CHEMISRY OF NATURAL PRODUCTS

FOR 2nd YEAR BIOLOGY STUDENTS

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2022/2023

Contents

- Introduction
- Classification of natural products
- Terpenoids
- Steroids
- Alkaloids
- Biosynthesis of natural products

المحاضرة الاولي

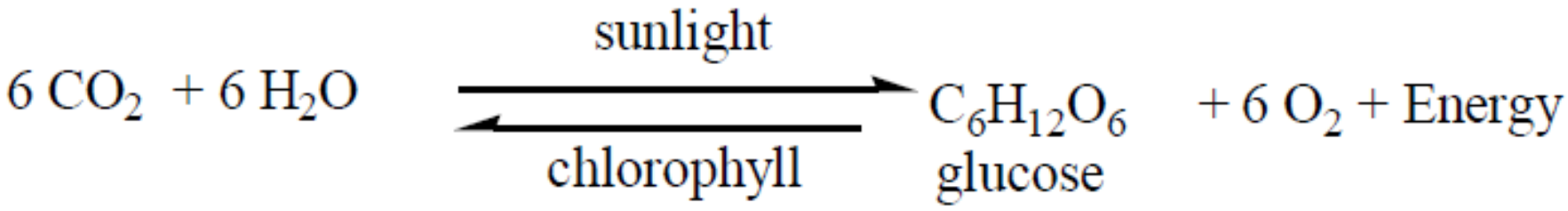
Introduction

- Natural products are chemical compounds or substance produced by a living organism that is found in nature.
- In the broadest sense, natural products include any substance produced by life.
- **Natural Products** is define as organic compounds and other chemicals synthesised by plants through metabolic processes aided by sunlight, involving CO2, H2O vapour and chlorophyll.
- Generally, natural products are characterised by specific functions they perform in plants and animals.
- Categories of natural Products are called **metabolites**.

Primary metabolites

A- Primary metabolites are usually found in all living organisms such as plants and animals. They form the fundamental nucles of living material e.g. mevalonic acids and nucleotides.

- Acetyl-coenzyme A (AScOA), Nucleotides and Mevalonic acids (MVA) constitutes primary metabolites from which secondary metabolites are derivable. A complex web of enzymecatalyzed reactions may involve the use of inorganic compounds such as H2O, CO2, solar energy through the process known as **Photosynthesis**. The reaction scheme is shown below.



Secondary metabolites

B- Secondary metabolites are chemicals synthesized by plants but are not directly used by them, but are used indirectly by man as a source of pharmaceutical preparations. Secondary metabolites are generally built from primary metabolites. Examples are steroids, terpenoids, alkaloids, and others.

- Some secondary metabolites are synthesised via biosynthesis and or biogenesis.
- Higher plants synthesised chemical compounds *in vivo* and degrade them by means of series of chemical reactions, each aided by enzymes, by a process known as **metabolism**

What is difference between biosynthesis and biogenesis?

What biosynthesis means?

the production of a chemical compound by a living organism.

What biogenesis means?

Biogenesis refers to all living things that come from other living things.

Life can only come from life

- is that biogenesis is the principle that living organisms are produced only from other living organisms while biosynthesis is (biochemistry) the synthesis of organic compounds within a living organism, especially the synthesis of large compounds from small ones.

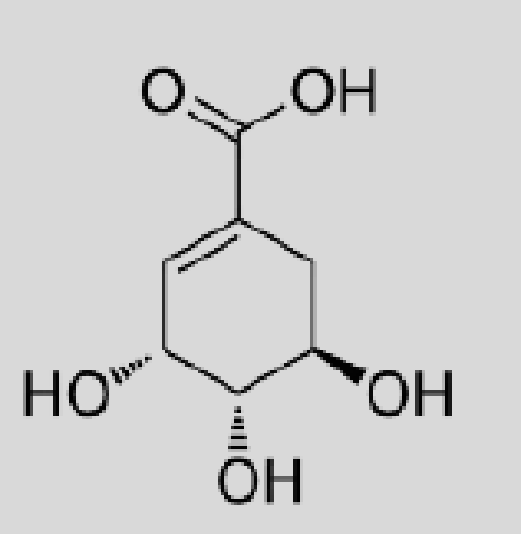
What are "Natural Products"?

Chemical characteristics

- Naturally-occurring small organic compounds
  - including heterocyclic compounds, and peptides.
  - does not include proteins, carbohydrates, and nucleic acids.
- MW: ~150 ~ <800 amu ("small molecule")
- Methods of extraction and purification are generally similar to the techniques used for organic compounds

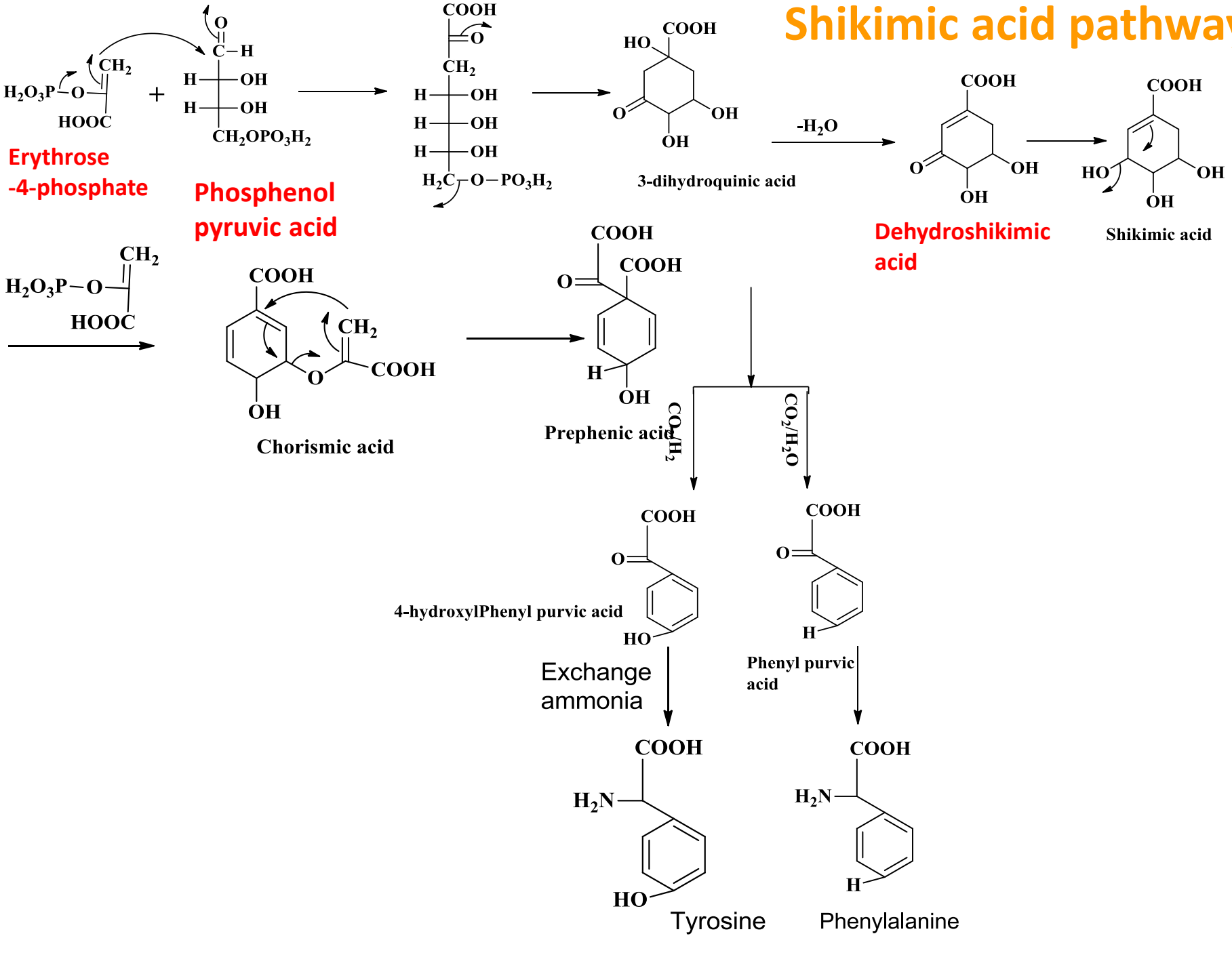
  (e.g., TLC, column chromatography, HPLC, GC)
- Methods of structural determination
  - NMR, MS, IR, X-ray, UV

Shikimic acid



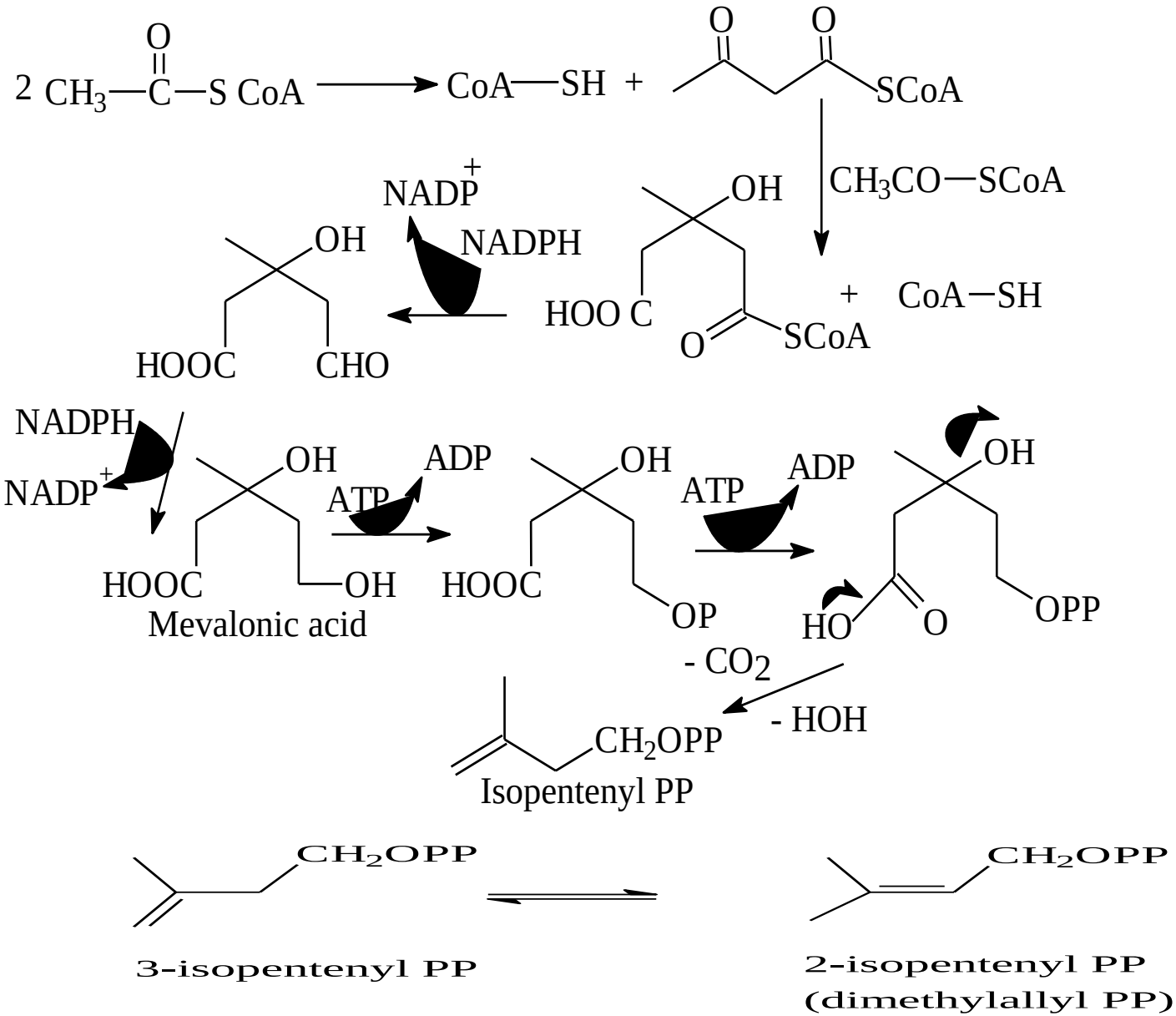
- It is an important biochemical metabolite in plants and microorganisms.
- The shikimate pathway is a seven step metabolic route used by bacteria, fungi, and plants for the biosynthesis of aromatic amino acids (phenylalanine, tyrosine, and tryptophan).
- This pathway is not found in animals; therefore, phenylalanine and tryptophan represent essential amino acids that must be obtained from the animal's diet.
- Animals can synthesize tyrosine from phenylalanine, and therefore is not an essential amino acid .

Shikimic acid pathway



Mevalonic acid pathway

The biogenesis of the isoprene unit :



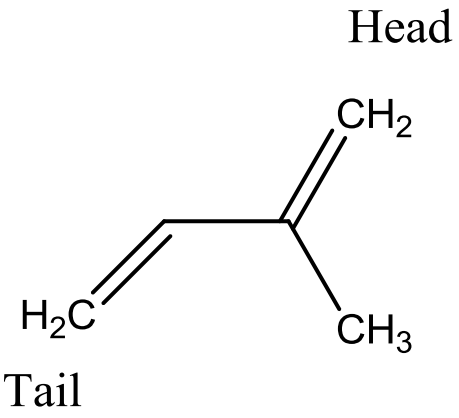
المحاضرة الثانية

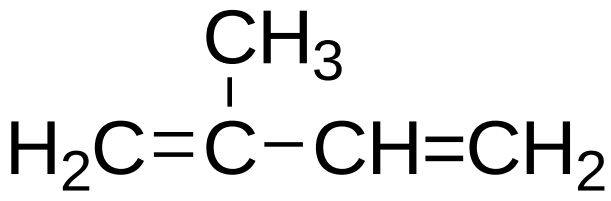
(I) Terpenoids

Terpenoids

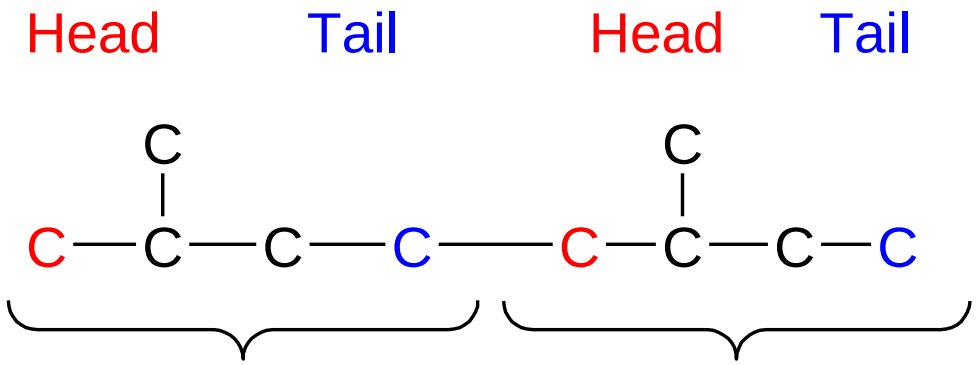
- Terpenoids are naturally occurring organic compounds, mostly found in plants.
- Terpenoids are structurally related as they are all composed of isoprene units repeated twice or more.
- They can be either hydrocarbons or oxygenated compounds.

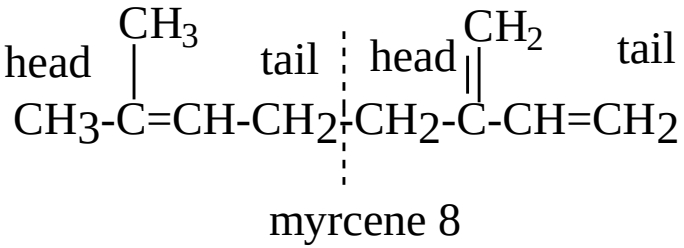
Isoprene Rule: All naturally occurring terpenoids consist of isoprene units $(C_5H_8)_n$ connected together in a head-to-tail arrangement.

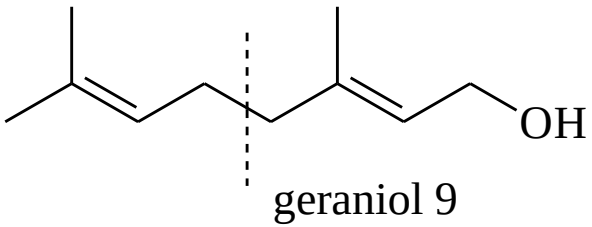




Isoprene

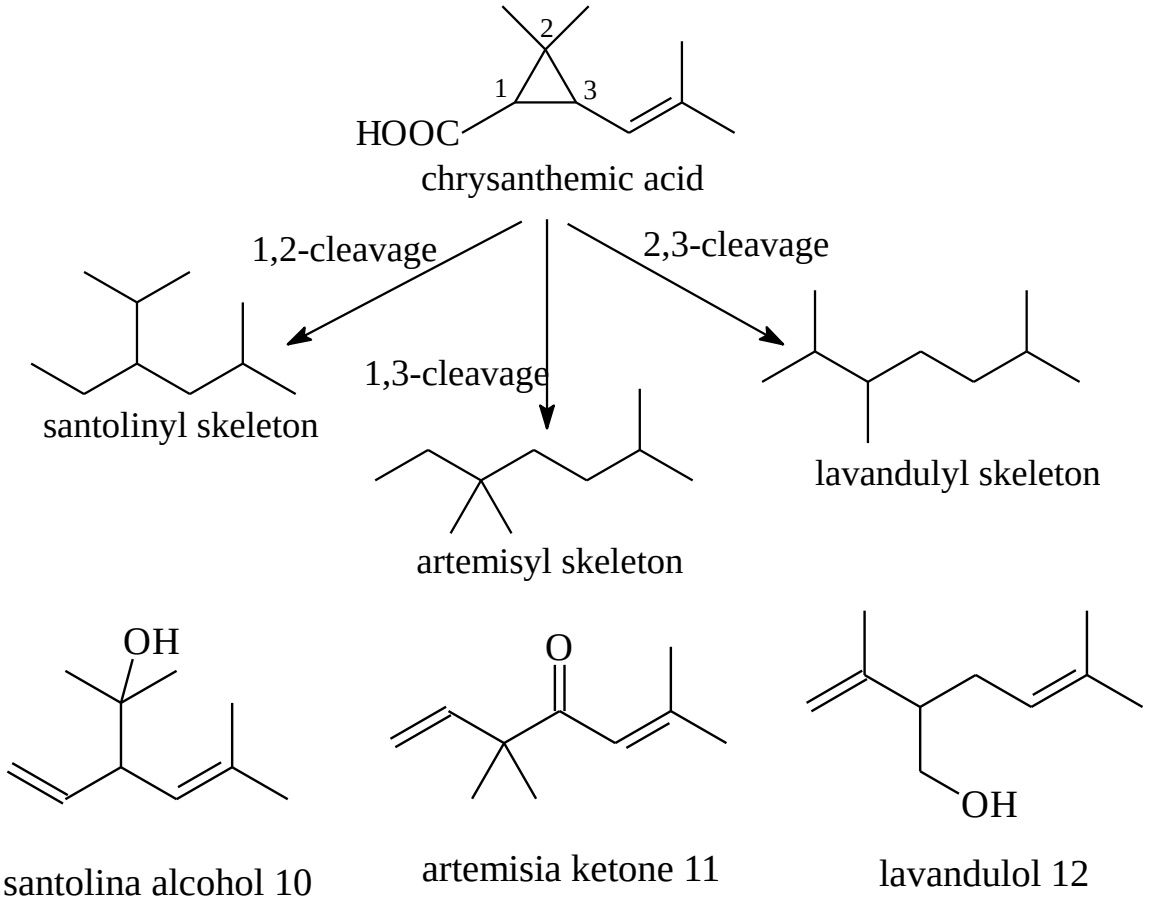

Head
Tail
Head
Tail
Isoprene unit
Isoprene unit


head
tail
head
tail
myrcene 8


OH
geraniol 9

Exceptions of the Special Isoprene Rule

irregular monoterpenes



Classification of Terpenoids:

Terpenoids are classified according to the number of isoprene units $(C_5H_8)_n$ into:

1- Hemiterpenes (n = 1), Ester and ether groups, C_5H_8

2- Monoterpenoids (n=2), Volatile oils, $C_{10}H_{16}$

3- Sesquiterpenoids (n=3), Volatile oils, $C_{15}H_{24}$

4- Diterpenoids (n=4), Gums and resins $C_{20}H_{32}$

5- Sesterterpenoids (n=5), Gums and resins, $C_{25}H_{40}$

6- Triterpenoids (n=6), Gums and resins, $C_{30}H_{48}$

7- Tetraterpenoids (n=8): $C_{40}H_{64}$ (Carotenoids)

8- Polyterpenoids (n is a large number) (Rubber)

Isolation of Mono- and Sesequiterpenes (essential oils)

There are four methods of extraction of the terpenoids

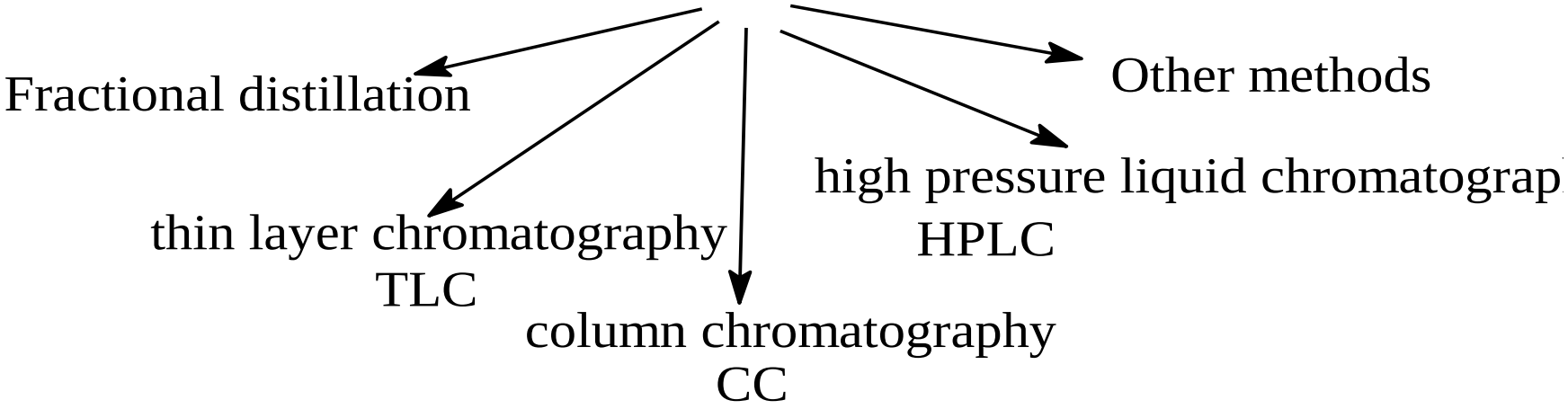
(i) Chromatography

(ii) Steam distillation

(iii) Extraction by means of volatile organic solvents

(iv) Adsorption on fats.

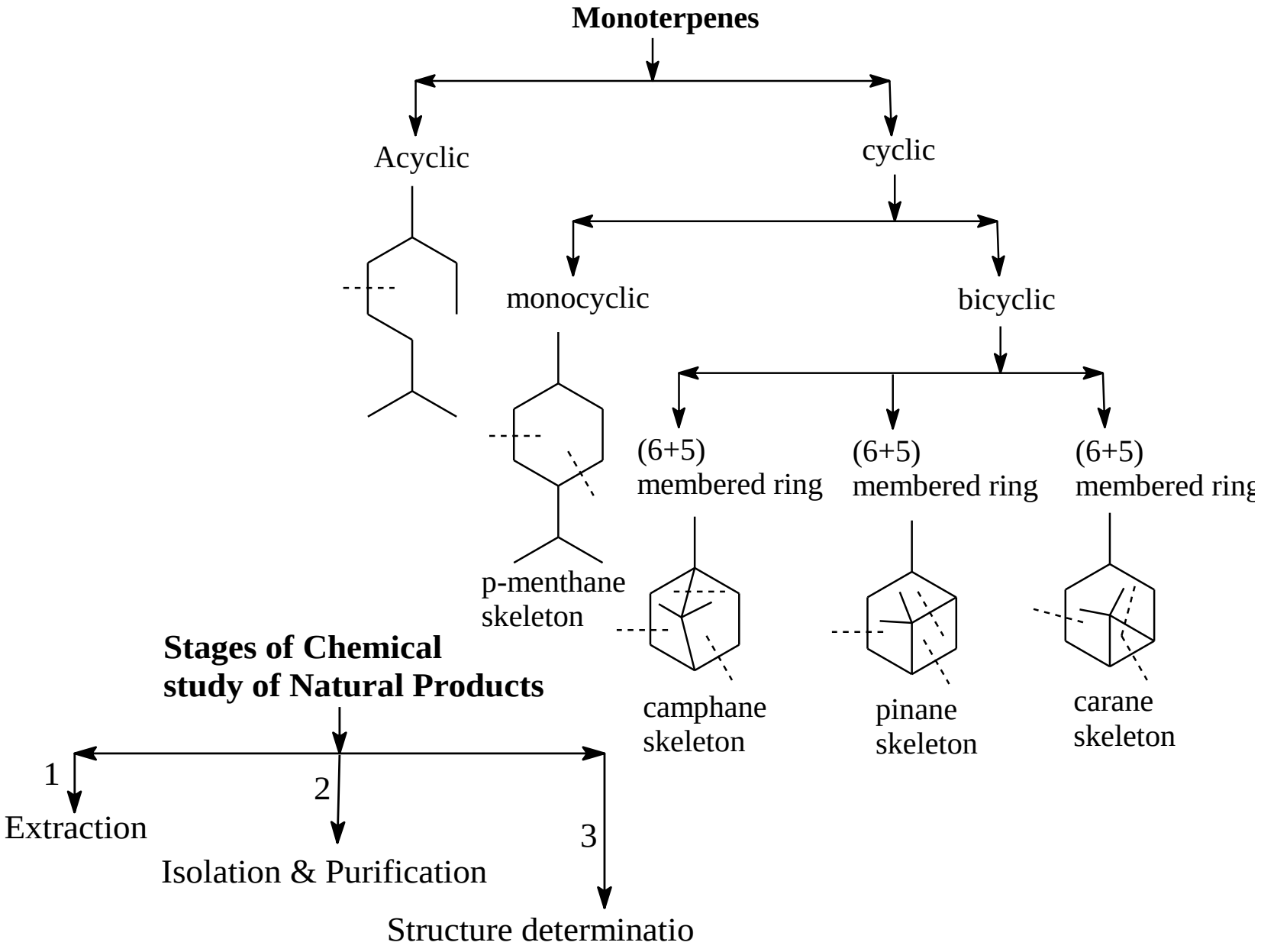
Method (ii) is the one most widely used. More recently, chromatography (in its various forms) has been used both for isolation and separation of terpenoids.


Methods for
Separation of mixtures
Fractional distillation
thin layer chromatography
TLC
column chromatography
CC
high pressure liquid chromatograp
HPLC
Other methods

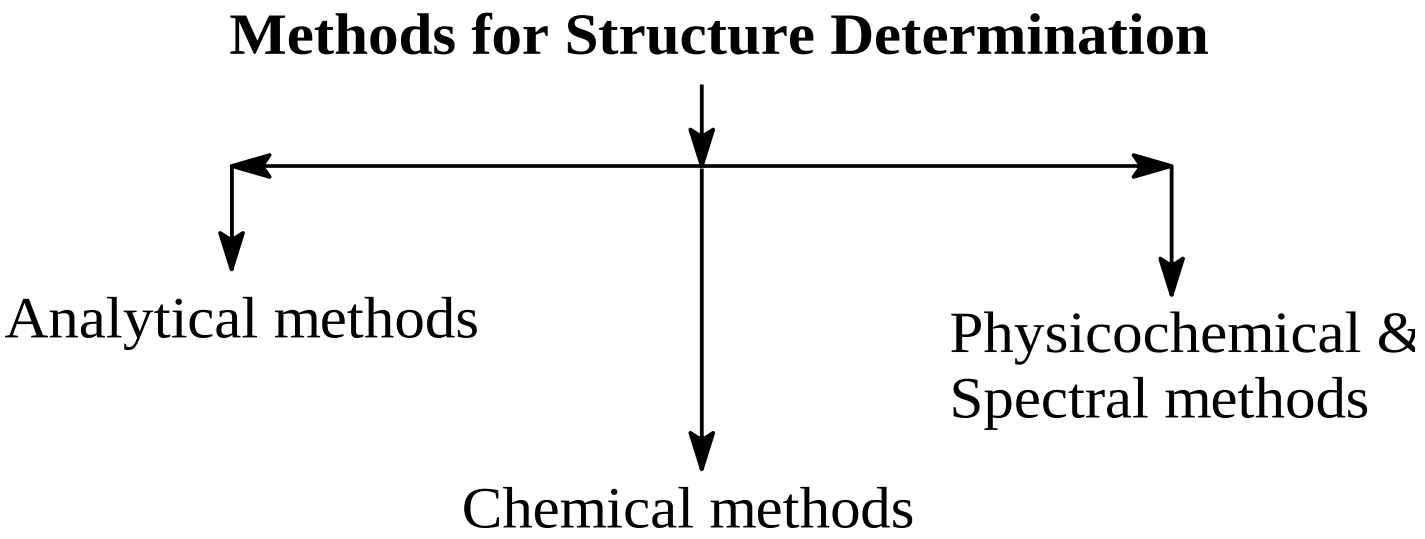
Monoterpenoids

Monoterpenoids may be subdivided into three groups:

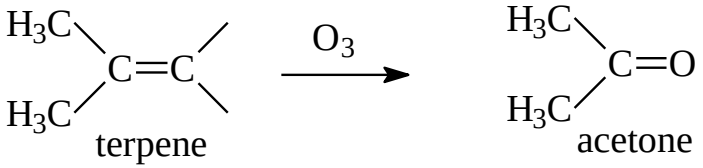
- Acyclic
- Monocyclic
- Bicyclic


Monoterpenes
Acyclic
cyclic
monocyclic
bicyclic
(6+5)
membered ring
(6+5)
membered ring
(6+5)
membered ring
p-menthane
skeleton
camphane
skeleton
pinane
skeleton
carane
skeleton
Stages of Chemical
study of Natural Products
1
Extraction
2
Isolation & Purification
3
Structure determinatio

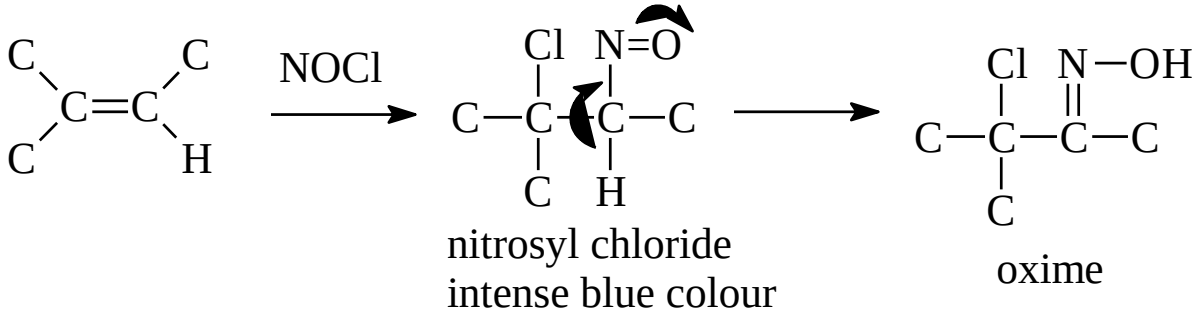
General Methods for Structure Determination of Terpenoids



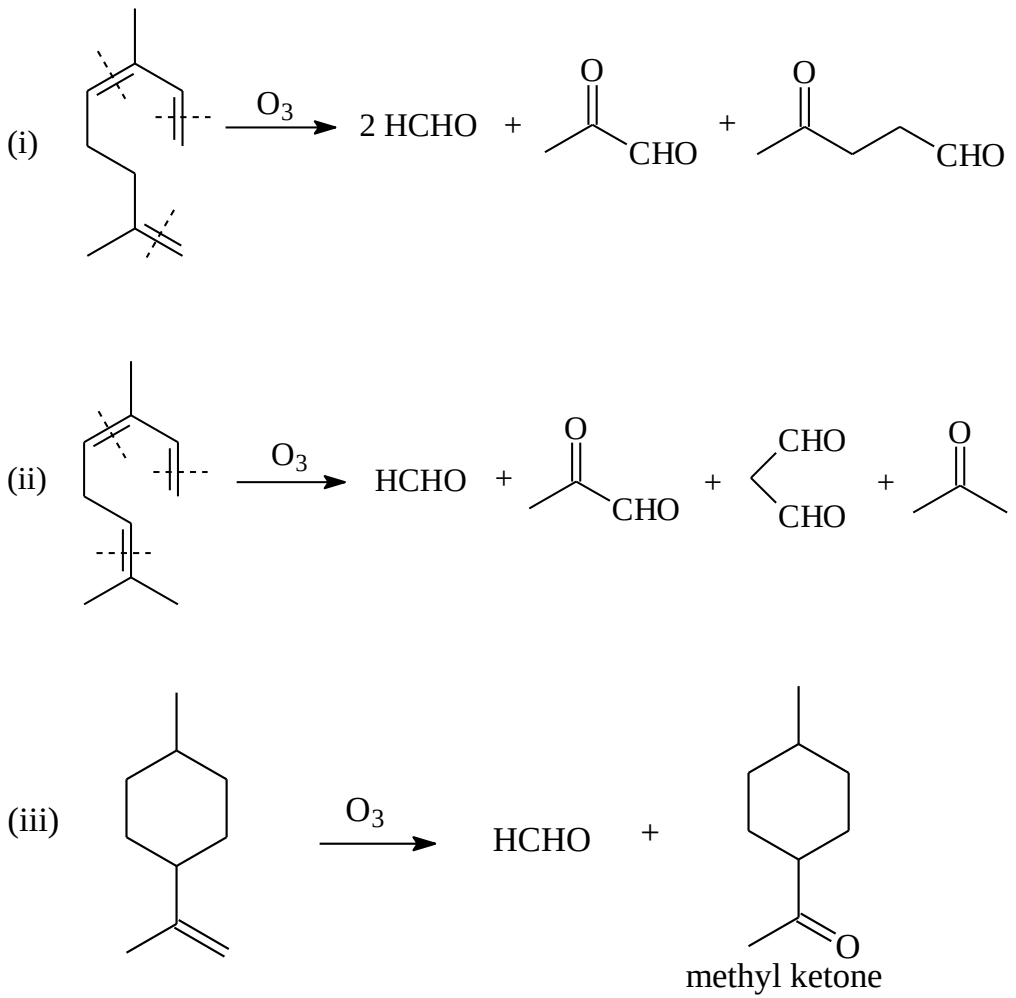
- **Analytical methods**
- Determination of % of C,H and O by molecular formula
- Degrees of unsaturation
- Estimation of groups
- · Active hydrogen
- Terpene + $LiA1H_4 \rightarrow H_2$ ----- estimated



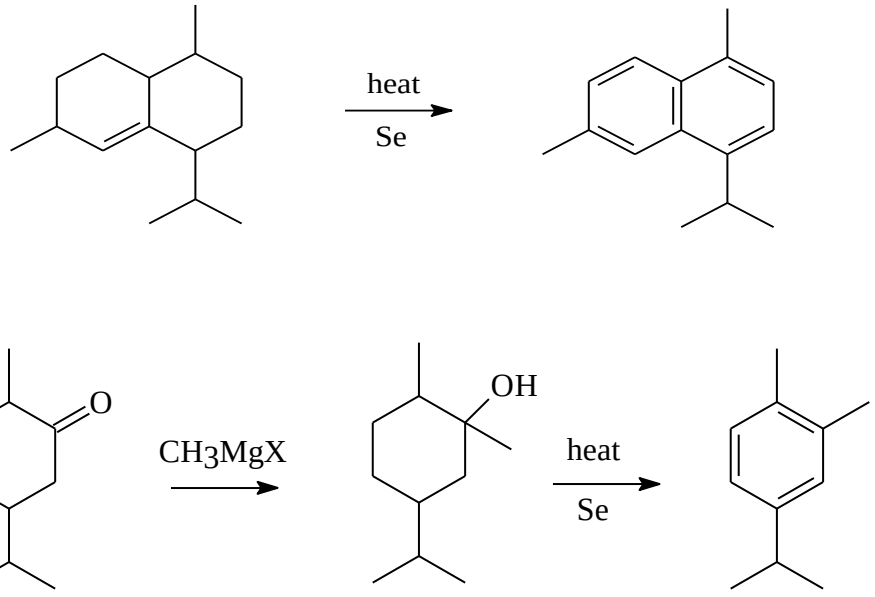
- Chemical methods
- Functional groups
- Unsaturation
- · by bromination (Br_2)
- · by nitrosyl chloride NOCl



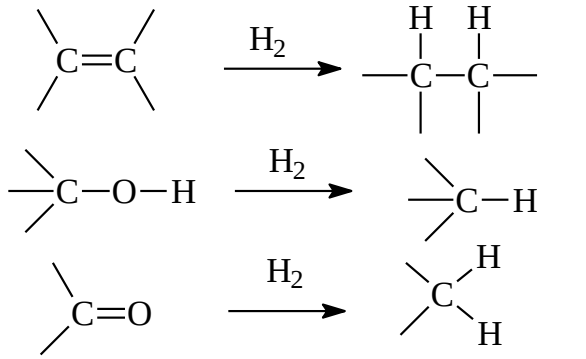
- Ozonolysis is an example of oxidative degradation methods (O_3, $KMnO_4$, CrO_3 & OsO_4).



- Conjugated and isolated double bonds are differentiated by Diel's Alder reaction.
- Dehydrogenation by heating the terpene with S or Se converts the terpene into aromatic derivative which is easily identified.



- Hydrogenation of the substance to the parent hydrocarbon leads to the cyclic nature of the terpene (acyclic, monocyclic, bicyclic, ... etc).



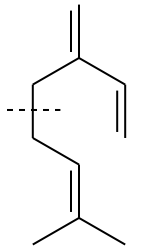
- · <u>Hydrocarbon</u> C_nH_{2n+2} ---------- Acyclic
- C_nH_{2n} ---------- Monocyclic
- C_nH_{2n-2} ---------- Bicyclic
- C_nH_{2n-4} ---------- Tricyclic
- C_nH_{2n-6} ---------- Tetracycl

- Physical and spectral methods
- a) Molecular refraction (refractive index, refractometer).
- b) Optical rotation α_D (polarimeter)
- c) IR absorption
- d) NMR (^{1}H-NMR & ^{13}C-NMR)
- e) X-Ray analysisf) UV (ultraviolet absorption)
- A final confirmation of the proposed structure is usually achieved by synthesizing the compound and comparing the spectral data with those of an authentic sample.

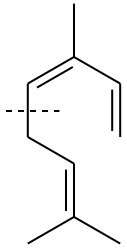
المحاضرة الثالثة

Examples for different terpenes

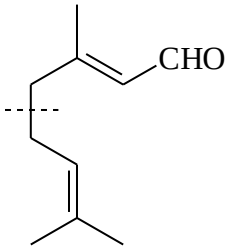
- **i)** Monoterpenes
- Acyclic



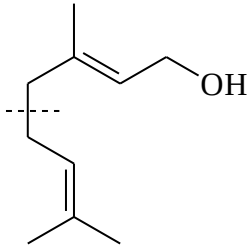
Myrcene
occurs in verbena and bay oil



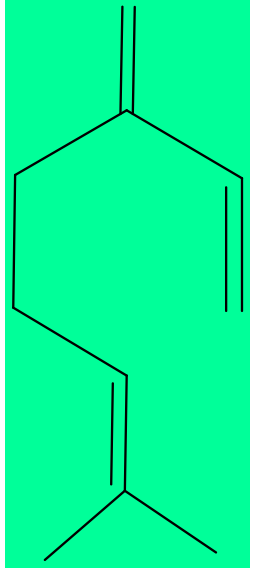
Ocimene
occurs in *Ocimum basilicum*



Citral
occurs in lemon grass oil



Geraniol
occurs in rose oil



1- Myrcene

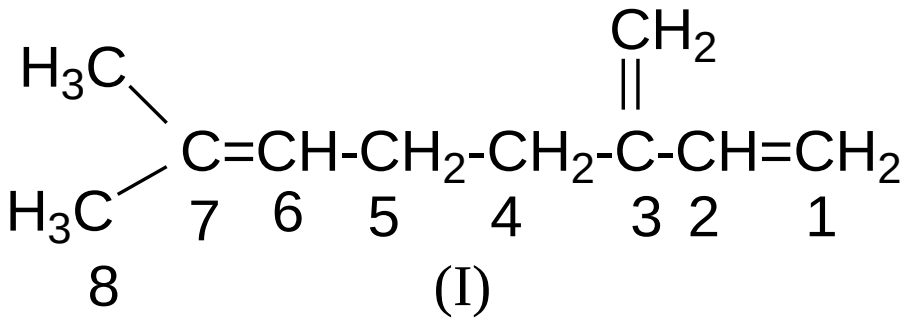
1- Molecular formula $C_{10}H_{16}$

2- Catalytic hydrogenation (platinum) converts myrcene into a decane $C_{10}H_{22}$ thus myrcene contains three double bonds, and is an open-chain compound.

