

B.Sc. Semester – VI

Subject: - CHE - 602: Terpenoids

Prepared By: - Dr. Dipen Shah

➤ Contents:

- ✓ Introduction
 - ✓ Occurrence
 - ✓ Classification of Terpenoids
 - ✓ Isolation of Terpenoids (mono and sesquiterpenoids)
 - ✓ General properties of Terpenoids
 - ✓ General methods of structure elucidation
 - ✓ Constitution and Synthesis of:
 - A. Citral
 - B. α -Terpineol
-

➤ Introduction

There are many different classes of naturally occurring compounds. Terpenoids also form a group of naturally occurring compounds majority of which occur in plants, a few of them have also been obtained from other sources. Terpenoids are volatile substances which give plants and flowers their fragrance. They occur widely in the leaves and fruits of higher plants, conifers, citrus and eucalyptus.

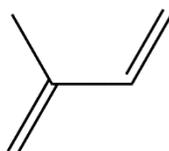
The term 'terpene' was given to the compounds isolated from turpentine, a volatile liquid isolated from pine trees. The simpler mono and sesqui terpenes are chief constituent of the essential oils obtained from sap and tissues of certain plant and trees. The di and tri terpenoids are not steam volatile. They are obtained from plant and tree gums and resins. Tetraterpenoids form a separate group of compounds called 'Carotenoids'.

The term 'terpene' was originally employed to describe a mixture of isomeric hydrocarbons of the molecular formula $C_{10}H_{16}$ occurring in the essential oils obtained from sap and tissue of plants, and trees. But there is a tendency to use more general term 'terpenoids' which include hydrocarbons and their oxygenated derivatives. However the term terpene is being used these days by some authors and scientist to represent terpenoids.

➤ Isoprene rule:

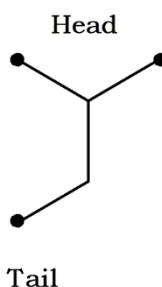
Thermal decomposition of terpenoids give isoprene as one of the product. Otto Wallach pointed out that terpenoids can be built up of isoprene unit. Isoprene rule states that the terpenoid molecules are constructed from two or more isoprene unit.

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



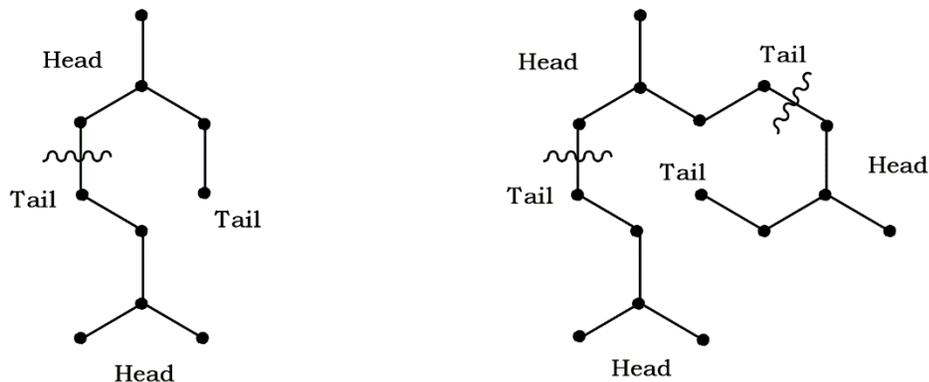
Isoprene Unit

Further Ingold suggested that isoprene units are joined in the terpenoid via 'head to tail' fashion. **Special isoprene rule** states that the terpenoid molecule are constructed of two or more isoprene units joined in a 'head to tail' fashion.

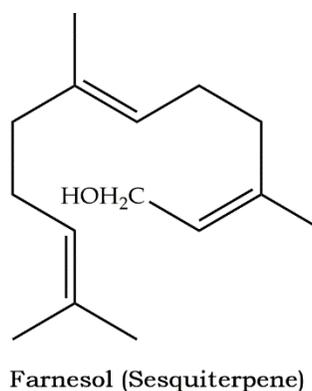
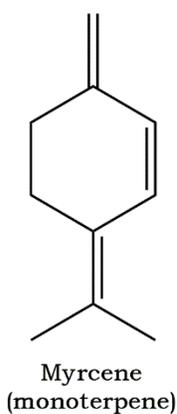


But this rule can only be used as guiding principle and not as a fixed rule. For example carotenoids are joined tail to tail at their central and there are also some terpenoids whose carbon content is not a multiple of five.

In applying isoprene rule we look only for the skeletal unit of carbon. The carbon skeletons of open chain monoterpenoids and sesqui terpenoids are,

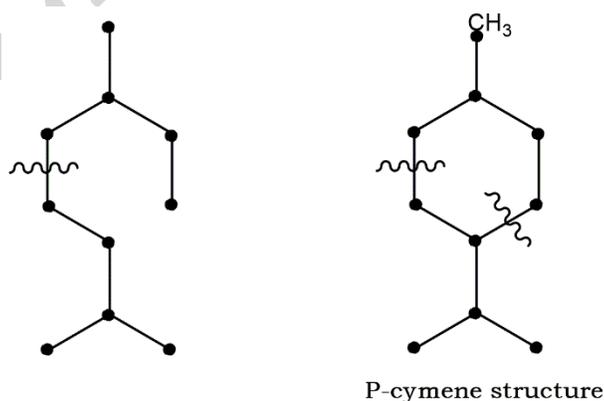


Examples

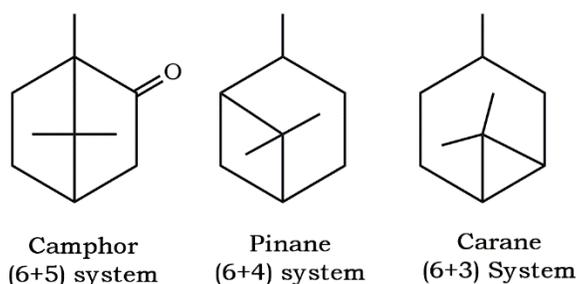


Ingold (1921) pointed that a gem alkyl group affects the stability of terpenoids. He summarized these results in the form of a rule called 'gem dialkyl rule' which may be stated as "Gem dialkyl group tends to render the cyclohexane ring unstable whereas it stabilizes the three, four and five member rings."

This rule limits the number of possible structure in closing the open chain to ring structure. Thus the monoterpene open chain give rise to only one possibility for a monocyclic monoterpene i.e. the p-cymene structure.



Bicyclic monoterpene contain a six member and a three member ring. Thus closure of the ten carbon open chain monoterpene gives three possible bicyclic structures.



➤ Classification of Terpenoids

Most natural terpenoid hydrocarbon have the general formula $(C_5H_8)_n$. They can be classified on the basis of value of n or number of carbon atoms present in the structure. Thus the classification can be given as follows.

