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# KARPAGAM ACADEMY OF HIGHER EDUCATION

*(Deemed to be University Established Under Section 3 of UGC Act 1956)*

Coimbatore – 641 021.

## LECTURE PLAN

## DEPARTMENT OF CHEMISTRY

**STAFF NAME**: Dr.M.R.Ezhilarasi & B.Prabha

**SUBJECT NAME**: CHEMISTRY OF NATURAL PRODUCTS **SUB.CODE**:15CHU601

**SEMESTER**: VI **CLASS**: III B.Sc., CHEMISTRY

| S.NO | Lecture Duration (Hr) | Topics to be covered | Support Materials |
|---|---|---|---|
| | | **UNIT-1 Terpenoids** | |
| 1 | 1 | Terpenoids : Introduction | T1: 368, T2 : 1.1 |
| 2 | 1 | Definition and Nomenclature | T1 : 368 , T2 :1.1 |
| 3 | 1 | General properties and isolation of Terpenoids | T1 : 368 , T2 :1.3 |
| 4 | 1 | Isoprene rule | T1 : 369 |
| 5 | 1 | General methods for determination of structure of terpenoids i) chemical properties | T1 :370 , T2 : 1.9 |
| 6 | 1 | General methods for determination of structure of terpenoids ii) Physical properties | T1 : 370 , T2 : 1.9 |
| 7 | 1 | Stuctural elucidation and Synthesis of geraniol | T1 : 370 , T2 : 1.40 |
| 8 | 1 | Structural elucidation of α – Terpineol | T1 : 383 , T2 : 1.54 |
| 9 | 1 | Synthesis and reaction of σ – Terpineol | T1 : 383 , T2 : 1.57 |
| 10 | 1 | Structural elucidation of α – Pinene – method (I) | T1 : 401 , T2 : 1.92 |
| 11 | 1 | Structural elucidation of α – Pinene – method (II) | T1 : 401 , T2 : 1.95 |
| 12 | 1 | Synthesis of α– Pinene | T1 : 403 , T2 : 1.96 |
| 13 | 1 | Stereochemistry of α– Pinene | T1 : 405 , T2 : 1.96 |
| 14 | 1 | Structural elucidation of Dipentene ( Limonene ) and Synthesis of Dipentene | T1 : 389 , T2 : 1.50 |
| 15 | 1 | Recapitulation and discussion of important questions | |
| | **Total No of Hours Planned For Unit 1=15** | | |
| | | **Unit-II** | |
| 1 | 1 | Alkaloids - Introduction, Nomenclature & classifications | T1:710,716,T3:3 |

| | | | |
|---|---|---|---|
| 2 | 1 | Isolation of alkaloids | T1:711,T3:3-4 |
| 3 | 1 | General properties | T1:711,T3:3-4 |
| 4 | 1 | General methods employed for determinining the structures of alkaloids | T1:711,T3:3-6 |
| 5 | 1 | Physical methods | T3:3.6-3.19 |
| 6 | 1 | Hofmann's exhaustive methylation | T1:712,T3:3.11 |
| 7 | 1 | Structural elucidation and Synthesis of nicotine | T1:731,T3:3.45 |
| 8 | 1 | Conine-constitution | T1:723,T3:3.33 |
| 9 | 1 | Synthesis of Conine | T1:727,T3:3.33 |
| 10 | 1 | Structural elucidation and Synthesis of piperine | T1:730 |
| 11 | 1 | Structural elucidation of papavarine | T1:758 |
| 12 | 1 | Synthesis of veratric acid and meta hemipinic acid | T1:759 |
| 13 | 1 | Synthesis of papavarine | T1:761,T3:3.87 |
| 14 | 1 | Multiple choice questions discussions | |
| 15 | 1 | Recapitulation and discussion of important questions | |
| | **Total No of Hours Planned For Unit 2=15** | | |
| | | **Unit-III** | |
| 1 | 1 | Vitamins-Introduction | T1:843 |
| 2 | 1 | Nomenclature of Vitamins | T4:1-2 |
| 3 | 1 | Classification of Vitamins | T4:1-2 |
| 4 | 1 | Structural Elucidation of Retinol(Vitamin-A) | T1:491,T4:3-6 |
| 5 | 1 | Synthesis of Retinol | T1:492,T4:6-14 |
| 6 | 1 | Structural elucidation of Thiamine(Vitamin-B1) | T1-844,T4:18 |
| 7 | 1 | Synthesis of Thiamine | T1:844,T4:23 |
| 8 | 1 | Structural Elucidation of Riboflovin | T1:848,T4:24 |
| 9 | 1 | Synthesis of Riboflovin | T1:849,T4:26 |
| 10 | 1 | Biological functions of vitamin –B6 | T1:861 |
| 11 | 1 | Ascorbic acid structural elucidation and synthesis (Vitamin-C) | T1:388,T4:64 |
| 12 | 1 | Some special reactions of Ascorbic acid | T4-71 |
| 13 | 1 | Biological functions of Ascorbic acid | T4:72 |
| 14 | 1 | Determination of ascorbic acid | T4:73-74 |
| 15 | 1 | Recapitulation and discussion of important questions | |
| | **Total No of Hours Planned For Unit 3=15** | | |
| | | **Unit-IV** | |
| 1 | 1 | Hormones: Introduction | T1:721,T4:317 |
| 2 | 1 | Adrenaline- Structural elucidation | T1:722 |
| 3 | 1 | Synthesis of adrenaline | T4:319 |
| 4 | 1 | Structural elucidation of Thyroxine | T1:668,T4:320 |
| 5 | 1 | Synthesis of Thyroxin | T1:669,T4:323 |
| 6 | 1 | Steroids : Introduction – Cholesterol | T1:531,T4:235 |
| 7 | 1 | Constitution of cholesterol – Structure of the nucleus | T4:237 |
| 8 | 1 | Position of the OH group an double bond | T1:533,T4:237 |
| 9 | 1 | Nature and position of the side chain | T1:537 |
| 10 | 1 | Position of the angular methyl group, | T4:241 |

| | | | |
|---|---|---|---|
| | | Stereochemistry | |
| 11 | 1 | Enzymes : Introduction, Nomenclature – classification | T1:697,T4:389 |
| 12 | 1 | Properties of enzymes and Chemical nature of enzyme | T1:698,T4:394,398 |
| 13 | 1 | Mechanism of enzyme action | T1 :700 – 702 |
| 14 | 1 | Synthetic approach and fermentation | T4 : 411 – 418 |
| 15 | 1 | Recapitulation and discussion of important questions | |
| | **Total No of Hours Planned For Unit 4=15** | | |
| | | **Unit-V** | |
| 1 | 1 | Chemotherapy : Introduction | T1 : 875 |
| 2 | 1 | Lethal dose, Sulpha drugs | W1, T1:875-877 |
| 3 | 1 | Antimalarial | T1:877-878 |
| 4 | 1 | Amoebicidal drugs and Antiseptics | R1:1070, 1072 |
| 5 | 1 | Antipyretics & Analgesic | T1:879,R1:1067 |
| 6 | 1 | Antibiotics – Introduction - classification | T4:98-100 |
| 7 | 1 | Production and isolation of penicillin | T1:879,T4:100 |
| 8 | 1 | Constitution and properties of penicillin | T4:102-109 |
| 9 | 1 | Production , Isolation ,Constitution and properties of streptomycin | T1:891,T4:116 |
| 10 | 1 | Production, Isolation ,Constitution and properties of Chloramphenicol ( Chloromycetin) | T1:895, T4:123 |
| 11 | 1 | Constitution and properties of tetracyclines | T1:892,T4:129 |
| 12 | 1 | Recapitulation and discussion of important questions | |
| 13 | 1 | Discussion of previous ESE question paper | |
| 14 | 1 | Discussion of previous ESE question paper | |
| 15 | 1 | Discussion of previous ESE question paper | |
| | **Total No of Hours Planned For Unit 5=15** | | |
| **Total Hour's Planned** | **75** | | |

**TEXT BOOKS:**

T1: Finar, I.L., 2013. Organic Chemistry, Vol. II, Pearson Education, Singapore.

T2: Gurdeep R.Chatwal, 2013. Organic Chemistry of Natural Products, Vol. II, Himalaya Publishing House, New Delhi

T3: Gurdeep R.Chatwal, 2007. Organic Chemistry Of Natural Products, Vol. I, Himalaya Publishing House, New Delhi

T4: Agarwal,.O.P, 2003. Natural Product Chemistry, Goel Publishing House, Meerut.

**REFERENCES**

R1: M.K./Jain, S.C.Sharma, 2012, Modern Organic chemistry, Vishal Publishing Co, Tagore press, Jalandhar.

**WEBSITE:**

W1: http// lethal dose

## UNIT-I

## SYLLABUS

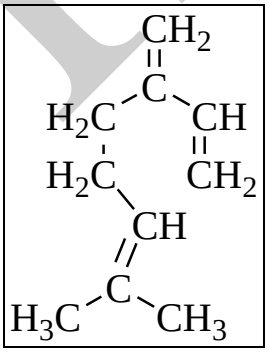
***Terpenoids** : Introduction – Classification – General methods of isolation – Isoprene rule- Structural elucidation and synthesis of geraniol, terpinol, dipentene and alpha-pinene.*

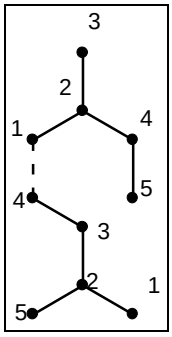
## Introduction

### *Definition*

- Originally, the term "terpene" was employed to describe a mixture of isomeric hydrocarbons of the molecular formula $C_{10}H_{16}$ occurring in the terpentine and many essential oils which are obtained from the sap and tissues of certain plants and trees.
- The oxygenated derivatives like alcohols, aldehydes, ketones, etc. at the time were called camphor's.
- As more compounds relating to terpenes and camphor's were discovered with the pace of time, both the terms "terpenes" and "camphors" were amalgamated into a single term called "terpenoids".
- The *Modern definition* of this term is,

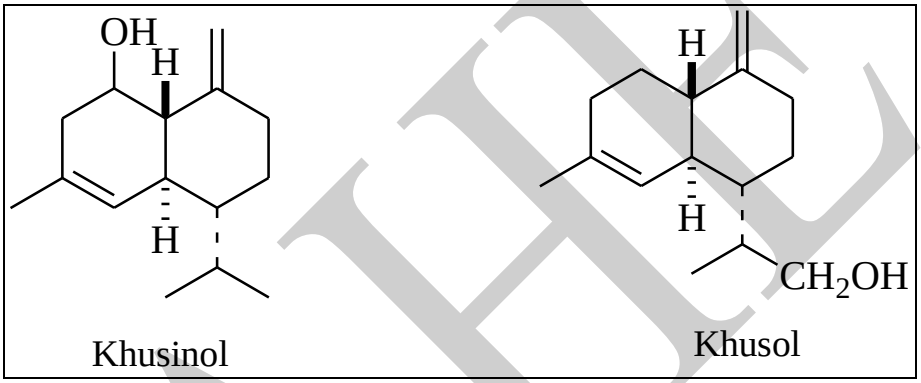
  It includes hydrocarbons of plant origin of the general formula $(C_5H_8)_n$ as well as their oxygenated, hydrogenated and dehydrogenated derivatives.
- As terpenoids are composed of isoprene units, these are sometimes called "isoterpenoids".
- Not only the carbon skeletons of terpenoids are divisible into isoprene units but the terpene hydrocarbons are usually exact multiplies of $C_5H_8$.
- An example is mycerene ($C_{10}H_{16}$) which has a carbon skeleton divisible into 2 isoprene units.






### *Nomenclature*

- Many terpenoids are known by their trivial names because these were isolated and described in the literature long before their structures were elucidated.
- Generally these trivial names are derived from their botanical origins.
- For eg: the crystalline sesquiterpene secondary alcohol belonging to the cadinane group was isolated from vetiver oil (Vetiveria Zizaniodides) and named 'khus' oil in India. Therefore, Its alcohol was called khusinol and another crystalline alcohol with also belonged to the same group and isolated from the same source was called khusol.




***Importance***

- In the recent part, biological activity of various substances has been related with terpenoids.
- Many sesquiterpenes have been found to be active against experimental tumours and the plant growth hormones like gibberellins and diterpenoids.
- As some terpenoids exhibit biological activity viz insecticidal anthelmintic or antiseptic activity. These are used in pharmacy.

***Occurrence***

- Terpenoids are most widespread, chemically interesting and provide structure of great diversity.
- Although the majority of terpenoids occur in plant kingdom, a few of them have also been obtained from other source.
- Most of the fragment components of plants are volatile with steam distillation, solvent extraction or other treatment of the plant. These components are called essential oils.
- These have been used in perfumery from the earliest times

- The simple mono and sesquiterpenoids are the chief constituents of the essential oils.
- However, the di, tri-terpenoids, which are not steam volatile are obtained from plant and resins.
- Unlike mono and sesquiterpenoids, these compounds donot possess any perfumery value.
- The tetraterpenoids constitute a group of compounds called carotenoids.

Important Essential oils with their terpenoids constituents:-

| S.NO | Essential Oil | Constituent Terpenoid |
|---|---|---|
| 1. | Bay | Eugenol |
| 2. | Bergamot | Linalool and its acetate |
| 3. | Caraway | Limonene, Carvone |
| 4. | Camphor | Camphor |
| 5. | Cardamon cajeput | Terpineol |
| 6. | Citronella | Farnesol, citronellal and geraniol |
| 7. | Clove | Eugenol |
| 8. | Coriander | Linalool, α-pinene |
| 9. | Eucalyptus | Cineole |
| 10. | Geranium | Geraniol esters, cintronellol |
| 11. | Ginger | Zinziberene |
| 12. | Jasmine | Linalool |
| 13. | Lavender | Linalool |
| 14. | Lemon | d, l- limonene, citral |
| 15. | Neroli | Nerolidol |
| 16. | Peppermint | Menthol and its esters |
| 17. | Rose | Geraniol, citronellol and Farnesol |
| 18. | Sandal wood | Santalol |
| 19. | Sweet orange | d- limonene |

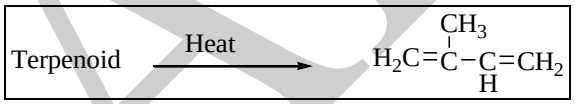
**General Properties of Terpenoids:-**

- Most of them are colourless liquids which are lighter than water and boil between 150-180ºC.

- A few are solids which are lighter than water, volatile in steam, usually highly refractive and insoluble in water but soluble in organic solvents.
- Many of them are optically active.

***Chemical Properties***

- They are unsaturated compounds (Open chain or cyclic with one or more carbon atom rings) having one or more double bonds.
  - It undergoes addition reactions with hydrogen, halogen and halogen acids, etc.
  - Some of them form hydrates
  - They also form characteristic addition products with $NO_2$, NOCl and NOBr. These addition products are found ti be useful in the identification of terpenoids.
  - A number of addition products have antiseptic properties.
- They undergo polymerization and also dehydrogenation in the ring.
- As they have olefinic bonds, they are very easily oxidized nearly by all the oxidizing agents.
- A number of terpenoids are labile and hence readily isomerised in the presence of acids in two more stable forms.
- On thermal decomposition, most of the terpenoids yield isoprene as one of the product.




**Isolation**

Due to their wide occurrence in nature, all the terpenoids could not be isolated and separated by a general method.

However, mono and sesqui-terpenoids have a common source. ie, essential oils and therefore isolation has been generalized, this is carried out in 2 steps.

1. Isolation of essential oils.
2. Separation of terpenoids from essential oils. Let us discuss these steps one by one.

***1. Isolation of essential oils***

As a plant having essential oils generally possess maximum concentration at some particular time.

Eg. Jasmine at sun-set, it becomes desirable to take the plant parts having essential oil at this particular time.

In general, our methods based on different principles have been developed for the extraction of oils.

These methods are discussed as follows:

a) **Expression method**

- This method is not used these days. However, it has the historical importance only.
- In this method, the plant material is cut in to small pieces. These pieces are then crushed to get the juice which is screened to remove longer the large particles.
- After screening, the juice is centrifuged in a high speed centrifugal machine when one-half of the oil is extracted and the rest half of the essential oil remains with the residue.
- From this residue, inferior quality of the oil is obtained by distillation.
- Expression method is generally used to extract citrus, lemon and grass oils.

b) **Steam distillation method**

- This method is one of the most widely used methods. In this method the plant materials are macerated and then steam distilled to get the essential oils into the distillate from which these are extracted by using pure organic volatile solvents like light petroleum and the solvent is then removed by distillation under reduced pressure.
- One should employ steam distillation method carefully because it suffers from the following demerits:-
  - i) Some essential oils undergo decomposition during steam distillation.
  - ii) Some constituents of essential oils eg. Esters, which are responsible for the odour and fragrance of the oil may undergo decomposition resulting in a perfume of inferior industry.

c) **Extraction by mean of volatile solvents**

- This method is widely used in a perfume industry. This method is generally used for such plants which yields oil or give low quantities of oil on steam distillation due to decomposition of essential oils.
- In such cases, the plant material is directly treated with light petrol at 50ºC. Under these conditions 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**

- This method is also known as enfluerage method and 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 rose and jasmine.
- In this method, the fat is warmed to 50ºC on glass plates. Then, the surface of the fat is covered with flower petals and it is allowed to be kept as such for several days until it becomes saturated with essential oils.
- Then the old petals are replaced by fresh petals and this process is repeated.
- After removing the petals, the fat is digested with ethyl alcohol when all the essential oils present in fat are dissolved in alcohol.
- Some quantity of fat is also dissolved in alcohol. This can be removed by cooling the alcohol extract at 20ºC, when the fat separates out.
- The alcohol distillate is then finally fractionally distilled under reduced pressure to remove the solvent.
- Recently, the fat has been replaced by coconut charcoal due to its greater stability and higher adsorptive capacity.
- After keeping the coconut charcoal in contact with petals for a number of days, the charcoal is submitted to steam distillation to get essential oils.
- This method is superior to the enfluerage method.

***2. Separation of terpenoids from essential oils***

The essential oils obtained from the step 1 generally contain a number of terpenoids and these are separated contain a number of terpenoids and these are separated by various physical and chemical methods.

**a) Chemical methods**

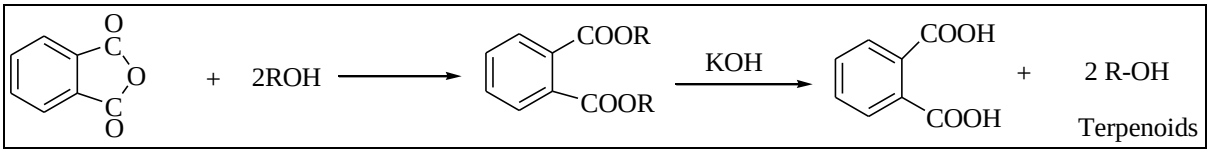
These methods are not used these days to separate various terpenoids from essential oils.

i) When essential oils containing terpenoid hydrocarbons are treated with nitrosyl chloride in chloroform, crystalline adducts of hydrocarbons having sharp melting points are obtained.

These are separated and decomposed in to their corresponding hydrocarbons.

ii) When the essential oils containing alcohols are treated with phthalic anhydride to form diesters, the primary alcohols react with phthalic anhydride readily, secondary alcohols less readily and tertiary alcohols do not react at all.

After extracting with sodiumbi carbonate, diesters are decomposed by alkali to the parent terpenoid alcohols.




iii) Terpenoid aldehyde and ketones are separated from essential oils by forming their adducts with the common carbonyl reagents like $NaHSO_3$, 2,4-dinitrophenyl hydrazine, phenyl hydrazine, semicarbozide, etc.

After separation, these are decomposed to regenerate terpenoid aldehydes and ketones.

**b) Physical Methods**

The various physical methods are as follows:-

**i) Fractional Distillation method**

- The various terpenoids present in essential oils are separated by fractionaldistillation method.
- The terpenoid-hydrocarbons distill over first, followed by the oxygenated derivatives.
- Distillation of the residue under reduced pressure yields the sesquiterpenoids and these are separated by fractional distillation.
- On an industrial scale, especially designed stills are employed and an efficient condensing system is necessary to minimize loss of more volatile hydrocarbons.
- Many times, the fractional distillation has to be carried out under reduced pressure and in the presence of an inert gas. These conditions are essential because many terpenes are sensitive to heat and atmospheric oxygen.

**ii) Chromatography**

- More recently, chromatography in its various forms has been widely used both for isolation and separation of terpenoids.
- In adsorption chromatography, the essential oil is made to flow through a particular adsorbent when the different types of terpenoids are adsorbed at different places on the adsorbent to form different chromatograms.
- Then, the various chromatograms are eluted by different solvent systems to get different eluates (each eluate is having terpenoids of a single group).
- Each eluate is then subjected separately to adsorption chromatography when different bands due to the various terpenoids present in eluate are obtained which are then eluted to yield different terpenoids.
- In adsorption chromatographic method, alumina and silica gel are generally used as adsorbents for separating the terpenoids, particularly triterpenoids.

- Other chromatographic techniques such as vapour phase chromatography, partition chromatography and counter-current separation method have been used for the separation of terpenoids.
- Gas chromatography has been particularly useful for isolating pure configurational forms of a given terpenoid from mixtures produced by synthesis.

**Isoprene Rule**

In 1887, Wallach enunciated the famous isoprene rule which may be stated as follows:-

"The skeleton structures of all naturally occurring terpenoids are built up of isoprene units".

From the above rule it follows that the divisibility into isoprene unit is regarded as a necessary condition to be satisfied by every naturally occurring terpenoid.

The isoprene rue has been deduced from the following facts:-

a) The empirical formula of almost all the naturally occurring terpenoids is $C_5H_8$.
b) The thermal decomposition of almost all terpenoids gives isoprene as one of the products. For example, rubber (polyterpenoid) on destructive distillation yields isoprene as one of the decomposition products.

$$(C_5H_8)_n \xrightarrow[\text{Distillation}]{\text{Destructive}} nC_5H_8$$
Isoprene

c) Isoprene rule has been confirmed by the fact that under special experimental conditions, isoprene undergoes polymerization to yield various terpenoids.
For example,
   i) Isoprene, when heated to 280ºC get dimerised to yield a widely distributed terpenoid called dipentene.

$$2\,C_5H_8 \xrightarrow{\text{Polymerization}} C_{10}H_{16}$$

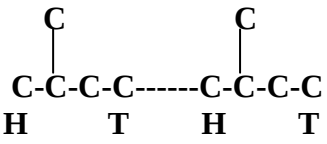
   ii) Isoprene may be polymerized to yield a rubber like product.

$$n\,C_5H_8 \xrightarrow{\text{Polymerization}} (C_5H_8)_n$$
Rubber (Polyterpenoid)

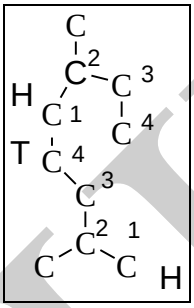
***Special Isoprene Rule:-***

- This rule proposed by ingold (1925), shows how the isoprene units in the terpenoid molecule are linked together.
- For this purpose, the branched end of the isoprene unit is considered as the head and the other end as the tail.

- According to the special isoprene rule, the isoprene units in terpenoids are linked in a head to tail fashion.
- Thus the basic carbon skeleton of a monoterpene according to the special isoprene rule will be as follows.




**or** **Where** H = Head
T = Tail



- It should be noted, however that this rule, which has proved very useful can only be used as a guiding principle and not as a fixed rule.
- Therefore, there are departures and violations of this rule in many compounds.

For example,

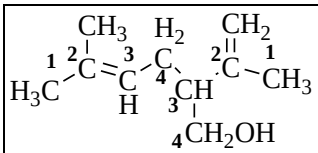
i) Certain terpenoids are known whose carbon content is not a multiple of five.
For example,
Cryptone, a naturally occurring ketonic terpenoid contains nine carbon atoms and therefore, it cannot be divided into two isoprene units.

ii) Certain terpenoids are known whose carbon content is a multiple of five but cannot be divided in to two isoprene units.

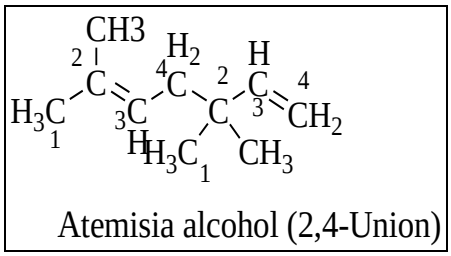
iii) Certain terpenoids are also known in which the special isoprene rule is violated.
For example,

- Lavandulol is composed of two isoprene units of isoprene with the unusual linkage of tail to tail but not head to tail linkage.
- Also the carotenoids are joined tail to tail at their centre.

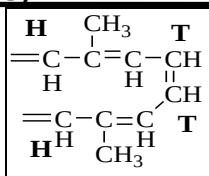
Cryptone
(Contains only 9 carbon atoms instead of 10)



Lavandulol(3,4-linkage)two isoprene units are linked through $C_3$ and $C_4$)



Atemisia alcohol (2,4-Union)


Part Structure of the Carotenoids showing tail to tail arrangement of the 2 isoprene units.

**General Methods for the Determination of structure of Terpenoids:-**

- The fundamental researches done by Wallach, Baeyer, Perkin, Semmler, Simonson, Ruzicka, etc are of great importance in elucidating the complicated structure of terpenoids.
- All the methods used for these have been grouped into five classes:-
    1. Analytical methods
    2. Synthetical methods
    3. Physical methods
    4. Knowledge of a molecular rearrangement
    5. Synthesis

***1. Analytical methods:-***

a) **Molecular formula**:-

After obtaining the pure terpenoid from the natural source, its molecular formula is ascertained by the usual methods of qualitative and quantitative analysis and also by means of mass spectrometry.

If the terpenoid is optically active, its specific optical rotation is measured. Sometimes, optical rotation may be used to make distinction between the structures as in limonene and carvone.

Then the other physical contants like melting point, boiling point, specific rotation, etc of terpenoids are also determined.

**b) Nature of the oxygen atom:-**

If oxygen is present in a terpenoid, its functional nature is ascertained by the usual methods. The terpenoids contain hydroxyl, aldehyde, keto or carboxylic groups.

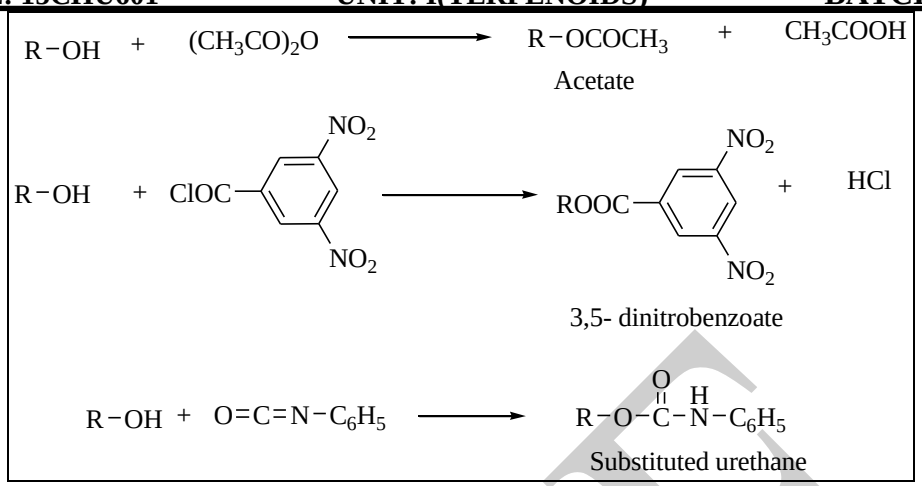
Other organic functional groups:-

Eg. $–OCH_3$, $-CONH_2$, $-NO_2$, etc have not been reported in terpenoids.

The various groups are detected in terpenoids by the following methods:-

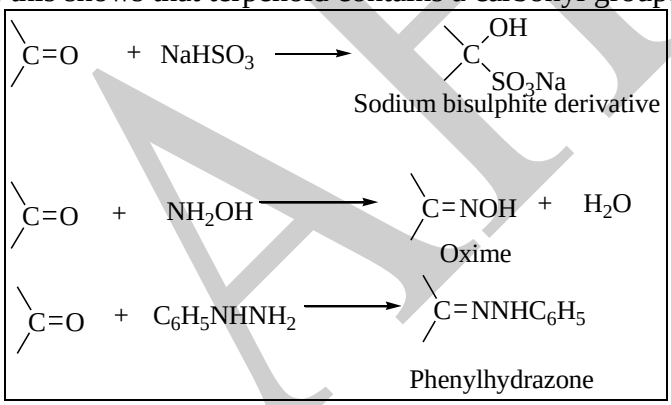
i) The hydroxy groups can be detected by the formation of crystalline acetates with acetic anhydride and benzoates with 3,5-dinitrobenzoyl chloride.

These also yield crystalline substituted urethans with phenylisocyanate.

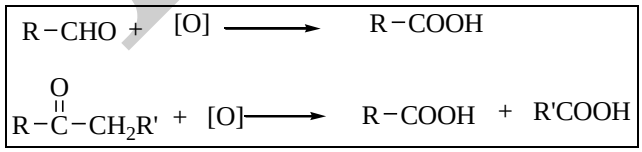



- Further information about the nature of hydroxy group is revealed by the rate of esterification.
  - For eg:- The 1º alcohol undergo esterification more readily than 2º and 3º alcohols. Thus α-terpeneol a tertiary alcohol is slowly esterified.

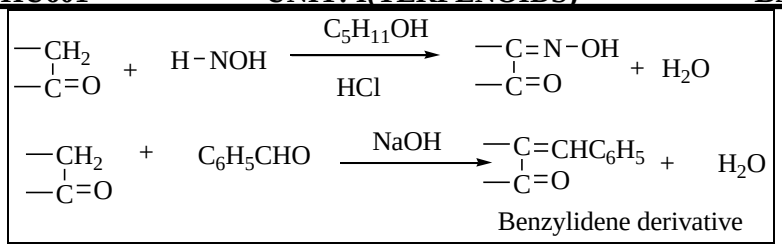
- If a terpenoid forms crystalline addition products like bisulphite derivative, oxime and phenylhydrazone, this shows that terpenoid contains a carbonyl group.



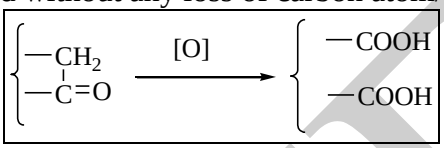

  - The carbonyl group may be present either in the form of aldehyde or keto groups. This can be ascertained by Oxidation.
  - The aldehyde on oxidation yields monocarboxylic acid without loss of carbon atom where as the ketone on oxidation yields a mixture of lesser number of carbon atoms.




- Terpenoids having $-CH_2CO-$ groups exhibit special properties. Such terpenoids form oximes with nitrous acid (liberated by action of hydrochloric acid on isoamyl nitrite) and benzylidene derivatives with benzaldehyde in the presence of alkali.

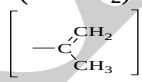



- If $–CH_2-CO-$ group is present in a ring, the terpenoid on oxidation will yield a dicarboxylic acid without any loss of carbon atom/atoms.



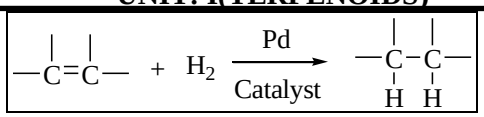

ii) If the terpenoid is soluble in ammonia and gives effervescence with sodium bicarbonate, these facts reveal that the terpenoid contains carbonyl group.

- Number of carboxylic groups is estimated by titration against standard alkali. Sometimes it becomes essential to ascertain whether the carbonyl group is attached to a 1º,2º or 3º carbon.
- This is done from the determination of rates of esterification of the acid which are in the following order.
- Tertiary < Secondary < Primary
- Tertiary –COOH groups are very difficult to be esterified and acids with such groups evolve carbonmonoxide with con.$H_2SO_4$.
- Also such acids donot form halogen substituted derivatives with are characteristic of the acids having α-hydrogen atoms.

iii) The C-alkyl groups are present frequently in the terpenoid molecules.
Three such important C-alkyl groups are
C-methyl (-C-$CH_3$-)
Isopropylidene (=$CMe_2$)
Isopropenyl 


**c) Unsaturation**

- The presence and number of olefinic double bonds in terpenoids have been ascertained by the formation of addition products with various reagents like halogens, halogen acids, hydrogen, peracids and Nitrosyl Chloride (Tilden Reagent)
- When a terpenoid possessing olefinic linkages is hydrogenated in the presence of catalyst, an addition compound called hydro compound is formed.
- From the amount of hydrogen consumed, the extent of unsaturation in a terpenoid can be calculated.
- For eg.
  - The catalytic reduction of cadinene yields tetrahydro cadinene, indicating that cadinene contains two double bonds.




**d) Number of rings:-**

- From the above steps, the number of olefinic double bonds and nature of functional groups may be known.
- Relation between general formula of compound and types of compound.

| General formula of the compound | Types 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 |

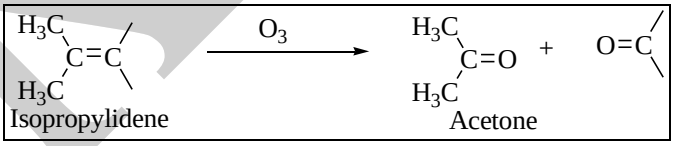
  - For eg.
- The molecular formula of citral is $C_{10}H_{16}O$ which contains 2 double bonds and one oxygen atom as carbonyl group.
- Thus the molecular formula of the parent hydrocarbon would be $C_{10}H_{16}O \equiv C_{10}H_{16} + 4H$ (for 2 double bonds) + 2H (for carbonyl oxygen).
  $\equiv C_{10}H_{22}$
- 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 products:-**

- Most of the terpenoid being olefinic in nature, a suitable oxidative method may be used to cleave the molecule in to simpler fragments of known structures which give important clues of the structures of the terpenoids.

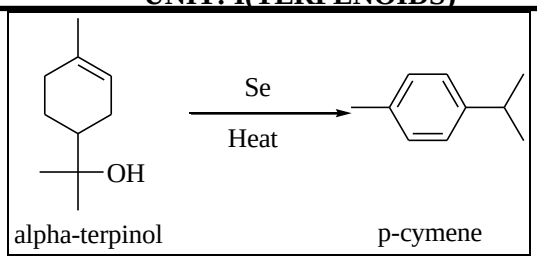
**f) Ozone**

- The ozonolysis is generally used to locate the position of double bonds in a molecule.




**g) Dehydrogenation**

- When terpenoids are heated with zinc, Iodine, bromine, Sulphur, Selenium, Palladium, etc
- They are converted into aromatic structures.
- Selenium is a better dehydrogenation reagent as it is milder and result in a fewer side reactions.

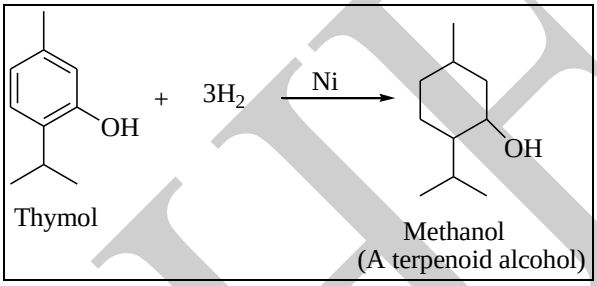



***2. Synthetic methods***

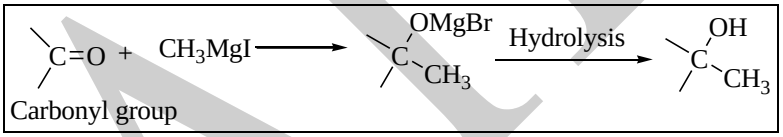
**a) Catalytic hydrogen:-**

- When aromatic compounds are hydrogenated catalytically under suitable condition, it is possible to obtain synthetic terpenoids.

For eg.

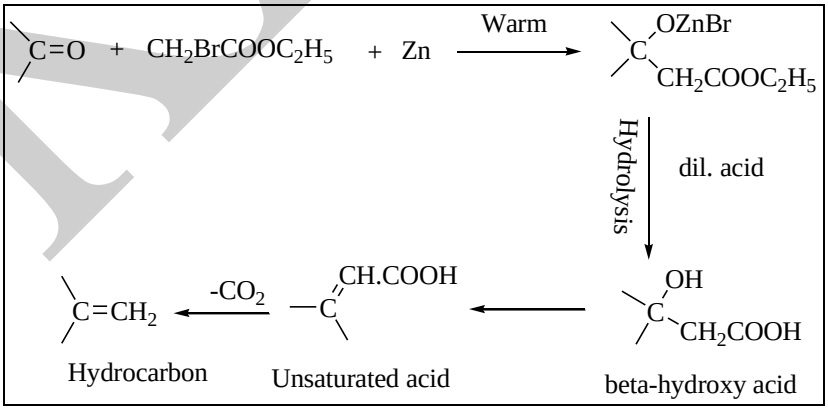



b) **Grignard's reaction**:-




**c) Reformatsky reaction:-**

- Similar to grignard's reaction, Reformatsky reaction is very useful in synthesizing many terpenoids and related compounds like Camphoronic acid, Geranic acid, etc




***3. Physical methods:-***

- A number of physical methods have been employed in elucidating the structure of natural terpenoids.

a) **Ultraviolet Spectroscopy**:-

This technique is widely used in terpenoid chemistry for the detection of conjugation.

The value of $\lambda_{max}$ for various types of terpenoids have been calculated.

i. For simple acyclic dienes $\lambda_{max}$ =217-228 nm (Σ 15000-25000). If the conjugated double bonds are not present in the same ring. ,ie heteroannular diene, $\lambda_{max}$ has been found to be 230-240 nm (Σ 1300-200000).

If the dinene is homoannular in which both double bonds are present in the same ring, $\lambda_{max}$ has been found to be 256-265 nm (Σ 2500-100000).

ii. For α,β- unsaturated carbonyl systems, $\lambda_{max}$ has been found to be 220-250 nm (Σ100000-17500). Such systems also show a weak band a $\lambda_{max}$ 315-350 nm (Σ 15-100).

iii. Substituents affect the absorption maximum of a diene system.

iv. Woodward (1942) studied the effect of substituents on $\lambda_{max}$ of diene systems and concluded that the value of the absorption maximum is dependent on their number and type.

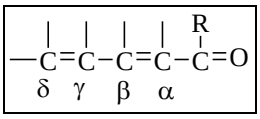
**Empirical Rules:-**

Polyenes

| Compounds | $\lambda_{max}$ value |
|---|---|
| Homoannular dienes (Basic value) | 253 nm |
| Hetero annular (and acyclic) dienes (Basic value) | 214 nm |
| Increment for each substituent | 5 nm |
| Increment for each exocyclic double bond | 5 nm |
| Increment for each double bond that extends conjugation. | 30 nm |

- It should be noted that a C-substituent may be an alkyl group or a ring residue.

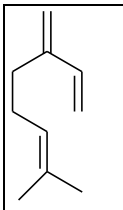
α,β- Unsaturated ketones




- R is an alkyl group or a ring residue and the parent system is C=C-C ( R)=O

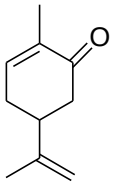
| Compounds | $\lambda_{max}$ value |
|---|---|
| Parent system (Basic value) | 215 nm |
| Increment for each C substituent | |
| At α-C | 10 nm |

| | |
|---|---|
| At β-C | 12 nm |
| At γ or δ-C | 18 nm |
| Increment for each exocyclic double bond | 5 nm |
| Increment for each double bond that extends conjugation | 30 nm |



myrcene

$\lambda_{max}$
Observed = 224 nm
Calculated (for an acylic diene with one C-Substituent)
214 + 5 = 219 nm



Carvone

$\lambda_{max}$ Observed = 235 nm
Calculated, Parent system = 215nm
C-substituent a-C = 10 nm
C-substituent at b-C = 12nm
$\lambda_{max}$ = 237 nm

**b) Infrared spectroscopy:-**

- In terpenoid chemistry, this technique is used for detecting the presence of a hydroxyl group (3400 $cm^{-1}$) or an oxo group (Saturated 1750-1700 $cm^{-1}$); α, β- unsaturated (1700- 1660 $cm^{-1}$).
- Infrared spectroscopy has been used to distinguish between cis and trans isomers.
- Also this is used for detecting the presence of the isopropenyl group.

**c) NMR Spectroscopy:-**

- This technique is much use in identifying double bonds and in determining the nature of end groups in terpenoid chemistry.
- This is also used to determine the number of rings present and also to reveal the orientation of $CH_3$ groups.

**d) Mass Spectrometry:-**

- This is quite a useful technique in terpenoid chemistry.
- This has been used successfully in elucidating the structure of terpenoids by determining their molecular weight, molecular formula, the nature of the various functional groups and the relative position of the double bonds.
- However, mass spectrometry should be employed with great care because even simple terpenoids yield complicated fragmentation patterns.

**e) Optical rotation:-**

- This technique has been applied to elucidate the structure of many terpenoids. ORD studies are used to ascertain absolute configuration.

**f) X-Ray analysis**

- This is a very useful technique which has been used successfully for elucidating structure and stereo chemistry of terpenoids.

**4. Knowledge of a molecular rearrangement:-**

- Molecular rearrangement is very useful in structure elucidation. An interesting example of this can be seen in the structure elucidating of α-pinene.
- When α-pinene is oxidized with $KMnO_4$, it gives piononic acid as one of the products.
- Piononic acid on oxidation with chromic acid is degraded to isoketo camphoric acid.
- Camphor oxime on acid catalysed dehydration and hydrolysis yields α- campholenic acid.

**5. Synthesis:-**

- The tentative structure elucidated by the above analytical and physical methods may be confirmed by its unambiguous synthesis.

## Geraniol

### Introduction

- Geraniol occurs either free or in the form of its esters in many essential oils like rose, lemon-grass, geranium, lavender and citronella oils.
- Geraniol is a pleasant smelling colourless liquid which boils at 229-230ºC at 757mm pressure.
- After extraction from essential oils, it is purified by crystallizing it as a complex compound with anhydrous calcium chloride.
- Geraniol is also prepared commercially by the reduction of citral with Na/Hg.
- Geraniol and its esters are mainly used in perfumery, particularly as a component of artificial rose scents.

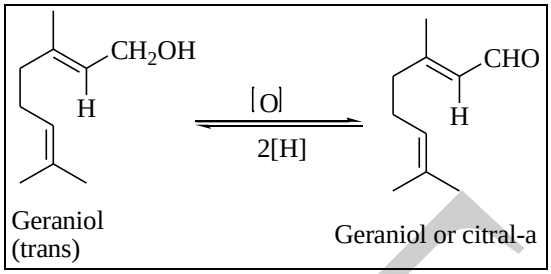
### Constitution:-

1. Its molecular formula has been found to be $C_{10}H_{18}O$.
2. As it adds on two moles of hydrogen, 2 moles of bromine etc, to form addition products, this shows that it contains 2 double bonds.

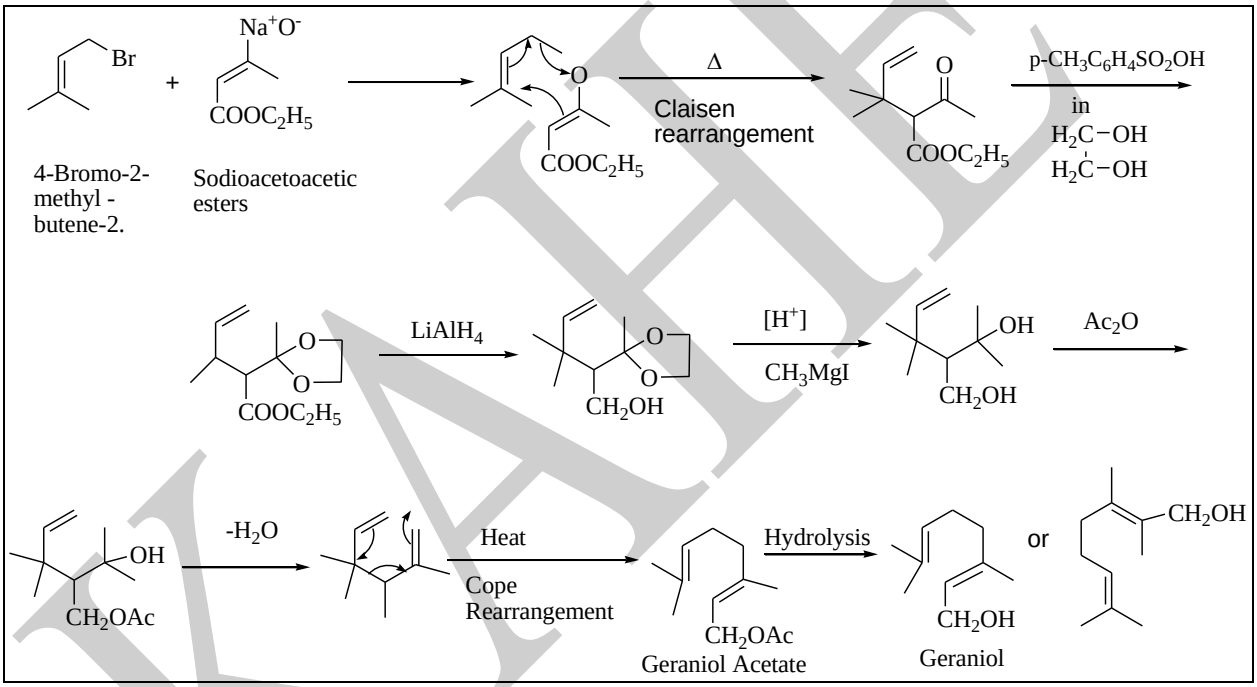
$$C_{10}H_{22}O \xleftarrow[Ni]{H_2} \underset{\text{Geraniol}}{C_{10}H_{18}O} \xrightarrow{2Br_2} C_{10}H_{18}O.Br_4$$

3. On oxidation, it yields an aldehyde (Citral-a) having the same number of carbon atoms, indicating that geraniol is a 1º OH.

- Further more, the aldehyde $C_{10}H_{16}O$ has been identified as citral-a or geraniol which could be reconverted into geraniol by reduction.
- The structure of geraniol may be represented as follows,




4. Finally, the structure of geraniol has been confirmed by its synthesis. This synthesis involves 2 novel steps Claisen and cope rearrangement.




, **α- Terpineol**

***Introduction***

- It is an optically active monoterpenoid that is widely distributed in nature in the (+), (-) or (±) form.
- It is an optically active solid having m.p 37-38 ºC and b.p 220ºC of the racemic modification.
- The (+) form occurs in oils of petitgrain and neroli, (-) form in camphor oils and (±) form in cajuput oil.
- ,α- terpineol is widely used in the preparation of the lilac perfumes and lilac scented soaps.

***Constitution:-***

This has been elucidated on the basis of following analytical synthetic evidences:-

1. Molecular formula
   From the analytical data and molecular weight determination , the molecular formula of α-terpineol has been found to be $C_{10}H_{18}O$.
2. Presence of double bond
   As α-terpineol adds on one mole of bromine and of nitrosyl chloride to form their respective addition compounds, it follows that α-terpineol contains one double bond.

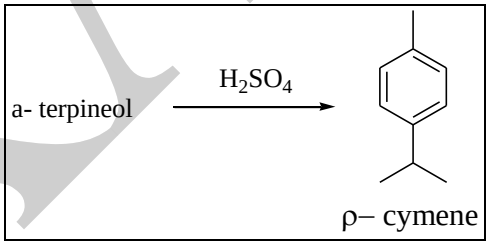
$$C_{10}H_{18}O + NOCl \longrightarrow C_{10}H_{18}O.NOCl$$

$$C_{10}H_{18}O + Br_2 \longrightarrow C_{10}H_{18}O.Br_2$$

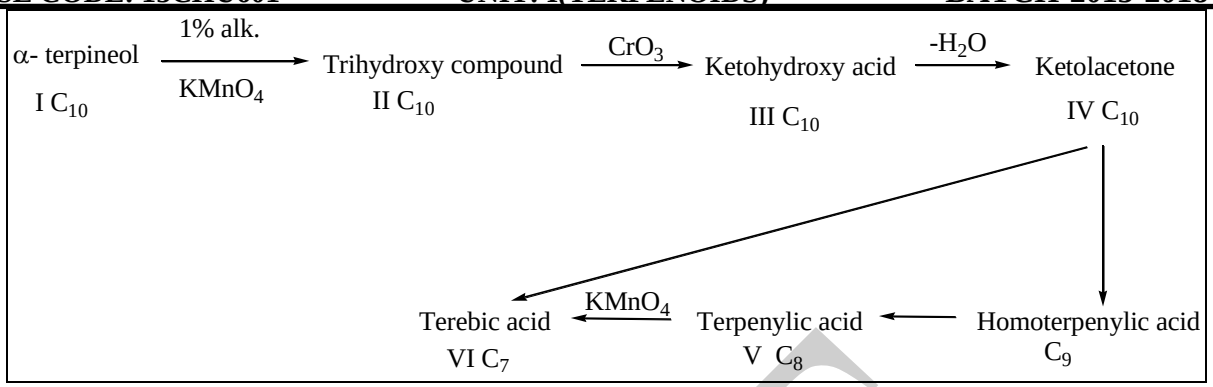
3. Presence of tertiary –OH group
   - ,α- terpineol, when treated with phenylisothiocyanate yields phenylurethane, indicating the presence of a hydroxyl group in terpineol.
   - Further α-terpineol is insoluble in NaOH solution.

$$C_{10}H_{18}O \xrightarrow{-H_2O} C_{10}H_{16}$$

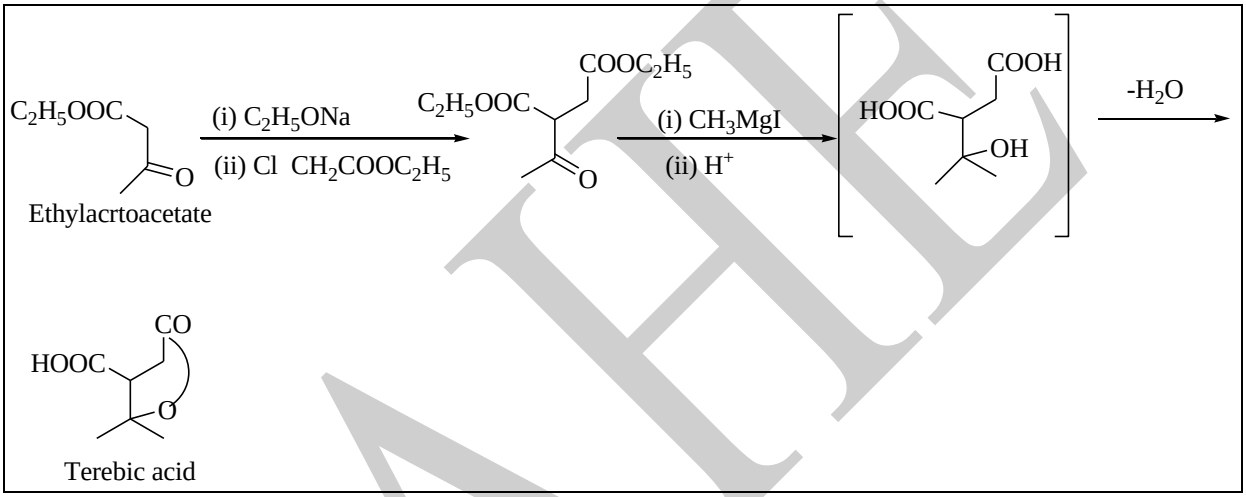
4. .α- Terpineol as a monocyclic compound:-
   - As α-terpineol contains one double bond, the molecular formula of fully saturated hydrocarbon of terpineol is ($C_{10}H_{18}$ + 2H of double bond – 1H of hydrogen atom of tertiary – alcoholic group + 1H of the monovalent alcoholic group).
   - This corresponds to $C_nH_{2n}$, the general formula of the monocyclic cycloalkanes and so it follows that α- terpineol is a monocyclic compound.
5. Carbon skeleton of α-terpineol:-
   - When α-terpineol is heated with $H_2SO_4$, it forms some p- cymene.



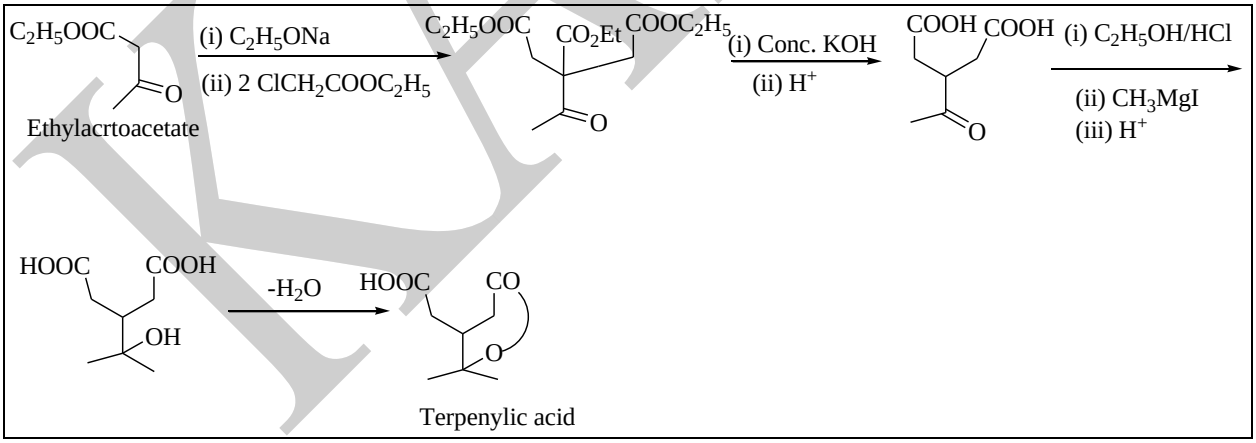

   - Taking the above observation with the tendative proposal that α- terpineol is monocyclic, it may be inferred that α-terpineol contains the p-cymene skeleton.
   - Thus, it may be concluded that α-terpineol may be p-methane (fully saturated p-cymene ) with one double bond and a tertiary alcoholic group.
6. Position of the double bond and a tertiary alcoholic group.
   - These have been ascertained by Wallach by means of graded oxidation.
   - Wallach degraded α- terpineol having $C_{10}$ to the well known $C_7$ acid called terebic acid.
   - The series of degradation reactions of α-terpineol are as follows.




- Synthesis of terebic acid (V)

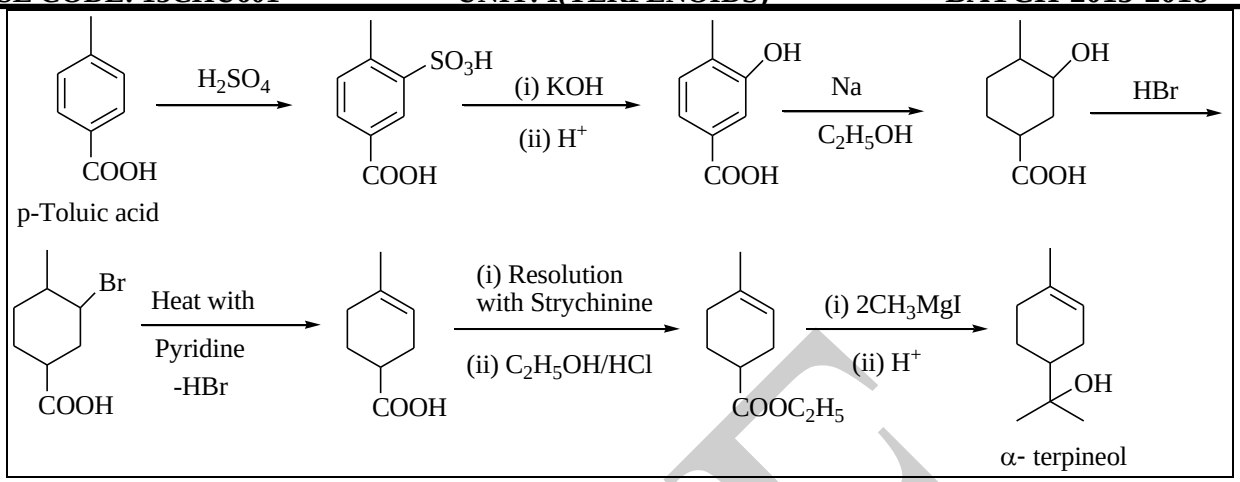



- Synthesis of terpenylic acid (VI)



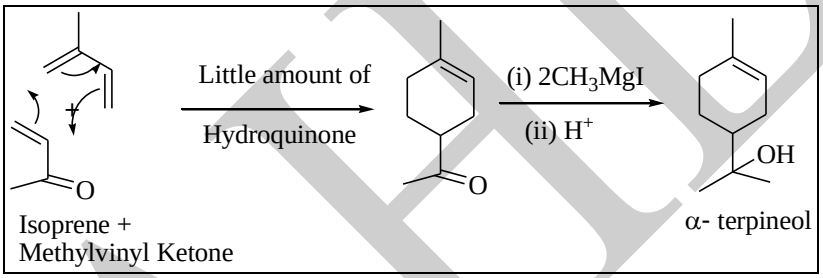

Synthesis of α-terpineol:-

(1) Perkin, junior and Meldrum et al. (1908) synthesis.



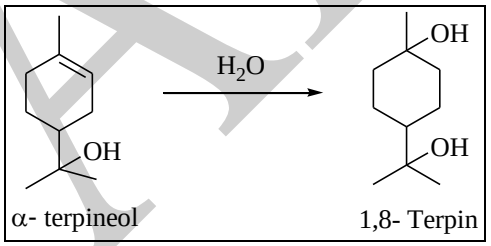

(2) Alder- Vogot's Synthesis:-

This synthesis makes use of the Diels-Alder reaction.

