B. Sc. SEM V: US05CCHE21: ORGANIC CHEMISTRY

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UNIT-IV : TERPENOIDS [2020]

1.1 General Introduction :

Originally, the term "terpene" was employed to describe a mixture of isomeric hydrocarbons of the Molecular Formula $C_{10}H_{16}$ occurring in the turpentine and many essential oils which are obtained from the sap and tissues of plants and trees.

The oxygenated derivatives like alcohols, aldehydes, ketones…etc. at that time were called "camphors"

The both terms "terpenes" and "camphors" were amalgamated into a single term called "terpenoids".

The modern definition is as follow :

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

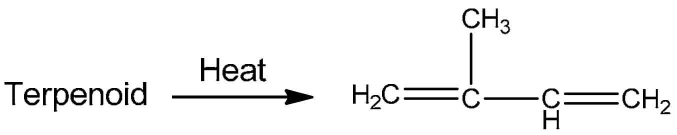
1.2 General properties of Terpenoids:

PHYSICAL PROPERTIES:

(1) Most of the terpenoids are colorless liquids.
(2) They are lighter than water and boil between 150 to 180°C.
(3) A few terpenoids are solid which are lighter than water and volatile in steam.
(4) They are insoluble in water but soluble in organic solvents. Many of these are optically active.

CHEMICAL PROPERTIES:

(1) They are unsaturated compound having one or more double bonds.
(2) Terpenoids undergo addition reaction with H_2, X_2, HX etc.
(3) They also form characteristic addition products with NO_2, NOCl and NaOBr.
(4) They undergo polymerization, also dehydrogenation in the ring.
(5) As they have olefinic bonds, they are very easily oxidized with all the oxidizing agents.
(6) On thermal decomposition, most of the terpenoids yield isoprene as one the products.



$$\text{Terpenoid} \xrightarrow{\text{Heat}} H_2C=\overset{\overset{CH_3}{|}}{C}-\underset{H}{C}=CH_2$$

Isoprene

1.3 ISOLATION:

Due to their wide occurrence in nature, all the terpenoids could not be isolated and separated by a general method. This is carried out in two steps as follows.

(1) Isolation of essential oils [Step-I]
(2) Separation of terpenoids form essential oils [Step-II].

[Plant Kingdom -- Step-I **---->** **essential oils ---** Step-II **--->** **terpenoids]**

(1) ISOLATION OF ESSENTIAL OILS [Step-I]

This methods are based on different principles have been developed for the extraction of oils. These methods are described as follows :

[a] Expression method:

This method is not used these days, due to certain limitations.

In this method, the plant material is cut into small pieces. These are them crushed to get the juice which is screened to remove 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. Form this residue, inferior quality of the oil is obtained by distillation.

[b] Steam distillation method:

This method is the one most widely used. In this method, the plant materials are macerated and then steam distilled to get the essential oils into the distillate form which these are extracted by using pure organic solvent (volatile) like light petroleum and then solvent removed by distillation under reduce pressure.

But this method employ carefully because it suffers from the following demerit:

(i) Some essential oils undergo decomposition during steam distillation.
(ii) Some constituents of the essential oils e.g. ester, which are responsible for the odour and fragrance of the oil may undergo decomposition, resulting in a perfume of inferior quality.

[c] Extraction by means of volatile solvents:

This method is widely used in perfume industry. This method is generally used for such plants which yield an oil or give low quantities of oil on stem distillation due to decomposition essential oils.

In such cases, the plant material is directly treated with light petrol at 50^0C under these condition the oil is taken up by the solvent along with the soluble colouring materials.

The essential oils from this extract are separated by removing the solvent by distillation under reduce pressure.

[d] Adsorption On purified fats [Enfleurage Method]

This method is also known as “enfleurage method” and is widely employed in France. This method is used to extract a large number of essential oil like Rose and Jasmine.

In this method, the fat is warmed at 50^oC on glass plates. Then, the surface of the fat is covered with flower petals. And it is allowed to kept 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 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 to 20^oC, when the fat separates out. The alcoholic distillate is then finally fractionally distilled under reduced pressure to remove the solvent.

Recently, the fat has been replaced by coconut charcoal. 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 [Step-II].

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

[a] Physical Methods and [b] Chemical method.

The Various physical methods are as follows:

[i] Fractional Distillation Method:

The various terpenoids present in essential oils are separated by Fractional distillation method. The terpenoid-hydrocarbons distil over First, followed by the oxygenated derivatives. Distillation of the residue under reduced pressure yields the sesquiterpenoids and these are separated by fractional distillation.

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 reduce pressure and in presence of an inert gas.

[ii] Chomatography:

Chromatography 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 elutes. Each elute is then subjected separately to adsorption chromatography when different bands due to the various terpenoids present in elute are obtained which are then eluted to yield different terpenoids.

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 useful for isolating pure configurational forms of a given terpenoid from mixtures produced by synthesis.

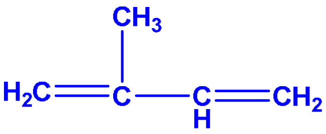
1.4 Isoprene Rule:

Q: What is isoprene rule? How it was deduced?

Ans: In 1887, Wall carried out the famous isoprene rule, which may be stated as follows.

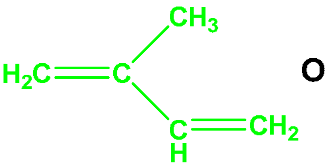
“The skeleton structures of all naturally occurring terpenoids are built up of isoprene units”.

Isoprene is 2-Methyl-1,3-butadiene and represented in various ways.

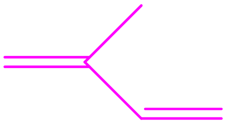


$$H_2C{=}\overset{CH_3}{\overset{|}{C}}-\underset{H}{C}{=}CH_2$$

OR



OR



The isoprene rule has been deduced from the following facts.

(1) The empirical formula of almost all the naturally occurring terpenoid is C_5H_8.

(2) The decomposition of terpenoids give isoprene as one of the products. e.g

$$\underset{\text{[Poly terpenoid]}}{\underset{\text{Rubber}}{(C_5H_8)_n}} \xrightarrow[\text{distillation}]{\text{Destructive}} \underset{\text{Isoprene}}{nC_5H_8}$$

It can be confirmed from the following facts :

(3) Various terpenoids can be prepared by the polymerization of isoprene.
e.g

(a) Isoprene, when heated at 280°C gets dimerized to yield dipentene.

$$\underset{\text{Isoprene}}{2C_5H_8} \xrightarrow[280^{o}C]{\Delta} \underset{\text{Dipentene}}{C_{10}H_{16}}$$

(b) Isoprene on polymerization to yield a Rubber.

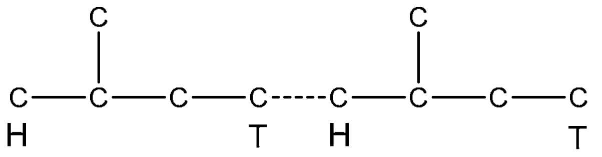
$$nC_5H_8 \xrightarrow{\text{polymerization}} \underset{\text{Rubber}}{(C_5H_8)_n}$$

Special Isoprene Rule

Q: Discuss in detail special isoprene rule. Why special isoprene rule is a guiding principle and not fixed rule?

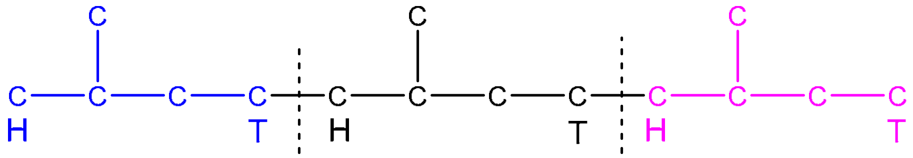
This rule was proposed by Ingold in 1925. It shows how the isoprene units in the terpenoid molecule are linked together. For this purpose, the branched end of the isoprene unit is considered as the head and the other end as the tail.

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.



where H=Head
T=Tail

Similarly, a sesquiterpenoid with three isoprene units will have the following skeleton.

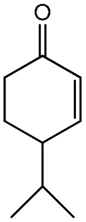


Special isoprene rule is a very suitable tool to limit the number of carbon skeletons of the structures of unknown terpenoids. Generally, the skeletons which do not follow isoprene rule are generally rejected.

However, this rule, which has proved very useful, can only be used **as a guiding principle and not as a fixed rule.** Therefore, there are limitations of this rule in many compounds. For example.

(i) Certain terpenoids are known whose carbon content is not a multiple of five.

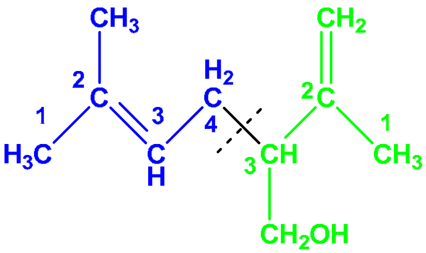
e.g. Crytone is a naturally occurring ketonic terpenoid contains nine C-atoms and therefore, it cannot be divided into two isoprene units.



Cryptone
[contains only 9-carbon atoms insteadof 10]

(ii) Certain terpenoids are known whose carbon content is a multiple of five but can not be divided into two isoprene units.

(iii) Certain terpenoids are also known in which the special isoprene rule is violated. e.g. Lavandulol is composed of two isoprene units with the unusual linkage of tail to tail but not head to tail.

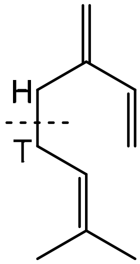


Lavandulol (3,4-linkage)

[two isoprene units are linked through C_3 and C_4]

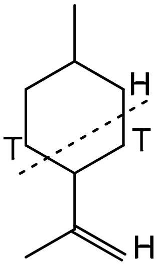
Q: Write the structure and how many isoprene units present in the following terpenoids. Also assigned them into head to tail carbon.

(i) Myrcene



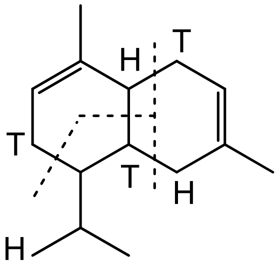
(2-isoprene units)

(ii) Limonene



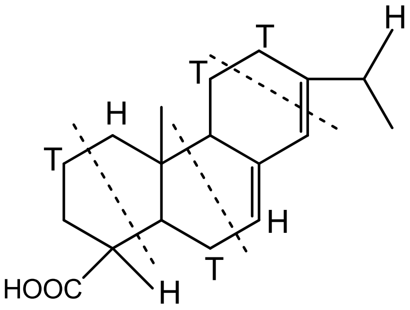
(2-isoprene units)

(iii) Cadinene



(3-isoprene units)

(iv) Abietic acid



(4-isoprene units)

1.5 Classification of Terpenoids:

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

No.	Class	No. of Isoprene Units (C_5H_8)	Molecular formula
1.	Hemiterpene or Isoprene	1	C_5H_8
2.	Monoterpenes or Terpenes	2	$C_{10}H_{16}$
3.	Sesquiterpenes	3	$C_{15}H_{24}$
4.	Diterpenes	4	$C_{20}H_{32}$
5.	Sesterterpenoid	5	$C_{25}H_{40}$
6.	Triterpenes	6	$C_{30}H_{48}$
7.	Tetraterpenes or Carotenoids	8	$C_{40}H_{64}$
8.	Polyterpenes or Rubber	N	$(C_5H_8)_n$

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

(1) Acyclic terpenoids: an open chain structure
(2) Monocyclic terpenoids: one ring in a molecule
(3) Bicyclic terpenoids: two ring in a molecule
(4) Tricyclic terpenoids: three ring in a molecule
(5) Tetracyclic terpenoids: four ring in a molecule

1.6 General Methods for the determination of structures of Terpenoids.

Method – I

[A] Analytical Methods: These include the following methods:

(a) Molecular formula:

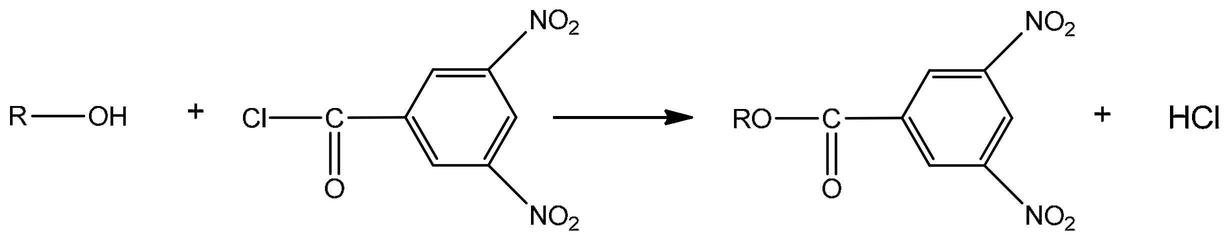
Molecular formula is determined by usual methods of qualitative and quantitative analysis and also by means of mass spectrometry.

(b) Nature of oxygen:

The terpenoids generally contain hydroxyl, aldehyde, keto or carboxylic groups. The various group are detected in terpenoids by the following methods:

(i) The hydroxyl group can be detected by the formation of crystalline acetate with acetic anhydride and crystalline benzoate with 3,5-dinitrobenzoylchloride suggest that **–OH group is present in terpenoid.**

$$R{-}OH + (CH_3CO)_2O \longrightarrow ROCOCH_3 + CH_3COOH$$



3,5-dinitrobenzoate

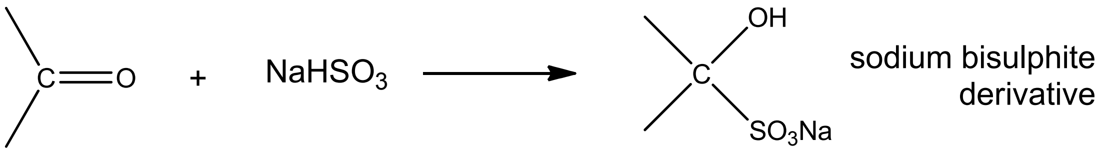
If –OH group is phenolic, this type of terpenoid is soluble in NaOH and reprecipitated, by CO_2. It also gives the coloration with $FeCl_3$.

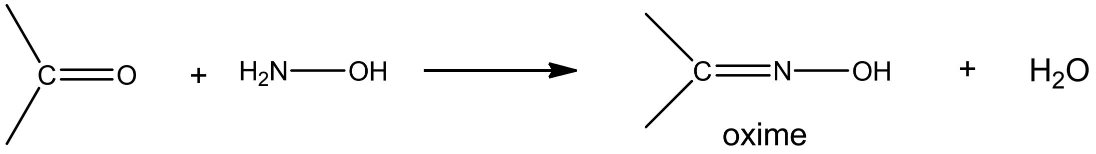
Therefore, –OH group is phenolic in nature.

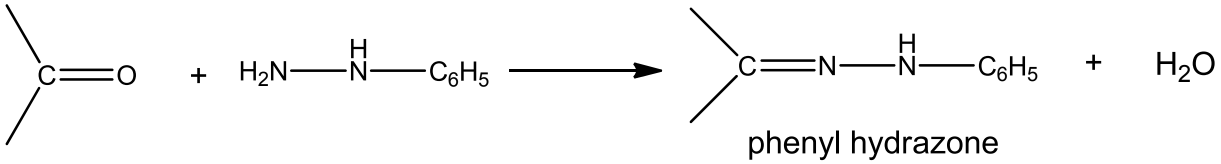
If –OH Group is alcoholic, the presence of alcoholic –OH group can be ascertained by dehydration with H_2SO_4 or P_2O_5.

Therefore, –OH group is alcoholic in nature.

(ii) If terpenoid forms crystalline addition products like bisulphate derivative, oxime and phenylhydrazone, this shows that terpenoid contains a “carbonyl group”.







Formation of crystalline product suggest that carbonyl group is present in terpenoid.

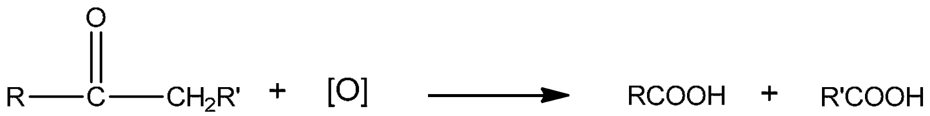
The carbonyl group may be present either in the form of aldehyde or keto groups. This can be ascertained by oxidation.

The aldehyde on oxidation yields mono carboxylic acid without loss of carbon atom.

$$R-CHO \quad + \quad [O] \longrightarrow R-COOH$$

Therefore, carbonyl group is in the form of aldehyde in terpenoid

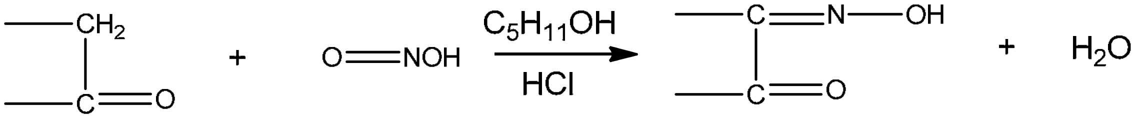
The ketone on oxidation yields a mixture of carboxylic acid of lesser number of carbon atoms.



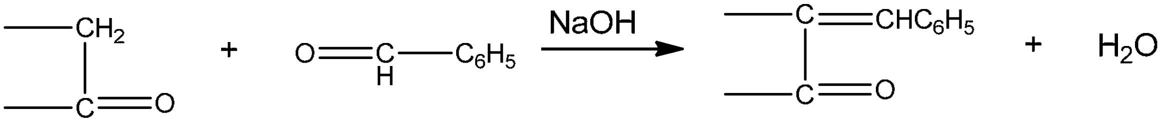
$$R-\overset{\overset{O}{\|}}{C}-CH_2R' \quad + \quad [O] \longrightarrow RCOOH \quad + \quad R'COOH$$

Therefore, carbonyl group is in the form of ketone in terpenoid

If terpenoids having –CH_2CO– groups exhibit special properties. This type of terpenoids forms oxime with HNO_2 and benzylidene derivatives with C_6H_5CHO in the presence of alkali.



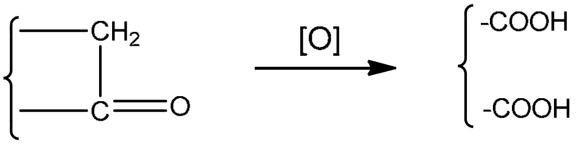
oxime



Benzylidene derivative

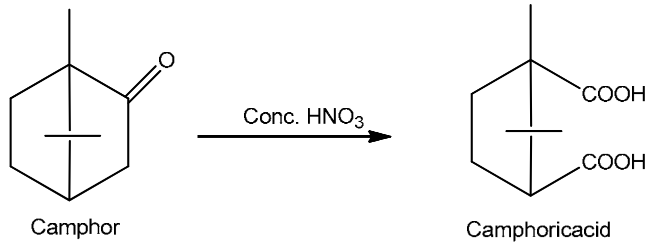
Therefore, carbonyl group is the part of aliphatic chain in terpenoid

If –CH_2CO– group is present in a ring, the terpenoid on oxidation yield a dicarboxylic acid without loss of C-atom.