S.No.	Number of carbon atoms	Value of n	Molecular Formula	Class	Examples
1	5	1	C_5H_8	Hemiterpenoids	Prenol, Isovaleric Acid
1	10	2	$C_{10}H_{16}$	Monoterpenoids	Myrcene, Limonene
2	15	3	$C_{15}H_{24}$	Sesquiterpenoids	Zingiberene, Farnesol
3	20	4	$C_{20}H_{32}$	Diterpenoids	Phytol, Abietic Acid
4	25	5	$C_{25}H_{40}$	Sesterpenoids	Ophiobolin A, Ceroplastol
5	30	6	$C_{30}H_{48}$	Triterpenoids	Hopane, Squalene
6	35	7	$C_{35}H_{56}$	Sesquarterpenoids	Ferrugicadiol
7	40	8	$C_{40}H_{64}$	Tetraterpenoids	Carotenoids, Lycopene
8	>40	>8	$(C_5H_8)_n$	Polyterpenoids	Rubber

Each class can be further subdivided into subclasses according to the number of rings present in the structure.

- i) Acyclic Terpenoids: They contain open structure. (e.g. Myrcene, Geraniol)
- ii) Monocyclic Terpenoids: They contain one ring in the structure. (e.g. Limonene)
- iii) Bicyclic Terpenoids: They contain two rings in the structure. (e.g. camphor)
- iv) Tricyclic Terpenoids: They contain three rings in the structure. (e.g. Copaene)
- v) Tetracyclic Terpenoids: They contain four rings in the structure. (e.g. Monoalide)

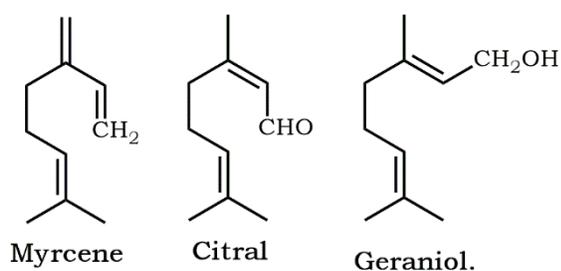
On the basis of the functional group the contain oxygen in various functional groups. The terpenoids can also be classified as follows.

S.No.	Name of the functional group	Formula of the functional group	Example
1	Hydroxyl (Alcoholic)	-OH	α -Terpenol, Menthol
2	Hydroxyl (Phenolic)	-OH	Carvacrol, Carnosol
3	Ketone	$>C=O$	Camphor, Capsorubin
4	Aldehyde	-CHO	Citral, Myrtenal
5	Carboxylic Acid	-COOH	Ursolic Acid, Betulinic Acid
6	Hydrocarbon	C_nH_m	α -Pinene, Zinziberene

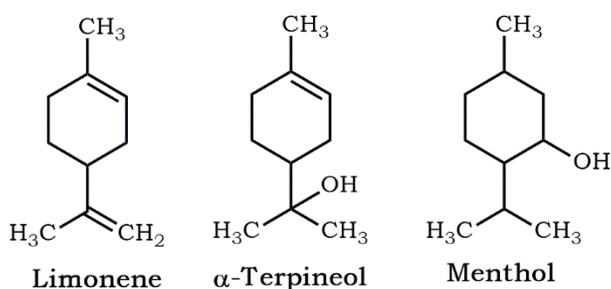
➤ Some examples of mono, sesqui and di Terpenoids

A) Mono Terpenoids

i) Acyclic Monoterpenoids



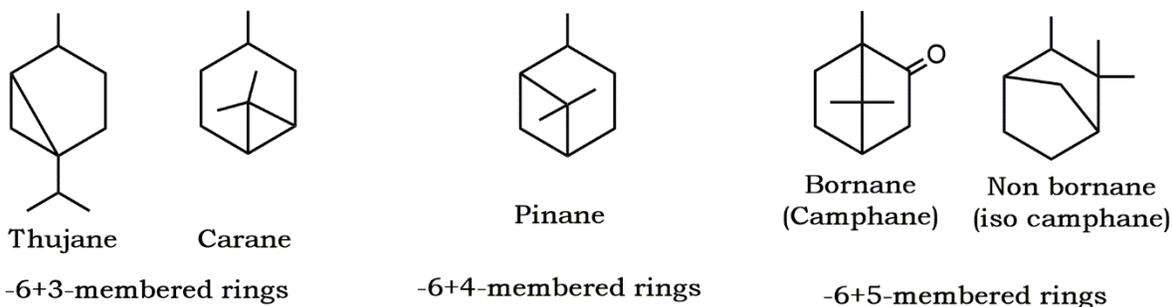
ii) Monocyclic monoterpenoids



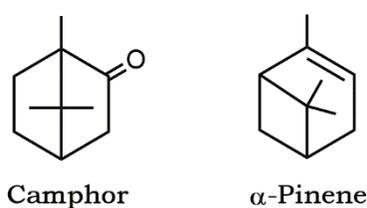
iii) Bicyclic monoterpenoids

These are further divided into three classes

- a) Containing -6+3 membered rings
- b) Containing -6+4 membered rings
- c) Containing -6+5 membered rings

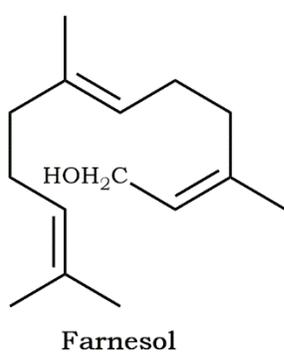


Some bicyclic monoterpenoids are

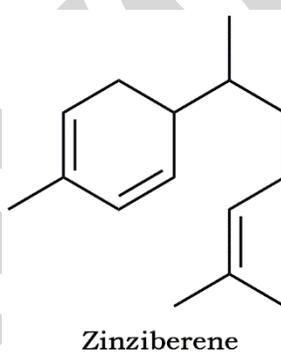


B) Sesquiterpenoids

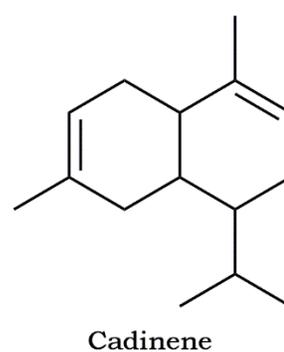
i) Acyclic sesquiterpenoids



ii) Monocyclic sesquiterpenoids

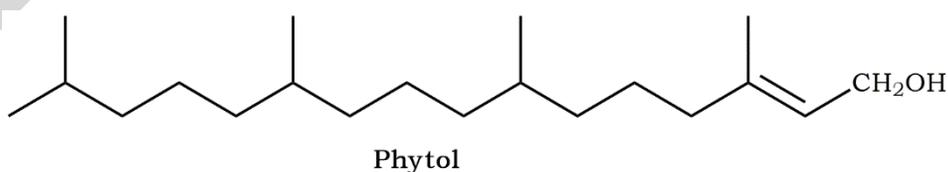


iii) Bicyclic sesquiterpenoids

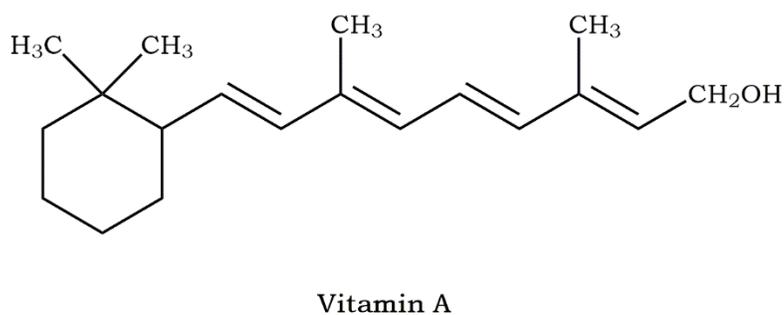


C) Diterpenoids

i) Acyclic diterpenoids



ii) Monocyclic diterpenoids



➤ Isolation of mono and sesquiterpenoids

Both mono and sesquiterpenoids have common source i.e. essential oils. Their isolation is carried out in two steps

