. The oxetane ring forms a slightly distorted square because the bond angle of this ring at the O-atom is 92°.The strain enthalpy of oxetane is 106.3 kJ mol^{-1} and so it is only 7.7 kJ mol^{-1} less than that of oxirane, while the bond angle of oxetane is 30° larger than oxirane.



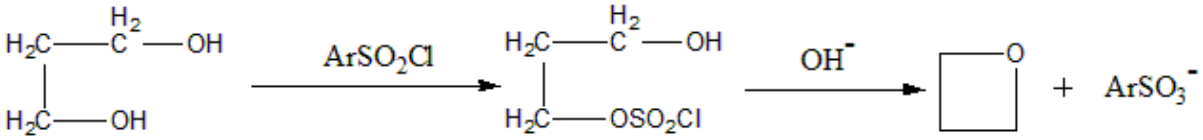
7.8.1 Methods of Preparation

(i) Intramolecular cyclization reaction

(a) Oxetanes are prepared by the Intramolecular cyclization of 3-halo alcohols in the presence of a base.

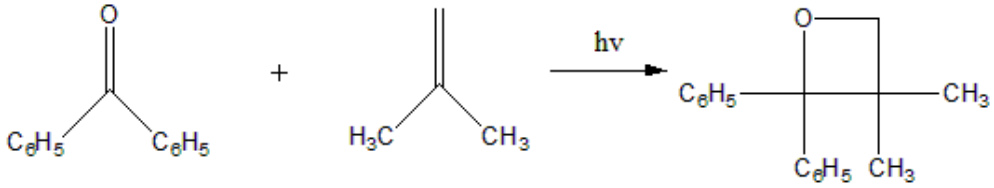


(b) Oxetanes can be prepared from 1,3-diols via aryl sulfonates.



(ii) Paterno-Büchi reaction

Photochemical [2+2] cycloaddition of carbonyl compounds and olefins gives oxetanes.This reaction is known as Paterno-Buchi reaction.

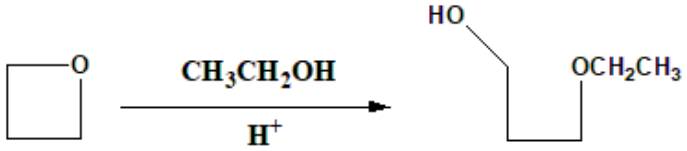


7.8.2 Physical Properties

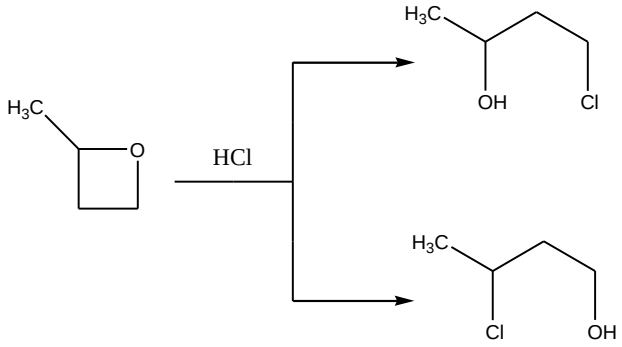
Oxetane is a colourless and water-miscible liquid of boiling point 48°C.

7.8.3 Chemical Reactions

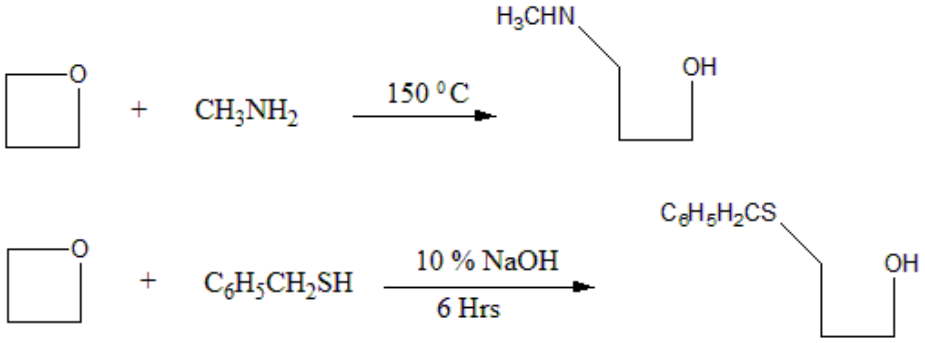
(i) Electrophilic ring opening reaction: Oxetane readily gives ring opening reactions under acidic conditions.



In unsymmetrically substituted oxetane, the direction of ring cleavage depends on the "push-pull" mechanism and generally two products are formed.

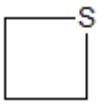


(i) Nucleophilic ring opening reaction: They give ring openingreactions with primary amines and thiols.



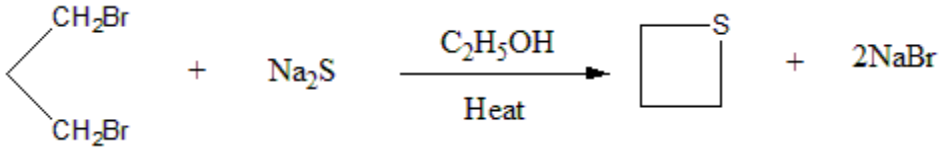
7.9THIETANES

Thietane are heterocyclic compounds containing a saturated four-membered ring with three carbon atoms and one sulfur atom in the ring.The strain enthalpy of thietane is only 80 kJ mol^{-1}.Theactivation energy for the ring inversion was found to be3.28 kJ mol^{-1} and lies above the four lowest vibration levels.

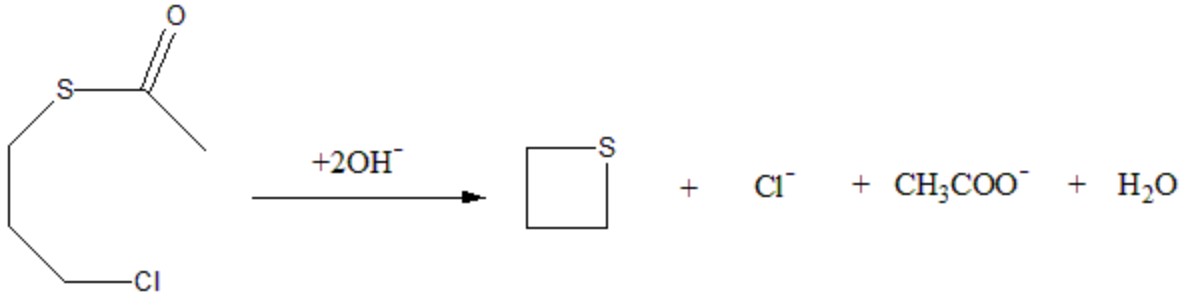


7.9.1 Methods of Preparation

(i) From 1, 3-Dihaloalkanes: 1, 3-Dihaloalkanes when heated with sodium sulphide in presence of alcohol gives thietanes.



(ii) Cyclization of *gamma*-halo thiols or their acetyl derivatives: The reaction *gamma*-halo thiols or their acetyl derivatives with base produces thietanes.



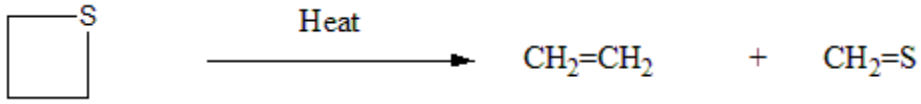
7.9.2 Physical Properties

Thietane is acolourless, water-insoluble liquid and itsboiling point is 94°C.

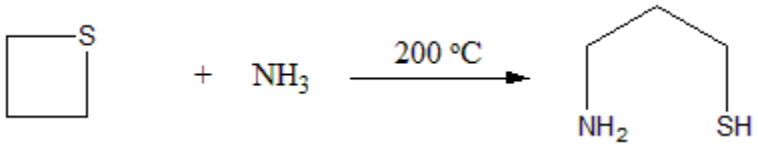
7.9.3 Chemical Reactions

(i) Ring opening reactions

(a) Thietane is cleaved on heating in gas phase to give ethylene and thioformaldehyde.

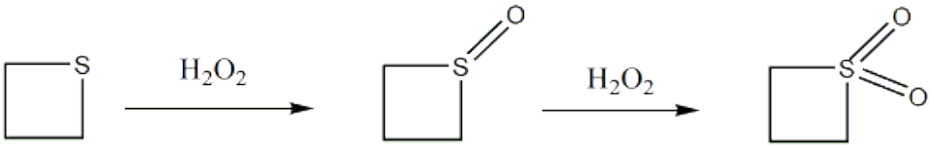


(b) Reaction with ammonia



(c) Reaction with Acetyl Chloride

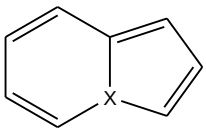
(d) Oxidation: Hydrogen peroxide or peroxy acids oxidize thietanes to give 1-oxides and finally 1,1-dioxides (cyclic sulfones).



7.10 .*BENZO-FUSED FIVE-MEMBERED HETEROCYCLES WITH ONE HETERO ATOM*

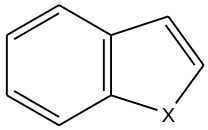
7.10.1General:

The benzene ring is fused with five-membered aromatic heterocyclic rings *i.e.*pyrrole, furan and thiophene, results in benzo[a], benzo[b] and benzo[c]fused heterocycles depending on the fusion side of the benzene ring on to the 'face*a '* (1,2-bond), 'face *b'* (2,3-bond) and 'face *c'* (3,4-bond), respectively.

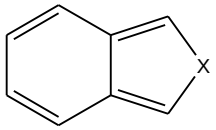


X = N lndolizine

Benzo[a] heterocycle



X= NH Indole
X= 0 Benzo[b]furan
X= S Benzo[b]thiophene
Benzo[b] heterocycles



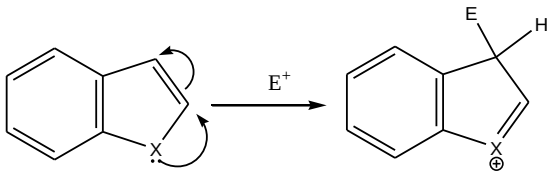
X= NH Isoindole
X= NH Isoindole
X= S Benzo[c]thiophene
Benzo[c] heterocycles

7.10.2. Reactivity

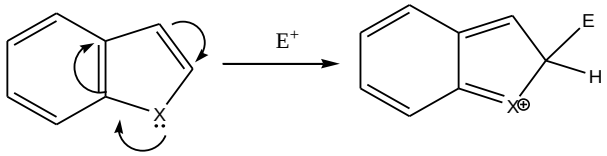
These bicyclic heterocycles have different chemical properties from non-benzo fused heterocyclic compounds. Electrophiles attack in the heterocyclic ring when the compound is non-substituted, but the presence of electron-withdrawing substituents on the heterocyclic ring or the electron-releasing substituents on the benzene ring facilitates the electrophilic substitution in the benzene ring. FusionBenzene to the 'face b' of furan or thiophene decreases reactivity towards electrophilic substitution reactions and this effect is more pronounced in the case of furan.

7.10.3 Orientation

Heteroatom in benzo[*b*]heterocycles mostly favorβ-substitution over α-substitution in the heterocyclic ring, which is due to the stability of σ-complex. Benzo[b]pyrrole (indole) and benzo[*b*]thiophene undergo β-substitution, while benzo[*b*]furan involves mainly α-substitution, becausethe oxygen atom hasa strong α-directing effect.



β-substitution (more stable σ-complex)

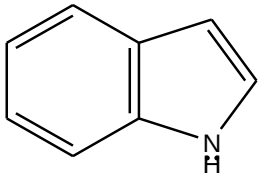


α-substitution(less stable σ-complex)
Orientation effect of heteroatom in benzo[b]heterocycles.

7.11 BENZOPYRROLES (*INDOLES)*

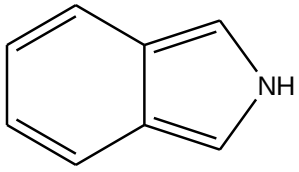
These are formed by the fusion of a benzene ring with a pyrrole ringin different ways and include the following heterocycles:

Indole(trivial name): Fusion of the benzene ring to the 'face *b'* (2 ,3-bond).



IUPACname	Other names
1H-benzo[*b*]pyrrole	α,β-benzopyrrole 1-azaindene 1-benzazole

Isoindole (trivial name): Benzene ring fused to 'face c' (3,4-bond) of the pyrrolering.



IUPAC name	Other name
2H-benzo[c]pyrrole	1H-isoindole

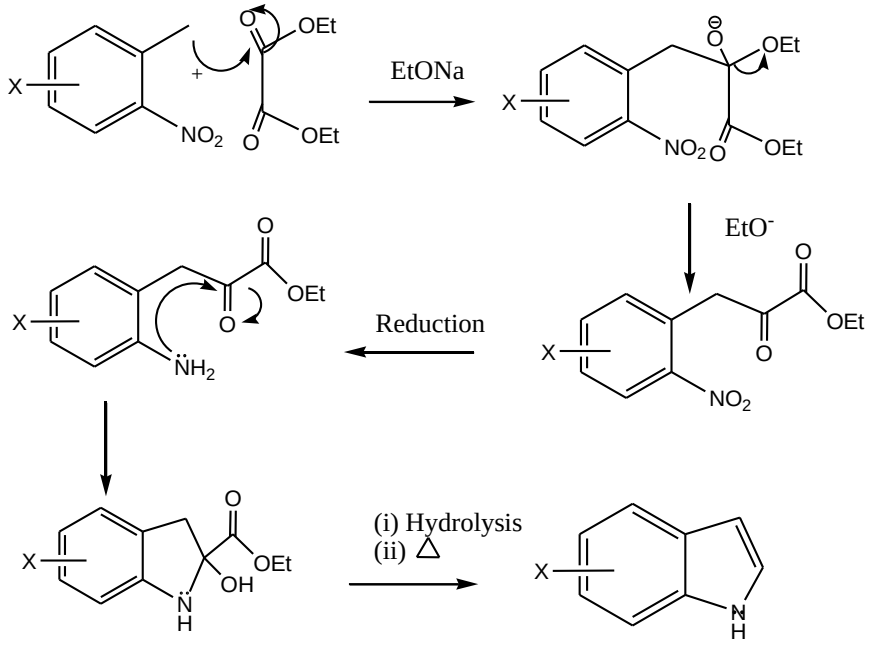
7.11.1 General

Indole is the most common compound of benzopyrroles. The chemistry ofindole has been an attractive field because of the presence of indole structural units in many of the natural products.

7.11.2 Synthesis

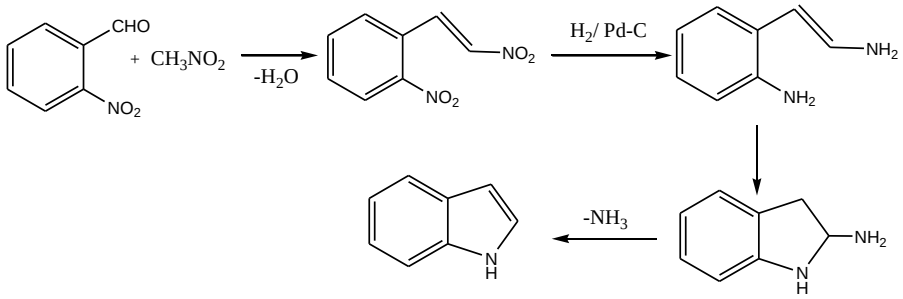
(a) Reaction of *o*-nitrotoluene with diethyl oxalate (ReissertIndole synthesis)

The reaction of *o*-nitrotoluene and diethyl oxalate in base (sodium ethoxide) produces *o*-nitrophenylpyruvate which on reductive cyclization and dehydration gives indole-2-carboxylate.

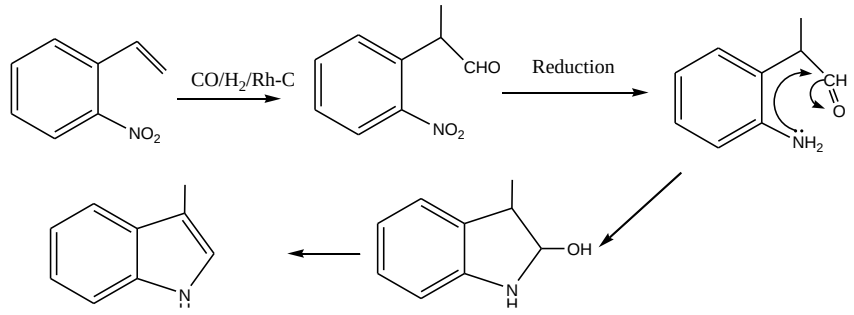


(b) From *o*-Nitrophenylnitroethylene (*o,ω*-Dinitrostyrene)

The reductive cyclization of *o*-nitrophenylnitroethylene, prepared by the reaction of *o*-nitrobenzaldehyde and nitromethane, followed by aromatization with the elimination of ammonia results in the formation of indole involving N-C_2 bond formation.

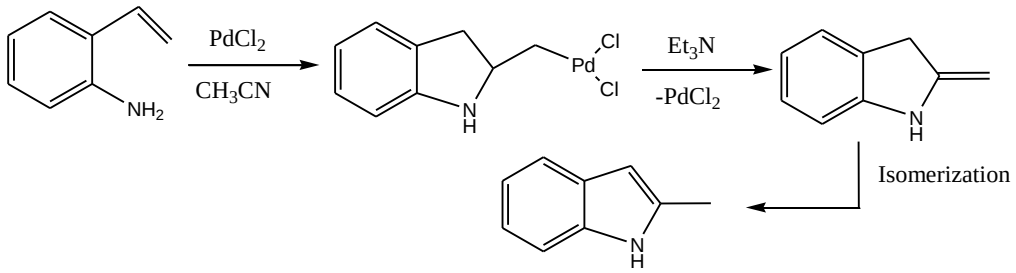


However, the reductive cyclization of aldehyde resulting from the hydroformylation of nitrostyrene provides 3-methylindole.



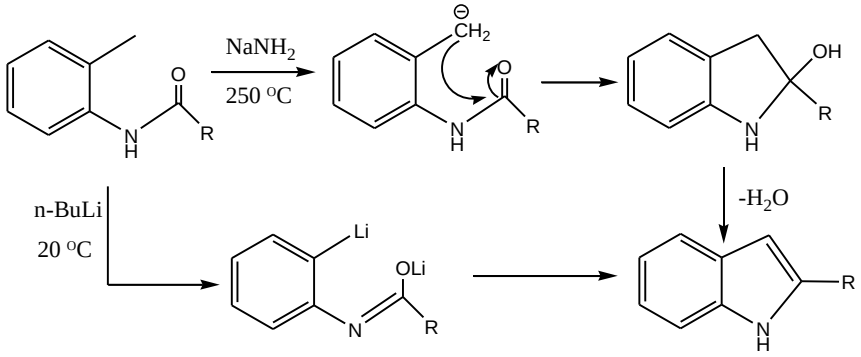
(c) Palladium Catalysed Cyclization

The reaction of *o*-allylaniline with palladium(II) chloride in acetonitrile involvespalladium ion catalysed nucleophilic cyclization and proceeds by the formationof organopalladium intermediate. This on subsequent reaction with triethylamineprovides 2-methylindole.



