Organic Reaction Mechanism & Name Reactions

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Organic Reaction Mechanism & Named Reactions

for

CSIR-UGC-NET/JRF|GATE

TIFR | BARC | DRDO | SLET | NTPC | ONGC-GT | HPCL | Geo-Scientist | Ph.D. Entrance

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PREFACE TO THE SECOND EDITION

The book "***Organic Reaction Mechanism & Named Reactions***" is written with the objective of providing description of principles involved in organic Chemistry including their application at a level suitable for graduate and post-graduate students of Chemistry in different universities. Starting with glimpse of general organic chemistry, the book deals with stereochemistry followed by basic principles of reaction mechanism. Later part of this book focuses on important name reaction and rearrangement reactions. Chemistry of synthetically important heterocyclic compounds is also discussed along with some challenging problems. This book will be highly useful for the candidates preparing for various competitive examinations at national and state levels such as CSIR-UGC-NET, GATE, SLET, etc.

In all the competitive examinations such as CSIR-UGC-NET/JRF, GATE, SLET, etc. the section of Organic Reaction Mechanism & Named Reactions carry approximately 10-12 percent weightage of total marks.

- In every year CSIR-UGC-NET/JRF includes at least 25 to 30 marks from this section out of 200 marks.
- In every year GATE paper includes at least 10 to 12 marks from this section out of 100 marks.

Apart from NET, GATE, PSUs this book will also be very useful to candidates appearing for various Ph.D. entrance examinations.

The book is designed and prepared in such a way that it provides the required information regarding almost all important topics. Students preparing for competitive examinations are advised to go through every topic for their understanding and conceptual clarity and then get into solving the problems. For more practice students are also advised to go through our classroom assignments.

Much care has been taken to minimize the typographical errors, yet if any noticed, then your suggestions are invited with a view to improve the book in future editions.

We would like to thank our respected faculty members for their valuable inputs in the book. Thanks to Mr. Ramashish Paul & Mr. Raj Pandey for their constructive support in doing corrections and proofreading. A note of thanks also to Mohammad Firoz for formatting, designing and type-setting the book.

Organic Reaction Mechanism & Named Reaction

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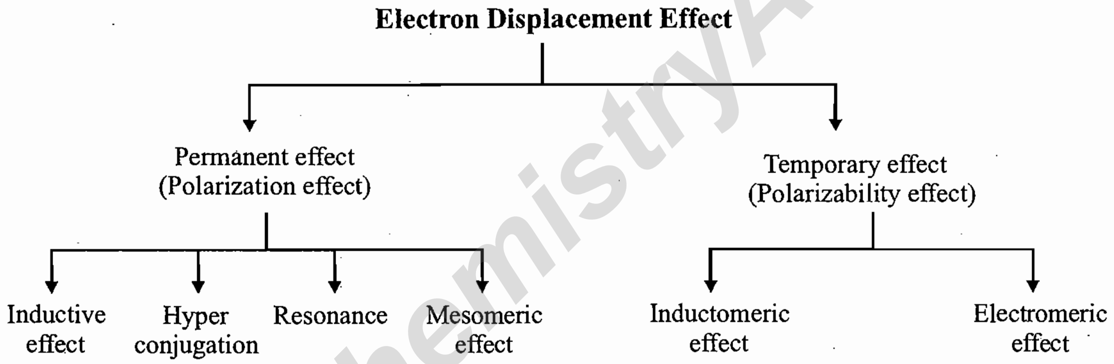
CHAPTER 1

General Organic Chemistry

1.1 Electron Displacement Effects:

Effect occuring due to displacement of electron in organic compound is called ***Electron Displacement Effect*** or Electron Delocalisation Effect.

Electron displacement effect is of mainly two types.

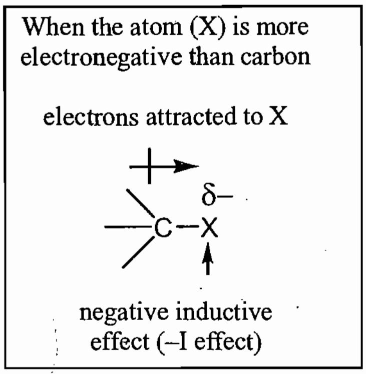


Other Effect:

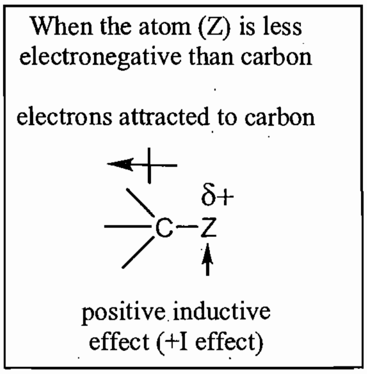
(a) Steric inhibition of resonance (b) Ortho effect.

(1) Inductive effects:

In a covalent bond between two different atoms, the electrons in the σ – bond are not shared equally. The electrons are attracted towards the most electronegative atom. An arrow drawn above the line representing the covalently bonded electrons shifts towards higher electronegative atom can show this. Electrons are pulled in the direction of the arrow.



–I groups



+I groups

X=Br, Cl, NO_2, OH, OR, SH, SR, NH_2, NHR, NR_2, CN, CO_2H, CHO, COR

Z=R(alkyl or aryl), metals (e.g. Li or Mg)

The more electronegative the atom(X), the stronger the –I effect

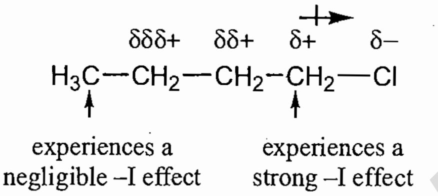
The more electropositive the atom (Z), the stronger the +I effect.

Pauling electronegativity scale

K = 0.8
C = 2.5
N = 3.0
O = 3.5
I = 2.5
Br = 2.8
Cl = 3.0
F = 4.0

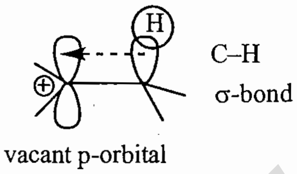
Higher the value, more electronegative will be atom

The inductive effect of the atom rapidly diminishes as the chain length increases



The overall polarity of a molecule is determined by the individual bond polarities, formal charges and lone pair contributions, and this can be measured by the dipole moment (μ). Higher the dipole moment (measured in debyes (D)), more polar will be compound.

(2) Hyperconjugation: A σ – bond can stabilise a neighbouring carbocation (or positively charged carbon) by donating electrons to the vacant p-orbital. The positive charge is delocalised or 'spread out', and this stabilising effect is known as "*no-bond resonance*".



The electrons in the σ-bond spend time in the vacant p-orbital

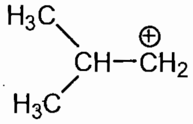
Points to Remember :
Number of α hydrogen $\propto$ number of hyperconjugating structure $\propto$ stability

$$\propto \frac{1}{\text{Heat of hydrogenation}} \propto \text{Polarity} \propto \text{dipole moment} \propto \frac{1}{\text{bond length}}$$

Problem : The correct order for the stability among following compound is

$CH_3\overset{\oplus}{C}H_2$ **(II)**

$CH_3CH_2\overset{\oplus}{C}H_2$ **(II)**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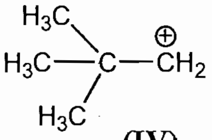

(IV)

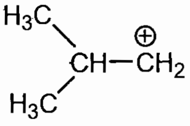
(a) I > II > III > IV (b) I > III > IV > II (c) IV > III > II > I (d) IV > III > I > II

Soln. Number of α hydrogen $\propto$ stability.

Thus,

(I) $CH_3\overset{\oplus}{C}H_2$

(II) $CH_3CH_2\overset{\oplus}{C}H_2$

(III)


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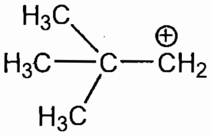
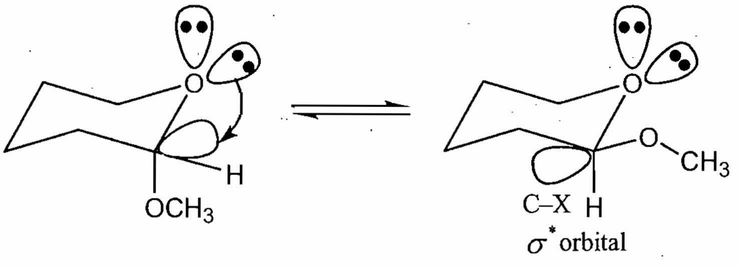


Number of α hydrogen 3 2 1 0

Stability, I > II > III > IV

Hence, option (a) is correct.

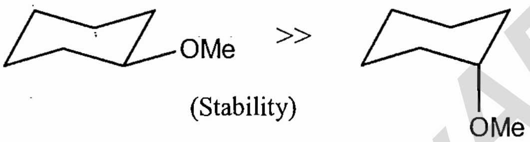
Problem : Which is more stable methyl α -D glucopyranoside or methyl β -D glucopyranoside.



Methyl α-D glucopyranoside Methyl β-D glucopyranoside

There is stabilising interaction i.e. hyperconjugation between the unshared pair on the hetero atom and σ^* orbital for the axial C–X bond in the case of α anomer. thus it is more stable as compared to its β analogue in which there is no such interaction.

Note : If oxygen is replaced by carbon, there is no such stability interaction as like as above. Thus, stability can only be decided on steric ground. Thus stability order for such species will be

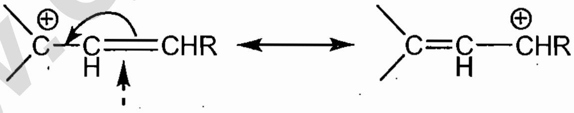


(Stability)

(3) Mesomeric effects: Whilst inductive effects pull electrons through the σ – bond framework, electrons can also move through the π – bond network. A π – bond can stabilise a negative charge, a positive charge, a lone pair of electrons or an adjacent bond by resonance (i.e. delocalisation or 'spreading out' of the electrons). Curly arrows are used to represent the movement of π or non-bonding electrons to give different resonance forms. It is only the electrons, not the nuclei, that move in the resonance forms and a double-headed arrow is used to show their relationship.

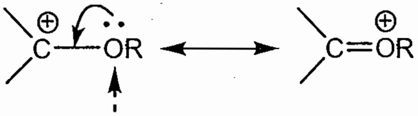
(a) Positive mesomeric effect:

- When a π -system donates electrons, the π -system has a positive mesomeric effect (+M effect).



donates electrons:
+M group

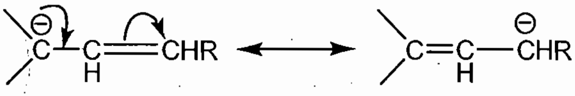
- When a lone pair of electrons is donated, the gorup donating the electrons has a positive mesomeric effect.



donates electrons:
+M group

(b) Negative mesomeric effect:

- When a π – system accepts electrons, the π – system has a negative mesomeric effect (–M effect).



Accept electrons:
–M group

The actual structures of the cations or anions lie somewhere between the two resonace forms. All resonance forms must have the same overall charge and obey the same rules of valency.

–M groups generally contain an electronegative atom(s) and/or a π-bond(s):

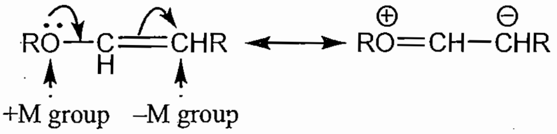
CHO, C(O)R, CO_2H, CO_2Me, NO_2, aromatics groups, alkenes etc.

+M groups generally contain atleast a lone pair of electrons or a π-bond(s):

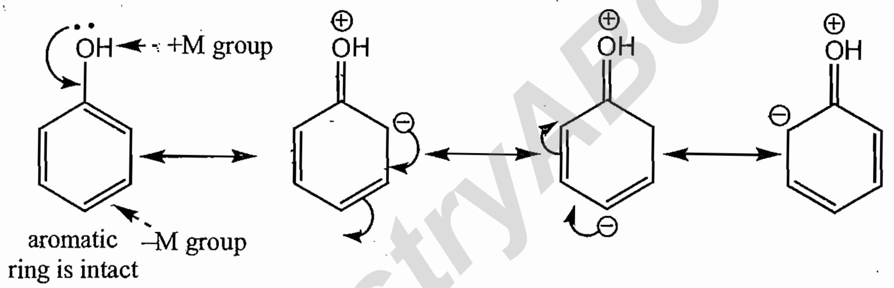
$:\!\ddot{\text{C}}\text{l}, :\!\ddot{\text{B}}\text{r}:, \ddot{\text{O}}\text{H}, :\!\ddot{\text{O}}\text{R}, :\!\ddot{\text{S}}\text{H}, \ddot{\text{N}}\text{H}_2, \ddot{\text{N}}\text{HR}, \ddot{\text{N}}\text{R}_2$, aromatics, alkenes etc.

Aromatic (or aryl) groups and alkenes can be both +M or –M effect.

In neutral compounds, there will always be a +M and –M groups(s):
One group donates (+M) the electrons and the other group(s) accepts the electrons(–M).



All resonance forms are not of the same energy. In phenol, for example, the resonance form which the intact aromatic benzene ring is expected to predominate.



As a rule of thumb, the more resonance structures an anion, cation or neutral π – system can have, the more stable it is.

Inductive versus mesomeric effects:

Mesomeric effects are generally stronger than inductive effects. A +M group is likely to stabilise an anion more effectively than a +I group.

Mesomeric effects can be effective over much longer distances than inductive effects, provided that conjugation is present (i.e. alternating single and double bonds). Whereas inductive effects are determined by distance, mesomeric effects are determined by the relative positions of +M and –M groups in a molecule.

1.2 Application of inductive effect, hyperconjugation and mesomeric effect:

Acidity and basicity:

Acids: An acid is a substance that donates a proton (Bronsted-Lowry). Acidic compounds have low pK_a-values and are good proton donors, as the anions (or conjugate bases), formed on the deprotonation, are relatively stable.

In water:

$$\underset{\text{Acid}}{HA} + \underset{\text{Base}}{H_2\ddot{O}} \underset{}{\overset{K_a}{\rightleftharpoons}} \underset{\text{Conjugate Acid}}{H_3\overset{\oplus}{O}} + \underset{\text{Conjugate Base}}{\overset{\ominus}{A}} \quad \text{where, } K_a \text{ is acidity constant}$$

The more stable the conjugate base the stronger the acid

$$K_a = \frac{[H_3O^+][A^-]}{[HA]}$$

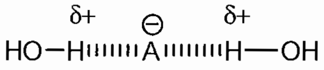
As H_2O is in excess

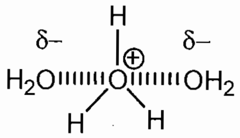
$pK_a = -\log_{10} K_a$
The higher the value of K_a, the lower the pK_a value and the more acidic is HA

The pK_a-value equals the pH of the acid when it is half dissociated. At pH above the pK_a the acid exists predominantly as the conjugate base in water. At pH below the pK_a, it exists predominantly as HA.

pH = 0 (strongly acidic)
pH = 7 (neutral)
pH = 14 (strongly basic)

The pK_a-values are influenced by the solvent. Polar solvents will stabilise cations and/or anions by solvation, in which the charge is delocalised over the solvent (e.g. by hydrogen-bonding in water).





The more electronegative the atom bearing the negative charge, the more stable the conjugate base (which is negatively charged).

pK_a	3		16		33		48
Most acidic	HF	>	H_2O	>	NH_3	>	CH_4

increasing electronegativity

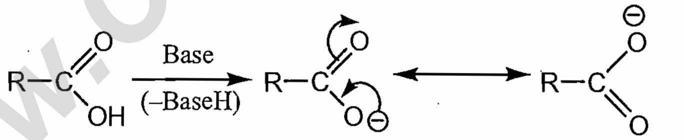
Therefore, $F^{\ominus}$ is more stable than $H_3C^{\ominus}$.

The conjugate base can also be stabilised by –I and –M groups which can delocalise the negative charge. (The more spread out the negative charge, the more stable it is)

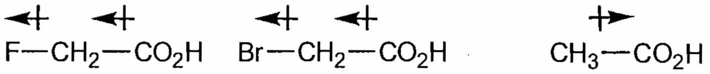
–I and –M groups therefore lower the pK_a, while +I and +M groups raise the pK_a

(a) Inductive effects and carboxylic acids:

The carboxylate anion is formed on deprotonation of carboxylic acids. The anion is stabilised by resonance (i.e. the charge is spread over both oxygen atoms) but can also be stablised by the R group if this has a –I effect.



The greater the -I effect, the more stable the carboxylate anion and the more acidic is carboxylic acid.



pK_a	2.7	2.9	4.8

Most acidic as F is more electronegative than Br and hence has a greater –I effect

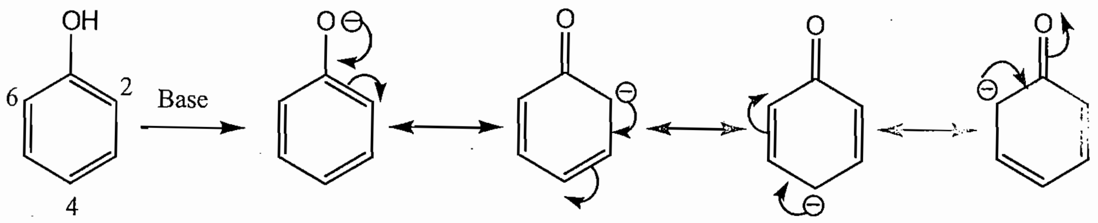
Least acidic as the CH_3 group is a +I group

(b) Inductive and mesomeric effects and phenols:

Mesomeric effects can also stabilise positive and negative charges.

The negative charge needs to be on adjacent carbon atom for a –M group to estabilise it
The poisitive charge needs to be on adjacent carbon atom for a +M group to stabilise it

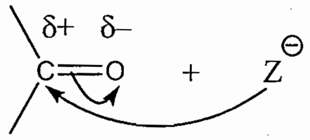
On deprotonation of phenol the phenoxide anion is formed. This stabilised by delocalisation of the negative charge at the 2-, 4-and 6-positions of the benzene ring.



Temporary Effect :

(a) Electromeric Effect :

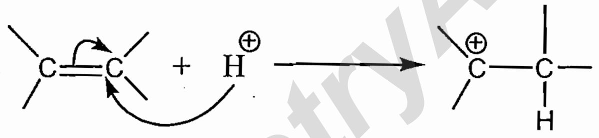
- Temporary effect.
- Takes place between two atoms joined by a multiple bond
- Occurs at requirement of attacking reagent.



Instantaneous shift of electron pair of carbonyl group towards oxygen.

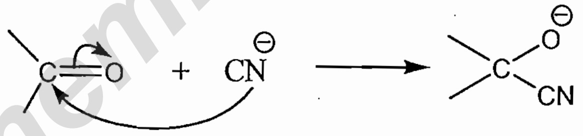
It is of two types.

(1) + E effect : Transition of electron towards the attacking reagent.



(2) –E effect :

Transition of electron away from attacking reagent.



(b) Inductomeric Effect ;

- Temporary effect.
- Takes place in sigma bonded system
- In presence of attacking reagent, transition of a electron cloud takes place more readily.

Example :

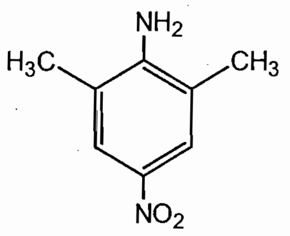
$$R—O \leftarrow H \; + \; \overset{\ominus}{B} \longrightarrow$$

In presence of base B, movement of sigma electron takes place faster.

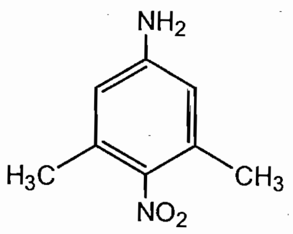
(3) Other Effect :

(a) Effect of inertia/steric inhibition of resonance:

Resonance ability of an atom is lost if it looses planarity with the other part of the system due to steric crowding by bulky group in adjacent positions.



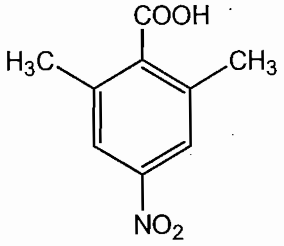
(A)



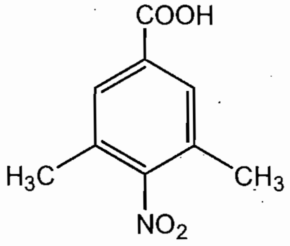
(B)

The above two compounds A and B have everything identical except position of the two methyl group. It is expected that A should be stronger base than B due to closeness of two electron donating methyl group to $-NH_2$. The fact is opposite to this. In compound B $-NO_2$ is surrounded by two bulky methyl group and they sterically repel the $-NO_2$ group. In order to minimize the steric repulsion by the two adjacent methyl group, the nitro group loses planarity with the benzene ring. So, now $-NO_2$ due to lack of planarity weigh ring, not able to resonate. This is known as steric inhibition of resonance. Thus in B, $-NO_2$ is not decreasing basic strength by resonance. In A $-NO_2$ lies in the plane of the ring, it is in resonance with the ring, decreases basic strength of $-NH_2$ by resonance, hence weaker base.

Similarly we can explain the acidic strength of C and D



(C)

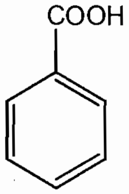


(D)

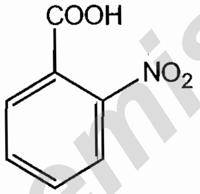
C is stronger acid inspite of closeness of two electron donating methyl group to $-COOH$.

(b) Ortho effect: If any group present on ortho position of the benzoic acid. It always increases acidic nature of acid because this group decreases outer resonance of the ring toward acidic nature. Similarly if any group present on ortho position of aniline, it decreases basic nature. This effect is known as ortho effect.

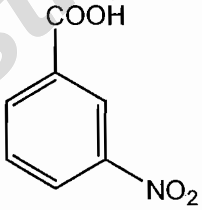
Problem : The correct order of acidity among the following compound I-IV is



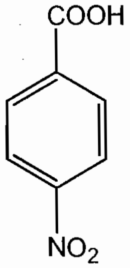
(I)



(II)



(III)



(IV)

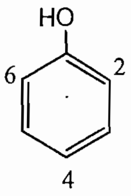
(a) II > III > IV > I (b) IV > II > III > I (c) II > IV > III > I (d) IV > III > II > I

Soln. Because of ortho effect o-nitro benzoic acid is most acidic followed by para and meta.
Thus order will be II > IV > III > I.
Hence, option (c) is correct.

Keynotes in Organic Chemistry:

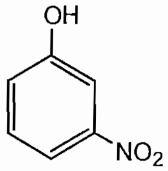
- If $-M$ groups are introduced at 2-, 4- and/or 6-positions, the anion can be further stabilised by delocalisation through the $\pi-$system, as the negative charge can be spread onto the $-M$ group. We can use double-headed curly arrows to show this process.
- If $-M$ groups are introduced at the 3- and/or 5-positions, the anion can not be stabilised by delocalisation, as the negative charge cannot be spread onto the $-M$ group. There is no way of using curly arrows to delocalise the charge onto the $-M$ groups.
- If $-I$ groups are introduced on the benzene ring, the effect will depend on their distance from the negative charge. The closer the $-I$ group is to the negative charge, the greater the stabilising effect will be. The order of $-I$ stabilisation is therefore 2-position > 3-position > 4-position.
- The $-M$ effects are much stronger than $-I$ effects.

Example: The NO_2 group is strongly electron-withdrawing; –I and –M.



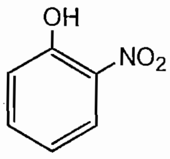
pKa 9.9

Least acidic as no –I or –M groups on the ring



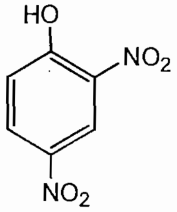
8.4

The NO_2 can only stabilise the anion inductively



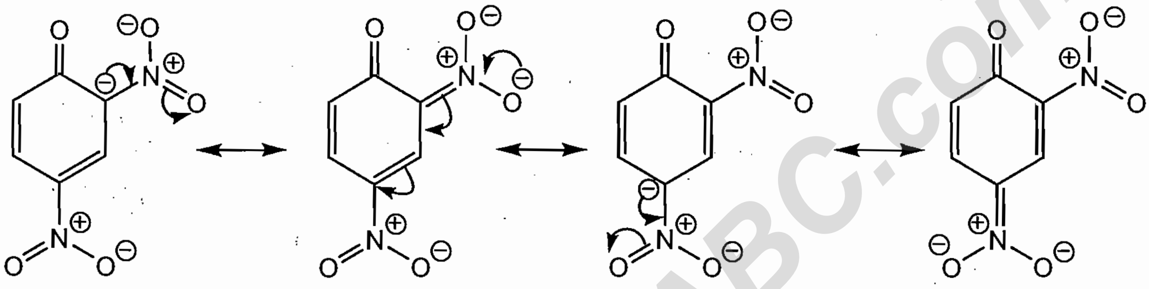
7.2

The NO_2 can only stabilise the anion inductively and by resonance



4.0

Most acidic as both NO_2 groups can stabilise the anion inductively and by resonance



Bases: A base is a substance that accepts a proton (Bronsted-Lowry). Basic compounds have high pK_a-values and are good proton acceptors, as the cations (or conjugate acids), formed on protonation, are relatively stable.

In water:

$$\underset{\text{Base}}{\ddot{B}} + \underset{\text{Acid}}{H_2O} \overset{K_b}{\rightleftharpoons} \underset{\text{Conjugate Acid}}{\overset{\oplus}{BH}} + \underset{\text{Conjugate Base}}{\overset{\ominus}{HO}}$$

where, K_b is basicity constant

The strength of bases are usually described by the K_a-and pKa-values of the conjugate acid.

$$\overset{\oplus}{BH} + H_2O \overset{K_a}{\rightleftharpoons} \ddot{B} + H_3\overset{\oplus}{O}$$

where K_a is acidity constant.

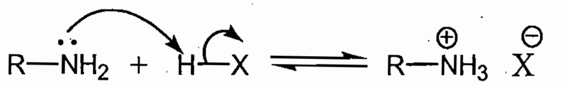
$$K_a = \frac{[B][H_3O^+]}{[^+BH]}$$

[As H_2O is in excess]

- If B is a strong base, then $\overset{\oplus}{BH}$ will be relatively stable and not easily deprotonated. $\overset{\oplus}{BH}$ will therefore have a high pK_a-value
- If B is a weak base, then $\overset{\oplus}{BH}$ will be relatively unstable and easily deprotonated. $\overset{\oplus}{BH}$ will therefore have a low pK_a-value.

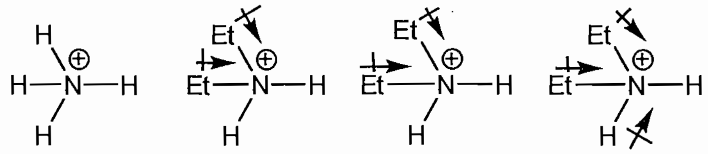
The cation can be stabilised by +I and +M groups, which can delocalise the positive charge. (The more 'spread out' the positive charge, the more stable it is).

(c) Inductive effects and aliphatic (or alkyl) amines: On protonation of amines, ammonium salts are formed.



$$R-\ddot{N}H_2 + H-X \rightleftharpoons R-\overset{\oplus}{N}H_3\ \overset{\ominus}{X}$$

The greater the +I effect of the R group, the greater the electron density at nitrogen and the more basic the amine. The greater the +I effect, the more stable the ammonium cation and the more basic the amine.



pK_a 9.3 10.7 10.9 10.9

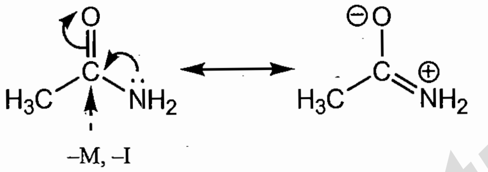
The pK_a-values should increase steadily as more +I alkyl groups are introduced on nitrogen. However, the pK_a-values are determined in water, and the more hydrogen atoms on the positively charged nitrogen, the greater the extent of hydrogen-bonding between water and the cation. This solvation leads to the stabilisation of the cations containing N–H bonds.

In organic solvents (which can not solvate the cation), the order of pK_as is expected to be as follows:

$$\underset{\text{most basic}}{R_3N} > R_2NH > RNH_2 > \underset{\text{least basic}}{NH_3} \qquad (R = +I \text{ alkyl group})$$

The presence of –I and /or –M groups on nitrogen reduces the basicity, and hence, for example, amides are poor bases.

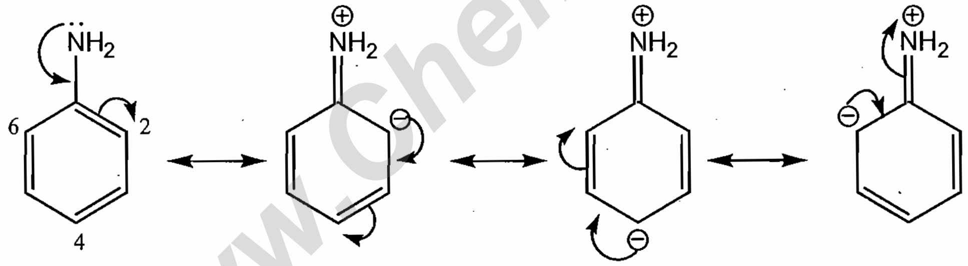
Ethanamide has a pK_a of –0.5.



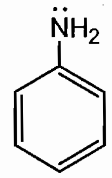
The C=O group stabilises the lone pair on nitrogen by resonance. This reduces the electron density on nitrogen

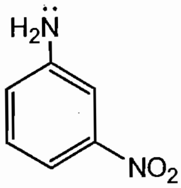
(d) Mesomeric effects and aryl (or aromatic) amines:

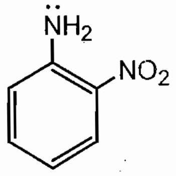
The lone pair of electrons on the nitrogen atom of aminobenzene (or aniline) can be stabilised by the delocalisation of the electrons onto the 2-, 4-and 6-positions of the benzene ring. Aromatic amines are therefore less basic than aliphatic amines.



- If –M groups are introduced at the 2-, 4-and/or 6-positions (but not at the 3- or 5-position), the anion can be further stabilised by delocalisation, as the negative charge can be spread onto the –M group. This reduces the basicity of the amine.
- If –I groups are introduced on the benzene ring, the order of –I stabilisation is 2-position > 3-position > 4-position. This reduces the basicity of the amine.







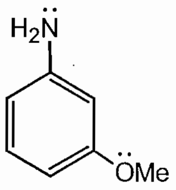
pK_a 4.6 2.45 –0.28

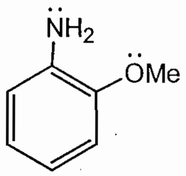
Most basic as no-I or –M groups on the ring

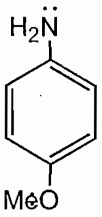
The NO_2 group can stabilise the lone pair inductively

Least basic: The NO_2 group can stabilise the lone pair inductively and by resonance

- If +M group (e.g. OMe) are introduced at the 2-, 4- or 6-position of aminobenzene, then the basicity is increased. This is because the +M group donates electron density to the carbon atom bearing the amine group.

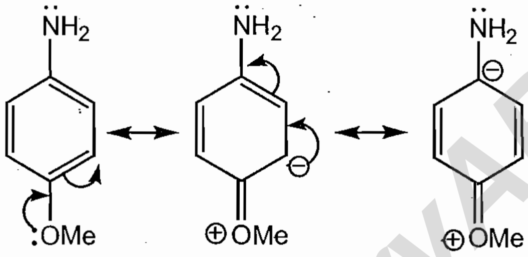






pK_a	4.2	4.5	5.3
	Least basic: The OMe group cannot donate electron density to the carbon atom bearing the nitrongen	The OMe group can donate electron density to the nitrogen but it has a strong –I effect as it is in the 2-position	Most basic: The OMe group can donate electron density to the nitrogen and it has a weak –I effect (as well apart from the nitrogen)

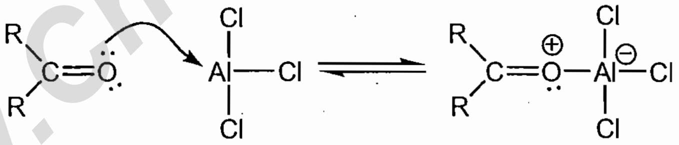
Curly arrows can be used to show the delocalisation of electrons onto the carbon atom bearing the nitrogen.



electron density adjacent to the nitrogen increases the basicity

(e) Lewis acids and base:

- A Lewis acid is any substance that accepts an electron pair in forming a coordinate bond. Examples include H^+, BF_3, $AlCl_3$, $TiCl_4$, $ZnCl_2$ and $SnCl_4$. They have unfilled valence shells and hence can accept electron pairs.
- A Lewis base is any substance that donates an electron pair in forming a coordinate bond. Examples include H_2O, ROH, RCHO, R_2CO, R_3N and R_2S. They all have a lone pair(s) of electrons on the hetero atom (O, N or S)



Lewis base Lewis acid

(f) Basicity and hybridisation:

The greater the 's' character of an orbital, the lower is energy the electrons and the more tightly the electrons are held to the nucleus. The electrons in an sp-orbital are therefore less available for protonation than those in an sp^2- or sp^3-hydrid orbital and hence the compounds are less basic.

most basic: $R_3N > R_2C{=}\ddot{N}H > RC{\equiv}\ddot{N}$ least basic

most basic: $R_3\overset{\ominus}{C} > R_2C{=}\overset{\ominus}{C}H > RC{\equiv}\overset{\ominus}{C}$ least basic

sp^3	sp^2	sp
(25%s)	(33%s)	(50%s)

CHAPTER 2

Aromaticity

Introduction

Aromaticity is a chemical property of organic compound, aromatic compound have following characteristics:

(i) It has high degree of stability

(ii) It shows electrophilic substitution reaction rather than electrophilic addition reaction. It means it does not decolourise bromine water solution.

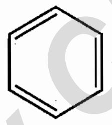
(iii) Aromatic compound follow Hückel rule. According to which A cyclic planar conjugated species having $(4n+2)\pi$ electrons (where n = 0, 1, 2, 3, ...) is aromatic in nature.

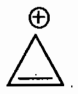
(iv) There is a diamagnetic ring current.

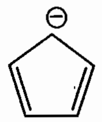
(v) Each carbon must be sp^2-hybridized or sp-hybridized.

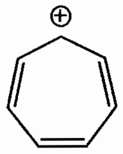
(vi) It has high degree stability due to filled bonding molecular orbital.

For example:


$4\times1+2=6\pi$
(Aromatic)


$4\times0+2=2\pi$
(Aromatic)

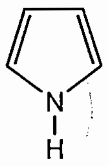

$4\times1+2=6\pi$
(Aromatic)


$4\times1+2=6\pi$
(Aromatic)

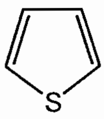
1. **High Degree of stability:** High degree of stability is associated with resonance energy. The compound which have more resonance energy is more stable. The compound which have more potential energy is least stable.

$$\text{Aromaticity} \propto \text{Resonance energy (R.E)} \propto \text{Stability} \propto \frac{1}{\text{Potential Energy (P.E.)}}$$

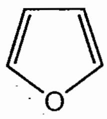
2. Greater the resonance energy higher will be the stability of compound. Resonance energy of some aromatic system are given below as



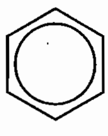
21 kcal/mol

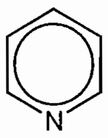


29 kcal/mol



16 kcal/mol

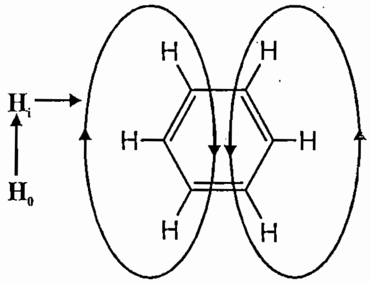

36 kcal/mol



32 kcal/mol

(3) Presence of diamagnetic ring current:

Aromatic compounds show diamagnetic ring current due to paired electron.

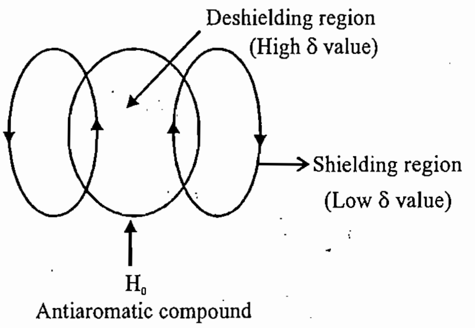


$H_{shielding}$(net) $= H_0 - H_i$

$H_{Deshielding}$(net) $= H_0 + H_i$

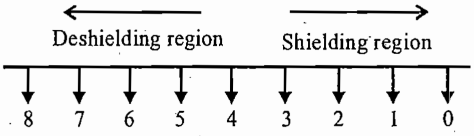
where, H_0 = external magnetic field
H_i = induced magnetic field

* Clockwise direction in electron present for aromatic compound.



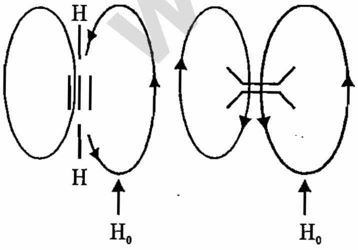
↑↑ deshielding region (down field)

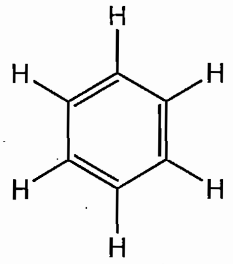
↓↑ shielding region (up field)

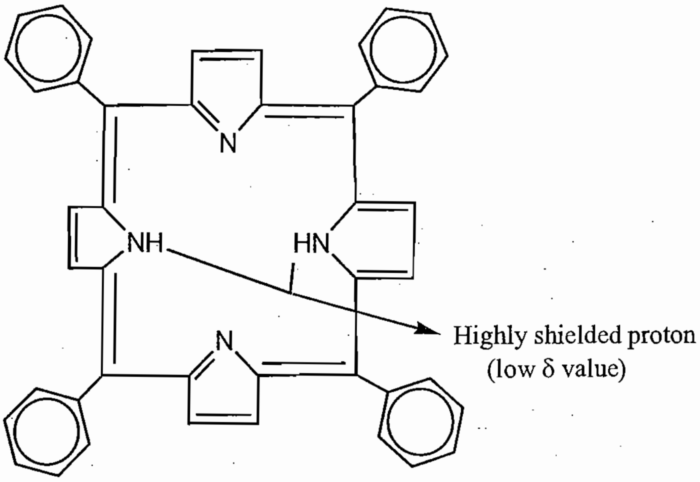


δ value – $sp^2 > sp > sp^3$ (decreasing order) due to anisotropic effect.

- Molecule in which outer protons are deshielded and inner protons are shielded is known as ***diatropic*** molecule. These type of molecules are always aromatic in nature.
- Similarly, molecule in which inner protons are shielded and outer protons are deshileded are known as ***paratropic*** molecule. Paratropic molecule is aromatic in nature.
- Antiaromatic compounds show paramagnetic ring current due to unpaired electron.







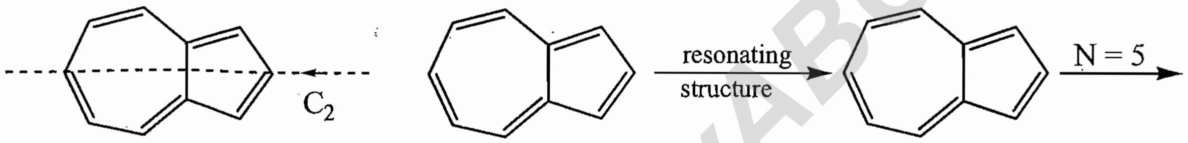
Hückel Rule: This is a very popular and useful rule to identify aromaticity in monocyclic conjugated compound. According to which a planar monocyclic conjugated system having $(4n+2)\pi$ delocalised (where, n = 0, 1, 2, ...) electrons are known as aromatic compound . For example: Benzene, Naphthalene, Furan, Pyrrole etc.

n = 0	$(4\times0+2)\ \pi e^- = 2\pi e^-$
n = 1	$(4\times1+2)\pi e^- = 6\pi e^-$
n = 2	$(4\times2+2)\pi e^- = 10\pi e^-$
n = 3	$(4\times3+2)\pi e^- = 14\pi e^-$
n = 4	$(4\times3+2)\pi e^- = 18\pi e^-$

- **Craig's Rule:** This rule is applicable for polyclic non-benzenoid compounds. If molecule contain C_2-axis then count total number of double bonds (N) and calculate value of N–1 which decide aromaticity in compound.

(1) If N – 1 = odd, compound is non-aromatic
(2) If N – 1 = even, compound is aromatic.
e.g. Azulene

(a)

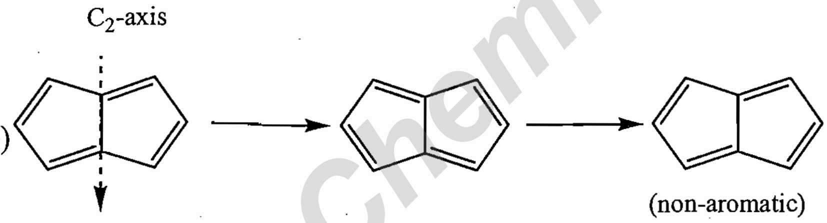


(A) (B)

N –1 = 4π bond (aromatic)

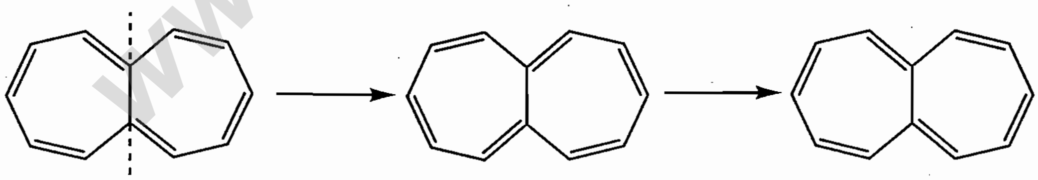
- In system C_2-axis must be present

(b)



(Pentalene) (non-aromatic)

N = 4
N–1 = 3, odd. Hence, compound is non-aromatic.



(Heptalene) (non-aromatic compound)

N = 6
N–1 = 5, odd. Hence compound is non-aromatic.

- Pentalene and heptalene is a non-aromatic compound. Since it does not follow craig's rule.
- The organic compound which show aromaticity are aromatic in nature or diatropic in nature and the protons (outside the rings) signal always exist away from the TMS (these protons are dishielded protons)
- Identification of aromatic, anti-aromatic and non-aromatic compounds.

Organic Compound

(1) Aromatic Compound

(a) Huckel rule

(i) Monocyclic system

(ii) Polycyclic benzenoid

(b) Craig's rule

Polycyclic non-benzenoid

(2) Anti-aromatic compound

4n πe^- delocalized

n = 1, 2, 3, 4, 5, ...

$n = 1 = 4\pi e^-$

$n = 2 = 8\pi e^-$

$n = 3 = 12\pi e^-$

system planar (sp and sp^2-hybridized)

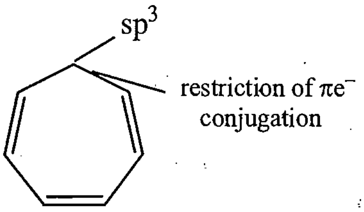
(system conjugated)

(3) Non-aromatic compound

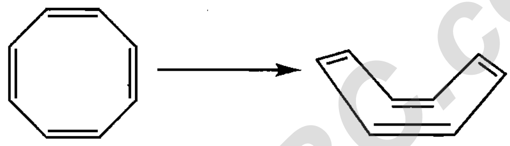
restriction of delocalization πe^-s

sp^3 **non-planar structure**

sp^3 hybdridized carbon atom insert



(non-aromatic)



COT (Cyclooctatetraene) Tub shaped

- **Order of stability and order of resonance energy:**

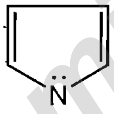
Aromatic > Non-aromatic > Anti-aromatic.

Calculation of π-electrons: During π-electron count double bond count 2π electron and triple bond count 2π electron. Also, lone pair in conjugation is also counted.

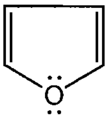
$= \rightarrow 2\pi e^-$

$\equiv \rightarrow 2\pi e$

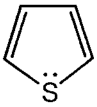
$1\,\ell p \rightarrow 2e$



$6\pi e^-(4\pi e + 1\ lp)$



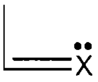
$6\pi e^-\ (4\pi e + 1\ lp)$

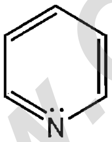


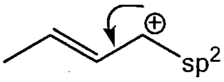
$6\pi e^-\ (4\pi e + 1\ lp)$

species in which lone pair is not in conjugation can not be counted:

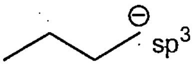
e.g.





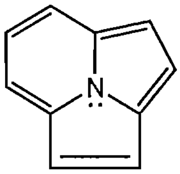


hybridized

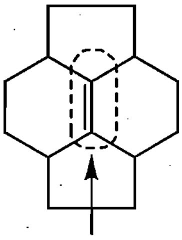


hybridized

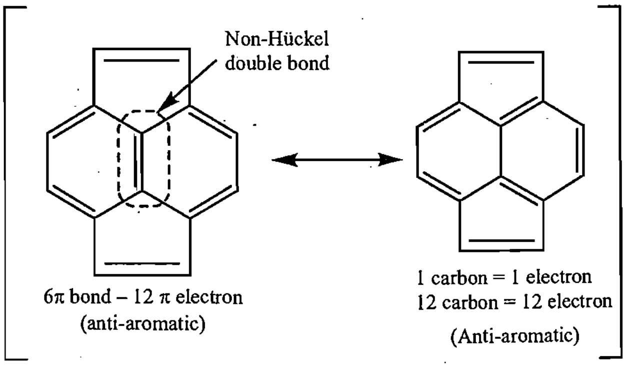
- Lone pair which participate in conjugation system and follow Hückel's rule are called Hückel lone pair while which lone pair does not participate in conjugation are known as non-Hückel lone pair.



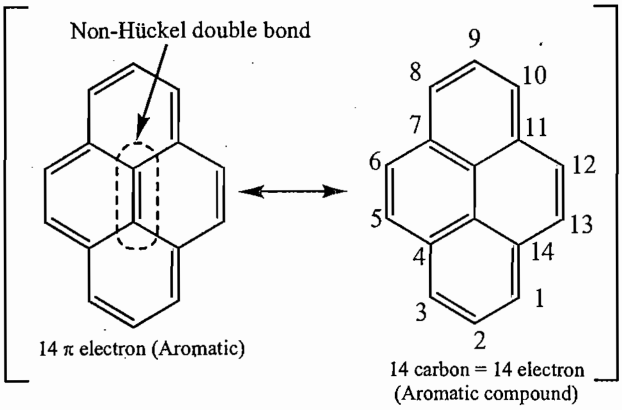
(Non-Hückel lone-pair because lone pair of nitrogen is not present at periphery.)



(non-Hückel double bond)

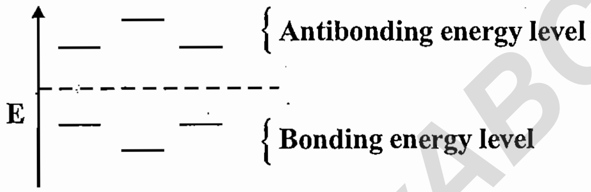


Resonance Structure



Resonance Structure

- Energy level of aromatic and anti-aromatic compounds can be shown by using **frost circle** or diagram. Energy levels of regular planar polygonic molecules with an even number of atoms form a symmetrical pattern as shown below.



If all bonding energy levels are filled then it is aromatic [Hückel criterion also required].

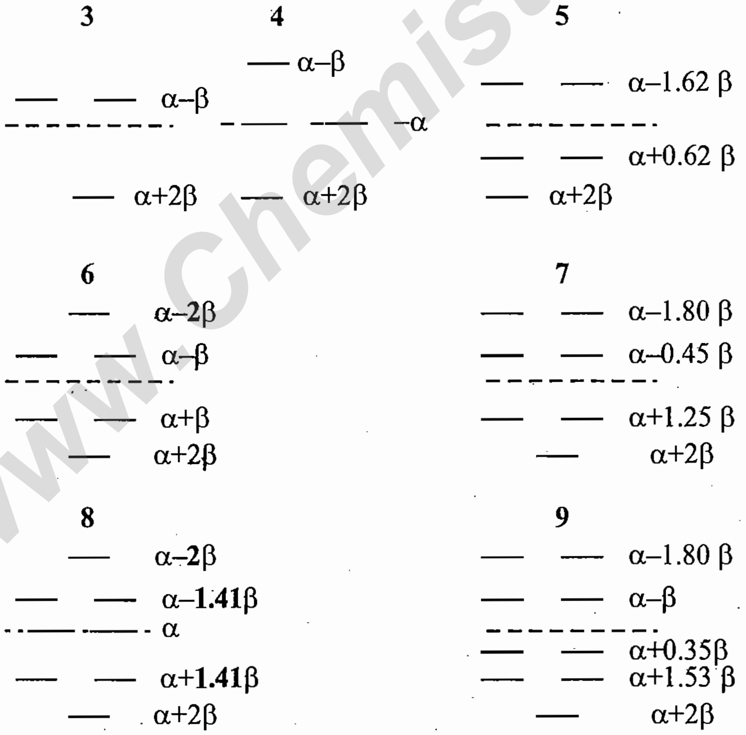
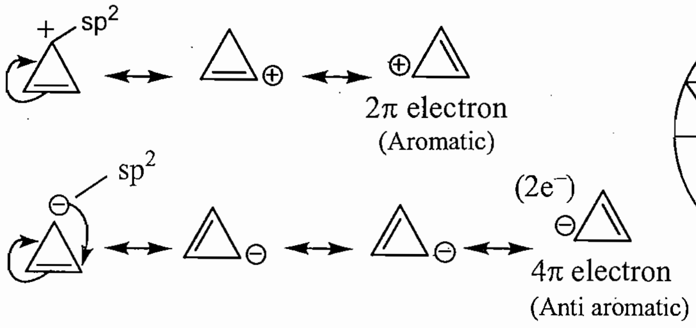
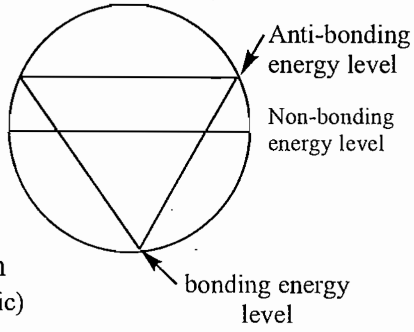


Figure : HMO energies for conjugated planar ring systems of three to nine carbon atoms.





Frost Diagarm for Cyclopropenyl system

- Anti-aromatic compound behaves as a biradical
- In anti-aromatic compounds two unpaired electron are present which are all paired.
- Oxygen also behave as biradical and triplet state.
- Carbene-triplet state are biradical.

Types of Aromatic Compounds

(A) 2π-electron system .

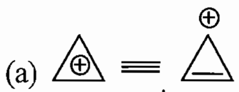
(i) It follow $(4n+2)\pi e^-$ system.

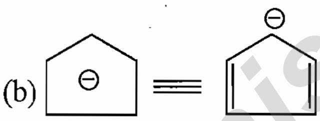
(ii) If electron delocalised then compound is aromatic.

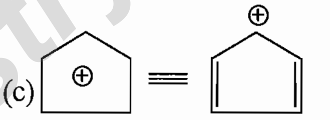
(iii) If electrons not delocalised then compound is non-aromatic

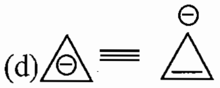
(iv) Compound will never be antiaromatic.

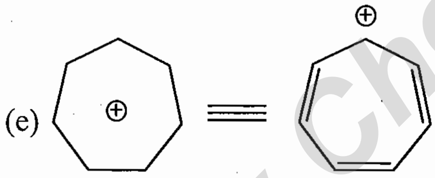
Examples:

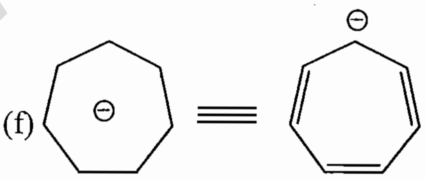
(a)

Aromatic

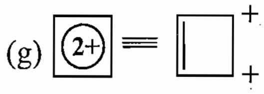
(b)

Aromatic

(c)

Anti-aromatic

(d)

Anti-aromatic

(e)


(f)

(anti-aromatic)

(g)


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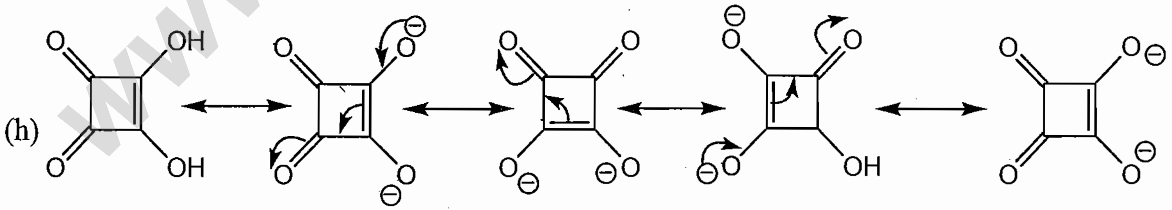
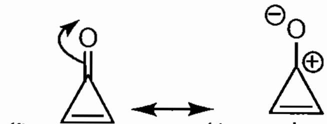


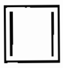
(i)

(Aromatic compound)

Displacement of electrons takes place towards higher electronegative atom.

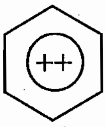
(B) 4π-electronic system:

(i) Belongs to 4n πe^- system doesnot follow Hückel rule.
(ii) If electron is delocalised then compound is antiaromatic.
(iii) If electron does not delocalised then compound never antiaromatic
(iv) If electron does not delocalised then compound is non-aromatic.

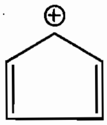
Examples:

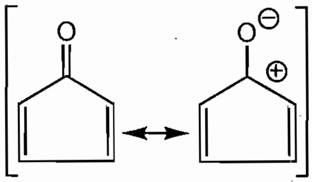
(a) 
A.A

(b) 
A.A

(c) 

A.A

(d) 
A.A

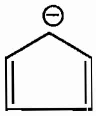
(e) 

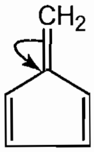
A.A

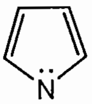
A.A. = Anti-aromatic

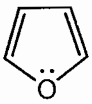
(C) 6π electron system:

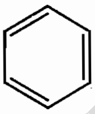
(i) Belongs to $(4n+2)\pi e^-$ system.
(ii) If electron is delocalised then compound will be aromatic.
(iii) If electron does not delocalise then compound must be non-aromatic
For example

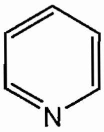


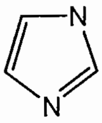


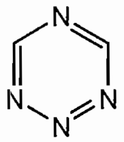


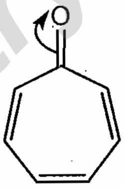


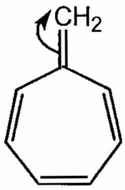




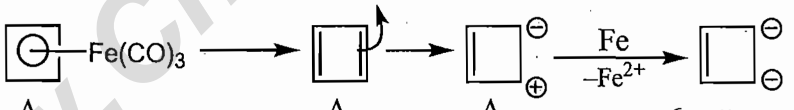








A

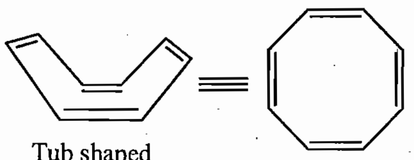


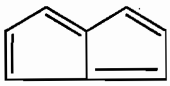
A A A

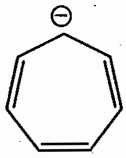
6π e⁻ system

(D) 8π electronic system :

(i) Belongs $(4n)\pi e^-$ rule
(ii) If electron is delocalised the compound must be anti-aromatic
(iii) If electron does not delocalise then compound is non-aromatic.


Tub shaped Non-aromatic


Non-aromatic


Anti-aromatic

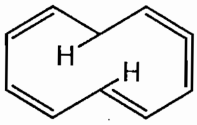
(E) 10π electronic system:

(i) Belongs $(4n+2)\pi e^-$ system.

(ii) If electron delocalised then compound aromatic in nature.

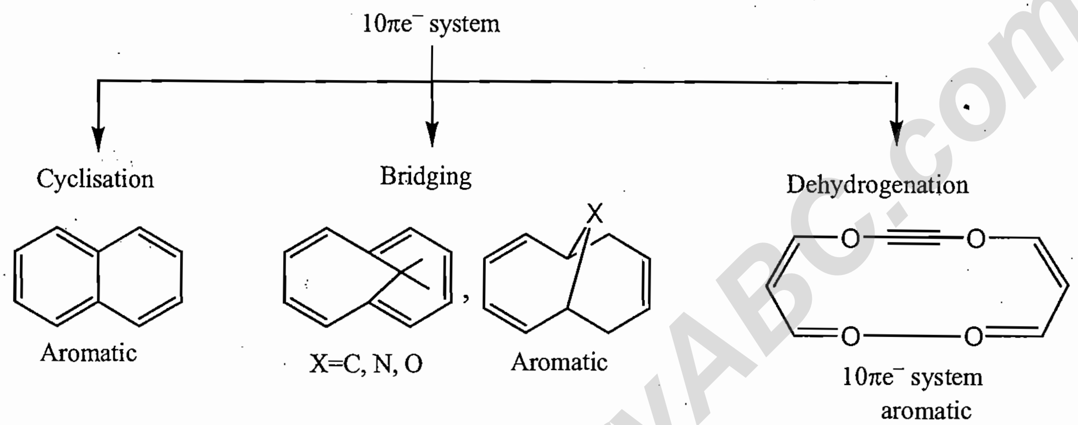
(iii) If electron does not delocalise then compound will be non-aromatic

(iv) Compound never be anti-aromatic.

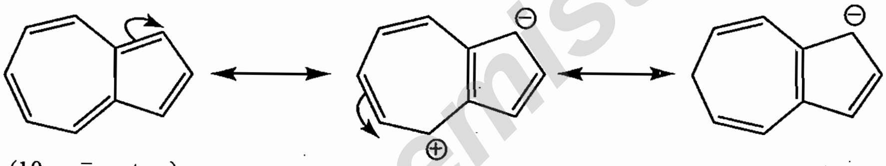


(Non-aromatic)

(Repulsion between H-hydrogen atoms, causes the compound to be non planar. So, compound is non-aromatic)

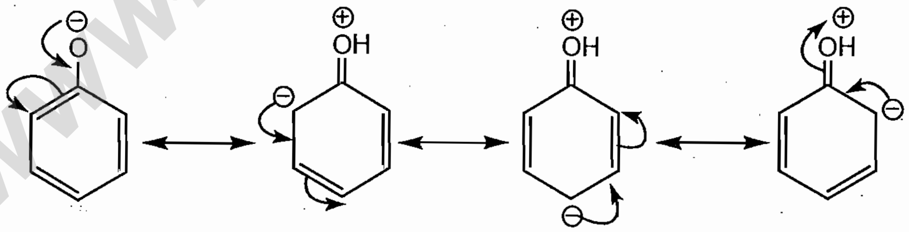


Azulene :



(10 π e$^-$ system)

- Azulene is the isomer of Naphthalene
- Azulene is less stable than naphthalene
- Azulene gives electrophilic substitution reaction
- Five membered ring gives substitution reaction (because small size, electronegativity)



like (same) charge must be at maximum distance and opposite charge must be at minimum distance for stability resonance structure.

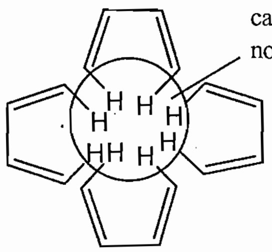
(F) 12 π electronic system:

(i) Belongs to $(4n)\pi e^-$ system

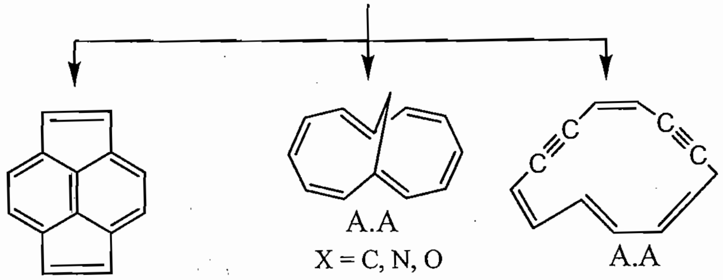
(ii) If electron is delocalise then compound is anti-aromatic

(iii) If electron does not delocalization then compound will be non-aromatic.

(iv) Compound never be aromatic



cavity size small → repulsion
non-planar → non-aromatic



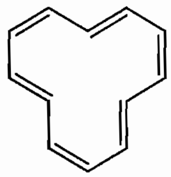
$12\pi e^-$ system

A.A

A.A
X = C, N, O

A.A

$$12\pi e^- \text{ system-(non-planar)} \xrightarrow[\text{metal}]{\text{reaction with}} \text{aromatic}$$



$\xrightarrow{2K}$ Aromatic

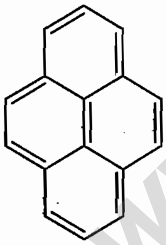
(G) 14 π electronic system:

(i) Belongs to $(4n+2)\pi e^-$ system

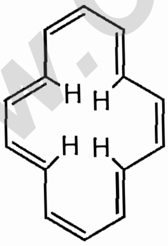
(ii) If delocalize electron then the compound is aromatic.

(iii) If electron does not delocalised then the compound non-aromatic

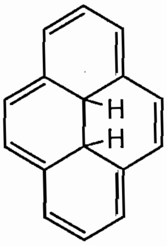
(iv) It never be antiaromatic.



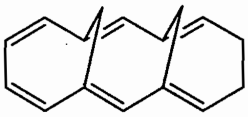
Aromatic



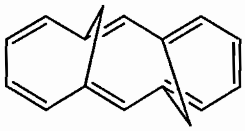
Aromatic



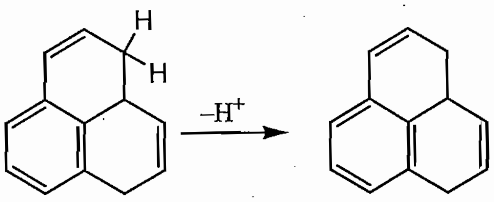
Aromatic



Aromatic

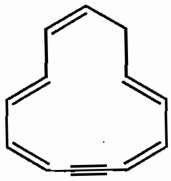


non-aromatic



pheneline

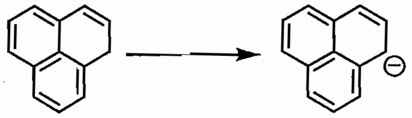
Phenelone ion
(aromatic)



14π(aromatic)

6. Phenelene is acidic in nature why?

Proton (H^+) remove from the phenaline and acidic in nature and system gain aromaticity.

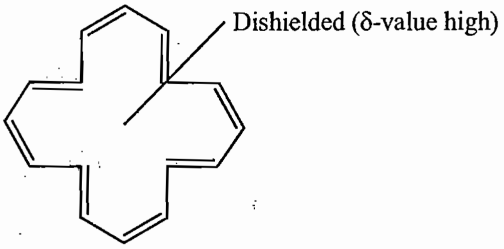


Phenelene

Aromatic
[14 electron system]

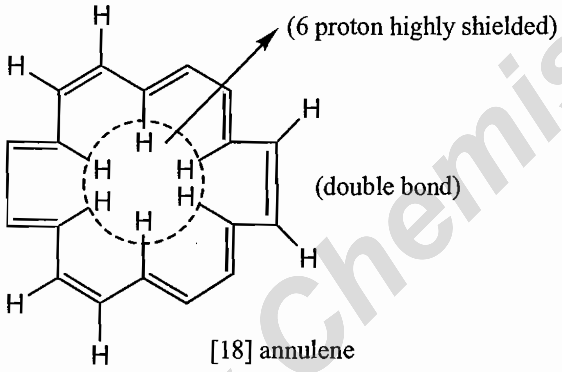
(H) 16π **electronic system:**

(i) Belongs to $4n\pi e^-$ rule.
(ii) If electron is delocalised then compound is anti-aromatic.
(iii) If electron does not delocalised then compound will be non-aromatic
(iv) It never be aromatic.



16π (Anti-aromatic)

(I) 18 π **electronic system:**

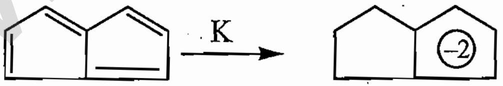


[18] annulene

$18\pi e^-$ (aromatic)

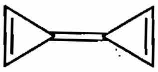
Completely conjugated monocyclic system called annulene

- 18 Annulene contain 3 cis close bond.

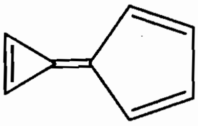


N.A.

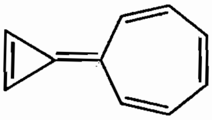
Other Aromatic System:
Fused ring aromatic.



triafulvalene

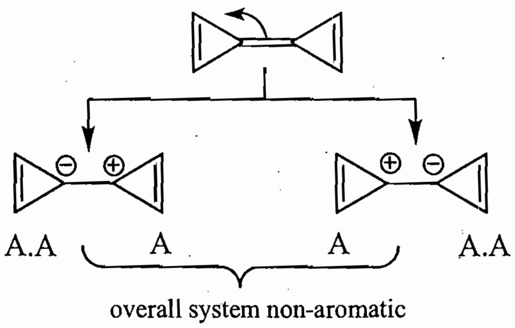


calicene

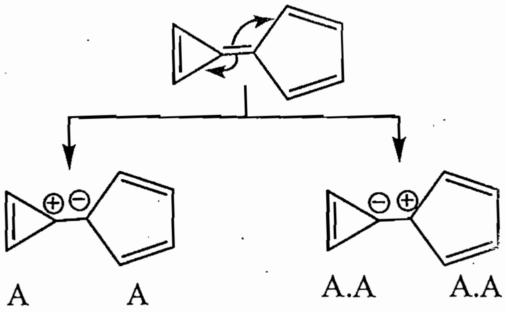


- Such type of systems is aromatic or non-aromatic but never be anti-aromatic
- If such type of system is aromatic then both ring must be aromatic after displacement of common double bond.

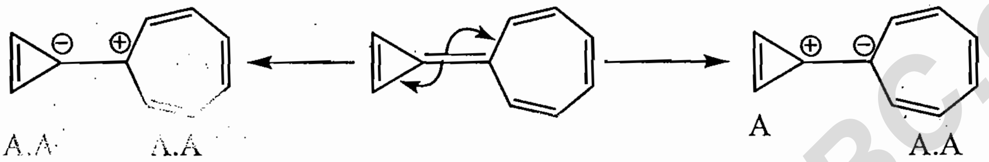
Otherwise both ring will not be aromatic



overall system non-aromatic

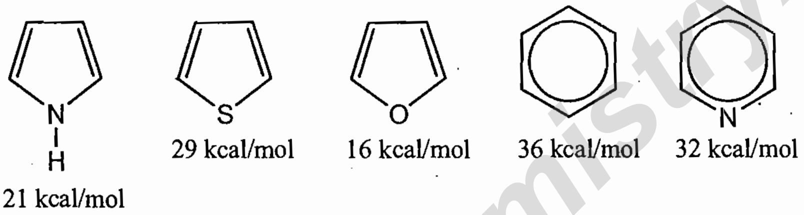


overall system aromatic

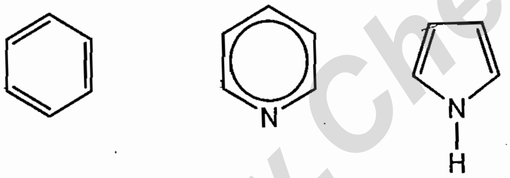


overall system → non-aromatic

Resonance energy of some aromatic system:



Pyrrole is called as super aromatic compound

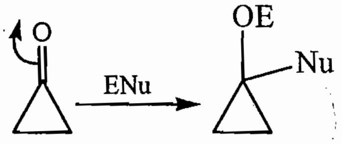


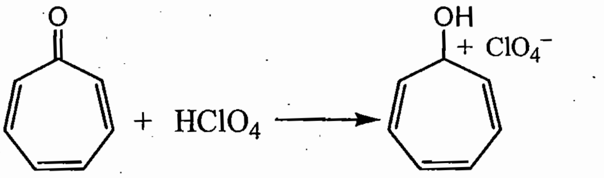
$$36 = \frac{6}{6} = 1 \text{ for C-atom energy. } \frac{(\text{total } \pi e^-)}{(\text{total C-atom})} \frac{6}{5} = 1.2 \text{ per C-atom}$$

According to electron density at per C-atom, pyrrole is electronically rich. So, pyrrole gives electrophilic substitution reaction more easily than benzene.

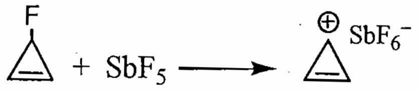
$$\text{Electrophilic substitution reaction} \propto \frac{1}{\text{resonance energy}(\text{aromaticity})}$$

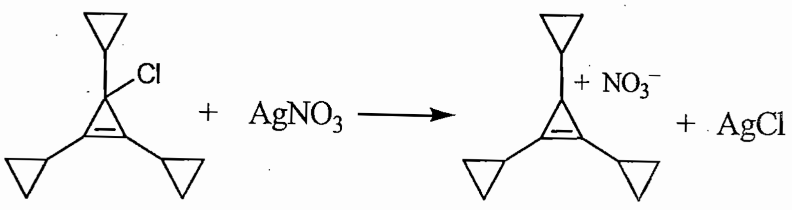
Quasi Aromatic Compound: These are generally ionic aromatic compound





Quasi aromatic compound

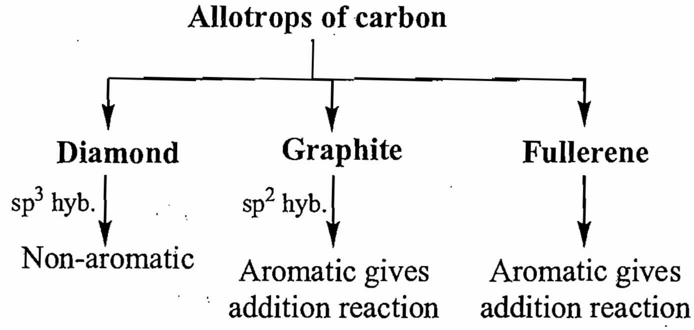




(Quasi aromatic compound)

Allotrops of Carbon:

(i) Diamond (ii) Graphite (iii) Fullerene



$\text{Unstable} \xrightarrow{\text{energy release}} (\text{stable})$

$(non-aromatic) \xrightarrow{change} (Aromatic)$

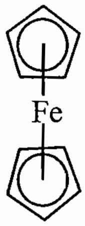
$Diamond \xrightarrow{change} \text{Graphite} \quad \Delta H = -ve$

$Graphite \xrightarrow{change} \text{Diamond} \quad \Delta H = +ve$

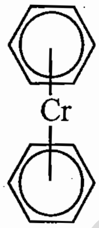
$(Stable) \xrightarrow{energy\ gain} (Unstable)$

Organometallic aromatic compound:

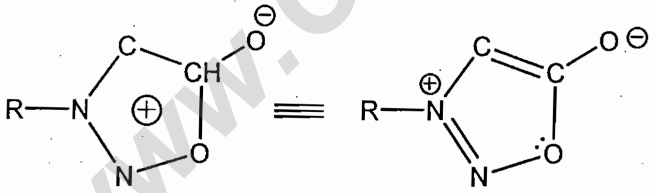
Ferrocence



Dibenzene chromium

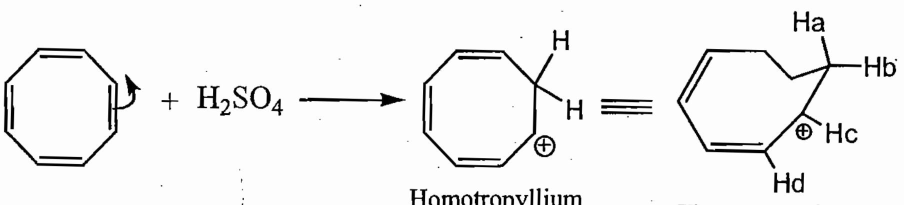


- Mesoionic Compound: Sydons is the first meso-ionic compound which show aromaticity.
- Meso-ionic compound gives electrophilic substitution reaction
- Meso-ionic compound also known as internal salt.



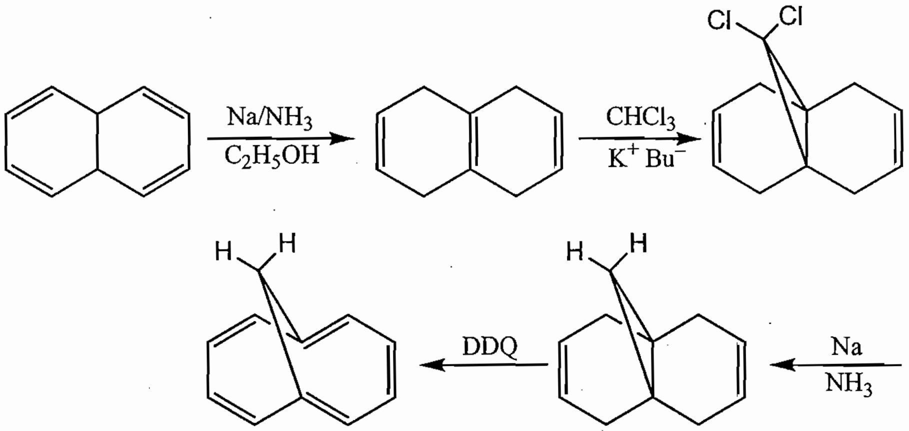
(Sydons)

- **Homo-aromatic compound :** Compound that contain one or more sp^3-hybridized C-atom in a conjugate cycle but sp^3-hybridized carbon atom are force to lie almost vertically above the plane of the aromatic system known as homoaromatic compounds.



Homotropyllium cation

Homotropyllium cation



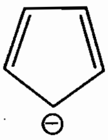
Homoaromatic compound

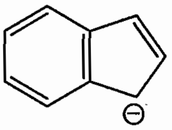
Stability: Aromatic > Homo-aromatic > non-aromatic> antiaromatic

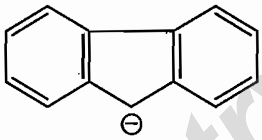
Annelation effect :

Each ring in fused system give the part of the aromaticity to the adjacent ring called **annelation effect**.

e.g.







- Number of benzene ring increases
- Aromaticity decreases

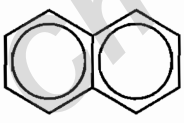
PROBLEMS

1. Arrange the following compound in correct order of aromaticity?

(A)

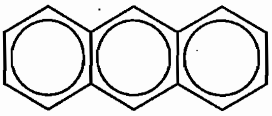
R.E. = 36

(B)



R.E. = –59

(C)



R.E. = 71

Soln. Resonance energy of each species is written below to structure as we known greater the resonance energy per benzene ring, higher will be the stability of molecule

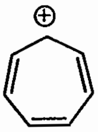
$$\frac{36}{1}=36 \qquad \frac{59}{2}=29.5 \qquad \frac{71}{3}=23.67$$

Depending upon the resonance energy per benzene ring the aromaticity of above compound can be arranged as A > B > C.

2. Which of the following compound is more stable.

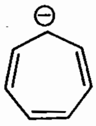
(i)

(ii)



Soln. **(ii)**

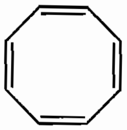
3. Which of the following compound is more anti-aromatic

(i)  (ii) 

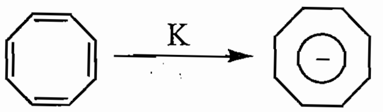
Soln. (i)  (More anti-aromatic because more planar)

The anti-aromatic compound have tandency to adopt the non-planar structure to maximize its stability.

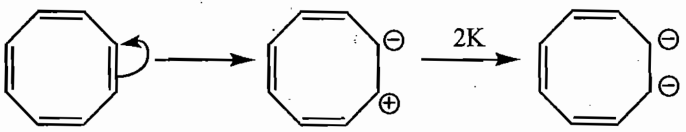
4. Which of the following compound gives H_2-gas with metal.

(i)  (ii) 

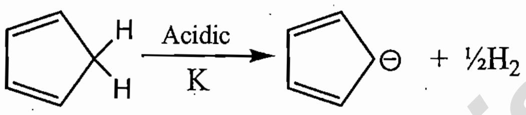
Soln. (ii), (i) both.



N.A. 10 π electron system



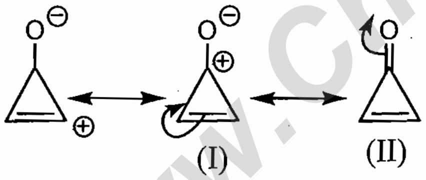
10 e^- (planar)



(Cyclopentadienyl) Aromatic (cyclopentadienyl anion)
N.A.

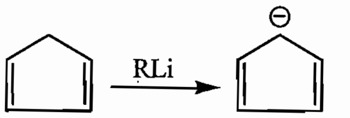
Cyclopentadiene is acidic in nature due to aromatic character of cyclopentadienyl anion.

5. Which of the compound have more dipole moment.

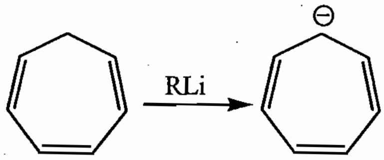


Maximum charge separation → maximum dipole moment
because $\mu = q \times d$, where, q = amount of charge, d = distance between two poles.
(I) have more dipole moment than (II)

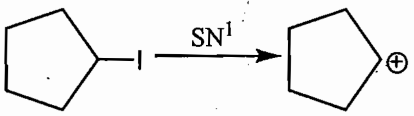
6. Which of the following reaction takes place.



(non-aromatic) (aromatic)



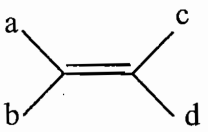
(Non-aromatic) (Anti-aromatic)
{Reaction is not possible because stability decrease}

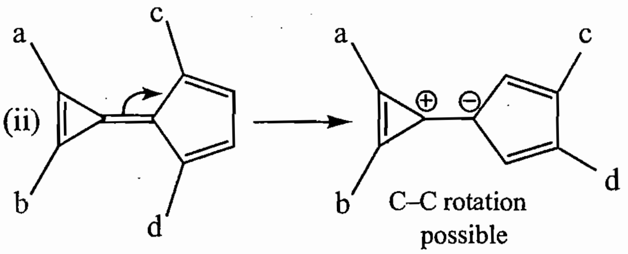


because 2° carbocation form.

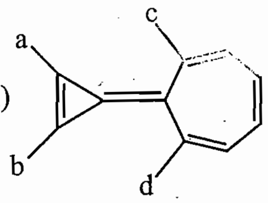
7. Which of the following compound gives geometrical isomerism.

For geometric isomerism: At this carbon for both group must be different and C–C bond rotation must be restricted.

(i) 

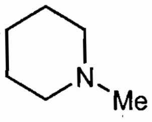
(ii) 

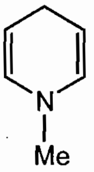
C–C rotation possible

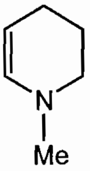
(iii) 

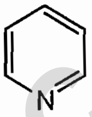
Non-aromatic

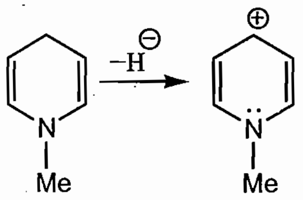
8. Which of the following compound is best hydride donor.

(i) 

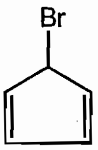
(ii) 

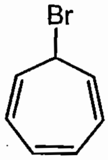
(iii) 

(iv) 

Soln. 

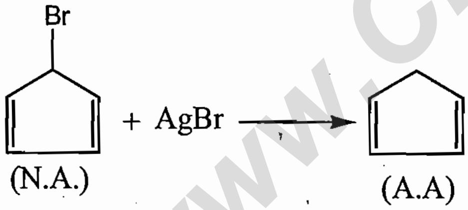
9. Which of the following compound gives ppt. with AgNO$_3$.

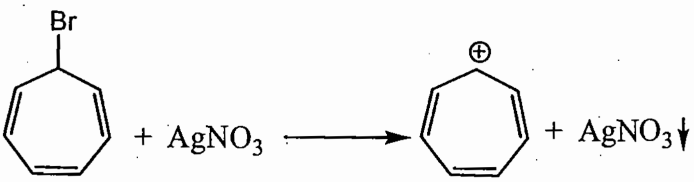
(i) 

(ii) 

(iii) 

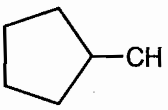
Soln. **(i) and (ii)**

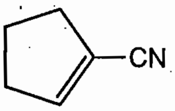


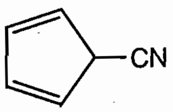


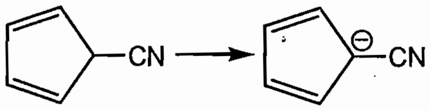
(Quasi aromatic compound)

10. Arrange these molecules in correct order of deprotonation.

(i) 

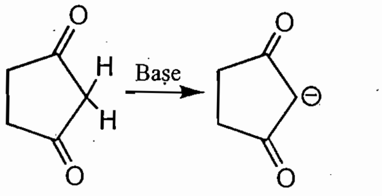
(ii) 

(iii) 

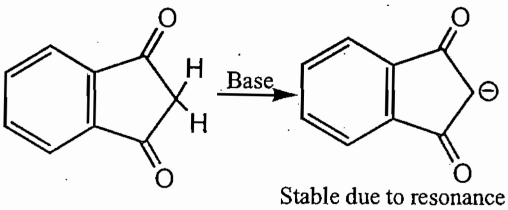


Soln. (iii) > (ii) > (i)

More acidic:

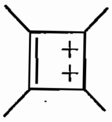
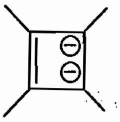
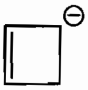
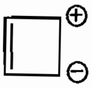


Stable due to resonance



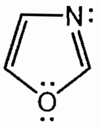
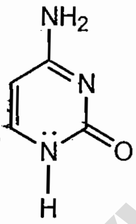
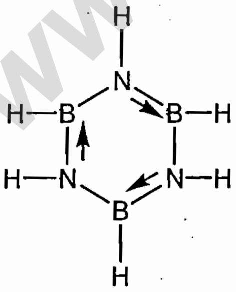
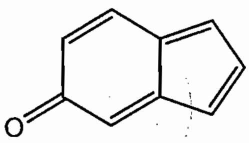
Stable due to resonance

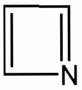
11 Match the following

Column-I	**Column-II**
(A) 	(i) Aromatic
(B) 	(ii) Anti-aromatic
(C) 	(iii) Non-aromatic
(D) 	(iv) $(4n+2)\pi e^-$

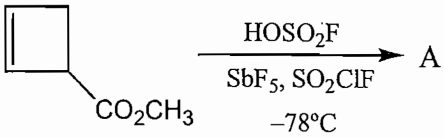
Soln. A-(i), (iv); B-(i), (iv), C-(iii), D-(ii)

12. Match the folloiwng

Column-I	**Column-II**
(A) 	(i) Aromatic
(B) 	(ii) Non-aromatic
(C) 	(iii) Anti-aromatic
(D) 	(iv) Heterocyclic

(E) 

Soln. A-(i), (iv); B-(i), (iv); C-(i), (iv); D-(ii); E-(iii)

13. 

