

# Notes on



*By*  
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# Introduction

1. Terpenes are the largest and most diverse group of naturally occurring compounds that are mostly found in plants, but larger classes of terpenes such as sterols and squalene can be found in animals.
2. The term terpene represents only hydrocarbons  $(C_5H_8)_n$  while the term terpenoids represent the hydrocarbons as well as the oxygenated derivatives, i.e. All compounds having  $(C_5)_n$ , so all the terpenes are terpenoids but not vice versa.
3. The modern definition of “terpenoids” is as follows: “It includes hydrocarbons of plant origin of the general formula  $(C_5H_8)_n$  as well as their oxygenated, hydrogenated and dehydrogenated derivatives”.
4. They are responsible for fragrance, taste and pigment of plants.
5. Fruits, flowers, leaves, stems, barks and roots of nearly all the plants have some pleasant smell. This pleasant smell of the fruits is actually due to the presence of some steam volatile oils known as essential oils.
6. The essential oils are complex mixtures of hydrocarbons and their oxygenated derivatives. Among the chief constituents of the essential oils are the terpenoids having carbon atoms up to  $C_{15}$  (i.e. mono and sesquiterpenoids) and their oxygenated derivatives such as alcohols, aldehydes and ketones etc.
7. Due to their pleasant smelling nature, the mono and sesquiterpenoids are of considerable commercial importance, particularly in the perfumery industry.
8. Terpenes have many functions in plants such as a thermoprotectant, signaling functions, and not limited to, pigments, flavoring, and solvents but also have various medicinal uses such as insecticidal, anthelmintic or antiseptic action, and are thus useful in pharmacy.

# Important essential oils with their main terpenoid constituents

Essential oils	Terpenoids	Essential oils	Terpenoids
Turpentine	Pinene	Lemon	D-Limonene, citral
Bergamot	Linalool and its acetate	Sweet orange	D-Limonene
Caraway	Carvone, $\alpha$ -Linalool	Peppermint	Menthol and its esters
Citronella	Geraniol, citronellal, farnesol	Rose	Geraniol, citronellol, farnesol
Coriander	Linalool, Pinene	Sandalwood	Santalol
Eucalyptus	Cineole	Cardamon, Cajeput	Terpineol
Geranium	Geraniol esters, Citronellol	Camphor	Camphor
Jasmine	Linalool	Neroli	Nerolidol
Lavender	Linalool	Ginger	Zinziberene



### Bisabolol

floral

#### Properties

anti-inflammatory  
anti-irritant  
anti-microbial



### Borneol

mint

#### Properties

anti-inflammatory  
antinociceptive



### Camphene

*fir needles, musky earth*

#### Properties

anti-oxidant  
skin lesion



### Caryophyllene

spicy

#### Properties

anti-bacterial  
anti-inflammatory  
anti-fungal



### Delta 3 Carene

pine, rosemary

#### Properties

anti-inflammatory  
bone stimulant



### Eucalyptol

mint

#### Properties

anti-bacterial  
anti-fungal



### Geraniol

peach, rose grass

#### Properties

anti-cancer  
anti-oxidant  
neuroprotectant



### Humulene

earthy

#### Properties

anti-bacterial  
anti-inflammatory  
anti-tumor effects



### Limonene

bitter citrus

#### Properties

anti-anxiety  
anti-cancer  
digestion, gallstones



### Linalool

floral

#### Properties

anti-anxiety  
anti-epileptic  
anti-psychotic  
pain killing



### Myrcene

citrus, cloves

#### Properties

relaxing  
sedating



### Pinene

pine

#### Properties

anti-depressant  
anti-inflammatory  
anti-microbial



### Phytol

balsamic, floral

#### Properties

anti-insomnia  
immunosuppressant



### Terpinolene

smoky, woody

#### Properties

anti-bacterial  
anti-fungal  
anti-insomnia  
antiseptic



### Trans-nerolidol

citrus, rose

#### Properties

anti-cancer  
anti-microbial  
anti-oxidant,  
anti-parasitic



### Valencene

sweet citrus

#### Properties


anti-inflammatory  
anti-melanogenesis  
antiallergic

# Isolation

The isolation of mono and sesquiterpenoids is effected in two steps, viz. isolation of essential oils from the plants, and separation of the individual terpenoids from the essential oils.

1. **Isolation of essential oils:** Plants containing essential oils usually have the greatest concentration at some particular time, e.g., jasmine at sunset, hence it is better to take the plant parts having essential oils at this particular time. In general, four methods have been developed for the isolation of essential oils, viz. (a) expression; (b) steam distillation; (c) extraction by means of volatile solvents; and (d) adsorption in purified fats (enfleurage).
  - a. **Expression method:** The plant material is crushed and the juice is screened to remove the large particles. The screened juice is centrifuged at a high speed centrifugal machine where nearly half of the essential oil is extracted. The other half of the oil is generally not extracted and such residue is used for the isolation of inferior quality of oil by distillation. Citrus, lemon and grass oils are extracted by this method.
  - b. **Steam distillation:** This is the most widely used method. The plant material is macerated and then steam distilled when the essential oils go into distillate from which they are extracted by the use of pure organic volatile solvents, like light petroleum. However, this method should be used with great care, since some essential oils are decomposed during distillation and some are hydrolysed to no- or less fragrant compounds.
  - c. **Extraction by means of volatile solvents:** Since some essential oils are sensitive to heat and hence decomposed during distillation, in such cases the plant material is directly treated with light petrol at 50 °C, and the solvent is then removed by distillation under pressure.



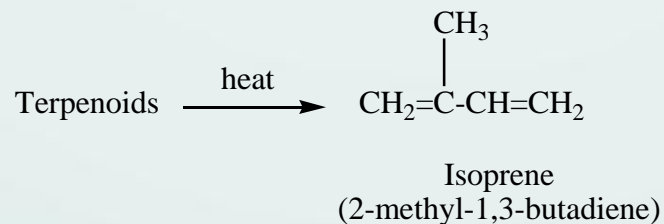


d. **Adsorption in purified fats:** The fat taken in glass plates is warmed to about 50 °C, then its surface is covered with the petals and it is allowed to be kept as such for several days until the fat is saturated with the essential oils for which the old petals may be replaced by the fresh ones. The petals are then removed and the fat is digested with ethyl alcohol when the essential oils present in the fat are dissolved in ethyl alcohol and if some fat is also dissolved during digestion it is removed by cooling to about 20 °. The extract having ethyl alcohol and essential oils is distilled under reduced pressure to remove the solvent. Recently the activated coconut charcoal is used in place of fat owing to the greater stability and more surface as compared to fat.

2. **Isolation and separation of terpenoids from essential oils:** The essential oils obtained in the first step generally contain a number of terpenoids belonging to mono and sesquiterpenoids. Physical methods, viz., fractional distillation and chromatography have been used for the isolation of individual terpenoids. During fractional distillation of the essential oils, the monoterpenoid hydrocarbons distil first followed by their oxygenated derivatives; while the residue containing sesquiterpenoids remain undistilled and then separated as monoterpenoids by distillation under reduced pressure. More recently, chromatographic techniques, viz., adsorption chromatography, vapour phase chromatography, partition chromatography and counter current separation have been used for the separation and isolation of the terpenoids.

