(ك 462)Organic Chemistry
النواتج الطبيـــعية Natural Products

الفرقة الرابعة بكلية العلوم
(١- شعبة كيمياء /ميكرو ٢- ك/نبات ٣-ك/علم الحيوان ٤- ك/جيولوجيا
٥- ك/علم الحشرات ٦-علم الحيوان ٧- علم الحشرات)
العام الدراسي ٢٠٢٢-٢٠٢٣ الفصل الدراسي الثاني

اعداد

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قسم الكيمياء – كلية العلوم

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Terpenoids	Definition –Extraction -*Structure elucidation -Classification –monoterpenoids* – Cyclic Monoterpenoids(Limonene-Menthol-Camphor)-Sesquiterpenoids-Diterpenoids-Triterpenoid-tetraterpenoids –Polyterpenoids (rubber)
Steroids	Definition of steroids Classification Determination of ring A in cholesterol and cholic acid Determination of the nucleus - Blanc Rule 1-Sterols (cholesterol **)** 2-Vitamin D(vitamin D2) 3-Bile Acids (cholic acid) 4- Steroidal Hormones or Sex Hormones(progesterone) 5- Adrenocortical hormones (cortisone)

تعريف النواتج الطبيعية –التقسيم
Definition of Natural Product -Classification

Natural products are organic compounds produced by living organisms, such as human organs, plants, animal organs, sea organisms and micro-organisms, as a result of the metabolism.

According to their physiological influence and according to their structural composition, and they are studied in groups as follows:

1. القلويدات (اشباه القلويات)Alkaloids
2. التربينات Terpenes
3. الاستيرويدات Steroids
4. الفلافونويدات والانثوسيانينات Flavonoids and anthocyanins
5. الكومارينات Coumarins
6. الفينانثرينات Phenanthrens
7. المضادات الحيوية Antibiotics
8. الفيتامينات Vitamins

And there are some interactions, for example, vitamin A, which is classified as diterpens . As for the modern classification, it is as follows It is classified into a smaller number of sects, namely :

1. القلويدات Alkaloids
2. التربينات Terpenes
3. الاستيرويدات Steroids
4. المركبات الفينوليه Phenolic compounds

ALKALOIDS --- القلويـدات

Definition of alkaloids

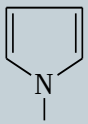
-All organic bases isolated from plants, and it covers wide variety of compounds.

-(Konigs)suggested that alkaloids should be defined as [naturally occurring organic bases which contain a pyridine ring] ,this definition include a limited number of compounds.

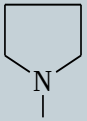
-(Ladenburg definition): natural plant compounds having a basic character and containing at least one nitrogen atom in heterocyclic ring .

Alkaloids have clear physiological effects, and are chemically related to pyrrole, pyridine, quinoline and isoquinoline, which are different heterocyclic rings, some of which are highly toxic, and some are used as medical drugs such as quinine used to treat malaria, morphine to remove pain or cocaine as a local anesthetic and atropine in surgery and ophthalmology.

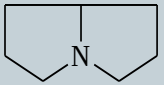
Different heterocyclic rings related to alkaloids



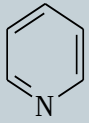
pyrrole



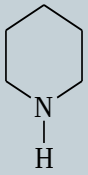
pyrrolidine



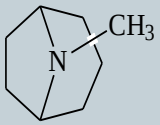
pyrrolizidine



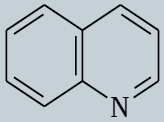
pyridine



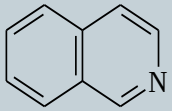
piperidine



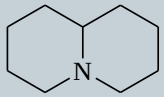
tropane
(piperidine-pyrrolidine)



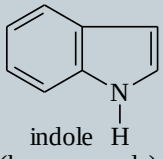
quinoline



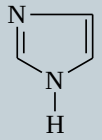
isoquinoline



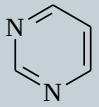
nor-hipinane



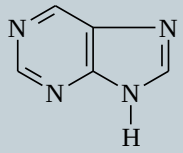
indole
(benzopyrrole)



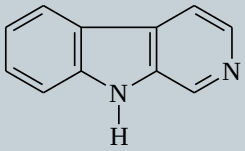
imidazole



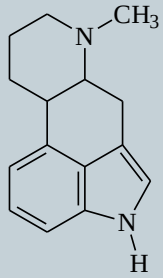
pyrimidine



purine



carboline



indole + hydroquinoline

Extraction of alkaloids استخلاص القلويدات

- Alkaloids are generally found in plants in the form of salts combined with some organic acids such as malic or citric acid .
- .Alkaloids are found mainly in fruits and seeds, as well as in tree bark.
- We extract the alkaloids from the plants by carefully cutting the plants, then adding a solution of hydrochloric or sulfuric acid to form their corresponding mineral salts.
- In this process, the alkaloids (bases) are liberated from the organic acids, and then the alkaloids are dissolved in the form of solutions of salts of hydrochloric or sulfuric acid with sugars and some other compounds found in the tissues of plants.
- As the alkaloids do not dissolve in water, they can be precipitated from chloride or sulfuric salts by adding bases such as sodium or potassium hydroxide.
- In the case of volatile alkaloids such as nicotine, the salt solution or the raw material is treated with the addition of alkali (sodium hydroxide) and treated by steam distillation, then the alkaloids are extracted by organic solvents such as, chloroform or other organic solvents.
- The mixture of alkaloids is separated by various methods into pure substances .

General Properties الخواص العامـــة

. Alkaloids are colorless, in crystalline form, and do not dissolve in water, but dissolve in organic solvents, such as, chloroform, ethyl alcohol ... etc.

But there are liquid alkaloids that can be mixed with water, such as coniin and nicotine, and some have a yellow color like piperine.

Most alkaloids have a bitter taste and optically active .

It generally contains one or two nitrogen atoms in a tertiary state in a ring.

Most alkaloids also contain an oxygen.

الطرق العامة لتعيين تركيب القلويدات
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- Functional nature of oxygen

The oxygen atom may be present in the form of alcoholic or phenolic hydroxyl (-OH), methoxyl (-OCH_3), acetoxyl $OCOCH_3$), benzoxyl (- COC_6H_5), carboxyl (-COOH) or carbonyl (C=O) group, various oxygen functional groups can be characterized according to the following characteristics

Functional nature of oxygen طبيعة ذرة الأكسجين

(A) 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.

(B) 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.

(C) 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.

Functional nature of oxygen

(D) 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 hydroiodic acid at its boiling point (126°C) when the alkoxy groups are converted into alkyl halides which can be easily estimated as silver iodide by treatment with ethanolic silver nitrate.

$$R\text{-}OCH_3 + HI \xrightarrow{126^{o}C} ROH + CH_3I \xrightarrow{AgNO_3} AgI\ (ppt.)$$

The number of moles of silver iodide is equivalent to the number of alkoxyl groups in the alkaloid.

(E) The related group, **methylene dioxy (-O-CH_2-O-)** is estimated on the basis that it liberates formaldehyde when treated with hydrochloric or sulphuric acid; thus the quantitative estimation of formaldehyde will give the number of methylene dioxy groups.

F)**Oxo group** the presence of an oxo group is readily determined by formation of an oxime ,semi carbazone and phenylhydrazone .

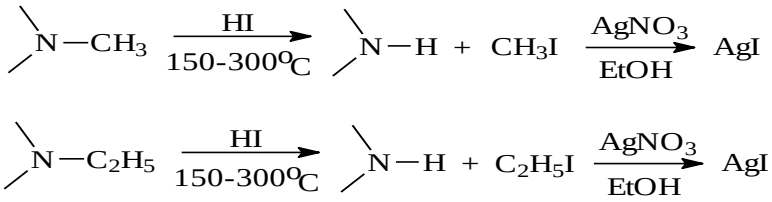
Alkaloids

Determination of the structure - The nature of N

a)The general reaction of alkaloid with acetic anhydride,methyl iodide and nitrous acid show the nature of the nitrogen

b)Distillation with aqu.pot.hydroxide gives information about the nature and number of alkyl groups attached to nitrogen

c) The N-alkyl groups are frequently estimated by Herzig Meyer method



d)Hydrolysis show the presence of an amide ,lactam ---in the alkaloid structure .

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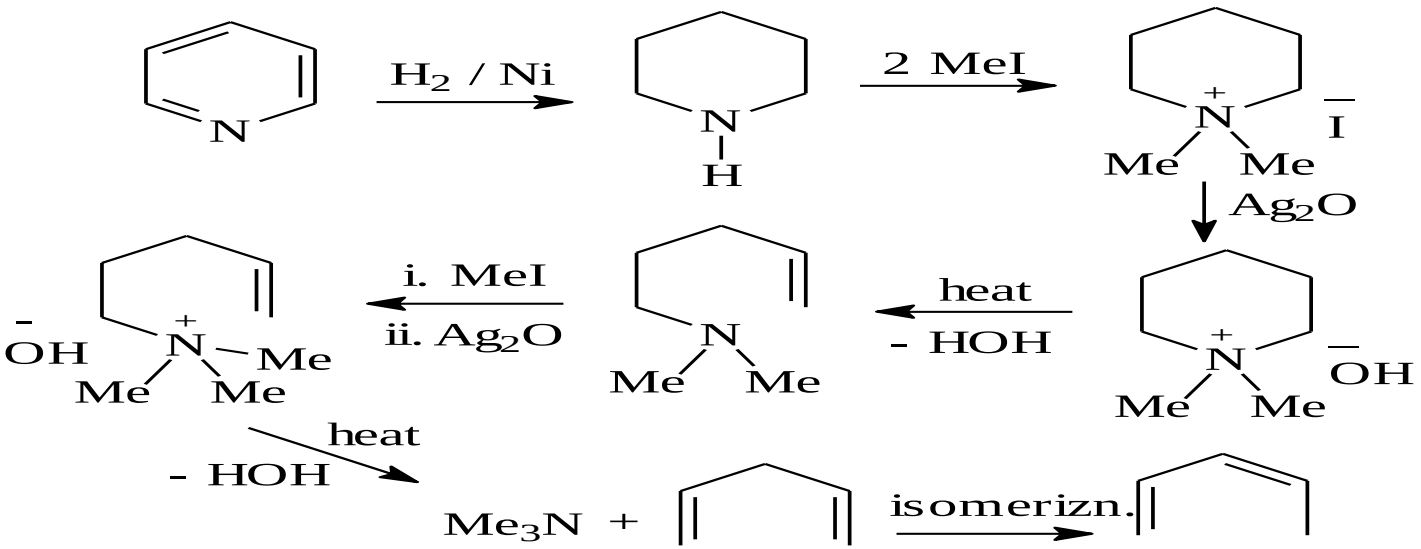
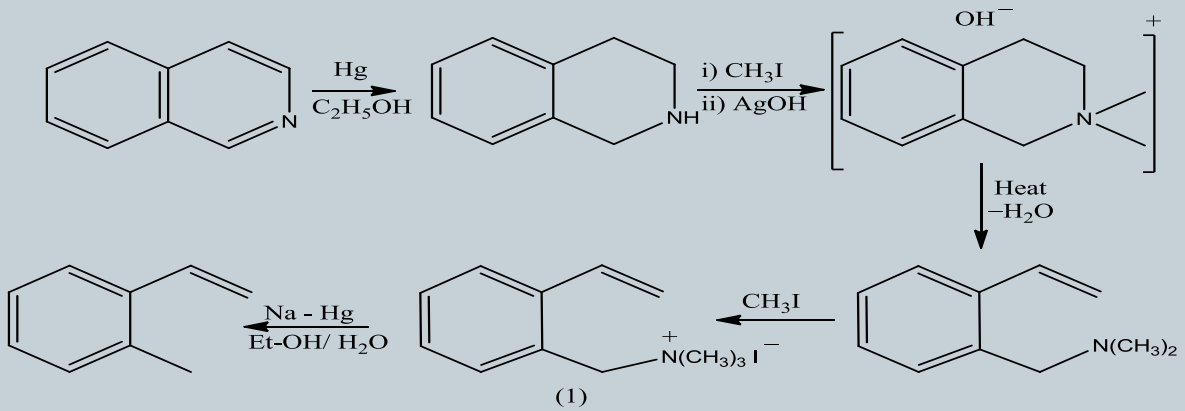
Determination of the structure
Functional nature of nitrogen

e)Hofmann exhaustive methylation :

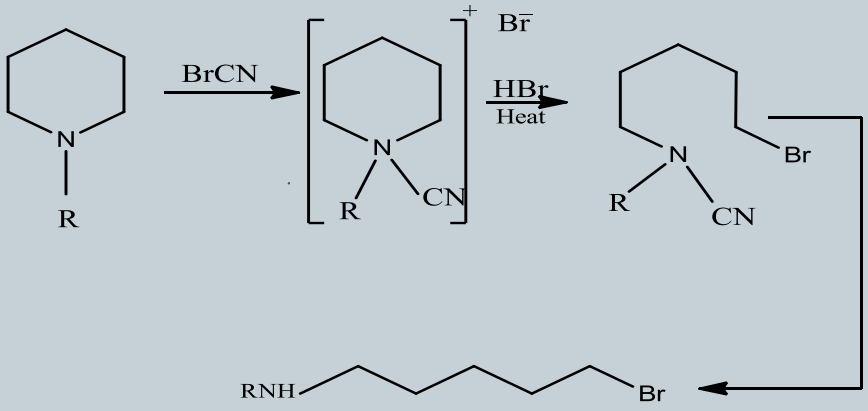


Functional nature of nitrogen

Emid modification

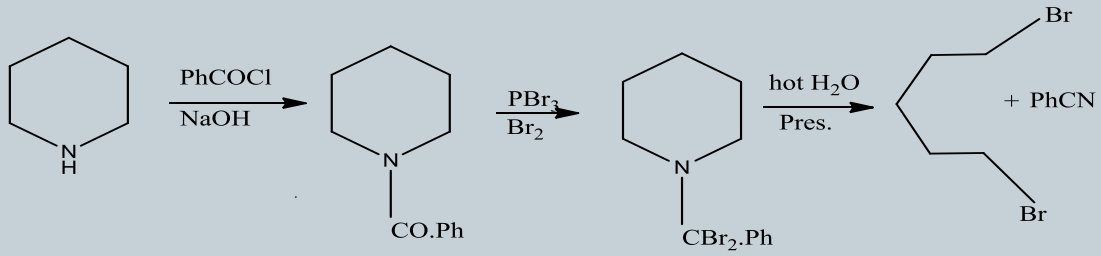


Von Braun methods for tertiary cyclic amines

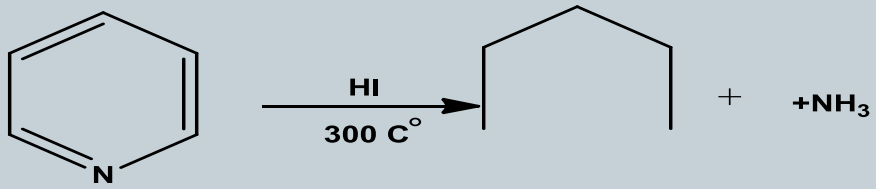


Functional nature of nitrogen

Von Braun methods for secondary cyclic amines



By using hydro iodic acid



Determination of the structure

4-Detection of the unsaturation : by addition of bromine and halogen acids or by reduction by means of sodium amalgam ,sodium and ethanol and hydrochloric acid etc----- .

5- Oxidation:
a)Mild oxidation (hydrogen peroxide-ozone- iodine in ethanolic solution ---)
b)Moderate oxidation (acid or alkaline pot.permenganate-chromium trioxide in acetic acid--) c)Vigorous oxidation (pot.dichromate in sulphuric acid–conc.nitric acid -chromium trioxide in sulphuric acid ---)
6- Alkali fusion: fusion with solid potassium hydroxide and investigation of the products .
7-Distillation with Zinc dust and investigation of the products .
8-Physical methods : (IR –NMR-MS-UV- X ray)
9- Synthesis :
Finally, the structure proposed by degradative methods is confirmed by the synthesis.

Classification of alkaloids

Phenylethyl amine alkaloids

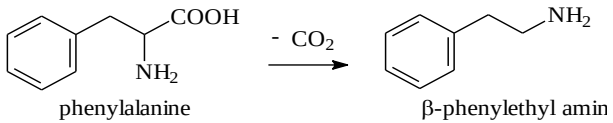
Classification of alkaloids

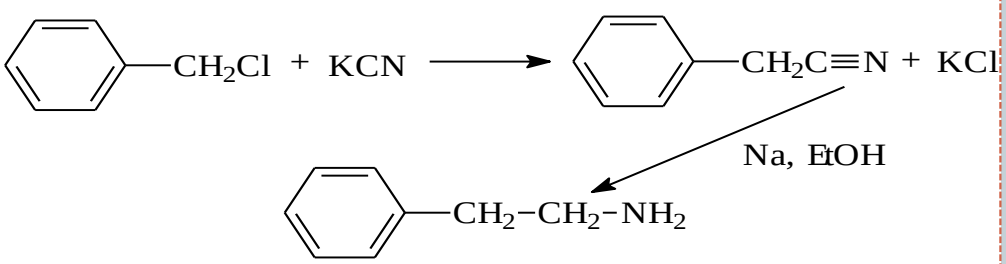
(1) Phenylethyl amine alkaloids
(2) Pyrrolidine alkaloids
(3) Pyridine or piperidine alkaloids
(4) Pyridine-pyrrolidine alkaloids
(5) Tropane alkaloids
(6) Quinoline alkaloids
(7) Isoquinoline alkaloids
(8) Phenanthrene alkaloids
(9) Indole alkaloids

Phenyl ethyl amine group

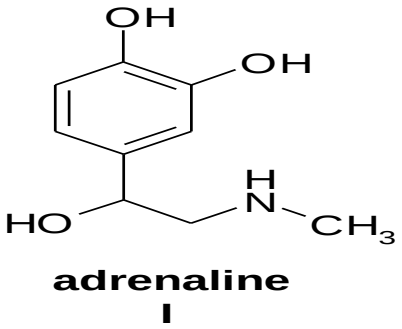
Many compounds of this group are known some natural and other synthetic .The physiological action is to increase the blood pressure .They are referred to as the blood - pressure drugs.

Synthesis of Beta phenyl ethyl amine



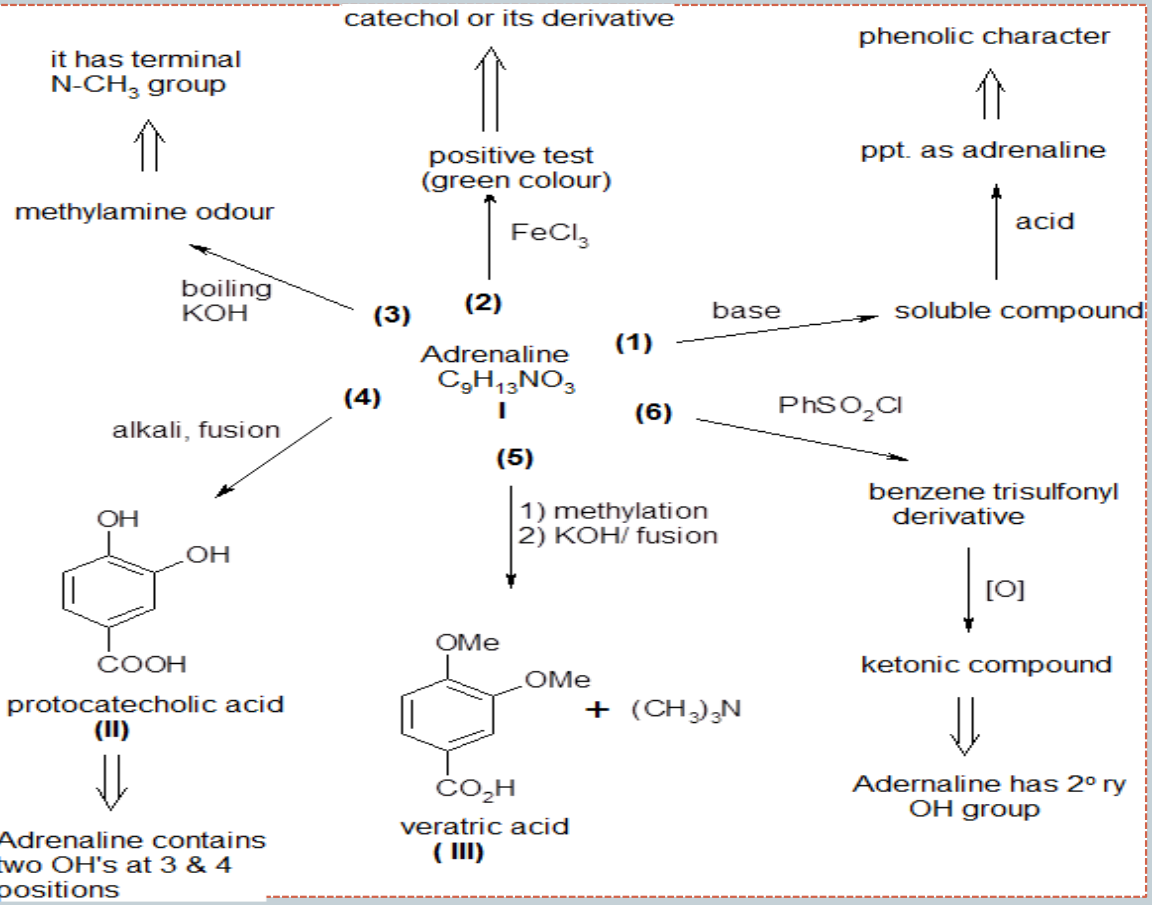


($C_9H_{13}NO_3$) Adrenaline الأدرينالين



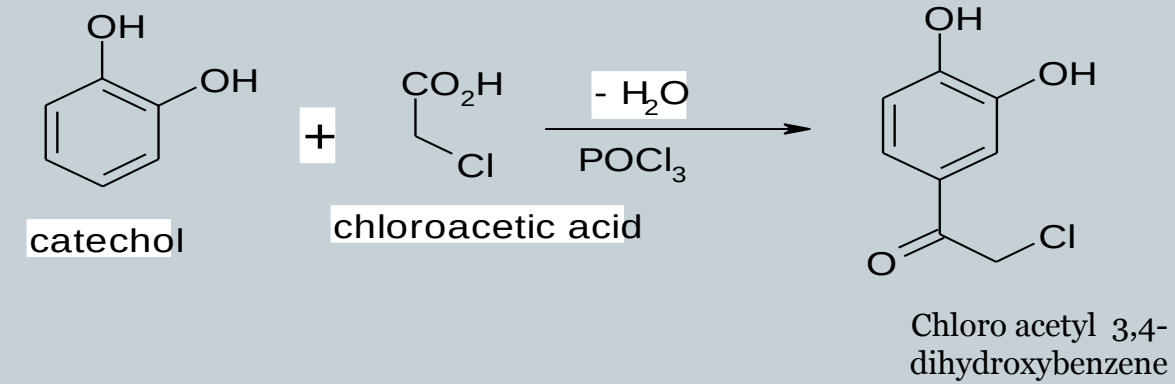
adrenaline
I

It is a non-steroid hormone. Adrenaline was the first hormone to be isolated in a crystalline form ,adrenaline is active only when given by injection , it raises blood pressure ,is used locally to stop hemorrhage.

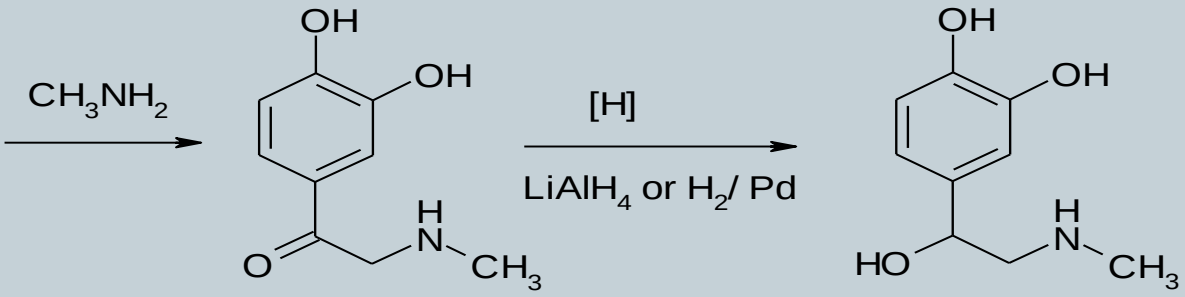


الأدرينالين ($C_9H_{13}NO_3$)

Synthesis of adrenaline

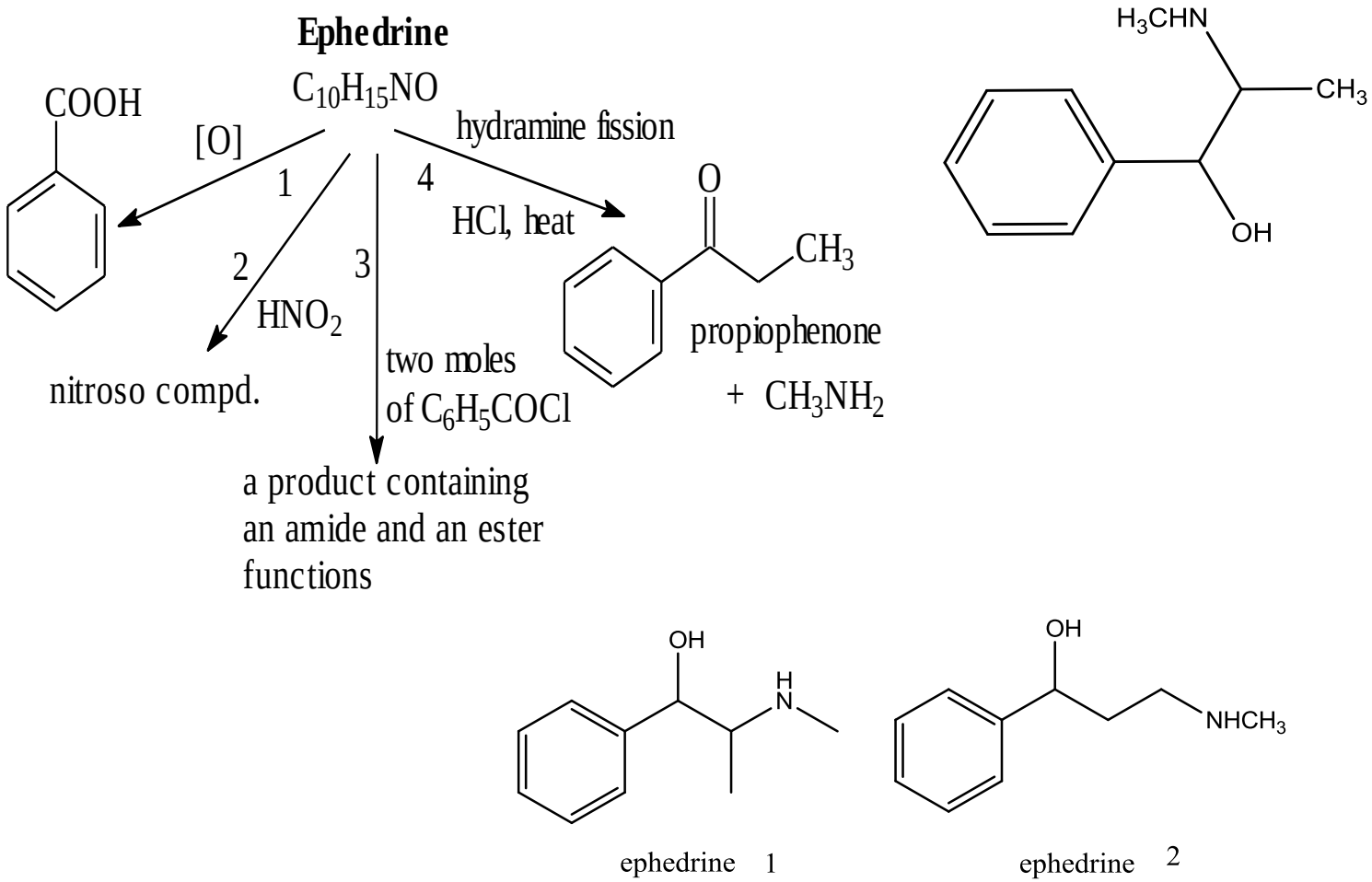


Chloro acetyl 3,4-dihydroxybenzene



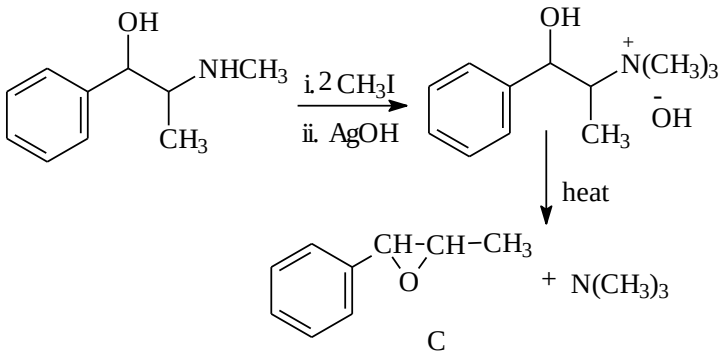
(±)- adrenaline

Ephedrine

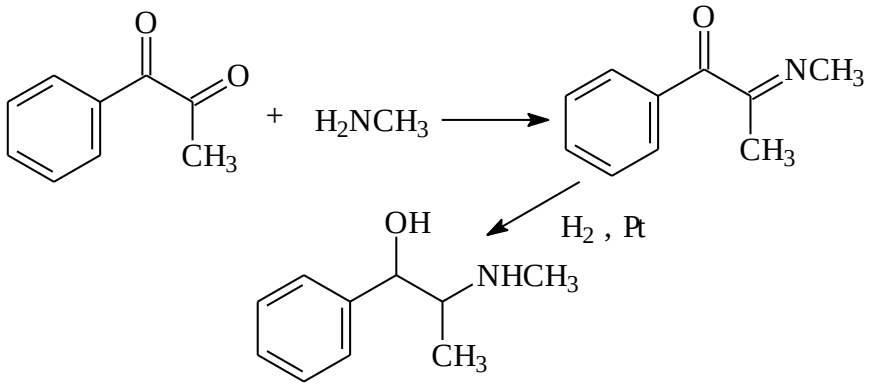

Ephedrine
$C_{10}H_{15}NO$
COOH
[O]
1
2
HNO_2
nitroso compd.
3
two moles
of C_6H_5COCl
a product containing
an amide and an ester
functions
hydramine fission
4
HCl, heat
O
CH_3
propiophenone
+ CH_3NH_2
H_3CHN
CH_3
OH
OH
H
N
ephedrine 1
OH
$NHCH_3$
ephedrine 2

Ephedrine

Hofmann exhaustive methylation :



Synthesis of ephedrine

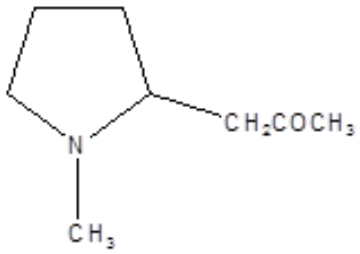


قلويدات مجموعة البيروليدين (Pyrrolidine group)

الهيجرين (Hygrine) $C_8H_{15}NO$

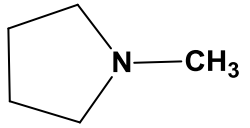
Confirmation of the structure

اثبات الشكل التركيبي للهيجرين :



$C_8H_{15}NO$ —Oxidation→ $C_6H_{11}NO_2$ —Dry distilation→

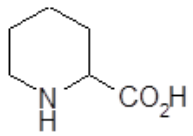
Hygrine — Hygrinic acid

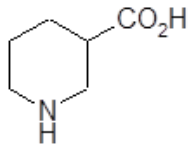


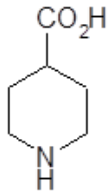
Methyl pyrrolidine

On oxidation of Hygrine ,Hygrinic acid is formed . Hygrinic acid was first believed to be a one from piperidine carboxylic acids but comparison with the three acids show ed this was incorrect.

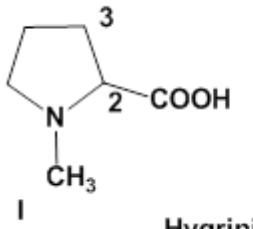
اكسدة الهيجرين كونت حمض الهيجرينيك الذي كان يعتقد انه حمض من احماض البيبريدين الكربوكسيلية الثلاثة والمقارنة اثبتت عدم صحة هذا الافتراض .





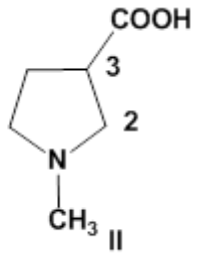


piperidine carboxylic acids



I

or



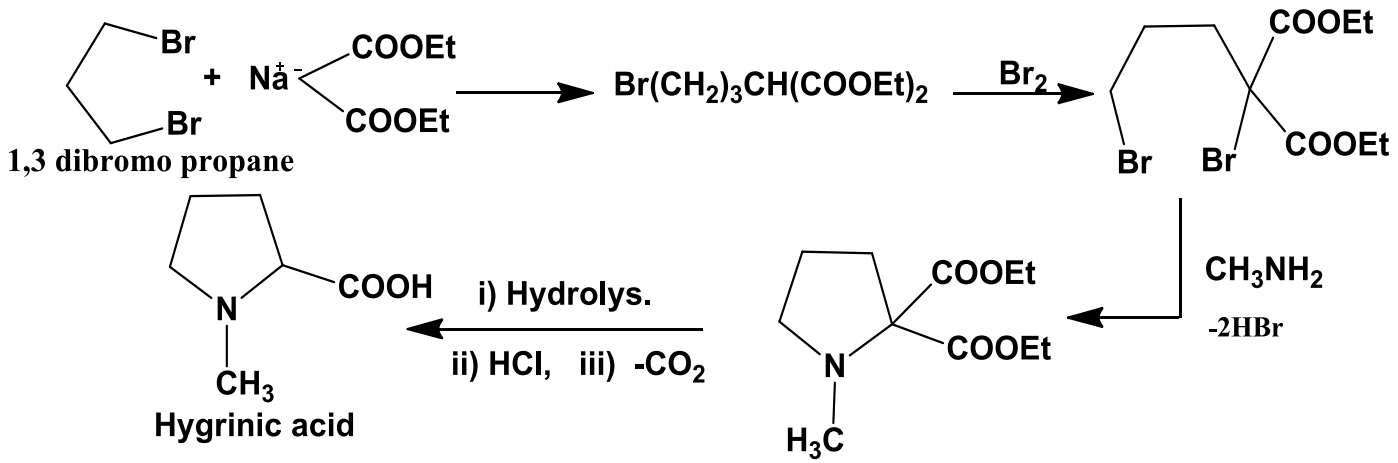
II

Hygrinic acid

الهيجرين (Hygrine)

تحضير حمض الهيجرينيك

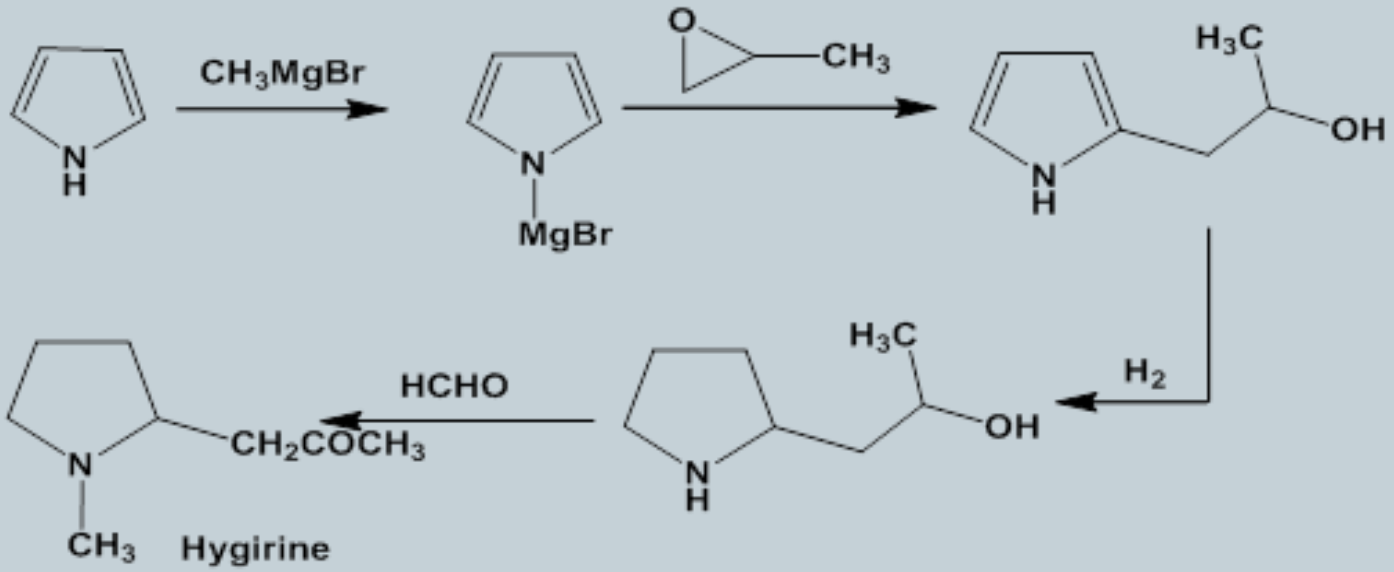
Synthesis of Hygrinic acid(N-methylpyrrolidine carboxylic acid)



Synthesis of Hygrine تحضير الهيجرين

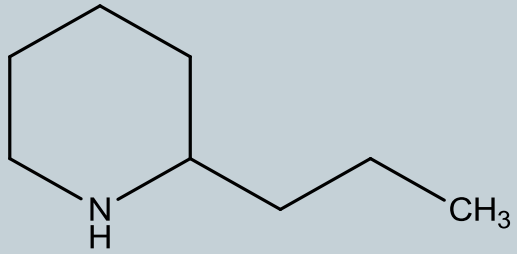
Synthesis of Hygrine

تحضير الهيجرين



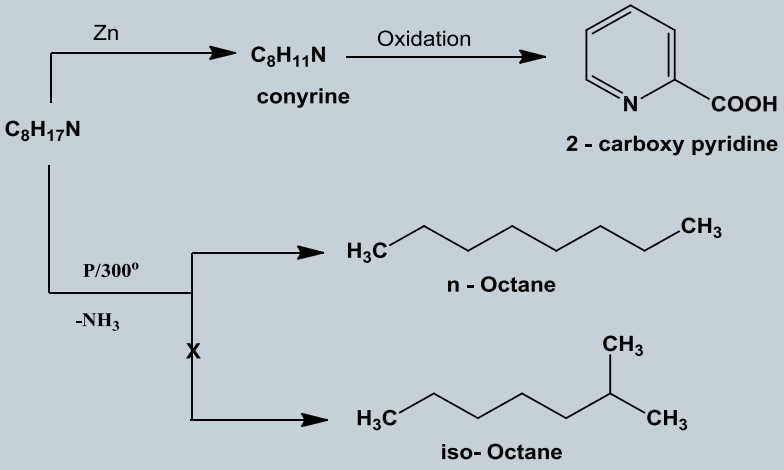
قلويدات مجموعة البيريدين

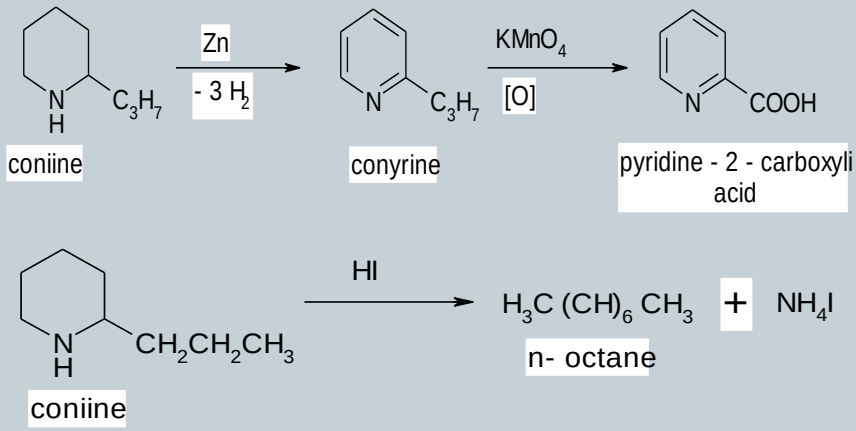
Pyridine alkaloids Coniine الكونييـن $C_8H_{17}N$



Confirmation of the structure اثبات الشكل التركيبي للكونيين

1-M.F $C_8H_{17}N$
2-Dry dist. with zinc dust coniine is converted into conyrine
3- Pyridine 2-carboxylic acid (α-picolinic acid)was obtained via oxidation of conyrine
4- Coniine is may be piperidine with side chain with three carbon atom
5- the side chain either n-propyl or iso propyl ,it may be n- produces n- propyl (heating coniine with hydroiodic acid octane not iso –octane,so Coniine is 2-n-propylpiperidine which confirmed by synthesis .

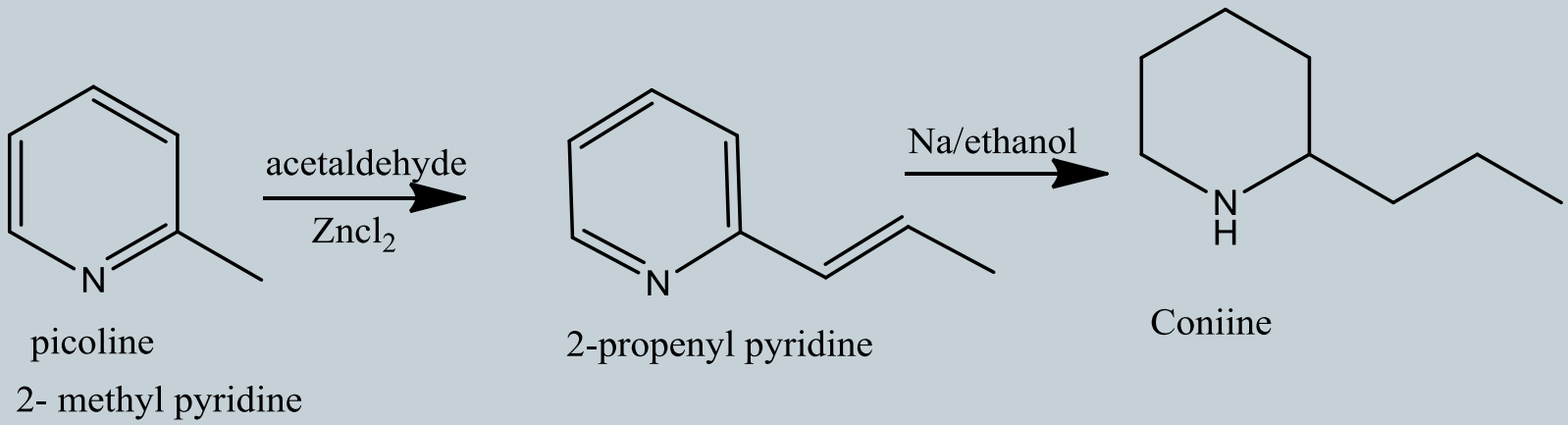




Coniine $C_8H_{17}N$

Synthesis of Coniine

تحضير كونيين



picoline

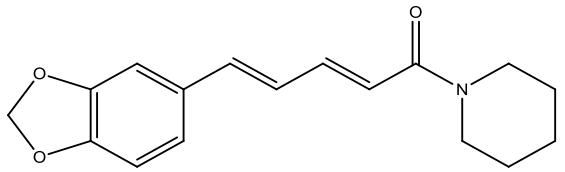
2- methyl pyridine

2-propenyl pyridine

Coniine

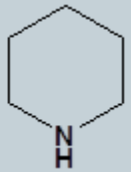
قلويدات مجموعة البيريدين - البيبـــرين $C_{17}H_{19}NO_3$

Pyridine alkaloids - Piperine

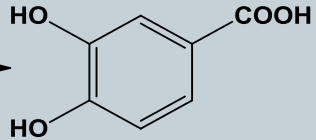


Confirmation of the structure

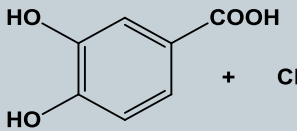
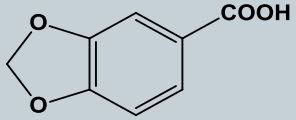
اثبات الشكل التركيبي للبيبرين

$C_{17}H_{19}NO_3$ (Piprene) $\xrightarrow{KOH / H_2O}$ $C_{12}H_{10}O_4$ (Pipric acid) + 

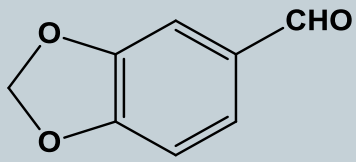
$C_{12}H_{10}O_4$ (Piperic acid) $\xrightarrow{KMnO_4}$ $C_8H_6O_3$ (Pipronal) $\longrightarrow$ $C_8H_6O_4$ (Pipronlic Acid)

$C_8H_6O_4$ (Pipronlic Acid) $\xrightarrow{HCl \ / \ 200\ C^O}$  + HCHO

Protocatecoic Acid

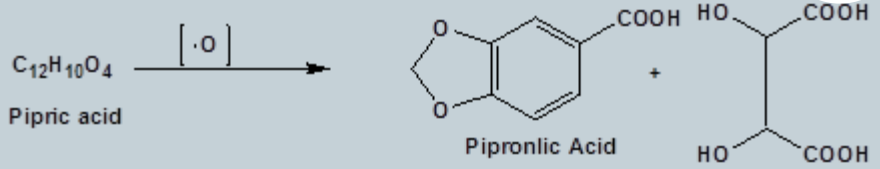
 + CH_2I_2 $\xrightarrow[Heat]{NaOH}$ 

Protocatecoic Acid — Pipronlic Acid

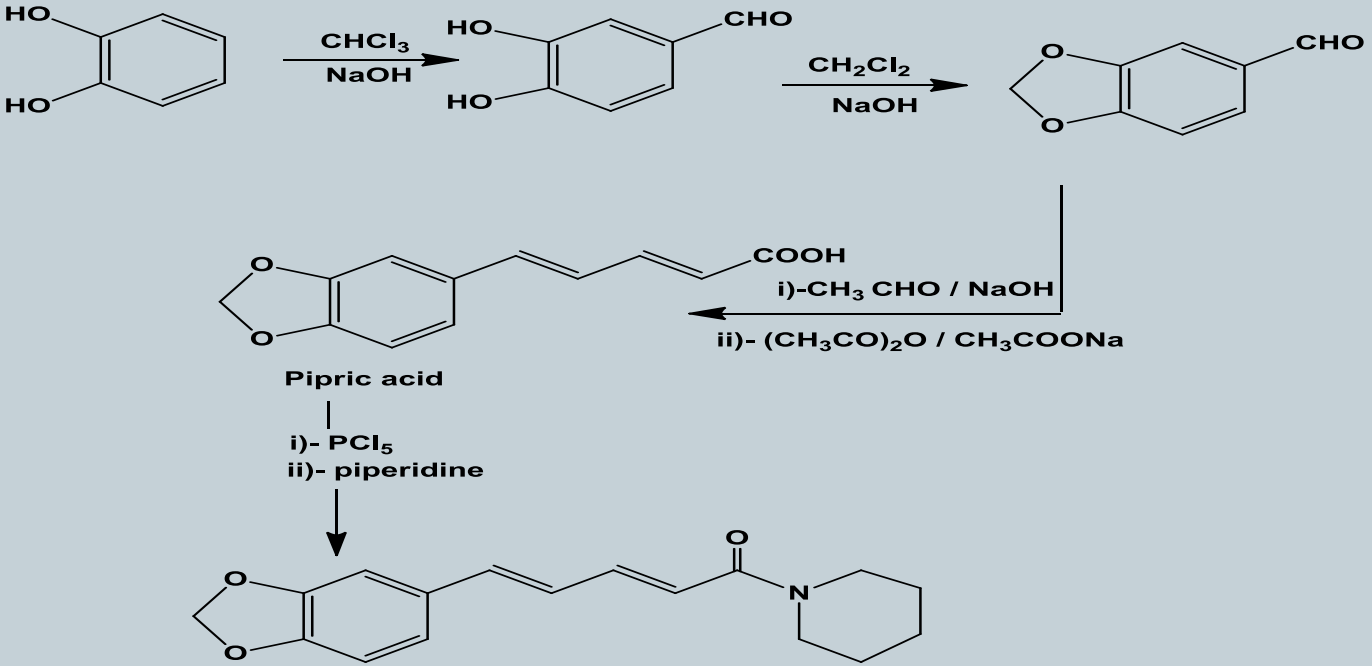


Pipronal

Piperine البيبرين

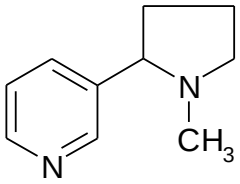


Synthesis of piperine

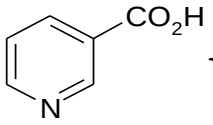


قلويدات مجموعة البيروليدين بيريدين (Pyrrolidine-pyridine group)
النيكوتيـن Nicotine($C_{10}H_{14}N_2$)

Confirmation of the structure
اثبات الشكل التركيبي للنيكوتين :



nicotine



nicotinic acid

$Na_2Cr_2O_7$ / H_2SO_4

(A) nicotine

CH_3I

(C) quaternary salt

(B)

CH_3COCl

No reaction

i.e. nicotine is tertiary amine

$K_2Fe(CN)_6$

mild conditions

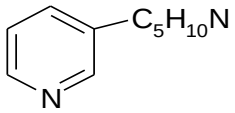
N - methyl nicotine

$Na_2Cr_2O_7$

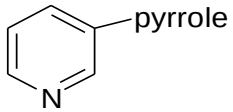
H_2SO_4

N - methyl pyrrole -2- carboxylic acid

nicotine has structural formula



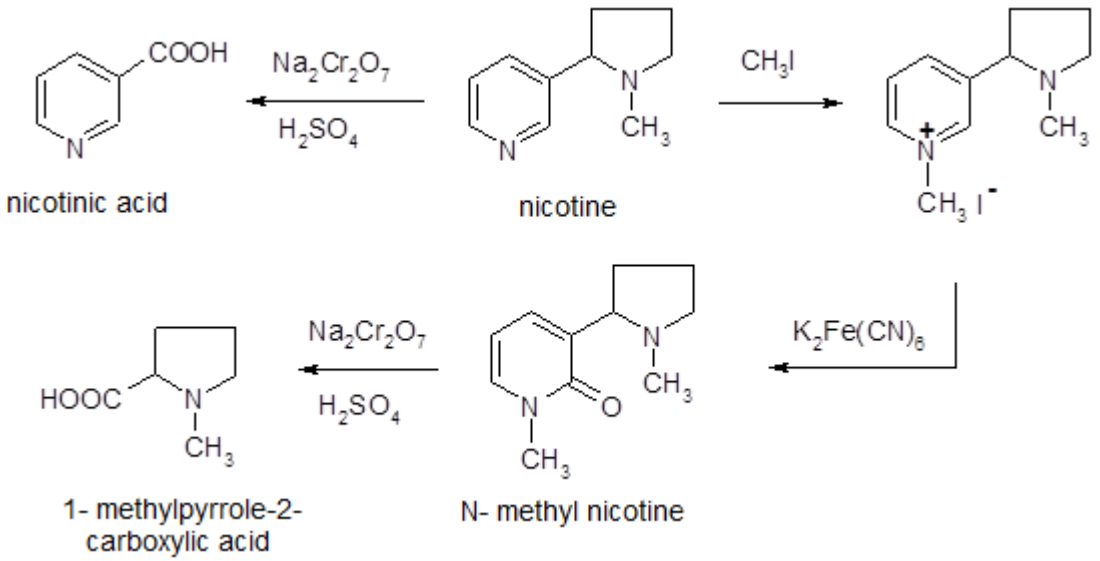
nicotine can be written as



Nicotine $(C_{10}H_{14}N_2)$ النيكوتيــن

Confirmation of the structure

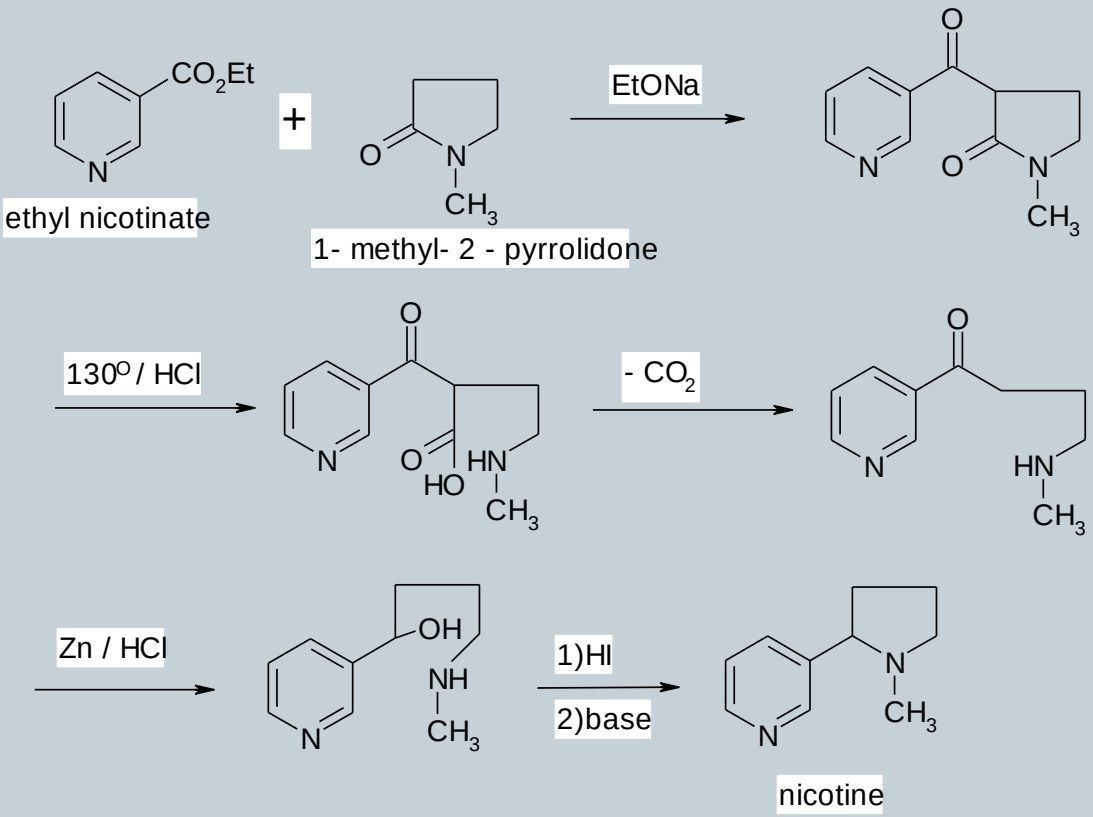
اثبات الشكل التركيبي للنيكوتين



Synthesis of Nicotine تحضير النيكوتين

Synthesis of Nicotine ***Spath and Bretsvchneider***

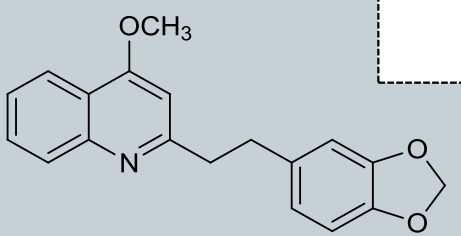
تحضير االنيكوتين طريقة سباث و برتشنيدر

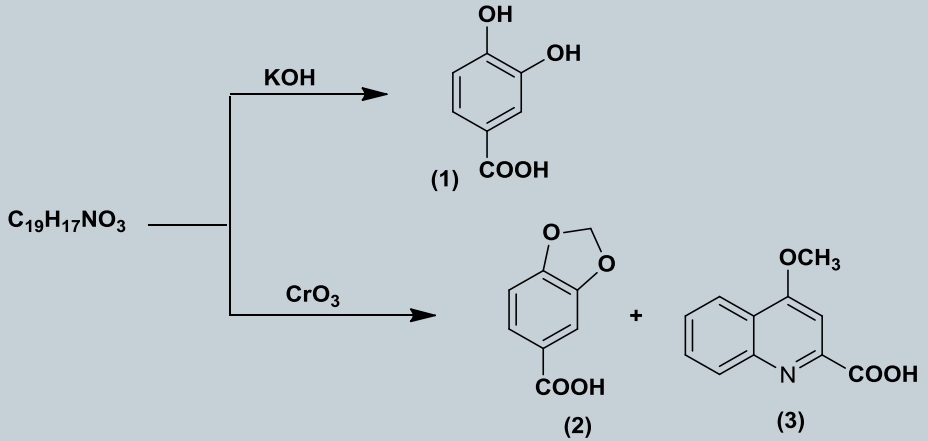


قلويدات مجموعةالكينولين الكسبارين $C_{19}H_{17}O_3N$

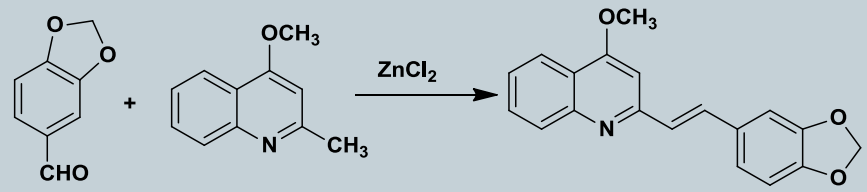
Quinoline alkaloids *Cusparine*

Confirmation of the structure اثبات الشكل التركيبي للكسبارين

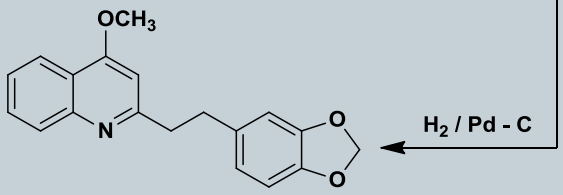




Synthesis of cusparine تحضير كسبارين



Pipronal 4-Methoxy-2-methyl-quinoline



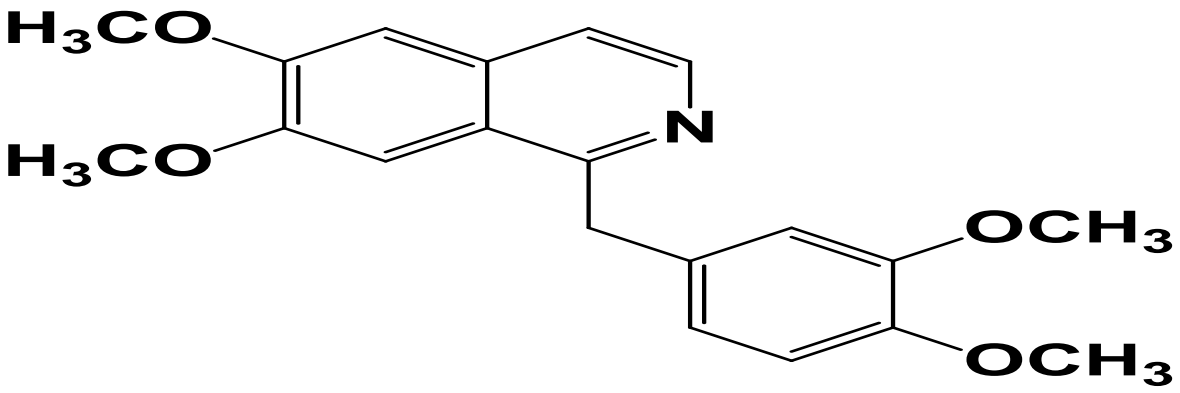
NATURAL PRODUCTS
ISOQUINOLINE ALKALOIDS

Dr. Awatef M. Elmaghraby

ISOQUINOLINE ALKALOIDS

($C_{20}H_{21}NO_4$) Papaverine الباباڤيريـن

The alkaloids of this group contain in their main composition an isoquinoline nucleus. Most of the members of this group have a physiological toxic effect and cause many diseases for many tissues of the body, especially cancer, and they also have a strong destructive effect on the nervous system of the person.