3- Myrcene forms an adduct with maleic anhydride, two of the double bonds are conjugated (Diels-Alder reaction).

4-Ozonolysis of myrcene produces acetone, formaldehyde and a ketodialdehyde, and the latter, on oxidation with chromic acid, gives succinic acid and carbon dioxide.

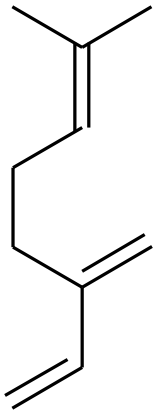
These results can be explained by assigning structure (I)



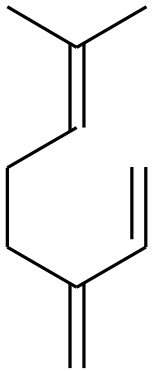
(I)

IUPAC name: 7-methyl-3-methylene-octa-1,6-diene

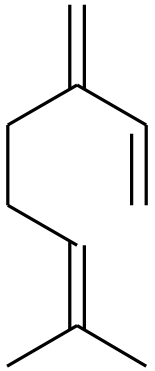
It is common to express the structure of myrcene as:



(II)

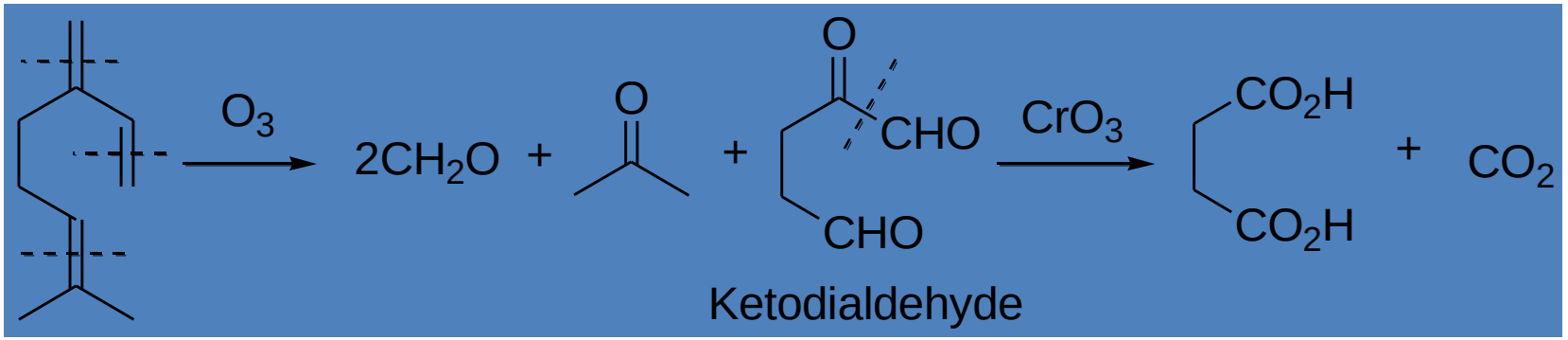


(III)

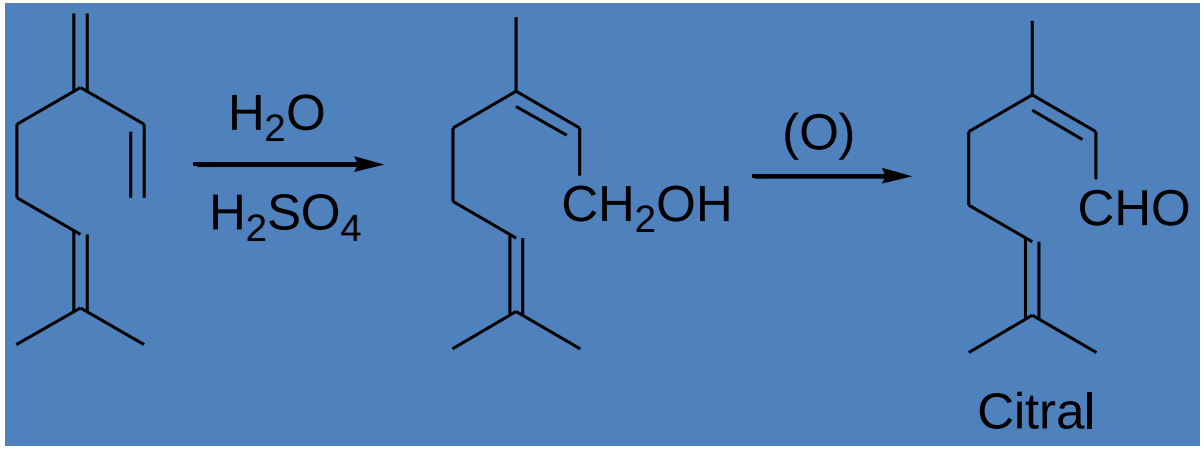


(IV)

The process of ozonolysis can be represented as shown:

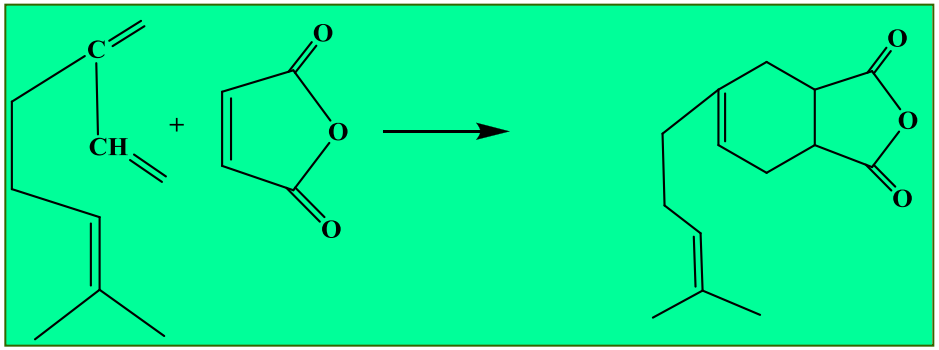


This structure for myrcene is supported by the fact that on hydration (under the influence of sulphuric acid), myrcene form an alcohol which, on oxidation gives citral:

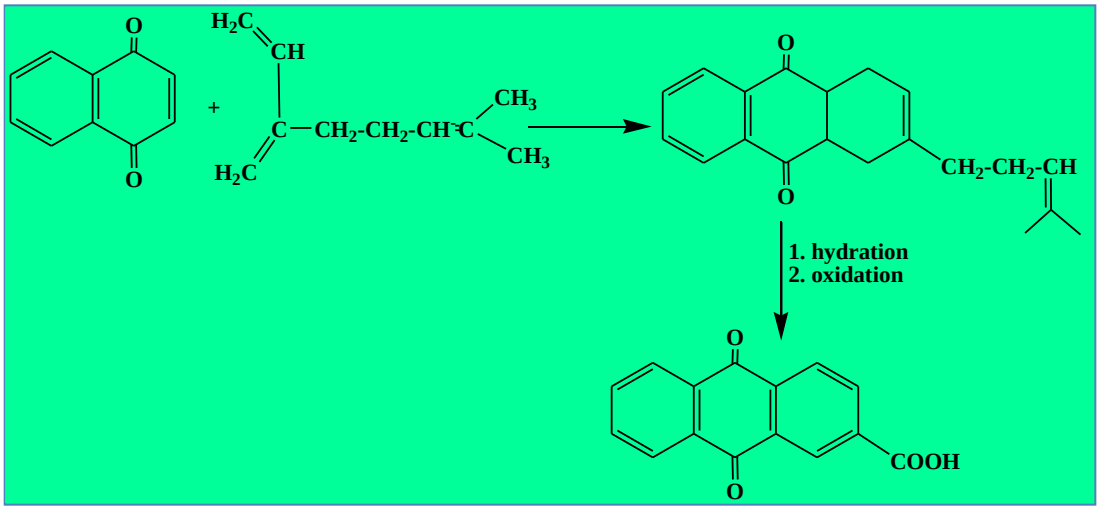


Diel's-Alder reaction of Myrcene

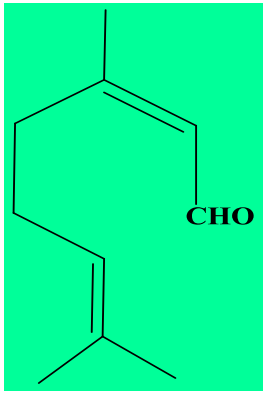
- Furthermore, since myrcene forms an adduct with maleic anhydride, two of the double bonds are conjugated.



- Moreover, evidence of chemical structure for Myrcene Diel's-Alder reaction of 1,4-naphthaquinone with Myrcene as follows:



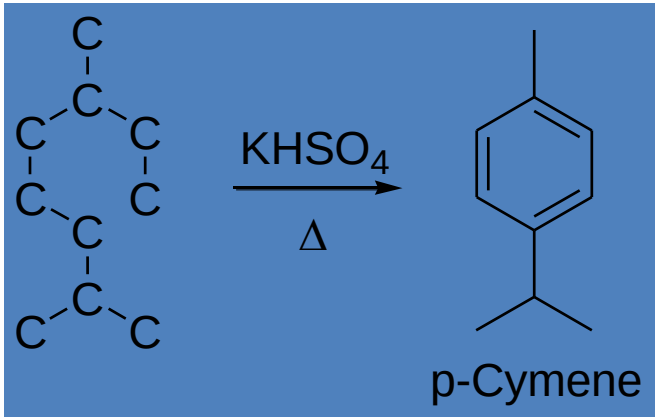
2- Citral



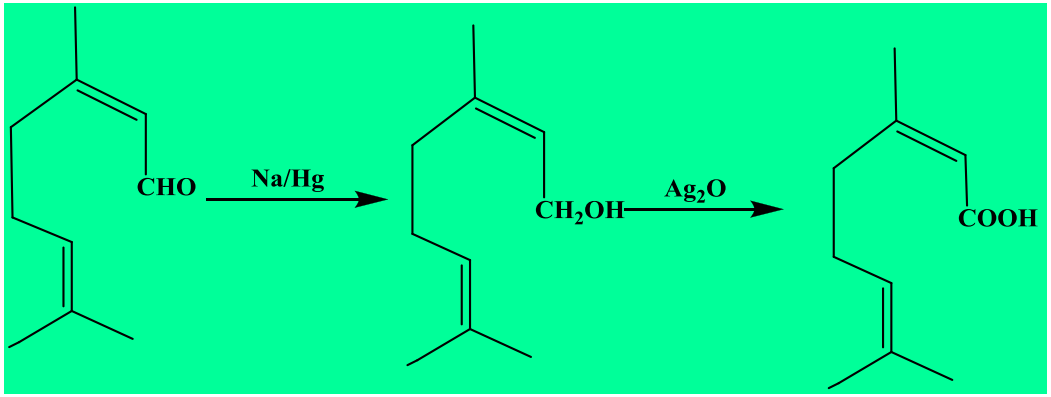
1- Molecular formula $C_{10}H_{16}O$.

2- Citral was shown to contain an oxo group, e.g. it forms an oxime

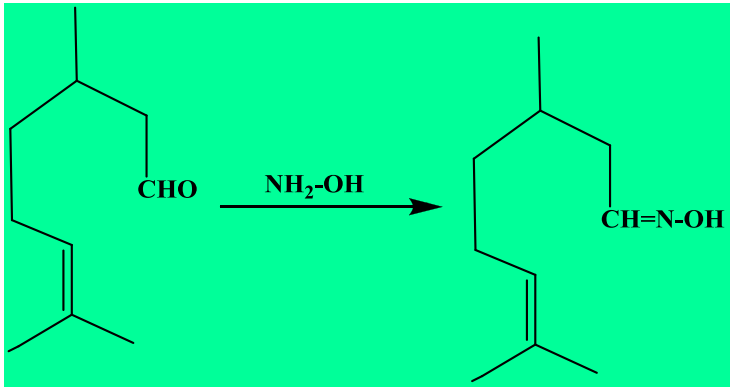
3- On heating with potassium hydrogen sulphate, citral forms p-cymene.



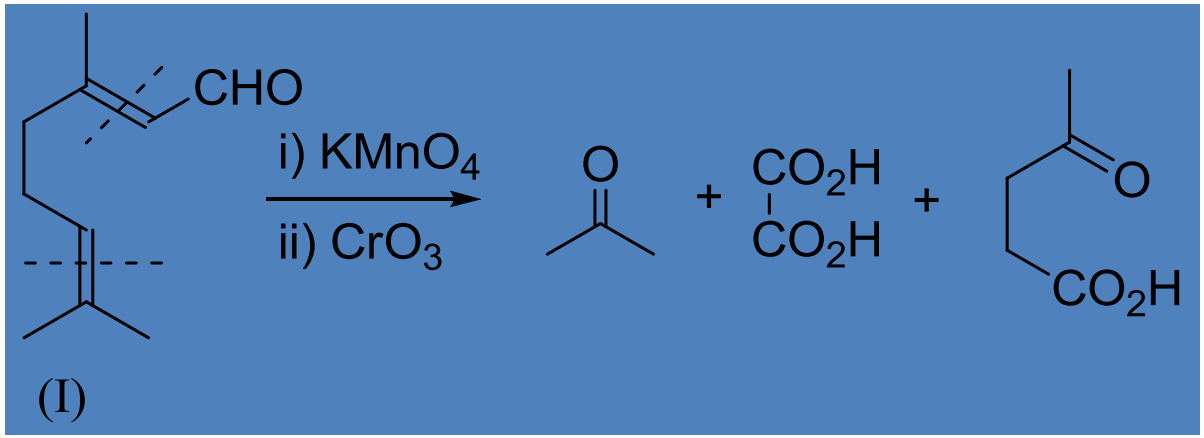
4- Citral is reduced by Na/Hg to an alcohol, geraniol, $C_{10}H_{18}O$ and is oxidized by Ag_2O to geranic acid, $C_{10}H_{16}O_2$, with no loss of carbon. Thus, the oxo group in citral is an aldehyde group.



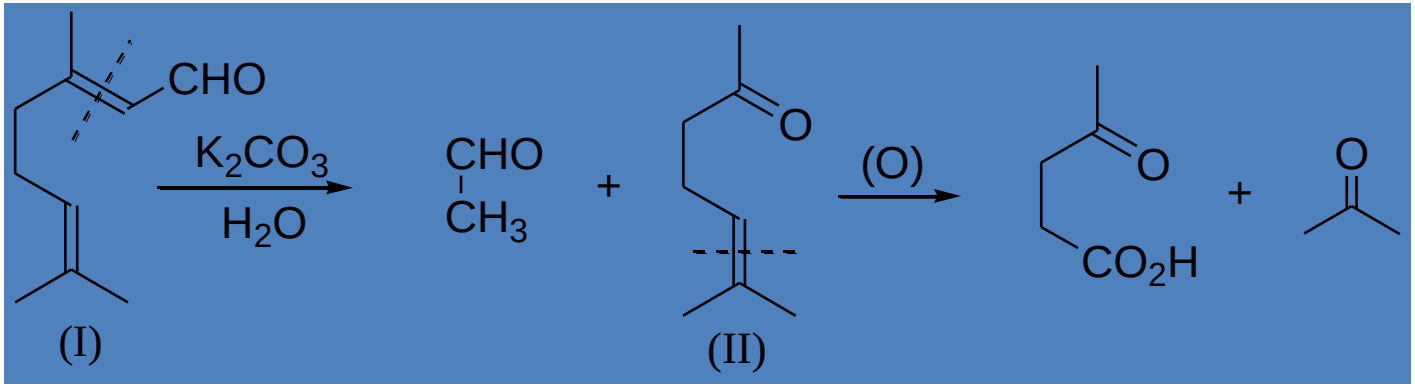
- Furthermore, the citral contains oxo group where it forms oxime and carbonyl group derivatives



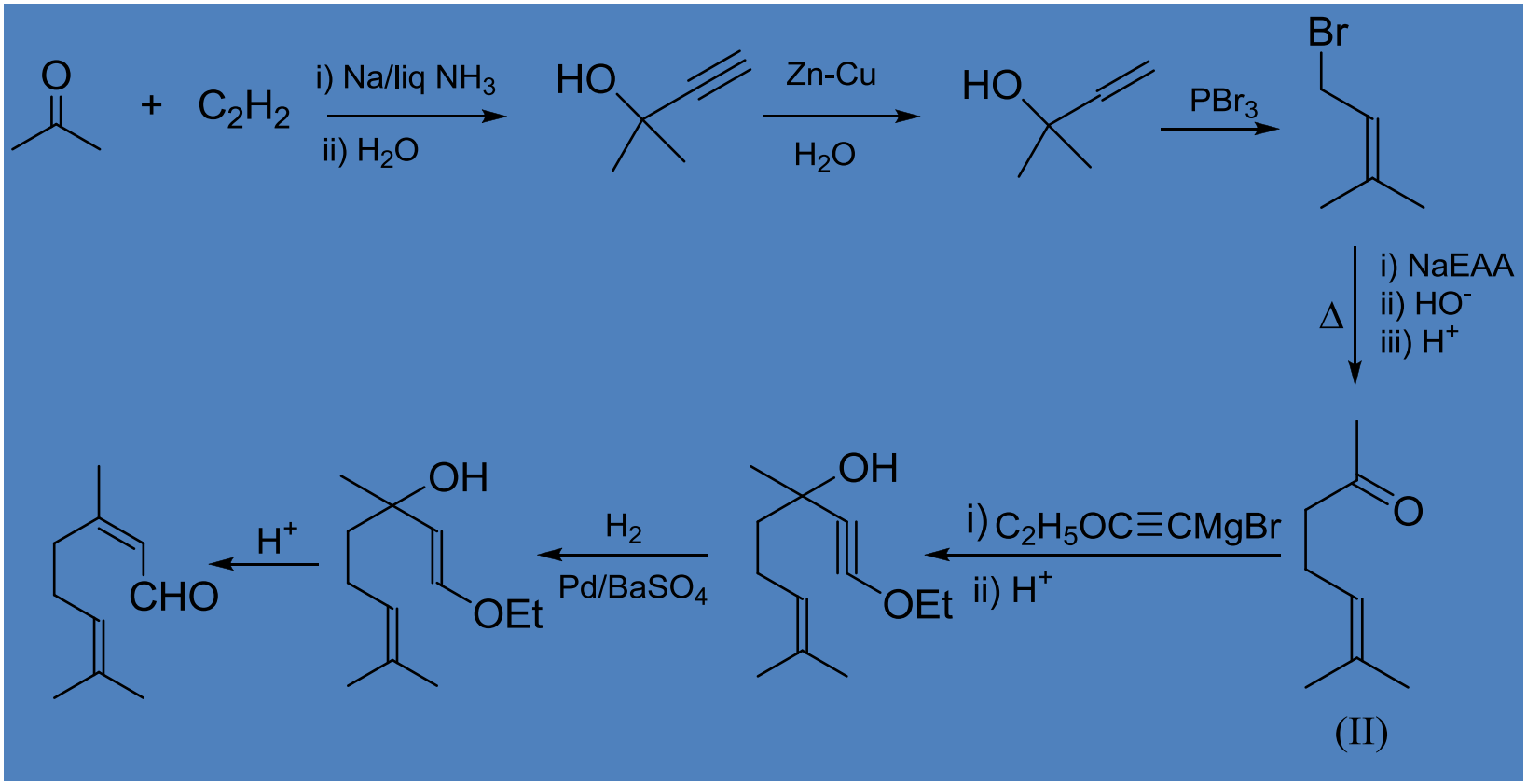
5- *Oxidation of citral with alkaline $KMnO_4$ followed by CrO_3 gives acetone, oxalic and laevulic acids. Thus, if citral has structure (I), the formation of this oxidation products can be represented as follows:*



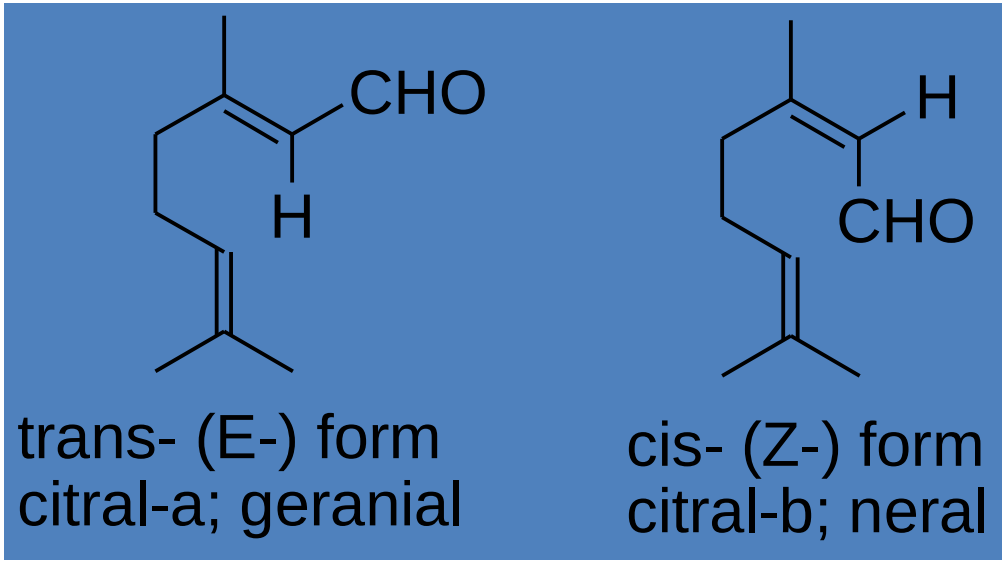
6- *aqueous potassium carbonate converted citral into 6-methylhept-5-en-2-one (II) and acetaldehyde. Furthermore, methylheptenone itself is also oxidized to acetone and laevulic acid; this in accord with structure (I).*



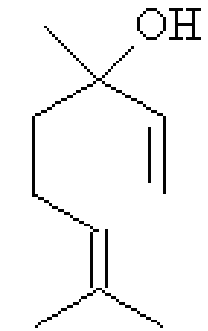
The structure of citral is finally proved by synthesis:



Two Geometrical isomers of citral exist:



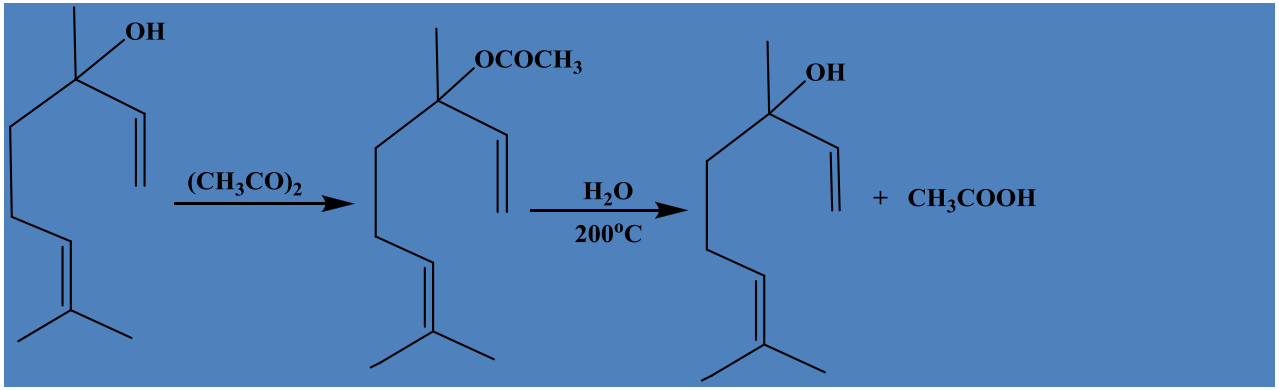
Linalool



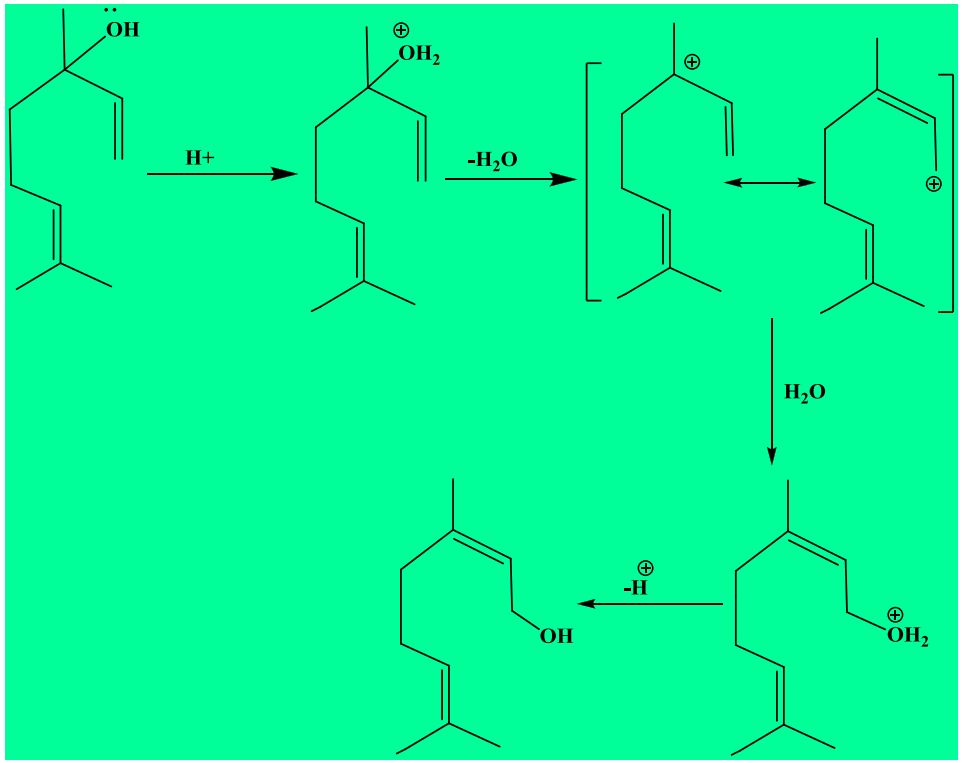
(±)-linalool

Linalool, $C_{10}H_{18}O$, b.p. 198-199°C. This is an optically active compound; the (-)-form occurs in rose oil and the (+)-form in orange oil.

- Oxygen occur as tertiary hydroxyl group.
- It contains two double bonds where it adds two hydrogen molecules during catalytic hydrogenation.
- When heating with acetic anhydride forming geranyl acetate which converts into lanalool again when heating with water at 200°C under pressure.

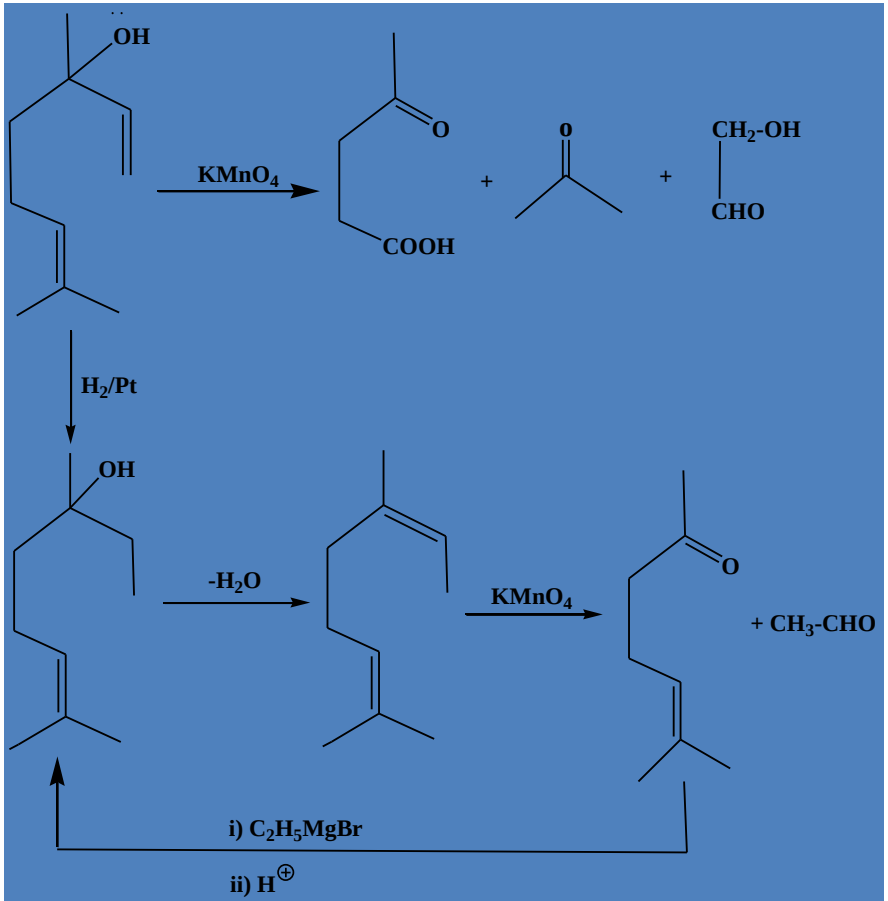


- Isomerization of Lanalool in the presence of acids into geraniol via allylic rearrangement

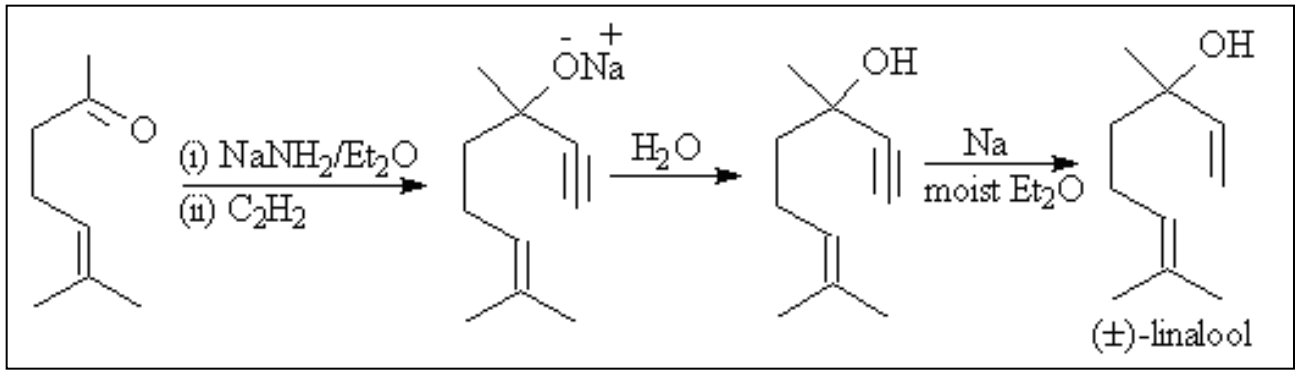


1. Oxidation of Lanalool using $KMnO_4$ forming *laevulic acid*, acetone and glycolaldehyde.

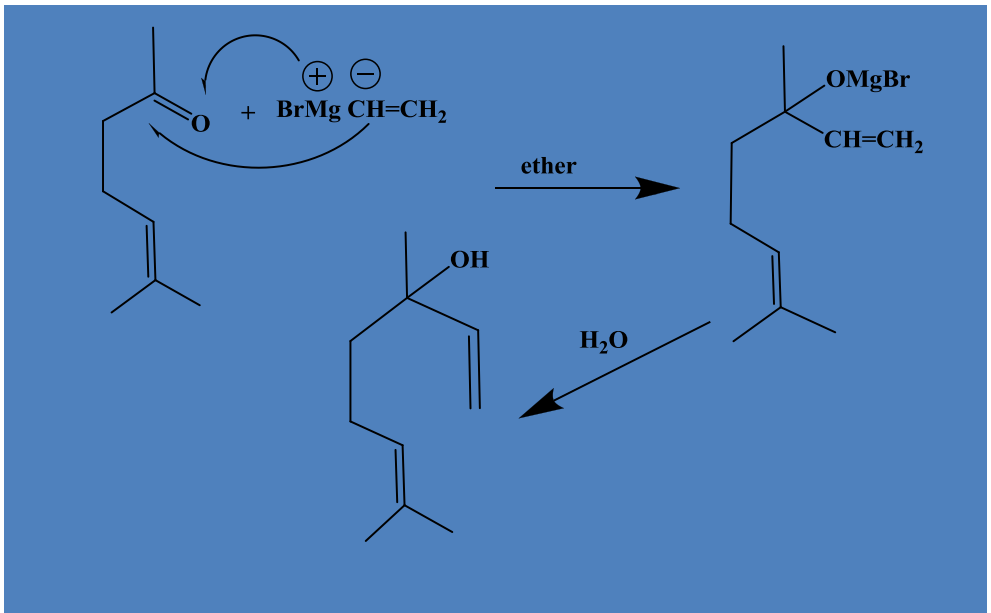
2. Evidence of presence of tertiary hydroxyl group in Lanalool is elimination of hydrogen from tetrahydrolanalool then oxidation the yield with $KMnO_4$ to form methyl isohexylketone as follows:



•The structure of linalool has been confirmed by synthesis of linalool by treating the sodium derivative of methylheptenone with acetylene, followed by partial reduction of the triple bond.



- It possible to synthyesis of Linalool in one step via Normant Synthesis as follows:

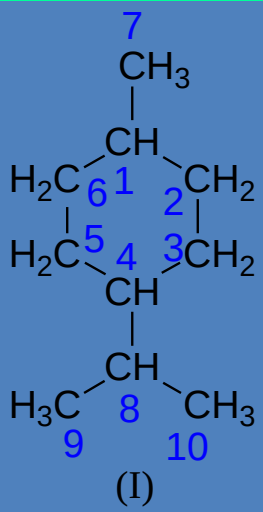


المحاضرة الرابعة

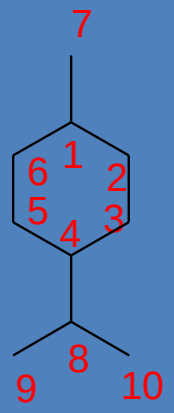
Monocyclic Monoterpenoids

Nomenclature:

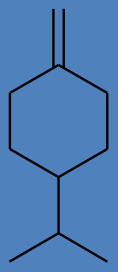
Monocyclic monoterpenoids are named as derivatives of p-menthane (*p*-methyl-isopropylcyclohexane).



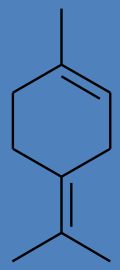
(I)



(II)

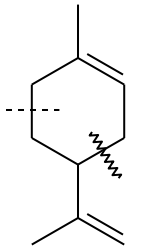


p-Menth-1(7)-ene



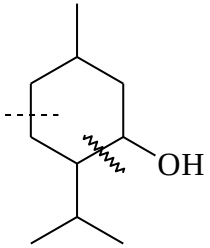
p-Menth-1,4(8)-diene

- Cyclic

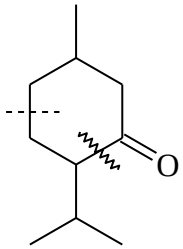


Limonene

occurs in lemon and orange oils

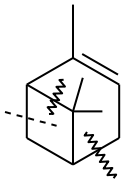


Menthol



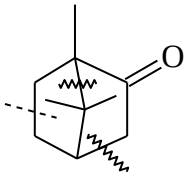
Menthone

both occur in pepermint oil



α-Pinene

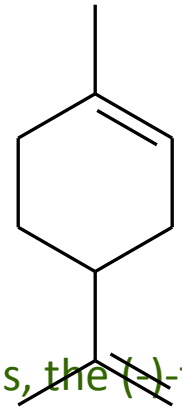
occurs in turpentine oil



Camphor

occurs in camphor tre

Limonene



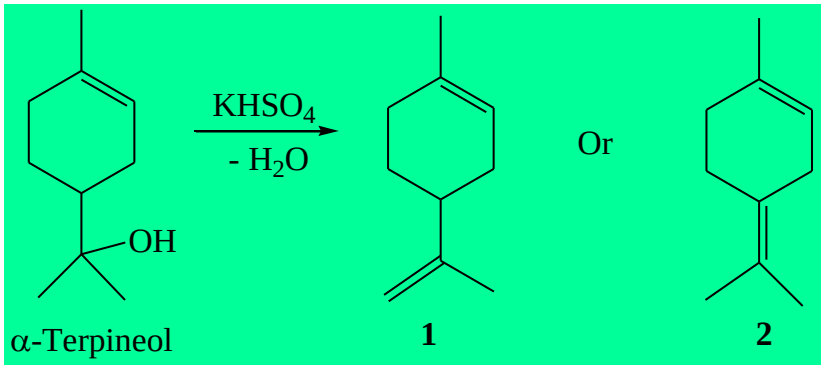
***p*-Menth-1,8(9) diene**

Limonene, $C_{10}H_{16}$, b.p. 175.5-176.5°C.

This is optically active; the (+)-form occurs in lemon and orange oils, the (−)-form in peppermint oil, and the (±)-form in turpentine oil.

- The racemic modification is also known as **dipentene**; this name was given to the inactive form before its relation to the active form (limonene) was known.
- Since limonene adds four bromine atoms, it therefore contain two double bonds.

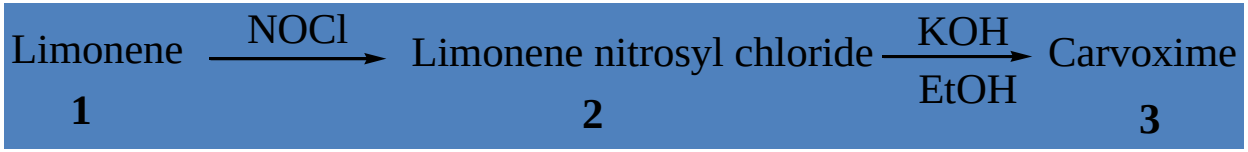
(+)-Limonene may be prepared by dehydrating (+)-α-terpineol with potassium hydrogen sulphate, and limonene (or dipentene) may be converted into α-terpineol on shaking with dilute sulfuric acid.



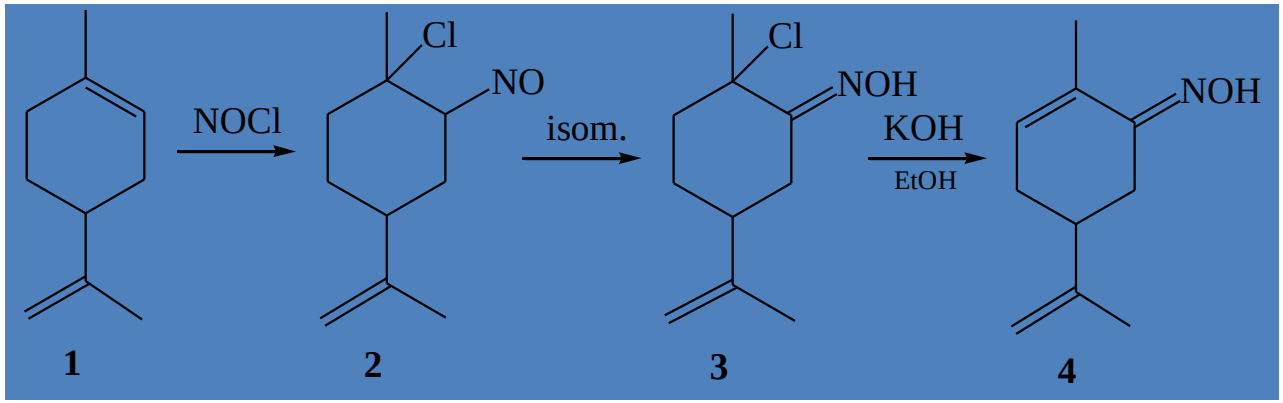
- The carbon skeleton and the position of one double bond in limonene are known. The position of the other double bond, however remains uncertain from this preparation; 1 or 2 is possible.

- Structure 1 contains a chiral center C-4, and hence can exhibit optical activity. Structure 2 is symmetric and so cannot be optically active. Therefore 1 must be limonene.