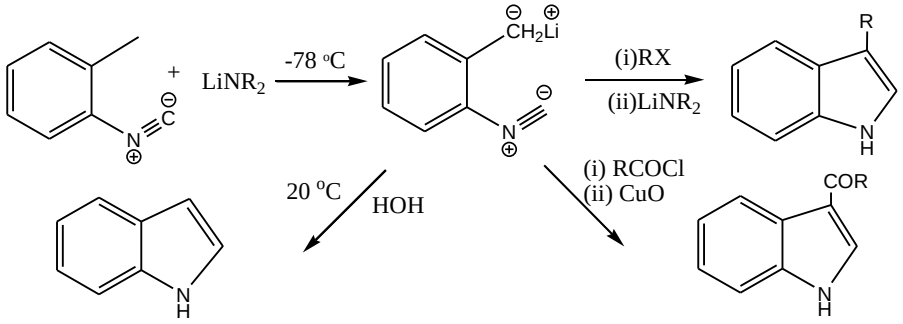
(d)Madelung Indole Synthesis

This reactionis the intramolecular cyclization ofN-acyl-o-aminotoluenes with a strong base, sodamide at 250 °C temperature. However, the strong bases, n-butyllithium and LDA, cause the reaction to occur relatively at lower temperature (20 °C).



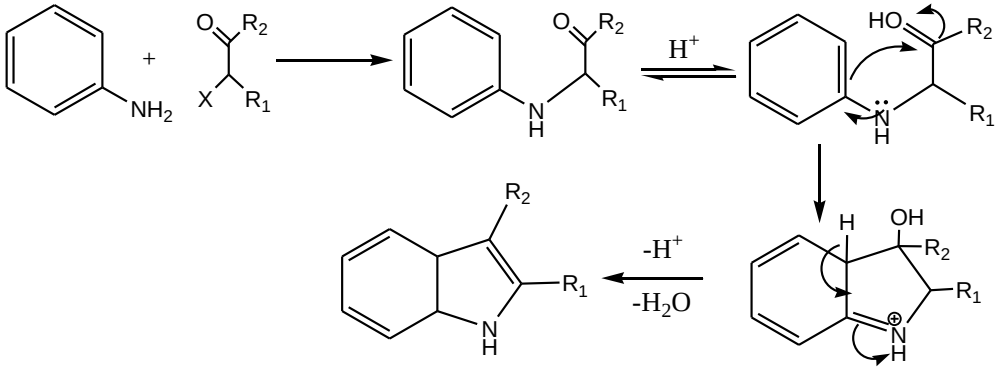
(e)Isonitrile Cyclization

The reaction of *o*-tolyl isocyanide with lithium dialkylamide at -78°C proceeds via lithiation of the methyl group affording lithiated intermediate which on cyclization at room temperature gives indole. Alternatively, when treated with alkyl halide and subsequently with additional LDA, the methyl group is alkylated before cyclization affording 3-alkylindole. This can also be achieved with acyl halide in the presence of cupric oxide produces 3-acylindole.



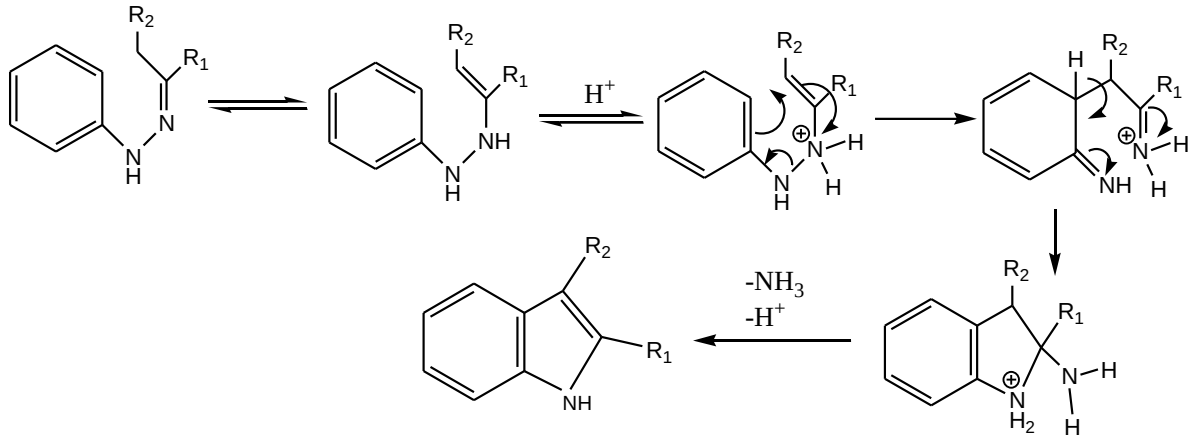
(f)Bischler Indole Synthesis

The reaction of α-hydroxyor α-halo ketones with arylamine in the presence ofan acid gives indoles involving the steps N-alkylation,electrophilic intramolecularcyclization and aromatization, respectively.



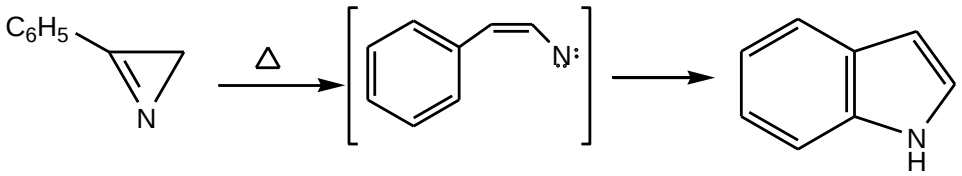
(g)Fischer Indole Synthesis

It is an acid catalysed cyclization of the arylhydrazones of appropriate aldehydes and ketones with the elimination of ammonia. Theacid catalysts used for cyclization are zinc chloride, boron trifluoride and polyphosphoric acid. However, the choice of the catalyst depends on the structure of arylhydrazone. This is the most widely used method for the synthesis of indoles.



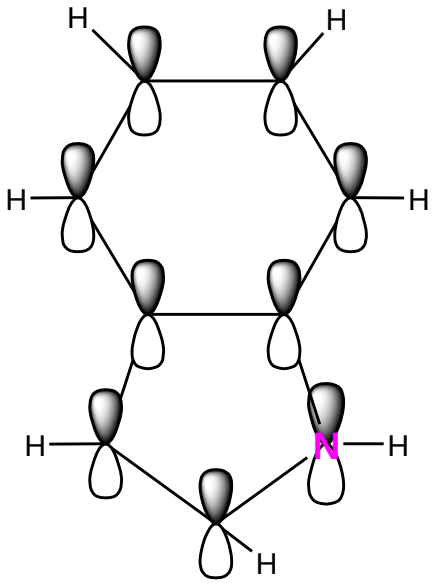
(h)From Azirines

2H-Azirines are thermally transformed to indoles. It involves nitrene formationwith the cleavage of carbon-nitrogen bond. This reaction can also be carried out at room temperature in the presence oftransition metal catalyst.

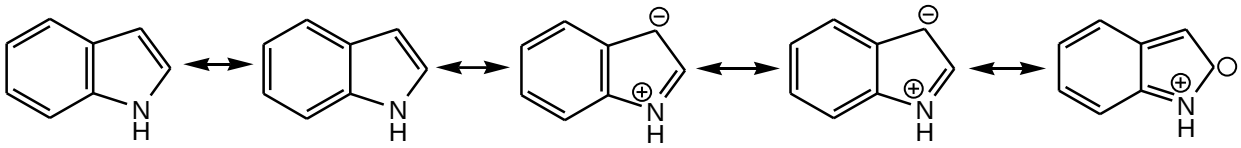


7.11.3 Structure

Indole is a planar molecule with carbon atoms and a nitrogen atom, all are sp^2-hybridized. The sp^2-hybrid orbitals of the carbon and nitrogen atoms overlap axially with each other and with s orbitals of the hydrogen atoms forming σ-framework. The unhybridized p-orbitals on the carbon atoms and nitrogen atom (perpendicular to the plane of σ -bonds) overlap sidewise forming a π-molecular orbital. Indole is considered to be a resonance hybrid of the following resonating structures. Indole is an aromatic heterocycle as it is cyclic planar with 10 delocalized π-electrons.



Molecular orbital structure of indole



Resonating structures of indole

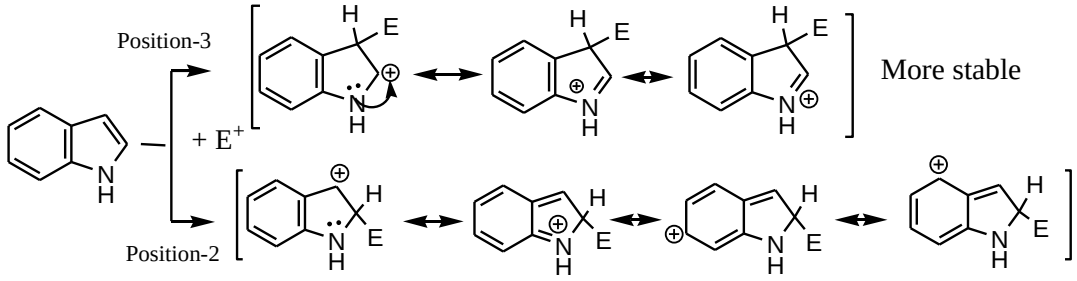
7.11.4 Reactions:

The reactivity of indole is expected to be similar to that of pyrrole.But the fusion of a benzene ring to the 'β-face' of a pyrrole ring deactivates theposition-2 of the resulting indole towards electrophilic attack (reverse of pyrrole).

(a)Reactions with Electrophiles

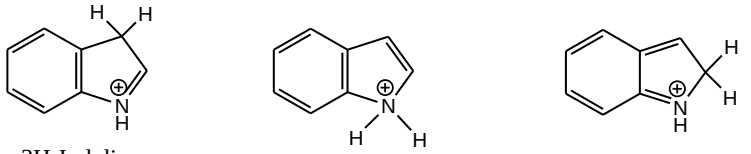
The π-electron excessive character of indole makes it extremely susceptible to undergo electrophilic substitution reactions. The electrophilic substitution at position-3 (β-substitution) is preferred over the substitution at position-2 (α-substitution). The preferential β-substitution over α-substitution in the pyrrole ring of indole is rationalized by the comparable stabilities of the σ-complexes (transition states) resulting from the electrophilic attack at the positions 2 and 3. The σ-complex resulting from the electrophilic attack at position-3 is contributed by the resonating

structures involving effective stabilization due to the involvement of lone pair on nitrogen without disruption of the benzenoid structure.



(b)Protonation: Reaction with Proton Acids

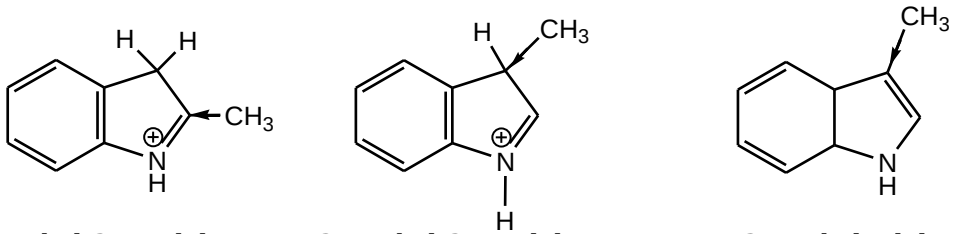
Protonation of indole by dilute acid produces stable 3H-indolium cation, whilein strong acid protonation occurs at the positions 1 and2 with the formation of l*H*-indolium and 2*H*-indolium cations.



3H-Indolium cation | lH-Indolium cation | 2H-Indolium cation

Basicity

Indoles are very weak bases. The methyl groups at the positions-1 and position-2 enhance basicity by 1000times but the methyl group at the position-3 decreasesbasicity. The enhanced basicity of 2-methylindole is due to stabilization of 2-methyl-3H-indolium cation, while the lower basicity of 3-methylindole than indole is because of its stabilization in unprotonated form due to the hyperconjugative stabilizing effect exerted by the methyl group at the position-3.



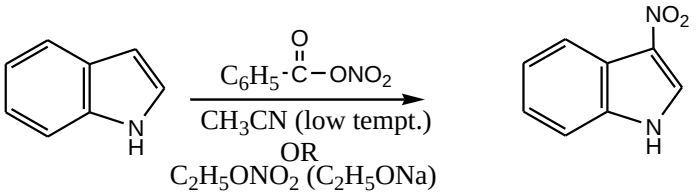
2-Methyl-3H-indolium cation | 3-Methyl-3H-indolium cation | 3-Methylindole

more stable | less stable | more stable

(c) Nitration

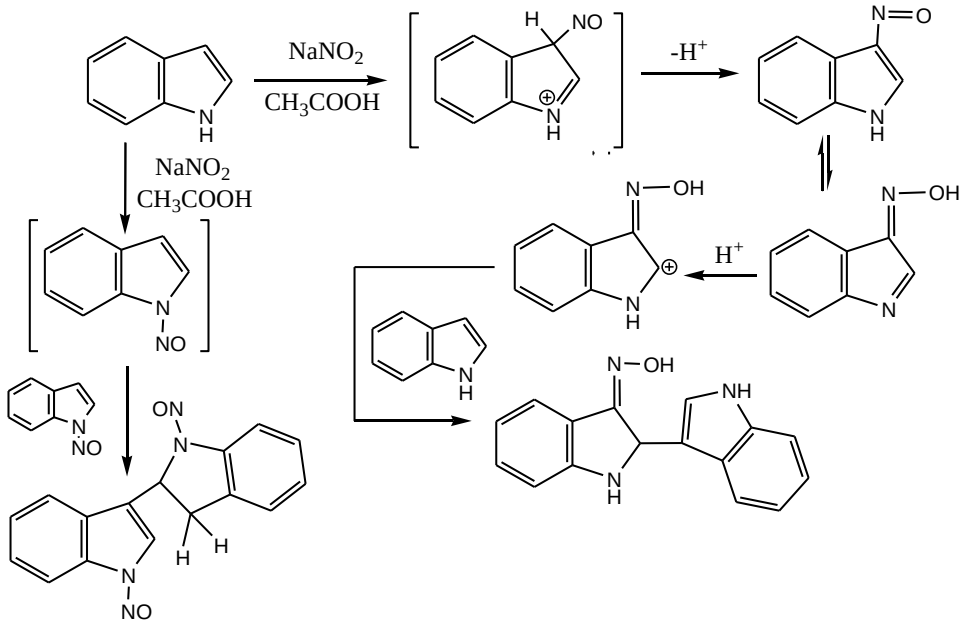
Thenitration of indole in strongacidic conditions with normal nitrating agents (conc.HNO_3 + conc. H_2SO_4) gives polymeric products. Nitration of indole by benzoyl nitrate in

acetonitrile or with ethyl nitrate in thepresence of sodium ethoxide at low temperature gives 3-nitroindole.

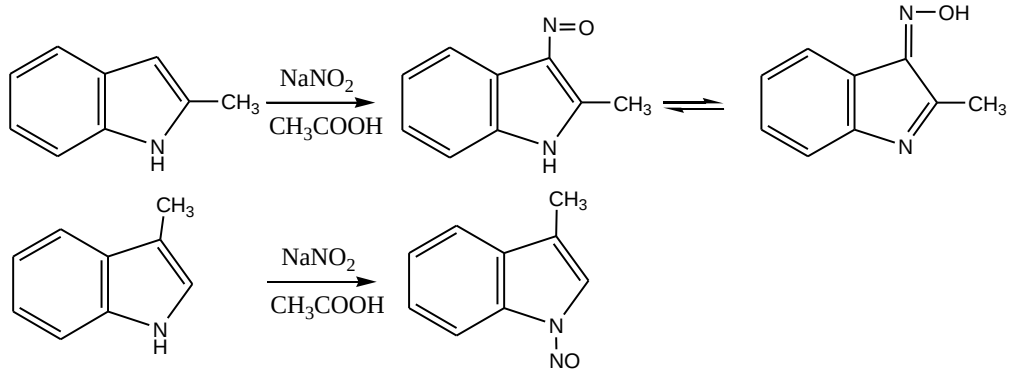


(d)Nitrosation

The reaction of indole with nitrous acid proceeds rapidly with the formation of a complex mixture containing dimericproducts andalongwith 3-nitrosoindole. This compound exists in equilibriumwith its stable tautomeric form 3-oximino-3H-indole**.**

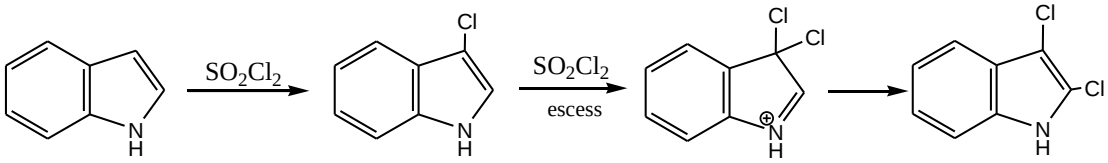


The nitrosation of 2-methylindoleby sodium nitrite in the presence ofacetic acid takes place at the position-3 with the formation of only 3-oximino-2-methylindole.If3-methylindole is nitrosated, N-nitroso-3-methylindoleis formed.

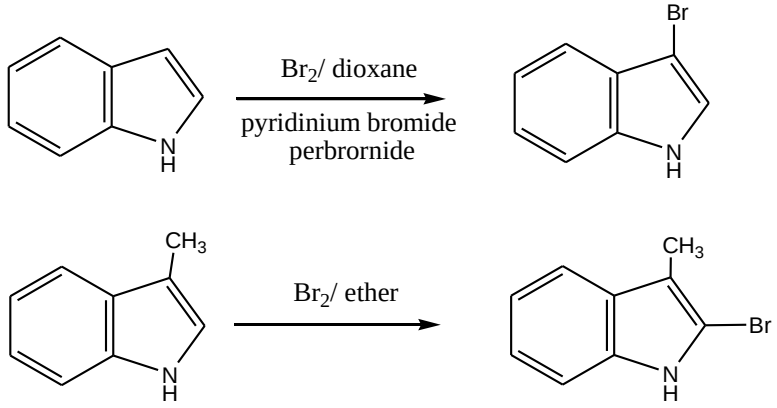


(e) Halogenation

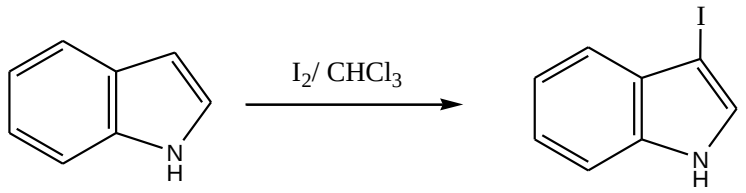
Chlorination: Chlorination of indole with sulfuryl chloride gives 3-chloroindole**.** But withan excess of sulfuryl chloride gives 2,3-dichloroindolevia formation of 3,3-dichloro-3H-indole.