Papaverine is a solid with a melting point of 147 ° C).

Golds-chmiedt et al established the structure as follow:

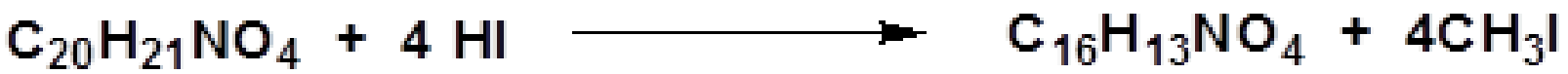
Papaverine
Determination of the structure

1-It has been proven that M.F $C_{20}H_{21}NO_4$

2-Papaverine is optically inactive , since it does not contain any chiral center (asymmetric carbon atom).

3- Since papaverine adds one molecule of methyl iodide to form a quaternary iodide salt, this indicates the presence of nitrogen in the tertiary state.

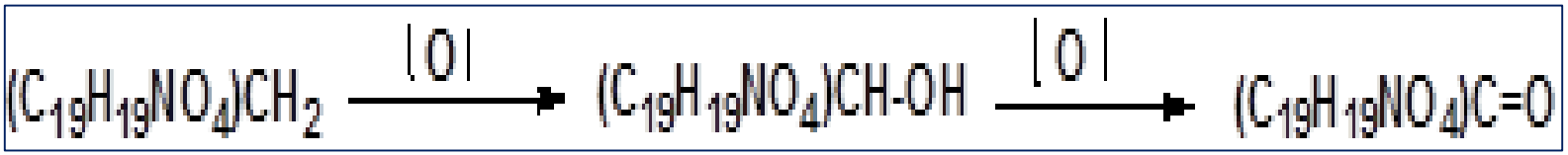
4- Papaverine contains four methoxy groups (Zeisel method).



باباڤيرينPapaverine **papaveroline باباڤيرولين**

Determination of the structure

5-Oxidation by cold dilute permanganate papaverinol is obtained ,thus more vigorous oxidation with hot dilute permanganate a ketone papaveraldine is obtained so papaverinol is a sec. alcohol and papaverine must be contain a methylene group(-CH_2-). The prolonged action of permanganate oxidize the ketone to papaverinic acid .



Papaverine باباڤيرين

papaverinol باباڤيرينول

papaveraldine باباڤيرالدين

6-When oxidized with hot permanganate ,papaverine (or the oxidized product)is broken down into small fragments:

1-Veratric acid

2- Meta hemipinic acid

3-Pyridine 2,3,4-tricarboxylic acid

4- 6,7-dimethoxyisoquinoline -1- carboxylic acid

Determination of the structure

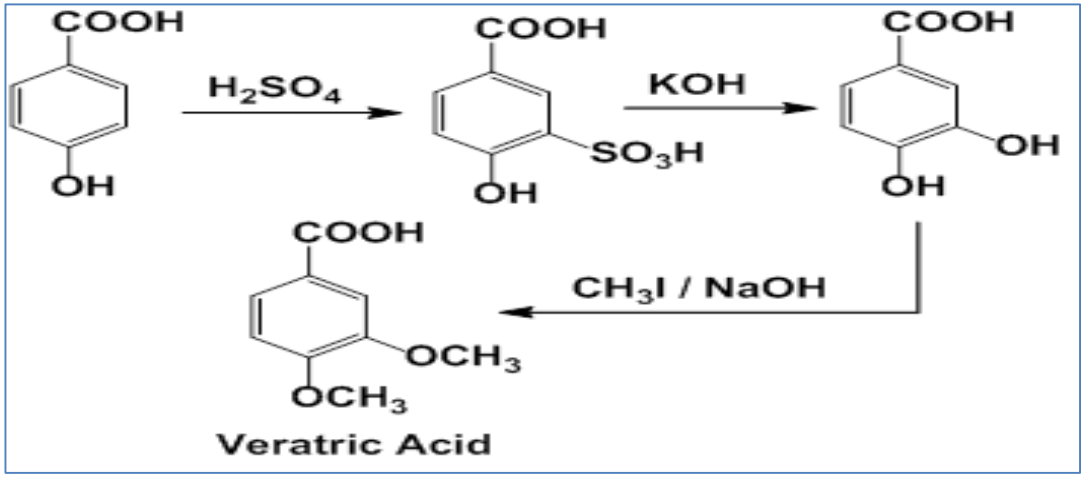
Now, let us consider the evidence for the structure of these compounds :

1- Veratric acid

a) Veratric acid contains one carboxyl group and two methoxy group

b) Decarboxylation of veratric acid veratrol is obtained. Since this is dimethoxy benzene ,so veratric acid is dimethoxy benzoic acid .

c) The position of the carboxyl with respect to methoxy groups established by the following synthesis :



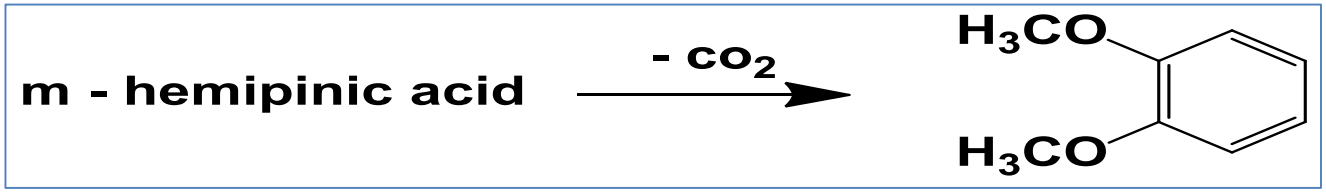
So veratric acid is 3,4 dimethoxy benzoic acid.

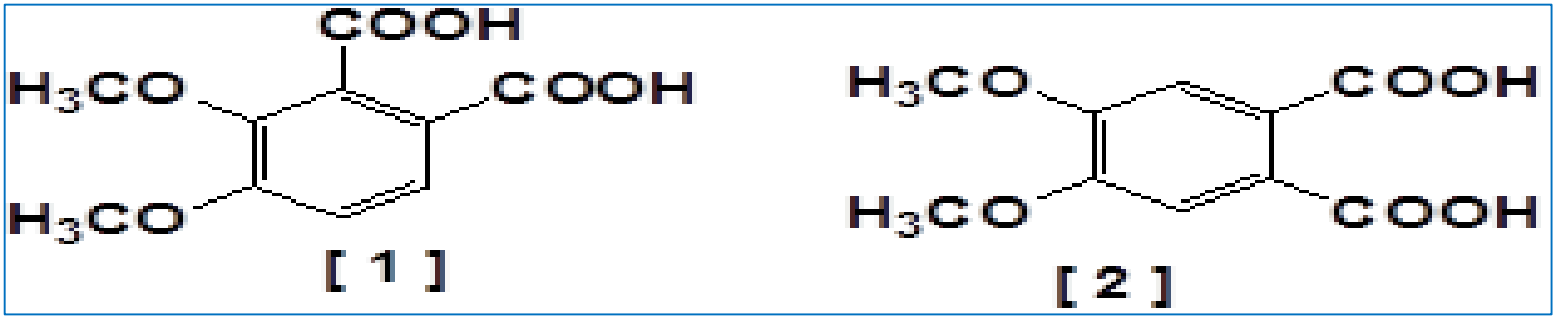
2-Metahemipinic acid:

a) This is dicarboxylic acid and decarboxylation with calcium oxide, veratrol is formed .

b) Meta hemipinic acid contains two methoxy group .

c) The meta hemipinic acid is either (1) or (2)

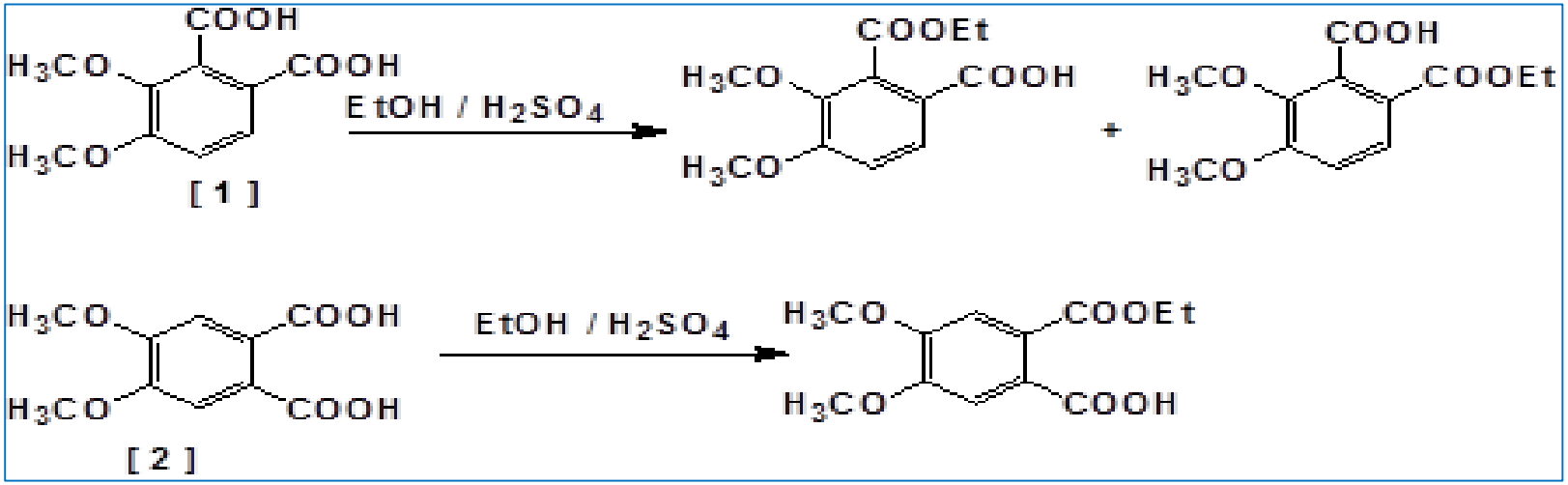




Determination of the structure

d)Heating the acid with acetic anhydride an anhydride is formed, so the two carboxyl group must be in the ortho position .

e)Meta hemipinic acid forms only mono ester (2) permits the formation of mono ester so the structure (2) is meta hemipinic acid.



Determination of the structure

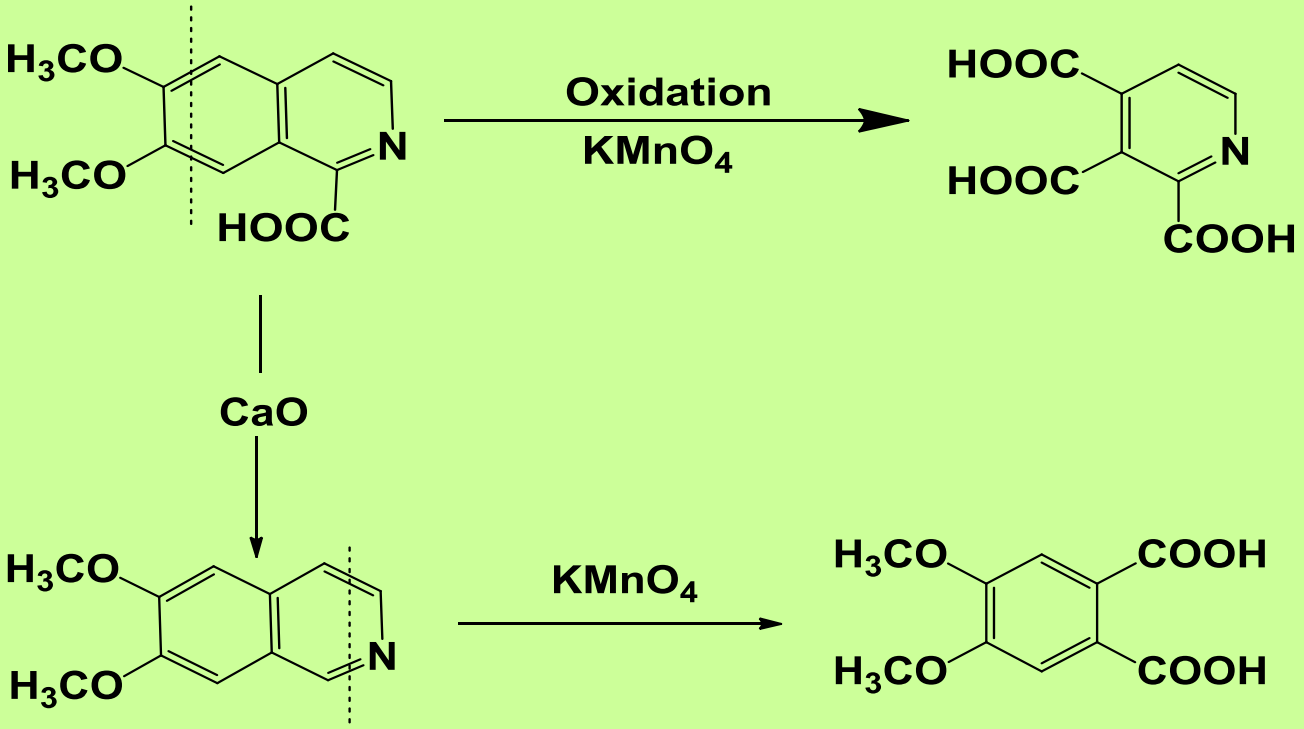
3-pyridine 2,3,4-tricarboxylic acid

a) It contains three carboxylic groups .

b) Decarboxylation gives pyridine .

The position of three carboxyl group is established by the following synthesis starting with lipidine(4-methyl quinoline).

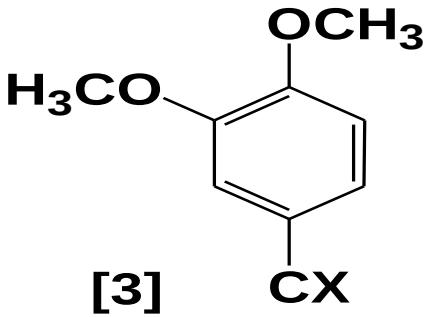
4- 6,7-dimethoxyisoquinoline -1- carboxylic acid



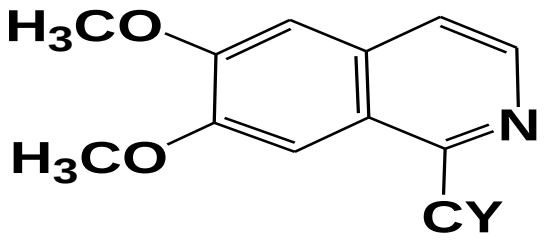
Elucidation of the structure

1-Separation of veratric acid indicates the presence of group [3] in papaverine.

2- The separation of the 6,7 dimethoxyi soquinoline - 1 - carboxylic acid indicates the presence of group [4] in the molecule..



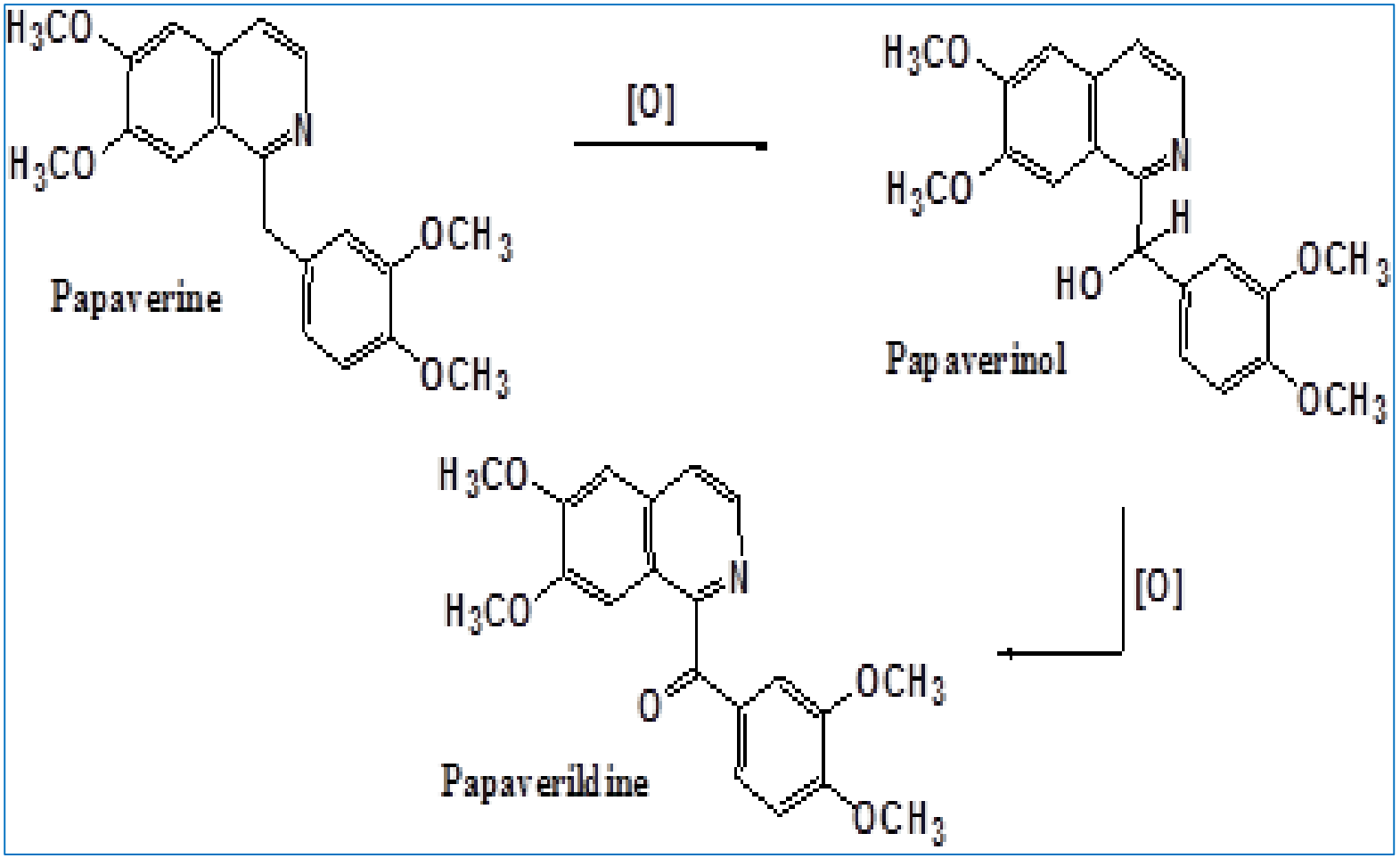
[3]



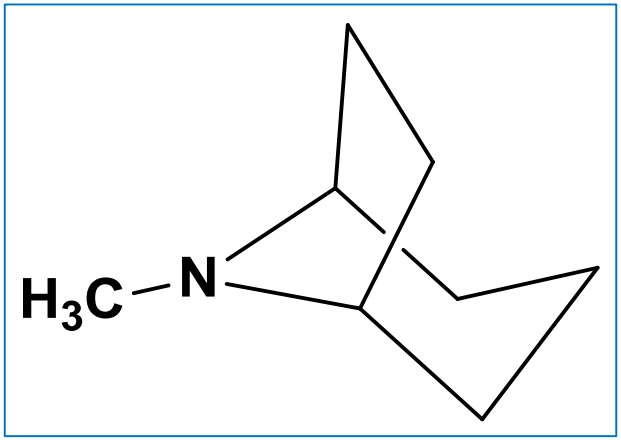
[4]

3- Given that the total number of carbon atoms in groups [3] and [4] is 21 carbon atoms, and papaverine contains only 20 carbon atoms. So, there must be a repeat carbon atom in each of the CX and CY groups. Given that the compound contains a group of CH2 (methylene), then it is likely that it is the same as the duplicated carbon atom.

If we assume that C-x and C-y are one and the same carbon atom of the ($X\text{-}CH_2\text{-}Y$) group, then the following structure of papaverine accounts for all the facts.



Fused pyrrolidine-pyridine group
Tropine alkaloids
قلويدات البيروليدين- بيريدين المتكاثفة
[قلويدات التروبين]



نواة التروبين

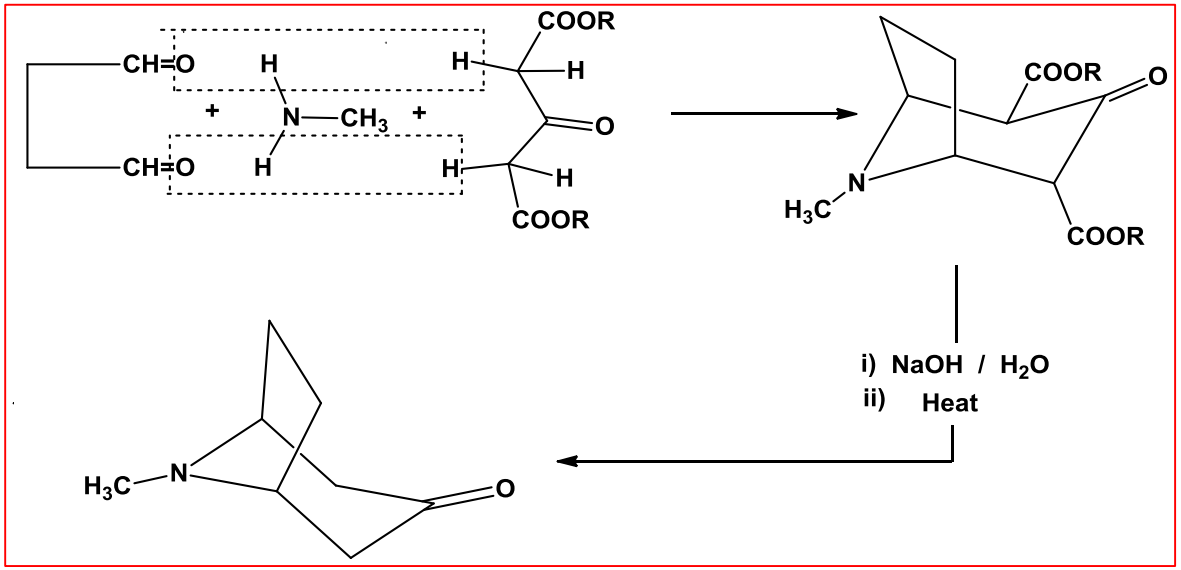
Tropine nucleus

8-methyl-8-azabicyclo[3.2.1]octane

Tropine alkaloids [8-methyl-8-azabicyclo[3.2.1]octane occur in (atropa belladonna). The most important alkaloids that can be obtained from these sources are atropine drugs, high amino acid, scopolamine, etc.

The heterocyclic tropic alkaloids as they consist of the fusion of the pyridine nucleus with the pyrrole nucleus. It is also possible to attribute all of these alkaloids. To the compound tropan.

Tropinone can be synthesized via heating succinaldehyde,methyl amine and alkyl acetondicarboxylate in the presence of hydrochloric acid as follow (Robinson method)



طريقة روبنسون Robinson's method

نبات ست الحسن
(atropa belladonna الاتروبابلادونا)

(hyoscyamus السكران
nizer)

الداتورا الصفراوية
Datura stramonium

Tropinone can be reduced to give tropanol (sec.alcohol) also it can be add hydrogen cyanide to give the cyanohydrine derivative which hydrolyzed into the corresponding hydroxy acid,.In this way it has been possible to create many of these compounds, which have such a structural structure for the purpose of studying their physiological effect.

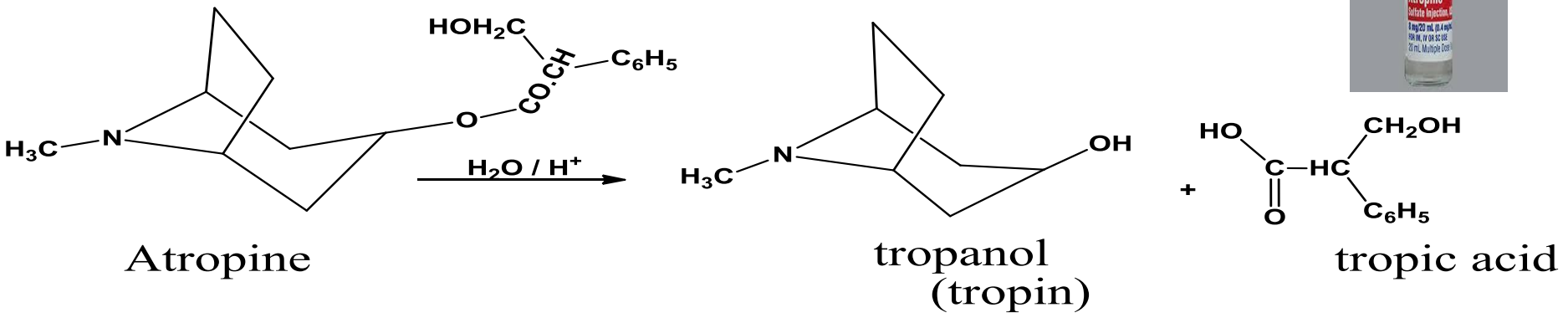
سير روبرت روبنسون جائزه نوبل ١٩٤٧ لتحقيقاته في المنتجات النباتية ذات الأهمية البيولوجية، وخصوصا القلويدات"

Atropine الأتروبيـــن:

Atropine is occurs in (atropa belladonna) together with hyoscyamine, atropine solid m.p118 ^{o}C

-It has been proven that molecular formula $C_{17}H_{23}NO_3$

-Atropine is hydrolyzed to tropic acid and tropine(tropanol),thus atropine is the tropanoyl ester of tropic acid ,atropine can be synthesized by heating of tropic acid with tropanol in the presence of hydrogen chloride. It is known that it is used in ophthalmology, since its solution with a concentration of ½ - 1% in oil causes an expansion in the eye (diffusive effect).



Atropine

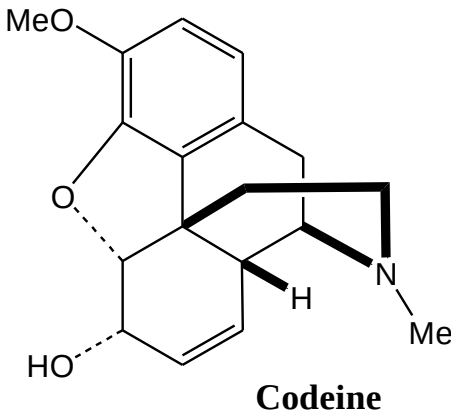
tropanol
(tropin)

tropic acid

Phenanthrene Group

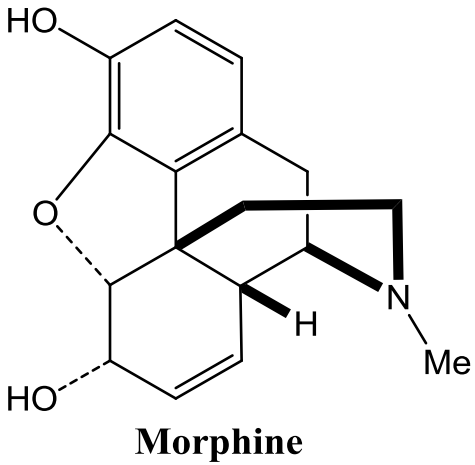
قلويدات الفينانثرين

Morphine, Codeine and Thebaine those are the three important opium alkaloids containing the Phenanthrene nucleus.



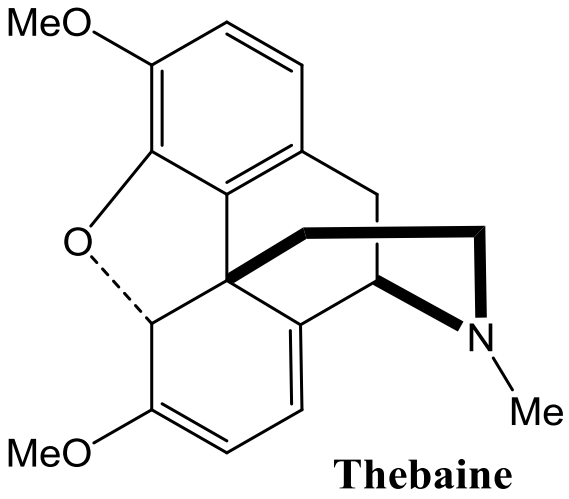
Codeine

قلويـد الكوديـن



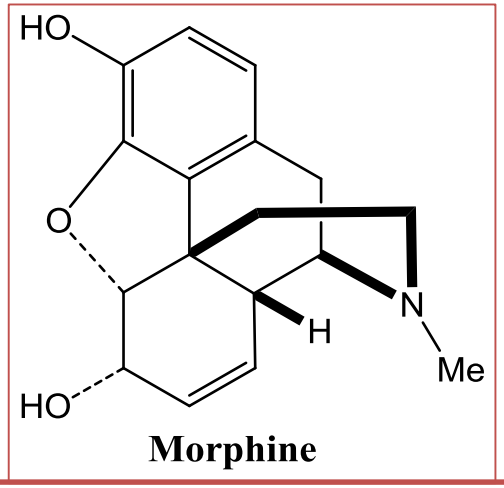
Morphine

قلويـد ا لمـورفيـن



Thebaine

قلويـد الثيبايين



Morphine

Morphine المورفين

Morphine is the chief alkaloid in opium and was the first alkaloid to be isolated ,the chemical structure was supported by:

1- It has been proven that molecular formula C_{17} $H_{19}NO_3$ (after purification, Qualitative and quantitative analysis, determination of empirical formula)

2- Routine tests confirmed that nitrogen in the tertiary state .

3- Acetylation of morphine gives morphine diacetate (Heroin),two hydroxyl groups are present in the molecule.

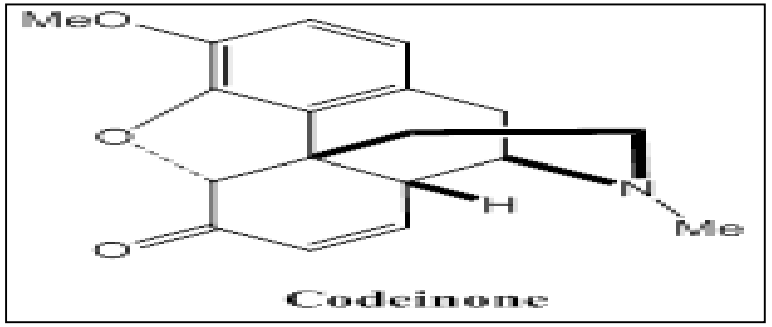
4-Morphine gives the ferric chloride test for phenols and dissolves in aqueous sodium hydroxide to form mono sodium salt ,and this is reconverted into morphine by the action of carbon dioxide,thus one of the hydroxyl groups is phenolic.

5--**Morphine with halogen acids converted morphine into mono halogeno derivative, one hydroxyl group being replaced by halogen atom thus the second hydroxyl is secondary alcoholic hydroxyl group.**

6-Morphine is methylated by heating with methyl iodide and aqueous potassium hydroxide to give Codeine, therefore follow that it is only the phenolic hydroxyl group in morphine has been methylated.

7- Oxidation of codeine by using chromic acid to give Codeinone ,(a ketone).Thus the hydroxyl group in codeine(and this one in morphine) is secondary alcoholic, and so codeine is the monomethyl (phenolic)ether of morphine .

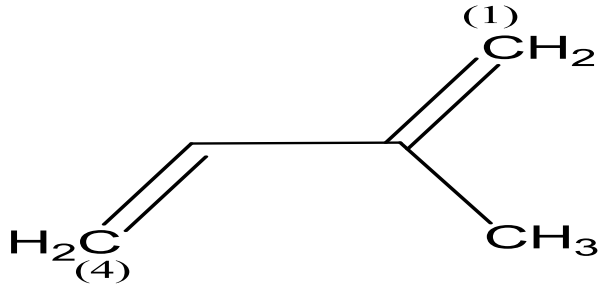
8-When morphine is distilled with zinc dust phenanthrene and other bases are produced .This suggests that phenanthrene nucleus is present.



Codeinone

Natural Product Terpenoids

The terpenoids form a group of compounds most of them occur in the plant kingdom. The distinctive aroma of many flowers and roses, as well as the colors of the fruits of some plants, such as carrots, tomatoes, etc., are attributed to terpenoids (terpenes). Terpenoids comprise most of the Kingdom's vegetable products and are involved in the synthesis of many volatile oils. They are also used to make perfumes, medicines and food flavors. This family also belongs to the natural rubber that we obtain as a white liquid from the rubber tree.



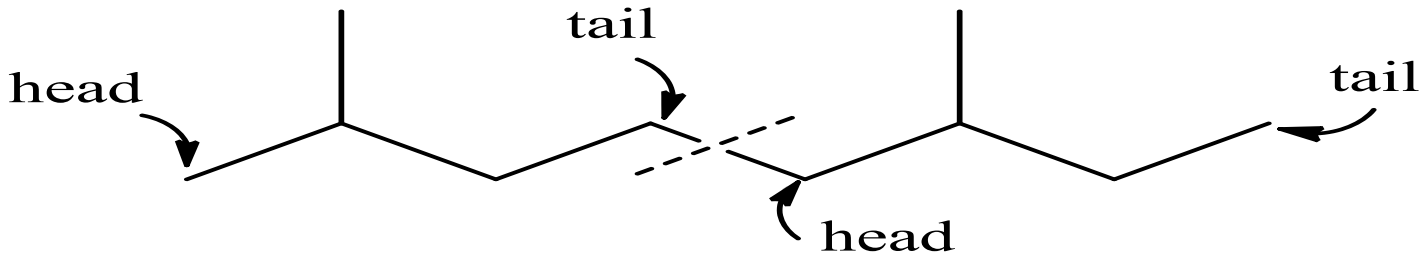
isoprene (2-methyl 1,3 butadiene

Classification of Terpenoids

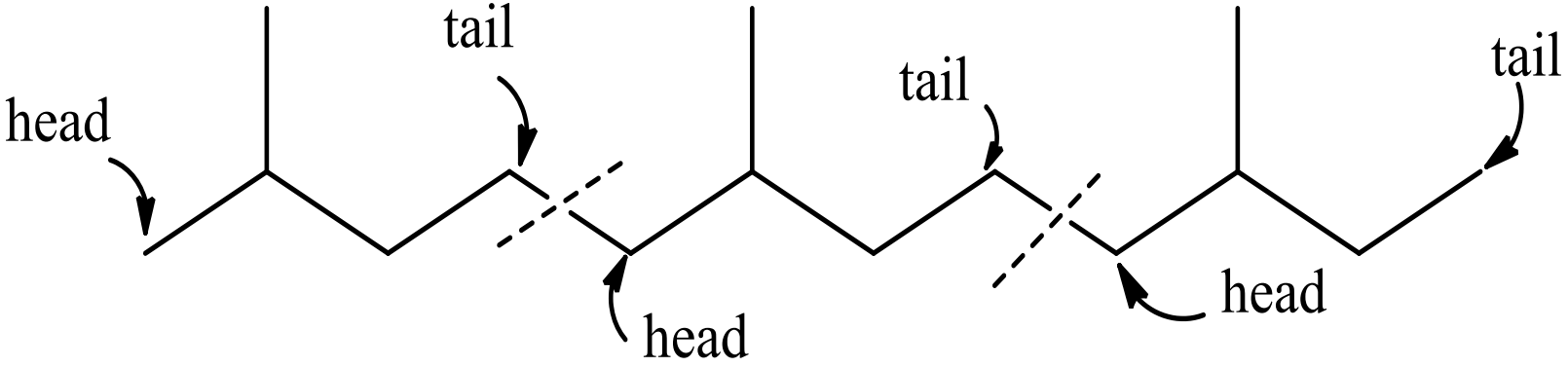
M.F$(C_5H_8)_n$

The thermal decomposition of almost all terpenoids gives isoprene as one of the products ,this led to suggestion that:
The skeleton structures of all naturally occuring terpenoids can built up of isoprene units this is known as the isoprene rule
Ingold pointed out that isoprene units in natural terpenoids were joined head to tail .
Several exceptions occur ,e.g.the carotenoids joined tail to tail .

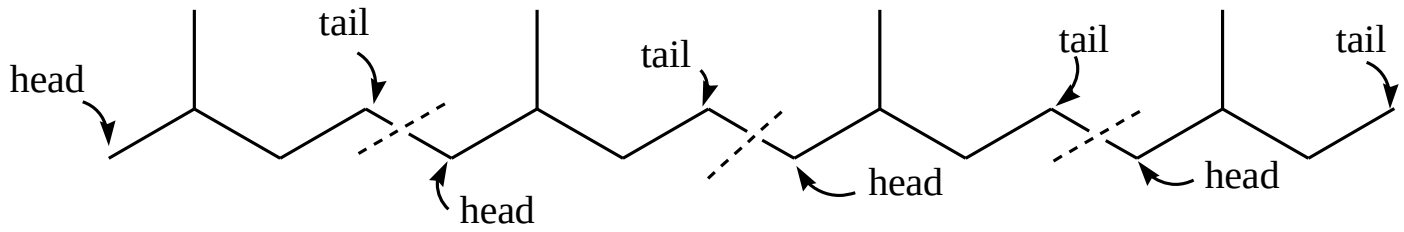
n	Number of carbon	Class	Formula	examples
٢	١٠	Monoterpenes	$C_{10}H_{16}$	Volatile oils
٣	١٥	Sesquiterpenes	$C_{15}H_{24}$	Volatile oils
٤	٢٠	Diterpenens	$C_{20}H_{32}$	Gums and resins
٥	٢٥	Sesterterpenes	$C_{25}H_{40}$	Gums and resins
٦	٣٠	Triterpenes	$C_{30}H_{48}$	Gums and resins
٨	٤٠	Tetraterpens	$C_{40}H_{64}$	Carotenoids
>٨	>٤٠	Polyterpenes	$(C_5H_8)_n$	Natural rubber



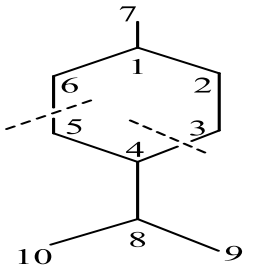
open chain monoterpenoid



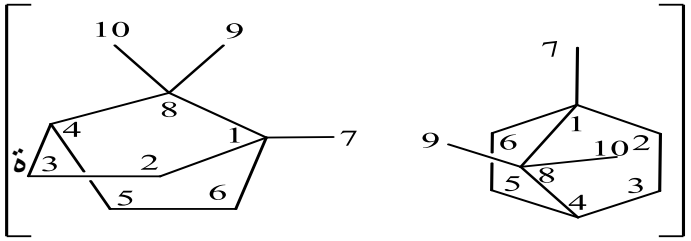
open chain sesquiterpenoids



Open chain diterpenoid **تربيـن ثنائي مفتوح السلسلـة**

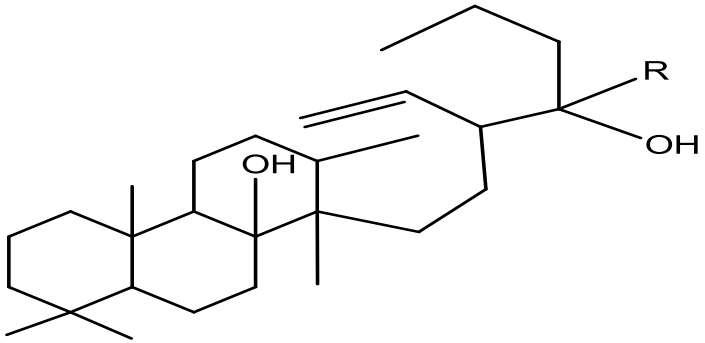


monocyclic monoterpenoid



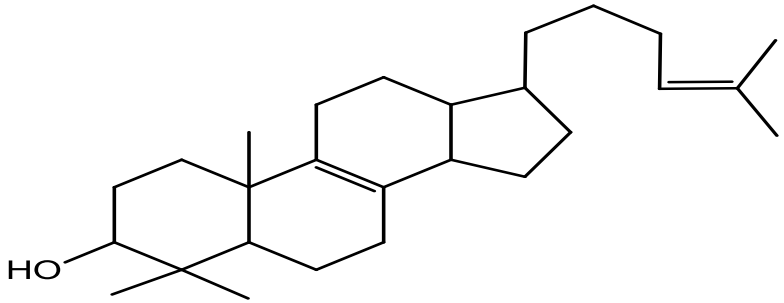
bicyclic monoterpenoid

تربيـن احادي أحـادى الحلقـة **تربيـن أحـادى ثنائي الحلقـة ملتحـم**



fused tricyclic triterpenoid

تربيـن ثلاثي ثلاثي ثلاثى الحلقـة ملتحم



fused tetracyclic triterpenoid

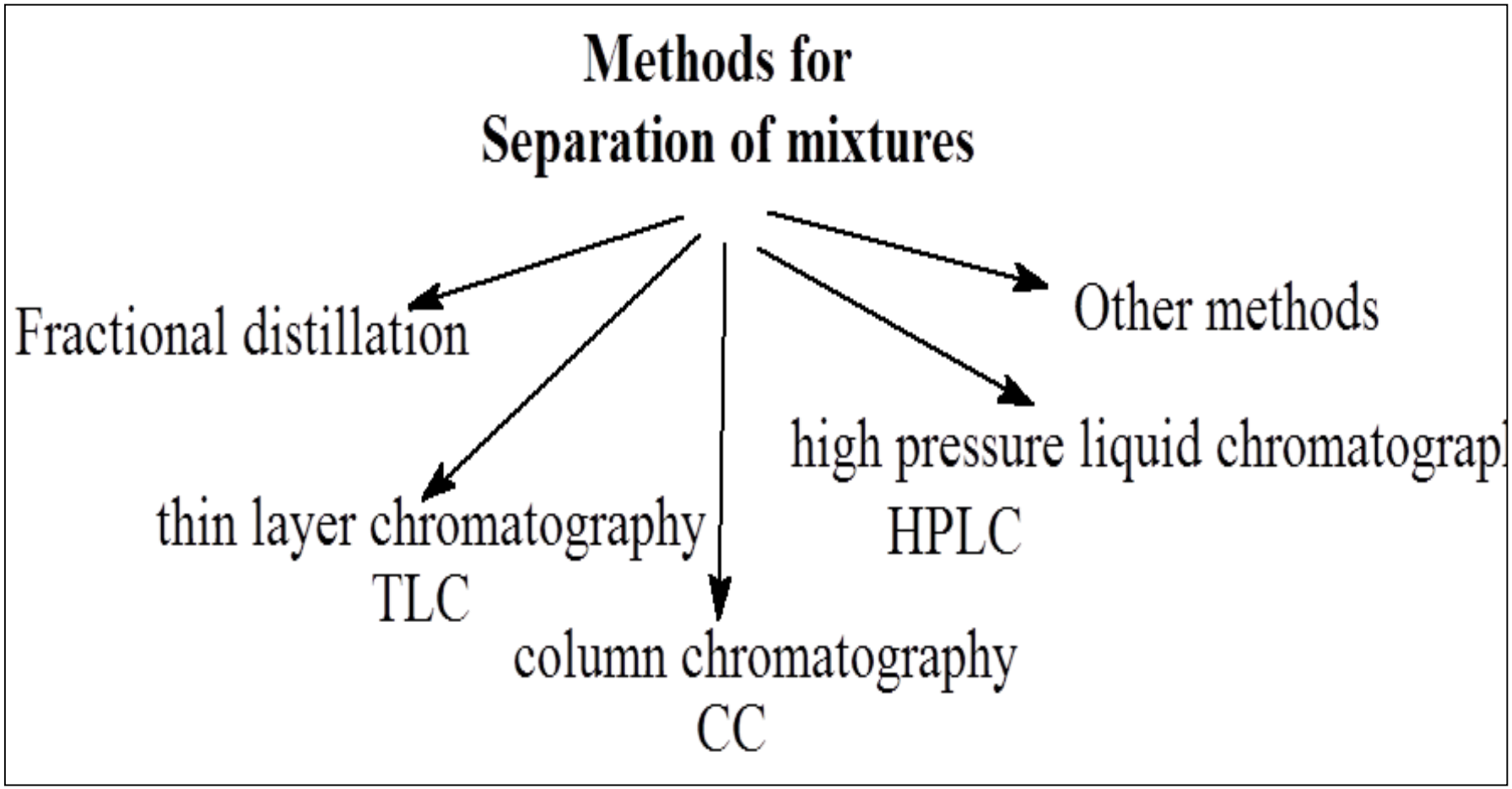
تربيـن ثلاثى رباعي الحلقـة ملتحـم

Separation and Extraction of Monoterpenoids and Sesquiterpenoids

1-Expression
2- Steam distillation
3- Extraction by means of volatile organic solvents
4- Adsorption on fats.

Steam distillation or extraction with volatile organic solvents is one of the most important multiple methods used to extract terpenes from plants, and the method of steam distillation is the most commonly used method, especially when extracting monoterpenes , sesquiterpenes and some diterpenes.

The method of extracting is summarized in grinding the vegetable parts well and then distilling them with steam. Volatile oils by fractional distillation. One of the methods widely used to separate terpenoids is the thin layer (TLC) or column method (CC) or HPLC, and the column method (on silica gel) is one of the most suitable methods of color separation for high terpenes such as di ,tri,and tetraterpenoids.


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

If the compound is decomposes due to the high temperature, it may be extract by means of several organic solvents, where the petroleum ether is used for extraction at a low temperature (50 ° C) and for a period sufficient to extract all types of terpenes, or at least most of them, The ether is then distilled at reduced pressure to maintain the terpenes without decomposition . Then the volatile oil mixture is separated by fractional distillation under reduced pressure or by column chromatography.

General methods of determining structure of terpenoids

1-After extraction and separation then purification of sample ,the molecular formula is ascertained by usual methods (qualitative and quantitative analysis – empirical formula-determination of M.Wt).

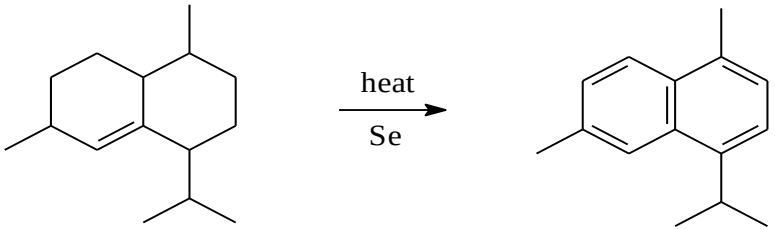
2-If the terpenoid is optically active ,its specific rotation is measured.

3-The nature of functional oxygen atom if it is present (hydroxyl-carbonyl -carboxyl --------- etc).

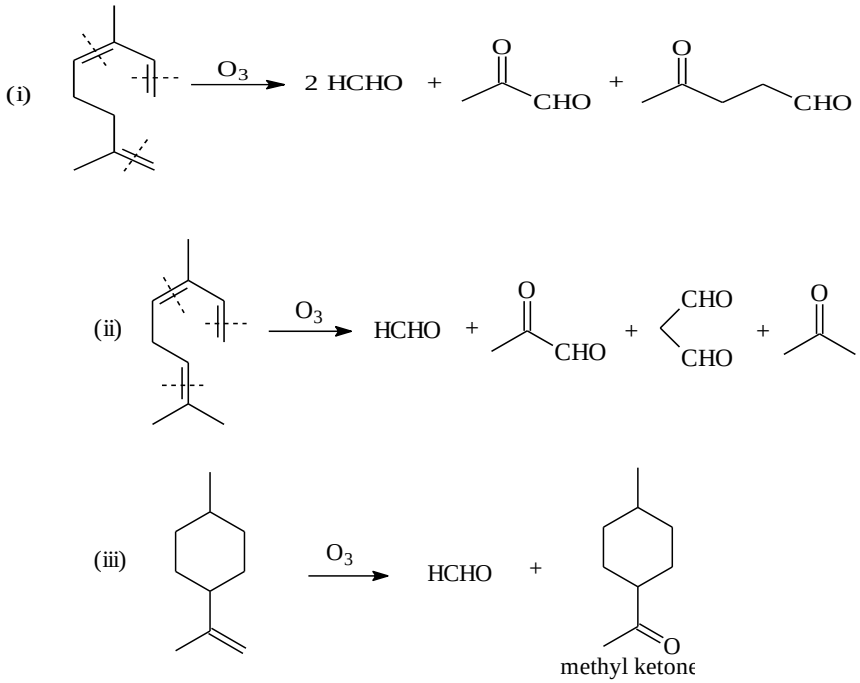
4-The presence of unsaturation olefinic bonds is ascertained by means of bromine and catalytic hydrogenation.

