Paper VI Organic Chemistry -II

Unit I :

UV, IR & Mass Spectroscopy

Absorption spectra of conjugated dienes & α, β – unsaturated carbonyl compounds – Woodward – Fieser rules – spectra of aromatic and heterocyclic compounds – Scott's rule – solvent effects.

Vibrational frequencies of alkanes, alkenes, alkynes, aromatic compounds, alcohols, ethers, phenols, amines, acids, esters, & amides.

Effect of hydrogen bonding & solvent effects on absorption frequencies Fermiresonance.

Molecular ion peak – Base peak – metastable peak – nitrogen rule – Mc, Lafferty rearrangement – isotopic peaks – fragmentation pattern of organic compounds.

Unit II

^{1}H-NMR-^{13}C – NMR, ORD & C,D

^{1}HNMR – principles of NMR – Chemical shift – spin – spin coupling, delta & tall values of aliphatic, olefinic, aldehydic, aromatic, carboxylic, enolic, phenolic, alcoholic protons.

Chemical exchange – deuteration – simplification of complex spectra – double resonance – shift reagents.

^{13}C NMR – chemical shift & coupling constants of aliphatic, aromatic & carbonyl carbons.

ORD & CD – Principle – Types of ORD curves – α, haloketone rule – octant rule – applications of these in the determination of configuration & conformation of simple monocyclic & bicyclic ketones.

Unit III Terpenes :

Structure and Synthesis of α, pinene, zingiberene, r-bisabolene α, – santonine, abietic acid – Biosynthesis of alkaloids.

Steroids :

Classification – structure elucidation of choleterol – synthesis of ergosterol androsterone, testosterone, estrone & progesterone – Bile acids.

Prostoglandins :

General study – structure & synthesis of PGE1 & PGF1

Vitamins:

Vitamin A1, B1, B2, B6, C, D, & E

Unit IV

Organic Photochemistry

Thermal & Photochemical reactions – Allowed & forbidden transitions – Jablonski diagram, photochemical reactions of metones – photosensitisation – Norrish Type I & II reactions – Paterno – Buchi reaction.

Pericyclic reactions – conservation of orbital symmetry – electrocyclic reactions - cycloaddition reactions and sigmatropic rearrangements – Applications of correlation diagram approach, Huekel – Mobius approach to the above reactions.

Molecular Rearrangement:

Migratory aptitude of groups – Mechanisms of the following rearrangements – Wagner – Meerwin, Demjanov, Baeyer Viilage oxidation – Favorski, dienone – Phenol, di – π – methane, Stevens, Sommelet – Hauser, Free radicals, Stability of free radicals. Barton, Ullmann, Hunsdiecker, Hofmann – Lofler – Freytag reactions.

Unit V

Reagents in Organic synthesis

Use of the following reagents in organic synthesis – complex metal hydrides – lithium dimethyl cuprate, lithium di-isopropylamide, DCC, Trimethyl silyl Iodide, DDQ, SeO_2, Peterson's synthesis.

Organiometallic reagents methyl lithium, aluminium tertiary butoxide, aluminium isopropoxide.

Planning Synthesis:

Synthon – synthetic equilvalent – Relay, Linear & Convergent synthesis functional group interconversions – use of activating & blocking groups – stereoselective problems of geometrical & optical isomerism – retrosynthetic analysis of γ-Bisabolene & cis – Jasmone.

Transition metal complexes in organic chemistry – homogeneous hydrogenation – diastereo selectivity enantioselectivity.

UNIT I

UV – VISIBLE SPECTROSCOPY

It is possible in molecules to have electronic excitation due to an electron transition from the highest occupied (HOMO) molecular orbital to the lowest unoccupied molecular orbital (LUMO), by absorption of light energy. Three such transitions can normally occur

1) $\sigma \rightarrow \sigma^*$

(bonding σ M.O to antibonding σ* M.O)

This transition occurs in the high energy far-UV region at around 150 nm, possible in saturated organic molecules.

2) $\pi \rightarrow \pi^*$

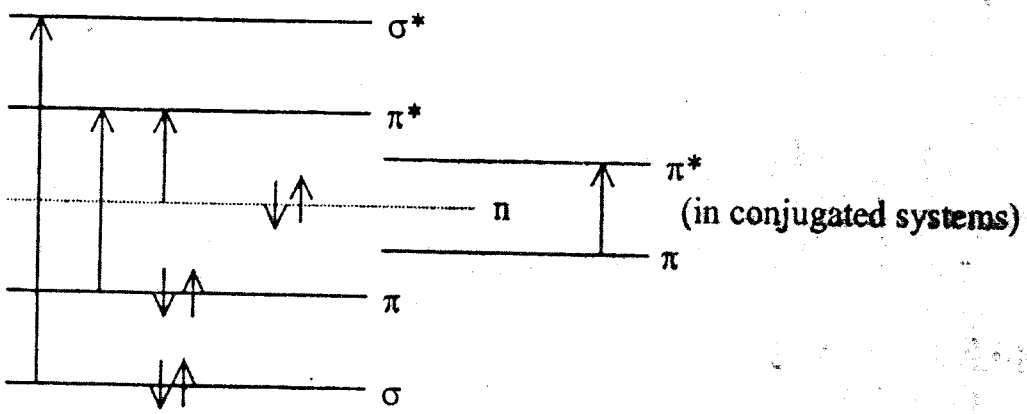
(bonding π M.O to antibonding π* M.O)

This transition occurs in a relatively lower energy but still in the far-UV region at around 170 – 185 nm, observed in unsaturated groups such as C = C, C = O etc, with high intensity.

3) $n \rightarrow \pi^*$

(non-bonding M.O to an antibonding π* M.O)

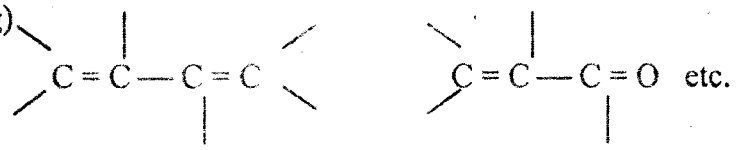
This transition occurs in molecules with lone pairs of electrons present in non bonding molecular orbitals, involving the lowest energy possible for any electronic transition, in the UV region (280 nm). However the intensity of this transition is very poor due to the forbidden nature of this transition.



(common electronic transitions observed in organic molecules)

A ($\pi \rightarrow \pi^*$) transition being the most intense among the possible electronic transitions, becomes important in unsaturated organic molecules, but this occurs in the far-UV region. However, it can be shifted well within the UV region, by

effecting conjugation in the unsaturated system. A conjugated diene, for example 1,3 - butadiene absorbs at 217 nm and a conjugated ketone at around 220 nm, with a shift of nearly 30 nm to the higher wavelength region. This portion of the molecule which is responsible for the UV absorption is called a chromophore.

(e.g)  etc.

The additional double bond present in the conjugated system has shifted the wavelengths of absorption (λ max) to a higher region and is called a red shift or bathochromic shift. Groups such as an alkyl, halide etc attached to the chromophore can also cause a red shift. Groups such as – OR, NH_2, NR_2 etc when attached to the chromophore can also cause bathochromic shift through involvement of their lone pairs of electrons in conjugation, and called auxochromes.

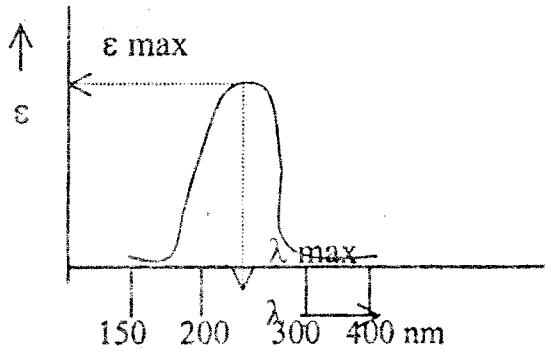
When the UV absorption is shifted towards a shorter wavelength it is called a blue shift or hypsochromic shift. (e.g) λ max of aniline changes from 280 nm to 203 nm when acidified, due to loss of lone pairs over nitrogen.

UV Spectrum

Absorption of UV light by molecules causing electronic transitions, is governed by the Beer – Lambert's law:

$\log (I_0 / I) = \varepsilon c l$ where $\log (I_0 / I)$ is called absorbance, I_0 being the incident light-intensity and I, the intensity of the transmitted light. ε is called the absorptivity or the molar extinction coefficient, and C and l are the concentration of the solute sample and length of the sample respectively.

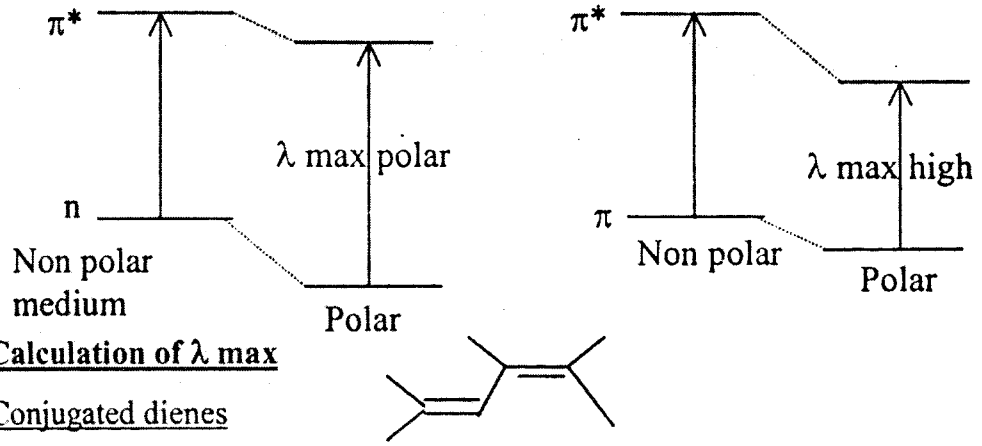
When absorptivity is plotted against the wavelengths of absorption, the UV absorption spectrum results.



The spectrum appears in the form of a band and not lines or peaks, as a single electronic transition is superimposed by a number of simultaneous vibrational and rotational transitions. For a UV spectrum both the λ max, the wavelength of maximum absorption as well as ε max, the maximum intensity of absorption, are significant. The intensity of absorption can be enhanced by attaching an auxochrome. This effect is called hyperchromic effect. The decrease in intensity of absorption by certain groups which causes distortion of the geometry of the molecule, is called hypochromic effect. The R – band of keto groups in aldehydes and ketones due to n → π* transition, has a very low intensity ($\varepsilon_{max} \sim 10^2$), whereas the K-band due to π → π* transition is highly intense ($\varepsilon_{max} \sim 10^4$). In contrast, the R-band appears at a higher λ_{max} (280 – 320 nm) compared to lower values for the K-band (210 – 240 nm).

Solvent Effect

It has been observed that the λ max is very much affected by the polarity of the solvent. The n → π* transition is shifted to shorter wavelengths and the π → π* band appears at longer λ max, since there is a greater stabilization of the nonbonding orbitals in polar solvents entering into hydrogen bonding, hence an increase of energy for the n → π* transition. The π* orbital is also more stabilized compared to a π orbital hence a decrease of energy for a π → π* transition.



Calculation of λ max

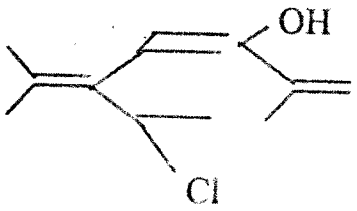
Conjugated dienes

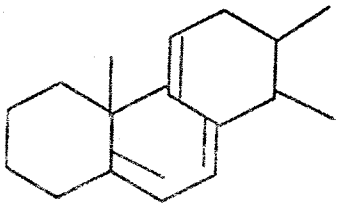
Conjugation of a double bond (C = C, C = O etc) has been found to be the single largest factor affecting the λmax of an olefinic or a keto group, apart from the attached auxochromes. The presence of these factors have an additive effect on the λmax, since each factor contributes by a certain increment. This facilitates calculation of λmax of cyclic as well as acyclic polyene systems, following certain empirical rules formulated by *Woodward* and *Fieser*.

1. Conjugated dienes have a base value of 215 nm, but homo-annular dienes absorb at a base value of 253 nm.
2. Each alkyl substituent attached to the chromophore contributes 5 nm. Ring residues can also be treated as alkyl groups.

3. Each extended conjugation contributes 30 nm.
4. An exocyclic double bond contributes 5 nm.
5. Auxochromes such as halogen and OR contributes 5 nm, whereas an SR function contributes 30 nm and NR_2 group 60 nm.

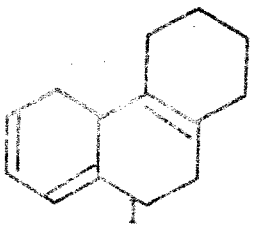
Based on these rules the λmax of the following compounds could be calculated.





Base value	= 215	Base value (homo annular diene)	= 253
extended conjugation	= 30	extended conjugation	= 30
4 alkyl group	= 20	ring residues 5×5	= 25
(no contribute for OH, Cl etc)		3 Exocyclic double bonds	=15
Total	= 265 nm		= 323nm

The rules are very helpful to distinguish between similar compounds using UV spectroscopy. The following pairs differ in their UV spectrum, as their λ max are different.



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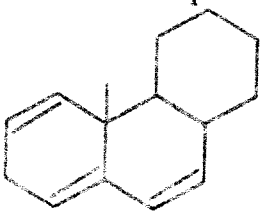


II

Base value (homo annular dine)	= 253 nm	Base value (homo annular dine)	= 215 nm
extended conjugation	= 0	extended conjugation	= 0
3 ring residues	= 15nm	3 ring residues	= 15nm
1 exocyclic double bond	= 5 nm	1 exocyclic double bond	= 5 nm
λmax	= 273 nm	λmax	= 235 nm

A cis and trans diene also differ (e.g) trans stilbene absorbs at λmax (295nm) compared to cis (283 nm).

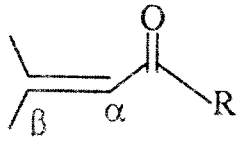
α,β -unsaturated Carbonyl Compounds

The Woodward – Fieser rules enable the calculation of λ max for the intense $\pi \rightarrow \pi^*$ transitions and not for the longer λmax of $n \rightarrow \pi^*$ transitions which are week.

Mass

The calculation is similar to that of the conjugated polyenes, but depending on the nature of the carbonyl group, the position of the substituent and the size of the ring, the value changes marginally. The rules may be summarized as under:

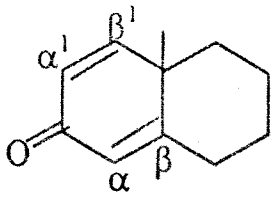
1. A base value of 215 nm, for all acyclic as well as cyclic (6 membered) ketones. Base value is 202 nm for 5 membered ring ketones.



R = H – aldehydes
R = alhyl – ketone
R = alkoxy – ester

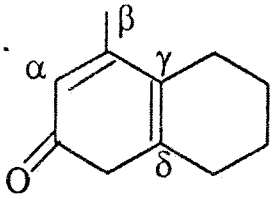
2. For aldehydes the base value is 207 nm and for esters it is 197 nm.
3. For each extended conjugation 30 nm is added.
4. When two double bonds are in Cis position, 40 nm is to be added.
5. When an alkyl group or ring residue is at α,β or γ position, 10,12 or17 nm respectively are added. Alkoxy groups at these positions contribute 35,30 0r 17nm. Hydroxyl groups contribute 35,30 and 30 respectively.
6. A Cl at α and β position contribute 15 and 12 nm whereas a Br contributes 25, and 30 nm respectively.
7. An exocyclic double bond contributes 5 nm.
8. A β - substituent like NR_2 or SR will contribute 95 and 85 nm respectively.

An application of UV spectroscopy to distinguish between the following pairs of isomeric ketones is illustrated as under.



Base value = 215
2 β sub = 24
1 exocyclic = 5
λ max = 244 nm

and

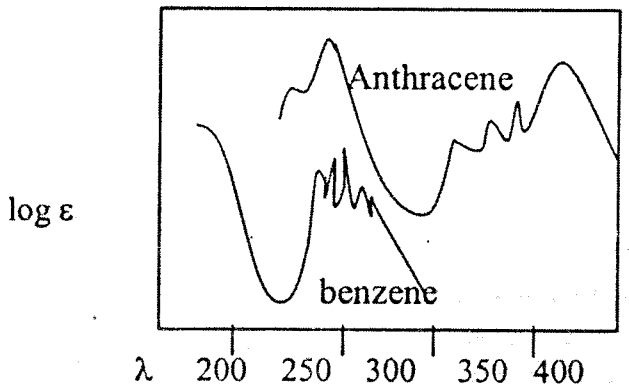


Base value = 215
Cis diene = 40
extended conjugation = 30
β-subs = 12
γ + 2δ sub = 54
λ max = 351

(In a system of cross conjugation, the more substituted chromophore results in the spectrum)

The above two spectra are hence drastically different, and the molecules could be easily distinguished. Similarly, an α, β unsaturated Cis and tran acids are distinguished by the UV spectrum, since the trans always absorbs at a higher λ max than the Cis. Trans cinamic acid absorbs at 272 nm and cis form, at 268 nm.

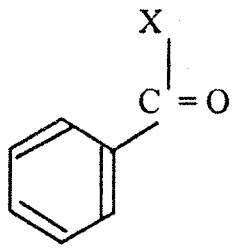
Aromatic Benzenoids



(uv fine spectrum of benzene and anthracene)

The UV absorption spectra of benzenoid compounds have a fine structure, well marked in the vapour phase, but in the liquid phase and in polar solvent it is less apparent. When substituted by alkyl groups λ max slightly increases due to hyper conjugation but electron releasing OH, NH_2, OR etc, not only enhance the λ max, but also destroy the fine structure. Benzene has absorptions at 184, 229, 234, 239, 243, 249, 254, 260 and 268 nm in ethanol with the intensity steadily increasing and then decreasing as in the diagram, with a fine structure. The $\pi \rightarrow \pi^*$ transition results in an intense band (K band) but below the UV region. The fine spectrum is due to the B band resulting from the superposition of vibrational absorption with electronic absorption. An $n \rightarrow \pi^*$ band called R band appears at a high λ max with low intensity.

Scott's Rules for λ max calculation of acylbenzene derivatives are as given below.



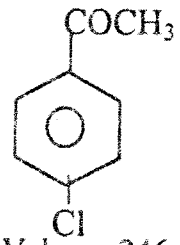
X = H – aldehyde
X = OH – acid
X = OR – ester
X = R – ketone

1. The base value is 246 nm when X is an alkyl group (ie) for a ketone
2. When X is H, (ie, for an aldehyde), it is 250 nm.

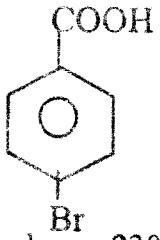
3. For an acid or an ester, the base value is 230 nm
4. For auxochromes substituted at the o,m and p-position, the increments are tabulated:

Position	R	OH,OR	Cl	Br	NH_2	NR_2	$O^{\ominus}$
Ortho	+3	7	0	2	13	20	11
Meta	+3	7	0	2	13	20	20
Para	+10	25	10	15	58	85	75

Applications of Scott's rules for substituted carbonyl compounds are given as under:



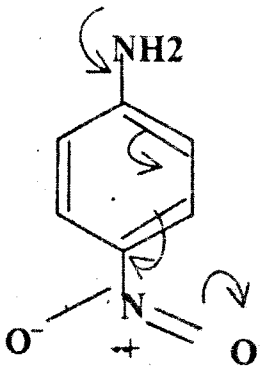
Base Value = 246
P-Cl subst = 10
λ max = 256 nm



Base value = 230
P – Br subst = 15
λ max = 245 nm

In a condensed system like anthracene where 3 benzene rings are fused together, the absorption is shifted to longer wavelength (λ ~ 400 nm), near the visible region, hence the molecule appears slightly coloured. Higher analogues of benzene are still intensely coloured. (e.g) naphthacene, λ max is 480 nm and yellow in colour, but pentacene; λ max is 580 nm appears as blue.

In disubstituted benzenes, when a – M group is para to a + M group, there is considerable shift of λ max, even more than the sum of their individual shifts. (aniline in methanol 230 nm and for nitrobenzene λ max is 268 nm). (e.g) p-Nitro aniline, the K band appear at λ max 381 nm. The spectra of o– & p- nitro aniline are similar but vastly different (λ max ~ 280 nm). Thus the p-nitro aniline appears yellow coloured since the absorption is near the visible region.

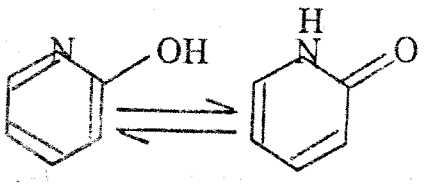


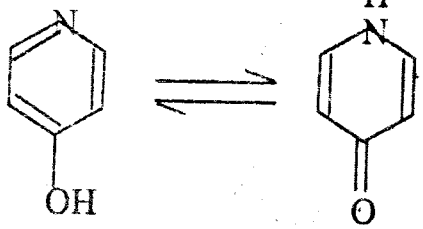
Heterocyclic Compounds

The UV spectrum of heterocyclic compounds also give a weak R-band ($n \rightarrow \pi^*$) due to the presence of lone pairs over the heteroatom, apart from an intense B-band ($\pi \rightarrow \pi^*$). The 5-membered hetero aromatics form these two bands comparable to cyclopentadiene.

Compound	nm B- band (ε max)	nm R-band (ε max)
Cyclopentadiene	200 (10,000)	238 (3400)
Furan	200 (10,00)	252 (1)
Pyrrole	209 (6700)	240 (300
Thiophene	231(7100)	270 (1.5)
Pyridine	257 (2750)	270 (450)
2-hydroxy pyridine	230 (10,000)	295 (6300)
4-hydroxy pyridine	239 (14,000)	

The spectrum of pyridine is similar to that of benzene. The B-band is more intense than that in benzene. An increase in solvent polarity produces a marked hyperchromic effect on the B-band of pyridine as well as its derivatives, probably due to strong hydrogen bonding with the lone pairs on the hetero atom. The marked increase in the intensity of absorption in 2-hydroxy and 4-hydroxypyridine is attributed to the existence of pyridone structures, due to tautomerisom.





INFRARED SPECTORSCOPY

Absorption of infrared radiations by molecules is enough to cause vibrations in a chemical band. The frequency of vibration is exactly the same as the frequency of absorption. Stretching of a bond requires more energy than bending hence the stretching frequencies are higher than the bending frequencies. The stretching frequencies normally appear in the 4000 – 1430 cm^{-1} region, compared to the bending frequencies at 1430 – 910 cm^{-1}. This smaller region is composed of a variety of absorption peaks very characteristic of different molecules, in the same way as the finger prints of persons. For this reason this region is called **finger print region**.

Vibrational Coupling (Fermi Resonance)

Apart from the stretching frequency and bending frequency of absorption for a particular bond, new frequencies of absorption have been observed for a number of molecules, due to vibrational coupling between two bonds of nearly the same vibrational frequency. When the fundamental stretching vibration of a bond couples with the overtone of another vibrational frequency resonance interaction occurs resulting in the formation of two new absorption bands of almost equal intensity at slightly different regions of absorption. This phenomemon is called **Fermi Resonance.** This may be illustrated as follows. For an aldehyde, C – H stretching absorption appears as a doublet at 2820 and 2720 cm^{-1}. This is due to resonance coupling between C – H stretching (fundamental at 3100 cm^{-1}) and C – H deformation (bending at about 1400 cm^{-1}) overtone at (2 × 1400) = 2800 cm^{-1}. Fermi resonance has also been observed in cyclic ketones, lactones, acid anhydrides, carbondioxide, in $CH_2 - CH_3$ groups etc.

Applications of IR Spectroscopy

IR absorption frequencies are characteristic of various functional groups. Hence IR spectrum is very useful in the identification of functional groups.

Hydrocarbons (alkanes, alkanes and alkynes)

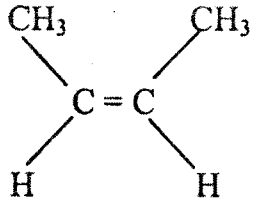
Alkanes have the C – H stretching at 2960 – 2850 cm^{-1} whereas the **alkenes** absorb at a higher value of 3100 – 3000 cm^{-1} compared to a still higher absorption of 3300 cm-1 for **alkynes**. The C – C absorption occurs at 1300 – 800 cm^{-1}, C = C near 1667 – 1640 cm^{-1} and the C ≡ C at 2200 cm^{-1}.

Conjugated dienes (symmetrical) (eg: 1,3-butadiene) absorb at 1600 cm^{-1} and those without a centre of symmetry eg: 1,3 pentadiene absorbs at 1650-1600 cm^{-1}. Cumulative dienes eg: C = C = CH_2 absorb at 2000-1900 cm^{-1} due to C = C = C , asymmetric stretching.

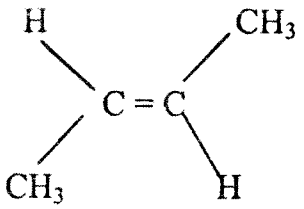
The C-H bending frequencies ($C\text{-}H_{def}$) also differ for alkanes, alkenes and alkynes being 1485 – 1340 cm^{-1}, 970 – 700 cm^{-1} and 650 – 610 cm^{-1} respectively. In gem-dimethyl groups (e.g) in isopropyl group, $C - H_{def}$ is noticed as a strong doublet of equal intensity at (1385 – 1380 cm^{-1}) and (1370 – 1365 cm^{-1}). This could be distinguished by a tert. butyl group where the C–H def is observed as a doublet in the region (1395–1385 cm^{-1}) and another near 1370 cm^{-1}.

The cis and trans olefins are also distinguished by their C – H bending frequencies at 700 cm^{-1} and around 970 cm^{-1} respectively.

(e.g) Cis -2-butene



trans-2-butene.



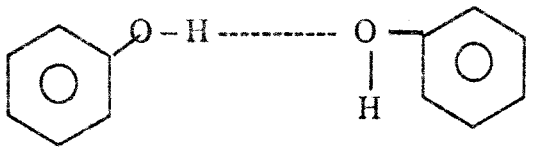
The aromatic hydrocarbons are distinguished from the aliphatic ones from the variations in their C – H stretching (3050 – 3000 cm^{-1}), C C str. (1650 – 1450 cm^{-1}) and the C – H def. (900–700 cm^{-1}).

Alcohols and Phenols

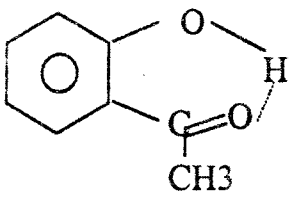
They exhibit a variable but intense band in the region 3700 – 3500 cm^{-1} due to free O – H stretching and O-H_{def} is observed at 1420 – 1320 cm^{-1} O – H. Another strong absorption is noticed at 1260–1000 cm^{-1}, due to C – O stretching. Coupling between C – O and C – C str. vibrations weakens this band. For benzyl alcohol, O – H str (intermolecular hydrogen bonded) is found at 3300 cm^{-1} and the C – O str. is observed at 1017 cm^{-1}. In phenol (e.g) p-hydroxyacetophenone, free O – H str is observed at 3600 cm^{-1} in dilute CCl4 solution, but hydrogen bonded O – H str. is found at 3100 cm^{-1} for a neat sample. A phenol and an aromatic alcohol are better distinguished from their O – H def. frequencies observed at 1360 $cm^{-1}$and 1208cm^{-1}respectively. The OH str. is strongly affected by hydrogen bonding as well as the polarity of the solvent.

Hydrogen Bonding – Solvent Effects

At high concentrations of alcohols and phenols, intermolecular hydrogen bonding is maximum hence the absorption is broadened and the absorption frequency is lowered. For the same reason, the polar solvents also shift the OH absorption to lower frequencies at 3570 – 3450 cm^{-1}. However, it is concentration dependent, since the intermolecular hydrogen bonding gets reduced, at lower concentrations when diluted by an inert solvent. Intramolecular hydrogen bonding also reduces OH str. but is not affected due to dilution by any solvent. Hence the IR spectra of alcohols and phenols make a clear distinction between intermolecular and intramolecular hydrogen bonding.



(OH str. 3333 cm^{-1})
Affected due to dilution



(OH str. 3077)
Not affected on dilution

IR spectra also make it possible to distinguish between primary, secondary, and tertiary alcohols, since their C – O stretching frequencies differ. They exhibit a strong doublet as under:

Primary alcohols C – O str	(i) 1350 – 1260 (ii) ~ 1050
Secondary alcohols C – O str	(i) 1350 - 1260 (ii) ~ 1100
Tertiary alcohols C – O str	(i) 1400 – 1310 (ii) ~ 1150

Ethers

The C – C stretching frequency in ethers is similar to that of hydrocarbons. But they are most characterized by the C – O – C str. For saturated aliphatic ethers it is observed in the range 1205 – 1124 cm-1, due to asymmetric stretching.

(e.g) $CH_3.CH_2.CH_2.CH_2 - O - CH_2.CH_2.CH_2.CH_3$

Methyl C – H str. at 2960 cm^{-1}
C – H def. at 1372 cm^{-1}
Asym. C – O str. at 1124 cm^{-1}

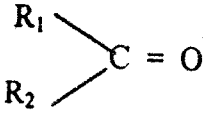
For, aromatic as well as α, β - unsaturated ethers, a strong asym. str. is observed at 1275 – 1200 cm^{-1}. The increase in str. is due to

$CH_2 = CH - \ddot{O} - CH_2R \leftrightarrow CH_2 - CH = O^{\oplus} - CH_2$ (R on CH_2, $\ominus$ on CH_2) resonace interaction of the lone pairs with the π electrons. For anisole, $C_6H_5 - OCH_3$, the C – O str. is observed at 1245 cm^{-1}.

The cyclic elthers show normal C – O str. absorption for 6 – membered rings but for smaller rings the frequency of absorption decrease due to decrease in asym stretching.

Carbonyl Compounds

Compounds such as aldehydes, ketones, carboxylic acids, acid chlorides, esters, amides and anhydrides show a characteristic intense absorption in the region 1650 – 1950 due to C = O stretching. The absorption frequency very much depends upon the nature of groups attached to the C = O group.



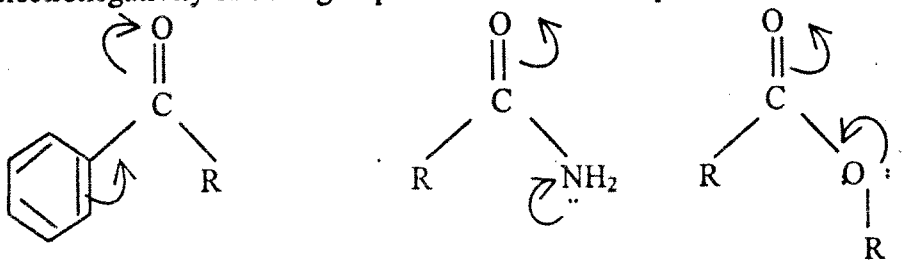
R_1 & R_2 = alkyl - ketone
R_1 = alkyl R_2 = H - aldehyde
R_1 = alkyl R_2 = NH_2 – amide
R_1 = alkyl R_2 = OR – ester

Generally, an electron releasing alkyl group weakens the C = O bond, hence ketones absorb at lower frequencies, than other carbonyl compounds. (e.g)

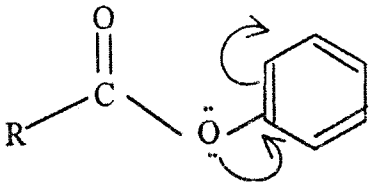
Acetone	- 1718 cm^{-1}
Acetaldehyde	- 1745 cm^{-1}
Acetic acid	- 1725 cm^{-1}
Ethyl acetate	- 1742 cm^{-1}
Acetyl chloride	- 1820 cm^{-1}

When electron withdrawing groups are attached to the C = O group, as in an acid chloride, the force constant increases along the C = O bond, thereby increasing the absorption frequency.

When the carbonyl group is attached to an aromatic, or conjugated system, or to a group such as NH_2 (amide) or – OR (ester), +M effect becomes predominant, thereby decreases the force constant and the absorption frequency. However the electronegativity of such groups enhances the absorption.

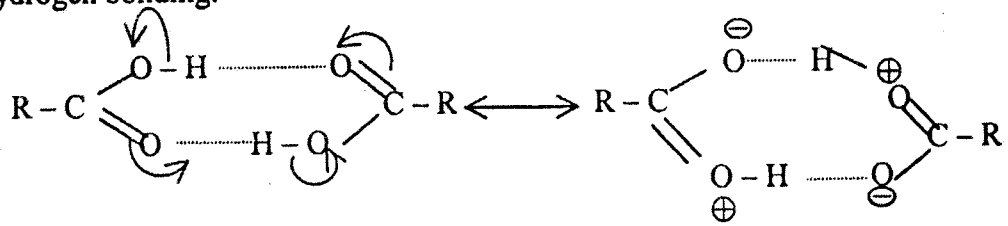


However, in aromatic esters, the lone pairs of electrons from the aryl oxygen, enter into resonance with the aryl group and the C = O group is free, hence C = O absorption moves to a higher frequency.



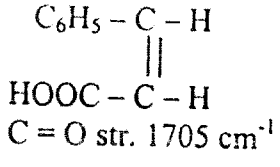
1) <u>Carboxylic Acids</u>

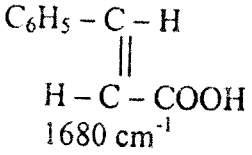
At high concentration, carboxylic acids exist as dimers due to strong hydrogen bonding.



As a result, the normal O – H str. as well as the C = O str. frequencies are considerably reduced. The O – H str. for the dimers is observed at 3300 – 2500 cm^{-1} as a broad intense band. A free O – H str. (~ 3520 cm^{-1}) is observed only in the case of a very dilute solution in non polar solvents or in vapour phase when hydrogen bonding is minimized. Similarly for a dimer, the C = O str. is observed only at 1720 – 1706 cm^{-1}. The C = O str. is reduced further in the case of intramolecular hydrogen bonding as observed in salicylic acid at 1665 cm^{-1}.

Conjugated acids, absorb at a slightly lower frequency compared to saturated acids, for the monomer as well as the dimer. For example, the c is and the trans form of cinnamic acid differ in absorption due to conjugation as well as difference in steric repulsion. Hence the c is form has a higher frequency of absorption compared to trans.

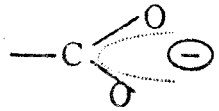




Identical values have been observed for the maleic and fumaric acids.

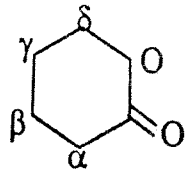
Apart from the carbonyl and OH str., two bands are observed for C – O str. and O – H banding near (1320 – 1210 cm^{-1}) and (1440 – 1395 cm^{-1}) respectively.

For carboxylate anions, an asymmetric as well as symmetric stretching give rise to two bands near (1660 – 1550 cm^{-1}) and 1400 cm^{-1} respectively.

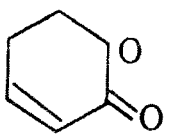


(ii) Esters and Lactones

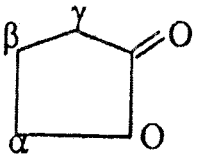
Saturated aliphatic esters have an intense band due to C = O str., in the region 1750 – 1735 cm^{-1}. Compared to the α,β unsaturated as well as the benzoate esters at a lower frequency of 1730 – 1715, in cyclic esters or lactones absorption depends on the size of the ring as well as conjugation. δ-Lactones absorb in the same region as that of aliphatic esters. But in smaller lactones, the large strain in the ring enhances the force constant of the C = O bond.



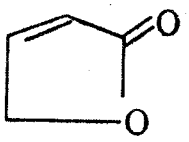
1745 cm^{-1}
(δ- lactone)



1720 cm^{-1}
(α,β - unsat)



1770 cm^{-1}
(γ - lactone)



1750 cm^{-1}
(α,β - unsat)

The C – O str. vibration also exhibits a strong band at 1300 - 1000 cm^{-1}. Saturated esters absorb very intensely at 1210 – 1163 cm^{-1}. Esters of aromatic acids have this absorption at a higher region, 1310 – 1250 cm^{-1}. This absorption in lactones occurs at 1250 – 1111 cm^{-1}.

Amines

Two weak bands are observed, one near 3500 $cm^{-1}$and another near 3400 cm^{-1} for primary amines due to free N – H str. (asymmetrical and symmetrical). But secondary amines show a single weak band at 3350 – 3310 cm^{-1}, and tertiary amines do not absorb in this regions for want of N – H group. Similar to alcohols and phenols, the N – H str. in armines are also influenced by solvent effects. Hydrogen bonding shifts the frequency of absorption to lower values, as the associated N – H bands are weaker, but sharper than the O – H bands.

Aromatic amines exhibit N – H str. at higher frequencies compared to their aliphatic counterparts.

(e.g) A simple aliphatic amine

(e.g) $CH_3 (CH_2)_7 NH_2$ - Hyedrogen bonded N – H str. at 3365 cm^{-1} and 3290 cm^{-1}

An aromatic amine - 3450 cm-1 and 3390 cm-1
(e.g) Aniline

N – H def. frequency is observed at 1650 – 1580 cm^{-1}, in general for aliphatic as well as aromatic amines.

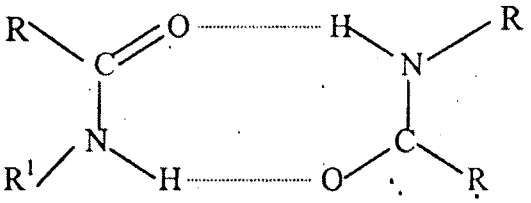
Aliphatic and aromatic amines are distinguished by their C – N str. observed in the region 1250 – 1020 cm^{-1} and 1342 – 1266 cm^{-1} respectively.

Amides

All primary amides exhibit two N – H str. vibrations due to the asymmetric and symmetric stretching and secondary amides show one in the region 3500 – 3000 cm^{-1}. Near 1650 – 1515 cm^{-1}, N – H bending frequencies are also observed for these amides. A strong absorption also occurs due to C = O str. for all amides near 1700 – 1600 cm^{-1}. However, the absorption frequencies depend very much on the physical state as well as the solvent polarity, since the degree of hydrogen bonding differs.

Solvent Effect – Hydrogen Bonding

Both, the N – H as well as the C = O absorption frequencies are significantly affected by hydrogen bonding.

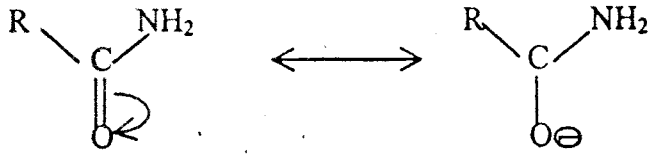


$\left\{\begin{array}{l} R^1 = H - \text{Primary} \\ R^1 = \text{alkyl - secondary} \end{array}\right\}$

In dilute solution of non polar solvents, the free N – H asymmetric and symmetric stretching vibration correspond to 3520 cm^{-1} and 3400 cm^{-1}, but in solids and samples at high concentration, the absorptions are reduced to 3350 cm^{-1} and 3180 cm^{-1} due to strong hydrogen bonding.

The N – H def. frequency is observed at 1655 – 1620 for solids and in dilute solutions it occurs at a lower frequency of 1620 – 1590 cm^{-1}. In concentrated solution of polar solvents multiple bands are observed due to free as well as bonded N – H def.

The C =O stretching frequency is observed at 1650 in the solid state. But in dilute solution of non polar solvents it is shifted to higher frequency (1690 cm^{-1}). But the C = O str. values are generally lower in amides compared to other carbonyl compounds, (> 1700) as the C = O str. is weakened due to resonance effect.



The tert. amides are however, not affected by the physical state, since there is no possibility of hydrogen bonding.

But they are influenced by polar hydroxylic solvents, as the C = O group enters into hydrogen bonding with the solvent. Accordingly N, N-diethyl acetamide absorbs at 1647 cm^{-1} in dioxane (non polar) and at 1615 cm^{-1} in methanol.

MASS SPECTROMETRY

When molecules are bombarded with a beam of electrons, they are broken up into different types of positively charged fragments, each having a definite mass by charge ratio (m/e). Most of these fragments are found singly charged. The intensity of each ion is a measure of their relative abundance. A mass spectrum results, when the

relative intensities of various ions (with reference to intensity of the most stable ion), is plotted against their m/e value. The most stable ion gives the most intense peak, called the **base peak**. The base peak is assigned a value of 100% intensity and all other ions are assigned intensities relative to that of the **base peak**.

An important aspect of mass spectrum is that it enables the calculation of molecular formula of the given organic molecule from the molecular ion peak which is formed as follows: when a molecule (M) is struck with an electron beam, an electron is removed first to form a molecular ion (M^+), with the same molecular weight.

$$M \xrightarrow[e^-]{} M^{\oplus\bullet} + e^-$$

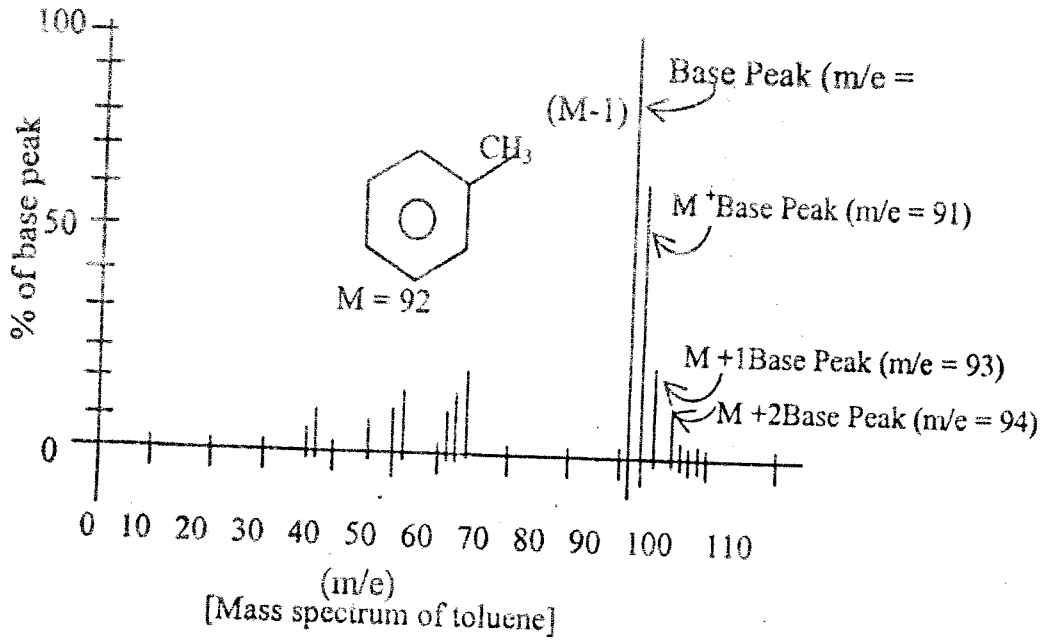
The peak formed corresponding to the molecular weight of the parent molecule is called the **molecular ion peak**. This molecular ion peak ($M^{\oplus}$ peak) itself may form the base peak if it constitutes the most stable ion formed. However, other ions are also formed depending upon the mode of fragmentation of the $M^{\oplus}$. (e.g) In the mass spectrum of toluene,

$$C_6H_5CH_3 \xrightarrow{\bar{e}} \left[C_6H_5CH_3 \right]^{\oplus}_{\bullet} \quad (m/e = 92) = M^+ \text{ Peak}$$

$$\left[C_6H_5CH_2 \right]^{\oplus} = M-1 \text{ peak} \quad (m/e = 91)$$

($-H^{\bullet}$)

the (M – 1) peak is the most stable peak with m / e = 91 and constitutes the base peak with 100% intensity whereas the molecular ion peak (m / e = 92) intensity is found to be only around 70%.



[Mass spectrum of toluene]

Isotopic Peaks

In mass spectrum, $M^{+\bullet}$ peak is not the peak corresponding to maximum mass, since (M + 1) and (M + 2) peaks are also formed depending on the isotopic abundance of the elements present. These are called **isotopic peaks.** For example, when bromine is present in the molecule, the (M + 2) peak is found to be almost as intense as the molecular ion peak since Br^{81} isotope has a relative natural abundance of 98%. Similarly, (M + 2) intensity is also affected due to the presence of chlorine, oxygen and sulphur as Cl^{37}, O^{18}, and S^{34} have a relative abundance of 32.5% (with 1/3 of the M^+ intensity) 0.20% and 4.40% respectively. Hence an (M + 2) peak in bromobezene corresponds to $C_6H_5Br^{81}$ or $C_6H_3D_2Br$. In benzenesulphonylchloride the (M + 2) may correspond to $C_6H_5S^{34}ClO_2$, $C_6H_5SCl^{37}O_2$ or $C_6H_5SO_2{}^{18}Cl$ or $C_6H_3D_2SO_2Cl$ etc. But the (M + 1) peak intensity is not considerable due to the low natural abundance of C^{13} or H^2 or O^{17} which is 1.08%, 0.016% and 0.04% respectively, compared to the abundance of C^{12}, H^1 or O^{16} taken as 100%.

However, the (M + 1) peak intensity is affected more considerably, by the presence of nitrogen and sulphur in the molecule, as N^{15} isotope has a relative abundance of 0.38% and S^{33} has 0.78%. To a lesser extend, it is also affected by deuterium isotope (ie) 1.08% abundance, and the (M + 1) peaks intensity is due to the following in Nitrobenzene such as $C_6H_4DNO_2$, and $C_6H_5N^{15}O_2$. This enables the calculation of the intensity of the isotopic peaks. (ie) (M + 1) and (M +2) peaks.

% of (M + 1) Peak Intensity

= 1.1 × number of C atoms + 0.36 × number of N atoms + (0.78 × number of S atoms if the (M + 2) intensity exceeds 4.2)

% of (M + 2) Peak Intensity

$= (1.1\times \text{number of C atoms})^2/200 + 0.20\times \text{number of O atoms.}$

Nitrogen Rule

Presence of nitrogen in the molecule can be ascertained using nitrogen rule. It states that a molecule of even numbered molecular weight should contain no nitrogen or even numbered nitrogen and if the molecular weight is odd, it should contain odd number of nitrogen atoms. For example, the molecular mass of aniline, $C_6H_5NH_2$, is odd (93), hence it contains odd number of nitrogen.

Determination of Molecular Formula

For an organic substance with molecular weight 205, the M + 1 and M + 2 peak intensities are 11.46 and 1.40 respectively. Since it has odd molecular weight,

there can be odd number of nitrogen atoms. Hence, (M + 1) intensity may be = 10×1.1 + 1×0.36 = 11.36 from the M + 2 intensity, presence of sulphur and halogens are ruled out. Hence, (M + 2) = $(10\times1.1)^2$ /200 + 0.20×number of oxygen. Since M + 2 = 1.4, it accounts for 4 oxygen. Therefore M + 2 intensity = $(10\times1.1)^2$ + 0.2×4 = 1.4. Hence the proposed molecular formula should be $C_{10}H_xNO_4$ = 205.

$\therefore x = 7$

Therefore the molecular formula should be $C_{10}H_7NO_4$ = 205.

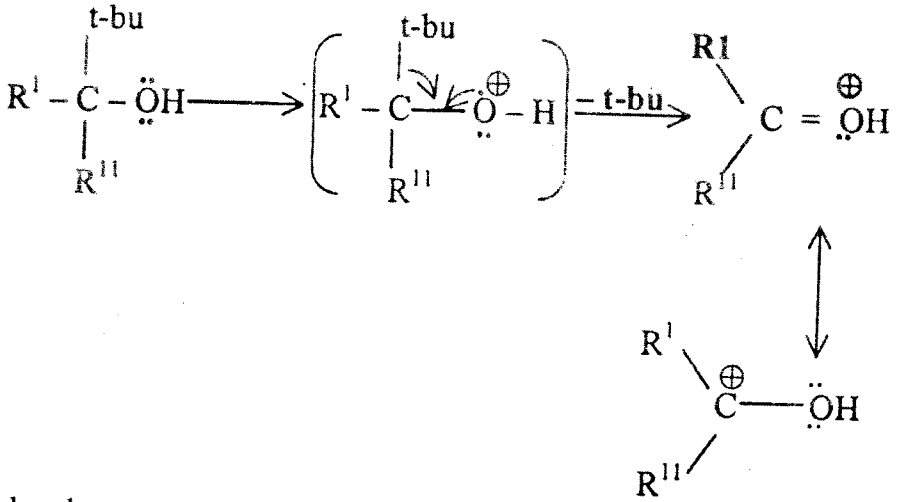
This molecular formula must be further supported by the fragmentation pattern of the molecule.

Fragmentation Pattern in Organic Molecules

Identification of the molecular ion peak is the key to the determination of molecular structure. By reducing the energy of the bombarding electron, the intensities of all but the $M^{+\bullet}$ peak are reduced thereby increasing the relating intensity of the $M^{+\bullet}$ peak. The most stable molecular ions are those of purely aromatic systems followed by conjugated systems and cyclic systems. The following points are helpful for predicting prominent peaks.

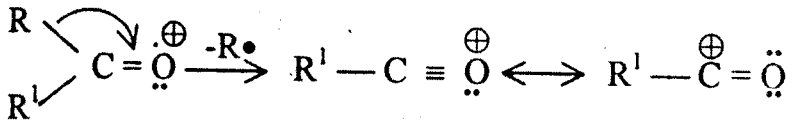
- $M^{\oplus\bullet}$ peak is relatively higher for straight chain molecules and decreases with increase of branching. But in a homologous series, the height decreases with increase of molecular weight.
- Fragmentation starts at the carbon which is more substituted and the

a) (eg)



C – C bond next to a hectroatom is usually cleaved, leaving the charge over the heteroatom, providing resonance stabilization.

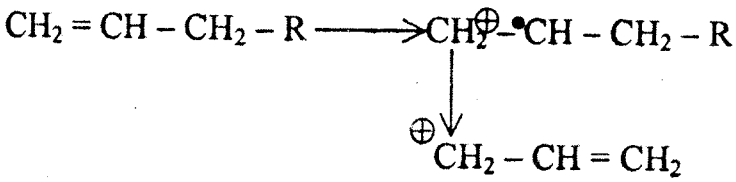
b) (eg)



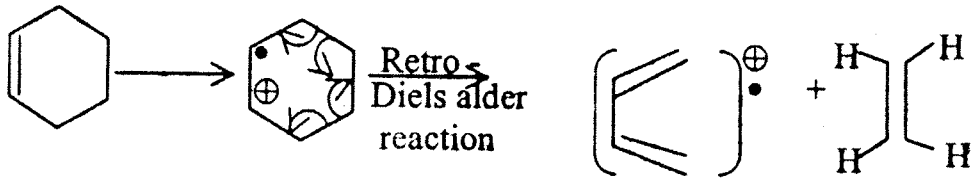
(R^1 = H aldehyde) (m/e 29 for aldehyde) (R^1 = CH_3 m/e 43, in acetyl groups)

- - bond in aliphatic or alicyclic systems favour the formation of (a) stable allylic carbonium ion or (b) stable conjugated diene and in aromatic system (c) they prefer the formation of a resonance stabilized benzyl cation or a tropylium ion.

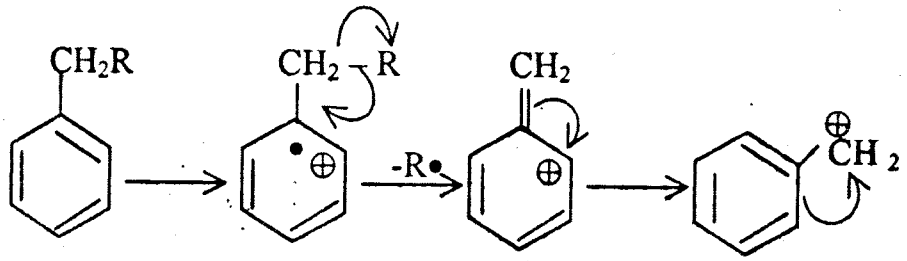
a) (e.g)



b)

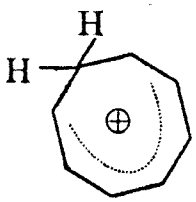


c)



(benzyl)

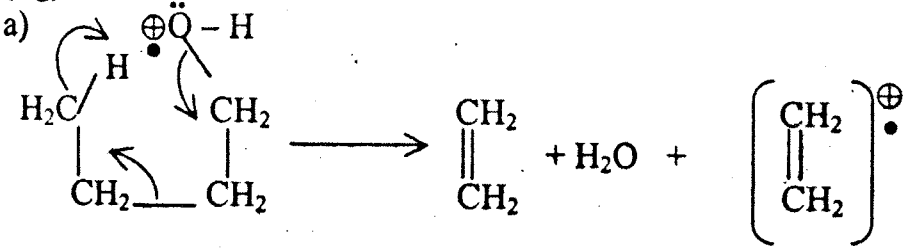
(m/e = 91)
(tropylium)



- cleavage most often results in the elimination of small stable neutral molecules, such as H_2O in alcohols (M – 18 peak and M – ethylene & H_2O), CO and ethylene in diphatic ketones CO in phenols H_2S in mercaptans (M – 34 peak) etc.

(e.g)

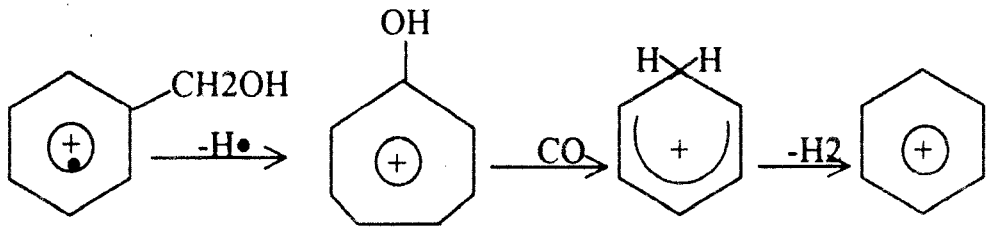
a)



(n – butylacohol)
M = m / e = 73

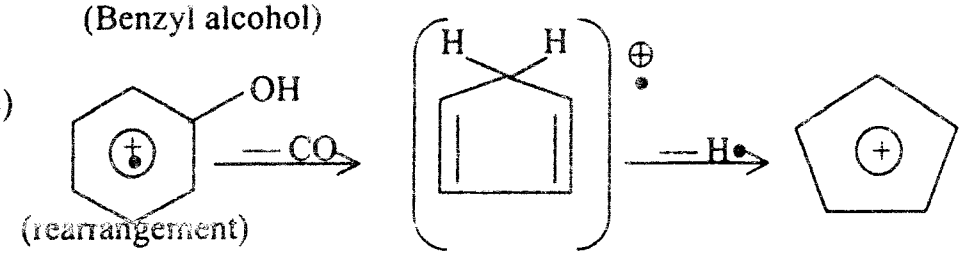
[M – (28 + 18) peak]

b)



m/e = 108 (Benzyl alcohol) m/e = 107 m/e = 79 m/e = 77

c)

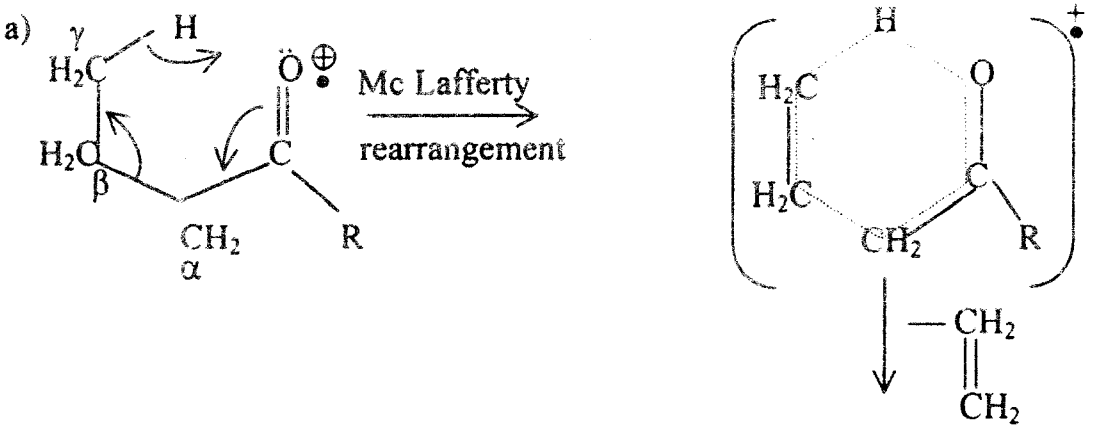


(rearrangement)

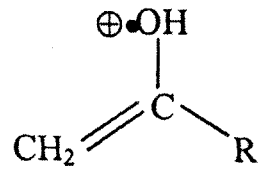
m/e 66 (M – 28) m/e 65

In aldehydes, ketones, acids,esters, amides, nitriles as well as in certain alkyl substituted aromatic compounds and in certain alkenes, a prominent peak is formed due to the formation of molecular ion, through a rearrangement known as **McLafferty rearrangement**. This proceeds through the formation of a six membered cyclic transition state in the above molecules, but with a γ - hydrogen, as revealed by the following examples.

a)



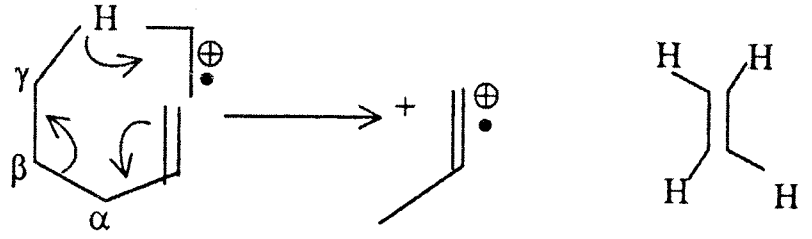
R = H - aldehyde
R = alkyl or aryl - ketone



(m / z 44 in aldehydes prominent)

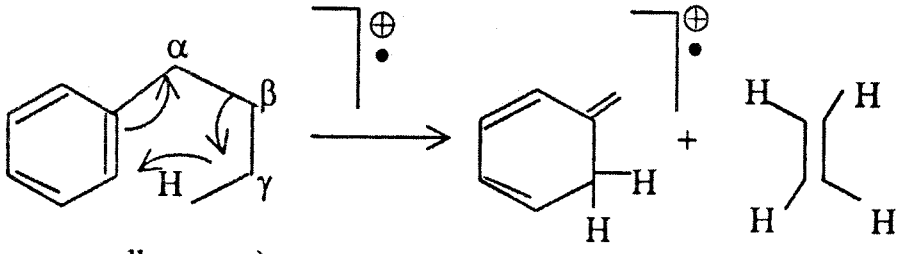
During the rearrangement, the α - β bond cleaves, leading to the elimination of a neutral molecule (olefin), with the formation of a prominent peak which form the base peak most often.

b)



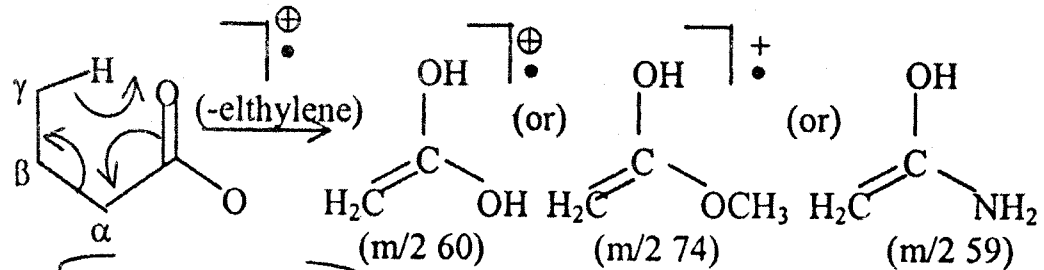
(Pentene –1) (m / z 42)

c)



(n – propylbenzene) (m / z =92)

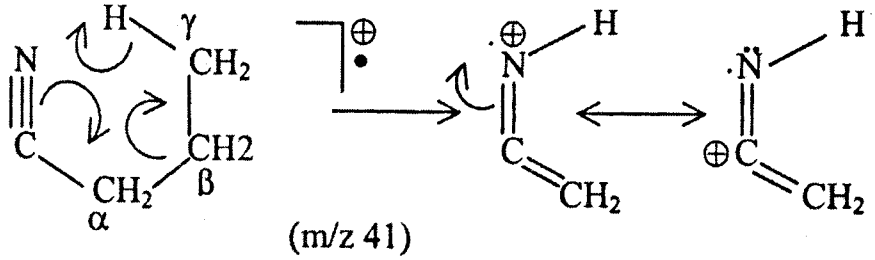
d)



R = H – acid
R = alkyl –ester
OR = NH_2 - amide

(m/2 60) (m/2 74) (m/2 59)

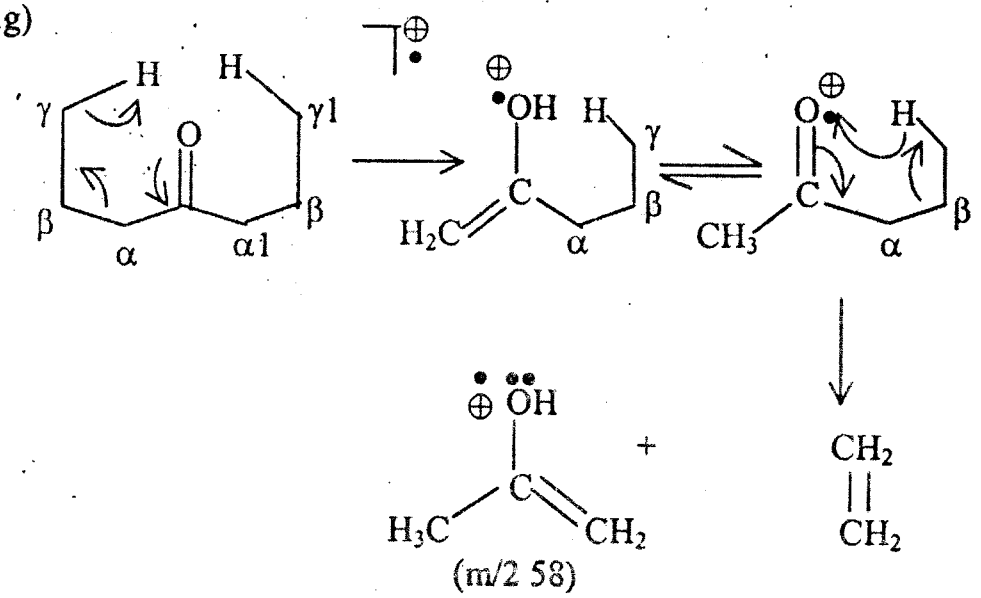
e)



(m/z 41)

In certain molecules with more than one γ – H, a double Mclafferty rearrangement has been observed.

(e.g)



Metastable Peak

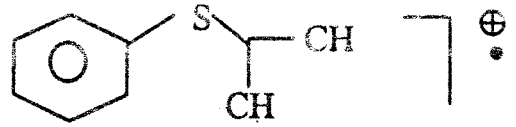
If a molecular ion $(M^+)^\bullet$ or a fragment (m_1^+) accelerated in a mass spectrometer, before the ion breaks down, then it may decompose into another ion (m_2^+) and a neutral fragment (m_3). The new ion (m_2^+) continues to get accelerated and is recorded as a metastable ion corresponding to a mass m*, with low intensity.

This ion is called a metastable ion. This weak broad peak doesn't have an integral value. A metastable ion has a very short life time of about 10^{-6}sec.

$$m_1^{\oplus} \longrightarrow m_2^{\ominus} + m_3$$

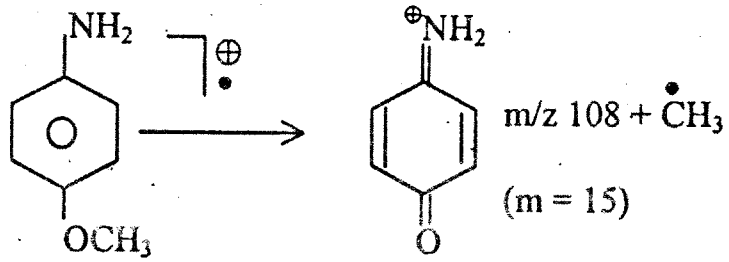
$$m^* = m_2^2 / m_1$$

examples: consider ⟶



(m/2 152)

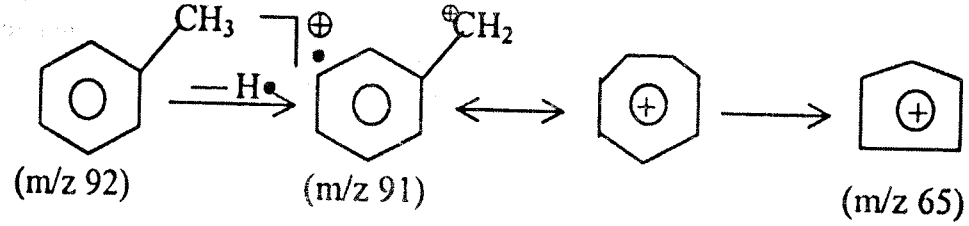
1) Mass spectrum of P-anisidnie shows a meta stable peak at 94.8. This may be interpreted as follows:



$$m^* = \frac{(108)^2}{123} = 94.8$$

Hence a CH_3 group should have been lost from the parent molecule.

2) Mass spectrum of toluene shows a metastable peak at 46.4. A possible fragmentation pattern may be as under:



(m/z 92) (m/z 91) (m/z 65) + HC ≡ CH (m = 26)

$$m^* = \frac{(65)^2}{91} = 46.4$$

A molecule of acetylene must have been lost from a tropylium cation (m/z 91) to form a cyclopentadienyl cation with m/z 65.

3) This isopropyl phenyl thioether with molecular formula $C_9H_{12}S$ ($M^{\oplus}$ 152) gave meta stable peaks at m/z 123, 79.6 and 54.1 and other peaks at 137, 110, 77, 66, 65 and 43. When m* = 123, if may be due to

$$152^{\oplus} \longrightarrow 137^{\oplus} + 15., \text{ since } m^* = \frac{(137)^2}{152} = 123$$

similarly m* = 79.6 may be due to

$$152^{\oplus} \longrightarrow 110^{\oplus} + 42., \; m^* = \frac{(110)^2}{152} = 79.6$$

and m* = 54.1 may be due to

$$110 \longrightarrow 77^{+} + 33., \; m^* = \frac{(77)^2}{110} = 54.1$$

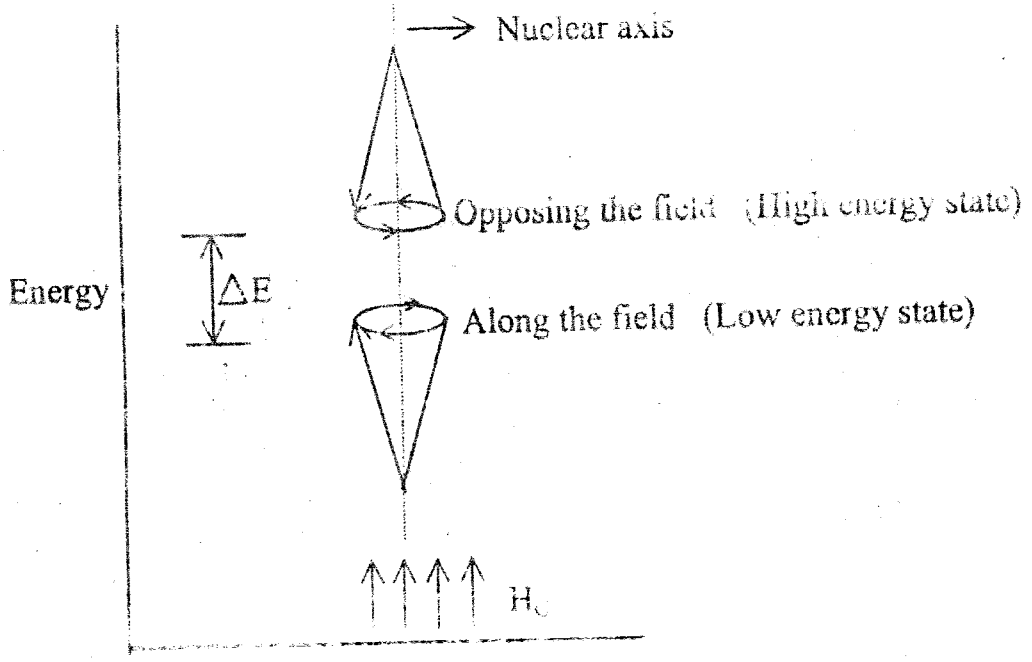
The above metastable peaks are helpful to identify the neutral fragments released during fragmentation, viz. A possible methyl group CH_3 (m = 15), a possible $(CH_3)_2C$. group (m = 42) and a HS• group (m = 33).

******

UNIT II

PROTON MAGNETIC RESONANCE SPECTROSCOPY

All nuclei having spin quantum number (I) greater than zero but with mass number odd, have a characteristic nuclear spin and behave like tiny bar magnets. Hydrogen nucleus with I = ½ and mass number odd, when placed in an external magnetic field can take up (2I + 1) number of orientations ie. two orientations, one aligning with the applied field and the other opposing the field. While aligning, or opposing, the nuclei spin along the nuclear axis, like a precessing top and the nuclei are in two different energy states as shown.



Applied magnetic field

It is possible to effect transition between the two energy states by supplying energy when the low energy nuclei absorb energy and move to the higher energy state. The energy required for the proton nuclei to flip over to the higher state exactly corresponds to the radio frequency which is same as the precessional frequency of the nucleus ($\Delta E = h\gamma$). When the absorbing radio frequency exactly matches the frequency of the spinning nucleus, the protons are said to be in a state of resonance and the phenomenon known as nuclear magnetic resonance (nmr) or proton magnetic resonance (pmr) or (HNMR). The absorption of energy from the radio frequency region is recorded in the form of a spectrum.

Recording the Spectrum

The frequency of absorption depends upon the applied magnetic field (Ho) as,

$\gamma = \mu B_0 / Ih$

The magnetic moment (μ), Bhor magneton (B_N) being constant for a nucleus, it is possible to select the region of absorption in the radio frequency region, by changing the magnetic field. In practice the magnetic field is kept constant at 14,000 gauss or 21,000 gauss and the sample (Proton) is exposed to a steadily changing radio frequency which results in nmr absorption in the region 60 MH_z or 90 MH_z respectively. A sharp signal is recorded as spectrum when resonance occurs due to the inducement of energy transition upwards or downwards between the two populations of the spinning nuclei.

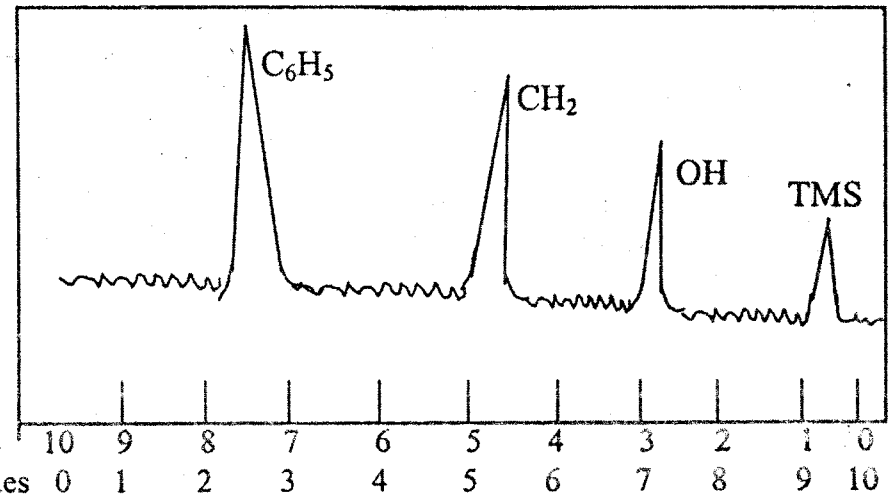
Chemical Shift

The precessional frequency of all protons is not the same even for a constant applied magnetic field, since it depends mainly upon the chemical and electronic environment of the nucleus. The hydrogen nucleus is shielded to some extent by the surrounding election cloud which varies with the type of proton held in different environments. The environment is decided by the following factors. (1) Inductive effect (2) Shielding effect (3) Anisotropic effects (4) Solvent effects. For instance, when a proton is attached to an electronegative hetero atom, the electron cloud is removed from the vicinity of the proton and it is subjected to less shielding. In certain molecules, the shielding causes the generation of a secondary magnetic field due to the circulation of the electron cloud around a particular proton. This results is variation in absorption positions of different hydrogen nuclei.

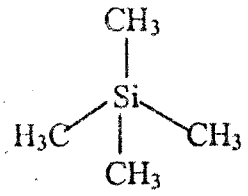
The difference in absorption position between a particular proton in a given molecule and a reference proton in chosen molecule is termed as chemical shift. It is also a measure of the extent of shielding on a given proton, compared to the protons in a magnetically isotropic molecule like tetra methyl silane (TMS). When the nmr spectrum of a given molecule is recorded in the presence of an internal standard (TMS), the absorption position of most of the protons is found to be away from the reference proton in TMS. The protons in most of the organic molecules are said to be deshielded, compard to that of TMS. When a proton absorbs very near the TMS proton, it is called an upfield shift whereas if it is away from the TMS signal, it is a downfield shift. The chemical shift values of different protons are expressed in δ units.

δ Values

$\delta x = (\gamma_x - \gamma_{TMS}) / \gamma_o$. Where γ_x and γ_{TMS} are the frequency of absorption of the respective protons in H_Z and γ_o is the operating frequency of the instrument in MH_Z. The δ values are found in a convenient form in ppm units between 0 and 10, for most of the protons. However, the values can be higher in certain cases. The spectrum of benzyl alcohol is illustrated as under.



The TMS signal is found at $\delta = 0$, is used as the internal standard. The use of TMS has also other advantages. It is chemically inert, hence does not interfere with the sample. Since it is volatile, the sample could be easily recovered.

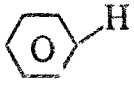


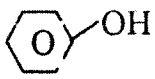
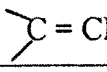
(TMS)

The magnetically isotropic nature of the TMS protons, make them one of the most highly shielded. The substance is also soluble in most organic solvents and easily miscible with the sample. The TMS signal does not interfere with the spectrum, as it is found at the extreme position with $\delta = 0$.

τ Values

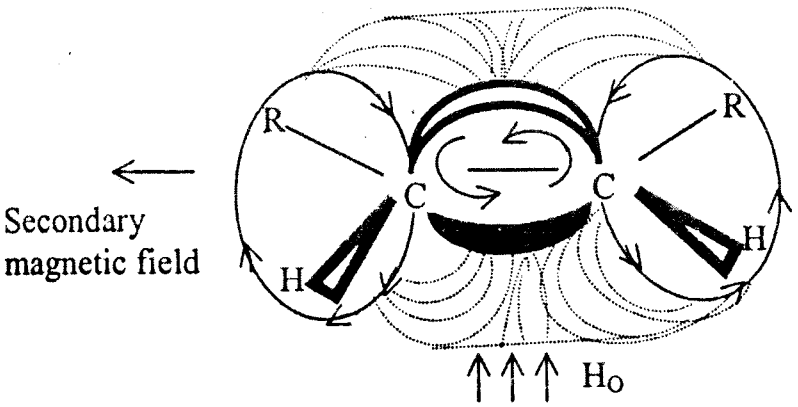
The chemical shift is also expressed in terms of τ which has a very low value for a deshielded proton and high value for shielded protons. It is obtained from the δ values subtracted from 10. $\tau = 10 - \delta$

Type of Proton	Chemical shift	
	δ	τ
Saturated aliphatic (RH)	0.5 – 1.5	9.5 – 8.5
$-CH_2X$ (X is a halogen)	2 – 4	8 – 6
H – C ≡ C – H	1.5 – 3.5	8.5 – 6.5
>C = CH	4.5 – 5.5	5.5 – 4.5
R – OH	2 – 5	8 – 5
CHO	9 – 10	1 – 0
	6 – 9	4 – 1

	RCOOH	10 – 12	0 to – 2
		4 – 12	6 to – 2
(enol)		15 – 17	–5 to –7

Unlike reference molecule TMS, the protons are not isotropic in behaviour. Diamagnetic and paramagnetic anisotropic effects have been observed in certain molecules.

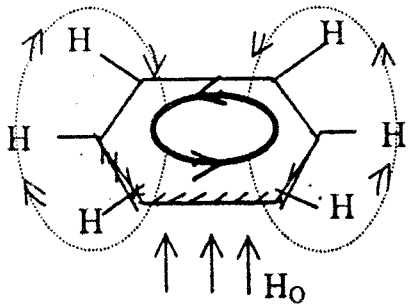
Alkenes



The π electrons of the olefinic system are caused to circulate under the influence of the applied field and generate a secondary magnetic field. Certain regions of the molecule (carbon atoms) experience diamagnetic an isotropic effect since the generated magnetic field opposes the applied magnetic field. But the regions occupied by H atoms experience a paramagnetic anisotropic effect due to the reinforcing of the generated magnetic field with the applied field, hence a downfield shift noticed in the nmr spectrum.

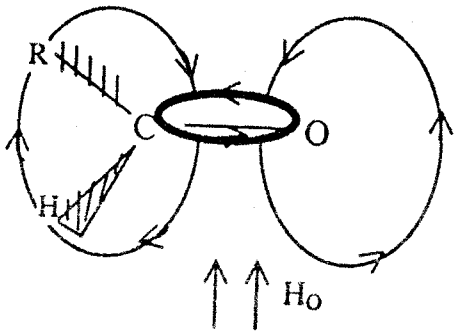
Aromatic Compounds

Aromatic protons experience a similar effect (ring current effect) as in olefins, since the protons occupy a region where they experience a paramagnetic anisotropic effect, due to reinforcing of the secondary magnetic field with the applied magnetic field. A downfield shift is noticed.



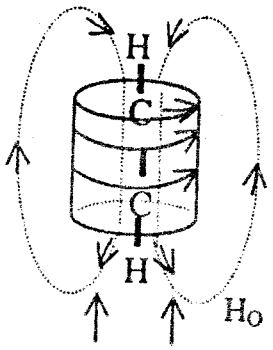
Aldehydes

The aldehydic protons also experience an abnormal deshielding effect. The effect is felt at the proton which occupies a position at the deshielding region of the induced magnetic field. Hence a paramagnetic deshielding effect is noticed



Acetylenes

The acetylenic protons experience an effect different from that of olefinic protons, since the protons are placed in a position where the shielding effect is most felt at the molecule. The π electron density is present in a cylindrical form which generates a secondary magnetic field in the presence of an external magnetic field, resulting in diamagnetic anisotropic effect, hence absorption in the upfield region.



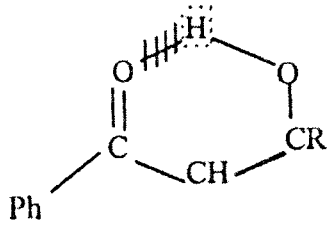
Aliphatic (Saturated)

The protons attached to a saturated carbon behaves very close to TMS protons, since they are attached to a more electropositive carbon compared to either an olefinic or an acetylenic carbon. Moreover, they are magnetically isotropic in character, hence no secondary shielding or deshielding is observed.

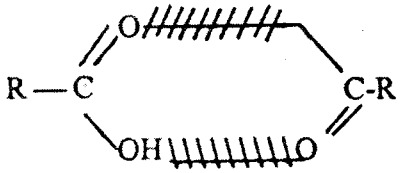
Solvent Effects

Aprotic solvents such as CCl_4, $CDCl_3$, D_2O and $(CD_3)_2SO$ are commonly used while recording the spectrum. However, the nmr spectrum measured is markely affected by the type of solvent used since polarity of the solvent can alter the δ values,

especially through hydrogen bonding. Hence the OH, COOH as well as NH and SH compounds give nmr signals over a wide range of δ values (e.g) ROH absorbs at δ = 2 – 5 and PhOH at 4 – 12. These protons at higher concentration show strong intermolecular hydrogen bonding which reduces the electron cloud around the protons shifting towards the more electronegative atom. Similarly enolic proton of β - diketones absorb at higher values (δ = 15 – 17) since they are intra molecularly hydrogen bonded, but the values do not change with change of concentration. Carboxylic acids also show strong deshielding effects which persists even in very dilute solution, (δ = 10 – 12) existing as a dimer.



(enols)

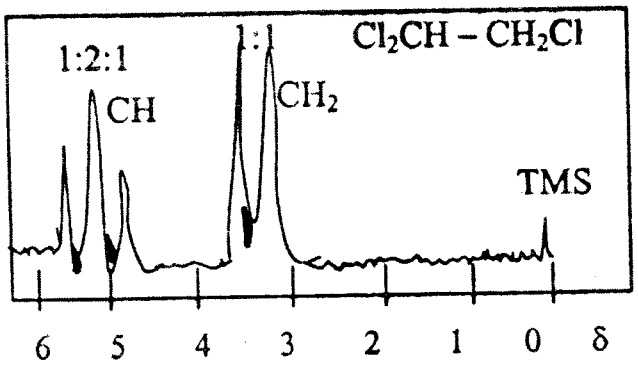


(Carboxylic acid)

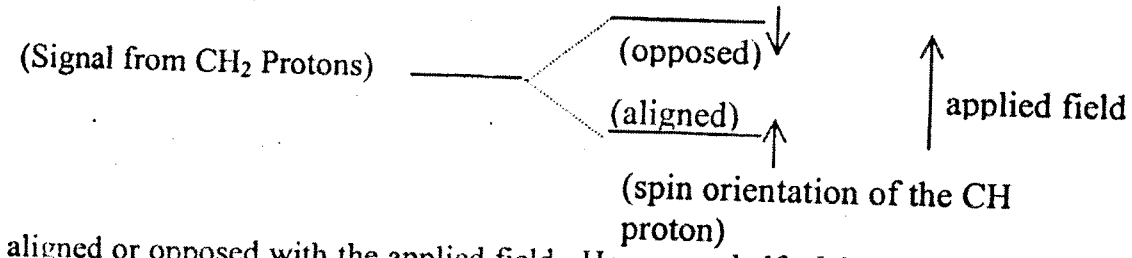
Spin-Spin Coupling

The number of nmr signals for a given compound is significant since it gives the various types of protons present. The peak area of each signal can indicate the number of protons of each type. However the number of neighbouring protons attached to a carbon can be ascertained from the splitting pattern of the signal, observed in molecules having different types of protons.

Consider the molecule $Cl_2CH - CH_2Cl$. The CH signal is found to be a triplet and the CH_2 protons appear as a doublet.

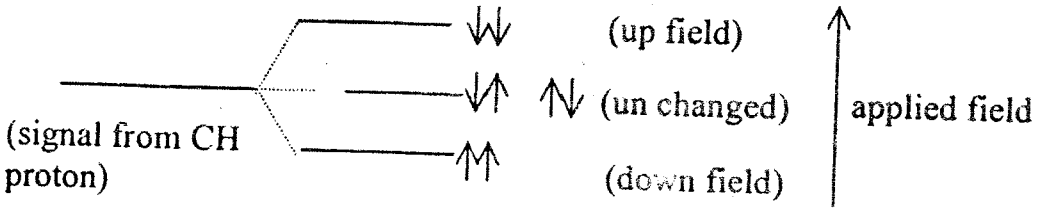


The splitting of the signals could be explained as follows: The two spin orientations of the CH proton are found to couple with the signal from the CH_2 protons. This coupling can lead to a net increase or decrease in magnetic field experienced by the proton, depending on whether it is



aligned or opposed with the applied field. Hence one half of the CH_2 protons experience a slight downfield shift and the other half an up field shift thereby producing a doublet of peak area or intensity of 1:1.

Similarly the spin orientations of the CH_2 protons couple with the signal from the neighbouring, CH proton in three different ways leading to a 1:2:1 triplet as given



(possible spin orientation of CH_2 proton)

This phenomeon of coupling of an nmr signal of a proton with the spin orientations of the neighbouring proton or protons, leading to a split in the corresponding signals is termed spin-spin splitting or spin-spin coupling. Following the above splitting patterns, a molecule like $CHCl_2$. CH_3, can give a quartett of 1:3:3:1 intensity for CH proton, and a 1:1 doublet for the CH_3 protons. Hence it could be generalized that splitting nmr signals could lead to a multiplet of (n + 1) lines where n is the number of neighbouring protons. However the splitting occurs subject to the following conditions.

(1) Signals of neighbouring protons do not split if the protons have the same chemical shift (e.a) $\overset{(a,s)}{CH_3}$. $\overset{(a,s)}{CH_3}$. Here only a singlet (s) is obtained.

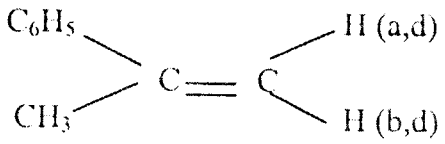
(2) Signals of neighbouring protons experiences split if they have different δ values. (e.a)

$$\overset{(a,t)}{CH_3} . \overset{(b,m)}{CH_2} . \overset{(c,t)}{CH_2Cl}$$

Thus, the CH_3 protons are a triplet (a,t), the CH_2Cl protons are also a triplet (c,t), but the CH_2 protons give a multiplet of 12 lines due to the split first by the methyl protons into a quartett and each line further split into a triplet by the two CH_2Cl protons.

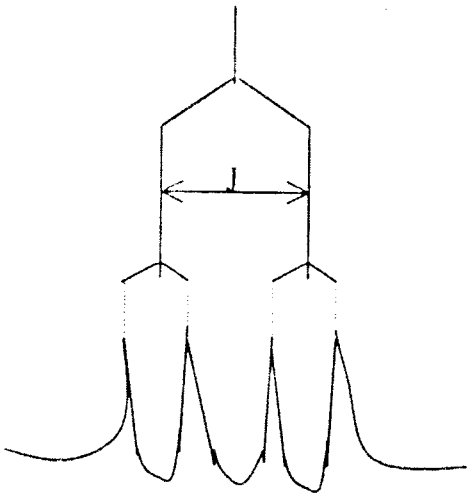
(3) Diasteriotopic protons attached to the same nucleus give different signals and they split each other following the (n + 1) rule, even though they are attached to the same carbon.

(e.a)



Coupling Constant

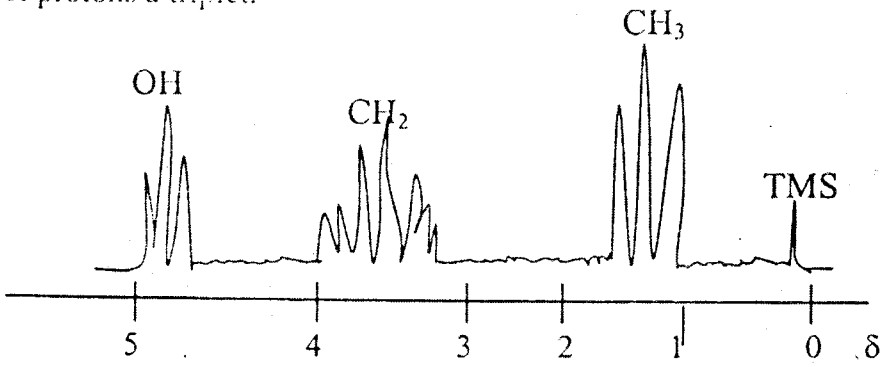
The effectiveness of coupling between neighbouring protons depends upon their difference in chemical shift. The magnitude of coupling is expressed in terms of J in H_Z. When the signal from a proton is split into quartet by the neighbouring methyl protons, the J could be given as below



For freely rotating carbon chain J~8. In rigid system J = 0 –12. J = 10 –18 for coupling involving protons in the same carbon. Trans coupling (J = 11 – 19) is stronger compared to cis coupling (J = 5 – 14)

Chemical Exchange

The nmr spectrum of a neat sample of ethanol shows the expected spin multiplicities as under, the CH_3 protons being triplet, CH_2 protons as a doublet of quartett (8 lines) and the OH protons a triplet.



However an impure sample containing acidic impurities is found to give the usual coupling for CH_3 (t). But the CH_2 protons are reduced to a quartett and the OH protons give a sharp singlet. This is because, the CH_2 protons are no longer able to split the usual quartet formed due to coupling with CH_3 proton, and the OH proton is also not split by the CH_2 protons. The OH protons are undergoing rapid chemical exchange with neighbouring molecules, and as a result, they do not reside for a longer time with a particular oxygen atom. Hence they do not have sufficient time to observe the spin-orientations of the neighbouring CH_2 protons.

$$Et\,OH_\alpha + Et\,OH_\beta \rightleftharpoons Et\,OH_\beta + Et\,OH_\alpha$$

In pure alcohol, such an exchange is limited, but acidic impurities catalyse the chemical change effectively. This is true in carboxylic acids, phenols, enols etc but in enols, which are strongly intra molecularly hydrogen bonded, the exchange is slow and the OH signal is broad.

Deuterium Exchange

When a few drops of D_2O are used as solvent for taking nmr spectrum of a sample of alcohol, the effect is similar to that of rapid chemical exchange catalysed by acid. The OH protons are rapidly exchanged by D atoms, and the original OH signal is lost. But a new signal appears at around that region ($\delta \sim 5$) due to the formation of H-O-D molecule. Moreover a deuterium nucleus has much smaller magnetic moment than a proton, hence no signal is observed.

$$ROH + D - O - D \rightleftharpoons ROD + H - O - D$$

This is a very useful technique to cut off the OH signals in alcohols, phenols etc containing active H atoms and also to simplify the spectrum. This is also a means to detect the presence of reactive methylene groups in β -diketones, β - keto ester as well as alcohols, phenols etc.

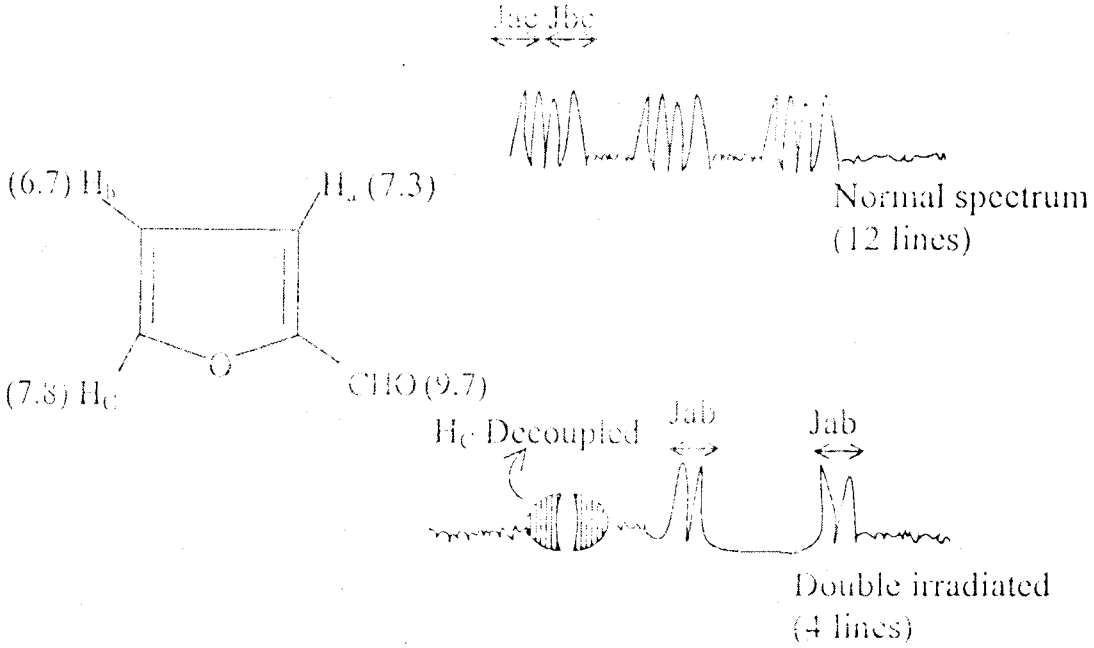
Simplification of nmr Spectrum

1) Double Resonance

When a proton is subjected to double irradiation ie. Irradiating the proton first with the operating radio frequency of the instrument and then using a much stronger beam of exact frequency, the nucleus comes into resonance twice and is called double resonance. The energy transitions are so rapid that the lifetime of any particular spin state is too short to undergo coupling with a neighbouring proton. Since the time needed to undergo spin – spin coupling (Δt) becomes very small after double resonance due to increase in rate of nuclear transition, coupling is not possible with a neighbouring proton. In other words, the process of double irradiation leading to double resonance causes spin

decoupling. This technique is very useful for simplifying a complicated nmr spectrum by effecting decoupling of a specified proton.

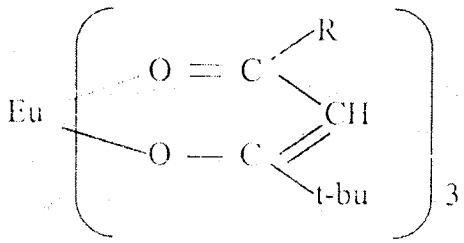
Consider the ^1H – NMR spectrum of furfural with 12 line of 3 quartets. The spectrum is complicated by the mutual coupling of the three protons a, b and c.



The c proton is subjected to double irradiation using the exact frequency of absorption of that proton in addition to the normal frequency beam of the instrument (60 MH_z). The coupling effect of the proton is lost and now spin – spin coupling is possible only between protons a and b, resulting in a simple 4 line spectrum. The process is successful if the chemical shift between the coupling protons is of the order of 1 ppm. When it is less than 1 ppm_s other techniques are employed.

2) Shift Reagents

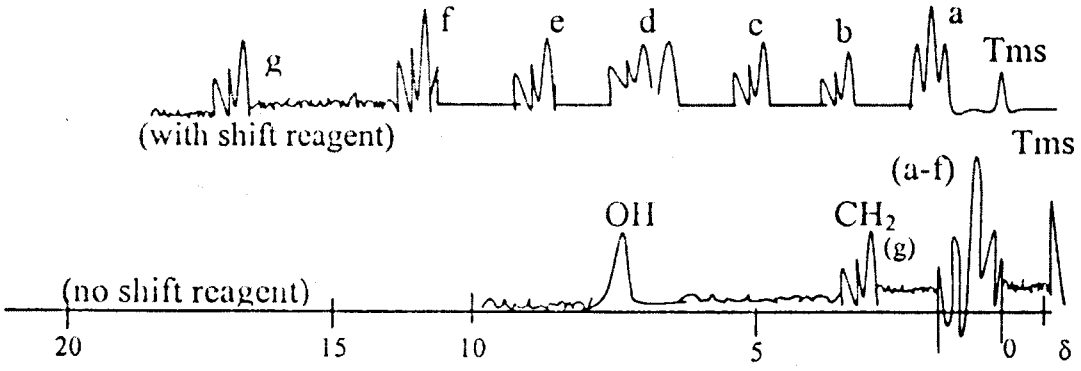
The nmr spectra of certain organic molecules are complex and it is very difficult to identify the peaks, as they are a close multiplet. These peaks can be dialated and pulled apart over a wide range of frequencies so that the spectrum is simplified to a first order spectrum where the splitting of the multiplets is well defined. This shifting or spreading of the absorption pattern is accomplished by the use of organo lanthanide complexes of *dip*ivaloyl *m*ethane (DPM), hepta *f*luorodimethyl *o*ctane *d*ione (FOD) and deca*f*luoro *h*eptane *d*ione (FHD) with enolic β - diketones. These complexes are soluble in CCl_4 and used as fully deuterated to avoid signals from these ligands.



When R = t-bu the reagent is called Eu $(DPM)_3$. When R = C_3F_7 the reagent is called Eu $(FOD)_3$. When R = C_2F_5 and the t-bu group is also replaced by C_2F_5, the reagent is called Eu $(FHD)_3$.

Consider the complex spectrum of the molecule

$CH_3 - CH_2 - CH_2 - CH_2 - CH_2 - CH_2 - CH_2OH$. Only the 'g' signal is interpretable in a down field region, all other signals having merged in to multiplet making it almost impossible to interpret. Upon addition of Eu $(DPM)_3$, the individual signals are found spread apart with respect to the TMS signal thereby facilitating easy interpretation.



Mechanism of Shift

The greater the concentration, greater is the distance of separation between the signals. The unpaired electrons in the paramagnetic Eu (111) ion is transferred through the intervening bonds to the protons of the organic molecule (alcohol, amine, ketone, aldehyde, ethers, esters etc). The spinning electron thus generates secondary magnetic fields through space around the protons, shifting their signals downfield.

C^{13} – NMR

Similar to hydrogen nuclei, a C^{13} nucleus has a spin number, I = 1/2, hence magnetic in character. By exerting a suitable external magnetic field, it must be possible to bring the nuclei into nuclear magnetic resonance. However, the natural abundance of this carbon isotope being only 1.1%, (compared to 99.8% in H^1 nuclei), and the magnetic moment only one fourth of H^1, the signals are less intense and weaker. Hence, larger amount of samples are required when the sensitivity of the signal is

enhanced several times by the summation of several signals using a technique called Computer Averaging of Transients (CAT), also known as Digital Signal Averaging (DSA). But the resulting spectrum is complex due to (1) the coupling between the H^1 nuclei attached to the C^{13} nucleus, and (2) the long range coupling $C^{13} - C - H^1$ and $C^{13} - C - C - H^1$, making it difficult for any interpretation. The problem is still complicated due to the large J values for the $C^{13} - H$ coupling (110-320Hz). These difficulties are overcome by the following decoupling processes.

(1) Broad Band – Noise Decoupling

The $C^{13} - H$ coupling is eliminated by double irradiation of all protons at their resonance frequencies. A decoupling signal having all the H^1 frequencies around 100 MHz is used to form a radio frequency noise. This results in a sharp single line for all the different types of carbon in the molecule. This spectrum has the advantage of all the $C^{13} - H$ couplings removed with an enhancement of the individual peak heights, but with the disadvantage of any coupling information.

2) Off – Resonance Decoupling

A simplified spectrum but with $C^{13} - H$ coupling information, can be achieved by off setting using a high-power proton decoupler by about 2000 Hz upfield of downfield from the proton frequency of the TMS. Consequently an incomplete collapse of the multiplicity results with the long range coupling lost completely, retaining the coupling due to the protons directly attached to the C^{13}. hence a methyl signal appears as a quartet, the methylene signal as a triplet and a methynic carbon (CH) as a doublet. A quarternary carbon will appear as a singlet.

Chemical Shift – C^{13}nmr

TMS is used as the internal reference as in H^1 nmr. A comparison of $C^{13} - H$ decoupled spectrum with the off resonance decoupled spectrum gives the following information.

1. The number of each type of carbon atoms
2. The number of protons if any, attached to each carbon and
3. The functional groups containing carbon atoms

For most of the organic compounds, the δ varies between the down field carbonyl carbon and the up field methyl carbon in the range zero to 220 ppm, as given below.

Functional group	δ (ppm)
$-CH_3$	0 – 30
$-CH_2-$	10 – 50
$\equiv CH$	25 – 60
$-OCH_3$	55 – 60
$-C \equiv C-$	65 – 90
$>C = C<$	80 – 145
C_6H_5	110 – 170
$-COOR$	160 – 178
$-COOH$	160 – 185
$-CHO$	190 – 210
$>C = O$	190 – 220

The state of hybridization is the dominant factor determining the chemical shift. A saturated carbon (SP^3 hybridized) absorbs in the high upfield and an unsaturated carbon (SP^2) in the downfield region. An SP hybridized carbon has intermediate absorption. All carbonyl as well as aromatic carbons absorb in the far downfield, due to electro negativity considerations. Substitution of an alkyl group on the carbonyl carbon causes a downfield shift and a phenyl group causes an upfield shift.

(e.g) Acetone absorbs at 204 ppm.

Acetophenone absorbs at 196 ppm.

Acetaldehyde at 199 ppm.

Benzaldehyde at 191 ppm.

Coupling Constant (J)

Coupling information regarding $C^{13} - H^1$, is observed in the off resonance decoupling spectrum. It ranges between 110 and 320 H_Z, increasing with the S character of the C – H bond, as well as with the substitution by electron withdrawing groups. C^{13} – H coupling also extends up to 3 neighbouring CH bonds, the value decreasing with increasing distance, in a saturated chain ranging from –5 to 60 H_Z. $C^{13} - C^{13}$ coupling is not usually observed, because of the low probability of two adjacent C^{13} atoms in a single molecule, the abundance of C^{13} being very low.

Optical Rotatory Dispersion (ORD) and Circular Dichroism (CD)

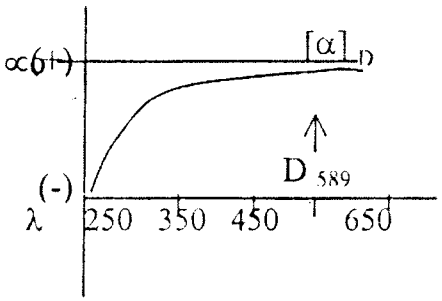
A plane polarized light (wave) may be considered to be made up of a right- circularly polarized wave and a left-circularly polarized wave. The electric vectors

The phenomenon of Cotton effect may well be studied through observation of optical rotatory dispersion of a chiral molecule, especially ketones, since they readily absorb in the ultraviolet region and Cotton effect occurs only near the U.V. absorption maximum.

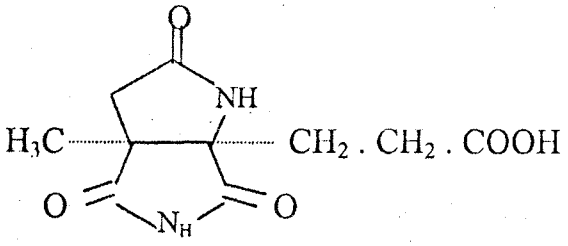
Types of ORD Curves and their Application

(1) Plain Curves

For compounds that absorb < 200nm (far U.V.) no Cotton effect is observed but a plain curve is formed showing an increase of optical rotation with decrease of wavelength, defined by Drude equation $[\alpha] = k / (\lambda^2 - \lambda^2_o)$ Where λ is the wave length at which specific rotation $[\alpha]$ is noticed and λ_o corresponds to the wavelength close to the U.V absorption maximum. It is observed that the specific rotations near the lower end of the curve are several orders higher than near the D line of sodium. Hence measurements of $[\alpha]$ could be made with less and less amount of the substance at the lower wavelength region, and the small changes in concentrations could be more readily followed. (e.g) 4 – cholestane and 5 – cholestane rotations differ by less than 10% near the D line of sodium but the difference is by a factor of 2 at 300 nm.



Plain curves are useful to decide whether a molecule is a recemate or optically active. (e.g) the degradation product of vitamin B_{12} does not show any appreciable rotation near the D line, but a considerable rotation at 365nm.



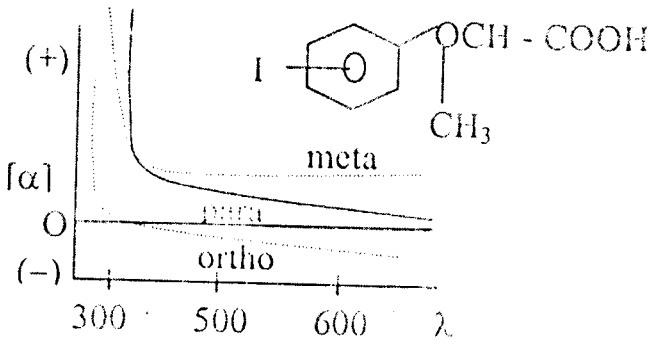
$[\alpha]_{589} \approx 0$

$[\alpha]_{365} = -165$

Hence the molecule is not a racemate, since a racemate will remain inactive at all wavelengths.

Plain curves have also been used to make configurational assignments. (e.g) In α - (Iodophenoxy) propionic acids, the dextrorotatory m and P – Iodoisomens

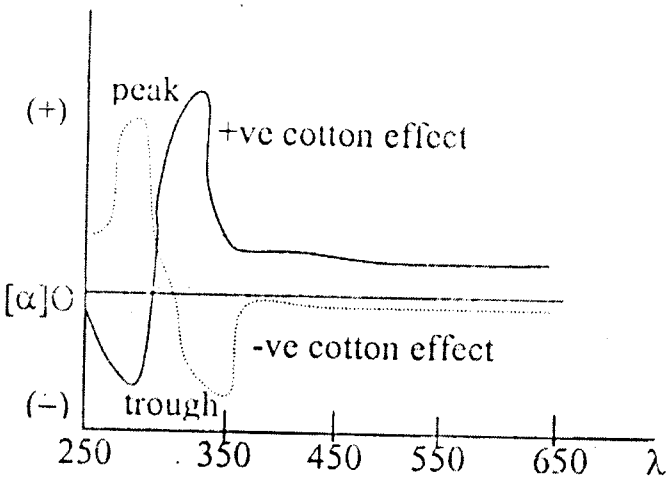
have the same configuration as that of the levorotatory O – isomes, at the D line of sodium, as inferred from the, shape of the curves. But they have the same rotation below 310 nm, since for the levorotatory O – isomes, the curve crosses the zero axis at 310 nm when inversion occurs. All these facts are apparent from the curves shown.



Plain curves have been found useful in determining the extent of helix formation in a polypeptide chain. In solvents which retard the formation of intramolecular hydrogen bonding, the peptides have a random conformation and they obey Drude equation to give a normal plain curve. But in other solvents, which permit intramolecular hydrogen bonds, there in more helical form as shown by a complex type of the curve.

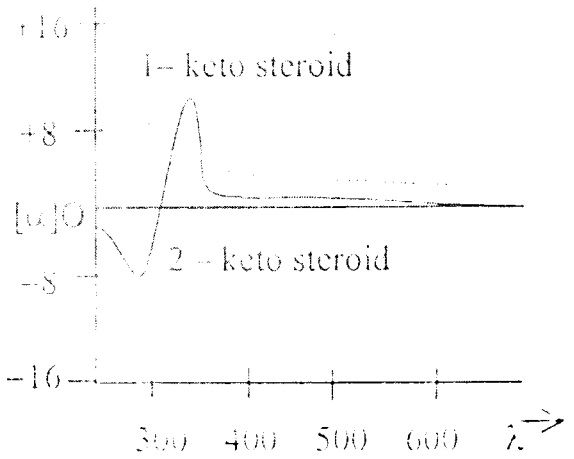
2) Anomalous Curves (Single +ve Cotton Effect or Single – ve Cotton Effect) :

When a molecule gives an absorption maximum near the λ max region it shows Cotton effect. While approaching the region of Cotton effect from longer wavelength if a peak is formed first, it is called positive Cotton effect and if a trough is formed first it is negative Cotton effect.

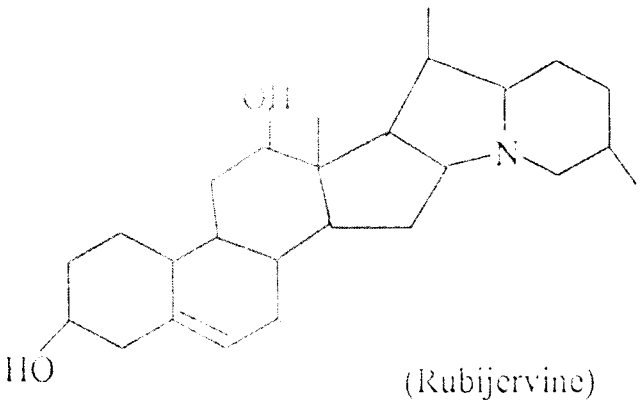


The point of intersection at the zero axis, is found correspond to the λ max of absorption in the uv region, and the lowest limit of absorption for such compands showing cotton effect is ~ 220 nm. Normally saturated ketones exhibit typical cotton effect, as the

carbonyl absorption at ~ 280 to 290 nm due to n → Π * transition is not strong enough to interfere with measurement of optical rotation in the region. (e.g) 3 – cholestanone exhibits positive cotton effect and crosses the zero axis at 285 nm which is also the λ max of this ketone. But 1 – cholestanone shows a drastically different curve, there by enabling to locate their functional groups in steroids. However 2 –cholestanone behaves very similar to 3 –cholestanone, hence indistinguishable by ORD curves.

