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UNIT – II Terpenes

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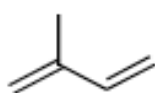
Terpenes: Classification, General methods of extraction and separation (Mono and sesquiterpenes), special isoprene rule and Structural elucidation of citral, carvone, menthol & camphor

Terpenes and Terpenoids constitute a large class of natural products built up from isoprene units.

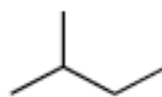
Terpenes are technically only hydrocarbons, while terpenoids are oxygenated.

Isoprene Rule:

- The basic molecular formulae of terpenes are multiples of $(C_5H_8)_n$ where n is the number of linked isoprene units.

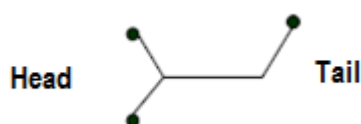


Isoprene

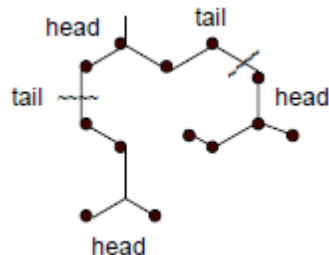
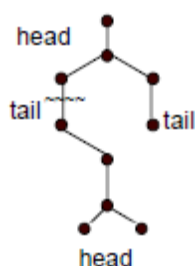


Isoprene Unit

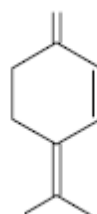
- Isoprene rule states that the terpenoid molecules are constructed from two or more isoprene unit.
- Further Ingold suggested that isoprene units are joined in the terpenoid via 'head to tail' fashion.
- Special isoprene rule states that the terpenoid molecules are constructed of two or more isoprene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



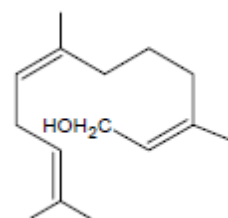
- But this rule can only be used as guiding principle and not as a fixed rule. For example carotenoids are joined tail to tail at their central and there are also some terpenoids whose carbon content is not a multiple of five.
- In applying isoprene rule we look only for the skeletal unit of carbon. The carbon skeletons of open chain monoterpenoids and sesqui terpenoids are,



Examples.

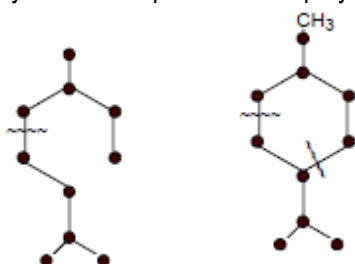


Myrcene (Monoterpene)



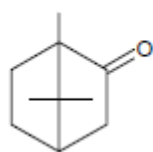
Farnesol (Sesquiterpene)

- Ingold (1921) pointed that a gem alkyl group affects the stability of terpenoids. He summarized these results in the form of a rule called 'gem dialkyl rule' which may be stated as "Gem dialkyl group tends to render the cyclohexane ring unstable where as it stabilizes the three, four and five member rings."
- This rule limits the number of possible structure in closing the open chain to ring structure. Thus the monoterpene open chain give rise to only one possibility for a monocyclic monoterpene i.e the p-cymene structure.

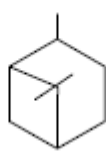


P-cymene structure

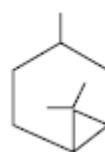
- Bicyclic monoterpenoids contain a six member and a three member ring. Thus closure of the ten carbon open chain monoterpenoid gives three possible bicyclic structures.



Camphor
(6+5) system



Pinane
(6+4) system



Carane
(6+3) System

CLASSIFICATION OF TERPENOIDS

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

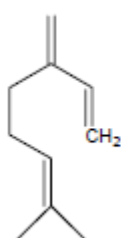
S.No.	Number of carbon atoms	Value of n	Class
1	10	2	Monoterpenoids ($C_{10}H_{16}$)
2	15	3	Sesquiterpenoids ($C_{15}H_{24}$)
3	20	4	Diterpenoids ($C_{20}H_{32}$)
4	25	5	Sesterpenoids ($C_{25}H_{40}$)
5	30	6	Troterpenoids ($C_{30}H_{48}$)
6	40	8	Tetraterpenoid ($C_{40}H_{64}$)
7	>40	>8	Polyterpenoids (C_5H_8) $_n$

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

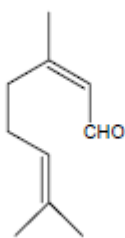
- I. **Acyclic Terpenoids:** They contain open structure.
- II. **Monocyclic Terpenoids:** They contain one ring in the structure.
- III. **Bicyclic Terpenoids:** They contain two rings in the structure.
- IV. **Tricyclic Terpenoids:** They contain three rings in the structure.
- V. **Tetracyclic Terpenoids:** They contain four rings in the structure.

A) Mono Terpenoids:

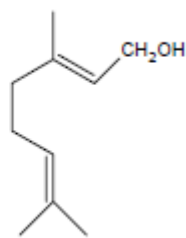
i) Acyclic Monoterpenoids



Myrcene

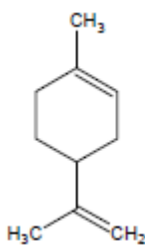


Citral

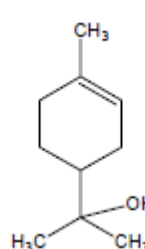


Geraniol

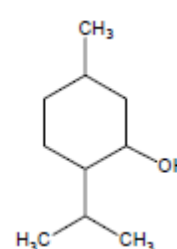
ii) Monocyclic monoterpenoids



Limonene



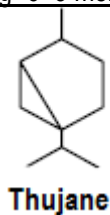
α -Terpineol



Menthol

iii) *Bicyclic monoterpenoids*: These are further divided into three classes.