In the above reaction, A is

(a) Antiaromatic (b) Homoaromatic (c) Non-aromatic (d) Antiaromatic

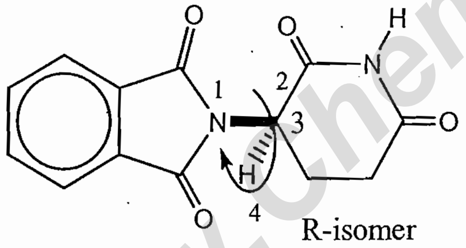
Soln. **(b)**

CHAPTER
3

Stereochemistry

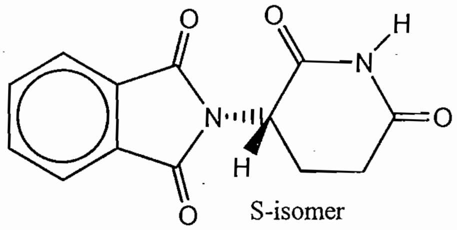
Stereochemistry :
It involves the study of the relative spatial arrangement of atoms within the molecules.
Dynamic stereochemistry: Dynamic stereochemistry is the study of the effect of stereochemistry on the rate of a chemical reaction.

First Stereochemist – Louis Pasteur (1849):
Significance of stereochemistry: One of the most infamous demonstration of the significance of stereochemistry was the ***Thalidomide disaster***. Thalidomide is a drug was first prepared in 1957 in Germany, prescribed for treating morning Sickness in pregnant women. It was discovered that one optical isomer i.e. R-Isomer of the drug was safe whereas the S-isomer had teratogenic effect, causing serious genetic damage to early embryonic growth and development.



R-isomer

Drug for morning sickness in pregnant women.

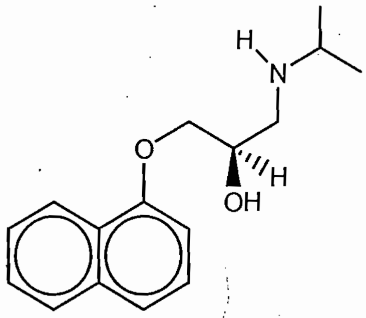


S-isomer

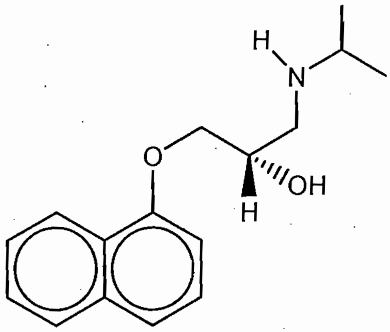
Teratogenic effect

[**Remark:** In human body, Thalidomide undergoes racemization: even if only one of the two stereoisomers is ingested, the other one is produced.]

Now we have another example - Propanolol.



R-Propanolol (contraceptive)



S-Propanolol (antihypertensive)

SOME TERMINOLOGY

Optical activity: The term optical activity derived from the interaction of chiral materials with polarized light.

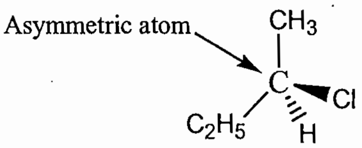
Scalemic: Any non-racemic chiral substance is called *Scalemic.*

- A chiral substance is enantio pure or homochiral when only one of two possible enantiomer is present.
- A chiral substance is enantio enriched or heterochiral when an excess of one enantiomer is present but not the exclusion of the other.

Three terms are used to designate a carbon atom bonded tetrahedrally to four different substituents in a chiral molecule.
(a) Asymmetric atom (*LeBell & Vant Hoff* for an atom attached with 4 different groups).
(b) Chiral centre
(c) Stereocentre.

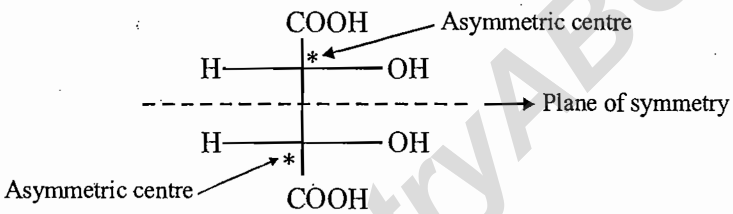
Asymmetric atom:

Compounds with one such atom are truly asymmetric as they lack symmetry. For example



No element of symmetry is present in the molecule.

However, there are molecules which also have atoms with four different substituents and which also have various symmetry element including plane of symmetry as in mesotartaric acid.

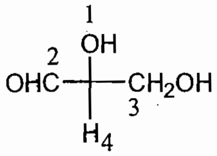


Two asymmetric center but also plane of symmetry.

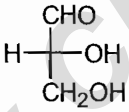
Chirality is a geometric property which influences and affects all parts of a chiral molecule.

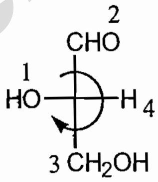
Stereogenic centre or Stereocentre:

A stereogenic centre or in short a stereocentre is an atom having groups of such nature that an interchange of any two groups will produce a stereocentre.



S-form



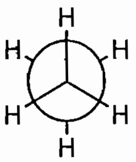


R-form

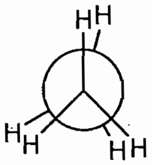
- A carbon atom that is a stereocentre is also called a stereogenic carbon.

Conformation: Structures that can be interconverted simply by rotation about single bonds are conformation of the same molecule.

For example:



Staggered conformation



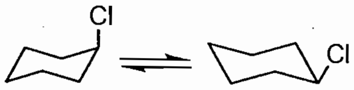
Eclipsed conformation

Note: These two are the conformation of ethane arises due to rational possibilites across C–C single bond.

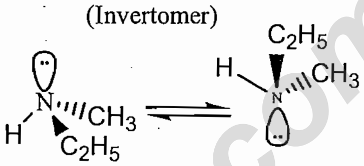
Configuration: Structures that can be interconverted only by breaking one or more bonds have different configuration and they are stereoisomers specifically known as configurational isomers.

Isomers

- Constitutional Isomers
  - → Chain Isomerism
  - → Position Isomerism
  - → Metamerism
  - → Tautomerism
  - → Valence Isomerism
- Stereoisomers
  - Conformational Isomer
    - Rotation about single bond.
    - Amine Inversion (Invertomer)
  - Configurational Isomers



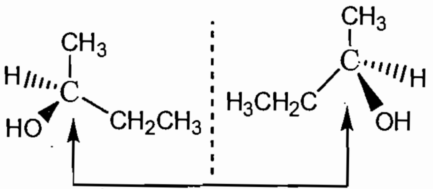
Conformational Isomer (conformers)



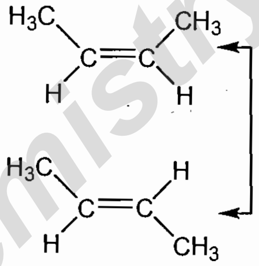
Invertomer (or Umbrella inversion)

Configurational Isomers

- Configurational Enantiomers
- Configurational Diastereomers



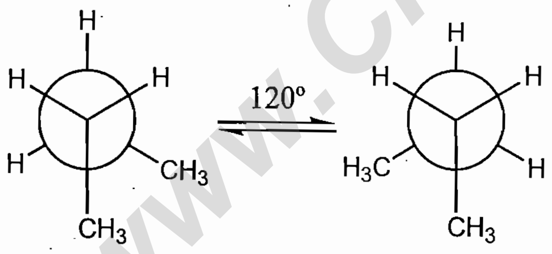
These two are enantiomers



These two are diastereomers

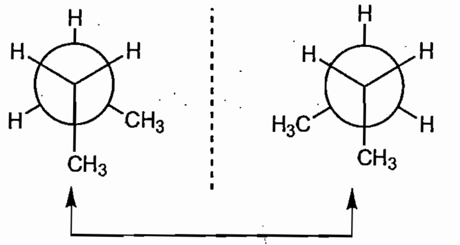
Conformational Isomers

- Conformational enantiomers
- Conformational diastereomers



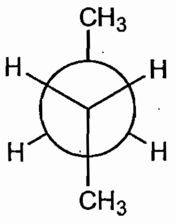
(A) **(S)**

So, (A) and (S) are mirror image of each other as shown below

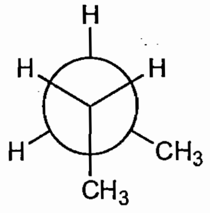


So, these two are conformational enantiomers

Now,

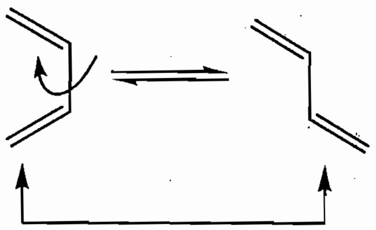


I



II

Since, I and II are not mirror image to each other so these two are conformational diasteromers.

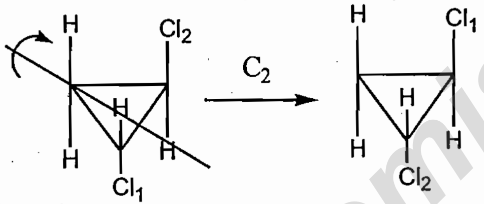


Conformational diastereomers

Structures that are not superimpossible on their mirror image, and can therefore exist as two enantiomers are called chiral.

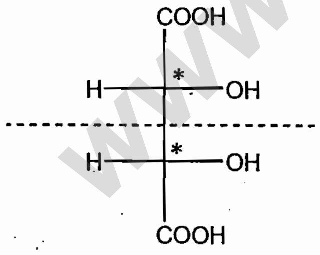
Essential criteria for a molecule to be chiral. There is no any single criterion.

1. There must be lack of element of symmetry.
   Note: It is not necessary and sufficient condition because there are some set of molecules which have some element of symmetry still they are optically active. For example.



Optically active but having C_2-symmetry.

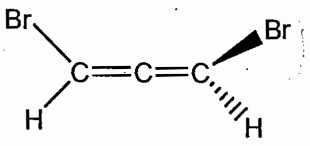
2. The carbon in the molecule should be attacked to four different groups.
   It is not a necessary and sufficient condition also because we have an example in which carbon have four different groups but it is still optically inactive.
   For example:



Two asymmetric centre but still optically in active owing to plane of symmetry.

On the other hand we have also an example in which there is not any chiral centre but still molecule is optically active.

For example: Properly substituted allene.



Not any chiral centre but still it is optically active.

Remrak: This compound is optically active not due to chiral centre but due to chiral axis.

3. There should be an absence of plane of symmetry.

SYMMETRY ELEMENT

A symmetry element is a geometrical entity such as a line, a plane, or a point with respect to which one or more symmetry operations may be carried out.

Symmetry Operation: A symmetry operation is the movement of a molecule about the symmetry element in such a manner that the resulting configuration of the molecule is indistinguishable from the original molecule. The molecule may assume an equivalent configuration or an identical configuration.

Group Theory: Mathematical study of symmetry is called group theory.

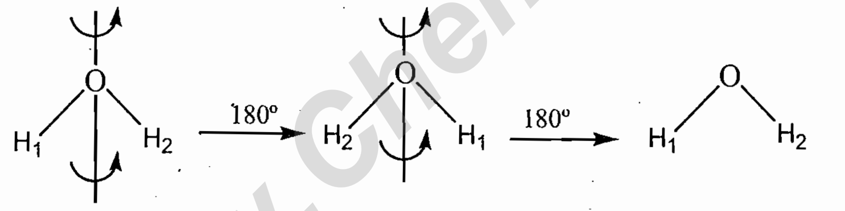
Symmetry element	**Symbol**	**Symmetry operation**
Axis of symmetry	C_n	do C_n
Alternating axis of symmetry	S_n	do S_n
Plane of symmetry	σ	do σ
Point of symmetry or centre of symmetry	i	do i
Identity	E	doing nothing.

Various types of elements of symmetry are explained below as:

(A) Axis of symmetry: An imaginary axis passing through the molecule, rotation on which by θ^0 gives an equivalent orientation of molecule. It is denoted by 'n'. Where, n = 1, 2, 3, 4, ...

Orientation: Orientation is three dimensional distribution of atoms and groups of molecule.

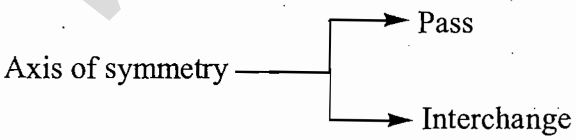
For example:



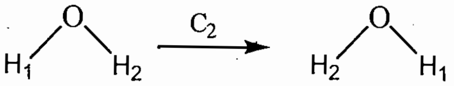
Initial orientation Equivalent orientation Identical orientation

So, the order of axis $C_n = \frac{360^\circ}{180^\circ} = 2$ i.e. C_2 (pronounced as C-two)

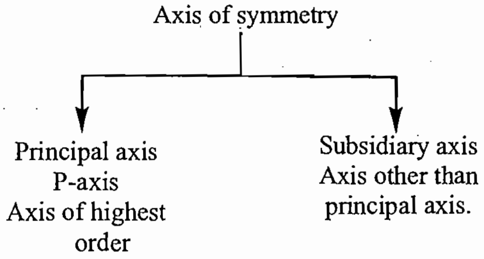
Two things do an axis of symmetry.



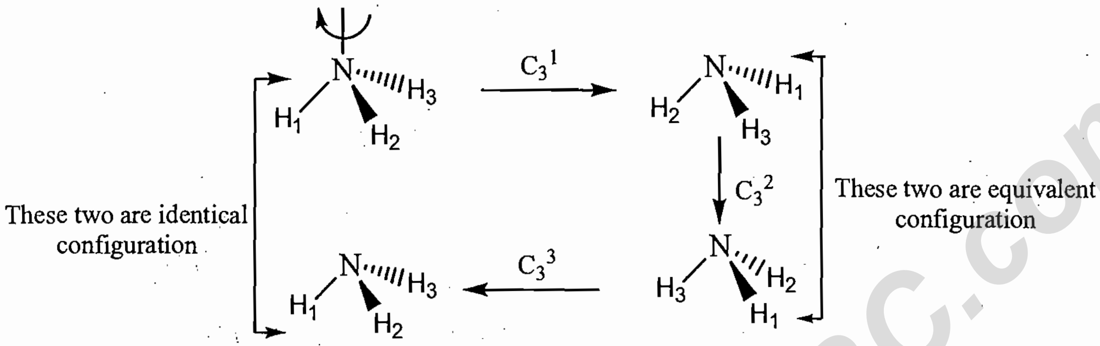
For example in H_2O.



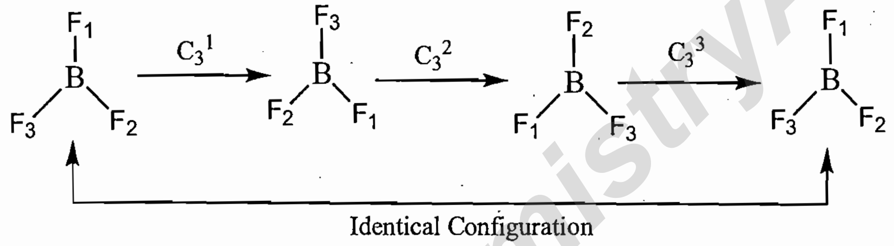
C_2–axis is passing through oxygen atom and interchanging H_1/H_2.



Let us consider another example of NH_3.



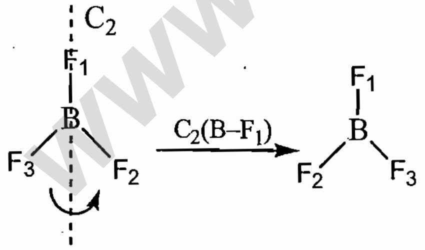
Let us consider an example of BF_3.
In BF_3 one C_3-axis is passing through B-atom which is perpendicular to the molecular plane.



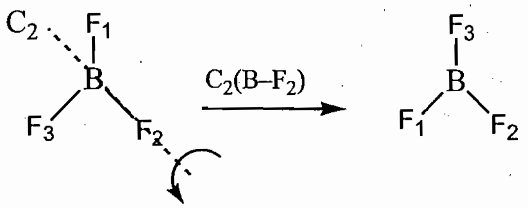
BF_3 molecule has also $3C_2$-axis.
(1) Passing through B—F_1 bond and interchanging F_2/F_3.
(2) Passing through B—F_2 bond and interchanging F_1/F_3.
(3) Passing through B—F_3 bond and interchanging F_1/F_2.

These three C_2-axis can be represented as

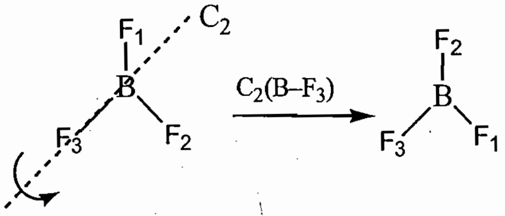
(1)



(2)



(3)

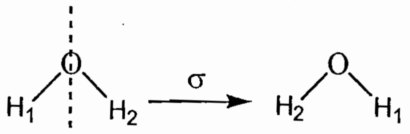


(B) Plane of symmetry: Imaginary plane passing through a molecule which can bisect the molecule into two mirror image halves.

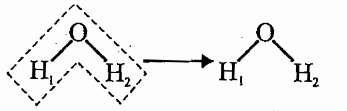
$$\text{There are two functions of a plane} \begin{cases} \rightarrow \text{Bisect} \\ \rightarrow \text{Reflect} \end{cases}$$

For example:

(i) bisecting oxygen atom and reflecting H_1/H_2.



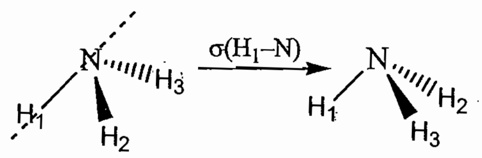
(ii) Bisecting all three atoms.



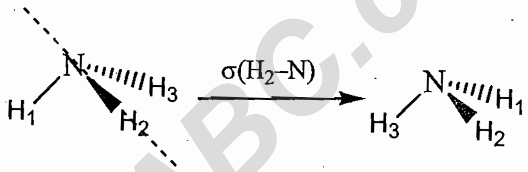
(iii) Ammonia have three plane of symmetry.

(1) Bisecting H_1–N bond and reflecting H_2/H_3.
(2) Bisecting H_2–N bond and reflecting H_1/H_3.
(3) Bisecting H_3–N bond and reflecting H_1/H_2.

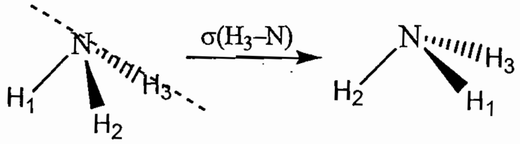
(1)



(2)



(3)

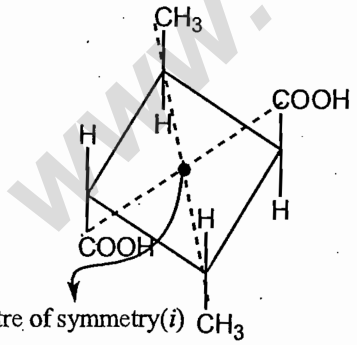


(iv) BF_3 is four plane of symmetry.

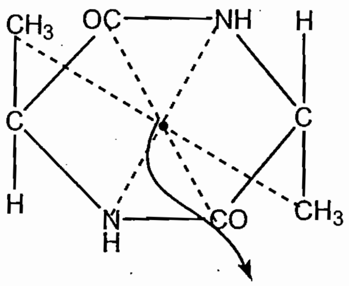
(1) Passing through F_1–B bond and reflecting F_2/F_3.
(2) Passing through F_2–B bond and reflecting F_1/F_3.
(3) Passing through F_3–B bond and reflecting F_1/F_2.
(4) Bisecting all the four atoms viz F_1, F_2, F_3 and B.

(C) Centre of symmetry: A centre of symmetry is a point from which lines, when drawn on one side and produced an equal distance on the other side, will meet identical point in the molecule.

For example: 2, 4-dimethylcyclobutane–1, 3-dicarboxylic acid.



Centre of symmetry(*i*)

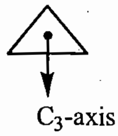


Centre of symmetry

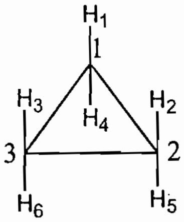
Now, we want to discuss symmetry element of cyclopropane for the purpose of optical activity.

Cyclopropane have one C_3 axis and three C_2 axis and four plane of symmetry.

1. C_3-axis is passing through centre of triangle and perpendicular to all the three C_2-axis.



2. $3C_2$-axis.



(a) Passing through C_1 and interchanging C_2/C_3 or H_1/H_4, H_5/H_3 and H_2/H_6.

(b) Passing through C_2 and interchanging C_1/C_3 or H_2/H_5, H_1/H_6, H_3/H_4.

(c) Passing through C_3 and interchanging C_1/C_2 or H_3/H_6, H_1/H_5 and H_2/H_4.

3. **4 plane of symmetry.**

(a) Bisecting H_3—C_3—H_6 and reflecting C_1/C_2, H_1/H_2 and H_4/H_5.

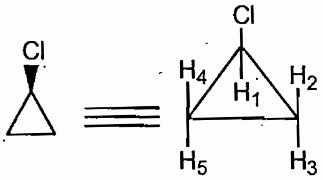
(b) Bisecting H_1—C_1—H_4 and reflecting C_2/C_3, H_2/H_3, H_6/H_5.

(c) Bisecting H_2—C_2—H_5 and reflecting C_1/C_3, H_1/H_3, H_4/H_6.

(d) Bisecting C_1, C_2 and C_3 and reflecting H_2/H_5, H_1/H_4 and H_3/H_6.

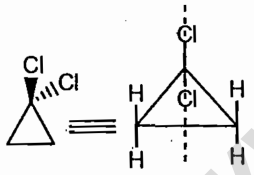
Now, we want to make cyclopropane molecule chiral for this we will have to remove all plane of symmetry from cyclopropane molecule. Because for a molecule to be chiral, plane of symmetry should not be present.

Case I: Mono substituted cyclopropane

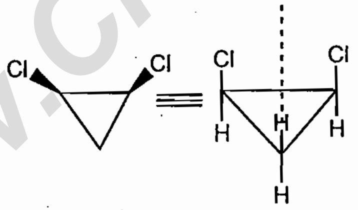


It has plane of symmetry bisecting Cl–C–H_1 and reflecting H_2/H_4 and H_3/H_5. So, this molecule is optically inactive.

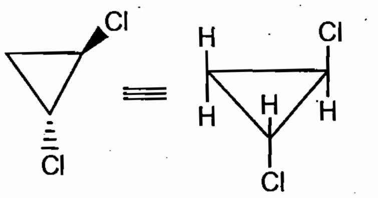
Case II: Homodisubstituted cyclopropane



→ Plane of symmetry
→ Achiral
→ Optically inactive

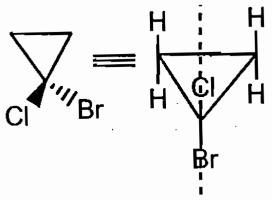


→ Plane of symmetry
→ Achiral
→ Optically inactive

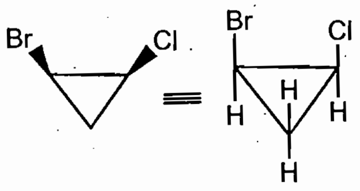


→ No plane of symmetry
→ But C_2-symmetry is present
→ Chiral molecule
→ Optically active.

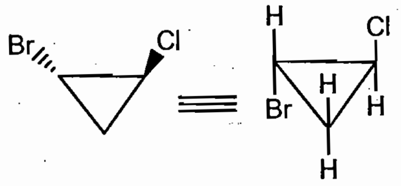
Case III: Heterodisubtituted cyclopropane



→ Plane of symmetry is present
→ Achiral
→ Optically inactive

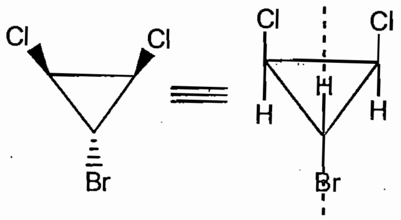


→ No plane of symmetry
→ No axis of symmetry
→ Chiral
→ Optically active

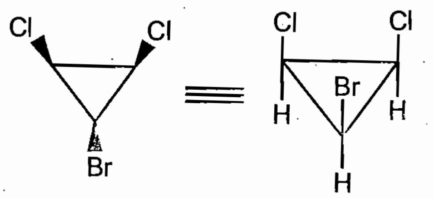


→ No plane of symmetry
→ No axis of symmetry
→ Chiral
→ Optically active

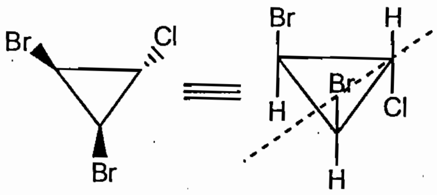
Case - III: Trisubstituted cyclopropane.



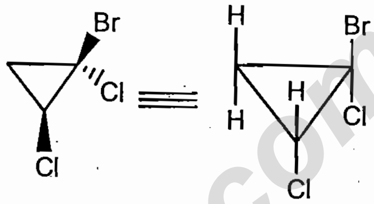
→ Plane of symmetry present.
→ Achiral
→ Optically inactive.



→ Plane of symmetry is present
→ Achiral
→ Optically inactive

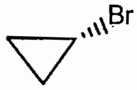


→ Plane of symmetry present
→ No axis of symmetry
→ Achiral

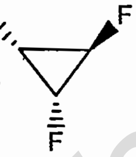


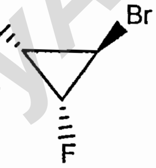
→ No plane of symmetry
→ Chiral
→ Optically active

Problem: Find out which of the following molecule is optically active.

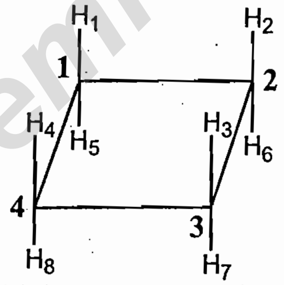
1. 

2. 

3. 

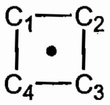
4. 

Symmetry properties of cyclobutane.



Cyclopropane have one C_4-axis and $4C_2$'s axis, $4\sigma_v$'s and one σ_h.

1. C_4-axis passing through centre of square and perpendicular to C_2' s axis.



2. $4C_2$'s axis.
(a) Passing through C_1 and C_3 and interchanging C_2/C_4, H_1/H_5, H_3/H_7, H_4/H_6, H_2/H_8.
(b) Passing through C_2 and C_4 and interchanging C_1 and C_3. H_4/H_8, H_2/H_6, H_1/H_7, H_5/H_3.
(c) Passing through C_1–C_4 and C_2–C_3 and interchanging H_3/H_6, H_2/H_7, H_1/H_8, H_4/H_5.
(d) Passing through C_1–C_2 and C_3–C_4 and interchanging. H_4/H_7, H_3/H_8, H_1/H_6, H_2/H_5.

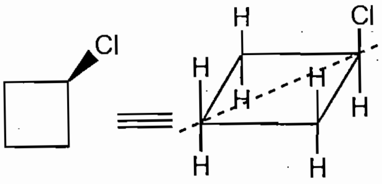
4 σ_v s
(a) Bisecting H_1–C_1–H_5 and H_3–C_3–H_7 and reflecting H_2/H_4, H_6/H_8
(b) Bisecting H_2–C_2–H_6 and H_4–C_4–H_8 and reflecting H_1/H_3, H_5/H_7.

(c) Bisecting C_2–C_3 and C_1–C_4 bond length and reflecting H_2/H_3, H_6/H_7, H_1/H_4, H_5/H_8.

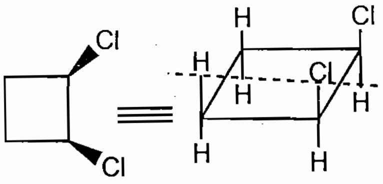
(d) Bisecting C_1–C_2 and C_3–C_4 bond length and reflecting H_1/H_2, H_5/H_6, H_3/H_4, H_8/H_7.

(e) Bisecting C_1, C_2, C_3 & C_4 and reflecting H_1/H_5, H_2/H_6, H_3/H_7 and H_4/H_8.

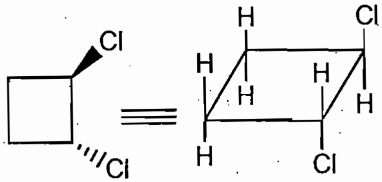
Now, let us consider a case of substituted cyclobutane



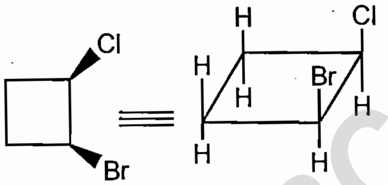
→ Plane of symmetry.
→ Achiral
→ Optically inactive.



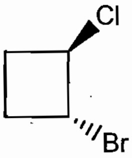
→ Plane of symmetry
→ Achiral
→ Optiacally inactive.



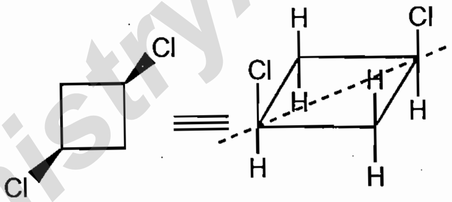
→ No plane of symmetry
→ Chiral
→ Optically active



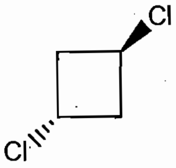
→ No plane of symmetry
→ Chiral
→ Optically active



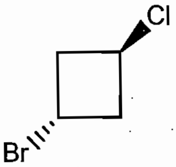
→ No plane of symmetry
→ Optically active



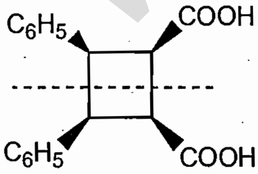
→ Plane of symmetry
→ Optically inactive
→ Achiral molecule.



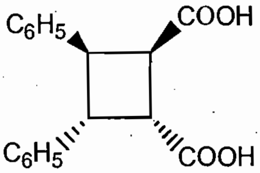
→ Plane of symmetry
→ Optically inactive



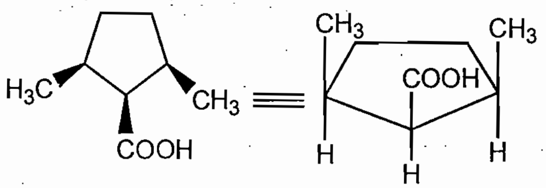
→ Plane of symmetry
→ Optically inactive



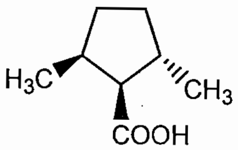
→ Plane of symmetry
→ Optically inactive



→ No plane of symmetry
→ Optically active
→ Chiral molecule.

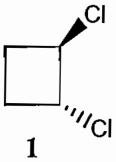


→ Plane of symmetry
→ Achiral molecule
→ Optically inactive.



→ No plane of symmetry
→ Chiral molecule
→ Optically active

Problem-2: Find out which molecules are/is optically active.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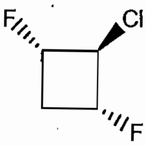
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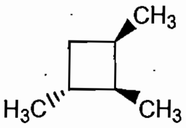
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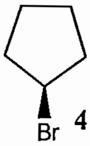
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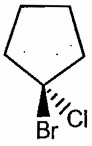
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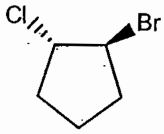
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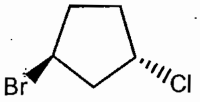
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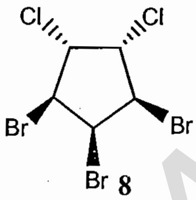

8

Specification of configuration R/S : Then is absolute configuration of chiral centre Proposed by R.S. Chan, Sir Christopher Ingold, V. Prelog.

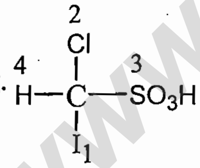
Sequence rule: Priority to the four atoms or groups of atoms attached to the chiral centre can be determined in accordance with sequence rule which are as follows.

Rule 1: If the four atoms attached to the chiral centre are all different, priority depends on atomic number, with the atom of high atomic number getting higher priority.

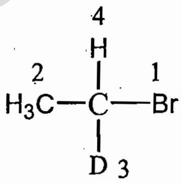
Rule 2: In case of isotope, the atom of higher mass number has the higher priority.
For example among Br, C, D, H priority order is

$Br > C > D > H.$

e.g.

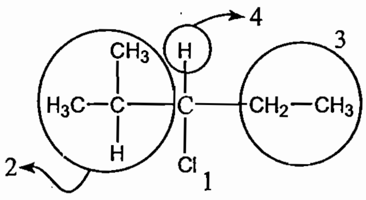


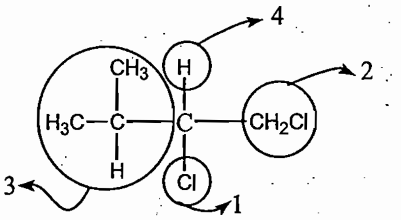
$$\overset{4}{H}-\overset{\overset{2}{Cl}}{\underset{\underset{I_1}{|}}{C}}-\overset{3}{SO_3H}$$



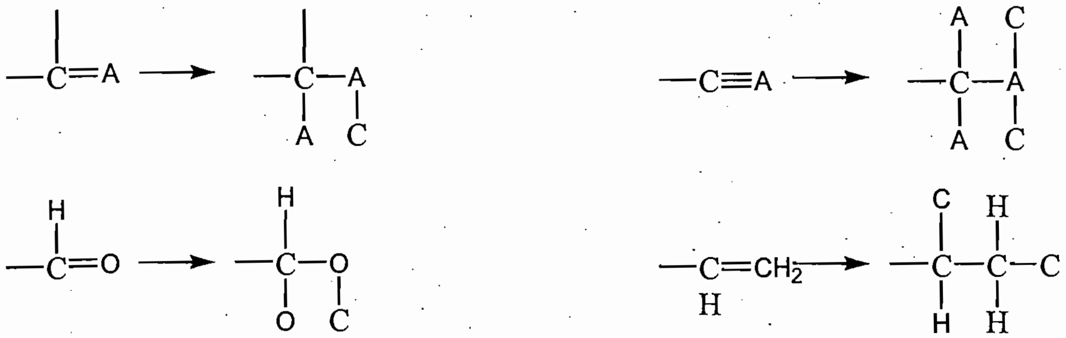
$$\overset{2}{H_3C}-\overset{\overset{4}{H}}{\underset{\underset{D\ 3}{|}}{C}}-\overset{1}{Br}$$

Rule 3: If the relative priority of two groups cannot be decided by rule mentioned above, then look for next atoms.



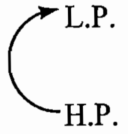


Rule 4: Where there is a double bond or triple bond, both atoms are considered to be duplicated or triplicated.



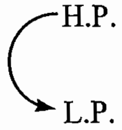
(1) Assign the priority sequence by above mentioned method.
(2) Find out position of the 4th group.
(3) Connect 1→2→3 making a circle.

Case I: If fourth group is below the plane.

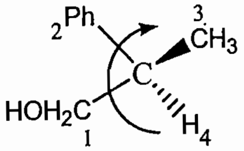


Clockwise → R

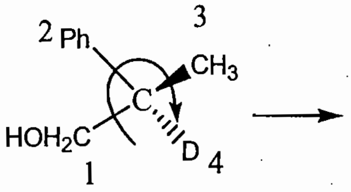
L.P → Low priority group.
H.P → High priority group.



Anticlockwise → S



Note: In this case 4th group 'H' is below the plane and rotation is clockwise so, it is 'R'.

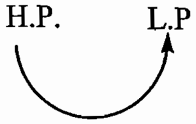


Movement is clockwise
So, it is R.

Case 2: If fourth group is above the plane.

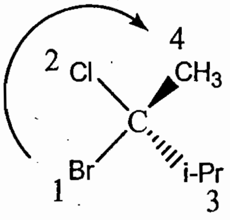
Then,

Clockwise movement → S



Anticlockwise movement → R

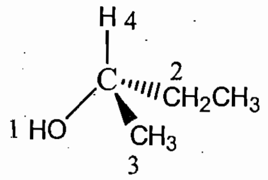
For example:



Note: In this case 4th group is above the plane,
So, clockwise movement gives 'S'.

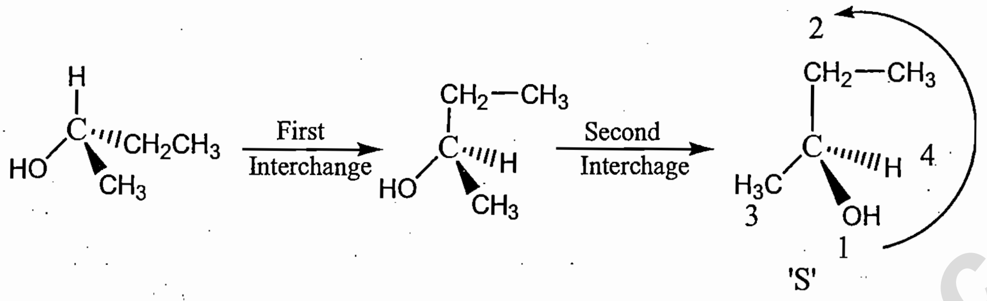
Case III: If the fourth group is on the plane then do double interchange in such a way that the 4th group undergoes below the plane.

For example:

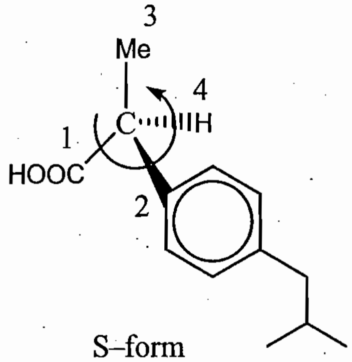


In this case 4th group is on the plane.

Double interchange can be done as

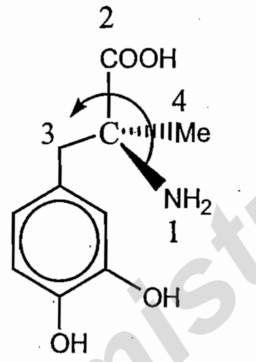


SOLVED PROBLEMS



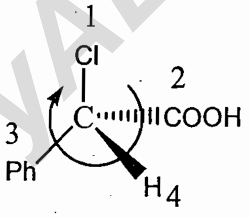
S–form

I



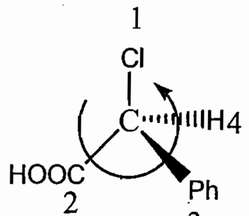
S–Methyl dopa

II



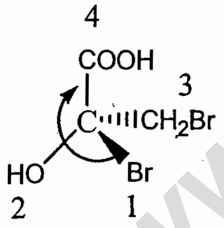
S

III

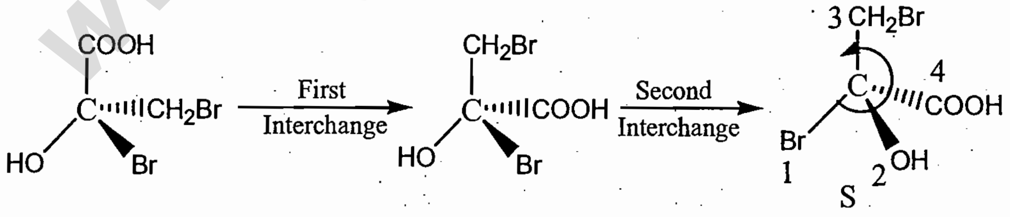


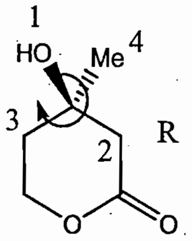
S

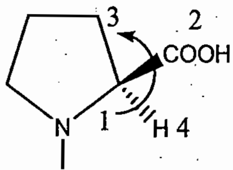
IV



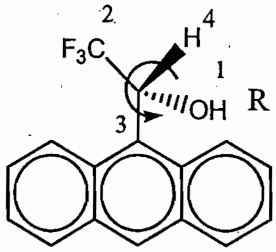
Note: In this case fourth group is on the plane. So, we will have to do double interchange as shown below

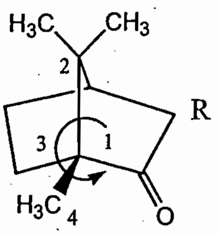






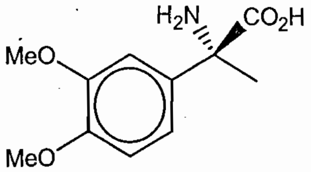
S-Proline





PROBLEMS

1. Find R/S of the following compounds



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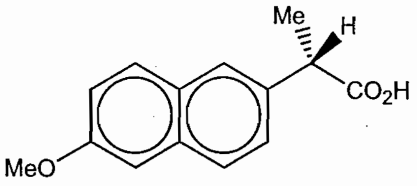

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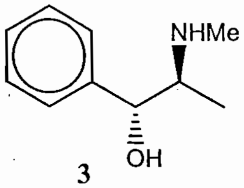

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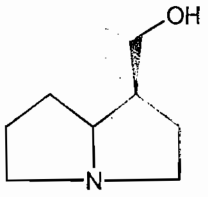

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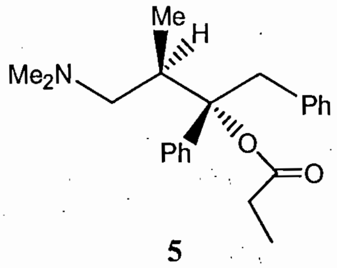

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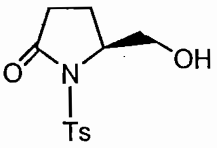

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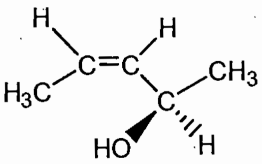

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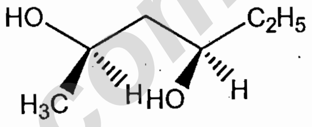

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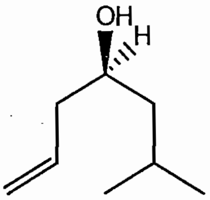

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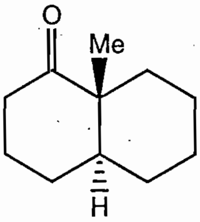

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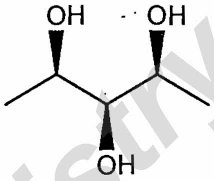

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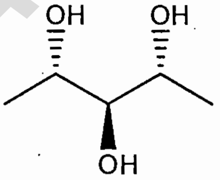
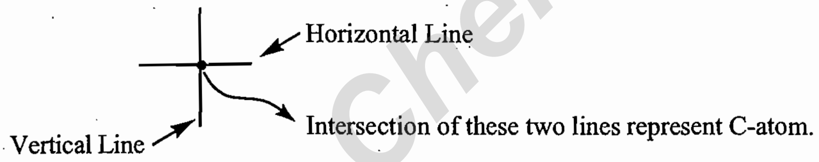
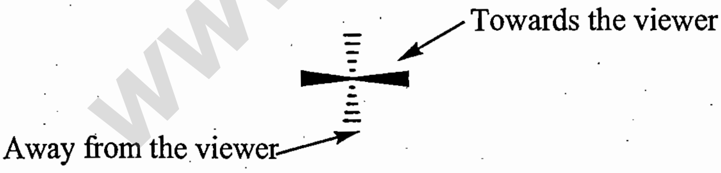


12

R/S Nomenclature in Fischer projection.



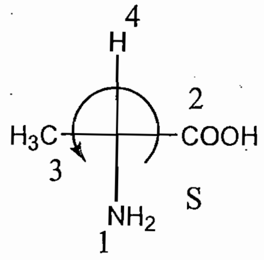
Vertical Line → away from the viewer.
Horizontal Line → Towards the viewer.

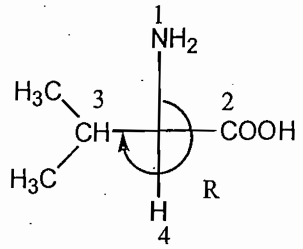


For R/S nomenclature.
Assign priority sequence.
Case I: If fourth group is present on the top or bottom of vertical line then

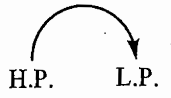
H.P. L.P. → Clockwise → R L.P. H.P. → Anticlockwise → S

For example:

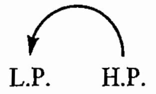




Case II: If 4th group is present on left or right side of the horizontal line then.

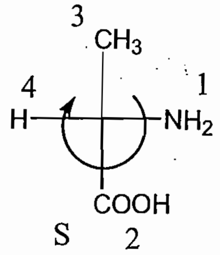


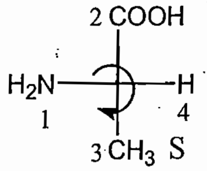
Clockwise → S



Anticlockwise → R

For example:





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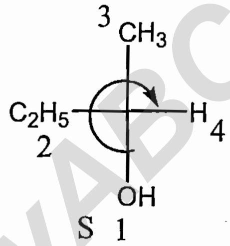
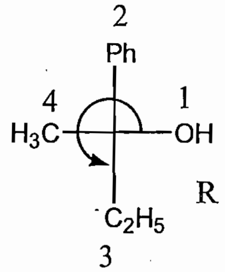
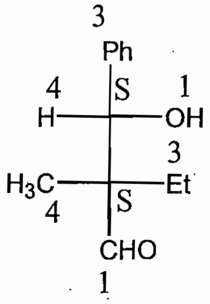
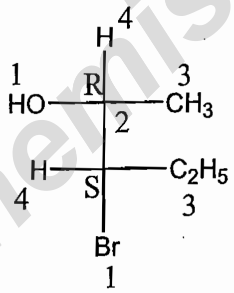




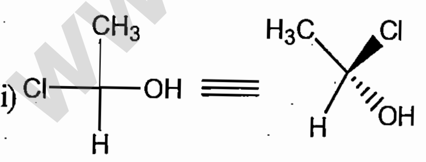
For example:



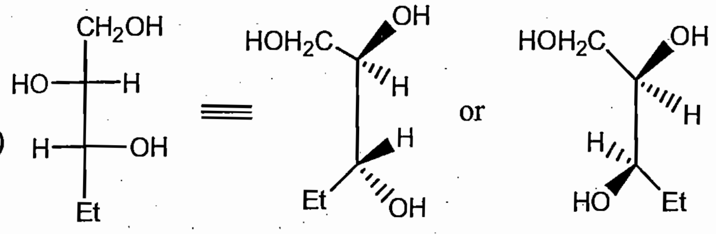


Conversion of Fisher → Wedge.

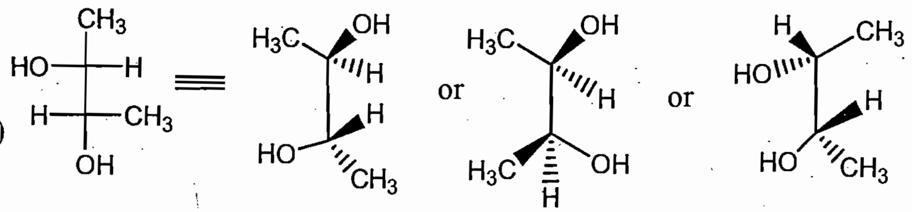
(i)



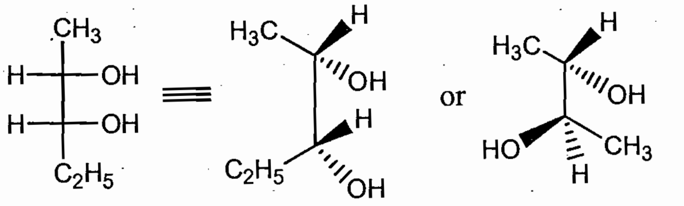
(ii)



(iii)

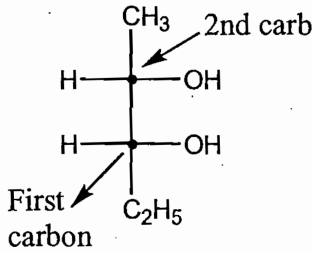


Note: In all conversion, the configuration (R/S) should not be change.

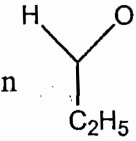
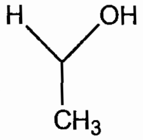


Conversion of fischer to sawhorse.

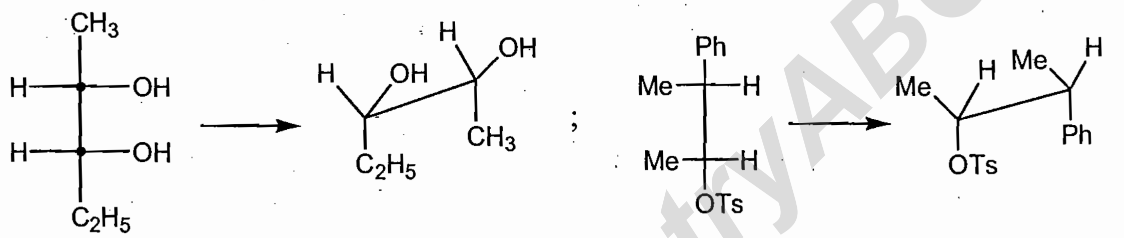
F → W



Note: Consider at first carbon shape like  (Pronounced 'Y')

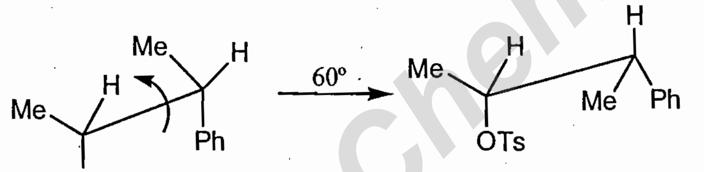
At first carbon  At 2nd carbon 

and then combine these two by a straight line like



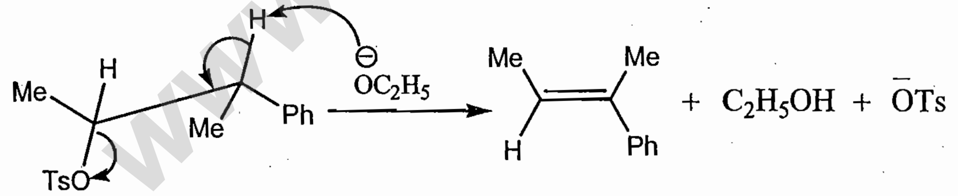
Note: Since Fischer projection is represented in eclipsed form so the resulting sawhorse should also be in eclipsed form if we have need of staggered form we can obtain it by simple rotation.

For example:

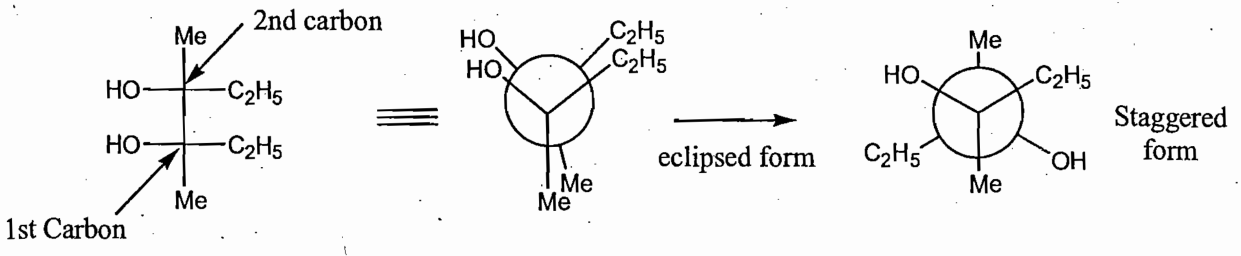


Eclipsed form

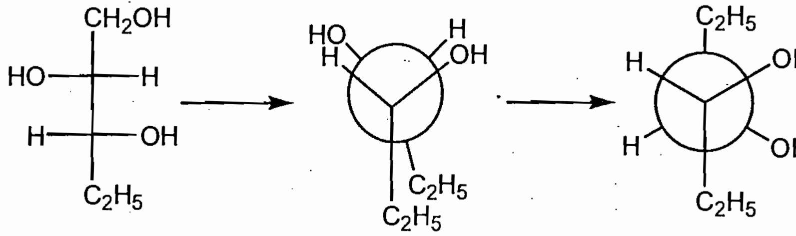
Staggered form is suitable for elimination reaction since, for E_2 elimination, the two departing group should be trans.



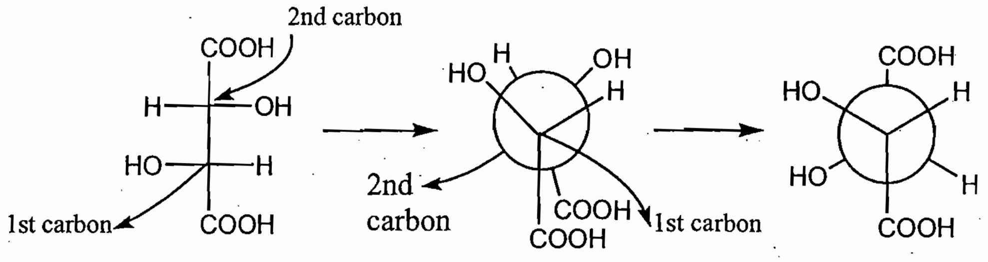
Conversion of Fischer to Newmann:



eclipsed form

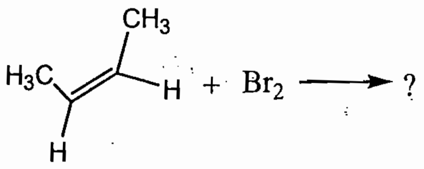


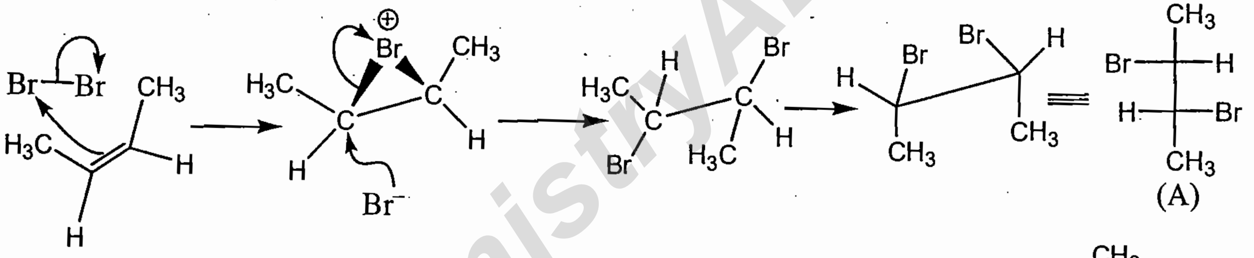
Eclipsed form

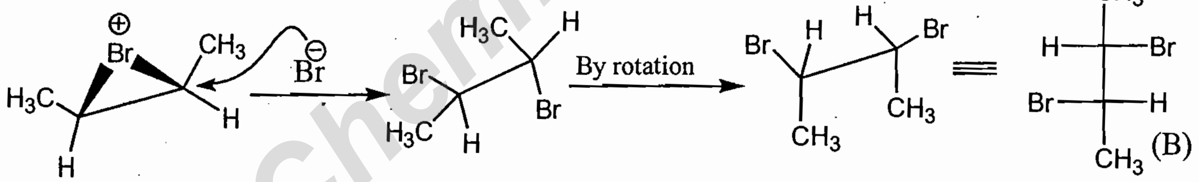


How we can apply these interconversion into reaction mechanism.

Let us consider addition of Br_2 on cis-2-butene.

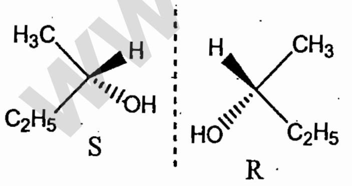
2. 





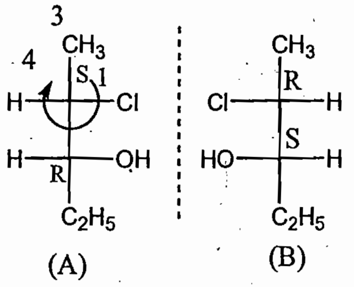
So, A and B are non superimposable mirror image to each other and hence They are enantiomers.

Enantiomers: Enantiomers are the stereoisomers which are non superimposable mirror images to each other. So these two steroisomers have opposite descriptor.



→ Non super imposable mirror image.

→ Opposite descriptor i.e. one is R and other is S.



So, in compound 'A' and 'B', the configuration at chiral centre are

In A	In B	
C_2—S	C_2—R	So, these two are enantiomer
C_3—R	C_3—S	

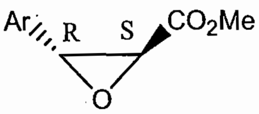
Properties of enantiomer:

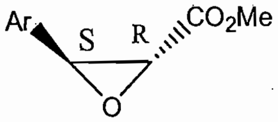
1. All physical properties such as M.P., refractive index, vapour pressure, relative density, NMR spectrum, IR spectrum are same except direction of optical rotation. (Magnitude is same but direction is opposite).
2. All the chemical properties of enantiomers towards achiral reagent are always identical.
3. The chemical properties of enantiomers will be different in the following condition.

	Reagent	Solvent	Catalyst	Result
1	Chiral	Achiral	Achiral	Difference in rate of reaction.
2	Achiral	Chiral	Achiral	Difference in rate of reaction
3	Achiral	Achiral	Chiral	Difference in rate of reaction

Note: If we run NMR spectrum of enantiomers in chiral solvent then it will be also different.

3. What is the relation between following compound.





So, these two compounds are enantiomer.

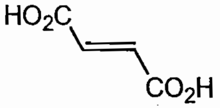
Diastereoisomers:

Diastereomers are the strereoisomers that are not enantiomers.

Some important points regarding the diastereoisomers.

1. Diastereomers can arise when structures have more than one stereogenic centre.
2. The magnitude of optical rotation of diastereoisomers are always different but the direction may be same or opposite.
3. The physical properties of diastereomers are always different but difference may be more or less.
4. The chemical properties of diastereomers toward chiral as well as achiral reagent is always different.

Examples of diastereoisomers:

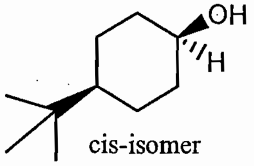


Fumaric acid
m.p. 299-300°C

Maleic acid
m.p. 140–142°C

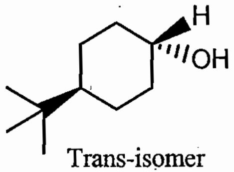
Note: geometrical isomers (i.e. cis and trans isomers) are always diastereoIsomers. A similar stereoisomers can exist in cyclic compounds.

For example: 4-t-butyl cyclohexanol.



cis-isomer

because –OH and t-Bu group are projected in same direction
m.p. 82-83°C

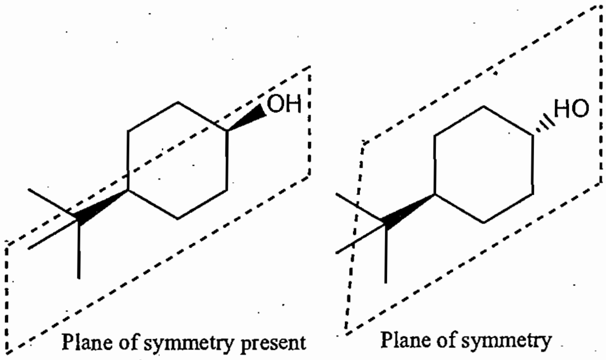


Trans-isomer
m.p. 80-81°C

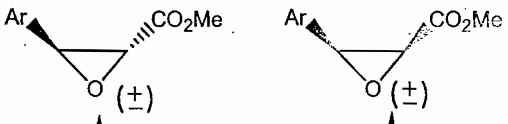
So, these two stereoisomers are called diastereomers.

Note: Diastereoisomers can be chiral or achiral.

(i)

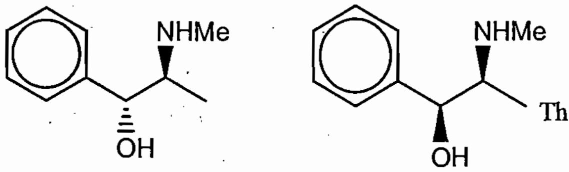


(ii)



These two diastereoisomers are chiral because plane of symmetry is not present.

So, achiral diastereoisomers.



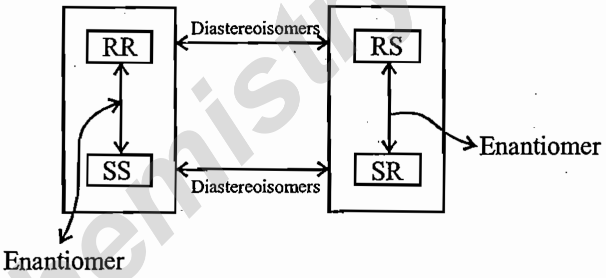
Ephedrine

Pseudoephedrine

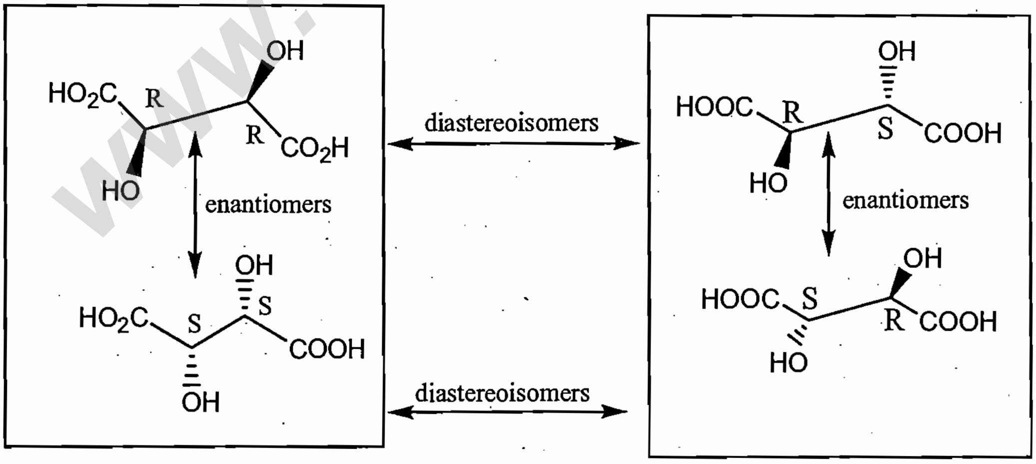
These two are diastereomers.

Remark: The diasteroisomers are different compounds with different names (For example ephedrine and pseudoephedrine) and different properties, while the pair of enantiomers are the same compound and differ only in the direction in which they rotate plane polarized light.

In summary if we have compound having two chiral centre each one R/S then



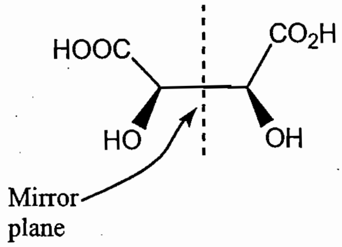
For example:

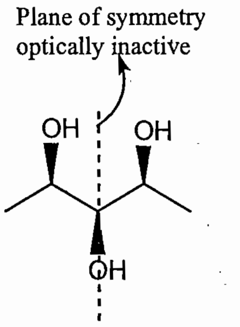


Meso Compounds:

Compounds that contain stereogenic centres but achiral are called meso compounds. This means that there is a plane of symmetry with R stereochemistry on one side and 'S' stereochemistry on the other.

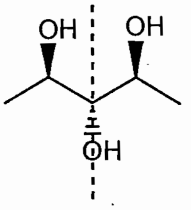
For example:





→ So Meso compound

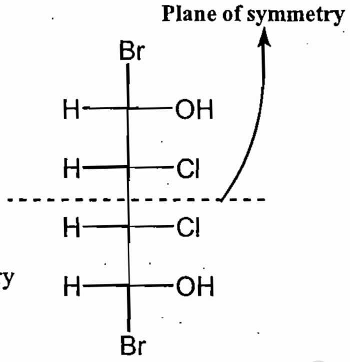
→ Optically inactive



→ Plane of symmetry

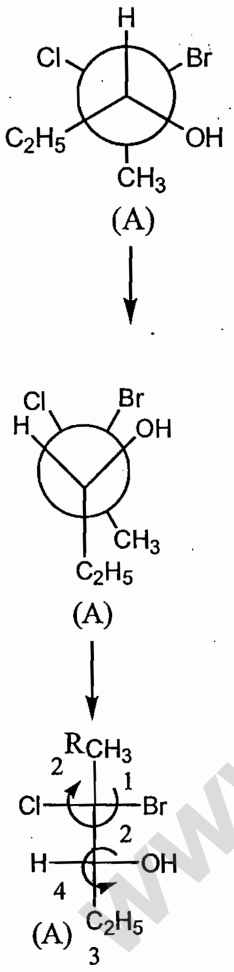
→ Achiral

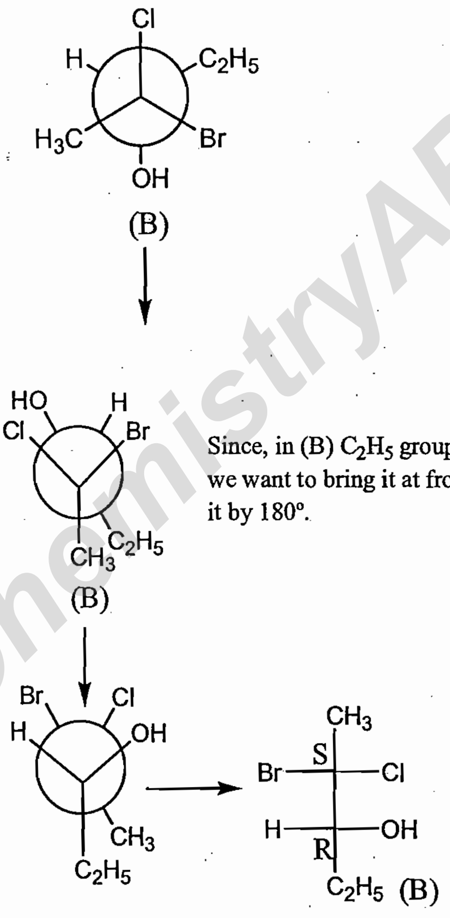
→Meso Compound



Meso Compound

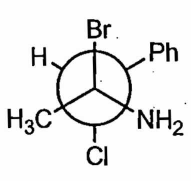
Conversion of Newmann into Fischer and relation between two compounds.





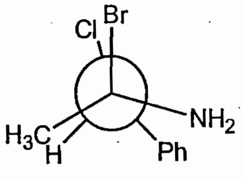
Since, in (B) C_2H_5 group is attached with back carbon and we want to bring it at front carbon so we will have to rotate it by 180°.

So, A and B are diastereomers.



(A)

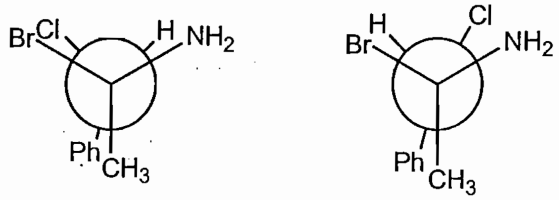
&



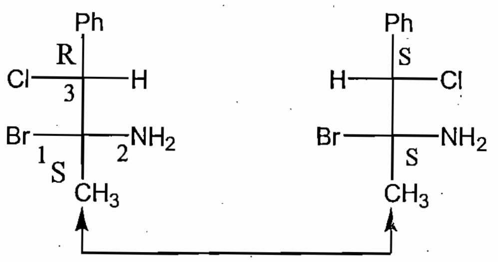
(B)

What is the relation between A and B.

(i)



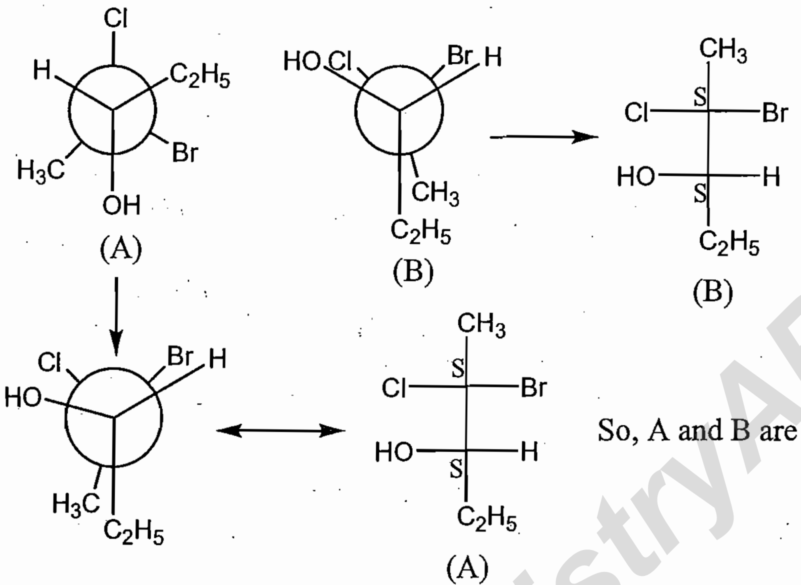
(ii)



So, these two are diastereomers

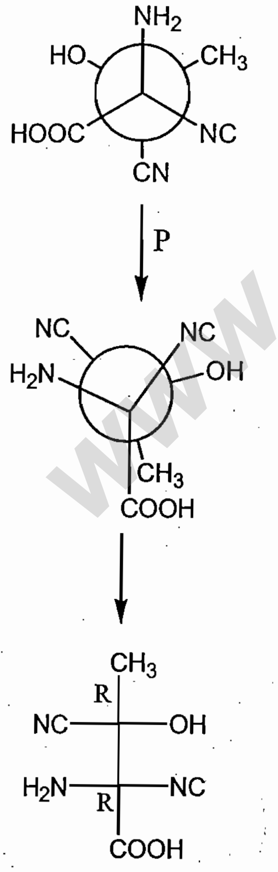
PROBLEMS

1. What is the relation between A and B.

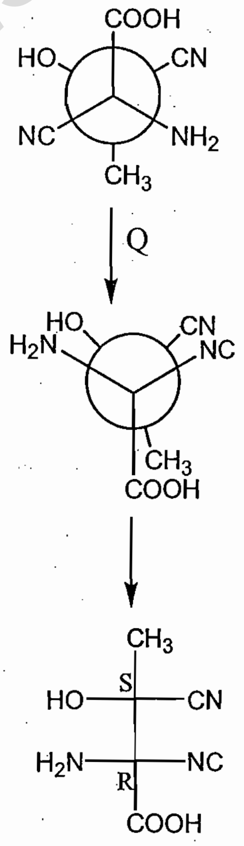


So, A and B are identical.

What is relation between P and Q.

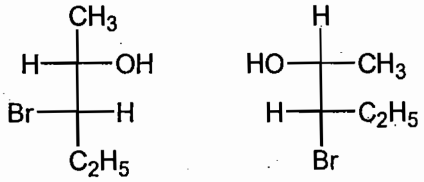


P



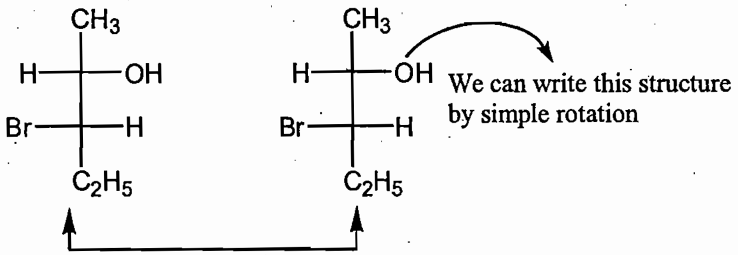
Q

So, P and Q are diastereomer.

2. 

The molecules represented by the above two structures are

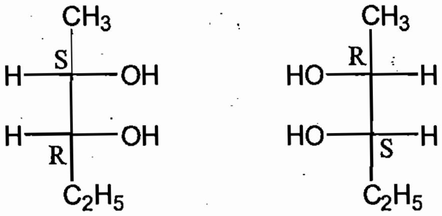
(a) Identical (b) Enantiomers (c) Diastereomers (d) Epimer



We can write this structure by simple rotation

So, these two compounds are identical.

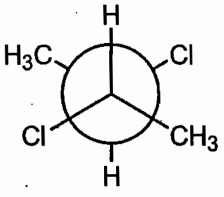
3. The following two compounds are



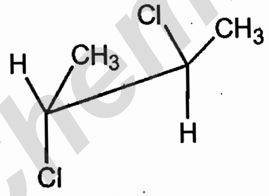
(a) Enantiomers (b) Diastereomers (c) Identical (d) epimer.

Soln. (a)

4. Which one of the following statement regarding the projections shown below is true?



(A)

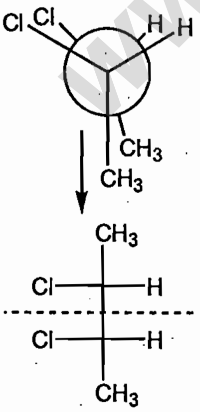


(B)

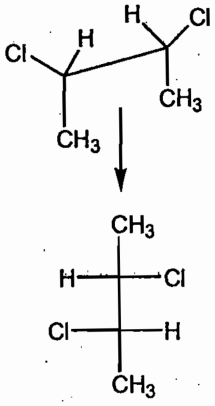
(a) A and B represent the same configuration. (b) Both A and B are optically active

(c) B is optically active. (d) A is optically active

Soln.



(A)



(B)

'A' is optically inactive due to presence of plane of symmetry. **(Correct answer is (a))**

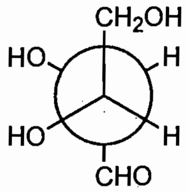
5. Match **List-I** with **List-II** and select the correct answer using the code given below the lists.

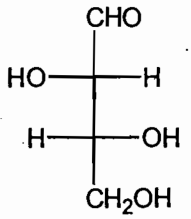
List-I	**List-II**
A. Meso compounds	1. An equimolar mixture of enantiomer
B. Enantiomers	2. Stereoisomers that are not mirror images
C. Diastereoisomers	3. Non-superimposable mirror images
D. Racemate	4. An optically inactive compound whose molecules are achiral even though they contain chiral centre.

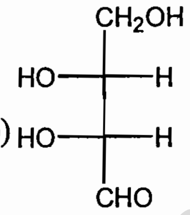
	A	B	C	D
(a)	3	4	1	2
(b)	3	4	2	1
(c)	4	3	1	2
(d)	4	3	2	1

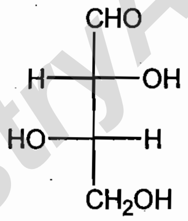
Soln. **(d)**

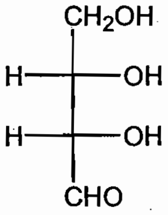
6. What is the correct Fischer Projection formula for the compound represented by the following Newmann Projection?

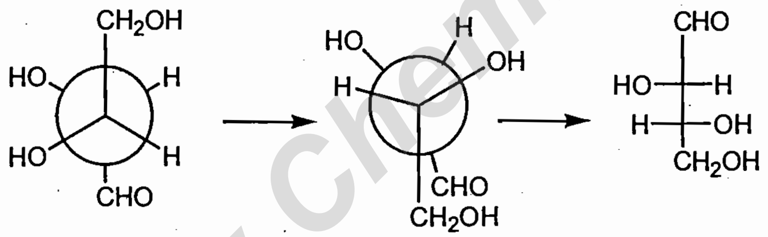


(a)


(b)


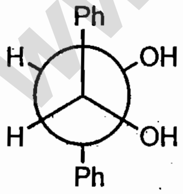
(c)


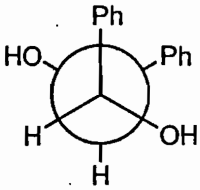
(d)


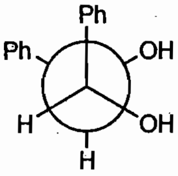
Soln.


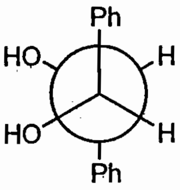
Correct answer is (a)

7. Which one of the following Newmann projection formulae correctly represents a meso structure?

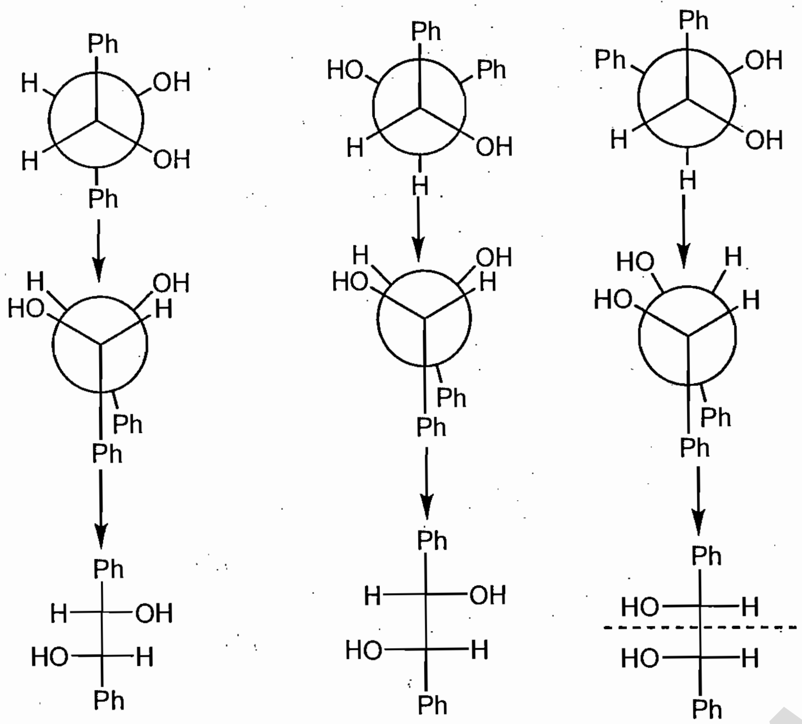
(a)


(b)


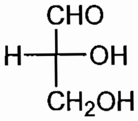
(c)


(d)


Soln.



'c' has plane of symmetry so, it correctly represents a meso compound.

8. 

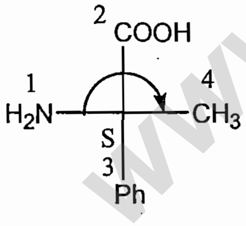
Which is the correct order of priority of groups attached to the chiral carbon in the compound given above while as assigning R or 'S' configuration.

(a) HO > CHO > CH_2OH > H (b) H > CH_2OH > CHO > OH

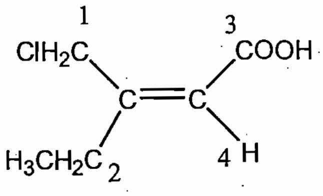
(c) CHO > OH > CH_2OH > H (d) CH_2OH > CHO > OH > H

Soln. (a)

9. Which one is the correct configurational assignment (in terms of CIP principle) for each of the compound listed below?



I

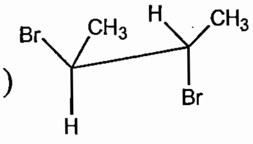


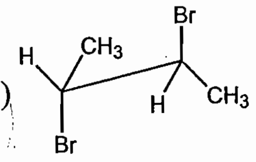
II

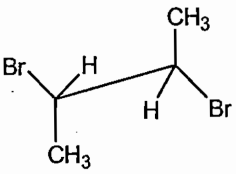
(a) I-R, II-S (b) I-S, II-E (c) I-L, II-S (d) I-S, II-Z

Soln. **(d)**

10. Consider the following configuration of 2, 3-dibromobutane.

(1) 

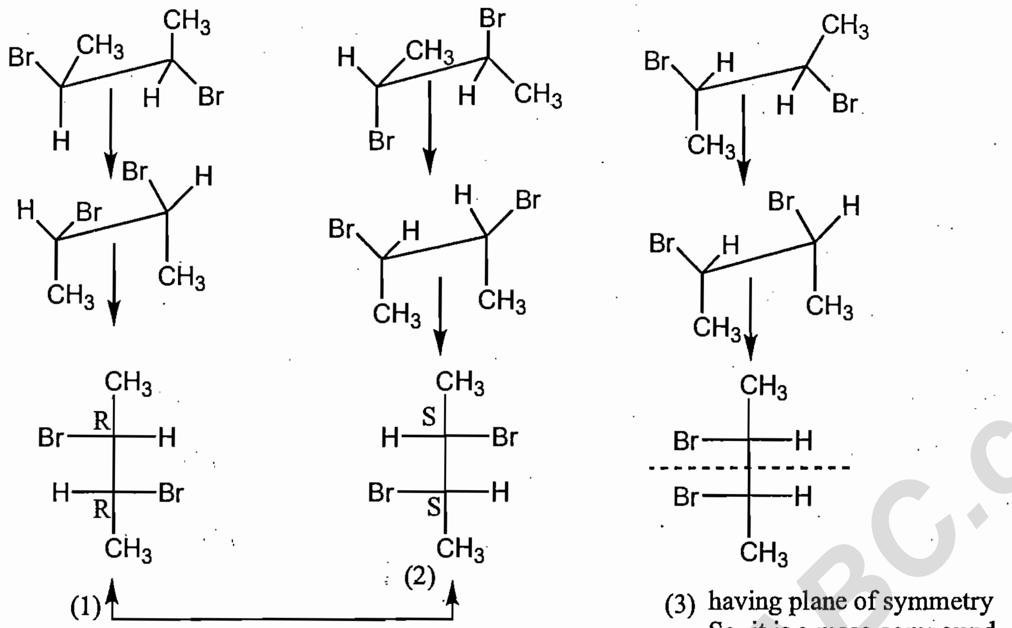
(2) 

(3) 

Which one of the following is the correct answer?