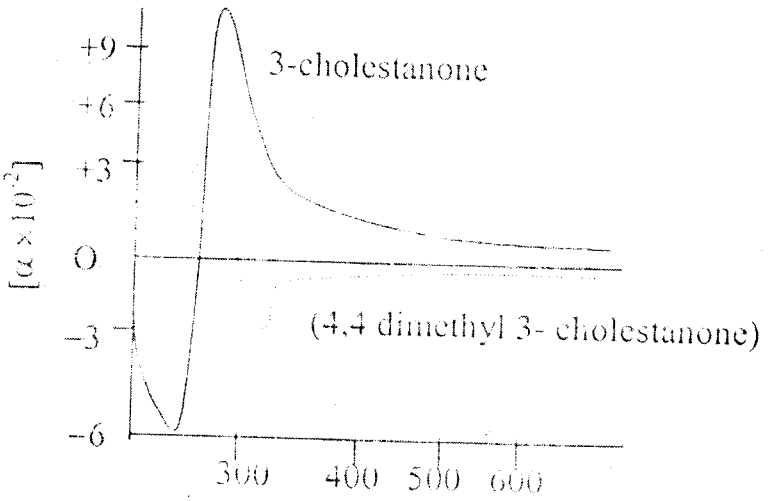


A 12 – keto steroid shows an entirely different curve though with positive cotton effect. (e.g) The steroid alkaloid, rubijervine with two OH groups, when partially oxidized gave a ketone whose ORD curve was found to be similar to that of a 12 – keto steroid, thereby confirming the oxidation of the corresponding OH group.



(Rubijervine)

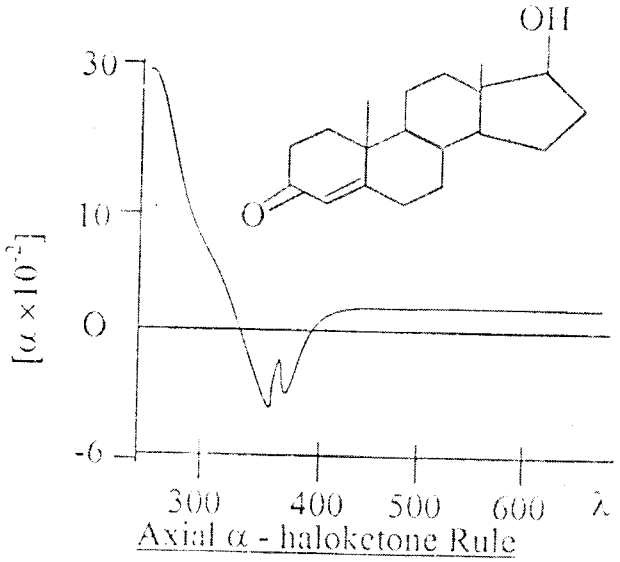
An interesting example of inversion of cotton effect, is noticed while introducing a gem-dimethyl group at C_4 position in 3 – cholestanone, This phenonmenon is applicable to fix positions of gem-dimethyl groups in similar molecules.



ORD studies have also proved to be helpful in the determination of configuration as well as conformation of molecules.

3) Multiple Cotton Effect Curves

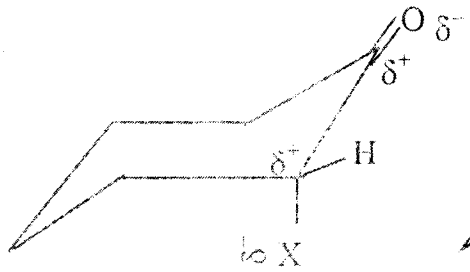
When two or more uv absorption bands result, multiple cotton effect curves are observed (e.g) testosterone is a conjugated ketone giving absorption due to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transition. Hence the curves are complex and difficult to interpret



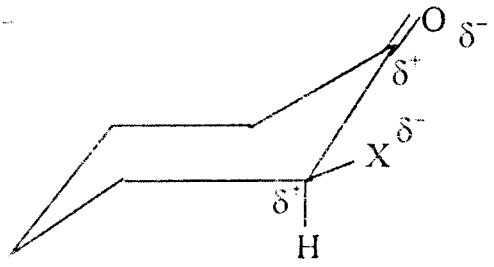
Axial α - haloketone Rule

Introduction of an α - halogen (not fluorine) substituent in a aliedic ketone, shifts the uv as well as IR absorption by more than 20 units, if the halogen is in the axial position. For example in chclohexanone, the uv absorption is shifted by 22 nm when a chlorine is introduced at the α, axial position, since it facilitates a stronger overlap of the π electrons of the carbonyl group with the lone pairs of the halogen. The IR absorption also increases by 22 cm^{-1} due to increase in C = O stretching caused by

dipolar repulsion while at the axial position. Presence of halogen at the equatorial position will lead to a field effect which reduces the stretching, resulting in a decrease in absorption.



(axial halocyclohexanone)



(equatorial halo cyclohexanone)

Corresponding changes have been observed in ORD values, at the presence of a halogen in the axial orientation, resulting in inversion of cotton effect. However, the inversion of cotton effect depends on the position, configuration and conformation of the haloketone. This may be stated in the form of a rule (Axial haloketone rule)

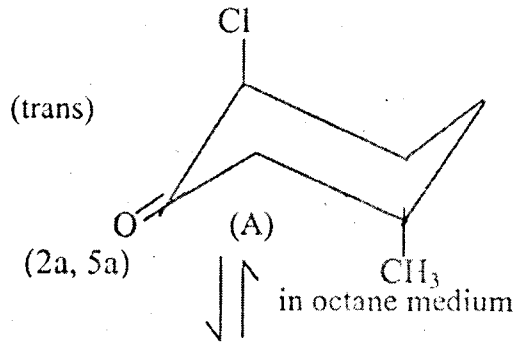
"When the halogen atom is viewed along the C = O group which forms the head of the chair form of the cyclohexane ring, if it falls on the left of the line of view, the compound will exert a negative cotton effect and it on the right, a positive cotton effect".

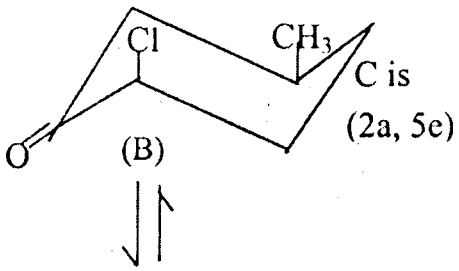
Application of Axialhaloketone Rule

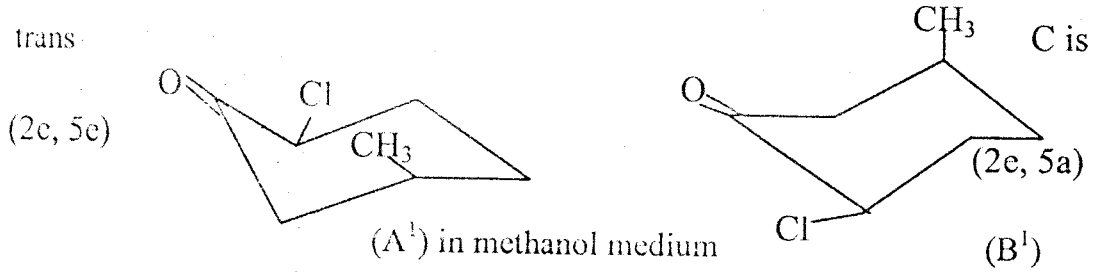
The rule is helpful to arrive at the position, configuration or conformation of a haloketone residue in any molecule, if two of these factors are known.

Conformation of 3 – methyl cyclohexanone

(+) –3 – methyl cyclohexanone has a configuration which on chlorination gives a mixture of two configurational isomers. Each of these may exist in two conformations. The configurational isomers are found to be A (trans) and B (Cis) of 2-chloro – 5 – methyl cyclohexanone, where the chlorine is axial





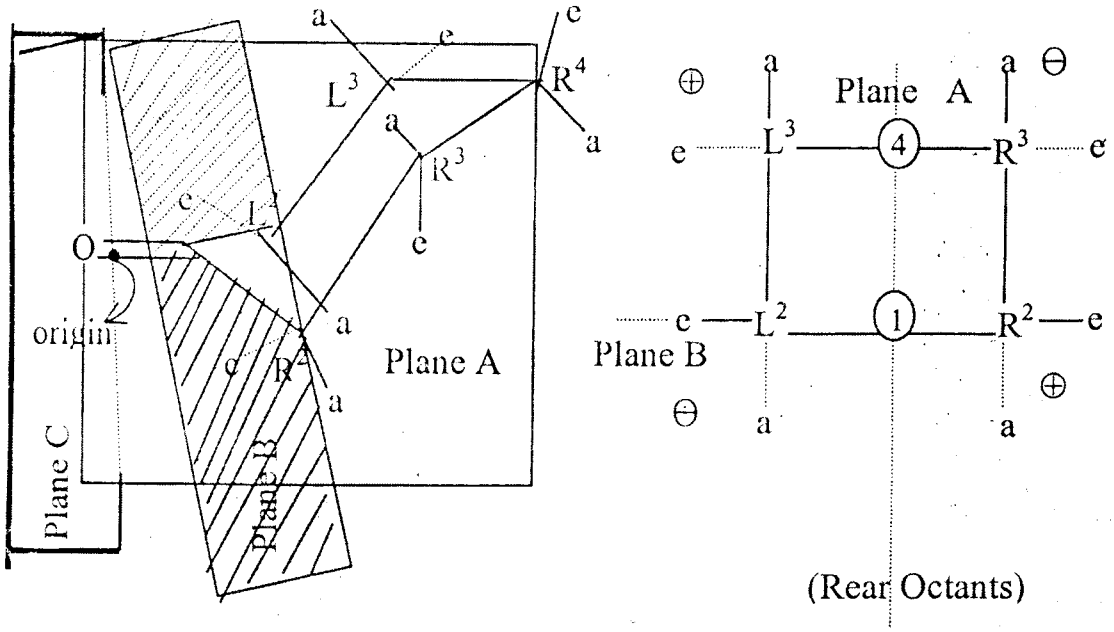


In octane medium, the molecule is found to have negative cotton effect. Hence the 2 – chlro – 5 – methyl cyclohexanone should have the configuration A and not B, since according to axial haloketone rule, the halogen is falling to the left of view along the carbonyl group. The ORD curve in methanol medium is found to have positive cotton effect, since the diaxial conformer should have changed over to the diequatorial form which is more stabilized being predominant.

Hence, by fixing the position of the substituent and configuration of the molecule, it is possible to predict the conformation of a molecule.

Octant Rule

This is an empirical rule which predicts the sign of cotton effect for a number of ketones from their structure, configuration and conformation.



The molecule is oriented in such a way that the three orthogonal planes A, Band C pass through the molecule. Plane A passes through C_4 and the carbonyl oxygen. Plan B is horizontal passing through C_1, R^2 and L^2. plane C is passing midway through the C = O axis. The molecule is viewed through the C = O axis, while the various parts

of the molecule (substituents) fall into different octants. Normally the front octants are empty whereas the rear octants hold the substituents, which decide the optical rotory dispersion of the molecule.

The octant rule states that the substituents of the alicyclic ketones, lying in the far lower right (R^2) and far upper left (L^3) make a positive cotton effect, whereas those in the far lower left (L^2) and the far upper right (R^3) make a negative cotton effect. Substituents falling along the coordinate axis do not contribute to the cotton effect, and substituents if any lying in the front octant, will have just opposite effect to those in the rear octants.

For the cyclohexanone molecule in the diagram, the axial substituents in R_2, and all the substituents in L_3, make a positive contribution whereas the axial substituents in L_2 and all the substituents in R_3, make a negative contribution. Substituents in C_4, fall on plane A and the equatorial substituent in R_2 and L_2 fall on plane B, hence do not make any contribution to cotton effect.

Applications

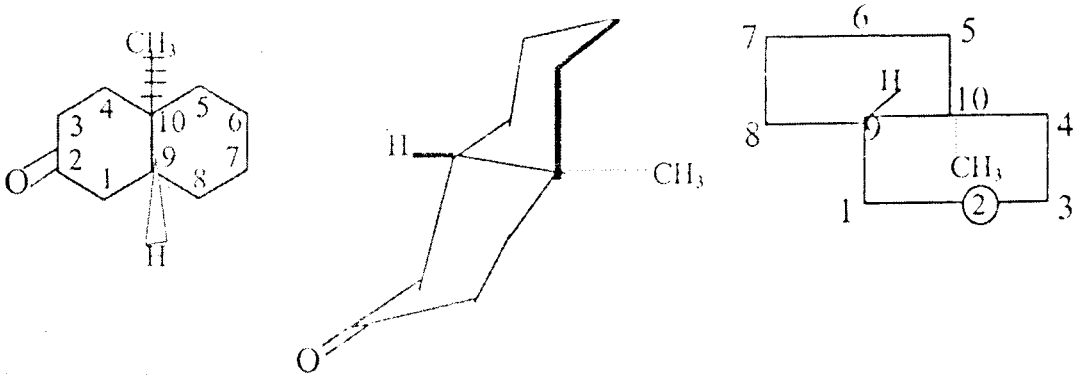
The applications of the rule can be illustrated from the following examples, to predict the cotton effect as well as to determine the configuration and conformation.

1) α - Axial Chloro Cyclohexanone

Applying the octant rule to α - axial chloro cyclohexanone molecule, shows that the only substituent at the α - axial position falls on the R_2 and it should exert a positive cotton effect. This has also been established using the axial haloketone rule. Hence, axial haloketone rule in a special case of octant rule.

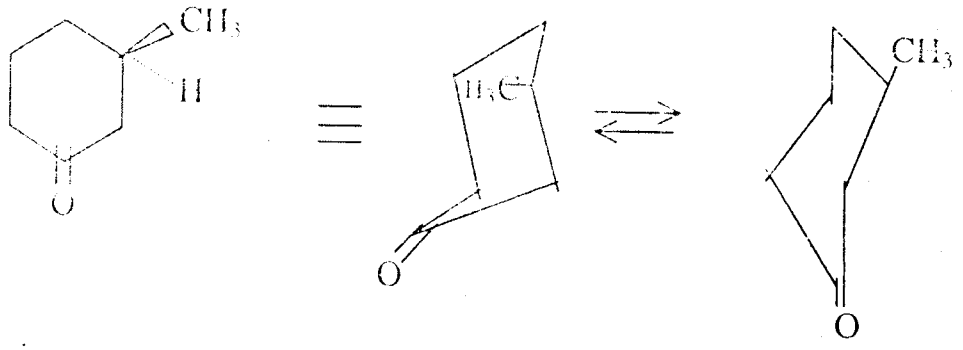
2) Configuration of (+) trans – 10 – methyl – 2 – decalone

The absolute configuration of this bicyclic molecule could be established from the sign of cotton effect of the molecule.



When the configuration of the molecule in trans as indicated in the diagram the C_{10} methyl substituent is in plane A, hence make no contribution. The substituents C_8, C_7 and C_6 being equatorially attached to C_9, are in the upper left octant (L_3 in the original diagram). They make positive contribution to cotton effect. Experimental values also indicate that (+) trans – 10 – methyl – 2 – decalone has a positive cotton effect. Hence the given configuration represents the absolute configuration of the given molecule.

3) Conformation of (+) –3 – methyl Cyclohexanone



R – isomer 3 - axial 3 –equatorial

The given molecule with R configuration can exist in the axial methyl or equatorial methyl conformation. On application of octant rule, the axial methyl group falls on the upper right octant (ie) R_3 in the original diagram, hence should have negative cotton effect. But the equatorial conformer should have positive cotton effect, since the substituent falls on the upper left (ie) L_3 in the original diagram. However, the molecule is stabilized only when the conformer has the 3 – methyl group at the equatorial orientation, hence the equatorial form predominates in the equilibrium mixture and the conformer with negative cotton effect is the predominant conformer.

Solved Problems

1) An organic compound C_7H_6O absorbs at 244 nm (Σmax 15,000), 280 nm (Σmax 1,500) and at 328 nm (Σmax, 20). It gave a negative iodoform test. It shows the following IR absorptions: 3037, 2825, 2717, 1700, 1390, 749, 699 cm^{-1}. Mass spectrum gives m/z = 106,78,77 and 51. Identify the molecule.

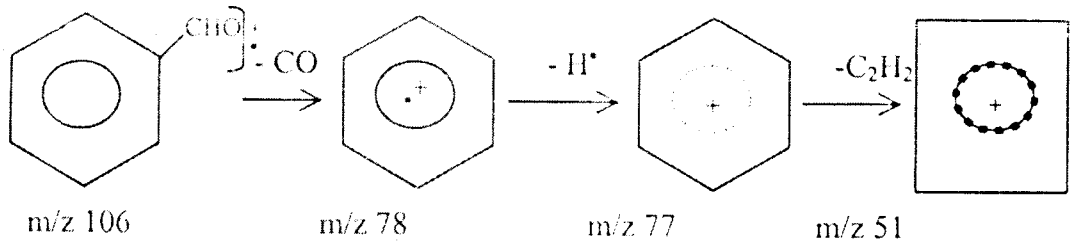
Solution:

The UV spectral data are indicative of an aromatic ring.

The IR absorption at 3037 cm^{-1} indicates the aromatic C-H str. This is further confirmed by the presence of mass spectral lines at 78 and 77 (m/z), due to the benzene ring. As the molecule doesn't answer iodoform test, there is no CH_3CO – group. The seventh carbon may be in the form of a carbonyl group, and possibly an aldehyde group. Then the UV absorption at 244 nm must be the $\pi - \pi^*$ transition, 280 nm due to $n \rightarrow \pi^*$ transition. The 328 nm absorption may be the R-band.

The presence of CHO group is confirmed by the IR absorption at 1700 cm^{-1}, and the doublet at 2825 and 2717 cm^{-1}. Hence the molecule is Benzaldehyde.

The mass spectrum may be interpreted considering the m/z values:



m/z 106 m/z 78 m/z 77 m/z 51

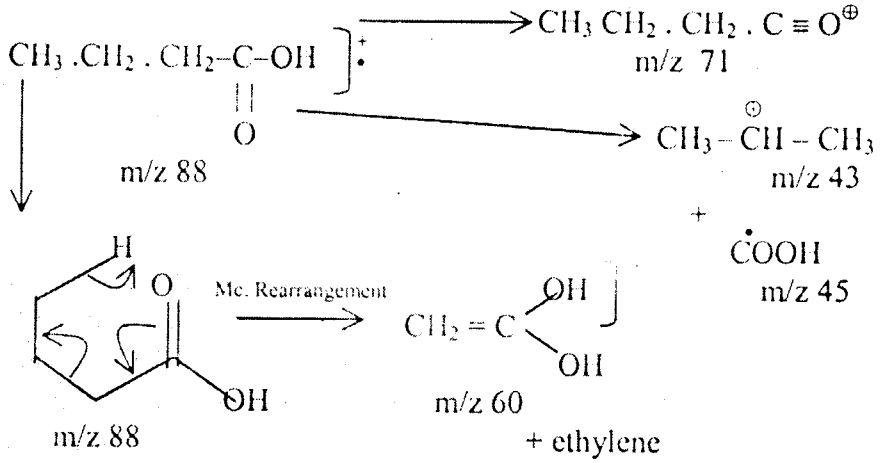
2) An organic molecule $C_4H_8O_2$ shows no UV absorption near or beyond 200 nm. IR absorptions are given at 1720 (sharp) and 3000 – 2900 (broad) apart from 2960, 2872 and 1490 cm^{-1}. Mass spectral lines are observed at m/z 88, 71, 60, 45 and 43. Identify the molecule and interpret the data.

Solution:

The absence of any UV absorption indicates there is no conjugation in the molecule. The molecule must be aliphatic since there is a possibility of a CH_3 group in the molecule due to a doublet in the IR spectrum at 2960 and 2872 cm^{-1}, characteristic of a CH_3 group. The absorption at 1490 cm^{-1}, is due to C-H def. The possible structure of the molecule is:

$CH_3 . CH_2 . CH_2 (CO_2H)$

The carbonyl function may be in the form of a COOH group. This is supported by the IR absorption at 3000 – 2900 cm^{-1} due to OH str. and the possible carbonyl absorption at 1720 cm^{-1}. The mass spectral data further confirms the structure.

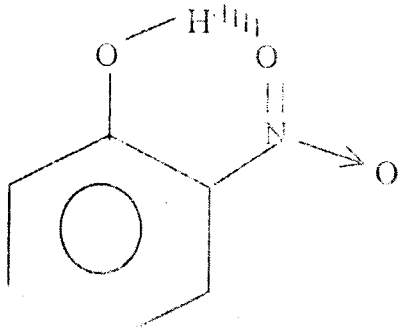


3) An organic compound $C_6H_6NO_3$ gave the following spectral data:
UV – 280 nm (Σmax 6600)
IR – 3460 (sharp), 3035, 1585, 1510, 1360, 1320 and 740 cm^{-1};
nmr – δ = 12, 1H (broad, singlet), δ = 7.39 – 7.25, 4H (unsymmetrical).
Identify the molecule.

Solution:

The molecule contains an aromatic ring as shown by the UV data and the C–H absorption at 3035 cm^{-1}. The 3460 cm^{-1} absorption may be due to a OH group. It is supported by the nmr (δ, 12). The sharp peak of OH may be due to intra-molecular H-bonding with some other group.

The unsymmetrical pattern of the aromatic protons shows that another group, probably a Nitro group is attached to the ring at the ortho position as indicated by the IR absorptions at 1585 and 1510 cm^{-1}. The given datas confirm the following structure.



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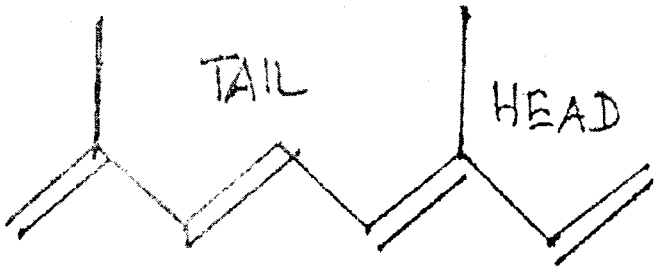
Unit III

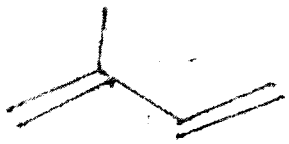
TERPENOIDS

Introduction:

They are a group of compounds mostly present in the essential oils obtained from plant kingdom. Initially the term terpenes was used to refer these compounds. "Enes" usually refer to unsaturated hydrocarbons and do not include other functional groups like allhydes, ketans etc. But the compounds obtained from essential oils may contain one or more of these functional groups. So to encompass all such components into one fold the term Terpenoids is used.

Any natural product obtained from plants which upon thermal decomposition gives isoprene as one of the products may be classified as a terpenoid. Wallach(1887) termed this behaviors of the natural plant materials as isoprene rule. Ingold(1925) pointed out the presence of 'head to tail' fusion in most of the Terpenoids (The substituted carbon side is the head and the unsubstituted side is the tail of the isoprene) . This is termed as special isoprene rule. The latter is only a guiding principle arriving at the structures of Terpenoids. Of course many exceptions are also there.





ISOPRENE UNIT

Terpenoids are classified on the basis of the number of isoprene units present in them.

No of Isopropene units	Formula	Classification
2	$C_{10}H_{16}$	Monoterpenoid
3	$C_{15}H_{24}$	Sesqueterpenoid
4	$C_{20}H_{32}$	Diterpenoid
5	$C_{25}H_{40}$	Sesterterpenoid
6	$C_{30}H_{}$	Triterpenoid

Terpenoids are usually isolated from their natural sources using steam distillation. Subsequently purified through fractional distillation.

For the general structure elucidation of terpenoids, the learners may look in unit III of I M.Sc organic chemistry lessons. UV,IR,NMR. Mass spectrometric techniques may also be used in the structure elucidation of terpenoids.

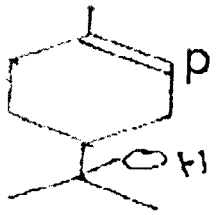
α-Pinene

This is a bicyclic monoterpenoid. It occours in turpentine oils in both (+) and (-) forms.

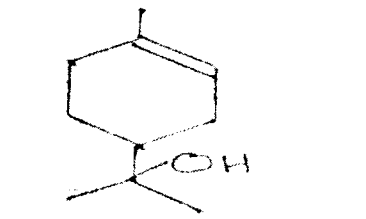
From analytical data the molecular formula of ά-pinene was found to be $C_{10}H_{16}$. Since it takes up one mole of bromine to form a dibromide ά-Pinene should contain one double bond. The saturated hydrocarbon formula $C_{10}H_{18}$, corresponds to CnH_2n-2, the general formula for compounds with two rings. Hence α-pinene should be bicyclic.

α-pinene on treatment with ethanolic sulphuric acid forms ά-terpenoi, whose structure is already known α- terpineol has a six membered ring. How to identify the second ring?(Since ά-pinene is bicyclic).

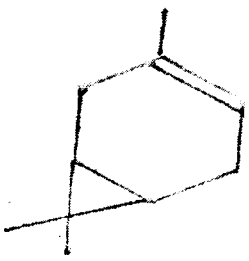
α -pinene ---------- (Ethanolic H_2SO_4) ---------->



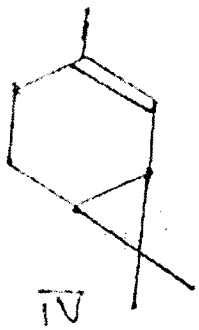
α-pinene is a hydrocarbon. It undergoes hydration to give ά-terpineol , an alchohol. So the carbon with the hydroxyl group may be involved in the bicyclic ring formation. This gives rise to four possible structures.



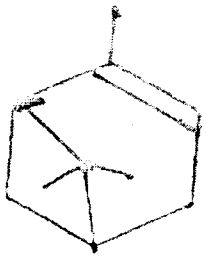
α-TERPENIOL



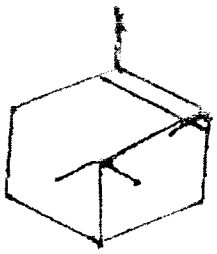
III



IV



I

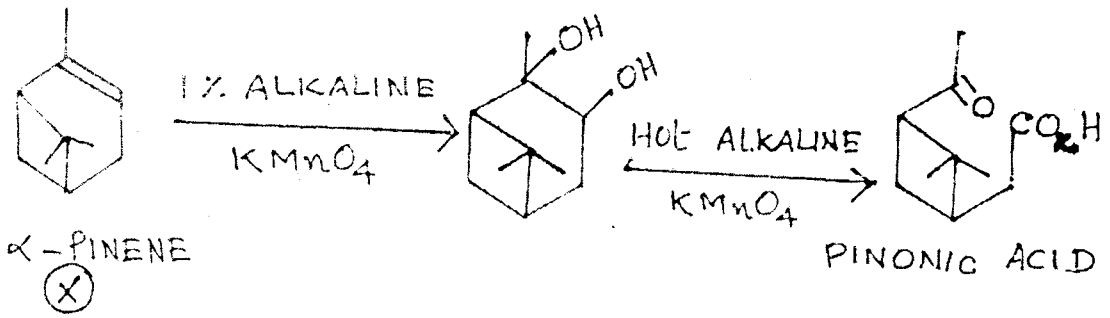


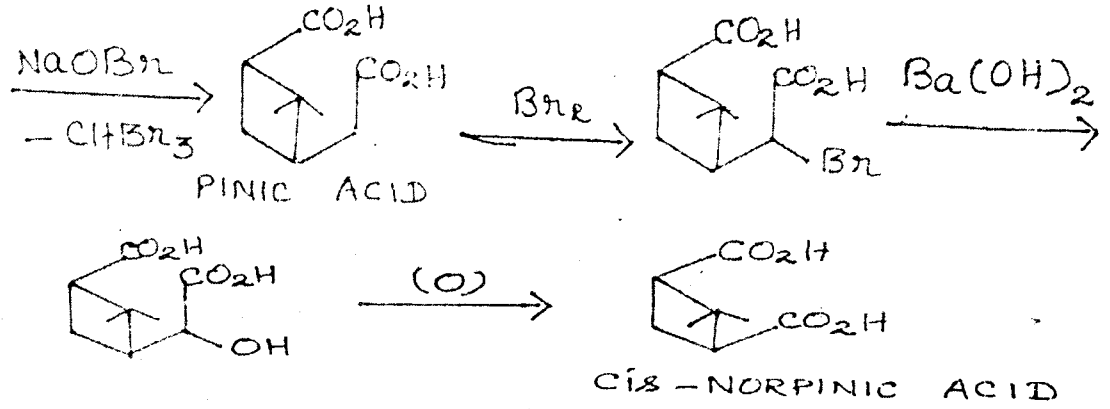
II

Two structures with four membered things and two structures with three membered things are possible. Structure II can be readily ruled out on the basis of Bredt's rule.(According to this rule, a double bond cannot terminate at the point of fusion of small size rings, because of ring strain). This leaves three structures in the fray. Baeyer(1896) showed that the second ring is four membered from the following reactions.

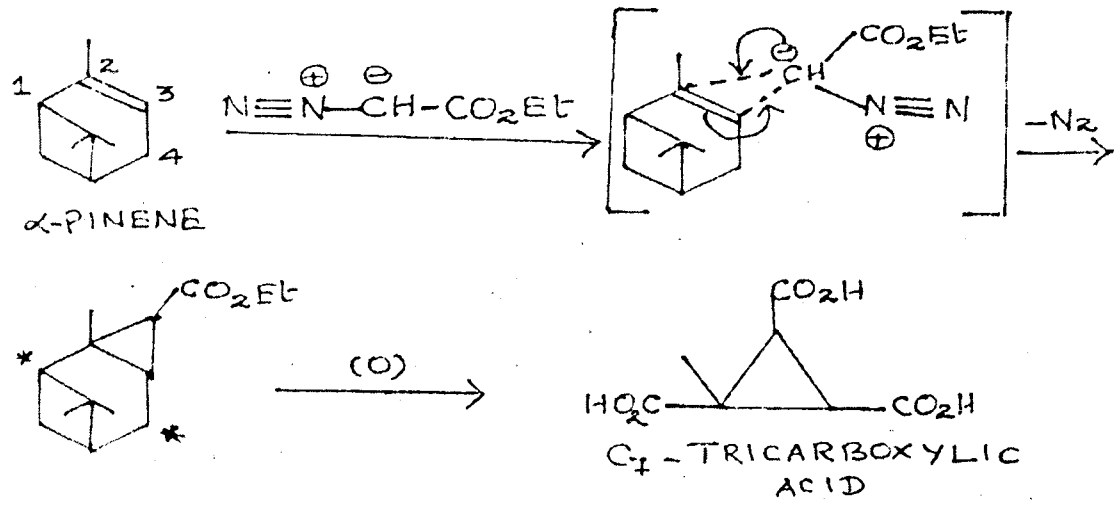
ά-pinene on oxidation with 1% alkaline potassium permanganate gives pinene glycol. The glycol when warmed with alkaline permanganate forms pinonic acid. These two products are due to the double bond present in ά-pinene. On treatment with alkaline hypobromite, pinonic acid undergoes iodoform reaction to give a saturated dicarboxylic acid. The latter acid on bromination followed by baryta treatment and oxidation gives cis-norpinic acid, again a saturated dicarboxyclic acid. The molecular formula of cis-norpinic acid is $C_8H_{12}O_4$.

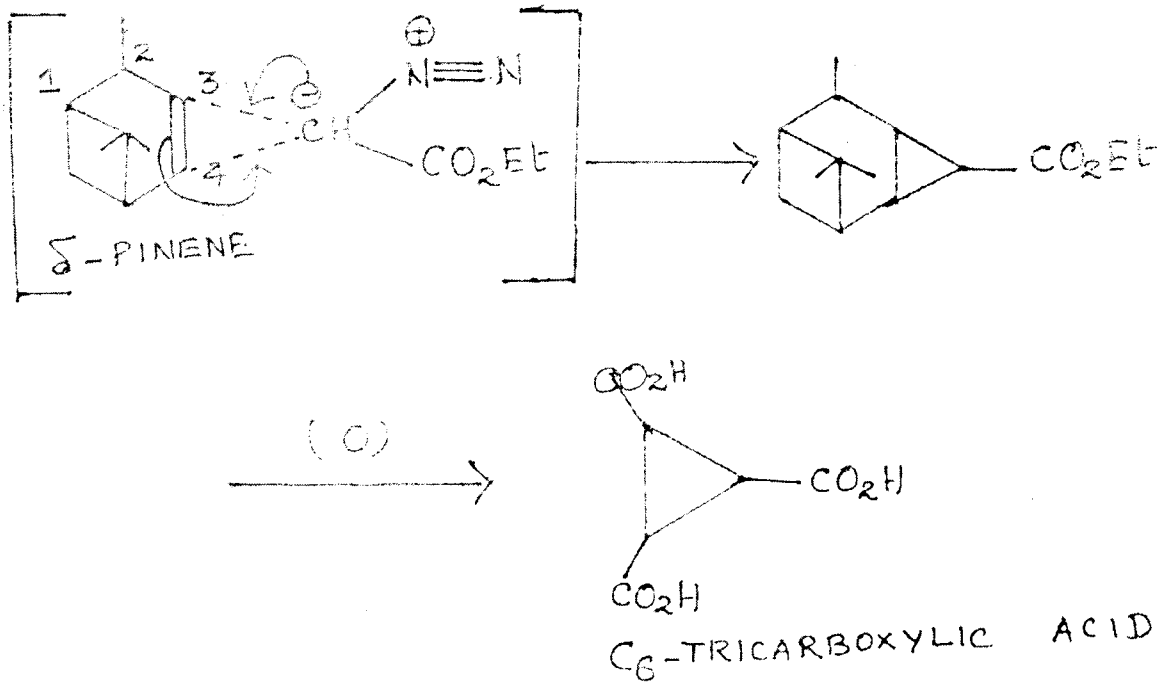
Considering the presence of two carboxylic acids and a gem- dimethyl group.(formation of ά-terpineol). The potential structure of the norpinic acid can be written as $(CH_3)_2\ C_4H_4(CO_2H)_2$. If the methyl groups and the carboxyl groups are considered as substituents, then the formula becomes C_4H_8, which corresponds to a cyclobutane derivative. So nor-pinic acid is probably a dimethyl cyclobutanedicarboxylic acid. In turn, pinic acid could therefore be a cyclobutane derivative with one side – chain of $-CH_2CO_2H$. All the above reactions can be formulated if we assume the structure of ά-pinene as (X),





The position of the double bond is confirmed as follows: Oxidation of the addition product formed by the addition of diazoacetic ester to ά-pinene gives C_7 tricarboxylic acid. This confirms that the position of double bond is in between C_2 and C_3 and not in between C_3 and C_4.



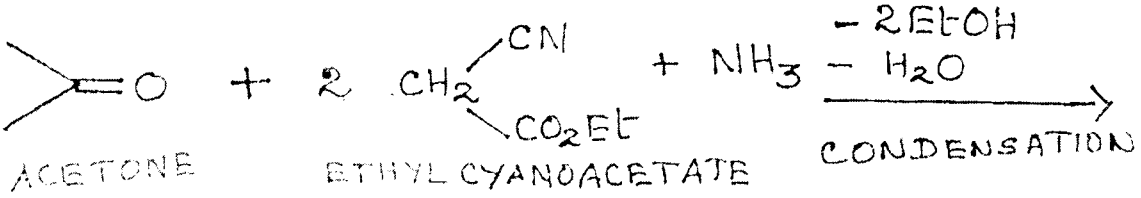


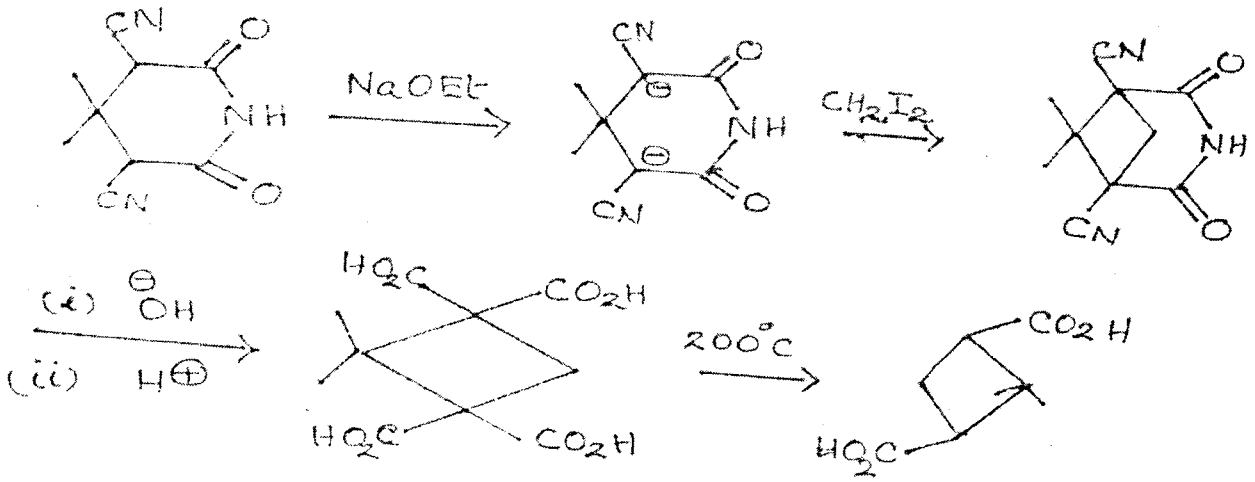
Finally the structure of α-pinene has been confirmed by its synthesis. This synthesis involves four stages.

i Synthesis of non-pinic acid(Kerr,1929)
ii Synthesis of pinic acid from nor- pinic acid (Guha etal 1934).
iii Synthesis of trans-pinonic acid from pinic acid.(Rao,1943).
iv Synthesis of α-pinene from trans-pinonic acid(Ruzicka 1970 – 74).

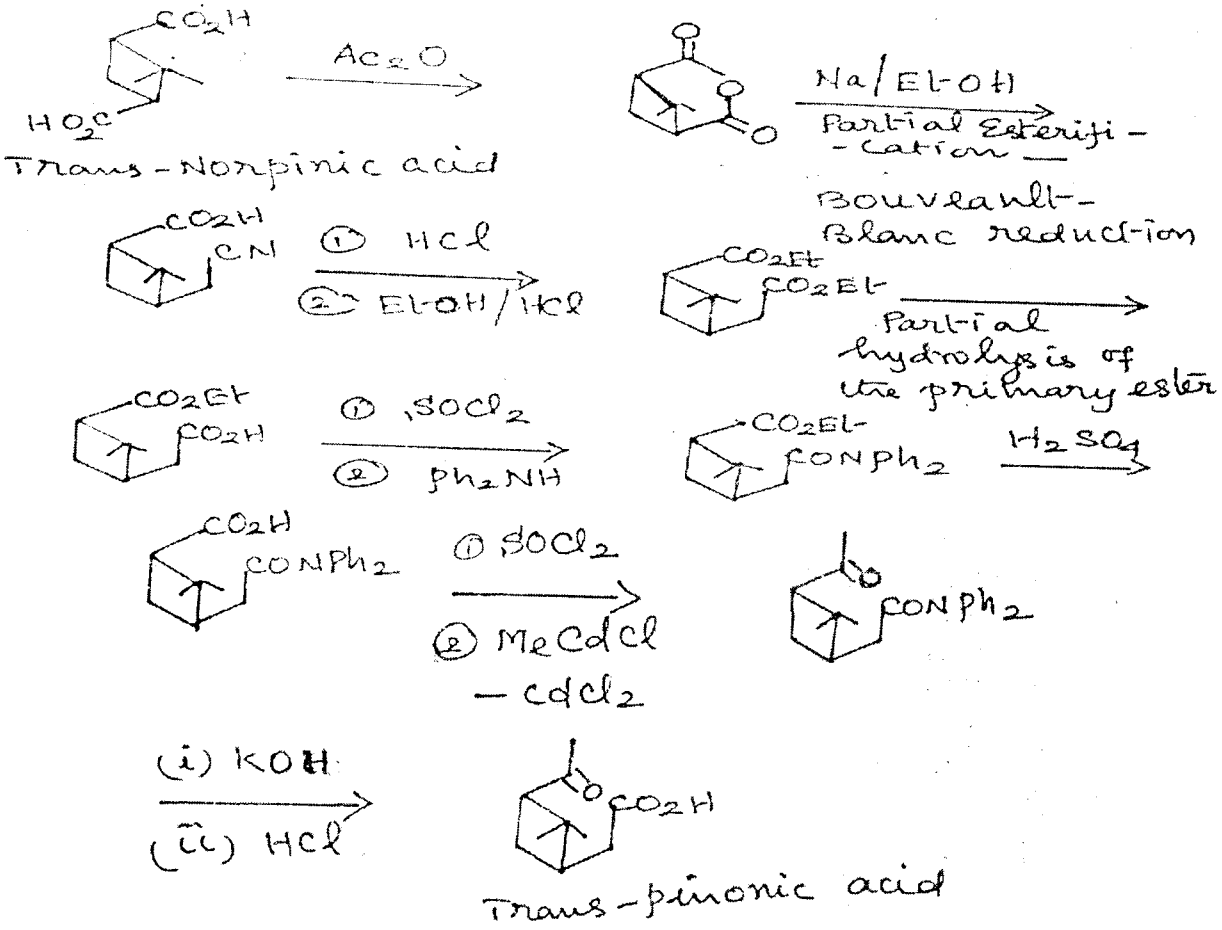
(The final part of the synthesis has already been done by Ruzicka using pinonic acid obtained from α-pinene. The total synthesis was delayed because of the delay in the synthesis of nor-pinic acid)

a. Synthesis of nor-pinic acid:

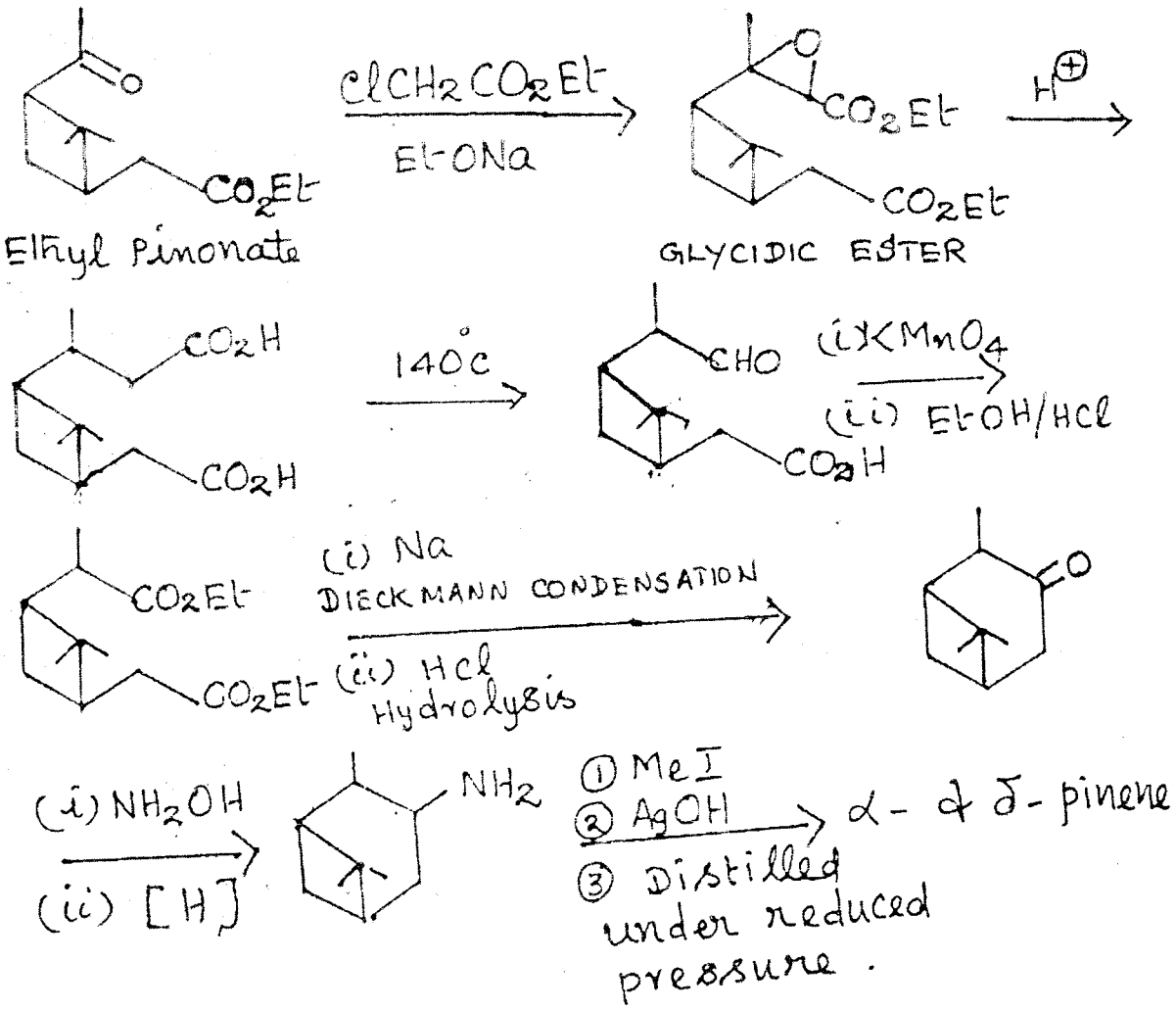




b. Trans-norpinic acid to trans-pinonic acid



c. Trans-pinonic acid ester to α-pinene:



ZINGIBERENE

This occours in the (-) form in ginger oil. From elemental analysis and molecular weight determination the molecular formula of this compound was found to be $C_{15}H_{24}$.

On catalytic hydrogenation zingiberene gives hexahydrozingiberene. This shows the presence of three double bonds.

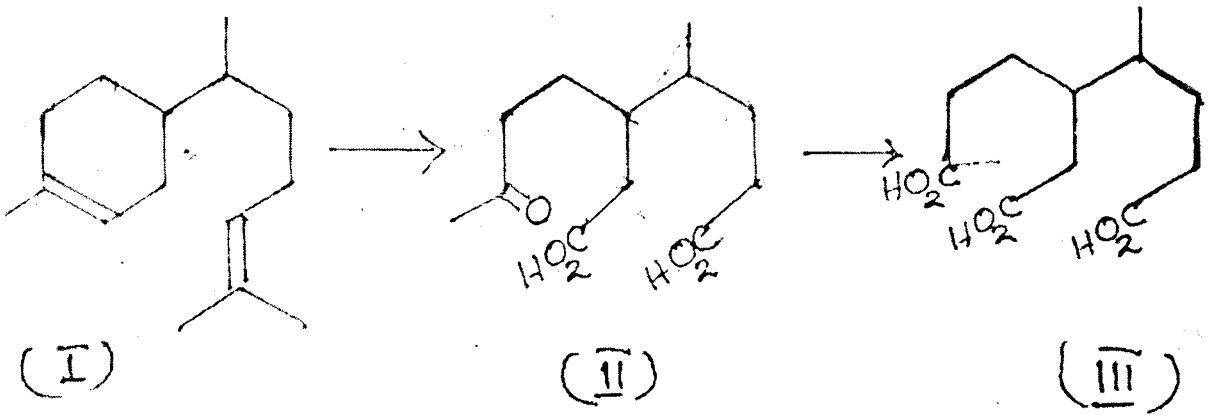
Thus the saturated hydrocarbon formula for zingiberene ($C_{15}H_{24}+6H = C_{15}H_{30}$) is deficient of 2H atoms to the acyclic paraffin analogue. Hence must be monocyclic.

Sodium alcohol reduction of zingiberene gives dihydrozingiberene. So probably two of the double bonds are conjugated. This is confirmed by the fact zingiberene

exhibits optical exaltation wheras dihydrozingiberene does not form an adduct with maleic anhydride. The λmax for zingiberene is 260 mm. This value is greater than 253mm, the base value for homoannular diene. So zingiberene must contain a cisoid diene system.

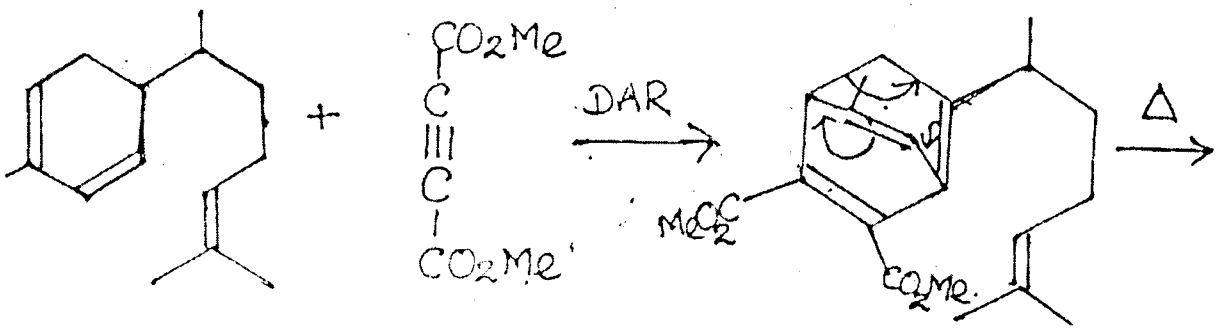
Zingiberene on ozonolysis gives acetone, laevulic acid and succinic acid. Bisabolene also forms these products during ozonolysis . So it appears probable that zingiberene and bisobolene have the same carbon skeleton.

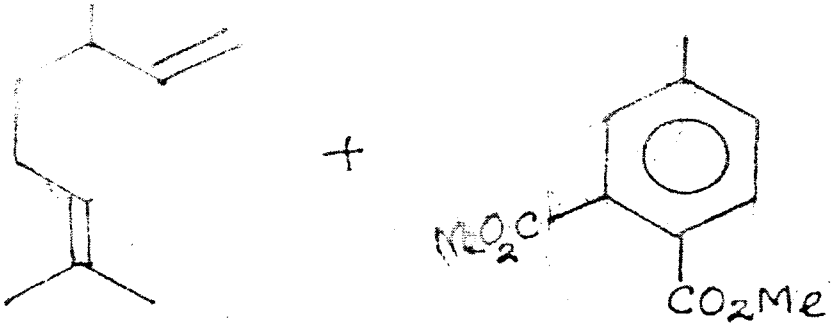
Oxidation of dihydrozingiberene (I) with permanganate gives a keto dicaboxylic acid, $C_{12}H_{20}O_5$ (II), which, on oxidation with sodium hypobromite forms a tricarboxylic acid, $C_{11}H_{18}O_6$ (III). Thus (II) must contain a methylketone (CH_3CO -) group, and so, if (I) be assumed as the structure of dihydrozingiberene, the forgoing oxidation reactions can be formulated as follows.



The positions of the conjugated double bonds are arrived at as follows.

Zingiberene forms an adduct with methylacetylenedicarboxylate (which was not isolated), the adduct on pyrolysis forms 1,6 – dimethylocta -3,6-diene and methyl-4-methylphthalate. The formation of these products can be explained if we assume the following structure for Zingiberene.



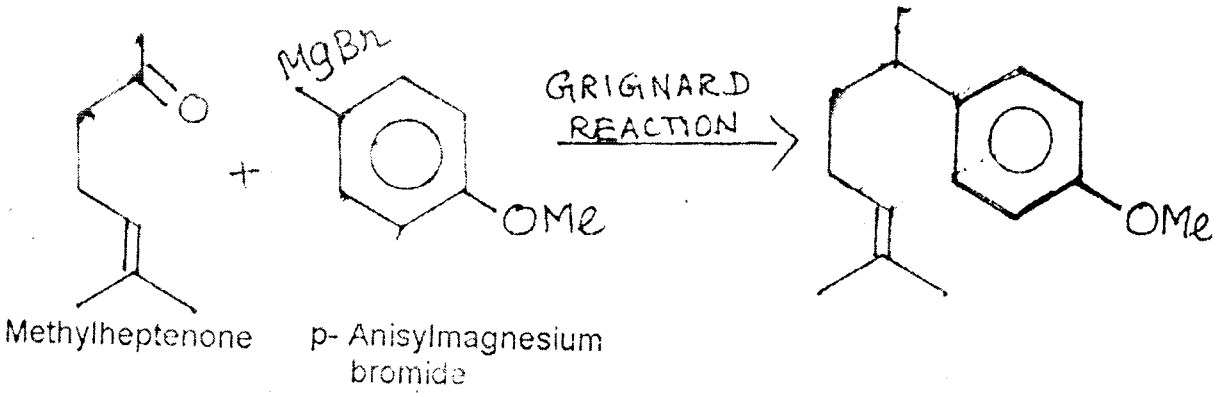


1,6 -Dimethylocta-3,6-diene

Methyl - 4 - methylphthalate

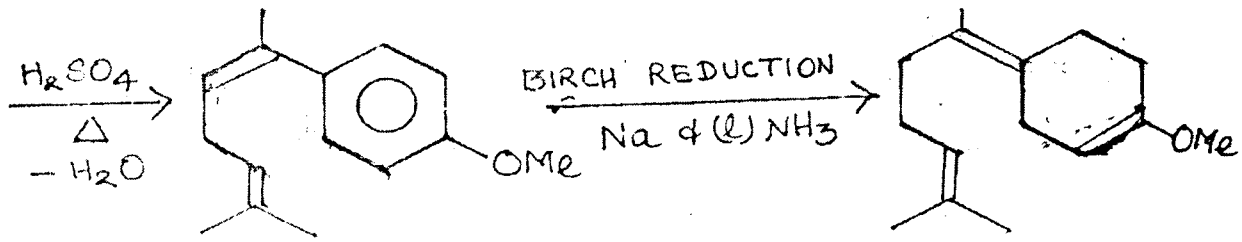
Finally its structure has been confirmed by its synthesis.

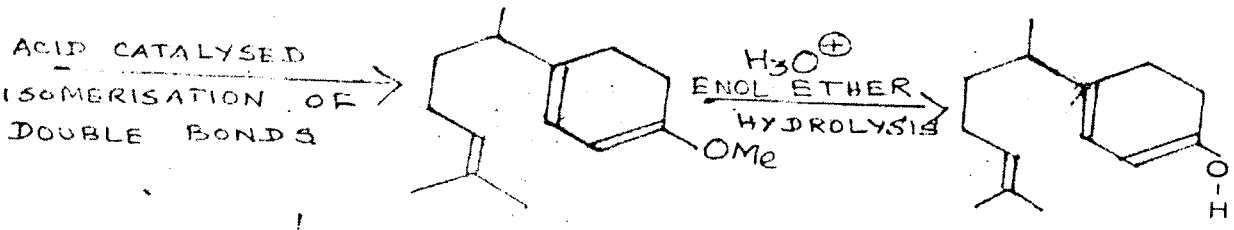
Synthesis:

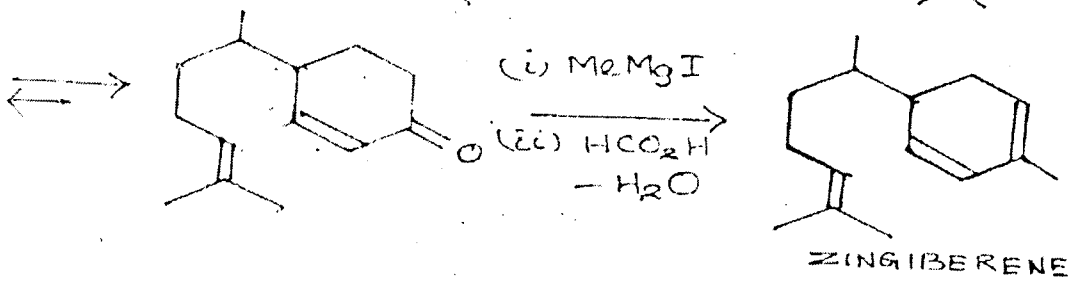


Methylheptenone

p- Anisylmagnesium bromide







ZINGIBERENE

√-BISABOLENE

This occours in the oil of myrrh and other essential oils.

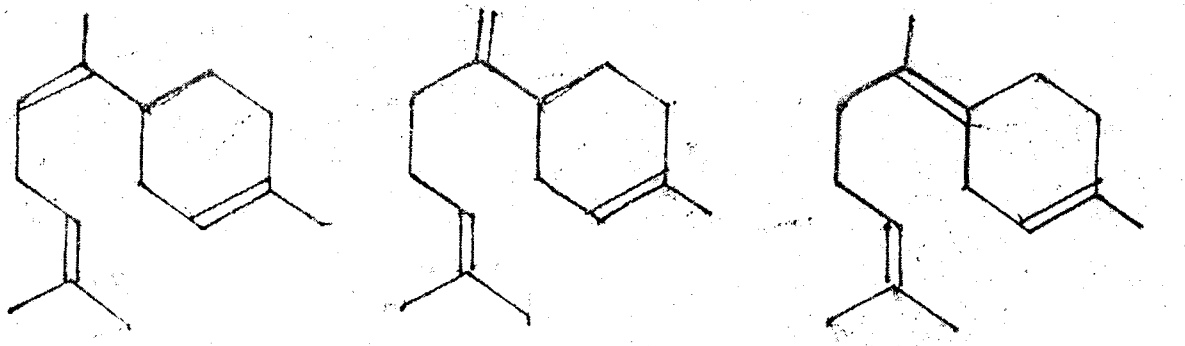
From elemental analysis and molecular weight determination the molecular formula of √ -bisabloene was found to $C_{15}H_{24}$.

Catalytic hydrogenation of √-Bisabolene gives a hexahydro derivative. This suggests the presence of three double bonds in γ-Bisabolene .

The saturated hydrocarbon formula for this compound is 2 hydrogen atoms defficient of the corresponding acyclic paraffin analogue. Hence γ-bisabolene should be monocyclic. The double bonds are not conjugated is evident from the fact that there is nó uv absorption above 225mm and there is no appreciable molal exaltation also. The structure of bisabolene is arrived at from the following set of reactions.

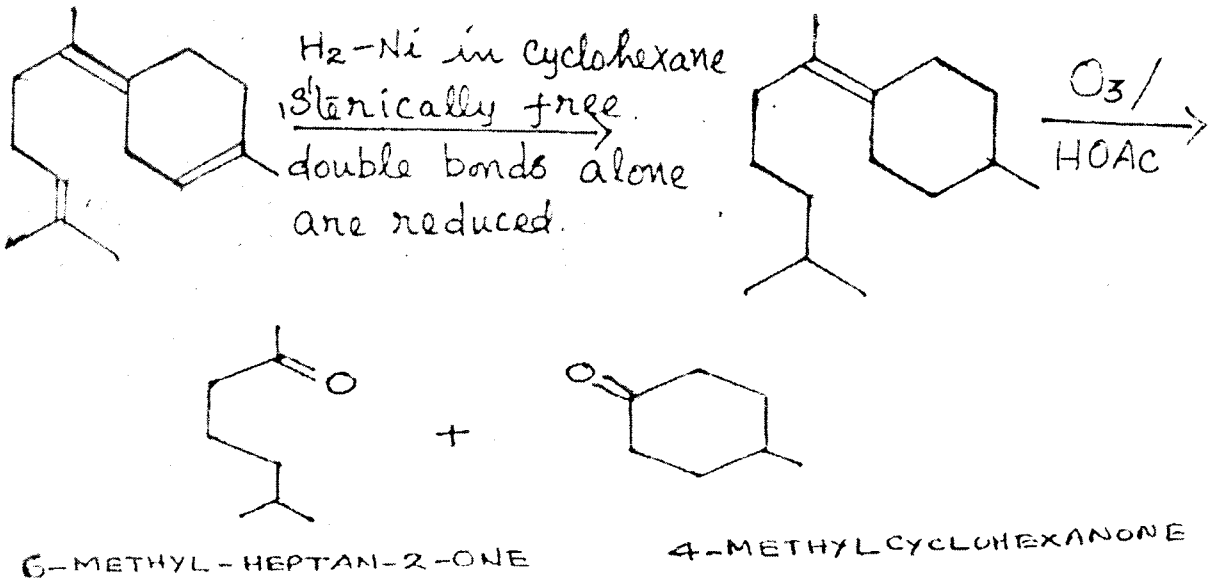
Dehydration of nerolidol gives a mixture of α- and β- farnesenes. This mixture on treatment with formic acid gives a monocyclic sesquiterpenoid. The latter gives bisabolene trihydrochloride when combined with hydrochloride. Treatment of the trihydrochloride with sodium acetate in acetic acid produces bisabolene. Based on this, three structures can be written for blsabolene(I to III),since all three would give the **same** bisabolene trihydrochloride.

Ruzicka et al (1929) showed that synthetic and natural bisabolene consisted mainly of the γ-isomer (III), since on ozonolysis,bisabolene gave acetone, laevulic acid and a small amount of succinic acid. Structure(III) could explain the formation of these products.



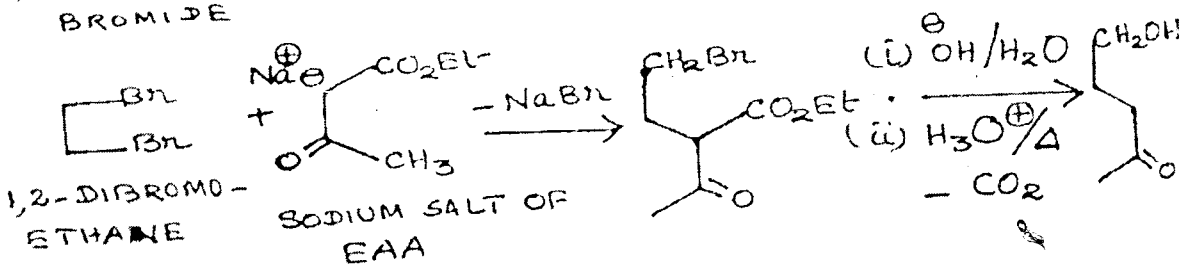
Structure II is ruled out on the basis of non-formation of formaldehyde from bisabolene during ozonolysis.

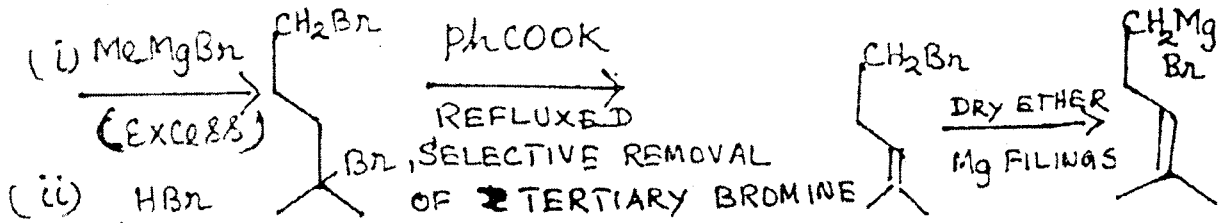
Semmler and Rosenberg established the position of the third double bond.



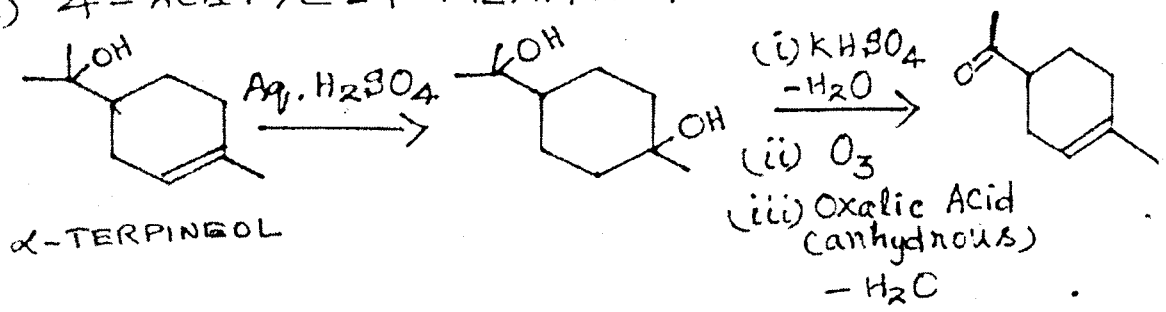
Synthesis:

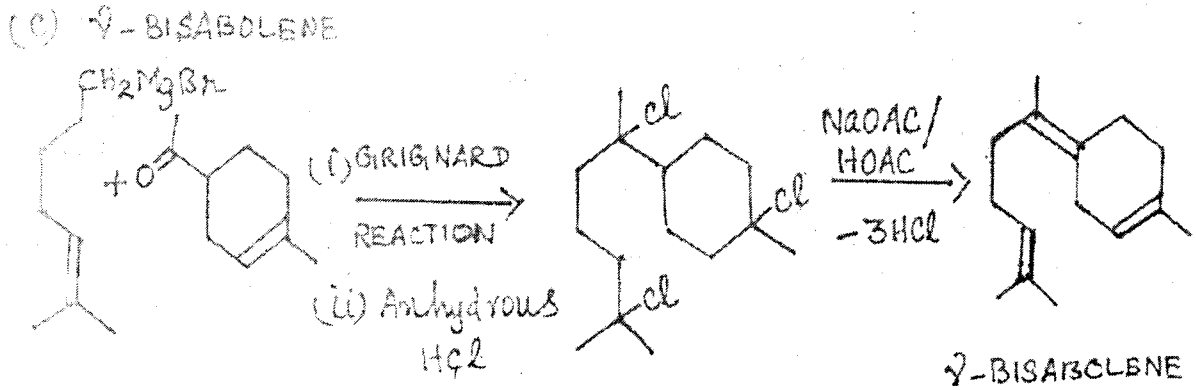
a) SYNTHESIS OF 4-METHYL-3-PENTYL-MAGNESIUM BROMIDE





b) 4-ACETYL-1-METHYL CYCLOHEXENE



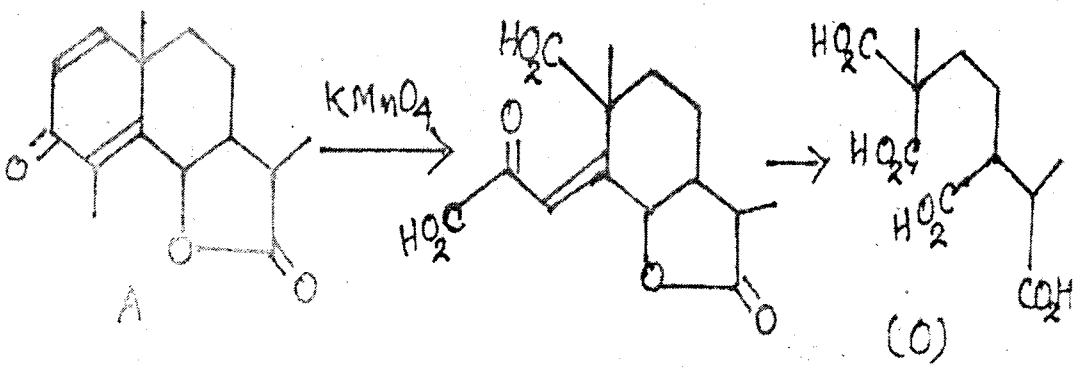


α-Santonin

This occours in various species of Artemesia (found in Asia). It is widely used in medicine as an anthelmintic (it has the power to expel intestinal worms).

From elemental analysis and molecular weight determination molecular formula of santonin(A) was found to the $C_{15}H_{18}O_3$. Santoine is found to be a lactone, since on treatment with alkali it gives a hydroxy acid, Santonic acid(B). Infrared spectrum showed it to be a γ-lactone. On catalytic hydrogenation it forms a tetrahydro derivative, indicating the presence of two double bonds.

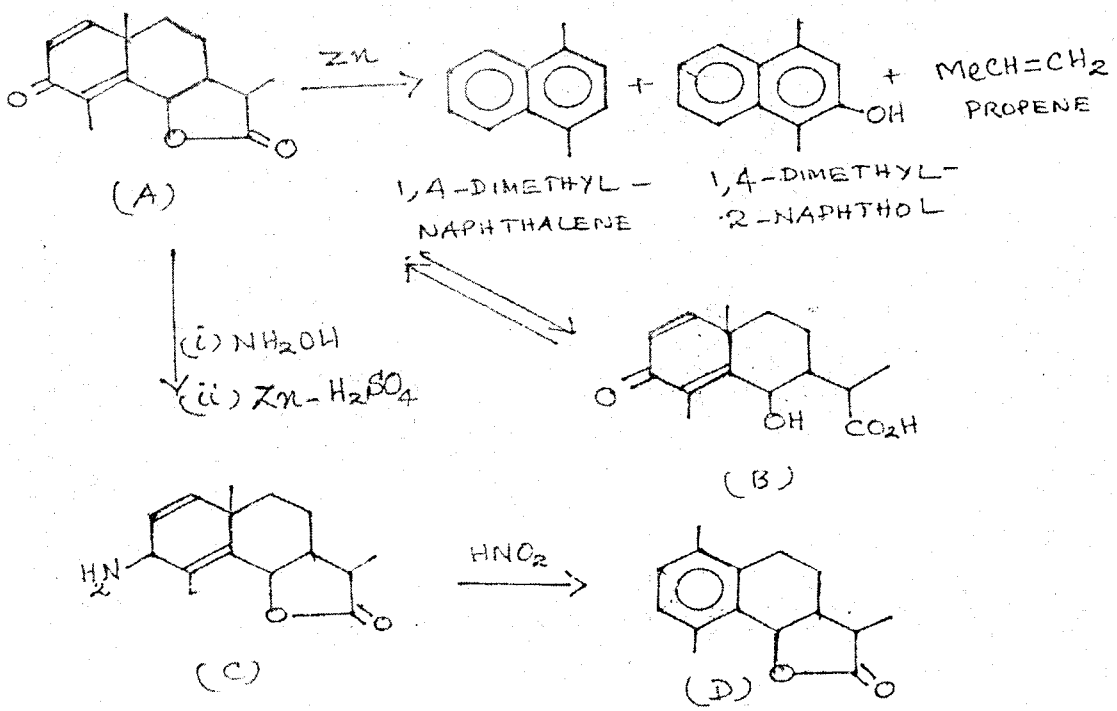
From UV absorption spectrum ($\lambda max_{,200}$ ^{236mm}) it was found to be an



α, β -unsaturated ketone.

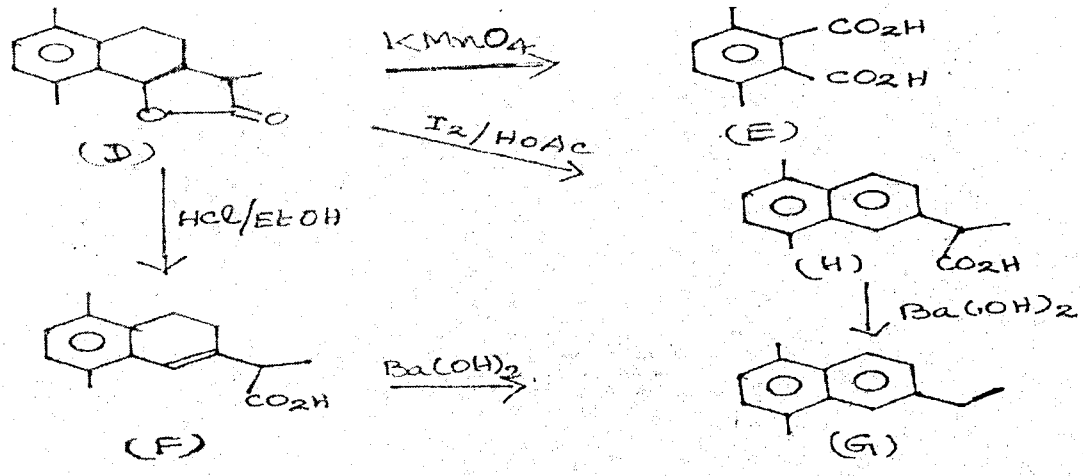
Zinc dust distillation of santonim gives 1,4-dimethylnaphthalene,propene and a small amount of 1,4 – dimethyl-2-naphthol. This indicates the presence of a naphthalene skeleton in santonim.

Santonin oxime on reduction gives santonamine-Cc. C on reaction with nitrous acid gives hyposantonin (D) through rearrangement . All these reactions can be formulated if we assume the structure of santonin to be (A).



The structure of hyposantonim was established as follows. Santonin on oxidation with permanganate gives 3,6-dimethylphthalic acid (E). when heated with ethanolic hydrochloric acid,(D) gives a mixture of two isomeric acids, dihydrosantinic acid (F) which, on heating with barium hydroxide, give the hydrocarbon(G).

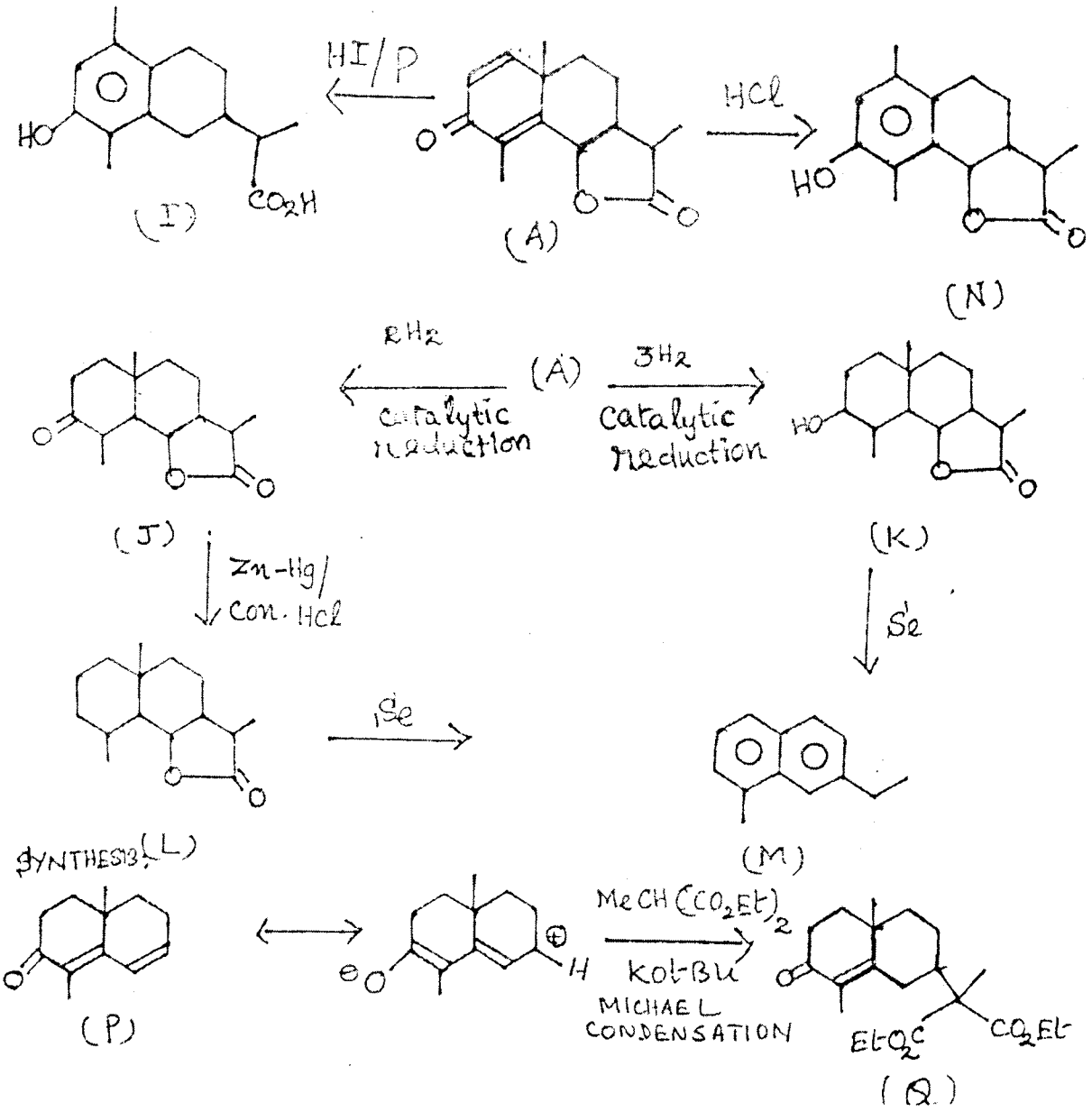
Both hyposantonin as well as dihydrosantinic acid on oxidation with iodine in acetic acid give santinic acid(II). The latter on heating with barium hydroxide also gives (G).



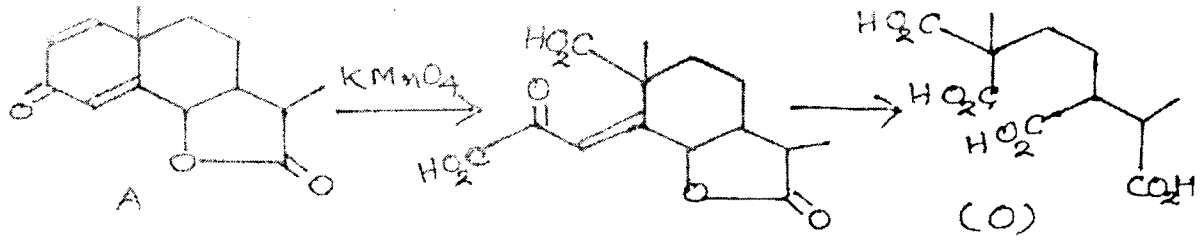
The following reactions were also carried out on santonin(A). santonin on reduction with hydroiodic acid and phosphorus gives santonous acid(I). Catalytic reduction of santonin gives a tetrahydro derivative (J)(reduction of olfinic bonds) and a hexahydro derivative (K) (reduction of both olefinic bonds and keto group).

Compound (J) on Clemmensen reduction gives deoxytetra hydrosantonin (L) and this on selenium distillation gave 7 – ethyl – 1- methylnaphthalene(M). Compound (K) forms the same hydrocarbon when distilled with selenium.

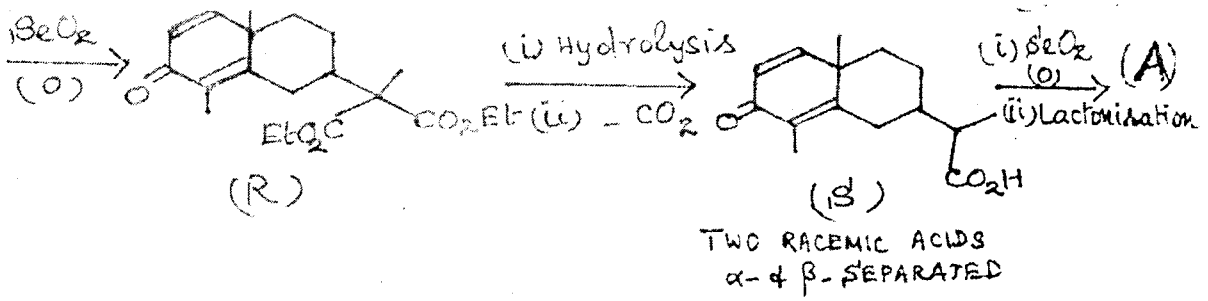
Santonin on treatment with cold fuming hydrochloric acid underwent a management to give desmotroposantonin (N). All these reactions can be formulated as follows.



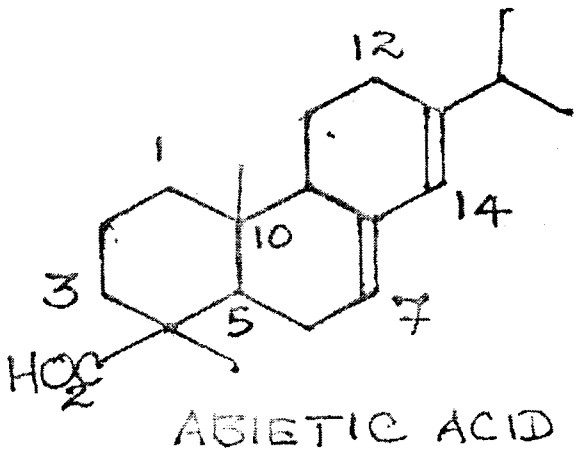
Permanganate oxidation of santonin gives (O). The formation of the latter was helpful in fixing the position of angular methyl group, which was confirmed by the synthesis of both (I) and (O),



Finally the structure of α-santonin has been confirmed by its synthesis.



ABIETIC ACID



It is a tricyclic diterpenoid, whose molecular formula from elemental analysis was found to be $C_{20}H_{30}O_2$

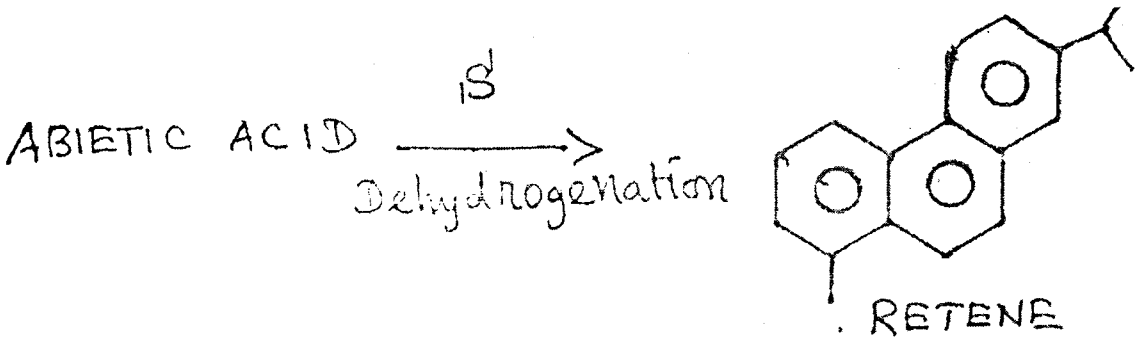
General reactions indicate it to be a monocarboxylic acid. The carboxylic acid group is very difficult to esterify and hence the carboxylic acid group must be attached to

a tertiary carbon. It is supported by the fact that abietic acid evolves carbon monoxide when warmed with an sulphuric acid.

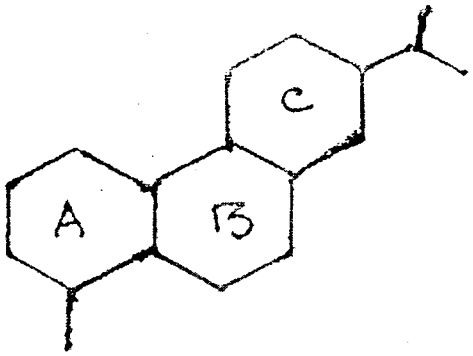
On catalytic hydrogenation, this gives tetrahydroabietic acid, $C_{20}H_{34}O_2$. Thus abietic acid contains two double bonds. Again since the parent hydrocarbon is $C_{19}H_{34}$ (regarding the carboxyl group as a substituent group), abietic acid is tricyclic.

The double bonds are in conjugation is evident from the fact that it absorbs at 238mm.

Abietic acid on dehydrogenation with sulphur (vesterberg), gave retene.

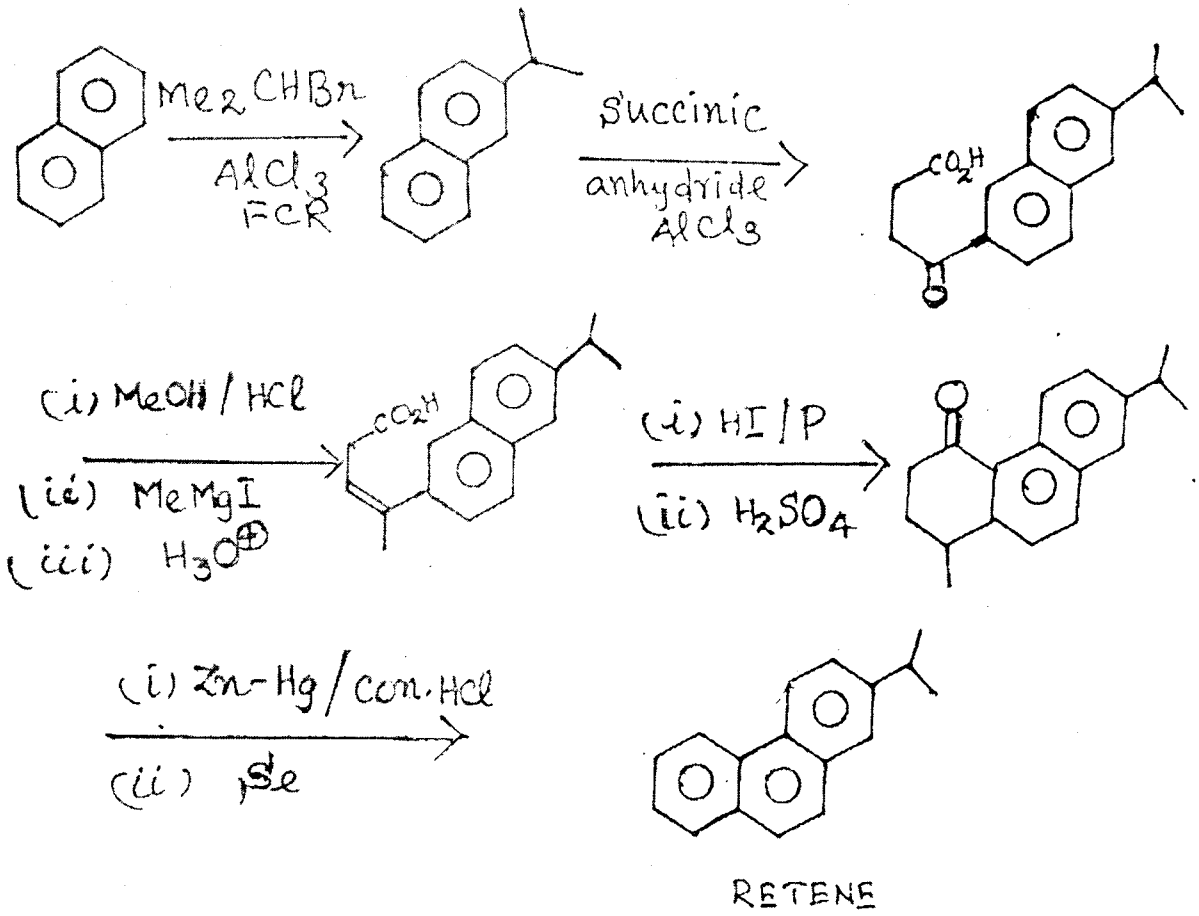


By oxidative degradation retene was shown to be 1-methyl-7-isopropyl-phenanthrene and the structure was latter confirmed by synthesis. Therefore abietic acid must contain the following carbon skeleton.



During the formation of retene there is a loss in two carbon atoms. It is known that during sulphur dehydrogenation carboxylic acid group and angular methyl group can be eliminated. So it is reasonable to assume that the two carbon atoms lost have been originally the carboxyl group and an angular methyl group.

Synthesis of Retene:



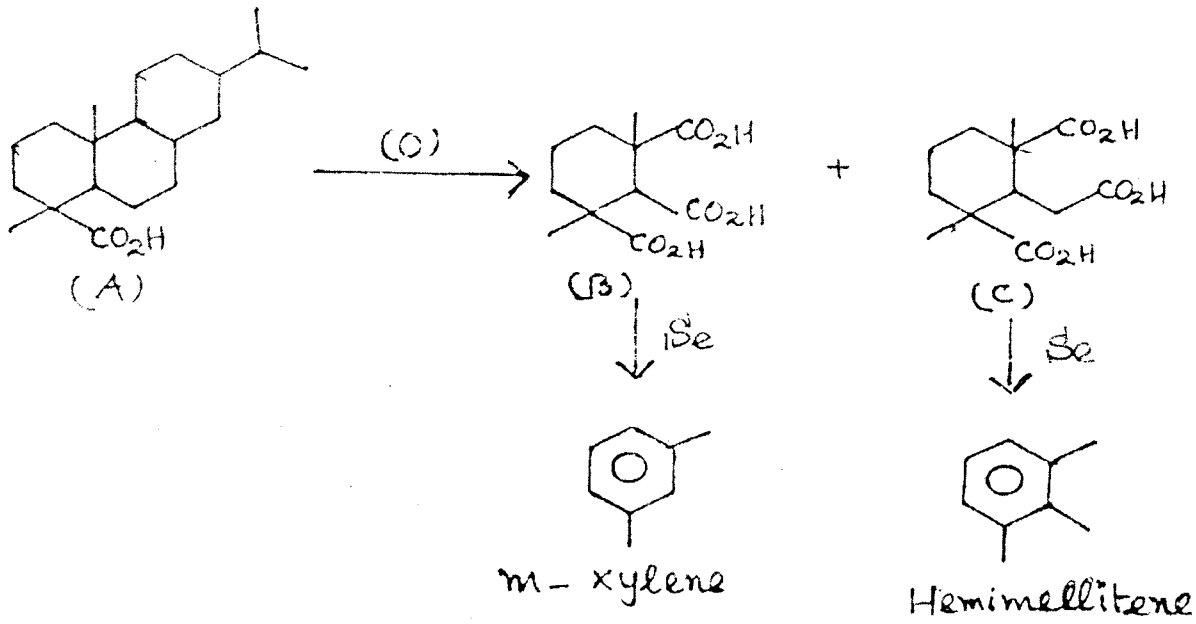
RETENE

Permanganate oxidation of abietic acid gives a mixture of two tricarboxylic acids, $C_{11}H_{16}O_6$(B) and $C_{12}H_{16}O_6$(C). They upon selenium dehydrogenation respectively gave m-xylene and heminellite (1,2,3 – trimethyl benzene). If we assume loss in 3 carbon atoms in both the cases, the two methyl groups in (B) and (C) must be in the m-position. Furthermore, since (B) and (C) each contain the methyl group originally present in abietic acid (position 4),acids (B) and (C) must contain ring (A) of abietic acid.

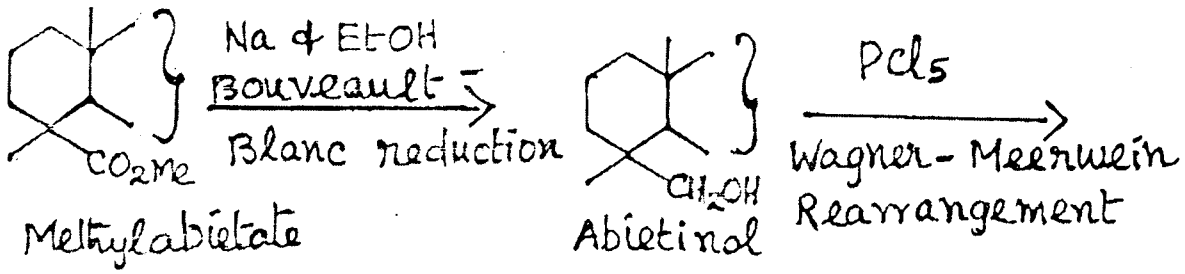
This suggests therefore that an angular methyl group at position 10, since it can be expected to be the eliminated from this position during selenium dehydrogenation of abietic acid, (this 10-methyl is meta to the 4-methyl group).

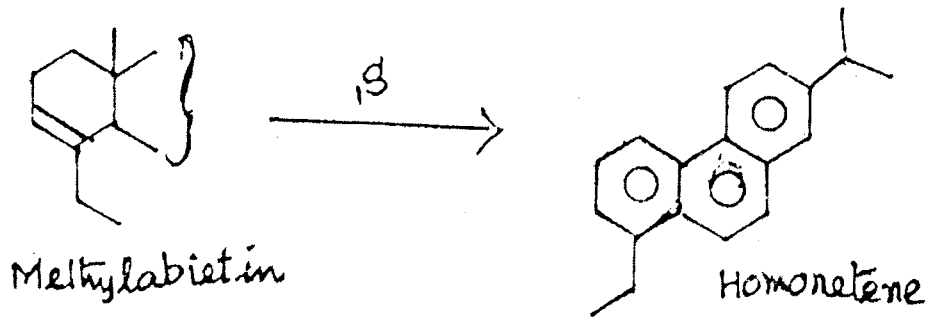
Acid (B) when heated with con. sulphuric acid evolved two moles of carbon monoxide,indicaing that two carboxylic acid group are attached to tertiary carbon atoms ; the most likely position of this is position 4, in abietic acid.

Assuming the skeleton of abietic acid to be (A) and also the assumptions made are correct the reactions can be formulated as follows:



The position of carboxyl group at position 4 in abietic acid (assumed above) was confirmed by Ruzicka et al.





Homoretene contains one carbon atom more than retene and on oxidation with alkaline potassium ferricyanide gives phenanthrene – 1,7 – dicarboxylic acid. The same product is obtainable from retene under similar conditions.

Position of double bonds:

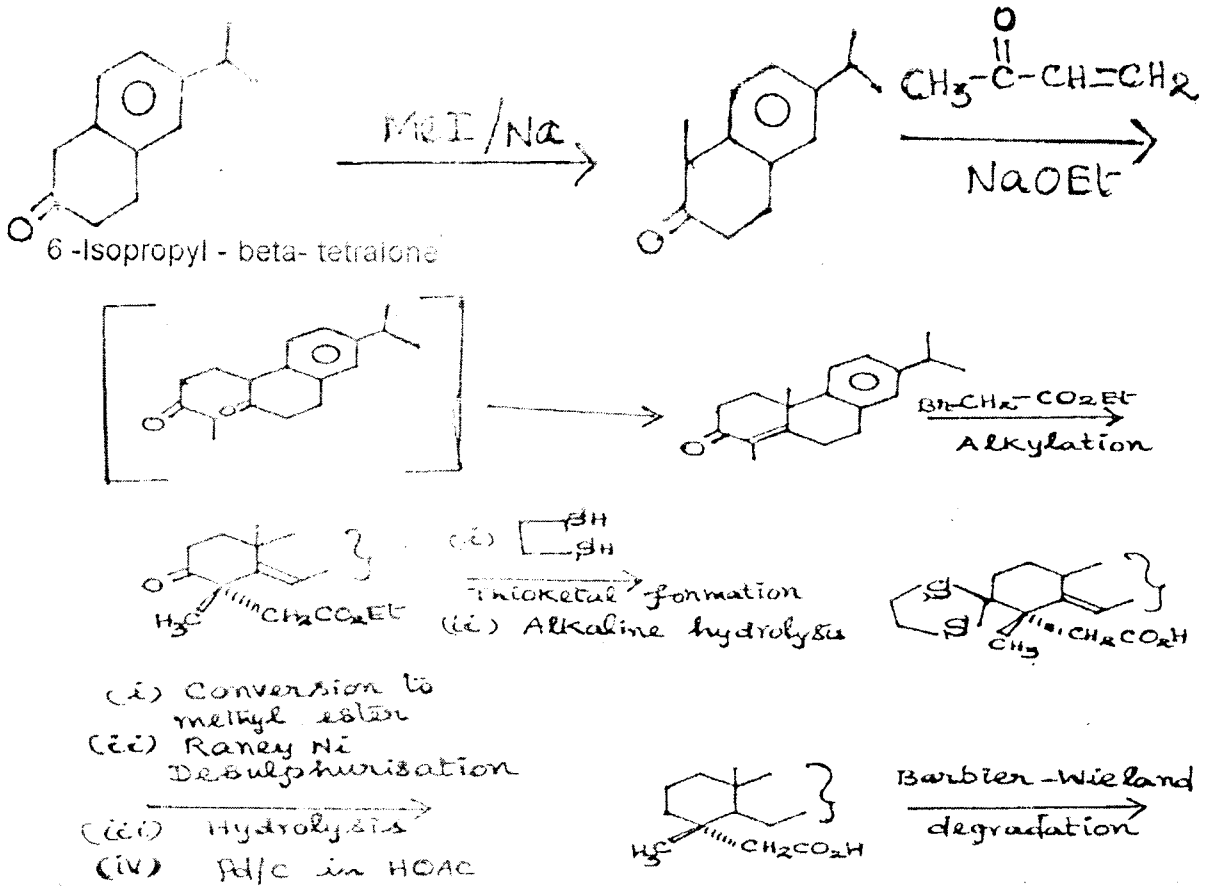
Oxidation of abietic acid with permanganate among other products gave isobutyric acid. This suggests that one double bond is in ring C. Though abietic acid forms an adduct with maleic anhydride above 100 ^{0} C, it is not a cisoid diene because,

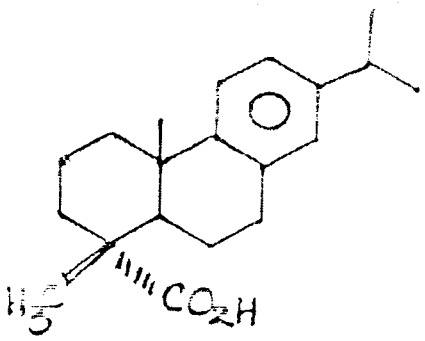
i) the UV value is only 238nm. The minimum UV value for homoannular diene would be 253 nm. So the double bonds must be transoid in nature

ii) The formation of the adduct may be explained by the fact that abietic acid isomerizes to levopimeric acid,above 100 ^{0} C.

The probable positions of the double bonds may be at 7:8 and 13:14. Further evidence for these positions is afforded by the fact that in the oxidation of abietic acid to give acids (B) and (C) in which ring A is intact, rings B and C are opened. This can be readily explained only if rings B and C each have a double bond.

Synthesis: (Stork etal)





(±) – DEHYDROABIETIC ACID

BIOSYNTHESIS OF ALKALOIDS

Biosynthesis of alkaloids describes the actual pathways whereby the alkalide are formed in nature (in plants, of course).It also states the individual steps which are involved in the synthesis.

Biosynthetic approach involves the break up of the complex structure into units from which the compound could plausibly be derived.

The alkaloids are generally classified on the basis of the heterocyclic nucleus present in them. Thus we have,

i) Quinoline Alkaloids -----ex. Quinine
ii) Pyrrolidine Alkaloids ----ex. Cocaine
iii) Indole alkaloide ----ex. Lysergic acid
iv)

There are some alkaloids which are classified on the basis of their reactions. Thus for examples PHENANTHRENE ALKALOIDS; these alkaloids give phenanthrene as one of the products during dehydrogenations.

Thus the alkaloids have a great diversity of structure. So it is impossible to develop only one pathway for the biosynthesis of alkaloids. As a result many pathways have been proposed, each one accounting for the biosynthesis of a number of alkaloids of related structure.

The most commonly posulated steps in biosynthesis are the extra skeletal processes like oxidation, hydrogenation, dehydration etc.

The biosynthetic techniques involve the use of isotopic labelling to trace the actual pathways in biosynthesis. The starting compounds invariably in these syntheses are the substances which are produced in the organism itself. Some examples in alkaloid biosynthesis are given below:

The biosynthetic conversion of amino acids into alkaloids involve many types of reactions. Some of them are,

i) Decarboxylation of alkylalanine results in the formation of an amine.

$$R\text{-}CH(NH_2)\text{-}CO_2H \longrightarrow RCH_2NH_2 + CO_2$$

Alkylalanine

ii) Formation of Schiff's base

$$RCHO + RNH_2 \longrightarrow RCH{=}NR'$$

iii)Mannich reaction-leading to the formation of a quaternary Schiff's base.

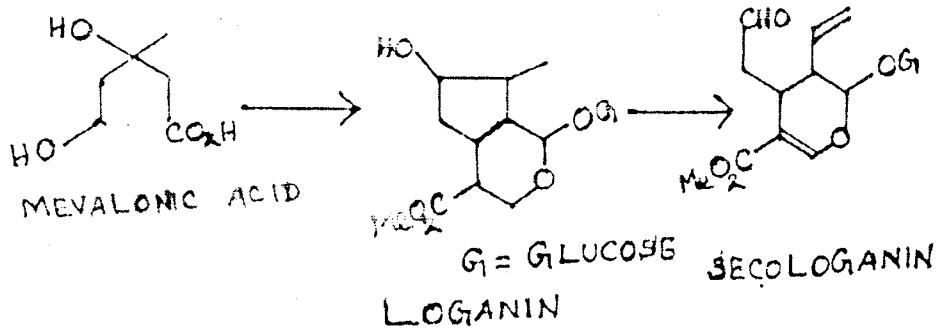
$$HCHO + Et_2NH \longrightarrow Et\overset{+}{I}H{=}CH_2 + H_2O$$

iv) Oxidative coupling of phenols with the help of oxidising agents.

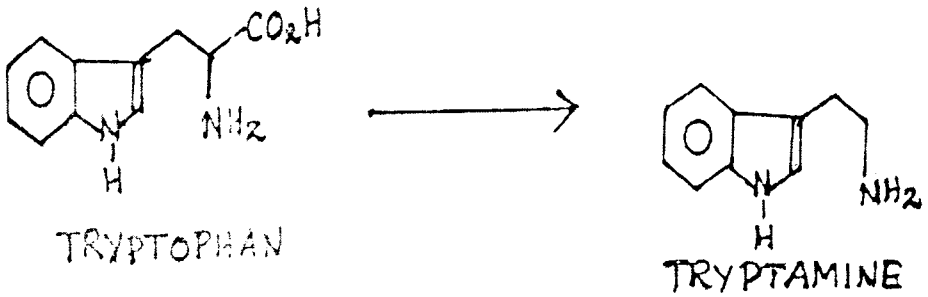
Biosynthesis of some classes of alkaloids are given below.

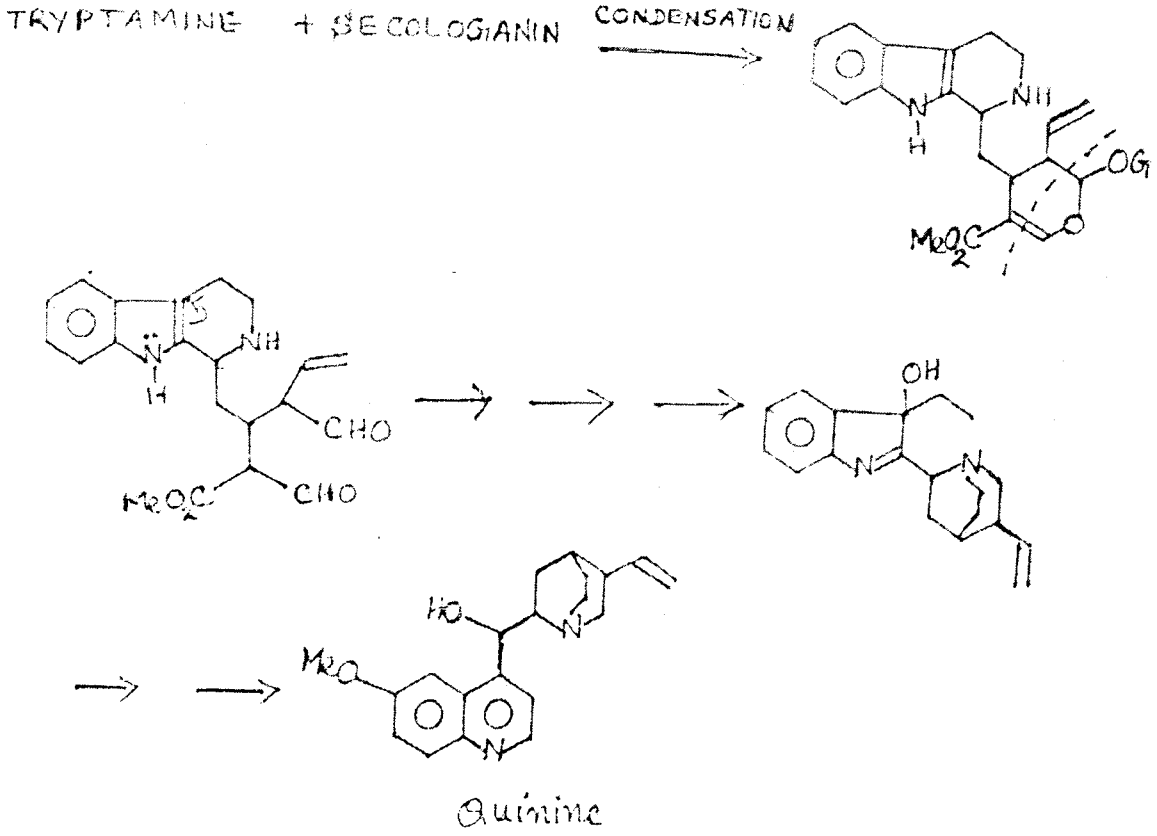
QUINOLINE ALKALOIDS

Tryptophan is believed to be the precursor for the biosynthesis of cinchona alkaloids. Secologanin is believed to be another precursor. The latter is obtained from Loyanin, a natural terpenoid, which is shown to be derived from Mevalonic acid. Thus,



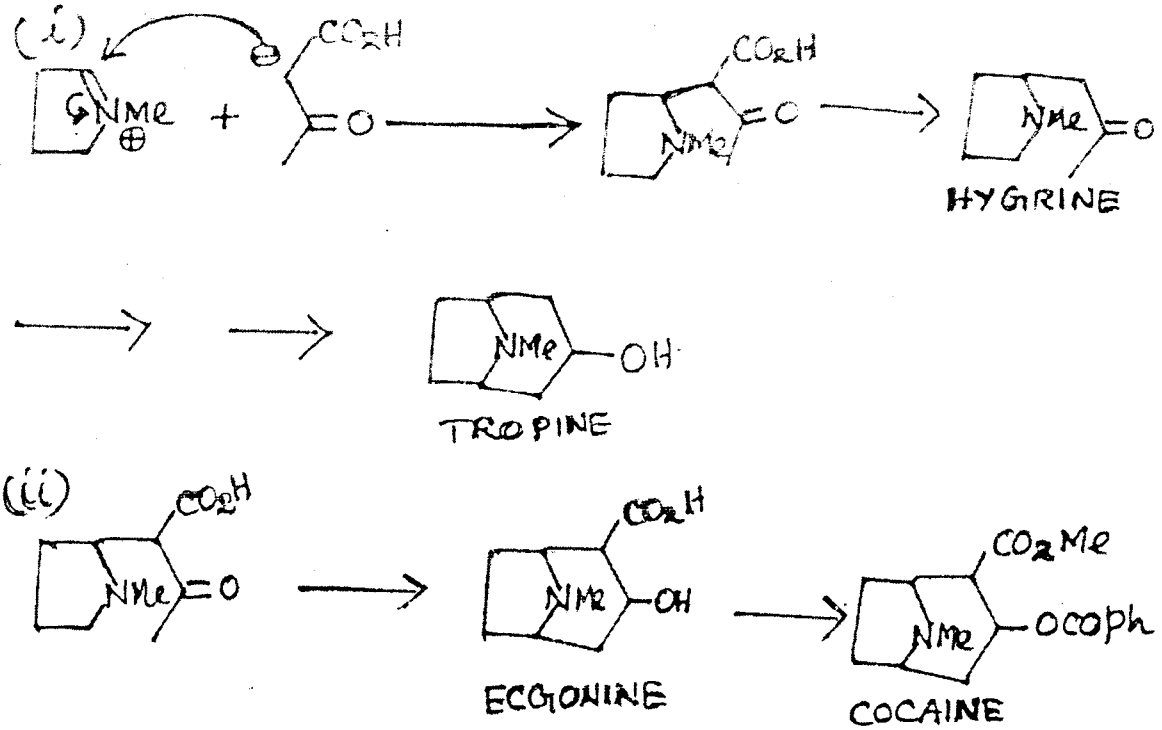
The biosynthetic process for quinine may be given as follows:





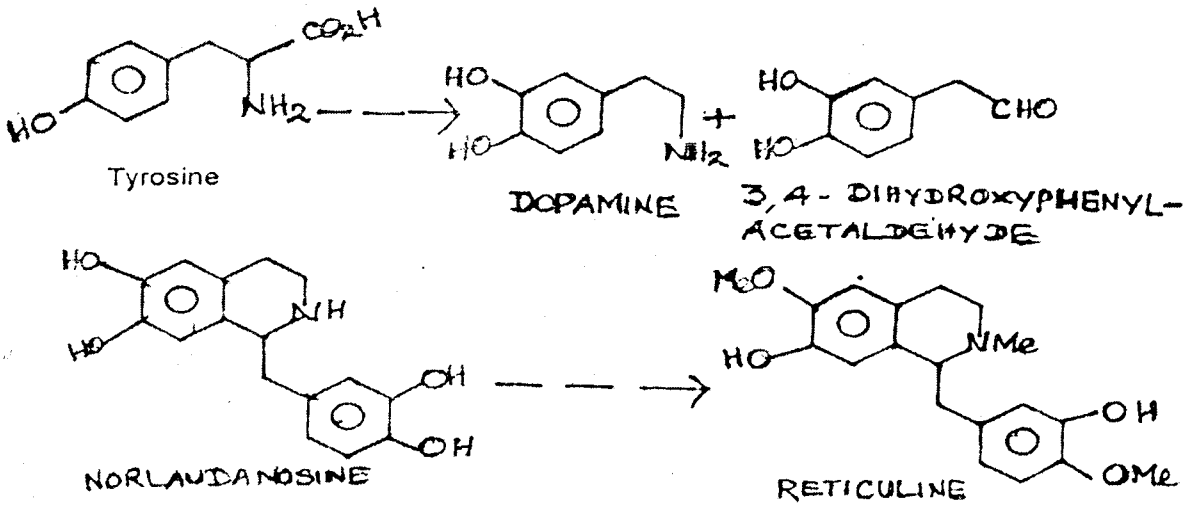
TROPANE ALKALOIDS

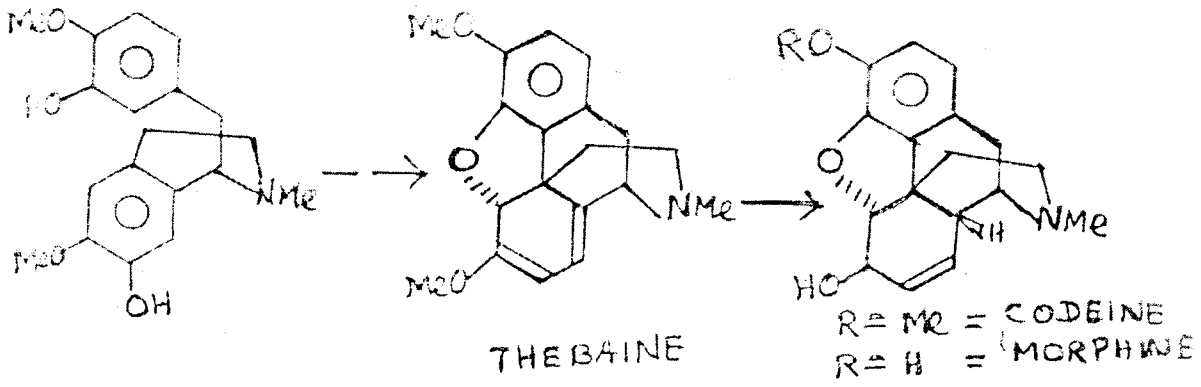
The precursors for this group of alkaloids include Ornithine, N-methylputreacine, Hygrine etc. However, in this case, 2-^{14}C-Ornithine gave rise to (tropine labeled at C-1.Also starting with N-methylputrescine (labeled), $NH_2N(CH_2)_4$ $^{15}NH^{14}CH_3$, produced tropine with $^{15}N^{14}CH_3$.This establishes the fact that the nitrogen atom in the alkaloid is derived from the aminoacid precursor. A possible biosynthetic pathway is,



PHENANTHRENE ALKALOIDS

The opium alkaoids are believed to be biosynthesized from the alkaloid Reticuline. Reticuline can be derived from Norlaudanosoline. The latter leads to the alkaloids, Thebaine, Codiene and Morphine, through oxidative coupling.Tracer experiments indicate the formation of Norlaudanosoline from Tyrosine. The biosynthetic process may thus be formlated as follows,





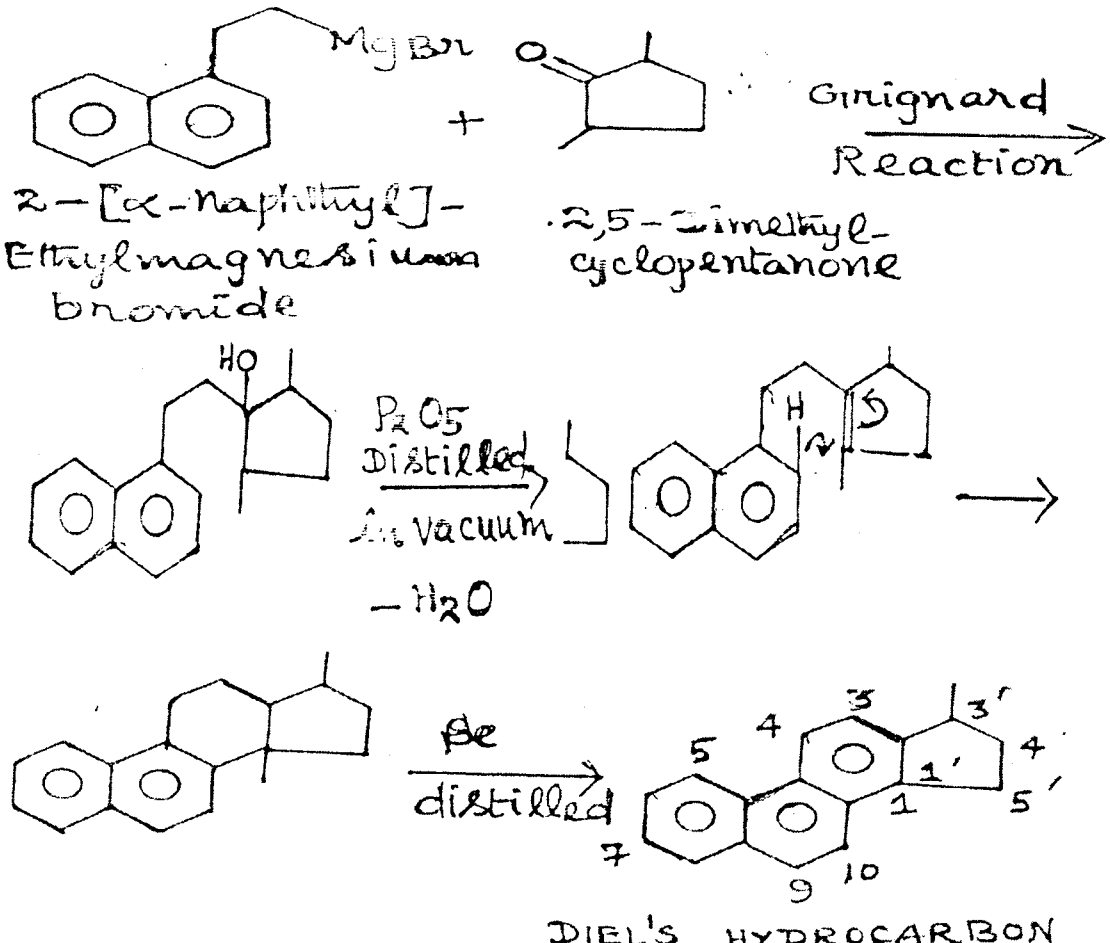
THEBAINE

STEROIDS

Any natural product which on selenium distillation gives Diel's hydrocarbon may be called as steroid.

