Chemistry of natural products

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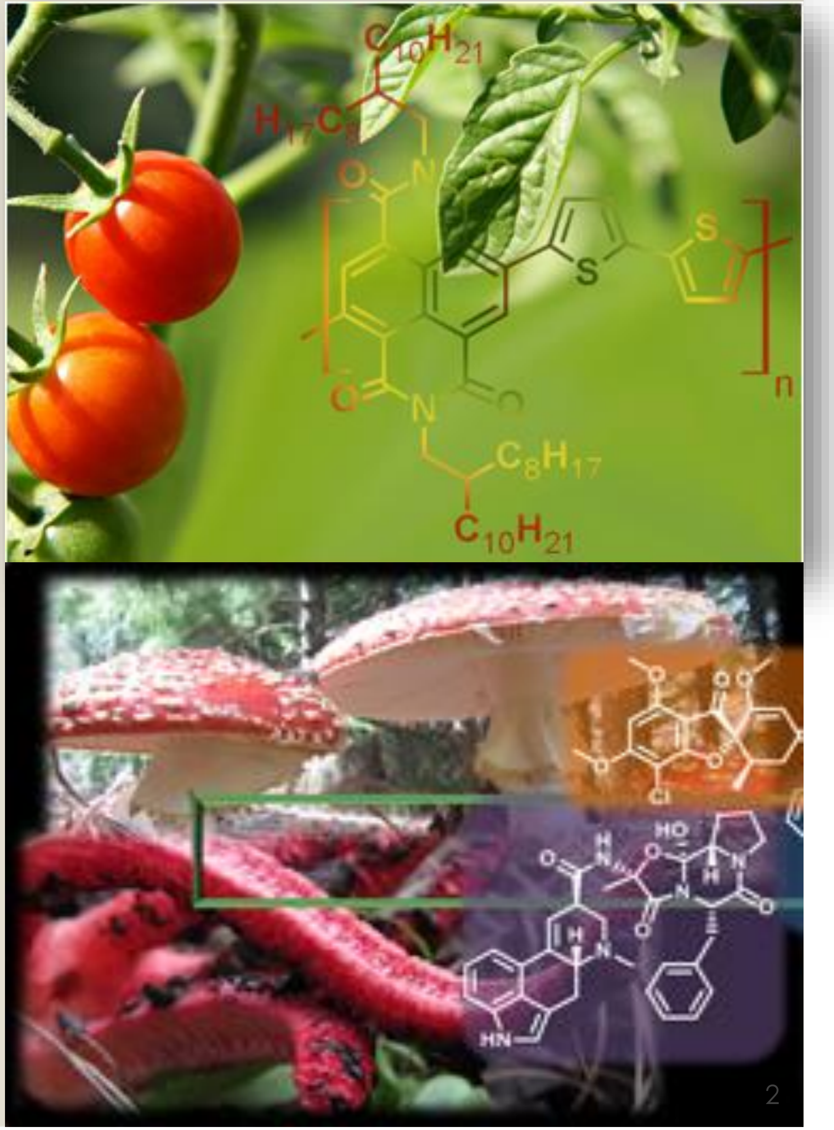
Introduction to Natural Products

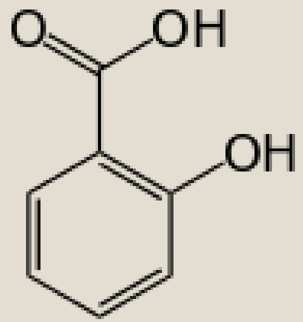
- Natural products are products from various natural sources, plants, microbes and animals.
- Natural products can be an entire organism (e.g. a plant, an animal or a micro-organism), a part of an organism (e.g. leaves or flowers of a plant, an isolated animal organ), an extract of an organism or part of an organism and an exudate, or pure compound (e.g. alkaloids, coumarins, flavonoids, lignans, steroids and terpenoids) isolated from plants, animals or micro-organisms.
- However, in practice, the term natural product refers to secondary metabolites, small molecules (molecular weight < 1500 amu), produced by an organism, but not strictly necessary for the survival of the organism.



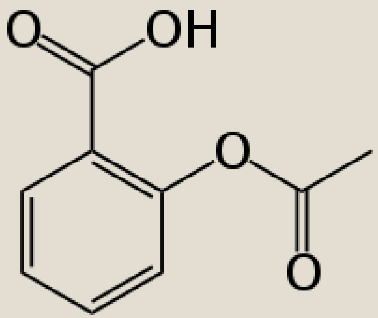
- ***Compounds from natural sources play significant roles in modern medicine:***

1. They provide a number of extremely useful drugs that are difficult, if not impossible, to produce commercially by synthetic means
2. Natural sources also supply basic compounds that may be modified slightly to render them more effective or less toxic
3. Their utility as prototypes or models for synthetic drugs possessing physiologic activities similar to the originals

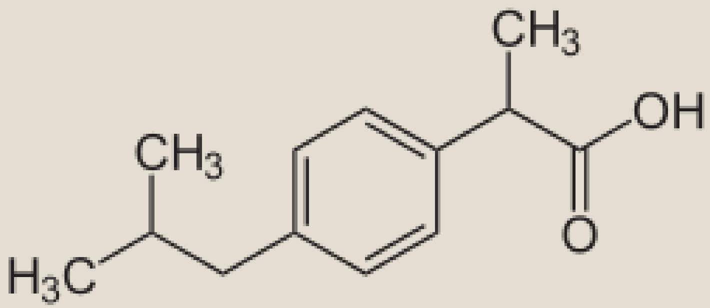
Spirea



salicylic acid

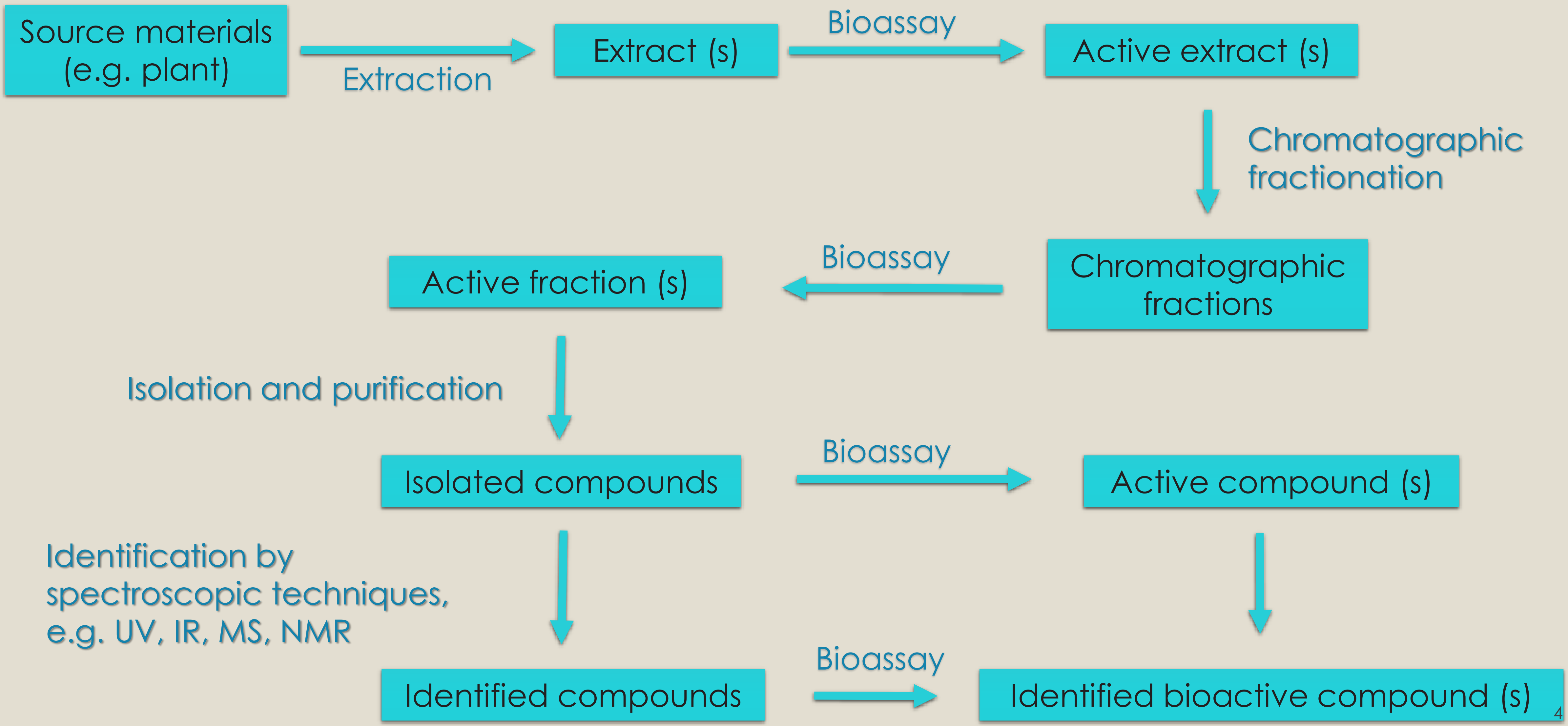


Aspirin



Ibuprofen

Overview of a bioassay-guided traditional natural product drug discovery process



Source materials (e.g. plant)

Extraction

Extract (s)

Bioassay

Active extract (s)

Chromatographic fractionation

Chromatographic fractions

Bioassay

Active fraction (s)

Isolation and purification

Isolated compounds

Bioassay

Active compound (s)

