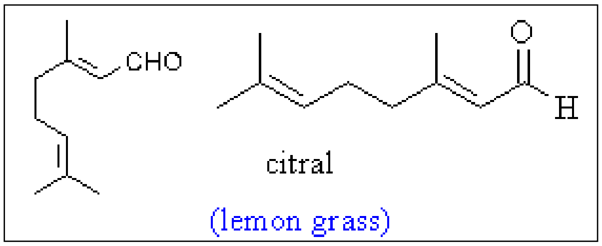
Citral



SOURCE OF CITRAL

Name of drug	**Part of plant**	**Biological source**	**Active constituents**	**use**
Lemon grass oil	Lemon grass oil is the oil distiiled	Cymbopogan flexuosus (Gramineae)	Citral , citronellal, geraniol	Flavouring agent, mosquitorepellent, source for preparation of beta ionone and vitamin A

Citral is acyclic monoterpenoids, it is a major constituent of lemon grass oil in which it occurs to an extent of 60-80%. It is a pale yellow liquid having strong lemon like odor and can be obtained by fractional distillation under reduced pressure from lemon grass oil. Since the structures of most of the other compounds in this group are based on that of citral ($C_{10}H_{16}O$). Citral is widely distributed and occurs to an extent of 60-80 percent in lemon grass oil. Citral is a liquid which has the smell of lemons.

EXTRACTION AND ISOLATION

Transfer 10ml of lemon grass oil, 100ml of water to a 250 ml round bottom flask. Place a boiling chip into the flask. Connect the flask to a simple distillation apparatus. Heat the mixture to boiling, and collect the distillate at graduated cylinder. Isolate the citral obtained from mixture of water and citral by extracting it with diethyl ether. Evaporate the ether layer to get citral.

1) Molecular formula of citral is ($C_{10}H_{16}0$), bp-77 c and Chemical name 3, 7-dimethyl -2, 6-0ctadienal.

2) Nature of oxygen atom include formation of oxime of citral indicate presence of an Oxo group in citral molecules.

$C_{10}H_{16}0 + NH_2OH \longrightarrow C_{10}H_{16} = NOH$ (oxime)

On reduction with Na/Hg it gives geraniol and on oxidation with silver oxide it give geranic acid,

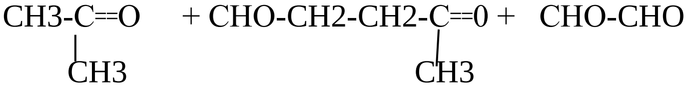
$C_{10}H_{16}0_2$ (geranic acid), $\xleftarrow{Ag_20}$ CITRAL ($C_{10}H_{16}0$) $\xrightarrow{Na/Hg}$ $C_{10}H_{18}0$ geraniol.

Both these reaction reveal that Oxo group in citral is therefore an aldehyde group. Citral reduces Fehling solution, furthermore confirm the presence of aldehyde group.

3) Presence of two double bond: when citral is treated with two molecules of to form citral tetra bromide.

$C_{10}H_{16}0 \xrightarrow{Br_2} C_{10}H_{16}0Br_4$ (citral tetra bromide)

On ozonolysis, it gives acetone, Laevualdehyde and glyoxal.



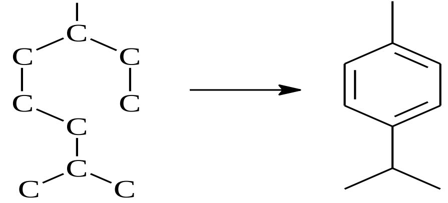
$$CH3\text{-}\underset{CH3}{C}{=}O \quad + CHO\text{-}CH2\text{-}CH2\text{-}\underset{CH3}{C}{=}0 + \quad CHO\text{-}CHO$$

Formation of above products shows that citral is an acyclic compound containing two double bond. Corresponding saturated hydrocarbon of citral (molecular formula $C_{10}H_{22}$) corresponds to the general formula CnH2n+2 for acyclic compound, indicating that citral must be an acylic compound.

4- C-skeleton of citral: when citral is heated with potassium hydrogen sulfate, it cyclises to p-cymene, indicate that citral is a acylic compound,.

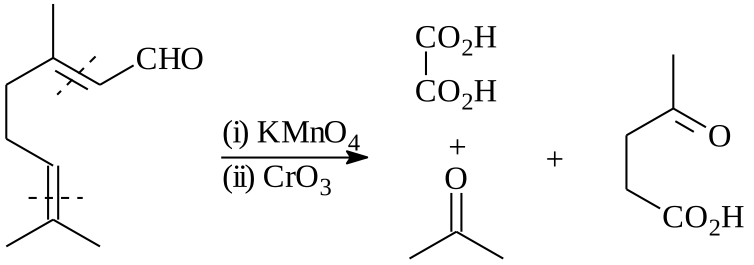
$C_{10}H_{16}0 \xrightarrow{KHSO_4} C_{10}H_{14}$ (p-cymene)

(II) Stuructre is para-cymene.



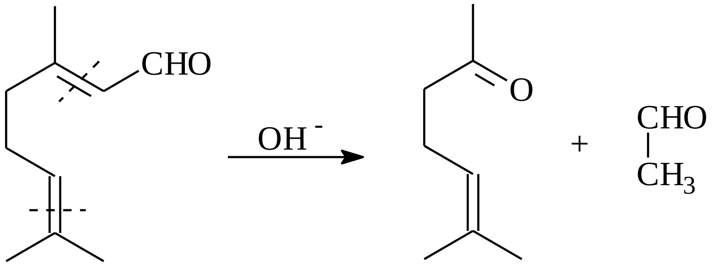
(I) **(II)**

5- Oxidation of citral with alkaline permanganate, followed by chromic acid, gives acetone, oxalic and laevulic acids.



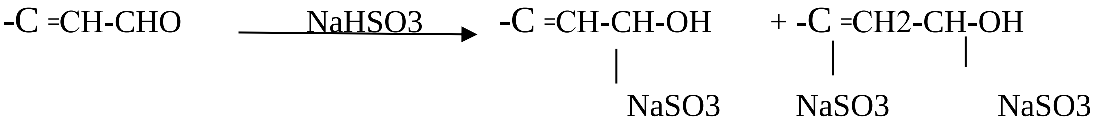
(III)

6- Citral on boiling with aqueous potassium carbonate converted into 6-methylhept-5-en-2-one (**IV**) and acetaldehyde. The formation of these products is readily explained that citral is product of aldol condensation of these two



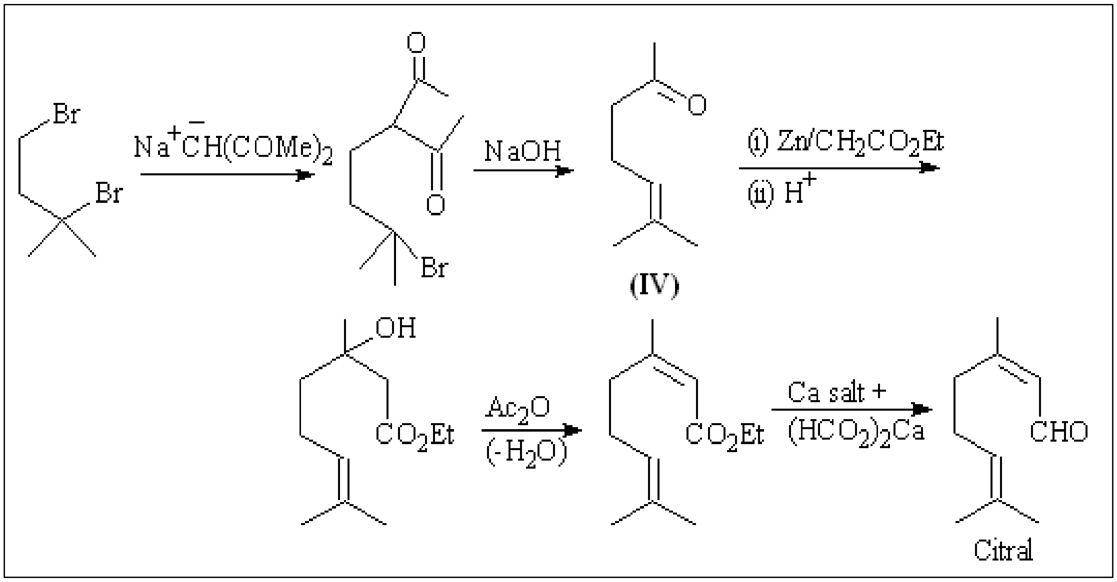
(III) **(IV)**

7-Citral is treated with sodium bisulfate to forms mono as well as bisulfite addition product, which indicates that one of the double bond is conjugated with carbonyl group.



$$-C{=}CH{-}CHO \xrightarrow{NaHSO3} -C{=}CH{-}\underset{\underset{NaSO3}{|}}{CH}{-}OH \quad + -\underset{\underset{NaSO3}{|}}{C}{=}CH2{-}\underset{\underset{NaSO3}{|}}{CH}{-}OH$$

8- The structure of citral was confirmed by the synthesis of methylheptenone, the conversion of this into geranic ester, which was then converted into citral by heating a mixture of the calcium salts of geranic and formic acids.