For example:

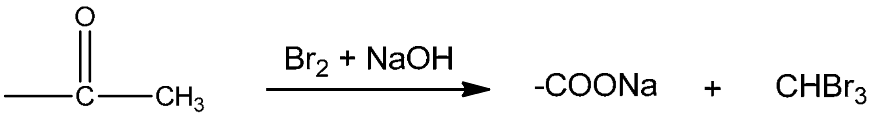
Camphor on oxidation with Conc. HNO_3 yield camphoric acid.



Therefore, carbonyl group is the part of cyclic ring in terpenoid

If a terpenoid contain –$COCH_3$ group. It can be detected by “Haloform reaction”.

e.g.



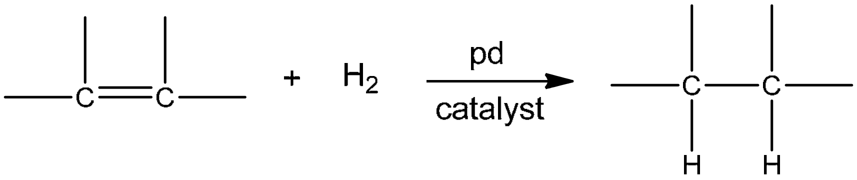
Formation of haloform suggest that terpenoid contain –$COCH_3$ group.

It a terpenoid is soluble in ammonia and gives effervescence with sodium bicarbonate, this indicates that **terpenoid contain –$COCH_3$ group**.

(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 and Nitrosyl chloride (NOCl) [Tilden's reagent]

(i) When a terpenoid possessing olefinic linkages is hydrogenated in presence of a catalyst to yield addition product. From the amount of hydrogen consumed, the extent of unsaturation in a terpenoid can be calculated.

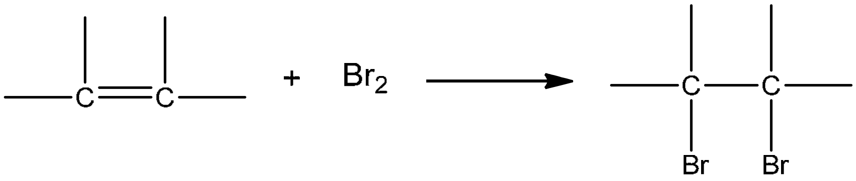


$$\mathrm{{>}C{=}C{<}} + H_2 \xrightarrow[\text{catalyst}]{\text{pd}} \mathrm{{-}CH{-}CH{-}}$$

For example:

The catalytic reduction of cadinene yields tetrahydrocadinene this indicates that cadinene contain two double bonds.

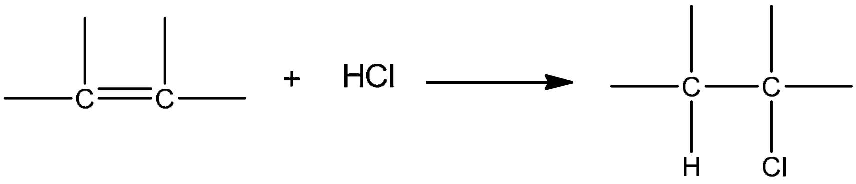
(ii) With halogens terpenoids containing olefinic linkages form addition products. The measurement of the amount of halogen used gives the amount of unsaturation.



$$\mathrm{{>}C{=}C{<}} + Br_2 \longrightarrow \mathrm{{-}C(Br){-}C(Br){-}}$$

(iii) With halogen acids like HCl or HBr, terpenoid yield addition compounds which can be characterized very easily.

In order to carry out halogenations, terpenoid is dissolved in a suitable solvent and them dry halogen acid gas is passed into it.



$$\mathrm{{>}C{=}C{<}} + HCl \longrightarrow \mathrm{{-}C(H){-}C(Cl){-}}$$

For example:

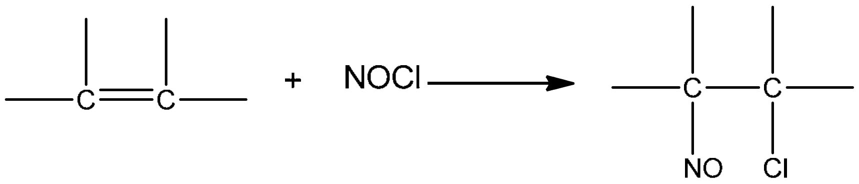
Limonene with HCl yields a crystalline dihydrochloride, this indicates that limonene contains two double bonds.

$$\underset{\text{Limonene}}{C_{10}H_{16}} + 2HCl \longrightarrow \underset{\text{Limonene dihydrochloride}}{C_{10}H_{16}2HCl}$$

Therefore, terpenoid contains double bond.

(d) Nitrosylchoride [NOCl] [Tilden's Reagent]

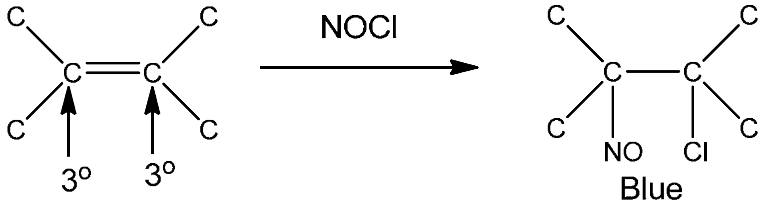
With NOCl, terpenoids containing olefinic double bond form addition compounds and may be used for identification and separation of terpenoids.



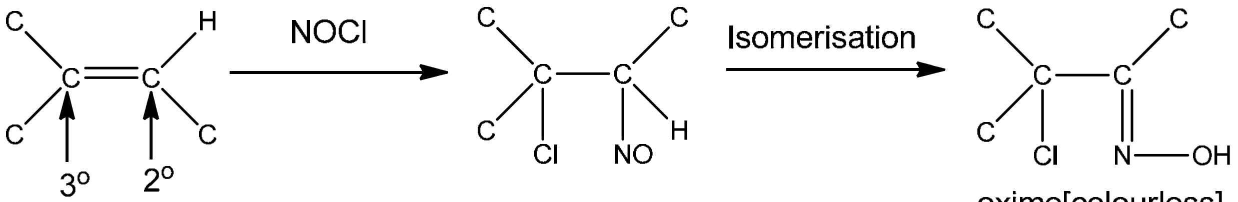
The addition of NOCl also gives idea about the nature of the carbon atoms having double bond in terpenoids.

For example:

If the product formed is Blue , the double bond is between two 3° carbon atoms and if product is colourless the double bond is between 3° and 2° carbon atoms.



Blue



oxime[colourless]

(d) Number of Ring :

Number of ring present in the terpenoid can be determined according to the general formula of it.

General Molecular Formula	Type of compound
C_nH_{2n+2}	Acyclic [open chain structure]
C_nH_{2n}	Moncyclic [One ring]
C_nH_{2n-2}	Bicyclic [Two rings]
C_nH_{2n-4}	Tricyclic [Three rings]
C_nH_{2n-6}	Tetracyclic [Four rings]

Q: Predict the number of rings present in the terpenoid having molecular formula

(i) $C_{10}H_{16}$ containing one double bond.
(ii) $C_{15}H_{24}$ containing two double bonds
(iii) $C_{10}H_{160}$ containing two double bonds and one oxygen atom as carbonyl group.

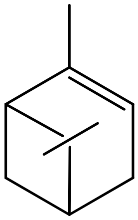
Ans:

(i) $C_{10}H_{16}$ containing one double bond.

Molecular Formula of parent hydrocarbon is ≡ $C_{10}H_{16}$ + 2H [For one double bond]

≡ $C_{10}H_{18}$

The Molecular Formula corresponds to C_nH_{2n-2} , the general formula of bicyclic compounds. i.e. contain two rings.



For example. **α-pinene**

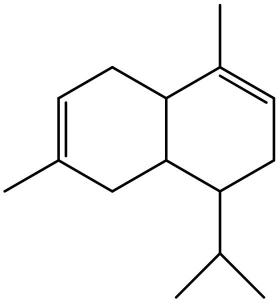
(ii) $C_{15}H_{24}$ [containing two double bonds]

Molecular Formula of parent hydrocarbon ≡ $C_{15}H_{24}$ + 4H [For one double bond]

≡ $C_{15}H_{28}$

The Molecular Formula $C_{15}H_{28}$ corresponds to C_nH_{2n-2} , the general formula of bicyclic compounds. i.e. contain two rings.

e.g.



cadinene

(iii) $C_{10}H_{16}O$ [containing two double bonds and one oxygen atom as carbonyl group]

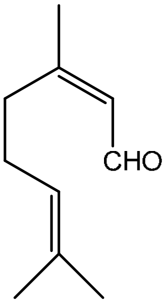
Molecular Formula of parent hydrocarbon

≡ $C_{10}H_{16}$ + 4H [For one double bond] + 2H [For one oxygen atom as carbonyl group]

≡ $C_{10}H_{22}$

The Molecular Formula $C_{10}H_{22}$ corresponds to C_nH_{2n+2} , the general formula of Acyclic compounds. i.e. open chain structure.

e.g.



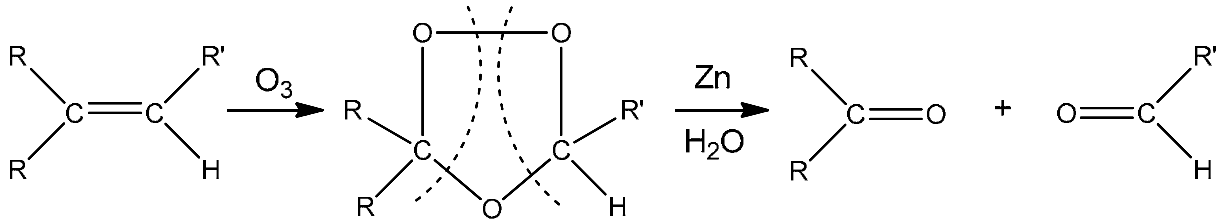
citral

(e) Oxidative Degradation Products:

Most of the terpenoids are olefinic in nature. This method may be used to cleave the molecule into simple fragments of known structure.

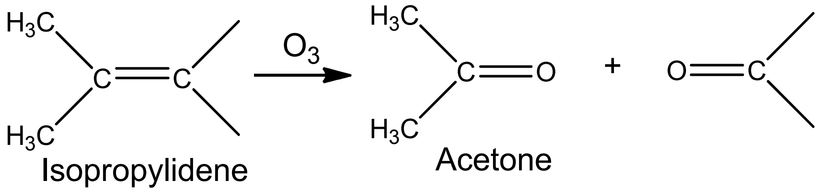
(i) Ozone (O_3) :

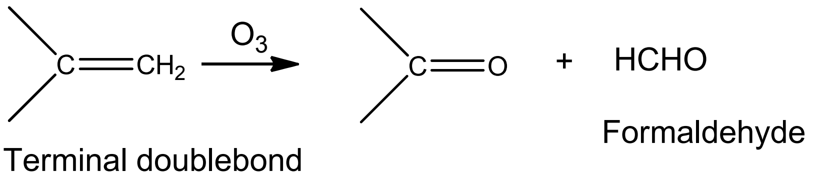
This reagent adds to olefinic double bond to form ozonide which upon decomposition by catalytic reduction or hydrolysis to yield carbonyl compounds.



The Ozonolysis is used to locate the position of double bond in a molecule.

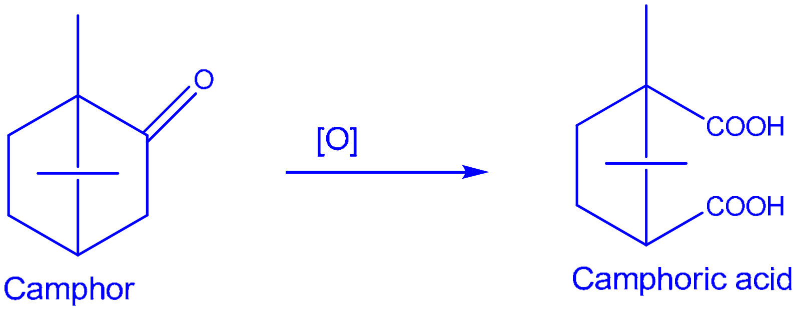
For example: The formation of acetone and formaldehyde reveals the presence of isopropylidene group and the terminal double bond.





Some time, ozonolysis may be used in the determination of structure of terpenoids. For example, ozonolysis has been used in the determination of structure of Citral.

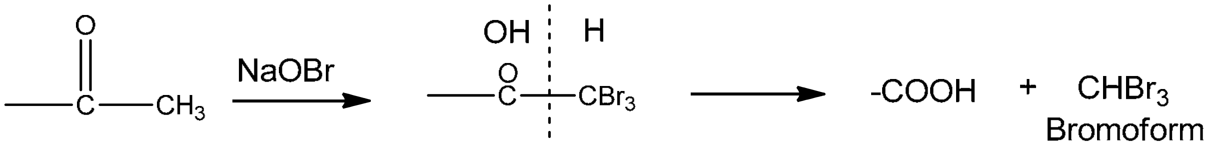
(ii) Nitric acid (HNO_3) : In a few cases, HNO_3 is also used to affect oxidative degradation. HNO_3 is a very powerful oxidizing agent, it degrades the terpenoid drastically to a mixture of aliphatic and aromatic acids.

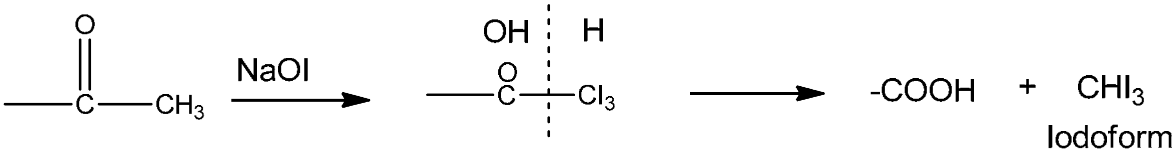


e.g. camphor upon oxidation with HNO_3 yields camphorinic acid.

(ii) Sodium Hypohalite : [Haloform Reaction]

This reagent is used for the removal of one carbon atom as a bromoform or iodoform from the methyl ketone ($-COCH_3$) group. This reaction is known as Haloform Reaction.

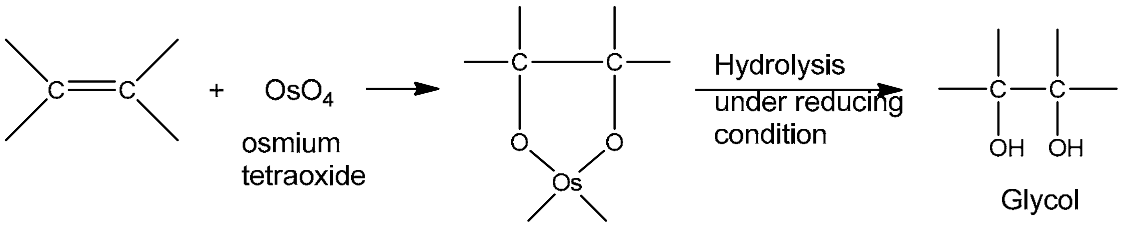




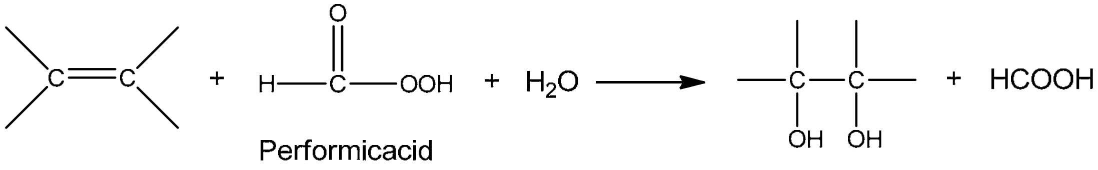
(iii) Hydroxylating Reagents:

When the hydroxylating reagents attack the olefinic double bond of terpenoids, 1,2-glycols will be obtained. These reagents are osmium tetraoxide, performic acid, Alkaline $KMnO_4$.

(i)

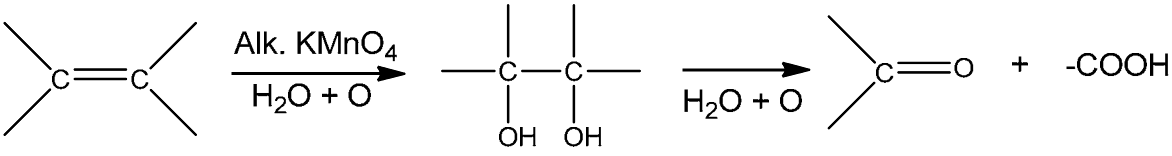


(ii)



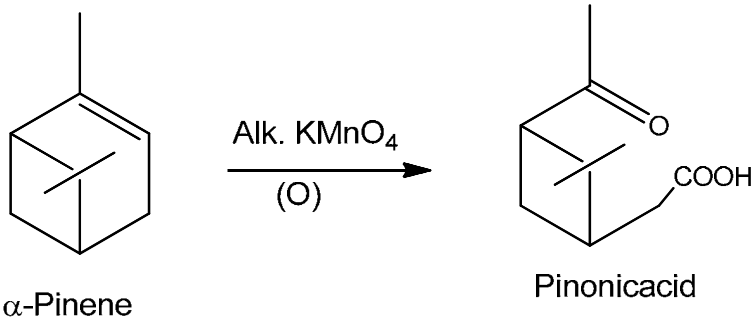
The alkaline $KMnO_4$ hydroxylates the double bond to give a glycol, which on further oxidation to give a mixture of ketone and acid.

(iii)



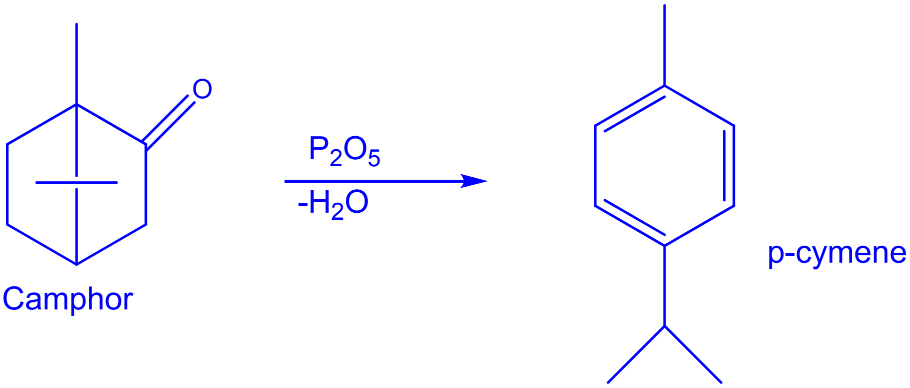
If double bond is present in the ring, then oxidation product keto acid or dicarboxylic acid is obtained without loss of C-atom.

e.g.