Bromination: Bromination of indole takes place at the position-3 and gives 3-bromoindole**.** If the position-3 of indole is already substituted, the bromination takes placeat the position2.

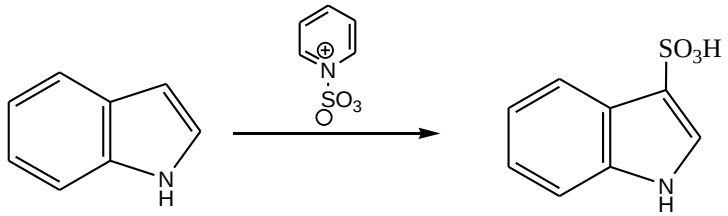


Iodination: The reaction of indole with iodine in the presence of chloroform at low temperatureproduces 3-iodoindole. If the position-3 is occupied, iodination takes place at theposition-2.



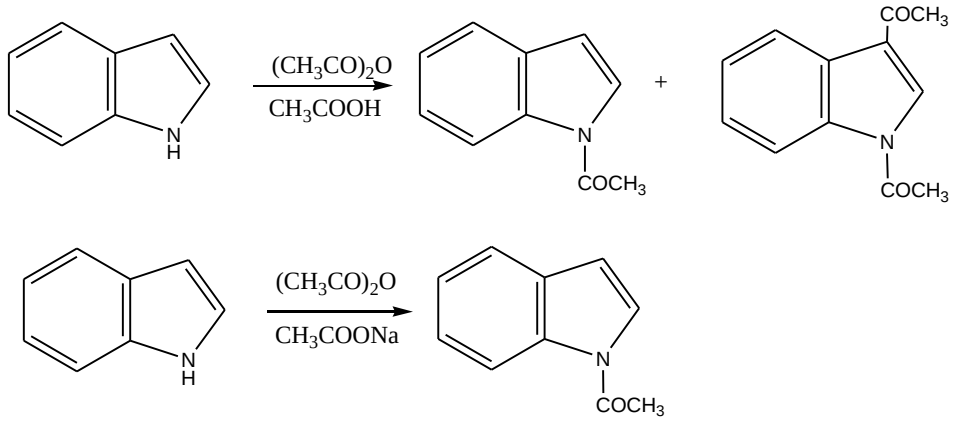
(f)Sulfonation

Indole, because of its acid sensitivity, is sulfonated with pyridine-sulfur trioxidecomplex and provides indole-3-sulfonic acid.



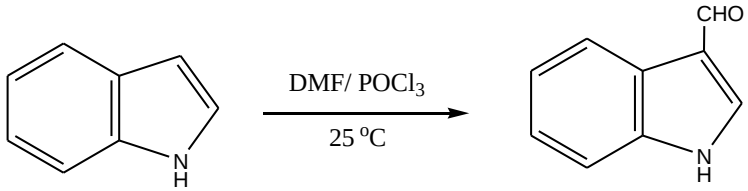
(g)Acylation (Friedei-Crafts Acylation)

Indole with acetic anhydride in the presence of acetic acidgives1-acetylindole and 1 ,3-diacetyl indole. But with acetic anhydride inthe presence of sodium acetate gives 1-acetylindole exclusively.

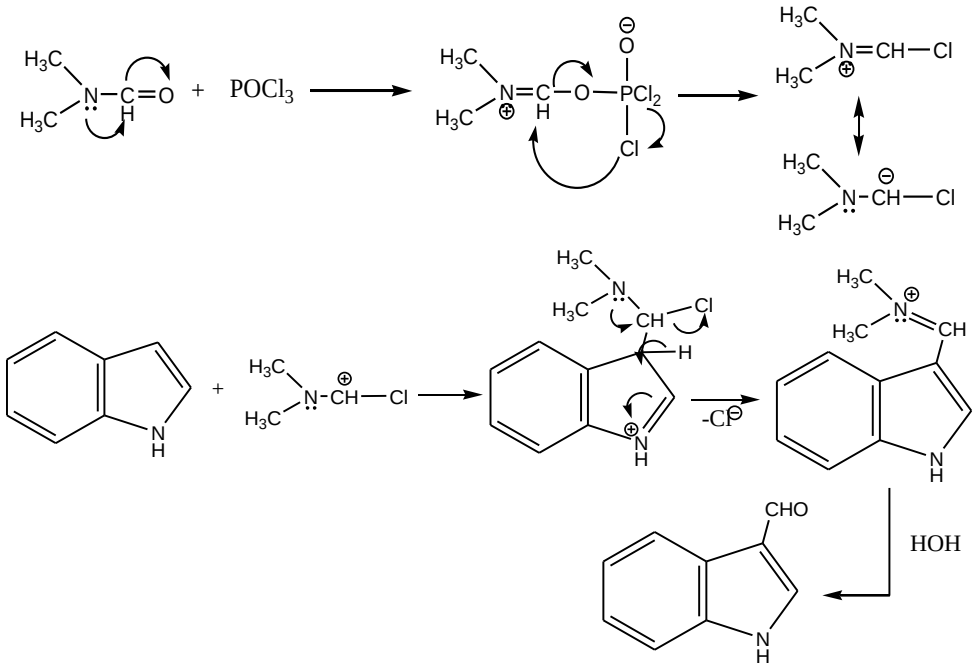


(h)Vilsmeier-Haack Formylation

Indole gives3-formylindolewhen treated with N,N-dimethylformamide (DMF) in the presence ofphosphorus oxychloride.



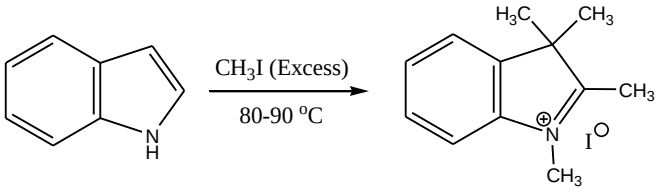
Mechanism:



The reaction proceeds by the attack ofimmonium chloride electrophile at the position-3.

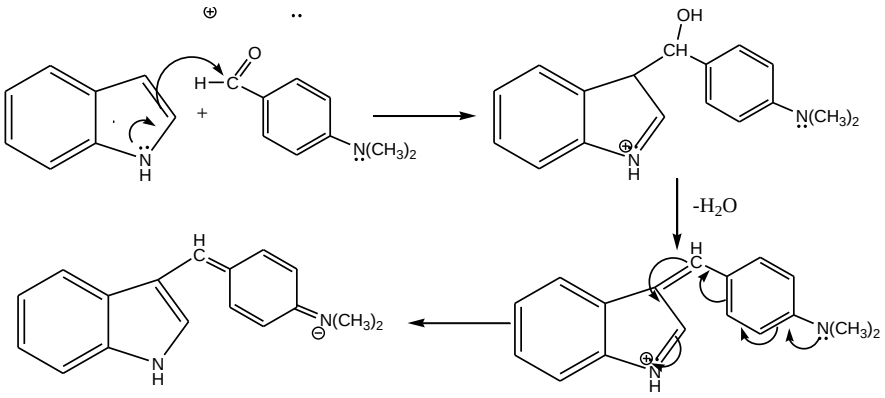
(i)Alkylation

Indole reacts with an excess of methyl iodide in DMFat 80-90°C gives 3-methylindole. But at an elevated temperature (>100°C)further methylation proceeds and finally leads to theformation of 1,2,3,3-tetramethyl-3H-indolium iodide.

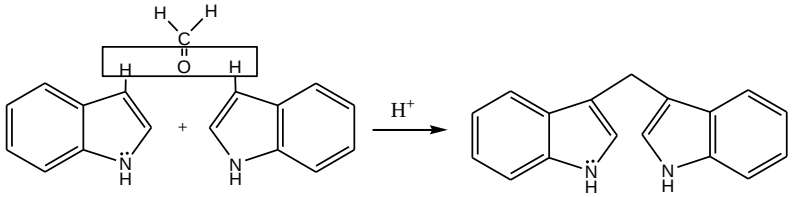


(j) Reactions with Aldehydes and Ketones (Ehrlich Test)

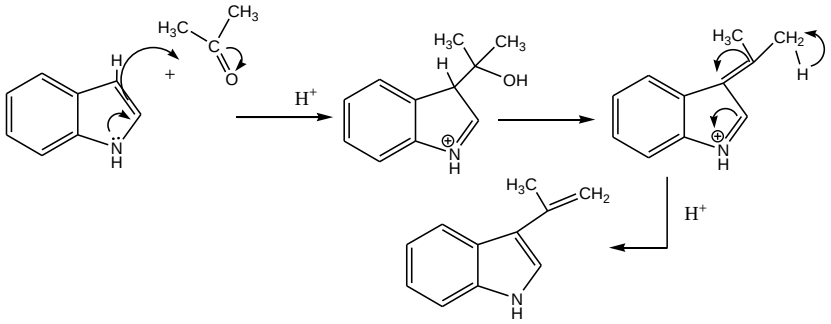
The acid catalysed reaction of *p*-N,N-dimethylaminobenzaldehyde with indolesproduces purple-redcolouration (due to formation of salt).



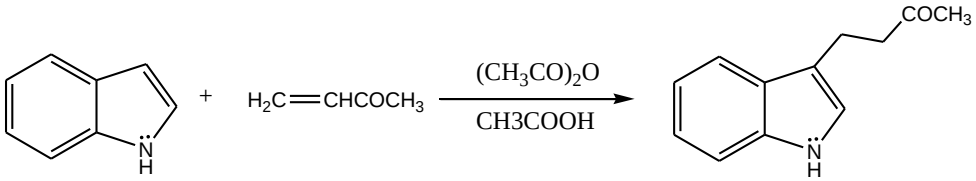
(k)With Aliphatic Aldehydes and Ketones:



(l)Reaction with ketone:

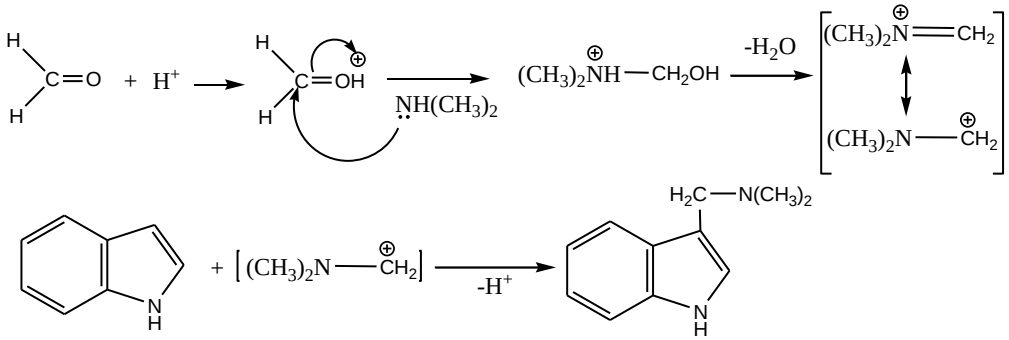


(m)With α, β-Unsaturated Ketones: Michael type additionat the position-3 of indole givesα, β-alkylated product.

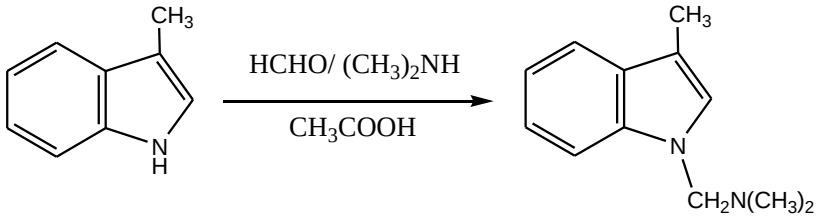


(n)Mannich Reaction

Indole reacts with formaldehyde and N,N-dimethylamine in a weak acid gives3-N,N-dimethylaminomethylindole.The reaction proceeds by*β*-attack of immonium ion, generated by the reaction of formaldehyde with N,N-dimethylamine.

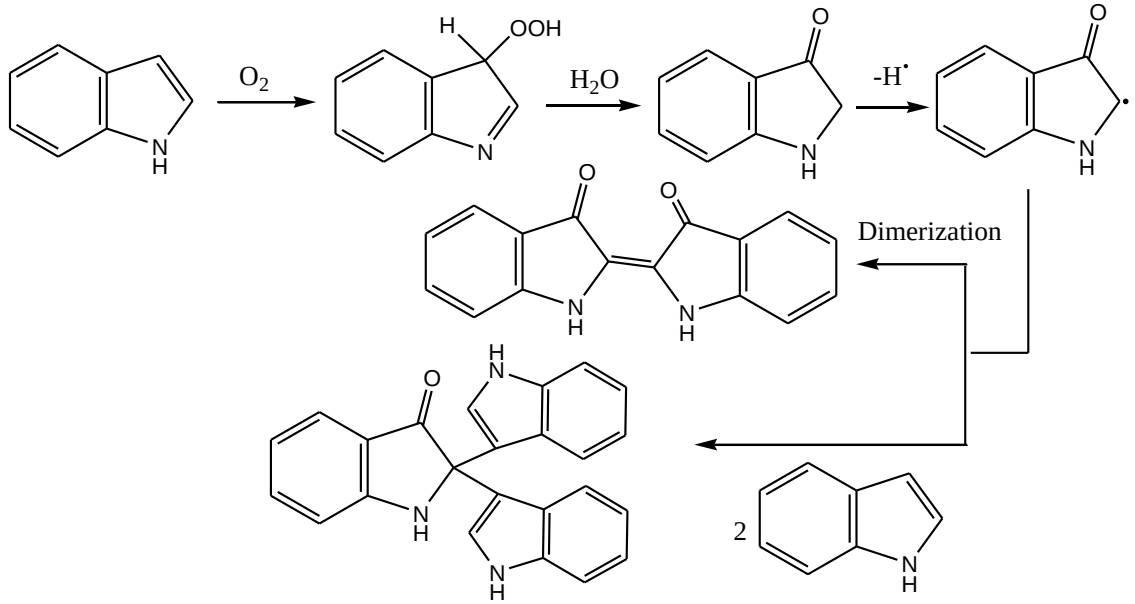


In case position-3is occupied, reaction takes place at the position-1, indicating low reactivity of the position-2

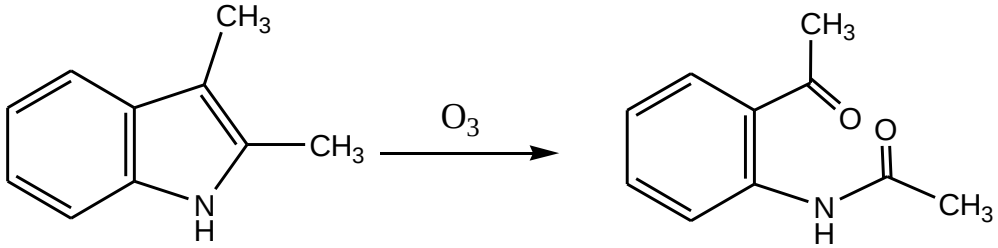


(o)Oxidation

lndoles are less susceptible than pyrrole for oxidation andproduce monomeric, dimeric and trimeric oxidation products. Electron-donating substituents increases the susceptibility of indoles towardsoxidation, while electron-withdrawing substituents are relatively inert.Indole is oxidized by air to give indolin-3-one (indoxyl)**.** The radicalformed by the removal ofhydrogen atom from the position-2 of indolin-3-oneis stabilized and dimerize to produce indigoor can react further.

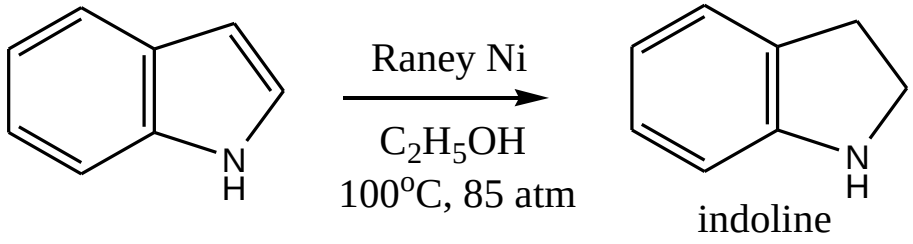


Oxidation of indoles with ozone results in the breaking of C2-C3 bond to give 2-acylaminophenyl ketones.



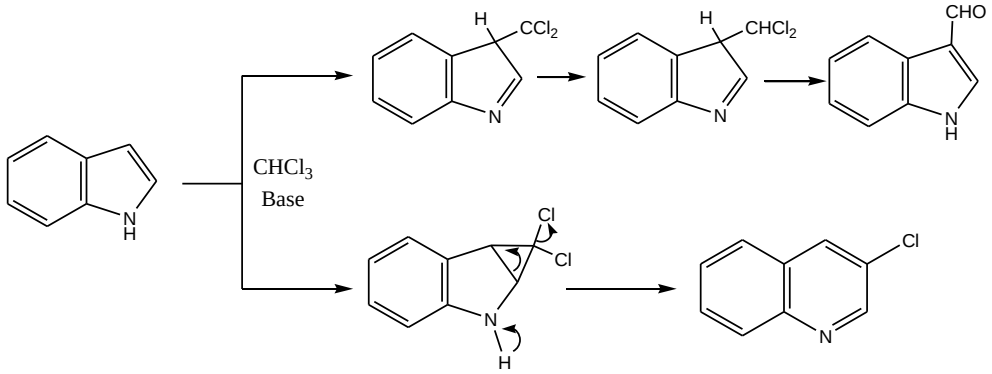
(p)Reduction

Indole is catalytically hydrogenated to indoline (selectively fivememberedring leaving six-membered ring intact), reagent: ethanolover Raney nickel at high temperature and high pressure.



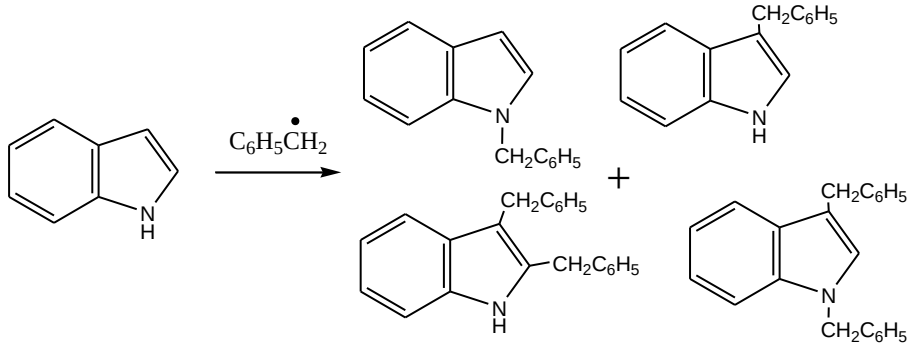
(q) Reactions with Electron-Deficient Species

Indole when treated with dichlorocarbene,generated from chloroform and strong base, gives a mixture ofindole-3-carbaldehyde and ring expanded product, 3-chloroquinoline. This reaction is similar to Reimer-Tiemann reaction.