MENTHOL

Menthol is a 10 carban monocylic terpenes alcohol with a molecular wt. of 156 and chemical formula $\mathbf{C_{10}H_{20}O}$ **.** It is obtained from the fresh flowering tops of mentha piperita.(labiate) . The active constituent is menthol, menthone, and limonene.

SOURCE OF MENTHOL

Name of drug	Part of plant	Biological source	Active constituents	use
PEPPERMINT	Fresh flowering top	Mentha piperita (Labiatae)	menthol , menthone, limonene	Flavouring agent,carminative. Used in tooth paste. Tooth poweder, shaving cream

Properties of menthol. Menthol is a covalent organic compound made synthetically or obtained from peppermint or other mint oils. It is a waxy, crystalline substance, clear or white in color, which is solid at room temperature and melts slightly above. The main form of menthol occurring in nature is (-)-menthol, Menthol has local anesthetic and counterirritant qualities, and it is widely used to relieve minor throat irritation.

EXTRACTION AND ISOLATION.

Extraction and isolation of menthol is done through steam distillation. Steam from a boiler is allowed in the vessel from the bottom, above which the plant material is placed on a grid and the steam carries the vapours of the essential oil to the condenser where they are condensed and collected.

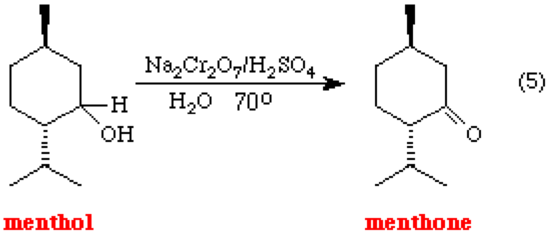
ELUCIDATION OF MENTHOL

Menthol, $C_{10}H_{20}O$.

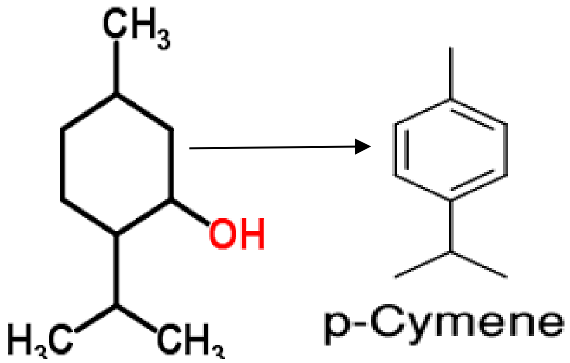
1- Molecular formula of menthol was determined as $C_{10}H_{20}O$.

2- On treatment with phosphorus pentachloride and phosphorus pentoxide menthol gave a chloride $C_{10}H_{19}Cl$ and a hydrocarbon $C_{10}H_{18}$ respectively, inferring that it is an alcohol.

3- Menthol was oxidized by chromic acid to a ketone, Menthone to prove that menthol contained a secondary hydroxyl group

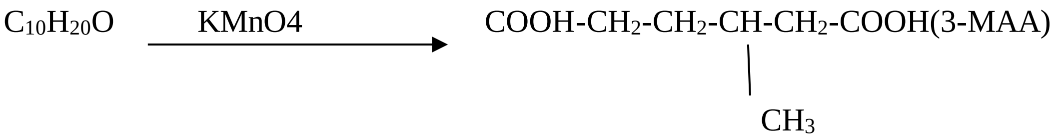


4-On dehydration followed by dehydrogenation, it yields p- cymene.



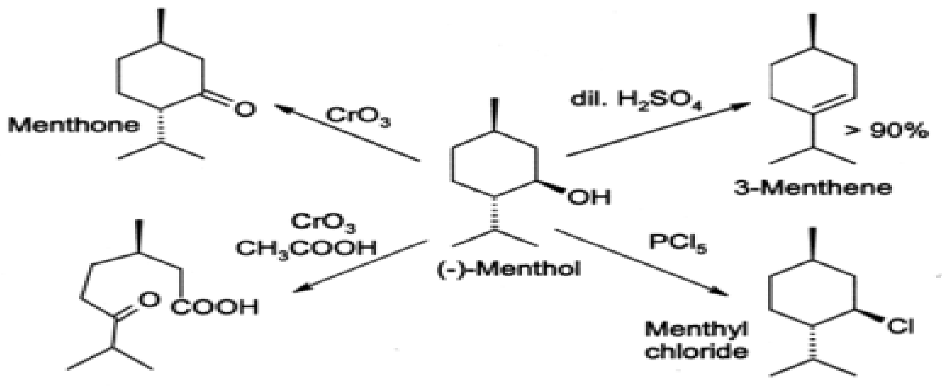
It Show the presence of cymene nucleus in menthol.

5-Menthone on oxidation with $KMNO_4$ yield keto acid $C_{10}H_{18}O_3$, which readily oxidized to 3- methyl adipic acid. These reaction can be explained by considering the following structure of menthol



$$C_{10}H_{20}O \xrightarrow{KMnO4} \underset{\displaystyle CH_3}{\text{COOH-CH}_2\text{-CH}_2\text{-}\underset{|}{\text{CH}}\text{-CH}_2\text{-COOH(3-MAA)}}$$

6-Menthol was converted to para cymene (1-methyl 4-isopropyl benzene), which was also obtained by dehydrogenation of pulegone. Pulegone on reduction yielded menthone, which on further reduction yielded menthol



MENTHOL SYNTHESIS

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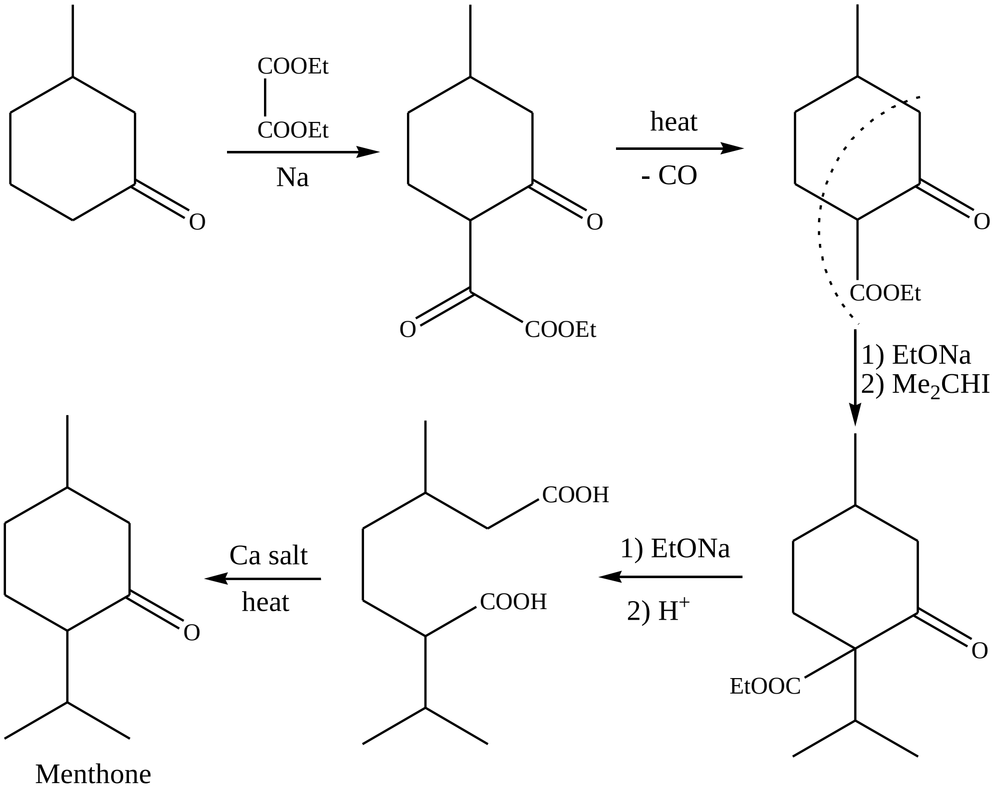
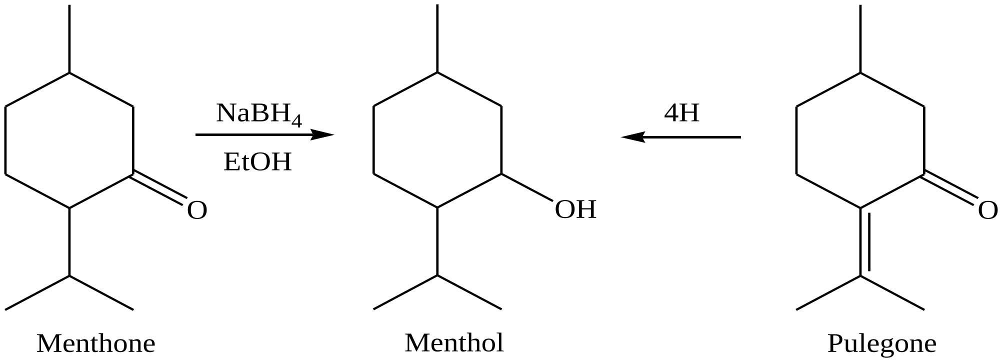