5-Conjugated and isolated double bonds are differentiated by Diel's Alder reaction also by using UV spectroscopy.

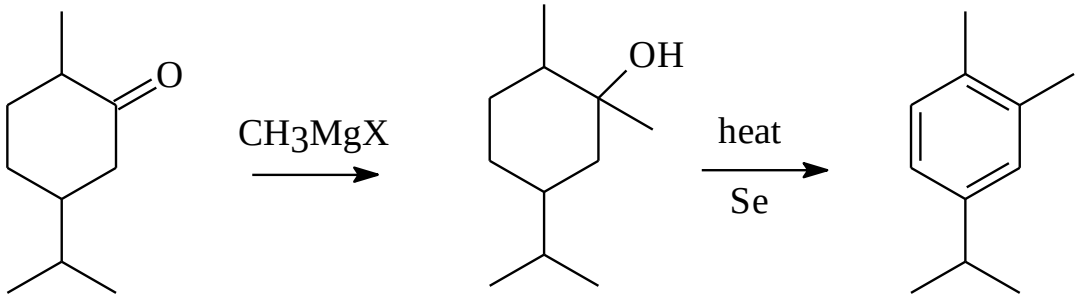
6-Dehydrogenation by heating the terpene with S or Se converts the terpene into aromatic derivative which is easily identified.



7- Ozonolysis is an example of oxidative degradation methods (O_3, $KMnO_4$, CrO_3 & OsO_4),this method produced two type of products, acetone arising from the terminal isopropylidene group($Me_2C=$) and formaldehyde arising from isopropenyl group($CH_2=CMe$) or terminal methylene group($CH_2=$).



8-Grignard reagent useful for detecting the position of carbonyl group in terpenoids.



9-Infrared spectroscopy (IR) is useful by detecting the presence of hydroxyl group ,carbonyl group -------- etc , NMR (^{1}H-NMR & ^{13}C-NMR give information about the nature and the number of hydrogen and carbon, Ultraviolet spectroscopy (UV),mass spectrometry and X-Ray analysis are very useful for elucidating structure and stereochemistry of terpenoids.

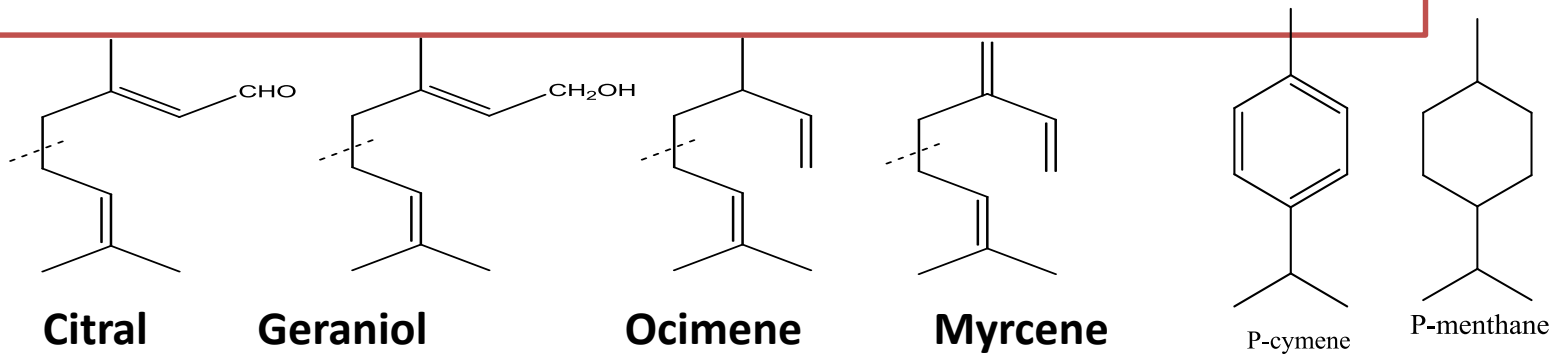
10- A final confirmation of the proposed structure is usually achieved by synthesizing the compound and comparing the spectral data with those of an authentic sample.

Monoterpenoids التربينــات الأحادية

Monoterpenoids are classified into three groups (acyclic,monocyclic,bicyclic)

Acyclic Monoterpenoids

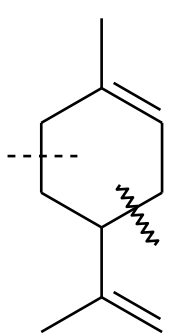
The carbon skeleton being formed by the head to tail of two isoprene units.



Monocyclic monoterpenoids contain a six membered ring and most natural monocyclic monoterpenoids are derivatives of p-cymene and the parent substance is named P-menthane.

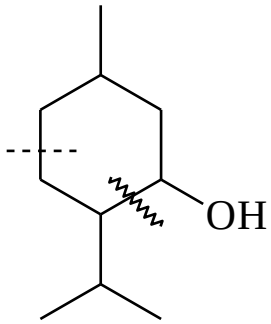
Bicyclic monoterpenoids contain a six membered ring and a three,four or five membered ring .

Monocyclic monoterpenoids

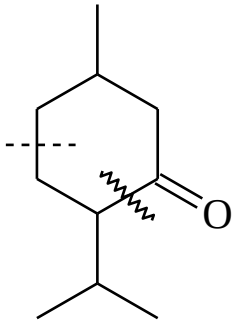


Limonene

occurs in lemon and orange oils



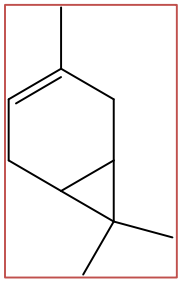
Menthol



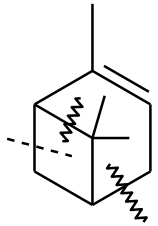
Menthone

both occur in pepermint oil

Bicyclic monoterpenoids

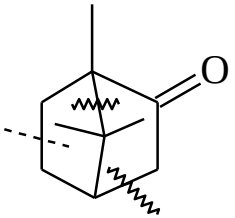


carene



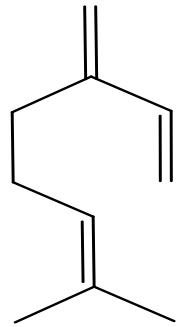
α-Pinene

occurs in turpentine oil



Camphor

occurs in camphor tr



($C_{10}H_{16}$)Myrcene المـايرسيـــــن

Myrcene occurs in verbena and bay oils ,myrcene is optically inactive and highly unsaturated.

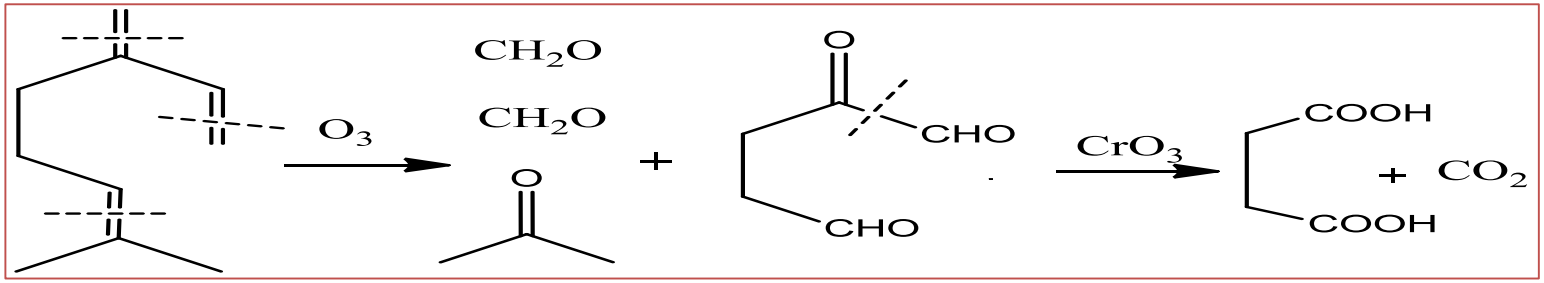
<u>Structure of myrcene is supported by</u> :

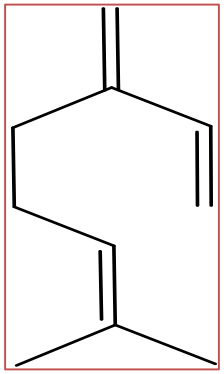
1-Molecular formula is $C_{10}H_{16}$.

2-Catalytic hydrogenation of myrcene gave saturated alkane$C_{10}H_{22}$ (isodecane) thus myrcene is an open chain and contains three double bond .

3-Since myrcene forms adduct with maleic anhydride, thus two of the double bond are conjugated .

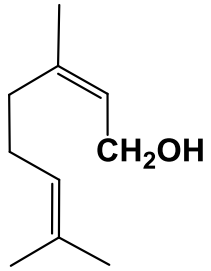
4-Ozonolysis of myrcene produces acetone ,two molecule of formaldehyde and ketodialdehyde which oxidized with chromic acid to give succinic acid and carbon dioxide.



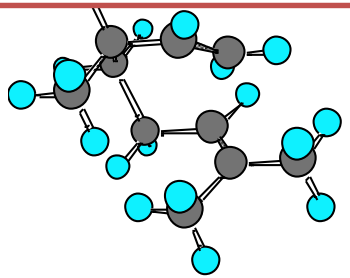


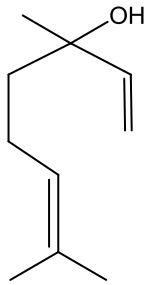
7-methyl-3-methylene-octa-1,6-diene

$(C_{10}H_{18}O)$ Linalool اللينـــالـــول



Geraniol





3,7-Dimethyl -octa-1,6-diene 3 -ol

Structure of Linalool : $(C_{10}H_{18}O)$ b.p:198-199C

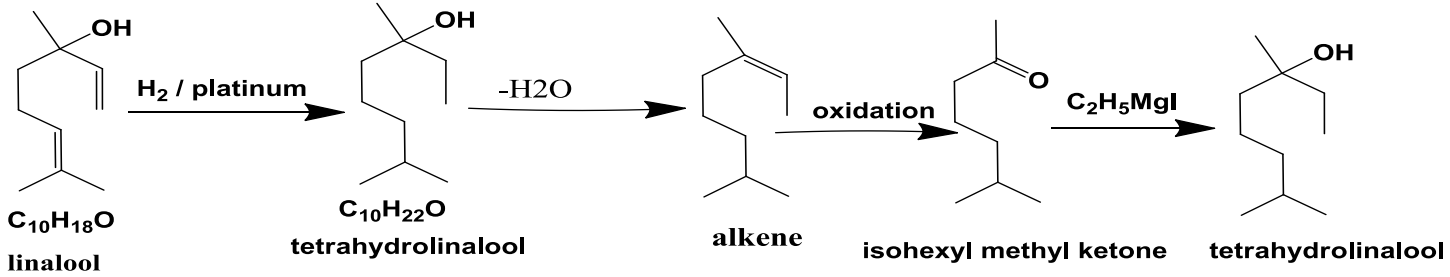
1- It is an optically active the (-)form occurs in rose oil and the (+) form in orange oil.

2- It adds on two molecule of hydrogen in catalytic hydrogenation ,and give negative with maleic anhydride it must be contain two (non conjugated) double bond .

3-It is converted into geranyl acetate by heating with acetic anhydride and converted into linalool by heating with steam at 200C under pressure , also linalool isomerizes in the presence of acid to geraniol .

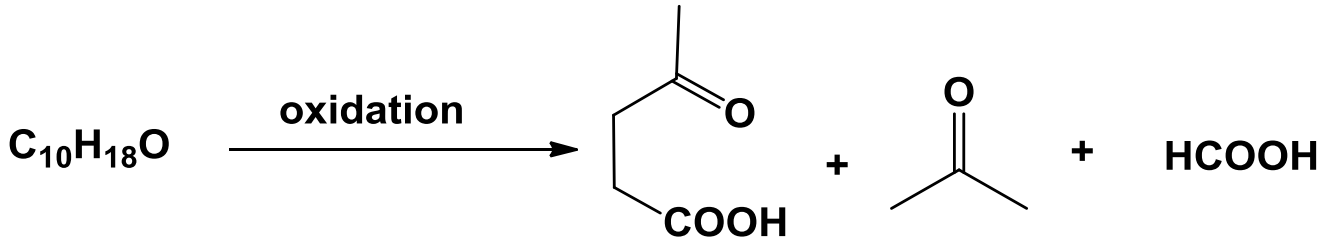
4-It has a tertiary alcoholic group and the position confirmed as follow:

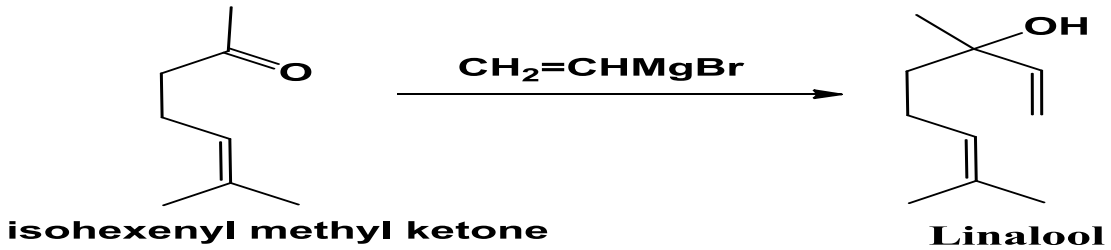
. .

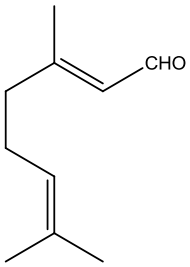


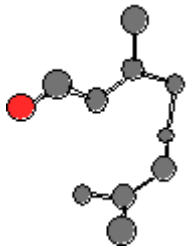
5-Oxidation of linalool by pot. Permenganate converted it into levulinic acid ,acetone and formic acid .

6-Normant has synthesized linalool in one step by the action of vinyl magnesium bromide with 6-methyl -5-heptene-2-one(isohexenyl methyl keton).







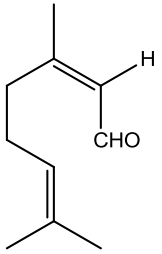


Citral ($C_{10}H_{16}O$)

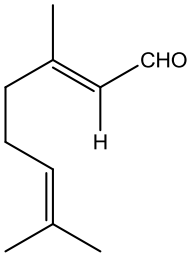
3,7 dimethyl 2,6 -octadienal

Citral occurs to an extent 60-80 per cent in lemon grass oil

Structure of citral was supported by:



cis form
citral b or neral



trans form
citral a or geranial

Citral
$C_{10}H_{16}O$

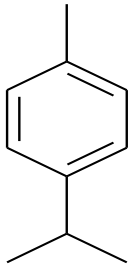
$2\ Br_2$ → $C_{10}Br_4H_{16}O$ tetrabromo derivative

H_2NOH → an oxime

$Na/\ Hg$ → $C_{10}H_{18}O$ geraniol

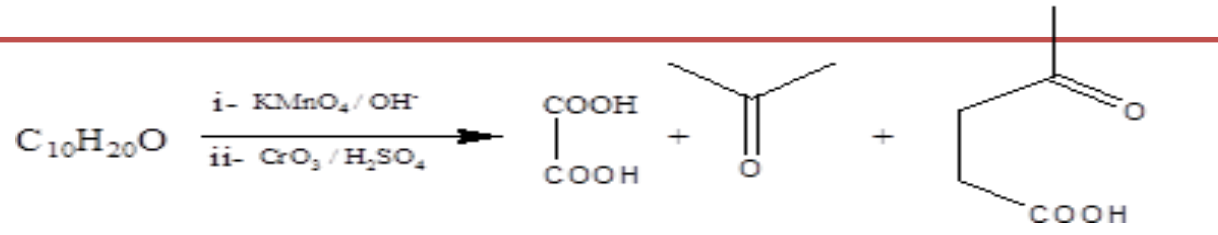
Ag_2O or Fehling reagent → $C_{10}H_{16}O_2$ geranic acid

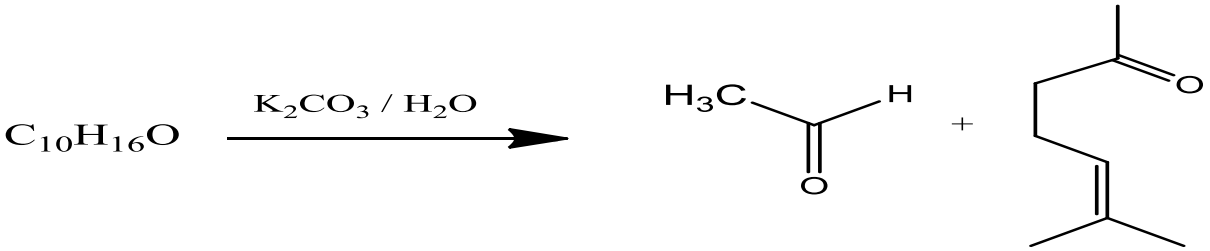
$KHSO_4$ / dil H_2SO_4 →



p- cymene

1-It has been proven by analysis that Molecular formula is **$C_{10}H_{16}O$** .
2-It added two molecule of bromine thus citral contains two double bond .
3-It forms oxime derivative with hydroxyl amine citral contains oxo group.
4-Citral can be reduced by sodium amalgam to an alcohol geraniol.
5-Citral oxidized with silver oxide to geranic acid since there is no loss of carbon oxidation to acid ,the oxo group in citral is t here an aldehyde group .
6-On heating with potassium hydrogen sulphate citral forms p-cymene ,this reaction was used to determine the position of methyl and isopropyl groups .
7-Oxidation of citral with alkaline permanganate,f ollowed by chromic acid ,gives acetone, oxalic acid and levulinic acid.
8-Citral with aqueous potassium carbonate gives acetaldehyde and 6-methylhept-5-en-2one .





Natural Products
Terpenoids
Cyclic Monoterpenoids
Limonene-Menthol-Camphor

استاذ المادة

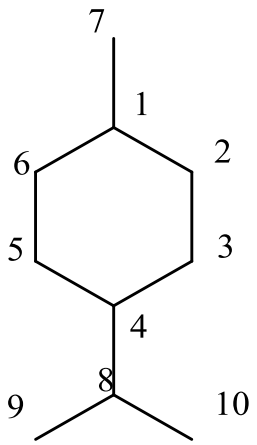
د /عواطف محمد المغربي

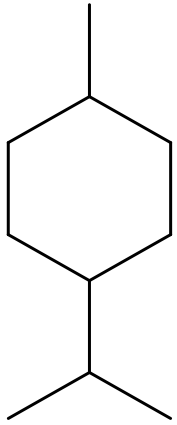
استاذ الكيمياء العضوية م

قسم الكيمياء – كلية العلوم

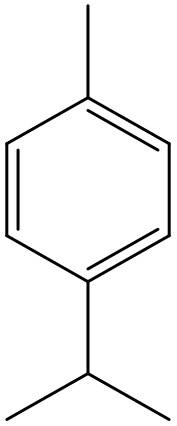
Monocyclic Monoterpenoids

Monocyclic Monoterpenes is subdivided into two groups the larger group with carbon skeleton which are related to P-cymene(4-isopropyl toluene), the smaller group with carbon skeleton are related to m-cymene.

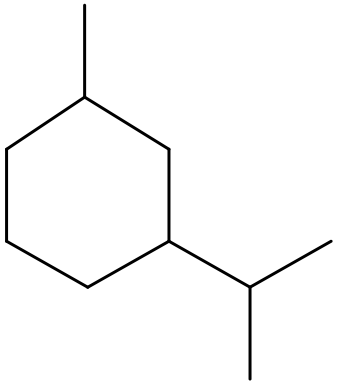




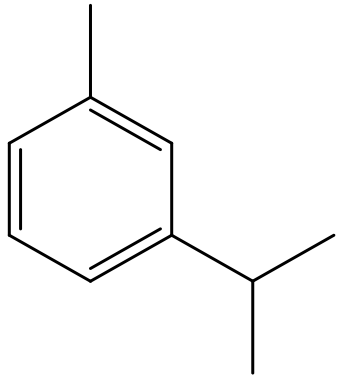
P-menthane



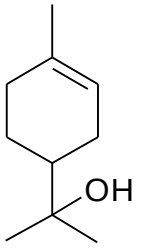
P-cymene



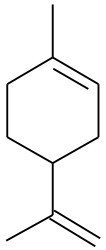
m-menthane



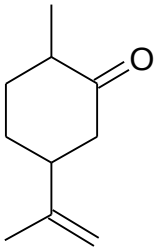
m-cymene



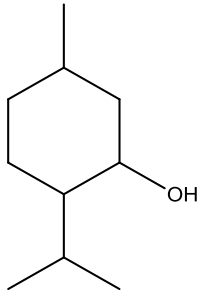
α – terpineol



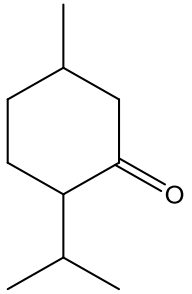
limonene



carvone



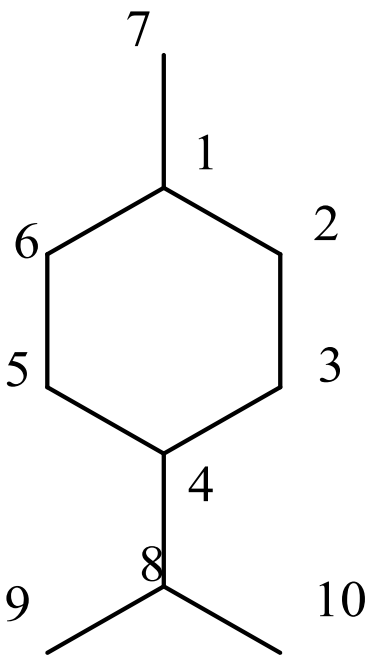
Menthol

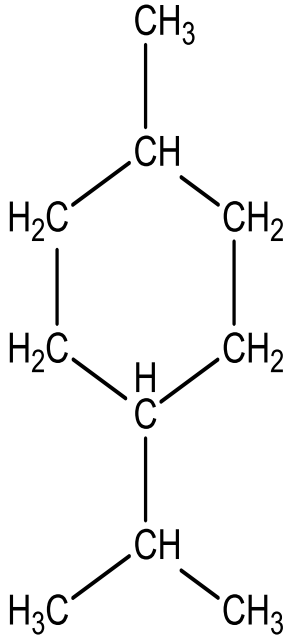


Menthone

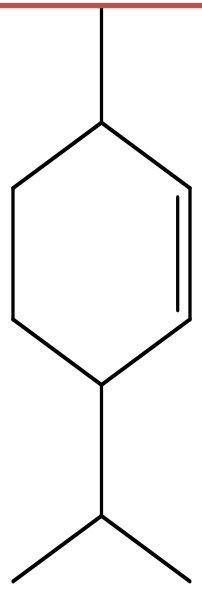
Nomenclature

The fully saturated compound p- methyl isopropylcyclohexane, hexahydro p-cymene or **p- menthane** $C_{10}H_{20}$ is used as parent substance.

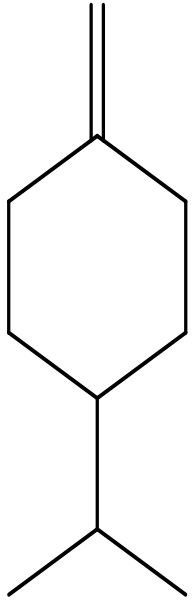




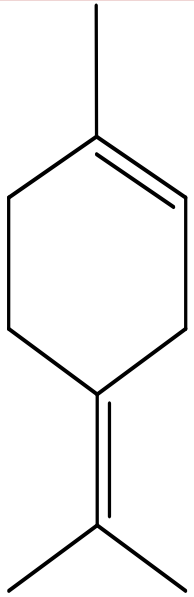
P-menthane



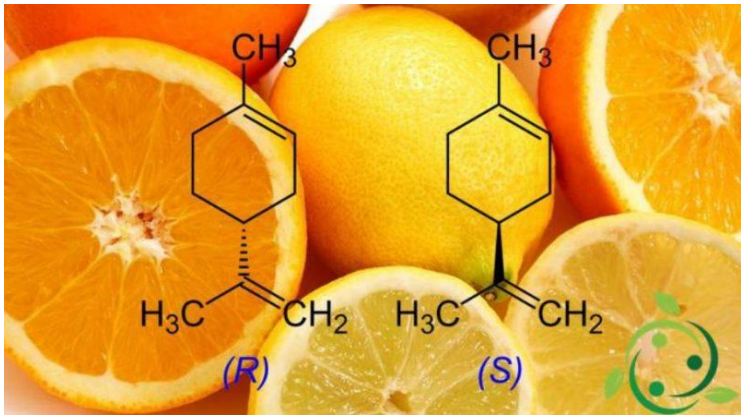
P-menthene-2
2-P-menthene
P-meth-2-ene

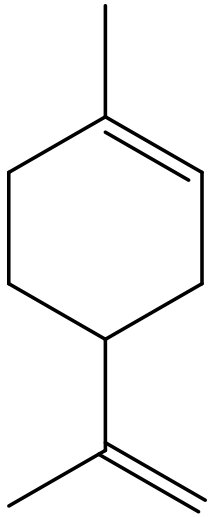


P-mentha-1(7) ene



P-meth-1,4(8)diene





Limonene
الليمونين $C_{10}H_{16}$

P-menth1,8(10)diene

Limonene

١،٨ بارامينثادايين

Limonene is optically active, (+) form in lemon,orange oils (-)form in peppermint oil and racemic mixture(dipentene) in turpentine oil b.p 175-176°C

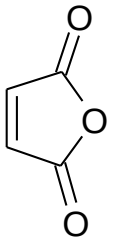
.

Structure of Limonene was supported by

tetrabromo derivative ⟹ limonene contains two double bonds

2 Br_2

(2)



(3) **Limonene**

Diels- Alder reaction

no cyclic adduct ⇓

the two double bonds are unconjugated

H_2/ Ni

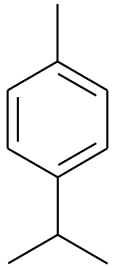
(1) → $C_{10}H_{20}$ ⇓

saturated compound with genera formula C_nH_{2n} i.e. it is cycloalkane

So limonene has cyclic structure

(4)

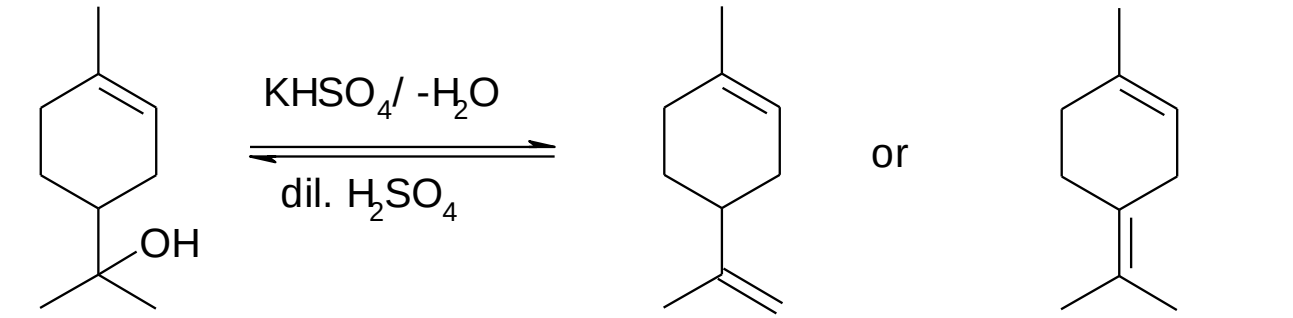
Se/ heat



p- cymene

⟸ limonene is p- menthane derivative

Structure of Limonene



α – terpineol

I

التركيب البنائي الصحيح لليمونين لأنه نشط ضوئيا

II

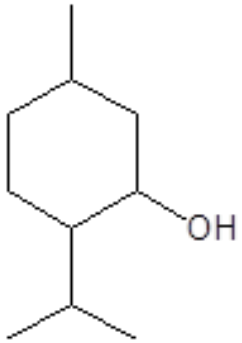
مستبعد لأنه تركيب بنائي غير نشط ضوئيا

5-limonene may be prepared by dehydrating α- terpineol by using potassium hydrogen sulphate ($KHSO_4$) ,and on shaking with dilute sulphuric limonene may be converted to α- terpineol .

6-The carbon skeleton and the position of double bond in limonene are known ,but the other double bond remains uncertain (may be C8-C10 or C4-C8).

7-Structure (I) contains a chiral center(C4)and hence can exhibit optical activating .

Structure (II) is symmetric and so cannot be optically active. Therefore (I) must be **Limonene**



المنثول
Menthol
$C_{10}H_{20}O$

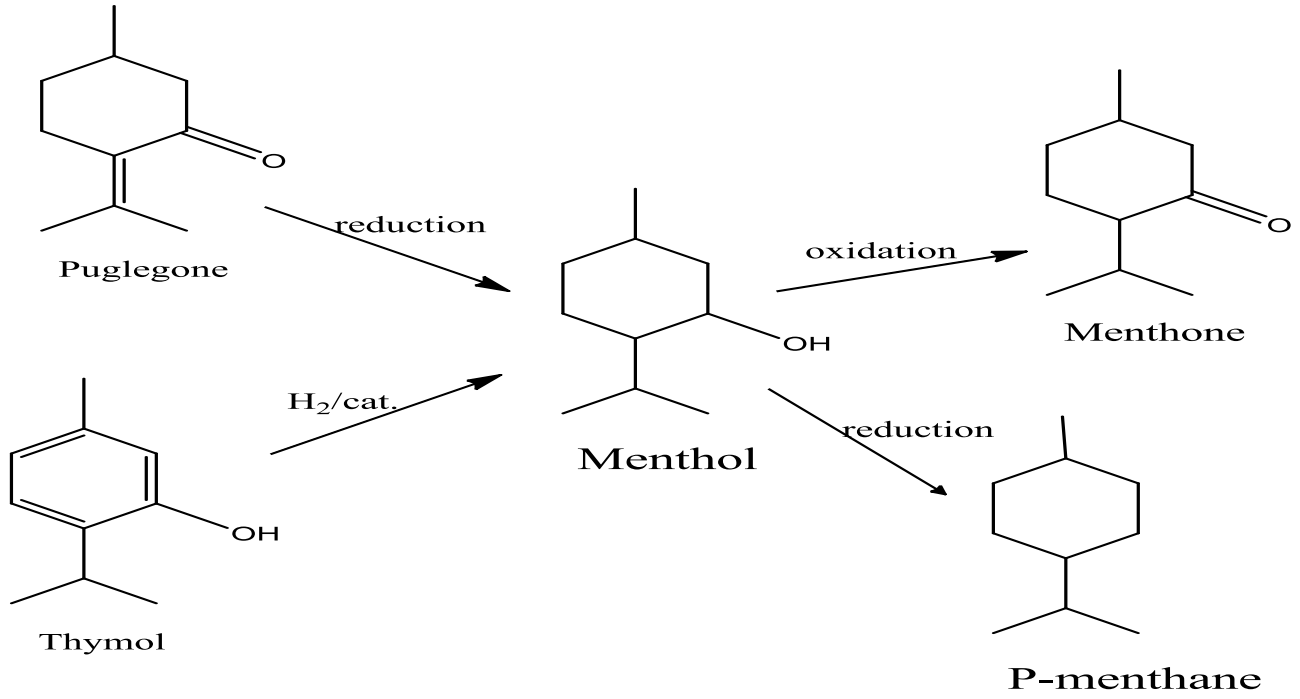
Menthol is optically active compound ,(-)form occurs in peppermint oil.

Menthol has medical uses :as anti-inflammatory ,analgesic, used in dental care as a topical antibacterial agent.

3-Hydroxy-4-Isopropyl-1-methyl cyclohexane , which is one of the most important monocyclic alcohols and contains three chiral carbon atoms (1,3,4), so that it can have eight enantiomers.

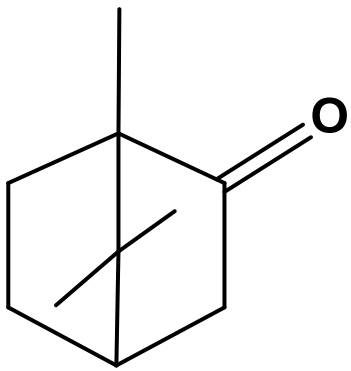
Structure of Menthol was supported by

1-It has been proven that molecular formula is $C_{10}H_{20}O$ and menthol is saturated compound .
2-The nature of oxygen atom is alcoholic (menthol forms ester).
3 -Oxidation of menthol gives menthone (a ketone)thus menthol is secondary alcohol.
4-Reduction using hydrogen iodide give p-menthane thus menthol contains this carbon skeleton.
5-Pulegone gives menthol on reduction .
6-Menthol can be synthesized by catalytic hydrogenation of thymol(3-hydroxy p-cymene)



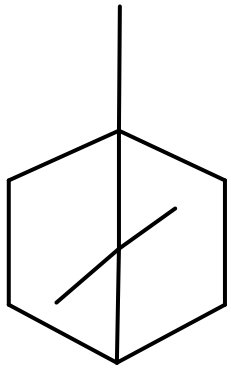
التربينات الأحادية ثنائية الحلقة

Bicyclic monoterpenoids



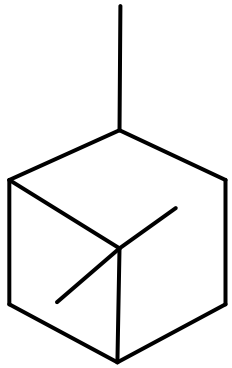
camphor

6+5



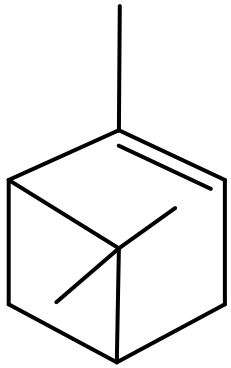
camphane
bornan

6+5



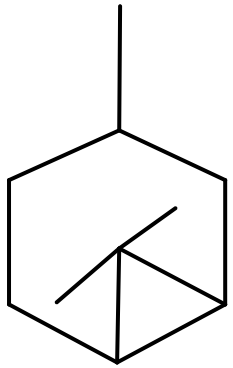
Pinane

6+4



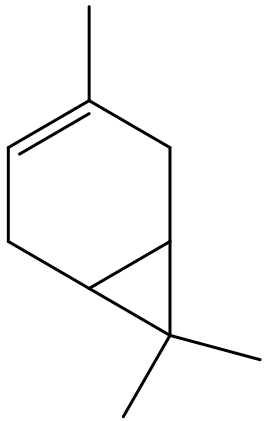
Pinene

6+4



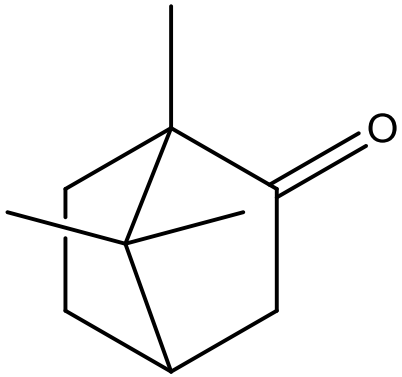
carane

6+3



Carene

6+3



Camphor الكافور

Camphor occurs in the camphor tree of Japan . It is an optically active solid with m.p 180 ° C the(-)and (+)forms occur naturally and racemic camphor is the usual form of synthetic camphor .

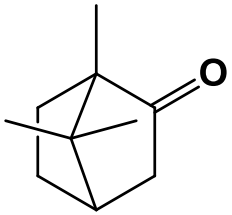
Camphor used in manufacture of cellulose as well as has many medical uses, including that it is used as a disinfectant and as a local anesthetic, and in the laboratories it is used as a solvent in experiments determining the molecular weight of organic compounds.

Structure of camphor was supported by :

1-The molecular formula of camphor is $C_{10}H_{16}O$,and the general reactions show that it is saturated .

Structure of Camphor

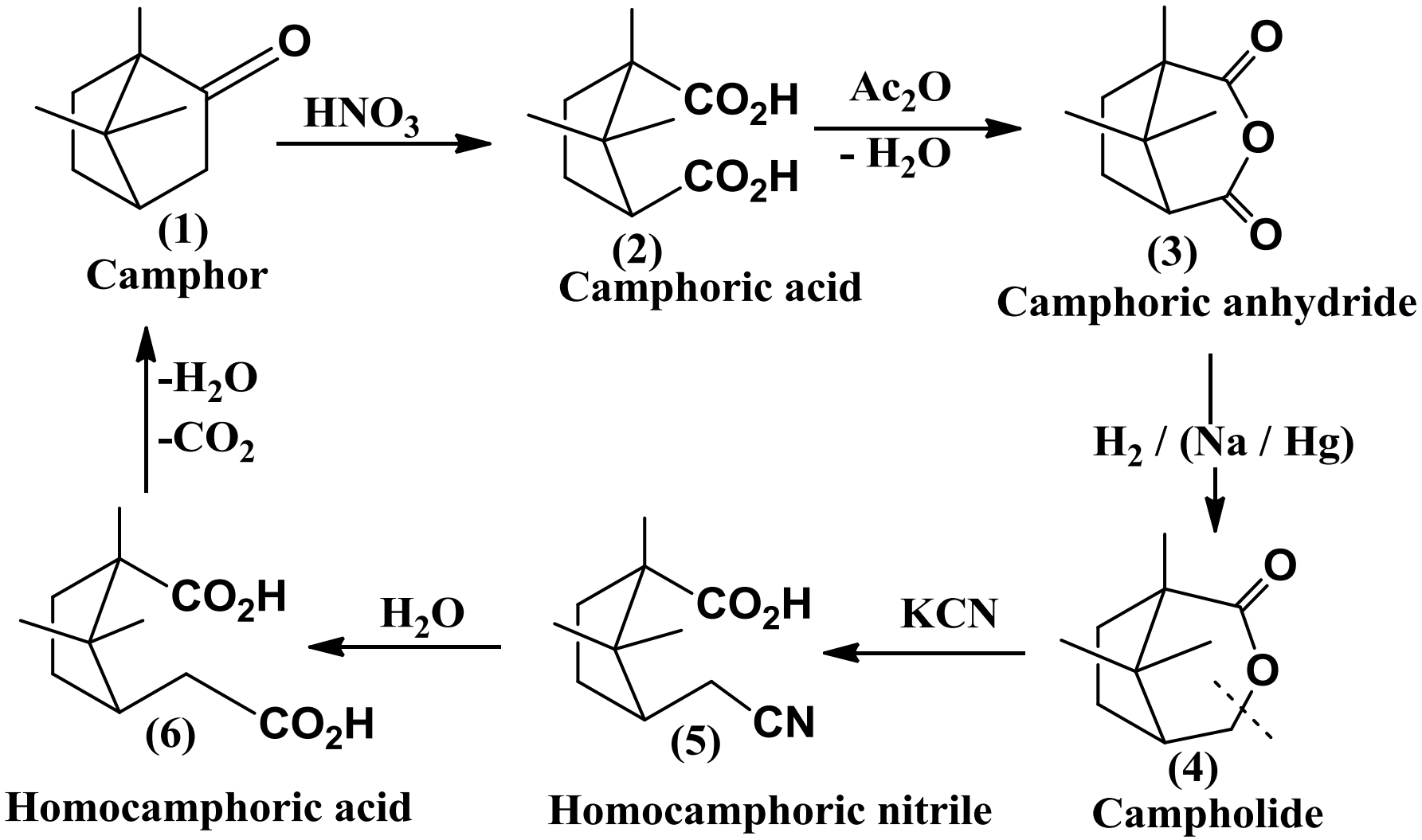
Camphor



- Br_2 → **(-ve) does not contain double bond**
- NH_2OH → **Camphor oxime , camphor contains carbonyl group**
- **Fehling reagent** → **-ve the carbonyl is ketonic**
- **clemensen reduction** → **camphane $C_{10}H_{18}$**

  Camphor is bicyclic monoterpenoid
- **dist.P_2O_5 or $ZnCl_2$** → **P-cymene, one of the two rings is 6 membered ring**
- HNO_3 **Oxid.** → **Camphoric acid $C_{10}H_{16}O_4$**
- **benzaldehyde phCHO** → **monobenzylidene derivative contains (-CO-CH2-)**

Structure of Camphor



النواتج الطبيـــعية

التربينات النصف ثلاثية والثنائية والرباعية والعديدة

Sesquiterpenoids,diterpenoids ,tetraterpenoidand poly terpenoids

د /عواطف محمد المغربي

قسم الكيمياء – كلية العلوم

التربينات النصف ثلاثيــة (السيسكوتربينات)

Sesquiterpenoids

The sesquiterpenoids are naturally occuring compounds containing fifteen carbon atoms, in general they form the higher boiling point fraction of the essential oils and may be acyclic or cyclic hydrocarbons ,alcohols , ketones or lactones ,the sesquiterpenoids structure is built up from three isoprene units but there are some exceptions.

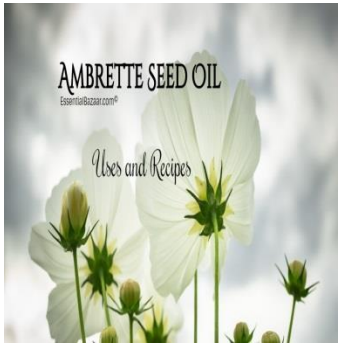
The sesquiterpenoids are classified into four groups :

1-Acyclic sesquiterpenoids contain four double bonds (farnesene) .

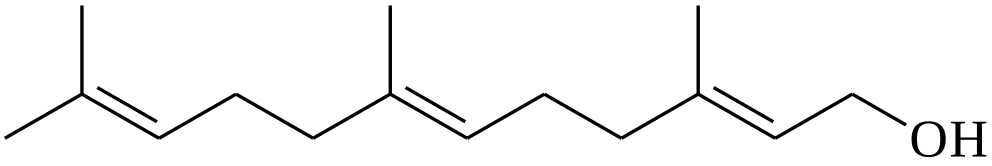
2-Monocyclic sesquiterpenoids contain three double bonds (zingiberene from ginger oil) .

3-Bicyclic sesquiterpenoids contain two double bonds (selinene occurs in celery oil).

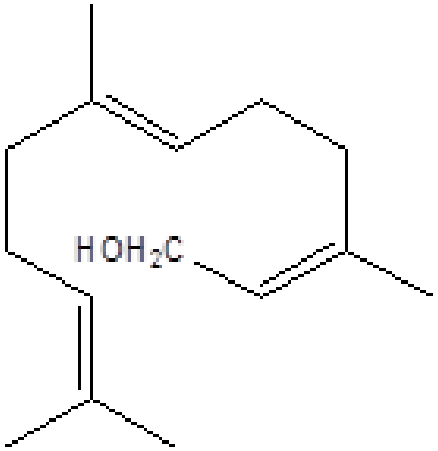
4-Tricyclic sesquiterpenoids contain one double bond (cedrol in sedar wood oil) .



(C15H26O)Farnesol الفارنيسول



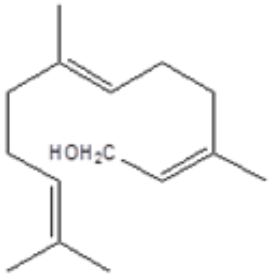
Farnesol
occurs in oil of ambrette seeds



Farnesol considered acyclic sesquiterpenoid contains 15 carbon atom and the carbon skeleton can be formed by the union of three isoprene units.

Farnesol is a primary alcohol ,it is used in perfume manufacture and it occurs in ambrette seeds.

الفارنيسول($C_{15}H_{26}O$)Farnesol
Determination of structure



Farnesol

catalytic hydrogenation

$3H_2$

(+ve) saturated alcohol Hexahydro - farnesol thus it contains 3 double bond

maleic anhydride

(-ve) the double bonds are unconjugated

Analysis

Molecular Formula $C_{15}H_{26}O$

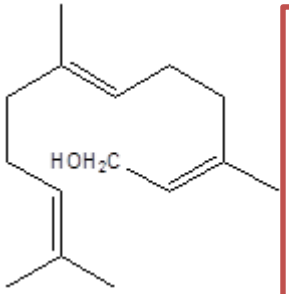
Oxidation

chromic acid

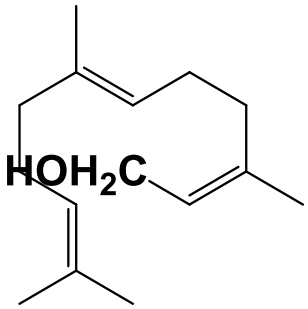
Farnesal $C_{15}H_{24}O$, farnesol is primary alcohol

Ozonolysis

acetone+2mole of Laevulaldehyde +glycolaldehyde

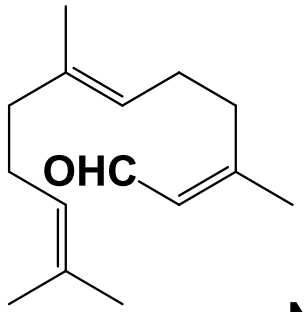


$(C_{15}H_{26}O)$Farnesol
Determination of structure



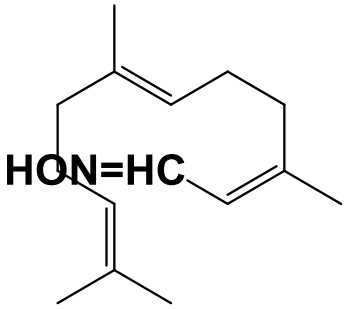
$C_{15}H_{26}O$
Farnesol
(1)

CrO_3



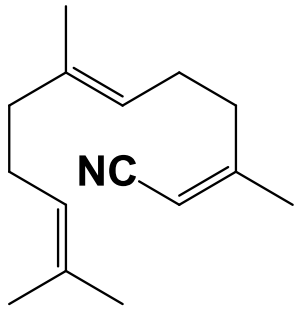
$C_{15}H_{24}O$
Farnesal
(2)

NH_2OH



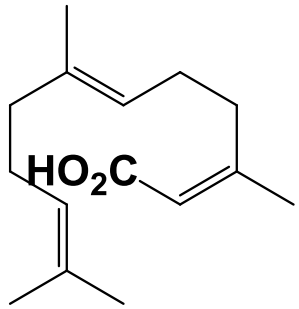
$C_{15}H_{25}NO$
Farnesal Oxime
(3)

$(Ac)_2O$



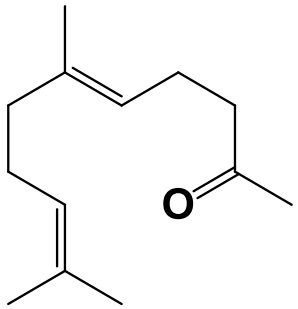
$C_{15}H_{23}N$
farnesal cyanide
(4)

i)- KOH
ii) - H^+



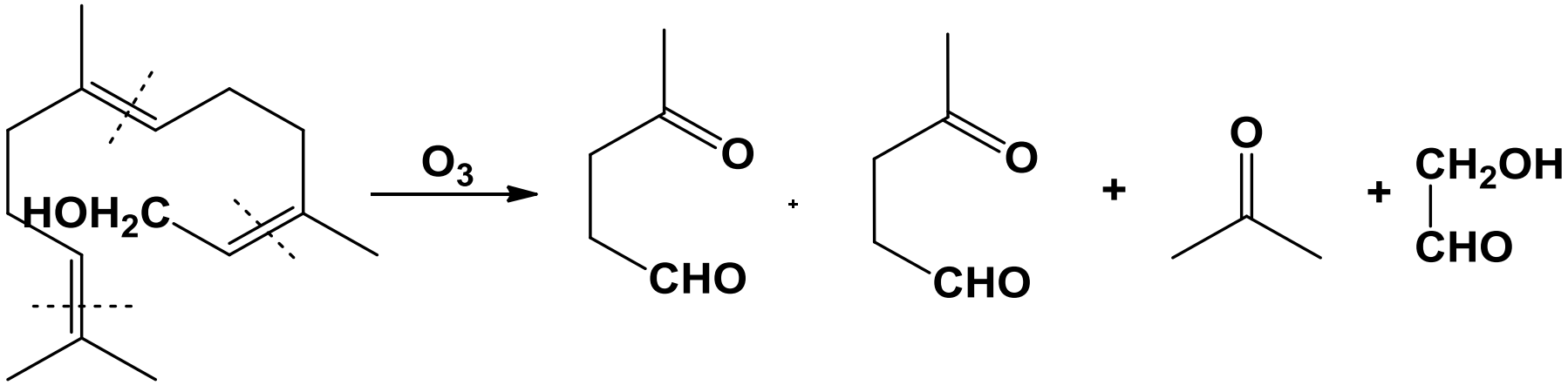
Farnesenic acid
(5)

+



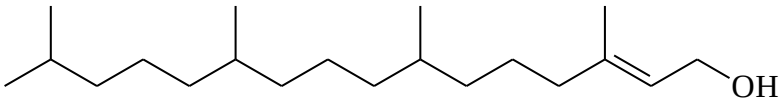
Geranylacetone
(6)

$C_{15}H_{26}O$ Farnesol
Determination of structure

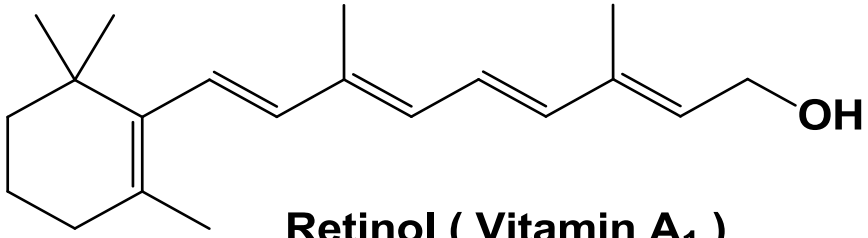


التربينات الثنائية (الداي تربينات)
Diterpenoids

The diterpenoids are naturally occurring compounds containing 20 carbon atoms and four isoprene units ,which distributed in plants kingdom. Diterpenoids are classified on the basis of the number of carbon ring present into acyclic (phytol) monocyclic (vitaminA1and vitaminA2) , dicyclic, tricyclic and tetracyclic diterpenoid .

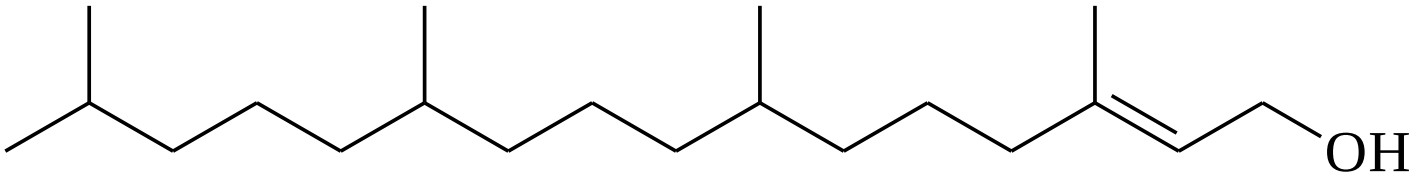


Phytol
is produced from hydrolysis of chlorophyll



Retinol (Vitamin A_1)

Phytol $C_{20}H_{40}O$



Phytol
is produced from hydrolysis of chlorophyll

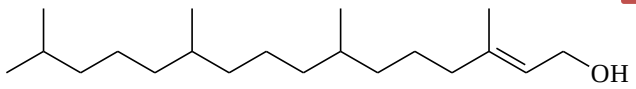
Phytol is an acyclic diterpenoid ,it is produced from hydrolysis of chlorophyll , and it forms a part of the molecules of vitamins E and K .

Determination of the structure

1-General reactions and analysis showed that molecular formula is $C_{20}H_{40}O$ and it is a primary alcohol .

2-On catalytic hydrogenation it forms dihydrophytol **$C_{20}H_{42}O$** so phytol is acyclic diterpenoid and contains one double bond.

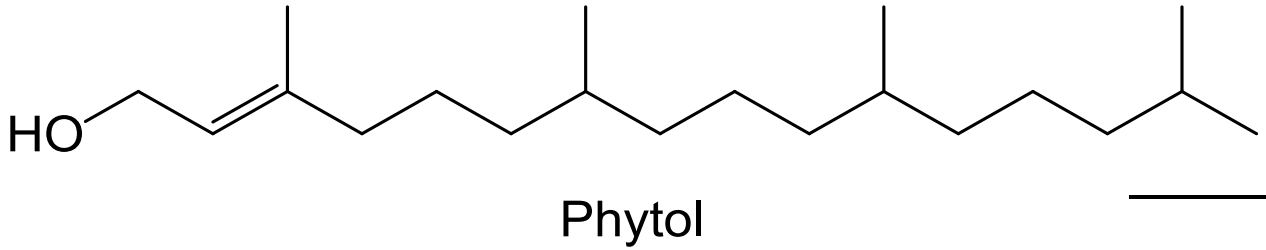
Phytol $C_{20}H_{40}O$
Determination of the structure

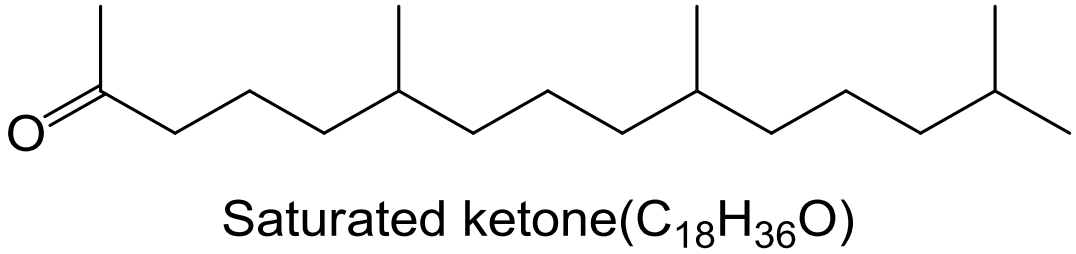


Phytol
is produced from hydrolysis of chlorophyll

3-Ozonolysis of phytol gives glycol aldehyde and a saturated ketone $C_{18}H_{36}O$.