(r)Reactions with Free Radicals

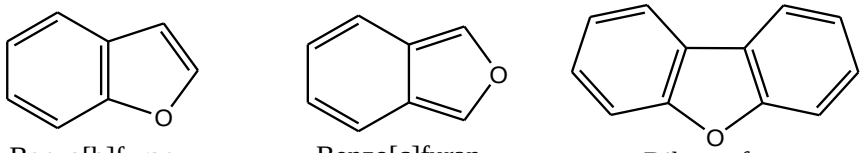
Indole reacts with benzyl radical to produce a mixture of benzylated indolesinvolving benzylation at the carbon and nitrogen atoms of five membered ring.



7.12 BENZOFURANS

7.12.1 General

Benzofurans exist into two isomeric structures depending on the position of fusionof furan ring with the benzene ring and one dinenzofuran.

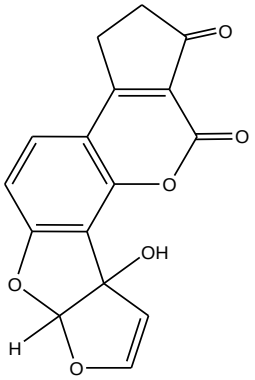


Benzo[b]furan Benzo[c]furan Dibenzofuran

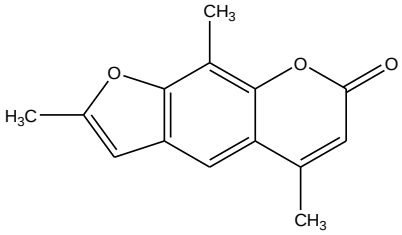
Medicinal applications:

Benzofuran ring system is common inmany natural products and synthetic pharmaceuticals of important biological andpharmacological activities. Some important benzofuran derivatives and their activities are asfollows:

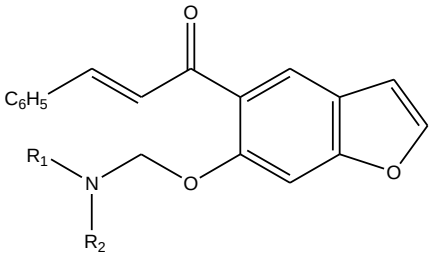
Aflatoxins: carcinogenic and toxic



Trimethylpsoralen: Photoreactive cross linking reagentsfor nucleic acids



Furocoumarins (Methoxalen): hypertensive, vasodilating and spasmolytic

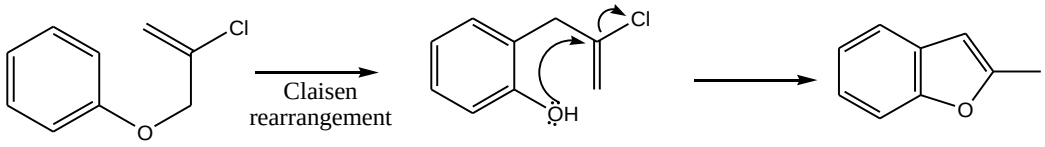


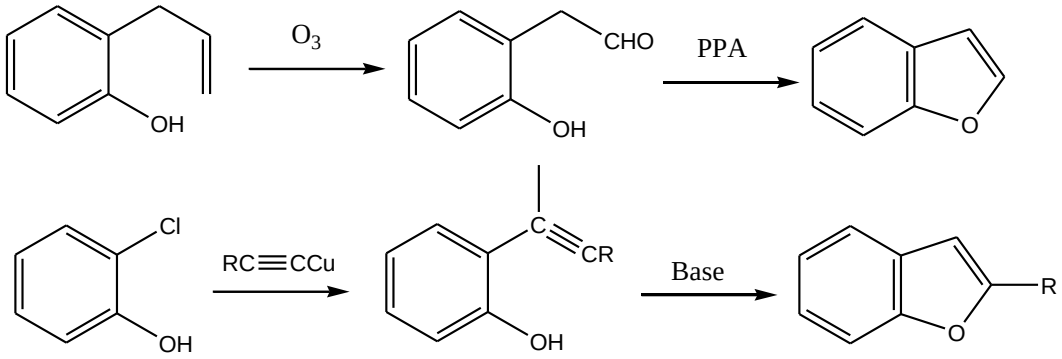
7.12.2 Benzo[b]furans Synthesis

It was prepared from coumarin for the first time and thus it was named as coumarone. Benzo[b]furan was isolated bydistillation of bituminous coal.

(a) Intramolecular Cyclization of *o*-Substituted Phenols

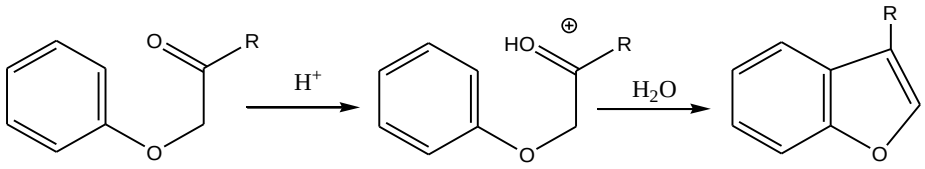
Cyclization of *o*-substituted phenols gives benzo[b]furans under given reaction conditions involving nucleophilic attack of the phenolic oxygen at carbon with the formation C-O bond.





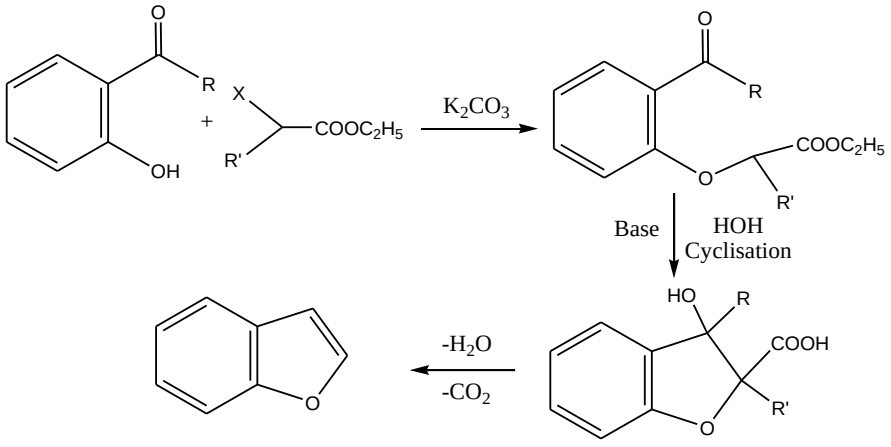
(b) Cyclodehydration of *α*-Aryloxyketones

α-Aryloxyketones undergo cyclodehydration (similar to Bischler indole synthesis) when treated with a dehydrating agent (H_2SO_4, $ZnCl_2$, $POCl_3$, KOH or PPA) and provide benzo[b]furans via cationic intermediate, generated by protonation of carbonyl group, with the formation of C-C bond.



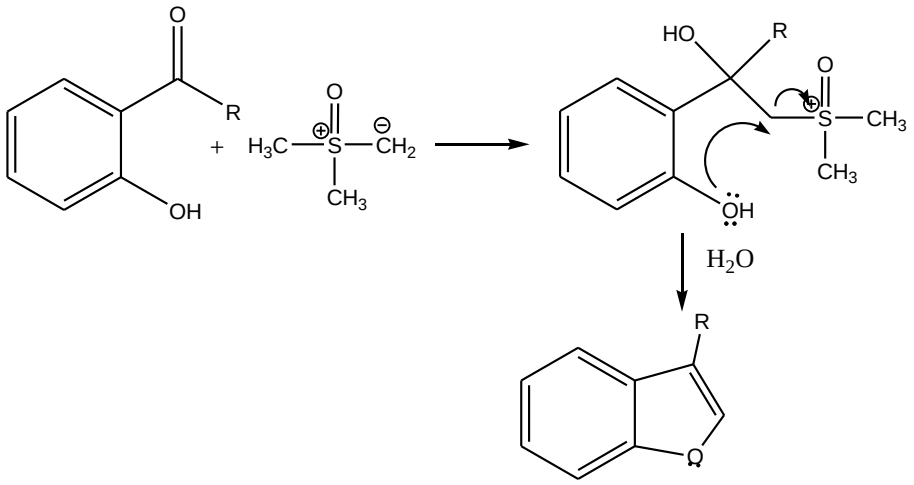
(c) Reaction of *o*-Acylphenols with *α*-Halo Ketones and Esters

The reaction of *o*-acylphenols with *α*-halo ketones or esters followed byintramolecular aldolization and subsequent dehydration results in the formation ofbenzo[b]furans. The reaction proceeds with the addition of carbanion to thecarbonyl carbon with the formation ofC_2-C_3 bond.



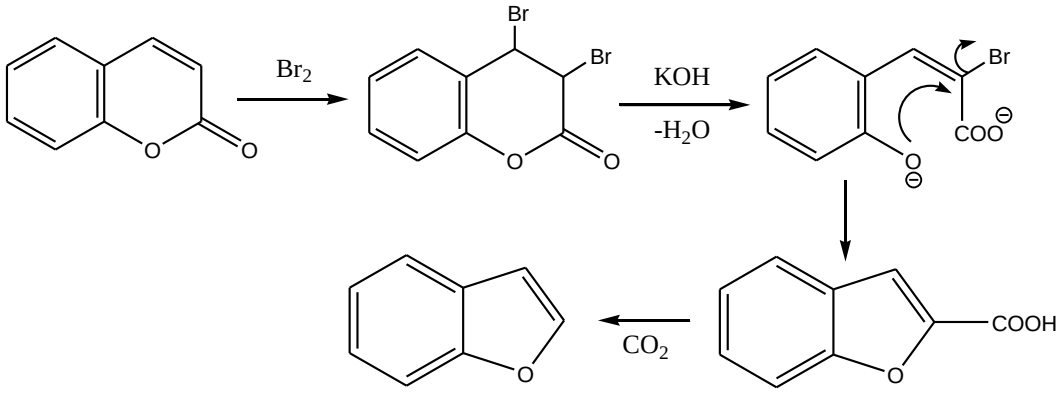
(d) Reaction of *o*-Acylphenols with Dimethylsulfoxoniummethylide

The reaction of *o*-acylphenols with dimethylsulphoxoniummethylide results in theformation of benzo[*b*]furans involving initial nucleophilic addition of sulfur ylideto the carbonyl group followed by nucleophilic attack of the phenolic oxygen atthe internal carbon with the formation of C-C and C-O bonds.



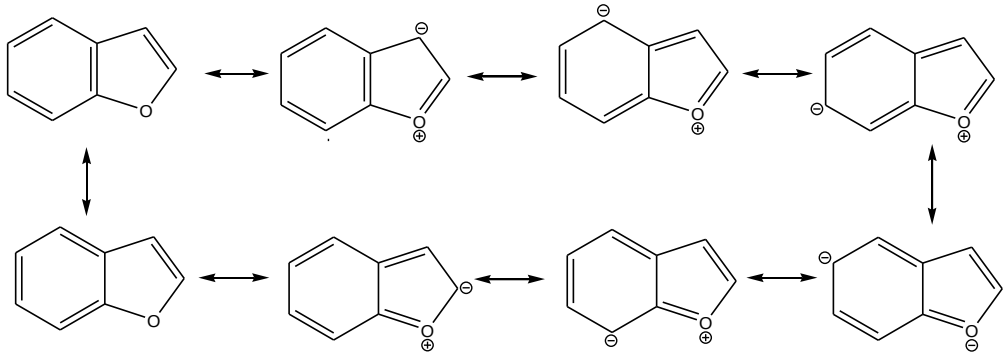
(e)Ring Contraction (From Coumarins)

Bromination of coumarin givesdibromocoumarinthis on alkaline degradation gives coumarilic acid which is decarboxylated to benzo[*b*]furan.



7.13.3 Structure

Structural feature in benzo[b]furan is 10π-electronsare distributed over the cyclic system.Benzo[b]furan is resonance hybrid of the following resonatingstructures.

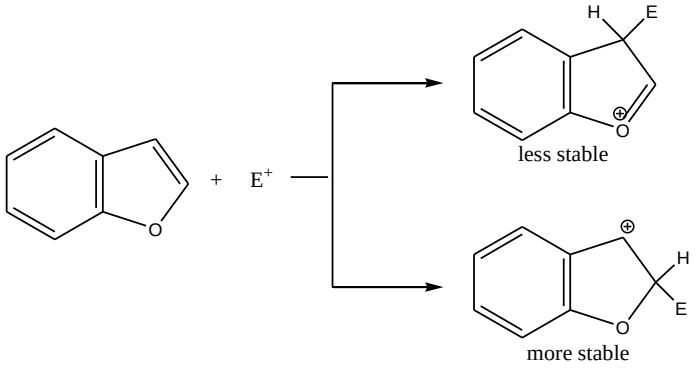


Resonating structures of benzo[b]furan

7.12.4 Reactions

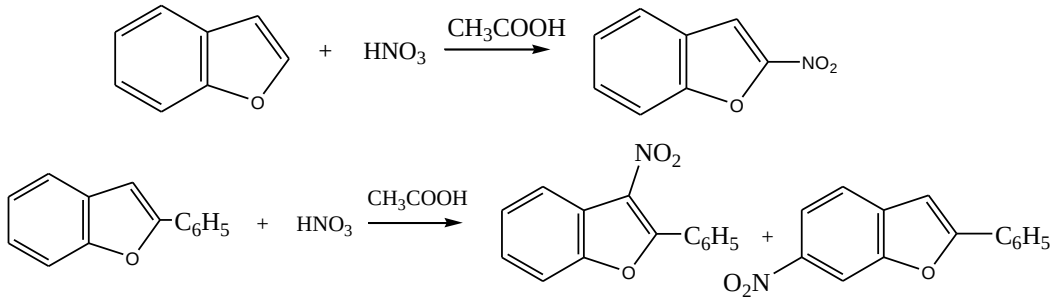
(a)Reactions with Electrophiles

In benzo[b]furan electrophilicsubstitution does not take place at β-position as in indole, but occursat the α-position because of α-directing effect of the oxygenatom in the ring. Cation intermediate is more stable for the attack at the α-position isbecause of the ring oxygen being highly electronegativeaccommodates positivecharge less stabilised.

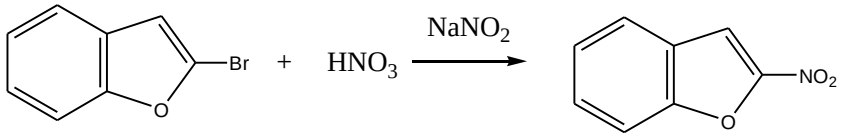


The presence of electron-donating substituents at the position-2 directs theelectrophile to the position-3, while the electron-donating substituent atthe position-3 causes electrophilic substitution to occur at the position-2.

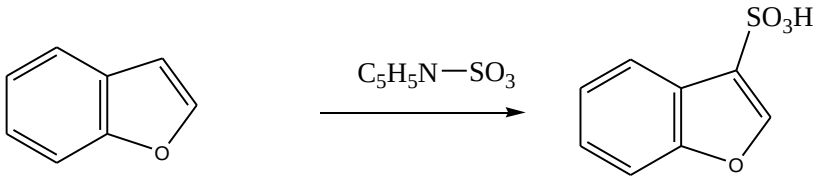
(b)Nitration: Nitration of benzo[*b*]furan by nitric acid and acetic acid produces 2-nitrobenzo[*b*]furan, but nitration of by same reagent 2-phenylbenzo[*b*]furan gives 3-nitro-2-phenyl and 6-nitro-2-phenyl- benzo[*b*]furans.



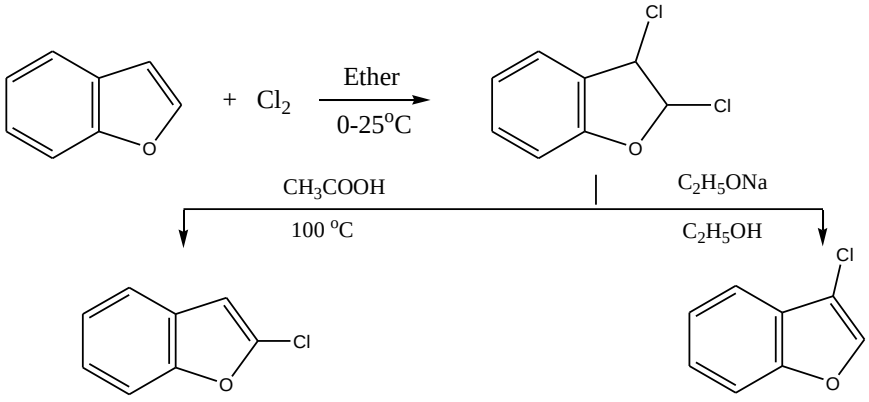
However, nitration of 2-bromobenzo[*b*]furan by nitric acid and sodiumnitrite proceeds by an addition-elimination mechanism and results in the formation of2-nitrobenzo[*b*]furan.



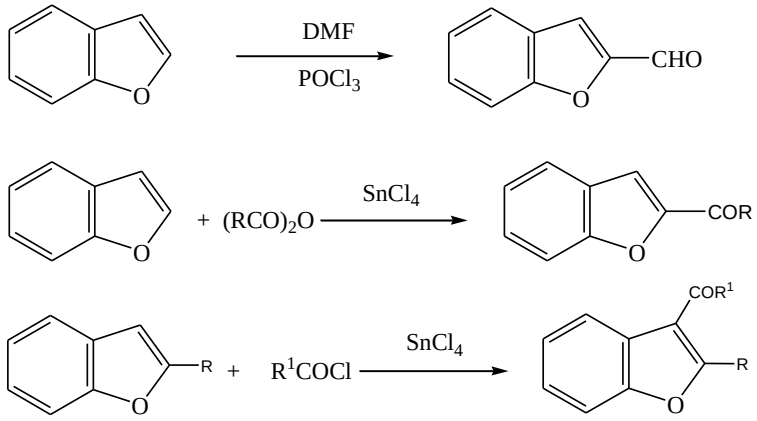
(c)Sulfonation: Benzo[*b*]furan is polymerized by sulfuric acid, but it can be sulfonated bysulfurtrioxidepyridinecomplex with the formation ofbenzo[*b*]furan-3-sulfonicacid(while other electrophilic substitutions in benzo[*b*]furan takes place at position-2).



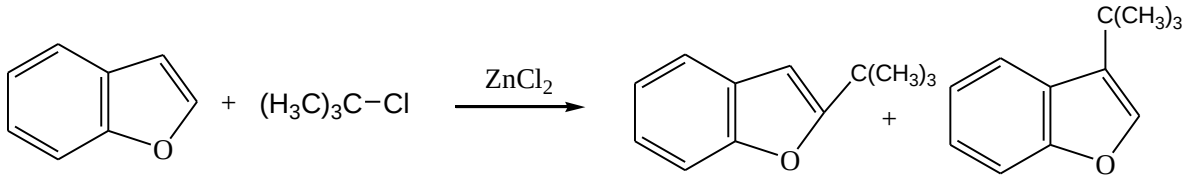
(d)Chlorination: Chlorination ofbenzo[*b*]furan in ether or CCl_4at 0-25°C givesa mixture of *cis*- and *trans*-2,3-dichloro-2,3-dihydrobenzo[*b*]furans. Product on treatment with basegives 3-chlorobenzo[*b*]furan and onheating at 100°C in acetic acid gives 2-chloro derivative.