The reduction of menthone using $NaBH_4$ in alcohol or pulegone in the presence of reduced catalyst gave the corresponding menthol



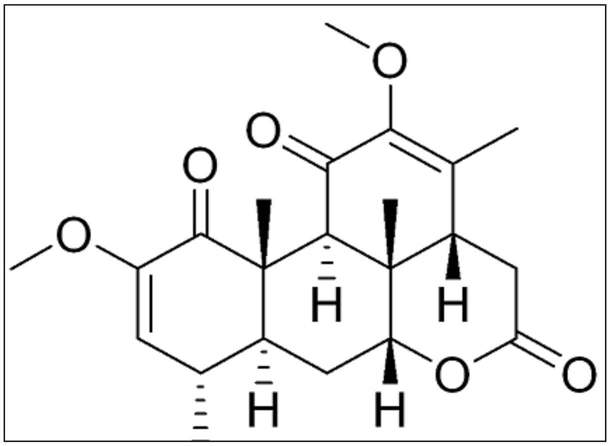
QUASSINOIDS

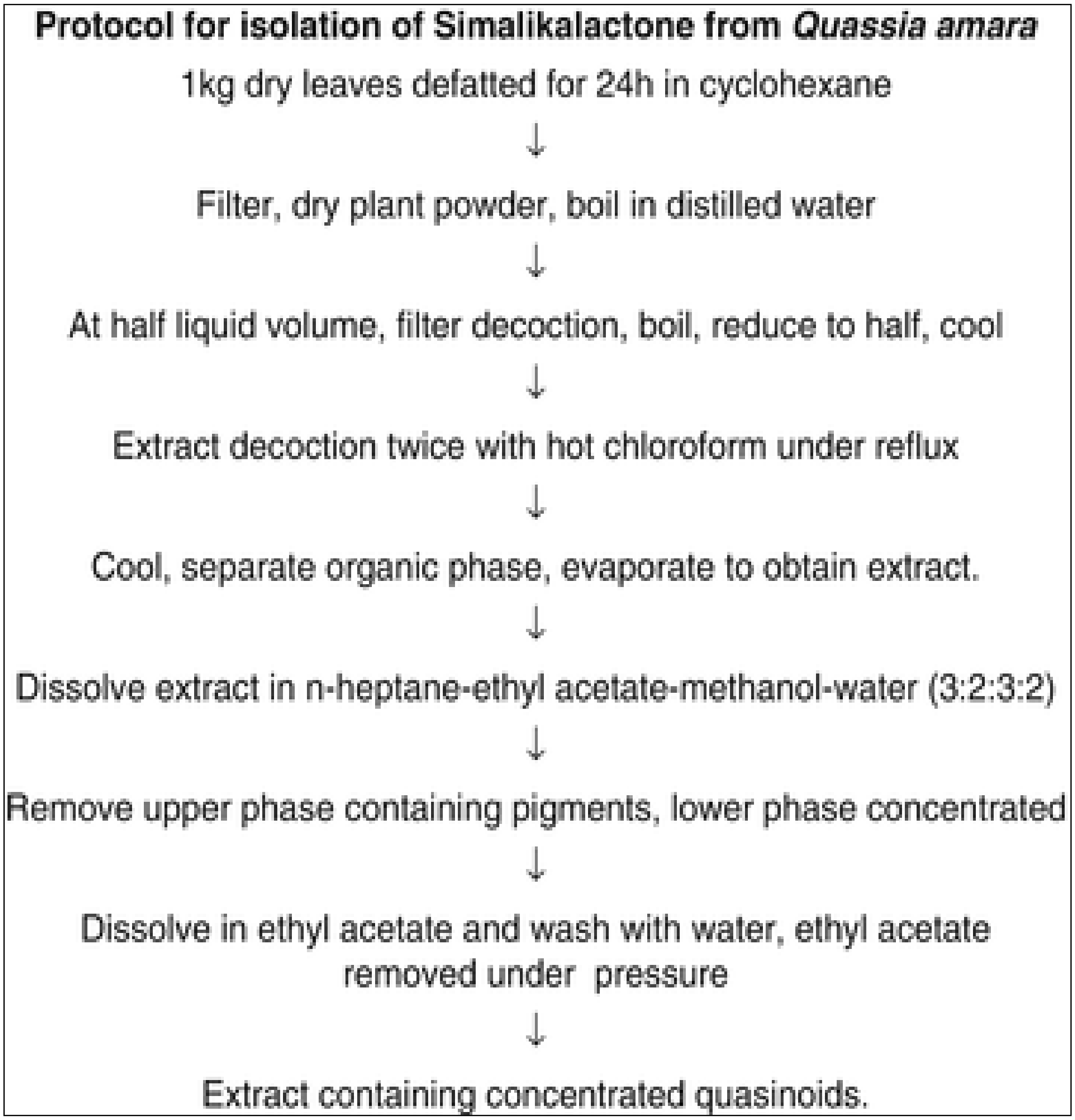
Quassinoids are degraded triterpene lactones (similar to limonoids) of the Simaroubaceous plant family grouped into C-18, C-19, C-20, C-22 and C-25 types. The prototypical member of the group, quassin, was first described in the 19th century from plants of the genus Quassia from which it gets its name.

It is one of the most bitter substance found in nature , with a bitter thresh old of 0.008 ppm and it is 50 times more bitter than quinine.

Among them C-20 quassinoids have especially been the subject of extensive investigations to dig their biological activities partially due to the discovery in the early 1970s by National Cancer Institute that some of these compounds possess marked antileukemic activity. The C-20 quassinoids can be further classified into two types, tetracyclic and the pentacyclic. The tetracyclic variety does not have oxygenationat C-20, while the pentacyclic quassinoids possess additional oxygenation at C-20 that allows for the formation of an additional ring. As studies on these compounds progress, however,other groups, especially C-19 quassinoids, have recently received more attention .Many of these quassinoids display a wide range of biological activities in vitro and/or invivo, including antitumor, antimalarial, antiviral, anti-inflammatory, antifeedant, insecticidal,amoebicidal, antiulcer and herbicidal activities.

It is white crystalline substance. It is bitter in taste and odorless





Protocol for isolation of Simalikalactone from *Quassia amara*

1kg dry leaves defatted for 24h in cyclohexane

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Filter, dry plant powder, boil in distilled water

↓

At half liquid volume, filter decoction, boil, reduce to half, cool

↓

Extract decoction twice with hot chloroform under reflux

↓

Cool, separate organic phase, evaporate to obtain extract.

↓

Dissolve extract in n-heptane-ethyl acetate-methanol-water (3:2:3:2)

↓

Remove upper phase containing pigments, lower phase concentrated

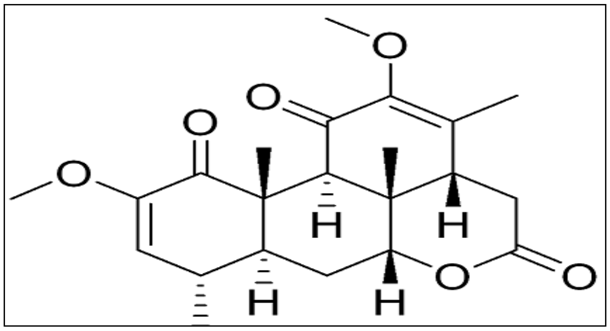
↓

Dissolve in ethyl acetate and wash with water, ethyl acetate removed under pressure

↓

Extract containing concentrated quasinoids.

EXTRACTION AND ISOLATION’



Structure elucidation- . for methoxy , ketonic and lactone and alkene.

CAMPHOR

SOURCE OF CAMPHOR:

S. No.	Name of drugs	Part of plant	Biological source	Active constituent	Uses
1.	Camphor	Solid ketone obtained from volatile oil.	*Cinnamonomum camphora* (lauraceae)	Camphor, cineol, pinene, limonene, camphene	Rubefacient, Carminative, Antiseptic, antiinfective, antipruritic, stimulant.