Identification by spectroscopic techniques, e.g. UV, IR, MS, NMR

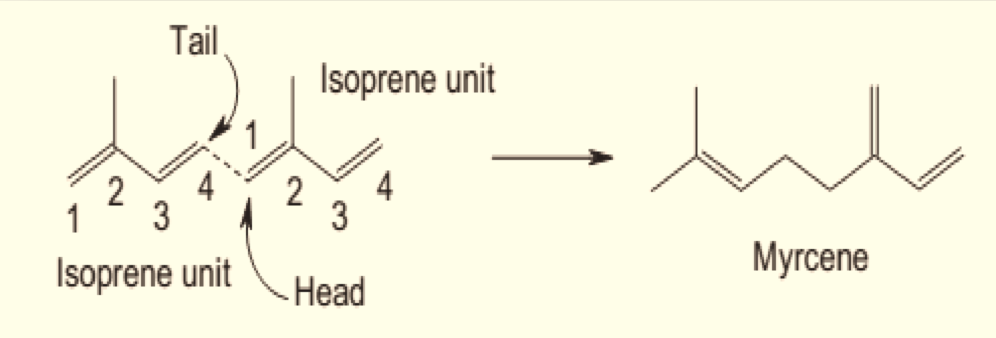
Identified compounds

Bioassay

Identified bioactive compound (s)

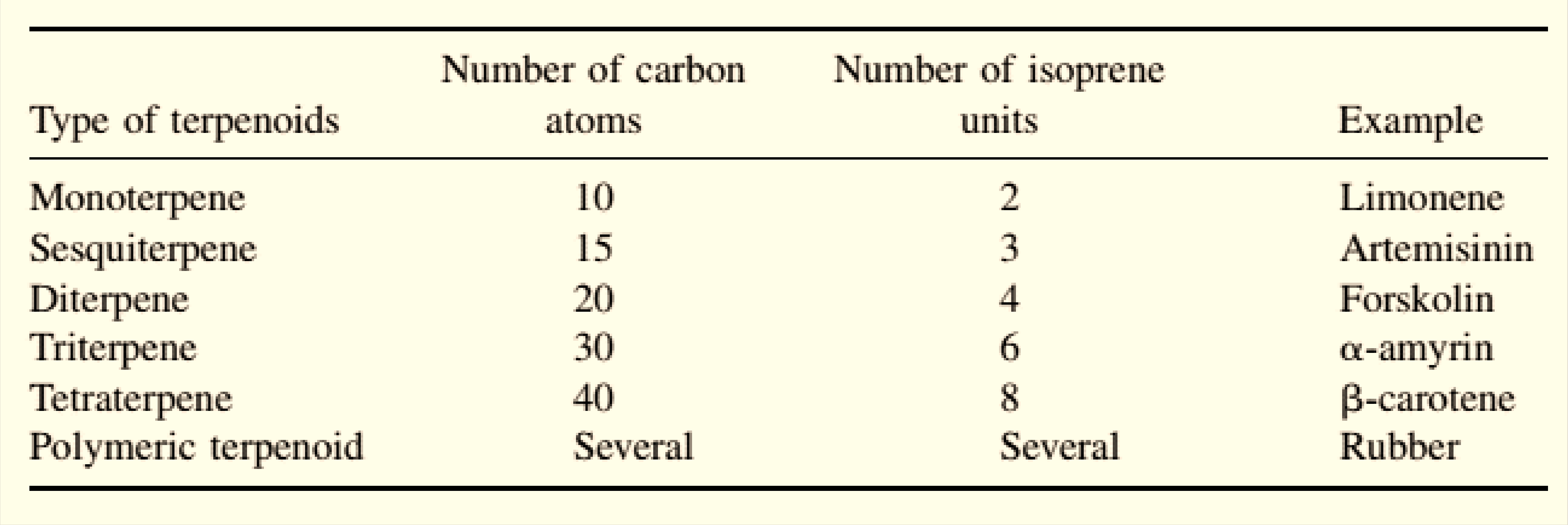
Terpenoids

- The odor of a freshly crushed mint leaf, like many plant odors, is due to the presence in the plant of volatile C_{10} and C_{15}, compounds, which are called terpenes.
- Terpenoids are compounds derived from a combination of two or more isoprene units. Isoprene is a five carbon unit, chemically known as 2-methyl-1,3-butadiene.
- According to the isoprene rule proposed by Leopold Ruzicka, terpenoids arise from head-to-tail joining of isoprene units. Carbon 1 is called the 'head' and carbon 4 is the 'tail'.
- For example, myrcene is a simple 10-carbon-containing terpenoid formed from the head to-tail union of two isoprene units as follows.

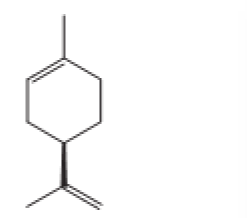


Classification

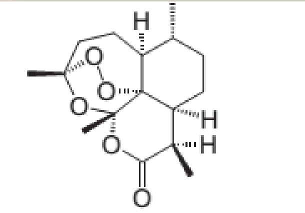
- **Terpenoids are classified according to the number of isoprene units involved in the formation of these compounds.**



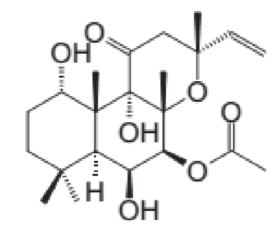
Type of terpenoids	Number of carbon atoms	Number of isoprene units	Example
Monoterpene	10	2	Limonene
Sesquiterpene	15	3	Artemisinin
Diterpene	20	4	Forskolin
Triterpene	30	6	α-amyrin
Tetraterpene	40	8	β-carotene
Polymeric terpenoid	Several	Several	Rubber



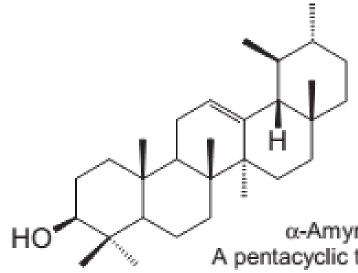
(+)-Limonene, a monoterpene



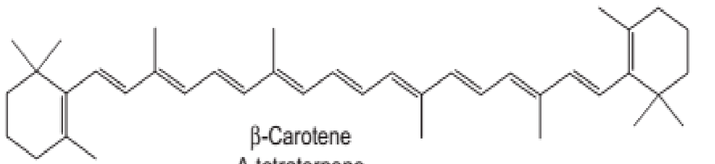
Artemisinin,
An antimalarial sesquiterpene