(a) Conformation (1) is the meso-form while (2) and (3) are an enantiomeric pair.
(b) Conformation (2) is the meso-form while (1) and (3) are an enantiomeric pair.
(c) Conformation (3) is the meso form while (1) and (2) are an enantiomeric pair.
(d) Conformation (1) and (2) are identical and (3) is the meso-form.

Soln.

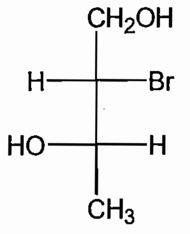


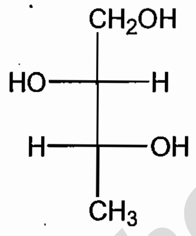
So, these two compounds are enantiomers

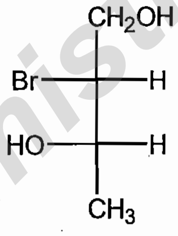
(3) having plane of symmetry
So, it is a meso compound.

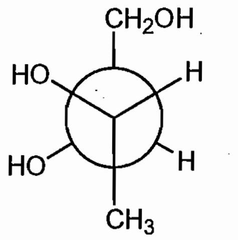
So, the correct statement is conformation (3) is the meso while (1) and (2) are an enantiomeric pair.

11. Consider the following statements regarding the given projections.


(A)


(B)

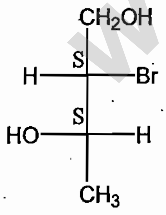

(C)

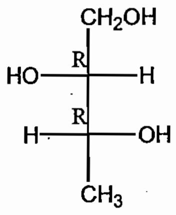

(D)

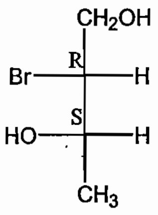
(1) (A) and (C) are diastereoisomers.
(2) (D) is the Newmann projectoin of (B).
(3) (B) may be named as thereo-1, 2, 3-butanetriol.
Which of the above statements are correct?

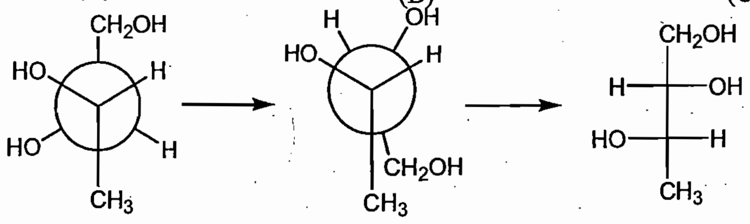
(a) 1, 2 & 3 (b) 1 & 2 (c) 2 & 3 (d) 1 & 3.

Soln.


(A)

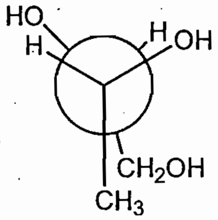

(B)


(C)


(D)

So, A and C → are diastereomers.
D is not the Newmann projection of B.

The Newmann projection of 'B' is

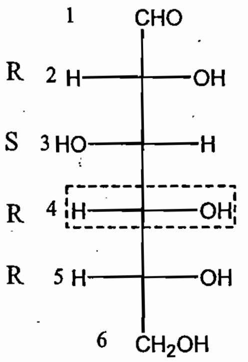


Soln. (d).

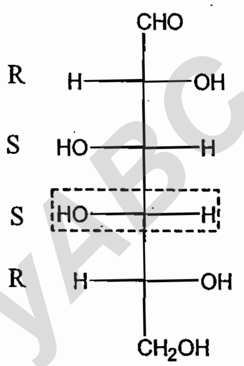
Epimers

Epimers are the diastereomers, differ in the stereochemistry at only one stereocentre.

The term can be applied only to the chiral compound having more than two chiral center.
For example glucose and glactose have difference in configuration at C_4 so they are epimers at C_4.

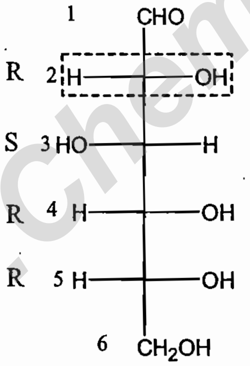


Glucose

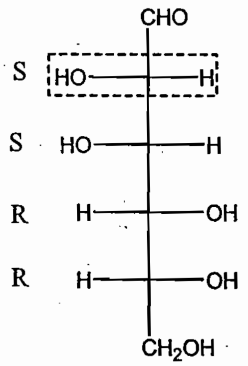


Glactose

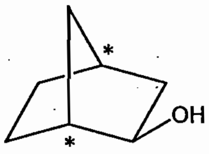
Similarly glucose and mannose have change in configuration at C_2 so they are epimers at C_2.



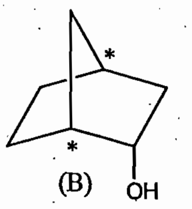
Glucose



Mannose



(A)

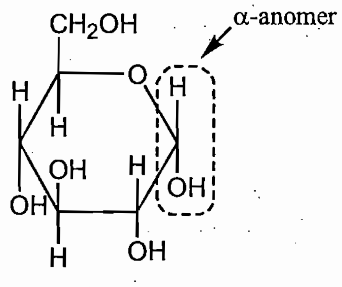


(B)

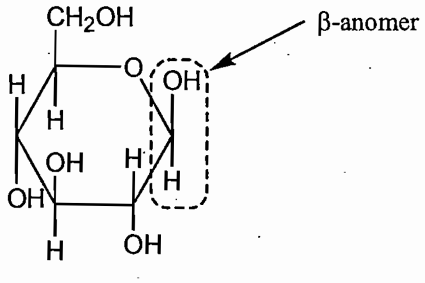
Compound (A) and (B) are epimeric pair.

Anomers:

Anomers are the diastereomers (in the case of a monosaccharide) which differ in the configuration at C_1 are called anomers.



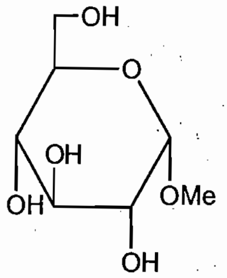
α-D-glucose



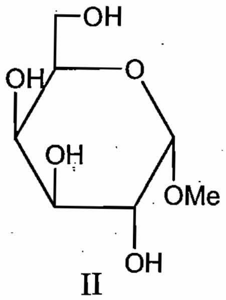
β-D-glucose

PROBLEMS

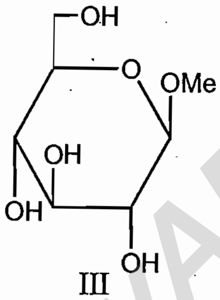
1. Identify the correct set of stereochemical relationship amongst the following monosaccharides I-IV.



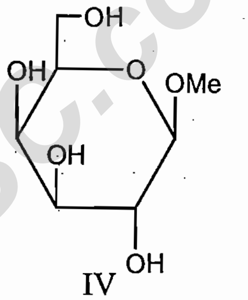
I



II



III



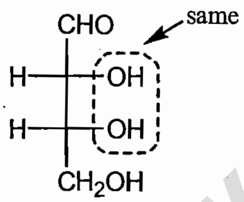
IV

(a) I and II are anomers; III and IV are epimers.
(b) I and III are epimer; II and IV are anomers.
(c) I and II are epimers; III and IV are anomers.
(d) I and III are anomers; I and II are epimers.

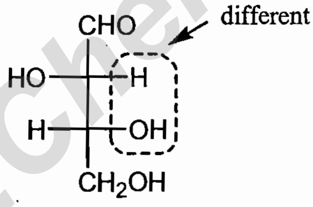
Soln. **(d).**

Threo and Erythro nomenclature

Threo and Erythro nomenclature are based on sugar chemistry.



D(–) erythrose



D(–) threose

- Erythrose and threose are diastereomers.
- A molecule with two adjacent stereocentres, when there are two groups which are common to each carbon while third is different i.e. $C_{abx}-C_{aby}$ gives rise to erythro and threo diastereomer.

Procedure for finding erythro and threo diastereomers.

Step I: Find out the group or atom which is not common on two adjacent asymmetric centre.

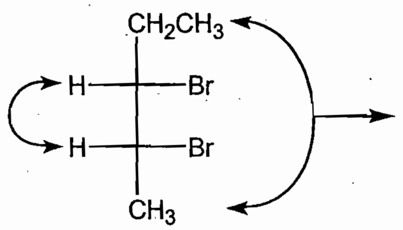
Step II: Placed this different group on top and bottom position of vertical line in Fischer projection formula.

Step III: And arrange the rest group or atoms around horizontal position of Fischer projection.

Case I: If two similar group are on the **same side** then it is called **erythro**.

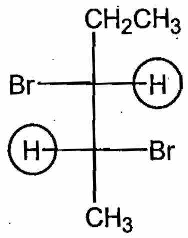
Case II: If two similar group on the **opposite side** then it is called **threo**.

For example:



These two are different group on the two asymmetric carbon placed at top and bottom.

These two H, atoms are projected in same side so, it is erythro



In this structure the two similar group viz H and Br are opposite so, it is threo.

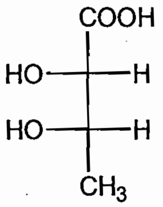
Note: The terms erythro and threo are generally applied only to those molecules which do not have symmetric ends.

In summary, condition for erythro and threo nomenclature:

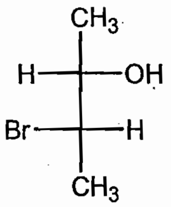
(1) Two asymmetric carbon should be there

(2) On two asymmetric carbon, two of the groups are the same and the third is different.

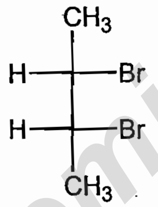
2. Consider the following statements about the Fischer projection A—D.



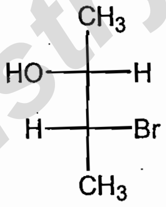
(A)



(B)



(C)



(D)

(1) A and B are erythro forms while C and D are threo forms.

(2) There must be two assymetric carbon

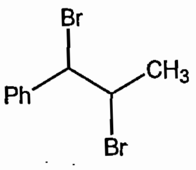
(3) C is a meso form while B and D are dL form.

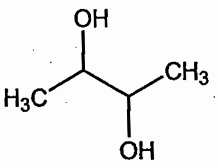
(4) A and B are meso-form while C and D are diastereomers which of the above statements are correct?

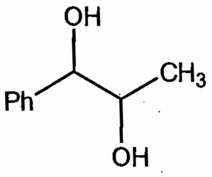
(a) 1, 2 and 4 (b) 2, 3 and 4 (c) 3 (d) 2 and 4

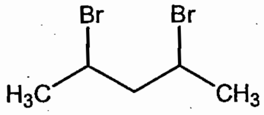
Soln. **(c)**

3. Which of the following compounds can be represented as threo and erythro isomers?

(1) 

(2) 

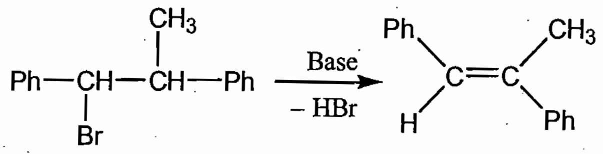
(3) 

(d) 

(a) 1 & 2 (b) 1 & 3 (c) 1 & 4 (d) 2 & 4

Soln. **(b) Hint**– Condition for erythro and threo are $C_{abx} - C_{aby}$.

4. Consider the following statements. In the elimination reaction.



(1) Of the various stereoisomers of the reactant, only stereoisomers of proper geometry, that is antiperiplanar conformation will undergo this elimination reaction.

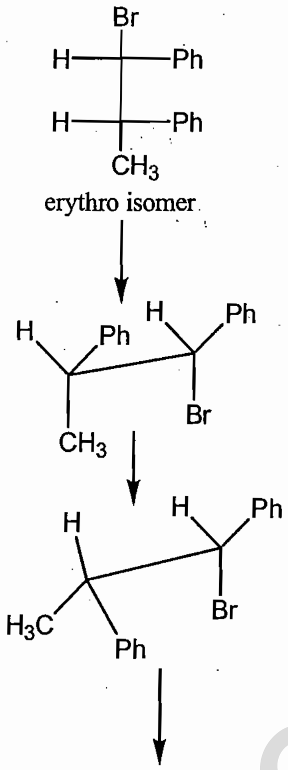
(2) Erythro isomer will undergo elimination reaction at a faster rate.

(3) The threo isomer will form the trans olefin of these statements.

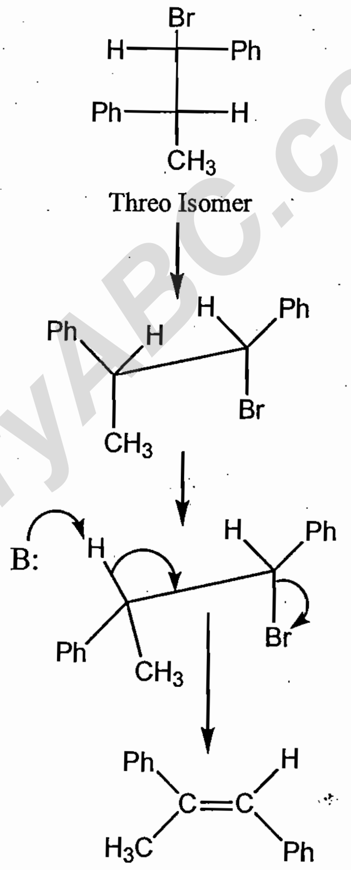
(a) 1, 2 & 3 are correct (b) 2 & 3 are correct

(c) 1 & 3 are correct (d) 1 & 2 are correct.

Soln.



Rate of elimination will not be faster because the two bulky Ph group projected in the same direction causes steri chindrance and will increase the activation energy of this conformation.



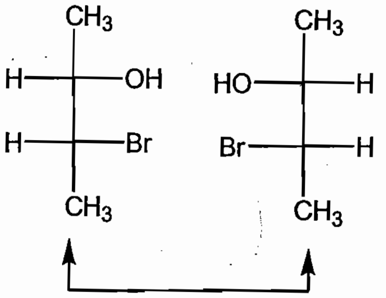
trans product

Correct answer is (c)

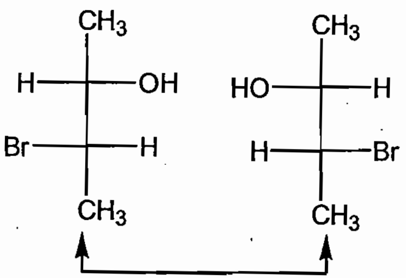
5. Find out the stereoisomers of 3-bromo-2-butanol

Soln. 3-bromo-2-butanol have two asymmetric centre. So, the total number of stereoisomers = $2^2 = 4$

These are



Erythro enantiomers



Threo enantiomers

(A) Optically activity in biphenyls

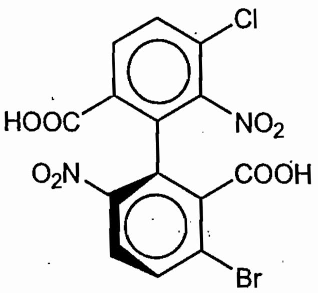
Two conditions are necessary for biphenyl compounds to exhibit optical activity.

(i) Neither ring have a vertical plane of symmetry.

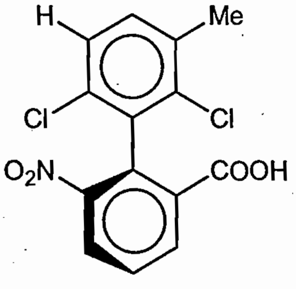
(ii) The substituents in ortho position must have a large size.

Note: There is no chiral centre in Biphenyl, it is the molecule as a whole which is chiral, due to restricted rotation. The chirality due to restricted rotation arround C–C single bond in biphenyl is known as atropisomers.

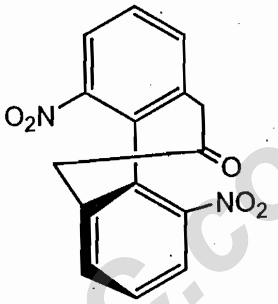
Remark: If H, F and $-OCH_3$ group are present on ortho position of biphenyl then rotation of the ring will not be prevent. Because the volume of these groups are too small to prevent the rotation about the single bond.



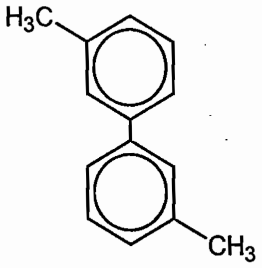
→ Properly substituted
→ Restricted rotation
→ So optically active



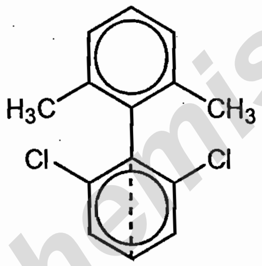
→ Properly substituted
→ Restricted rotation
→ So optically active



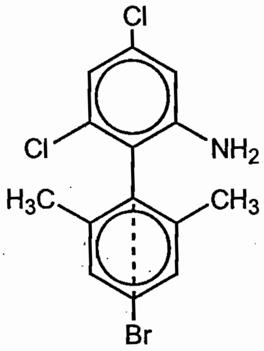
→ Properly substituted
→ Restricted rotation
→ So optically active



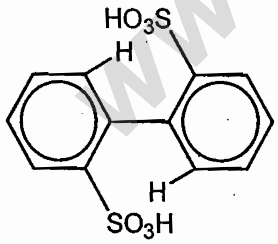
→ Properly substituted
→ Not restricted rotation
→ So optically inactive



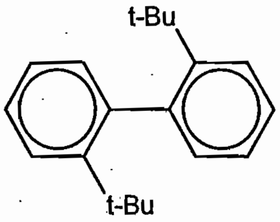
→ Not properly substituted
→ Restricted rotation
→ Optically inactive



→Achiral (restricted rotation
→But not properly substituted)
→ Optically inactive



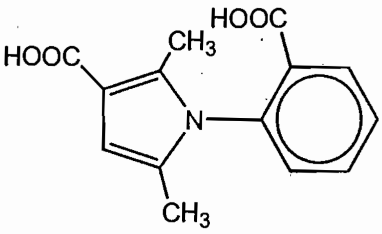
Optically active



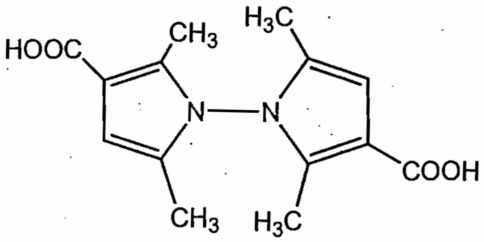
Optically active
t-Bu is bulky

Some more examples of biphenyl type compounds are as follows:

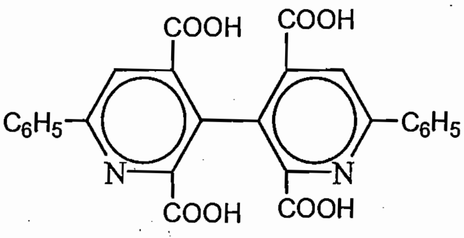
(1)



(2)



(3)



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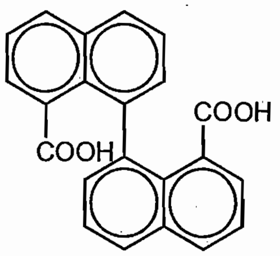

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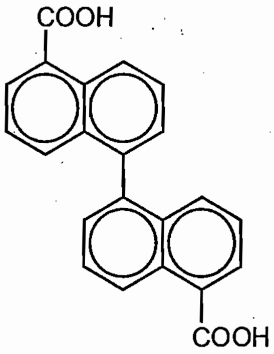

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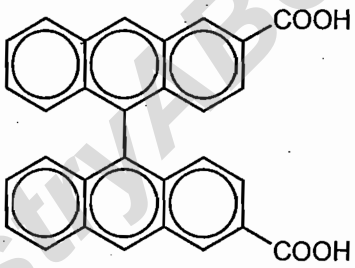

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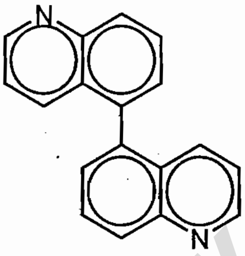

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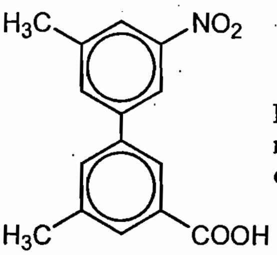
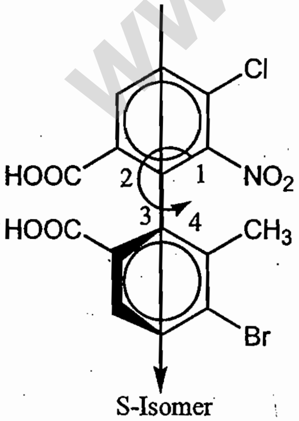


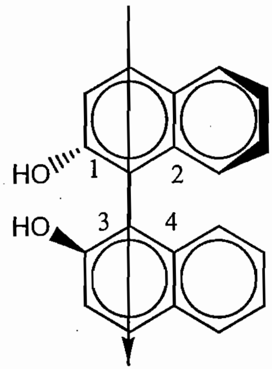
Properly substituted but not ristricted rotation.So, optically inactive.

R/S in Biphenyl:

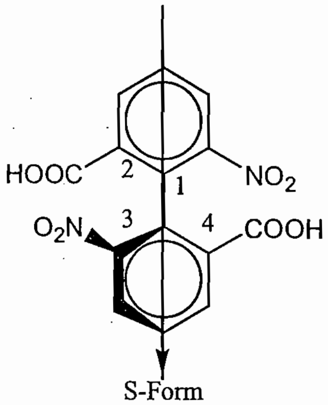


S-Isomer

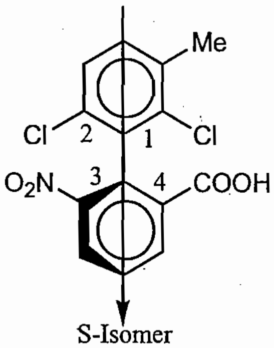
Put the head of the arrow on which side where configuration of the ring is defined in the problem and then assign priority sequence as per CIP rule.



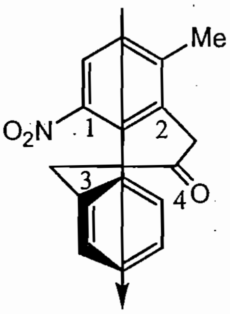
R-Isomer



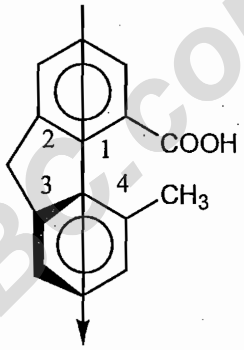
S-Form



S-Isomer



R



S-Isomer

(B) Chirality in Allenes

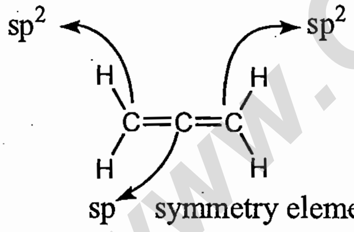
Allenes are chiral due to chiral axis.

Essential criteria for chirality of allene.

(1) Proper substitution

(2) Number of double bond should be even.

Properly substituted means that terminal carbon of allene should have two different groups, so that it deprive from plane of symmetry.



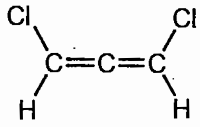
symmetry element

$3C_2'S$

$2\ \sigma v$

Problem-1:

(1)

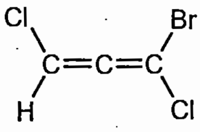


→ Number of double bond = even

→ Properly substituted

→ So it is chiral

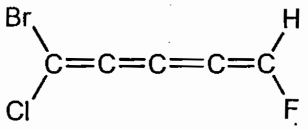
(2)



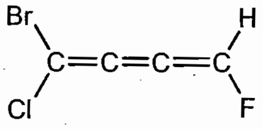
→ Number of double bond = even

→ Properly substituted.

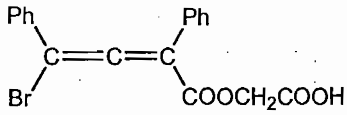
→ So it is chiral.

(3)


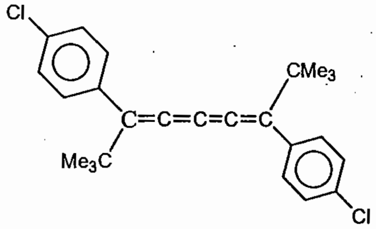
→ Number of double bond = even
→ Properly substituted
→ So, it is chiral.

(4)


→ Number of double bond = odd
→ Properly substituted
→ Achiral, optically inactive.

(5)


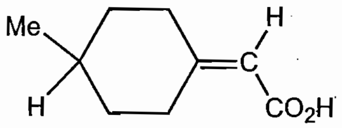
→ Number of double bond = even
→ Properly substituted
→ Chiral, optically active.

(6)


→ Number of double bond = even
→ Properly substituted
→ Chiral, Optically active.

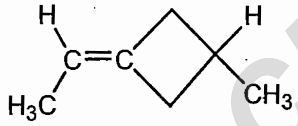
Note: One of the double bond of allene may be replaced by a four, five & six membered ring and the general shape of the allene molecule is retained.

For such a system. Optically activity arises if **Number of doubled bond + ring = even** and criteria for properly substitution is same.



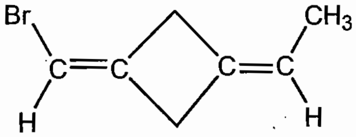
→ 1 double bond + one ring = 2 = even
→ Properly substituted
→ Chiral and hence optically active.

Problem-2:

(1)


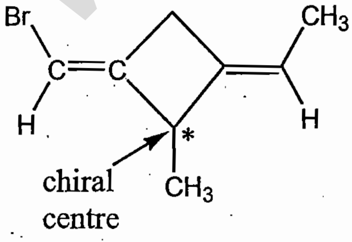
chiral

→ 1 double bond + 1 ring = even
→ Properly substituted
→ Chiral, optically active.

(2)


→ 2 double bond + 1 ring = odd
→ Properly substituted
→ Achiral, optically inactive.

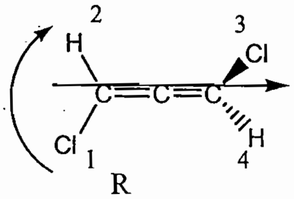
Problem-3:



→ 2 double bond + 1 ring = odd
→ Properly substituted
→ It is chiral, due to chiral centre but not chiral axis.

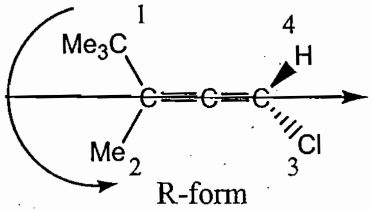
R/S in allene.

(1)



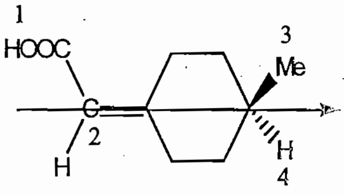
R

(2)



R-form

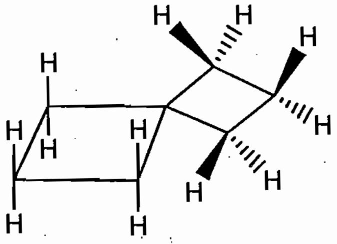
(3)



S-Form

(C) Optical Activity in Spirane:

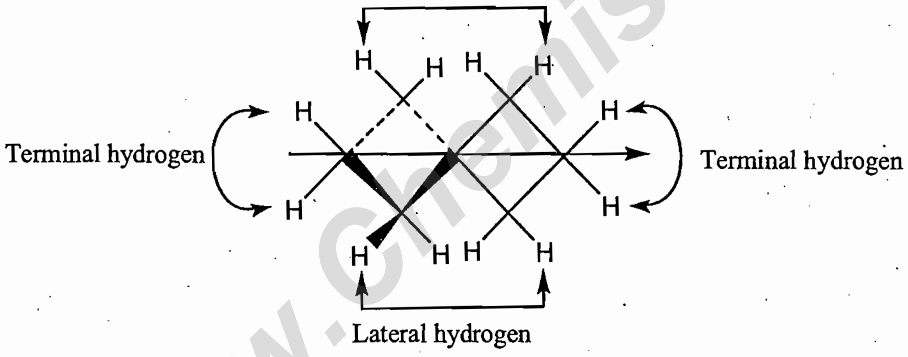
- If both double bonds in allene are replaced by ring system, the resulting molecules are spiranes.

- 

Examinations of these formulae show that the two rings are perpendicular to each other, and hence suitable substitution will produce molecules with no element of symmetry, thereby giving rise to optically active forms.

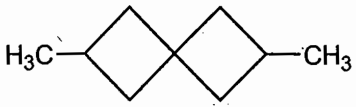
Essential criteria for chirality due to chiral axis.

1. Even number of ring in spiro compound (Odd number of spiro carbon)
2. Proper substitution at only terminal H.
   Spirane has two types of hydrogen
   (1) Lateral (2) Terminal.



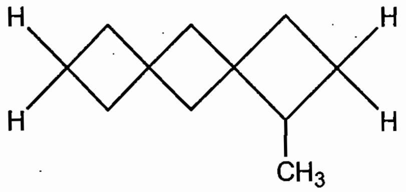
4H's are terminal, 8H's are lateral.

- Chirality due to chiral centre can be generated in any spirane compound (even or odd number of ring) by substitution at lateral hydrogen (Plane of symmetry should not be there).
- Chirality due to chiral axis can be generated in spiranes having even numbers of rings by proper substitution.

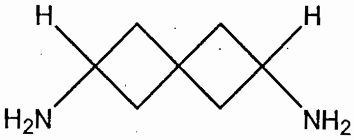


chiral

→ Number of rings = even
→ Properly substituted
→ Chiral due to chiral axis.



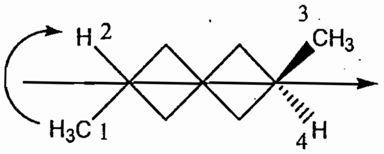
→ Number of rings = odd
→ Not properly substituted
→ But chiral due to chiral centre not due to axis.



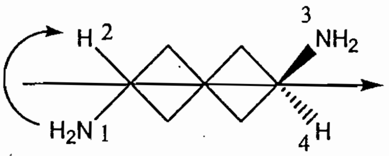
→ Number of rings = even
→ Properly substituted
→ Chiral, due to chiral axis.

R/S nomenclature in spirane

Similar to allene and biphenyl.

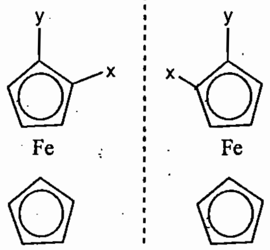


R-Isomer

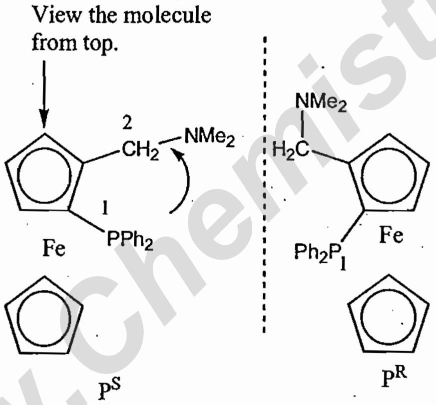


R-Form

Planar Chirality:

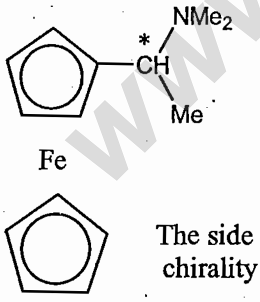


- Specific type of chirality known as planar chirality.
- Chirality can not be removed it is permanent.



P^S → This 'P' stand for planar.

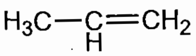
Note:



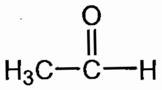
The side chain has a chiral centre such type of chirality is called lateral chirality.

Conformational Analysis

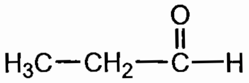
Conformation studies of unsaturated compounds and compounds containing the oxo group have led to some unexpected results. For example, microwave spectroscopy has shown that the preferred conformation of propene and acetaldehyde are the eclipsed forms and NMR spectroscopy has shown that the predominant conformation of propionaldehyde is the one in which methyl group and oxygen atom are eclipsed. The reason for these observation is uncertain.



$H_3C-\underset{H}{C}=CH_2$

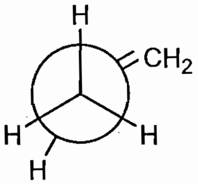


$H_3C-\overset{O}{\overset{\|}{C}}-H$

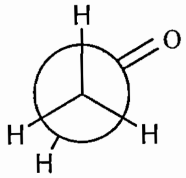


$H_3C-CH_2-\overset{O}{\overset{\|}{C}}-H$

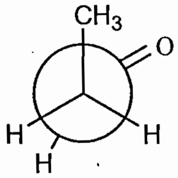
Propionaldehyde



Propene



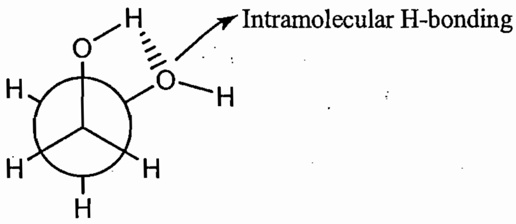
Acetaldehyde



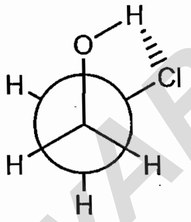
Propionaldehyde

Remark: Molecule such as ethylene chlorohydrin or ethylene glycol, intramolecular hydrogen bonding is possible in the skew form but not in the staggered form, due to this intramolecular H-bonding the molecule is stabilised by about 20-29 kJ/mol and this is enough to make the skew form more stable than the staggered form.

Evidences–I.R. spectroscopy has shown that the skew form predominates.



Gauche form of ethylene diol



Gauche form of ethylene chlorohydrine

Method used to investigate the conformation of molecules.
- Thermodynamic calculation
- Dipole moment.
- X-ray and electron diffraction
- IR and UV spectroscopy
- Chemical method.
- NMR spectroscopy

Conformational Analysis of Cyclohexane

Factor affecting the stability of conformations

(1) **Angle strain:** Any deviation from normal bond angle

(2) **Torsional strain:** Any deviation from the staggered arrangement.

(3) **Vander waals strain(Steric Strain):**

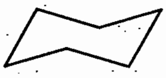
Any two atoms (or group) that are not bonded to each other can interact in several ways depending on

(a) Their size (b) Polarity (c) How closely they are brought together.

These non bonded interaction can be either repulsive or attractive, and the result can be either destabilization or stabilization of the conformation.

Bayer suggested (incorrectly) there should be certain amount of strain in cyclohexane.

Two most stable form of cyclohexane are as follows:



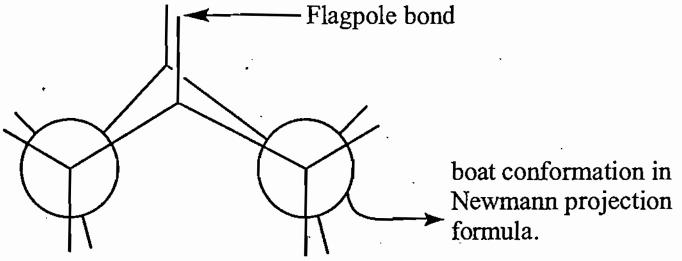
Chair form

Boat form

Chair form is more stable than that of boat form due to following fact.

Chair form	**Boat form**
(1) No angle strain	(1) No angle strain
(2) No torsional strain	(2) Torsional strain is present.
(3) No flagpole interaction	(3) Flagpole interaction is present (vander waal strain)
(4) No any eclipsed ethane condition	(4) Two eclipsed ethane condition (will creat torsional strain)

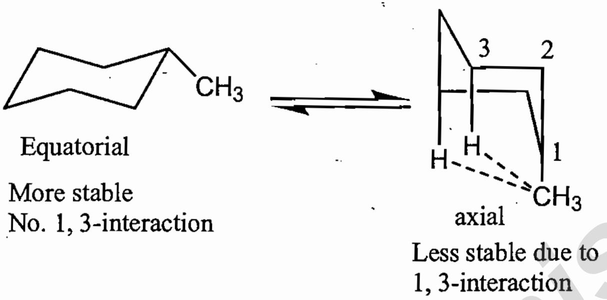
Conclusion: The boat conformation is less stable than the chair conformation.

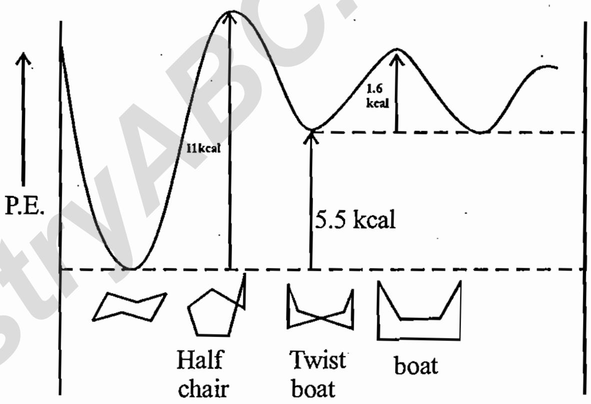


Potential energy relationship among conformation of cyclohexane.

Stability order: Chair > twist boat > boat > half chair

Mono substituted cyclohexane:





Remark: Except for **'H'**, a given atom or group has more room in an equatorial positions than the axial position. Most molecule (about 99% at room temperature) exist in the conformation with methyl in uncrowded equatorial position.

Disubstituted cyclohexane:

1, 2-disubstituted cyclohexane

Homo disubstituted

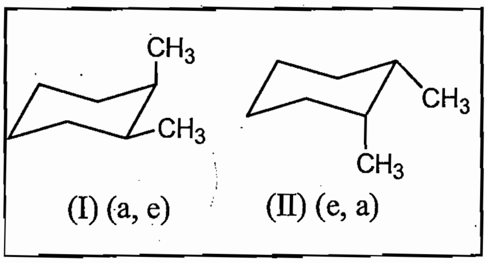
Hetero disubstituted cyclohexane.

Cis and trans relationship in disubstituted cyclohexane can be understood as

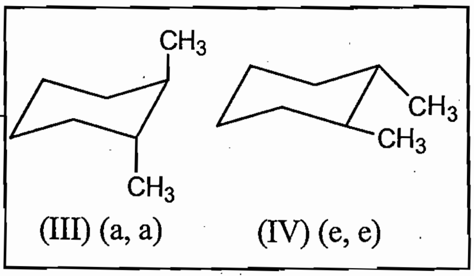
1, 2-disubstituted cyclohexane.	1, 4-disubstituted cyclohexane.	1, 3-disubstituted cyclohexane.
Cis — (a, e) or (e, a)	Cis — (a, e) or (e, a)	Cis — (a, a) or (e, e)
Trans — (a, a) or (e, e)	Trans — (a, a) or (e, e)	Trans — (a, e) or (e, e)

Let us consider an example of 1, 2-disubstituted cyclohexane.

Cis–



Trans–

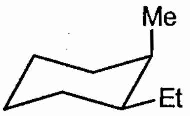


I & II are degenerate because both have one 1, 3-interaction.
III & IV are non degenerate
III is least stable because in this case both methyl group is placed at axial position and suffer 1, 3-interaction.

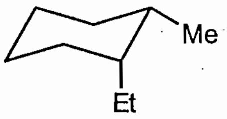
So, the stability order is IV >I > II > III

1, 2-disubstituted cyclohexanes with two different substituents.
Let us consider an example of 1-ethyl-2-methyl cyclohexane.

Cis-isomer



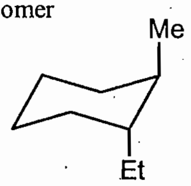
(1) (a, e)



(2) (e, a)

Trans-Isomer

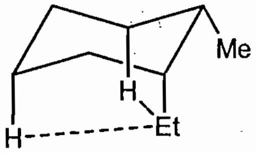
(3) (e, e)



(4) (a, a)

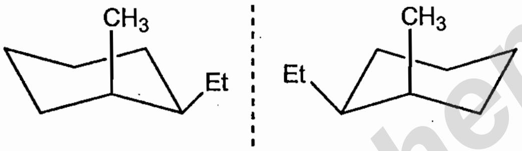
1 and 2 are non degenerate.

Remark: Energy of conformation (2) will greater than that of (1) because, the bulky ethyl group is at axial position which suffer more 1,3-interaction.

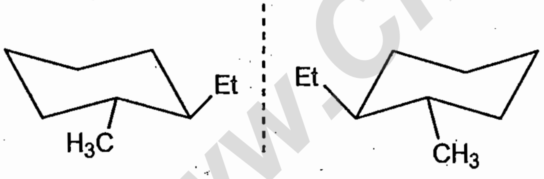


3 and 4 are also non degenerate, out of these two conformations, (4) has maximum energy because both, methyl and ethyl are placed at axial position where they suffer severe 1, 3-interaction.
So, overall stability order is 3 > 1 > 2 > 4.

Optical activity:



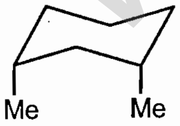
A pair of enantiomer



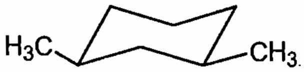
A pair of enantiomer

1, 3-disubstituted cyclohexanes (1, 3-dimethyl cyclohexane)

Cis-1, 3-dimethyl cyclohexane.

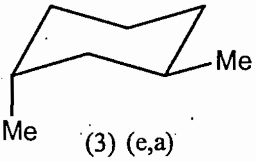


(1) (a,a)

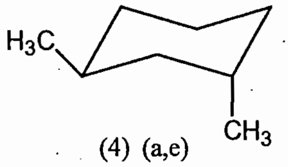


(2) (e,e)

Trans-1, 3-dimethyl cyclohexane.



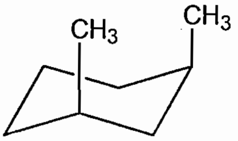
(3) (e,a)



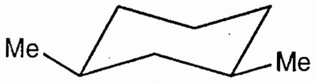
(4) (a,e)

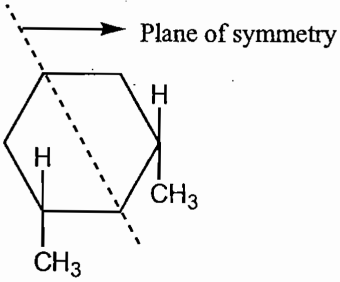
3 and 4 are degenerate.
1 and 2 are non degenerate.
Energy order 1 > 3 ~ 4 > 2.
Stability order 2 > 3 ~ 4 > 1

Note: In Cis-1, 3-dimethyl cyclohexane, plane of symmetry is present in both (a, a) or (e, e) conformation.



(a, a)

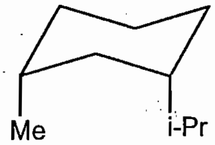




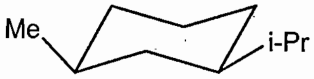
However, trans 1, 3-dimethyl cyclohexane, does not have a plane of symmetry and exist as a pair of enantiomers.

Let us consider the case of 1-isopropyl-3-methyl cyclohexane.

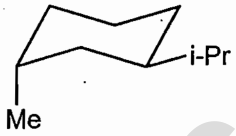
cis-1-isopropyl-3-methyl cyclohexane. trans-isoprophyl-3-methyl cyclohexane.



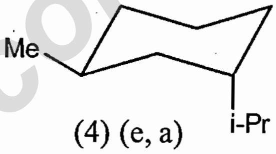
(1) (a, a)



(2) (e,e)



(3) (a, e)



(4) (e, a)

1 and 2 are nondegenerate.

3 and 4 are non degenerate.

Stability order:

2 > 3 > 4 > 1

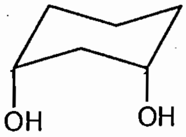
1 → Both group at axial position

4 → Bulkier group (i-Pr) at axial position.

2 → Both group at equitorial position

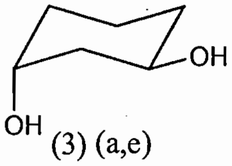
Let us consider an example of 1,3-dihydroxy cyclohexane.

Cis-1,3-dihydroxy cyclohexane. trans-1, 3-dihydroxycyclohexane.

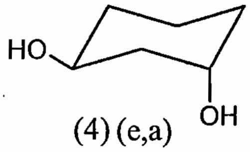


(1) (a, a)

(2) (e,e)



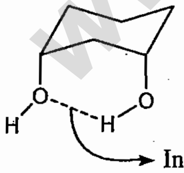
(3) (a,e)



(4) (e,a)

Stability order 1 > 2 > 3 ~ 4

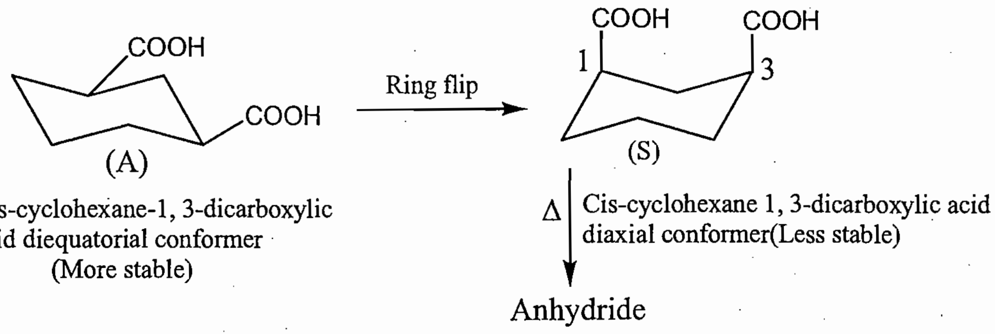
Conformer (1) is more stable than that of (2) because of the fact that in case of (1) intramolecular H-bonding is possible.



Intramolecular H-bonding.

PROBLEMS

1. From which conformation of cis-1, 3-cyclohexane dicarboxylic acid anhydride will be form.

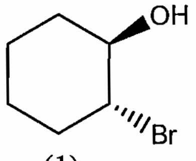


Soln. Cis-cyclohexane-1, 3-dicarboxylic acid diequatorial conformer (More stable)

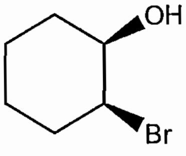
Cis-cyclohexane 1, 3-dicarboxylic acid diaxial conformer(Less stable)

Remark: The –COOH grop in (A) are far apart for anhydride formation. Ring flip to give (S) brings them with in reacting distance.

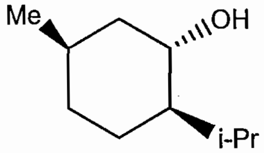
2. Draw the favoured conformation of following compounds



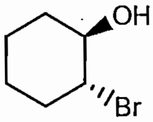
(1)

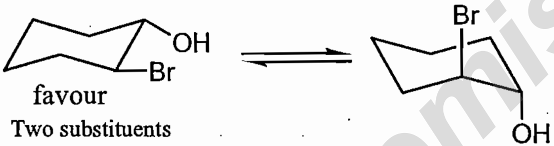


(2)



Soln. (1)

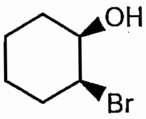




favour
Two substituents equatorial (non-axial)

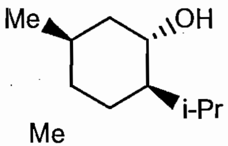
No substituents equatorial two (axial).

(2)

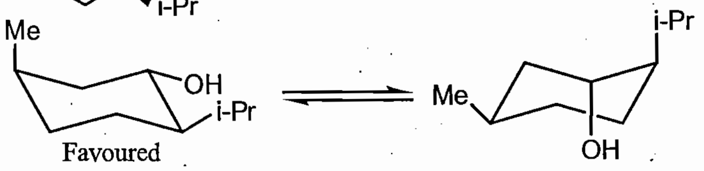


Since Br > OH (in size)

favoured



(3)

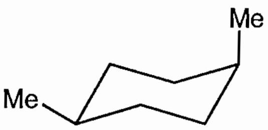


Favoured
Two substituents equatorial one axial.

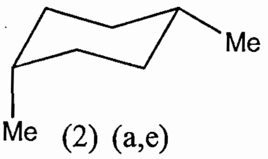
One substituent equatorial two axial.

1, 4-disubstituted cyclohexane: Let us consider an example f 1, 4-dimethyl cyclohexane.

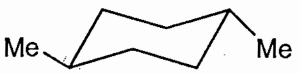
Cis-1, 4-dimethylcyclohexane. trans-1, 4-dimethylcyclohexane.



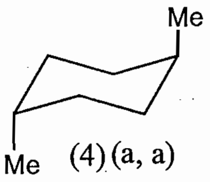
(1) (e,a)



(2) (a,e)



(3) (e,e)



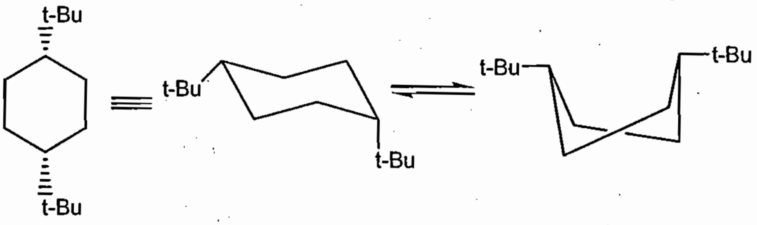
(4) (a, a)

Stability order: $1 > 1 \sim 2 > 4$.

SOLVED PROBLEMS

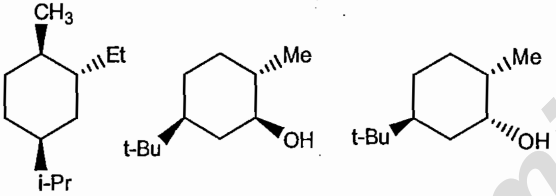
1. Draw the most stable conformation of cis-1, 4-di t-butylcyclohexane.

Soln.

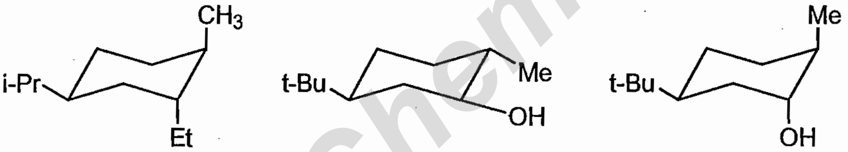


Remark: An axial t-butyl group is very unfavourable form. In Cis-1,4-di-t-butyl cyclohexane, one t-butyl group would be forced axial if the compound existed in a chair conformation, to avoid this, the compound prefers to pucker into a twist boat so that the two large groups can both be in equatorial positions (or Pseudoequatorial, since this is not a chair).

2. Draw the most stable configuration of

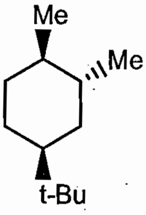


Soln.

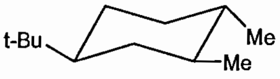


Remark: The bulky t-butyl group is particularly prone to occupy an equatorial position if other substituents are considerably smaller than t-butyl, the molecule is virtually locked in a single conformation. The one with an equatorial t-butyl group. t-butyl group has been widely used as a holding group to permit the study of physical and chemical properties associated with a purely axial or purely equatorial substituent.

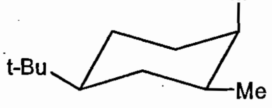
3. The most stable conformation of the following compound is:



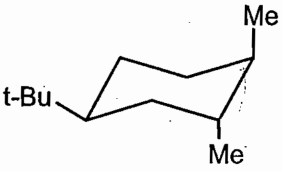
(a)



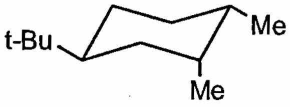
(b)

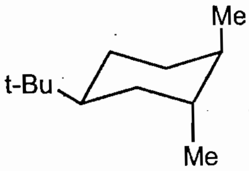


(c)



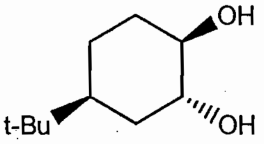
(d)

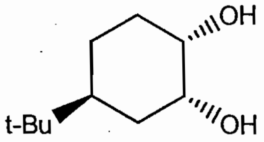


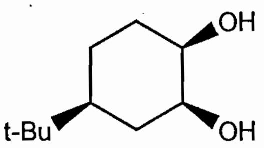
Ans. 

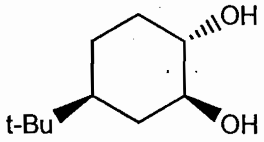
. Because t-butyl group is locking group.

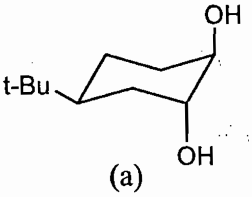
4. The favoured vicinal diols shown below only three are cleaved by HIO_4. The diol which is not cleaved HIO_4 is:

(a) 

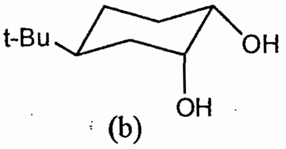
(b) 

(c) 

(d) 

Soln. 

(a)



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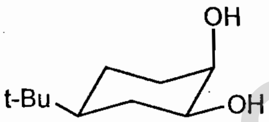

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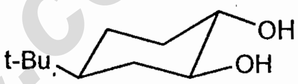
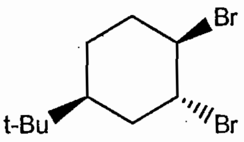


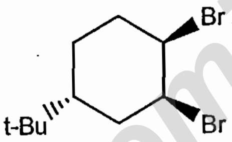
(d)

(a) Because in this case the two-OH groups are diaxial, so there is more distance between two OH groups and hence will not interact with HIO_4 effectively.

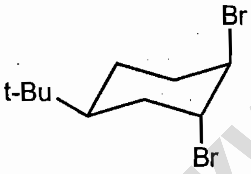
5. Accouts for the fact that only one of the following compounds A and B give the expected elimination product with KI acetone.



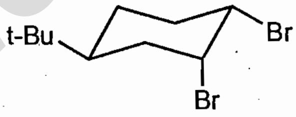
(A)



(B)

Soln. 

(A)

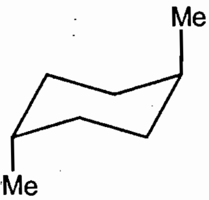


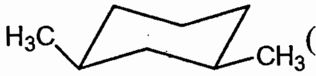
(B)

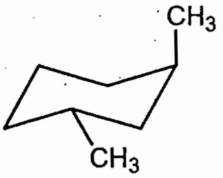
(A) will give the expected elimination product with KI in acetone because for E2-elimination. The two departing group should be placed at diaxial position (or antiperiplanar) such requirement is only fulfilled by compound (A).

6. Which of the following is a cis-isomer?

(a) 

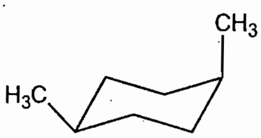
(b) 

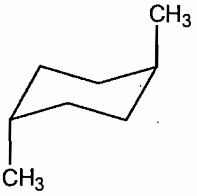
(c) 

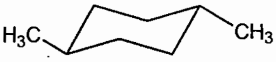
(d) 

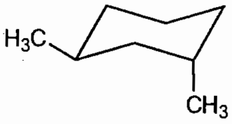
Soln. **(c)** Because in case of 1, 3-disubstituted cyclohexane cis means (e, e) or (a, a).

7. The stable form of trans-1,4-dimethyl-cyclohexane is represented as

(a)


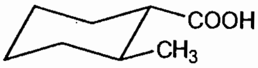
(b)


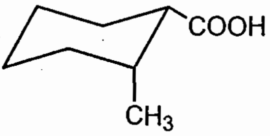
(c)


(d)


Soln. (c) because both groups are at equatorial position.

8. Identify the hydroxycyclohexane carboxylic acid, which upon heating readily gives a bicyclic lactone

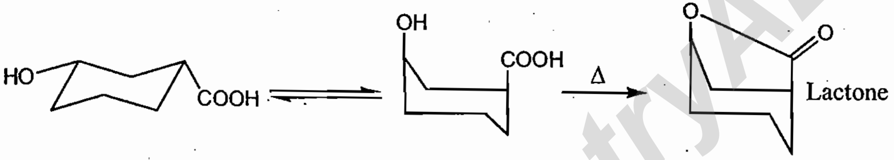
(a)


(b)


(c)

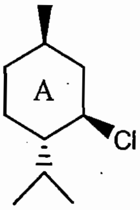

(d)

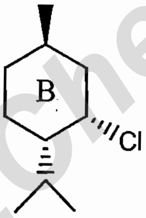

Soln. (d) Because after filiping of the ring the two groups OH and COOH come nearer to each other.

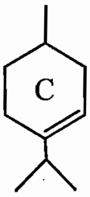


No one conformation will give this geometry.

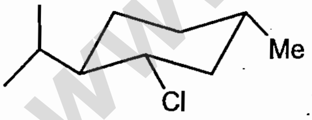
9. Menthyl chloride (A) and neomenthyl chloride (B) both react with base to lose a molecule of HCl by E_2 mechanism. The products are regio isomers (C) and (D). Identify which product is formed from which starting compound. Also mention starting compound (A) or (B) which will react faster. Give reasons for your answer.



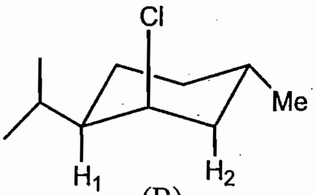




Soln.

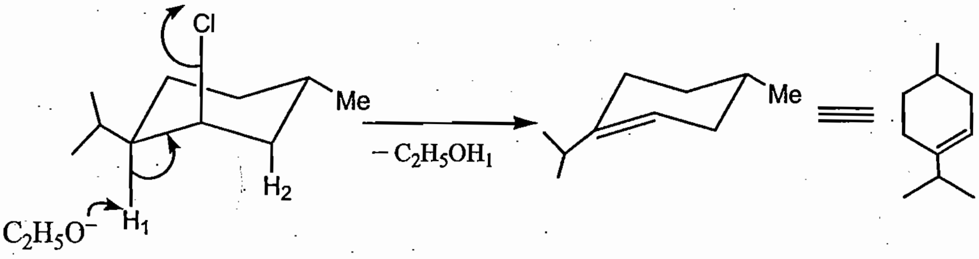


(A)

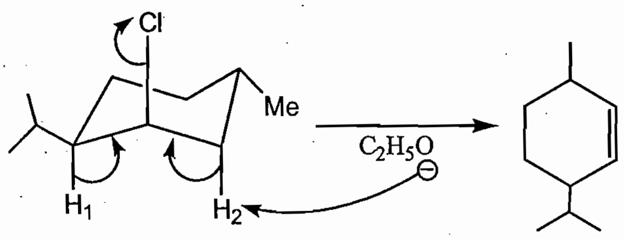


(B)

In case of (B) for elimination of HCl with base Cl have diaxial relationship with H_1 and H_2 which is the demand of E_2 elimination.

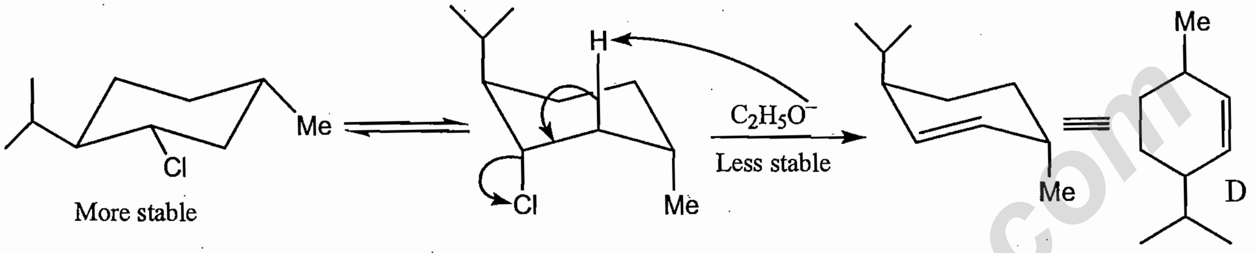


If proton H_2 will remove by base such as:

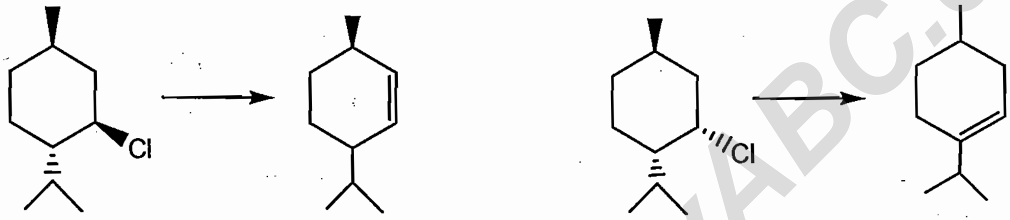


This product will also obtain but more highly alkylated product (C) will be formed.

In the chair conformation (A) Cl–atom is equatorially placed and we know for E_2 elimination. The two departing group should be antiperiplanar, on this demand the conformation flip will occur such as

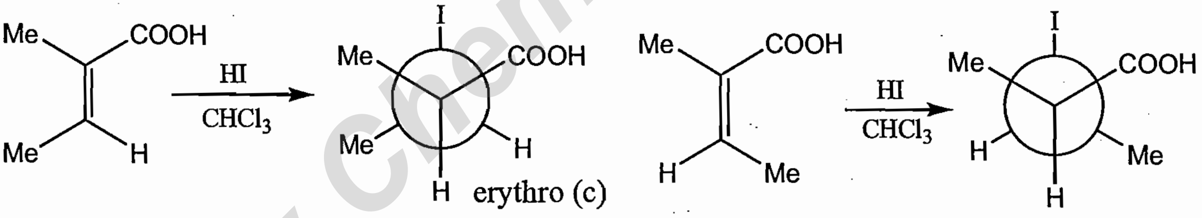


So,

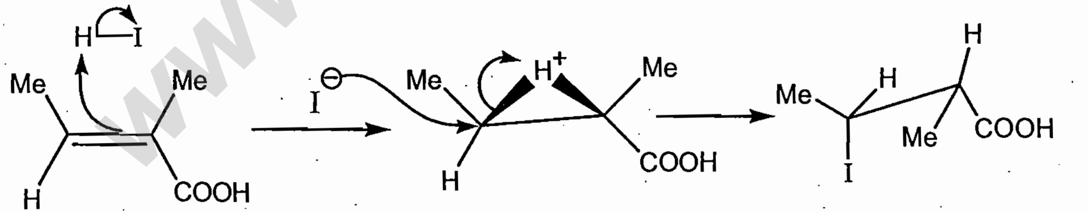


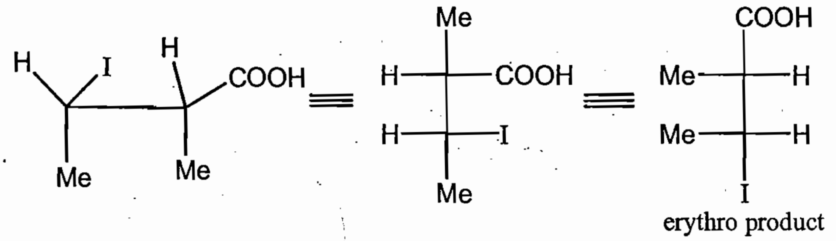
Rate of elimination of (B) is faster than that of A because elimination of (A) occur from high activation energy conformation.

10. How would you explain the addition of HI to *tiglic acid* (A) and *angelic acid* (B) to give stereospecifically the erythro and threo-β-Iodo acid, (c) and (d) respectively instead of a mixture of both the acids (c and d) in each case?

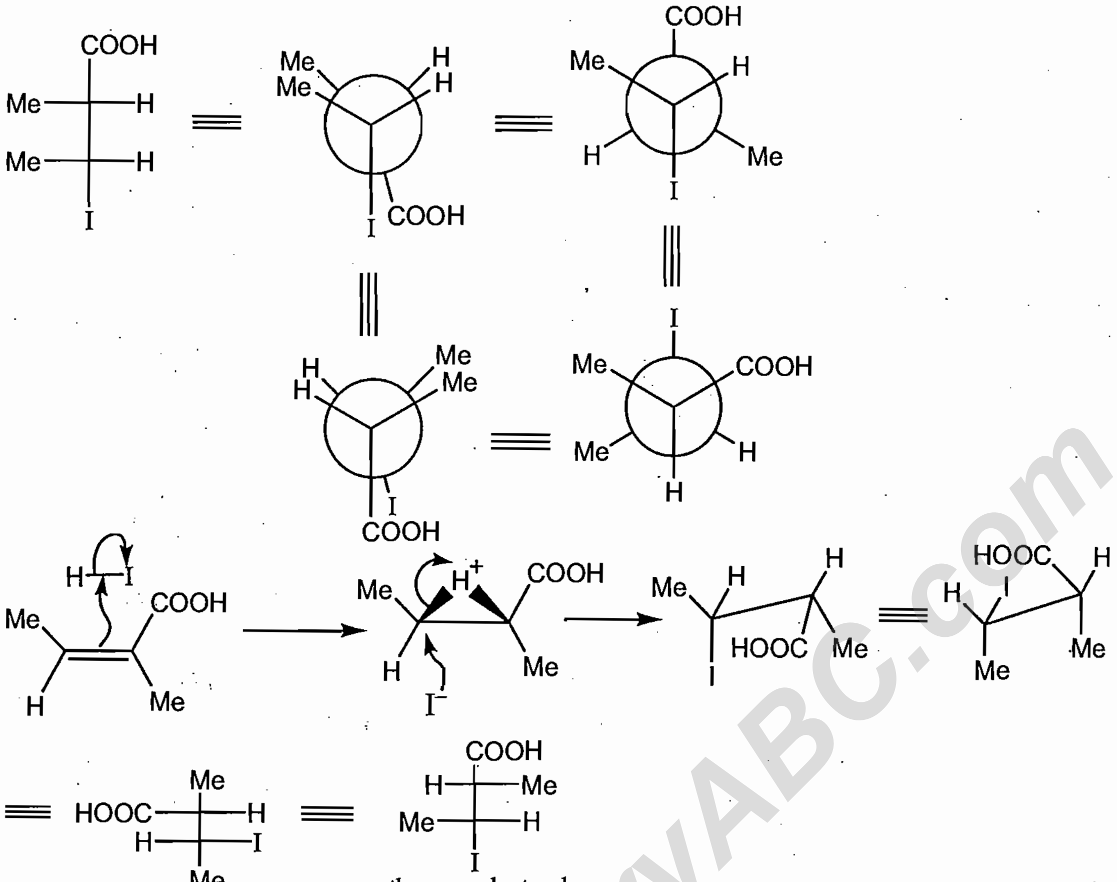


Soln.





erythro product



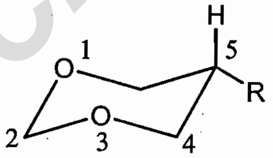
threo product only

Conformation in six membered rings containing hetero atoms

In six membered ring containing hetero atoms, the basic principles are the same i.e. there are chair, twist and boat forms, axial and equatorial groups etc, but in certain compounds a number of new factors enter the picture.

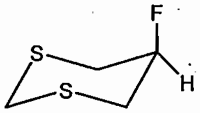
For example:

In 5-alkyl-substituted 1, 3-dioxane, the 5-substitutent has a much smaller preference for the equatorial position than in cyclohexane derivatives.

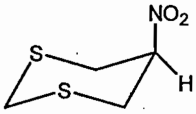


This indicate that lone pairs on the oxygen have a smaller steric requirement than the C–H bonds in the corresponding cyclohexane derivatives.

Similar behaviour is found in the 1, 3-dithiane with certain nonalkyl substitution (eq, F, NO_2, SOMe, $\overset{+}{N}Me_3$) the axial positions is actually preferred.

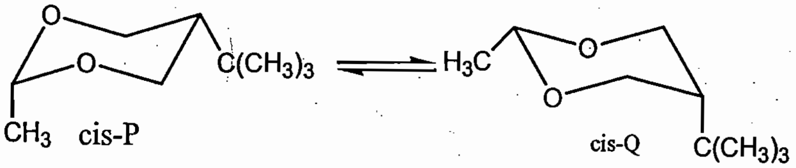


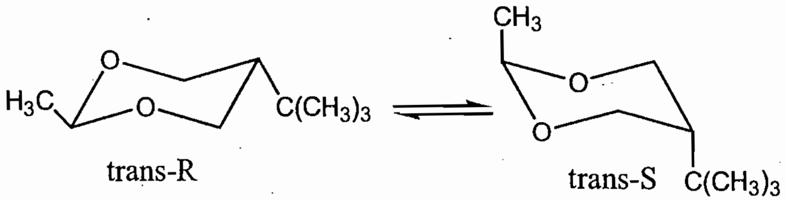
Preferred form



Preferred form

11. Cis–and trans–2–methyl–5-tbutyl–1, 3-dioxane each can exist as two conformers as shown below.





The preferred conformations for the cis and trans–compounds will be

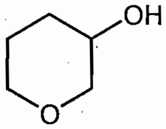
(a) P, R (b) Q, S (c) P, S (d) Q, R

Soln. **(b)**

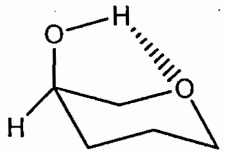
Hints: In Q the bulky group (t-butyl) does not suffer 1, 3-interaction because carbon is replaced by oxygen.

Conclusion: In heterocyclic rings the steric repulsion for axial substituents are reduced due to the replacement of methylene groups of cyclohexane by oxygen or nitrogen.

12. Draw the most stable conformation of



Soln.



The presence of an oxygen atom in the ring allows hydrogen bonding that can stablize hydroxyl groups in the axial position.

Specific Rotation

Specific rotation as optical rotation of 1 gm/mL concentrated solution when path length 10 cm (1 dm) at particular wavelength (l) of light.

$$[\alpha] = \frac{\alpha}{c.\ell}$$

Note: Most $[\alpha]$ values are quoted as $[\alpha]_D$ (where the D indicates the wavelength of 589 nm, the D line of a sodium lamp) or $[\alpha]_D^{20}$, the 20 indicating $20°C$.

Enantiomeric Excess

Enantiomeric excess or e e is a measure for how much f one enantiomer is present compared to the other.

For example, in a sample with 40% e e in R, the remaining 60% is racemic with 30% of R and 30% of S so that the total amount of R is 40% + 30% = 70%.

$$\text{\% optically purity} = \frac{[\alpha]_{obs}}{[\alpha]_{max}} \times 100$$

assuming a linear relationship between $[\alpha]$ and concentration, which is true for most cases. The optical purity is equal to percent excess of one enantiomer over the other

So,

$$\text{Optical purity} = \text{percent enantiomeric excess} = \frac{[R]-[S]}{[R]+[S]} \times 100 = \%R - \%S$$

$$\boxed{\text{Optical rotation} = \frac{e\,e}{100} \times \text{specific rotation}}$$

13. 20 mg mandelic acid was dissolved in 1 cm^3 of ethanol and the solution placed in a 10 cm long polarimeter cell. An optical rotation α of –4.35°C was measured (that is, 4.35° to the left) at 20°C with light of wavelength 589 nn. What is the specific rotation of the acid?

Soln. $[\alpha]_D^{20} = \frac{\alpha}{c \times \ell}$

Since, $\alpha = -4.35°$

$c = 28\ mg/cm^3$ $\qquad \ell = 10\ cm = 1\ dm$

$c = 28 \times 10^{-3}\ g/cm^3$

$c = 0.028\ g/cm^3$

So, $[\alpha]_D^{20} = \frac{\alpha}{c \times \ell} = \frac{-4.35}{0.028 \times 1} = -155.4$

So, the specific rotation of mandolic acid = –155.4°.

14. Calculate the optical rotation from the given data

sp = 20°

D = 90%

L = 10%

Soln. e e = 90% – 10%

e e = 80%

So, Optical rotation $= \frac{80}{100} \times 20 = 16$

$$\boxed{e\,e = \frac{\text{Optical rotation}}{\text{specific rotation}} \times 100}$$

15. Calculate enantiomeric excess from the given data

sp rotation = 20°

optical rotation = 18°

Soln. $e\,e = \frac{18}{20} \times 100$

e e = 90%

$$\begin{aligned} \text{Since,}\quad & \%\text{ of } d + \%\,\ell = 100 \\ & \underline{\%\text{ of } d - \%\,\ell = 90 = e\,e} \\ \text{So,}\quad & \%\text{ of } 2d = 190 \end{aligned}$$

$\therefore$ of $d = \frac{190}{2} = 95\%$ & $\%\,\ell = 5\%$

Optical activity of compounds having symmetric carbon

Case I: If the molecule has no plane of symmetry and molecule has 'n' asymmetric carbon atoms then–

Number of optically active forms = 2^n = a

Number of enantiomeric pair = a/2

Number of racemic mixture = a/2

Number of meso form = 0

Case II: If the molecule has plane of symmetry, then the number of configuration isomers depend on the number of asymmetric carbon atoms.

(1) When compound has even number of asymmetric carbon atoms i.e. n = 2, 4, 6, ...

(a) Number of optically active forms = a = 2^{n-1}.

(b) Number of enantiomeric pairs = a/2

(c) Number of racemic mixture = a/2

(d) Number of meso forms = m = $2^{\frac{n}{2}-1}$.

(e) Total number of configurational isomer = a + m

For example:

$$HOOC—\overset{*}{C}H(OH)\,\vdots\,\overset{*}{C}H(OH)—COOH$$

n=2

Number of optical isomer $= a = 2^{n-1} = 2$

Number of meso form $= m = 2^{n/2-1} = 2^{2/2-1} = 1^{\circ} = 1$

Total number of configurational isomers = 2+1=3

Let us consider another example

$$Ph—\overset{*}{C}HCl—\overset{*}{C}HCl\,\vdots\,\overset{*}{C}HCl—\overset{*}{C}HCl—Ph$$

n= 4

$a = 2^{4-1} = 2^3 = 8$

$m = 2^{(n/2)-1} = 2^{4/2-1} = 2^{2-1} = 2^1 = 2$

So, the total number of configurational isomers $= 8 + 2 = 10$

Case III: When compound has odd number of asymmetric carbon atoms and plane of symmetry i.e. n = 3, 5, 7, 9, 11...........

(a) Number of optically active forms

$$a = 2^{n-1} - 2^{(n-1)/2}$$

(b) Number of enantiomeric pair = a/2

(c) Number of racemic mixture = a/2

(d) Number of meso forms = m = $2^{(n-1)/2}$

(e) Total number of configurational isomers = a + m.

For example:

$$HOH_2C—\overset{*}{C}HOH—\overset{*}{C}HOH—\overset{*}{C}HOH—CH_2OH$$

n=3

$a = 2^{n-1} - 2^{(n-1)/2} = 2^{3-1} - 2^{3-1/2} = 2^2 - 2^1 = 2\times2-2 = 4-2 = 2$

$m = 2^{(n-1)/2}$

$m = 2^{3-1/2} = 2^1 = 2$

Hence total number of configurational isomers = 2 + 2 = 4

Number of Geometrical Isomers in Polyenes

(a) When compound has 'n' doube bonds and ends of polyene are different, the number of geometrical isomers = 2^n.

where n = Number of double bonds.

$Ph-CH=CH-CH=CH-CH=CH-CH=CH-Cl$

$n = 4$

(b) When the ends of polyene are same

Case I: When number of double bond is even.

Then the number of geometrical isomers.

$$2^{n-1} + 2^{n/2-1}$$

Let us consider another example

$Cl-CH=CH-CH=CH-CH=CH-CH=CH-Cl$

$n = 4$

Number of geometrical isomers $= 2^{n-1} + 2^{n/2-1} = 2^3 + 2^1 = 8 + 2 = 10$

Case II: When the number of double bonds are odd

Number of geometrical isomer $= 2^{n-1} + 2^{n-1/2}$

$Ph-CH=CH-CH=CH-CH=CH-Ph$

Number of geometrical isomers $= 2^2 + 2^{\frac{3-1}{2}} = 2^2 + 2^1 = 4 + 2 = 6$

Topocity :

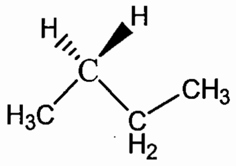
Topocity is the strereochemical relationship of substituents relative to the structure to which theyare attached, depending on the relationship, such groups can be heterotopic, homotopic enantiotopic, or diastereotopic.

Homotopic:

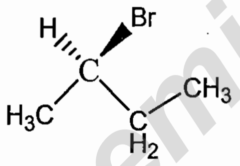
- Homotopic atom, are always identical in any environment.
- Homotopic NMR - active nuclei have the same chemical shift in an NMR spectrum.

eq– CH_4 all 4H's are potential. So homotopic with one another.

Enantiotopic:

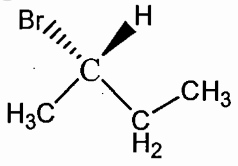


Butane



R-2–bromobutane

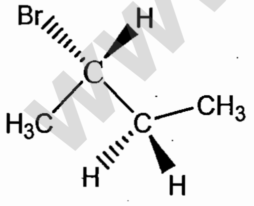
+



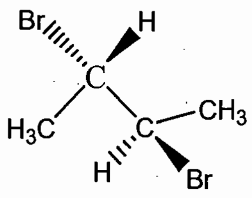
(S)–2–bromo butane

- Enantiotopic groups are identical and indistinguishable except in chiral environment
- Enantiotopic pairs of NMR active nuclei are also indistinguishable by NMR and produce a single signal..........

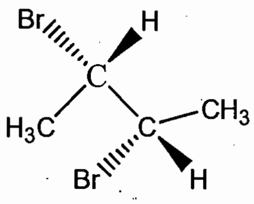
Diastereotopic groups are often, but not always identical group attached to the same atom in a molecule containing at least one chiral centre.



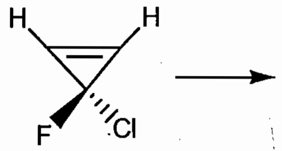
(S)–2–bromobutane



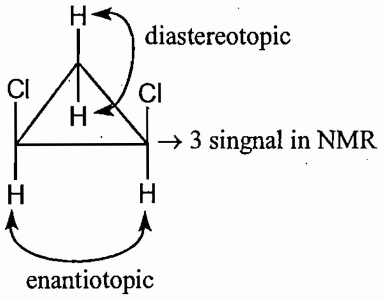
(2S,3R)–2,3–dibromobutane

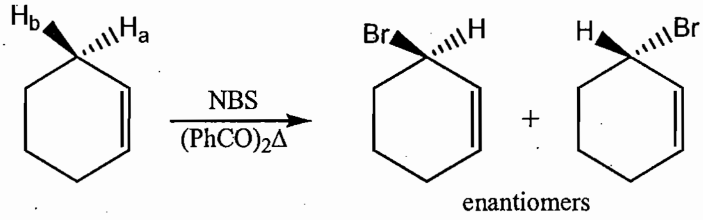


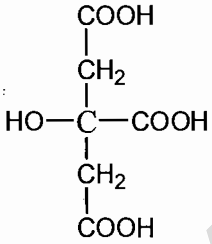
(2S,3S), –2, 3–dibromobutane



enantiotopic face



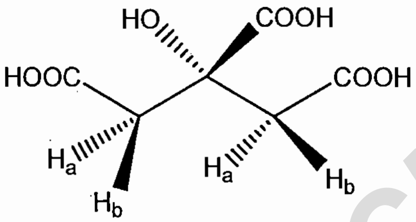




$$\begin{array}{c} COOH \\ | \\ CH_2 \\ | \\ HO-C-COOH \\ | \\ CH_2 \\ | \\ COOH \end{array}$$

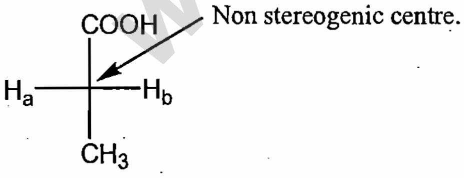
Citric acid

Citric acid has the prochiral centre the two chain CH_2COOH are enantiotopic.
This is an interesting example where enantiotopic and diastereotopic H', co-exist.

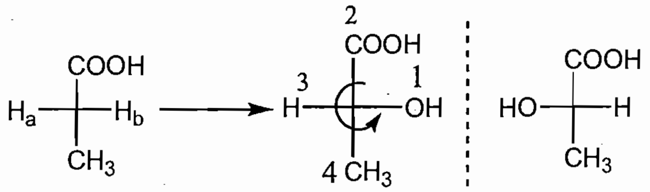


A plane of symmetry perpendicular to the page and passing through the middle carbon make H_a's enantiotopic and H_b's also enantiotopic. No Plane of symmetry can pass between each CH_2 group protons *a* and *b* on each CH_2 group diastereotopic.

Prochirality: Prochirality is the property of certain molecules due to which these can be converted into stereoisomers. (enantiomers or diastereoisomers).



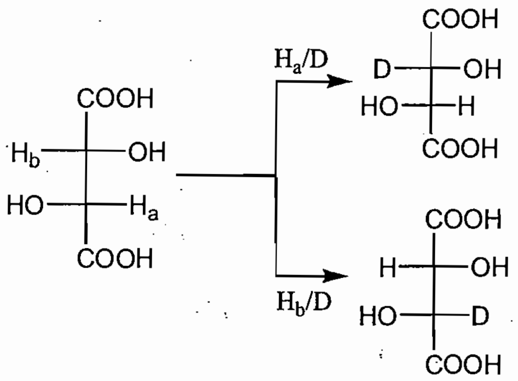
Propionic acid



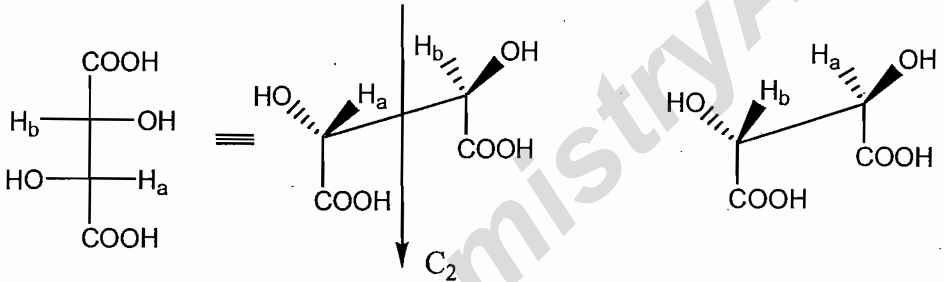
R-lactic acid S-lactic acid

Homotopic ligands and Faces:

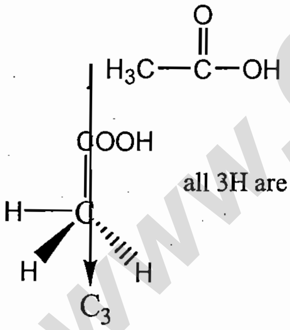
- If the substitution of each one of them by another atom or group leads to the same structure.