PROPERTIES OF CAPMOHR:

It is a solid having melting point 180 C. it forms a colorless, transparent mass of characteristic smell and burning taste, it is optically active; the (-) and (+) forms occurs natura

EXTRACTION AND ISOLATION:

Camphor occurs in all parts of the camphor tree, it is extracted by distillation procedure. Camphor can also be produced from Alfa pinene, which is abundant in the oil of coniferous trees and can be distilled from turpentine produced as a byproduct of chemical pulping. With acetic acid as the solvent and with catalysis by strong acid. Alfa pinene undergo to the camphene, which in turn undergoes Wagner rearrangement into isobornyl cation, which is captured by acetate to give isobornyl acetate. Hydrolysis into isobornyl followed by oxidation give camphor.

ELUCIDATION OF CAMPHOR:-

1. Molecular formula of camphor is $C_{10}H_{16}O$.
2. Camphor forms substitution product like monobromocamphor, monochlorocamphor, camphor-sulphonic acid. The formation of these products proves that camphor is a saturated compound.
3. Presence of keto group:

(i) Camphor forms an oxime with hydroxylamine.

(ii) Camphor forms phenylhydrazone with phenylhydrazine.

(iii) Camphor is distilled with iodine, it forms carvacrol. The presence of phenolic group in carvacrol proves that the presence of ketonic group in camphor.

$C_{10}H_{16}O$. + $NH_2OH \xrightarrow{\qquad} C_{10}H_{16}$ ==NOH (camphor oxime)

4. Camphor is treated with amyl nitrite and HCl, it forms isonitroso camphor in which two hydrogen atoms have been replaced by =NOH group, proves presence of –CH_2CO group.

   -Camphor is condensed with benzaldehyde, to forms monobenzylidene, proves presence of –CH_2CO group.

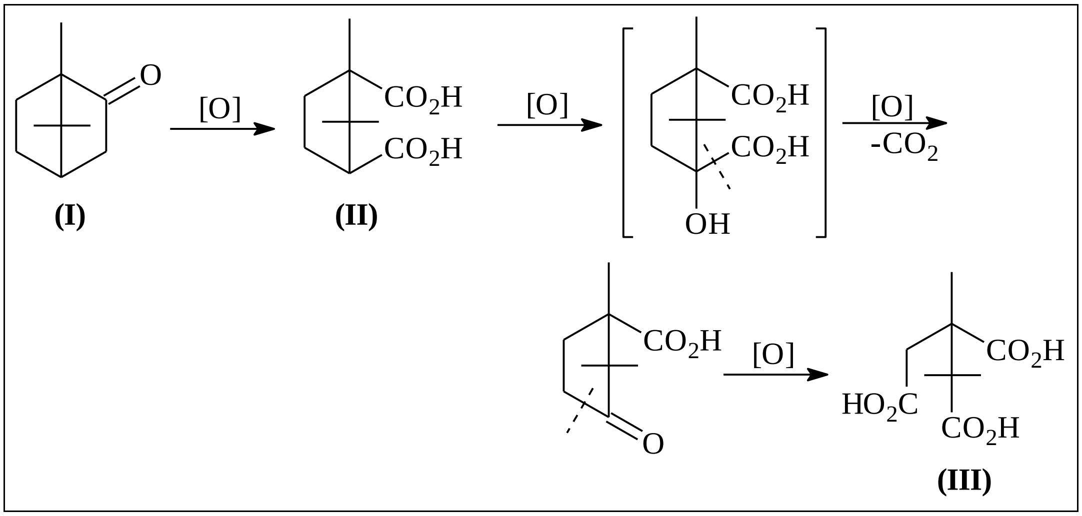
   $C_{10}H_{16}O \xrightarrow{\text{amyl nitrate}} C_8H_{14}\text{-}CH_2\text{-}C\text{=}NOH$

   5-Camphor is distilled with zinc chloride or phosphorous pentoxide to forms p-cymene. This shows presence of one six membered ring in camphor.

   $C_{10}H_{16}O \xrightarrow{ZnCl_2}$ P-cymene

6- Oxidation of camphor **(I)** with nitric acid gives **camphoric acid**, $C_{10}H_{16}O_4$ **(II)** (b) oxidation of camphoric acid with nitric acid gives **camphoronic acid**, $C_9H_{14}O_6$ **(III)**

$C_{10}H_{16}O$ (**I**) $\xrightarrow{HNO_3}$ $C_{10}H_{16}O_4$ (**II**) $\xrightarrow{HNO_3}$ $C_9H_{14}O_6$ (**III**)



7-**STRUCTURE OF CAMPHORONIC ACID:**

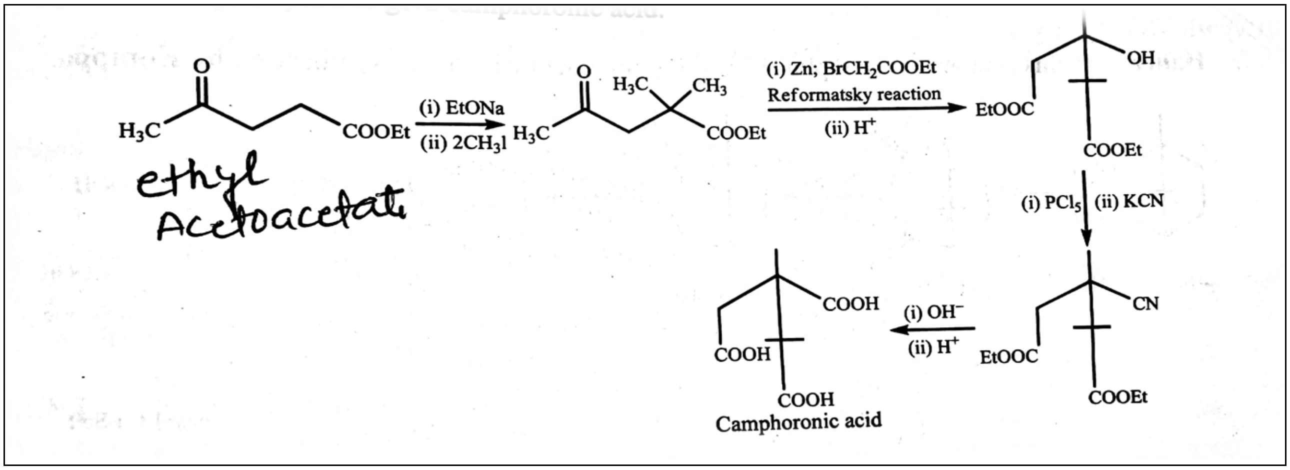
(i) Molecular formula of camphoronic acid is $C_9H_{14}O$.

(ii) 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 be C_6H_{14} which corresponds to the general formula (C_6H_{2n+2}) for acyclic compound, shown that camphoronic acid is an acyclic compound.

(iii) Camphoronic acid is not easily decarboxylated under ordinary conditions its three carboxylic groups are attached to three different carbon atoms.

(iv) When camphoronic acid is distilled at atmospheric pressure it yields isobutyric acid, trimethylsuccinic acid, carbon dioxide and carbon. Presence of α, β-trimethy tricarboxylic acid in camphoronic acid.

(v) Structure of camphoronic acid is confirmed by synthesis:



8-**STRUCTURE OF CAMPHORIC ACID**:

i) Molecular formula of camphoric acid $C_{10}H_{16}O_4$.