- i)** Isolation of essential oils from plant parts **ii)** Separation of Terpenoids from essential oils

i) Isolation of essential oils from plant parts

The plants having essential oils generally have the highest concentration at some particular time. Therefore better yield of essential oil plant material have to be collected at this particular time. e.g. From jasmine at sunset. There are four methods of extractions of oils.

- a) Expression method
- b) Steam distillation method
- c) Extraction by means of volatile solvents
- d) Adsorption in purified fats

Steam distillation is most widely used method. In this method macerated plant material is steam distilled to get essential oils into the distillate form these are extracted by using pure organic volatile solvents. If compound decomposes during steam distillation, it may be extracted with petroleum ether at 50 °C. After extraction solvent is removed under reduced pressure.

ii) Separation of Terpenoids from essential oil

A number of terpenoids are present in essential oil obtained from the extraction. Definite physical and chemical methods can be used for the separation of terpenoids. They are separated by fractional distillation. The terpenoid hydrocarbons distill over first followed by the oxygenated derivatives.

More recently different chromatographic techniques have been used both for isolation and separation of terpenoids.

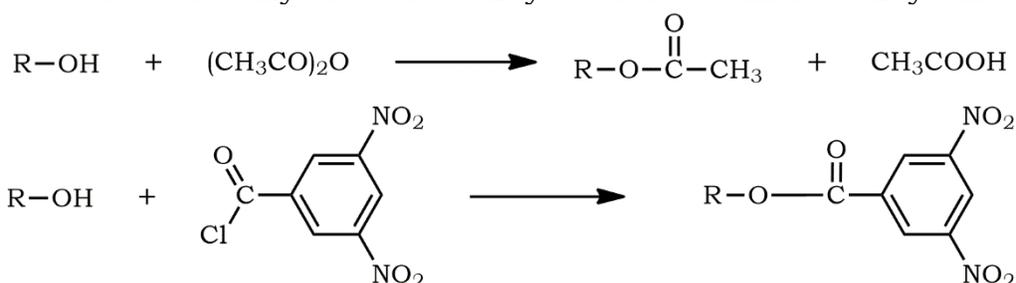
➤ General properties of Terpenoids

- i)** Most of the terpenoids are colourless, fragrant liquids which are lighter than water and volatile with steam. A few of them are solids e.g. camphor. All are soluble in organic solvent and usually insoluble in water. Most of them are optically active.
- ii)** They are open chain or cyclic unsaturated compounds having one or more double bonds. Consequently they undergo addition reaction with hydrogen, halogen, acids, etc. A number of addition products have antiseptic properties.
- iii)** They undergo polymerization and dehydrogenation.
- iv)** They are easily oxidized nearly by all the oxidizing agents. On thermal decomposition, most of the terpenoids yields isoprene as one of the product.

➤ General Methods of structure elucidation

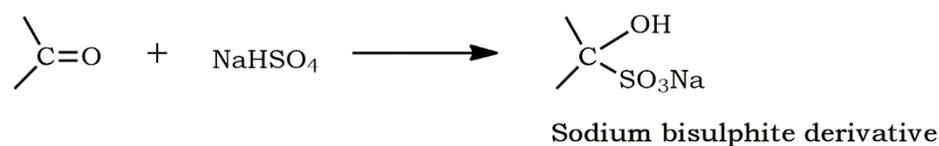
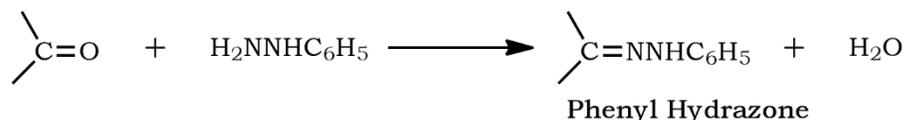
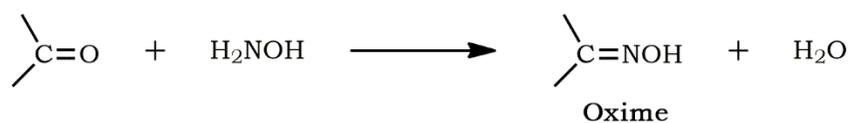
- i)** Molecular formula: molecular formula is determined by usual quantitative analysis and molecular weight determination methods and by means of mass spectrometry. If terpenoid is optically active, its specific rotation can be measured.
- ii)** Nature of oxygen atom present: If oxygen is present in terpenoids its functional nature is generally as alcohol aldehyde, ketone or carboxylic groups.

- a) Presence of -OH group:** Presence of -OH group can be determined by the formation of acetates with acetic anhydride and benzoyate with 3,5-dinitrobenzoyl chloride.



Primary alcoholic group undergo esterification more readily than secondary and tertiary alcohols.

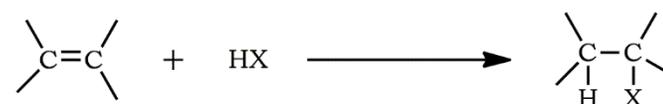
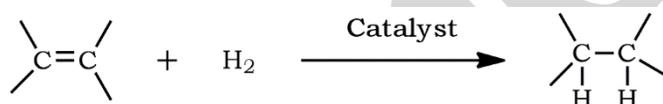
b) Presence of >C=O group: Terpenoids containing carbonyl function form crystalline addition products like oxime, phenyl hydrazone and bisulphite etc.



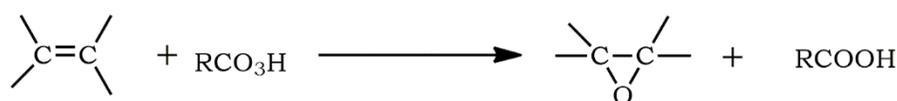
If carbonyl function is in the form of aldehyde it gives carboxylic acid on oxidation without loss of any carbon atom whereas the ketone on oxidation yields a mixture of lesser number of carbon atoms.

iii) Unsaturation: The presence of olefinic double bond is confirmed by means of bromine, and number of double bond determination by analysis of the bromide or by quantitative hydrogenation or by titration with monoperphthalic acid.