So, two hydrogens H_a and H_b are homotopic through rotational around



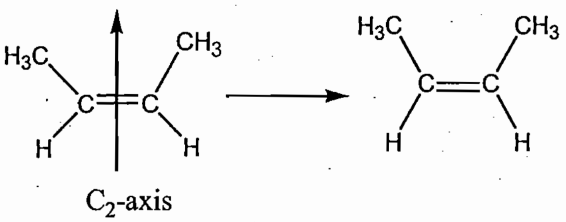
Problem:

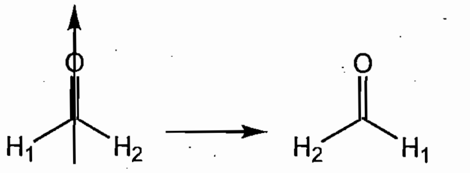


$H_3C-\overset{\overset{\Large O}{\|}}{C}-OH$

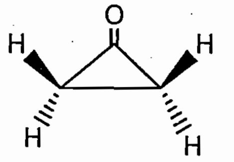
all 3H are identicals, so homotopic in nature

Homotopic face:



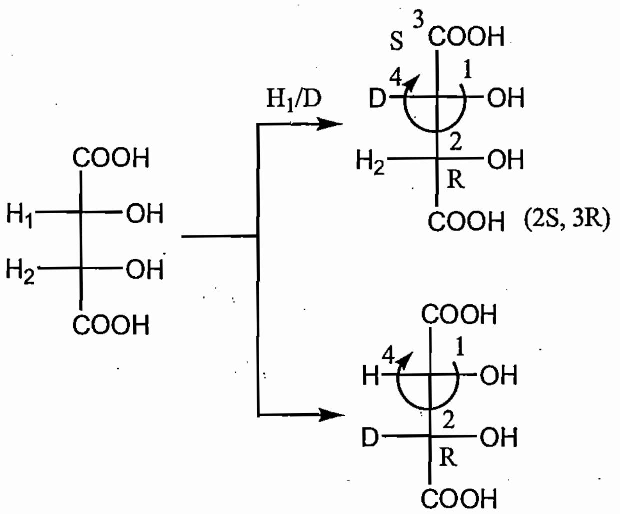


homotopic face

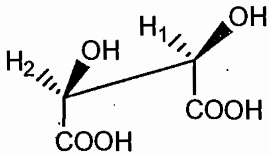


homotopic face

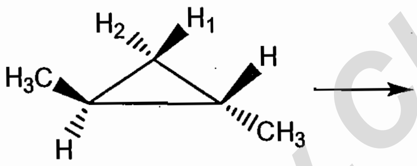
Enantiotopic ligand and faces



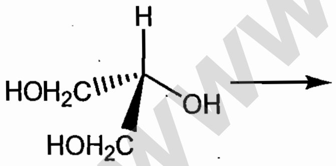
These two are not non super imposable mirror images to each other but still diastereoiomers.



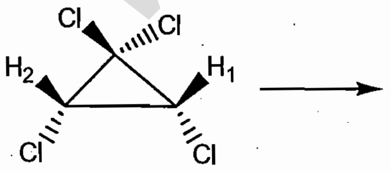
H_1 and H_2 are reflected by a plane
So, these two are enantiomers to each other.



H_1/H_2 are homotropic becaue it is
interchanged with C_2-symmetry.

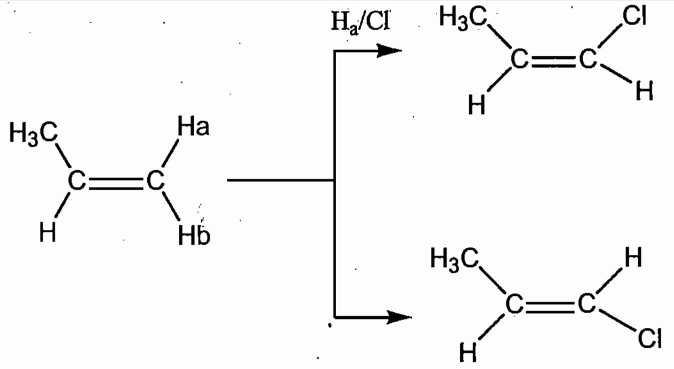


enantiotopic



H_1/H_2 → are enantiotopic

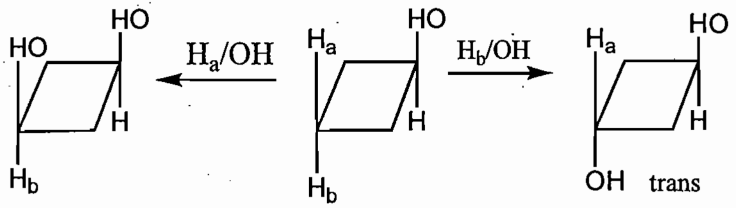
Diastereotopic ligands and faces:



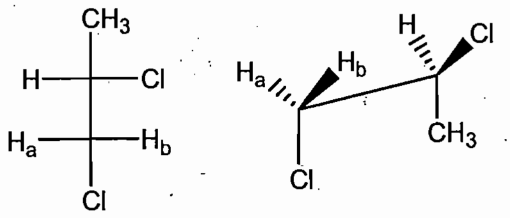
So, these two are diasteroismers

cis(z)

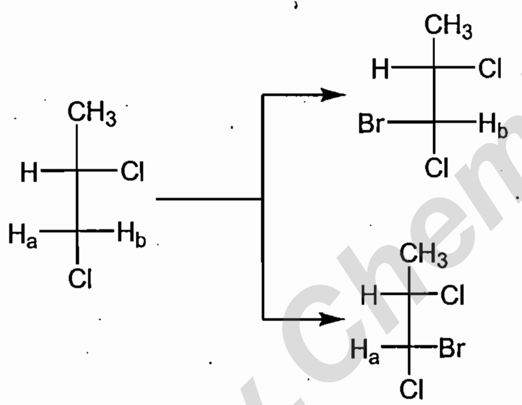
trans (E)



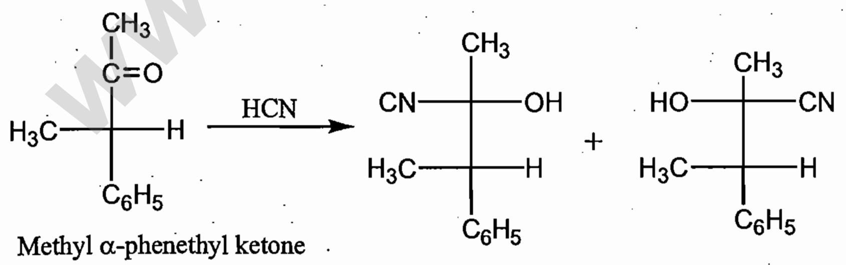
So, H_a and H_b diastereoisomers



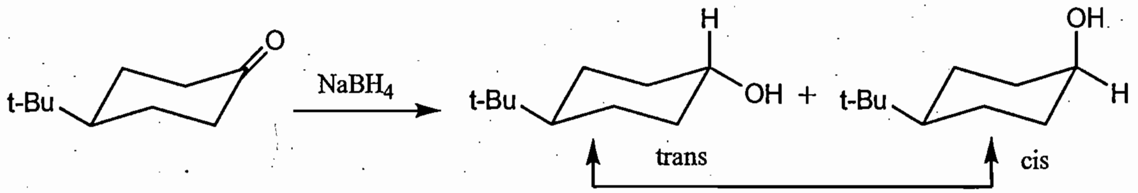
So, H_a and H_b → are diastereotopic.



Diastereotopic face:

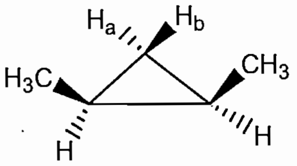


Methyl α-phenethyl ketone

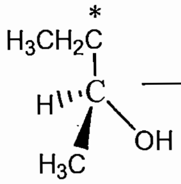


So this face is diasterotopic

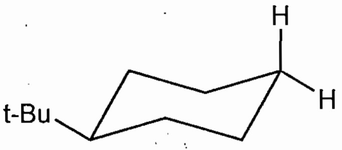
PROBLEMS

1. 

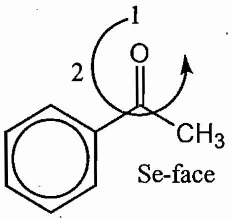
So, H_a/H_b are diasrereoisomers because it is bisected from a plane.

2. (i) 

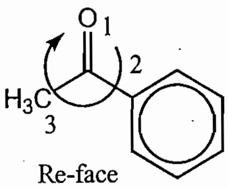
$\longrightarrow$ diastereotopic

(ii) t-Bu 

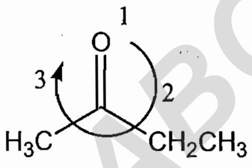
$\longrightarrow$ diastereotopic



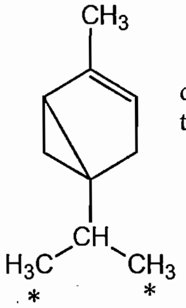
Se-face



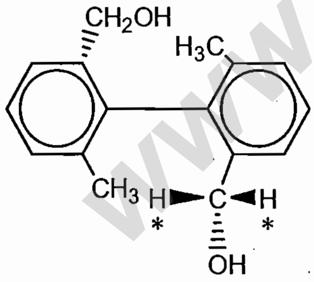
Re-face



Re-face

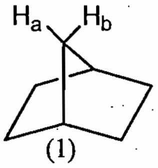
3. 

diastereotopic since there is no symmetry and the two methyl group are close to a stereogenic centre.



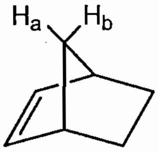
diastereotopic when the rotation of the ring is slow when rotation becomes fast these protons become enantiotopic (average mirrorplane)

4. Indicate H_a and H_b are homotopic, enantiotopic or diastereotopic.

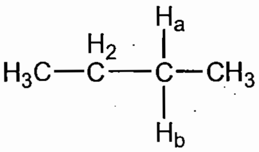


(1)

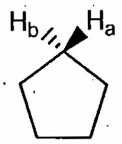
homotopic



diastereotopic replacement test would give syn and anti compounds which are diastereomers.

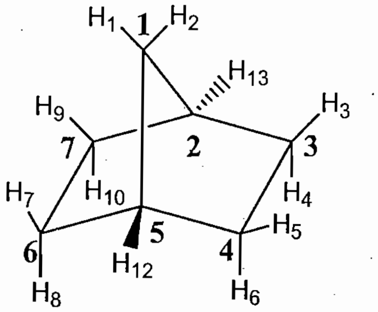


enantiotopic



homotopic

Let us consider an example of norborane system first we want to discuss the symmetry properties of this system.



It has one C_2 axis passing through C_1 and interchanging C_2/C_5, C_3/C_6, C_4/C_7. H_1/H_2, H_{12}/H_{13}, H_3/H_7, H_5/H_9, H_4/H_8, H_6/H_{10}.

So, these protons are identical (as we know the protons which are interchanging with an axis are identical i.e. homotopic protons).
Now, It has two σ_v.

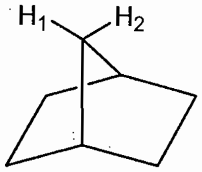
(a) σ_{v1}–bisecting C_1–C_2–C_5, H_{13}, H_{12} reflecting C_3/C_7, C_4/C_6, H_1/H_2, H_3/H_9, H_5/H_7, H_6/H_8, H_4/H_{10}.

(b) σ_{v2}–bisecting C_1, H_1, H_2 and reflecting C_2/C_5, C_3/C_4, C_7/C_6, H_{13}/H_{12}, H_3/H_5, H_4/H_6, H_9/H_7, H_{10}/H_8.

The protons which are reflected with plane are enantiotopic where as those which are bisected with plane are diasterotopic.

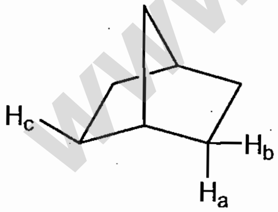
Note: If a protons are interchanging with C_2 axis and also reflected by plane the priority will be given to interhanging by axis and hence it will be homotopic but not enantiotopic.

For example



H_1/H_2 are interchangabe with C_2-axis and also reflected by a plane. So, in this case priority will be given to former not latter and hence H_1/H_2 are homotopic proton.

5. Identify the correct stereochemical relationship amongst the hydrogen atoms H_a, H_b and H_c in the following molecule. **[GATE-2006]**

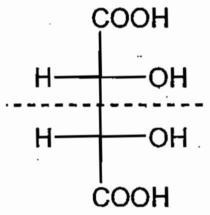


(a) H_a and H_b:enantiotopic
(b) H_a and H_b : diastereotopic
(c) H_a and H_c: enantiotopic
(d) H_b and H_c : diastereotopic

Soln. Since, H_a and H_b do not have direct relationship with any symmetry element. So, we will have to see chemical environment around H_a and H_b since the chemical environment is different viz H_b is exo where as H_a is endo so these protons are diastereotopic.
H_c/H_b are reflected with plane hence it will be enantiotopic.
$H_a/H_c \rightarrow$ diastereotopic

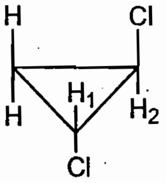
Correct answer is (b)

6. The two H's at C–2 and C–3 in (2R, 3S) tartaric acid.
(a) enantiotopic (b) diastereotopic (c) homotopic (d) constitutionally heterotopic



Soln. These two hydrogenes are reflected by a plane.
So, it is enantiotopic.

7.

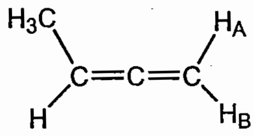


The relation between H_1/H_2 are
(a) Homotopic (b) Diastereotopic (c) enantiotopic **CSIR-JRF-2008**

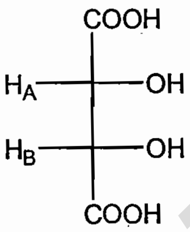
Soln. Since H_1 and H_2 are interchangable with C_2-axis so these two are homotopic.

8. Consider the hydrogen atoms labelled as H_A and H_B in the following molecules. **[IAS-2008]**

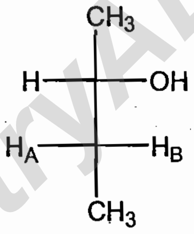
(1)



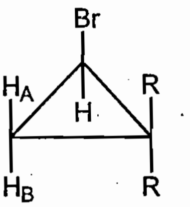
(2)



(3)



(4)

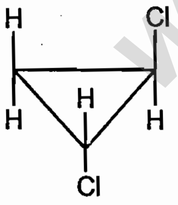


In which of the above are H_A and H_B diastereotopic
(a) 1, 2 and 3 (b) 2, 3 and 4 (c) 1, 3 and 4 (d) 1, 2 and 4

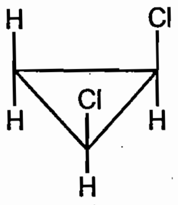
Soln. (b) have plane of symmetry so H_A and H_B are enantiotopic in the case of (3). H_A and H_B are adjacent to the chiral centre so these two protons are diastereotopic while in case of (4) no direct relationship with symmetry element while chemical environment of these two protons are different so these two are diasterotopic.
So, the correct answer is (c)

9. Consider the following molecule S: **[IAS-2007]**
1. trans-1, 2-dichlorocyclo propane.
2. cis-1, 2-dichlorocyclo propane
3. 1, 1, 2-trichlorocyclopropane.
In which of the above molecules is/are the sets(s) of methylene hydrogen(s) diasterotopic?
(a) 1 only (b) 1 and 3 (c) 2 and 3 (d) 2 only

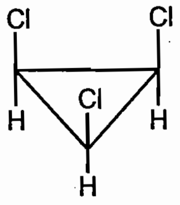
Soln.



1.



2.

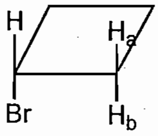


3.

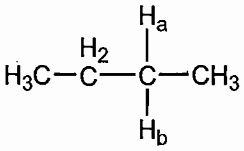
In case of (1) the methylene H's are exchangable with C_2 symmetry so, these two are homotopic while in (2) methylene protons are bisected with a plane so these two are diastereotopic

In case of (3) No methylene protons are present.
So, correct answer is (d).

10. Consider the following compounds.

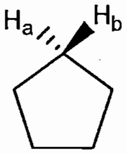


I



$H_3C-\overset{H_2}{C}-\overset{H_a}{\underset{H_b}{C}}-CH_3$

II



III

Identify H_a and H_b hydrogens in the above compounds.

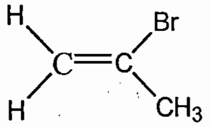
(a) diastereotopic, enantiotopic, homotopic respectively.

(b) Enantiotopic, diastereotopic, homotopic respectively.

(c) Homotopic, diastereotopic, diastereotopic respectively.

(d) diastereotopic, enantiotopic, diastereotopic respectively.

Soln. (a)

11. 

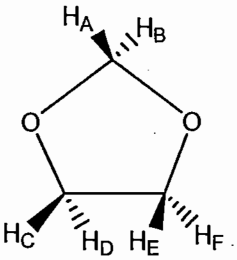
[IAS - 2006]

What are the two methylene protons in the above compound called?

(a) Homotopic protons (b) Tautomeric protons

(c) Diastereotopic protons (d) Enantiotopic protons.

Ans. (c)

12. 

Consider the following statements concerning the features of the protons of the structure given above

1. H_A and H_B are homotopic
2. H_C and H_D are enantiotopic
3. H_E and H_F are diastereotopic
4. H_C and H_E are vicinal and cis.

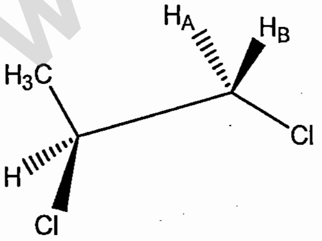
Which of these statements are correct?

(a) 1 and 2 (b) 2 and 4 (c) 1, 2 and 4 (d) 2, 3 and 4 **[IAS-2003]**

Soln. H_A and H_B are homotopic because they are exchanged with C_2-axis.
H_C and H_D are enantiotopic because they are reflected with a plane.

H_E and H_F are not diastereotopic because they reflected with a plane but not bisected.
So, the correct answer is (c).

13. In the compound **[IAS-2001]**



The two hydrogen atoms marked as the H_A and H_B are

(a) enantiotopic (b) diastereotopic

(c) homotopic (d) anomer.

Soln. (b) because these two methylene protons are adjacent with chiral centre.

CHAPTER

4

Reaction Intermediates

Reactive intermediates are believed to be transient intermediates in majority of reactions. The main types of reactive intermediates of interest to organic chemists are carbocations, carbanions, radicals, radical ions, carbenes, nitrenes, arynes etc.

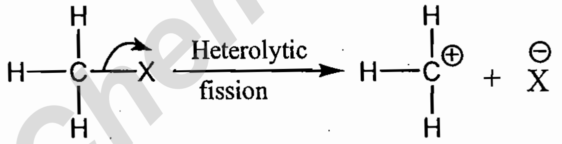
Reactive intermediates are usually short lived, very reactive and very seldom isolated under normal reaction conditions. However, their structures are established either by means of chemical trapping or spectroscopically or sometimes by isolating them at very low temperature. The shapes of these intermediates become important when considering the stereochemistry of reactions in which they play a role.

4.1 Carbocation

Carbocation has a positively-charged carbon atom which has only **six electrons** in its outer valence shell.

(A) Structure and stability of carbocations:

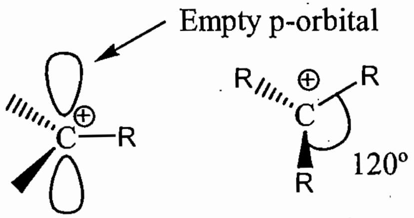
The heterolytic fission of a C-X bond in an organic molecule (X is more electronegative than carbon atom) generates the negatively charged anions (X^-) and positively charged species known as carbocations



$$H_3C{-}X \xrightarrow[\text{fission}]{\text{Heterolytic}} H_3C^{\oplus} + X^{\ominus}$$

Carbocation

The carbon atom in a typical carbocation is sp^2 hybridized. The p_z, orbital is empty and is perpendicular to the plane of the other three bonds. Thus carbocation adopts a *trigonal planar* shape.



Side View Top View

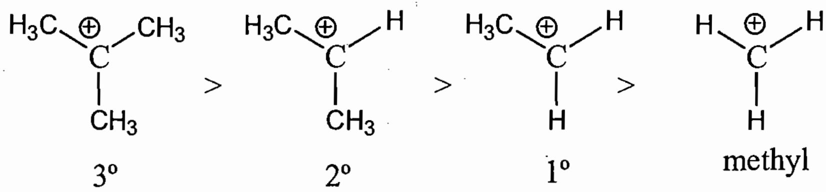
Carbocation

Planar structure of carbocation is more stable than pyramidal structure this has been shown by quantum mechanical calculations and confirmed by NMR and IR spectroscopy. That is why formation of carbocation is prohibited at bridge head position due to formation of non-planar carbocation.

Ned-Arnett measured directly carbocation stability by measuring the enthalpy of reaction for the ionization of RX process in $SbF_5/FSO_3H/SO_2ClF$ at -40 °C.

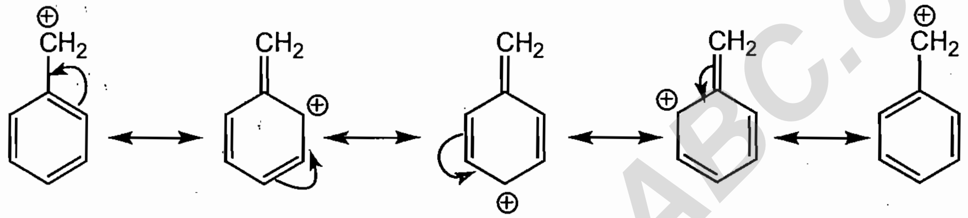
$$R{-}X \longrightarrow R^{\oplus} + X^{\ominus}$$

The stability of the carbocation increases when electron donating groups are present. The reason for the order of alkyl carbocation stability was simply as inductive stabilization of the positively charged carbon by its attached electron-releasing alkyl substituents and by hyperconjugation ("no-bond resonance"). This explains why a tertiary carbocation is more stable than a secondary carbocation which in turn is more stable than a primary carbocation.



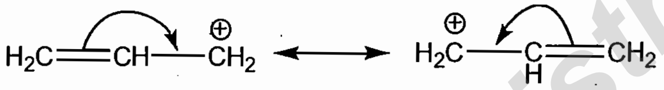
However, the presence of electron attracting groups (like nitro, carbonyl etc.) adjacent to the carbon atom bearing positive charge makes the carbocation less stable.

Resonance effects can further stabilize carbocations. By resonance the positive charge on the central carbon atom gets dispersed over other carbon atoms and this renders stability to the carbocation. The more the canonical structures for a carbocation, the more stability will be.



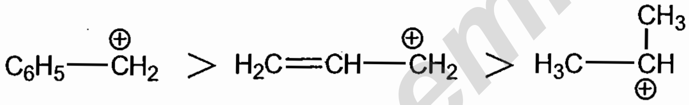
Benzyl carbocation

An allylic carbocation has two resonance structure.



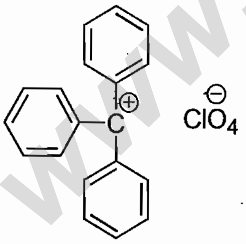
$$H_2C{=}CH{-}\overset{\oplus}{C}H_2 \longleftrightarrow H_2\overset{\oplus}{C}{-}\underset{H}{C}{=}CH_2$$

The order of stability of the benzyl, allyl and iso-propyl carbocations is:

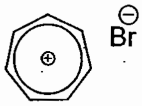


$$C_6H_5{-}\overset{\oplus}{C}H_2 > H_2C{=}CH{-}\overset{\oplus}{C}H_2 > H_3C{-}\underset{\oplus}{\overset{CH_3}{CH}}$$

In certain cases, the carbocations are so stable that their solid salts have been isolated. For example the tropylium bromide is stabilized by aromatization. The tropylium cation is planar and has 6 p electrons like benzene.



Triphenylmethyl perchlorate
(real crystalline solid)



Tropylium bromide
(yellow solid)

The order of stability of tropylium, triphenylmethyl, benzyl and allyl carbocations is:

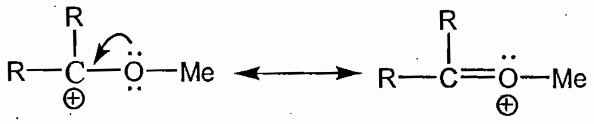
Tropylium cation $> (C_6H_5)_3\overset{\oplus}{C} > C_6H_5\overset{\oplus}{C}H_2 > H_2C{=}CH{-}\overset{\oplus}{C}H_2$

Triphenyl methyl carbocation; Benzyl carbocation; Allyl carbocation

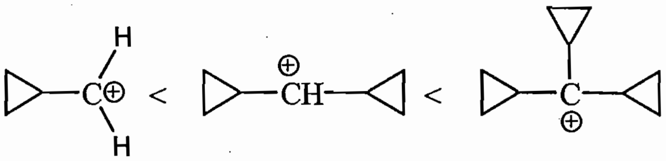
The carbocation stability order of alkyl (1°, 2° & 3°), allyl and benzyl carbocations.

$$\overset{\oplus}{CH_3} < CH_3\overset{\oplus}{CH_2} < (CH_3)_2\overset{\oplus}{CH} = H_2C{=}CH{-}\overset{\oplus}{C}H_2 < C_6H_5\overset{\oplus}{CH_2} < (CH_3)_3C^{\oplus}$$

The carbocation stability is also increased due to the presence of heteroatom having an unshared pair of electrons, e.g. oxygen, nitrogen or halogen, adjacent to the cationic center. Such carbocations are stabilized by resonance. The methoxymethyl cation is obtained as a stable solid, $MeOCH_2^+SbF_4^-$.



The stability of the cyclopropyl carbocation increases with each additional cyclopropyl group.



(B) Generation of carbocation:

(1) From alcohols :
Alcohols on treatment with concentrated acids get protonated and then may lose a molecule of water to form carbocations.

$$R{-}OH + H^{\oplus} \longrightarrow R{-}\overset{\oplus}{O}H_2 \xrightarrow{-H_2O} R^{\oplus}$$

(2) From alkyl halides:
Ionization of alkyl halides give carbocations.

$$R{-}X \xrightarrow{\text{Solvent}} R^{\oplus} + X^{\ominus} \quad (X{=}I, Br, Cl)$$

The process is accelerated by the presence of powerful ion-solvating medium, metal ions such as, Ag^+ ions or Lewis acid. In place of alkyl halides, alkyl tosylates and alkyl mesylates can also be used.
Friedel-Crafts alkylation of aromatic compounds involves the formation of a carbocation that acts as electrophile.

$$R{-}X + AlCl_3 \rightleftharpoons \left[\overset{\delta+}{R}{-}{-}X{-}{-}\overset{\delta-}{AlCl_3}\right] \rightleftharpoons \overset{\oplus}{R} + \left[X{-}AlCl_3\right]^{\ominus}$$

(3) From alkenes:

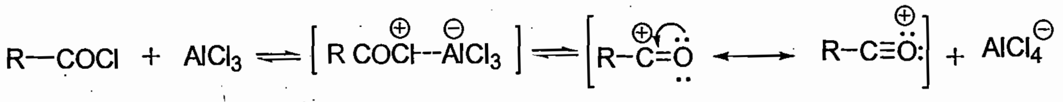
Addition of proton to alkenes or other unsaturated species give carbocations.

$$(CH_3)_2C{=}CH_2 + H{-}Br \longrightarrow \underset{3^{\circ}\text{ Carbocation}}{(CH_3)_2\overset{\oplus}{C}{-}CH_2H} \xrightarrow{\overset{\ominus}{Br}} \underset{t\text{-butyl bromide}}{(CH_3)_3CBr}$$

(4) From diazonium ions:
The alkyl diazonium ions are unstable and decompose at room temperature to give carbocations.

$$R{-}\overset{\oplus}{N}{\equiv}N \longrightarrow R^{\oplus} + N_2$$

(5) From acyl halides: The acyl halides on treatment with anhydrous aluminium chloride gives a complex, which decomposes to give acyl carbocations. In most Friedel-Crafts acylation, the electrophile appears to be an acylium ion.



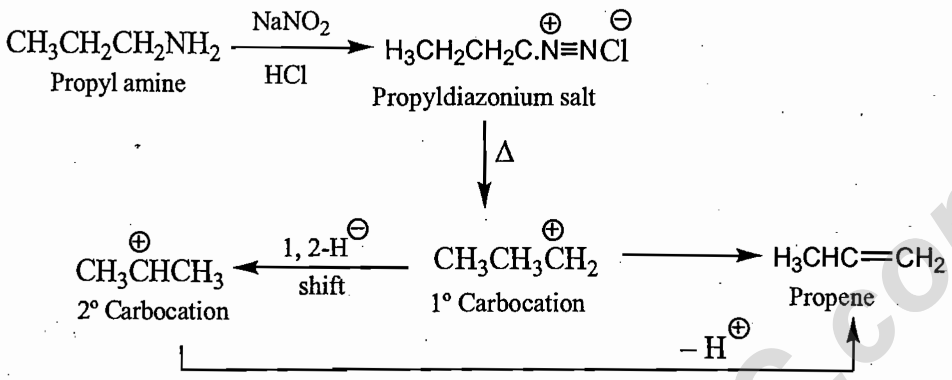
$$R{-}COCl + AlCl_3 \rightleftharpoons \left[R\,CO\overset{\oplus}{C}l{-}{-}\overset{\ominus}{A}lCl_3\right] \rightleftharpoons \left[R{-}\overset{\oplus}{C}{=}\ddot{O} \longleftrightarrow R{-}C{\equiv}\overset{\oplus}{O}{:}\right] + AlCl_4^{\ominus}$$

An acylium ion

(C) Reactions of carbocation:

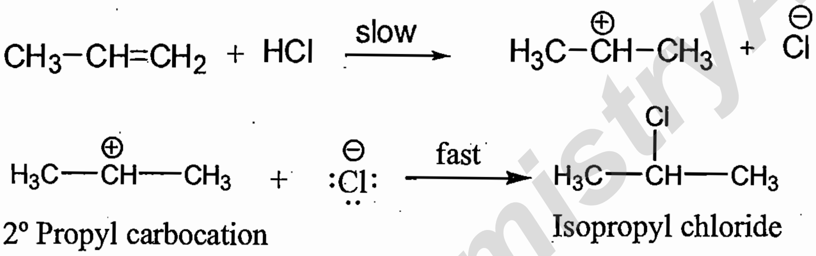
Carbocation usually undergoes elimination reactions, addition reactions, reactions with nucleophiles and rearrangements.

1. **Elimination of a proton:** A carbocation may loose a proton to form an alkene. For example, 1-propyl carbocation generated from diazonium salt may eliminate a hydrogen ion to form an alkene (propene). Alternatively, 1-propyl carbocation may rearrange to more stable secondary carbocation, which may also loose a proton to give propene.



2. **Reaction with nucleophile:**

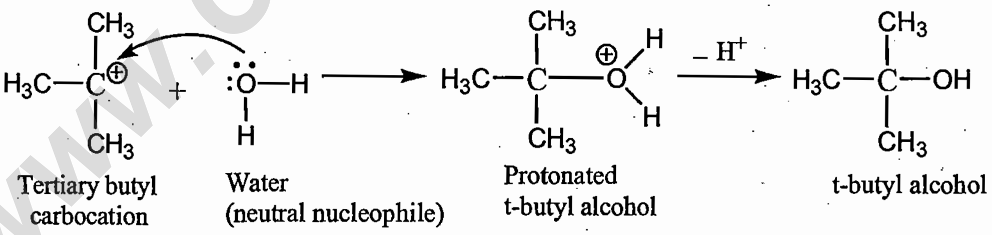
A carbocation may combine with a nucleophile to form a new bond.



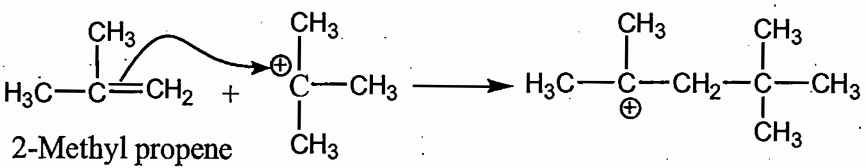
$$CH_3-CH=CH_2 + HCl \xrightarrow{slow} H_3C-\overset{\oplus}{C}H-CH_3 + \overset{\ominus}{Cl}$$

$$H_3C-\overset{\oplus}{C}H-CH_3 + :\overset{\ominus}{Cl}: \xrightarrow{fast} H_3C-\overset{Cl}{\overset{|}{C}H}-CH_3$$

The reaction of a carbocation with a neutral nucleophile such as water gives a protonated alcohol. For example, Tertiary butyl carbocation reacts with water (neutral nucleophile) to give protonated *t*-butyl alcohol, which eliminates a proton to give *t*-butyl alcohol.

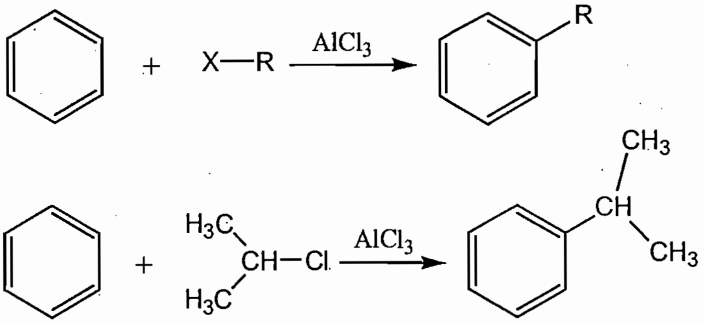


3. **Reaction with alkenes and aromatic systems:** A carbocation may react with an alkene to produce another carbocation.

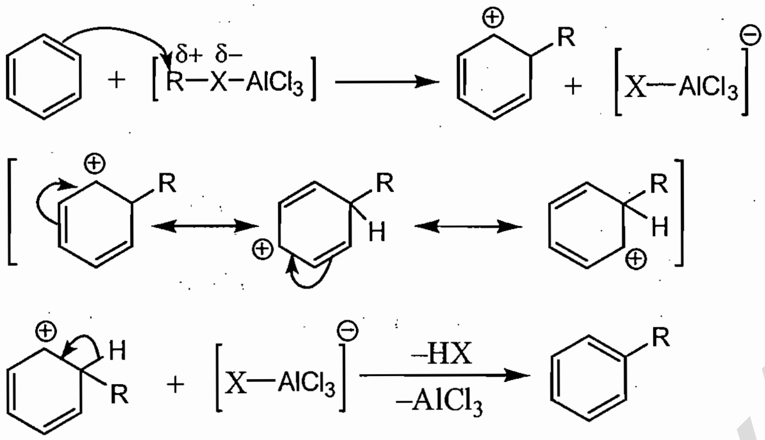


The alkyl carbocation formed from alkene, alcohols or alkyl halides and act as an electrophile in an Friedel-Crafts alkylation reaction.

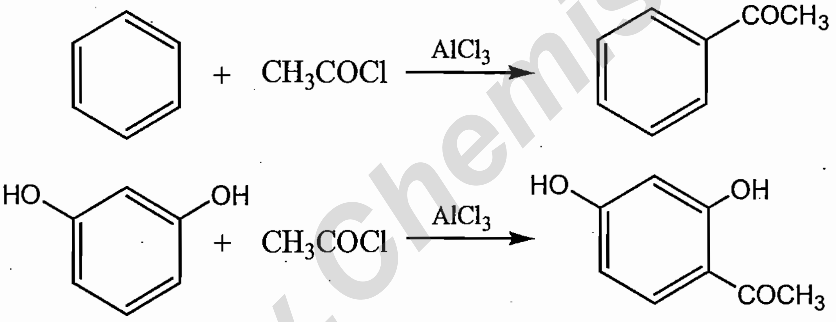
e.g.



***Mechanism*:**

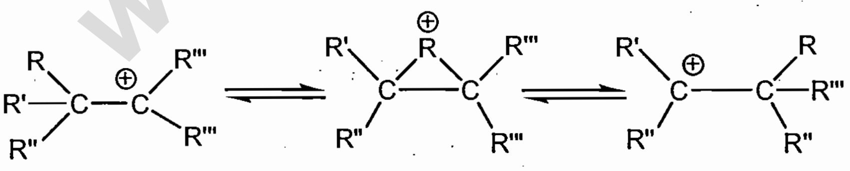


In a similar manner ($R-C\equiv\overset{\oplus}{O}:$) acyl carbocations formed from acyl halides or acid anhydrides act as electrophile in Friedel Crafts acylation.



4. **Rearrangement of carbocation:**

Molecular rearrangements involving carbocations as reactive intermediates are very common in organic chemistry. The 1, 2-shift of a migrants, to an electron-deficient carbon atom is the most widespread.



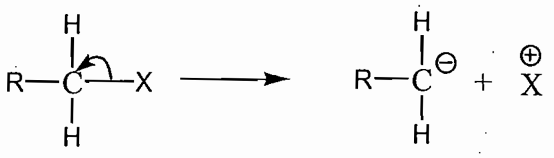
The 1, 2-shift of either H or alkyl occur in cases where a more stable carbocation can results.

4.2 Carbanion

A carbanion can be considered as a species containing a trivalent negatively charged carbon.

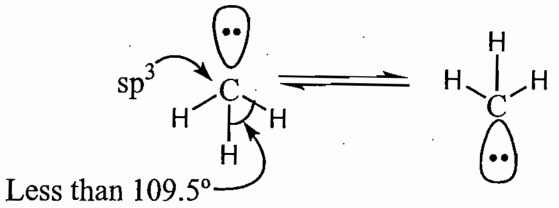
(A) Structure and stability of carbanion:

Carbanion are considered to be derived by the heterolytic fission of the C-X bond in an organic molecule, in which carbon is more electronegative than X.



(C is more electronegative than X) Carbanion

The shape of simple carbanions is determined on the basis of a number of experiments is found to be pyramidal, similar to that of amines. These species invert rapidly at room temperature, passing through a higher energy planar form in which the electron pair occupies a *p*-orbital.



However, when the carbanion is stabilized by delocalization, it assumes sp^2 hybridization for effective resonance.

In practice any organic compound having a C-H bond can donate a proton to a suitable base, the species obtained as a result is the carbanion.

$$R_3C{-}H + B: \rightleftharpoons R_3\overset{\ominus}{C} + \overset{\oplus}{BH}$$

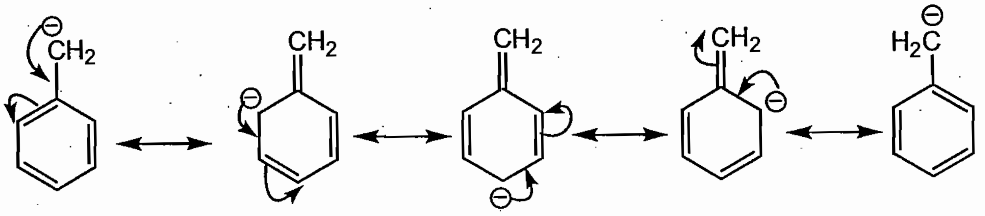
A carbanion possesses an unshared pair of electrons and is therefore a base. Thus, the carbanion may accept a proton to give its conjugate acid. In fact, the stability of a carbanion depends on the strength of the conjugate acid. The weaker is the acid, the greater is the basic strength and therefore lower will be the stability of the carbanion. Following table (table 2.1) shows the conjugate base obtained from the corresponding acid along with p*Ka* values.

Table: Relative stability of the carbanions:

Acid	Base	pKa
RCH_2CN	$R\overset{\ominus}{C}HCN$	25
$HC\equiv CH$	$HC\equiv C^{\ominus}$	25
Ar_3CH	$Ar^3C^{\ominus}$	31.5
Ar_2CH_2	$Ar_2CH^{\ominus}$	33.5
$PhCH_3$	$PhCH_2^{\ominus}$	38
$H_2C=CH_2$	$H_2C=CH^{\ominus}$	44
Cyclopropane		46
$(CH_3)_2CH_2$	$(CH_3)_2CH^{\ominus}$	51

The carbanion being electron rich are very reactive intermediates and are readily attacked by electrophiles (electrons-deficient reagents). The stability of carbanion is increased if an electron-attracting group (like C≡N or carbonyl) is present in the molecule. However, the stability is decreased if an electron-releasing group is present in the molecule. Thus, 3°< 2°< 1°is the order in solution due to destabilization of e-donating alkyl groups.

Like carbocations, the carbanions are also stabilized by resonance. Thus, benzyl carbanion is more stable than ethyl carbanion. The stabilization by resonance is due to the delocalization of the negative charge, which is distributed over other carbon atoms. The canonical forms of benzyl carbanion are given below.



Canonical structures of benzyl carbanion

The stability of the carbanion is found to be in the order:

Benzyl > vinyl > phenyl > cyclopropyl > ethyl > n-propyl > iso-butyl > neopentyl > cyclobutyl > cyclopentyl

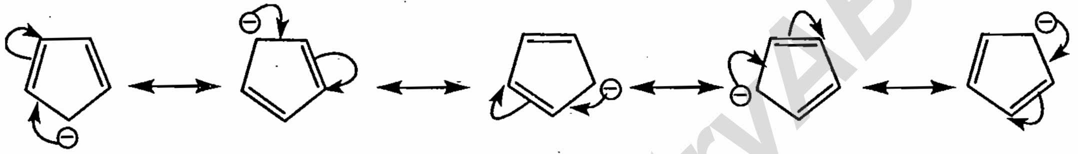
The stability of the carbanion when a functional group (X) is present in the a-position, is of the order:

$NO_2 > RCO > COOR > SO_2 > CN \sim CONH_2 > \text{halogens} > H > R$

Carbanion increase in stability with an increase in the amount of 's' character at carbanionic carbon. Thus the order of stability is:

$RC{\equiv}\overset{\ominus}{C} > R_2C{=}\overset{\ominus}{C}H \approx Ar^- > R_3C{-}\overset{\ominus}{C}H_2$

If the unshared pair of a carbanion is involved in ring current and system becomes aromatic, thus, carbanions became greatly stabilized.

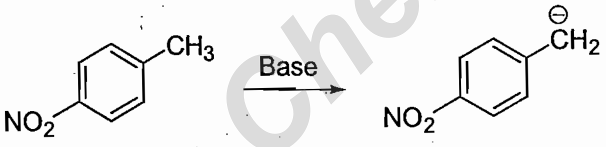


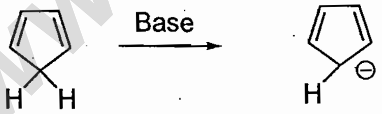
(B) Generation of carbanions:

Following methods are generally used for their generation.

(1) Abstraction of H by a base:

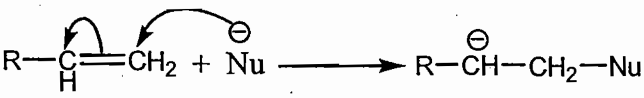
An appropriate organic substrate having a C-H bond on treatment with a suitable base results in the abstraction of hydrogen to generate a carbanion.





(2) From unsaturated compounds:

Addition of a nucleophile to C=C double bond generates a carbanion.



$R{-}\underset{H}{C}{=}CH_2 + \overset{\ominus}{Nu} \longrightarrow R{-}\overset{\ominus}{C}H{-}CH_2{-}Nu$

(3) From alkyl halides:

Reduction of carbon-halogen bond by metal yields carbanion. Reaction of alkyl halide with Mg turning in presence of anhydrous ether as solvent generates Grignard reagent. The alkyl group in Grignard reagent, behaves like a carbanion.

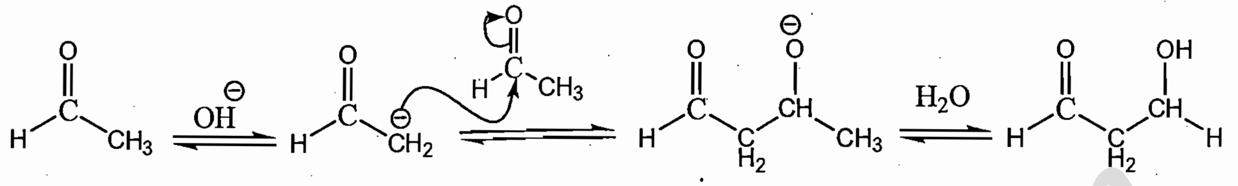
$R{-}X + Mg \xrightarrow{\text{ether}} RMgX$

(C) Reactions of carbanions:

Carbanions take part in the usual types of reactions, *viz.*, addition, elimination, displacement, rearrangement etc.

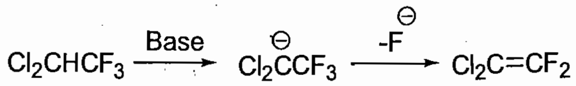
(1) Addition reactions:

The carbanions being electron rich behave like nucleophiles. These add to the carbonyl group for example aldol condensation, claisen condensation, Perkin reaction etc.



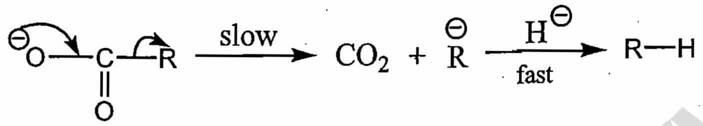
(2) Elimination reactions:

Carbanions are involved as intermediates in E_{1CB} elimination reactions.

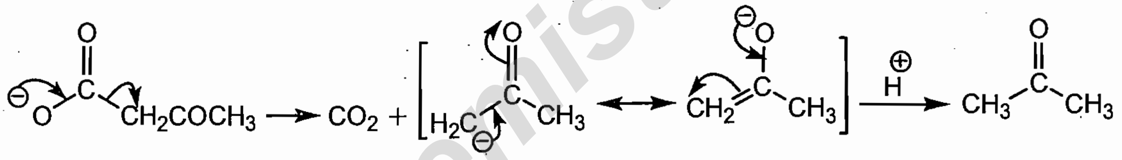


$$Cl_2CHCF_3 \xrightarrow{\text{Base}} Cl_2\overset{\ominus}{C}CF_3 \xrightarrow{-\overset{\ominus}{F}} Cl_2C{=}CF_2$$

In decarboxylation, the loss of CO_2 from carboxylate anion is believed to involve a carbanion intermediate, which acquires a proton from solvent or other sources.

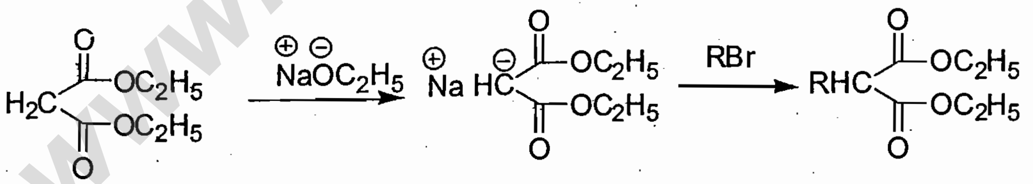


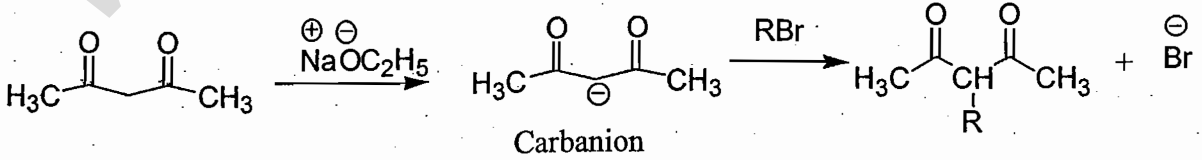
The anion of β-keto acids can undergo facile decarboxylation.



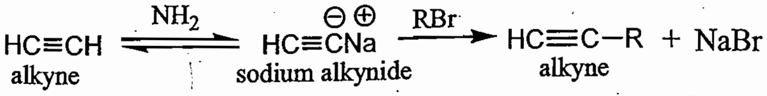
(3) Displacement reactions:

The carbanions are involved in a number of displacement reactions. The synthetic applications of β-ketoesters (e.g. diethyl malonate) and 1,3-diketones (e.g. acetylacetone) are due to the formation of the reactive intermediate, carbanion.





The alkynide carbanion undergoes alkylation in a similar manner.



$$\underset{\text{alkyne}}{HC{\equiv}CH} \underset{}{\overset{NH_2}{\rightleftharpoons}} \underset{\text{sodium alkynide}}{HC{\equiv}\overset{\ominus\oplus}{CNa}} \xrightarrow{RBr} \underset{\text{alkyne}}{HC{\equiv}C{-}R} + NaBr$$

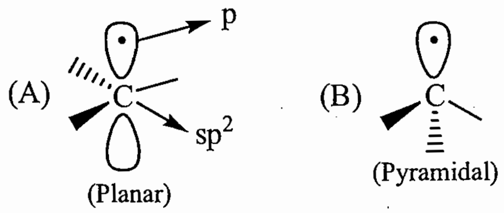
4.3 Free Radicals

A radical (often, but unnecessarily called a free radical) is an atom or group of atoms that have one or more unpaired electrons. Thus, carbon radicals have only seven valence electrons. They readily react with O_2, thus their reactions must be carried out under an inert atmosphere.

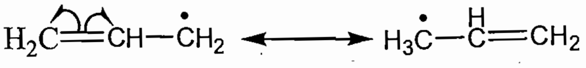
A radical is paramagnetic and so can be observed by electron spin resonance (e.s.r) spectroscopy. Radicals are often uncharged (neutral) but radical cations and radical anions also exist.

(A) Structure and stability of free radicals:

Radicals are planar in configuration but the energy difference between pyramidal and planar forms very small.

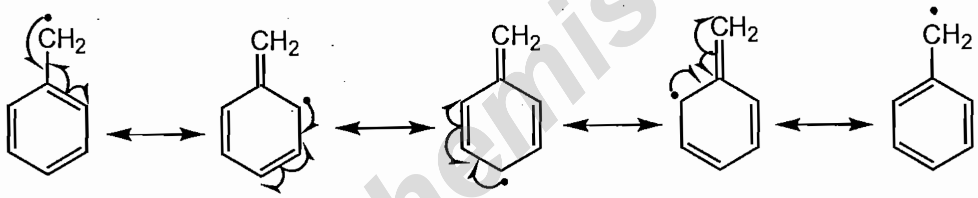


The stability of radical depends upon (i) the nature of the atom that is the radical centre; (ii) the electronic properties of the groups attached to the radical. As in the case of carbocations, the order of stability of free radicals is: tertiary > secondary > primary methyl. This can be explained on the basis of hyperconjugation as in the case of carbocation. The stability of the free radicals also increases by resonance possibilities. Thus, allylic and benzylic free radicals are more stable and less reactive than the simple alkyl radicals. This is due to the delocalization of the unpaired electron over the p orbital system in each case.

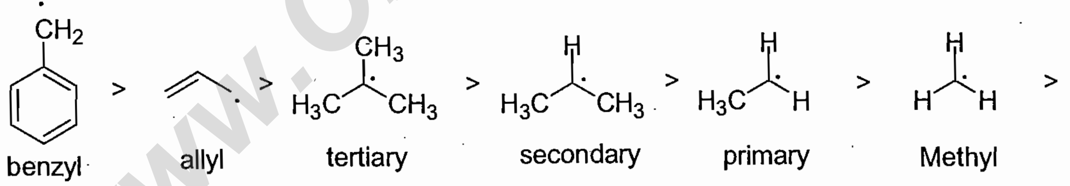


$$H_2C{=}CH{-}\dot{C}H_2 \longleftrightarrow H_3C{-}\overset{\bullet\ H}{C}{=}CH_2$$

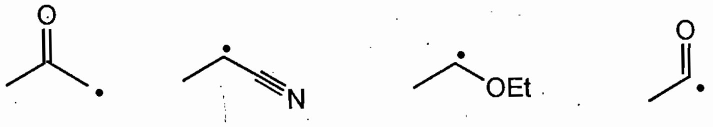
Canonical structure of allyl radical.



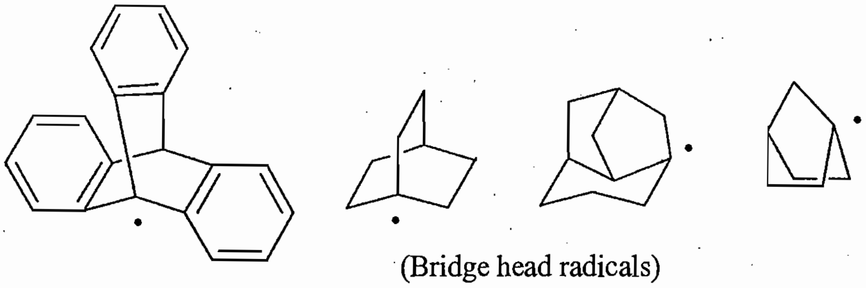
The decreasing order of stability of few radicals is as follows:



- The stability of a radical increases as the extent of potential delocalization increases. Therefore, $Ph_2CH^\bullet$ is more stable than $PhCH_2^\bullet$ and $Ph_3C^\bullet$ is a reasonably stable radical.
- Adjacent functional groups, electron-withdrawing or electron-donating, both seem to stabilize radicals.



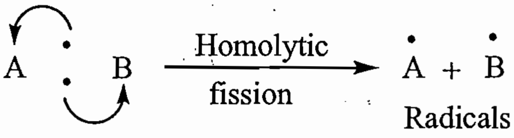
Certain radicals have rigid molecular structures with fixed bond angles and dihedral angles. These are known as **bridge head radicals** and have pyramidal structure. This has been supported on the basis of physical and chemical evidences.



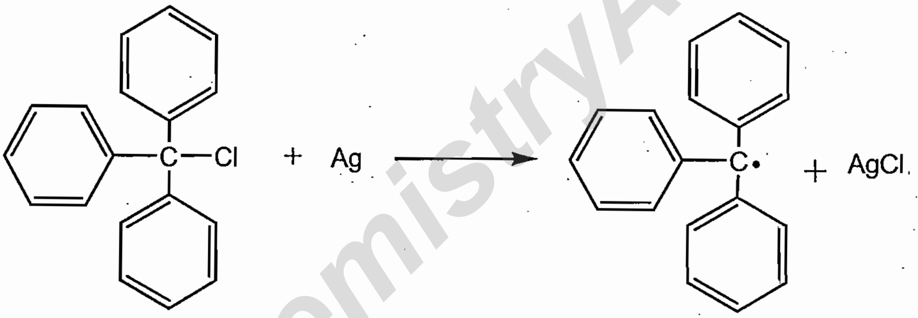
(Bridge head radicals)

(B) Generation of free radicals:

The homolytic cleavage of a covalent bond generates a pair of free radicals. Energy in the form of ultraviolet-visible light, heat, or some other form is needed to break a covalent bond.



Example:



Triphenylmethyl chloride

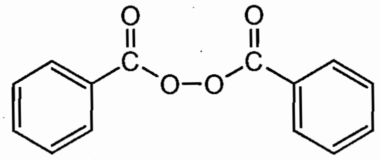
Triphenylmethyl radical

The following table lists standard bond energies (D) for the C–C, C–O and C–H bonds commonly found in organic compounds, together with bond energies for some weaker bonds that have been found useful for generating radicals. Approximate homolysis temperatures at which half the bonds are cleaved in one hour are also given.

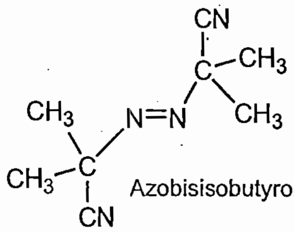
Bond	D-Kcal/mole	T^0C	Bond	D-Kcal/mole	T^0C	Bond	D-Kcal/mole	T^0C
C-C	85	670	O-O	34	160	C-Cl	49	280
C-H	99	850	N-N	39	230	C-I	51	350
C-O	84	680	S-S	55	440	C-Br	67	480

Table -4.1: Sumerizes some standard bond energies and approximate homolysis temprature

Though the dissociation energies of C-C, C-X, C-O and C-N bonds are quite high, the very weak O–O bonds of peroxides are cleaved at relatively low temperatures. Organic azo compounds (R–N=N–R) are also easily decomposed to alkyl radicals and nitrogen. The thermodynamic stability of nitrogen provides an overall driving force for this decomposition. Thus homolysis of several weaker bonds initiate the carbon radical reactions and then subsequent transfer of radical to carbon occurs. Typical initiator are H_2O_2, dibenzoyl peroxide and azobisisobutyronitrile (AIBN)



Benzoyl peroxide

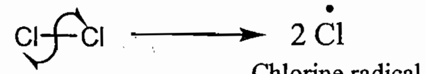


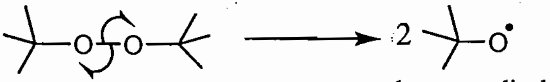
Azobisisobutyronitrile (AIBN)

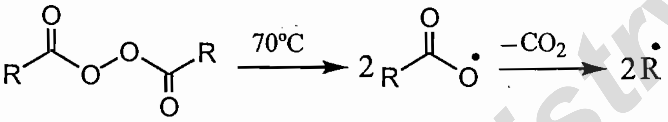
(B) Generation of free radicals also takes place by:

1. **Thermolysis:**

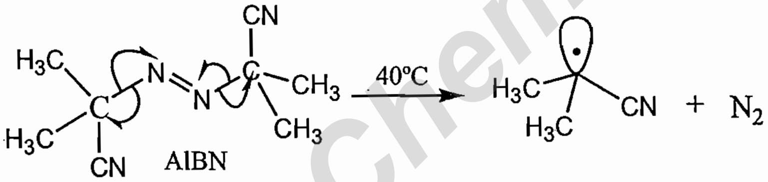
The radicals are formed by heating the appropriate substrate at suitable temperature. For example, on heating, chlorine forms chlorine radicals. Peroxides form alkoxy radicals. Peresters fragment to acyl radicals, which lose carbon dioxide to give alkyl radicals. Azo compounds evolves nitrogen to give a pair of alkyl radicals. The cleavage of bond can be achieved by heating in non-polar solvents or the vapors phase.







R=Ph(benzoyl peroxide)
R=$(CH_3)_3C$ (di-t-butyl peroxide)



2. **Photolysis:**

Compounds having absorption bands in the visible or near ultraviolet spectrum may be electronically excited to such a degree that weak covalent bonds undergo homolysis.

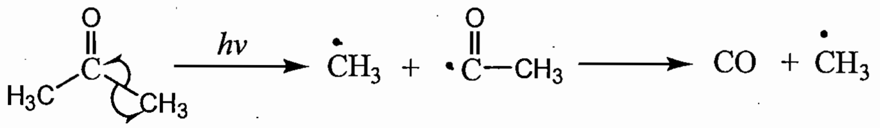
Bond dissociation energy

$Cl-Cl \xrightarrow{hv} \dot{Cl} + \dot{Cl}$ 58 K cal/mol

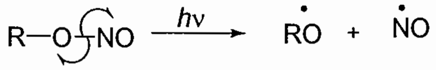
$Br-Br \xrightarrow{hv} \dot{Br} + \dot{Br}$ 46 K cal/mol

$I-I \xrightarrow{hv} \dot{I} + \dot{I}$ 36 K cal/mol

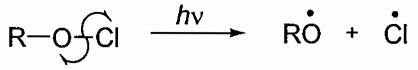
Acetone in vapour phase is decomposed by light having a wave length of about 320 nm (3200 Å). In this reaction two molecules of methyl free radicals are generated.



Certain other species that undergo easily photolysis are alkyl nitrites and alkyl hypochlorites. Both these molecules generate alkoxy radicals.



Alkyl nitrite



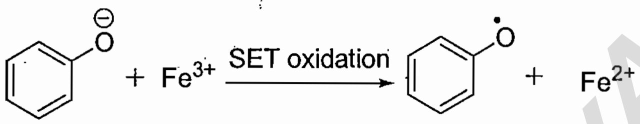
Alkyl hypochlorite

(1) Redox reactions:

An electron can be removed from an anion, and the process is known as oxidation process. In redox reactions there is one-electron transfer in generating the free radicals. The process is known as **single electron transfer (SET) reduction.** For example, the phenoxide ion is oxidised by Fe^{3+} to give the phenyl oxygen radical and the Fe^{3+} is co-reduced to Fe^{2+}.

$$\overset{\ominus}{X} \longrightarrow \overset{\bullet}{X} + e$$

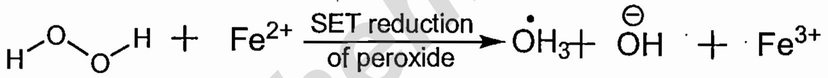
(a)



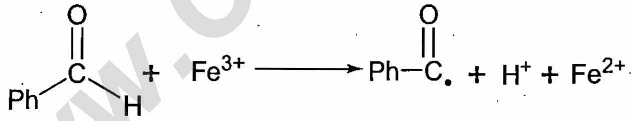
$$\overset{\oplus}{X} + e \longrightarrow \overset{\bullet}{X}$$

The source of single electron transfer is the metal ion (e.g, Cu^+, Fe^{2+} etc).

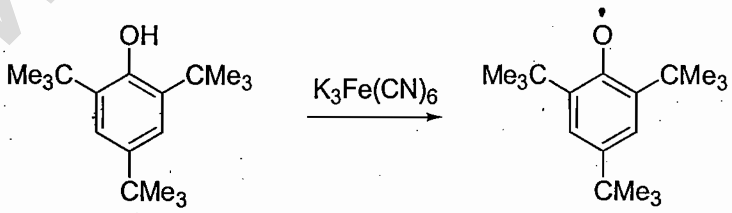
The Fe^{2+} ion can reduce hydrogen peroxide to hydroxyl radical and hydroxide ion. The mixture of H_2O_2 and Fe^{2+} is known as **Fenton's reagent**. The effective oxidizing agent is the hydroxyl radical, $HO^{\bullet}$.



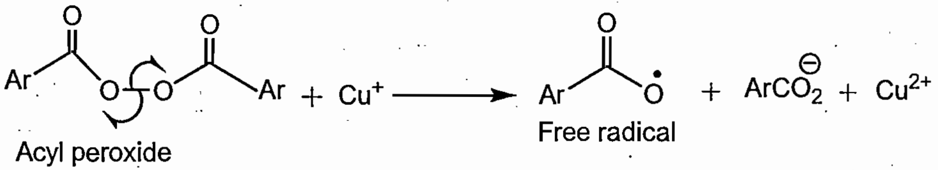
(b) The autoxidation of benzaldehyde is also catalysed by metal ions which are capable of single electron transfer.



(c) Stable phenoxy radical can also be generated by one electron oxidation with $K_3Fe(CN)_6$.



(d) Cu^+ ions are used for the decomposition of acyl peroxide.



This is a convenient method for the generation of ArCOO$^\bullet$ radicals especially because in thermolysis, the ArCOO$^\bullet$ radicals further decomposes to Ar$^\bullet$ + CO_2.

(f) Cu^+ also finds application in **Sandmeyer reaction,** involving decomposition of diazonium salts. In this reaction the free radical, Ar$^\bullet$, is formed as an intermediate.

$$ArN_2 + \overset{\ominus}{Cl} \xrightarrow{CuCl} ArCl + N_2$$

The dimerization of carbanions with iodine also takes place *via* a free radical.

$$2(CH_3CO)_2\overset{\ominus}{C}H \xrightarrow{I_2} 2(CH_3CO)_2\overset{\bullet}{C}H \longrightarrow (CH_3CO)_2CH{-}CH(COCH_3)_2$$

4. **Kolbe reaction** for the synthesis of alkanes also involves the radicals as intermediate.

Examples:

(i) $2\,RCO\overset{\ominus}{O} \xrightarrow{e^-} 2\,RCO\overset{\bullet}{O} \xrightarrow{-CO_2} 2\overset{\bullet}{R} \longrightarrow R{-}R$

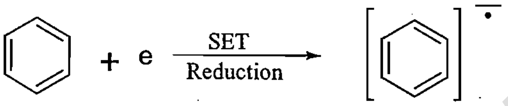
(ii) $CH_3(CH_2)_4\,CO\overset{\ominus}{O} \xrightarrow{-e} CH_3(CH_2)_4\,CO\overset{\bullet}{O} \xrightarrow{-CO_2} CH_3(CH_2)_3\overset{\bullet}{C}H_2$

(iii) $2\,CH_3(CH_2)_3\overset{\bullet}{C}H_2 \longrightarrow CH_3(CH_2)_8CH_3$

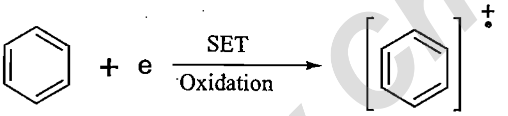
Radicals are also formed as intermediates in pinacol reduction with sodium or magnesium and in acylion condensation.

(C) Classification of radical:

A **radical ion** is a free radical species that carries a negative charge or radical positive charge, radical cations. When a neutral, spin-paired species gains a single electron it becomes both a radical and an anion, a **radical anion**. Likewise, when a neutral, spin-paired species loses an electron it becomes a **radical cation**. Radical anions and radical cations are dual classified as both radicals and lewis acid / base species.



Benzene radical anion



Benzene radical anion

Radical cations and radical anions are known in the gas phase. They are routinely generated and studied in the complementary techniques of mass spectrometry and negative ion mass spectrometry.

(a) Radical anion:

Many aromatic compounds can undergo one-electron reduction by alkali metals (such as Na, Li etc.). For example the reaction of naphthalene with sodium in an aprotic solvent yields the naphthalene **radical anion** - sodium ion salt. In the Birch reduction radical anion is protonated in the presence of a proton source. For example, anthracene radical anion forms mainly (but not exclusively) 9,10-dihydroanthracene.

(b) Radical cation:

Cationic radicals are much less stable and noticed prominently in mass spectroscopy. When a molecule in gas phase is subjected to electron ionization, one electron is abstracted by an electron in the electron beam to create a **radical cation** $M^{+\bullet}$. This species represents the molecular ion or parent ion, which on fragmentation gives a complex mixture of ions and uncharged radical species. For example the *methanol* radical cation fragments into a *methyl* cation CH_3^+ and a *hydroxyl* radical. Secondary species are generated from *proton* gain (M+1) and proton loss (M-1).

(D) Reactions of radical:

Radicals are very reactive reaction intermediates and their half-life period is very short. Some of the reactions of radicals are given below.

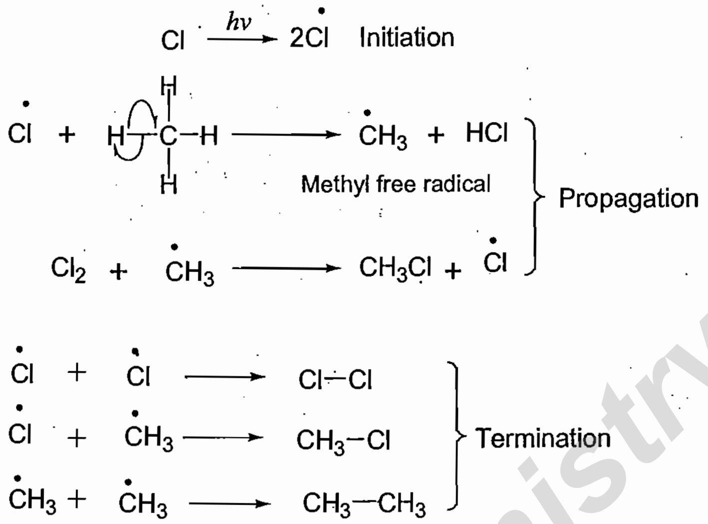
(1) Substitution Reactions:

***Halogenation of alkane*:**

The reaction of methane with chlorine in presence of UV light gives a mixture of methyl chloride, methylene chloride, chloroform and carbon tetrachloride. When excess of chlorine is used and by prolonging time of the reaction, the final product is predominantly carbon tetrachloride.

$$CH_3Cl + Cl_2 \xrightarrow{\text{UV light}} CH_2Cl_2 + CHCl_3 + CCl_4$$

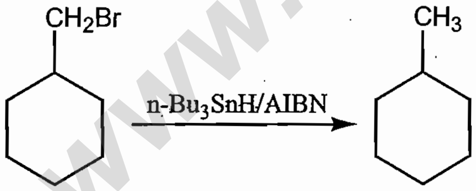
The free radical halogenation of alkanes take place in three steps, i.e., initiation, propagation and termination.



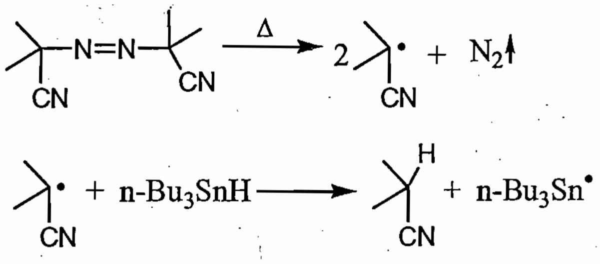
(2) Radical defunctionalization reactions:

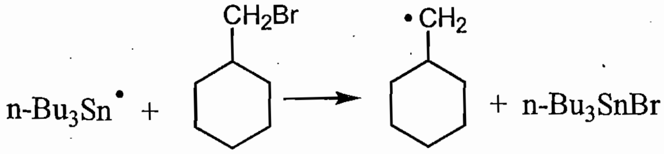
***Dehalogenation*:**

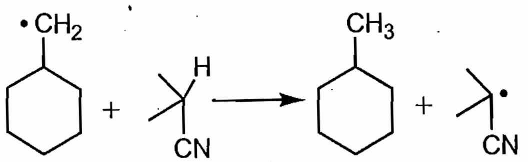
Dehalogenation of haloalkanes (R-X) is carried out often with trialkyltinhydrides in presence of AIBN. The reactivity of R-X is: R-I > R-Br > R-Cl, (R-F being inert); tertiary > secondary > primary > aryl or vinyl.



***Mechansim*:**







4.4 Carbene

Carbenes are uncharged, electron deficient molecular species that contain a divalent carbon atom surrounded by a sextet of electrons . Though non-bonding electron pair on the carbon atom gives carbenes nucleophilic character. But as a rule, the electrophilic character dominates carbene reactivity.

The parent species, $:CH_2$ is known as methylene. $:CCl_2$ is known as dichlorocarbene. However, it can also be called dichloromethylene.

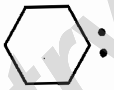
$:CH_2$ Methylene

$:CCl_2$ Dichlorocarbene or dichloromethylene

Names for acyclic and cyclic hydrocarbons containing one or more divalent carbon atoms are derived from the name of the corresponding carbon chain using the suffix -ylidene.

$H_2C{=}C:$ Ethenylidene

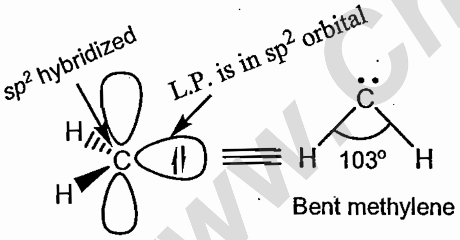
$CH_2{=}CHCH:$ Prop-2-en-1-ylidene



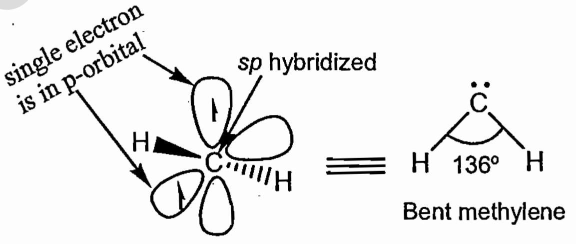
Cyclohexylidene

(A) Structure and stability of carbene:

When two nonbonding electrons are spin-paired then carbene is in ***singlet state*** but if they are unpaired then carbene is in ***triplet state***. There is no magnetic moment for singlet state. On the other hand triplet state has magnetic moment. The substituents affect the ground state multiplicity.

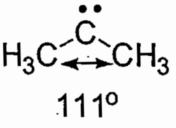


Singlet state of carbene

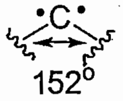


Triplet state of carbene

Thus singlet carbene is carbocation-like in nature with trigonal planar geometry. Since the triplet carbene is a diradical, it has been investigated by E.P.R or E.S.R specroscopy measurements. The results show that the triplet carbene is a bent molecule with an angle of about 136°. However, e.s.r. measurements can not be made with singlet carbene. On the basis of electronic spectra of $:CH_2$ formed in the flash photolysis of diazomethane, it was found that the singlet carbene is also a bent molecule with an angle of about 103°. Singlet $:CCl_2$ and $:CBr_2$ have also been found to be bent molecules with angles of 100° and 104°, respectively.

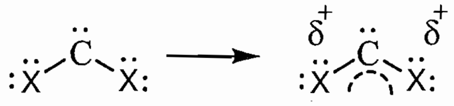


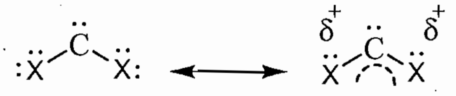
Bent Singlet



Triplet

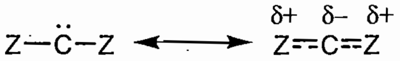
When steric bulkness increases the bond angle increases thus triplet is favored.





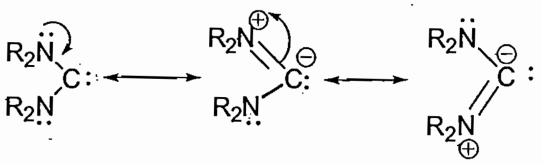
Dimethoxy carbene or dihalo carbene

X: =R (–F, –Cl, –Br, –I, –NR$_2$, PR$_2$, –OR, –SR


$Z-\ddot{C}-Z \longleftrightarrow \overset{\delta+}{Z}=\overset{\delta-}{C}=\overset{\delta+}{Z}$ Linear Singlet Carbene

Z= –R(–COR, –CN, CF$_3$, –BR$_2$, –SiR$_3$)

Though several carbenes were generated by Staudinger reaction by the decomposition of diazo compounds and Ketones. Carbenes in which the carbene carbon is attached to two atoms, each bearing a lone pair of electrons, are more stable due to resonance.



The triplet carbene where substituents R$_1$ and R$_2$ are not electron donor groups. In 1995 Tomioka et al synthesized stable triplet carbene by photolysis of diazo compound.

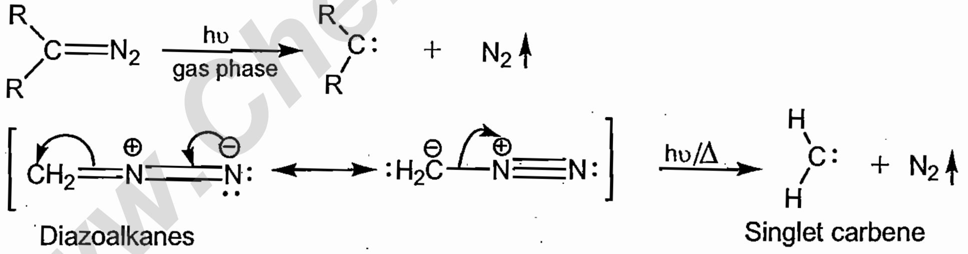
(B) Generation of carbenes:

Depending on the mode of generation, a carbene may be initially formed in either the singlet or triplet state, irrespective of its stability. Following methods are used for the generation of carbenes.

1. **From aliphatic diazo compounds:**

Aliphatic diazo compounds can be decomposed either photolytically, thermally or metal ion catalysis to generate carbenes.

(a)



(b) $RCOCHN_2 \longrightarrow RCO\ddot{C}H + N_2\uparrow$

Acyl diazo compound → Acyl carbene

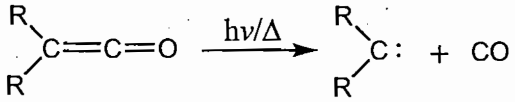
(c) $N_2CHCOOC_2H_5 \longrightarrow :CHCOOC_2H_5 + N_2\uparrow$

Diazoacetic ester → Carbethoxy carbene

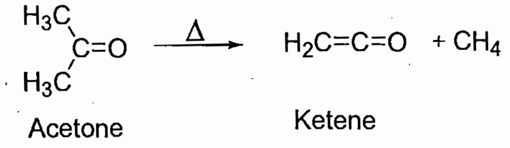
(d) $R_2C=N-\overset{\ominus}{N}SO_3Ar \xrightarrow{h\nu/\Delta} R_2C: + N_2 + Ar\overset{\ominus}{SO_2}$

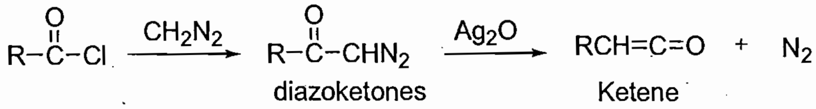
Salts of sulfonyl hydrazones

2. **From ketenes:** Ketenes can be decomposed thermally or photolytically to generate carbenes.



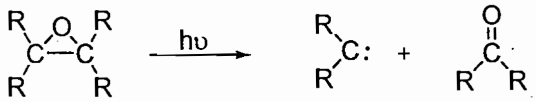
The starting ketene can be obtained by pyrolysis of acetone or from diazoketones.



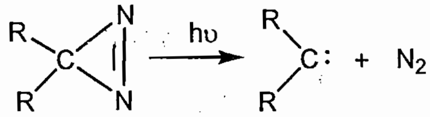


$$R{-}\overset{\overset{O}{\|}}{C}{-}Cl \xrightarrow{CH_2N_2} R{-}\overset{\overset{O}{\|}}{C}{-}CHN_2 \xrightarrow{Ag_2O} RCH{=}C{=}O + N_2$$

3. **From epoxides:** Photolytic decomposition of epoxides generate carbenes.



4. **From diazirines:** Decomposition of diazirines generate carbenes.

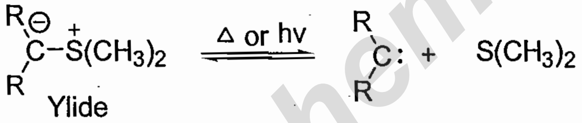


5. **From alkyl halides:** This method is commonly used for generation of chlorocarbenes. Thus, loss of a proton from chloroform by a base followed by expulsion of chloride ion generates dichlorocarbene.

$$CHCl_3 \xrightarrow{BuLi} \overset{\ominus}{C}Cl_3 \longrightarrow :CCl_2 + Cl^{\ominus}$$

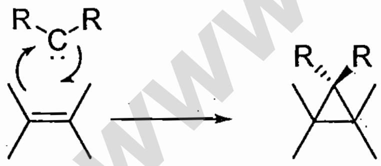
6. **From ylides:**

Thermal or photolytic decomposition of ylides generate carbenes.



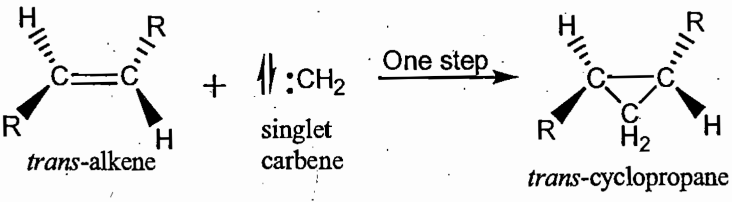
(C) Reactions of carbene: Carbenes are highly reactive and undergo C–H, O-H or N–H insertion, addition to C=C and form ylides.

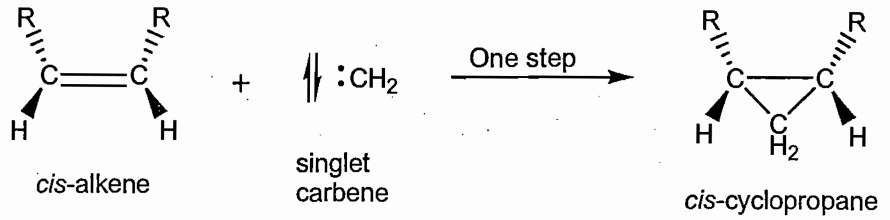
1. **Cycloaddition :** Carbenes add on to an olefinic double bond giving a cyclopropane derivative.



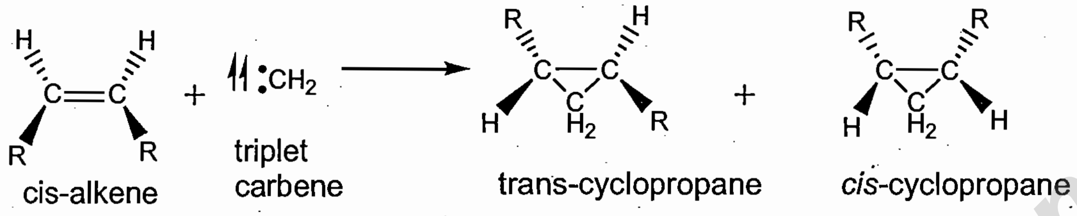
Singlet carbenes add to C=C bonds in a one-step, stereospecific manner. Triplet carbenes add to C=C bonds in a two-step, non-stereospecific manner.

Thus, *cis*-alkene reacts with singlet carbene to give *cis*-cyclopropane and *trans*-alkene gives *trans*-cyclopropane.

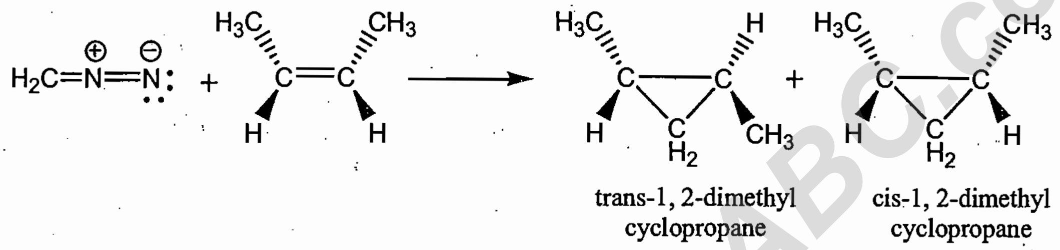




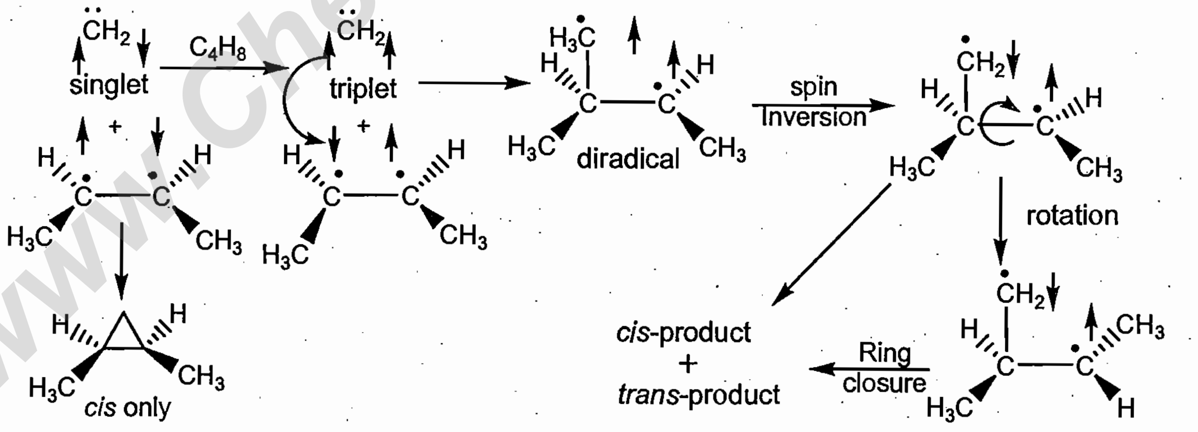
Howerver, triplet carbene reacts with cis-alkene or trans alkene to give mixture of *cis* and *trans*- cyclopropanes.