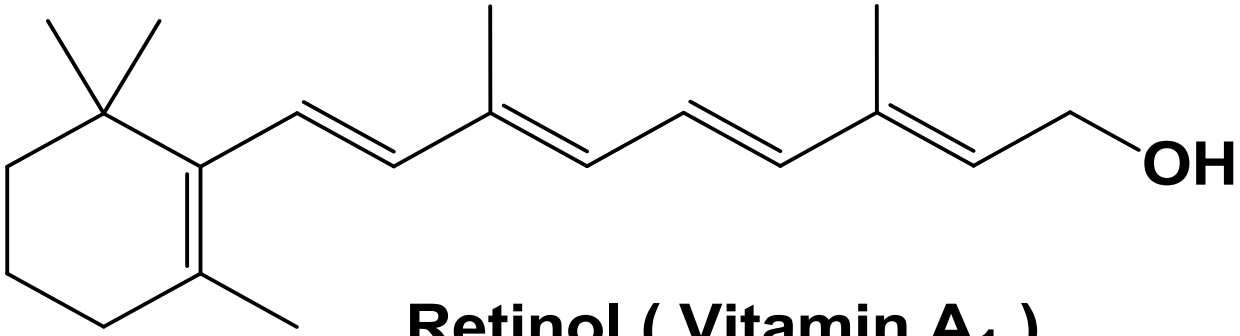
4-Phytol contains four isoprene units connected (head-tail).





Monocyclic Diterpenoids

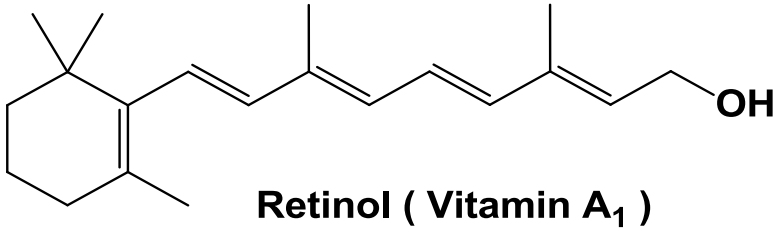
Retinol VitaminA_1 ($C_{20}H_{30}O$)



Retinol (Vitamin A_1)

- Retinol or Vitamin **A_1** is a monocyclic diterpenoid occurs in many flowers and carrots as a β-carotene which converted into vitamin A_1 by hydrolysis .
- Retinol occurs free and as esters in fats in fish liver and in blood,it was originally isolated as viscous yellow oil ,but later it was obtained as crystalline solid .
- Vitamin **A_1** is estimated by the blue color reaction it gives with a solution of antimony trichloride in chloroform .
- Vitamin **A_1** influences growth in animals and increased the resistance to disease . ***Night blindness*** is due to Vitamin **A_1** deficiency .

($C_{20}H_{30}O$) Retinol VitaminA_1



Retinol (Vitamin A_1)

Structure of Retinol was supported by

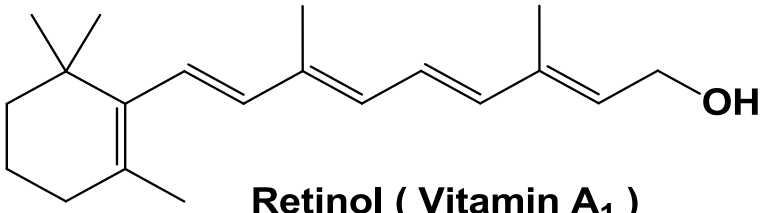
1-Routine tests confirmed that M. F **$C_{20}H_{30}O$** and it is a primary alcohol since mild oxidation it yields the corresponding aldehyde retinal **$C_{20}H_{28}O$.**

2-Catalytic hydrogenation converts it into perhydro vitamin A_1

$C_{20}H_{40}O$ thus it contains five double bond and vitamin A_1 must be monocyclic.

3-Ultra violet absorption measurements show the presence of conjugation, so it is a conjugated polyene alcohol .

Retinol VitaminA$_1$ ($C_{20}H_{30}O$)

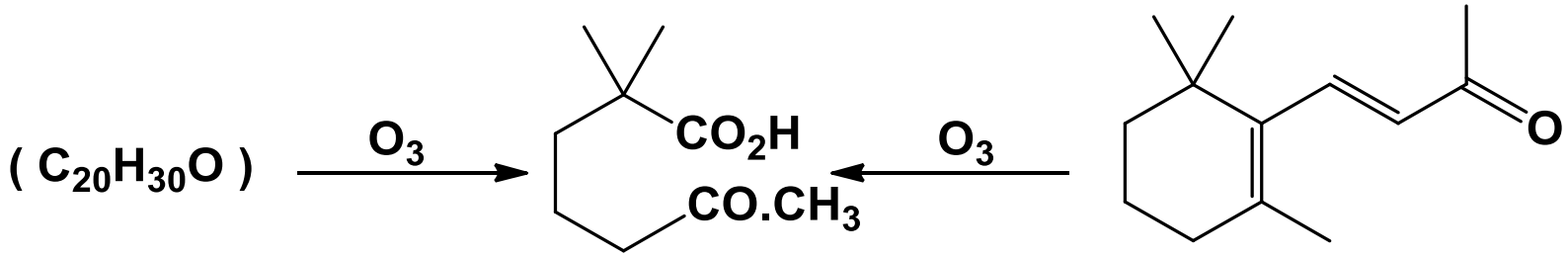


Retinol (Vitamin A_1)

4-Ozonolysis of retinol afforded one molecules of geronic acid which was isolated also from oxidative degradation of β-ionone nucleus .

5-Application of isoprene rule led to confirmation of carbon skeleton .

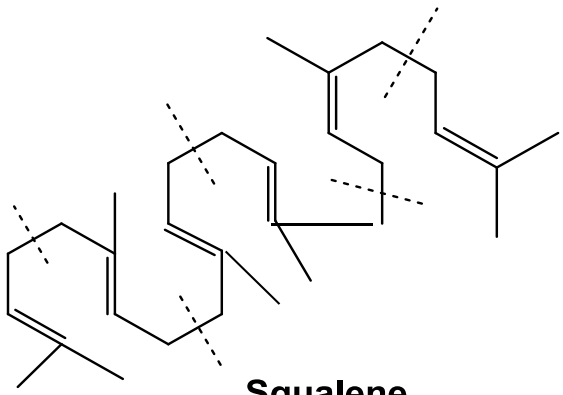
6- The structure of retinol also can be confirmed by using β-ionone as a starting material in synthesis .



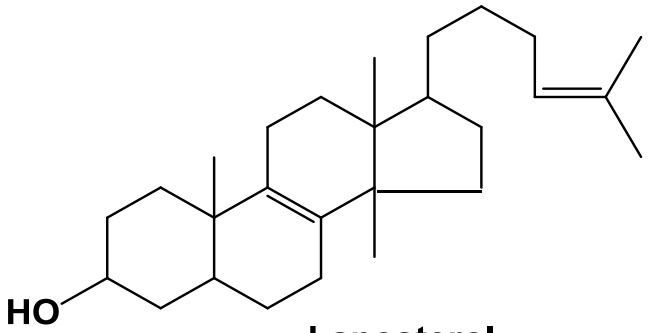
Retinol (Vitamin A_1) Geronic acid B - Ionone

Triterpenoids
التربينات الثلاثية

- Triterpenoid compounds are widely distributed in nature mainly in plants where they found in resins and plant saps in the free state and as esters . A few have been found in animal sources as in the liver oils of certain fish .
- Triterpenoids contain 30 carbon atom and most of them have carbon skeleton which may be built up by the union of six isoprene units , they may be acyclic or cyclic.
- Squalene is acyclic triterpenoid occurs in the fraction of liver oil and also in various plant sources and it is an intermediate in the biosynthesis of cholesterol from acetic acid .
- Lanosterol is a very important tetracyclic triterpenoid which contains the steroid carbon skeleton.



Squalene



Lanosterol

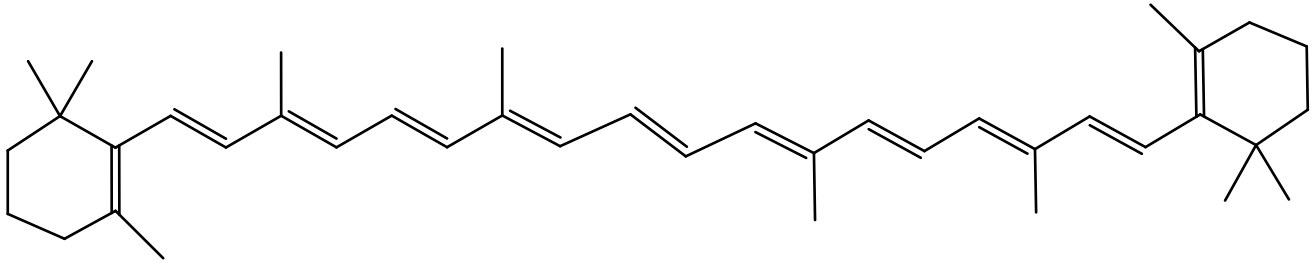
Tetraterpenoids

التربينات الرباعية (التترا تربينات)

1- The tetraterpenoids more commonly referred to as the carotenoids , are compounds containing eight isoprene units and 40 carbon atoms , constitute a group of natural pigments which are widely distributed in plants and animals.

2- A characteristic reaction shown by carotenoids is the formation of deep blue color with antimony trichloride in chloroform solution .

3- β-Carotene was isolated from carrots and M.F $C_{40}H_{56}$, and isolated by extraction with light petroleum .



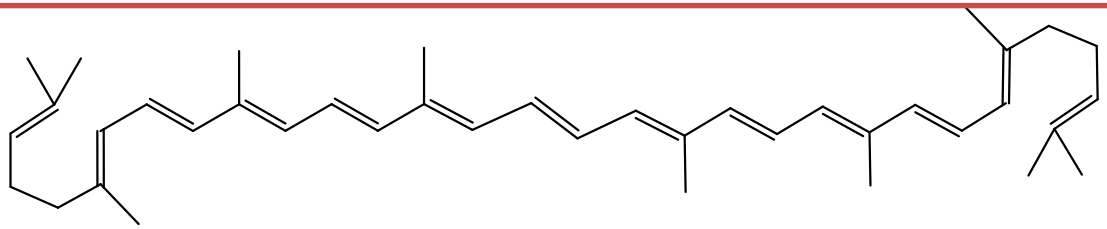
B - Carotene

التربينات الرباعية (التترا تربينات) الكاروتينات
(Carotenoids) Tetraterpenoids

4- Lycopene is a carotenoid that is the red tomato pigment .

5-Lycopene is considered the acyclic isomer of β-Carotene and β-Carotene shows vitamin A activity owing to the fact that it is converted into vitamin A in animal blood .

6—Carotenoids are polyenes , most of them the central portion of the molecules is composed of long conjugated chain comprised of 8 isoprene unites , the center two of which are joined tail to tail .

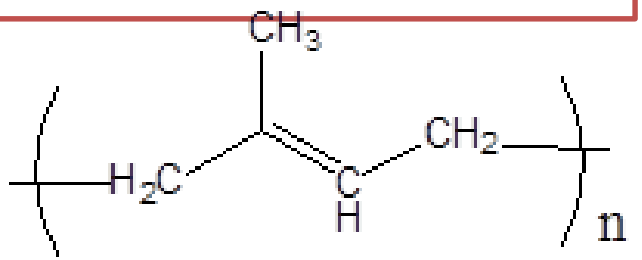


Lycopene $C_{40}H_{56}$

Poly terpenes- التربينات العديدة Rubber

- Poly terpenoids consist of several units of isoprene connected together in large chains .
- Natural rubber is the most important example ,rubber is obtained from latex which is an emulsion of rubber particles with water , it is obtained from the inner bark of many types of trees which grow in the tropic and sub tropics .
- Addition of acetic acid coagulate the rubber which is separate from the liquor either pressed into blocks or rolled into sheets finally dried in a current of warm air
- Crude latex rubber contains in addition to the actual rubber hydrocarbon , proteins, sugar, fatty acids and resins the amount of these substance depends on the source .

Poly terpenes-Rubber



Structure of natural rubber

1-The destructive distillation of rubber gives isoprene as one of the main products thus rubber is a polymer of isoprene and molecular formula $(C_5H_8)_n$.

2-Rubber is unsaturated hydrocarbon , on catalytic hydrogenation at high temperature and pressure ,the product is ***hydro rubber which*** is an elastic solid which is fully saturated and resistant to oxidation.

3-Rubber reacts with hydrogen chloride or hydrogen bromide to give rubber hydrochloride or rubber hydrobromide formed by the addition of hydrogen halide to the double bonds ***(Markwnikoff) .***

Natural Products
Steroids

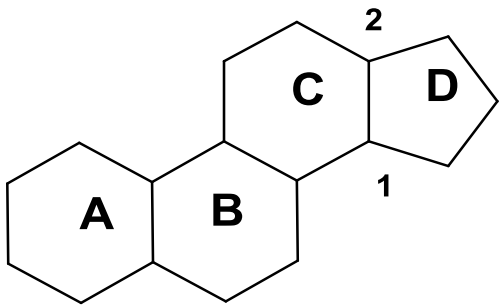
Dr. Awatef Mohamed El-maghraby

Chemistry Department

Faculty of Science

South Valley University

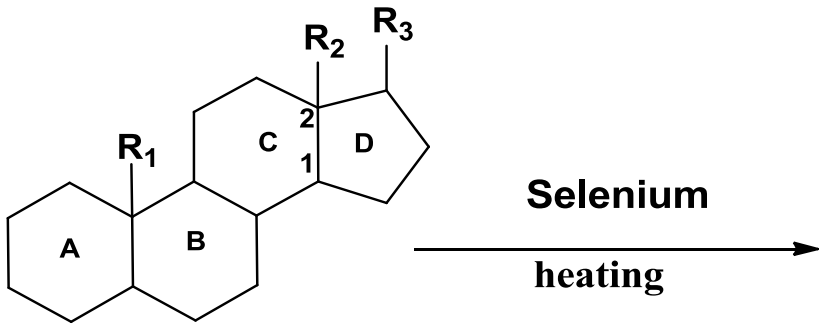
Steroids



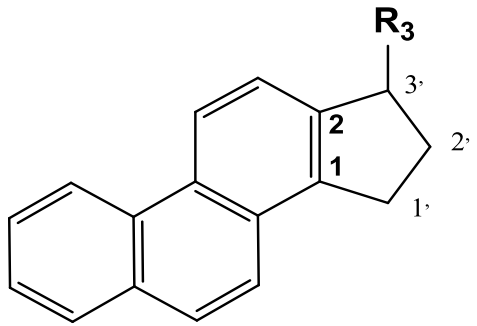
Perhydro-1,2-cyclopentanophenanthrene

Definition of steroids

Saturated natural products possessing the tetracyclic carbon skeleton ,ring **A,B,C** are six membered ring while ring **D** is five membered ring, the side chain R1, R2 and R3. R1 may be absent when ring **A** is aromatic ,R1 and R2 are generally methyl groups . The side chain R3 may be absent .



Steroid

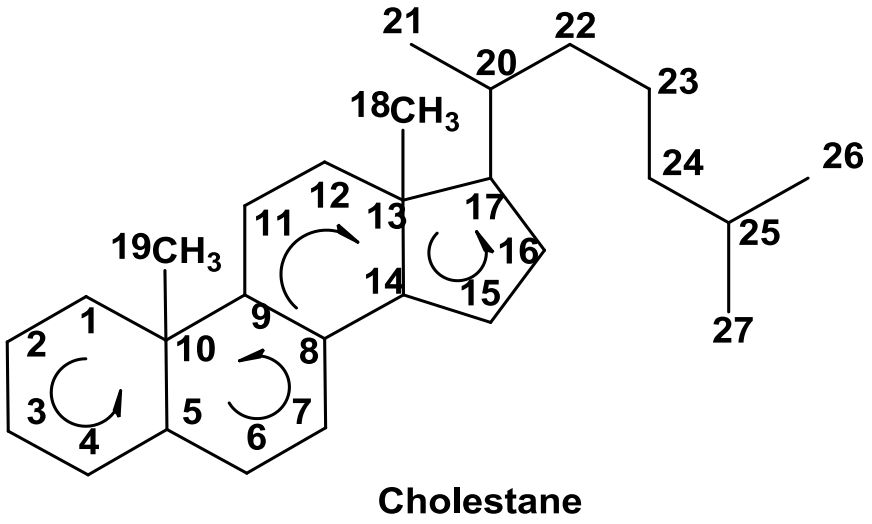


R_3=Me (Diels hydrocarbon)
3'-methyl-1:2-cyclopentenophenanthrene
R_3 = H 1: 2-cyclopentenophenanthrene

A steroid could be defined, in another way, as any compound which gives Diel's hydrocarbon(beside other products) when distilled with selenium.

Classification of Steroids

The carbon skeleton of the hydrocarbon cholestane is given which shows the correct numbering of the system .



Cholestane

Classification of Steroids

1- **Sterols (cholesterol)**

2-Vitamin D(vitamin D2)

3-Bile Acids (cholic acid)

4- Steroidal Hormones or Sex Hormones(progesterone)

5- Adrenocortical hormones (cortisone)

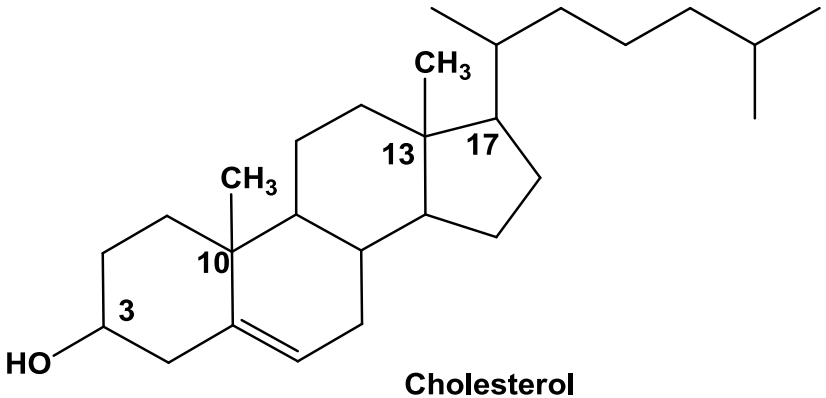
6-Cardiotonic glycosides

7- Saponins and Sapogenins

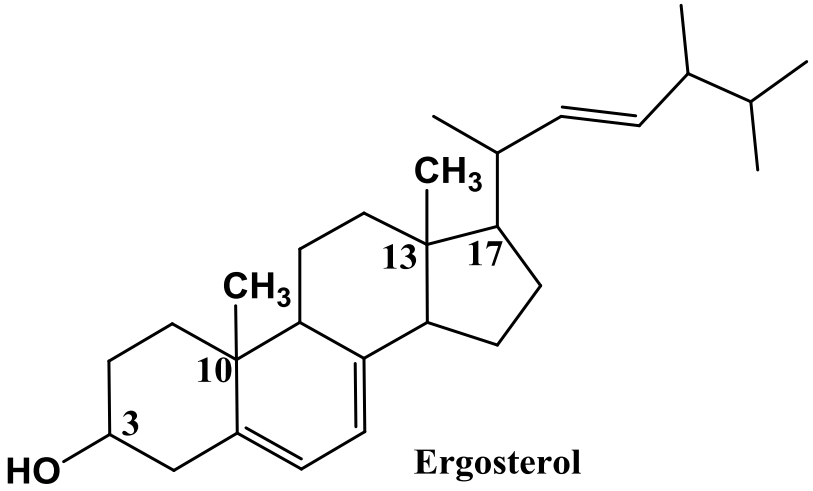
Sterols

Sterols are steroid alcohol containing an aliphatic side chain they are crystalline, widely Distributed in nature .

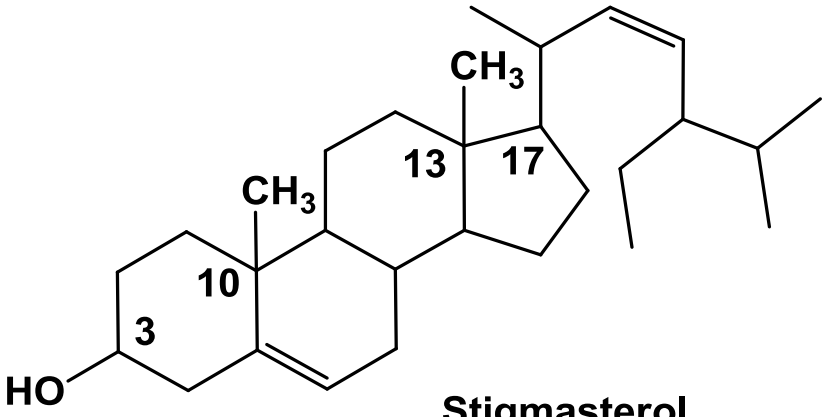
Sterols may be classified on the basis of occurrence as Zoo sterols(animal), Phytosterol (plants), mycosterol (yeast and fungi) and marine sterols(sponges).



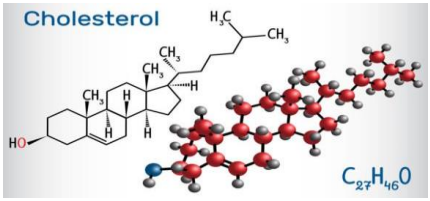
Cholesterol
Zoo sterol



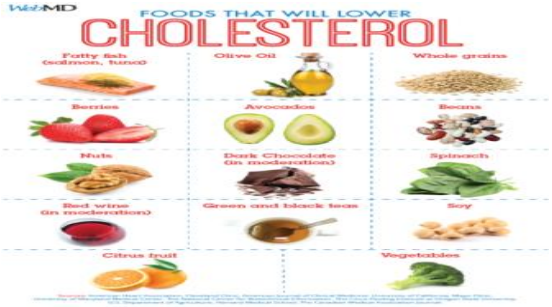
Ergosterol
mycosterol
occurs in yeast

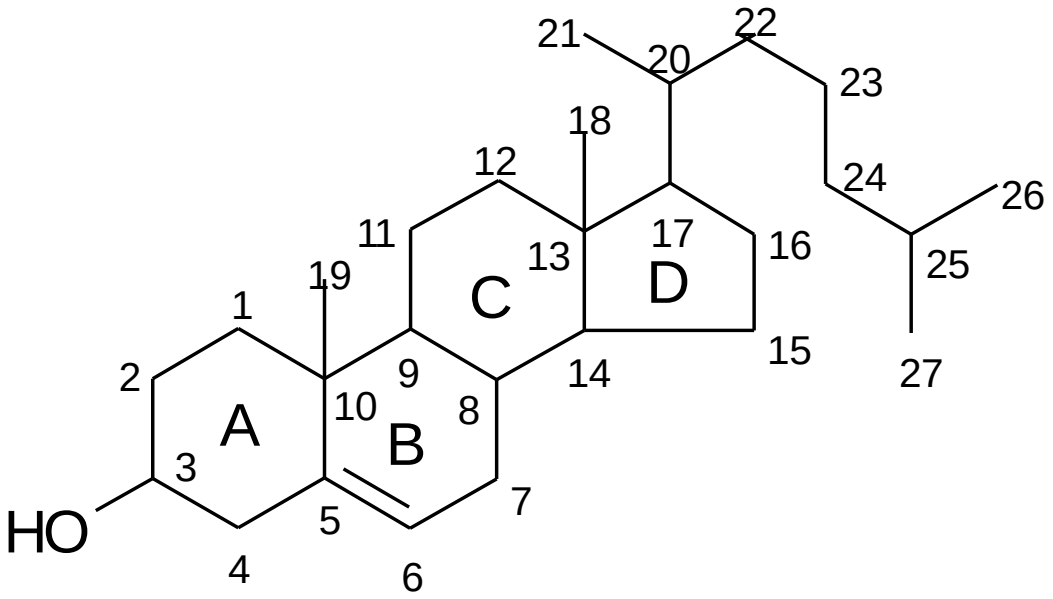


Stigmasterol
Phytosterol
obtained from soya bean oil



كوليسترولCholesterol





characteristic features :-

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

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

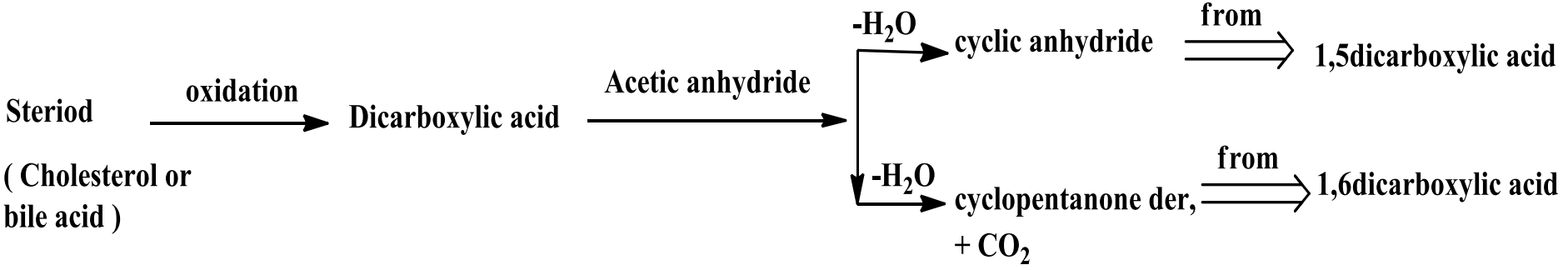
3- There are two angular methyl groups at C-10 and C-13, and a saturated side-chain C_8H_{17} at C-17.

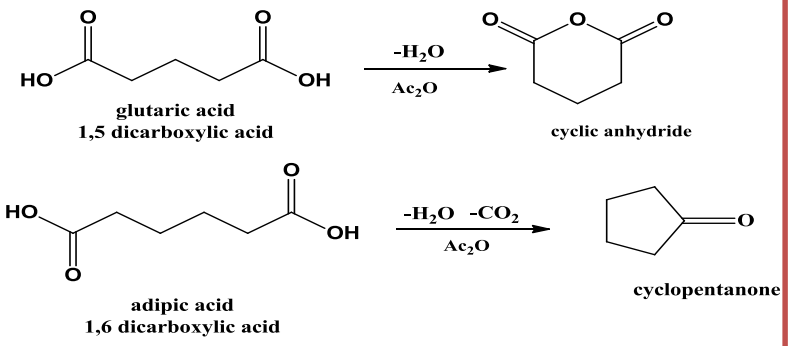
Determination of the nucleus - Blanc Rule

All the steroids possess the same tetracyclic carbon skeleton (cyclopentaneperhydrophenanthrene) ,it has been confirmed by heating steroid with selenium which gives cyclopentenophenanthrene derivative.

The rings of the steroid nucleus were opened by oxidation to give dicarboxylic acid and the relative position of the two carboxyl groups were determined by the application of **Blanc rule:**

Heating with acetic anhydride,1,5-dicarboxylic acids forms cyclic anhydride and 1,6-dicarboxylic acids form cyclopentanones with elimination of carbon dioxide





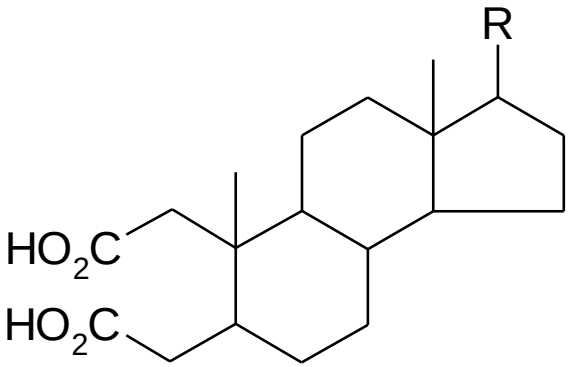
كل الستيرويدات تتكون من هيكل كربوني رباعي الحلقة (سيكلوبنتان بيرهيدرو فينانثرين) وهذا تم اثباته عند تسخين الستيروييد مع السيلينيوم ليعطي مشتق سيكلوبنتينوفينانثرين .

ولإثبات حجم كل حلقة في الستيرويدات تجري الاكسدة للستيرويد فتفتح الحلقات لتعطي احماض ثنائية الكربوكسيل ولمعرفة طبيعة هذه الاحماض تطبق قاعدة بلانك والتي تنص علي :

عند التسخين مع اسيتيك انهيدريد الاحماض ١،٥ داي كربوكسيليك تكون انهيدريد حلقي مع فقد ماء اما الاحماض ١،٦داي كربوكسيليك فتكون سيكلوبنتانون مع فقد ثاني اكسيد الكربون بالإضافة لفقد الماء.

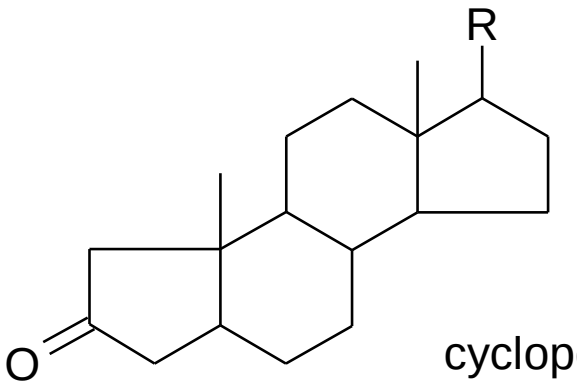
Determination of ring A in cholesterol and cholic acid

cholesterol and/ or cholic acids



(A)

Ac_2O

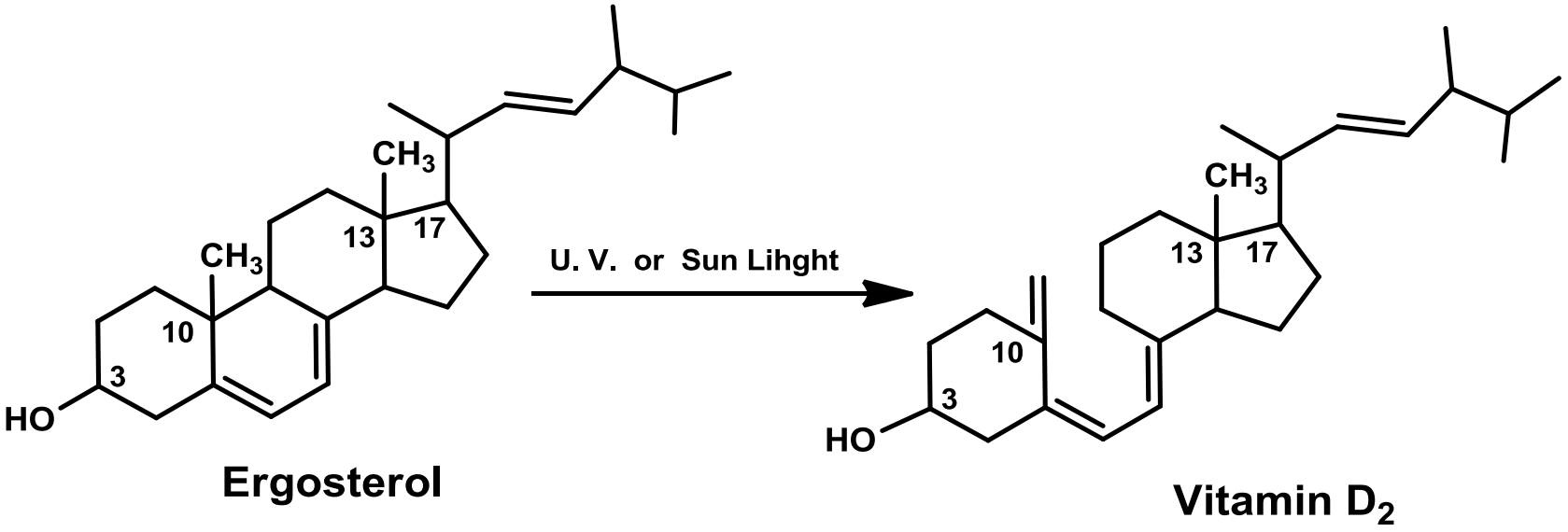


cyclopentanone deriv.

Cholesterol and cholic acid were converted into the dicarboxylic acid by oxidation which gave a cyclopentanone derivative by heating with acetic anhydride according to blanc rule and the acid 1,6 dicarboxylic acid and ring A is six membered ring (R is the appropriat side chain).

Ergocalciferol
Vitamin D2

Conversion of Ergosterol into VitaminD_2

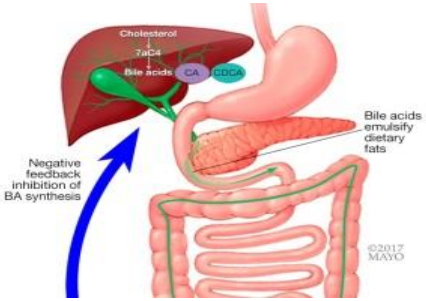


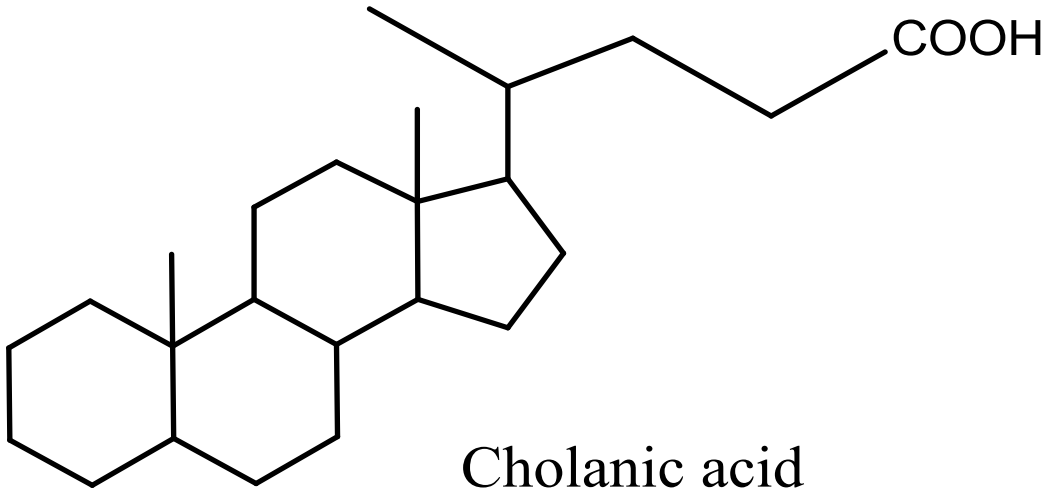
Ergosterol

Vitamin D_2

Vitamin D is anthracitic vitamin They are about seven compounds (Vitamin D1 - D7) with the ring B being opened. Vitamin D2 (or calciferol) is formed from ergosterol by the sunlight irradiation

Bile acids

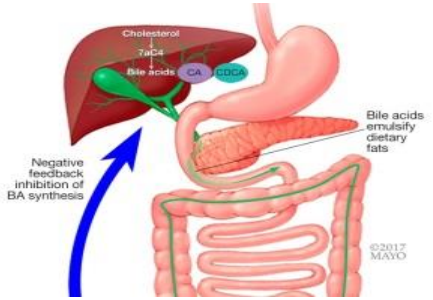


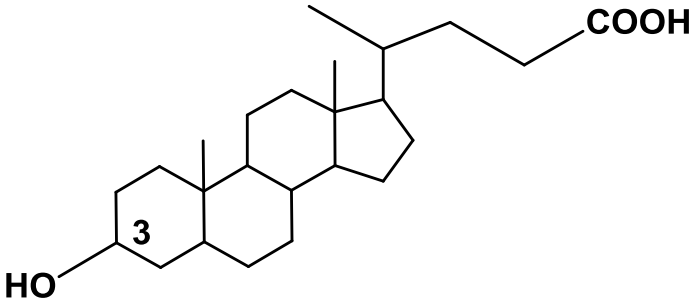


Cholanic acid

The natural bile acids are generally hydroxy derivatives of cholanic acid .They are produced in the liver either synthetically or by degradation of cholesterol and occur in bile as water soluble sodium salts of peptide conjugate with glycine or taurine.

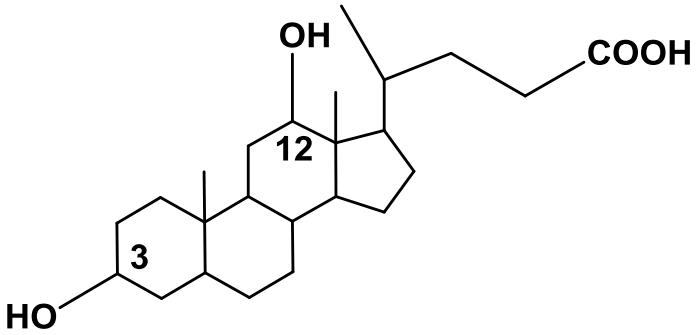
Bile acids





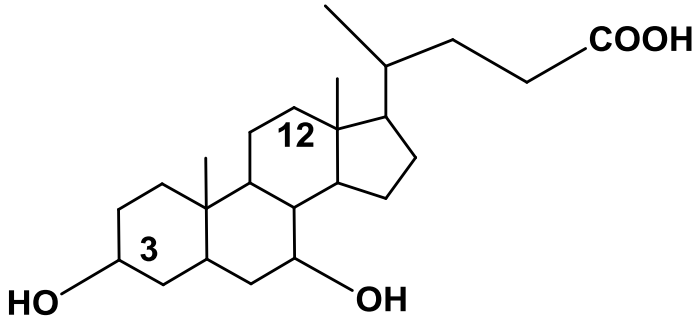
3-Hyrdroxycholanic acid

Lithocholic acid



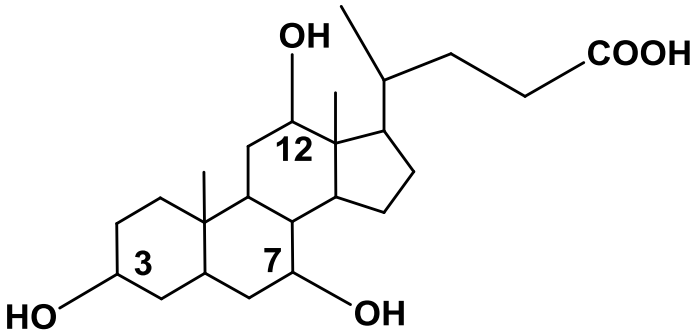
3,12-dihyrdroxycholanic acid

Deoxycholic acid



3,7-Dihyrdroxycholanic acid

Chenodeoxycholic acid

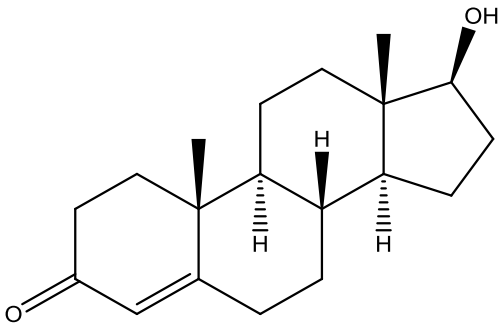


3,7,12-Trihyrdroxycholanic acid

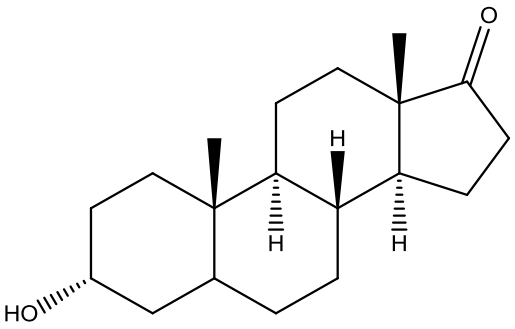
Cholic acid

Sex Hormones

1-Androgens (Male Hormones)(androsterone –testosterone)

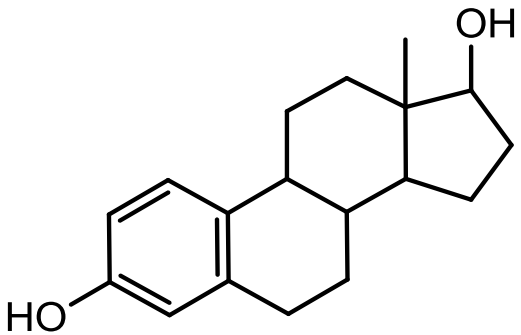


Testosterone

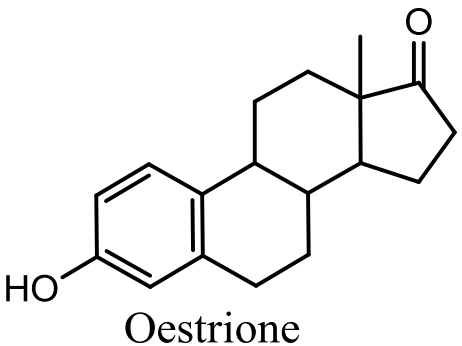


Androsterone

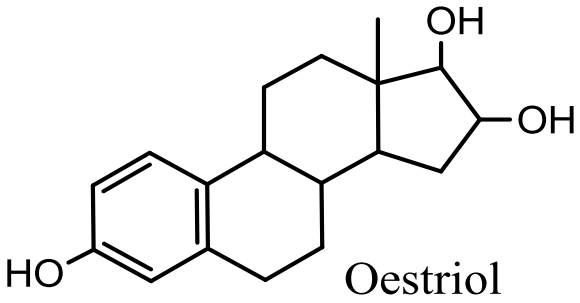
2-Oestrogens (Female Hormones)



Oestradiol



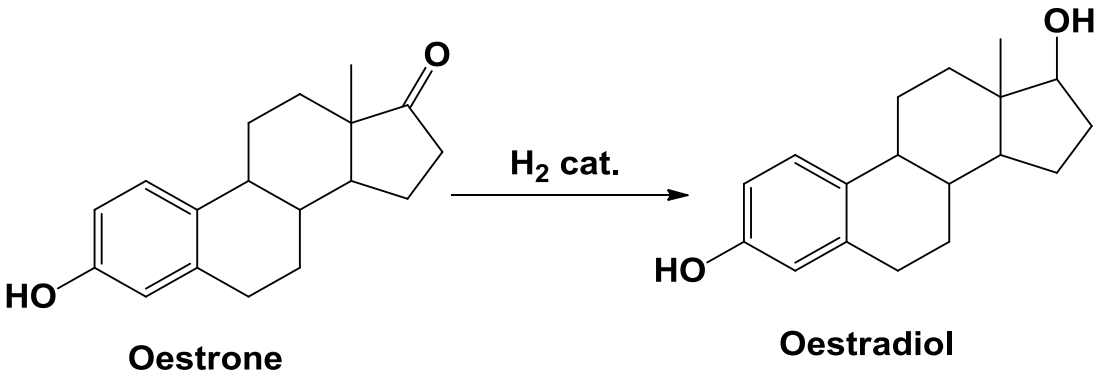
Oestrione



Oestriol

Oestrogens (Female Hormones) all of them contain phenolic hydroxyl group at C3 and may be prepared from dehydroepiandrosterone(D.E.A) which can be synthesized from cholesterol.

(Oestrogens)

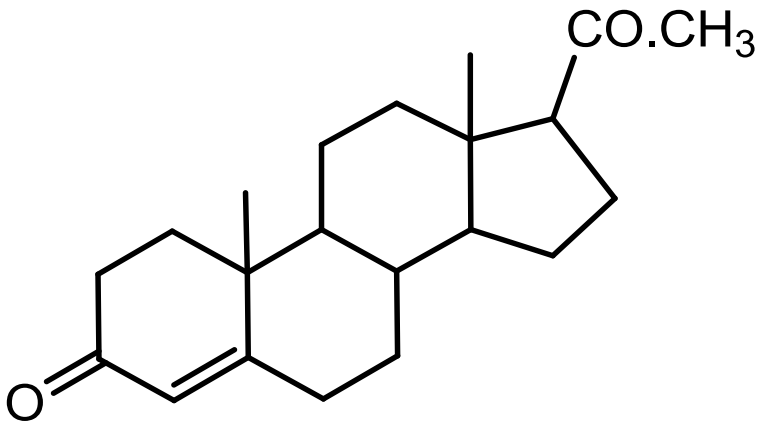


Oestrone

Oestradiol

Oestrone may be reduced to oestradiol by catalytic hydrogenation or by lithium aluminium hydride .

3- (Gestogens) Progesterone



Progesterone

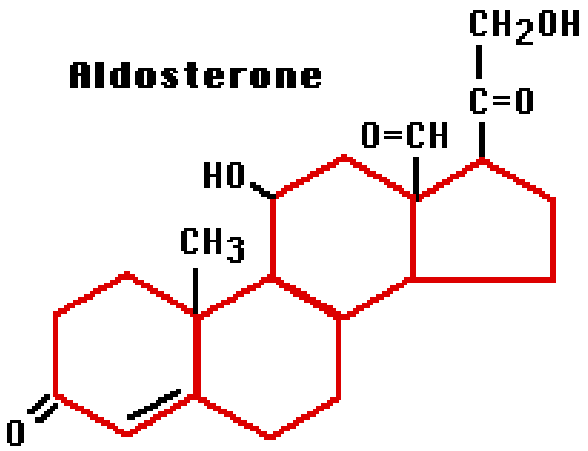
These are essential hormones which responsible for pregnancy.

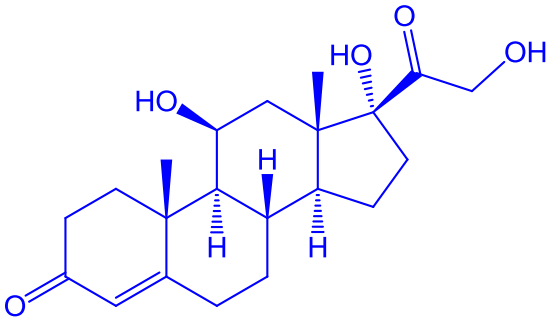
Progesterone is α,β-unsaturated ketone and synthesized from both D.E.A and Ergosterol .

Adrenocortical hormones

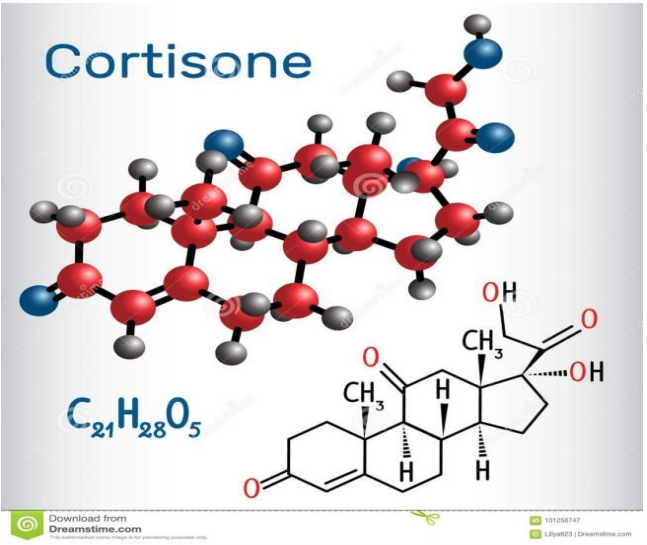
They are produced by the cortex of the adrenal glands ,their main functions are the control of carbohydrate and protein metabolism and control of balance of water and electrolytes.

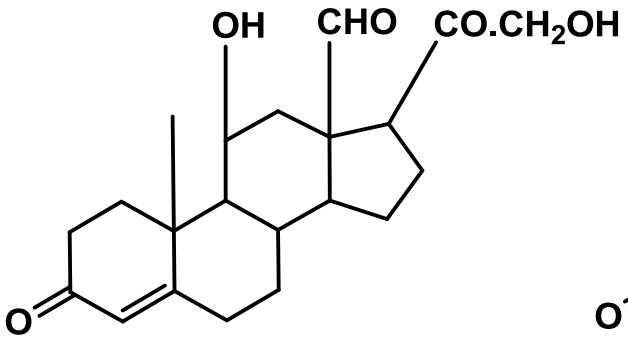
Cortisone is also used in the treatment of allergies and immune diseases.



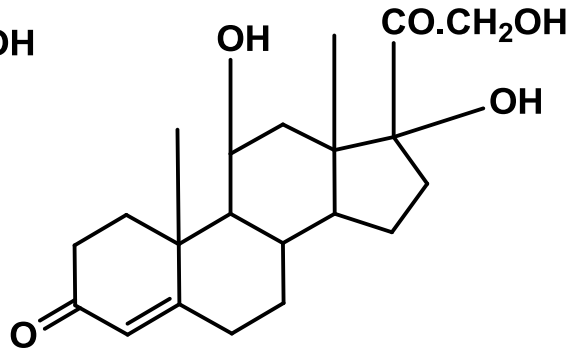


cortisol (stress hormone)

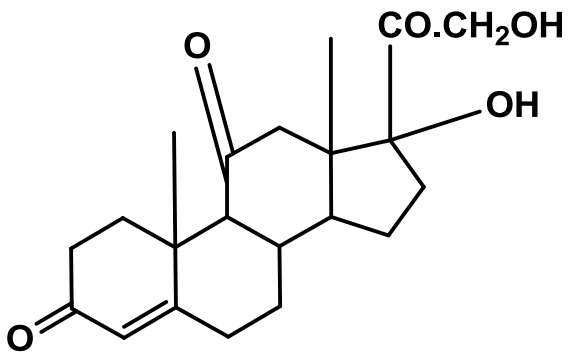




Aldosterone



Cortisol



Cortisone

References

1- I.L.FINAR Organic Chemistry VOL2

SOUTH VALLY UNIVERSITY

FACULTY OF SCIENCE
AT QENA

Chemotherapy

اعداد
د. امنية سيد زكي
كلية العلوم – قسم الكيمياء
العام الجامعي
٢٠٢٣

المحتوي :-

Chemotherapy

Paul ehrlich (1907 s) is the first scientist who introduced the term " chemotherapy “ . The higher plants made the earliest druge discovered , herbal remedies have been important throughout human history , crude plant product such as opium and belladonna have been valuable for centuries.

This field has changed when the antibiotics were discovered and change into drug biosynthesis.

In recent year the introduction of new synthesis pharmaceuticals has outpaced that of natural product . furthermore ,the isolated and purified active material superseded preparation of the parent crud drug.

These factors led to de-emphasis on chemotherapy in the pharmacy curriculum and often to its combination with medicinal chemistry.

Classification of drug on the basis of their origin

1-Drug from natural origin: Herbal or plant or mineral origin, some drug substances are of marine origin.

2-Drug from chemical as well as natural origin: Derived from partial herbal and partial chemical synthesis Chemical, example steroidal drugs

3-Drug derived from **chemical synthesis**.

4-Drug derived from animal origin: For example, hormones, and enzymes.

5-Drug derived from microbial origin: **Antibiotics**

6-Drug derived by biotechnology genetic-engineering, hybridoma technique for example

7-Drug derived from radioactive substances

A sampling of classes of medicine includes

1-Antipyretics: reducing fever (pyrexia/pyresis)

2-Analgesics: reducing pain (pain killers)

3-Antimalarial drugs: treating malaria

4-Antibiotics: inhibiting germ growth

5-Antiseptics : prevention of germ growth near burns, cuts

Definition of medicinal chemistry

Medicinal chemistry is the science which deals with the synthesis, chemistry of mode of action, chemical assay of drug substance.

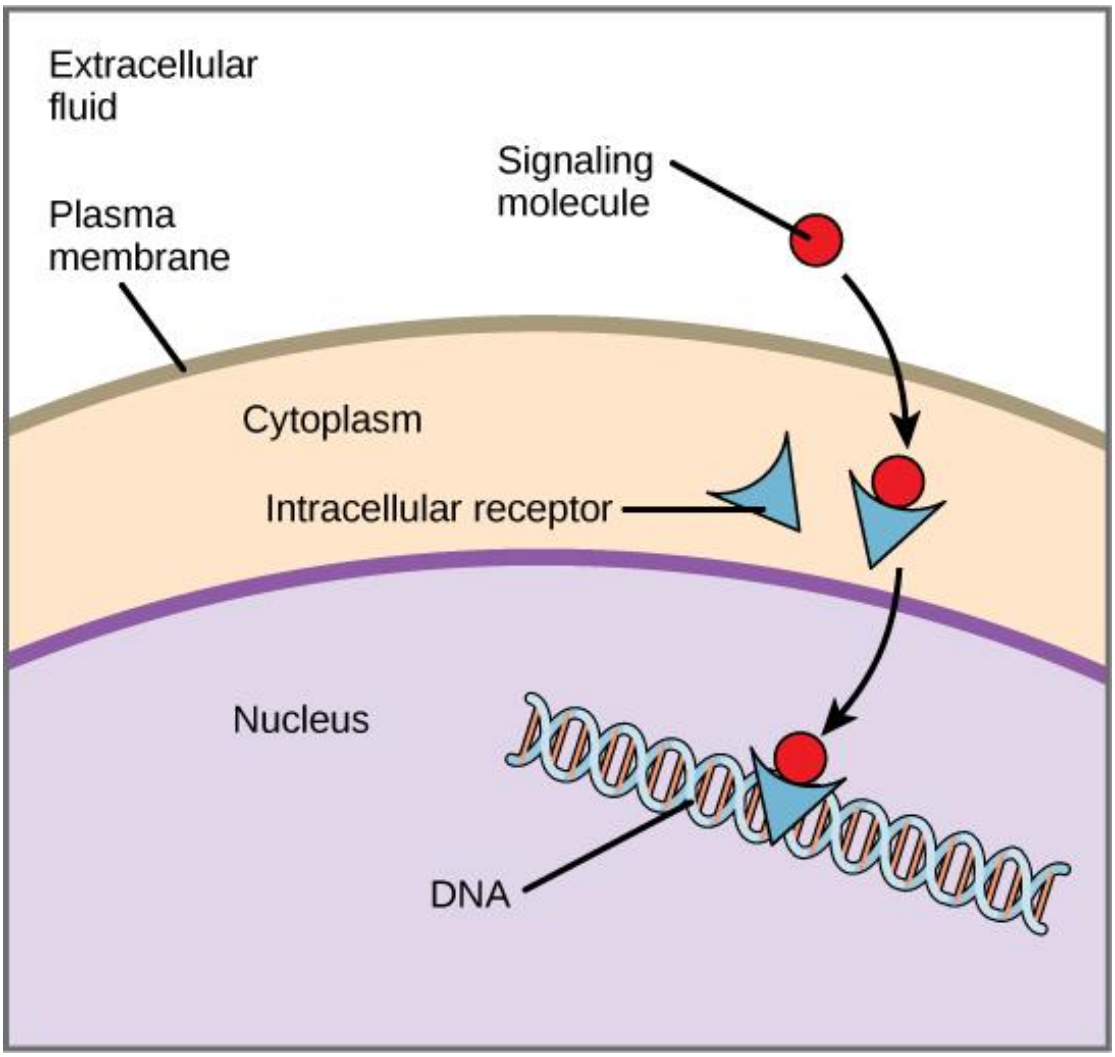
Definition of drug

Drug is any substance presented for treating, curing or preventing disease in human beings or in animals. It may also be used for making a medical diagnosis or for restoring, correcting, or modifying physiological functions.