Generally they are obtainable from the unsaponifiable portion of fats and oils.

Synthesis of Diel's hydrocarbon

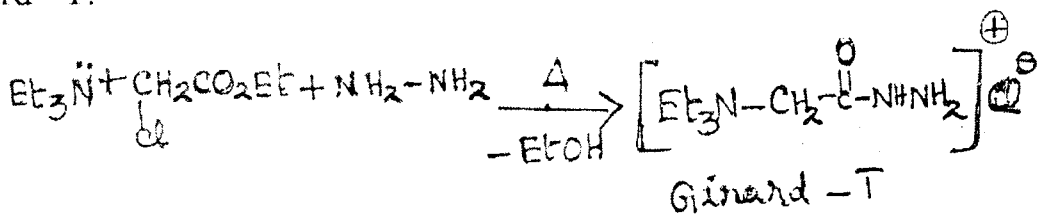


DIEL'S HYDROCARBON

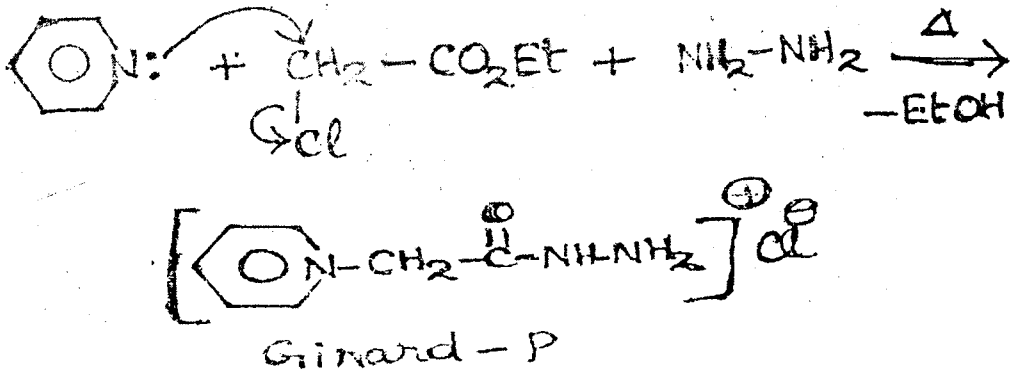
So, the characteristic feature of a steroid is the presence of prehydrophenanthrene skeleton.

Before going to the actual structural elucidation of steroids, let us have a look at the following which may be useful in the structure elucidation of steroids. Structure elucidation of steroids or that matter any natural product is usually done through oxidative degradations. Separation of steroidal ketones from other oxidation products is difficult, as both the steroidal ketones as well as their derivatives are soluble in ether. In order to overcome this problem two reagents have been developed by Girard, i) Girard– T ii) Girard – P.

Griard - T:

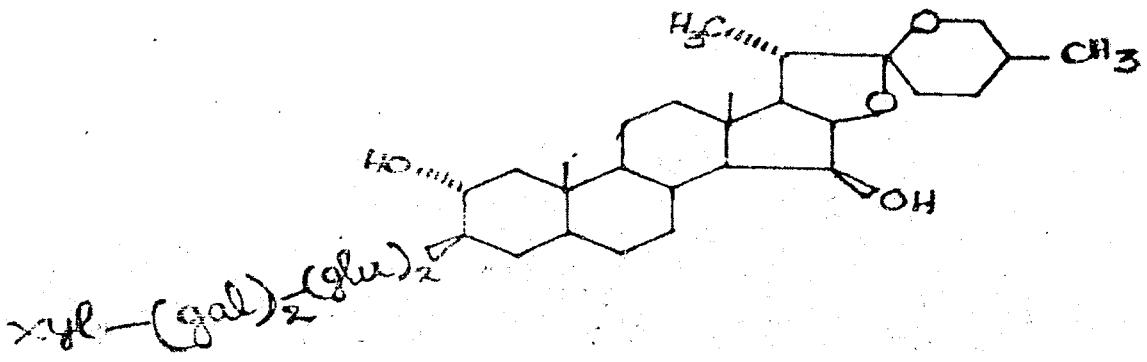


Girard – P:



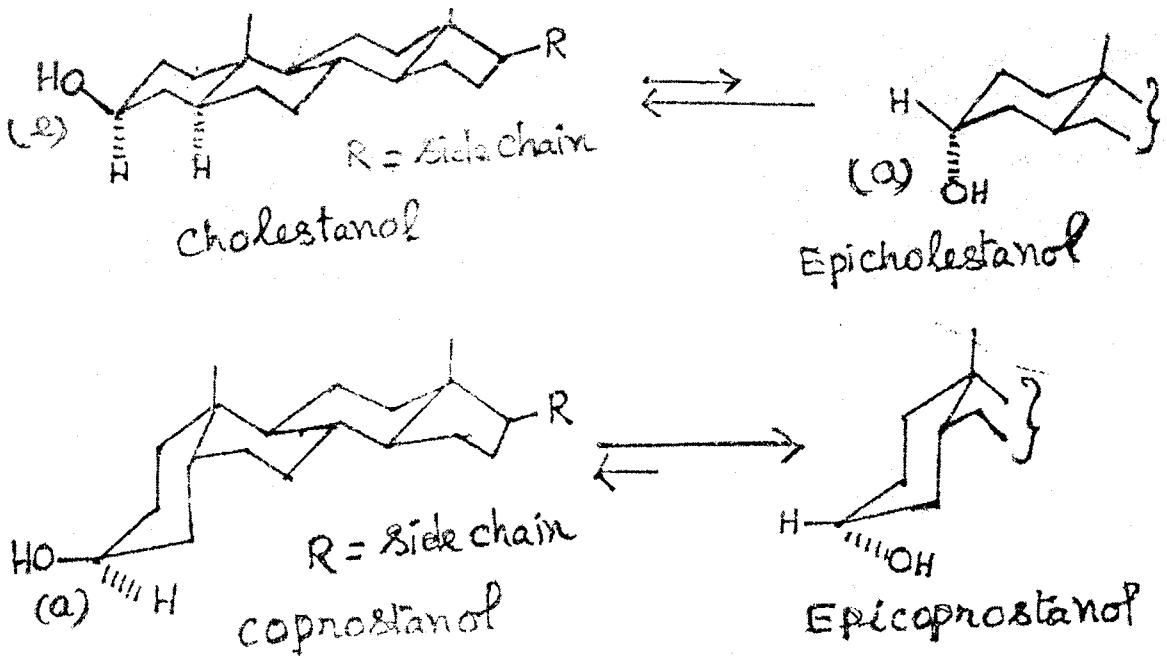
Since the reagent is polar, it's derivatives are also likely to be polar. So will be insoluble in ether and hence can be separated easily from other oxidation products.

Digitonin:



This has "homolytic"(affinity towards haemoglobin) action and ruptures the blood corpuscles.Cholesterol prevents this homolytic action.

When digitonin is added to a steroid suspended in water, 1:1 addition complex soluble in pyridine is obtained. On adding ether to this, the digitonin gets precipitated and the steroid can be recovered as its ethereal solution, Evaporation of either may give the steroid. This is characteristic of 3β-OH groups irrespective of the conformatinal nature and fusion of the rings (A/B).



Steroidal ring systems:

The B/C and C/D ring fusions in steroids are trans. This makes the steroidal systems rigid. But the ring A/B fusion can be cis or trans. This will have a direct bearing on the reactivity of sterols, as the 3 – hydroxyl can be either axial or equatorial. It can be exemplified by taking the following examples.

Consider the above equilibrium mixtures. In the first case, the equilibrium will be shifted more towards cholestanol. In the other, it will be shifted more towards epicoprostanol. This is because in cholestanol and epicoprostanol the hydroxyl group is equatorial. This is to be expected, since in cyclohexane ring systems the equatorial isomers are more stable than the axial (1,3-non-bonded interactions)

Development of micro techniques:

The amount of steroids obtainable from natural sources are of the order of micro grams. It may be difficult to adopt conventional methods for the analysis of them. This necessitated the development of micro techniques.

Angular methyl groups:

Presence of angular methyl groups is a special feature associated with steroids. The angular methyl groups are always 'B' in configuration.

Protecting /activating groups:

The complexity of the steroidal nucleus and the presence of eight asymmetric centers in the nucleus of a saturated steroidal nucleus are responsible for the development of activating and protecting groups, for their synthesis.

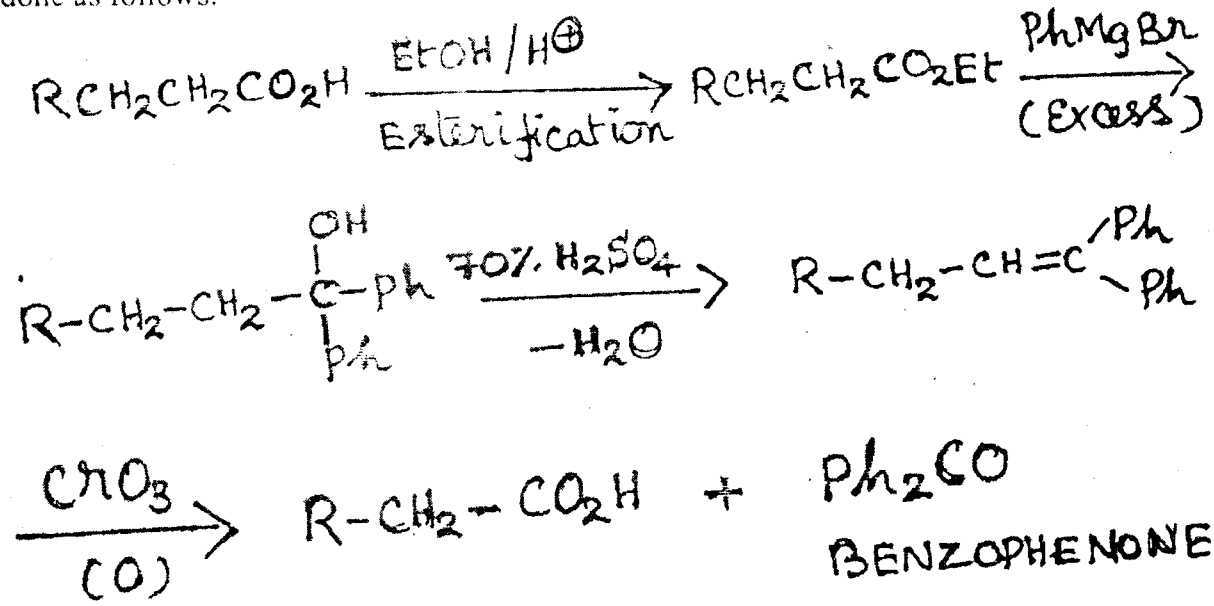
Nomenclature:

Generally steroidal systems with ring A/B fusion trans are given the normal name, thus we have chlestanol (A/B fusion trans).The sterol with ring A/B fusion cis is known as coprostanol or epicholestanol. But in bile acid nomenclature the reverse is true. i.e bile acids with ring A/B fusion cis will have the normal name. Thus

i) Cholanic acid (ring A/B fusion cis)
ii) Allocholanic acid (ring A/B fusion trans).

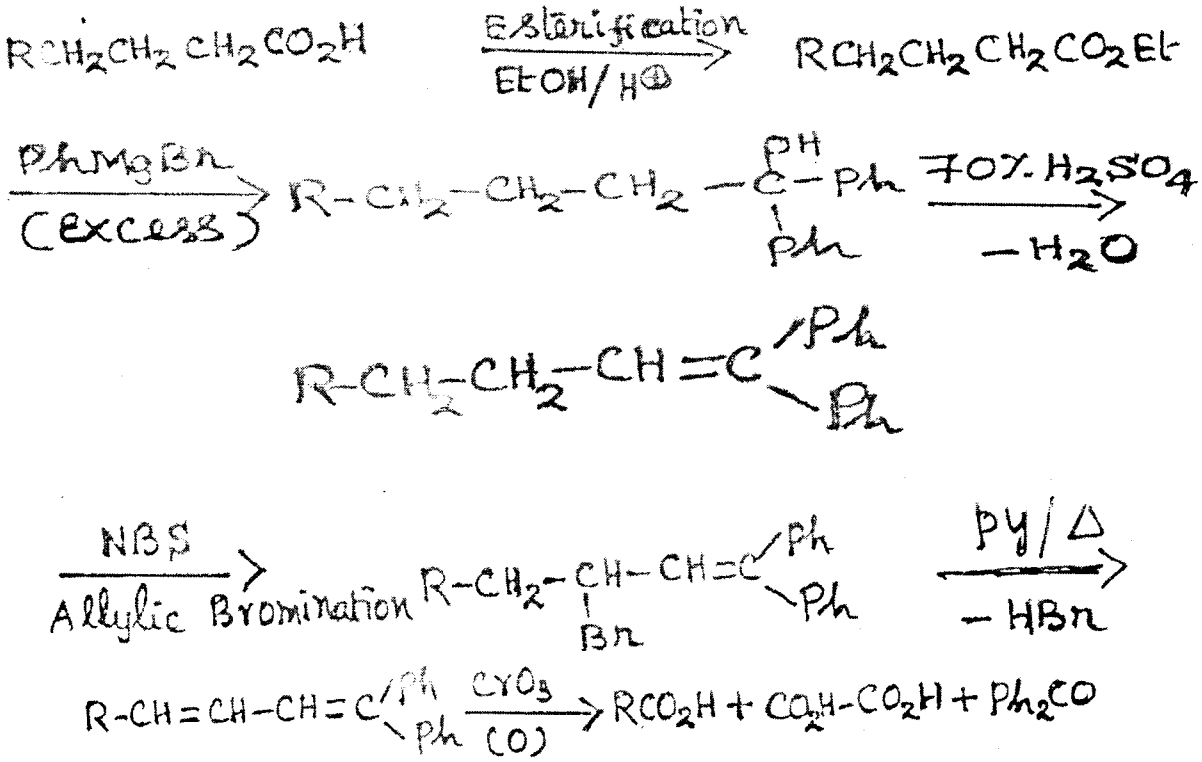
Barbier – Wieland degradation (BWD):

Stepping down of a carboxylic acid by one carbon atom is the basis of BWD. It is done as follows.

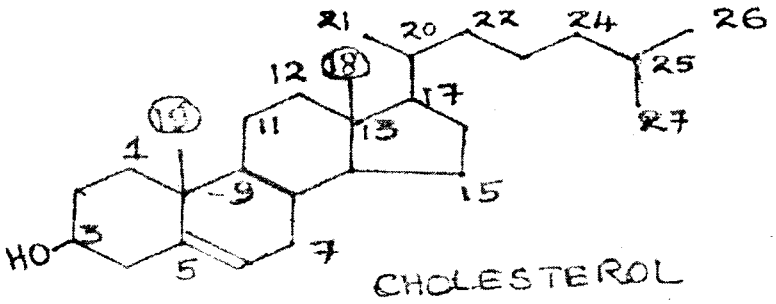


Meischer – wield degradation(MWD) :

Stepping down of a carboxylic acid by three carbon atoms at a stretch is the essence of MWD. The scheme runs as follows:



CHOLESTEROL



Source :

Occurs free (or) as fatty acids in the brain and spinal cord of cattle.

Color Reactions : SALKOWSKI REACTION

When con.sulphuric acid is added to a chloroform solution of cholestrol, a red colour is produced in the chloroform layer.

LIEBERMANN BURCHARD REACTION: When a chloroform solution of cholestrol is added to a mixture of con. Sulphuric acid and acetic anhydride a green colour is developed.

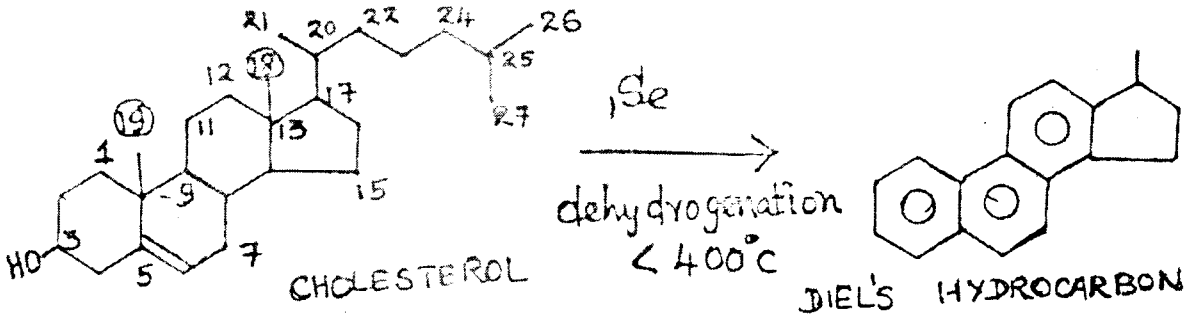
Constitution:

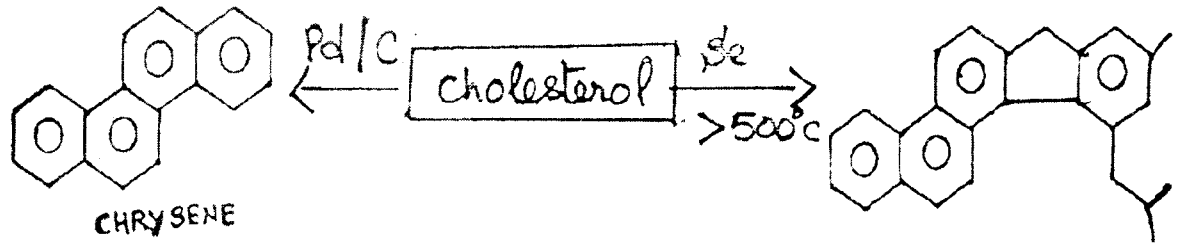
i) From elemental analysis and molecular weight determination the molecular formula of cholesterol was found to be $C_{27}H_{46}O$.

ii) Chromium trioxide oxidation of it gives a ketone, so must contain a secondary alcoholic group.

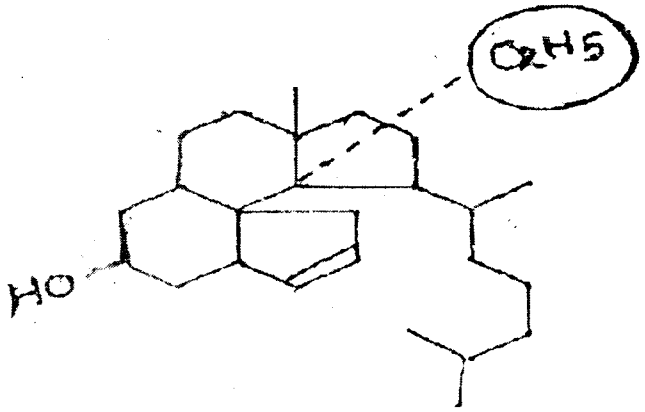
iii) On catalytic reduction it takes up one mole of hydrogen and so must contain one double bond.

iv) On selenium hydrogenation it gives Diels's hydrocarbon.





At a time, when physical methods have not been used much for structure elucidation, Wheland and Windaus proposed the following structure.

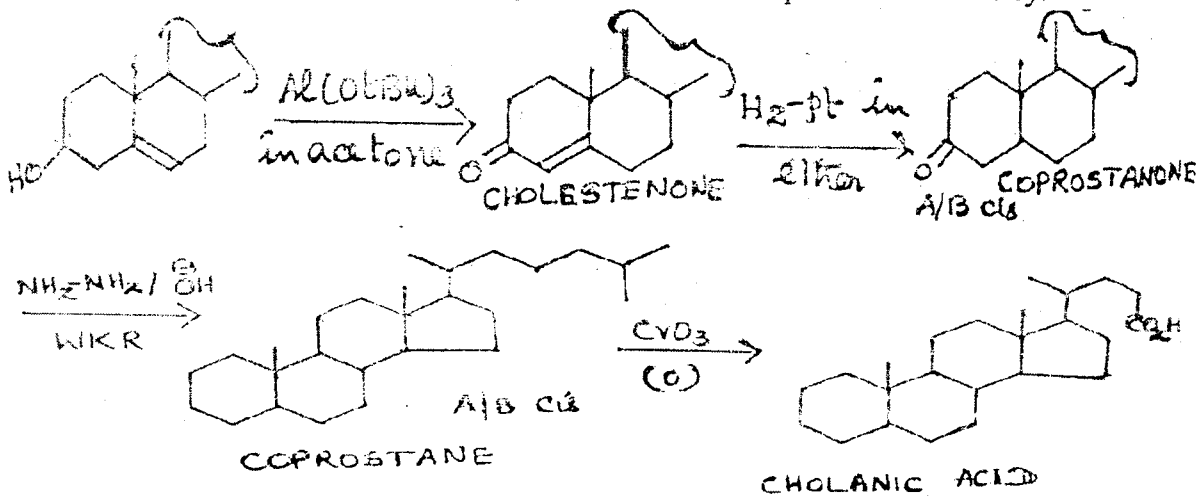


But X-ray measurements by Bernal have shown the molecule to be long and thin.

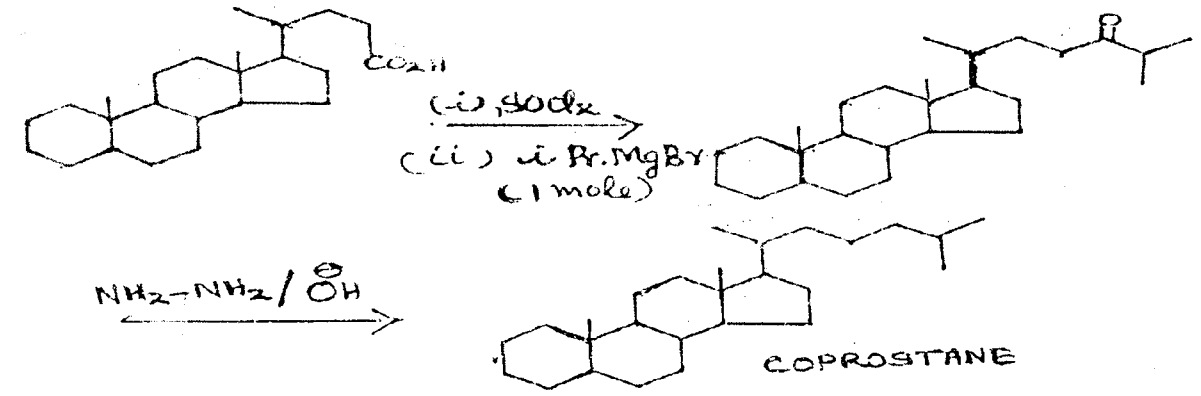
The structure of cholesterol has been confirmed by oxidative studies and inter conversions, where it is converted into compounds of known structure.

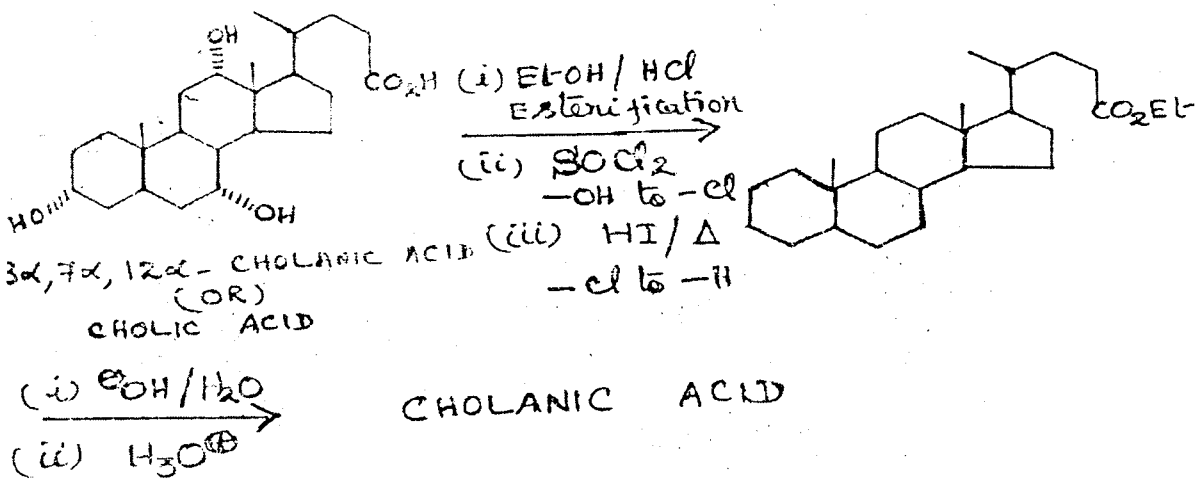
i) cholesterol to cholanic acid:

*Writing part structures are permitted in natural products chemistry.



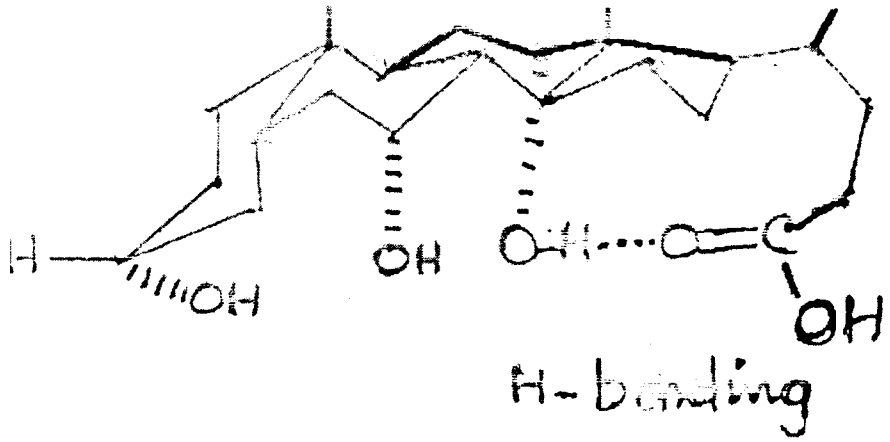
ii) cholanic acid to coprostane:





iii) cholanic acid to 20-methylcholanthrene:

Because of their conformational nature, the three hydroxyl groups in cholic acid have differing reactivity. The hydroxyl groups at position 3 is equatorial Whereas the other two hydroxyls are axial. Among the 7 & 12-hydroxyls, 12-axial hydroxyl group is involved in H-bonding with the side chain carboxyl group. Thus the environment of the three hydroxyls are different. Because their environments are different, their reactions are also different.



Oxidation of alcohols is a reaction in which an sp^3 hybridised carbon is converted into sp^2-hybridised. ie it will lead to steric relief or steric acceleration. In cyclohexane systems it is this factor, which makes the axial alcohols more reactive than equatorial in such systems. Among the two axial hydroxyl at 7 & 12, the latter is involved in H-bonding with the side chain carboxyl. Hence the 7(a) –OH reacts faster than the 12-α -isomer. The least reactive one is the equatorial hydroxyl. Thus the order of reactivity of the three hydroxyls is,

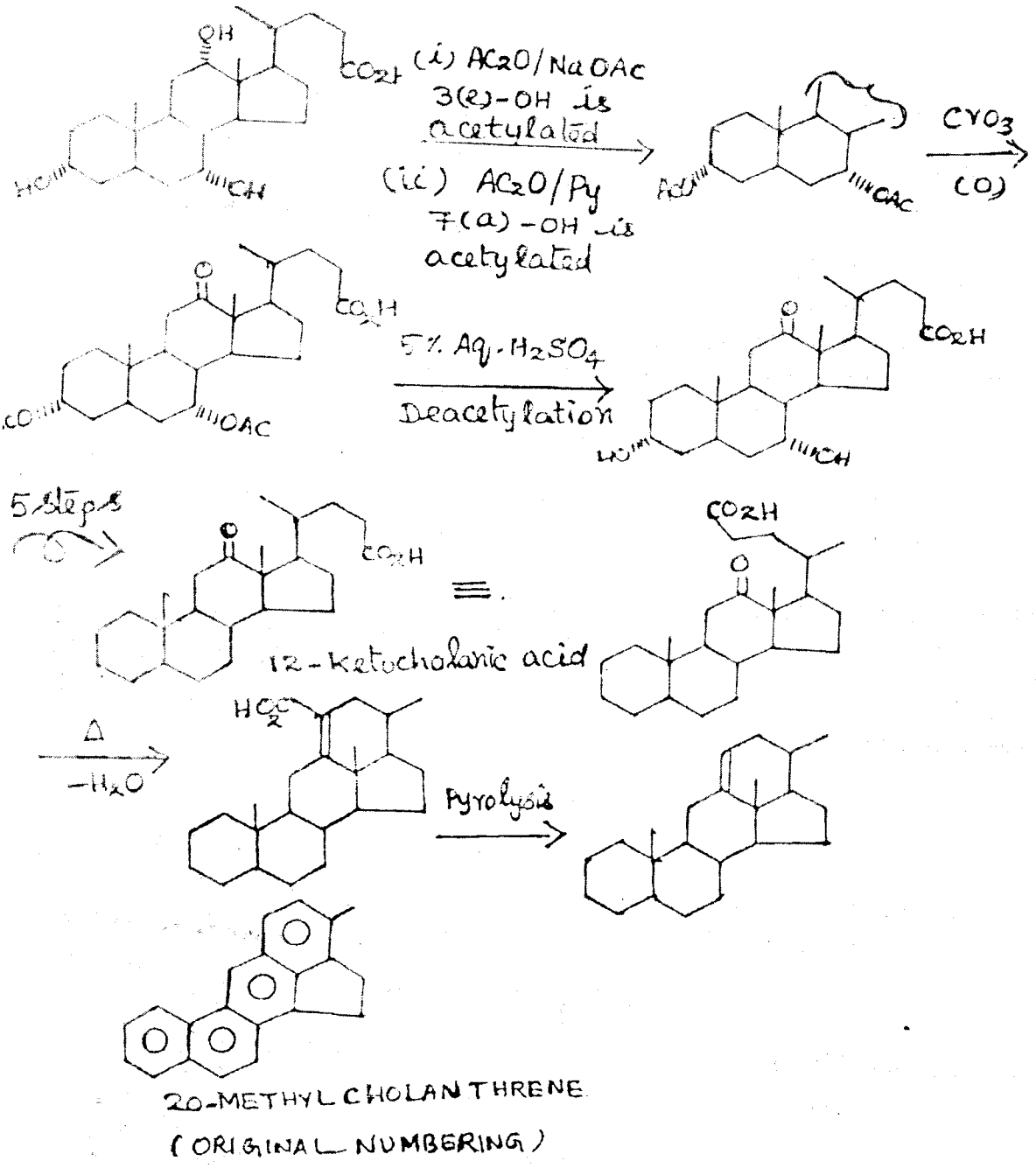
7(a)>12(a)>3(e).

Acetylation is a reaction which increases the size of the group. ie. steric retardation. Naturally in a cyclohexane systems, the isomers react faster than their axial counterparts. So the order of reactivity of the three hydroxyls towards acetylation is

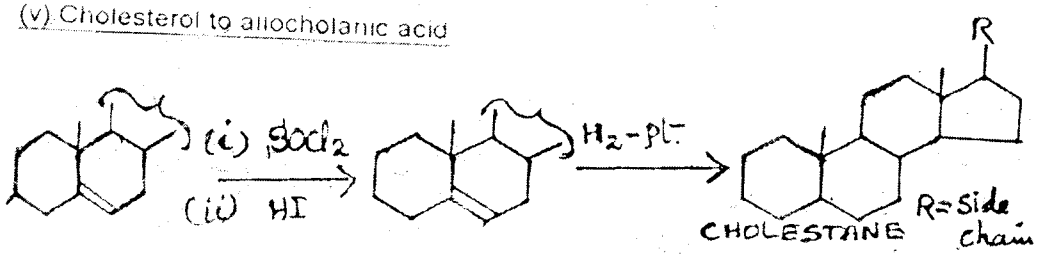
3(e) >7(a)>12(a)

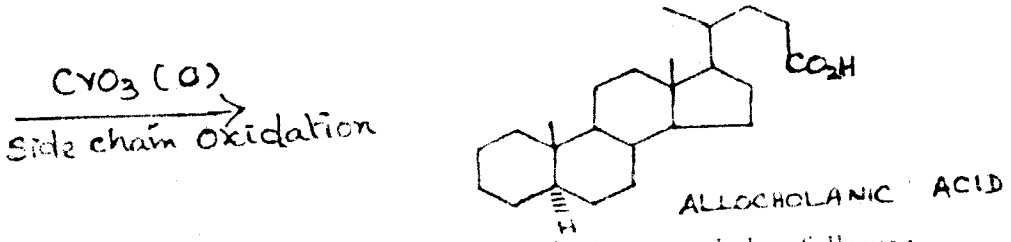
(Again, since the 12-hydroxyl is hydrogen bonded to the side chain carboxyl, the 7(a)isomer reacts faster than the 12(a) isomer.

Now we can formulate this conversion smoothly as follows, now the selective oxidation of 12-OH is achieved, the other two hydroxyls can be deprotected and removed. The steps involved in the conversion of cholic acid to cholanic acid may be repeated on this keto acid.



(v) Cholesterol to allocholanic acid





5.The structural skeleton of cholesterol is further revealed as follows :

i) Position of double bond and hydroxyl group.

ii) Configuration of hydroxyl group.

iii) Size of various rings in cholesterol .

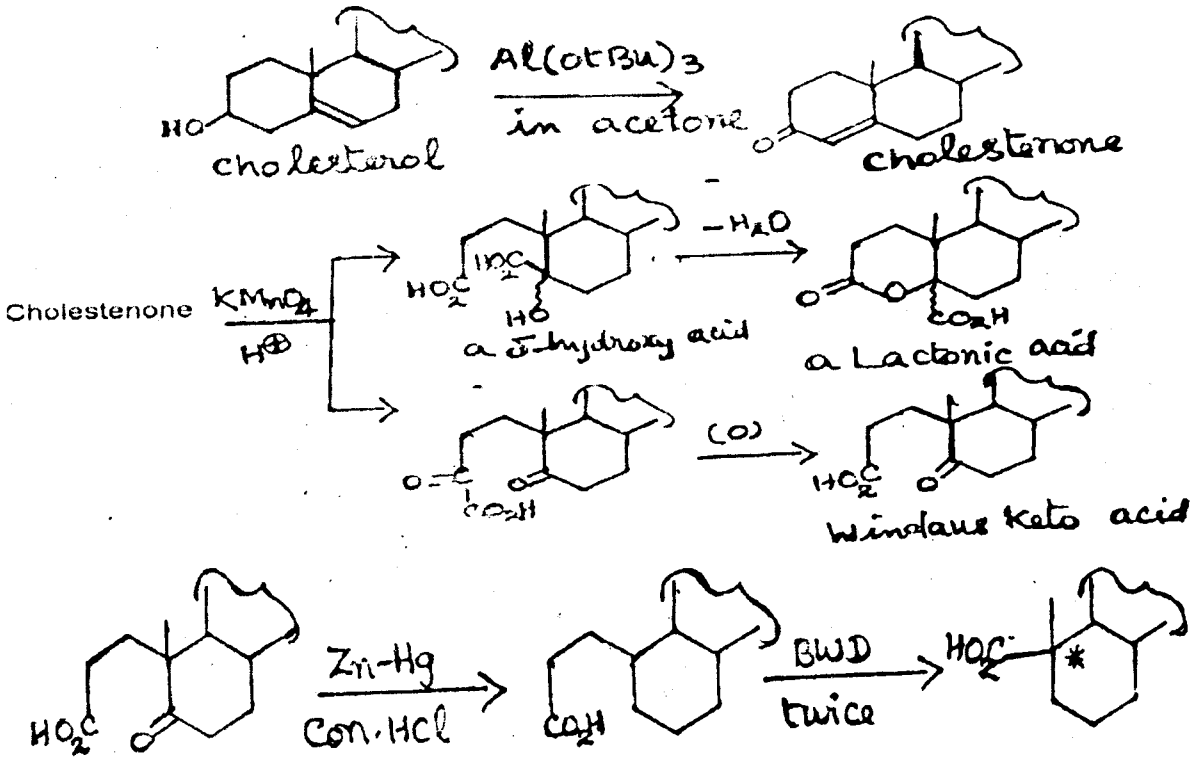
iv) Number and positions of angular methyl groups

v) The nature and position of side chain

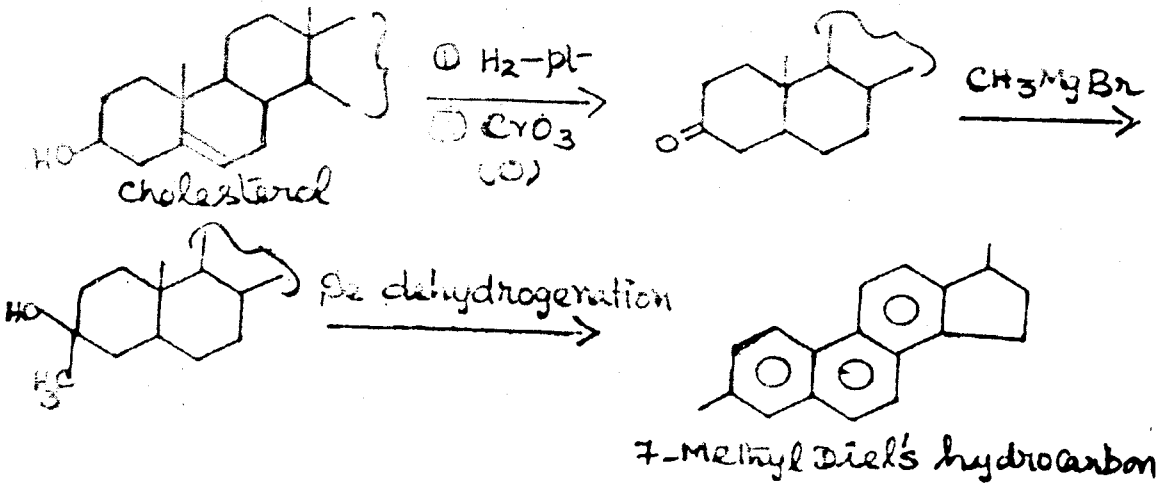
vi) Finally the total synthesis of cholesterol (the first synthesis of cholesterol in the laboratory took about 25 years to accomplish because of the complexity of the molecule)

<u>i) Position of double bond and hydroxyl group</u>

The following oxidative study has been done on cholesterol. The windaus keto acid obtained is subjected to Clemmensen reduction and the product subjected to BWD twice. The third BWD cannot be done on the acid formed .This is because it has been found to be a tertiary carboxylic acid from its difficult esterification.

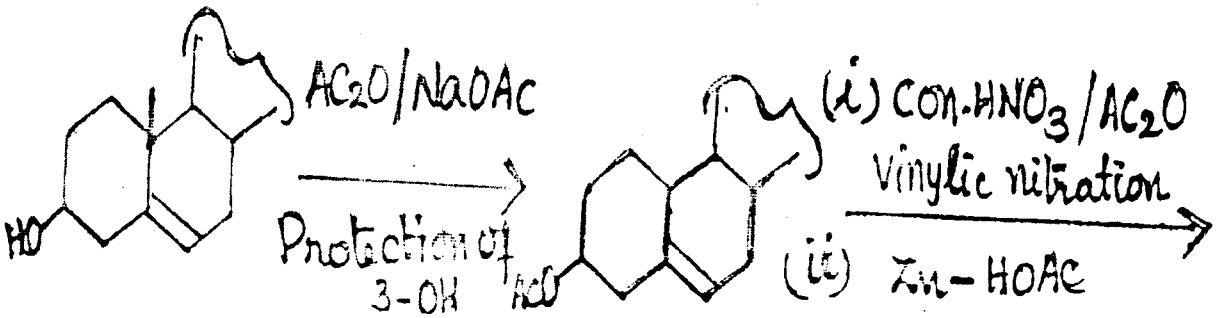


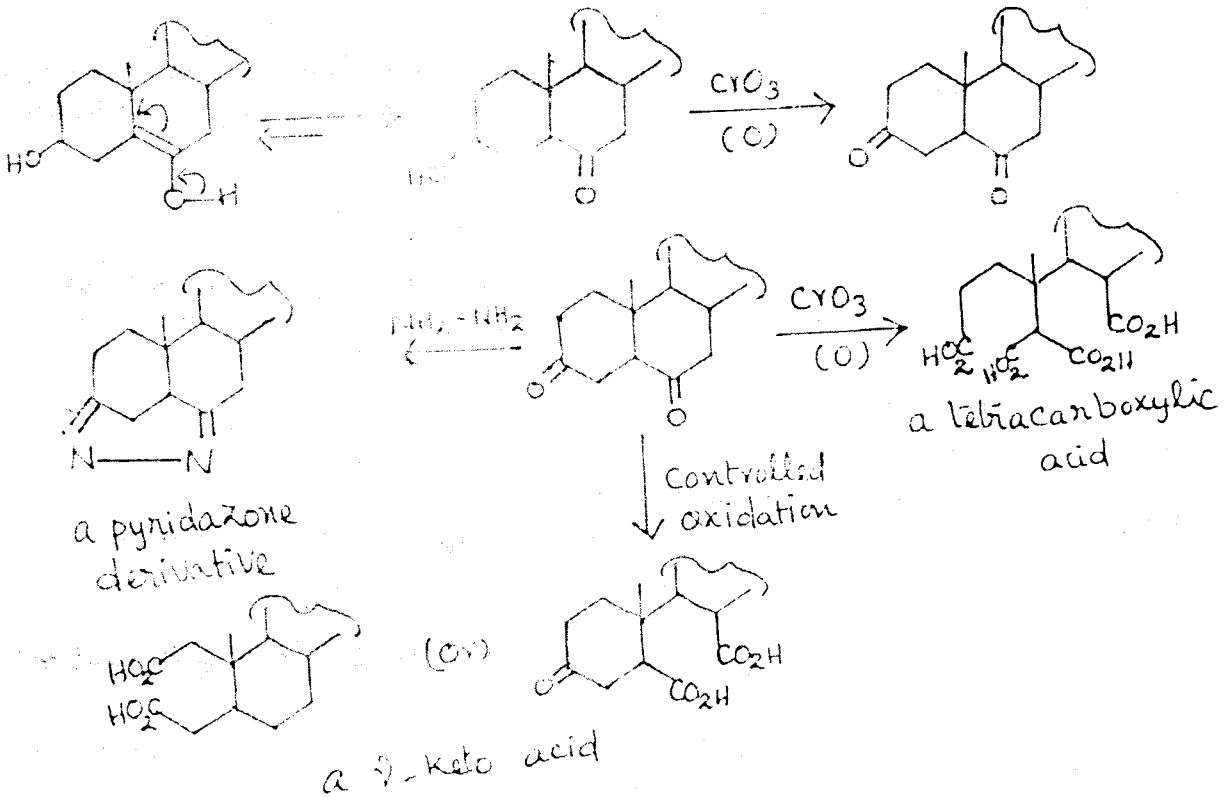
The carboxylic acid group was obtained by the oxidation of a keto group at that position : The keto group in turn has been obtained by the oxidation of hydroxyl group at that position. So the position of hydroxyl group should be 3. The position of hydroxyl group was found to be 3 by Kan et al as follows:



The introduction of a new methyl group at position 7 of the phenanthrene nucleus is a conclusive proof that the position of hydroxyl group is 3 in cholesterol.

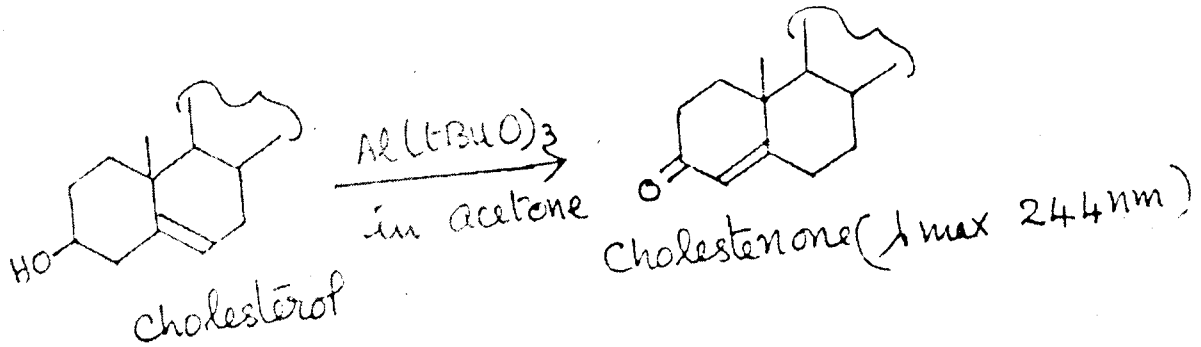
Position of double bond:



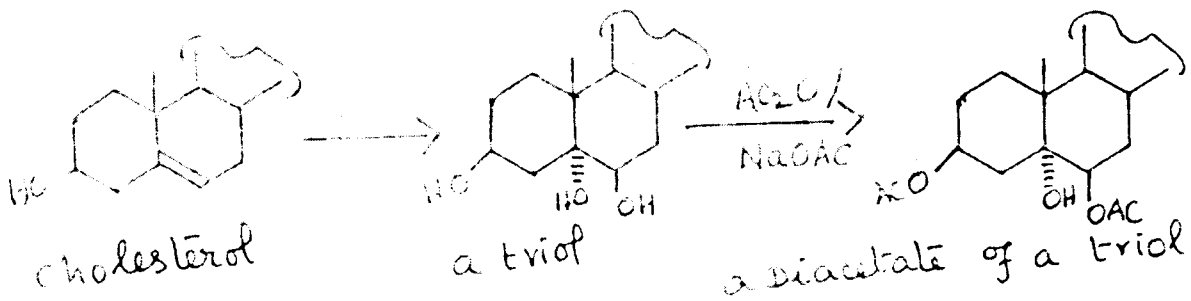


The dione with hydrazine forms a pyridazone derivative. This proves it to be a (-diketone. On oxidation it gives a tetracarboxylic acid with same number of carbon atoms. This shows that the two carbonyl groups are in two different rings (Had they been in one ring, then the product would been a dicarboxylic acid with lesser number of carbon atoms, in this case). Controlled oxidation gives a stable keto acid .So it must be either a √ or δ keto-acid. But it is √ has been inferred from the pyridazone derivative. These reactions can be formulated above.

Furthermore cholesterol on oppenauer oxidation gives a ketone which was found to be conjugated, ie, the double bond moves into conjugation. This is possible only if the double bond is placed in between 5 and 6.This would account for the formation of the (-diketone as well as the conjugated enone.

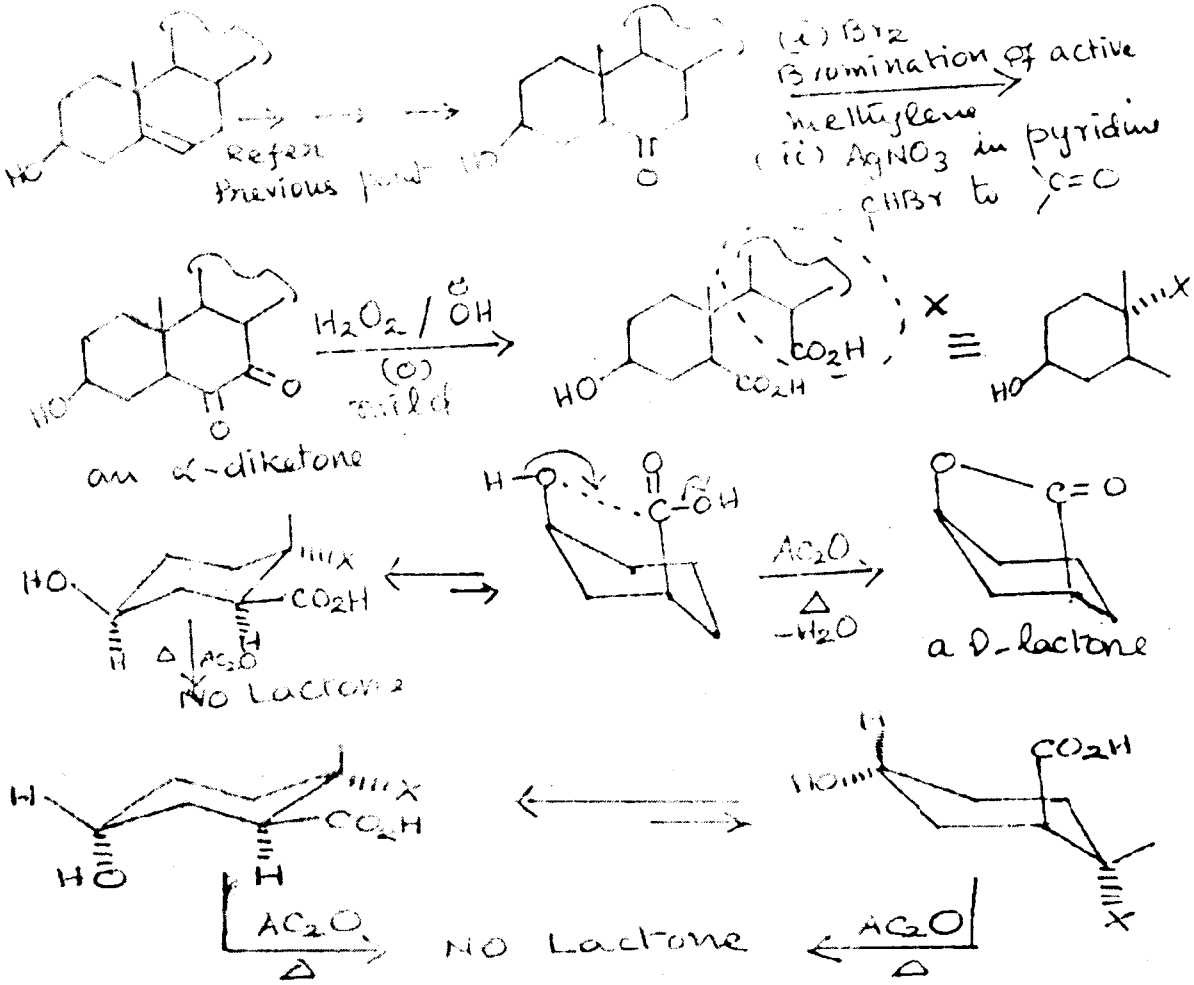


This is proved by the hydroxylation studies done on Cholestrol. Hydroxylation of cholestrol gives a triol. The triol could be only diacetylated. Thus one of the hydroxyl group is tertiary. This again is possible only if the double bond is placed in between 5 and 6.



Configuration of hydroxyl group: (Shoppee et al)

The configuration of hydroxyl group was established by shoppee et al as follows:



This acid was heated with acetic anhydride to form a lactone.The configuration of the C_5 – Carboxyl is considered to be beta . In order for lactonisation to occur the configuration of hydroxyl group also should be beta. This is how the configuration of hydroxyl group is fixed. The various possible conformations and their impact on lactorisation have been depicted above.

Size of various rings in Cholesterol

To find the size of various rings in cholestrol the following procedure is adopted.

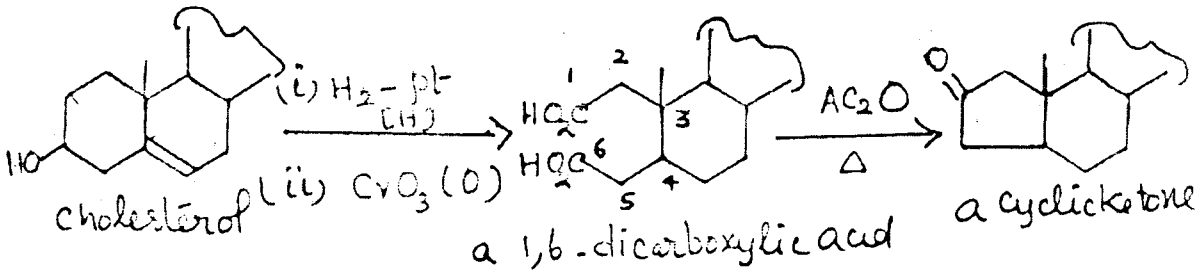
i) Selective opening of a particular ring to give a dicarboxylic acid. This is done by removing any easily oxidisable group found in other rings.

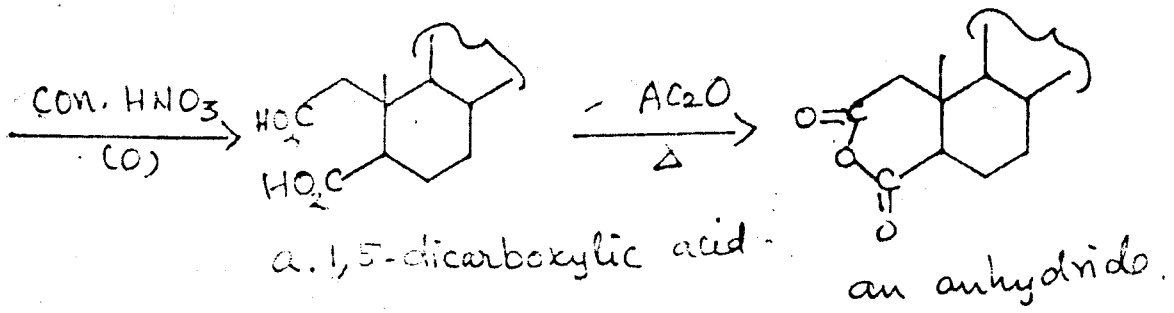
ii) Application of Blanc's rule on the dicarboxylic acid will throw light on the size of that ring.

ie 1,4 and 1,5 –dicarboxylic acid on heating will give a cyclic anhydride whereas 1,6 and 1,7 – dicarboxylic acids on heating will give a cyclic ketone less by one carbon.

One serious disadvantage here is the Blanc's rule fails in cases where the two carboxyl groups are attached to two different rings. In such cases their heavy metal salts are heated.

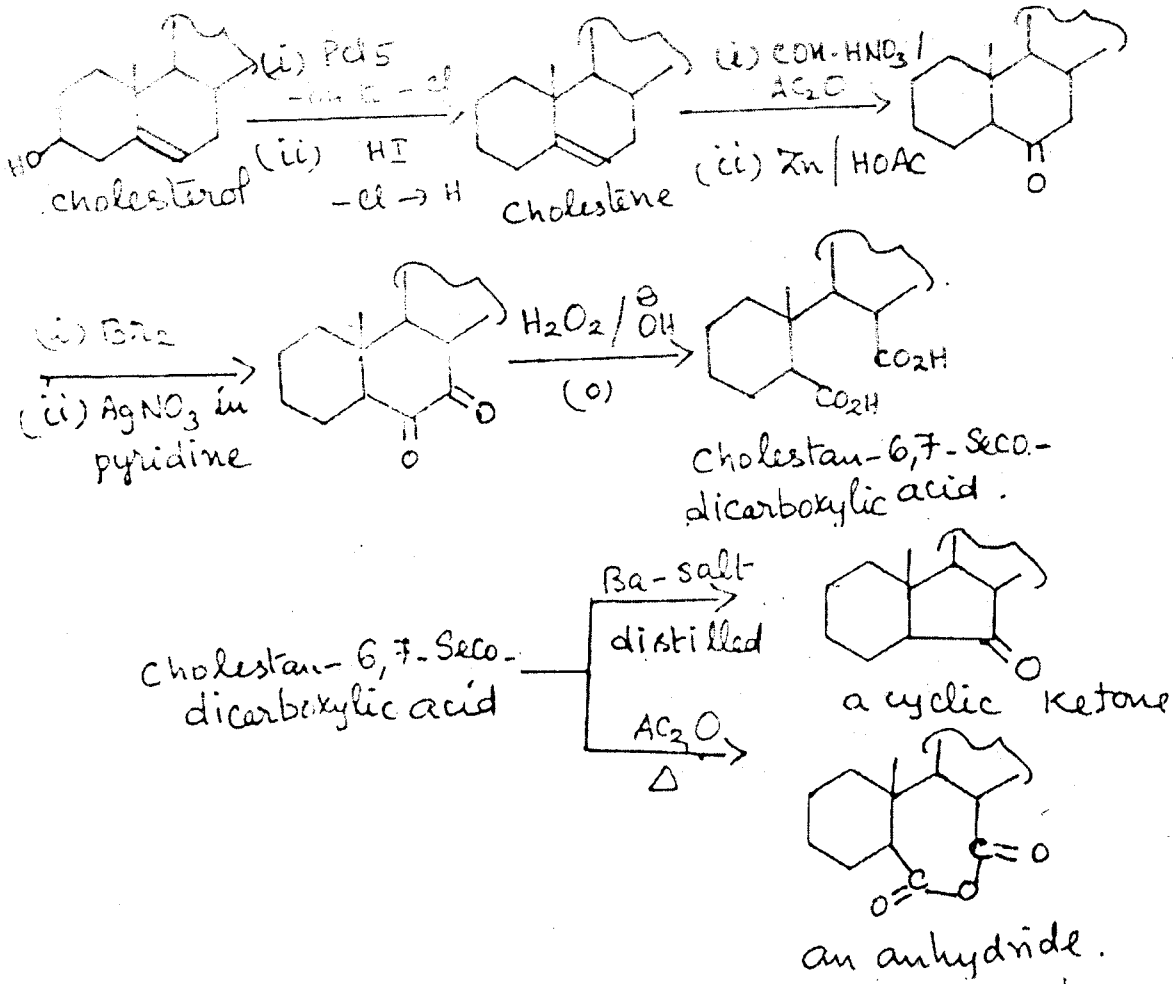
Size of ring A:





The first acid formed a cyclic ketone. The second acid formed a cyclic anhydride . Thus the first one must be a 1,6-dicarboxylic acid and the latter a 1,5-dicarboxylic acid. Thus the size of ring A is six-membered.

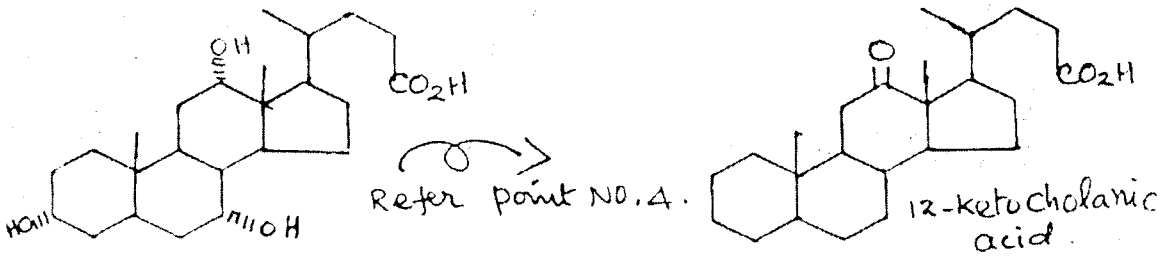
Size of ring B:

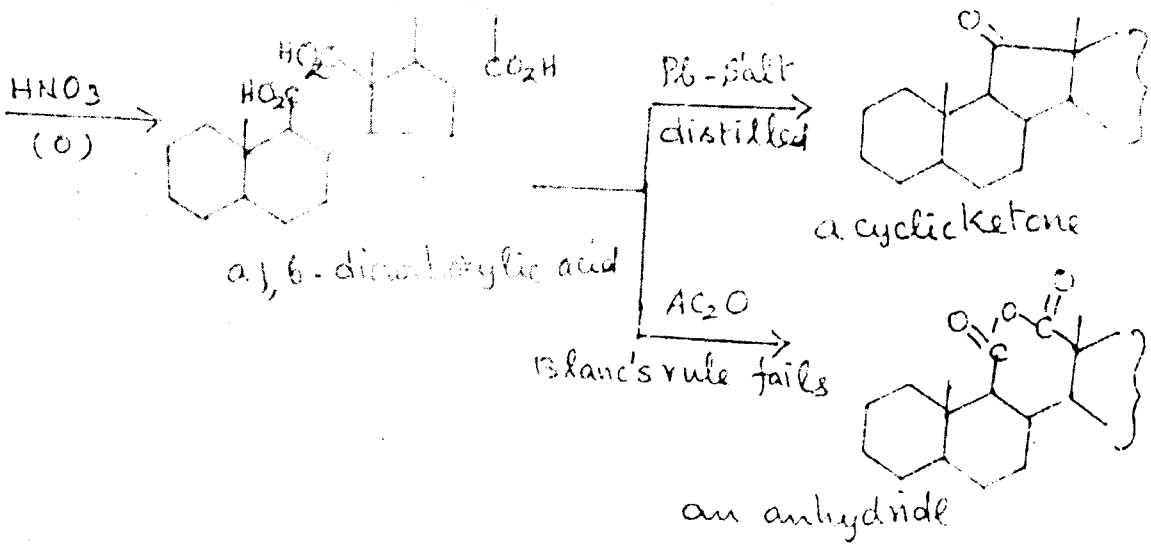


Based on the above observations ring B in cholesterol is also found to be six-membered.

Size of ring C:

Cholesterol does not contain any easily oxidisable functional groups in ring C. So we have to depend on the studies done on cholic acid only. (The structural relationship between cholesterol and cholic acid has already been established.)

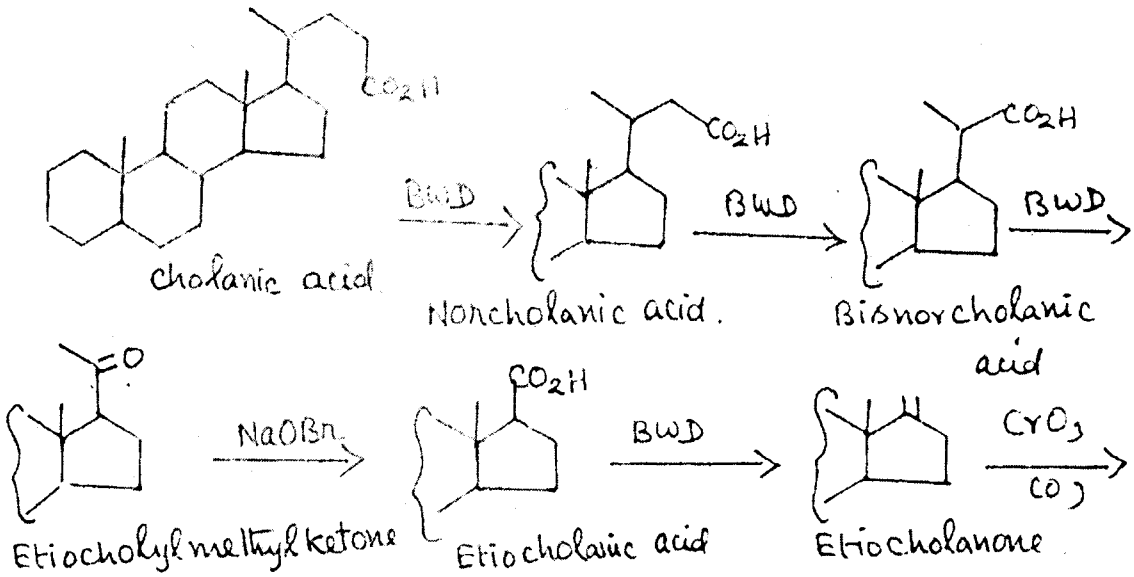


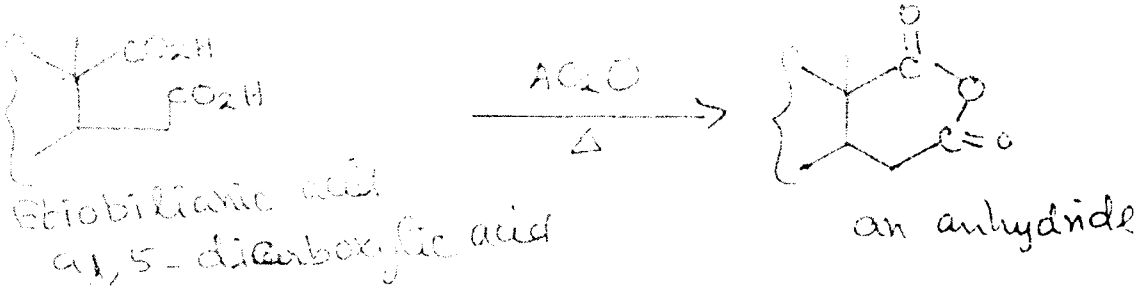


So ring C in cholesterol is also found to be six-membered.

Size of ring D:

Cholanic acid on successive BWD(thrice),alkaline hypobromite oxidation,again BWD followed by oxidation gives a dicarboxylic acid. This formed a cyclic anhydride on heating with acetic anhydride. Thus ring D in cholesterol is found to be five-membered.



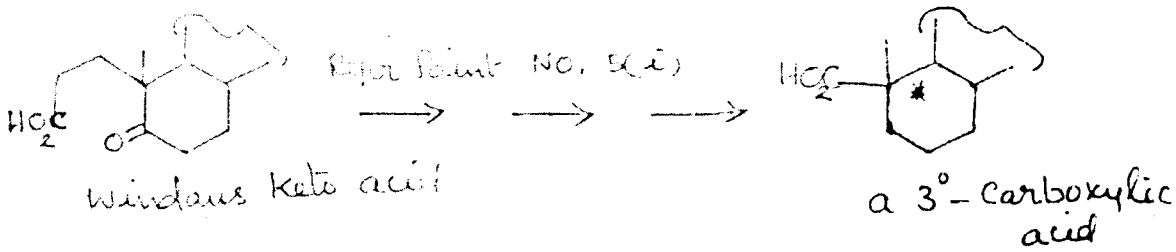


Cholesterol-------Cholanic acid----refer point number 4.

Positions of angular methyl groups:

When the number of carbon atoms in the side chain and the ring carbons were put together, there was found to be a shortage of two carbon atoms. These carbon atoms were found to be present in the angular positions of the steroidal skeleton. That gives atleast five positions for them in the nucleus of cholesterol. But were found to be present at positions 10 and 13 as follows.

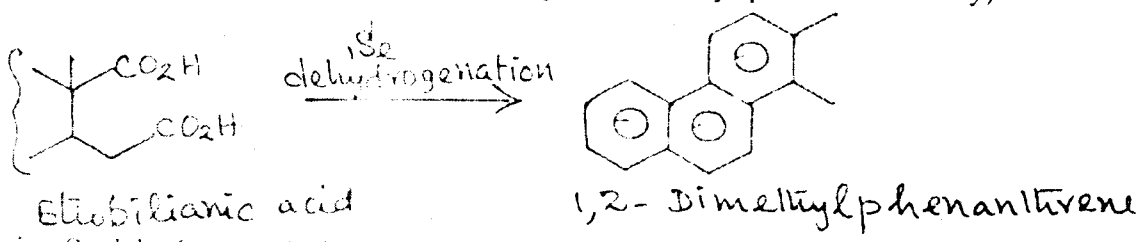
C_{10} – angular methyl group:



The Windaus keto acid obtained by opening ring A of cholesterol on Clemmensen reduction gives a carboxylic acid. This acid can be subjected to BWD only twice. The resulting acid was found to be tertiary in nature because of its difficult esterification. The tertiary nature of the carboxylic acid is attributed to the presence of an angular methyl group at that position.

C_{13} – angular methyl group: [refer point number 5(iii)]

The etiobilianic obtained by the opening of ring D in cholesterol on se dehydrogenation gives 1,2- dimethylphenanthrene. The formation of the latter is possible only if the angular methyl group is present at C_{13} and not at C_{14}(Had it been at C_{14}, then se dehydrogenation would have given 1-methyl-phenanthene only)



[During Se dehydrogenation several things could happen

i) dehydrogenation of ring
ii) Hydrogenation of olefinic bonds in the side chain and the other unsaturated functional groups present.
iii) Decarboxylation.
iv) Expulsion of easily polarisable groups if present along with other groups.]

The nature and position of side chain

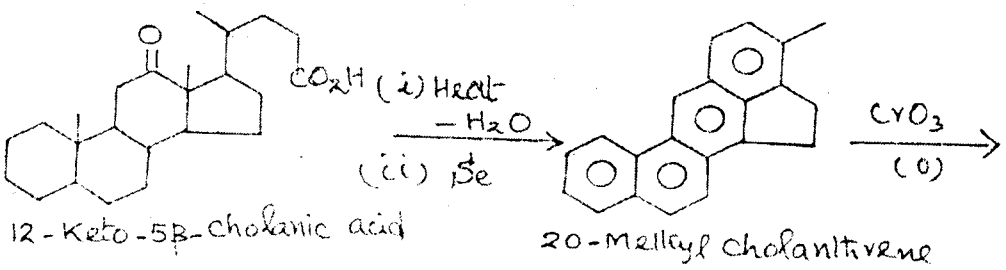
Oxidation of either cholesterol or its acetate gives a ketone remniscent in smell of methylisohexyl ketone(Smell is used as one of the tools used for identification of compounds formerly). So the side chain is believed to contain a methylisohexyl nucleus (ie. 8 carbon atoms).

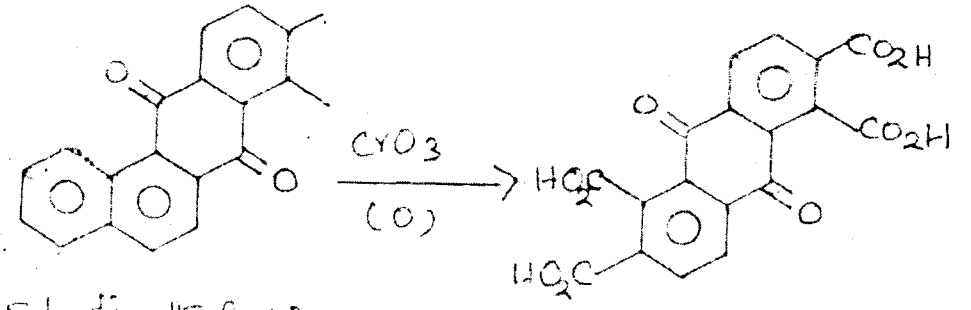
Conversion of cholanic acid to coprostane and counting of carbon atoms done on cholanic acid side chain add additional support to this fact (refer point numbers 4 and 5).

All the steroids on Se dehydrogenation give Diel's hydrocarbon as one of the products. The latter contains a methyl group at position 17. corresponding to the cholesterol nucleus. They may be due to degradation of side chain into a methyl group at that position: position 17 is also supported by evidence obtained from X-ray photographs and surface film measurements.

The chemical evidence for the attachment of the side chain at position 17 is given as follows:

5β-cholanic acid may be obtained by the oxidation of 5β - cholestane. 5β - cholanic acid may also be obtained by the oxidation of deoxycholic acid followed by a Clemmensen reduction. Thus the side chain in cholesterol and deoxycholic acid are in the same position. Now deoxycholic acid can also be converted into 12 – keto - 5β - cholanic acid which on heating to 320 ^{0} C, loses water and carbon dioxide to form dehydronorcholene. This, when distilled with selenium forms 20-methylcholanthrene. The structure of the latter is known by its oxidation to 5,6-dimethyl-1,2-benzanthraquinone, which, in turn, gives on further oxidation, anthraquinone -1,2,5,6 – tetracarboxylic acid. Finally the structure of 20 – methylcholanthrene has been confirmed by its synthesis. The foregoing facts can be explained only if the side - chain in cholesterol is in position 17 thus,





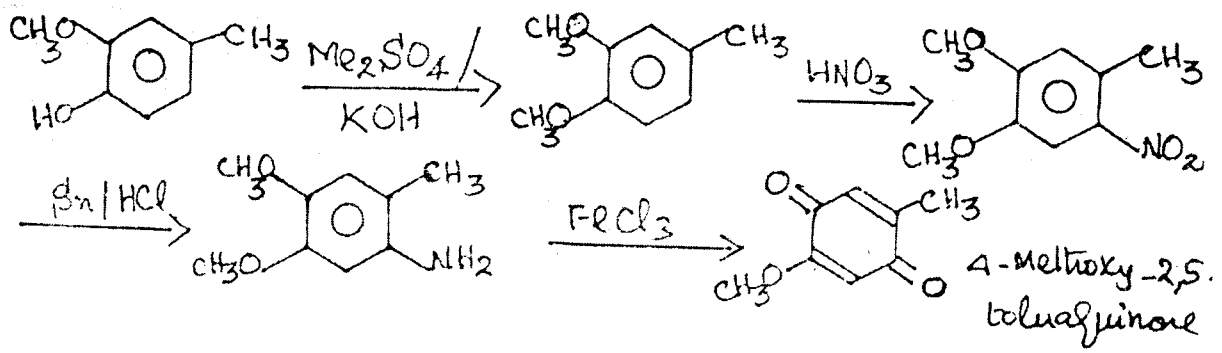
5,6-dimethyl-1,2-benzanthraquinone

Anthraquinone-1,2,5,6-tetracarboxylic acid

Finally the structure of the cholesterol is confirmed by its synthesis. The synthesis described here is that which was done by Woodward et al. The nucleus of cholesterol has eight asymmetric centers. That means 256 optically active forms are possible. To synthesise the biologically active one (ie. Which is present in the animal kingdom), lot of stereochemical and regiochemical controls are to be applied. Here goes the synthesis of cholesterol.

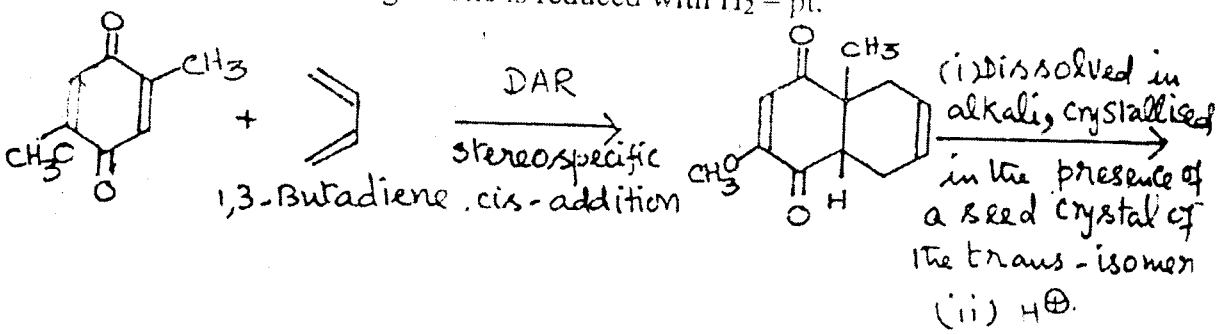
SYNTHESIS:

The starting material for this synthesis namely, 4 – methoxy-2,5 – toluaquinone was prepared from 2- methoxy –p-cresol as follows:

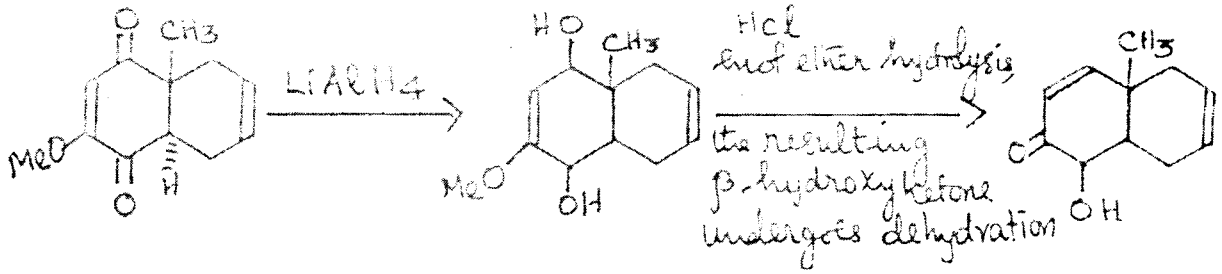


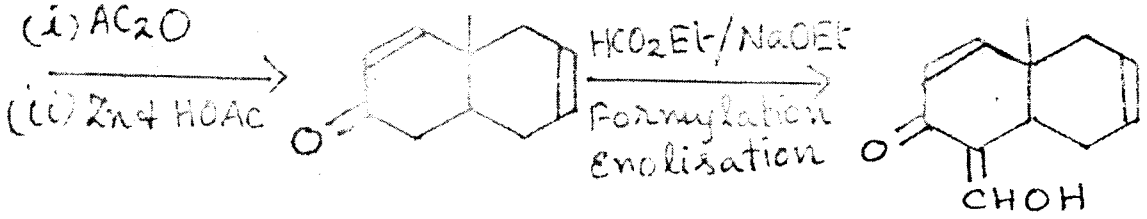
4-Methoxy-2,5-toluaquinone

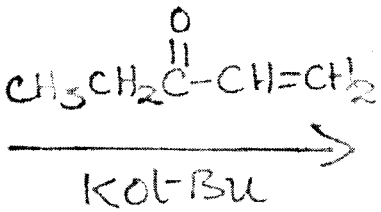
This ketone was a racemate resolved by reduction of the ketone with sodium borohydride. The (+) form of 3β-OH is separated. Reoxidised by oppenauer oxidation. Then the resulting ketone is reduced with H_2 – pt.

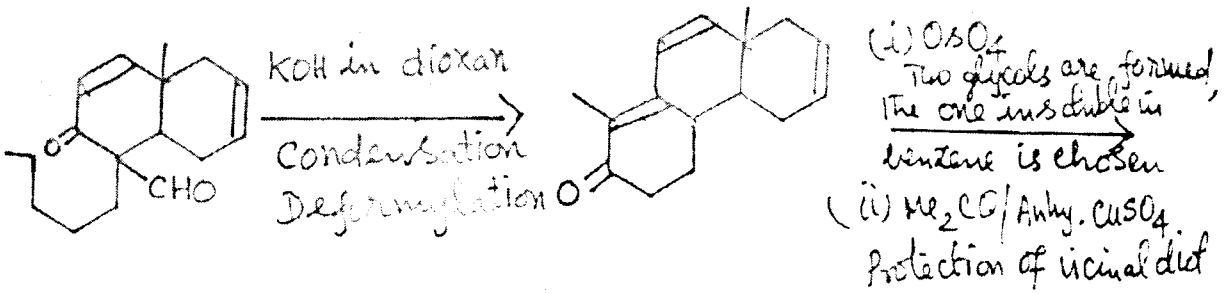


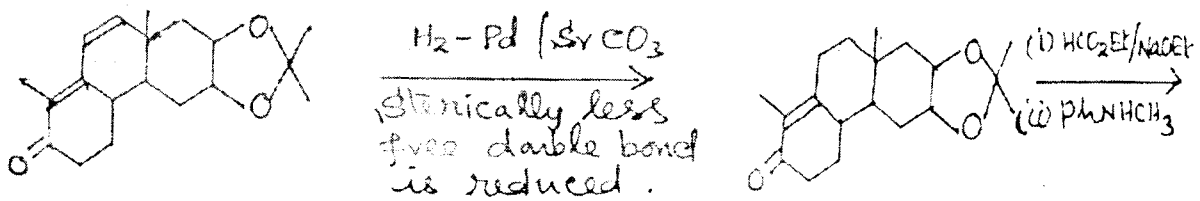
1,3-Butadiene

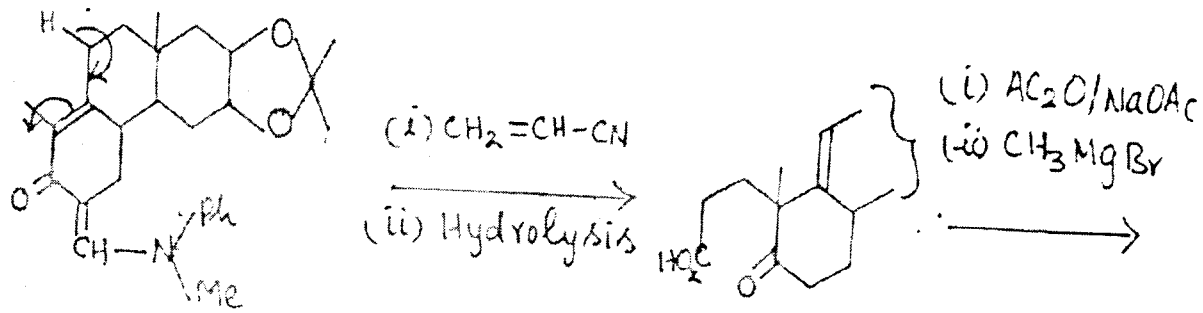

LiAlH4
HCl
enol ether hydrolysis
the resulting
β-hydroxyketone
undergoes dehydration

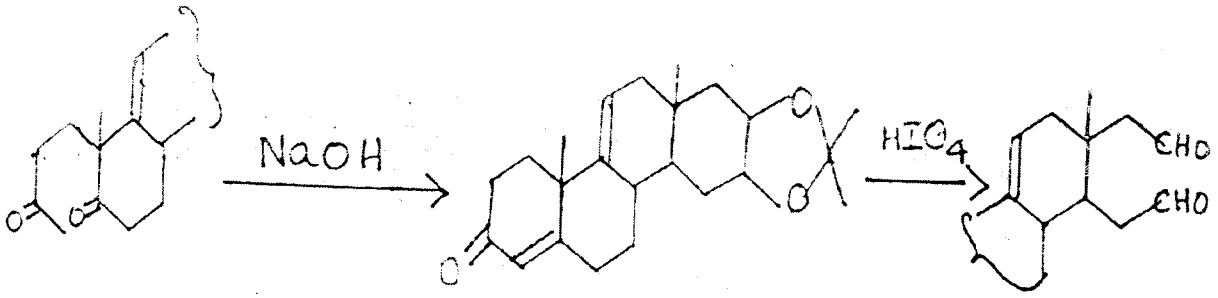

(i) Ac2O
(ii) Zn+ HOAc
HCO2Et/NaOEt
Formylation
Enolisation

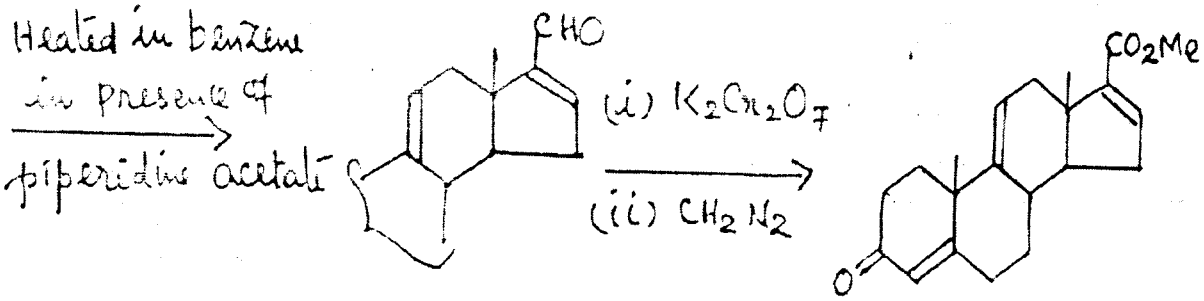

KOt-Bu

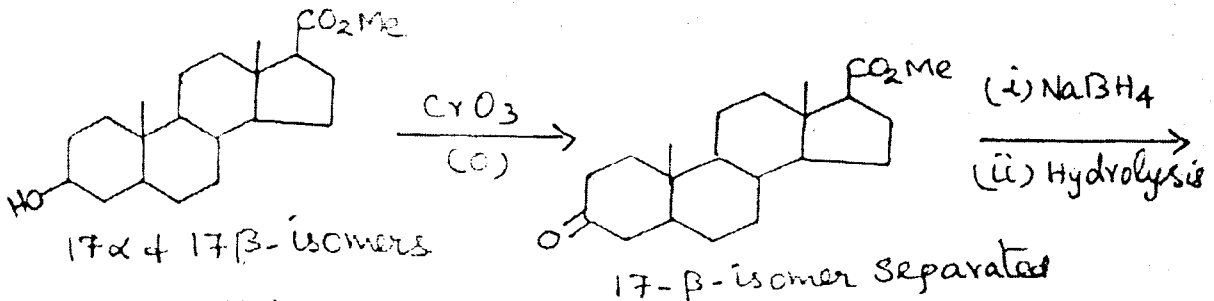

KOH in dioxan
Condensation
Deformylation
(i) OsO4
Two glycols are formed,
the one insoluble in
benzene is chosen
(ii) Me2CO/Anhy. CuSO4
Protection of vicinal diol


H2 - Pd/SrCO3
Sterically less
hyed double bond
is reduced.
(i) HCO2Et/NaOEt
(ii) PhNHCH3


(i) CH2=CH-CN
(ii) Hydrolysis
(i) Ac2O/NaOAc
(ii) CH3MgBr

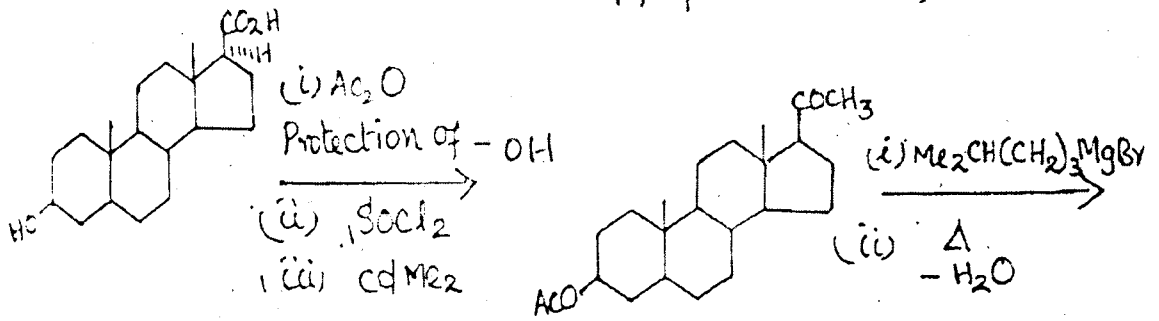


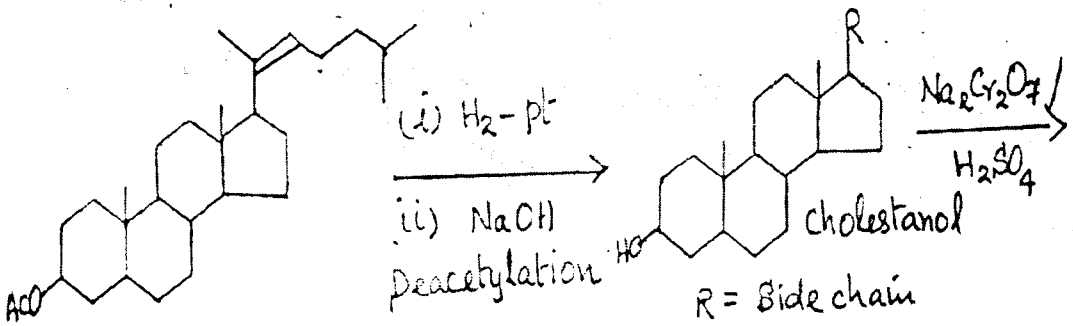




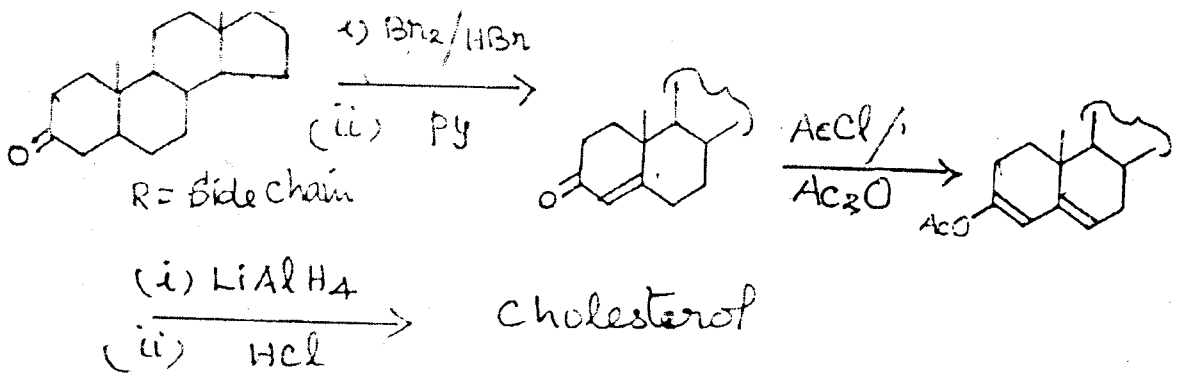
17α & 17β-isomers

17-β-isomer separated



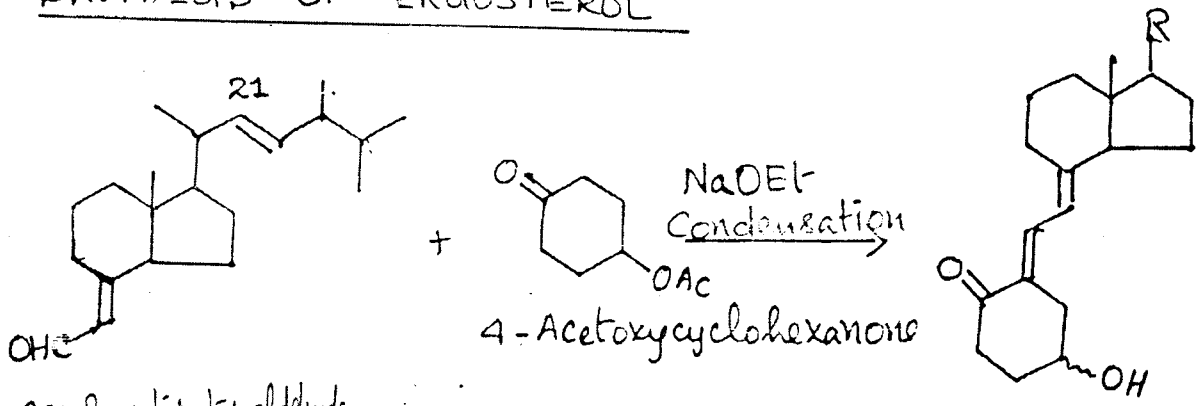


R = Side chain

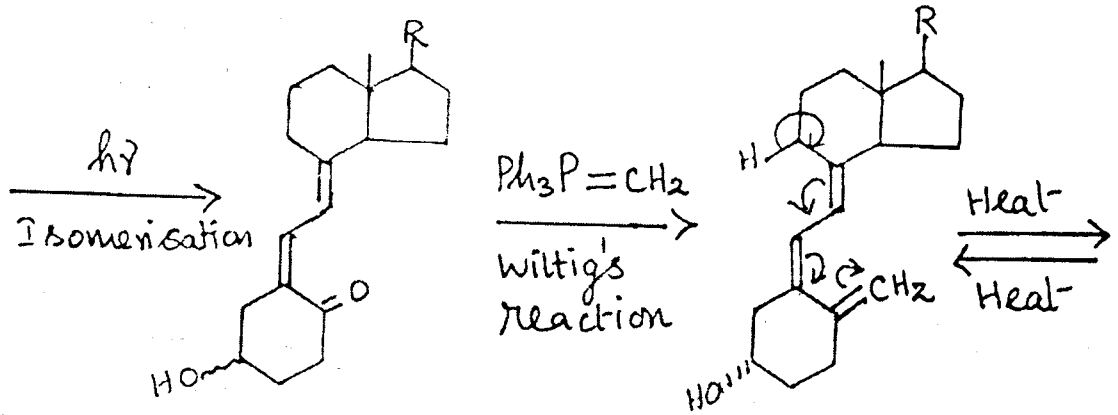


(Steroids by Feiser & Feiser)

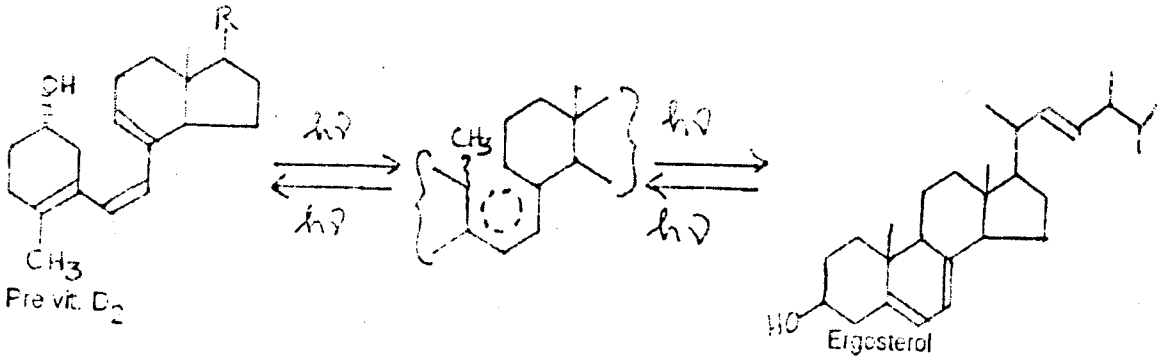
SYNTHESIS OF ERGOSTEROL



C-21 unsaturated aldehyde
(Steroidal numbering)

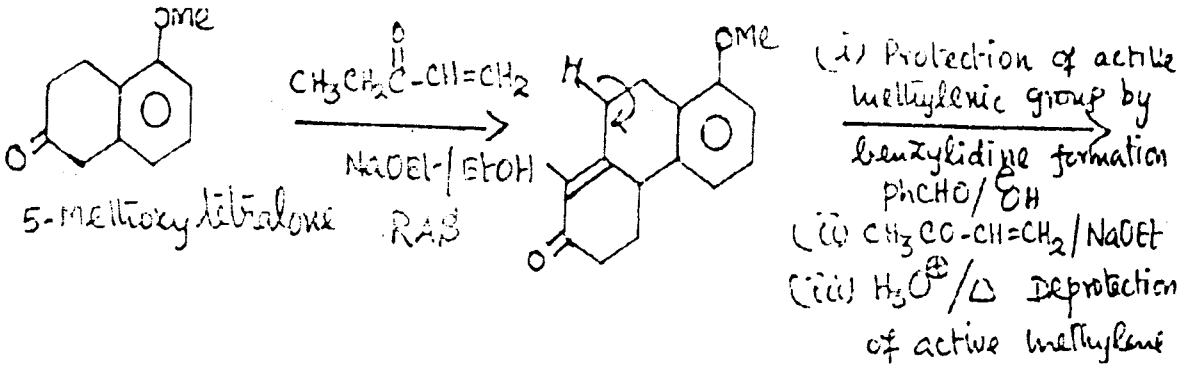


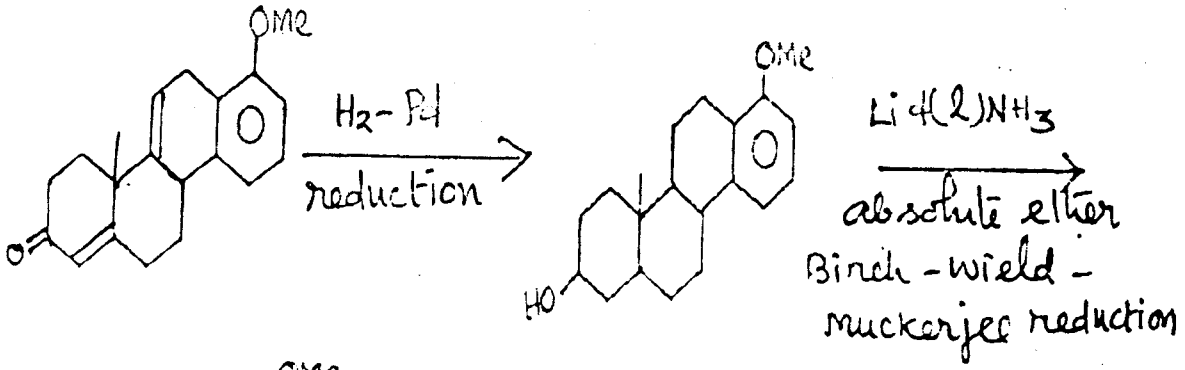
Vitamin D_2 or Ergocalciferol

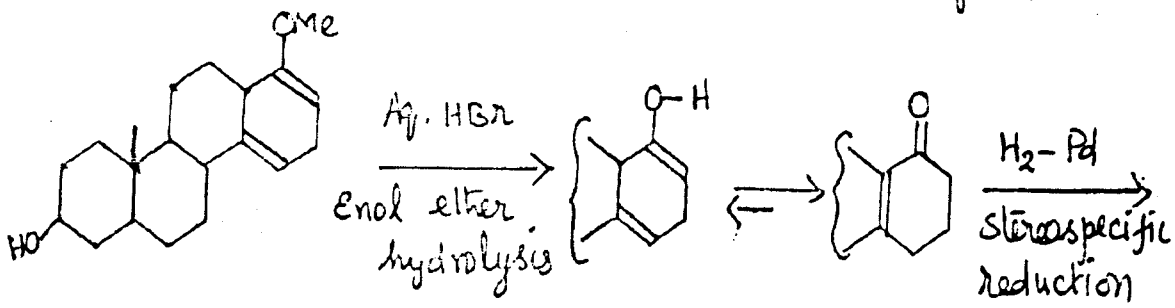


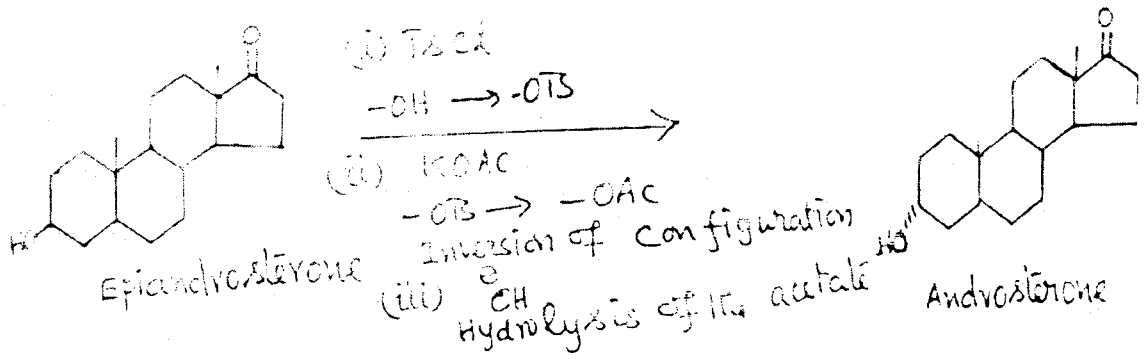
MALE SEX HORMONES

Synthesis of androsterone:

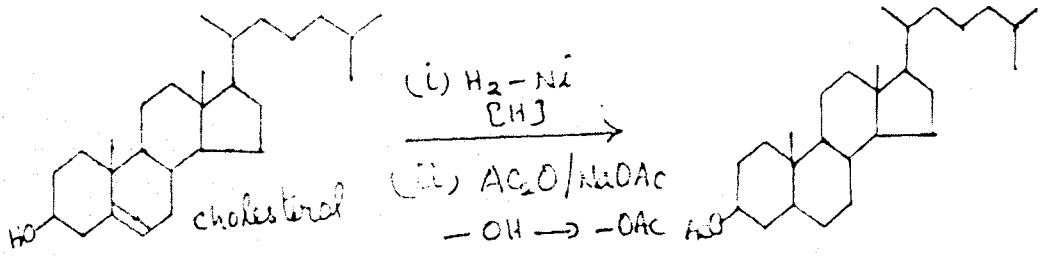


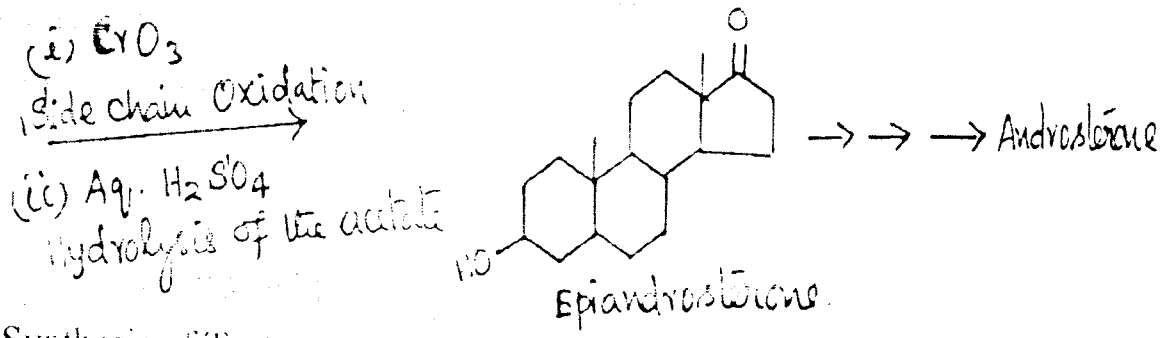




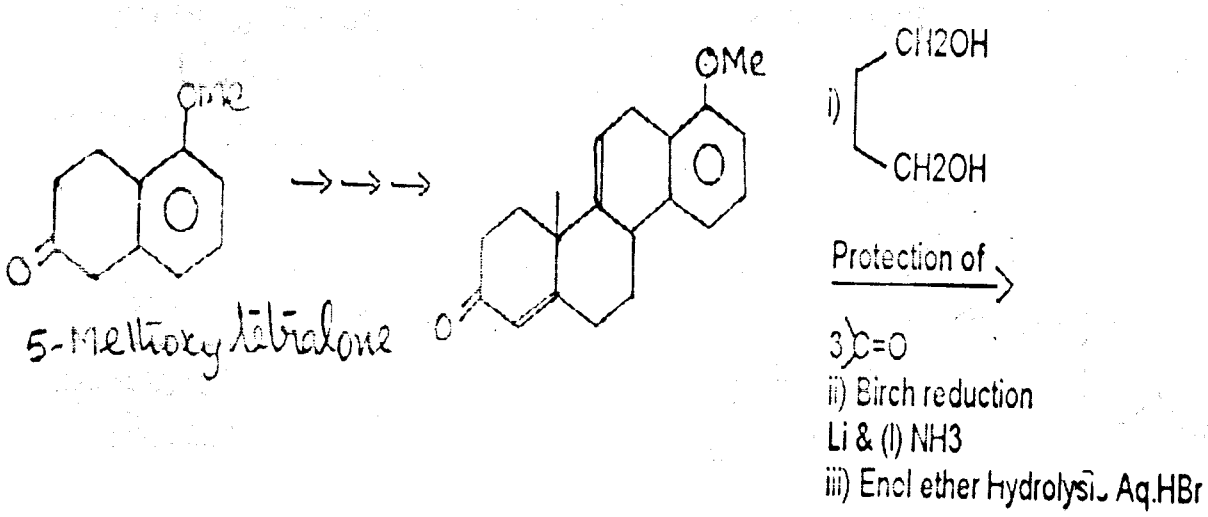


Cholesterol to androsterone:

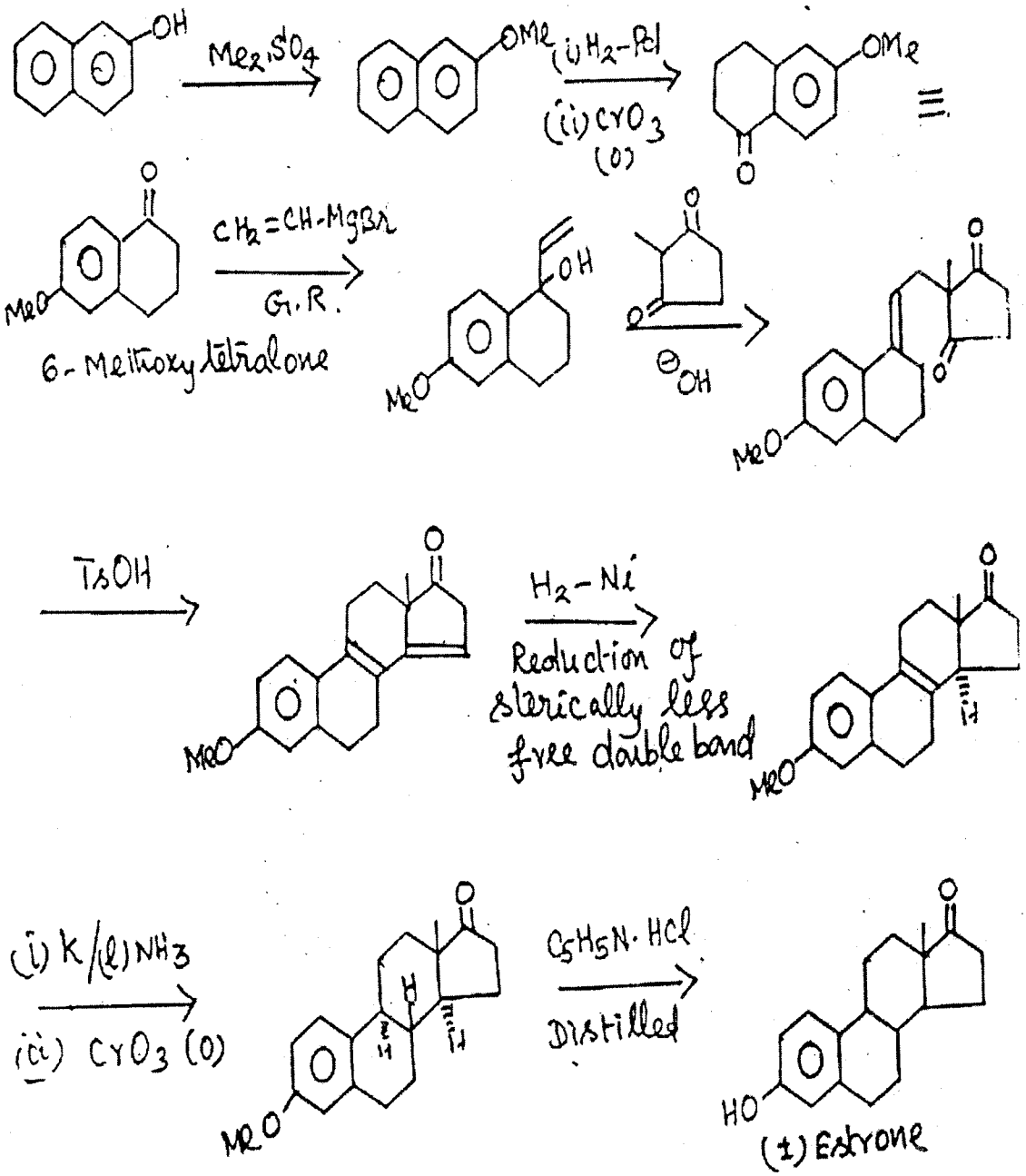




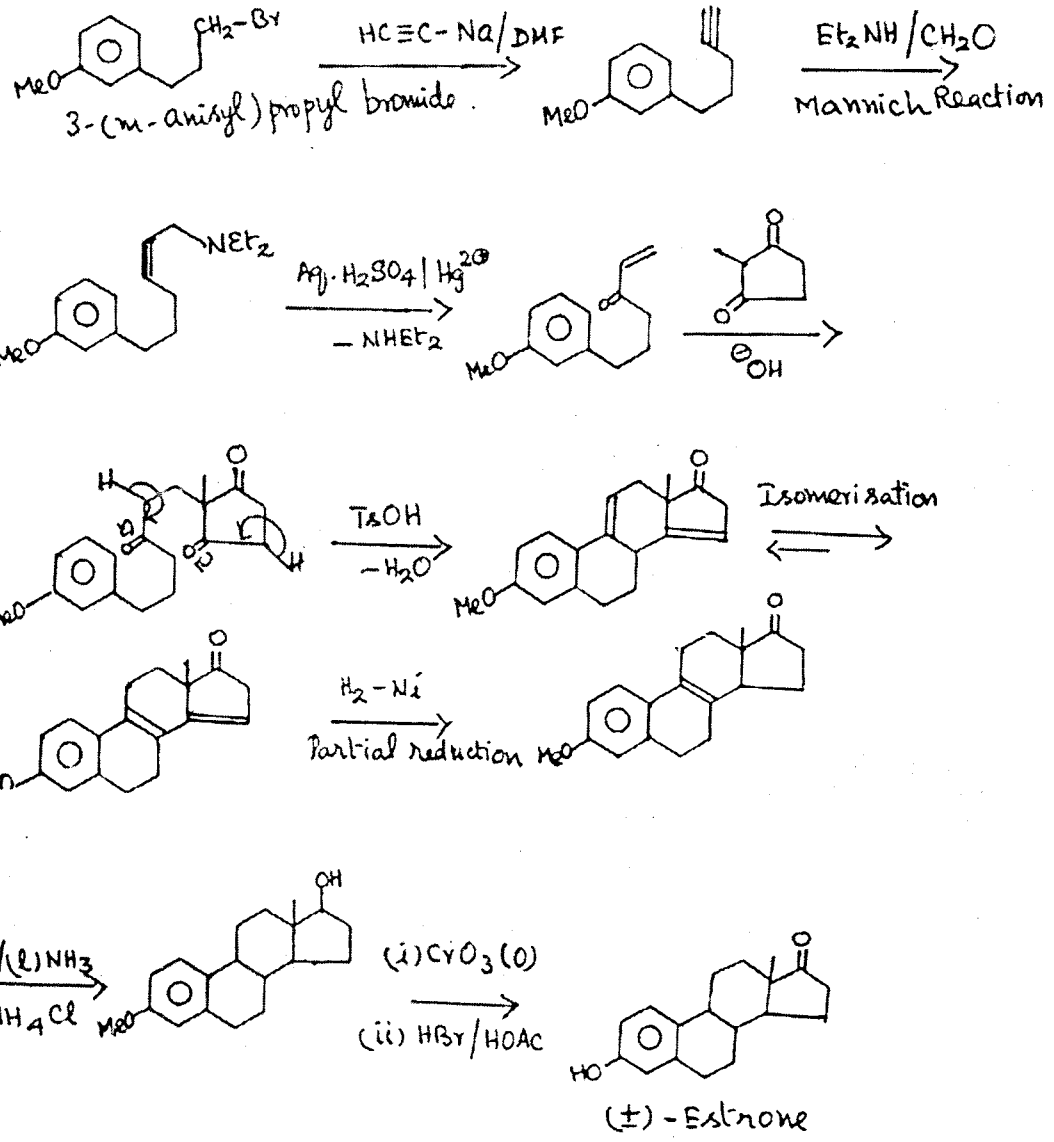
Synthesis of Testosterone:



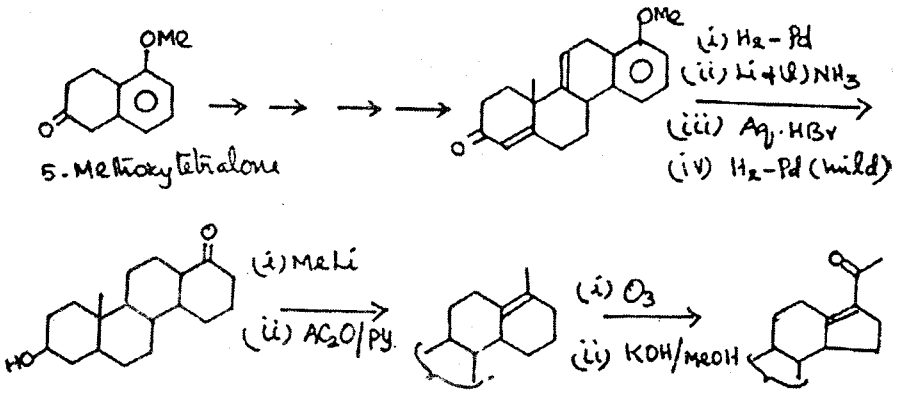
Estrone : Synthesis I

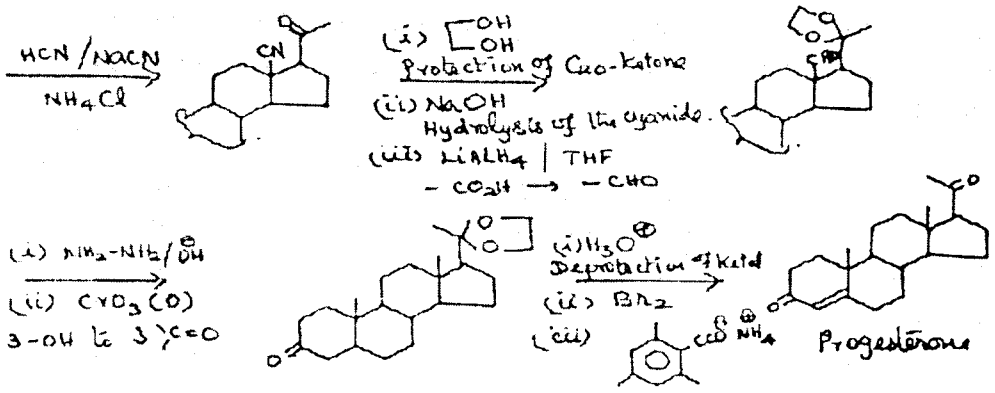


Synthesis II: (Hughes etal)

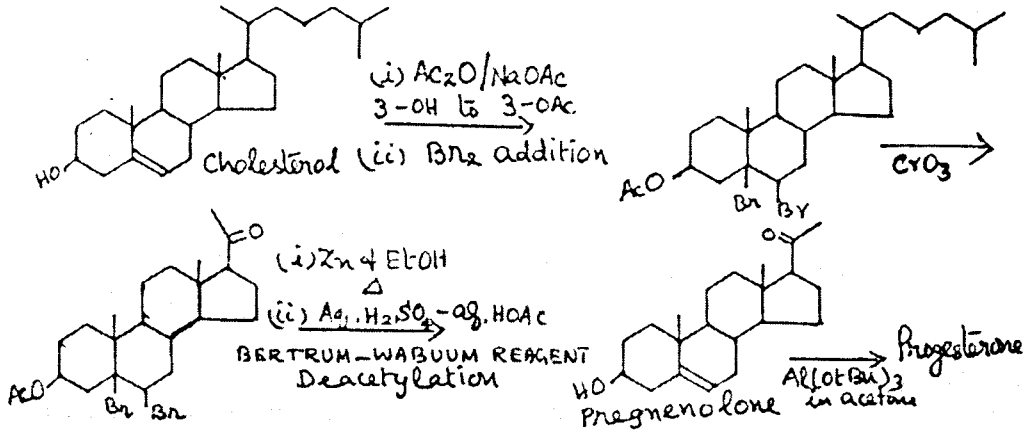


Synthesis of Progesterone.