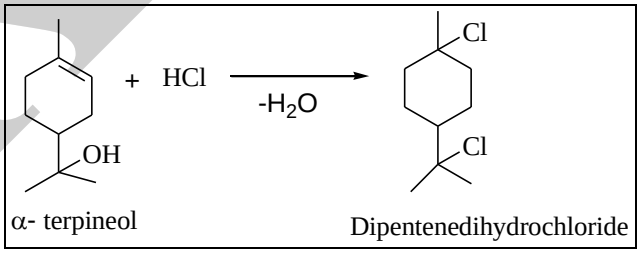



7. Reaction of α-terpineol

a) Hydration of α-terpineol




b) Action of HCl:-




**Dipentene**

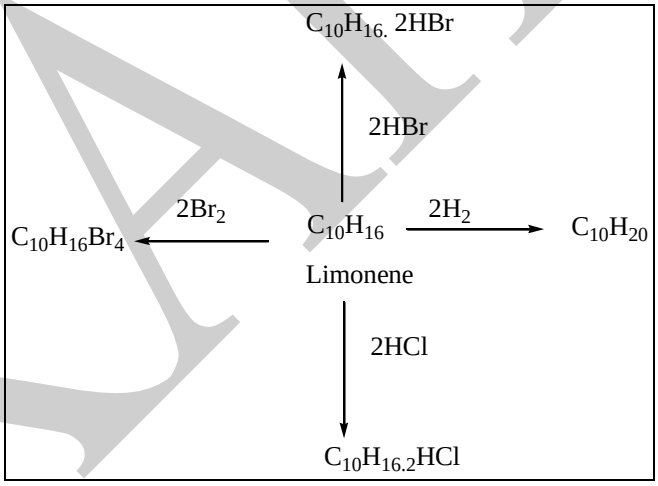
***Introduction***

- It is the most important monoterpenoid which is widely distributed in nature.
- Its (+) form occurs in lemon and organic oils, the (-) form occurs in peppermint oil where as the (±) form occurs in turpentine oil.
- The racemic modification of limonene ± form is known as dipentene.
- Limonene is an optically active liquid which boils as 117ºC.
- Mainly, limonone is produced as a byproduct in the citrus fruit industry, (±) – limenone (dipentene) is also produced by heating either of the active form or by mixing equal amounts of (+) and (-) limonenes.

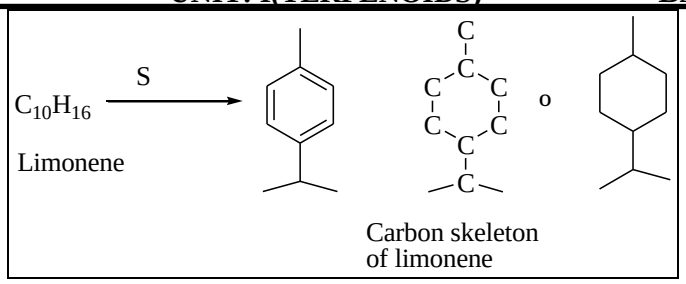
***Constitution***

1. Molecular Formula
   - From analytical data, the molecular formula of limonene has been found to be $C_{10}H_{16}$.
2. Presence of 2 olefinic bonds:-
   - This has been revealed on the basis of following facts:-

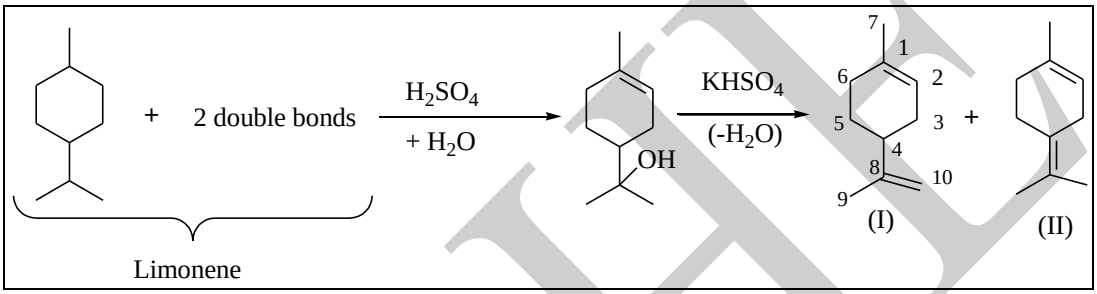
a) It adds on 4 bromine atoms to form a tetrabromide
b) On catalytic reduction, it adds on 4 atoms of hydrogen to form tetrahydro derivative.
c) With HCl, a dihydrochloride is formed
d) With HBr, it yields a dihydro bromide.




3. As a monocyclic derivative:-
   - The molecular formula of the saturated parent hydrocarbon corresponding to limonene is $C_{10}H_{20}$ which corresponds to the general formula $C_nH_{2n}$ (n =10) for the monocyclic compound. Hence, the limonene contains monocyclic system.
4. Nature of the carbon Skeleton
   - Limonene, when heated with sulphur, undergoes dehydrogenation to yield p-cymene, thus indicating that the carbon skeleton of p-cymene is present in limonene.




5. Position of double bonds:-
   - Now the only problem is ascertain the position of the 2 double bonds in the fully saturated nucleus of p-menthane (p-cymene). This has been done by its relation to α-terpineol and carvone.



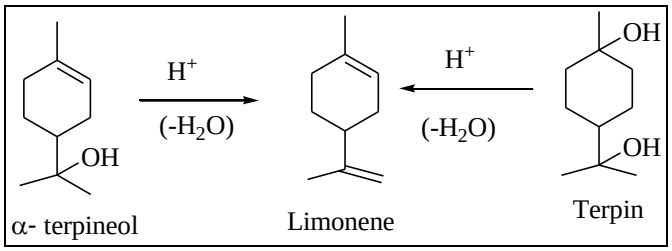

   - Out of the 2 structures, either (I) or (II) must be limonene. But both of these structures have one double bond between $C_1$ and $C_2$.
   - Therefore, in Limonene there should be a double bond between $C_1$ and $C_2$.
   - This position of one of the double bonds in limonene has been further confirmrd by the fact that limonene when oxidized with $KMnO_4$ yields terpenylic acid and terebic acids.
   - The position of one double bond is fixed between $C_1$ and $C_2$.
   - What is the position of second double bond?
   - This has been found to be between $C_8$ and $C_{10}$ on the basis of following facts:-

     a) As limonene is optically active, it must possess at least one asymmetric carbon atom which is possible only in structure (I) ($C_4$ is asymmetric).

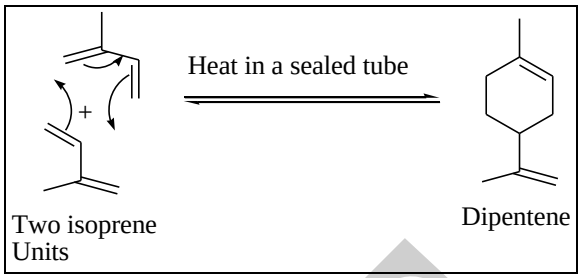
- The structure (II) has no such asymmetric carbon atom and hence must be optically inactive. Actually, it is found to be so and this compound (II) was identified as terpinolene. Hence structure (I) must be limonene.

6. Synthesis of Limonene:-

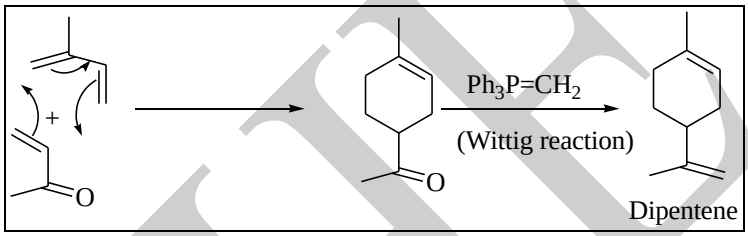
   i) Limonene is prepared by the dehydration of terpin or α-terpineol.



ii) Dipentene is obtained although in poor yield by the dimerisation of isoprene in a sealed tube.




iii) It is also produced by Diels Alder reaction between isoprene and Methylvinyl Ketone.




**α-Pinene:-**

***Introduction***

- It is the most important member of pinane class which is the chief constituent of the oil of turpentine.
- It occurs in both the (+) and (-) forms in all turpentine oils.
- The (+) isomer occurs in American, German and Russian oil of turpentine, While the (-) isomer occurs in French turpentine oil.
- The inactive or (±) isomer is obtained from turpentine oil which is the volatile fraction obtained by steam distillation of oleoresin produced by pine trees.
- The inactive α-pinene is separated by repeated fractional distillation of turpentine oil.
- Then the purification of α-pinene so obtained is done by formation of its crystalline nitrosyl chloride derivative with nitrosyl chloride.
- The addition product is then decomposed by aniline to yield pure α-pinene.
- α-pinene is liquid which boils at 156ºC.
- When α-pinene is exposed to air, it undergoes autooxidation.

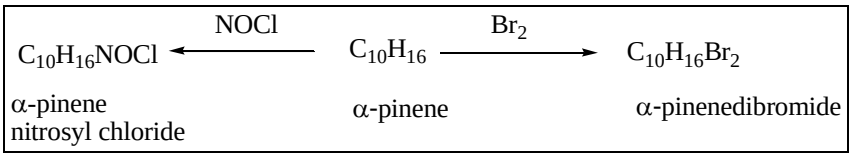
***Constitution:-***

***Method I:***

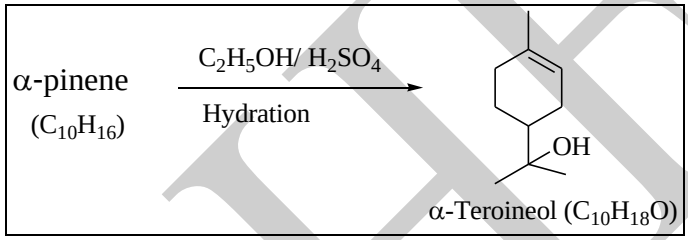
1. Molecular formula:-
   $C_{10}H_{16}$

2. Presence of a double bond:-

As α-pinene adds on 2 Br atoms, this means the α-pinene contains double bond.



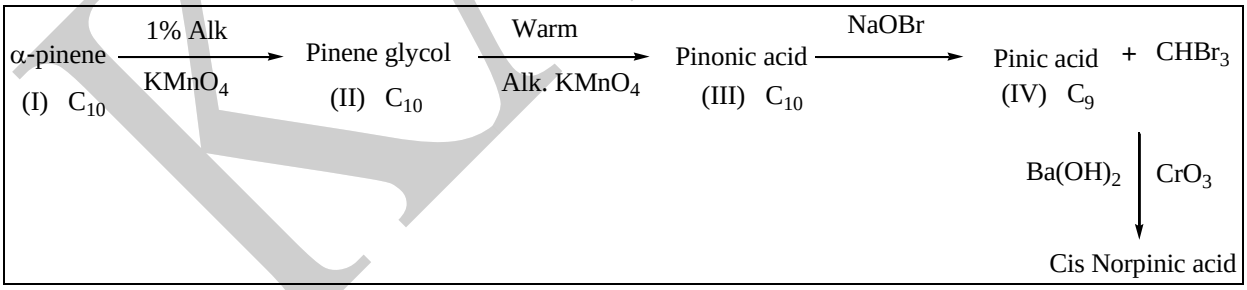

3. Presence of a bicyclic compound:-
   - The molecular formula of α-pinene is $C_{10}H_{16}$. But it contains one double bond. Therefore, its parent hydrocarbon is $C_{10}H_{18}$ which corresponds to the general formula $C_nH_{2n-2}$ of compounds containing two rings.
   - It follows that α-pinene is bicyclic.
4. Presence of six-membered ring




**The formation of α- Terpineol from α-pinene leads to the following facts:-**

a) In α-pinene a six membered ring having the double bond of α-terpineol is present.
b) In α- Terpineol, the hydroxyl group is present at $C_8$. But this is not present in α-pinene.
c) The gem-dimethyl group (-$CHMe_2$) of α-Terpineol is not present in the six membered ring of α-pinene and therefore it must be present in other ring.

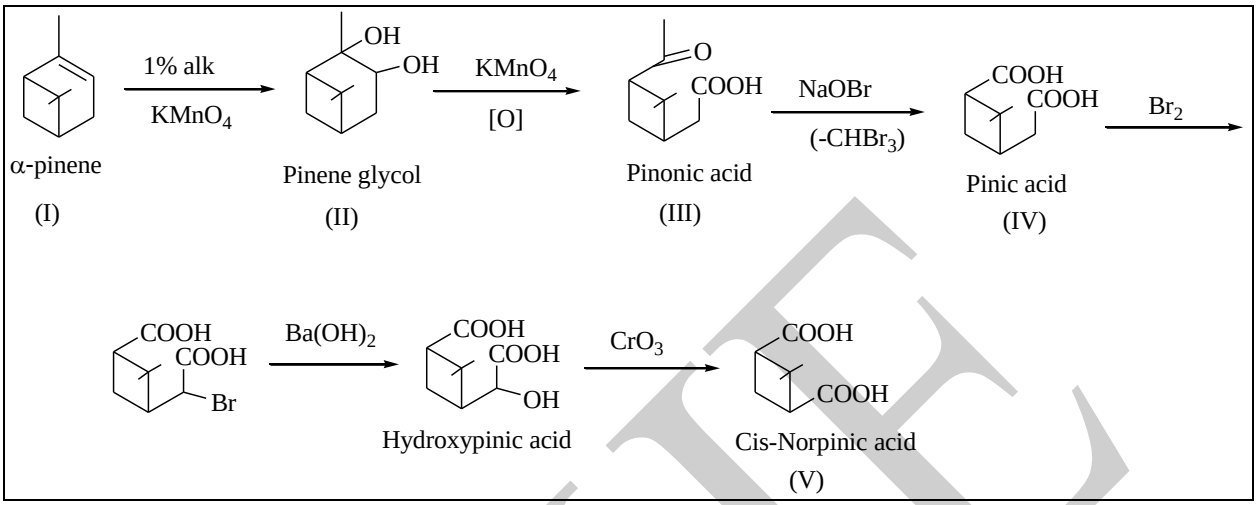
5. Oxidative degradation of α-pinene:-




The above set of oxidative degradation led to the following conclusions:-

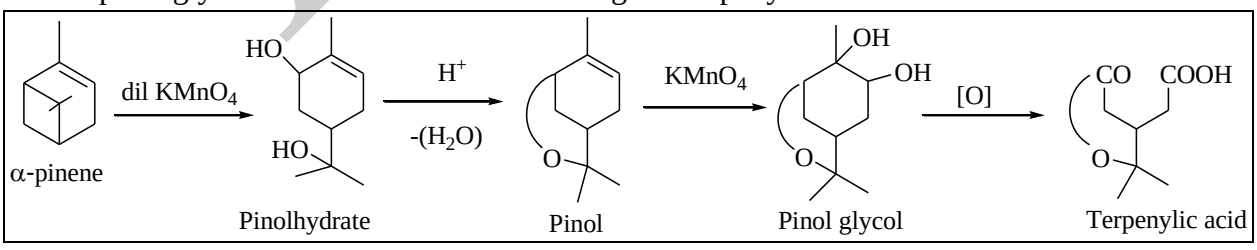
i. When (I) is oxidized to (II), the double bond of the former is hydroxylated.
ii. We have already proved that the double bond is present in the six membered ring. Therefore, the oxidation of II to III occurs due to scission of the glycol bond. At the same time, a small amount of pinoyl formic acid is also formed. Ie) MeCO of III is now HOOC-CO
iii. The formation of pinic acid IV and bromoform from the oxidation of pinonic acid III reveals that the acetyl group is present in pinonic cid.

iv. Pinic acid has been shown to be a saturated dicarboxylic acid. This when treated first with bromine, then with barium hydroxide and finally with the oxidizing agent like $PbO_2$, yields cis-norpinic acid, $C_8H_{12}O_4$.

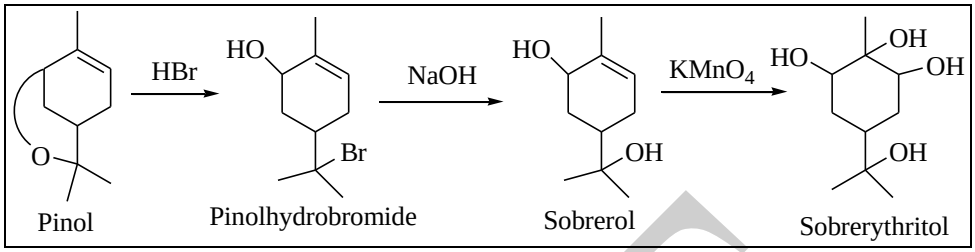



***Method II:- (Wagner's work)***

1. Molecular formula:-
   - $C_{10}H_{16}$
2. Presence of double bond:
   - As α-pinene adds on one mole of bromine, this shows that α-pinene contains one double bond.
3. As a bicyclic compound:-
   - The parent hydrocarbon of α-pinene is $C_{10}H_{18}$ which corresponds to the general formula $C_nH_{2n-2}$ for bicyclic compounds and therefore α-pinene is bicyclic.
4. Conversion into pinol:-
   - Pinol contains one double bond because it adds on one mole of bromine to form pinol dibromide.
   - The latter compound, when treated with lead hydroxide is converted into pinol glycol $C_{10}H_{16}O(OH)_2$ which upon oxidation yields terpenylic acid.
   - A-pinene on treatment with dil $KMnO_4$ gives pinol hydrate which on dehydration by means of acid gives pinol. The latter on oxidation with potassium permanganate gives pinol glycol which on further oxidation gives terpenylic acid.

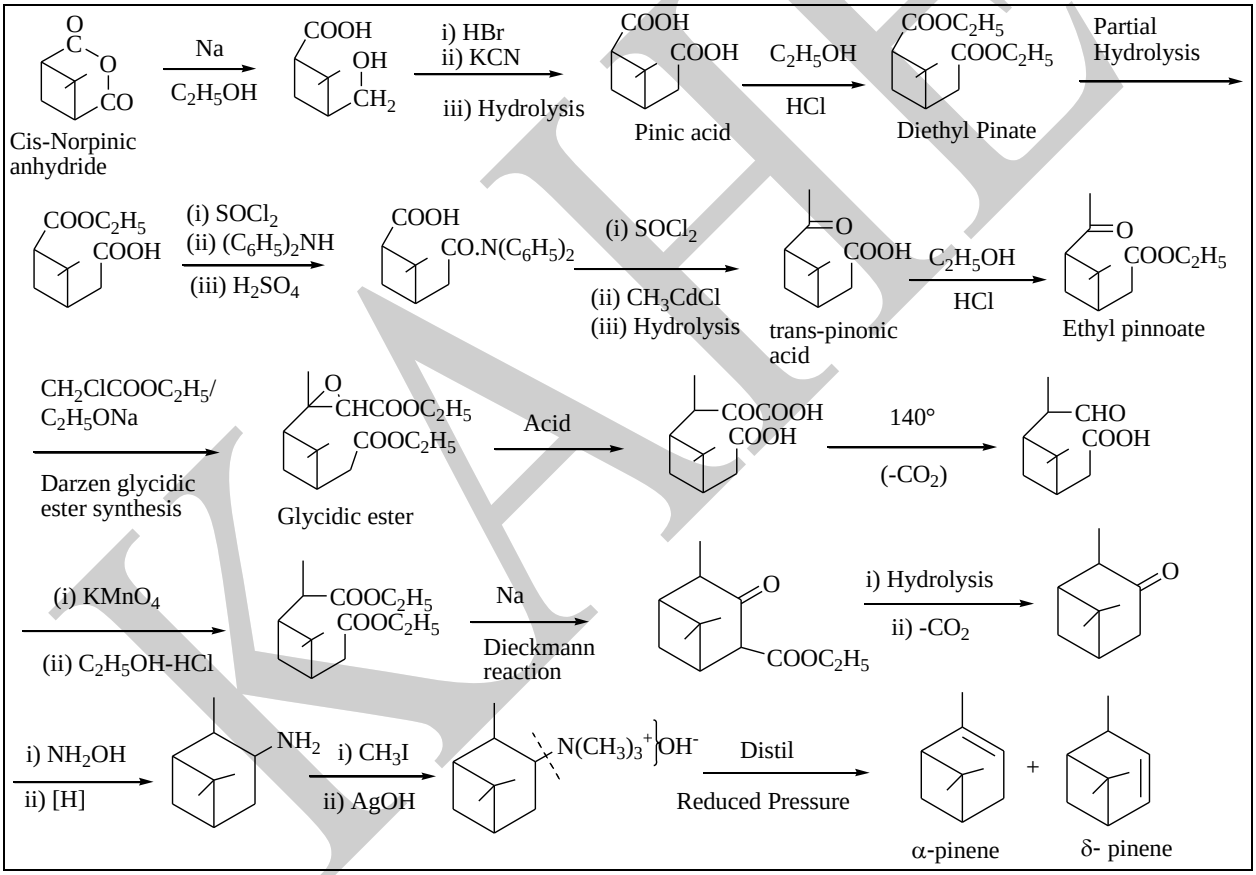


- Further support for pinol (III) is derived from the fact that Sobrerol (Pinolhydrate) gives a tetrahydric alcohol, sobrerythritol.
- Sobrerol is itself prepared by treating pinol with HBr followed by NaOH.




- All the above reactions of α-pinene is considered to be (I) as given by wagner.

5. Synthesis:-




**TEXT BOOKS:-**

$T_1$: Finar, I.L, 2013, "Organic Chemistry", Vol.II, Pearson Education, Singapore.

$T_2$: Gurdeep R. Chatwal, 2013, "Organic Chemistry of Natural Products", Vol. II, Himalaya Publishing House, New Delhi.

## POSSIBLE QUESTIONS:

### Part-A (1 Mark)

### Multiple Choice Questions (Each Question Carry One Mark)

1. Citral is treated with aqueous $Na_2CO_3$ it gives
**(a) methylheptenone and acetaldehyde** (b) Methylheptenone and benzaldehyde
(c)Ethylheptenone and acetaldehyde (d)Ethylheptenone and benzaldehyde

2. Geraniol is oxidized with $Na_2Cr_2O_2$/ $H_2SO_4$ it gives
**(a) Geranic acid** (b) Geranial (c ) Dipentene (d) Menthol

3. Isoprene is heated in a sealed tube at 280°c
(a) Methene **(b) Dipentene** (c ) Menthol (d) Cyrene

4. Thymol is heated with hydrogen in the presence of nickel catalyst
(a) Dipentene (b) Menthene **(c ) menthol** (d) Cyrene

5. 1. Menthol is heated with $KHSO_4$ it gives
(a) Dipentene **(b) Menthene** (c )menthol (d) Geraniol

6. α- pinene is heated with dilute $H_2SO_4$ it gives
(a) Geraniol (b) Cyrene (c ) Myrcene **(d) α- Terpenol**

7. Dipentene is treated with sulphur it gives
**(a) Para – Cymene** (b) para – Menthane (c ) Myrcene (d) Geraniol

8. On oxidation of geraniol with $KMnO_4$ it gives
**(a) Levulinic acid** (b) α - Terpinol (c)Nerol (d) Menthol

9. Lemmon grass is sources of
(a) Thymol **(b)citral** (c)Myrcene (d)Menthol

10. β-Carotene imparts orange colour to
(a) Orange (b) papaya **(c) carrots** (d)Mango

11. Lycopene imparts red colour to
(a)Apple (b)Plums **(c)watermelon** (d) Cherry

12. Dipentene is treated to $280^0$C it gives
(a) p-menthane **(b)Isoprene** (c)P-cymene (d) myrcene

13. Dipentene is heated with HBr gives
**(a)Dihydrobromide** (b)Tetrabromide (c) Menohydrobromide

(d)Trihydrobromide

14. What is the isoprene rule
(a)Terpenes contains tait to tail connected isoprenes (b) Terpenes contain 5n atoms
**(c)Terpenes contains head to tail connected isoprenes** (d)Terpenes contain head to head connected isoprenes

15. What constituted a terpene"head" ?
**(a) A branched alkyl group** (b) A carboxylate group (c ) A C = C double bond
(d) An aldehyde group

16. Which is the systematic name of isoprene ?
**(a) 2 - methyl - 1, 3 – butadiene** (b) 3 - methyl - 1, 2 - butadiene
(c ) 3 - methyl - 1, 3 – butadiene (d) 2 - methyl - 1, 2 - butadine

17. Geraniol can be obtained by the reduction of …….
**(a) citral – a** (b) geranine acid (c ) p – cymene (d) α - terpineol

18. The fundamental unit in terpenes / terpenoids is
(a) 1,3 - butadiene **(b) 2 - methyl - 1, 3 – butadiene** (c ) allene (d) 1,2 - butadiene

19. Which of the following is a sesquiterpene
(a) limonene (b) rubber **(c ) zingiberene** (d) squalene

20. Which of the following is a bicyclic monoterpene
**(a) α – pinene** (b) zingiberene (c ) menthol (d) limonene

## Part-B (Each Carry 8 Marks)

1. Explain the separation of terpenoids from essential oils.
2. Convert the following
   i.alpha-pinene to Terpenylic acid
   ii. Pinol to Sebreythritol
3. Illustrate the synthesis of alpha-pinene.
4. Explain the synthesis and constitution of Dipentene.
5. Explain the structural elucidation and synthesis of Geraniol.
6. Explain the general methods for the determination of structure of terpenoids.
7. Discuss the position of double bond and tertiary alcoholic group in alpha terpineol.
8. Explain the Isoprene Rule with suitable example.
9. Illustrate the structural elucidation and synthesis of α-pinene by Wagner's method.
10. Explain the physical methods in the determination of structure of terpenoids.

15CHU601

Karpagam Academy of Higher Education

Coimbatore-21

(For the candidate admitted on 2015 onwards)

Department of Chemistry

VI- semester

Chemistry of Natural Products

**UNIT I- Objective Questions for online examination (Each carry 1 Marks)**

| Question | Option-A | Option-B | Option-C | Option-D | Answer |
|---|---|---|---|---|---|
| Citral is treated with aqueous Na2CO3 it gives | methylheptenone and acetaldehyde | Methylheptenone and benzaldehyde | Ethylheptenone and acetaldehyde | Ethylheptenone and benzaldehyde | Methylheptenone and benzaldehyde |
| Geraniol is oxidized with Na2Cr2O2/ $H2SO_4$ it gives | Geranic acid | Geranial | Dipentene | Menthol | Geranic acid |
| Isoprene is heated in a sealed tube at $280^0$c | Methene | Dipentene | Menthol | Cyrene | Dipentene |
| Thymol is heated with hydrogen in the presence of nickel catalyst | Dipentene | Menthene | menthol | Cyrene | Menthol |
| Menthol is heated with KHSO4 it gives | Dipentene | Menthene | menthol | Geraniol | menthene |
| α- pinene is heated with dilute H2SO4 it gives | Geraniol | Cyrene | Myrcene | α- Terpenoil | α- Terpenoil |
| Dipentene is treated with sulphur it gives | Para - Cymene | para - Menthane | Myrcene | Geraniol | Para - Cymene |
| Menthol is prepared by catalytic hydrogenation of | Para - Cymene | para - Menthane | Thymol | 3 - Menthane | Thymol |
| Gerniol treated with Bromine it gives | 2,3,6,7 - Tetrabromo-3,7-dimethyl -1-0ctanol | 2,3,6,- Tribromo-3,7-dimethyl -1-0ctanol | Geranyl bromide | 3,7-dimethyl -1-0ctanol | 2,3,6,7 - Tetrabromo-3,7-dimethyl -1-0ctanol |
| Geraniol on treated with cro3 it gives | Geranial | Geranial bromide | α-Terpineol | Never | Geranial |
| On oxidation of geraniol with KMnO4 it gives | Levulinic acid | α - Terpinol | Never | Menthol | Levulinic acid |
| Lemmon grass is soures of | Thymol | Citral | Myrcene | Menthol | litral |
| β-Carotene imparts orange colour to | Orange | papaya | carrots | Mango | carrots |
| Lycopene imparts red colour to | Apple | Plums | watermelon | Cherry | watermelon |
| Dipentene is treated to $280^0$c it gives | p-menthane | Isoprene | P-cymene | myrcene | isoprene |
| Dipentene is heated with HBr it gives | Dihydrobromide | Tetrabromide | Menohydrobromide | Trihydrobromide | Dihydrobromide |
| What is the isoprene rule | Terpenes contains tail to tail connected isoprenes | Terpenes contain 5n atoms | Terpenes contains head to tail connected isoprenes (d)Terpenes contain head to head connected isoprenes | Terpenes contain head - to - head connected isoprenes | Terpenes contains head to tail connected isoprenes |
| What constituted aterpene"head" ? | A branched alkyl group | A carboxylate group | A C = C double bond | An aldehyde group | A branched alkyl group |
| Which is the systematic name of isoprene ? | 2 - methyl - 1, 3 - butadiene | 3 - methyl - 1, 2 - butadiene | 3 - methyl - 1, 3 - butadiene | 2 - methyl - 1, 2 - butadine | 2 - methyl - 1, 3 - butadiene |
| What is the fundamental structural unit of terpene molecules? | pinene | styrene | isobutylene | isoprene | isoprene |
| What is the minimum number of carbon atoms present in a terpene? | 5 | 10 | 12 | 15 | 10 |
| How many isoprene units are there in a mono terpene? | 1 | 2 | 3 | 4 | 2 |
| How many carbon atoms are in diterpene? | 10 | 15 | 8 | 20 | 20 |
| How many isoprene units are there in a diterpene? | 4 | 2 | 1 | 3 | 4 |

| | | | | | |
|---|---|---|---|---|---|
| How many double bonds occur in the triterpene squalene? | 1 | 2 | 3 | 6 | 6 |
| How many double bonds occur in the mono terpene geraniol? | 1 | 2 | 3 | 6 | 2 |
| Geraniol undergo oxidation to give……. | Geraniol acid | para - cymene | citral -a | myrcene | citral -a |
| P - Menthane is a …… Monoterpene | monocyclic | dicyclic | tricyclic | tetracyclic | monocyclic |
| Dipentene occurs in …… | terpentine oil | lemon grass oil | orange blossom oil | caustor oil | terpentine oil |
| Lycopene is the example of | sesquiterpenes | di terpenes | tri terpenes | tetra terpenes | tetra terpenes |
| β- carotene is the example of | sesquiterpenes | di terpenes | tri terpenes | tetra terpenes | tetra terpenes |
| mono terpenes contain ……. Carbon atoms | 5 | 6 | 8 | 10 | 10 |
| Sesquiterpenes contain …… Carbon atoms | 15 | 8 | 10 | 12 | 15 |
| Diterpenes contain ……..carbon atoms | 15 | 20 | 25 | 30 | 20 |
| Teiterpenes contain …… Carbon atoms | 20 | 30 | 40 | 50 | 30 |
| Tetraterpenes contain …… carbon atoms | 20 | 30 | 40 | 50 | 40 |
| Polyterpenes contain ……carbon atoms | 2n | 3n | 4n | 5n | 5n |
| How many isopre units are there in a triterpene? | 2 | 3 | 4 | 6 | 6 |
| How many isoprene units there in a sesquiterpenes? | 2 | 3 | 4 | 6 | 3 |
| How many isoprene units there in a tetra terpenes? | 2 | 4 | 6 | 8 | 8 |
| Geraniol does not form an oxime with ……. | hydroxylamine | phenylhydrazine | Na - Hg | H - Pd | hydroxylamine |
| Geraniol can be obtained by the reduction of ……. | citral - a | geranine acid | p - cymene | α - terpineol | citral - a |
| The fundamental unit in terpenes / terpenoids is | 1,3 - butadiene | 2 - methyl - 1, 3 - butadiene | allene | 1,2 - butadiene | 2 - methyl - 1, 3 - butadiene |
| Which of the following is a sesquiterpene ? | limonene | rubber | zingiberene | squalene | zingiberene |
| Which of the following is a bicyclic monoterpene? | α - pinene | zingiberene | menthol | limonene | α - pinene |
| Which is the following methods is used for isolation of terpenoids? | distillation | solvent extractions | centrifuge process | evaporation | solvent extraction |
| Myrcene on hydration followed by oxidation gives | myecenol | citral | 2,6 - dimethylloctane | 2 - oxopentanedial | citral |
| Which one of the following on ring closure with $H_2SO_4$ gives α - terpineol? | Geraniol | menthol | lemonene | Camphor | Geraniol |
| Which one of the following terpenoid occur in peppermint oil? | citral | pulegone | menthol | camphor | menthol |
| Which one of the following terpene is a provitamin A ? | camphor | β - carotene | squalene | zingiberene | β - carotene |
| Which one of the following compound on oxidation gives β - ionone? | camphor | α - terpineol | borneol | β - carotene | β - carotene |
| A terpenoid which is used in the manufacture of celluloids and also as a moth repellent is | menthol | α - pinene | camphor | zingiberene | camphor |
| …… is an important acyclic monoterpenoids ,occurs up to 80 % in lemon grass oil | carotenoids | citral | camphor | ephedrine | citral |
| …… are yellow or red pigments found mainly in plants | carotenoids | citral | camphor | ephedrine | carotenoids |
| …….. Is used as moth repellent and as preservative in cosmetics | carotenoids | citral | camphor | ephedrine | ephedrine |
| Camphor is a …… compound | mono cyclic | bicyclic | tricyclic | tetracyclic | bicyclic |

| | | | | | |
|---|---|---|---|---|---|
| Which one of the following is the main contituents of synthetic lemon? | myecene | citral | camphor | geraniol | citral |
| Which one of the following is used in the synthesis of synthetic rose scents? | citral | geranic acid | geraneol | menthol | geraneol |
| Which one of the following terpenoids is used in paint and varnishes as a thinner? | α - pinene | α - terpineol | menthol | camphor | menthol |
| Natural rubber is a polymer of | cis - isoprene | trans - isoprene | 1,3 - butadiene | 1,5-Pentadiene | cis - isoprene |
| Terpentine oily mainly contain …….. | pinene | camphor | geraniol | citral | pinene |

## UNIT 2

## SYLLABUS

Alkaloids – Introduction –Classification – General characteristics – General methods of determining structures – Hofmann's exhaustive methylation, structural elucidation and synthesis of Nicotine, Conine, Piperine and Papaverine.

## INTRODUCTION

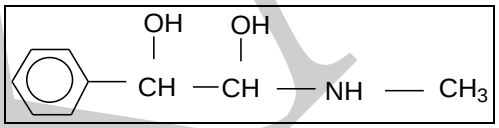
- The term alkaloid meaning, 'alkali-like' has been used to designate.
- The compounds of plant origin having one or more basic nitrogen atoms in heterocyclic ring systems, which induce pronounced physiological activity in aeimals and man
- The above definition of the alkaloids is by no means perfect and does not cover all compounds classed as alkaloids

1) piperine , the alkaloid of pepper, is not basic and has practically no physiological activity.

2) purines such as caffeine (in coffee and tea) and 1herobromine (in cocoa bean ), which stimulate the nervous system, and are heterocycles containing nitrogens ,conform to the definition of alkaloids but are frequently not included in this class

3) Opium (containing the alkaloid morphine ) and hashish or bhang, are both habit forming drugs ,yet the active principle of the latter does latter does not contain nitrogen .

4) Ephedrine is a straight-chain alkaloid that is produced by animal glands , and has marked physiological activity




In fast, no precise definition of the term "alkaloid" is possible but in general it designates compounds having the following common features

a) they are found in plants ,although a few are of animal origin

b) they are basic in character and show marked physiological activity

c) they have heterocyclic rings containing nitrogen as a part of their structures

## OCCURRENCE AND ISOLATION

- Alkaloids occur chiefly in plants of the dicotyledons families and are localised in seeds, leaves , bark, or root of the plant .Each site may contain several closely related alkaloids

- They occur largely as sets of common plants acids such as acetic acid ,oxalic acid ,lactic acid, malic acid, tartaric acid ,citric acid or of certain special organic acid
- For extraction of alkaloid ,the plant material is macerated
- If the material is rich in fat (seeds) it is first extracted with ligroin or petroleum ether for their removal
- The plant residue is then extracted with methanol and the cellulosic material separated by filtration
- The filtrate is evaporated to give the crude plant extract
- This is then dissolved in dilute acid and extracted with ether
- The acid solution of alkaloid salts is then basified and extracted with ether
- Evaporation of ether solution gives a solid mixture of crude alkaloids, it is then subjected to fractional crystallization for separation into individual pure alkaloids
- In modern practice the isolation is effected by column chromatography, gas chromatography and by counter current distribution →
- The general scheme for the extraction of alkaloids

Macerated plant

↓

Step 1

1, extract with ligroin

2, filter

Filtrate _*orate*_.> FATS

PLANT RESIDUE

↓

STEP 2

1. extract with $CH_3OH$
2. filter out cellulosic material
3. evaporate filtrate

crude plant extract

↓

step 3

1. Dissolved in dil. inorganic acid

2. Extract with ether

↓

Ether solution <u>evaporate></u> non basic material

acid solution of alkaloid salts

step 4 ↓

1. NAOH solution
2. Extract with either

↓ → aqueous residue

Ether solution

Step 5 ↓

1. Evaporate

Alkaloids

Procedure for the isolation alkaloids from plants

## GENERAL PROPERTIES

1) Alkaloids are usually colourless , crystalline ,non-volatile solids ,while a few of them (coniine nicotine ) are liquids
2) Expect the liquid alkaloids which are soluble in water but dissolve readily in ethanol ,ether, chloroform, and benzene.
3) They are basic with bitter taste, and dissolve in mineral acids to form salts
4) They are optically active , the majority being leavo-rotatory
5) Physiological activity
   *most of them possess marked physiological activity when orally administered
   *coniine is a violet poison
   *quinine is an antimalarial
   *cocaine acts as local anaesthetic
   *morphine relieves pain
   *atrophine dilates pupil of the eye

6) **Basic character**

- The molecule of alkaloid contains one or more basic nitrogen
- Most alkaloids are tertiary monoacid, while a few are secondary bases
- These they form well defined crystalline salts with mineral acids, the hydrochloride and nitrate being generally readily soluble in water

**Alkaloidal reagent**

The solutions of alkaloids in dilute mineral acids when treated with certain reagents form insoluble precipitates, after having characteristics colour and melting points such reagents as are frequently spoken of as alkaloidal reagents

The common ones are;-

Chloroplatinic acid $H_2PtCl_6$, phoshphomolybdic acid, phosphotungstic acid, picric acid tannic acid, etc

## CLASSIFICATION OF ALKALOIDS

- They are classified according to the heterocyclic ring system

They are

1) Pyrrolidine
2) Piperidine alkaloids
3) Pyridine-pyrrolidine alkaloids
4) Piperidine piperidine alkaloids
5) Quinoline alkaloids
6) Isoquinoline alkaloids
7) Iodole alkaloids

**Pyrrolidine alkaloids ;-**

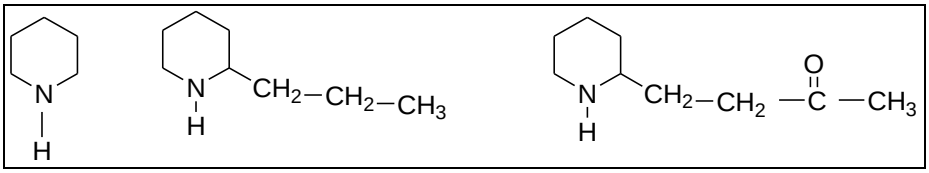
They contain the pyrrolidine (tetra hydropyrrole) ring system eg;- hygrine and cuscohygrine.


Pyrrolidine Hygrine cuscohygrine

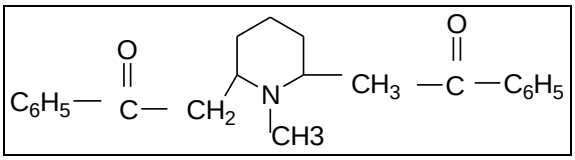
- Hygrine is isolated form the leaves of the Peruvian coca shrub
- Cuscohygrine is found in "cuscon leaves

**Piperidine alkaloids**

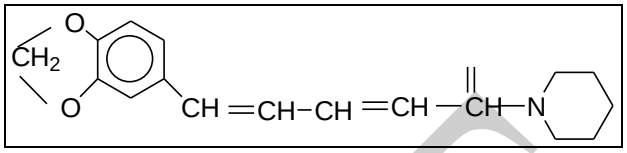
- They have piperidine (hexahydro pyridine ) as the heterocyclic structural unit ~~e.g~~ ;-coriine ,isopelletierine lobeline and piperine




Piperidine coniine isopelletierine



Lobeline



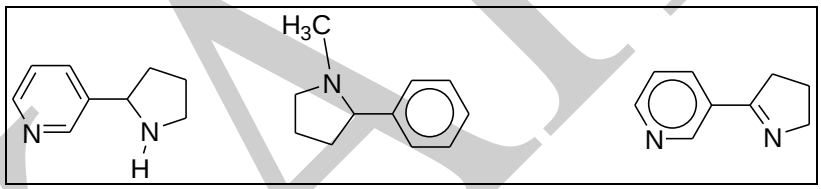
Pierine

- Coniine occurs in the oil of hemlock and is poison to humans
- Isopelletierine is isolate from bark of pomegranate tree
- Lobeline obtained from the seeds of Indian tobacco is used in medicine as a respiratory stimulant and as a tobacco substitute

**Pyrrolidine –pyridine alkaloids**

The heterocyclic ring system present in these alkaloids is pyrrolidine-pyridine

EX;- ricotine or mysomine

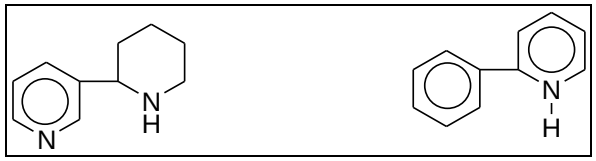


Pyrrolidine nicotine mysomine

- Nicotine is isolated from tobacco leaf .it is highly toxic which is very small doses causes respiratory stimulation and in large doses causes respiratory failure and death
- Mysomine also occurs in tobacco and aroma of tobacco smoke is due to it

**Pyridine-piperidine alkaloids**

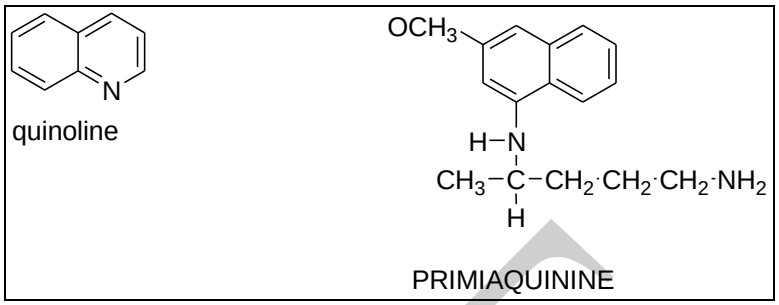
- This family if alkaloids contains a pyridine ring system joined to a piperidine ring system
- The simplest member is anabasine ,the chief alkaloid isolate from the poisonous
- Another alkaloid of this class is anatabine.

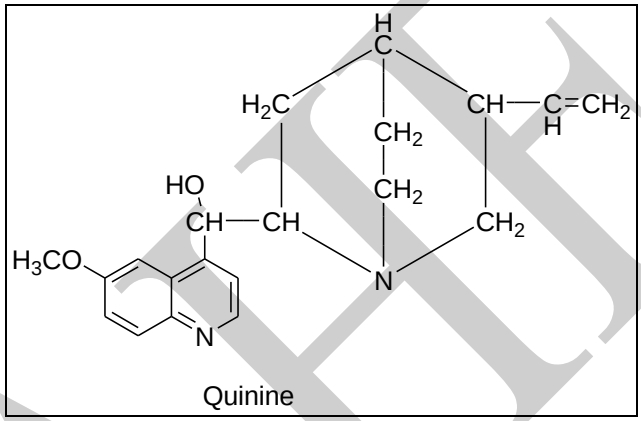


ANABASINE ANATABINE

**Quinlodine alkaloids;-**

- These have the basic heterocyclic ring system quinoline e,g quinine primaquinine

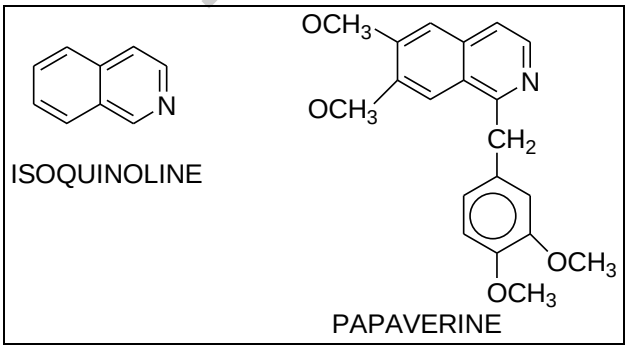


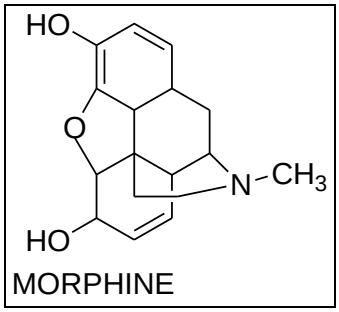




- Quinine occurs in the bark of cinchona tree. it has used for centuries for treatment of malaria synthetic drugs such as primaquinine have largely replaced quinine as an antimalarial

**Isoquinoline alkaloids**

- They contain the hetrocyclic ring system isoquinoline
- E,g papaverine and morphine
- Papavarine is isolated from the unripe seed capsule of the opium poppy
- It find use as medicine in the treatment of spasms of the stomach or intestines
- Morphine is isolated from opium it is used in medicine as hypnotic (sleepproducing) and (pain relieving )

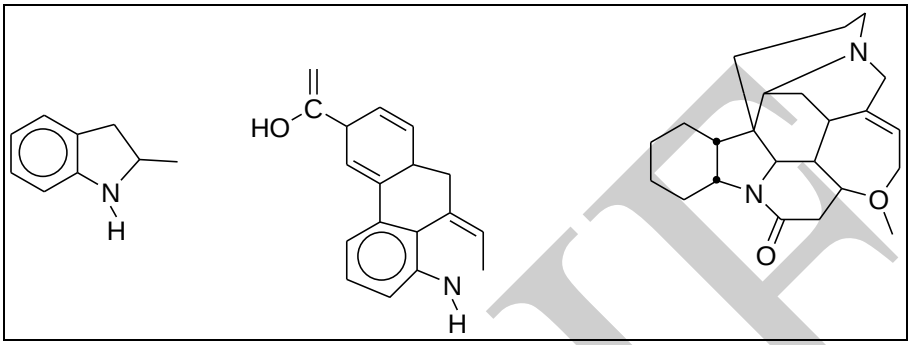


- Unfortunately, prolonged intake of morphine leads to addiction and hence it use is sharply restricted

**Indole alkaloids**

- Alkaloids based upon the indole skeleton are widely distributed in nature ,the physiological action of this substances may rest in the fact that derivatives of indole play important roles in the chemistry of the brain.




Indole lysergic acid strychnine

## GENERAL METHODS OF DETERMINATION OF STRUCTURES

1. **Determination of molecular formula**
   The molecular formula of the given unknown alkaloid is first determined by suitable methods
2. **Detection of groups ;-**
   The presence of various functional groups in the molecular is ascertained by applying specific tests.
3. **Nature of Oxygen Function ;-**

Oxygen is present as Alcoholic, Phenolic, Carbonyl, Carboxyl, Methoxy or Ester group

a) Hydroxyl group OH

The alkaloid treated with acetic anhydride , acetyl chloride or benzenyl chloride to defect the presence of hydroxyl group (note that $-NH_2$ group also reacts with these reagents) ,the OH group may be phenolic or alcoholic .it is phenolic. if the alkaloid,

i) gives a colouration with ferric chloride.
ii) is soluble in NaoH and is reprecipitated by $CO_2$

If the above tests are given in negative ,the OH group is alcoholic. $1^0$ OH group $CH_2OH$, forms esters and on oxidation yields aldehydes .

The $2^0$ OH group >CHOH ,forms esters and on oxidation gives a ketone

b) Carboxyl group ;-COOH

The presence of COOH group is indicated by the formation of salts and ethers, and the evolution of $CO_2$ with $NaHCO_3$ solution.

c) Methoxy group ;- $-OCH_3$

This groups produces methyl iodide on heating with hydriodic acid

$-OCH_3+HI \rightarrow -OH+CH_3I$

d) Carboxyl group ;- .>c=o

The presence of carboxyl group is detected by the formation of oxione and hydrazone

e) Ester group ;- -CO-OR

The alkaloid containing the ester group gives an acid and an alcohol on hydrolysis

**4. Natrual of Nitrogen Function ;-**

a) Amino group ,-$NH_2$

- The alkaloids containing an amino group form salts with acids ,the nature of the amino group is decided.
- On the basis of the following fords reactants

1) Aliphatic –$NH_2$ group reacts with nitrous acid to give a $1^0$ OH with evolution of nitrogen

2) Aromatic –$NH_2$ group forms diazonic salts and dyes coupling reaction

3) $2^0$ amino group ,-NH-reacts with nitrous acid to form nitrosoamines

4) $3^0$amino group .>N-, react with methyl iodide to form quaternary salts

b) Amide group .-$CONH_2$

Upon hydrolysis , the alkaloids containing an amide group yield the corresponding carboxylic acid and ammonia.

c ) Presence unsaturation

The presence of unsaturation in alkaloids is indicated by treatment with Na/Hg sodium and ethanol , presence of unsaturation

5. **Estimation of groups** ;-

**a)** Hydroxyl groups

The no. of –OH group is determined by acetylating the alkaloid and hydrolysing the acetyl derivative with a known volume of 1N-NaOH

$$R\text{-}OH \rightarrow R\text{-}CO\text{-}CH_3 \rightarrow R\text{-}OH + CH_3COONa$$

The excess of alkali is estimated by titration with a standard solution of hydrochloric acid The no. of acetyl group or OH groups can be calculated by from the volume of alkali used for hydrolysis

b. Carboxyl groups ;-

The no. of carboxyl group may be determined volumetrically by titration against a standard barium hydroxide solution using phenolphthalein as indicator or gravimetrically by "silver salts method "

c. Methoxy groups (zeisel's method )

The no. of methoxy groups is estimated by heating the alkaloid with con HCL .the $CH_3$ evolved is absorbed in ethanolic silver nitrate when silver lodide is precipitated

$$R(OCH_3)_n + n\ HI \rightarrow R(OH)_n + n\ CH_3I$$

$$n\ CH_3I + n\ Ag\ No_3 \rightarrow n\ AgI + nCH_3NO_3$$

The precipitate of AgI is boiled with $HNO_3$, filtered, washed, dried and weighed , from the weight of the precipitate formed ,the no/-of $-OCH_3$ groups can be calculated.

d) -$NH_3$, >NH and –N< groups :

These can be estimated .

1. By forming the hydrochloride and titrating its aqueous solution against W/10 KOH using phenolphthalein as indicator ; and
2. By the platinicchloride method.

**6. Degradation;**

The alkaloid is decomposed by treating with suitable reagent to give simpler compounds which can be identified easily.

1) Hydrolysis:

An alkaloid containing an ester or amide group gives simpler products on hydrolysis.

$$C_{11}H_9O_2\text{-CO-NH}_2 + H_2O \rightarrow C_{11}H_9O_2\text{-CO-OH} + C_5H_{10}\text{-NH}$$

Piperine piperic acid piperidine

From this we infer that piperine is an amide of piperic acid.

2) Oxidation:

Oxidation of alkaloid with $KMnO_4$,$K_2Cr_2O_7$, or with $H_2O_2$ can bring about several changes. Thus with $KMnO_4$ the molecule may be oxidised away leaving a COOH group at root.

3) Distillation with Zinc dust:

When distilled with Zn dust, many alkaloids yield the parent compound or are dehydrogenated.

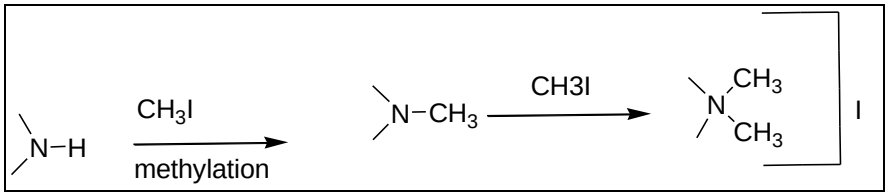
4) Hofmann's Exhaustive Methylation:

This is an important method used to find a recognisable moiety in an unknown alkaloid.

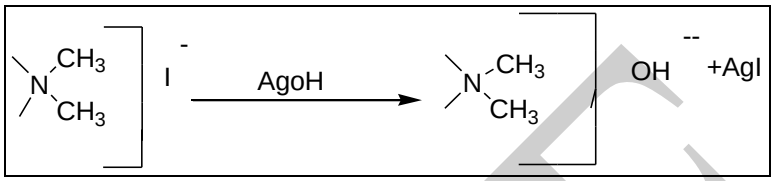
This is accomplished by degradation of the alkaloid by the following steps.

a) The heterocyclic ring of the alkaloid is reduced if unsaturated.

b) The alkaloid (or the reduced alkaloid) is treated with excess of methyl iodide when the >NH of the ring system is methylated and the converted to the respective quaternary ammonium iodide




a) The quaternary ammonium iodide is changed to the corresponding hydroxide by reaction with moist silver oxide (AgOH)




d) Quaternary ammonium hydroxide on pyrolysis splits out a molecule of water the OH group extracting a H atom from the β-position with respect to N-atom.

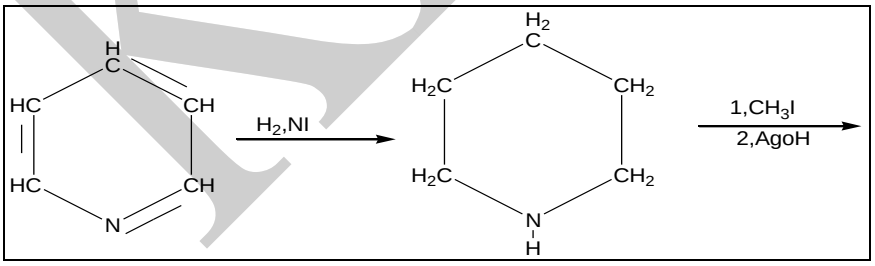
As a result, the C-N bond on the side of the β-hydrogen concentrated ruptures to give an opened chain unsaturated amine.

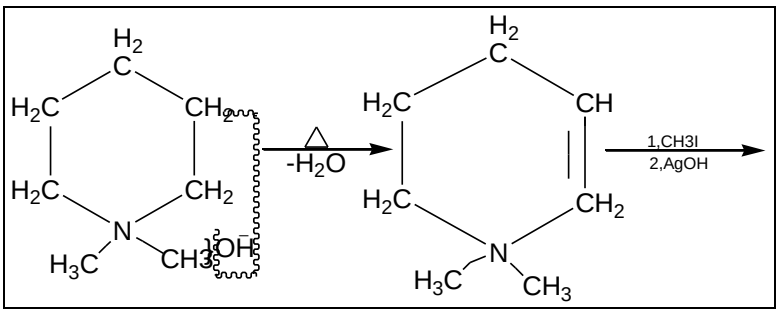
e) The above sequence of reaction listed in steps a, b, c, d are repeated with excess of $CH_3I$ when rupture of the second C-N bond occurs and N atom is eliminated as $(CH_3)_3N$.

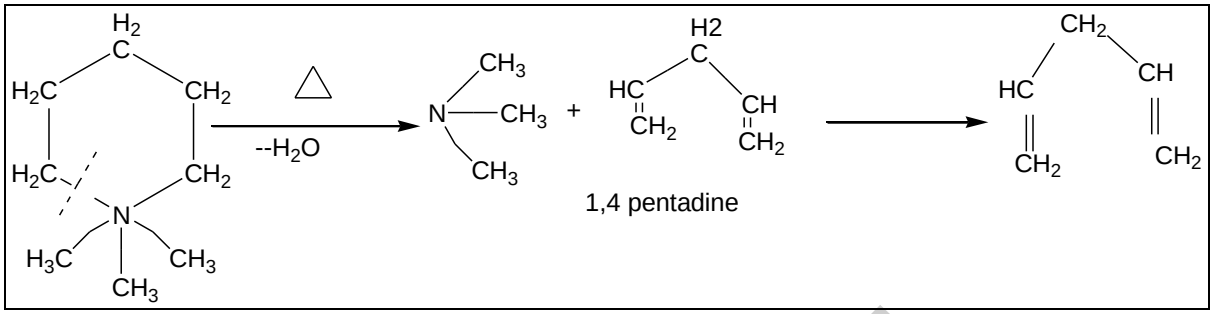
The unsaturated hydrocarbon left behind, which often isomerises to a conjugated diene, is identified by the usual analytic methods.

The overall process mentioned in the steps above the involving repeated methylation to get the degradation end-products is called exhaustive methylation.

The nature of these products helps in arriving at the structure of the parent alkaloid. This may be illustrated by taking example of pyridine ring system.






Thus the made of linking the ring system is established. The method has been best exploited in the elucidation of structure of coniine.

Hofmann's exhaustive methylation is applicable as long as β-hydrogen is available for elimination of $H_2O$, otherwise it fails.Thus it does not apply in cast of quinoline and isoquinoline derivatives.

**7. Newer physical methods**

In conjugation with the chemical methods mentioned earlier more recent and sophisticated techniques are now frequently used to elucidate the structure of alkaloids

1) Infrared spectra are used to detect the presence of many functional groups

2) UV spectra are employed so as to project the possible type of structures present in the molecule

3) X-Ray analysis has provided a means to fit in the various structural units indicated to be present in the molecule, thus giving a sure procedure to give the final structure of the alkaloid accurately.

4) NMR spectroscopy:

It is a more recent and sophisticated method for deleting many functional groups such as alkene protons N-, O- and C- methyl group.

**8. Synthesis:**

The analytical procedure discussed above will project the tentative structure for the alkaloid under investigation.

The synthesis will ever remain a fruitful method for confirming the proposed structure as it might as well provide a newer way of obtaining an alkaloid rather than depending only on a natural sources.

## NICOTINE;-

**Introduction ;-**

- Nicotine is the chief alkaloid of tobacco plant (nicotina tabacum)
- It accurs in the plant leaves as salts of malic acid and citric acid to the extent of 4 to 5%
- The alkaloid was named after the Frenchman Nicot who introduced tobacco in France in 1560

**Isolation of nicotine**

1. Waste parts of the tobacco plant are finely powdered and extracted with dilute acid. The water soluble salts of alkaloids are thus removed in solution, leaving the insoluble cellulose, chlorophyll etc behind.

2. The acid extract is then made basic with lime or NaOH and steam distilled.

Steam distillation separates the nicotine from water soluble non-volatile materials (sugars, inorganic salts& etc).

3. The distillate is acidified to about $PH_3$ with solid oxalic acid and concentrated to syrup.

On cooling, the crystalline salt of nicotine and oxalic acid separates. Other alkaloids not forming slightly soluble oxalates are left in the solution.

4. The crystalline nicotine oxalate is then transferred to a separating funnel and treated with excess of aqueous KOH. The nicotine thus set free rise to the surface as a brown oil and separated by extraction with ether.

5. The ethereal solution of the alkaloid is dried over solid anhydride KOH and the ether evaporated.

For further purification, the residue is fractionally distilled under vaccum.