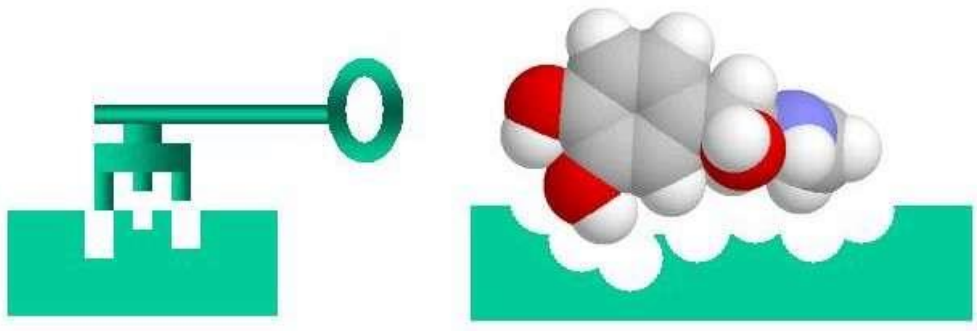



Definition of receptor

Receptor: It is a membrane bound or intracellular macromolecular protein which is capable of binding the specific functional groups of the drug with body.



LOCK & KEY" model of RECEPTORS



Four types of binding takes place between the receptor and the drug molecule

1. Van der Waals forces
2. Hydrogen bonding
3. Ionic interaction
4. Dipole- dipole bonding
5. Covalent bonding

1. Van der Waals Attraction

■weakest intermolecular force (0.5-1.0 kcal/mole)

■electrostatic

■occurs between nonpolar groups (e.g. hydrocarbons)

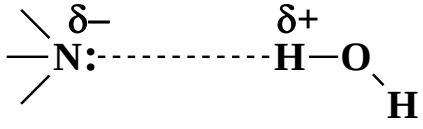
■highly distance and temperature dependent

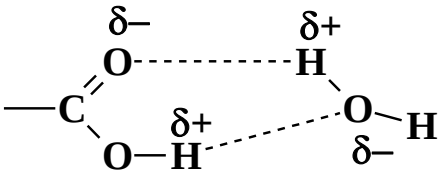
2. Dipole-Dipole Bonding

■stronger (1.0 to 10 kcal/mole)

■occurs electrostatically between electron deficient and electron excessive /ric atoms (dipoles)

■hydrogen bonding is a specific example of this bonding and serves as a prime contributor to hydrophilicity



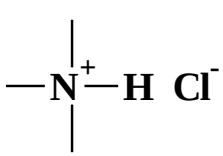


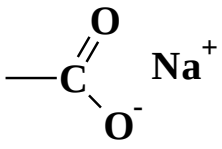
3.Ionic Bonding

■electrostatic attraction between cations and anions

■common in inorganic compounds and salts of organic molecules

■relatively strong (5 kcal/mole)





4.Ion-Dipole Bonding

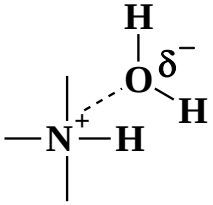
■electrostatic between a cation/anion and a dipole

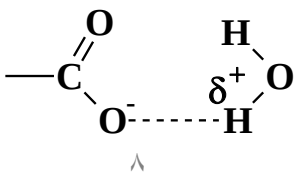
■relatively strong (1-5 kcal/mole)

■low temperature and distance dependence

■important attraction between OMAs**(organic medicinal agents**) and H2O

- **hydrophilic.....water loving**
- **lipophobic.....lipid hating**
- **lipophilic.....lipid loving**
- **hydrophobic.....water hating**

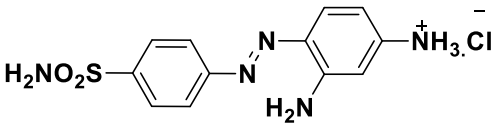




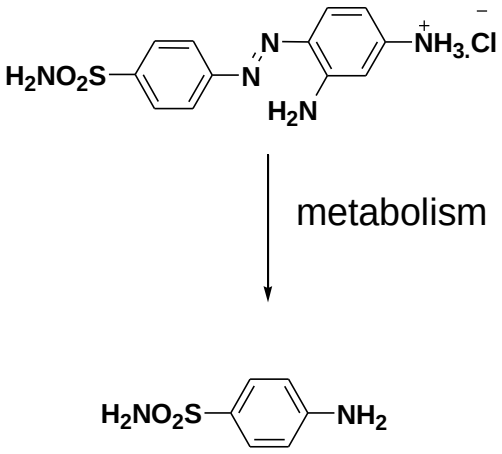
Sulpha drugs

Sulfonamides:-

The sulfonamide are synthetic ,not of natural origin which called " antimicrobials " and not antibiotics. They were the first antibacterial drugs that were not overtly toxic to human.

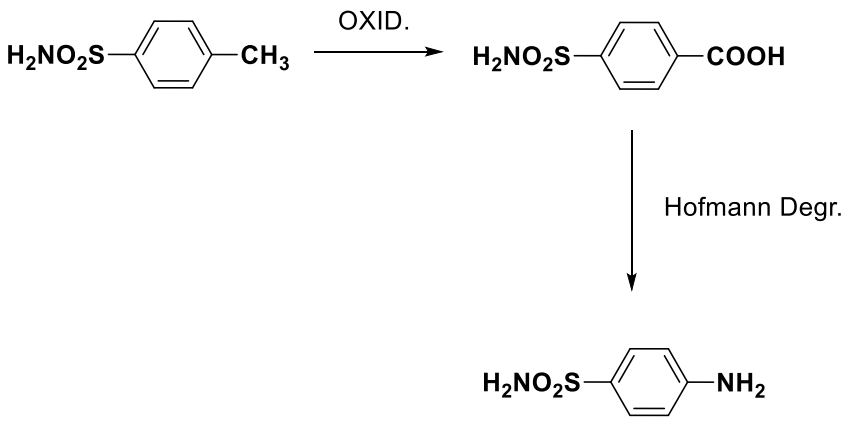


Prontosil which is 2,4-diamino-4-sulphamyl azobenzen hydrochloride was the first sulpha drug to be used in medicine ,it is red dye and metabolized in the body to p-aminobenzene sulphonamide.



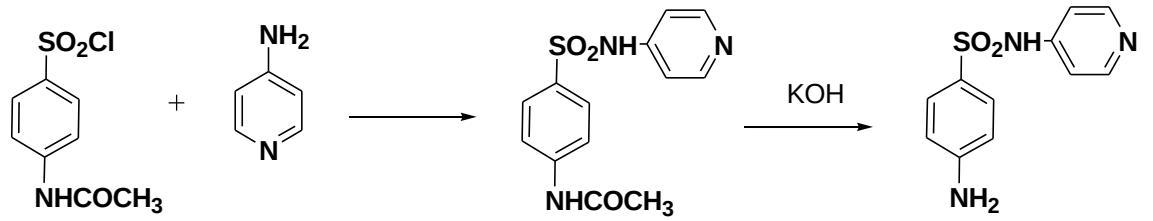
Synthesis of sulphanilamides derivative :-

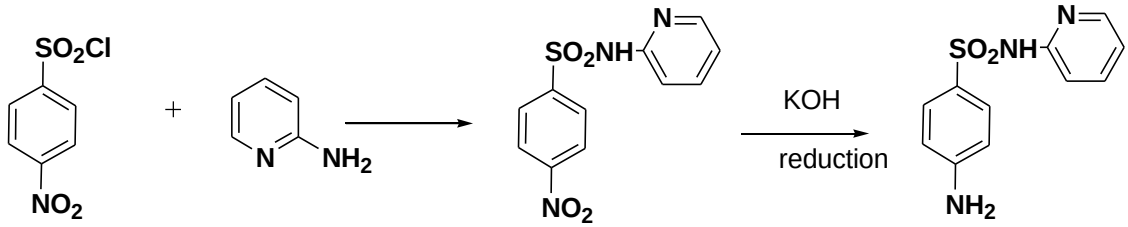
Oxidation of p-toluenesulphonamide to p-sulphamidobenzoic acid fallowed by Hoffmann degradation.



Sulpha pyridine

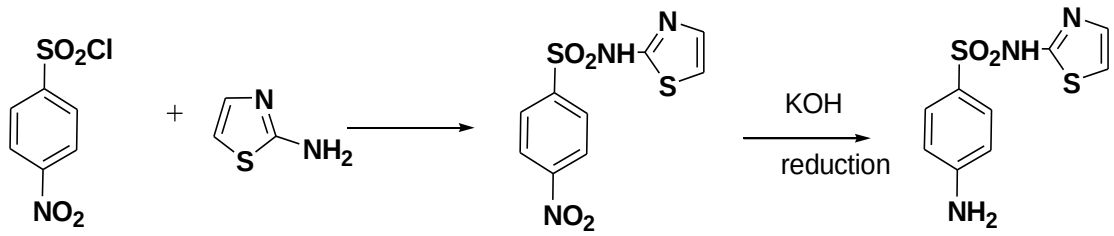
Used to treatment the cocci pneumonia ,but it high toxicity in men ,it is rarely used any longer.





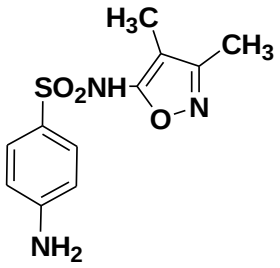
Sulpha thiazole

2-thiazolyl sulponilamide is more patent than sulphapyridine and less toxic ,it most highly bacteriostatic drug which has a permanent place in the pharma.



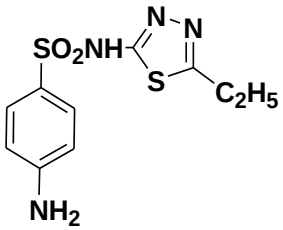
Sulphaisoxazole

Is soluble over a wide pH range ,which have highest bacteriostatic activity and rapid excretion through the kidney.



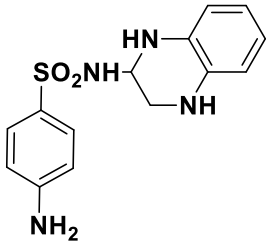
Sulphathiadiazole :-

2-sulphanilamide-5-ethyl-1,3,4-thiadizole is highly soluble and rapidly excretion from the kidney in urine so it consider the most suitable for urinary tract infection.



Sulphaquinoxaline :-

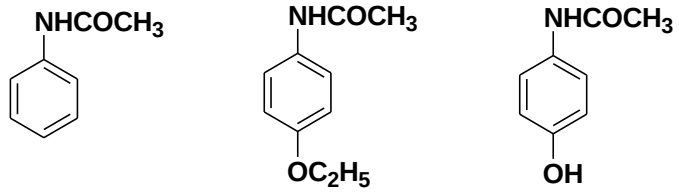
It is widely used in the treatment of coccidiasis infection caused by Eimeria tenella in chickens pheasants.



Antipyretic and analgesics

Aniline and p-aminophenol derivative :-

They have analgesic activity comparable to that of aspirin but don't have anti-inflammatory activity e.g. acetanilide , paracetamol and phenacetin .



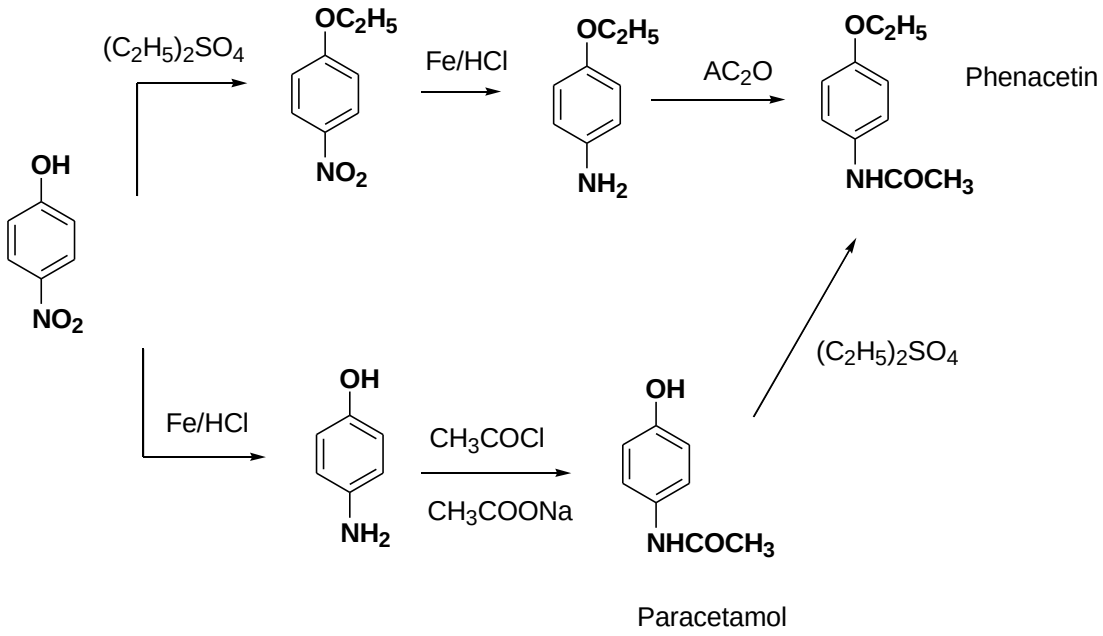
acetanilide phenacetine paracetamol

Acetanilide was introduced into therapy in 1886 as antipyretic-analgesic but it found later too toxic.

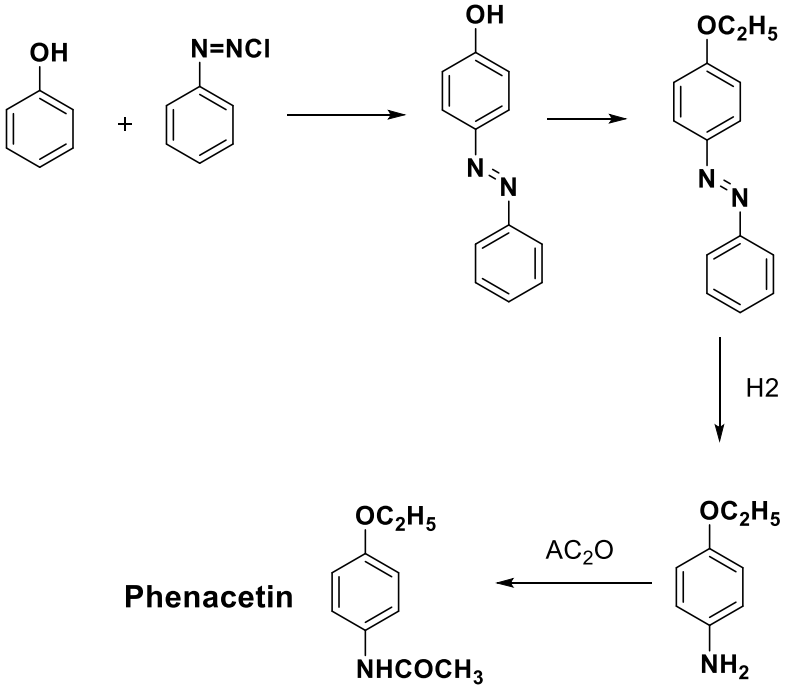
Phenacetin was introduced in the following year and it was widely used but recently it found nephrotoxicity.

Paracetamol is subseguently introduced in 1893 and it remains the only popular agent for this group.

Synthesis of paracetamol

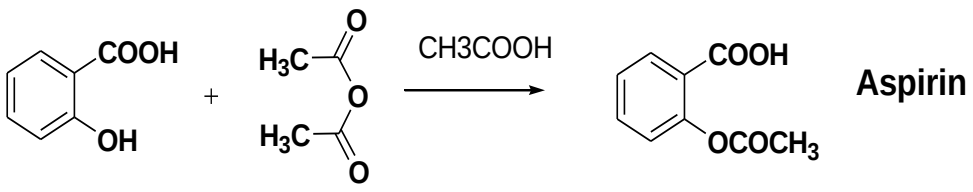


Industrial method for phenacetine



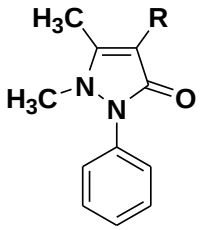
Salicylic acid derivatives

The major chemical classes of salicylates used in medicine are the ester ,the most common one is aspirin .

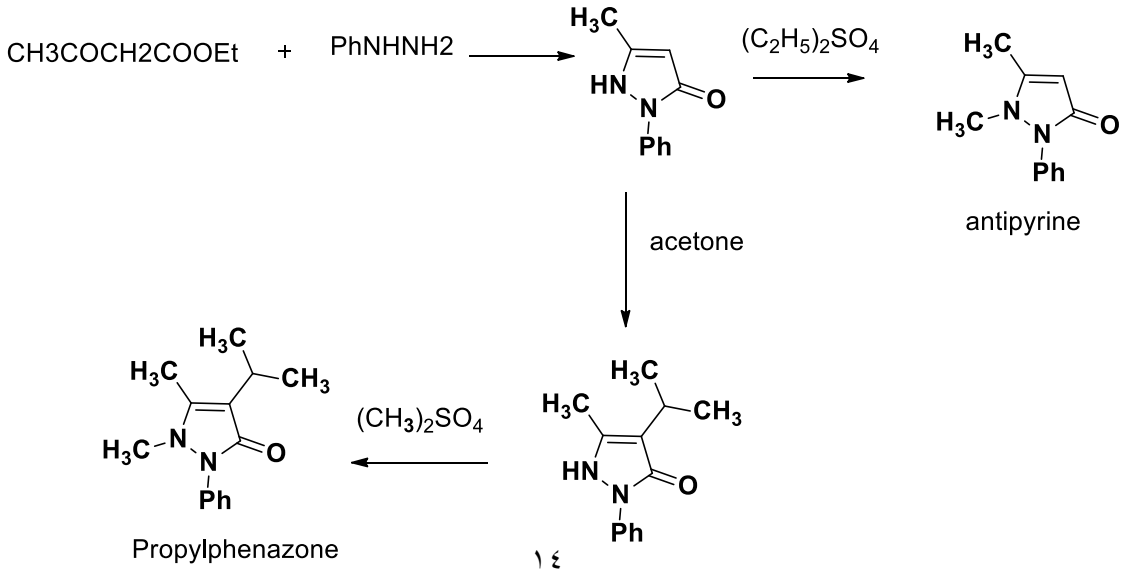


3-pyrazolone derivatives

Antipyrine(phenazone) and propylphenazone have analgesic, antipyretic and antirhumatic activities similar to those of aspirine and used for the same purpose.



Synthesis of antipyrine



Aryl and hetroarylacetic acid derivative

(aryl alkanoic acid derivative)

This class of compounds represents the largest group of NSAIDS (Nonsteroidal anti-inflammatory drugs). They have the following general chemical structure .

Ar-CH(R)-COOH

(R = H,CH3,alkyl ….)

(Ar = Aryl or heteroaryl)

- The main type of NSAID include
- ibuprofen.
- naproxen.
- diclofenac.

Ketoprofene (Propionic acid derivatives)

- mefenamic acid.
- etoricoxib.
- indomethacin.
- high-dose aspirin (low-dose aspirin is not normally considered to be an NSAID)

NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) are medicines that are widely used to relieve pain, reduce inflammation, and bring down a high temperature.

They're often used to relieve symptoms of headaches, painful periods, sprains and strains, colds and flu, arthritis, and other causes of long-term pain.

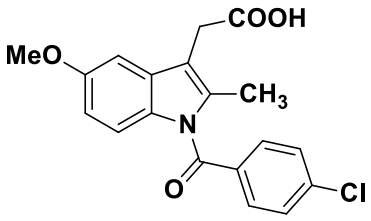
Although NSAIDs are commonly used, they're not suitable for everyone and can sometimes cause troublesome side effects.

Indoleacetic acid derivative

1- indomethacin

Indemethacin is one of the most potent non-steroidal anti-inflammatory agents.

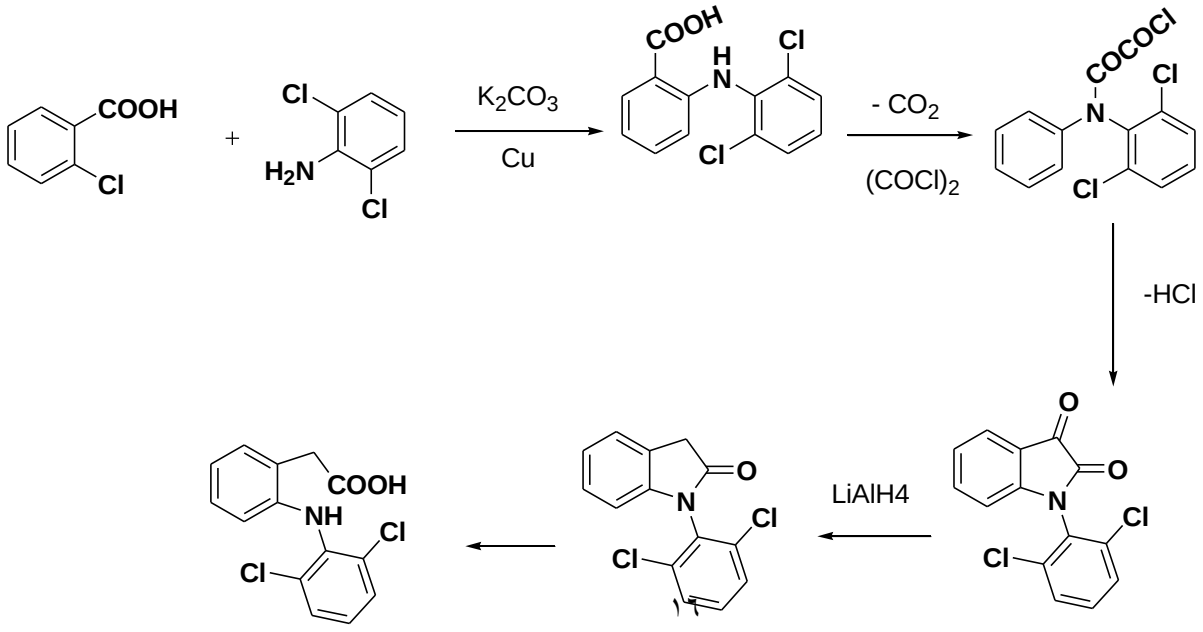
Substitution of a methyl group on the carbon atom separating the acid center from the aromatic ring tends to increase anti-inflammatory activity groups .



Phenylacetic acid derivatives (diclofenac sodium)

Diclofenac is available in 120 different countries and the most widely used NSAIDA in the world It is 6 time more potent than indomethacin and 40 time more potent than aspirin as antipyretic.

Synthesis of diclofenac

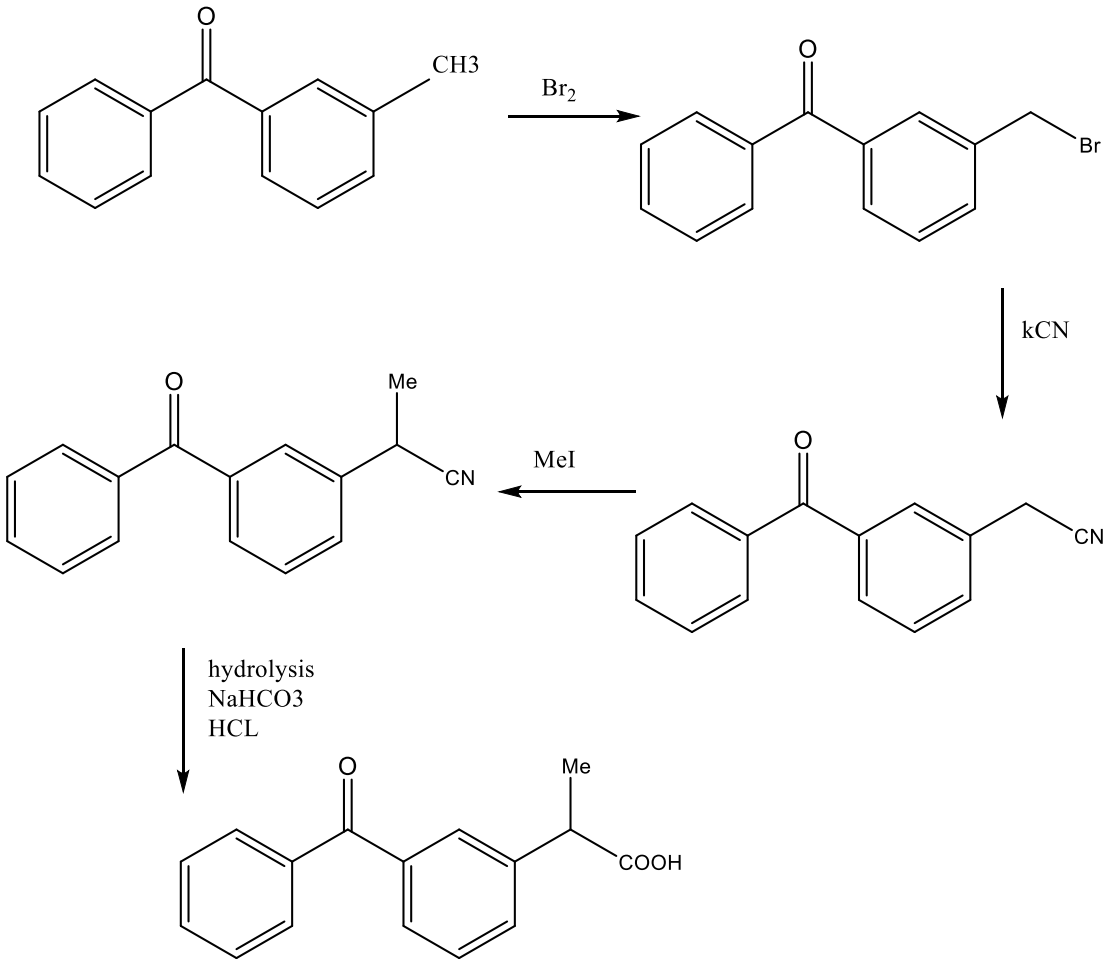


Ketoprofen

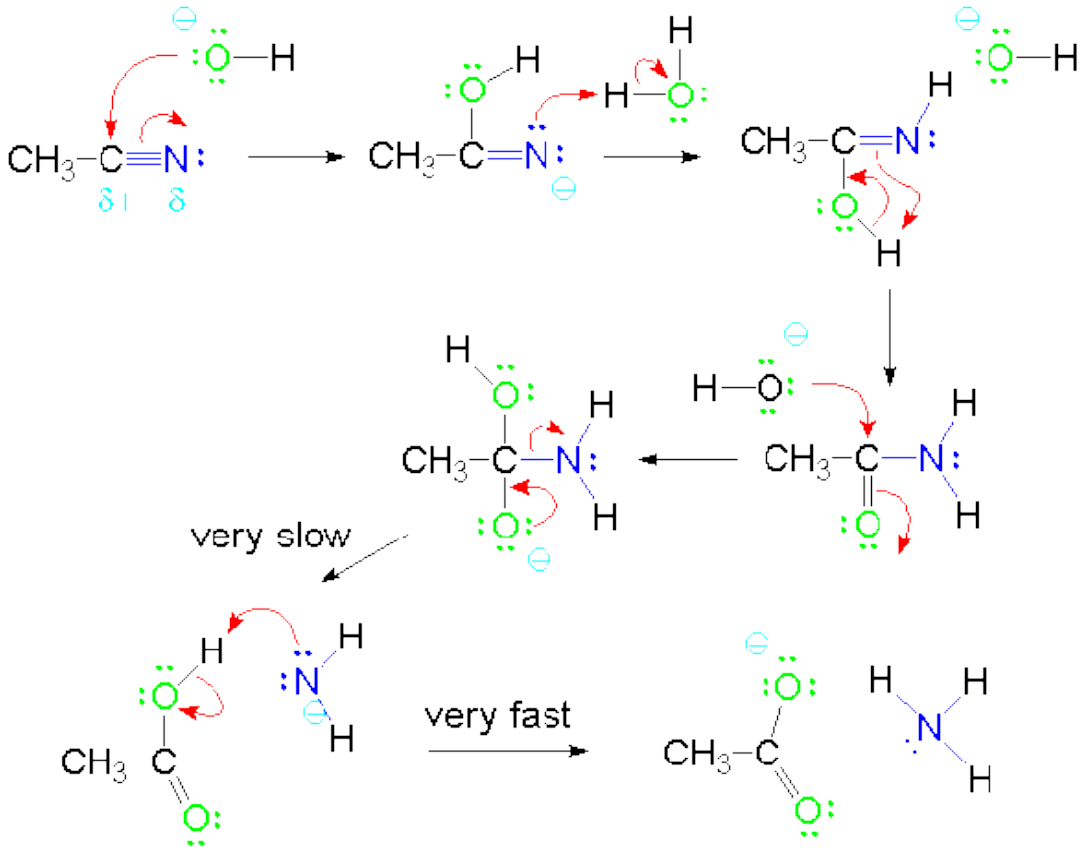
is one of the propionic acid class of nonsteroidal anti-inflammatory drugs (NSAID)with analgesic and antipyretic effects It acts by inhibiting the body's production of prostaglandin.

(The prostaglandins are **a group of lipids made at sites of tissue damage or infection that are involved in dealing with injury and illness**. They control processes such as inflammation, blood flow, the formation of blood clots and the induction of labour)

Synthesis of ketoprofen

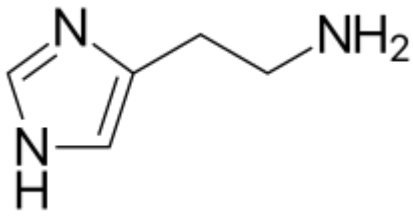

O
CH3
Br2
O
Br
kCN
O
CN
MeI
O
Me
CN
hydrolysis
NaHCO3
HCL
O
Me
COOH

Hydrolysis of cyanide group to carboxylic group



Antihistamine

Histamine



Histamine is an organic nitrogenous compound involved in local immune responses, histamine is produced by basophils and by mast cells found in nearby connective tissues. Histamine increases the permeability of the capillaries to white blood cells and some proteins, to allow them to engage pathogens in the infected tissues.

The discovery of the H1and H2 antagonist burimamide in the early 1970 opened a new ear in the history of the attempt to explane histamine related physiologic processes

Antihistamine

Antihistamines are drugs which treat allergic rhinitis, common cold, influenza, and other allergies. Typically, people take antihistamines as an inexpensive, not patented (generic), drug that can be bought without a prescription and relieves from nasal congestion, sneezing, or hives caused by pollen, dust mites, or animal allergy with few side effects. Antihistamines are usually for short-term treatment.

Mechanism of action

1-Antihistamines are reversible blockers of histamine H1 receptor (**H_1 antagonists**, also called **H_1 blockers**, are a class of medications that block the action of histamine at the H_1 receptor, helping to relieve allergic reactions.) on tissues, such as skin ,bronchi ,eye….etc.

2- Antihistamines are reversible blockers of histamine H2 receptor on tissues, such as stomach ,intestine….etc.

3-Many of antihistamines also possess adrenaline-antagonism which act as anesthetic

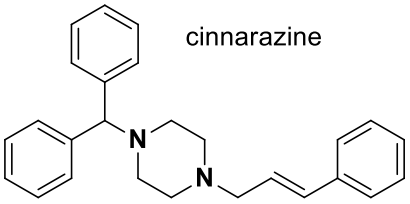
(The adrenal (suprarenal) glands are located at the top of both kidneys. The produce hormones that regulate the immune system, blood pressure, metabolism, and the stress response. In addition, also helps your body do the following:

- Promoting proper cardiovascular function
- Helps in how we respond to stress
- Properly utilizing carbohydrates and fats
- Helps distribute stored fat
- Gives you body odor and pubic hair
- Promotes healthy gastrointestinal functions

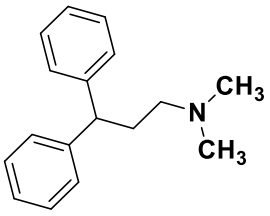
4- many of the traditional antihistamines (first generation) possess some sedative and antimuscarinic effects

5-Now developed antihistamines (second generation) free from these side effect which known as " non-sedating antihistamines "

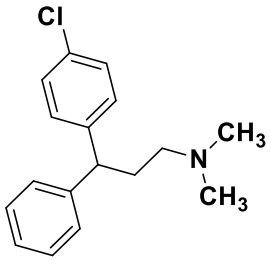
6-some like cinnarazine (second generation) act by inhibiting calcium ions transfer from the outside to inside of the cell so it is value in motion sickness and in vascular disorders



7- Substituents in one of the aryls influence the antihistaminic potency



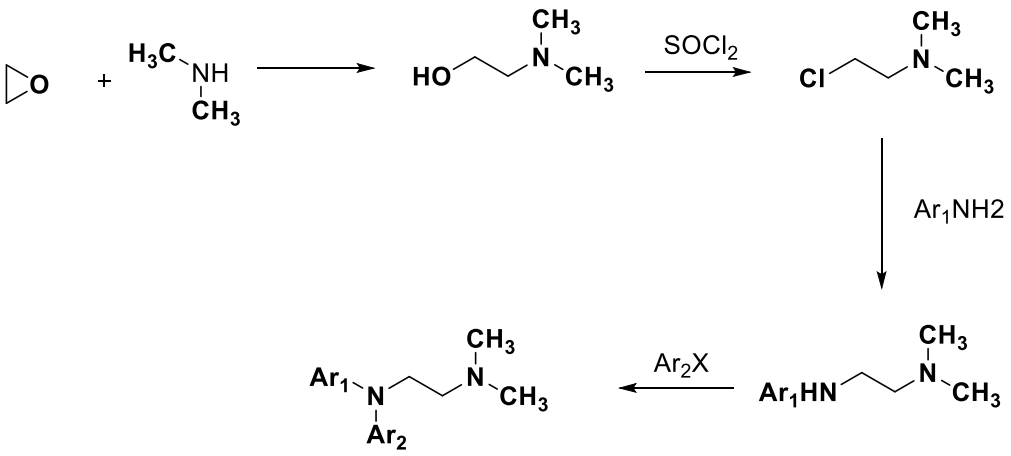
Pheniramine
Usual dose is 20-40mg
Three times daily

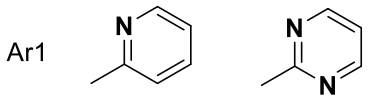


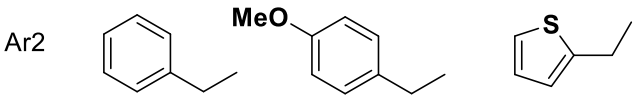
chlorpheniramine
Usual dose is 2-4mg
Three times daily

8- antazoline is a weak antihistamine but potent local anesthetic which used in the eye allergic condition.

General Synthesis of Antazoline derivatives



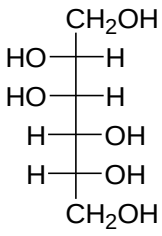


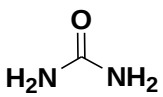


Diuretic

A diuretic is any substance that promotes the production of urine.

In medicine, diuretics are used to treat heart failure, liver cirrhosis, influenza, water poisoning, and certain kidney diseases.

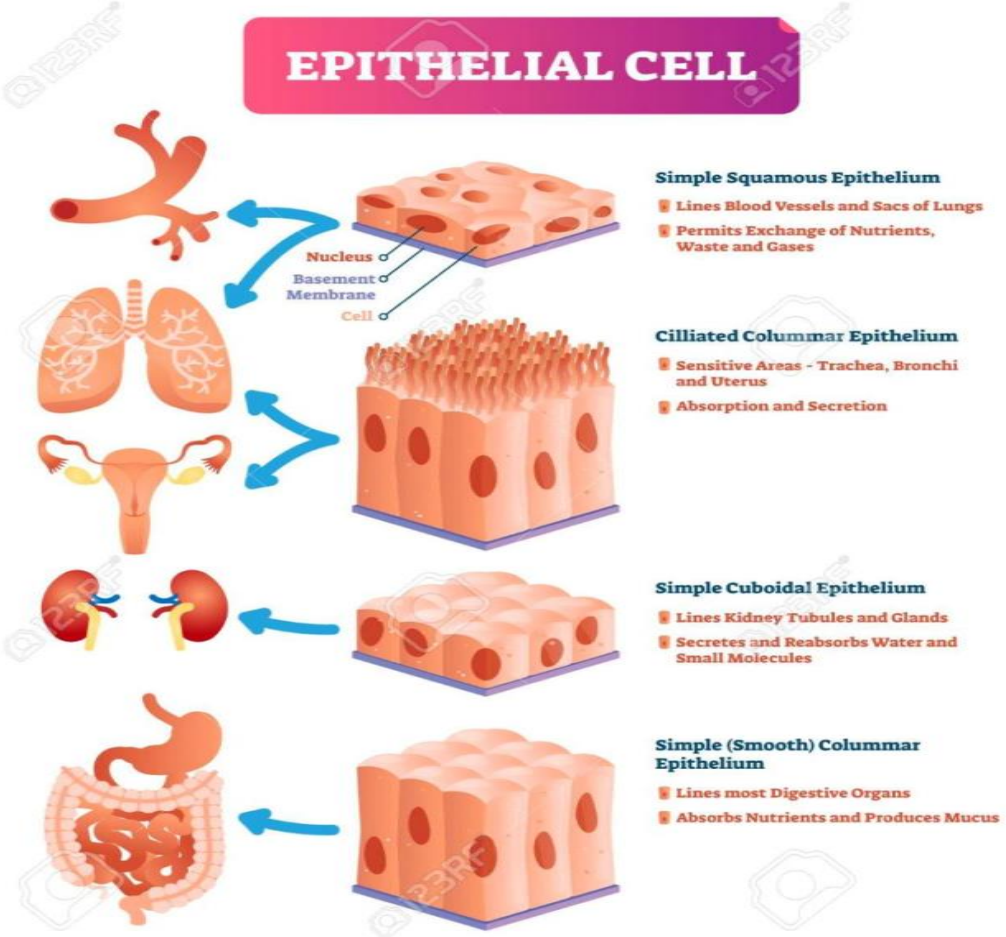




Osmotic diuretics

Osmotic diuretics (e.g. mannitol and urea) are substances that increase osmotlality but have limited tubular **epithelial cell** permeability.

They work primarily by expanding extracellular fluid and plasma volume, therefore increasing blood flow to the kidney.



Mechanism of action

1-Diuretics they effectively reduce blood pressure

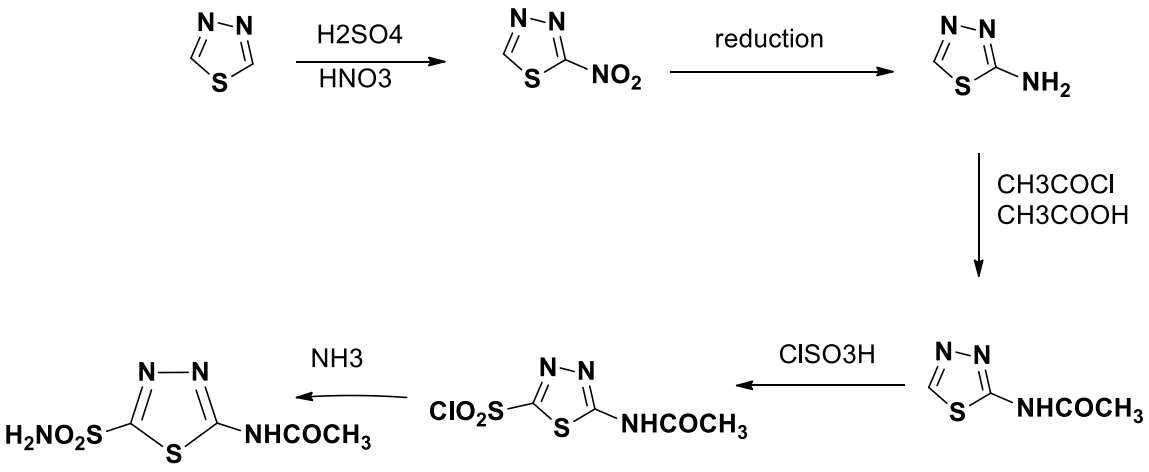
2- Diuretics are a diverse group of compounds that either stimulate or inhibit various hormones that naturally occur in the body to regulate urine production by the kidneys .

Carbonic anhydrase inhibitors: They increase the excretion of sodium, potassium, bicarbonate, and water. Some types of carbonic anhydrase inhibitors include:

Methazolamide .

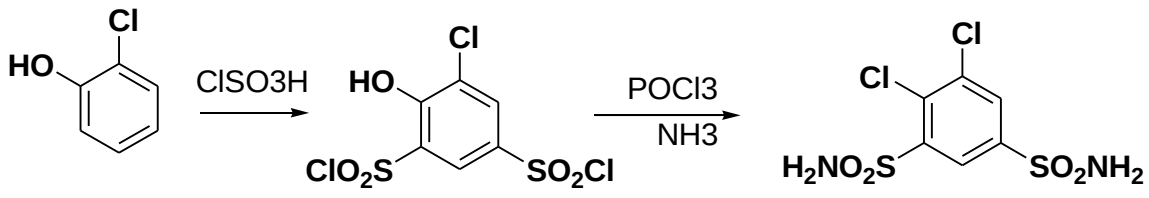
acetazolamide

carbonic anhydride inhibitors (acetazolamide)



2-acetylamino-1,3,4-thiadiazole-5-sulfonamide

dichlorphenamide (Daranide)

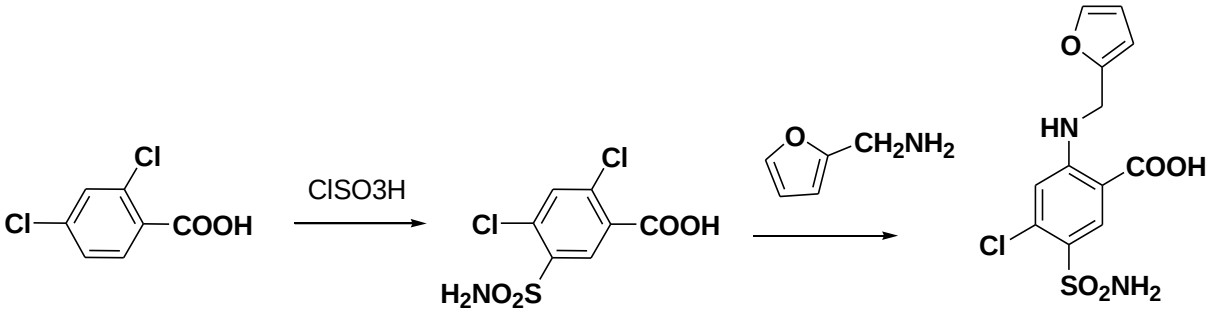


4,5-Dichloro-benzene-1,3-disulfonic acid diamide

Lasix

is a drug choice for urine secretion

(it reduce the body water content and the undesirable salts.)



Local anesthesia

is any technique to induce the absence of sensation in a specific part of the body by block the generation and the conduction of impulses analog a nerve fiber .

It uses :-

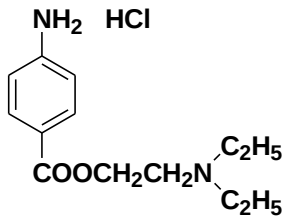
It allows patients to undergo surgical , spinal cord anesthesia and dental procedures with reduced pain and distress Reduced pain caused by minor burns, insect bites, allergic response .

Chemistry

1- ester derivatives e.g cocaine which dose not penetrate the skin ,but absorbed from mucous membranes

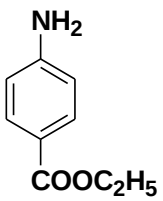
2- amino benzoic acid derivative

a- procaine.HCl



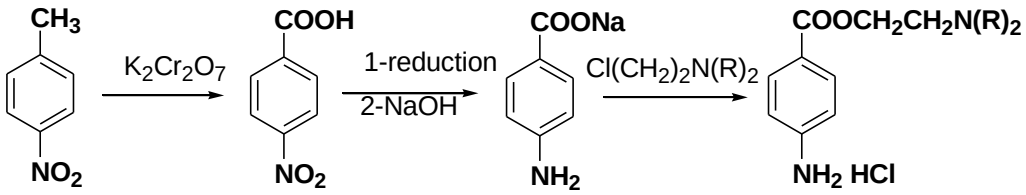
Effective in contact skin or mucous membrane

b- Ethyl p-aminobenzoate



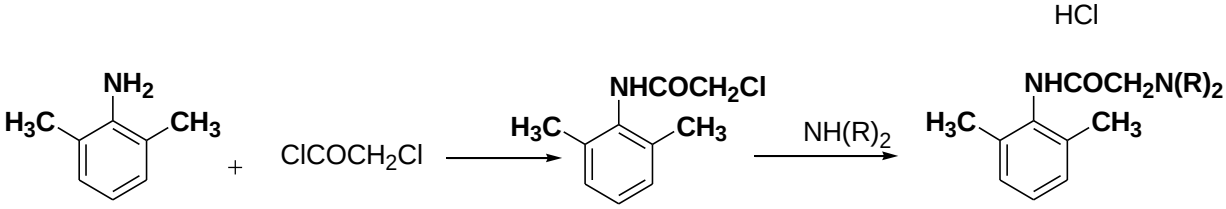
It used in the form of ointment and cream

synthesis of procaine and it's derivative



3-amide derivatives

lidocaine which used in injection, ointment, eye drop .



R= C_2H_5

Diabetes

Diabetes is a disease that occurs when your blood glucose, is too high. Blood glucose is your main source of energy and comes from the food you eat.

Insulin, a hormone made by the pancreas, helps glucose from food get into your cells to be used for energy.

Sometimes your body doesn't make enough—or any—insulin or doesn't use insulin well. Glucose then stays in your blood and doesn't reach your cells.

Antidiabetics

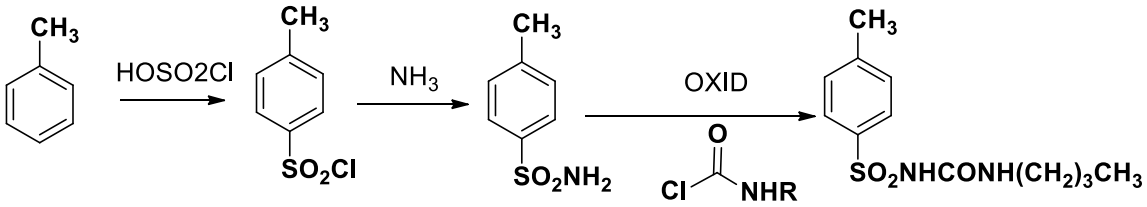
Drugs used in diabetes treat diabetes mellitus by lowering glucose levels in the blood for example :-

1- Type 1 diabetes is a condition in which your immune system destroys insulin-making cells in your pancreas. These are called beta cells. The condition is usually diagnosed in children and young people which treatment with insulin.

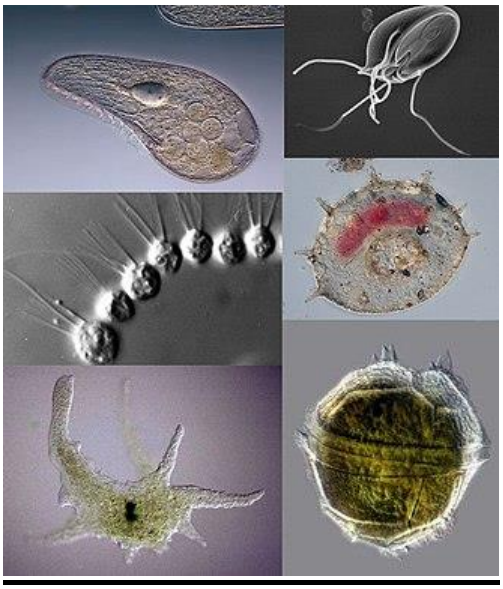
2- type 2 diabetes, in which your body doesn't respond to insulin which treatment with different kind of drug like

sulfonylurea (tolbutamide)

Synthesis of tolbutamide



Anti protozoa drugs

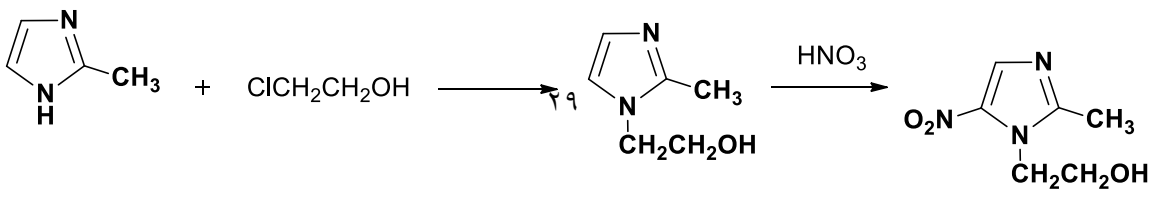


Protozoa Historically, the protozoa were regarded as "one-celled animals", either free-living or parasitic, which feed on organic matter such as other microorganisms or organic tissues

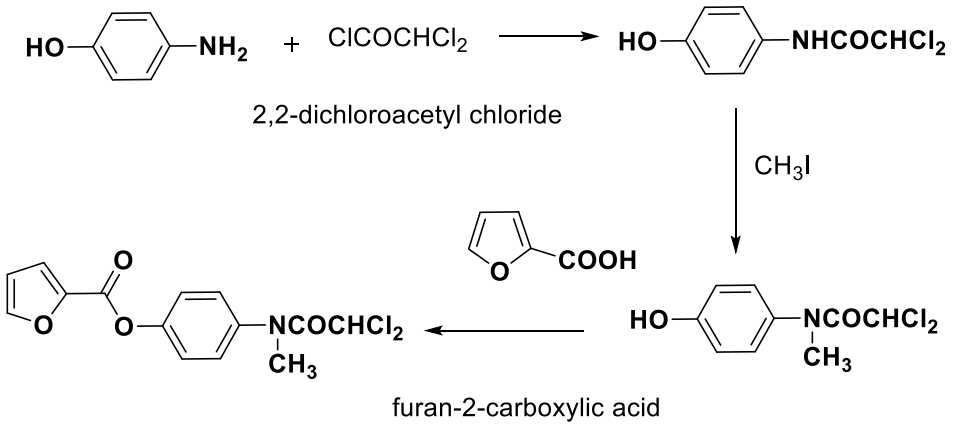
which considered a tropical disease

Treatment:-

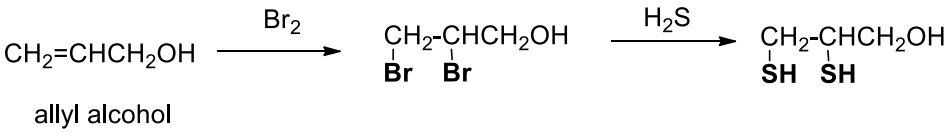
1-Metronidazole (M)



Diloxanide furoate



Dimercaptal



Antifungal agent

Fungi infect skin and lungs and cause diseases

Fungi treatment include:-

1- polyenes :- is a molecule with multiple conjugated double bonds

2- thiazole

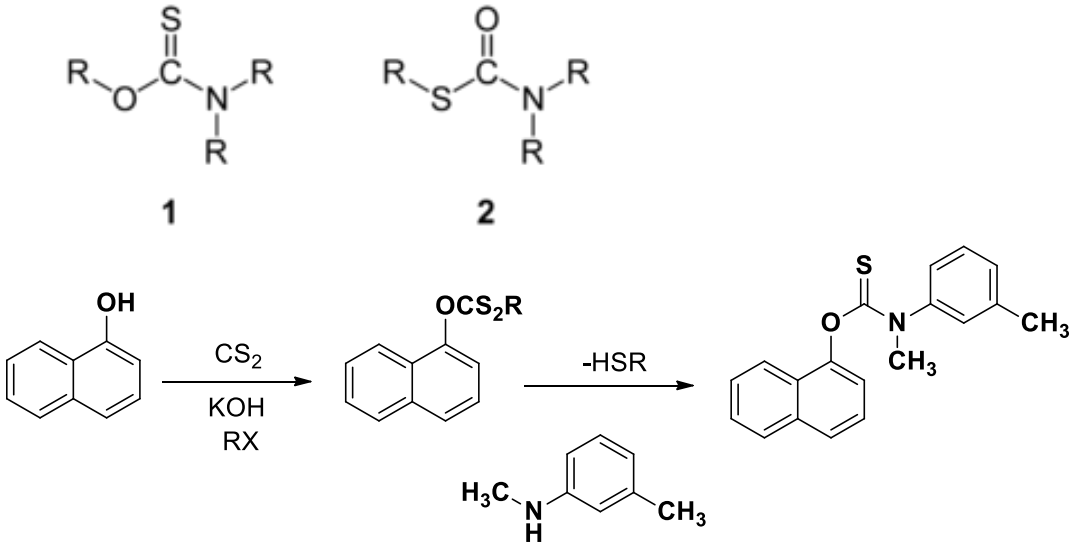
3- unsaturated fatty acid derived from natural castor oil

4-Imidazoles

5- tolnaftate – a thiocarbamate antifungal

synthesis of tolnaftate

Tolnaftate is a synthetic thiocarbamate



Antibiotics

Antibiotics or antibacterials are a type of antimicrobial used in the treatment and prevention of bacterial infection. They may either kill or inhibit the growth of bacteria. Several antibiotics are also effective against fungi and protozoans, and some are

toxic to humans and animals, even when given in therapeutic dosage. Antibiotics are not effective against viruses such as the common cold or influenza, and may be harmful when taken inappropriately

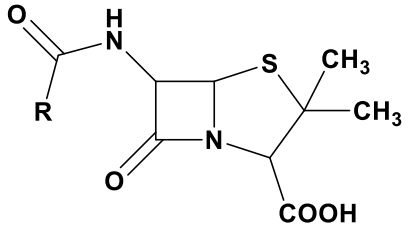
Penicillin (PCN or pen) is a group of antibiotics which include penicillin G (intravenous use), penicillin V (oral use), and benzathine penicillin (intramuscular use). They are derived from Penicillium fungi.