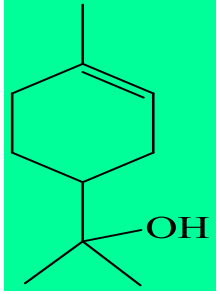
Chemical proof for position 8 is afforded by the following reactions:



- Since the structure of carvoxime is known, it therefore follows that (1) must have one double bond in position 8; thus the above reactions may be written as:



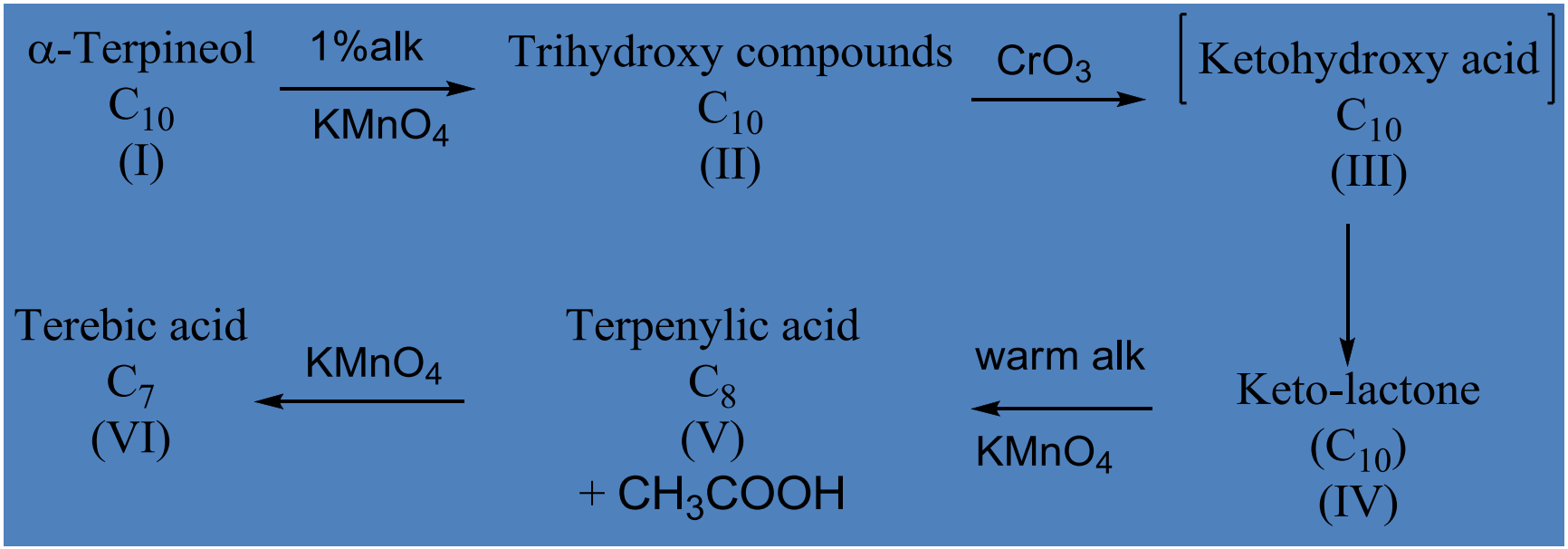
α-Terpineol



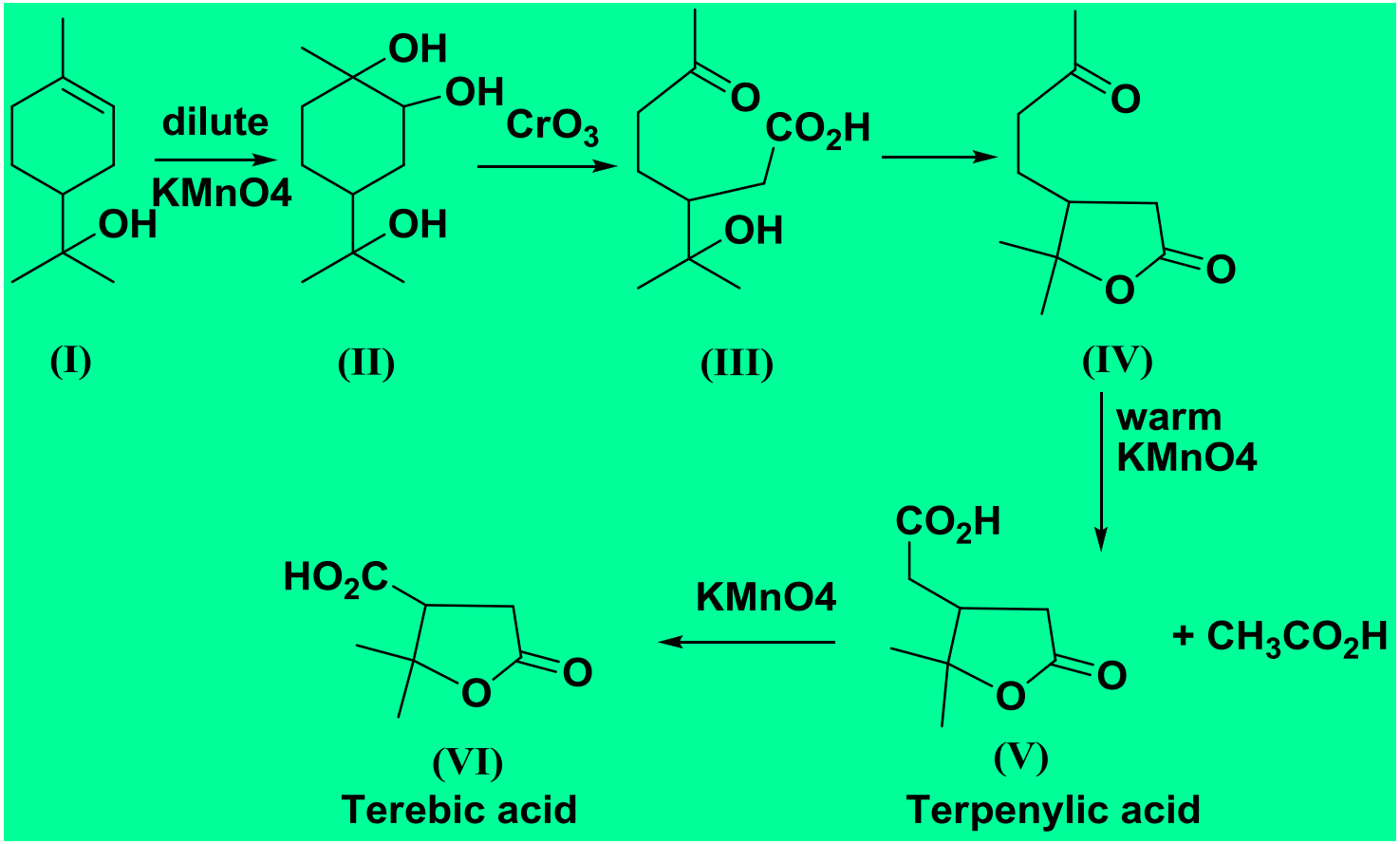
- *1- Molecular formula $C_{10}H_{18}O$.*
- *2- This is an optically active monoterpenoid, and the oxygen atom is shown to be present as a tertiary alcoholic group.*
- *3- α-Terpineol adds on two bromine atoms, thus it contains one double bond. Thus the parent hydrocarbon of α-terpineol has the molecular formula C10H20. This corresponds to CnH2n, the general formula of the (monocyclic) cycloalkanes, and so it follows that α- terpineol is a monocyclic compound.*

4- *When heated with sulphuric acid, α-terpineol forms some p-cymene. Thus, α-terpineol contains the p-cymene skeleton, i.e. it is probably p-menthane with one double bond and a tertiary alcoholic group.*

5- *The positions of the functional groups in α-terpineol were ascertained by graded oxidation.*

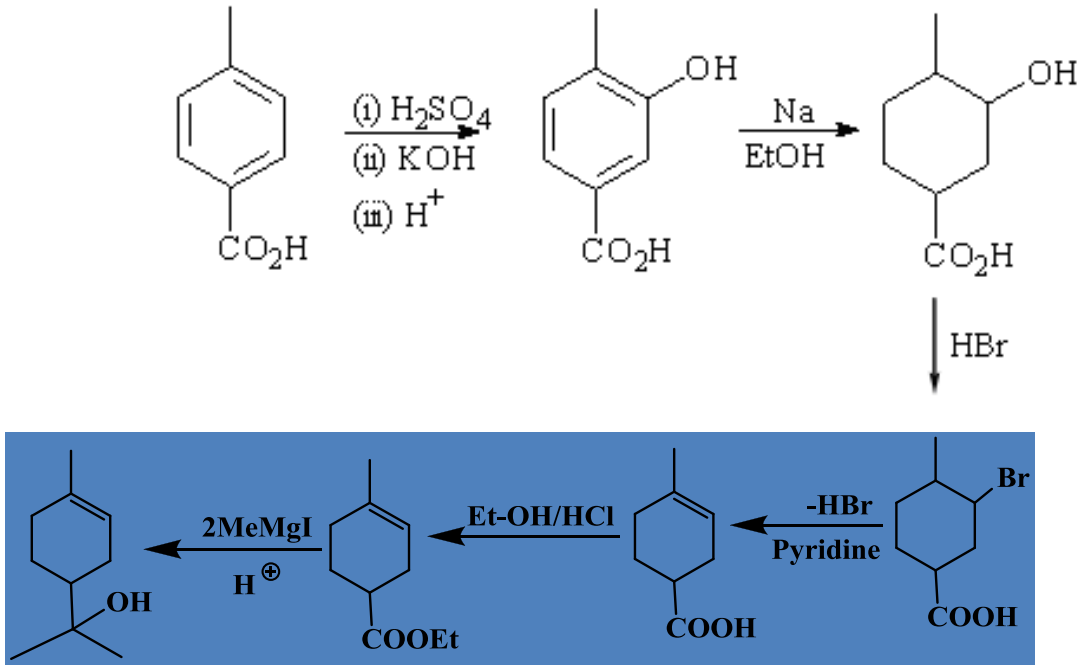


6- *The above reaction sequence can be explained as follows:*

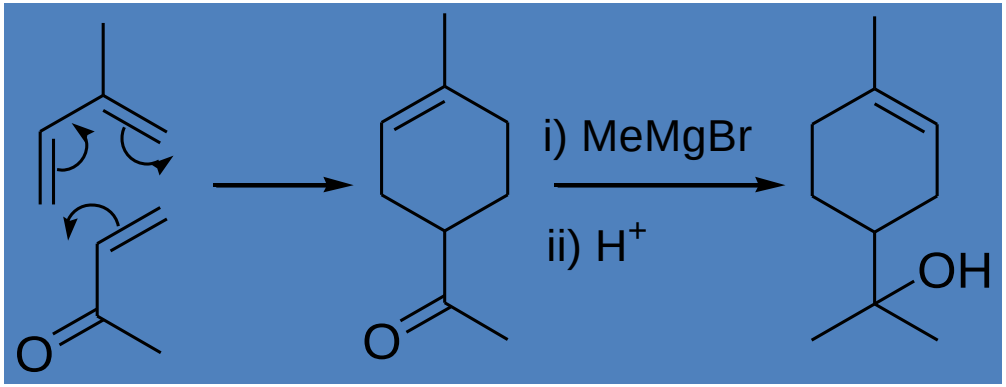


- **Synthesis of α-terpineol starts with *p*-toluic acid:**

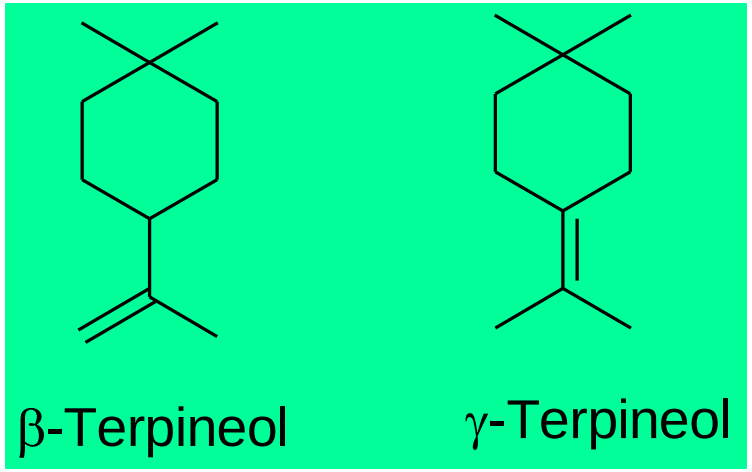
The synthesis of α-terpineol has been carried out by Perkin, jr with Meldrum and Fisher (1908) starting with *p*-toluic acid.

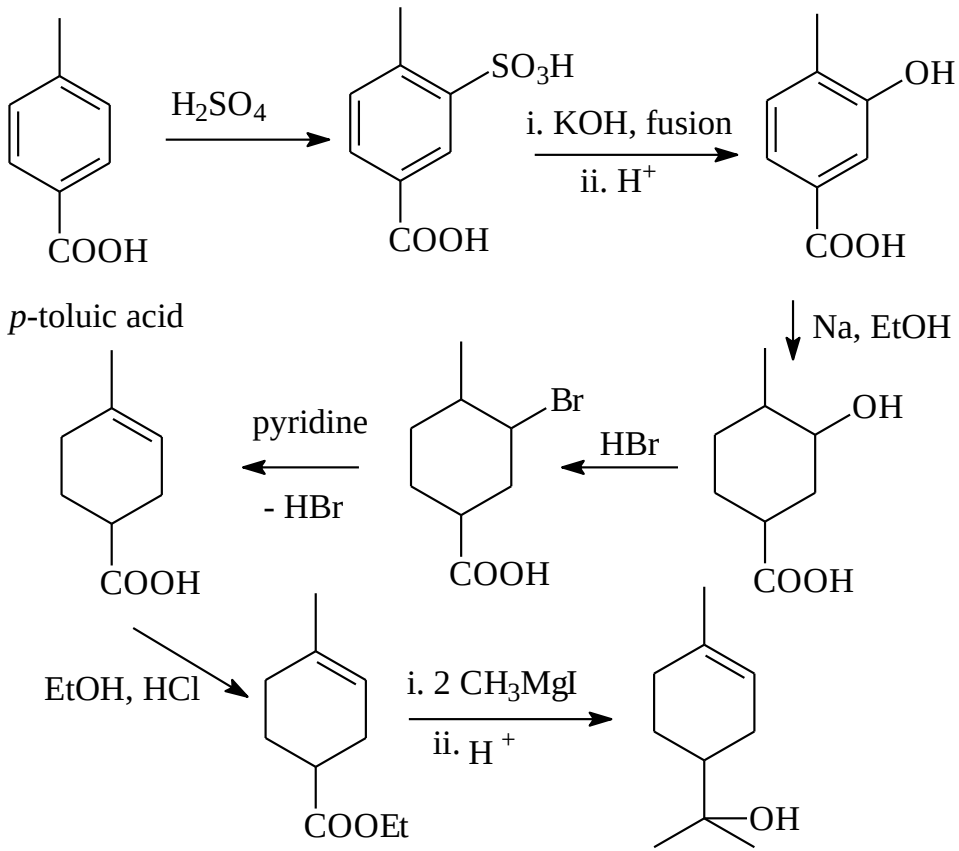


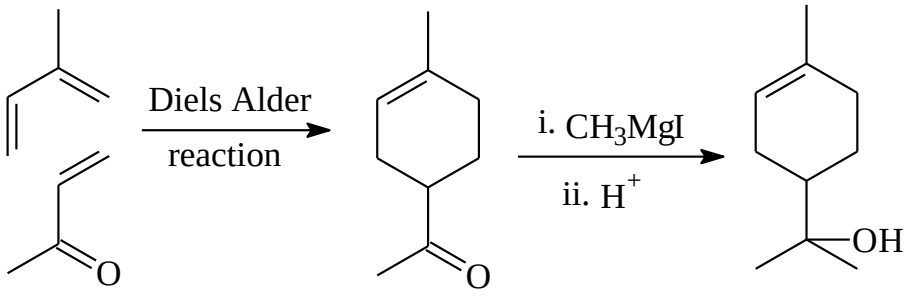
7- Finally the structure assigned for α-terpineol was confirmed by its synthesis via Diels-Alder reaction, using isoprene and methyl vinyl ketone as the starting materials.



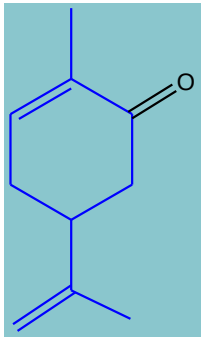
Two other terpineols are also known: β- and γ-terpineols




H_2SO_4
SO_3H
COOH
i. KOH, fusion
ii. H^+
OH
COOH
p-toluic acid
Na, EtOH
pyridine
- HBr
Br
HBr
OH
COOH
COOH
COOH
EtOH, HCl
i. 2 CH_3MgI
ii. H^+
COOEt
OH

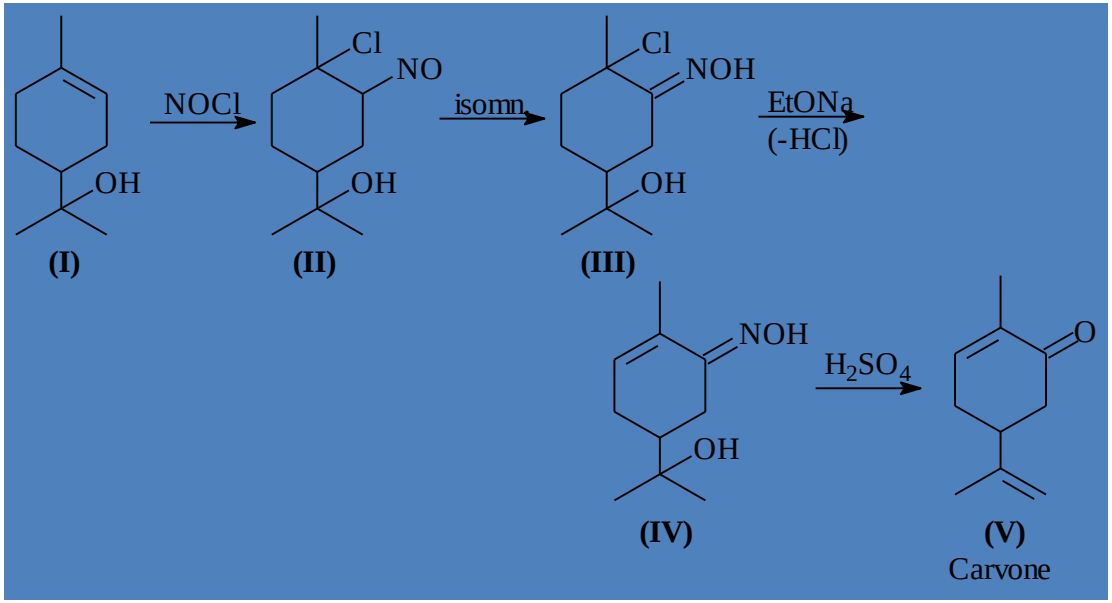

Diels Alder
reaction
O
i. CH_3MgI
ii. H^+
O
OH

Carvone



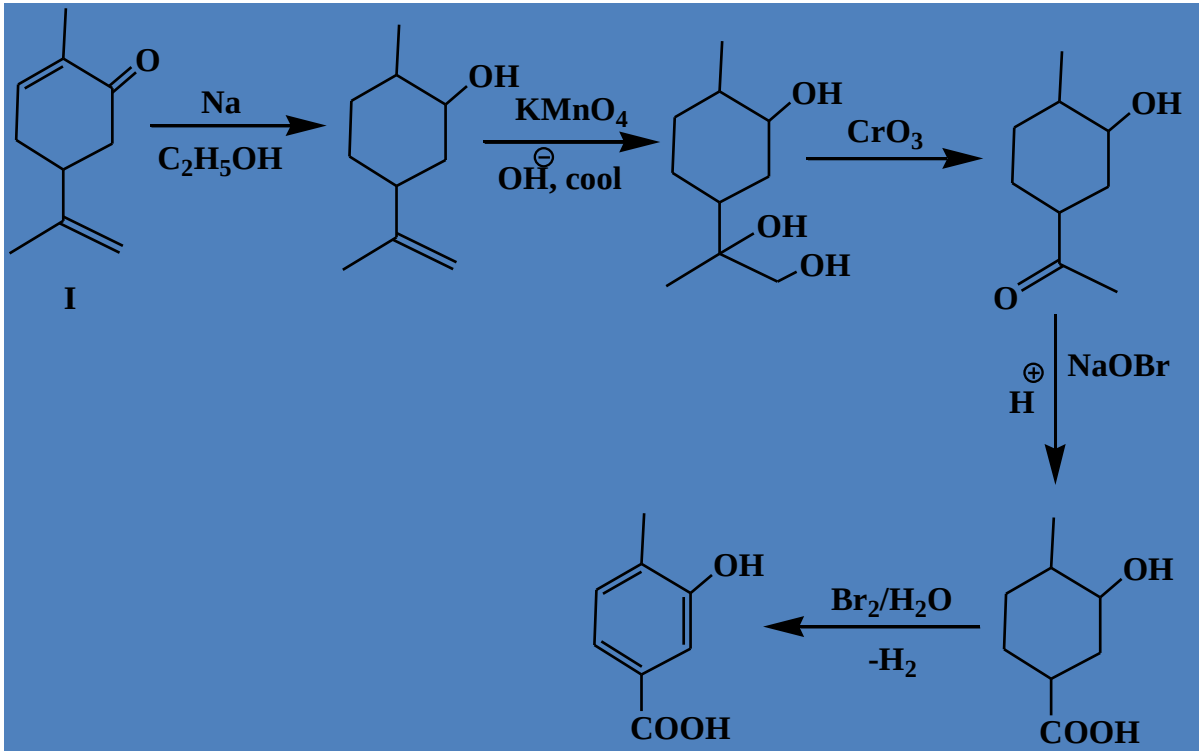
1. Carvone, $C_{10}H_{14}O$, b.p. 230°C/755 nm.
2. **IUPAC name** is *p*-menth-6,8(9)-dien-2-one.
3. It contains functional carbonyl group; therefore it behaves ketone reactions.
4. It adds four bromine atoms (2 molecules) i.e. carvone contans two double bonds.

- The structure of carvone is largely based on the fact that carvone may be prepared from α-terpineol as follows:

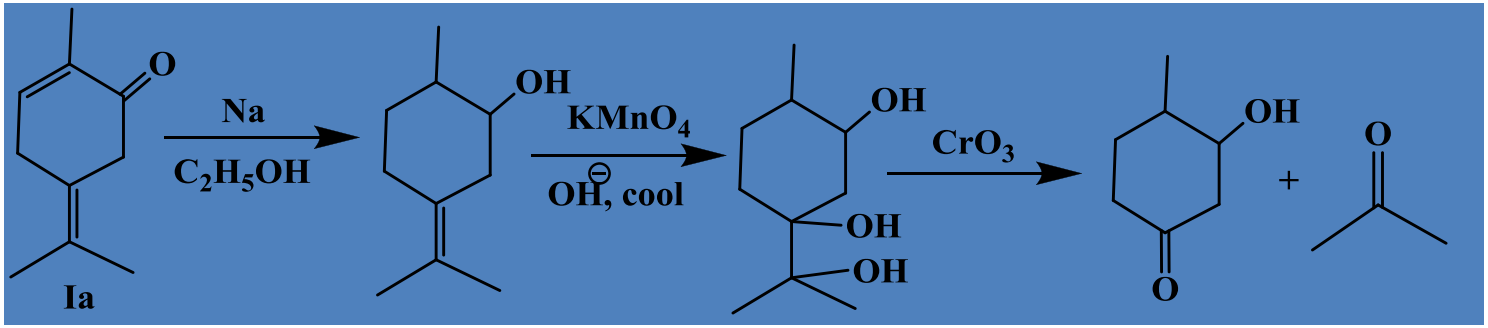


Proof of double bond in position 8

By Tiemann-Semmler reaction as follows:

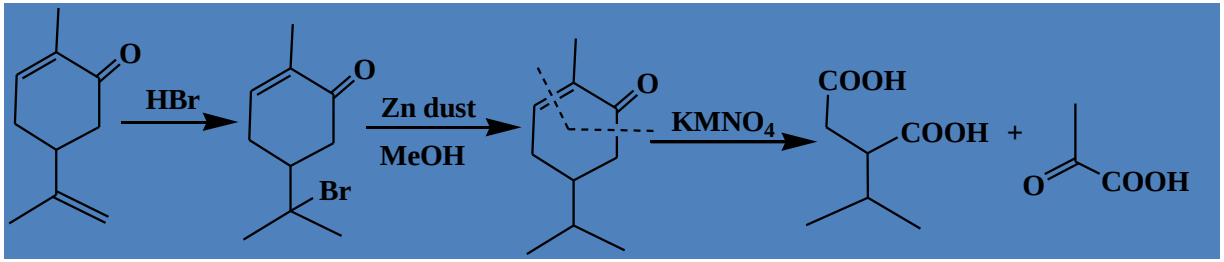


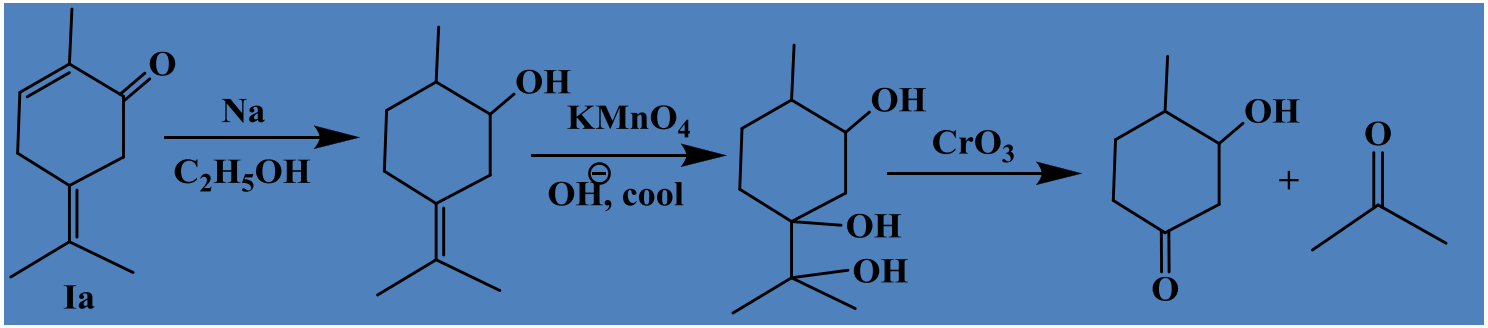
Proof that double bond in position 4(8)



- This suppose is cancelled due to the compound I is unsymmetric but the compound Ia is symmetry therefore it doesn't appear optically active hence the carvone is known opticaly active.

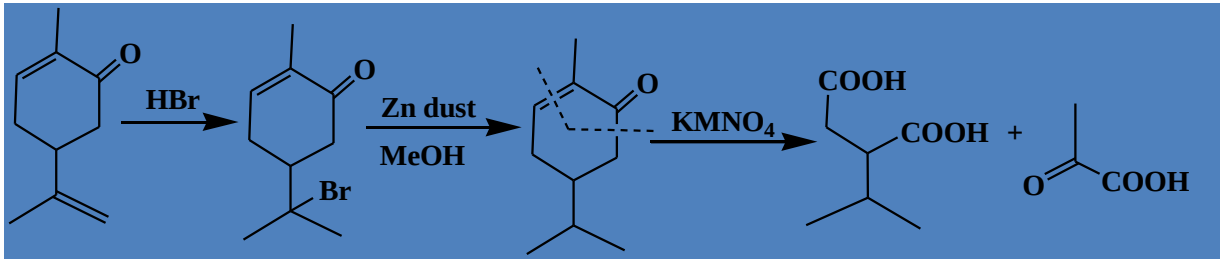
- **Proof that the second double bond in position 6 or 1(6)**





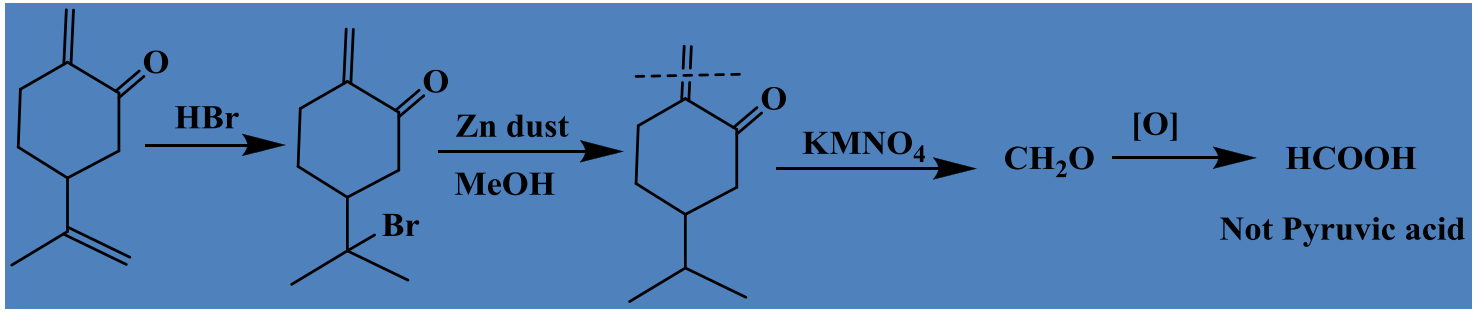
- This suppose is cancelled due to the compound I is unsymmetric but the compound Ia is symmetry therefore it doesn't appear optically active hence the carvone is known opticaly active.

- **Proof that the second double bond in position 6 or 1(6)**



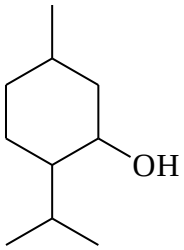
Proof that the second double bond in position 1(7)

- This suppose is cancelled due to formation of formic acid not pyruvic acid as cited before if the double bond is 1(6) and supported by UV and NMR.

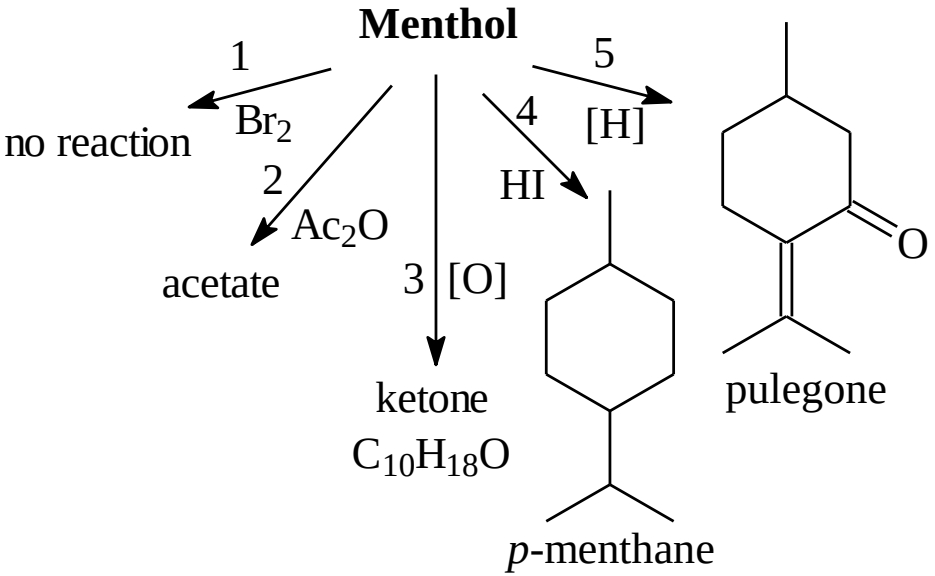


المحاضرة الخامسة

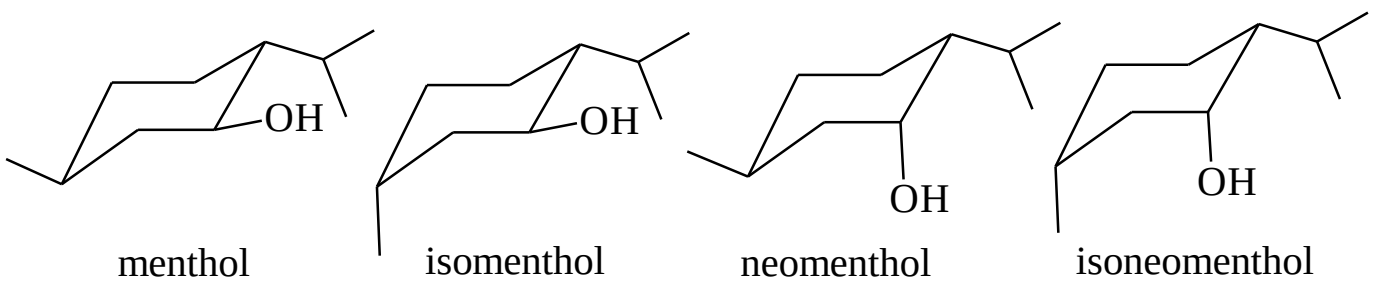
- Menthol 22

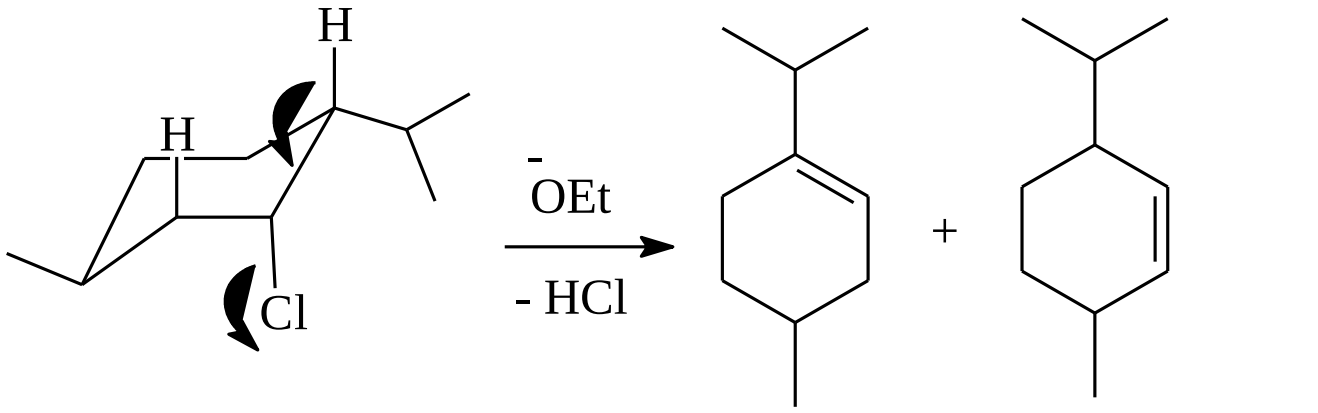


22



- **Stereochemistry of menthol**

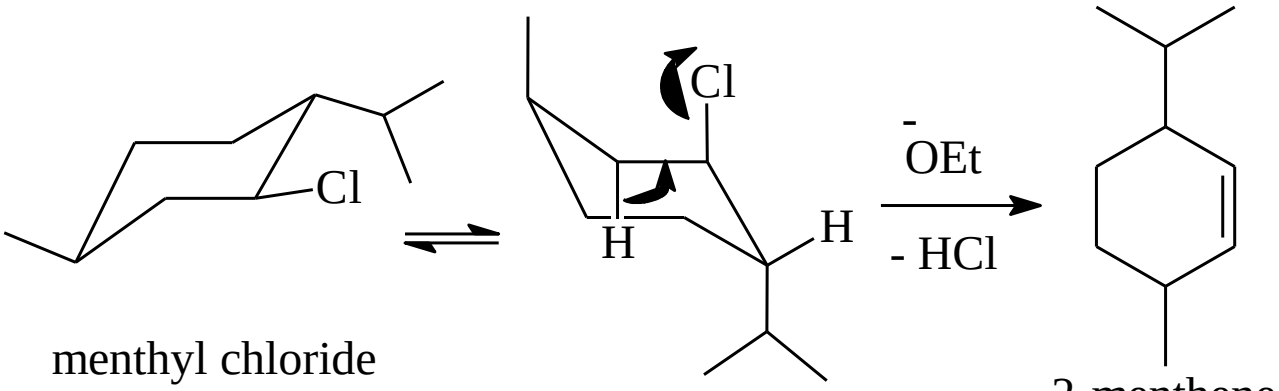




neomenthyl chloride

3-menthene, 75%

2-menthene, 25%



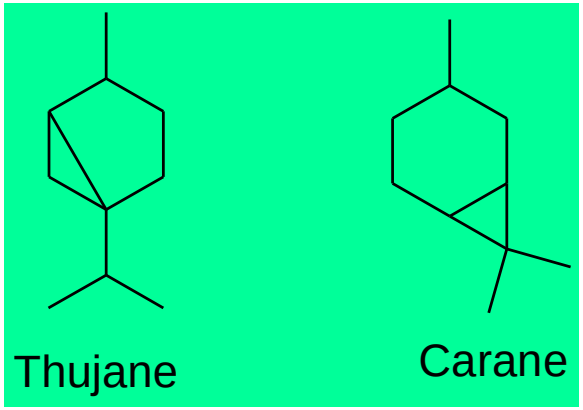
menthyl chloride

2-menthene

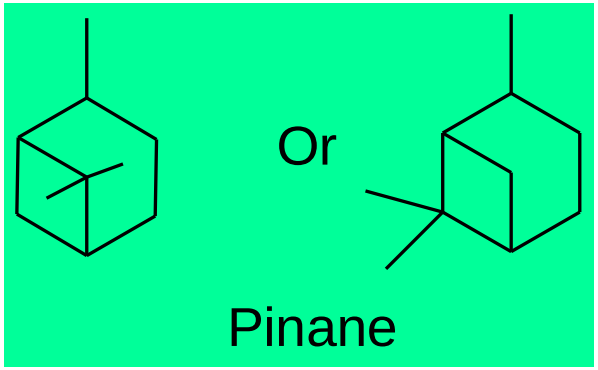
Bicyclic Monopenoids

The bicyclic monoterpenoids may be divided into three classes according to the size of the second ring, the first being a six-membered ring in each class

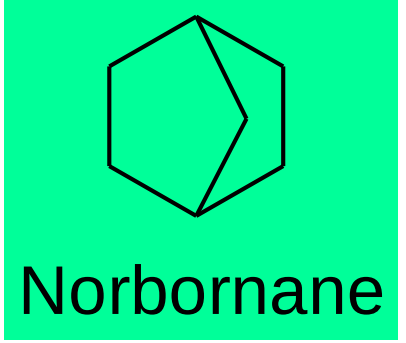
Class I (6+ 3 membered ring)



Class II (**6 +4** membered ring)

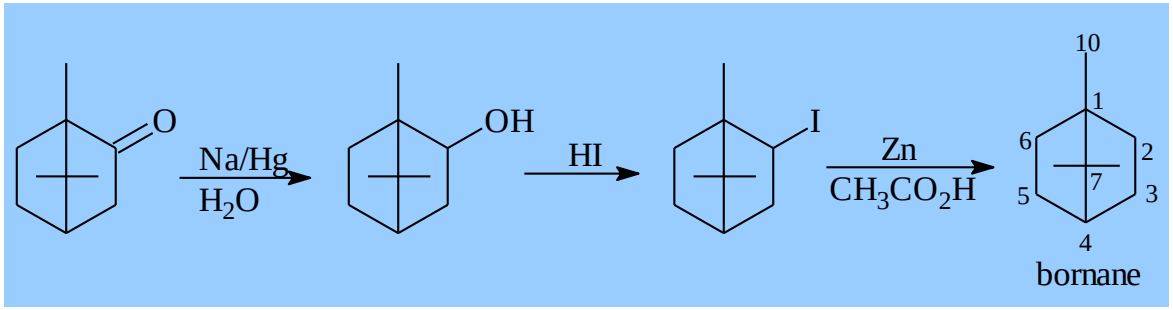


Class III(6+5 membered ring)

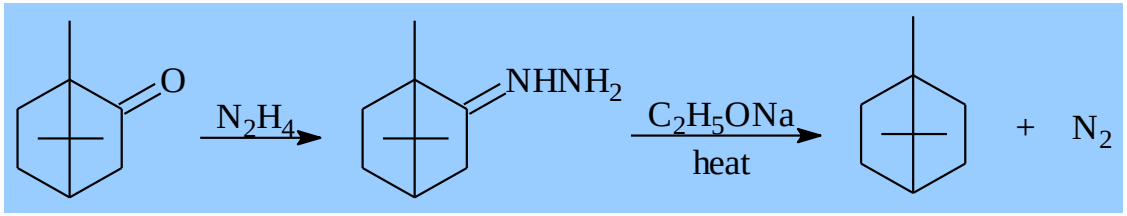


- The bornane (camphene)-norbornane (isocamphane) group

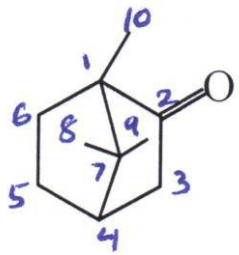
- Bornane is solid, m.p. 156°C; it is optically inactive.
- Bornane (camphene), $C_{10}H_{18}$. This is a synthetic compound and may be prepared from camphor, e.g.,
- (i) By the reduction of camphor to a mixture of borneols, these then converted to the bornyl iodides which are finally reduced to bornane.

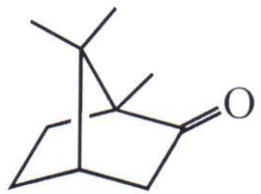


- (ii) Camphor may also be converted into bornane by means of Wolff-Kishner reduction.