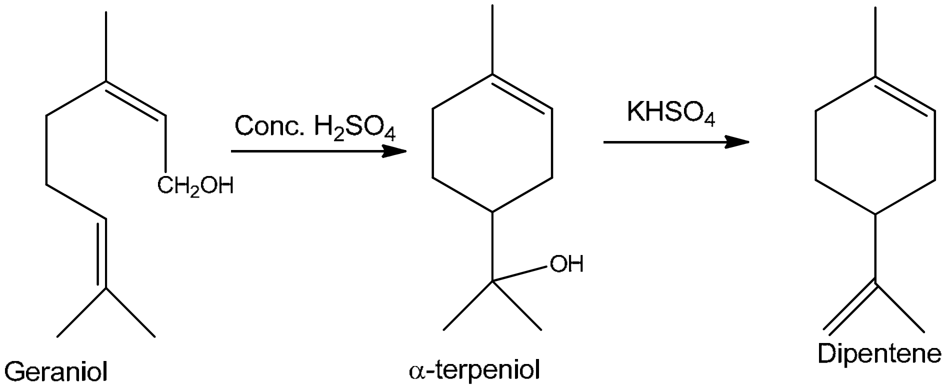


(f) Dehydration :

When terpenoids containing the alcoholic and ketonic groups, are heated with dehydrating agents converted into simple aromatic compounds. e.g.



Open chain [Acyclic] terpenoids on dehydration with Conc. H_2SO_4 to yield cyclic compounds. e.g. Geraniol on dehydration is converted into α-terpeniol which further dehydrated with $KHSO_4$ (Potassium bisulphate) to yield dipentene.



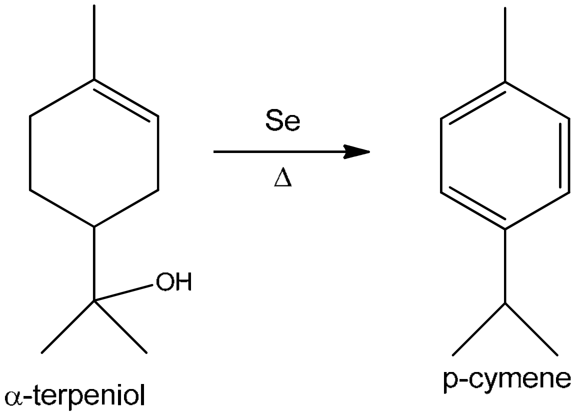
(g) Dehydrogenation :

When terpenoids are heated with Zn, I_2, Br_2, S, Se, pd etc. they are converted into aromatic compounds of known structure.

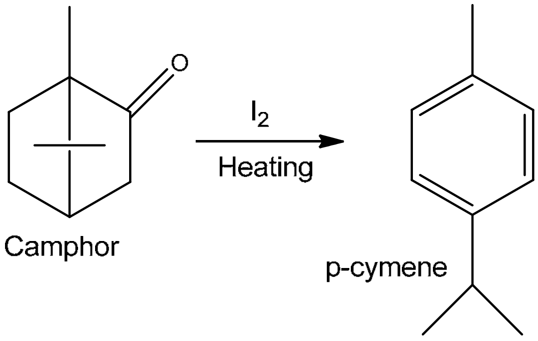
By this method, the skeleton structure and position of the side chain in the original terpenoids can be determined.

For example :

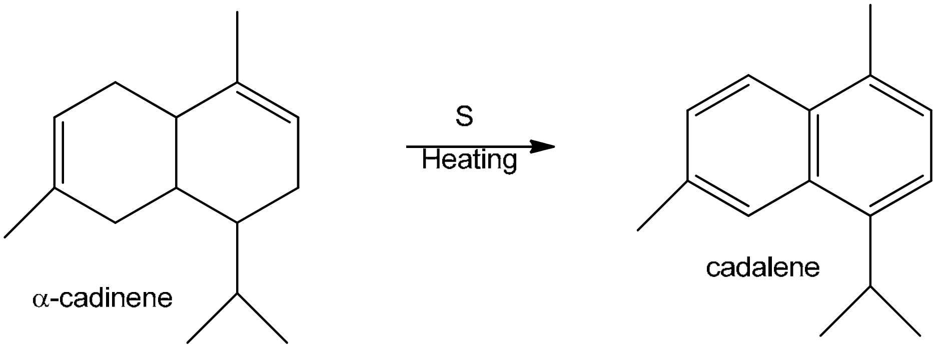
(i) α-terpineol is heated with selenium yields p-cymene.



(ii) Camphor is heated with I_2 yields p-cymene.



(iii) α-cadinene is heated with sulphur yields cadalene.



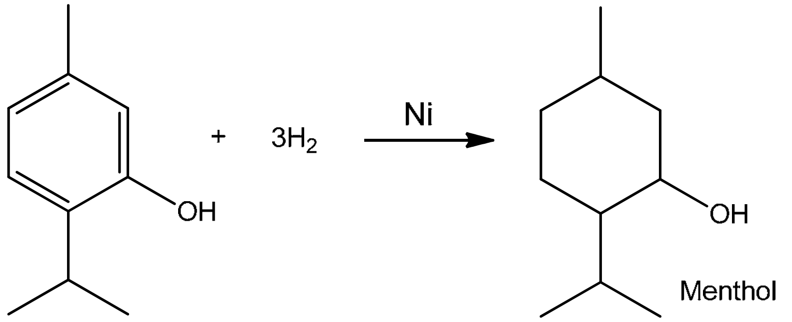
[B] Synthetical Methods :

These methods are as follows:

(a) Catalytical Hydrogenation :

When aromatic compounds are hydrogenated catalytically under suitable condition yields synthetic terpenoids.

e.g.

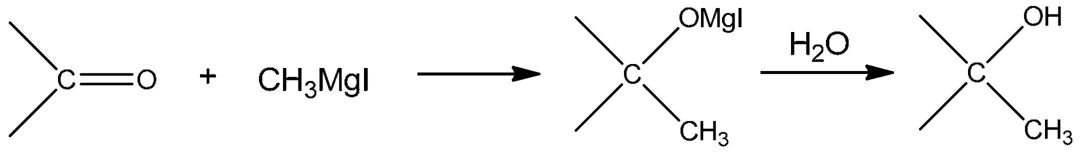


Thymol
[An aromatic compd.]

Menthol
[A terpenoid alcohol]

(b) Grignard Reaction :

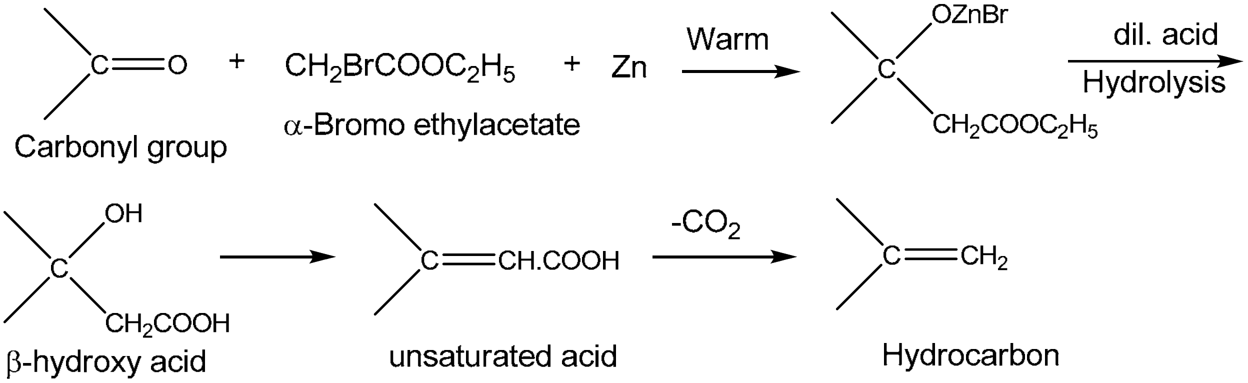
This reaction is the most important in terpenoid chemistry. This reaction was successfully employed by Perkin *et. al.* To synthesize a large number of compounds which are related to terpenoids. By Grignard reagent, methyl or isopropyl groups can be introduced into a compound having carbonyl group.



Carbonyl group

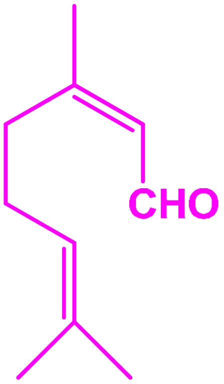
(c) Reformatsky reaction :

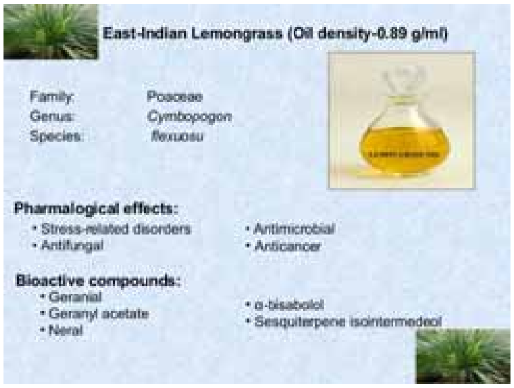
This reaction is very useful in the synthesis of terpenoids and related compounds. Like camphoranic acid, geranic acid etc.



1.11 Structure elucidation of citral

Structure:





East-Indian Lemongrass (Oil density-0.89 g/ml)

Family: Poaceae
Genus: Cymbopogon
Species: flexuosu

Pharmalogical effects:

- Stress-related disorders
- Antifungal
- Antimicrobial
- Anticancer

Bioactive compounds:

- Geranial
- Geranyl acetate
- Neral
- α-bisabolol
- Sesquiterpene isointermedeol

It is acyclic monoterpenoid.

It occurs in 60 to 80 percent in Lemon grass oil.

It is a pale yellow liquid having a strong lemon like smell.

Constitution of citral :

1. Molecular Formula is $C_{10}H_{16}O$.

2. Presence of two double bonds:

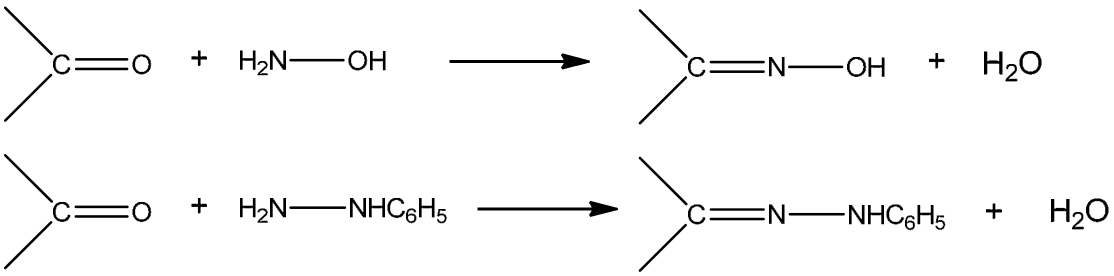
As citral adds on two moles of hydrogen or bromine, this shows that citral contain two double bonds.

$$C_{10}H_{20}O \xleftarrow[Pd]{2H_2} C_{10}H_{16}O \xrightarrow{2Br_2} C_{10}H_{16}OBr_4$$

Tetrahydro citral Citral Citral tetralbromide

3. Presence of an aldehyde group :

With hydroxylamine and phenylhydrazine, citral forms oxime and phenylhydrazone. This reaction indicates that citral must contain one oxo group.



Citral on reduction with sodium amalgam yield geraniol [an alcohol] and is oxidized with silver oxide yield geranic acid. Formation of both products contain same number of C-atoms as citral. **Both these reactions reveal that oxo group in citral is therefore an aldehyde group.**

$$C_{10}H_{16}O_2 \xleftarrow[Ag_2O]{[O]} C_{10}H_{16}O \xrightarrow[Na\text{-}Hg]{2[H]} C_{10}H_{18}O$$

Geranicacid Citral Gerniol

Citral reduce Fehling’s solution further confirming the presence of an aldehyde group.

4. Citral as an acyclic compound :

The presence of two double bonds and an aldehyde group in citral leads to a unsaturated hydrocarbon of M.F. $C_{10}H_{22}$ which corresponds to the general formula C_nH_{2n+2} for acyclic compounds indicating that citral must be an acyclic compound.

5. Carbon skeleton of citral :

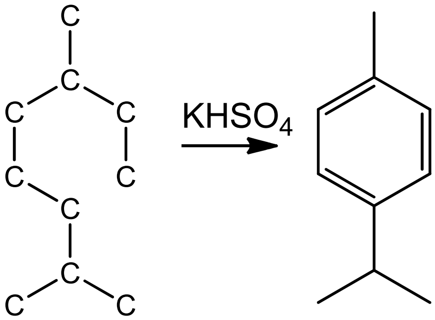
When citral is heated with potassium hydrogen sulphate, it cyclize to yield p-cymene.

$$C_{10}H_{16}O \xrightarrow[-H_2O]{KHSO_4} C_{10}H_{14}$$

Citral p-cymene

Formation p-cymene reveal that c-skeleton (I) of citral contains two isoprene units which are joined by head to tail arrangement.

The formation of p-cymene also reveals the relative positions of methyl and isopropyl groups in citral.

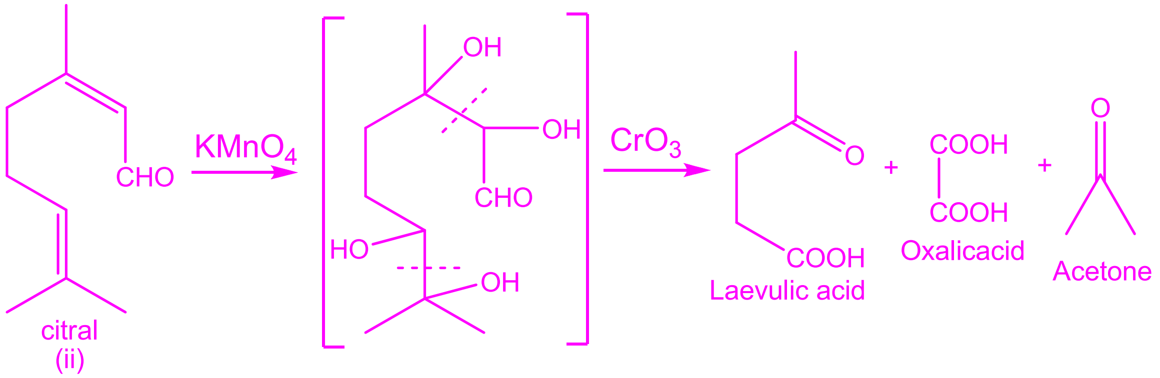


Carbon skeleton of citral
(i)

p-cymene

6. Structure of citral :

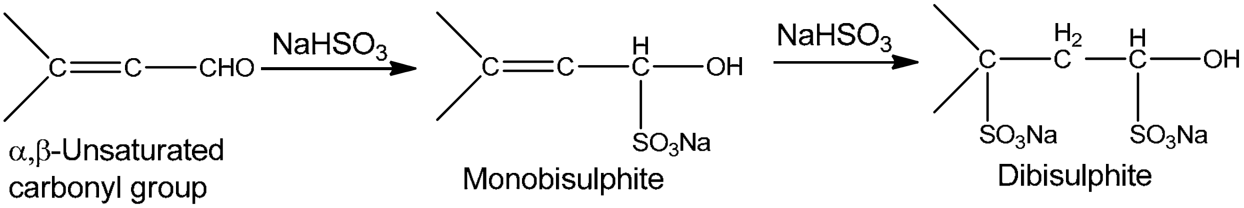
Citral on oxidation with alkaline KMnO$_4$ followed by CrO$_3$ yields acetone, oxalic acid and laevulic acid. The formation of these oxidation products can only be explained if citral has structure (ii).



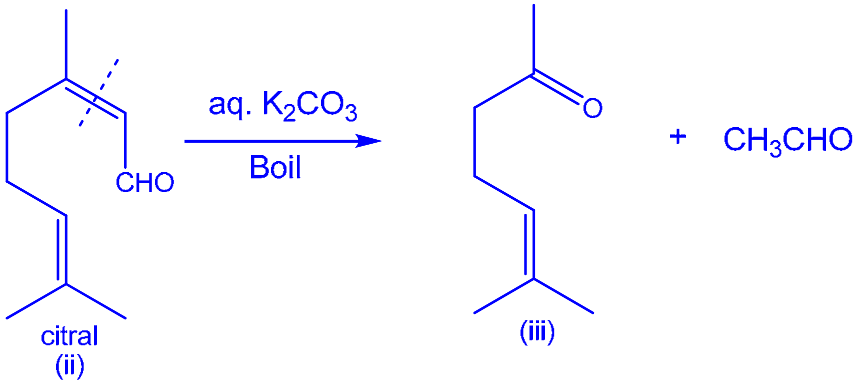
7. Support for structure of citral (ii) :

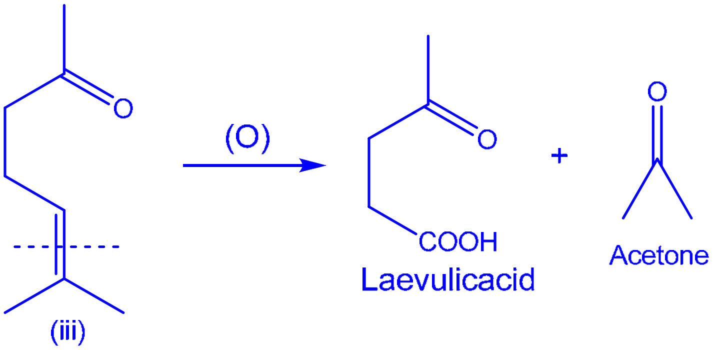
Following evidence have been confirmed the structure (ii) of citral.

[a] Citral is treated with two moles of sodium bisulphite forms mono as well as di-sulphite addition products. This indicates the presence of α, β-unsaturated aldehyde group.