(e)Acylation: Benzo[*b*]furan undergoes Vilsmeier- Haack reaction to give benzo[*b*]furan-2-carbaldehyde.

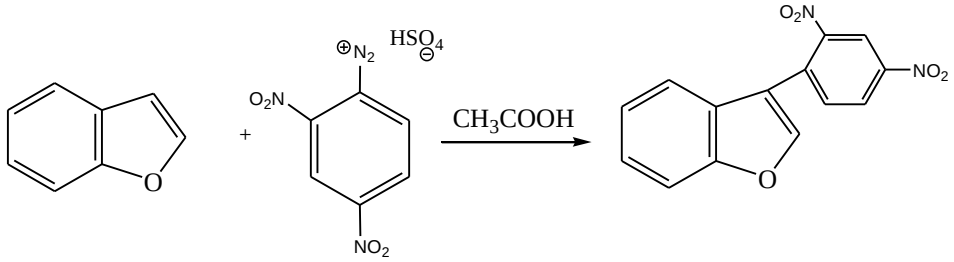


(f)Alkylation: Alkylation ofbenzo[b]furan with *tert*-butyl chloride in zinc chlorideas catalyst gives a mixture of 2 and 3-substituted benzo[*b*]furansin 1:2 ratio.



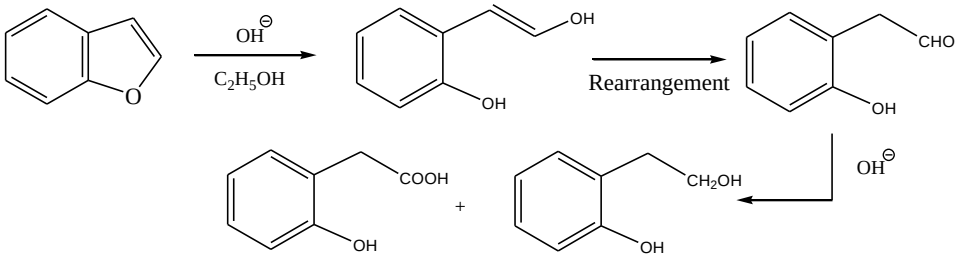
(g)Reaction with Diazonium Salts

Benzo[*b*]furan is arylated at the position-3, when treated with 2,4-dinitrobenzenediazonium sulfate in aqueous acetic acid.



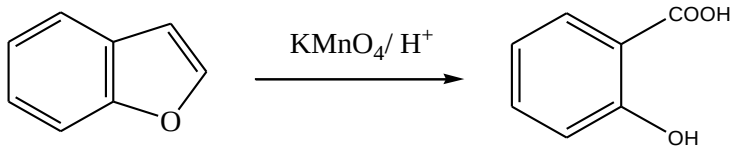
(h) Reactions with Nucleophiles

Benzo[*b*]furanreacts with ethanolic hydroxide under the drastic conditions proceeds by the cleavageof furanoid ring.

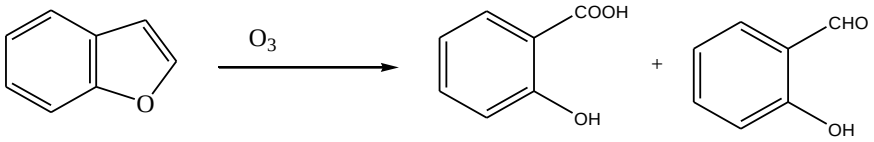


(i)Oxidation

Benzo[*b*]furan is oxidized by cleavage of the furanoid ring.Oxidation of benzo[*b*]furan with permanganate and chromic acid gives2-hydroxybenzoic acid.

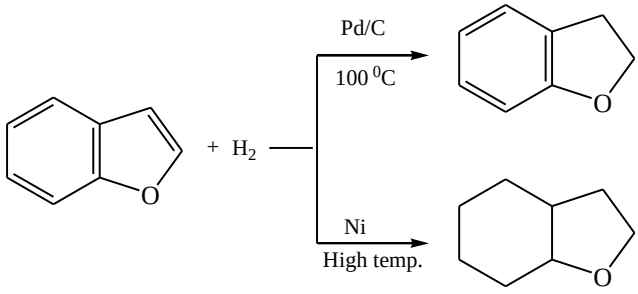


Ozonolysis of benzo[*b*]furan gives a mixture of 2-hydroxybenzaldehyde and2-hydroxybenzoic acid.



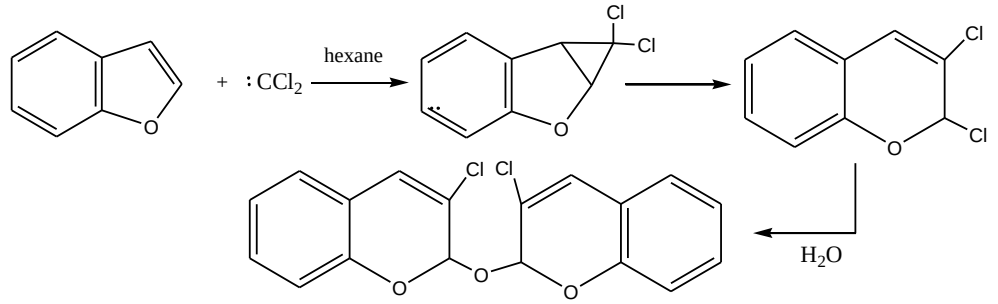
(j) Reduction

Benzo[b]furan is reduced by hydrogen/palladium or sodium/alcoholwith the formation of 2,3-dihydrobenzo[b]furan. While the reduction with hydrogen/nickel at higher temperature causesreduction of both the benzenoid and furanoid rings.



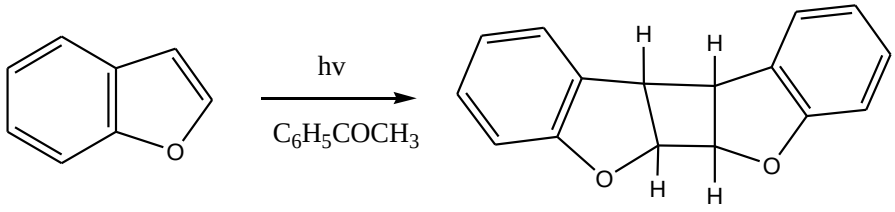
(k) Reactions with Electron-Deficient Species

Benzo[*b*]furan react with dichlorocarbene in hexane and gives an unstableaddition product which rearranges to benzopyran. This on treatment with water is dimerized to chromenyl ether.



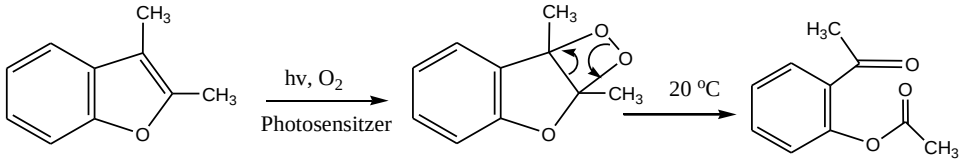
(l)Photodimerization

Benzo[*b*]furan undergoes photodimerization providing low yields of *syn*and *anti*-dimers. Acetophenone is taken as photosensitiser.



(m0Photooxygenation

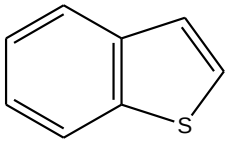
Benzo[*b*]furan and 2-methylbenzo[*b*]furan do not give photooxygenation reaction. While2,3-dimethylbenzo[*b*]furan undergo photooxygenation and givesan unstable peroxide at -78°C. At higher temperature unstable peroxide rearranges to2-acetoxyacetophenone.

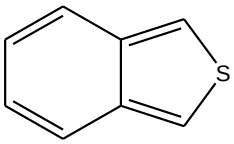


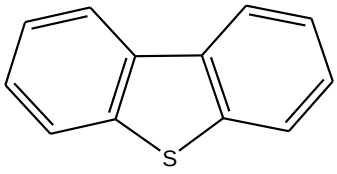
7.13 BENZOTHIOPHENES

7.13.1 General

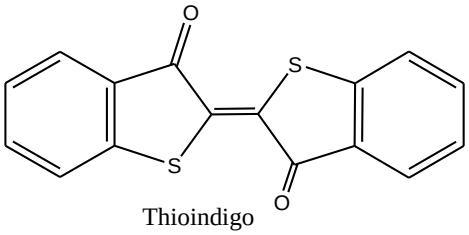
The fusion of benzene ring(s) and thiophene ring results in formation of benzo[*b*]thiophene, benzo[*c*]thiophene or dibenzothiophene, these all belongs to the class ofbenzothiophenes.

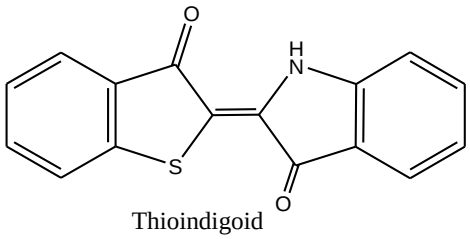

benzo[b]thiophene


benzo[c]thiophene

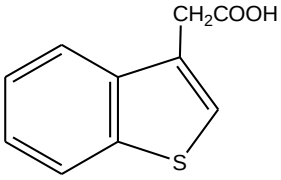

dibenzothiophene

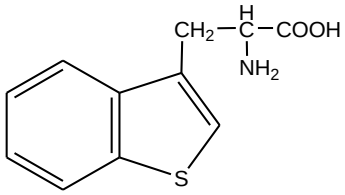
Benzo[*b*]thiophenes and chromophoric systemscondensed to form an interesting class of thioindigo andthioindigoid dyes.


Thioindigo

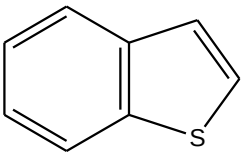

Thioindigoid

The bioisosteric relationship of benzo[*b*]thiophene with indole, so bothhave similar biological activities.

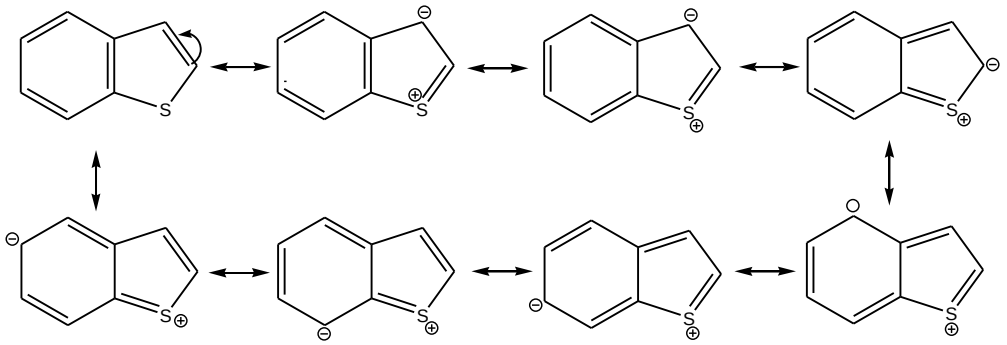

exhibits plant growth promoting activity similar to indole acetic acid


effective antagonist of tryptophan

Benzo[b]thiophenes


benzo[b]thiophene

Benzo[*b*]thiophene is low-melting solid (m.p. 32°C and dipole moment 0.62D) andrepresented by the following resonating structures.



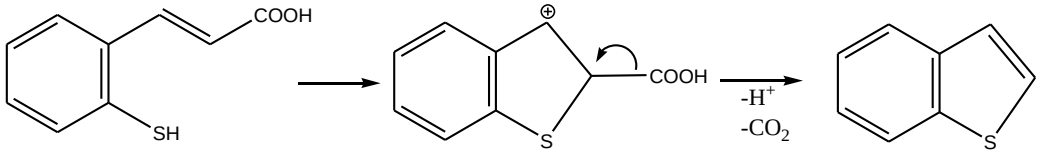
Resonating structures of benzo[b]thiophene

The resonating structures with destruction of the benzenoid 6π-electronsystem contribute less to the resonance hybrid.

7.13.2 Synthesis

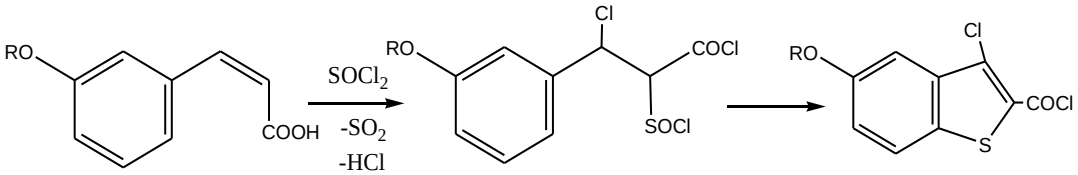
(a) Oxidative Cyclization of Mercaptocinnamic Acids

Cyclization of *o*-mercaptocinnamic acid by alkalinesolution of potassium ferricyanide gives benzo[*b*]thiophene. This reaction proceeds by the loss of carbon dioxide involving sulfenium ion as an intermediate.



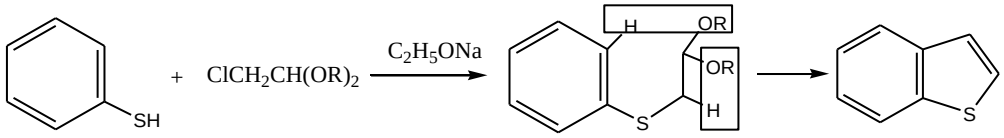
(b)Reaction of Cinnamic Acid with Thionyl Chloride

Cinnamic acid derivativetreated with thionyl chloride in pyridineprovides benzo[*b*]thiophene-2-carbonyl chloride. The cyclization is promoted,if electron-donating substituent is present at para-position of the site of ringclosure, while retarded with an electron-withdrawing substituent.



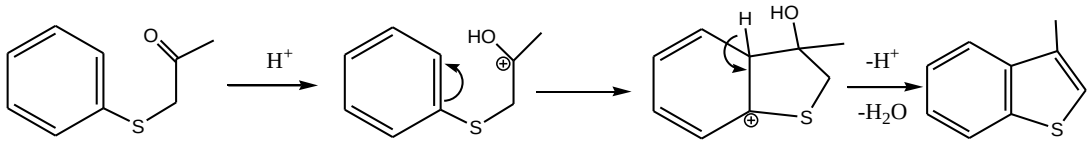
(c) From Arylthioaceta1dehyde Acetals

This method is the most widely used method for the synthesis of benzo[*b*]thiophenes andproceeds by dehydrative cyclization of arylthioacetaldehyde acetals bypolyphosphoric acid or other acid catalyst.



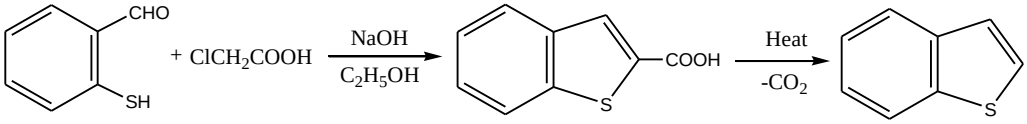
(d)From Arylthiomethyl Ketones

Arylthiomethylketones undergo dehydrative cyclization bypolyphosphoric acid or other acid catalysts, as conc. H_2SO_4, HF, $AlCl_3$, $ZnCl_2$or $P_2O_5$to give benzo[*b*]thiophenes.



(e)Reaction of Mercaptoaldehyde or Acid with *α*-Halo Acidsor Ketones

The condensation and decarboxylation of *o*-mercaptobenzaldehydewith chloroacetic acid ina base givesbenzo[*b*]thiophene.

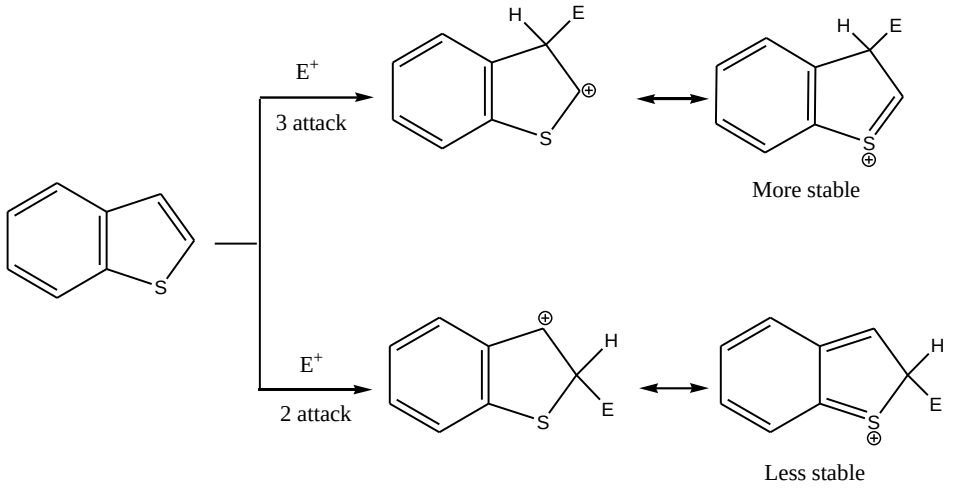


7.13.3 Reactions

(a)Reactions with Electrophiles

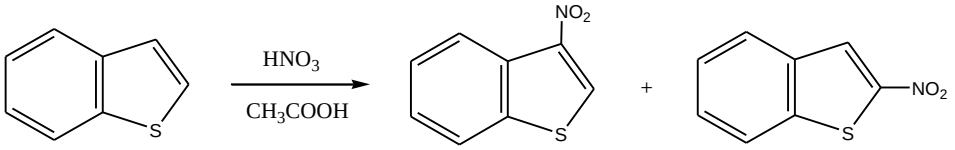
The fusion of a benzene ring to the face *'b'* decreases thereactivity and so benzo[*b*]thiophene exhibit lower reactivity thanthiophene towards electrophilic substitution reactions.

Benzo[*b*]thiophene undergo electrophilic substitution reactionspreferentially at the 3-position in the five-membered ring similarly as in indole. The preferential attack of electrophile atthe *β*-position (3-position) can be explained by comparing the stability of the transition states.

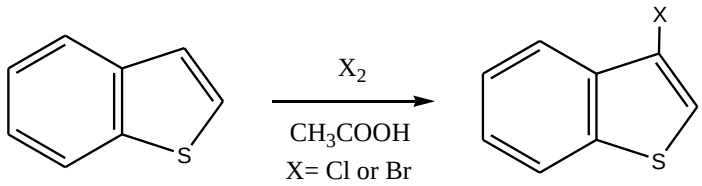


Order of reactivity = 3 > 2 > 6 > 5 > 4 > 7.