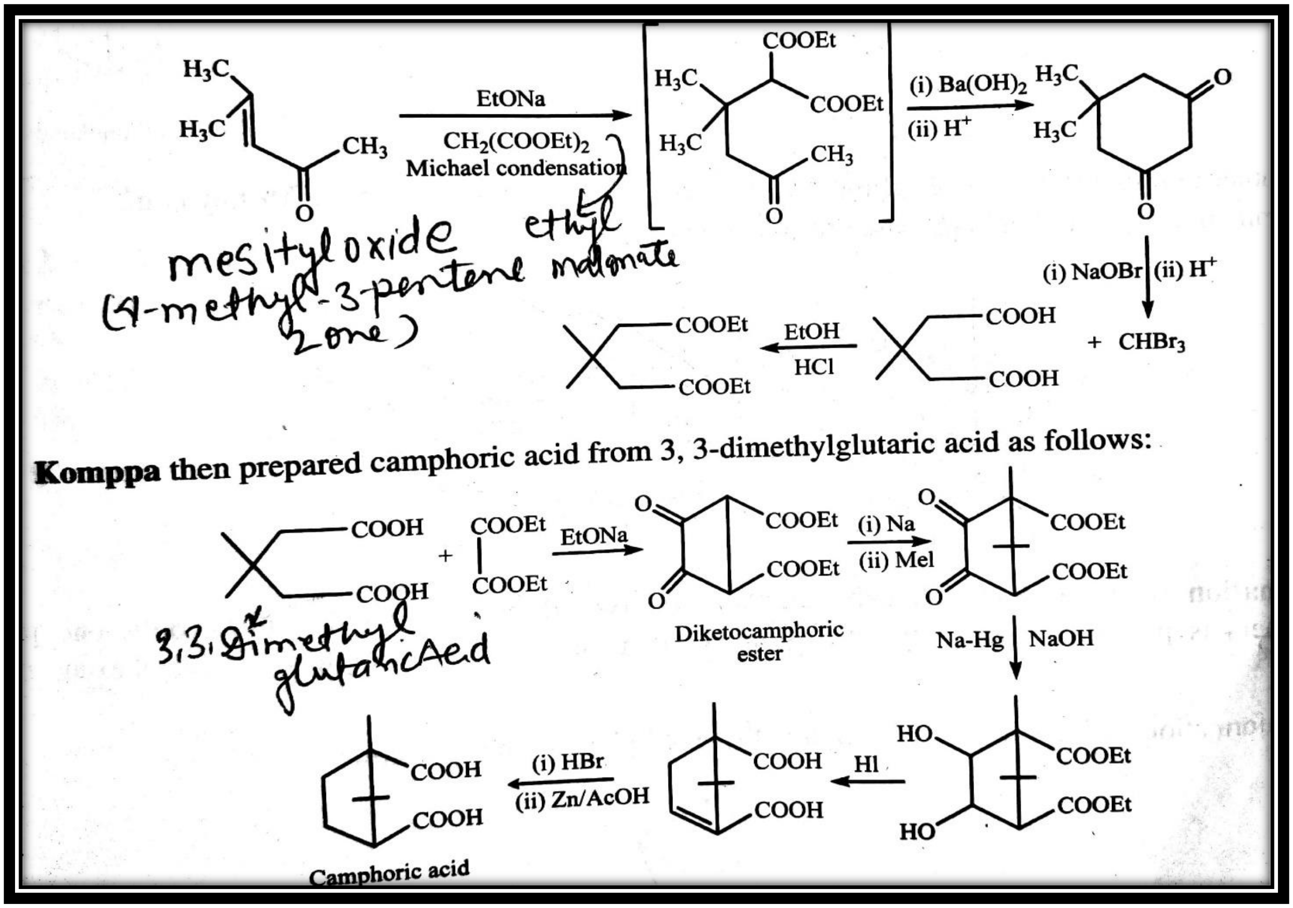
ii) Camphoric acid has been shown to be a saturated dicarboxylic acid.

iii) Its oxidized product camphoric acid has a gem dimethyl group and separate methyl group, camphoric acid and camphor also must have three methyl groups. Thus the formula for camphoric acid may be written $Me_3C_5H_5(COOH)_2$ which leads to C_5H_{10} as its saturated parent hydrocarbon. The molecular formula C_5H_{10} i.e. (C_nH_{2n}) of its saturated parent hydrocarbon show that camphoric acid is a cyclopentane dicarboxylic acid.

iv) Camphoric acid forms monoester very easily but diester with some difficulty that the two carboxylic groups are not similar i.e. one is primary or secondary, and the other is tertiary. This is confirmed by the fact camphoric acid forms only monobromo derivative which is possible only when one the camphoric groups are secondary.

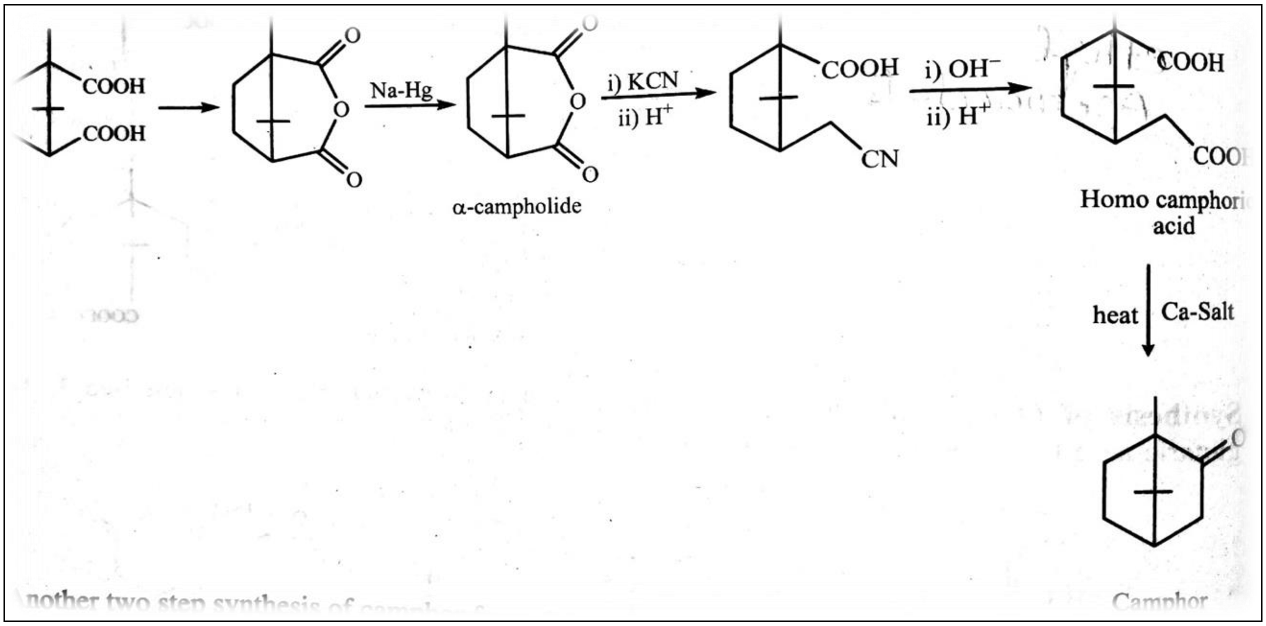
v) Camphoric acid is found to be a ring- substituted glutaric acid on the basis of Blanc rule which state that on heating with acetic anhydride-glutaric acid gives anhydrides, adipic acids give cyclopentanones, and pimelic acids give cyclohexanones, since camphoric acid gives an anhydride; it must be glutaric acid derivative.

vi) Structure of camphoric acid confirmed by synthesis.



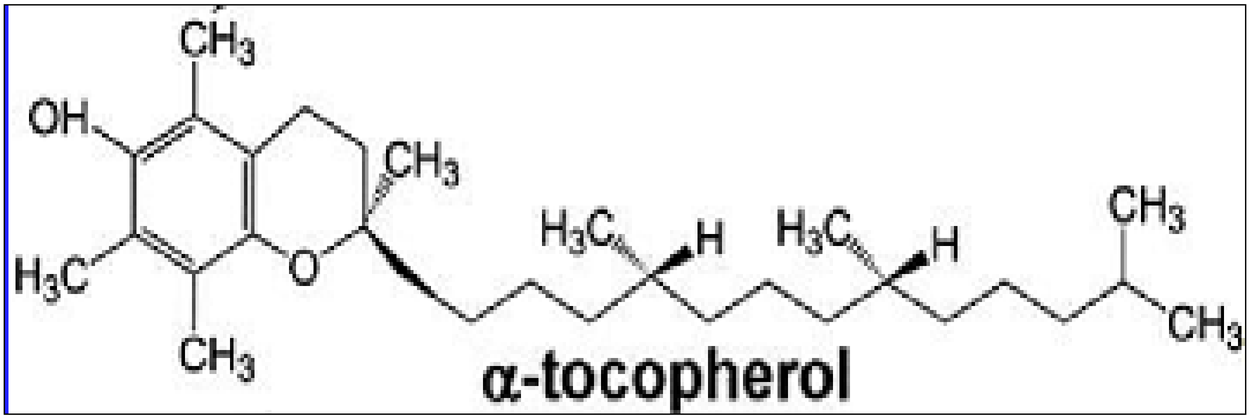
Komppa then prepared camphoric acid from 3, 3-dimethylglutaric acid as follows:

9- Synthesis of camphor: Structure of camphor is confirmed by synthesis



α -TOCOPHEROL

The term 'vitamin E' refers to a group of closely related compounds which occur naturally and which are, to different degrees, anti-sterility factors. Eight compounds. Collectively called tocopherols, have been characterized: $\alpha^{-,}$ β^-, γ^-, δ^-, ε^-, ζ_1^-, ζ_2^-, and η-tocopherol. The most biologically active one is α-tocopherol, with the β- and γ-compounds exhibiting about half the activity of the α-compound. Only the first four will be discussed here. The main source of α and β-tocopherol is wheat germ oil; the γ-compound is obtained from cotton seed oil. Wheat germ oil was first subjected to chromatographic analysis to remove sterols, etc., and then the α and β-tocopherol were purified by conversion into their crystalline allophones or 3,5-dinitrobenzoates. Hydrolysis of these derivatives gave the tocopherols as pale yellow oils.