Presence of double bond also confirmed by means of catalytic hydrogenation or addition of halogen acids. Number of moles of HX absorbed by one molecule is equal to number of double bonds present.

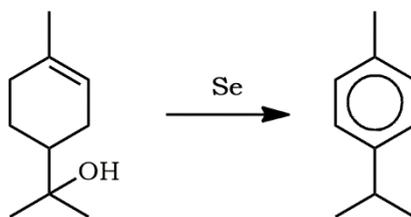


Addition of nitrosyl chloride (NOCl) (**Tilden's reagent**) and epoxide formation with peracid also gives idea about double bonds present in terpenoid molecule.

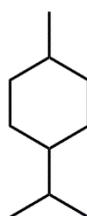


iv) Dehydrogenation: On dehydrogenation with sulphur, selenium, polonium or palladium terpenoids converted to aromatic compounds. Examination of these products the skelton structure and position of side chain in the original terpenoids can be determined.

For example α -terpeneol on Se-dehydrogenation yields p-cymene.



Thus the carbon Skelton of terpeneol is as follows.



- v) **Oxidative degradation:** Oxidative degradation has been the parallel tool for elucidating the structure of terpenoids. Reagents for degradative oxidation are ozone, acid, neutral or alkaline potassium permanganate, chromic acid, sodium hypobromide, osmium tetroxide, nitric acid, lead tetra acetate and peroxy acids. Since oxidizing agents are selective, depending on a particular group to be oxidized, the oxidizing agent is chosen with the help of structure of degradation products.
- vi) **Number of the rings present:** With the help of general formula of corresponding parent saturated hydrocarbon, number of rings present in that molecule can be determined.

Relation between general formula of compound and type of compounds:

General formula of parent saturated Hydrocarbon	Type of structure
C_nH_{2n+2}	Acyclic
C_nH_{2n}	Monocyclic
C_nH_{2n-2}	Bicyclic
C_nH_{2n-4}	Tricyclic
C_nH_{2n-6}	Tetracyclic

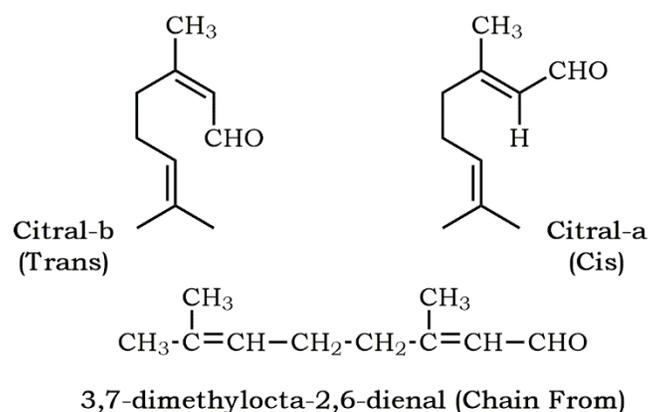
For example limonene (mol. formula. $C_{10}H_{16}$) absorbs 2 moles of hydrogen to give tetrahydro limonene (mol. Formula $C_{10}H_{20}$) corresponding to the general formula C_nH_{2n} . It means limonene has monocyclic structure.

- vii) **Spectroscopic studies:** All the spectroscopic methods are very helpful for the confirmation of structure of natural terpenoids and also structure of degradation products. The various methods for elucidating the structure of terpenoids are;
- a) **UV Spectroscopy:** In terpenes containing conjugated dienes or α,β -unsaturated ketones so UV spectroscopy is very useful tool for detecting of this type of group. The values of λ_{max} for various types of terpenoids have been calculated by applying Woodward's empirical rules. There is generally good agreement between calculation and observed values. Isolated double bonds, α,β -unsaturated esters, acids, lactones also have characteristic maxima.
- b) **IR Spectroscopy:** IR spectroscopy is useful in detecting group such as hydroxyl group ($\sim 3400\text{cm}^{-1}$) or an oxo group (saturated $1750\text{-}1700\text{ cm}^{-1}$, α,β -unsaturated $1700\text{-}1600\text{cm}^{-1}$). Isopropyl group, cis and trans also have characteristic absorption peaks in IR region.
- c) **NMR Spectroscopy:** This technique is useful to detect and identify double bonds, to determine the nature of end group and also the number of rings present, and also to reveal the orientation of methyl group in the relative position of double bonds.
- d) **Mass Spectroscopy:** It is now being widely used as a means of elucidating structure of terpenoids. Used for determining mol. Wt., Mol. Formula, nature of functional groups present and relative positions of double bonds.
- viii) **X-ray analysis:** This is very helpful technique for elucidating structure and stereochemistry of terpenoids.
- ix) **Synthesis:** Proposed structure is finally confirmed by synthesis. In terpenoid chemistry, many of the synthesis are ambiguous and in such cases analytical evidences are used in conjunction with the synthesis.

Citral

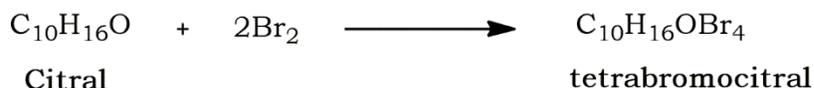
Introduction:

Citral is an acyclic monoterpenoid. It is a major constituent of lemon grass oil in which it occurs to an extent of 60-80%. It is pale yellow liquid having strong lemon like odour and can be obtained by fractional distillation under pressure from lemongrass oil. It also present in the oil of citrus fruits (Citron, Orange, Lemon etc.). It exists in two isomeric forms Citral-a (Cis) and Citral-b (Trans - CH_3 and - CHO group) It is obtained in a mixture of Citral-a (90%) and Citral-b (10%). Citral is used in the perfume and flavour industry to stimulate lemon like odour.

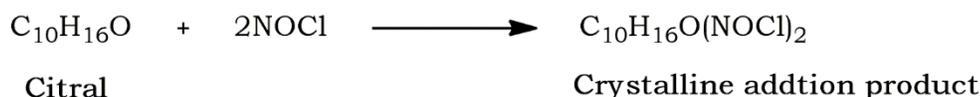


➤ **Constitution of Citral:**

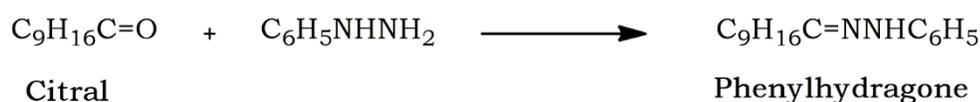
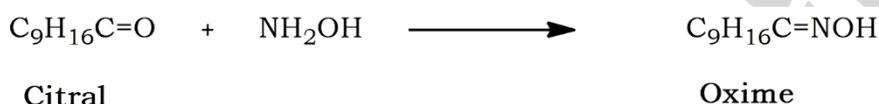
1. Elemental analysis and molecular weight determination show that the molecular formula is $C_{10}H_{16}O$. Its boiling point is $229\text{ }^{\circ}\text{C}$. ($77\text{ }^{\circ}\text{F}$ isolation temperature at under reduced pressure)
2. **Presence of two ethylenic bond (C=C):** Citral forms tetrabromocitral on reaction with Br_2 , it adds two moles of Br_2 indicating the presence of two ethylenic bonds (C=C).