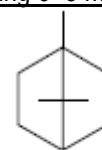
- Containing -6+3 membered rings



- Containing 6+4 membered rings

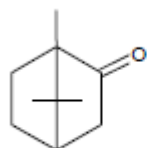


- Containing 6+5 membered rings

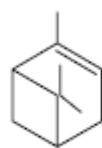


**Borneane
(Camphane)**

- Some bicyclic monoterpenes are



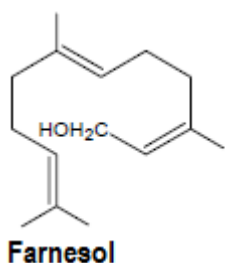
Camphor



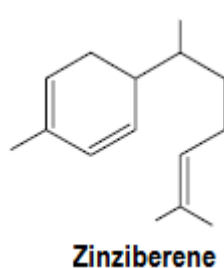
alpha-pinene

B) Sesquiterpenoids:

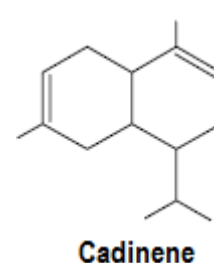
i) *Acyclic sesquiterpenoids*



ii) *Monocyclic sesquiterpenoids*

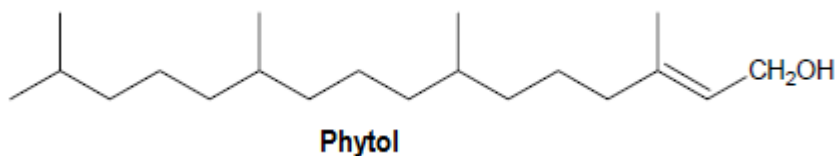


iii) *Bicyclic sesquiterpenoids.*

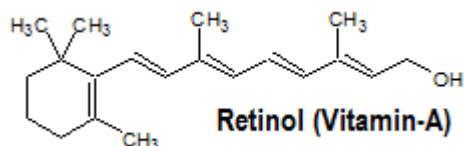


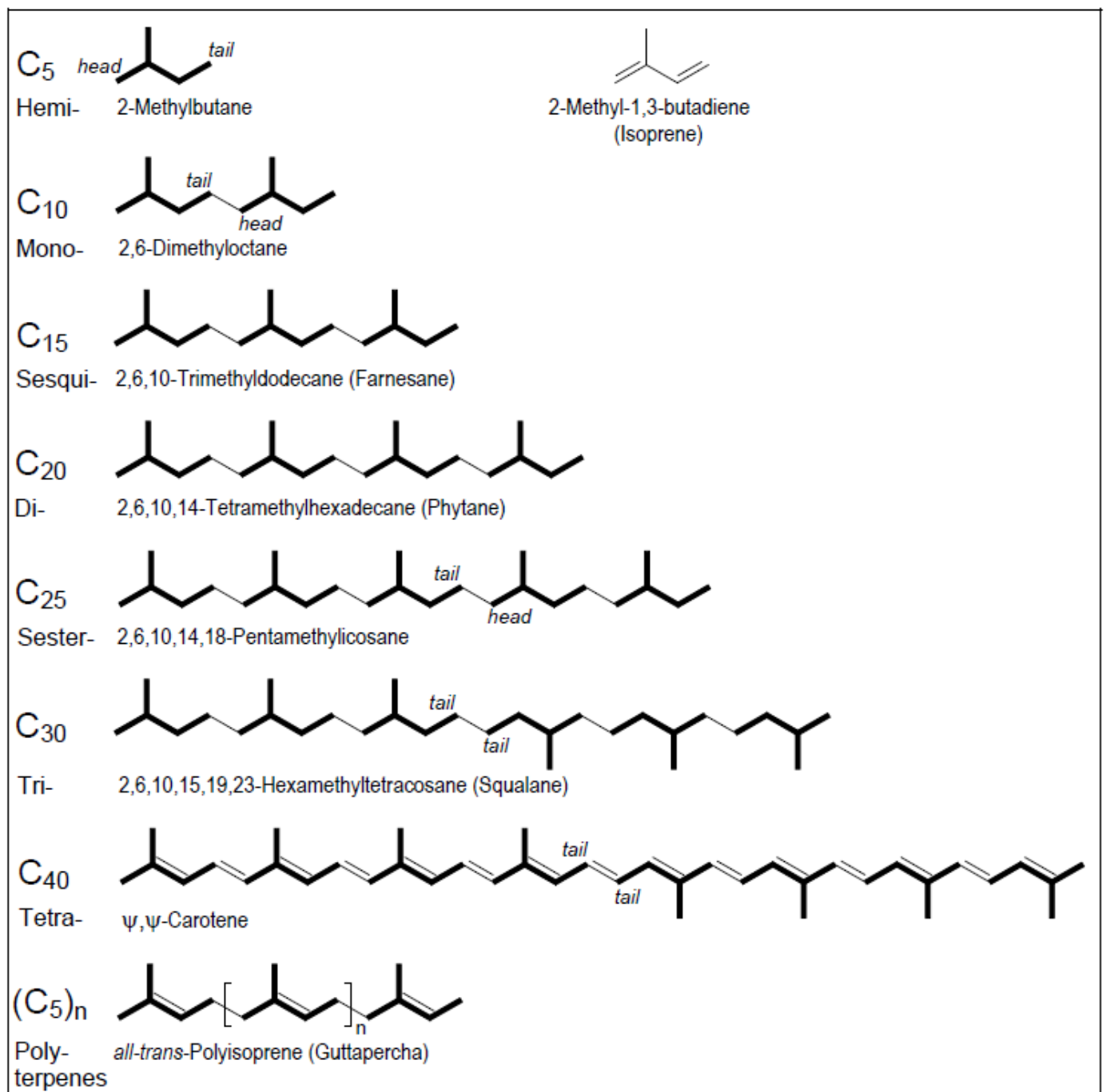
C) Diterpenoids:

i) *Acyclic diterpenoids*



ii) *Mono cyclic diterpenoids:*





ISOLATION OF MONO AND SESQUITERPENOIDS

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

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

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

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

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

ii) Separation of Terpenoids from essential oil: A number of terpenoids are present in essential oil obtained from the extraction.