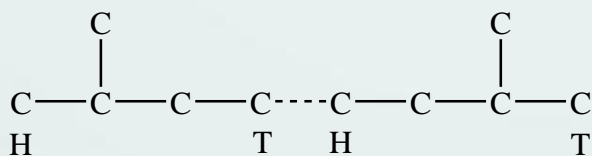
# General characteristics of terpenoids

1. Terpenoids are colourless, pleasant smelling liquids or solids, insoluble in water and readily volatile in steam with a few exceptions.
2. Most of them are optically active.
3. Since almost all of the terpenoids have one or more double bonds they add on all the olefinic reagents like halogens, hydrogen halides, nitrosyl chloride, nitrosyl bromide etc.
4. Some of the terpenoids having conjugated system of double bonds undergo Diels-Alder reaction.
5. Owing to the presence of olefinic bonds, they are very easily oxidised nearly by all oxidising agents.
6. A number of terpenoids are labile and hence readily isomerised in presence of acids into more stable forms.
7. On thermal decomposition almost all the terpenoids yield isoprene as one of the products.

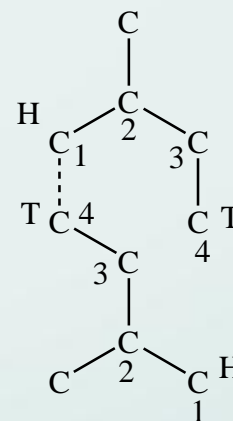


# Isoprene rule

1. The thermal decomposition of almost all terpenoids gives isoprene as one of the products and this has led to the suggestion that the skeleton structures of all naturally occurring terpenoids can be built up of isoprene units; this is known as isoprene rule.
2. This rule was first pointed out by O' Wallach in 1887.
3. The divisibility into isoprene units may be regarded as a necessary condition to be satisfied by the structure of any plant synthesized terpenoid.
4. In 1925, Ingold pointed out that isoprene units in natural terpenoids were joined 'head to tail' (the head being the branched end of isoprene). This divisibility into isoprene units and their head to tail union may be referred to as 'special isoprene rule'.



Or





# Classification

Terpenoid hydrocarbons are classified on the basis of the number of isoprene units which they contain.

	<b>Class</b>	<b>No. Of isoprene units (C<sub>5</sub>H<sub>8</sub>)</b>	<b>Molecular formulae</b>
1	Hemiterpene or isoprene	1	C <sub>5</sub> H <sub>8</sub>
2	Monoterpenes or terpenes	2	C <sub>10</sub> H <sub>16</sub>
3	Sesquiterpenes	3	C <sub>15</sub> H <sub>24</sub>
4	Diterpenes	4	C <sub>20</sub> H <sub>32</sub>
5	Triterpenes	6	C <sub>30</sub> H <sub>48</sub>
6	Tetraterpenes or Carotenoids	8	C <sub>40</sub> H <sub>64</sub>
7	Polyterpenes or Rubber	n	(C <sub>5</sub> H <sub>8</sub> ) <sub>n</sub>

Each class of terpenoid, except hemiterpene is further classified into following sub-classes on the basis of the number of rings present in the molecule.

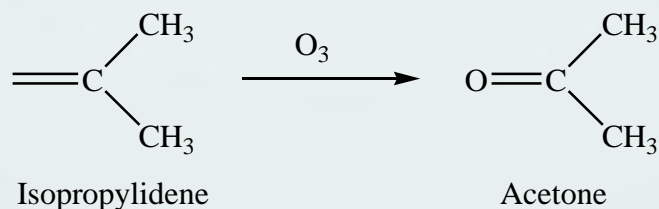
- Acyclic : those having an open chain structure.
- Monocyclic : those having one ring in their structure.
- Bicyclic : those having two rings in their structure.
- Tricyclic : those having three rings in their structure.

# Determination of structure of terpenoids

In general, elucidation of structure of a terpenoid involves the following points:

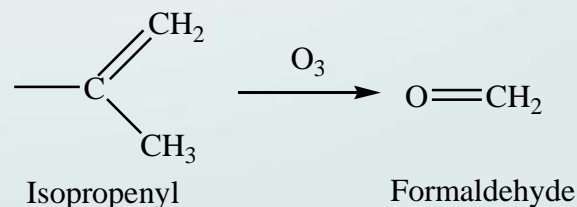
1. The first step is to determine the molecular formula of a pure specimen by qualitative analysis.
2. If the terpenoid is optically active, its specific rotation is measured since optical activity is used as a means of distinguishing the two or more possible structures.
3. The functional nature of oxygen, if present, is ascertained as in alkaloids. Terpenoids are found to possess alcoholic, aldehydic, ketonic and ether groups.
4. The C-alkyl groups are frequently present in the terpenoid molecules. Three such important C-alkyl groups are C-methyl (-C-CH<sub>3</sub>), isopropylidene (=CMe<sub>2</sub>) and isopropenyl. The C-methyl group is detected and estimated by the oxidation of the terpenoid with chromic acid when all the C-methyl groups are converted into CH<sub>3</sub>COOH molecules (Kuhn-Roth method) which is estimated volumetrically.

The isopropylidene group is detected by the ozonolysis to acetone. The amount of acetone is estimated volumetrically and thus the number of isopropylidene groups is determined.

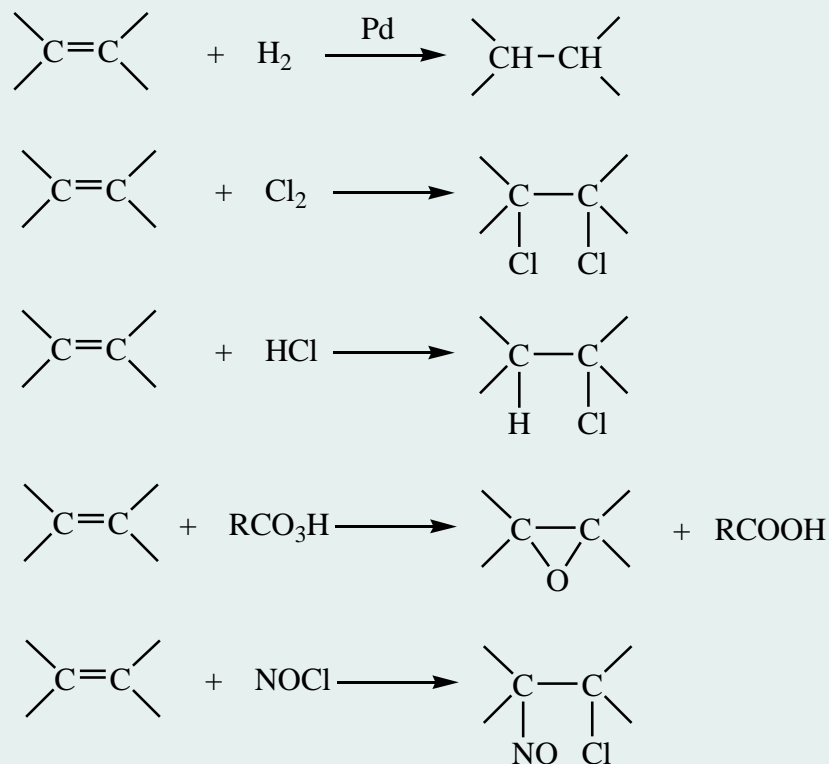


On similar treatment, isopropenyl group yields HCHO.