Example:

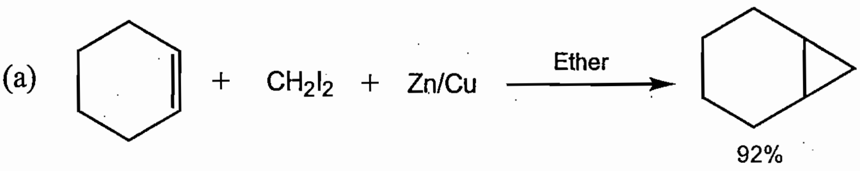


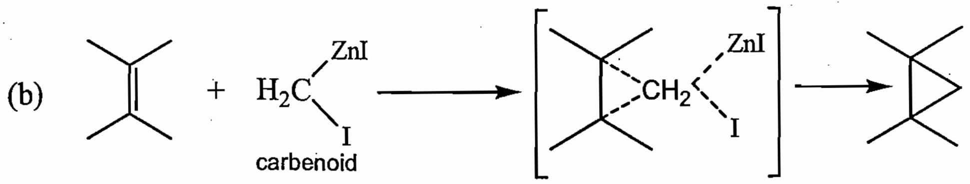
The stereochemistry of these cycloadditions is so specific that **Skell** used it as a diagnostic test for distinguishing between singlet and triplet carbenes. According to skell, the addition of singlet carbene to an olefin occurs in a concerted manner and therefore is stereospecific. However, in case of triplet carbene, both the unpaired electrons can not form a new covalent bond because of their parallel spins. Therefore, in this case the reaction will take place in two steps. In the first step a triplet diradical is formed, which undergoes spin inversion and then ring closure. For this the radical has to wait for appropriate type of collision. During this time, there is free rotation, and a mixture of *cis* and *trans*-cyclopropane is obtained.



In the above cycloaddition reactions, carbene is generated *in situ*. A more convenient way is to use **Simmons-Smith reagent** which transfers methylene from methylene iodide and zinc-copper couple to a C=C double bond. In the above reaction free carbene is not generated. The intermediate is believed to be ICH_2ZnI, which behaves as an electrophile known as **carbenoid**.

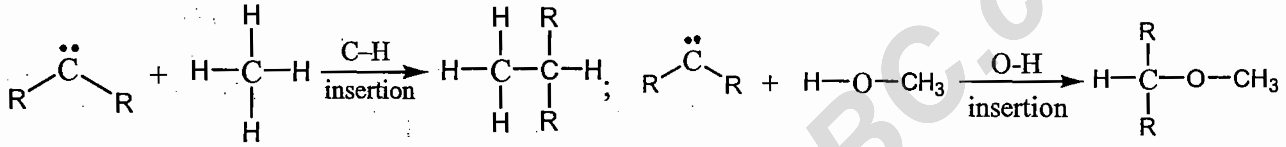
Examples:



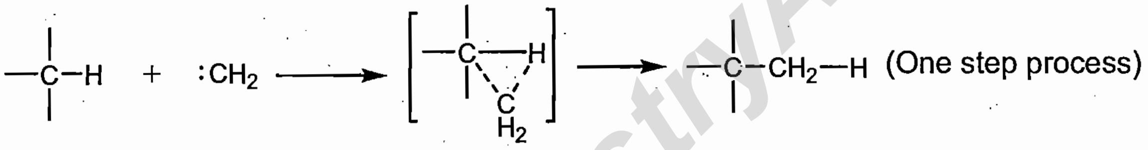


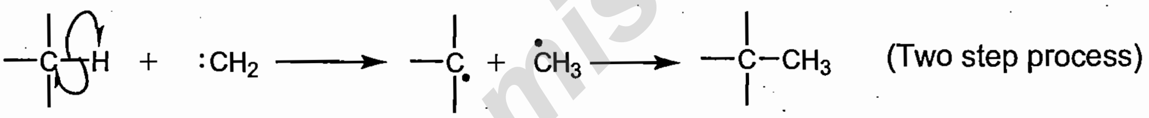
Instead of expensive methylene iodide, comparatively cheaper dibromomethane with zinc dust and cuprous chloride can be used to give better yield of the adduct.

2. **Insertion reactions:** Carbenes can insert into a C-H single bond as follows:

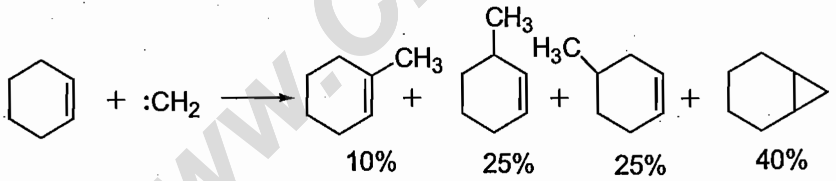


Mechanism:





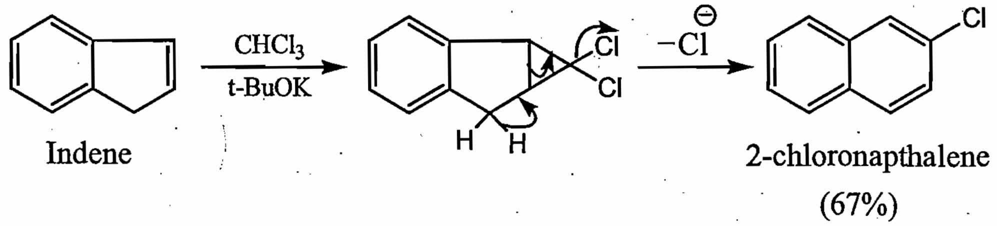
The reaction of alkenes with carbene gives cyclopropane, products in which methylene is inserted into C–H single bond are also obtained.



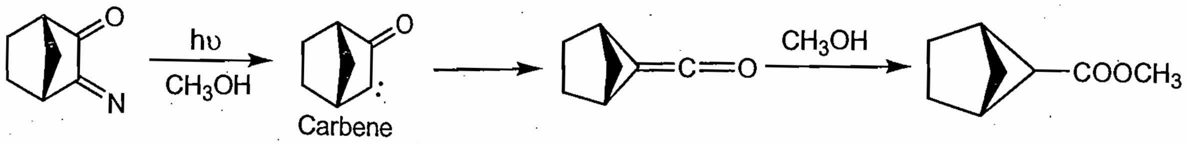
Singlet carbenes insert into alkyl C–H bonds randomly, with retention of configuration. Triplet carbenes insert into alkyl C–H bond selectively, but not stereospecifically.

3. **Ring expansion:**

In certain substrates, addition of carbene involves ring expansion. Thus, the reaction of indene with dichlorocarbene (:CCl_2) gives 2-chloronaphthalene.



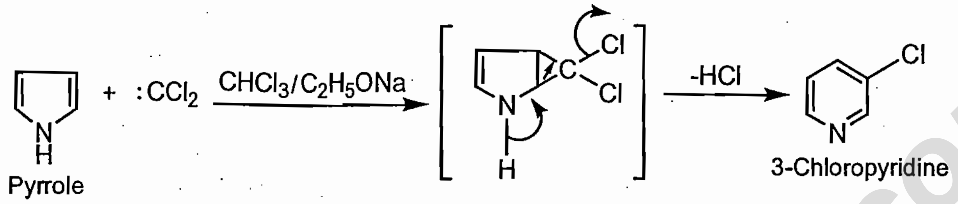
When a cyclic diazoketone is decomposed the rearrangement results in ring contraction. The reaction takes place via the intermediate carbene.



Some other examples of ring expansion are:

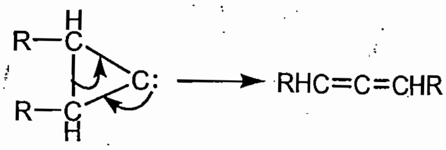
(a) $$\mathrm{CHCl_3} \xrightarrow{\overset{\ominus\,\oplus}{\mathrm{C_2H_5ONa}}} \overset{\ominus}{\mathrm{CCl_3}} \longrightarrow \ddot{\mathrm{C}}\mathrm{Cl_2} + \mathrm{Cl}^{\ominus}$$

(b)



4. **Rearrangements:**

Alkyl carbenes can undergo rearrangement involving migration of an alkyl group or hydrogen.

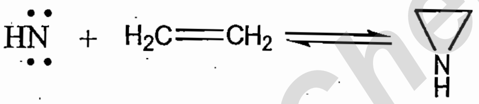


2.5 Nitrene

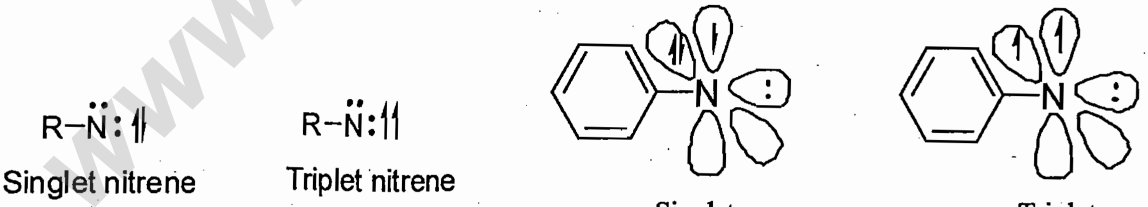
Nitrenes are very reactive species and normally not isolated. A nitrene can be trapped by its reaction with carbon monoxide and alkenes.

$$\mathrm{PhN_3} \xrightarrow{\Delta} \mathrm{Ph\ddot{N}} \xrightarrow{\mathrm{CO}} \mathrm{PhN{=}C{=}O}$$

Nitrene Phenyl isocyanate



(A) Structure and stability of nitrene: The nitrogen atom in nitrenes has a sextet of electrons. As in the case of carbenes, the nitrenes exist in singlet and triplet states.

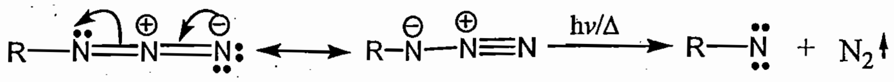


Singlet nitrene Triplet nitrene Singlet Triplet

(B) Generation of nitrene

1. **From azides:**

Thermolysis or photolysis of azides give nitrenes with expulsion of nitrogen. This method is analogous to the formation of carbenes from diazo compounds.



$$\underset{\text{Acyl azide}}{\mathrm{RCON_3}} \xrightarrow{h\nu} \underset{\text{Acyl nitrene}}{\mathrm{RCO\ddot{N}}} + \mathrm{N_2}$$

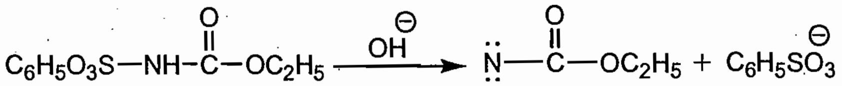
2. **From isocyanates:**
Alkyl nitrenes can also be obtained by the photolysis of isocyanates with the expulsion of carbon monoxide, a method analogues to carbene formation from ketenes.

$$\underset{\text{Alkyl isocyanate}}{R{-}N{=}C{=}O} \xrightarrow{h\nu} \underset{\text{Alkyl nitrene}}{R{-}\ddot{\underset{\cdot\cdot}{N}}} + CO$$

3. **From sulfonyl amines:**
Pyrolysis of sulfonyl amines generate nitrenes.

$$Ph{-}N{=}S{=}O \xrightarrow[\text{Gas phase}]{\Delta} Ph{-}\ddot{\underset{\cdot\cdot}{N}} + SO$$

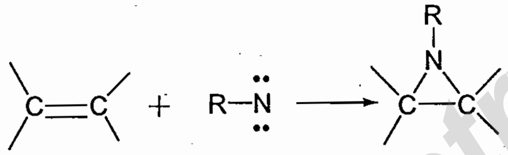
4. **From N-benzene sulfonoxy carbamates:**
The reaction of N-benzene sulfonoxy carbamate with a base results in the formation of carboalkoxy nitrene with the elimination of benzene sulfonate anion.



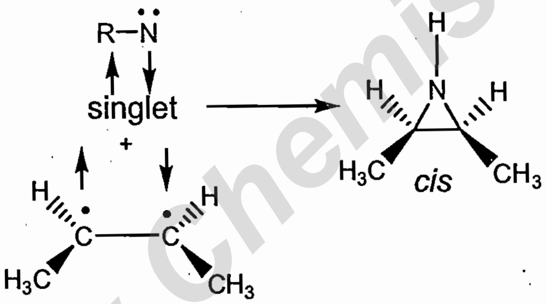
$$C_6H_5O_3S{-}NH{-}\overset{\overset{O}{\|}}{C}{-}OC_2H_5 \xrightarrow{\overset{\ominus}{OH}} \ddot{\underset{\cdot\cdot}{N}}{-}\overset{\overset{O}{\|}}{C}{-}OC_2H_5 + C_6H_5\overset{\ominus}{SO_3}$$

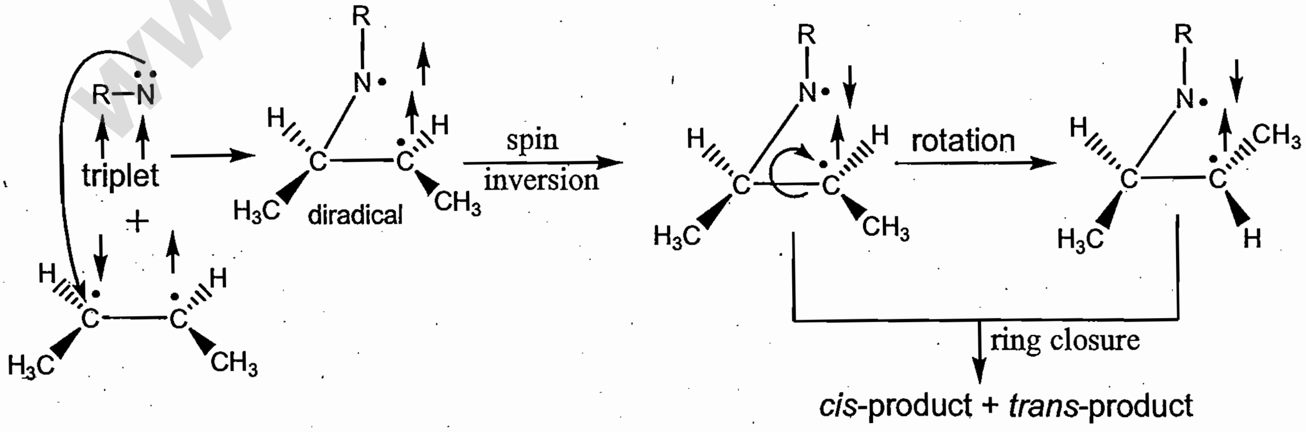
(C) Reactions of nitrenes:

1. **Addition to C=C bonds:**
Nitrenes add to C=C bonds to give aziridine. Like carbenes, the addition of nitrenes to a C=C bond is stereospecific with singlet and non-stereospecific with triplet nitrenes.



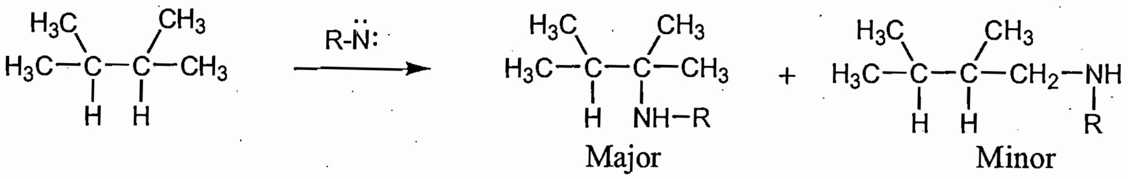
Mechanism:

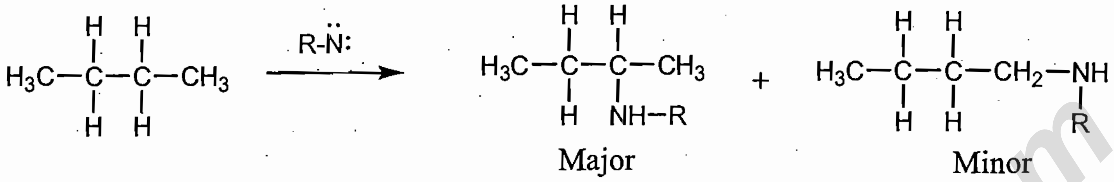




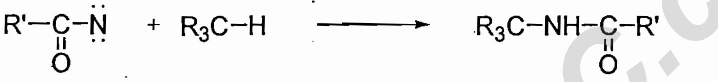
2. **Insertion:** Nitrenes, insert into C-H bonds yielding an amine or amide.

Alkane **Relative reactivities**



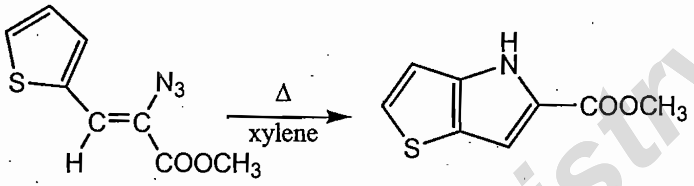


Order of reactivity: Tertiary C–H > secondary C–H > primary C–H



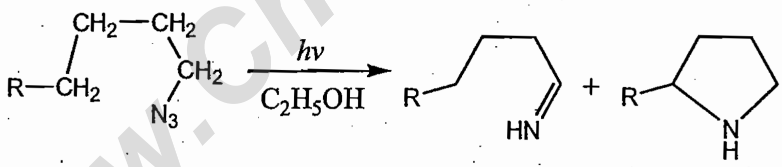
$$R'-\underset{\underset{O}{\|}}{C}-\ddot{N} + R_3C-H \longrightarrow R_3C-NH-\underset{\underset{O}{\|}}{C}-R'$$

Nitrenes can also undergo insertion into C-H single bonds leading to ring closure. Thus, vinyl azidothiophenes have been found to be useful precursors for annulation of pyrroles and thiophenes.



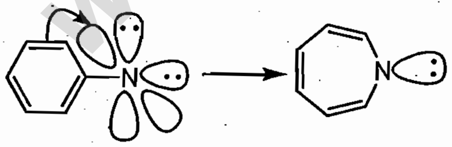
Singlet nitrenes insert into alkyl C-H bonds selectively with retention of configuration. Triplet nitrenes do not insert into alkyl C-H bonds.

3. **Hydrogen abstraction:** Hydrogen abstraction from the carbon to the nitrogen leads to the formation of imines. This process is of considerable synthetic importance. When hydrogen abstraction takes place from 4- and 5-position which is followed by ring closure, the product formed are pyrrolidines and piperidines, respectively.

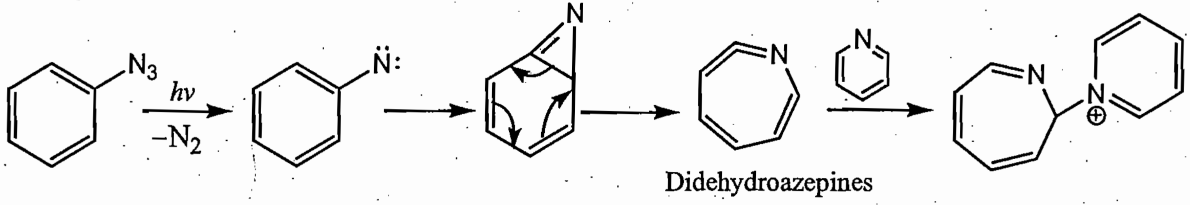


4. **Arylnitrene ring-expansion and ring-contraction:** Aryl nitrenes show ring expansion to 7-membered ring. The mechanism of ring expansion involves the Wagner and Meerwein rearrangement.

Ring expansion:



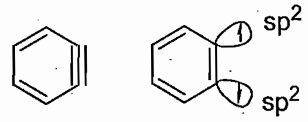
Example:



Nitrenes are also obtained as reaction intermediates in **Hoffmann, Curtius, Schmidt** and **Lossen** rearrangements.

4.5 Benzyne

Benzynes are neutral, highly reactive reaction intermediates, in which the aromatic character is not markedly disturbed. Benzynes (or arynes) contain a carbon-carbon triple bond and may be regarded as aromatic counterpart of acetylene. It is believed that the new bond of benzyne is formed by the overlap of sp^2 orbitals belonging to two neighbouring carbon atoms. As the sideways overlapping is not very effective, the new bond is weak and so the benzyne is strained and highly reactive species.



Benzyne

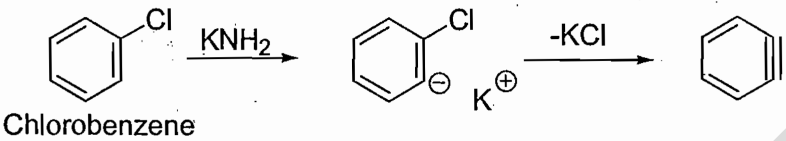
(A) Generation of benzyne:

1. **From aryl halides:**

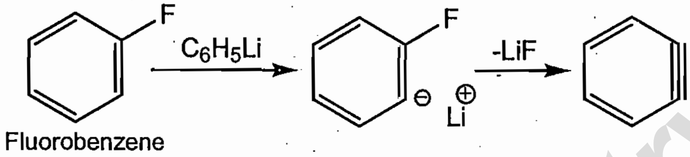
Aryl halides on treatment with strong base like KNH_2, C_6H_5Li etc., generate benzyne.

Examples:

(a)

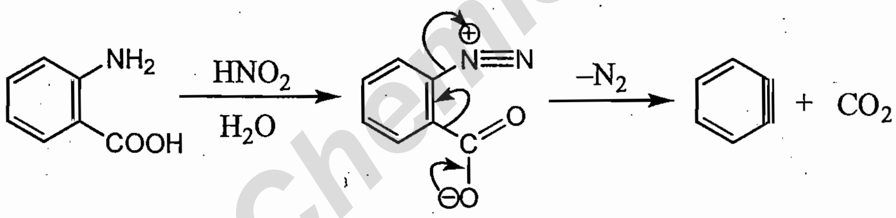


(b)



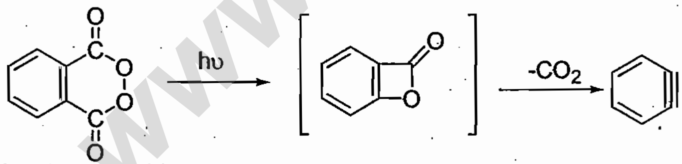
2. **From *o*-aminobenzoic acid:**

The *o*-aminobenzoic acid on diazotization followed by decomposition of the diazo compound generates benzyne.



3. **From phthaloyl peroxide:**

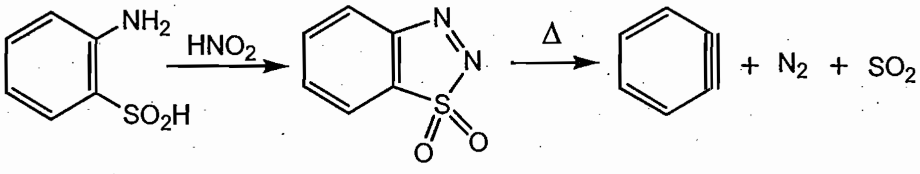
Phthaloyl peroxide on photolytic decomposition generates benzyne *via* lactone intermediate.



Phthaloyl peroxide

4. **From benzthiadiazole-1,1-dioxide:**

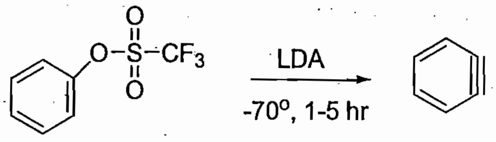
Thermal decomposition of benzothiadiazoate-1,1-dioxide generates benzyne.



Benzthiadiazole-1,1- dioxide

5. **From benzene trifluoro methane sulfonate:**

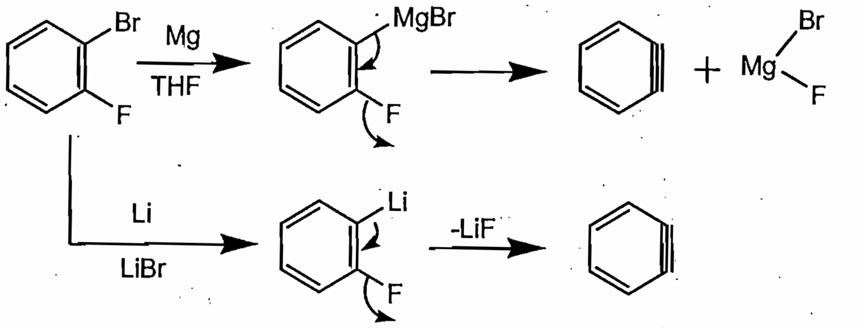
Benzene trifluoro methane sulphonate on treatment with a strong base generates benzyne.



Benzene trifluoromethane sulphonate

6. **From 1,2-dihalobenzene:**

Benzyne can also be generated from 1,2-bromofluorobenzene by formation of Grignard reagent.



(B) Reactions of benzyne:

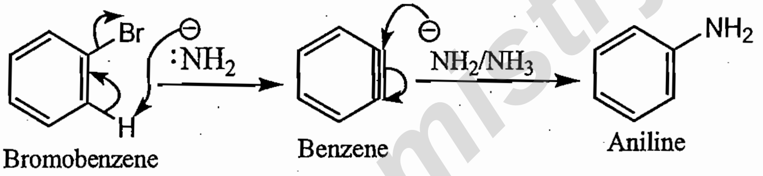
Benzyne is an extremely reactive specie and is generated *in situ* for obtaining various products.

1. **Reaction with nucleophile:**

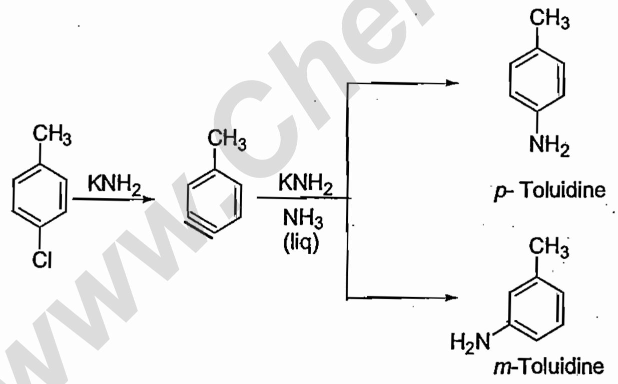
As already stated aryl halide on treatment with strong base such as KNH_2 produces benzyne. The benzyne further reacts with nucleophile to give aniline.

Examples:

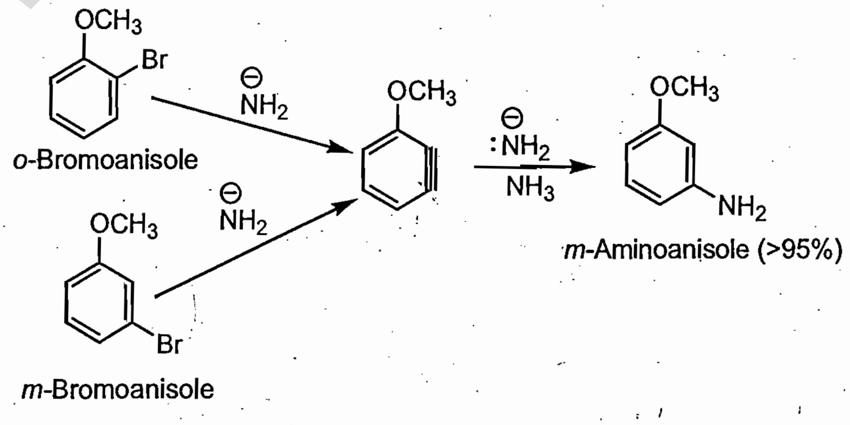
(a)



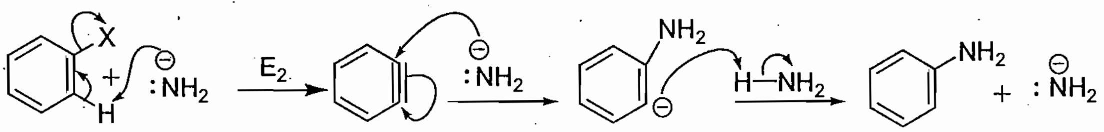
(b)

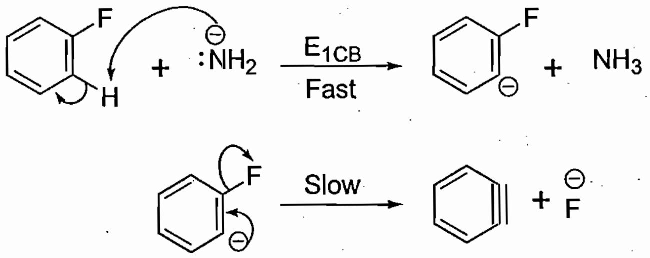


(c)

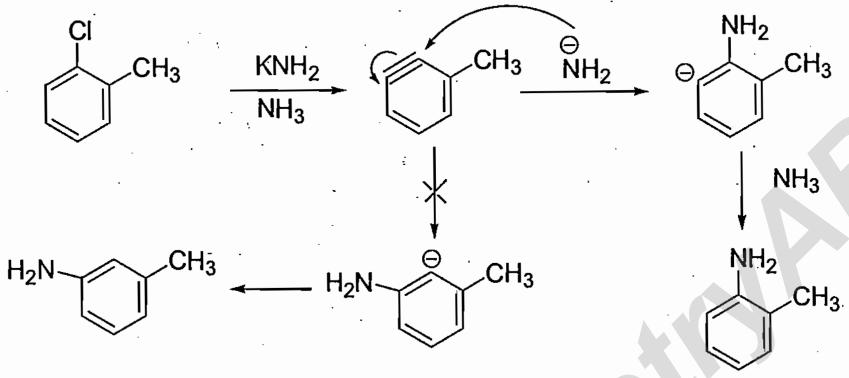


When X is I, Br or Cl then the loss of H and X can occur in concerted fashion (E_2). But when X is F, then ortho hydrogen becomes more acidic thus E_{1CB} pathway follows and benzene is formed in two steps.





Substituted benzynes gives mixture of products. This is illustrated by the example shown below:

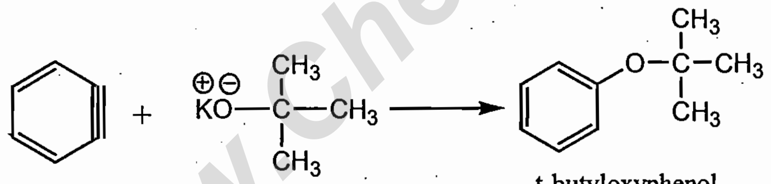


Note: However substituted benzyne without ortho hydrogen gives no reaction

A number of products can be synthesised by the reaction of a benzyne with various reagents and compounds.

Examples:

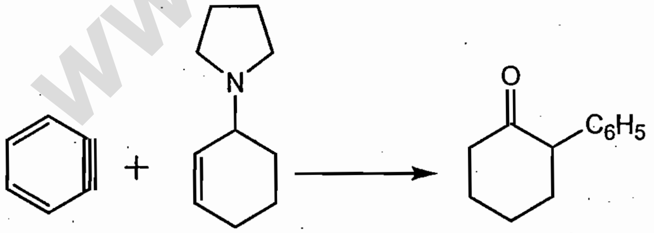
(a)



Potassium salt of t-butanol

t-butyloxyphenol

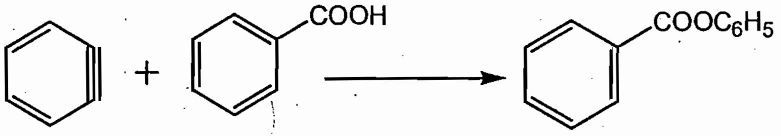
(b)



Enamine

o-phenyl cyclohexanone

(c)

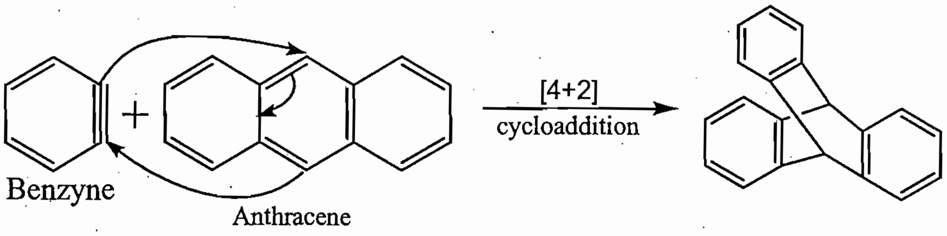


Benzoic acid

Phenyl benzoate

2. Cycloaddition:

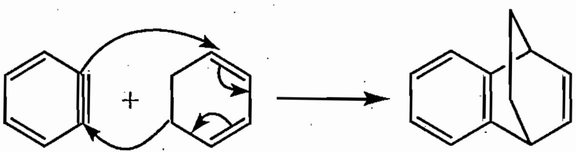
Benzyne underogoes [4+2] as well as [2+2] cycloaddition reaction with unsaturated alkenes, heterocyclic compounds etc.



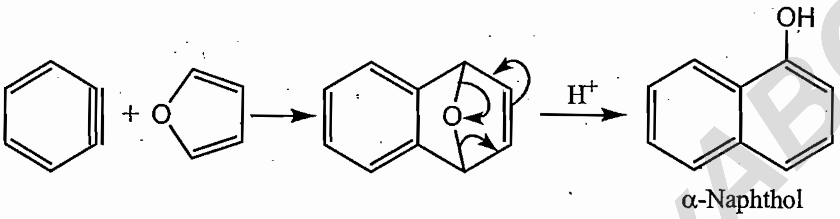
Diels- Alder reaction of benzynes give fused ring systems

Examples:

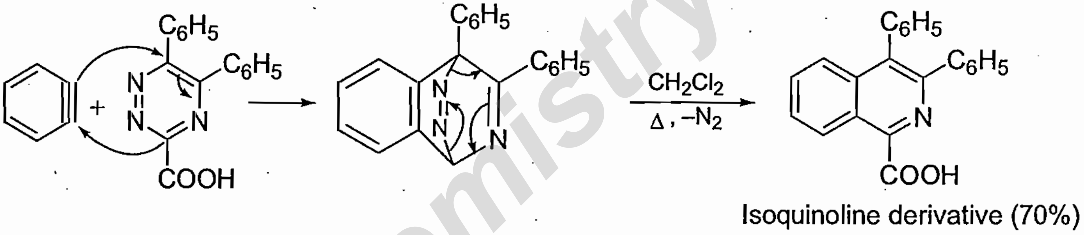
(a)



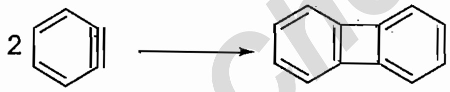
(b)



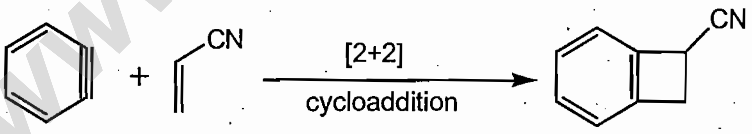
(c)



In the absence of any nucleophiles benzyne undergoes dimerization.

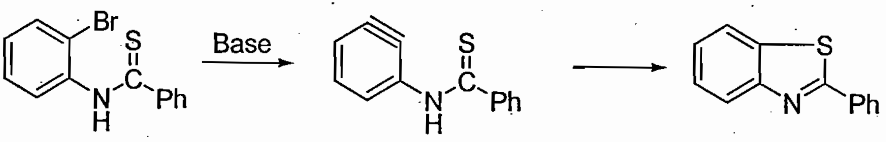


Benzyne undergoes [2+2] cycloaddtion reaction with olefins and heterocyclic compounds to give four-membered rings (2+2) cycloaddition.

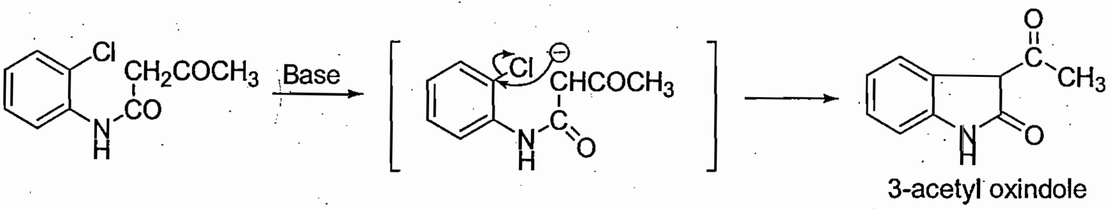


(C) Application in synthesis of heterocyclic compounds:

1.



2.



CHAPTER 5

Reaction Mechanism

5.1. Nucleophilic substitution

Types of Nucleophilic Substitution reactions:

(i) The S_N2 Mechanism:

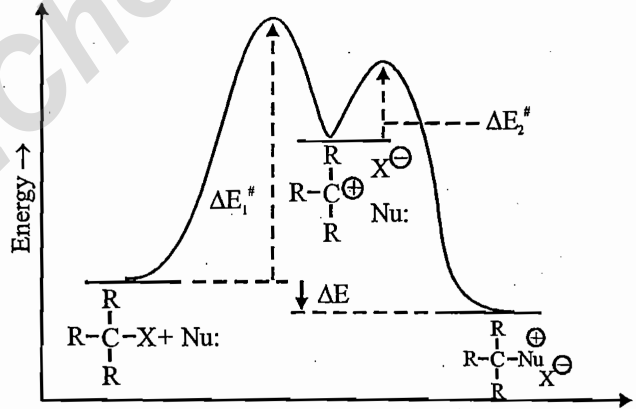
The reaction is preceded by a common single-step mechanism of second order reaction. The features of the S_N2 mechanism are inversion at the alpha-carbon, increases reactivity with increasing nucleophilicity of the nucleophilic reagent.

(ii) The S_N1 Mechanism:

It not only shows first order kinetics, but the chiral 3°-alkyl bromide reactant undergoes substitution by the modest nucleophile water with extensive racemization.

$$(CH_3)_3C-Cl+H_2O \longrightarrow (CH_3)_3C-\overset{\oplus}{O}H_2+Cl^- \xrightarrow{-H^+} (CH_3)_3C-OH+HCl$$

PES diagram for S_N1 reaction



The first order kinetics of these reactions suggest a two-step mechanism in which the rate-determining step consists of the ionization of the alkyl halide. In this mechanism, a carbocation is formed as a high-energy intermediate, and this form bonds immediately to nearby nucleophiles.

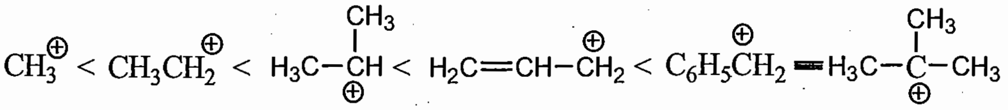
Various features for S_N1:

(i) The only reactant that is undergoing change in the first (rate-determining) step is the alkyl halide, so we expect such reactions would be unimolecular and follow a first-order rate equation. Hence the name S_N1 is applied to this mechanism.

(ii) Since nucleophiles only participate in the fast second step, recombination of the halide anion with the carbocation intermediate simply reforms the starting compound. Note that S_N1 reactions in which the nucleophile is also the solvent are commonly called **solvolysis** reactions. The hydrolysis of t-butyl chloride is an example.

(iii) The Hammond postulate suggests that the activation energy of the rate-determining first step will be inversely proportional to the stability of the carbocation intermediate. The stability of carbocations was discussed earlier, and a qualitative relationship is given below.

Carbocation Stability:



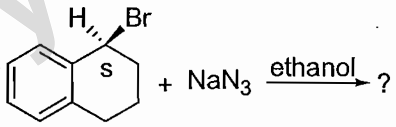
$$\overset{\oplus}{CH_3} < CH_3\overset{\oplus}{CH_2} < H_3C-\underset{\oplus}{\overset{CH_3}{CH}} < H_2C{=}CH-\overset{\oplus}{CH_2} < C_6H_5\overset{\oplus}{CH_2} \approx H_3C-\underset{\oplus}{\overset{CH_3}{C}}-CH_3$$

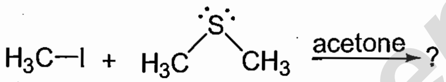
(iv) In order to facilitate the charge separation of an ionization reaction, as required by the first step, a good ionizing solvent will be needed. This characteristic is related to the **dielectric constant,** ε, of the solvent. Solvents having high dielectric constants, such as water (ε = 81), formic acid (ε = 58), dimethyl sulfoxide (ε = 45) and acetonitrile (ε = 39) are generally considered better ionizing solvents than some common organic solvents such as ethanol (ε = 25), acetone (ε = 21), methylene chloride (ε = 9) and ether (ε = 4).

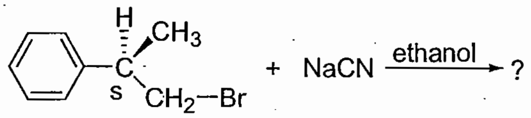
(v) The stereospecificity of these reactions may vary. The positively-charged carbon atom of a carbocation has a trigonal (flat) configuration (it prefers to be sp^2 hybridized), and can bond to a nucleophile equally well from either face.

Problem: Predict which of the following reaction is occured by S_N1, S_N2 and neither S_N1 nor S_N2 mechanism

(1)


(2)


(3)


(4)


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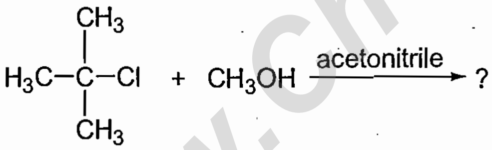
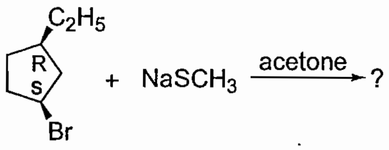


(6)


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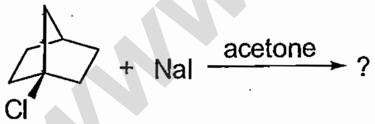

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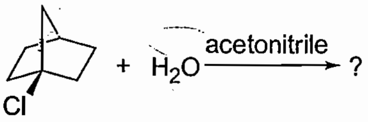


Activation by electrophilic cations:

Heterolytic cleavage of the carbon-halogen bond of alkyl halides may be facilitated by the presence of certain metal cations. In the extreme, carbocations may be generated as shown in the following equation, where R is alkyl or hydrogen, and M = Al (n=3) or Fe (n=3) or Sn (n=4) or Zn (n=2).

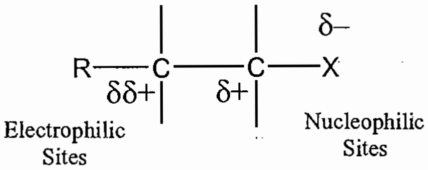
$$R_3C-X+MX_n\ (\text{reactivity} = Al > Fe > Sn > Zn) \longrightarrow R_3C^{\oplus} + MX_n-X^-$$

In aqueous or alcoholic solution it promotes ionization of the alkyl halide and the formation of S_N1 products. When silver nitrate is used with 1° or 2°-alkyl halides, rearrangement may occur before the product formation stage. For example:

$$(CH_3)_3CCH_2-Br+H_2O+AgNO_3 \longrightarrow (CH_3)_2C(OH)CH_2CH_3+AgBr+HNO_3$$

5.2 Elimination versus Substitution:

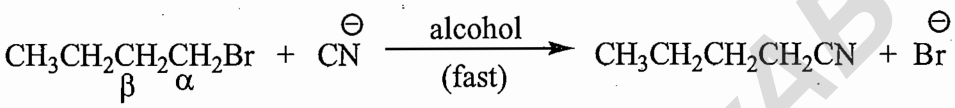
For many combinations of alkyl halides and nucleophiles, elimination reactions may compete with substitution,



In describing these, it is useful to designate the halogen-bearing carbon as **alpha** and the carbon atom adjacent to it as **beta**, as noted in the first four equations shown below. Replacement or substitution of the halogen on the α-carbon by a nucleophilic reagent is a commonly observed reaction, as shown in equations **1, 2, 5, 6 & 7** below. Also, since the electrophilic character introduced by the halogen extends to the β-carbons, and since nucleophiles are also bases, the possibility of base induced H-X elimination must also be considered, as illustrated by equation **3**. Finally, there are some combinations of alkyl halides and nucleophiles that fail to show any reaction over a 24 hour period, such as the example in equation **4**. For consistency, alkyl bromides have been used in these examples. Similar reactions occur when alkyl chlorides or iodides are used, but the speed of the reactions and the exact distribution of products will change.

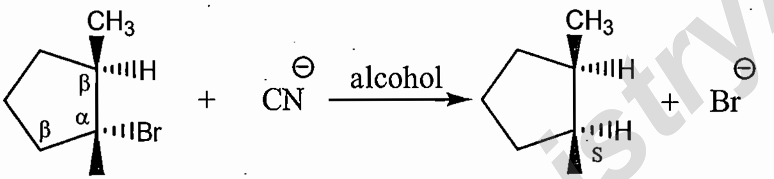
- Nucleophiles having basic characater give elimination reaction.
- Nucleophiles having non-basic character give substitution reaction.

1.

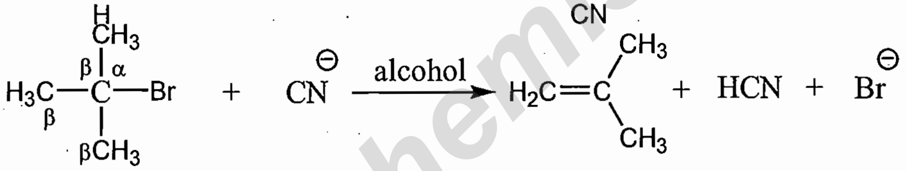


$$CH_3CH_2\underset{\beta}{CH_2}\underset{\alpha}{CH_2}Br + \overset{\ominus}{CN} \xrightarrow[\text{(fast)}]{\text{alcohol}} CH_3CH_2CH_2CH_2CN + \overset{\ominus}{Br}$$

2.



3.



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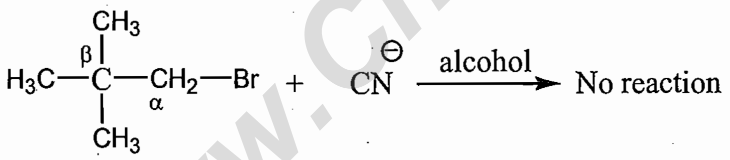

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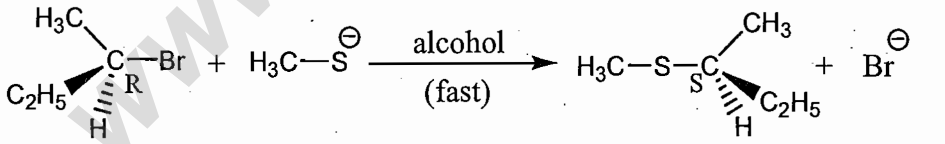

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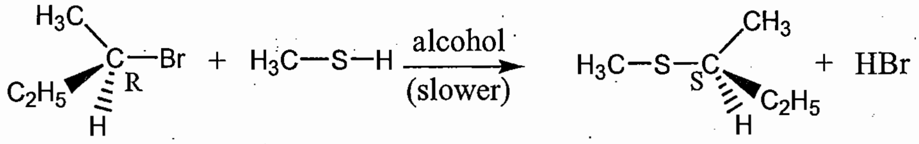

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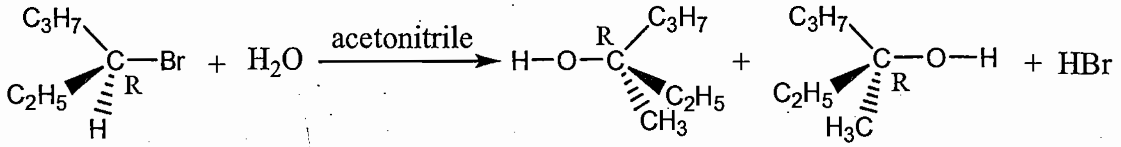
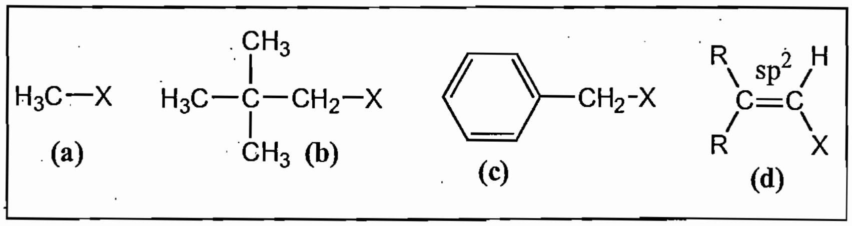


$$R-X+Nu:\xrightarrow{\text{Solvent}}\text{Product}$$

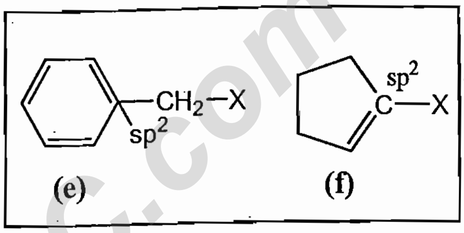
R = alkyl group
X = Cl, Br or I
Nu := nucleophile

One conclusion, relating the structure of the R-group to possible products, should be immediately obvious. If **R- has no beta-hydrogens an elimination reaction is not possible**, unless a structural rearrangement occurs first. The first four halides shown below (a, b, c, d) do not give elimination reactions on treatment with base, because they have no β-hydrogens. The two halides on the right (e, f) do not normally undergo such reactions because the potential elimination products have highly strained double or triple bonds.

It is also worth noting that sp^2 hybridized C–X compounds, such as the three on the right, do not normally undergo nucleophilic substitution reactions, unless other functional groups perturb the double bond(s).



no β-hydrogents



strained elimination product

Using the general reaction shown above as our reference, we can identify the following variables and observables.

Variables	**R** change α-carbon from 1° to 2° to 3° if the α-carbon is a chiral center, set as (*R*) or (*S*) **X** change from Cl to Br to I (F is relatively unreactive) **Nu:** change from anion to neutral; change basicity; change polarizability **Solvent** polar vs. non-polar; protic vs. non-protic
Observables	**Products** substitution, elimination, no reaction. **Stereospecificity** if the α-carbon is a chiral center what happens to its configuration? **Reaction Rate** measure as a function of reactant concentration.

1. Nucleophilicity:

Nucleophilicity is thereby related to the relative rate of substitution reactions at the halogen-bearing carbon atom of the reference alkyl halide. The most reactive nucleophiles are said to be more nucleophilic than less reactive members of the group. The nucleophilicities of some common Nu : reactants vary as shown in the following

Nucleophilicity: $CH_3CO_2^- < Cl^- < Br^- < N_3^- < CH_3O^- < CN^- < SCN^- < I^- < CH_3S^-$

Increasing Nucleophile Strength:

The cumulative results of studies of this kind has led to useful empirical rules pertaining to nucleophilicity:

(i) For a given element, negatively charged species are more nucleophilic (and basic) than equivalent neutral species.

(ii) For a given period of the periodic table, nucleophilicity (and basicity) decreases on moving from left to right.

(iii) For a given group of the periodic table, nucleophilicity increases from top to bottom (*i.e.* with increasing size), although there is a solvent dependence due to hydrogen bonding. Basicity varies in the opposite manner.

2. Solvent effects:

Solvation of nucleophilic anions markedly influences their reactivity. Polar, aprotic solvents such as DMSO (dimethyl sulfoxide), DMF (dimethylformamide) and acetonitrile do not solvate anions nearly as well as methanol, but provide good solvation of the accompanying cations. Consequently, most of the nucleophiles discussed here react more rapidly in solutions prepared from these solvents. These solvent effects are more pronounced for small basic anions than for large weakly basic anions. Thus, for reaction in DMSO solution we observe the following reactivity order :

Nucleophilicity:

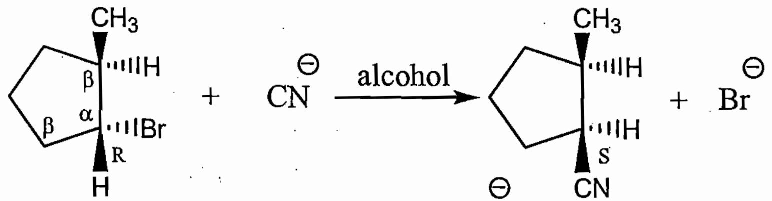
$$I^- < SCN^- < Br^- < Cl^- < N_3^- < CH_3CO_2^- < CN^- < CH_3O^- < CH_3S^-$$

3. The Alkyl Moiety:

- Crowded alkyl moiety gives elimination reaction.
- Less crowded alkyl moiety gives substitution reaction.

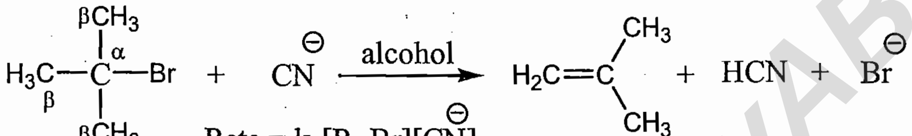
1. $$\underset{\text{1°-bromide}}{CH_3CH_2\underset{\beta}{C}H_2\underset{\alpha}{C}H_2Br} + \overset{\ominus}{CN} \xrightarrow[\text{(fast)}]{\text{alcohol}} CH_3CH_2CH_2CH_2CN + \overset{\ominus}{Br}$$

$$\text{Rate} = k_1[R\text{–}Br][\overset{\ominus}{CN}]$$

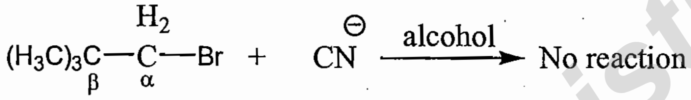
2. 

2°-bromide

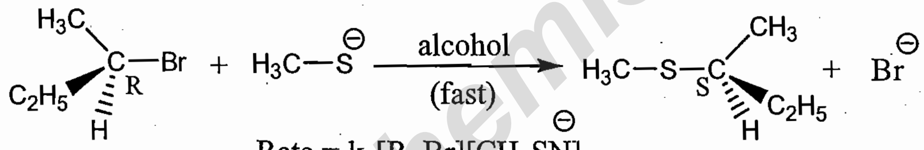
$$\text{Rate} = k_2[R\text{–}Br][\overset{\ominus}{CN}]$$

3. 

$$\text{Rate} = k_3[R\text{–}Br][\overset{\ominus}{CN}]$$

4. 

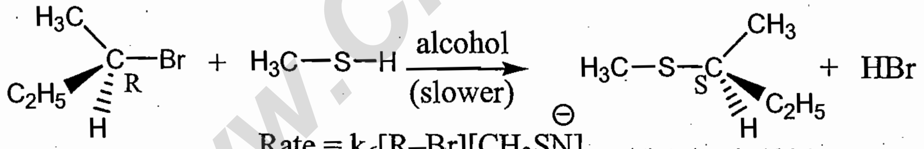
$$(H_3C)_3\underset{\beta}{C}\text{—}\overset{H_2}{\underset{\alpha}{C}}\text{—}Br + \overset{\ominus}{CN} \xrightarrow{\text{alcohol}} \text{No reaction}$$

5. 

(R)-2-bromobutane

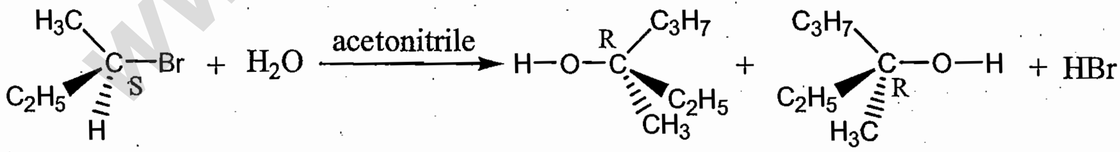
$$\text{Rate} = k_5[R\text{–}Br][CH_3\overset{\ominus}{S}N]$$

(S)-2-(methylthio)butane

6. 

$$\text{Rate} = k_6[R\text{–}Br][CH_3\overset{\ominus}{S}N]$$

(S)-2-(methylthio)butane

7. 

(S)-3-bromo-3-methylhexane

racemic 3-methyl--hexanol

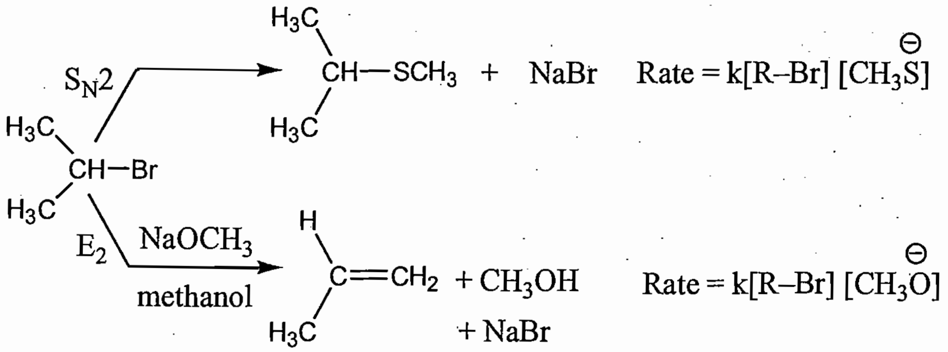
$$\text{Rate} = k_7[R\text{–}Br]$$

Types of Elimination reaction:

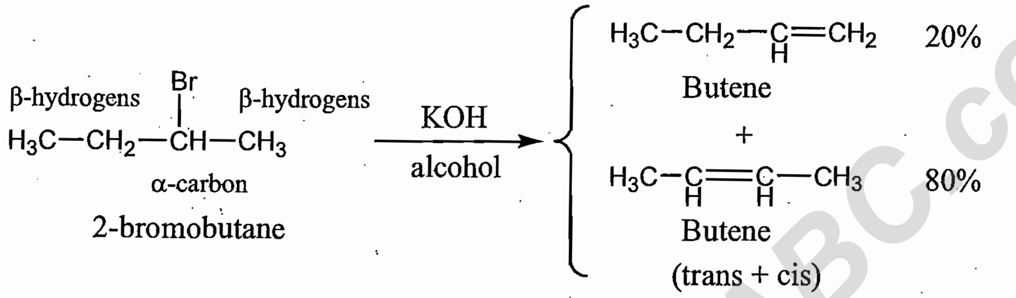
(1) **The E_2 Reaction:** We have not yet considered the factors that influence elimination reactions, such as example 3 in the group presented at the beginning of this section. Elimination of second order is called E_2 reaction.

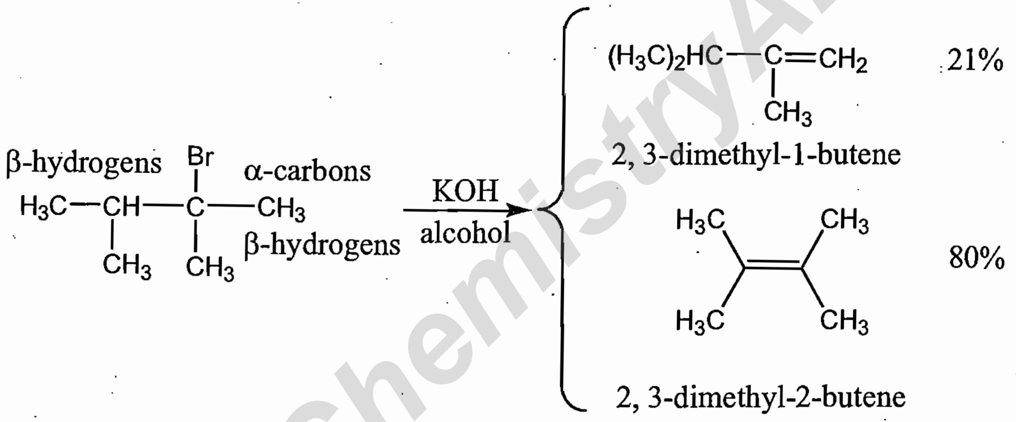
$$(CH_3)_3C-Br + CN^- \longrightarrow (CH_3)_2C=CH_2 + Br^- + HCN$$

For E_2 reaction, there is no formation of intimate ion pair that is carbocation (if formed) is not stable.



If two or more structurally distinct groups of beta-hydrogens are present in a given reactant, then several constitutionally isomeric alkenes may be formed by an E_2 elimination. This situation is illustrated by the 2-bromobutane and 2-bromo-2,3-dimethylbutane elimination examples given below.

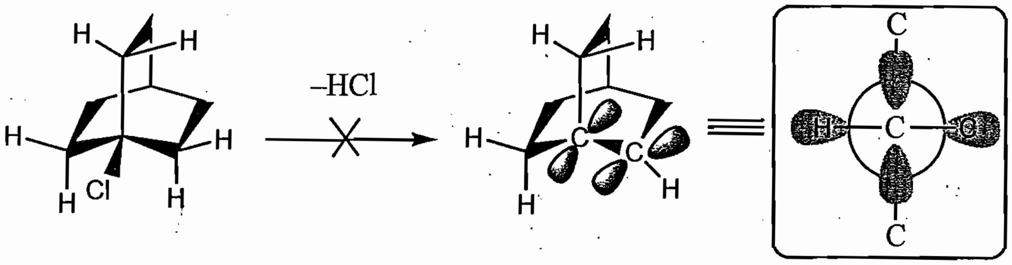


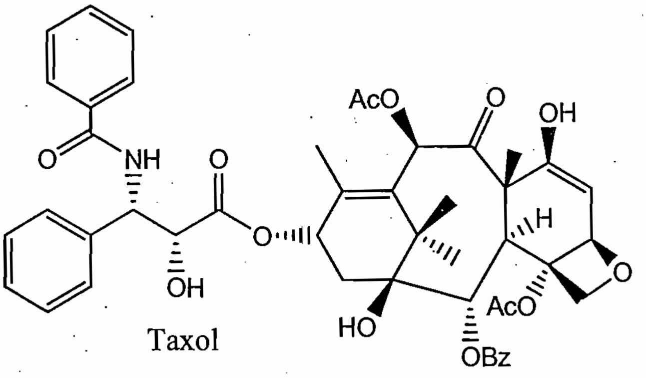


These results point to a strong regioselectivity favoring the more substituted double bond, an empirical statement generally called the **Zaitsev's Rule.**

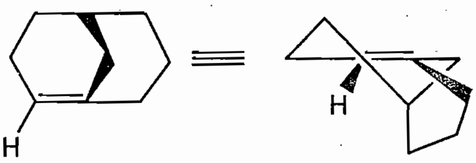
The Zaitsev's rule is a good predictor for simple elimination reactions of alkyl chlorides, bromides and iodides as long as relatively small strong bases are used. Thus hydroxide, methoxide and ethoxide bases give comparable results. Bulky bases such as tert-butoxide tend to give higher yields of the less substituted double bond isomers, a characteristic that has been attributed to steric hindrance.

Bredt's Rule: Double bond can never be formed to bridge head carbons in bicyclic system due to impossibility of formation of planarity at bridge head carbon.





Taxol

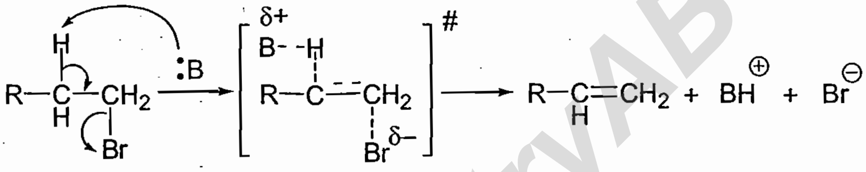


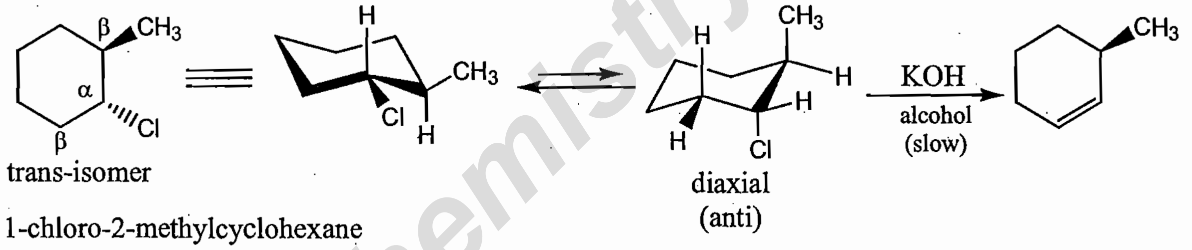
A brigehead double bond in 1-bicyclo[3, 3, 1]octene

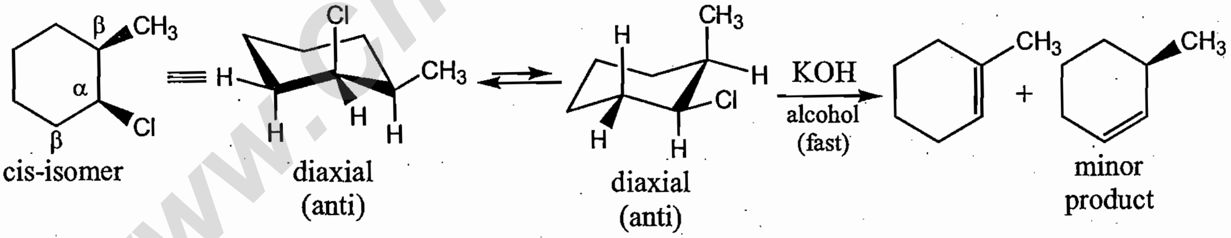
2. Stereochemistry of the E_2 Reaction:

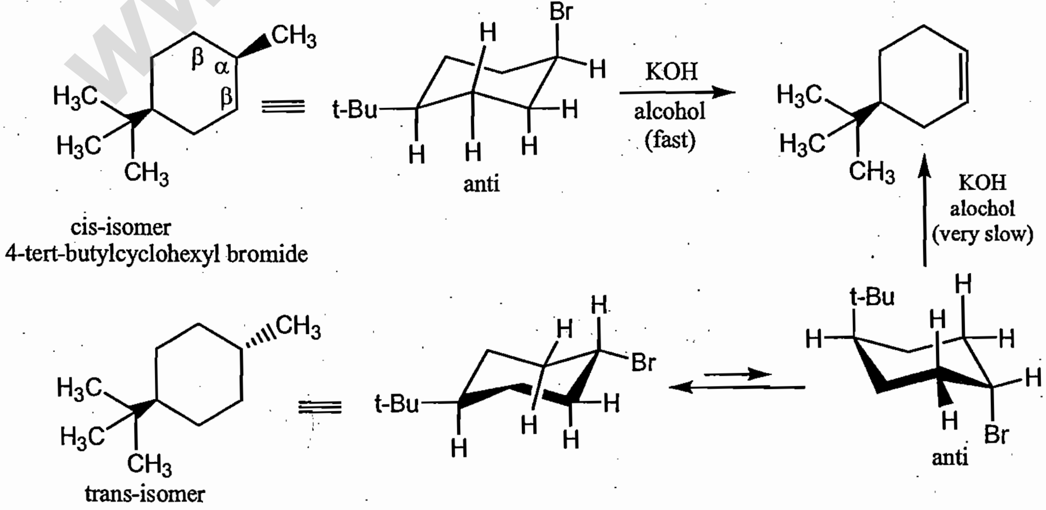
E_2 elimination reactions of certain isomeric cycloalkyl halides show unusual rates and regioselectivity that are not explained by the principles thus far discussed. For example, trans-2-methyl-1-chlorocyclohexane reacts with alcoholic KOH at a much slower rate than does its cis-isomer. Furthermore, the product from elimination of the trans-isomer is 3-methylcyclohexene (not predicted by the Zaitsev rule), whereas the cis-isomer gives the predicted 1-methylcyclohexene as the chief product.

Unlike open chain structures, cyclic compounds generally restrict the spatial orientation of ring substituents to relatively few arrangements.





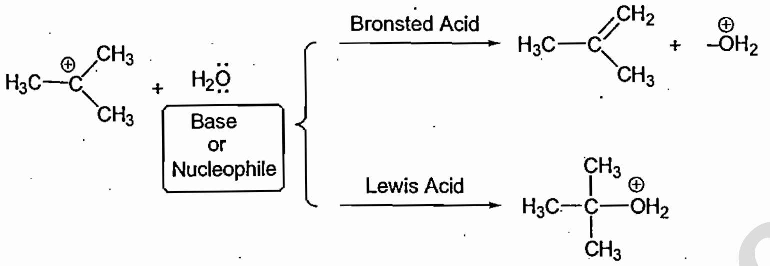




Note: Both eleminating group must be antiperiplanar to each other.

3. The E_1 Reaction:

Just as there were two mechanisms for nucleophilic substitution, there are two elimination mechanisms. The E_1 mechanism is nearly identical to the S_N1 mechanism, differing only in the course of reaction taken by the carbocation intermediate. As shown by the following equations, a carbocation bearing beta-hydrogens may function either as a Lewis acid (electrophile), as it does in the S_N1 reaction, or a Brønsted acid, as in the E_1 reaction.



$$(CH_3)_3C-Cl + H_2O \longrightarrow [(CH_3)_3C^+)] + Cl^- + H_2O \longrightarrow (CH_3)_3C-OH + (CH_3)_2C=CH_2$$
$$+ HCl + H_2O$$

To summarize, when carbocation intermediates are formed one can expect them to react further by one or more of the following modes:

1. The cation may bond to a nucleophile to give a substitution product.
2. The cation may transfer a beta-proton to a base, giving an alkene product.
3. The cation may rearrange to a more stable carbocation, and then react by mode E_1 or E_2.
Since the S_N1 and E_1 reactions proceed via the same carbocation intermediate, the product ratios are difficult to control and both substitution and elimination usually take place.
The most important being the structure of the alkyl group and the nature of the nucleophilic reactant.

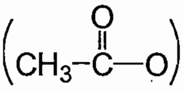
Note that halogens bonded to sp^2 or sp hybridized carbon atoms do not normally undergo substitution or elimination reactions with nucleophilic reagents.

Nucleophile	Non-Basic Anionic Nucleophile	Basic Anionic Nucleophile	Neutral Nucleophile
Alkyl Group	(Weak Bases: I^-, Br^-, SCN^-, N_3^- ,$CH_3CO_2^-$, RS^-, CN^- etc.) pKa's from -9 to 10 (left to right)	(Strong Bases: HO^-, RO^-) pKa's > 15	(H_2O, ROH, RSH, R_3N) pKa's ranging from -2 to 11
Primary RCH_2-	Rapid S_N2 substitution. The rate may be reduced by substitution of β-carbons, as in the case of neopentyl.	Rapid S_N2 substitution. E_2 elimination may also occur. *e.g.* $ClCH_2CH_2Cl + KOH \rightarrow CH_2{=}CHCl$	S_N2 substitution. ($SH^- > NH_2^- > OH^-$)
Secondary R_2CH-	S_N2 substitution and / or E_2 elimination (depending on the basicity of the nucleophile). Bases weaker than acetate (pKa = 4.8) give less elimination. The rate of substitution may be reduced by branching at the β carbons, and this will increase elimination.	E_2 elimination will dominate.	S_N2 substitution. ($SH^- > NH_2^- > OH^-$) In high dielectric ionizing solvents, such as water, dimethyl sulfoxide & acetonitrile, S_N1 and E_1 products may be formed slowly.
Tertiary R_3C-	E_2 elimination will dominate with most nucleophiles (even if they are weak bases). No S_N2 substitution due to steric hindrance. In high dielectric ionizing solvents, such as water, dimethyl sulfoxide & acetonitrile, S_N1 and E_1 products may be expected.	E_2 elimination will dominate. No S_N2 substitution will occur. In high dielectric ionizing solvents S_N1 and E_1 products may be formed.	E_2 elimination with nitrogen nucleophiles (they are bases). No S_N2 substitution. In high dielectric ionizing solvents S_N1 and E_1 products may be formed.
Allyl $H_2C{=}CH{-}CH_2$	Rapid S_N2 substitution for 1° and 2° - halides. For 3° -halides a very slow S_N2 substitution or, if the nucleophile is moderately basic, E_2 elimination. In high dielectric ionizing solvents, such as water, dimethyl sulfoxide and acetonitrile, S_N1 and E_1 products may be observed.	Rapid S_N2 substitution for 1° halides. E_2 elimination will compete with substitution in 2° - halides, and dominate in the case of 3°-halides. In high dielectric ionizing solvents S_N1 and E_1 products may be formed.	Nitrogen and sulfur nucleophiles will give S_N2 substitution in the case of 1° and 2° -halides. 3°-halides will probably give E_2 elimination with nitrogen nucleophiles (they are bases). In high dielectric ionizing solvents S_N1 and E_1 products may be formed. Water hydrolysis will be favorable for 2° & 3°-halides.
Benzyl $C_6H_5CH_2$-	Rapid S_N2 substitution for 1° and 2° - halides. For 3° -halides a very slow S_N2 substitution or, if the nucleophile is moderately basic, E_2 elimination. In high dielectric ionizing solvents, such as water, dimethyl sulfoxide & acetonitrile, S_N1 and E_1 products may be observed.	Rapid S_N2 substitution for 1° halides (note there are no β hydrogens). E_2 elimination will compete with substitution in 2°-halides, and dominate in the case of 3°-halides. In high dielectric ionizing solvents S_N1 and E_1 products may be formed.	Nitrogen and sulfur nucleophiles will give S_N2 substitution in the case of 1° and 2°-halides. 3°-halides will probably give E_2 elimination with nitrogen nucleophiles (they are bases). In high dielectric ionizing solvents S_N1 and E_1 products may be formed. Water hydrolysis will be favorable for 2° and 3° halides.

5.3. Neighbouring Group Participation

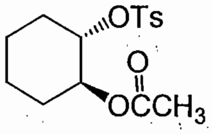
The presence of nucleophilic groups in molecule undergoing nucleophilic substitution affects the kinetics and stereochemistry of reaction. The involvement of nearby nucleophilic substitutents such as lone pair electrons of group, in a substitution process is called neighbouring group participation.

The leaving group and participating group are in the trans-position **Saul Winstein** coined the term "anchemeric assistance" to indicate the fact that such reaction occurs more readily than would be expected without neighbouring group participation, neighbouring group that are generally involved are acetoxy, OH, oxygen, halogen, C=C , C–C, phenyl group etc.

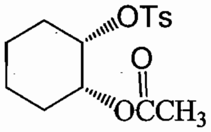


1. Acetoxy $\left(CH_3-\overset{\overset{O}{\|}}{C}-O\right)$ group:

The rate of solvolysis of the cis and trans isomers of 2-acetoxy cyclohexyl p- toluene sulfonate differs by a factor of about 670, trans isomers being more reactive one and the products obtained are also different.

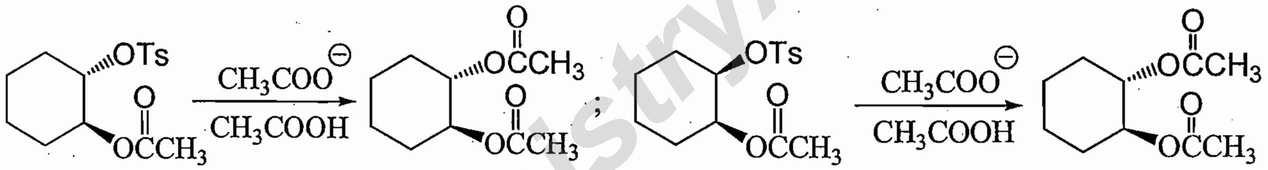


K = 1.9 × $10^{-4}S^{-1}$(100°C)



K = 2.9 × $10^{-7}S^{-1}$(100°C)

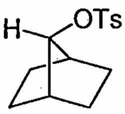
The diacetate obtained from the cis isomer is the trans-isomer (inverted stereochemistry) whereas retention of configuration is observed for the trans isomer.



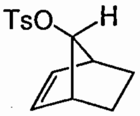
The results can be explained by the participation of the trans acetoxy group in the ionisation process. The assistance provided by the acetoxy carbonyl group facilitates the ionisation of the tosylate group, accounting for the rate enhancement. This kind of backside participation by adjacent acetoxy group is both sterically and energetically favorable. The cation which is formed by participation is stabilised by two oxygen atoms and is for more stable than a secondary carbocation. The acetoxonium ion is subsequently opened by nucleophilic attack with inversion at one of the two equivalent carbons leading to the observed trans product. Whereas in case of cis isomer, simple S_N2 mechanism is involved.

2. The electron of C=C bond:

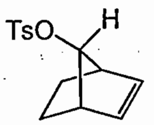
C=C bond are also envolved in neighbouring group participation reaction e.g. the anti tosylate isomer in norbornyl systems are found to be more reactive toward acetolysis than that of saturated isomer by a factor of about 10^{11}. The product is also retention in configuration. This is due to being participation of π-electron of C=C bond to give ion which is more stabilised by delocalisation of the positive charge.



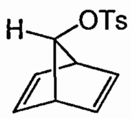
$K_{rel} = 1$
Norbornyl
Tosylate



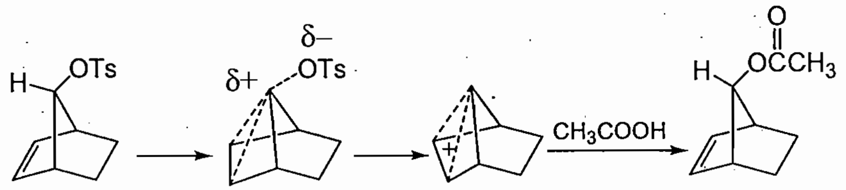
$\approx 10^4$
Norbornenyl
Tosylate (syn)



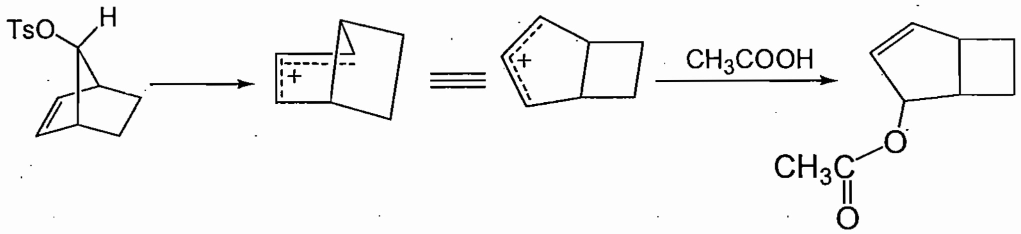
$\approx 10^{11}$
Norbornenyl
Tosylate (anti)



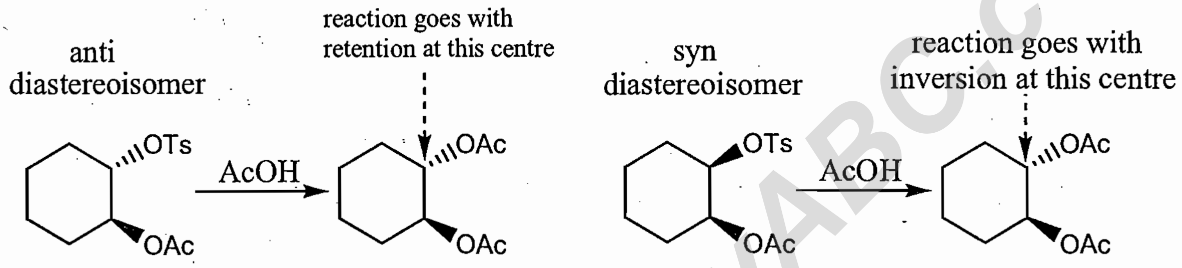
$\approx 10^{14}$
Norbornadienyl
Tosylate



In contrast, syn isomers in which the double bond is not in the position to participate in the ionisation step therefore it reacts 10^7 times slower than that of anti isomer. The reaction product is derived from a rearranged carbocation ion that is stabilised by virtue of being allylic

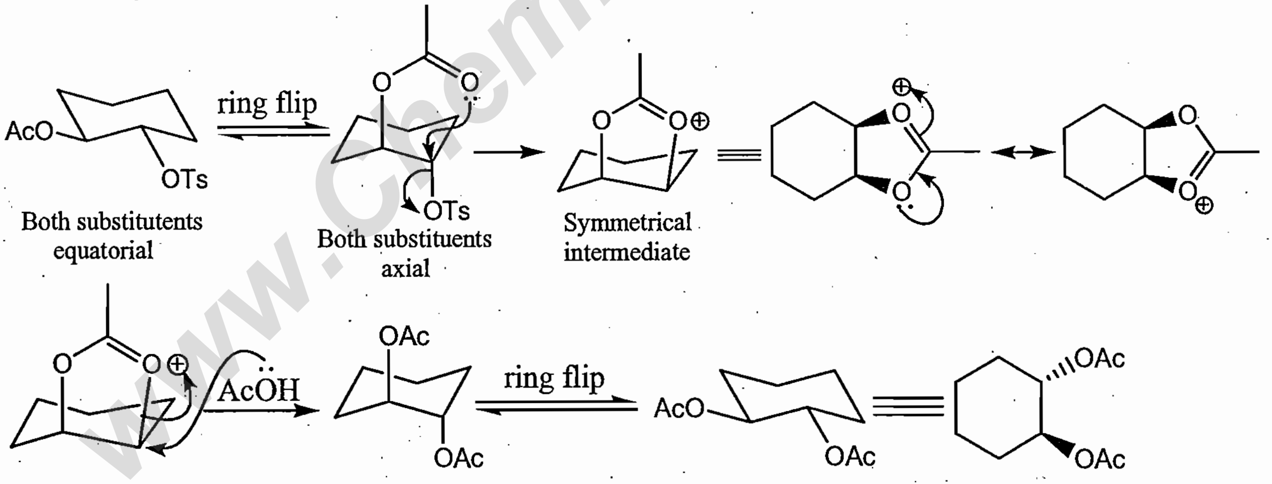


***Stereochemistry can indicate neighbouring group participation*:**



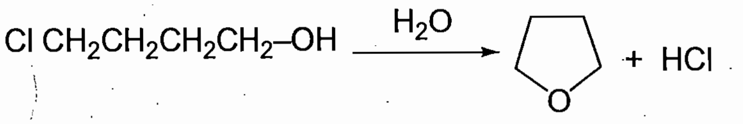
Although one starting material has syn and the other anti stereochemistry, the products have the same (anti) stereochemistry: one substitution goes with retention and one goes with inversion. Again, neighbouring group participation is the reaction. To explain this, we should first draw the six-membered rings in their real conformation. For the anti compound, both substituents can be equatorial.

However, not much can happen in this conformation–but, if we allow the ring to flip, you can see immediately that the acetate substituent is ideally placed to participate in the departure of the tosylate group.