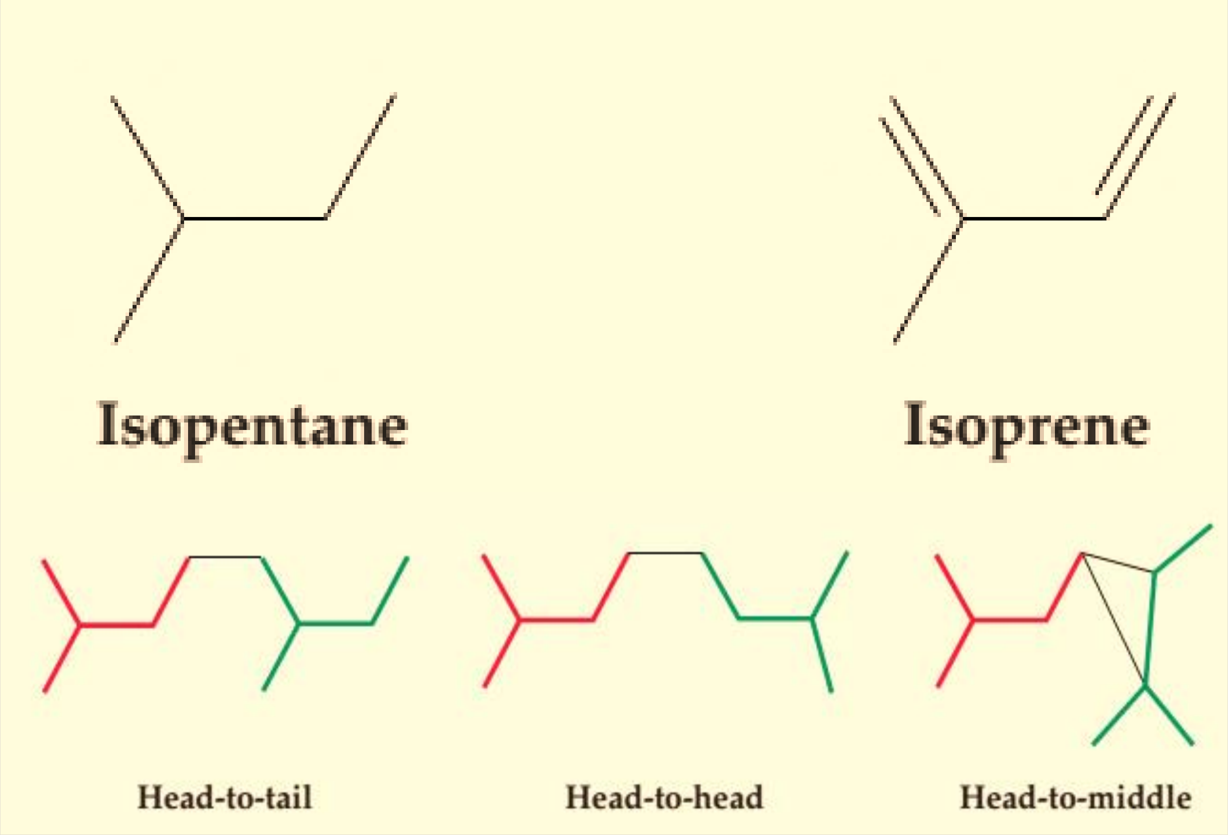
Forskolin
An antihypertensive diterpene



α-Amyrin
A pentacyclic triterpene

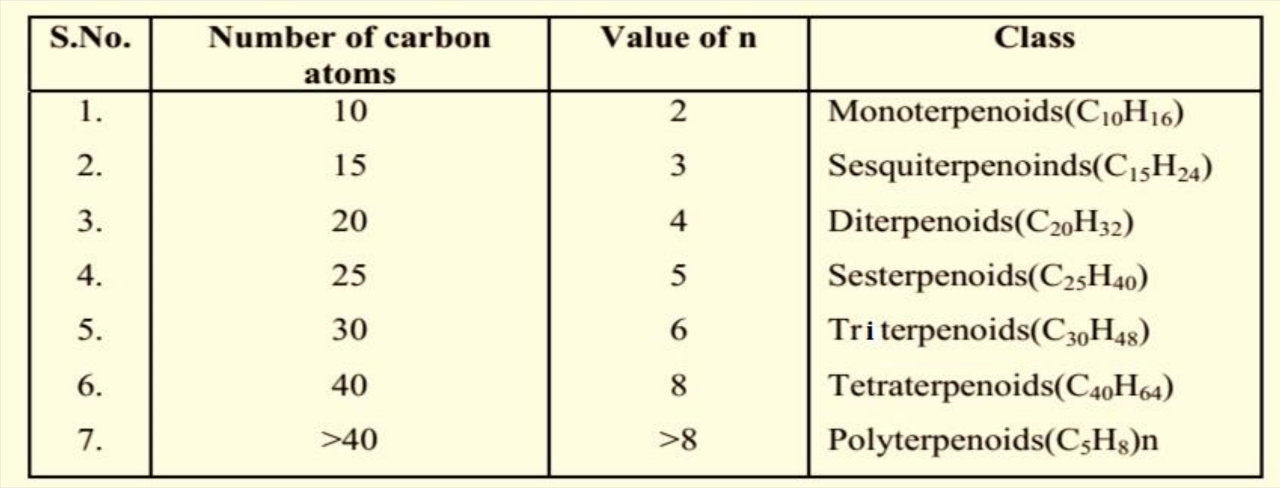


β-Carotene
A tetraterpene


Isopentane
Isoprene
Head-to-tail
Head-to-head
Head-to-middle

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	Sesquiterpenoinds$(C_{15}H_{24})$
3.	20	4	Diterpenoids$(C_{20}H_{32})$
4.	25	5	Sesterpenoids$(C_{25}H_{40})$
5.	30	6	Triterpenoids$(C_{30}H_{48})$
6.	40	8	Tetraterpenoids$(C_{40}H_{64})$
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.

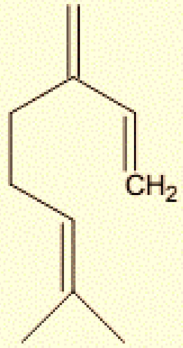
iii) Bicyclic Terpenoids: They contain two rings in the structure.

iv) Tricyclic Terpenoids: They contain three rings in the structure.

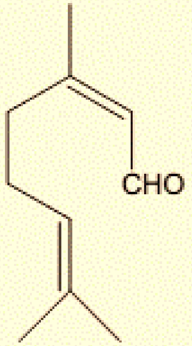
v) Tetracyclic Terpenoids: They contain four rings in the structure.

A) Mono Terpenoids:

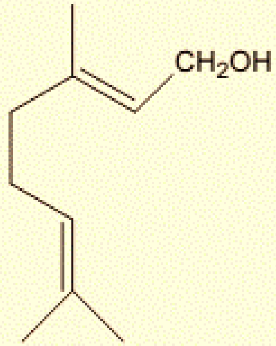
i) Acyclic Monoterpenoids



Myrcene

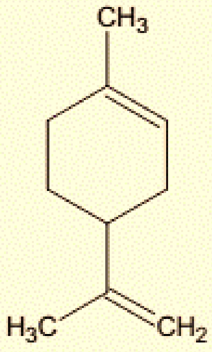


Citral

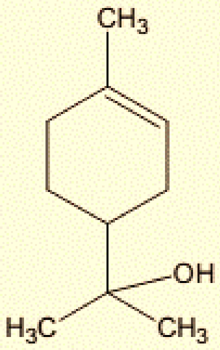


Geraniol.

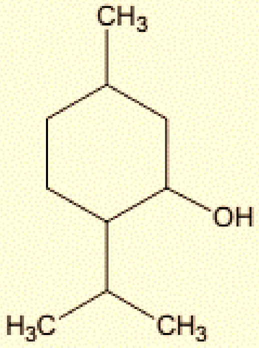
ii) Monocyclic monoterpenoid



Limonene



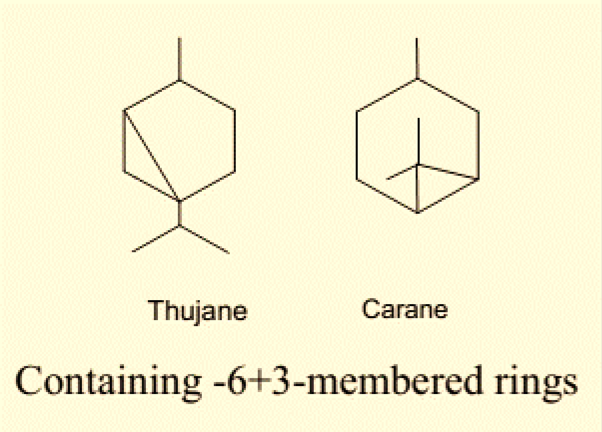
α-Terpineol



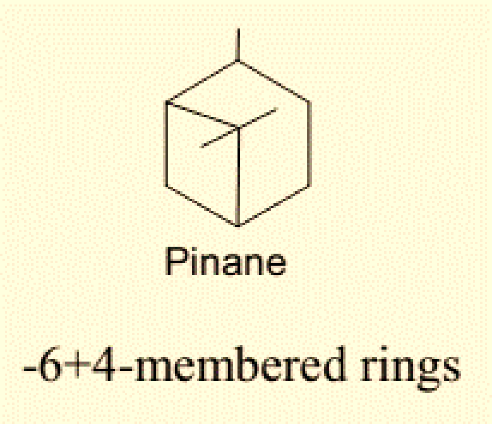
Menthol

A) Mono Terpenoids:

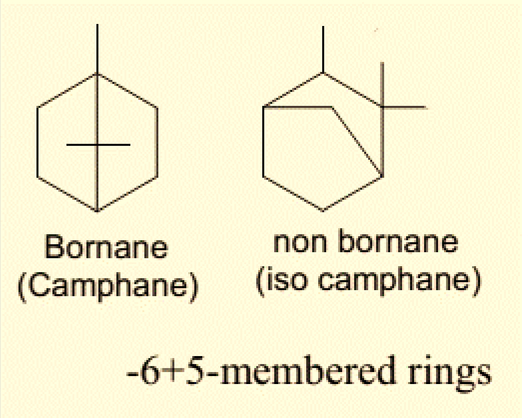
- **iii)Bicyclic monoterpenoids: These are further divided into three classes.**



a) Containing -6+3-membered rings



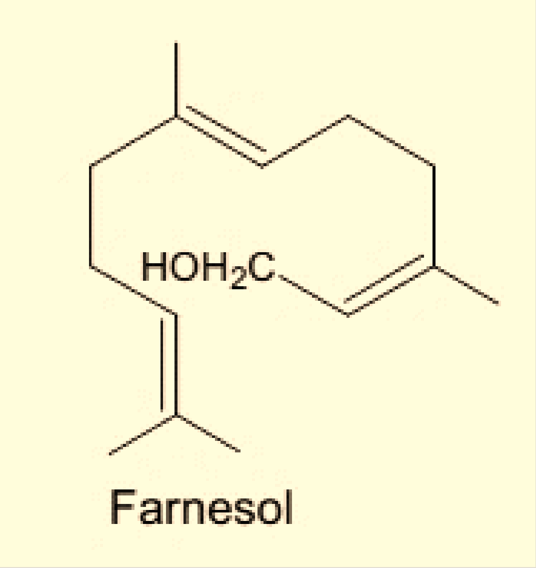
b) Containing -6+4-membered rings.



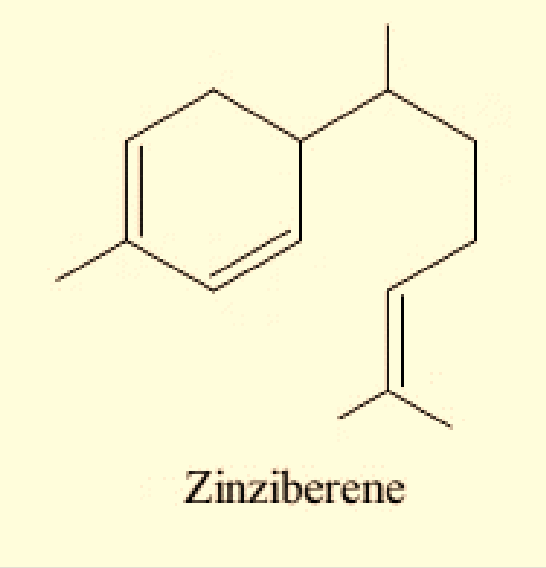
c) Containing -6+5-membered rings.

B) Sesquiterpenoids:

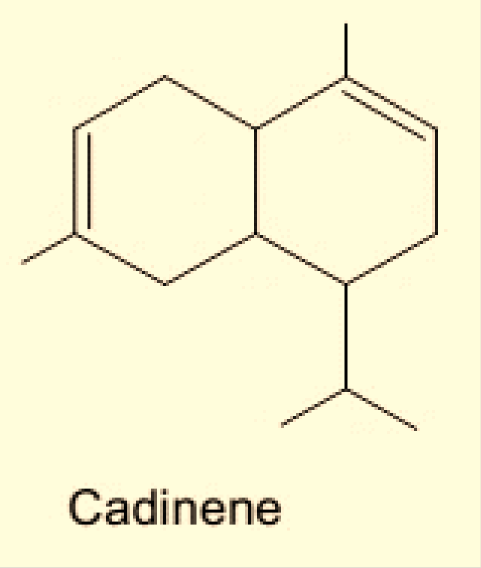
- i) Acyclic sesquiterpenoids ii) Monocyclic sesquiterpenoids iii) Bicyclic sesquiterpenoids.