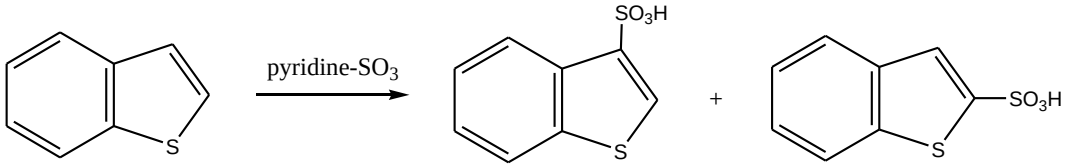
(b)Nitration: Nitration of benzo[b]thiophene with concentrated nitric acid in acetic acid gives a mixture of 3-nitroand 2-nitrobenzo[*b*]thiophenesin 5 : 1ratio.



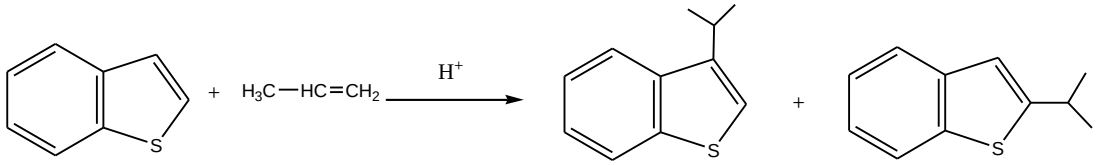
(c) Halogenation: Chlorination/bromination of benzo[*b*]thiophene by chlorine/bromine i naceticacid under controlled conditions gives 3-chloro/bromobenzo[*b*]thiophene.



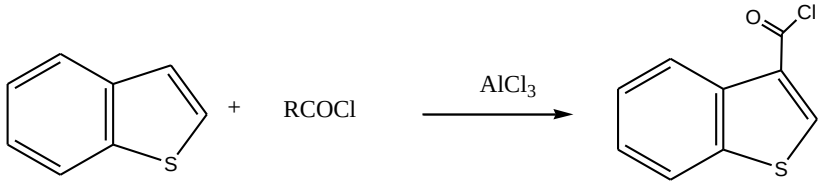
(d) Sulfonation: Benzo[b]thiophene reacts with pyridine-sulfur trioxide to give benzo[*b*]thiophene-3-sulfonic acid as the major product alongwith benzo[*b*]thiophene-2-sulfonic acid as the minor product.



(e)Alkylation: Alkylation of benzo[*b*]thiophene by alkenes or alkanols in the presence of anacid gives a mixture of2 and 3-alkylbenzo[*b*]thiophenes.

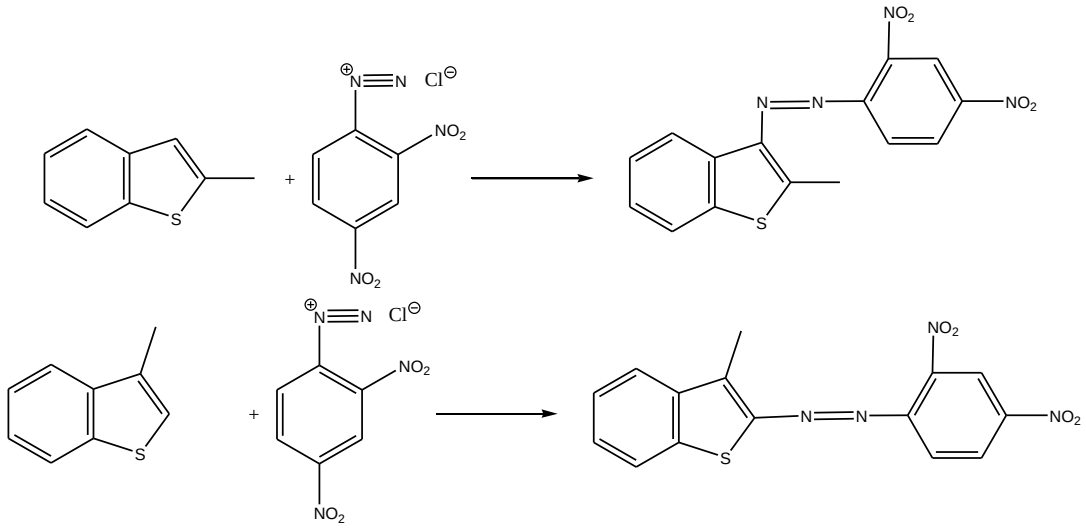


(f)Acylation: Benzo[*b*]thiophene undergoes Friedel-Crafts acylation by Lewisacid catalyst ($AlC1_3$, BF_3, $SnCl_4$, H_2SO_4) to give 3-acylbenzo[b]thiophene asthe major product.



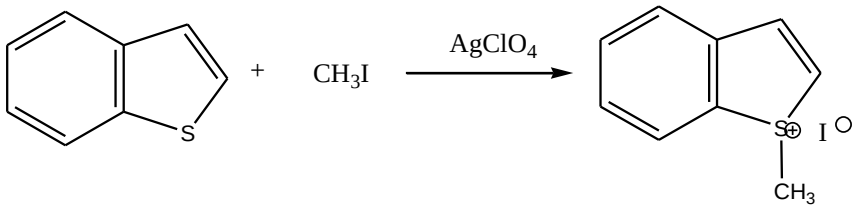
(g)Diazo Coupling

3-Methylbenzo[*b*]thiophenes and 2-methylbenzo[*b*]thiophenes both undergo diazo coupling with 2,4-dinitrobenzenediazoniumsalts at the position-2 and 3, respectively with the formationof azo dyes.



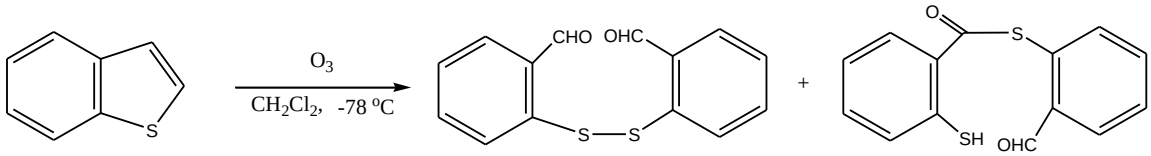
(h)Electrophilic Attack at Sulfur

Benzo[*b*]thiophenes give S-alkylation reaction with strong alkylating reagents containingClO_4^-, PF_6^- and BF_4^- ions.



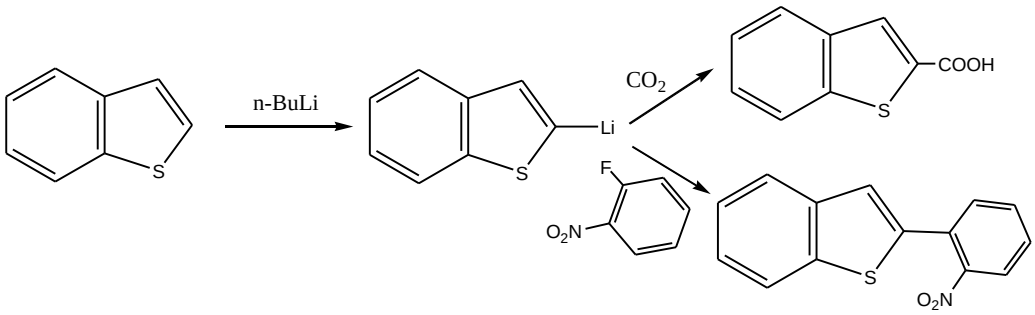
(i)Oxidative Ring Opening

Ozonolysis of benzo[*b*]thiophene in dichloromethane at low temperature undergo the cleavage of five-membered thiophene ring and results in the formation of aldehydes.



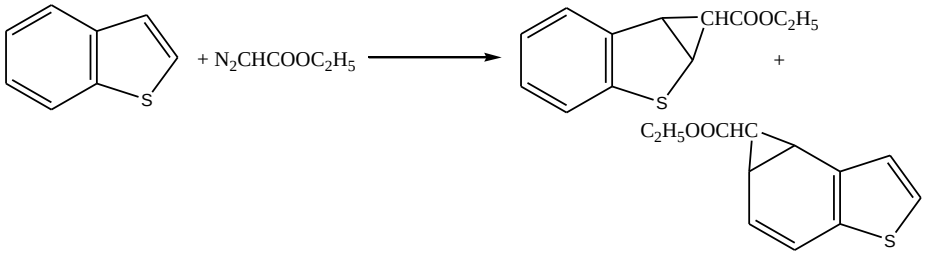
(j)Metallation

Benzo[*b*]thiophene is lithiated at the position-2 by reaction withn-butyllithium. Obtained 2-lithiobenzo[*b*]thiophene can be usedto prepare 2-substituted derivatives.



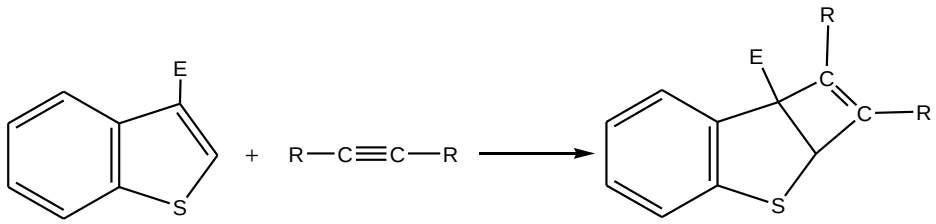
(k)Reactions with Carbenes

The reaction of benzo[*b*]thiophene andethyldiazoacetate proceeds by theaddition of carbene at the C_2-C_3 and C_4-C_5 bonds.



(l)Thermal (2 + 2) Cycloaddition Reactions

Benzo[*b*]thiophenes having electron-withdrawing substituents at theheterocyclic ring undergo (2 + 2) cycloaddition with electron-rich alkynes. It is a thermal reaction.



- The reactivity of the heterocyclic compounds is determined mainly by the ring strain and also by the nature of the heteroatom.
- A typical reaction of three-membered heterocycles is nucleophilic ringopeningreactions resulting in the formation of 1,2-disubstituted aliphatic compounds.
- Due to the presence ofnonbonding electron pairs inthree or four membered heterocycles they behave as Brönsted bases as well as Lewisbases. Accordingly, they will react with Brönsted acids and also withelectrophiles.
- Appropriate reagentsreacts with three membered heterocycles to form alkenes(deoxygenation, desulfonation, deamination) and heteroatoms are removed.
- Oxygen-containing heterocycles can be synthesized by the action of peroxycompounds or per acids on alkenes, ketones or imines.
- Ring-opening by nucleophiles proceeds more slowin case of threememberedheterocycles and is catalysed by acids.

7.14 SUMMARY

The reactivity of the heterocyclic compounds is determined mainly by the ring strain and also by the nature of the heteroatom.

A typical reaction of three-membered heterocycles is nucleophilic ringopeningreactions resulting in the formation of 1,2-disubstituted aliphatic compounds.

Due to the presence ofnonbonding electron pairs inthree or four membered heterocycles they behave as Brönsted bases as well as Lewisbases.

Accordingly, they will react with Brönsted acids and also with electrophiles. Appropriate reagentsreacts with three membered heterocycles to form

alkenes(deoxygenation, desulfonation, deamination) and heteroatoms are removed.

Oxygen-containing heterocycles can be synthesized by the action of peroxycompounds or per acids on alkenes, ketones or imines.

Ring-opening by nucleophiles proceeds more slowin case of three memberedheterocycles and is catalysed by acids.

7.15 REFERENCES :

1. R.R. Gupta, M. Kumar and V. Gupta, Heterocyclic Chemistry I, Springer, 1998.
2. Raj K. Bansal, Heterocyclic Chemistry, IV Edition, New Age International publishers, 2009.

7.16 TERMINAL QUESTIONS:

1. Give the methods of preparation and chemical reactions of aziridines.
2. Give the methods of preparation and chemical reactions of oxiranes.
3. Give the methods of preparation and chemical reactions of thiiranes.
4. Give the methods of preparation and chemical reactions of azetidines.
5. Give the methods of preparation and chemical reactions of oxetanes.
6. Give the methods of preparation and chemical reactions of thietanes.
7. Give the methods of preparation and chemical reactions of indol.
8. Give the methods of preparation and chemical reactions of benzothiophenes.

UNIT 8 : SMALL RING HETEROCYCLES

CONTENTS:

8.1 Introduction

8.2 Objective

8.3 Nomenclature

8.4 Phosphorinanes

8.4.1 Methods of Preparations

8.4.2 Physical Properties

8.4.3 Chemical Properties

8.5 Phosphorines

8.5.1 Methods of Preparations

8.5.2 Physical Properties

8.6.3 Chemical Properties

8.6 Phospholanes

3.5.1 Methods of Preparations

3.5.2 Physical Properties

3.5.3 Chemical Properties

8.7 Phospholes

8.7.1 Methods of Preparations

8.7.2 Chemical Reactions

8.8 Summary

8.9 Terminal Questions

8.10 References and further studies

8.1 INTRODUCTION:

HETEROCYCLIC SYSTEM CONTAINING PHOSPHORUS

The official start of phosphorus-carbon heterocyclic chemistry took place in 1915and first described compound 1-phenylphosphinane, but the actual development of thisfield wasbegun only after 1970.Heterocyclic chemistry has a significant contribution to medicinal, pharmacological chemistry and biochemistry. Phosphorus-containing heterocycles are important structural moieties for most drugs. Many phosphorus heterocycles are potential bioactive compounds and exhibit anti-inflammatory, antitumoral, antibacterial, antihypertensive and insecticidal activities. Although some of the compounds are still of academic interest only.Phosphorus, an excellent and versatile building block of aromatic systems, is an element with less electronegativity than that carbon. This makes the efficient replacement of carbon with phosphorus possible. This versatility is attributable to the many different bonding modes available for the phosphorous element. The phosphorous heterocycles can be classified based on the ring size (specifically five- or six-membered) and by their saturated or unsaturated character.

The five-membered saturated phosphorus heterocycles, known as phospholanes, have found use in asymmetric synthesis as chiral ligands. They exhibit high activity and enantioselectivity in a vast array of catalytic transformations such as the hydrogenation of unsaturated substrates, reductive amidation, allylboration of ketones, and hydroformylation of olefins and [4+1] cycloaddition. The five-membered unsaturated heterocycles known as phospholes are the phosphorus analogues of pyrrole and serve as ligands for transition metals and as precursors to more complex organophosphorus compounds. The six-membered phosphorus-containing unsaturated heterocyclic compound, known as phosphinine (also known as phosphorine), is an analogue of pyridine, containing a phosphorus atom instead of a nitrogen atom. Their derivatives are used in transition metal-mediated reactions including palladium or nickel-catalyzed coupling reactions. The saturated six-membered heterocyclic compound is known as phosphinane and is used as a ligand in hydrogenation processes.

This unit focuses on the synthesis and propertiesof heterocycles. It evokes new interest in the field and gives a direct impact on further developments and discoveries. The main emphasis

is placed on the five- and six-membered phosphorus heterocycles of different substitution, constitutional, and annulation patterns. Each heterocyclic system is represented with the discussion on properties, general applications, and supported thoroughly by an illustration of synthetic methods. The discussion of the particular heterocyclic system begins with a general overview of the structural varieties and discussion of applications, followed by a short analysis of chemical properties, with the focus on the protocols that are used or can be used for the synthesis of complex organophosphorus compounds. The chapter discusses the properties, applications, and synthetic scope, covering the literature of the past 30 years, with an emphasis on the recent literature sources.

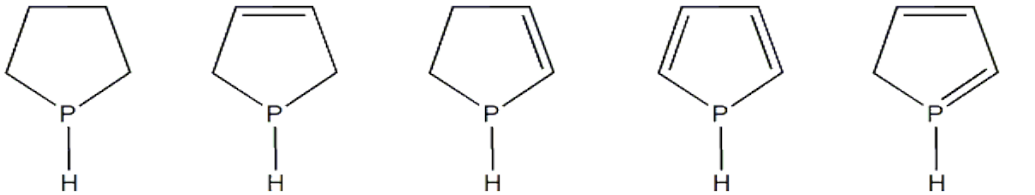
8.2 OBJECTIVE:

Organophosphorus compounds are organic compounds containing carbon-phosphorus bonds, these compounds are mostlyusedprimarily in pest control. These compounds are good insecticides, although some are lethal to humans and some of these compounds arethe most toxic manmadesubstances ever created

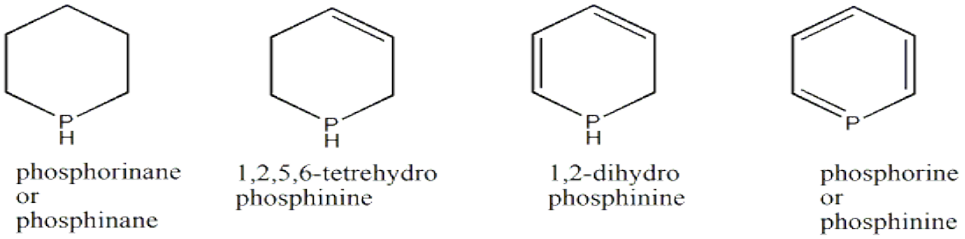
8.3 NOMENCLATURE:

Five-membered phosphorus heterocycles are analogous to pyrrole and six-membered phosphorus-containing heterocycles are pyridine analogues.

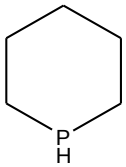
(a) 5-Membered ring system: Tertiary phosphine incorporated in the saturated five-membered ring are mostly stable and exhibits all of the usual properties. This is also true of the two isomeric systems that contain one double bond*i.e.*3-phospholene and 2-phospholene.



(b) 6-Membered ring system: Tertiary phosphine incorporated in the saturated six-membered ring are mostly stable and exhibits all of the usual properties.



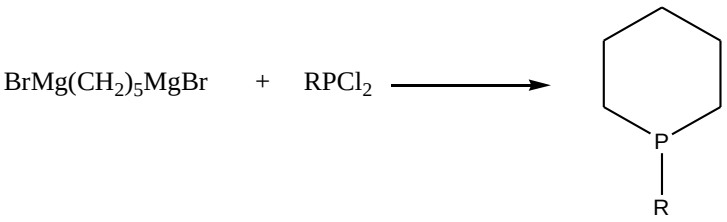
8.4 PHOSPHORINANES:



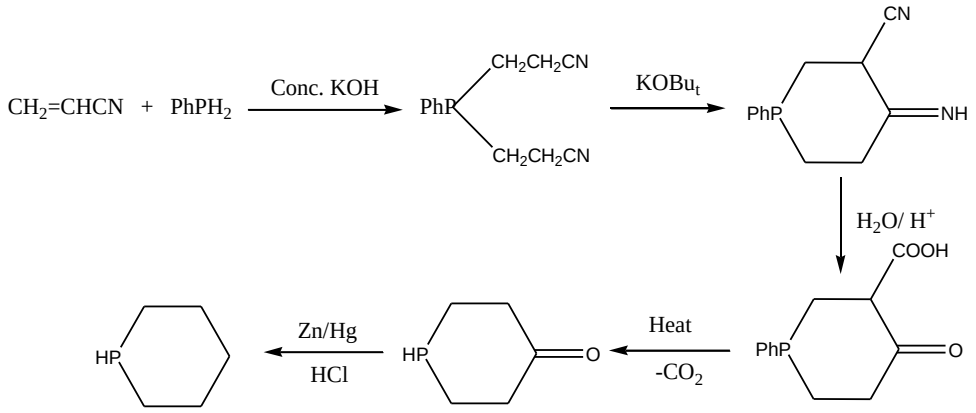
The saturatedphosphorinanes are also known as phosphinanes.Phosphinane is an organophosphorus compound with the formula $(CH_2)_5PH$. This compound is the parent member of the family of six-membered, saturated rings containing phosphorus. The structure of this ring is flexible cyclohexane-like chair conformation.Phosphinanesare mainly of academic interest.