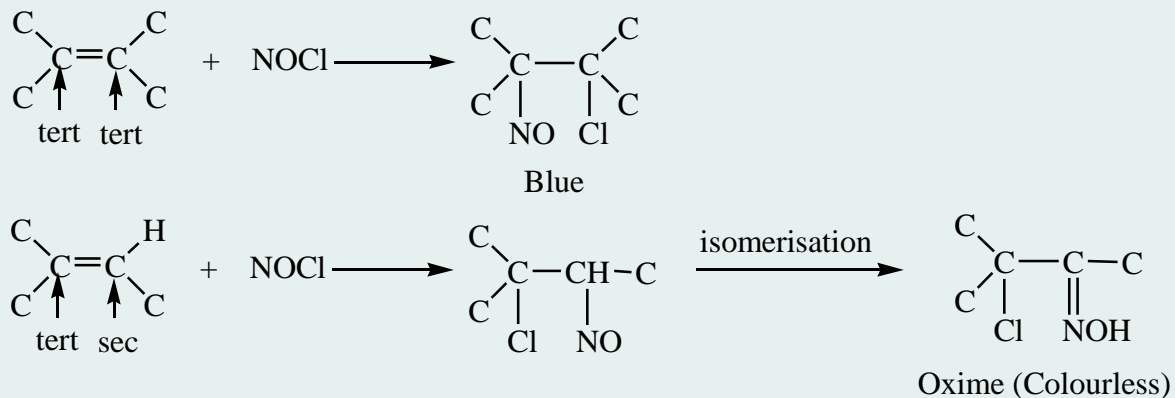
Lastly, two groups are distinguished by IR spectrum.



- Sometimes dehydrogenation of terpenoids with sulfur, selenium, platinum and palladium gives well known aromatic compounds and thus one can judge the carbon framework of the molecules. This step is generally useful for cyclic terpenoids.
- The presence and number of double bonds are ascertained by the common olefinic reagents, viz. hydrogens, halogens, halogen acids, per acids and nitrosyl chloride (Tilden reagent).



The last reaction i.e. Addition of Tilden's reagent is of more importance as it gives idea about the nature of the carbon atoms having double bond because if the two carbon atoms joined by a double bond are tertiary, a blue colored nitrosyl chloride is formed while if one of the carbon atoms joined to double bond is tertiary and the other is secondary, a colourless nitrosyl chloride is obtained.



With the help of the number of double bonds and the nature of the functional groups, the molecular formula of the terpenoid is converted into its fully saturated parent hydrocarbon and then compared with the following formulae for the various types of compounds and thus the number of rings in a terpenoid molecule is ascertained.

General formula of compound	Type of compound
$C_nH_{2n+2}$	Acyclic
$C_nH_{2n}$	Monocyclic
$C_nH_{2n-2}$	Bicyclic
$C_nH_{2n-4}$	Tricyclic
$C_nH_{2n-6}$	Tetracyclic and so on

7. Presence of conjugated system of double bonds is generally detected by Diels Alder reaction.

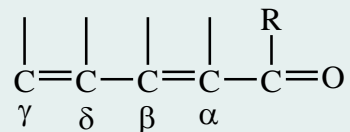
**8. Physical aids to terpenoids:** The presence of conjugation in terpenoids can be established by the use of ultraviolet spectroscopy. In simple acyclic dienes,  $\lambda_{\text{max}}$  is 217-228 nm. In case the diene is homoannular, i.e. the two conjugated double bonds are in the same ring,  $\lambda_{\text{max}}$  is 256-265 nm; while when the diene is heteroannular i.e. The conjugated double bonds are not in the same ring,  $\lambda_{\text{max}}$  is 230-240 nm. If an  $\alpha,\beta$ -unsaturated carbonyl group is present, the  $\lambda_{\text{max}}$  is 220-250 nm and there is also a weak bond at  $\lambda_{\text{max}}$  315-330 nm.

According to Woodward, the absorption maximum of diene system is dictated by its number, type and degree of substitution. For this Woodward developed a set of empirical rules for calculating the absorption maximum from the molecular structure of the compound.

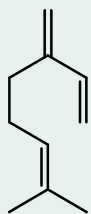
### Polyenes

Basic chromophore	nm
Acyclic and heteroannular dienes	214
Homoannular diene	253
For each double bond extending conjugation	30
For each exocyclic double bond	5
For each C-substituent	5
$\lambda_{\text{max}}$ of the compound	Total

## $\alpha,\beta$ -unsaturated ketones



Parent system	215
For each double bond extending conjugation	30
For each exocyclic double bond	5
For each C-substituent:	
at $\alpha$ -C	10
at $\beta$ -C	12
at $\gamma$ or $\delta$ -C	18
$\lambda_{\text{max}}$ of the compound	Total



$\lambda_{\text{max}}$ :

Observed = 224 nm

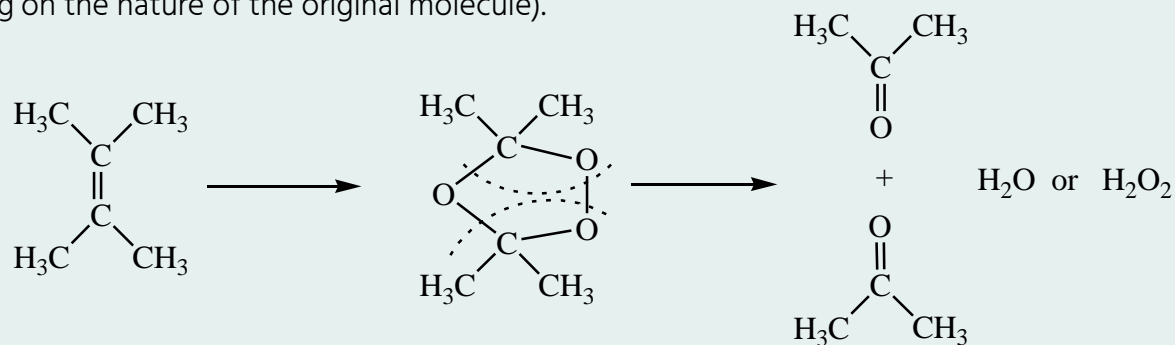
Calculated = 214 (for an acyclic diene) + 5 (for one C-substituent) = 219



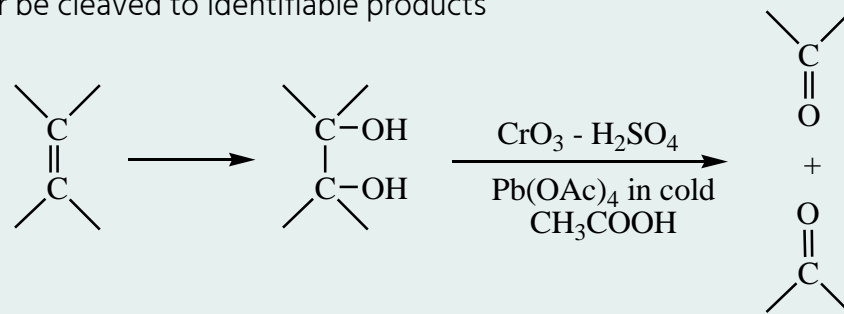
In addition to ultraviolet spectroscopy, other spectroscopic methods such as IR, NMR and mass spectroscopy, X-ray studies have been used for establishing the structure of terpenoids.