Tocopherol are fat soluble vitamin E isomer and the major antioxidant of vegetable oil. It is light yellow oil.it is not destroyed by acid or alkali. It is the antisterility factor. Vitamin e represent a group of eight compound which are collectively called tocopherol. Its molecular formula is $C_{29}H_{50}O_2$

EXTRACTION AND ISOLATION

Wheat germs are dried and pressed to collect the oil. The oil is then treated with 20% alcoholic KOH in absence of oxygen. The unsaponified portion contain sterol and vitamin E, the former are removed by precipitation with digitonin. Now the distillation of the remaining oil gives vitamin E fraction at 200-250 0c under reduced pressure, this process gives less yield of vitamin.

In another method the oil, obtained after removing sterol, is converted into ester allophanates by treating the oil with cynic acid gas. By means of fractional crystallization the two ester, Alfa tocopherol ester and beta tocopherol ester, are separated. Ester on hydrolysis give the respective tocopherol. Similarly. Gamma tocopherol can be obtained from cotton seed oil

ELUCIDATION OF TOCOPHEROL-

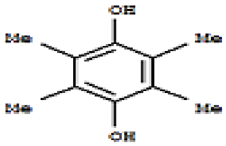
1-Molecular formula is $C_{29}H_{50}O_2$

2. α -Tocopherol forms monoacetate. Monoester and monoether. Indicate that one of the oxygen atom is present as hydroxyl group.

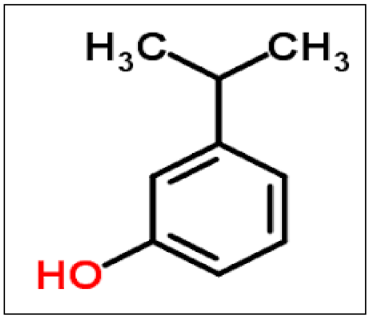
3-the second oxygen atom was found to be present as a cyclic ether.

4-α -Tocopherol is heated with with 350 0c to yield duroquinol indicating presence of benzenoid nucleus.

$C_{29}H_{50}O_2 \xrightarrow{350\ 0c}$

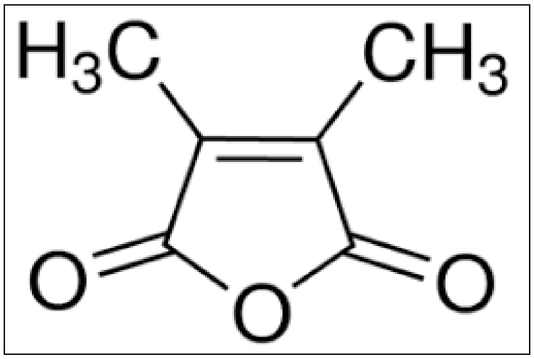


5-α -Tocopherol is heated with HI gives Ψ-cumenol. This is shown that presence of one free hydroxyl group.

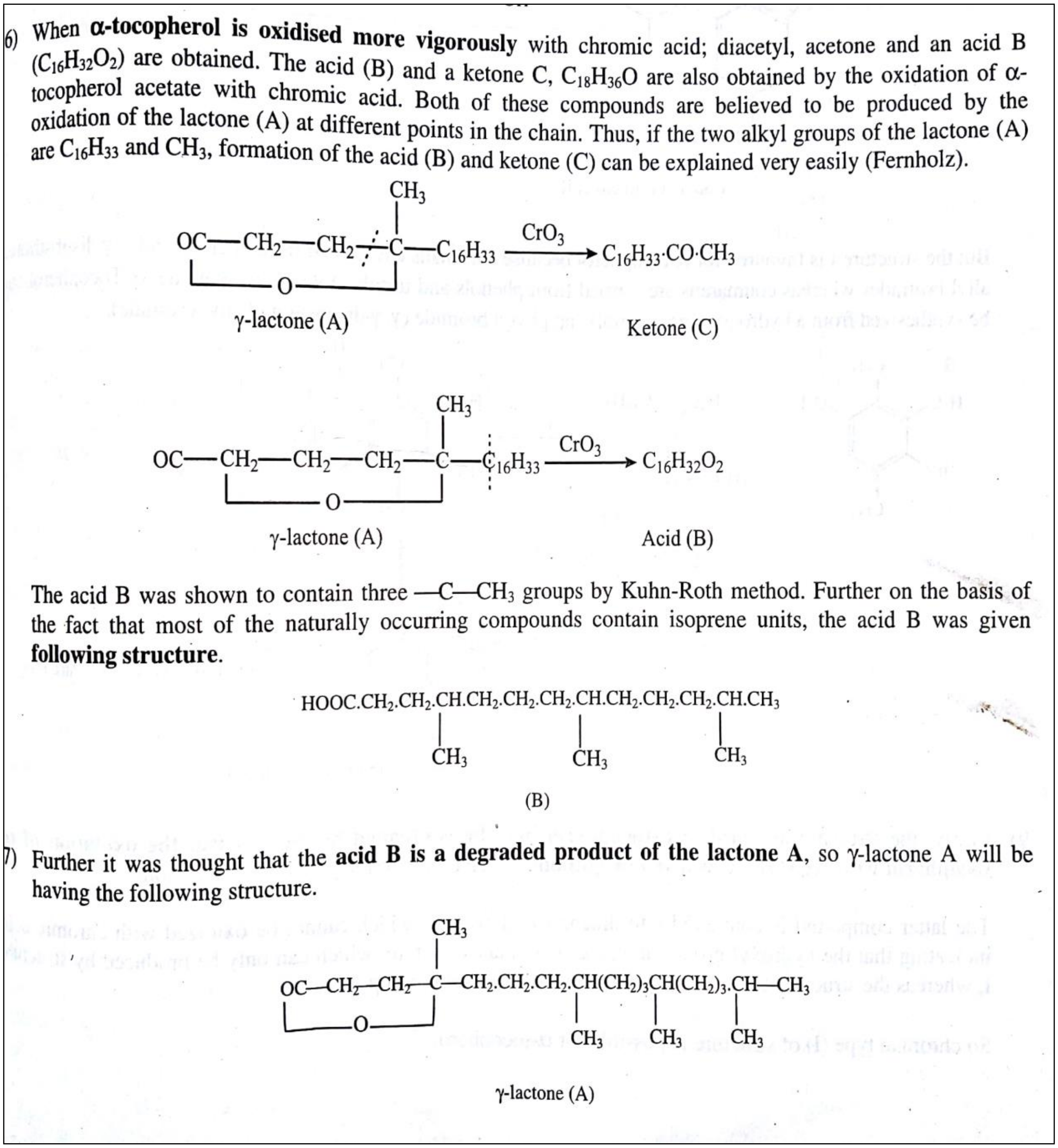


6-oxidation of α -tocopherol with chromic acid under mild condition yields dimethyl maleic anhydride and an optically active saturated lactone A.

$C_{29}H_{50}O_2 \xrightarrow{CrO3} C_{21}H_{40}O_2$ **(**Lactone**) +** dimethyl maleic anhydride



7- α -tocopherol acetate, on oxidation with chromic acid, forms an acid, $C_{16}H_{32}O_2$(B) and a ketone, $C_{18}H_{36}O$ (C). Both of these compounds must be produced by the oxidation of the lactone at different point in the side chain. This show that presence of methyl group.