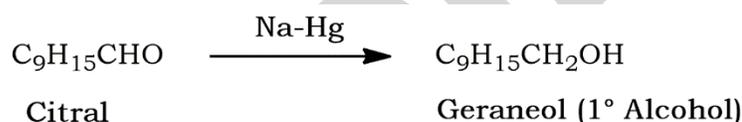
The presence of two ethylenic (C=C) bonds in Citral is further confirmed by the reaction of Citral with two moles of nitrocylo chloride (NOCl) to form a crystalline addition product.



3. **Presence of Carbonyl (>C=O) group:** Citral undergoes an addition reaction with NH_2OH and $C_6H_5NHNH_2$ to form the corresponding oxime and phenyl hydrazone respectively. This indicates the presence of a carbonyl group in citral.



4. **Presence of Aldehyde (-CHO) group:** Citral on reduction with Na-Hg forms a primary alcohol Geranol. This reaction indicates the presence of a -CHO group in citral.

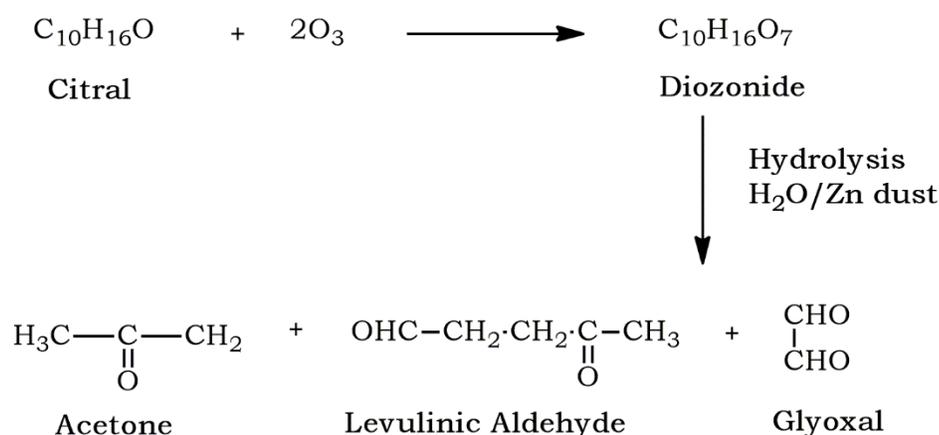


On oxidation with silver oxide (Ag_2O) citral forms a monocarboxylic acid Geranic acid having the same number of C-atoms. This reaction confirms the presence of a -CHO group in citral.



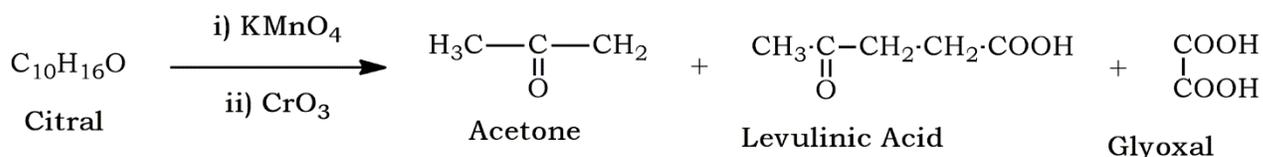
Thus it can be concluded that citral is an unsaturated aldehyde.

5. **Acyclic structure:** The presence of two double bonds (4H) and an aldehyde group (2H) in citral $C_{10}H_{16}O$ leads to $C_{10}H_{22}$ as the molecular formula of its fully saturated hydrocarbon. Now as $C_{10}H_{22}$ corresponds to the general formula C_nH_{2n+2} citral must be an acyclic compound.
6. **Presences of isopropylidene group or Ozonolysis of citral:** Citral on reaction with two moles of ozone (O_3) forms the corresponding which on hydrolysis in the presence of Zn dust gives three main products, Acetone, levulinic aldehyde and Glyoxal. As one of the products on complete ozonolysis is Acetone so citral possesses a $(CH_3)_2C$ - group (isopropylidene group).

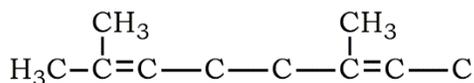


7. Oxidation of citral or Determination of carbon skeletal and position of C=C:

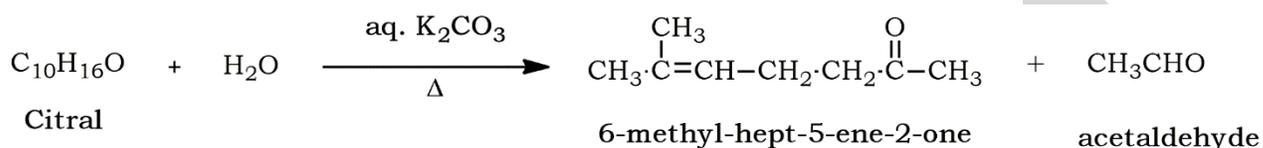
Oxidation of citral first with KMnO_4 and then with chromic acid forms Acetone, Levulinic acid and oxalic acid.



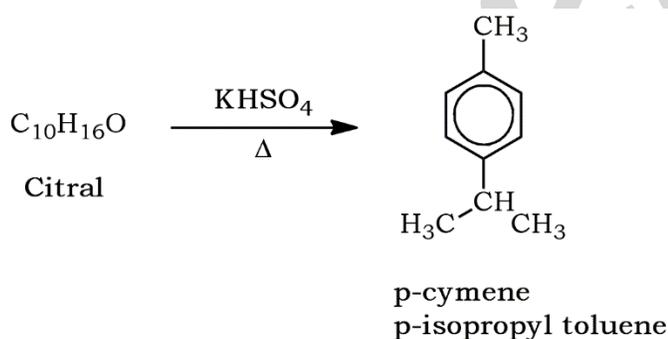
The formation of this products would be possible if the carbon skeletal of citral containing the double bonds it follows.



8. α, β unsaturated compound: On heating citral with aqueous K_2CO_3 one mole of water is added forming 6-methyl-hept-5-ene-2-one and acetaldehyde. The formation of acetaldehyde indicates that the compound is α, β unsaturated ($-\text{C}=\text{CH}-\text{CHO}$).