**Properties:**

1. Nicotine is one of the few alkaloids known to exist in a liquid form, colourless, boiling point $246^0$ C.

2. It has to be tobacco –like smell and burning alkaline taste.

3. It is soluble in water and also in organic solvents such as ethanol, ether and benzene.

4. The natural alkaloids is Leavorotary $[\alpha]_D = -169^0$

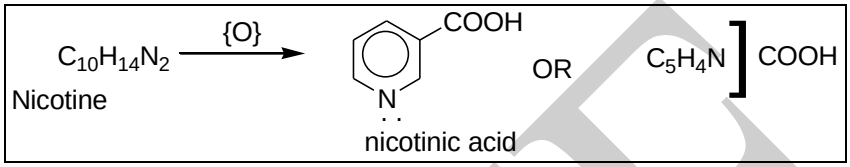
5. It is deadly poison to animals and is used commercially as an insecticidal spray for plants and animals.

6. In small quantities, nicotine stimulates the nervous system for a while, which is followed by depression.

A low nicotine content tobacco is used for smoking purpose even though it is definitely injurious to health, causing diseases like asthma and lung cancer.

**Structure:**

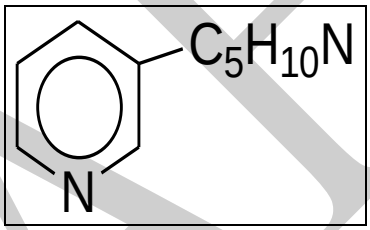
1. Elemental analysis and molecular weight determination leads to the molecular formula $C_{10}H_{14}N_2$ for nicotine.
2. It absorbs 2 molecules of $CH_3I$, suggesting the tertiary nature of both the nitrogen atoms.
3. On oxidation with chromic acid, nicotine yields nicotinic acid (pyridine-3-carboxylic acid).




This shows that the alkaloid contains a pyridine nucleus with a side chain at the 3-position.

That is the side chain has the composition ($C_{10}H_{14}N_2$-$C_5H_4N$) = $C_5H_{10}N$

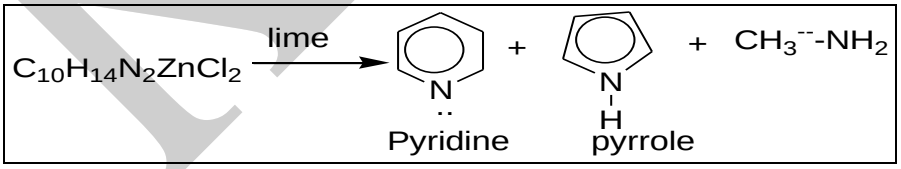
The formula for nicotine may be written as




From the above formula it is evident that the side chain must be saturated.

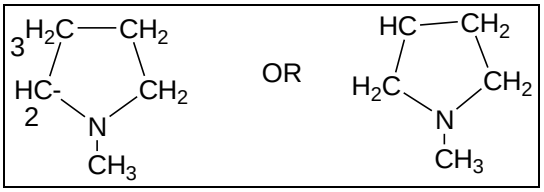
4. Nature and position of the side chain:

- The alkaloid forms an addition compound with Zinc chloride. $C_{10}H_{14}N_2ZnCl_2$, which when heated lime water yields pyridine, pyrrole and methylamine.



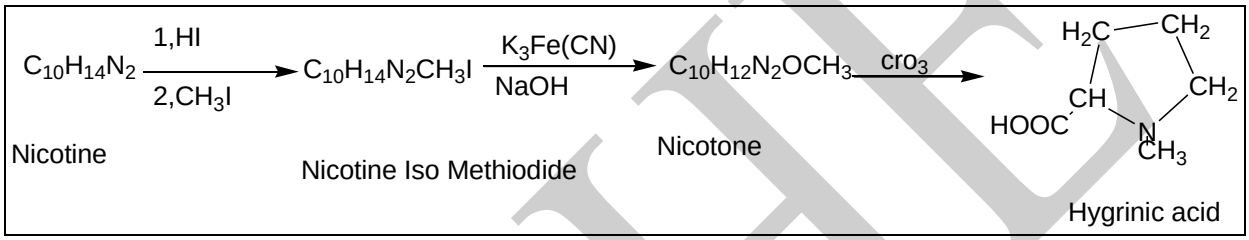

- This suggestion that the side chain, $C_5H_{10}N$ is a pyrrole derivative.
- When heated with concentrated hydriodic acid at 200-300$^0$C (Herzig and Meyer ), Nicotine yields $CH_3I$, showing that methyl group is attached to N-atom.

It appears that the side chain could be N-methyl pyrrolidine.



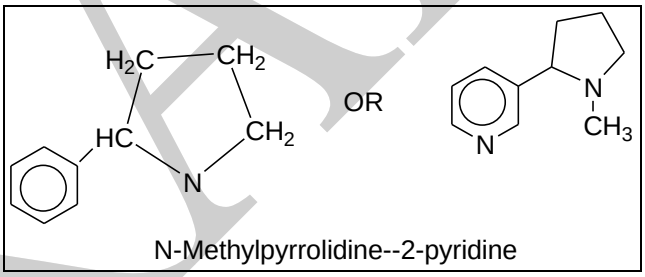

However, the point of attachment of the side chain to the pyridine nucleus could be $C_2$ or $C_3$ as shown above

- Nicotine hydriodide when treated with $CH_3I$,forms nicotine isomethiodide which on oxidation with potassium ferriccyanide yields nicotine
- This on further oxidation with $Cro_3$ produces hygrinic acid

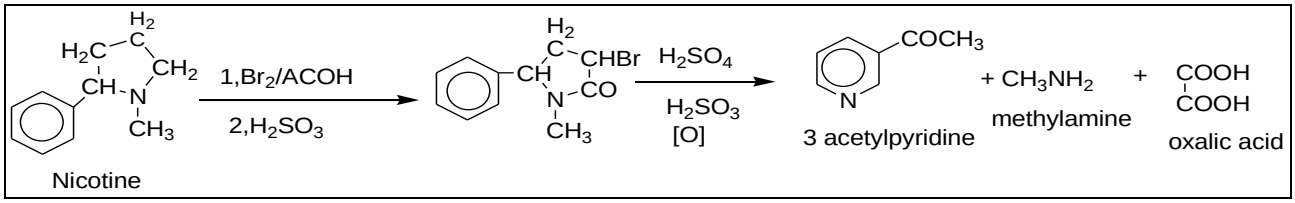



The formation of hygrinic acid as above proves beyond doubt that side chain ,N-methylpyrrolidine is attached to the pyridine rucles thorough $C_2$

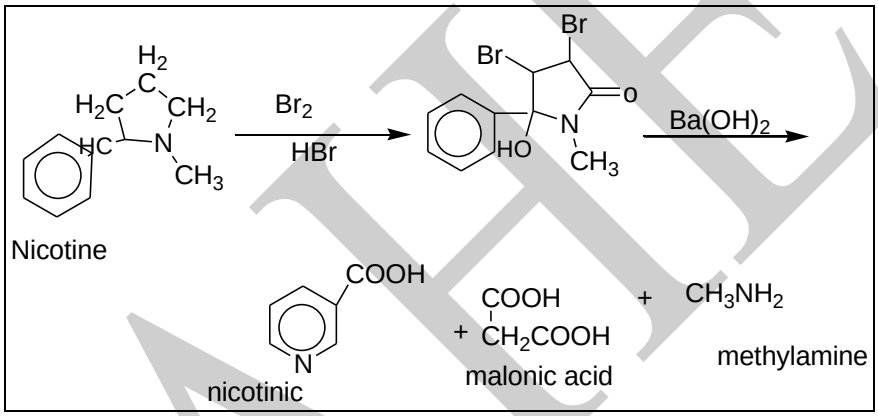
5. From the foregoing considerations the structural formula of nicotine may be written




6. The above structure of nicotine is further confirmed us it explains the following reactions of the alkaloid admirably
    - Nicotine when treated with bromine in acetic acid followed by aqueous sulphurous acid gives dibromonicotine, $C_{10}H_{10}ON_2Br_2$. This upon oxidation with mixture of sulphurous acid and sulphuric acid at $130 – 140^0$ yields 3-aceetylphyridine ,oxalic acid and methylamide (pinner,1892)

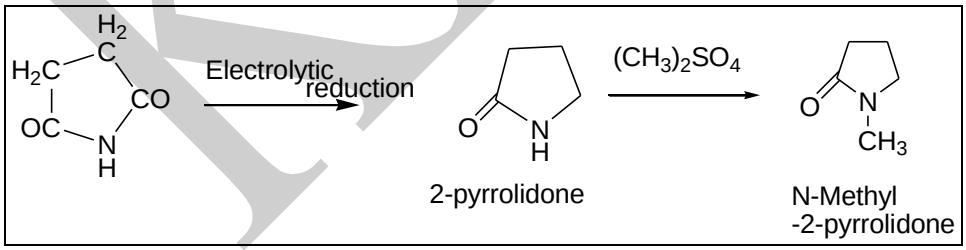



- Nicotine on reaction with bromine in hydrobromic acid gives which when heated with $Ba(OH)_2$ solution at $100^0$C,yields nicotinic acid, malonic acid and methylamine.



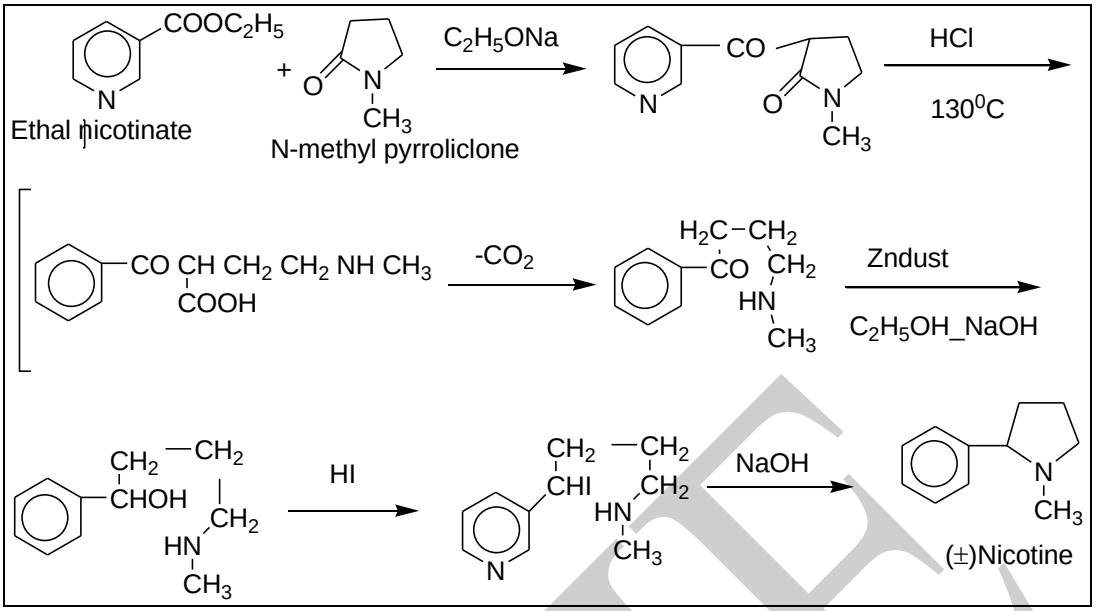

7. Finally the structure of nicotine was confirmed by the following synthesis accomplished by spath (1928)

a) Synthesis of N-methyl-2-pyrrolidone




b. Synthesis of nicotine

- N-methyl-2-pyrrolidone produces as step(a) under goes reaction to yield nicotine




The dl-nicotine is resolved by means of (+)tartaric acid the synthetic (-)nicotine is identical with the natural compound.

**CONINE:**

**Introduction**:

- It is the principal toxic substance present in the hemlock herb (conine maculatum) and is now of historical interest only.
- The extract of hemlock containing coniine was used as official state poison by Greeks for the execution of criminals.
- The famous philosopher Socrates was put to death in 400 B.C by being required to drink hemlock extract.

**Isolation:**

- The seeds of hemlock are powdered and distilled with sodium hydroxide solution.
- Conine is then recovered from the distillate by on evaporation leaves behind the alkaloid

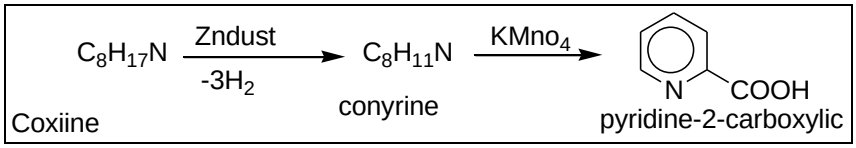
**Properties:**

- It is a colourless and poisonous oily liquid (B.P $167^0$)
- It is soluble in water and has burning taste.
- It yields a crystalline hydrochloride and picrate and is a secondary amine, yielding a crystalline 3,5-dinitrobenzoyl derivative and a N-nitroso derivative.

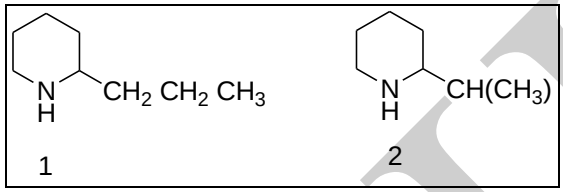
**Constitution:**

1. Molecular formula $C_8H_{17}N$.

2. Formation of nitroso derivative with nitrous acid and a quaternary ammonium iodide with 2 moles of methyl iodide indicates amine that coniine is a $2^0$ amine




3. The formation of pyridine-2-carboxylic acid indicates that conyrine must be a pyridine derivative with a side chain $–C_3H_7$ at α-position.
   But coniine is a $2^0$ amine, loses 6 H atom to form conyrine. It is obviously the corresponding piperidine derivative.
4. On the basis of the side chain, coniine may be either (1) or (2)



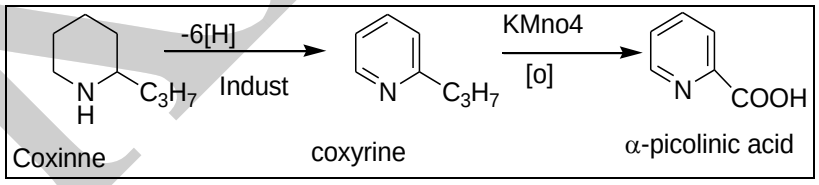

Out of the above structures, coniine is found to be, (1).on the basis of the following observation.

a) Coniine →n- octane and not isooctane. Which would have been formed if structure (2) for coniine was correct.
   - From this evidence it therefore follows that coniine is 2-n-propylpiperidine.

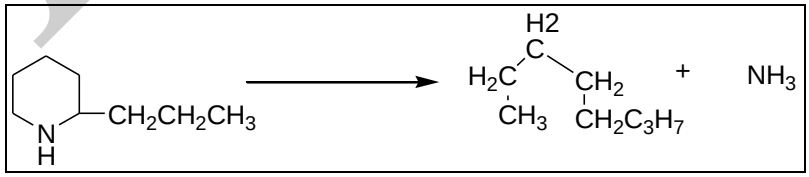
b) Complete exhaustive methylation of coniine followed by reduction yields n-octane.

c) Von Braun degradation of coniine yields 1,5-dichloro-octane.
   - All the above reaction can be explained by the structure (1) of coniine in the following way.

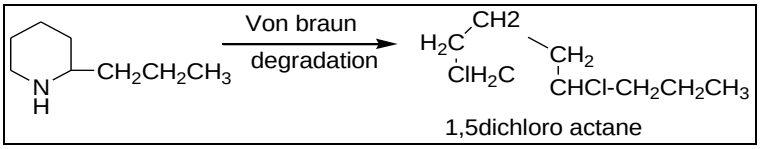
i)




ii)

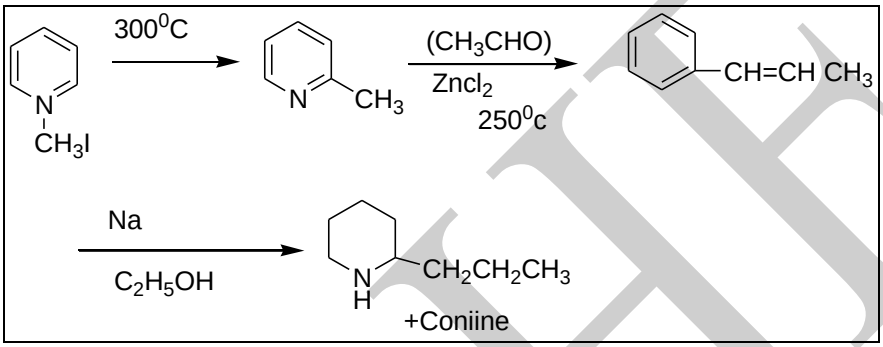


iii) Von Braun's degradation



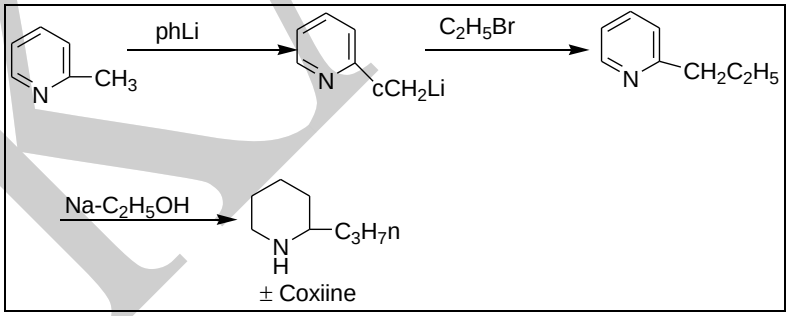

5. Synthesis:

a) Ladenburg's synthesis (1866)

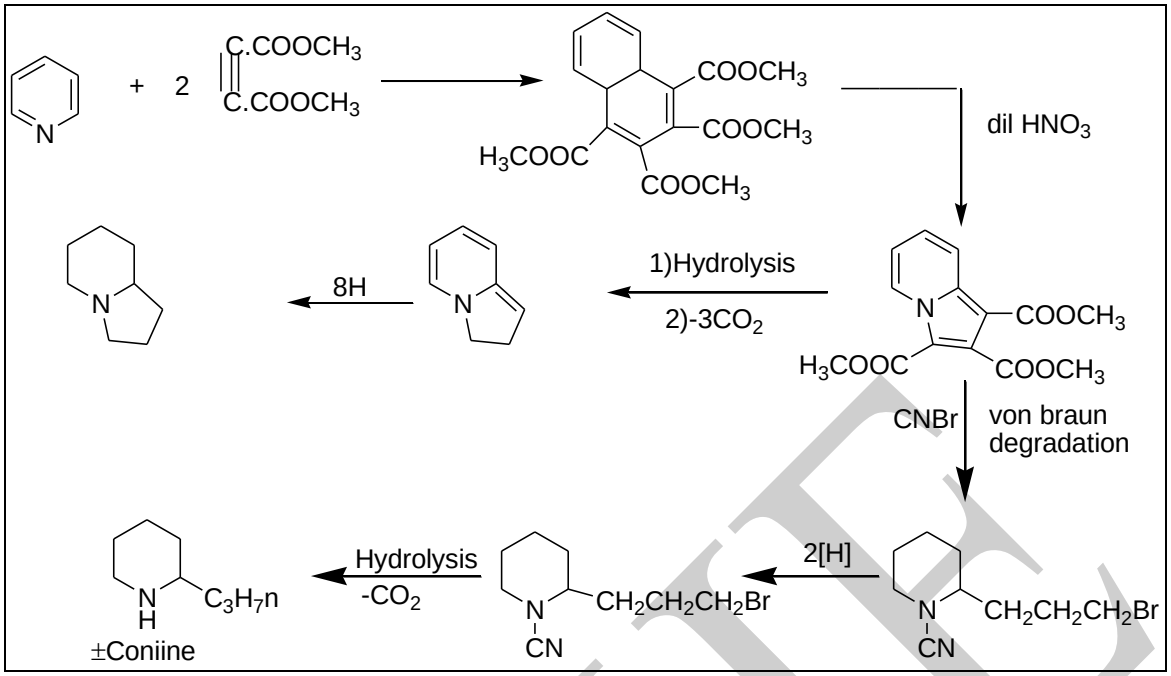



- Coniine so synthesised is racemic mixture and is resolved by forming salts with(+)tartaric acid. The salt of (+) coniine being less soluble, crystalline out first.
- This on treatment with alkali gives (+) coniine which is found to be identical with the natural compound.

b) Bergmann's synthesis




c) Diels alder synthesis (1932)




**PIPERINE**

- This alkaloid occurs in the ripe fruits (white pepper) and in the unripe fruit (black pepper ) of piper nigrum .
- It occurs in the kernel of the black pepper to the extent of 5 to 10 % was isolated from this source by oerstedt (1819)

**Extraction:**

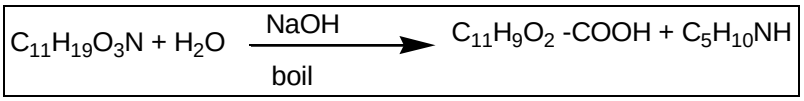
- Piperine is obtained by extracting the powdered black peppers with ethanol.
- The extract is evaporated and the solvent free residue is treated with NaOH to remove the resin.
- The insoluble residue is again dissolved in warm ethanol or ether. From the solution, piperine crystallises out on cooling.

**Properties:**

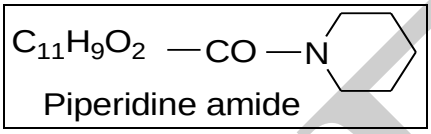
- Piperine forms beautiful colourless crystals.
- Melting point 128-129.5$^0$C
- It is neutral to litmus and has the characteristic sharp flavour and taste of black pepper.
- It is difficultly soluble in water but dissolves readily in ethanol and water.
- Its toxicity is much feeble as compared to other alkaloids.
- It is optically active.

**Structure:**

1. Molecular formula $C_{17}H_{19}O_3N$.
2. On hydrolysis with alkali it gives piperic acid and a base piperidine.

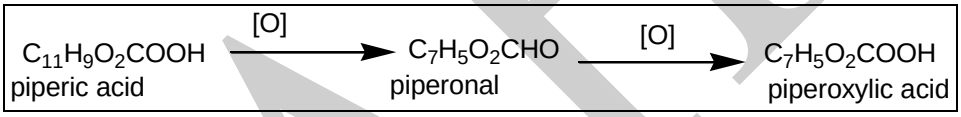



Obviously, piperine is the piperidine amide of piperic acid. The piperidine amide of piperic acid, the structure of is already known and hence we could represent the alkaloid as,

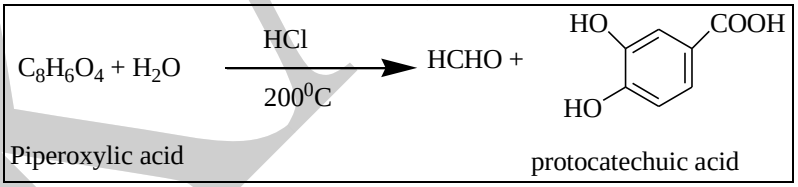



Thus to have complete picture of the structure of piperine we should know the structure of piperic acid

3. Structure of Piperic acid
   a. Piperic acid on oxidation with potassium permanganate first gives piperonal and then piperonylic acid

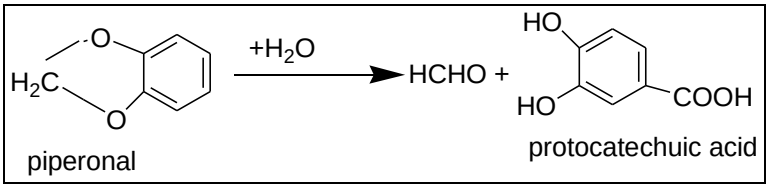



   b. The structure of piperonylic acid is deduced from the fact that when it is heated with HCl at $200^0$c under pressure , it forms formaldehyde and protocatechuic acid (3,4-dihydroxy benzoic acid)

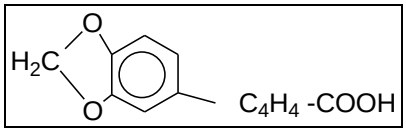



Since one carbon has been eliminated as HCHO and a result 2 free OH groups appeared in protocatechuic acid it follows that piperonylic acid is 3,4 methylenedioxy benzoic acid

The above reaction can be visualised to have proceeded as follows

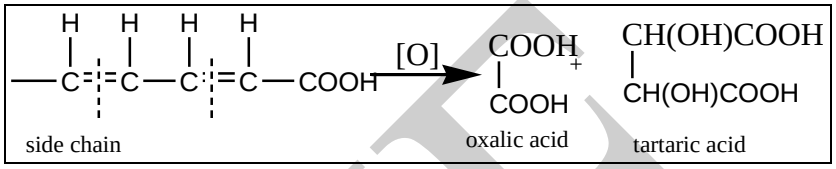



   c. As indicated on step (a)above ,the structure of piperic acid may now be written as

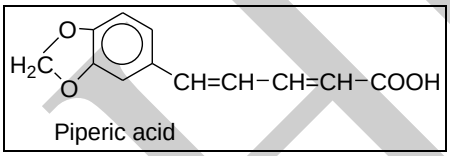



d. The structure of the side chain in piperic acid becomes clear from the fact that.

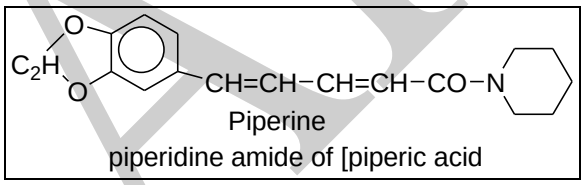
1. It takes up readily for bromine atoms showing the presence of 2 double bonds.
2. On careful oxidation with $KMnO_4$ it decomposes to form a molecule of tartaric acid and oxalic acid each, indicating the presence of 2 double bonds in alternate position.




3. Hence the complete structure of piperic acid can be written as,

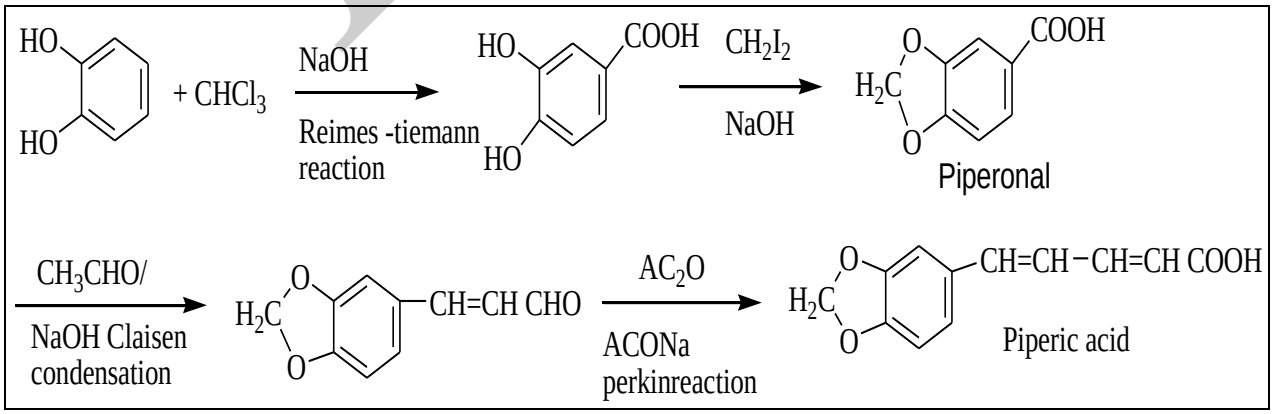



4. Knowing the molecular structure of piperic acid and piperidine the structural formula of piperine can be derived by joining the 2 as amide.

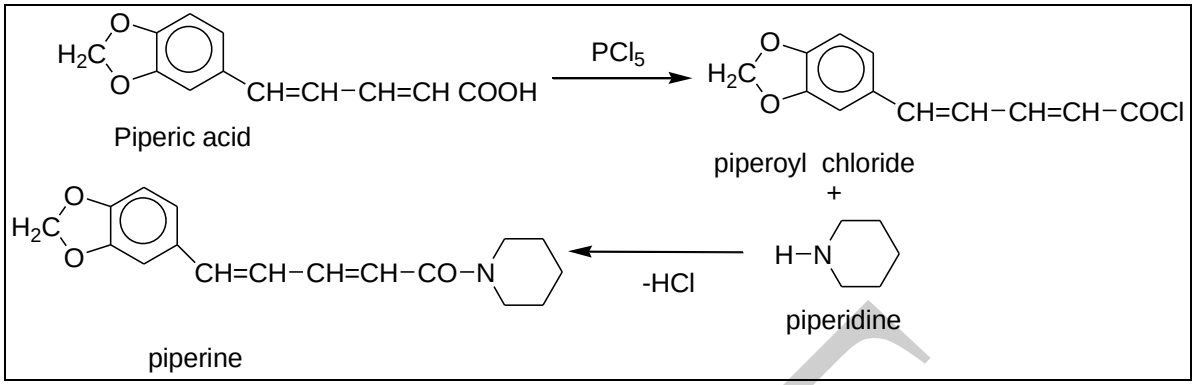



5. The synthetic evidence for the structure of piperine was afforded by first synthesising piperic acid and then preparing from it the alkaloid.

a) <u>The Synthesis of Piperic acid</u>



b) Preparation of piperine from piperic acid




**PAPAVERINE:**

**Introduction:**

- Papaverin, together with nearly 24 other alkaloids such as laudanosine, laudanine, narcotine, narceine, morphine etc.
- Occurs in opium poppy.
- Major alkaloids from opium

| | | | |
|---|---|---|---|
| Morphine | 10-16 % | papaverine | 0.5-2.5 % |
| Narcotine | 4-8 % | | |
| Codenine | 0.8-2.5 % | Thebaine | 0.5-2.0 % |

**Isolation:**

- The dried latex obtained from unripe seed couple of poppy is digested with milk lime when the alkaloids of morphine series remain dissolved where as those of papaverine series are precipitated.
- They are then extracted with a suitable solvent like chloroform, ether etc
- Papaverine is then obtained by fractional precipitation from the mixture
- It is further purified as its hydro-oxalate salts

**Properties:**

- It is a colourless solid
- M.P $147^0$C
- It is optically active tertiary base ($pK_a$ 6-2)
- It is insoluble in water but soluble in hot alcohol and chloroform.

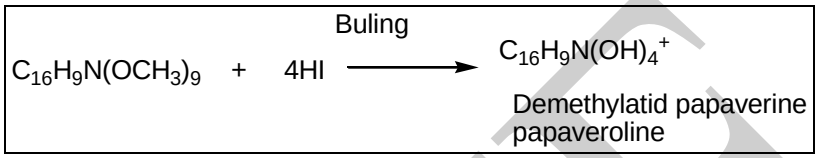
**Constitution:**

1. Molecular formula $C_{20}H_{21}NO_4$.
2. Presence of a tertiary base:

- It adds on one molecule of methyl iodide to yield a quaternary methiodide derivative, indicating that nitrogen present in papaverine is tertiary

$$C_{20}H_{21}NO_4 + CH_3I \rightarrow C_{20}H_{21}O_4N.CH_3I$$

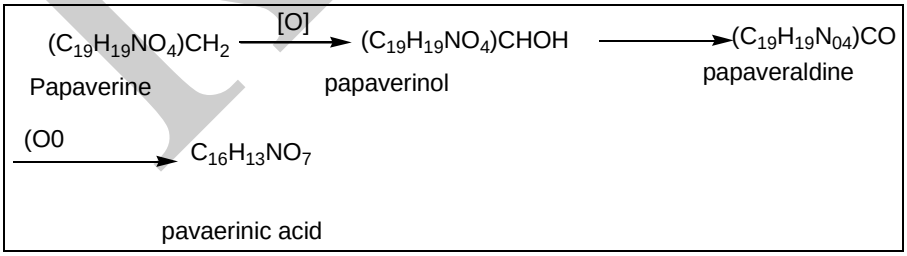
3. Presence of 4-methoxyl groups




This reaction reveals that papaverine contains 4-methoxy ($-OCH_3$) groups.

- It means that all the 4 oxygen atoms of papaverine are present as $-OCH_3$ groups
- The de-methylated product is known as papaverilone .

4. Presence of a methylene ($-CH_2$)group
   - When papaverine is oxidised with cold dil $KMno_4$,it yields $2^0$ OH papaverioxl, $C_{20}H_{19}NO_5$
   - Formation of this ketone reveals that papaverinol is a $2^0$OH
   - Finally ,the prolonged action of hot $kmno_4$ causes the oxidation of papaveraldine to papaverinc acid $C_{16}H_{13}NO_7$
   - The papaveriaic acid is a dibasic which still contains the keto group present in its precursor because it form an oxime, etc
   - Papaveraic acid also contains 2 $OCH_3$ groups all the foregoing reactions suggest that papaverine contains a methylene group




5. Papaverine when fused with KOH mainly yields 2 compounds ;-

- A, $C_{11}H_{11}NO_2$
- B, $C_9H_{12}O_2$ along with some vatic acid now the molecular formula of the compound A and B account for the 20 carbon atoms

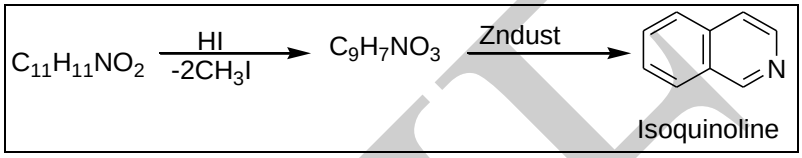
- The 2 compounds must constitute the molecule of papaverine, so it becomes essential to know their constitutions

6. Structure of compound A $C_{11}H_{11}NO_{2;}$-

1. Nitrogen atom in the compound has been found to be $3^0$ one as in the parent compound papaverine.

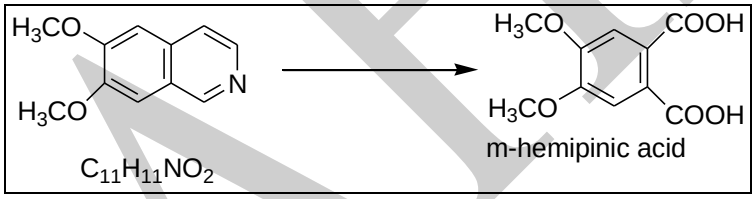
2. It has be found to be contain 2 $–OCH_3$ groups by Zeisel's method

3. On demethylation followed by zinc dust distillation it yields isoquinoline reveals that it is dimethoxy isoquinoline

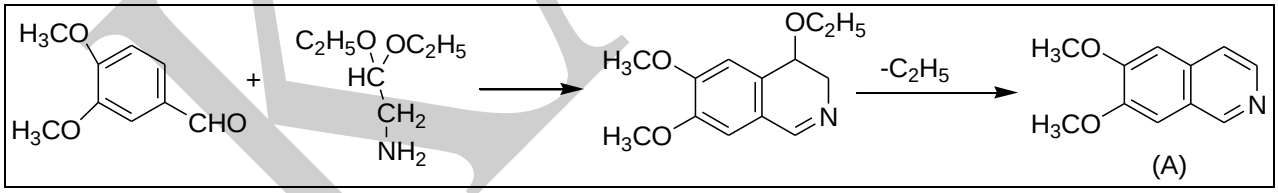



4. It is possible to know the position of 2-$OCH_3$ group by the oxidation of the compound A to m-hemipinic acid

Hence the compound A is 6,7 –dimethoxyisoquinoline




- It can be proved by the synthesis from veratric aldehyde and aminoacetal

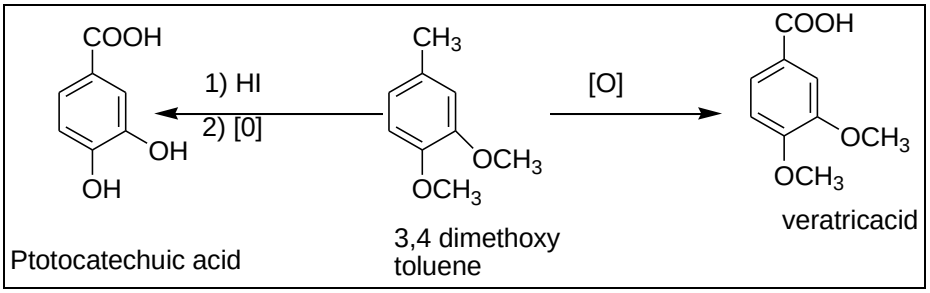



7. Structure of compound B $C_9H_{12}O_2$

The two oxygen atoms have been found to be present as two methoxy groups

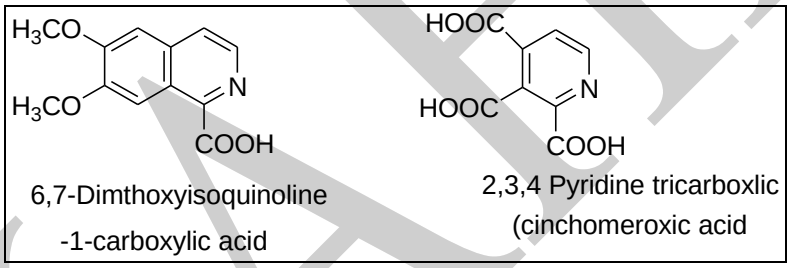
1. On oxidation it yields veratric acid which was identified as 3,4 –demethoxy benzoic acid.

Secondly, On demethylation followed by oxidation, B yields protocatechuic acid, the compound B yields protocatechuic acid, hence the compound B should be 3.4-dimethoxytoluene (homoveratrole)



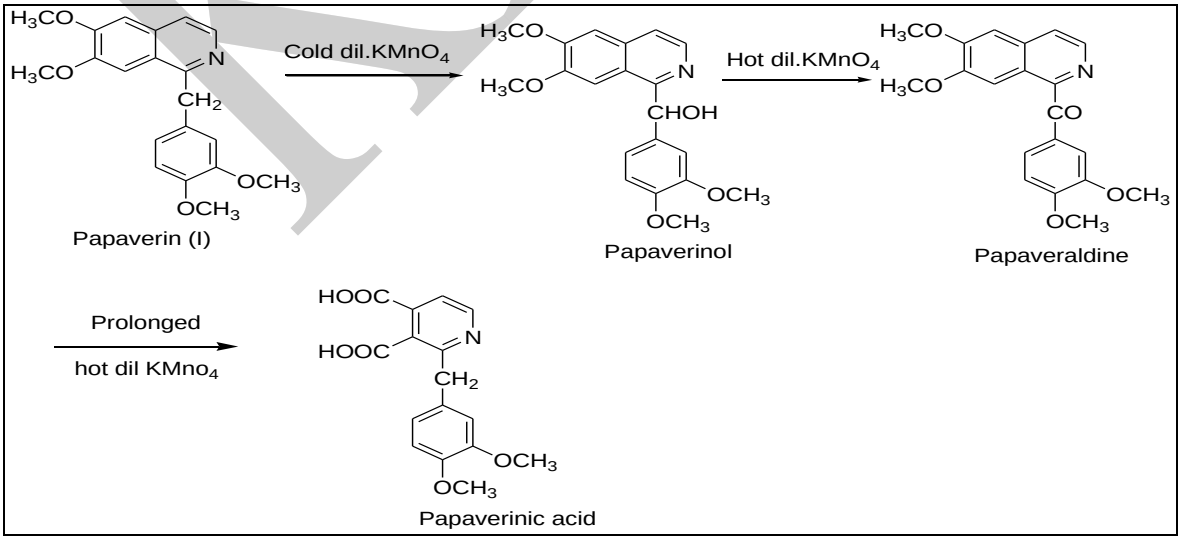

8. Point of linkage between compounds A and B

- As papaverinc is having 4 methoxy groups it means that the 2-componets (having 2-$OCH_3$ group each )cannot be linked through the –$OCH_3$ groups
- Thus the compound B should be linked to A either via the carbon atom of the methyl group
- But the formation of veratric acid during fusion or oxidation reveals that the unit B is linked via the carbon atom of the $CH_3$ group
- The paint of linkage of isoquinoine nucleus can be decided by the oxidation of papaverine to 6,7 dimethoxy isoquinoline -1-carboxy;ic acid (Cinchomeronic acid )

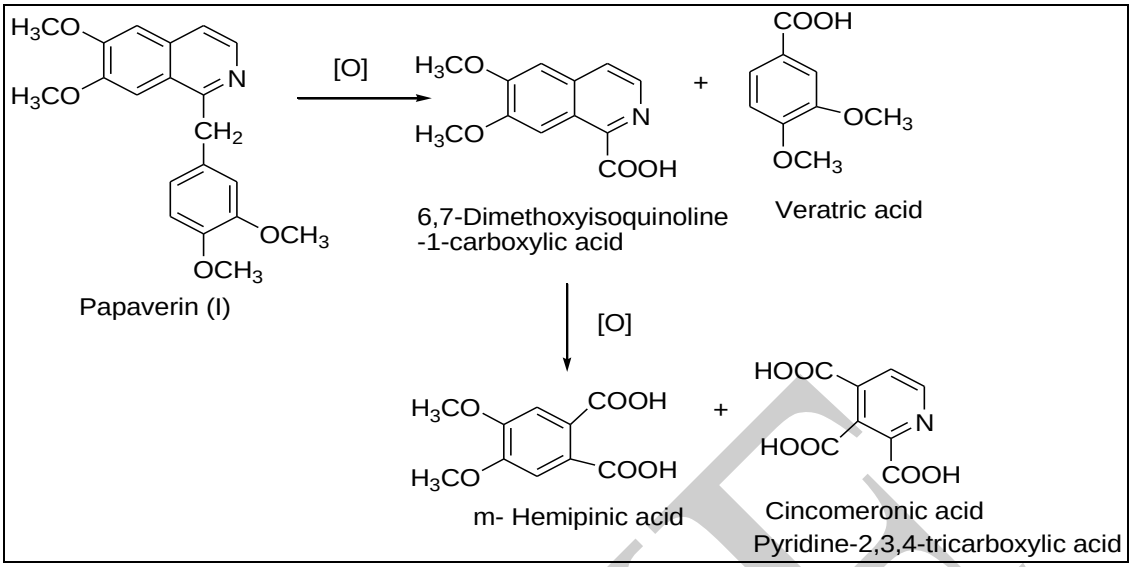



9. Hence the structure of papaverine may be written as (1) which is able to explain all the reaction given in earlier points

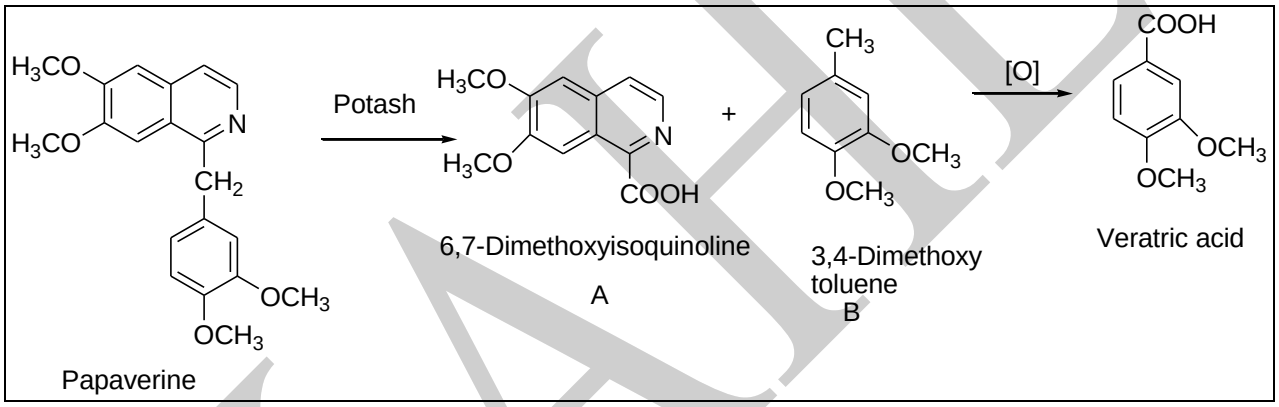
a) <u>Oxidation by dilute permanganate may be put as follows</u>




b) <u>Oxidation of Papaverine</u>




c) Fusion with Potash may be put as follows:-




**Text Books:**

T1: Finar, I.L., 2013. Organic Chemistry, Vol. II, Pearson Education, Singapore.

T2: Gurdeep R.Chatwal, 2013. Organic Chemistry of Natural Products, Vol. II, Himalaya Publishing House, New Delhi

T3: Gurdeep R.Chatwal, 2007. Organic Chemistry Of Natural Products, Vol. I, Himalaya Publishing House, New Delhi

## POSSIBLE QUESTIONS:

**Part-A (1 Mark)**

**Multiple Choice Questions (Each Question Carry One Mark)**

1. Smokers crave cigrattes because they _____?
a. Like the smell of cigarette smoke
**b. Are addicted to nicotine**
c. Like the way cigarettes make them look
d. Feel to reduce our tension

2. _____ is isolated from tobacco leaf?
**a. Nicotine**
b. Coniine
c. Quinine
d. Morphine
3. Give one example of pyrroline-pyridine alkaloids?
a. Coniine
**b. Nicottine**
c. Anabasine
d. Morphine
4. Give one example of piperidine alkaloids?
**a. Coniine**
b. Nicottine
c. Anabasine
d. Morphine
5. Nicotinic acid reacts with soda lime to give
a. Pyrrole
b. Piperidine
c. Pyrrolidine
**d. Pyridine**
6. Which of the following is used as a local anaesthetic?
a. Quinine
**b. Cocaine**
c. Morphine
d. Reserpine
7. Oxidation of conynine with KMnO4 GIVES
**a. α - picolinic acid**
b. β - picolinic acid
c. γ - picolinic acid
d. Tropic acid
8. On fusion with con. KOH quinine gives
**a. 6 - methoxy quinoline + lipidine**
b. Quininic acid
c. Meroquinene
d. 6 - hydroxy quinoline
9. Quinine on oxidation with chromic acid gives quininic acid and
a. Lutidine
**b. Meroquinene**
c. Formic acid
d. Pyridine - 3 - carboxylic acid
10. Meroquinene on reduction with Zn & HI gives
a. γ - picoline
**b. Cincholoipon**
c. Cincholoipoxic acid
d. Loipidic acid
11. Cocaine hydrolysed under controlled condition to give
**a. Benzolecgonine**
b. Ecgonine
c. Tropinone
d. Pyridine
12. Quinine contains a 6 - methoxy quinoline nucleus linked to position - 8
a. CH2 group t A - Position
b. **- CHOH group at A - position**

c. CH = CH2 group at A - position
d. Two - CH2 groups at A- position

13. Poisonous shrub hemlock cotains an alkaloids that was givenn to rates
a. Cocaine
**b. Coniine**
c. Nicotine
d. Morphine

14. Atropine when moistened with fuming HNO3 followed by evaporation
a. Violet
**b. Yellow**
c. Red
d. Green

15. Which of the following alkaloids contains phenanthrene group
a. Cinchonine
b. Papaverine
c. Cocaine
**d. Morphine**

16. …… is a straight chain alkaloid that is produced by animal glands and has physiological activity.
a. Carotenoids
b. Citral
c. Camphor
d. **Ephedrine**

17. Which one out of the following is not an alkaloids
a. Nicotine
b. Ephedrine
c. **Adrenaline**
d. Quinine

18. Wagners reagent is
a. Potassium mercuric iodide
b. **Iodine dissolved in potassium iodide**
c. Potassium bismuth iodide
d. Picric acid solution

19. Mayer's reagent is
a. **Potassium mercuric iodide**
b. Iodine dissolved in potassium iodide
c. Potassium bismuth iodide
d. Picric acid solution

20. Dragendorff's reagent is
a. Potassium mercuric iodide
b. Iodine dissolved in potassium iodide
c. **Potassium bismuth iodide**
d. Picric acid solution

## Part-B (Each Carry 8 Marks)

1. Illustrate Hofmann's exhaustive methylation with suitable example

2. Explain the following synthesis.
   i). Ladenburg's synthesis ii).Bergmann's synthesis
3. Discuss the structural elucidation of nicotine?
4. Explain the synthesis of piperic acid.
5. Discuss the structure of piperic acid.
6. Discuss the oxidation reactions of papavarine.

7. Explain- Hofmann's exhaustive methylation with suitable example.
8. Explain the synthesis of nicotine.
9. Write notes on occurrence, isolation and extraction of alkaloids?

15CHU601

Karpagam Academy of Higher Education

Coimbatore-21

(For the candidate admitted on 2015 onwards)

Department of Chemistry

VI- semester

Chemistry of Natural Products

**UNIT II- Objective Questions for online examination (Each carry 1 Marks)**

| Question | Option-A | Option-B | Option-C | Option-D | Answer |
|---|---|---|---|---|---|
| What are alkaloids? | amines containing an aromatic ring | amines derived from alkenes | amines containing a nitrogen atom as part of a ring structure | biologically active amines usually found in plants | biologically active amines usually found in plants |
| Alkaloids are | natural products, found in animals thatv contain one or more alcohol group | natural products,found in animal that contain one or more nitrogen hetero atoms | natural products, found in plants, that contain one or more nitrogen hetero atoms | aicohol - like compounds | natural products, found in plants, that contain one or more nitrogen hetero atoms |
| Quinine is obtain from the back of which free? | cinchona | red wood | bunyan | eucalyptus | cinchona |
| Nicotine causes which of these changes in the body? | lowers body temperature | decreases heart rate | increase blood pressure | higher the body temperature | increase blood pressure |
| What happens when nicotine comes into contact with the brain? | tissues smell | dopamain is released | nerve centers shutdown | adrenaline increases | dopamain is released |
| Which of these is the most significant health risk for smokers? | cancer | high blood pressure | heart attacks | arthritis | cancer |
| smokers crave cigrattes because they _____? | like the smell of cigarette smoke | are addicted to nicotine | like the way cigarettes make them look | feel to reduce our tension | are addicted to nicotine |
| _____ is isolated from tobacco leaf? | nicotine | conine | quinine | morphine | nicottine |
| Give one example of pyrroline-pyridine alkaloids? | conine | nicottine | anabasine | morphine | nicottine |
| Give one example of piperidine alkaloids? | conine | nicottine | anabasine | morphine | conine |
| Nicotinic acid reacts with soda lime to give | pyrrole | piperidine | pyrrolidine | pyridine | pyridine |
| Which of the following is used as a local anaesthetic? | quinine | cocaine | morphine | reserpine | cocaine |
| Oxidation of conynine with KMnO4 GIVES | α - picolinic acid | β - picolinic acid | γ - picolinic acid | tropic acid | α-picolinic acid |
| On fusion with con. KOH quinine gives | 6 - methoxy quinoline + lipidine | quininic acid | meroquinene | 6 - hydroxy quinoline | 6 - methoxy quinoline + lipidine |
| Quinine on oxidation with chromic acid gives quininic acid and | lutidine | meroquinene | formic acid | pyridine - 3 - carboxylic acid | meroquinene |
| Meroquinene on reduction with Zn & HI gives | γ - picoline | cincholoipon | cincholoipoxic acid | loipidic acid | cincholoipon |
| Cocaine hydrolysed under controlled condition to give | benzolecgonine | ecgonine | tropinone | pyridine | benzolecgonine |
| Quinine contains a 6 - methoxy quinoline nucleus linked to position - 8 | CH2 group t A - Position | - CHOH group at A - position | CH = CH2 group at A - position | Two - CH2 groups at A-position | CHOH group at F84A - position |
| Poisonous shrub hemlock cotains an alkaloids that was givenn to rates | cocaine | conine | nicotine | morphine | conine |
| atropine when moistened with fuming HNO3 followed by evaporation | violet | yellow | red | green | yellow |
| Which of the following alkaloids contains phenanthrene group | cinchonine | papaverine | cocaine | morphine | morphine |
| …… is a straight chain alkaloid that is produced by animal glands and has physiological activity | carotenoids | citral | camphor | ephedrine | ephedrine |

| | | | | | |
|---|---|---|---|---|---|
| Which one out of the following is not an alkaloids | nicotine | ephedrine | adrenaline | quinine | adrenaline |
| Wagners reagent is | potassium mercuric iodide | iodine dissolved in potassium iodide | potassium bismuth iodide | picric acid solution | iodine dissolved in potassium iodide |
| Mayer's reagent is | potassium mercuric iodide | iodine dissolved in potassium iodide | potassium bismuth iodide | picric acid solution | potassium mercuric iodide |
| Dragendorff's reagent is | potassium mercuric iodide | iodine dissolved in potassium iodide | potassium bismuth iodide | picric acid solution | potassium bismuth iodide |
| Hagers reagnt is | potassium mercuric iodide | iodine dissolved in potassium iodide | potassium bismuth iodide | picric acid solution | picric acid solution |
| Morphine on heated with Zn to gives | phenanthrene | coxyine | nicotine | quinoline | phenanthrene |
| Conine on heating with Zn to | phenanthrene | coxyine | nicotine | quinoline | coxyine |
| quinine is used as drug for | typhoid | tuberculosis | malaria | leprosy | malaria |
| Nicotine salts are use as …….. | insecticides | pesticides | fungicides | antialergic | insecticides |
| piperic acid on reduction with H2 in the presence of Ni or Pd/C to give | tetrahydropiperic acid | piperonol | piperoxylic acid | protocatecheric acid | tetrahydropiperic acid |
| Conyrine is a ……. Derivative | piperidine | pyridine | pyrrole | isoquinoline | pyridine |
| When heated with HI at $300^0$cnunder pressure conine gives | iso octane | n - octane | n - hexane | n- pentane | n - octane |
| Nicotine is a …….. Derivatives | pyridine | pyrrole | piperidine | isoquinoline | pyridine |
| Nicotine present in tobacco is a | alkaloid | terpene | steroid | protein | alkaloid |
| The poisonous alkaloid resent in the oil of hemolck is | conine | nicotine | cocaine | quinine | conine |
| Alkaloids are usually purified by extraction with | ether | dil. HCL | NaOH | aqu. $NH_3$ | dil. HCL |
| The no of N - Me groups in alkaloids is best estiated with the help of | HI | H2SO4 | $(CH_3\ CO)_2\ CO$ | CH3MgI | HI |
| Morphine is extracted from | cinchona officinalis | papaver somniferum | rauvolfia serpentina | aconitum nepallus | papaver somniferum |
| From which part of cinchonaa , a drug is obtained | pericap | endosperm | stem of hevea | leaves of ocimum | leaves of ocimum |
| The earliest ndian treatiseon medicinal plant is | charak samhita | susruta samhita | rigveda | vriksharyurveda | rigveda |
| The alkaloid cocaine is obtained from the species of | cola | theobroma | erthroxylum | majoranaa | erthroxylum |
| Raw opium is purified in a factory at | varanasi | ghazipur | pune | ludhiana | ghazipur |
| Toacco is a native of | china | india | europe | america | america |
| The most important alkaloids present in tobacco leaves is | nicotine | codenine | thebaine | narceine | nicotine |
| cinchona plant is also known as | prickly | turmeric bark | peruvian bark | devils | peruvian bark |
| The total % of alkaloids in crude optium is around | 10 | 20 | 25 | 35 | 25 |
| The species of tobacco first grown in virginia USA | nicotinia rustica | Nicotinia tobacum | bidis | cigars | (a) nicotinia rustica |
| Curing of tabacco leaves is done for | decreacing haemful alkaloids | increasing stimulating efficiency | drying leaves | providing aroma and texture | providing aroma and texture |
| Which of the following is a temperate plant? | piperbetle | Nicotinia tobacum | areca catechu | salmonberry | salmonberry |
| How many times lancing is generally done on an opium poppy fruits? | 3 - 4 times | 1 - 2 times | 6 - 8 times | 10 - 12 times | 3 - 4 times |
| Tobacco rearchh institute is localed at | rajahnundry | coimbatore | nagpur | ahmedabad | rajahnundry |
| Quinine is cheifly used in | cosmetic inddustry | rubber industry | medicinal field | protection of silk | medicinal field |
| The formula of quinine is | $C_{20}H_{24}O_2N_2$ | $C_{10}H_{22}N_2O$ | $C_{19}H_{22}O_2N_2$ | $C_{19}H_{24}O_2N_2$ | $C_{20}H_{24}O_2N_2$ |
| Opium poppy is cultivated most extersively in | Himalayas | uttar pradesh | madhya pradesh | andra pradesh | madhya pradesh |
| The bark of which plant yields a famous drug of malaria | cinchona | quercus | betula | anogeissus | cinchona |
| Opium is extracted from | datura innoxia | papaver somniferum | hyoscyamus niger | rauvolfa serpentina | papaver somniferum |
| Which one of the following is a stimulant | LSD | Cocaine | opium | heroin | Cocaine |

## UNIT 3

## SYLLABUS

Vitamin's – Introduction – Importance of vitamins – structural elucidation and synthesis of Retinol, Thiamine, Riboflavin, Ascorbic acids.

## INTRODUCTION:

- Vitamins are the organic compounds which are required (in addition to fats, carbohydrates, proteins, minerals salts and water) bacteria and micro-organisms for the maintenance and normal growth of life, as they cannot be synthesized by them except vitamin D.
- They resemble hormones in their function and both of them are required in small quantities.
- On the other hand, they differ from each other in the respect that the vitamins are supplied to the organism through food whereas hormones are produced inside the body.
- Eg: Thyroxine from thyroid, adrenaline from body, insulin from pancreas, etc.
- Appropriate amount, which is prepared by some processes which result in the loss or deficiency of some vitamins in the food.
- The deficiency of a particular vitamin causes a specific disease which can only be cured by the intake of that vitamin.

## DISCOVERY

- In 1992, funk found that there are some compounds in the food which prevent beriberi, scurvy, pellagra, rickets, etc.
- According to him all compounds contain nitrogen, and thus due to their vital function and basic nature, he called such compounds as 'vitamin' (L.vita, life +amine).

## CLASSIFICATION AND NOMENCLATURE OF VITAMINS:

- In the beginning, vitamins were classified as 'fat soluble A' which cured night blindness and 'water soluble B' which cured beriberi.
- Later on anti-scurvy factor was discovered and was known as vitamin C, and similarly other vitamins were discovered and namely by alphabet in the order of discovery.
- Eg: vitamin D, E, H, etc.
- After sometimes it was found that water soluble vitamin B is a complex mixture of some compounds which were differentiated by subscripts Eg: vitamin B, $B_2$, etc.
- Other vitamins were also namely by subscripts.