6) When **α-tocopherol is oxidised more vigorously** with chromic acid; diacetyl, acetone and an acid B ($C_{16}H_{32}O_2$) are obtained. The acid (B) and a ketone C, $C_{18}H_{36}O$ are also obtained by the oxidation of α-tocopherol acetate with chromic acid. Both of these compounds are believed to be produced by the oxidation of the lactone (A) at different points in the chain. Thus, if the two alkyl groups of the lactone (A) are $C_{16}H_{33}$ and CH_3, formation of the acid (B) and ketone (C) can be explained very easily (Fernholz).

$$\underbrace{OC—CH_2—CH_2—\overset{\displaystyle CH_3}{\overset{|}{C}}}_{O}—C_{16}H_{33} \xrightarrow{CrO_3} C_{16}H_{33}\cdot CO\cdot CH_3$$

γ-lactone (A) Ketone (C)

$$\underbrace{OC—CH_2—CH_2—CH_2—\overset{\displaystyle CH_3}{\overset{|}{C}}}_{O}—C_{16}H_{33} \xrightarrow{CrO_3} C_{16}H_{32}O_2$$

γ-lactone (A) Acid (B)

The acid B was shown to contain three —C—CH_3 groups by Kuhn-Roth method. Further on the basis of the fact that most of the naturally occurring compounds contain isoprene units, the acid B was given **following structure**.

$$HOOC.CH_2.CH_2.\underset{\displaystyle CH_3}{\underset{|}{CH}}.CH_2.CH_2.CH_2.\underset{\displaystyle CH_3}{\underset{|}{CH}}.CH_2.CH_2.CH_2.\underset{\displaystyle CH_3}{\underset{|}{CH}}.CH_3$$

(B)

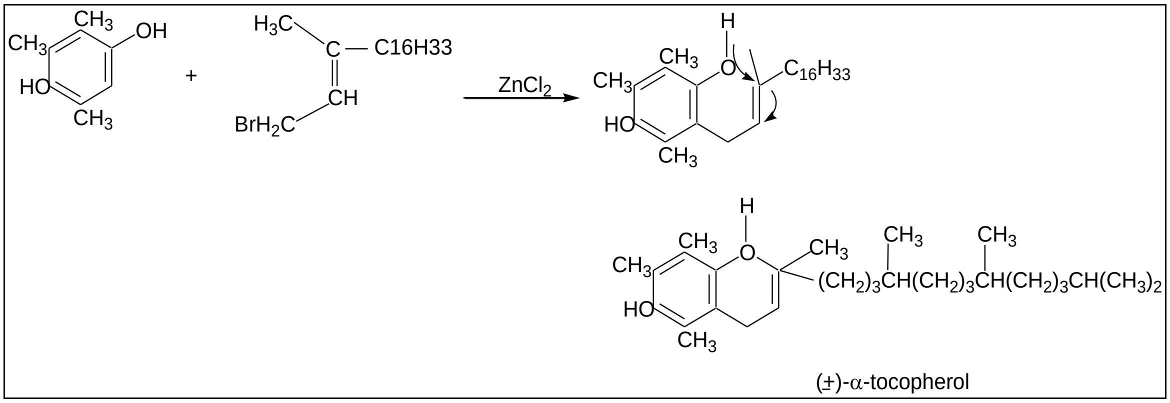
7) Further it was thought that the **acid B is a degraded product of the lactone A**, so γ-lactone A will be having the following structure.

$$\underbrace{OC—CH_2—CH_2—\overset{\displaystyle CH_3}{\overset{|}{C}}}_{O}—CH_2.CH_2.CH_2.\underset{\displaystyle CH_3}{\underset{|}{CH}}(CH_2)_3\underset{\displaystyle CH_3}{\underset{|}{CH}}(CH_2)_3.\underset{\displaystyle CH_3}{\underset{|}{CH}}—CH_3$$

γ-lactone (A)

8- **structure of α-tocopherol** is confirmed by synthesis

It have synthesized (±)-α-tocopherol by condensing **trimethylquinol with phytyl bromide.**



(±)-α-tocopherol

CAROTENOIDS (β-CAROTENE)

Chemically, the carotenoids are polyenes, and almost all the carotenoids hydrocarbon also, since the carbon skeleton of these compounds has polyisoprene structure, they may be regarded as tetrapenes. The color of the carotenoids is attributed to the extended conjugation of the central chain. B-Carotene is precursor of vitamin A. Beta carotene is biosynthesized from geranyl pyrophosphate. It is deep orange colored , soluble in chloroform , carbon disulfide,

Isolation and extraction of β-CAROTENE:

Following Step-

1-carrots are dried and powdered it

2- Powder is extracted with petroleum ether repeatedly at room temperature .the extract are combined and then concentrated at 30-40 c under reduced pressure.

3- In concentrated extract carbon disulfide is added, then small amount of ethanol is added to this solution to remove the colorless impurities.

4- In mother liquor ethanol is added from which crude carotenes are precipitated and filtered off.

5- Finally carotenes are recrystallized from petroleum ether

ELUCIDATION OF BETA CAROTENE

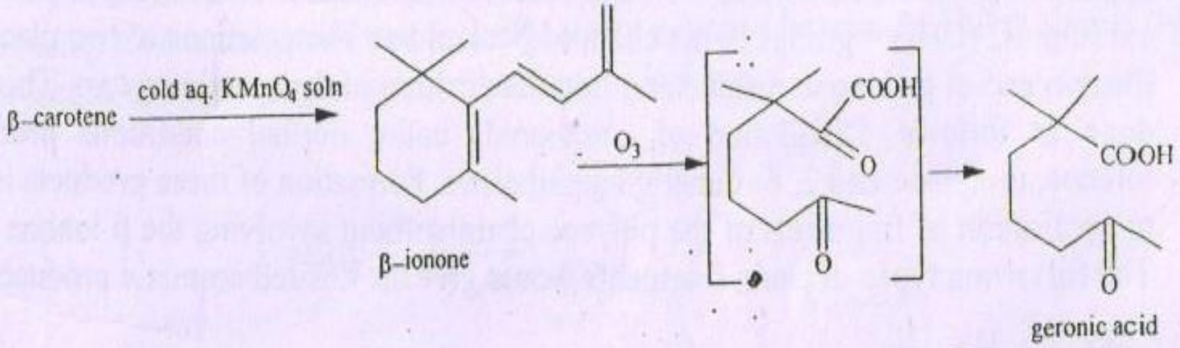
ELUCIDATION OF β- CAROTENE:

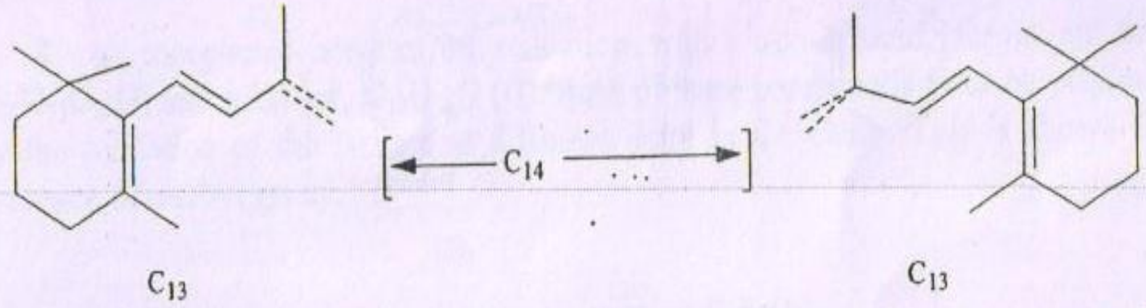
1. Molecular formula of β- carotene is $C_{40}H_{56}$.

2. β- Carotene is catalytically hydrogenated with eleven molecules of hydrogen to forms perhydro- β- carotene. This shows presence of 11 double bond in β- carotene.

3. β- Carotene is treated with five molecules of maleic anhydride to form a crystalline product. This shows that it contains fie conjugated double bonds.

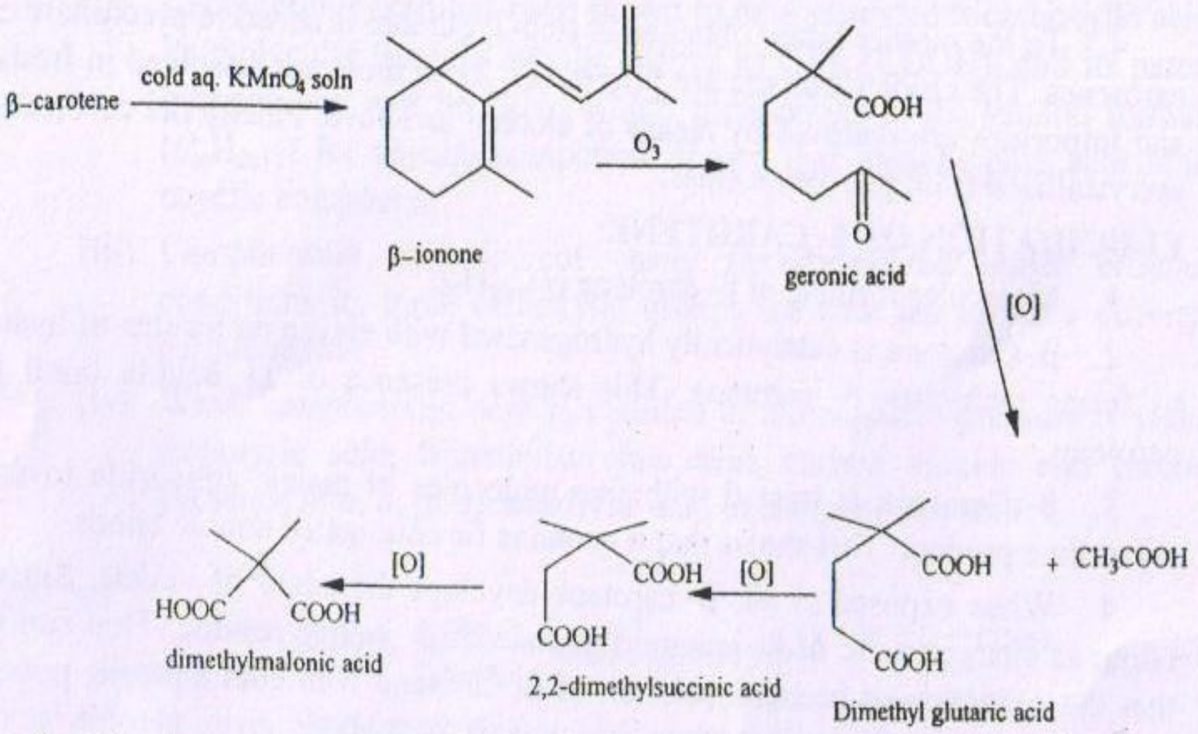
4. When exposed to air, β- carotene develops the odour of violets. Since this odour is characteristic of β- ionone. Presence of β- ionone residue. This confirmed that the oxidation of benzene solution of β- carotene with cold aqueous potassium permagnate gives β- ionone. Now β- iononeis ozonolysis gives geronic acid this shows that presence of two β- ionone residue in β- carotene.