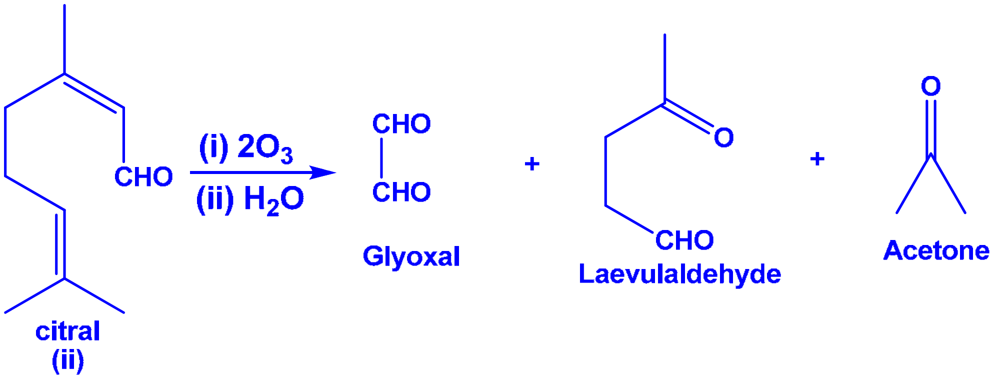


[b] In 1897 Verley found that citral on boiling with aq.K_2CO_3 yields 6-Methylhept-5-en-2-one [Methyl heptenone] - iii and Acetaldehyde structure-iii, itself oxidized to yield lavevulic acid and Acetone. This is again accounted that structure-ii is a structure of citral.

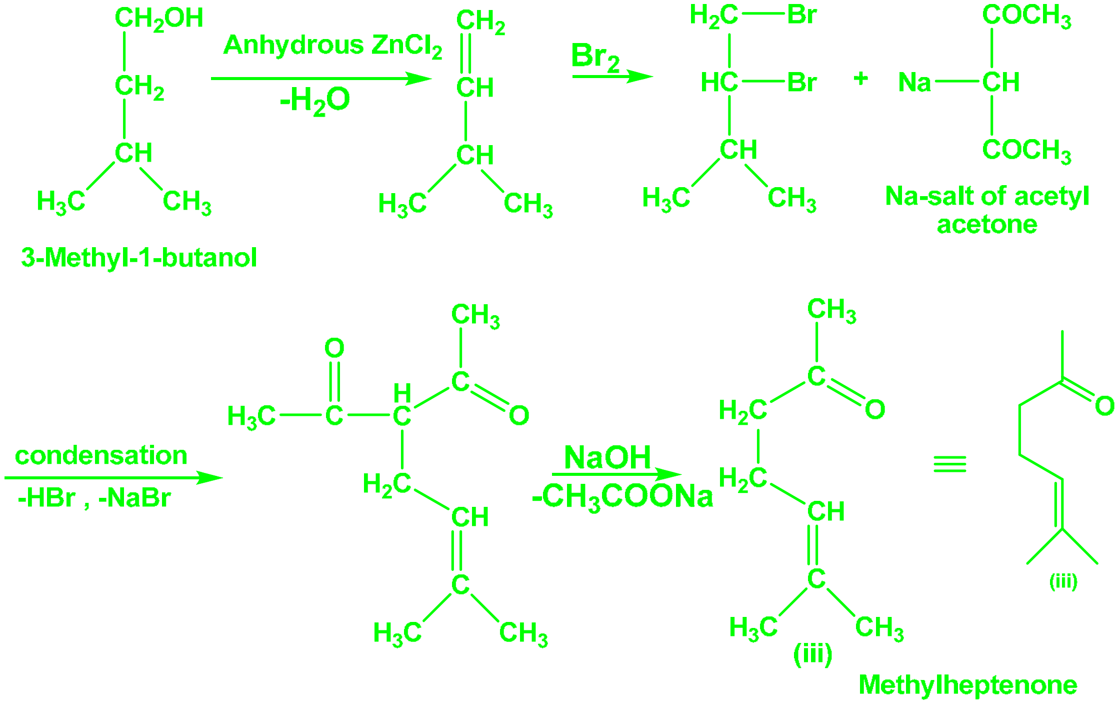




[c] The structure (ii) for citral has been further confirmed by ozonolysis of citral forms a diozonide which on hydrolysis yields glyoxal, laevulaldehyde and acetone.

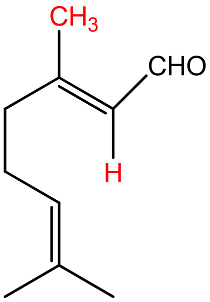


[d] The structure (ii) of citral is further confirmed by the synthesis of methyl heptenone(iii) fro 3-methyl-1-butanol.



8. Isomerism in citral :

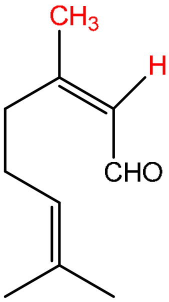
The natural citral is a mixture of two isomers are called citral-a and citral-b. They are actually geometrical isomers with respect to C_2-C_3 double bond. If methyl group and a hydrogen atom are trans to each other, it is citral-a [Geranial].



trans-Cittral
or
Citral-a
or
Geranial

Liquid
B.P-118^{o} to 119^{o}c

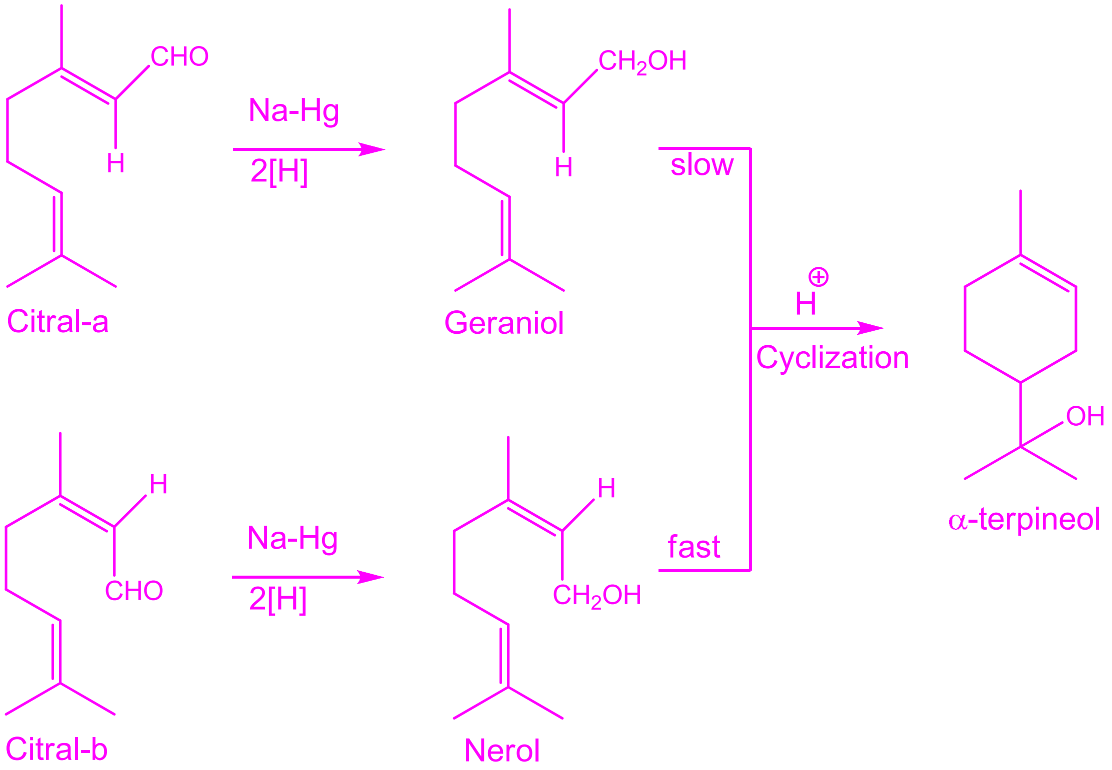
If methyl group and a hydrogen atom are cis to each other, it is citral-b [Neral].



cis-Cittral
or
Citral-b
or
Neral

Liquid
B.P-118^{o}c

Citral-a react faster with sodiumbisulphite in acetic acid than citral-b. Therefore, mixture of two isomers is treated with half of its weight of sodiumbisulphite in acetic acid. Then most of citral-a reacts to form crystalline derivatives where as citral-b remains in solution. Thus, the two isomers can be separated by repetition of this process. The above configuration has been assigned on the basis of following cyclization reaction.

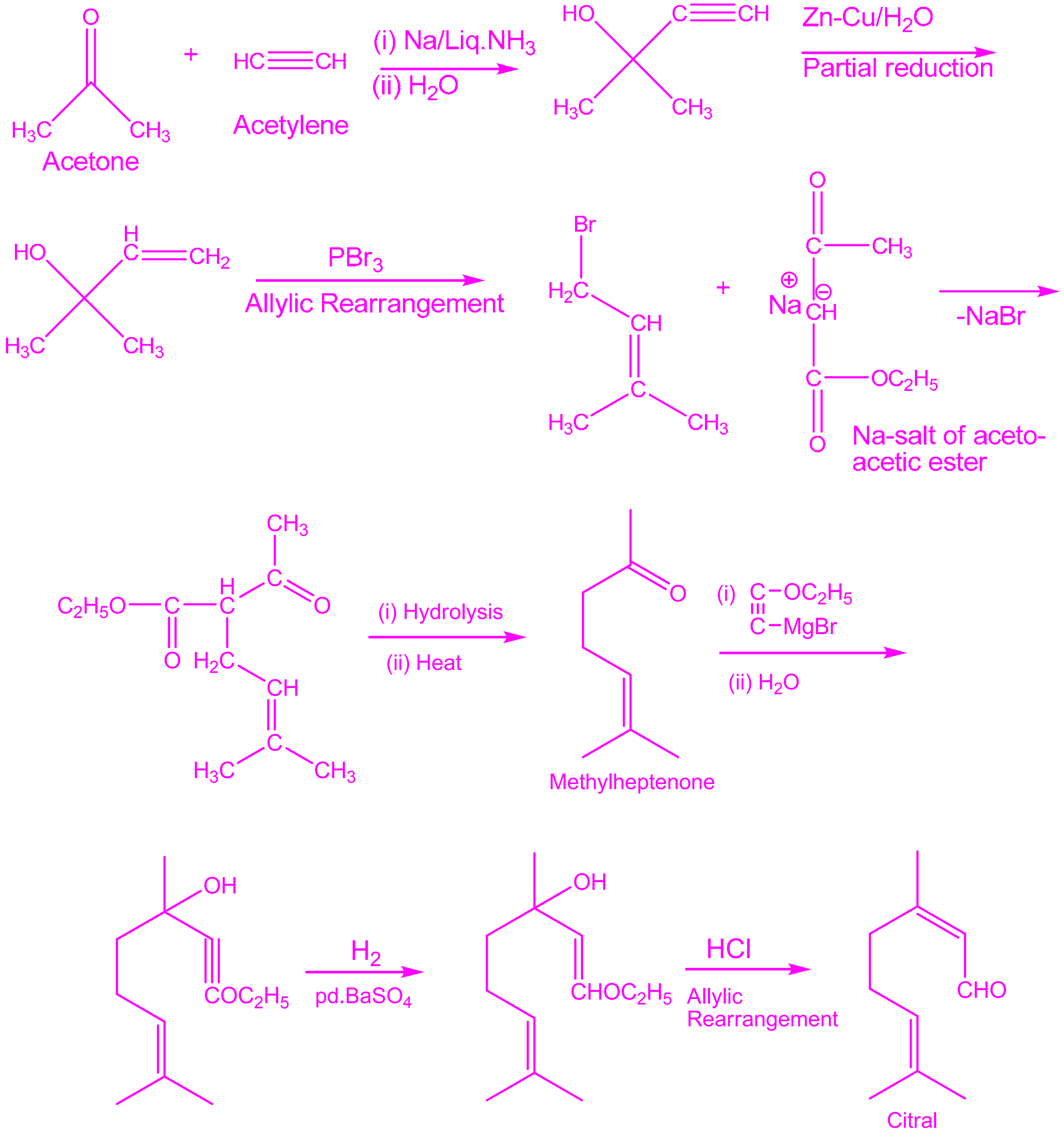


Citral-a and citral-b on reduction with Na-Hg forms corresponding alcohol [Geraniol and Nerol]. Then, on treatment with acid both geraniol and Nerol get cyclized into α-terpineol. But nerol cyclizes about nine times faster than Geraniol because in Nerol the alcoholic group and other double bond nearest to each other and hence it must be cis isomers.

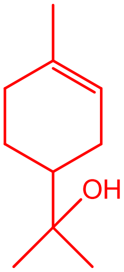
9. Finally, the structure (ii) for citral has been confirmed on the basis of synthesis as follows :

Arens-Van Dorps Synthesis [1948]

In this synthesis Acetone on condensation with Acetylene in presence of Na and NH_3 yields the products which on reduction followed by treatment with PBr_3 undergo allylic rearrangement. The product so obtained is treated with Na-salt of Acetoacetic ester and then hydrolyzed to yield methylheptenone. The latter compound on condensation with Ethoxyacetylene magnesium bromide followed by partial reduction and acidification yield a citral by Allylic rearrangement.


Acetone
+
Acetylene
(i) Na/Liq.NH3
(ii) H2O
Zn-Cu/H2O
Partial reduction
PBr3
Allylic Rearrangement
+
Na-salt of aceto-acetic ester
-NaBr
(i) Hydrolysis
(ii) Heat
Methylheptenone
(i) C−OC2H5 ≡ C−MgBr
(ii) H2O
H2
pd.BaSO4
HCl
Allylic Rearrangement
Citral

(ii) Structure elucidation of α-terpineol :



- It is an optically active mono-terpenoid.
- It is solid having m.p. 35°C.
- Its (+) form occurs in petigrain and neroli oils.
- Its (-) form occurs in camphor oils.
- Its (±) form occurs in cajuput oil.
- α-terpineol is widely used in the preparation of lilac perfumes and lilac-scented soaps.

Constitution:

1. Molecular formula is $C_{10}H_{18}O$.
2. Presence of one double bond:

- α-terpineol adds on one mole of Br_2 and NOCl to form their respective addition products, this indicates that α-terpineol contain one double band.

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

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

3. Presence of tertiary alcoholic group:

   α-terpineol, when treated with phenyl isothiocynate indicating the presence of a hydroxyl group in α-terpineol.

   Further, α-terpineol is insoluble in NaOH this shows that the hydroxyl group can not be phenolic.

   Also, α-terpineol undergoes dehydration readily, when heated with H_2SO_4 forming terpenoids like dipentene and terpinolene. Moreover α-terpineol does not undergo oxidation.

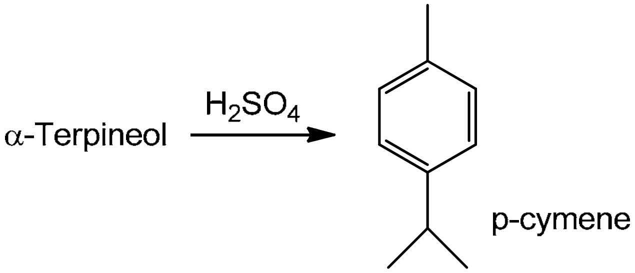
$$\underset{\alpha\text{-terpineol}}{C_{10}H_{18}O} \xrightarrow[-H_2O]{\text{conc. } H_2SO_4} \underset{\text{Terpinolene}}{C_{10}H_{16}}$$

   All the facts reveal that the hydroxyl group in α-terpineol is present as a tertiary alcoholic group.

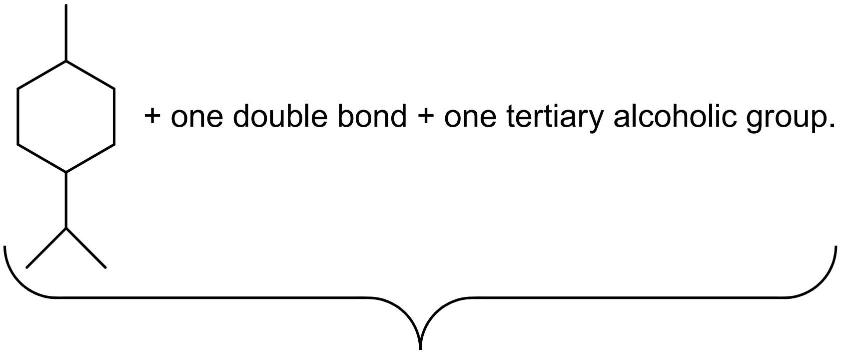
4. α-terpineol as a monocyclic compound, as α-terpineol contain one double bond M.F. of parent hydrocarbon is
   ≡ $C_{10}H_{18}$ + 2H [For one double bond]
   = $C_{10}H_{20}$

The M.F. $C_{10}H_{20}$ is correspond to the M.F. of C_nH_{2n} i.e. the general formula of monocyclic terpienoid. This indicates that α-terpineol as a monocyclic compound.

5. Carbon skeleton of α-terpineol:
   When α-terpineol is heated with H_2SO_4 to form p-cymene. This indicates that α-terpineol contains the p-cymene skeleton. Thus, it may be concluded that α-terpineol may be p-menthane [Fully saturated p-cymene] with one double bond and 3^o-alcoholic group.



Thus, the part structure of α-terpineol may be written as follows.



Part structure of α-terpineol

6. Position of a double bond and tertiary alcoholic group:
   These have been ascertained by Wallach by using graded oxidation. The series of degradation reactions of α-terpineol are as follows :

$$\begin{tikzcd}
\begin{array}{c}\alpha\text{-Terpineol}\\ \text{(i) } (C_{10})\end{array} \arrow[r, "1\%\ \text{Alk. } KMnO_4"] & \begin{array}{c}\text{Trihydroxy compound}\\ \text{(ii) } (C_{10})\end{array} \arrow[r, "CrO_3"] & \begin{array}{c}\text{Ketohydroxy acid}\\ \text{(iii) } (C_{10})\end{array} \arrow[d, "-H_2O"] \\
\begin{array}{c}\text{Terbic acid}\\ \text{(vi) } (C_7)\end{array} & \begin{array}{c}\text{Terpenylic acid}\\ \text{(v) } (C_9)\end{array} \arrow[l, "KMnO_4"'] & \begin{array}{c}\text{Kero-actone}\\ \text{(iv) } (C_{10})\end{array} \arrow[l, "\text{Alk. } KMnO_4"', "\begin{array}{c}\text{warm}\\ -CH_3COOH\end{array}"]
\end{tikzcd}$$

From the above set of degradative products, the following conclusions could be obtained.

(a) α-terpineol (i) when oxidized with 1% alkaline $KMnO_4$, undergo hydroxylation at double bond to produce trihydroxy compound (ii). This compound (ii) further oxidized with CrO_3 yields a compound (iv). This compound (iv) contains a ketonic group and does not give any reaction with Sodium bicarbonate and is, therefore, neutral.