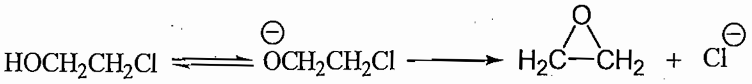


3. Hydroxy group (–OH) and oxygen atom :

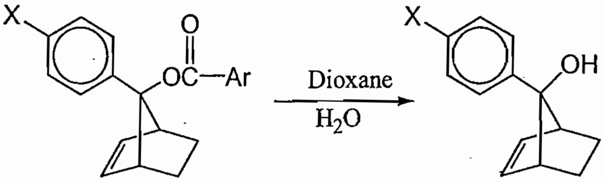
The hydroxy group acts as an intramolecular nucleophile i.e.; solvolysis of 4- chloro butanol in water gives a product i.e; tetrahydrofuran. The reaction is much faster than solvolysis of 3-chloro prapanol under similar condition



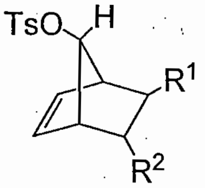
In basic solution, the alkoxide ions formed by deprotonation are even more effective nucleophile. In ethanol containing sodium ethoxide, 2-chloro-ethanol reacts about 5000 times faster than ethyl chloride. The product is ethylene oxide confirming the involvement of oxygen atom as a nucleophile.



The extent of participation of carbon - carbon double bond in the ionisation of anti - 7 - norbornenyl system is a function of the substitution at C - 7 position. The placement of an aryl substituent at C –7 diminishes the relative rate (accelerated rate due to participation by C = C bond). Evidently, the extent of participation is a function of the stability of potential carbocation when an aryl group is present at C–7 position, the resulting benzyl - typed stabilisation decreases the relative importance of participation by double bond.



The factors which can affect C = C bond π-electron cloud, may also affect on the relative rate.



Relative rate

$R^1 = R^2 = H \longrightarrow 1.4 \times 10^{12}$

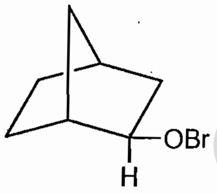
$R^1 = H\ R^2 = CF_3 \longrightarrow 15 \times 10^6$

$R^1 = R^2 = CF_3 \longrightarrow 1$

4. C-C bond or bonds as Neighbouring Group Participation:

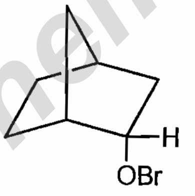
Winstein and Trifan found that solvolysis in acetic acid of optically active exo - 2 - norbornyl brosylate gave a racemic mixture of two exo - acelate.

Exo - isomer solvolysed about 350 time faster than that of endo isomer.



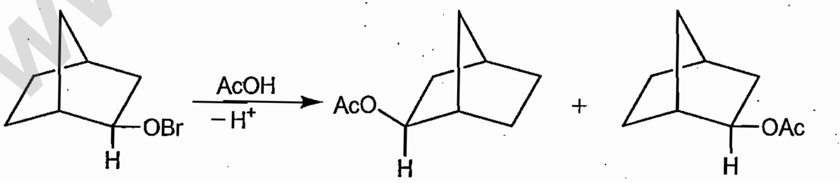
Exo-isomer

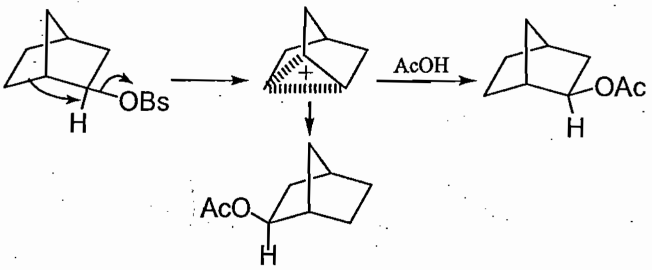
>



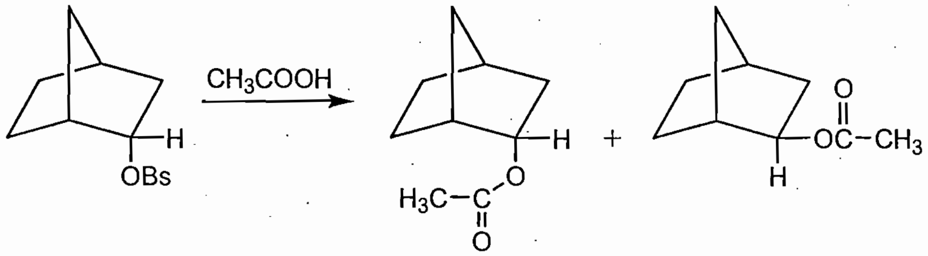
Endo-isomer

This is due to that 1, 6 bond assist in departure of the leaving group (OBs-p-bromo benzene sulphonate) and forming non-classical intermediate (carbocation) in Exo-isomer.

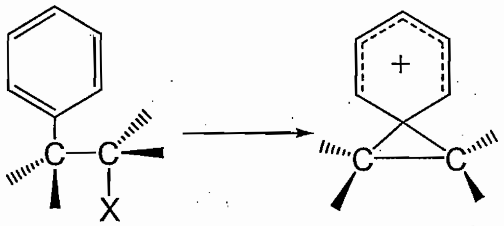




Whereas in case of endo isomer. The position is not favorable therefore it does not involve neighbouring group participation but it reacts normally

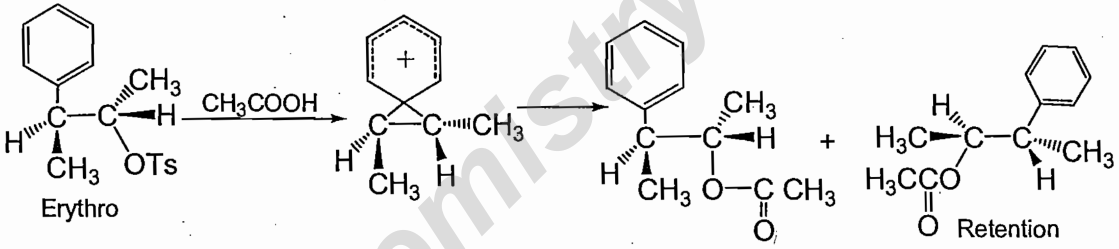


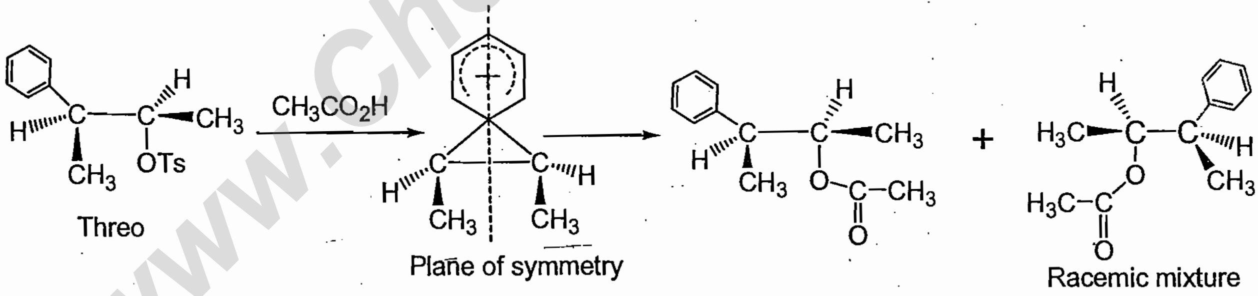
5. Aromatic π-electron participation :



Phenonium ion

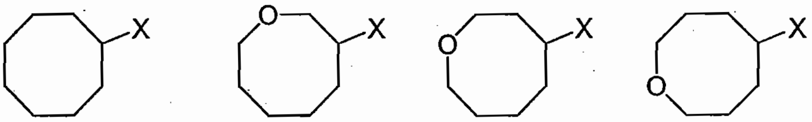
Such participation leads to a bridged ion with positive charge delocalised into the aromatic ring. e.g. stereochemistry of solvolysis of 3-phenyl, 2-butyl tosylate. The erythro isomer gives largely retention of configuration in the product. The result can be explained by/via the bridged ion intermediate. Threo isomer where participation leads to an achiral intermediate which gives racemic threo products.





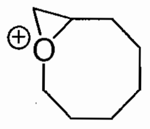
6. Trans annular ether oxygen as Neighbouring Group Participation:

The relative rate for molecules show that three is a large acceleration in the case of replacement of 5-CH_2 group by an ether oxygen.

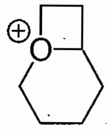


Relative rate : 1.0 0.014 0.14 4.85×10^4

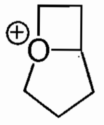
The huge difference in rate that results from the alternative placement of oxygen in eight membered rings reflects the relative stability of various oxonium ions that results from participation. *B* ion is much more favorable than A and the rate retardation in first two case can be attributed to an unfavorable polar effect of the C-O bond.



(A)

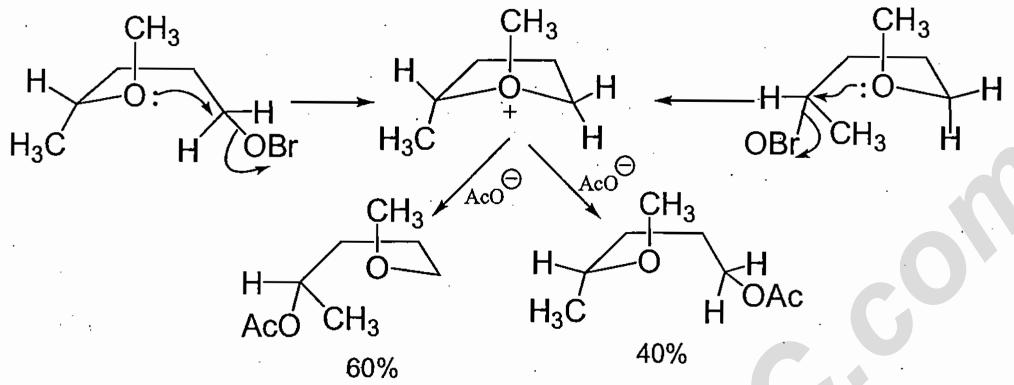


(B)



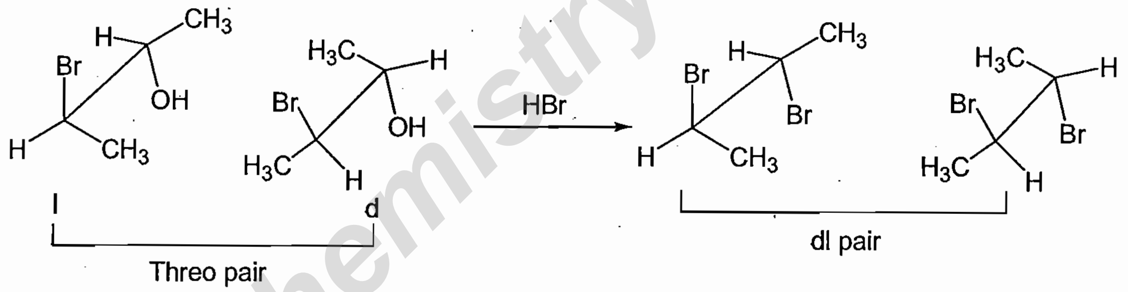
(C)

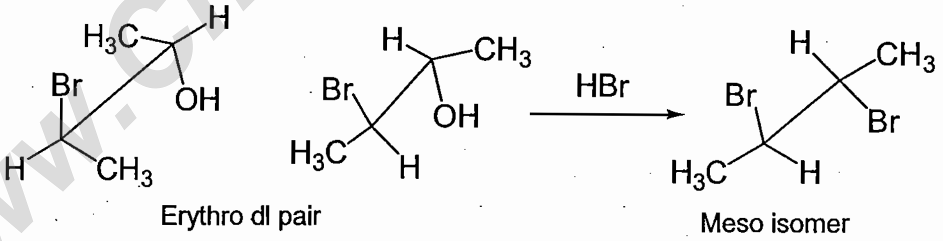
Acetolysis of both 4-methoxy - 1-pentyl brosylate and 5- methoxy-2- pentyl brosylate give the same mixture of product is evidence of participation by ether oxygen in neighbouring group participation reaction



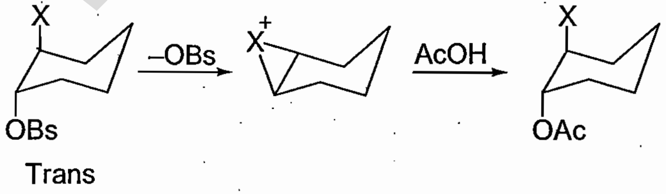
7. Halogen Groups as Neighbouring Group Participation :

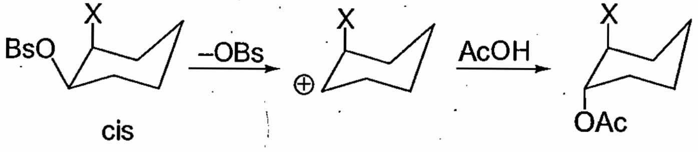
X-halogens (Cl, Br, I) are usually Participating in neighbouring group participation reaction for example, threo dl pair of 3-bromo - 2- butanol when treated with HBr give dl 2, 3-dibromobutane whereas erythro pair give the meso isomers





Weinstein et al (1948, 1951) studied another reaction e.g; acetolysis of cis and trans - 2- halogen - cyclohexyl brosylate





The relative rates :

$$\frac{\text{Rate of trans isomer}}{\text{Rate of cis isomer}} = \frac{2.7\times10^{6}}{1} \quad \text{when x = Iodine(I)}$$

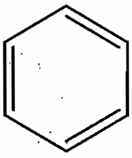
$$\frac{\text{Rate of trans isomer}}{\text{Rate of cis isomer}} = \frac{800}{1} \quad \text{when x = Bromide(Br)}$$

$$\frac{\text{Rate of trans isomer}}{\text{Rate of cis isomer}} = \frac{3.8}{1} \quad \text{when x = Chloride(Cl)}$$

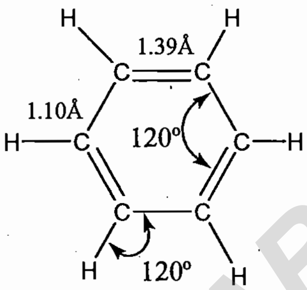
These relative rates are due to different nature of neighbouring group. The rate is dependent on the electron density of halogen group present in the molecule.

5.4. Electrophilic Aromatic Substitution Reactions:

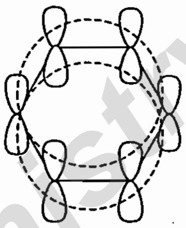
Benzene is one of the most important aromatic compound, which undergoes electrophilic aromatic substitution reaction.



Benzene

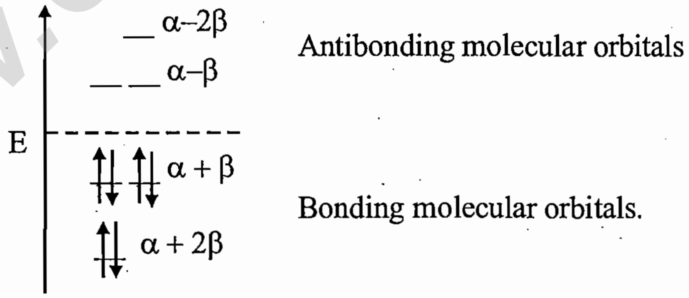


Molecular orbital diagram of benzene:



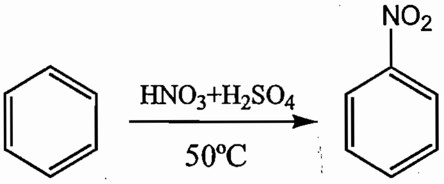
Benzene is a flat molecule with every carbon and every hydrogen lying in the same plane. Each carbon atom has an unhybridised 'p'-orbital which is perpendicular to the molecular plane and overlap with adjacent orbitals and forms a delocalised electron clouds. Electron clouds are equally distributed above and below the molecular plane due to this loosely held π electron clouds benzene undergoes electrophilic attack after that generally expulsion of proton occur **in order to restore aromatic** character of benzene nucleus.

The six π-electrons of the benzene occupy bonding molecular orbitals.



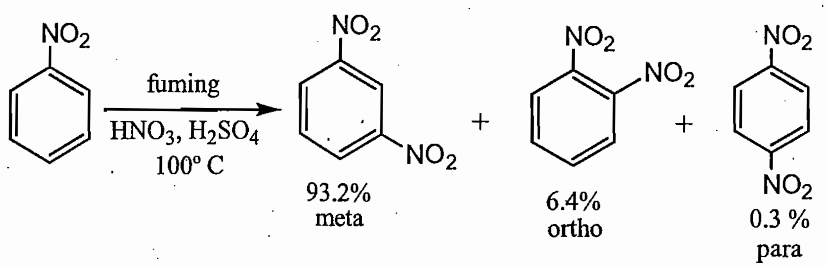
Orientation in electrophilic aromatic substitution:

Benzene is nitrated by a mixture of concentrated nitric and sulfuric acids at 50°C.



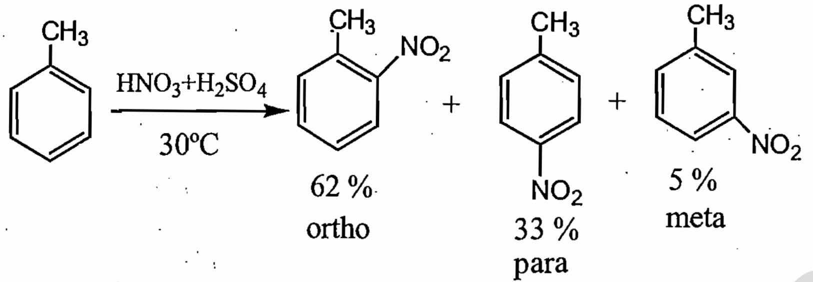
Further nitration of nitrobenzene is considerably more difficult. Stronger acid and higher temperature are required, the product is primarily m-dinitrobenzene.

Example:



On the other hand, toluene undergoes nitration more rapidly than benzene. In this case, the predominant products are the ortho and para isomers.

Example:



***Conclusion*:**

- As shown by these examples, the reactivity of an aromatic ring is influenced by the group attached to it.
- The orientation of an incoming group is also a function of the substituent already present.
- Substituents are generally characterized as being ortho, para or meta directors.

***Remarks*:**

Ortho and para produced together, although the ortho/para ratio may vary with different groups and under different conditions.

On the basis of activating and deactivating, the substitution may be classified as:

1. *Ortho, para directing and activating group.*

   For example: alkyl group, $-NH_2$, $-NR_2$ and $-NH-\overset{O}{\overset{\|}{C}}-R$

   (amino, alkylamino and amido) $-OH$, $-OR$, $-O-\overset{O}{\overset{\|}{C}}-R$
2. *Ortho, para directing and deactivating group*

   $-F$, $-Cl$, $-Br$, and $-I$.
3. *Meta directing and deactivating group*

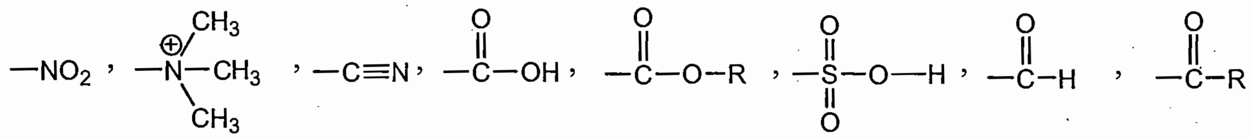
   $-NO_2$, $-SO_3H$, $-\overset{O}{\overset{\|}{C}}-OH$, $-\overset{O}{\overset{\|}{C}}-OR$, $-\overset{O}{\overset{\|}{C}}-H$, $-\overset{O}{\overset{\|}{C}}-R$

Note: All activating groups are ortho, para directing and all meta directing groups are deactiviting.

Ortho/para directing groups are of three kind

Strongly activating group	Moderately activating group	Weakly activating group
$-NH_2$ ($-NHR$, $-NR_2$)$-OH$	$-OCH_3$($-OC_2H_5$) $-NH-\overset{O}{\overset{\|}{C}}-CH_3$	$-C_6H_5$, $-CH_3$($-C_2H_5$)

***Meta Directing*:**



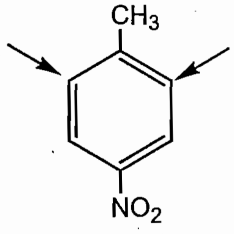
$$-NO_2,\ -\overset{\oplus}{N}(CH_3)_3,\ -C\equiv N,\ -\overset{\overset{O}{\|}}{C}-OH,\ -\overset{\overset{O}{\|}}{C}-O-R,\ -\underset{\underset{O}{\|}}{\overset{\overset{O}{\|}}{S}}-O-H,\ -\overset{\overset{O}{\|}}{C}-H,\ -\overset{\overset{O}{\|}}{C}-R$$

Orientation in disubstituted benzene:

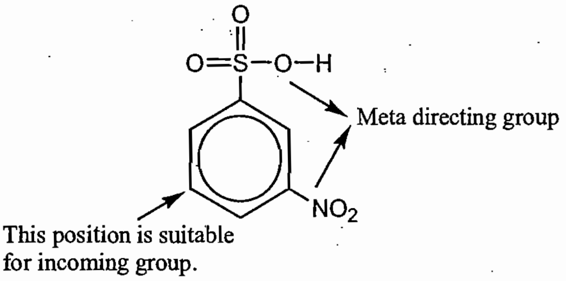
The presence of two substituents on a ring makes the problem of orientation more complicated however, it is possible in certain case to make predictions in accordance with the following generalization.

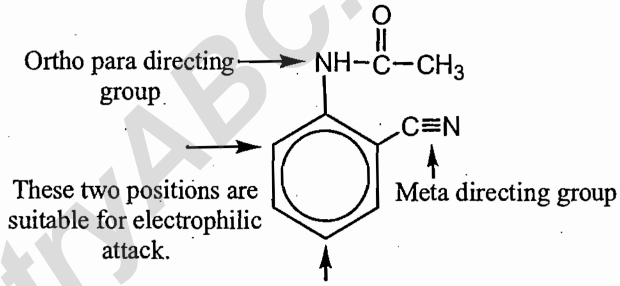
1. The two substituents may be located so that the ***directive influence of one reinforce the other***

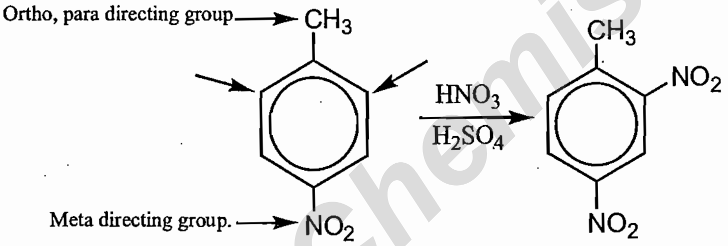
Example **:**

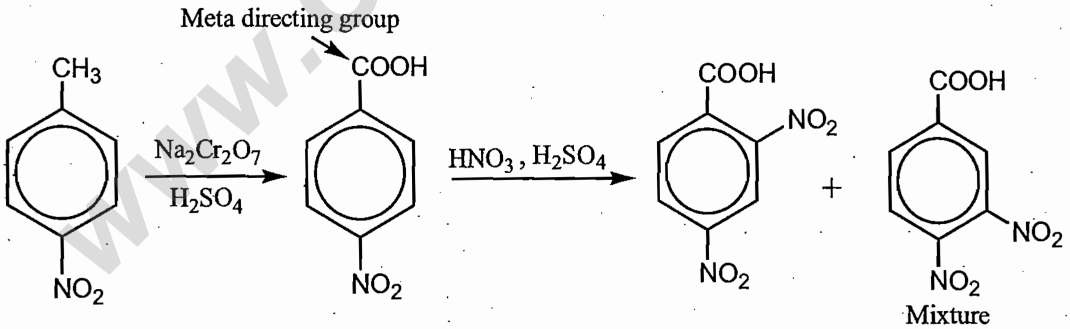


$-CH_3$ group is ortho/para directing and $-NO_2$ group is meta directing so the indicated arrow positions are common position for these two groups for directing the incoming group.



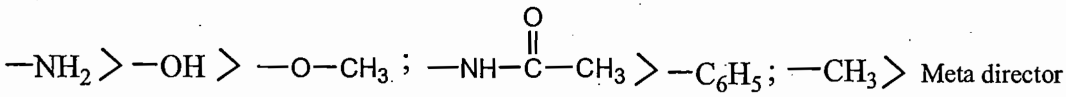




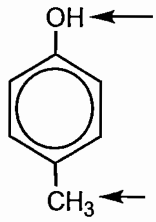


So, the first route is preferred for a preparation of 2, 4-dinitrobenzoic acid.

2. **Strongly activating groups** with deactivating or weakly activating group.
The differences in directive power in the sequence



$$-NH_2 > -OH > -O-CH_3\ ;\ -NH-\overset{\overset{O}{\|}}{C}-CH_3 > -C_6H_5\ ;\ -CH_3 > \text{Meta director}$$

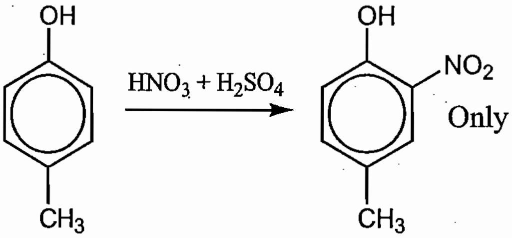


OH ← Strong activating group. so, it will direct the incoming group at ortho and para position, but para position is already blocked. So, the incoming electrophile will attack at ortho position.

CH_3 ← Weak activating group

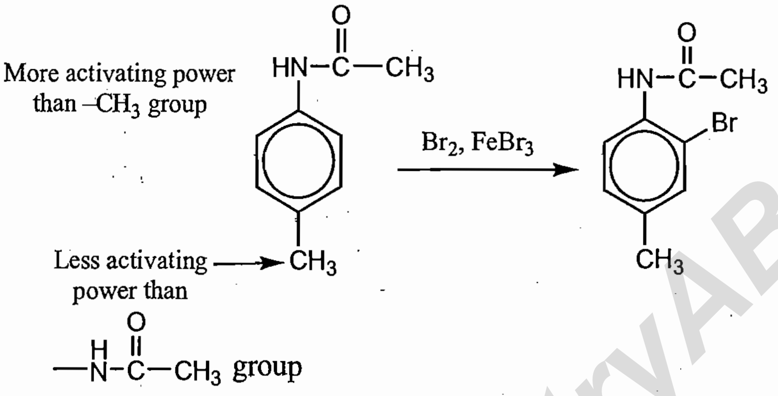
***Examples*:**

(i)



Only one product is obtained.

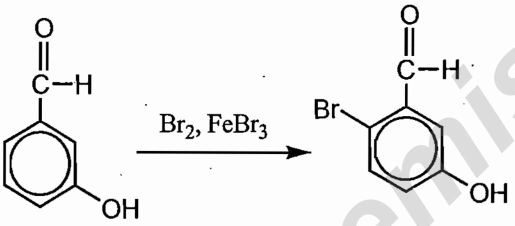
(ii)



More activating power than –CH_3 group

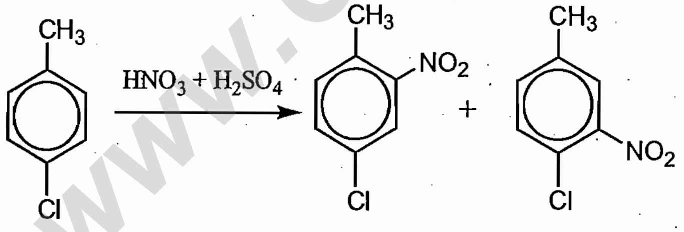
Less activating power than $-\overset{H}{N}-\overset{O}{\overset{\|}{C}}-CH_3$ group

(iii)



***Remark*:**

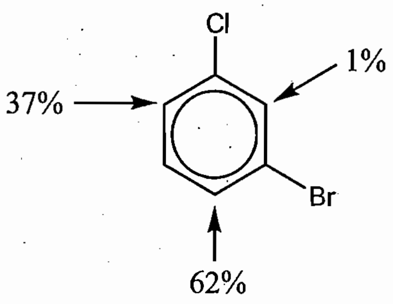
There must be a large difference in the effects of the two groups for appropriate result, otherwise one gets result like these.



58 % 42%

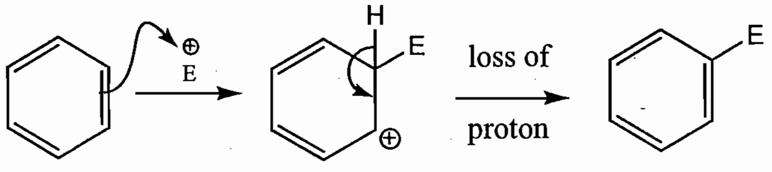
3. There is often less substitution between two groups that are meta to each other.

Example:



Reactions on benzene ring:

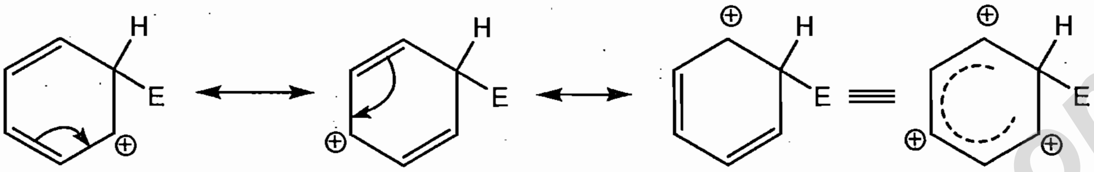
General mechanism for electrophilic aromatic substitution.



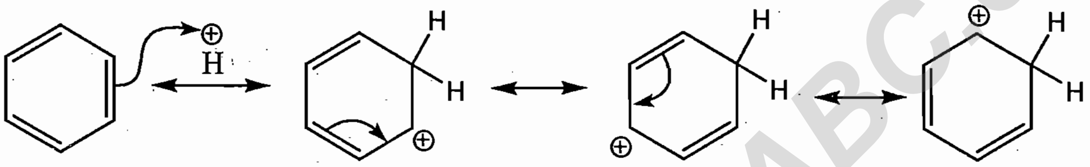
Intermediate cation

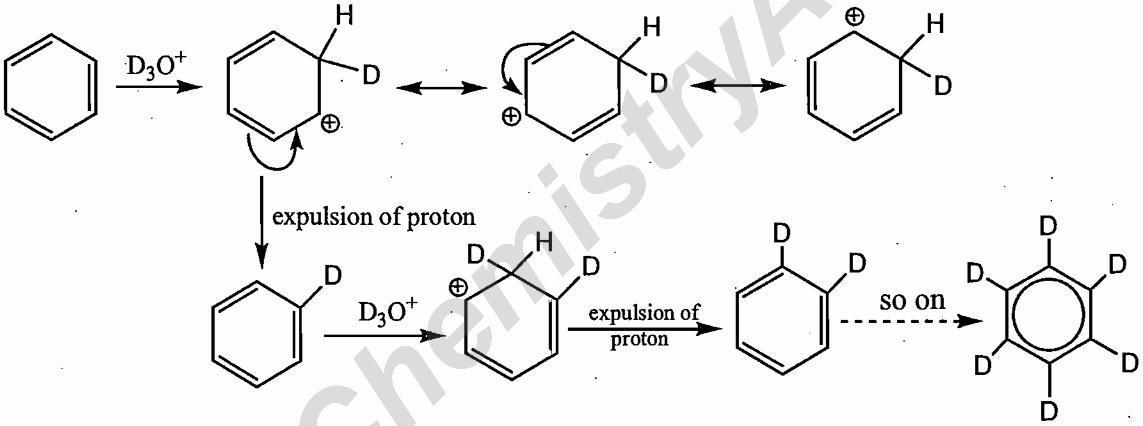
Important points:

- The cation intermediate is less stable than the starting material or the product.
- The cation is reasonably stable because of delocalization around the six-membered ring.

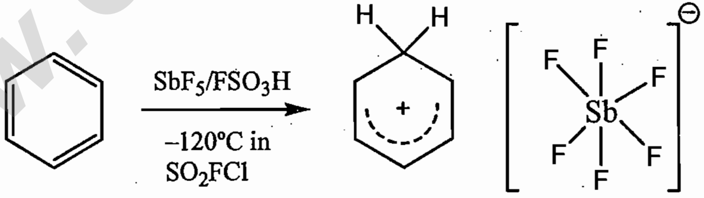


- In strong acid, the electrophile would be a proton, the reaction would be the exchange of the proton in benzene ring. For example:



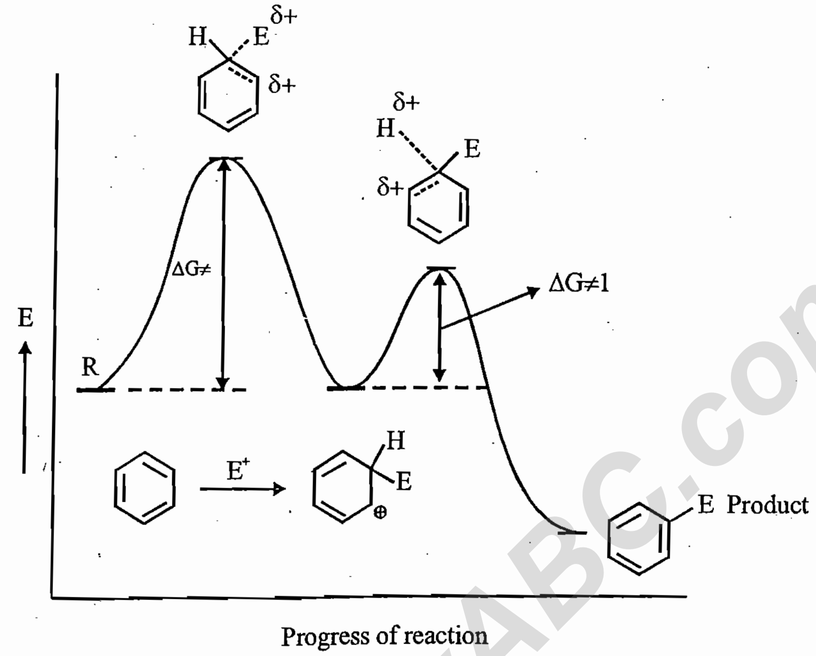


Ultimately lead to C_6D_6 which is useful solvent in NMR.



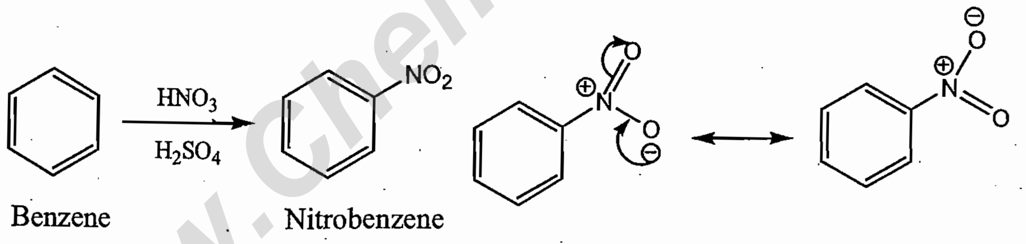
Potential energy diagram:

- Two step process.
- Since the first step involved the temporary disruption of the aromatic π system, therefore it is rate determining step.
- Second step is the fast step.



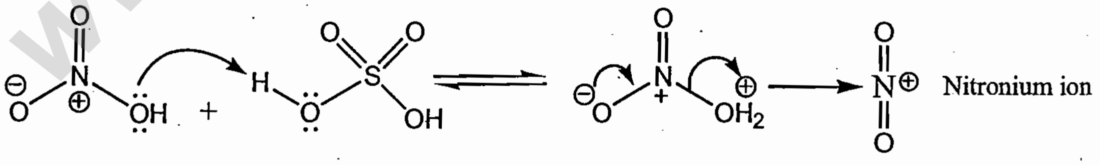
(i) Nitration of benzene: Important points about nitration reaction.

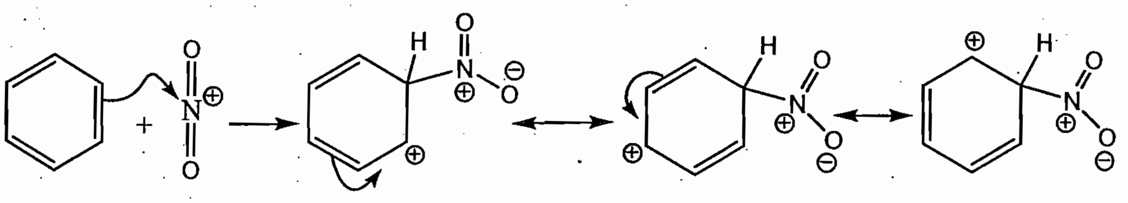
- Introduction of nitro group into an aromatic system.
- It provides a general entry into aromatic nitrogen compounds.
- This reaction is not available for aliphatic nitrogen compounds.
- Aromatic nitration requires very powerful reagents.
- Generally nitrating agent is mixture of concentrated nitric acid and sulphuric acid.



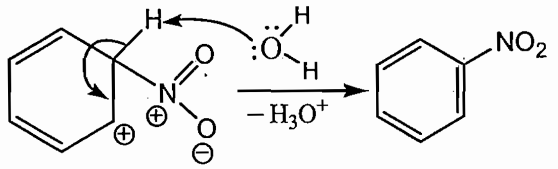
***Mechanism*:**

Step-I: Formation of a very powerful electrophile. Sulphuric acid is the strong acid and it protonates the nitric acid.





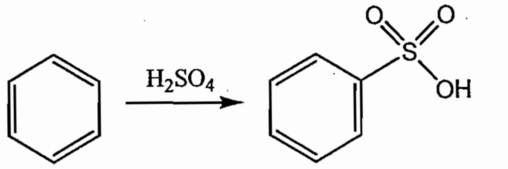
Step-II: Expulsion of proton



***Conclusion*:** Nitration converts aromatic compounds into nitrobenzene using $\overset{\oplus}{NO_2}$ from ($HNO_3 + H_2SO_4$).

(ii) Sulphonation of benzene:

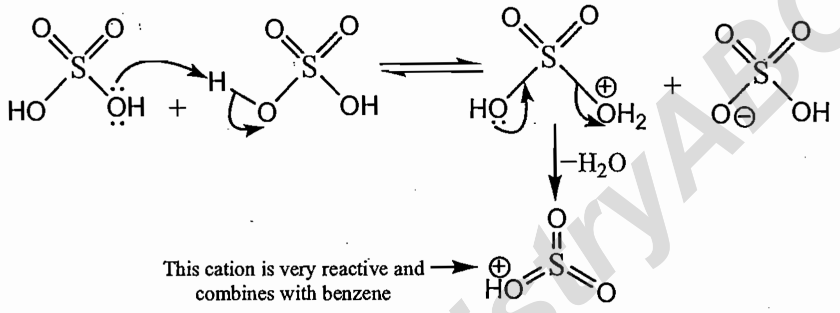
Benzene reacts slowly with H_2SO_4 acid alone to give benzene sulphonic acid.



Benzene sulphonic acid

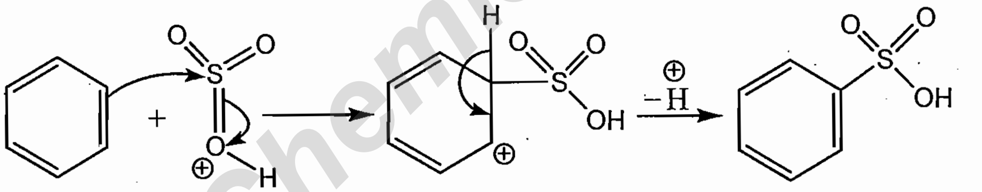
***Mechanism*:**

Step-I:



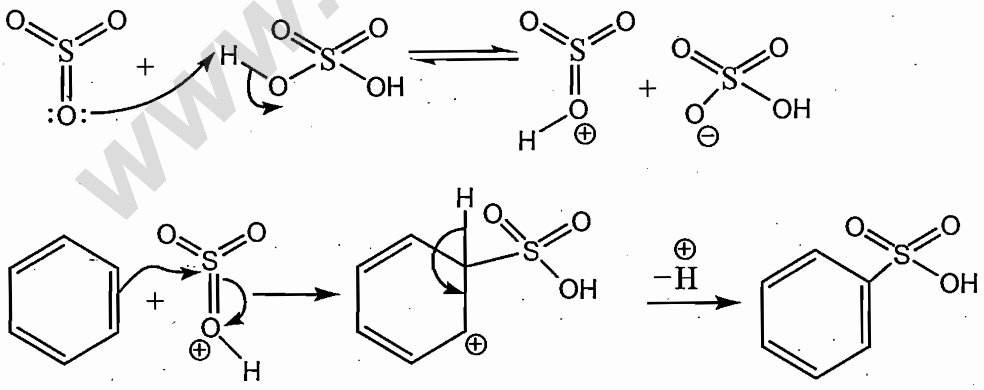
This cation is very reactive and combines with benzene

Step-II:



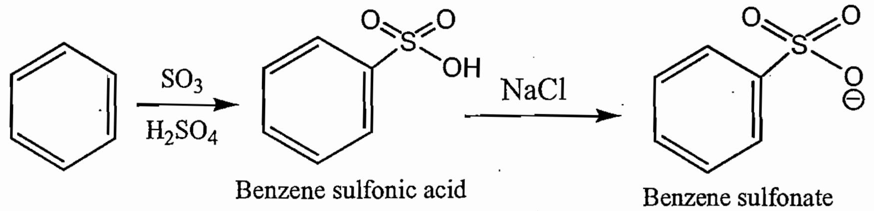
Benzene sulphonic acid

The cation intermediate can also be formed by the protonation of SO_3.



PROBLEMS

1.



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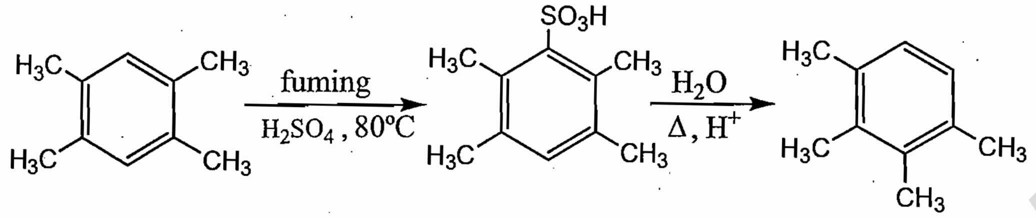
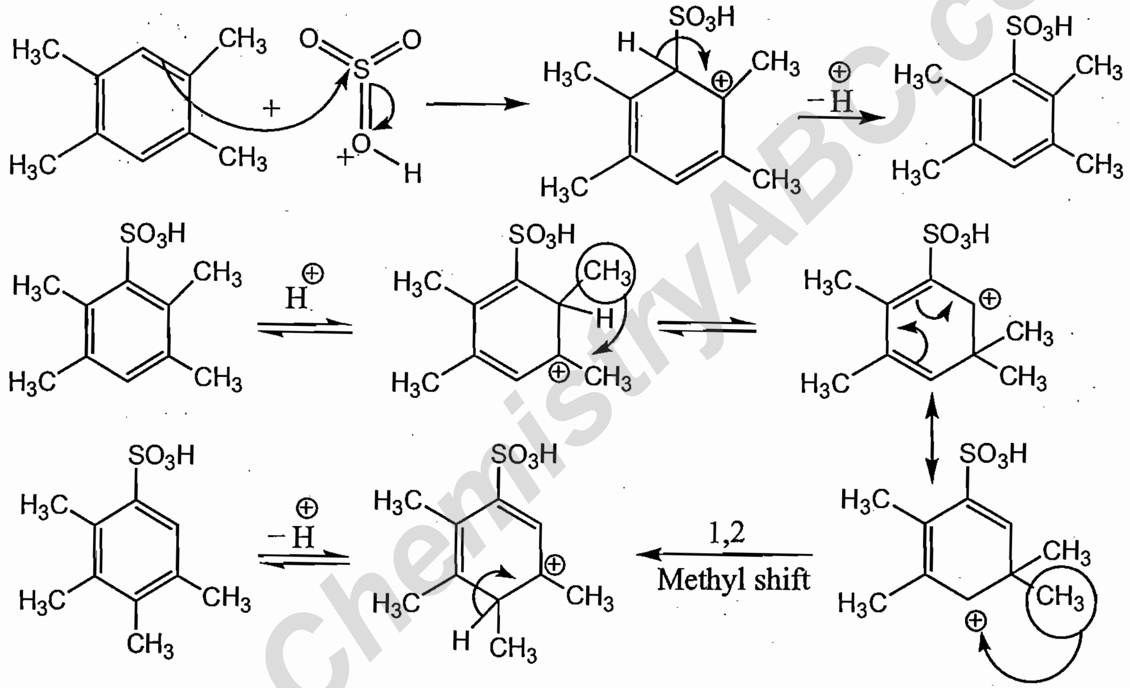
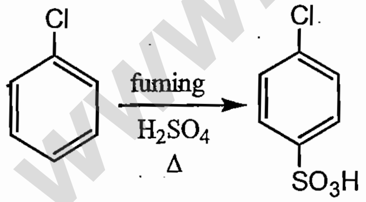


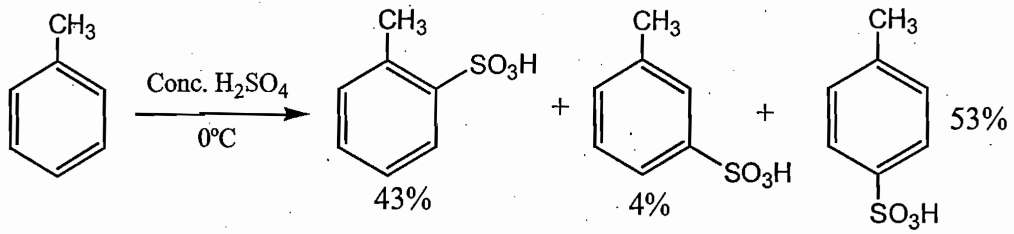
***Mechanism*:**



This rearrangement of polyalkyl benzene by use of sulfuric acid is known as the ***Jacobsen reaction***.

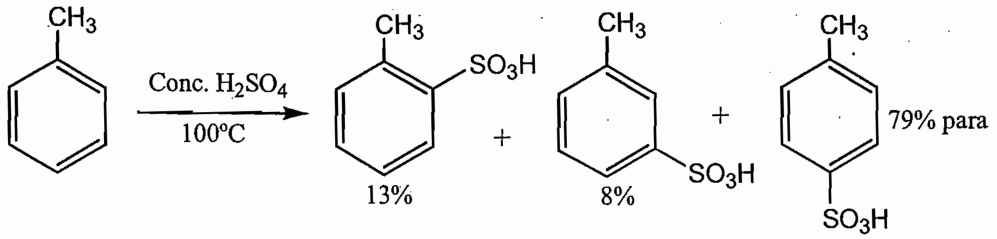
3.





***Remark*:** The isomer distribution often depends on the exact experimental conditions.

Example: The product composition from toluene at 100° C is:



The sulfonation reaction is **reversible** and the product depends on whether the reaction conditions favour.

Kinetic or thermodynamic control:

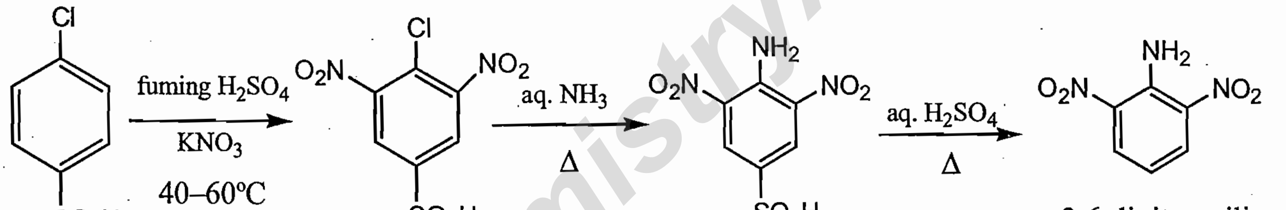
In the sulfonation of toluene at low temperature, the reaction product is the product of kinetic control; that is the product composition reflect relative energies of transition state. At higher temperature, the reverse reactions have a significant rate and the reaction takes on the aspects of an equilibrium.

$$\mathrm{Ar{-}H} + \mathrm{SO_3} \rightleftharpoons \mathrm{Ar{-}SO_3H}$$

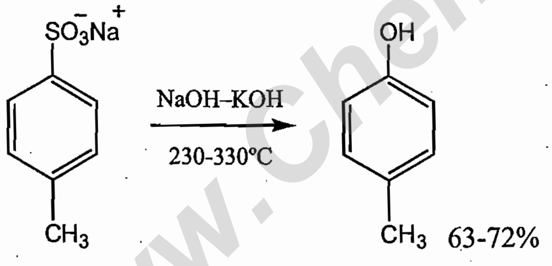
The sulfonic acid group is bulky group and steric hindrance interactive with ortho substituent is significant. At equilibrium, the relatively unhindered p-toluenesulfonic acid dominates over o-toluenesulfonic acid.

Note: The reversal of sulfonation can be carried out by heating the sulfonic acid in dilute aqueous sulfuric acid. In this way sulfonic acid group can serve as a protecting group to direct aromatic substitution into other position.

Example:

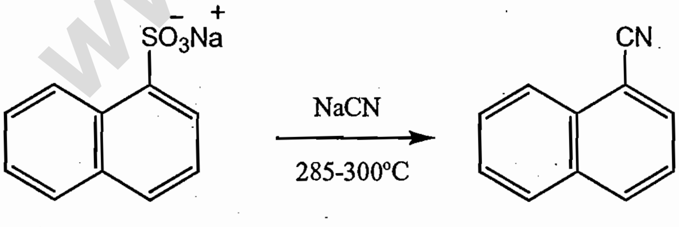


2,6-dinitroaniline



Sodium p-toluenesulfonate

p-cresol



sodium 1-naphthalene sulfonate

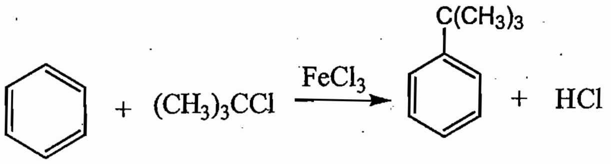
60-70%
1-naphthonitrile

5.5. Preparation of Aromatic Hydrocarbon

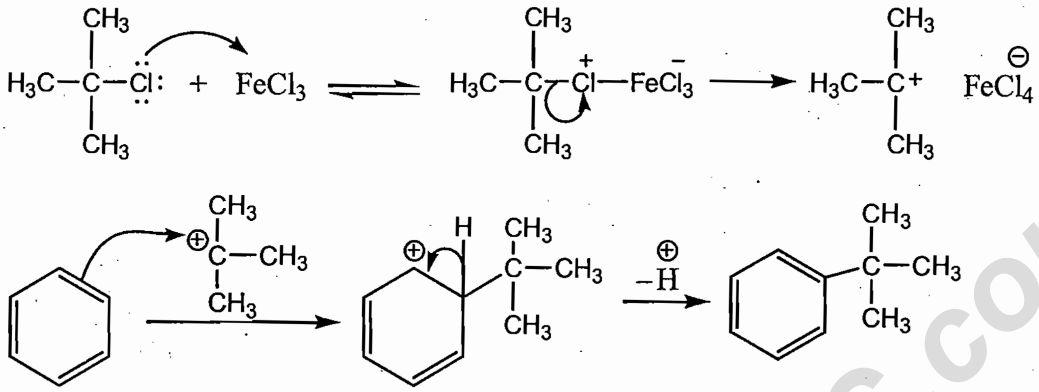
(i) Friedel-Crafts alkylation:

- Benzene and some substituted benzene undergo alkylation when treated with an alkyl halide and Lewis acid as a catalyst like $FeBr_3$ or $AlCl_3$.

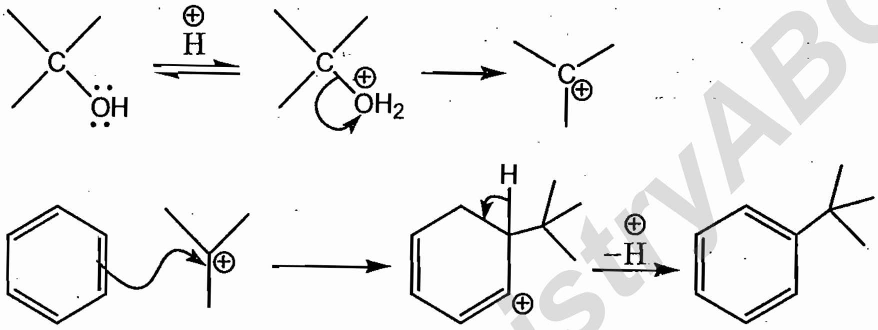
Example:



Mechanism:



4.



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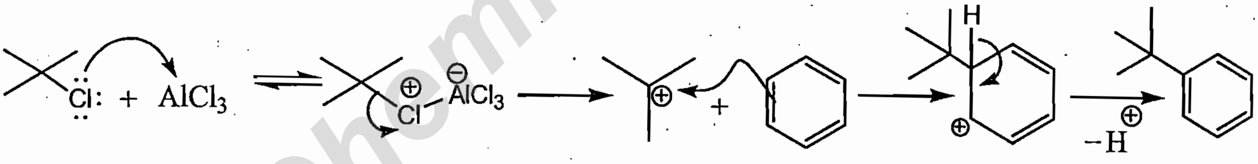
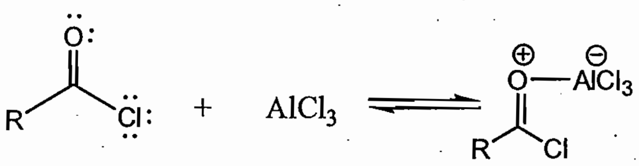
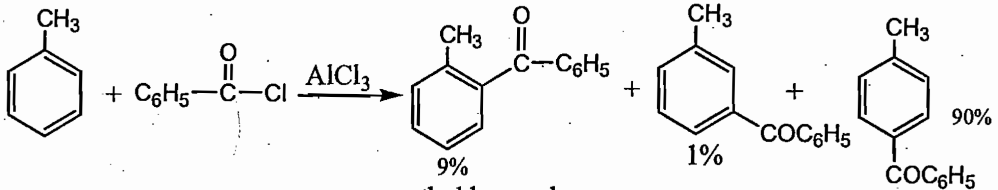


- The reaction of aromatic rings with acid chlorides or anhydrides and a Lewis acid.
- The reactive reagent is an electrophilic complex between the acid chloride or anhydride and the Lewis acid.

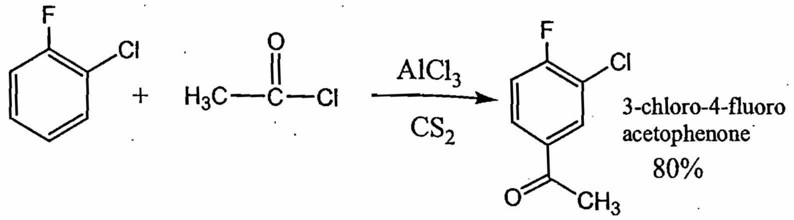


- These species appear to be effectively bulky; para substitution tends to dominate substantially over ortho.
- In Friedel–Crafts acylation reactions with substituted benzene, the para acylation product is often obtainable in pure form and in high yield.

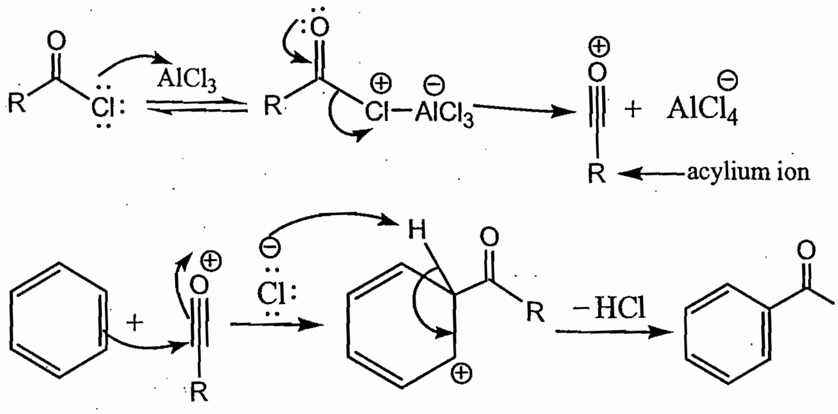
Example:



o-methyl benzophenone

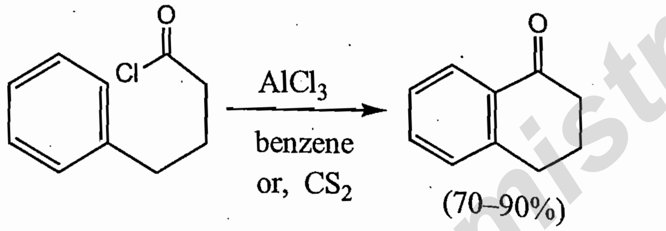


Mechanism of Friedel-Crafts Acylation:



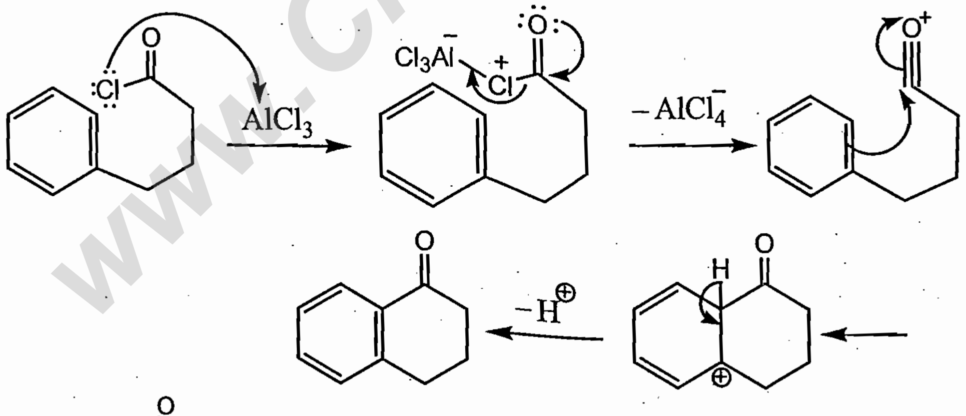
Remark:

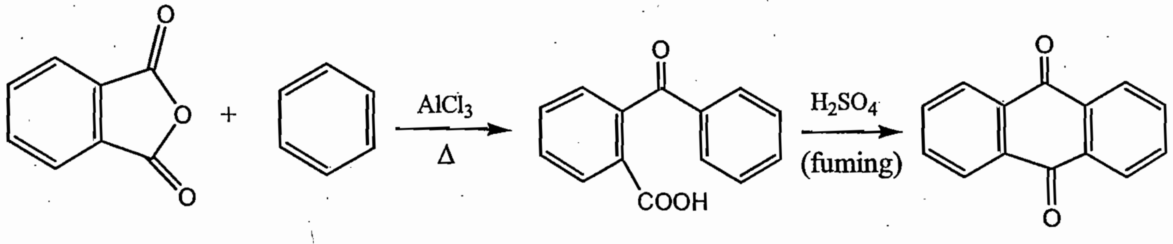
- The acylation is better than the alkylation because it does not require any particular structural feature in the acyl chloride. –R can be almost anything. The acylation stops clearly after one reaction whereas the alkylation gives mixture of products.
- Cyclic anhydrides generally work well in Friedel-Crafts acylations.

6. 

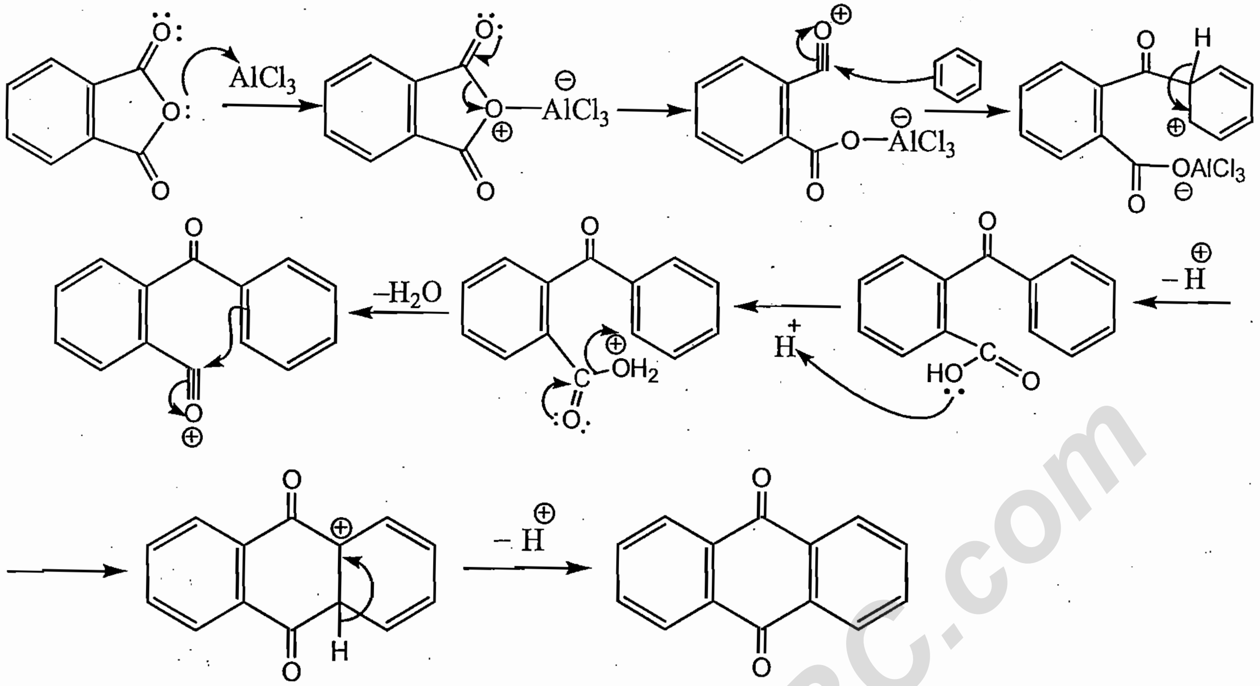
1–oxo–1,2,3,4-tetrahydro
natphthalene α–tetralone.

Mechanism:



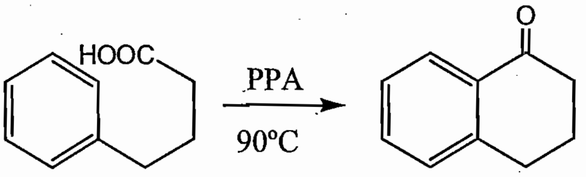
7 

***Mechanism*:**



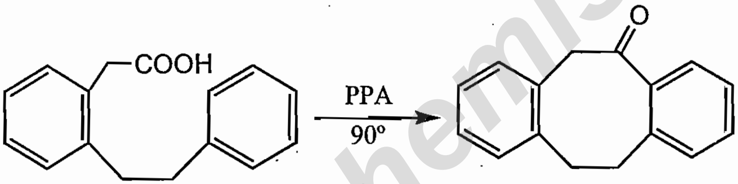
Note: PPA(polyphosphoric acid) is also convenient reagent for carrying out such cyclization.

8.



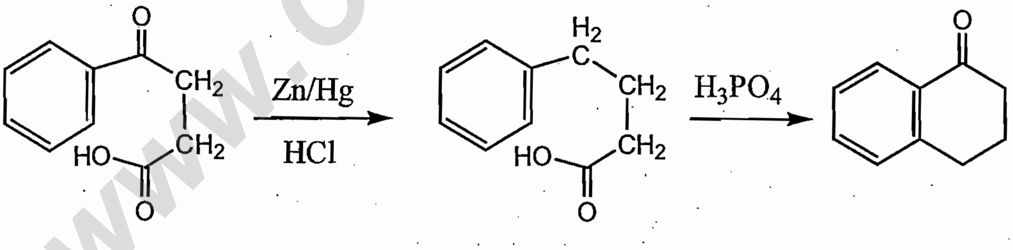
(75–86%)

9.



93%

10.



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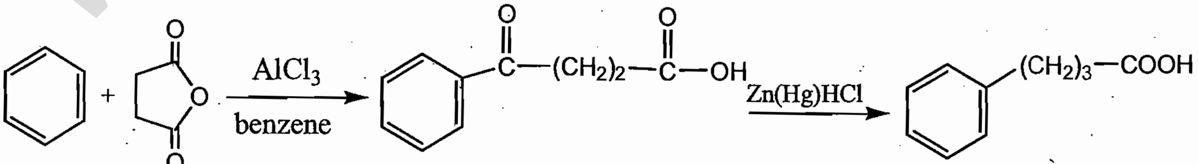
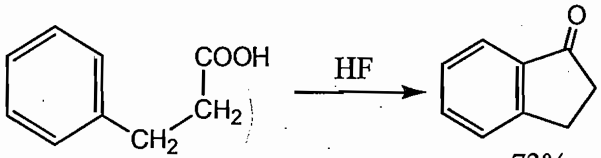


84%

82–89%

12.

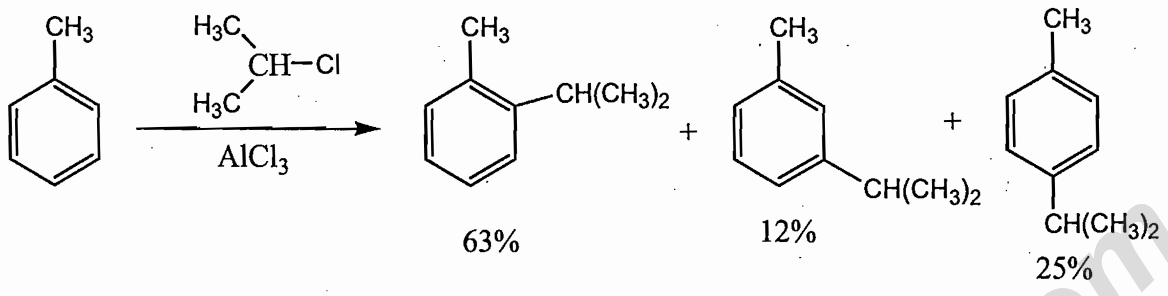


73%
(I–indane)

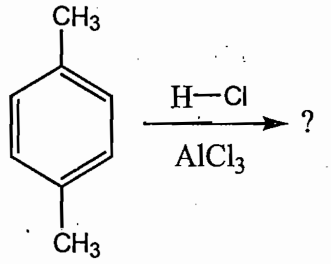
(ii) Friedel-Crafts alkylation of substituted benzene

Relatively non specific because of the high reactivity and low selectivity of alkylations.

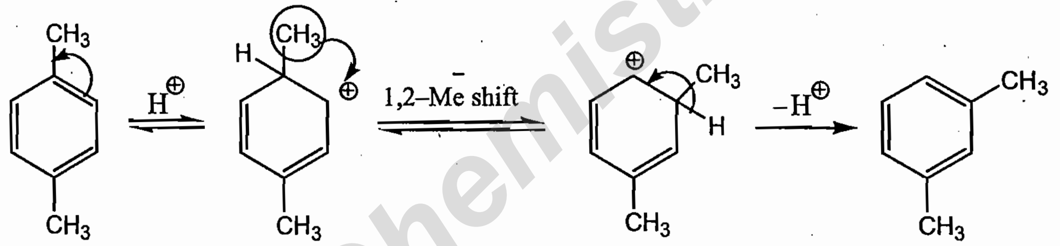
Example:
Under mild conditions with aluminium chloride in acetonitrile, isopropylation of toluene gives predominantly the expected ortho, para orientation but with substantial amount of meta product.



Note: The order of effectiveness of lewis acid catalyst has been shown to be
$AlCl_3 > FeCl_3 > BF_3 > TiCl_3 > ZnCl_2 > SnCl_4$



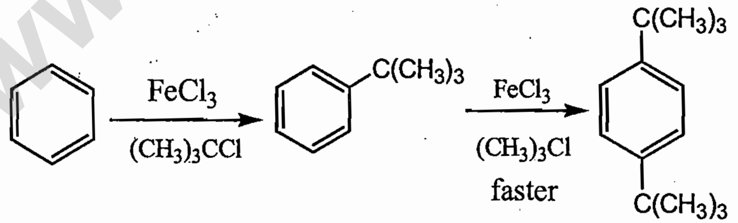
Mechanism:

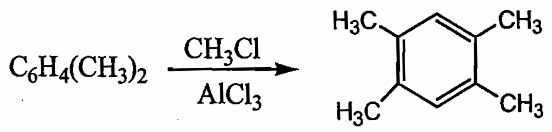


Limitations of Friedel-Crafts alkylation reaction:

1. The alkyl benzene is generally **more reactive in electrophilic aromatic** substitution than in benzene itself, hence, the alkyl benzene reaction product tends to react **to give di, and higher alkylated products.**

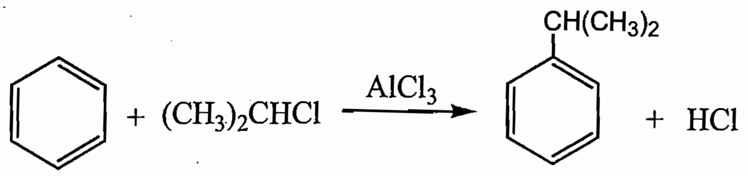
Example:



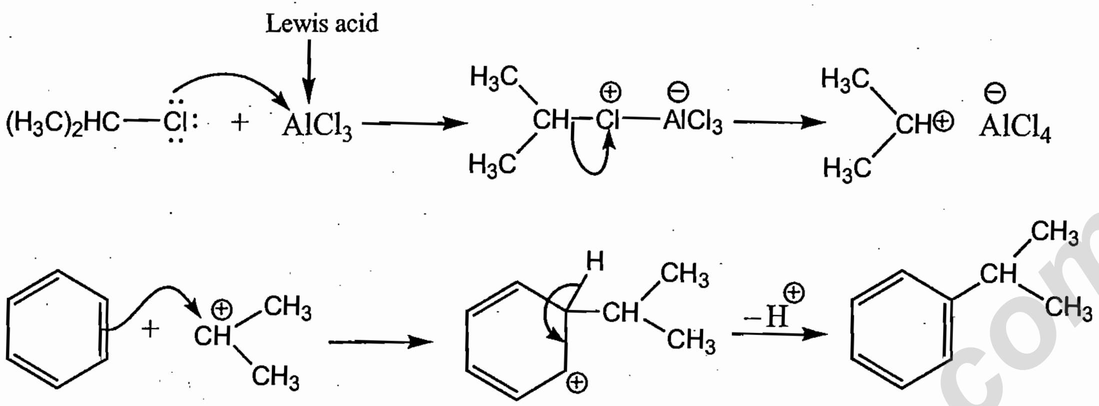


2. Rearrangement to isomeric carbonium ion.

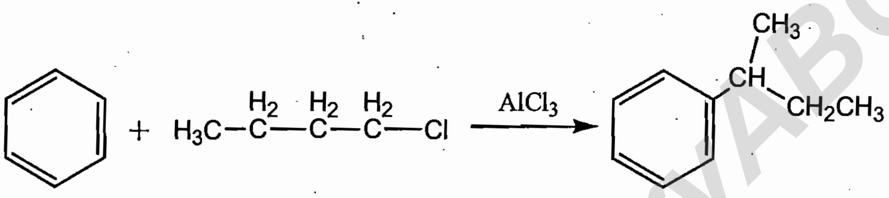
Example:
Isopropyl chloride or bromide reacts normally with aluminium chloride and benzene to give isopropyl benzene.



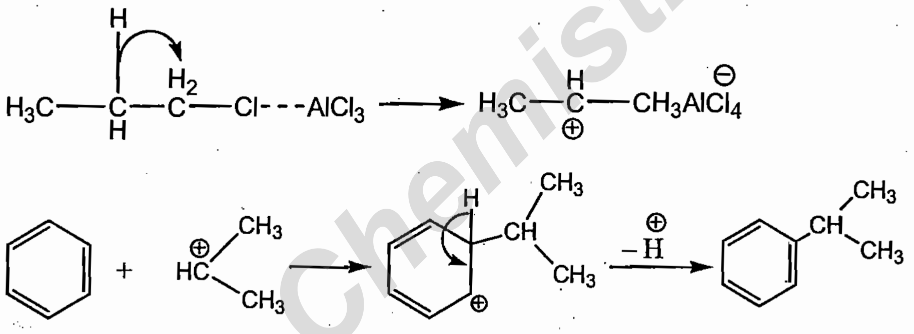
Mechanism:



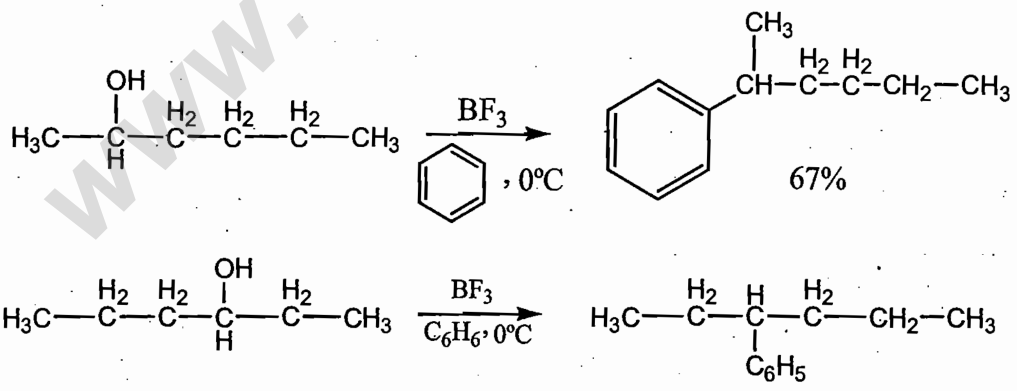
However 1-chloropropane also gives isopropyl benzene under these conditions.



Mechanism:

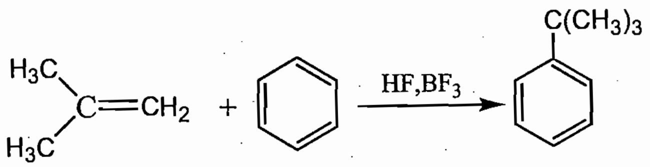


3.

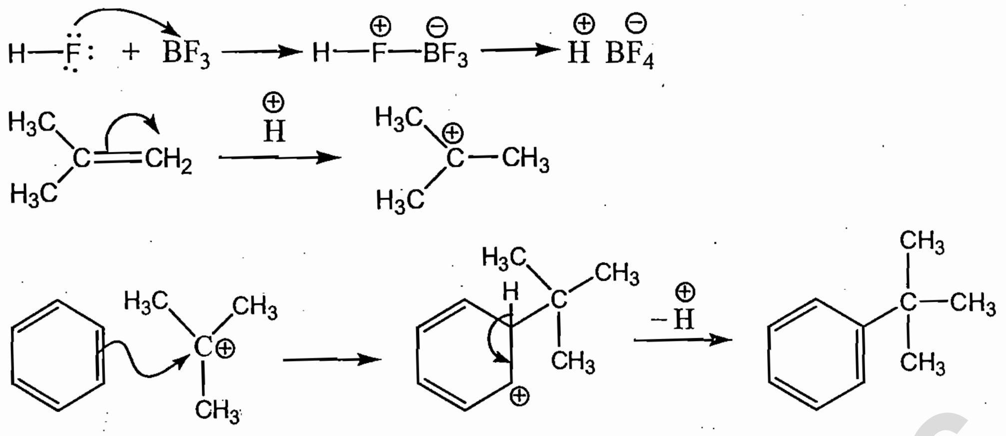


Alkylation reactions can also be accomplished with alkenes.
Catalyst used : H–F, –BF_3 and HCl–$AlCl_3$.

Example:

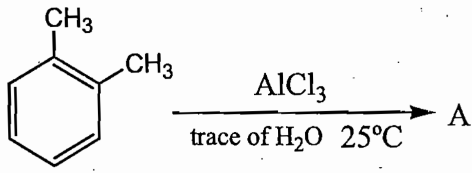


Mechanism:



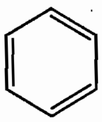
PROBLEMS

1.

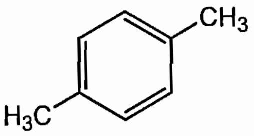


A. The major product (A) is:

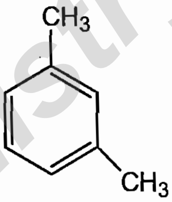
(a)



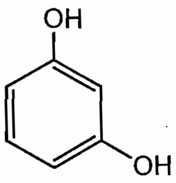
(b)



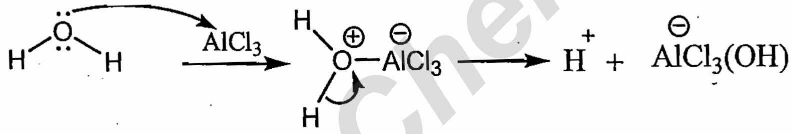
(c)

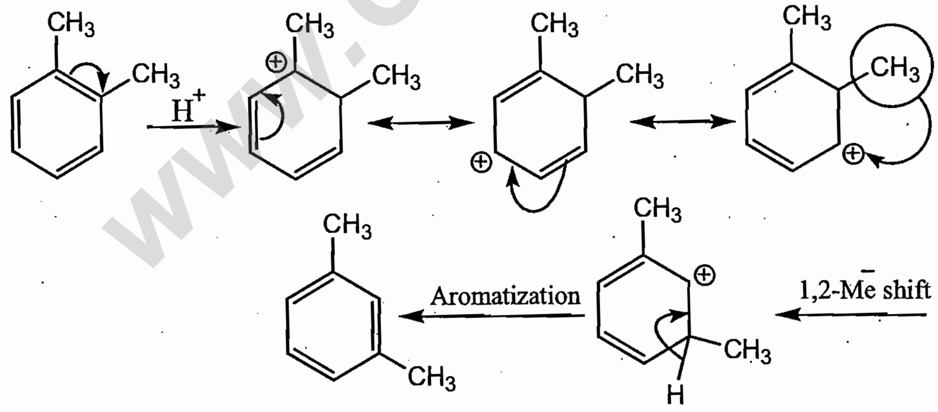


(d)

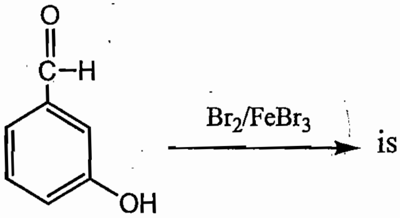


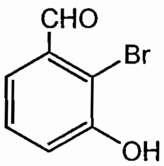
Soln.





2. The major product of the reaction



(a)


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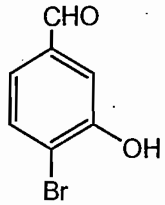
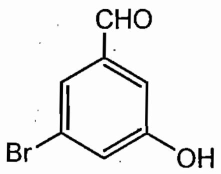
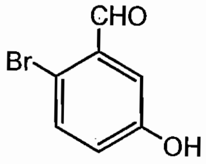
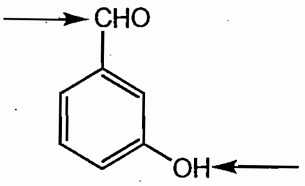


(c)


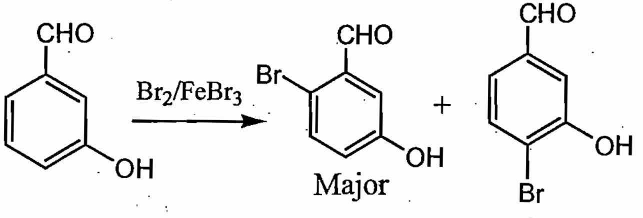
(d)


Soln. Meta directing group.



ortho, para directing group

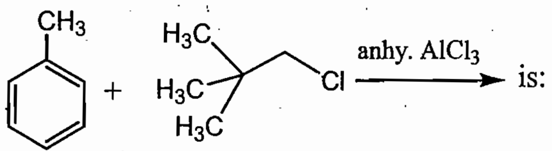
So, the ortho, para directing group directs the incoming exclusively at para position.

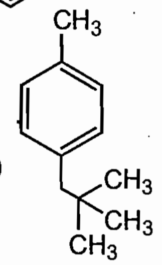


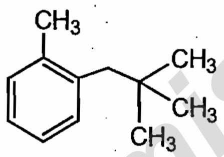
Major

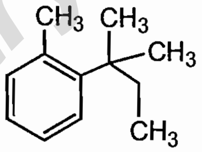
Minor

3. The major product of the following:



(a)


(b)


(c)


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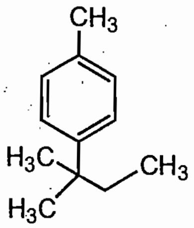
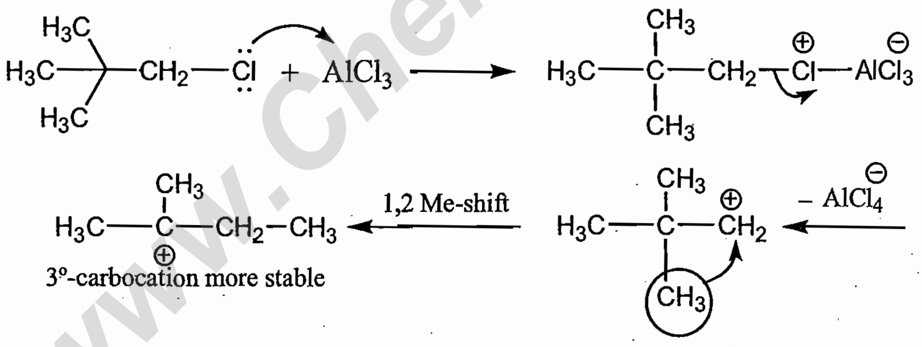
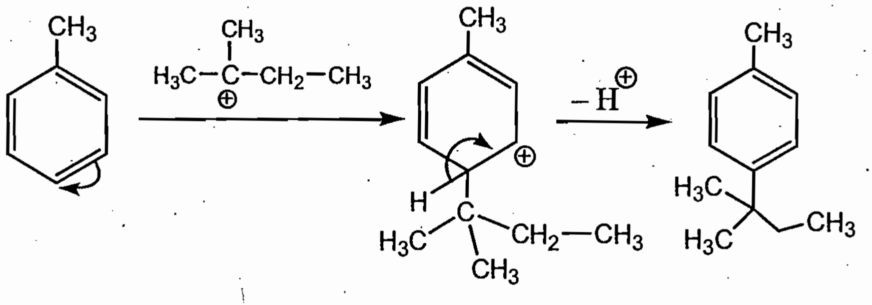


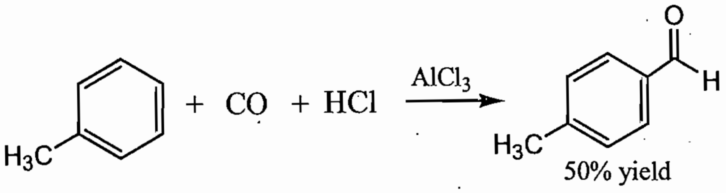
Soln.