9. After knowing the various functional groups and the number of rings in the given terpenoid, it is degraded to obtain small identifiable fragments. Oxidative methods play a large part in determining the structure of the terpenoids. Ozone is the most important reagent in oxidative degradation.

a. Ozone: This reagent attacks the olefinic linkage of the molecule or form ozonide which may be decomposed either by hydrolysis or catalytic reduction or reduction with zinc dust to the corresponding carbonyl compounds (depending on the nature of the original molecule).



b. Hydroxylating reagents: A group of reagents such as lead tetraacetate in hot CH<sub>3</sub>COOH, per acids, osmium tetroxide, H<sub>2</sub>O<sub>2</sub>, KMnO<sub>4</sub> etc. when attack on terpenoids, the double bonds are hydroxylated to form 1,2-glycols. This 1,2-glycols may further be cleaved to identifiable products



10. Lastly, the structure proposed by the degradative methods is proved by unambiguous synthesis.

# Citral

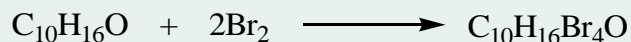
This is the most important member of acyclic monoterpenoids. Citral is widely distributed and occurs to an extent of 60-80 percent in lemon grass oil. Citral is a liquid which has the smell of lemons. This compound has biological activities such as antibacterial, antifungi, analgesic, and antiinflammation. Citral also has importance for its use as starting material for the synthesis of Vitamin A.

## Isolation method

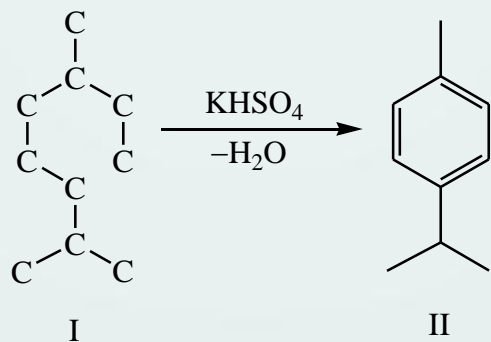
- The quantity of lemongrass oil and water are taken in the distillation flask according to the volume ratio (oil : water). 600 mL of distilled water was taken in the steam generation flask for generating steam. In presence of steam, the mixture of lemongrass oil and water was volatilized at a temperature close to 100 °C at atmospheric pressure. The mixtures of hot vapors were allowed to pass through a condenser to form a liquid in which the oil and water comprise two distinct layers. The top layer is oil and the bottom layer is water, which was separated by separating funnel. Some amount of water may be present in separated oil layer that was removed by adding diethyl ether. Then, the oil layer should be extracted from the co-distilled water by using the fact that the oil was insoluble in water and is soluble in non-polar solvents like Diethyl ether. Ether was added to the Oil-Water mixture in a separating funnel. This funnel allows the two solvents to layer and subsequently, one solvent layer could be drained away from the other. After a few moments of shaking, the oil will partition into the ether layer. Draining the water layer from the ether removes the oil from the water. So an extraction is usually carried-out multiple times. The resulting ether layers were collected and combined. The ether boils at a low enough temperature that it can simply be boiled off from the oil layer. After the ether is stripped off, isolation of the citral oil is complete.

# Structure elucidation of citral

1. Molecular formula of citral is  $C_{10}H_{16}O$ .
2. It adds two molecules of bromine to form a tetrabromide, which indicate the presence of two  $C=C$  double bonds.

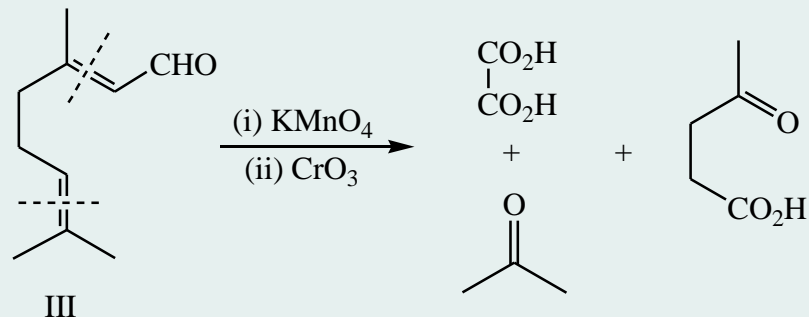


3. Citral was shown to contain an oxo group, e.g., it forms an oxime etc.
4. On heating with potassium hydrogen sulphate, citral forms p-cymene (II). This reaction was used by Semmler to determine the positions of the methyl and isopropyl groups in citral. Semmler identified that the citral molecule was acyclic, and gave it the skeleton structure I (two isoprene units joined head to tail).

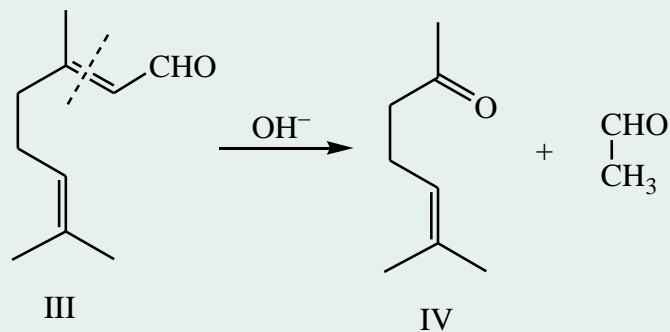


5. Citral can be reduced by sodium amalgam to an alcohol, geraniol,  $C_{10}H_{18}O$ , and is oxidised by silver oxide to geranic acid,  $C_{10}H_{16}O_2$ . Since there is no loss of carbon on oxidation to the acid, the oxo group in citral is therefore an aldehyde group.