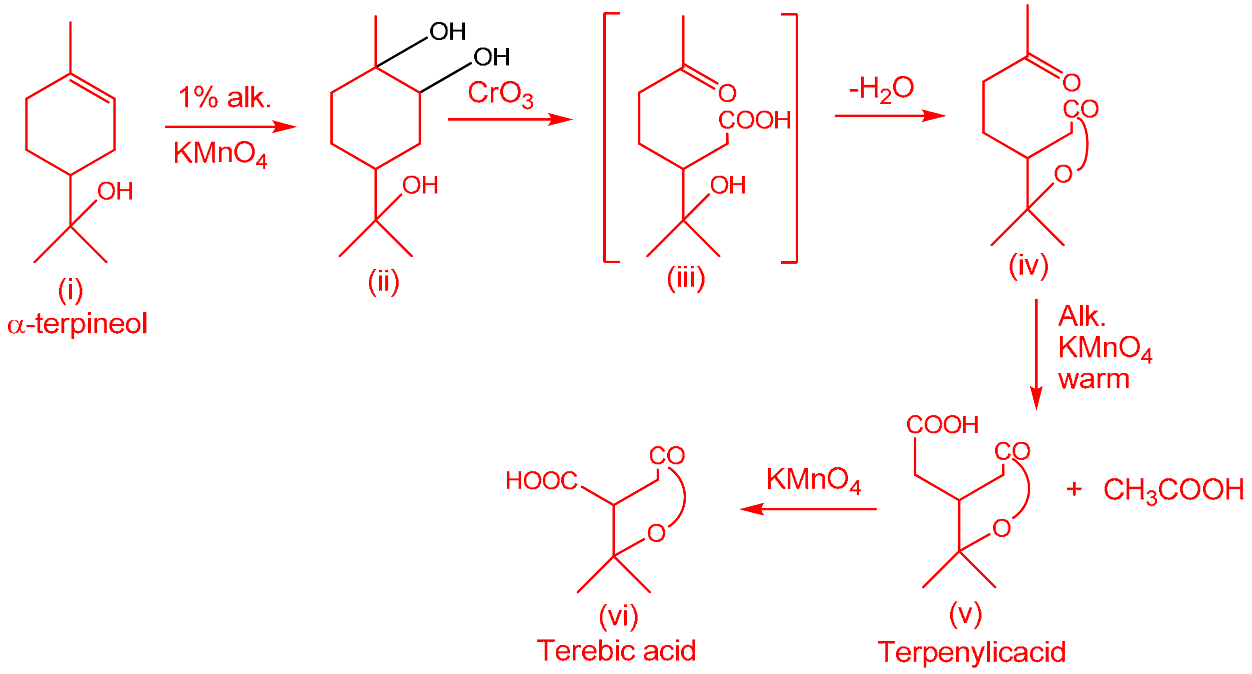
Furthermore compound (iv) is refluxed with excess of standard alkali followed by back titration, it is found that the amount of alkali consumed corresponds to the present of one carboxyl group. Thus compound (iv) may be lactone of a mono carboxylic acid.

(b) The formation of compound (iv) due to the breaking of glycol bond in compound (ii) without ant loss of c-atom it means that double bond must be present in the ring of compound (i).

(c) When the compound (iv) is warmed with alkaline $KMnO_4$ yields acetic acid and compound (v).

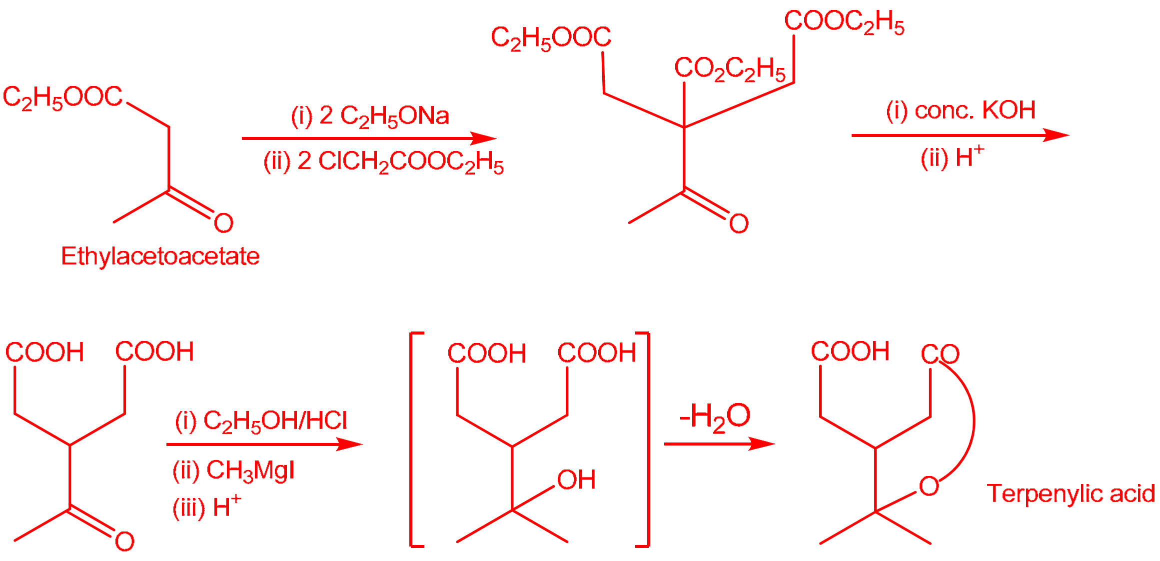
Formation of acetic acid reveals that the compound (iv) contains CH_3CO group i.e. the compound (iv) is a methylketone.

All the above reactions have been formulated on the basis of structure (i) as the structure of α-terpineol.

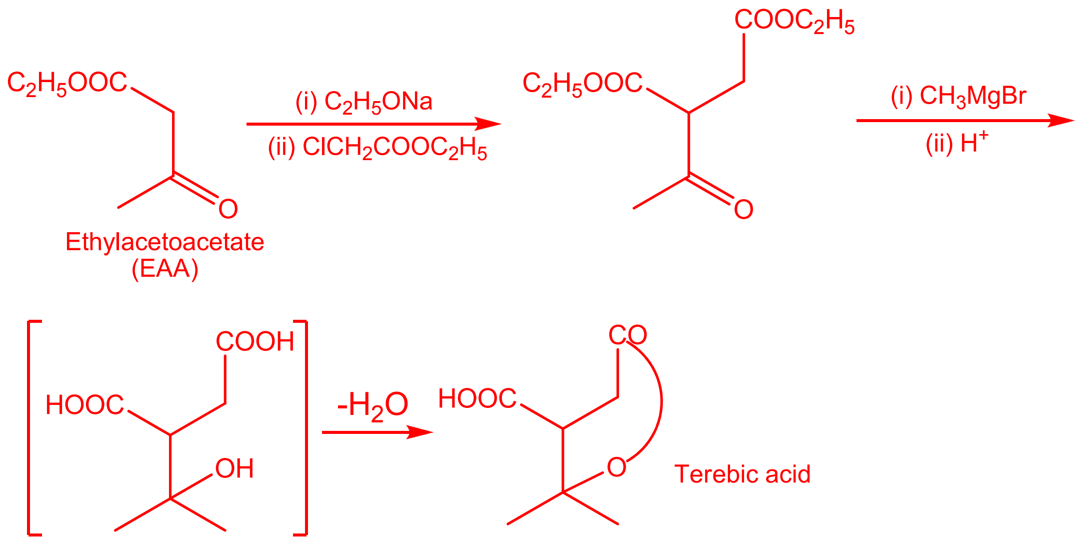


The structure of Terebic acid and Terpenylic acid have been proved by their synthesis [Simmonsen 1907].

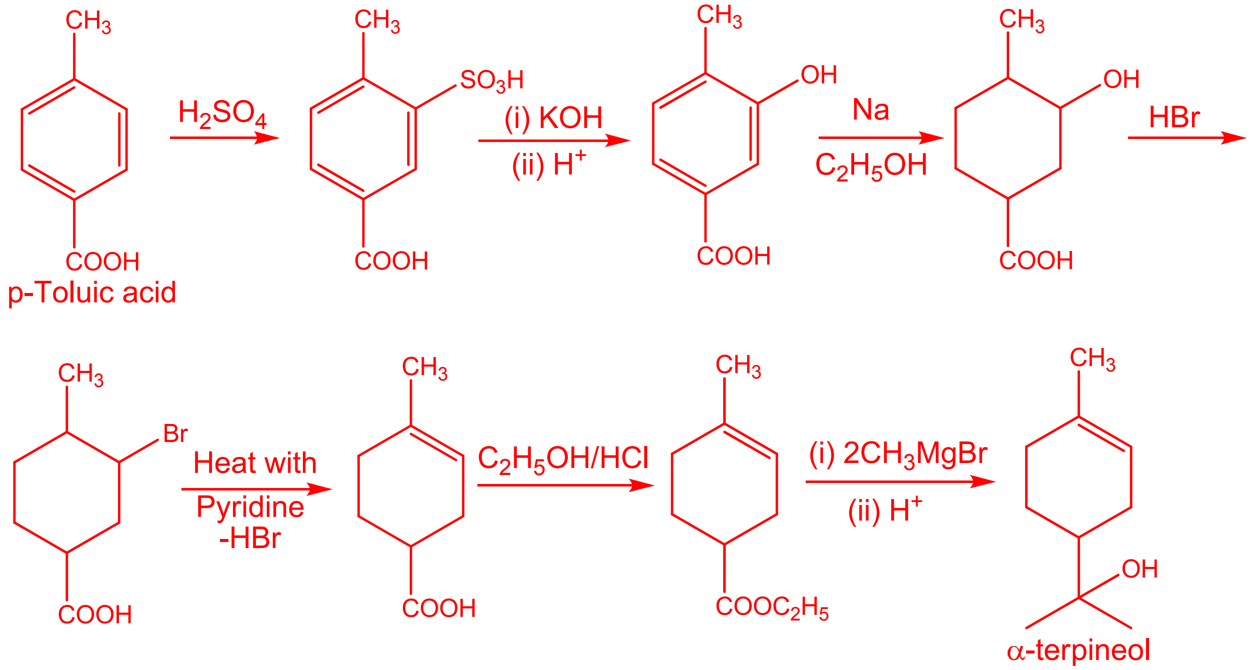
Synthesis of Terebic acid:



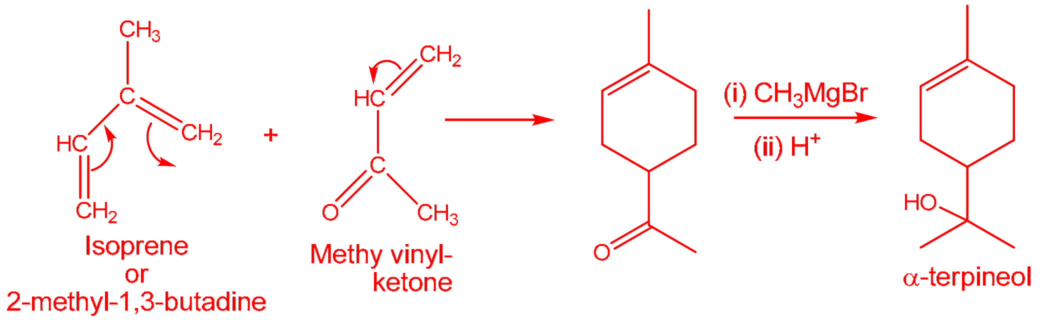
Synthesis of Terpenylic acid:



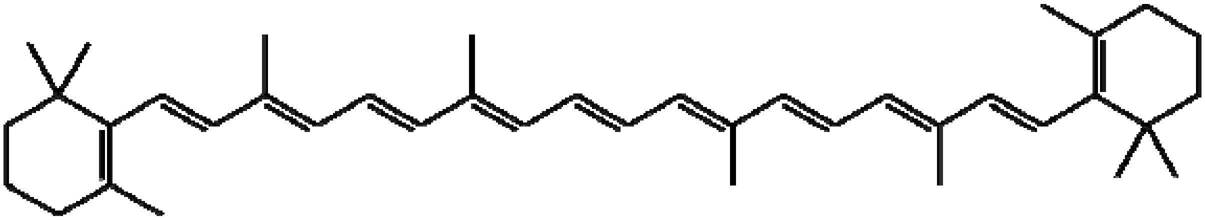
7. **Synthesis: Finally, structure (i) has been confirmed by Perkin-Junior-Meldrum synthesis:**



Alder-Vogt's synthesis:



(iii) Structure elucidation of β- CAROTENE:



Introduction : In nature β-Carotene occurs in all green plants along with chlorophyll. Carrots are considered to be the richest source of β- Carotene. [**ORANGE RED COLOUR**]

Isolation : It is isolated from carrots by employing following steps:

(a) The carrots are dried and then crushed to a fine powder.

(b) The dried carrot powder is extracted with petroleum ether repeatedly at room temperature. The extracts are combined and then concentrated as far as possible at 30-40^{0}C under reduced pressure.

(c) To the concentrated extract carbon disulfide is added. Then a small amount of ethanol is added to this solution to remove the colourless impurities which are removed by decantation.

(d) To the mother liquid obtained in step (b), ethanol is added to precipitate crude carotenes. The crude carotenes are filtered off. Then these are dissolved in fresh CS_2 and impurities are removed by means of alcohol. Finally the carotenes are recrystallized from petroleum ether.

(e) The mixture of α, β, ۷ **-** carotenes obtained from (d) is separated by employing column chromatography using calcium hydroxide as a adsorbent and petroleum ether as a solvent. Finally, the carotenes were eluted using ether containing 50% alcohol.

Properties : β **–** carotenes forms a red crystals having melting point 187-187.5 ^{0}C. It is optically inactive.

Constitution of β- Carotene:

Structure of β **–** carotene can be elucidated on the basis of following facts :

(i) Molecular formula :

M.F. of β – carotene is $C_{40}H_{56}$.

(ii) Presence of double bond :

β – carotene undergo addition of eleven molecules of hydrogen to form perhydro-β – carotene. This shows that β – carotene contains 11 double bonds.

$$C_{40}H_{56} \quad + \quad 11\ H_2 \quad / \text{Pt} \quad \longrightarrow \quad C_{40}H_{78}$$

(iii) β – carotene is a bicyclic compounds:

Molecular formula of β – carotene is $C_{40}H_{56}$ having 11 double bonds, therefore saturated β – carotene will have molecular formula $C_{40}H_{78}$, this corresponds to the general formula C_nH_{2n-2} for bicyclic compounds and hence β – carotene contains two rings.

(iv) Presence of five conjugated double bonds :

β – carotene undergo addition of five moles of maleic anhydride in presence of benzene solutions to form a crystalline adduct, indicate that it contains five conjugated double bonds.

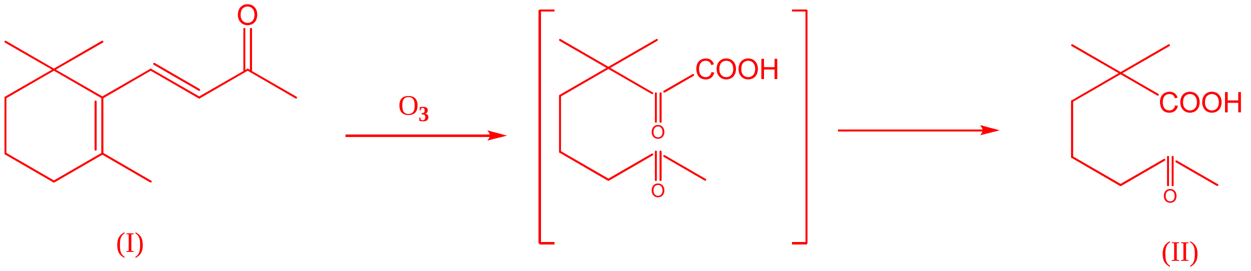
$$C_{40}H_{56} \quad + 5\ C_4H_2O_3 \xrightarrow{\text{Benzene}} C_{40}H_{56}\,(C_4H_2O_3)_5$$

(v) Presence of two β – ionone units:

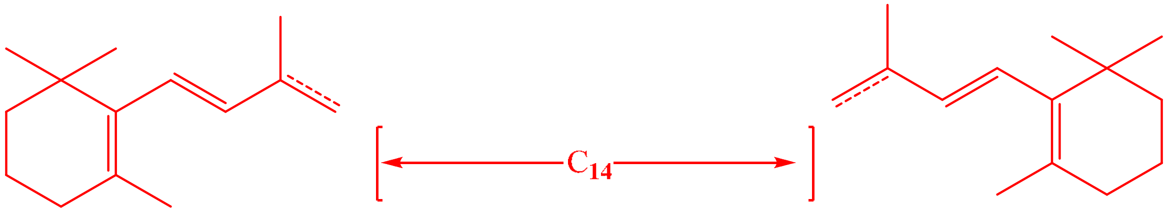
(a) When β – carotene is exposed to air, it develops the odour of violets (scent of their flowers) and is the characteristics of β – ionone. Therefore, we one can say that β – carotene must contain β – ionone nucleus in its molecules.

(b) Oxidation of β – carotene in benzene solution using cold alkaline $KMnO_4$ solution gives β – ionone.

(c) When β – ionone (I) is ozonolyzed it yields geronic acid in an amount corresponds to the presence of two β – ionone residues.



Thus, partial structure of β – carotene can be represented as :



β – ionone residue β – ionone residue

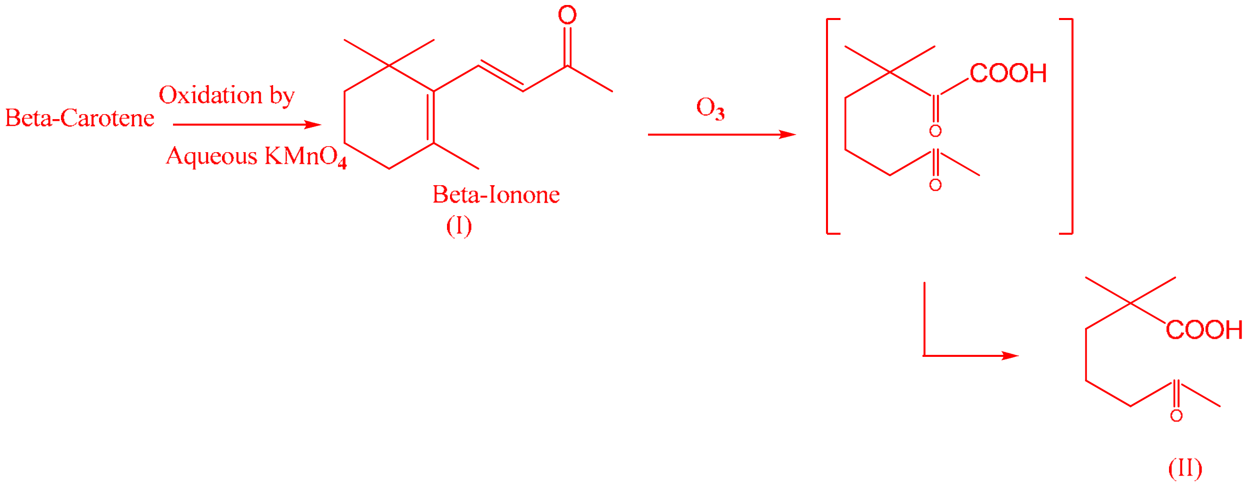
β – carotene is red-orange coloured pigment due to extended conjugation, it follows that C_{14} portion of the molecule is conjugated. The presence of conjugation in this central portion has been confirmed by the fact that β – carotene forms an adduct with **5** molecules of maleic anhydride.