- So the vitamins which are discovered until now are given below, with their sources and the deficiency disease they cause.

| NAME OF THE VITAMIN | SOURCE | DEFICIENCY DISEASE |
|---|---|---|
| Vitamin $A_1$ | Fish liver oils | |
| Vitamin $A_2$ | | Night blindness |
| Vitamin $B_1$ | | |
| Vitamin $B_2$ | Rice polishing, yeast, egg, | Beriberi cheilosis, correal |
| Pantothenic acid ($B_3$) | milk, some animal organs, etc. | opacity chick dermatitis |
| Folic acid (vitamin $B_c$) | | Macrocyclic anemia (deficiency of RBC) |
| Nicotinic acid (vitamin $B_5$) | | |
| Pyridoxine(vitamin $B_6$) | | Pellagra |
| Biotin (vitamin H) | | Dermatitis in rats |
| Meso-inositol | | Dermatitis |
| p-amino benzoic acid | | No evidence(as it occurs in food). |
| vitamin $B_{12}$ | | Retardation of growth |
| vitamin C | Citrus fruits, green vegetables, etc | Pernicious anemia |
| vitamin D | Fish liver oil | Scurvy |
| vitamin E | Wheat grem oil | Rickets |
| vitamin K | Cereals, leafy tissues | Stericity |
| vitamin P | Grape fruit, orange, lemon, etc. | Haemorrhagic condition |
| | | Haemorrhagic condition. |

**Even to-day vitamins are classified as:**

- Fat soluble eg vitamin A, D, and E
- Water soluble eg vitamin B complex and C. however, vitamin H is neither fat soluble not water soluble.

**PROVITAMINS OR PRECURSORS:**

- There are some biologically inactive compounds which are quite similar to the vitamins in structure and are quiet similar to the vitamins in structure and are converted easily into active vitamins in vivo. Such compounds are known as provitamins or precursors.
- For example, β-carotene and ergosterol are the provitamin A and $D_2$respectively.

**BIOLOGICAL FUNCTION (PHYSIOLOGICAL FUNCTION) OF THE VITAMINS:**

- The biological function of the vitamins is mainly due to their coenzyme in l and ll, pyridoxal phosphate is coenzyme of transminase, riboflavin is present in FAT and pantothenic acid in coenzyme A.
- The detailed discussions about the biological function of the various vitamins are described under the individual vitamin.
- The followed chart indicates the relationship between vitamins and coenzymes along with the metabolic relations in which they participate.

| NAME OF VITAMIN | NAME OF COENZYME | TYPE OF REACTIONS |
|---|---|---|
| Thiamine($B_1$) | Thiamine pyrophosphate | Decarboxylation of α-ketoacids |
| Riboflavin($B_2$) | Flavin-mononucleotide, flavin adenine dinucleotide | Oxidation-reduction reactions |
| Pyridoxine($B_6$) | Pyridoxal phosphate | Decarboxylation, transamination of amino acids |
| Nicotinamide | Diphosphopyridine nucleotide, triphospho pyridine nucleotide | Oxidation reduction reactions<br>Transference of acetyl group |
| Pantothenic acid | Coenzyme A | $CO_2$ fixation reactions |
| Biotin | Biotin | Various reactions involving single carbon compounds |
| Folic acid | Tetra hydrofolic acid | Carbon chain isomerisation |
| Cyanocobalamine($B_{12}$) | Cobamide coenzymes | |

**RETINOL (VITAMIN-A):**

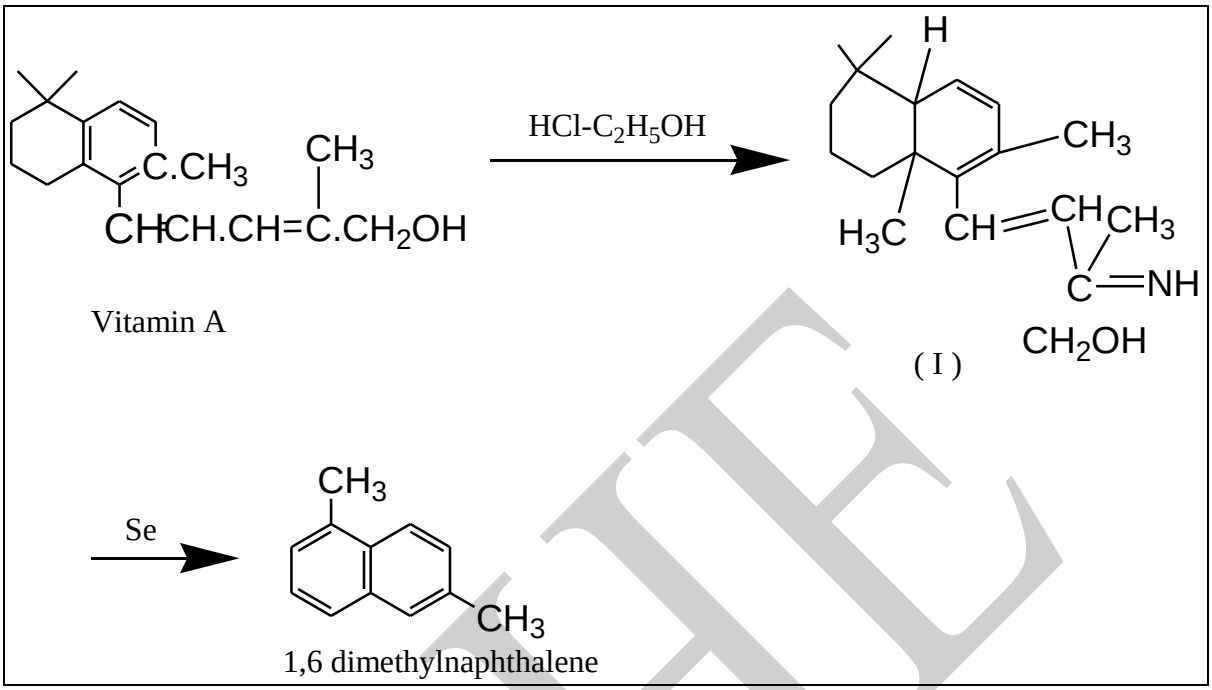
The structure of vitamin A (also known as vitamin $A_1$) is established as under:

- Elemental analysis and molecular weight determination of vitamin A shows its molecular formula to be $C_{20}H_{30}O$.
- On catalytic hydrogenation, vitamin $A_1$ is converted into per hydro vitamin A, $C_{20}H_{40}O$. It shows the presence of five double bonds in vitamin A.

$$C_{20}H_{30}O \xrightarrow{5H_2} C_2H_{40}O$$

vitamin A perhydro vitamin A

- Vitamin A forms an ester with p-nitroenzoic acid. It means vitamin A contains a hydrocarbon of vitamin A is $C_{20}H_{40}$.
- Ozonolysis of vitamin A produces one molecule of geronic acid (a substance of known structure) per molecules of vitamin A.
  This indicates the presence of one β-ionone nucleus.
- Oxidation of vitaminA with $KMnO_4$ produces acetic acid.
  This shows the presences of some $-C(CH_3)=$ groups in the chain.
- We know from common knowledge that β-carotene is converted into vitamin A in the intestinal mucosa. These suggest that vitaminA is half the β-carotene structure.
- On heating vitamin $A_1$ in an ethanolic solution of hydrogen chloride, compound 1 is obtained which on dehydrogenation with selenium forms 1:6-dimethylnaphthalene.
  The following structure of vitamin A explains these reactions

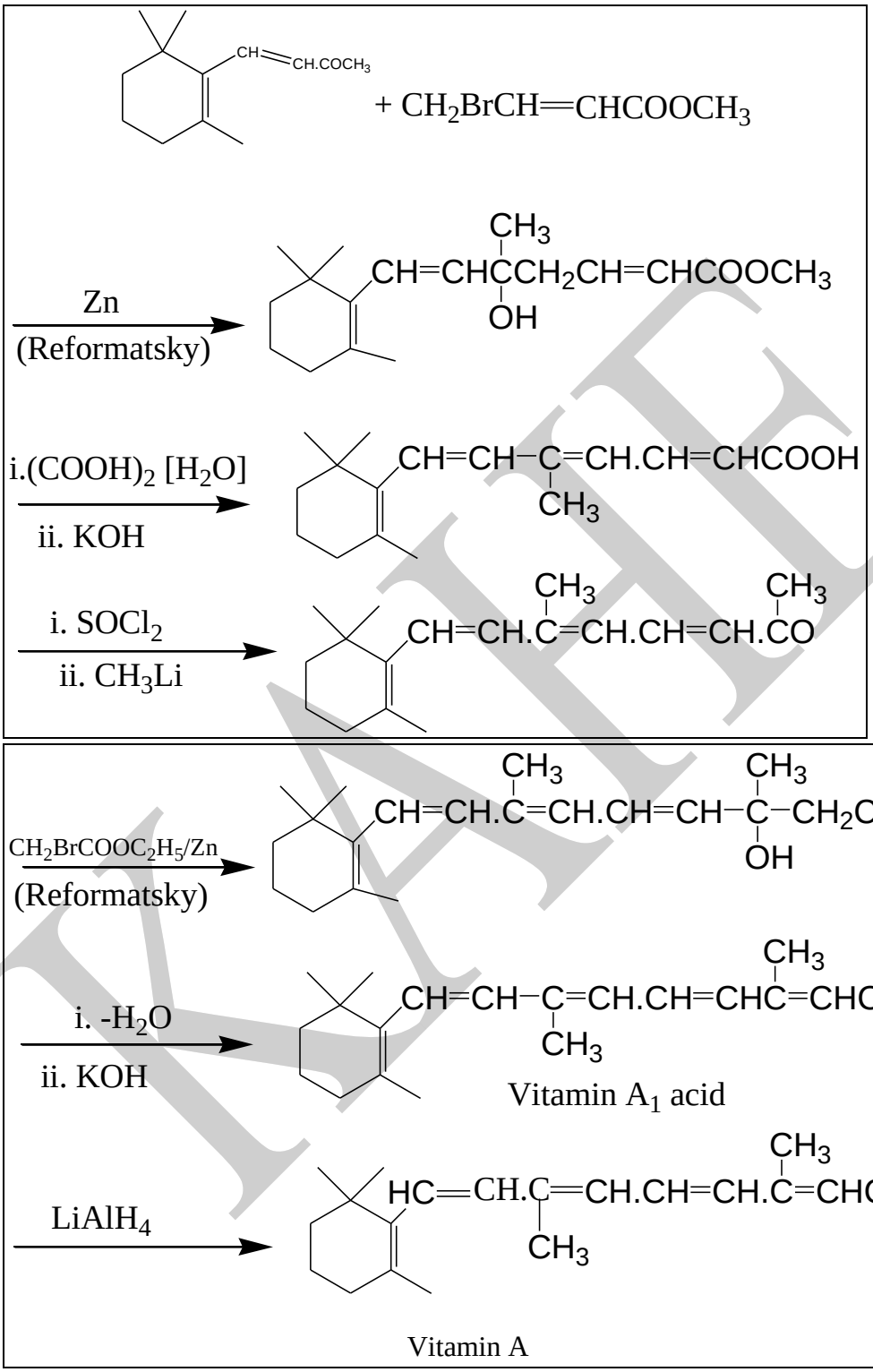



Perhydro vitamin $A_1$ (step 2 above) has been synthesised from β-ionone which is identical with that obtained by reducing vitamin A.

This leads support to the above structure of vitamin A.

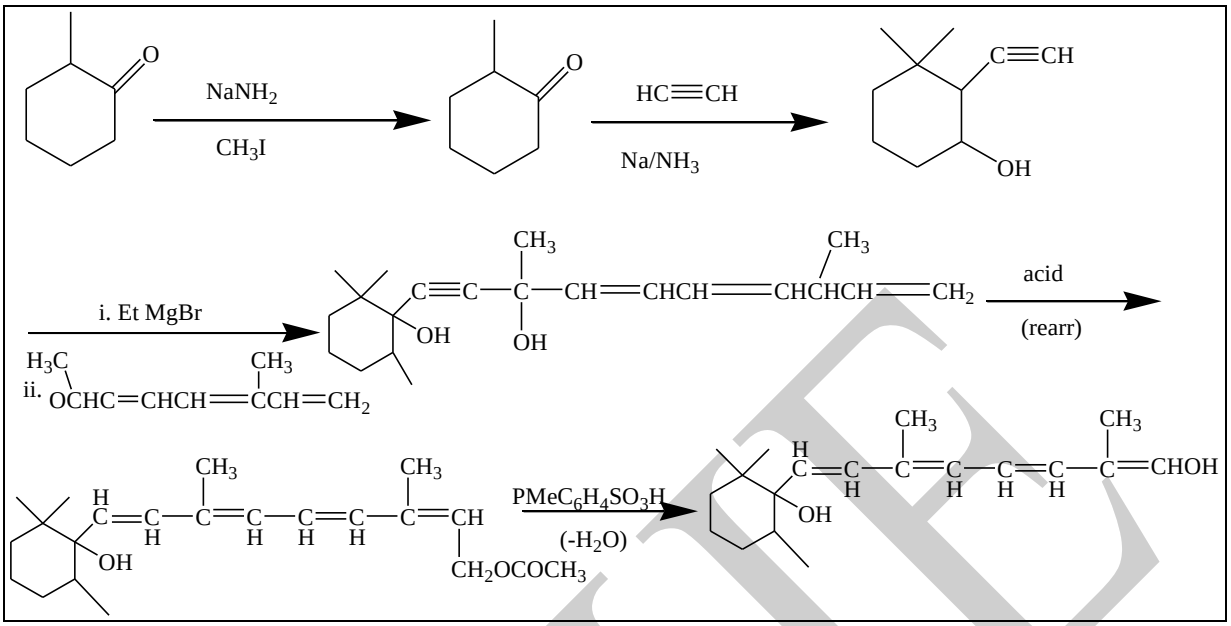
Final confirmation of the above structure is provided by synthesis. Two synthesis are given.

I. This synthesis is due to van drop et.al. (1946) who prepared vitamin $A_1$ acid which was then reduced by means of lithium aluminum hydride to vitamin A1 by Thishler(1949); β-ionone and methyl γ-bromocrotonate are the starting materials.




Vitamin A

II. Attenburrow et al (1952) have also sunthesised vitamin $A_1$ starting from 2-methyl cyclohexanone.




## VITAMIN $B_1$. THIAMINE(ANEURIN).

- Elemental analysis and molecular mass determination of thiamine chloride hydrochloride (the crystalline salt of thiamine) shows the molecular formula as $C_{12}H_{18}ON_4Cl_2S$.
- On treatment with sodium sulphite at room temperature, thiamine is decomposed quantitatively into two compounds A and B as shown below.

$$C_{12}H_{18}ON_4Cl_2S + Na_2SO_3 \longrightarrow \underset{A}{C_6H_9ONS} + \underset{B}{C_6H_9O_3N_3S} + 2NaCl$$

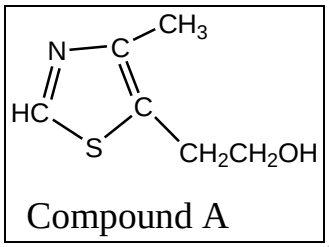
Thus we shall first discuss structure of A and B separately.

### Compound A ($C_6H_9ONS$)

1. This compound shows basic nature and does not react with $HNO_2$. It can be held that nitrogen is present as tertiary amino group.
2. Compound A reacts with HCl to produce a chloro group. This shows that oxygen is present in the molecule in the form of hydroxyl group.
3. The absorption spectrum of chloro compound obtained by treating thiamine with HCl is the same as that thiamine, proving, therefore, that the alcoholic group is in the side-chain.
4. Compound A does not give reactions of a mercapto group or of a sulphide and the sulphide and the sulphur in the compound is unreactive.

This indicates that sulphur is present in a heterocyclic ring. We observe that spectrum of compound A has similarity with that of thiazole.

5. Based upon the above observations the following structure for compound A is proposed:

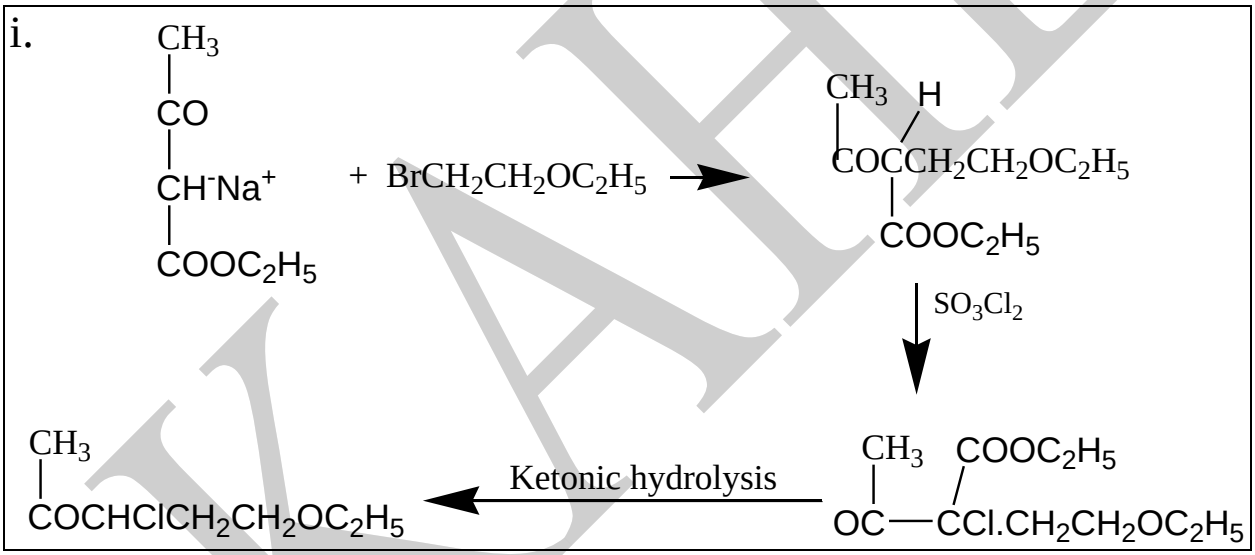



Compound A

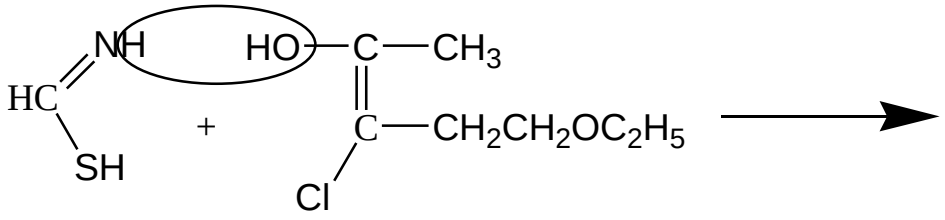
6. The alcoholic group in compound B is primary and not secondary. This is borne out by the fact that this compound does not give iodoform test.

The structure of compound A is confirmed by its synthesis.

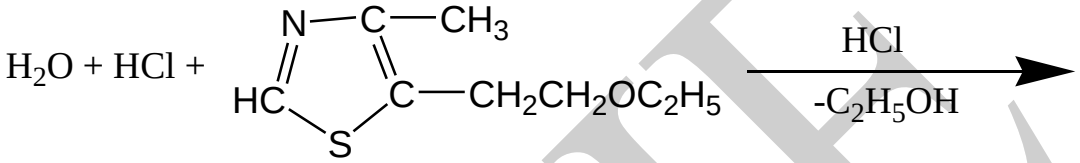
**Synthesis of compound A:**

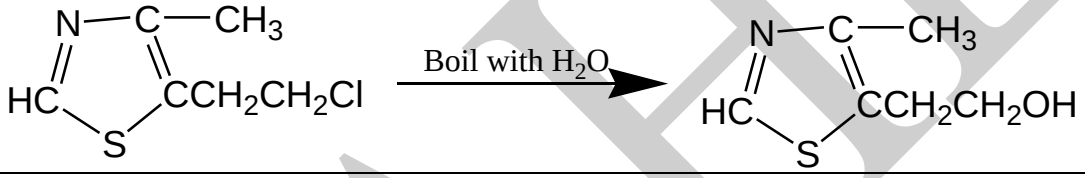


ii.

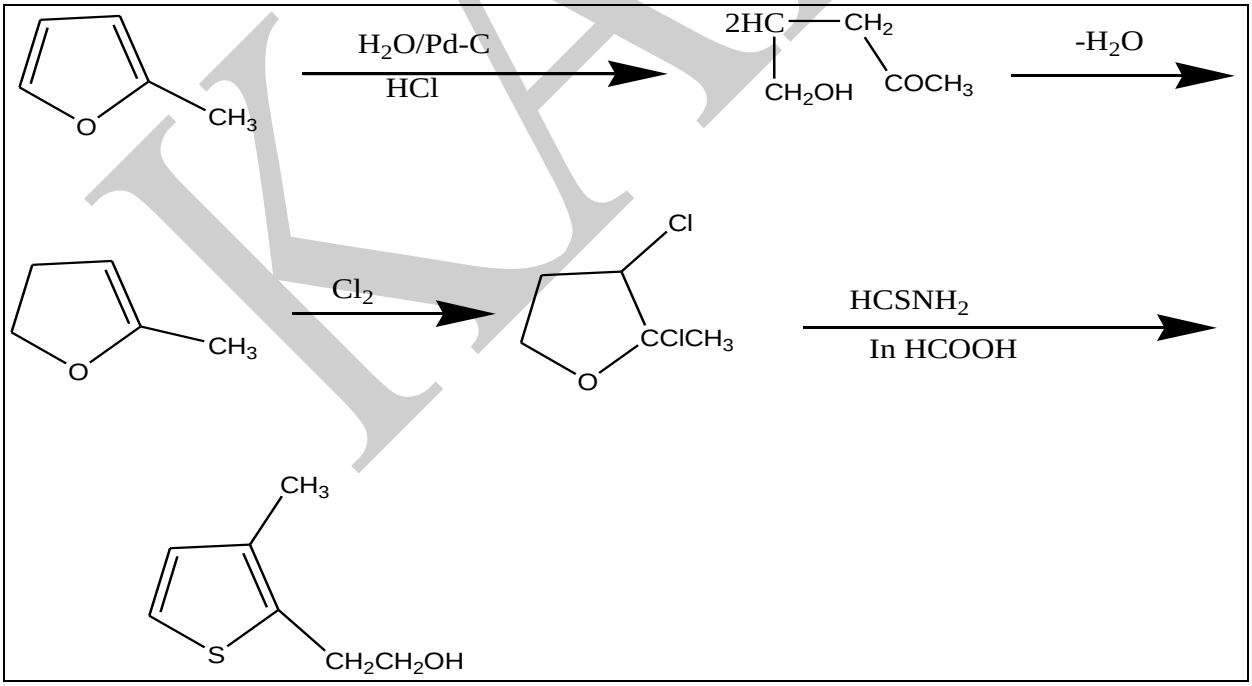



Thioformamide




**Londergan synthesis:**



**COMPOUND B ($C_6H_9O_3N_3S$)**

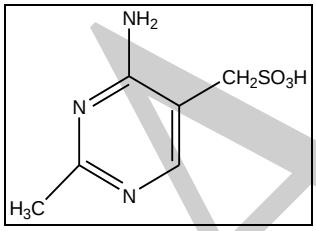
1. Compound B on heating with steam at 200$^O$C gives sulphuric acid. Thus it is a sulphonic acid.
2. On treatment with $HNO_2$ it evolves nitrogen. Therefore, it must contain one or more amino groups. Since the treatment with $HNO_2$ produces hydroxyl groups, the quantitative analysis showed that compound B contains only one $–NH_2$ group.

   $-NH_2 + HNO_2 \longrightarrow -OH + N_2 + H_2O$
3. Evolution of nitrogen as mentioned above and the reaction of compound B with benzoyl chloride are slow. This suggests that B contains an amide structure.
4. When compound B is heated with HCl at 150$^O$C under pressure, a compound C along with ammonia are obtained. It indicates that an amino group is replaced by hydroxyl group.

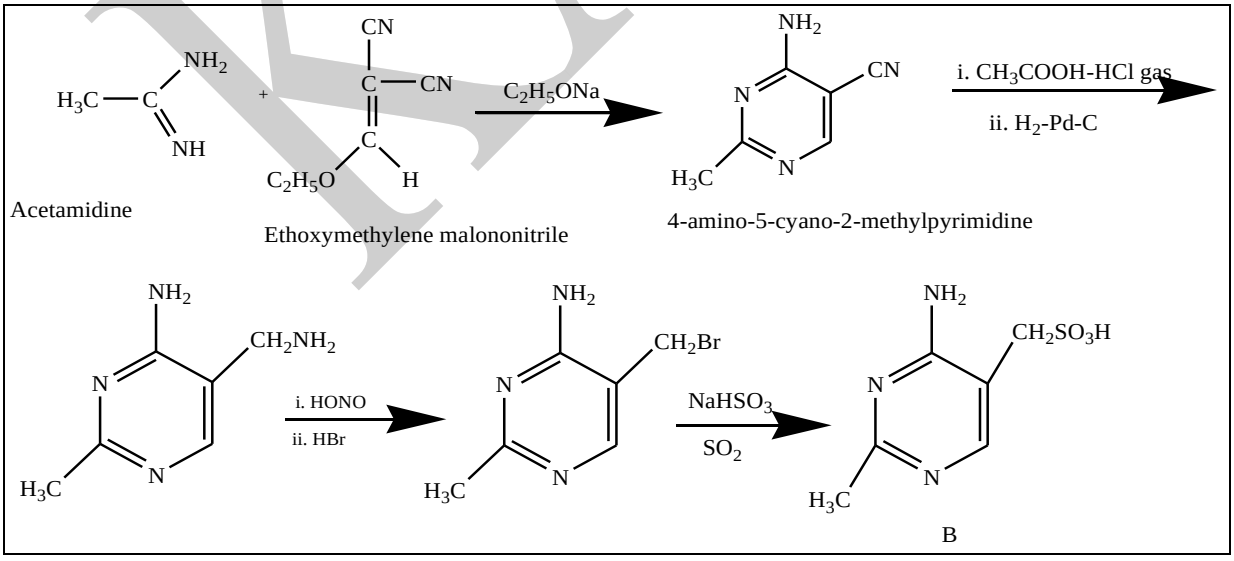
   This type of reaction is characteristic of 2 and 6-aminopyrimidines. Also the spectrum of compound C is similar to that of synthetically prepared 6-hydroxypyrimidines.

   Thus compound B is probably 6-aminopyridine.

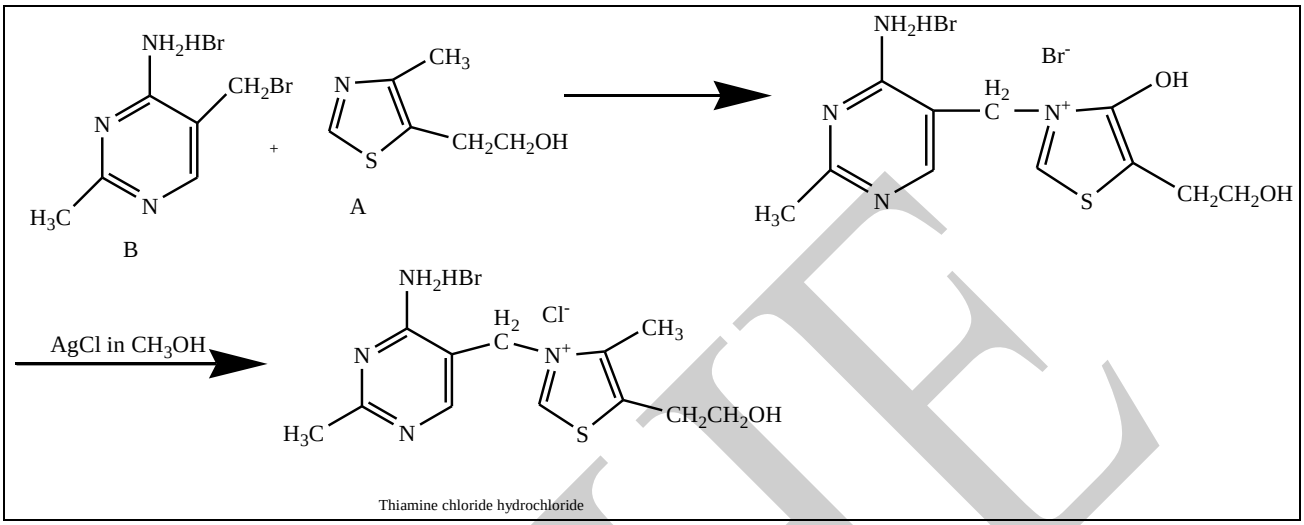
Thus B has the following structure:



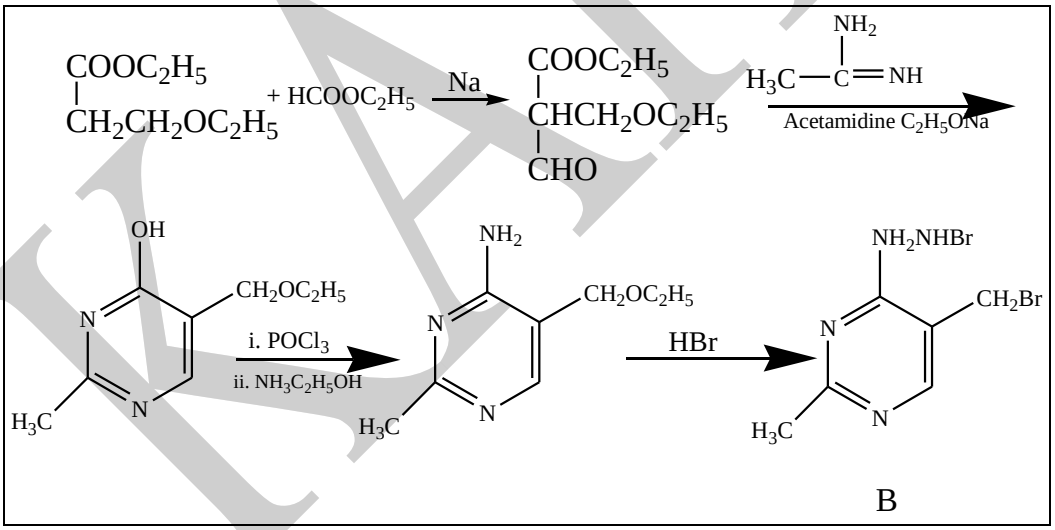

The structure is confirmed by synthesis:



The compound A and B are condensed together followed by treat with AgCl to give vitamin $B_1$ chloride hydrochloride.




Pyrimide unit is compound B is usually prepared as below.




## VITAMIN $B_2$, RIBOFLAVIN OR LACTOFLAVIN:

### Constitution:

The constitution is established by the work of Kuhn and Karrer.

It is based on the following analytical and synthetic evidences.

1. The molecular formula of riboflavin is $C_{17}H_{20}N_2O_6$
2. Silver salt of riboflavin on acetylation gives a tetra-acetate, indicating the presence of flour hydroxyl groups.
3. Oxidation of riboflavin with lead tetra- acetate yields formaldehyde.

   It indicates the presence of a primary alcoholic group.

4. There is no primary amino group since riboflavin does not react with nitrous acid.
5. Alkaline hydrolysis of the vitamin yields urea, indicating the presence of fragment –NH-CO-NH.
   The other two nitrogen atoms are tertiary.
6. Irradiation of an alkaline solution of riboflavin yields a new compound lumiflavin or photoflavin; whereas similar treatment of the vitamin in acid or neutral solution gives lumichrome.

   The structure of the vitamin is largely derived from the structures of these two photolysis products

7. **Structure of Lumiflavin:**
   - I. The molecular formula of lumiflavin in $C_{13}H_{12}N_{12}O_2$
   - II. The photolysis reaction of riboflavin to produce lumiflavin can be represented as below.

$$C_{17}H_{20}N_4O_6 \xrightarrow{h\gamma} C_{13}H_{12}N_4O_2 + C_4H_8O_4$$

   - III. Lumiflavin can neither be acetylated nor oxidized by lead tetra-acetate showing thereby that the $C_4$ fragment is a tetrahydroxy butyl side chain.

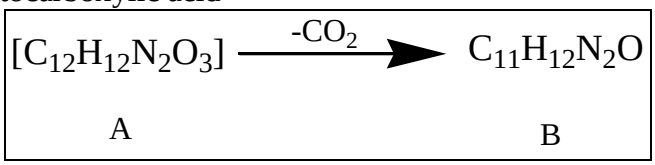
$$R\text{-}CHOH\text{-}CHOH\text{-}CHOH\text{-}CH_2OH$$

   - IV. Lumiflavin was shown to contain a methyllimino (>N-$CH_3$) group which was not present in riboflavin.
     Therefore, the methylimino group must have replaced the missing side chain must be attached in riboflavin at the position occupied by the methylimino group in lumiflavin.
   - V. Alkaline hydrolysis of luminflavin yields urea and aminocarboxylic acid A.

$$C_{13}H_{12}N_4O_2 + 2H_2O \xrightarrow{Ba(OH)_2} \underset{A}{C_{12}H_{12}N_2O_3} + \underset{Urea}{CH_4N_2O}$$

- Since two molecules of water are required in the reaction, urea must come from a ring system, and not from a side chain ureide or guanidine group which would require only one molecule of water for hydrolysis.

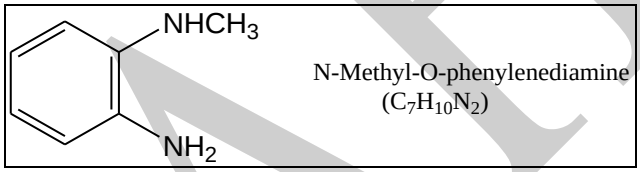
- The acid a easily eliminates a carbohydrates molecule to give a substance B. This suggest that A is a β-ketocarboxylic acid



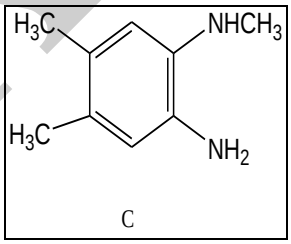

- The compound B shows the properties of lactam and gives one molecule of glyoxalic acid and a compound c on boiling with sodium hydroxide solution.


**Structure of the compound C:**

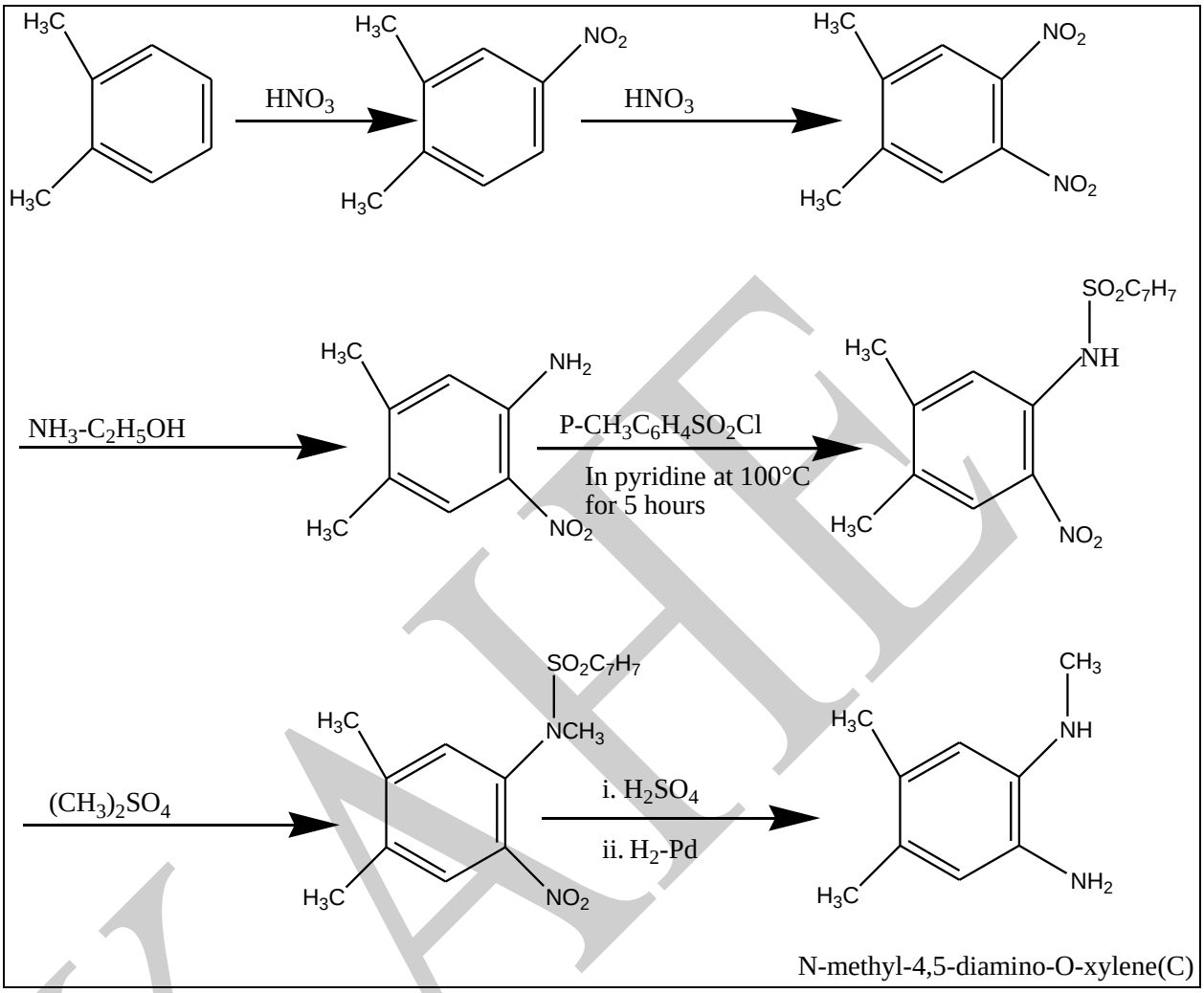
- By the usual tests, compound C was found to be an aromatic diamino compound. Since it gave a blue precipitate with ferric chloride, it must have N-methyl-O-phenylene diamine nucleus.



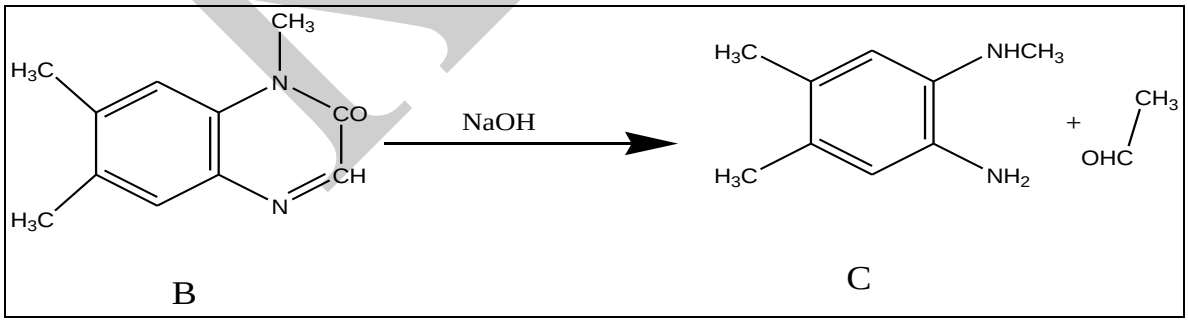

- The molecular formula of the compound C-$C_9H_{14}N_2$ and the above mentioned nucleus ($C_7H_{10}N_2$) show that $C_2H_4$ should be accounted for.
- This can be done by assuming the presence of either an ethyl groups in the benzene ring.
- But Kuhn showed the presence of two methyl groups by a series of synthetic reactions and thus the compound C was identified as N-methyl-4, 5-diamino-O-xylene.



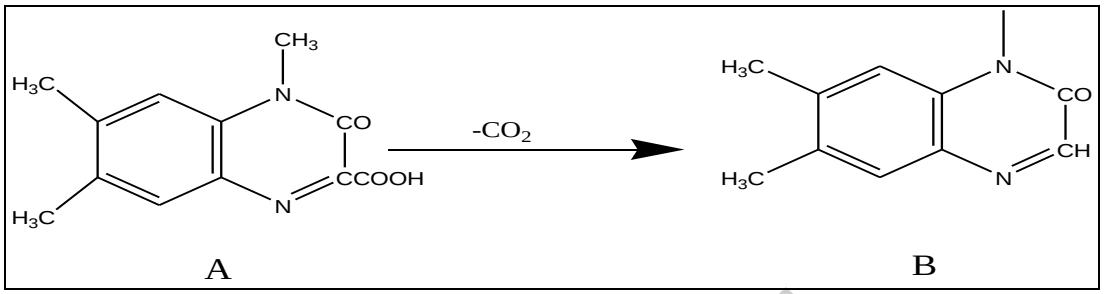

The above structure for compound C is proved by its synthesis:



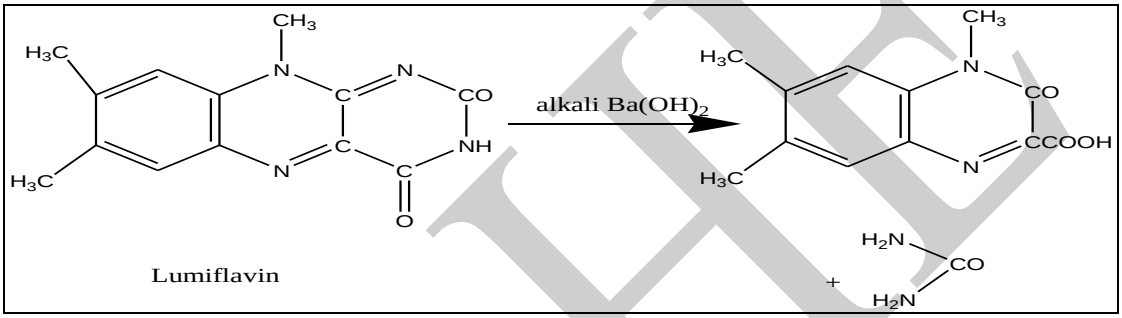

VI. Therefore the structure of the compound B can be represented as follows which also explains the required products of hydrolysis.



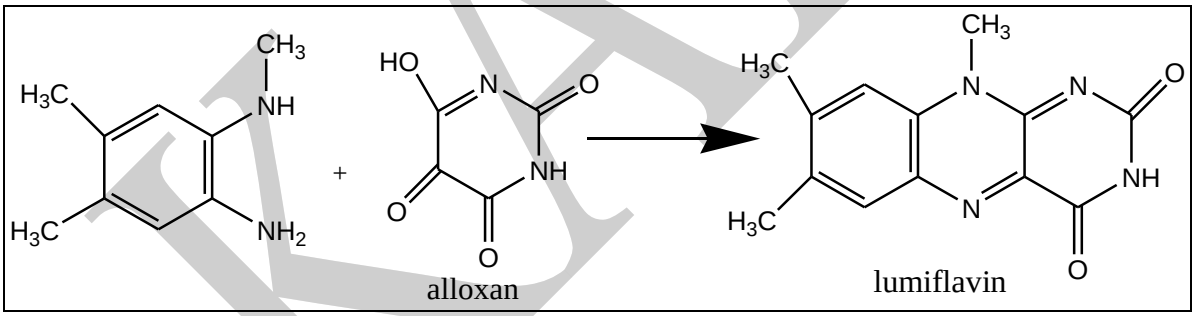

- Since A is a β-ketocarboxyic acid of B, it can be represented as represented as below.




- Since A and one molecule of urea are obtained from lumiflavin; the latter would be 6,7,9-trimethyl isoalloxazine(6,7,9-trimethylflavin).

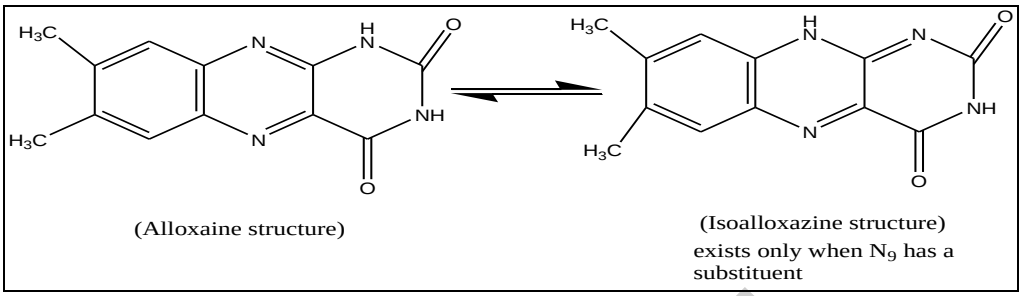



VII. Finally, the structure of lumiflavin has been confirmed by synthesis (Kuhn, 1934) which involves the condensation of N-methyl-4,5-diamino-O-xylene with alloxan.

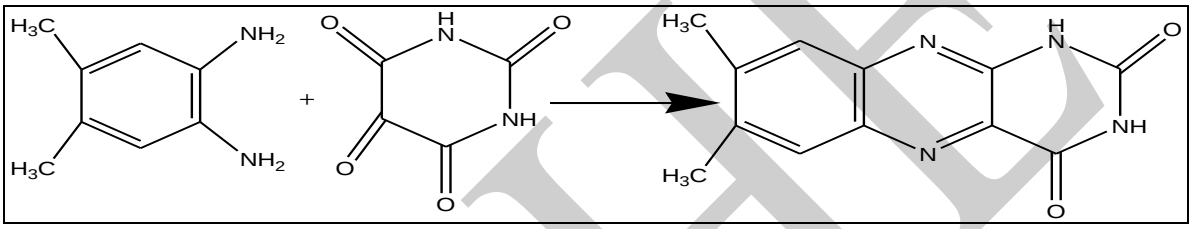



**8. <u>Structure of lumichrome</u>**

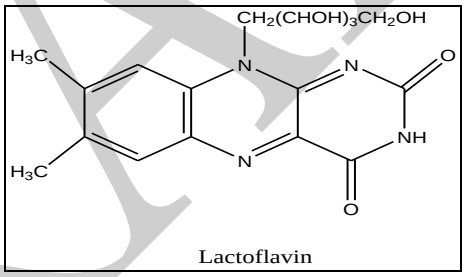
It is obtained when riboflavin is irraoliated in acid solution. Analytical work similar to that described for lumiflavin showed that the structure of lumichrome is I(6,7-dimethylalloxazine).




**Synthesis of Lumichrome**:

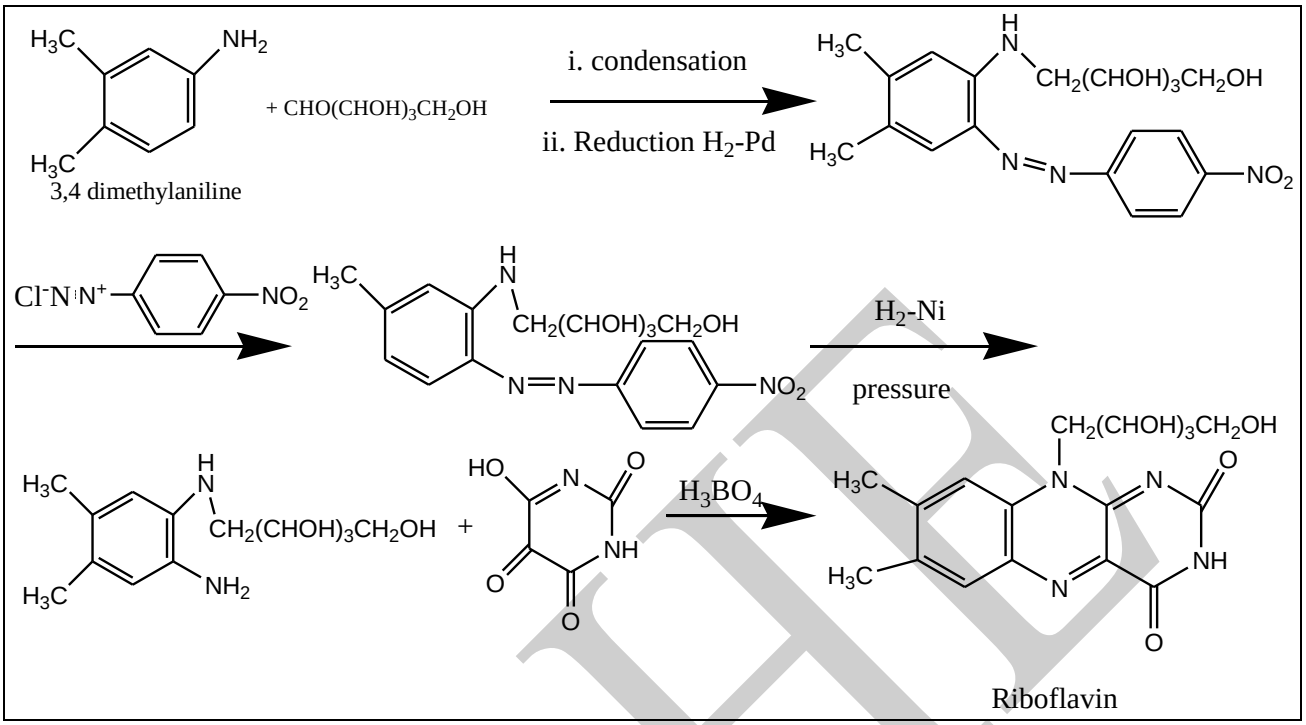


9. **Side chain of Riboflavin**:
   The reaction mixture from which lumichrome was isolated gave positive reaction for a pentose sugar, so the side is a sugar having five carbon atoms.
10. Thus riboflavin can be written as below.




**Synthesis:**

**Karrer synthesis:**




## VITAMIN $B_6$, PYRIDOXINE OR ADERMN:

Actually the word vitamin $B_6$ refers to a group of three compounds, namely, pyridoxine or adermin, pyridoxal and pyridoxamine which are interconvetible in the form of their phosphates.

But as pyridoxine is the first member of this group it is alone also known as vitamin $B_6$.

As the vitamn is antidermatitic factor for rats, it is also known as adermin.

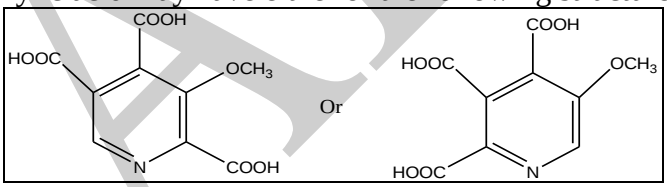
## Constitution:

1. The molecular formula is $C_8H_{11}NO_3$.
2. Pyridoxine behaves as a weak base, and the usual tests showed the absence of methoxy, methylamine and primary amino groups.
3. Zerewitnoff method showed the presence of three active hydrogen atoms.
4. The formation of deep red colour with $FeCl_3$, and monomethyl ether with diazomethane point out that one hydroxyl group is present as phenolic.

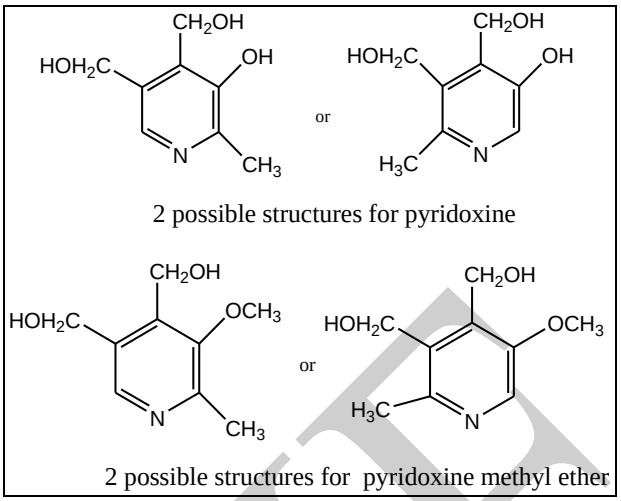
This is supported by the fact that the UV spectrum of pyridoxine is quite similar with that β-hydroxypyridine.

The uv spectrum thus, also indicates the presence of a pyridine nucleus in pyridoxine.

5. The monomethyl ether of pyridoxine does not give colour reaction with $FeCl_3$; it forms diacetate with acetic anhydride and a hydrobromide of a dibromide with HBr indicating thereby that the –OH group are alcoholic in nature.
6. Monomethyl ether of pyridoxine is not attacked by lead tetraacetate, indicating the absence of two adjacent –OH group in a side chain.
7. Kuhn-Roth method of oxidation (oxidation by chromic anhydride) points out the presence of one $–C-CH_3$ groupin pyridoxine.
8. Monomethyl ether of pyridoxine, when oxidized very carefully with alkaline $KMnO_4$ gives a methoxy pyridine tricarboxylic acid ($C_9H_7NO_7$).
    - This tricarboxylic acid gives a Blood-red colour with ferrous sulphate, a characteristic reaction of pyridine-2-carboxylic acid.
    - Thus one of the three acidic groups in the tricarboxylic acid must be in the 2-position.
    - On the other hand, usual oxidation of the monomethyl ether of pyridoxine with alkaline $KMnO_4$ gives a molecule of carbondioxide and an anhydride of a carboxylic acid.
    - The formation of anhydride indicates that in the parent dicarboxylic acid, the 2-COOH groups are in the ortho positions.
    - Furthermore, since the O-dicarboxylic acid (obtained by the hydrolysis of the anhydride) does not give a red colour with ferrous sulphate, it does not have a carboxyl group in the 2-positions.
    - Therefore, it follows that, on decarboxylation, the tricarboxylic acid eliminates the 2-carboxyl group to form the anhydride.
    - Thus the tricarboxylic acid may have either of the following structures.

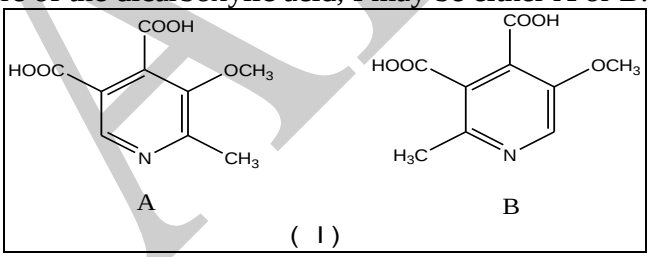



    - Now we know that pyridoxine methyl ester has one $–OCH_3$ and two alcoholic groups; thus the two –COOH groups in the tricarboxylic acid could arise from the two alcoholic groups ($-CH_2OH$). The third thus must have arrived from a methyl group.
    - Thus the following structures are possible for the pyridoxine and its corresponding mether ether.

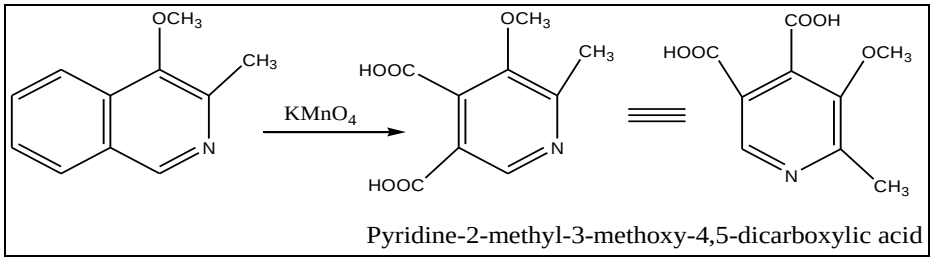



- A decision b/w the two structures was made on the basis of the following point.

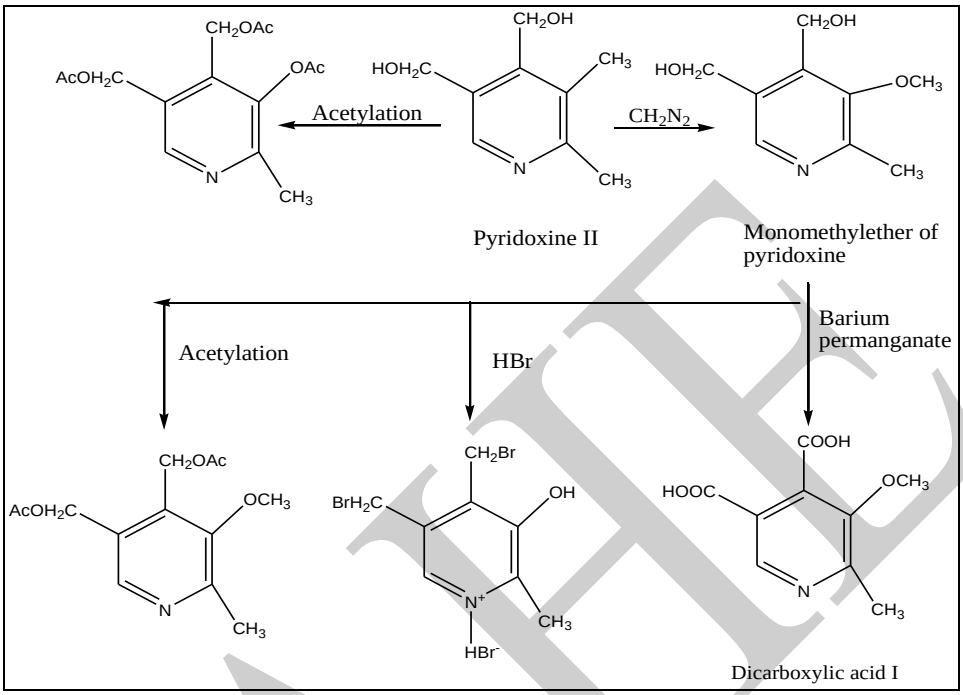
9. Vitamin $B_6$ monomethyl ether on oxidation with barium permanganate gives a dicarboxylic acid I.
   - The dicarboxylic acid forms anhydride with acetic anhydride and gives a fluorescent dye with acetic anhydride and gives a fluorescent dye with resorcinol indicating that two –COOH groups are in O-positions to each other.
   - Moreover, the dicarboxylic acid 1 does not give colour with $FeSO_4$ solution showing that neither of the two –COOH groups is in α-position to the nitrogen.
   - Hence the structure of the dicarboxylic acid, I may be either A or B.




   - The position of the 2-COOH groups in I corresponding to the two alcoholic groups in pyridoxine.
   - However, Kuhn compared these two dicarboxylic acids with the synthetic compounds and found that the dicarboxylic acid obtained from pyridoxine is A as it resembles with the synthetic dicarboxylic acid from 4-methoxy-3-methyl isoquinoline.