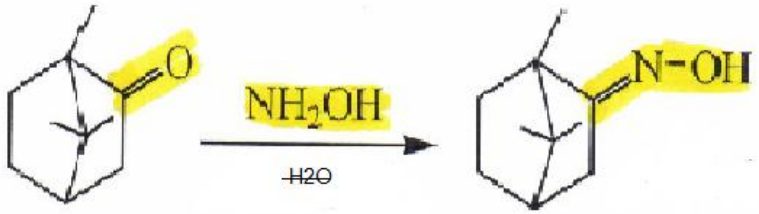


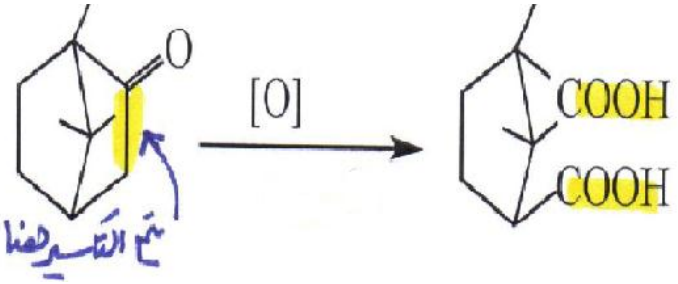
- **Camphor**



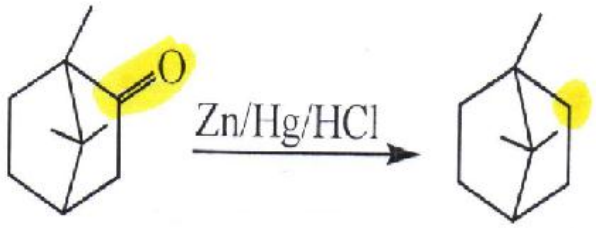


- Chemical name of Camphor
- 1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one
- **Camphor.** This occurs in nature in the camphor tree of Formosa and Japan. It is a solid, mp. 180°C, and is optically active.
- Camphor $C_{10}H_{16}O$ and is saturated compound.
- Oxygen the functional group in camphor is oxo (C=O) therefore its formed oximes and oxidation produce acid dicarboxyl not mono carboxyl i.e. not contains aldehydic group.

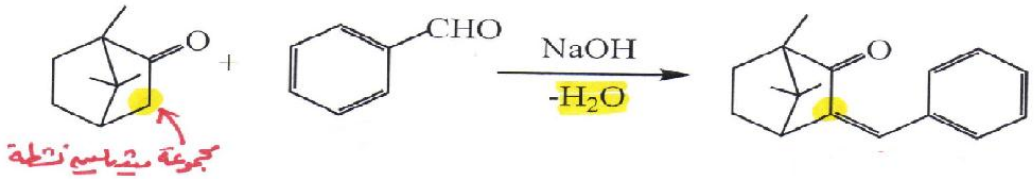




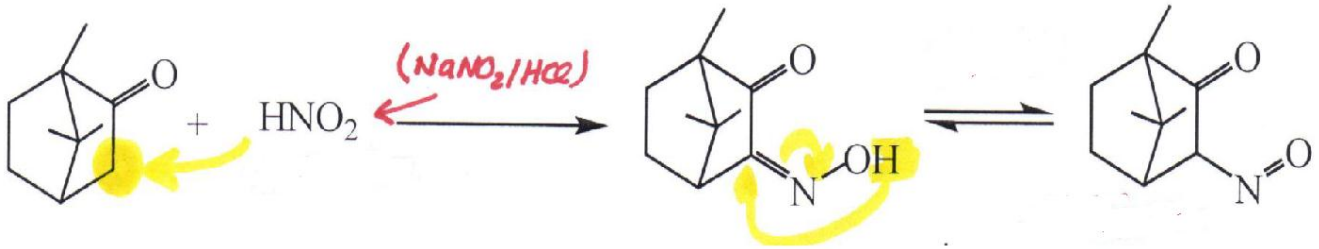
- Reduction of camphor gave camphane (Bornane) which has molecular formula $C_{10}H_{20}$ (C_nH_{2n-2}); this means camphor is bicyclic.



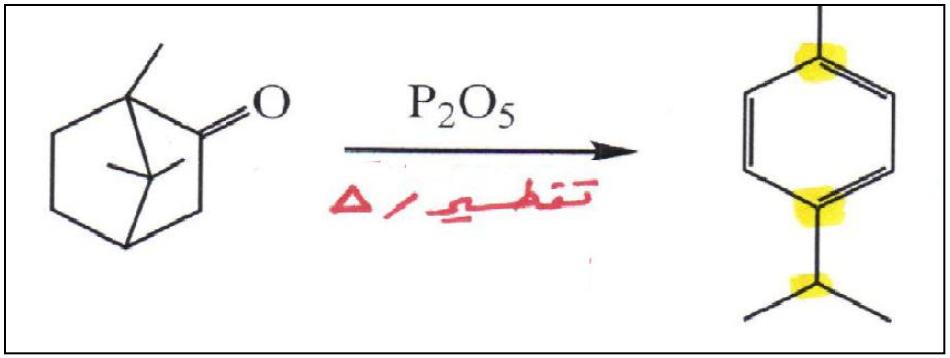
- Camphor reacts with benzaldehyde in basic media to give benzylidene compound, this means that the carbonyl group neighbering one active methylene group



- Also, camphor reacts with nitrous acid to give iso nitroso compound, this means that the presence of active methylene group.

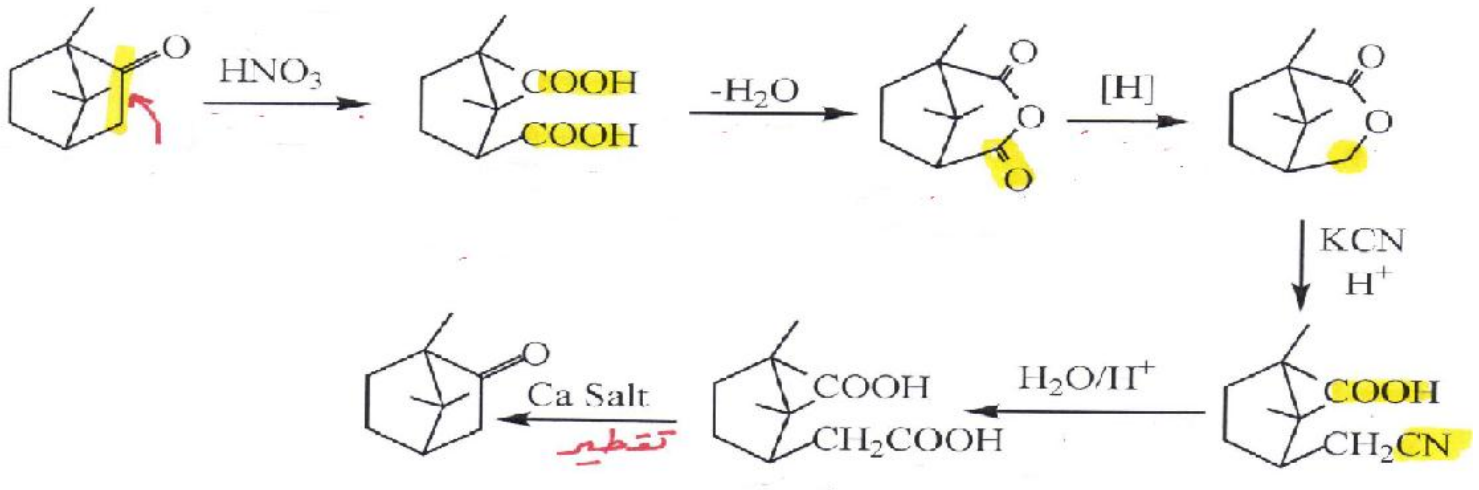


- Heating of camphor with P2O5 gave p-cymene, this means that camphor has six-member ring and position of fused with other ring in 1,4 due to the substitution of p-cymene structure in 1,4 position.

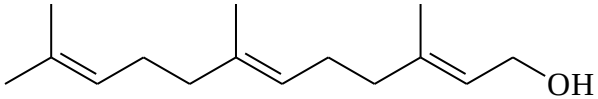


- **Synthesis of camphor (Haller, 1896).**

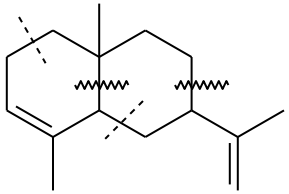
Haller started with camphoric acid prepared by the oxidation of camphor, but since the acid was synthesized later by Komppa, we now have a total synthesis of camphor.



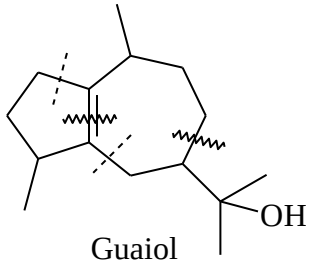
- Sesquiterpenes



Farnesol
occurs in oil of ambrette seeds

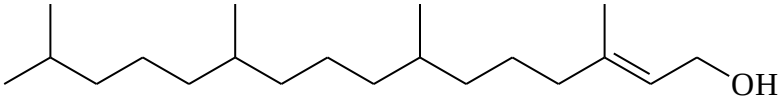


α-Selinene
occurs in celery oil

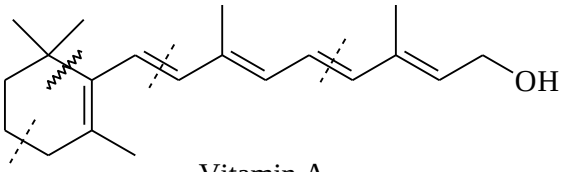


Guaiol
occurs in guaicum wood oil

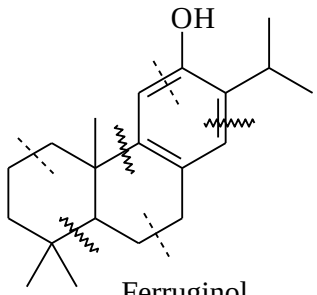
- Diterpenes



Phytol
is produced from hydrolysis of chlorophyll

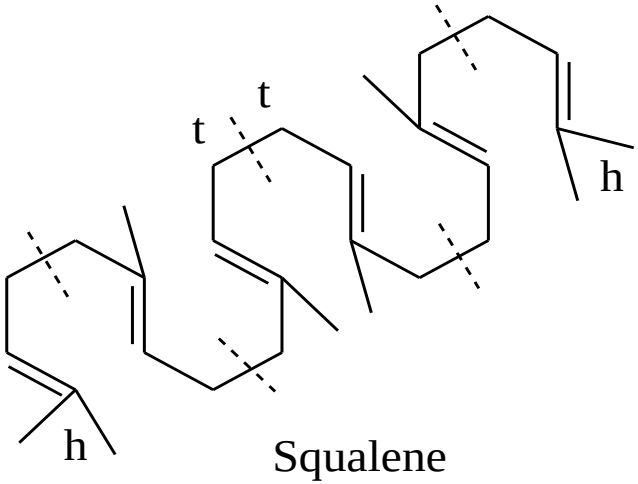


Vitamin A
occurs in carrot

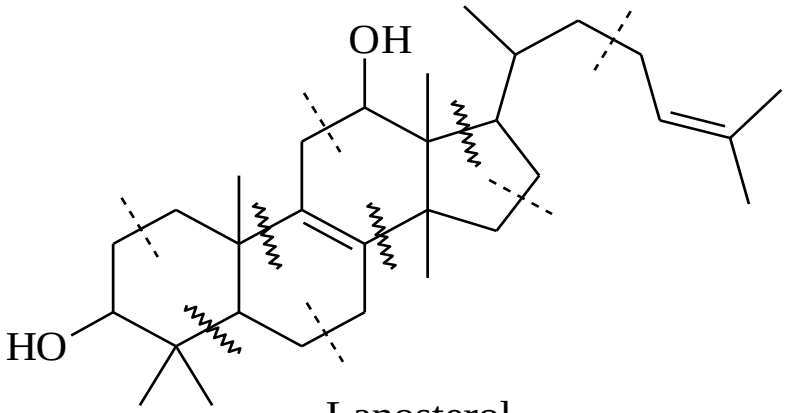


Ferruginol
occurs in *Podocarpus ferrugineus*

- Triterpenes

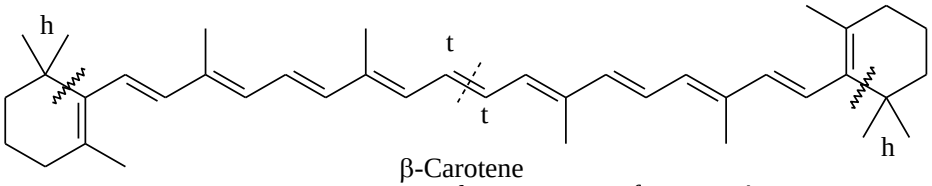


Squalene
occurs in olive oil



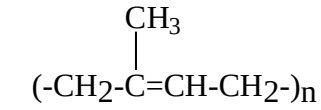
Lanosterol

- Tetraterpenes



β-Carotene
occurs in carrot, it is the precoursor of vitamin A

- Polyterpenes



Polyisoprene, natural rubbe

المحاضرة السادسة

STEROIDS

The important class of lipids called **steroids**

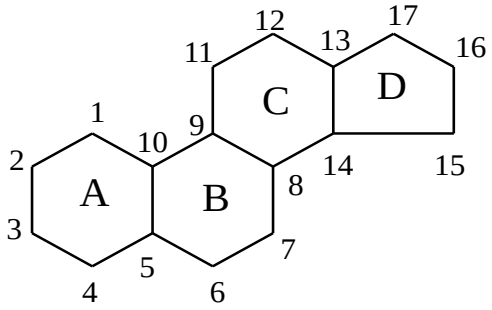
- Steroids may be recognized by their tetracyclic skeleton, consisting of three fused six-membered and one five-membered ring, as shown in the diagram to the right. The four rings are designated A, B, C & D as noted below. The substituents designated by R are often alkyl groups, but may also have functionality.

- The most common locations of functional groups are C-3, C-4, C-7, C-11, C-12 & C-17. Ring A is sometimes aromatic.

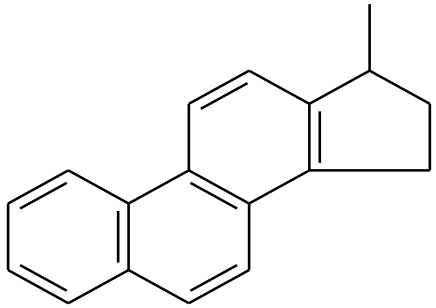
- Steroids are solid alcohols that are widely distributed in animal and plant kingdoms. The basic skeleton consists of 17 carbon atoms arranged in the form of perhydrocyclopentenophenanthrene.

Steroids

- Steroids (Gk., stereos = solid) are solid alcohols that are widely distributed in the animal and plant kingdoms. The basic skeleton consists of 17 carbon atoms arranged in the form of a perhydro-cyclopentenophenathrene 25. A steroid could be defined, in another way, as any compound which gives Diel's hydrocarbon 26 when distilled with selenium.

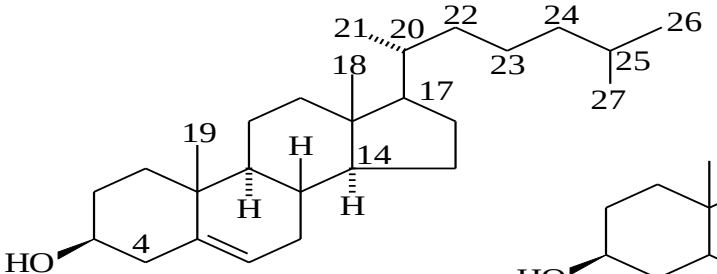


steroid nucleus 25

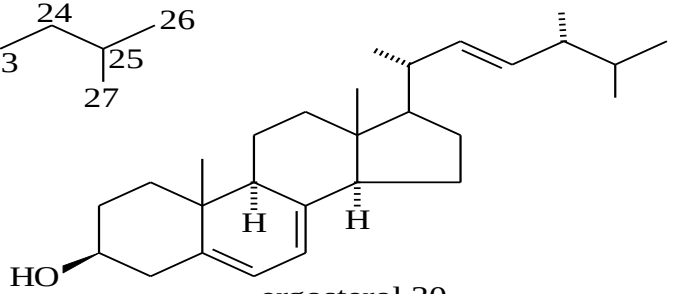

Diel's hydrocarbon 26

- **Classes of steroids**
- **Sterols**

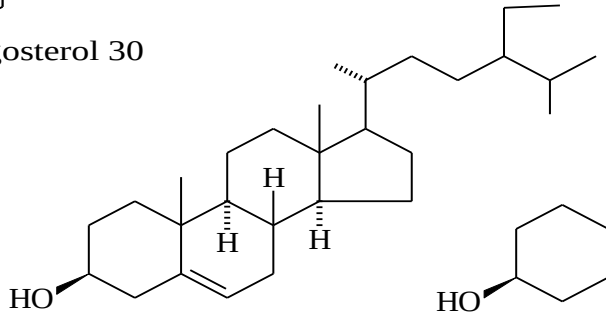
Sterols of plants are called ***phytosterols*** and sterols of animals are called ***zoosterols***. Important zoosterols are cholesterol and some steroid hormones; notable phytosterols include stigmasterol, campesterol, and sitosterol.



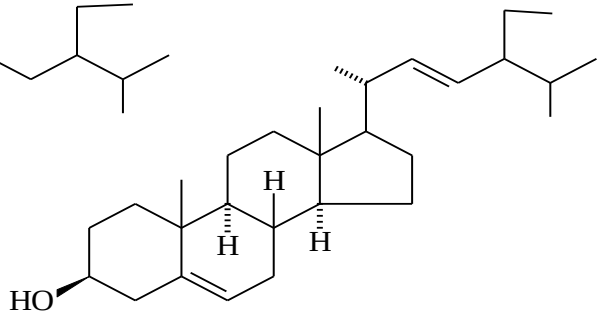
cholesterol 29



ergosterol 30

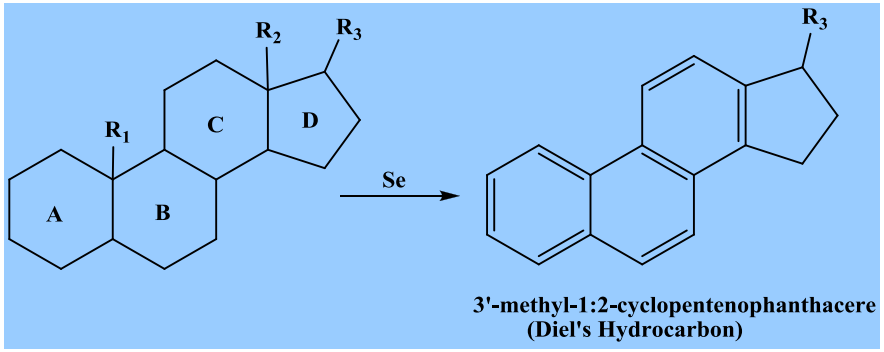


β-sitosterol 31



stigmasterol 32

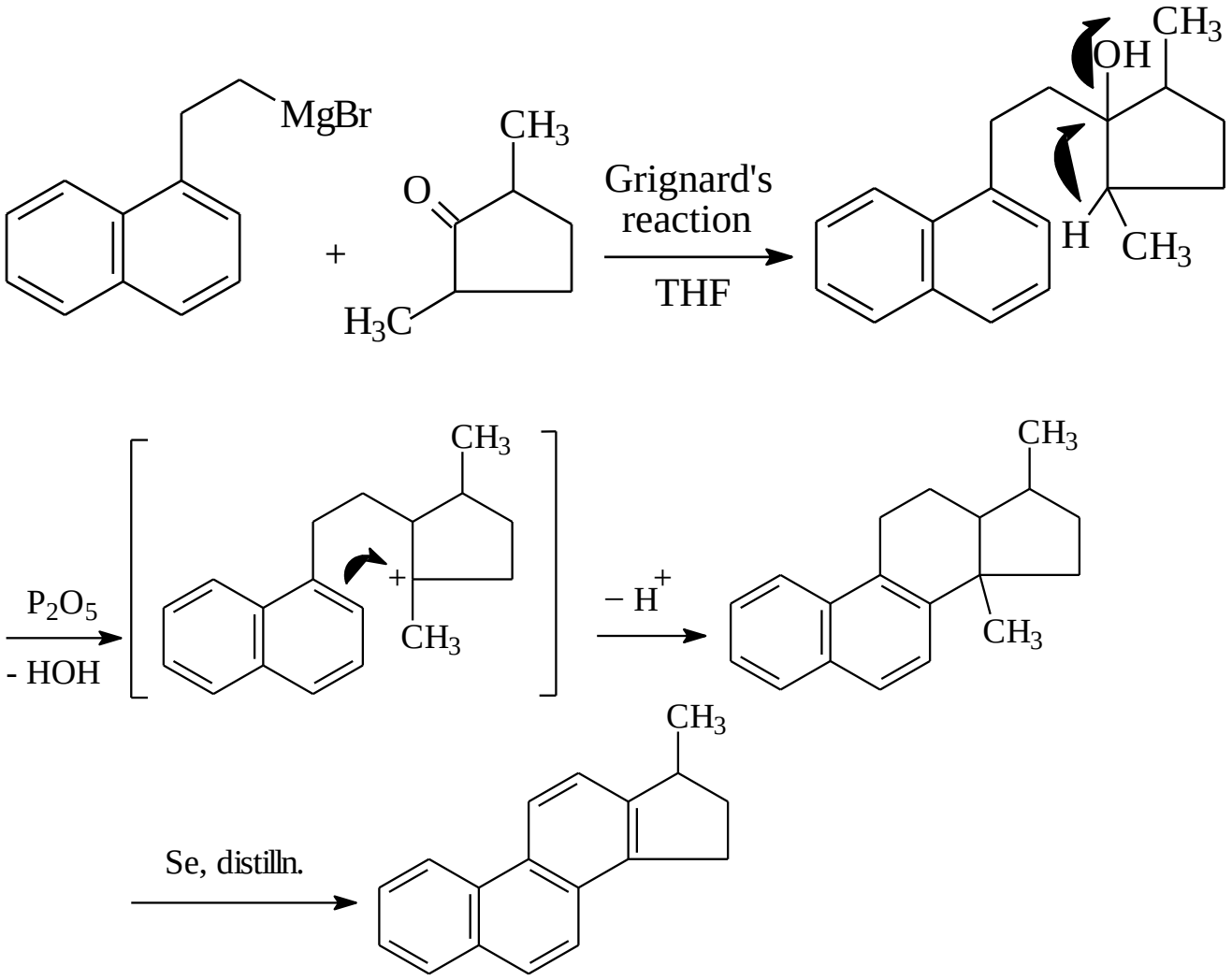
- All steroids forming Diel's hydrocrbon.
- Therefore it is possible to definition of steroids are all the compounds which forming Diel's hydrocrbon when distilled with selenium metal.



- **Diel's hyrdocarbon**

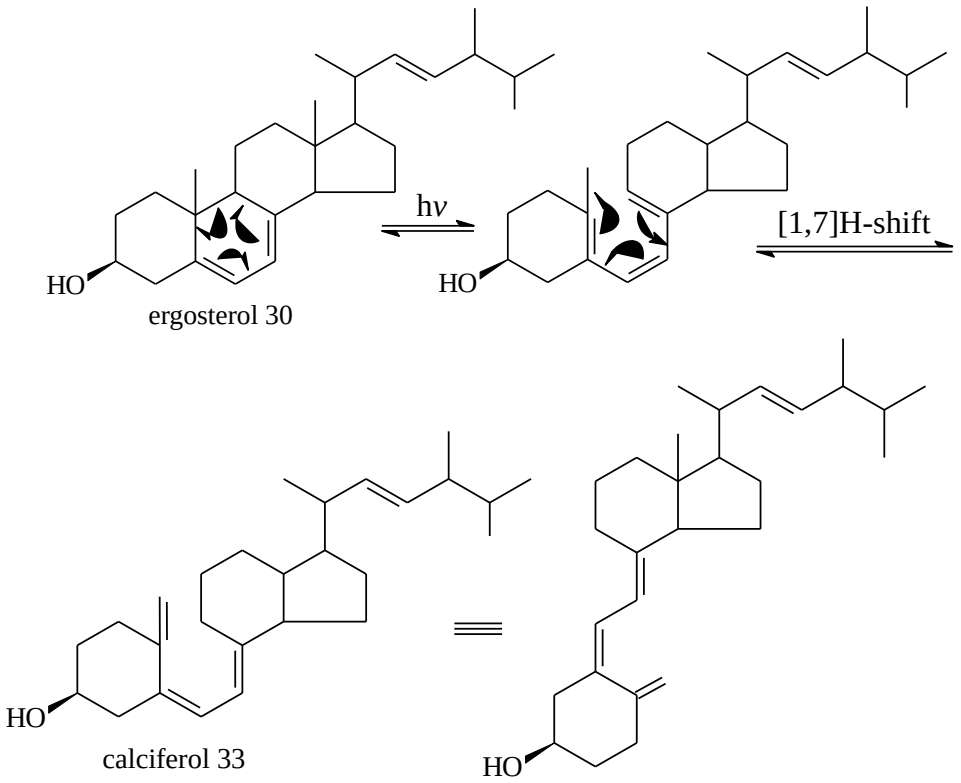
• It is a solid C18 H16 composed of hydrogen and carbon only . The structure of which was proved to be 3'-methyl-1:2-cyclopentenophenanthrene. It was established by synthesis starting from 2-(1-naphthyl)-ethyl magnesium bromide and 2,5-dimethylcyclopentanone as indicated by the following scheme:

- **Diel's hydrocarbon**
- 3’-methyl-1:2-cyclopentenophenanthrene 26

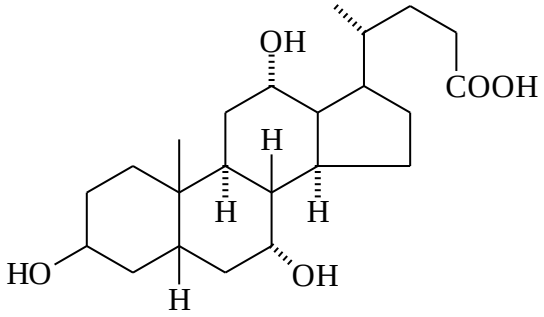


Diel's hydrocarbon 26

- **Vitamine D group**
- · they are about seven compounds (Vitamin D1 - D7) with the ring B being opened. Vitamin D2 33 (or calciferol) is formed from ergosterol 30 by the sunlight irradiation.

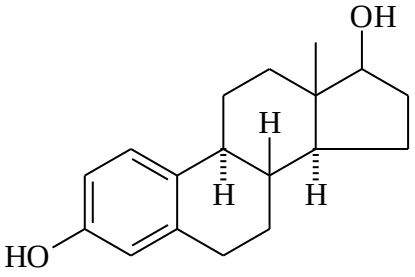


- **Bile acids**
- are isolated from the bile of various animals



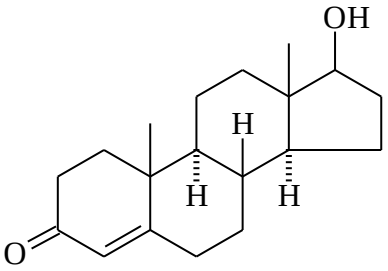
cholic acid 34

- **Sex hormones**
- *Estrogens* (female sex hormones)



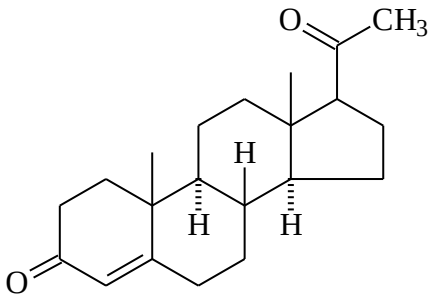
α-oestradiol 35

- *Androgens* (male sex hormones)



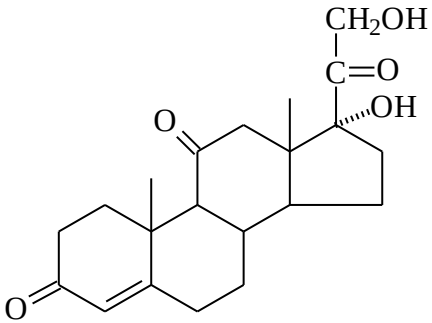
testosterone 36

- *Gestogens*
- hormones which are responsible for the maintenance of pregnancy



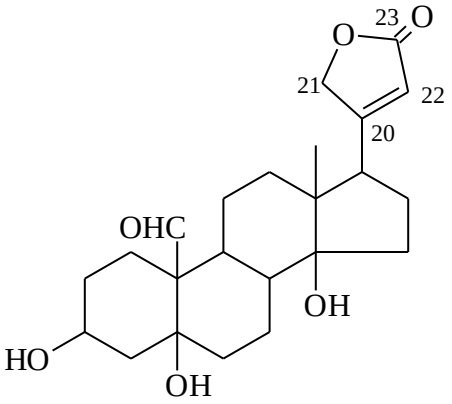
progestrone 37

- **Adrenocortical hormones**
- produced by the cortex of the adrenal glands



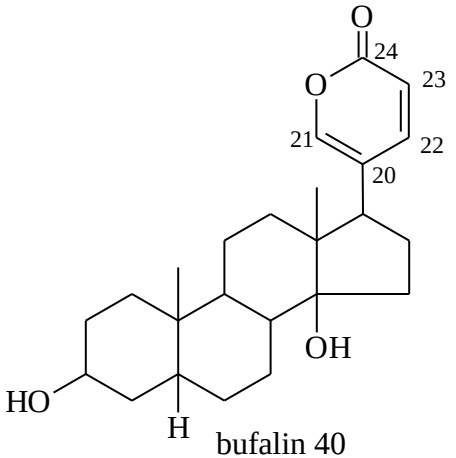
cortisone 38

- **Cardenolides**
- Cardiac glycosides have powerful cardiotonic activity and can be used for treatment of some heart diseases



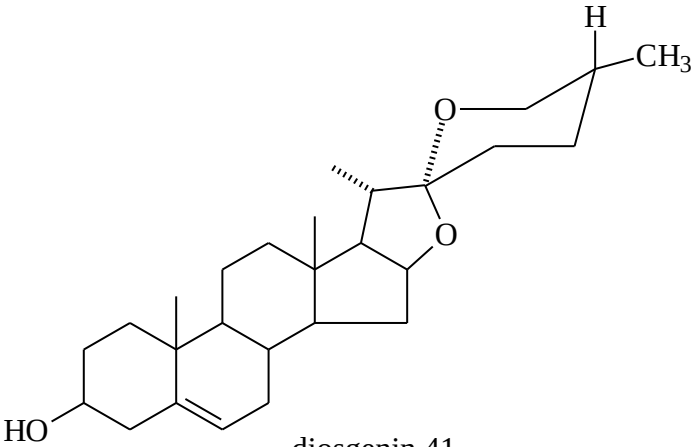
strophanthidin 39

- **Bufadienolides**
- present in the toad venoms secreted from the parotid glands and also some of these compounds were isolated from plants



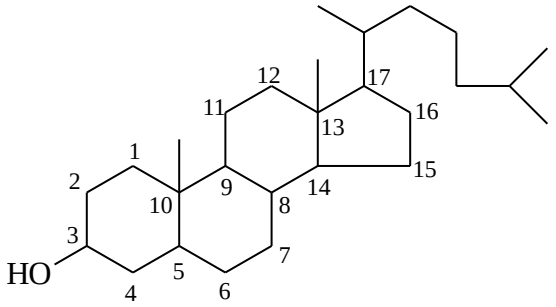
bufalin 40

- **Sapogenins**
- are the aglycones of saponins (named spirostane)

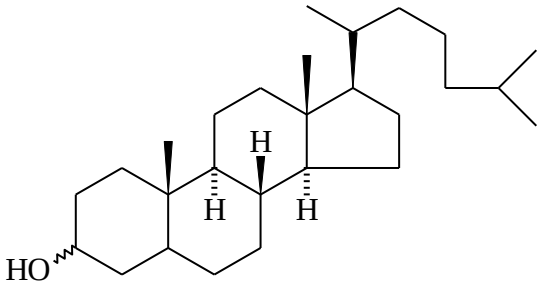


diosgenin 41

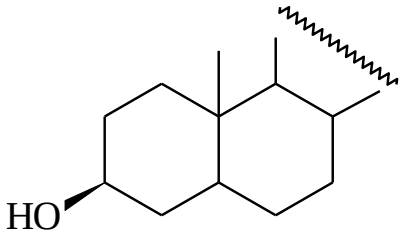
- **Stereochemistry of the steroid nucleus**
- there are eight dissimilar chiral centers in the nucleus (3,5,8,9,10,13,14 and 17). Thus there are 2^8 = 256 possible optical isomers



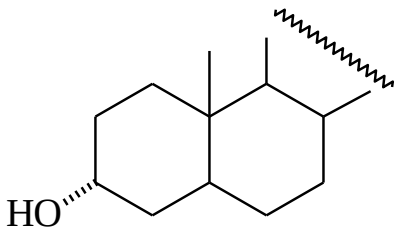
- In most naturally occuring sterols the configuration at C-8, C-9, C-10, C-13, C-14 and C-17 is definite, i.e. does not change from one molecule to the other



- Concerning the 3-OH group, the majority of the sterols have the 3-OH configuration

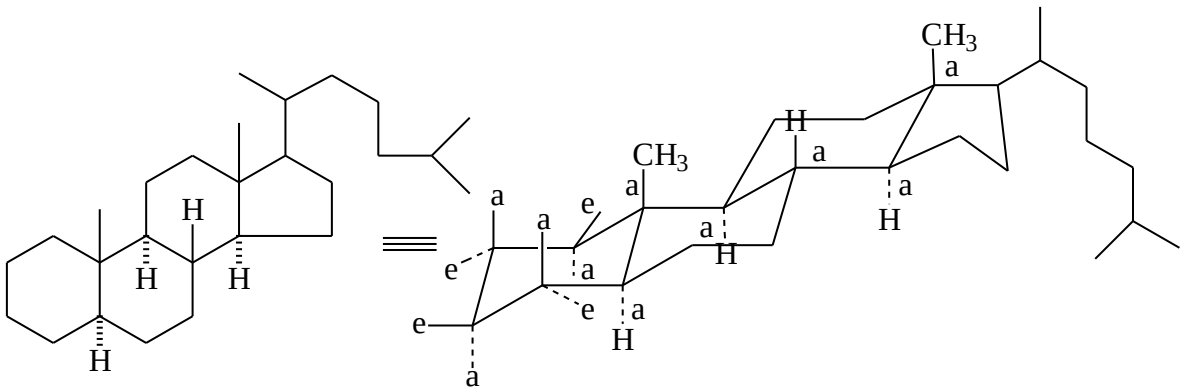


3 β-OH

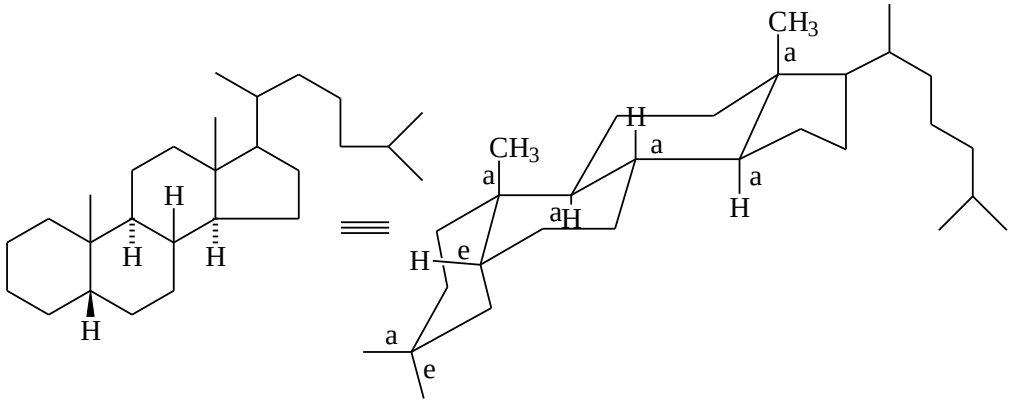


3 α-OH

- In cholestane there are two series according to the configuration at C-5; the 5-cholestane (named cholestane) and the 5-cholestane (named coprostane).
- <u>Cholestane series</u>



- Coprostane series



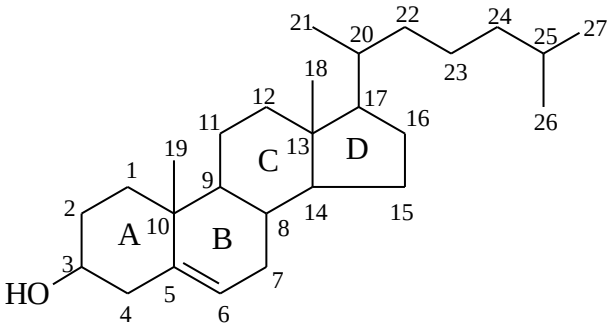
- ***Conformational Analysis of Steroids***

position	5 α-series		5 β-series	
	α-config.	β-config.	α-config.	β-config.
1	a	e	e	a
2	e	a	a	e
3	a	e	e	a
4	e	a	a	e
5	a^{AB}			$e^{B}a^{A}$
6		a^{AB}		$a^{B}e^{A}$

المحاضرة السابعة

Structure elucidation of some steroids by chemical methods

- · Cholesterol 29



29

- · characteristic features :-
- i) The nucleus of cholesterol is tetracyclic composed of three six-membered rings (A, B and C) and one five-membered (D) ring.
- ii) There is a secondary OH group at C-3, and a double bond at C-5 (between C-5 and C-6).
- iii) There are two angular methyl groups at C-10 and C-13, and a saturated side-chain C_8H_{17} at C-17.

- Examination of the above formula shows the following characteristic features:

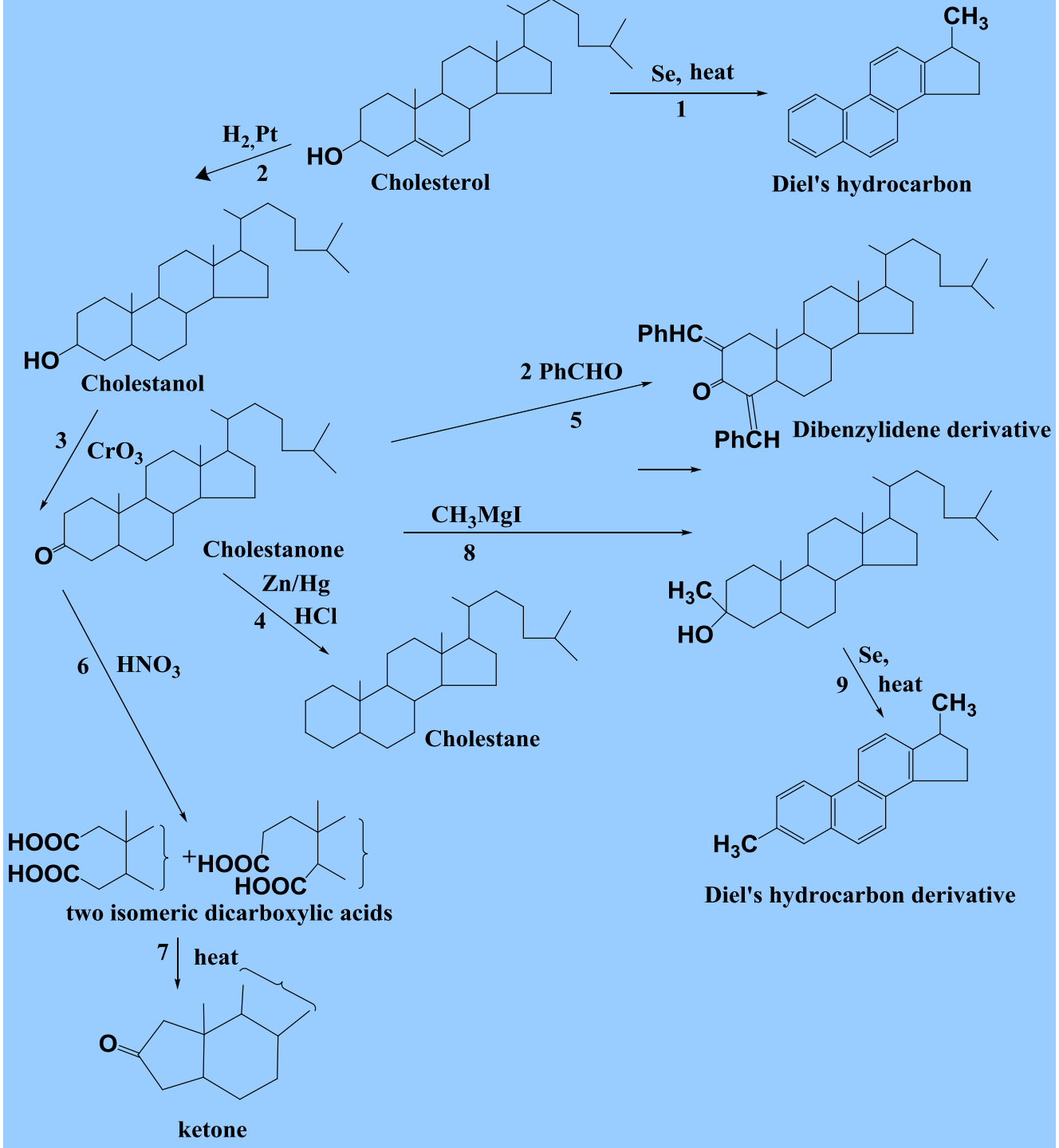
1- The nucleus of cholesterol is tetracyclic composed of three six membered rings (A,B and C) and one five memberd ring (D).

2-There is a β-secondary OH group at C-3 and a double bond at C-5 (between C-5 and C-6)

3- There are two β-angular methyl groups at C-10 and C-13 and a saturated side chain C_8H_{17} at C-17.