Penicillin antibiotics were among the first medications to be effective against many bacterial infections caused by staphylococci and streptococci.

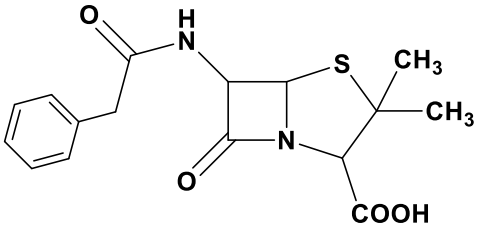
Penicillins are still widely used today, though many types of bacteria have developed resistance following extensive use. All penicillins are β-lactam antibiotics.

About 10% of people report that they are allergic to penicillin

Pencilline derivative

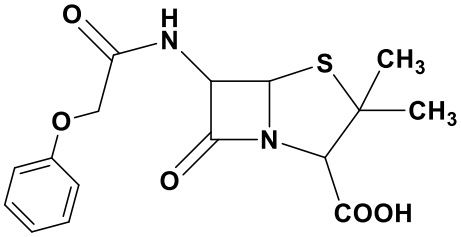


Pencilline G
Benzylpenicillin



As an antibiotic, Penicillin G is noted to possess effectiveness mainly against Gram-positive organisms. Some Gram-negative organisms

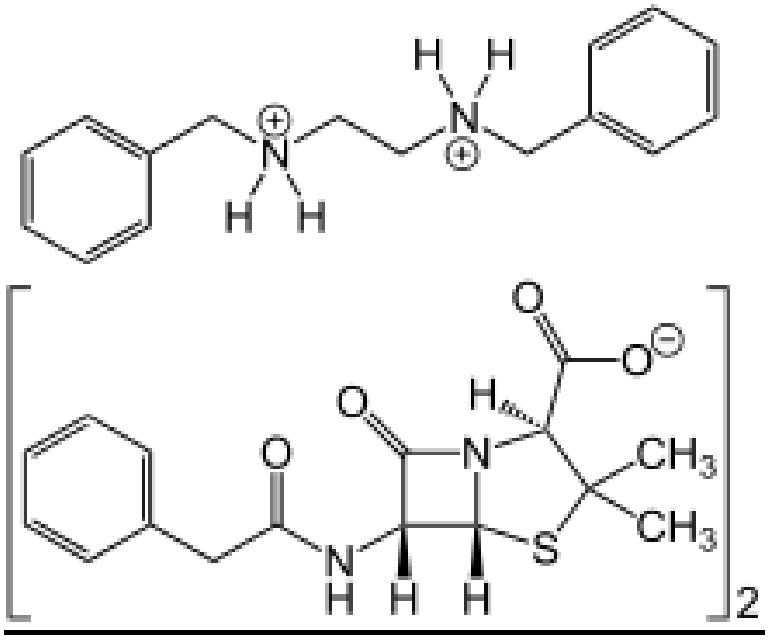
Pencilline v
Phenoxymethylpenicillin



penicillin V, is an antibiotic useful for the treatment of a number of bacterial infections. It is a penicillin that is orally

active. It is less active than benzylpenicillin (penicillin G) against Gram-negative bacteria.

benzathine penicillin
Benzathine benzylpenicillin



It is slowly absorbed into the circulation, after intramuscular injection, and hydrolysed to benzylpenicillin in vivo. It is the drug-of-choice when prolonged low concentrations of benzylpenicillin are required and appropriate, allowing prolonged antibiotic action over 2–4 weeks after a single IM dose

Medical uses for benzathine penicillin include: prevention of rheumatic fever

Spectra II

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كلية العلوم

قسم الكيمياء

2023/2022

- Faculty of Science
- Fourth Year
- Second Semester

Chapter 13:
NMR Spectroscopy

NMR Spectroscopy

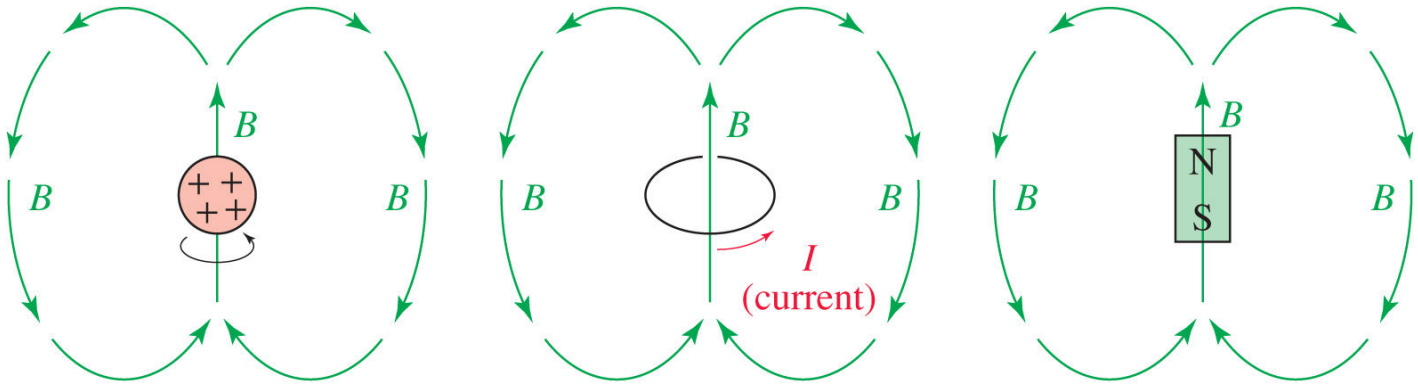
- **By far the most important and useful technique to identify organic molecules. Often the only technique necessary.**

- **NMR spectrum can be recorded for many different nuclei (they need to have magnetic properties) such as: ^{1}H, ^{3}H, ^{13}C, ^{15}N, ^{19}F, ^{31}P**

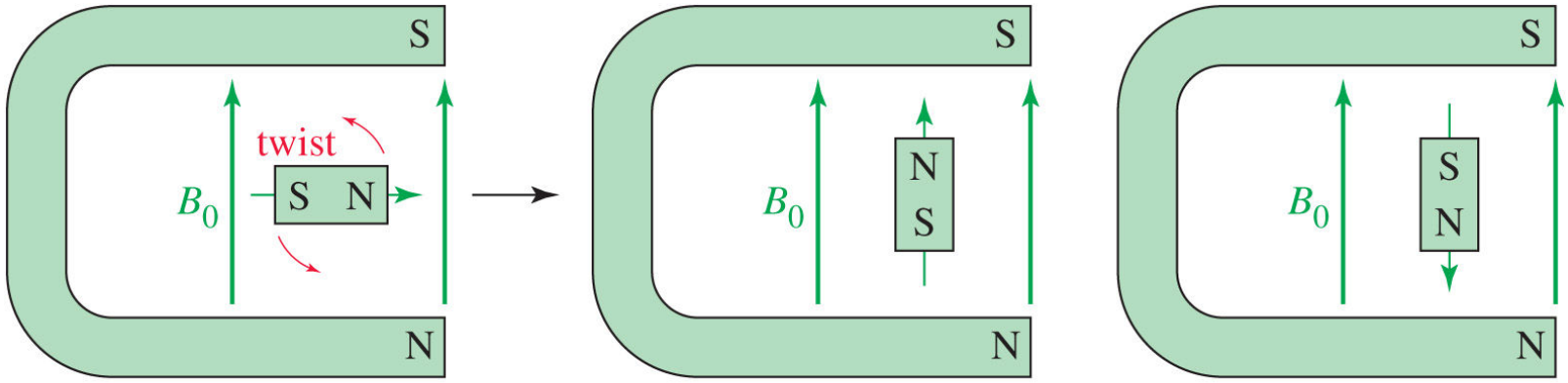
- **We will focus only on proton (^{1}H) nmr here**

Nuclear Spin

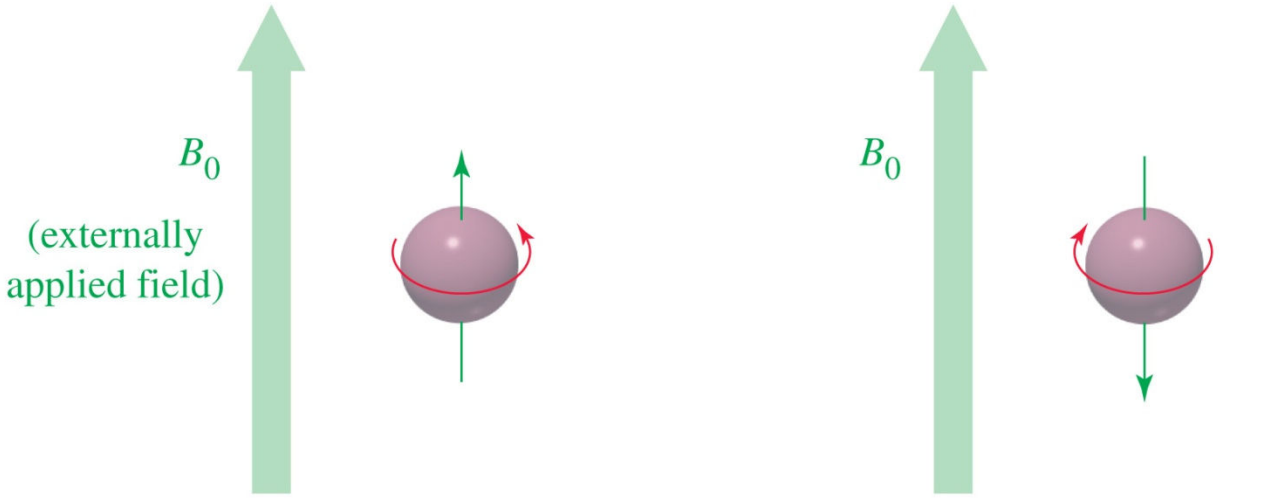
- **A nucleus with an odd atomic number or an odd mass number has a nuclear spin.**
- **The spinning charged nucleus generates a magnetic field.**

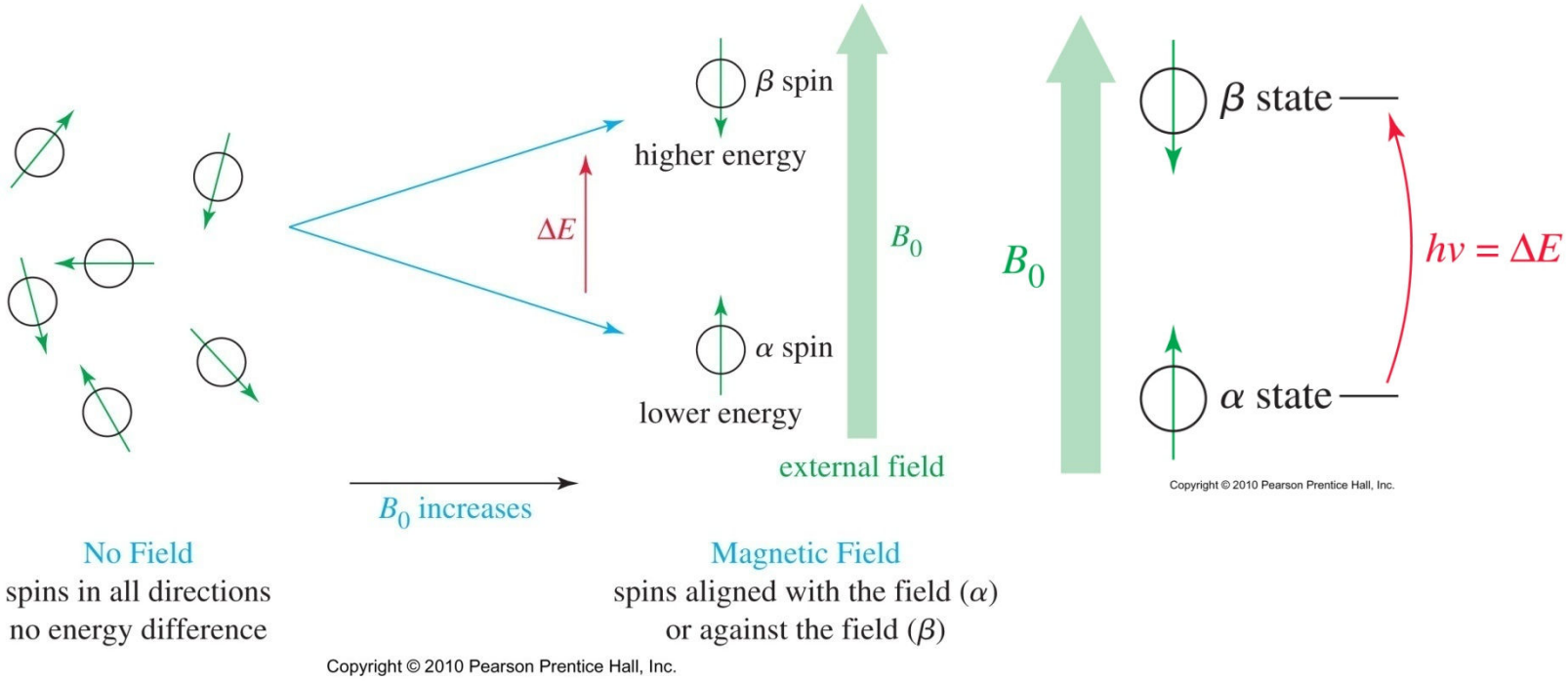


- **An external magnetic field (B_0) applies a force to a small bar magnet, twisting the bar magnet to align it with the external field.**
- **The arrangement of the bar magnet aligned with the field is lower in energy than the arrangement aligned against the field.**



- **The lower energy state with the proton aligned with the field is called the *alpha-spin state*.**
- **The higher energy state with the proton aligned against the external magnetic field is called the *beta-spin state*.**





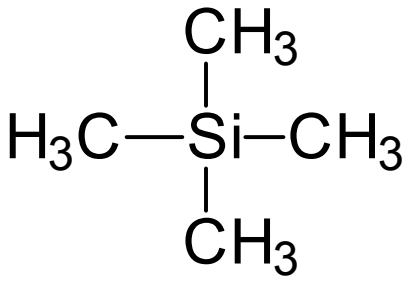
A nucleus is in resonance when it is irradiated with radio-frequency photons having energy equal to the energy difference between the spin states.

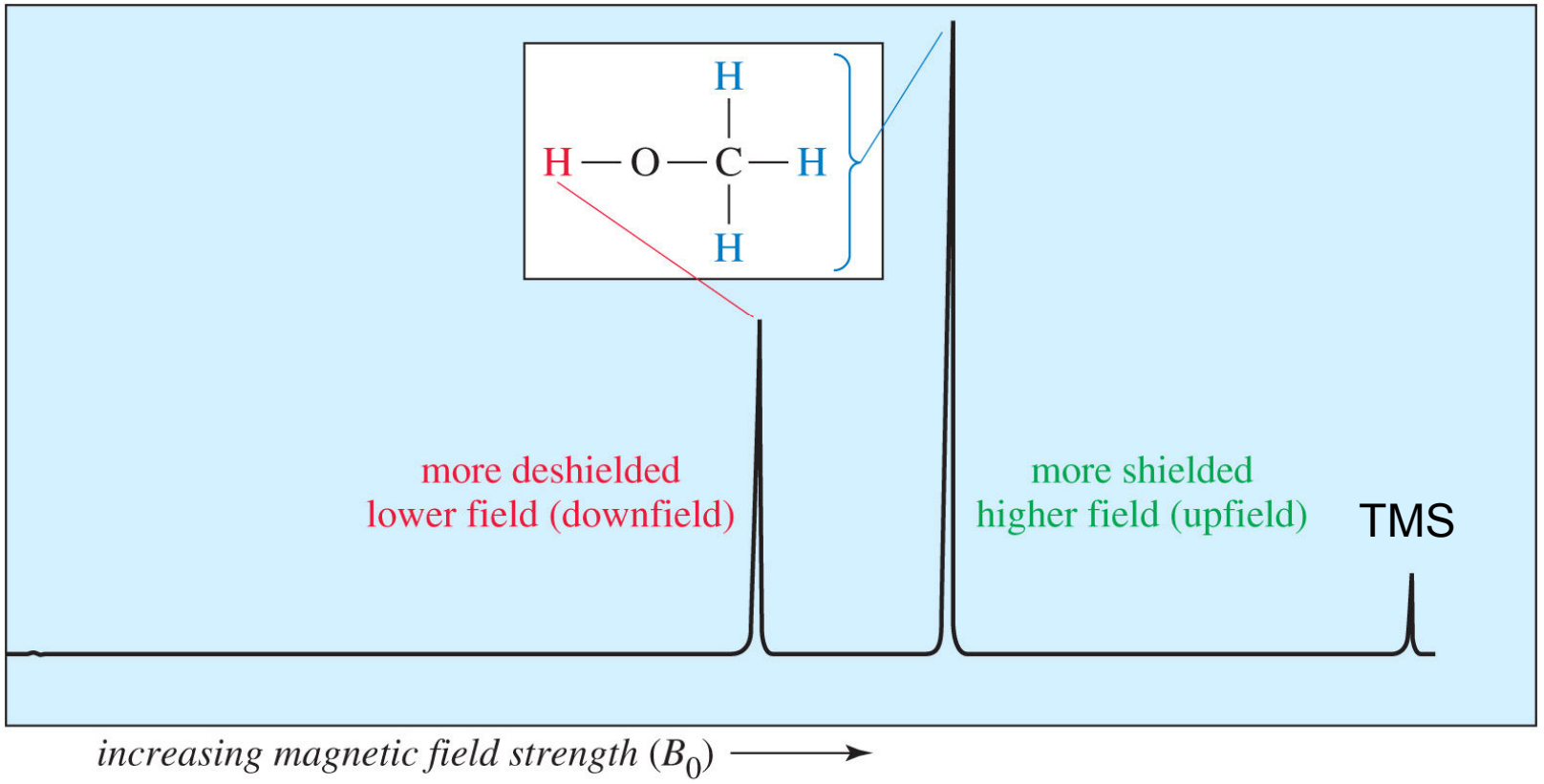
Under these conditions, a proton in the alpha-spin state can absorb a photon and flip to the beta-spin state.

Chemical shift (13.5-13.7)

- **Is the position of a nmr absorption. It depends on:**
  - **Electron density in the vicinity of an hydrogen atom…this electron density is affected by the molecular structure of the molecule**
  - **Chemical shifts are reported on the horizontal axis of the spectrum (the δ scale is in ppm) from the reference (TMS).**

Tetramethylsilane (TMS) is added to a solution and arbitrarily assigned a chemical shift of "0". All other signals are reported relative to that position.





- **Since electron density is the determining factor in the chemical shifts observed, dipole in the molecule will have an effect in donating or removing electrons from the vicinity of a given proton. This effect is described as**

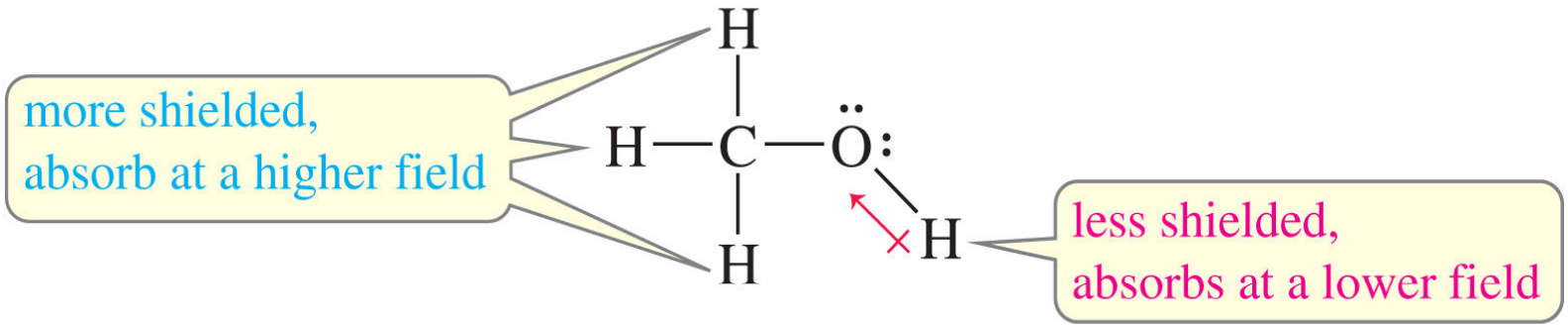
  - **Shielding: more electron in the proton's vicinity (dipole effect minimum)**

  - **Deshielding: less electron in the proton's vicinity**

    (dipole effect is increased)

Shielding and Deshielding (13.3)

No dipole, therefore, maximum electron density near the protons in CH_3 Shielded



Strong dipole pulling electrons Away from hydrogen atom, Therefore, electron density is reduced Near protons Deshielded

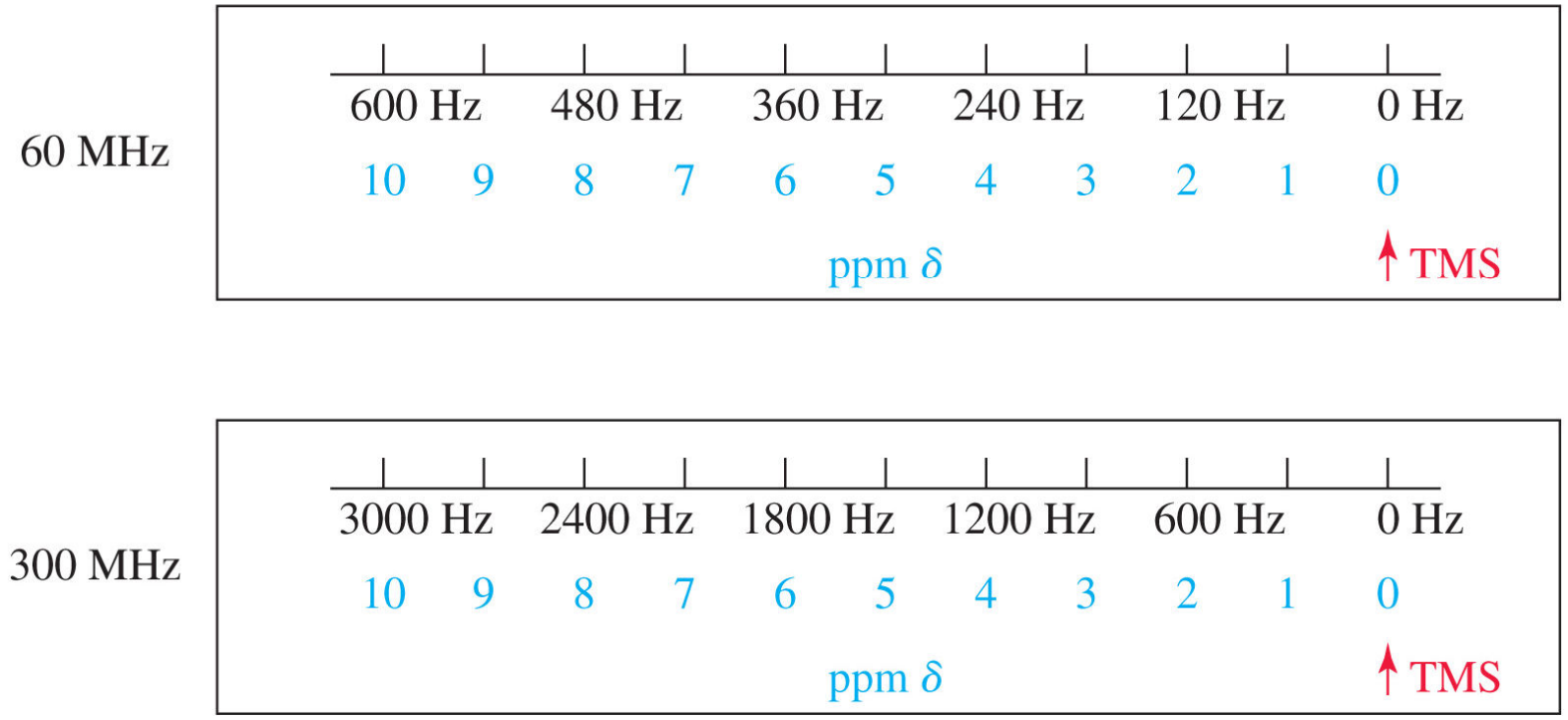
The conclusion is that shielded protons absorb radiation at higher fields (frequency) while the deshielded protons will absorb at lower fields (frequency).

- **Therefore, protons affected by the proximity of different functional groups will absorb at different fields (because of the difference in dipole moment). This can be used to identify the structure of molecules.**

- **The chemical shift:**
  - Measured in parts per million.
  - Ratio of shift downfield from TMS (Hz) to total spectrometer frequency (MHz).
  - The chemical shift has the same value regardless of the machines (same value for 60, 100, or 300 MHz machine).
  - Called the delta scale.

The Delta Scale

$$\text{chemical shift, ppm } \delta = \frac{\text{shift downfield from TMS (in Hz)}}{\text{spectrometer frequency (in MHz)}}$$



- **Different tables and graphs exist describing the general effect of functional groups on NMR absorptions. These represent only guidelines to follow. Effects of more than one functional group will normally be additive.**

TABLE 13-3

Typical Values of Chemical Shifts

Type of Proton	Approximate δ	Type of Proton	Approximate δ
alkane (—CH_3) methyl	0.9	$>C{=}C<$ allylic CH_3	1.7
alkane (—CH_2—) methylene	1.3	Ph—H aromatic	7.2
alkane (—CH—) methine	1.4	Ph—CH_3 benzylic	2.3
—C(=O)—CH_3 methyl ketone	2.1	R—C(=O)—H aldehyde	9–10
—C≡C—H acetylenic	2.5	R—C(=O)—OH acid	10–12
R—CH_2—X (X = halogen, O)	3–4	R—OH alcohol	variable, about 2–5
		Ar—OH phenol	variable, about 4–7
$>C{=}C<$ vinyl H	5–6	R—NH_2 amine	variable, about 1.5–4

Note: These values are approximate, as all chemical shifts are affected by neighboring substituents. The numbers given here assume that alkyl groups are the only other substituents present. A more complete table of chemical shifts appears in Appendix 1.

TABLE 13-2

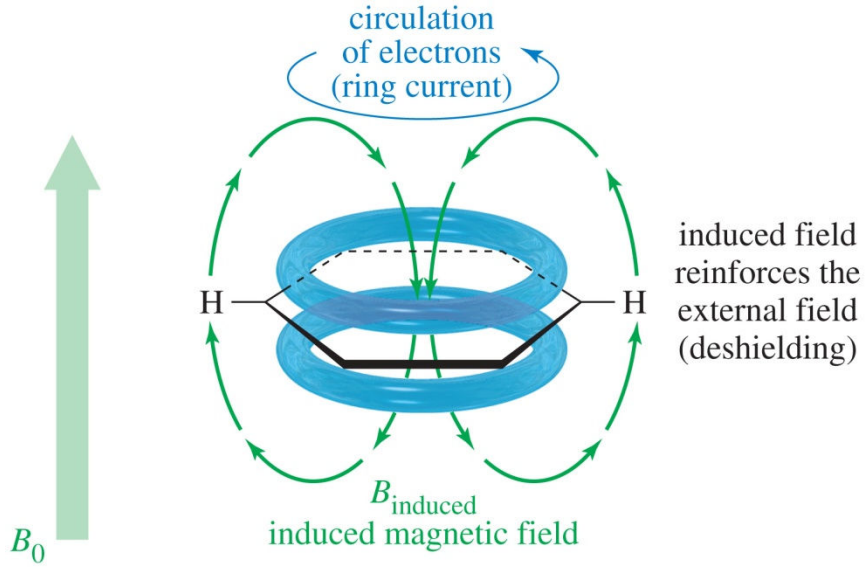
Chemical Shifts of the Chloromethanes

Compound	Chemical Shift	Difference
CH_4	δ 0.2	
		2.8 ppm
CH_3Cl	δ 3.0	
		2.3 ppm
CH_2Cl_2	δ 5.3	
		1.9 ppm
$CHCl_3$	δ 7.2	

Note: Each chlorine atom added changes the chemical shift of the remaining methyl protons by 2 to 3 ppm. These changes are nearly additive.

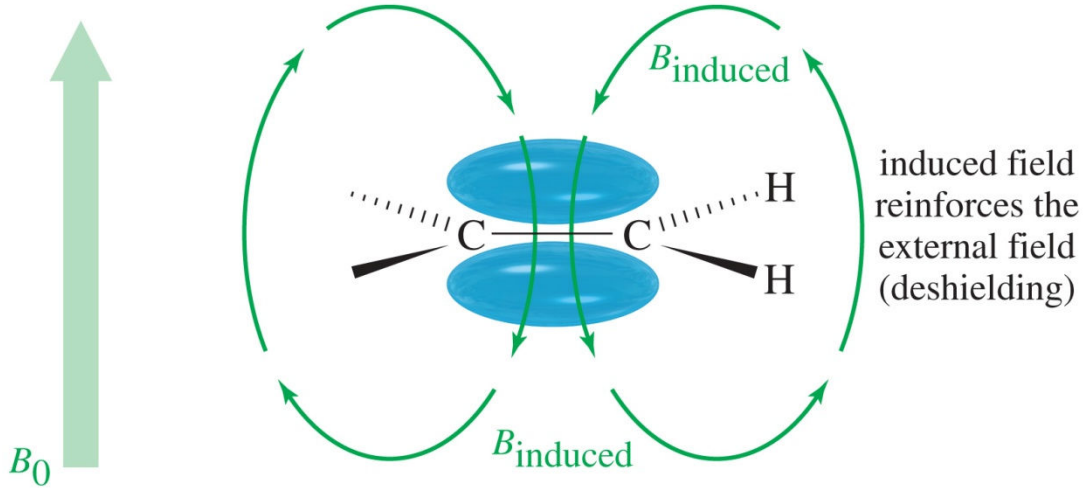
Magnetic Fields of Aromatics

- **The induced magnetic field of the circulating aromatic electrons opposes the applied magnetic field along the axis of the ring.**
- **Protons in the region where the induced field reinforces the applied field are deshielded and will appear at lower fields in the spectrum between δ7–8.**



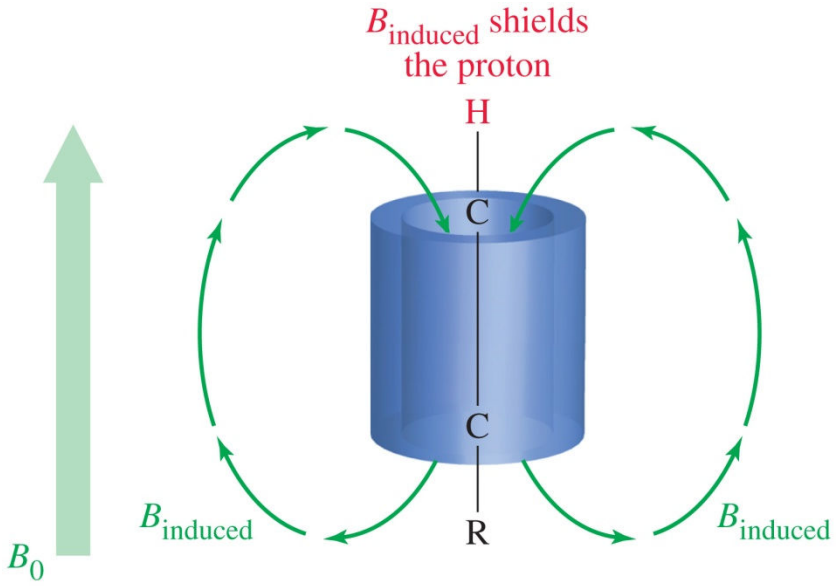
Magnetic Field of Alkenes

- **The pi electrons of the double bond generate a magnetic field that opposes the applied magnetic field in the middle of the molecule but reinforces the applied field on the outside where the vinylic protons are located.**
- **This reinforcement will deshield the vinylic protons making them shift downfield in the spectrum to the range of δ5–6.**



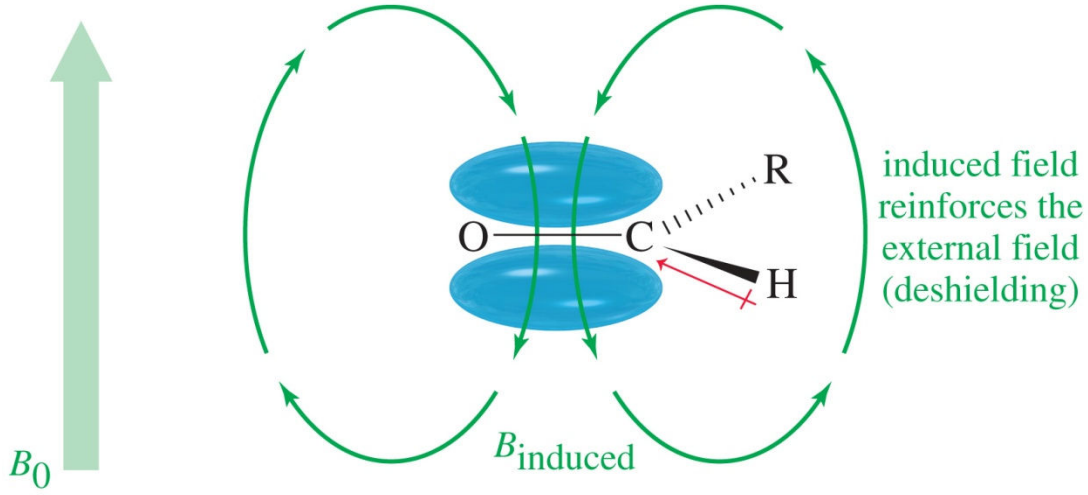
Magnetic Field of Alkynes

- **When the terminal triple bond is aligned with the magnetic field, the cylinder of electrons circulates to create an induced magnetic field.**
- **The acetylenic proton lies along the axis of this field, which opposed the external field.**
- **The acetylenic protons are shielded and will be found at δ2.5 (higher than vinylic protons).**



Deshielding of the Aldehyde Proton

- **Like a vinyl proton, the aldehyde proton is deshielded by the circulation of electrons in the pi bond.**
- **It is also deshielded by the electron-withdrawing effect of the carbonyl (C=O) group, giving a resonance between δ9–10.**

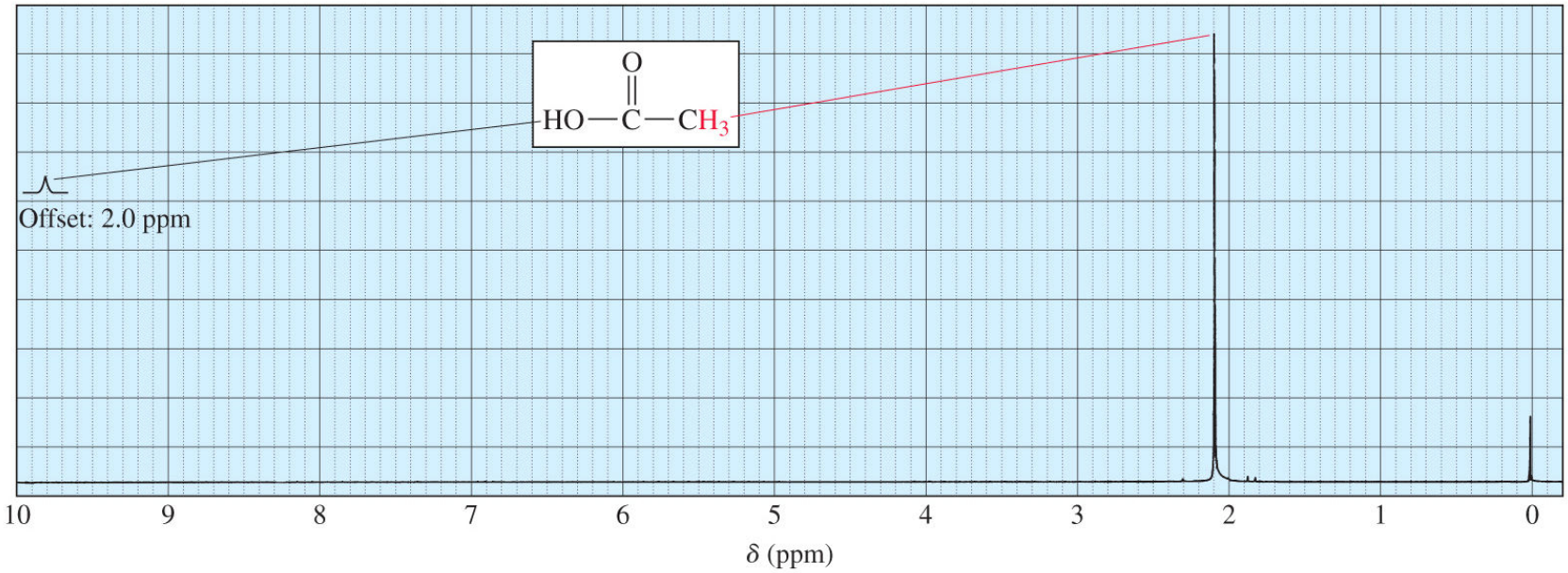


O-H and N-H Signals

- **The chemical shift of the acidic protons depends on concentration.**
- **Hydrogen bonding in concentrated solutions deshield the protons, so signal is around δ3.5 for N—H and δ4.5 for O—H.**
- **Proton exchanges between the molecules broaden the peak.**

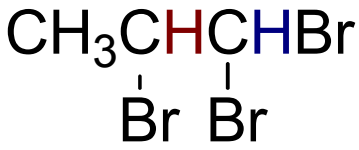
Carboxylic Acid Proton

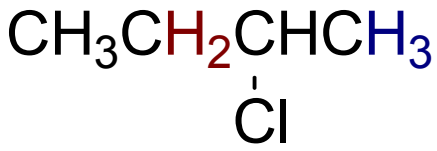
- **Because of the high polarity of the carboxylic acid O—H bond, the signal for the acidic proton will be at shifts greater than δ10.**

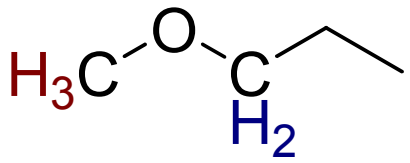


Practice Questions

- **For each of the following compounds, which of the protons (in red and blue) has the greater chemical shift?**





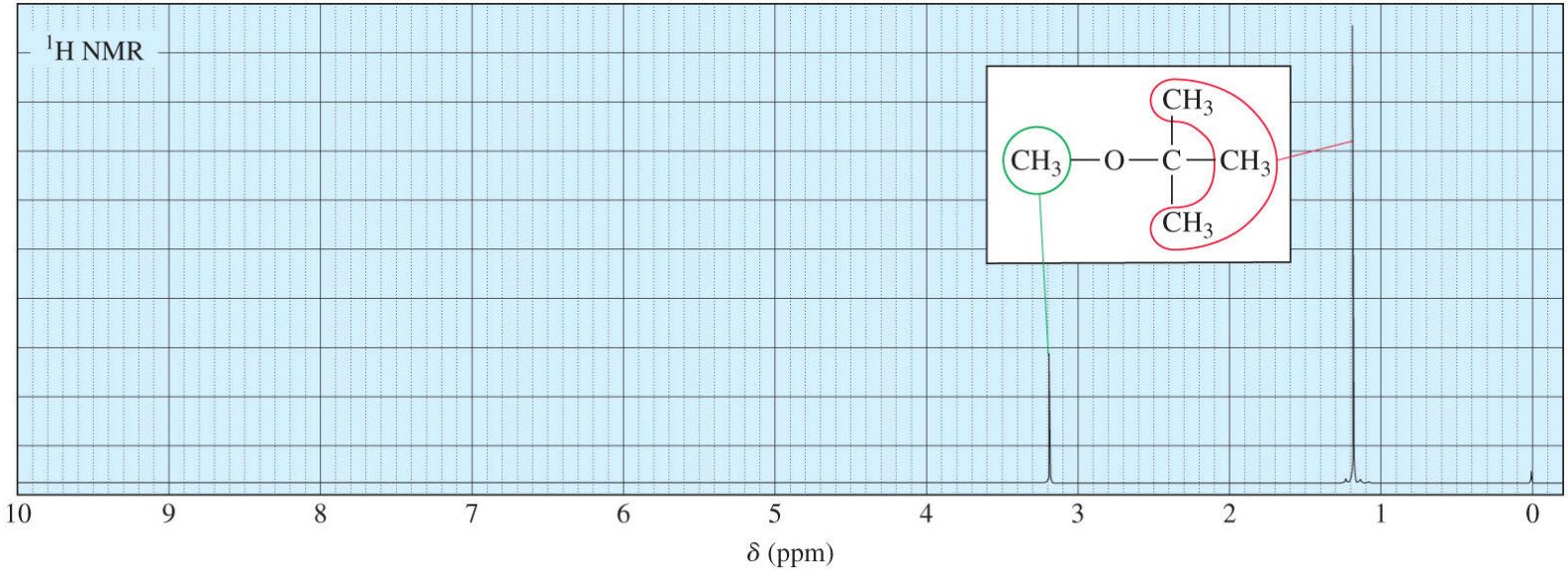


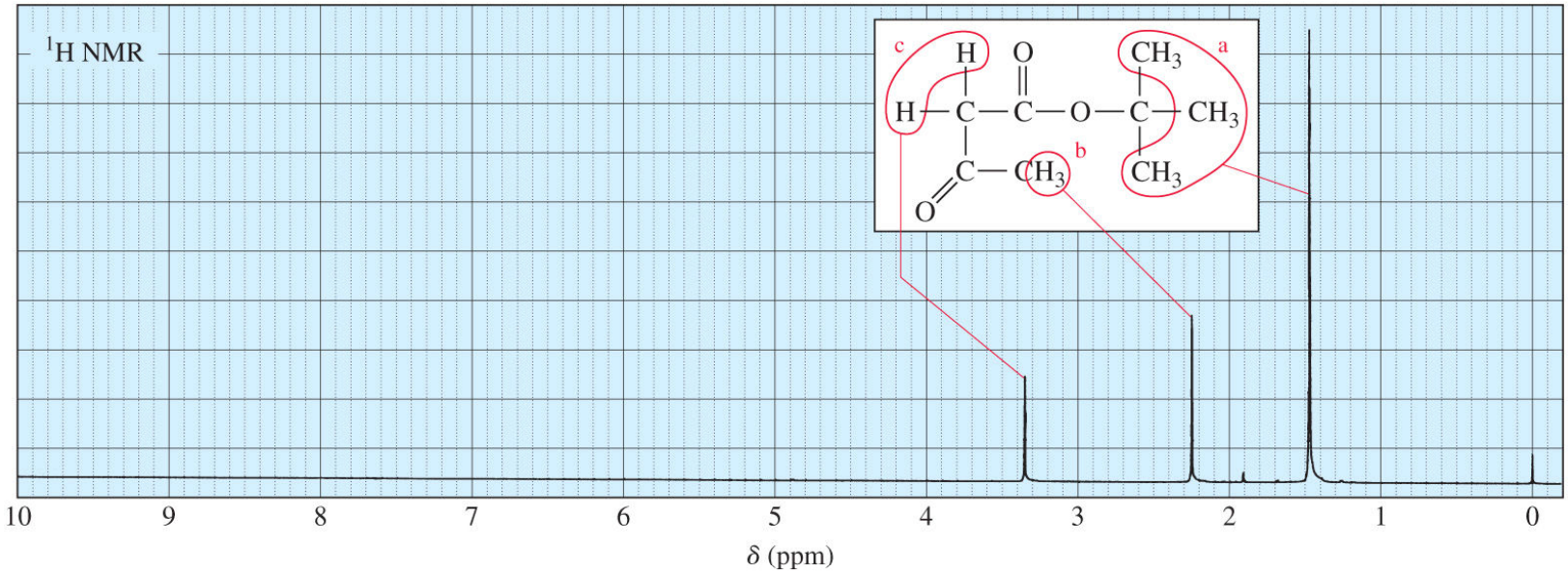
Number of Signals (13.6)

- **Chemically different protons will have signals at different positions.**

CH_3CH_2Br

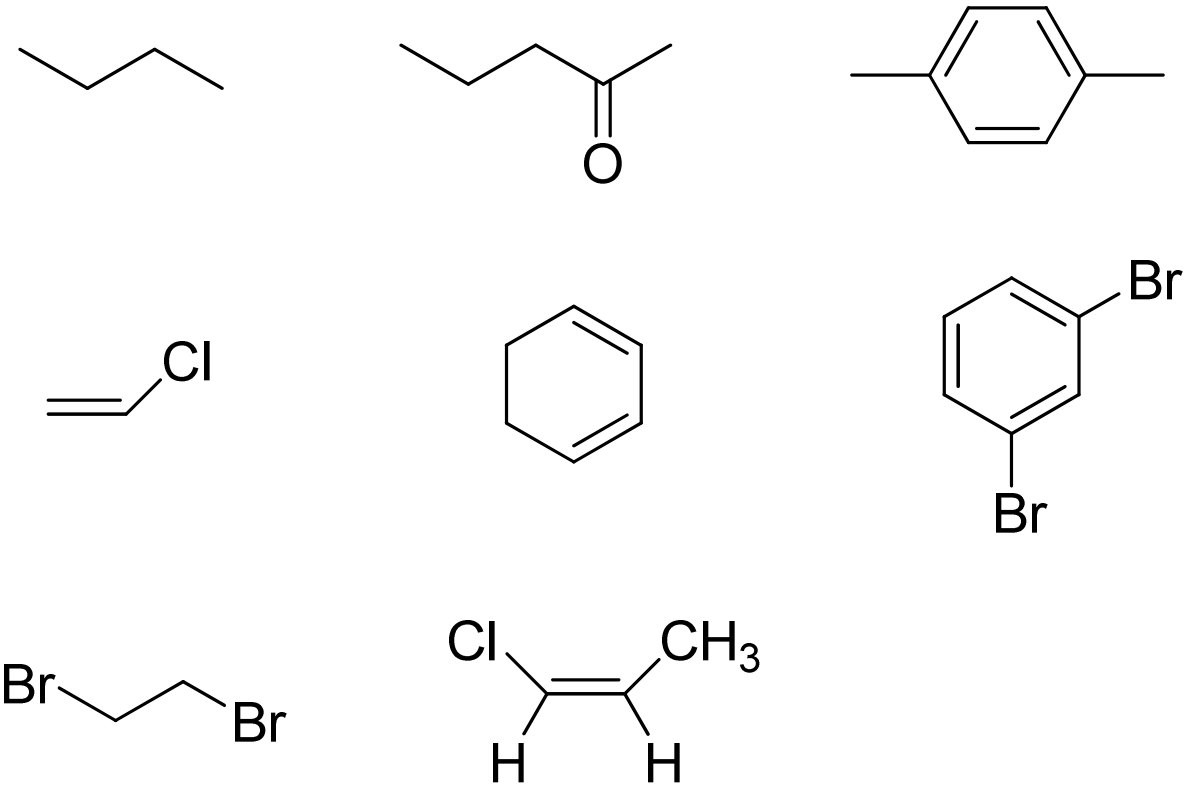
- **Chemically identical protons will have different signals if they are environmentally different**





Practice Question

- **How many signals would you expect to see in the ^{1}H-NMR spectrum of the following compounds?**



Area Under the Peaks (13.9)

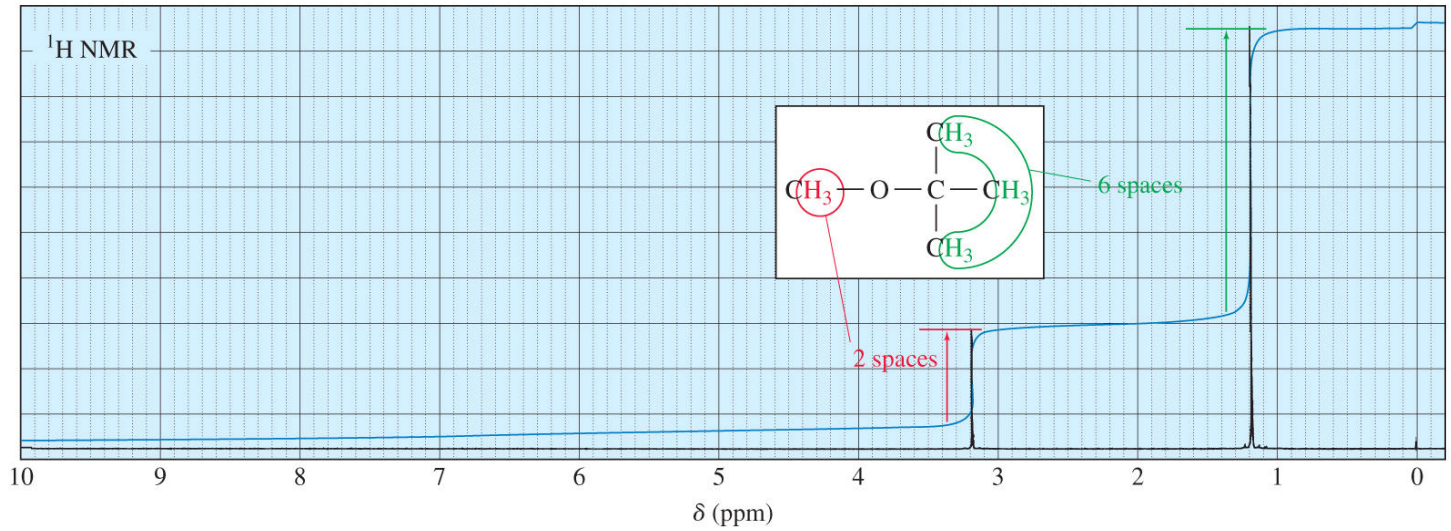
- **Another line (looks like steps) usually appears on a NMR spectrum. It is the integral line.**

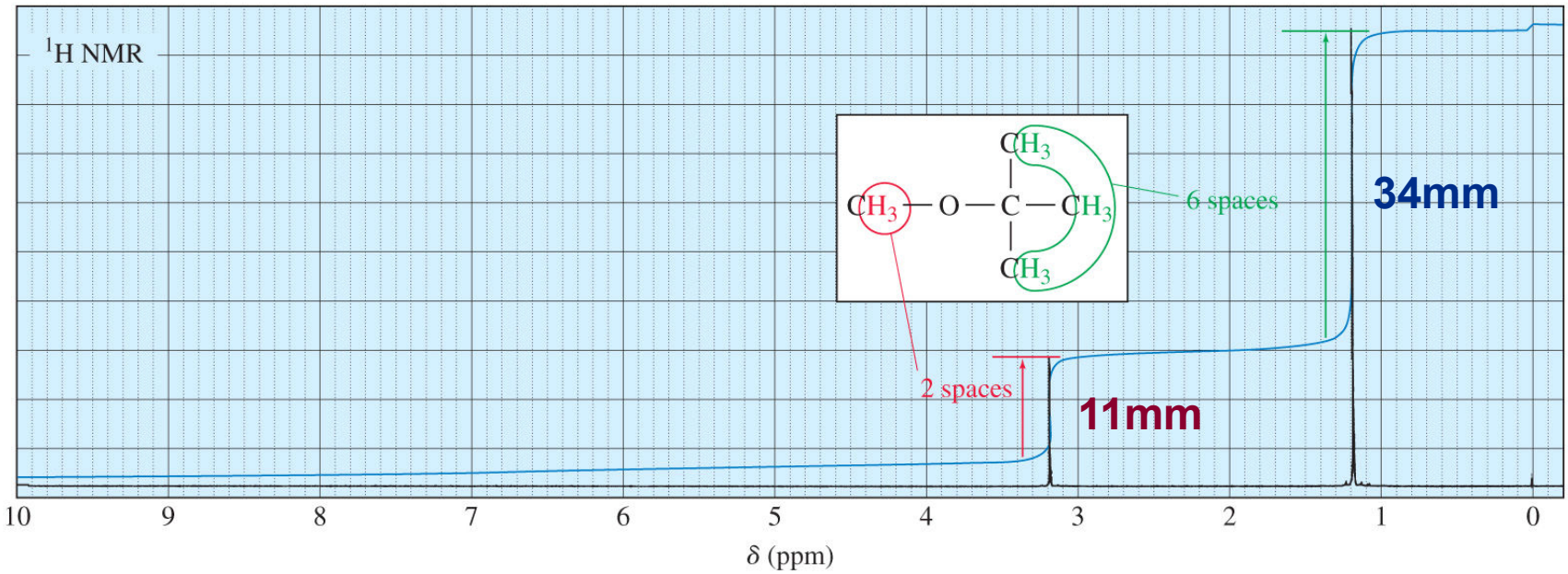
- **This line is used to determine the number of hydrogen responsible for a given absorption or signal. It is a relative scale so if only one signal appear in the spectrum, this line is usually not present.**

- **However when more than one signal is observed, this integral line will appear and help determine the structure of certain groups.**

- **The integration is relative between signals: ie**

  the more H's of one kind (equivalent) the more intense the corresponding absorption relative to the other ones.