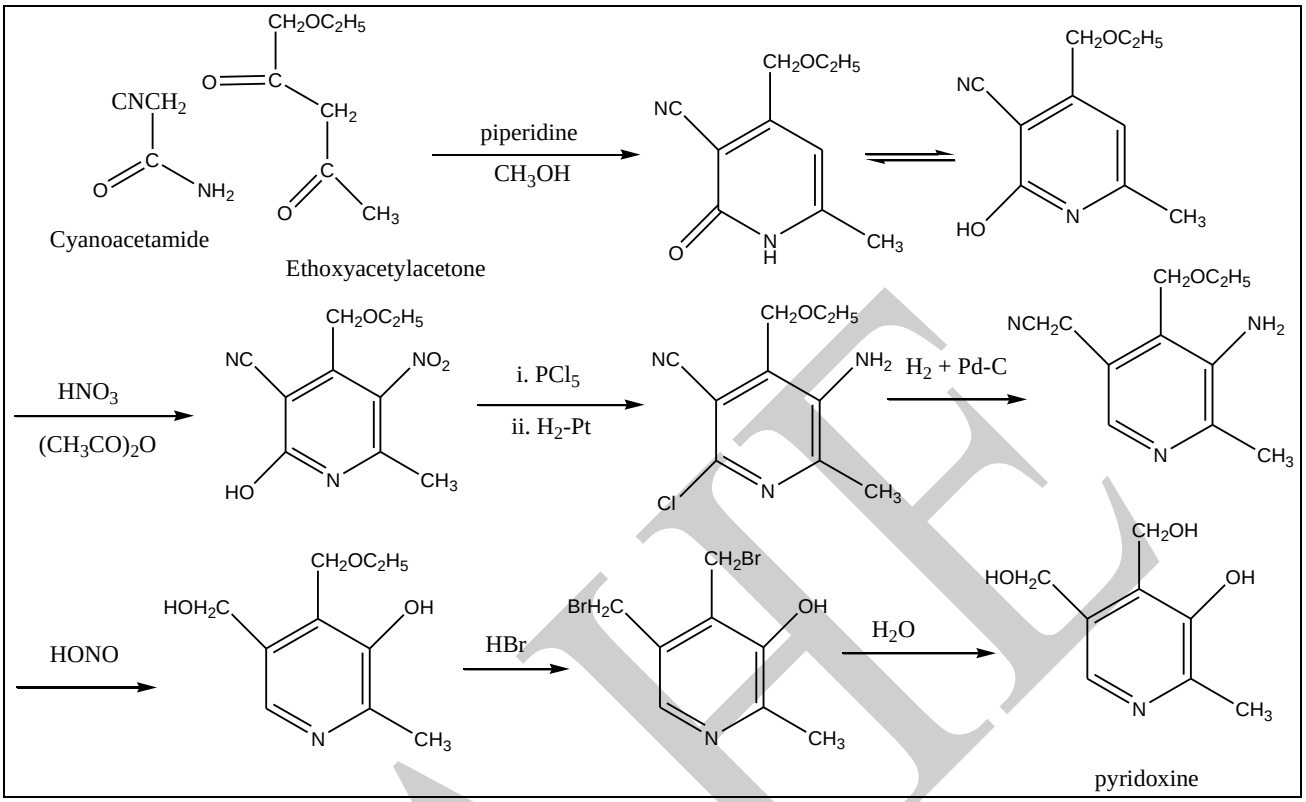
- Hence the correct structure for I is A and thus pyridoxine will be II which explains all the reactions.




**Synthesis:**

The structure assigned to pyridoxine has been confirmed by synthesis

**Harris and Folkers (1939):**




## VITAMIN C OR L-ASCORBIC ACID (CEVITAMIN OR HEXURONIC ACID OR ANTISCORBUTIC FACTOR)

### Occurrence:

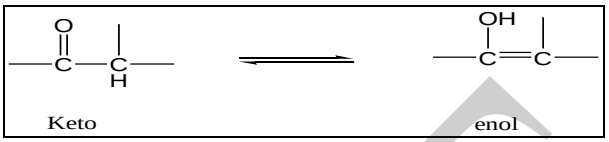
- This vitamin is distributed both in plants and animal kingdom.
- In plant community the important sources are leaves and flowers (eg. Rosehips, pine needles),and green vegetables (eg. Cabbage, beans, tomatoes, etc) and potatoes.
- In animals vitamin occurs in tissues and various glands or organs eg. Liver, adrenal gland, thymus, corpus luteum, etc.
- Milk and blood also contain small quantity of ascorbic acid.
- Meat and egg contain very little amount.

### Deficiency disease:

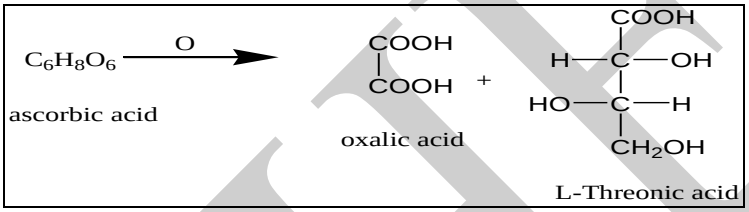
- Its deficiency in the diet cause scurvy (is tendency to haemorrhage) and brittleness of bones. In severe deficiency gums swell and bleed very easily and teeth become loose. As it curves scurvy it is known as antiscorbutic factor.
- Most of the animal, but not man, cans synthesis vitamin C themselves.

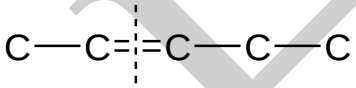
### Constitution:

1. The molecular formula is $C_6H_8O_6$
2. Ascorbic acid forms mono-ozonide showing the presence of one double bond.
3. It behaves as a strong reducing agent and also forms a phenylhydrazone. It gives a violet colour with ferric chloride.
   Reactions at points 2and 3 suggest that a keto-enol system is present in ascorbic acid

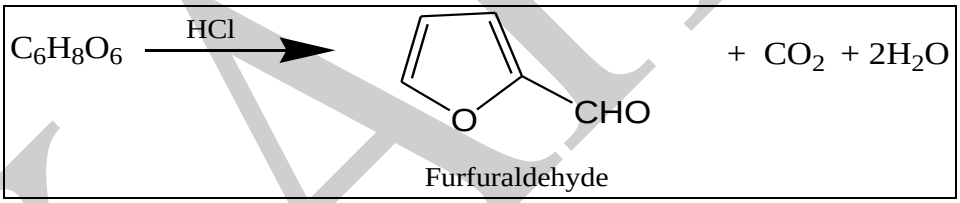



4. On oxidation with acidic $KMnO_4$,it yields oxalic acid and L-threonic acids indicating that the molecule contains a four carbon atoms system by means of a double bond.



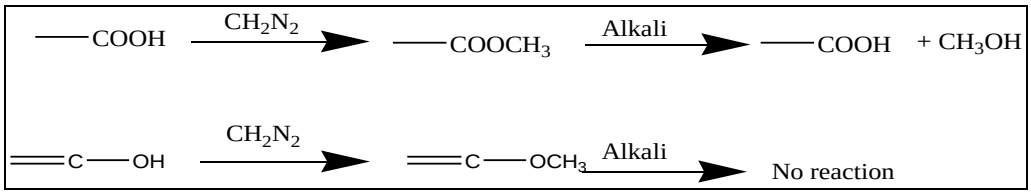

Hence the skeleton is : 

5. When boiled with hydrochloric acid, it gives furfuraldehyde



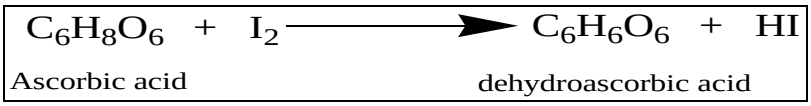

- The formation of furfuraldehyde indicates that the vitamin contains at least five carbon atoms in a straight chain.

6. With sodiumbicarbonate it liberates $CO_2$ and forms the mono sodium salt showing the presence of an acidic group.
7. This develops deep violet colour with $FeCl_3$ indicating the presence of enolic (-OH) group.
   - This is further confirmed by the formation of a dimethyl derivative with diazomethane.
   - This derivative does not give $CH_3OH$ on treatment with alkali showing the absence of –COOH group in the vitamin but the presence of enolic group.



- This behavior of dimethyl derivative along with the vitamin contains a lactone ring.

**8.** Ascorbic acid when treated with aqueous iodine solution gives dehydroascorbic acid, two atoms of iodine are consumed and two molecules of hydrogen iodine are produced during the reaction.



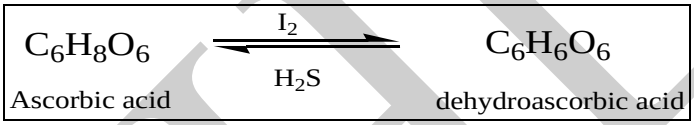

**a)** It is neutral and does not give enolic reactions.

**b)** It forms osazone with phenylhydrazine, so it must have 2 adjacent carbonyl groups.

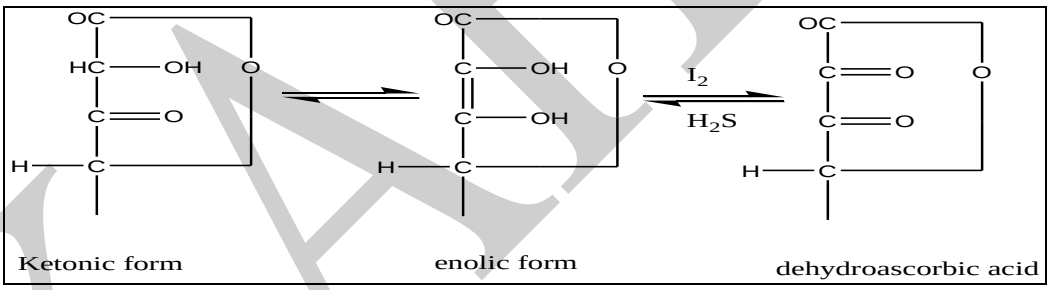
**c)** It behaves as a lactone of a monobasic hydroxy acid.

**d)** On reduction with hydrogen sulphide, it is reconverted into ascorbic acid.

- Now since the oxidation reduction process is carried out with mild reagents, the lactone structure of dehydroascorbic acid must also be present in ascorbic acid.




- Thus ascorbic acid may be given the following part structure (I) which explain all reactions.

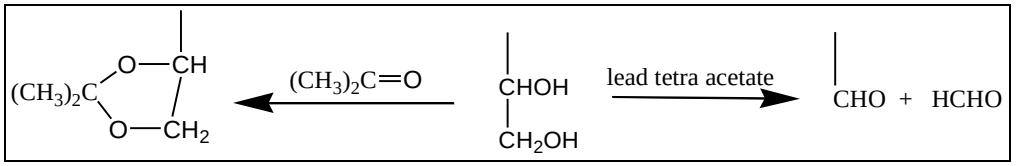



- The above structure of ascorbic acid also explains its reducing property and formation of phenylhydrazone because it may also exist in the ketonic form which has an (α-hydroxy ketones are important reducing agents).

**9.** The dimethyl derivative of the vitamin further gives diacetate on acetylation indicating the presence of two alcoholic groups which can be further confirmed by the following facts.

**I.** The dimethyl ether ascorbic acid on oxidation with lead tetra-acetate yields HCHO.

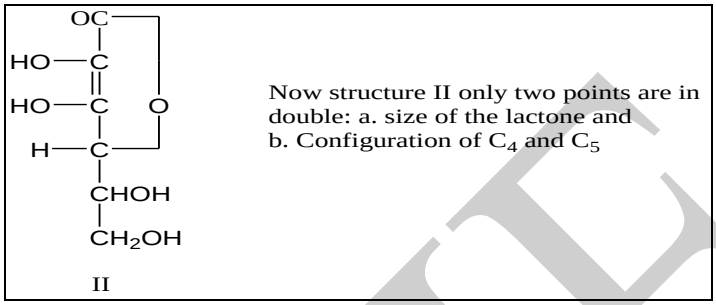
- The formation of formaldehyde also indicates that one of the alcoholic groups is primary in nature.




**II.** Ascorbic acid as well as its dimethyl derivative condenses with acetone to give monoisopropylidene derivative.

**III.** Moreover, the presence of total four hydroxyl groups in the vitamin can be proved by the formation of tetra-acetate and tetramethyl derivative on acetylation and methylation($Ag_2O/CH_3I$) respectively.

- so the part structure I may now be expanded to II to the full structure of ascorbic acid.



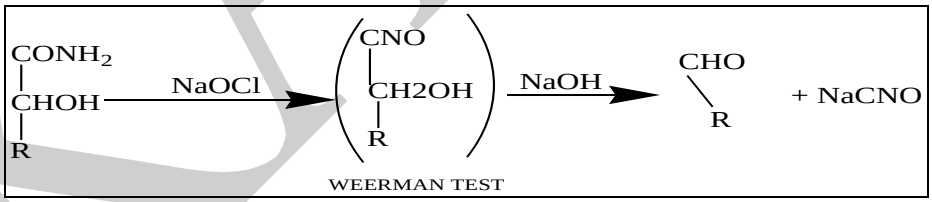

**10.** The size of the lactone was shown to be γ(five membered) by the following facts.

**I.** Ascorbic acid (is lactone is stable towards alkali.

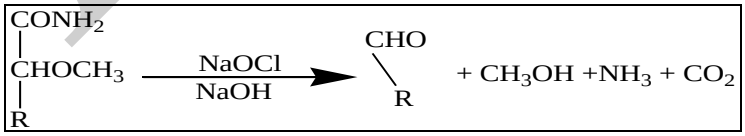
**II.** The rate of hydrolysis of dehydroascorbic acid corresponds to the rate of hydrolysis of γ-lactone.

**III.** Ozonolysis of the tetramethyl derivative of ascorbic acid give a neutral compound III having same number of carbon atoms showing the presence of a ring system.

- The production of three carboxylic groups on ozonolysis clearly proves that the starting compound is a lactone.
- L-Threonic acid is (IV) converted into amide V which gives weerman test (α-hydroxy amides on treatment with sodium hypochlorite give cyanates).

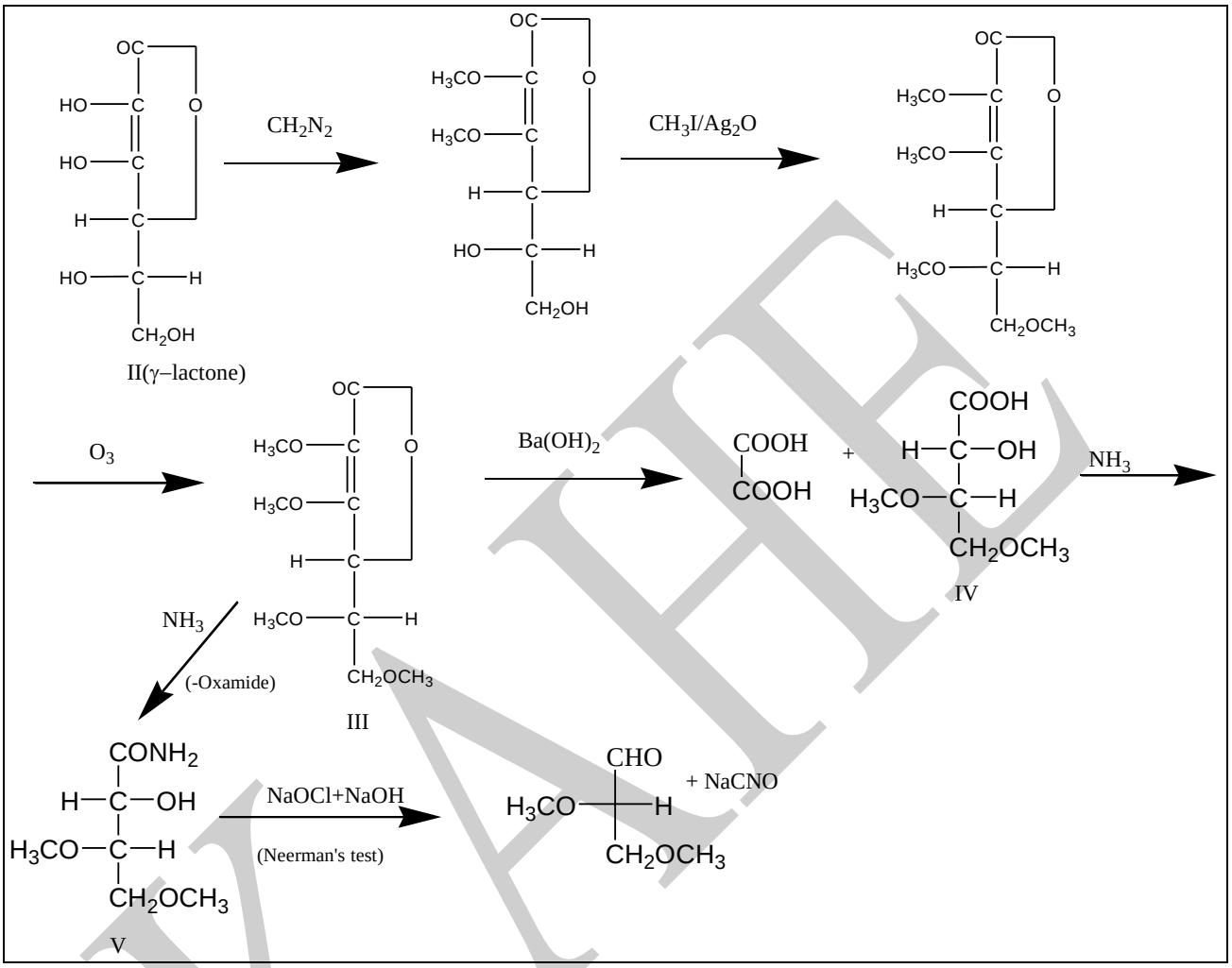



- In case the α-carbon atom does not have a free hydroxyl group, ie. It has a methoxy group, treatment with alkaline sodium hypochlorite will give an aldehyde, methanol, ammonia and carbon dioxide




- So the compound V must contain an α-hydroxy amide group and thus the compound IV has a free α-hydroxy group and subsequently it will be 3,4-di-O-methyl-L-threonic acid which can only be formed if the ring is γ; since the which does not give weerman test.

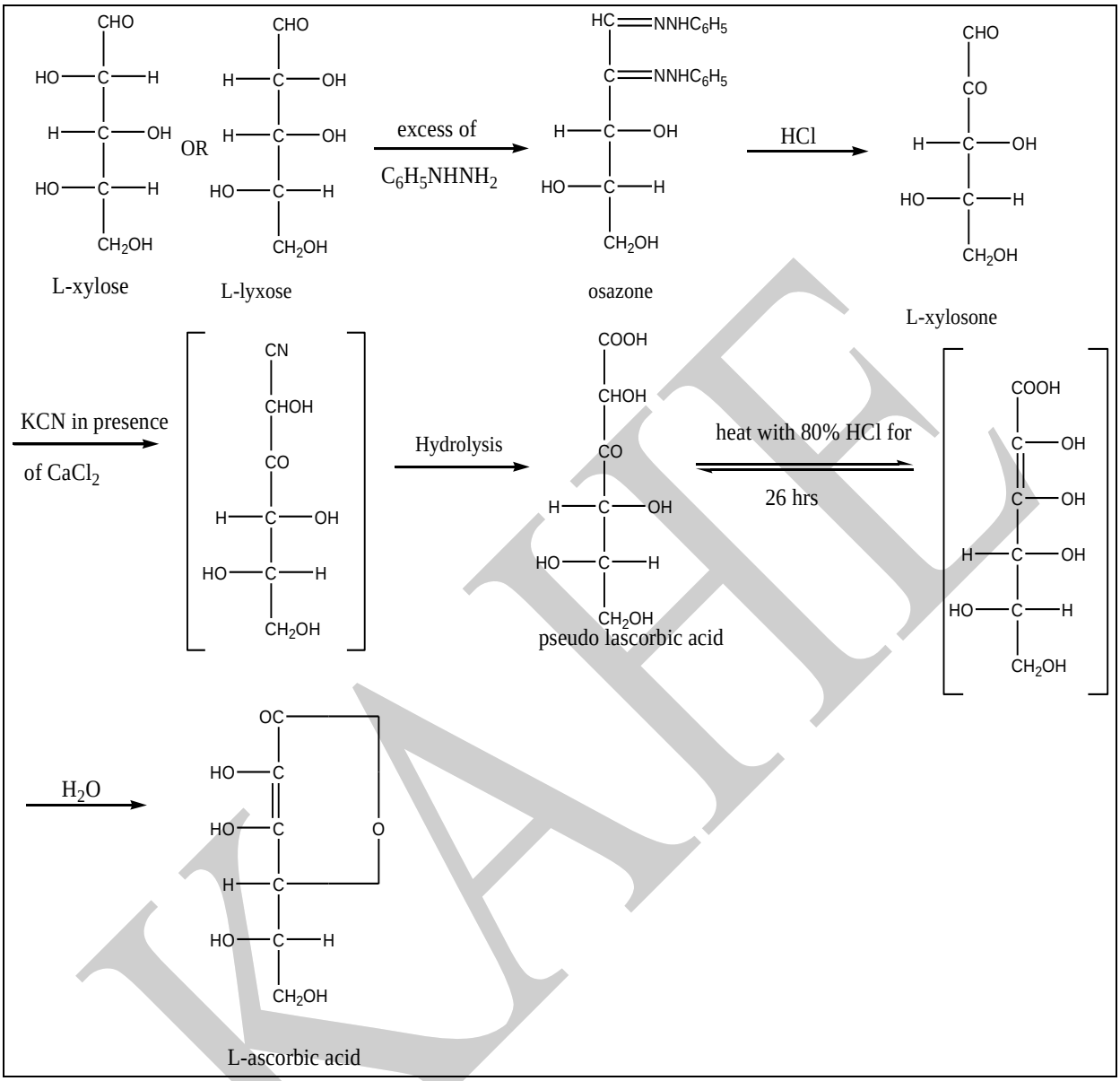
- All these reactions are explained taking II as structure for ascorbic acid.

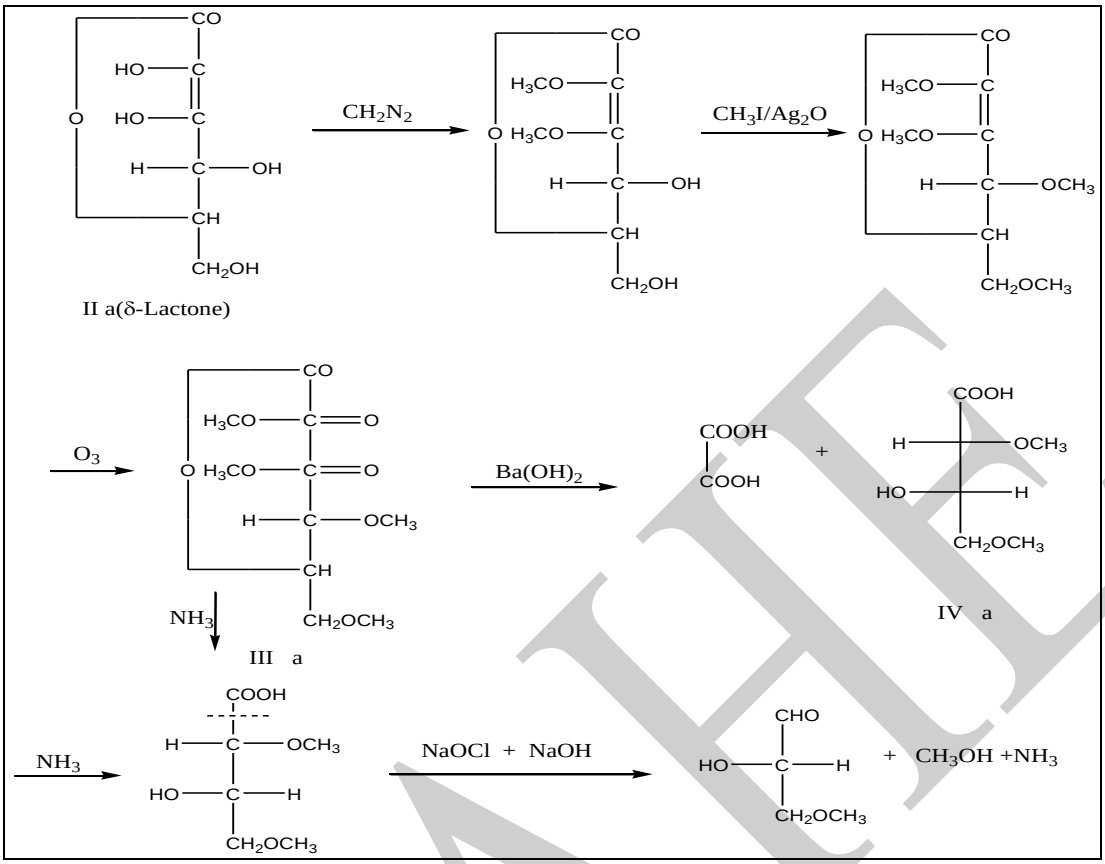



**11.** Lastly the structure II assigned to ascorbic acid is confirmed by its synthesis.

- The first synthesis was given by Haworth and hirst in 1933 in which L-lyxose or L-xylose is the starting material.
  Both of these compounds can be obtained from D-glucose

D-glucose ⟶ D-galactouronic acid ⟶ D-galactonic acid ⟶ L-lyxose

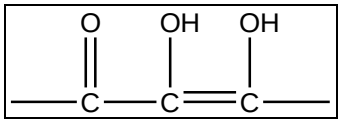

L-xylose
OR
L-lyxose
excess of
$C_6H_5NHNH_2$
osazone
HCl
L-xylosone
KCN in presence
of $CaCl_2$
Hydrolysis
pseudo lascorbic acid
heat with 80% HCl for
26 hrs
$H_2O$
L-ascorbic acid



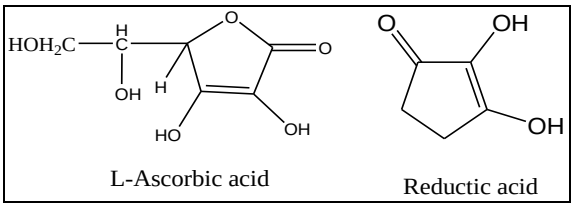

The exact configuration of $C_4$ and $C_5$ were derived from its relation to L- threonic acid.

**Some special reactions of Ascorbic acid:**

1. Ascorbic acid is not stable to heat.
2. In aqueous solution, hydrogen atom of the $C_3$-enol group of ascorbic acid ionizes.
3. In alkaline solution, hydrogen atom of the $C_2$-enol group is replaced by the metal.
4. Unlike ketones, ascorbic acid is not reduced by lithium aluminium hydride. This indicates that the ketonic group of ascorbic acid is not a normal ketonic group and its ketonic group was named as reductone (compound containing the ene-α-carbonyl grouping).




- Reductones are not reduced by $LiAlH_4$. Examples of reductones are ascorbic acid and reductic acid.




L-Ascorbic acid Reductic acid

**Biological Function:**

- The biological activity of this vitamin is due to its reversible oxidation.

$$\text{Ascorbic acid} \underset{H_2S}{\overset{I_2}{\rightleftharpoons}} \text{Dehydroascorbic acid}$$

- It has been seen that there are special enzymes or compounds which help in oxidation & reduction of ascorbic acid.

Eg: glutathione reduces the oxidized form of vitamin C where as some purines (xanthine ,uric acid, theophylline, etc) protect the vitamin against oxidation of ascorbic acid.

- On the other hand, the enzyme ascorbic acid oxidase brings about oxidation of ascorbic acid.
- On the basis of the above behavior of ascorbic acid, Szent-Gyorgyi suggested that the vitamin takes part in the respiratory system according to the following reactions.

$$\text{Ascorbic acid} + O_2 \xrightarrow[\text{hexoxidase}]{\text{copper ions}} \text{Dehydroascorbic acid} + H_2O \longrightarrow 1$$

$$\text{Havone} + H_2O_2 \xrightarrow{\text{peroxidase}} \text{oxidized flavone} + H_2O \longrightarrow 2$$

$$\text{Oxidised flavone} + \text{ascorbic acid} \longrightarrow \text{Dehyhydroascorbic acid} + \text{flavone} \rightarrow 3$$

$$\text{Dhydroascorbic acid} + \text{Glutathione} \longrightarrow \text{Ascorbic acid} + \text{oxidised glutathione} \rightarrow 4$$

$$\text{oxidised glutathione} + \text{Glucose phosphate} \longrightarrow \text{Glutathione} + CO_2 + H_2O \longrightarrow 5$$

- In the absence of the compounds such as flavones, the reactions II and III are replaced by

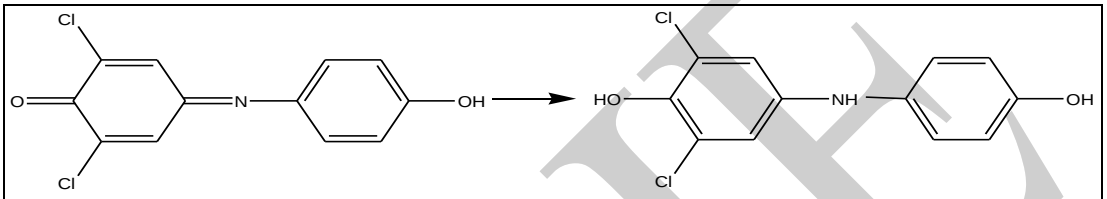
$$H_2O_2 \longrightarrow H_2O + 1/2\ O_2$$

- Ascorbic acid is also found to be linked the amino acid metabolism. Ascorbic acid is believed to help the body in resistance to certain diseases.
- Ascorbic acid is necessary for the formation and maintenance of the substance found b/w the cell which helps to hold them together, especially in the capillary walls, cartilage, bones and teeth.

- Thus the deficiency of ascorbic acid causes the loss of intracellular substance and hence leads to structural weakness and thus scurry. Hemorrhage is due to weakness of the capillary walls, fragile bones to weakness in the bony tissues, and loose teeth to degeneration of the tissues of the jaw bone.

**Determination (Estimation of vitamin C)**

- Among the various available physical and chemical methods for the estimation of vitamin C, titration with 2,6-dichlorophenol-indophenol is the most widely used method today.



2,6-dichorolophenol-indophenol

- Since a certain amount of vitamin C in solution is generally present in the dehydro-form which is not determined by the indophenols titration, it is necessary to convert this form into ascorbic acid.
- Although the reduction can be achieved by means of hydrogen sulphide at pH 4-7, the results are not trustworthy and hence the following method consisting of 4 points is suggested.

**I.** Total amount of the vitamin C is converted into the dehydro form by passing through norite or by ascorbic acid oxidase.

**II.** The oxidized mixture is titrated against 2,6-dichlorophenol indophenols and the amount of remaining ascorbic acid is determined.

**III.** Now the dehydroascorbic acid is reduced to ascorbic acid by means of $H_2S$.

**IV.** The resulting solution is titrated for vitamin C with indophenols.

- The difference b/w the value from the second titration and the value of the first titration gives fairly reliable result of the total amount of the total amount of ascorbic acid present which is capable of slow reduction with hydrogen sulphide to indophenols reducing substances.
- The end point of the titration with the indophenols dye may be determined by visual observation or with the help of a colorimeter or a photo-electrometer.

**Text Books:**

T1: Finar, I.L., 2013. Organic Chemistry, Vol. II, Pearson Education, Singapore.
T2: Gurdeep R.Chatwal, 2013. Organic Chemistry of Natural Products, Vol. II, Himalaya Publishing House, New Delhi
T4: Agarwal,.O.P, 2003. Natural Product Chemistry, Goel Publishing House, Meerut.

## POSSIBLE QUESTIONS:

### Part-A (1 Mark)
### Multiple Choice Questions (Each Question Carry One Mark)

1. Which of the following is the best source of vitamin A?
a. Honey
**b. Carrot**
c. Orange
d. Apple
2. Vitamin c is also called
a. Ffolic acid
b. Niacin
c. Citric acid
**d. Ascorbic acid**
3. Which vitamin is produsedin the body by ultraviolet rays?
a. Vitamin A
**b. Vitamin D**
c. Vvitamin E
d. Vitamin K
4. The vitamin which is easily destroyed during cooking as well as strorage is……..
**a. Vitamin C**
b. vitamin K
c. Vitamin D
d. Vitamin A
5. The deficiency of vitamin D causes
a. **Rickets**
b. Scurvy
c. Beriberi
d. Nightblindness
6. The deficiency of vitamin A causes
**a.** Rickets
**b.** Scurvy
**c.** Beriberi
**d. Nightblindn**ess
7. In humans, thiamine deficiency produce a disease called
**a.** Rickets
**b.** Scurvy
**c. Beriberi**
**d.** Nightblindness
8. Green leafy vegetables are common sources of
**a.** Vitamin A
**b.** Vitamin k
**c. Vitamin B complex**

**d.** Vitamin c

9. Pyridoxine deficiency causes in rats

**a. Dermatites**
**b.** Leucopenia
**c.** Diarrhoea
**d.** Glossitis

10. Riboflafvin deficiency causcs

**a.** Scurvy
**b.** Night blindness
**c.** Beriberi
**d. Cheilosis**

11. Sunshine vitamin is

**a.** E
**b.** C
**c. D**
**d.** A

12. A good source of vitamin A & D is

**a.** Whole cereal
**b. Cod liver oil**
**c.** Yeast
**d.** Watermelon

13. Ascorpic acid acts as an

**a. Reducing agent**
**b.** Oxidizing agent
**c.** Redox
**d.** Dehydrating

14. Vitamin $B_{12}$ ( cobalamin) is only synthesized by

**a.** Fishes
**b. Micro - organism**
**c.** Plants
**d.** Animals

15. The absence of ascorbic acid in the human diet gives rise to

**a.** Rickets
**b. Pernicious anemia**
**c.** Cataract
**d.** Beriberi

16. Vitamins are essential because the organism

**a. Cant synthesisize these ( [pols at all) synthesisize these partially cant synthesisize these ( pols in the adequate amount**
**b.** Can synthesize these partially
**c.** Cant synthesisize these ( pols in the adequate amount
**d.** Can synthesisize these quaterly

17. Lipoic acid exists in

**a.** Oxidizes form

**b.** Redused form
**c.** **Oxidized and redused form**
**d.** Dehydrating

18. Vitamin $B_{12}$ is useful in the provention and treatment of
**a.** **Pernilious anemia**
**b.** Scurvy
**c.** Cataract
**d.** Beriberi

19. In the co-enzyme $B_{12}$ the position occupied by a cyanide ion in vitamin $B_{12}$ is bonded directly to the of the ribose of adenoside
**a.** **Adenine**
**b.** 5-6-dimethylbenzimidazole
**c.** Hydroxycobalamin
**d.** Cyanocobalamin

20. An early sign of retinol deficiencies in man is
**a.** **Night blindness**
**b.** Keratinization
**c.** Xeropthalmia
**d.** Rickets

## Part-B (Each Carry 8 Marks)

1. Discuss the reaction and biological functions of ascorbic acid.

2. Discuss the Structural elucidation and synthesis of Retinol.

3. Give the synthesis of thiamine.

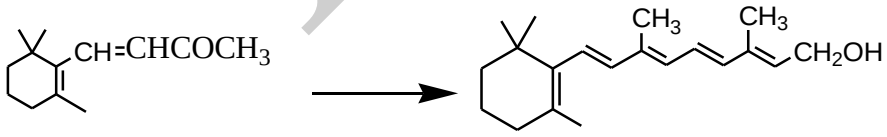
4. Discuss the structural elucidation of riboflavin?

5. Elucidate the structure of Retinol.

6. Explain the constitution and synthesis of ascorbic acid.

7. Discuss the reaction and biological functions of ascorbic acid.

8. Give the possible synthesis of the following reaction



15CHU601

Karpagam Academy of Higher Education

Coimbatore-21

(For the candidate admitted on 2015 onwards)

Department of Chemistry

VI- semester

Chemistry of Natural Products

**UNIT III- Objective Questions for online examination (Each carry 1 Marks)**

| Question | Option-A | Option-B | Option-C | Option-D | Answer |
|---|---|---|---|---|---|
| Orange provides……. | vitamin B | vitamin C | vitamin D | vitamin E | vitamin C |
| Milk butter and ghee provide | vitamin A and D | vitamin B and C | Vitamin E and K | vitaminA & E | vitaminA & E |
| Deficieny of vitamin c in the body cause | Scurvy | cancer | Beriberi | rickets | Survy |
| which of the following is the best source of vitamin A? | Honey | carrot | orange | Apple | carrot |
| Vitamin c is also called | folic acid | niacin | citric acid | Ascorbic acid | Ascorbic acid |
| Which vitamin is produsedin the body by ultraviolet rays? | vitamin A | vitamin D | vitamin E | vitamin K | vitamin D |
| The vitamin which is easily destroyed during cooking as well as strorage is…….. | | vitamin C | vitamin K | vitamin D | vitamin C |
| The deficiency of vitamin D causes | rickets | scurvy | beriberi | Nightblindness | rickets |
| The deficiency of vitamin A causes | rickets | scurvy | beriberi | Nightblindness | Nightblindness |
| In humans, thiamine deficiency produce a disease called | rickets | scurvy | beriberi | Nightblindness | beriberi |
| Green leafy vegetables are common sources of | vitamin A | vitamin k | vitamin B complex | vitamin c | vitamin B complex |
| pyridoxine deficiency causes in rats | dermatites | leucopenia | diarrhoea | glossitis | dermatites |
| Riboflafvin deficiency causcs | Scurvy | night blindness | beriberi | cheilosis | cheilosis |
| Sunshine vitamin is | E | C | D | A | D |
| A good source of vitamin A & D is | whole cereal | cod liver oil | yeast | watermelon | cod liver oil |
| Ascorpic acid acts as an | reducing agent | oxidizing agent | redox | dehydrating | reducing agent |
| Vitamin $B_{12}$ ( cobalamin) is only synthesized by | fishes | micro - organism | plants | animals | micro - organism |
| The absence of ascorbic acid in the human diet gives rise to | rickets | pernicious anemia | cataract | beriberi | pernicious anemia |
| vitamins are essential because the organism | cant synthesisize these ( [pols at all) synthesisize these partially cant synthesisize these ( pols in the adequate amount | can synthesize these partially | cant synthesisize these ( pols in the adequate amount | can synthesisize these quaterly | cant synthesisize these ( [pols at all) synthesisize these partially cant synthesisize these ( pols in the adequate amount |
| Lipoic acid exists in | oxidizes form | redused form | oxidized and redused form | dehydrating | oxidized and redused form |
| Vitamin $B_{12}$ is useful in the provention and treatment of | pernilious anemia | scurvy | cataract | beriberi | pernilious anemia |
| In the co-enzyme $B_{12}$ the position occupied by a cyanide ion in vitamin $B_{12}$ is bonded directly to the of the ribose of adenoside | adenine | 5-6-dimethylbenzimidazole | hydroxycobalamin | cyanocobalamin | adenine |
| An early sign of retinol deficiencies in man is | night blindness | keratinization | xeropthalmia | rickets | night blindness |
| what cpd of raw egg white causes a syndrome similar to vitamin B deficiency | avidin | betabindin | ovalbumin | albumin | avidin |
| The disease beriberi is due to a dietacy deficiency in | vitamin $B_1$ ( thiamine) | vitamin B2 ( riboflovin ) | vitamin $B_6$ (pyridoxine ) | vitamin $B_{12}$ | vitamin $B_1$ ( thiamine) |
| Which of these is a symptom of vitamin a deficiency | osteoporosis | impaired taste perpection | blindness | impaired taste clotting | blindness |
| Vitamin - c is considered as a | water soluble | water insoluble | fat & water soluble | fat soluble | water soluble |

| | | | | | |
|---|---|---|---|---|---|
| vitamins riboflovin is part of the …….. Molecules | Ferredoxin | FAD | Pyridoxal phosphate | pyrophosphate | FAD |
| Vitamin niacic is part of the ……. Molecule | Ferredoxin | Pyridoxal phosphate | pyrophosphate | NAD+ | NAD+ |
| The most prominent role that tocopherol has in in - vitro system ia as a strong | antioxidants | reducing agents | oxidizing agants | dehydration | antioxidants |
| Lipoic acis is a co - factors of | pyruvic dehydrogenase | ketoglutaric dehydrogenase | dehydrogenase | di - hydrorotate dehydrogenase | pyruvic dehydrogenase |
| β- carotene together with α- carotene and cryptoxanthine are synthesized | plants | animals | plants & animals | human beings | plants |
| A dificancy of vitamin - results in a decrease level of | prothrombin | thrombin | fibrin | fibrinogen | prothrombin |
| The vitamin riboflovin which occurs as a yellow pigment in egg yolk and milk become | colour on reduction | colour on oxidation | more deep in colour on reduction | more deep colour in oxidation | colour on reduction |
| Which of the following compounds belongs to the vitamin - B6 group? | pyrodoxal | pyridine | amine | pyrrole | pyrodoxal |
| What metal ion is specifically bound by vitamin B12? | cobalt | copper | zinc | iron | cobalt |
| A fact soluble vitamin that regulats blood clotting is | vitamin - A | vitamin - K | vitamin - c | niacin | vitamin - K |
| Which of these is a vitamin A precursor? | cobalamin | pyridoxine | betecarotene | thiamine | betecarotene |
| In one iron - metalloflavo protein, the iron is present as a | heme - protein | none heme type | protein | flavin moiety | heme - protein |
| Vitamin K, was first isolated from alflalfa and has the pytyl side chain consisting of | 4 isoprene units | 6 isoprene units | 9 isoprene units | 8 isoprene units | 4 isoprene units |
| Which of these molecules is vitamin - H ? | Biotin | carnitite | folic acid | calpol | Biotin |
| Who discovered vitamin C? | paul berg | linus pauling | albert szent-gyorgyl | kervy mull | albert szent-gyorgyl |
| A deficiency of niacin causes | pellagra | scurvy | cataract | aremia | pellagra |
| selexium is an essential compoxent of the enzyme glutathioue peroxidase with | scavengers toxic hydroperoxy compounds in tissuses | reduces toxic hydroperoxy cpds in tissuses. | Oxidizes toxic hydoperoxy cpds in tissuses. | Scavengers toxic activity in cell | scavengers toxic hydroperoxy compounds in tissuses |
| The vitamin from among the fpllowing is | salphanilamide | chloramphenicol | pepsin | Riboflavin | Riboflavin |
| Ascorpic acid is vitamin | A | $B_{12}$ | D | C | C |
| The chemical name for vitamin C is acid | Citric | nicotinic | ascorbic | salicylic | ascorbic |
| The metal present in vitamin $B_{12}$ | Mg | Co | Fe | Cu | Co |
| Cobalt is present in | vitamin $B_{12}$ | vitamin $A_1$ | vitamin C | Vitamin D | vitamin $B_{12}$ |
| Mg is present in | vitamin $B_{12}$ | thyroxine | haemoglobin | chlorophyll | chlorophyll |
| Pellagra is caused due to the deficiancy of C | Niacin | riboflovin | thiamine | pyridoxine | Niacin |
| The story of vitamins dates back to | 15 th century | 16 th century | 17 th century | 18 th century | 18 th century |
| In papaya fruit …….. Vitamins with be more | A | C | D | E | A |
| Sunlight converts ……. Present in foods in the body in to vitamin D | Cholesterol | amino acid | protein | vitamins | Cholesterol |
| Oxidation of riboflovin with lead tetra acetate yields | Formaldehyde | acetaldehyde | benzaldehyde | teryphthaldehyde | Formaldehyde |
| Riboflovin does not react with | nitrous acid | nitric acid | sulphuric acid | sulphorous acid | nitrous acid |
| The molecular formula of riboflovin | $C_{17}H_{20}N_2O_6$ | $C_{18}H_{23}N_2O_6$ | $C_{18}H_{23}N_2O_6Cl$ | $C_{17}H_{20}N_2O_2Cl$ | $C_{17}H_{20}N_2O_6$ |
| The monomethyl ether of pyridoxine does not give reation with | $Fecl_3$ | NaOH | HCl | $H_2SO_4$ | $Fecl_3$ |
| Milk and blood also contain small quantity of | Ascorbic acid | acetic acid | aceticanhydride | NaOH | Ascorbic acid |
| Ascorpic acid react with HCL to form | acetaldehyde | benzaldehyde | formaldehyde | furfuraldehyde | furfuraldehyde |

# UNIT-IV

## SYLLABUS

Hormones: Introduction – Structural elucidation and synthesis of adrenaline and thyroxin.

Steroids: Introduction -Chemistry and structure of cholesterol. Synthesis (not necessary), Enzymes.

### 1. ADRENALINE :-

***Introduction:-***

- The medulla part of the adrenal gland (suprarenal gland secretes two harmones, epinephrine (adrenaline, adrenine) and norepinephrine (noradrenaline, arterenol).
- These secreted in the ratio of about 4:1. The naturally occurring forms are l-Rotary, where as the synthesis leads to racemic mixture , the former is twice active than the latter.
- The main function of adrenaline is to increase the blood pressure by increasing glucose and lactic acid content of the blood by enhancing their metabolism.
- It is also used to stop the local blood haemorrhage (bleeding).
- This harmone is active only when given in the form of injection.

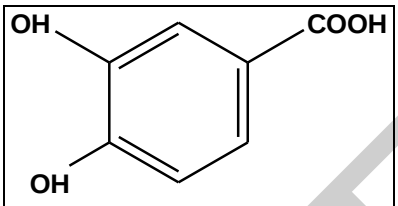
***Isolation :-***

- Adrenaline was the first hormone to be isolated by Talkamine and Aldrich in 1901 simultaneously.
- The gland is minced, extracted with acidulater water and heated to coagulated proteins.
- The latter is removed by filteration and filtrate is concentrated and treated with alcohol.
- The impurities are removed, the filtrate is again concentrated in vaccum to remove alcohol and the harmone is precipitated by the addition of ammonia solution.
- It can be further purified with the help of alcohol and oxalic acid.
- It is a colourless crystalline solid, m.p $211^0$. It is soluble in acids and alkalies. It is insoluble in water.

***Constitution:-***

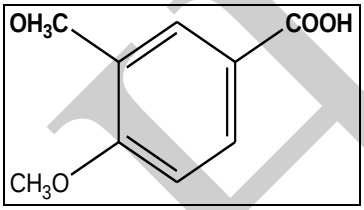
1. The molecular formula is $C_9H_{13}O_3N$.
2. It is soluble in alkali and reprecipitated by carbondioxide indicating the presence of phenolic hydroxyl group.

3. With ferric chloride it gives green colour showing the presence of a catechol unit.
4. On boiling with aqueous KOH it gives methylamine indicating the presence of methylamino group.
5. On fusion with KOH it gives protocatecholic acid.




**Protocatecholic acid**

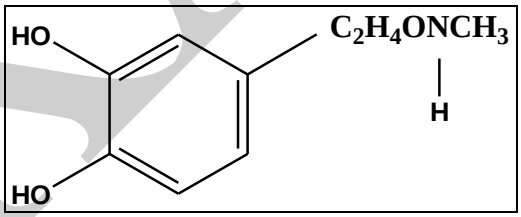
6. Adrenaline on methylation followed by oxidation yields veratric acid and trimethylamine.




Veratric acid

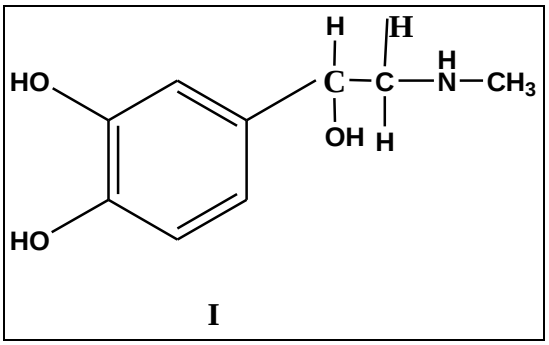
All the above reactions clearly show that adrenaline has a catechol unit in which the side chain ($C_3H_8NO$) is attached at the carbon atom to which –COOH group of veratric acid is present.

The formation of $(CH_3)_3$ N indicates that the nitrogen atom must be present at the end of side chain. Moreover, we are also getting methyl amine as one of the products, So the part structure of adrenaline can be written as below.

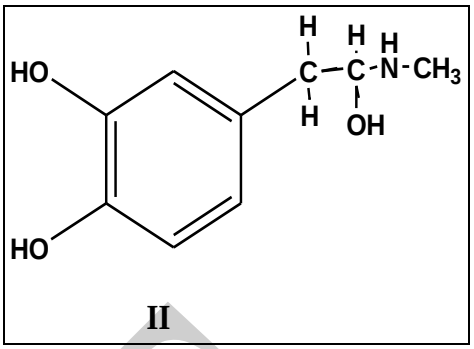



7. As adrenaline contains 3 oxygen atoms, two of which are present as phenolic(already proved) , the third must be present as alcoholic (because adrenaline does not give any carbonyl group reaction)

This is also proved by the formation of a ketone from tribenzoyl derivative of adrenaline on oxidation. So the adrenaline may be either I or II.




I

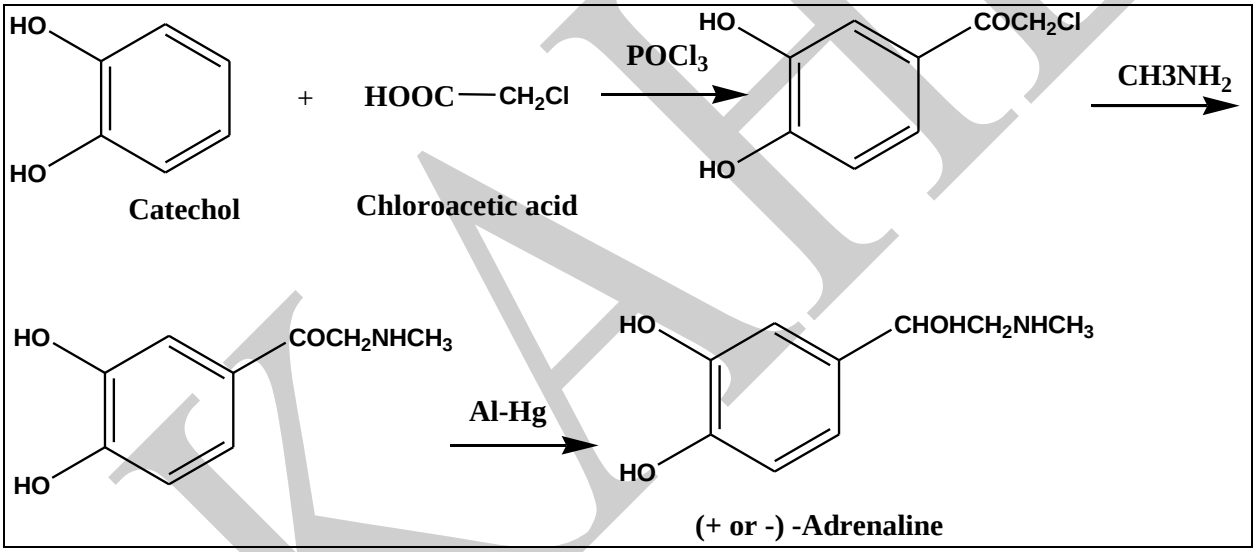



II

Structure I on oxidation will give benzoic acid derivative while II will give phenyl acetic acid derivative. But in our discussion we are getting benzoic acid derivative (protocatechuic acid).

Hence I is the structure for adrenaline which is confirmed by its various synthesis.

**i) by Stolz (1904)**

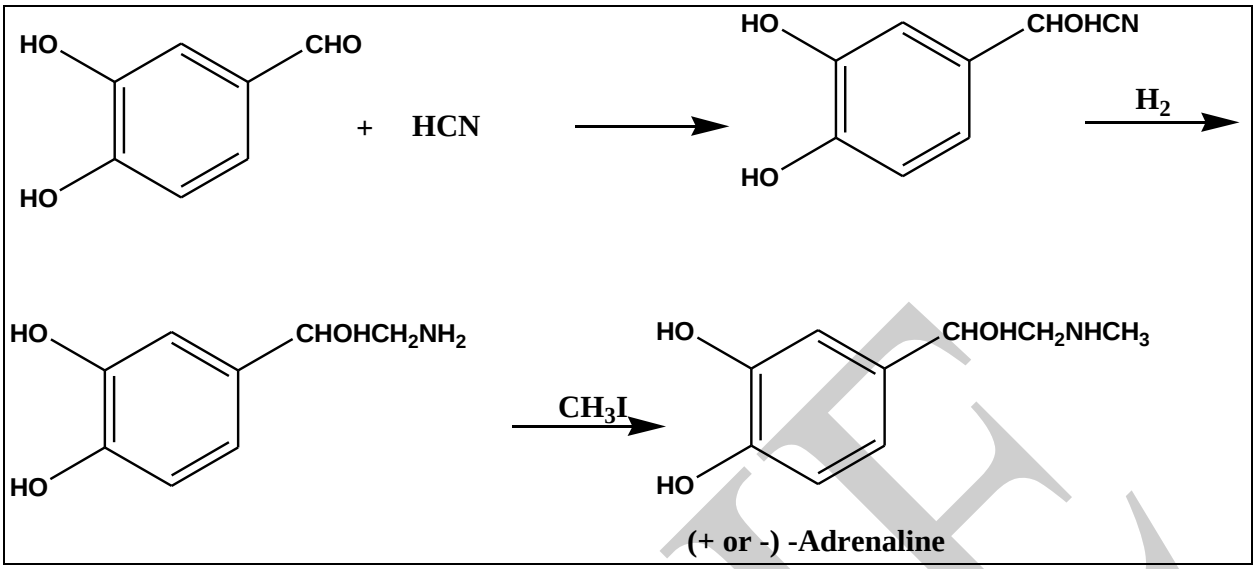



Some modifications have been made in the above method to increase the yield.

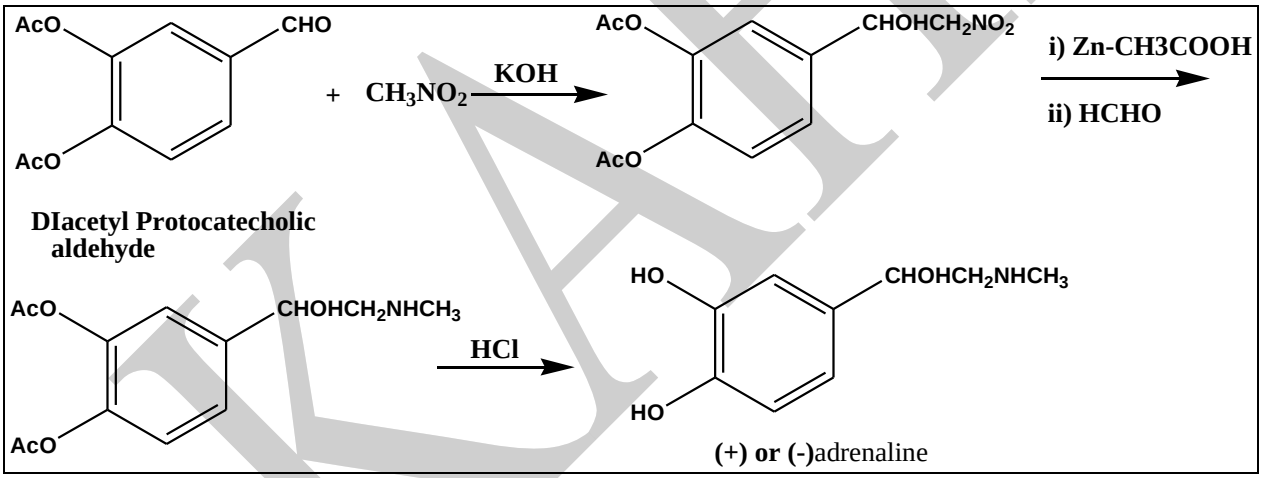
a) Equal quantities of catechol and chloro acetic acid are heated together in the presence of boiling benzene to give ester which on heating with $POCl_3$ gives chloroaceto catechol. The condensation by this method reduces tar formation.

b) $H_2$- Pd can be used in place of Al-Hg as reducing agent.

**ii) By Ott (1926)**




**iii) By Nagai(1918):-**

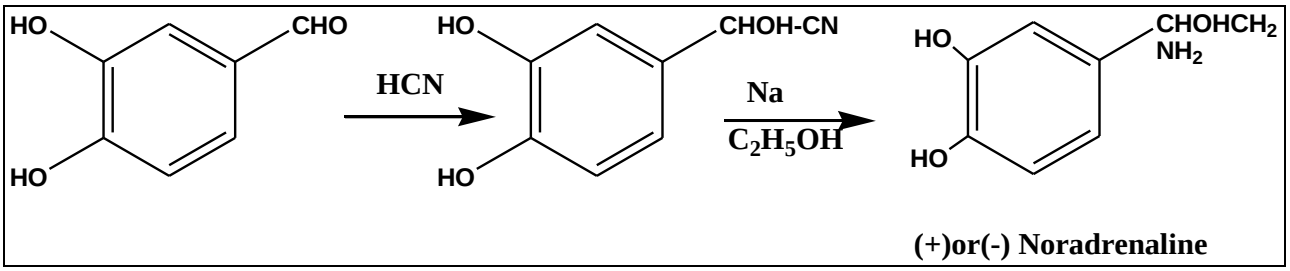



The racemic mixture adrenaline is resolved by means of (+)tartaric acid.

**Noradrenaline (Norepinephrine):-**

It is also present in the medulla part of adrenal body. The natural compound is leavorotatory, and is the most powerful compound known.

The molecular formula is $C_8H_{11}O_3N$ and its structure is determined on the same pattern at that of adrenaline. The structure is confirmed by various synthesis.




**(+)or(-) Noradrenaline**

**2. THYROXINE (THYROXIN) :-**

***Introduction :-***

- It is secreted by thyroid gland in the form of a protein thyroglobulin. The latter on hydrolysis yields mainly thyroxine (tetra iodo thyronine) with the formation of other products such as mono-, di-(3,3'-)-iodo thyronine and tri-iodo thyronines (two forms are 3,3',5 and 3,3',5'-tri-iodo thyronine); 3,3',5-tri-iodo thyronine is four to ten times more active than thyroxine.
- Most of the iodine content of the organism is present in the form of thyroxine. The deficiency of thyroxine causes disturbances in metabolism of carbohydrates, lipids, proteins, electrolytes and water resulting in the cessation of growth.
- The deficiency of this harmone in childhood causes metal deficiency in adults it leads to a state of myxedema.
- The over production of thyroxine causes the rapid heart beat and nervous irritability.