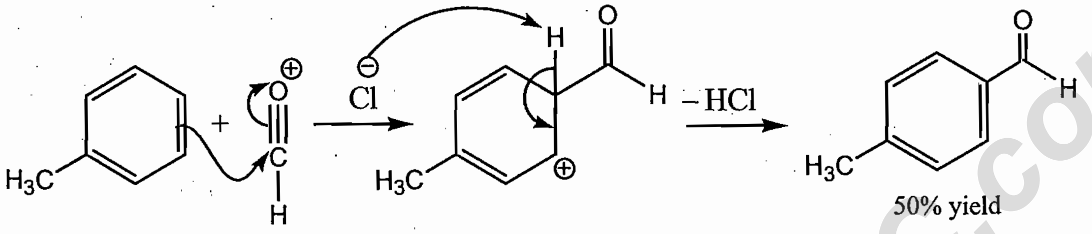
(iii) Gattermann-Koch Reaction

- It is formylation of benzene and substituted benzene in the presence of Lewis acid.
- Electrophile is formylium ion.



***Mechanism*:**

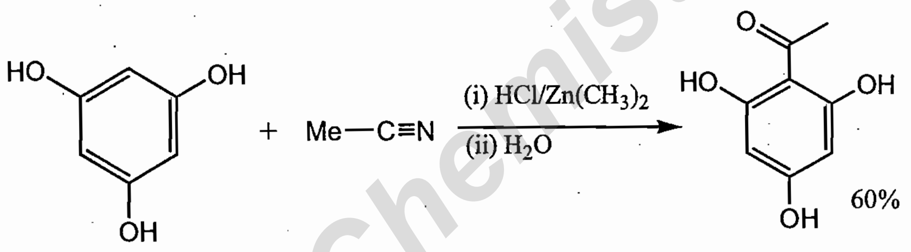
$$\mathrm{H{-}Cl} + \overset{\ominus}{\mathrm{C}}{\equiv}\overset{\oplus}{\mathrm{O}} + \mathrm{AlCl_3} \rightleftharpoons \mathrm{H{-}C}{\equiv}\overset{\oplus}{\mathrm{O}} + \overset{\ominus}{\mathrm{AlCl_4}}$$



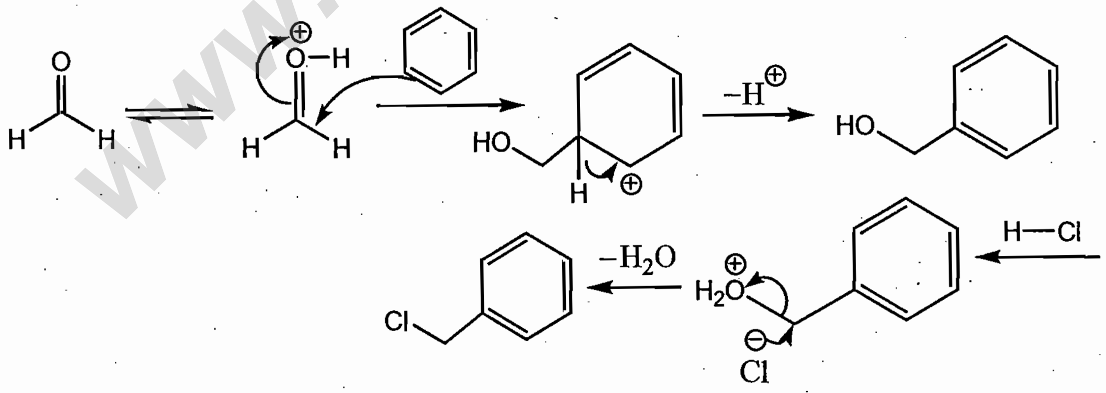
Remark: Gattermann-Koch reaction does not work with phenolic or amino aromatic species due to complex formation with lewis acid.

(iv) Gattermann Reaction

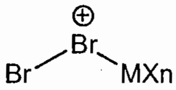
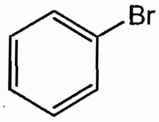
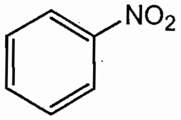
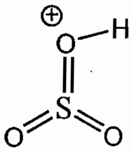
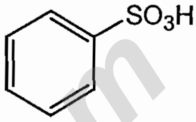
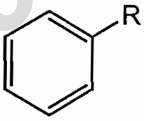
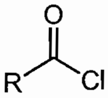
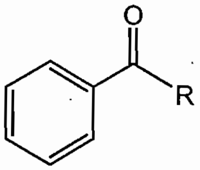
- Modification of Gattermann-Koch reaction:
- Instead of using protonated carbon monoxide protonated hydrogen cyanide is used.
- The reaction goes via an imine intermediate, which under the condition of the reaction is hydrolysed to aldehyde.



Chloromethylation:

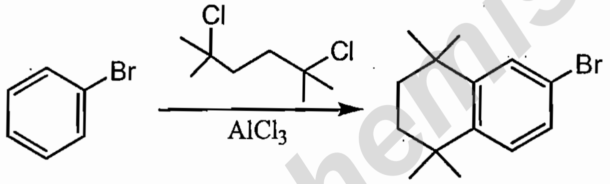


Summary of the main electrophilic substitutions on benzene:

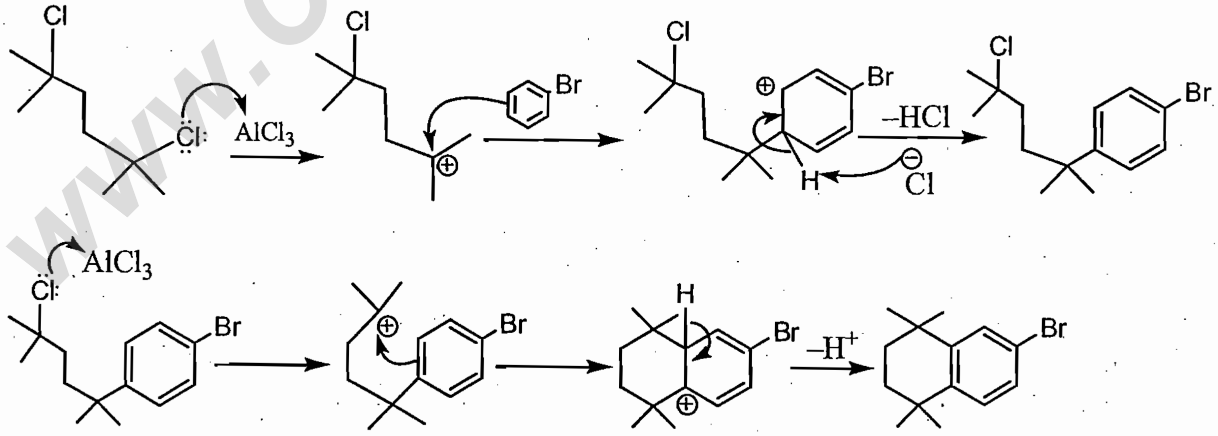
Reaction	Reagents	Electrophile	Product
Bromination	Br_2 and Lewis acid eg. $AlCl_3$, $FeBr_3$ Fe powder.		
Nitration	$HNO_3 + H_2SO_4$	$O{=}\overset{\oplus}{N}{\longrightarrow}O$	
Sulfonation	conc. H_2SO_4 or H_2SO_4 + SO_2 (Oleum)		
Friedel-Crafts alkylation	R–X + Lewis acid usually $AlCl_3$.	$\overset{\oplus}{R}$	
Friedel-Crafts acylation	 + Lewis acid usually $AlCl_3$	$R-\!\!\equiv O^{\oplus}$	

PROBLEMS

1.



***Mechanism*:**



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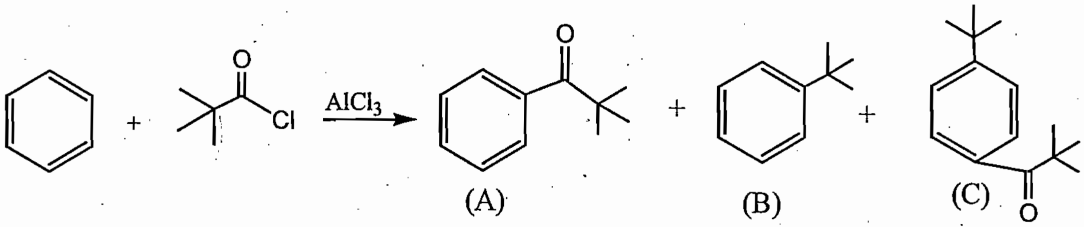
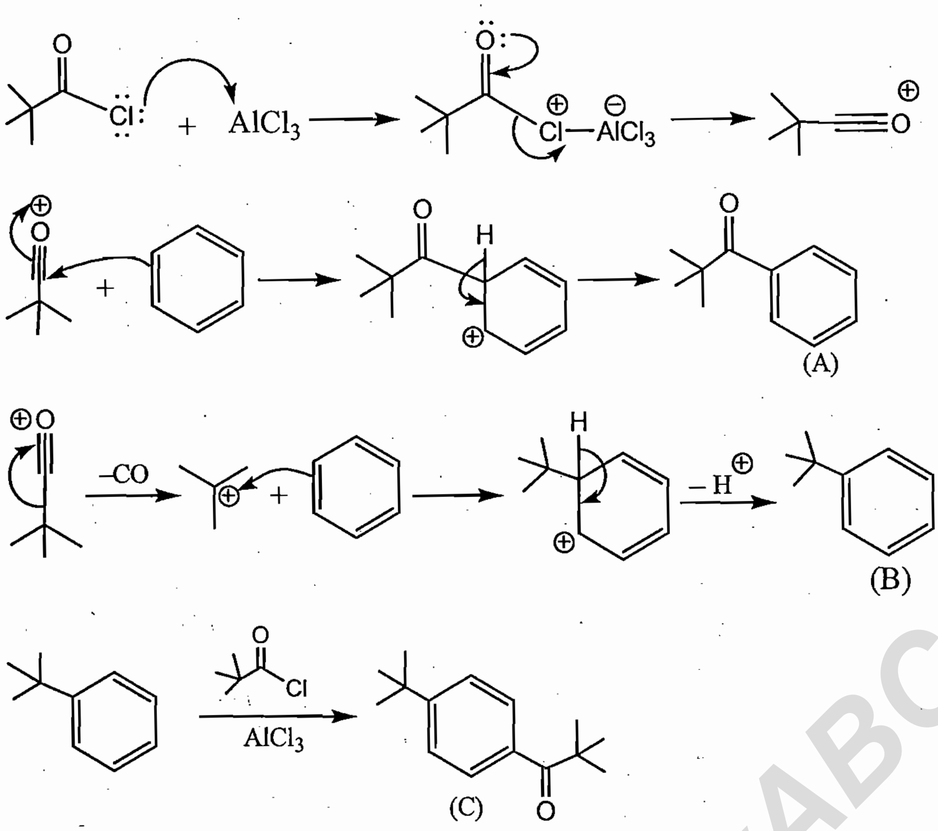


Explain the formation of product.

Soln.



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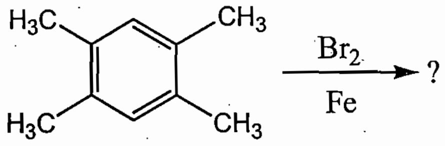
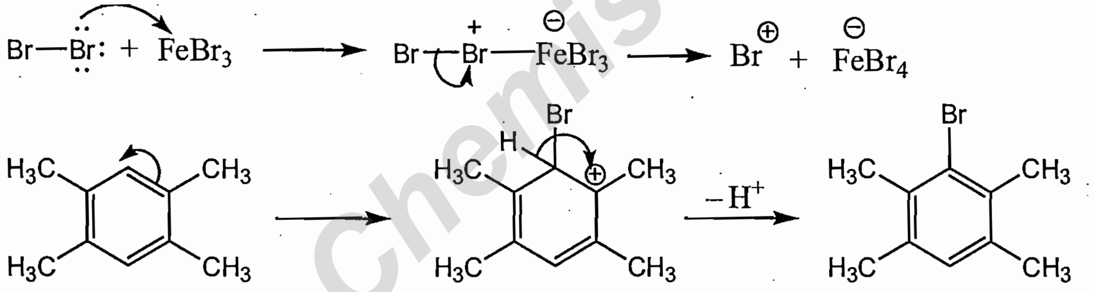


Soln.



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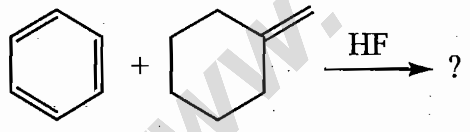
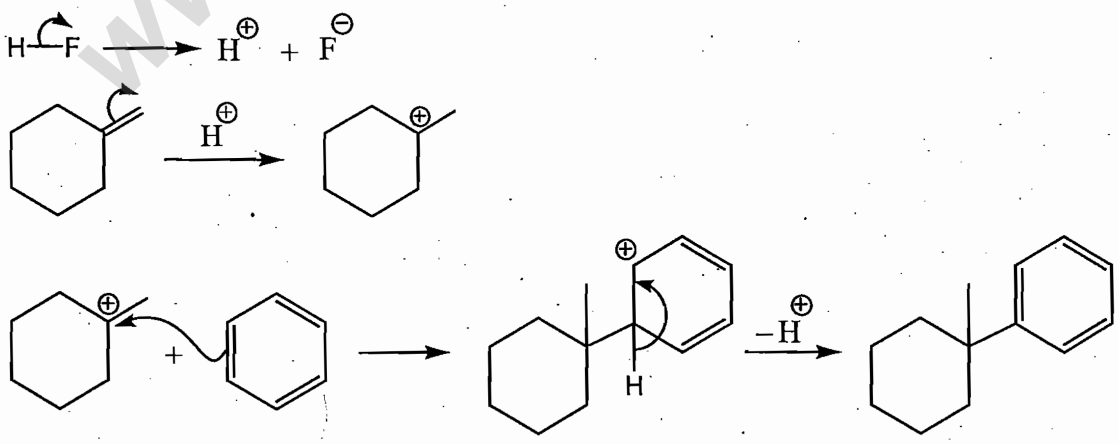
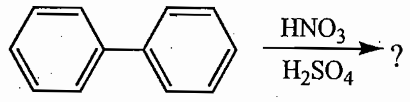
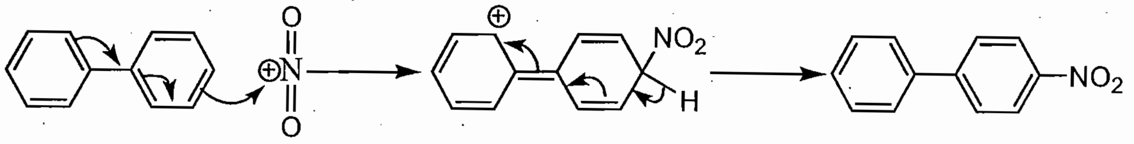
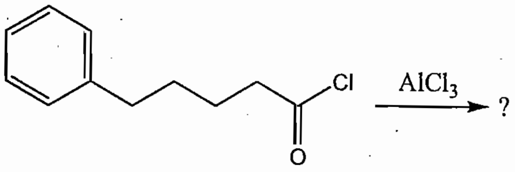


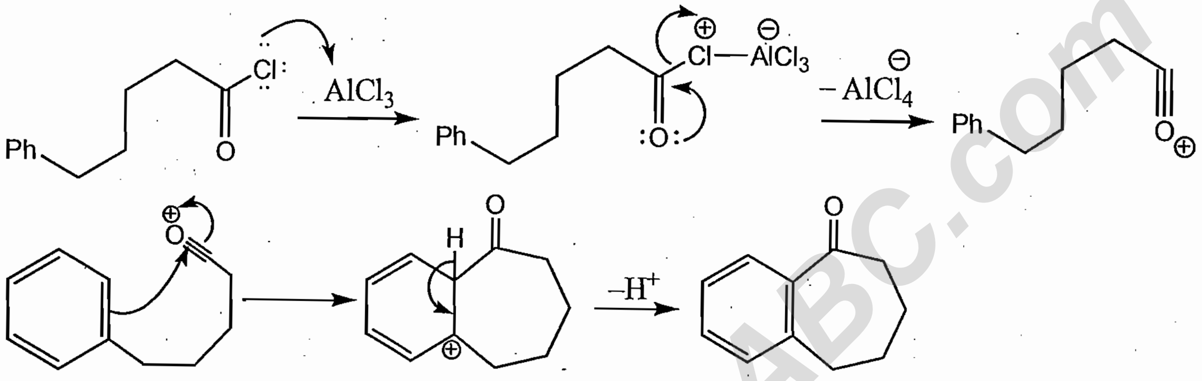
Soln.

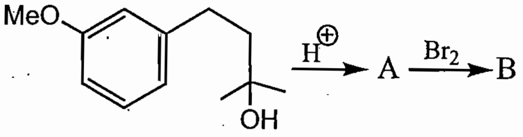


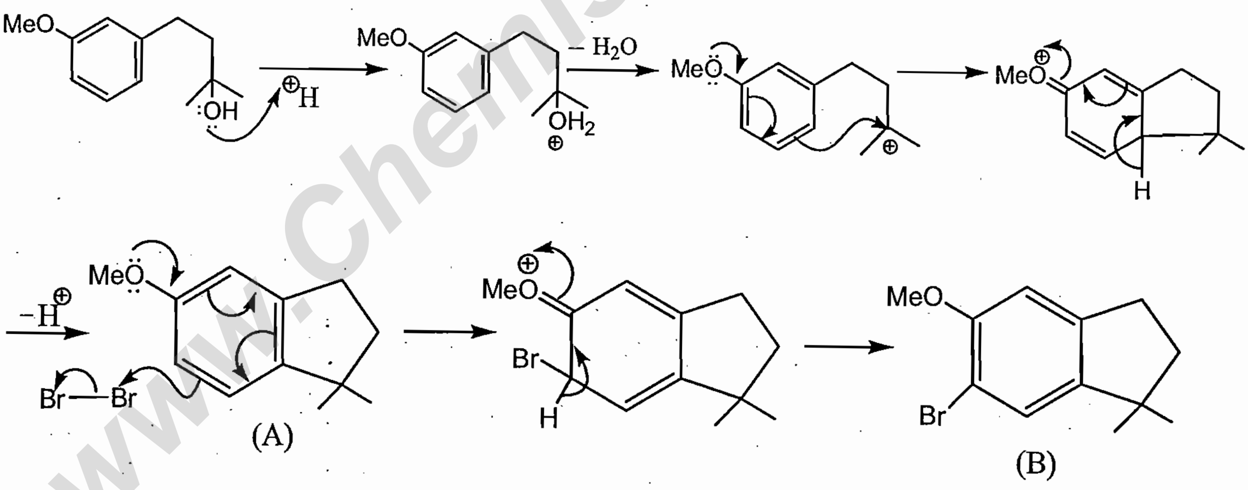
5. 

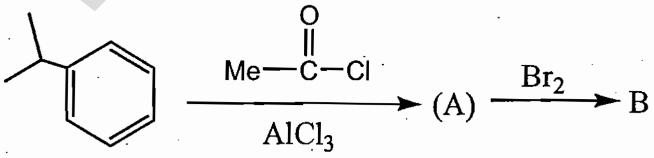
Soln. 

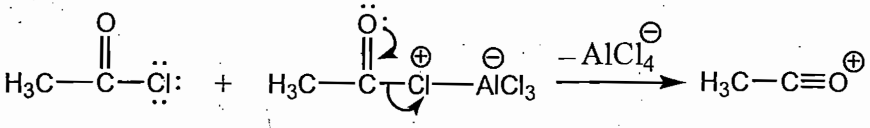
6. 

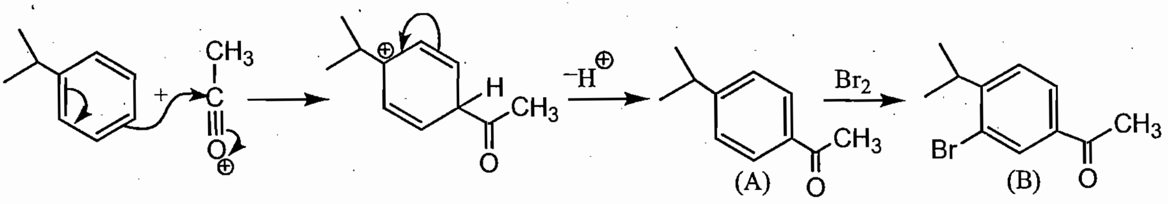
Soln. 

7. 

Soln. 

8. 





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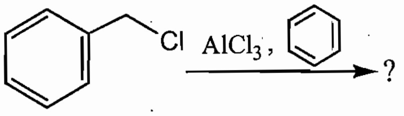

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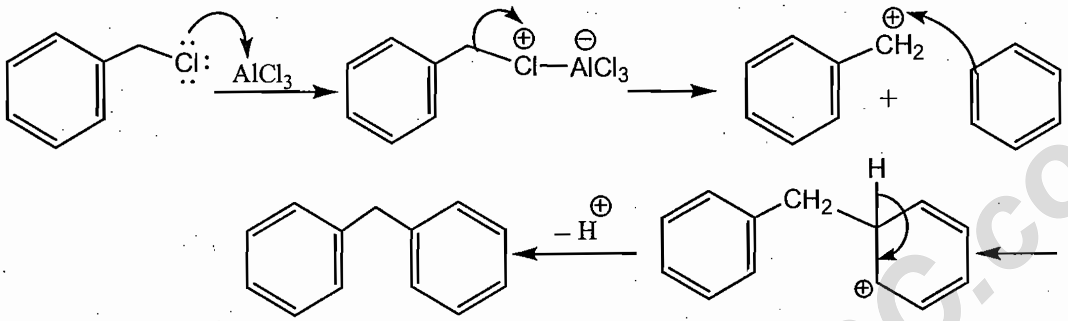

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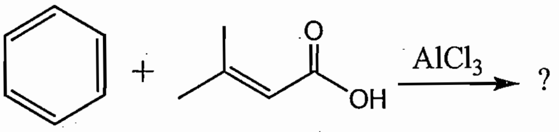

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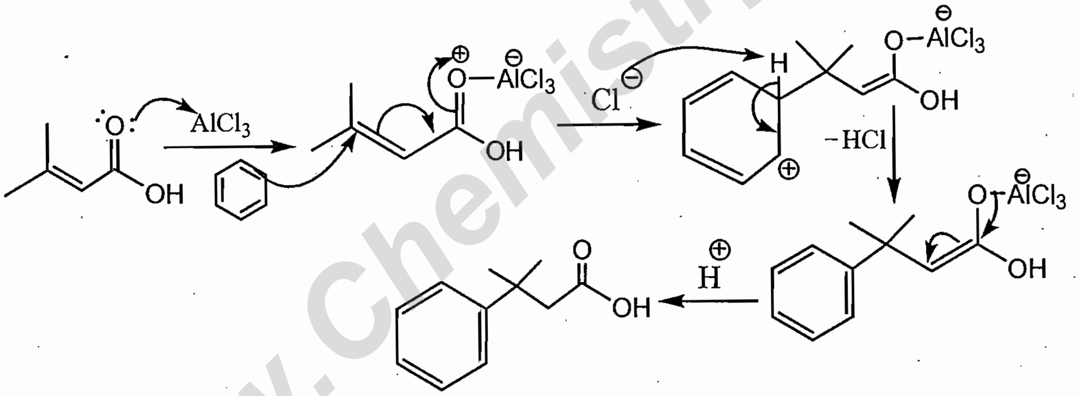
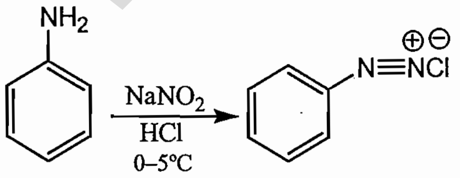
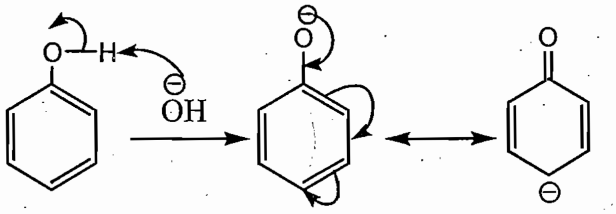
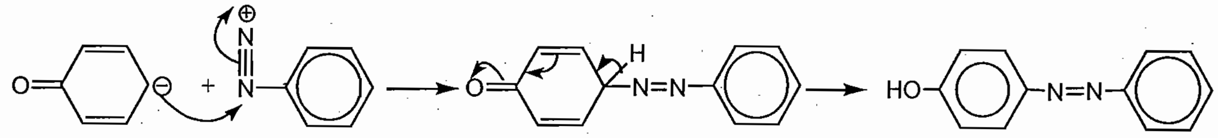


(v) Diazo coupling reaction:

- Phenols react in basic solution with diazonium salt to give the corresponding arylazo phenols.
- The reaction is an electrophilic aromatic substitution reaction by a weak electrophile, the diazonium ion, on an aromatic ring which is highly activated by the oxide anion.

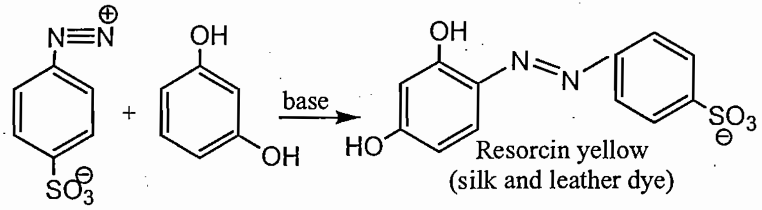




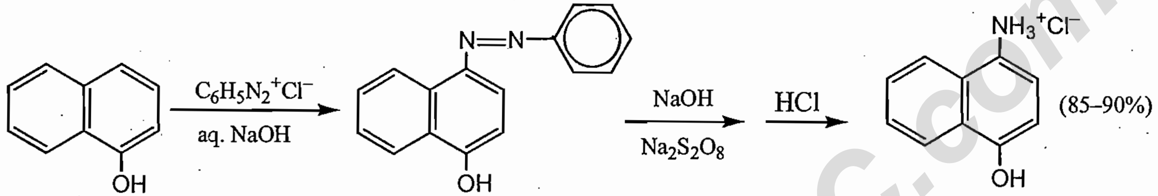


p-phenylazophenol

- The product is almost exclusively the para isomer. The ortho isomer is formed to the extent of only 1%.



Resorcin yellow
(silk and leather dye)



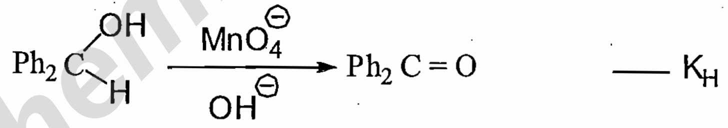
4-amino-1-naphthol
hydrochloride

5.6 Kinetic Isotopic effect

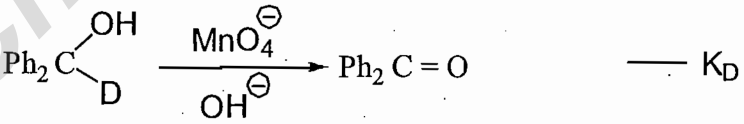
Isotopic substitution usually has no effect on the qualitative chemical reactivity of the substrate but it often has an easily measured effect on rate which is called kinetic isotopic effect (K.I.E). This effect is of two type primary kinetic isotope effect and secondary kinetic isotope effect.

(i) Primary kinetics isotope effect:

Primary kinetic isotopes are those in which a bond to the isotopically substituted atom is broken in the rate determining step. The weaker C–H bond is broken more rapidly than the stronger C–D bond. The rate difference, K_H/K_D is 7 at 25°C. It is also found that Ph_2 CHOH is oxidised 6.7 times as rapidly as Ph_2CDOH. This reaction is also said to exhibit a primary kinetic isotope effect.



$$Ph_2C(OH)H \xrightarrow[OH^{\ominus}]{MnO_4^{\ominus}} Ph_2C=O \quad \text{—— } K_H$$



$$Ph_2C(OH)D \xrightarrow[OH^{\ominus}]{MnO_4^{\ominus}} Ph_2C=O \quad \text{—— } K_D$$

Primary kinetic isotope effect can provide two very useful pieces of information about a reaction mechanism.

(i) The existence of a substantial isotope effect is $K_H/K_D > 2$ is strong evidence that the bond to that particular hydrogen is being broken in the rate determining step.

(ii) The magnitude of the isotope effect provide on quantitative indication of where the TS lies with regard to product and reactant.

A relatively low primary isotope effect implies that the bond to hydrogen is either only slightly or nearly completely broken at the TS. That is, the TS must occur quite close to reactant or product.

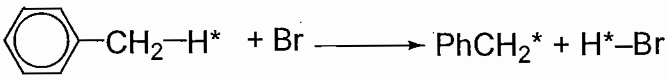
(ii) Secondary Kinetic isotope Effect :

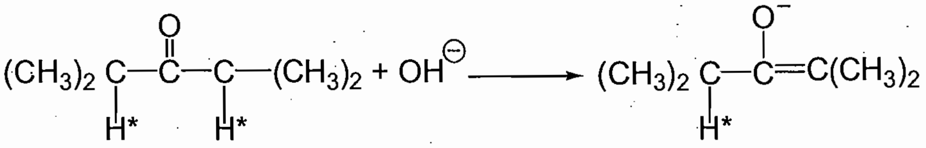
Isotope effect may also be observed when the substituted hydrogen atom is not directly involved in the reaction. Such effects known a secondary kinetic isotope effect. They are smaller than primary effect and are usually in the range of $K_H/K_D = (0.7 \text{ to } 1.5)$ and are also classified as α or β etc depending on the location of the isotopes substitution relative to the reaction site.

Secondary effect results from fightening or loosening of C-H bond at TS. The strength of the bond may change because of hybridisation change or a change in the extent of hyperconjugation for example, if an sp^3 carbon is converted to sp^2 as reaction occurs a hydrogen bound to the carbon will experience decreased resistance to C-H bending, tightening, freeing of the vibration for C-H bond is greater than for a C-D bond because the former is slightly longer and vibration has a larger amplitude. This will result in an normal isotope effect.

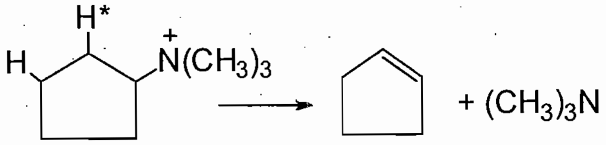
An inverse isotope effect will occur if coordination at the reaction centre increases in TS. The bonding Vibration will become more restricted. Cyanohydrin of carbonyl is an example of conversion of tricoordinate carbonyl group to a tetra valent cyanohydrin it has secondary isotope effect of 0.73.

***Reaction Primary Kinetic Isotopic Effect* :** K_H/K_D(°C)

(1)  4.6 (77)

(2) 

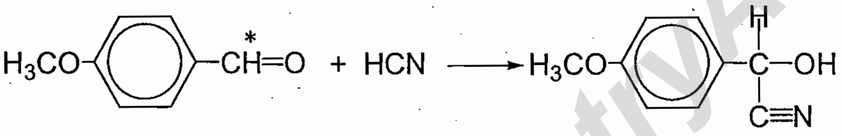
$(CH_3)_2CH^*-CO-CH^*(CH_3)_2 + OH^{\ominus} \longrightarrow (CH_3)_2CH^*-C(O^-)=C(CH_3)_2$ 6.1 (25)

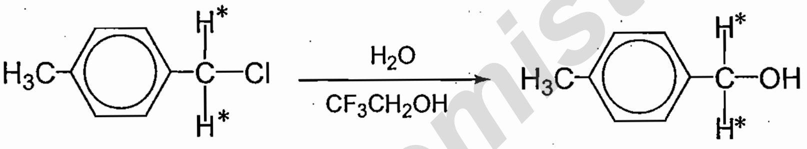
(3)  4.0 (191)

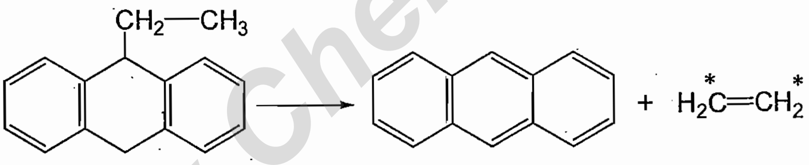
(4) $^*CH_3-I + OH^{\ominus} \longrightarrow OH-CH_3 + I^-$ $\frac{k_{12C}}{k_{14C}} = 1.09$

(5) $Ph\overset{*}{C}H_2Cl + H_2O \longrightarrow Ph\,CH_2-OH + HCl$ $-\frac{k_{35Cl}}{k_{37Cl}} = 1.0076(25)$

Secondary Kinetic Isotope Effect :

(1)  0.73 (25)

(2)  1.30 (25)

(3)  1.37 (50)

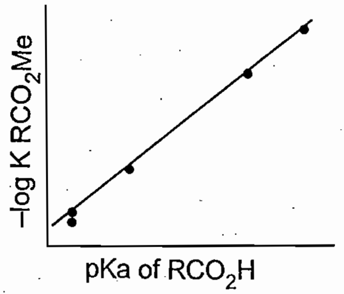
5.7. Hammett Plot (1933)

He studied the series of reaction of methyl ester with NMe_3

$$RCO_2Me + NMe_3 \xrightarrow{K} RCO_2^{\ominus} + \overset{\oplus}{N}Me_4$$

The rate of reactions were directly related to the ionisation constant in water of corresponding carboxylic acid

$$RCO_2H + H_2O \overset{K}{\rightleftharpoons} RCO_2^{\ominus} + H_3O^{\oplus}$$



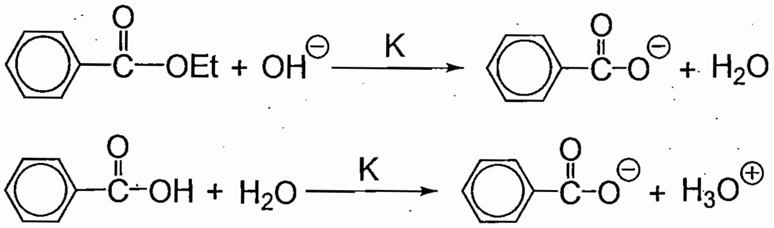
On plotting - log k for the reaction of esters against log K for ionisation of the acids a reasonable straight line results. Equilibrium constant K and rate constant *k* are each related to free energy change (ΔG) in the relevant reaction in the following way :

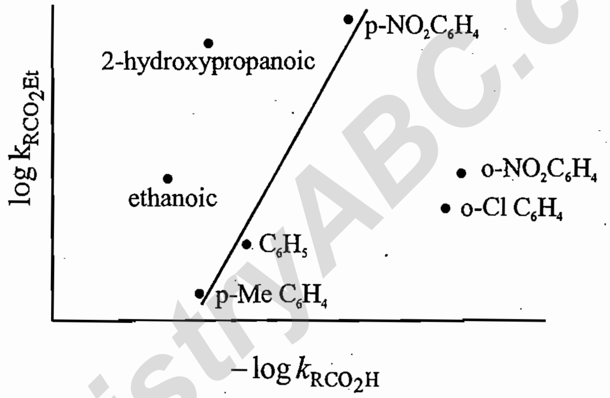
$$\log k = \frac{\Delta G^{o}}{2.303RT}$$

$$\log k = \frac{\Delta G^{*}}{2.303RT} + \log\left[\frac{k'T}{h}\right]$$ Where k' = Boltzmann's constant, h = Plank's Constant

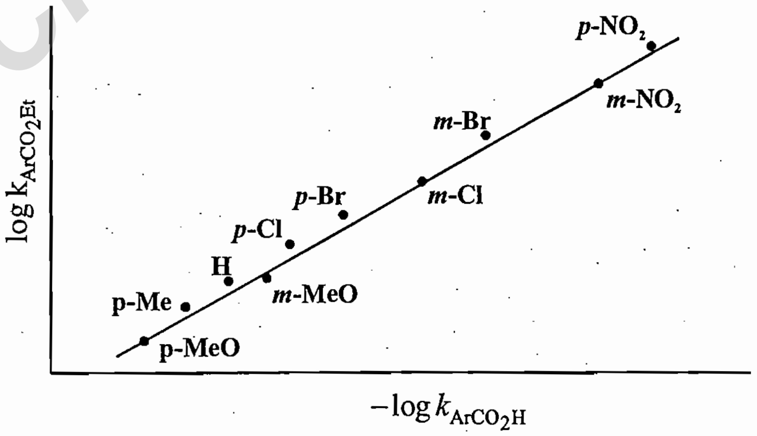
The fact that there is a straight line relationship between log k for reaction of esters and logK for ionisation of the corresponding carboxylic acid in water, emplies that there is also a straight line relationship between ΔG^*, the free energy change of activation for ester reaction and ΔG^o, the standard free energy change for ionisation of the acids in water. Because of this straight line relationship between the free energy terms for these two different reaction series, straight line plot is known as **linear free energy relationship** (LFER).
Hammett also studied another reaction that is Base-catalysed hydrolysis of a group of ethyl esters and plated log k and log k for ionisation in water of the corresponding carboxylic acids. e.g.;

$RCO_2Et + OH^{\ominus} \xrightarrow{k} RCO_2^{\ominus} + EtOH$; $R\,CO_2H + H_2O \overset{k}{\rightleftharpoons} R\,CO_2^{\ominus} + H_3O^{\oplus}$

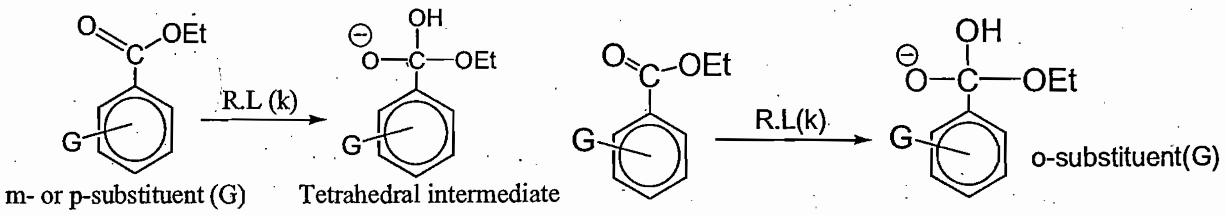


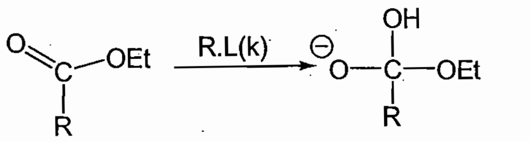


The plots were totally different but there is a straight line relationship for benzoic acid and its p-Me and p-NO_2 derivatives etc, but o-NO_2 and o-Cl. Benzoic acid derivatives then lies far off to one side of this straight line, while the aliphatic derivatives of Ethanoic and 2-hydroxypropanoic acids lies far off to other side. He founded that straight line was not generally obtained if reaction data for either o-substituted benzene derivatives or aliphatic species were included in the plot. There is excellent linearity for very wide reactions of m- and p-substituted derivative of benzene.



The reason for such non-conformity on the part of o-substituted benzene and aliphatic derivative is not far to seek i.e. Base catalysed hydrolysis of esters.





Aliphatic molecule

where, R.L. = Rate Limiting

m-or p-substituent is far removed from reaction centre and can exert no steric effect upon it. By the o-substituent is closed at hand in tetrahedral intermediate and leading to increasing crowding in the transition state and results in slowing down of formation of tetrahedral intermediate. These results are very much similar for more flexible molecule of the aliphatic esters also such steric effects will be much smaller if in red apparent at all in the removal of the peripheral H from the $-CO_2H$ group by H_2O in acid ionisation.

Hammett Equation :

The general equation of straight line is Y = mx + c
This can be applied to the straight line of the plots.

$$\log K_x = \rho \log K_x + c - \text{substituted} \qquad \dots (1)$$

Where ρ is the slope of the straight line, *C* is intercept ; *x* - *m* or *p*-substitutent in Benzene ring and

$$\log K_H = \rho \log K_{H+C} - \quad \text{unsubstitued} \qquad \dots (2)$$

Substracting equation (2) from equation (1), we have

$$\log K_x - \log K_H = \rho\left(\log K_x - \log K_H\right)$$

$$\log\left(\frac{K_x}{K_H}\right) = \rho \log\left(\frac{K_x}{K_H}\right)$$

Substituent Constant(σ_x):

Hammets designated the ionisation in water at 25°C of m- and p-substituted, Benzoic acid as his standard reference reaction.

$$\sigma_x = \log \frac{K_x}{K_H}$$

where σ_x is a substituent constant whose value will remain constant for a specific substitutent in a specific position (m or ρ).

then, $\log \frac{K_x}{K_H} = \rho\sigma_x$ _____ Hammett equation

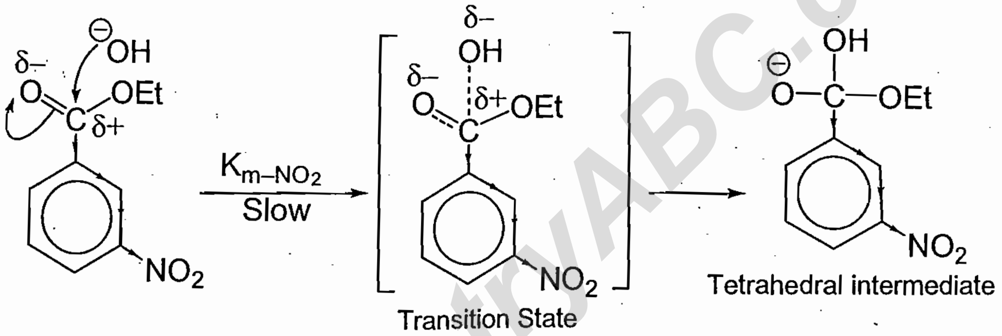
The values of σ_x substituent constant :

Substituent	**σm**	**σp**
CH_3CONH	0.14	0.0
CH_3CO_2	0.39	0.31
NH_2	–0.09	–0.30
Br	0.37	0.26
$(CH_3)_3C$	–0.09	–0.15
Cl	0.37	0.204
CN	0.62	0.70
C_2H_5O	0.1	–0.14
C_2H_5	–0.08	–0.13
H	0	0
OH	0.13	–0.38
CH_3O	0.10	–0.12

CH_3	–0.06	–0.14
NO_2	0.71	0.81
	0.05	0.05

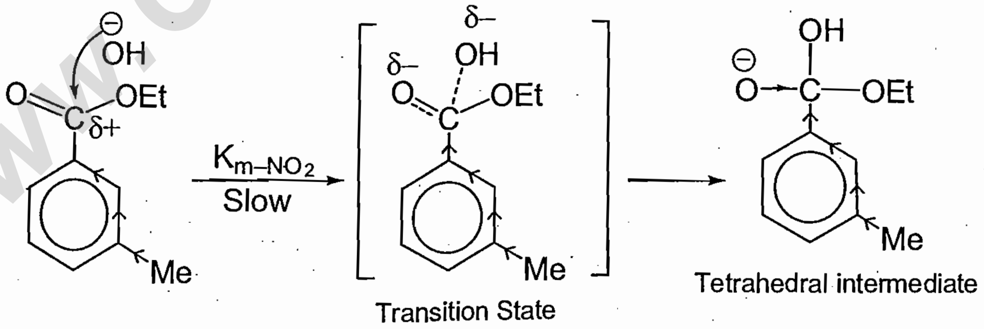
***Physical Significance of* σ_x :**

m-$(CH_3)_3C$ and m-CH_3 each have a small negative value and H has the value by difinition of zero while all the other m-substituted have positive values. The change in sign (–ve → +ve) does, of course parallel the change in direction (electron - donating → electron - withdrawing) of the inductive effect exerted by these substituents. The substituents may also exert a field effect, operating through the medium, but this will act in the same direction as the inductive effect. It would thus seem that $\sigma_{m\text{-}x}$ represents, both in direction and magnitude, a measure of the total polar effect exerted by the substituent (x) on the reaction centre. This can be explained by a comparison of the rate of Base catalysed hydrolysis of m-NO_2 and of m-CH_3 substituted ethyl benzoate with that of the substituted ester. A reaction in which the slow and hence rate determining step is initial attack on ester by OH^-.



$\sigma_{m-NO_2} = 0.71$ $\qquad$ $\frac{K_{m-NO_2}}{K_H} = 63.7$

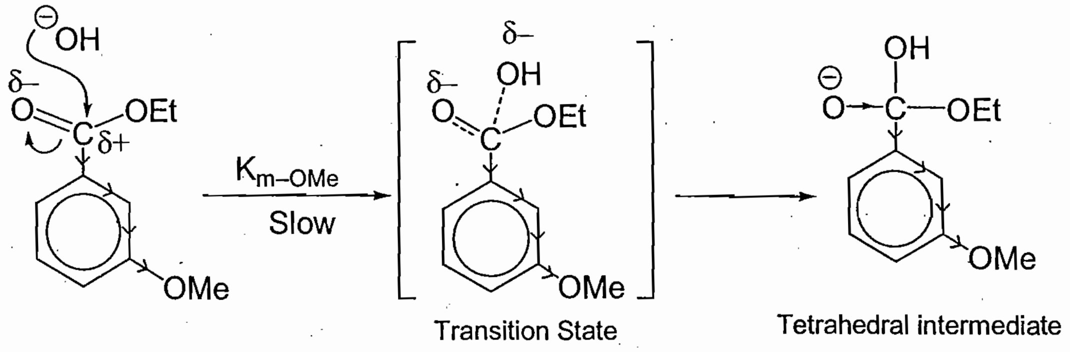
The $m-NO_2$ ester with m–$NO_2 = 0.71$ is hydrolysed 63.7 times as fast as the unsubstituted ester (Powerful electron withdrawal markedly assisting OH^- attack on the carbonyl carbon atom and stabilising the transition state leading to the negatively charged tetrahedral intermediate).



$\sigma_{m-Me} = -0.06$ $\qquad$ $\frac{K_{m-Me}}{K_H} = 0.66$

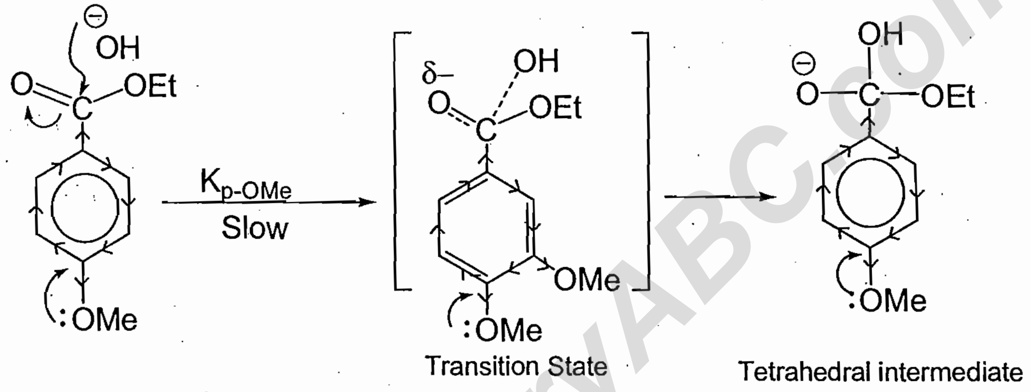
The m- Me ester with $\sigma_{m-Me} = 0.06$ is hydrolysed 0.66 times as fast as the unsubstituted ester (very weak electron donating group slightly inhibiting OH^- attack)

It was also found that not only does the $\sigma_{p\text{-}x}$ value for a particular substituent (x) vary in magnitude from σ_{m-x} value for the same substituent, it may differ in sign also. As is the case with m- and p-OMe. An examination of the effect of m-OMe and p-OMe substituent on base catalysed ester hydrolysis makes the reason for this change in sign.



$\sigma_{m-OMe} = +0.1$ $K_{m-OMe} > K_H$

In the m-position, the electronegative oxygen atom of the OMe group exerts an electron-withdrawing inductive effect $(\sigma_{m-OMe} = 0.1)$ and hydrolysis is faster than with the unsubstituted ester



$\sigma_{p-OMe} = -0.14$ $K_H > K_{p-OMe}$

In the p-position, OMe will still exert an electron withdrawing inductive effect but in addition it can through its electron pairs, exert an electron - donating mesomeric effect on the ring carbon atom to which the CO_2Et group is attached. The latter effect because it involves the more readily polarisable π-electron system is the greater of the two, and the overall result is therefore net - electron-donating (σp-OMe= –0.14) therefore, p-OMe ester is hydrolysed markedly more slowly than the unsubstituted compound.

Hammet therefore conducted that σ_x can be regarded as a measure of the overall polar effect exerted by a substituent (x) on the reaction centre. Its sign indicates the direction (–ve = electron - donating; + ve = electron withdrawing) and its magnitude the extent of the effect that exert - compared of course with the effect exerted by H.

Reaction Constant (ρ) :

The values of σ_x can be used to calculate the values of ρ, the reaction constant. This is often done graphically by drawing the plot of log (K_X/K_H) against σ_x; the slope of the resulting straight line will be the value of ρ for this reaction. For example. It turns out to be +0.82 for hydrolysis of base catalysed m-and p-substituted ethyl 2-aryl ethanoate. When carried out in aqueous ethanol at 30°C. The *e* values for quite a wide range of different reaction of m-and p-substituted benzene derivatives were calculated and given in the following :

	Reaction	**Type**	**ρ**
(1)	$ArCO_2H \rightleftharpoons ArCO_2 + H^+, H_2O$	K	1 – (standard reaction)
(2)	$ArCO_2H \rightleftharpoons ArCO_2^{\ominus} + H^+, EtOH$	K	1.57
(3)	$ArCH_2CO_2H \rightleftharpoons ArCO_2^{\ominus} + H^+, H_2O$	K	0.56
(4)	$ArCH_2CH_2CO_2H \rightleftharpoons ArCH_2CH_2CO_2^{\ominus} + H^+, H_2O$	K	0.25
(5)	$ArOH \rightleftharpoons ArO^{\ominus} + H^+, H_2O$	K	2.26

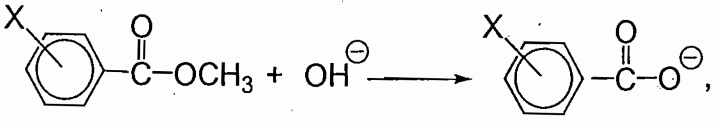
(6) $Ar\,NH_3^+$ □ $ArNH_2 + H^+, H_2O$ **(7)** $ArCO_2Et \xrightarrow{OH^{\ominus}} ArCO_2^{\ominus} + EtOH$

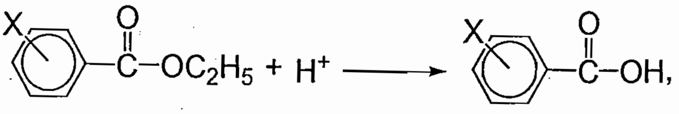
(8) $ArCH_2Cl + H_2O$ □ $ArCH_2OH + HCl$ K $-1.31(-4.5)$

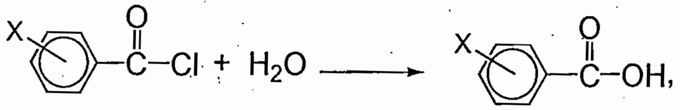
(9) $ArCH_2CO_2Et + \overset{-}{OH} \longrightarrow ArCH_2CO_2 + EtOH$ K 1.00

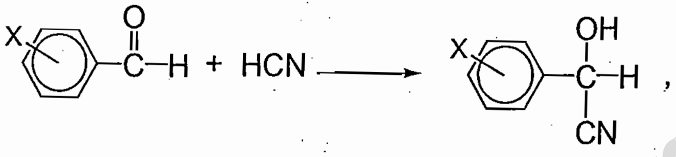
(10) $ArC(CH_3)_2\,Cl + H_2O \longrightarrow ArC(CH_3)_2\,OH + HCl,$ K -4.48

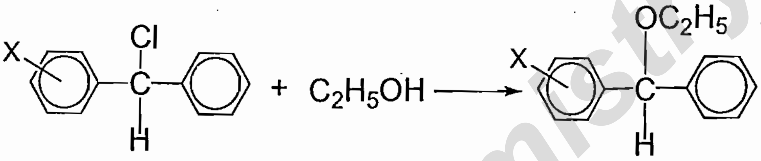
(11) $ArNH_2 + PhCoCl \longrightarrow ArNHCOPH + HCl,$ K -3.21

(12)  60% acetone K 2.229

(13)  60% acetone K 0.106

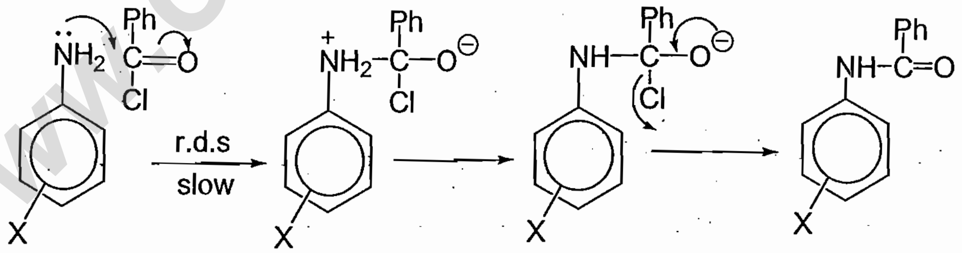
(14)  50% acetone K 0.797

(15)  95% ethanol K 2.329

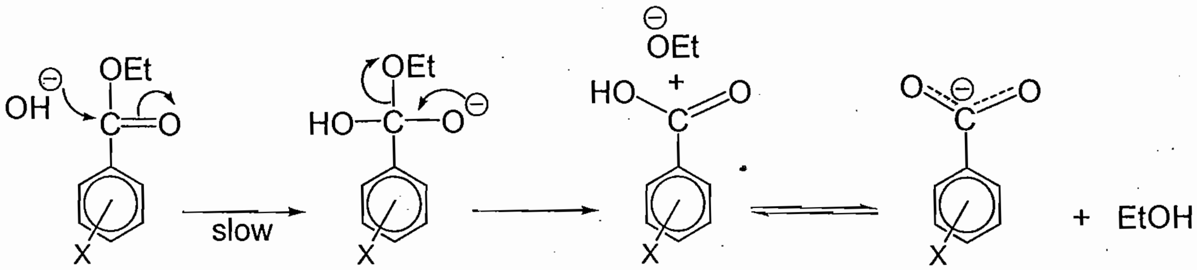
(16)  ethanol K –5.090

The value of the reaction constant, ρ for a particular reaction remain constant, no matter what the m-or p-substituents present in the compounds involved.

Physical Significance of ρ : Considering the reaction with negative value of ρ i.e.; Benzoylation of m - and p-substituted aniline with $\rho = -3.21$



The slow, rate - limiting step of this reaction is found to be initial attack by the electron pair of the nitrogen atom of the substituted aniline on the carbonyl carbon atom of the acid chloride. This results in the development of +ve charge at the reaction centre. The N-atom attached to directing to the substituted benzene ring in the forming intermediate. The reaction is thus accelerated by electron - donating substituents which help delocalise this forming +ve charge in the transition state leading to the intermediate and corresponding by retarded by electron - withdrawing substitutents. This behaviour is found to hold in general for reaction with –ve P values. Another reaction with a + ve ρ value are also considered. For example; The base-catalysed hydrolysis of m- and p-substituted ethyl benzoates.



This has ρ -value of +2.61, the known slow rate - limiting step in this reaction is attended by the development of–ve charge adjacent to the reaction centre in the transition state leading to the intermediate and the overall reaction is accelerated by electron - withdrawing and retarded by electron - donating substituent.

Thus, ρ can be regarded as a measure of susceptibility of a reaction to the electron - donating or withdrawing effect exerted by a substituent (x); relative, of course, to the susceptibility (towards such a substitutent) of the standard reaction - the aqueous dissociation of m and p - substituted benzoic acid at 25°C for which ρ = + 1.00 by definition.

The sign of ρ is of diagnostic value ; negative value indicates the development of positive charge at the reaction centre during the formation of the T.S in the rate - limiting step of the overall reaction whereas positive value indicates the development of negative charge at that centre. The magnitude of ρ can be regarded as a measure of the change in charge density of the reaction centre during formation of the T.S.

PROBLEM

1. The pKa of p-chloro benzoic acid is 3.98. that of benzoic acid is 4.19. calculate σ for p-Cl.

Soln. $\sigma = \log \frac{K_{p-Cl}}{K_H} = \log K_{p-Cl} - \log K_H$

$= -\log K_H - (-\log K_{P-Cl}) = pk_H - pk_{P-Cl} = 4.19 - 3.98 = 0.21$

2. The ρ value of alkali saponification of methyl ester of substituted benzoic acid is 2.38 and the rate of saponification of methyl benzoate under the condition of interest is $2\times10^{-4}\ m^{-1}S^{-1}$. Calculate the rate constant for hydrolysis of methyl m-nitrobenzoate

Soln. $\log \frac{K_{m-NO_2}}{K_H} = \sigma_{m-NO_2} \times \rho = 0.71 \times 2.38 = 1.69$; $\frac{K_{m-NO_2}}{K_H} = 49$; $K_{m-NO_2} = 98\times10^{-4} m^{-1}S^{-1}$

3. Calculate how much faster p-bromo benzyl chlororide will solvolyse in water than will p-intro benzyl chloride.

Soln. $\log \frac{K_{p-Br}}{K_H} = (-1.31)(0.26)$; $\log K_{p-Br} - \log K_H = -0.34$

$\log K_{p-Br} + 0.34 = \log K_H$; $\log \frac{K_{p-NO_2}}{K_H} = (-1.31)(0.81)$

$\log K_{p-NO_2} - \log K_H = -1.06$; $\log K_{p-NO_2} + 1.06 = \log K_H$

$\log K_{p-Br} + 0.34 = \log K_{p-NO_2} + 1.06$; $\log K_{p-Br} - \log K_{p-NO_2} = 0.72$

$\log \frac{K_{p-Br}}{K_{p-NO_2}} = 0.72$; $\frac{K_{p-Br}}{K_{p-NO_2}} = 5.25$

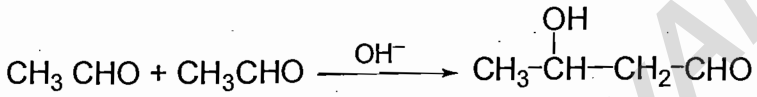
CHAPTER

6

Named Reactions

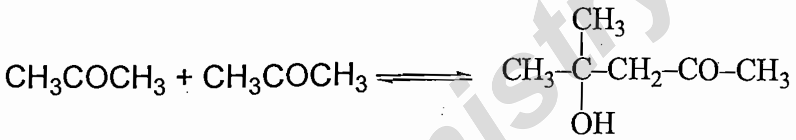
6.1. Aldol Condensation

Aldehyde containing an α-hydrogen atom undergoes a reversible self addition in presence of dil. alkali to give condensation product β-hydroxy aldehyde or ketone. In every case the addition occurs in such a way that α-carbon of the first carbonyl compound get attached to the carbonyl carbon of the second.



$$CH_3CHO + CH_3CHO \xrightarrow{OH^-} CH_3\text{-}\overset{OH}{\overset{|}{C}H}\text{-}CH_2\text{-}CHO$$

β-hydroxy aldehyde

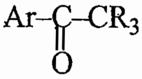


$$CH_3COCH_3 + CH_3COCH_3 \rightleftharpoons CH_3\text{-}\underset{\underset{OH}{|}}{\overset{\overset{CH_3}{|}}{C}}\text{-}CH_2\text{-}CO\text{-}CH_3$$

β-hydroxy ketone

Note: If an aldehyde and ketone do not contain α-H, the self condensation reaction donot occur.

e.g. ArCHO, HCHO, $(CH_3)_3C\text{-}CHO$, Ar-CO-Ar,

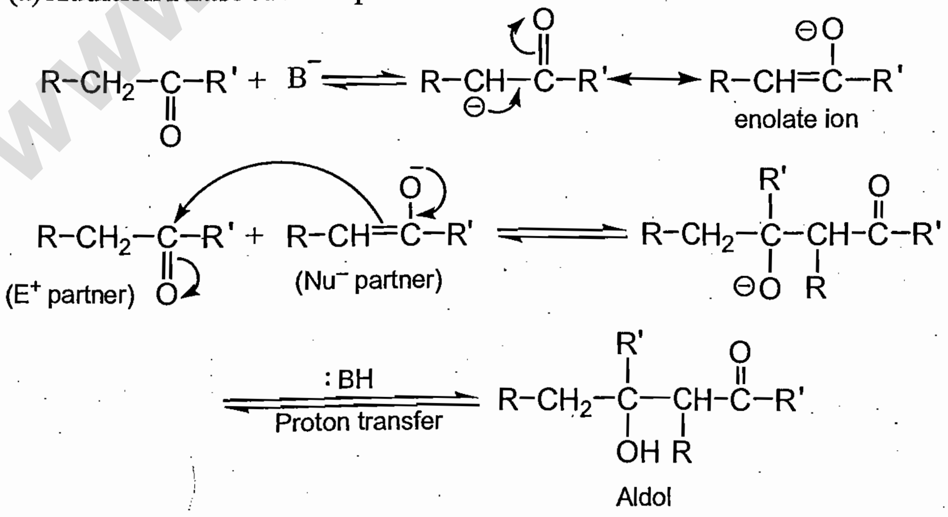


$Ar\text{-}\underset{\underset{O}{\|}}{C}\text{-}CR_3$ can't undergo self condensation due to absence of α H-atom.

Mechanism:

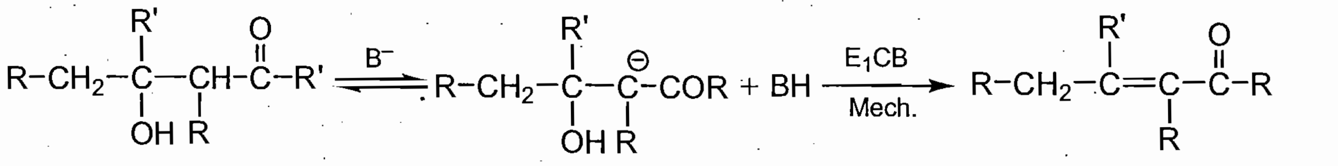
(1) Base - Catalysed mechanism

(a) Addition Phase : Nucleophilic addition.



Proton transfer reactions are always reversible reaction.

(b) Dehydration Phase :



α, β-unsaturated aldehyde / ketone

In general the aldol reaction is reversible in both acidic and basic condition, but when reaction conditions are favourable to cause dehydration, predominantly in acidic medium the reaction goes to completion.

The reaction is unfavourable usually for acyclic ketones this is because -

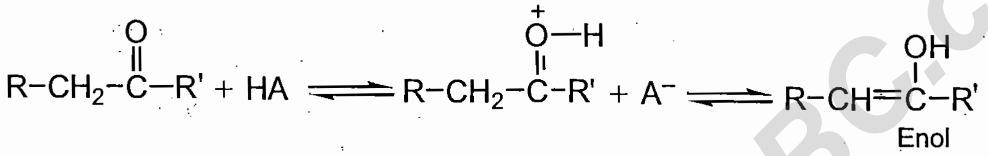
1. Carbonyl carbon of the ketone is less electrophilic because of the +I effect of the alkyl groups.
2. Due to steric hindrance the probability of nucleophilic attack by enolate or enol is decreased.

(2) Acid Catalyed Mechanism :

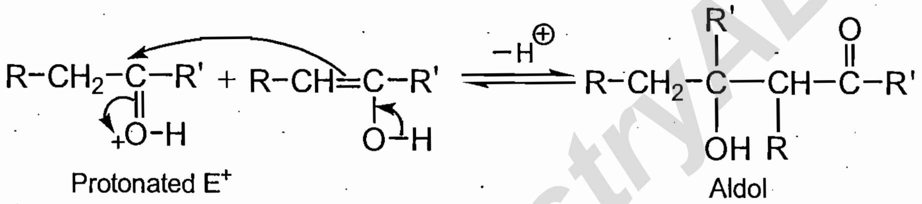
Enol is less nucleophilic than enolate.

(a) Addition Phase :

(i)

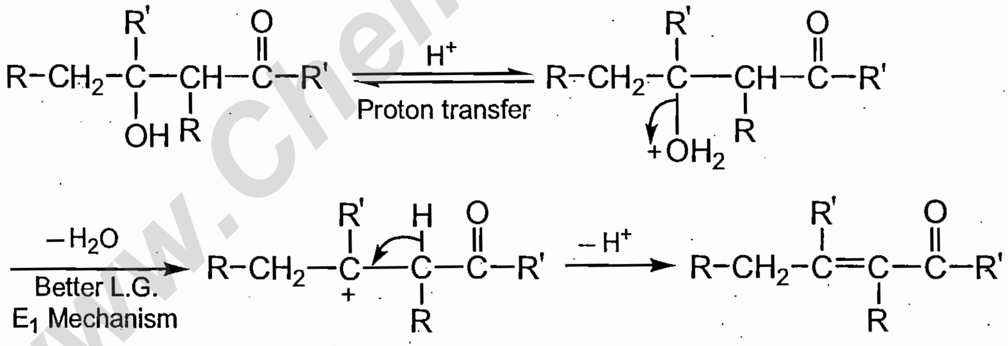


(ii)



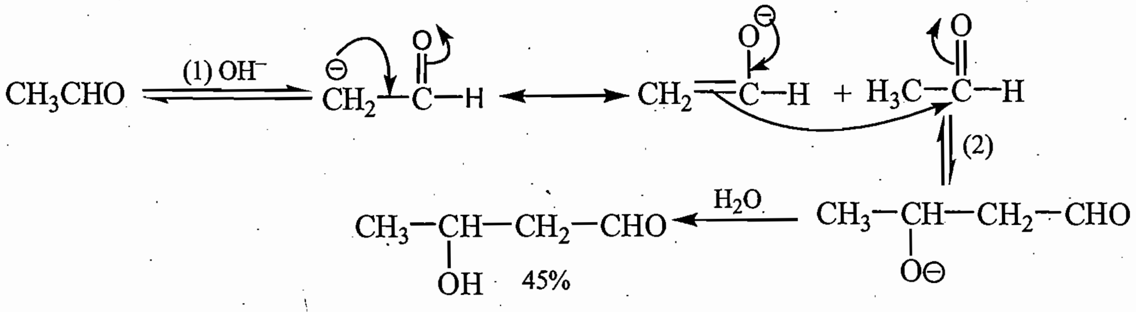
Protonated E⁺
(Better electrophile than the
unprotonated aldehyde/ketone)

(b) Dehydration Phase :

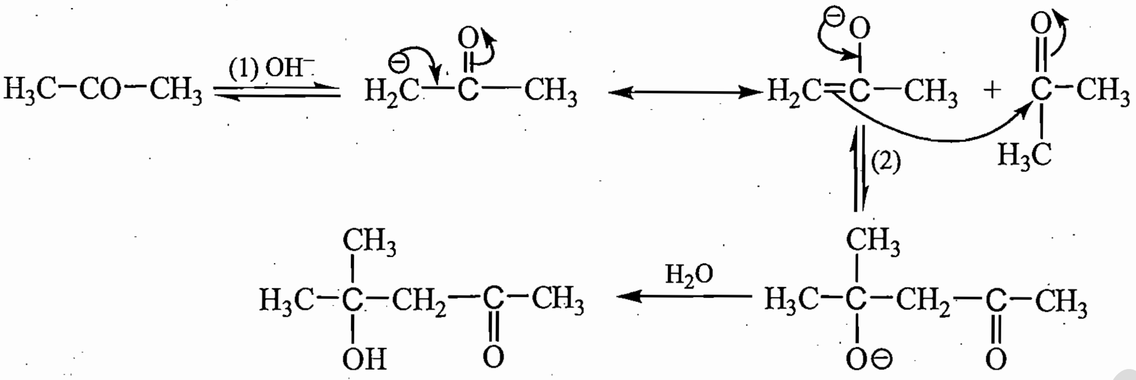


Experimental Evidence :

Aldehyde :



Ketone :



Carrying out a reaction with D_2O fails to result in the incorporation of any deuterium to the CH_3 group of aldehyde to produce $D-CH_2-CHO$ but it produces $D-CH_2-COCH_3$ in case of ketone. This indicates that the step two is faster than reversal of state one in case of aldehyde and slower in case of ketone.

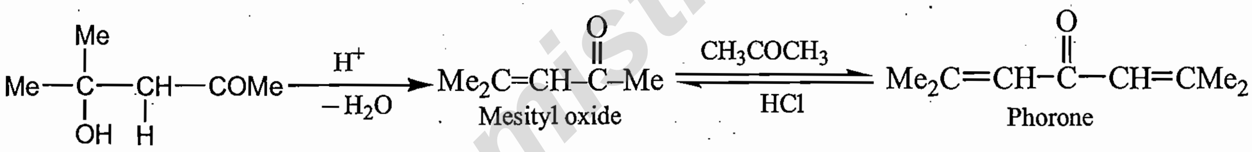
The reaction can be made of synthetic importance by :

(1) Continuous distillation of the products in a Soxhlet Apparatus (Reaction move forward following Le - Chatelier Principle) using $Ba(OH)_2$ base.

(2) Using acid catalysis tendency of dehydration of aldol products is increased producing more stable α-β unsaturated aldehyde / ketone.

(3) To stop at the aldol stage the best catalyst are *basic ion exchange resin.*

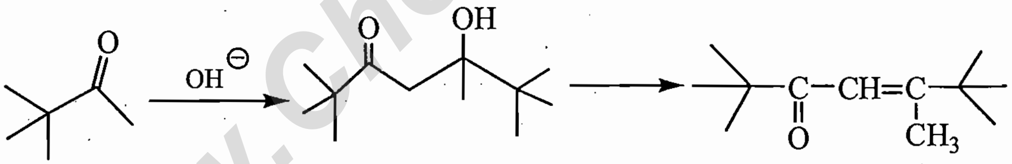
(4) A 3° alcohol always undergoes dehydration through E_1 mechanism. $E_1\left(3^\circ > 2^\circ > 1^\circ\right)$



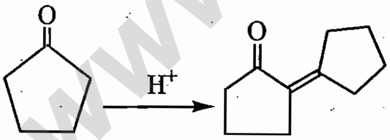
$$\mathrm{Me}-\underset{OH}{\overset{Me}{C}}-\underset{H}{CH}-COMe \xrightarrow[-H_2O]{H^+} \underset{\text{Mesityl oxide}}{Me_2C=CH-\overset{O}{\overset{||}{C}}-Me} \underset{HCl}{\overset{CH_3COCH_3}{\rightleftharpoons}} \underset{\text{Phorone}}{Me_2C=CH-\overset{O}{\overset{||}{C}}-CH=CMe_2}$$

***Example*:**

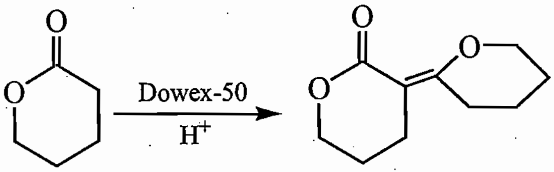
(i)



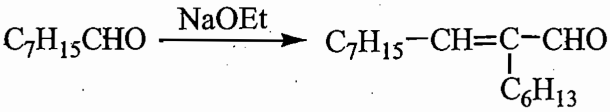
(ii)



(iii)

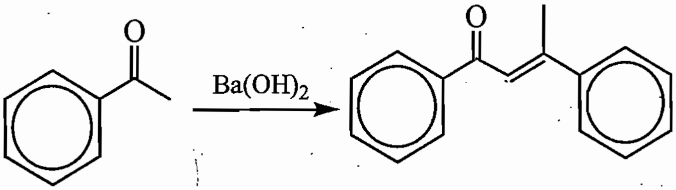


(iv)



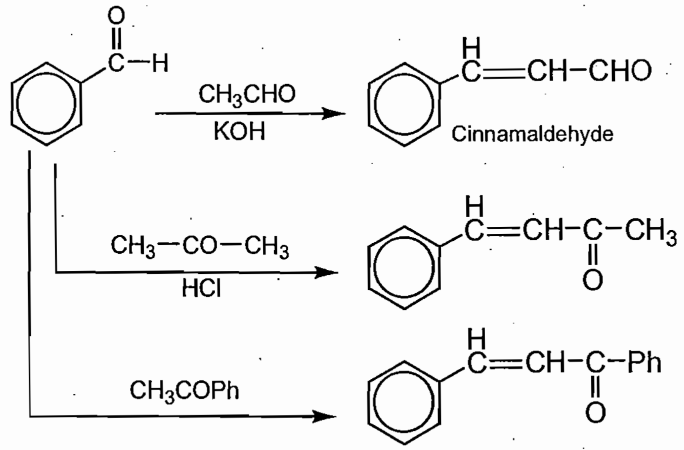
$$C_7H_{15}CHO \xrightarrow{NaOEt} C_7H_{15}-CH=\underset{C_6H_{13}}{\underset{|}{C}}-CHO$$

(v)

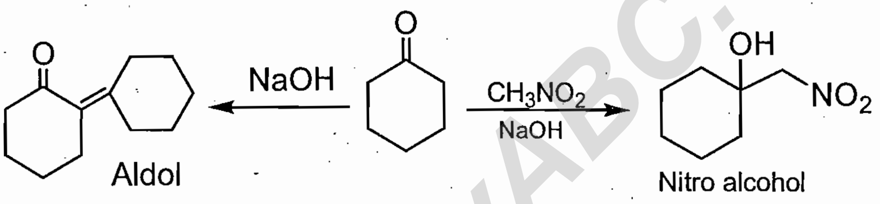


Crossed-Aldol / Mixed Aldol : (Claisen-Schmidt Condensation)

When one of the partner in a crossed aldol condensation is benzaldehyde which can only act as a E^+ and any other aldehyde or ketone which can form either enol or enolate then this type of mixed condensation is known as Claisen - Schmidt Condensation.



Electron donating groups in benzaldehyde will make the reaction slower and e^- withdrawing groups make the reaction faster.



Conditions For Crossed Aldol :

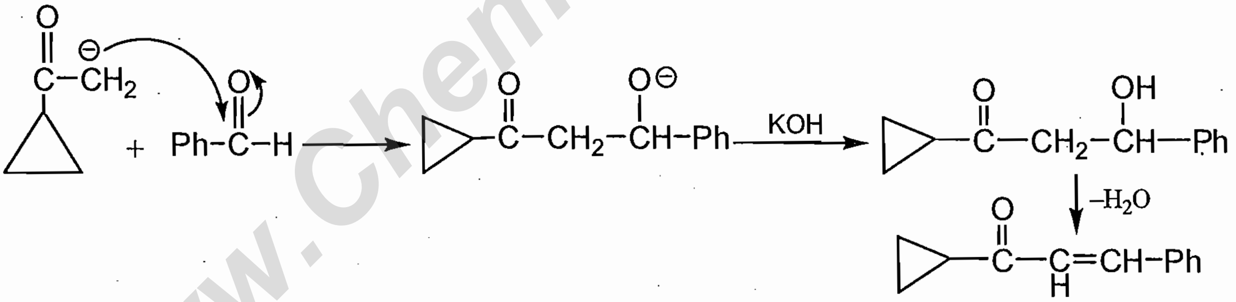
(i) Only one enolizable component (aldehyde / ketone having α-H)

(ii) No other compound containing more acidic hydrogens than aldehyde/ketone eg. CH_3NO_2

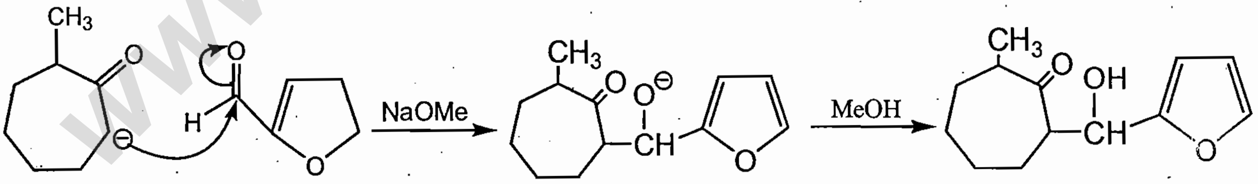
(iii) The carbonyl E^+ should be more reactive than the compound being enolised)

***Example*:**

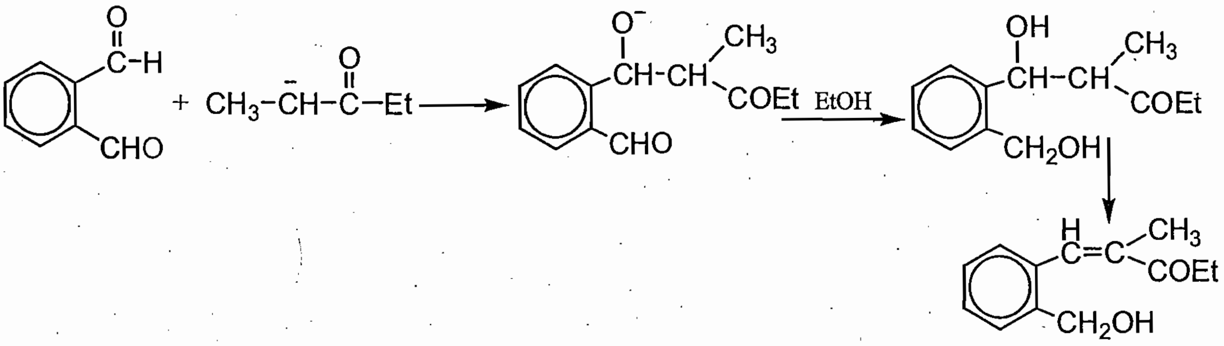
1.



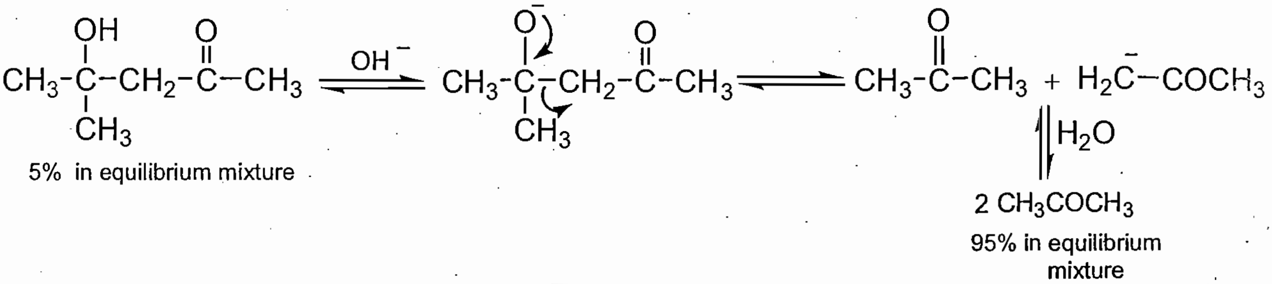
2.



3.



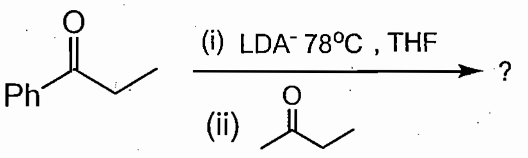
Retro Aldol : Because the aldol reaction is reversible, so when the aldol product is heated with a strong base then it reverse back to an equilibrium mixture which mainly contain initial reactant.



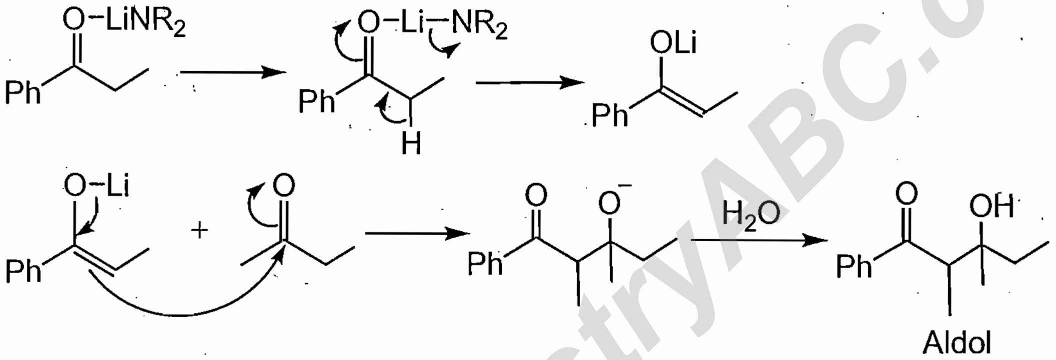
$$CH_3-\overset{OH}{\underset{CH_3}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-CH_3 \xrightleftharpoons{OH^-} CH_3-\overset{O^-}{\underset{CH_3}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-CH_3 \rightleftharpoons CH_3-\overset{O}{\overset{\|}{C}}-CH_3 + H_2\overset{-}{C}-COCH_3 \xrightleftharpoons{H_2O} 2\,CH_3COCH_3$$

PROBLEMS

1.



Soln.



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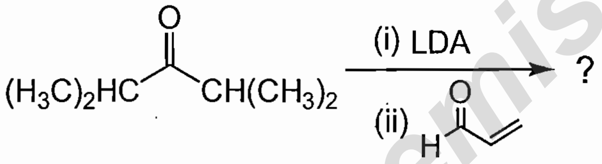
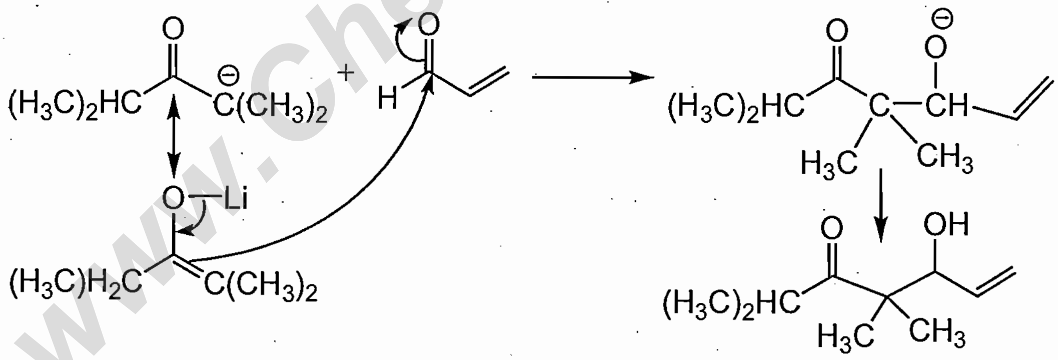
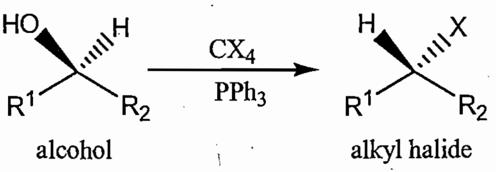


Soln.