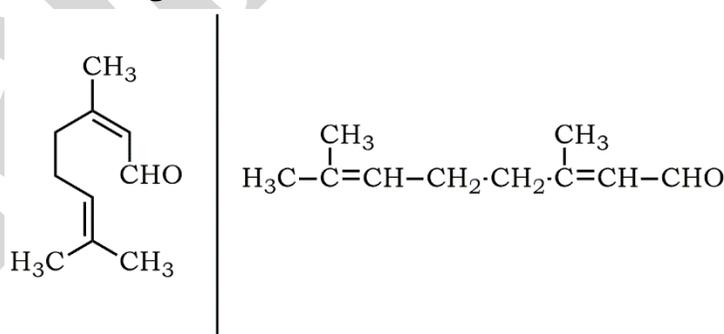


9. Position of side branches and determination of structure of citral: On heating with KHSO_4 citral undergoes cyclization forming p-cymene.



Thus citral is open chain structure made up of two isoprene units joined by head to tail linkage. Moreover p-cymene contains a $-\text{CH}_3$ at first carbon and isopropyl group at the 4th position. Hence the position of side branches can be determined.

The structure of citral can be given as follows

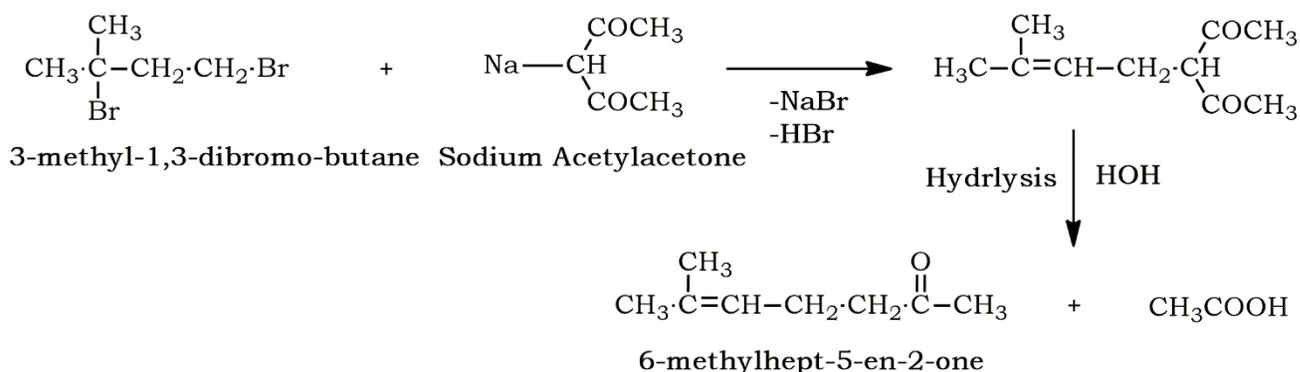


Synthesis of Citral:

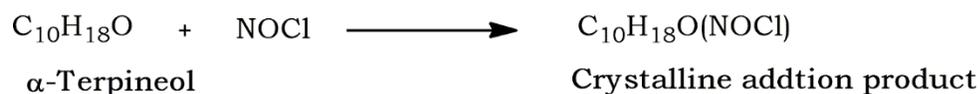
Synthesis of citral can be carried out in the following three stages

1. Synthesis of 6-methyl-hept-5-ene-2-one

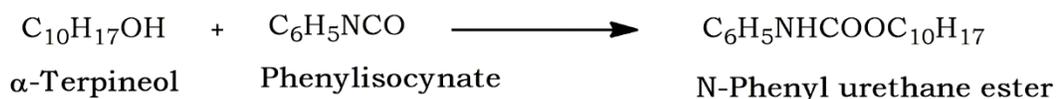
3-methyl-1,3-dibromobutane react with sodium acetylacetonate give adduct product which on hydrolysis gives 6-methyl-hept-5-ene-2-one.



The presence of one ethylenic (C=C) bond in α -Terpineol further confirmed by the reaction of α -Terpineol with one moles of nitrocytle chloride (NOCl) to form crystalline addition product.



- 3. Presence of Hydroxyl (-OH) group:** α -Terpineol reacts with phenyl isocyanate forming N-phenyl urethane (ester). This reaction indicates the presence of -OH group.



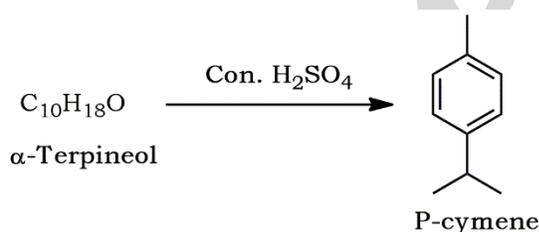
α -Terpineol also react with acetic anhydride and gives acetyl derivative.

- 4. Presence of Alcoholic Hydroxyl (-OH) group:** α -Terpineol is insoluble in NaOH indicate that the -OH group in α -Terpineol is alcoholic group.

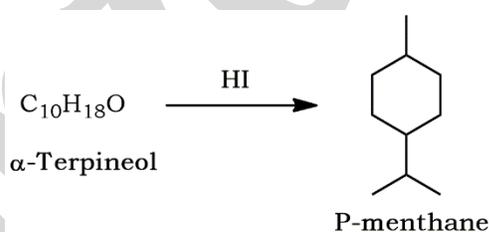
α -Terpineol do not oxidize easily so -OH group present as tertiary (3°) -OH group.

- 5. Monocyclic structure:** The presence of one double bonds (2H) and an alcoholic hydroxyl group (OH) in α -Terpineol $\text{C}_{10}\text{H}_{18}\text{O}$ leads to $\text{C}_{10}\text{H}_{20}$ as the molecular formula of its fully saturated hydrocarbon. Now as $\text{C}_{10}\text{H}_{20}$ corresponds to the general formula C_nH_{2n} α -Terpineol must be monocyclic compound.

- 6. Determination of carbon skeletal of α -Terpineol:** On reaction with H_2SO_4 α -Terpineol forms p-cymene.



Reduction with HI α -Terpineol gives p-menthane.

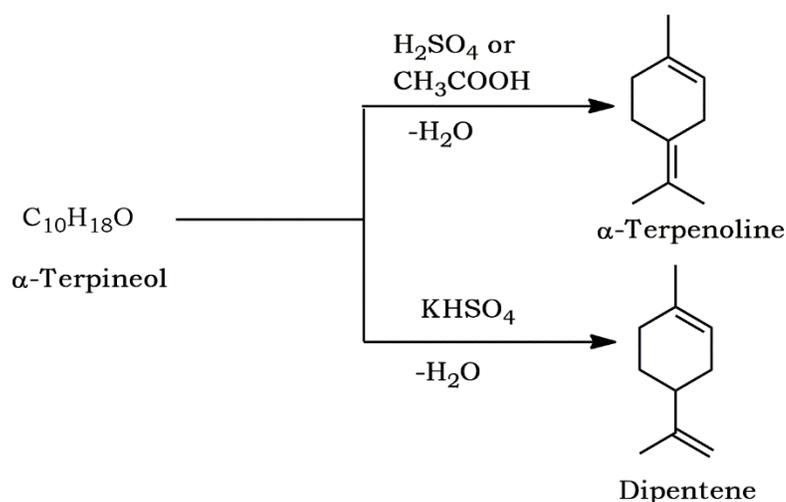


Thus α -Terpineol possesses a six membered cyclic structure having a side chain one carbon at C_1 and three carbon at C_4 .