***Isolation :-***

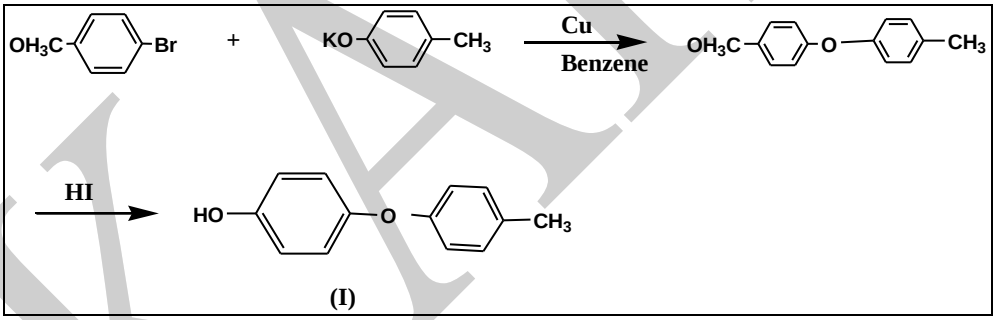
- The thyroid gland is dried and treated twice with $Ba(OH)_2$ solution, first with 10% solution and then with 40%.
- The so formed barium salt of thyroxine is suspended in 1% hot NaOH sol. And treated with sodium sulphate solution to remove barium as $BaSO_4$.
- Then thyroxine is obtained by the acidic hydrolysis of the sodium salt. Further purification may be carried out with alcohol and $CH_3COOH$.
- The harmone so obtained is a racemic mixture which can be resolved into l-isomer by trypsin.

***Constitution:-***

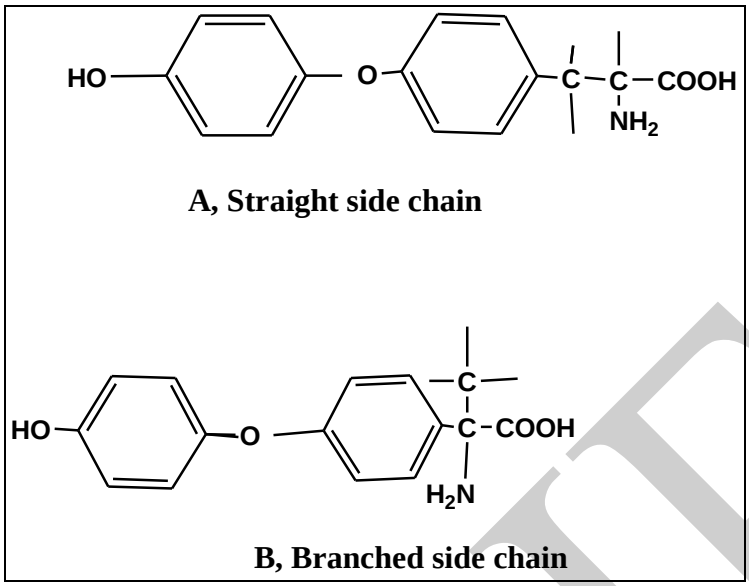
1. The molecular formula is $C_{15}H_{11}O_4NI_4$.
2. It was found to contain one acidic group by the normal reactions such as it forms mono ester.
3. On acetylation it forms mono ester indicating the presence of either –OH or $NH_2$ group.

4. On catalytic reduction ($H_2$-Pd) in alkaline solution, it gives thyronine ($C_{15}H_{15}NO_4$) by replacing iodine atoms by hydrogen.

5. **Constitution of thyronine :**
   a. The molecular formula is $C_{15}H_{15}NO_4$.
   b. Thyronine gives a brick red coloration with Mitlon's reagent (Hg in $HNO_2$) indicating thereby the presence of hydroxyphenyl (phenol)  group.
   c. iii) On treatment with ninhydrin, it gives blue colour showing the presence of alpha-amino acid.
   d. iv) On fusion with KOH in an atmosphere of hydrogen, it gives a mixture of p-hydroxy benzoic acid, quinol, oxalic acid and ammonia.
   e. v) On fusion with KOH at $250^0$, it yields quinol, p-hydroxy benzoic acid, a diphenyl derivative $C_{13}H_{12}O$ (I), oxalic acid and ammonia.
   f. The structure of compound (I) is established by its synthesis starting from p-bromoanisole and p-cresol.



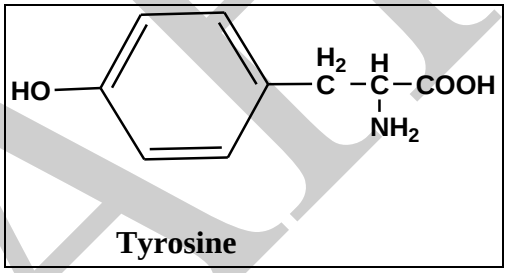

   g. These results clearly indicate that the thyronine molecule contains two benzene nuclei linked by an ether linkage (-$C_6H_4$-O-$C_6H_4$-) and one of the nuclei carries a hydroxyl group in the para position to the ether linkage.
   h. So the rest of the carbon atoms ($C_{15}$-$C_{12}$=$C_3$) must be present in the side chain.
   i. Moreover, thyronine is also found to be an alpha-amino acid iii) so the part structure of thyronine may be either A or B.




**A, Straight side chain**

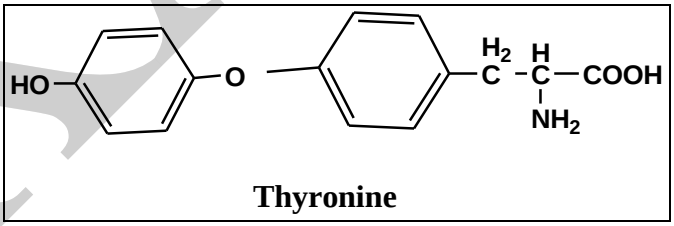
**B, Branched side chain**

j. Thyronine on boiling with HI gives tyrosine which clearly indicates that the side chain in thyronine is straight.



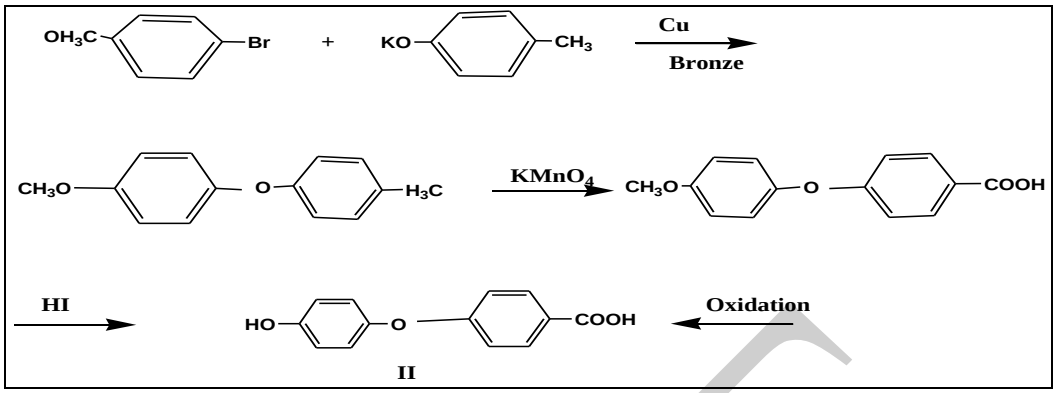

**Tyrosine**

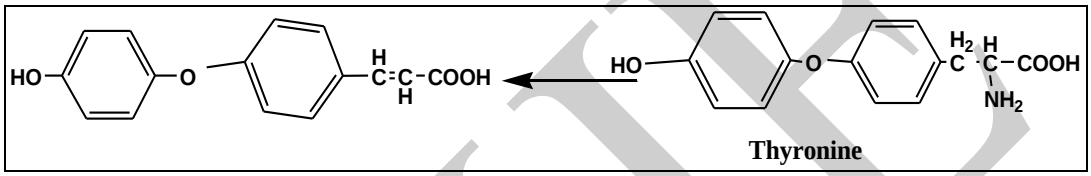
k. Thus, the structure of thyronine will be as below.




**Thyronine**

l. The above structure of thyronine also explains its Hofmann exhaustive methylation followed by oxidation to a compound –II identical with the synthetic compound from p-bromo anisole and p-cresol.

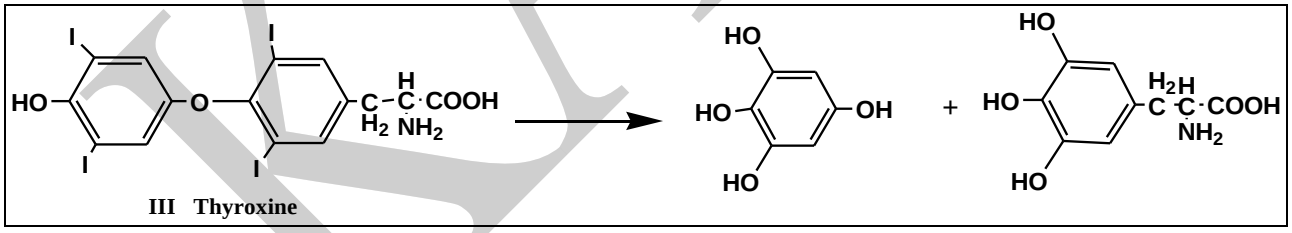



6. Now the only problem in elucidating the structure of thyroxine is to specify positions of the iodine atoms in thyronine.

This can be ascertained by the following experiment. Thyroxine on fusion with alkali (KOH) gives two pyrogallol compounds (replacement of iodine atoms by –OH groups).

The formation of pyrogallol derivatives clearly indicates that the two iodine atoms are in o-positions to the original hydroxyl group in each benzene nuclei. Thus the structure of thyroxine will be III.



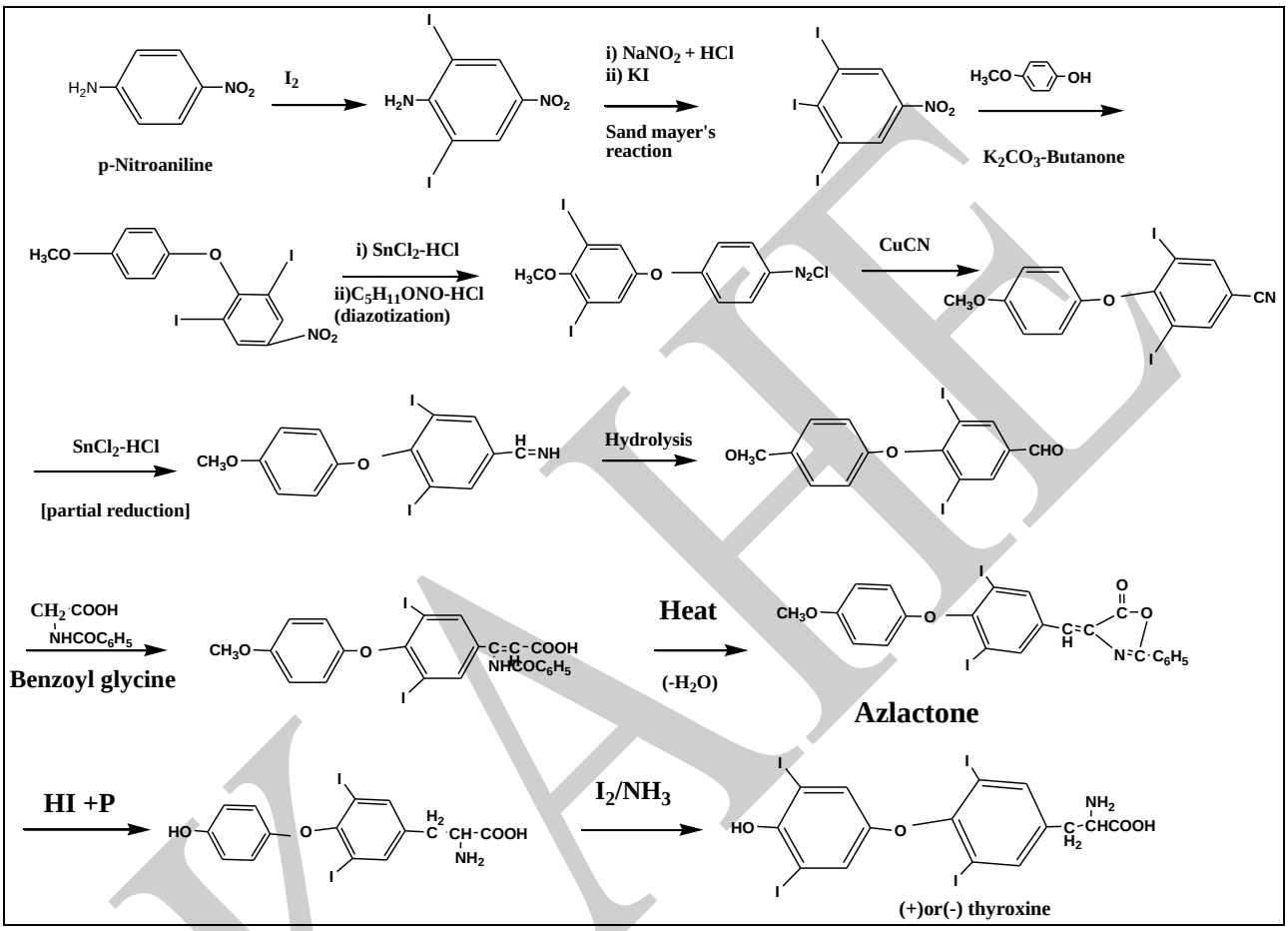

The above structure can further be proved by the following specific reaction of phenols iodinated in both the ortho positions.

Thyroxine on treatment with nitrous acid gives a yellow colour which deepens on boiling and changes to red on cooling followed by addition of ammonia.

**Thyroxine** $\xrightarrow{HONO}$ **Yellow Colour** $\xrightarrow{Boil}$ **Colour deepens** $\xrightarrow[NH_3]{Cool}$ **Red**

7. Finally the structure can be proved by its synthesis.

**i) By Harington and Barger in(1927):-**




The racemic mixture may be resolved by active formic acid.

### 3. STEROLS:-

- There are found in animal and plant oils and fats. These are crystalline compounds containing a secondary alcoholic group.
- So they differ from common alcohols in being solid and due to this reason they are known as sterols.

**Cholesterol :-**

- It is an animal sterol and occurs either free or as fatty esters.

- The main sources are brain, spinal cord, gallstone and fish liver oils.
- It forms about one-sixth of the dry weight of nerve and brain tissue and is obtained commercially by the extraction of cattle spinal cords.
- As it was first of all isolated from human gallstone deposited in the bile duct, it is known as cholesterol.
- The human body not only can synthesize cholesterol but can also absorb it form from through the intestine into the blood stream.
- Too high a concentration of cholesterol in the blood can lead to its precipitation in the circulatory vessels, resulting in high blood pressure and arteriosclerosis.
- It is a white crystalline optically active solid with m.p $149^0$ and specific rotation$[alpha]_D$ $39^0$.
- Cholesterol (other sterols) gives the following colour reactions.

i) The salkowski reaction:

A solution of cholesterol in chloroform, when treated with conc. sulphuric acid, develops a red colour in the chloroform layer.

ii) The Libermann-Burchard reaction:

A solution of cholesterol in chloroform, when treated with conc.$H_2SO_4$ and acetic anhydride gives a greenish colour.

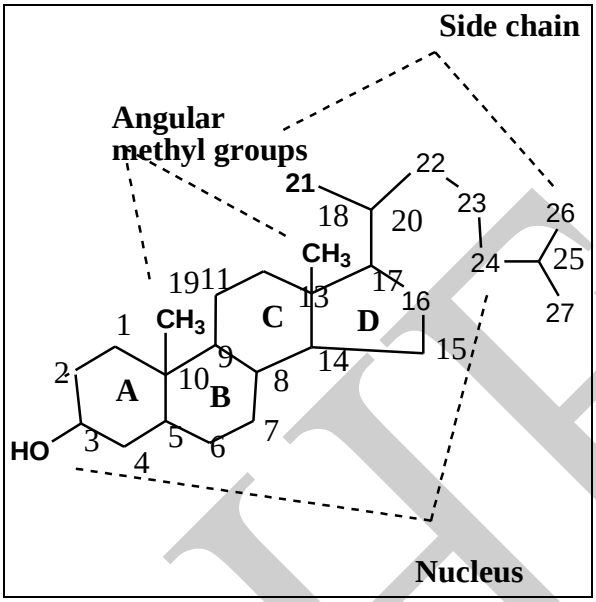
iii) Ethanolic solution of cholesterol, when treated with a ethanolic solution of digitonin (a saponin), gives a white precipitate of cholesterol digitonide.

- The molecular complex of cholesterol digitonide when dissolved in pyridine, dissociates to its components.
- The individual components may be separated by ether when cholesterol remains in solution while the digitonin is precipitated.
- Alternatively the digitonide is dissolved in dimethyl sulphoxide and the solution is heated on a steam bath. On cooling, only in the sterol is precipitated. (Issidorides ef al,1962).
- Actually digitonide formation is used for the estimation of cholesterol.

**Constitution of Cholesterol:-**

- The constitution of cholesterol was elucidated by Wieland, Windaus and their co-workers (1903-1932).

- For the sake of simplicity we will consider the established structure of cholesterol at the beginning of our discussion.




So the complete constitution of cholesterol may be dealt in the following headings.

A) Structure of the nucleus

B) Position of the hydroxyl group and double bond

C) Nature and position of side-chain

D) Position of the angular methyl group

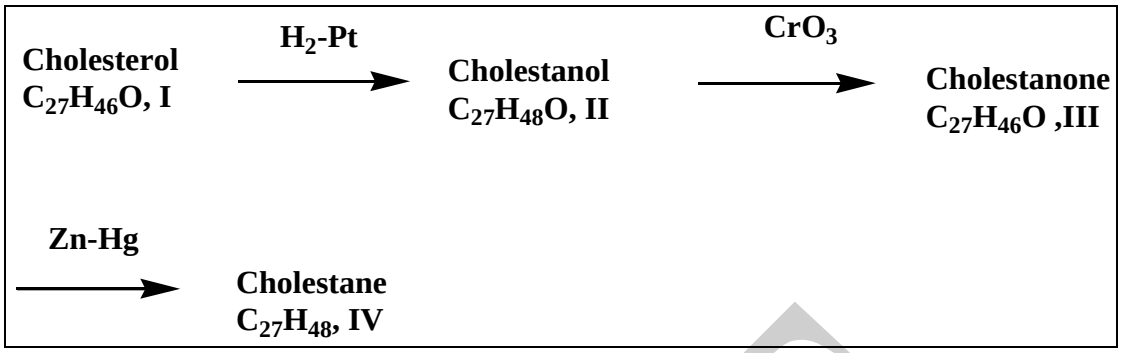
**A) Structure of the nucleus:**

1. The molecular formula of cholesterol is $C_{27}H_{46}O$.

2. On acetylation it forms monoacetate indicating the presence of one hydroxyl group.

3. It adds up two bromine atom suggesting the presence of one double bond.

4. Cholesterol on reduction gives cholesterol which on oxidation which chromic acid yields cholestanone. The latter on reduction gives cholestane.



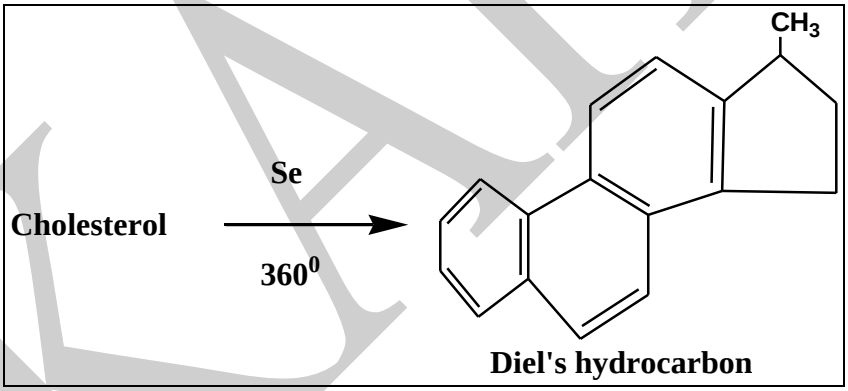

This led to the following conclusions:

i) The conversion of I to II proves the presence of the double bond.

ii) Oxidation of II to III (a ketone) shows that cholesterol is a secondary alcohol.

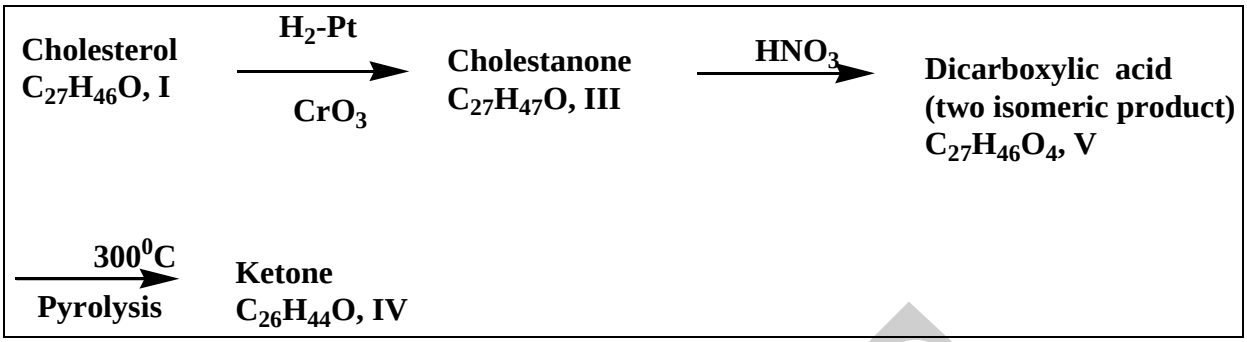
iii) The saturated parent hydrocarbon (cholestane $C_{27}H_{48}$, IV) of cholesterol corresponds to the general formula ($C_nH_{2n-6}$)for tetra cyclic compounds, hence cholesterol is a tetracyclic alcohol.

5. On selenium distillation at $360^0$, cholesterol gives Diel's hydrocarbon and chrysene; the formation of the former compound suggests that cholesterol has Diel's hydrocarbon nucleus in its structure.




***B) Position of the hydroxyl group and double bond:-***

1. Cholestanone , III on oxidation with nitric acid gives a dicarboxylic acid, V which on pyrolysis yields a ketone, VI.




**Leading to the following conclusions:**

i) The oxidation of III to V indicates that the ketonic group is present inside the ring [had it been in a side-chain, an acid having lesser number of carbon atoms would have been formed].

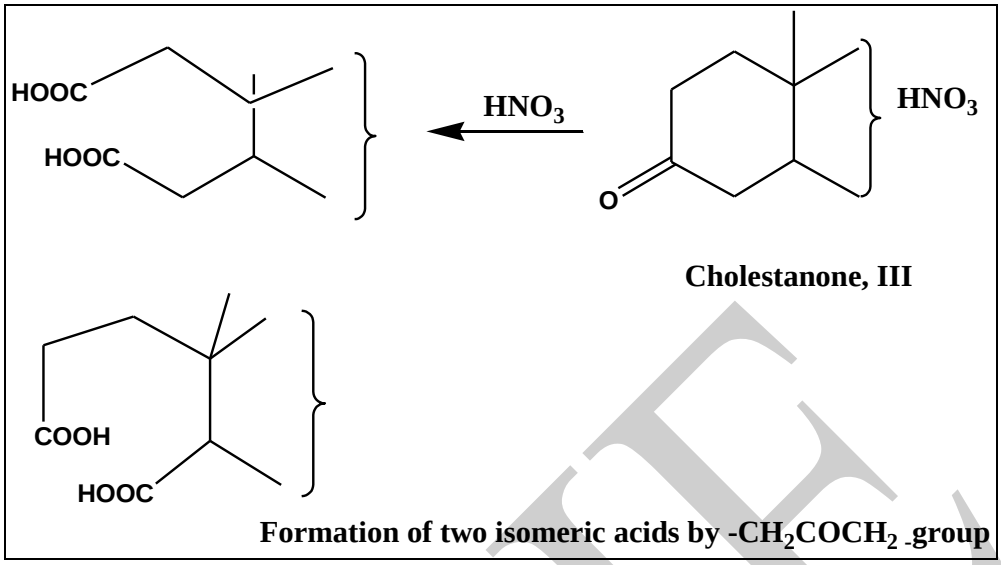
ii) The conversion of dicarboxylic acid, V to a ketone, VI indicates that V is either a 1,6 or 1,7-dicarboxylic acid [Blanc rule].

Now we see that this dicarboxylic acid is obtained from the hydroxyl group of cholesterol which cannot be present in ring D as it would form a 1,5-dicarboxylic acid instead of 1,6 or 1,7-dicarboxylic acid on the above treatment.

Hence the hydroxyl group may be either in ring A, B or C.

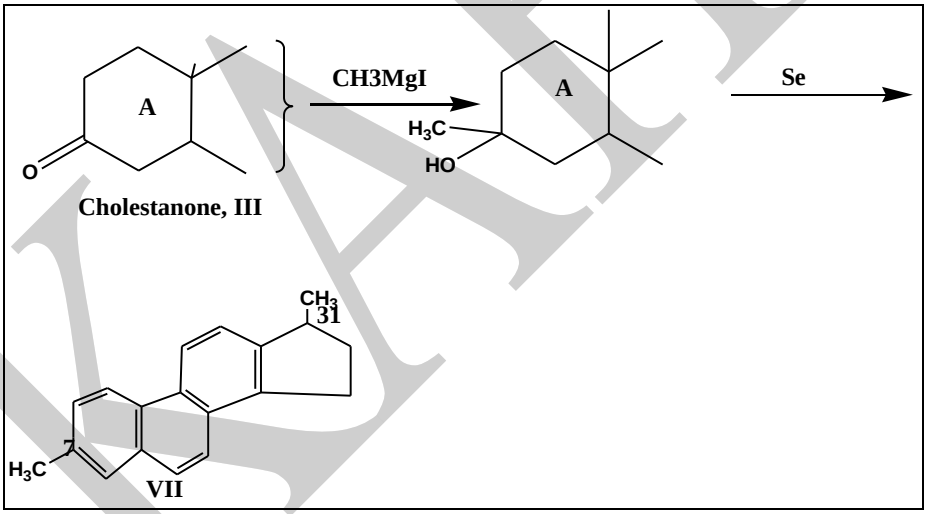
iii) The formation of two isomeric dicarboxylic acids V, suggest that the keto group in cholestanone is flanked by a methylene group on either side ($-CH_2COCH_2-$).

Examination of the proposed structure I, of cholesterol or the structure of Diel's hydrocarbon indicates that such as an arrangement is possible only if the hydroxyl group is present in the ring A and in position 2 or 3.




**Formation of two isomeric acids by -$CH_2COCH_2$ -group**

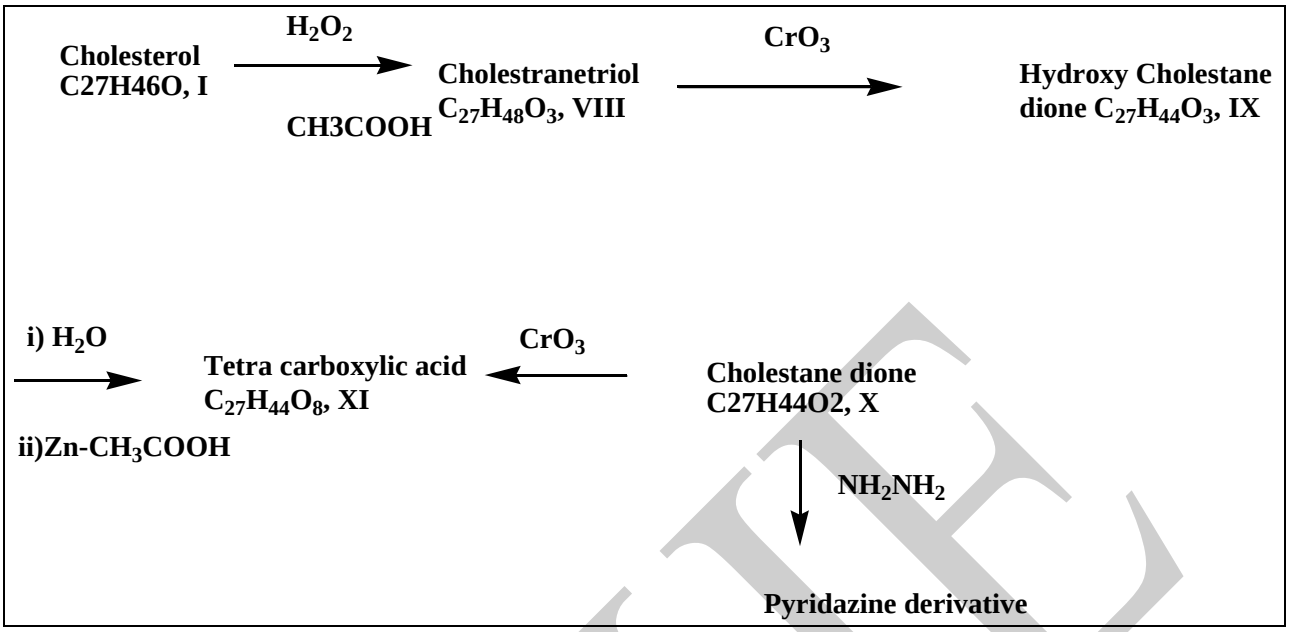
2. Cholestanone, III on treatment with methyl magnesium iodide followed by selenium dehydrogenation yield's 3',7-dimethyl cyclo pentenophenanthrene, VII (Kuhn 1937,1939), the structure of which is proved by its synthesis.




The formation of VII suggests that the hydroxyl group in cholesterol is present in position 3 which corresponds with the position 7 in VII.

***3. Position of the double bond:-***

Let us consider the following set of reactions.




**These reaction leads to the following conclusions.**

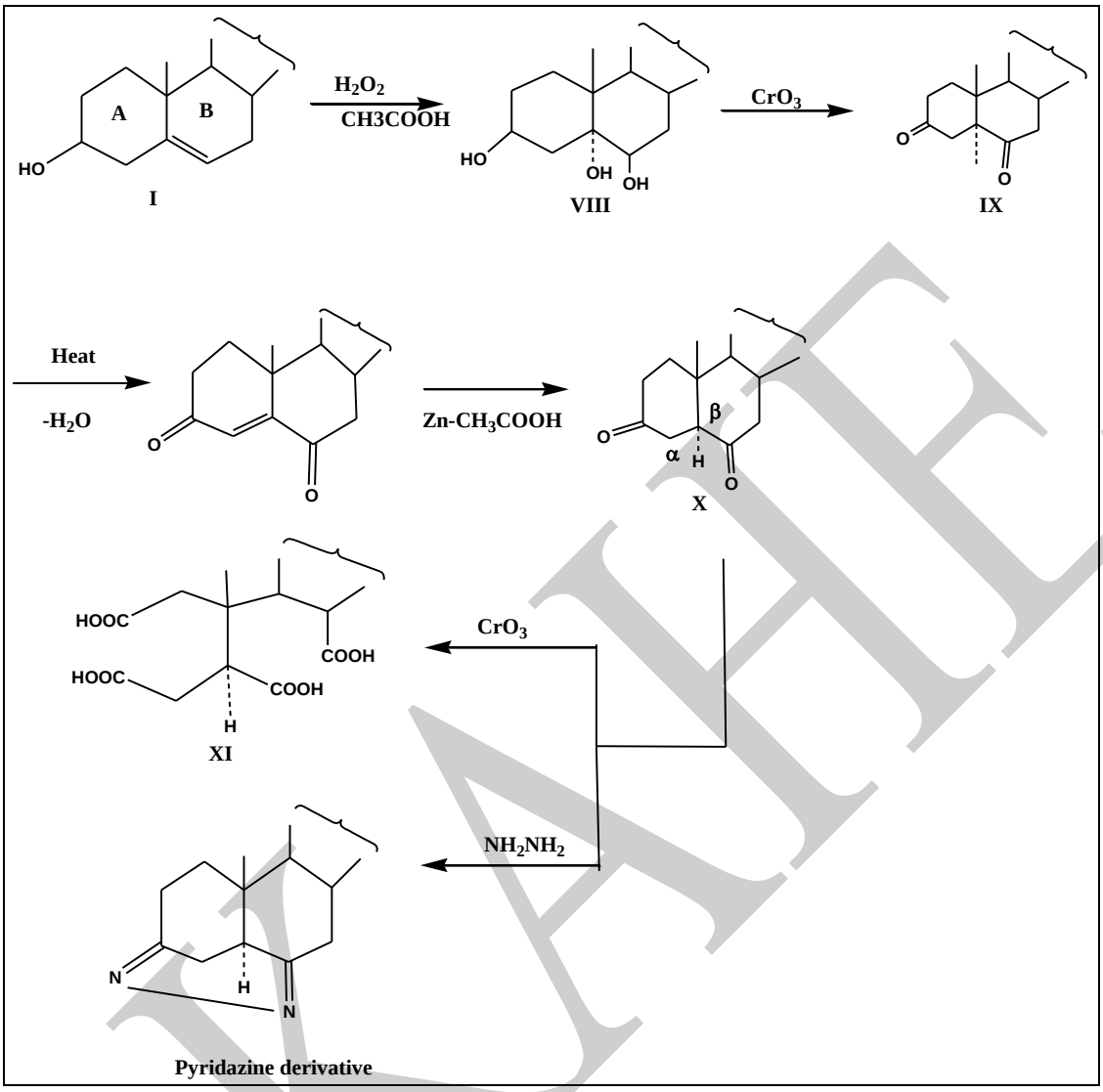
i) The conversion of I to VIII represents the hydroxylation of the double bond.

ii) Cholestanediol VIII, on oxidation gives a diketone, IX, indicating that in VIII two of the hydroxyl groups are secondary in nature and the third (resistant to oxidation) is tertiary one.

iii) The oxidation of cholestane dione, X to a tetracarboxylic acid, XI, without loss of any carbon atom suggests that the two ketonic groups in X are present in different rings [had they been in the same ring, then carbon atom would have been lost during oxidation], (ie),the double bond and the hydroxyl group in cholesterol are present in two different rings and as we have seen already that the hydroxyl group of cholesterol is present in ring A, therefore the double bond must be present either in ring B,C or D.

iv) Since cholestanedione, X, can form a pyridazine with hydrazine, the two ketonic groups of X are in gamma positions w.r.t each other which is possible only if the double bond is present in between $C_5$ and

$C_6$ and thus all the above reactions can be written as below.




4. The position of double bond is further proved by the following set of reaction:

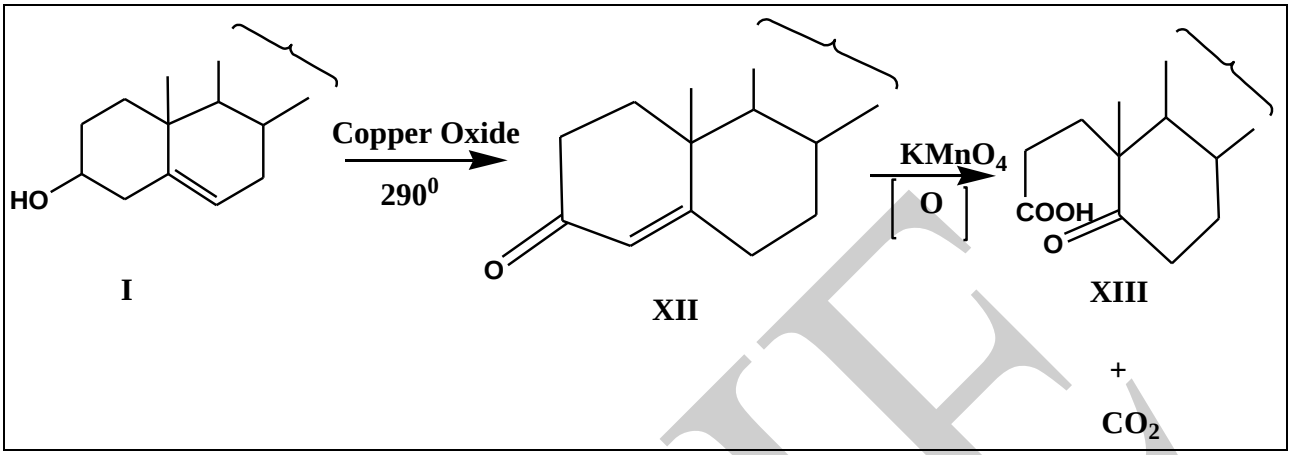
| | | | | |
|---|---|---|---|---|
| **Cholesterol** **I** | **Copper Oxide** **$290^0$** | **Cholestenone** **XII** | **$KMnO_4$** **(O)** | **Keto acid + $CO_2$** **XIII** |

**Which lead to the following conclusions.**

i) Oxidation of XII to XIII with loss of one carbon atom indicates that the keto group and the double bond in XII are in the same ring.

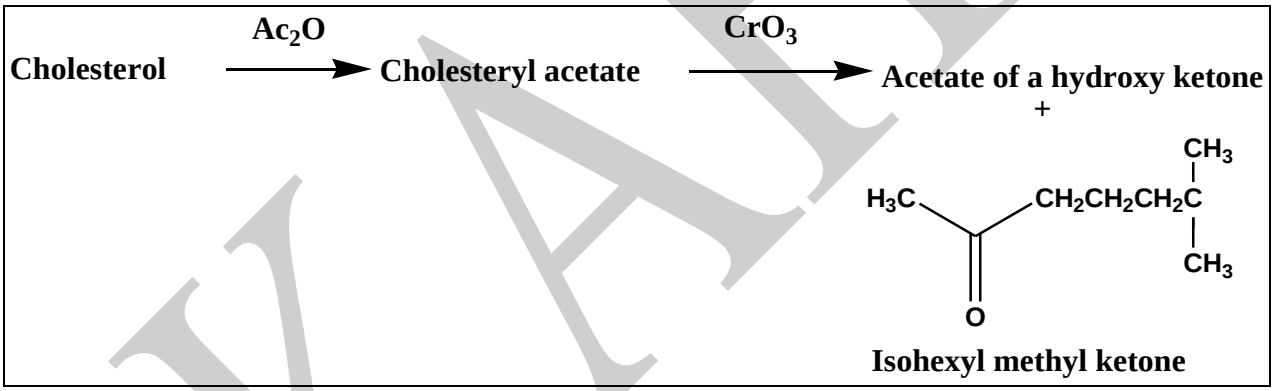
Moreover, ultra violet absorption spectrum of XII, $\lambda_{max}$ 240 nm, shows that the keto group and the double bond are conjugated. These results can be explained on the assumption that there is a migration

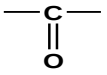
of the double bond of cholesterol during the formation of cholestenone, XII, which is possible only if the double bond is present in between $C_5$ and $C_6$.




***C) Nature and position of the side chain:***

1. Cholesterol acetate on oxidation with chromic acid forms an acetate of a hydroxyl ketone and a steam volatile ketone, isohexylmethyl ketone .

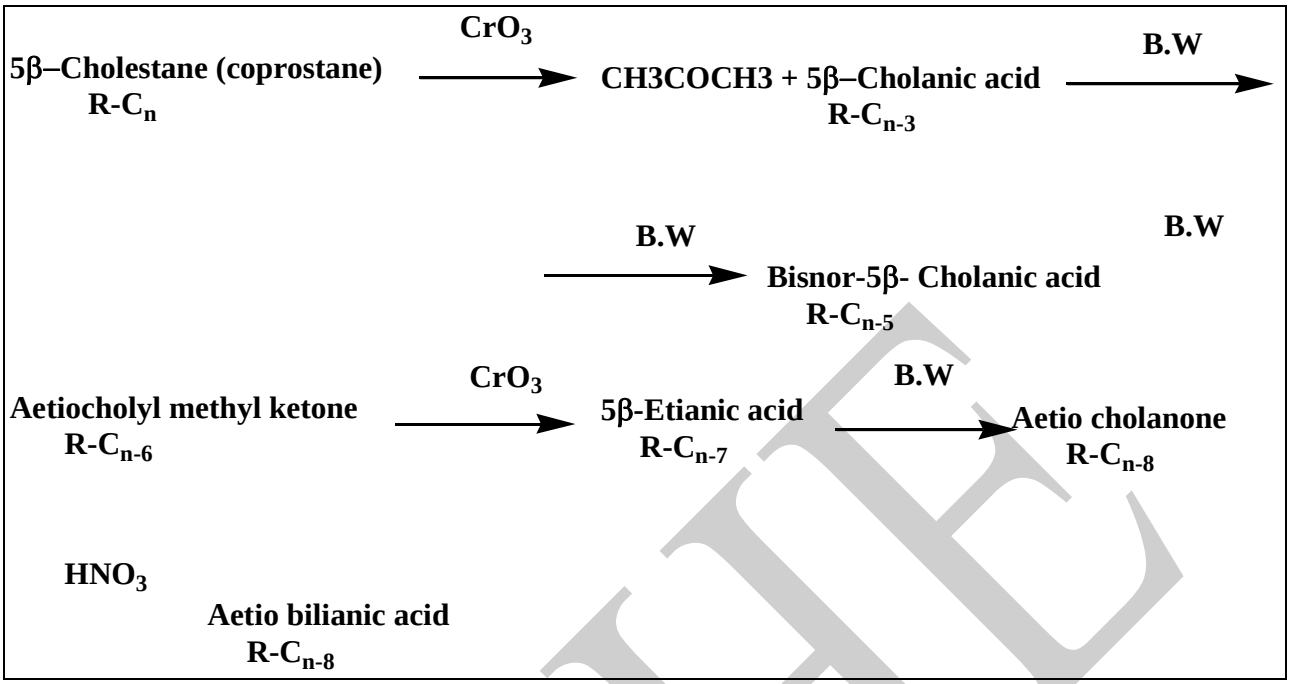



The above result shows that the isohexylmethyl ketone forms the side chain of cholesterol and is attached to the nucleus of cholesterol through the carbon atom oxidise to  group.

2. The nature of the side chain can further be elucidated by the application of Barbier-Wieland degradation (B-W) in the following manner.

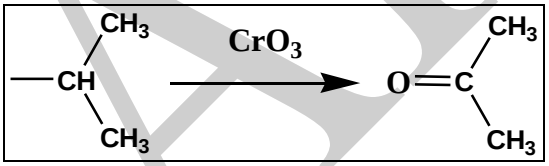
Cholesterol is converted into 5beta-cholestane, also known as coprostane (a stereo isomer of the cholestane,IV) and now if we represent the whole of the nucleus of coprostane by R and the side chain by $C_n$ then the coprostane molecule will be represented by $R.C_n$.

Now let us degrade the side chain of this molecule by oxidation and B-W degradation.




These degradation reactions lead to the following conclusions;

i) The formation of acetone from coprostane indicates that the side-chain ($C_n$) of the coprostane terminates in an isopropyl group.

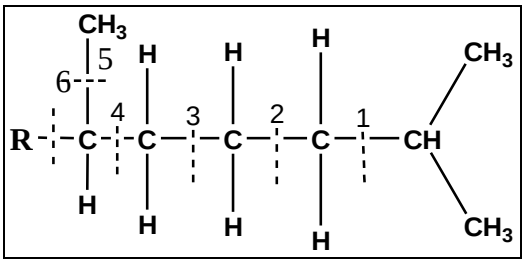



ii) The conversion of bisnor-5/3-cholanic acid to the ketone , aetiocholyl methyl ketone indicates that the alpha-carbon atom of the acid is secondary in nature. (ie) there is an alkyl group on the alpha-carbon atom in bisnor-5beta-cholanic acid.

iii) Oxidation of aetio cholyl methyl ketone to etianic acid with the loss of one carbon atom suggests that the alkyl group in aetio cholyl methyketone and in bisnor-5 beta-cholanic acid is methyl.

iv) The oxidation of aetiocholanone to aetiobilianic acid without any loss of carbon atom suggests that in the ketonic group is present in the ring.

From the foregoing discussion we came to know that the coprostane (and hence cholesterol) contains a side-chain of eight carbon atoms arranged in the following order.




**3. Point of attachment of the side chain to the nucleus (R) :-**

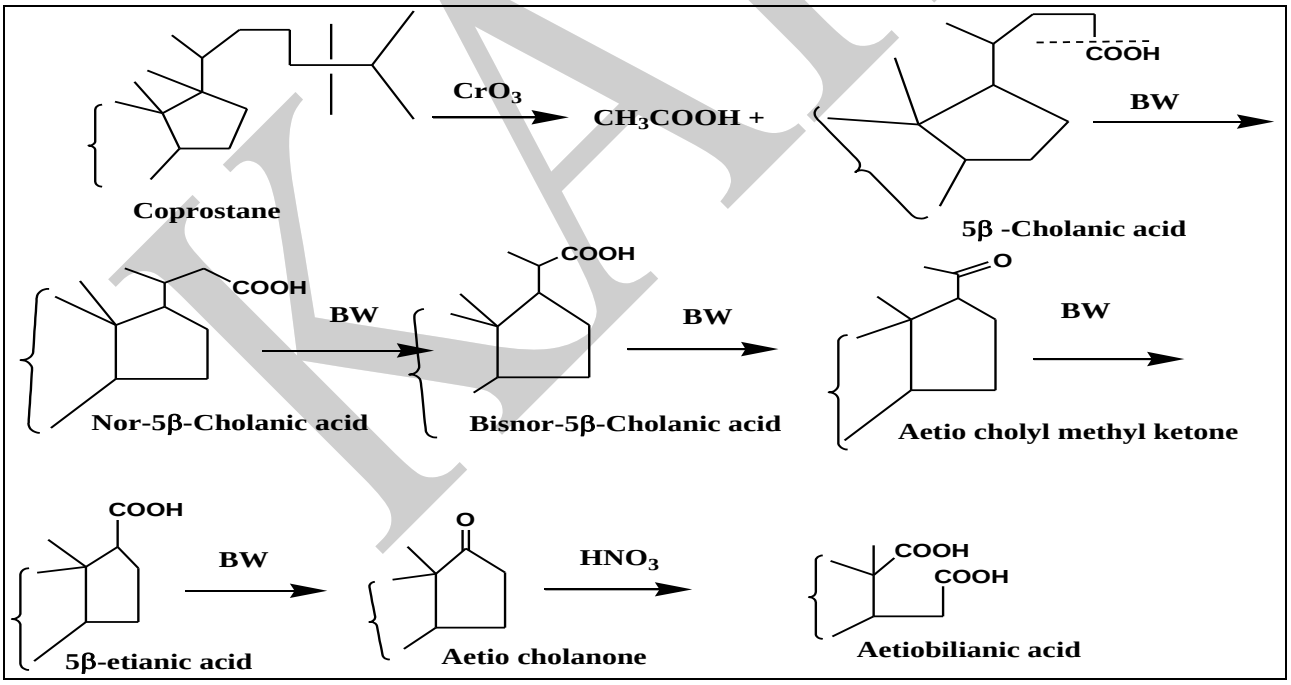
a) The dicarboxylic acid, aetiobilianic acid(obtained above) on heating with acetic anhydride form an anhydride suggesting that it is a 1,5-dicarboxylic acid [Blanc rule].

1, 5-Dicarboxylic acid can only be obtained from a five membered ring; hence the side chain is attached to the five membered ring D.

b) Cholesterol on selenium dehydrogenation yields Diel's hydrocarbon indicating that the side-chain is attached to $C_{17}$ in cholesterol.

This position is further proved by X-ray photographs and surface film measurements.

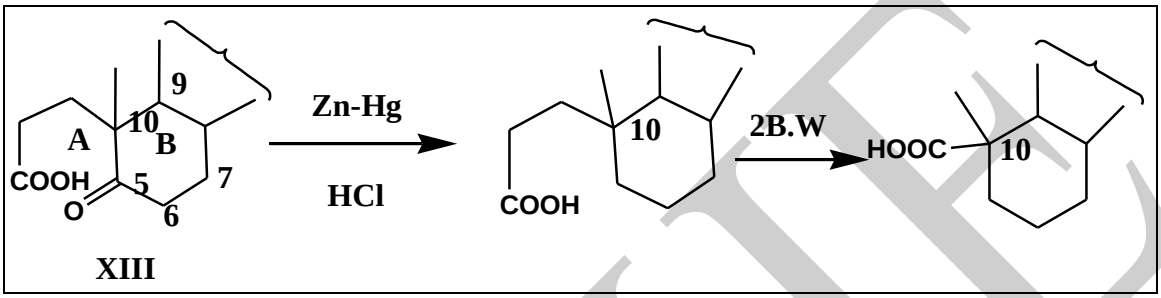
4. Thus, now we know the nature and position of the side-chain and hence we can formulate the conversion of coprostane into aetiobilianic aid as follows [only ring D is shown in the structures].




***D. Position of the angular methyl groups:-***

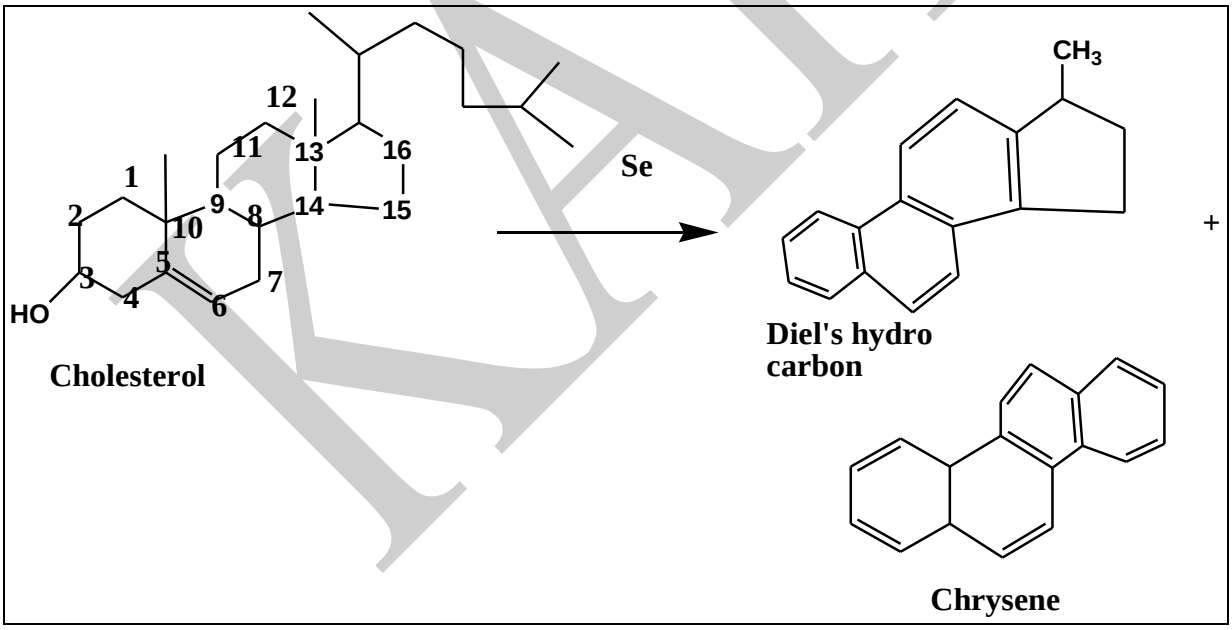
The cyclopentanophenanthrene nucleus and the side-chain of the cholesterol account for 17 and 8 carbon atoms respectively, thus 25 out of 27 carbon atoms of cholesterol have been accounted for, the rest two carbon atoms are found to be present as angular methyl groups by the following facts.

i) The keto-acid XIII [obtained in point(B)4(i)], on clemmenson reduction followed by twice B-W degradations gives a tertiary acid, so one of the angular methyl groups must be present on $C_{10}$ [Tschesche, 1932].




XIII

ii) On selenium dehydrogenation, cholesterol yields Diel's hydrocarbon and chrysene; the formation of the latter is explained by the fact that there is an angular methyl group at either $C_{13}$ or $C_{14}$ which enters the five membered ring (D) of cholesterol to form a six membered ring of chrysene.

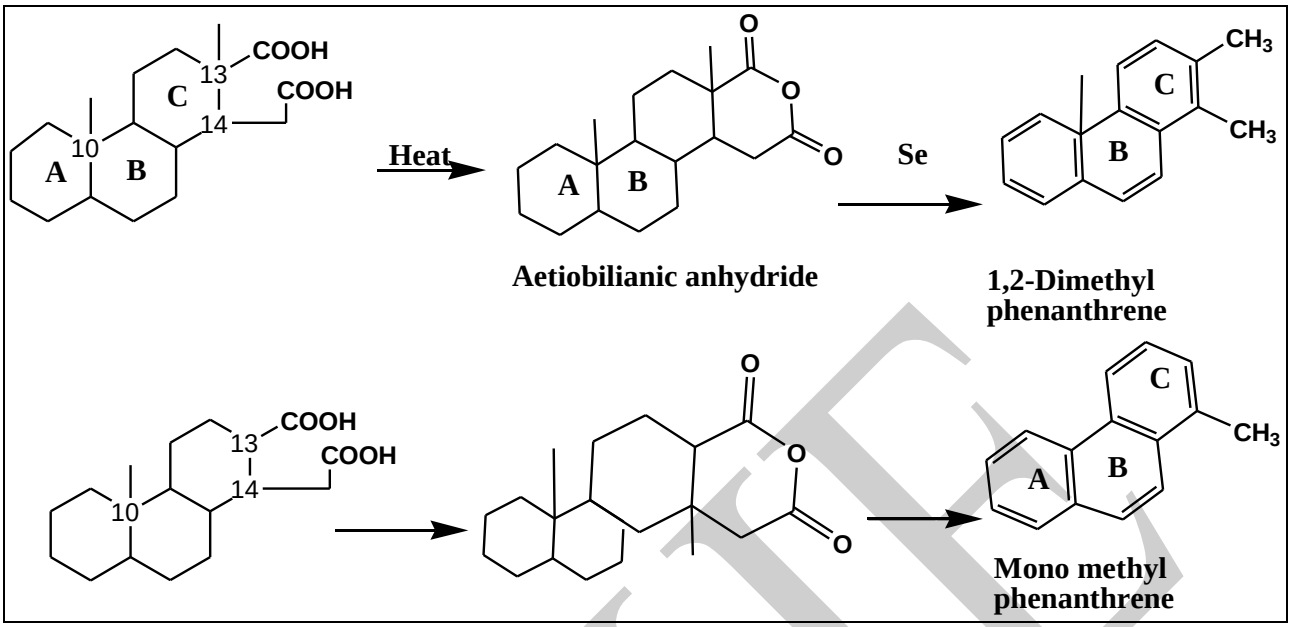



Cholesterol

Diel's hydro carbon

Chrysene

iii) Aetiobilianic anhydride on distillation with selenium gives 1,2-dimethyl phenanthrene indicating that the methyl group is present in position 13; that it been on $C_{14}$ then only mono methyl phenanthrene would have been found.




**ENZYMES:-**

***Introduction:***

- The group of complex proteinoid organic compounds, provided by living organisms which catalyze specific organic (or even inorganic) reactions are called enzymes.
- Practically all biological processes such as digestion, respiration etc are performed by enzymes.
- A biological process such as digestion, for example, requires the participation of several enzymes, each catalyzes a specific reaction.
- The term enzymes (Gr.enzymes, in yeast) for these bio-organic catalysts was first used by Kuhne in 1878, as yeast was among the earliest sources of these catalytic agents.
- Many enzymes are now well-defined , crystalline substances * with highly reproducible physical properties and catalytic activities, but their isolation in a crystalline form continues to be a very tedious process involving highly specialized skill.
- They may be simple or conjugated proteins. The relatively low molecular weight non-proteinoid prosthetic group of enzymes is called coenzymes. The residual proteinoid part is known as apoenzyme.
- Both, the enzyme and the apoenzyme must be present for the overall activity of the enzyme.
- The coenzyme may be composed of heterocyclic ring system (e.g. pyrrole, pyridine, pyrimidine, purine,etc.), a sugar residue (e.g.D-ribose) and a phosphoric acid residue.

- Vitamins of the B group act as coenzymes for several enzymes.
- Infact, the apoenzyme (simple protein/ peptide) is catalytically inactive by itself, but its activity can be restored by the addition of coenzyme.
- They are many metallo protein enzymes in which the metal ions (e.g. $Zn^{+2}$, $Mn^{+2}$, $Mg^{+2}$ etc.) bonded either to the apoenzyme or to the coenzyme are known as enzyme activators.
- It is beleive that metal ions form a coordinate complex between the enzyme and substrate to activate the substrate by promoting electronic shifts.

***Nomenclature and Classification:-***

- Enzymes are usually named by adding the suffix –ase to the root of the name of the substrate. For example, urease is the enzyme that catalyszes yhe hydrolysis of urea : sucrase acts upon sucrose and proteases act on proteins as their substrates, etc.
- Sometimes, an enzyme is named after the product given by their catalytic activity. For example, sucrase is also called invertase, as it produces invert sugar (glucose + fructose) from sucrose.
- They are also named according to the type of reactions in which they are involved (e.g. pyruvic carboxylase and lactic dehydrogenase).
- Trival names, however, continue to be used for certain enzymes (e.g.trypsin, pepsin, emulsin etc.).

***Classifications:-***

- Enzyme have been classified into two main groups, namely, hydrolytic enzymes and oxidative enzymes.
- Hydrolytic enzymes (or hydrolases) catalyze the hydrolysis (and resynthesis) of substrates like esters, proteins, carbohydrates, lipids etc, whereas oxidative enzymes control the various oxidation-reduction reactions, such as dehydrogenation (dehydrogenases), oxidation (oxidases),etc.
- Hydrolases are mostly simple proteins but oxidative enzymes are generally conjugated proteins.
- Table: Lists some enzymes of the two important types, together with the relevant substrates and products:

**Table: Some Typical Enzymes**

| Name | Substrate | Products |
|---|---|---|
| **A. Hydrolytic enzyme** | | |
| 1. Esterase : | | |
| a) Lipase | Glycerides | Fatty acids + Glycerol |
| b) Phosphatases | Phosphate esters | H3PO4 + alcohols |
| 2.Proteinase and Peptidases : | | |
| a)Rennin | Casein (a milk protein) | Paracasein |
| b)Trypsin | Proteins | Poly peptides, amino acids. |
| 3.Glycolase: | | |
| a)Maltase | Maltose | Glucose |
| b)Amylase | Starch(amylum) | Maltose |
| c)Lactase | Lactose(milk sugar) | Glucose + Galactose |
| d)Invertase | Sucrose | Glucose + Fructose |
| 4.Amidases: | | |
| Urease | Urea | CO2 + NH3 |
| B. Oxidative enzymes : | | |
| 1.Dehydrogenases: | | |
| Alcohol dehydrogenase | Ethanol | Acetaldehyde |
| 2.Oxidases : | | |
| Ascarbic acid Oxidase | Ascorbic acid | Dehydroascorbic acid |
| Catalase | Hydrogen peroxide | Water + $O_2$ |

**Chemical Nature of Enzymes :-**

- Analysis of enzymes has shown that all enzymes studied so far are proteins.
- They belong to either Simple, globular or conjugated globular class of proteins.
- Hence, their chemical and physical properties are same as proteins of the globular class.