Definite physical and chemical methods can be used for the separation of terpenoids. They are separated by fractional distillation.

The terpenoid hydrocarbons distill over first followed by the oxygenated derivatives.

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

GENERAL PROPERTIES OF TERPENOIDS

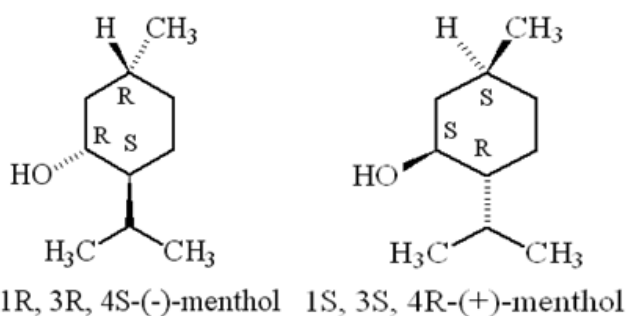
1. Most of the terpenoids are colourless, fragrant liquids which are lighter than water and volatile with steam. A few of them are solids e.g. camphor. All are soluble in organic solvent and usually insoluble in water. Most of them are optically active.
2. They are open chain or cyclic unsaturated compounds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

MENTHOL

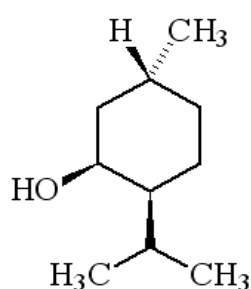
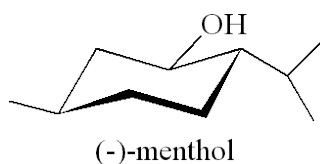
- Menthol is an organic compound made synthetically or obtained from peppermint or other mint oils.
- It is the major constituent of *Mentha piperita*.
- It is a waxy, crystalline substance, clear or white in color, which is solid at room temperature and melts slightly above (m.p. 41 to 43°C).
- Menthol has local anesthetic and counterirritant qualities, and it is widely used to relieve minor throat irritation. Menthol also acts as a weak *kappa opioid receptor agonist*.

CHEMISTRY

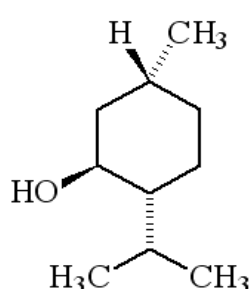
- The main form of menthol occurring in nature is (-)-menthol, which is assigned the (1R, 3R, 4S) configuration.



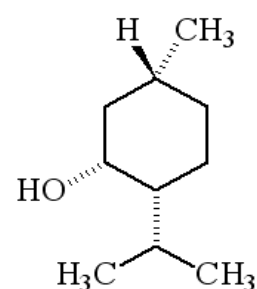
- The molecule can exist as a pair of optical isomers, though natural menthol only contains the (-) form produced in biosynthesis. Menthol has **three asymmetric** (chiral) carbon atoms in its cyclohexane ring; it therefore occurs as four pairs of **optical isomers**. The other isomers are known as **isomenthol**, **neomenthol** and **neoisomenthol**. In menthol, all three bulky groups [OH, CH₃ and CH(CH₃)₂] are in equatorial positions, making menthol more stable than the other three isomers.