Structure of the ring system and functional groups:

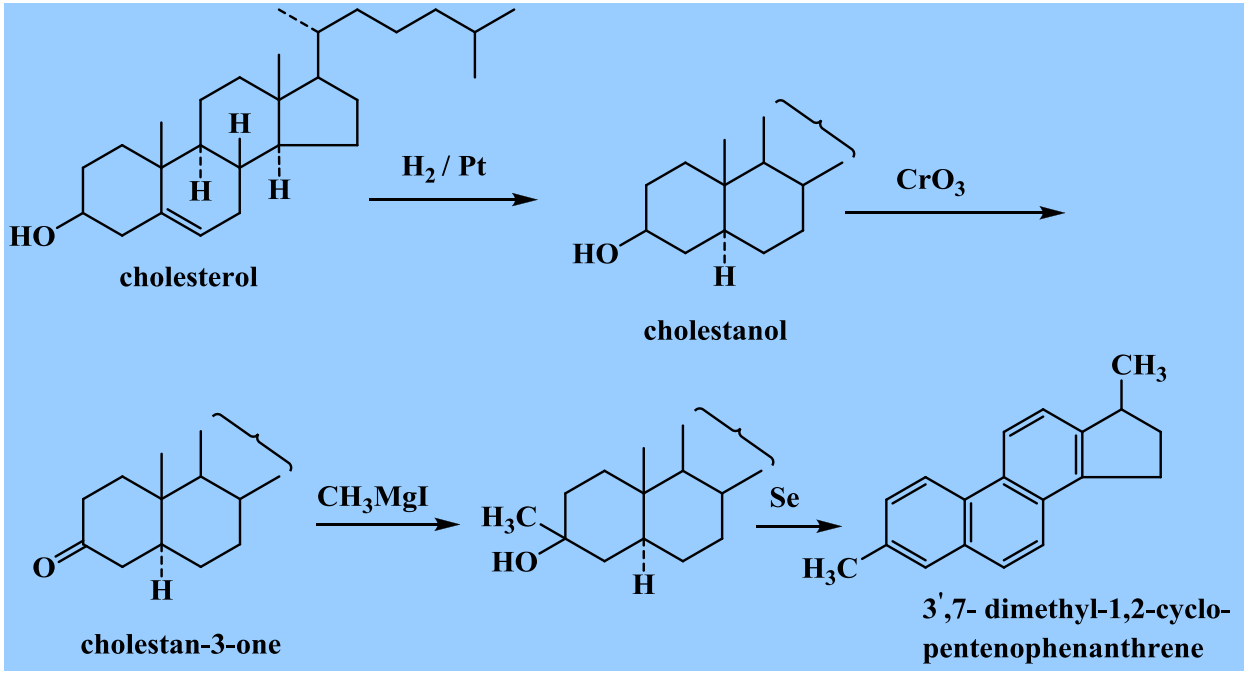
The following scheme showed the reactions which described the nature of the ring system in addition to the function groups of cholesterol


Cholesterol
Se, heat
1
Diel's hydrocarbon
H_2, Pt
2
Cholestanol
2 PhCHO
5
Dibenzylidene derivative
3
CrO_3
Cholestanone
CH_3MgI
8
Zn/Hg
4
HCl
Cholestane
6
HNO_3
Se,
heat
9
Diel's hydrocarbon derivative
two isomeric dicarboxylic acids
7
heat
ketone

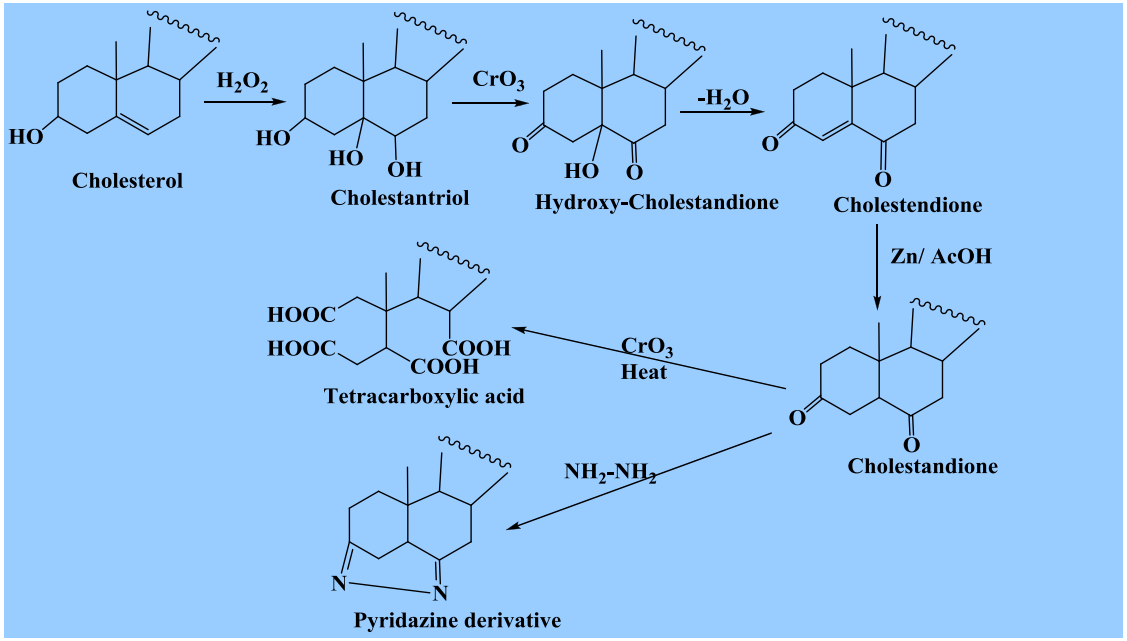
- Reaction 1 indicated Diel's hyrocarbon is the carbon skeleton in cholesterol.
- Reaction 2 indicated the presence of one double bond.
- Reaction 3 indicated OH group in the cholesterol is secondary alcohol.
- Reaction 4 indicated that the formation cholestane as saturated hydrocarbon has formula CnH2n-6 this means that cholestrol is teracyclic ring
- Reaction 5 indicate the presence of keto group (which was originally a secondary hydroxylic function) flanked by two methylene groups.
- The hydroxyl group must be located in a sex membered ring as indicated by reactions 6 and 7.
- The conversion of cholestanone to 3′,7-dimethy-cyclopentenophenanthrene (reactions 8 and 9) indicated the location of the secondary hydroxyl group at C-3 of the steroid nucleus.

The OH group at C-3

A direct proof that the hydroxyl group of cholesterol is at C-3 is furnished by its hydrogenation to cholestanol, oxidized to cholestan-3-one, this with methyl magnesium iodide give methyl carbinol, dehydrogenation by selenium to 3',7 - dimethyl-1,2-cyclopenteno phenanthrene.



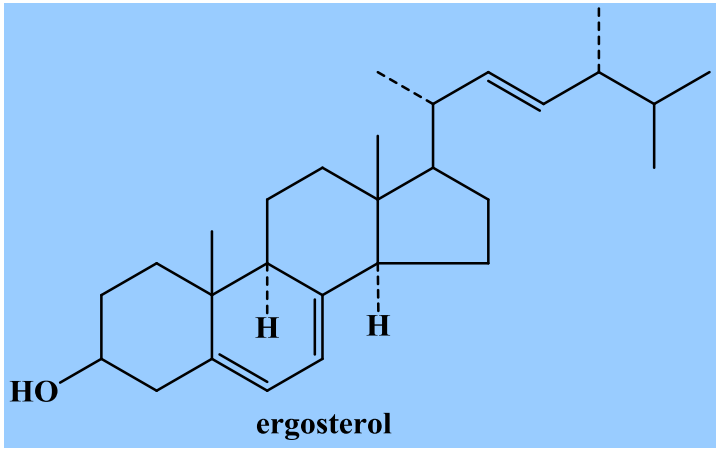
- **Determination of the position of C=C group**



- **From the previous Scheme we can conclude that:**
- **Formation of the hydroxy-cholestanedione means that the triol has one 3ry OH (not oxidizable) and two 2ry OH groups.**
- **Formation of the pyridazine derivative from cholestanedione means that two C=O in the latter are 1,4-positioned.**
- **Formation the tetracarboxylic acid without loss of C-atoms means that the two C=O groups in cholestanedione are not in the same ring but one in ring A and the second in ring B.**
- **From the above results, the C=C group can present only between C5 and C6 in cholesterol.**

phytosterol (Mycosterol)
Ergosterol: $C_{28}H_{44}O$

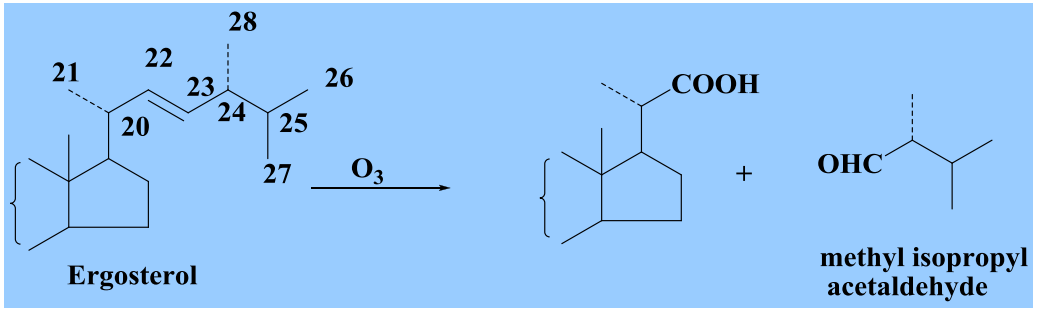
- This occurs in yeast, Ergosterol forms an esters e.g. an acetate with acetic anhydride, thus there is a hydroxyl group present in ergosterol.



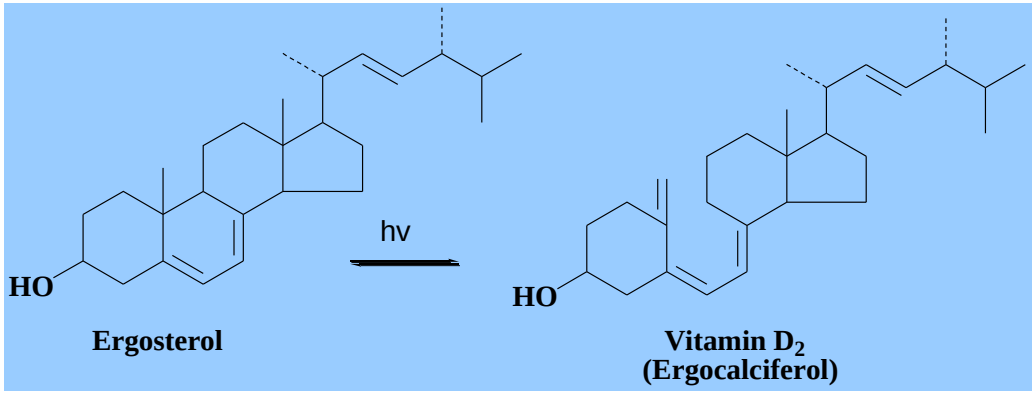
ergosterol

- Catalytic hydrogenation (platinum) of ergosterol produces ergostanol $C_{28}H_{50}O$, hence there are three double bonds in ergosterol.

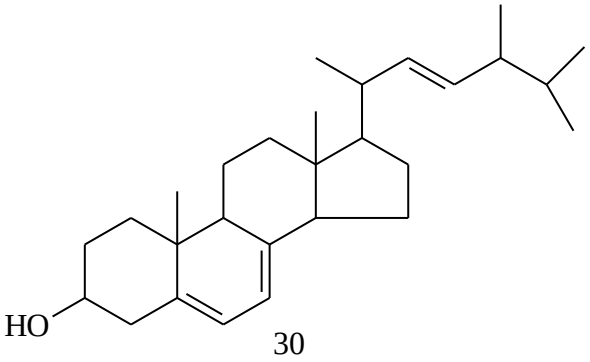
Ozonolysis of ergosterol gives, among other products, methyl isopropyl acetaldehyde which proves a methyl group at C_{24} and Δ^{22} unsaturation. The side chain must contain only one double bond, since if more than one were present, more than one fragment would have been removed on ozonolysis.



- When heated with maleic anhydride at 135°C, ergosterol forms an adduct, and so it follows that the two double bonds (in the nucleus) are conjugated.
- Now ergosterol has an absorption maximum at 282 nm. Conjugated acyclic dienes absorb in the region of 220-250
- The ultraviolet light effect on ergosterol resulted in the isolation of vitamin D_2 or ergocalciferol.



- · Ergosterol 30



Ergosterol

$C_{28}H_{44}O$

Acetylation 1 → monoacetate

CrO_3 △ 4 → acetate of 3β -hydroxy-norallo-cholanic acid

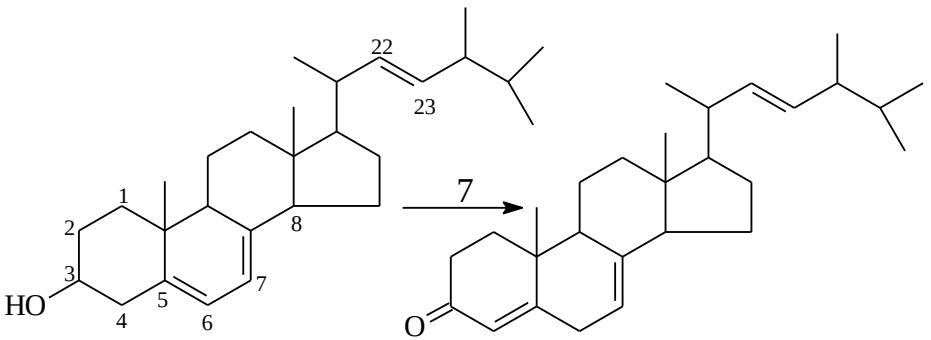
2 [O] r.t. CrO_3/Pyr → ketone

H_2/Pt 3 → ergostanol $C_{23}H_{50}O$

5 O_3 → OHC + other products

6 maleic anhydride → one adduct

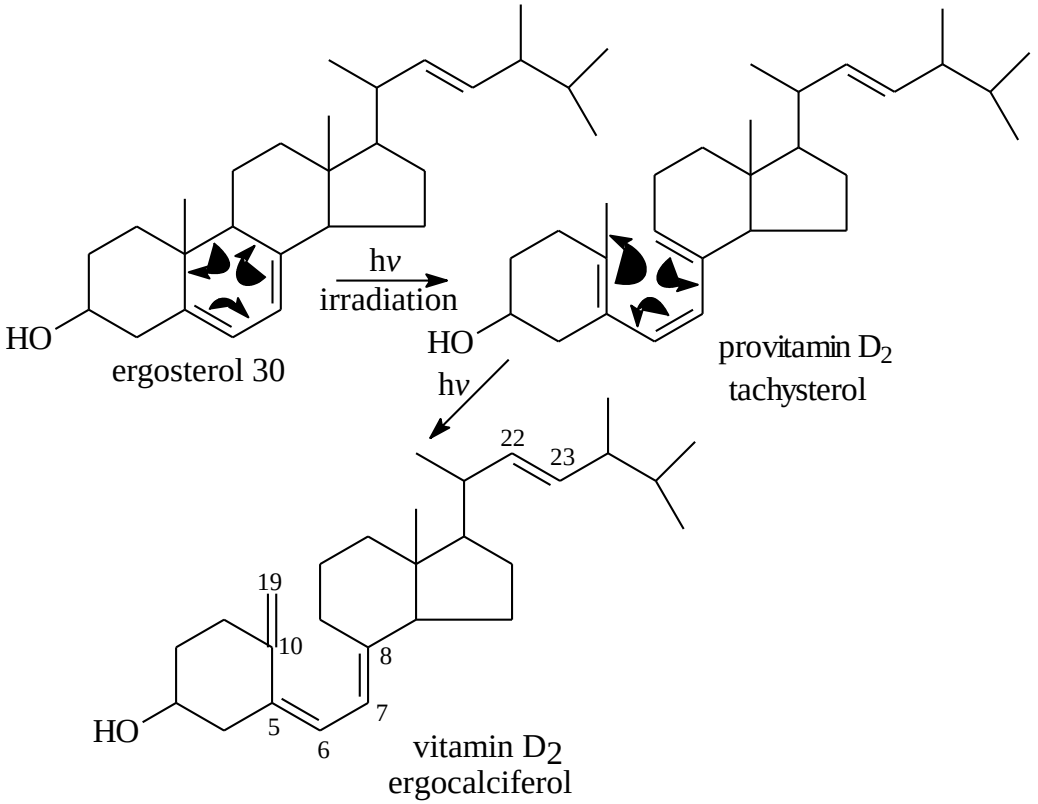
Al(O-isopropyl)$_3$ Oppenauer Oxidn. 7 → α,β- unsat. ketone



ergosterol 30

λ_{max} found 235 nm, calc. 239 nm

- Formation of vitamin D_2 from ergosterol 30 by sunlight irradiation.

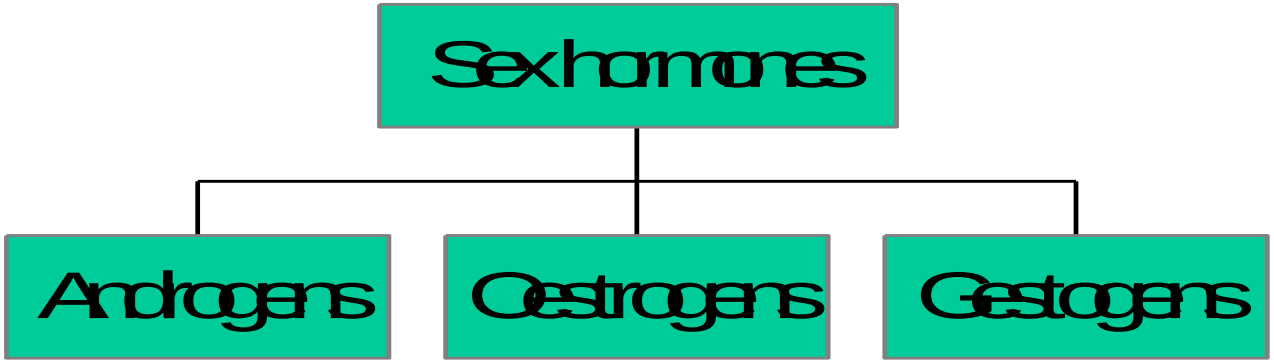


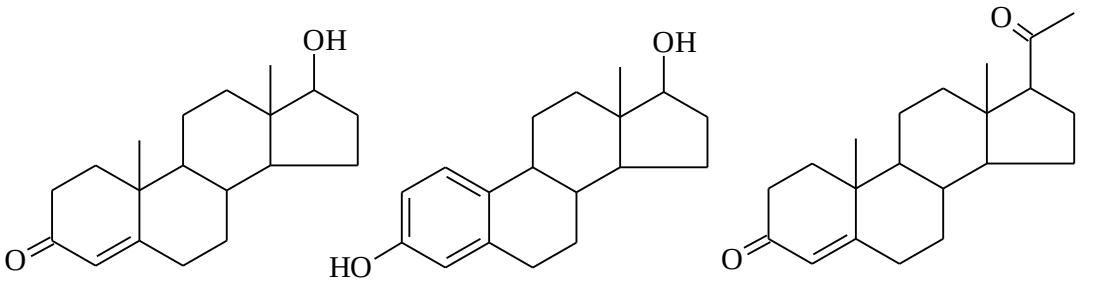
3.Steroid hormones

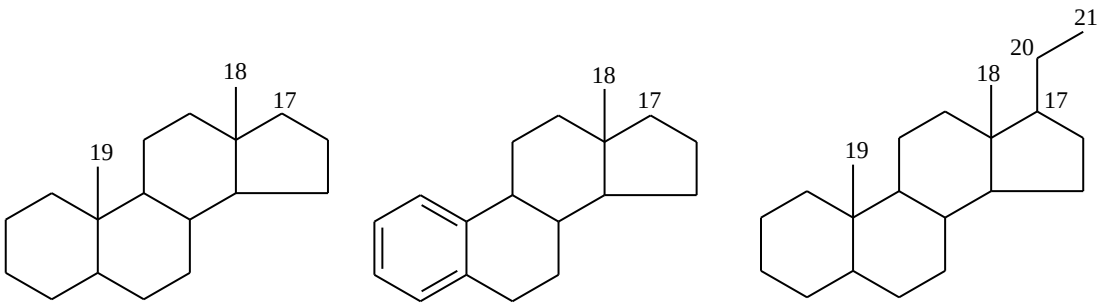
- Hormones are substances which are secreted by the ductless glands, and only minute amounts are necessary to produce the various physiological reactions in the body.

- The sex hormones belong to the steroid class of compounds, and are produced in the gonads الغدد التناسلية(testes in the male, and ovaries in the female). Their activity appears to be controlled by the hormones that are produced in the anterior lobe الفص الامامي of the pituitary gland الغدة النخامية .

- **Sex hormones**



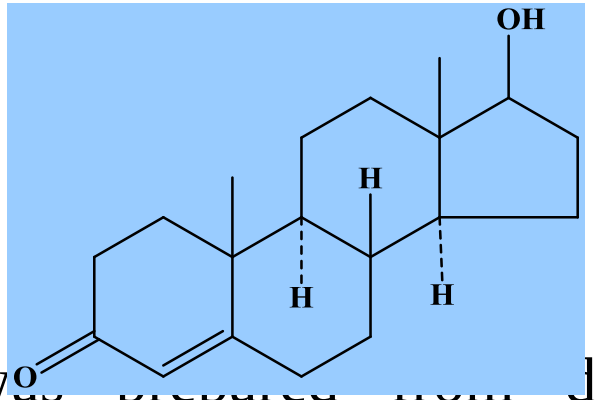




Androgens

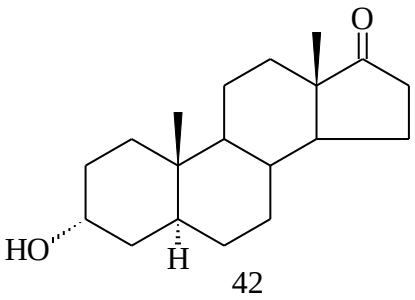
- Androsterone has MF $C_{19}H_{30}O_2$ with mp. 183 °C
- It was extracted, for the first time, from male urine in 1931 by Betenandt
-15 mg of Androsterone could be extracted from 15000 Litre of male urine !!!!!-

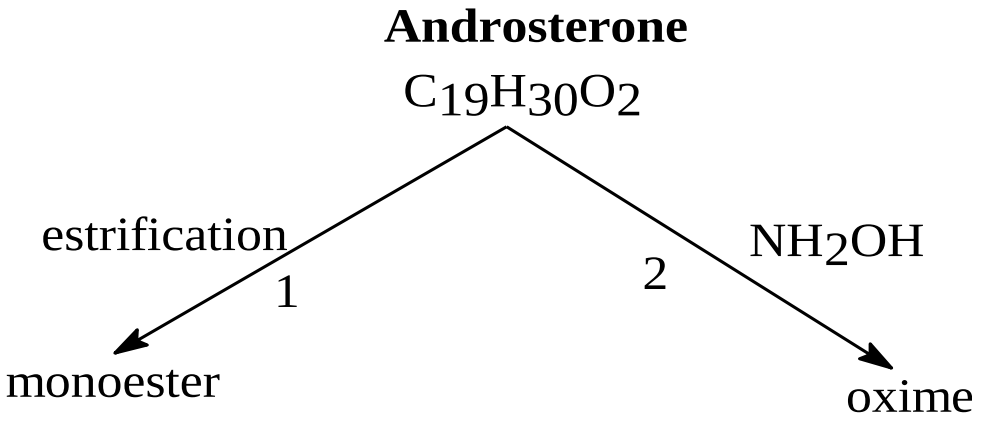
Testosterone: $C_{19}H_{28}O_2$, m.p. 155°C, $[\alpha]_D$ +109°

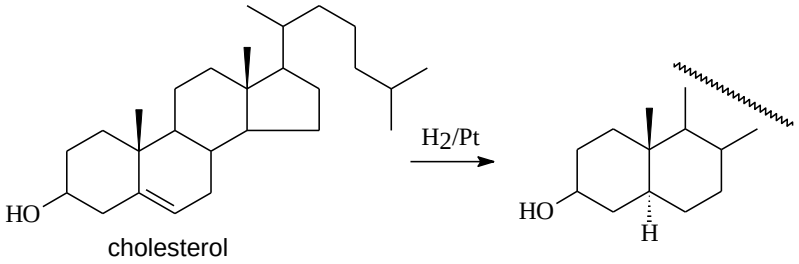


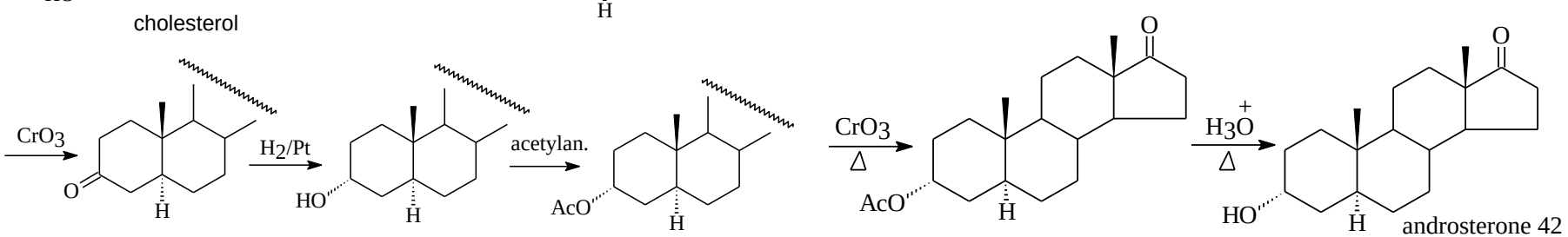
Testosterone was prepared from dehydroepiandrosterone (DEA) which, was available from natural product. **<u>The dehydroepiandrosterone is the most important and useful Intermediate of sex hormones.</u>**

- **Androgens**
- Androsterone 42



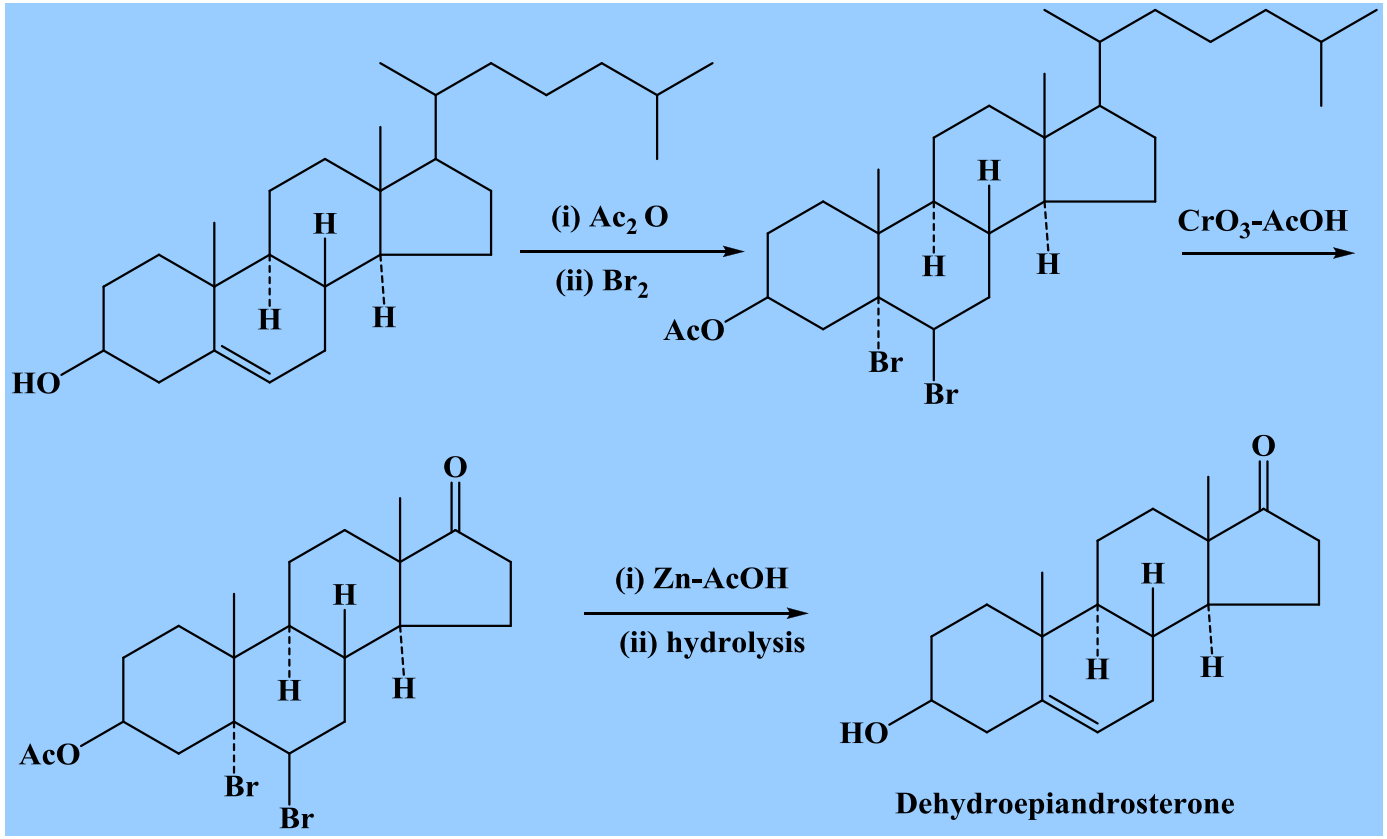




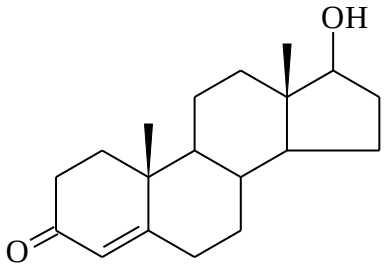


المحاضرة الثامنة

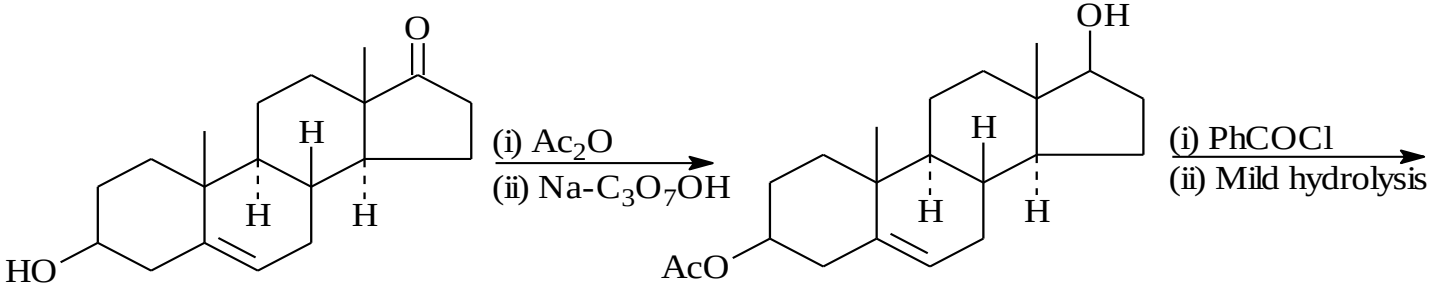
- **Synthesis of Dehydroepiandrosterone (DEA)**



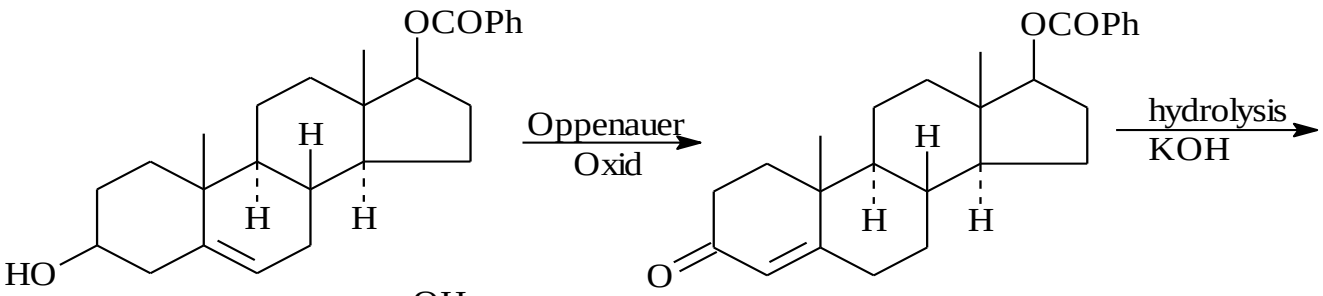
- <u>Testosterone 36</u>
- manufacture of testosterone 36

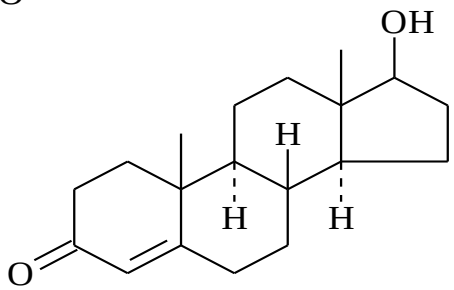


36



Dehydroepiandrosterone



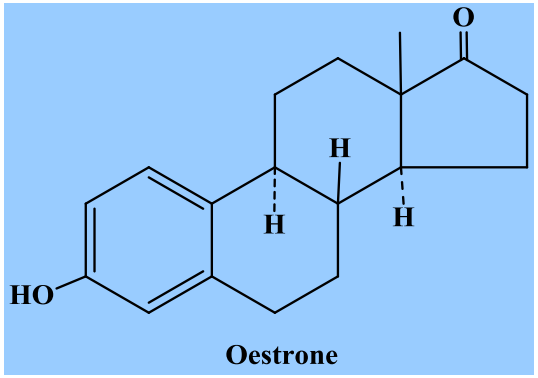


Testosterone

Oestrogens

- It has been known for a long time that there are hormones which control the uterine cycle دورة الرحم.
- **Oestrone** is the first known member of the sex hormones, and soon after its discovery two other hormones were isolated, **oestriol**, and **oestradiol**.

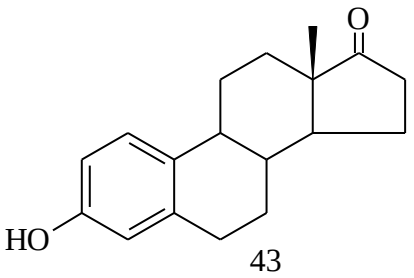
- **Oestrone**



Oestrone

- Oestrone, m.p. 259°C, $[\alpha]_D$ +170°, has the molecular formula $C_{18}H_{22}O_2$.
- It was isolated from the urine of pregnant women
- It behaves as a ketone (forms oxime,etc), and contains one hydroxyl group (this hydroxyl group is phenolic; oestrone couples with diazonium salts in alkaline solution).

- **Oestrogens**
- Oestrone 43



43

Oestrone

$C_{18}H_{22}O_2$

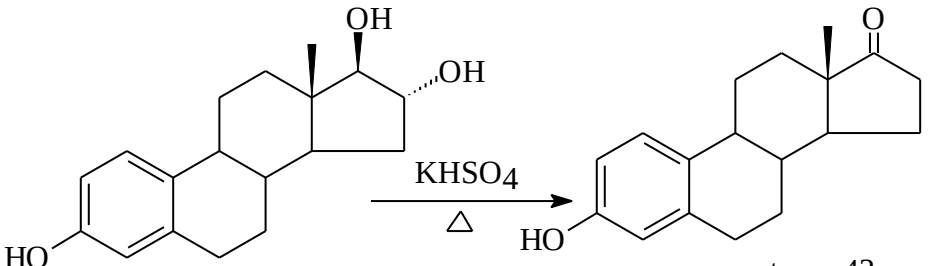
1 NH_2OH → oxime

2 $ArN_2^+Cl^-$ → couples with diazonium salts in alkaline solution

3 MeI → monomethyl ether

4 Ac_2O → monoacetate

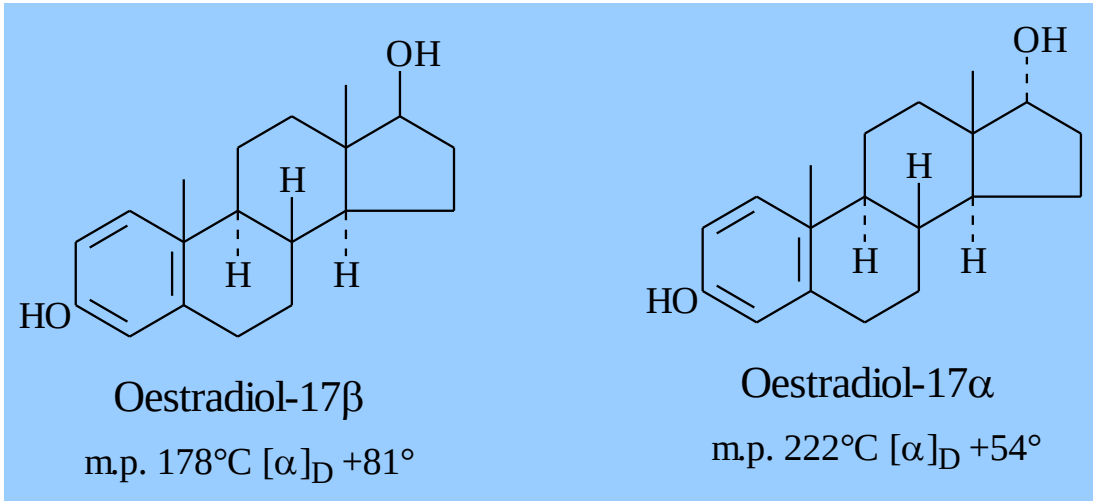
5 catalytic reduction → octadhdro-oestrone $C_{18}H_{30}O_2$



oestriol 44 oestrone 43

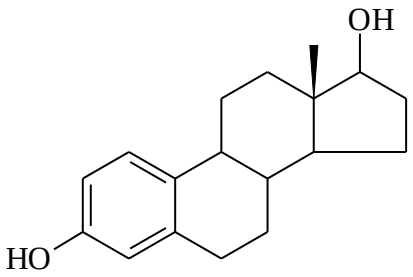
Oestradiol: $C_{18}H_{24}O_2$

There are two stereoisomeric oestradiol,α-and β-;

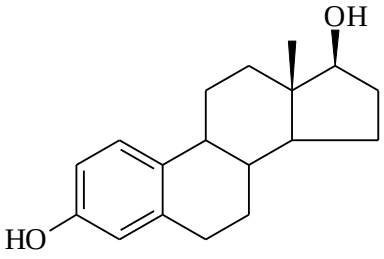


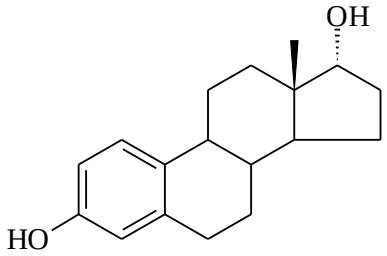
- Oestradiol-17α has been isolated from the pregnancy urine of mares فرسة . Oestradiol-17β is much more active than oestrone, whereas oestradiol-17α is much less active. It appears that oestradiol is the real hormone, and that oestrone and oestriol are metabolic products.