- For example, they are readily denaturated by heat and a variety of chemical agents.
- They posses amphoteric nature and show definite isoelectric point for a particular enzyme.
- Some purified enzymes when injected in the body produce specific antibodies which fight against harmful bacteria.
- On the basis of chemical composition, enzymes can be divided into three classes namely (1) simple globular protein (2) globular metalloprotein and (3) globular protein or metallo protein attached to a prosthetic (non protein) group called coenzyme.
- For example, pepsin is an example of simple globular protein, ascorbic acid oxidase (copper proteinate ) is a globular metallo protein; transaminase (pyridoxal pyrophosphate-proteinate) is a globular protein attached to a prosthetic group and catalase (iron-porphyrin-proteinate) is a globular metallo protein containing porphyrin prosthetic group.
- The enzymes of class (3) are known as haloenzymes, the protein part is known as 'apoenzyme' and reminder as 'coenzyme'.

***Salient characteristics:-***

These are as follows:

1. Most of the enzymes are colourless solids, but some are yellow, blue, greenish or brown.

2. They are mostly soluble in water or dil. salt solutions, but they can be precipitated out of their aqueous solutions by protein precipitating agents.

3. They are colloidal in nature and do not pass through dialysing membranes, although the prosthetic groups of enzymes (or coenzymes) can be easily separated by dialysis from the proteinoid part (or apoenzymes).

4. They usually contain C, H, N and S, although phosphorus and metallic ions are also present occasionally.

5. They have high molecular weights. Pepsin has, for example, a molecular weight of 39,200.

6. As catalysts they are effective in very small amounts. The number of moles of substrate converted by one mole of an enzyme per minute is termed the turnover number of the enzyme and the turnover number of enzymes range from 100 to 30,00,000.

7. Most of the enzymes get inactivated, presumably through denaturation, when heated above $80^0$C. The optimum temperature for enzyme action is about 20 to $40^0$C.

8. They show an extraordinary specificity of action.

They may be specific for particular substrate or a particular type of reaction.(e.g. urease hydrolyses urea only; phosphatases hydrolyse the esters of phosphoric acid only; etc), they may show a relative specificity (e.g. pepsin is most active for those peptide links in which the amino group belongs to an aromatic amino acid and the carbonyl group is derived from a dicarboxylic amino acid); or they may exhibit stereo specificity (e.g. maltase hydrolyses alpha-glycosides only whereas emulsion hydrolyses beta-glycosides only), lactic acid dehydrogenase catalyses oxidation of L-lactic acid only.

9. Enzyme actions are greatly influenced by $P^H$ variations. The optimum $P^H$ for most of the enzyme actions is about 7.

10. Enzyme actions are usually carried out in dilute solutions, as high concentration of the solution of the substrate renders the enzymes inactive.

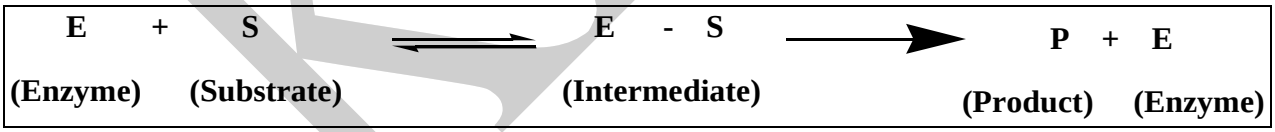
***Mode of Enzyme Action :- (Or) Mechanism Of Enzyme Action:-***

- Arrhenius suggested a scheme to account for the catalytic activity of enzymes.
- He belived that an enzyme (a biocatalyst) functions to combine with a reactant (substrate, say S) to form an intermediate compound (E-S), which affords a lower energy reaction pathway and is more reactive than initial uncombined species.
- The mechanism of the enzyme reactions can be explained in two steps:

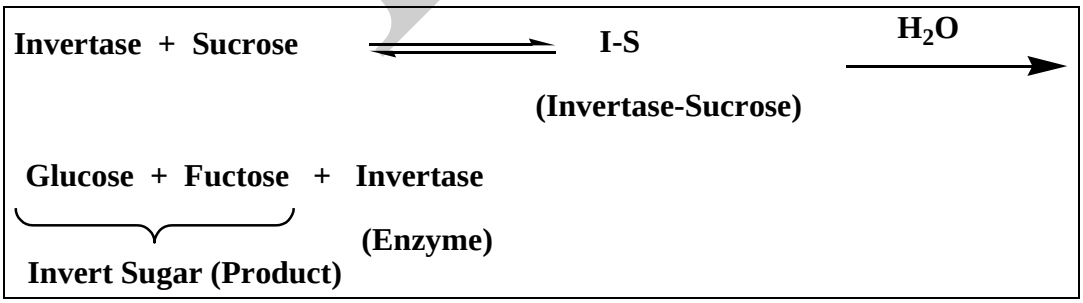
Step 1: A molecule of the enzyme (say, E) and a molecule of substrate (say, S) collide to form an intermediate, E-s complex (more reactive) with decrease in energy of activation ($\Delta$ E).

Step 2: It involves the formation of the products, which releases from the surface of the enzyme(P +E).

The entire process can be represented as follows;

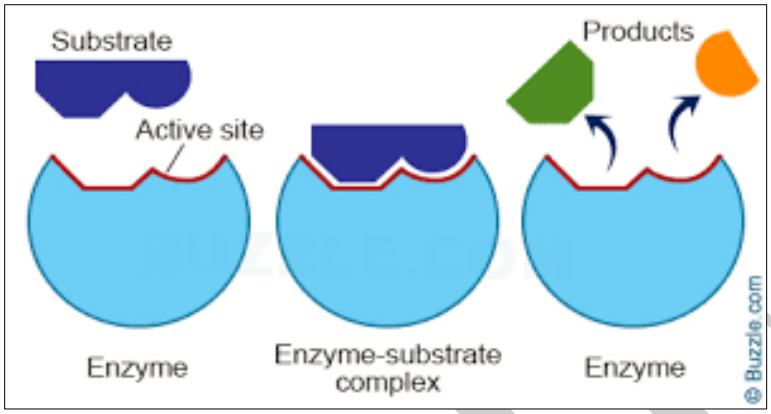



For example,



Arrhenius –scheme and existence of intermediate (E-S complex) has been verified by spectroscopic and experiments.

The above scheme can be diagramatically presented as




**Active site and specificity :-**

- The section of the enzyme surface which combines with the substrate to form E-S complex and the transformation of substrate to products occurs is known as active site of the enzyme.
- According to Emil-Fischer the confirmation of the active site and the substrate are complementary one fits into the other just like a particular key fits into a particular lock only.
- This key and lock theory explains the specificity of the enzyme, as a particular enzyme can catalyze a particular reaction only.

The characteristics of the active site are :

1. The site must offer perfect steric fitness for the substrate molecule(key & lock).

2. The site should offer mild attractive binding force to catch the molecule from solution and hold in the correct orientation for reaction.

Hydrogen bonds, ionic attractions and rapidly reversible covalent bonds fulfil this property.

3. The site should also provide whatever acidic or basic catalyst needed for reaction.

4. The product formed must not be tightly bound to the enzyme. It should rapidly leave after reaction.

**Factors influencing enzyme activity :-**

The following factors have an important influence on enzyme activity.

1. Substrate concentration

2. Enzyme concentration

3. Temperature

4. Effects of PH

5. Activators

6. Coenzymes / metabolic functions

7. Inhibitors.

**USES/APPLICATIONS:-**

The effectiveness of enzyme in biological processes is indeed, remarkable.

A chemist has to boil an average protein with 20% HCl acid for one day before he can break it down to amino acids completely, but our body does the same thing with the help of enzymes in less than four hours without using strong acids or high temperatures.

Thus enzymes are remarkably useful in carrying out some of the most vital biological processes. Enzymes have found a number of other applications also. For example,

**1.Fermentation :-**

Fermentation processes (ie. Processes not involving oxygen but carried on through the agency of enzymes) for the production of a variety of industrially important organic compounds like ethyl alcohol, butyl alcohol, acetic acid, lactic acid, citric acid, etc. have already been referred to.

The fermentation reactions are also employed extensively for the production of optically active substances like alkaloids [e.g. (-)-ephedrine], antibiotics (e.g.penicillin, streptomycin, etc), vitamins (e.g. vit $B_{12}$), etc.

Alcoholic beverages, cheese, curd (dahi) are also produced through fermentation techniques.

2. They have been used as an aid to medical treatment e.g. they can remove pus and dead tissue in severe burns to facilitate healing.

3. They have been used to clear wines which become cloudy on chilling.

4. They have been used to remove the stains of blood, beer, coffee, egg, etc, from clothes.

5. Tanning of leather is a complex process involving the actions of several enzymes.

6. Certain enzymes are useful in analytical work. For example, Urease is used in the estimation of urea.

7. Enzyme streptokinase is used to dissolve blood cloting, responsible for heart attack.

8. Their deficiency causes many diseases in man.

For example, lack of enzyme tyrosinase causes the disease albinism. Deficiency of phenyl alanine hydroxylase is responsible for congenital disease, phenyl ketone urea, causes accumulation of some compound in the body can causes brain damage and mental retardation.

**Text Books:**

**T1**: Finar, I.L., 2007. Organic Chemistry, Vol. II, Pearson Education, Singapore.

**T4**: Agarwal,.O.P, 2003. Natural Product Chemistry, Goel Publishing House, Meerut.

## POSSIBLE QUESTIONS:

### Part-A (1 Mark)

### Multiple Choice Questions (Each Question Carry One Mark)

1. Which one of the following statements is true?
a. Enzymes have names ending in ese
**b. Enzymes are highly specific in their action**
c. Enzymes are living organisms
d. Enzymes get activated on heating
2. Enzymes activity is controlled by
**a. $P^H$ of the solution**
b. Constant tempereture
c. Constant pressure
d. Harmones
3. Which of the following statement is not true regarding enzymes?
a. They catalyse only a paticular type of reaction
b. They remain active even after separation from the source
**c. They are destroyed after the competion of the reaction they catalyse**
d. They are irreversible destroyed at high temperature
4. The number of enzymes known is about
a. 10000
b. 100
**c. 750**
d. 26
5. Cholesterol is trasported from liver to extrahepatic tissues by
a. Chylomicrons
b. VLDL
c. HDL
**d. LDL**
6. Which two harmones are released from the posterior lobe of the pituitary gland?
a. ADH & GH

b. ACTH & TSH
**c. ADH & oxytocin**
d. TRH & CRH
7. Hormones released by nerve cells of the …… regulate hormones secreted by the
a. Hypothalamus, anterior pituitary
**b. Hypothalamus, posterior pituitary**
c. Anterior pituitary, hypothalamus
d. Cerebellum,posterior pituitary
8. What is the function of insulin ?
a. Agonistic to glucagon
b. Decreases glycogen storage in liver and muscle
**c. Reduce hyperglycemia**
d. Increase hyperglycemia
9. Which of these hormones is secreted in the liver?
a. Renin
**b. Somatomedin**
c. Erythropoietic
d. Estrogen
10. What is the ultimate purpose of hormones?
a. To maintain growth
b. To keep the brain functioning
c. To stimulate metabolism
**d. Biochemical massenger**
11. What is another name for thyroxine?
**a. Tetraiodothyronine**
b. Thyroid
c. Thymus
d. Triodothyronine
12. What is the target of ACTH?
a. Most cells
b. Thyroid gland
c. Mammary gland
**d. Adrenal cortex**
13. Addrenaline is ……
a. Produced by the adrenal cortex
**b. Adrenal cortex**
c. Released when the parasympathetic nervous system is stimulated
d. Thyroid gland
14. The plant hormone which is essential for cell division is
a. Ethylene
b. Auxin
c. Gibberellin
**d. Cytokinin**
15. The activities of the internal organs are controlled by the
a. Central nervous system

b. Peripheral nervous system
**c. Autonomic nervous system**
d. Enzymes

16. The seat intelligence andvoluntary action in the brain is
a. Diencephalon
**b. Cerebrum**
c. Cerebellum
d. Medulla oblongata

17. The gap between 2 neurons is known as
**a. Synapse**
b. Synopsis
c. Impluse
d. Synaptic node

18. Which one of the following is a plant hormone?
a. Thyroxin
**b. Cytokinin**
c. Insulin
d. Oestrogen

19. Part of brain that controls respiration,heart beat and peristalisis is ……
a. Cerebrum
b. Cerebellum
c. Pons
**d. Medulla**

20. The brain is responsible for
**a. Thinking**
b. Harmones
c. Enzymes
d. Produce thyroid

**Part-B (Each Carry 8 Marks)**

1. Discuss the position of angular methyl groups in cholesterol.

2. What are the salient characteristics of enzymes.

3. Discuss the constitution of Tyronine.

4. Illustrate the position of double bond in Cholesterol

5. Discuss the constitution of Tyronine.

6. Discuss the mechanism of enzyme action.

7. Illustrate the position of angular methyl groups and the structure of nucleus in cholesterol.

15CHU601

Karpagam Academy of Higher Education

Coimbatore-21

(For the candidate admitted on 2015 onwards)

Department of Chemistry

VI- semester

Chemistry of Natural Products

**UNIT IV- Objective Questions for online examination (Each carry 1 Marks)**

| Question | Option-A | Option-B | Option-C | Option-D | Answer |
|---|---|---|---|---|---|
| An example of a digestive hormone is | lipasc | pepsin | amylase | gastrin | gastrin |
| Ecolic ACP has its molecular weight as around | 9000 | 19000 | 39000 | 90000 | 9000 |
| The human body does not produce its | enzyme | DNA | Protein | Vitamin | Vitamin |
| Penicilin has | strongly basic | carboxylic group | no sulphur group | an amine | an amine |
| Carboxilic acid is | $CH_3COOH$ | $(COOH)_2$ | $C_6H_5OH$ | $C_6H_5COOH$ | $C_6H_5OH$ |
| Which one of the following statements is true? | enzymes have names ending in ese | enzymes are highly specific in their action | enzymes are living organisms | enzymes get activated on heating | enzymes are highly specific in their action |
| Enzymes activity is controlled by | $P^H$ of the solution | constant tempereture | constant pressure | harmones | $P^H$ of the solution |
| Which of the following statement is not true regarding enzymes? | they catalyse only a paticular type of reaction | they remain active even after separation from the source | they are destroyed after the competion of the reaction they catalyse | they are irreversible destroyed at high temperature | they are destroyed after the competion of the reaction they catalyse |
| The number of enzymes known is about | 10000 | 100 | 750 | 26 | 750 |
| Cholesterol is trasported from liver to extrahepatic tissues by | chylomicrons | VLDL | HDL | LDL | LDL |
| Which two harmones are released from the posterior lobe of the pituitary gland? | ADH & GH | ACTH & TSH | ADH & oxytocin | TRH & CRH | ADH & oxytocin |
| Hormones released by nerve cells of the …… regulate hormones secreted by the | Hypothalamus, anterior pituitary | Hypothalamus, posterior pituitary | anterior pituitary, hypothalamus | cerebellum,posterior pituitary | Hypothalamus, posterior pituitary |
| What is the function of insulin ? | agonistic to glucagon | decreases glycogen storage in liver and muscle | reduce hyperglycemia | increase hyperglycemia | reduce hyperglycemia |
| Which of these hormones is secreted in the liver? | renin | somatomedin | erythropoietic | estrogen | somatomedin |
| What is the ultimate purpose of hormones? | To maintain growth | To keep the brain functioning | To stimulate metabolism | biochemical massenger | biochemical massenger |
| What is another name for thyroxine? | tetraiodothyronine | thyroid | thymus | triodothyronine | tetraiodothyronine |
| What is the target of ACTH? | most cells | thyroid gland | mammary gland | adrenal cortex | adrenal cortex |
| Addrenaline is …… | produced by the adrenal cortex | adrenal cortex | released when the parasympathetic nervous system is stimulated | thyroid gland | adrenal cortex |
| The plant hormone which is essential for cell division is | ethylene | auxin | gibberellin | cytokinin | cytokinin |
| The activities of the internal organs are controlled by the | central nervous system | peripheral nervous system | autonomic nervous system | enzymes | autonomic nervous system |

| | | | | | |
|---|---|---|---|---|---|
| The seat intelligence andvoluntary action in the brain is | diencephalon | cerebrum | cerebellum | medulla oblongata | cerebrum |
| The gap between 2 neurons is known as | synapse | synopsis | impluse | synaptic node | synapse |
| Which one of the following is a plant hormone? | thyroxin | cytokinin | insulin | oestrogen | cytokinin |
| Part of brain that controls respiration,heart beat and peristalisis is …… | cerebrum | cerebellum | pons | medulla | medulla |
| The brain is responsible for | thinking | harmones | enzymes | produce thyroid | thinking |
| Which of the following hormones is released by thyroid? | insulin | thyroxin | trypsin | pepsin | thyroxin |
| Which body organ is surrounded by meanings? | heart and lungs | brain and heart | brain and spinal cord | spinal cord and lungs | brain and spinal cord |
| Part of brain that controls muscular coordination | cerebrum | cerebellum | pons | medulla | cerebellum |
| Which of the following hormones contains iodine? | adrenaline | testosferone | thyroxine | insulin | thyroxine |
| Which part of brain controls the posture and balance of the body? | cerebrum | cerebellum | pons | medulla | cerebellum |
| Which of the following best describes hormones? | hormones are relatively unstable and work | hormones are stable,long asting chemical | all hormones are lipid soluble | hormones are chemicalmessengers that are related | hormones are stable,long asting chemical |
| The receptor for steroid hormones lies | In the cytoplasms | With in the plasma memberane | with in the nuclear envelope | in the blood plasma | In the cytoplasms |
| Second messengers are activated in response to | steroid hormones | thyroxine | peptide hormones | they are irreversible destroyed at high temperature | peptide hormones |
| …… Regulates the kidney's retention of water its secretion | prolactin | oxytocin | thyroxine | vaspressin (ADH) | vaspressin (ADH) |
| …….. Hormones stimulates the adrenal cortex to produce several of its hormones | follicle - stimulating | luteinizing | adrenocorticotropic | growth | adrenocorticotropic |
| Parathyroid hormone acts to ensure that | calcium levels in the blood never drop too law | sodium levels in urine are constant | potassium levels in the blood don't escalate | the concentration of water in the blood is sufficient | calcium levels in the blood never drop too law |
| The adrenal cortex releases……. Which stimulates Na+ reabsorption by the kidneys | epinephrine | aldosterone | glucose | cortisol | aldosterone |
| A haloenzyme is | functional unit | enzyme | harmones | thyroid | functional unit |
| Adrenaline was the first harmones to be isolated by …….. | talkamine | walksman | langlykke | Benedict | talkamine |
| The molecular formula of adrenaline is | $C_9H_{13}O_3N$ | $C_9H_{12}O_3NCl$ | $C_{10}H_{15}O_3N$ | $C_{10}H_{15}O_4N$ | $C_9H_{13}O_3N$ |
| Adrenaline on treatment with ferric chliride it gives | blue colour | red colour | green colour | colourless | green colour |
| On fusion with KOH adrenalines gives ……. | vetatric acid | salicylic acid | protocatechuic acid | catechuic acid | protocatechuic acid |
| Adrenaline on methylation followed by oxidation it yields | veratric acid | protocatechuic acid | catecuic acid | salicylic acid | veratric acid |
| The dificiency of thyroxine hormones in childhood cause …….. | mental dificiency | blood haemorrhage | bone dificiency | beriberi | mental dificiency |
| A molecular weight of pepsin is | 39,200 | 40,000 | 39,000 | 39,800 | 39,200 |

| | | | | | |
|---|---|---|---|---|---|
| The optimum temperature for enzyme action is about | 30 - $40^0$c | 40 - $80^0$c | 20 - $40^0$c | 20 - $30^0$c | 20 - $40^0$c |
| enzyme actions are greatly influenced by …….. Variations | $P^H$ variations | heat variations | $P^{ka}$ variations | harmone | $P^H$ variations |
| The optimum $P^H$ for most of the enzyme action is about | 8 | 7 | 6 | 5 | 7 |
| Enzyme actions are usually carried out in ……. | concentrated solutions | dilute solutions | colloidal solutions | gelly | dilute solutions |
| The catalytic activity of enzymes are suggested by | Arrhenius | alexander fleming | paul berg | kerry mull | Arrhenius |
| Urease is used in the estimations of …… | Urea | thiourea | hydrazine | phenyl hydrazine | urea |
| Phenyl ketone urea cause ……. | heart diseases | brain damage | stomach diseases | bone deficiency | brain damage |
| Thyronine gives a brickred coloration with | milllon's reagent | fehling's solution | tollen's reagent | winkler's solution | millon's reagent |
| One treatment with ninhydrine thyroxine give …….. Colour | green colour | blue colour | red colour | colourless | blue colour |
| Noradrenaline is present in the …….. Part of adrenal body | medulla | cerebrum | cerebellum | bones | medulla |
| The molecular formula for cholesterol is | $C_{27}H_{46}O$ | $C_{27}H_{48}O$ | $C_{27}H_{46}O_4$ | $C_{26}H_{44}O$ | $C_{27}H_{46}O$ |
| Cholesterol react with selenium at $360^{0\,C}$ to yields | aldehyde | ketone | dicarboxylic acid | diel's hydrocarbon | diel's hydrocarbon |
| The form enzymes for these bio-organic catalysts was first used by | kuhne | waksman | Benediet | viuillemin | kuhne |
| Which one of the following is not a enzyme? | lipase | Rennin | urease | salicylic acid | salicylic acid |
| Vitamins of the group act as coenzymes for several enzymes | B | C | E | D | B |
| The residual proteinoid part is known as | enzyme | coenzyme | apoenzyme | enzymes activators | apoenzyme |

## UNIT-V
## SYLLABUS

***Chemotherapy:*** *Introduction – Classification of drugs – lethal dose –chemistry and application of sulpha drugs, Antimalarials, and Amoebicidal drugs, Antiseptics, Antipyretics, Analgesics and Antibiotics, Penicillin, Streptomycin, Chloromycetin, Tetracycline- Structure and uses only.*

## Introduction:

- Chemical substances used to prevent and cure disease by destroying infectious micro-organisms without destroying host tissues and keep us in a state of normal health are called drugs.
- Such chemical substances are known as chemotherapeutic agents. the system using these chemotherapeutic agents in prevention and treatment of disease is known as chemotherapy. These drugs/chemotherapeutic agents can be organic or inorganic in nature.

**Organic drugs may be classified as:**

1. **Natural drugs :**

- Drugs obtained from natural sources are called natural drugs. These are mostly obtained from plant kingdom.

  For example morphine (the pain killer ex opium),quinine (the antimalarial ex-cinchona)and reserpine or sarpagandha (anti-hypertensive from rauwolfia serpentine)etc, are some of the natural organic drugs.

2. **Synthetic organic drugs:** however , constitute an overwhelming number of drugs listed in the pharmacopoeias of the world .

- The science of drug is known as pharmacology. It deals with the knowledge of both chemistry and biochemistry.
- The drugs approved by the Govt are listed in pharmacopeia( a book on drugs approved by the Govt).

**Classification:** Synthetic drugs have been classified in a number of ways.These can be classified on the basis of application.

**For example:**

1. Antibacterial drugs,used against disease producing bacteria called pathogens.
2. Antiviral drugs,used for the treatment of disease caused by viruses.
3. Central nerves system drugs,used against nervous diseases.

4. Antipyrectics and analagesics,used to lower body temperature and to relieve pain e.g paracetamol,asprin,phenylbutazone,etc.
5. Antimalarials used against malarial parasite ie.plasmodium.
6. Antiseptic drugs eg. Chloromine-T, Dettol,etc.
7. Drugs in cancer therapy.

Yet another method of classification is based on the chemical structure of drugs.

Sulphonamides, Salicylates, Pyrazolones, Barbiturates, Tetracylines etc. belong to the system.

Drug is too vast subject to be discussed in a detail in a book of this type.

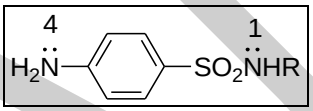
**Sulpha drugs:**

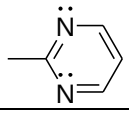
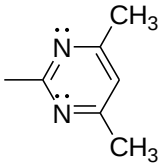
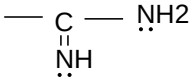
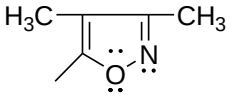
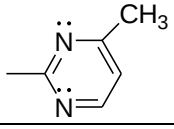
Table lists the commonly used sulpha drugs also called sulphnamides,with their structures and name .

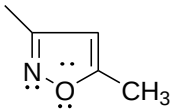
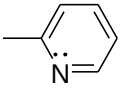
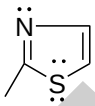
For naming them, the sulphonamide nitrogen is numbered $N^1$ and the amino nitrogen is numbered $N^{4.}$

**Table: Some commonly used sulpha drugs**

Basic structure:



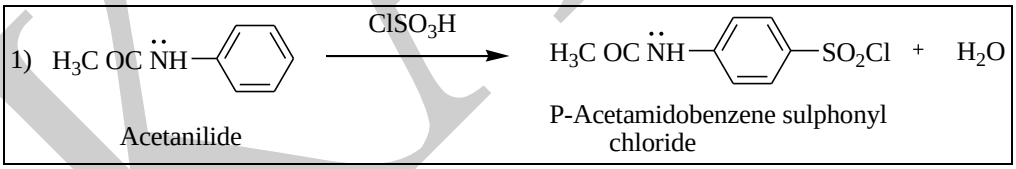

| S.No | Drug | R |
|---|---|---|
| 1 | Sulphanilamide | H |
| 2 | Sulphacetamide | $COCH_3$ |
| 3 | Sulphadiazine |  |
| 4 | Sulphaolimidine |  |
| 5 | Sulphaguanidine |  |
| 6 | Sulphisoxazole |  |
| 7 | Sulphamerazine |  |

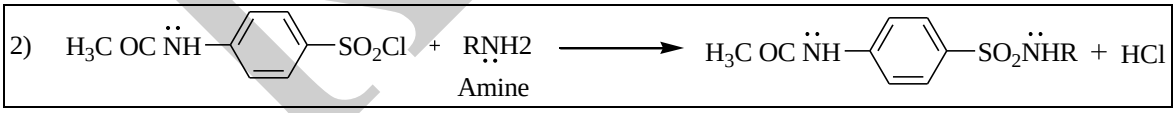
| | | |
|---|---|---|
| 8 | Sulphamethoxazole |  |
| 9 | Sulphapyridine |  |
| 10 | Sulphathiazole |  |

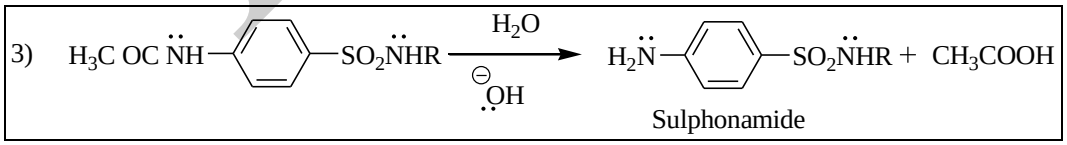
- The simplest and oldest sulpha drug is sulphanilamide .The other members are the derivatives of sulphanilamide. These drugs are effective against pathogenic bacteria which causes pneumonia,urinary tract infections, tuberulosis, gonorrohea, leprosy, lower respiratory infection, H-Influenza,etc.
- When hydrogen atom of $-SO_2NH_2$ group in sulphanilamide is replaced by other groups,a large variety of sulpha drugs can be synthesized.
- Their therapeutic use can be enhanced when hydrogen atom are sulphanilamide is replaced by a heterocyclic group.
  For example: sulphathiazole, sulphapyridine, sulphamerazine, etc.
- Sulphacetamide was mainly used for curing urinary tract infections.
- Sulphathiazole has saved the lives of wounded soldiers during the world war –II sprinkling on wounded to prevent infection.
- These derivatives are more effective than sulphanilamide towards infections.

**1. General synthesis of sulphonamides :**

- It can be synthesized from acetamide as follows :



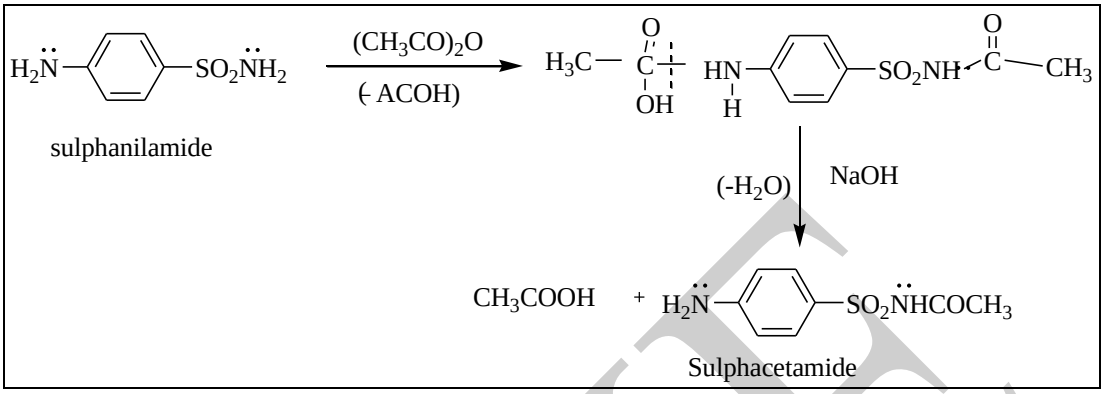




Remember that in step (3)-CONH Group is hydrolyzed more readily than $-SO_2NH$ Group.

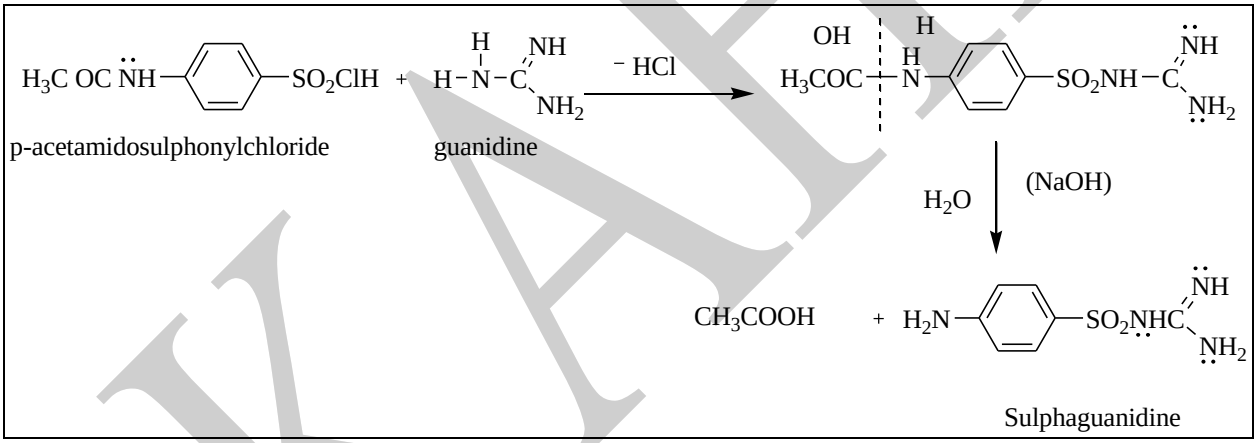
**2. Sulphacetamide:**

It can be synthesized from sulphanilamide by the acetylation of both $-NH_2$ and $-SO_2NH_2$ groups, followed by the selective alkaline hydrolysis of one acetyl group.



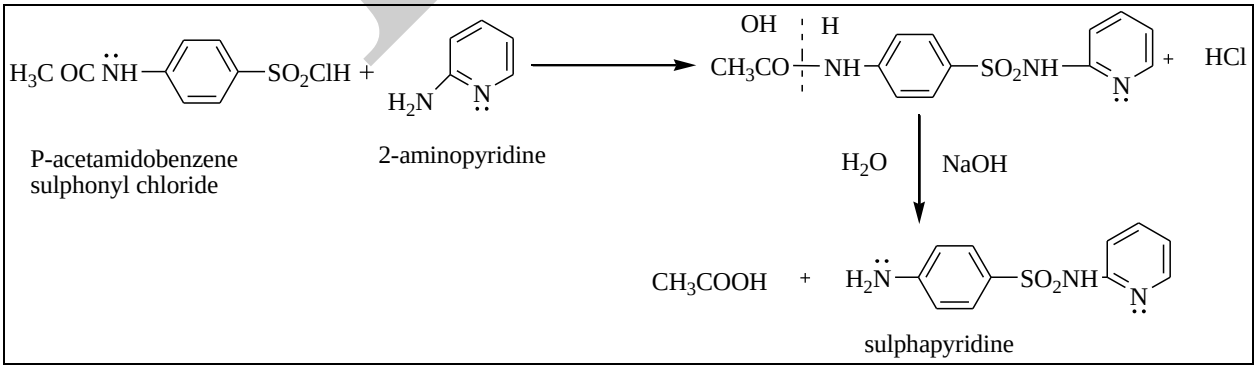

### 3. Sulphaguanidine:

It is synthesized by treating p-acetamidobenzene sulphonyl chloride formed in above synthesis 1(i) with guanidine.



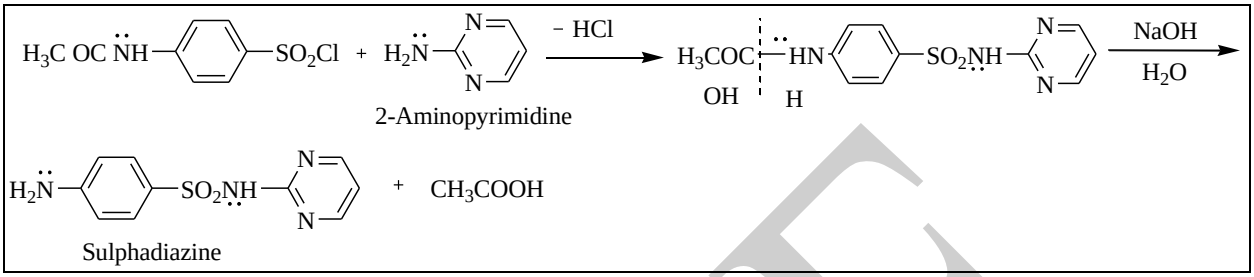

### 4. Sulphapyridine:

It is synthesized by the action of 2-aminopyridine on p-acetamidobenzene sulphonyl chloride.



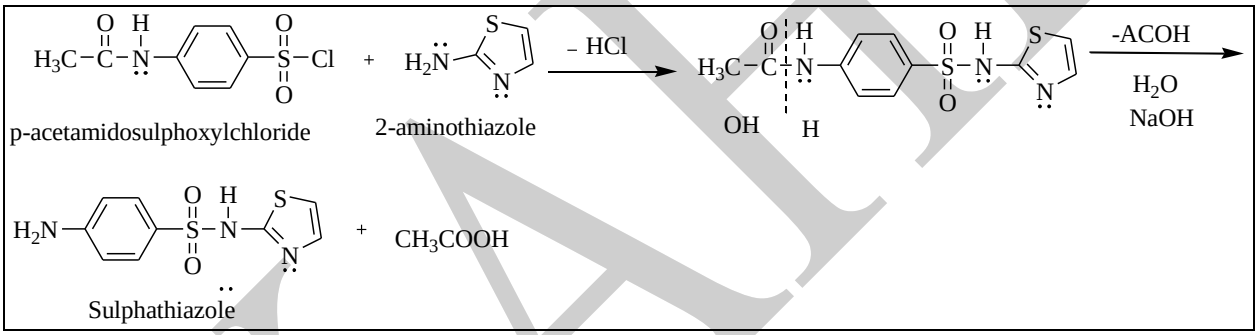
### 5. Sulphadiazine:

It is synthesized by the reaction of 2-aminopyrimidine on p-acetamidobenzene sulphonyl chloride followed by hydrolysis.




### 6. Sulphathiazole:

It is synthesized by the reaction of p-acetamidobenzene sulponylchloride with 2-aminothiazole followed by the hydrolysis.




**Uses:**

- The sulphonamides are the first effective chemotherapeutic agents used for the prevention and cure of bacterial infection in man.
- Those derived from pyrimidine (1,3-diazine) have been most successful in the clinical world.
- Although sulphonamides have been largely replaced by antibiotics in the treatment of infections, but they are still used where patients are intolerant to antibiotics.
- The individual sulphonamides do not differ much in their activity against specific microorganisms.
- However, they differ from one another in their degree of absorption, their diffusion to the body tissues and their rate of elimination from the body.
- Sulphadiazine (pyrimal), sulphadimidine, sulphapyridine, sulphisoxazole, sulphamethoxazole, and sulphathiazole for example are readily absorbed by the body.
- Sulphisoxazole(sulphafurazole), sulphamethizole, sulphamethoxazole and sulphaphenazole are used in the treatment of urinary tract infections.
- Sulphapyridine is useful in the treatment of certain type of dermatitis.

- Sulphadioxine has been used also in the treatment of leprosy.
- Sulphacetamide sodium in the form of the popular brands albucid and locula are applied locally in infections of the eyes.
- Sulphaguanidine which is poorly absorbed by the intestinal mucosa, has been used in the treatment of bacillary dysentery. It can be given in large doses without the development of high blood cevels and toxic side effects.
- Sulphathiazole is more patent than sulphapyridine in the treatment of streptococcal, staphylococcal, pnemococcal and gonococcal infections and is generally the drug of choice in the treatment of these infections.

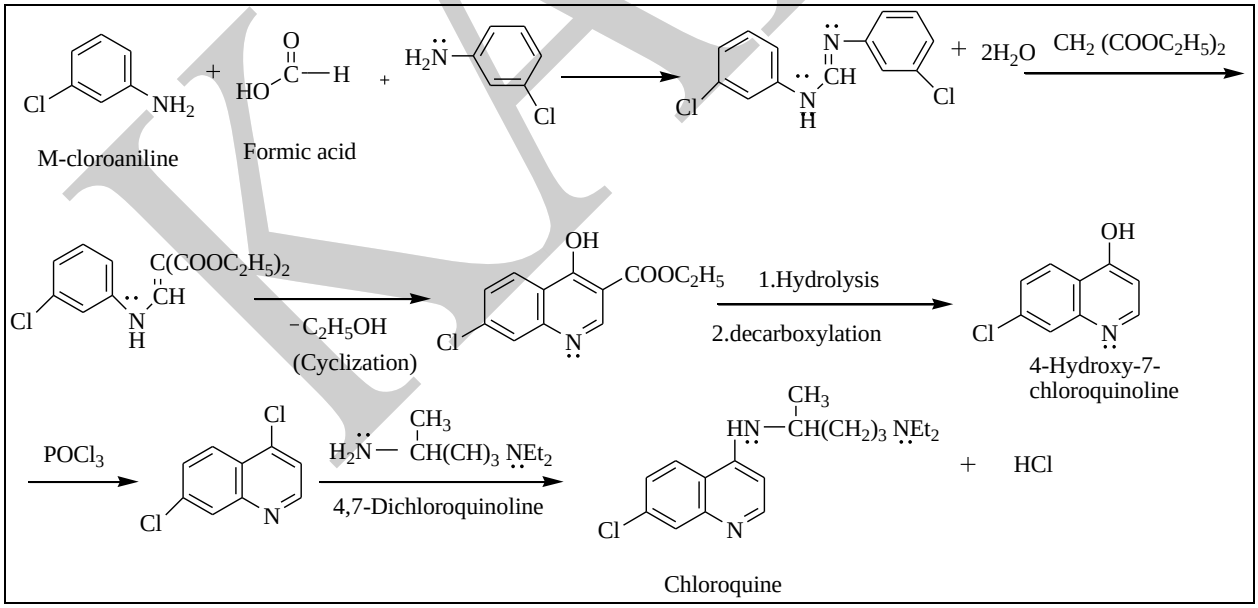
**Antimalarials:-**

- The drug used for suppression and treatment of the tropical disease malaria are called antimalarials. The chincona alkaloid quinine ( a quinoline derivative) was the well known natural antimalarial.
- Quinine has now been mostly replaced by synthetic antimalarials.

**Some representative synthetic antimalarials are described below:**

1. **Chloroquine:**

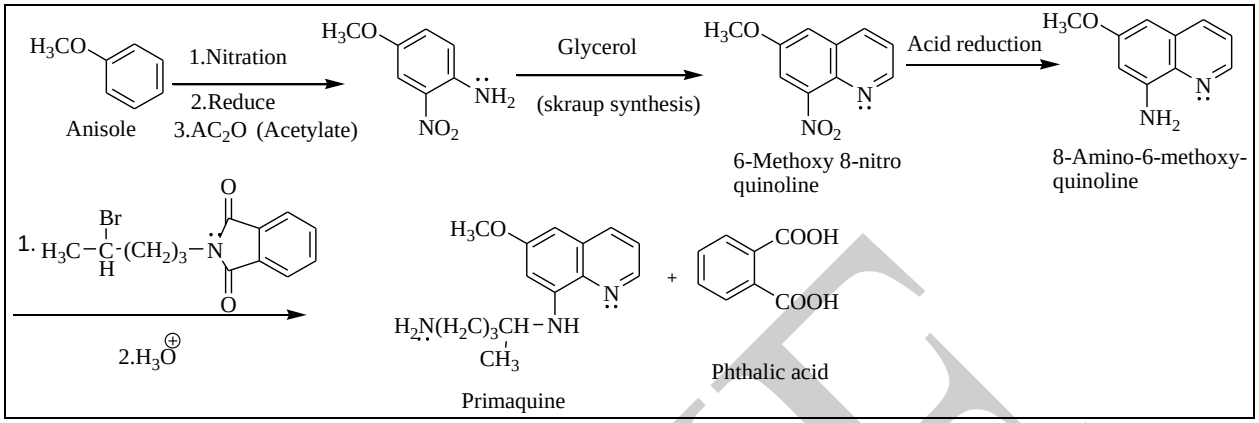
- It is much more effective antimalarial than quinine. Its synthesis from m-chloroaniline (2 mole) and formic acid is outlined below.




2. **Primaquine:**

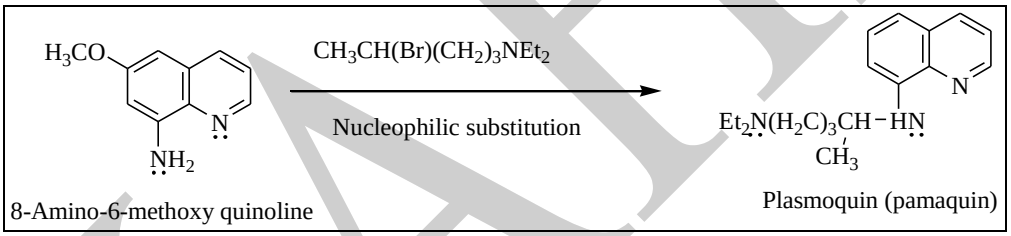
- It is a curative antimalarial with little suppressive action .it is a derivative of 8-amino-6-methoxy quinoline.

- Its synthesis from anisole (methoxy benzene) can be outlined as follows:



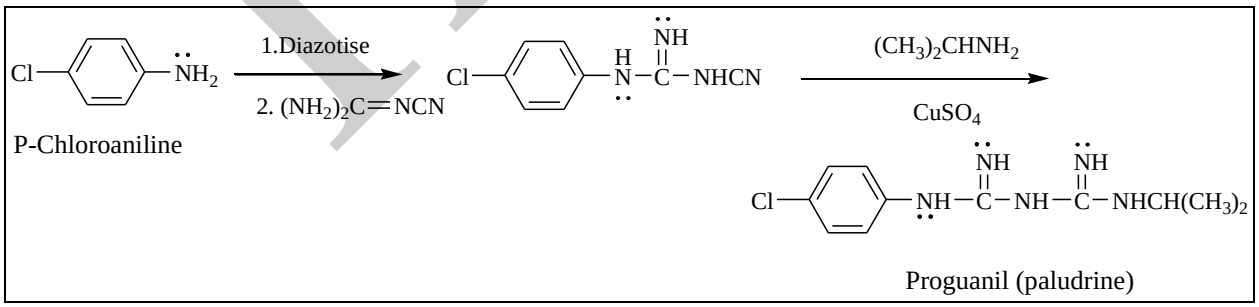

### 3. Plasmoquine (pamaquin):

It is closely related to primaquine. It may be regarded as N,N-diethyl substituted primaquine, utilizing $CH_3CH(Br)(CH_2)_3\ddot{N}(C_2H_5)_2$ in the last step of the synthesis of primaquine.




### 4. Proguanil (paludrive, chloroquanide)

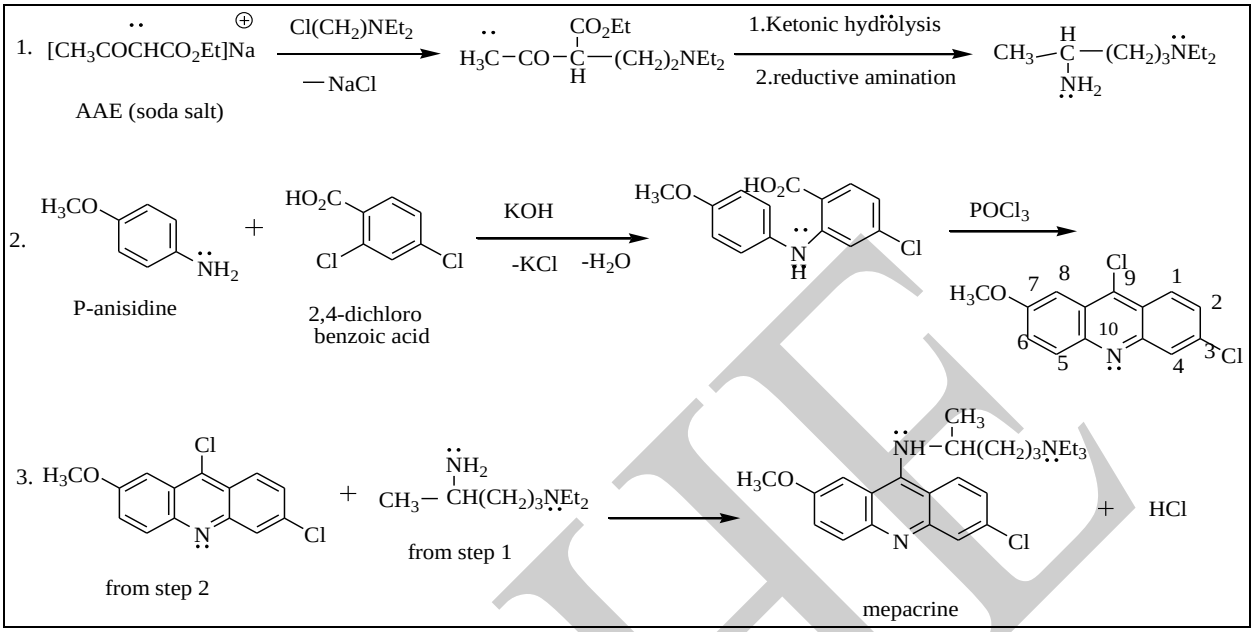
- **$N^1$ P-Chloro phenyl-$N^5$-isopropyl biguanide**
- It is an effective oral antimalarial with low toxicity and mild side effects.
- It is superior to chloroquine and mepactrine. It can be synthesized from p-chloroaniline as follows:




### 5. Mepacrine (Atebrine,Quinacrine)

- **3-chloro-9-($4^1$-dimethylamino-methylbytylamino)-7- methoxycridine**

- It is also a reputed antimalarial that can be synthesized as follows:




**Side effects:**

- Common side effects observed on prolonged use of antimalarials are abdominal pain, vomiting and cyanosis.
- Mepacrine may produce toxic effects in central nervous system.
- The foregoing account is by no means an exhaustive treatment of synthetic drugs used in modern clinical practice.

**Antipyretics and analgesics:**

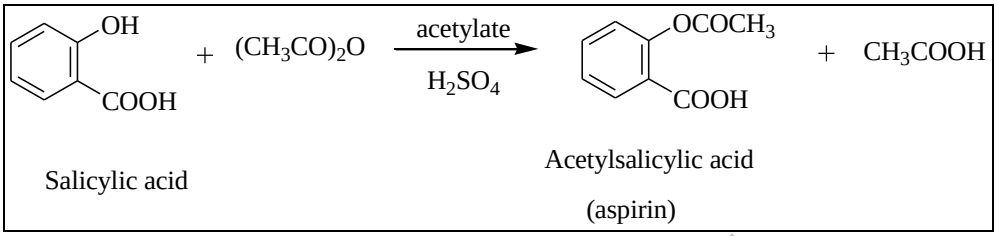
- Drugs used to lower body temperature in feverish conditions are called antipyretics.
- Analgesics are the drugs used to relieve pain in various conditions of health without loss of consciousness.
- The antipyretic action and the analgesic action are usually found together in the same drug. Many synthetic analgesic and antipyretics are known today common being aspirine, phenacetain,paracetamol, phenylbutazone,etc. some representative analgesics and antipyretics are described below:

**1. Aspirin (Aspro,Empirin,Acetylsalicylic acid):**

- Among salicylic acid derivatives, this is the most important synthetic analgesic,antipyretic and anti-inflammatory agent.
- It is also used as a blood thinner to prevent heart attack.

**Synthesis:**

- It consists in acetylating salicylic acid with acetic anhydride.

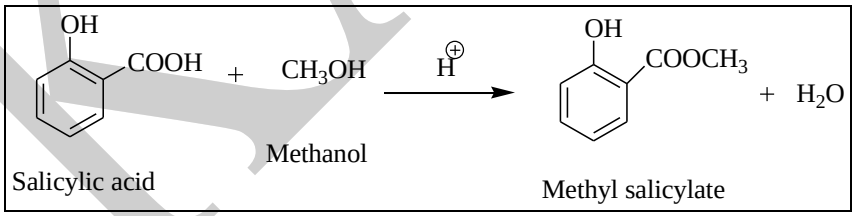



**Uses:**

- It is a common remedy for the relief of headache, muscular pain and toothache.
- However, its use in children is not recommended.
- The toxic side effect of "aspirin-therapy" is gastric irritation leading to ulceration.
- Therefore, it should not be taken on an empty stomach.
- It is used orally alone or in conjugation with caffeine or codeine (methyl ether of morphine).
- It is widely used in the treatment of acute and chronic states of rheumatism gout etc.
- The calciumsalt of aspirin, which is soluble in water, is better than simple aspirin, in that it has fewer undesirable side –effects and induces analgesia faster than aspirin.
- A familiar preparation of soluble aspirin is "Disprin". Disprin contains calcium carbonate and anhydrous citric acid besides aspirin and this renders aspirin water soluble.
- Disprin relieves pain faster than aspirin.
- It is also given to heart patients as blood thinner in combination with clopidogrel.

**2. Methyl salicylate (oil of winter green)**

- It can be prepared as follows:



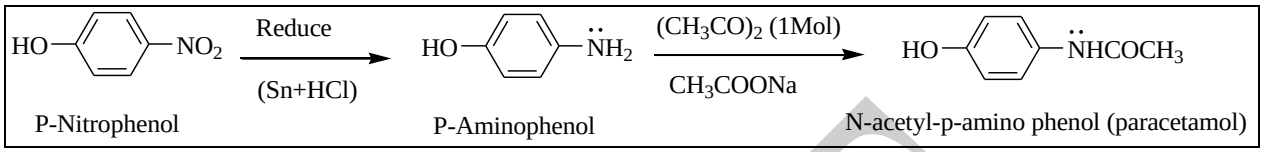

**Uses:**

- It occurs in nature and it can be made synthetically too.
- It is applied as such or in liniments and ointments, for the relief of pain of lumbago, sciatica and rheumatic conditions.
- It is also used as a flavouring agent.
- It is the main constituent of pain reliever ointments like "Iodex".

### 3. Paracetamol (Acetaminophen, p-acetamidophenol, N-acetyl-p-aminophenol).

**Synthesis:**

- It can be synthesized from p-nitrophenol as outlined below.

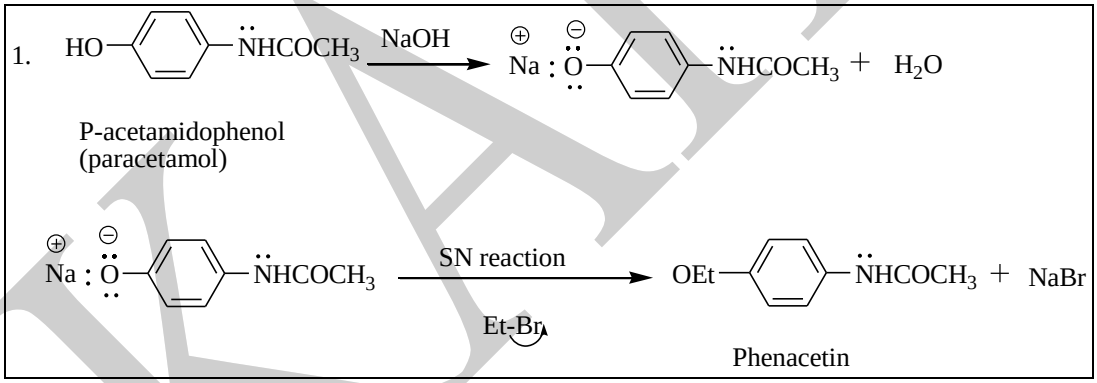


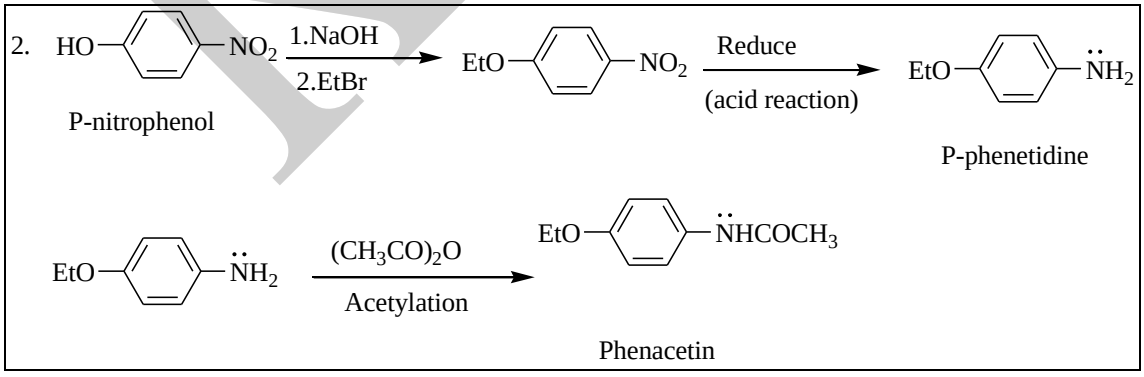

**Uses:**

- It has analgesic and antipyretic activities.
- It is being used as such under various trade names like crocin, metacin, etc.
- It is also marketed in combination with aspirin and caffeine.

### 4. Phenacetin (Acetophenetidine)

- It is the ethyl ether of paracetamol.
- **Synthesis:** it can be synthesized by either of the following schemes.



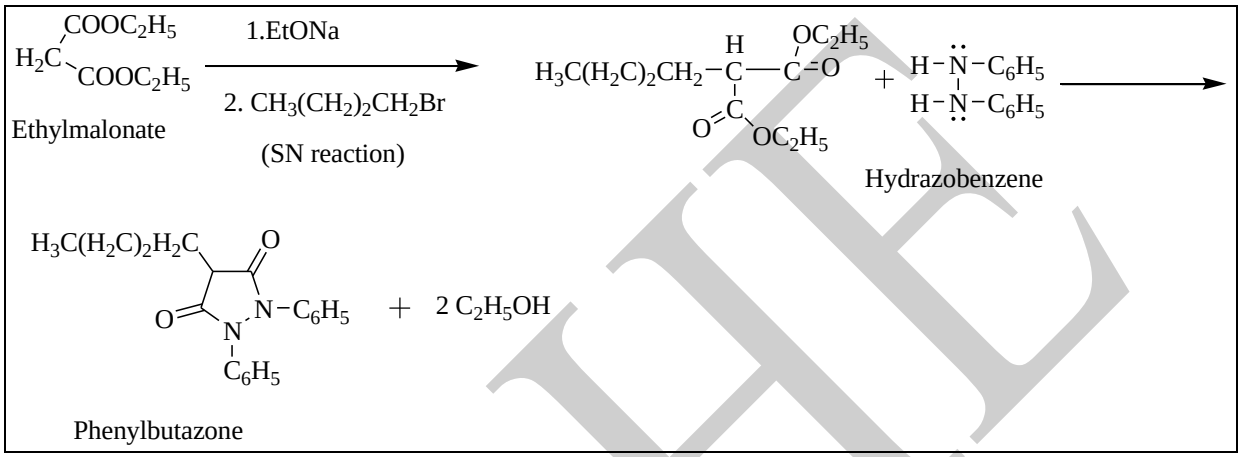




**Uses:**

- It has been widely used as an analgesic and an antipyretic, usually in combination with aspirin, caffeine and codeine.
- It has been found to be somewhat toxic in nature. It may damage kidneys, if used over long periods.

**5. Phenylbutazone (butazolidine or 4-n-butyl-1,2- diphenyl-3,5-pyrazolidinedione)**

- **Synthesis:** it can be synthesized from malonic ester.

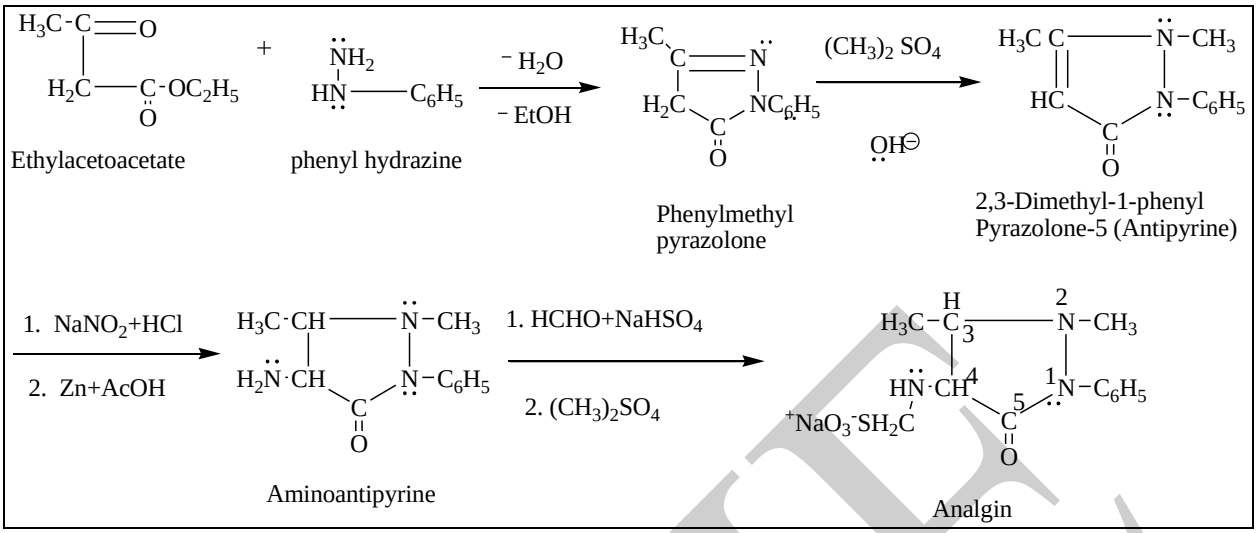



**Uses:**

- It is commonly used as an antiarthritic and anti inflammatory agent. Since it has many undesirable, **size effects**, it should be used under strict supervision of a doctor.