Farnesol



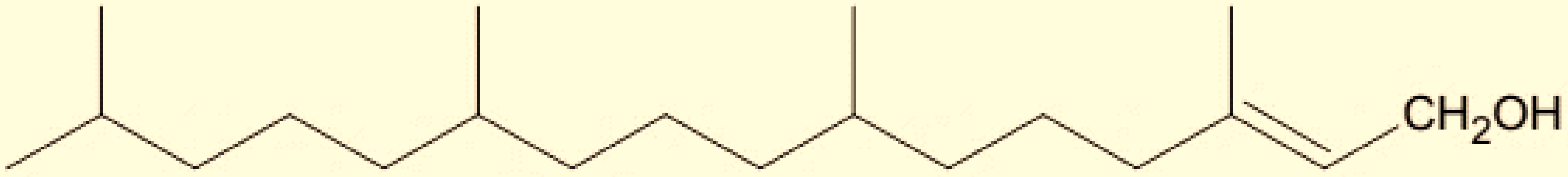
Zinziberene



Cadinene

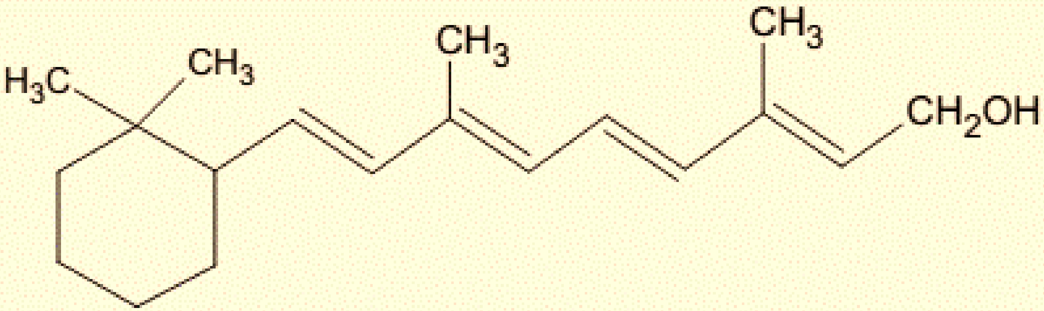
C) Diterpenoids:

i) **Acyclic diterpenoids**



Phytol

ii) **Mono cyclic diterpenoids:**



Vitamin A

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: 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 طريقة التقطير بالبخار

c) Extraction by means of volatile solvents الاستخلاص عن طريق المذيبات المتطايرة

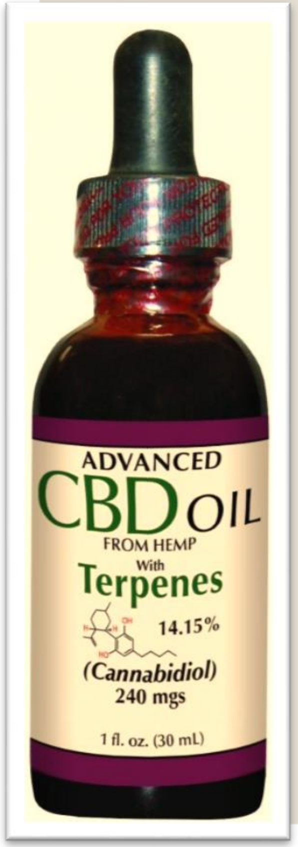
d) Adsorption in purified fats الامتزاز في الدهون المنقى

Isolation of mono and sesquiterpenoids

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

ii) Separation of Terpenoids from essential oil: A number of terpenoids are present in essential oil obtained from the extraction. Definite physical and chemical methods can be used for the separation of terpenoids. They are separated by fractional distillation. The terpenoid hydrocarbons distill over first followed by the oxygenated derivatives. More recently different chromatographic techniques have been used both for isolation and separation of terpenoids.

General properties of Terpenoids



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.

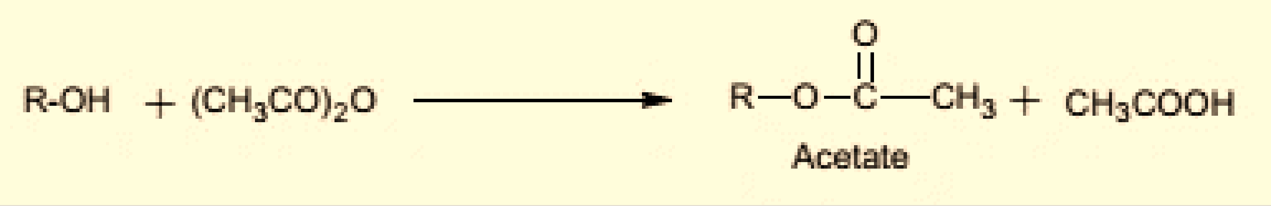
General Methods of structure elucidation

Terpenoids

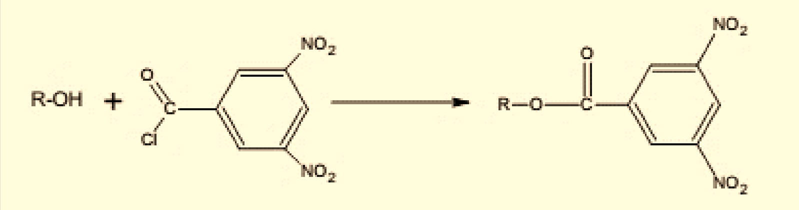
i) **Molecular formula:** molecular formula is determined by usual quantitative analysis and mol.wt determination methods and by means of mass spectrometry. If terpenoid is optically active, its specific rotation can be measured.

ii) **Nature of oxygen atom present:** If oxygen is present in terpenoids its functional nature is generally as alcohol aledhyde, ketone or carboxylic groups.

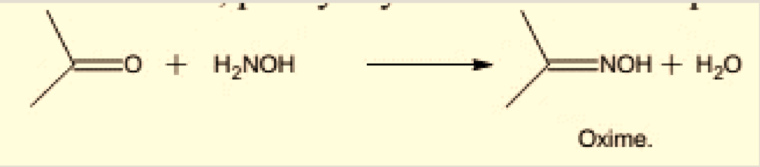
a) **Presence of oxygen atom present:** presence of –OH group can be determined by the formation of acetates with acetic anhydride and benzoyate with 3,5-dinitirobenzoyl chloride.



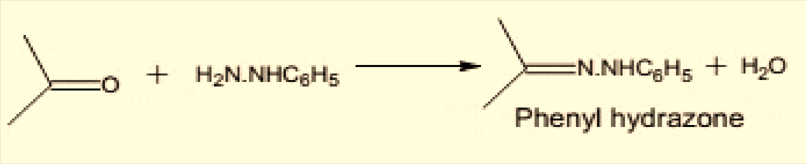
Acetate



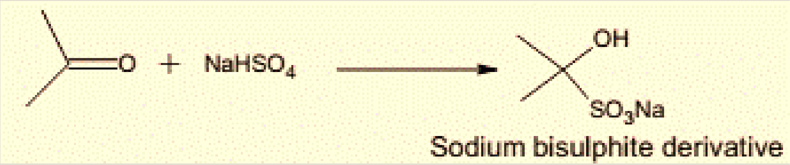
b) **Presence of >C=O group:** Terpenoids containing carbonyl function form crystalline addition products like oxime, phenyl hydrazone and bisulphite etc.



Oxime.



Phenyl hydrazone

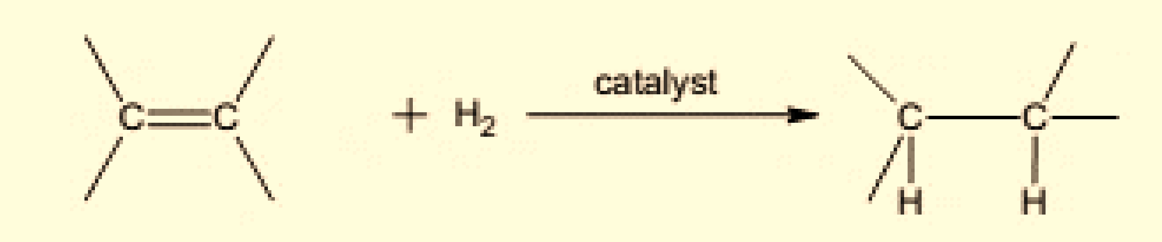


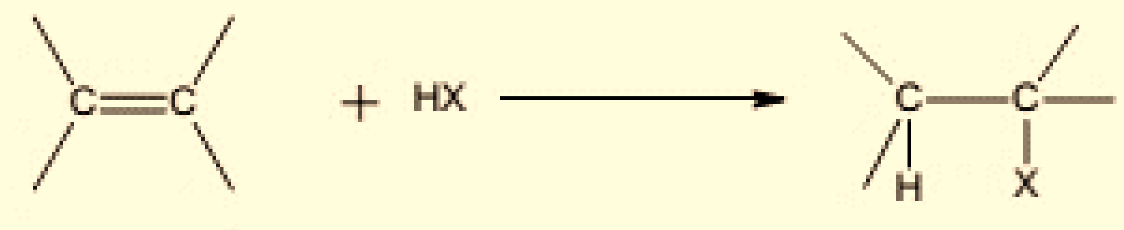
Sodium bisulphite derivative

General Methods of structure elucidation

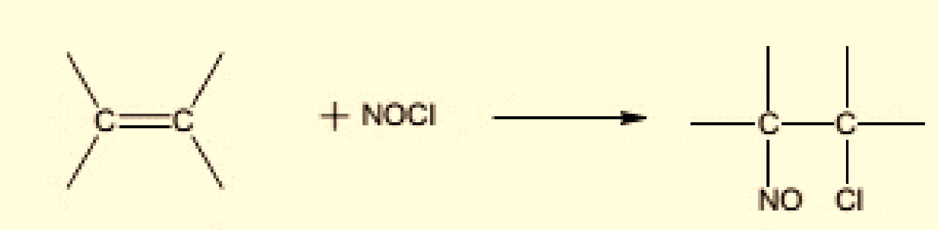
iii) Unsaturation:

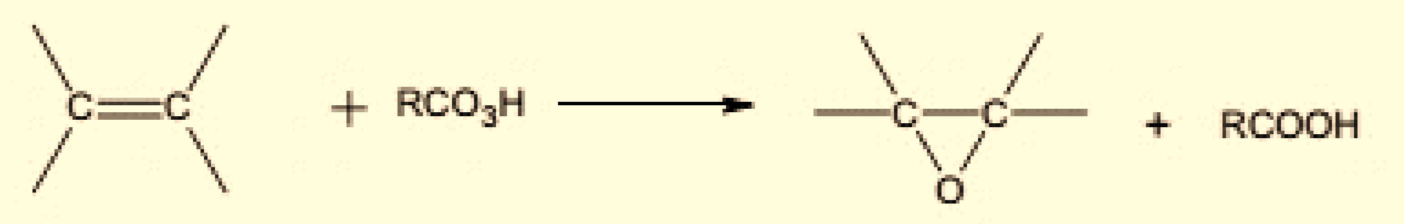
The presence of olefinic double bond is confirmed by means of bromine, and number of double bond determination by analysis of the bromide or by quantitative hydrogenation or by titration with monoperpthalic acid. Presence of double bond also confirmed by means of catalytic hydrogenation or addition of halogen acids. Number of moles of HX absorbed by one molecule is equal to number of double bonds present.





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

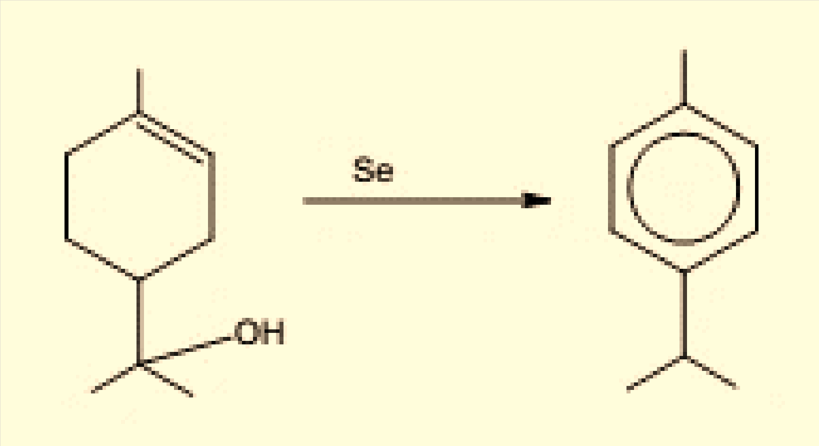




General Methods of structure elucidation

iv) Dehydrogenation:

- On dehydrogenation with Sulphur or selenium, terpenoids converted to aromatic compounds. Examination of these products the skelton structure and position of side chain in the original terpenoids can be determined. For example **α-terpineol** on **Se-dehydrogenation** yields **para-cymene**.



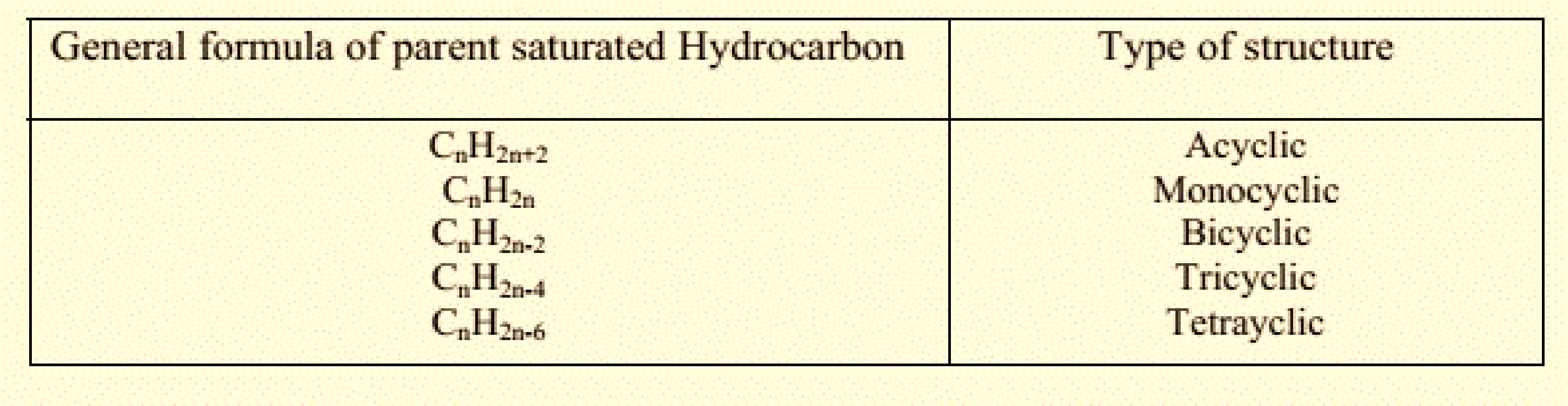
v) Oxidative degradation:

- Oxidative degradation has been the parallel tool for elucidating the structure of terpenoids. Reagents for degradative oxidation are **ozone**, acid, neutral or alkaline potassium permanganate, chromic acid, sodium hypobromide, osmium tetroxide, nitric acid, lead **tetra acetate** and **peroxy acids**. Since oxidizing agents are selective, depending on a particular group to be oxidized, the oxidizing agent is chosen with the help of structure of degradation products.

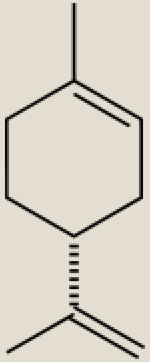
General Methods of structure elucidation

vi) Relation between general formula of compound and type of compounds:

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



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



limonene

vii) Spectroscopic studies:

UV Spectroscopy: In terpenes containing conjugated dienes or a,β-unsaturated ketones, UV spectroscopy is very useful tool, **IR Spectroscopy:** IR spectroscopy is useful in detecting group such as hydroxyl group (~3400cm^{-1}) or an oxo group (saturated 1750-1700cm^{-1}), **NMR Spectroscopy, Mass Spectroscopy, and X-ray analysis**

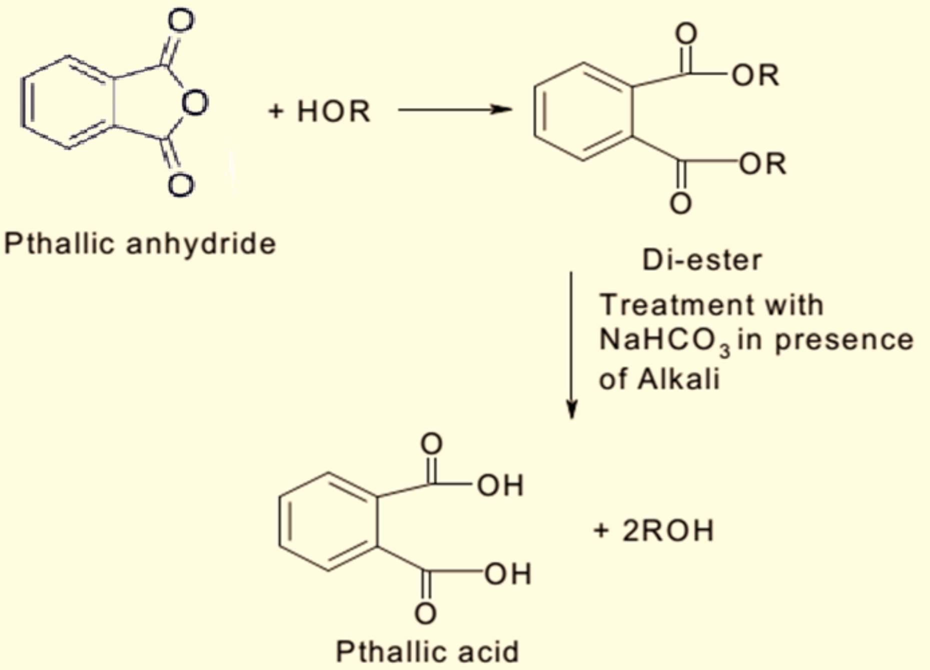
Separation and isolation of terpenoids from volatile oil

- ## Chemical method:

1) Separation of terpenoid hydrocarbon: These are separated by using **Tilden's reagent** composed of solution of **Nitrosyl chloride** (NOCl) in **chloroform**. The terpenoid hydrocarbons on treatment with Tilden reagent forms **crystalline adduct** having sharp m.p., which is separated from volatile oil followed by hydrolysis or decomposed to get back the terpenoid hydrocarbon.

2) Separation of terpenoid alcohol:

Terpenoid alcohols on reaction with Pthallic anhydride forms di-ester, which precipitate out from volatile oil. These di-esters on treatment with $NaHCO_3$ in presence KOH, yields back terpene alcohol and Pthallic acid



3) Separation of terpenoid aldehyde and ketone: Terpenoid aldehydes and ketones forms crystalline adduct on reaction with $NaHSO_3$ and phenyl hydrazines etc. These crystalline adducts can be hydrolyzed to get back carbonyl compounds.