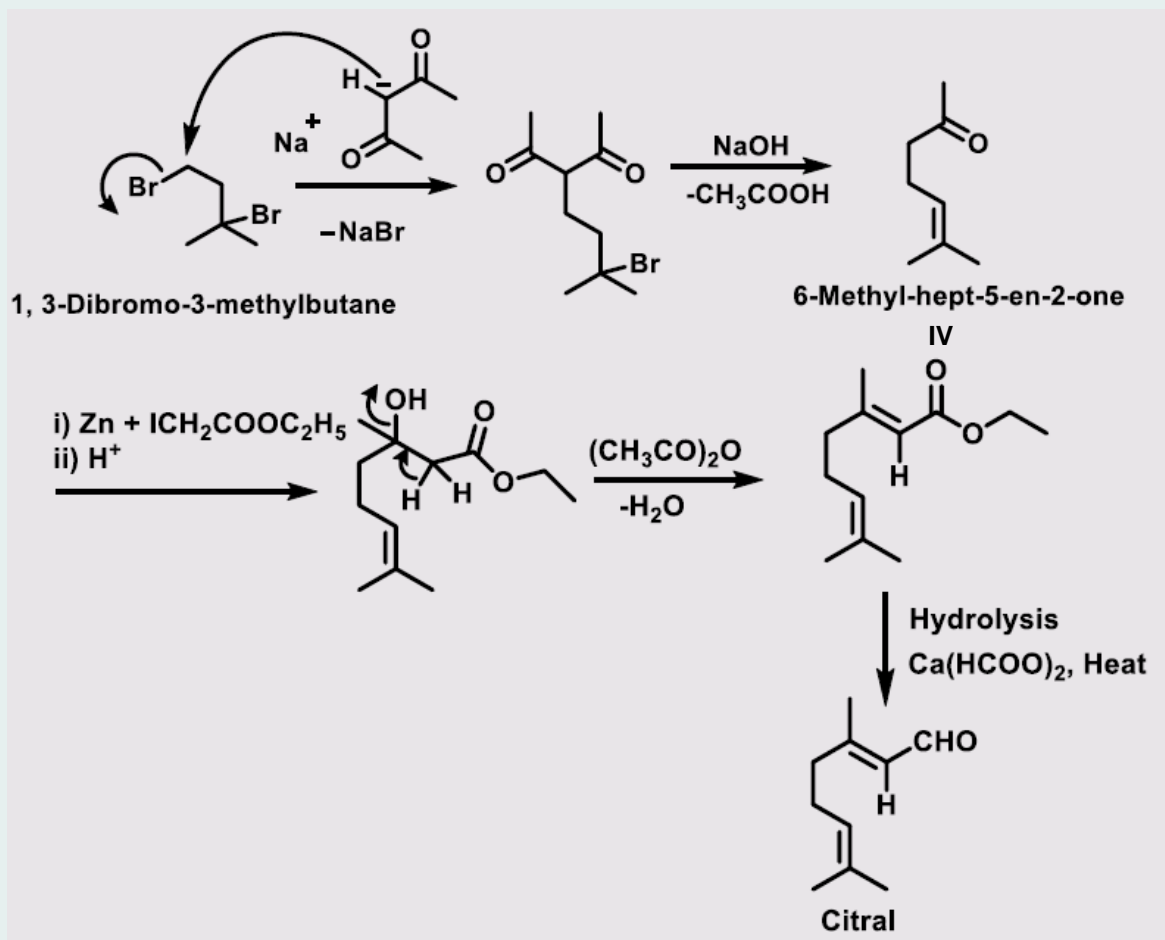
6. Oxidation of citral with alkaline permanganate, followed by chromic acid, gives acetone, oxalic and laevulic acid. Thus, if citral has structure III, the formation of these oxidation products may be accounted for.



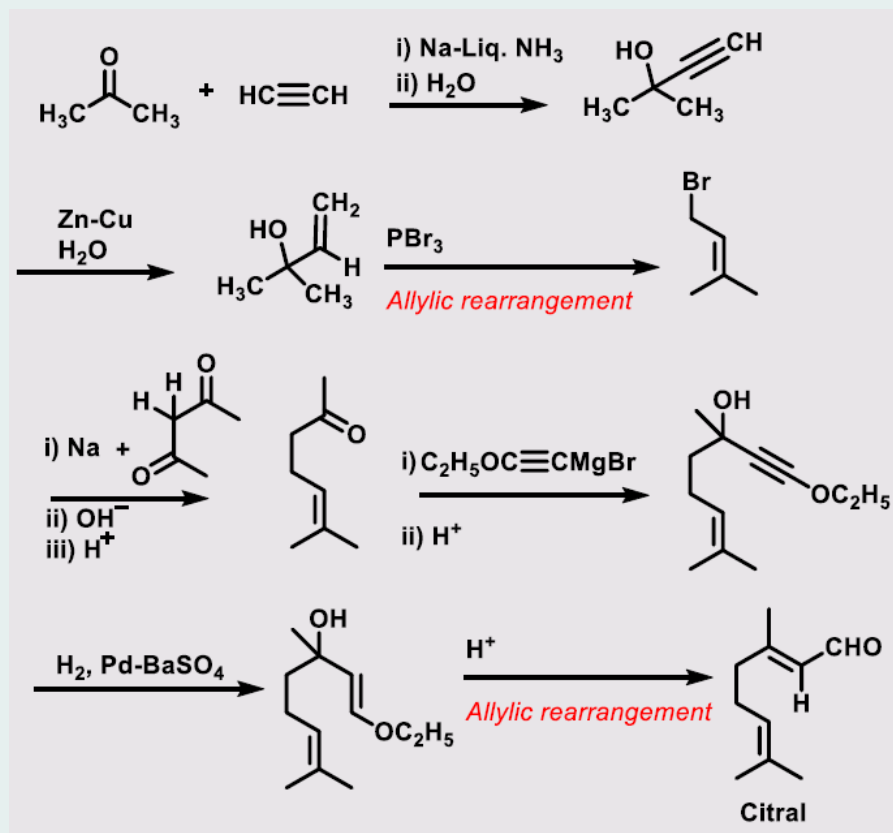
7. This structure is supported by the work of Verley (1897), who found that aqueous potassium carbonate converted citral into 6-methylhept-5-en-2-one (IV) and acetaldehyde. The formation of these products is readily explained by assuming III undergoes cleavage at the  $\alpha$ ,  $\beta$ -double bond; this cleavage by alkaline reagents is a general reaction of  $\alpha$ ,  $\beta$ -unsaturated oxo compounds. Furthermore, methylheptenone (IV) itself is oxidised to acetone and laevulic acid, this is in accord with structure III.



8. The structure of citral was confirmed by the synthesis of methylheptenone (IV), 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.



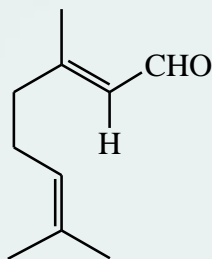
A more recent synthesis of citral is that of Arens et al. (1948)



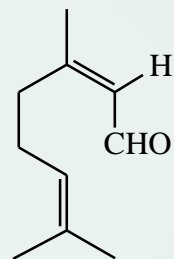


# Isomers of citral

Examination of the formula of citral shows that two geometrical isomers are possible. The functional group aldehyde is either trans or cis with respect to the methylene group of the main chain. Both isomers occur in natural citral; both forms of citral itself have also been obtained: citral-a (also known as geranial) has a b.p. 118-119 °C and citral-b (also known as neral) has a b.p. 117-118 °C