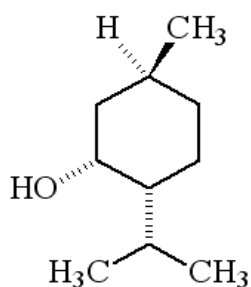
1R, 3S, 4S-(+)-neomenthol



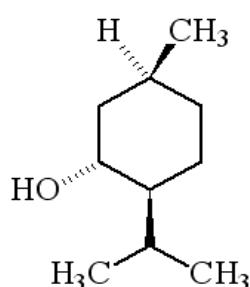
1R, 3S, 4R-(+)-isomenthol



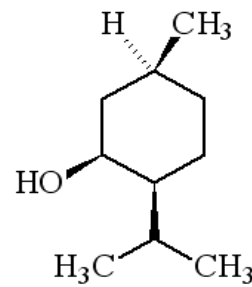
1R, 3R, 4R-(+)-neoisomenthol



1S, 3R, 4R-(-)-neomenthol



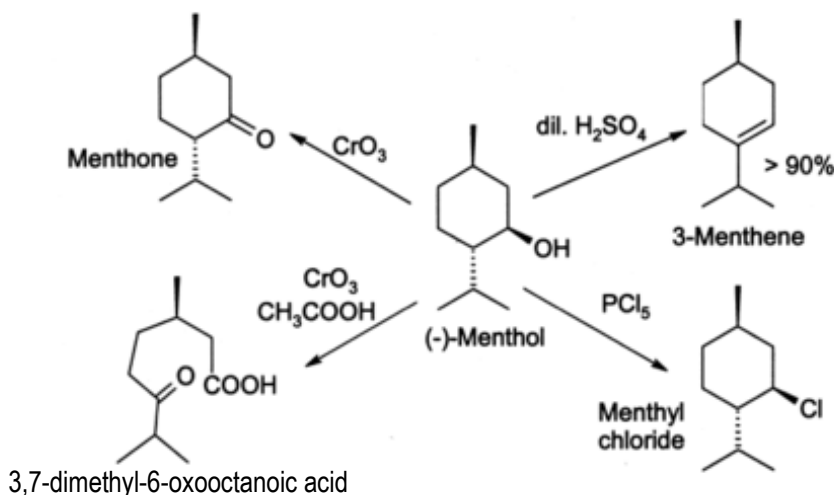
1S, 3R, 4S-(-)-isomenthol



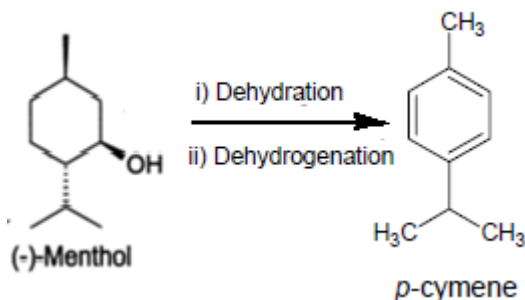
1S, 3S, 4S-(-)-neoisomenthol

STRUCTURE ELUCIDATION

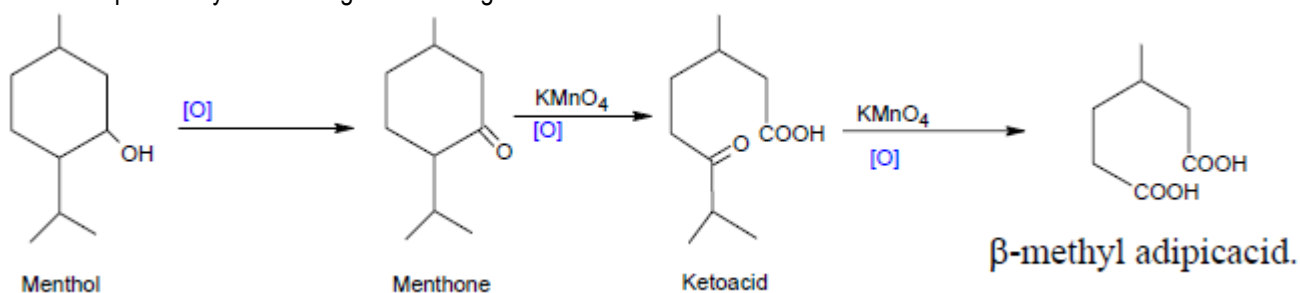
- Mol formula was determined as $C_{10}H_{20}O$
- Menthol forms esters readily with acids and oxidized to yield ketone it means that it must possess alcoholic group, which is 2° in nature.



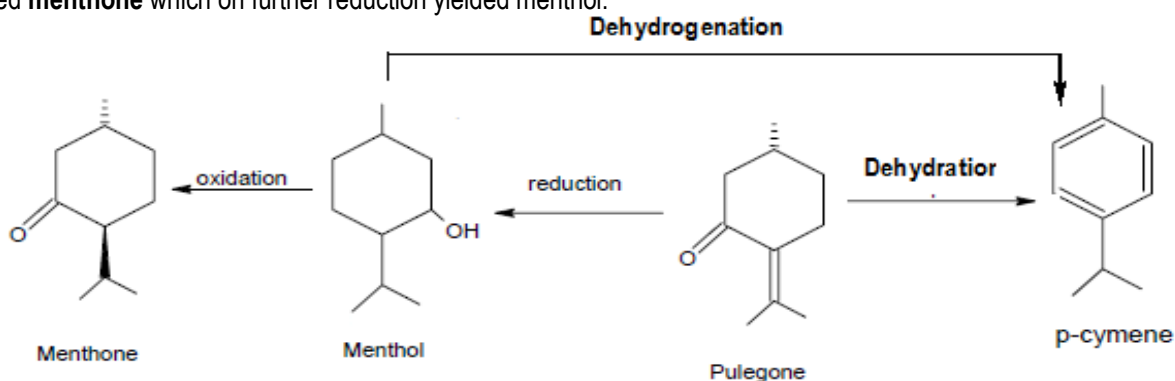
- On dehydration followed by dehydrogenation it yields **p-cymene**