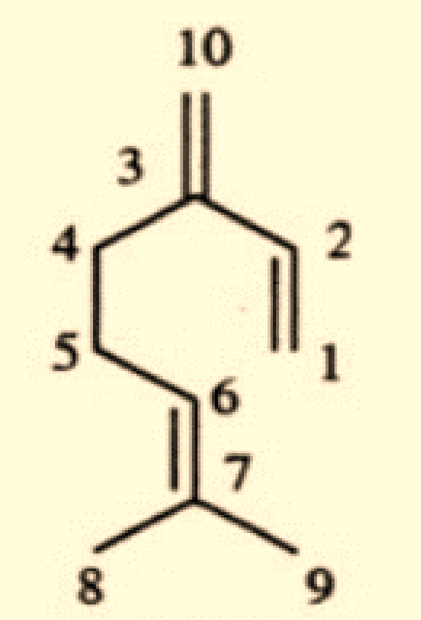

Plantain in Olive Oil
8/17/09


www.com

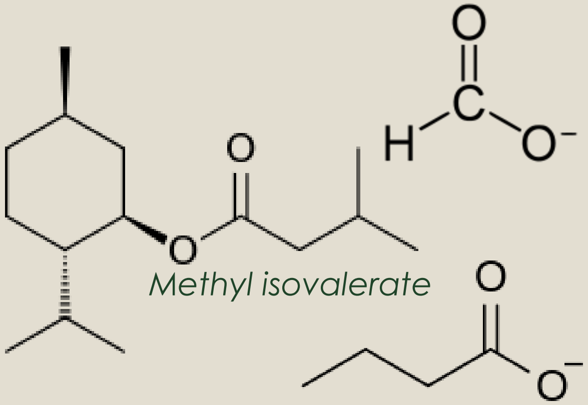
Myrcene

- Chemical formula: $\mathbf{C_{10}H_{16}}$, b.p. 166-168°C. $\eta^{20}{}_{D}$ 1.4692
  Myrcene is an acyclic monoterpene hydrocarbon occurring in Verbena oil. is a colorless, liquid with a pleasant odor.

UV: λ_{max} 225 nm.
IR: υ_{max} , 1672, 1634, 1597, 997. 900, 893 cm^{-1}.
^{1}H NMR: δ 1.56, 1.63 (6H, C-7 methyls), 4.83-5.07 (m, 5H, H-1a, H-1b, H-10a, H-10b and H-6), 6.19 (dd. 1H. H-2).
^{13}C NMR: δ 15.5 (C- 1), 139.0 (C-2), 145.9 (C-3), 30.8 (C-4), 26.1 (C-5), 124.4 (C-6), 131.0(C-7), 17.1 (C-8). 25.1 (C-9). 112.6 (C-10).



Geraniol



- Chemical formula: **$C_{10}H_{18}$**, b.p. 229-230 °C. $\eta^{20}{}_{D}$ 1.4777
- **Geraniol** occurs in citronella, rose, lemon grass and lavender oils. It is present in either free state or as esters. Its various esters such as acetate, formate, butyrate and isovalerate are extensively used in perfumery.

IR: υ_{max}, 3400 (OH), 1695, 1105, 1090, 1000, 830 cm^{-1}.
^{1}H NMR: δ 1.62, 1.68 (6H, C-7 methyls), 4.15 (2H, α allylic CH_2OH), 5.12 (1H, m, H-6), 5.45 (t, 1H, H-2).

^{13}C NMR: δ 58.7 (C-1), 124.5 (C-2), 137.2 (C-3), 39.7 (C-4), 26.6 (C-5). 124.9 (C-6), 131.2 (C-7), 25.5 (C-8), 17.4 (C-9), 16.0 (C-10).

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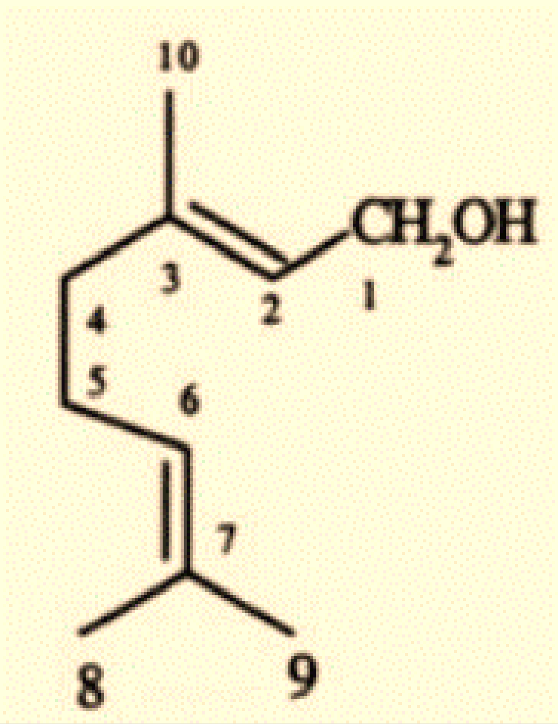
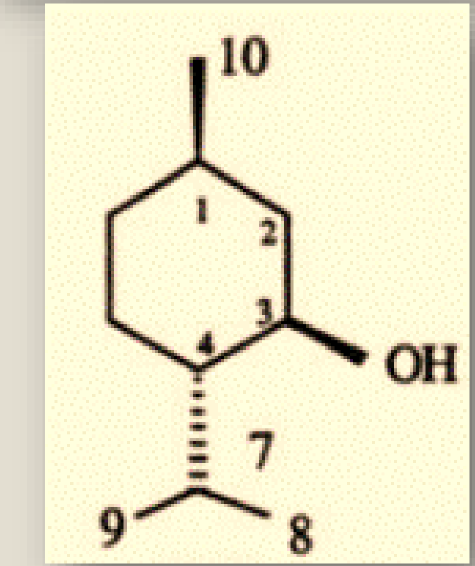


(-)-Menthol

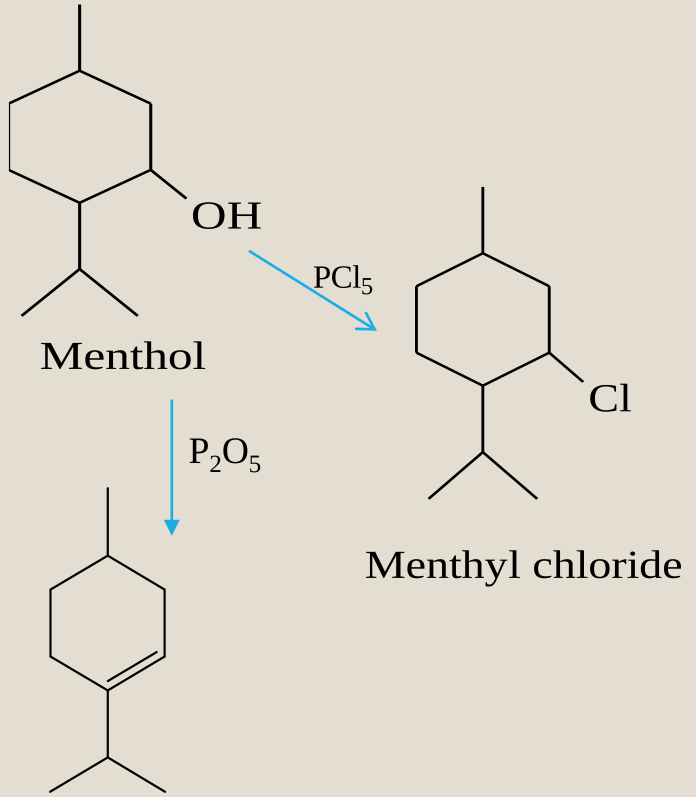
- Chemical formula: **$C_{10}H_{20}O$**, m.p. 34 °C, b.p. 213 °C, $[\alpha]_D$ -50°, η^{20}_D 1.4661.
- Menthol is the major constituent of *Mentha piperita* and has been known in India, China and Japan since ancient times. It is mainly used as flavouring agent and has a cooling effect. Medicinally it exhibits antiseptic and anaesthetic properties. It is the ingredient in cold balms.

IR: υ_{max} , 3333, 1048, 1028, 994, 977, 920, 876, 845 cm^{-1}.
^{1}H NMR: δ 0.82 (3H, d, C-1 Me), 0.90, 0.93 (3H each, d, C-7 methyls), 3.42 (1H,m, H-3).
^{13} C NMR: δ 31.7 (C-1). 45.2 (C-2), 71.5 (C-3), 50.2 (C-4), 23.3 (C-5), 34.6(C-6), 25.8 (C-7), 16.1
MS: m/z 71 (100), 81, 95, 41, 55, 82, 43, 123.