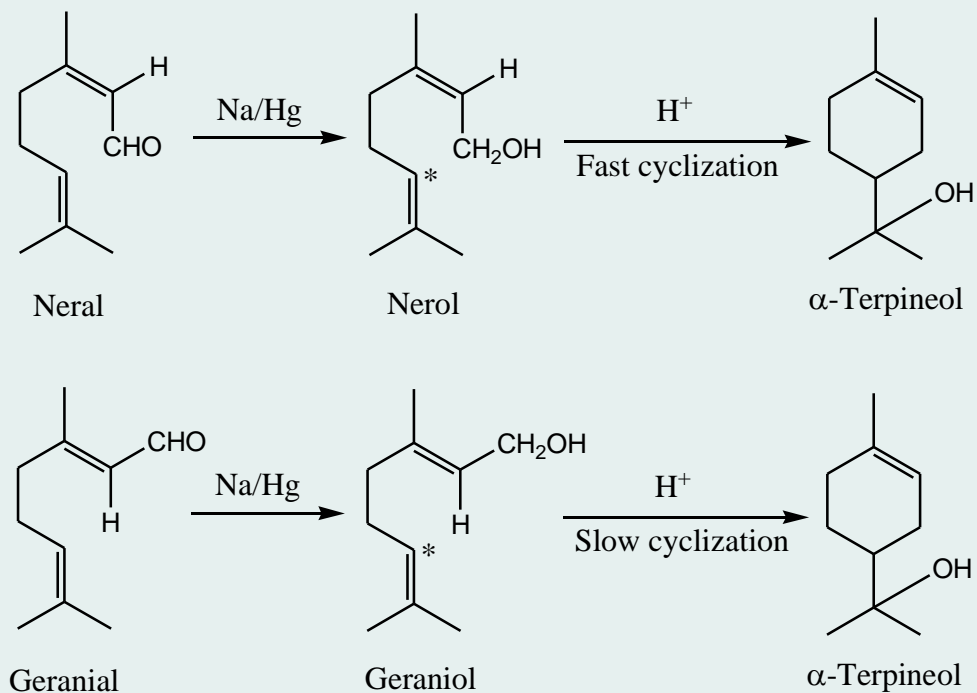
trans- (or E-) form;  
citral-a; geranial



cis- (or Z-) form;  
citral-b; neral

The existence of the two isomeric citrals in natural citral has been confirmed chemically due to the formation of two different semicarbazones and formation of geraniol and nerol on reduction. As the trans-citral yields geraniol on reduction, it is known as geranial or citral-a. Similarly as cis-citral on reduction yields nerol, it is called neral or citral-b.

The configurations of the two geometrical forms of citral have been determined from readiness with which the ring closure of the corresponding stereoisomeric primary alcohols, namely geraniol and nerol takes place. The citral which cyclises easily to terpineol, is cis-isomer while the other which does not isomerise readily is called trans isomer. As nerol cyclises nine times as rapidly as geraniol, nerol is assigned the cis-configuration and geraniol the trans; hence nerol is cis-citral whereas geraniol is trans-citral.



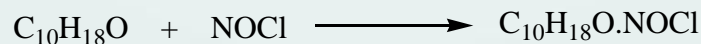
# $\alpha$ -Terpineol

It is an optically active monoterpenoid that is widely distributed in nature in the (+)-, (-)-, and ( $\pm$ )- forms. The (+)- form occurs in oils of petitgrain and neroli, (-)- form in camphor oils and ( $\pm$ )- form in cajuput oil.

$\alpha$ -Terpineol is widely used in the preparation of the lilac perfumes and lilac scented soaps. It is regarded as the most important monocyclic monoterpenoid because the elucidation of its structure confirmed the structures of many other monoterpenoids.

## Structure elucidation of $\alpha$ -Terpineol

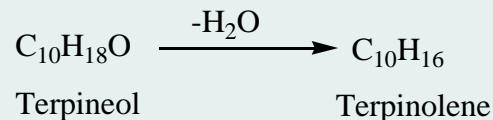
1. From analytical data and molecular weight determination, the molecular formula of  $\alpha$ -terpineol has been found to be  $C_{10}H_{18}O$ .
2. As  $\alpha$ -terpineol adds on one mole of bromine and of nitrosyl chloride to form their respective addition compounds, it suggests that  $\alpha$ -terpineol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



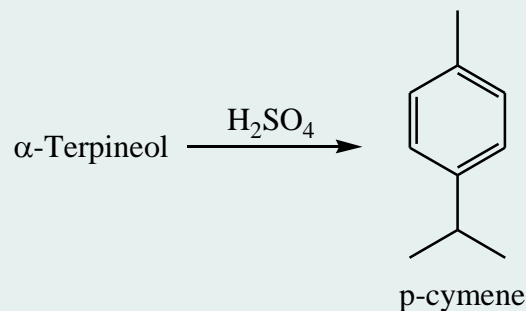
3.  $\alpha$ -terpineol when treated with phenylisothiocyanate forms phenylurethane, indicating the presence of a hydroxyl group in terpineol.

Further,  $\alpha$ -terpineol is insoluble in sodium hydroxide solution which suggests that the hydroxyl group cannot be a phenolic one.

Terpineol undergoes dehydration readily, when heated with sulfuric acid in glacial acetic acid, forming terpenoids like dipentene and terpinolene. Moreover,  $\alpha$ -terpineol does not undergo oxidation readily. These facts reveal that the hydroxyl group in  $\alpha$ -terpineol is present as a tertiary alcoholic group.



4. As  $\alpha$ -terpineol contains one double bond and one tertiary alcoholic group, the molecular formula of fully saturated hydrocarbon of terpineol is  $\text{C}_{10}\text{H}_{20}$  ( $\text{C}_{10}\text{H}_{18} + 2\text{H}$  of double bond  $- 1\text{H}$  of hydrogen atom of tertiary alcoholic group  $+ 1\text{H}$  of the monovalent alcoholic group). This corresponds to  $\text{C}_n\text{H}_{2n}$ , the general formula of the monocyclic cycloalkanes and thereby,  $\alpha$ -terpineol is a monocyclic compound.
5. When  $\alpha$ -terpineol is heated with sulfuric acid it forms p-cymene.



Taking the above observation in conjunction with the above proposal that  $\alpha$ -terpineol is monocyclic, it may be inferred that  $\alpha$ -terpineol contains the p-cymene skeleton. Thus, it may be concluded that  $\alpha$ -terpineol may be p-menthane (fully saturated p-cymene) with one double bond and one tertiary alcoholic group.