Cholesterol to progesterone:

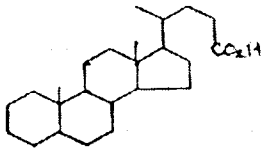


[Side chain oxidation takes place at all the branching points giving different products]

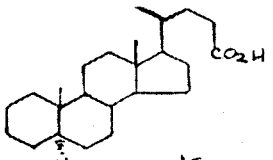
Bile Acids

They occur as amides of glycine ($NH_2CH_2CO_2H$) or taurine (NH_2-$CH_2CH_2SO_3H$) and are found in bile, a secretion of liver . (Ex) glycocholic acid (glycine + cholic acid) taurocholic acid (taurine + cholic acid). The bile acids are present as their sodium salts and they act as emulsifying agents in the intestinal tract. They latter action makes the fats, which are water insoluble into soluble and thereby help in their absorption in the intestinal tract.

About twenty bile acids have been found in nature. They are mostly the hydroxyl derivatives of 5β and 5α - cholanic acids



A/B fusion cis
5β-cholanic acid

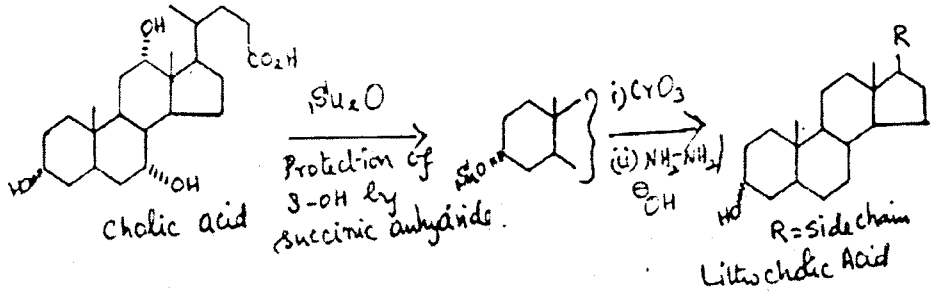


A/B fusion trans
Allocholanic acid

The positions of the hydroxyl groups are any one or more of the following: 3,6,7,11,12 and 23. Almost all the hydroxyl groups are 'α' in configuration. Some of the more important bile acids are:

Name	Hydroxyl groups	Source
Cholic acid	3α, 7α, 12α	Man, Ox
Deoxycholic acid	3α, 12α	Man, Ox
Lithocholic acid	3α	Man, Ox
Chenodesoxycholic acid	3α, 7α	Man, Ox, Hen
α -Hydroxycholic acid	3α, 6α	Pig

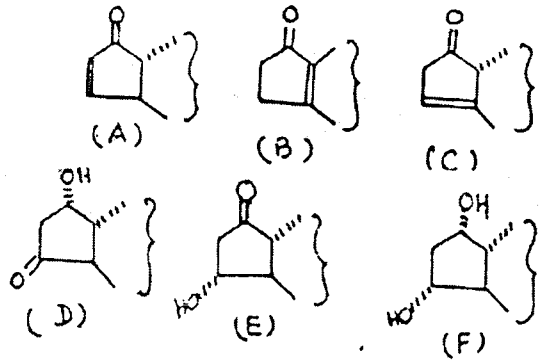
By selective protection and oxidation of hydroxyl groups in cholic acid all but α - hydroxycholic acid can be obtained. For ex



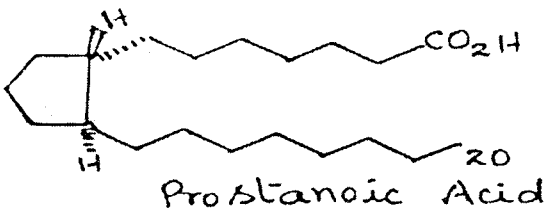
PROSTAGLANDINS

They are chiefly present in human seminal plasma and sheep vesicular glands. They also occur in a number of tissues including pancreas, lungs, brain, kidney etc.

Structural classification:

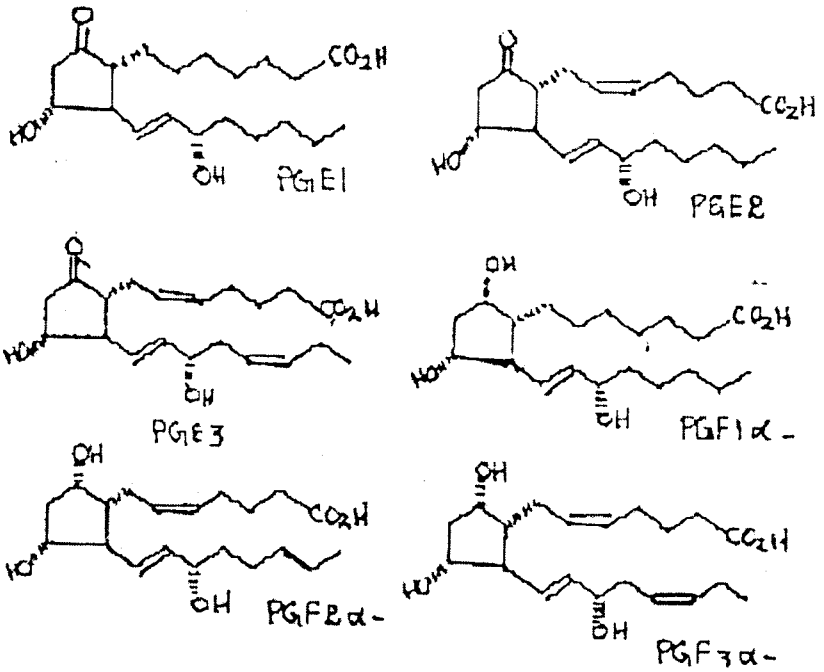


Prostanoic acid: This has no hormonal activity. They are divided into 6 major classes.



In every series,there are three types of compounds. For eg PGE_1 PGE_2 &PGE_3 & PGF_1,PGF_2 &PGF_3 etc.

In all the compounds the side chain is the same. 1,2,3 contain respectively 1,2,3 – double bonds. The following 6 prostaglandins are considered as prostaglandins and these are the one isolated from natural source.



Norprostaglandins and homoprostaglandins are not biogically active.

Biological Properties

PGE_2 lowers B.P.$PGF_2\alpha$ – raises B.P. Low doses of PGE_2 and $PGFf_2\alpha$ - stimulates contraction of the uterus. Infusion of PGE_2 at the rate of 0.05 mg/min. has been found to induce delivery within a few hours.

Prostaglandins are used in the prevention of peptic ulcers. An aerosel preparation of PGE_1 can improve inflow by relaxing the smooth muscles of the bronchial tubes.

The infusion of PGE_1 and PGA_1 produces an increase in the flow of urine and sodium ions. This indicates that prostaglandin in the body help to regulate the blood pressure. Experiments have shown that PGA_1 can lower blood pressure.

PGE_1 has been found effective in widening the nasal passages by constriction of the blood vessels.

Structure elucidation of PGE_1, $PGF_1\alpha$, $PGE_1\beta$:

Both PGE_1 and PGF_1 form monoesters with alcohols indicating the presence of the carboxyl group. When PGE_1 and PGF_1 α - are reduced with Adams catalyst in (PtO_2) ethanol ,we get dihydro $PGE_1$and PGF_1. The dihydro derivatives do not have the IR bands in the region 960 – 970 cm -1. This shows the absence of the trans double bonds.

Both PGE_1 and $PGF_1\alpha$ form acylated derivatives with p-nitrobenzoyl chloride.PGE_1 & PGF_1 contain 2&3 –OH groups repectively. The IR spectrum of PGE_1 showed two carbonyl absorptions one at 5.87μ(1700 – 1725 cm-1)and the other at 5.77μ (740 – 1750 cm^{-1}). The first one corresponds to carbonyl absorption of the carboxylic acid group and the latter due C=O group to which corresponds to cyclopentane carboxyl. Hence PGE_1 has a cyclopentanone ring.

The relationship between PGE_1 and $PGF_1\alpha$ was established by the formation of the latter on reduction of the former with $NaBH_4$ ie PGE_1 on $NaBH_4$ reduction gives $PGF_1\alpha$. This reaction involved the reduction of the keto group in PGE_1 and also gives rise to a second reaction product of PGE_1. when PGE_1 is subjected to CrO_3 oxidation. Suberic acid was obtained in high yield $HOOC(CH_2)_6$ COOH. This shows that six unsubstituted methylenic groups are present in the chain.

Oxidative ozonolysis of the methyl ester acetate fo PGE_1 gave α -acetoxyheptanoic acid

HO_2C-CH-$(CH_2)_4CH_3$
|
OAC.

This indicates that seven other carbon atoms are present with the following structure.

$$=CH\text{-}CH\text{-}(CH_2)_4\ CH_3$$
$$|$$
$$OH$$

The above 7-carbon chain may be directly bound to the ring through the double bond or attached in a - CH = group and that one of the carboxyl groups in the suberic acid originates from the ring carbon.

Periodate-permanganate oxidation of the trimethyl ether of the methyl ester of $PGF_1\alpha$ followed by mass spectral analysis of the fragments isolated by gas chromatography revealed the formation of a cyclopentane carboxylic acid derivative. This indicates that the double bond is disubstituted and placed atleast one carbon away

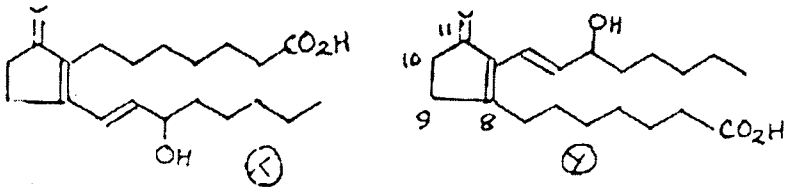
from the ring. This further suggests that the carboxyl group of the suberic acid must therefore originate from the 5 – membered ring and the 2nd hydroxyl group in PGE_1 must also be present in the ring.

From the above discussions it is clear that PGE_1 is a cyclopentanone derivative containing two side chains with carbon atoms 7&8 and the double bond and one of the hydroxyls in the C_8 chain.

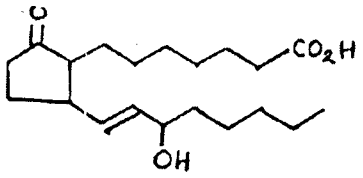
When PGE_1 was treated with alkali (0.5 N NaOH) it gave a compound found to be identical with PGB_1 (UV 278mm). The acylated methyl ester of PGB_1 give on oxidative ozonolysis, suberic acid monomethyl ester, succinic acid and α -acetoxyheptanoic acid.

$$PGB_1 \xrightarrow{O_3} HO_2C(CH_2)_6\,COOMe + HO_2C\,(CH_2)CO_2H + CH_3(CH_2)_4 - \underset{\underset{OAc}{|}}{CH} - CO_2H$$

(i.e) all but one of the carbon atoms of PGE_1 are accounted for. The formation of succinic acid showed that 2 vicinal methylene groups are present in the 5 membered ring and accordingly the carbon atoms carrying side chains and the keto group must be adjacent. Now two alternate structures can be drawn for PGB_1.



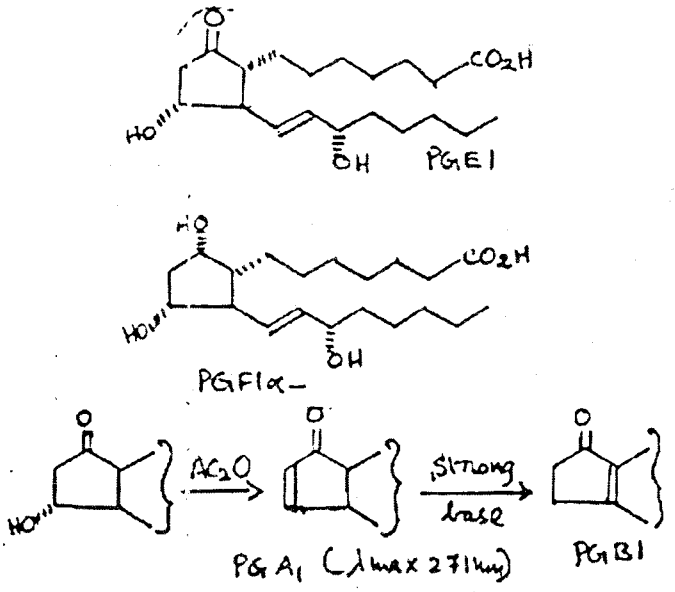
If PGB_1 has structure (Y) then on oxidation it would have given a eleven carbon γ - ketodicarboxylic acid. Since this acid was not formed structure (X) should be the structure of PGB_1. Now the partial structure of PGE_1 can be written as



If we establish the position of the second hydroxyl group then the structure of PGE_1 and hence PGF_1 are established.

The second hydroxyl group is in the cyclopentane ring and four positions are available. The 3^0 . nature is excluded by acetylation experiments and hence only two positions are left with. The placement of the - OH group at the 2 carbon atom α - to the keto group was also ruled out by the failure of PGE_1 as well as PGF_1 to undergo oxidation with HIO_4 or $Pb(OAc)_4$. Hence the second –OH group should be at β -position w. r. to the carbonyl and hence the structures of PGE_1 and PGF_1 are

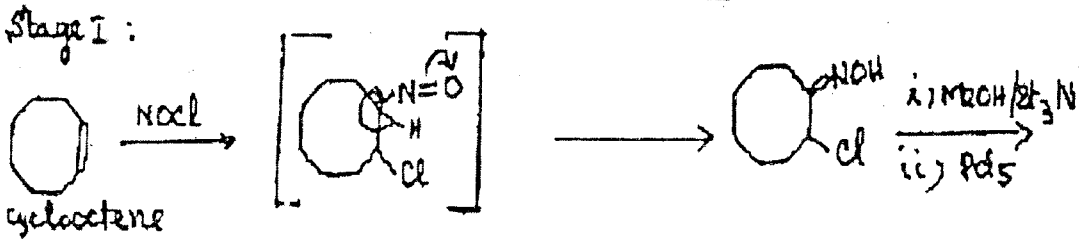
The β-ketol structure for PGE_1 is also supported by the fact that on treatment with weak alkali or acetic anhydride it gives the α, β-unsaturated ketone PGA_1 which rearranges to PGB_1 with strong base.

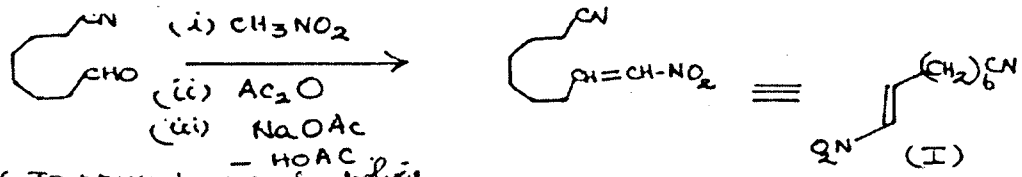


SYNTHESIS

SYNTHESIS: (Ref. NATURE, 212, 38 (1966)

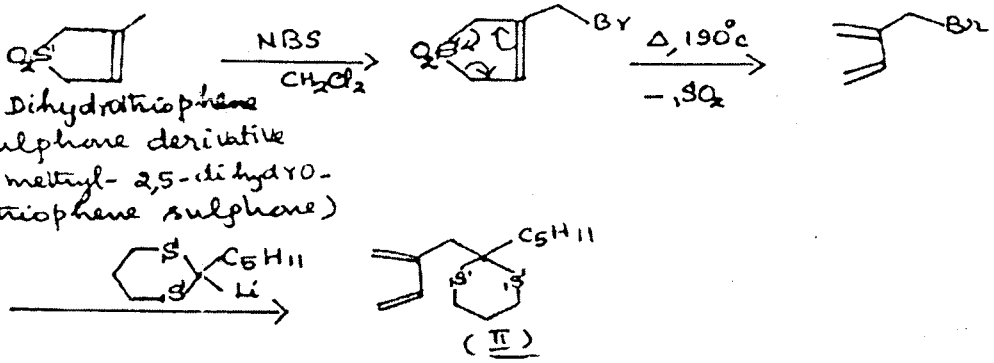
Stage I :





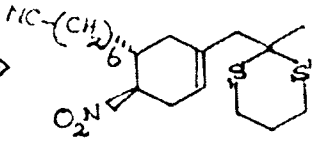
(To prevent the hydrolysis of cyanide, no acid / alkali used for dehydration)

Stage II



Stage III

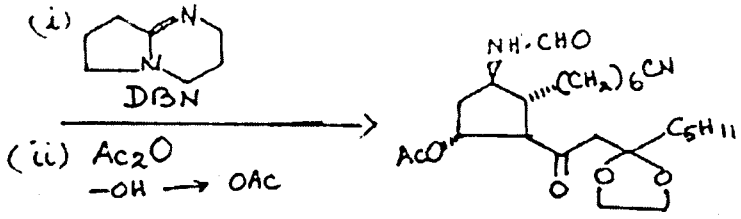
I + II $\xrightarrow[\text{DAR}]{110^\circ C}$



(i) Al–Hg, $-NO_2 \rightarrow -NH_2$

(ii) HCO_2Et N-formylation

(iii) / $HgCl_2$

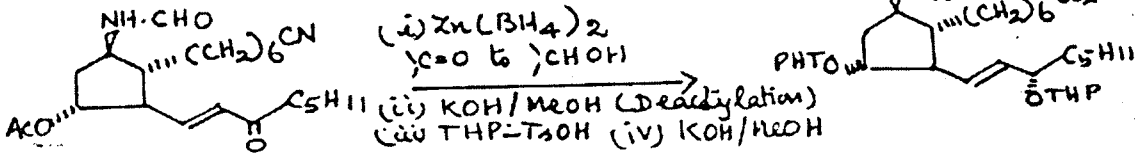


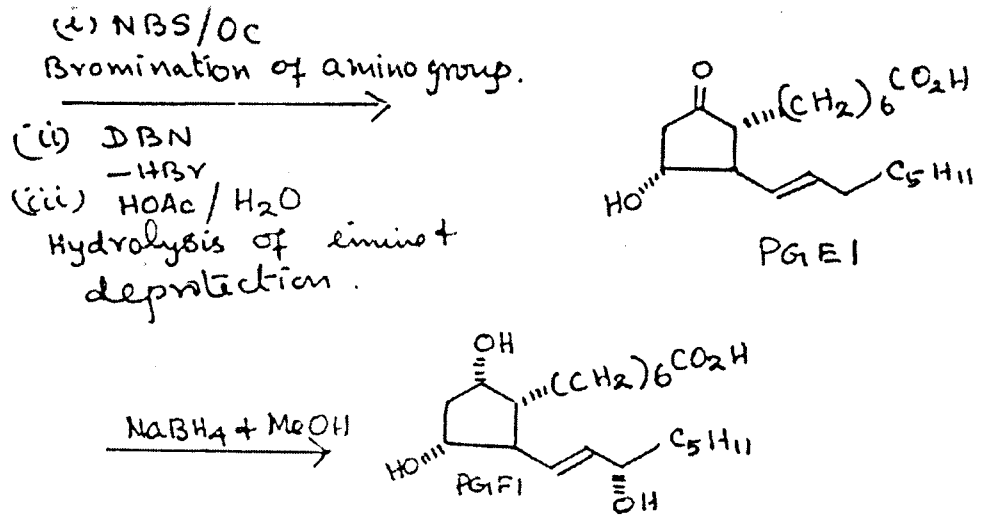
(i) $Zn(BH_4)_2$ >C=O to >CHOH

(ii) $H^\oplus$ Deprotection of ketal

(iii) DCC / $CuCl_2$ – Et_2O * – H_2O

* Attachment of DCC at the hydroxyl followed by dehydration without disturbing the C_{11}-acetate.





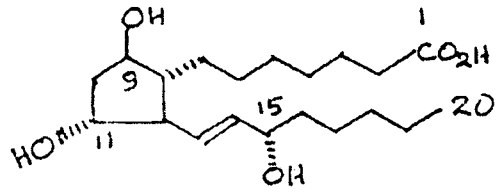
Stereochemistry:

The PGF compounds are having the maximum number of asymmetric centres ie 5. These are C_8, C_9, C_{11}, C_{12}, & C_{15}.

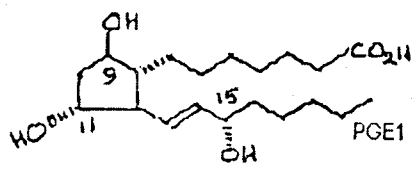
PGE compounds have 4 asymmetric centres at C_8, C_{11} C_{12} & C_{15}.

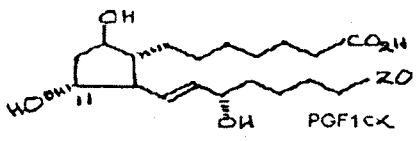
Reduction of PGE_1 with $NaBH_4$ gives a mixure of PGF_1 α and PGF_1 β which are epimeric at C_9. The absolute configuration of PGF_1 β has been examined by S.Abraham etal by X-ray crystallography.

From the study of X-ray crystallograpy of tri-p-bromobenzoate of the methyl ester of PGF_1 βAbraham represented the str of PGF_1 βas



Consequently the structure of PGF_1 and PGE_1 can be written easily.

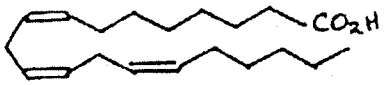




The absolute congfiguration of these prostaglandins has also been determined by chemical methods.

Oxidative ozonolysis of the acetoxymethyl ester of PGE_1 gave 2-acetoxyheptanoic acid.This on hydrolysis with alkali gave 2-hydroxy-heptanoic acid.This compares with a reference compound of 2(s)- hydroxyheptanic acid . Hence the configuration at C_{15} is S.

The derivation of the absolute configuration at C_{11} depended on the results of model biosynthetic experiments (The enzyme system present in the vesicular glands of sheep which converts all cis-8,11,14-eicosatrienoic acid into PGE_1 was allowed to react with 11-cis , 14-cis- eicosadienoic acid when 11-hydroxy- 12-trans -14 – cis-eicosa-dienoic acid resulted.)



All cis – 8, 11, 14 - Eicosatrienoic acid

The 11-hydroxy-12-trans -14-cis-eicosa-dienoic acid ws shown to have R-configuration at C_{11} by comparison with standard conpounds.

This C_{11} position corresponds to C_{11}-position in PGE_1 also and hence the configuration at C_{11} is R.

The stereochemistry at C_8 & C_{12} was deduced from ORD data as C_8-α and C_{12} β. PGE_1 is laevorotatory and shows a strong negative. C.E. at about 300nm. This can be explained when the carbonyl and side chain is α-oriented and the methyl end side chain is β-oriented. All the naturally occuring protaglandins have the same absolute configuration at the asymmetric centres,

	$F_1\alpha$	$F_1\beta$
C_8	R	R
C_9	S	R
C_{11}	R	R
C_{12}	R	R
C_{15}	S	S

VITAMINS

General Information:

In addition to oxygen, water, proteins, fats, carbohydrates and certain inorganic salts, a number of organic compounds are also necessary for the life , growth and health of animals (including man). These compounds are known as the accessory dietary factors or vitamins and are only necessary in very small amounts.

Our body cannot synthesize vitamins (exception vitamin D – which may be produced in the skin by irradiation of sterols), so have to be supplemented in food.

Vitamins are arbitrarily classified into the 'fat soluble group' (Vitamins A,D,E and K)and the 'water –soluble group'. (the reminder of the vitamins). Though the water – soluble vitamins have different chemical structure, their chemical reactions are common in one feature ie. They all take part in reversible oxidation - reduction processes in the body. Thus they form a part of various co – enzymes.

Vitamin A_1 (Retinol or Axerophthol)

Introduction:

It occurs free as esters in fats,growth in animals and helps to build resistance towards diseases.Deficiency of vitamin A_1 can lead to night blindness. Prolonged deficiency of it may lead to xerophthaalmia (hardening of the cornea) Carotenoids are converted into vitamin A_1 in the intestinal mucosa and feeding experiments showed that the potency of α - and γ carotenes is half that of β - carotene. This provitamin nature of α - carotene led to the suggestion that vitamin A_1 is half of the molecules of β- carotene.

Structure elucidation:

From elemental analysis and molecular weight determination the molecular formula of vitamin A_1 was found to be $C_{20}H_{30}O$

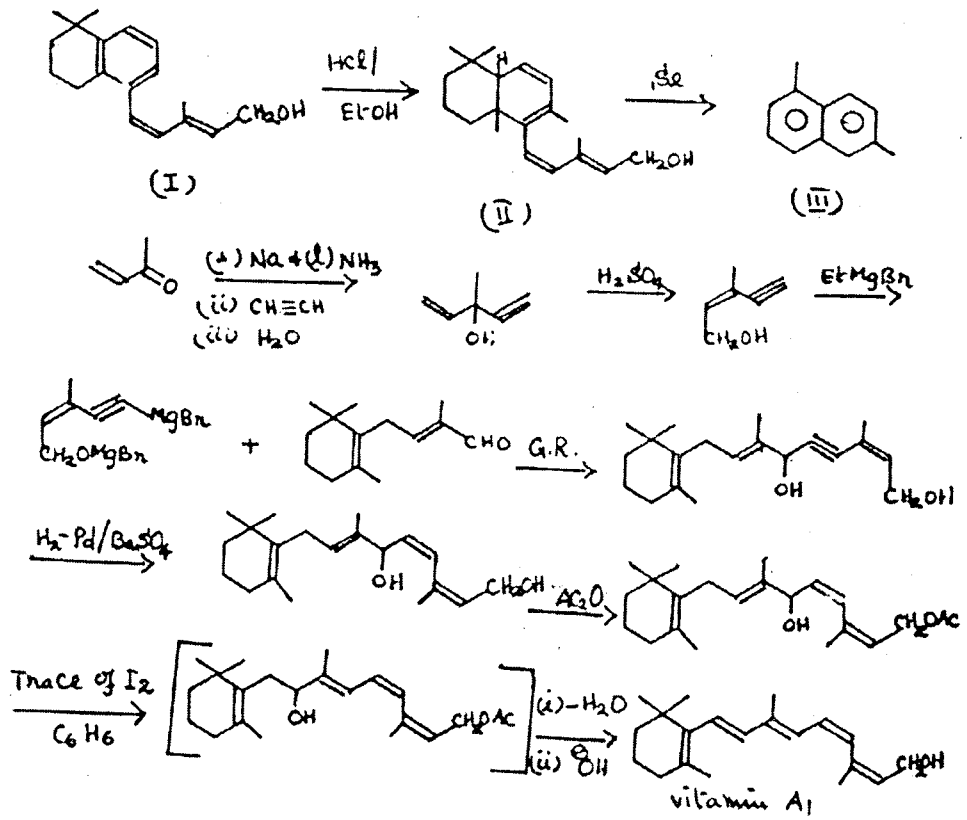
Vitamin A_1 on catalytic hydrogenation gives perhydro vitamin A_1 ($C_{20}H_{40}O$). this shows that vitamin A_1 contains a hydroxyl group indicated by its ester formation with p-nitrobenzoic acid. Hence the parent hydrocarbon of vitamin A_1 is $C_{20}H_{40}O$ and consequently the molecule contains one ring.

Ozonolysis of vitamin A_1 produces are molecule of geronic acid per molecule of vitamin A_1. this indicates the presence of a α-ionone nucleus in the molecule .

Permanganate oxidation of Vitamin A_1 gives acetic acid. This suggests the presence of some $-C(CH_3)=$groups in the chain.

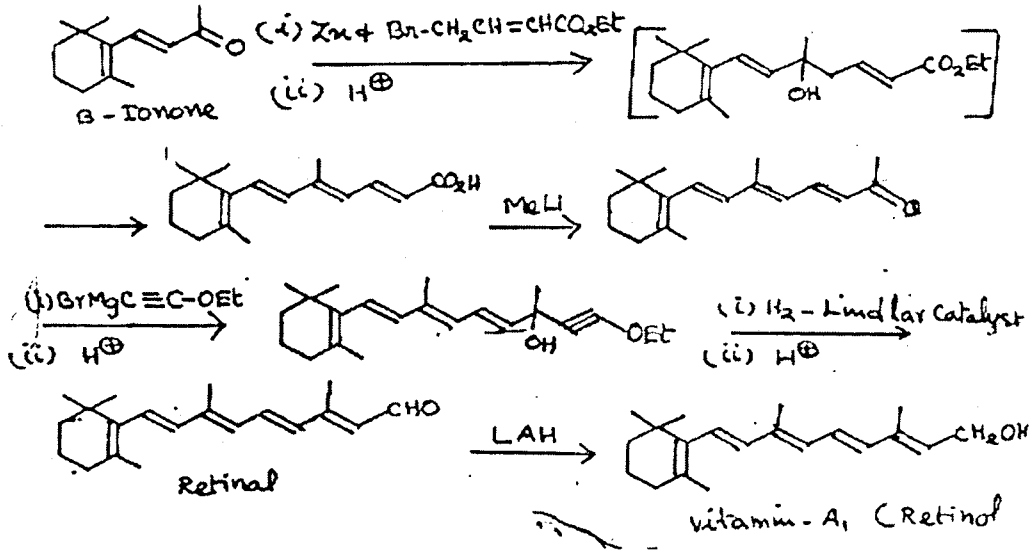
All the foregoing facts are in consonance with the suggestion that vitaminA_1 is half the β - carotene structure.

Vitamin A_1 on heating with ethanolic hydrogen chloride forms compound II. The latter on dehydrogenation with selenium forms 1,6 – dimethyl – naphthalene (III). The above reactions can be formulated as follows, if we assume structure (I) for vitamin A_1 (Heilbron et al).



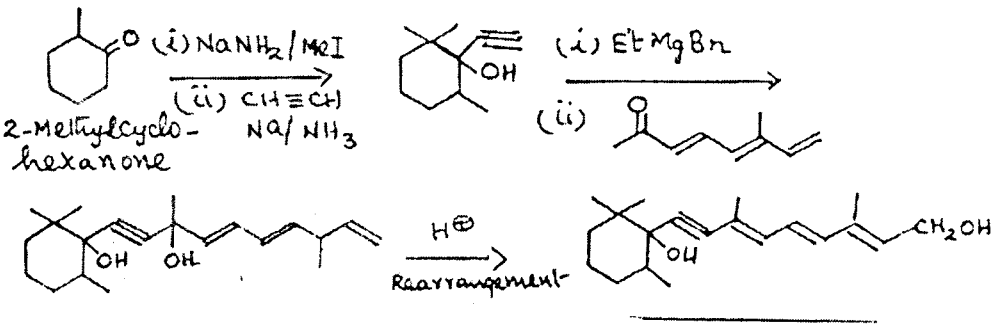
Karrer synthesised perhydrovitamin A_1 from β-ionone, which was found to be identical with the compound obtained by reducing vitaminA_1. This synthesis is given as an evidence to support the structure assigned to vitamin A_1. Finally its structure has been confirmed by the synthesis of vitamin A_1 itself.

Synthesis I (Isler etal)



Synthesis II (Van Dorp etal)

Synthesis III (Allenburrow et-al)



Vitamin-B complex

Introduction:

This complex includes all the water soluble vitamins found in yeast,liver,rice polishing etc. This group contains a vitamin known as B_1, which is destroyed by heat. Various compounds, most of which are stable to heat, known as B_2 complex.

B_1 (thiamine (or) aneurin

The absence of this causes beriberi in man and this vitamin is the antineuritic factor (hence the name aneurin) Rice polishings, yeast and eggs are rich source of this vitamin.

i) The molecular formula of thiamine chloride hydrochloride was found to be $C_{12}H_{18}N_4Cl_2OS$

ii) When treated with a solution of sodium sulphite saturated with sulpher dioxide at room temp, it is cleaved into two compounds, I & II. The structure of this vitamin is established by a study of the structures of these two compounds.

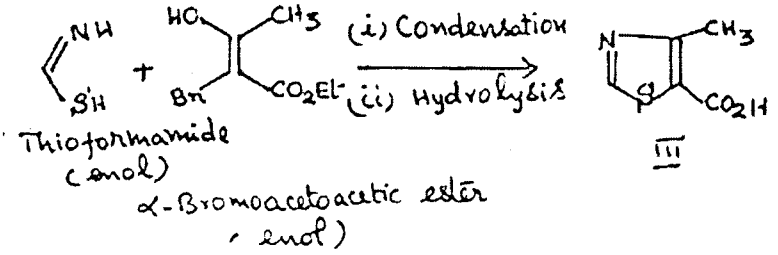
$$C_{12}H_{18}N_4Cl_2OS + Na_2SO_3 \xrightarrow{SO_2} \underset{I}{C_6H_9NOS} + \underset{II}{C_6H_9N_3O_3S} + 2NaCl$$

iii) It was found to be basic and the nitrogen tertiary (because it does not react with nitrous acid)

iv) The presence of one hydroxyl group was established from the formation of monochloro compound with hydrogen chloride. UV studies indicate it to be in the side chain.

v) The sulphur atom ws found to be in the thiazole ring from UV studies. This is further confirmed by the loss of sulphur while treating with alkaline plumbite solution.

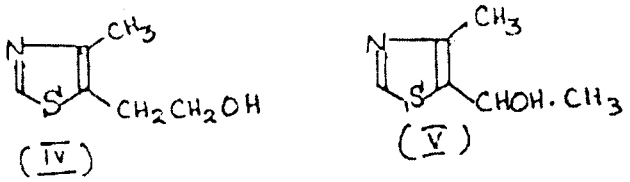
vi) Compound (I) an oxidation with nitric acid gives an acid which was found to be 4-methylthiazole-5-carboxylic acid(III). The structure of which has been confirmed by its synthesis.



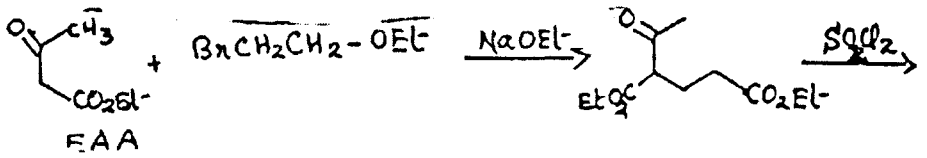
Thus compound (I) has a structure similar to (III).The formula difference between (I)&(III) is one of the side chains ie, substituent at C_5 in compound (III).

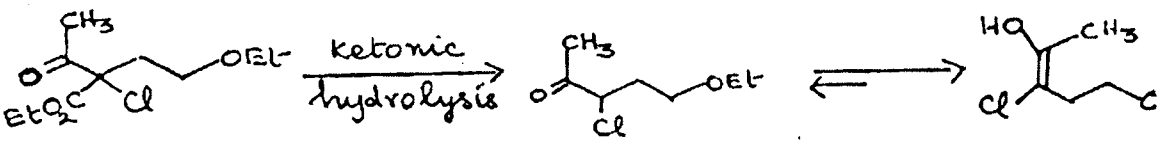
From the difference in molecular formula between (I) and (III) ie,C_2H_5O-, we can write two possible structures for (I) ie(IV) & (V).

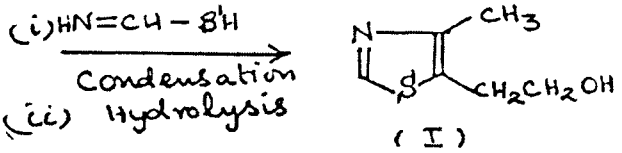
On oxidation either of these compounds could be converted to compound (III).Compound (I) is optically inactive and doesn't give iodoform reaction.Hence the correct structure for (I) is structure (IV).



Synthesis:







Structure of Compound II

i) Analytical data indicate the molecular formula to be $C_6H_9N_3O_3S$.

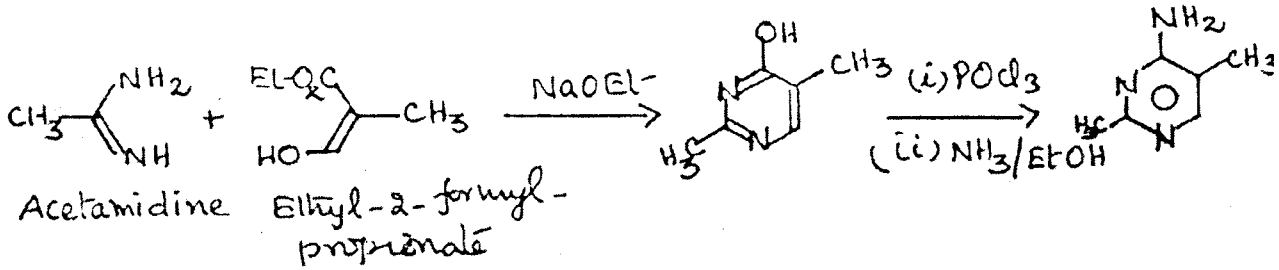
ii) On heating with sodium hydroxide it yields sodium sulphate, indicating the presence of a sulphonic acid group in compound(II). It also forms sulphuric acid, when heated with water under pressure at 200^{O} C.

iii) On reaction with nitrous acid it gives a monohydroxy derivative indicating the pressure of an amino group. The above reaction is slow indicating that compound (II) has an amidine structure.

iv) $$C_6H_9N_3O_3S + H_2O \xrightarrow[150^\circ C]{HCl} C_6H_8N_2O_4S + NH_3$$

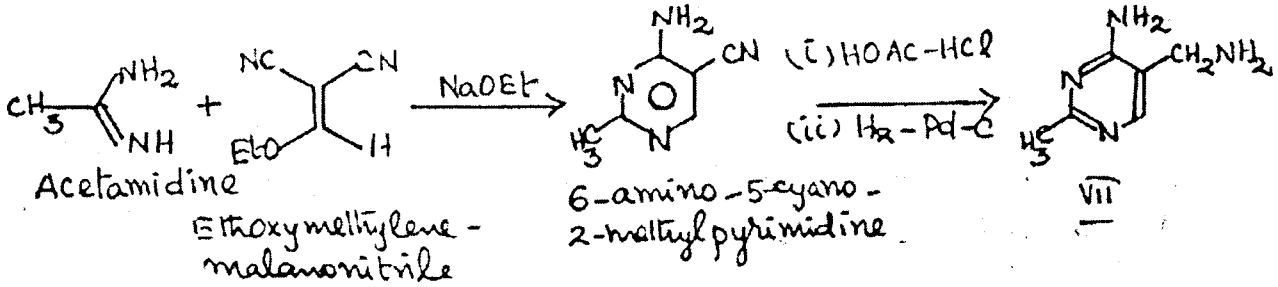
Compound (II) on heating with hydrogen chloride under pressure yields ammonia and compound (VI). The UV spectrum of VI is very similar to that of 6-hydroxypyrimidine. So compound (II) is probably a 6-aminopyrimidine derivative.

v) Sodium and liquid ammonia reduction of (II) gives 6-amino-2,5-dimethylpyrimidine. It was confirmed by the comparison of its UV spectrum with that of synthetic compounds. This ws further confirmed by its synthesis.

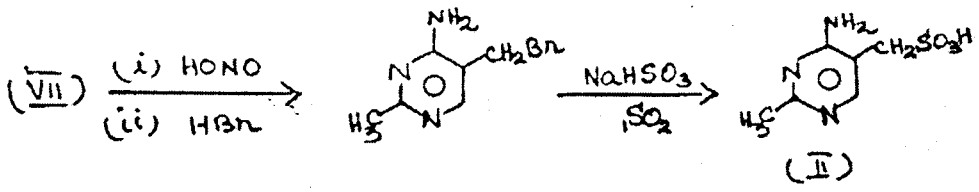


vi) Since the amino group is found to be free, the sulphonic acid group may be attached to either of the two methyl groups.

vii) Sodium and liquid ammonia reduction of thiamine gives compound (VII), which was found to be 6-amino-5-aminomethyl-2methylpyrimidine by comparing the spectrum of synthetic compounds .It was further confirmed by its synthesis.

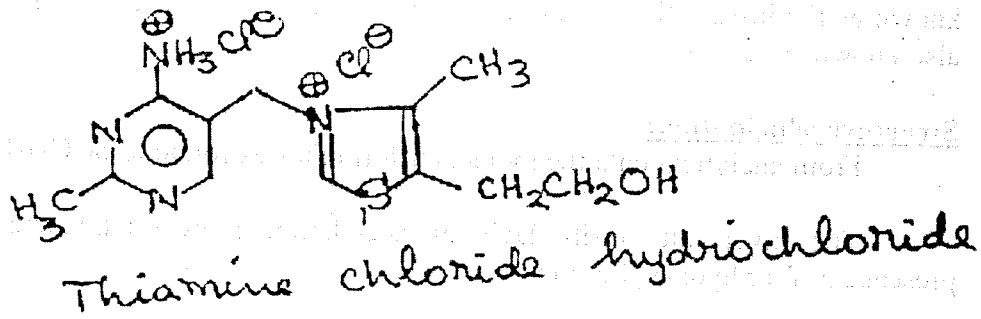


Thus in compound (VII), there is an amino group instead of the sulphonic acid group in (II). Hence the sulphonic acid group in (II) is attached to the methyl group at position 5 and thus (II) can be represented as below which is proved by its synthesis.



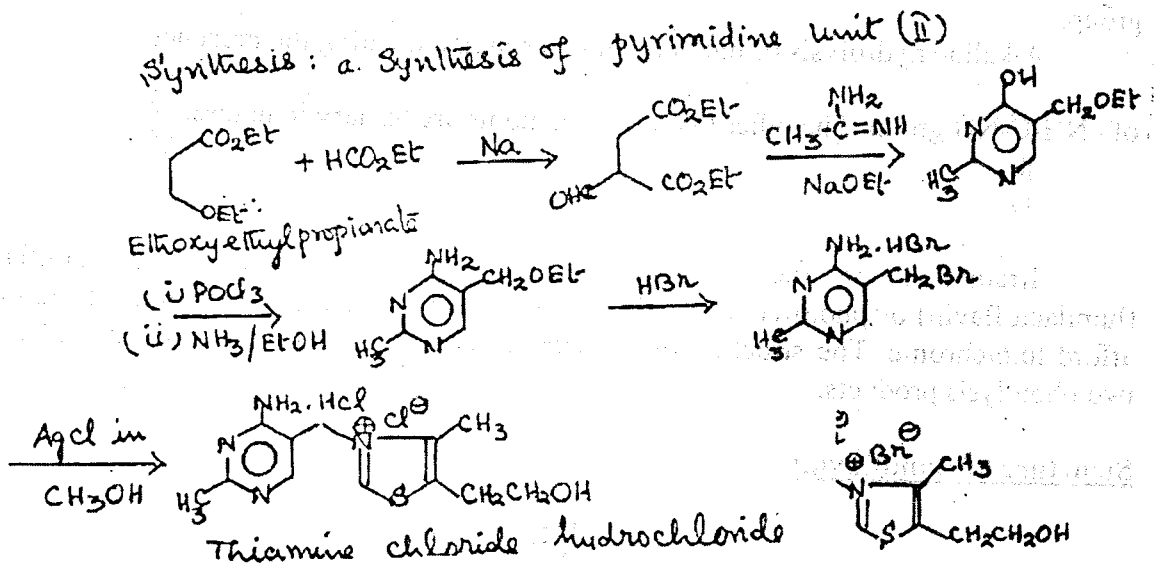
Thiamine doesnot contain sulphonic acid group but the hydrolytic product (II) obtained by treating the vitamin with sodium sulphite contains sulphonic acid group. That means the carbon carrying the sulphonic acid group must be the point of linkage to the molecule(I).

To account for the formation of(VII), fragment (II)must be linked to the nitrogen atom of fragment(I).In this position, the nitrogen atom of the thiaole ring is in a quaternary state, and so accounts for the chloride hydrocholoride of thiamine, Had (II) been connected to (I) through a carbon atom of the latter, it would not be easy to account for the ready fission of this carbon, carbon bond by means of sodium and liquid ammonia, nor for the fact that thiamine does not form a dihydrochloride. Thus the chloride hydrochloride of thiamine is

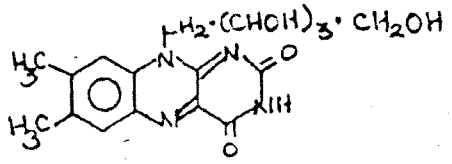


This structure has been confirmed by synthesis (William etal)

Synthesis : a) Synthesis of pyrimidine unit(II)



Vitamin B_2 (or) Riboflavin (or) Lactoflavin:



Introduction:

It is a bright yellow powder, showing a green fluorescence. It is necessary for growth and health and is widely distributed in nature. Eg.yeast, green vegetables, milk, meat etc. It occurs free or as the phosphate, or joined to specific proteins to form enzymes. Chemically, vitamin B_2 is closely related to the yellow water-soluble pigments known as flavins(isoalloxazines), and since it was first isolated from milk, vitamin B_2 is also known as lactoflavin.

Structure elucidation:

From analytical data the molecular formula was found to be $C_{17}H_{20}N_4O_6$.

The silver salt of riboflavin on acetylation gives a tetraacetate indicating the presence of four hydroxyl groups in it.

The presence of a primary hydroxyl group is inferred by the lead tetraacetate oxidation, which gives formaldehyde.

Negative reaction with nitrous acid precludes the presence of a primary amino group.

Alkaline hydrolysis of the vitamin gives urea indicating the presence .

of –NH-C-NH group. The other two nitrogen atoms are tertiary in nature.

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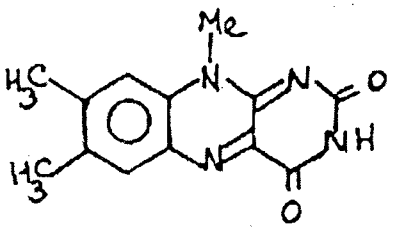
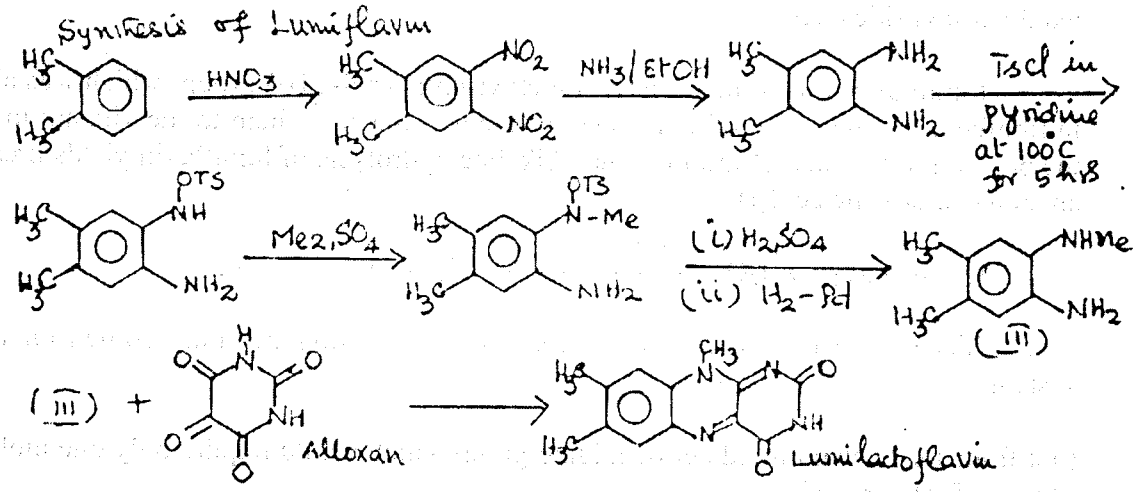
Irradiation of the vitamin under alkaline conditions yield lumiflavin (lumilactoflavin) or photoflavin. Irradiation of the same under acid or neutral conditions afford lumichrome. The structure of the vitamin is derived from the structures of these two photolysis products.

Structure of Lumiflavin:

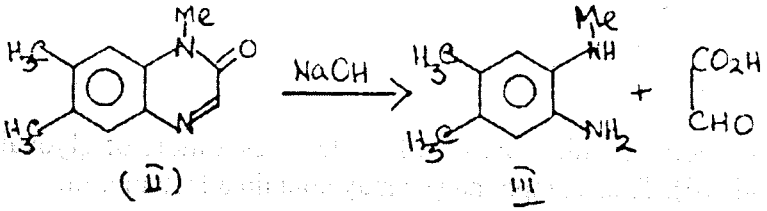


Kuhn through a series of synthetic reactions indicated the presence of two methyl groups in compound (III). Thus compound (III) was identified to be N – methyl – 4,5 – diamino – O – Xylene.

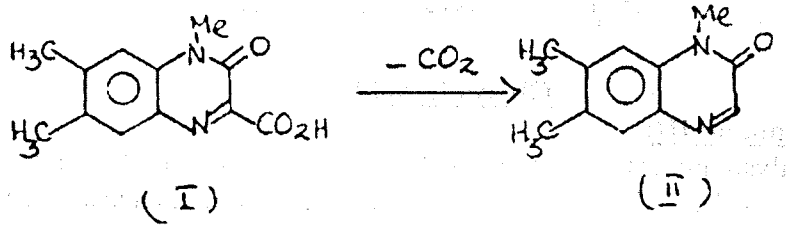
Synthesis of Lumiflavin:



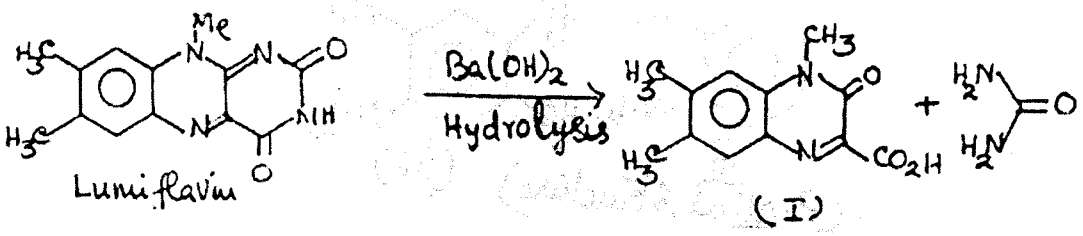
Thus the structue of II and hydrolysis reaction's of it can be confirmed as follows:



Since (I) is a β - keto acid of (II), it can be represented as below.

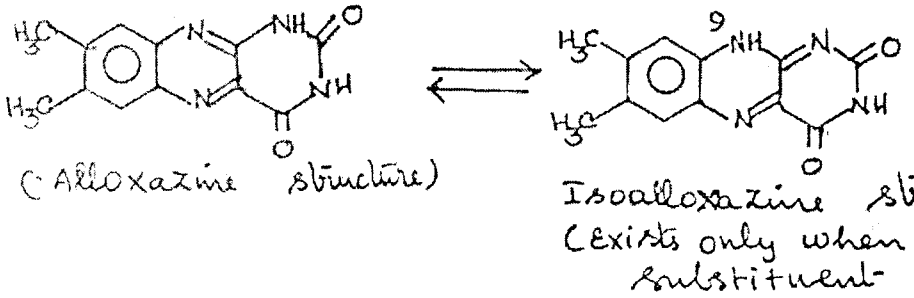


Since lumiflavin on hydrolysis gives fragment (I) and a molecule of urea, the former could be 6,7,9 – trimethylisoalloxazine (6,7,9 – trimethylflavin)

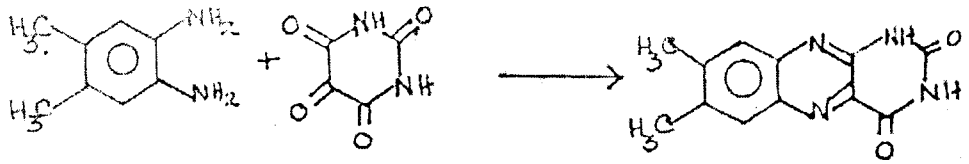


Structure of Lumichrome:

Irradiation of riboflavin in acid solution gives lumichrome. Sequences of study similar to the above lead to the conclusion that lumichrome is 6,7–dimethylalloxazine.



Synthesis:



Thus the lumichrome is lumiflavin with a hydrogen atom instead of a methyl group at position 9(N_9).

Side chain:

The reaction mixture from which lumichrome was isolated gave positive reaction for a pentose sugar. So the side chain is a sugar having five carbon atoms.

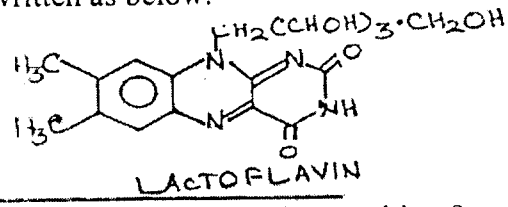
Zerewittinoffs' method shows that riboflavin has five active hydrogen atoms. Since one active hydrogen atom is present on the N_3 of lumiflavin, the rest four active hydrogen atoms must be present in the side chain in the form of four hydroxyl groups.

Lead tetraacetate oxidation of riboflavin gives formaldehyde. So one of the hydroxyl groups must be present as a terminal - CH_2OH group. Furthermore riboflavin forms a diisopropylidene derivative with acetone, two 1,2–glycollic systems must be present in the side chain(riboflavin).

The above points lead to the following structure of the side chain of riboflavin.

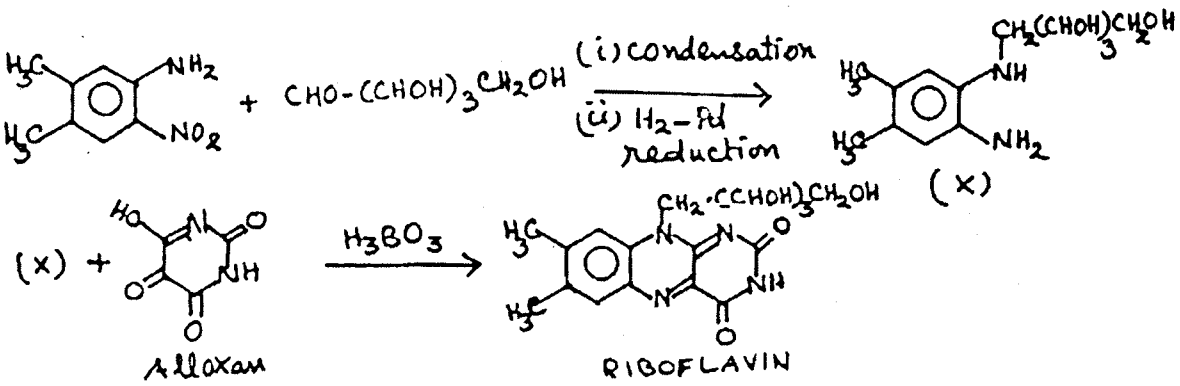
$$-CH_2-(CH(OH))_3 - CH_2OH$$

Thus riboflavin can be written as below.



The actual nature of the side chain(D – ribityl) at position 9 was proved by synthesis.

Synthesis (Kuhn etal):



Riboflavin
Vitamin B_6 (or) PYRIDOXINE (or) ADERMIN

Introduction:

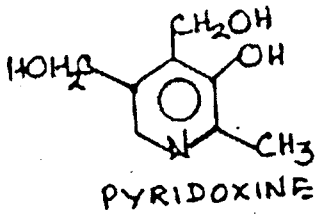
It is actually a combination of pyridoxine, pyridoxyl, and pyridoxamine. They are interconvertible in the form of their phosphates. This is obtained from rice bran and yeast. It cures dermatitis in rats.

Structure elucidation:

Analytical data indicate the molecular formula of the compound to be $C_8H_{11}NO_3$. Pyridoxine behaves like a weak base .

From zerewittinoff's active hydrogen determination, the vitamin was found to have three active hydrogens.

Color reaction with ferric chloride and monomethyl ether formation with diazomethane point to the presence of a phenolic hydroxyl. This is further confirmed by its UV spectrum and was similar to that of β- hydroxypyridine. The UV spectrum also indicates the presence of a pyridine nucleus in pyridoxine.



The above monomethylether,

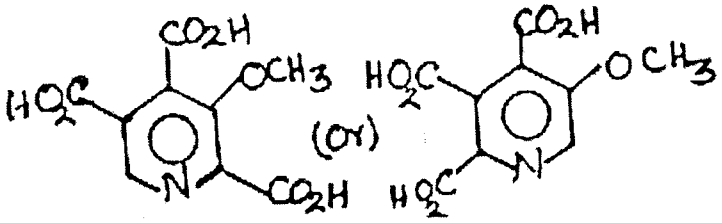
(i) forms a diacetate with acetic anhydride indicating the presence of two alcoholic groups.

(ii) is unaffected by lead tetraacetate indicating that they are not on adjacent carbon atoms.

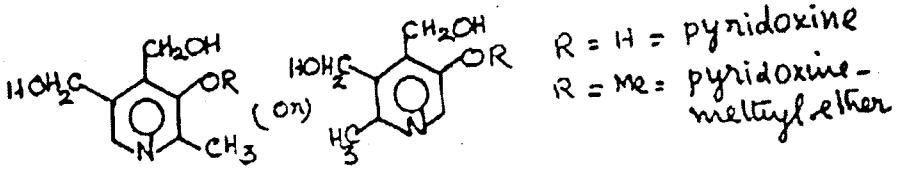
(iii) On careful oxidation with alkaline permanganate, gives a methoxy pyridine tricarboxylic acid ($C_9H_7NO_7$). The latter gives a blood - red color with ferrous

sulphate a reaction characteristic of pyridine – 2 – carboxylic acid. Thus one of the three acidic groups in the tricarboxylic acid must be in the second position.

iv) usual oxidation of it with alkaline permanganate gives a mole of carbondioxide and an anhydride. The formation of anhydride indicates them to be at o– positions. The dicarboxylic acid obtained by the hydrolysis of this anhydride doesn't answer the color test with ferrous sulphate. That means , the second carboxylic acid group is lost during decarboxylation.



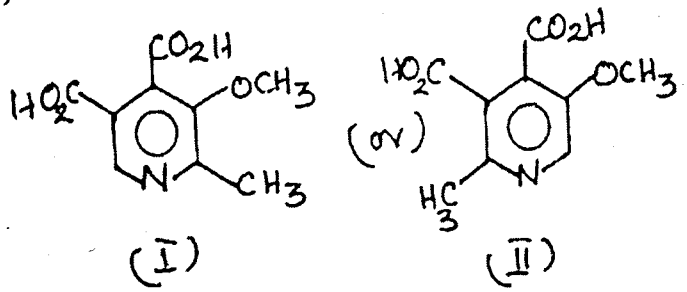
From Kuhn – Roth estimation, it was found to have one C-Me group. Since pyridoxine methyl ether has one methoxy and alcoholic groups, two carboxylic acid groups of the tricarboxylic acid must be derived from two alcoholic groups ($-CH_2OH$) and one from the methyl group. Thus the following structures are possible for the pyridoxine and its corresponding methyl ether.



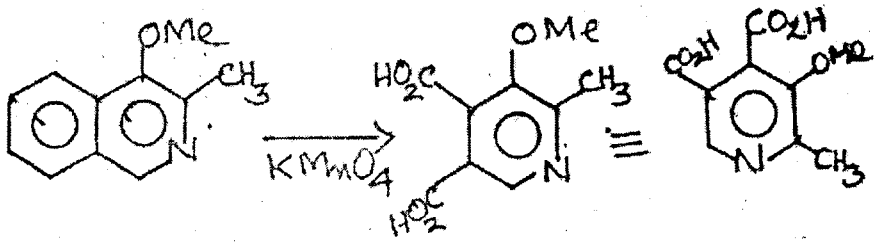
The two possible structures for pyridoxine.

The correct structure for pyridoxine was found out as follows:

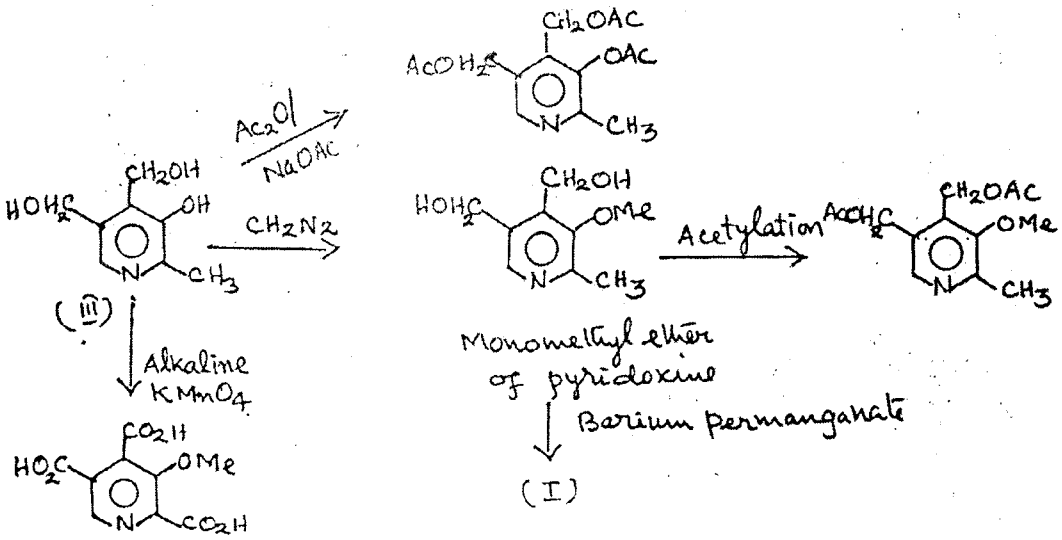
Barium permanganate oxidation of monomethyl ether of the vitamin gives a dicarboxylic acid. This forms an anhydride with acetic anhydride and also gives a fluorescent dye with resorcinol suggesting that the carboxyl groups are ortho to each other. Again, it doesn't give colour reaction with ferrous sulphate indicating that the carboxyl groups are not ortho to the nitrogen. Hence the dicarboxylic acid may have the structure (I) or (II)



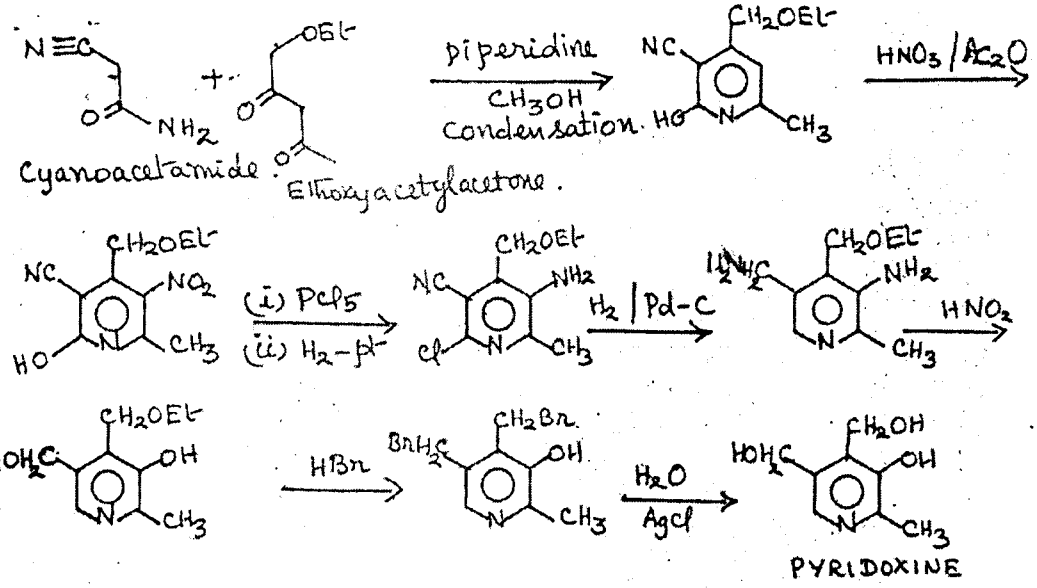
The positions of the two carboxylic groups correspond to the two alcoholic groups in pyridoxine. Kuhn found that acid (I) resembled with the synthetic dicarboxylic acid from 4- methoxy – 3 – methylisoquinoline.



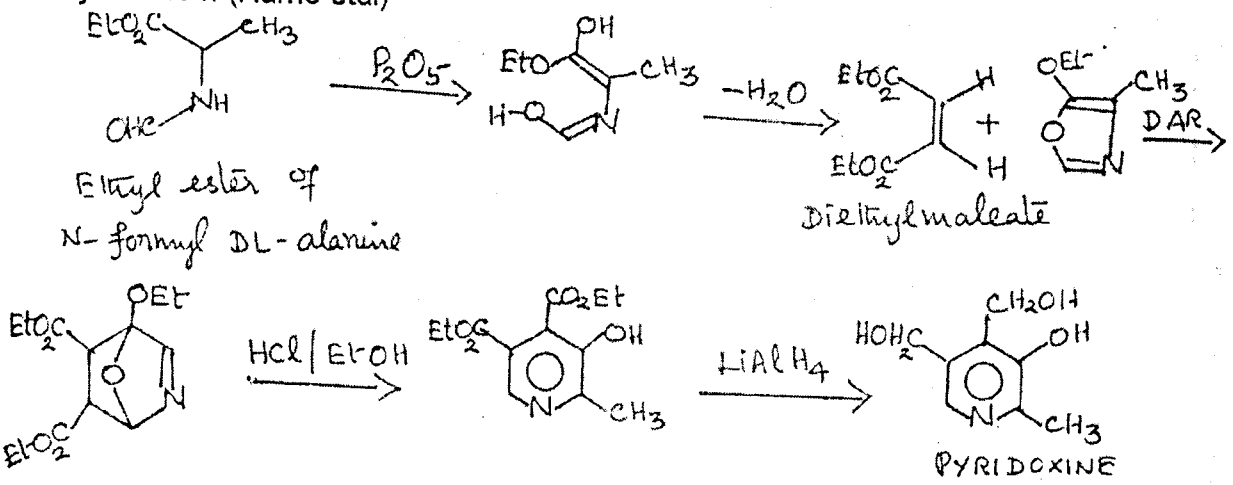
Hence the correct structure for the dicarboxylic acid is (I)and thus pyridoxine must be (III) which may explain all the reactions.



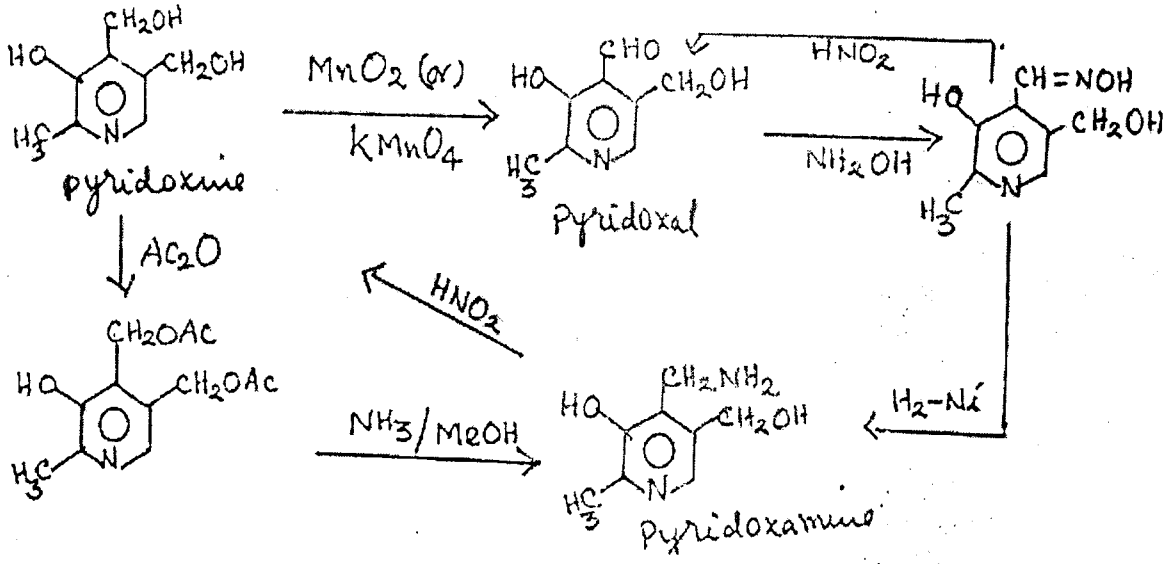
Synthesis I



Synthesis II (Harris etal)



Although pyridoxine has vitamin activity , it was subsequently shown by Snell etal that the related compounds pyridoxal and pyridoxamine and more active than pyridoxine . Furthermore, it was established that these compounds were produced by rats from ingested pyridoxine. Thus pyridoxine, pyridoxal and pyridoxamine are now collectively referred to as vitamin B_6.They are produced as follows:



Introduction :

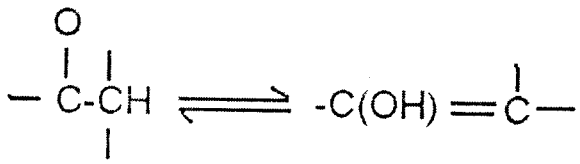
Mainly found in citrous fruits like lemons, oranges etc and green vegetables like cabbage, beans and tomatoes .The deficiency of this vitamin causes scurvy in infants and adults.

Most of the animals can synthesize vitamin C themselves and therefore, they have not to depend upon the external supply. But human beings; monkeys and pigs are unable to synthesize this vitamin and hence they have to depend upon external supply.

Constitution of Ascorbic Acid:

The molecular formula of ascorbic acid from analytical data was found to be $C_6H_8O_6$.

The presence of a Keto-enol system in this vitamin is evidenced as follows:



i) Ozonolysis of ascorbic acid takes place without producing fragments, indicating that it contains one double bond (in a cyclic ring)

ii) Acts as a strong reducing agent.

iii) Violet coloration with ferric chloride shows the presence of an enolic-OH group.

iv) Forms phenyl hydrazone ($\rangle C{=}O$) with phenylhydrazine.

v) Negative Schiff's test precludes the presence of aldehydic group.

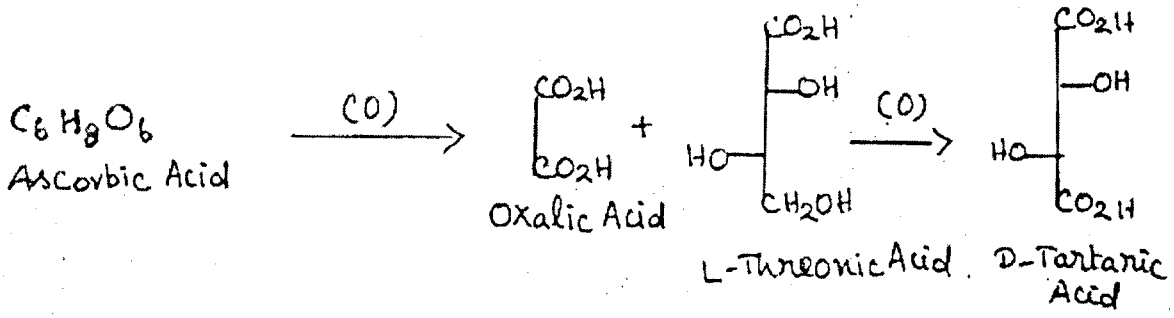
Presence of carboxyl group:

This does not give effervescence with bicarbonate, but forms monosodio, potassio derivatives, indicating that it may contain $-CO_2H$ group but not free.

Nature of the carbon skeleton:

Ascorbic acid may contain a four carbon system joined to a two carbon system by a two carbon system by a double bond.ie C-C=C-C-C-C, is evidenced by the following sequence of reactions. Oxidation with acidified permanganate gives oxalic acid and L-threonic acid (trihydroxybutyric acid)

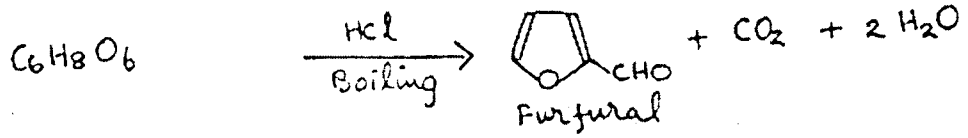
The latter acid on further oxidation yields D-tartaric acid



The skeleton given above may be confirmed by the following facts:

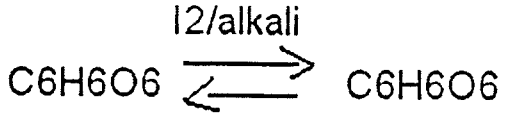
i) Ozonolysis of ascorbic acid takes place without producing fragments, indicating the presence of only one double bond in ascorbic acid.

ii) Ascorbic acid, when boiled with hydrochloric acid gives a quantitative yield of furfuraldehyde. This reaction resembles the conversion of an aldopentose into furfural. Therefore, similar to aldopentose, ascorbic acid must contain atleast 5 carbon atoms in a straight chain and also that there are a number of hydroxyl groups present in it.



Presence of hydroxyl groups:

i) Oxidation with iodine in alkali yields dehydroascorbic acid, $C_6H_6O_6$ which can be reduced back to ascorbic acid by passing hydrogen sulphide gas into it.

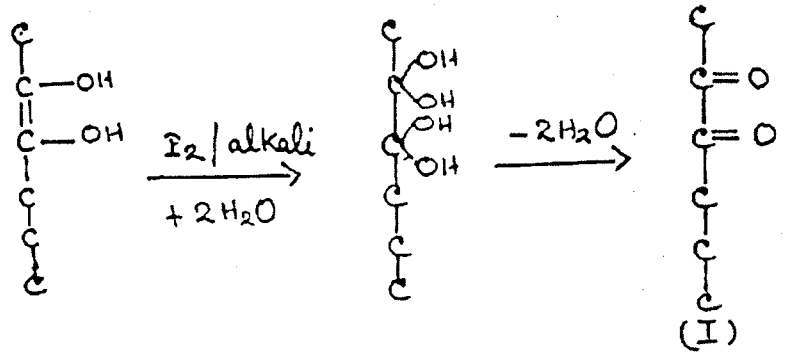


The above reactions in combination with,

i) Violet colouration of ascorbic acid with ferric chloride (characteristic of enolic groups) and formation of dimethyl derivative with diazomethane indicates the presence of two enolic hydroxyl groups in ascorbic acid.

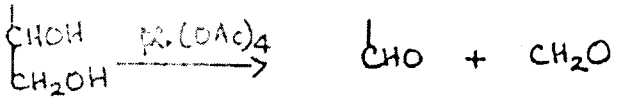
ii) Dehydroabsorbic acid does not give enolic reactions but forms an osazone with phenylhydrazine indicating that two carboxyl groups are present adjacent to each other.

Thus , the reversible oxidation may be explained by writing the part structure of ascorbic acid as(I)

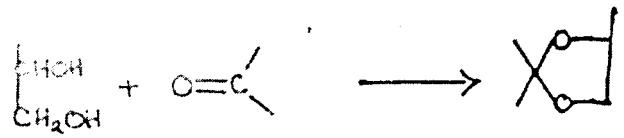


iii)The above dimethyl derivative may be further methylated with methyl iodide in the presence of dry silver oxide, which indicates the presence of two more alcoholic groups in ascorbic acid.

iv)Lead tetraacetate oxidation of the dimethyl ether of ascorbic acid gives formaldehyde as one of the products. This suggests the presence of two adjacent hydroxyls in the ether, one of which is primary.



v)The above fact is further confirmed by acetonide formation of the above ether with acetone.



vi)Formation of tetraacetate, tetramethyl derivatives confirm the presence of total four hydroxyl groups in ascorbic acid.

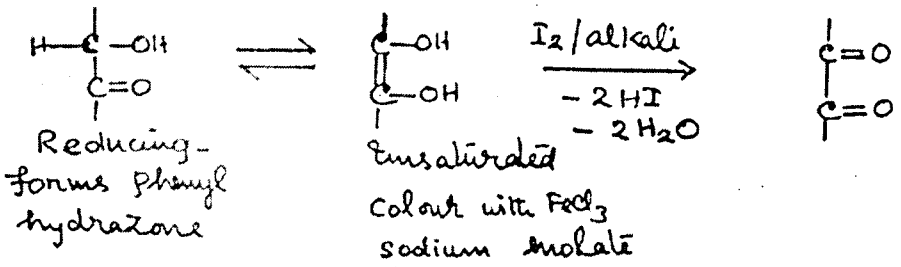
Presence of lactone ring:

Dehydroascorbic acid (obtained by the Iodine/alkali oxidation of ascorbic acid) which is neutral and behaves as the lactone of a monobasic hydroxy acid. Also dehydroascorbic acid on reduction with hydrogen sulphide is reconverted into ascorbic acid.

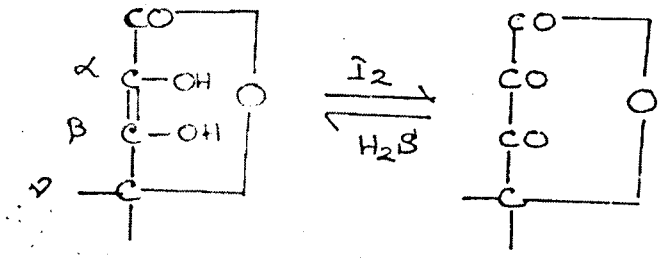
As the above oxidation -reduction process is carried out with mild reagents, it leads to the conclusion that ascorbic acid like its oxidation product dehydroascorbic acid(which is a lactone) is a lactone and not an acid.

Again, the salt forming property of ascorbic acid may be attributed to an enol group; the presence of which has already been proved.

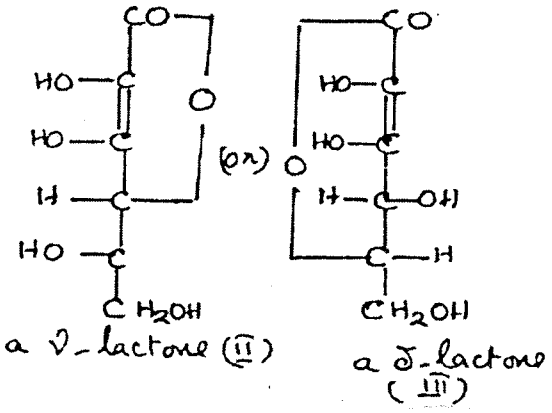
As all the preceding reactions are characteristic of α-hydroxyketones, it means that ascorbic acid must contain an α-hydroxyketone grouping.



On the basis of the above the reversible oxidation of ascorbic acid may be written as follows:



On the basis of all the foregoing facts, the structure of ascorbic acid may be either of the following two structures.



Size of lactone ring:

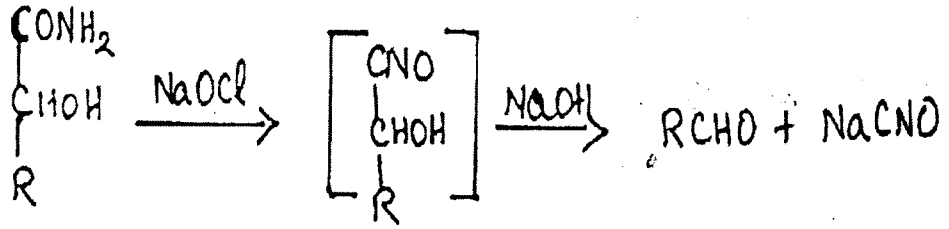
The size of the lactone ring has been found to be υ -on the basis of the following facts.

a) Rate of hydrolysis of dehydroascorbic acid is comparable to a υ – lactone.
b) IR of ascorbic acid shows a band at 1757cm^{-1}. The compound therefore, must be a υ -lactone.
c) Ozonolysis of the tetramethyl derivative of ascorbic acid yields a neutral compound (IV), which has the same number of carbon atoms showing a ring system.

The compound (IV), when hydrolysed with barium hydroxide solution, yields oxalic acid (having two carboxyl groups) and 3,4-dimethyl-L—threonic acid (V) (having one carboxylic group). The formation of three carboxylic groups on ozonolysis clearly demonstrates that the starting compound is a lactone.

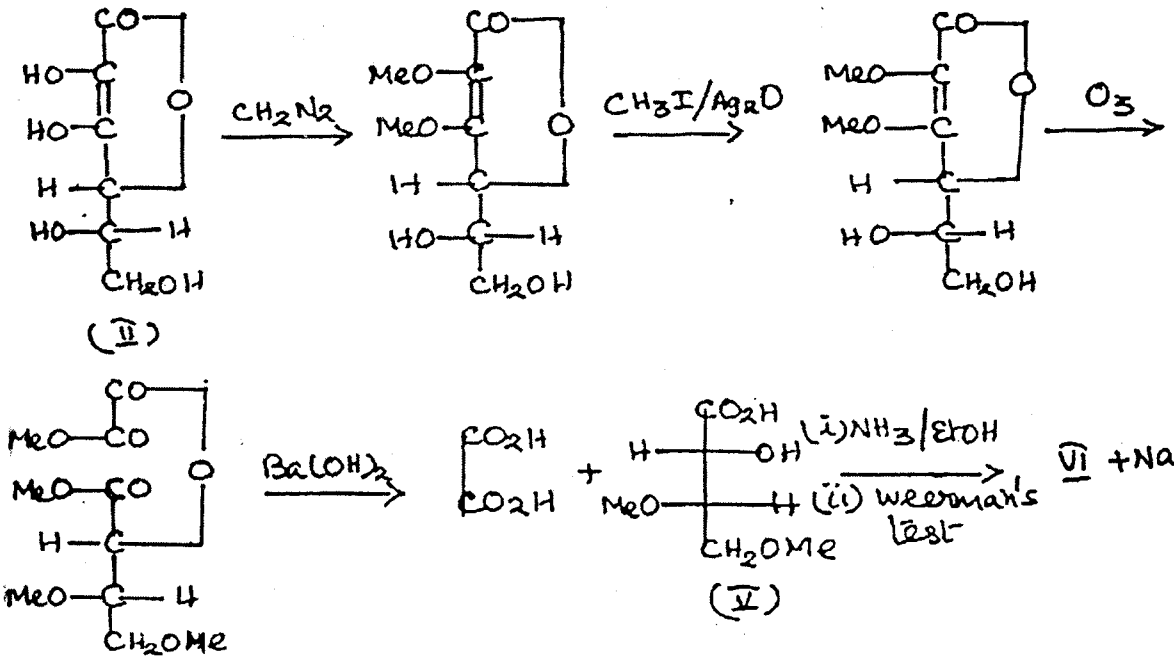
Further compound (IV) (or) (V) may be converted into an amide with methanolic ammonia,(VI).

The latter compound responds to Weerman's test in which the amide of 3,4-dimethyl-L-threonic acid, on treatment with alkaline sodium hypochlorite, yields an aldehyde and sodium cyanate.



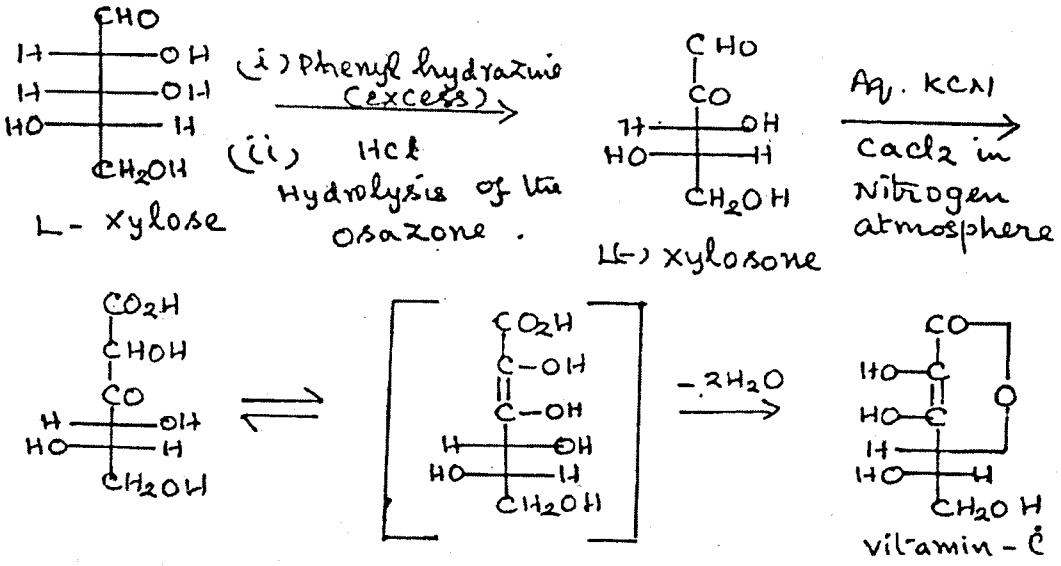
The for Had it been δ- it would have yielded 2,4-di-O-methyl-L-threonic acid.

On the basis of structure(II), the foregoing reactions may be explained as follows:



The exact configurations of C_4 & C_5 were derived from its relation to L-threonic acid

Synthesis:



Vitamin D

Introduction :

Vitamin D_2 is also called as Ergocalciferol. It is a molecular compound of Calcifercol and lumisterol.(Formerly the name calciferol or vitamin D_1 was used for the active compound). The natural vitamin D obtainable from Cod-liver oil is slightly different from ergocalciferol and is named as vitamin D_3.The vitamin D, obtainable by the irradiation of 22, 23-dihydroergosterol is called as vitamin D_4. All these vitamin D, have anti rachitic properties. They are essential for bone formation. The function of this vitamin in the body is to control the calcium and phosphorus metabolism.

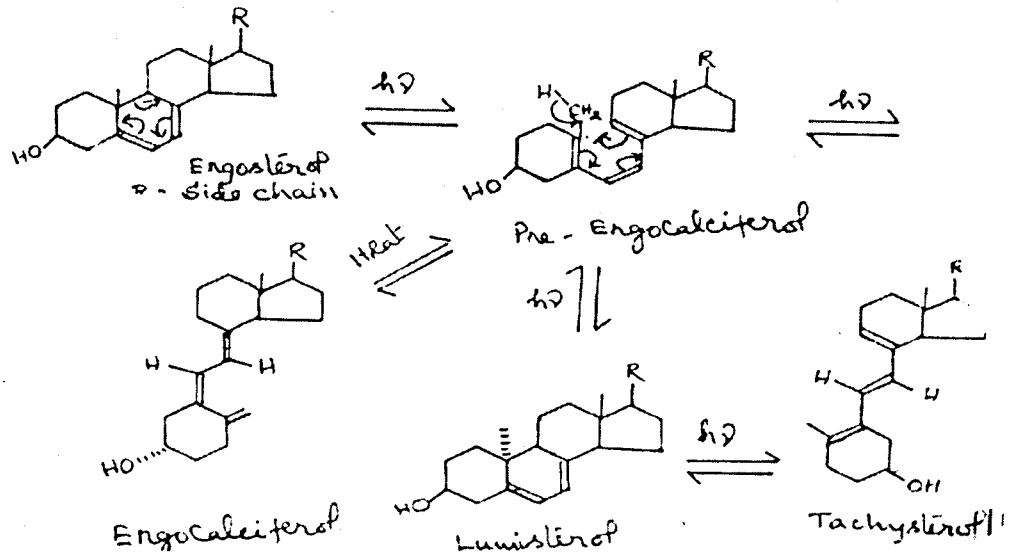
Constitution:

The molecular formula from analytical data was found to be $C_{28}H_{44}O$. This formula is the same as that for ergosterol, there by, indicating that vitamin D_2 and ergosterol are isomers to each other. This is also confirmed by the fact that the irradiation of ergosterol (I) with UV light yields a mixture of products from which pure vitamin D_2 is isolated.

$$\text{Ergosterol} \underset{}{\overset{h\nu}{\rightleftharpoons}} \text{Vitamin } D_2$$

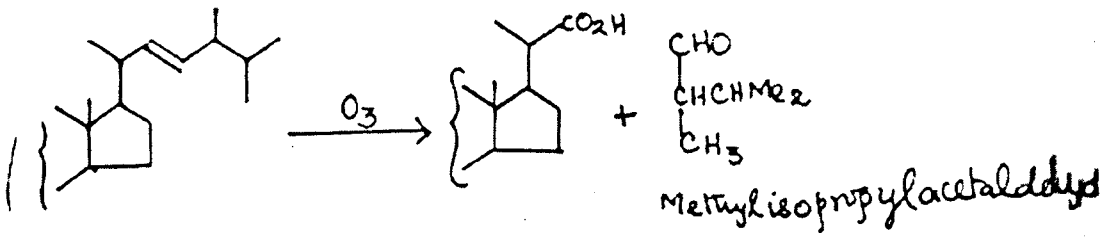
It was formed to have a secondary alcohol, as oxidation gives a ketone.

Irradiation products of ergosterol



Nature of the side chain:

Ozonolysis of ergocalciferol produces among other products, methylisopropylacetaldehyde. This shows that the side chain in both vitamin D_2 and ergosterol are the same. Formation of isopropylacetaldehyde is possible, only if the side chain is present as,



Complete hydrogenation of ergocalciferol gives octahydroergocalciferol, $C_{28}H_{52}O$. This indicates the presence of four double bonds in it, on are of which is present in the side chain.

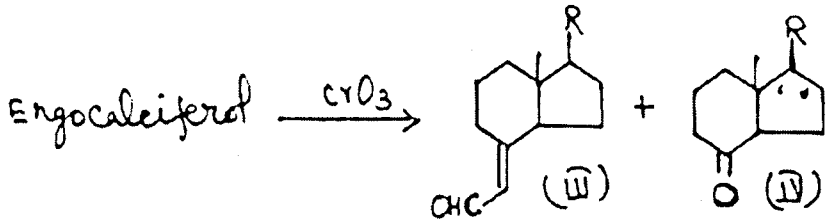
The parent hydrocarbon of ergocalciferol, $C_{28}H_{52}$, being 6 hydrogen atoms deficient to the corresponding acyclic paraffin analogue should be tricyclic. This is supported by the fact that ergocalciferol on selenium dehydrogenation doesn't produce Diel's hydrocarbon.

Since vitamin D_2 is tricyclic naturally the question arises which one of the rings in ergosterol is open.

The following reactions of ergocalciferol may be readily explained, if we assume structure (II) for ergocalciferol.

Chromium trioxide oxidation of vitamin D_2 gives an α, β – unsaturated aldehyde (III) and a ketone (IV)

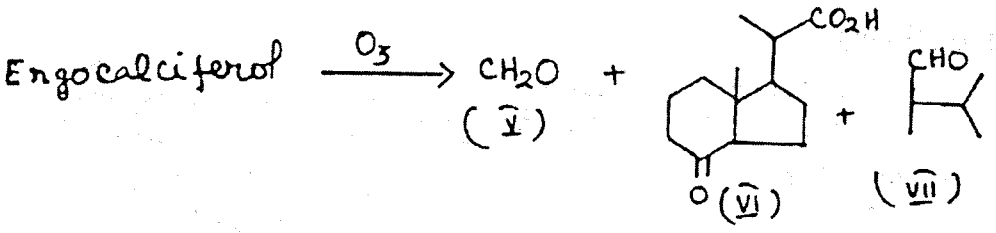
The absence of hydroxyl group and the carbon content of (III) indicate the absence of ring A.



These facts suggest that in ergocalciferol ring 'B' is open between C_9 & C_{10} and that (III) arises by scission of the molecule at a double bond in position 5,6 and can be an α, β –unsaturated aldehyde only if there is a double bond at 7,8 (these double bonds are also present in ergosterol). The isolation of the ketone (IV) confirms the presence of the double bond at 7,8. Thus the positions of three bonds are fixed.

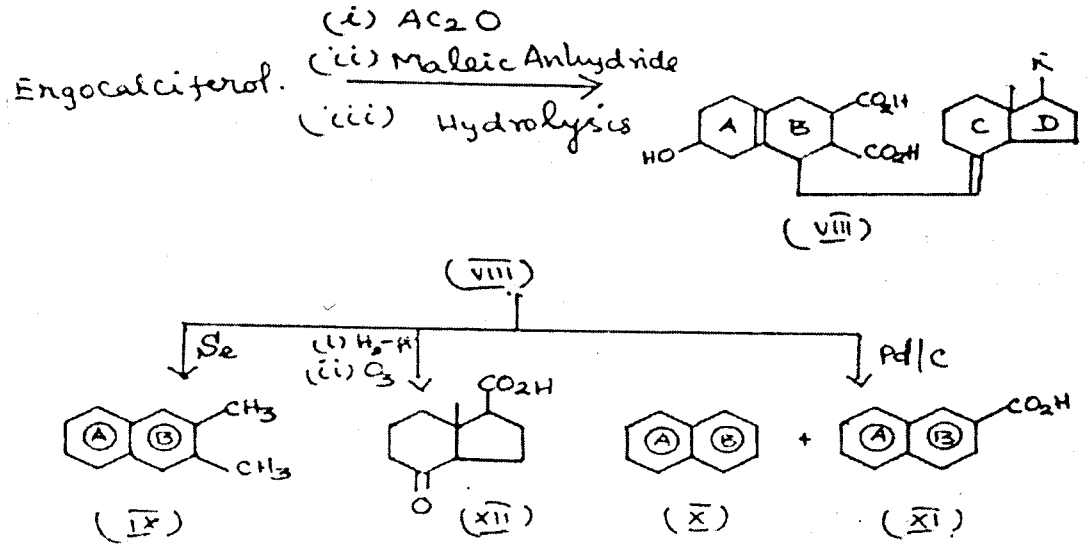
The fourth double bond is fixed as follows:

Ozonolysis of vitamin D_2 gives formaldehyde (V) as one of the products. This shows the presence of an exocyclic methylene group, and the presence of this group at C_{10} is in keeping with the opening of ring B at 9,10.



Isolation of the ketoacid(VI) confirms the presence of double bonds at positions 7,8 and $C_{22,23}$. The position of the latter double bond is confirmed by the isolation of methylispropylacetaldehyde.

Structure (II) for ergocalciferol is also supported by the formation of VIII obtained by converting the acetate of vitamin D_2 into the corresponding maleic anhydride adduct, which in turn is converted into the dicarboxylic acid. The structure of (VIII) has been confirmed by the isolation of compounds (IX) to (XII).

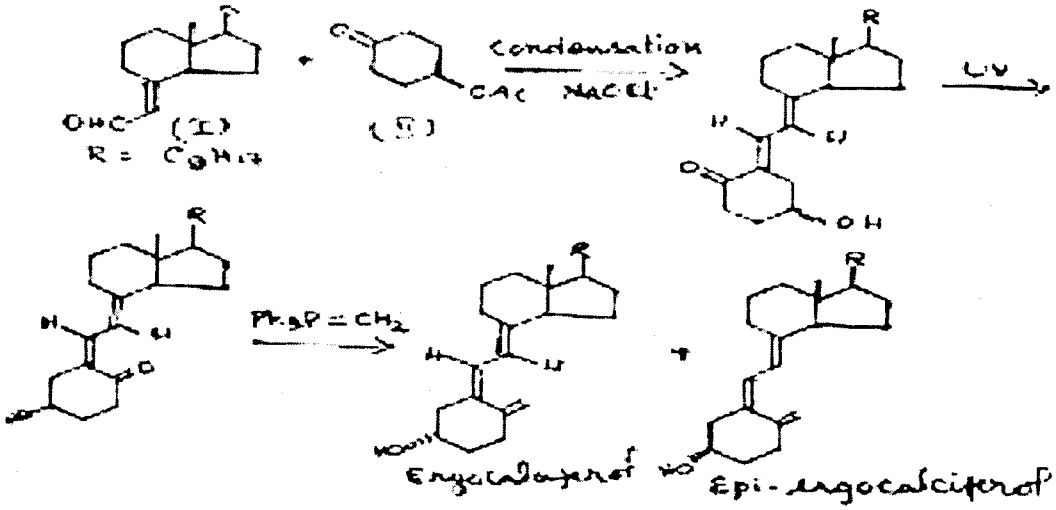


The formation of 2,3-dimethylnaphthalene (IX), is in keeping with the fact that carboxyl groups sometimes give rise to methyl groups as selenium dehydrogenation.

Similarly, the formation of naphthalene (X) and naphthalene -2-carboxylic acid (XI) shows the presence of rings (A) and (B) in (VIII).

Catalytic reduction of(VIII) (to reduce the double bond in the side-chain only), followed by ozonolysis, gives (XII).Thus the formation of these compounds (IX) to (XII) establishes the structure of (VIII) and shows that the double bonds are at 5,6,10,19 & 7,8.(The presence of the two double bonds at 5,6 & 7,8 gives rise to the possibility of various geometrical isomeric forms for ergocalciferol.

Partial Synthesis:



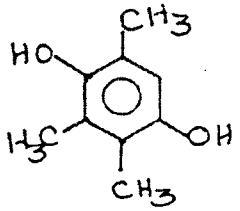
Vitamin E

Introduction:

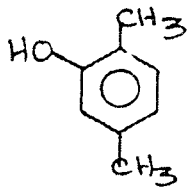
The term 'vitamin E' refers to a group of closely related compounds which occur naturally and which are, to different degrees, anti-sterility factors, Eight compounds, collectively called tocopherols, have been characterized.

The main source of α- & β- tocopherol is wheat germ oil. The ν -compound is obtained from the cotton seed oil.