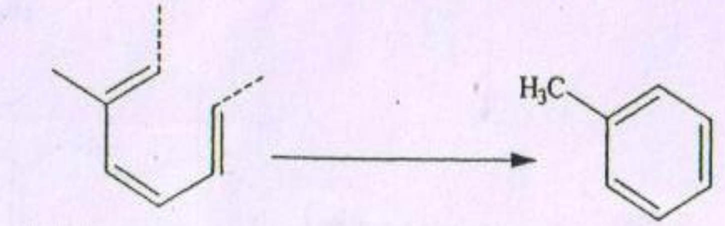


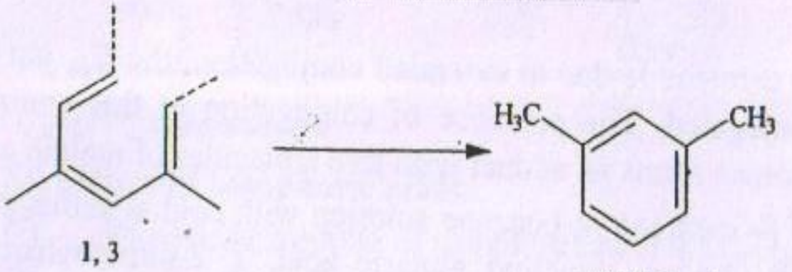
The colour of β- carotene is due to extended conjugation, the C_{14} portion of the molecule will be conjugated. The presence of conjugation in this central portion confirmed that β- carotene forms an adduct with five molecules of maleic anhydride.

5. Oxidation of β- carotene in benzene solution with cold aqueous permagnate gives a mixture of β- ionone, dimethyl glutaric acid, 2, 2-dimethylsuccinic acid dimethyl malonic acid and acetic acid. Presence of two β- ionone residues. Some methyl side chains in the central C_{14} portion of the molecule.

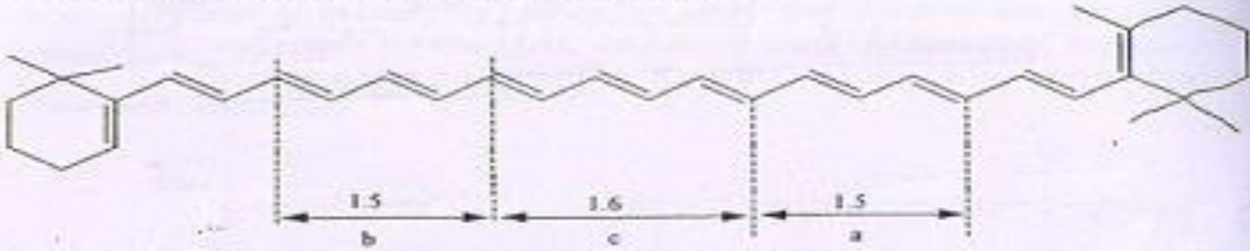


6. Number and position of side chain: Kuhn-Roth side chain determination is applied to β- carotene, it yield ~ 5.4 molecules of acetic acid. This indicates that there are four –C (CH$_3$) = groups in the chain of β- carotene. The positions of two placed in the two end of β- ionone residue and find the position of the remaining two. This was done as follows. Distillation of carotenoids under normal conditions produces toluene, m-xylene and 2, 6- dimethylnaphthalene. Formation of these products is due to cyclisation of fragments of the polyene chain without involving the β-ionone ring. The following types of chain fragments would give the desired aromatic products:

- 

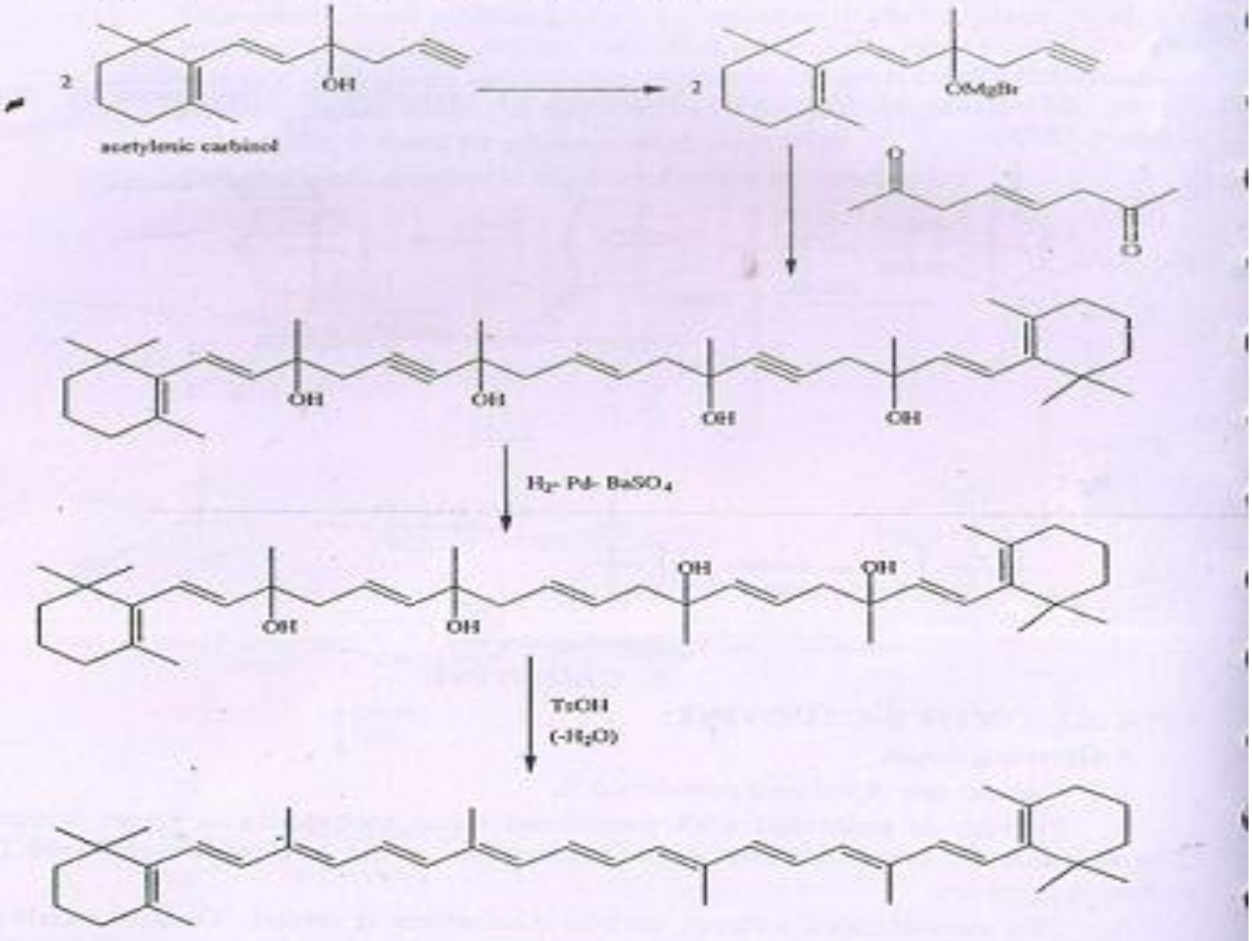
- 

7. **Symmetrical structure of β- carotene: the requirements of a, b and c; the ta to tail union of the two isoprene units at the centre.**



8. Synthesis: the structure of β- carotene is confirmed by synthesis

(a) (Karrer et al: 1950): (Yield was poor)



β–carotene