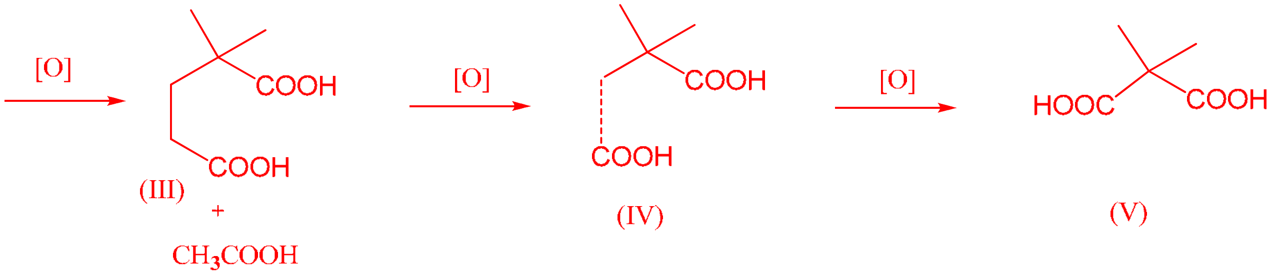
(vi) Presence of methyl side chain :

When β – carotene in benzene solution is oxidized with cold aqueous permanganate ($KMnO_4$) it yield a mixture of β – ionone (I), geronic acid (II), α,α-dimethylglutaric acid (III), α, α-dimethyl succinic acid (IV) and α,α-dimethyl malonic acid (V), and acetic acid (Vi).

All this products are also obtained during oxidation of β – ionone with cold aqueous permanganate ($KMnO_4$).

However, the amount of acetic acid (four molecules) obtained during the oxidation of β – carotene, is more than that could be accounted for by the presence of two β – ionone nuclei which will give only two molecules of acetic acid. This set of reactions reveals that some methyl side chains are present in the central portion (C_{14}) of partial structure of β – carotene.





(VII) Number and position of side chain :

To determine the exact number of methyl side chains in β– carotene Kuhn-Roth method was used. Initially this method involves use of alkaline $KMnO_4$, but have certain drawbacks, that it oxidize the fragment ==C(CH_3)—CH== to acetic acid but oxidation of fragments like ==C(CH_3)—CH_2 is incomplete or not at all.

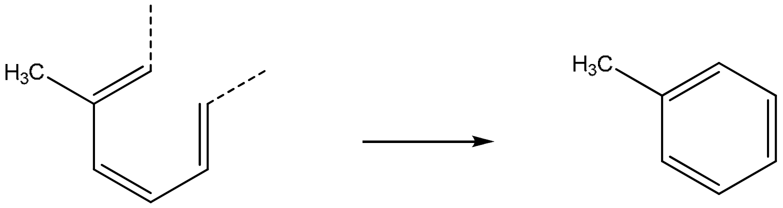
To overcome this issue **Kuhn-Roth** used chromic acid (chromium trioxide in sulphuric acid). Due to use of chromic acid side chains —C(CH_3) == CH, ==C(CH_3)—CH== and ==C(CH_3)—CH_2---- to acetic acid, isopropylidene end group also yields acetic acid , this end group is also determined by ozonolysis and the acetone so formed is estimated volumetrically.

When **Kuhn-Roth** method applied to β– carotene, it yields 5.4 molecules of acetic acid. This indicates that four —C(CH_3) == groups are present in the chain of β-carotene molecule. Out of these two are present in the two end β-ionone residues.

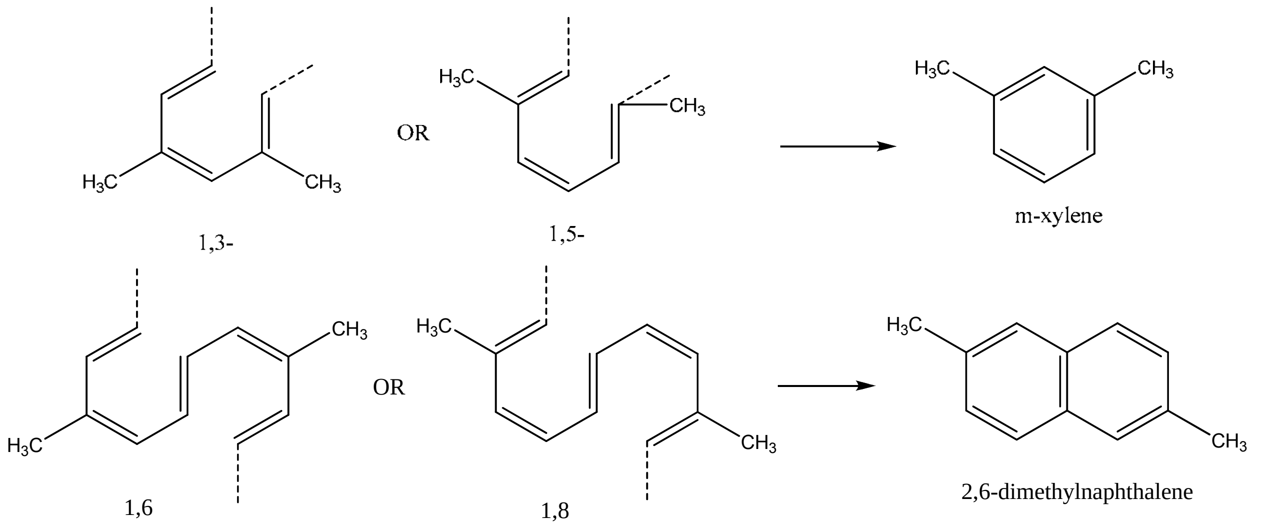
Now to determine the position of the remaining two side chain following method was used :

When β-caretone is distilled it produce mixture of toluene, m-xylene and 2,6-dimethyl napthalene. The formation of these products is due to cyclization of fragments of the polyene chain without involving the β-ionone rings. In order to get these desired aromatic products, the following types of chain fragments would be present in β-carotene.

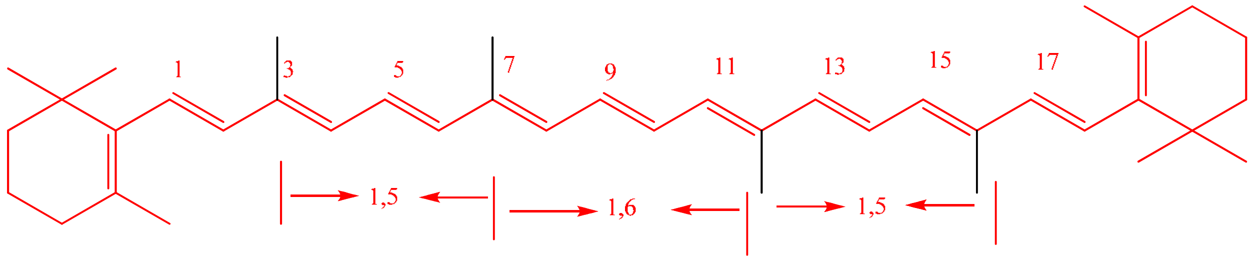
$$\text{Beta-caretone} \xrightarrow{\text{distillation}} \text{toluene} + \text{m-xylene} + \text{2,6-dimethyl napthalene}$$



toluene



From the steps (a), (b) and (c) the following symmetrical structure for β-carotene can be proposed.



In the above structure of β-carotene, the first two isoprene units from either side of the β – ionone units are joined head to tail fashion but the two isoprene units at the centre are linked by means of tail to tail fashions

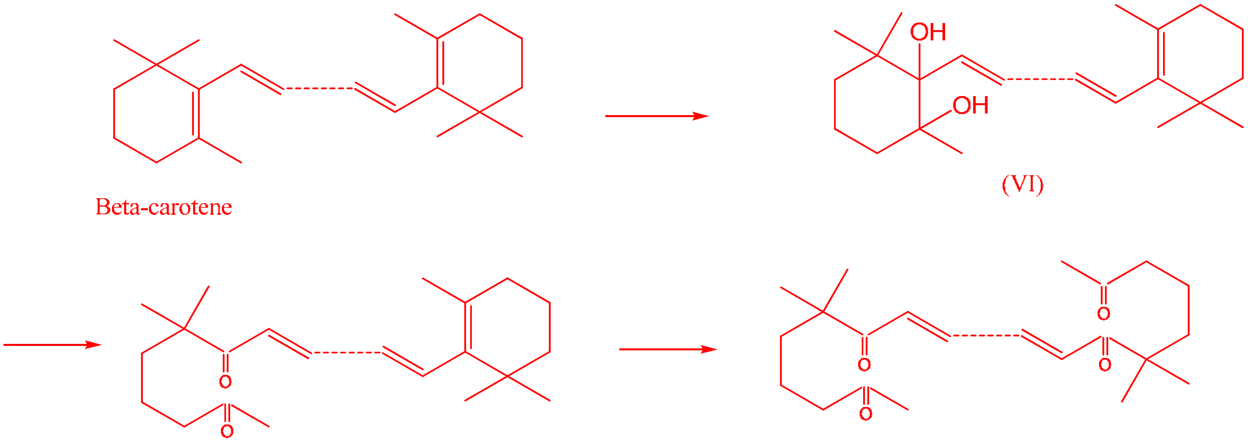
(viii) Confirmation of structure of β-carotene:

It can be confirmed by the following oxidation experiments:

When β-carotene is oxidized with potassium dichromate it yields dihydroxy- β-carotene (VI), 'VI' when further oxidize with lead tetraacetate yields semi- β-carotenone (VII), a diketone. As same number of carbon atoms are present in structure VI and VII and in β-carotene, it shows that the double bond in one of the β-ionone rings has been oxidized, so chain oxidized and there have been chain shortening (chain scission).

When semi-β-carotenone (VII) has been oxidized with CrO_3, β-carotenone (tetraketone) (VIII) having same number of carbon atom as β-carotene is obtained. This reveals that in the formation of compound - VIII, from VII, the other β-ionone ring is opened.

As only one dixydroxy-β-carotene and one semi--β-carotene are obtained, the above symmetrical structure for β-carotene is correct and its oxidation reactions are summarized as follows :



Beta-carotene

(VI)

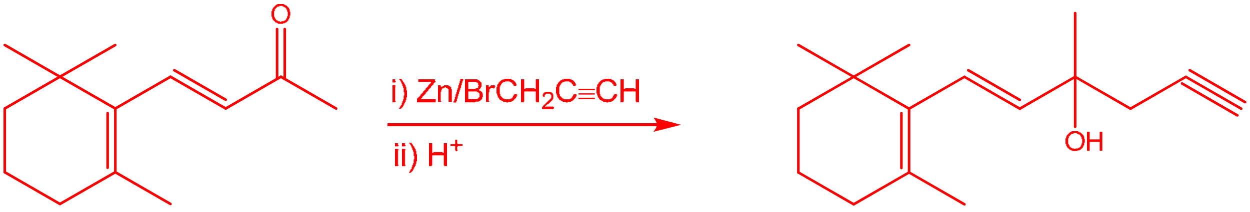
(VII)

(VIII)

Synthesis of β-carotene : Karrer *et. al.* :

It involves following steps :

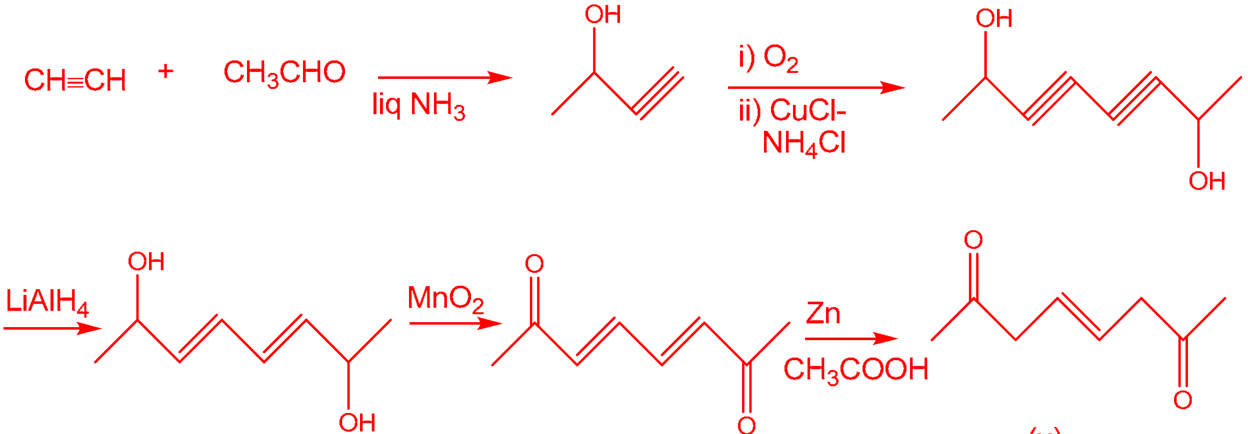
(i) First of all the acetylenic carbinol (IX) is prepared by treating β–ionone with propargyl bromide in the presence of zinc (reformatsky reaction)



β-Ionone

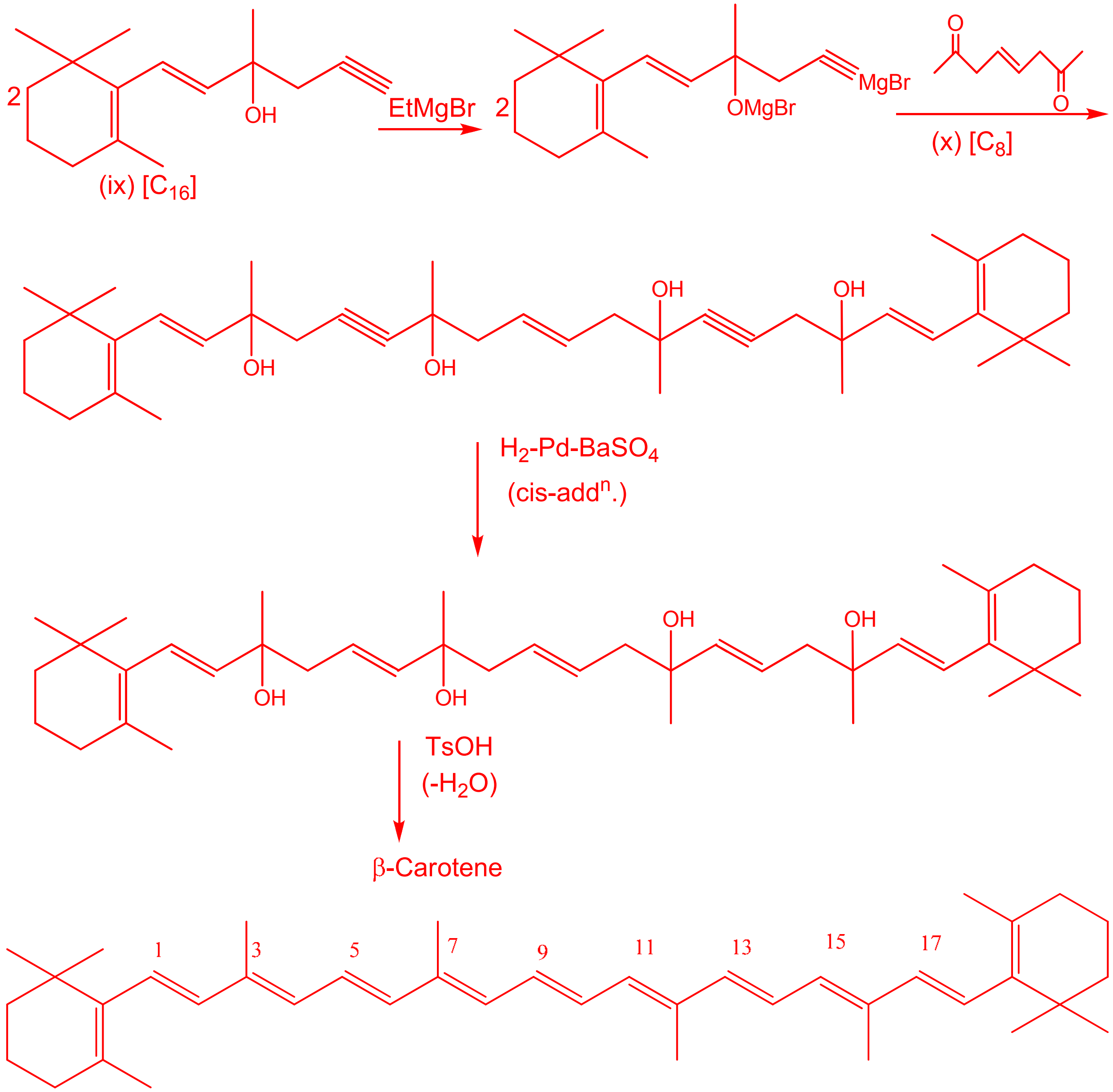
(ix)

(ii) Then, oct-4-ene-2, 7-dione (x) is prepared form but-1-yn-3-ol (Inhoffen et. al. 1951)



(x)

(iii) From compounds (ix) and (x), β-carotene is prepared as follows :


2
OH
(ix) [C16]
EtMgBr
2
OMgBr
MgBr
O
O
(x) [C8]
OH
OH
OH
OH
H2-Pd-BaSO4
(cis-addn.)
OH
OH
OH
OH
TsOH
(-H2O)
β-Carotene
1
3
5
7
9
11
13
15
17

(iv) Structure elucidation of CAMPHOR :

Introduction : This occurs in nature in the camphor tree of Formosa (Taiwan) and Japan. It is present in all the parts of the tee. However, the highest proportion is present in the trunk.

Isolation : When the wood and leaves of camphor tree are boiled with water in a vessel covered with a dome, camphor sublimes and collects on the surface of the dome. Further purification of camphor is done by resublimation.