8.4.1 Methods of Preparations:

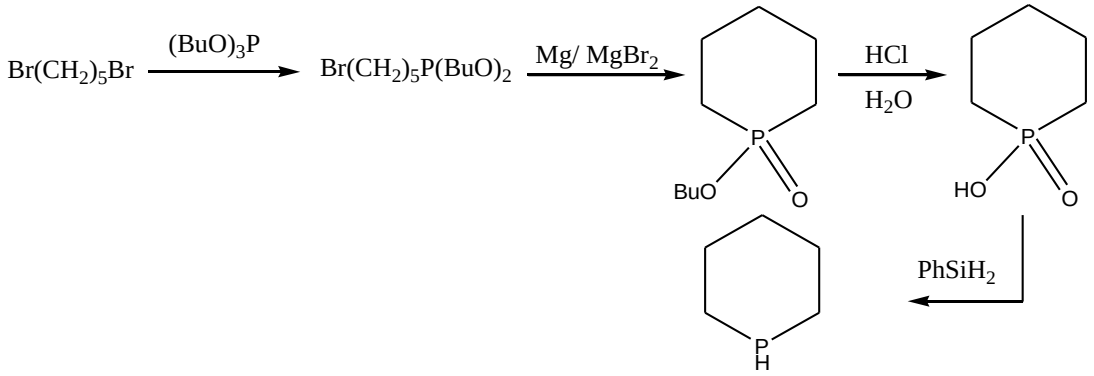
(i) From 1,5- pentane derivatives:1,5-pentane dimagnesiumbromide on treatment with alkyl derivative of phosphorus trichloride gives alkyl derivative of phosphorinanes.



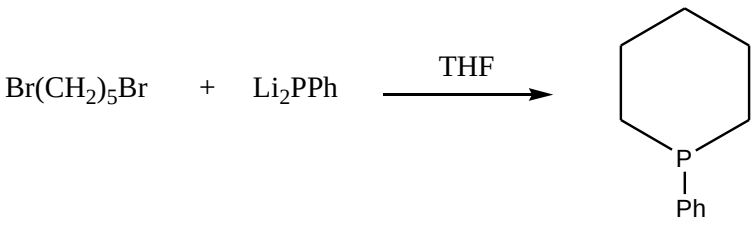
(ii) From cyanoalkene:Cyanoalkene on treatment with phenyl phosphene in presence of conc. KOH gives the addition product which cyclizes in presence of potassium *tert.* butoxide. This on hydrolysis and reduction gives phosphorinane.



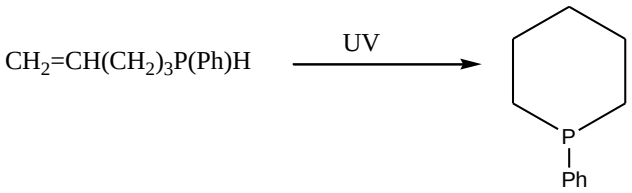
(iii) From 1,5- dibromo pentane:1,5- dibromo pentaneis treated with phosphine tributoxide to obtain a substitution product. This cyclises and reduced to obtain phosphorinane.



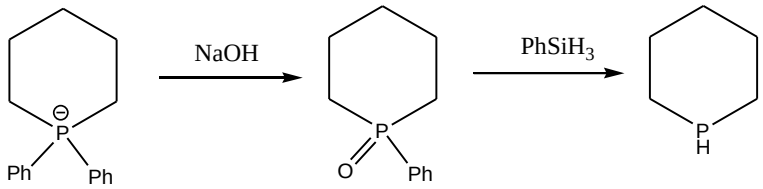
(iv) From pentane derivatives:1,5-dibromopentane when directly treated with Li_2PPh in presence of tetrahydrofuran to give phosphorinane.



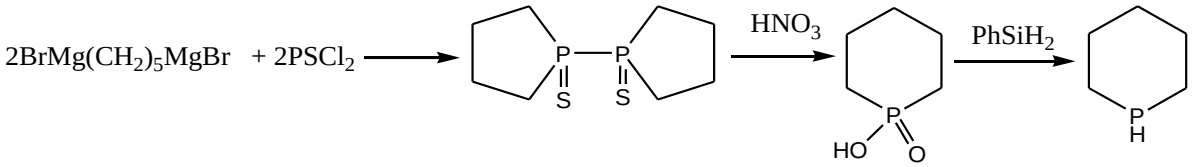
(v) By photochemical reaction: Photochemical cyclisation of trialkenyl phenyl phosphorus hydride gives phosphorinane.



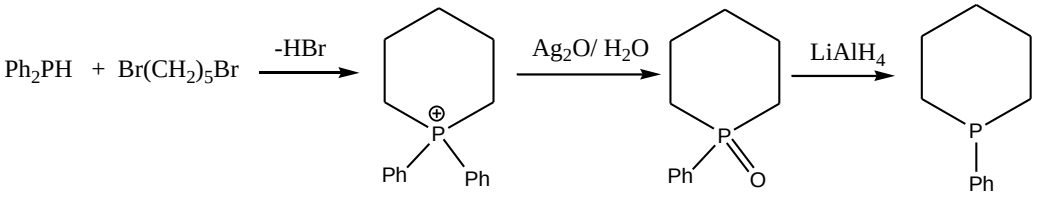
(vi) By phosphonium salts: Diphenyl phosphonium salt gets oxidised by NaOH which further on reduction gives phosphorinane.



(vii) From pentane 1,5-dimagnesium bromide: The product obtained by reaction of pentane 1,5-dimagnesium bromideand $PSCl_2$ is further rearranged to phosphorinane.



(viii) From diphenylphosphine: 1,5-dibromopentane on treatment with diphenylphosphine gives diphenyl phosphonium salt which on oxidation and reduction produces phosphorinane.

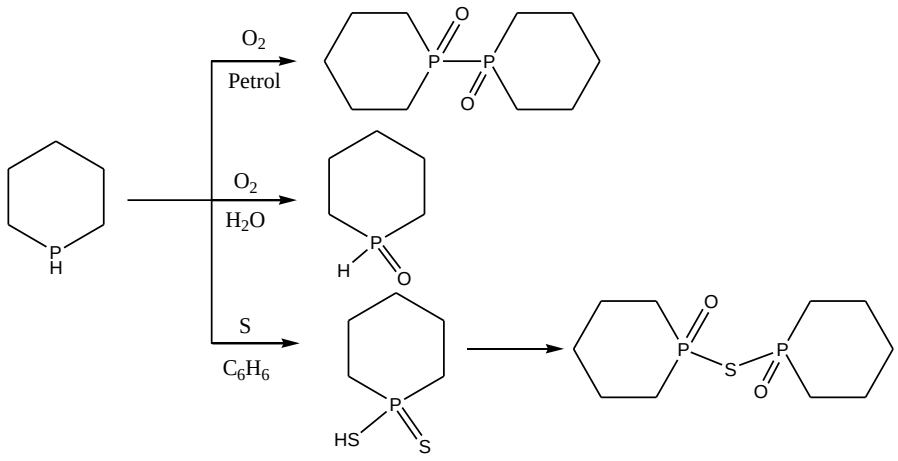


8.4.2 Physical Properties:

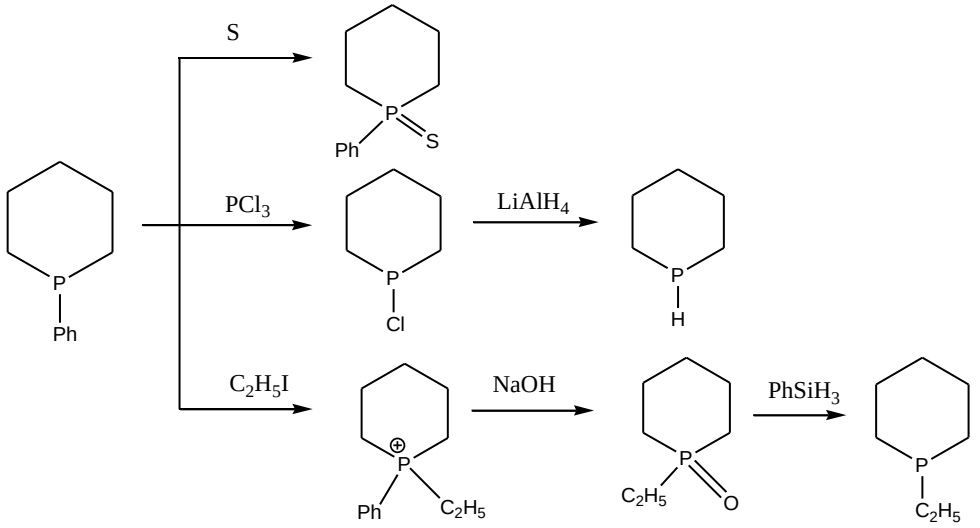
Phosphorinane is a colourless liquid and has a boiling pointbetween 118-121°C. It has a characteristic phosphine odour.

8.4.3 Chemical Properties

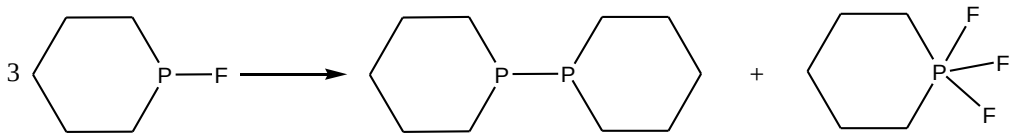
(i) Phosphorinane can be oxidised by O_2 or S in organic solvent or water to obtain different products. The product is oxidised at phosphorus atom or may also be dimerised. The reaction is shown below-



(ii) 1-phenylphosphorinane when treated with sulphur it getssulfonated at sulphur. 1-phenylphosphorinane give phosphorinane when treated with phosphorus trichloride and lithium aluminium hydride stepwise.It also gives 1-ethylphosphorinane on treatment with ethyl iodide, sodium hydroxide and phenyl silane, stepwise.



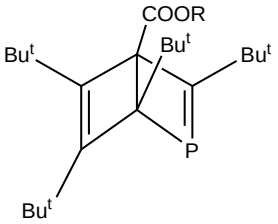
(iii) Fluorophosphorinane undergoes disproportionation by keeping for a long time.



Fluorophosphorinane

8.5 PHOSPHORINES:

The discovery of 2,4,6-triphenylphosphinine byMarkl in 1966 was a landmark ofphosphorus chemistry. It proved simultaneously that simple compounds containingdicoordinate phosphorus could be stable and that phosphorus could participatein a cyclic delocalization. The somewhat less stable parent system wascharacterized five years later by Ashe. Since phosphorus is less, whereas nitrogenis more, electronegative than carbon, the heteroatom is electron-poor in phosphinanes and electron-rich in pyridines. Thus, although both systems are highlyaromatic, their chemistry is completely different.



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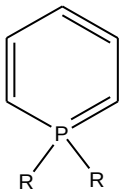
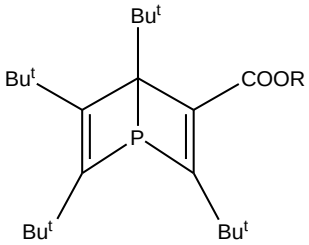
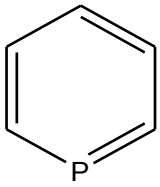


2



3

Phosphorine (IUPAC name: phosphinine) is an analogue of pyridine, containing a phosphorus atom instead of aza moiety. It is also called phosphabenzene and belongs to the phosphaalkene class. Phophorine is generally stable against air and moisture. It also can be handled without special inert Atmosphere equipment. This stability of phosphorine comes from the close electronegativities of phosphorus and carbon.



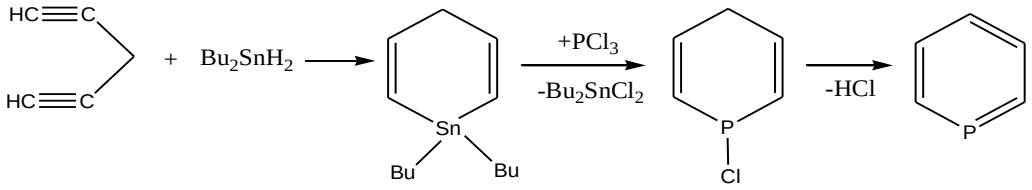
Spectral, Structural and Theoretical Studies

Phosphinines have been extensively characterized by ^{1}H, ^{13}C, and ^{31}P NMRspectroscopy. Phosphinines display the characteristiclow-field shifted ^{31}P resonances of phosphaalkenes. The huge ^{1}J (C-P) coupling is also noteworthy. Conversely, l5-phosphinines show more conventionalylid-like resonances. The 1,1-dimethyl derivative **2** (R=Me)displays a ^{31}P resonancearound 0 ppm and shows highly shielded Ha and Ca resonances at 3.98 and67.5 ppm, respectively. These data are in line with the high concentration of negative charge at thea- and c-positions of 2.

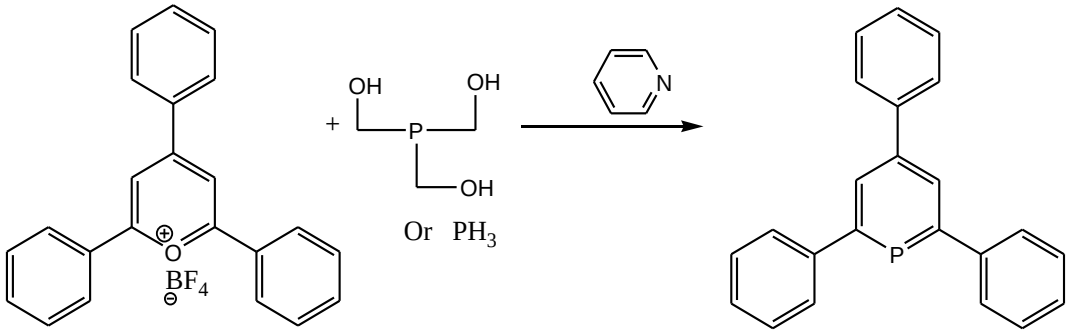
8.5.1 Methods of Preparations

(i) From alkyne derivatives: Pent-1,4-diyne when treated with dibutylstannoushydidegets cyclised, this on further treatment phosphorus trichloride gives phosphorine. The synthesis

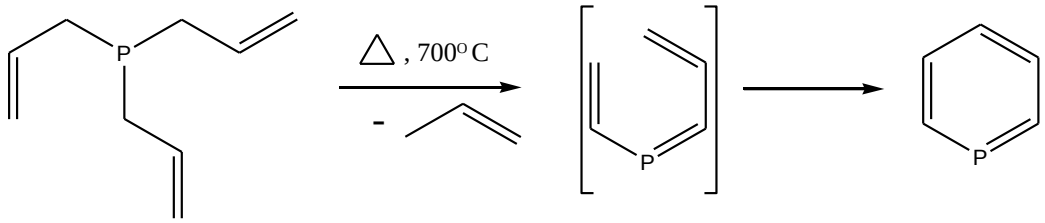
of the parent phosphinine by Ashe [94] relies on a tin to P exchange in a1,4-dihydro-stannabenzene.



(ii) From pyrylium salt: There is a wealth of synthetic methods for making phosphinines and discriminating between those which, ultimately, will prove the most useful is difficult. The initial method ofMarkl relying on theO^+ to Pexchange in pyrylium salts is still a method of choice due to its simplicity.



(iii) The parent phosphinine is more easily obtained by pyrolysis of vinyldiallylphosphine.



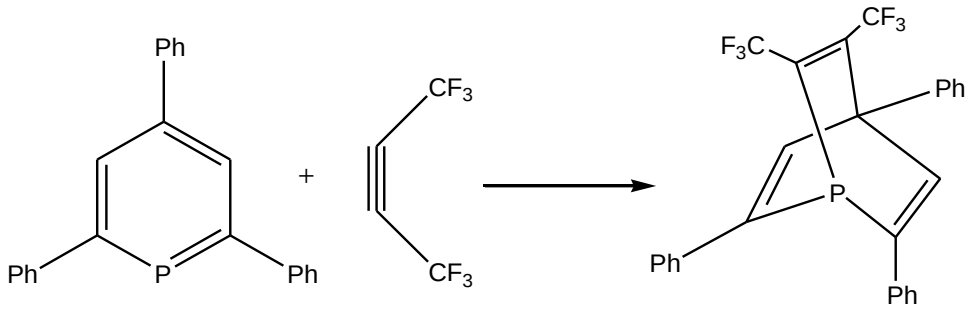
8.5.2 Physical Properties

Phosphorine is a colourless volatile liquid which is very reactive, air sensitive and characteristic odour.

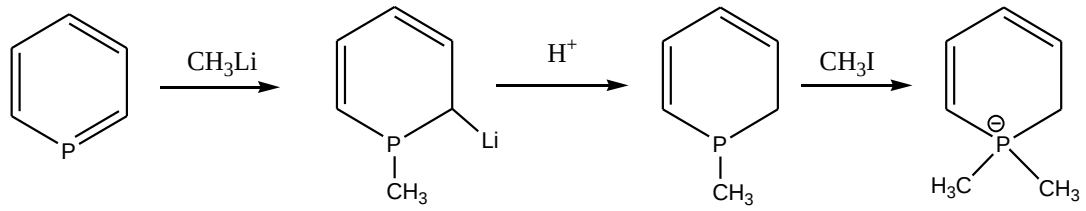
8.5.3 Chemical Properties

Phosphorine is a planar aromatic compound with 88% of the aromaticity of benzene.

(i) Diels alder reaction:

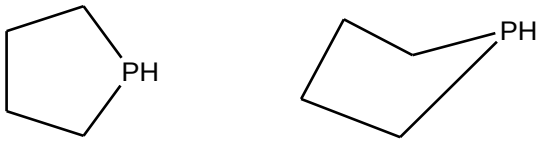


(ii)Reaction with methyl lithium: It reacts with methyl lithium in the acidic medium it gives 1,1-dimethyl phosphorinium salt.



8.6 PHOSPHOLANES:

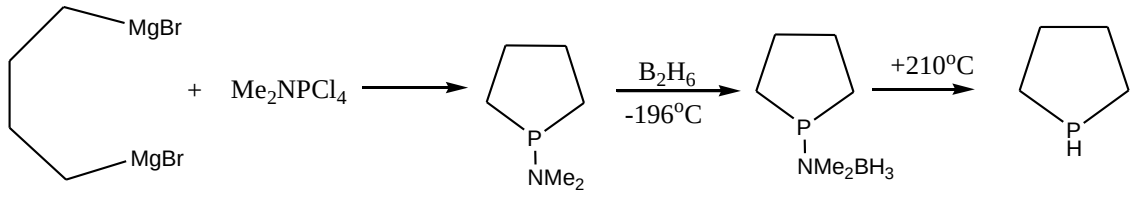
Phospholane is the organophosphorus compound with the formula $(CH_2)_4PH$. Phospholaneusually adopts a folded envelope configuration with which there are two possible alternative arrangements 1 and 2.