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

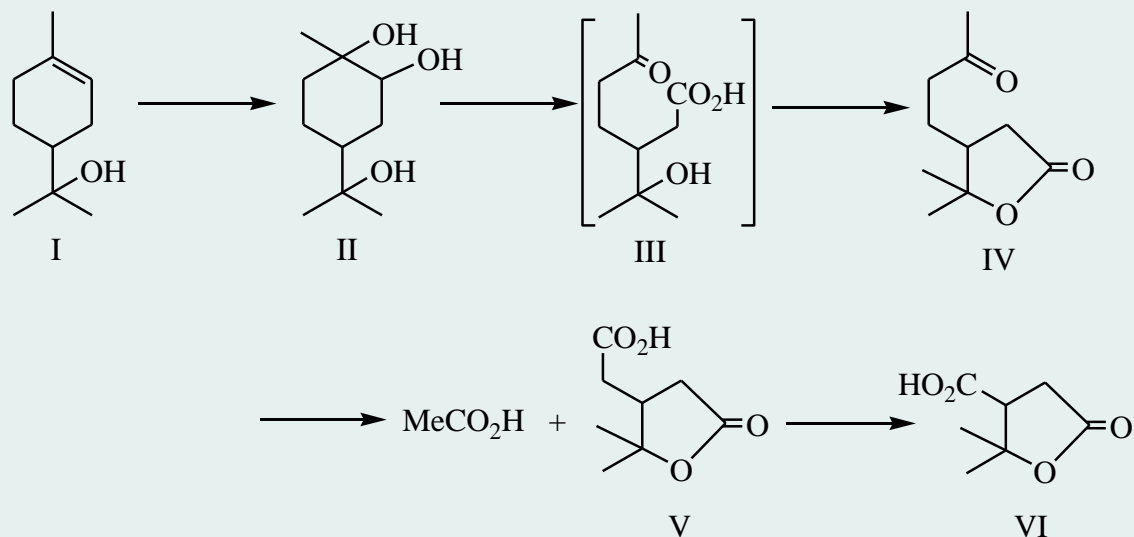
- a) Oxidation of  $\alpha$ -terpineol (I) with 1 per cent alkaline potassium permanganate hydroxylates the double bond to produce the trihydroxy compound (II),  $C_{10}H_{20}O_3$ . This on oxidation with chromic acid, produces a compound with the molecular formula  $C_{10}H_{16}O_3$  (IV). This compound was shown to contain a ketonic group and it was neutral since it gave no reaction with sodium carbonate solution. However, when IV was refluxed with excess of standard sodium hydroxide solution and then back titrated, it was found that alkali had been consumed, the amount corresponding to the presence of one carboxyl group. Thus, compound IV appears to be the lactone of a monocarboxylic acid which has been produced due to the lactonisation of  $\gamma$ - or  $\delta$ -hydroxy acid, i.e., IV is a  $\gamma$ - or  $\delta$ -lactone and therefore III is a  $\gamma$ - or  $\delta$ -hydroxy acid.
- b) As compound IV is formed due to the breaking of the glycol bond in II without any loss of carbon atoms in the process, it means that the double bond must be present in the ring of compound I.
- c) When the compound IV is warmed with alkaline permanganate, it yields acetic acid and a compound  $C_8H_{12}O_4$  (V).

The formation of acetic acid reveals that IV is a methyl ketone i.e. A  $CH_3CO$  group is present. Thus, IV is a methyl ketone and lactone; it is known as homoterpenyl methyl ketone and the structure assigned to it has been confirmed by synthesis by Simonsen et al.

A study of the properties of terpenylic acid (V) showed that it was the lactone of a monohydroxydicarboxylic acid. Further oxidation of terpenylic acid gives terebic acid,  $C_7H_{14}O_4$  (VI), which is also the lactone of a monohydroxydicarboxylic acid.

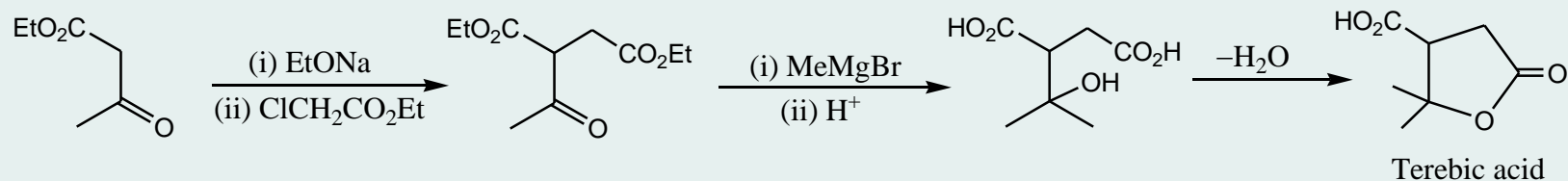


The above reactions can be formulated as below, assuming I (p-menth-1-en-8-ol) as the structure of  $\alpha$ -terpineol. These reactions were formulated by Wallach, who adopted formula I which had been proposed by Wagner in 1894.

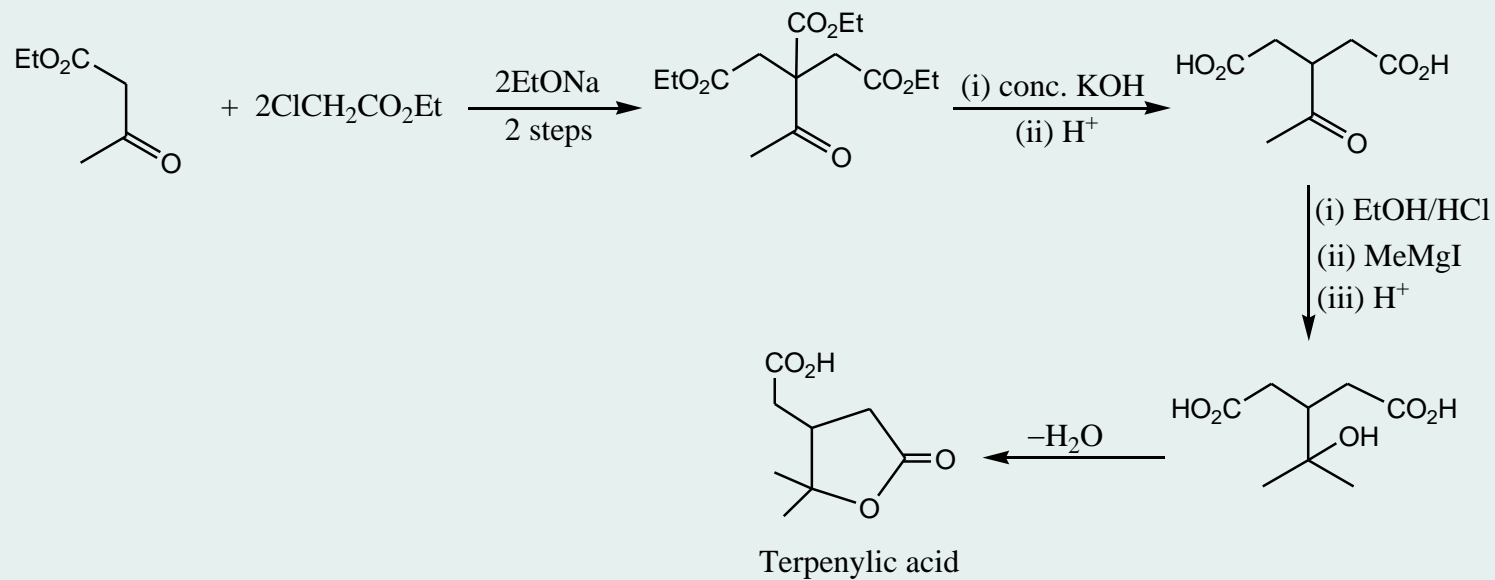


d) The structure of terpenylic (V) and terebic acids were established by synthesis.