- Oestradiol 35



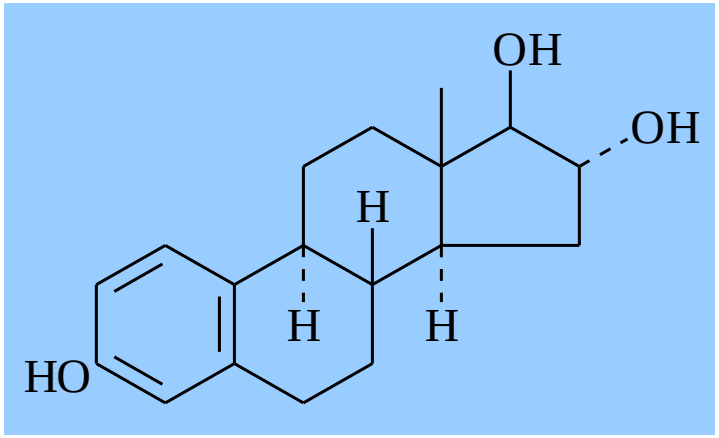
35





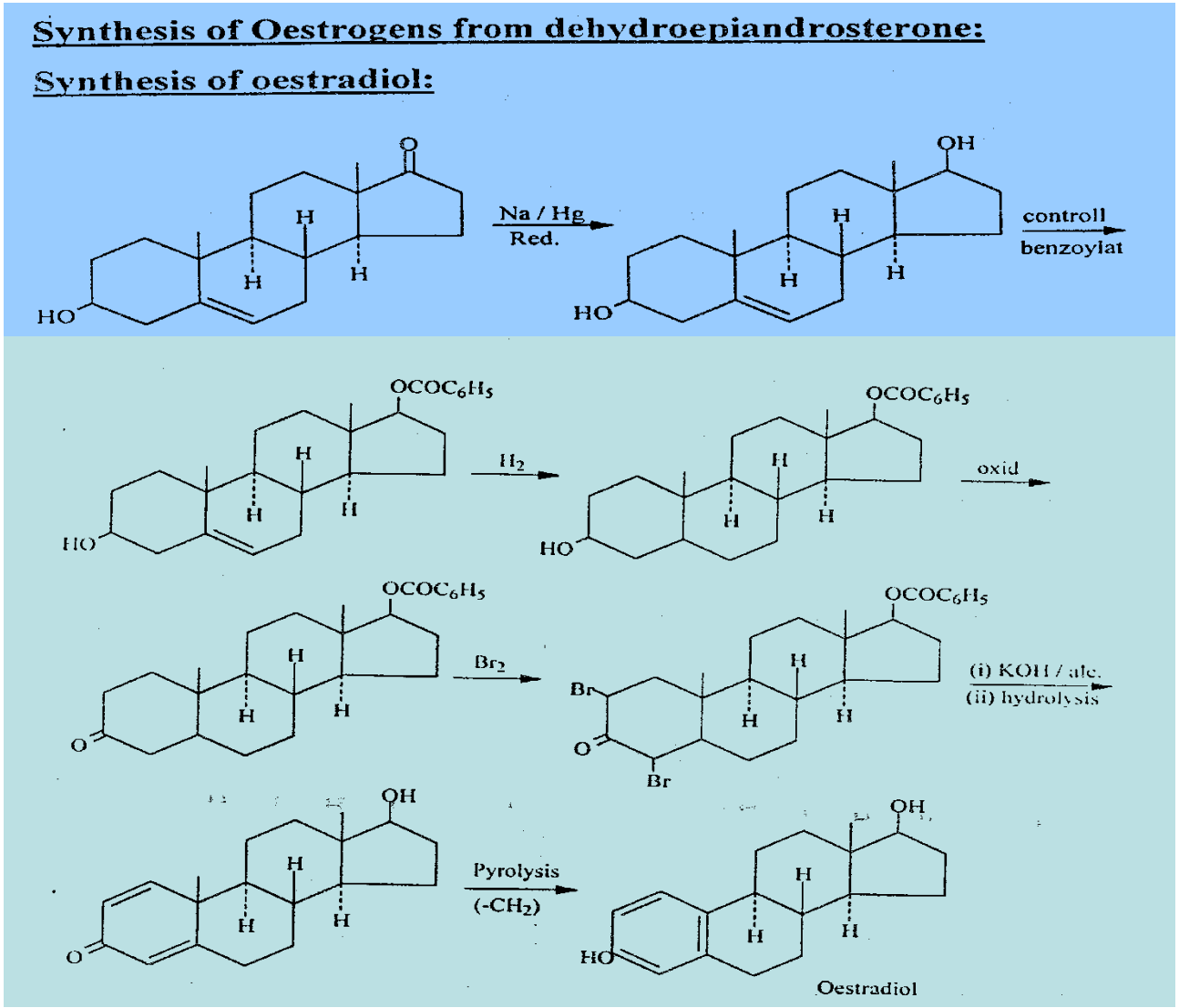
- **35a,** α-oestradiol (oestradiol-17 β) **35b,** β-oestradiol (oestradiol-17 α)
  - m.p 178^{o}C m.p 222^{o}C

Oestriol

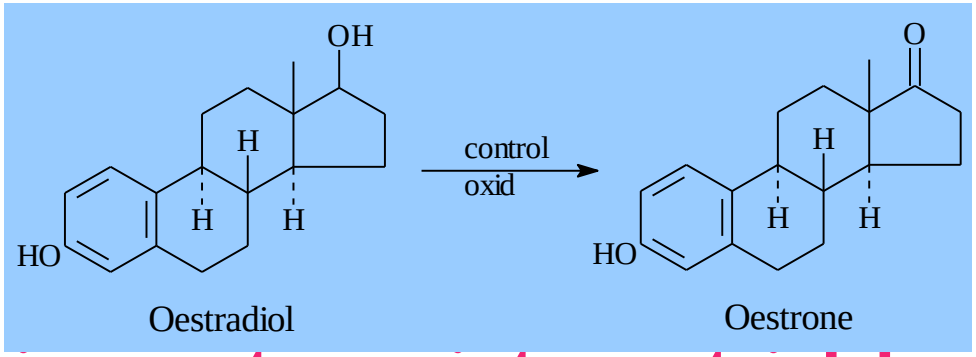


- Oestriol $C_{18}H_{24}O_3$, m.p. 281°C, $[\alpha]_D$ +61°
- Oestriol was isolated from human pregnancy urine by Marrian (1930).
- Since oestriol forms a triacetate, three hydroxyl groups must be present in the molecular, one was shown to be phenolic, and the other two secondary alcoholic, since, on oxidation, a diketone is produced. When oestriol is heated with potassium hydrogen sulphate, one molecule of water is removed and oestrone is produced.

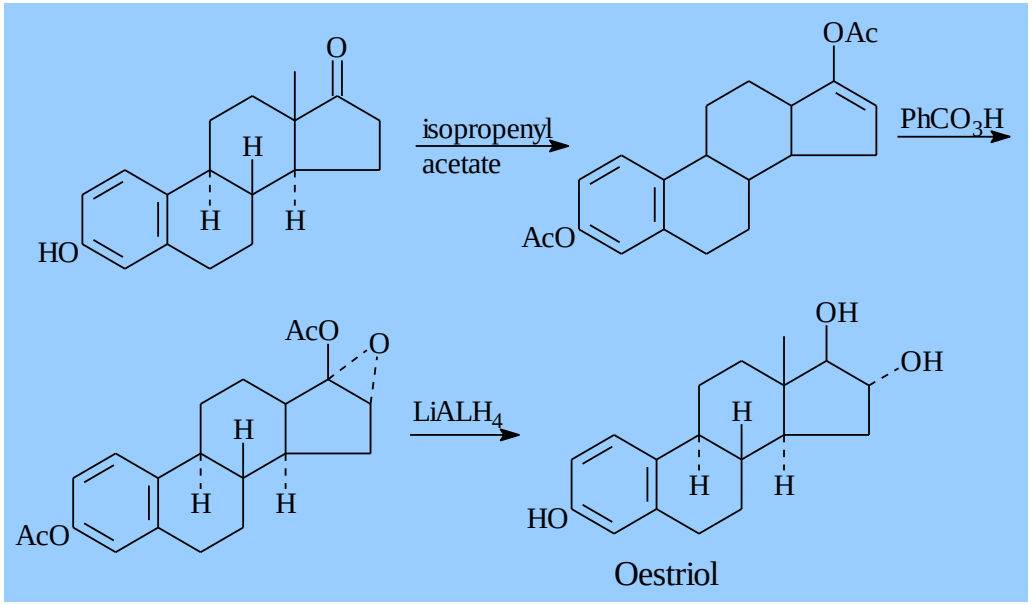
- **Synthesis of Oestradiol and Oestrone**



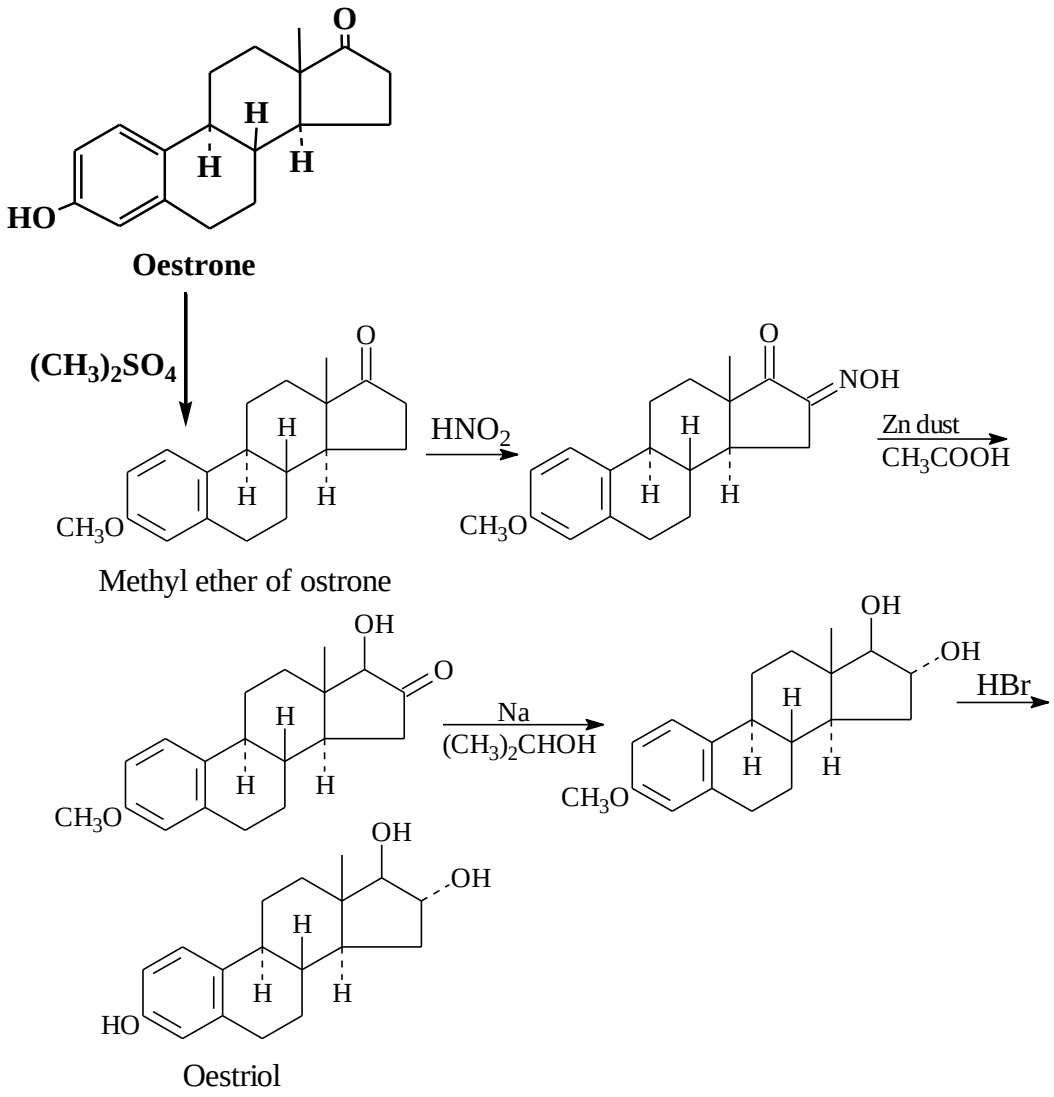
- **Conversion of oestradiol to oestrone:**



- **Conversion oestrone into oestriol by Leeds *et al.* (1954) :**



- Conversion of oestrone into oestriol as follows (Huffman *et al.*):

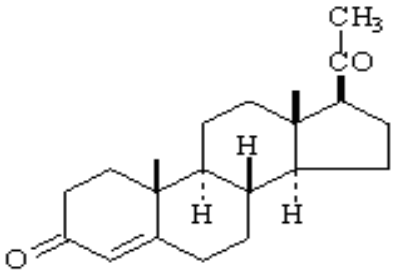


Oestriol

Gestogens

Progesterone

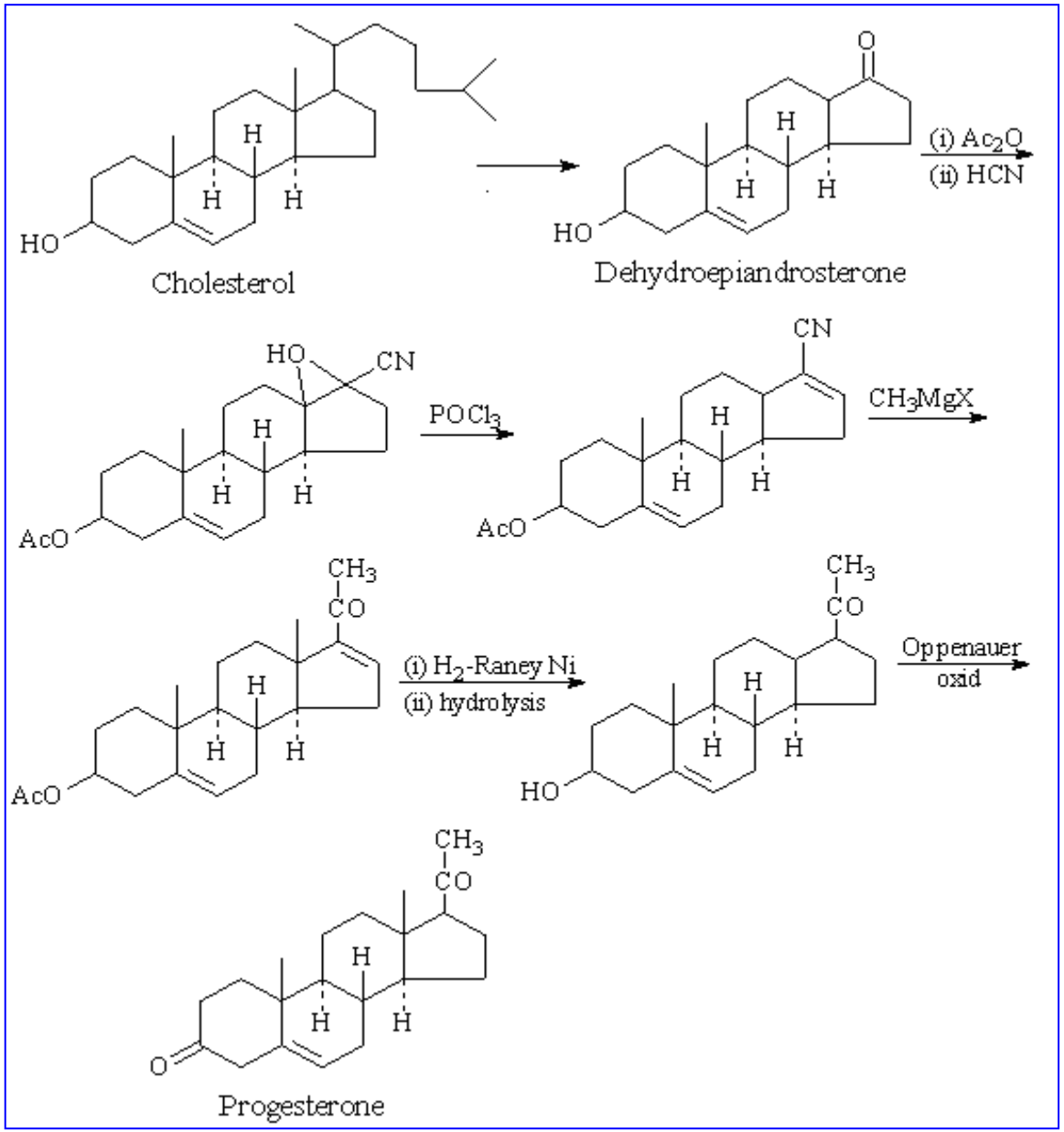
- Progesterone: $C_{21}H_{30}O_2$, mp. 128°C, [α]D +192°



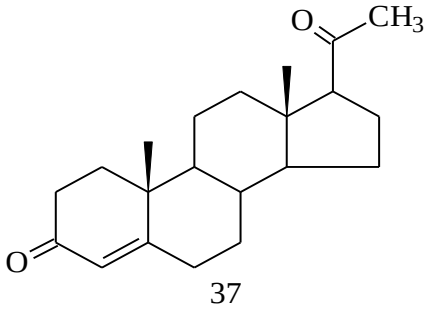
progesterone

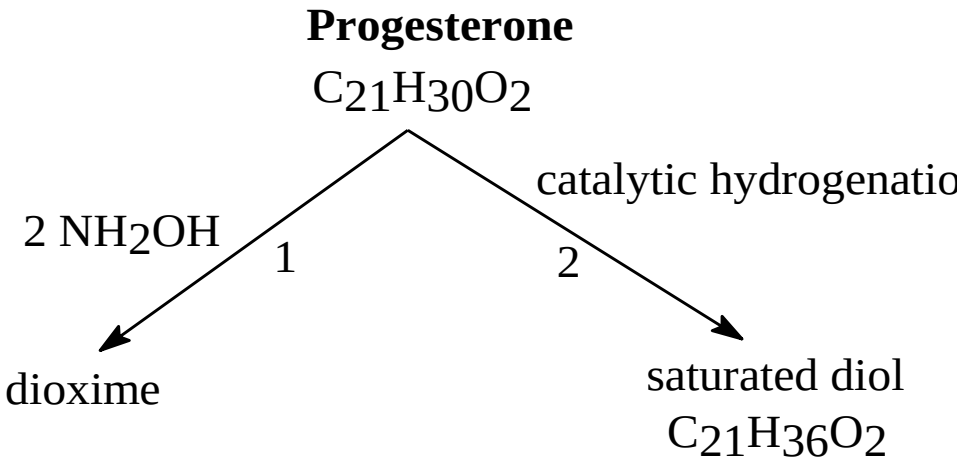
- This was first isolated in a pure form from the corpora luteal of pregnant sow.
- The chemical reactions of progesterone show that there are two keto groups present, and since on catalytic reduction three molecules of hydrogen are added to form the dialcohol $C_{21}H_{36}O_2$, it therefore follows that progesterone contains one double bond (four hydrogen atoms are used to convert the two keto group to alcohol groups) thus the parent hydrocarbon of progesterone is therefore tetracyclic ($C_{21}H_{36}O_2$ 21+1 – 36/2= 4 rings).
- The absorption spectrum of progesterone, however, shows that it is an α,β-unsaturated ketone (λ_{max} 240 nm).

- **Synthesis of progesterone from cholesterol:**

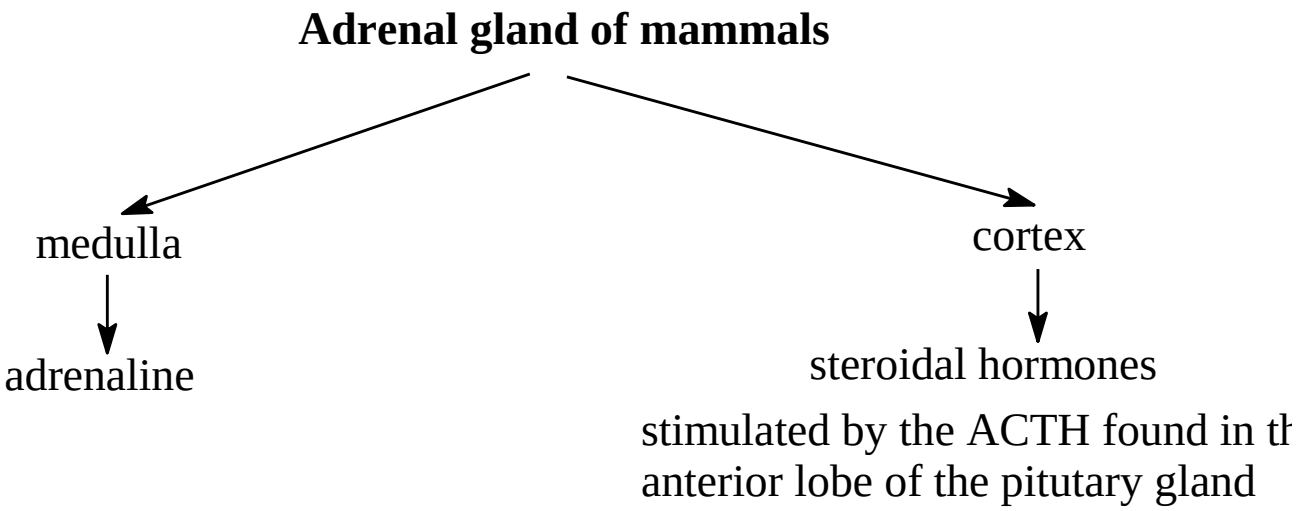


- **Gestogens**
- Progesterone 37

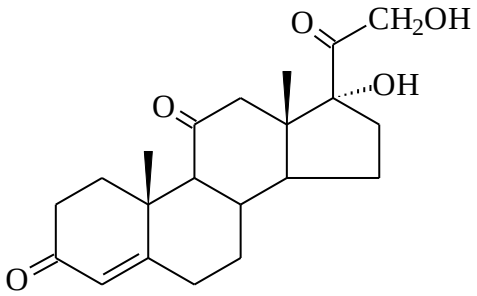




- **Adrenocortical hormones**

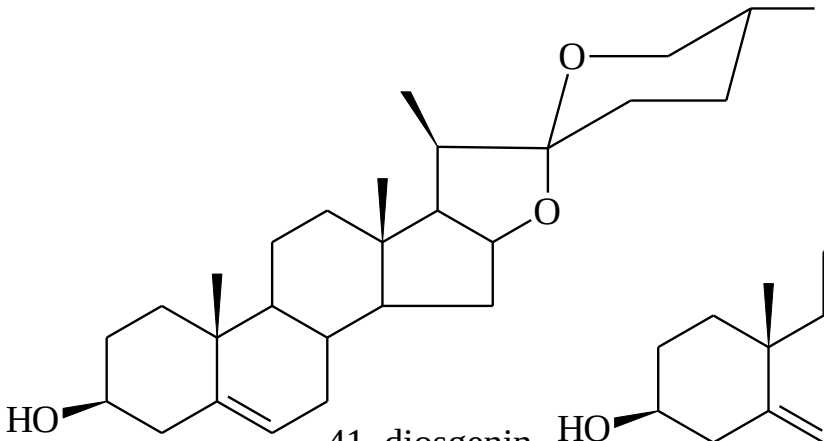


- · **Cortisone** 38 is an adrenocortical hormone and is used for rheumatoid arthritis and rheumatic fever.

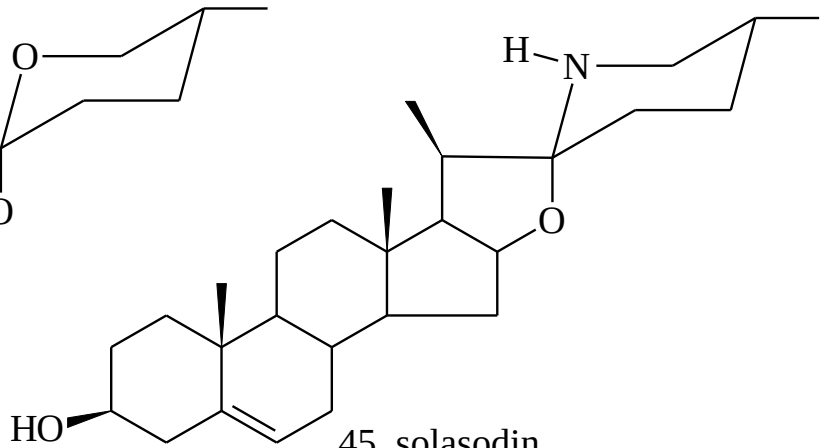


cortisone 38

- **Hormone Precursors**
- Diosgenin 41 and solasodin 45 are natural products known as hormone precursors. Diosgenin is a steroidal sapogenin, while solasodin belongs to steroidal alkaloids.

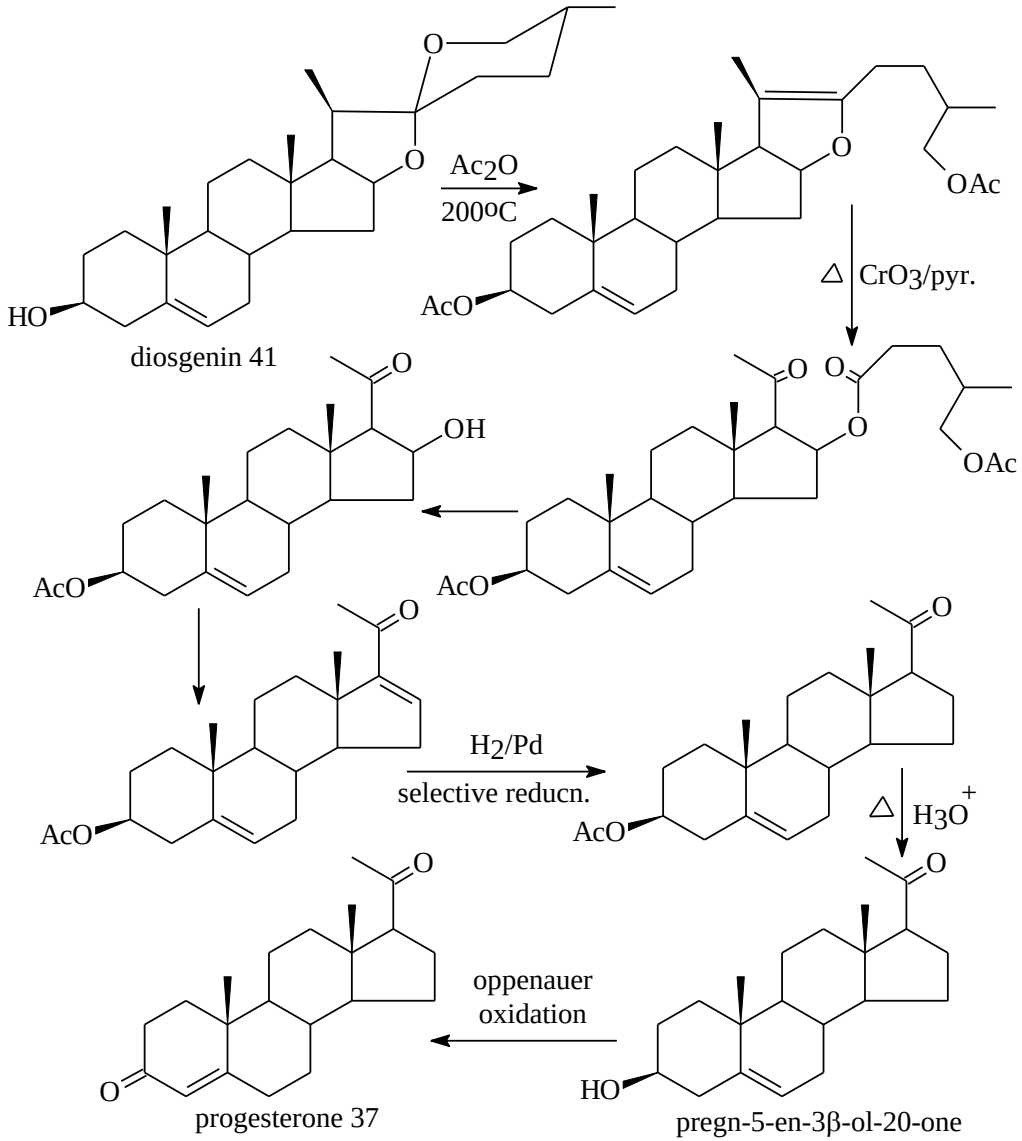


41, diosgenin



45, solasodin

- Marker's degradation method of preparation of progesterone 37 from diosgenin 41.



المحاضرة التاسعة

Alkaloids

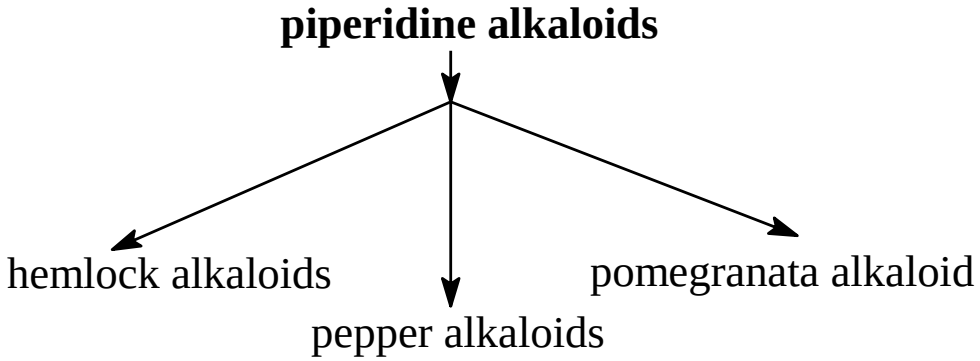
General properties

- The alkaloids are usually colourless, crystalline non-volatile solids which are insoluble in water, but are soluble in ethanol, ether, chloroform, etc.
- Some alkaloids are liquid which are soluble in water e.g., coniine and nicotine, and a few are coloured, e.g. berberine is yellow.
- Most alkaloids have a bitter taste and are optically active (laevorotatory).
- They are generally tertiary nitrogen compounds and contain one or two nitrogen atoms usually in the tertiary state in a ring system; most of the alkaloids are contain oxygen.
- Some of reagents are also used as a means of detecting alkaloids in paper and thin layer chromatography.

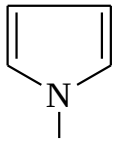
Alkaloids

- **Structure and classification of alkaloids**
- The alkaloids were earlier classified according to the plant general in which they occur, e.g. conitum, cinchona, ephedra, opium, rauwolfia, and strychnos alkaloids.
- Nowadays alkaloids are chiefly classified according to the main ring system which is common to a group of alkaloids. In this way, although numerous classes of the alkaloids are possible, but only the following common classes will be mentioned here.

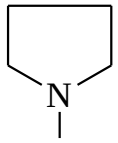
- (1) Phenylethyl amine alkal
- (2) Pyrrolidine alkaloids
- (3) Pyridine or piperidine alkaloids
- (4) Pyridine-pyrrolidine alkaloids
- (5) Tropane alkaloids
- (6) Quinoline alkaloids
- (7) Isoquinoline alkaloids
- (8) Phenanthrene alkaloids
- (9) Indole alkaloids
- (10) Tropolone alkaloids



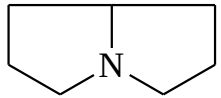
- **Basic nuclei of alkaloids**



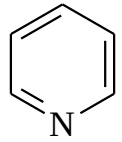
pyrrole



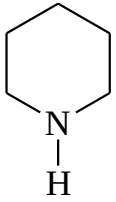
pyrrolidine



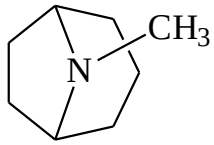
pyrrolizidine



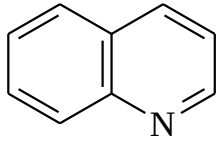
pyridine



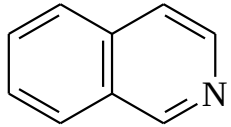
piperidine



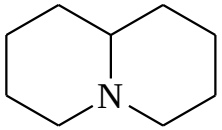
tropane
(piperidine-pyrrolidine)



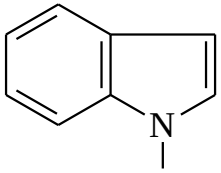
quinoline



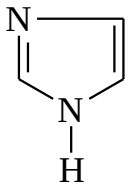
isoquinoline



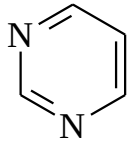
nor-hipinane



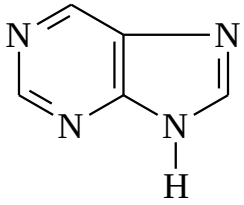
indole (benzopyrrole)



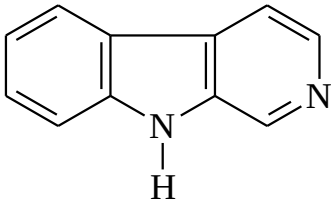
imidazole



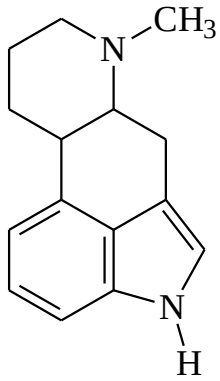
pyrimidine



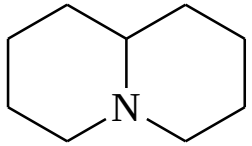
purine



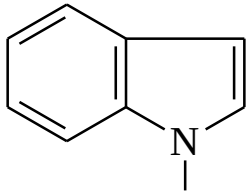
carboline



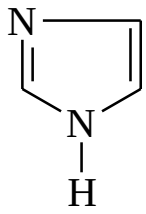
indole + hydroquinoline



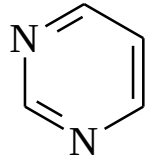
nor-hipinane



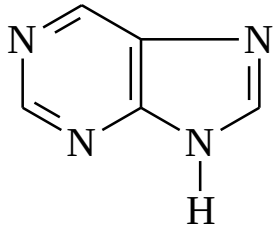
indole (benzopyrrole)



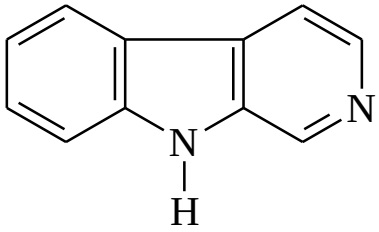
imidazole



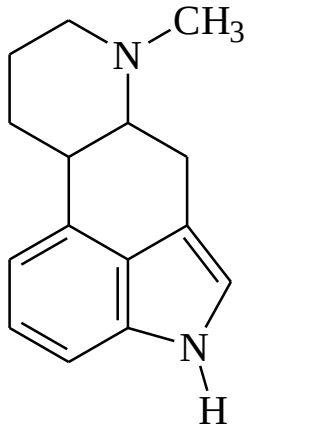
pyrimidine



purine



carboline

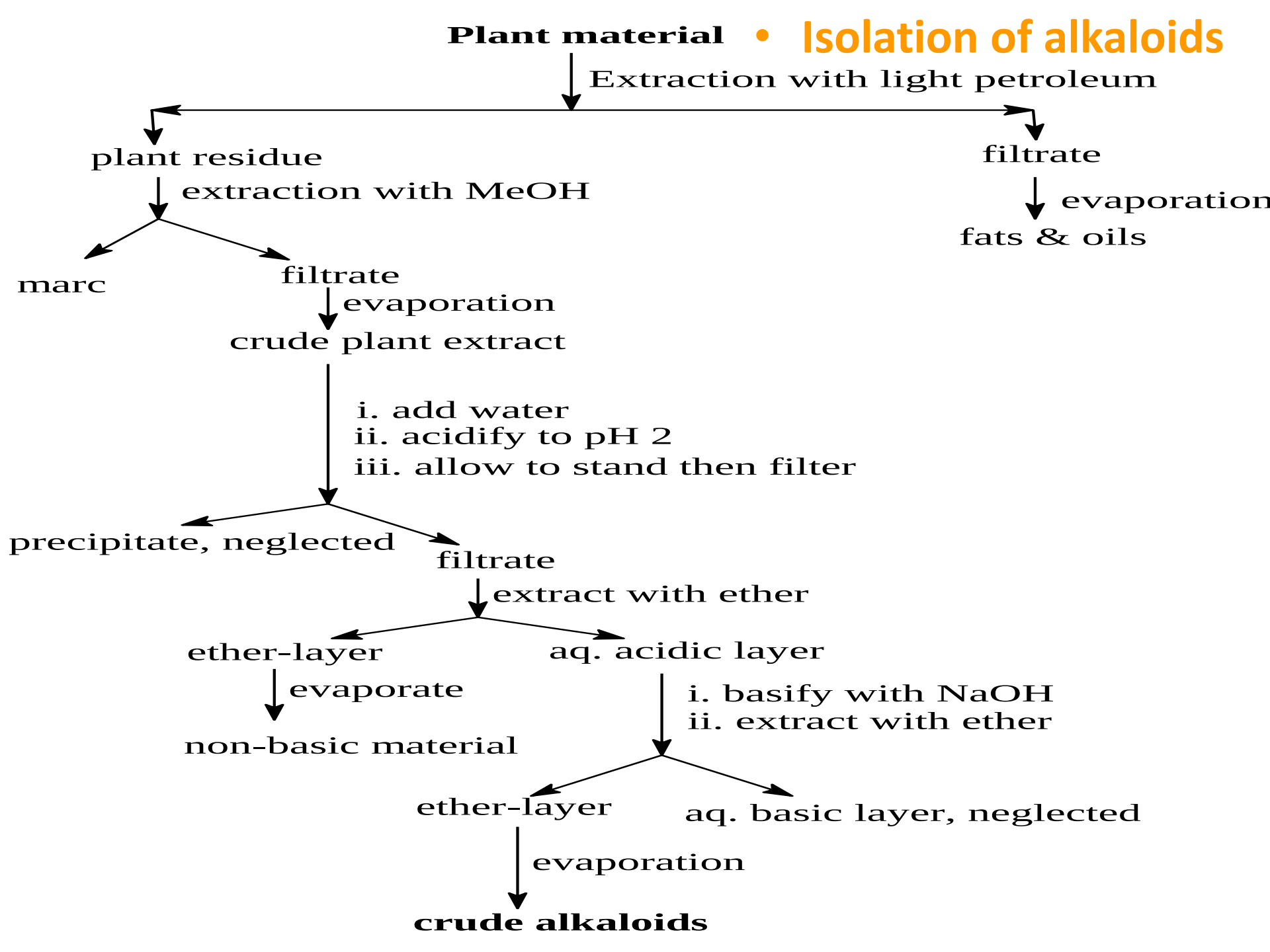


indole + hydroquinoline

- **Extraction of alkaloids**

- Alkaloids are usually found in seeds, root, leaves, or bark of the plant, and generally occur as salts of various plant acids, e.g., acetic, oxalic, citric, malic , tartaric, etc.
- A common method of isolation of alkaloids is as follows. The plant is dried, then finely powdered and extracted with boiling methanol. The solvent is distilled off, and the residue treated with inorganic acids, where upon the bases are extracted as their soluble salts. The free bases are liberated by addition of sodium carbonate and extracted with various solvents, e.g., ether, chloroform, etc.
- The mixtures of bases thus obtained are separated by various methods into the individual compounds. More recent methods of separation involve the use of chromatography [column chromatography (CC) and/or thin layer chromatography (TLC) and high pressure liquid chromatography (HPLC)].

Isolation of alkaloids



- **Structure-elucidation of alkaloids**
- 1- The first step in determining the structure of a pure alkaloid consists in ascertaining its molecular formula and optical rotatory power.
- 2- The presence of unsaturation in an alkaloid may ascertained by the addition of bromine or halogen acids or by hydroxylation with dilute alkaline permanganate.
- 3- Frequently an alkaloid is cleaved into simple fragments by hydrolysis with water, acid or alkali and the fragments so obtained are examined separately since the structure of the fragment may easily be established than that of the whole molecule.
- 4- The next step involves in ascertaining the functional nature of oxygen and nitrogen atoms either in the molecule itself or in its fragments obtained by hydrolysis as in step 2.
- 5- Functional nature of oxygen: The oxygen atom may be present in the form of alcoholic or phenolic hydroxyl (-OH), methoxyl (-OCH_3), acetoxyl reOCOCH_3), benzoxyl (- COC_6H_5), carboxyl (-COOH) or carbonyl (C=O) group, various oxygen functional groups can be characterized according to the following characteristics

- **(i) Phenolic hydroxyl group (=C-OH)** : The phenolic hydroxyl group is characterized by alkali solubility followed by reprecipitation by carbon dioxide, a colour reaction with ferric chloride, acylation to an ester and alkylation to an ether. The number of phenolic hydroxyl groups is estimated by acetylation.
- **(i—) Alcoholic hydroxyl group (-C-OH)** : The alcoholic hydroxyl group is generally indicated by its acylation reaction along with the negative tests for phenolic group. It is further confirmed by characteristics like dehydration, oxidation, and absorption spectrum in the infrared. The three possible alcoholic groups are usually differentiated by their oxidation reactions.
- **(iii) Carboxyl group (-COOH)** : The carboxyl group is indicated by its solubility in weak bases, like $NaHCO_3$, NH_3, *etc.,* esterification with alcohols, and specific absorption in the infrared. The groups are generally estimated quantitatively either by acid-alkali titration or by silver salt method.

- **(IV) Alkoxyl group (-OR)** : The alkoxyl groups, generally methoxy (-OCH_3) and sometimes ethoxy (-OC_2H_5) occur frequently in the alkaloids. It is detected as well as estimated by Zeisel method which involves boiling of the alkaloid with concentrated hydriodic acid at its boiling point (126^oC) when the alkoxy groups are converted into alkyl halides which can be easily estimated as silver iodide by treatment with ethanolic silver nitrate.

- The number of moles of silver iodide is equivalent to the number of alkoxyl groups in the alkaloid.
- The related group, methylenedioxy (-O-CH_2-O-) is estimated on the basis that it librates formaldehyde when treated with hydrochloric or sulphuric acid; thus the quantitative estimation of formaldehyde will give the number of methylenedioxy groups.