Thus the carbon Skelton of α -Terpineol is as follows.

- 7. Dehydration of α -Terpineol:** α -Terpineol undergoes dehydration in presence of different dehydrating agent.

On dehydration by sulfuric acid or oxalic acid and glacial acetic acid α -Terpineol forms α -Terpinoline and dehydration with potassium bisulphate (KHSO_4) dipentene formed.

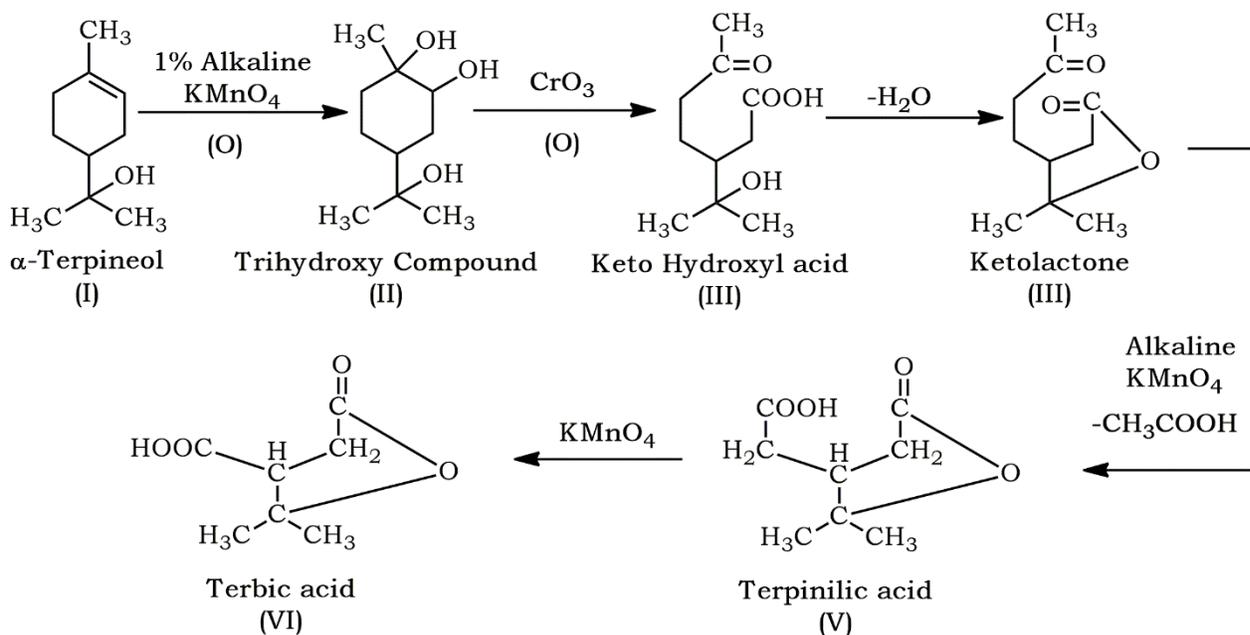


Thus dehydration reaction indicates that -OH group in α -Terpineol must be at C_8 because in both reactions the second double involves C_8 between $\text{C}_4\text{-C}_8$ and $\text{C}_8\text{-C}_9$.

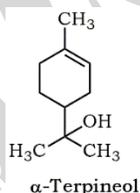
8. Oxidation of α -Terpineol (position of double bond): Oxidation of α -Terpineol explained by Wallach is useful to arrive at the structure of α -Terpineol.

- When α -Terpineol (I) is oxidized by 1% KMnO_4 the double bond undergoes hydroxylation forming and trihydroxy compound (II) obtained. That indicate the presence of double bond between C_1 and C_2 .
- On oxidation with CrO_3 glycol compound give an unstable keto hydroxyl acid (III) which then forms a ketolactone (IV) on removal of a water molecule.
- Oxidation of ketolactone by alkaline KMnO_4 removes a molecule of acetic acid and give terpinilic acid (V) that has a lactone ring and further oxidation of terpinilic acid gives terbic acid (VI).

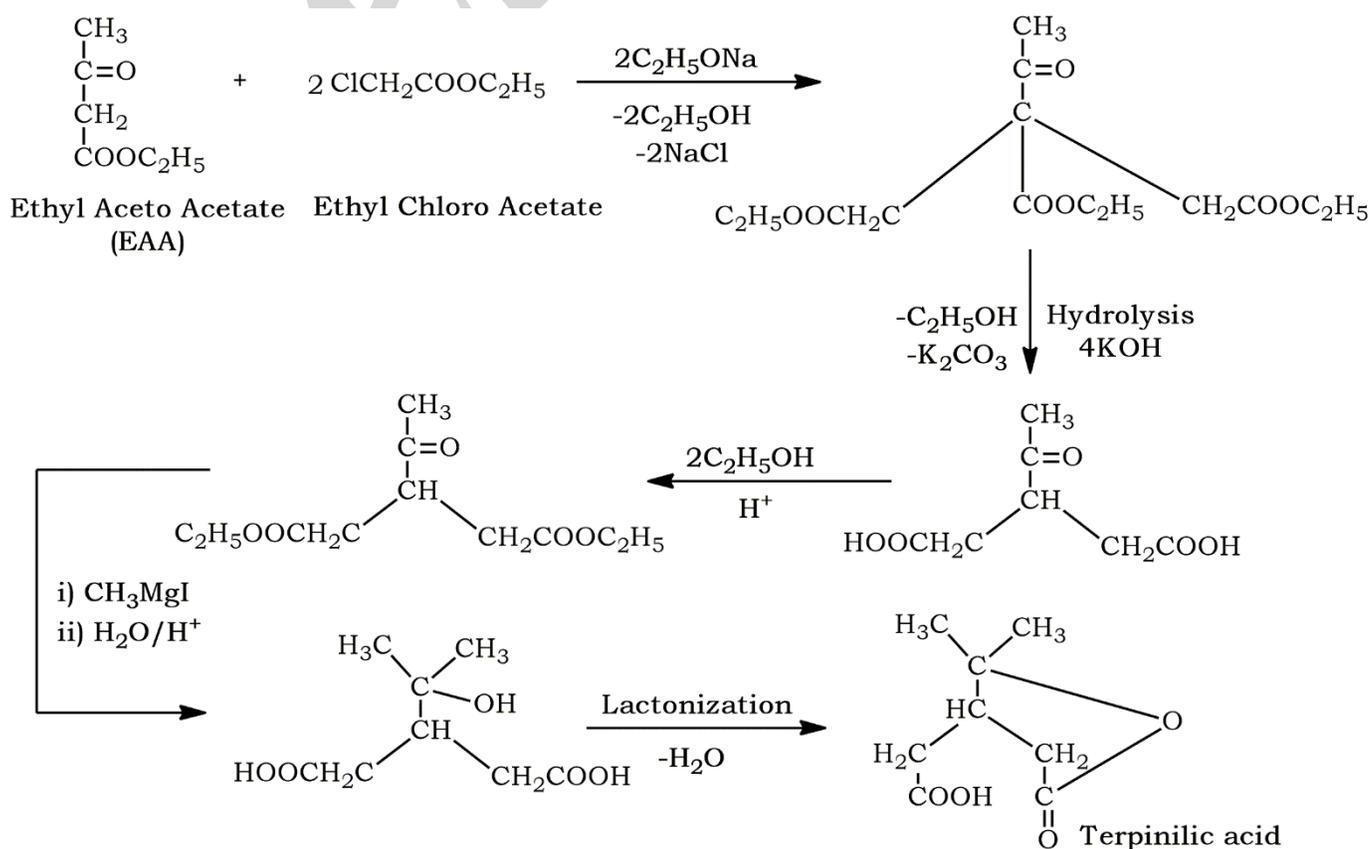
This oxidation of α -Terpineol can be explained by the following structure.