Deficiency of this vitamin causes i)Sterility, ii)blood anaemia (increase in WBC)



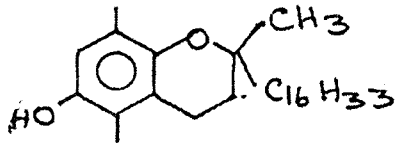
(I)



(II)

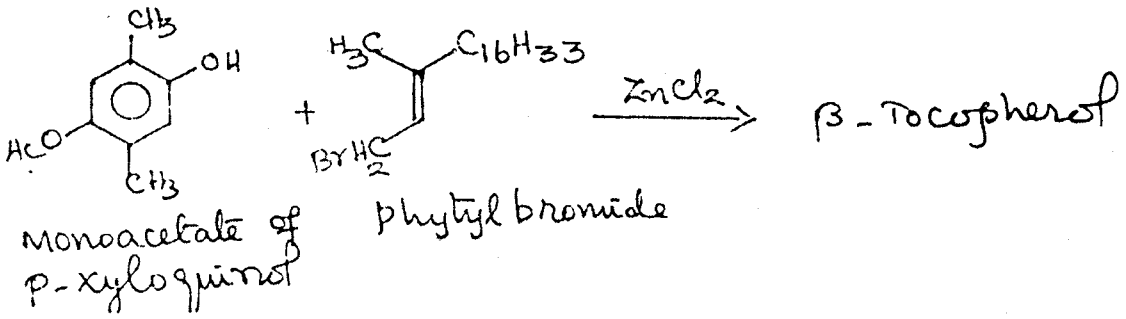
Oxidation of β-tocopherol with chromium trioxide gives the same lactone ($C_{21}H_{40}O_2$) as that obtained from α -tocopherol.

Thus the only difference between the two tocopherols is that the α -compound has one more methyl group in the benzene ring than the β.Hence the latter is,



(±) β -Tocopherol

This has been confirmed by synthesis.

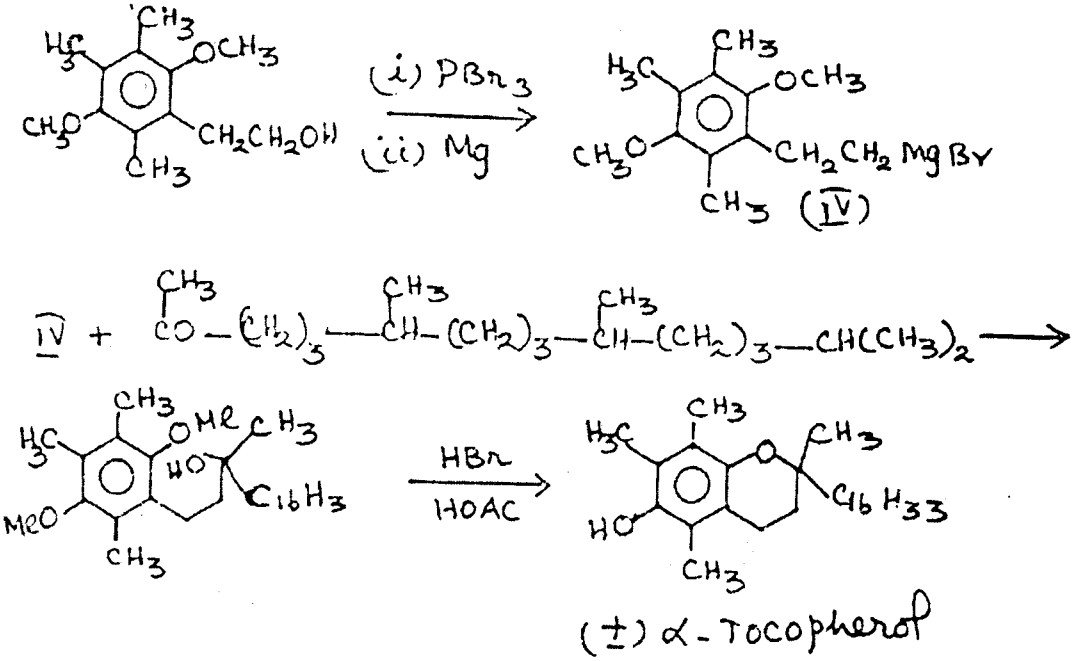


ν-Tocophercol

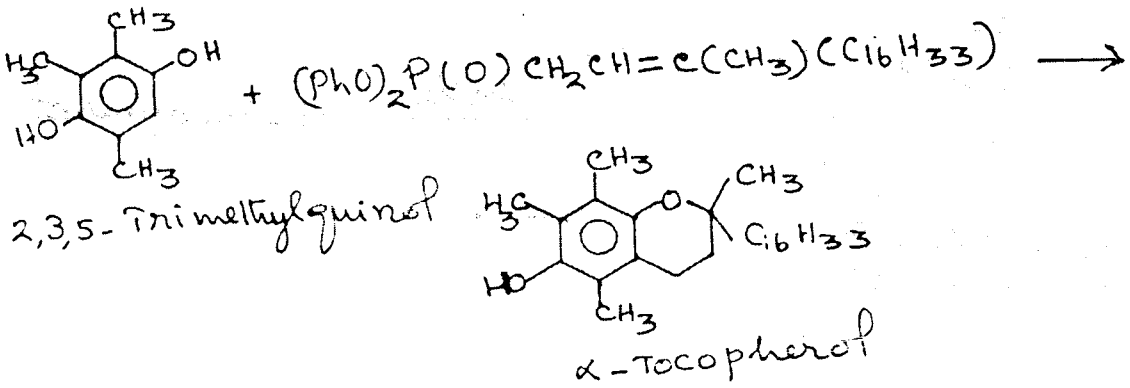
This is isomeric with the β -compound.The only difference between the β and the ν-isomers is the position of the methyl group in the benzene ring.(Ex) When heated with hydroiodic acid, the ν-isomer gives O-xyloquinol. Thus ν- tocopherol is,

Hence, α-tocopherol is either a chroman (or) Coumaran derivative. According to Fernholz, the oxidation products are best explained on the basis of the chroman structure. This has been supported by UV spectra of α-tocopherol.

Synthesis I (Smith etal)



Synthesis II

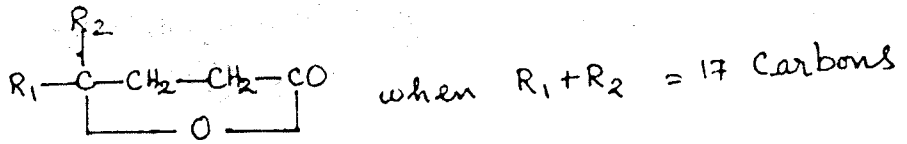


β-Tocopherol

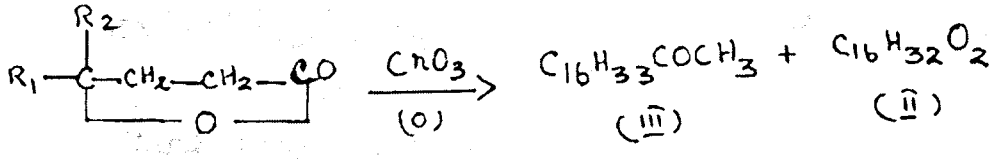
The formula difference between α -& β -tocopherols is $-CH_2$ as the analytical data indicate the molecular formula of α -tocopherol to be $C_{28}H_{48}O_2$.It shows an UV absorption at 293nm.

β -Tocopherol on thermal decomposition gives trimethylquinol(I) and heating with hydroiodic acid gives p-xylenol(II)

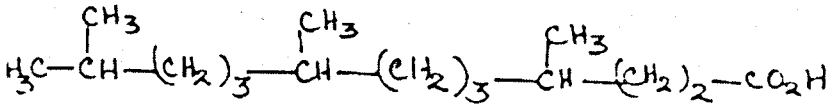
This latter compound was shown to be an optically active saturated lactone. This lactone was shown to be derived from a ν– hydroxy acid in which the hydroxyl group is tertiary (EX) the acid lactonised immediately its salt was acidified, and also could not be oxidised to a keto acid. Thus the structure of this lactone may be written as follows;



Oxidation of α -tocopherol acetate with chromium trioxide forms an acid (II) and a ketone (III).



Kuhn-Roth oxidation indicates the presence of three C-Me groups. Since most of the natural products contain the isoprene unit, Fern holz proposed the following structure for acid(II).



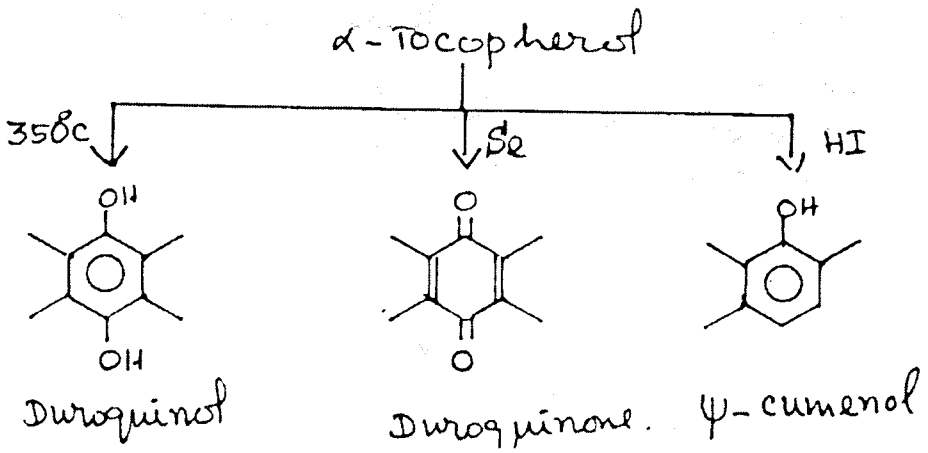
The evidence so far obtained indicates the presence of a substituted benzene ring and a long side chain in α -tocopherol. When the monoethers of duroquinol were oxidized with silver nitrate solution the action took place far more slowly than for α -tocopherol when oxidized under the same conditions.

Furthermore, whereas the former compounds were oxidized to duroquinone, the latter compound gave a red oil which appeared to have approximately the same molecular weight as α -tocopherol. Since duroquinone is not split off during this oxidation, it suggests that the side chain is connected to the aromatic ring by a carbon bond as well as an ether link.

β – tocopherol

Constitution:

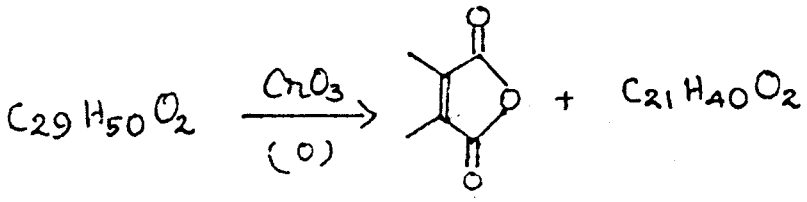
Analytical data indicate the molecular formula of α - tocopherol to be $C_{29}H_{50}O_2$. When α-tocopherol is heated at 350°C, duroquinol is obtained. On the otherhand when heated with selenium, α- tocopherol forms duroquinone. Finally when heated with hydroiodic acid, φ - cumenol is obtained.

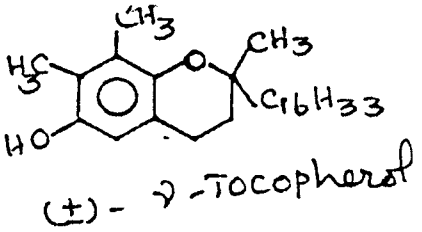


The formation of these products suggest that α – tocopherol is the monoether of duroquinol, the possibility that it might be a diether was ruled out by the fact that α - tocopherol forms an allophanate, which indicates the presence of one free hydroxyl group. This was confirmed by the fact that the U.V. spectrum of α -tocopherol showed the presence of a hydroxyl group and that it was phenolic.

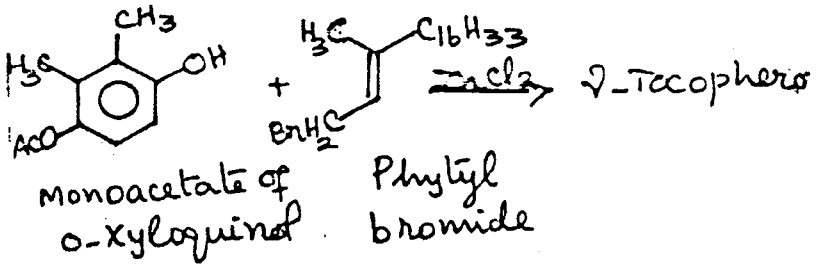
However, this monoether structure was shown to be incorrect by the fact that the U.V. spectra of various monoethers of duroquinol were different from that of α - tocopherol.

Chromium trioxide oxidation of α- tocopherol gives dimethylmaleic anhydride and a compound, $C_{21}H_{40}O_2$ (I).





Synthesis:



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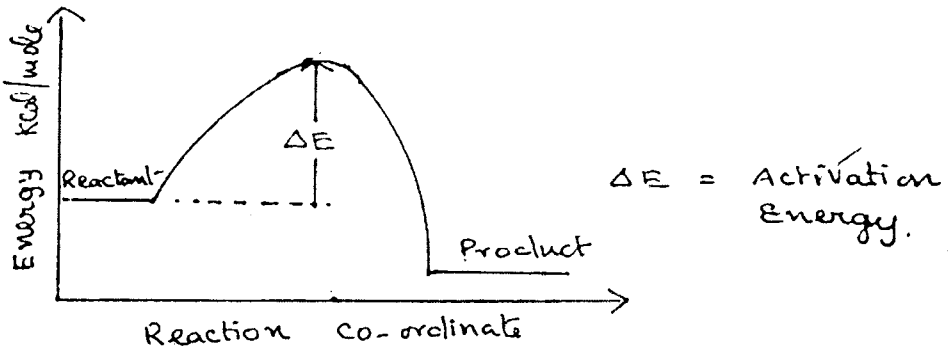
Unit IV

ORGANIC PHOTOCHEMISTRY

Thermal reactions – photochemical reactions

The total energy of a molecule is a sum of electronic, vibrational, rotational and translational energies of it. The first three are quantised ie their values can increase only in discrete quantities. The last one is not quantised.

For any reactant to go to product it has to cross some energy barrier, which is called as the activation energy. The energy of the molecules will have a distribution ie. Some molecules will have high energy, some medium energy & some low energy. Only molecules, whose energy is over and above the activation energy for a particular reaction will go to the product



The energy of the molecules may be increased so that it can cross the energy barrier. This can be done in two ways

(i) Thermal energy
(ii) Photochemical energy

Thermal energy

The molecules vibrate even at absolute zero. As temperature increases, the higher vibrational levels get populated. At still higher temperature, enough vibrational energy may be absorbed to bring about rupture of a bond. The minimum energy required to do this is known as the bond dissociation energy. This energy may vary depending upon the atoms involved and the nature of the bond. Typical bond dissociation energies are 101 Kcal/mole for the C-H bond in methane and 83 Kcal/mole for the C-C bond in ethane.

Photochemical Energy

Here the molecules are excited using electromagnetic radiations. The energy of the radiation depends on the wavelength of it. $E=h\nu$, E= is the energy per molecule, h is planck's constant and ν is the frequency of radiation. Say for example, the energy of light of 1 Kcal/mole corresponds to radiation of wavelength 286000A°

$$\frac{10^8 A^o/cm}{286,000 A^o} = 353 cm^{-1}$$

(The frequency $\bar{\nu}$ and wavelength 8 are inversely related)

When the molecules absorb the radiation in the IR region, the higher vibrational levels are populated. Similarly with the absorption of UV light excitations in the electronic levels take place.

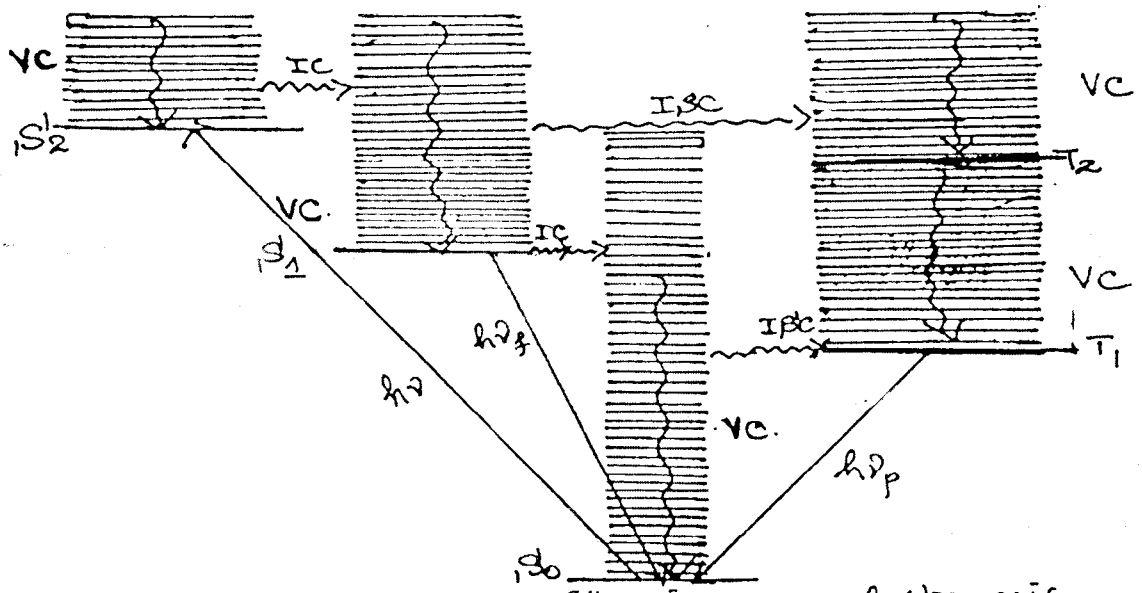
Absorption of light provides the means of introducing varying amounts of energy into a molecule. Clearly, the introduction of such energy will have profound effects on the moloecule. Photochemistry is the study of the chemistry of electronically excited molecules produced by the absorption of electromagnetic radiation.

Thermal excitation and photochemical excitation provide two complementary methods of introducing energy into molecules. And the excited molecules undergo various reactions depending upon the amount of energy absorbed.

Allowed and forbidden transitions

In absorption of light, electronic transitions which involve a change in multiplicity are forbidden. Most organic molecules have singlet ground states(all electrons paired). Thus absorption of light results in singlet-singlet electronic transitions. Transitions involving singlet-singlet (or) vice-versa involve change in multiplicity. Hence are forbidden transitions.

Jablonski's Diagram



Jablonski diagram showing the electronic transitions between excited and ground states

Jablonski diagram showing the electronic transitions between excited and ground states.

$h\nu_f$ =fluorescence ; $h\nu_p$ = phosphorescence
VC= vibrational cascade
ISC=Intersystem crossing
IC=Internal Conversion
$h\nu$= Absorption of light

The various photochemical processes involved in the absorption of light molecules is shown in the Jablonski diagram.

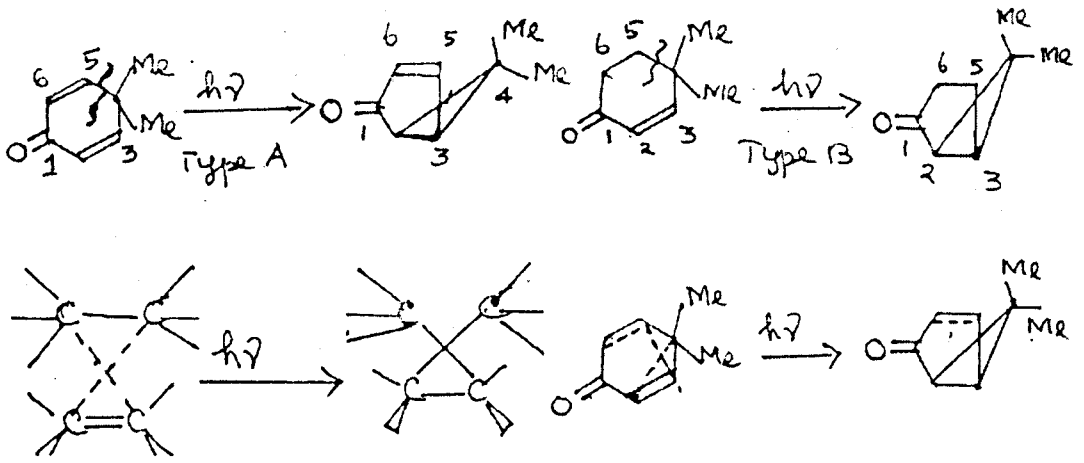
Electronic transitions are considered to be rapid with respect to the frequency of vibration and thus should occur without change in molecular geometry (Franck – Condon principle) If the energy of the photon absorbed by the molecule is slightly excess of that required to excite the molecule from the ground electronic state(S_o in the figure), the excess energy will appear as vibrational excitation in the upper excited state.

In solution, thermal equilibration of the excited molecule with its environment will be very rapid.Conversion of upper excited singlet states to the lowest excited singlet state (S_1) is also quite rapid. Rate constants for this process are of the order of $10^{11 \text{ to } 10^{13}}Sec^{-1}$. This conversion is generally a nonradiative process. An exception to this is the observed S_2 to S_0 transition of azulene.

Converison of S_1 state to the ground state(S_0) is somewhat slower.Typical fluorescence (ie. Emission of light from S_1 with return to S_0) rate constants for organic molecules are 10^7 to 10^8 Sec^{-1} . This means that the life ttime of even the longest-lived lowest excited singlet state is very short.Inversion of spin in an excited state(ISC) leads ultimately to the lowest energy triplet state(T_1).ISC rates are of the order of 10^8 to 10^{10} sec^{-1}. Typical phosphorescence (emission of light from T_1 with return to S_0) rate constants are 10^0 to 10^3 sec^{-1}. The lowest triplet state(T_1) thus has a lifetime greater than 10^{-3} sec. The longer lifetime of the low-lying triplet is a consequence of the spin-forbidden transition (T_1 to S_0).Reactions of excited states in solution usually involve either the S_1 or T_1 states because of their longer lifetimes. The fact that T_1 states have a lifetime 10^4 (or more) times that of the S_1 state strongly favours the T_1 state in intermolecular reactions.

PHOTOCHEMISTRY OF CYCLOHEXADIENONES

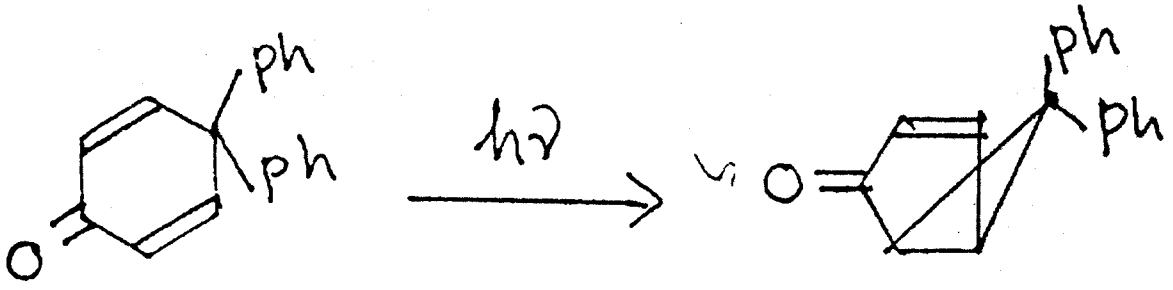
The primary photochemical reaction of a dienone is conversion into a cyclopropyl ketone. This is termed a Type A reaction and involves the rupture of the C_4-C_5 bond with formation of new bonds between C_2-C_4 and C_3- C_5.

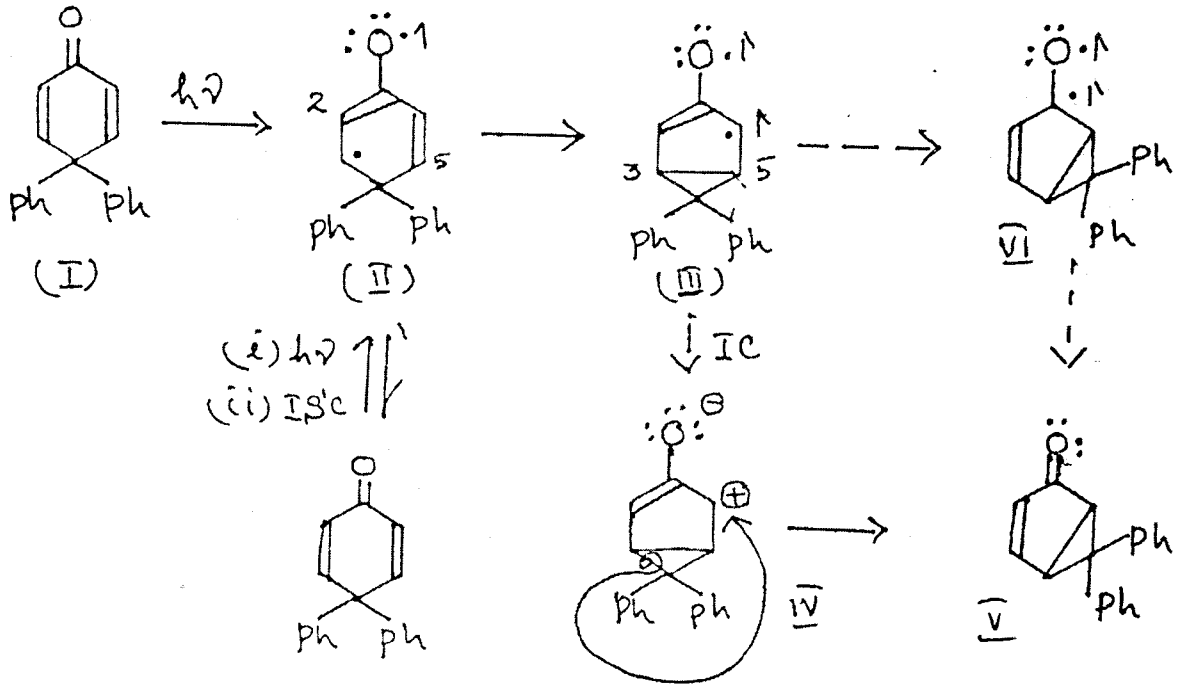


This reaction sequence is also general for cyclohexenones and it is then termed a Type B reaction.

The reaction can be formally represented as a 2 + 2 cycloaddition reaction involving the addition of two pi-electrons to two sigma-electrons, viz a [σ_2+A_2] cycloaddition. The quantum yield of the unsensitised and acetophenone-sensitised reactions of 4,4-diphenylcyclohexadienone to give 6,6-diphenylbicyclo[3,1,0]-hex-3-ene-2-one, are within experimental error, identical (ϕ = 0.85+0.81 respectively).

The identity of quantum yield suggests that both reactions involve the same excited triplet state, reflecting an efficient intersystem crossing (S_1 to T_1) in the unsensitised reaction.





Mechanism as given by Zimmermann

The suggested mechanism involves C_3-C_5 bonding from the excited triplet state(II) to (III).In this mechanism, the excitation energy gained in going from the G.S.(I), to the excited triplet state(II), is lost after C_3-C_5 bonding (III), to give the zwitterion(IV), which subsequently rearranges to the product 6,6-diphenyl-bicyclo[3,10]-hex-3-ene-2-one.(V).

A most significant feature of these dienone rearrangement is the degree of stereospecificity in the reaction.

Photosensitisation

Excitation of a ground state molecule during photolysis, by energy transfer from another excited species is termed as photosensitisation. The deactivation of the excited species is termed quenching.

The sensitiser in the ground state absorbs energy(photochemical) to go to the excited singlet state. From where it undergoes ISC to excited triplet state.(the efficiency of the ISC varies from sensitiser to sensitiser).This excited triplet state energy is transferred to the ground state acceptor. This results in the acceptor going to the excited triplet singlet state, from where it undergoes chemical reactions, while the sensitiser comes to the ground state. The process is again and again repeated to continue the process of photosensitisation. Photosensitisation can be generally represented as,

$$D_{S_0}(1\nu) \xrightarrow{h\nu} D_{1}S_1(1\nu) \xrightarrow{ISC} D_{T_1}(11)$$

$$D_{T_1}(11) + A_{1}S_0(1\nu) \longrightarrow D_{S_0}(1\nu) + A_{1}S_1(1\nu)$$

$$D_{T_1}(11) + A_{S_0}(1\nu) \longrightarrow D_{S_0}(1\nu) + A_{T_1}(11)$$

D_{S_0} = Donor ground state

$D_{1}S_1$ = Donor (excited singlet state)

D_{T_1} = Donor (excited triplet state)

A_{S_0} / $A_{1}S_1$ / A_{T_1} = Acceptor ground state / excited singlet / excited triplet.

To understand the process of photosensitisation we may consider here two typical examples.

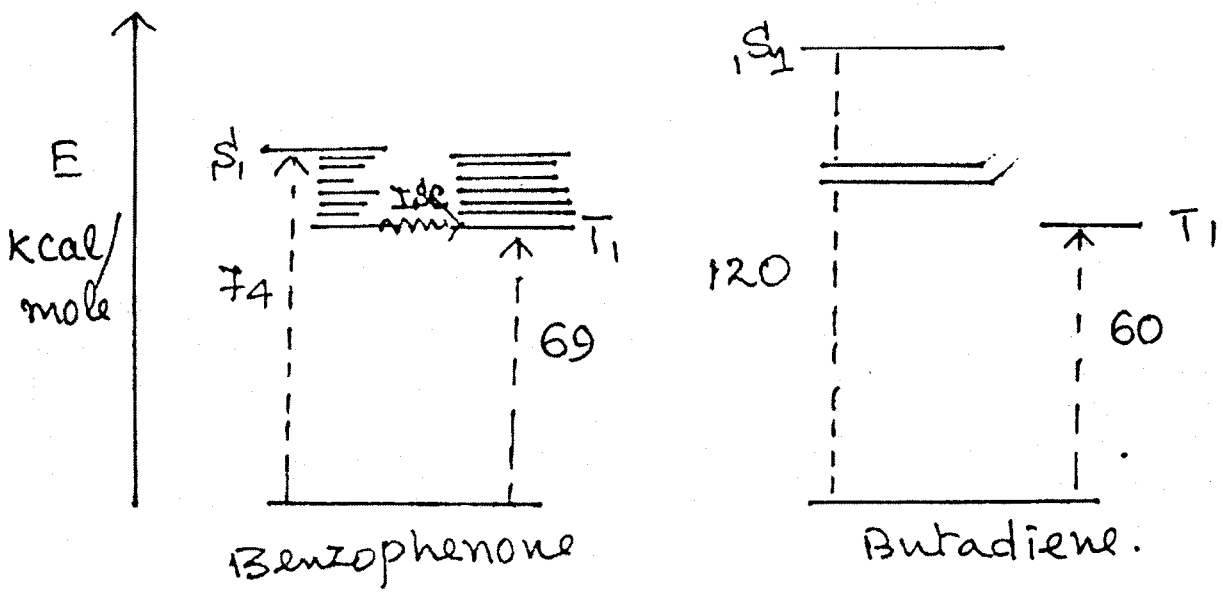
(i) photochemical excitation of butadiene with and without a sensitiser.

(ii) Photochemical cis-trans isomerisation of cis-& trans-stilbenes.

Butadiene gives different products on photochemical excitation, with and without benzophenone.

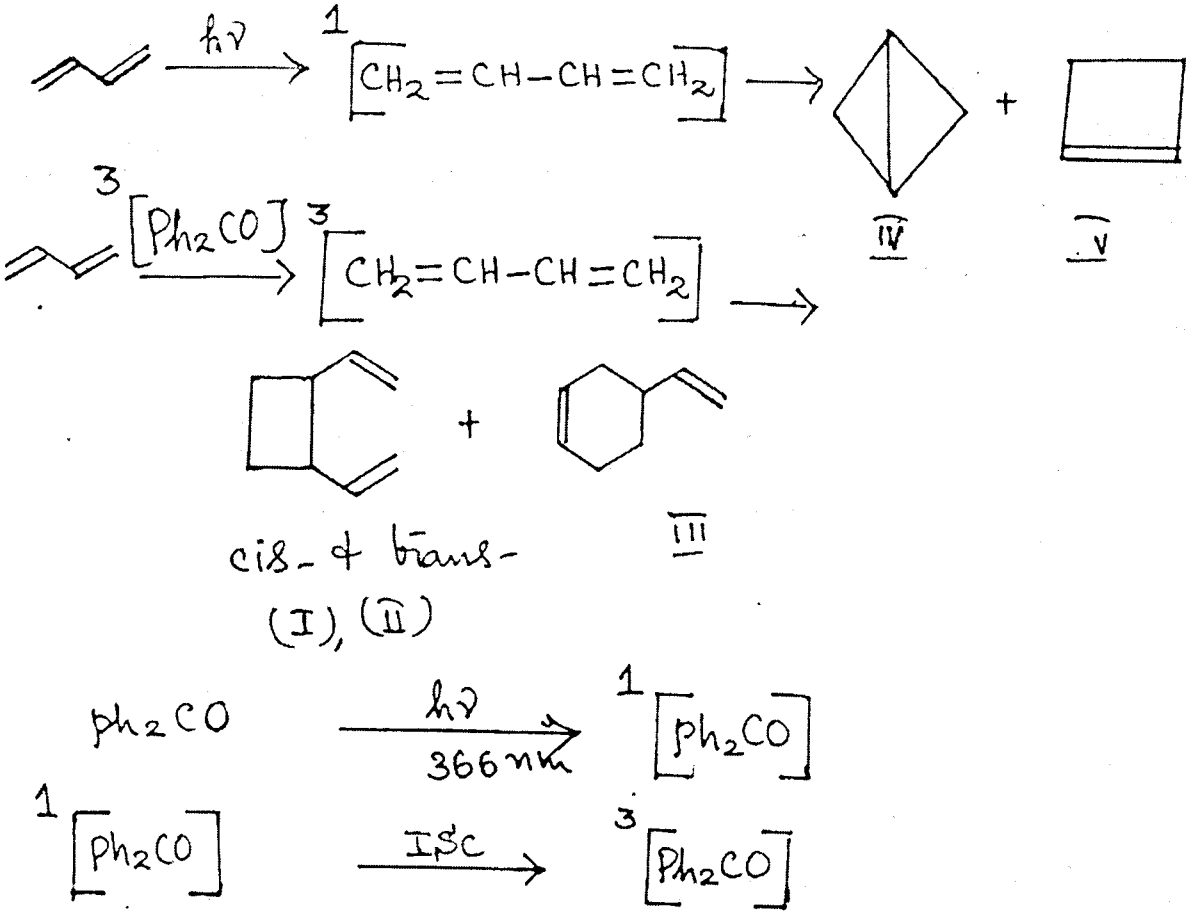
For photosensitisaton to be effective the E_T(donor) must be atleast greater by 5 Kcal/mole than E_T (acceptor)

The photochemical excitation of butadiene can be represented as follows:



The energy difference between the excited singlet & triplet states is very high in the case of butadiene (120 & 60 respectively).As a result no ISC is to be expected in this case. This results in only valence isomerisation giving bicyclo[1.1.0] butane[IV] and cyclobutene[V].

Whereas when the photochemical excitation is done in the presence of benzophenone, a sensitizer, the situation becomes different. Since the energy difference between the excited singlet and triplet states of benzophenone is only 5 Kcal/mole, there is efficient ISC, giving almost 100% excited triplet of benzophenone.The triplet excited state of butadiene has an energy of 60Kcal/mole.So excitation of butadiene takes place readily by the sensitiser leading to the formation of dimeric products.



$Ph_2CO \xrightarrow[366\,nm]{h\nu} {}^1[Ph_2CO]$

${}^1[Ph_2CO] \xrightarrow{ISC} {}^3[Ph_2CO]$

${}^3[Ph_2CO] + CH_2=CH-CH=CH_2 \longrightarrow Ph_2CO + {}^3[CH_2=CH-CH=CH_2]$

${}^3[CH_2=CH-CH=CH_2] + CH_2=CH-CH=CH_2 \longrightarrow$ Dimeric products

Comparison of the UV absorption spectra of benzophenone and 1,3- butadiene showed that 366 nm light will be absorbed only by benzophenone(Absorption of UV light by butadiene > 250 nm is negligible). Transfer of singlet energy from excited singlet benzophenone to 1,3-butadiene is not possible as the E_{S1} (benzophenone) is much lower than E_{S1} (butadiene)

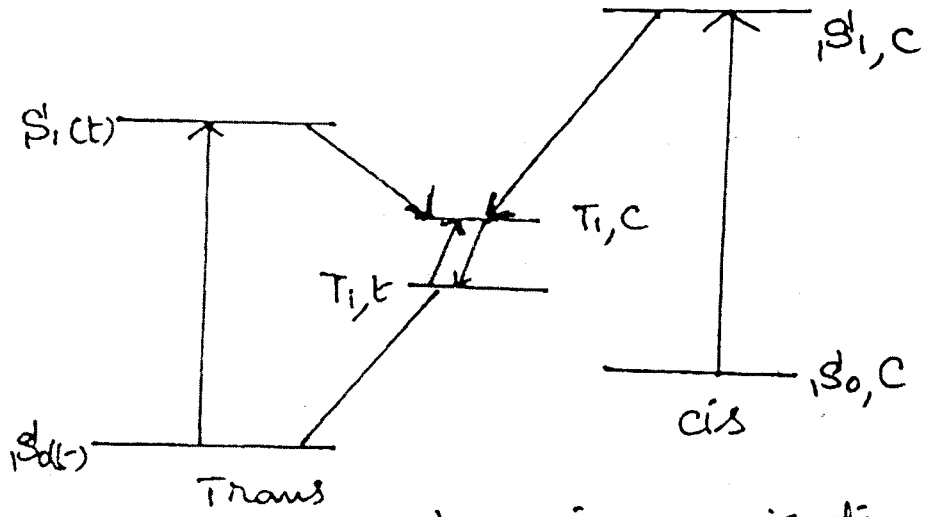
Cis-trans Isomerisation

Cis-trans isomerisation can be carried out(usually in solution) by irradiation alone or in the presence of a sensitiser or catalyst.

In general, because of steric effects the cis-isomer has a higher energy content than the trans in the ground state, and this also (usually) the case for corresponding excited states.

Because of the longer steric effects, the molar absoptility of the cis-isomer is less than that of the trans. As a result, the population of the trans excited state is greater than that of the cis.These excited states can come to their respective ground states. Alternately cis*(T_1) and trans*(T_1) become interconvertible.

In the above conversion cis –to- trans is favourable. Nevertheless, the overall process favours the trans---cis-interconversion. The reasons are,



photochemical cis-trans isomerisation

photochemical cis-trans isomerisation

i) the population of the trans is greater than cis
ii) cis-cis* transition is difficult to achieve compared to trans-trans*

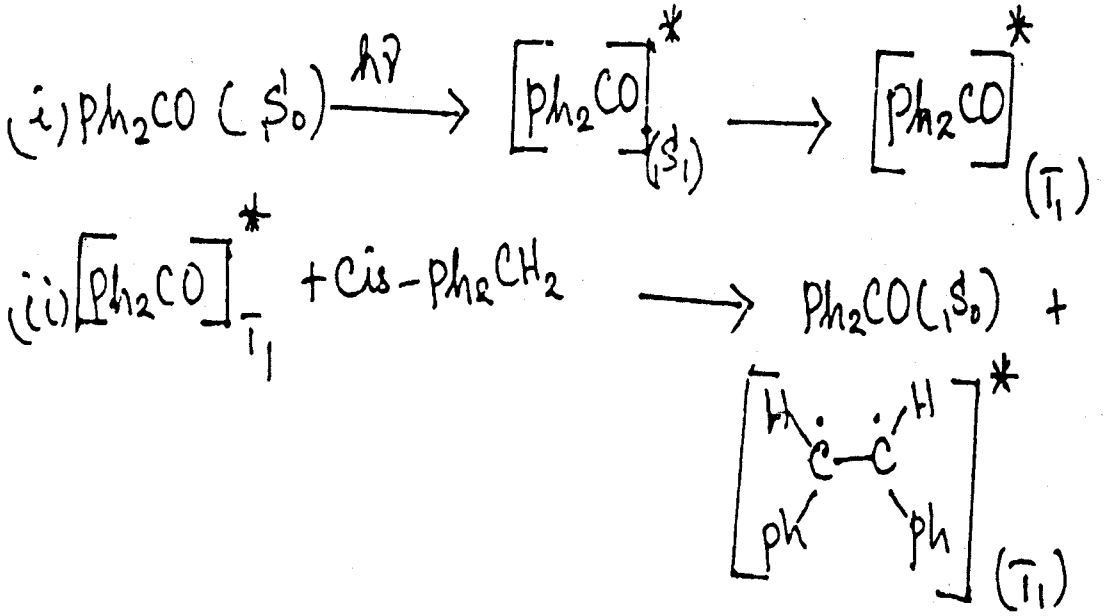
After sometime, an equilibrium is reached. At this stage, the cis-trans ratio remaining constant, no matter how much longer the irradiation is continued. This condition called a photostationary state, is independent of which isomer is the starting material and always contains predominantly the cis-isomer. The actual ratio of the cis-trans forms of course depends upon a number of factors.

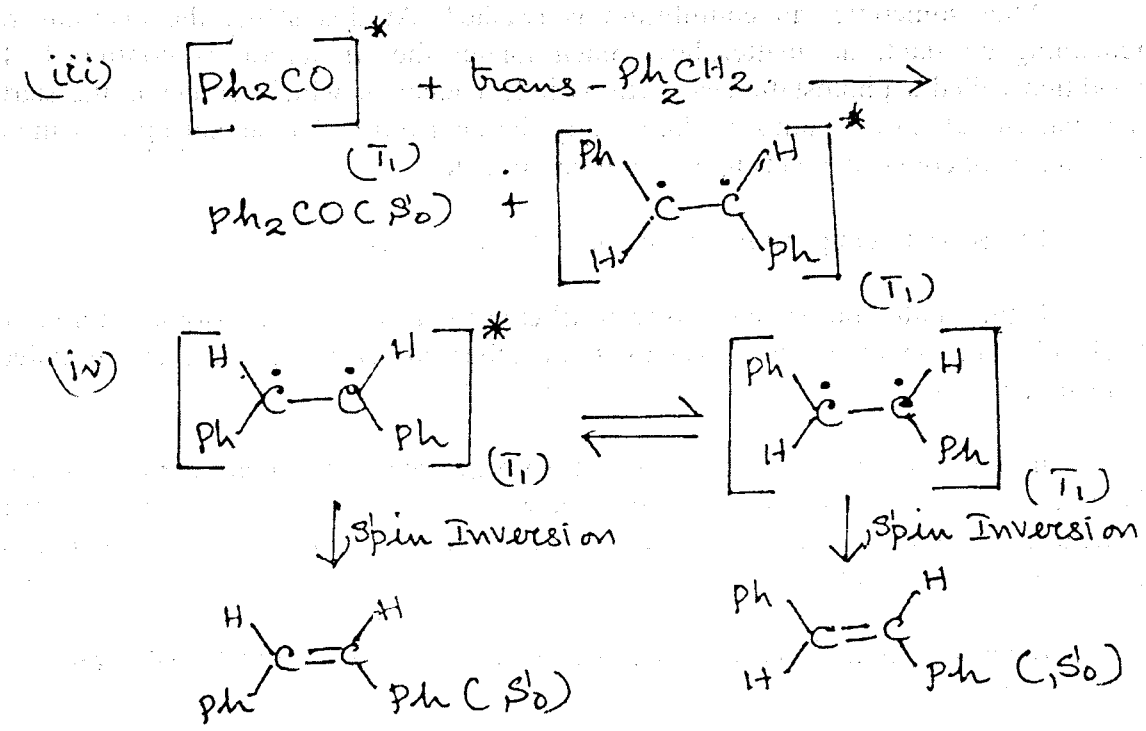
Ex. Solvent, temperature, nature of the sensitiser etc.

If the irradiation wavelength were filtered to allow only one isomer in a mixture to absorb radiation, complete conversion to the other isomer would occur.This is called as optical pumping.

In the cis-trans isomerisation of stilbene, another triplet is believed to be involved, which is intermediate in energy between the cis and trans-triplets. This triplet state, usually a forbidden transition, can be reached directly from the ground state. Hence called a phantom triplet.

If benzophenone is used as the sensitiser the mechanism can be written as,



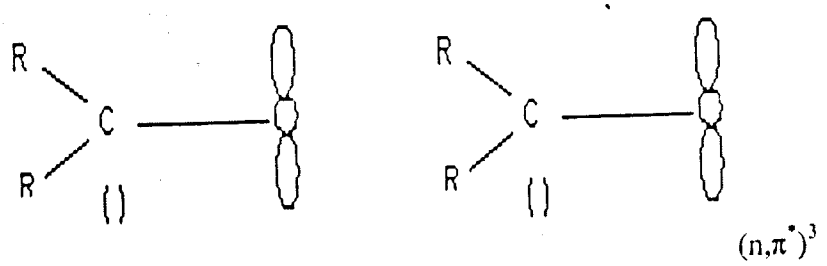


NORRISH TYPE I & II PROCESSES

The study of the fate of excited state ketones is referred to as Norrish Type I and II processes, depending upon the nature of cleavage of the ketones. If they undergo cleavage between the carbonyl carbon and the alpha carbon, then it is reerred to as Norrish Type I reactions.

If the cleavage takes place after the transfer of a gamma-hydrogen to the carbonyl then it is referred to as Norrish Type II reaction.

Ketones have two readily accessible electronic transitions i.e. $\eta \rightarrow \pi^*$ & π to π^*. Out of this the $\eta \rightarrow \pi^*$ excited state is important because they are much more reactive than the π,π^* excited states(less reactive and long-lived). The η, π^* excited state of the ketone with a singly occupied n-orbital may be represented as follows:



$(n,\pi^*)^3$

NORRISH TYPE 1

This is characterised by the initial cleavage of the carbonyl-carbon bond to give acyl and an alkyl radical which can undergo stabilization by one of the following routes.

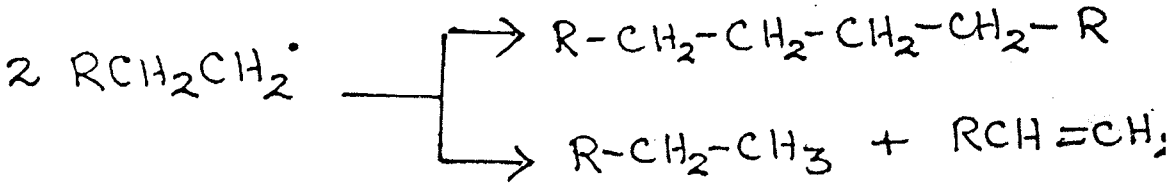
$$RCH_2\ CH_2\text{—}C(=O)\text{—}CH_2CHR_2 \xrightarrow{h\nu} RCH_2CH_2\text{—}C(=O)\text{—}CH_2CHR_2$$

a. The alkyl radical may abstract an alpha-hydrogen, to from a ketene and alkane.

$$RCH_2CH_3 + R_2CHCH=C=O$$

(the formation of the ketene intermediate may be established by trapping it as the carboxylic acid or ester derivative with water or methanol as nucleophilic species).

b. The acyl radical may undergo decarbonylation to give CO and an alkyl radical. The latter may recombine to give an alkane or form an alkene and alkane by intramolecular hydrogen abstraction.

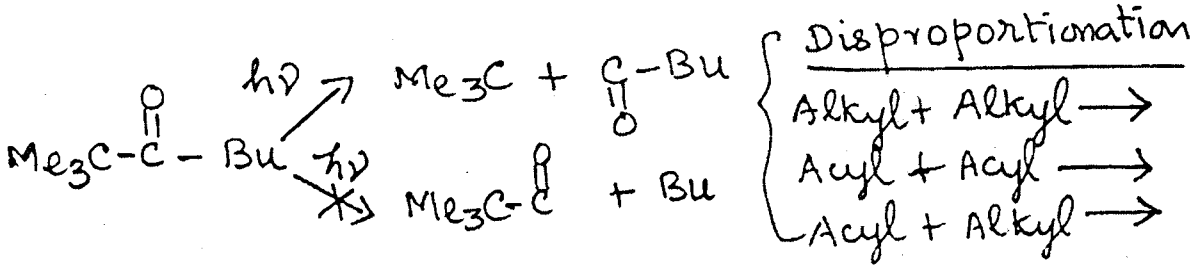


c. Intermolecular H-abstraction by the acyl radical from the alkyl radical to give an aldehyde and an alkene.

$$RCH_2CH_2\cdot + C(=O)\text{—}CH_2\text{—}CHR_2 \longrightarrow RCH=CH_2 + R_2CHCH_2CHO$$

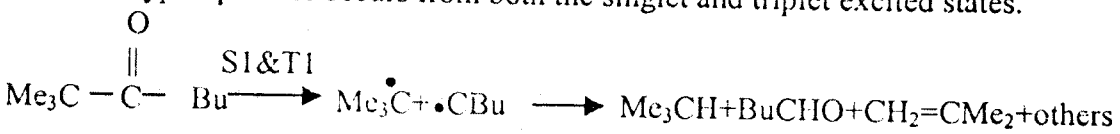
Though the condensed phase photolysis of 2,2 –dimethyl heptan – 3 –one illustrates both N.T.I and N.T II processes, here the type I process is discussed.

In the N.T. I process there is a preference for cleavage of the bond linking the carbonyl group to the more highly alkylated carbon.

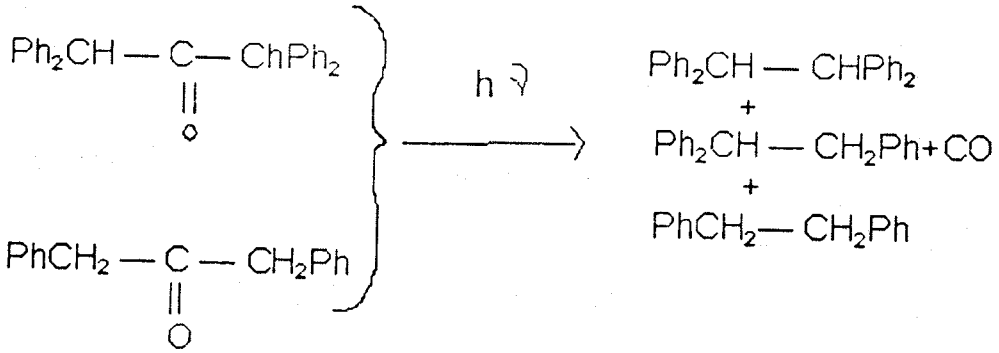


This is a result of the relative bond dissociation energies of the C-C bonds and the stabilities of the resultant free radicals. In this example, cleavage of the C_2-C_3 bond to give the tertiary butyl radical, which is more stable than the alternative primary butyl radical occurs.

Studied with triplet quenchers, such as penta -1,3-diene have shown that in this reaction the type I process occurs from both the singlet and triplet excited states.

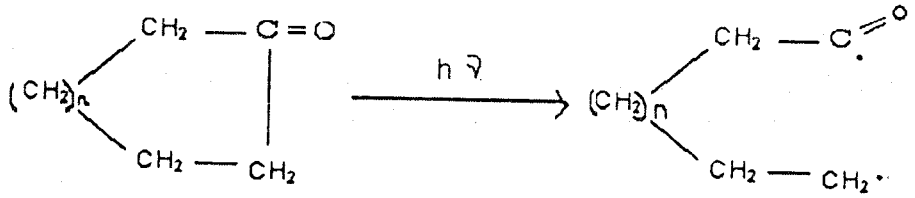


The type I alpha – cleavage can be followed by decarbonylation to give CO and a radical. The presence of such radical intermediates is readily demonstrated by photolysis of a mixture of ketones which give products from mixed radical recombination.

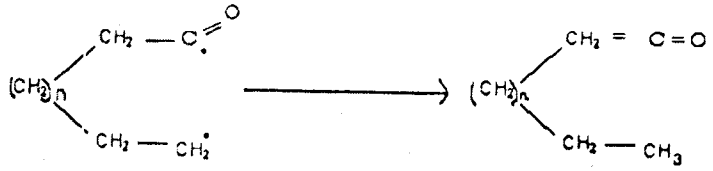


The photochemistry of saturated cyclic carbonyl compounds is demonstrated by the N.T. I process involving the initial cleavage of a carbon- carbonyl bond.

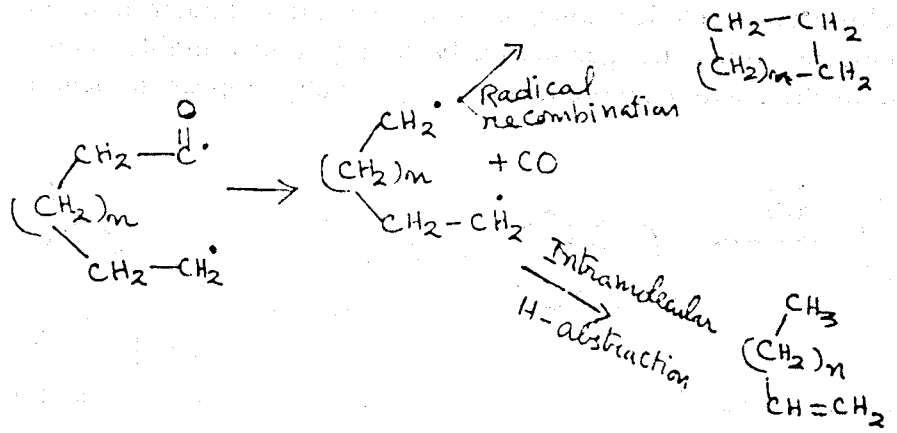
The resultant diradical follows the course of acyclic carbonyl.



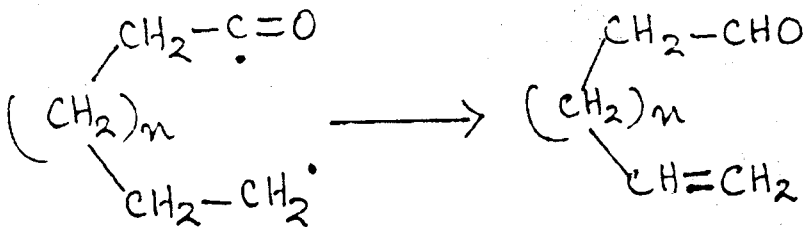
a. Intramolecular alpha – hydrogen abstraction by the terminal alkyl radical to produce a ketene. In the case where n =0, ketene and ethylene are formed.



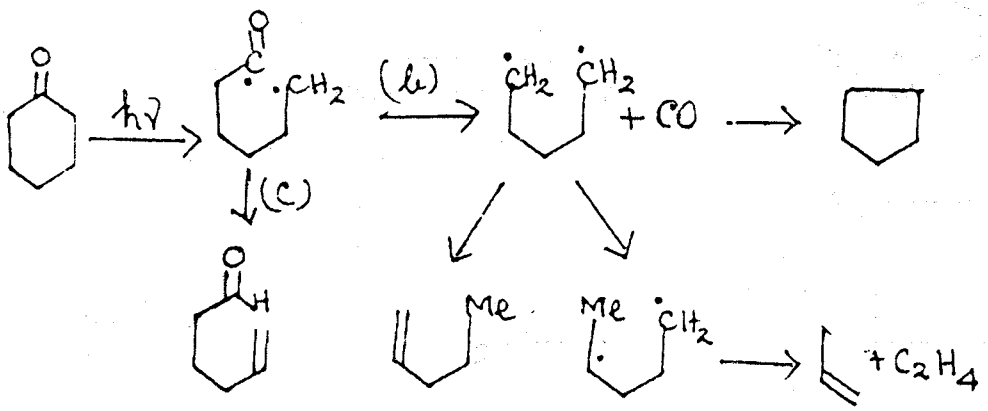
b. Photodecarbonylation to give CO, an alkene and/ or a cyclic alkane.



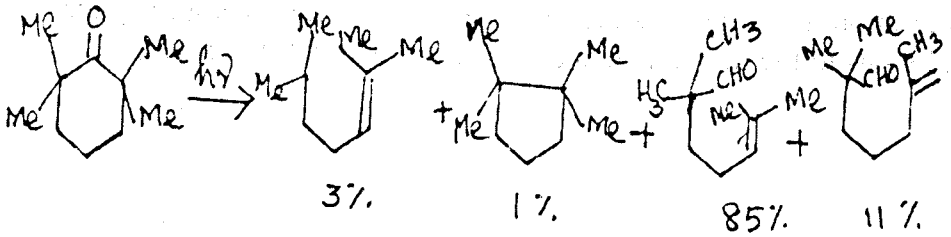
c. Intramolecular hydrogen abstraction by the carbonyl carbon atom to give an unsaturated aldehyds.



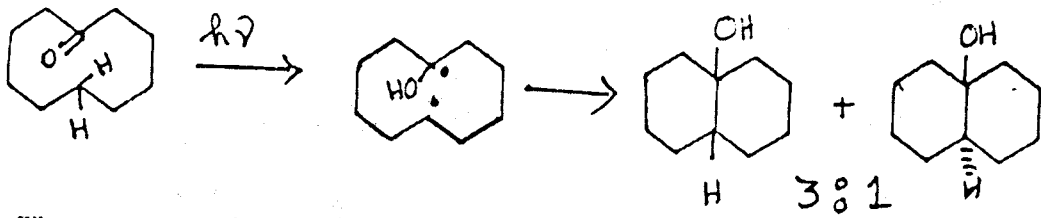
The vapour phase photolysis of cyclohexanone affords products from both paths b and c.



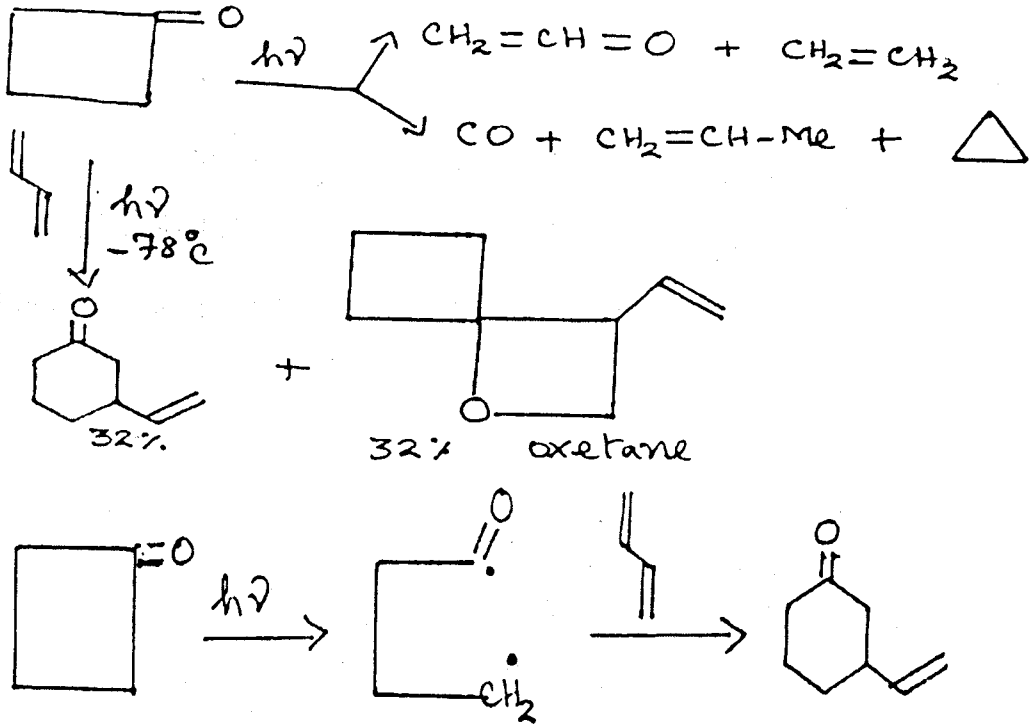
The photolysis of 2,2,6,6-tetramethylcyclohexanone was found to involve both S_1 and T_1 excited states.



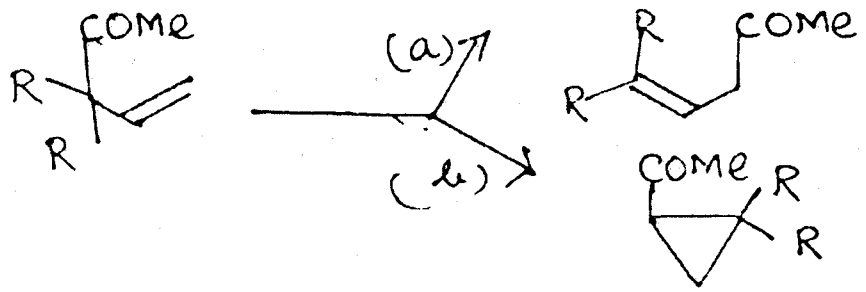
For carbonyl compounds contained in medium sized rings, intramolecular H- transfer reactions can lead to bicyclic products. In the formation of trans – 9 – hydroxydecalin from cyclodecanone, a concerted Transannular hydrogen transfer with ring closure would be geometrically highly unfavourable, consequently a diradical intermediate with its more favourable geometry, appears to be more likely.



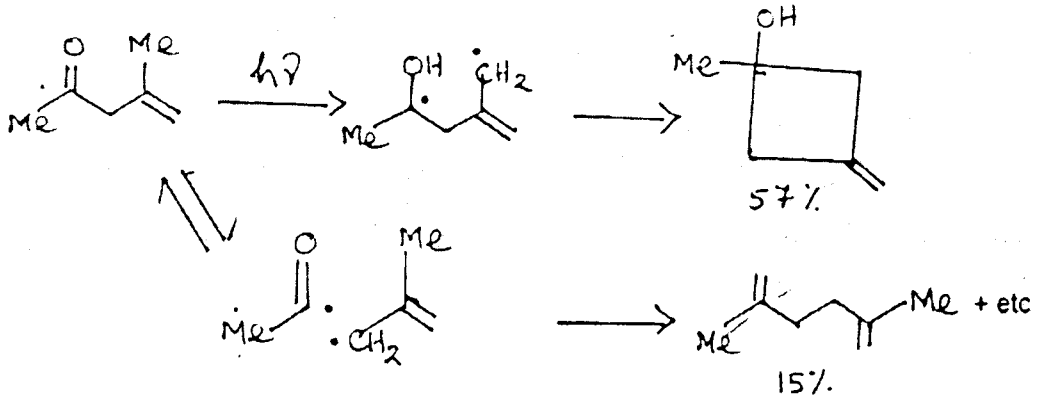
The vapour phase direct photolysis of cyclobutanone gives products of photoeleimination and photodecarbonylation.



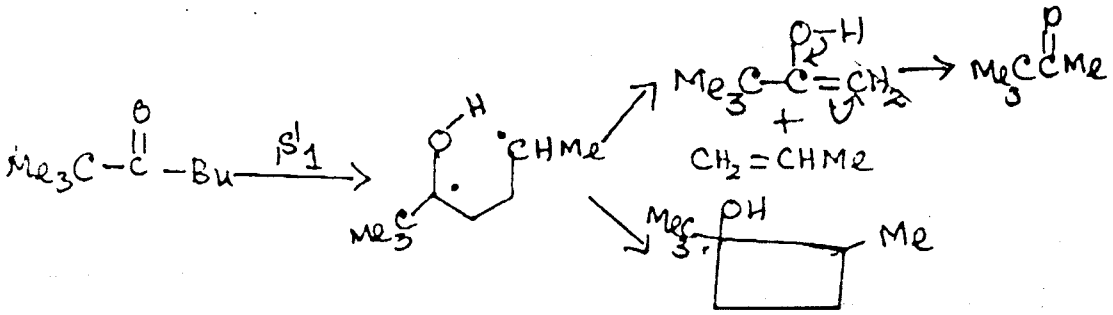
β, γ - unsaturated ketones, in addition to undergoing the normal photochemical reactions of saturated ketones (cyclobutanol formation and decarbonylation), undergo carbonyl migration by a [1,3] shift and form cyclopropylketones (Path b) by a reaction analogous to the di – π methane rearrangement of 1,4 – dienes.



Solution phase photolysis of 4 – methylpent – 4-ene-2-one gives as the major product, the cyclobutanol. The reaction proceeds from the singlet or from an exceedingly short lived triplet state, the quantum yield being comparable with those for saturated ketones but greater than those for conjugated ketones.

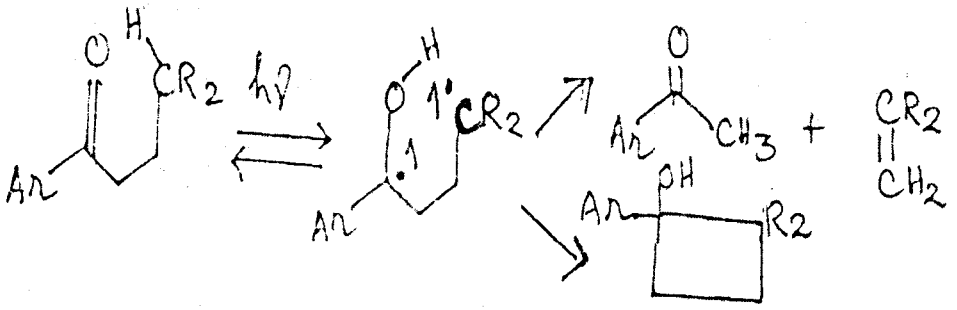


NORRISH TYPE II



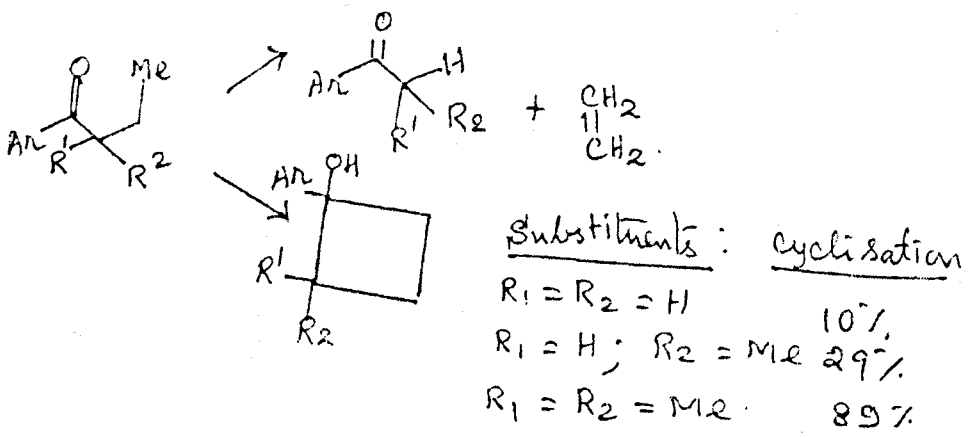
The reaction proceeds from the excited singlet state.For aryl and alkyl ketones both reaction to give cyclobutanols and cleavage to form alkene and an enol(which isomerizes to a methylketone) are thought to proceed by way of a triplet which leads to a 1,4 – diradical.

The diradical may, of course, revert to starting material by re – abstraction of hydrogen by the gamma-carbon radical.



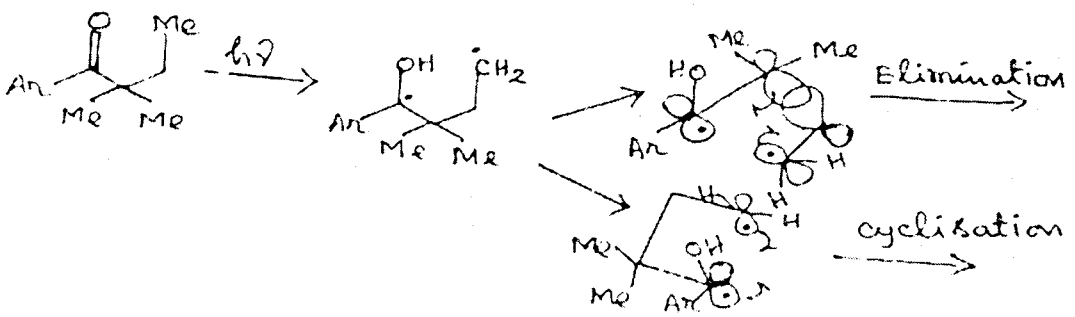
The gamma- hydrogen transfer occurs through a intramolecular cyclic six-membered T.S.. Ex N.T II reaction of 5,5 – dideuterohexan – 2 –one giving, 1–deutero– acetone and 2– deuteropropene. This transfer of hydrogen in the n π^* excited state occurs to the localized, half – filled, n– orbital of the oxygen atom which lies in the nodal plane of the π – bond.

For aryl alkyl ketones the electron releasing p-methyl and p-methoxy substituents decrease the rate constant and quantum yield for Type II cleavage. Following this trend p – hydroxy, p – amino and p – phenyl substituents inhibit the reaction completely. This effect is thought to be a consequence of an increase in importance of the $\pi \rightarrow \pi^*$ triplet as it becomes lower in energy than the n π^* triplet state.



The rate of radical recombination to give cyclobutanols compared with alpha, beta -bond cleavage is often dependent on alpha-substitution.

While the formation of the T.S for cyclisation of a 1,4 diradical intermediate only requires overlap of the radical centers, C-C bond cleavage requires the radical centers also to overlap with the bond undergoing cleavage as shown below for one possible conformation.



The magnitude of the resultant eclipsing interactions, primarily along the C_1-C_2 bond,will be greatest for elimination . with substituents at C_2, adjacent to the carbonyl group an increase in the magnitude of these eclipsing interactions will favour cyclisation by way of the non- planar 1,4 – diradical.

PATERNO-BUCHI REACTION

The formation of oxetanes by photocycloaddition of aldehydes and ketones to olefins is known as Paterno –Buchi reaction. EX Addition of acetophenone to 2-methyl-2 butene. The oxetane is formed via the diradical(A).

Intermediate (A) is more stable than the other possible diradicals (C to E). The formation of major cycloaddition product may be predicted on the basis of the most stable biradical intermediate.

Apart from the above four expected products, non-oxetane products are also produced.

Generally ketones which undergo photochemical reduction through the triplet add smoothly to olefins. It has been suggested that the reactive state in oxetane formation is the triplet state of the carbonyl component just as it is in photoreduction of benzophenone.

Side products derived from reactions (dimerization, for example) of the olefin substrate sometimes compete with or even completely suppress the Paterno-Buchi reactions. These side products result form contact transfer of the energy from the triplet excited state of the carbonyl compound to the olefin. This may be schematically represented as follows:

$$D \xrightarrow{h\nu} {}^1D \text{ (Excitation)}$$

$${}^1D \longrightarrow {}^3D \text{ (ISC)}$$

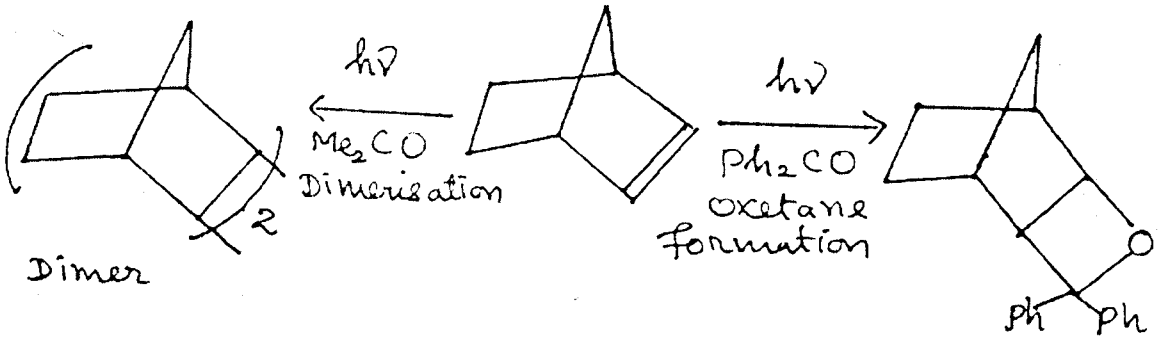
$${}^3D + A \longrightarrow {}^3A + D \text{ (triplet energy transfer)}$$

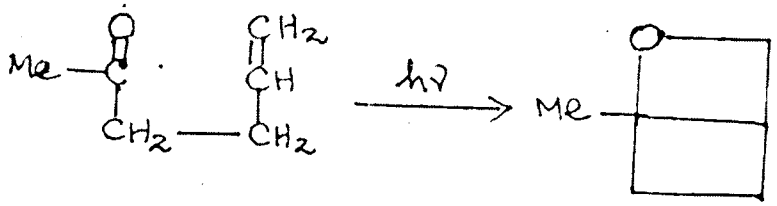
$${}^3A + A \longrightarrow \text{Products (side reaction)}$$

D = Carbonyl Compound. A = acceptor (Olefin)

Excitation of the carbonyl compound (D) produces an excited singlet state which undergoes intersystem crossing giving the low – lying triplet excited state. Energy transfer then occurs on collision (the collision cross section may be larger than the molecular diameter) with the olefin. The triplet excited state of the olefin then reacts.

The probability of the energy transfer in a collision depends heavily on the relative triplet energies of the carbonyl compound and the olefin. When the triplet energies of the donor and acceptor are similar, energy transfer occurs but at such rate other processes (for example photocycloaddition) can compete.





Energy transfer from the carbonyl component to the olefin places a fundamental limit on the generally of the Paterno-Buchi reaction. Intramolecular Paterno-Buchi reactions have even been observed.

For example 5-hexen – 2 –one gives oxabicyclohexane.

PERICYCLIC REACTIONS

In 1965 Woodward-Hoffmann published a series of papers which formed the is for pericyclic reactions.

What are pericyclic reactions?

Reactions in which the peri $e^{\ominus}$ s participate in some sort of a cyclic manner of the participating atomic orbitals are called as pericyclic reactions.

What are peri electrons?

The electrons present in the Highest Occupied Molecular Orbital are called as the peri electrons.

What is a HOMO? How to identify that?

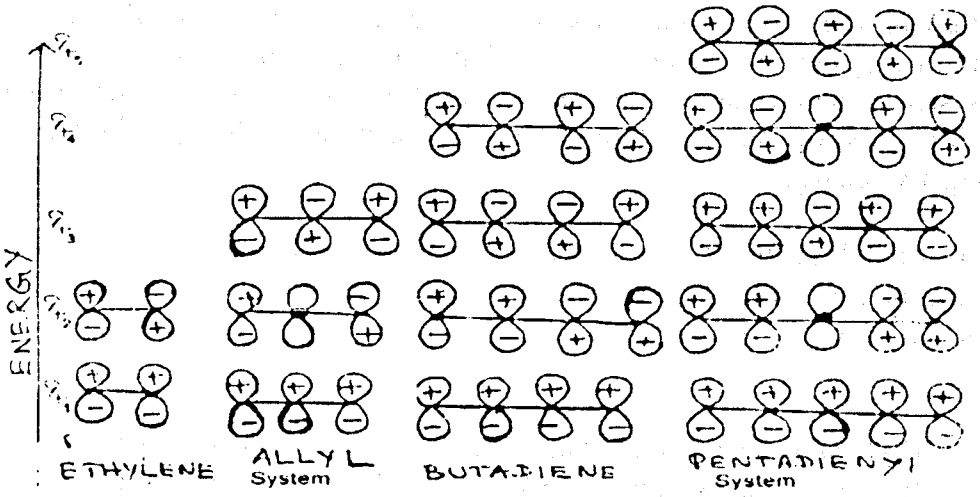
HOMO is the highest occupied molecular orbital. Just like the atoms have the valence shells, the molecules have the molecular orbitals.

In general 'n' number of atomic orbitals will give rise to 'n' number of molecular orbitals.

How do we generate the molecular orbitals?

The molecular orbitals are obtained by the lateral overlap of the unhybridised 'p' orbitals of the carbon atoms present in the Π- systems.ie.we are considering the conjugated system of ΠΠ- bonds for the construction of molecular orbitals.

We can pictorially represent the generation of Π- molecular orbitals from 'p' orbitals. We start with the simplest Π- system namely ethylene and go up step by step.



What do we observe in the M.O.S?

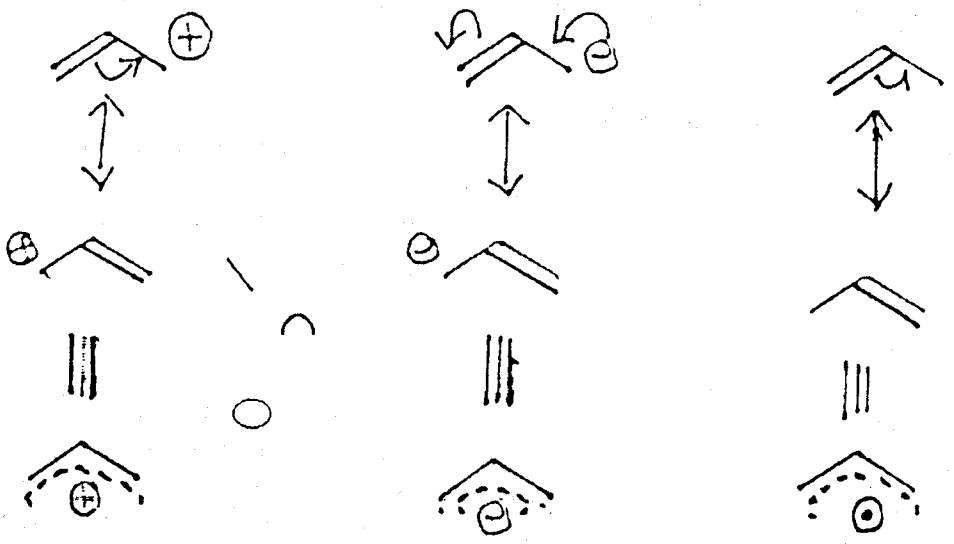
a) The odd numbered MOS(ψ_1, ψ_2, ψ_3 etc) irrespective of the system are symmetric at the ends.

b) The even numbered MOS(ψ_2, ψ_4, ψ_6 etc) irrespective of the systems are antisymmetric at the ends.

c) An important feature is the odd numbered systems. For a bond to be formed we need even number of orbitals. So one of the orbitals will remain non-bonding. For the construction of MOS we need conjugated system of 'p' orbitals.

How can the odd numbered systems become conjugated?

This is possible only if the system is conjugated. Conjugation is possible only if the system is any one of the following: a) a cation b)an anion c)a free radical. For example, allylsystem can be represented as



In drawing the MOS symmetry should be preserved ie. we should have the sign distributions in a systematic manner. So in drawing the even numbered MOS of odd numbered systems, the middle orbital is kept vacant. ie there is no sign put on it.(Please make sure, it is only a positive and negative sign and it has nothing to do with positive charge or negative charge.

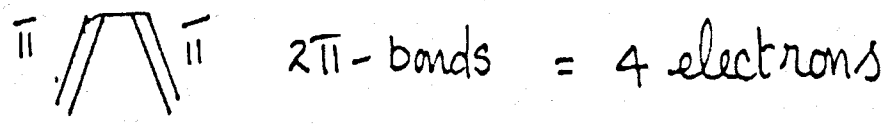
Each Π- bond has two Π- electrons. So form the number of Π -bonds, the number of Π -e$^{\ominus}$s, can be found out. Just like filling the atomic orbitals with electrons, we have to fill up the MOS with these Π -electrons. The following procedure is adopted for this purpose.

i) Each MO can accommodate a maximum of only 2 electrons.

ii) Before filling a high energy orbital the low energy orbital should be completely filled.

iii) Under photochemical conditions promotion of one electron takes place from the HOMO to the LUMO along the reaction co-ordinate.

For example for butadiene we have 4 electrons.(2Π bonds. So 2 x 2=4)



Because it has two Π -bonds which are conjugated.ie 4 'p' orbitals are in conjugation, 4 MOS are possible. Applying the above rule we have ψ_1^2, ψ_2^2, ψ_3^2, ψ_4^2. In this case ψ_1 and ψ_2 are occupied. Which is the highest occupied orbital? It is ψ_2. So in this case the HOMO is ψ_2.

Now what are the orbitals which are unoccupied? ψ_3 and ψ_4. But which is the first lowest unoccupied orbital? It is ψ_3.

So for the butadiene system under thermal conditions ψ_2 is the HOMO & ψ_3 is the LUMO.

In the case of odd numbered systems depending upon the nature of the system the total number of electrons will vary.

For example, allyl system.
allyl cation = 2Π electrons + O = 2 $e^{(-)}$s
allyl anion = 2Π electrons +2 electrons from the negative change =4$e^{(-)}$ s
allyl free radical = 2ΠB electrons +1 electron from the free radical=3$^{(-)}$s
For the allyl system the electron fill up will be as follows

Allyl cation : ψ^2 ψ^0 ψ^0

Allyl anion : $\psi_1^2 \cdot \psi_2^2 \cdot \psi_3^0$

Allyl free radical : $\psi_1^2 \cdot \psi_3^1 \cdot \psi_3^0$

For the allyl cation under thermal conditions ψ_1 is the HOMO and ψ_2 is the LUMO. For the allyl anion under thermal conditions ψ_2 is the HOMO and ψ_3 is the LUMO. For the allyl free radical under thermal conditions ψ_2 is the HOMO and ψ_3 is the LUMO.

So now we have an idea as to how to construct an MO for a Π -system and to identify the HOMO & LUMO. The electrons present in HOMO becomes the peri electron for that system. From the number of electrons and from the nature of the system we can predict the HOMO & LUMO for a given system even without drawing the MOs. We have noted early how the peri electrons participate in pericyclic reactions.

what are the characteristic features of these reactions?

a) Either the reactant or product (or) both the reactant and product may be an unsaturated system.
b) A 'sigma' bond is formed or scissoned and a 'pi' bond is consumed or generated.
c) The electronic reorganisation takes place in some sort of a cyclic manner of the participating atomic orbitals.
d) All these reactions are reversible in nature.
e) They cann either be catalysed nor influenced by acid or base.
f) They are concerted reactions ie.they donot involve the formation of intermediates.

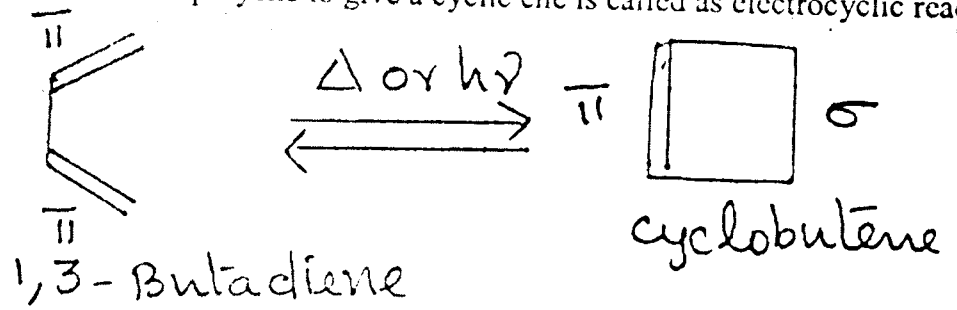
How many types of pericyclic reactions are there and what are they?

There are three types of pericyclic reactions

a) Electrocyclic reaction
b) Cycloaddition reaction
c) SIgmatropic rearrangement

1.Electrocyclic reaction

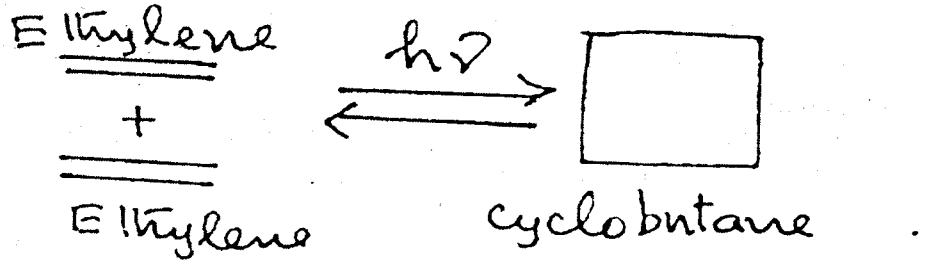
Cyclisation of a polyene to give a cyclic ene is called as electrocyclic reaction.



2.Cycloaddition reaction

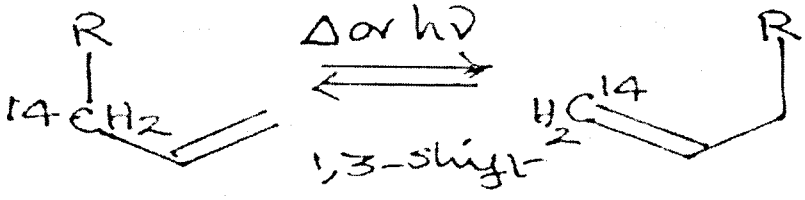
Cyclic addition of enes or unsaturated compounds to give a cyclic product is called as cycloaddition reaction.

(Ex) The simplest reaction is the cycloaddition of one ethylene to another ethylene (or) cyclic addition of one ethylene to another ethylene to give cyclobutane.



3. Sigmatropic Rearrangement

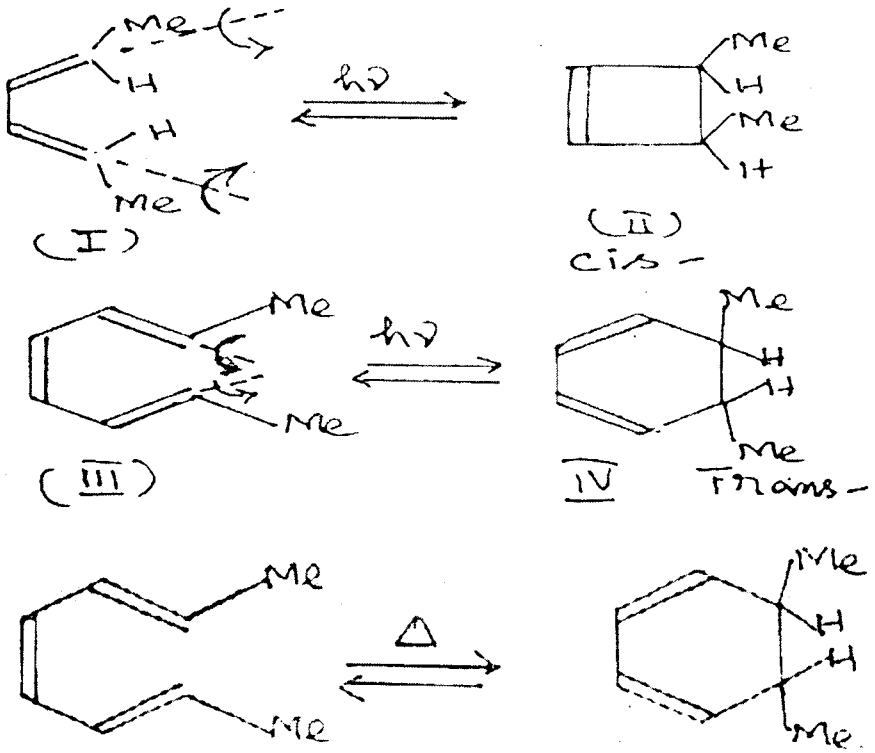
Migration of an atom or group from one end of the polyene to the other end is called as sigmatropic rearrangement.



Conversation of orbital Symmetry:

A striking feature of these reactions is their high degree of stereospecificity. For example, under photochemical conditions , trans, trans- (I) hexa-2,4-diene (II) on cyclisation gives only cis-3,4-dimethylcyclobutene.Similarly trans, cis, trans-octa-2,4,6-triene (III) under similar conditions on cyclisation gives only dimethylcyclohexa-1,3-diene(IV).

When cyclisation of this latter suustrate is effected thermally, cis-5,6-trans- 5,6 dimethylcyclohexa-1,3-diene (V) is produced in contrast to the photochemically induced cyclisation in which the trans- dimethyl isomer is obtained.



This remarkable stereospecificity is attributed to the convertion of orbital symmetries during pericyclic reactions.

How many methods are available to explain these reactions?

There are four methods available to explain these reactions.

What are they?

i)Frontier Molecular Orbital Method (or)
FMO method (FUKUI)

ii) Conservation of orbital symmentry method(Woodward-Hoffmann)

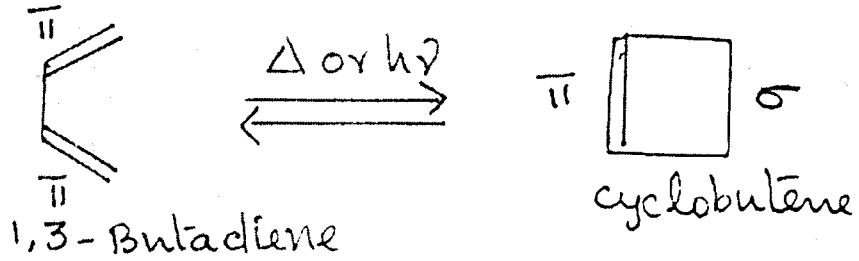
iii) Perturbed Molecular Orbital Method (or)
PMO method (Huckel, Mobius and Zimmermann)

iv) Generalised Woodward-Hoffmann rule

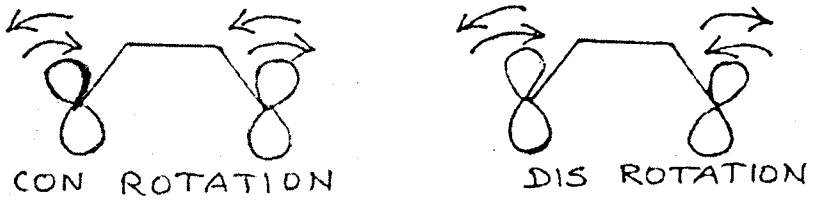
FMO Method

Here the stress is given for the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital(LUMO).

First we can consider the electrocyclic reaction of butadiene to cyclobutene. What do we observe in this reaction? The reactant has two Π bonds



and the product has one reorganised Π-bond and one σ-bond. How to convert a Π bond into a σ- bond. Actually what is happening here is the 'p'-orbitals of the Π- system that are present at the two ends are made to form the σ- bond or σ- orbitals. For a Π- orbital to become a σ- orbital, we have to rotate th e'p' orbital of the Π- system through 90°, i.e. bring it horizontally. This we can do in two ways.(i)both the end orbitals can be rotated in the same direction (clockwise or anticlockwise) through 90^0. This is called as con rotation.



(ii) one of the orbitals is rotated clockwise and the other anticlockwise of course both through 90^0.This is called as dis rotation.

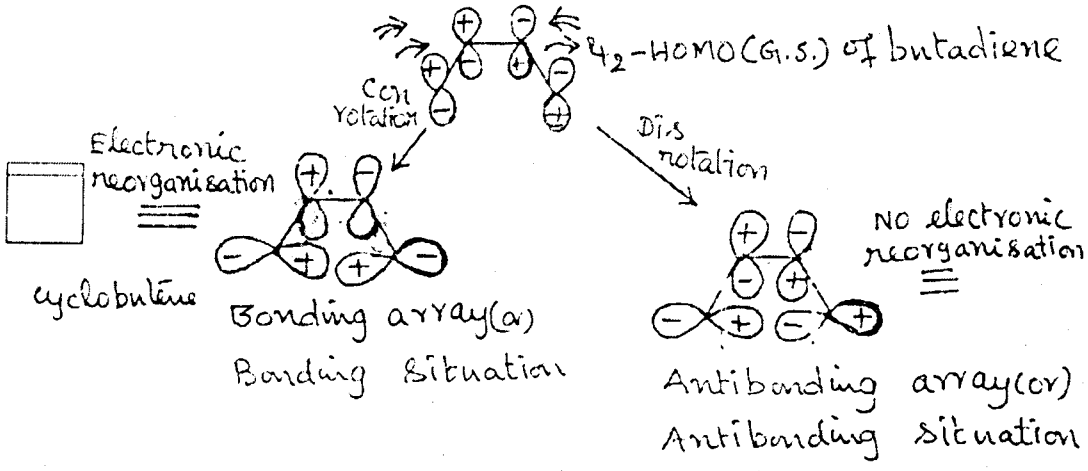
Now we can discuss how the actual cyclisation is taking place?

The molecule butadiene has 2Π- bonds. That means the system has 4 electrons.

The electronic configuration of Butadiene (Ground State or G.S) = $\psi_1^2 \cdot \psi_2^2 \cdot \psi_3^0 \cdot \psi_4^0$

HOMO (G.S) of butadiene = ψ_2

LUMO (G.S.) of butadiene = ψ_3



What is a bonding array?

What is an antibonding array?

When orbitals of same sign are brought together it is called as a bonding array.

When orbitals of opposite sign are brought together it is called as an antibonding array.

In the case of cyclisation of butadiene to cyclobutene the con rotatory closure gives a bonding array and the dis rotatory closure gives an antibonding array.That means the former pathway is symmetry allowed and the latter symmentry forbidden. The following conclusion can be made out of it.

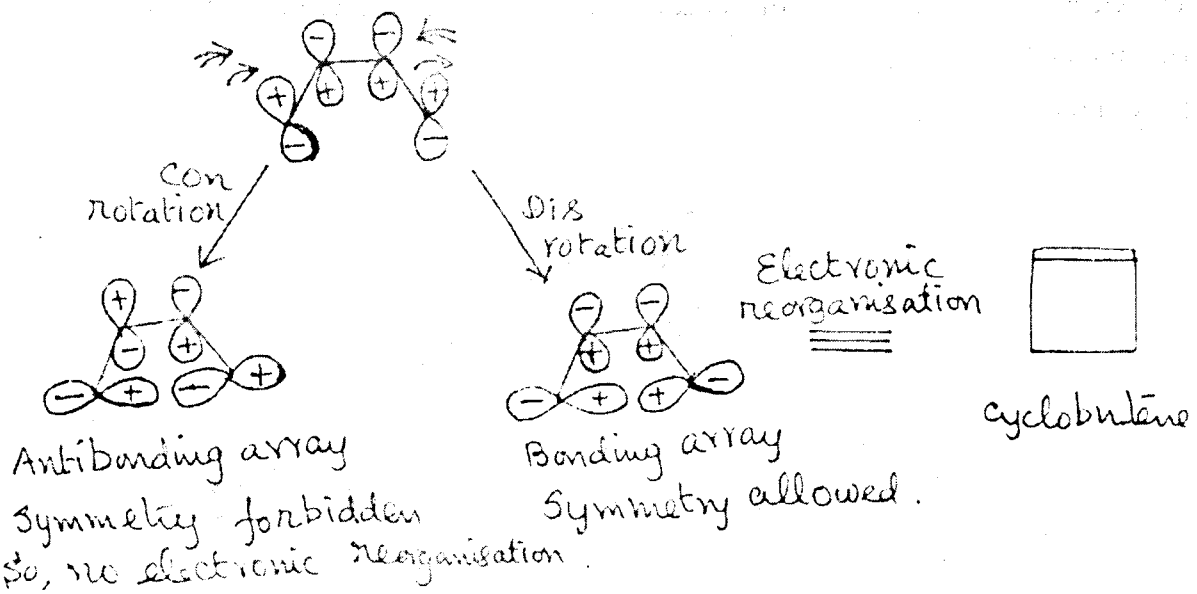
"Con rotatary closure of butadiene to cyclobutane is a symmetry allowed process whereas the dis rotatory closure of the same is symmetry forbidden under thermal conditions."

Now what will happen under photochemical conditions?

Under photochemical conditions promotion of one electron takes place from HOMO to LUMO ie.from ψ_2 to ψ_3 in this case. So the electronic configuration of butadiene under photochemical conditions would be $\psi_1^2 \psi_2^1 \psi_3^1 \psi_4^0$

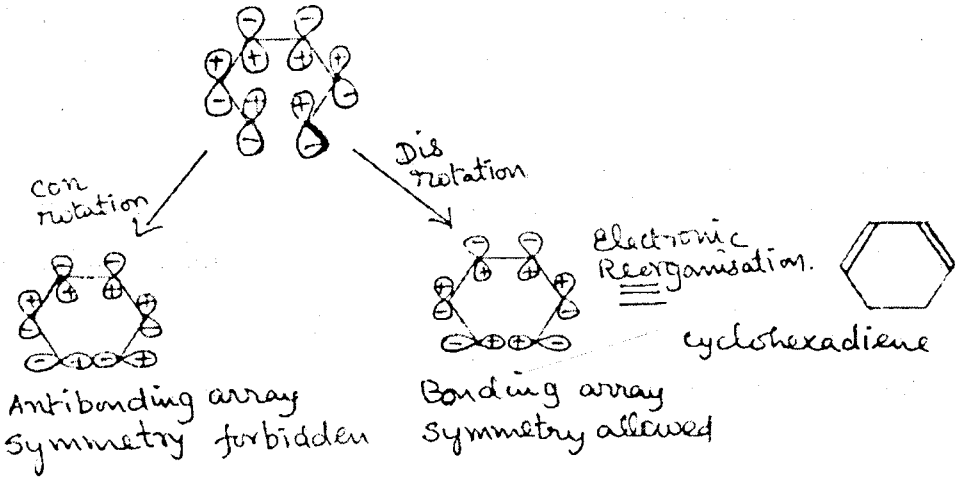
Therefore HOMO (E.S) of butadiene-ψ_3 LUMO (E.S) of butadiene-ψ_4

Now we can consider the cyclisation of butadiene to cyclobutene under photochemical conditions (or) excited state conditions.



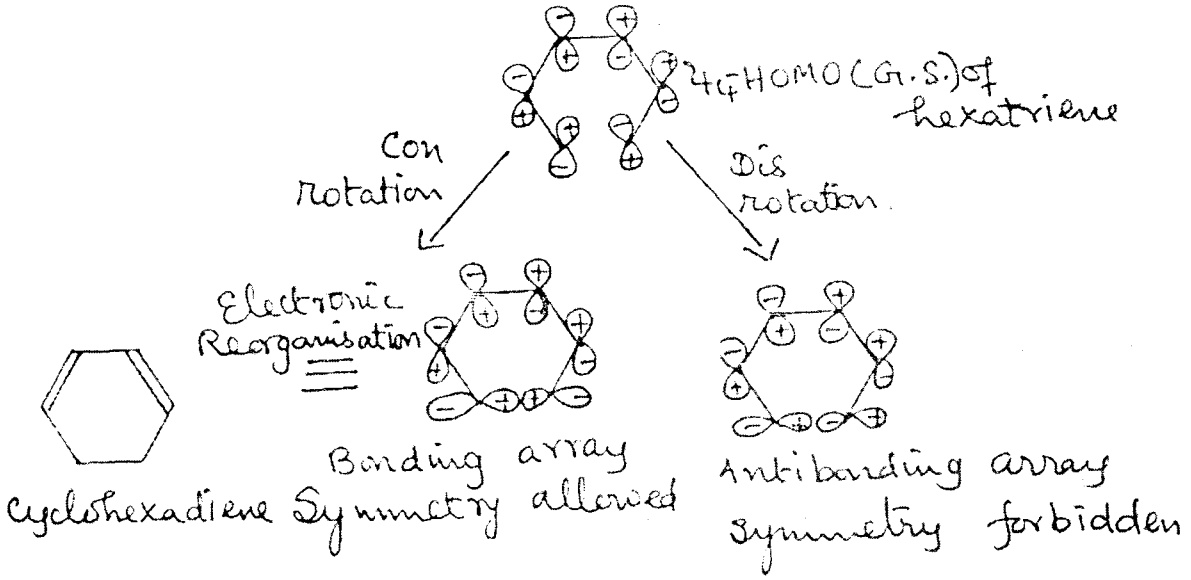
Con rotatory closure of butadiene to cyclobutene is symmetry forbidden because it leads to an antibonding array, whereas that of the same via disrotatory closure is symmetry allowed as it leads to a bonding array under photochemical conditions.

For the cyclisation reaction involving hexatriene to cyclohexadiene similarly we can find the HOMO under thermal condition to be ψ_3 and under photochemical condition to be ψ_4. As with butadiene we can draw the HOMO under thermal & photochemical conditions and find the preferred method of rotation(cyclisation) G.S.electronic configuration of hexatriene = $\psi_1^2 \psi_2^2 \psi_3^2 \psi_4^0 \psi_5^0 \psi_6^0$



Cyclisation of hexatriene to cyclohexadiene via con rotation is symmetry forbidden under thermal conditions as it leads to an antibonding array. Whereas the same via disrotation is symmetry allowed as it leads to a bonding array.

Under photochemical conditions promotion of one electron takes place from HOMO to LUMO. ie. from ψ_3 to ψ_4. The E.S. electronic configuration of hexatriene= $\psi_1^2\psi_2^2\psi_3^1\psi_4^1\psi_5^0\psi_6^0$ cyclisation of this molecule under photochemical conditions may be considered



Con rotatary closure of hexatriene to cyclohexadiene under photochemical conditions is symmentry allowed as it leads to a bonding array. whereas the disrotatory closure of the same under similar conditions is symmetry forbidden as it leads to an antibonding array.

What do we observe in the above two examples?

whenever the end orbital symmetries happened to be antisymmetric the preferred mode of cyclisation is con rotation. Again whenever the end orbital symmetries are antisymmetric, the preferred mode of cyclisation is disrotation.

This different modes of cyclisations under different conditions (say thermal/photochemical) will affect the stereochemistry of the products formed.

How are we to relate the mode of cyclisation and stereochemistry?

Take the example of 2,4-hexadiene (or) 1,4-dimethylbutadiene.

$CH_3 - CH = CH - CH = CH - CH_3$

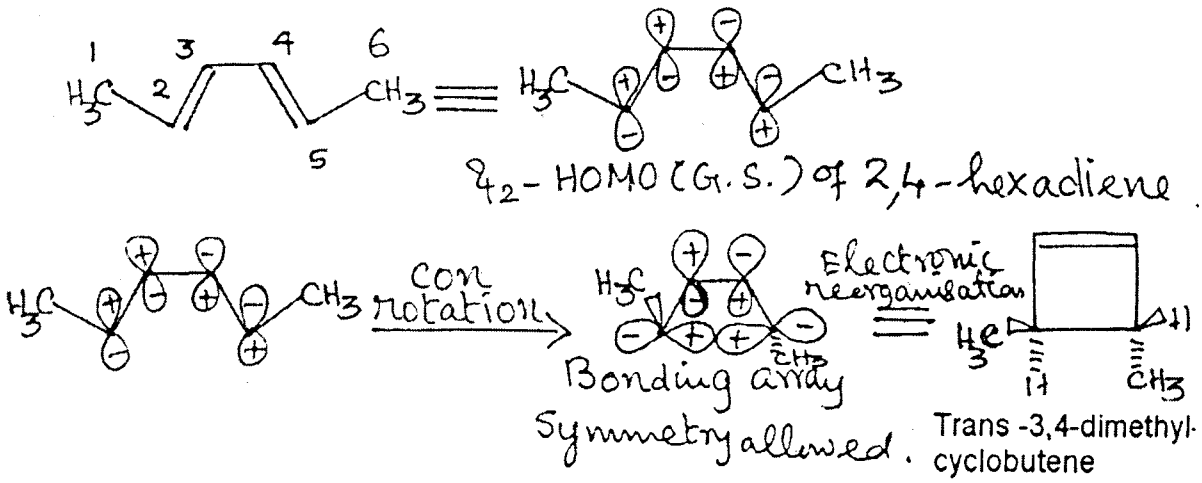
In this example though there are 6 carbon atoms, only 4 carbon atoms are in conjugation ie.there are only 4 MOS that can be written for the molecule.

The total number of electrons for this system is $4e^{\ominus}$s. The ground state electronic configuration of this molecule is $\psi_1^2 \psi_2^2 \psi_3^0 \psi_4^0$.

HOMO(G.S) of butadiene system = ψ_2

LUMO (G.S) of butadiene system= ψ_3

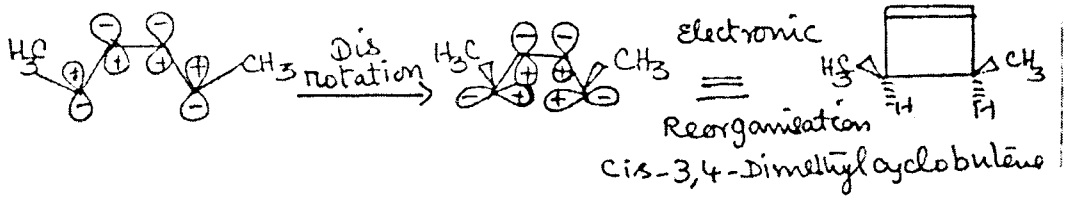
Since the HOMO is an even numbered M.O., the end orbitals symmetries will be antisymmetric.From our experience above this should lead to con rotation



Under photochemical conditions promotion of one electron takes place from HOMO to LUMO ie. from ψ_2 to ψ_3.Therefore the excited state electronic configuration of the 2,4- hexadiene is,

$$\psi_1^2 \psi_2^1 \psi_3^1 \psi_4^0$$

In this case the HOMO is ψ_3, which is an odd numbered wave function. Again from our experience the odd numbered systems will cyclise via dis rotation.



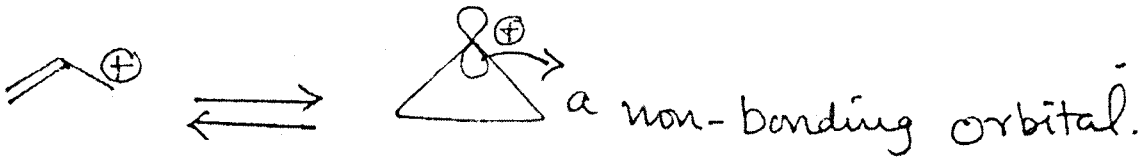
Thus we can say that the occupied orbital of high energy decides the stereochemistry of the products formed during electrocyclic reactions.

So far, we have considered systems with even numbered MOS ie. butadiene, hexatriene etc.

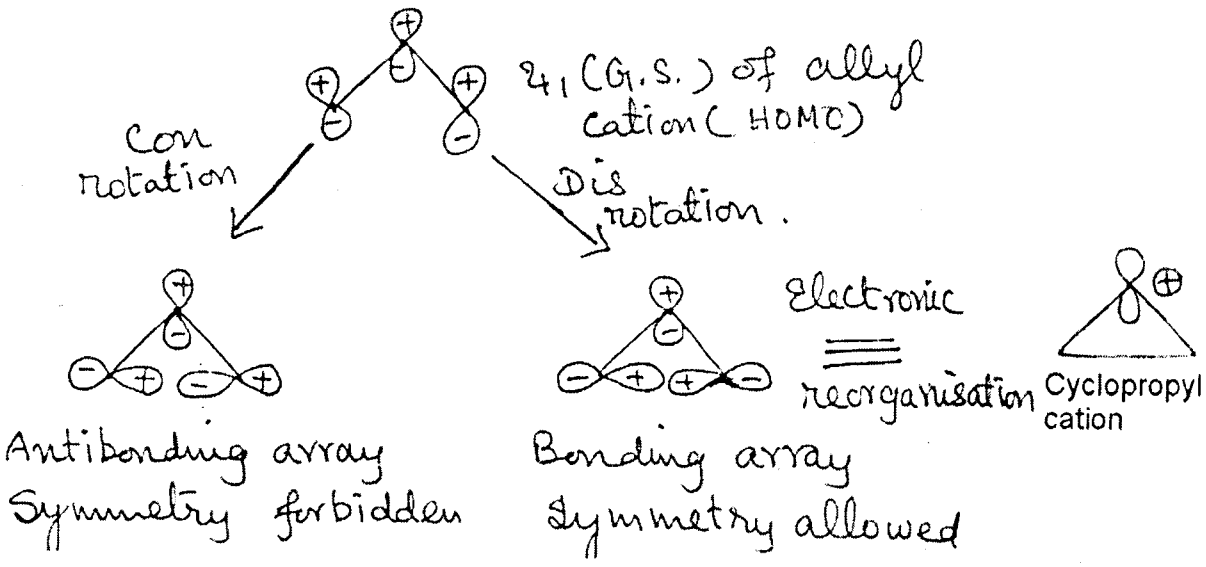
What about the odd-numbered systems?

For odd numbered systems also we follow the same procedure as we did for the even numbered systems. Their products will be slightly different in the sense, they may contain a non-bonding orbital with or without electrons (allyl system) (or) a conjugated ionic or radical species(pentadienyl system).Depending upon the reactants, the products may be a cation/anion /free radical. ie. a cationic reactant will give a cationic product and so on.

Eg. Allyl cation ⇌ cyclopropyl cation



The G.S. electronic configuration of allyl cation is $4_1^2\, 4_2^0\, 4_3^0$ (as allyl cation has only the two π electrons). Thus the HOMO (G.S) of allyl is 4_2 and that of LUMO is ψ_2.Now the cyclisation of this cation may be attempted.



The cyclisation of allyl cation to cyclopropyl cation is a symmetry allowed process under thermal condition, via dis rotation, because it leads to a bonding array. Whereas the same process is symmetry forbidden via con rotation. This is a (4n+2) electron system similar to 1,3,5- hexatriene.Here also we get the same result.