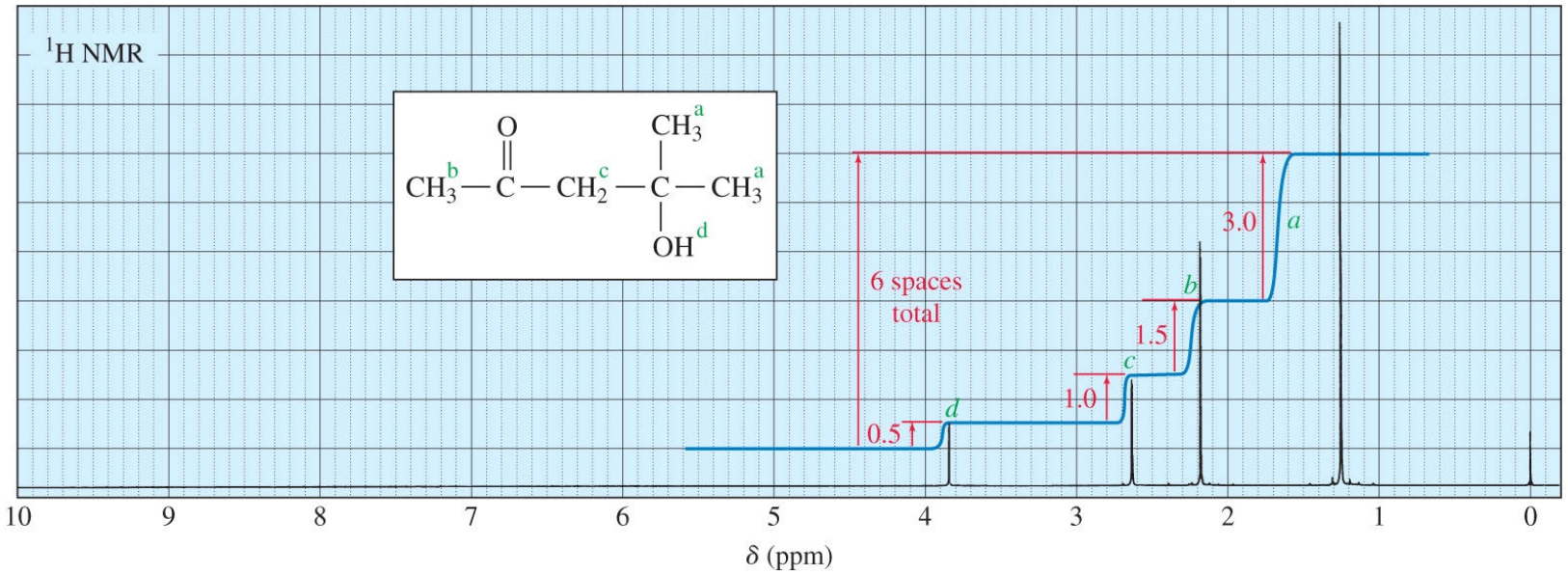




1) **Measure each steps botton to top in a measurable unit:**
2) **Divide each value by the smallest one recorded. This will give the smallest signal a value of 1 proton**

11/11 = 1 **34/11= 3**

3) **If the ratio obtained gives fractions, multiply until you get to a value that is close to a whole number**



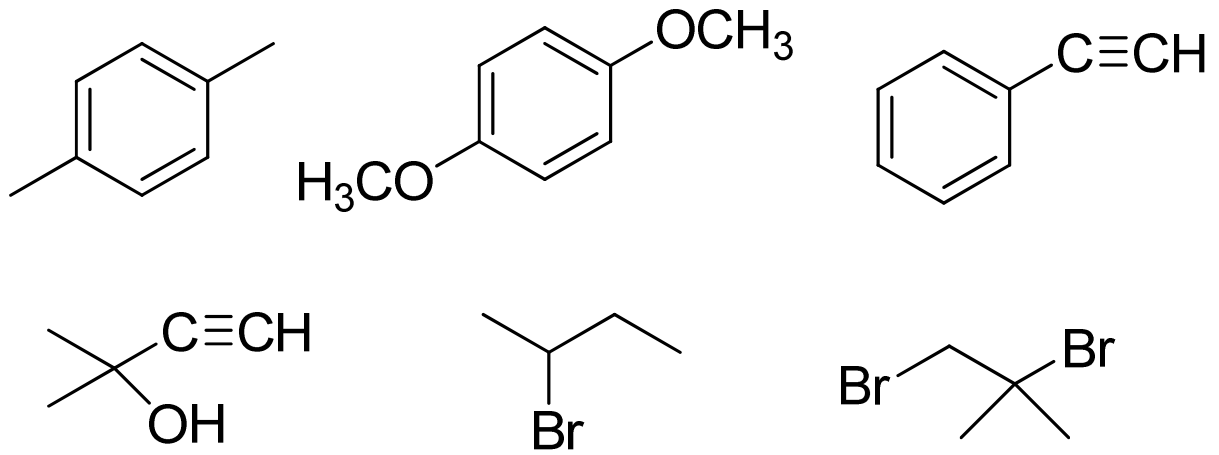
1) **Ratios are: 0.5 : 1.0 : 1.5 : 3.0**

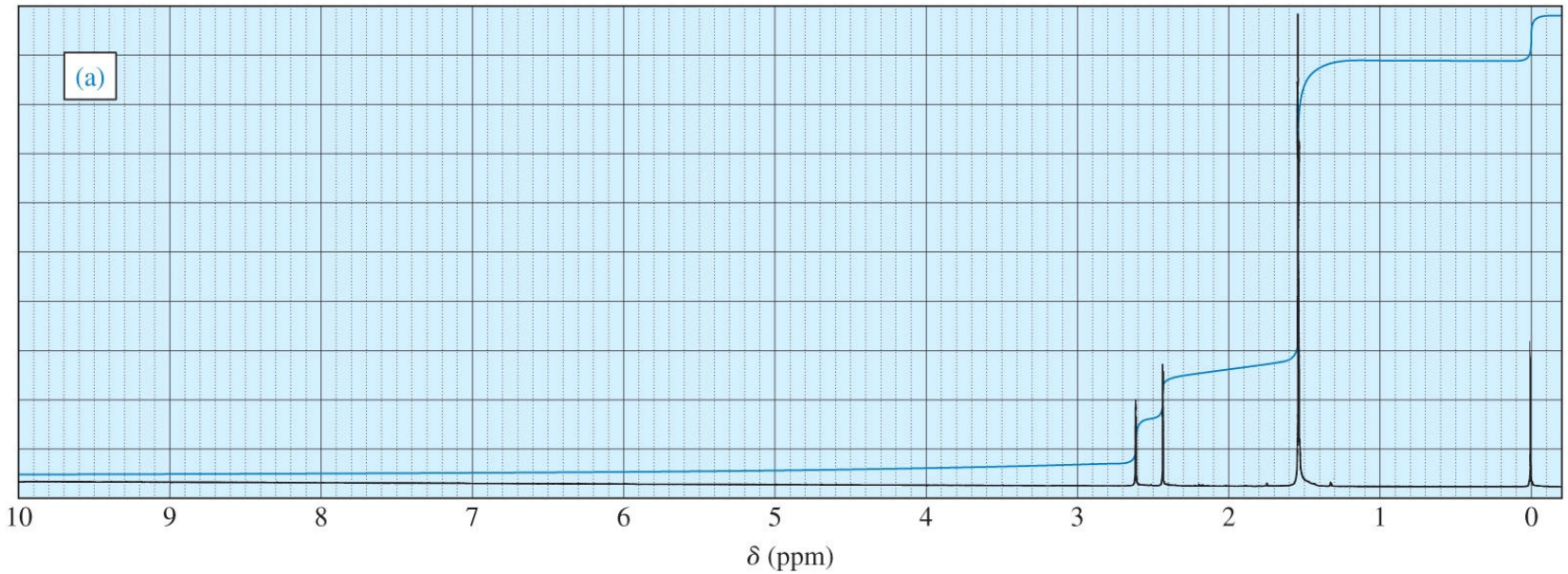
2) **Since it is not possible to have 0.5 proton, multiply by 2**

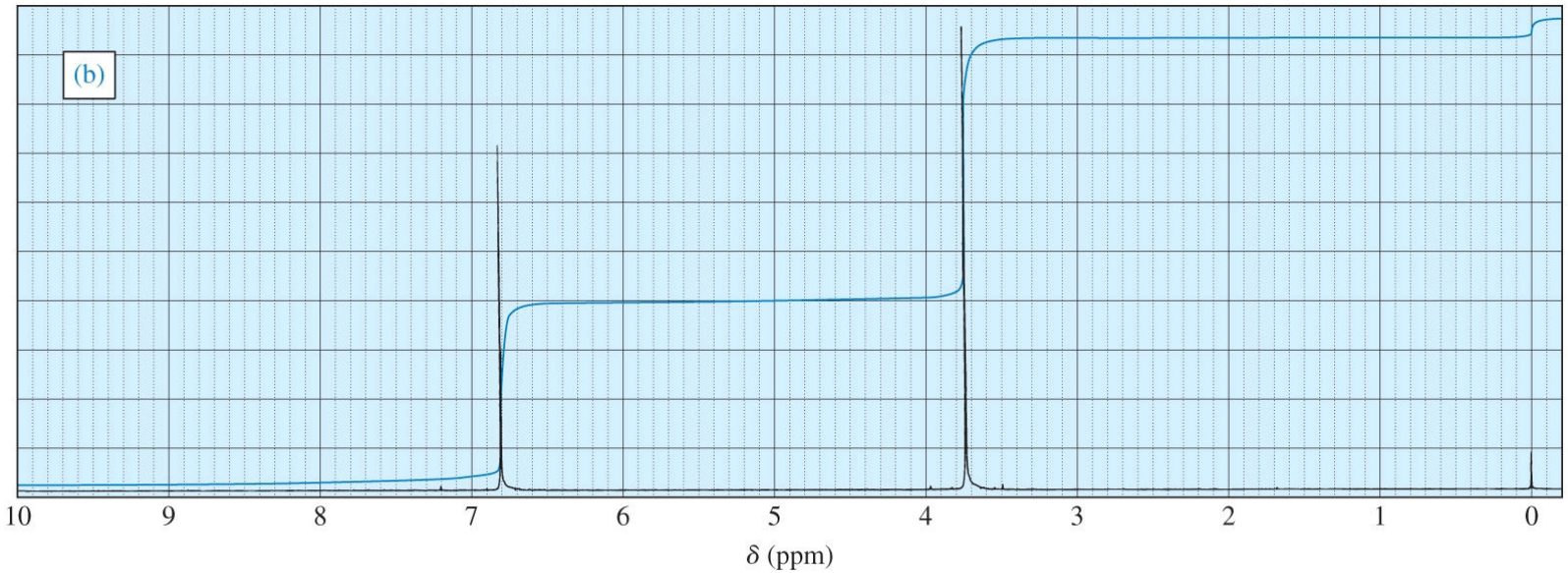
3) **Final ratios are: 1 : 2 : 3 : 6**

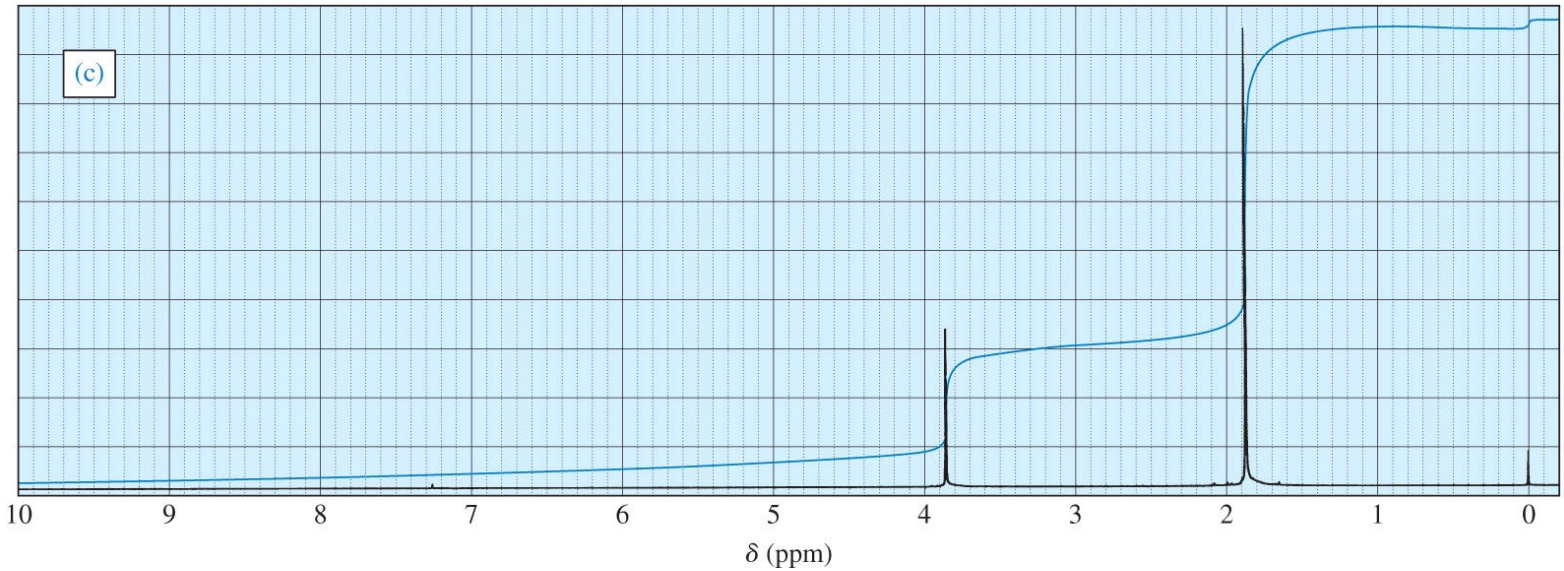
Practice Question (Question13-6)

- **Determine the ratios of the peak areas in the following spectra. Then use this information, together with the chemical shift, to pair up the compounds with their spectra. Assign the peaks in each spectrum to the protons they represent in the molecular structure. Possible compounds:**









Spin-Spin Splitting (13.8)

- **When 2 adjacent carbon atoms have chemically or environmentally different H's, the signals for a given set of H's on a carbon will be coupled (split) into more than one line.**

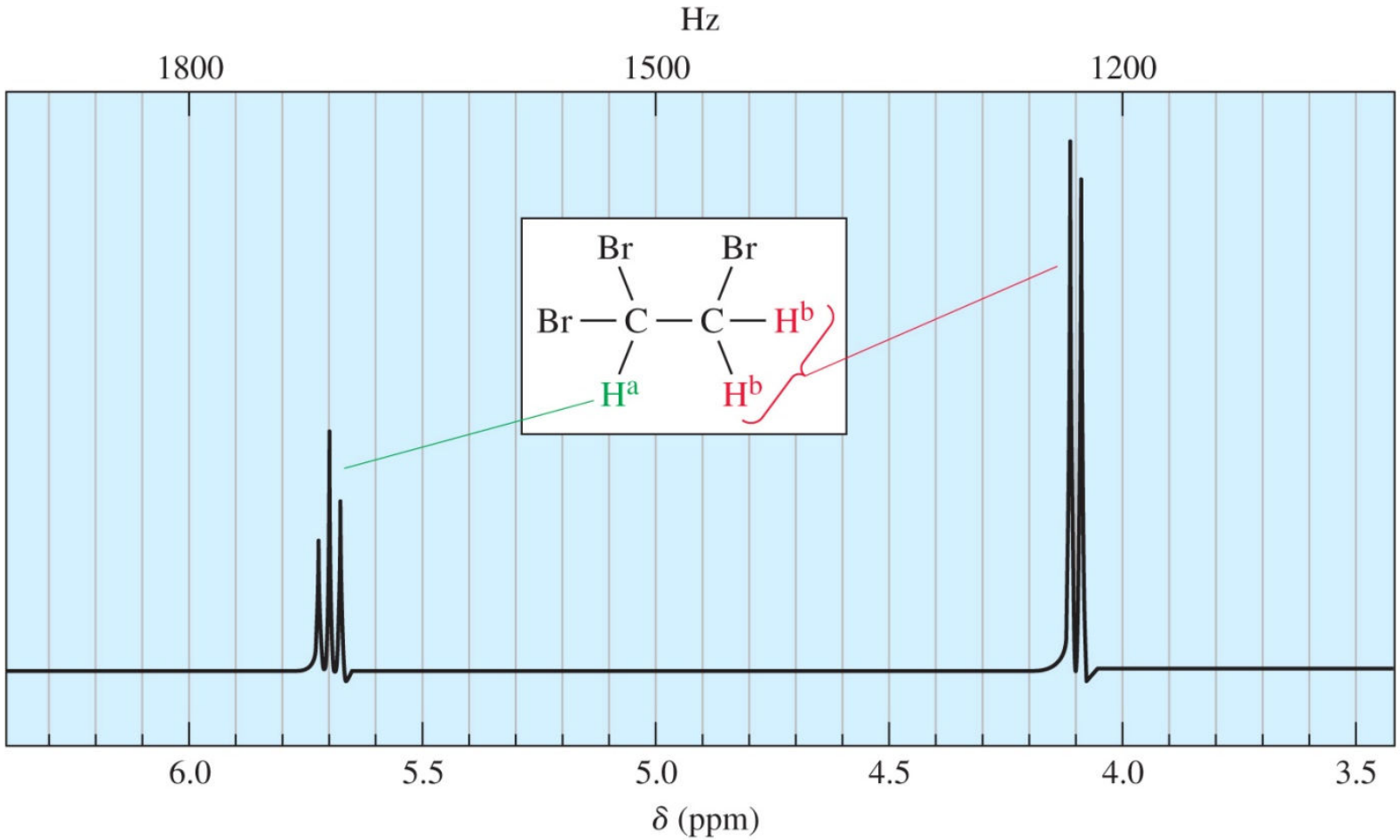
- **For simple molecules, the observed pattern is predictable following the n + 1 rule**

  # lines of a signal = n + 1

  where n = # neighbouring H's

Both H^b are identical and have one neighbouring proton (H^a), signal for H^b will be split: 1 + 1 = 2 lines (a doublet)

H^a has 2 neighbouring Hs (H^b), signal for H^a will be split: 2 + 1 = 3 lines (a triplet)



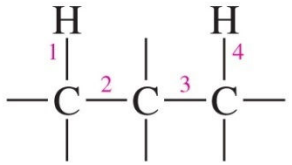
- **Number of lines in a signal is called multiplicity. Coupling between protons is mutual.**

- **The coupling effect between protons is limited to the neighbouring protons. Further away will usually have no effect (except due to conjugation). Nonequivalent protons on the same carbon will be coupled.**

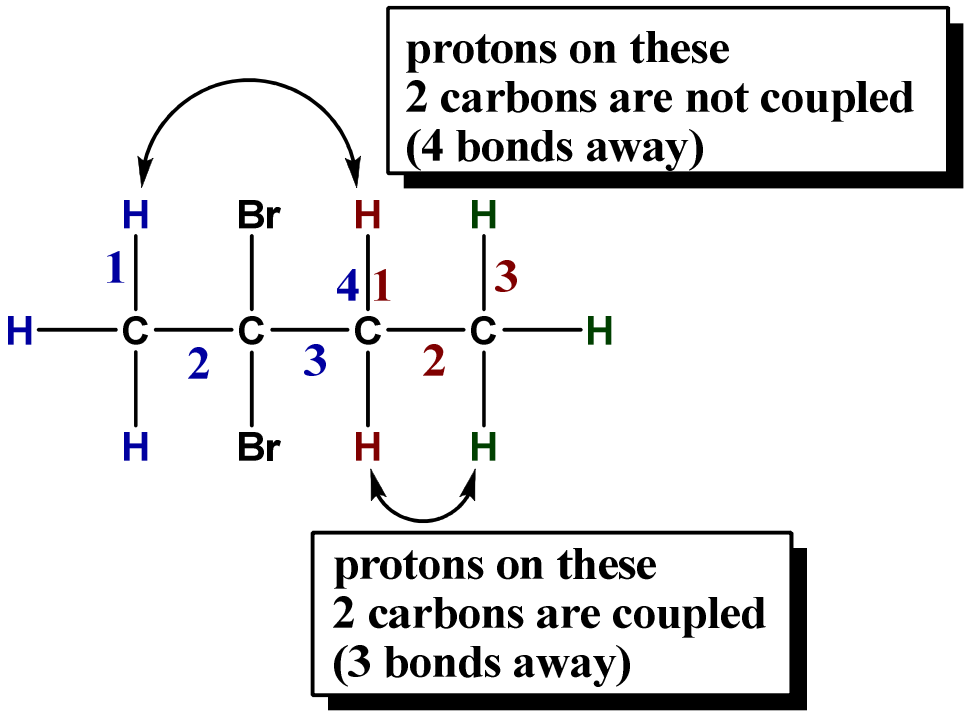
General Splitting Rules

- **Equivalent protons do not split each other.**
- **Protons bonded to the same carbon will split each other if they are nonequivalent.**
- **Protons on adjacent carbons normally will split each other, unless they are equivalent.**
- **Protons separated by four or more bonds will not split each other.**

- **The coupling effect between protons is limited to the neighbouring protons. Further away will usually have no effect (except due to conjugation). Nonequivalent protons on the same carbon will be coupled.** *Bonded to nonadjacent carbons: four or more bonds between protons*



spin-spin splitting is *not* normally observed



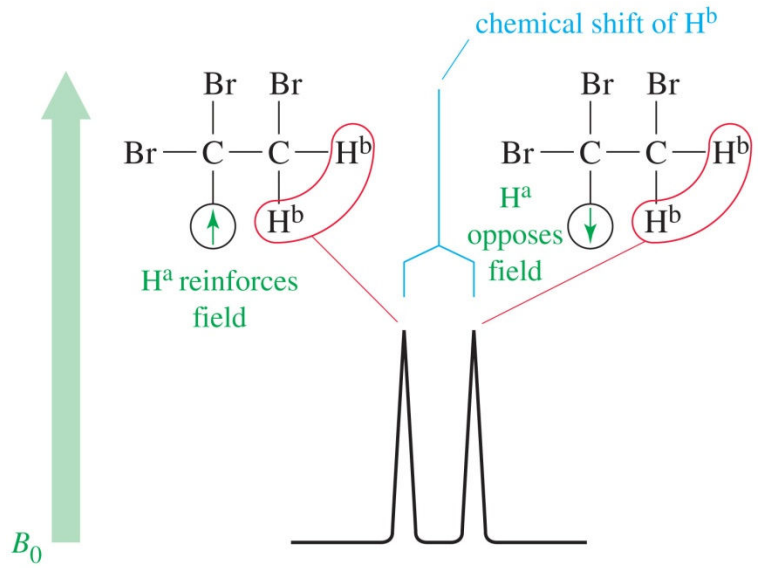
Multiplicity of Signals

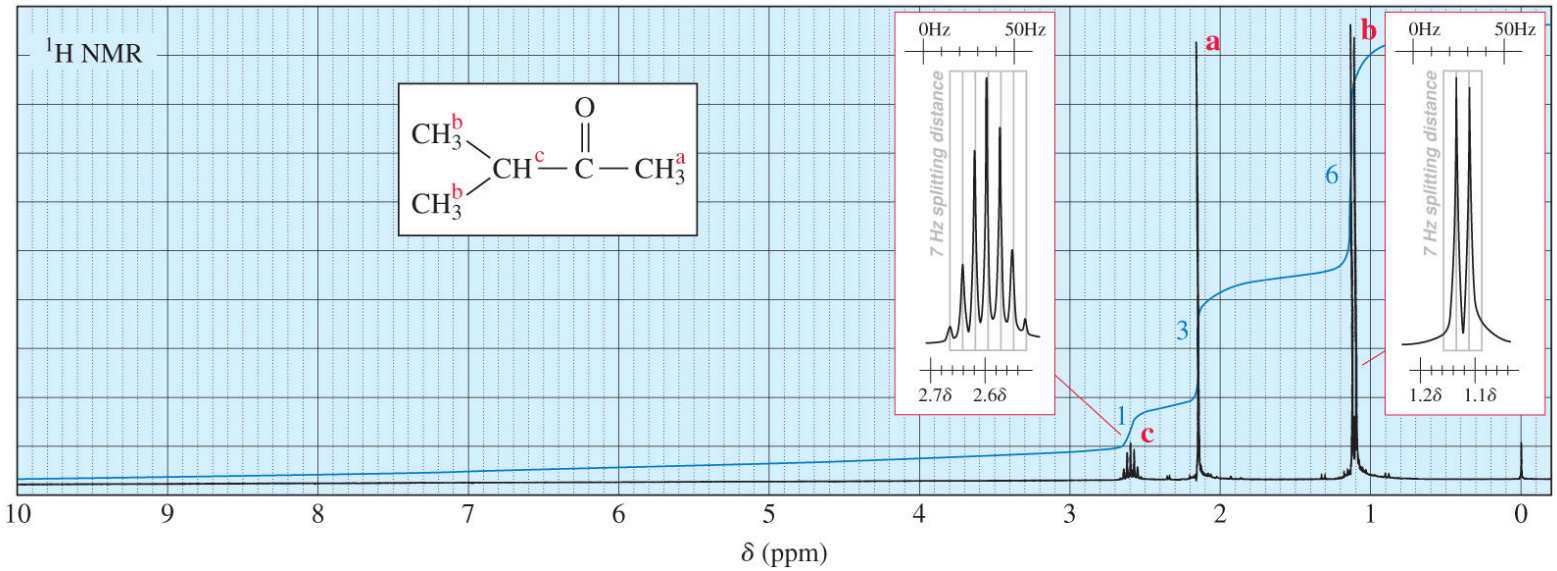
- **The shape and intensity of the line in a signal can help determine the type of groups present in a molecule.**

Relative Peak Intensities of Symmetric Multiplets

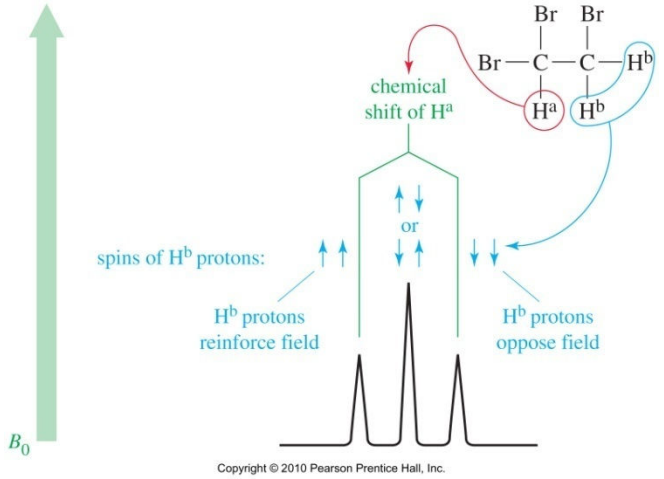
Number of Equivalent Protons Causing Splitting	Number of Peaks (multiplicity)	Area Ratios (Pascal's triangle)
0	1 (singlet)	1
1	2 (doublet)	1 1
2	3 (triplet)	1 2 1
3	4 (quartet)	1 3 3 1
4	5 (quintet)	1 4 6 4 1
5	6 (sextet)	1 5 10 10 5 1
6	7 (septet)	1 6 15 20 15 6 1

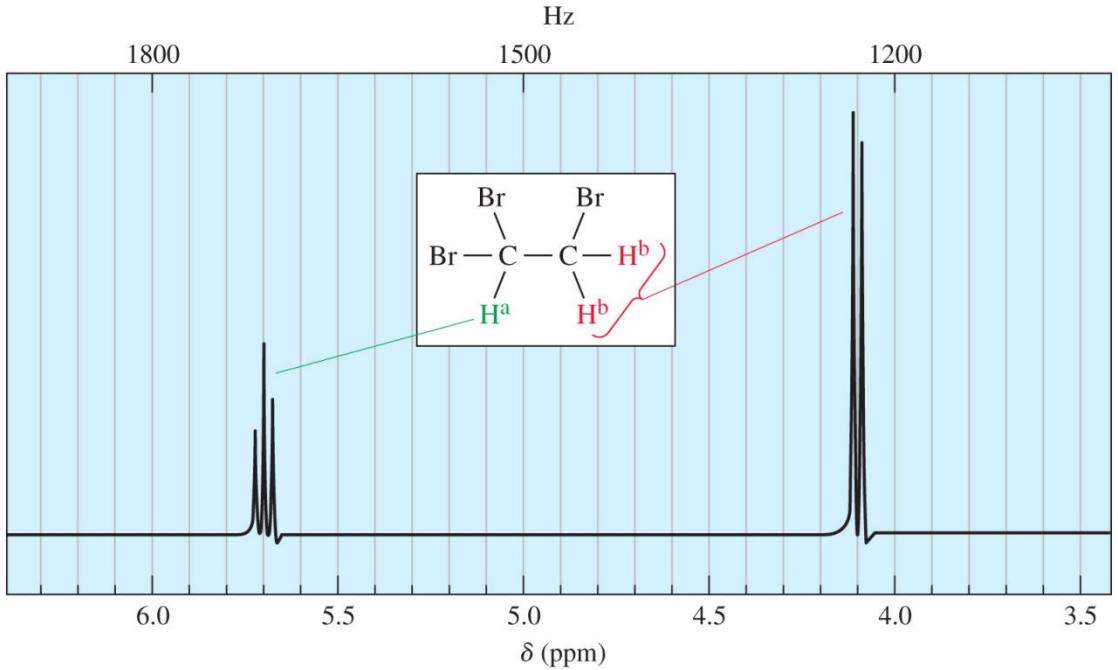
- Doublets always have 2 lines almost of equal heights.



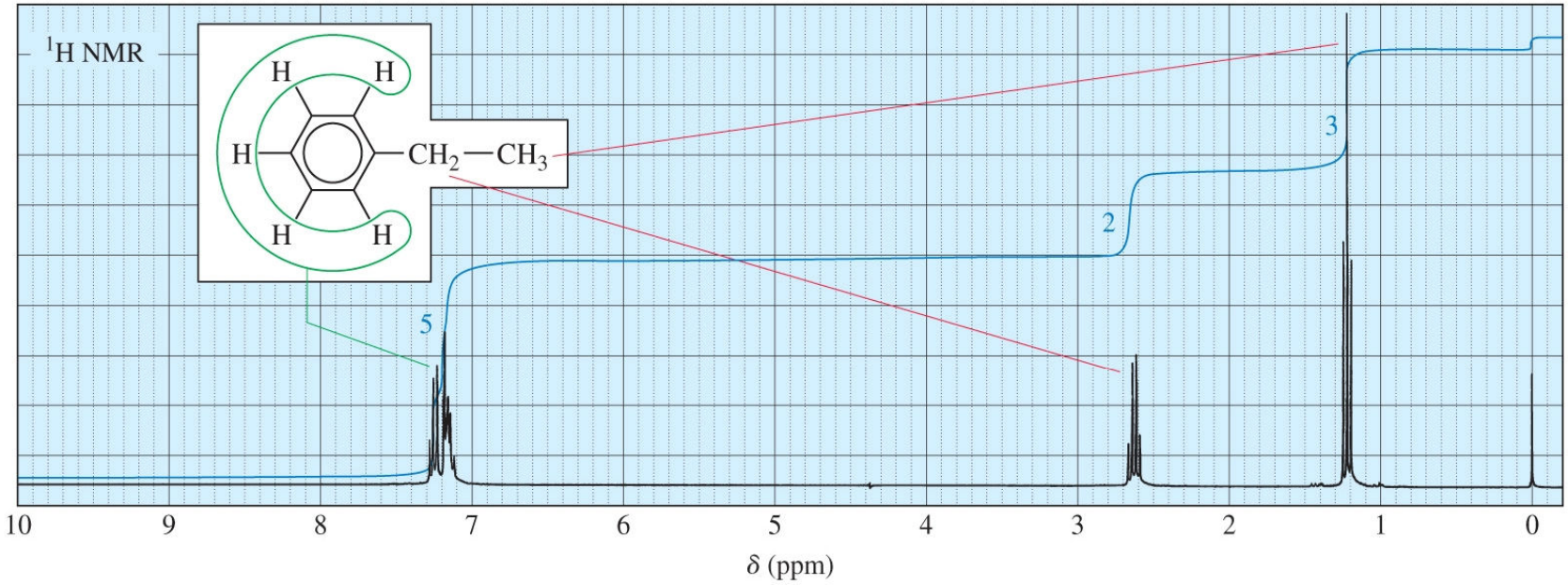


- **Triplets: will always have a 1:2:1 ratio for the lines in that signal**



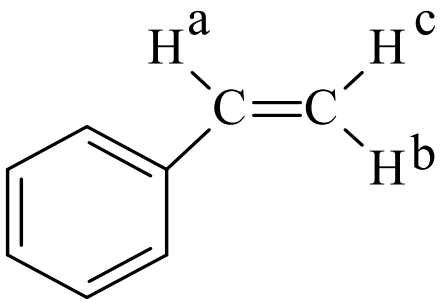


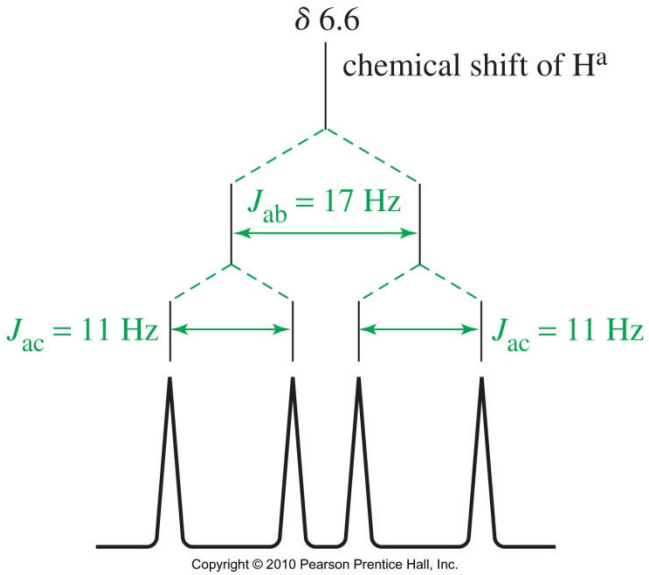
- Quartets are easy to assign with their 1:3:3:1 ratio.

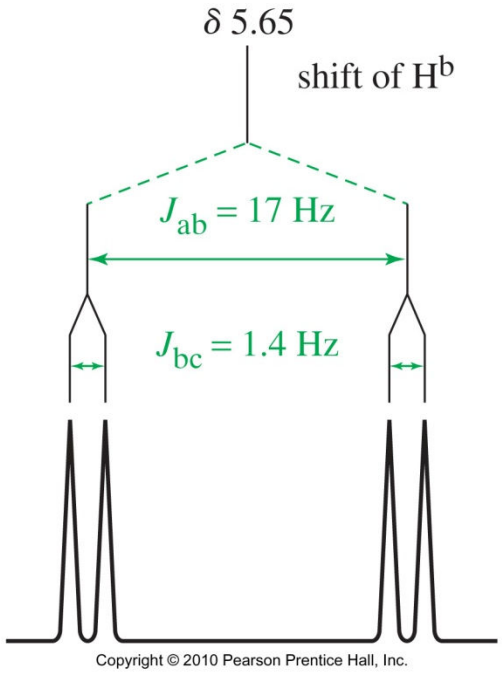


Second order coupling (13.13-13.14)

- **Second order coupling will be observed when a given proton has more than one non-equivalent neighbours. In this case, the number of neighbours does not add up, but must be taken separately.**

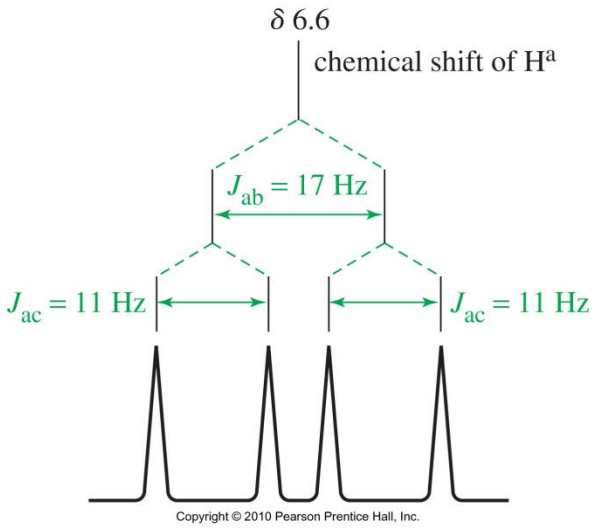




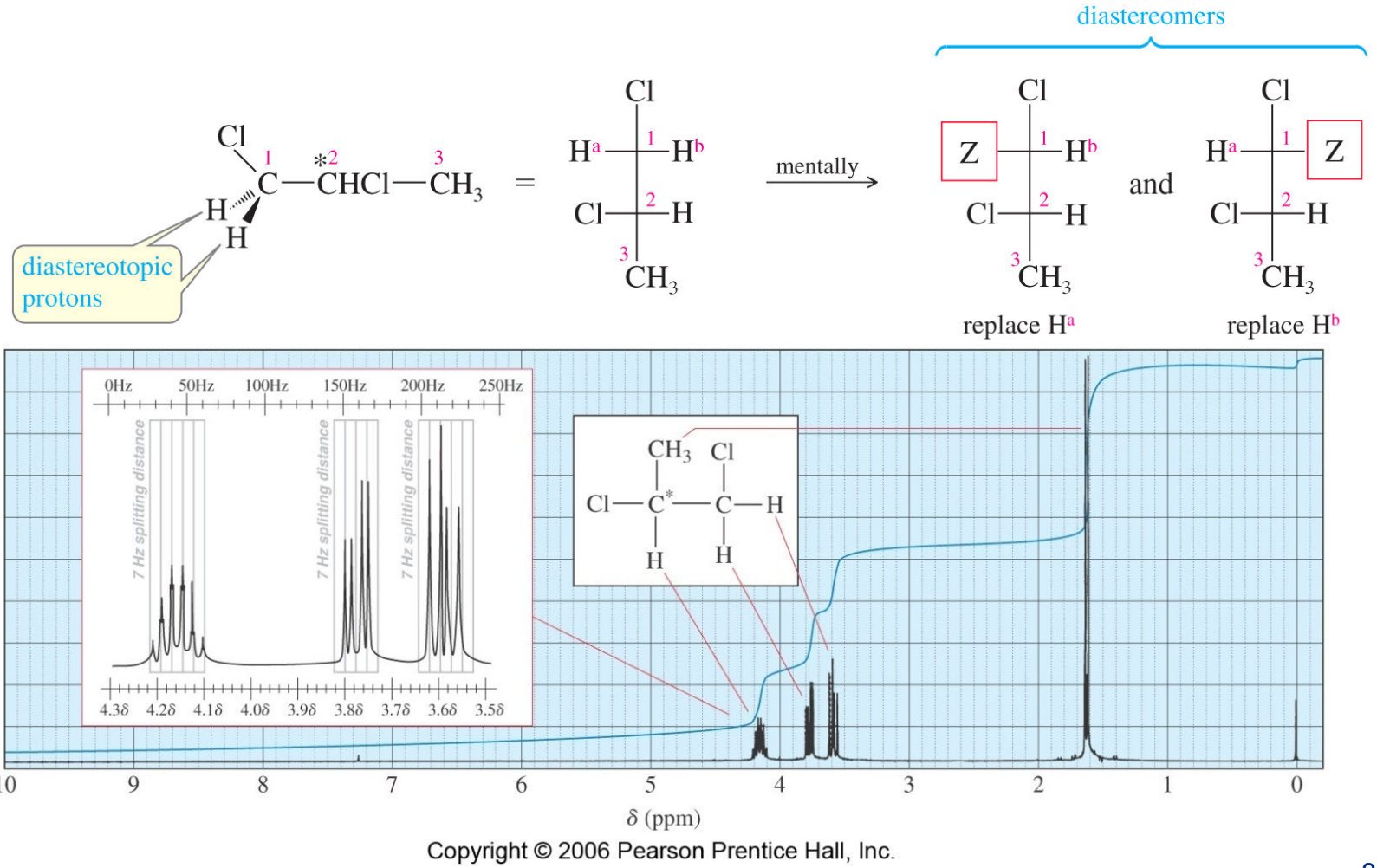


- **Second order coupling usually give lines that do not match the simple multiplicity found in the Pascal's triangle . Hence, while it is important to look at the number of lines, the shape will also give you clues.**

- **For example the signal below is not a quartet although it has 4 lines, it is a doublet of doublets since all the lines are even. A quartet would have the 1:3:3:1 ratio.**

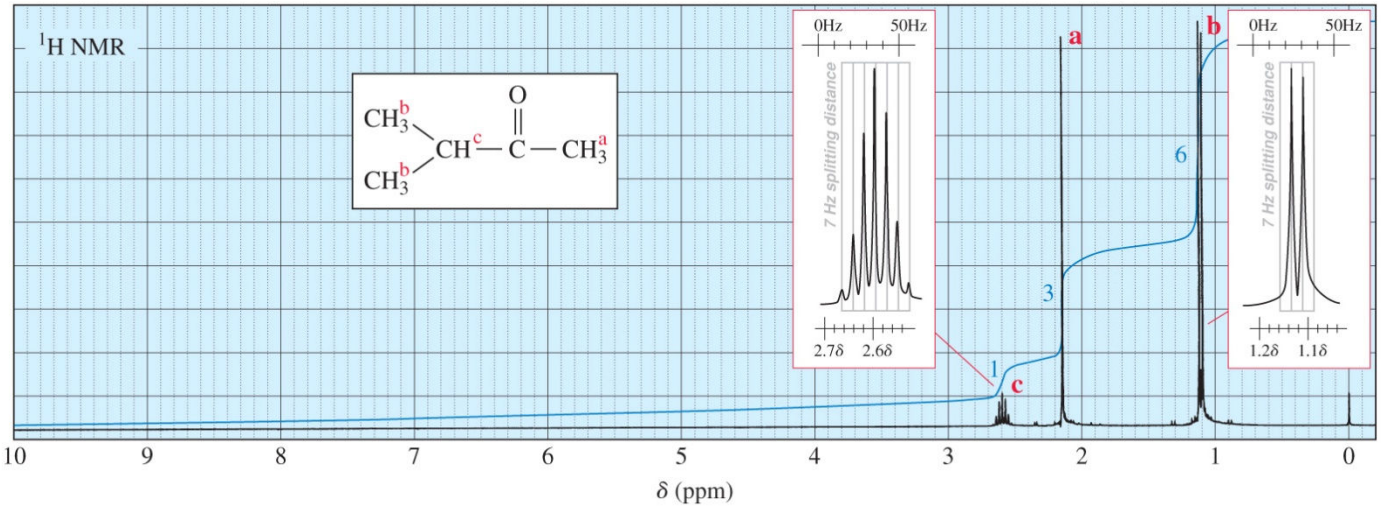


- **These kinds of patterns are often found in chiral molecules where protons on a given carbon appears identical, but because of the chiral center, these may actually be diastereotopic.**

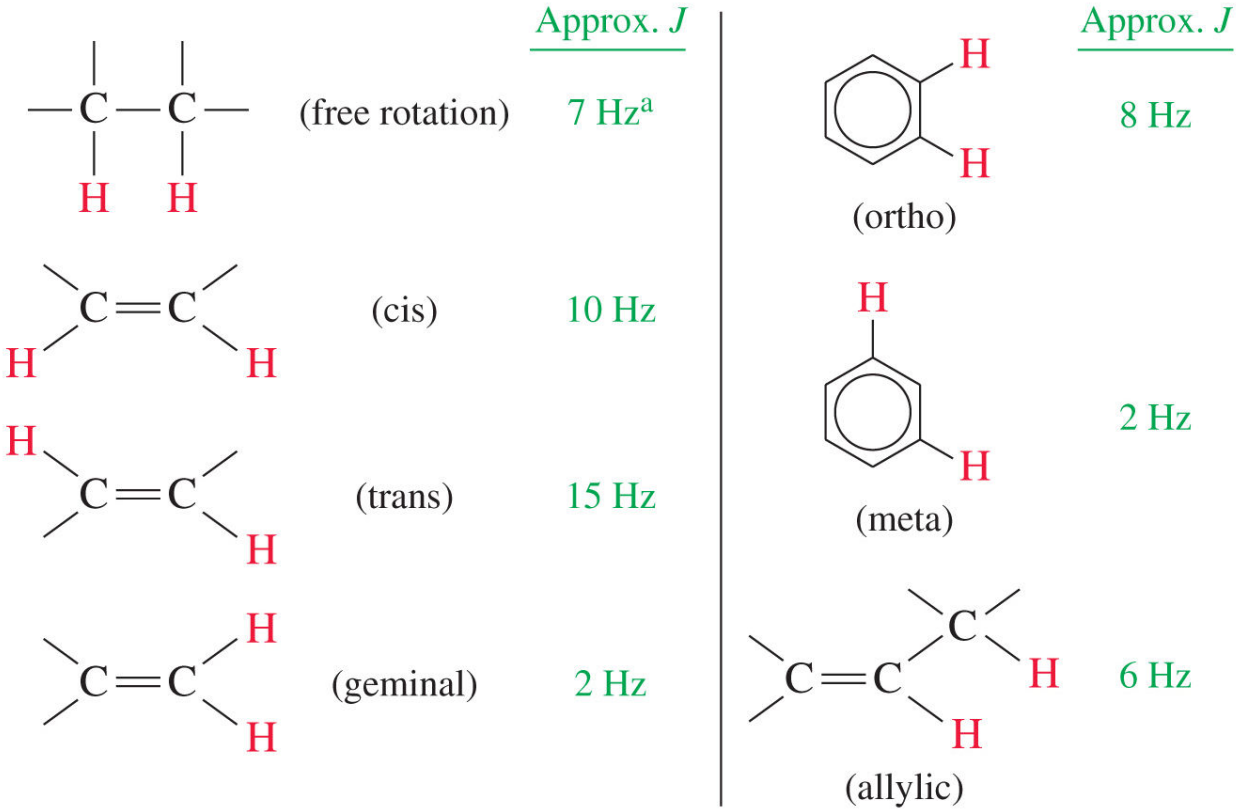


Coupling constant (J) (13.12)

- **The coupling constant is the distance found between lines in a pattern due to splitting. It is measured in Hertz.**
- **When two different protons are coupled, the coupling constant for H_a will be the same as that found for H_b.**
- **This can help identify some groups.**



- **The coupling constant can also help to identify specific groups**

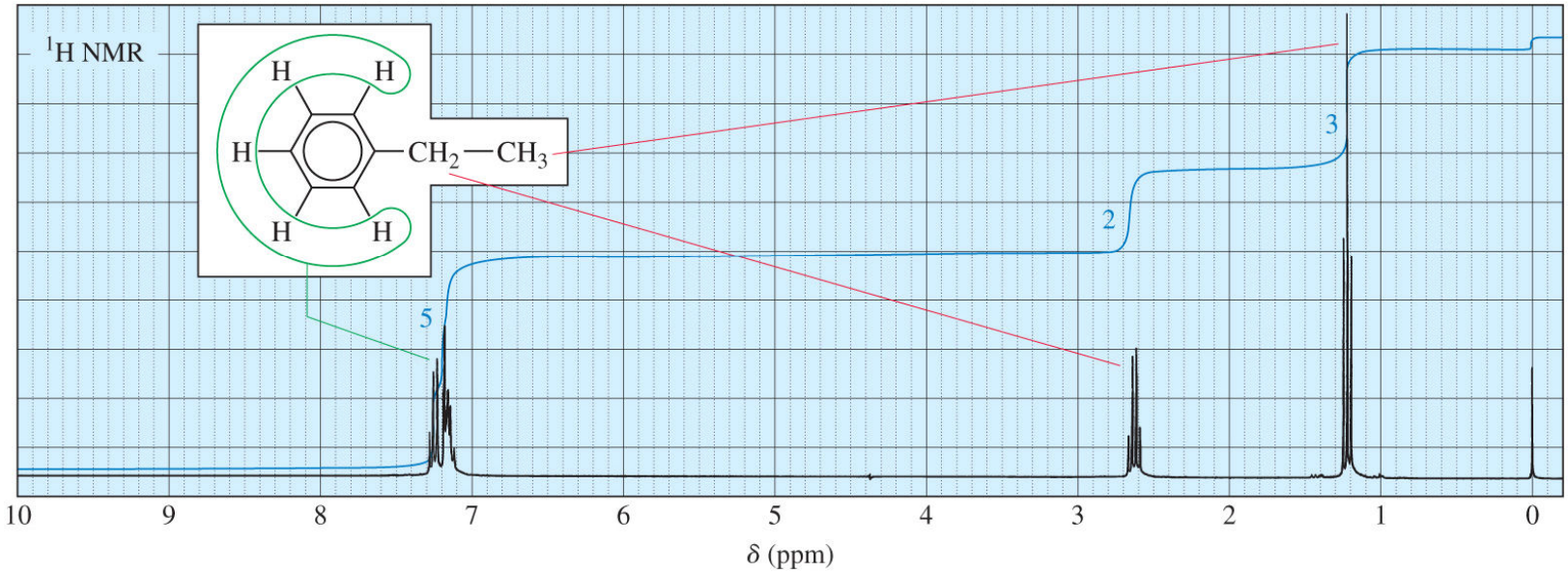


[a]The value of 7 Hz in an alkyl group is averaged for rapid rotation about the carbon–carbon bond. If rotation is hindered by a ring or bulky groups, other splitting constants may be observed.