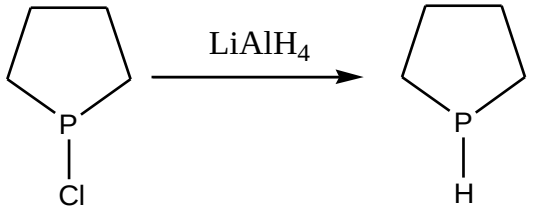
1 **2**

8.6.1 Methods of Preparations

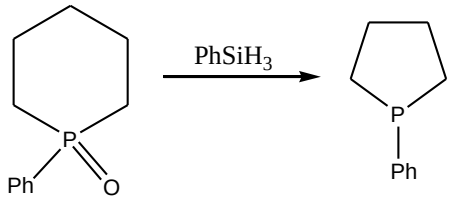
(i) Phospholane can be prepared via the dimethylamine borane adduct.



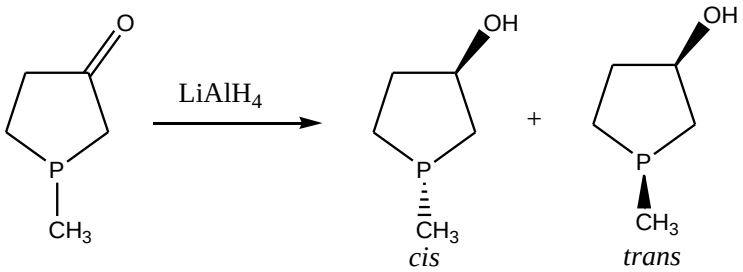
(ii) From chloro derivative: 1-chlorophospholane on reduction by lithium aluminium hydride gives phospholane.



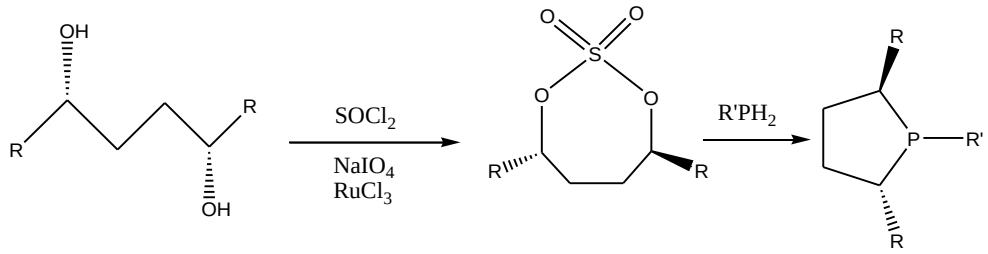
(iii) From phenyl phospholane-1-oxide: Phenyl phospholane-1-oxide when reduced by phenyl silane gives phospholane.



(iv) 3-oxo-1-methylphospholane on reduction by lithium aluminium hydride gives *cis* and *trans-3-hydroxy-1-methylphospholane*.



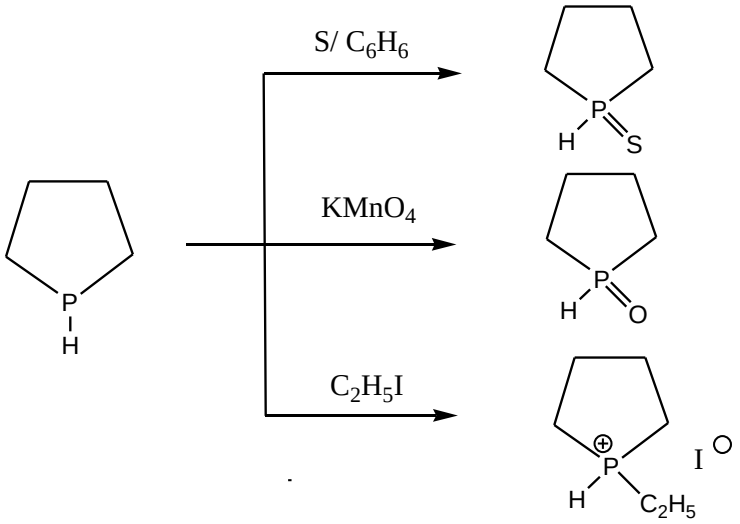
(v) 1,4-Dialkylbutan-1,4-diol when treated with thionyl chloride and further oxidised by sodium periodate gives a cyclic sulphone ether. This product on treatment with alkyl phosphine gives trialkyl phospholane.

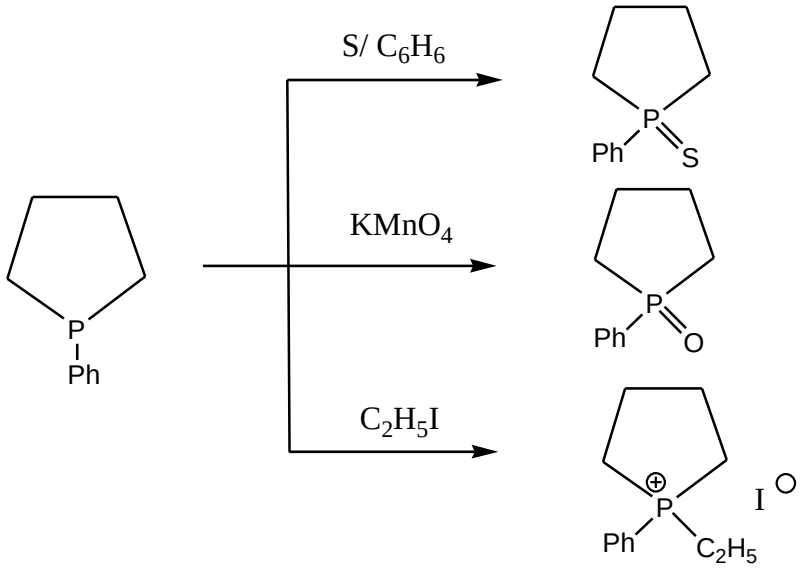


8.6.2 Physical Properties

It is acolourless liquidwitha boiling pointof 103°C.

8.6.3 Chemical Properties

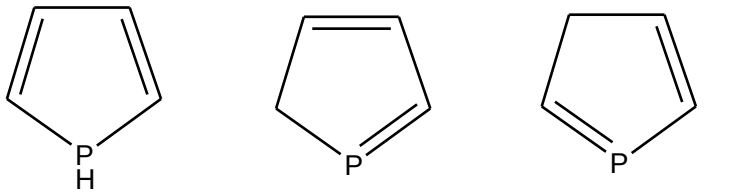




8.7 PHOSPHOLES:

The story of phospholes started in 1959 with the discovery of the pentaphenyl derivative. It is a phosphorus analogue of pyrrole.The unstable parent system was characterized by NMR spectroscopyat low temperatures in 1987. Phospholes are pyramidal at P. The reason lies in the intrinsically high inversionbarrier of trivalent phosphorus, which overcomes the aromatic stabilization of theplanar state. As a result, phospholes are poorly aromatic and their chemistry is widelydifferent from that of pyrroles.

Three isomers of the phosphole system are known, namely, the 1H-, 2H-, and 3H-phospholes but, in practice, the 2H and 3H systems incorporatingdicoordinate P-centers are unstable except when fully substituted by bulkygroups and mainly intervene in the chemistry of phospholes as reactive intermediates.Conversely, the phospholide ion, isoelectronic with thiophene, is highlystable and aromatic.



1H-phosphole **2H-phosphole** **3H-phosphole**

Spectral, Structural and Theoretical Studies:

Phospholes have been characterized mainly by ^{1}H, ^{13}C, ^{31}P-NMR spectroscopy andX-ray crystal structure analysis and thoroughly studied from a theoretical standpoint.Broadlyspeaking, the NMR spectra of phospholes do not show any exceptionalfeatures, for example, δ31P (1-methylphosphole) = 8.7 ppm (85% H_3PO_4 asexternal reference, δ positive for downfield shifts). In contrast, whereas phosphide ions resonate around 0 ppm (Ph_2P δ-19 ppm in THF with Na^+ as the counterion), the parent phospholide (Li^+)resonates at δ 77.2 ppm in THF, and resonances at much lower fields can beobserved according to the substitution scheme (e.g., with 2,5-dibenzoyl-3,4-dimethyl, δ 209.6ppm). This deshielding has been explained by the presence of the in-planeP-lone pair, which is only weakly coupled to the ring and induces a largedownfield paramagnetic shift of the ^{31}P resonance.

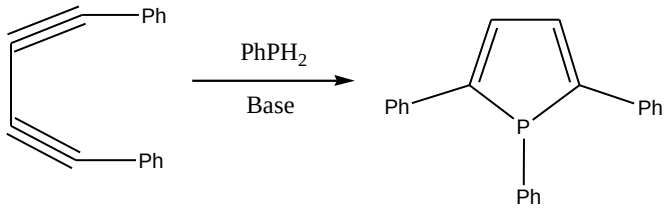
X-Ray structural studies of phospholes show a somewhat flattened P-pyramid andsome shortening of the P_C ring bonds. The alternation between single and doubleCC ring bonds is higher than in the corresponding pyrroles, thiophenes and furans.The structure of 1-benzyphosphole is given as an example: ring P-C, 1.783 Å;C-C, 1.343 Å; C-C, 1.438Å; internal <C-P-C, 90.7°. Thesedata reflect the low aromaticity of the phosphole ring. Sizeable variations have beenobserved in the pyramidality of the phosphole phosphorus. Presently, the mostpyramidal structure has been recorded for 1-cyano-3,4-dimethylphosphole.

Hydrogen migrates very easily from phosphorus to the α-carbon, themigrating ability varies widely for other groups. Some groups such as alkyl or alkoxydo not migrate under conditions that are compatible with the stability of thephosphole ring, while others migrate under acceptable heating such as aryl, alkynyl,CN, SR, and so on, and others migrate even below room temperature, such as acyland silyl.

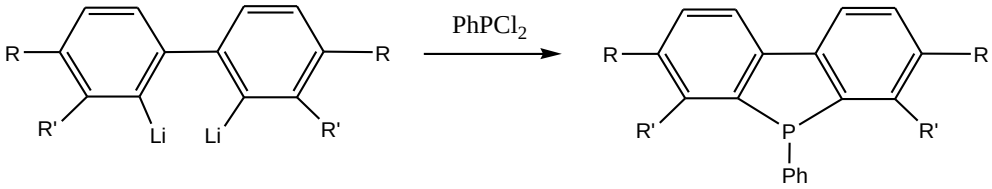
8.7.1 Methods of Preparations

There are three main syntheses of the phosphole ring.

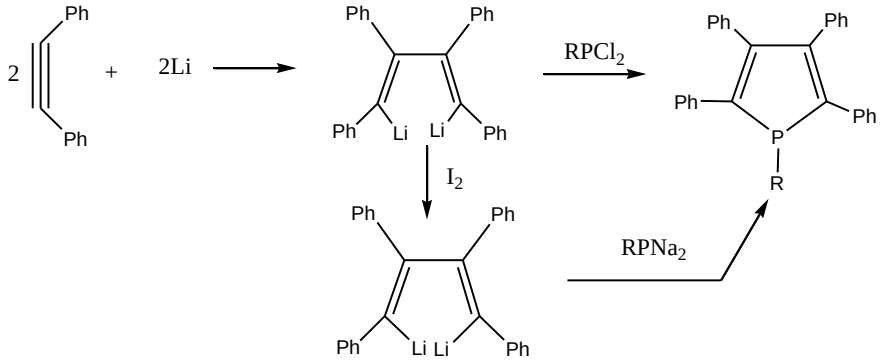
(i) From aryl alkyne derivative:It involves the cycloaddition of primary phosphines with substituted 1,3-diynes. The reaction is catalyzed by strong bases (in general BuLi) and provides convenient access to 1,2,5-trisubstituted phospholes. This method has been used to prepare a phosphole with two optically active(-) phenyl substituents at the 2,5-positions.



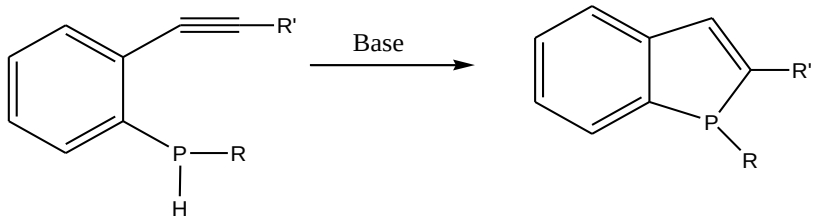
(ii) From aryl lithium compound:



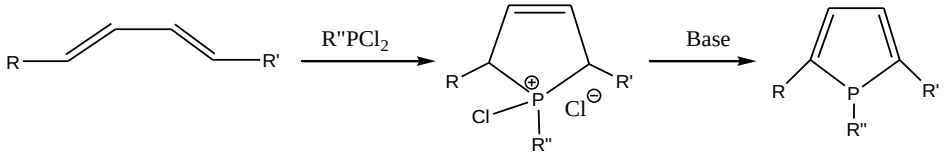
(iii) From substituted alkyne:



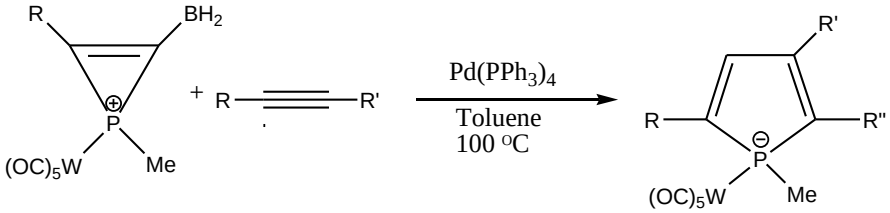
(iv) From aryl phosphine :



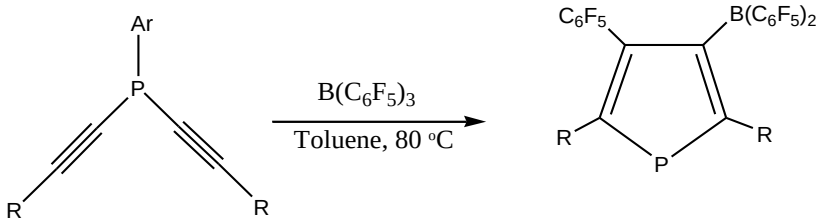
(v) From substituted diene :



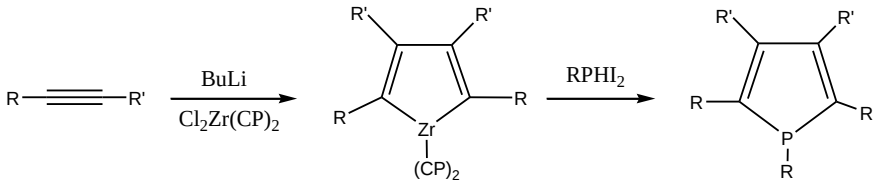
(vi)



(vii)



(viii)

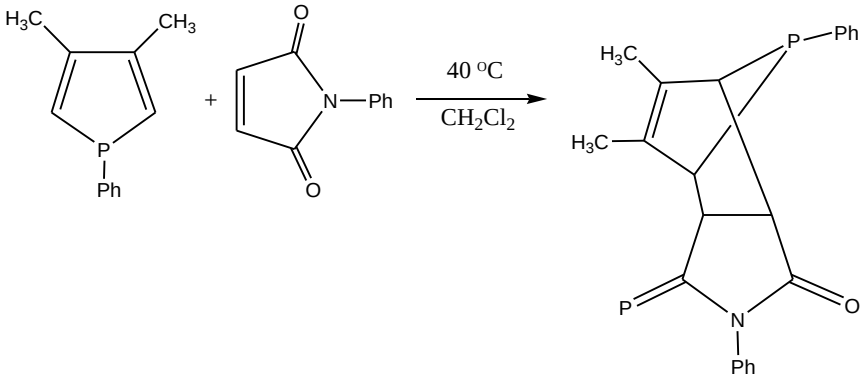


Reactivity

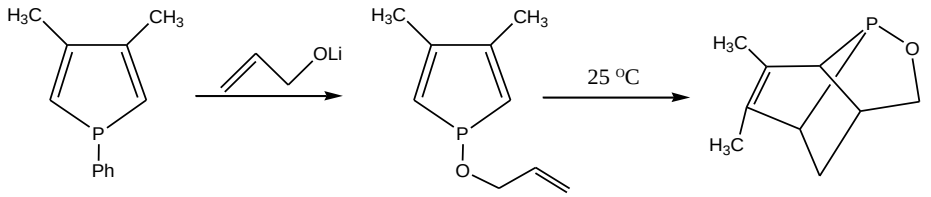
Since phospholes are not aromatic, their chemistry is completely different from thatof their nitrogen, oxygen or sulphur analogues. The classical electrophilic substitutionreactions are unknown and the ring can behave either as phosphine or as cyclopentadiene. It is quite convenient to divide the reactions of phospholes betweenthose taking place at P, at the diene, the [1,5]sigmatropic shifts, the functionalizationreactions, the ring openings and the ring expansions. A few words on the rich anddiverse complexation chemistry will close this survey.

8.7.2 Chemical Reactions

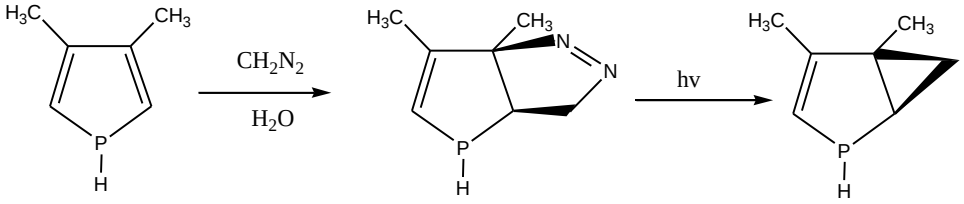
(i)



(ii)



(iii)



8.8 SUMMARY

Pyridine has good electrondonating ability than phosphorine. The lone pair of electrons on pyridine is its HOMO. On the other hand,the lone pair of phosphorineis located at the lower energy level*i.e.*LUMO. Thesephosphorines are much better π- acceptor ligands. Phosphorinesundergo electrophilic substitution reactions like aromatic compounds *e.g.* bromination, acylation etc.

8.9 TERMINALQUESTIONS:

Q.1. What are phosphorinanes? Give any two methods of preparation ofphosphorinanes.

Q.2. What is the difference between phospholes and phosphorines?

8.10REFERENCES AND FURTHER STUDIES:

1.Modern Heterocyclic Chemistry, First Edition. Edited by Julio Alvarez-Builla, Juan Jose Vaquero, and José Barluenga. Wiley-VCH Verlag GmbH & Co. . Published 2011.