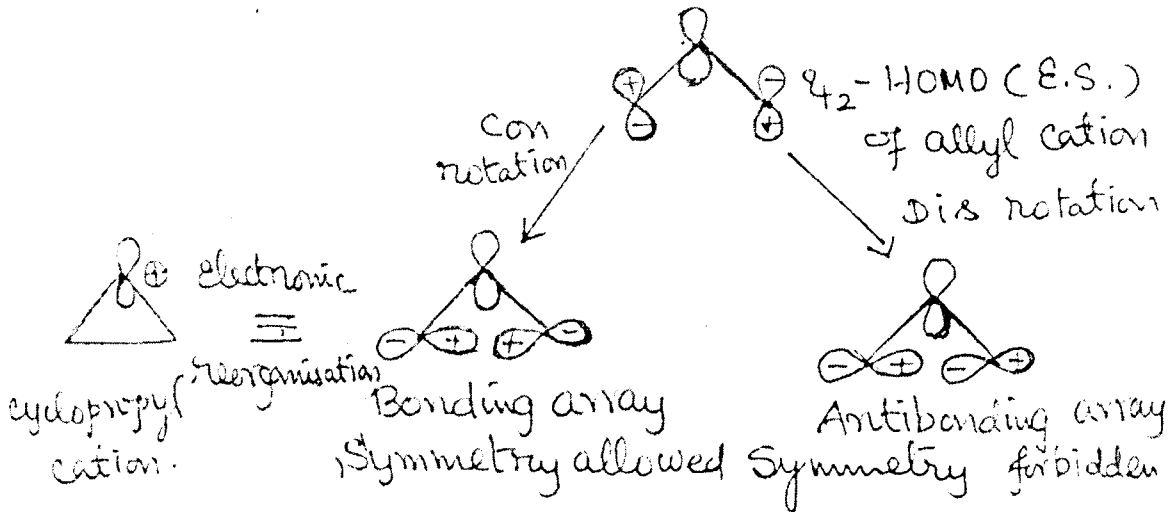
Under photochemical conditions promotion of one electron takes place from HOMO to LUMO ie. from ψ_1 to ψ_2 in this case. The excited state electronic configuration of allyl cation is,

$$\psi_1^1 \psi_2^1 \psi_3^0$$

The HOMO of allyl cation (E.S) is ψ_2

The LUMO of allyl cation (E.S) is ψ_3

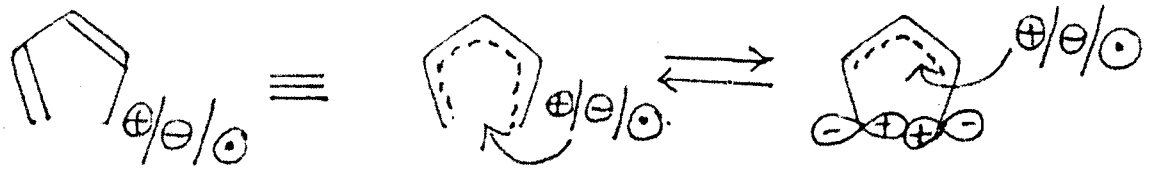
This cyclisation may be attempted as above.



The cyclisation of allyl cation to cyclopropyl cation is a symmetry allowed process via con rotation, under photochemical conditions, because it leads to a bonding array. Whereas that of the same symmetry is forbidden via dis rotation, under similar conditions, as it leads to an antibonding array.

For allyl anion /free radical cyclisation process can be written as before.

For pentadienyl system, out of the two Π- bonds one will be used for ring closure (σ- bond formation).The other double bond conjugates with the cation/anion/free radical to produce an allyl system in the cyclopentenyl system. (1σ bond + an allyl system).



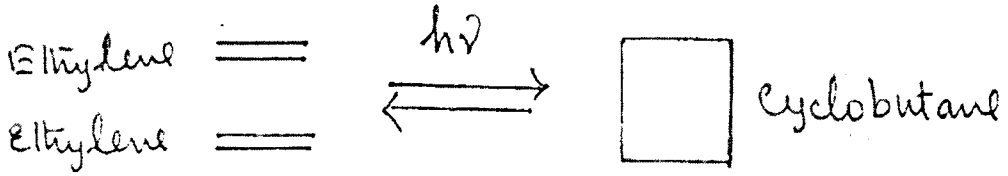
But for this everything else is the same for the pentadienyl system.
So, we can now write the orbital symmetry rules concerning the electrocyclic reaction.

Electron System	allowed	h ν allowed
4n	Con	Dis
4n+2	Dis	Con

CYCLOADDITION

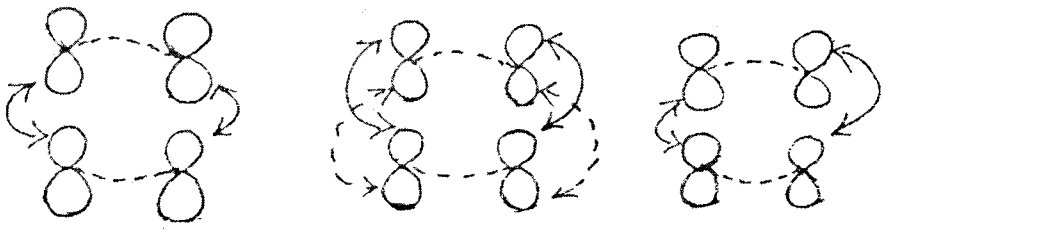
For any addition reaction to take place a donor and an acceptor are necessary. Here donor is the M.O. which can donate the electrons & the acceptor is the M.O. which accepts the electrons. Naturally in cycloadditions, one molecule has to play the roll of a donor and the other an acceptor. Which orbital can act as a donor? The one which can part with the electrons readily. i.e. HOMO which orbital will act as an acceptor? The one which is unoccupied. The natural choice is LUMO. So, for cycloaddition reactions, we have to consider the HOMO for one molecule and LUMO for the other.

The simplest cycloaddition reaction is the addition of one ethylene to another ethylene to give cyclobutane.



This reaction is possible only under photochemical conditions, To understand this, we need to have a look at the different modes of cycloaddition, just like the different modes of cyclisation (in electrocyclic reactions).The "p" orbitals are dump-bell shaped. During cycloaddition (i) the lower lobe of one molecule and the upper lobe of another molecule may interact to form a bond. This we call as 'supra' mode of addition (ii) the lower lobe/upper lobe of one molecule may interact with the lower lobe/upper lobe respectively of the second molecule. This we call as 'antara' mode of addition.

In cycloadditions two sigma bonds are formed, unlike are sigma bond in electrocyclic reactions. This gives rise to three possibilities which may be pictorially represented as below,

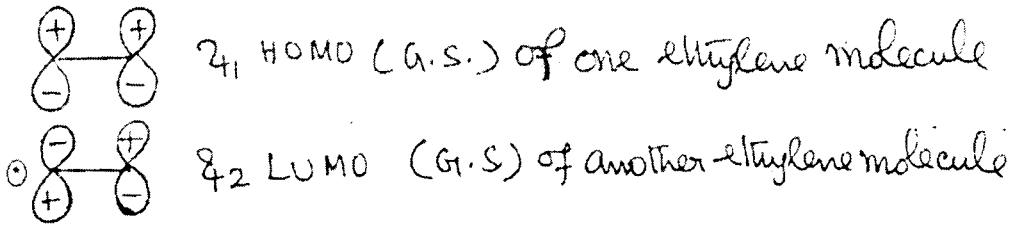


Coming back to the dimerisation of ethylene, the G.S. electronic configuration of ethylene is. $\psi_1^2 \psi_2^0$

HOMO(G.S.) of ethylene is ψ_1

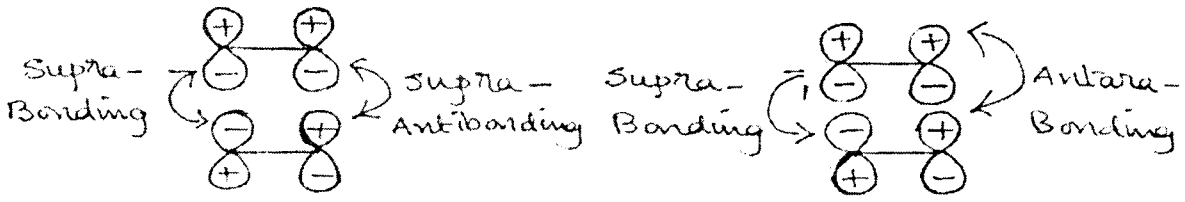
LUMO (G.S.) of ethylene is ψ_2

Because the other reactant is also an ethylene molecule, the HOMO & LUMO are likely to be the same. Let us see what happens when one ethylene adds to the other.



* In writing the lobes of the second molecule the plus/minus signs are written to match that of the first molecule. So that we can easily show the supra-supra mode, wherever it is possible. Again the readers should make one thing clear. The plus and minus signs are there to differentiate the upper and lower lobes of the 'p' orbital. Depending on our need we may start with plus sign or minus sign while drawing the M.O of a molecule .To avoid confusion normally we start with plus sign to represent the M.O.S of various molecules.

When the lobes of the two molecules meet on one side we see bonding array and the other side anti-bonding. So the dimerisation of ethylene cannot take place via the supra-supra (antara-antara) process under thermal conditions. Consider the other option, namely supra-antara



On symmetry considerations the supra-antara process is O.K. ie. on both sides we get bonding arrangement. But ethylene is a small molecule. So geometrical constraints will prevent this dismerisation taking place under thermal conditions. That is why we say that the dimerisation of ethylene is not at all possible under thermal conditions.

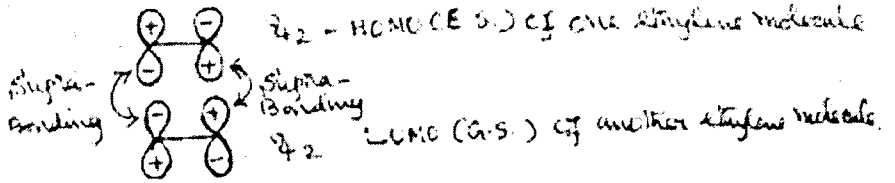
The reaction under photochemical condition is slightly different from electrocyclic reaction.This is because here we have atleast two reactants instead of one in the case of electrocyclic reaction. For energy transfer to take place, we consider one molecule under thermal or G.S. conditions and the other molecule under photochemical (or) E.S. conditions. For both the reactants we can have HOMO & LUMO under both thermal/photochemical conditions. This gives rise to four possibilities. Let us consider reactants A & B interact to give the products. Then the possibilities are,

Reactant A		Reactant B
HOMO (G.S)	+	LUMO (E.S)
LUMO (G.S)	+	HOMO (E.S)
HOMO (E.S)	+	LUMO (G.S)
LUMO (E.S)	+	HOMO (G.S)

To avoid embarrassments we consider that possibility in which the HOMO(E.S) is considered for the smaller among the two reactants.(Why should it be like that? For molecule like ethylene we can have only two M.O.S. In such a situation we cannot have LUMO (E.S) for ethylene. For this we wuld need a third M.O, which is out of question as far as ethylene is concerned)

What about the photodimaisation of ethylene?

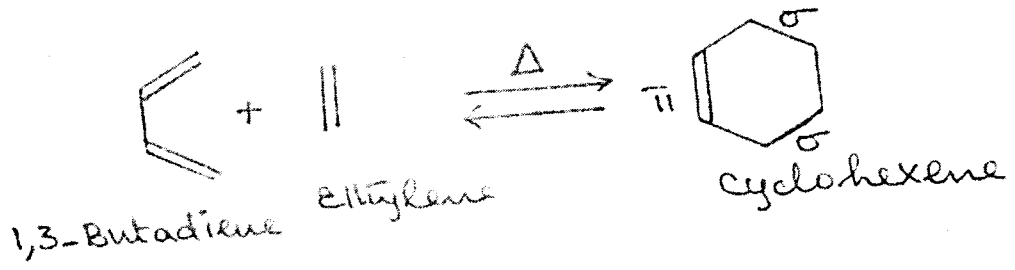
The E.S. electronic configuration of ethylene molecule is $\psi_{+1}^1 \psi_{+2}^1$. So the HOMO (E.S) of the excited ethylene is ψ_{+2}. The other ethylene in the G.S will have ψ_{+2} as the LUMO. (There are only two B-eletrons in ethylene. That goes to fill up ψ_{+1}.So ψ_{+2} is unoccupied under thermal conditions)



The interacting lobes in the suprabonds have bonding arrangements on either side.As a result the photodimerisation of ethylene is set to take place.

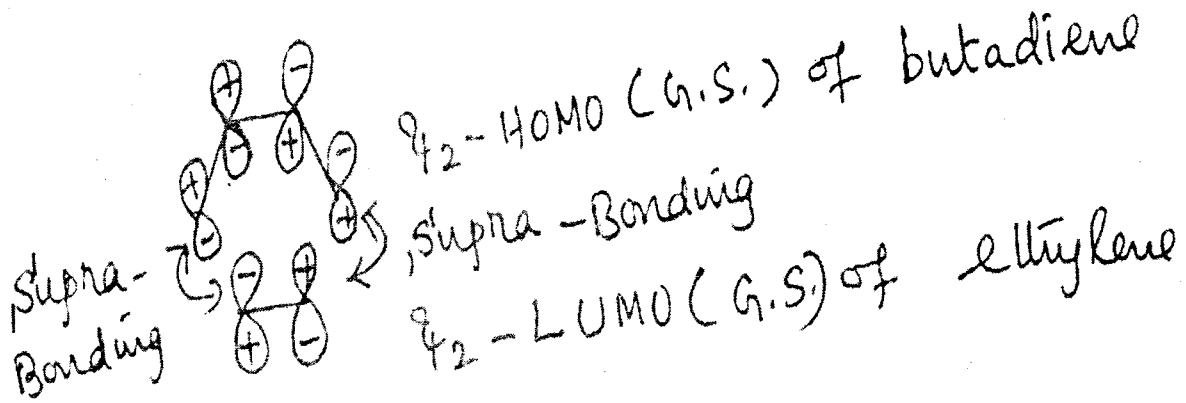
From what we have learnt so far, it is clear that the dimerisation of ethylene is possible only under photochemical conditions

The cycloaddition of ethylene to entadiene may be considered.



The G.S. electronic configuration of butadiene is $\psi_1^2 \psi_2^2 \psi_3^0 \psi_4^0$ and that of thylene is $\psi_1^2 \psi_2^0$.

The HOMO(G.S) of butadiene and LUMO (G.S) of ethylene may be taken to ormulate this cycloaddition.



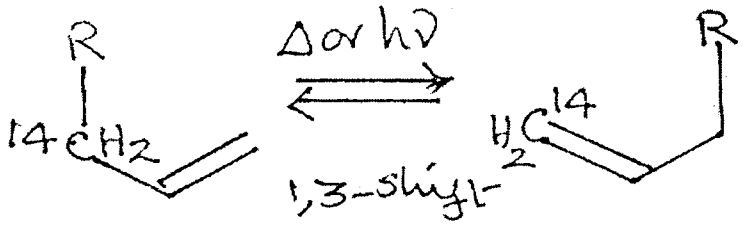
The cycloaddition of ethylene to butadiene is a symmetry allowed process under hermal conditions via supra-supra mode as it leads to bonding-bonding arrangement.

The selection rules for the cycloaddition reactions can be given as below:

Electron System	allowed	hν allowed
4n	Supra-Antara	Supra-supra
4n+2	Supra-supra	Supra-antara

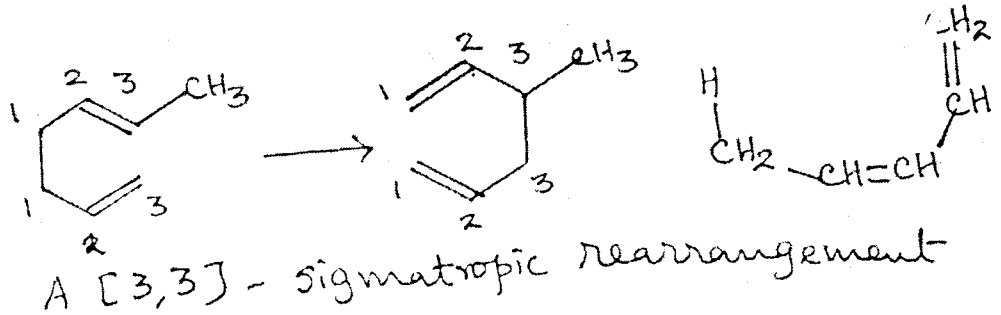
Sigmatropic rearrangement

In migration of an atom or group from one end of the polyene to the other end is called as simatropic rearrangement. The sigmatropic reaction given as [i,j] "i" refers to the initiation point and "j" refers to the terminus. The sigmatropic order is given as (i+j). Thus for a a[1,3]-sigmatropic reaction the order of the reaction is 1+3=4. In a way the sigmatropic order refers to the number of electrons actually involved in the reaction.



In cope rearrangement both ends of the bond are attached in new positions in the product. The cope rearrangement is an example of a sigmatropic rearrangement of order [3,3]. Sigmatropic rearrangement of this type involves the movement of a sigma bond across two parts of a polyene system. So the numbers of both termini are indicated.

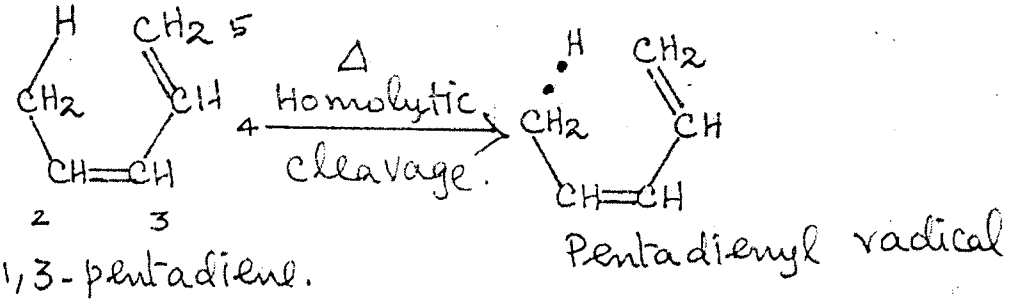
Thus migration in the 1,5-pentadienyl system below is a [3,3] sigmatropic rearrangement (cope rearrangement).



We can use the HOMO-LUMO approach to analyse the symmetry characteristics of sigmatropic rearrangements. In setting up the requisite frontier orbitals it is the sigma bond undergoing cleavage separates homolytically into two free radicals. The reader has to bear in mind that this is only a conceptual approach for the analysis and does not represent the actual concerted process.

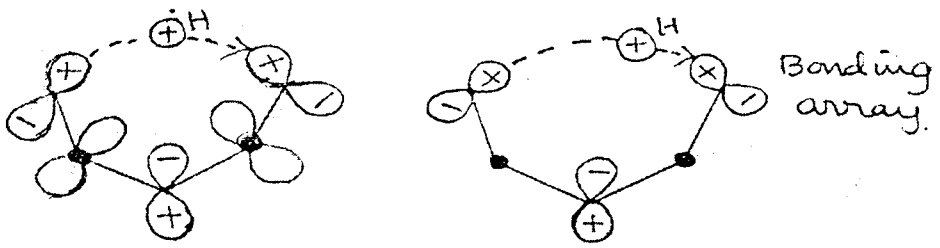
Though the cleavage has taken place, we say that the bonding character is maintained, between the "two separated sigma orbitals", throughout the migration process. If we donot imagine like this, it would be difficult for us to explain the stereochemistry of this reaction.

For a [1,5]-shift of a hydrogen atom, the pentadienyl system should form the pentsdienyl radical by the homolytic cleavage of the migrating C-H bond.



HOMOLYTIC

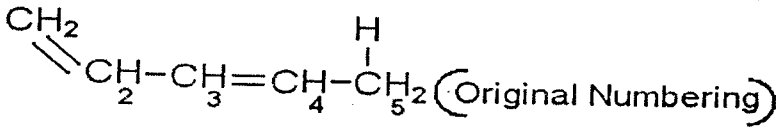
Now the homolytic cleavage of the C-H bond has given rise to a pentadienyl radical. The electronic configuration for the pentadienyl radical (G.S) is $\psi_1^2 \psi_2^2 \psi_3^1 \psi_4^0 \psi_5^0$, so the OMO (G.S) of pentadienyl radical is ψ_3.It is an odd numbered wave function and hence the end orbitals will be symmetric. Since the end orbitals are symmetric the migration can take place m the same side of the pi –system, which we refer as suprafacial migration.



The dotted lines indicate the bonding character (though they are supposed to be separated)

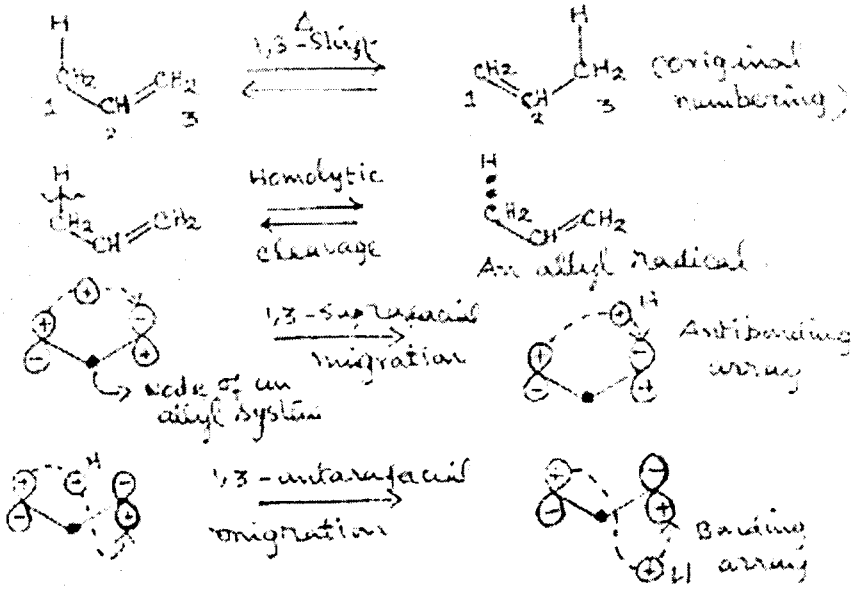
Since the migration terminus has the same symmetry as the migrating atom, these [1,5]-shift is an allowed process, suprafacially under thermal conditions.

Now electronic reorganisation takes place to give the new set of pi –bonds.

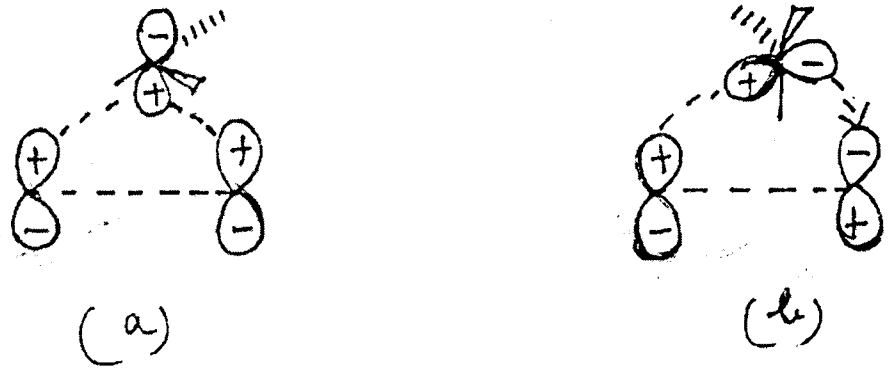


The G.S. electronic configuration of an allyl radical is $4_1^2\, 4_2^2\, 4_3^0$

The HOMO (G.S) of allyl radical is 4_2. This is an even numbered M.O. So the end orbitals will be antisymmetric. As a result the migration of hydrogen or the same face of the pi –system is not possible naturally the migration has to take place on to the bottom lobe.

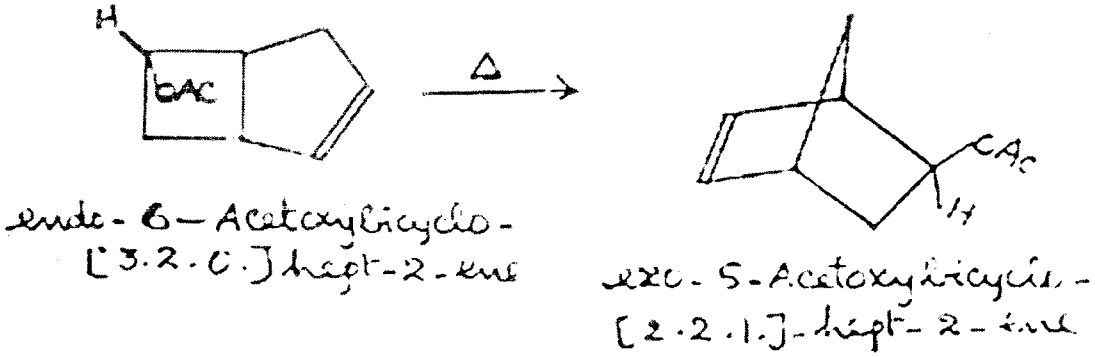


Such a migration of the atom from one face of the pi –system to the other, is termed as antarafacial. Thus for a [1,3]-shift the allowed mode of migration is antarafacial. This would be geometrically difficult for a concerted reaction and is not an experimentally observed process. When an alkyl group migrates, an additional aspect of stereochemistry must be considered. This is because the migrating hydrogen is envisioned with a symmetrical 1s orbital, the pathway of carbon migration involves electrons in a 'p' orbital. Orbital symmetry can be maintained by using either the same or opposite lobes of this 'p' orbital in bond breaking and bond making.

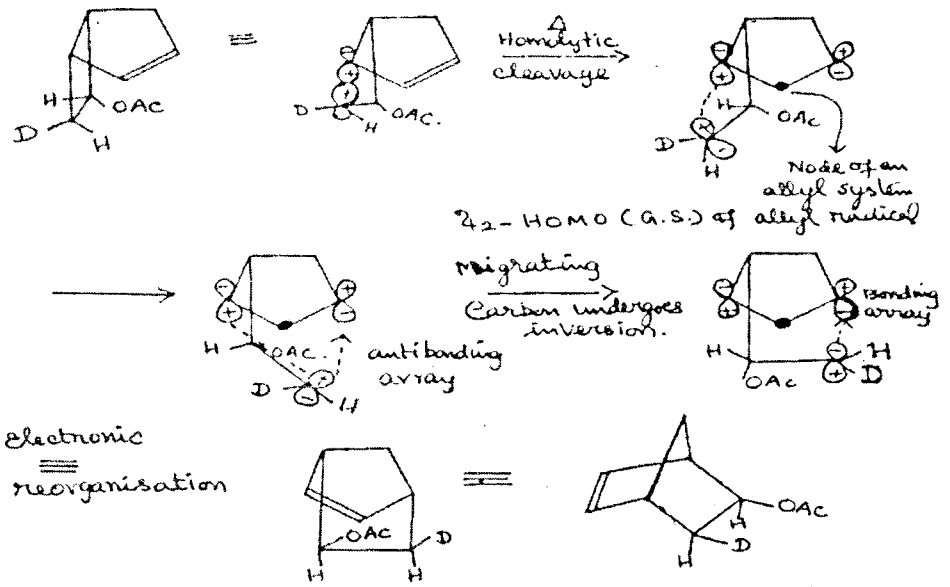


Pathway(a) is called as suprafacial migration. In pathway(b) there is inversion of the migrating carbon (to facilitate bond formation). Though the migration is suprafacial (i.e same face of the pi-system) the migrating carbon undergoes inversion. So the total migratiory process is termed as antatafacial.

The thermal isomerisation of endo-6-acetoxybiclo[3.2.0]-hept-2-ene to exo-5-acetoxy bicycle[2.2.1.] hept-2-ene is an example of this category.



The rearrangement, however proceeds with inversion at the carbon atom that moves. This inversion is shown by a denterium labeling experiment. The transformation with inversion is allowed because inversion permits smooth overlap of the carbon undergoing inversion with the HOMO(π_2) of the three-carbon unit, an allyl radical.



CORRELATION DIAGRAMS

(Longuet – Higgins)

Principle:

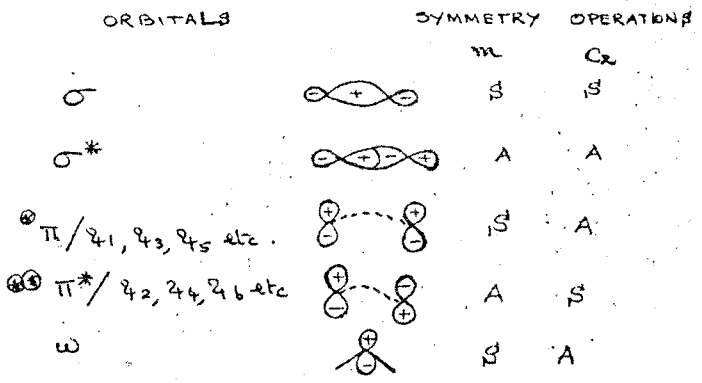
The symmetry elements characteristics of the reactants are preserved or conserved throughout the process and will be found in the products also.

Unlike the previous method, where we concentrated only on the HOMO-LUMO, this method takes all the orbitals into account. It not only examines the orbitals of the reactant polyene but also considers the orbitals of the product. This consideration of the orbitals of the product leads to a situation where it is known which reactant orbital gives rise to a specific product orbital. Such a representation is known as a correlation diagram and the whole method relies on a consideration of the basic symmetry of the product and the reactant orbitals. The basic thing, therefore, for the success of the approach is that there is no net change in the symmetry of the orbitals in moving from the reactant to the product or vice versa. Thus for a reaction to be concerted it must take place with the conservation of orbital symmetry.

Precisely for the same reason we cannot draw correlation diagrams for a sigmatropic reaction, because symmetry is not maintained throughout the reaction, although it does appear in the transition state. The starting material, for example, does not have σ or C_2 symmetry present in the transition state.(For consideration of symmetry of orbitals, in correlation diagram, we take into account only two symmetry operations of importance, either a mirror plane (m or σ) or a two-fold axis (C_2) relationship.

For the construction of the correlation diagram it is essential to have the symmetries of all the orbitals with respect to mirror plane and C_2 axis of symmetry.

*/** Since the end orbitals of all odd numbered wave functions are symmetric at the ends, they correspond to a Π orbital. This is possible because we preserve symmetry in drawing the M.O.S.



Again the end orbitals of all even numbered wave functions are antisymmetric at the ends, they correspond to a Π^* orbital.

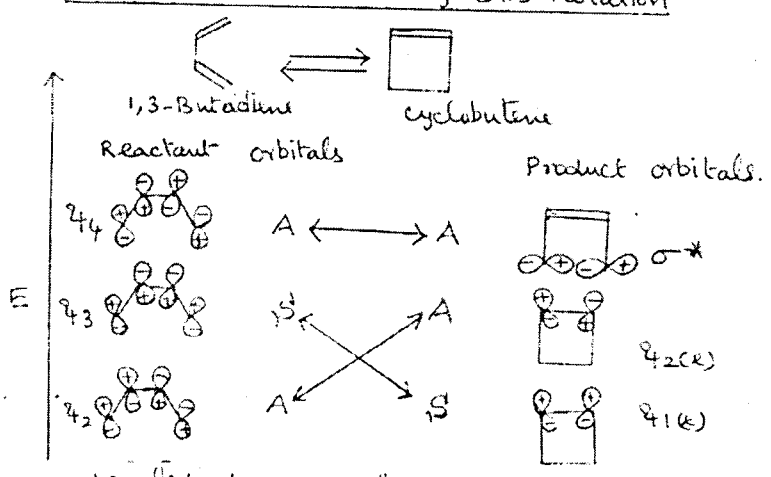
Orbital symmetry rules for the construction of correlation diagram:

1. Arrange the reactant and product orbitals in increasing order of energy along the reaction co-ordiante
2. Assign symmetry elements w.r.to m or C_2 symmetry as the case may be to the reactant and product orbitals.
3. Draw correlation lines between orbitals lying as close as possible along the reaction co-ordinate.
4. Each molecular orbital can accommodate a maximum of 2 electrons only.
5. Before filling a high energy orbital, the low energy orbital must be completely filled.
6. Now, if the expected and actual orbital symmetries (including electronic configuration) of the reactant and product orbitals correlate with each other, then the reaction is said to be symmetry allowed. If the orbital symmetries do not correlate with each other, then the reaction is said to be symmetry forbidden.
7. Under photochemical conditions, promotion of one electron takes place from the HOMO to LUMO along the reaction co-ordinate (both on the reactant and product sides)

The T.S. for the disrotation resembles that of a mirror plane and that of con rotation resembles C_2 symmetry. So while constructing correlation diagrams for disrotation we consider mirror plane symmetry for the reactant and product orbitals. Similarly for con rotation we consider C_2 symmetry for the reactant and product orbitals.

With this basic idea, we can construct the correlation diagram for the electrocyclic and cycloaddition reactions.

We can consider the dis rotatory closure of butadiene to cyclobutene. The reactant orbitals are ψ_1, ψ_2, ψ_3 and ψ_4. The product orbitals are σ, $\psi_{1(e)}$, (or) Π, $\psi_{2(e^-)}$ (or) Π^*, σ^*. (In electrocyclic reactions the cyclised product invariably has a Π- system either conjugated or simple. Of course in an allyl system we will have only a non-bonding orbital and not a Π- system. For simplicity, we consider the molecular orbitals i.e. ψ_1, ψ_2 etc of the Π- system rather than the Π-bond themselves. In order to differentiate between the reactant MOS and the MOS which are embedded in the product orbitals, the latter is given a suffix, depending on the Π-system. For example in cyclobutene we have $\psi_1(e)$ and $\psi_2(e)$, because the Π-system is ethylene. In cyclohexadiene we have $\psi_{1(b)}$, $\psi_{2(b)}$, $\psi_{3(b)}$ and $\psi_4(b)$ because the pi-system is butadiene. Similarly for cycloctatriene there are $\psi_1(h)$ $\psi_2(h)$ $\psi_3(h)$ $\psi_4(h)$ $\psi_5(h)$ and $\psi_6(h)$ because the pi- system is hexatriene.



Simplified correlation diagram for the cyclisation of butadiene to cyclobutene

G.S. electronic configuration of

reactant orbitals	product orbitals
$\psi_1^2 \psi_2^2 \psi_3^0 \psi_4^0$	$\sigma^2 \psi_{1(e)}^2 \psi_{2(e)}^0 \sigma^{*0}$ (expected)
-do-	$\sigma^2 \psi_{2(e)}^2 \psi_{1(e)}^0 \sigma^{*0}$ (actual)

The expected and actual orbital symmetries of the reactant and product orbitals symmetries of the reactant and product orbitals do not correlate with each other. So the disrotatory closure of butadiene to cyclobutene is a symmetry forbidden process under thermal conditions.

Under photochemical conditions, promotion of one electron takes place from HOMO to LUMO ie. From ψ_2 to ψ_3 on the reactant side and from $\psi_{1(e)}$ to $\psi_{2(e)}$ on the product side. Thus the excited state electronic configuration of

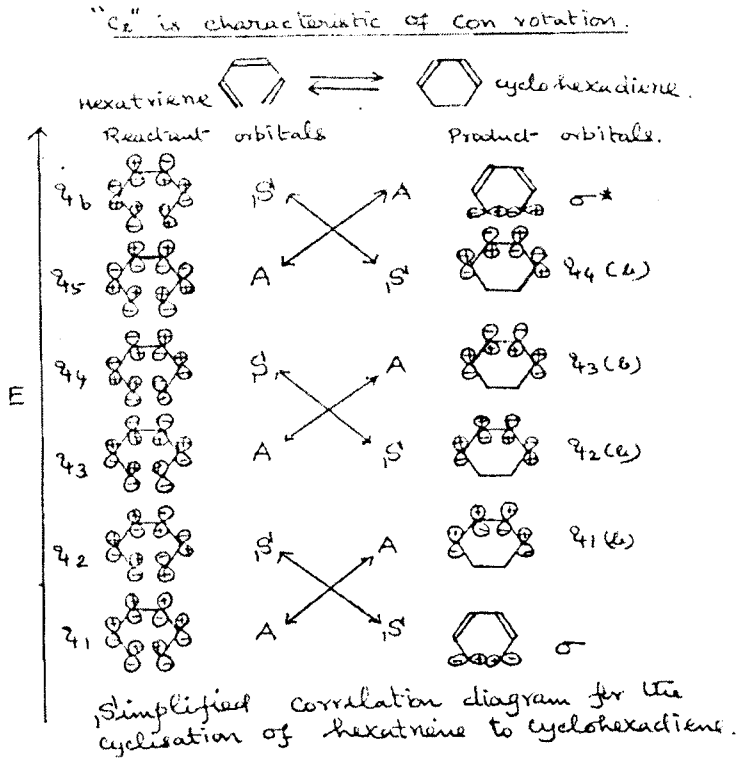
Reactant Orbitals	Product Orbitals
$\psi_1^2 \psi_2^1 \psi_3^1 \psi_4^0$	$\sigma \psi_{1(e)}^1 \psi_{2(e)}^1 \sigma^{*o}_{(exp)}$
-do-	$\sigma \psi_{2(e)}^1 \psi_{1(e)}^1 \sigma^{*o}_{(actual)}$

The expected and actual orbital symmetries of the reactant and product orbitals correlate with each other. So the cyclisation of butadiene to cyclobutene is a symmetry allowed process under photochemical conditions.

The same correlation diagram can be used for con rotation but for the symmetry of the orbitals, we have to use the C_2 symmetry.

We shall consider next, the cyclisation of hexatriene to cyclohexadiene. The reactant orbitals are $\psi_1, \psi_2, \psi_3, \psi_4, \psi_5$ and ψ_6 and the product orbitals are σ, $\psi_{1(b)}$, $\psi_{2(b)}$, $\psi_{3(b)}$, $\psi_{4(b)}$ and σ^*

Electronic Configuration



C.S. electronic configuration of

reactant orbitals

$\psi_1^2\ \psi_2^2\ \psi_3^2\ \psi_4^0\ \psi_5^0\ \psi_6^0$

-do-

product orbitals

$\sigma^2\ \psi_{1(s)}^2\ \psi_{2(a)}^2\ \psi_{3(s)}^0\ \psi_{4(a)}^0\ \sigma^{*0}$

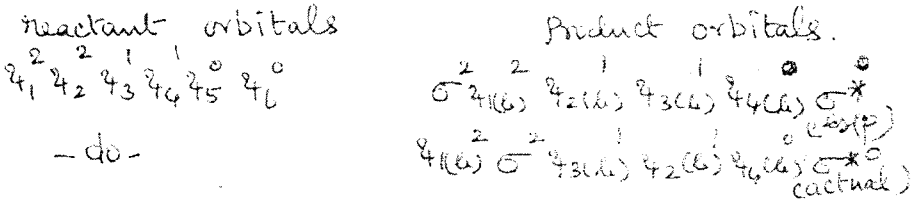
$\psi_{1(s)}^2\ \sigma^2\ \psi_{3(s)}^2$ (i.e. exp)

$\psi_{2(a)}^0\ \sigma^{*0}\ \psi_{4(a)}^0$

(actual)

The expected and actual orbital symmetries of the reactant and product orbitals do not correlate with each other. So the cyclisation of hexatriene to cyclohexadiene is a symmetry forbidden process under thermal conditions via con rotation.

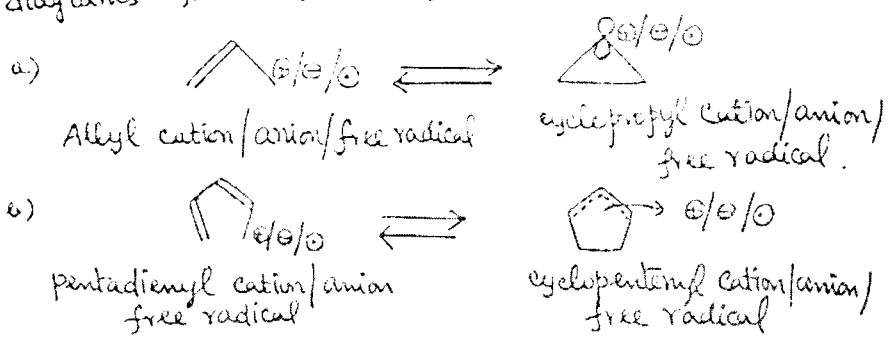
Under photochemical conditions promotion of one electron takes place from HOMO to LUMO. i.e. from ψ_3 to ψ_4 along the reactant side and $\psi_{2(b)}$ to $\psi_{3(b)}$ along the product side. Thus the excited state electronic configuration of



The expected and actual orbital symmetries of the reactant and product orbitals correlate with each other. So the cyclisation of hexatriene to cyclohexadine is symmetry allowed under photochemical conditions via con rotation.

Similarly with respect to mirror plane symmetry the correlation diagram can be drawn for the above reaction, we get the same result with the correlation diagram method as we did in FMO method.

The learner may try the correlation diagrams for the following reactions.



In both the cases the correlation diagram will be the same for all the three categories (cation/ anion/free radical). The only difference is the number of electrons.

Correlation diagrams for cycloaddition

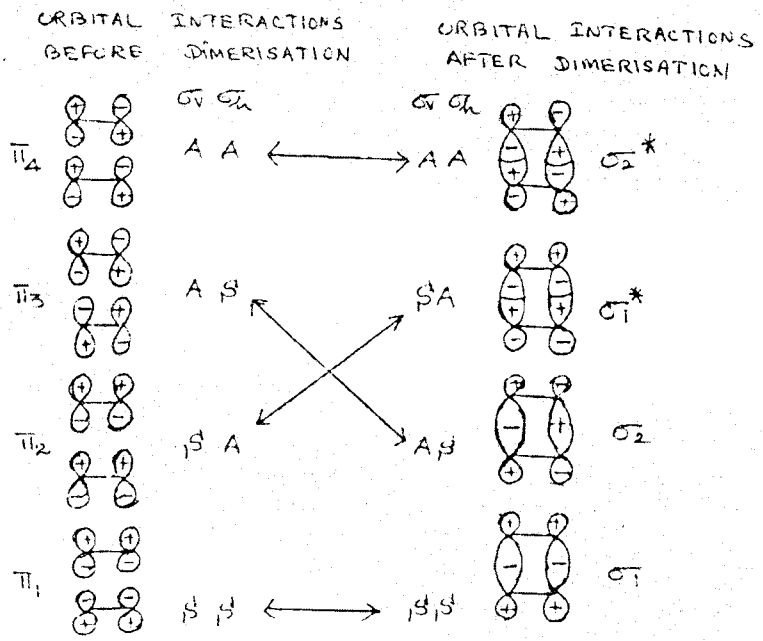
Here we shall consider two cycloaddtion reactions, one for the 4n electron category and the other for the 4n+2 electron category. For the former we shall consider the dimerisation of ethylene to give cyclobutane and for the latter the famous DAR between butadiene and ethylene is considered. Unlike the electrocyclic reaction, here sigma bonds are to be formed. In the construction of the correlation diagram for the dimerisation of ethylene, a few extra points are to be considered.

(i) since both the reacting molecules are the same, we cannot distinguish th orbitals of one molecule with other for energy considerations. So what we will do is, we will consider the orbital interactions of both the ethylene molecules before and after dimerisation.

(ii) Because of the high symmetric nature of both the reactants and product, we will consider two mirror planes, one vertical and the other horizontal.

The π- MOs(ψ_1) of both the ethylene can interact in a bonding manner (bonding + bonding ⟶ bonding ie. π_1) and antibonding manner (bonding + bonding⟶ antibonding i.e. π_2). Similarly the bonding and antibonding interactions of the π* MOs (ψ_2) of both the ethylene can give rise to π_3 and π_4 respectively. This order of energy is to be expected, considering their basic status of bonding and antibonding nature.

Out of the two sigma bonds the one which is lower in energy comes from the bonding set of orbitals and the other from the antibonding set of orbitals.



G. S. electronic configuration of orbitals

Before dimerisation

$\pi_1^2\ \pi_2^2\ \pi_3^0\ \pi_4^0$

-do-

After dimerisation.

$\sigma_1^2\ \sigma_2^2\ \sigma_1^{*0}\ \sigma_2^{*0}$ (Exp)

$\sigma_1^2\ \sigma_1^{*2}\ \sigma_2^0\ \sigma_2^{*0}$ (actual)

The expected and actual orbital symmetries before and after dimerisation do not correlate with each other. So the dimerisation of ethylene to cyclobutane is a symmetry forbidden process under thermal conditions via s-s process.

Under photochemical conditions promotion of one electron takes place from HOMO to LUMO i.e. from Π_2 to Π_3 on the reactant side and σ_2 to σ_1^* on the product side. So the excited state electronic configuration,

Before dimerisation **after dimerisation**

$\Pi_1^2 \Pi_2^1 \Pi_3^1 \Pi_4^0$

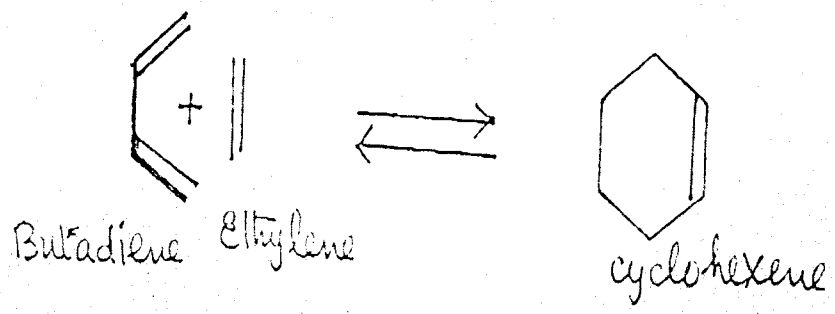
-do-

$\sigma_1^2 \sigma_2^1 \sigma_1^{*1} \sigma_2^{*0}$ (exp)

$\sigma_1^2 \sigma_1^{*1} \sigma_2^1 \sigma_2^{*0}$ (actual)

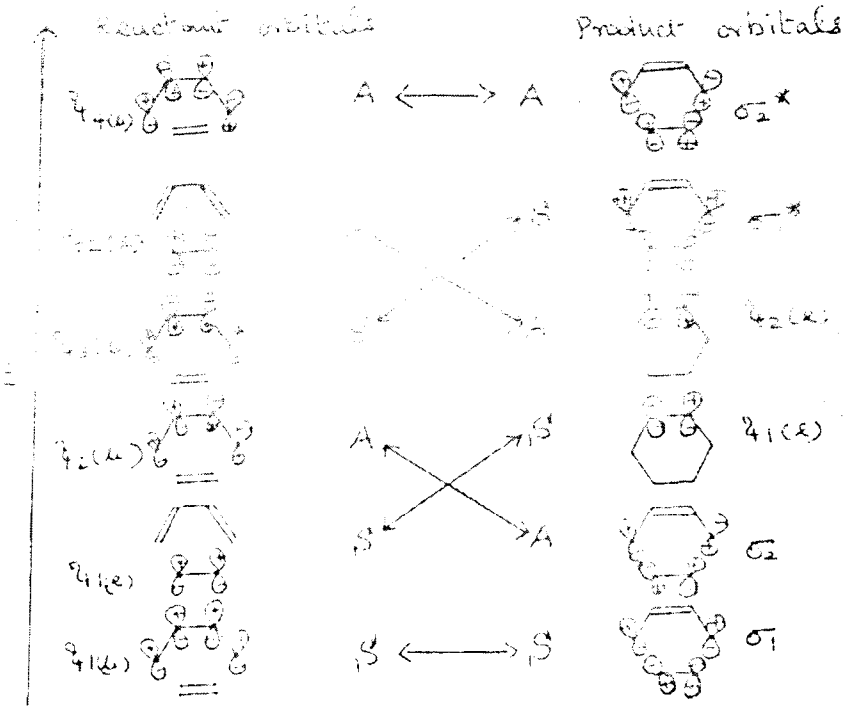
The expected and actual orbital symmetries before and after dimersation correlate with each other. So the dimerisation of ethylene to cyclobutane is a symmetry allowed process under photochemical conditions via s-s process.

In the cycloaddition reaction between butadiene and ethylene we consider only the vertical mirror plane symmetry. This is because here we are dealing with two different molecules.



[The molecule for which symmetry is considered will be shown with its MOs while the other molecule will be drawn plain. Thus when we consider the MOs of butadiene the ethylene will be plainly written and vice-versa.

As with the dimerisation of ethylene one sigma bond comes from the bonding set and the other from an antibonding set.]



G.S.electronic configuration of

Reactant orbitals

$\psi_{1(a)}^2\ \psi_{1(s)}^2\ \psi_{2(a)}^2\ \psi_{3(a)}^0\ \psi_{2(s)}^0\ \psi_{4(a)}^0$

Product orbitals

$\sigma_1^2\ \sigma_2^2\ \psi_{1(s)}^2\ \psi_{2(s)}^0\ \sigma_1^{*0}\ \sigma_2^{*0}$ (exp)

– do –

$\sigma_1^2\ \psi_{1(s)}^2\ \sigma_2^2\ \sigma_1^{*0}\ \psi_{2(s)}^0\ \sigma_2^{*0}$ (actual)

The expected and actual orbital symmetries of the reactant orbitals and product orbital correlate with each other. So the cycloaddition of ethylene to butadiene to give cyclohexene is a symmetry allowed process under thermal conditions via S-S process. This is a case of $\Pi 4s + \Pi 2s$

Under photochemical conditions promotion of one electron takes place from HOMO to LUMO i.e. from $\psi_{2(b)}$ to $\psi_{3(b)}$ along the reactant side and from $\psi_{1(e)}$ to $\psi_{2(e)}$ along the product side. Thus the excited state electronic configuration of

Reactant orbitals product orbitals

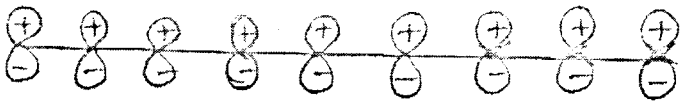
$\psi_1^2(L)\,\psi_1^2(R)\,\psi_2^1(L)\,\psi_3^1(L)\,\psi_2^0(R)\,\psi_4^0(L)$ $\sigma_1^2\sigma_2^2\psi_1^1(R)\,\psi_2^1(R)\,\sigma_1^{*0}\,\sigma_2^{*0}$ (Exp)

- do - $\sigma_1^2\,\psi_1^2(R)\,\sigma_2^1\,\sigma_1^{*1}\,\psi_2^0(R)\,\sigma_2^{*0}$ (Actual)

The expected and actual orbital symmetries of the reactant and product orbitals do not correlate with each other. The cycloaddition of ethylene to butadiene to give cyclohexene is a symmetry forbidden process under photochemical conditions via s-s process.
Here too, we get the same results as we did with the FMO method.

Huckel – Mobius Method

In this method, in applying the orbital symmetry principle we are not concerned with ground states, but with transition states, i.e we do not examine the molecular orbitals themselves, but rather the 'P' orbitals before they overlap to form the molecular orbitals.



Arrange the P-orbitals in a row. Assign signs in the best manner possible for overlap. Such a set of orbitals are called as basis sets. In investigating the possibility of a concerned reaction, we put the basis sets into the position they would occupy in the transition state. We look for sign inversions in the T.S. If there are zero or even number of sign inversions, they are called as Huckel systems. And if there are odd number of sign inversions, they are called as Mobius systems(Similar to Mobius strip, the one-sided surface, mathematical model. It can be obtained by giving a twist of 180° to a strip of paper and join the ends).

Now the orbital symmetry rules can be predicted as follows.

A thermal pericyclic reaction involving a Huckel system is allowed only if the total number of electrons is 4n+2. A thermal pericyclic reaction involving a Mobius system is allowed only if the total number of electrons is 4n. For photochemical reactions these rules are reversed.

These rules are given on the basis of the statements given by the following scientists.

HUCKEL:

A cyclic planar conjugated polyene with 4n+2 electrons will be aromatic.

Mobius:

Systems with 4n electrons will be aromatic, if they have odd nodes.

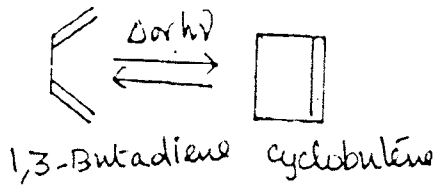
Zimmermann:

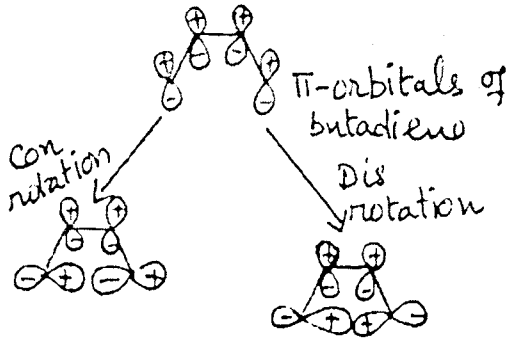
A thermal pericyclic change leading to aromatic T.S. will be symmetry allowed.

This orbital symmetry rule may be applied to the three classes of pericyclic reactions.

Electrocyclic reaction:

Cyclisation of butadiene to cyclobutene





1node
Mobius System
4 electrons
Aromatic T.S
Thermally allowed

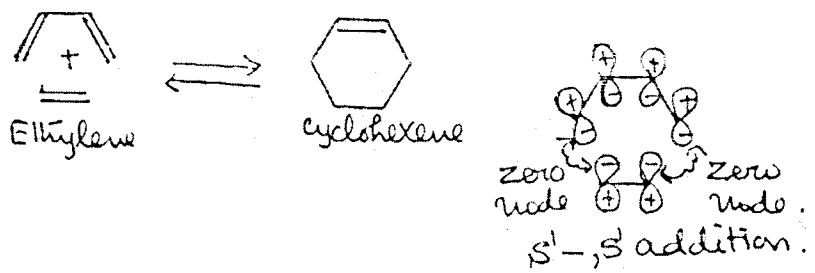
zero node
Huckel System
4n+2 electrons
Antiaromatic T.S.
Photochemically allowed

Con rotatory closure of butadiene to cyclobutene is a symmetry allowed process under thermal conditions, because it leads to an aromatic T.S.(odd mode, 4n electrons, Mobius system).

Disrotatory closure of butadiene to cyclobutene is a symmetry allowed process under photochemical conditions, because it leads to an antiaromatic T.S. (Zero node, 4n electrons, Huckel system)

Cycloaddition Reaction

The cycloaddition of ethylene to butadiene to give cyclohexene may be given as follows:

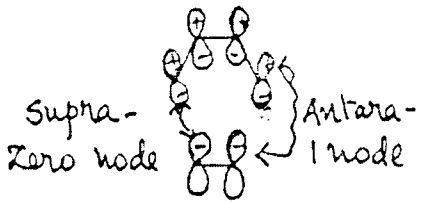


The cycloaddition of ethylene to butadiene via S-S process is symmetry allowed under thermal conditions, because it leads to an aromatic T.S. (The total number of nodes is zero node, 4n+2 electrons, Huckel system, Aromatic T.S.)

Total number of nodes = Zero + Zero = Zero node

Huckel System
4n+2 electrons
Aromatic T.S.
Thermally allowed.

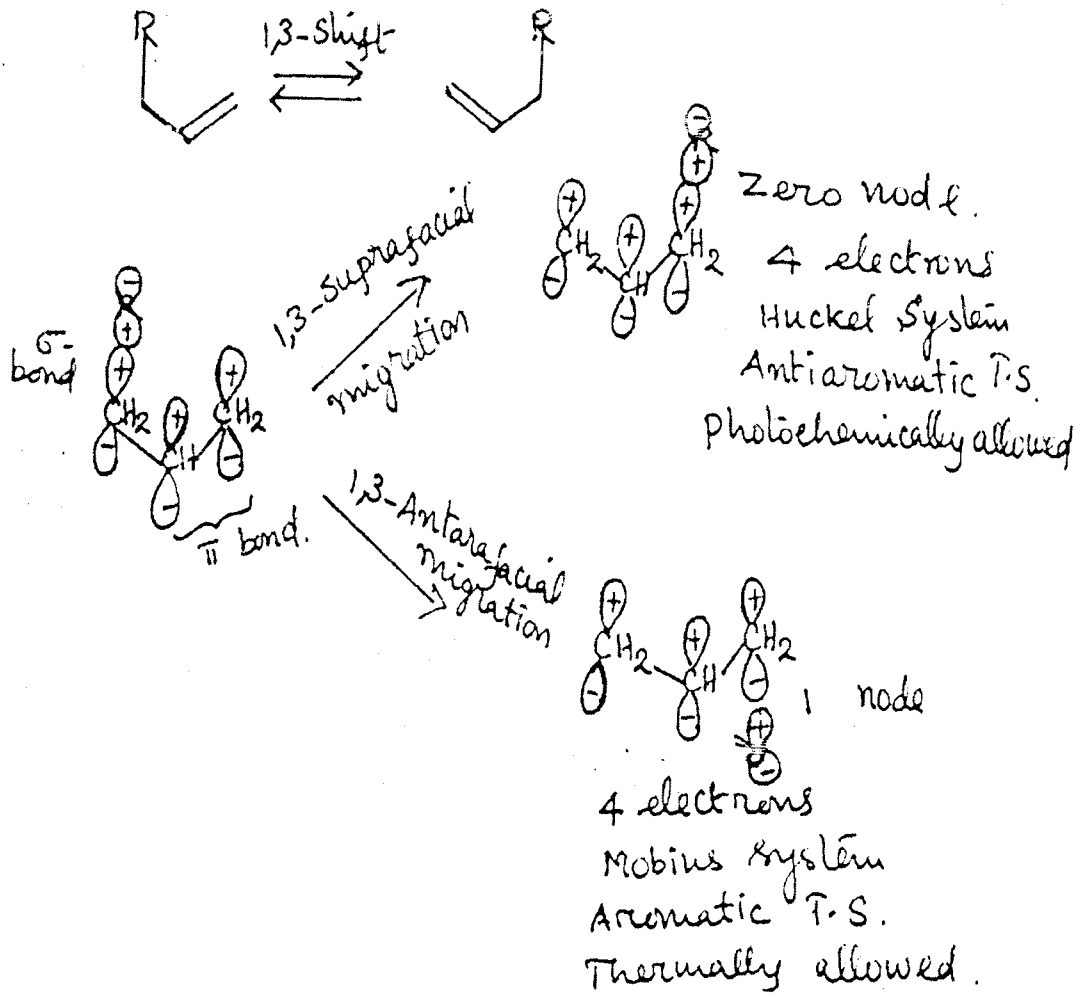
The cycloaddition of ethylene to butadiene via S-A process is symmetry allowed under photochemical conditions, because it leads to an antiaromatic T.S(Total number of nodes is 1, 4n+2 electrons, Mobius system, antiaromatic T.S.)



Total number of nodes = Zero + 1 = 1 node

Mobius System ; 4n+2 electrons

Aromatic T.S. ; photochemically allowed



1,3-suprafacial migration is a symmetry allowed process under photochemical conditions because it leads to an antiaromatic T.S.(4 electrons, zero node, Huckel system.)

1,3-antarafacial migration is a symmetry allowed process under thermal conditions because it leads to an aromatic T.S. (4 electrons,1 node, Mobius system).

Molecular Rearrangements

Introduction:

Generally in a rearrangement reaction a group moves from one atom to another in the same molecule. Most of these migrations take place from one atom to an adjacent one (called 1,2-shofts), but some are over longer distances.

The migration can be of three types

a) Nucleophilic (or) anionotropic rearrangement (here the migrating group moves with its electron pair).
b) Electrophilic or cationotropic rearrangements (here the migrating group moves without its electron pair).
c) Free radical rearrangements (here the migrating group moves with one electron only).

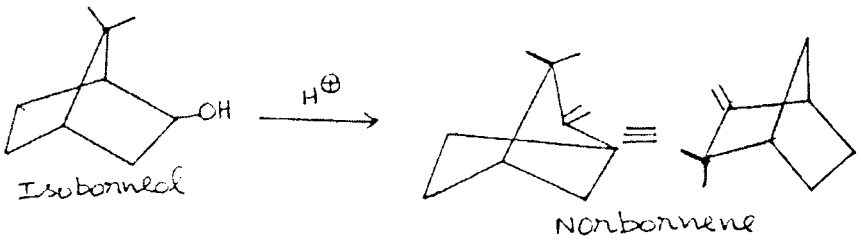
Reactions which follow cyclic transition states do not fall under these categories.

Depending upon the nature of the migrating group, under each category, their ability to move from one atom to another in the molecule may vary. This ability of the migrating group in a rearrangement reaction is referred to as the migratory aptitude of groups. This we shall discuss as and when we proceed with the mechanisms of various rearrangements. This is because the migratory aptitude of a group discussed for one reaction may not be applicable as it is for another reaction.

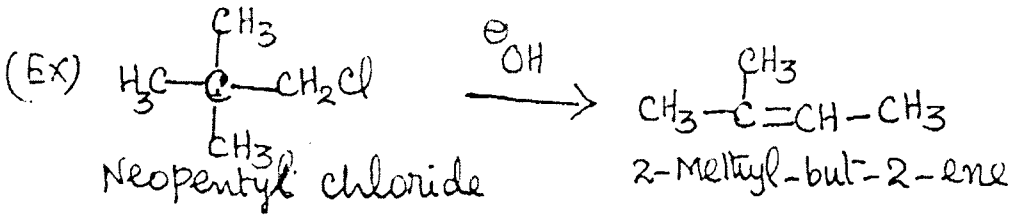
Wagner-Meerwein Rearrangement:

β- alkyl (or) aryl substituted (especially di or tri substituted) alcohols on treatment with acid undergo a rearrangement, called Wagner-Meerwein rearrangement.

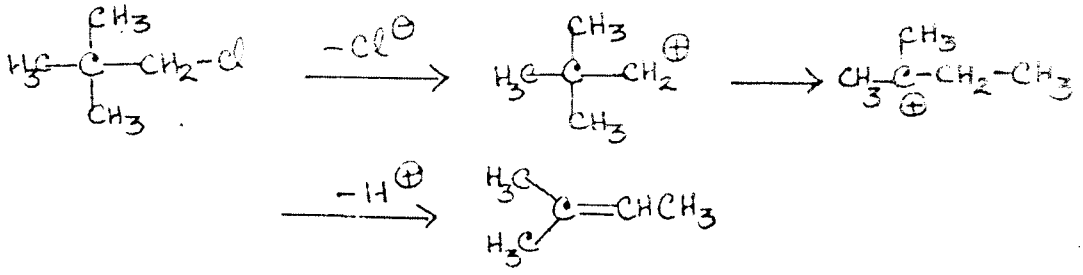
Wagner-Meerwein rearrangements were first discovered in the bicyclic terpenes **(ex)**



The leaving group need not always be water, but can be any departing species whose loss creates a carbocation

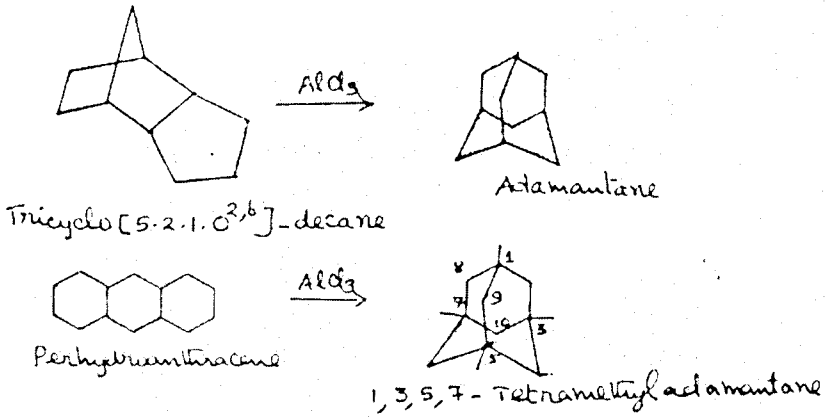


Initial ionisation gives a primary carbonium ion, which rearranges to a tertiary carbonium ion. The latter loses a proton to give the olefin (Saytzeff's rule).

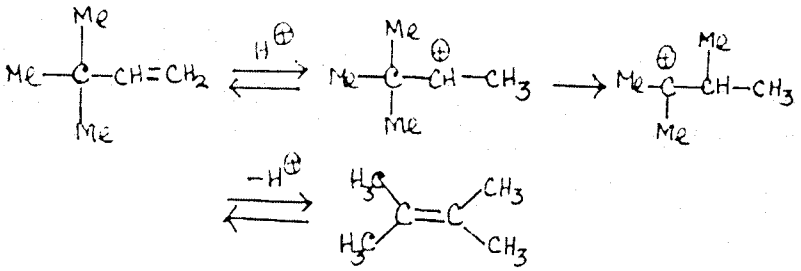


The direction of rearrangement is usually towards the most stable carbocation, which is tertiary > secondary > primary. The term "Wagner-Meerwein rearrangement is not precise. Some use it to refer to the pinacol-pinacolne rearrangement. Some use it only when an alcohol is converted to a rearranged olefin. Nametkin rearrangement is used to refer to the migration of a methyl group (in terpene chemistry).

An important application of this rearrangement is the conversion of tricyclic hydrocarbons into adamantane and its derivatives, under the influence of Lewis acids, like $AlCl_3$ and a small amount of initiator.



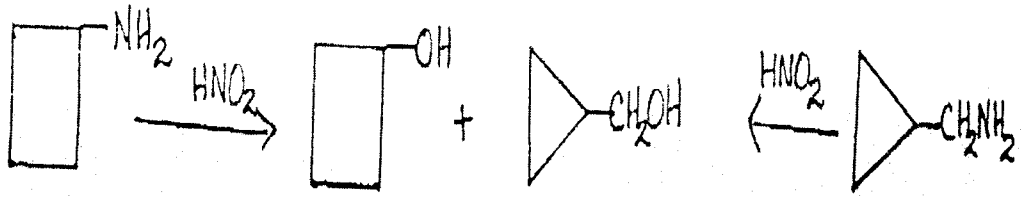
Wagner-Meerwein rearrangement is usually nucleophilic in nature.
Protonations of alkenes can also lead to WMR as in the following case.



This relatively ready rearrangement can be a nuissance in the preparative addition of acids, eg. Hydrogen halides to alkenes, (or) in their acid catalysed hydration. Mixed products that are difficult to separate may result or, in unfavourable cases, practically none of the desired product may be obtained.

Demjanov rearrangement:

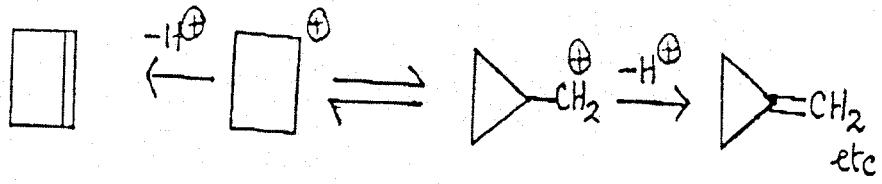
Rearrangements involving the carbocation formed by the diazotisation of an amine is called as Demjanov rearrangement. Eg. Cyclobutylamine and cyclopropylmethylamine give similar mixtures of the two alcohols on treatment with nitrous acid.



In the former case ring contraction, producing a ring that is one carbon smaller than the original.

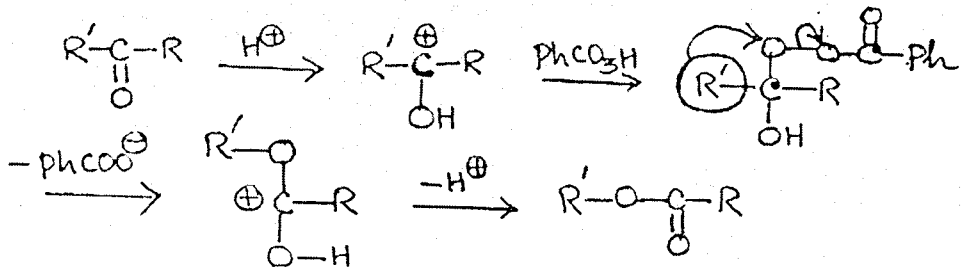
In the latter case a positive charge is placed on a carbon α- to an alicyclic ring. This leads to ring expansion.

The new carbocation, and the old one, may then give products by combination with a nucleophile (e.g) the alcohols shown above); or by elimination.



Baeyer – Villiger Oxidation:

The oxidation of a ketone to ester by treatment with peracids, in the presence of acid catalysts, is called as Baeyer-Villiger oxidation. Hydrogen peroxide, perbenzoic or peracetic acid may be used. But peroxytrifluoroacetic acid with disodium hydrogen phosphate has been found to be a good reagent. The reaction is rapid and clean, giving high yields of product. The following is the mechanism for this reaction.



Evidence:

1.When benzophenone-^{18}O was subjected to this reaction, it gave ester entirely labeled in the carbonyl oxygen, with none in the alkoxy oxygen.

2.Carbon-14 isotope-effect studies on acetophenone showed the aryl migration in the rate determining step. This demonstrates that migration of aryl group is concerted with departure of OCOph (It is hardly likely that migration would be the slow step if the leaving group departed first to give anion with a positive charge on an oxygen atom, which would be a highly unstable species) Further a chiral R' is found to migrate with its configuration unchanged.

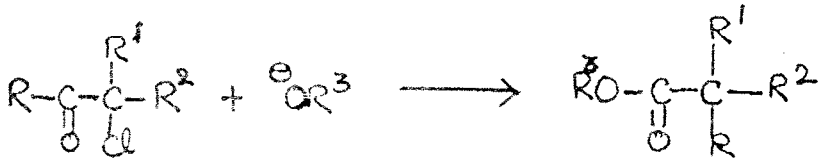
For unsymmetrical ketones the approximate order of migration is tertiary alkyl>secondary alkyl, aryl>primary alkyl >methyl.

The migrating ability of aryl groups is increased by electron-donating and decreased by electron-withdrawing substituents.

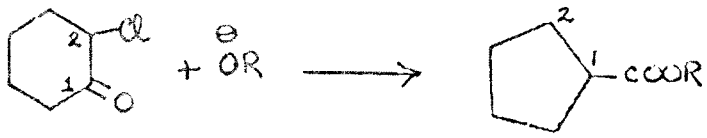
One useful application of this reaction is the preparation of lactones from cyclic ketones.

FAVORSKI REARRANGEMENT:

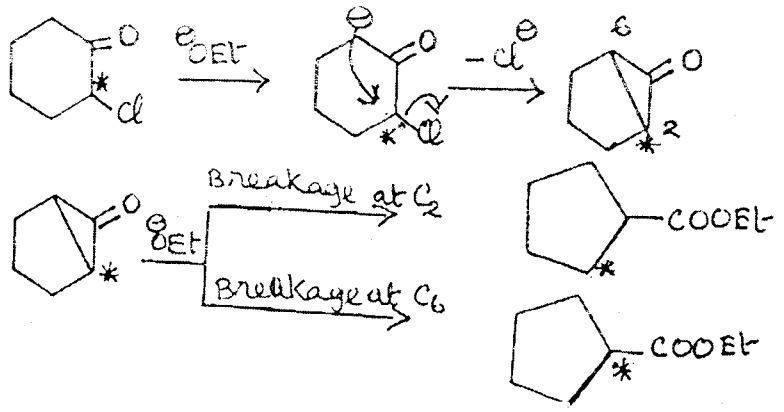
α – Halo ketones when heated with alkoxide ions give rearranged esters. This reaction is known as favorski rearrangement.



If hydroxide ion is used then the product is an acid and not ester. Cyclic α - halo ketones under similar conditions give products with ring contraction.

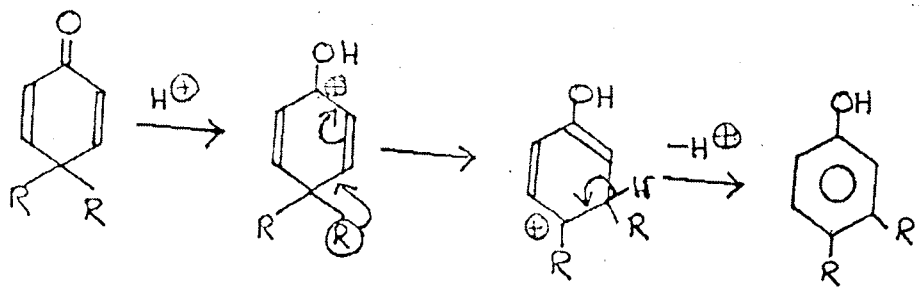


Labeling experiments with the ketone labeled with C14 at the chlorinated carbon, showed half of the labeled carbon at C_α in the ester and the other half at C_β . This suggests the intervention of a symmetrical intermediate in which C_α and C_β are equivalent. So a possible mechanism for the above observation is as follows:



DIENONE-PHENOL REARRANGEMENT:

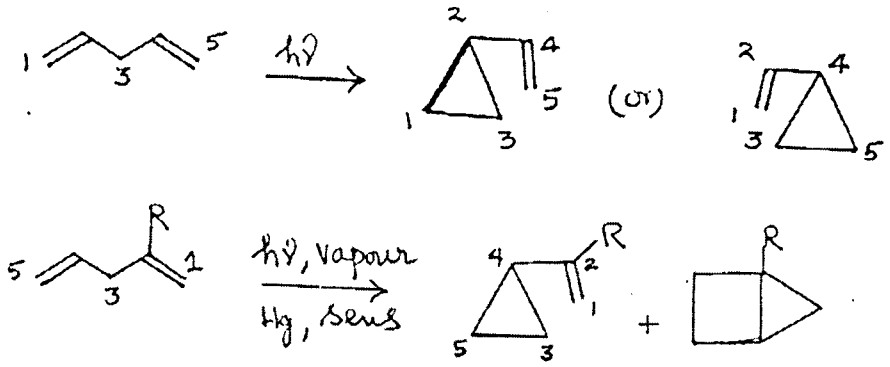
p-disubstituted cyclohexadienone on acid treatment give a phenol derivative, with the migration of one of the substituent to the meta-position.



The driving force in this reaction is of course, aromatisation of the dienone. The dienone nucleus embedded in other compounds can also undergo this rearrangement.

Di- Π –METHANE or ZIMMERMAN REARRANGEMENT

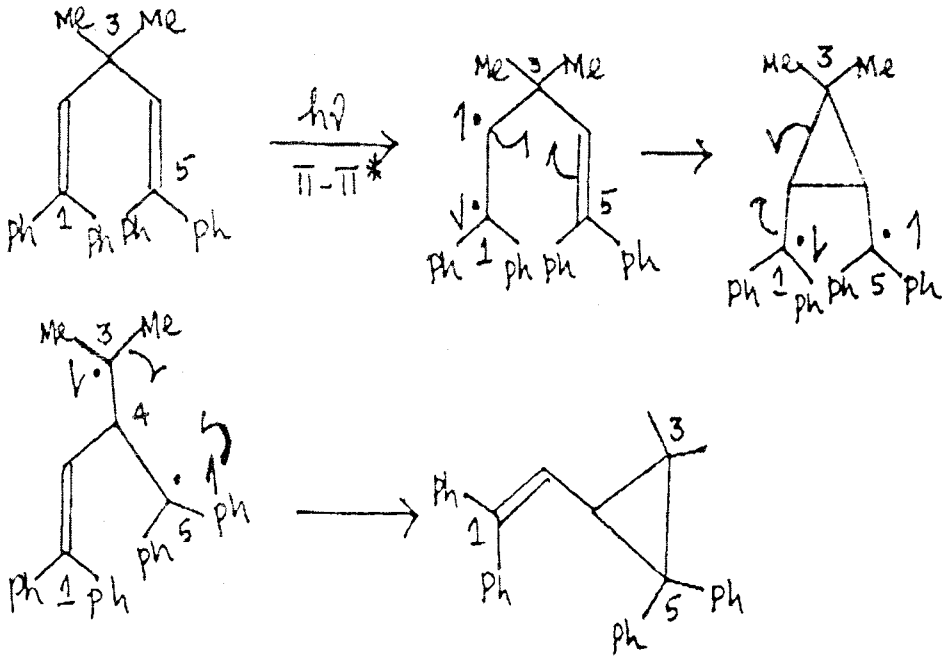
In this reaction a 1,4-diene is converted into a vinylcyclopropane under the influence of light. A di-Π-methane unit involves a saturated carbon atom directly attached to two sites of unsaturation.(E.g) 1,4-pentadiene.



Penta 1,4- diene and its alkyl derivatives possess isolated alkenic chromophores which do not absorb light above 200mm. Hence only the triplet-sensitised reactions of these molecules have been examined. In addition to vinylcyclopropane formation the diene

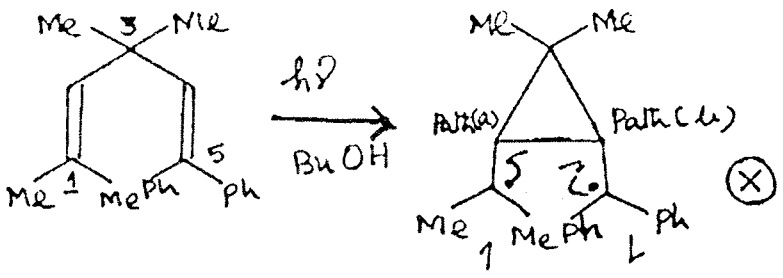
can undergo a symmetry-allowed photochemical. $[\pi^2_s + \pi^2_s]$ intramolecular cycloaddition to give a bicycle [2-1-0] pentane.

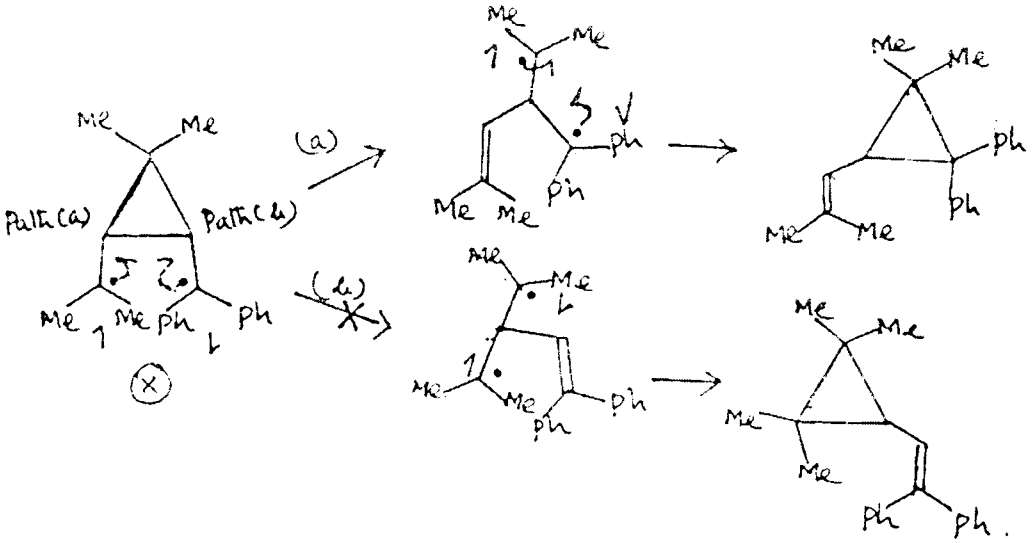
Direct photolysis of 3,3-dimethyl 1,1,5,5-tetra phenylpenta-1,4-diene has been found to give the vinylcyclopropane as the sole primary photoproduct.



With different substituents at C_1 & C_5, two reaction routes(path (a) and path (b)) become possible. However for this substrate the rearrangement occurs exclusively by path(a) to give 1,1-dimethyl-2,2-diphenyl-3-(2,2-dimethyl) vinylcyclopropane. This regiospecific process reuslts from cleavage of the three membered ring of diradical towards the isopropyl radical (Path (a)) rather than towards the more stable diphenylmethyl radical (Path (b).

Regiospecificity may be defined as exclusive reaction at one region of the molecule as opposed to an alternative region.



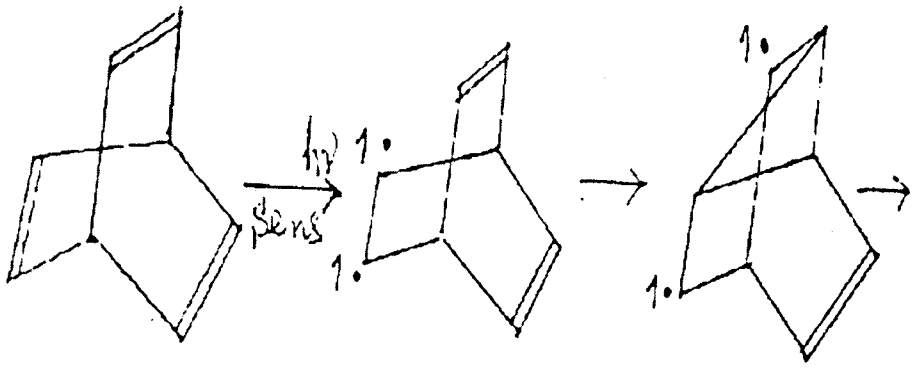


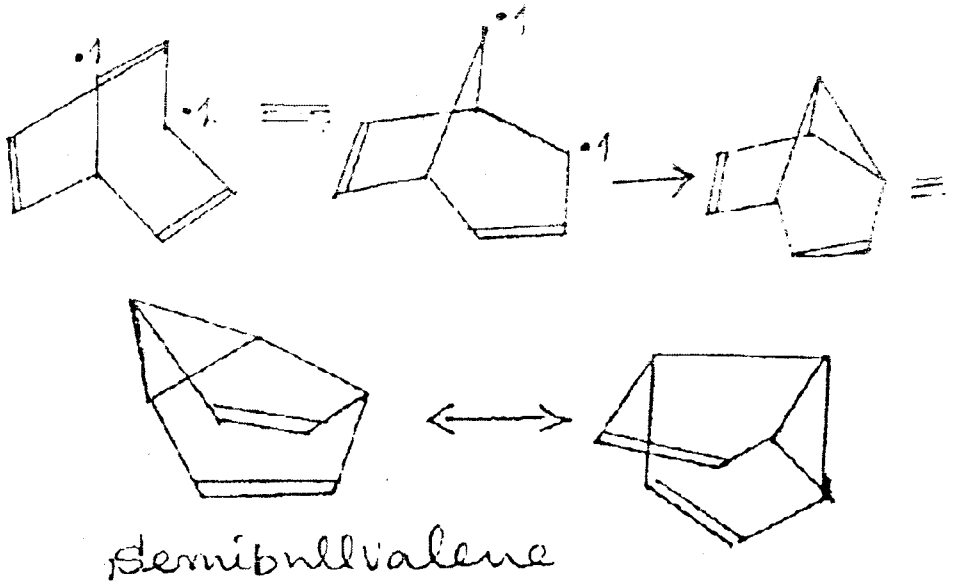
For each substrate, cleavage of the cyclopropane diradical occurs towards what is considered to be the more electron-rich centre.

The above aryl substituted dienes undergo Zimmerman rearrangement in the singlet excited state but are recovered unchanged when subjected to sensitised photolysis. However, when one of the alkenic groups carries dissimilar terminal substituents, triplet sensitisation results in observable geometrical isomerisation. Rearrangement occurs on direct irradiation, but without alkene isomerisation. Thus reaction from the S_1 state is both regiospecific and stereospecific.

The di-Π- methane rearrangement proceeds by a singlet mechanism for acyclic and monocyclic systems whilst the triplet sensitised reactions of the dienes usually result in geometrical isomerisation Bicyclic 1,4-dienes also undergo this reaction but via a triplet & not a singlet process.

For. E.g. barrelene(bicyclo[2.2.2]-octatriene) rearranges to semibullvalene, a molecule which undergoes rapid valence bond tautomerism. The sensitised process is thought to follow a stepwise fashion.

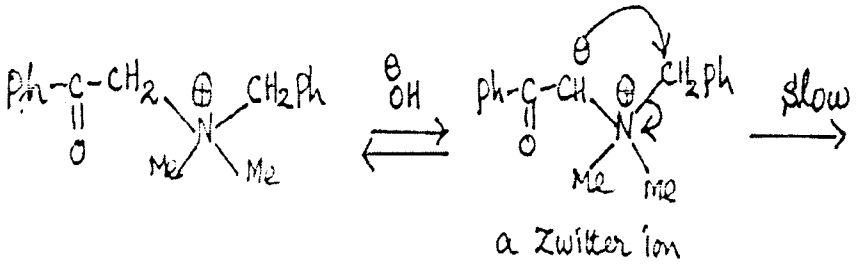




Stevens Rearrangement:

Rearrangement of a quaternary ammonium salt, containing an electron withdrawing group on one of the carbons attached to the nitrogen atom, with a strong base is called as Stevens rearrangement.

The mechanism for this reaction is given with an early example known,

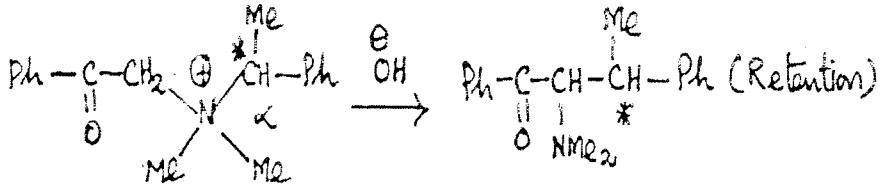


The evidences for the proposed mechanism are

a) the arrangement does not proceed readily when the benzoyl group is replaced by a phenyl or alkyl group, these being relatively ineffective in "labilizing " the hydrogens as an adjacent methylene group.

b) although the reaction is accelerated by a base a limit is reached when slightly more than one equivalent is added, at which point virtually all of the substrate has been converted to its conjugate base (the Zwitter ion, above)

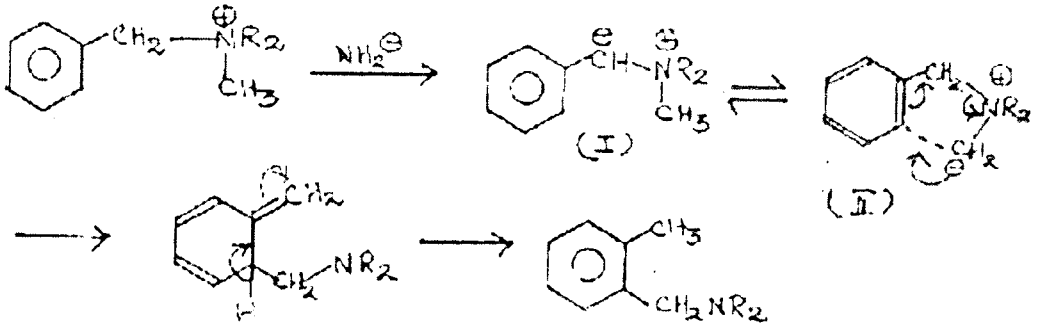
d) when the rearrangement is carried out on the optically active ammonium ion, below, the α-phenylethyl group migrates with retention of configuration. This indicates that the new C-C bond is formed and the old C-N bond breaks on the same side of C_α .



Finally the rearrangement is retarded by incorporation of electron-attracting substituents (-Cl, NO_2 etc) into the benzoyl group. This is because these substituents lower the electron density at the negatively charged attacking carbon.

SOMMELET-HAUSER REARRANGEMENT :

This reaction is a SNi'-type analog (internal nucleophilic substitution with allylic rearrangement) of the Stevens rearrangement. When benzyltrimethylammonium salts are treated with sodamide in liquid ammonia, it forms a benzyl tertiary amine, it can be further alkylated and the product again subjected to the rearrangement. This process can be continued around the ring until an ortho position is blocked. The mechanism is,



The benzyl hydrogen is most acidic and is the one that first loses a proton to give the ylide (I), however ylide (II) which is present in smaller amount, is the species that undergo the rearrangement, shifting the equilibrium in its favour. This mechanism is an example of a [2, 3]-sigmatropic rearrangement.

The rearrangement can be done with various groups present in the ring. The reaction is most often carried out with three methyl groups on the nitrogen, but other groups can also be used.

Stevens rearrangement is a competing process. When both rearrangements are possible, the Stevens is favoured at high temperatures and the Sommelet Hauser at low temperatures.

Free Radicals

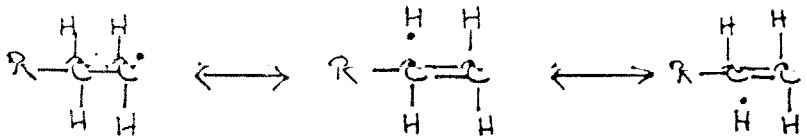
A free radical may be defined as a species that contain one or more unpaired electrons. Because they contain unpaired electrons (one or more), there is a net moment and are paramagnetic.

Free radicals can be detected from magnetic susceptibility measurements. For this a large concentration of them is required. Another important method is electron spin resonance (esr) (or) electron paramagnetic resonance (epr) method.

Yet another magnetic technique is CIDNP(Chemically Induced Dynamic Nuclear polarization)

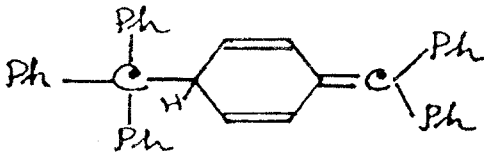
If an nmr spectrum is taken during the course of a reaction, certain signals may be enhanced either in the positive or negative direction; others may be reduced. This type of behaviour found in a reaction is called CIDNP. And it means that at least a portion of the product was formed via the intermediacy of a free radical.

The stability order of free radicals is tertiary > secondary > primary, which is similar to the stability of carbocations.



If resonance is possible as in benzylic allylic, triphenylmethyl free radicals, the stability of the free radicals increases. They are more stable than their alkyl radicals, but have transient existence. However the triphenylmethyl and similar radicals are stable enough to exist in solution at room temperature. But are in equilibrium with the dimeric form.

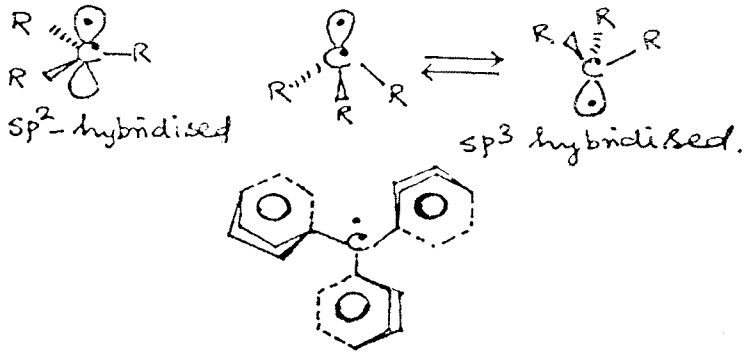
The concentration of triphenylmethyl radical in benzene solution is about 2% at room temperature. For many years it was assumed that ph_3C°, the first stable free radical known, dimerized to hexaphenylethane (ph_3C-Cph_3), but UV & nmr showed its structure to be as given below,



Although triphenylmethyl– type radicals are stabilised by resonance, the major cause of stability is attributed to steric hindrance to dimerisation and not resonance.

There are two possible structures for simple alkyl radicals. They might have sp^2 bonding, in which case the structure would be planar with the odd electron in a 'p' orbital. Alternately, the bonding might be sp^3, which would require a pyramidal structure and the odd electron is to be placed in an sp^3 orbital. Esr spectra of CH_3 and other simple alkyl radicals as well as other evidences indicate that these radicals have planar structure.

Formation of free radicals at bridgehead carbons point to the fact that pyramidal structures are not impossible. But are formed less readily than the open chain free radicals. In sum, the available evidence indicates that though simple alkyl free radicals prefer a planar or near-planar shape, the energy difference between a planar and a pyramidal free radical is not great,



Formation & fate of free radicals:

1. Gas phase decomposition of acylperoxides & azo compounds at high enough temperatures can produce free radicals.

$$R-\underset{\underset{O}{\|}}{C}-O-O-\underset{\underset{O}{\|}}{C}-R \xrightarrow{\Delta} 2\,R\underset{\underset{O}{\|}}{C}-O^{\cdot}$$

$$RN=NR \xrightarrow{\Delta} 2R^{\cdot} + N_2$$

2. Photochemical cleavage of chlorine and ketones may be effected using a light of 600 to 300 mm

$$Cl_2 \xrightarrow{h\nu} 2Cl^{\cdot}$$

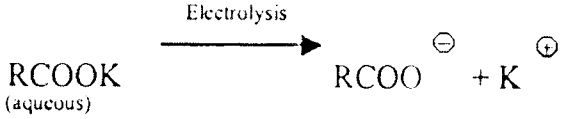
$$R-\underset{\underset{O}{\|}}{C}-R \xrightarrow[\text{vapour phase}]{h\nu} R-\overset{\cdot}{\underset{\underset{O}{\|}}{C}} + R^{\cdot}$$

3. Radicals once formed may break down to other free radicals (or) combine with other molecules to generate new free radicals.

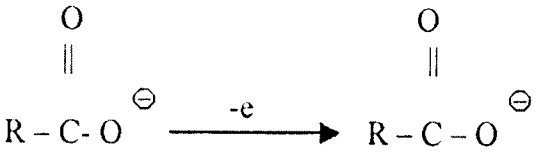
Eg. Decomposition of benzoate free radical formed by the cleavage of benzoyl peroxide.

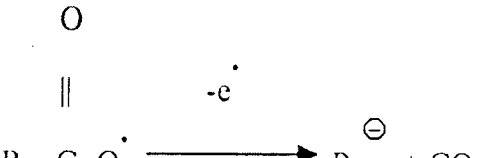
(ii) The phenyl free radical may add to olefins to produce new free radicals.

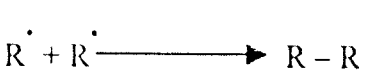
4.Kolbe's electrolysis of aqueous solution of potassium salts of carboxylic acids produce free radicals.



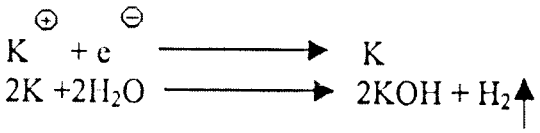
At the anode,







At the cathode:

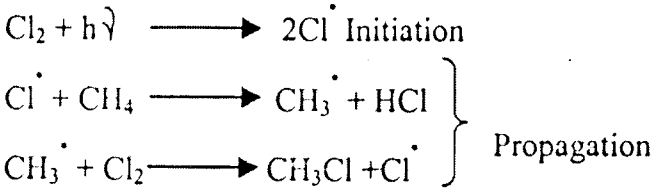


Reactions:

1.Generally the radical reactions involve three steps

a)Generation b)Propagation c)Termination

To illustrate this we may consider the photochemical chlorination of methane



$$CH_3^{\bullet} + Cl^{\bullet} \longrightarrow CH_3Cl$$
$$2CH_3^{\bullet} \longrightarrow CH_3 - CH_3 \quad \text{Termination}$$
$$2Cl^{\bullet} \longrightarrow Cl_2$$

2. The radicals can undergo disproportionation as a means of termination.

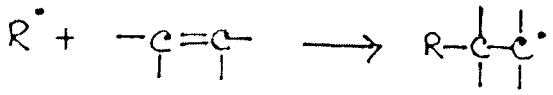
$$2CH_3 - CH_2^{\bullet} \longrightarrow CH_3 - CH_3 + CH_2 = CH_2$$

There are four principal propagation reactions, of which the first two are most common.

1.Abstraction of another atom or group, usually a hydrogen atom

$$R^{\bullet} + R - H \longrightarrow R - H + R^{\bullet}$$

2. Addition to a multiple bond.



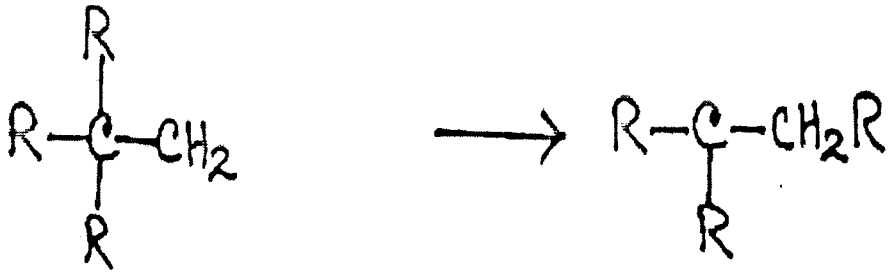
The radical formed here may add to another double bond etc. This is one of the chief mechanisms for polymerisation reactions.

3.Decomposition :

This may be illustrated by the decomposition of the benzoxy free radical.

4. Rearrangement:

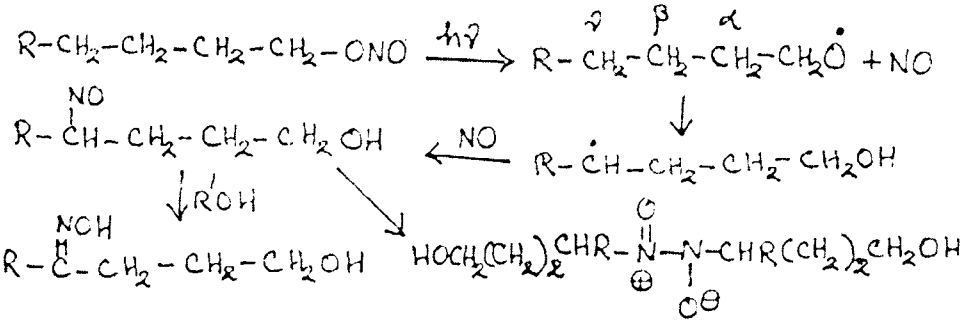
Substrates like neopentyl systems can undergo rearrangement of the initial free radical to form a more stable free radical.



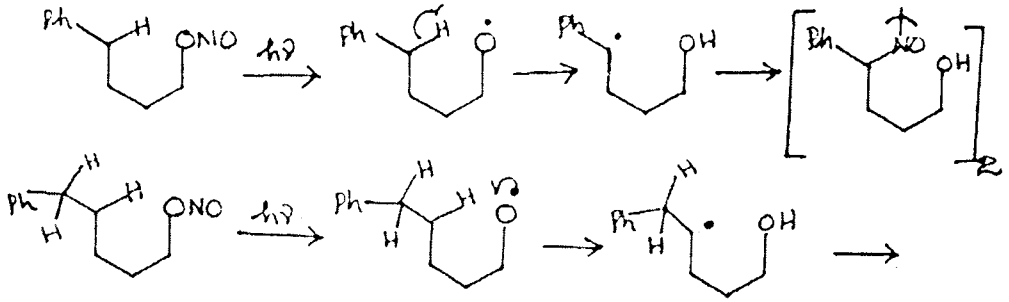
Besides these reactions, free radicals may be oxidised to carbocations (or) reduced to Carbanions

BARTON REACTION

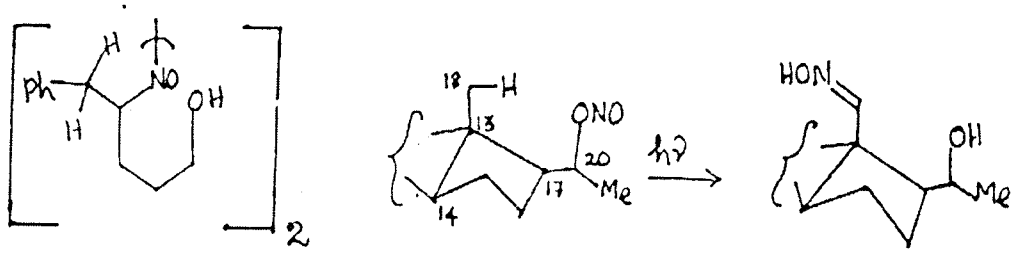
The reaction involving the nitric oxide migration produced by the photolysis of organic nitrites is called as Barton reaction. In the alkoxy radical produced during photolysis γ - hydrogen migration, if there is one, takes place. The nitric oxide combines with this new alkoxy radical to produce nitroso alcohol, nitrosodimers oxime (in protic solvents) etc. These are the characteristics of Barton reaction. It can be schematically



Like the Norrish type II reaction, the intramolecular 1,5-hydrogen transfer to the alkoxy radical involves a six-membered cyclic transition state structure, as demonstrated by the photolysis of a series of ω-phenyl alkyl nitrites.



The Barton reaction has been used in funcitonalising the angular methyl groups of steroids.(e.g.) 3β-acetoxy-5α-Pregnan-20β-ol nitrite in protic solvents, forms the aldoxime by nitric oxide migration.



Ullmann reaction:

The compling of aryl halides with copper is called the Ullmann reaction. This reaction is used to prepare both symmetrical and unsymmetrical biaryls. When a mixture of two different aryl halides is used there are three possible products, but often only one is obtained. For example, picryl chloride and iodobenzene gave only 2,4,6- trinitrobiphenyl. Often aryl iodides are used as iodine is a good leaving group.

The mechanism of this reaction is not known with certainty.

Step1: $ArI + Cu \longrightarrow ArCu$

$ArCu + AI \longrightarrow ArAr$

The species represented as ArCu may not actually have this structure, but some kind of a complex is formed. It is unlikely that step I involves the generation of free radicals. Step II may well be a nucleophilic attack by Arcu or ArI.

HUNSDIECKER REACTION

$$RCOOAg + Br_2 \longrightarrow RBr + CO_2 + AgBr$$

Preparation of alkyl halides by the reaction of a silver salt of a carboxylic acid & bromine is called Hunsdiecker reaction. This is a way of decreasing the length of a carbon chain by one unit.

Since pure silver salts are difficult to prepare, alternative methods may also be used. Some are (i) treatment of thallium (I) carboxylates (which are easy to prepare and purify) with bromine. (ii) treatment of carboxylic acids with lead tetraacetate and halide *ions* (Cl^-, Br^- *or* I^-) (iii) reaction of the acids with lead tetraacetate and N-chlorosuccinimide, which gives secondary & tertiary halides in good yields, *but not* primary or phenyl (iv) the reaction between an acylperoxide and $CuCl_2$, $CuBr_2$ or CuI_2 (v) treatment of acyl chlorides with a sodium salt of N-hydroxy –pyridine-2-thione in CCl_4.

The mechanism of the Hunsdiecker reaction is believed to be as follows:

Step 1 $RCOOAg + X_2 \longrightarrow R-\overset{\overset{O}{\|}}{C}-O-X + AgX$

Step 2 $R-\overset{\overset{O}{\|}}{C}-OX \longrightarrow RCOO^{\bullet} + X^{\bullet}$ (Initiation)

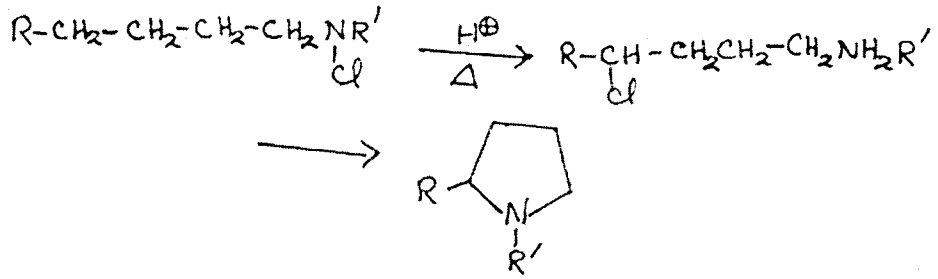
Step 3 $RCOO^{\bullet} \longrightarrow R^{\bullet} + CO_2$

Step 4 $R^{\bullet} + RCOOX \longrightarrow RX + RCOO^{\bullet}$ (Propagation)

Step 5 $R^{\bullet} + X^{\bullet} \longrightarrow RX$ (Termination)

Among the evidence for the mechanism is that optical activity at R is lost. If R is neopentyl, there is no rearrangement, which would certainly happen with a carbocation. Furthermore, the formation of R-R, one of the side products, is consistant with a free-radical mechanism.

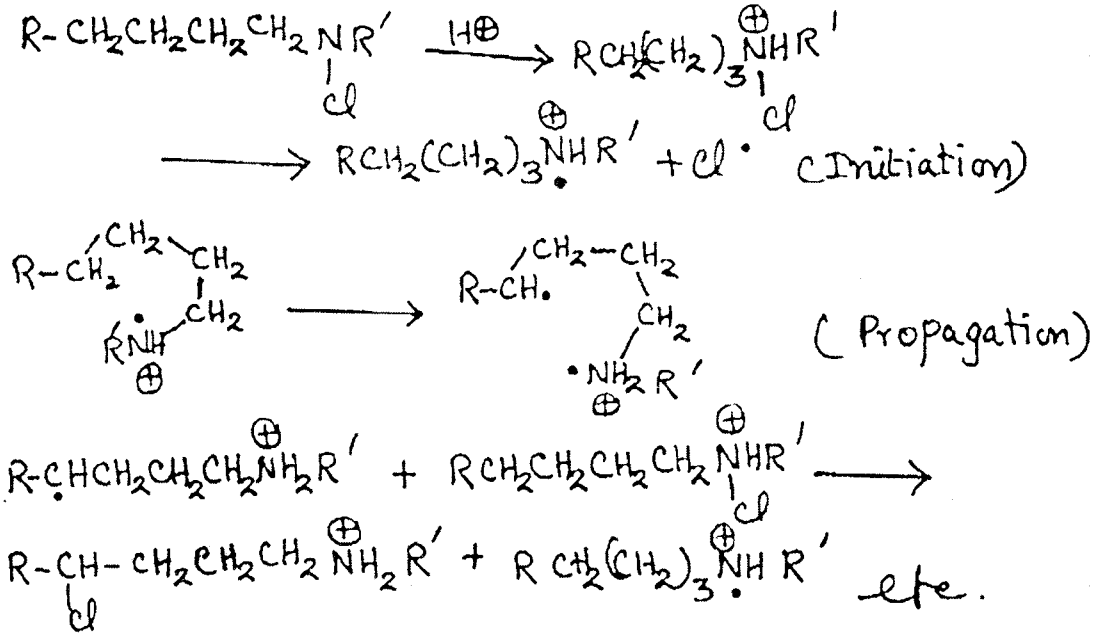
HOFMANN-LAFFLER FREYTAG REACTION:



A striking feature in this reaction is that they serve to introduce functionality at a position remote from functional groups already present.

When N-haloamines in which one of the alkyl group has a hydrogen in the 4 or 5 position are heated with sulphuric acid, pyrrolidines or piperidines are formed.

The first step of the reaction is a rearrangement, with the halogen migrating from the nitrogen to the 4 or 5 position of the alkyl group and in the second step ring closure takes place.



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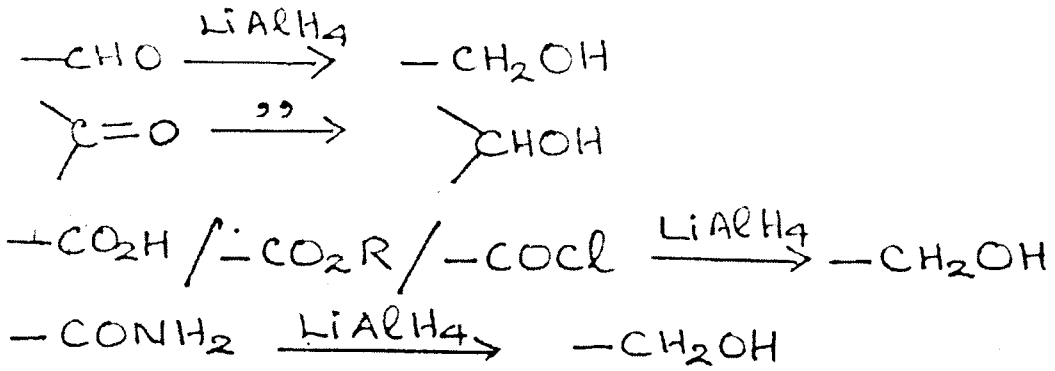
UNIT - V

REAGENTS IN ORGANIC SYNTHESIS

Complex metal hydrides:

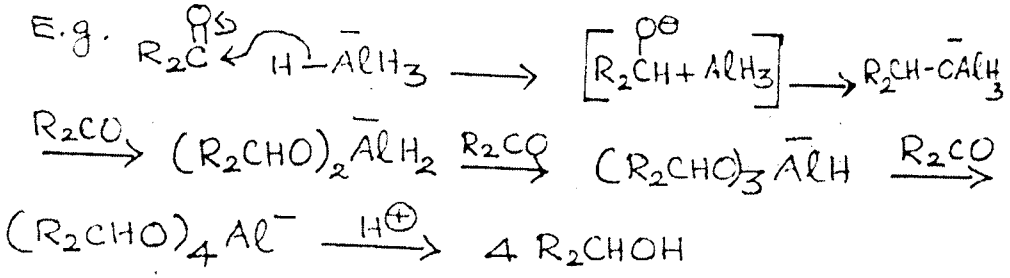
Many complex metallic hydrides reduce various functional groups. The most versatile reagent is lithium aluminium hydride(LAH) This reduces most functional groups, but does not normally reduce the olefinic bond. An usual feature of this reagent is its reduction of the carbonyl group to primary alcohol.



Reductions with lah are usually carried out in ethernal solutions.