The quantity of camphor isolated from camphor tree is not sufficient to meet the world demand. Therefore, it is prepared from α-pinene (which is obtained from the turpentine oil) by the following series of reaction :

$$\text{(a)}\quad \alpha\text{-Pinene} \xrightarrow[10^{o}\text{C}]{\text{HCl gas}} \text{Bornyl Chloride} \xrightarrow[\text{-HCl}]{\text{AcONa}} \text{Camphene}$$

$$\xrightarrow[H_2SO_4]{\text{AcOH}} \text{Isobornyl acetate} \xrightarrow{\text{NaOH}} \text{Isoborneol} \xrightarrow{PhNO_2} \text{Camphor}$$

$$\text{(b)}\quad \alpha\text{-Pinene} \xrightarrow[10^{o}\text{C}]{\text{HCl gas}} \text{Bornyl Chloride} \xrightarrow[\text{-HCl}]{\text{AcONa}} \text{Camphene}$$

$$\xrightarrow{\text{HCOOH}} \text{Isobornyl acetate} \xrightarrow{\text{NaOH}} \text{Isoborneol} \xrightarrow[\text{Ni ; }200^{o}\text{C}]{O_2} \text{Camphor}$$

$$\text{(c)}\quad \alpha\text{-Pinene} \xrightarrow{\text{Isomn.}} \text{Camphene} \xrightarrow[\text{rearr.}]{\text{AcOH}} \text{Isobornyl acetate}$$

$$\xrightarrow{\text{NaOH}} \text{Isoborneol} \xrightarrow[\text{Dehydrogen.}]{\text{Catalytic}} \text{Camphor}$$

Properties : It is a solid having m.p. 180^{o} and is optically active; the (+) and (-) forms occur naturally whereas racemic camphor is the usual form of synthetic camphor.

Uses : Its various uses are as follows :

- (i) As a plasticizer for the manufacture of celluloid and photographic films.
- (ii) For the manufacture of smokeless powders and explosives.
- (iii) As a mild disinfectant and stimulant for the heart muscles.
- (iv) As an insect repellent.
- (v) As a solvent in the Rast camphor method for the determination of molecular weights.

Constitution of Camphor :

A tremendous amount of work was done before the structure of camphor was successfully elucidated by Bredt (over 30 structures have been proposed) on the basis of following analytical and synthetic evidences :

1. **Molecular formula :** From analytical data and molecular weight determination, it follows that the molecular formula of camphor is $C_{10}H_{16}O$.
2. **Saturated characteristics** : Camphor does not add reagents like bromine, nitrosyl chloride (NOCl), etc. However, it forms mono-substitution products like mono-bromocamphor, mono-chlorocamphor, camphor-sulphonic acid. The formation of these products reveals that camphor is a saturated compound and does not contain any double bond. This is further supported by the facts that it does not react with 1% alkaline $KMnO_4$.
3. **Presence of a keto group :** The nature of oxygen atom is found to be cyclic ketonic on the basis of following facts :

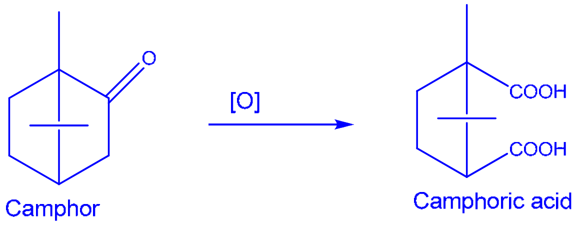
(i) It forms an oxime with hydroxylamine

$$\underset{\text{Camphor}}{C_{10}H_{16}O} + H_2NOH \longrightarrow \underset{\text{Camphor oxime}}{C_{10}H_{16}=N\text{-}OH}$$

(ii) It forms semicarbazone with semicarbazide

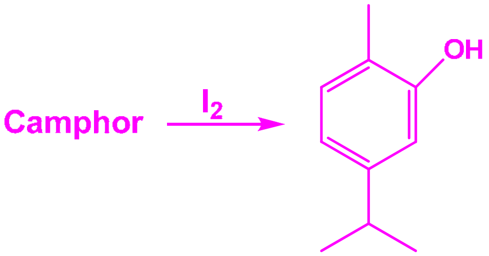
(iii) It forms pheylhydrazone with phyelhydrazine.

(iv) Camphor, when oxidized with nitric acid, yields a dicarboxylic acid called camphonic acid without loss of carbon atoms.



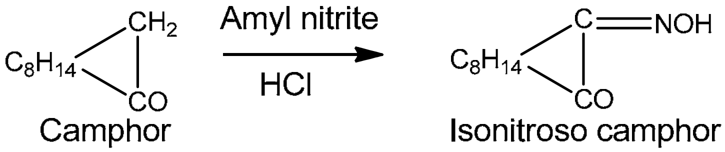
Further, camphor when reduced with sodium amalgam, yields a secondary alcohol called borneol. Hence, camphor must beta-cyclic ketone.

(v) When camphor is distilled with iodine, it yields carvacrol.

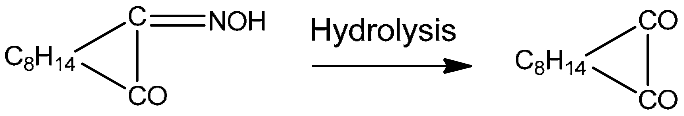


The presence of phenolic group in carvacrol reveals the presence of ketonic group in camphor.

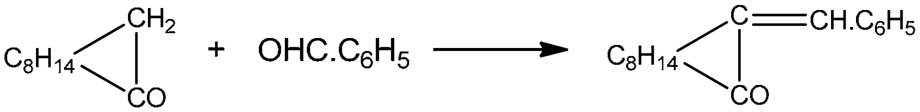
4. **Bicyclic system :** The molecular formula of saturated parent hydrocarbon of camphor is $C_{10}H_{18}$ which corresponds to the general formula C_nH_{2n-2} of bicyclic compounds and, therefore, camphor is a bicyclic compound.
5. **Presence of –CH_2CO group :** When camphor is treated with amyl nitrite [$CH_3(CH_2)_4NO_3$] and hydrochloric acid, it yields an iso-nitroso (oximino) Camphor in which two hydrogen atoms have been replaced by =NOH group. This reaction reveals that the >C=O group is directly attached to a –CH_2 group.



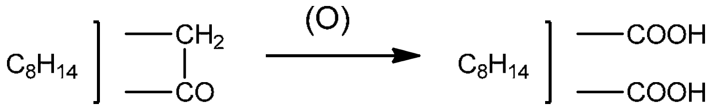
Iso- nitroso camphor when hydrolyzed yields camphonquinone, thus confirming the presence of a –CO-CH_2 group.



When camphor is treated with benzaldehyde, it yields benzylidene derivative. Again, this reaction is characteristic of the reactive methylene group attached to a -- CO group. This shows that camphor must contain –CH_2CO group.

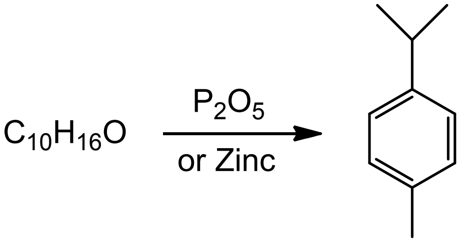


The presence of –CO-CH_2 grouping in a ring of camphor has been further confirmed by the fact that camphor, when oxidized, yields camphoric acid, a dibasic acid having the same number of carbon atoms. The oxidation takes place by opening of the ring.



$$C_8H_{14}\left]\begin{array}{l}—CH_2\\ \;|\\ —CO\end{array}\right. \xrightarrow{(O)} C_8H_{14}\left]\begin{array}{l}—COOH\\ \\ —COOH\end{array}\right.$$

6. **Presence of a six membered ring:** When camphor is distilled with zinc chloride or phosphorus pentoxide, it yields p-cymene. Formation of p-cymene reveals the presence of six-membered ring, methyl and gem dimethyl groups in camphor.



p-Cymene

When camphor is heated with hydriodic acid [HI], it yields tetra-and hexa-hydro m-xylene, confirming that camphor contains a six-membered ring.

7. **Nature of the carbon-frame in camphor:** When camphor is oxidized with nitric acid, it yields a crystalline dibasic acid, camphoric acid, $C_{10}H_{16}O_4$. As camphonic acid possesses the same number of carbon atoms as camphor, it means that the keto group must be present in one of the rings in camphor. Further, camphoric acid is a dicarboxylic acid and its molecular refraction reveals that into it is also saturated. Thus, during the conversion of camphor into camphoric acid there occurs the opening of ring containing the keto group and, therefore, camphoric acid must be a monocyclic compound.

   When camphoric acid is further oxidized with nitric acid, camphoronic acid is obtained.

$$\underset{C_{10}H_{16}}{\text{Cmphor}} \xrightarrow[\text{[O]}]{HNO_3} \underset{C_{10}H_{16}O_4}{\text{Camphoric acid}} \xrightarrow[\text{[O]}]{HNO_3} \underset{C_{10}H_{16}O_6}{\text{Camphoronic acid}}$$

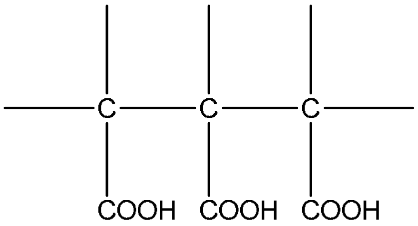
   In order to elucidate the structure of camphor, the structures of camphoric acid and camphoronic acid should be known with certainty.

8. **Structure of camphoronic acid:** This can be elucidated as follows:

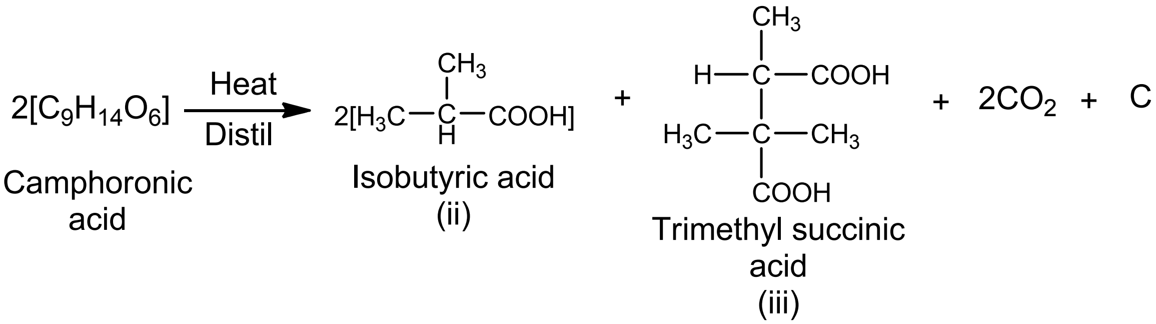
(a) The molecular formula of camphoronic acid is $C_9H_{14}O_6$.

(b) As camphoronic acid has been shown to be a saturated tricarboxylic acid, its molecular formula may be written as $C_6H_{11}(COOH)_3$ and its parent hydrocarbon will, therefore, be C_6H_{14} which corresponds to the general formula (C_n H_{2n+2}) for acyclic compound, indicating that camphoronic acid is an acyclic compound.

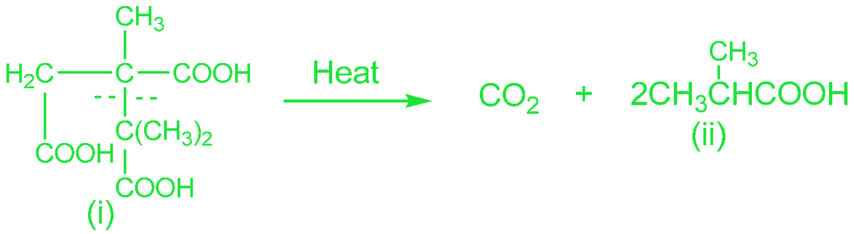
(c) As camphoronic acid does not undergo decarboxylation under ordinary conditions, it means that its three carboxyl groups should be attached to three different carbon atoms.

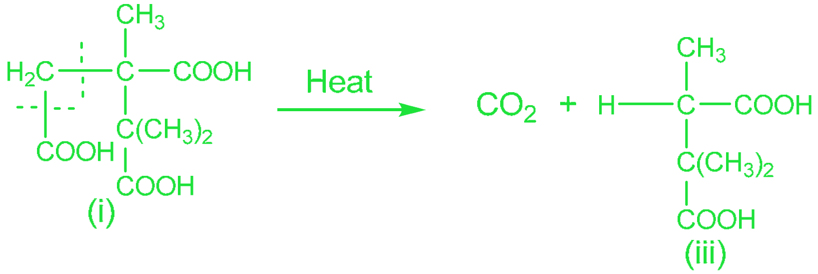


(d) When camphoronic acid is distilled at atmospheric pressure, it yields isobutyric acid (ii), trimethylsuccinic acid (iii), carbon dioxide and carbon.

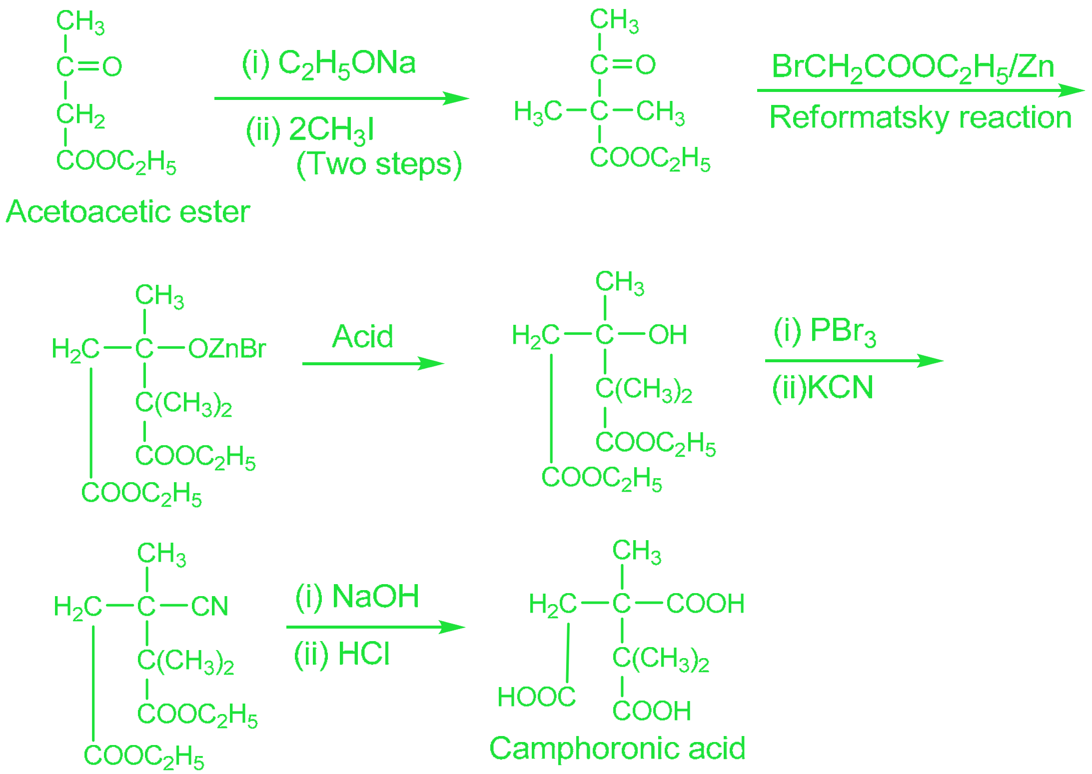


In order to explain the formation of these products, Bredt (1893) suggested that camphoronic acid is α, α, β-tricarballylic acid (i).





(e) The structure (i) for camphoronic acid has been confirmed by its synthesis given by Perkin Junior and Thorpe (1897). In this synthesis acetoacetic ester is converted into the dimethyl derivative which is then subjected to Reformatsky reaction with ethyl bromoacetate. The product so obtained is concerted into halide and then into a cyanide. Finally, the latter compound when hydrolyzed yields camphoronic acid.

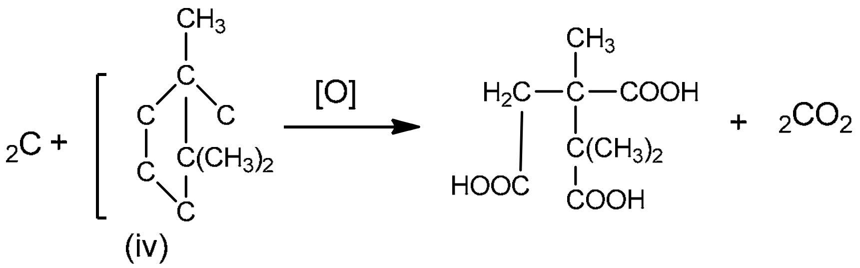


9. Structure of camphoric acid. It is elucidated as follows:

(a) The molecular formula of camphoric acid is $C_{10}H_{16}O_4$.

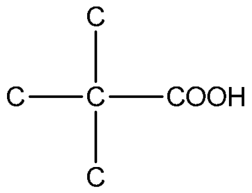
(b) By usual tests, camphoric acid has been shown to be a saturated dicarboxylic acid.

(c) If camphoronic acid has structure (i), then camphoric acid (and hence camphor) must possess three methyl groups. On this basis, the molecular formula of camphoric acid, $C_{10}H_{16}O_4$, may be written as $(CH_3)_3C_5H_5(COOH)_2$. The parent (saturated) hydrocarbon corresponding to camphoric acid is C_5H_{10} which corresponds to general formula of C_nH_{2n} for a monocyclic derivative and, therefore, camphoric acid is a monocyclic derivative. This also agrees with the previous evidence that camphoric acid is monocyclic. Thus, the oxidation of camphoric acid to camphoronic acid may be written as follows:



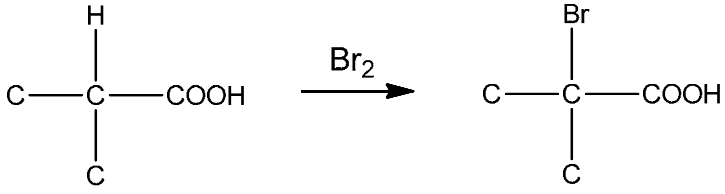
The skeleton (iv) plus one carbon, having arrangement with two carboxyl groups, will lead to the structure of camphoric acid.