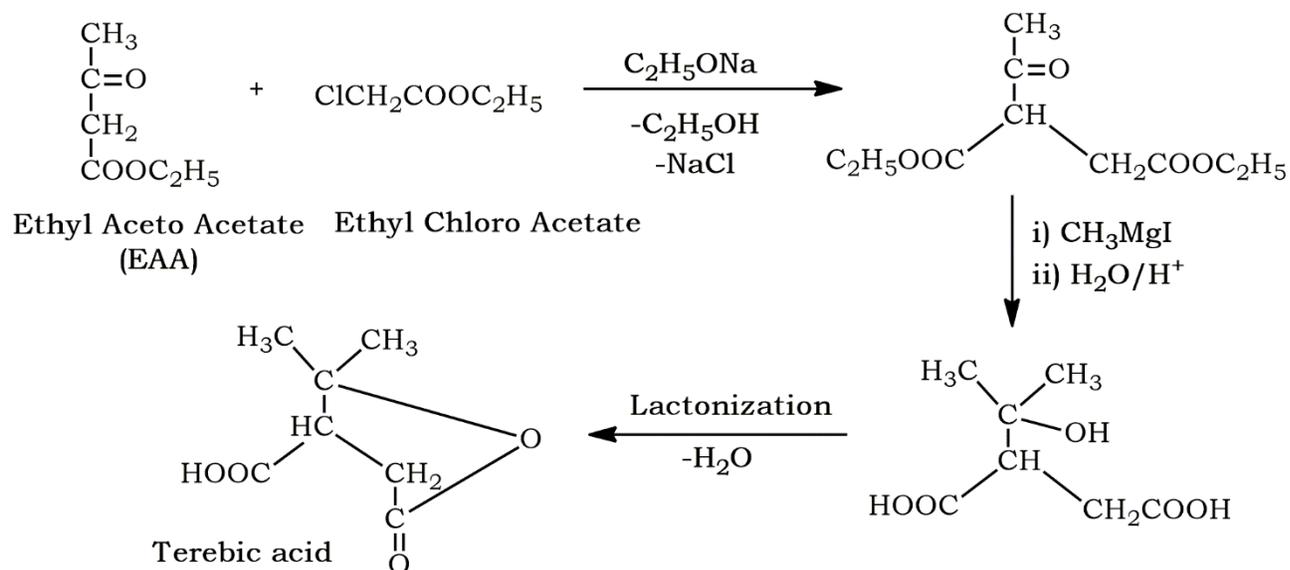
The structure of terpinilic acid and terbic acid prove by their synthesis so structure of α -Terpineol is as follows.



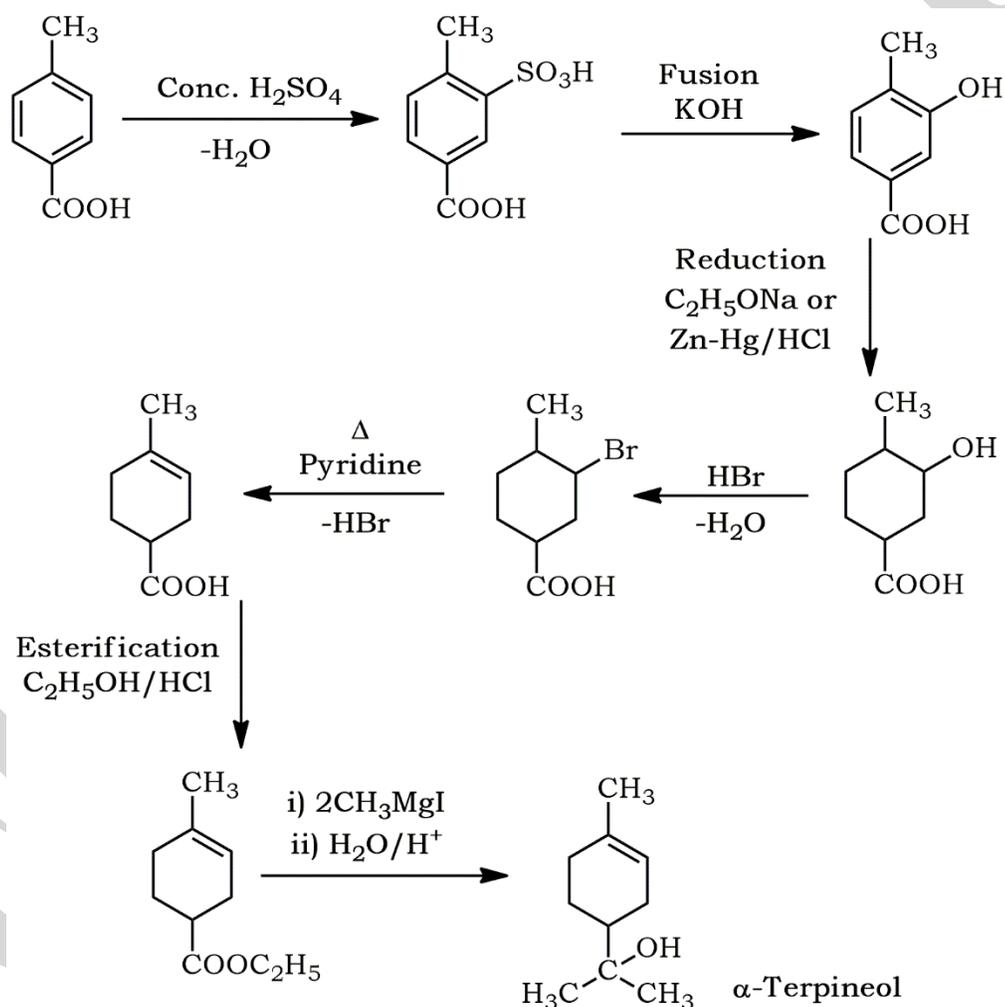
Synthesis of terpinilic acid:



Synthesis of terbic acid:



Synthesis of α -Terpineol:



Best of Luck