Sodium borohydride is insoluble in ether so an ethanolic solution of it is used to reduce carbonyl compounds. One important exception to this is carbonyl group. It does not normally reduce esters, but reduction to primary alcohol can often be effected by use of a large excess of reagent in methanol.

The reduction of the carbonyl group by LAH or $NaBH_4$ occurs in a stepwise manner; each step involving hydride ion transfer.

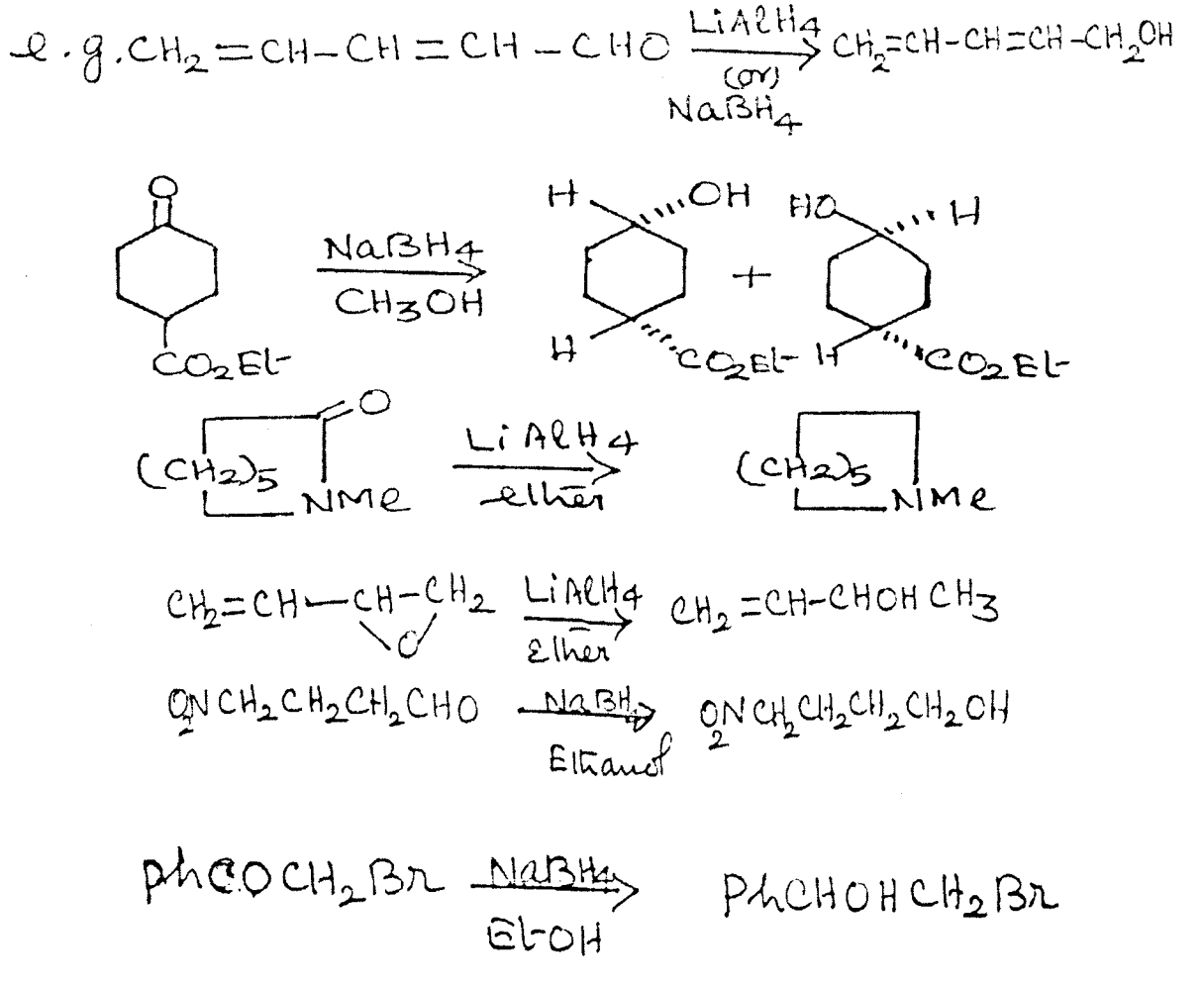


The nature of the solvent and the presence of other compounds affect the reducing power of LAH. E.g. LAH and aluminium chloride in ether form AlH_3, AlH_2Cl or $AlHCl_2$ according to the proportion of reagents used. Hence the reducing power of the reagent will depend on which one is actually present. All are milder reducing agents than LAH. E.g. LAH - $AlCl_3$ does not reduce alkyl halides. Similarly LAH in pyridine, when

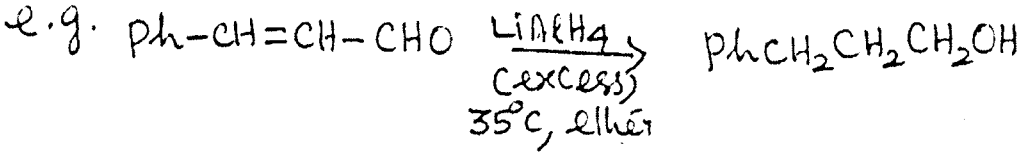
allowed to stand will reduce a carbonyl group but not a carbonyl or carbalkoxy group. Thus LAH can be used as a milder reducing agent.

But sodium borohydride –aluminium chloride (in diethylene glycol dimethyi ether, i.e diglyme) is more reactive than sodium borohydride itself.

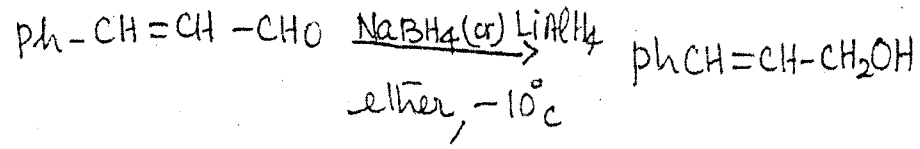
It is normally possible to reduce aldehydes and ketones selectively with these reagents in presence of a variety other functional groups.



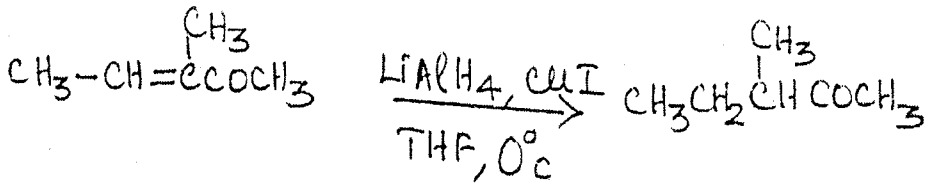
There are some exceptions to the general rule that olefinic double bonds are not attacked by hydride reducing agents.



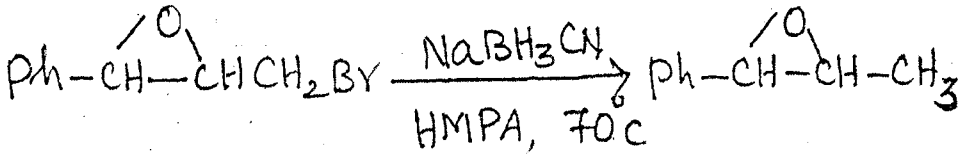
In such cases selective reduction of carbonyl group can be effected by lowering the temperature of reduction.



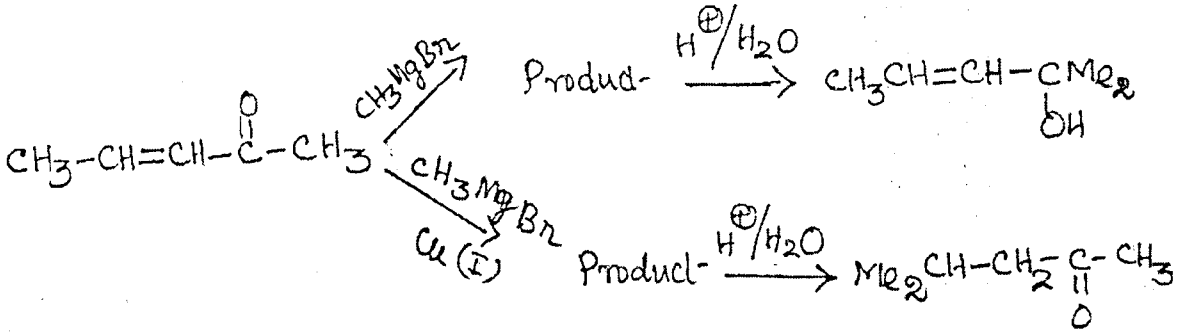
LAH modified by the addition of copper (I) iodide is an effective reagent for the reduction of open-chain conjugated enones to the saturated ketones.



Similarly a number of reagents derived from sodium borohydride by replacement of one or more of the hydrogen atoms by other groups has been developed in order to achieve more selective reduction.



Organocopper intermediates are an useful tool in the hands of an organic chemist. This reagent assumed importance from the conjugate addition of G.R. to α, β-unsaturated ketones i.e. in presence of cu(I) salts conjugate addition is favoured with α , β– unsaturated ketones.



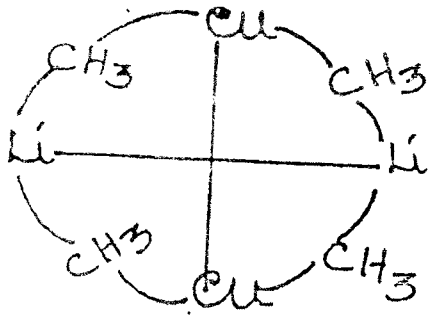
Mechanic studies pointed to a very rapid reaction by an organo copper intermediate

$RLi + Cu(I) \rightarrow RCu + Li^+$

$2RLi + Cu(I) \rightarrow R_2CuLi + Li^+$

$3RLi + 2Cu(I) \rightarrow R_3CuLi_2 + Li^+$

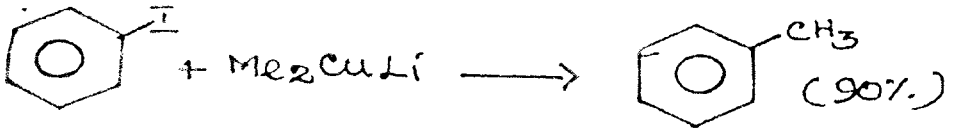
The species from the 2:1 mole ratio are known as cuprates and have been the most useful synthetic reagents. In solution lithium dimethyl cuprate exists as a dimer[Licu Me_2]2, but the precise sturucture of the reagent is not known. It is often represented as four methyl groups attached to a tetrahedran of metal atoms.

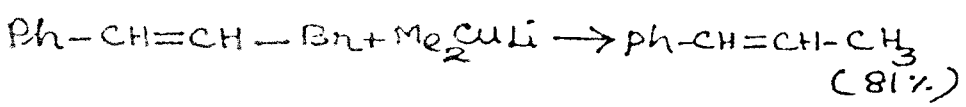


The temperature of preparation and solvent have noticeable influence on reactivity of the cuprates. The most general description of the organo cuprate reagents is that they are extremely reactive nucleophiles at soft carbon centers.

The most characteristic reactions displacement of halides and sulphonates α, β - unsaturated ketones at both sp^3 and sp^2 carbon, allylc displacement, epoxide ring opening conjugate addition to α, β - unsaturated carbonyl compound and additions to acetylenes.

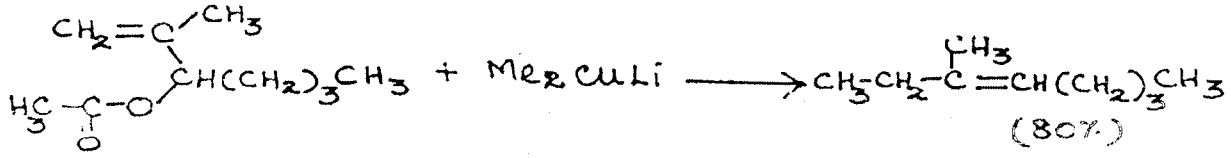
Corey and Posner discovered that lithium dimethyl cuprate could replace iodine or bromine by methyl in a variety of compounds including aryl and vinyl halides. This method of replacement of halide by alkyl is much more satisfactory and general than displacement by Grignard or lithium reagents.



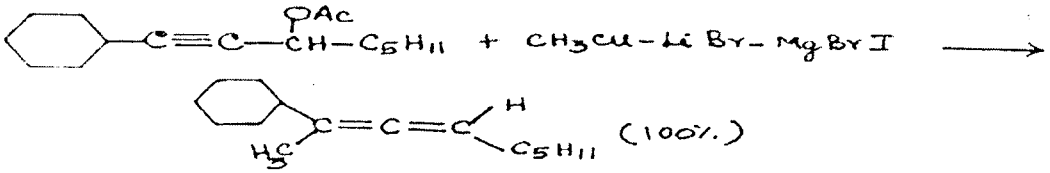


Allylic halides give usually both S_N2 and S_N2' products although RCu BF_3, is reported to give nearly completely the S_N2 product.

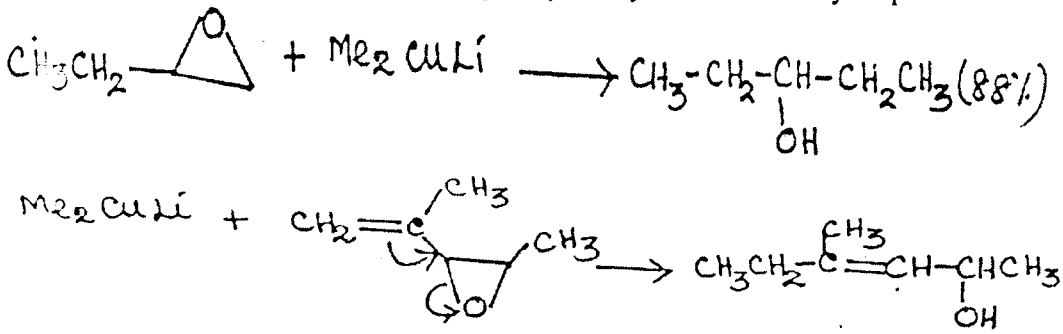
Allyl acetates undergo displacement with allylic shift.



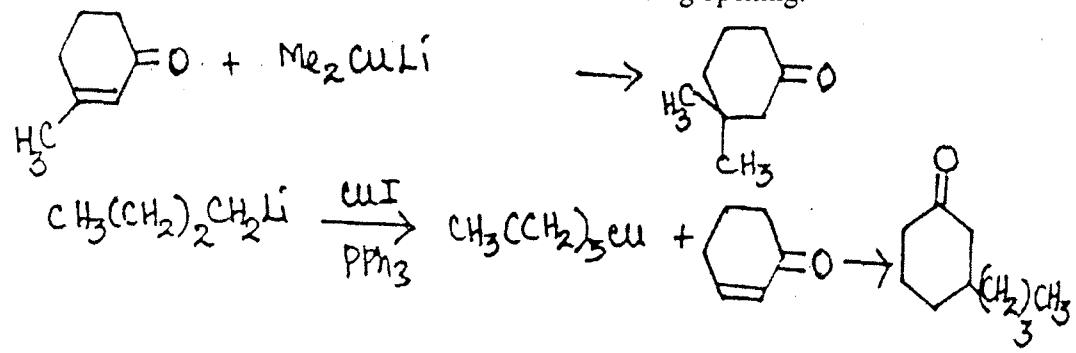
Propargylic acetates, halides and sulfonates react to give substantial amount of allenes, resulting from attack at the acetylenic bond with shift of an electron pair.



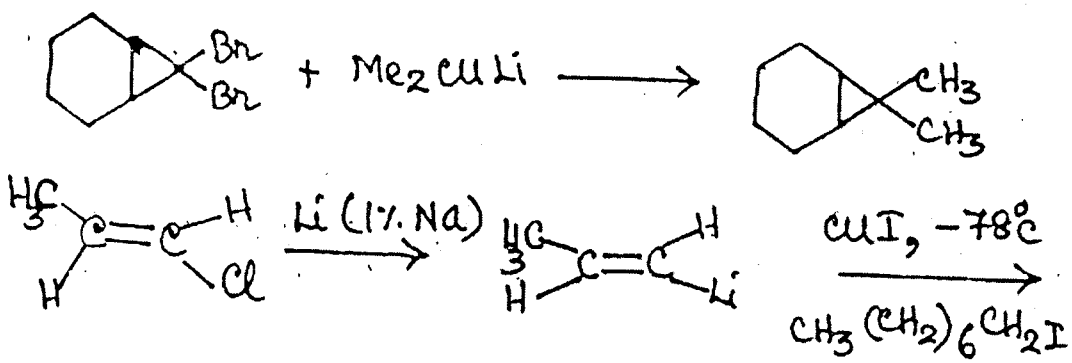
Saturated epoxides are opened in good yield by lithium dimethyl cuprate.

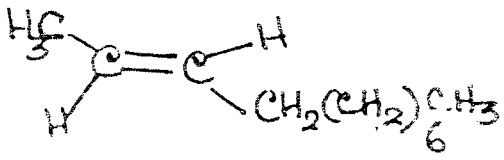


Epoxides having vinyl substituents undergo attack by the reagent at the double bond with a concomitant shift of the double bond and ring opening.

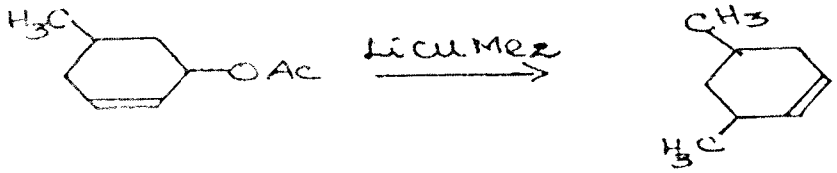


Halide Substitution

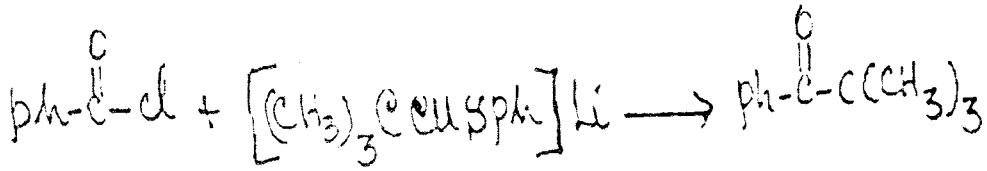




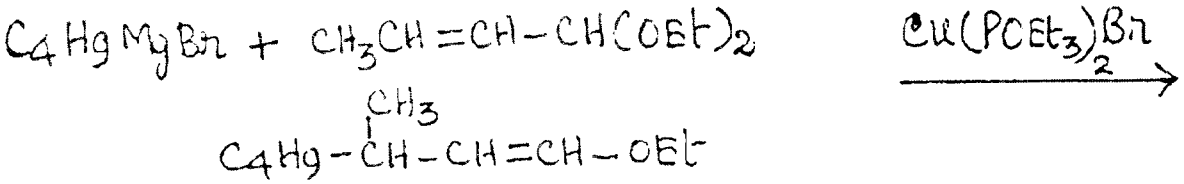
Displacement of allylic acetates



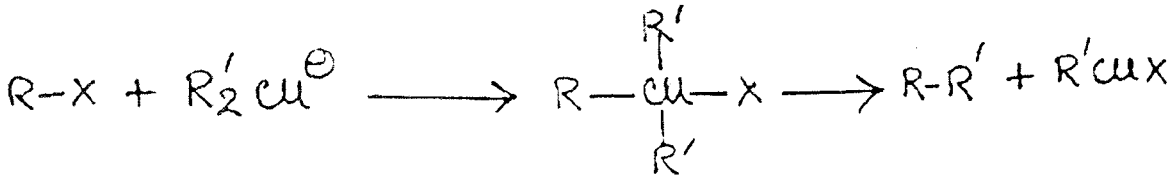
Ketones from acid chlorides



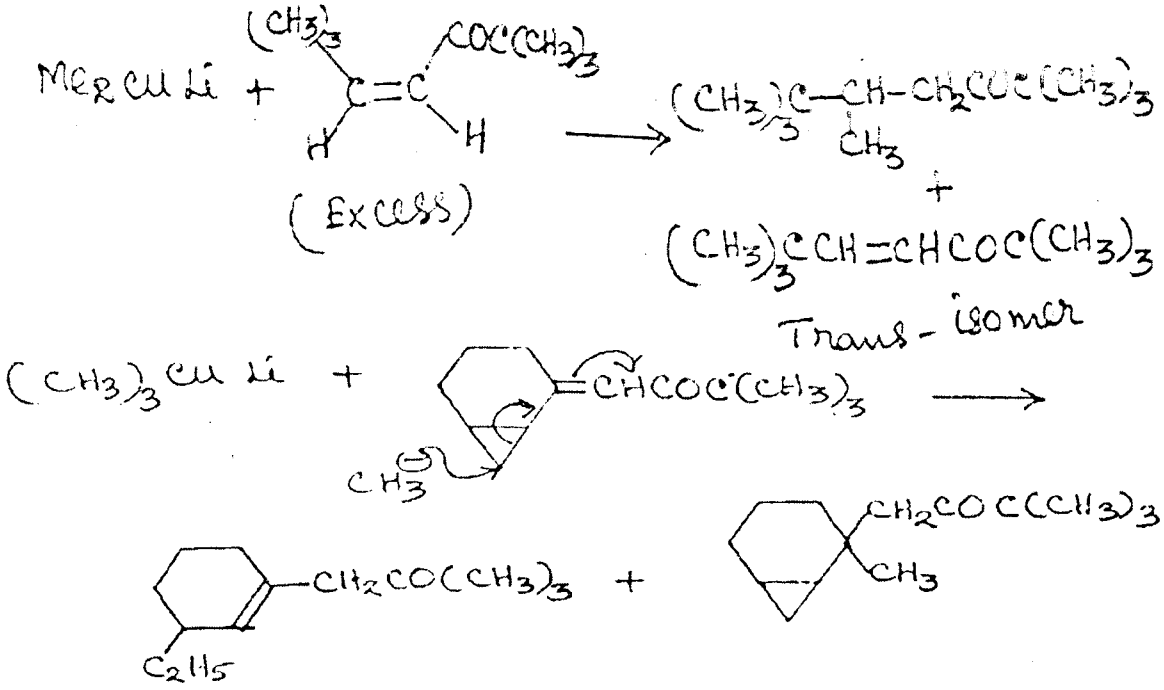
Cuprates from G.R.s react with allylic acetals to give vinyl ethers.



These reactions are generally considered to be direct displacement reactions on the substrate.The overall reaction consists of two steps. First an oxidative addition to the metal in which the copper acts as a nucleophile. This is followed by migration of one of the alkyl group from copper

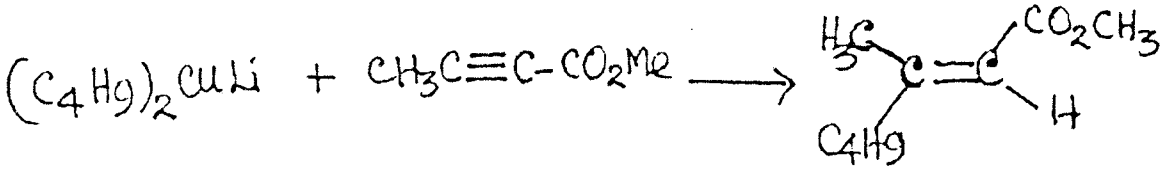


The conjugate addition reactions probably occur by an $e^{(-)}$ transfer mechanism. The products of the electron transfer step must combine faster than they diffuse apart so no free radicals are generated. The intermediacy of a radical anion species can be detected in special cases by double bond isomerization or rearrangement.

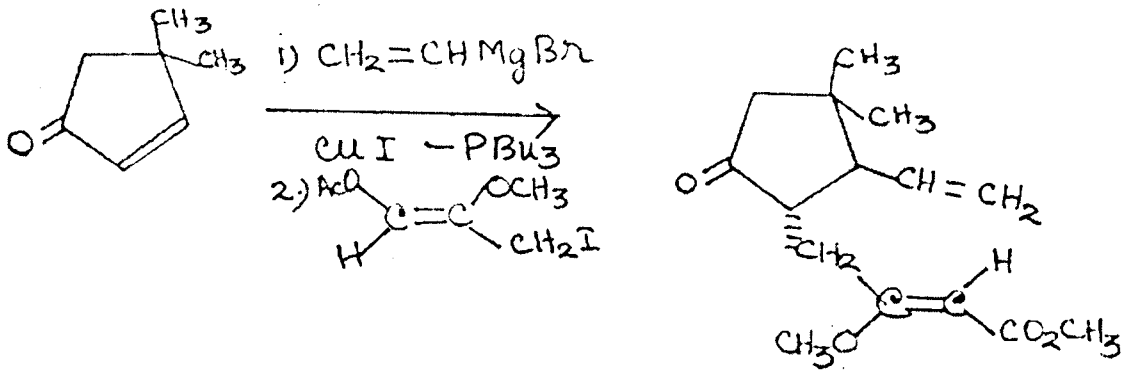


Both the double bond isomerization and cyclopropane ring opening can be accounted for by a radical anion intermediate.

Conjugate acetylenic esters react readily into cuprate reagents, with <u>syn</u> addition being the kinetically preferred mode of addition.



Prior to protonolysis, the products of conjugate addition to unsaturated carbonyl compounds are enolates, and, therefore potential nucleophiles. A useful elaboration of the conjugate addition is to combine it with an alkylation which can add a second organic group. This is done by taking advantage of the nucleophilicity of the enolate intermediate.

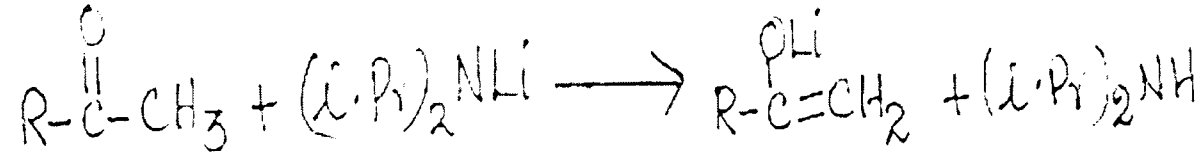


LDA

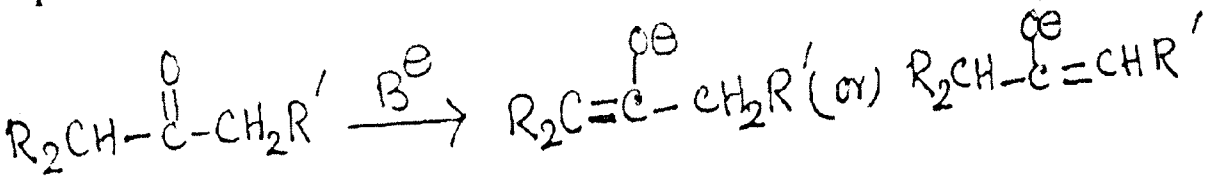
LDA is generated by the addition of n-butyllithium to diisopropylamine.

It is a very strong base, yet is sufficiently bulky so as to be relatively nonnucleophilic - a feature that is important in reducing number of side reactions. It is used to get enolates, which are essential for alkylation.

Enolates are formed by deprotonation of the carbon α - to a carbonyl group(the resulting amion usually has the negative charge on the oxygen atom i.e. exists as an enolate)

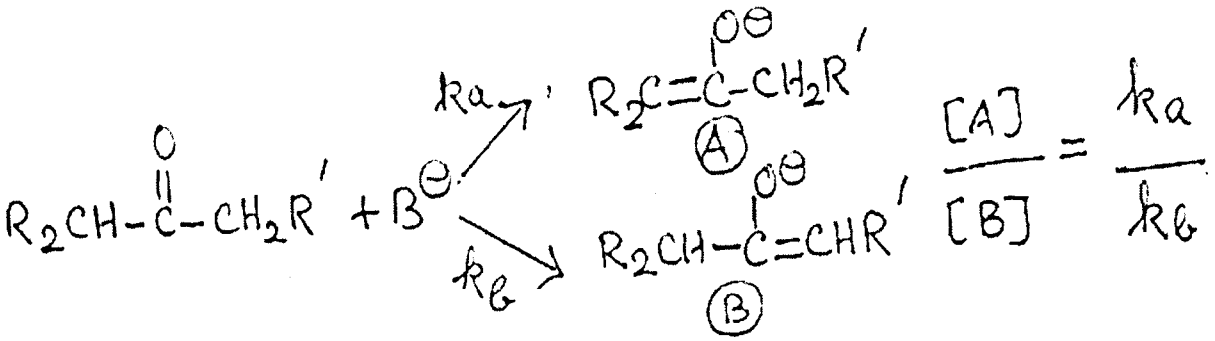


An unsymmetrical dialkylketone can form two regioisomeric enolates on **deprotonation**

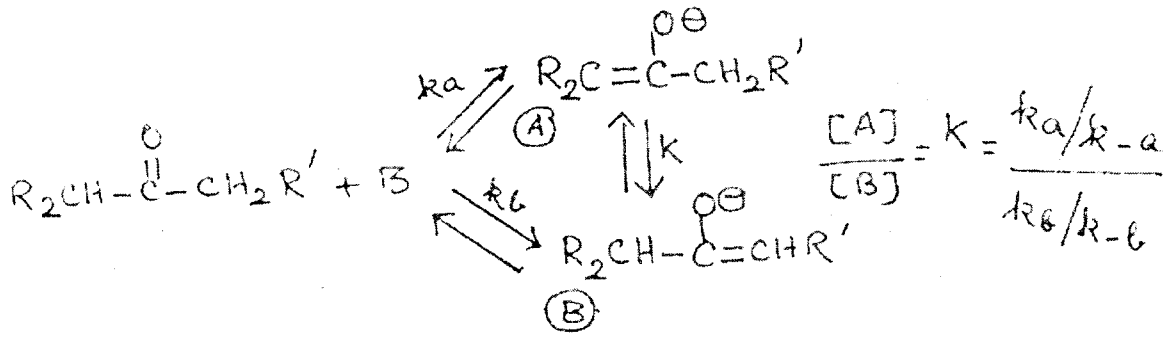


In order to exploit fully the synthetic potential of enolate ions, some control over the regioselectivity of their formation is required. While, in most cases, it is not possile to direct deprotonation so as to form one enolate to the exclusion of the other, experimental conditions can be chosen which will provide a reasonable excess of the desired regioisomer.(So that we may understand the reasons why a particular set of experimental conditions leads to the preferential formation of one enolate while a different set leads to the other].

The composition of the enolate mixture may be governed by kinetic or thermodynamic factors. In the former case, the product composition is favoured by the relative rates of two competing proton- abstraction reactions. The enolate ratio is governed by kinetic control.



On the otherhand, if enolates A&B can be interconverted rapidly, equilibrium can be established and the product compostition will reflect the relative thermodynamic stability of the enolates. The enolate ratio is governed by thermodynamic control.

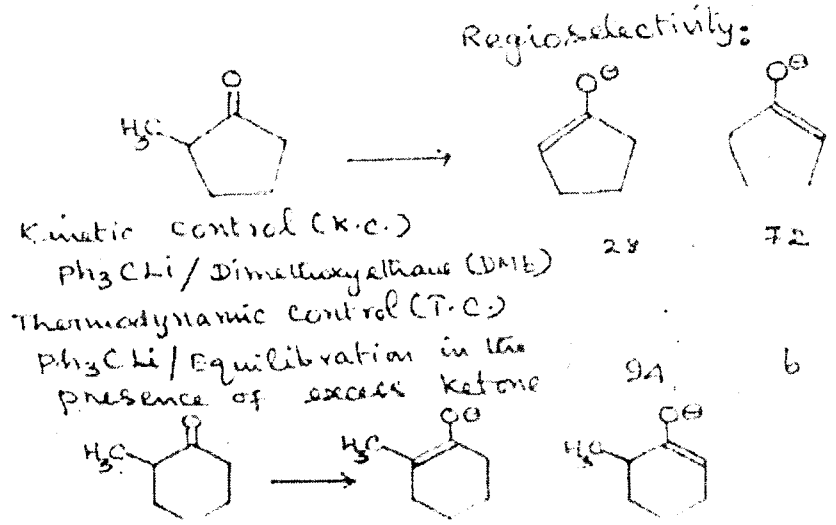


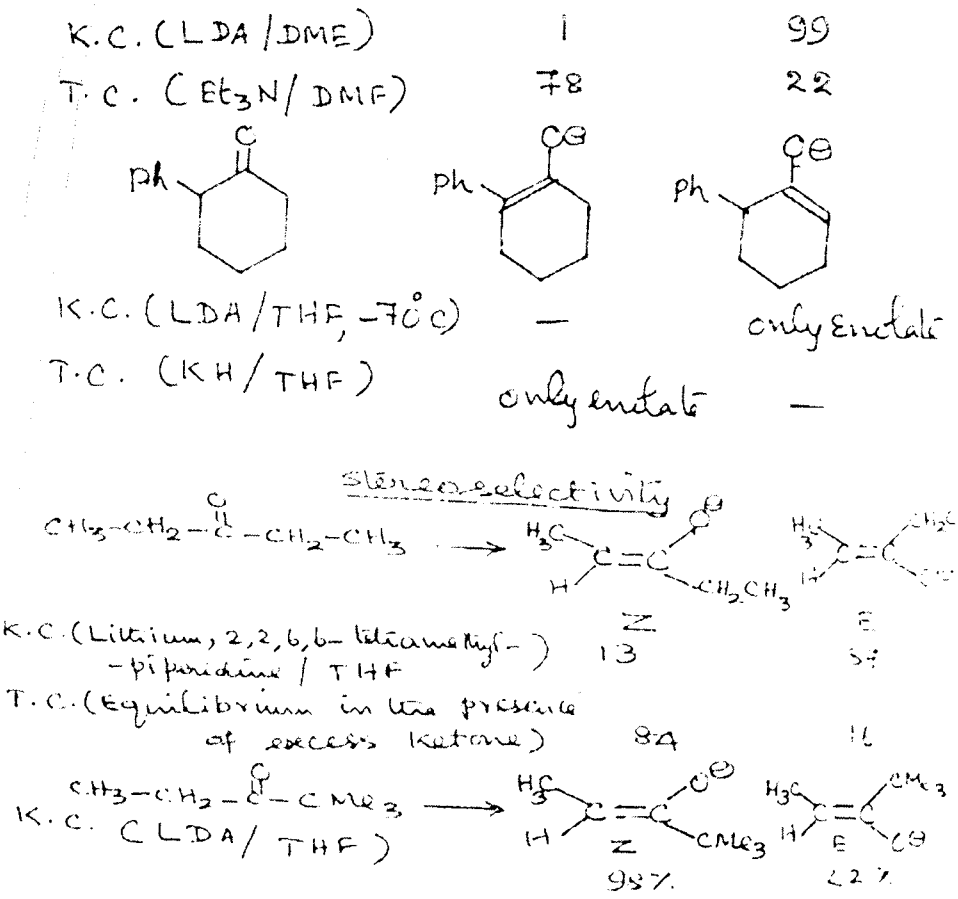
By adjusting the conditions underwhich an enolate mixture is formed from a ketone, it is possible to establish either kinetic or thermodynamic control. Ideal conditions for kinetic control of enolate formation are those in which the deprotonation is rapid,quantitative and irreversible.

This condition is approached experimentally by using a very strong base such as LDA or Ph_3CLi in an aprotic solvent in the absence of excess ketone.

Lithium as the counterion is better than sodium or potassium for regioselective generation of the kinetic enolate. Protic solvents promote enolate equilibration by allowing protonation- deprotonation path ways to operate on the isomeric enolate. Excess ketone seems to catalyse equilibration in much the same way by acting as a proton source.

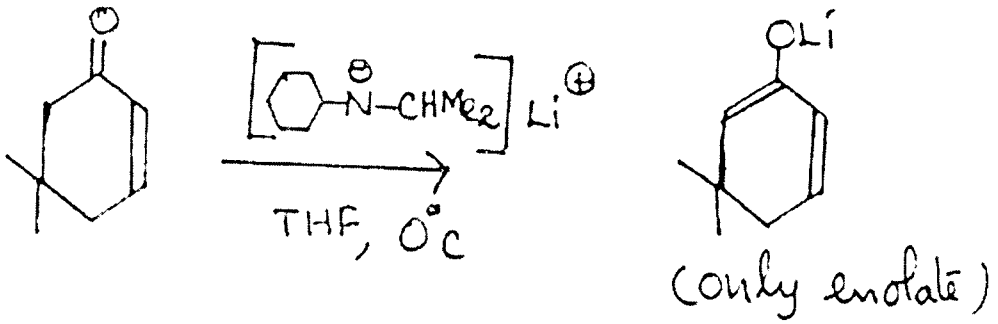
Conditions of kinetic control usually favour the less-substituted enolate. The principal reason for this result is that removal of the less hindered hydrogen is more rapid, for steric reasons, than removal of more hindered protons. And this more rapid reaction leads to the less substituted enolates(LDA or Ph_3CLi).



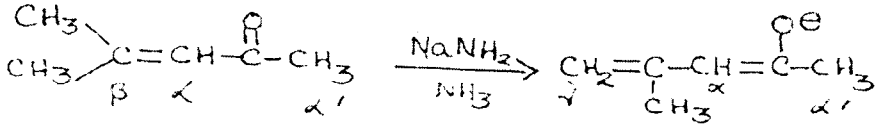


On the otherhand, at equilibrium it is usually the more substituted enolate is the dominant species. The stability of C-C double bonds increase with increasing substitution. And it is this substituent effect that leads to the greater stability of the more substituted enolate.

Kinetic deprotonation of α, β - unsaturated ketones usually occurs preferentially adjacent to the carbonyl group. The electron- withdrawing inductive effect of the carbonyl group is probably resposible for the faster rate of deprotonation at this position.

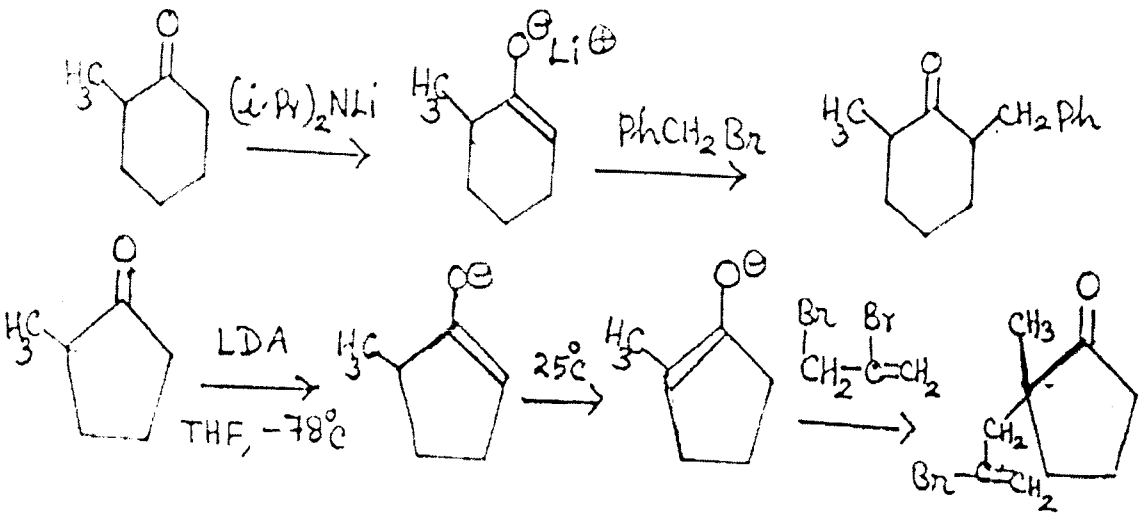


Under conditions of thermodynamic control it is the enolate corresponding to deprotonation of the γ carbon atom which is present in greater amounts.

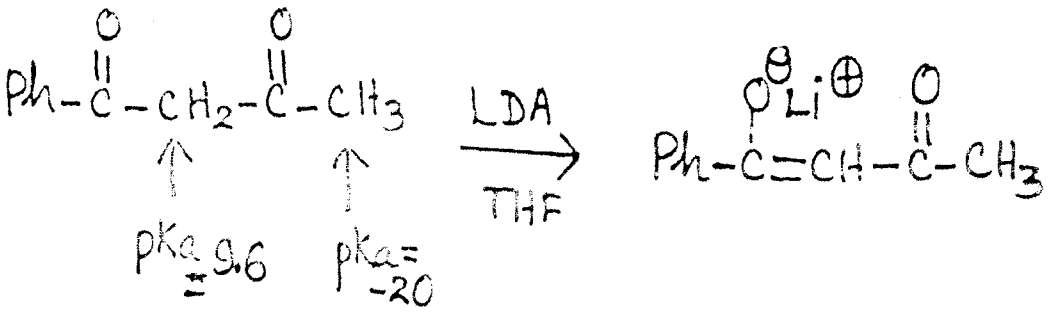


The alkylation of relatively acidic substances such as β- diketones, β -keto esters and esters of malonic acid can be carried out in alcoholic solvents using metal alkoxides as bases. The presence of two electron-withdrawing substituents favours formation of a single enolate by removal of a proton from the carbon situated between them. Alkylation then occurs by an S_N2 process.The alkylating agents must be a reactive one towards nucleophilic displacement. Primary halides and sulfonates; esp. allylic and benzylic ones are the best alkylating agents. 2° substrates usually give poor to moderate yields because of competing elimination. 3° halides give only elimination products.

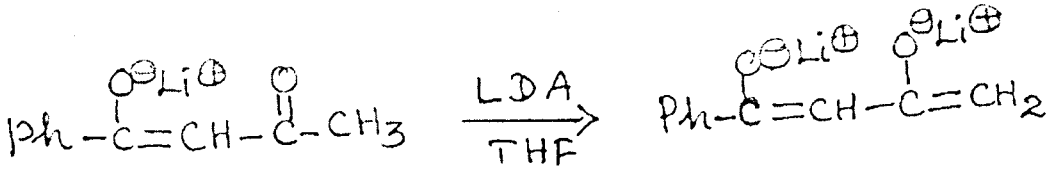
Regioselective Enolate Alkylation:



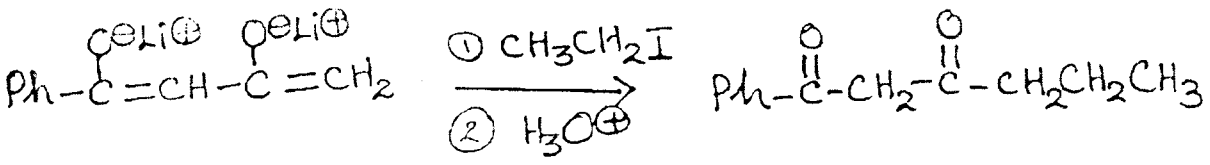
In the presence of very strong bases such as an alkyllithium, potassium or sodium amide, or litium di-isopropylamide, 1,3-dicarbonyl compounds may be converted to their dianions by sequential deprotonation. For example, reaction of benzoyl-acetone with LDA leads first to the



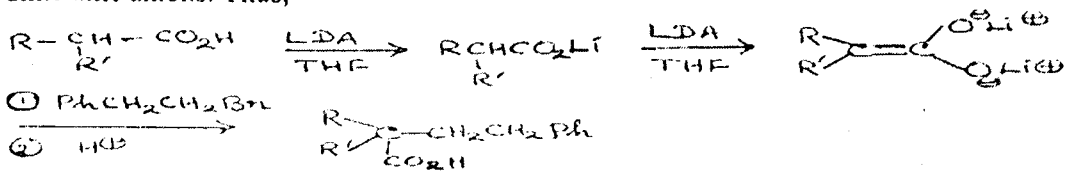
enolate generated by deprotonation of the methylene group between the two carbonyl groups. A second equivalent of base can deprotoonate the methyl group to give a dienolate.



Alkylation reactions occur at the more basic enolate function.

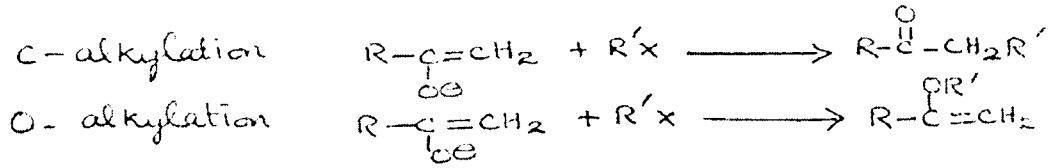


LDA can be used for the α- alkylation of carboxylic acids, first by forming a dimetallic anions. Thus,



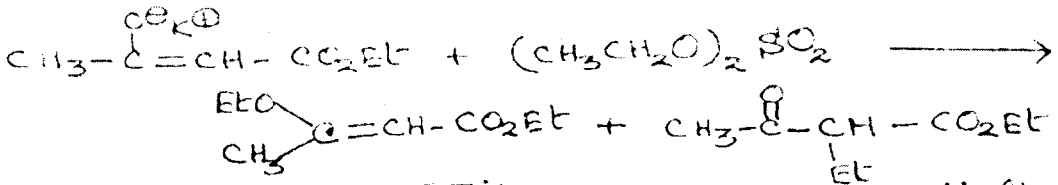
Oxygen Vs carbon as the site of alkylation :

Enolate anions are ambident nucleophiles. Alkylation may occur at carbon or oxygen.



Since most of the negative charge of an enolate is on the oxygen atom, it might be expected that O-alkylation would dominate. A number of factors other than charge density can intervence to affect the C/O alkylation ratio. However, it is normally possible to direct the alkylation of enolates toward carbon in synthetically useful amounts.

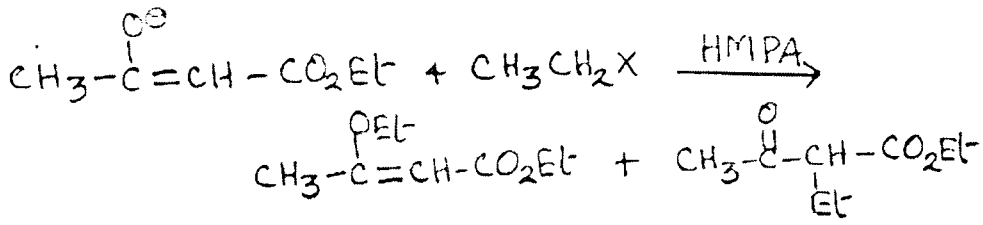
O-alkylation will be most pronounced when the enolate ion is most free. When the potassium salt of AAE is treated with ethyl suphate in the polar alrotic solvent hexamethyl phosphoric triamide(HMPA, $O=P[N(CH_3)_2)_3$, the major product, is O-alkylated. In THF, where ion pairing occurs, all of the product is C-alkylated. In t-butanol where AAE anion is londed to the solvent, again only C-alkylation is obseverd.



HMPA	83%	15%. (2% dialkyl)
t-Butanol	0%	94%. (6% ")
THF	0%	94% (" ")

Higher C/O ratios are observed with alkyl halide than with alkyl p- toluene sulphonates.

Leaving group effects on the ratio of C- to O- alkylation are customarily correlated w.r.to the hard-soft acid-base(HSAB) rationale. Of the two nucleophilic sites in an enolate ion, oxygen is harder than carbon. Nucleophilic substitution reactions of the S_N2 type proceed best when the nucleophile and the leaving group are either both hard or both soft. Consequently, ethyl iodide, with the very soft leaving group iodide, reacts preferentially with the softer carbon site rather than the harder oxygen. Oxygen-containing leaving groups (p- toluene sulphonate and sulfate) are hard, and alkylating agents derived from them react faster with the harder nucleophilic site(Oxygen) of the enolate.

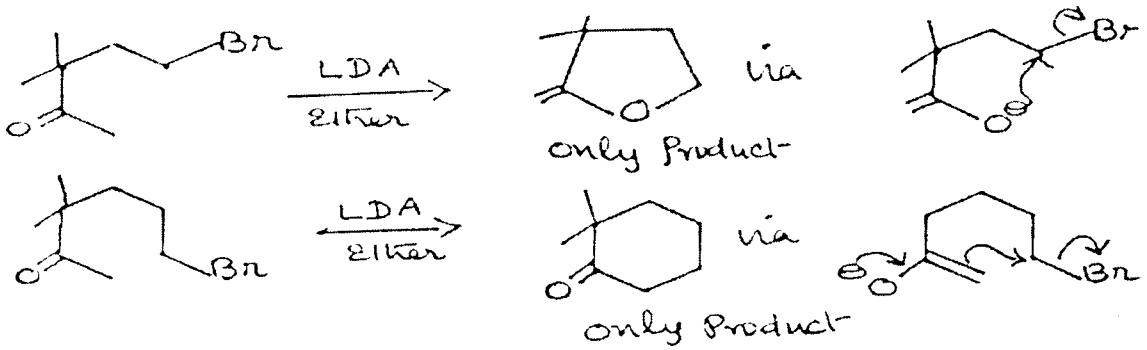


X = OTs	88%	11%. (1% dialkyl)
= Cl	60%	32%. (8% dialkyl)
= Br	39%	38%. (23% ")
= I	13%	71%. (16% ")

More basic enolates exihibit generally similar behaviour. The sodium enolate of isobutyrophenone reacts with ethyl-bromide in dimethoxyethane to give five times as much C-alkylation as O-alkylation.

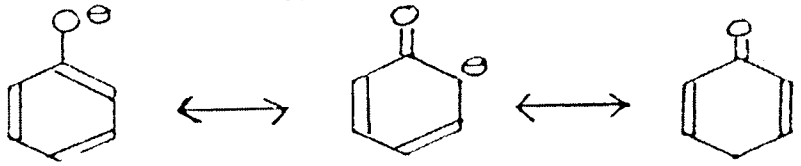
In brief, we can maximize the amount of O-alkylation through the use of an alkyl-p-toluene sulfonate in a polar aprotic solvent. We can maximize the amount of C-alkylation by using an alkyl iodide in a non-polar (or) hydrogen bonding solvent.

Cyclization of enolate anions by intramolecular nucleophilic substitution is subject to an element of stereo electronic control which determines whether C-or O-alkylation occurs. This can be illustrated by the following reactions.

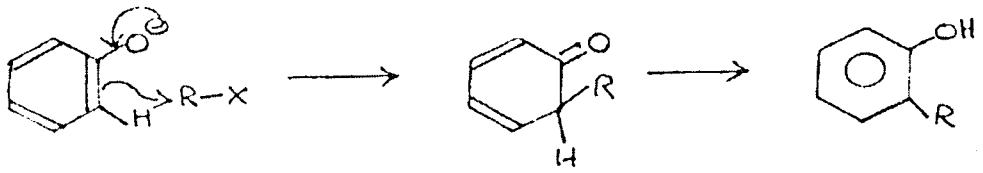


When the ring to be closed is six-numbered C-alkylation occurs. Instead if it is five-numbered then O-alkylation occurs.

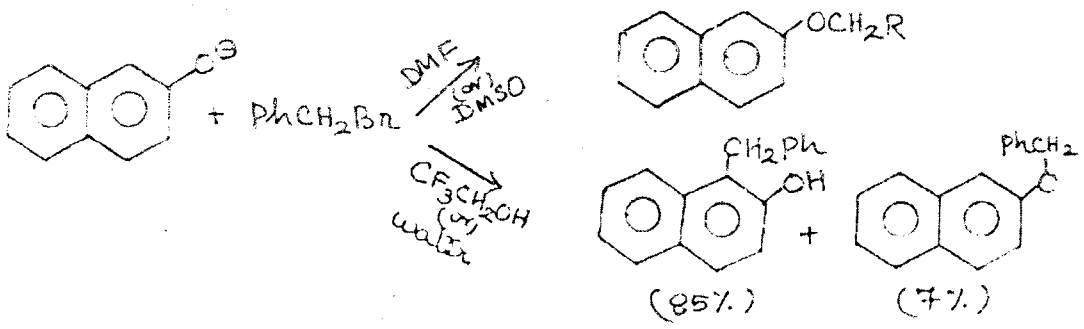
Phenoxide ions offer opportunities for both C-/ O- alkylations



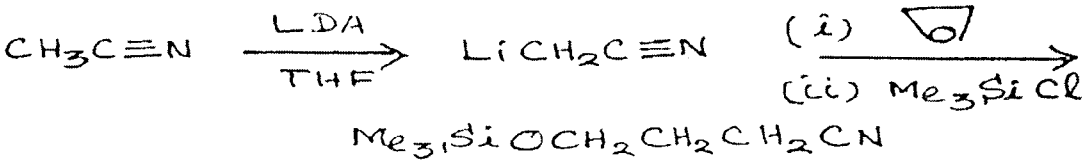
In this case, C-alkylation is burdened energetically by the fact that aromaticity is destroyed as C-alkylation proceeds.



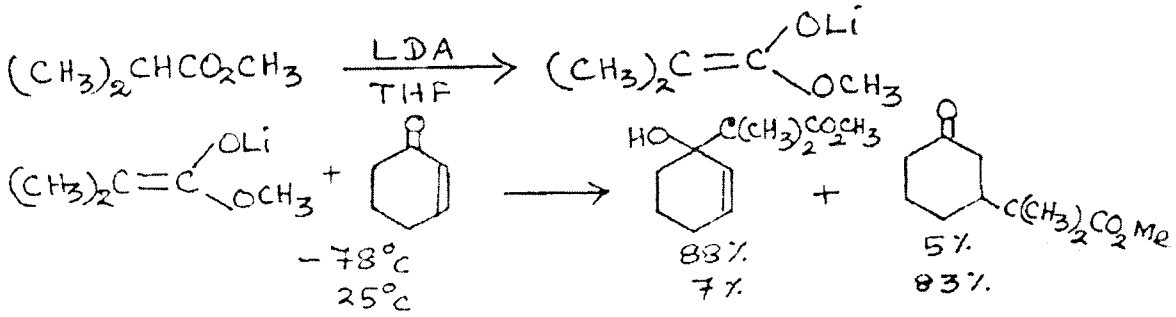
The effect of solvent in the site of alkylation is given by the following reactions.



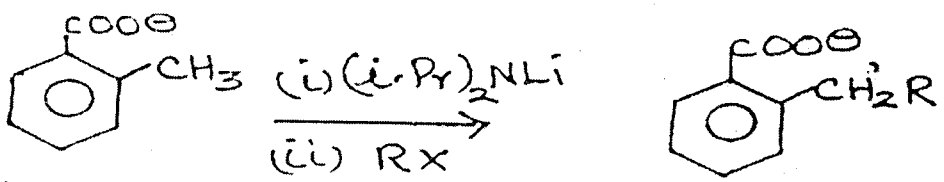
Acetonitrile can be deprotonated provided relatively strong non- nucleophilic bases such as LDA, are used. The lithio derivative can be alkylated at the carbon.



The addition of ester enolates to the carbonyl group of α, β -unsaturated ketones can be faster than conjugate addition. Conjugate addition leads to the stable product. And is carried out under conditions of equilibrium control,

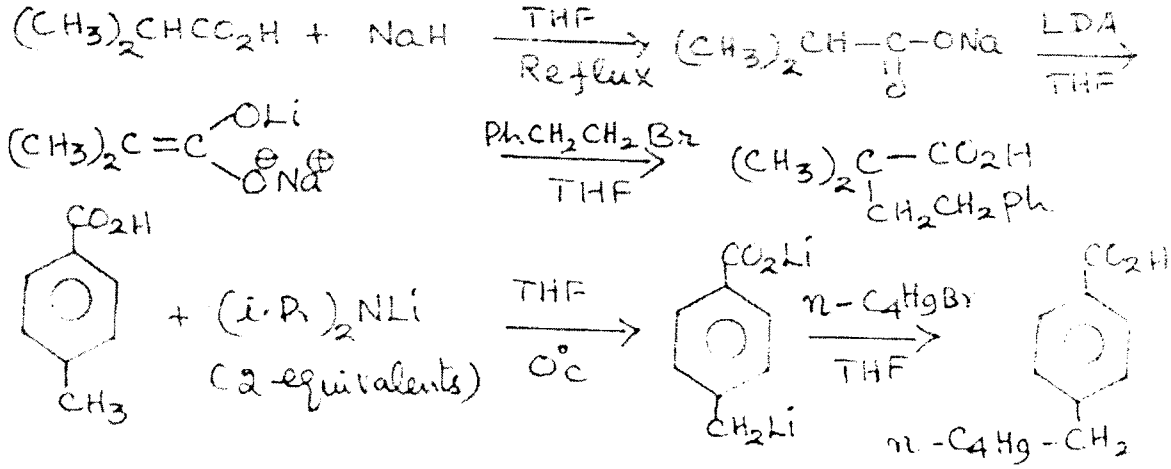


Similar α - alkylation of carboxylic acids via dianions, aromatic acids can also be methylated.

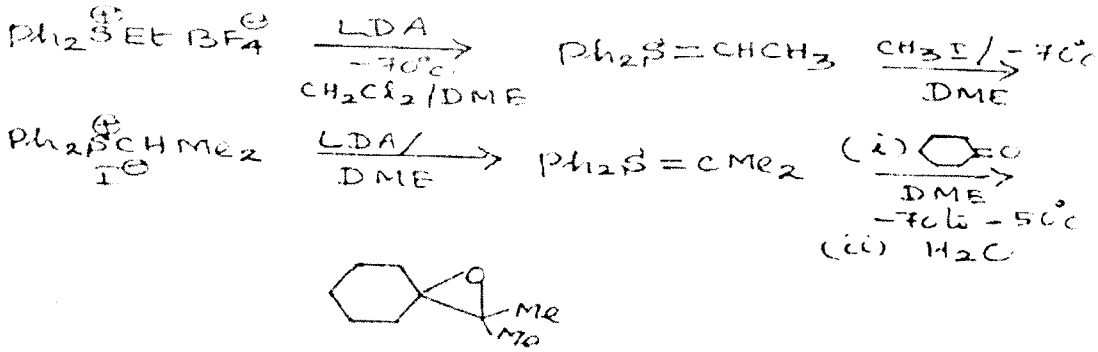


$(i.Pr)_2NLi$ reduce only the halogen of ∀- haloketones leaving the carbonyl group intact.

C-alkylation via dianions of carboxylic acids can be achieved using LDA.

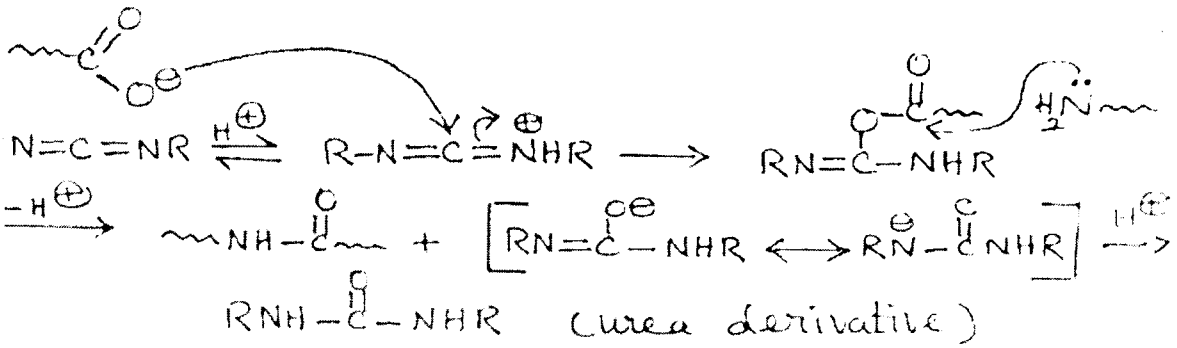


Alkylidene sulfuranes with two alkyl substituents at the carbon adjacent to sulphur are very unstable and are best obtained using LDA. Because of their instability these dialkylylids should be used immediately after they have been prepared.

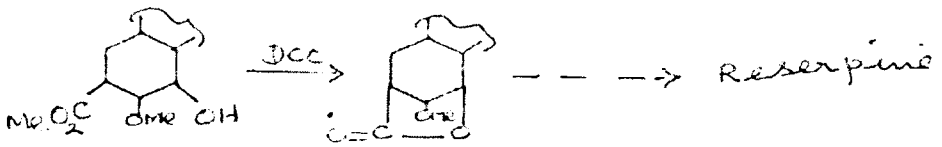


DCC

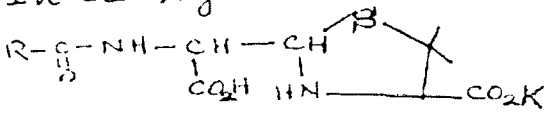
A neutral dehydrating agent used in the preparation of polypeptides. The reagent is $-CO_2H$ react readily with amines in the presence of acid & DCC, a disubstituted urea precipitating from solution. The probable mechanism is:



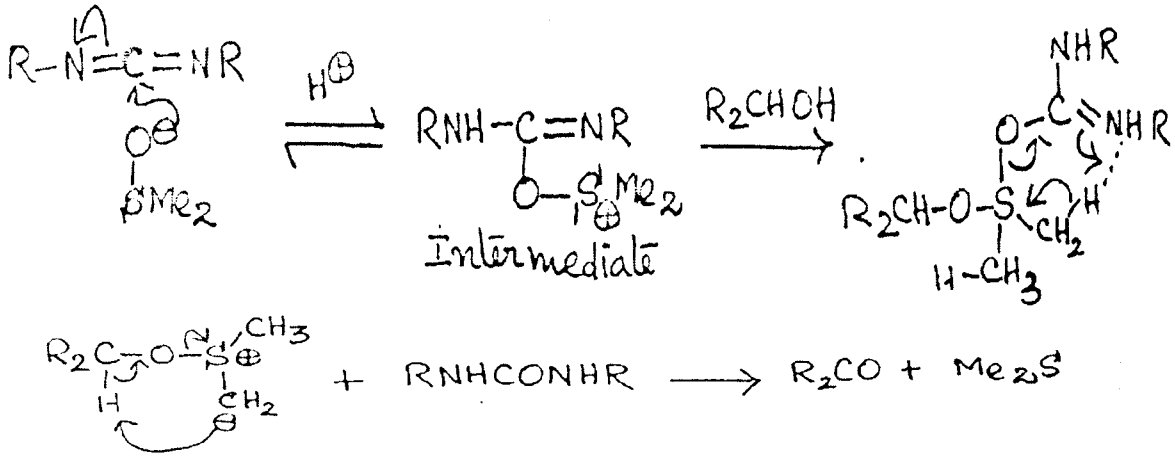
This technique is used in Merrifield solid-phase peptide synthesis. This method is suitable only for stepwise synthesis of peptides, for carboxyl-terminating peptides are racemized by these procedures.



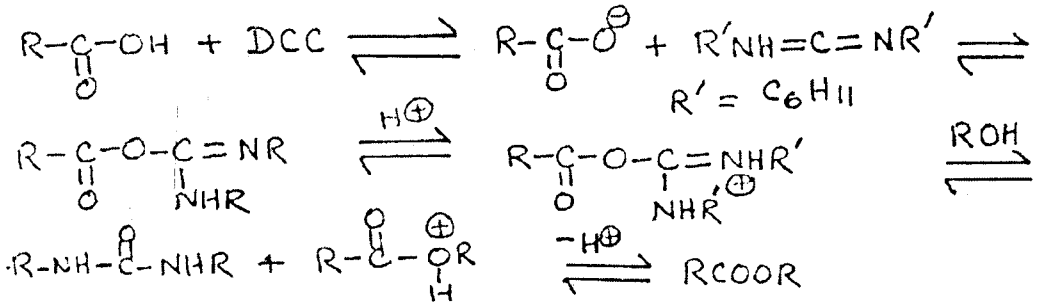
In the synthesis of Penicillin



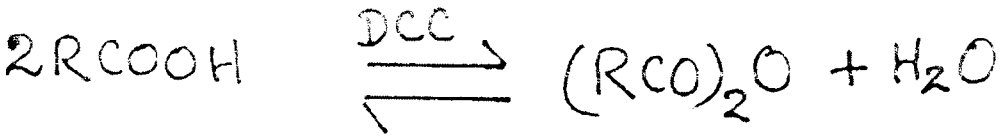
DCC is used in the oxidation of molecules that are sensitive to more powerful oxidants. This is done by combining DMSO-DCC first. Then this intermediate reacts with the alcohol to convert it into a ketone. A major part of the driving force for the reagent is derived from the conversion of the diimide to a urea, with formation of an amide carbonyl. The reaction is,



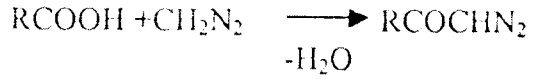
DCC can be used for the esterification of –CO2H.



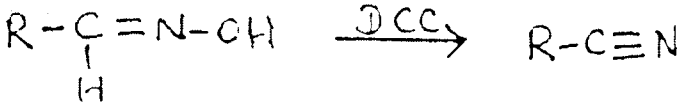
To form anhydrides from ordinary carboxylic acids DCC can be used.



Diazoketones (Arndt-Eistert) can be prepared from carboxylic acid & diazomethane using DCC



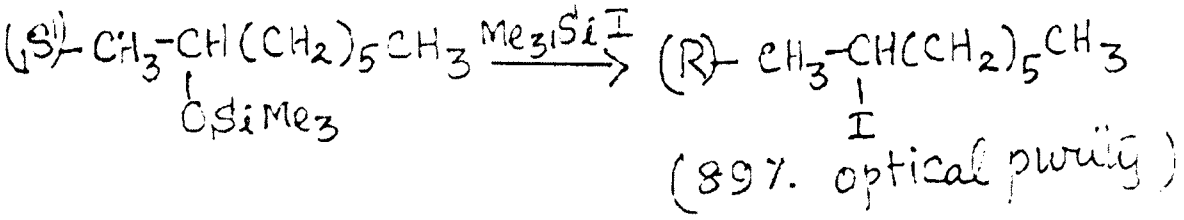
Aldoximes can be dehydrated to nitriles (normally AC_2O is used) under mild conditions using DCC in presence of Et_3N & Cu^{2+} ions.



TRIMETHYLSILYL IODIDE

Trimethylsilyl ethers of alcohols are converted to iodides by reaction with trimethylsilyl iodide. This transformation can be carried out by in situ generation

of trimethylsilyl iodide from trimethylsilyl chloride and sodium iodide. The silyl ethers are easily prepared from alcohols by reaction with trimethylsilylchloride in pyridine. The method appears to be quite general and good yields have been reported for 1°, 2°, 3° & benzylic alcohols. Secondary systems react with predominant inversion of configuration.

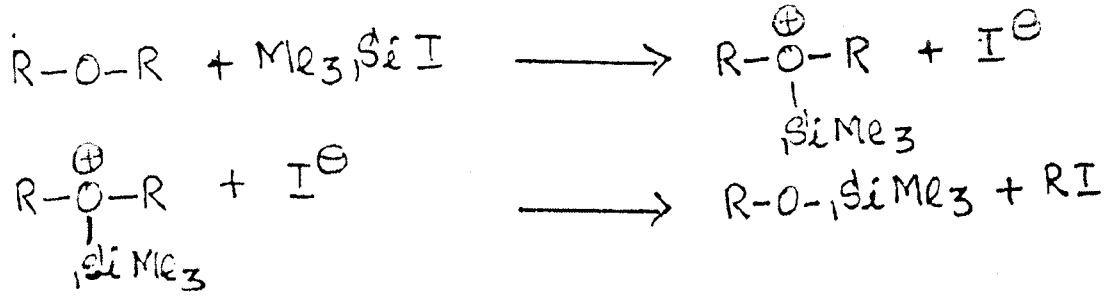


Nucleophilic cleavage of C-O bonds in ethers & esters

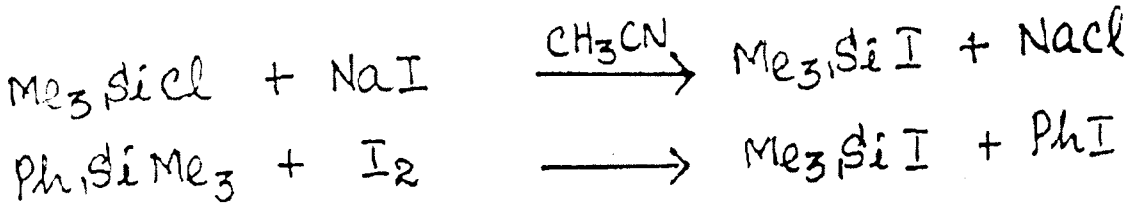
The cleavage by nucleophilic substitution of C-O bonds in ethers or in esters is frequently a desirable synthetic transformation. The objective may be to remove a temporary blocking group or in the case of esters, for example, to liberate a carboxyl group under nonhydrolytic conditions. The classical ether cleavage reactions involving con.hydrogen halides are much too strenuous for most polyfunctionalised molecules.

Some milder reagents in this line are boron tribromide and boron trifluoride in the presence of thiols.

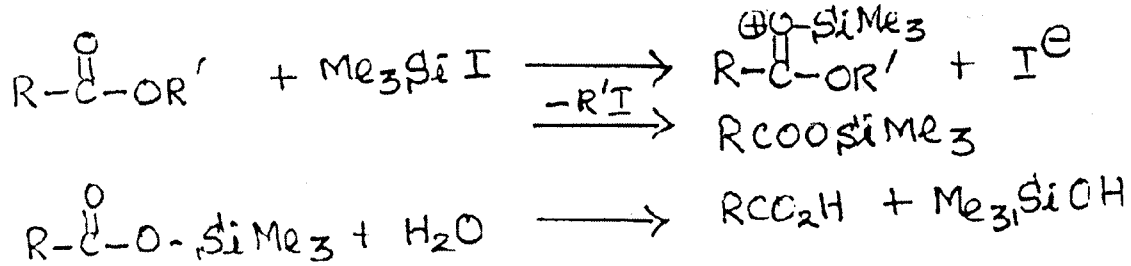
Trimethylsilyl iodide cleaves methyl ethers in a period of a few hours at room temperature. Benzyl & t-butyl systems are cleaved very rapidly, whereas secondary systems react over 10-50 hours. The reaction presumably proceeds via an initially formed oxonium intermediate.



The direction of cleavage in unsymmetrical ethers is determined by the relative ease of O-R bond breaking by either S_N2(methyl, etc) or S_Nl(t-butyl etc) processes. Trimethylsilyl iodide is rather expensive and is also difficult to store & handle. So, alternative procedures which generate the reagent in situ from other sources have been reported. In the presence of an ether, the cleavage reaction proceeds as the trimethylsilyl iodide is generated.



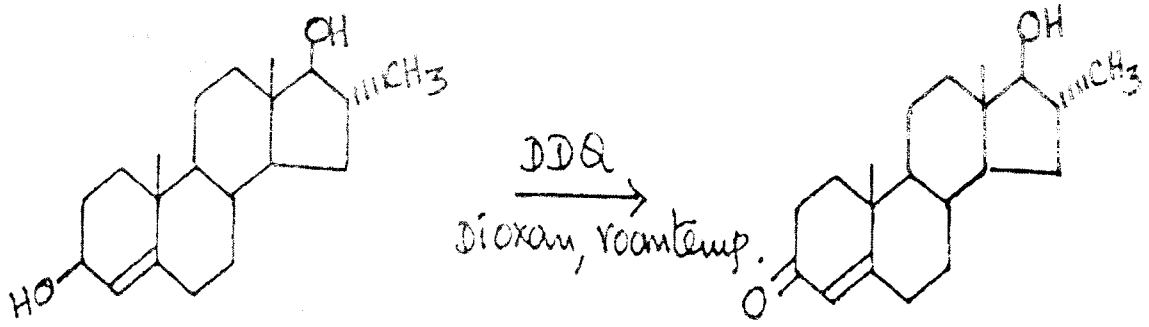
Trimethylsilyl iodide also effects rapid cleavage of esters. The first products formed are trimethylsilyl esters but these are hydrolyzed on exposure to water.



Benzyl, methyl & t-butyl esters are rapidly cleaved, but secondary esters react more slowly. In the case of the t-butyl esters, the initial silylation is followed by a rapid ionization to the t-butyl cation.

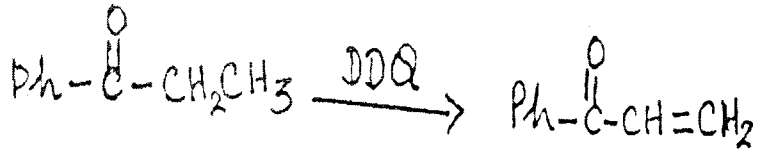
2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)

It is a mild oxidizing agent, used for the oxidation of allylic alcohols. Saturated alcohols are left unaffected.

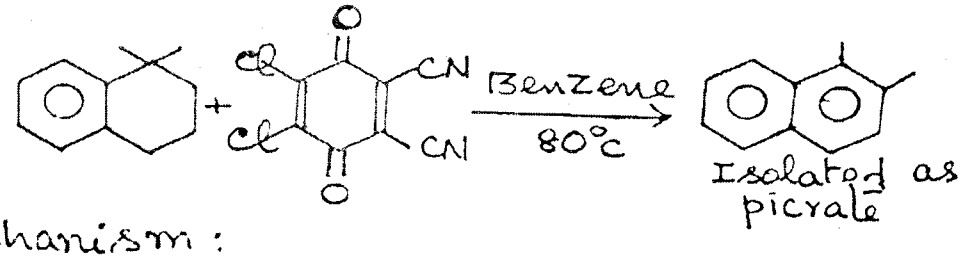


Oxdidation of ketones with oxidizing agents like CrO_3 etc lead to rupture of the bonds adjacent to the carbonyl group with the formation of carboxylic acids controlled methods of oxidation leading to α, β - unsaturated ketones are synthetically important.

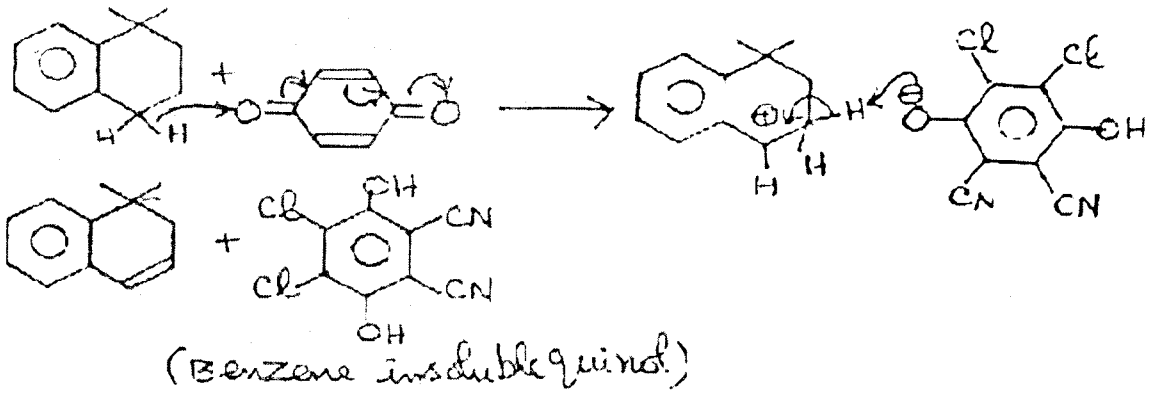
One such reagent is the dichlorodicyanobenzoquinone,



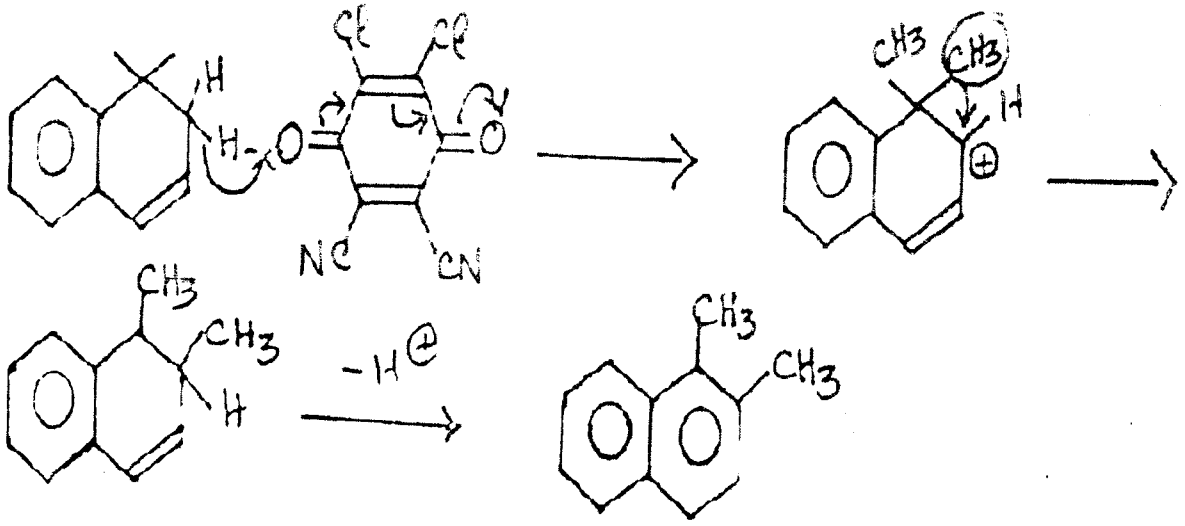
For the conversion of cyclohexenes or cyclohexadiene to benzene derivatives it can be used as solutions in boiling benzene.



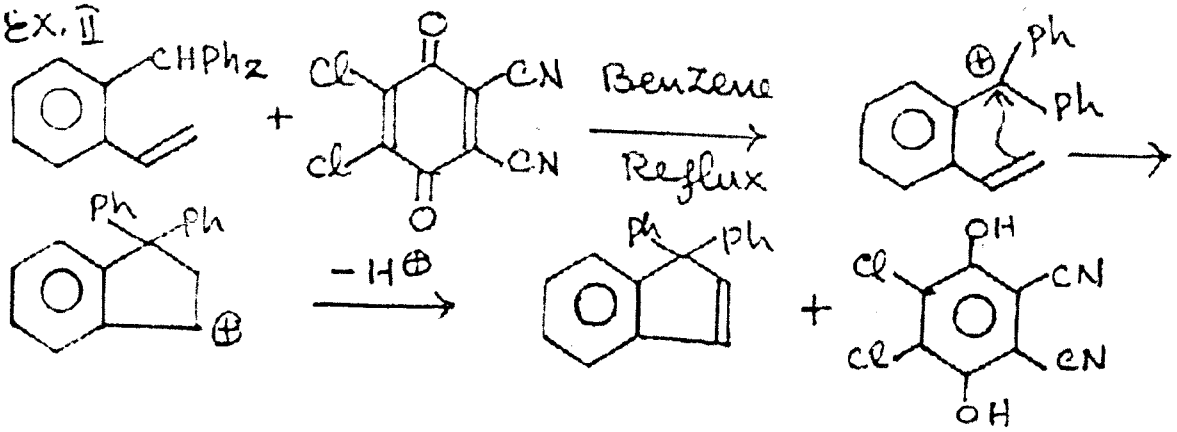
Mechanism :



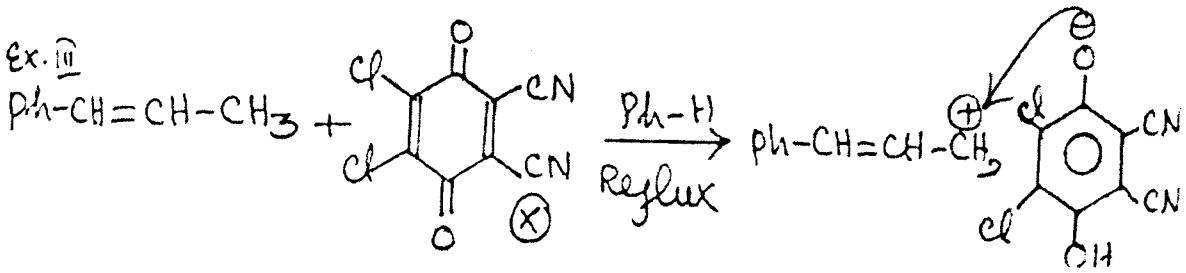
(Benzene insoluble quinol)

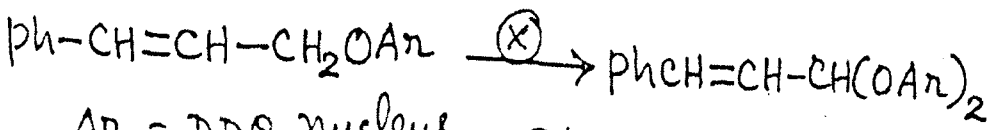


Ex. II

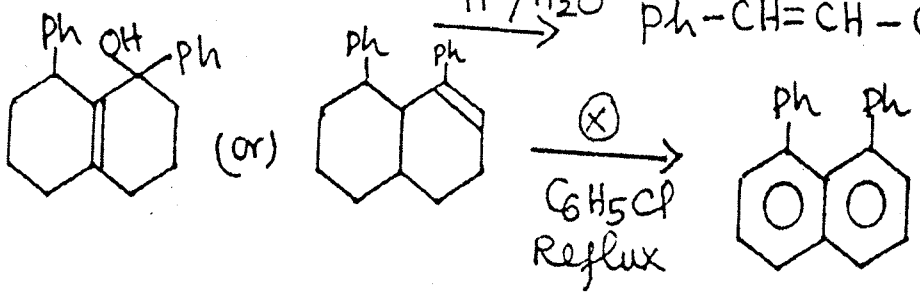


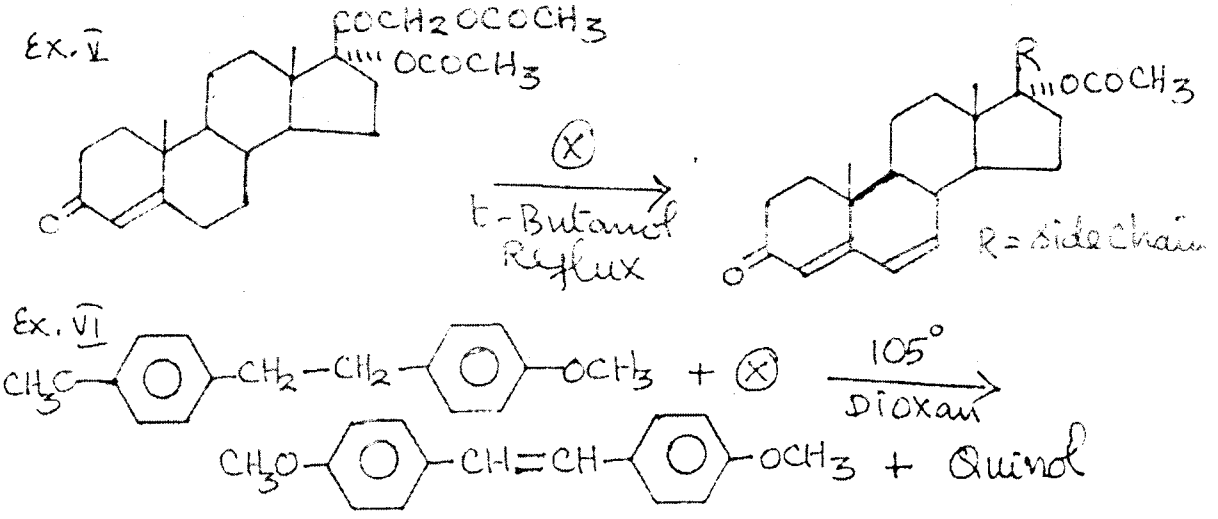
Ex. III





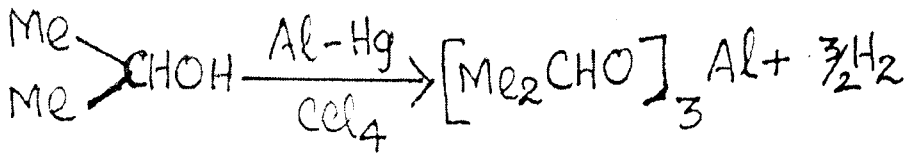
Ex. IV





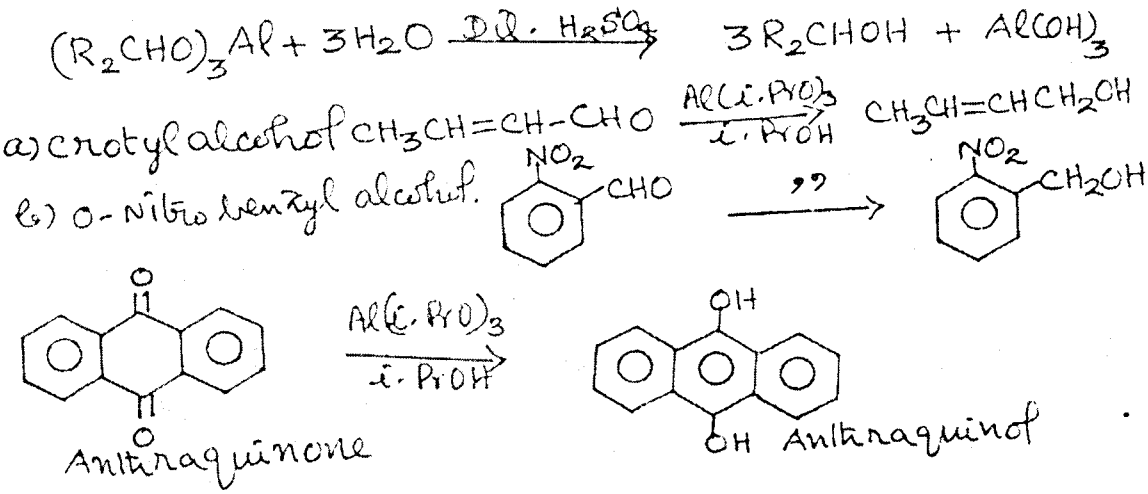
$[Me_2CHO]_3Al$ **Aluminium isopropoxide**

It may be prepared by heating the anhydrous alcohol with amalgamated aluminium in the presence of a trace of CCl_4 as catalyst.

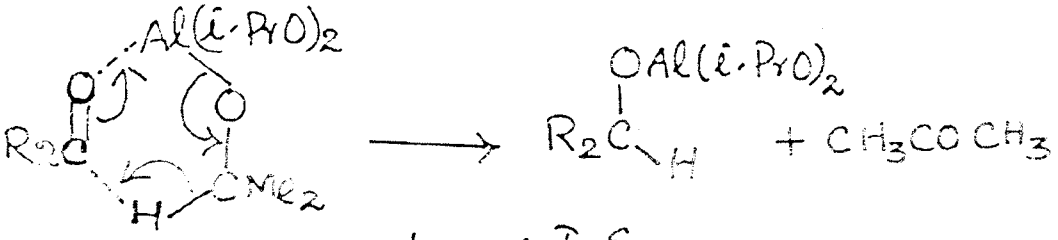


Uses:

This is a specific reducing agent towards carbonl group. So it can be used for reducing aldehydes & ketones containing some other reducible group, such as a double bond, a nitro or an ester group which are not reduced under these conditions.



Mechanism:



a cyclic 6-membered T.S.

$$\longrightarrow Al(OCHR_2)_3 + 3CH_3COCH_3$$

Aluminium t-butoxide is prepared by the action of Al-Hg on the t-butyl alcohol in the presence of traces of carbon tetrachloride which acts as a catalyst.

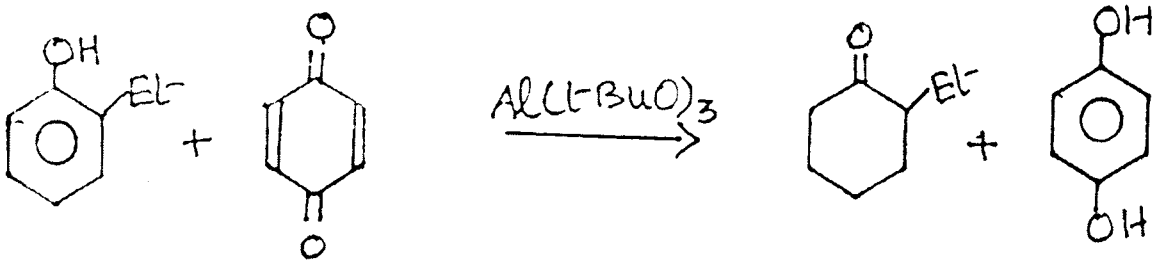
$$3\,Me_3C-OH + Al \longrightarrow (Me_3C-O)_3Al + 3/2\,H_2$$

It is a catalyst in Oppenauer oxidation.

(Ex) MeCH(OH)–CH_2–CH_3 $\xrightarrow{Al(t\text{-}BuO)_3}$ $CH_3COCH_2CH_3$

in acetone, C_6H_6

Synthesis of 2-ethylcyclohexanone



(O) of unsaturated alcohols (as it does not affect the double bond)

$$CH_3-CH(OH)-CH=CH-CH=C(CH_3)-CH=CH_2 \xrightarrow[CH_3COCH_3,\,C_6H_6]{Al(t\text{-}BuO)_3}$$

6-Methyl-3,5,7-octatriene-2-ol

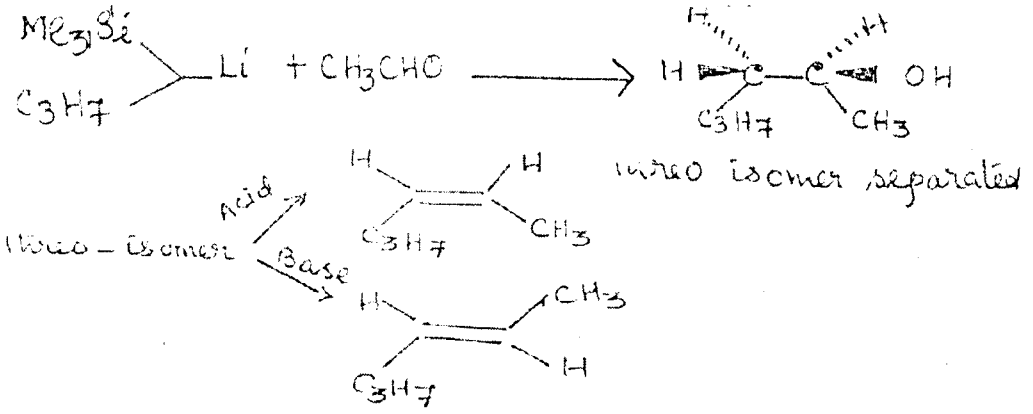
$$CH_3-C(=O)-CH=CH-CH=C(CH_3)-CH=CH_2$$

6-Methyl-3,5,7-octatriene-2-one.

PETERSON OLEFIN SYNTHESIS

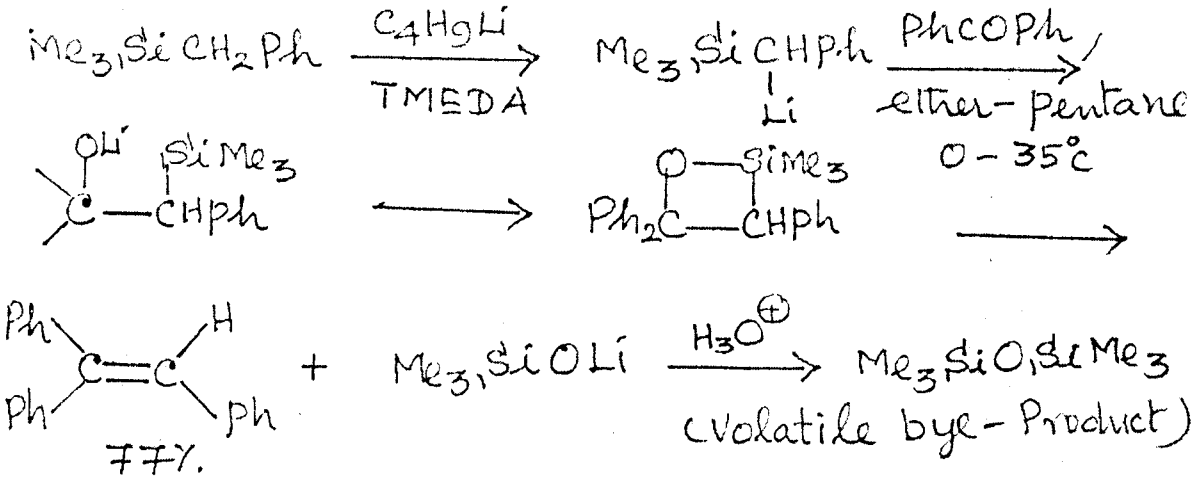
This is a modified Wittigs reaction. Instead of phosphorous here silicon is used. In this reaction Me_3SiOH is eliminated from a β - hydroxyalkyltrimethylsilane, This by-product is more volatile than the triphenylphosphine oxide (Wittigs reaction).

In this reaction both cis & trans olefines can be obtained from the hydroxysilane, depending on how th elimination is effected.

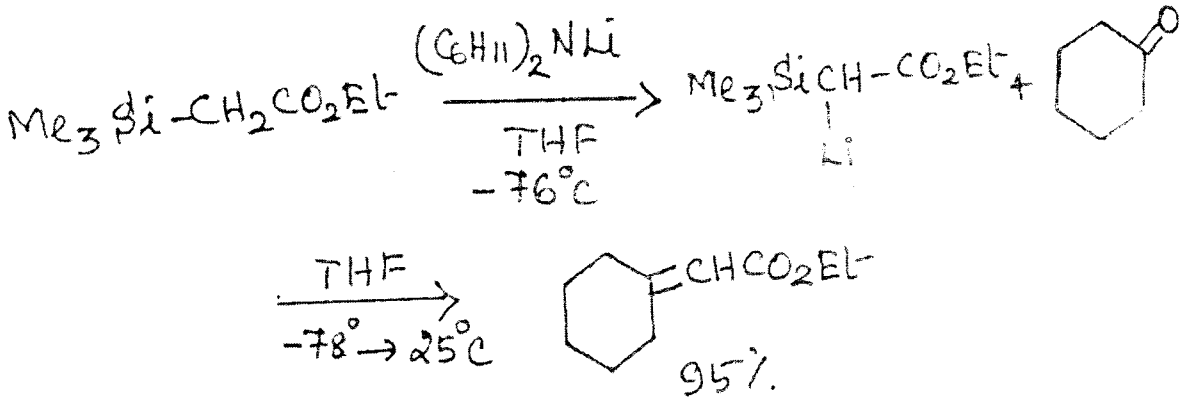


The scheme runs as follows:

α- chlorosilanes form α- silyl carbanions on reaction with magnesium or lithium. These carbanions readily react with carbonyl compounds, forming lithio derivatives of β - hydroxysilanes. The latter eliminate the trimethylsilyloxy group spontaneously in THF solution to give olefins in good yield.

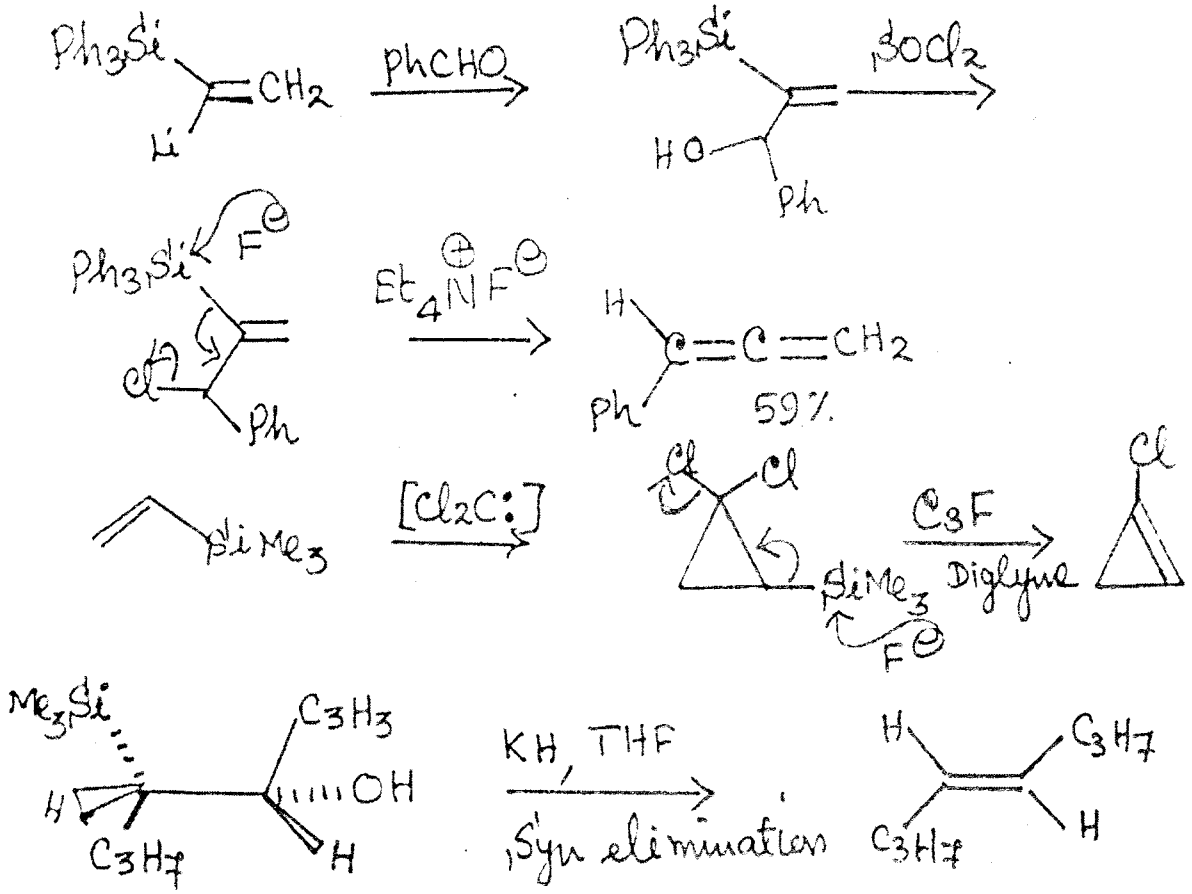


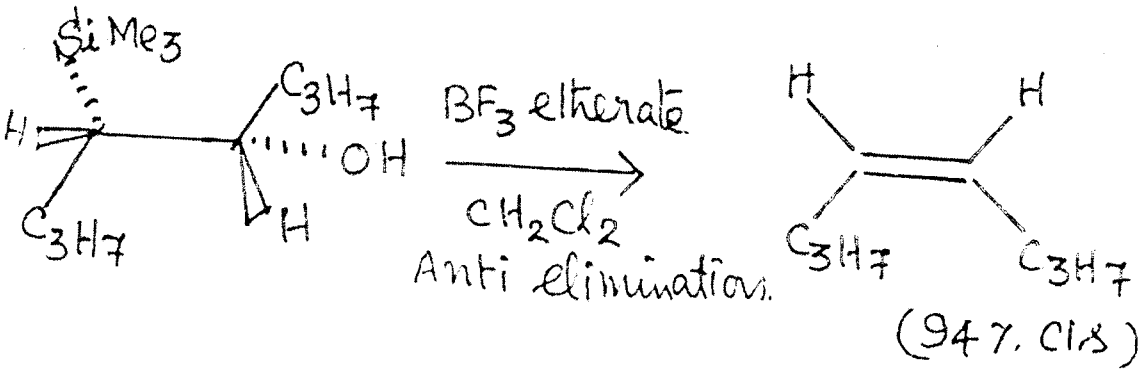
It can be used to prepare α,β-unsaturated esters.



Strained alkenes like, allenes, cyclopropenes can be prepared by elimination from β- halogenosilanes, using fluoride ion .

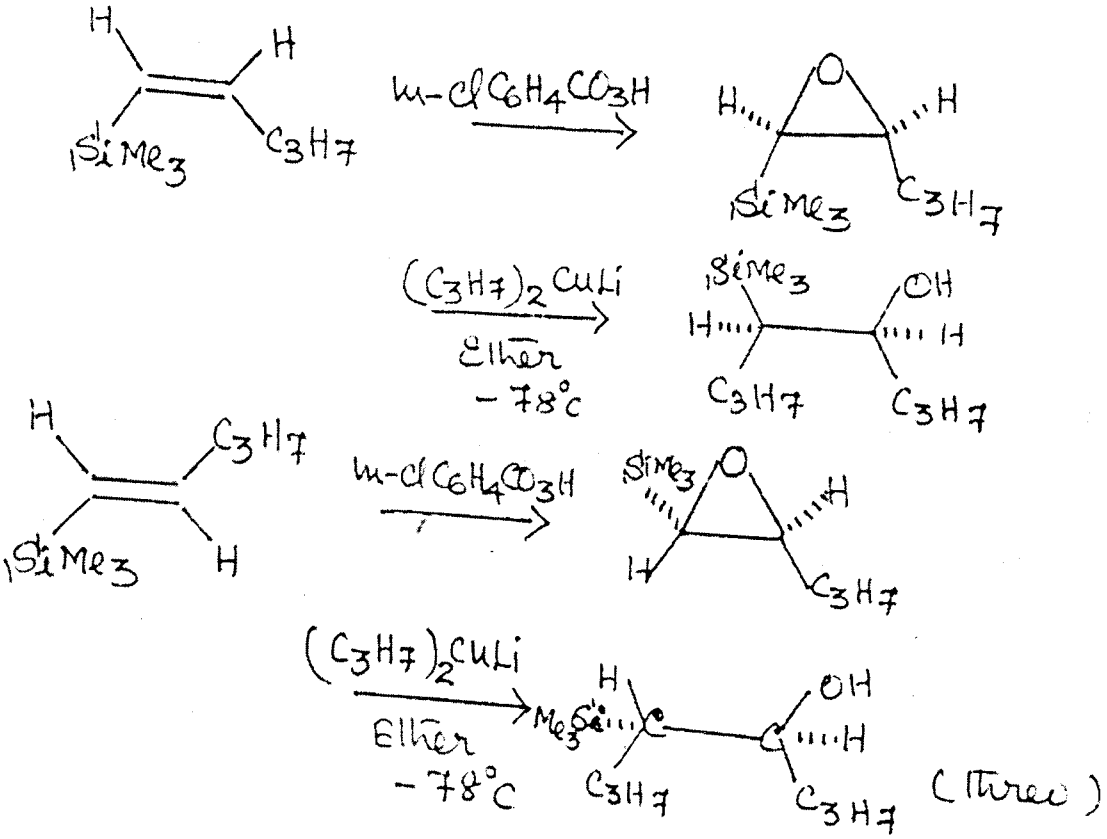
When ordinarily effected Peterson reaction gives a mixture of Cis & trans – olefins. The actual elimination however is highly stereoselective. So with a pure diastereoisomer of the hydroxysilane elimination can be controlled to give either the Cis or the trans olefin.



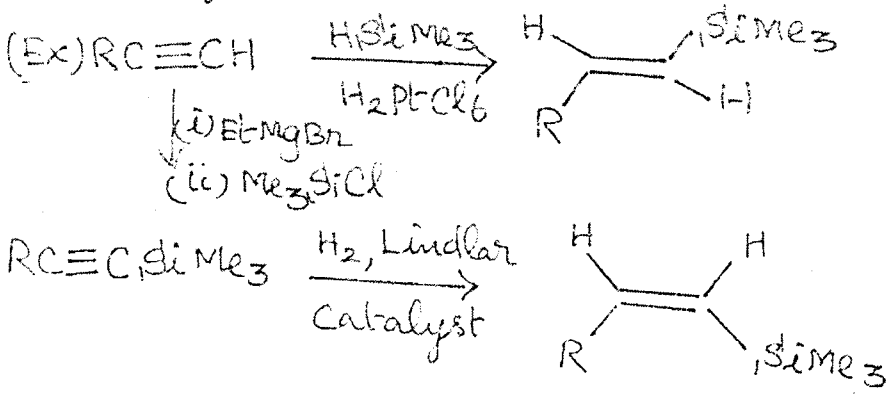


The diastereoisomeric β - hydroxysilanes are obtained from the appropriate α, β-epoxysilanes by reaction with lithium organocuprates reaction occurs selectively at the carbon bearing the silicon atom to give the erythro hydroxysilane from the cis-epoxide and the threo hydroxysilane from the trans-epoxide.

The series of reactions therefore furnishes a method for the stereoselective synthesis of olefin from 1-alkenylsilanes.



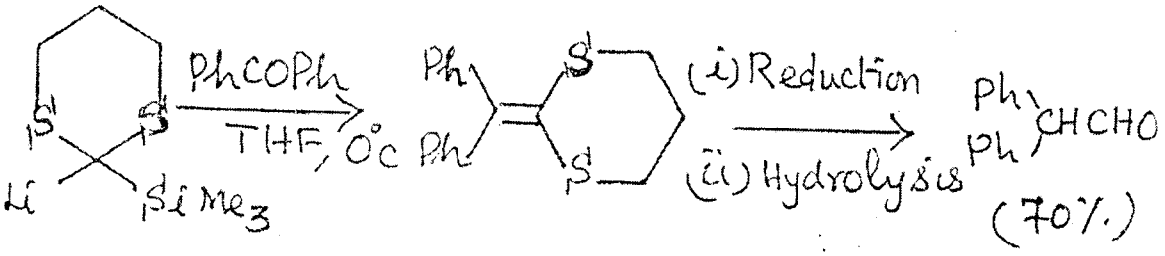
1-Alkenylsilanes can be made in a no. of ways



The Peterson reaction has been used to prepare ketene thioacetals by reaction of aldehydes (or) ketones with 2-lithio-2-trimethylsilyl-1,3-dithiane. The latter can be readily obtained from 1,3-dithiane.

The ketene thioacetals are useful synthetic intermediates.

On hydrolysis they give carboxylic acids ($RR^1CO \longrightarrow RR^1CHCO_2H$) & followed by hydrolysis gives aldehydes, alkylation before hydrolysis leads to ketones.



SELENIUM DIOXIDE (first of all it is used as an oxidizing agent by H.L.Riley in 1932)

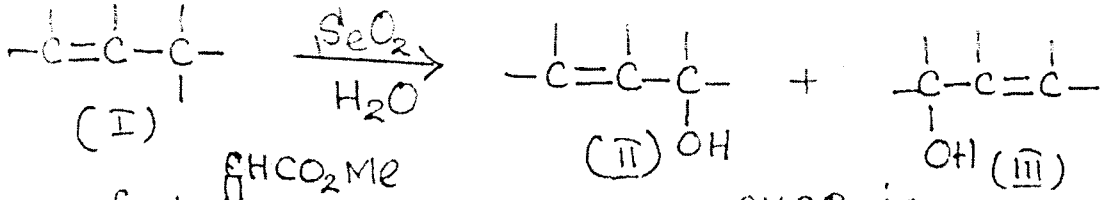
Preparation : Prepared by heating strongly in air in the presence of traces of nitrogen dioxide as a catalyst.

$$Se + O_2 \longrightarrow SeO_2$$

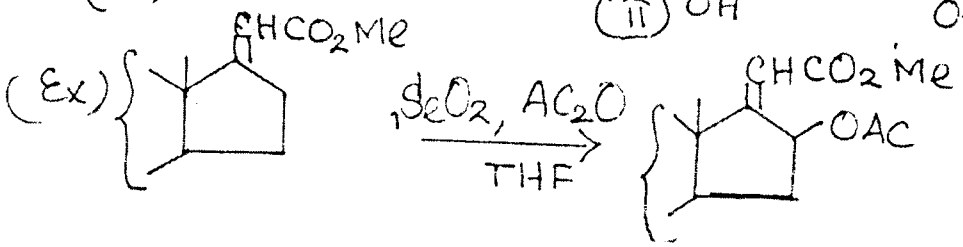
2) By passing the vapour of sulphuryl fluoride over selenium & silica contained in a glass vessel.

$$2SO_2F_2 + SiO_2 + Se \longrightarrow SeO_2 + 2SO_2 + SiF_4$$

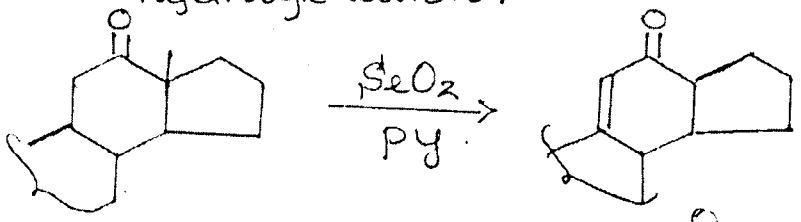
Allylic oxidation: SeO_2 in aqueous or alcoholic solution is used to get allylic alcohols.