**6. Analgin ( metamezole, sodium 2,3- dimethyl-1- phenyl-5-pyrazolone-4-yl-N-methylaminomethane sulphonate)**

- **Synthesis:** it can be synthesized from ethyl acetoacetate.




**Uses:**

- It widely used for its analgesic and antipyretic properties.

**Antiseptics and disinfectants:**

**Antiseptics:**

- The chemical which retards the growth and multiplication of micro-organisms responsible for pus formation in skin cuts and wounds without harming the host tissues are called antiseptics.
- These are bacteriostatic and applied directly to infectious parts. These are often used the first aid treatment of cuts and abrasions.
- Their incorporation in mouth washes, toothpaste etc is generally observed.

**Disinfectants:**

- These are bactericides used to destroy harmful micro organisms. Their action is instant and short lived and generally applied to nonliving objects like surgical instruments, cloths, etc.

**Halo compound:**

1. **chloromine-T or chlorozone:**

- It is obtained from p-toluene sulphoxyl chloride. it is used as an antiseptic and disinfectiant(due to hypochlorite formed in situ).
- Its (.2%) aqueous solution is used to mucous membranes and 1%solution is used to dress wounds.
- Its disinfectant lotion is used in infectious diseases like scarlet fever, measles and in mouth washes.

2. **Dichloramine-T:**

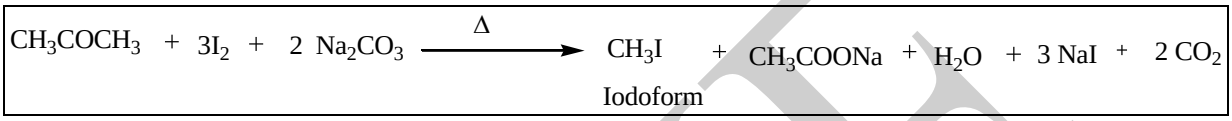
- It is obtained by treating p-toluene sulphonamide with bleaching powder.
- Its 5% solution in chlorinated paraffin is used in dressing wounds and 1% solution applied to mucous surfaces.

**3. Halozone(p- dichlorosulphamonyl benzoic acid):**

- It is obtained by the oxidation of dichloramin-T.it is a white crystalline powder with chlorine like odour and therefore, used for sterilizing drinking water.

**4. Iodoform:**

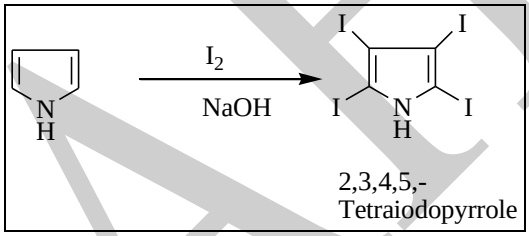
- It is prepared by heating acetone or alcohol with iodine and sodium carbonate solution.




- Its antiseptic property is due to slow release of iodine. It is mainly used as an antiseptic for dressing wounds.

**5. Tetra iodopyrole (Iodol):**

- It is prepared by the iodination of alkaline solution of pyrrole.




- Its antiseptic properly is similar to that of iodoform. It has advantage over iodoform due to its odourless and non-irritant property.

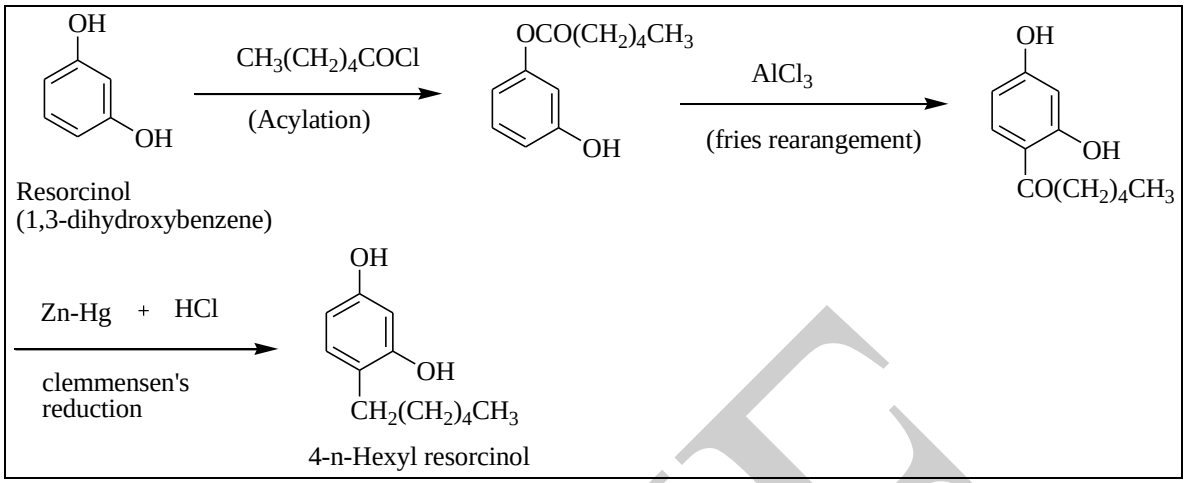
**6. Tincture of iodine:**

- It is a 2% solution of iodine in 50% alcohol containing 2.4gm NaI per 100ml of alcohol.
- The role of sodium iodide is to facilitate the dissolution of iodine.

**Phenolic compounds:**

**1) n-hexylresorcinol:**

- It is a urinary antiseptic and disinfectant for surgical instruments. Its phenol coefficient (Rideal walker value) is 147.



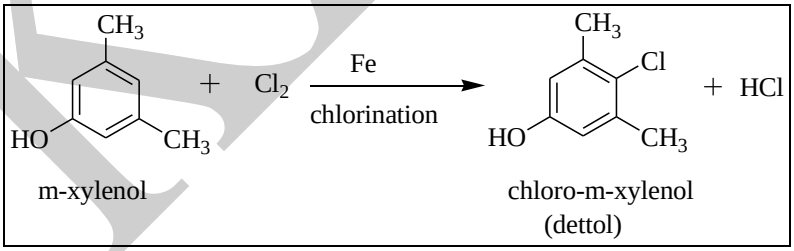

**Rideal walker value:**

The minimum concentration of phenol, which kills a 24 hours culture of B.typosus in certain length of time is first determined and then the concentration of the unknown antiseptic substance. Which produces the same condition is determined. This relation is termed as phenol coefficient (Rideal walker value).

$$\text{phenol coeff} = \frac{\text{conc. of antiseptic required to kil the the microorganism in unit time}}{\text{conc.of phenol required to kill the micro organism in unit time}}$$

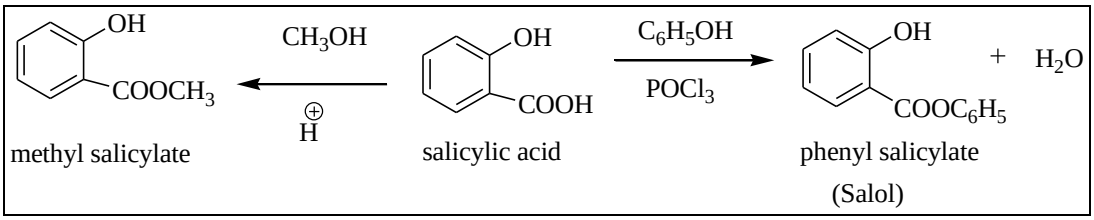
**2) Dettol(chloro-m-xylenol)**

It is obtained by chlorinating m-xylenol in presence of halogen carrier and in absence of light.




Its alcoholic solution, known as Dettol is widely used as an antiseptic for skin cuts and in dressing wounds.

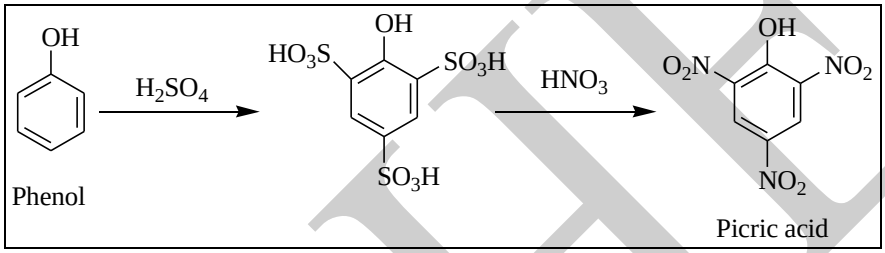
**3) Salol(phenyl salicylate)**




It is a powerful external as well as internal antiseptic.

**4) Picric acid:(2,4,6-trinitro phenol):**

Its therapeutic use is in the case of burns. It is four times more powerful as an antiseptic than phenol.

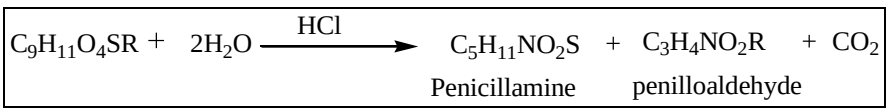



**The penicillins:**

- Penicillin is a generic term which refers to a class of compounds of the molecular formula $C_9H_{11}N_2O_4SR$. Produced by various strains of penicillium notatum, penicillium chrysogenum and various other moulds(fermentation)
- Moreover chemical studies of penicillin revealed that the initial product was a mixture of several different and closely related compounds.

**Constitution:**

1. The general molecular formula for the penicillins is $C_9H_{11}N_2O_4SR$.
2. They form mono salts indicating the presence of a carboxyl group.
3. Penicillins are not found to possess a free amino or thiol group.
4. On hydrolysis with hot dilute inorganic acids all the penicillins are degraded to the equimolecular amount of an amine,penicillamine, and an aldehyde, penilloaldehyde along with the elimination of one carbon atom as carbon dioxide.



Now since the fragment R comes in the aldehyde portion , all penicillins give the same amine,but different aldehydes.

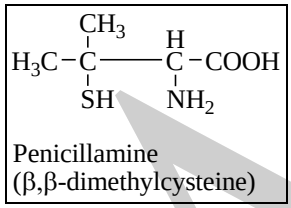
**5. Structure of D-penicillamine, $C_5H_{11}NO_2S$**

i. It gives colour reactions with sodiumnitroprusside and ferric chloride indicating the presence of a thiol (SH) group.
The presence of thiol group in penicillamine is again indicated by its oxidation to a sulphonic acid .

ii. Electrometric titrations of penicillamine show three pka values;1.8,7.9and 10.5 corresponding to carboxyl ,ά-amino,and thiol groups ,respectively.

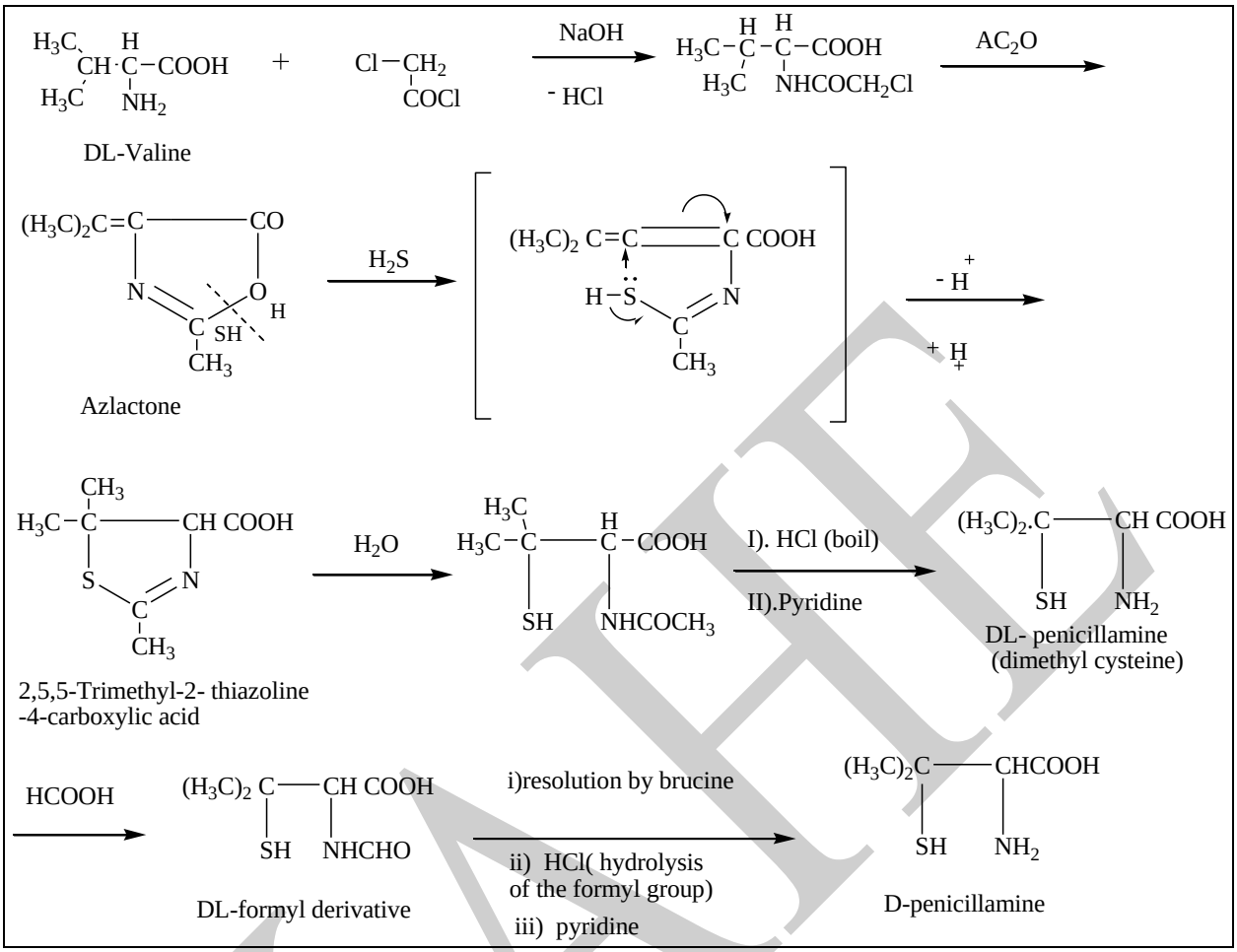
iii. Penicillamine when treated with acetone gives an isopropylidene derivative.
The latter does not contain any free amino or thiol groups are present on the adjacent carbon atoms of penicillamine.

iv. The Kuhn –Roth determination of methyl side chains gave a very low value (~0.2 molecules) indicating that the compound contains an isopropyl end-group and not a methyl end-group.
On the basis of the above points, penicillamine may be given the following structure.



Penicillamine
(β,β-dimethylcysteine)

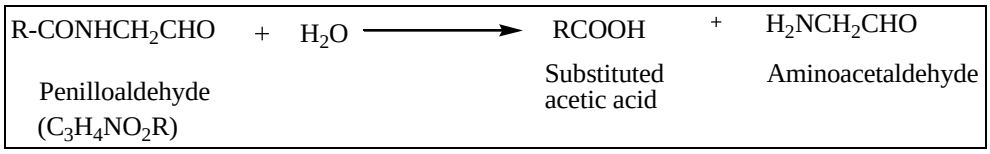
v. Finally ,penicillamine is proved to be D- β, β -dimethylcysteine by its synthesis.




**The above synthetic D-penicillamine was found to be identical with the natural penicillamine**

6. Pencillin on treatment with diazomethane is converted into its methyl ester which on treatment with an aqueous solution of mercuryl chloride gives the gives the methylester of penicillamine. This set of reactions clearly indicates that the carboxyl group of penicillamine is the carboxyl group of penicillin itself.
7. **Structure of penilloaldehyde ,$C_3H_4NO_2R$:**

i) The structure of penilloaldehydes as acylated derivatives of aminoacetaldehyde is proved by their vigorous hydrolysis to aminoacetaldehyde and a substituted acetic acid.

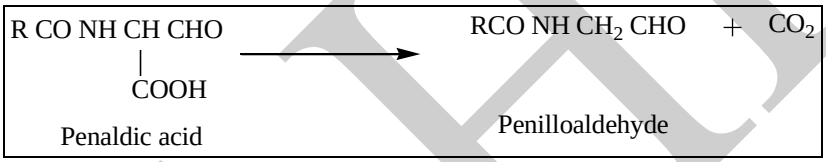


ii) The above structure for penilloaldehyde has been confirmed by synthesis from the corresponding acidchloride and aminoacetal.


iii) From point 4 it is obvious that a molecule of carbondioxide is obtained during acidic hydrolysis of pencillin .

The formation of $CO_2$ molecule suggests that some unstable acid is formed as an intermediate which on decarboxylation gives $CO_2$.

Such an acid is β -ketoacid and hence penilloaldehyde carboxylic acid (penaldic acid) must be formed as an intermediate in the hydrolysis of penicillin.



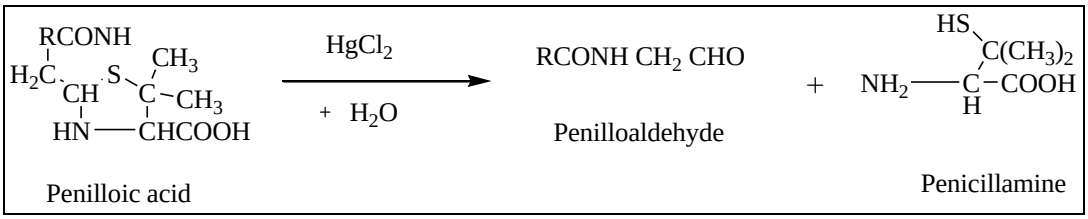

**8.** Now the problem at hand is to link the penicillamine and penilloaldehyde fragments to give penicillin in such a manner that the product also explains the formation of penaldic acid (to explain the formation of $CO_2$).This is established by the following fact.

Penicillin on hydrolysis with dilute alkali or with the enzyme penicillinase gives a dicarboxylic acid, penicilloic acid, which readily eliminates a carbondioxide molecules to yield a monocarboxylic acid ,penilloic acid.

This suggests that in penicilloic acid one of the carboxylic groups is in the β -position with respect to the negative groups (penaldic acid).

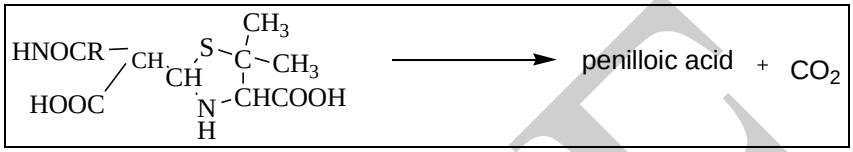
The structure of penilloic acid is established by its hydrolysis with aqueous mercuric chloride to penicillamine and penilloaldehyde ( a characteristic reaction of thiazolidine ring).

The thiazolidine type of nucleus in penicillin is proved by the fact it has neither free amino group nor a free thiol group.

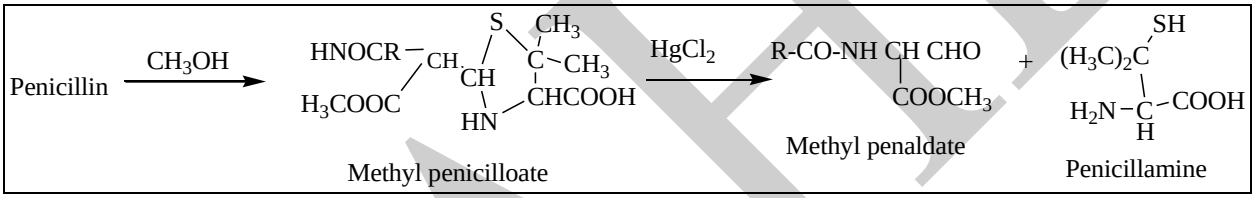



Penilloic acid — Penilloaldehyde — Penicillamine

Hence penicilloic acid must have the following structure .

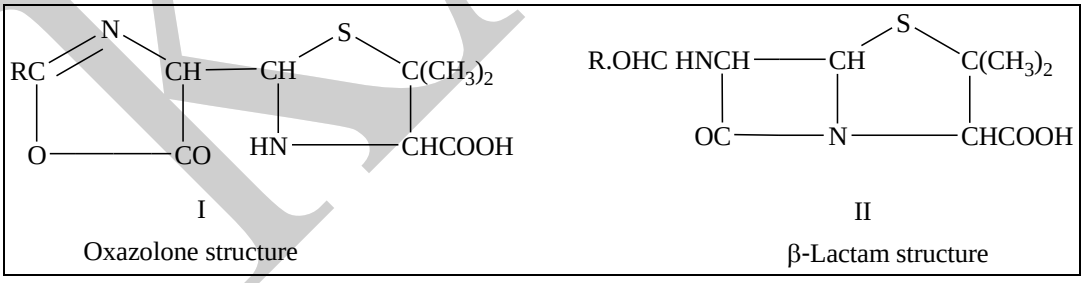



The above structure for penicilloic acid is proved by the fact that penicillin on treatment with methyl alcohol gives methyl penicilloate which on hydrolysis with aqueous mercuric chloride gives penicillamine and methy penaldate.

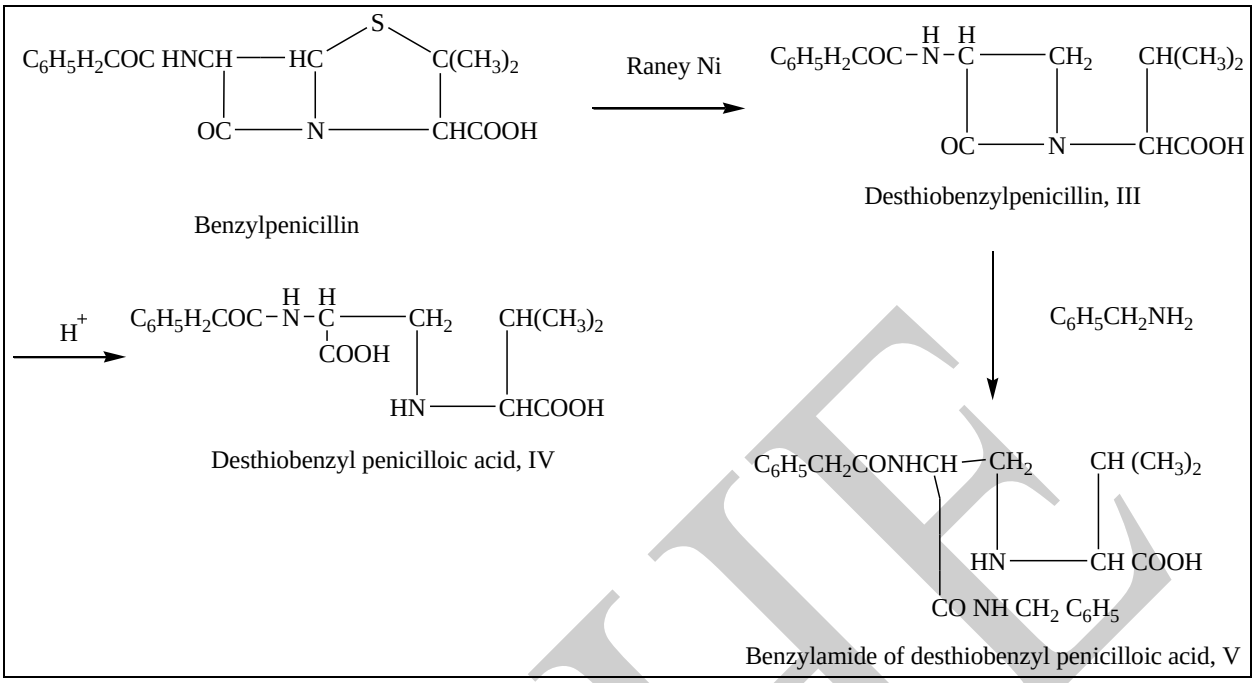



Methyl penicilloate — Methyl penaldate — Penicillamine

**9.** But we know that penicillin is monocarboxylic acid and the carboxyl group is present in the penicillamine molecule which is coming from the thiazolidine nucleus, the secondary carboxyl group of penicilloic acid may be present either as oxazolone or as β- lactum and thus penicillin might be I or II.

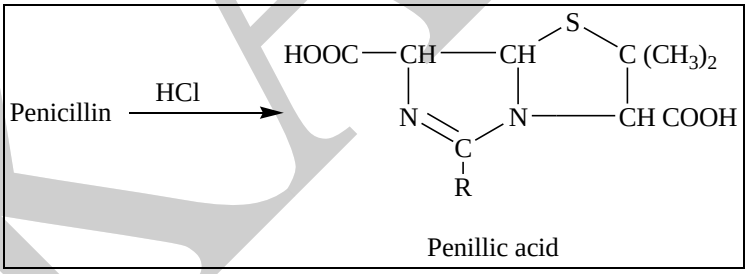



**10.** Definte evidence of the existence of the nickel to give desthiobenzylpenicillin III,which on hydrolysis by acid gives desthiobenzylpenicilloic acid IV or on boiling with benzylamine in dioxane solution gives benzylamide of desthiobenzylpenicilloic acid V.




The compound IV and V can be obtained by the desulphurization (with Raney nickel )of benzylpenicilloic acid and its benzylamide respectively.

**11.** However,it was not possible to decide the two possible structures of penicillin on chemical evidence alone,since penicillin readily undergoes molecular rearrangement ,e.g on treatment with dilute acid ,penicillin rearranges to penillic acid.




Hence, it was necessary to examine the molecule by some physical methods also.

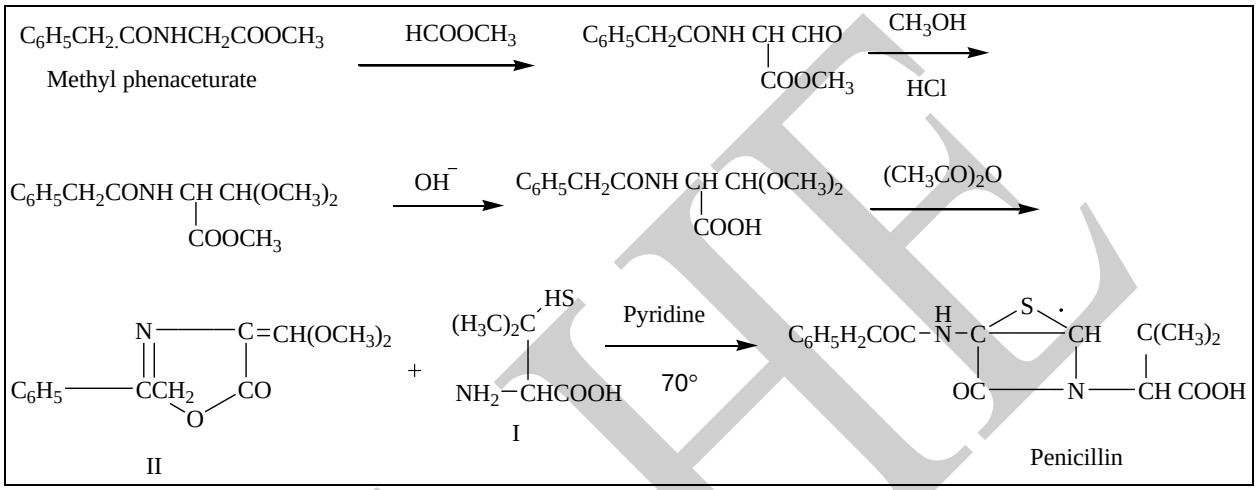
Infrared spectra of the methyl ester and sodium salt of benzylpenicillin correspond to the functional group of the β-lactum type structure and not to oxazolone type structure.

Moreover the X-ray analysis of the sodium, potassium and rubidium salts of benzylpenicillin showed the presence of a - β lactum ring.

**12. Synthesis of penicillins**

i) De vigneaud et al.(1946) obtained small quantities of penicillin by condensing D-penicillamine, I with 2-benzyl-4-methoxy methylene oxazolone, II in pyridine at 70◦c,the benzylpenicillin was isolated as the crystalline triethyl amine salt.

The starting material II is again obtained from methylphenaceturate in the following manner




**Chloramphenicol (chloromycetin):**

**D-(-)-threo-2-dichloroacetamido-1-p-nitrophenyl-propane-1,3-diol:**

It is the first antibiotic to be produced commercially by a synthetic process,rather than by a microbiological process.

It is also the first of the widely used broad spectrum antibiotics, ie antibiotics effective against both gram negative and gram positive bacteria.

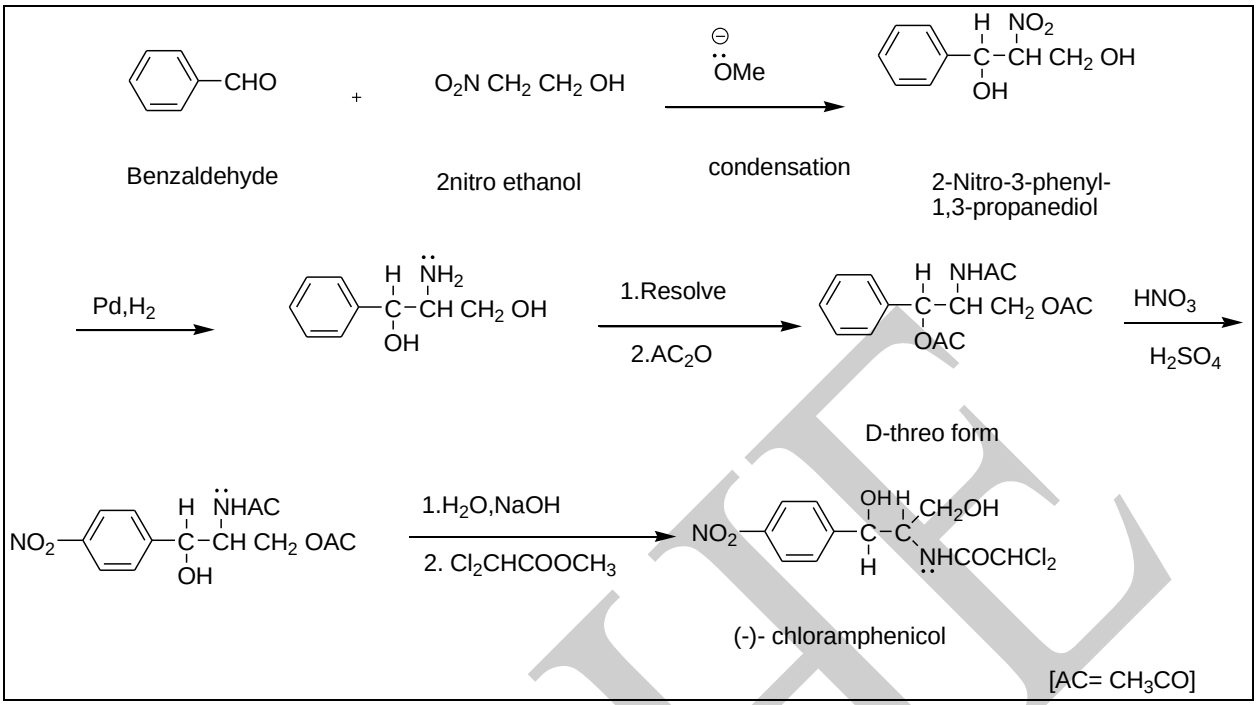
It was isolated by Ehrlich et al in 1947 from streptomyces venezuelea (an organism found in soil sample collected from Venezuela).

**Synthesis:**

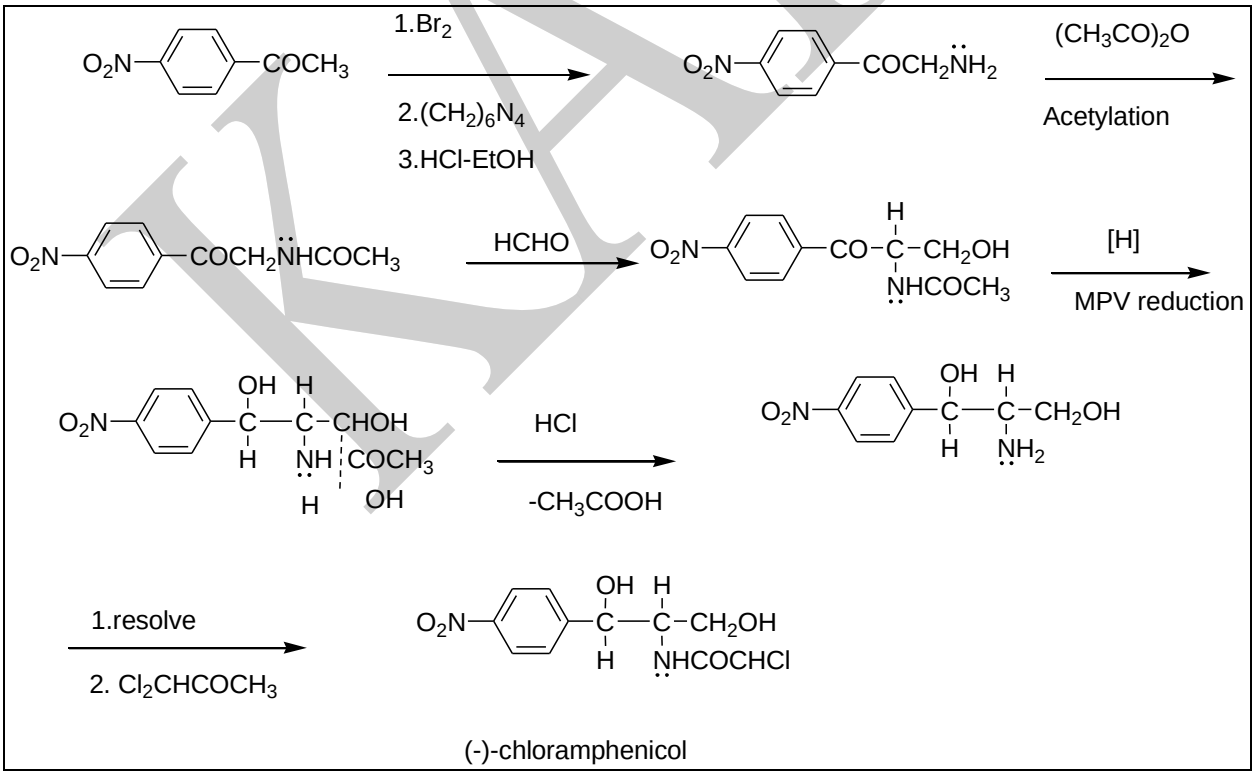
A number of synthetic routes are known.

Two such routes are described below.

**i)From benzaldehyde:**




**ii) From p-nitroacetophenone:**



It may be noted that chloramphenicol contains two chiral asymmentric carbons.Of the four possible stereo isomers,only one of them (leave form)with D-threo-configuration is the active chloramphenicol.

**Uses:**

It is very effective against a number of infections not responding to other drugs. It is practically effective in typhoid and paratyphoid fever.

However, its prolonged use can lead to many toxic reactions.

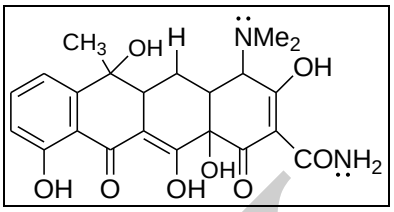
It is therefore, used only,when other antibiotics fail and that too under strict medical supervision.

**Tetracyclines:**

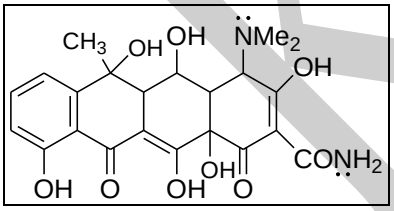
These are also broad spectrum antibiotics,having a bacteriostatic effect against a wide variety of gram +ve and gram –ve bacteria.

The following seven tetracyclines,commonly used in medical practices are:

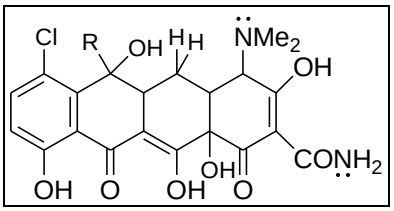
**1.Achromycin**




**2.Oxytetracycline or Terramycin:**

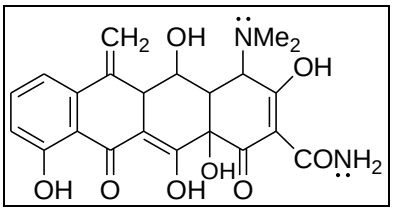



**3.chlorotetracycline (R=$CH_3$) or Auromycin:**

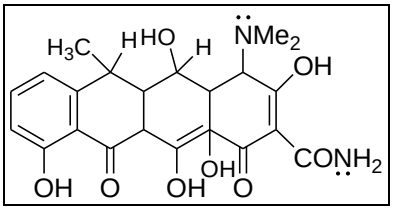


**4.Dimethyl Chlorotetracycline (R=H)**

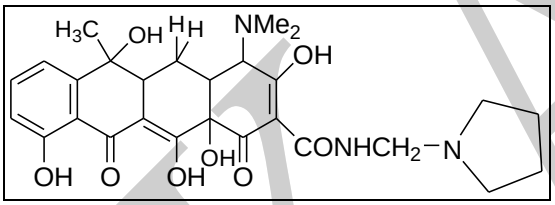
**5.Methacycline**




**6.Doxycycline**




**7.Rolitetracycline**




**Uses:**

These are widely used in the infections of the respiratory tract(e,g acute and chronic bronchitis),bacillary dysentery,urinary tract infections and in the treatment of typhus fever,Q-fever and undulant fever.

**Side effects:**

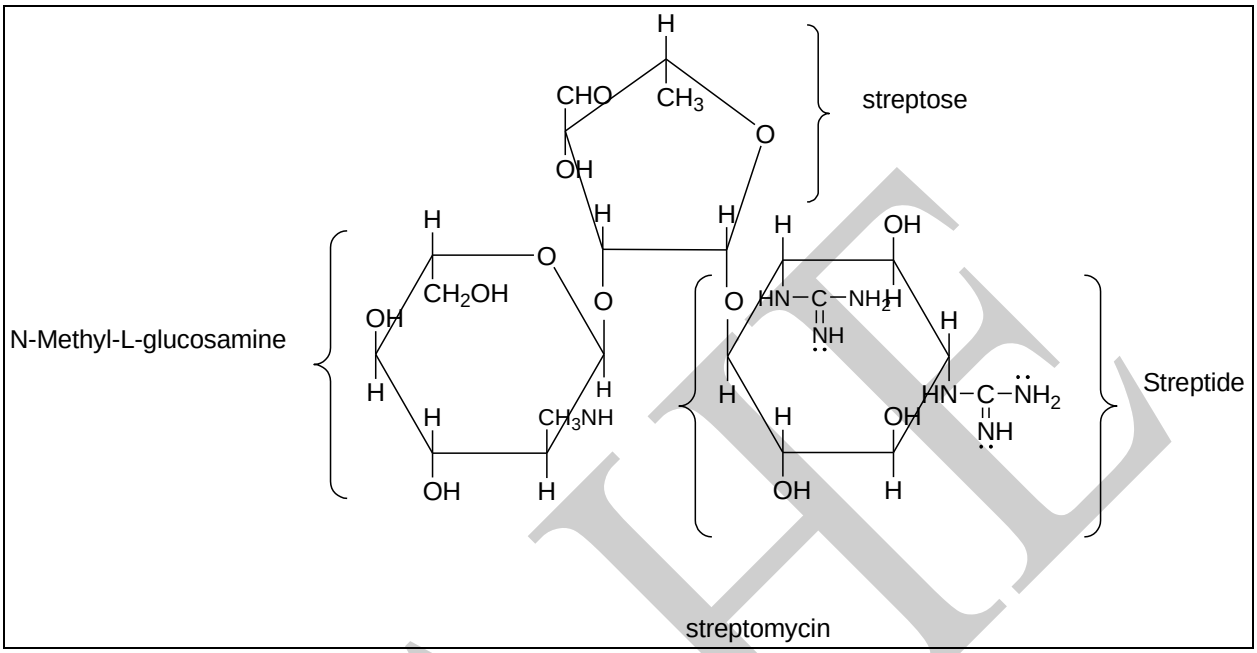
The commen side effects are nausea, vomiting,diarrohea and stomatitis.

**Streptomycin:**

It is a useful and effective drug in the treatment of pneumonia ,tuberculosis and meningitis.

It is leavorotatory and also used for throat and lung infections.

Its structure consists three units namely-streptose,N-methyl-L-glucosamine and streptidine.




**TEXT BOOKS:-**

**$T_1$**: Finar, I.L, 2013, "Organic Chemistry", Vol.II, Pearson Education, Singapore.

**$T_2$**: Gurdeep R. Chatwal, 2013, "Organic Chemistry of Natural Products", Vol. II, Himalaya Publishing House, New Delhi.

**REFERENSE:**

**R1**: M.K./Jain, S.C.Sharma, 2012, Modern Organic chemistry, Vishal Publishing Co, Tagore press, Jalandhar.

**WEBSITE:**

**W1**: http// lethal dose

## POSSIBLE QUESTIONS:

### Part-A (1 Mark)

### Multiple Choice Questions (Each Question Carry One Mark)

1. Aspirin is also knows as
**a. Acetylsalicylic acid**
b. Salicylic acid
c. Catecuric acid
d. Protocatecuic acid
2. Salicylic acid react with methanol to give
a. Acetylsalicylate
**b. Methyl salicylate**
c. Aspirin
d. Phenyl salicylate
3. Aspirin is used as a
**a. Blood thinner**
b. Flavouring agent
c. Analgesic
d. Antiarthritic
4. Which of the following is best definition of antibioties?
a. Chemicals that inhibit or kill microorganisms
b. Chemical produsedby microbes that inhibit or kill other microorganisms but are relatively harmless to
c. Chemicals that inhibit or kill bacteria
**d. Chemicals produced by microbes that inhibit or kill other microorganisms**
5. Bactericidal agents typically work by
**a. Inhibiting cell wall synthesis**
b. Inhibiting protein synthesis
c. Inhibiting harmone synthesis
d. Enhancing cell wall synthesis
6. Penicillin and gentarmycin 2 different classes of antibiotic have been shown to engage in with each other in certain infectionms
**a. Synergism**
b. Antagonism
c. Indifference
d. Antisynergism
7. Which of the following antibiotic is a tetracycline?
a. Chloramphenitol
**b. Doxycycline**
c. Erythromycin
d. Streptomycin
8. Which of the following antibiotics is responsible for greybaby syndrome?
**a. Chloramphenitol**
b. Doxycycline
c. Erythromycin
d. Streptomycin
9. What crucial feature of a penicillin is involved in its mechanism of action?
a. Carboxylic acid
**b. β - lactum ring**
c. Acylside chain

d. Thiazole ring

10. Sulpha drugs are used as ……
a. Antimalarial
b. Analgesic
**c. Antibacterial**
d. Antipyretics

11. Which one is the main constituent of pain reliever index?
a. Acetyl salicylic acid
**b. Methyl salicylate**
c. Phenacetin
d. Paracetamol

12. The main constituent of the drug crocin ( used an antipyretic and analgesic
a. Phenacetin
b. Acetylsalicylic acid
c. Phenyl butazone
**d. Paracetamol**

13. Methyl salicylate is also called as
**a. Iodex**
b. Paracetamol
c. Chloramphenicol
d. Calpol

14. Barbiturates are generally used as
**a. Sadatives**
b. Antiseptics
c. Disinfectants
d. Antitubercular

15. Thiacetazone in combination with isoniazid is used as a drug for
a. Malaria
**b. Tuberculosis**
c. Typhoid
d. Cancer

16. Tetracyclines are used as an ……
**a. Antibiotics**
b. Antimalarial
c. Antileprotic
d. Antitubercular

17. Peropandid is used as an ……
a. Analgesic
**b. Intravenous anaesthetic**
c. Antibiotic
d. Anticeprotic

18. Which one of the following drugs is used in the treatment of lymphocytic leukaemia?
**a. Chlorambucil**
b. Neosalvarson
c. Atoxyl
d. Chloral

19. Which one of the following drugs is used as dilator of arteries and veins?
a. Procaine
b. Lignocaine

c. Livodopa
**d. Glyceryl trinitrate**

20. The drug used to lower body temperature are called …….
**a. Antipyretics**
b. Analgesics
c. Disinfectants
d. Antimalarial

**Part-B (Each Carry 8 Marks)**

1. Explain the synthesis and uses of Aspirin.

2. Illustrate the structure of Penicillamine

3. Write notes on Antiseptic-halo compounds?

4. Discuss the synthesis and uses of Chloremphenicol.

5. Explain the preparation and properties of the following Sulpha drugs
(i) Sulphacetamide (ii) Sulpha guanidine (iii) Sulpha pyridine

6. Discuss the synthesis and uses of Chloromycetinl.

7. Illustrate the structure of Penicillamine.

8. Explain the synthesis of the following compounds.
(i)Chloroquine (ii) Proguanil

9. What are antiseptics? Explain any three syntheses of antiseptics?

15CHU601

Karpagam Academy of Higher Education

Coimbatore-21

(For the candidate admitted on 2015 onwards)

Department of Chemistry

VI- semester

Chemistry of Natural Products

**UNIT V- Objective Questions for online examination (Each carry 1 Marks)**

| Question | Option-A | Option-B | Option-C | Option-D | Answer |
|---|---|---|---|---|---|
| The science of drug is know as | pharmakokineties | pharmacology | pharmacopoea | chemotherapy | pharmacology |
| Antibacterial drugs, used againest disease producing bactoria called | pathogens | viruses | nervous diseases | plasmodium | pathogens |
| Sulphapyridine is useful In the treatment of | leprosy | urinary tract infections | dermatitis | eye infection | dermatitis |
| Sulphadioxine is used in the treatment of | leprosy | uinary tract infections | dermatitis | eye infection | leprosy |
| Aspirin is also knows as | acetylsalicylic acid | salicylic acid | catecuric acid | protocatecuic acid | acetylsalicylic acid |
| Salicylic acid react with methanol to give | acetylsalicylate | methyl salicylate | aspirin | phenyl salicylate | methyl salicylate |
| Aspirin is used as a | Blood thinner | flavouring agent | analgesic | antiarthritic | Blood thinner |
| Which of the following is best definition of antibioties? | chemicals that inhibit or kill microorganisms | chemical produsedby microbes that inhibit or kill other microorganisms but are relatively harmless to | chemicals that inhibit or kill bacteria | chemicals produced by microbes that inhibit or kill other microorganisms | chemicals produced by microbes that inhibit or kill other microorganisms |
| Bactericidal agents typically work by | inhibiting cell wall synthesis | inhibiting protein synthesis | inhibiting harmone synthesis | enhancing cell wall synthesis | inhibiting cell wall synthesis |
| Penicillin and gentarmycin 2 different classes of antibiotic have been shown to engage in with each other in certain infectionms | synergism | antagonism | indifference | antisynergism | synergism |
| Which of the following antibiotic is a tetracycline? | chloramphenitol | doxycycline | erythromycin | streptomycin | doxycycline |
| Which of the following antibiotics is responsible for greybaby syndrome? | chloramphenitol | doxycycline | erythromycin | streptomycin | chloramphenitol |
| What crucial feature of a penicillin is involved in its mechanism of action? | carboxylic acid | β - lactum ring | acylside chain | thiazole ring | β - lactum ring |
| Sulpha drugs are used as …… | antimalarial | analgesic | antibacteril | antipyretics | antibacteril |
| Which one is the main constituent of pain reliever index? | acetyl salicylic acid | methyl salicylate | phenacetin | paracetamol | methyl salicylate |
| The main constituent of the drug crocin ( used an antipyretic and analgesic | phenacetin | acetylsalicylic acid | phenyl butazone | paracetamol | paracetamol |
| Methyl salicylate is also called as | iodex | paracetamol | chloramphenicol | calpol | iodex |
| Barbiturates are generally used as | sadatives | antiseptics | disinfectants | antitubercular | sadatives |
| Thiacetazone in combination with isoniazid is used as a drug for | malaria | tuberculosis | typhoid | cancer | tuberculosis |
| Tetracyclines are used as an …… | antibiotics | antimalarial | antileprotic | antitubercular | antibiotics |
| Peropandid is used as an …… | analgesic | intravenous anaesthetic | antibiotic | anticeprotic | intravenous anaesthetic |
| Which one of the following drugs is used in the treatment of lymphocytic leukaemia? | chlorambucil | neosalvarson | atoxyl | chloral | chlorambucil |
| Which one of the following drugs is used as dilator of arteries and veins? | procaine | lignocaine | livodopa | glyceryl trinitrate | glyceryl trinitrate |
| The drug used to lower body temperature are called …… | antipyretics | analgesics | disinfectants | antimalarial | antipyretics |
| Paludraine belongs to which class of drug | analgesic | antimalarial | antileprotic | disinfectant | antimalarial |
| Penicillin has …… thiazolidine structure | β - lactum | γ - lactum | δ - lactum | pyrimidine | β - lactum |
| Antiseptics are | bactericidal | bacteriostatic | antileprotic | anaesthetic | bacteriostatic |

| | | | | | |
|---|---|---|---|---|---|
| Neosalvarsan is used as a drug in the treatment of | leprosis | syphilis | tuberclobis | malaria | syphilis |
| Phenyl salicylate is also called as …….. | picric acid | salol | dettol | tincture | salol |
| 2,4,6 - trinitrophenol is also called as …….. | picric acid | salol | dettol | tincture | picric acid |
| The cinchona alkaloid …….. Was the well known natural antimalarial | quinine | isoquinine | primaquine | chloroquine | quinine |
| Chemicals tht inhibit the growth of microbes re called | antibiotics | antigen | antibodies | anticoagulate | antibodies |
| Sulphapyridine is useful in the treatment of……. | dermatitis | leprosy | urinary track infections | eye infections | dermatitis |
| Sulphadoxine as been used also in the treatment of ……. | dermatitis | leprosy | urinary track infections | eye infections | leprosy |
| Streptomycin was isolated by …… | waksman | fleming | ehrlich | Khun | waksman |
| Chloramphenicol was isolated by | waksman | fleming | ehrlich | Khun | ehrlich |
| Chloramphenicol is …….. Taste | bitter | sweet | salty | hot | bitter |
| Tetracyclines contain ……skeleton as a characteristic structure unit | hydronaphthacene | naphthacene | isoprene | anthracene | hydronaphthacene |
| …….is considered as the queen of drugs | penicillin | chloro mycetin | tetracyclines | streptomycin | penicillin |
| The general moleculer formula for the penicillin is | $C_9H_{11}N_20_4SR$ | $C_9H_{12}N_20_4SR$ | $C_{10}H_{11}N_20_4SR$ | $C_9H_{11}N_30_4SR$ | $C_9H_{11}N_20_4SR$ |
| Electromeric titrations of penicillamine show three $P^{ka}$ valuse | 1.8 , 7.9 & 10.5 | 1.8 , 7.8 & 10.5 | 1.8 , 7.9 & 10.4 | 1.8 , 7.7 & 10.5 | 1.8 , 7.9 & 10.5 |
| Penicillamine when treated with acetone gives an …… derivatives | isopropane | isopropylidene | isobutane | isobutylidene | isopropylidene |
| Penicilins are all strong mono basic acids with a $P^H$ value of about …….. | 3 | 2.8 | 2.6 | 2.4 | 2.8 |
| …… is a widely used antibiotic as it inhibits the growth of both gram positive and negative bacteria | amphicillin | erythromylin | chloromycetin | acethromycin | amphicillin |
| Penicillin treated with HCL it gives | penilloic acid | penilic acid | penicilloic amine | penilloaldehyde | penilic acid |
| Antibiotic has been derived from the word | antibiotics | antimalarial | antifungal | antitumor | antibiotics |
| The term antibiotic was first of all introduced by | vuillemin | waksman | benedict | langlykke | vuillemin |
| What type of ring system present in steroils? | 1,2 - cyclopentano phenentrene | 1,3 - cyclopenten | 1,2 - cyclohexene | benzene | 1,2 - cyclopentano phenentrene |
| Penicillic acid form when treated with penicillin and…….. | Hcl | $H_2S0_4$ | $HN0_3$ | $NH_40H$ | Hcl |
| Fleming was discovered by | penilloic | penillo aldehyde | penillic acid | penilloic acid | penilloic |
| Actyl salicylic acid is also known as | salicylic acid | protocatecuic acid | aspirin | methyl salicylate | aspirin |
| Penicillin treated with ….. It gives penillic acid | Hcl | $H_2S0_4$ | $HN0_3$ | NaoH | Hcl |
| Penicilliamine when treated with…….gives an isopropylidene | acetone | chloroform | Ammonia | $H_2S0_4$ | acetone |
| What is the another name of salol? | phenylsalicyclate | picric acid | dettol | tincture | phenylsalicyclate |
| What is the another name of iodex? | Methyl salicyclate | Paracetamol | Chlorampinicol | phenyl salicylate | Methyl salicyclate |
| Methyl salicylate form, when …….react with ……? | Salicyclic acid, methanol | Salicylate,methanol | Paracetamol,ethanol | Salicylate, ethanol | Salicylic acid, methanol |
| Which of the following used as a blood thinner ……..? | Analgesic | Antianthritic | aspirin | Salicyclic acid | aspirin |
| Which of the following used as a dermatitis ……..? | Sulpha pyridine | Leprosy | aspirin | methyl salicylate | Sulpha pyridine |
| Picric acid is also called …….? | 2,4,6 - Trinitrophenol | 2,4,5 - Trinitrophenol | 1,3,5 - Trinitrophenol | 2,4,6 - Trinitrophenol | 2,4,6 - Trinitrophenol |

Reg.No.....

[15CHU601]

**KARPAGAM ACADEMY OF HIGHER EDUCATION**
**COIMBATORE-21**
**(For the candidates admitted from 2015 & onwards)**
**B.SC DEGREE EXAMINATION**
**SIXTH SEMESTER**
**CHEMISTRY**
**CHEMISTRY OF NATURAL PRODUCTS**
**INTERNAL TEST-I**

**DATE:** **SUBJECT CODE: 15CHU601**
**TIME: 2 HRS** **TOTAL: 50 MARKS**

**SECTION-A** **(20x1=20)**

**ANSWER ALL THE QUESTIONS:**

1. Citral is treated with aqueous $Na_2CO_3$ it gives
(a) Methylheptenone and acetaldehyde (b) Methylheptenone and benzaldehyde
(c)Ethylheptenone and acetaldehyde (d)Ethylheptenone and benzaldehyde

2. Geraniol is oxidized with $Na_2Cr_2O_7$/ $H_2SO_4$ it gives
(a) Geranic acid (b) Geranial (c ) Dipentene (d) Menthol

3. Isoprene is heated in a sealed tube at 280°c
(a) Methene (b) Dipentene (c ) Menthol (d) Cyrene

4. Thymol is heated with hydrogen in the presence of nickel catalyst
(a) Dipentene (b) Menthene (c ) Menthol (d) Cyrene

5. Menthol is heated with $KHSO_4$ it gives
(a) Dipentene (b) Menthene (c )Menthol (d) Geraniol

6. α- pinene is heated with dilute $H_2SO_4$ it gives
(a) Geraniol (b) Cyrene (c ) Myrcene (d) α- Terpenol

7. Dipentene is treated with sulphur it gives
(a) Para – Cymene (b) para – Menthane (c ) Myrcene (d) Geraniol

8. On oxidation of geraniol with $KMnO_4$ it gives
(a) Levulinic acid (b) α - Terpinol (c)Nerol (d) Menthol

9. Lemmon grass is sources of
(a) Thymol (b)citral (c)Myrcene (d)Menthol

10. β-Carotene imparts orange colour to
(a) Orange (b) Papaya (c) Carrots (d)Mango

11. Lycopene imparts red colour to
(a)Apple (b)Plums (c)Watermelon (d) Cherry

12. Dipentene is treated to 280°C it gives
(a) p-menthane (b)Isoprene (c)P-cymene (d) myrcene

13. Dipentene is heated with HBr gives
(a)Dihydrobromide (b)Tetrabromide (c) Menohydrobromide
(d)Trihydrobromide

14.What is the isoprene rule
(a)Terpenes contains tait to tail connected isoprenes (b) Terpenes contain 5n atoms
(c)Terpenes contains head to tail connected isoprenes (d)Terpenes contain head to head connected isoprenes

15. Oxidation of conine with $KMnO_4$ gives
(a) α - picolinic acid (b) β - picolinic acid (c ) γ - picolinic acid
(d) tropic acid

16. On fusion with con. KOH quinine gives
(a) 6 - methoxy quinoline + lipidine (b) quininic acid (c ) meroquinene
(d) 6 - hydroxy quinoline

17. Quinine on oxidation with chromic acid gives quininic acid and
(a) Lutidine (b) Meroquinene (c ) Formic acid (d) Pyridine - 3 - carboxylic acid

18. Meroquinene on reduction with Zn & HI gives
(a) γ – picoline (b) Cincholoipon (c ) Cincholoipoxic acid (d) Loipidic acid

19. Give one example of piperidine alkaloids?
(a) Conine (b) Nicotine (c ) Anabasine (d) Morphine

20. Nicotinic acid reacts with soda lime to give
(a) Pyrrole (b) Piperidine (c ) Pyrrolidine (d) Pyridine

**SECTION- B** **(3x10=30)**

**ANSWER ALL THE QUESTIONS:**

21. (a). Explain the synthesis and constitution of Geraniol.

OR

(b). Convert the following
i.alpha-pinene to Terpenylic acid

ii. Pinol to Sebreythritol

22. (a).Explain the structural elucidation and synthesis of Dipentene.

OR

(b).Explain isoprene rule with suitable example.

23. (a).Discuss the structural elucidation of nicotine?

OR

(b). Illustrate Hofmann's exhaustive methylation with suitable example.