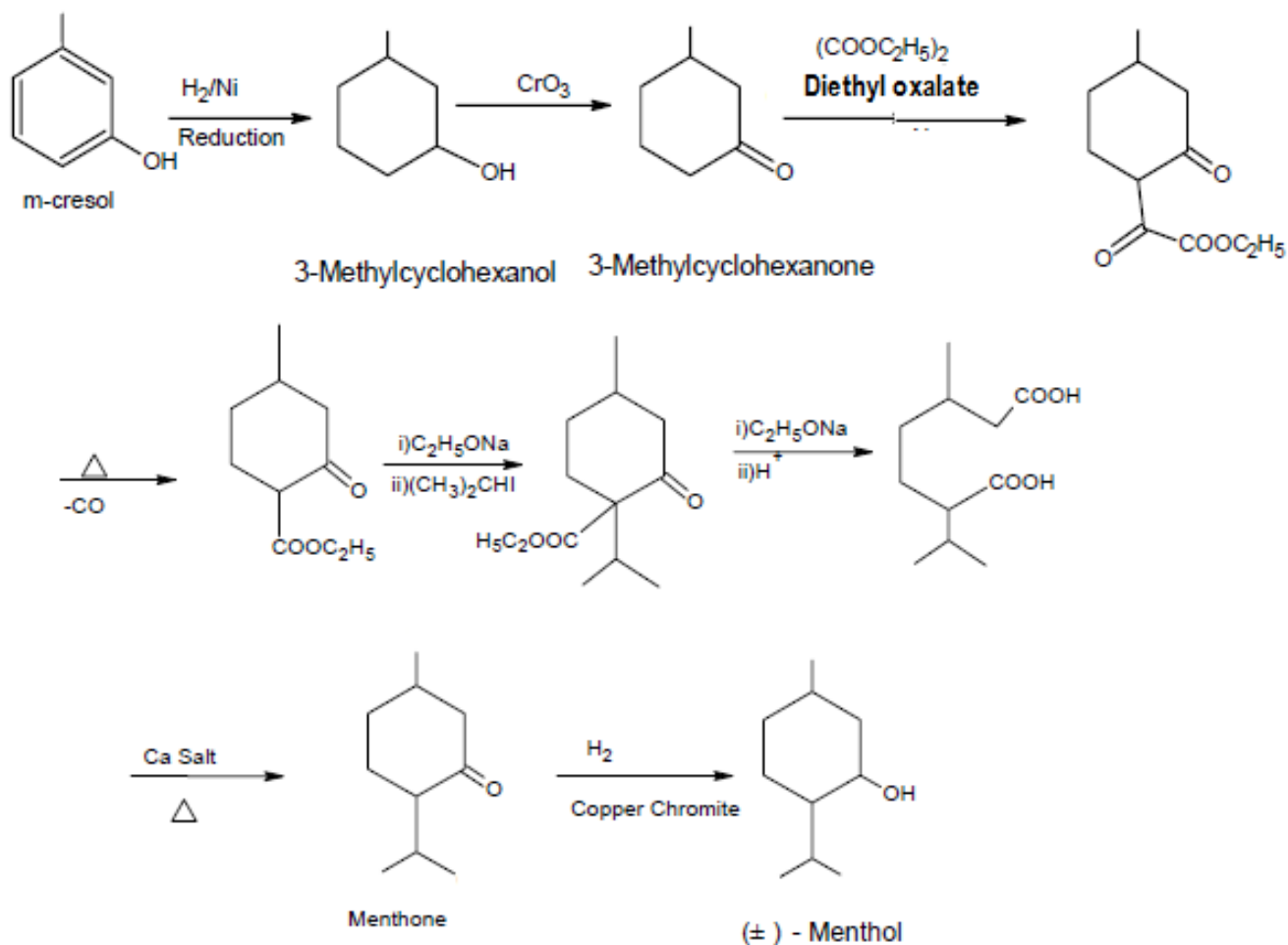
- Menthone on oxidation with $KMnO_4$ yields ketoacid $C_{10}H_{18}O_3$ which readily oxidized to 3-methyladipic acid. These reactions can be explained by considering the following structure of menthol.



- Menthol was converted to **p-Cymene**, which was also obtained by dehydrogenation of **pulegone**. Pulegone on reduction yielded **menthone** which on further reduction yielded menthol.



- Thus the correlation of pulegone with menthol proved the structure of menthol.
- Finally the structures of menthone and menthol have been confirmed by the synthesis given by **Kotz** and **Hese** from **m-cresol**.

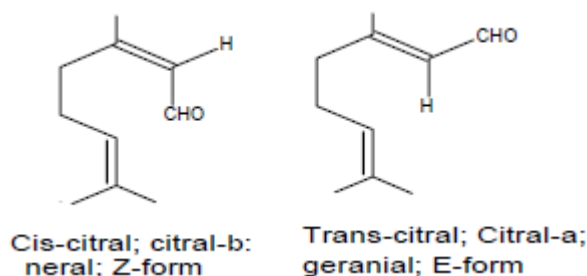


BIOLOGICAL PROPERTIES

- Menthol's ability to chemically trigger the cold-sensitive **TRPM8** receptors in the skin is responsible for the well-known cooling sensation, when inhaled, eaten, or applied to the skin.
- Menthol's analgesic properties are mediated through a selective activation of **κ-opioid receptors**.
- Menthol also blocks voltage-sensitive sodium channels, reducing neural activity that may stimulate muscles.
- Menthol also enhances the efficacy of **Ibuprofen** in topical applications via **vasodilation**, which reduces skin barrier function.
- It is used in oral hygiene products and bad-breath remedies, such as mouthwash, toothpaste
- As an additive in certain cigarette brands, for flavor, to reduce the throat and sinus irritation caused by smoking
- As an antispasmodic and smooth muscle relaxant in upper gastrointestinal endoscopy.
- As an antipruritic to reduce itching

CITRAL

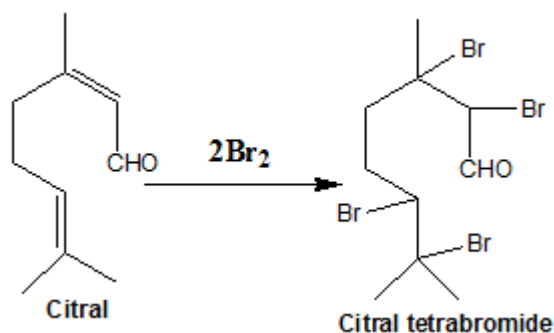
- Citral is an acyclic monoterpene. It is a major constituent of lemon grass oil in which it occurs to an extent of 60-80%.
- It is pale yellow liquid having strong lemon like odour, boiling point 224-228° C and can be obtained by fractional distillation under reduced pressure from Lemongrass oil.
- Isomerism of citral: Two geometrical isomers occur in nature. The **cis-isomers** is known as **Citral-a** and **trans-isomers Citral-b**.
- Ordinary citral obtained from lemongrass oil is, in fact, mixture of **Citral-a (90%)** and **Citral-b (10%)**.