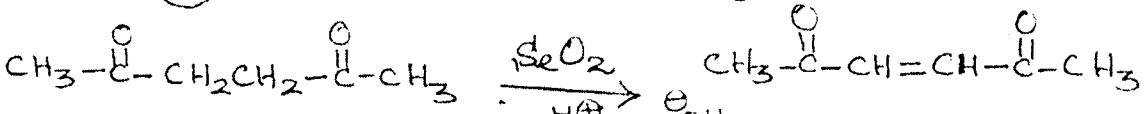


(I) (II) (III)

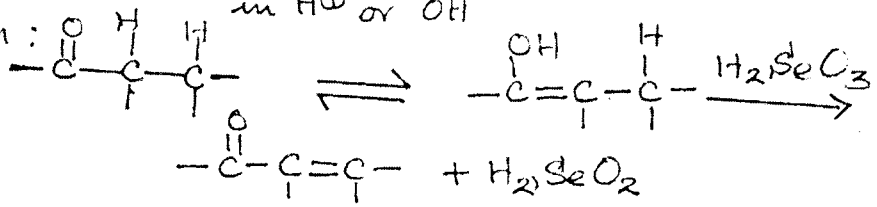


Dehydrogenation:

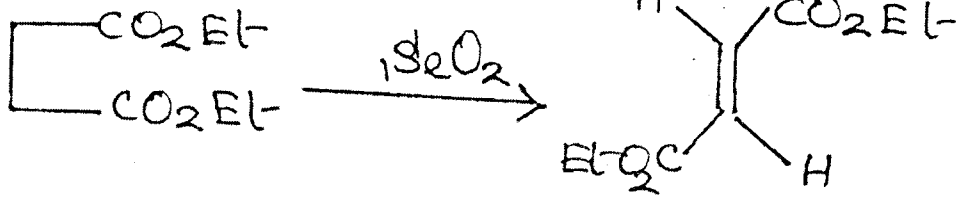




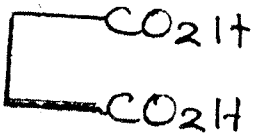
Mechanism:



(i)



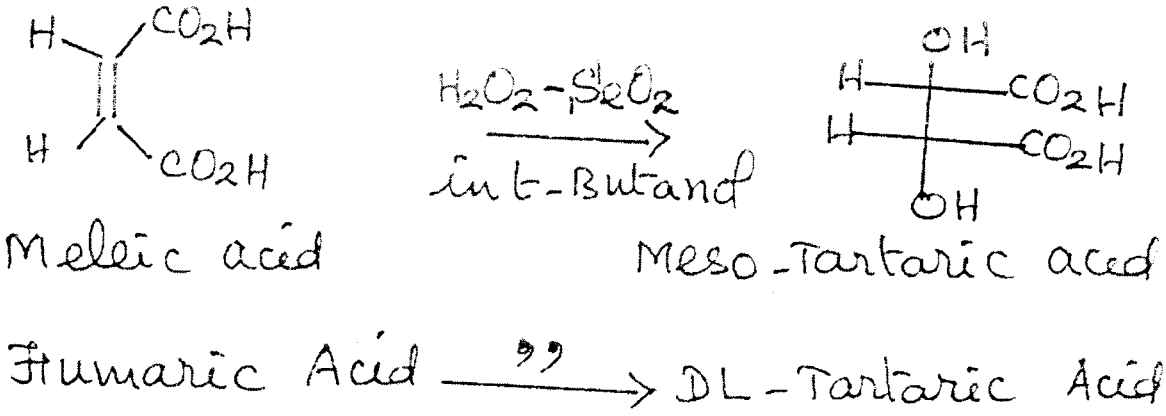
(ii) $2CH_3COOH \xrightarrow{\text{''}}$



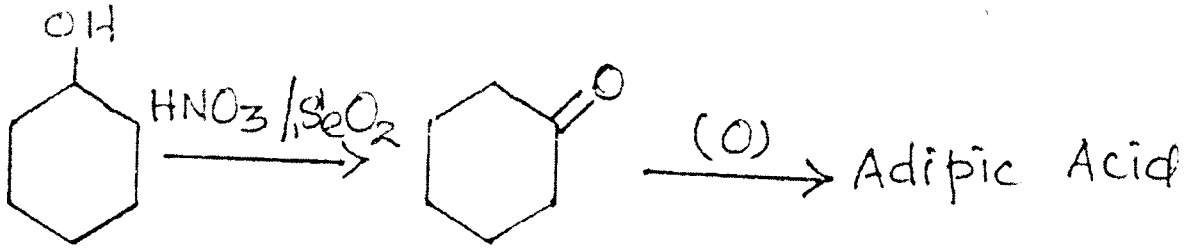
(iii) $C_6H_5CH_2OH \xrightarrow[\text{ills b.-pl.}]{SeO_2\ al.}$ PhCHO

As a Catalyst:

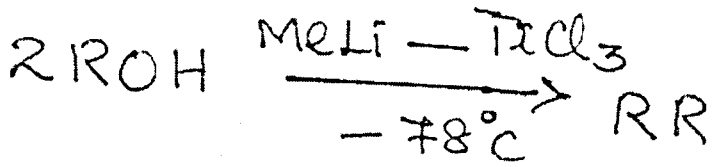
SeO_2 catalyses the trans hydroxylation by H_2O_2 of some unsaturated compounds.



It catalyses the oxidation of cyclohexanol.

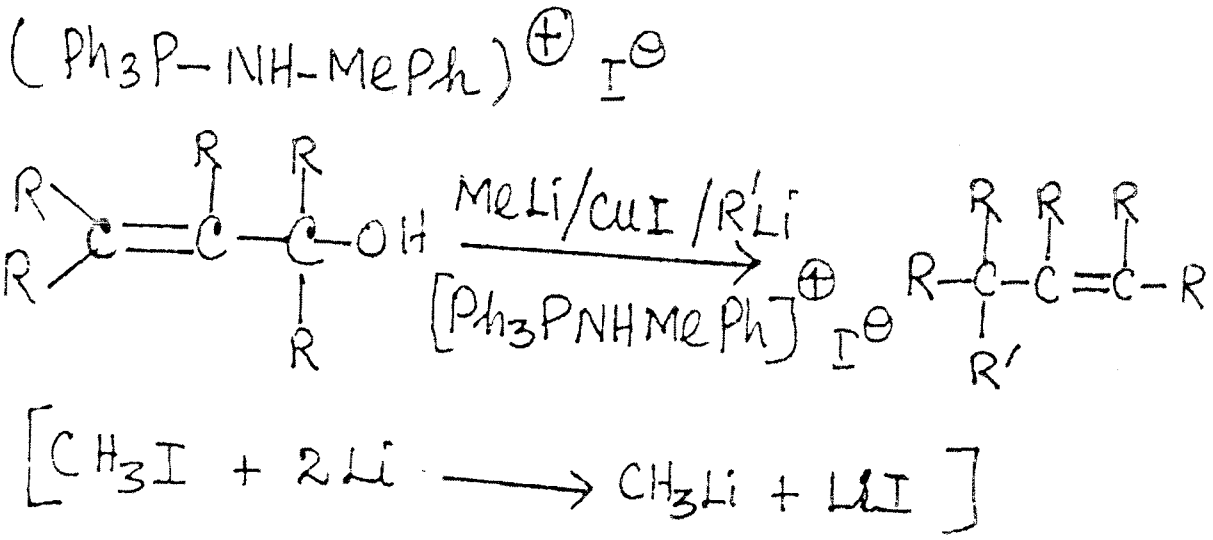


Methyl Lithium :

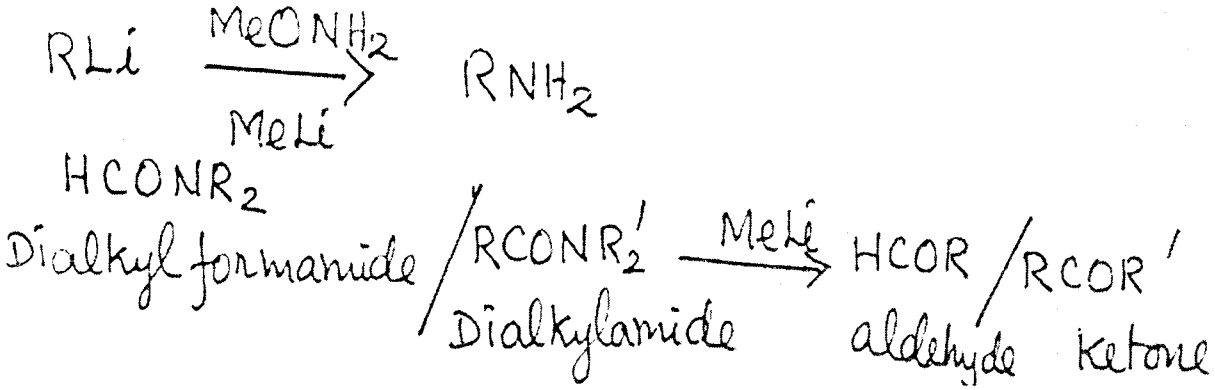


Methyl lithium can be used for the symmetrical coupling of allylic or benzylic alcohols. The alcohols are treated with methyl lithium and $TiCl_3$ at –78°C with allylic alcohols, a mixture of products is produced ie normal & rearranged allylic products.

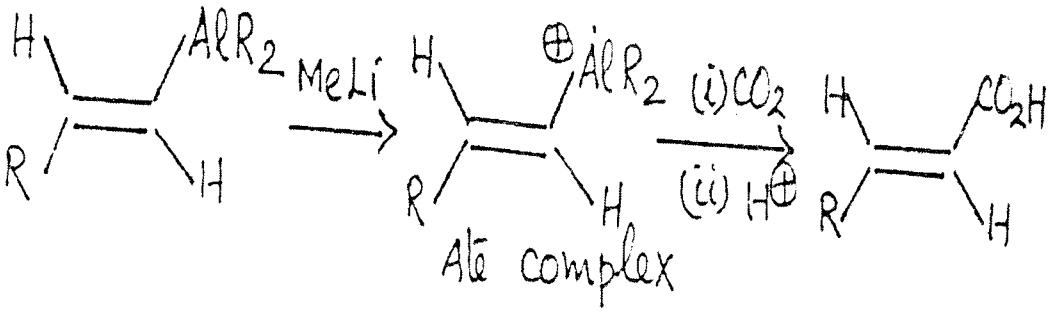
Methyl lithium is used to get alkenes from allyl alcohols i.e. the alcohol is coupled with a mixure of Me Li, CuI & RLi(*lithium alkoxy alkylcuprates) in presence of* N-methyl – N- phenylamiontriphenylphosphonium iodide,



Alkyl and aryllithium compounds can be converted to 1° amines by treatment with methoxyamine and methyl lithium in ether at – 78°C



α, β - unsaturated acids can be prepared by carbonation if an ate complex of a vinylalane.



PLANNING SYNTHESIS

Introduction:

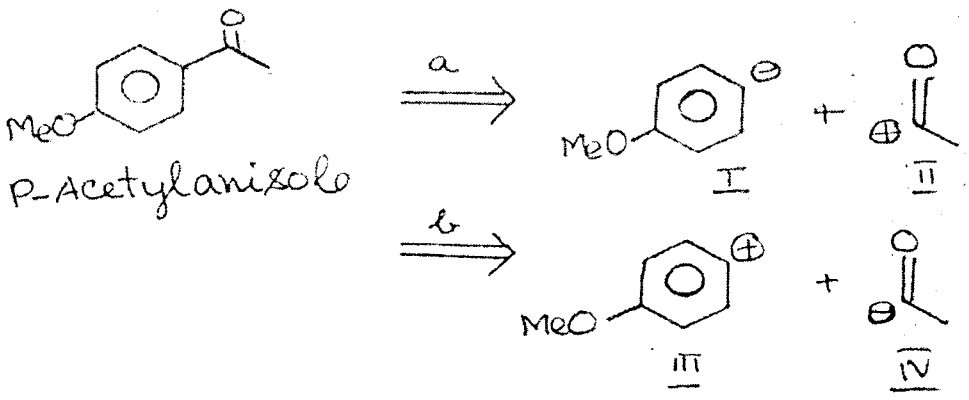
The term synthesis may be defined as a series of reactions carefully chosen to bring about the desired transformation in the highest field and the shortest time.

The lessons of many failures and a few successes have taught the organic chemist that a haphazard or uninformed approach to a synthesis is almost always doomed. So, only the most careful and meticulous plans laid on a foundation of knowledge and facts will help one to get the desired compound. In some respects organic chemist is like a sculptor. Just as the sculptor builds intrigue and enthralling structures with his raw materials, the organic chemist also tries to build complex and exotic organic molecules with the help of his raw materials and a few chosen reagents.

Here in this, we are going to see a glimpse of the basic tenets of organic synthesis. Given the magnitude of organic synthesis, even this would be a difficult task to contain it in a small space. Let us unfold the things one after another.

Synthon -Synthetic Equivalents:

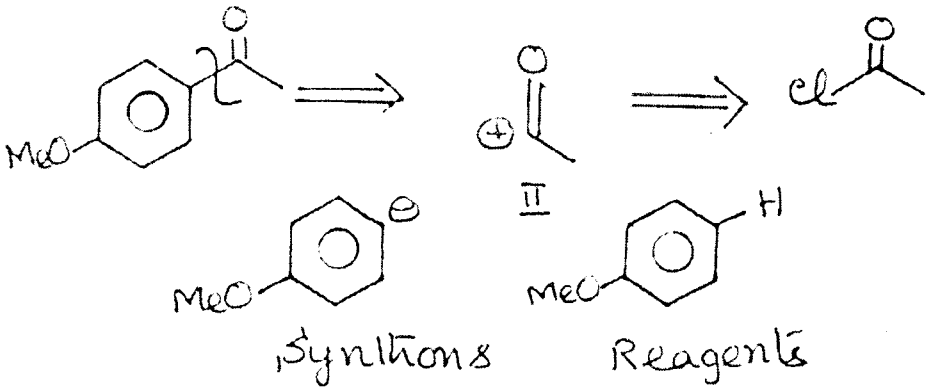
For the synthesis of a given a compound a number of routes may be available in view of the wide variety of organic reactions and reagents placed at the disposable of an organic chemist. So one has to make an analysis and lay-out a plan for the synthesis. A term, which will be most useful for the discussion of synthetic analysis and planning, is synthon. Now, what is a synthon? It refers to a structural unit which has the potential for some specific synthetic operation (or) an idealized fragment, usually a cation or an anion, resulting from a disconnection. May or may not be an intermediate in the corresponding reaction. Consider the following:



Our search for the identification of potential structural units (synthons) for this target molecule gives atleast two possibilities (Path a & b). The two fragments I & II are possible synthons for the construction of the target molecule (and not III & IV). Because from our knowledge of chemical reactions, it is easy to get an acyl cation from acid

chlorides. By using the "Unpolung" technique, we can readily access a carbanion in an aromatic nucleus.

The second pathway introduces nucleophilic carbon at the carbonylcarbon. This is not a vialble proposition, as the carbon is attached to an electrophilic oxygen. SO it can not act as a good structural unit for this target molecule. Obviously I and II are the synthons for the construction of p-acylanisole. These fragments may or may not be involved in the reaction, but can help us to work out the reagents to use. Here as it happens, II and not I, is an intermediate in the synthesis. When the analysis is complete, the synthons must be replaced by reagents for practical use. For an anionic synthon, the reagent is often the corresponding hydrocarbon. For a cationic synthon the target is often the corresponding halide.



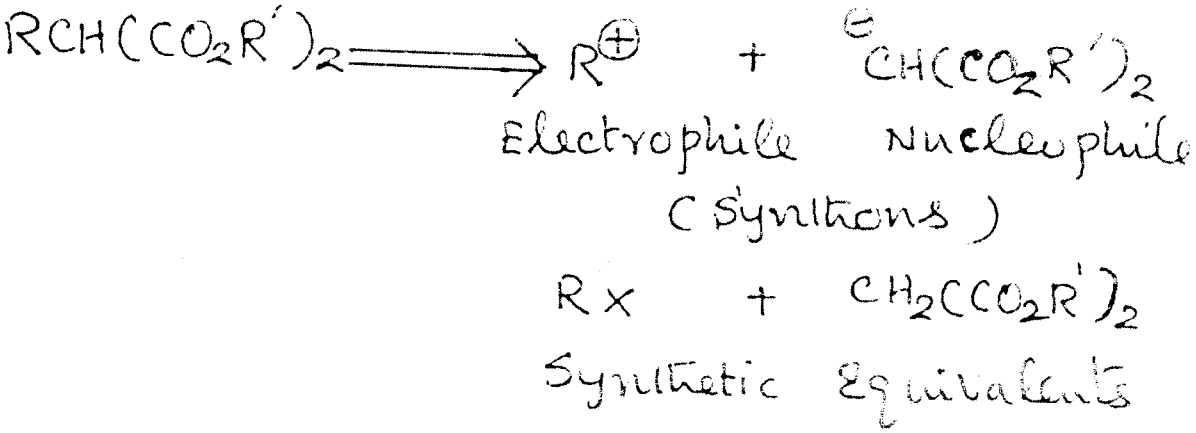
The mathematical symbol " $\Longrightarrow$" is used to place of the word implies. This arrow is distinct from the arrow we normally use ($\longrightarrow$) to represent a chemical transformation. The process is called "disconnection" and the fragments "Synthons".

The reagents used to get "Synthons" are called as synthetic equivalents" ie. in a chemical transformation it is these reagents that actually participate in the reaction and not necessarily the synthons.

In the above example the acid chloride is the synthetic equivalent for the acyl cation. Similarly for the anion, the hydrocarbon nucleus, anisole, is the synthetic equivalent.

Again for the molecule, $RCH(CO_2R')_2$,

$R^{(+)}$ (electrophile) and $^{0}CH(CO_2R')_2$ (nucleophile) may be the synthons.Their respective synthetic equivalents will be RX(halide) and CH2(C0R')$_2$. Thus we can represent this as follows

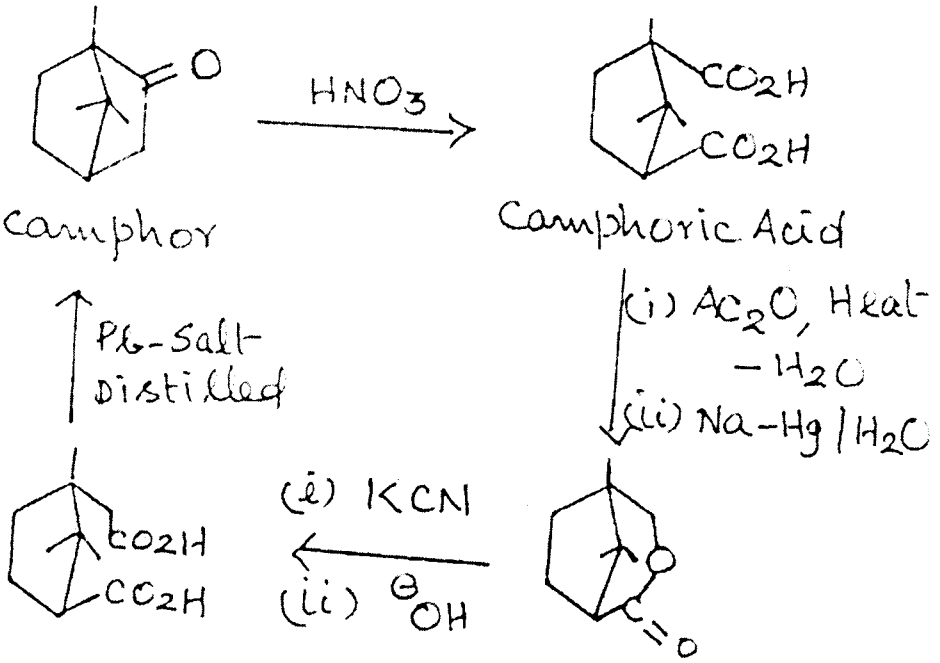


For more information about synthons and synthetic equivalents see reference 8 and 11.

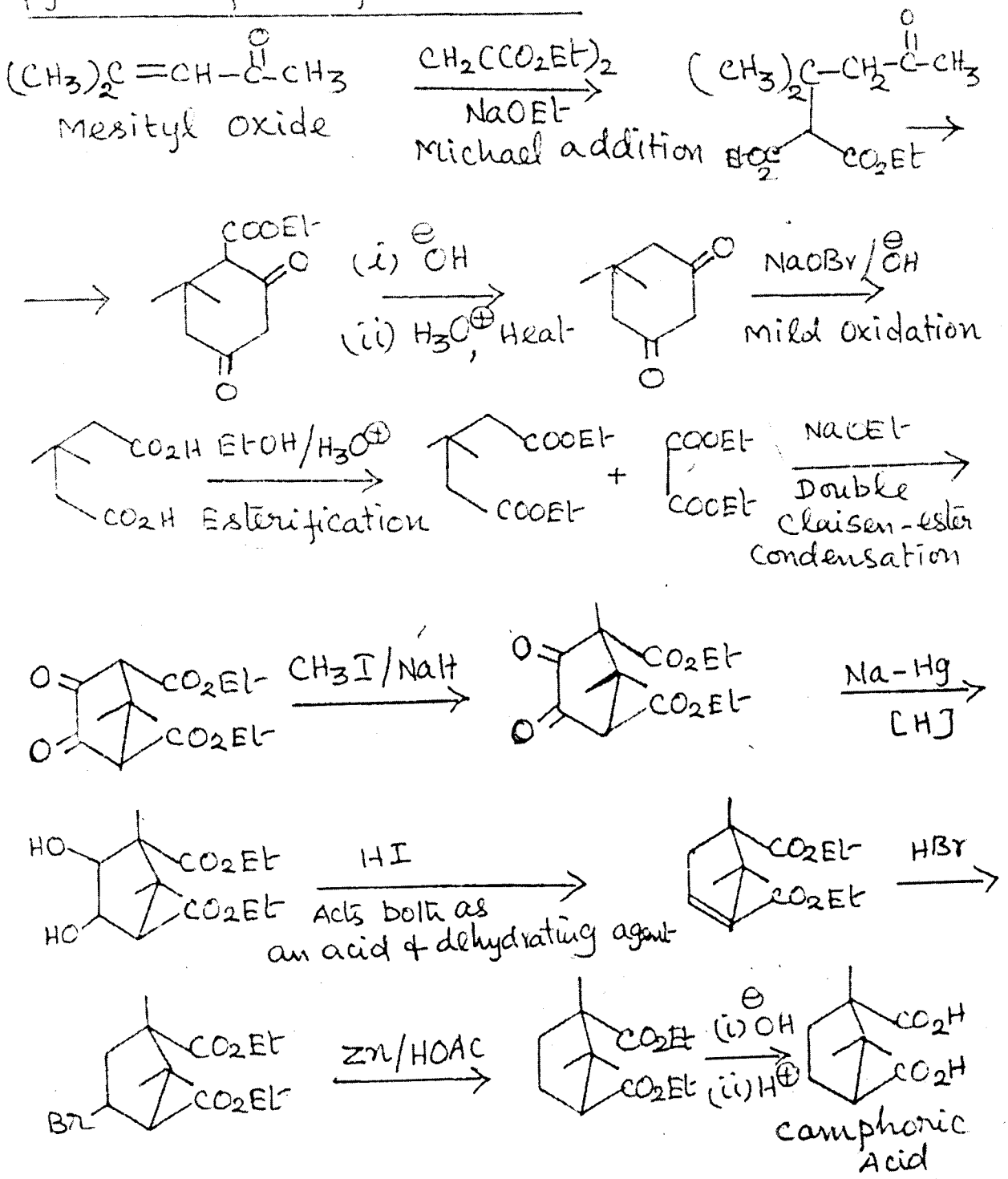
Key Intermediate – Relay Approach:

Sometimes during the degradative work of a natural substance, a key substance may be obtained. From the key substance the synthesis of the natural material may be accomplished. This type of synthetic method is termed as "Relay approach" to synthesis. Now the synthesis of the key substance from commercially available materials may complete the cyclic of operation.

Systematic degradation of camphor gave camphoric acid. To establish the structural change that attends this degradation, camphoric acid is reconverted to camphor through a series of reactions.



Synthesis of Camphoric Acid :



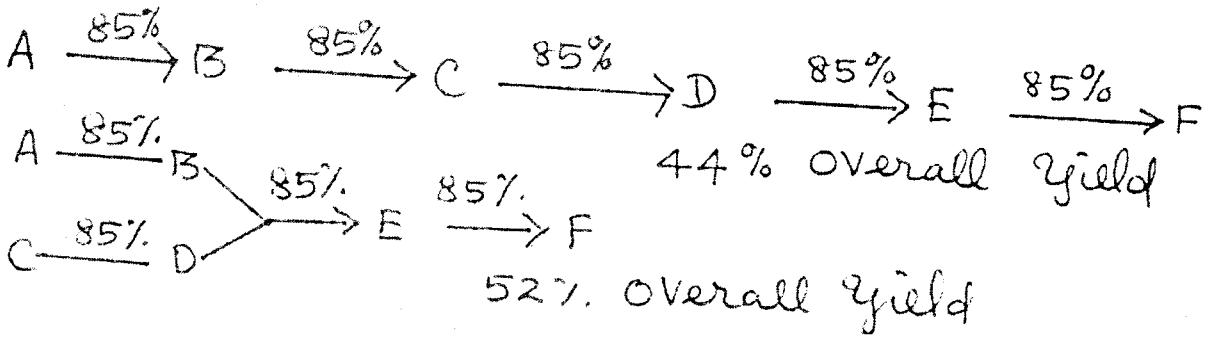
The camphoric acid obtained was resolved and found to be identical with the natural substance. Thus the synthesis of camphoric acid completed the synthesis of camphor.

Linear & Convergent synthesis :

The molecular size has a prominent role to play in the design of synthetic sequence. Greater the size of the molecule desired greater will be the number of steps. Our aim should be to get the most done in minimum number of steps and in the highest yield. Thus a two step synthesis of 2-methyl-3-phenylpropanol is achieved in 68% overall yield whereas a seven step synthesis of estrone, the female sex hormone, is achieved in 8.5% overall yield. Of course the synthesis of the latter compound needs more tailoring.

What are the prospects of a long synthetic scheme? The prospects are not encouraging. Consider a five step synthesis each involving 85% overall yield. In practice one cannot hope to have all these reactions in a particular sequence. Even if one succeeds in stitching these reactions together the overall yield will be only 44%. To overcome this difficulty the synthesis may be carried out in parallel. i.e. construct two large chunks of a molecule separately and then join them to arrive at the desired skeleton. This way we can better our yield.

The advantage of the second scheme may be illustrated as follows: The five step synthesis each yielding 85% overall yield may be first linked in a linear fashion, then in a convergent manner. First procedure can afford us only a 44% overall yield whereas the second one will entail us with 52% overall yield.



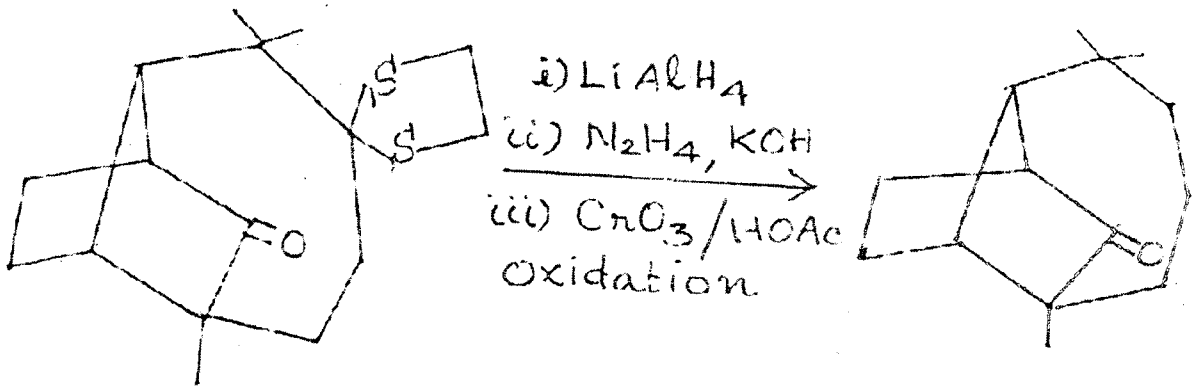
In summary, three factors decide the overall yield in any synthetic plan. They are,

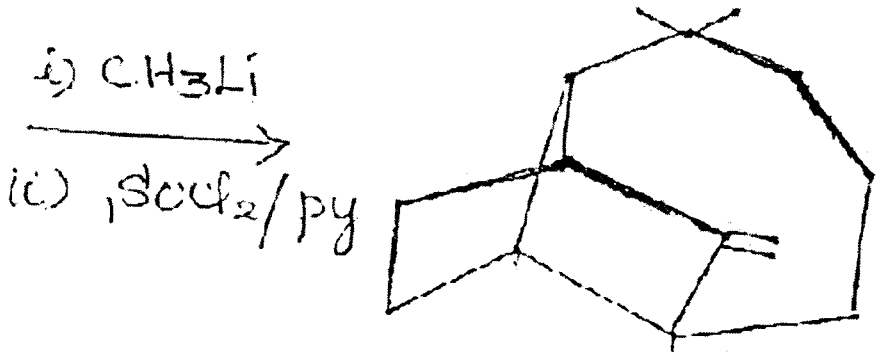
i. Starting material
ii. Number of steps
iii. Type of reactions proposed under each scheme.

FUNCTIONAL GROUP INTERCONVERSIONS:

Synthesis of a compound at times may require multistep transformations involving simple reactions. In these reactions the functional group in a molecule may be converted into another. Then the latter may be reconverted into the former. In between many chemical transformations may take place. To do these things one should have a vast memory and an extensive knowledge of chemical reactions.

Consider the following transformations (it is the final phase of synthesis of the sesquiterpenoid longifolene).





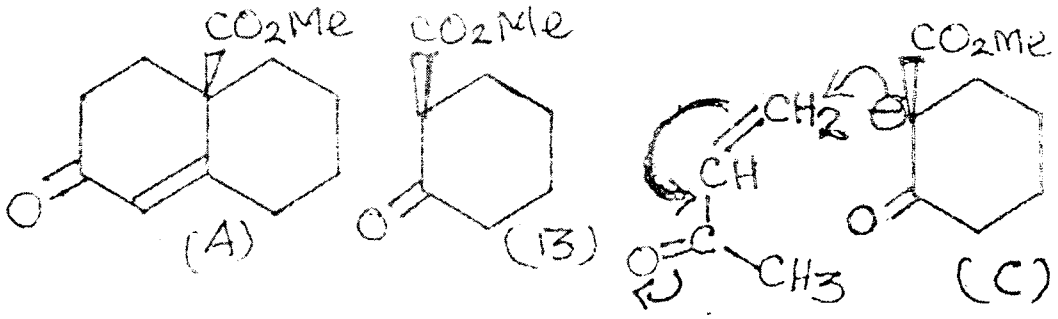
LONGIFOLENE

In the above transformation, we are to remove the dithiol group using Wolff-Kishner reduction. If we leave the carbonyl group as it is, it may also have been removed. To prevent this it is reduced first to an alcohol. Then Wolff – Kishner reduction is done. The reoxidation of the alcohol restores the keto group. The latter is then subjected to further chemical reactions leading to longifolene. This interconversion indicated is just a tip of the ice-berg only. Only experience and wide reading will help one to make the functional group inter-conversions at ease.

Another aspect in synthesis is most of the carbon-carbon bond forming reactions do not give the desired functional group.Further functional group transformations (or) conversions are imminent in most of the cases. An exception to this is the carbon-carbon bond forming reactions using Kolbe's electrolysis technique.

Activating group:

Groups which activate reaction at a particular site are referred to as activating groups. In the construction of the following bicyclic ketone (A), from the cyclohexanone derivative (B), the carbomethoxyl group lends assistance to the carboxyl group in the generation of the desired carbanion(C), thereby facilitating the Michael addition to take place at the desired position.



Here the carbomethoxy and carbonyl groups activate the hydrogens attached to the carbon flanked by these groups. Further the carbomethoxy group can be manipulated to give " angular methyls", which is a rarity to achive. If unwanted could be knocked out easily. Thus it could be used for the purpose of activation or preparation. This in effect is the Robinson Annelation sequence.

Normally a double bonded olefinic compound undergoes electrophilic substitution. But when it is in conjugation with a carboxylic group, the favoured addition is ' nucleophilic' at the beta-carbon w.r.to the carbonyl group. This is the principle of cyanoethylation '.Here again the presence of cyano group, an electron withdrawing group directs the attack of the nucleophile to the beta carbon w.r.to the cyanide group. Thus the conjugated carbonyl and cyano groups activate the beta carbon w.r.to their placement.

Protecting /Blocking Groups

During the course of an organic synthesis we may have to employ polyfunctional molecules. In such cases, the proposed reactions should not interfere with other functional groups, than the one desired. If such a possibility is feared, then it's better to lend protection to them. The group so serves is known as a protecting or blocking group (see foot note)*.

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* From the stand point of the functional groups, these groups lend protection to them from the attack of the reagents, accordingly they are termed as protecting groups. When they occupy ring carbons, especially in aromatic nuclei, they block the entry of the reagents to that particular carbon. Hence are called blocking groups.Of course this concept is valid only under certain environments. Since a group that serves the above purpose under alkaline conditions may not be able to do so under acid medium. This is because deprotection might set in.

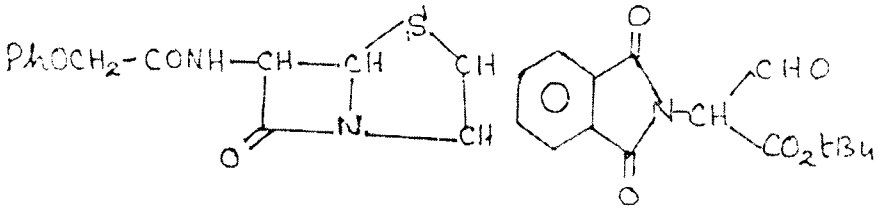
Both the nomenclatures are employed throughout the literature, of course, one at a time .

What is a protecting group?

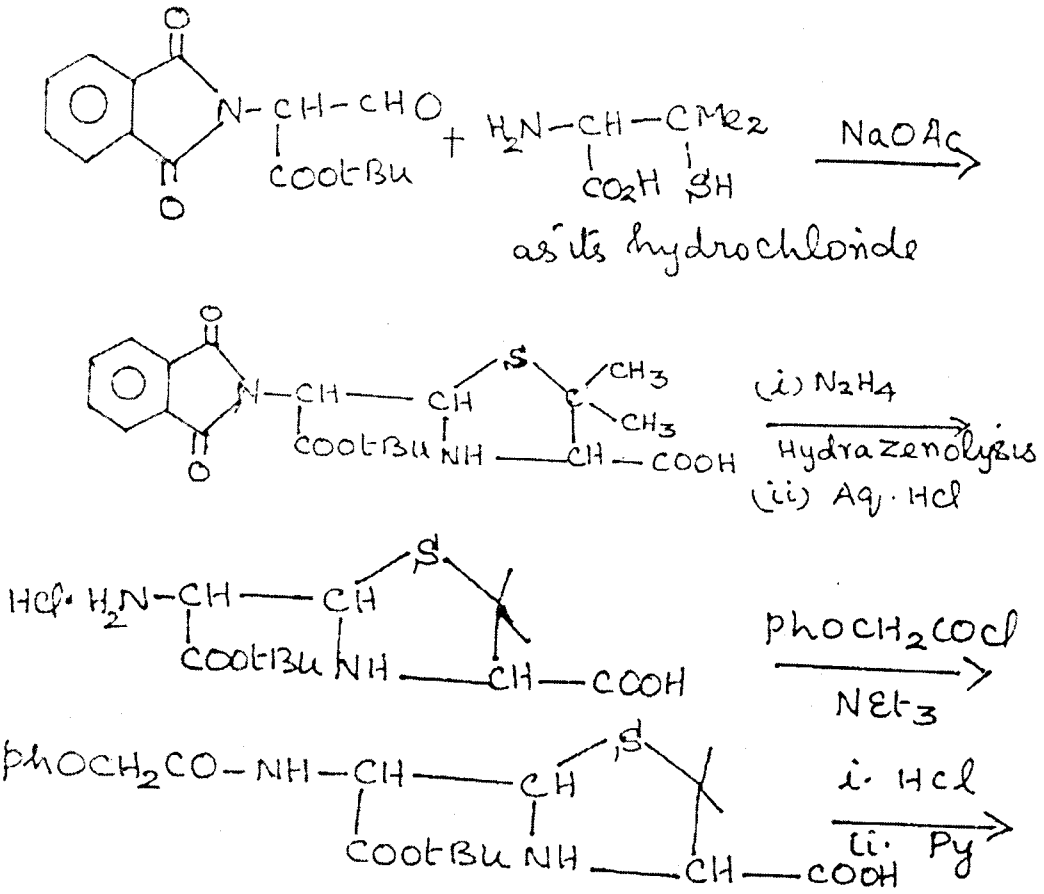
"A protecting group is one in which should prevent erosion of the particular functional group, withstand the proposed reaction conditions, at the same time should be

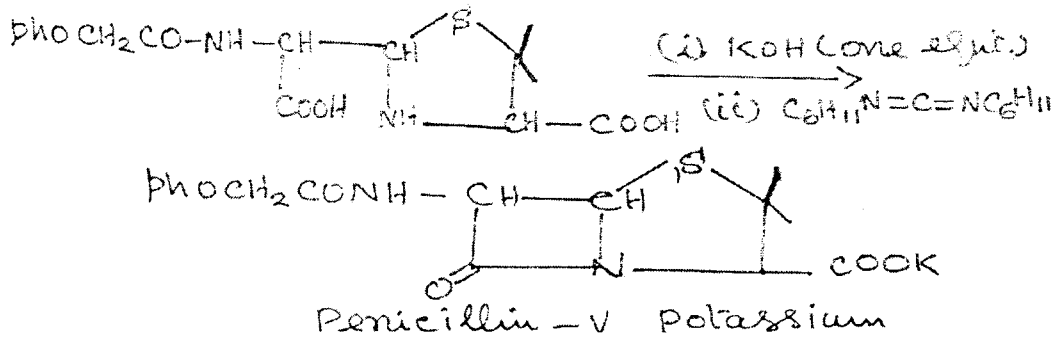
in a position to be removed at the desired stage." Thus in Sheehan's synthesis of penicillin, the amino group in aminoacetal (i.e. the starting material for this synthesis), is protected ,with phthalimido group in order to prevent self-condensation of the aminoacetal and the acid group is protected as its t-butyl ester, a group which is acid sensitive, base insensitive and are removed at a convenient stage later in the synthesis.

Sheehan's synthesis (Phthalimido



Sheehan's synthesis (Phthalimido derivative)



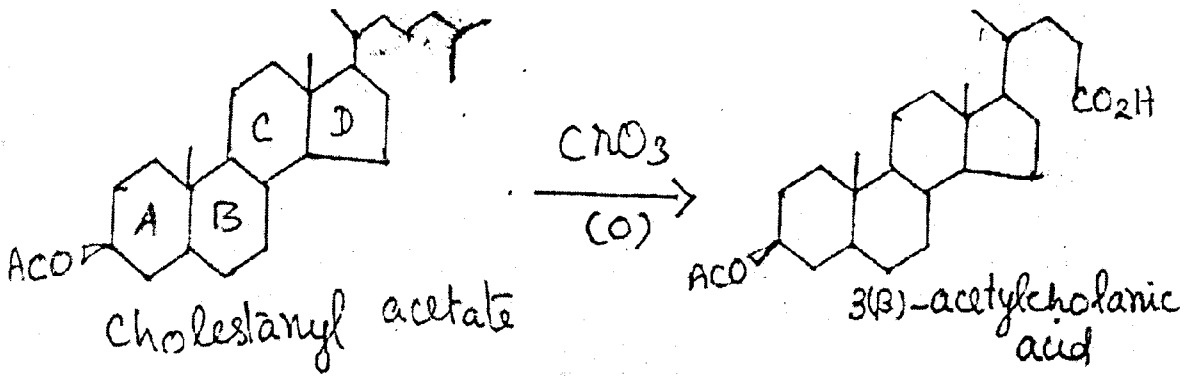


The synthesis of the penicillin is so planned that majority of the c – c bond forming processes are incorporated in the starting stage itself. It in effect is like the convergent scheme of synthesis. The more labile beta-lactum Unit is introduced only at the final stage to facilitate the synthesis.

t-Butylphthalimidomalonaldehyde is first condensed with penicillamime hydrochloride in the presence of sodium acetate, to yield the corresponding amil. Hydrazenolysis of it followed by treatment with aq. HCl affords the free amine hydrochloride ie the amino group is protected, since no more protection is needed at this stage.

The necessary R-groups to generate various pencillins are introduced at this stage. Having constructed the skeleton, the closure of the synthesis a compound with reactive and sensitive groupings was given birth to in the laboratory by the proper grading and masking of the functional groups. Indeed in some instances, the proper choice of the functional group masking will make the difference between success and failure in a syntbesis.

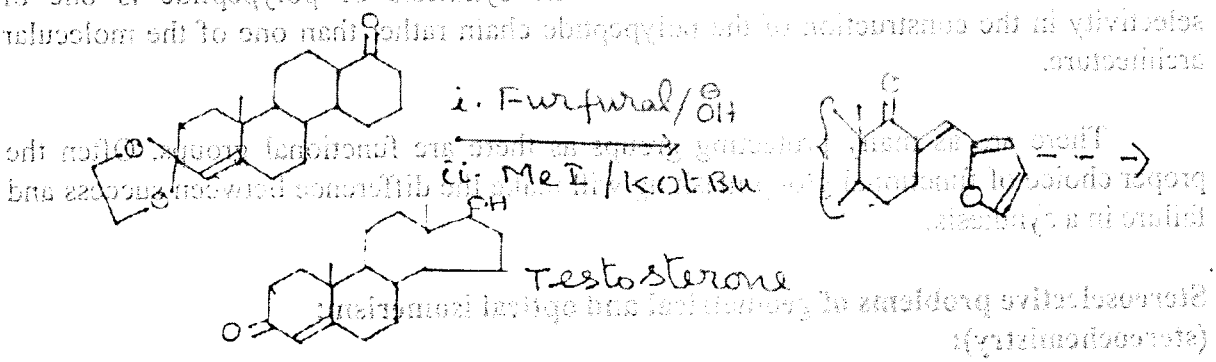
During the side chain oxidation of cholesterol (in order to access the nature of the side chain) the hydroxyl group is given protection by means of acetylation. Acetyl ester sustains the rigorousness of C_rO_3 oxidation.



If desired the acetyl group can be washed off by simply boiling with aqueous sulphuric acid.

Syntheses of many steroids involve the introduction of C-13-angular methyl at one stage or other along the way to the destination (the C-10 angular methyl is normally introduced along with the construction of ring A).

This is done by utilizing the activating ability of C-17 carbonyl group. Activation is possible both at ,C-13 and C-16 positions. Selective activation at C-13 is achieved by blocking the active methylenic site at C-16 with furfural. Thus C-13 angular is introduced in the synthesis of testosterone, the primary sex hormone of male.

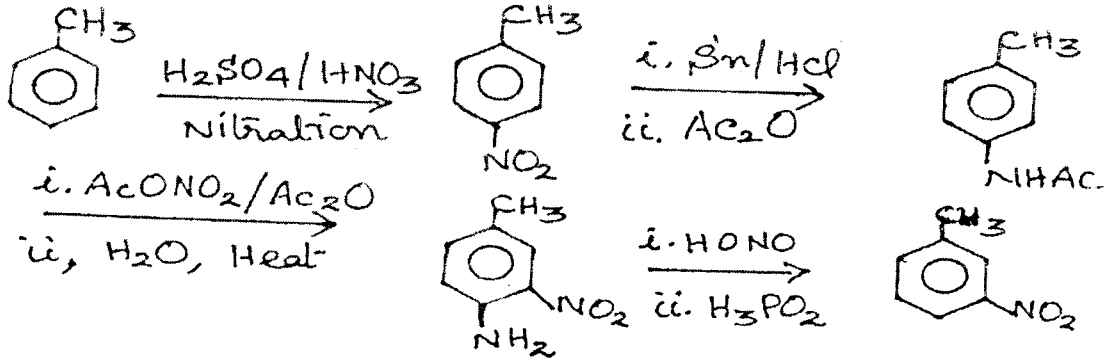


Sometimes the protecting/blocking groups may even serve the purpose of activation, as in the preparation of m-nitrotoluene.

The methyl group is ortho-, para-directing in electrophilic substitution reactions. Nitration begin an electrophilic substitution, essentially enters either o- or p- to the methyl. The latter is preferred over the former on steric grounds. Practically one cannot hope to get m-nitrotoluene with an unhelping methyl group.

The target is achieved by converting the initially formed nitro compound into acetamido derivative. The acetamido group is O-, P-directing like the methyl. When further nitration is attempted with this disubstituted derivative a competition ensues between the two groups, i.e. methyl and acetamido. The acetamido group wins the battle, by its powerful mesomeric effect which far outweighs the inductive effect of the methyl. This forces the nitro group to enter the m-position w.r.to methyland o- w.r.to the acetamido group. The final stage is accomplished by knocking off the acetamido group.

In this case acetamido group not only protected (blocked) the p-position w.r.to the methyl towards further nitration, but also helped in the nitration process to the desired direction.



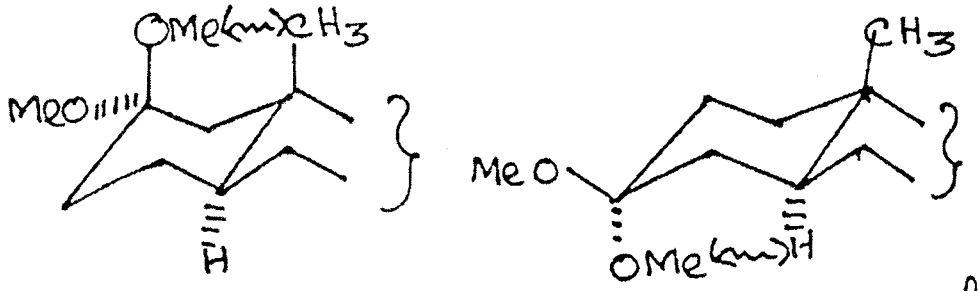
The use of protecting groups in syntheses, have made synthetic selectivity possible where none existed before. Thus the synthesis of polypeptide is one of selectivity in the construction of the polypeptide chain rather than one of the molecular architecture.

There are as many protecting groups as there are functional groups. Often the proper choice of functional group masking will make the difference between success and failure in a synthesis.

Stereoselective problems of geometrical and optical isomerism: (stereochemistry):

So far we have been concentrating very heavily on the logistics and scheduling of functional groups during organic synthesis. But we cannot hope to neglect the problem of steric crowding and geometrical and optical isomerisms.

Steric crowding will have a direct bearing on some of the reactions. Thus for example, cholestan -2-one failed to undergo ketalisation whereas cholestan- 3- one undergoes ketalisation to the extent of 30%. This piece of information is used to distinguish between the two ketones. Why the former failed,

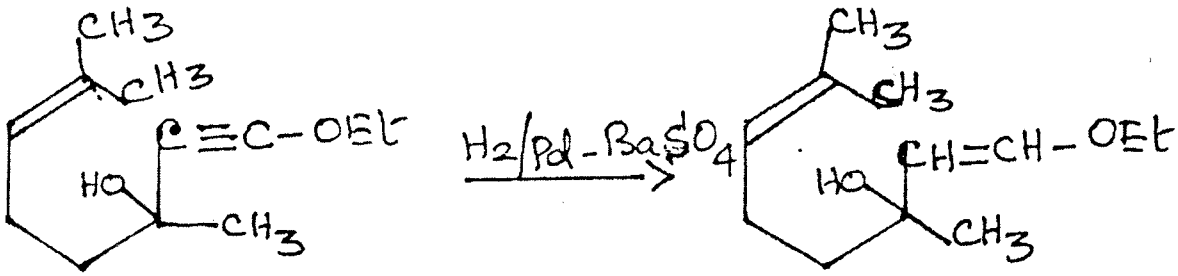


ketal of cholestan-2-one ketal of cholestan-3-one

while the latter ketone formed ketal (to some extent atleast) ? The answer is to be found in the severe 1,3 – non – bonded interaction between methoxyl of the ketal ,and C_{10} - angular methyl group, in the first isomer, which is somewhat less in the second one. The second isomer has only reduced 1,3 non-bonded interactions, between methoxyl and hydrogen atoms.

Next comes the problem of geometrical isomerism. Control can be exercised with less effort if the material involved is cyclic. If acyclic, our labour becomes manyfold. The reason is not far to seek; its simply because the acyclic compounds have no fixed conformations unlike their cyclic counterparts. Some generalizations can be made in this direction but one has to face the problem individually depending on the material at hand.

Catalytic reductions generally lead to cis-isomers. The initial step is the adsorption of the unsaturated compound on the surface of the catalyst followed by addition of hydrogen from the bottom face. Acyclic cis-olefins are obtained normally by reducing the corresponding acetylenic compound using Lindlar's catalyst. The reduction stops with the olefinic stage. Thus the fact that triple bonds are reduced to double bonds faster than double bonds themselves are reduced is being exploited in the synthesis of vitamin-A.



Here $BaSO_4$ used in Lindlar's catalyst acts a catalytic poison slowing the catalytic activity, thus preventing further reduction of the olefin. Chemical reductions being random will generate both cis- & trans –isomers.

Another important aspect of the synthesis is the problem of optical isomerism. If a target molecule has 'n' chiral centers, there are 2^n stereoisomers possible theoretically. Even with one or two chiral centers, the problem of isomer separation can be a serious obstacle to the smooth flow of synthesis. So it is better to think ahead before we leap. This problem can be a manageable one provided one uses optically active starting materials. Many modern syntheses begin with one stereoisomer of a naturally occurring material such as terpene, a carbohydrate or an amino acid.

There are two aspects of the problems associated with optical isomerism that one has to encounter, in synthesis.

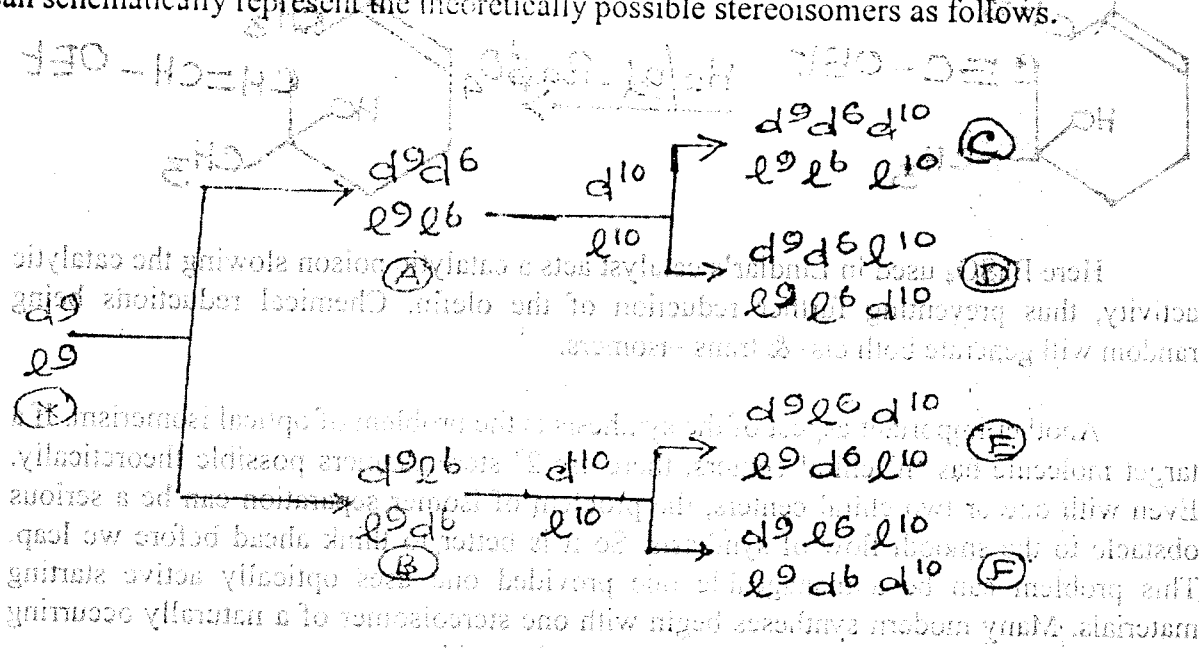
i. Control of asymmetry.

ii. Separation of optical isomers.

When more than one stereoisomer of the desired product is possible, it is necessary to design a synthesis that will yield only that isomer. In such cases it is important to use reactions that are stereoselective i.e the reactions yielding largely one stereoisomer when two or more might result.

Sodium borohydride or lithium borohydride reduction of cyclic ketones usually lead to the more stable equatorial isomer, whereas $H_2.P_t$ reduction in acid medium gives the less stable axial isomer. Thus reduction of cyclohexanone with $NaBH_4$ or $LiBH_4$ gives the more stable equatorial isomer whereas reduction with the latter gives the axial alcohol. If properly substituted can generate two optical isomers, in this instance, but can be controlled to give the preferred one.

When more number of asymmetric centers are involved , the situation becomes in character. We need more restraint and restructuring of our schedule. For example, the synthesis of 6-(beta)-hydroxy-5,5,9-(beta)-trimethyl-trans-1-decalone, from octalin-1,6-dione. This ketone contains only one asymmetric carbon atom, i.e. at position 9. The desired end product contains three chiral centres. i.e. two more are created, one at position 6 and the other at position 10. In fact we may end with eight enantiomers. We can schematically represent the theoretically possible stereoisomers as follows.

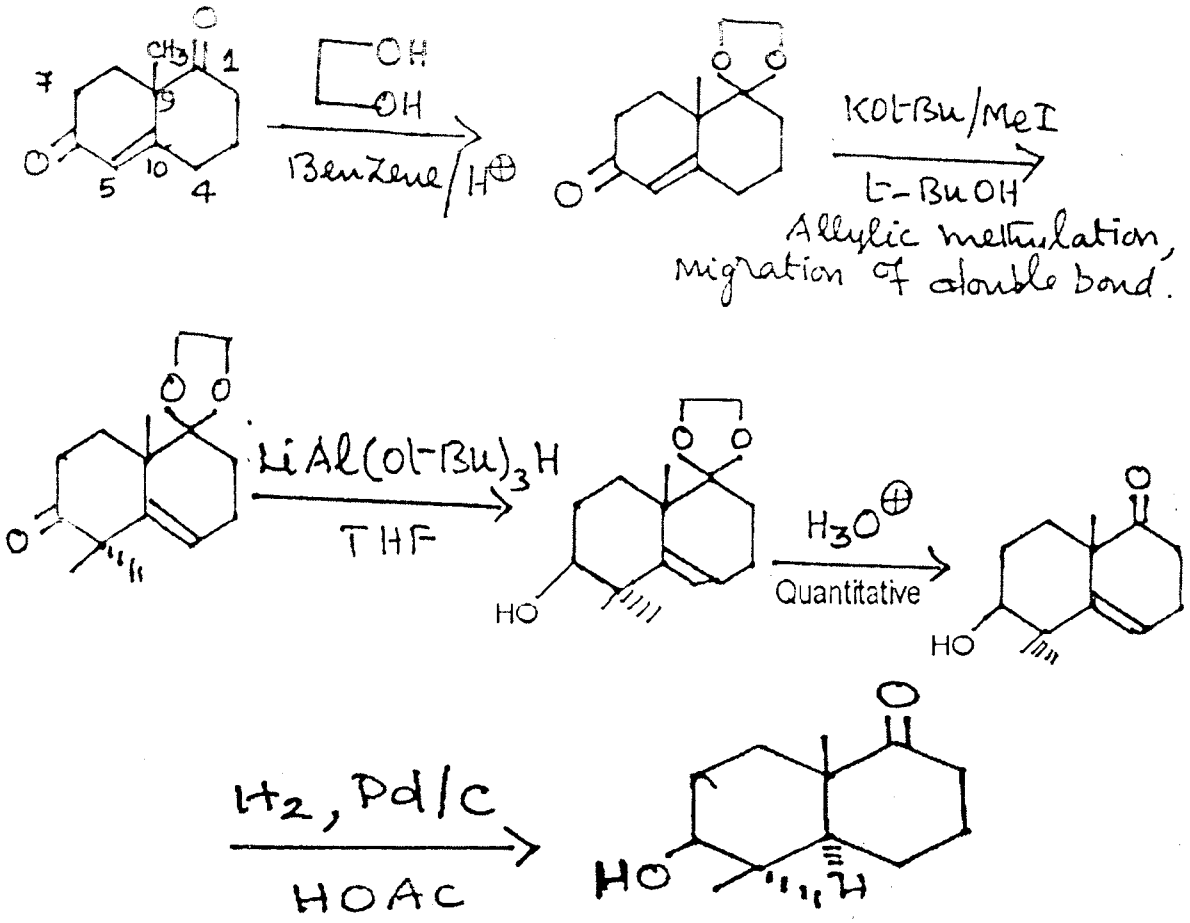


First, octalin-1,6-dione is converted to the ketone, (X) through a sequence of selective ketalisation and allylic methylation. Selective ketalisation is possible because the alpha, beta-carbonyl is less reactive towards acidic reagents.

Lithium aluminum tri-t-butoxy hydride reduction will result in product development control, i.e. will help form the equatorial alcohol in predominant amount.

Instead, if catalytic hydrogenation is sought the axial isomer predominates the scene, i.e. kinetic control. Thus we are able to get the diastereoisomer (A) over (B) by proper choice of the reducing agent.

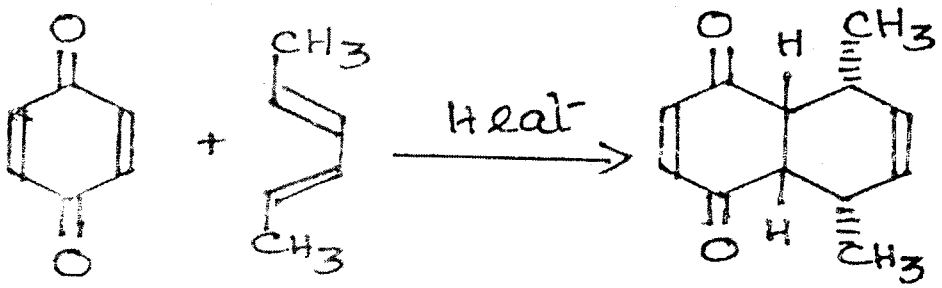
(C) over (D) during catalytic reduction. It is done as follows.



After the reduction of C_6-ketone, the function of ketal is over, the presence of which in subsequent steps will provide no further useful service. Also it will hinder the saturation of the double bond. Removal of a protecting group at the earliest convenient stage is generally the best policy.

During the hydrogenation step the presence of angular methyl group (beta-face) forces the hydrogen to attack from the alpha-face ,preventing the possibility of stereoisomers. Thus a selective reduction is made possible. The net outcome of this synthesis is a stereoselective, stereorational route.

In the foregoing example we are forced to tailor our synthesis sequence with the procision of an artist. But in certain reactions, like the Diels-Alder reaction, we may be able to exercise control over generation of upto four chiral centres at one time as in the following example.



Sometimes it will not be possible to control a synthesis so that only the desired stereoisomere is produced because a method that will accomplish that goal is lacking. In such a case the next best solution is to prepare the mixture of isomers and separate the desired isomer.

Separation or resolution of the racemic end products can be achieved through several means. To cite an example, we can consider the separation of alpha- & beta-forms of glucose from a solution of it. Glucose, in solution is present as an equilibrium mixture of the alpha- & beta forms. The position of the equilibrium depends only slightly on solvent. When a solution of glucose in ethanol is concentrated the less soluble alpha-isomers crystallizes first, and this disturbs the equilibrium so that more of that form is produced in solution. This will crystallize again, and so on. Crystals of entirely one form being obtained in this way. If the same is carried out in pyridine solvent, then the beta-form will crystallize out in preference to the alpha – form and the process will be repeated as before.

RETROSYNTHETIC ANALYSIS

Introduction:

To achieve success in any synthesis, it is better to work the problem backwards step by step to commercially available starting materials. It in effect is making a forward leap in the chosen built-in track. This type of approach to synthesis is referred to as retrosynthetic analysis.

The structure of the target molecule can be formally divided into two parts :

i. It's carbon skeleton
ii. Functional groups located on the skeleton.

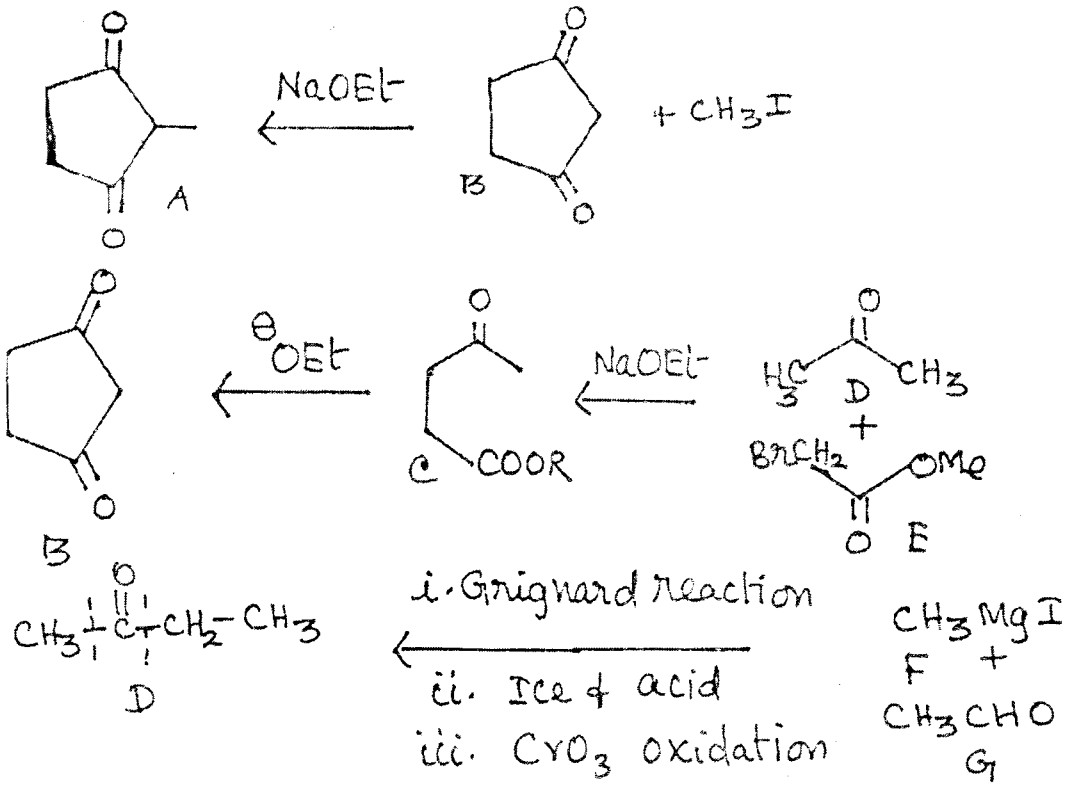
CARBON SKELETON:

In any synthesis , the structure of the complex molecule can be broken down to smaller units- the synthons –from which it must be possible to reconstruct the skeleton by linking these smaller units. Such construction reactions form the central nerve system of any synthesis design. Thus the synthesis of methylcyclopenta –2,5-dione may be thought of from simple precursors by working the target molecule backwards (A to G).

Since the carbon carrying methyl group is an active methylenic group, it is possible for the target molecule to have been constructed from 2,5 –cyclopentadione and methyl iodide in the presence of sodium ethoxide. Compound B could have been formed by an internal claisen condensation between an active methylenic group and carbonyl of an ester.

Since functional groups are generally the link for the construction of carbon skeleton, the molecule C can be broken down into a 3+2 unit i.e. D & E. Compound E could be obtained by HVZ reaction of acetic acid, which is commercially available. Compound D & E unite to form C.

Compound D can be further fragmented at the carbonyl function to give F & G and D could be obtained by the direct reaction of F & G followed by CrO_3 oxidation.



Thus the seemingly difficult synthesis, has been made a simpler one involving synthons of one / three carbon units which could be easily obtained either in the market or made in the laboratory.

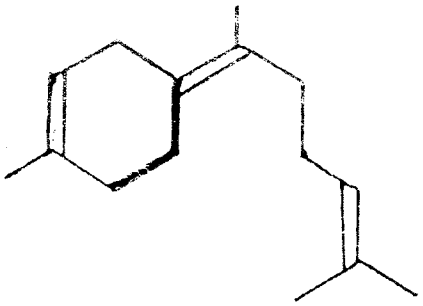
FUNCTIONAL GROUPS:

Functional groups are located at specific places on the target skeleton which can tell us what reactions might be used.In any design for a successful synthesis the construction reactions normally centre around the carbon atoms bearing functional groups. Since functional groups can be altered in many ways at one skeletal location and

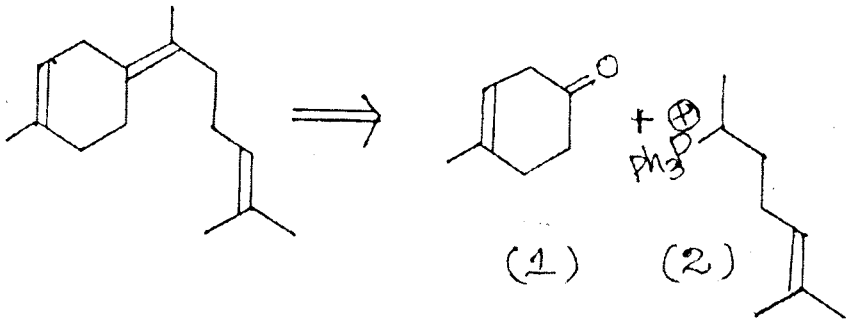
even removed altogether, its location, more than the actual nature of it in the target molecule is to be our prime concern. Another important thing is, a functional group can seldom be introduced if there are only hydrogen atoms already present on the carbon atom in question.

Keeping this two points in mind, i.e. skeleton & functional groups, we must break the target molecule step by step to lend sub-targets till arrive at commercially available starting materials. The process may produce many possibilities, and we must use our chemical knowledge of the individual steps to select the best route among them.

- **-Bisabolene**



It is a sesquiterpernoid. It has a cyclohexene nucleus in it. So the disconnection of the molecule may be attempted at the bond connecting the ring member atom to the side chain and we get

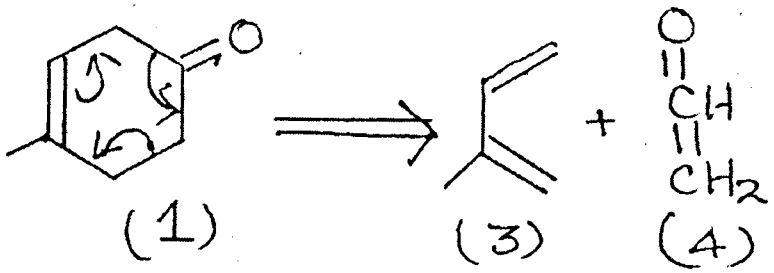


molecules (1) and (2). These two can combine to give γ-Bisabolene.

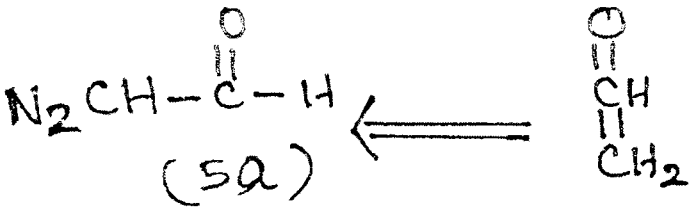
The two molecules can be further disconnected to commercially available starting materials.

Molecule 1:

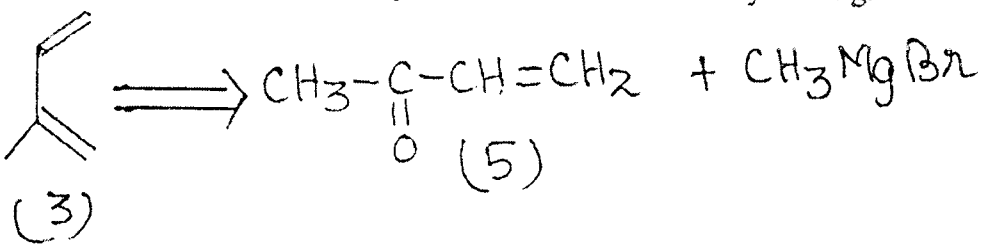
This being a cyclohexane nucleus, we can think of a way of constructing the molecule through Diels-Alder reaction.



The ketone (4) can be obtained by the decomposition of diazoacetaldehyde.

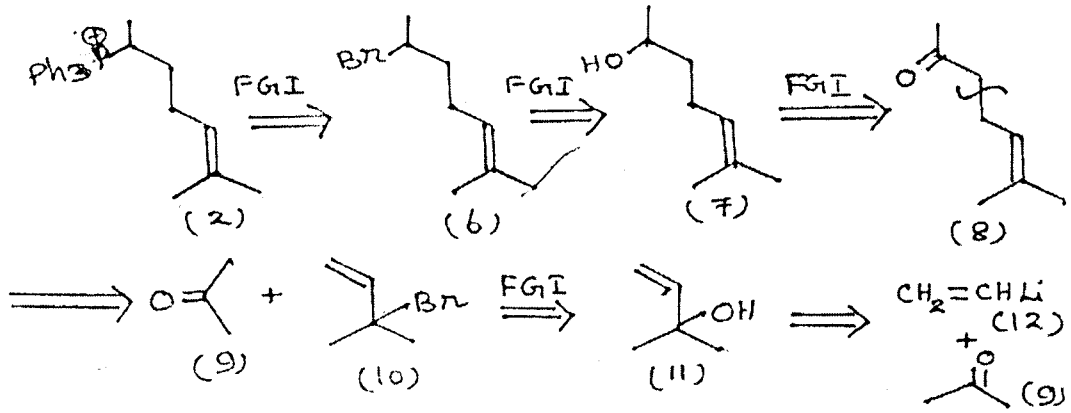


Isoprene(3) can be obtained by the Grignard reaction of methylvinylketone with methyl magnesium bromide, followed by dehydration. The former can be prepared by the aldol condensation between formaldehyde and acetone followed by heating.



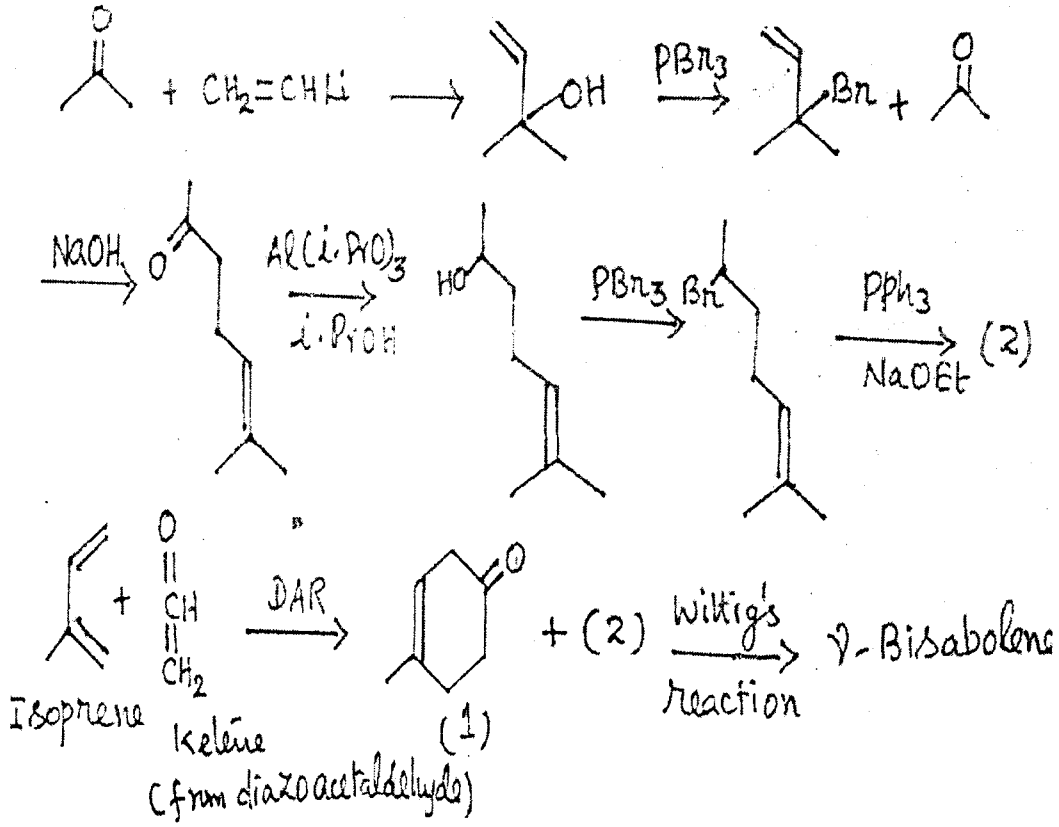
Molecule 2:

This wittigs reagent can be disconnected as follows,

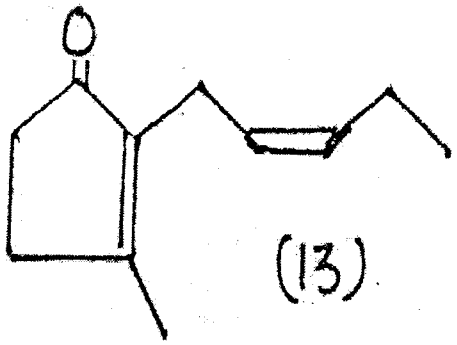


Through functional group interconversions (FGI) compound (2) can be brought down to (8), compound (8) can be dismantled at the C-C bond connecting the two methylenic groups (one is an active methylene and the other an allyl methylene) The result, acetone(9) and the allylic compound (10) are obtained. Compound(10) through FGI (11) and nucleophiclic addition gives (12) and acetone. The molecule γ-Bisabolene can be reconstructed from acetone.

Synthesis :

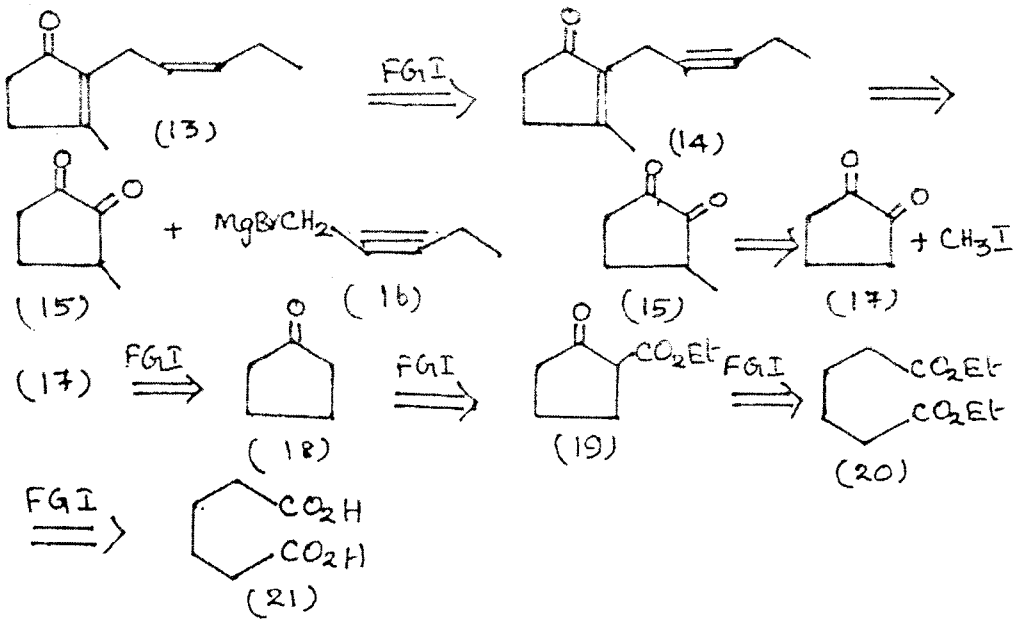


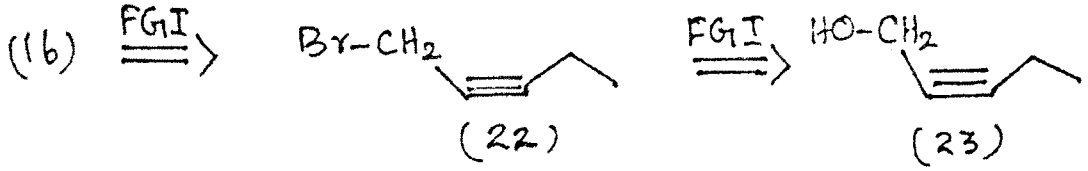
Cis – Jasmone

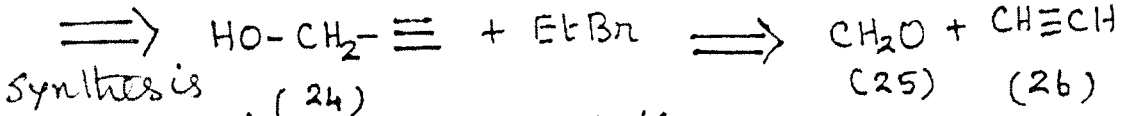


The retrosynthetic analysis of the molecule may be done as follows:

The side chain double bond is cis in orientation. The latter can be obtained by the Lindlar's reduction of the triple bond. The side chain is adjacent to the carbonyl carbon and also an olefinic carbon. So a Grignard reaction may be attempted on an α -diketone followed by dehydration. The α -diktone can be produced through a Dieckmann reaction, hydrolysis, followed by selenium dioxide oxidation. We may attempt the disconnection of the molecule (13).

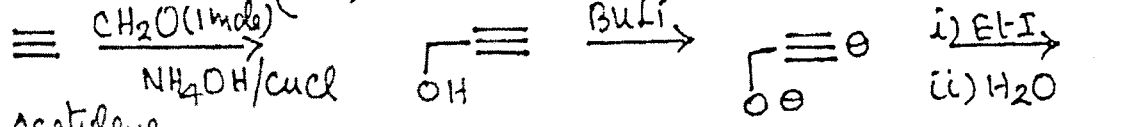




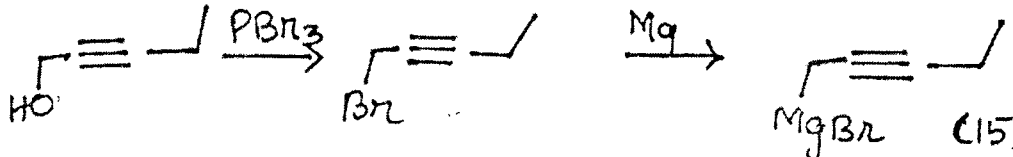


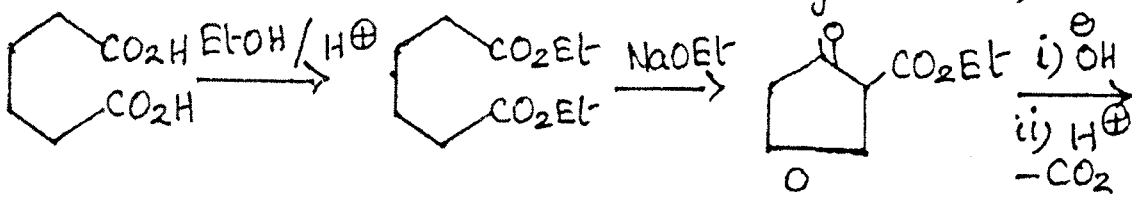
Synthesis

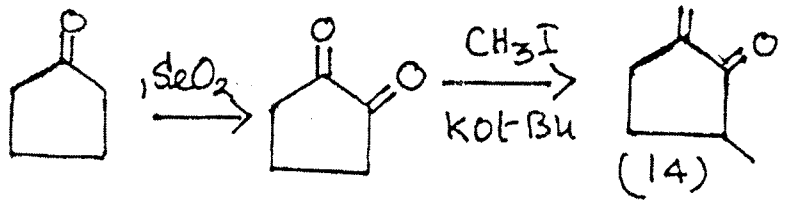
(24)

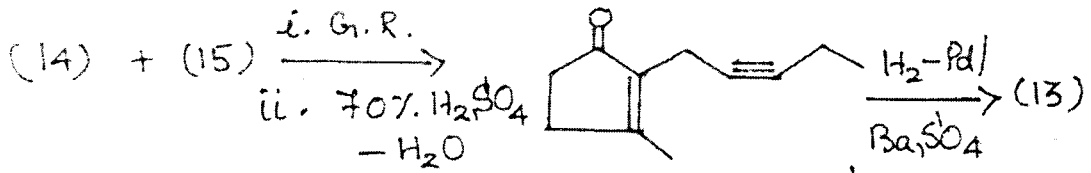


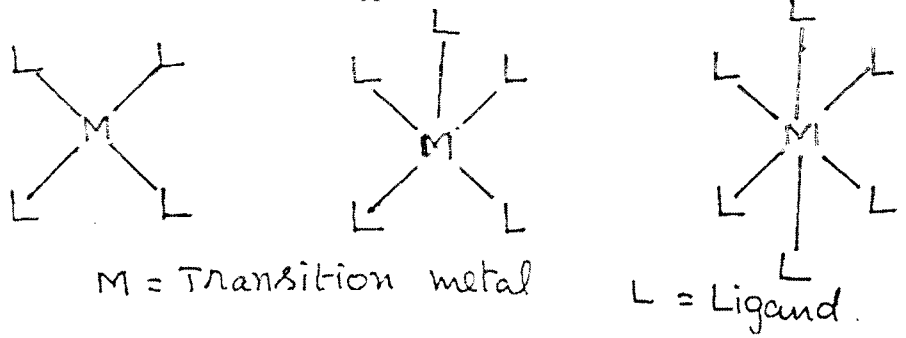
Acetylene

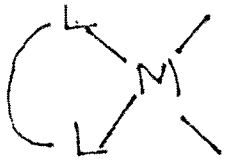












Homogeneous hydrogenation –Transition metal complexes :

A metal complex is made up of the metal and certain ions and molecules, called ligands (from the Latin, ligare, to bind), that are held by it.Each ligand (L) is bonded to the metal by the overlap of an empty orbital on the metal with a filled orbital on the ligand.

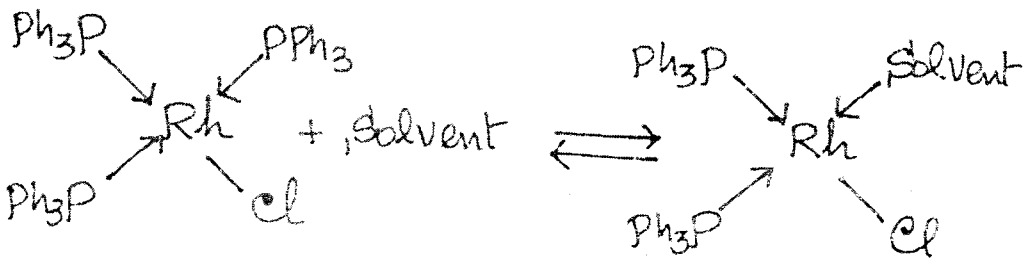
If the ligand molecules have atoms with more than one electron pair to bind (or) share, they are called as bidentate, tridentate etc.(that is to say, "two-toothed," "three-toothed" etc). Binding of this type is called Chelation (Greek:Chele, claw)

These ligands take no direct part in the reaction that is being catalyzed, but their presence on the metal is absolutely necessary. Like substituents in an organic molecule, ligands can – through their electronic (or) steric effect, their lipophilicity (or) their chirality-help to determine the course of reaction. They stabilize the complex, modify its reactivity make it soluble in organic solvents, and can even bring about stereoselectivity in the product formed.

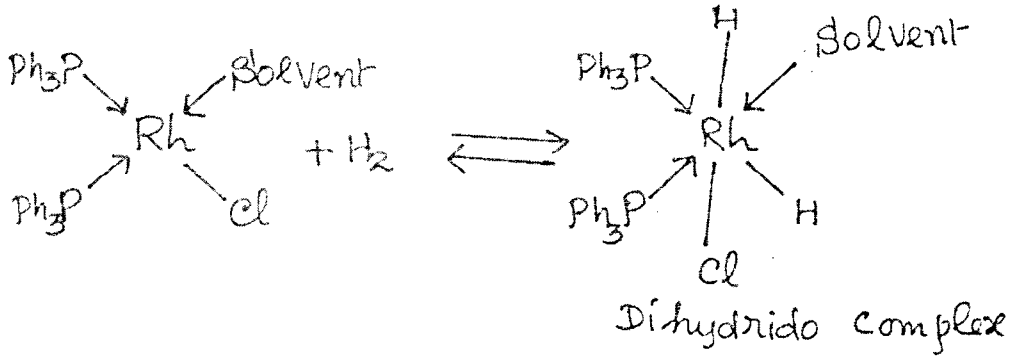
We can explain the catalytic activities of these metal complexes by taking the example of **Wilkinson's Catalyst**. It is nothing but tris(triphenylphosphine) chlororhodium (I), $RhCl(PPh_3)_3$. This is a widely used catalyst for homogeneous hydrogenation.

The catalytic processes involving this catalyst may be given as follows:

First, in solution the complex is believed to exchange reversibly one phosphine for a loosely held solvent molecule.

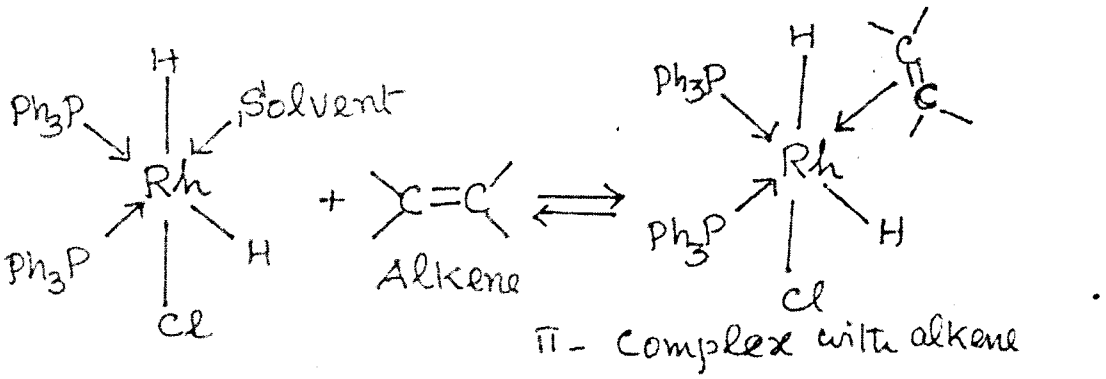


Thus the catalyst is brought into contact with the reactants, the alkene and molecular hydrogen. In the next step, the complex forms a dihydrido complex, $RhH_2Cl(PPh_3)_2$. In this process the metal uses one of its pair of electrons, while it itself being oxidized to the rhodium(III) state.



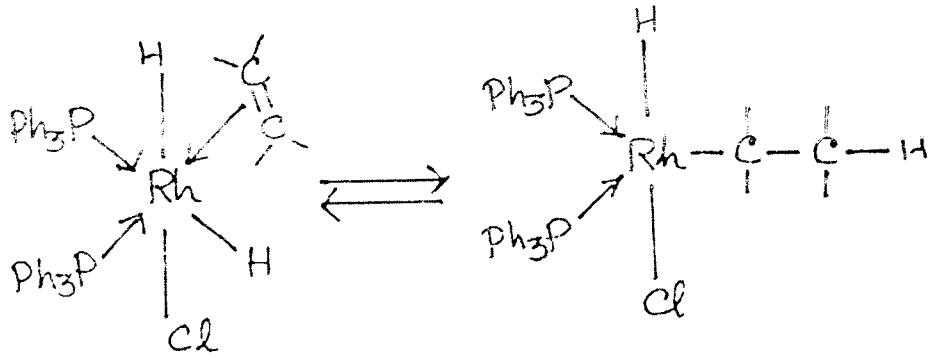
The two hydrogen atoms get attached to the metal, separately.

In the next step, the alkene enters the co-ordination sphere, probably by replacing the solvent molecule. This is done by the overlap of the π-electrons with the empty orbital of the metal.

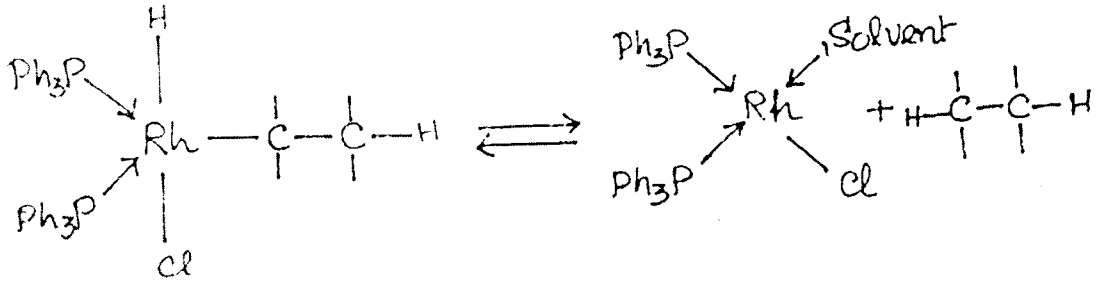


At this point, both reactants are bonded to rhodium, and the stage is set for hydrogenation to occur. The two hydrogen atoms are transferred to the definic carbon one after the other, in two separate steps.

One of the hydrogen atoms migrate to the olefinic carbon. Simultaneously a metal-alkyl bond is formed with the other olefinic carbon.



Finally the second hydrogen migrates from the metal to the second olefinic carbon.



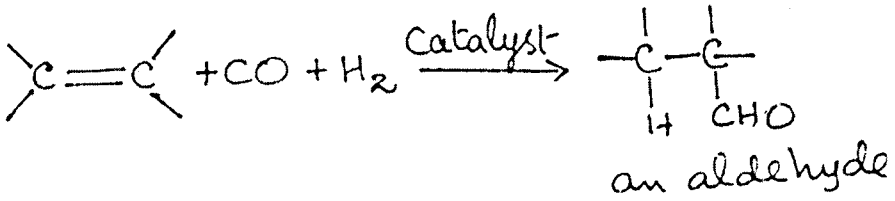
The hydrogenation is complete and the alkane leaves the co-ordination sphere while the solvent enters the co-ordination sphere. Thus once again the catalyst is ready to begin its catalytic activity.

The overall effect may be termed as " symphoria" i.e. the reacting atoms are being held in the proper positions for the reaction to occur.

Before going to the stereochemical aspects of homogeneous hydrogenation, let us consider one more application of the transition metal complexes in organic chemistry i.e. the "OXO" process.

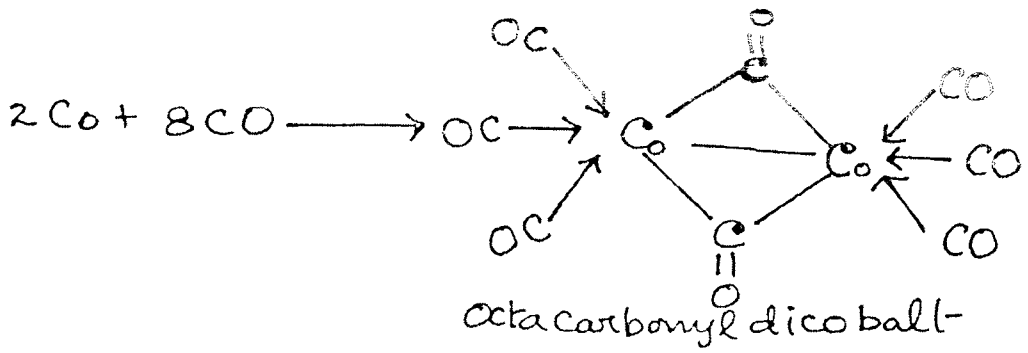
The OXO process

This is an important method of making alcohols on a large scale.In the presence of the proper catalyst, alkenes react with carbon monoxide and hydrogen to yield aldehydes.



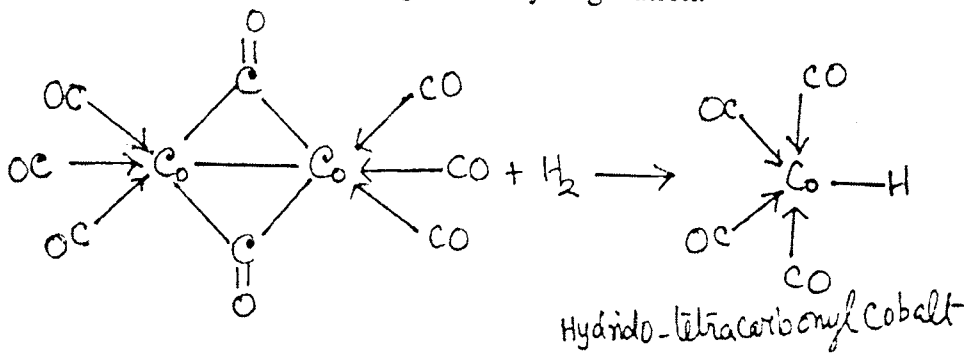
The aldhydes upon reduction give primary alcohols.

The catalyst used for this purpose is octacarbonyldicobalt, $Co_2(CO)_8$. It can be prepared by the reaction of metallic cobalt with carbon monoxide.

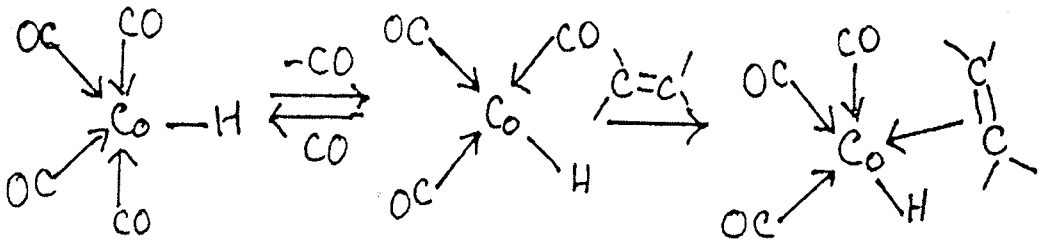


The following steps are believed to be involved in the oxo process.

In the first step the catalyst reacts with hydrogen to form the hydrido complex, $CoH(CO)_4$, the active catalyst. The active catalyst is soluble in hydrocarbons.Thus this reaction also becomes a case of homogeneous hydrogenation.



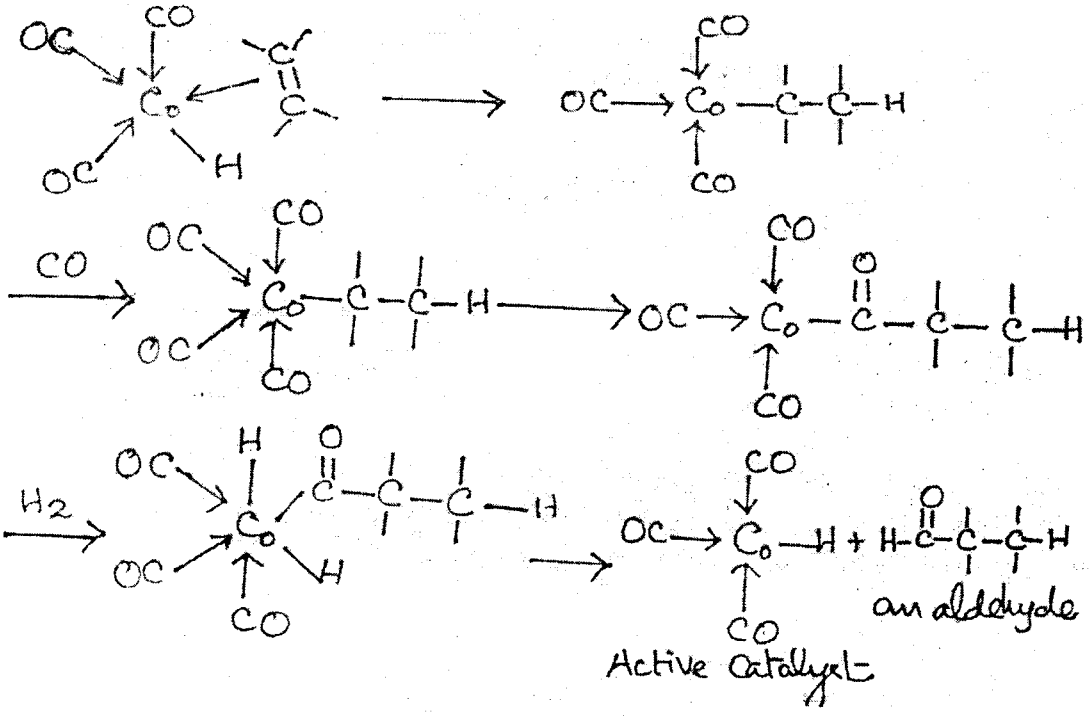
Next, the alkene replaces one molecule of carbon monoxide to form a Π-complex.



At this point, the alkene, carbon monoxide and a hydrogen are held together by cobalt, as ligands. Next, a hydrogen migrates from the active catalyst to one of the definic carbon atoms.The other definic carbon simultaneously forms a metal alkyl with cobalt. This acquires an additional molecule of carbon monoxide.

The key step is to follow next i.e. the second olefinic carbon migrates to the carbon of one of the carbon monoxide ligands. In this step a carbon- carbon bond is formed. The carbonyl group gets inserted between the metal atom and the olefinic carbon.

Now hydrogen is absorbed to form a dihydrido complex. One of these hydrogens migrates to carbon of the c=o group to form an aldehyde molecule, which leaves the co-ordination sphere of the regenerated catalyst.

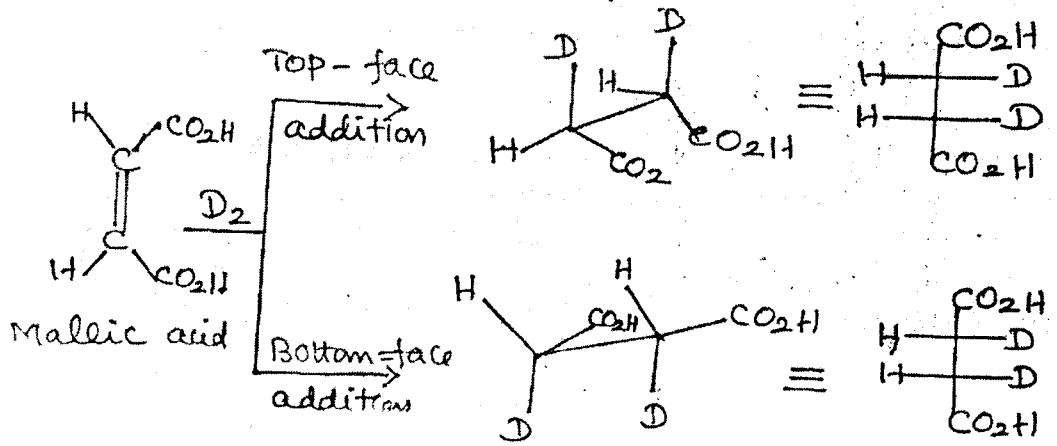


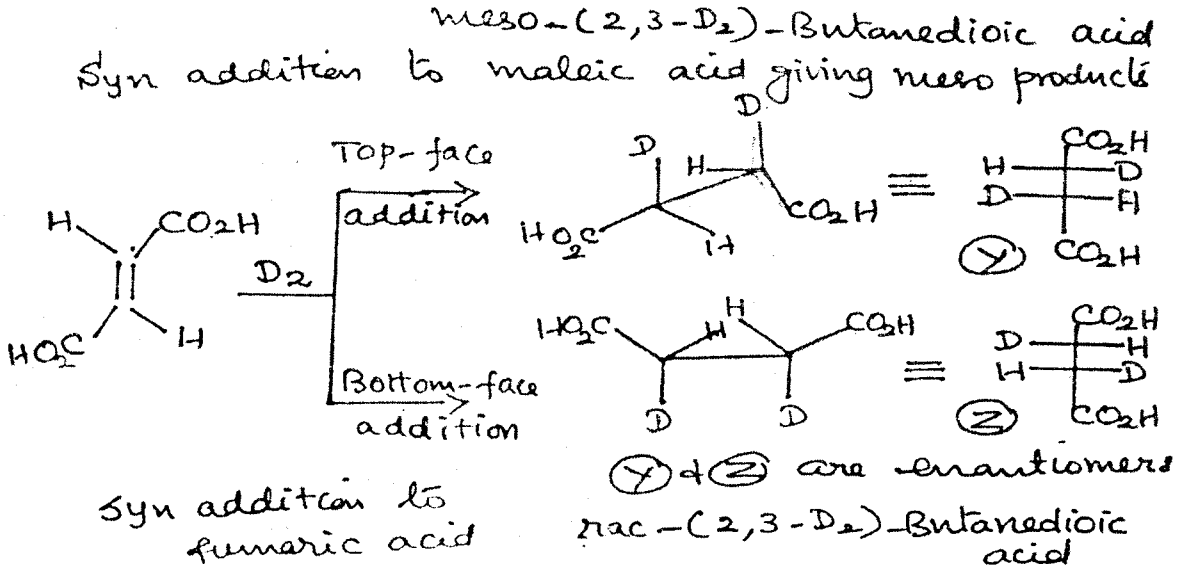
Stereochemistry of homogeneous hydrogenation :

Diastereoselectivity :

Stereochemically different geometric isomers yield stereochemically different products. ie. the reaction is not only stereoselective but also stereospecific. This is referred to as diastereoselectivity.

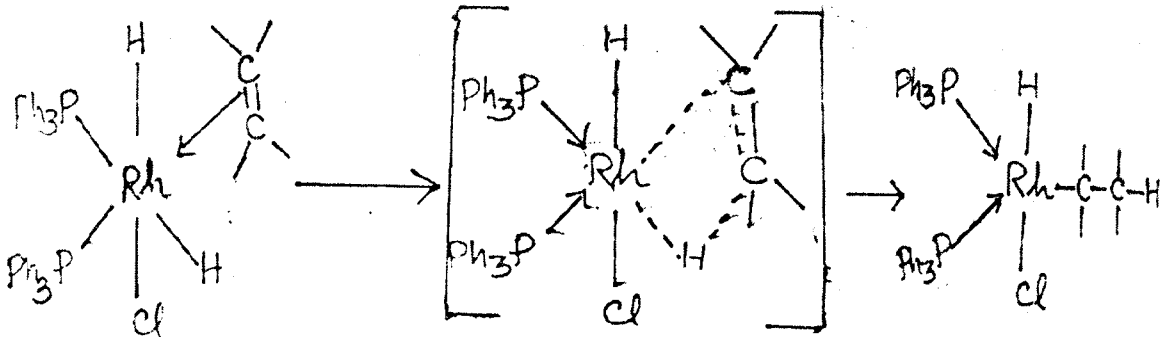
(Ex) When the deuteration of maleic acid and fumaric acid are done using wilkinson's catalyst they give respectively the meso-(2,3-D_2) butane dioic acid and dl-(2,3-D_2) butane dioic acid. From this it is evident that the hydrogenation process involving the wilkinson's catalyst is stereoselectivly SYN. Thus





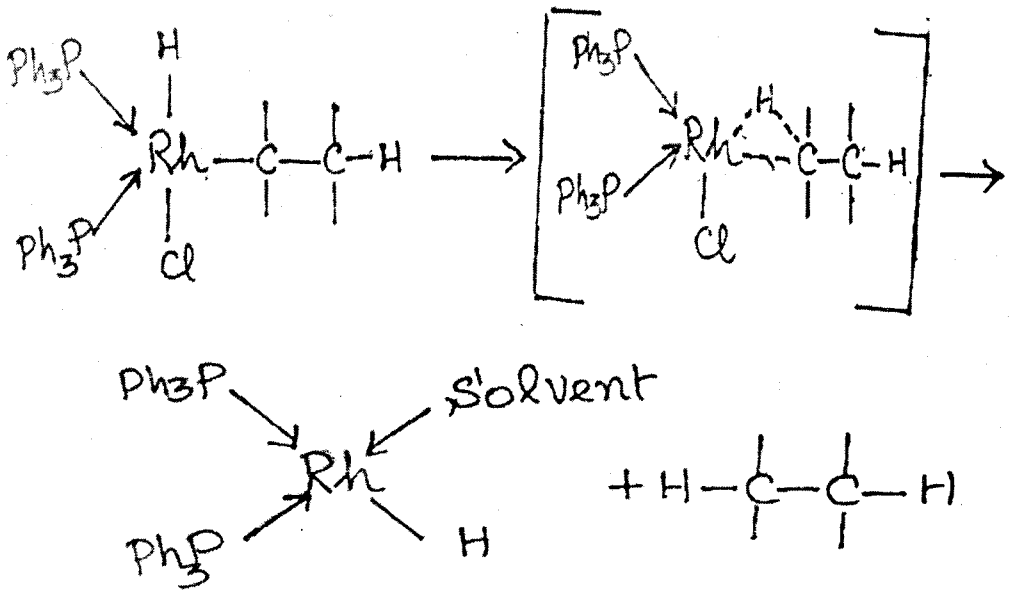
This observed overall syn addition is explained as follows:

The dihydrido complex having the olefin in the co-ordination sphere is considered (see Homogeneous hydrogenation- Transition metal complexes).



The metal and a hydrogen simultaneously attach to the olefinic carbon at the T.S. as indicated above. Because of the juxtaposition of metal and hydrogen – they are bonded to each other in the reactant-this addition of the two atoms necessarily on geometric grounds, takes place to the same face of the double bond. This step thus involves syn-addition.

In the next step, the hydrogen migrates from the metal to carbon, and in doing this attaches itself to the same face of carbon that was attached to the metal. That is, there is front-side attack leading to retention of configuration about the carbon. The alternative, backside attack is impossible, again on geometric grounds; the hydrogen is held near the front-side of carbon by the metal, which in the T.S. is bonded to both hydrogen and carbon.

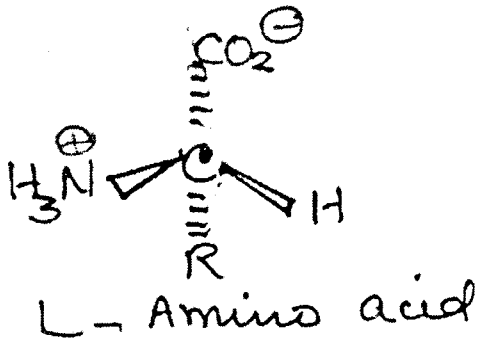


The overall addition of hydrogen to the olefinic bond thus becomes "SYN".

Stereochemistry of homogeneous hydrogenation:

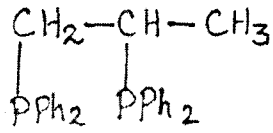
Enantioselectivity:

An important application of homogeneous hydrogenation using Wilkinson's catalyst is selective preparation of one enantiomer ie. enantioselectivity. Amino acids have the general formula,

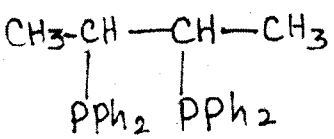


The amino acids have a chiral centre. Preparation of amino acids from an optically inactive substrate and optically inactive reagents, leads to an equal amount of the two enantiomers, that is, racemic modification. But naturally occurring amino acids that help build amino acids are optically active and have the absolute configuration,

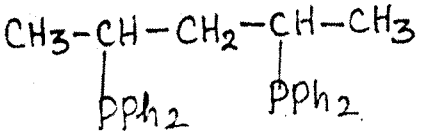
So, to prepare a synthetic protein, one needs to start with amino acids that are optically active and of the correct configuration. For this we need a synthesis of amino acids that yields directly only one enantiomer- an enantioselective synthesis. To achieve this, optically active ligands must be attached to the Wilkinson's catalyst. For example,



1,2-Bis (diphenylphosphino) Propane
(or) PROPHOS



2,3-Bis (diphenyl phosphino) butane
(or) CHIRAPHOS.



2,4-Bis (diphenylphosphino) pentane
(or) SKEWPHOS.

These are bidentate ligands, and chelate with rhodium to give optically active catalysts. Using these chiral catalysts amino acids and other compounds have been prepared with a high degree of enantioselectivity.

The enantioselectivity may be inserted in two ways.

(i) There could be preferential binding of the metal to one of the faces of the alkene rather than the other. ie. one diastereoisomeric Π-complex is formed in preference to another.

(ii) Both Π-complexes may be formed, but one reacts preferentially over the other.

Just which enantiomer is obtained can be controlled by the choice of configuration of the chiral ligand: (R)-prophos, for example, gives amino acids of the natural, L-configuration, (S, S)- Chiraphos gives amino acids of the opposite configuration.

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Question Pattern

Marks : 1OO

SECTION - A (5×5=25 Marks)

Answer any FIVE out of EIGHT.

SECTION - B (5×15 = 75 Marks)

Answer any FIVE out of EIGHT.