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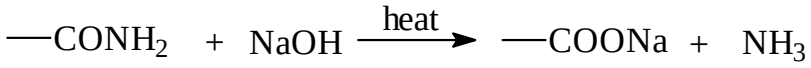
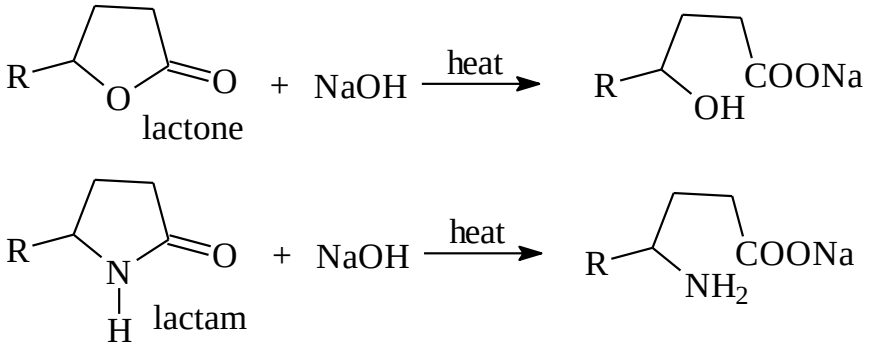
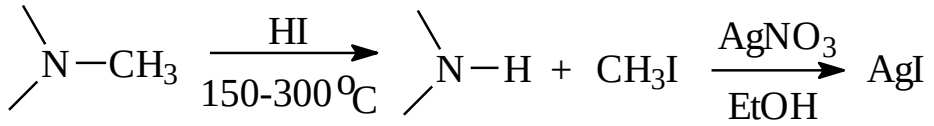
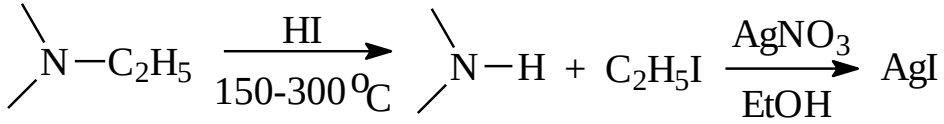
- **(vi) Ester groups (-OCOR)** : Esters (such as -$OCOCH_3$, -$OCOC_6H_5$) and related groups like amide, lactone, and lactam are detected by their hydrolysis with water, dilute acids, alkali to hydroxyl and acidic compounds. The nature is established by knowing the nature of the acid.



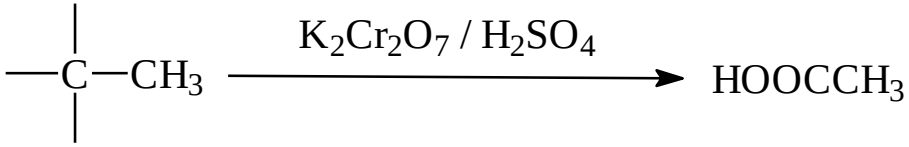


- **Functional nature of nitrogen**
- The N-alkyl groups are frequently estimated by Herzig Meyer method

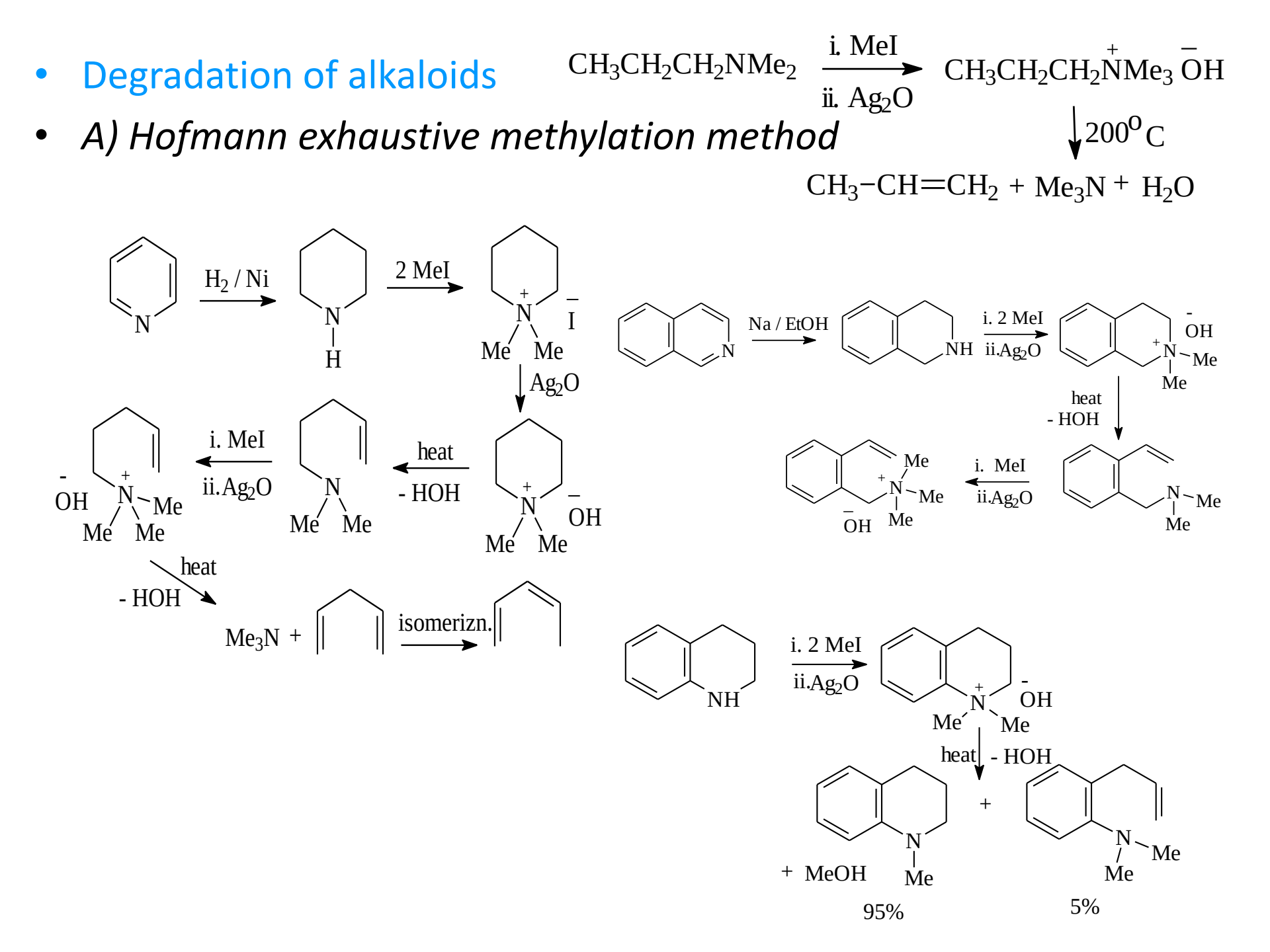




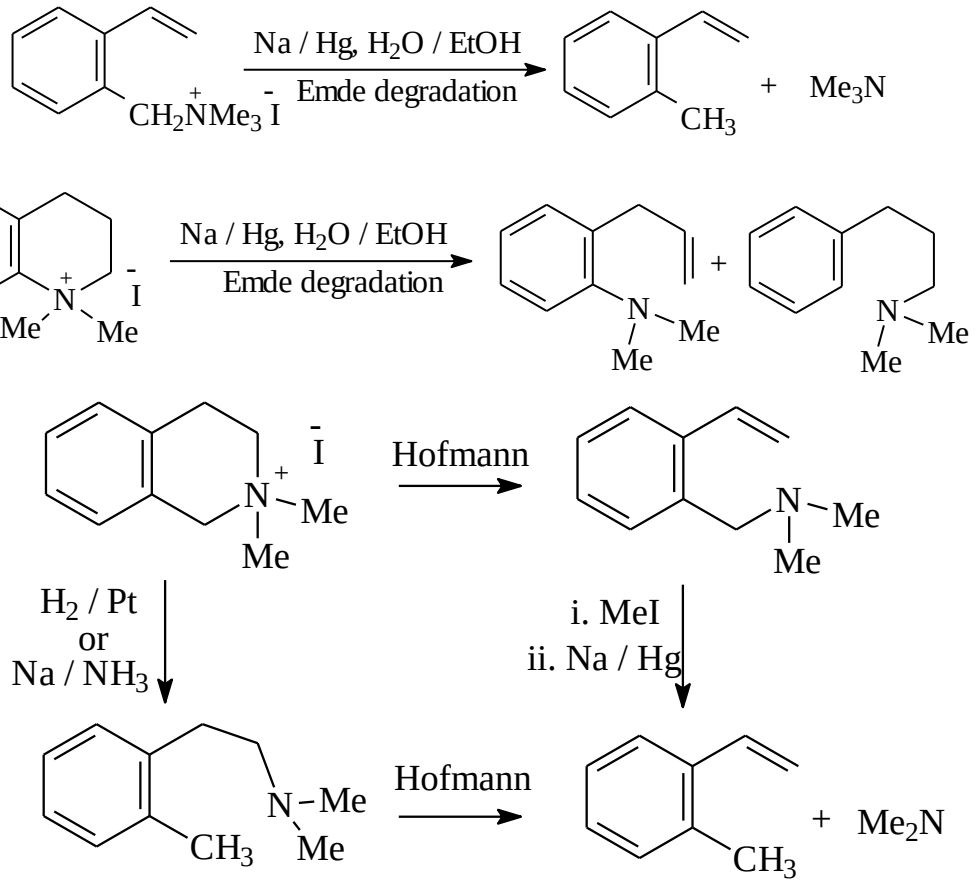
- Estimation of C-methyl groups



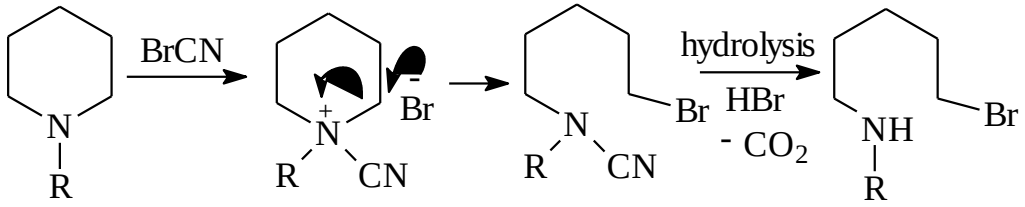
- Degradation of alkaloids
- *A) Hofmann exhaustive methylation method*



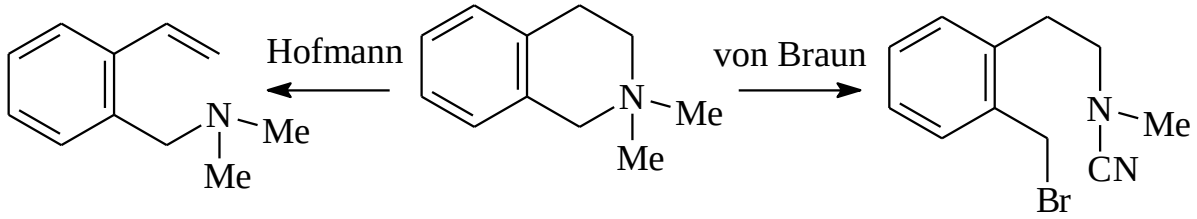
- · *(B) Emde method*
- involves reducing an aqueous or alcoholic solution of the quaternary ammonium halide with sodium amalgam in aqueous ethanol, sodium in liquid ammonia or catalytically.



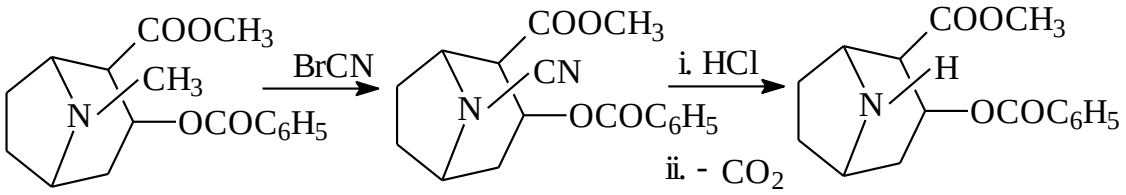
- (C) *Von Braun methods for tertiary cyclic amines*
- the alkaloid containing tertiary nitrogen atom in the ring is treated with cyanogen bromide, CNBr



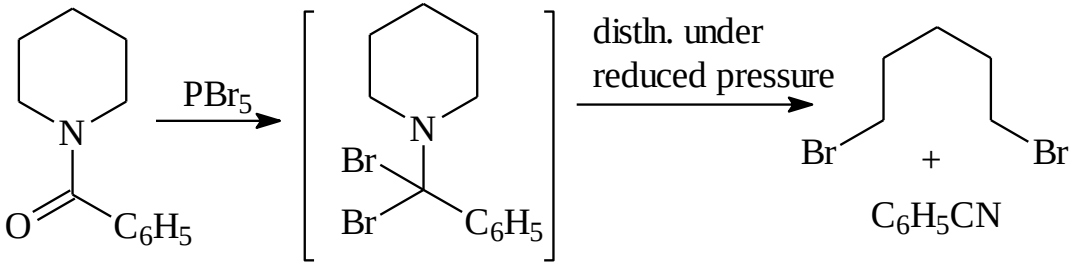
- Von Braun's cyanogen method may successfully be applied on compounds which do not respond to Hofmann method. Furthermore, in cases where both the methods are applicable, ring opening takes place at different points of the ring, *e.g.*



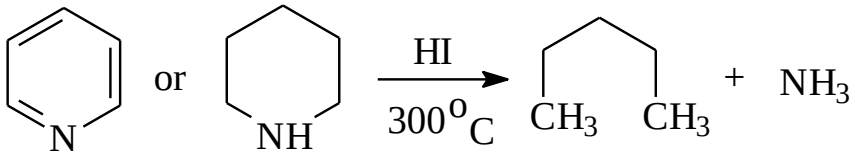
- However, a second possibility in the same Von Braun method is the dealkylation of the N-alkyl group without ring cleavage in the following way :-



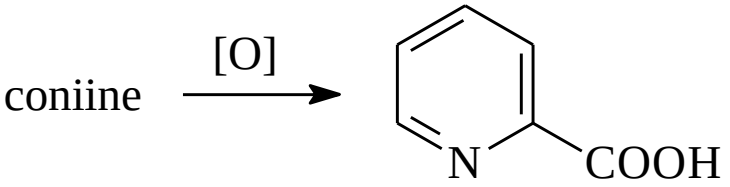
- (i) The second von Braun method is meant for secondary cyclic amines and involves the treatment of its benzoyl derivative with phosphorus halide when the nitrogen atom is eliminated as benzonitrile with the formation of α,ω -dihalo compound.

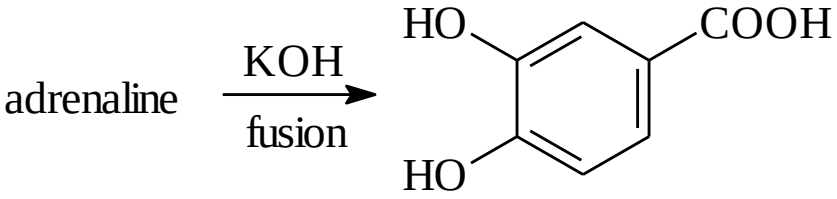


- *(D) Reductive degradation*

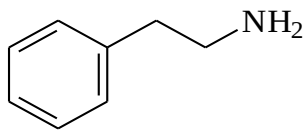


- *(E) Oxidation*
- *(F) Zinc dust or alkali distillation*
- *(G) Alkali fusion*
- *(H) Dehydrogenation*
- **Physical methods**
- **Finally**, the structure proposed by degradative methods is confirmed by the unambiguous synthesis

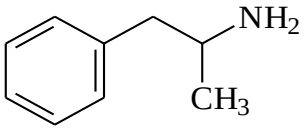




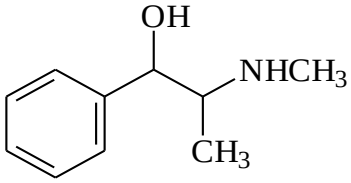
- **Phenylethyl amine Alkaloids**



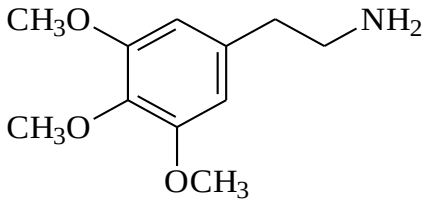
β-phenylethyl amine 47



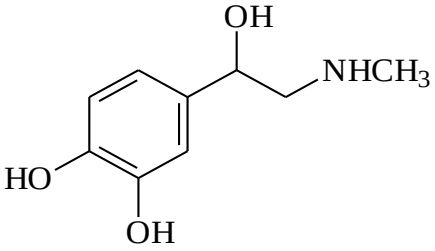
amphetamine 48



ephedrine 49

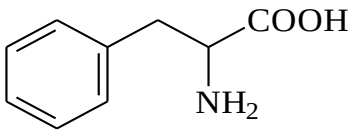


mescaline 50

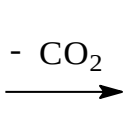


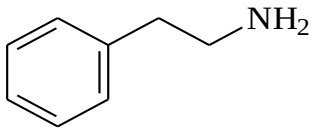
adrenaline 51

- β-Phenylethyl amine 47

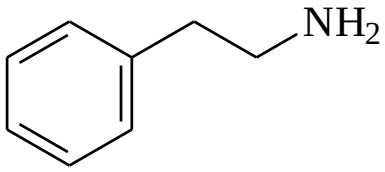


phenylalanine

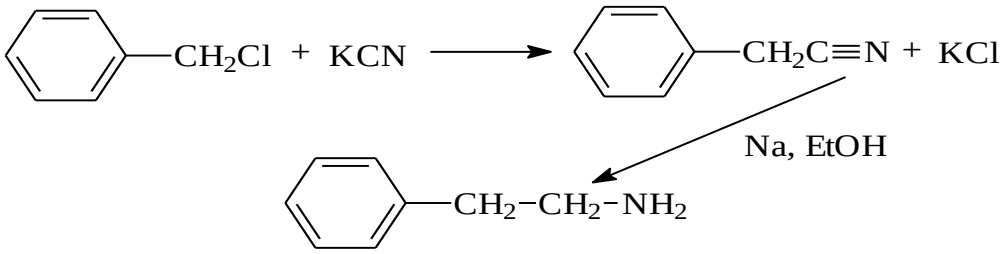




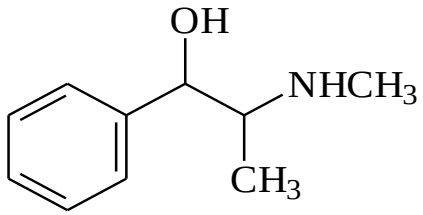
β-phenylethyl amin



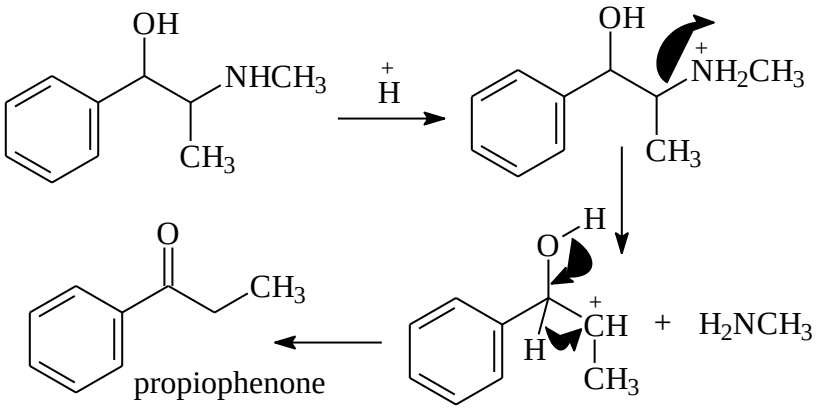
47



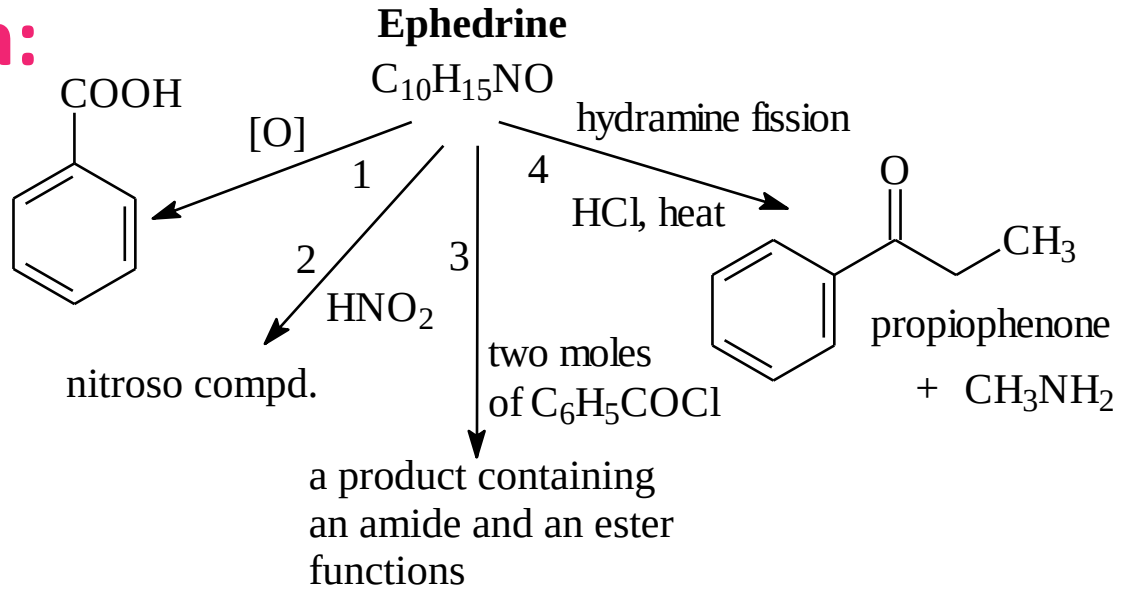
- **D-(-)-Ephedrine: MF: $C_{10}H_{15}NO$**
- **D(-) Ephedrine occurs in the genus, Ephedra, along with other alkaloids.**
- **It has mydriatic action, heart stimulant, as a result of its astringent action, it is used in treatment of hay fever and bronchial asthma.**
- **(-) Ephedrine is a solid, m.p. 38°C, [α]D = -6.3°.**



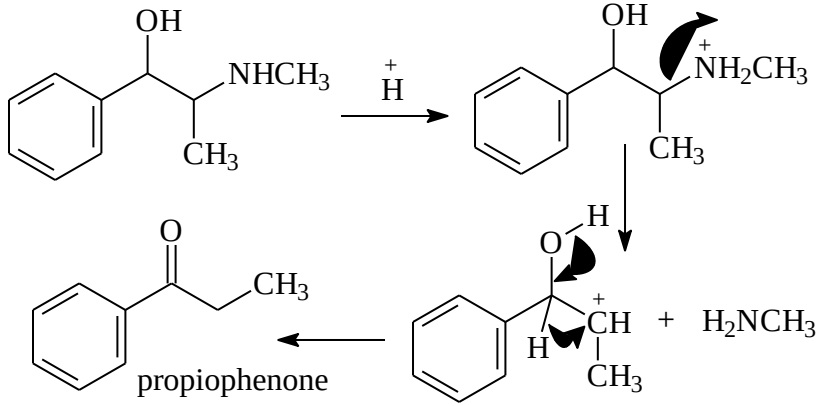
49

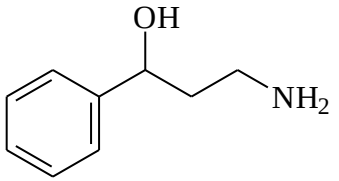


Structure Elucidation:

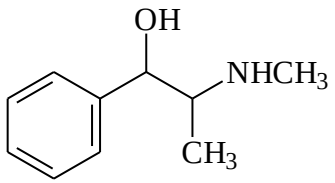


- The formation of benzoic acid in reaction 1 indicated that ephedrine is a monosubstituted benzene derivative (benzene ring,+ one side chain).
- Ephedrine is a secondary amine, as shown from reaction 2.
- From reaction 3, the oxygen atom in ephedrine is present as a hydroxylic function.
- The formation of methylamine and propiophenone from ephedrine by heating with hydrochloric acid (reaction 4) suggests that ephedrine is one of the following two structures:





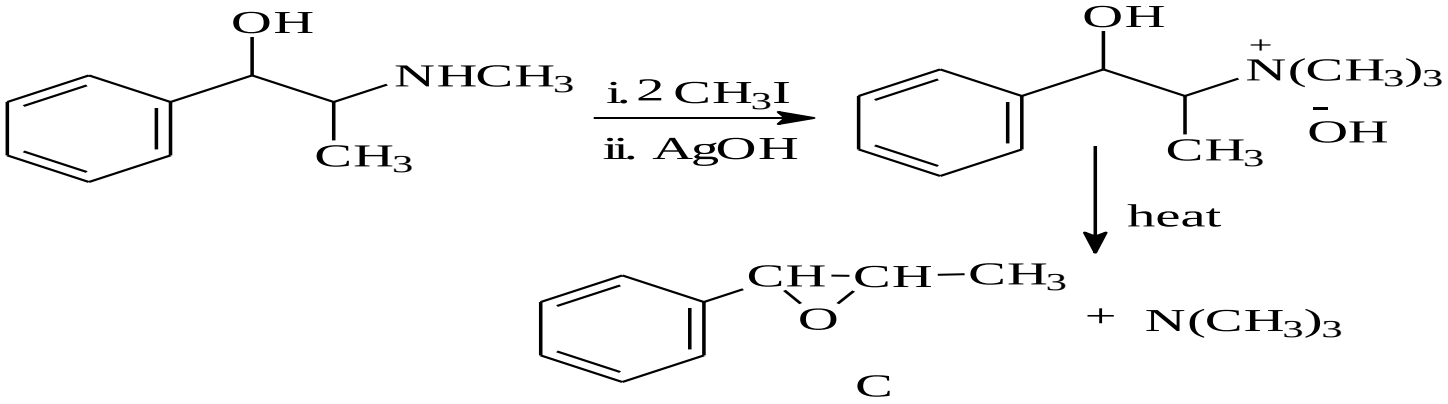
A



B

The reaction is known as hydramine fussion:

Structure B is more favored than A, because: 1. when B is subjected to Hofmann exhaustive methylation ephedrine forms 1,2-methylphenyl-ethylene oxide (C) which cannot be expected from A.

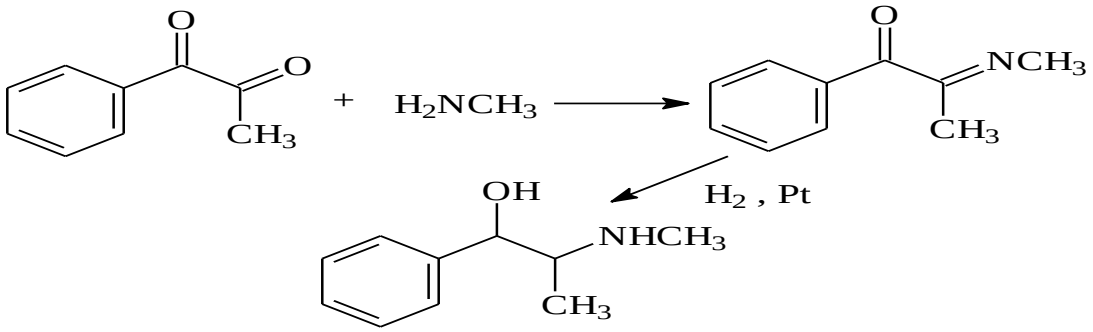


C

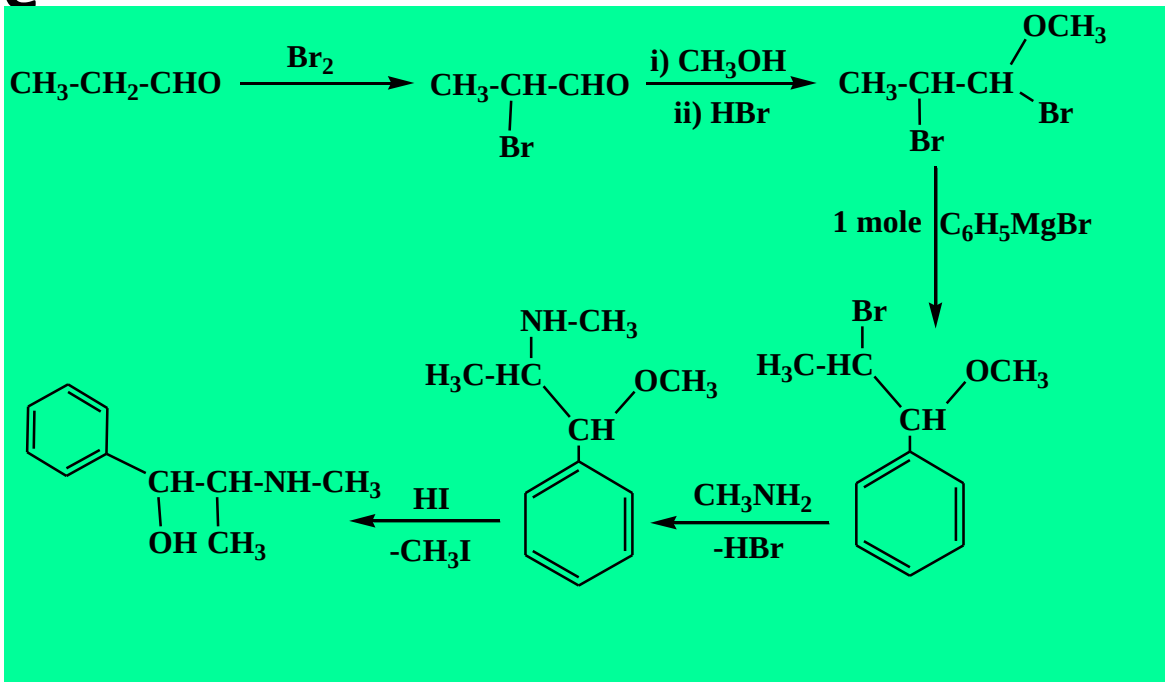
2. Structure A contains chiral carbon atom and when substitute the hydroxyl group by hydrogen atom, it will be produce a compound has (achiral) optically inactive. But structure B contains two chiral carbon atoms and when one substitutes the hydroxyl group by hydrogen atom, it will be produce a compound has chiral carbon atom (optically active); therefore it prefer structure B.

- **Synthesis of ephedrine 49**

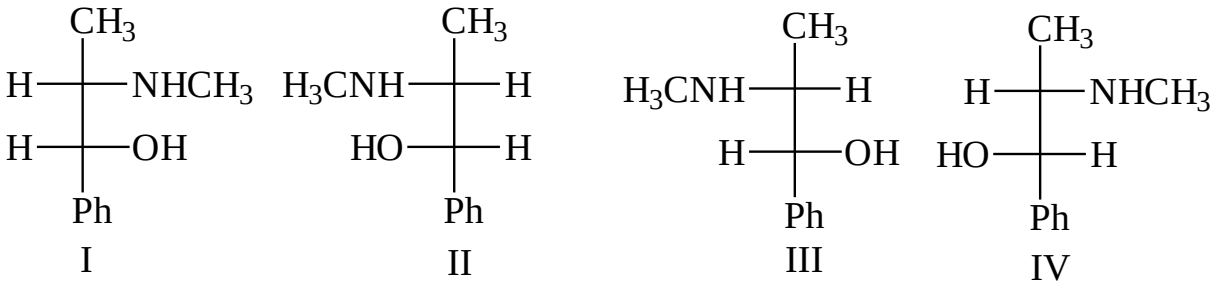
❑ **From 1-phenylpropane-1,2-dione (benzoylacetyl).**



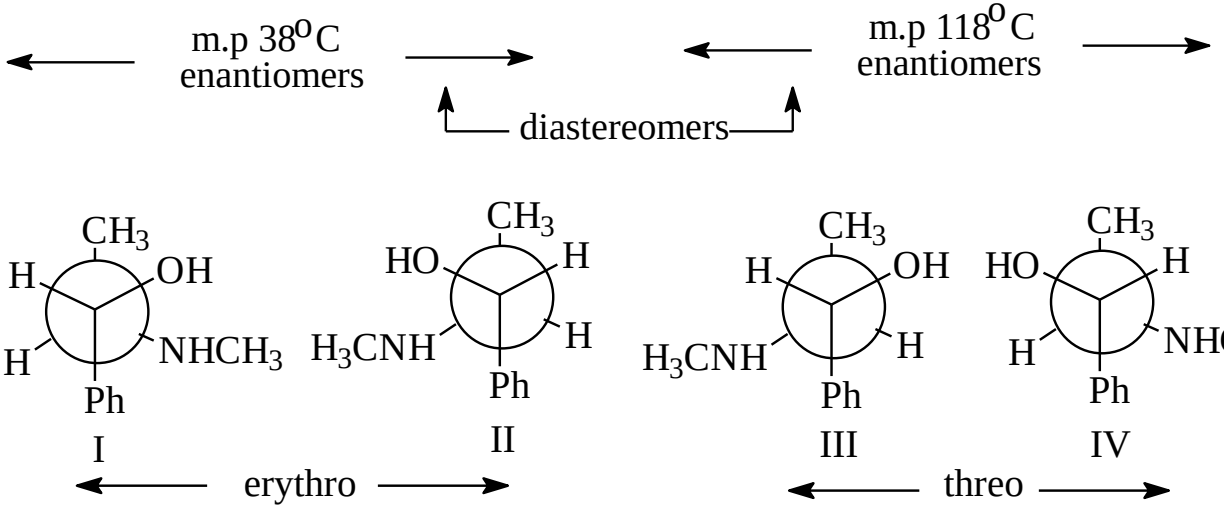
❑ **From propanaldehyde**



- Stereochemistry of ephedrine 49
- I = $2^n = 2^2 = 4$ optically active isomers, *i. e.* two enantiomeric pairs

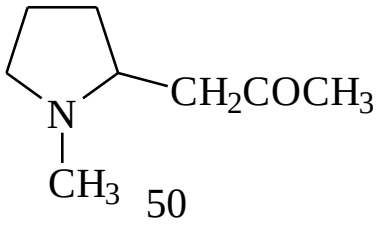


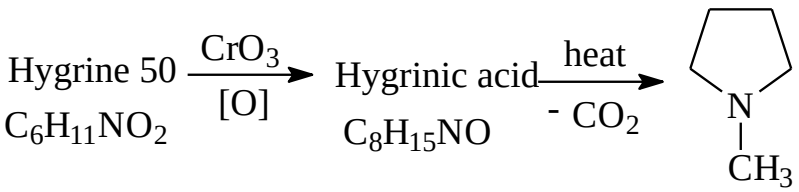
- D(-)-ephedrine L(+)-ephedrine D(-)ψ-ephedrine L(+)ψ-ephedrine
  - $[\alpha]_D$ – 6.3 $[\alpha]_D$ + 6.3 $[\alpha]_D$ – 51.2 $[]\alpha]_D$ + 51.2



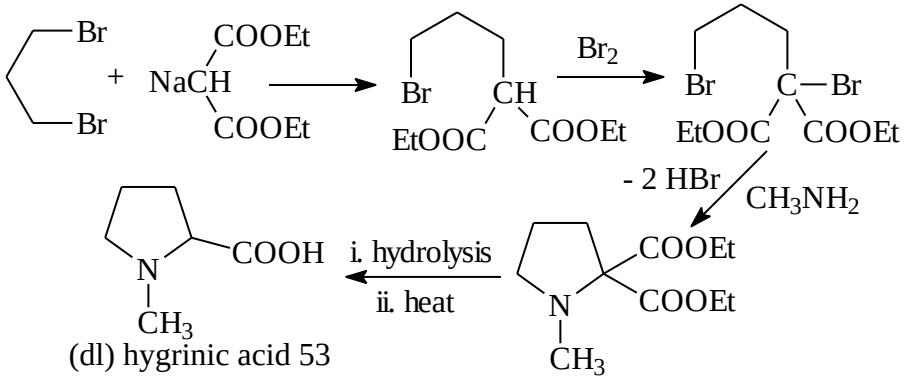
المحاضرة العاشرة

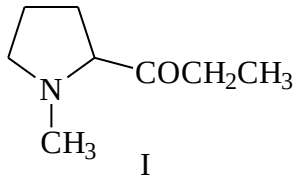
- **Pyrrolidine Alkaloids**
- **Hygrine 50**

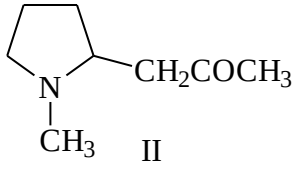


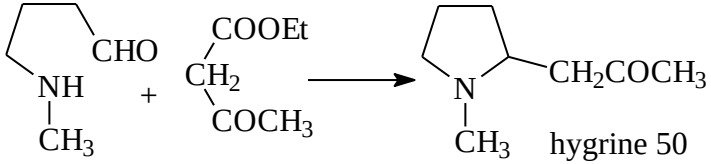


- Synthesis of hygrinic acid 53
- Based on the above results, hygrine 50 may be formulated either I or II.
- Synthesis of hygrine 50

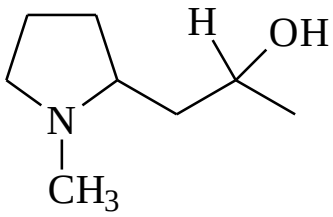




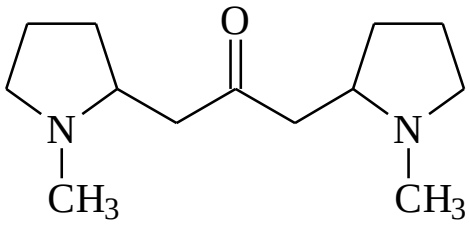




- Structures of other coca alkaloids

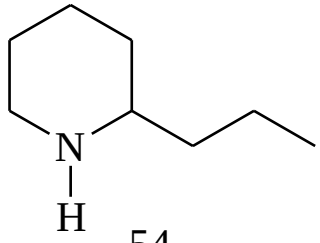


hygriline 51

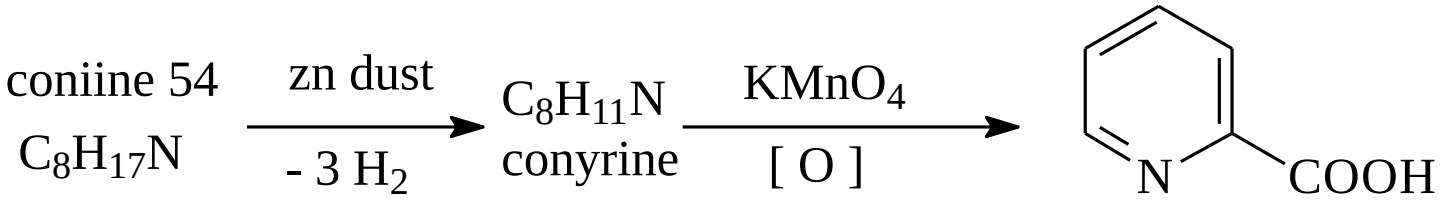


cushygrine 52

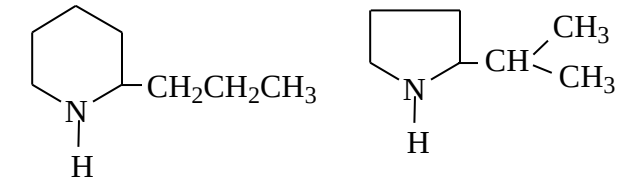
- **Pyridine or Piperidine alkaloids**
- Coniine 54