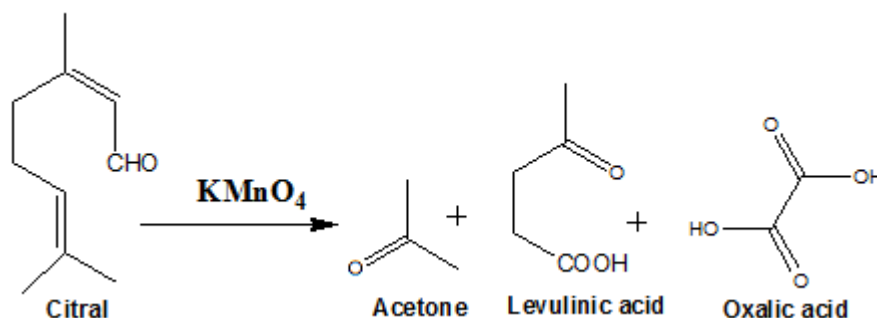
- **Uses**: It is extensively used in perfume and flavour industry and manufactures of vitamin A. Recently it become as a drug for reducing blood pressure.

STRUCTURE ELUCIDATION

- Mol formula was determined as $C_{10}H_{16}O$
- Presence of two C=C: It adds two molecules of bromine to form a tetrabromide, which indicate the presence of two carbon-carbon double bonds.

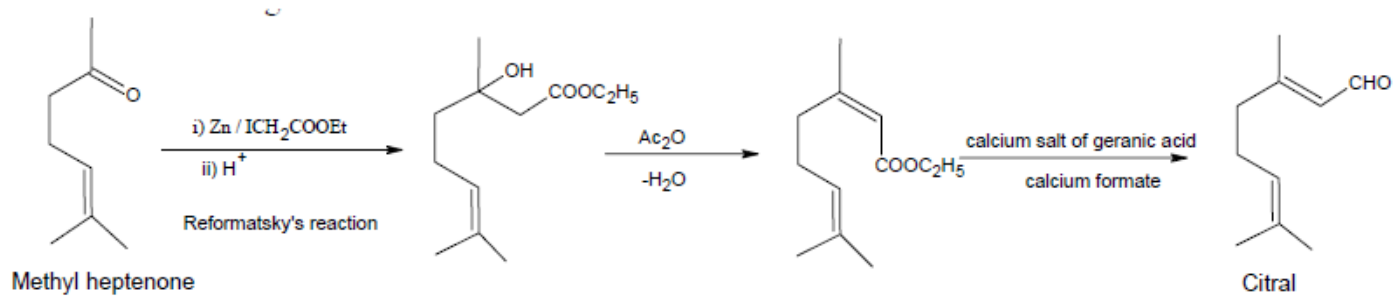


- *Position of C=C bonds indicate*: Oxidation of citral with alkaline $KMnO_4$, gives **Acetone**, **Levulinic acid** and **Oxalic acid**.



SYNTHESIS OF CITRAL

Barbier-Bouveault-Tiemann's synthesis: In this synthesis methyl heptenone is converted to geranic ester by using Reformatsky's reaction. Geranic ester is then converted to citral by distilling a mixture of calcium salts of geranic and formic acids.

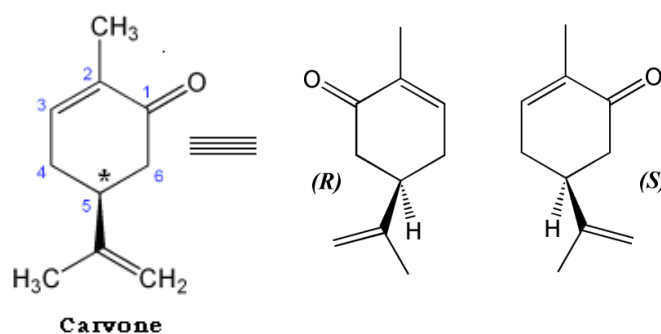


Monocyclic monoterpene – CARVONE

- **Carvone** is a cyclic mono terpenoids.
- Carvone is found naturally in many essential oils, but is most abundant in the oils from seeds of caraway (*Carum carvi*) and dill.

Note By: Dill is an aromatic herb (*Anethum graveolens*) native to Eurasia, having finely dissected leaves and small yellow flowers clustered in umbels. The leaves or seeds of this plant, used as a seasoning.

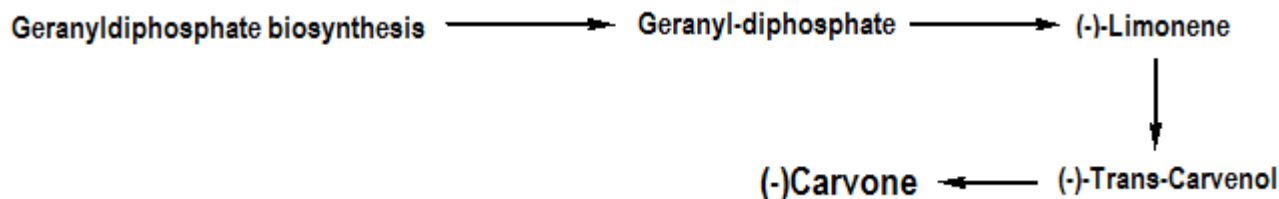
- Carvone forms two mirror image forms or enantiomers: **S-(+)-carvone** smells like **caraway**. Its mirror image, **R(-)-carvone**, smells like **spearmint**. The fact that the two enantiomers are perceived as smelling differently is proof that olfactory receptors must contain chiral groups, but not all enantiomers have distinguishable odors.