Structure elucidation

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



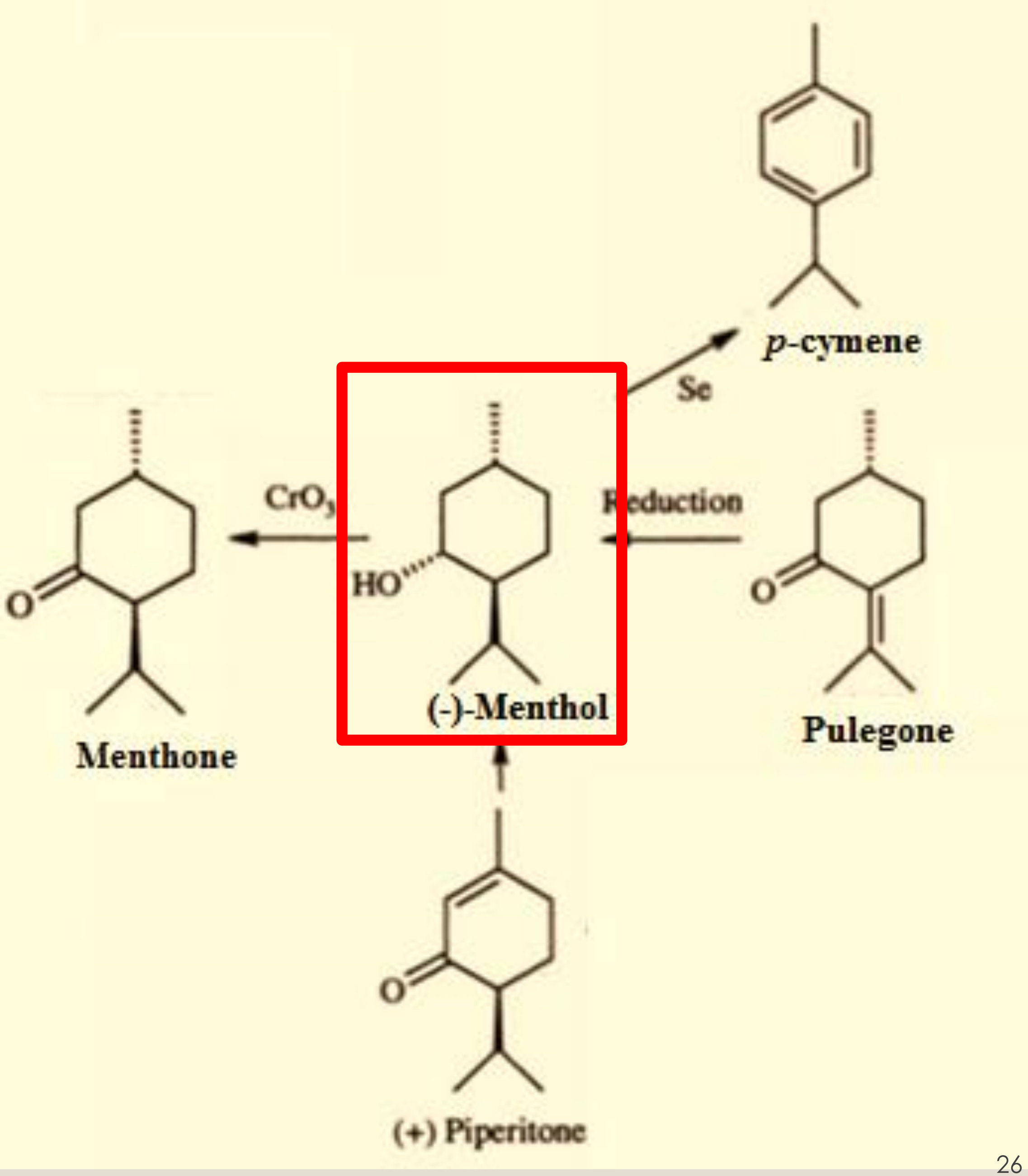
Structure elucidation

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

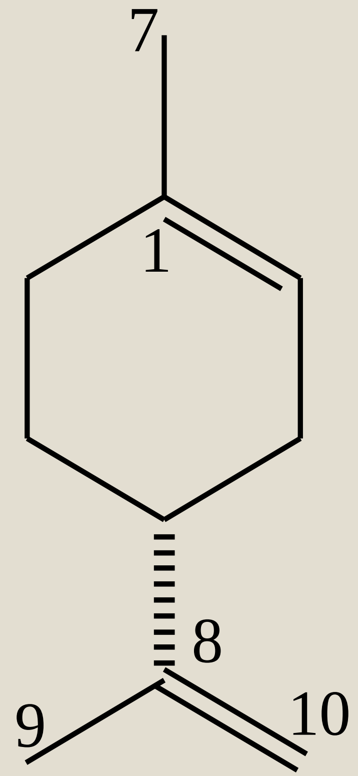
- **Menthol** was converted to ***p*-cymene** identified as 1-methyl-4-isopropylbenzene, which was also obtained by the dehydrogenation of **pulegone** whose structure was established as *p*-menth-4-(8)-en-3-one by chemical methods and confirmed by its synthesis.

- Therefore **menthol** must possess the same skeleton as **pulegone.**

- **Pulegone** on reduction yielded menthone, which on further reduction gave menthol.
- correlation of pulegone with menthol proved the structure of menthol.



Limonene



Occurrence:

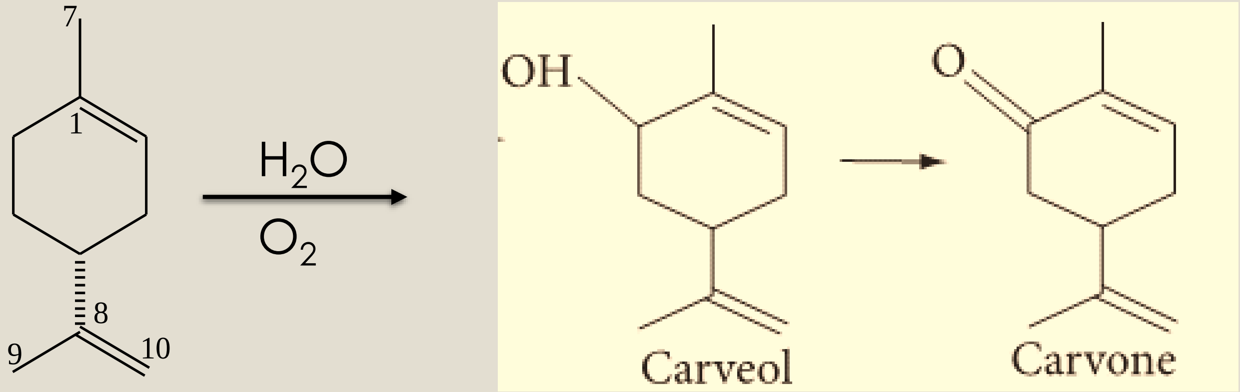
- Limonene is one of the most widely distributed terpene, occurring in many volatile oils especially in citrus oils.
- The d- form (+) is present orange (90%), lime, grapefruit, bitter orange, mandarin, neroli, dill fennel.
- The 1 form (-) is less common, accur in peppermint, spearmint. The recemic form *dl* (±) is known as dipentine and occurs in volatile oils of lemon grass, nutmeg, neroli, fennel etc.

Isolation:

- Limonene is isolated from the volatile oil either by careful fractional distillation, b.p 176°C without decomposition, or via certain derivative (adducts) e.g., tetrabromide m.p 104°-105°C. and the hydrocarbon may be regenerated by debromination with zinc and acetic acid.

Limonene

- **Limonene** is identified by the preparation of a crystalline nitrosochloride m.p 103°-104°C., by the reaction with nitrosyl chloride gas and the crystalline tetra bromide, m.p 104°-105°C.
- **Autoxidation of limonene** to corveol and carvone under the influence of air and moisture, is most probably one of the principal factors in the spoilage of poorly stored oils that contain high percentage of limonene e.g. citrus oils. This is particularly noticeable in old orange oils by showing peculiar caraway odor.

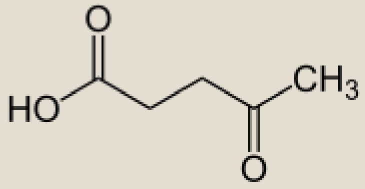


Uses :

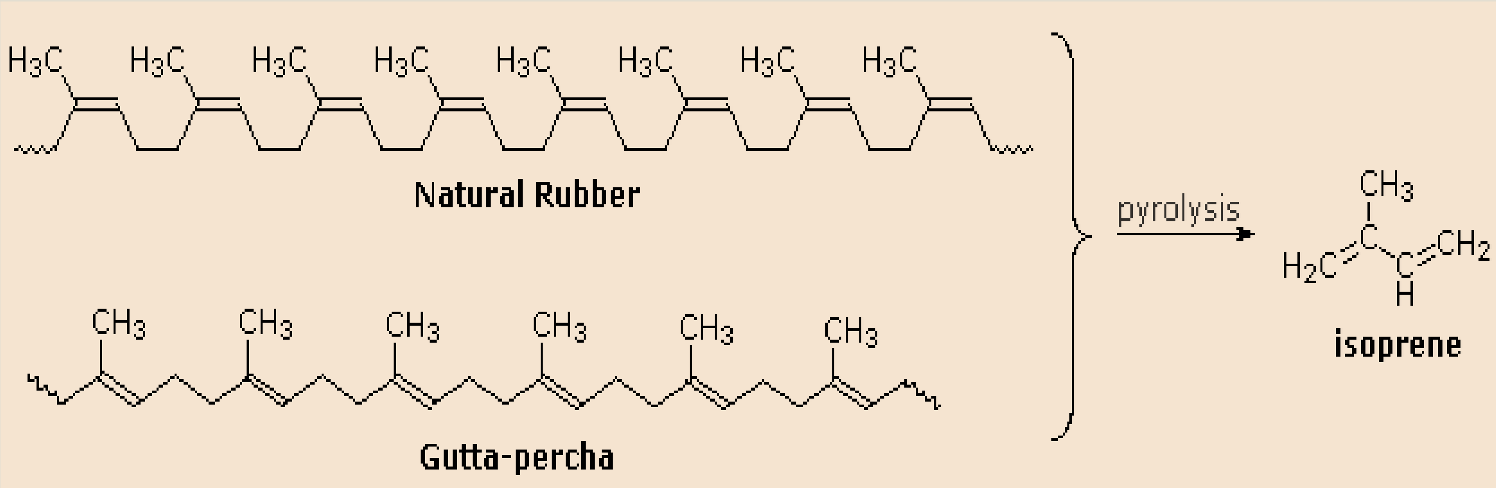
- Limonene is widely employed for scenting cosmetics, soaps as well as for flavoring pharmaceuticals.