54



pyridine-2-carboxylic acid

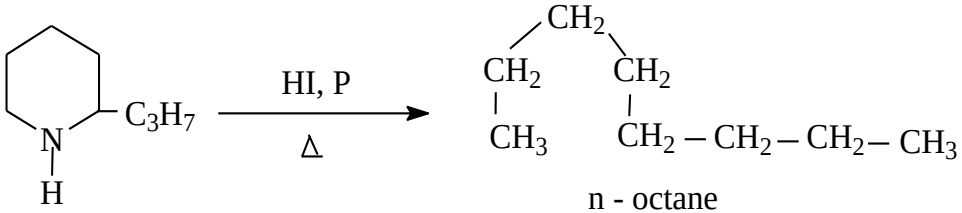


I

2-n-propylpiperidine

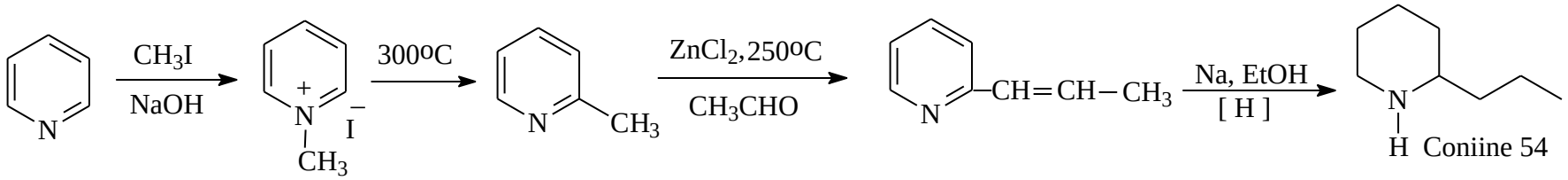
II

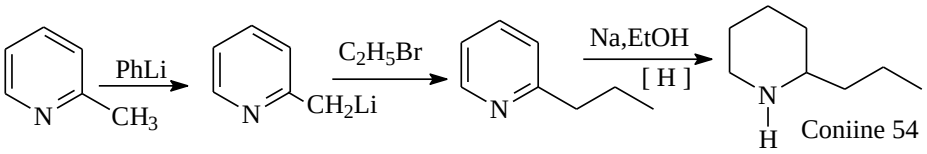
2-isopropylpiperidine



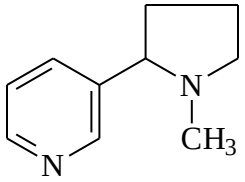
n - octane

- **Synthesis of Coniine 54**

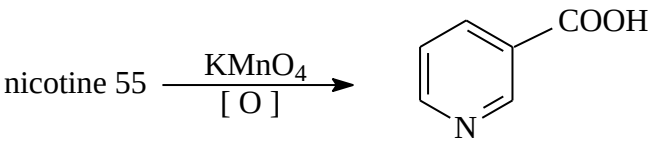


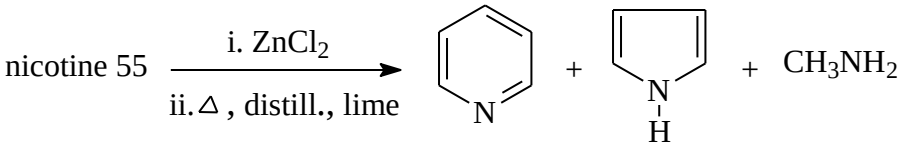


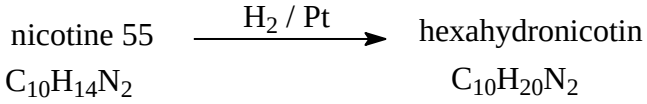
- # Nicotine 55

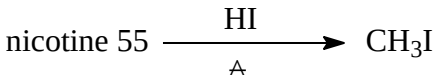


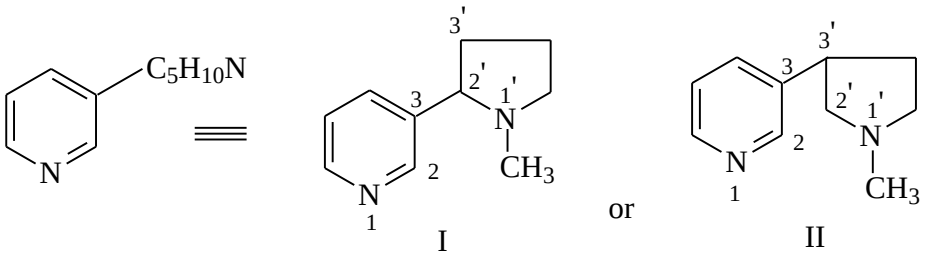
55

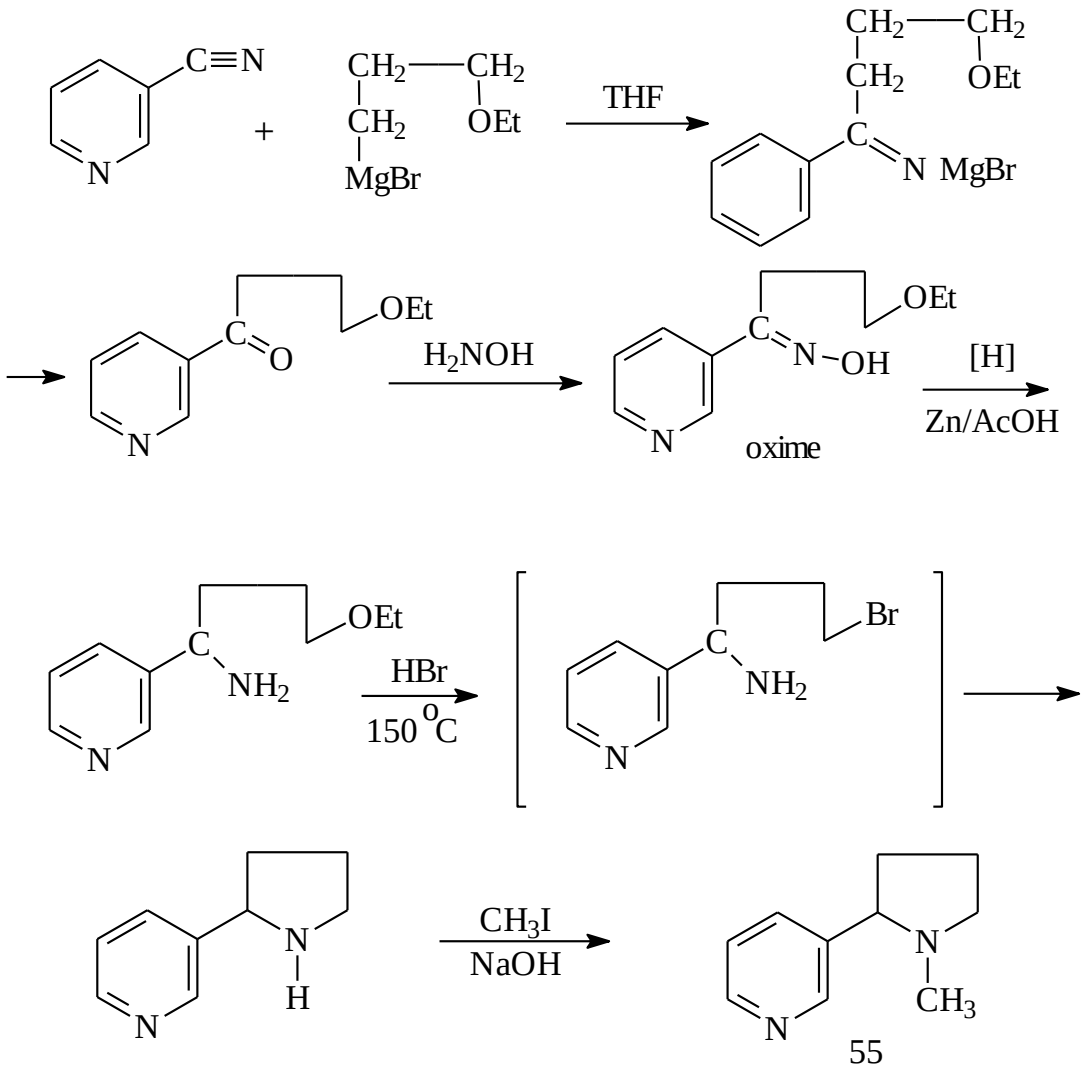






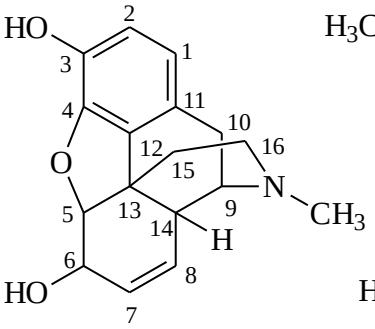




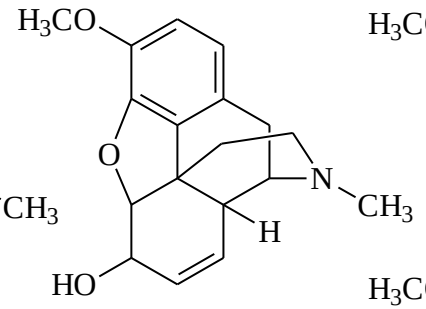

C≡N
N
+
CH2—CH2
CH2 OEt
MgBr
THF
CH2—CH2
CH2 OEt
C
N MgBr
OEt
C
O
N
H2NOH
OEt
C
N OH
N
oxime
[H]
Zn/AcOH
OEt
C
NH2
N
HBr
150 °C
Br
C
NH2
N
N
H
CH3I
NaOH
N
CH3
N

- **Opium alkaloids**
- The opium alkaloids may be classified into the following groups according to the chemical structure :-
- 1- The benzyl isoquinoline alkaloids, *e.g.* papaverine, laudanine, landanosine and nascapine (narcotine).
- 2- The phenyl ethylamine alkaloids, *e.g.* narceine.
- 3- The phenanthrene alkaloids, *e.g.* morphine, codeine and thebaine.
- 4- The diisoquinoline alkaloids, *e.g.* cryptopine and protopine.

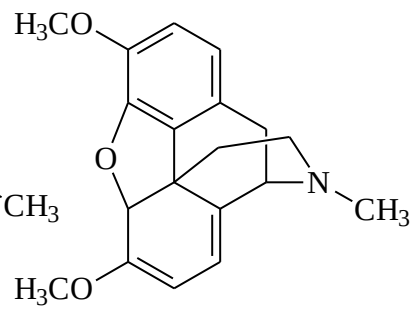
- **Phenanthrene alkaloids**
- <u>Morphine 56, codeine 57 and thebaine 58</u>



morphine 56

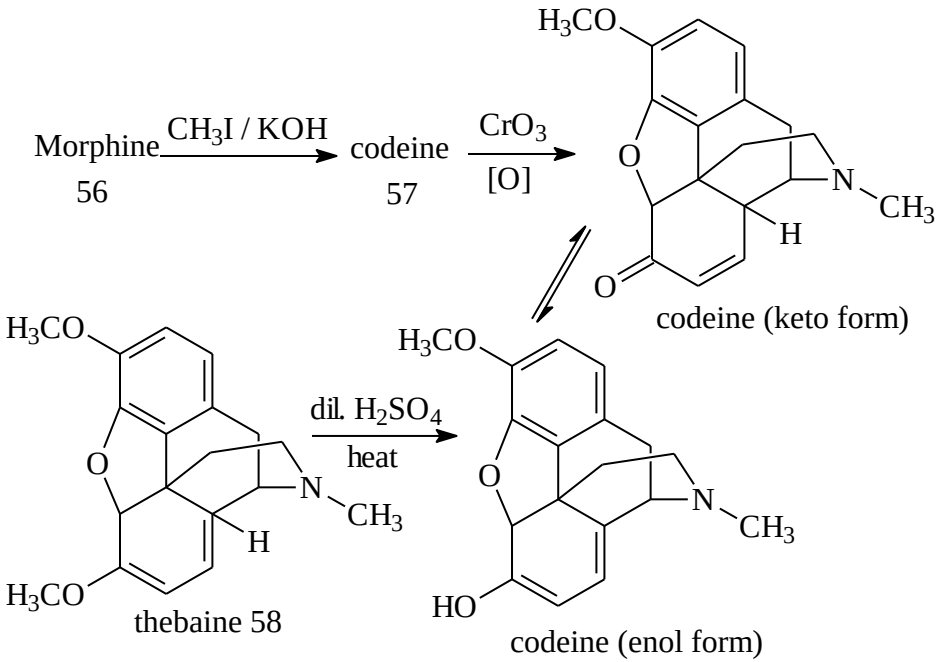


codeine 57

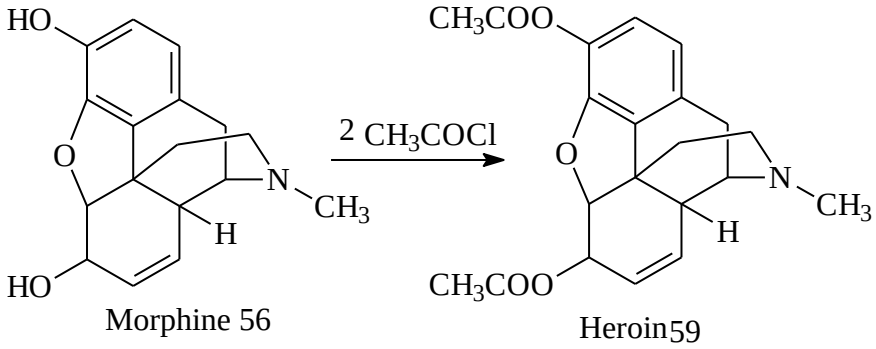


thebaine 58

- The relationship between morphine 56, codeine 57 and thebaine 58.

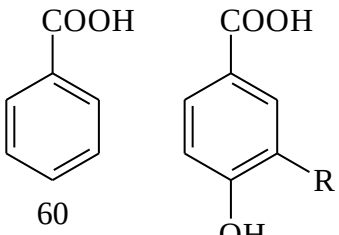


- <u>Heroin 59</u>



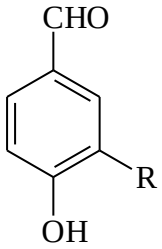
Shikimates

- **Benzoic acid and related compounds (C6-C1)**

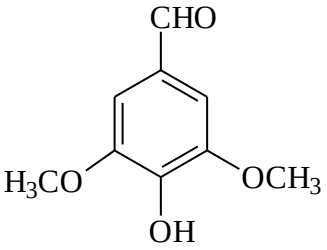


60

61; R = H
62; R = OH
63; R = OMe

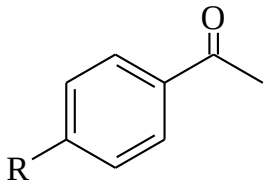


64; R = H
65; R = OMe

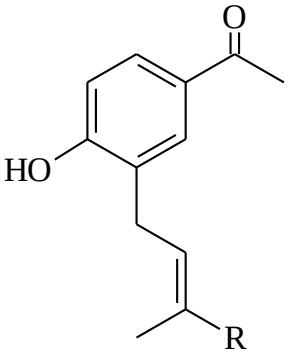


66

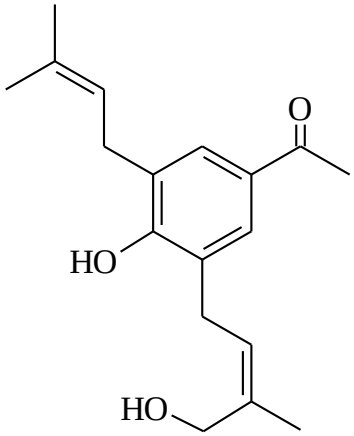
Acetophenones and related compounds (C6-C2)



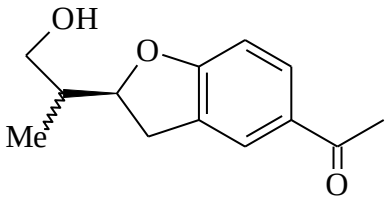
67; R = OH
68; R = OMe



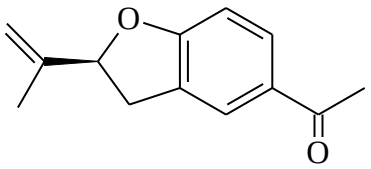
69; R = Me
70; R = CH_2OH



71

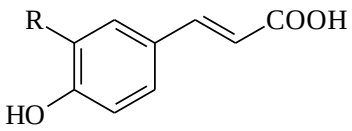


72; R = α-Me
73; R = β-Me

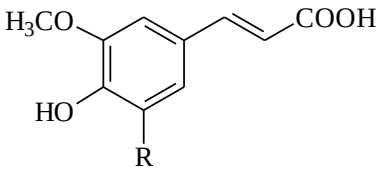


74

- **Phenylpropanoids (C6-C3)**
- **Cinnamic acids**

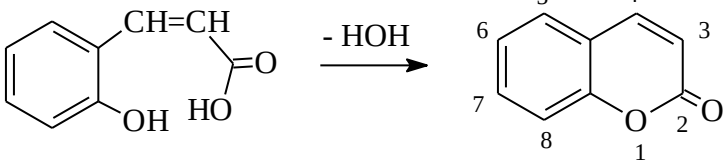


75; R = H
76; R = OH

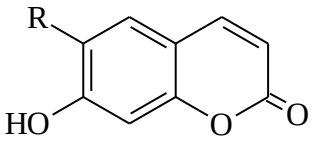


77; R = H
78; R = OMe

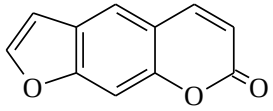
- **Coumarins**



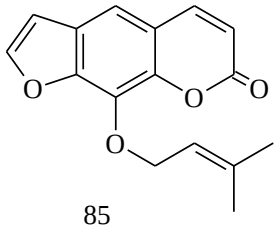
79 80



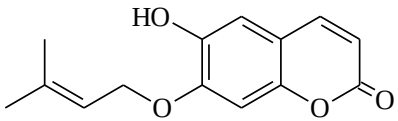
81; R = H
82; R = OH
83; R = OMe



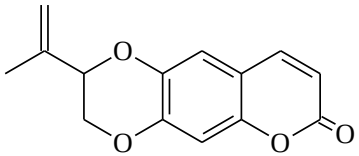
84



85

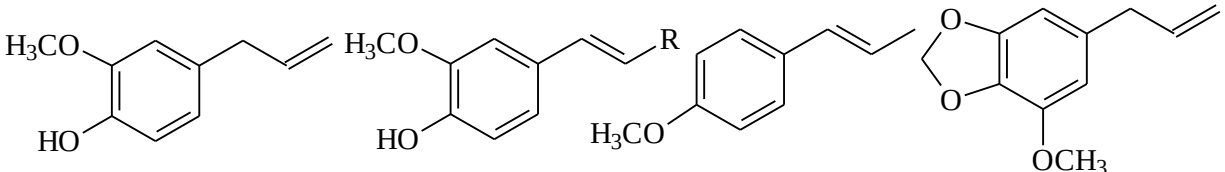


86



87

- **Phenyl propenes**

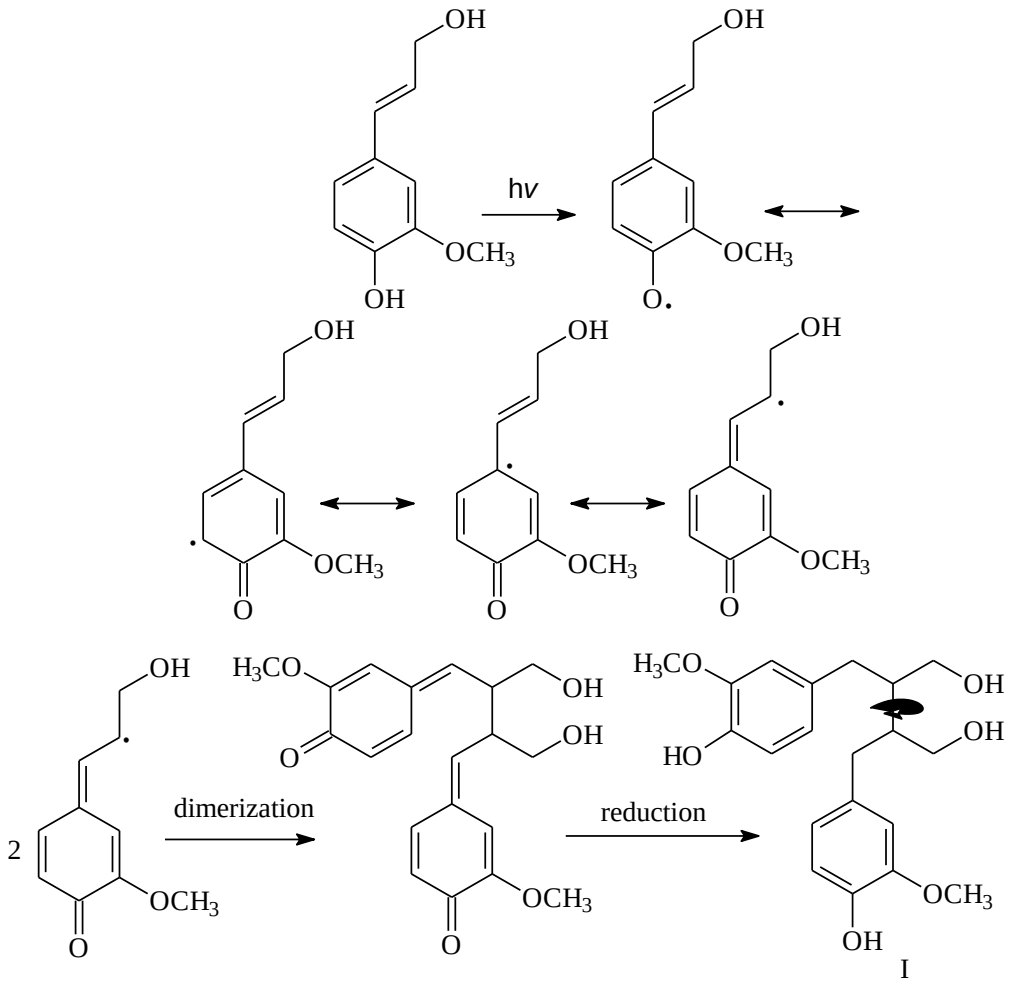


88 89; R = Me 90 91

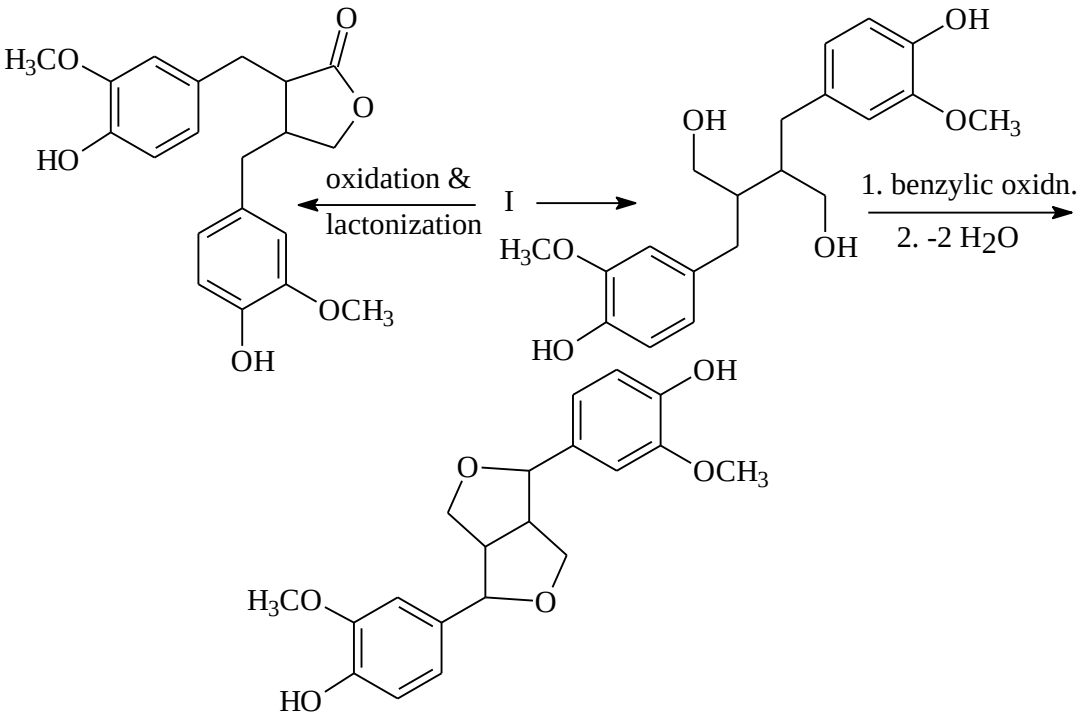
92; R = CH_2OH

93; R = CHO

- **Lignans**

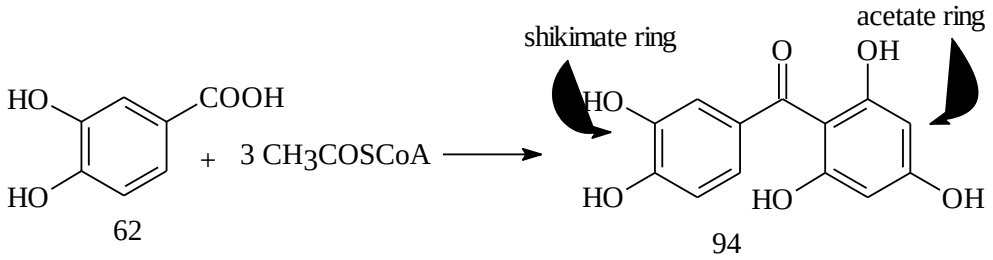


I

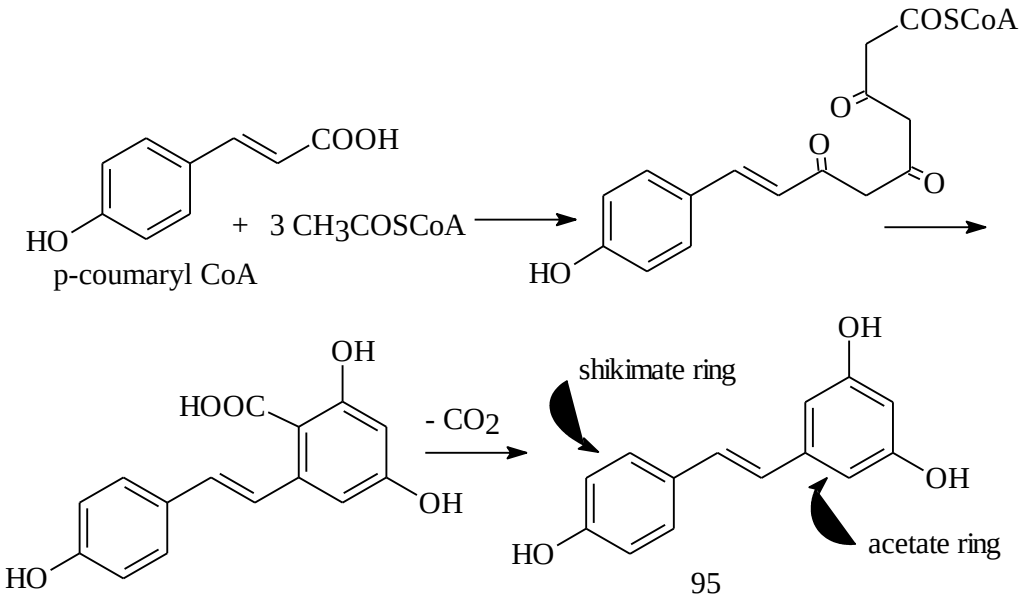

O
H3CO
O
HO
OCH3
OH
oxidation &
lactonization
I
OH
OH
OCH3
1. benzylic oxidn.
2. -2 H2O
H3CO
OH
HO
OH
O
OCH3
H3CO
O
HO

Compounds containing “shikimate” ring

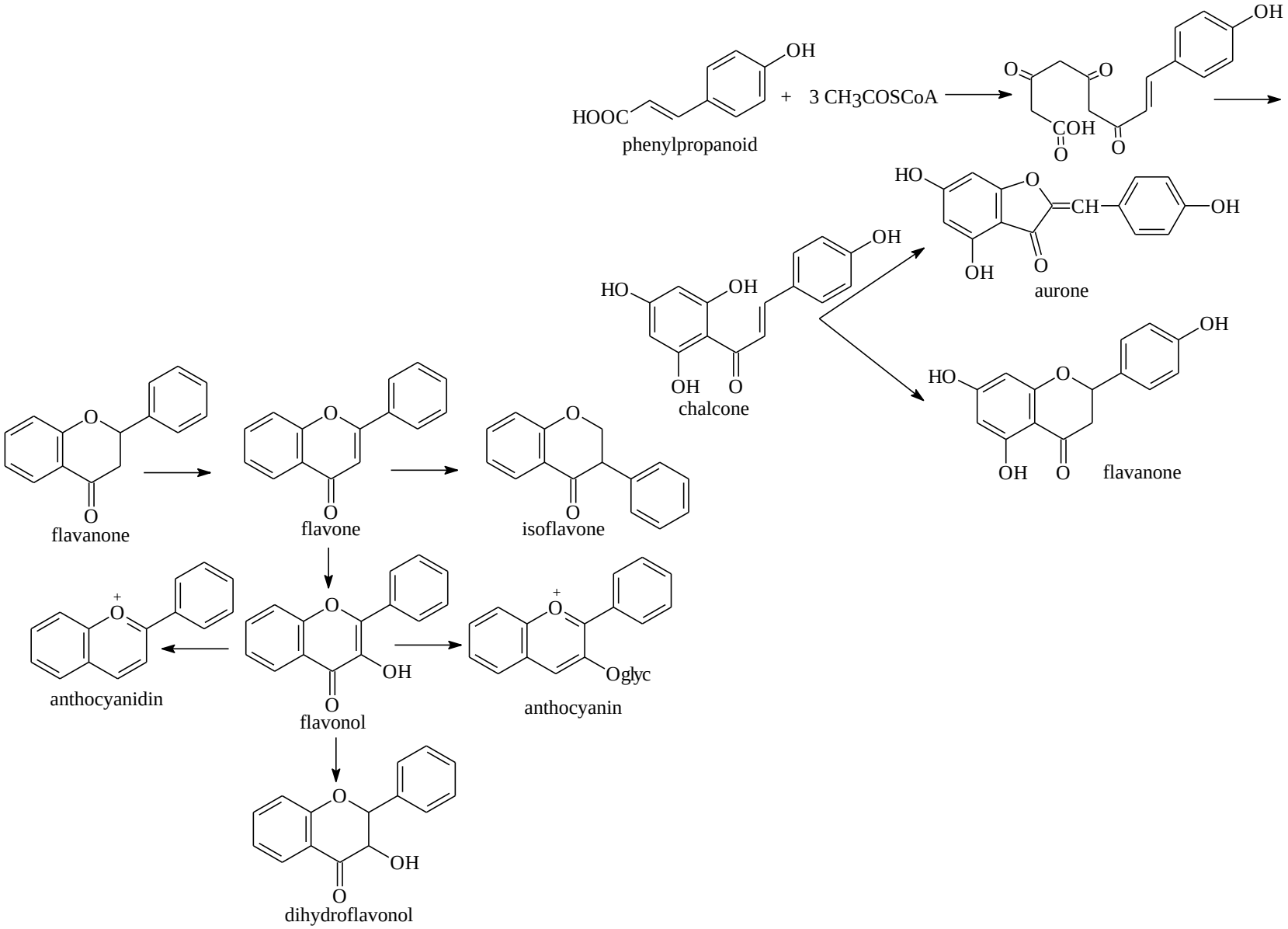
- **Benzophenones (C6-C1-C6)**



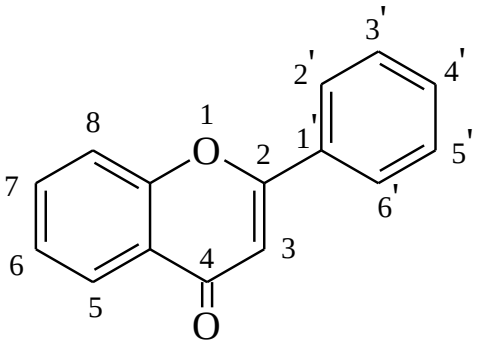
- **Stilbenes (C6-C2-C6)**



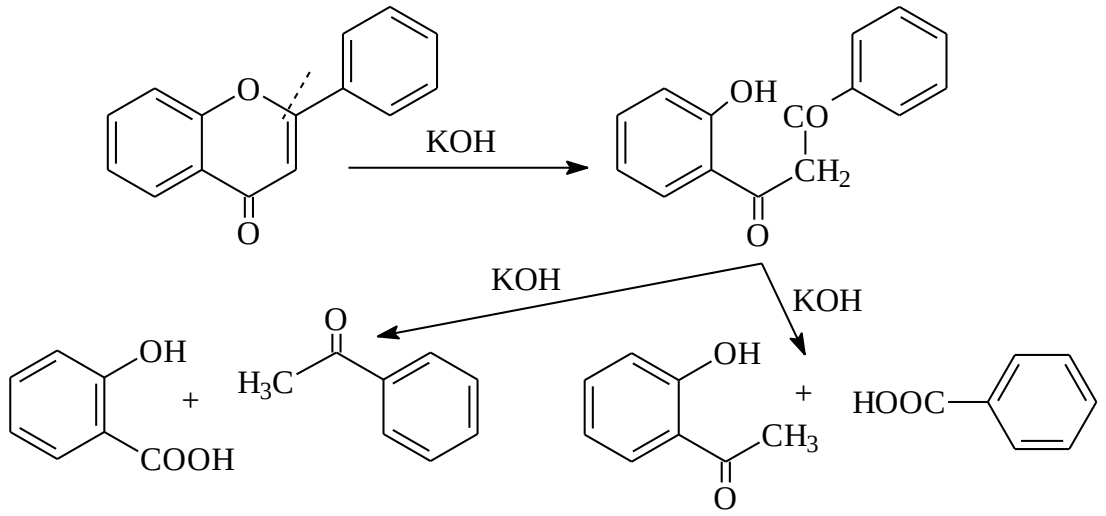
- **Flavonoids (C6-C3-C6)**



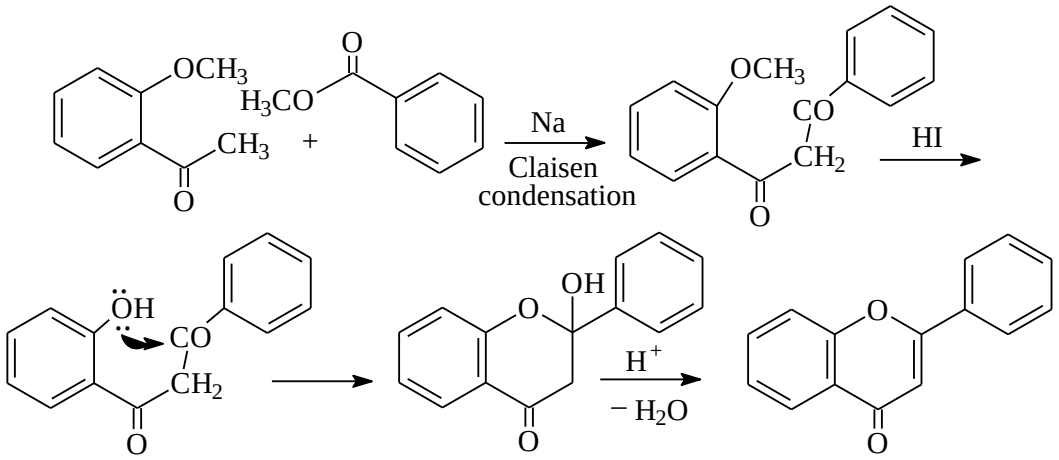
- **Structure-elucidation of some flavonoids**
- Flavone, 102, $C_{15}H_{10}O_2$



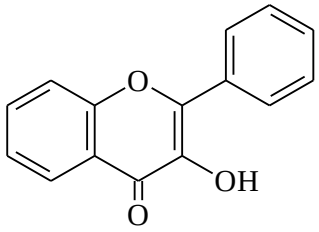
102



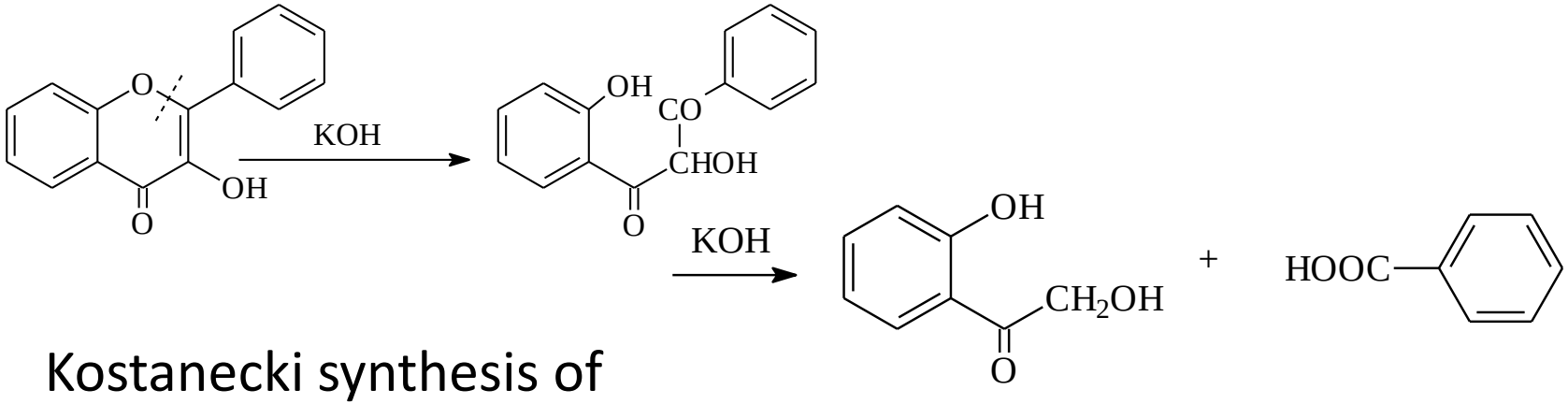
- general method for synthesizing flavones



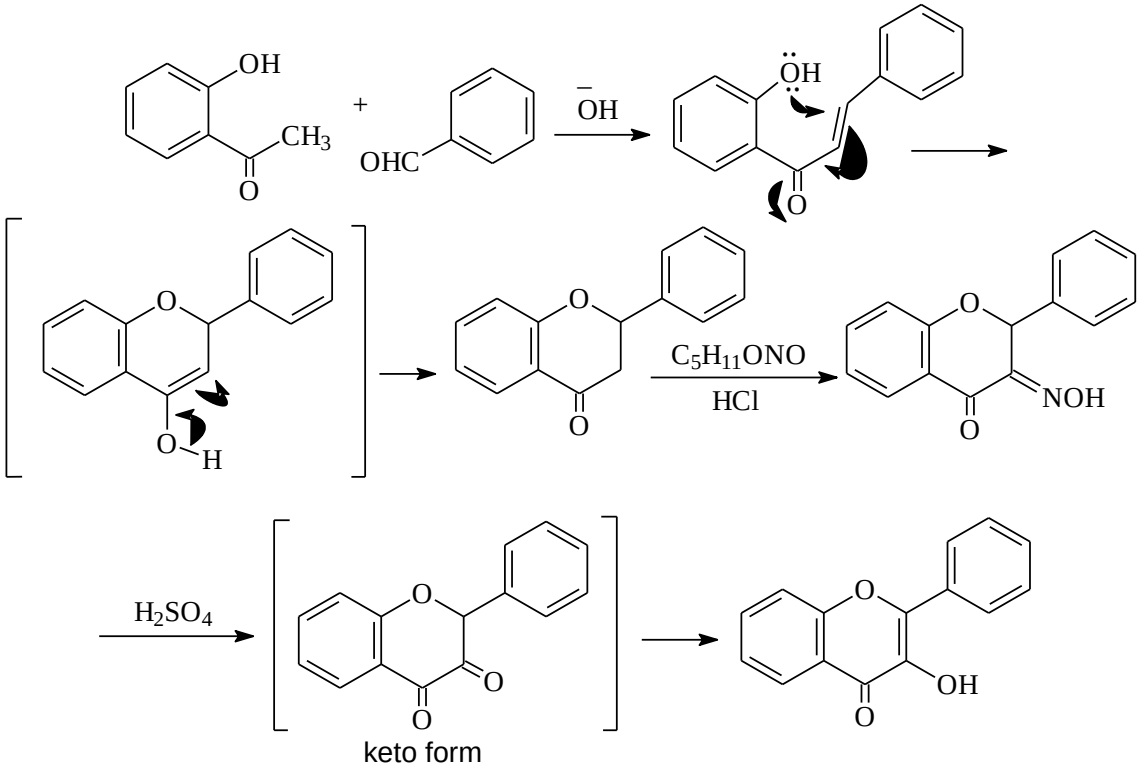
- Flavonol (3-hydroxyflavone), 103, $C_{15}H_{10}O_3$



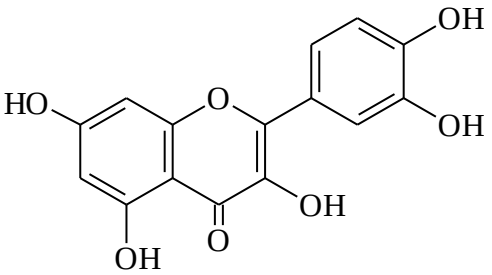
103



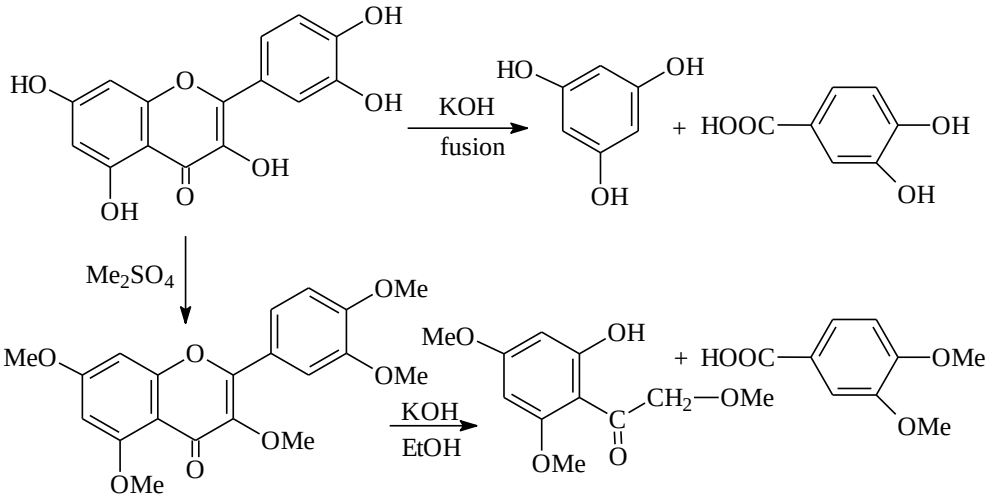
- Kostanecki synthesis of flavonol 103



- Quercetin, 104, $C_{15}H_{10}O_7$



104



- Kostanecki synthesis of quercetin 104