- **S-(+)-Carvone** is the principal constituent (50-70%) of the oil from caraway seeds (*Carum carvi*; Family: Umbelliferae) and It also occurs to the extent of about 40-60% in **dill seed oil** (from *Anethum graveolens*), But **R(-)-Carvone** is present at levels greater than 51% in spearmint oil (*Mentha spicata*; Family: Lamiaceae).
- *Characteristic features:*

Form	B.P (°C)	Density (g/cm ³)	Index of refraction	[α] ²⁰ _D
<i>d</i> - Carvone	230	0.965	1.498	+61.2 ⁰
<i>l</i> - Carvone	230-231	0.965	1.498	-61.46 ⁰
<i>dl</i> - Carvone	230-231	0.964	1.500	-

- The biosynthesis of carvone is by oxidation of limonene.



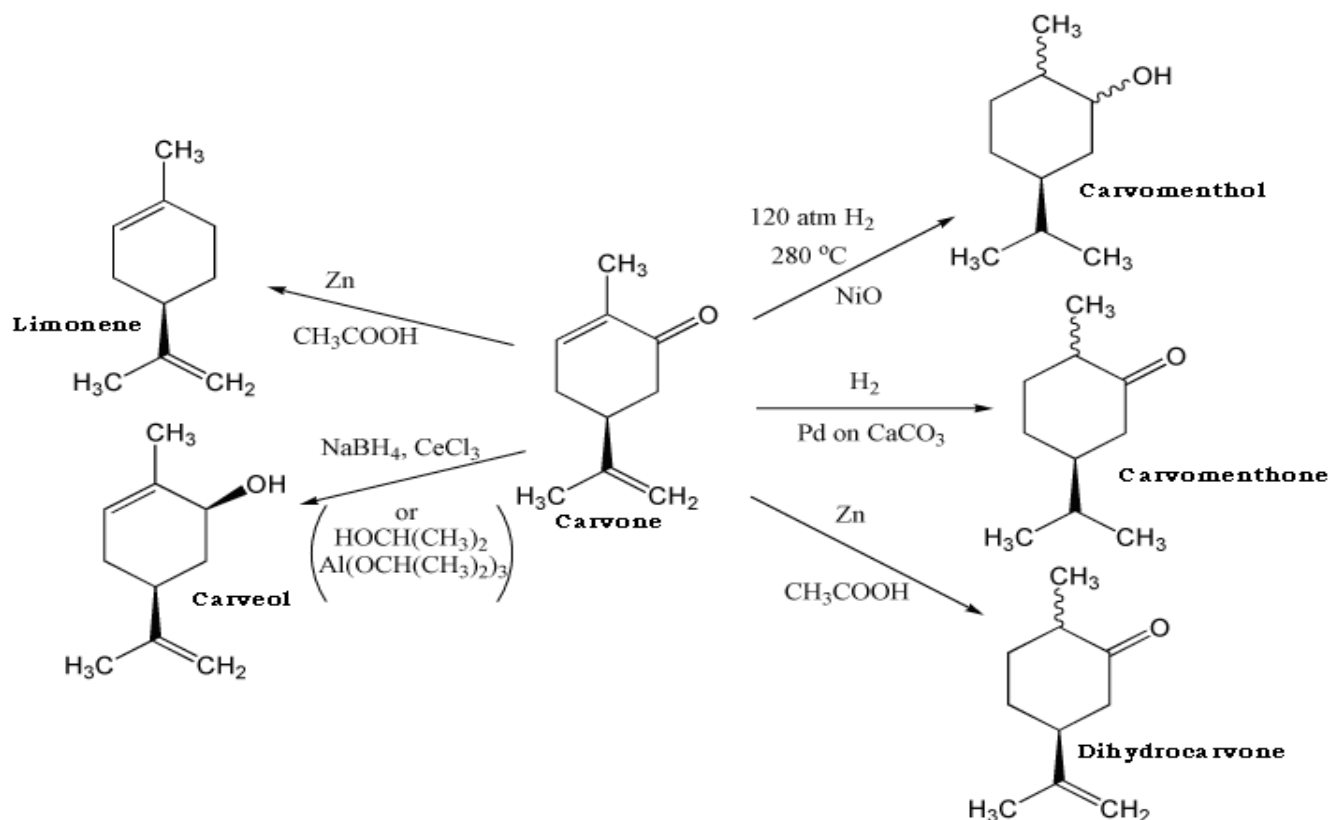
- **USES:**

- Both carvones are used in the food and flavor industry. *R*-(-)-Carvone is also used for air freshening products and, like many essential oils, oils containing carvones are used in aromatherapy and alternative medicine.
- S*-(+)-Carvone is also used to prevent premature sprouting of potatoes during storage.
- R*-(-)-carvone has been proposed for use as a **mosquito repellent**.