### Terebic acid

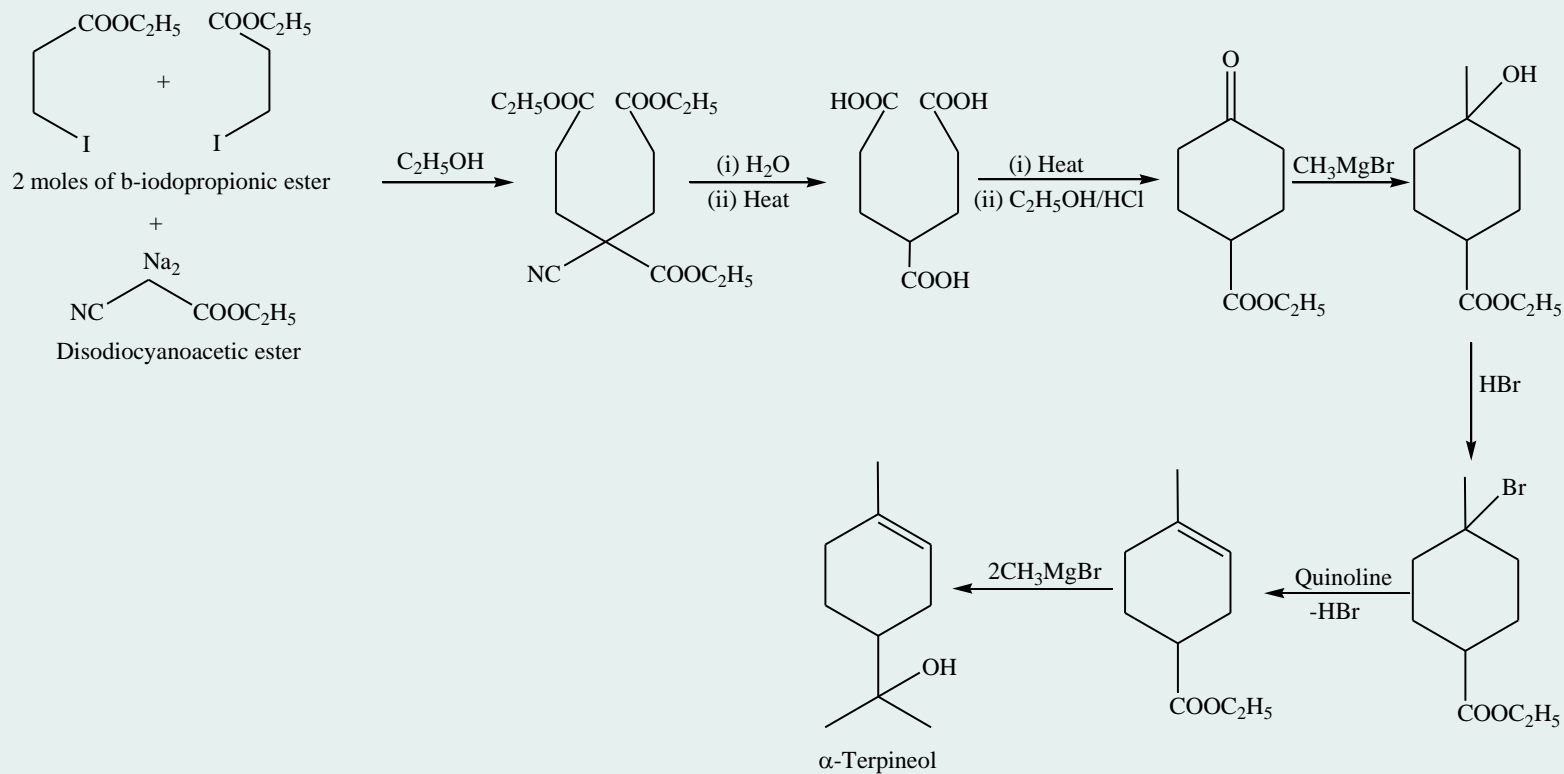


## Terpenylic acid

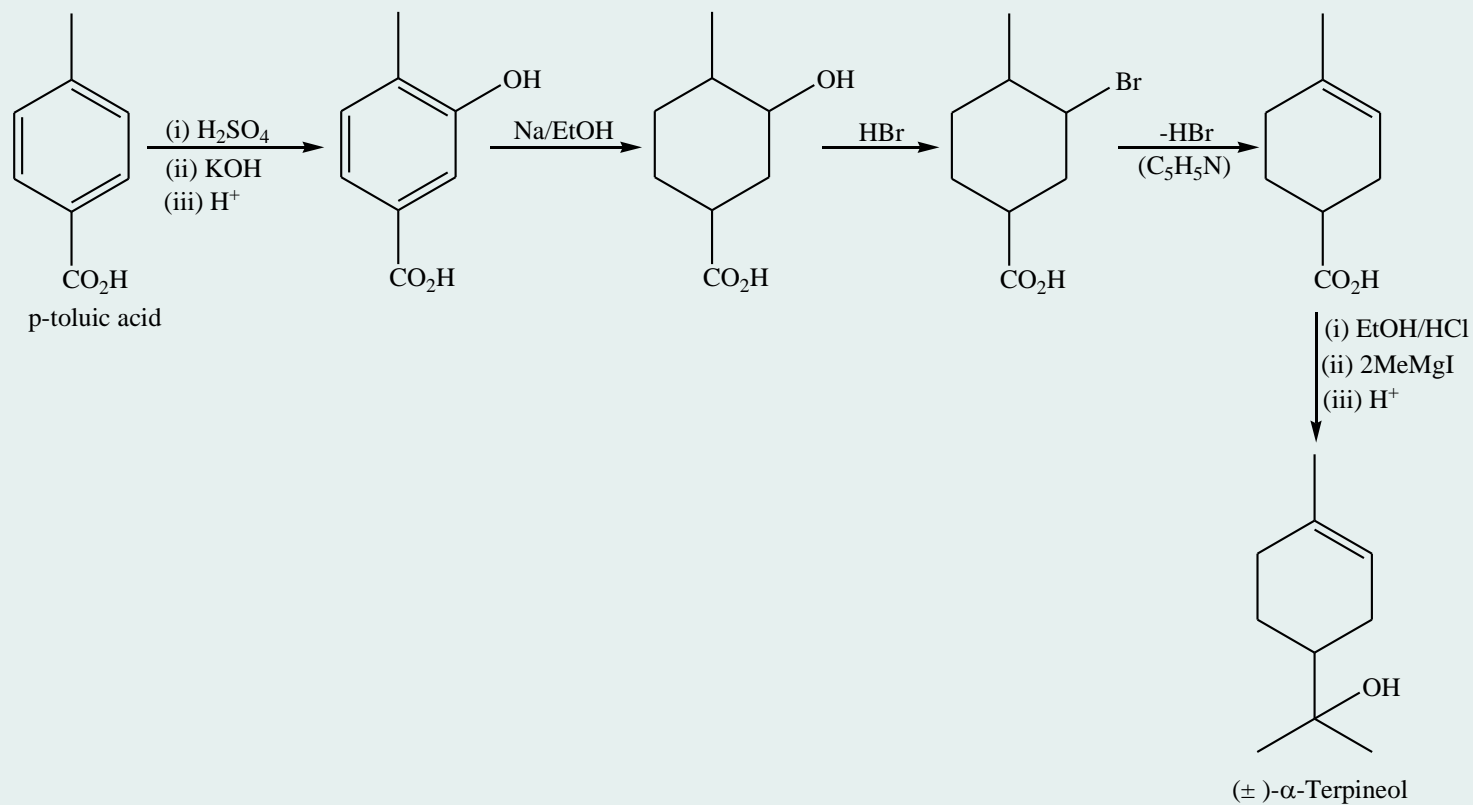


6. Finally, the structure of  $\alpha$ -terpineol has been confirmed by its various synthesis as follows:

(a) Perkin's synthesis (1904):



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



(c) Alder-Vogot's synthesis :