(d) As camphoric acid is able to form a monoester readily but if forms diester with difficulty, this shows that the two carboxyl groups are not similar, i.e., one is primary or secondary and the other is tertiary. This is confirmed by the fact that camphoric anhydride forms only one monobromo derivative with phosphorus/bromine. The formation of this monobromo derivative is only possible if one of the carboxyl groups is secondary, i.e., the carbon atom of one carboxyl group must be $_1$C.



$$C-\overset{\overset{C}{|}}{\underset{\underset{C}{|}}{C}}-COOH$$

t-Carboxyl group (esterified with difficulty)

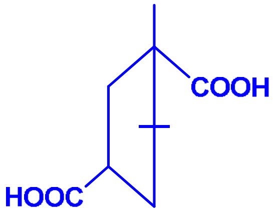


$$C-\overset{\overset{H}{|}}{\underset{\underset{C}{|}}{C}}-COOH \xrightarrow{Br_2} C-\overset{\overset{Br}{|}}{\underset{\underset{C}{|}}{C}}-COOH$$

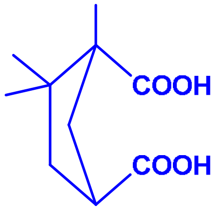
Sec-Carboxyl group (easily esterified)

Monobromo derivative

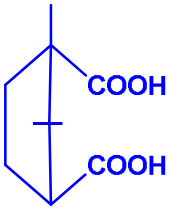
(e) In the step (d), the position of one carboxyl group has been ascertained. Now the next problem is to ascertain the position of other carboxyl group in camphoric acid. Its position should be such that when there occurs the opening of cyclopentane ring of camphoric acid to yield camphoronic acid, one carbon atom is readily lost. If this fact is taken into account, then there are two reasonable structures for camphoric acid, (v) and (vi). The structure (v) may be rewritten as (vA).



(v)



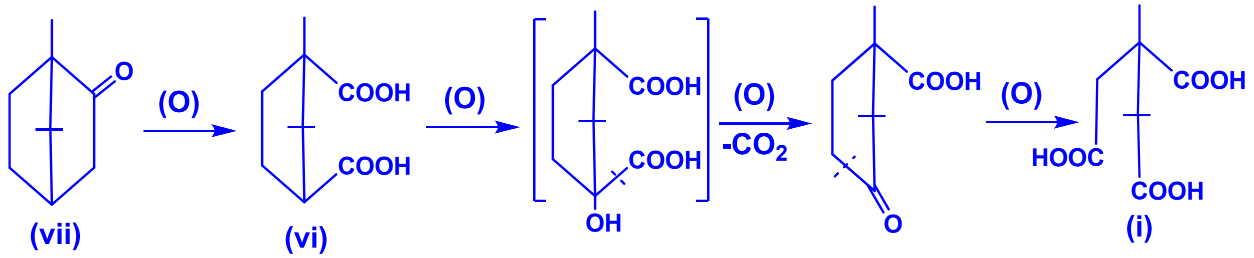
(vA)



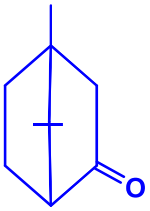
(vi)

10. **Structure of camphor:** The camphoric acid is obtained by the oxidation of –CH_2-CO- group of camphor. Therefore, the structure of camphor would be obtained by joining the carbon atoms of the carboxyl groups in camphoric acid. Hence, the structure of camphor obtained form (vA) would contain a six-membered ring with a gem dimethyl group. But this structure could not explain the conversion of camphor into p-cymene. Thus, the structure (vA) and hence (v)

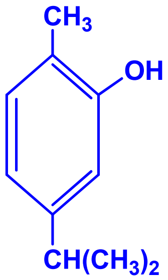
was rejected. On the other hand, structure (vi) explains all the foraging facts and the structure (vii) of camphor corresponding to structure (vi) would be the correct structure. This argument was given by Bredt, who proposed the following reactions to reveal the relationships between camphor, camphoric acid and camphoronic acid.



Bredt also proposed structure (viii) for camphor. This structure also explains all the foregoing facts but he rejected this in favour of (vii). The simple reason for its rejection is that camphor when distilled with iodine yields carvacrol (ix). The formation of this compound can be explained only on the basis of structure (vii) but not on (viii).



(viii)

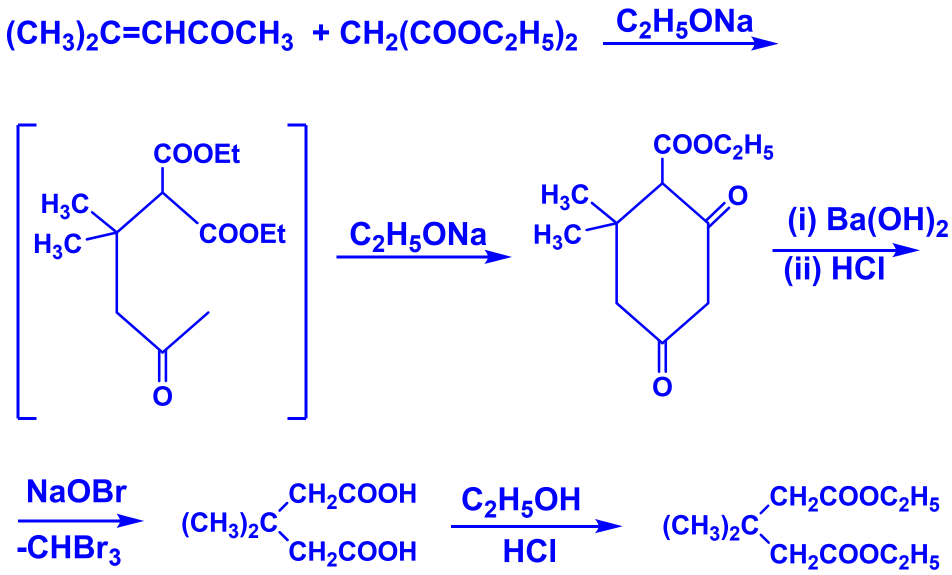


(ix)

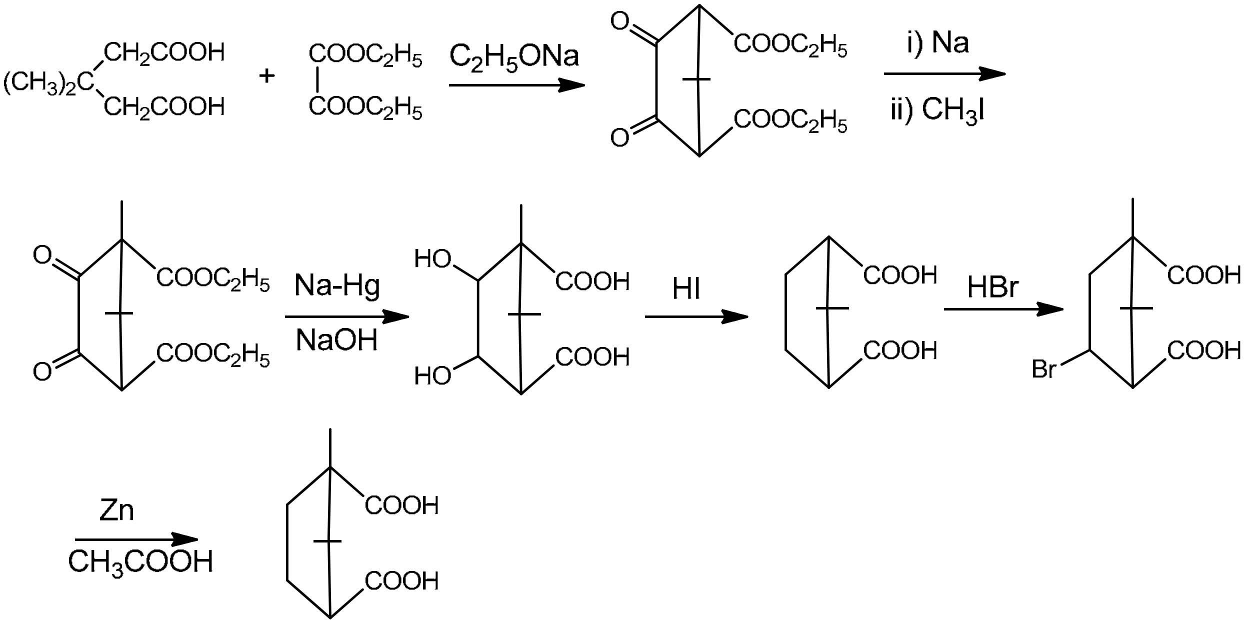
Finally, the structure of camphoric acid (vi) and camphor (vii) have been confirmed by their respective synthesis.

11. **Synthesis of (±) camphoric acid:** This was given by Komppa. His synthesis involves the two steps :

(a) First step involves the preparation of 3, 3-dimethylglutaric acid from mesityl ketone and ethyl malonate.

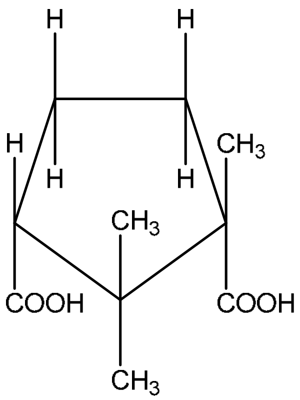


(b) Second step Involves the conversion of 3,3-dimethyl-glutaric acid into camphoric acid as follows :

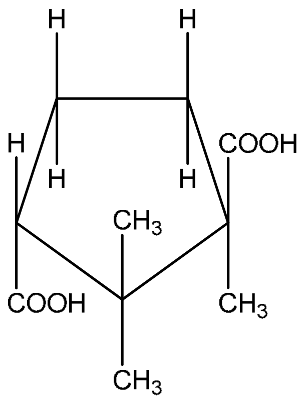


(vi)

There are two geometrical isomeric forms of camphoric acid, i.e., cis and trans. Neither of these has any elements of symmetry. Hence, there may be four optical isomers of camphoric acid. However, all are known that would correspond to the (+) and (-) forms of camphoric acid and isocamphoric acid. Further, camphoric acid on heating yields anhydride whereas isocamphoric acid does not yield anhydride. This means that camphoric acid is cis-isomer whereas isocamphoric acid is the trans-isomer.

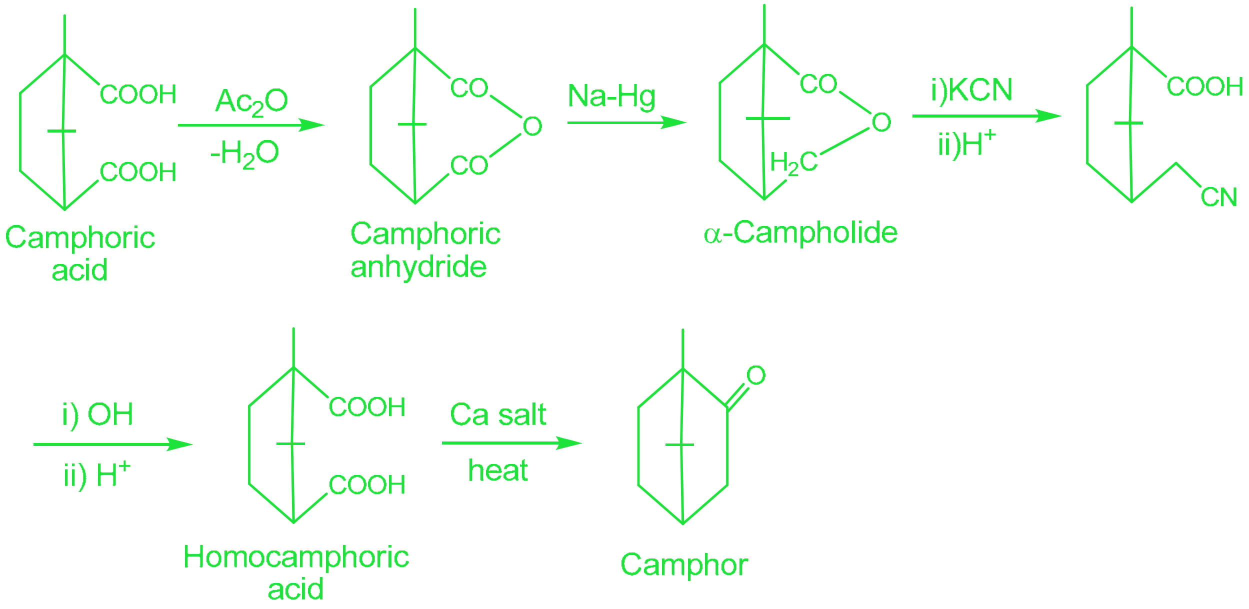


Comphoric acid
m.p. 187^{o}C

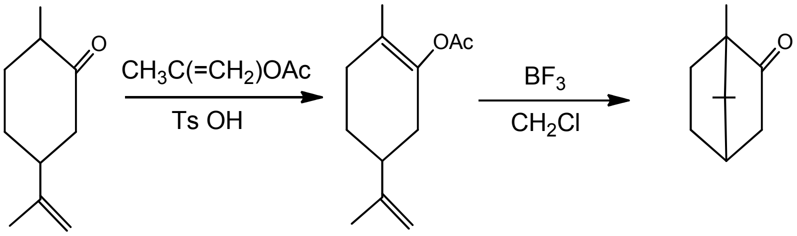


Isocomphoric acid
m.p. 171^{o}-172^{o}

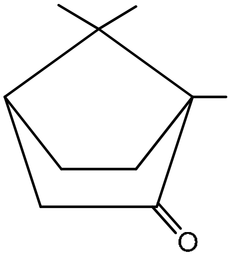
12. **Synthesis of camphor :** (a) This was synthesized form camphoric acid by Haller (1896).



(b) Another synthesis was given by Money et al. (1969). This involves a two-step synthesis of (+) camphor form dihydrocarvone.

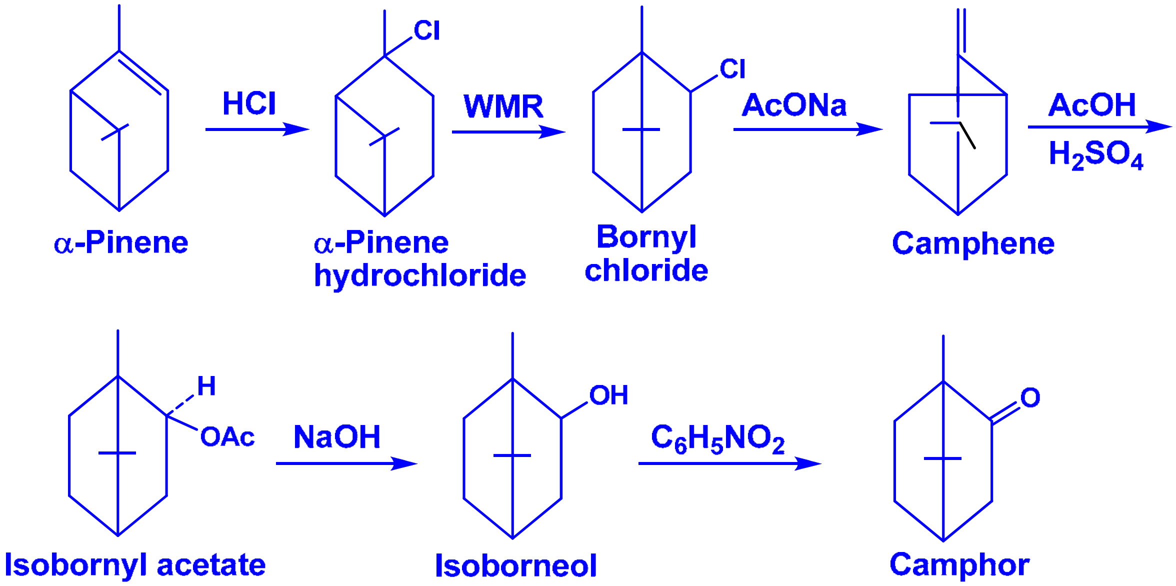


13. **Stereochemistry of camphor :** Similar to camphoric acid, camphor contains two dissimilar chiral centers. Therefore, its two pairs of enantiomers are known. However, only one pair of enantiomer due to cis-form is possible because other pair of enantiomer is not possible due to the impossibility of the trans- fusion of the gem-dimethylmehylene bridge to the cyclohexane ring. Camphor as well as its derivatives exists in the boat conformation. Since the gem-dimethyl bridge must be cis, the cyclohexane ring exhibit the boat form.



Camphor

14. **Commercial preparation of camphor :** On a large scale, camphor is prepared from α-pinene which is commercially available from turpentine oil. The reaction involves number of Wagner-Meerwein rearrangements (WMR) which cause a complete change in carbon skeleton. The various steps for the synthesis of camphor are as follows :



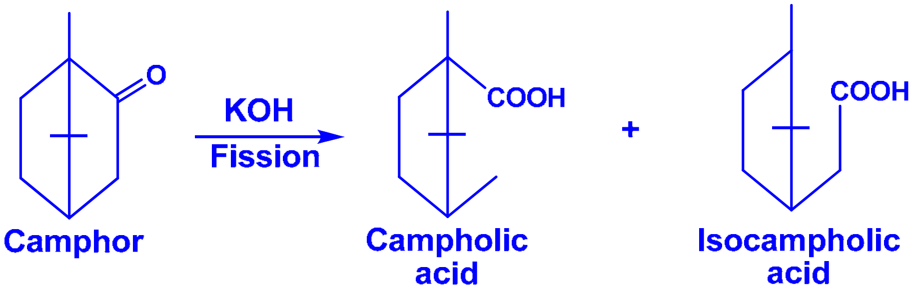
For other methods, see isolation of camphor.

Reactions of Camphor. These are of two types :

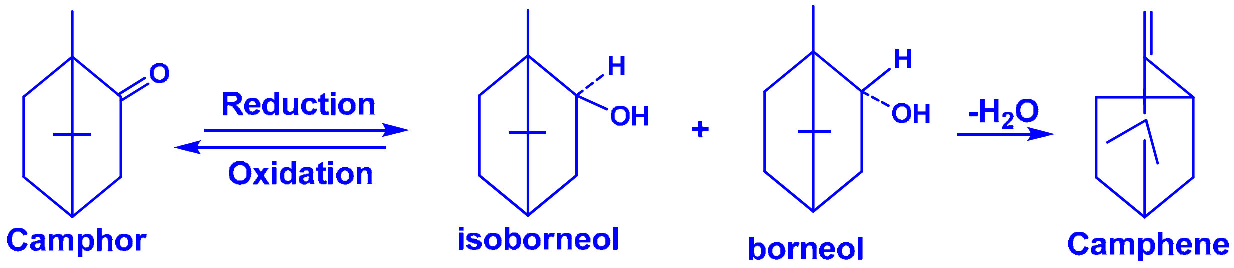
(a) Fission reactions and (b) Reduction reactions.

We shall discuss these one by one :

(a) When camphor is heated with KOH, fission will take place at that bond which involves the least substituted carbon atom adjacent to the carbonyl group. This fission occurs according to the general rule for acyclic ketones. Thus, camphor yields a mixture of campholic and isocampholic acids (Guerbet); the former being the major product.



(b) When camphor is reduced, it yields a mixture of two isomeric alcohols, borneol and isoborneol (both these alcohols belong to the camphene group). The relative proportion of borneol to isoborneol is mainly dependent upon the nature of the reducing agent. Both borneol and isoborneol on dehydration yield camphene and on oxidation yield camphor.



Reference Book : organic chemistry of natural products vol- II By GURDEEP CHATWAL