• **CHEMICAL PROPERTIES:**

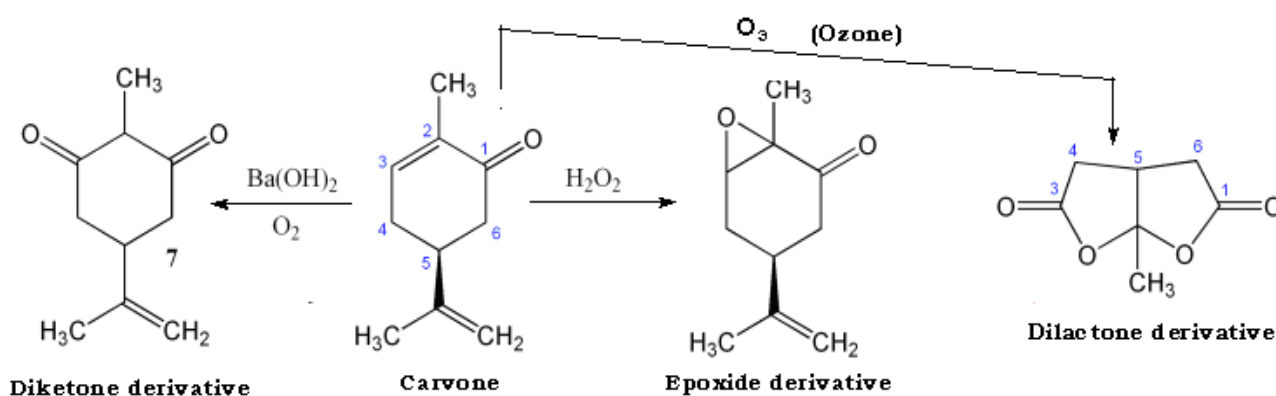
a. *Reduction:* There are three double bonds in carvone capable of reduction; the product of reduction depends on the reagents and conditions used.

- ✓ Catalytic hydrogenation of carvone can give either **carvomenthol** or **carvomenthone**.
- ✓ Zinc and acetic acid reduce carvone to give **dihydrocarvone**.
- ✓ MPV reduction using propan-2-ol and aluminium isopropoxide effects reduction of the carbonyl group only to provide **carveol**; a combination of sodium borohydride and CeCl_3 (*Luche reduction*) is also effective.
- ✓ Hydrazine and potassium hydroxide give **limonene** via a *Wolff-Kishner* reduction.



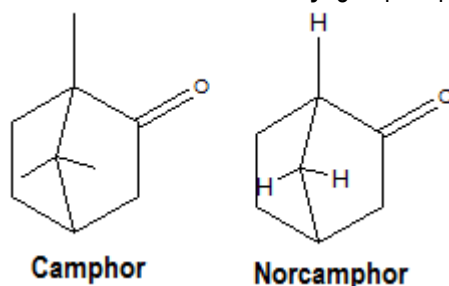
b. *Oxidation:*

- ✓ On oxidation of carvone in presence of an alkali such as $\text{Ba}(\text{OH})_2$, carvone is oxidised by air or oxygen to give the **diketone** derivative.
- ✓ With hydrogen peroxide the **epoxide** derivative is formed.
- ✓ Carvone may be cleaved using ozone followed by steam, giving **dilactone** derivative.



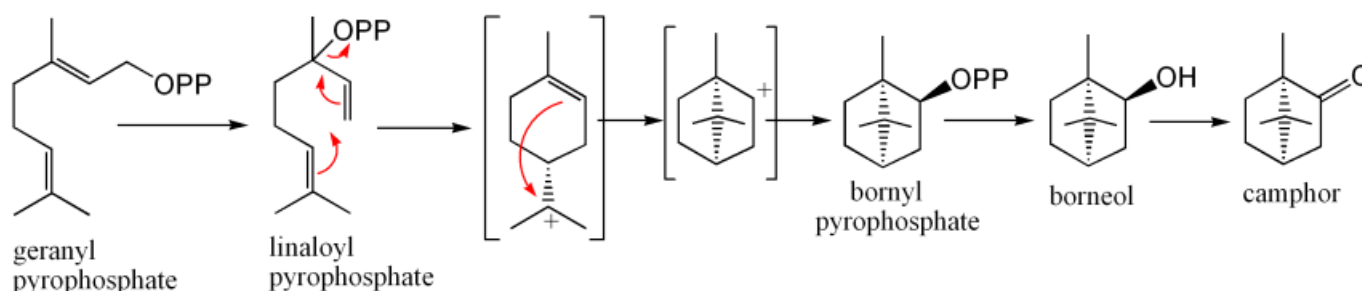
CAMPHOR

- ✓ **Camphor** occurs in camphor tree of **Camphor laurel** (*Cinnamomum camphora*)
- ✓ It is a terpenoid with the chemical formula $C_{10}H_{16}O$ and it is optically active; the (+) and (-) forms occur in nature. It is waxy, white or transparent solid with a strong, aromatic odor and having m.p. $180^{\circ}C$. It is obtained by steam distillation of wood, leaves or bark of camphor tree and it sublimates at room temperature
- ✓ **Norcamphor** is a **camphor** derivative with the **three methyl** groups replaced by **hydrogen**.



BIOSYNTHESIS

In biosynthesis, camphor is produced from **geranyl pyrophosphate**, via cyclisation of **linaloyl pyrophosphate** to **bornyl pyrophosphate**, followed by hydrolysis to **borneol** and oxidation to **camphor**.



USES

- Camphor as a plasticizer for nitrocellulose, as an antimicrobial substance, also as a cough suppressant and in fireworks.
- Solid camphor releases fumes that form a rust-preventative coating and is therefore stored in tool chests to protect tools against rust.
- Some folk remedies state camphor will deter snakes and other reptiles due to its strong odor. Similarly, camphor is believed to be toxic to insects and is thus sometimes used as a repellent and is widely used in Hindu religious ceremonies.
- Currently, camphor is used as a flavoring, mostly for sweets
- Camphor is readily absorbed through the skin and produces a feeling of cooling similar to that of menthol, and acts as slight local anesthetic and antimicrobial substance.
- **Camphor Toxicity:** camphor is poisonous when ingested and can cause seizures, confusion, irritability, and neuromuscular hyperactivity. In extreme cases, even topical application of camphor may lead to hepatotoxicity. Lethal doses in adults are in the range 50–500 mg/kg (orally). Generally, two grams cause serious toxicity and four grams are potentially lethal.