Polyterpenoids

- **Polymeric isoprenoid hydrocarbons** ; Rubber is occurs as a colloidal suspension called latex in a number of plants mainly in a rubber tree (*Hevea brasiliensis*).
- Rubber is a polyene, and exhibits all the expected reactions of the C=C function. Bromine, hydrogen chloride and hydrogen all add with one molar equivalent per isoprene unit.
- Ozonolysis of rubber generates a mixture of levulinic acid ($CH_3COCH_2CH_2CO_2H$) and the corresponding aldehyde.
- Pyrolysis of rubber produces the diene isoprene along with other products.

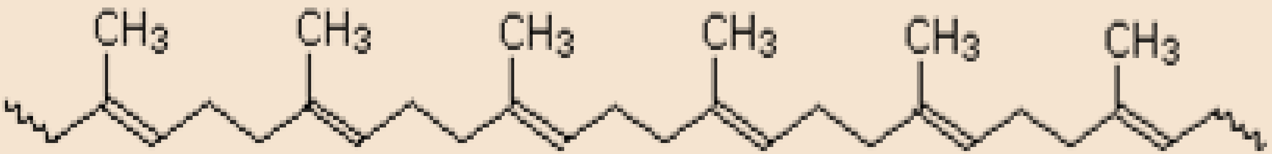


Levulinic acid



Polyterpenoids

- The **double bonds** in rubber all have a **Z-configuration,** which causes this macromolecule to adopt a coiled conformation and high molecular weight (about one million).
- Physical properties of rubber: crude latex rubber is a soft, sticky, elastic substance.



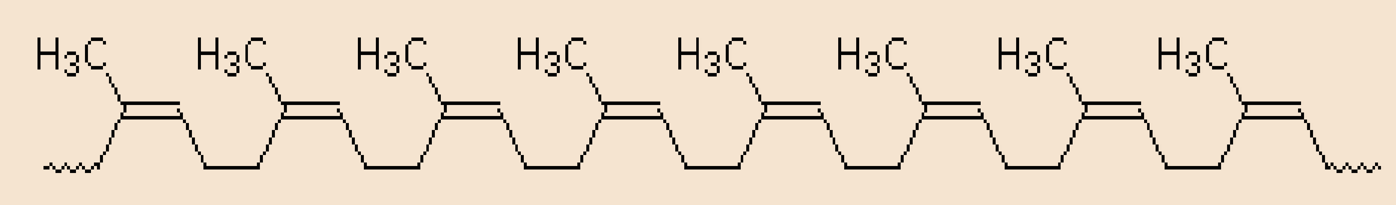
Gutta-percha

- Chemical modification of this material for commercial applications: **Gutta-percha** (structure above) is a naturally occurring ***E*-isomer** of rubber.
- Here the hydrocarbon chains adopt a uniform *zig-zag* conformation, more rigid and tough substance. **Uses**: surgical devices and during root canal therapy and Electrical insulation.
- gutta-percha is the *trans*-form. Gutta-percha is hard and has a very low elasticity.

Polyterpenoids

Rubber:

- Rubber is obtained from latex, which is an emulsion of rubber particles in water that is obtained from the inner bark of many types of trees which grow in the tropics and sub-tropics.
- When the bark of the rubber trees is cut, latex slowly exudes from the cut.
- Addition of the acetic acid coagulates the rubber, which is then separated from the liquor and either pressed into blocks or rolled into sheets, and finally dried in a current of warm air, or smoked.



Natural Rubber

After coagulation, the cake of raw rubber must be rolled to remove the water and washed to remove the acid

Rubber

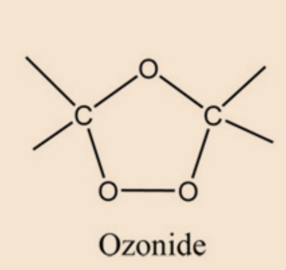
- Crude latex rubber contains, in addition to the actual rubber hydrocarbons (90-5 percent), proteins, sugars fatty acids and resins, the amounts of these substances depending on the source.
- Crude rubber is soft and sticky, becoming more so as the temperature rises.
- It has a low tensile strength and its elasticity is exhibited only over a narrow range of temperature.
- When treated with solvents such as benzene, ether, light petrol, a large part of the crude rubber dissolves; the rest swells but does not dissolve. This insoluble fraction apparently contains almost all of the protein impurity.
- On the other hand, rubber is insoluble in acetone, methanol, etc.
- When un-stretched, rubber is amorphous; stretching or prolonged cooling causes rubber to crystallize.

Structure of rubber

- The destructive distillation of rubber gives isoprene as one of the main products; this led to the suggestion that rubber is a polymer of isoprene,
- and therefore to the molecular formula $(C_5H_8)_n$. This molecular formula has been confirmed by the analysis of pure rubber.
- Crude rubber may be purified by fractional precipitation from benzene solution by the addition of acetone.
- This fractional precipitation, however, produces molecules of different sizes, as shown by the determination of the molecular weights of the various fractions by osmotic pressure, viscosity and ultracentrifuge measurements; molecular weights of the order of 300 000 have been obtained.

Structure of rubber

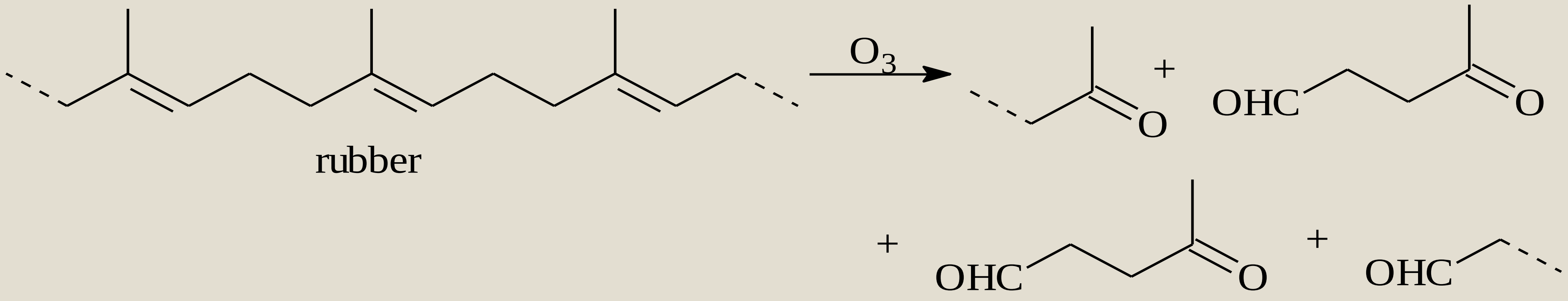
- The halogens and the halogen acids readily add on the rubber, *e.g.*, bromine gives an addition product of formula $(C_5H_8Br_2)_n$, and the hydrogen chloride the addition product $(C_5H_9Cl)_n$.
- Pummerer in 1922 showed that Pure rubber has been hydrogenated to the fully saturated hydrocarbon $(C_5H_{10})_n$ – this is known as **hydrorubber** – by heating with hydrogen in the presence of platinum as catalyst.
- Rubber also forms an ozonide of formula.



- All these addition reactions clearly indicate that rubber is an <u>unsaturated</u> compound, and the formulae of the addition products show that there is one double bond for each isoprene unit present.

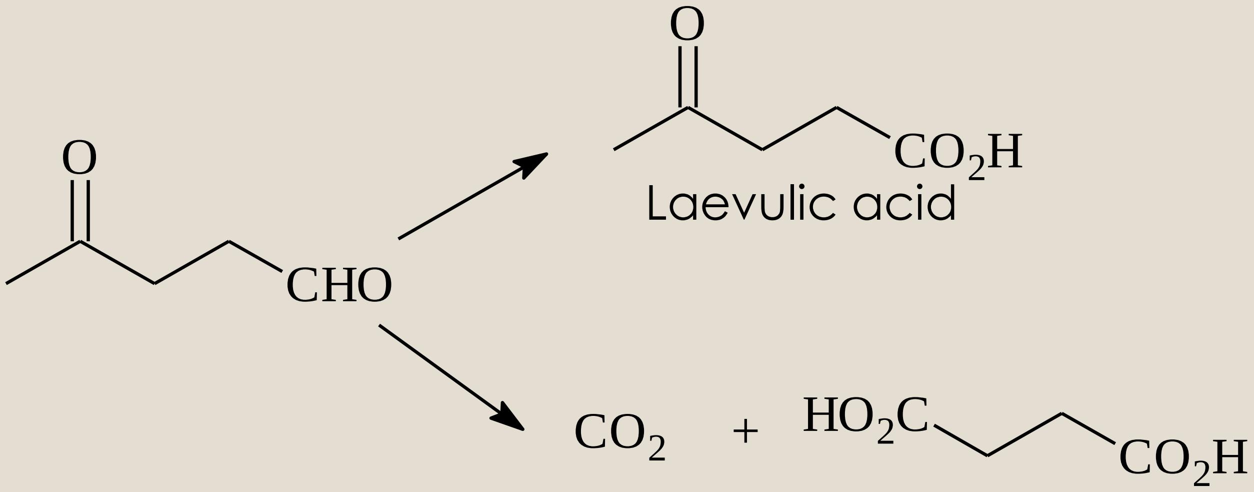
Ozonolysis

- **Ozonolysis** of rubber produces laevulaldehyde and its peroxide, laevulic acid and small amounts of carbon dioxide, formic acid and succinic acid
- laevulic derivatives comprised about 90 percent of the products formed by the ozonolysis.



Ozonolysis

- This observation led to the suggestion that rubber is composed of isoprene units joined head to tail. Thus, if rubber has the following structure, the formation of the products of ozonolysis can be explained as in the previous scheme.
- Some of the laevulaldehyde is further oxidized to laevulic and succinic acids.



Laevulic acid

succinic acids

Thank You