Easily Identified patterns

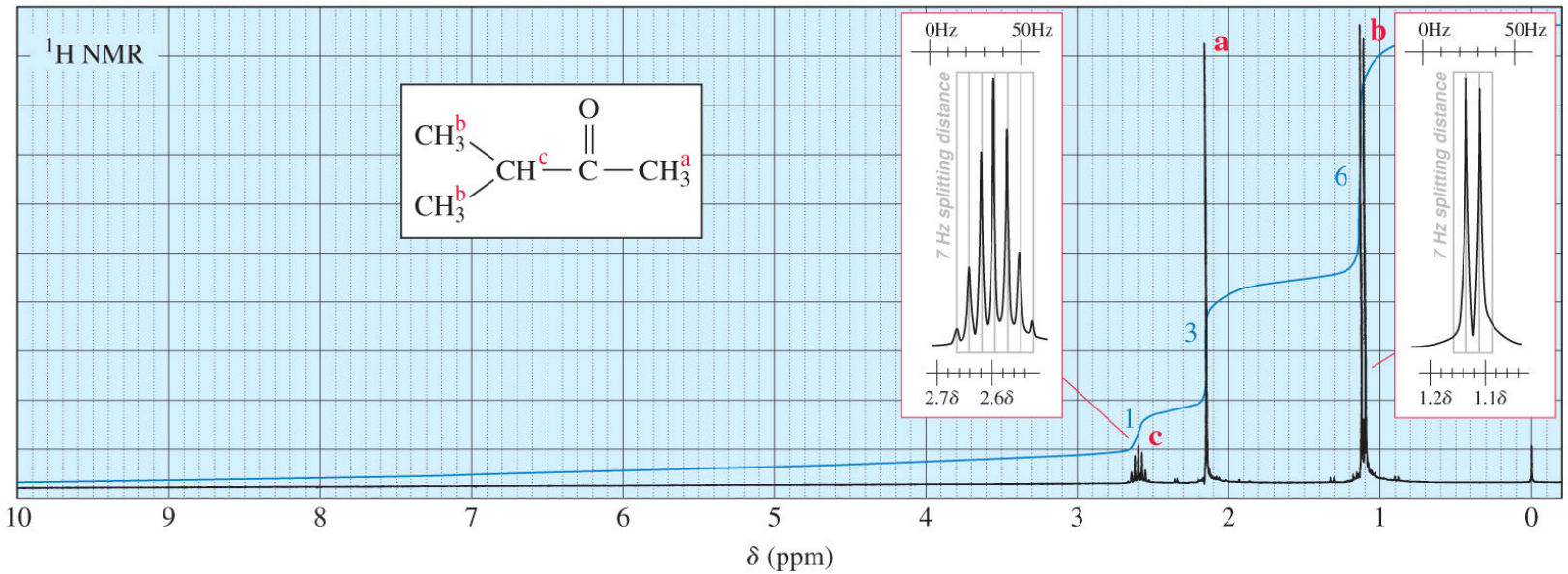
Ethyl group, CH_3-CH_2- : its position on the spectrum depends on the other groups in the molecule

quartet/triplet pattern integrating for 2 and 3



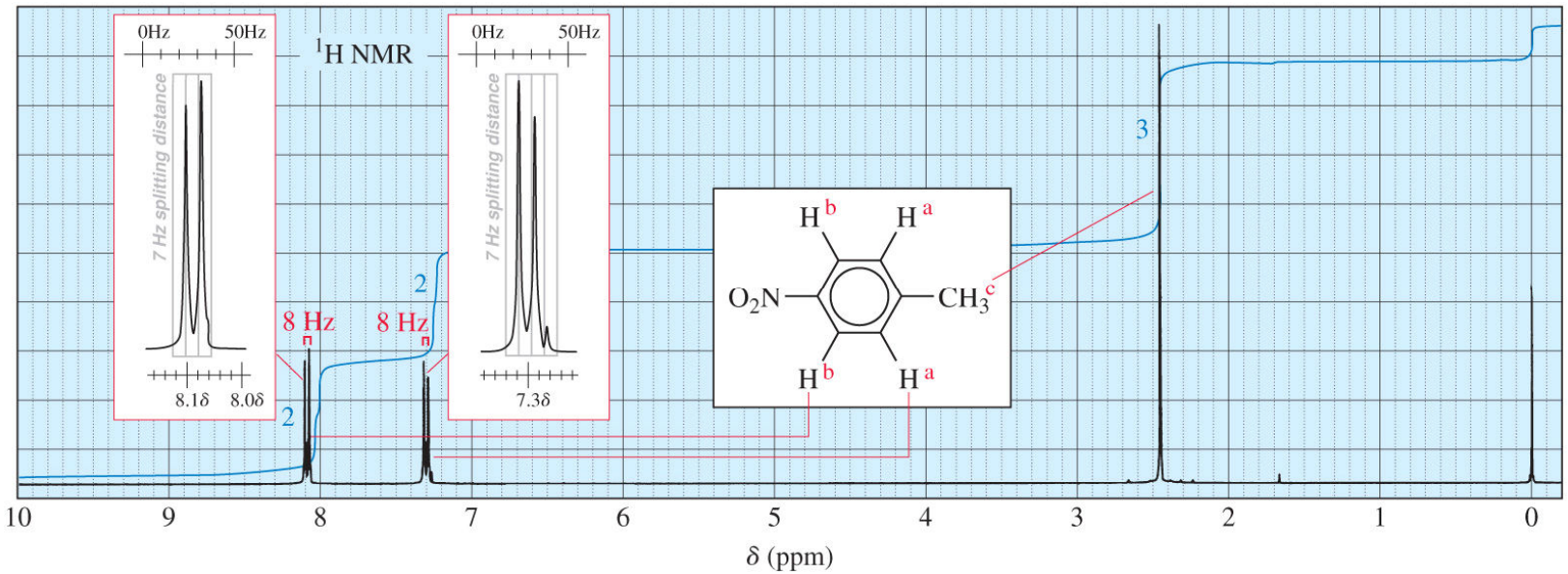
Isopropyl group CH_3-CH-CH_3

Septet/doublet pattern integrating for 1 and 6

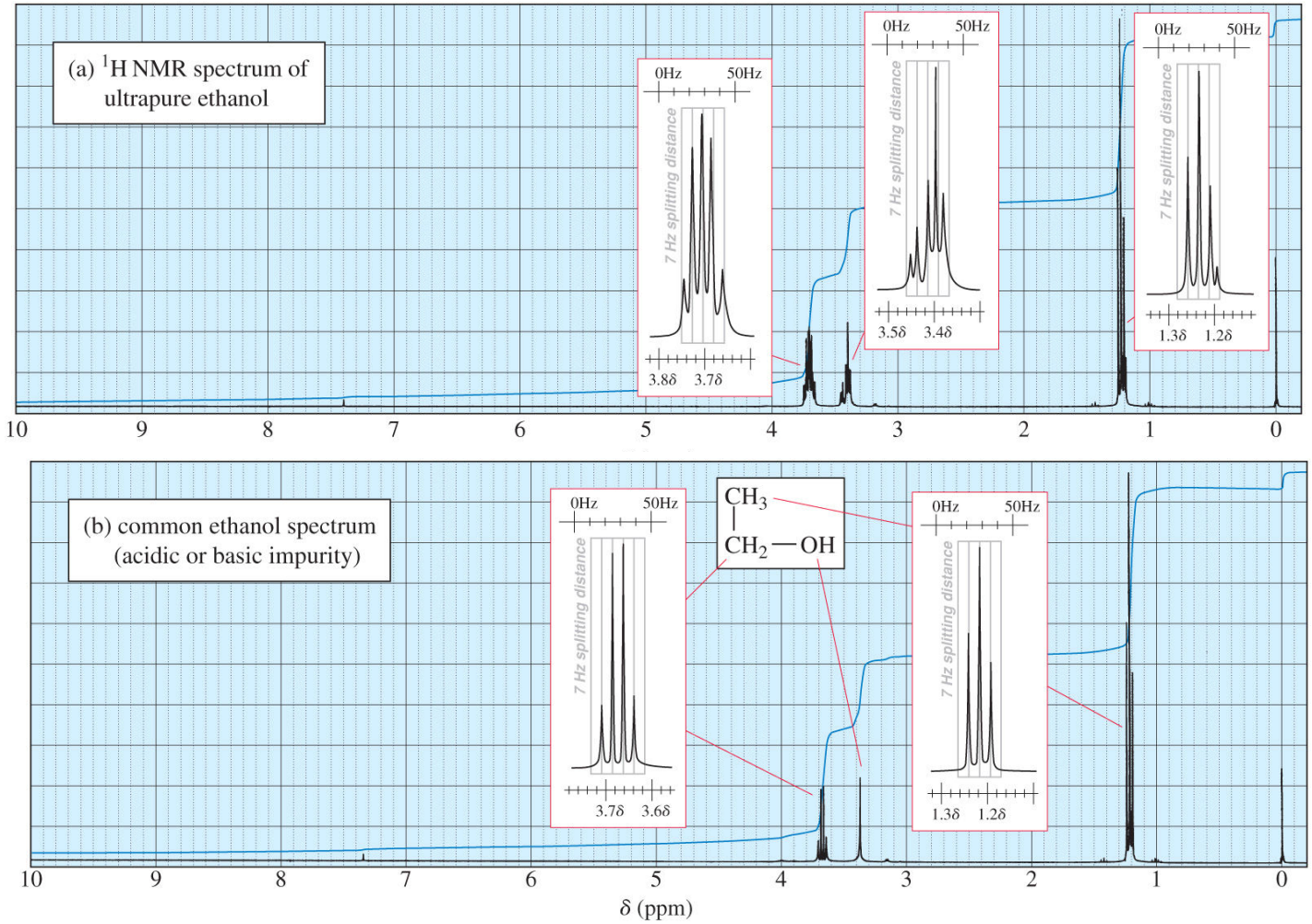


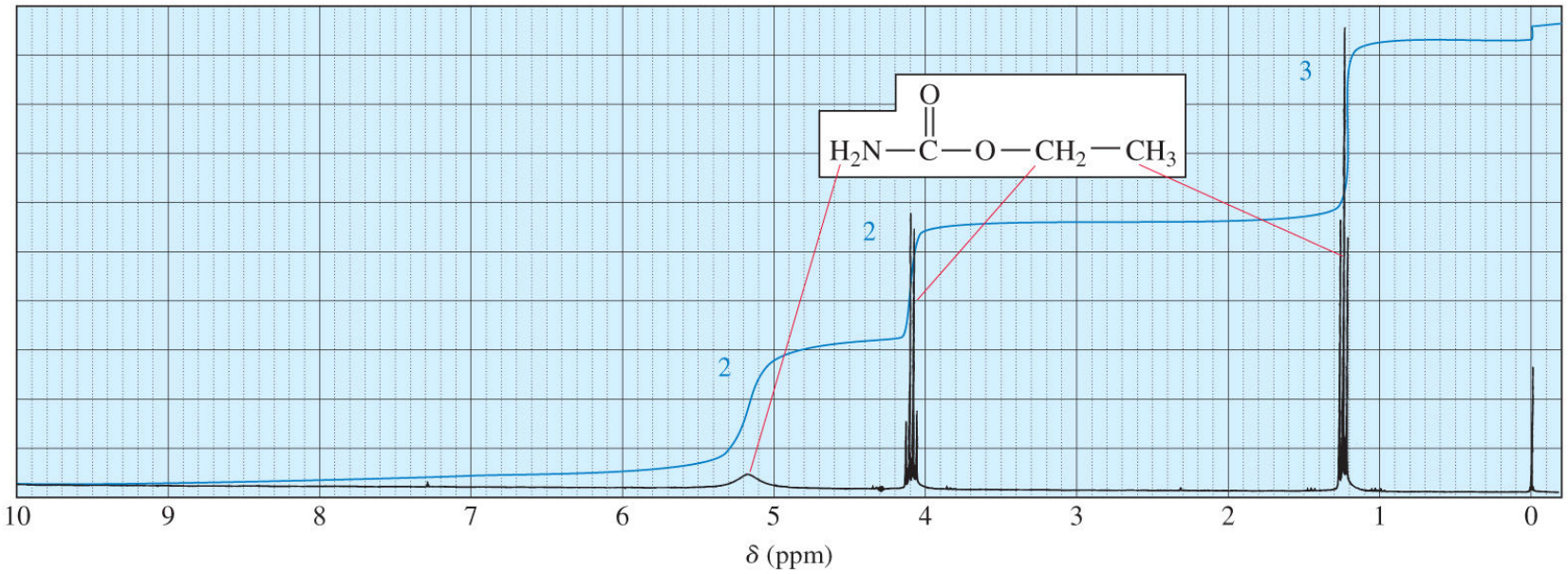
p-disubstituted aromatics

2 doublets integrating for 2 H each

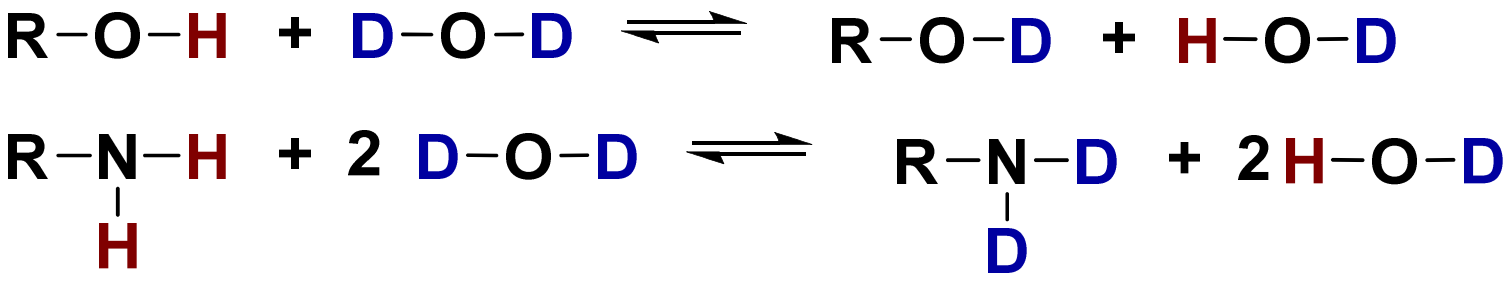


Signals for proton on heteroatoms (NH, OH) are often broad and difficult to see and may not be split. This depends on the concentration and purity of the sample.



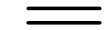
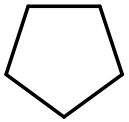
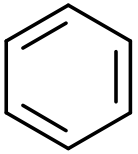


- **Usually these protons can be exchanged with D_2O.**
- **To verify that a particular peak is due to O—H or N—H, shake the sample with D_2O too exchange the H for a D. The deuterium is invisible in the proton NMR so the original signal for the OH will disappear.**



Index of Unsaturation (3.1)

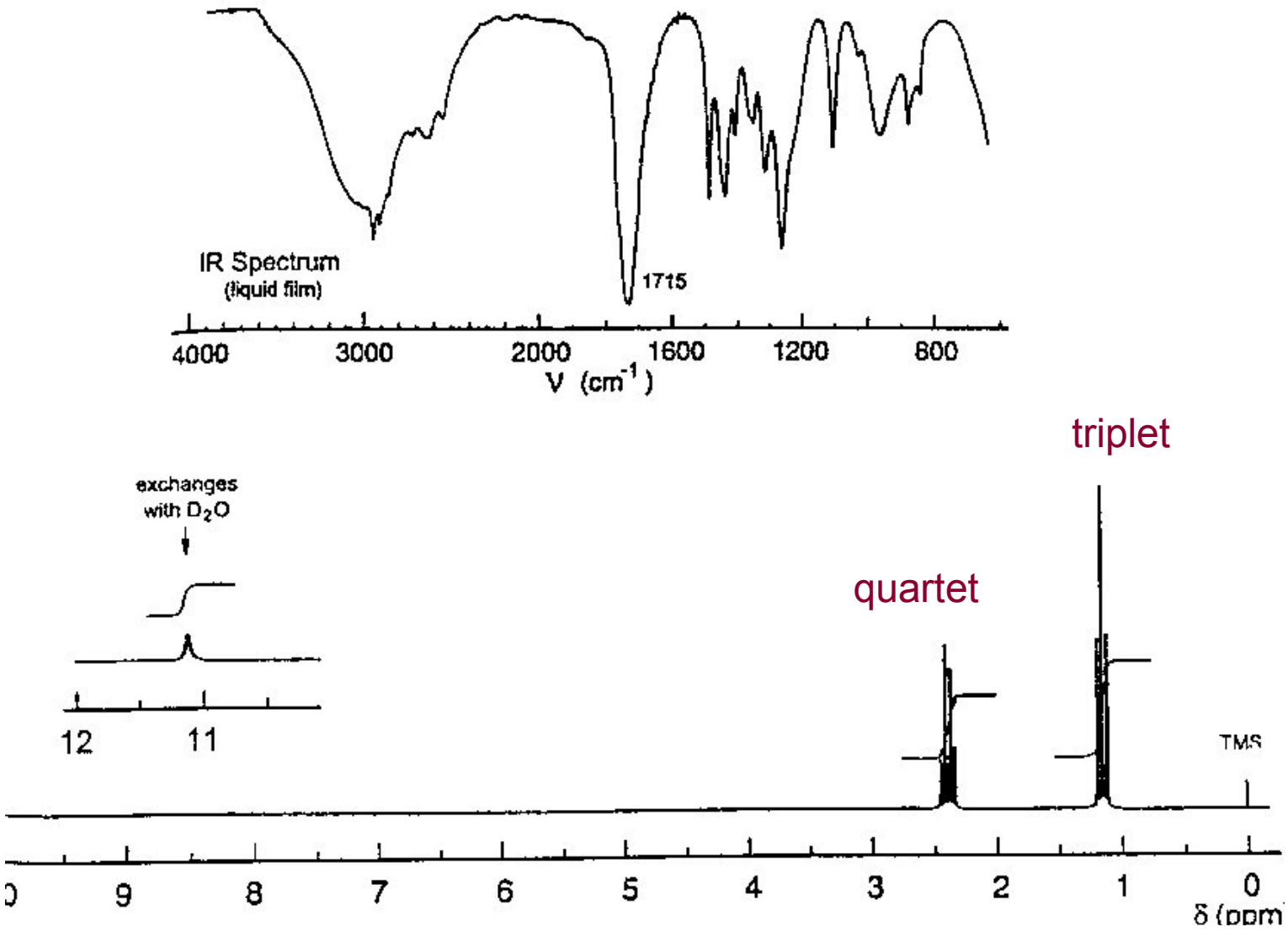
- **This is useful to help determine some characteristics (ring, double bonds, etc…) of the structure of an unknown compound. It represents the # of H_2 molecules one would have to add to a structure to get a fully saturated compound (see CHEM201).**

groups	unsaturation index
	1
C=O	1
	1
	2
C≡N	2
	4
combination	adds up

Steps to determining structure

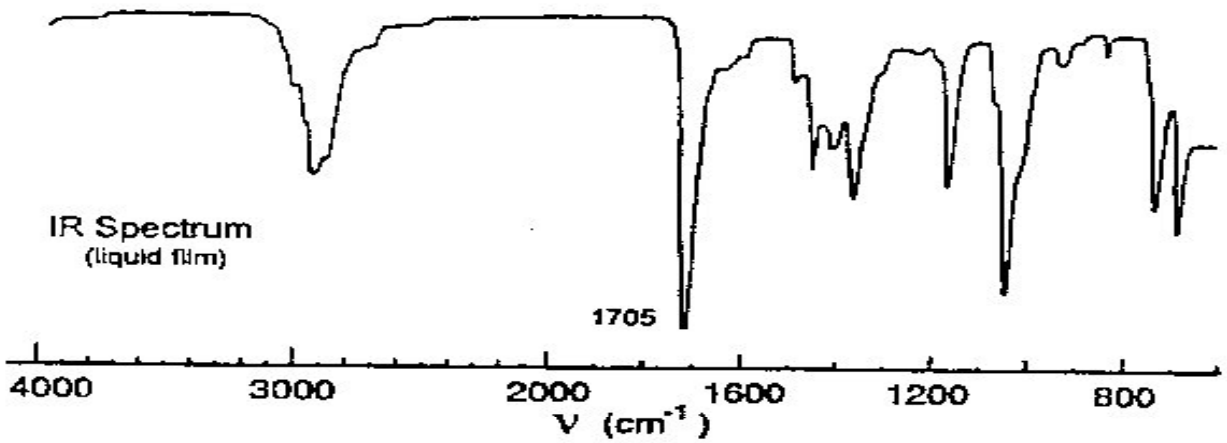
1) Determine unsaturation index from formula
2) If you have no formula, find M^+ in mass spectrum and note the mass
3) From IR, determine possible functional groups
4) From NMR, determine portion of structure from chemical shifts, splitting patterns, and integration
5) Substrat the groups that you have already found from the molecular formula as you go until you have found all the pieces of the puzzle. Then put pieces together.

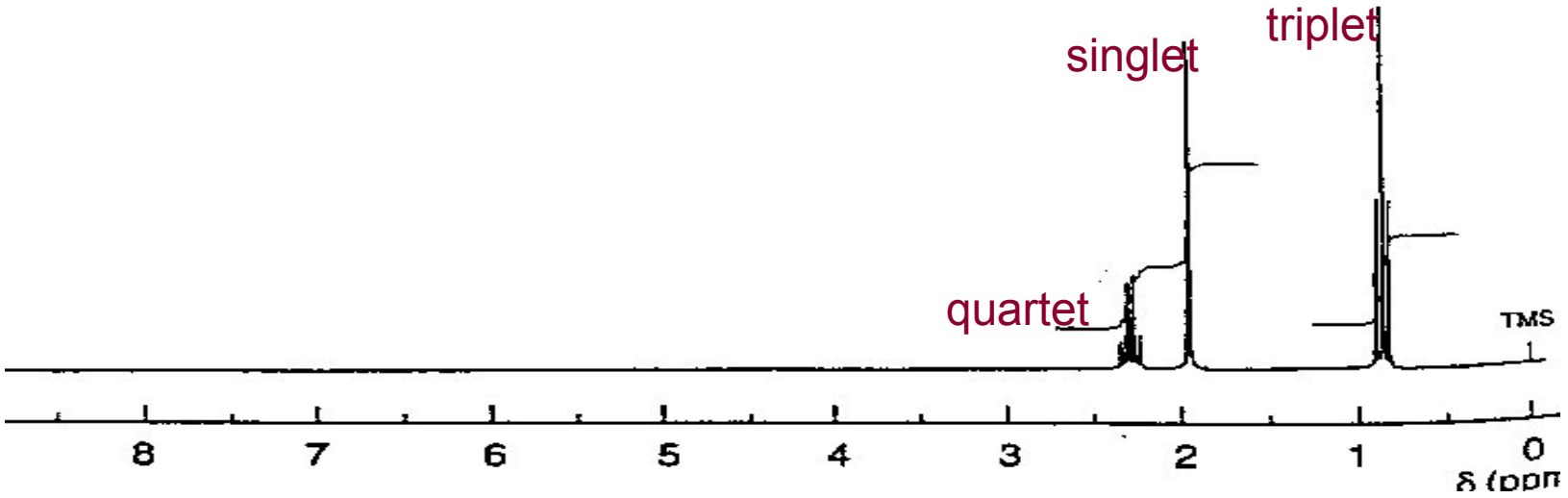
Unknown #1: $C_3H_6O_2$



Unknown #1: $C_3H_6O_2$ Summary

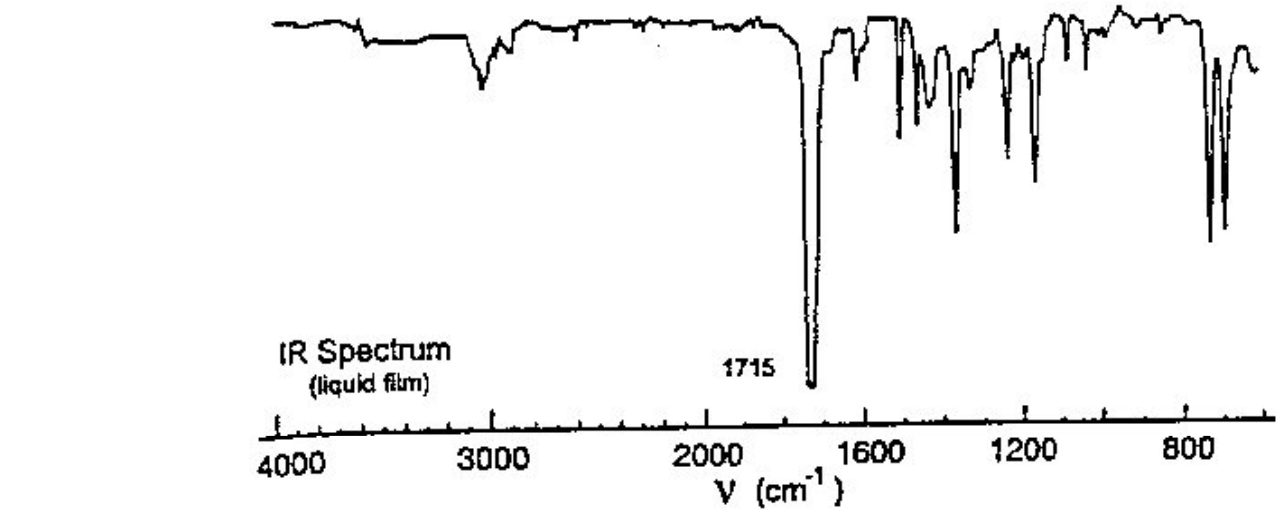
Unknown #2: C_4H_8O

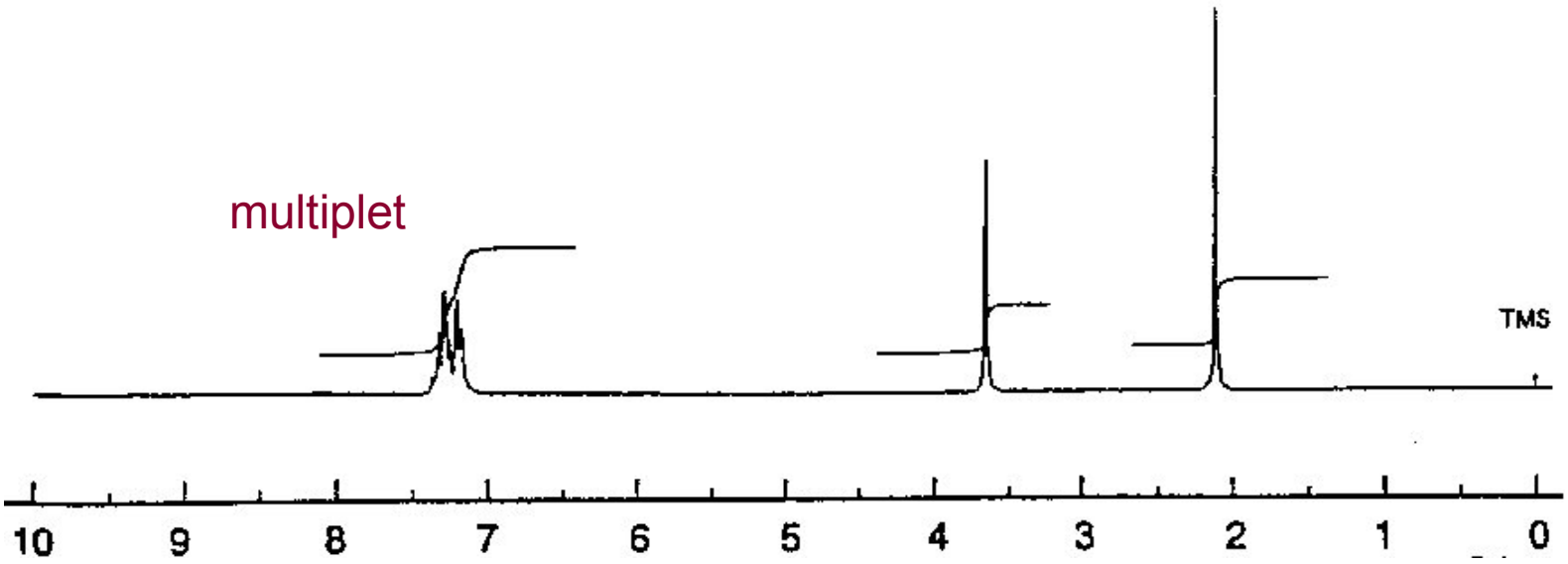




Unknown #2: C_4H_8O Summary

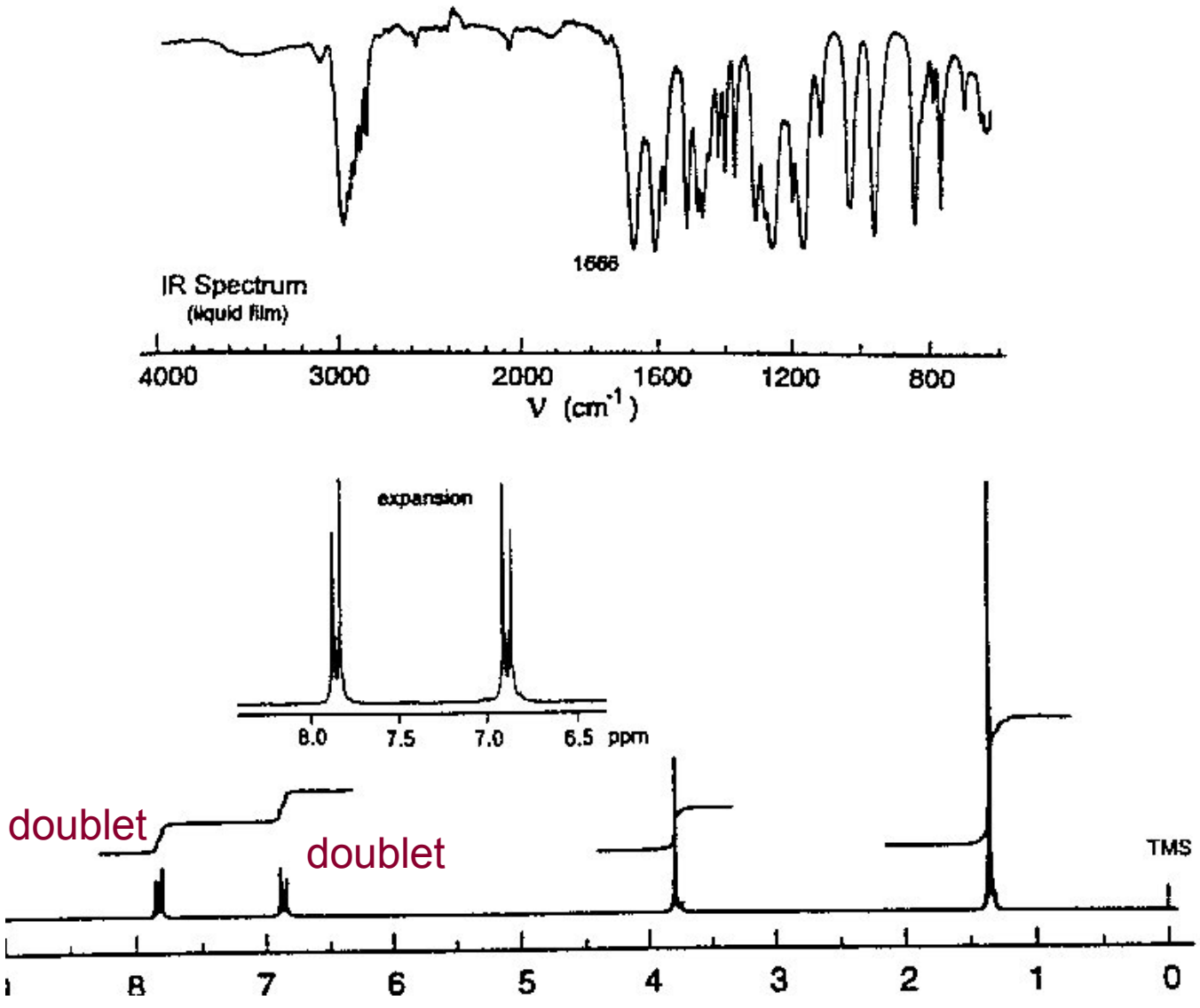
Unknown #3: $C_9H_{10}O$





Unknown #3: $C_9H_{10}O$ Summary

Unknown #4: $C_{12}H_{16}O_2$



Unknown #6: $C_{12}H_{16}O_2$ Summary

Lecture 1
Mass Spectra

Mass spectroscopy can be used can be used to:-

1) Measure relative molecular masses (molecular weights).

2) Detect the places in molecules at which it prefers to fragment.

The principle of the mass spectroscopy:-

The function of mass spectrometer may be divided into four sections sample injection, ion generation, mass separation and ion detection.

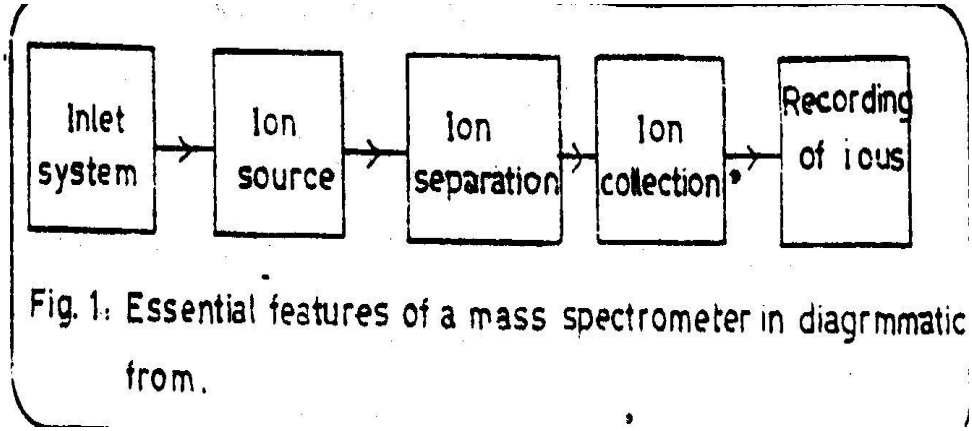


Fig. 1: Essential features of a mass spectrometer in diagrmmatic from.

a- sample injection:-

There are two ways to inject the sample the spectrometer one is the gas inlet and the other is the direct inlet.

gas inlet application:-

for liquid or gaseous sample, liquid can either be injected with micro syringe and it can be heated (max. temperature during continuous service is usually 150°c). Gaseous sample can be introduced into the reservoir though a container fitted with a break-seal, volatile substance via a gas chromatograph (GC) or liquid chromatograph (LC, HPLC).

b- direct inlet application:- crystalline, lacquer-like or viscous liquid samples. The sample is placed in a metal crucible, which is fixed on the tip of a heat able probe and the probe is inserted into a lock-chamber. After evacuating the chamber, the cold tip of the probe is brought into the ion source and slowly heated until the sample vaporizes.

Ion generation:- from one of the inlet system, a fine and constant beam of the molecules streams into the ion source where it intersect with an electron beam,

where 60 to 100 eV can be used, although 70 eV is used for normally employed, the interaction between the electrons and the neutral molecules generates positively charged molecular ion according to:

$$[M] - e^- \rightarrow [M]^{+\bullet} + 2e^-$$

The various positive ions generated by electron impact are then accelerated through a second slit by a repelled potential applied between and (A) and (B)

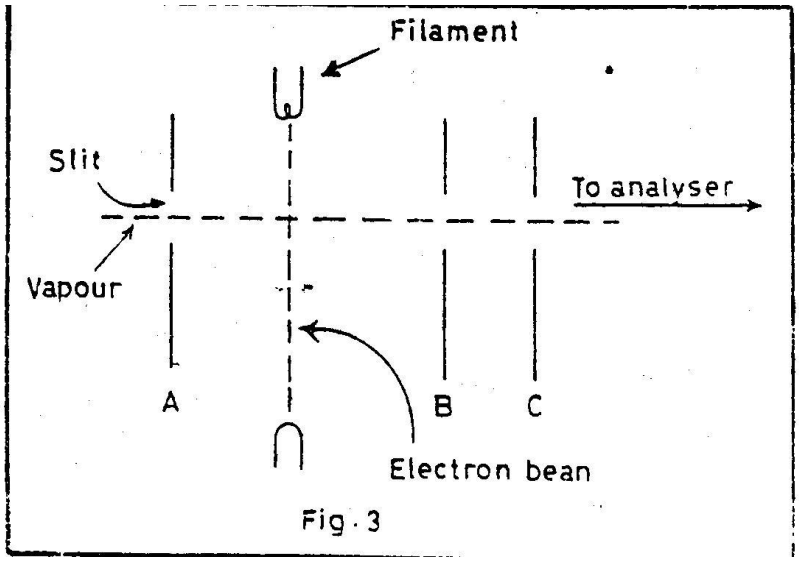


Fig . 3

Finally, a large accelerator potential is applied between B and C, and the positive ion travel with a high velocity according to equation (1).

$\frac{1}{2}$ $mv^2 = ev$……..(1)

(m) is the mass of the ion, (e) the electronic charge, (v) the potential of the ion accelerating plate, and (v) the velocity of the particle.

Mass separation:-

The accelerated ions then pass into the magnetic field (H) generated between the two poles of an electromagnetic in the magnetic field the ions are deflected along the circular path according to Eq. (2).

$r = mv/eH$ ……(2)

r is the radius of the path

From Eq. (1) and (2) we can deduce the Eq. (3)

$m/e = H^2r^2/2V$

From this we can conclude that, at given values of (H) and (V), only particles with a particular mass-to-charge will arrive at the collector slit placed along the fixed path (r) in recording mass spectra of organic compounds, most of the

particles are singly charged, the radial paths of allowed by in the magnetic field are illustrated in Fig. (4)

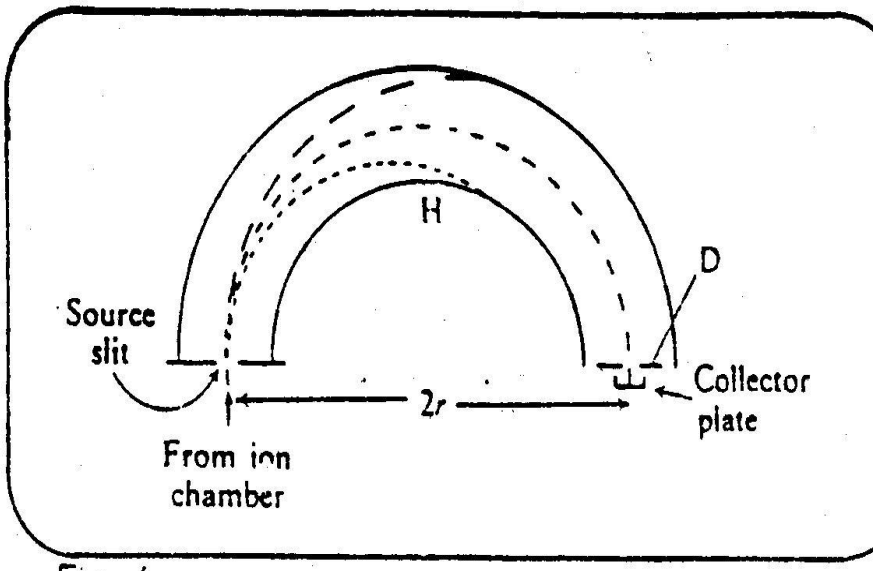


Fig.4:

Lecture 2

Determination of molecular formula

The molecular weight of methyl bromide is 94.95 on chemical scale. But in mass spectra we can find the following molecular ion peaks according to isotopes occur. They called M, M+1, M+2, M+3,……..

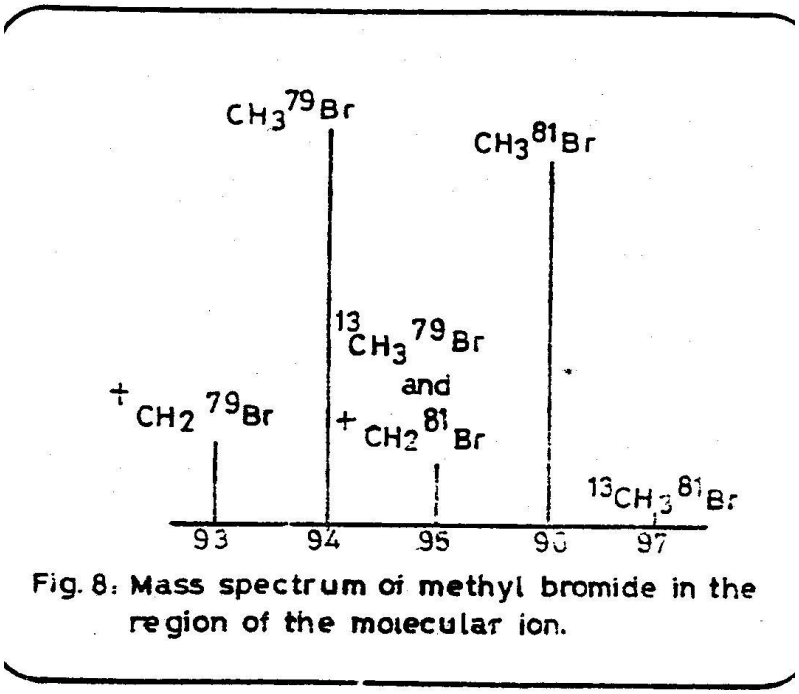


Fig. 8: Mass spectrum of methyl bromide in the region of the molecular ion.

Elemental composition at nominal mass 43

Mass vs. elemental composition at nominal mass 43

Mass	Elemental composition
43.0058	CHNO
43.0184	C_2H_3O
43.0269	CH_3N_2
43.0421	C_2H_5N
43.0547	C_3H_7

Elemental composition at nominal mass 28

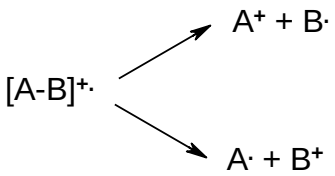
(Table 1)

Exact masses of some common isotopes and simple molecular species.

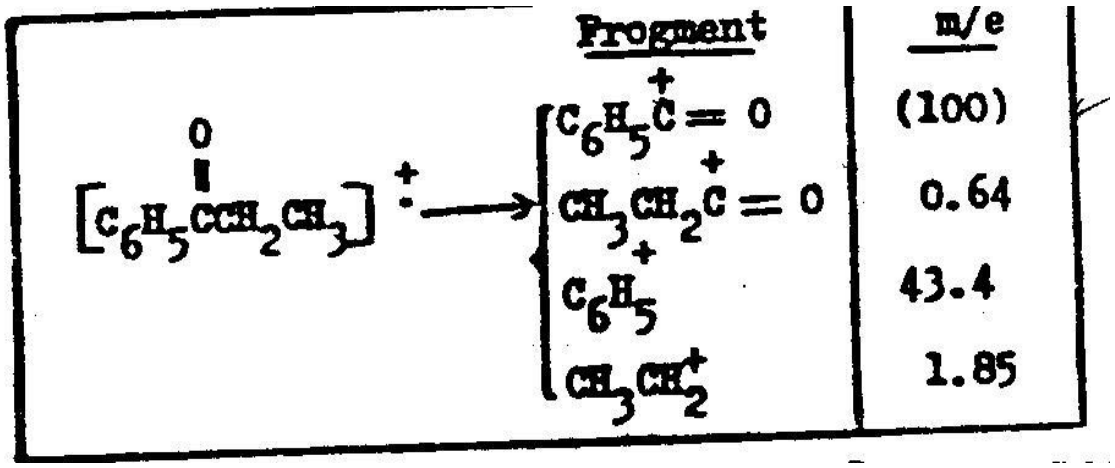
Species	^{1}H	^{16}O	^{14}N	CO	$CH_2{=}CH_2$	N_2
Mass	1.00782	15.9949	14.0031	27.9949	28.0313	28.0061

Fragmentation

Fragmentation are best interpreted based on the know stability of the carbonium ions and free radical.



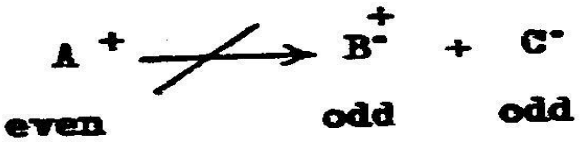
In the cases where both A+ and B+ contions are of similar stability, the positive charge will reside with the highest-molecular weight cationic fragment. e.g. the following table:-



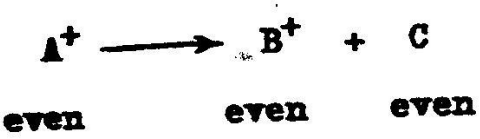
The $C_6H_5O^+$ ion at mass (105) in the spectrum of propiophenone can be characterized as (M-29) or the (M-C2H5) ion.

(i) The even-electron rule:-

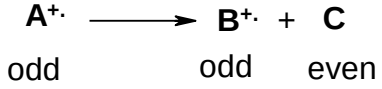
Even-electron spices will not fragment to two odd-electron species.



An ion will degrade to another ion and a neutral molecule.



Radical ion is odd-electron species so it will degrade to a radical ion and a neutral molecule.



Also radical ion also degrades to ion radical and ion.

ion as coproduct

$$A^{+\cdot} \longrightarrow B^{+} + C$$

(odd) (odd)(even)

Radical ions can also degrade to a radical and an ion

$$A^{+\cdot} \text{ (odd)} \longrightarrow \begin{cases} B^{+} + C^{\cdot} \text{ (even) (odd)} \\ B^{\cdot} + C^{+} \text{ (odd) (even)} \end{cases}$$

Lecture 3

(ii) Most of the important types of fragmentation are summarized in general form below.

A. Simple carbon-carbon bond cleavages

a. $\left[R-\overset{|}{\underset{|}{C}}-\right]^{+\cdot} \longrightarrow R^{+} + \cdot\overset{|}{\underset{|}{C}}-$

b. $R-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}^{+} \longrightarrow R^{+} + \diagdown C{=}C \diagup$

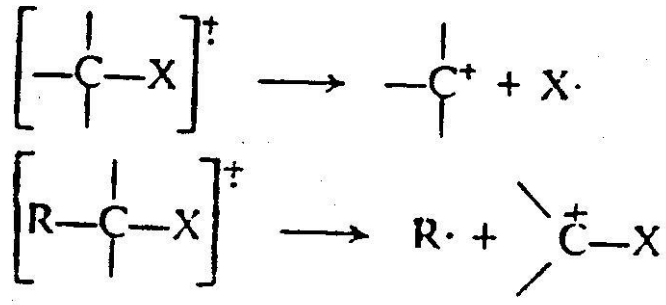
$CH_3 < CH_2R' < CHR'_2 < CR'_3 < CH_2{-}CH{=}CH_2 <$ 

c. $\left[R-\overset{O}{\overset{\|}{C}}-R\right]^{+\cdot} \longrightarrow R\cdot + R\overset{+}{C}{=}O$

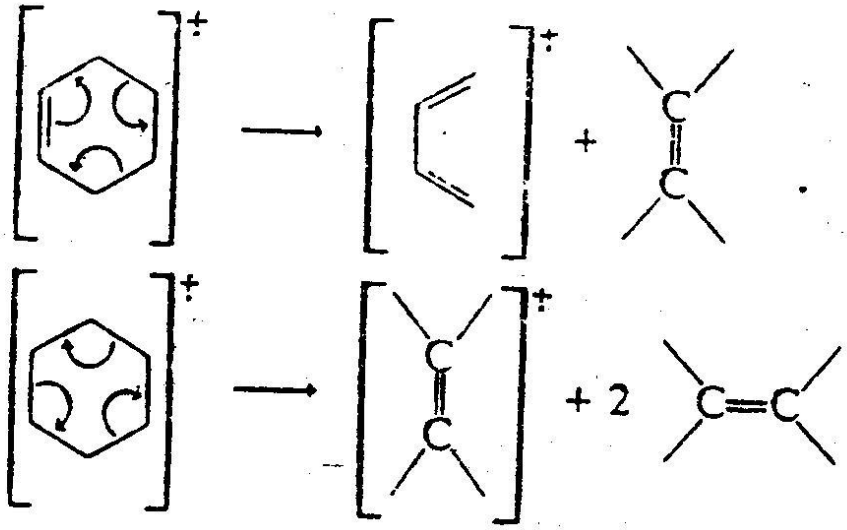
d. $R-\overset{+}{C}{=}O \longrightarrow R^{+} + C{=}O$

B. Cleavages involving heteroatoms:

X = halogen, OR′, SR′, NR'_2 (R′ = H, Alkyl, Aryl)



C. Concerted cleavages:



(iii) Factors influencing fragmentation

a) Functional groups:-

Some functional groups may direct the course of fragmentation, while other functional groups may have little effect.

b) Thermal decomposition:-

Thermal decomposition of some compounds may occur before ionization leading to difficulty in interpreting the mass spectra, alcohols may dehydrate before ionization, loss of water in this case leads to a peak at M-18.

Whether the loss occurs before or after ionization, but thermal dehydration may extensive enough to eliminate entirely the appearance of a molecular ion in the spectrum.

If the thermal decomposition is suspected, the compound can be ionized in a cooled ion source, so that electron bombardment of the whole molecule takes place.

c) Bombardment energies:-

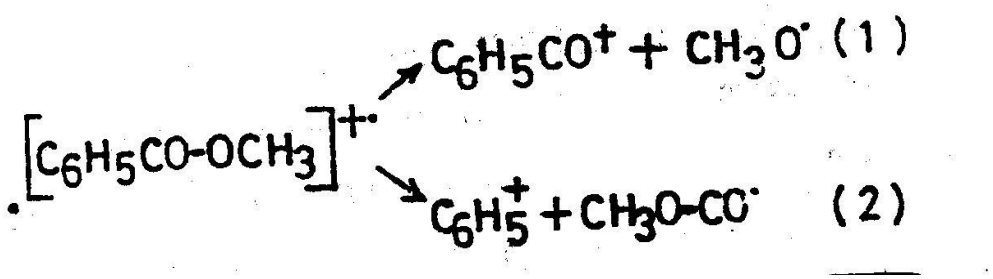
≈ 70 eV is used for ordinary spectra, molecular ions posses a maximum of ≈ 6 eV in excess of their ionization potentials, if this energy is reduced to ≈ 20 eV it will be sufficient for giving weaker spectra for the organic molecules.

d) Relative rates of competing fragmentation routes:-

The formation of B^+ and $C^{\cdot}$ or $B^{+\cdot}$ and C from the molecular ion $A^{+\cdot}$ depends on the excitation energy possessed by $A^{+\cdot}$ and the heats of formation of all the products.

e) Stability of fragmentation products:-

An ion fragments when it possesses an excess internal energy sufficient to exceed the activation energy for the reaction considered. (See the following figure)



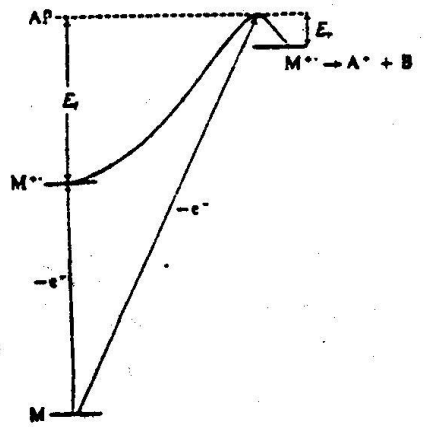


Fig. 9: Energy diagram showing the relationship between the activation energies (E_f, E_r) for the forward and backward reactions in the decomposition of the ion ($M^{+\cdot}$) to fragments (A^+, $B^{\cdot}$). The appearance potentail for the process is marked (AP).

The activation energy for the reverse reaction (E_r) is very small.

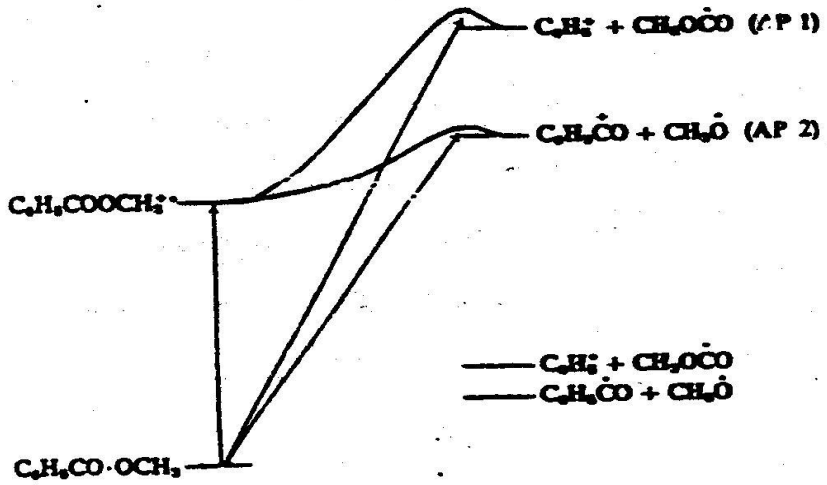


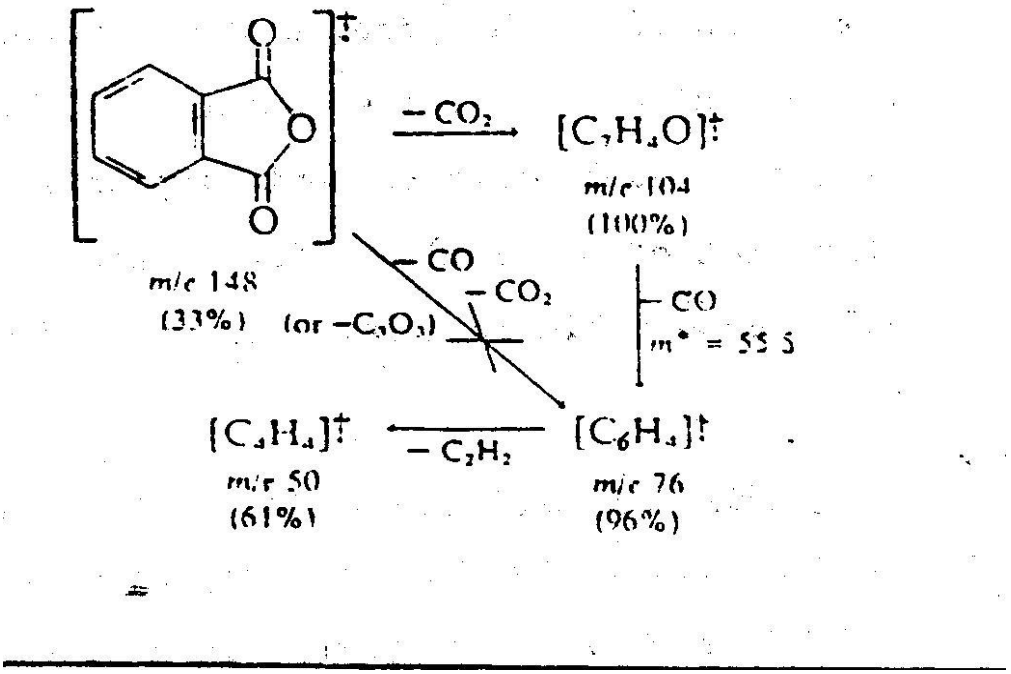
Fig.10: Energy diagram showing relation between competing fragmentation processes from one state of the molecular ion of methyl benzoate. The appearance potentials (AP1, AP 2) relate to the two reactions.

Lecture 4

IV- Metastable peak

Metastable peaks are very important in the deduction of fragmentation mechanisms because they indicate that the fragment of the mass (m_2) is formed in a one-step process from (m_1) will decompose into fragments while traveling through the accelerating region of the instruments. Such ions will at first be accelerated as (m_1), decompose with loss of some kinetic energy to the neutral fragment, and then continue to be accelerated and deflected as (m_2). Which appear as abroad peak of low intensity (m*).

$$m^* = (m_2)^2 / (m_1)$$



In the above example the metastable peak

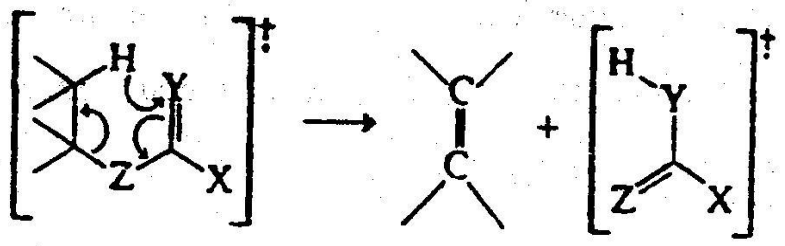
(m*) at 55.5, this mean that the ion at m/e=76 (m_2) formed from the m/e 104 (m_1) ion and not by concerted loss of carbon monoxide and carbon dioxide from the molecular ion.

V-Rearrangements

There are fragment peaks in the mass spectra which can not be interpreted by the simple methods of the normal cleavage. So there are some specific rearrangements occur to molecules as follow:-

a- McLafferty rearrangement:-

This type of rearrangement involves migration of hydrogen to π-electron system via a six-membered ring transition state.

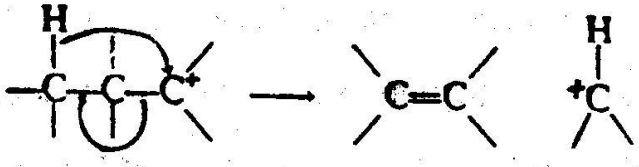


X, Y, and Z can be O, N, C, S, and any combinations thereof.

b- 1,3-migration in carbonium ions:-

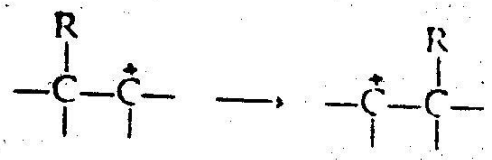
This involves migration of hydrogen atom from C4 to C3 in the same molecule with elimination of an alkane.

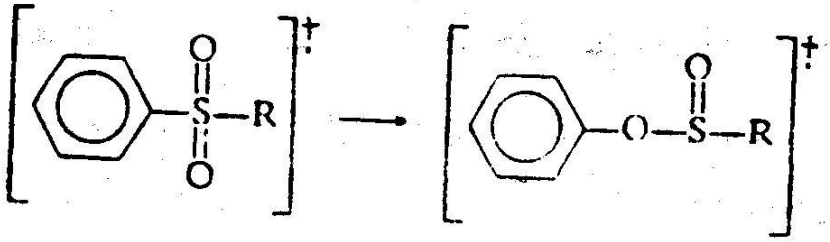
(ii) Carbenium ions undergo 1,3 migrations with elemination of an alkene.



c)- 1,2- shifts:-

This type of rearrangement is to formation more stable species.





The most famous rearrangement of this type is the formation of <u>tropoylium ion</u> before loss of hydrogen atom, thus <u>tropoylium ion</u> $C_7H_8^{+\cdot}$ has equivalent hydrogen, when it loses one hydrogen atom it converts to the most abundant ion $C_7H_7^+$ of mass (91) according to the following:-