6.2. *Appel Reaction*

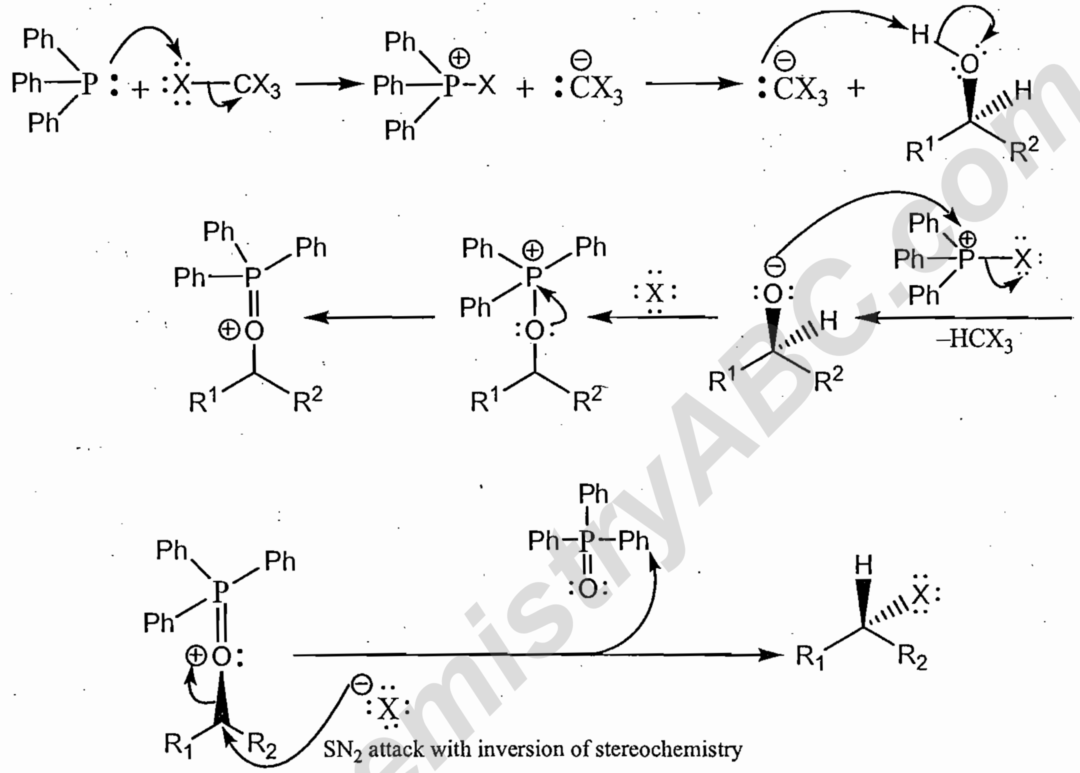
X = Cl, Br



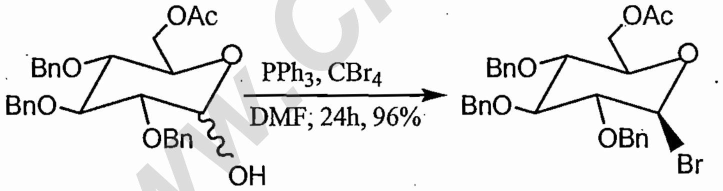
substitution with inversion of stereochemistry

The Appel Reaction is used to convert an alcohol to an alkyl halide using a tetrahalomethane and tripheynylphosphine. The reaction begins with the halogenation of triphenyl-phosphine followed by the formation of the alkoxide from the alcohol starting material. The alkoxide subsequently attacks the phosphorous, releasing the halide leaving group. In a nucleophilic substitution reaction (S_N2), the halide (nucleophile) attacks the carbon stereocentre resulting in the final alkyl halide product with inverted stereochemistry. Triphenylphosphine oxide is a byproduct of this reaction and the formation of the strong P = O double bond is a driving force for this reaction. The reaction is somewhat similar to Mitsunobu reaction.

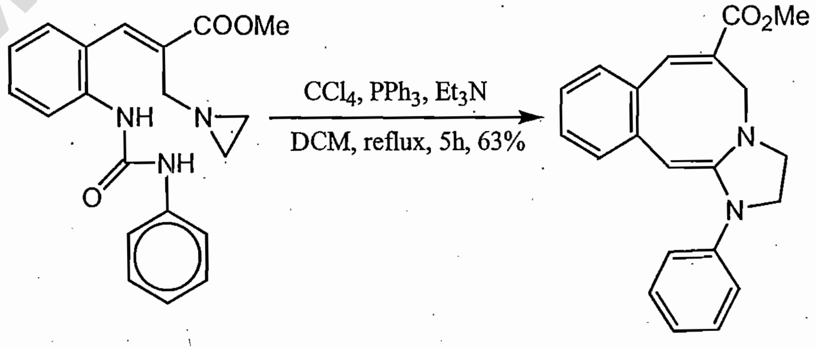
***Mechanism*:**



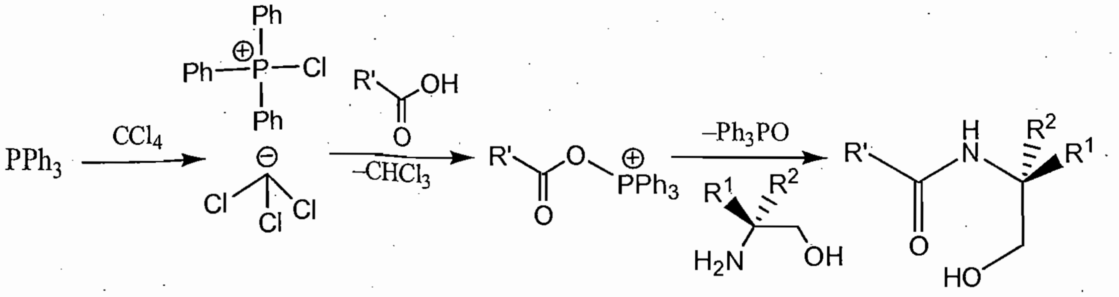
***Example*:**



- Appel salt as a dehydrating agent.



The Appel reaction is also effective on carboxylic acids; this has been used to convert them to oxazolines, oxazines and thiazolines.

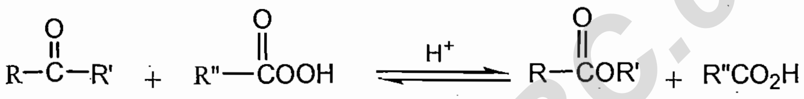


Drawbacks of the reaction :

The use of toxic halogenating agents and the coproduction of organophosphorus product which must be separated from the organic product. The phosphorus reagent can be used in catalytic quantities.

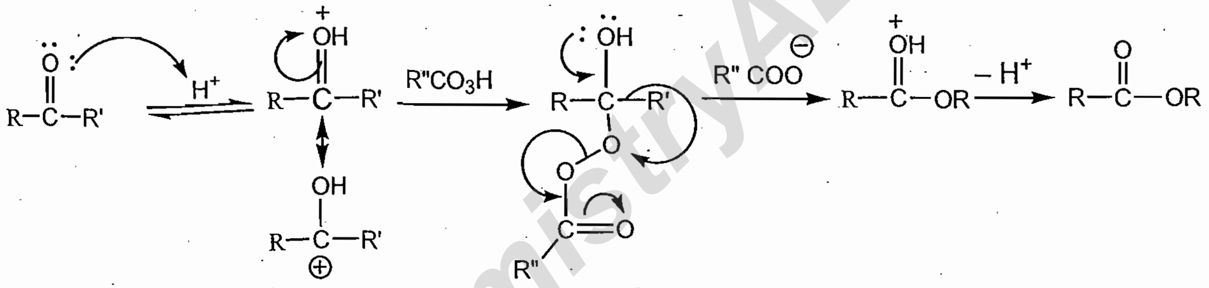
6.3. *Baeyer - Villiger Oxidation Reaction*

Oxidation of ketone to ester by reacting reactant (ketone) with hydrogen peroxide or peroxy compound or peracid(RCO_3H) in presence of acid catalyst.



$$R-\overset{O}{\overset{\|}{C}}-R' + R''-\overset{O}{\overset{\|}{C}}OOH \xrightleftharpoons{H^+} R-\overset{O}{\overset{\|}{C}}OR' + R''CO_2H$$

Mechanism :

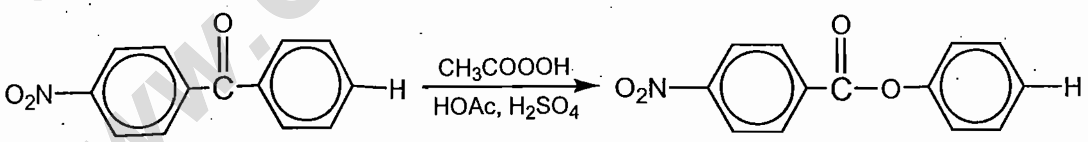


When unsymmetrical ketones are used, then order of migration of alkyl group, is : *tert-alkyl, sec-alkyl* > Benzyl, Phenyl > Prim - alkyl > cyclopropyl > methyl. For Benzophenone, p-OCH_3 > CH_3 > H > Cl > NO_2 *in para - position.*

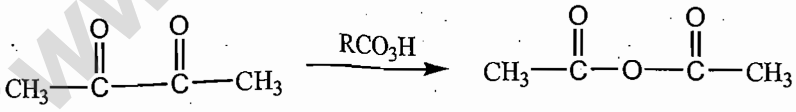
Note: Peroxy trifluoro acetic acid and m-chloro peroxy Benzoic acid can also be used :

Examples:

(i)

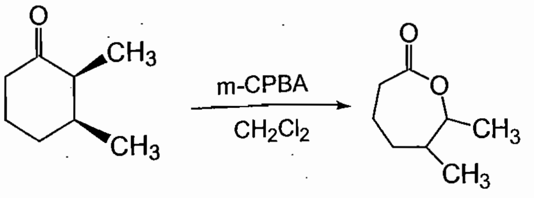


(ii)

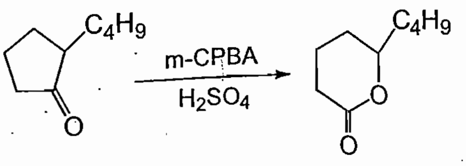


$$CH_3-\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}-CH_3 \xrightarrow{RCO_3H} CH_3-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-CH_3$$

(iii)



(iv)



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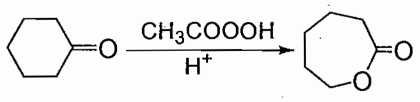

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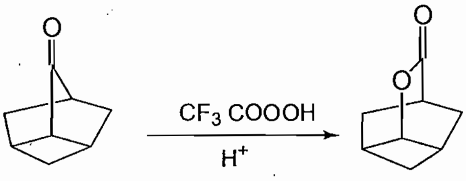
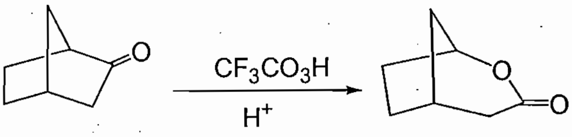


(vii)



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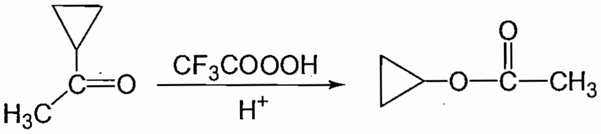
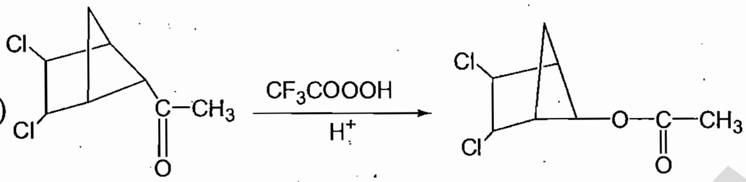
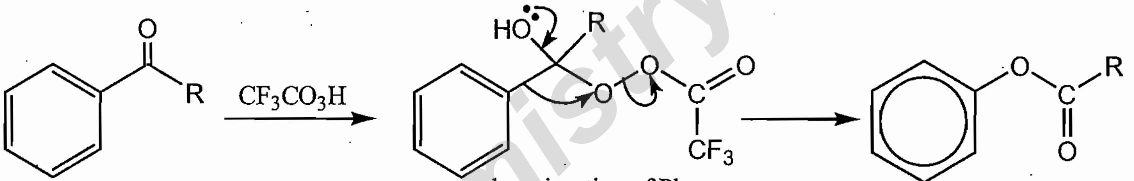


(ix)



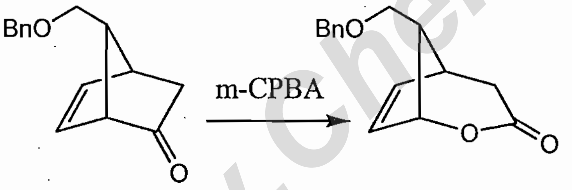
PROBLEMS

(i)

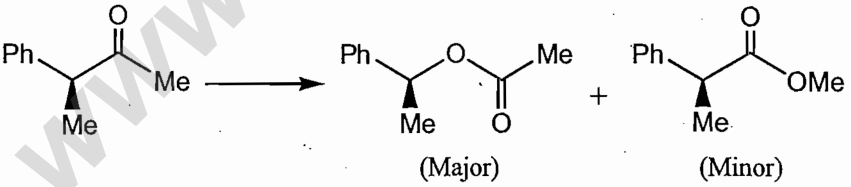


by migration of Ph

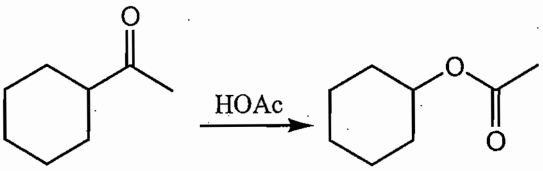
(ii)



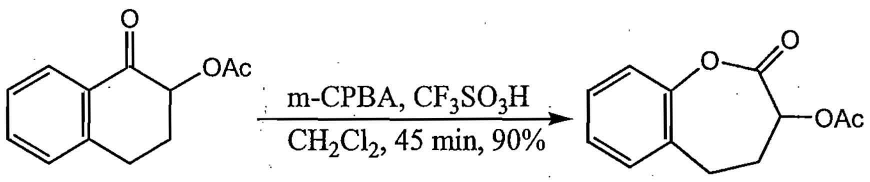
(iii)



(iv)

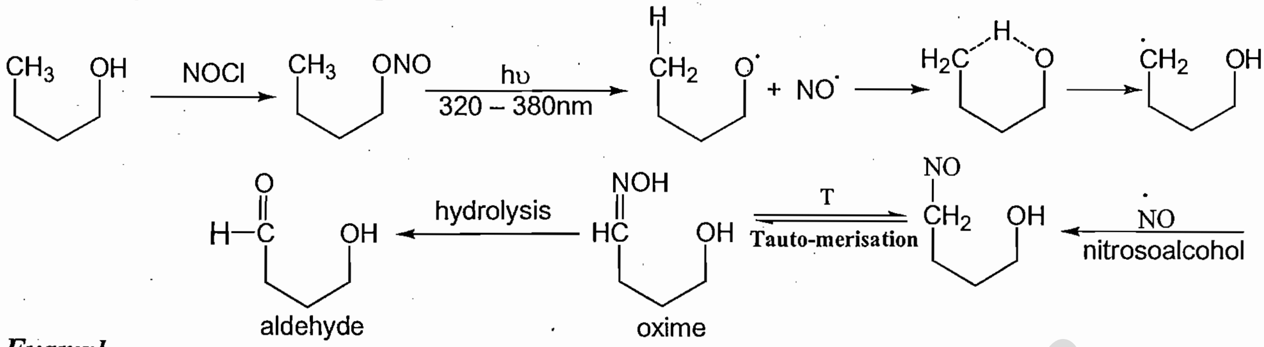


(v)

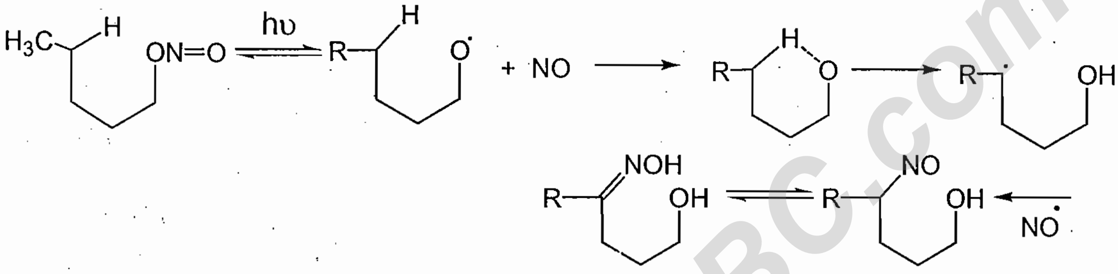


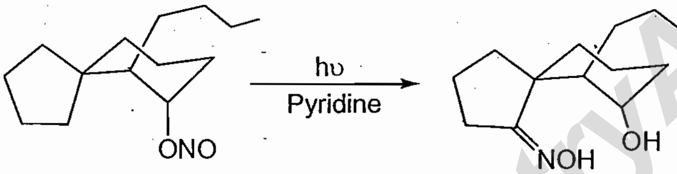
6.4. Barton Reaction

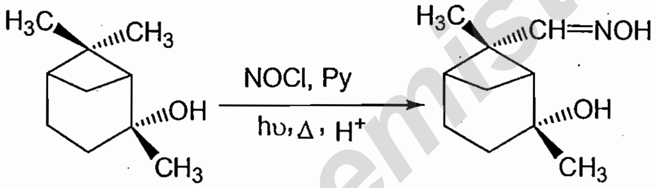
The photolytic conversion of organic nitrite into nitroso alcohol is known as *Barton reaction*.



Examples:

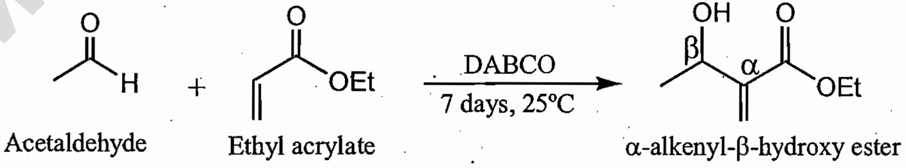
(i)


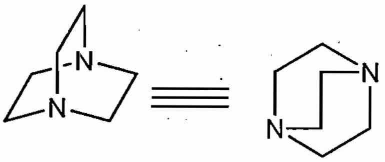
(ii)


(iii)


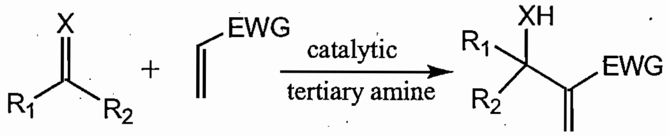
6.5. Baylis-Hillmann Reaction

Baylis-Hillman reaction offers a method for carbon-carbon bond formation between α-carbon of a conjugated carbonyl system and an aldehydic carbon in presence of a suitable base (as catalyst) such as DABCO (1, 4-diazabicyclo [2.2.2.] octane) or trialkylphosphins. Here is a typical example:



DABCO =


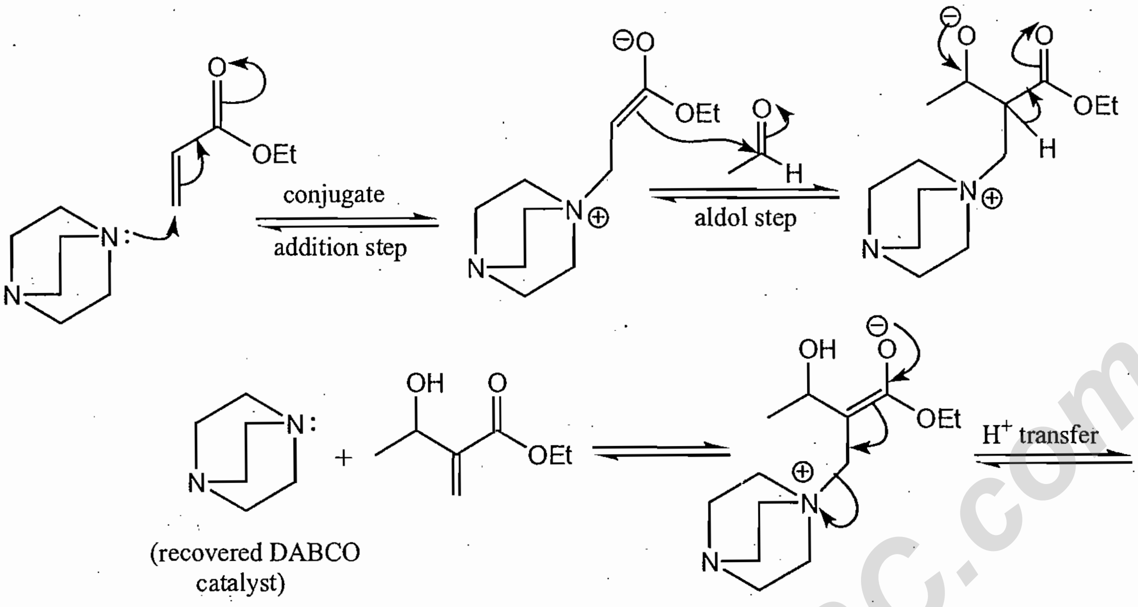
The reaction may be extended to a number of substrates, and a general scheme is shown:



Where, X = O, NR_2.

EWG = COOR, COR, CHO, CN, SOOR, SO_3R, $CONR_2$, $PO(OEt)_2$.

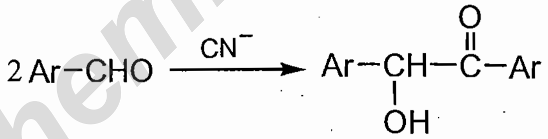
Mechanism:



A disadvantage of this reaction is that the rate is low-several days are required for completion of reaction. Under certain conditions (e.g. under pressure, microwave irradiation), rate enhancements have been observed. As a catalyst, DABCO is the best because it is a good nucleophile as well as a good leaving group –DABCO's combination of nucleophilicity and leaving group ability is best suited here.

6.6. Benzoin Condensation

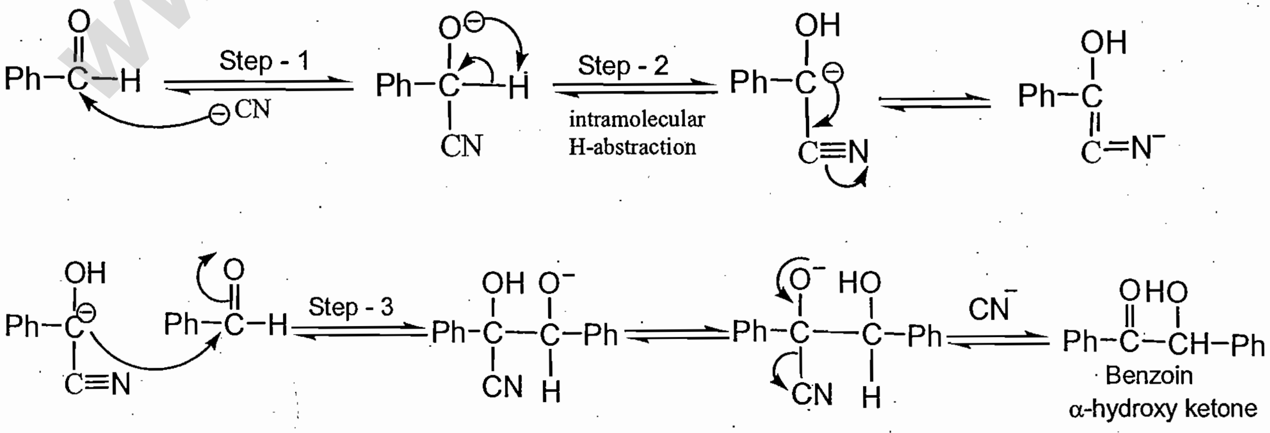
Condensation of aromatic aldehyde in presence of CN^- ion to give condensation products called benzoin, is known as Benzoin Condensation.



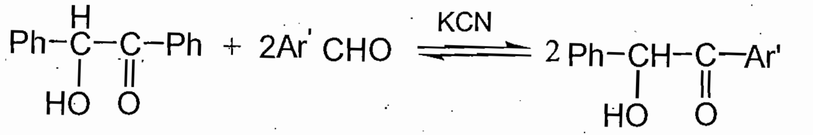
$$2\,Ar{-}CHO \xrightarrow{CN^-} Ar{-}\underset{\displaystyle OH}{\underset{|}{C}H}{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}Ar$$

When Ar = Ph, it is called benzoin rate law $r = K[ArCHO]^2[CN^-]$

The reaction involves attack of CN^- ion on the carbonyl carbon but in this reaction instead of H^- transfer (as that of cannizzaro reaction) it is now a carbanion addition of the one aromatic aldehyde to the carbonyl carbon of the other aromatic aldehyde. The reaction is of 3rd order.



1. This reaction is completely reversible, the reversibility indicated by the fact that when benzoin is heated with an another aromatic aldehyde, mixed products are obtained.

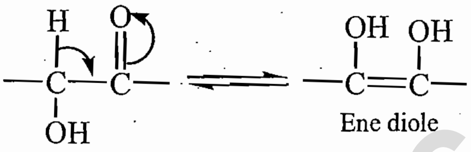


This reaction is intermolecular

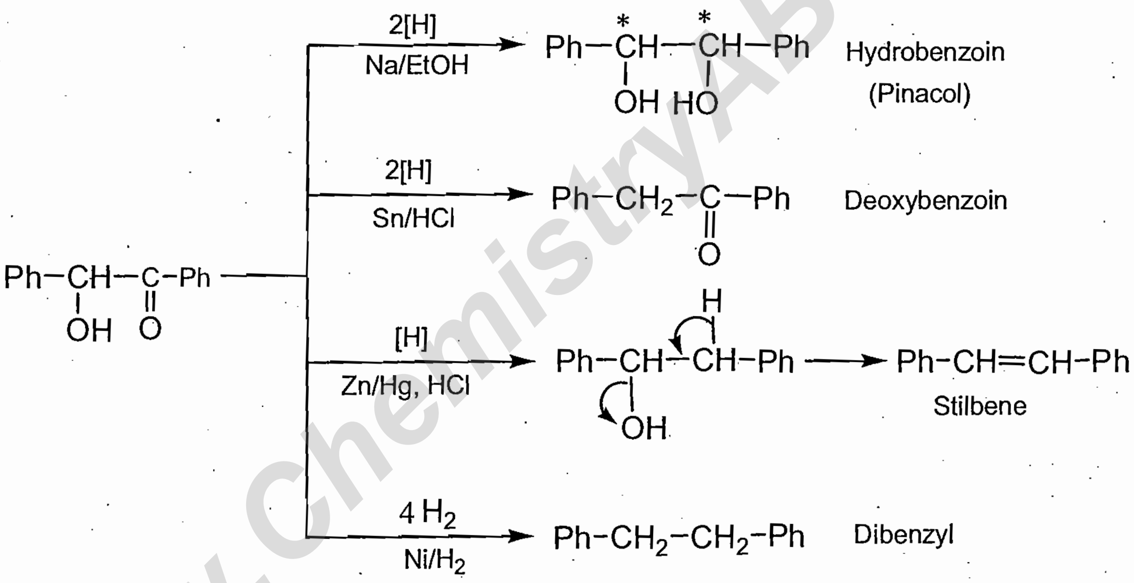
mixed product
reversible reaction

2. CN$^-$ catalyses the reaction because :
(i) It is good nucleophile
(ii) It is good leaving group
(iii) It increases the acidity of the C–H bond and stabilises the carbanion that results from the loss of proton from C.

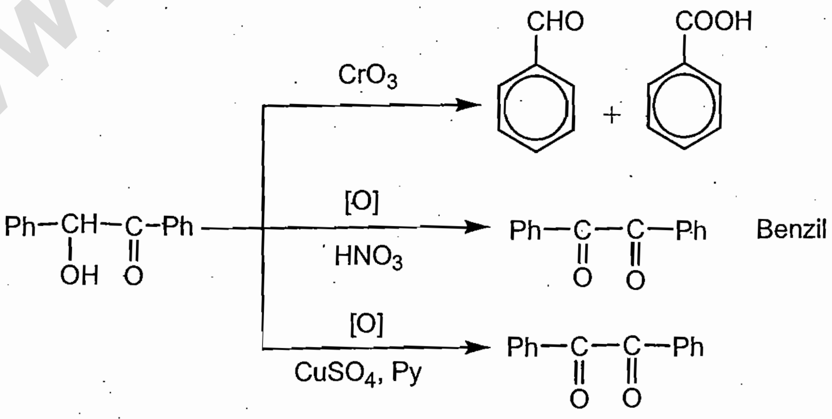
3. Benzoin is a colourless solid (M.P. 157°C) which assumed to tautomerise to ene diols.



Reduction of Benzoin :

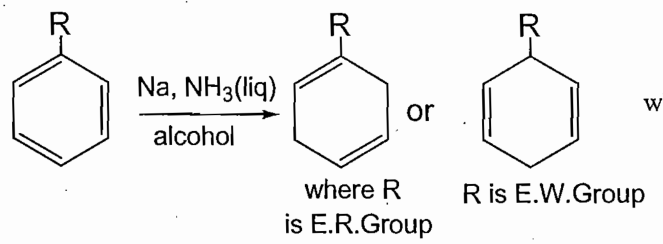


Oxidation of Benzoin :



6.7. *Birch Reduction*

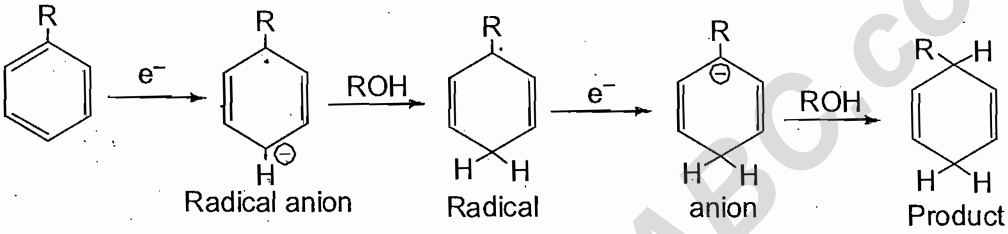
Reduction of aromatic ring by means of alkali metals (sodium or lithium) in liquid ammonia or amine with ethanol as proton donor to give mainly conjugated dihydro derivatives. Ethers are sometimes used as a co-solvent to dissolve the aromatic compound. Use of *t*-butanol fulfils the dual role of proton donor and co solvent.



where
E.W → electron withdrawing group.
E.R. → electron releasing group.

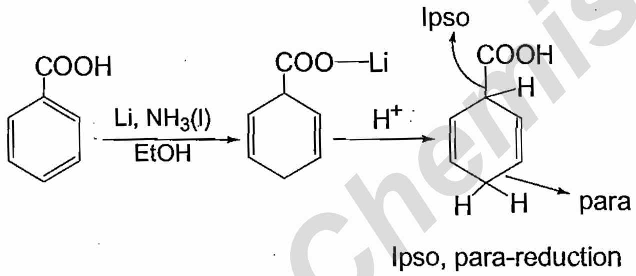
Mechanism **:** Solvated electrons are reducing agent.

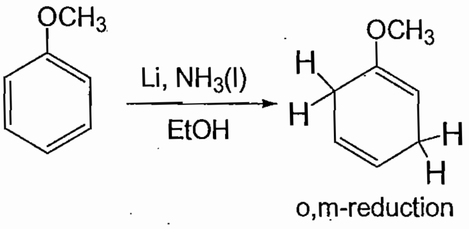
$$Na\ (NH_3) \longrightarrow Na^+\ (NH_3)X + \overset{\ominus}{e}(NH_3)X$$



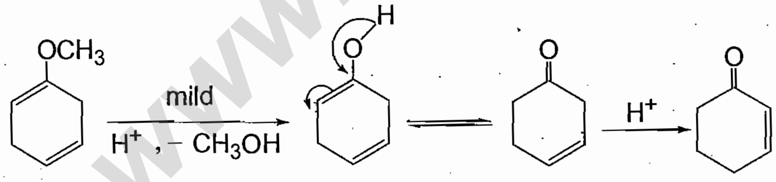
Effect of Substituent on Aromatic Ring (Regioselectivity) :

Electronic Factor : Electron withdrawing groups make the ring more susceptible towards reduction and hence increases the rate of reaction on the other hand electron donating groups decrease the rate of reaction. Electron withdrawing groups promote ipso & para reduction whearas electron donating groups promote meta and ortho reduction.

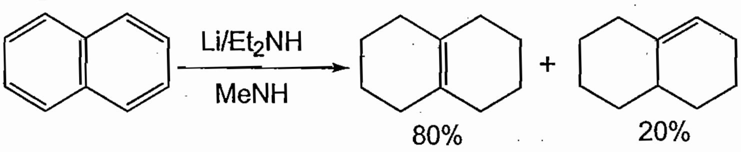
(i) 

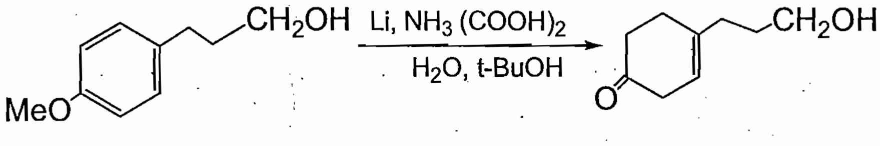
(ii) 

To Produce Cyclohexanones :



Example:

(i) 

(ii) 

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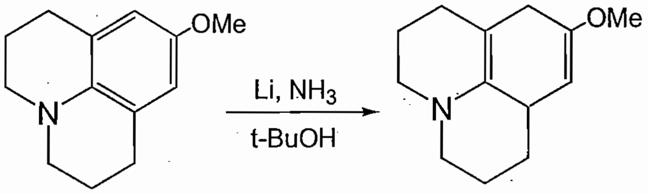

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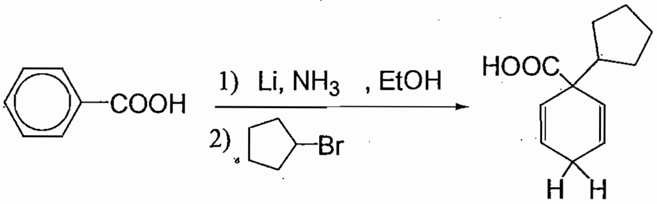

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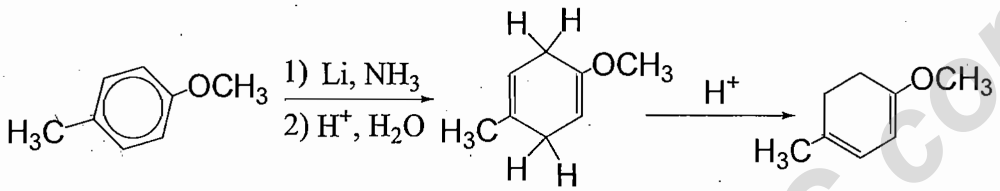

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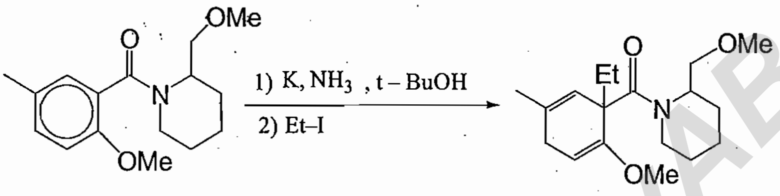
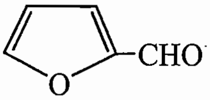


6.8. *Cannizzaro Reaction*

Under the influence of strong and conc. base, aldehyde which has no α-H (non enolazable) undergoes self oxidation reduction reaction (disproportionation) to produce corresponding alcohol and acid. This is knwon as Cannizzaro reaction.

e.g. Aldehyde - HCHO, PhCHO, R_3C-CHO, 

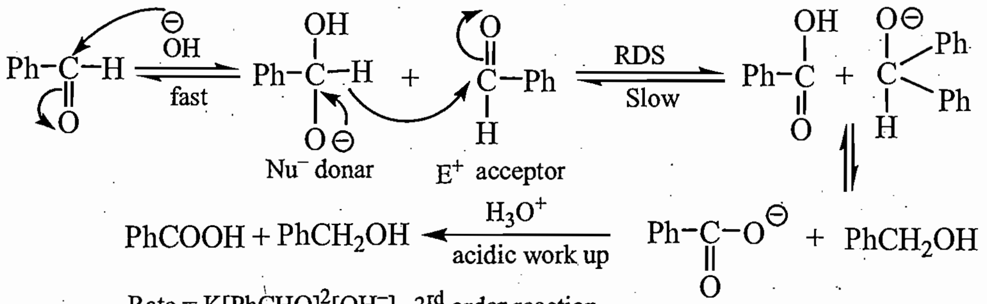
Aldehydes which have α-H undergo aldol reaction much faster than the cannizzaro reaction.

$$2\,PhCHO \xrightarrow[2)\ H_3O^+]{1)\ Conc.NaOH} Ph{-}COOH + PhCH_2OH$$

Benzoic acid (Oxidised) — Benzyl alcohol (Reduced)

Disproportionation

Mechanism: The mechanism involves intermolecular hydride transfer



Rate = $K[PhCHO]^2[OH^-]$ 3rd order reaction

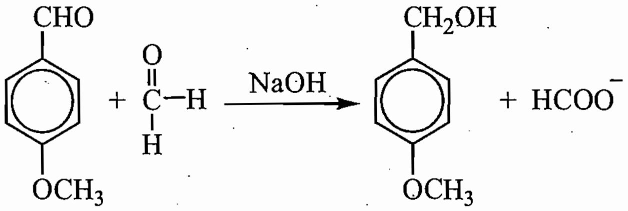
Cannizzaro reaction is a third order reaction.

6.9. *Crossed Cannizzaro Reaction*

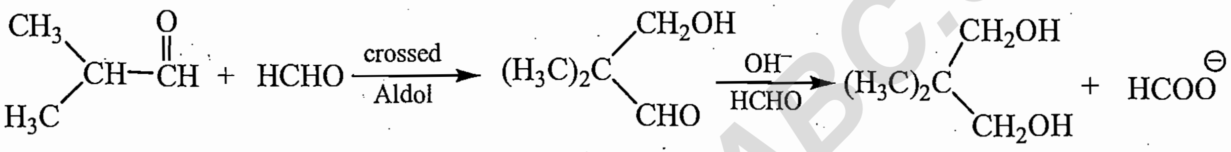
Reaction between different aldehyde

$$PhCHO + HCHO \xrightarrow[NaOH]{Conc.} PhCH_2OH + H{-}COO^-$$

1. When formaldehyde undergoes a cannizzaro reaction with other aldehyde without a α-H, then it is observed that the formaldehyde is oxidised and other is reduced. This is because the nucleophilic attack occurs on formaldehyde much easily than on any other aldehyde.



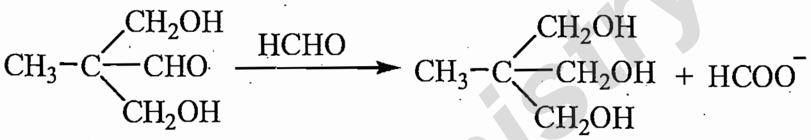
2. When HCHO reacts with other aldehyde with α-H then first the cross aldol reaction takes place followed by cross-cannizzaro reaction.



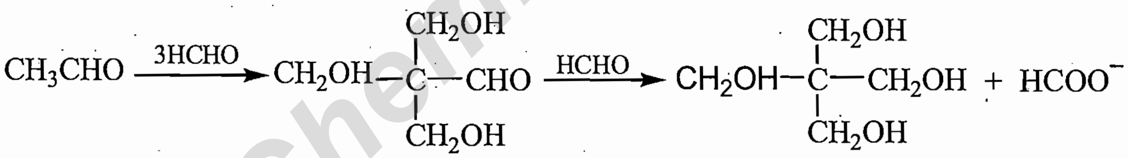
Crossed Cannizzaro

Example:

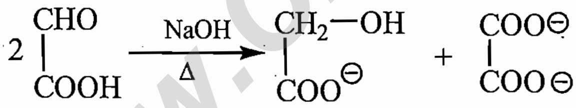
(i)



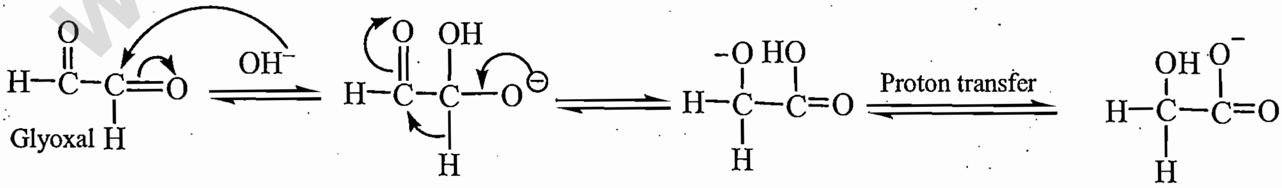
(ii)



(iii)



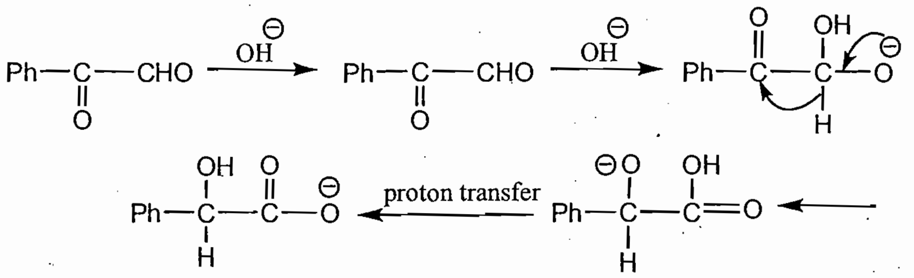
Intramolecular Cannizaro Reaction: Dialdehyde and α-keto aldehyde undergo suitable I.C.R.



$$\text{rate} = K\begin{bmatrix} CHO \\ | \\ CHO \end{bmatrix}\left[OH^-\right] \quad 2^{nd} \text{ order reaction}$$

Hence, intramolecular cannizzaro is a second order reaction.

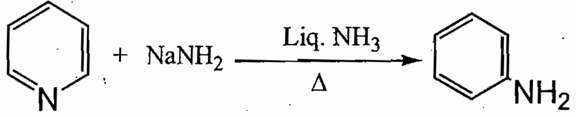
Normal Cannizzaro : 3rd Order Reaction: Cannizaro in strongly basic medium ⟶ 4th order
Internal cannizaro - 2nd order



H⁻ ions come from aldehyde

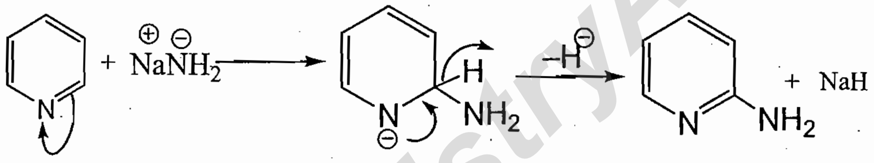
6.10. *Chichibabin Reaction*

Substitution Reaction: Pyridine reacts with sodamide in the presence of liquid ammonia at about 100°C to form 2-amino pyridine.



2-amino pyridine

***Mechanism*:**

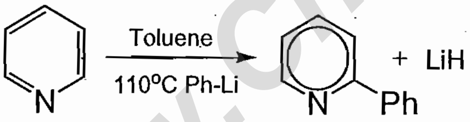


$$NaH + NH_3 \longrightarrow NaNH_2 + H_2$$

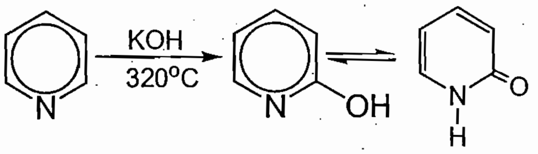
The reaction is initiated by attack of nucleophilic at C-2 or C-6. This because the negative charge on the adduct formed by the additon of nucleophile is stabilised by delocalisation on the electronegative nitrogen atom.

***Examples*:**

(i)

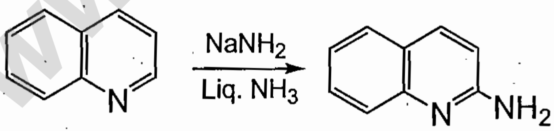


(ii)



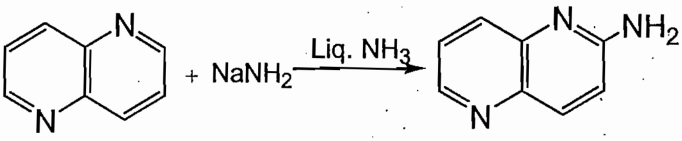
2– Pyridone

(iii)

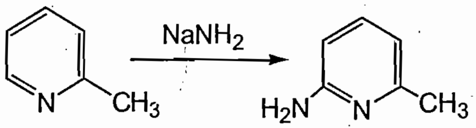


Quinoline

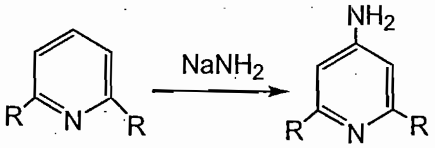
(iv)



(v)

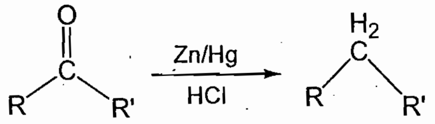


(vi)



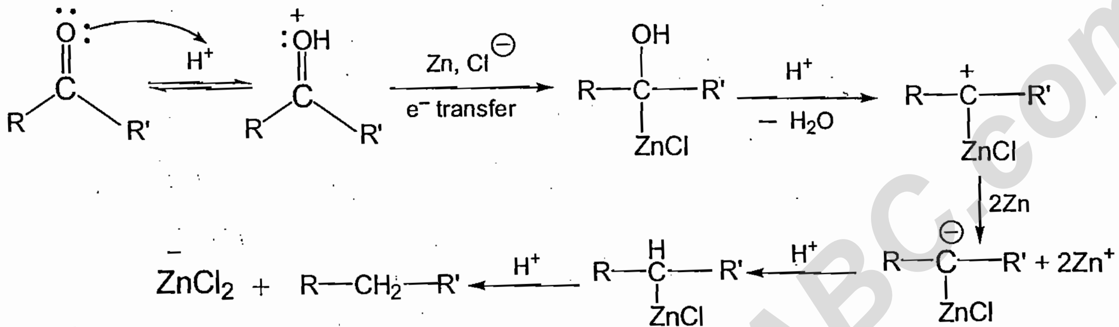
6.11. *Clemmensen Reduction*

Ketone and aldehyde on reduction with zinc amalgam and hydrochloric acid give the corresponding hydrocarbon i.e, carbonyl group is converted into methylene group.



The mechanism of Clemmensen reduction is uncertain. The following expected reaction pathway involve the transfer of electron from the metal surface to the carbon atom of the protonated carbonyl group. Transfer of 4e$^-$ from Zn to one molecule is expected to occur.

***Mechanism* :**

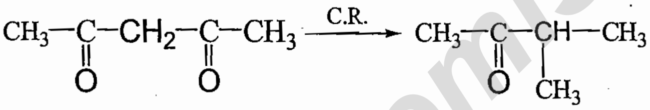


Special Features:

(i) The acid should be conc. (aq. phase should be low) to prevent the bimolecular condensation reaction of carbonyl compound.

(ii) The reduction fail with acid sensitive and high molecular weight substrate.

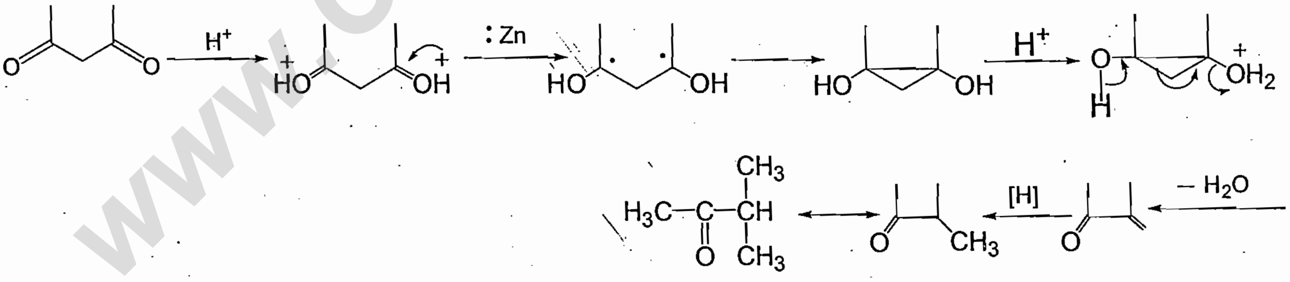
(iii) Certain types of aldehyde and ketones do not give the normal reduction products alone.

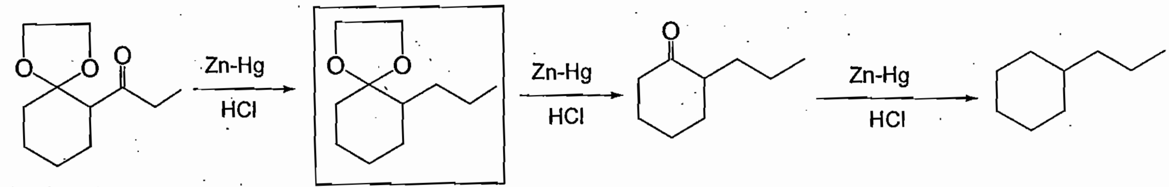
(a) 

$$CH_3-\underset{O}{\underset{\|}{C}}-CH_2-\underset{O}{\underset{\|}{C}}-CH_3 \xrightarrow{\text{C.R.}} CH_3-\underset{O}{\underset{\|}{C}}-\underset{CH_3}{\underset{|}{CH}}-CH_3$$

***Mechanism* :**

Through Rearrangement

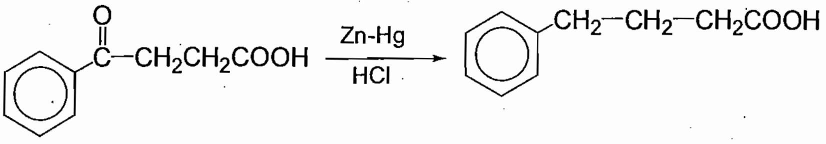


(b) 

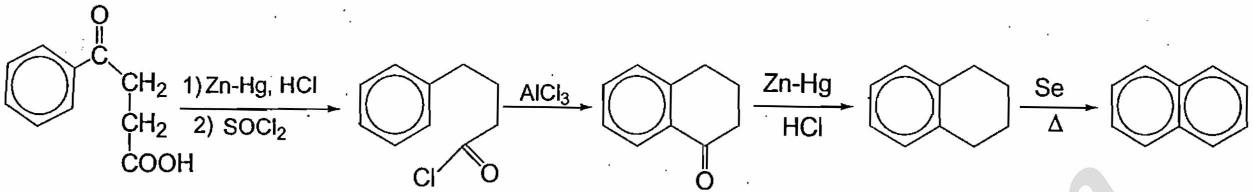
This ring is stable
in basic medium. In acidic medium
it will be break.

Application :

(1) To reduce keto acid :

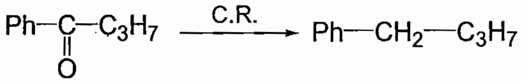


(2) To prepare napthalene :



Example:

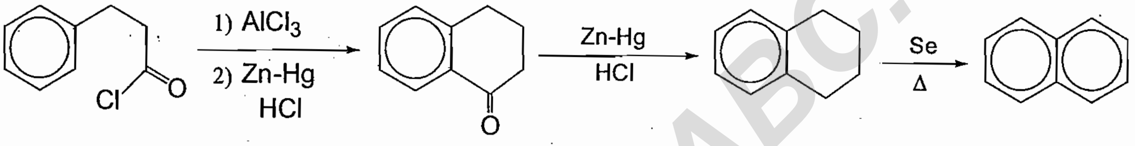
(i)



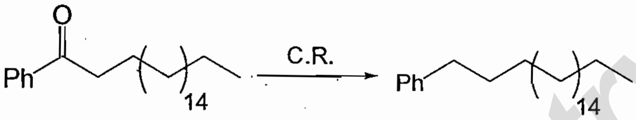
$$Ph-\underset{\underset{O}{\|}}{C}-C_3H_7 \xrightarrow{C.R.} Ph-CH_2-C_3H_7$$

(ii) $CH_3(CH_2)_7-CHO \xrightarrow{C.R.} CH_3(CH_2)_7-CH_3$

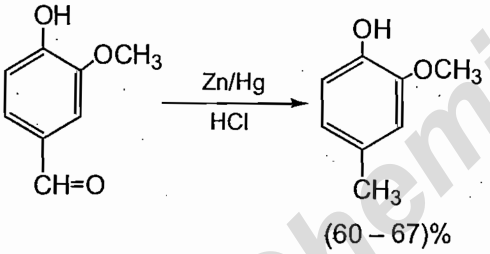
(iii)



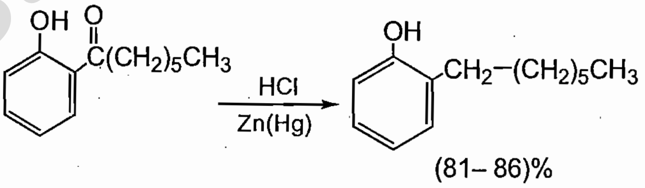
(iv)



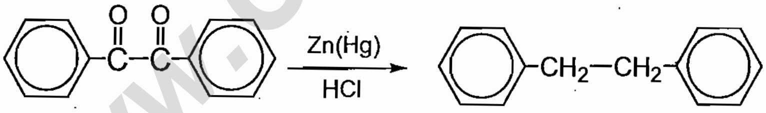
(v)



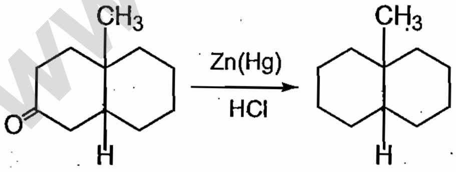
(vi)



(vii)

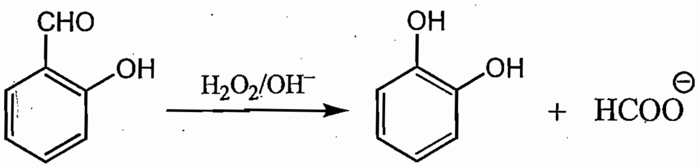


(viii)

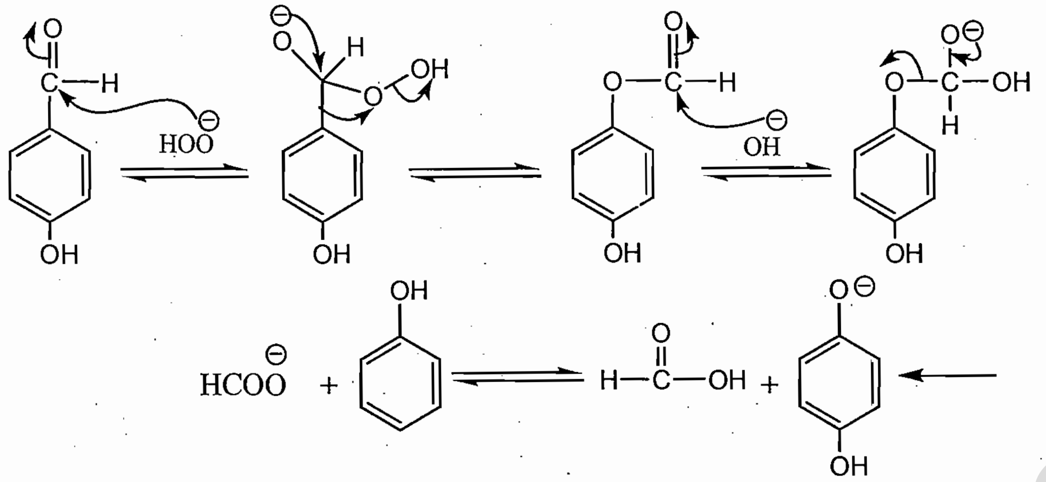


6.12 Dakin Reaction

Aromatic carbonyl compounds having a hydroxy or amino group in either ortho or para position can be converted to phenols on treatment with alkaline hydrogen peroxide.

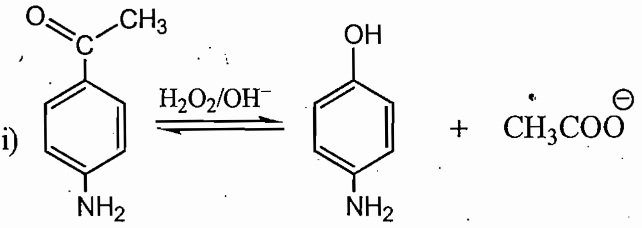


Mechanism:

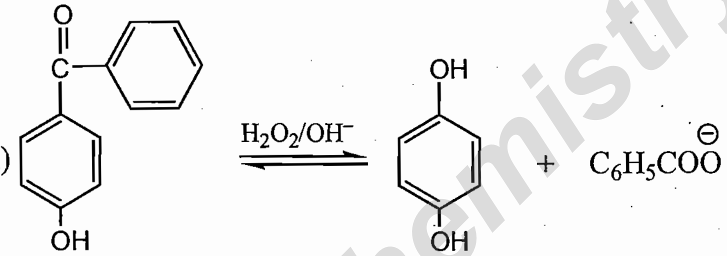


Examples:

(i)

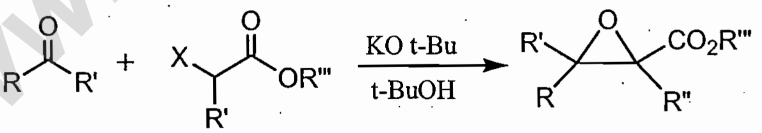


(ii)

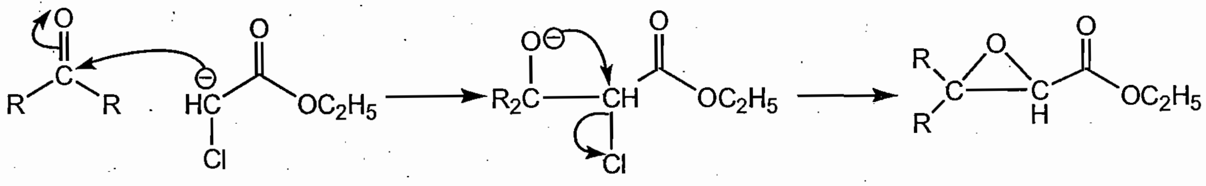


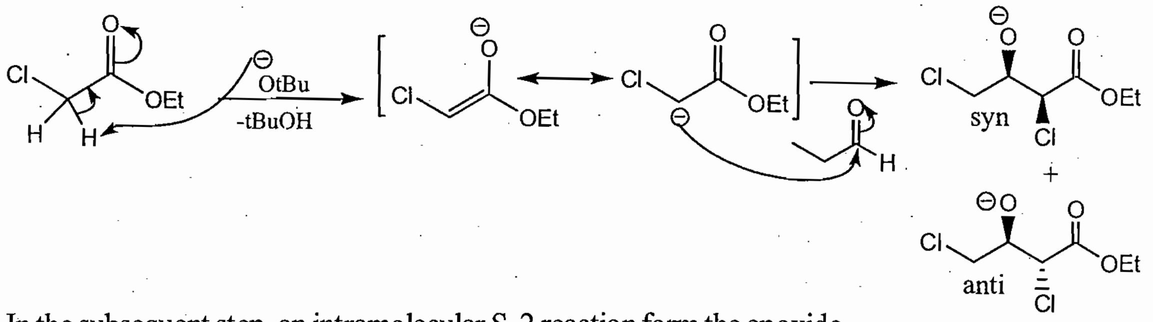
6.13. *Darzens Reaction*

The Darzens reaction is the condensation of a carbonyl compound with an α – haloester in the presence of a base to form an α, β – epoxy ester.

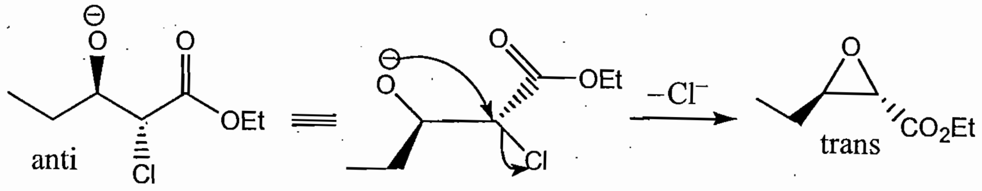


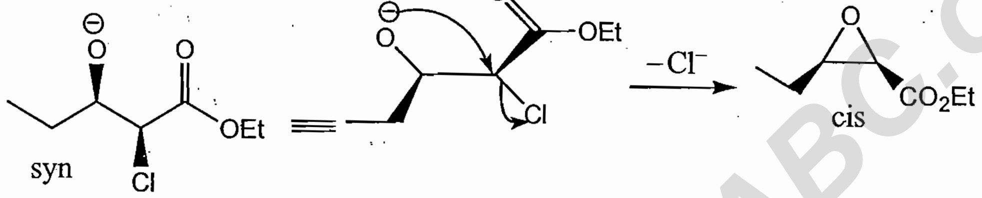
Mechanism: The first step in this reaction is addition of enolate of the α – haloester to the carbonyl compound. After this alkoxide oxygen formed in the addition does nucleophilic attack, displacing the halide and forming α, β – epoxy ester(also called glycidic ester)





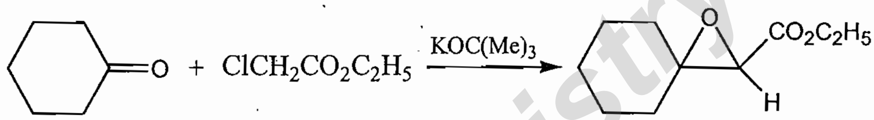
In the subsequent step, an intramolecular S_N2 reaction form the epoxide.



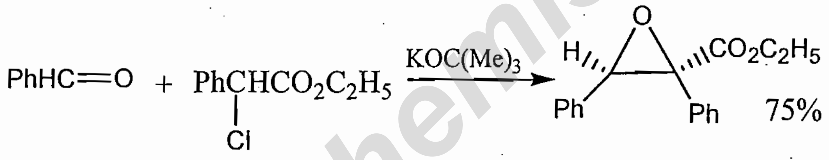


PROBLEMS

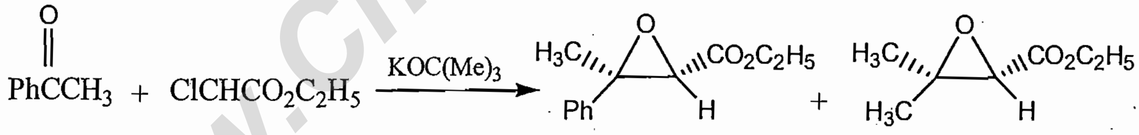
1.



2.

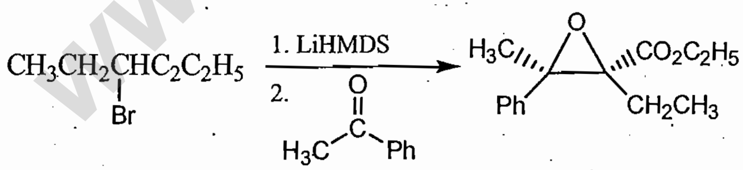


3.



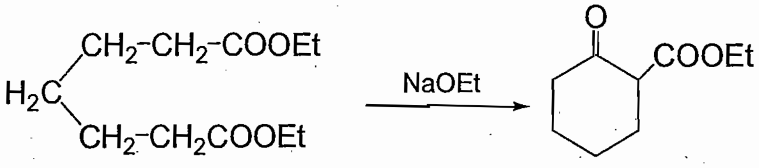
(1:1 mixture of isomers)

4.

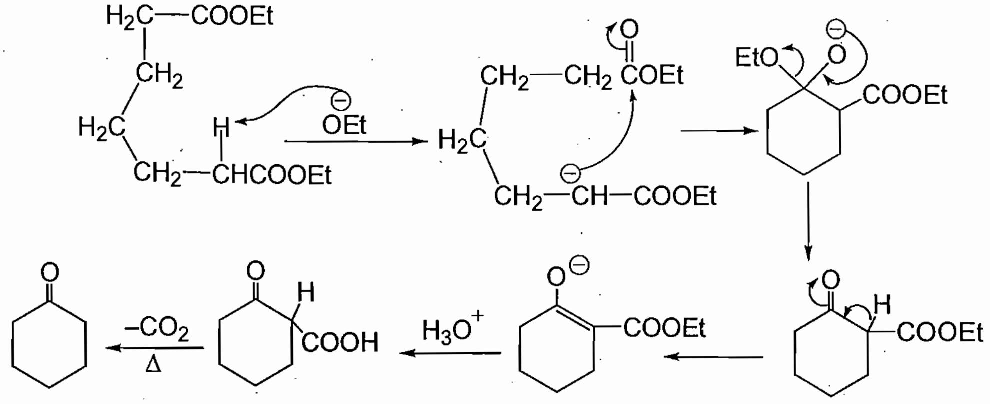


6.14. *Dieckmann Condensation / Cyclisation*

It is an intramolecular claisen condensation and is used for preparation of cyclic ketone. Intramolecular claisen reaction where both esters groups (COOEt) are part of the same molecule acting as a Nucleophile and electrophile to give cyclic stable 5, 6 or sometimes 7 membered rings is known as ***Dieckmann-Cyclisation***.



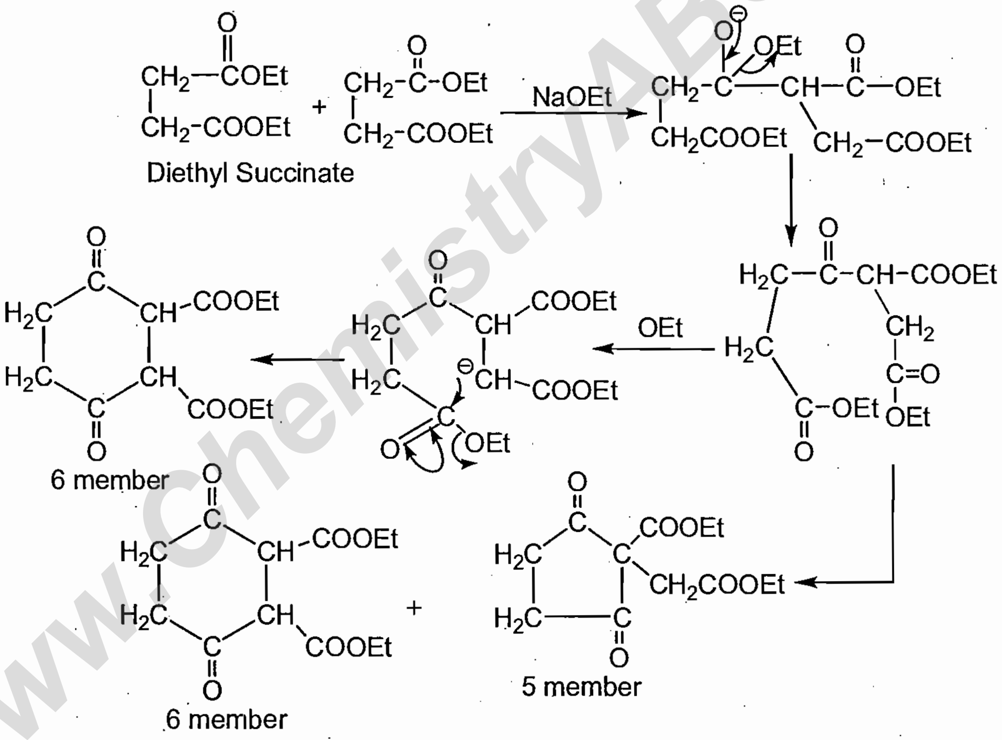
***Mechanism* :**



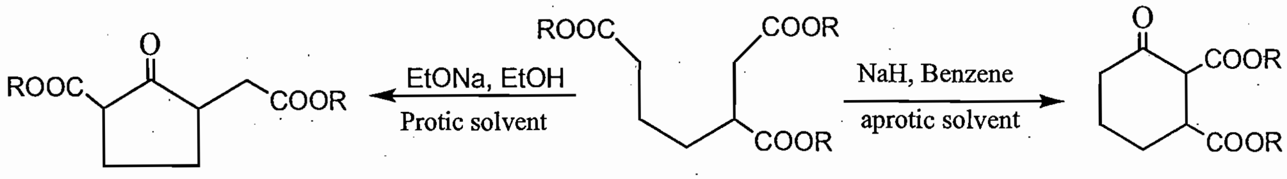
Effect of Dilution :

(1) On dilution the solvent separates the molecules and as a result the intermolecular distance of the reacting group is greater than the intramolecular distance. So the intramolecular cyclization is favoured by dilution. And intermolecular condensation is minimised.

(2) Ester of the acids lower than adipic acid acid initially undergo intermolecular condensation followed by cyclization intramolecular.

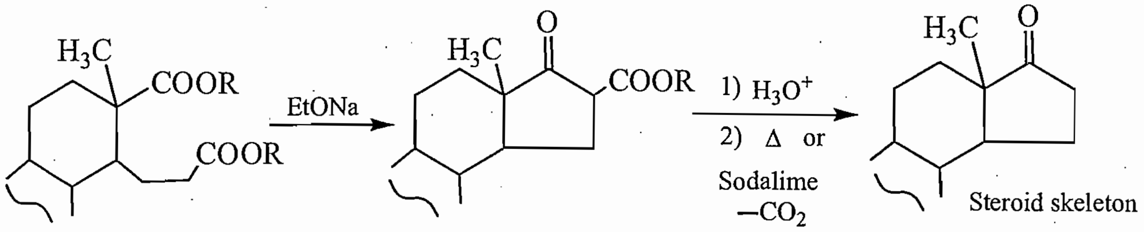


Experimental condition also affect the size of ring.

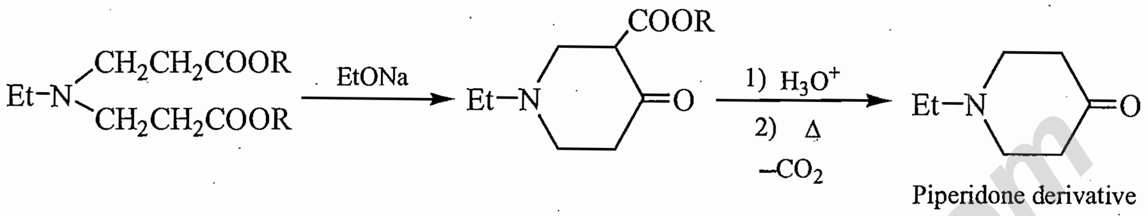


Application:

(1) Synthesis of steroids :

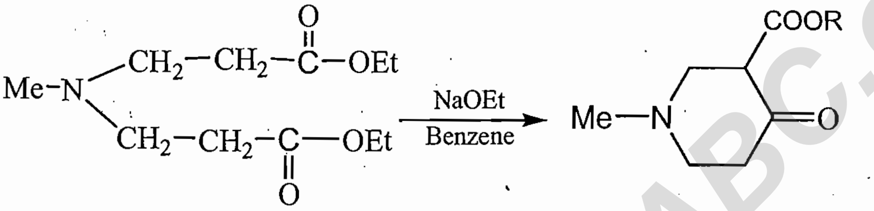


(2) Heterocyclic ketoesters :

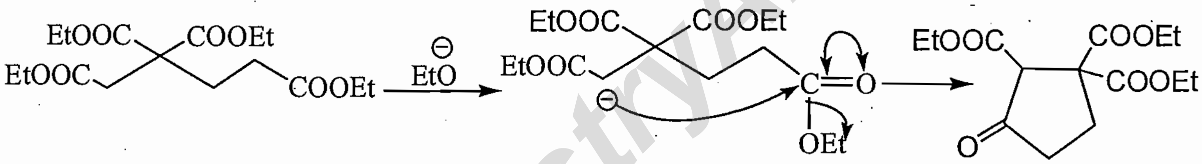


Example:

(i)

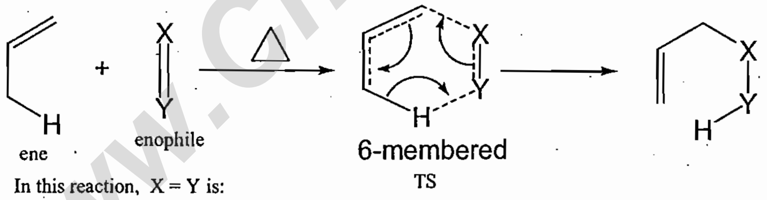


(ii)



6.15. *Ene Reaction*

Any alkene having an allylic hydrogen atom reacts thermally with enophile to form a new bond to the terminal carbon of allylic group. This involves 1, 5- migration of allylic hydrogen and change in the position of the allylic double bond. It is like $6\pi e^-$ electrocyclic reaction. (The Diels -Alder reaction). Two electrons of allylic C – H, or σ bond in place of two π-electrons of the diene as in Diels-Alder reaction. The activation energy is greater than Diels Alder therefore high temperature is required.

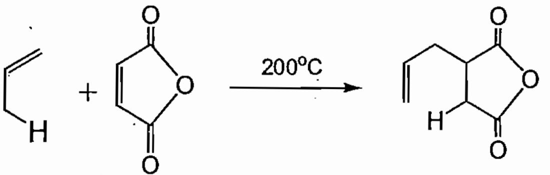


In this reaction, X = Y is:

C = C
C = O
C = S
N = O
N = N etc.

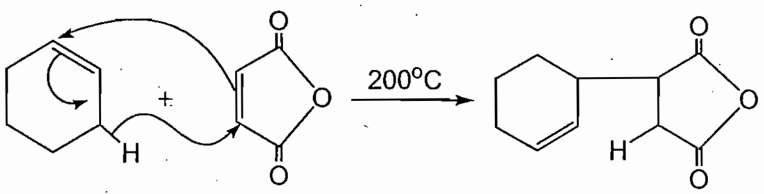
Examples:

(i)



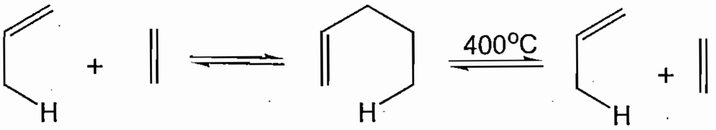
Maleic anhydride

(ii)

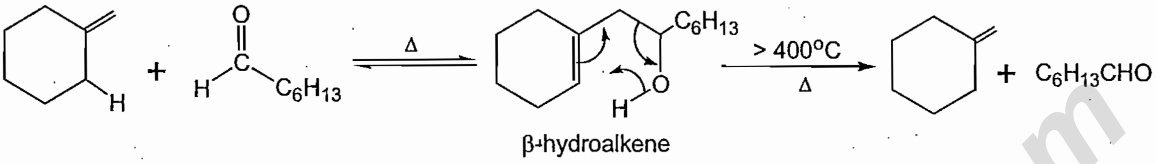


- Ene Reaction is reversible in very high temperature.

(iii)

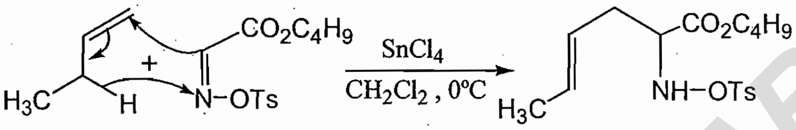


(iv)

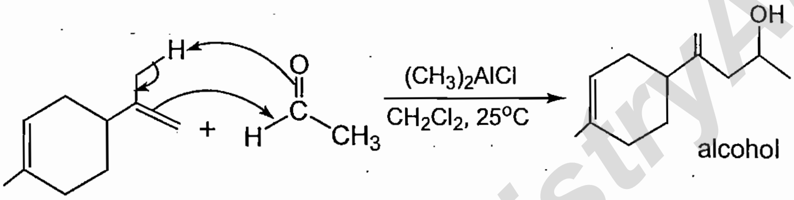


Many ene reaction can also be undergone in presence of lewis acid which catalyse the reaction. Advantage of lewis acid is that the reaction is done at room temperature or below r.t. Lewis acid used are $AlCl_3$, $SnCl_4$, $TiCl_4$ etc. The best result was found with allyl aluminium halide.

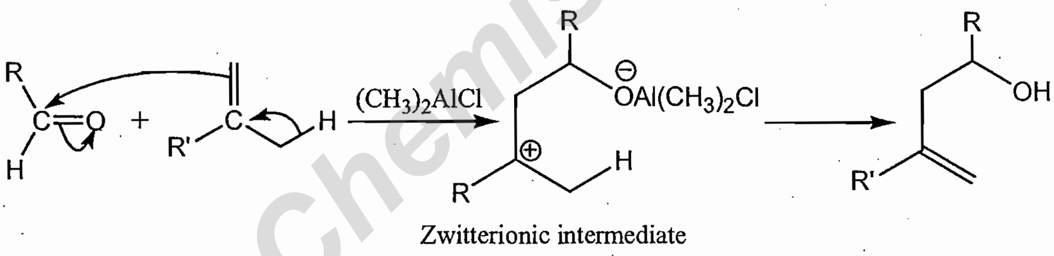
(v)



(vi)

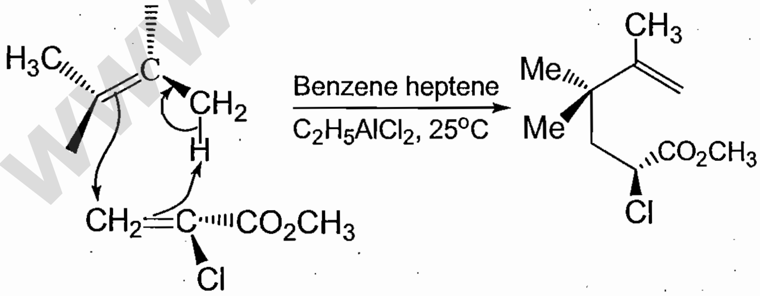


(vii)



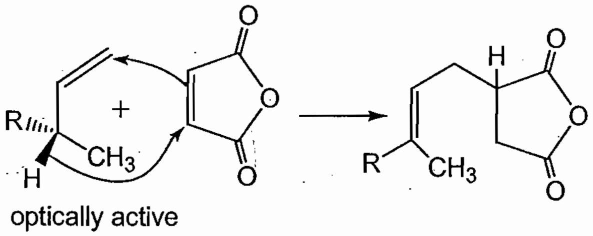
Optical Active :

(viii)

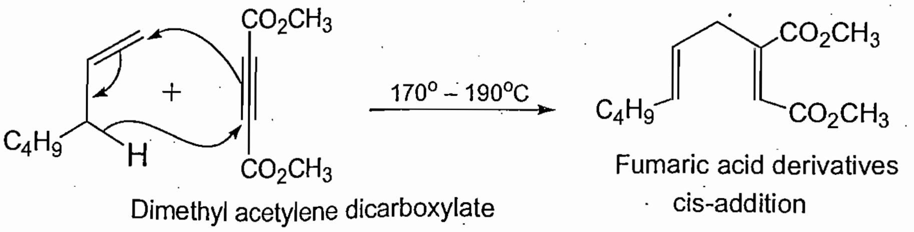


R : Phenyl

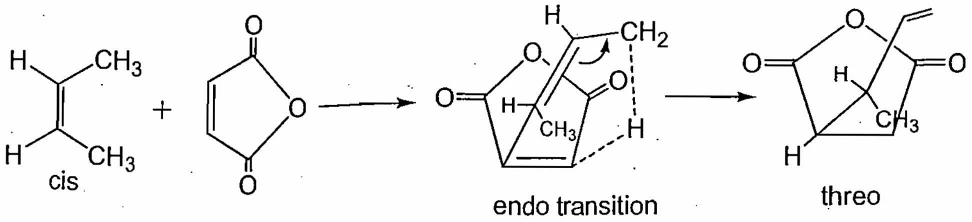
(ix)



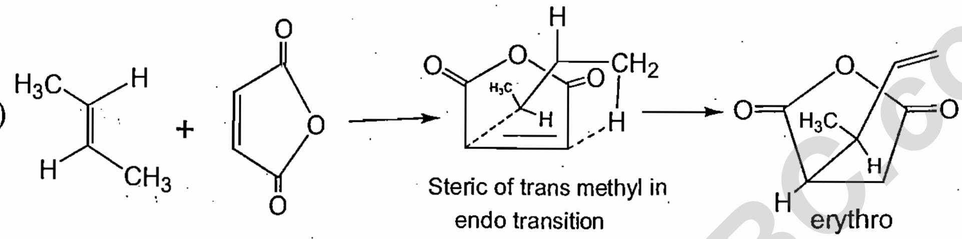
(x)



(xi)

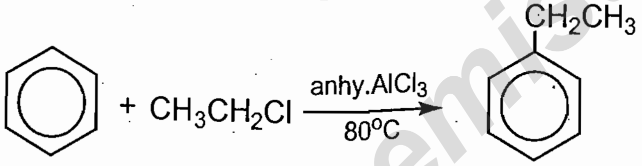


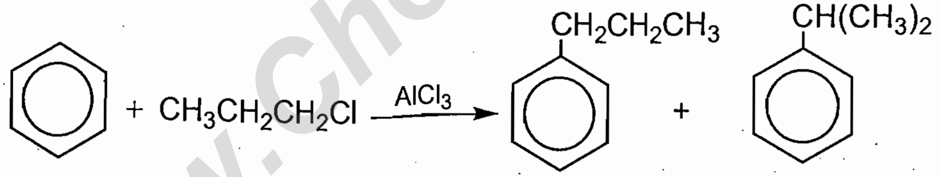
(xii)



6.16. *Friedel Craft's Reaction*

1. Friedel Craft's Alkylation : This reaction involves the introduction of alkyl group in the benzene nucleus in presence of a catalyst. The aromatic compounds are usually hydrocarbons, aryl halides, phenols, ethers etc. and certain heterocyclic compounds. The reaction is actually electrophilic aromatic substitution. Where the alkyl group acts as a electrophile and the benzene nucleus as the nucleophile



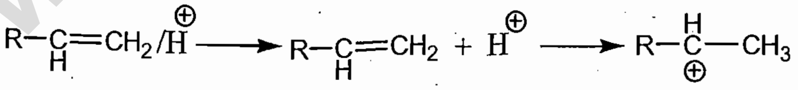


***Mechanism* :** Various combination of reagents can be used to produce the alkylating group. Three usual reagents are :

(1) Alkyl halide (RX) / Lewis acid

(2) $ROH / H^+ \longrightarrow ROH + H^+ \longrightarrow R{-}OH_2^+ \longrightarrow R^+$

(3)



$$R{-}\underset{H}{C}{=}CH_2/\overset{\oplus}{H} \longrightarrow R{-}\underset{H}{C}{=}CH_2 + \overset{\oplus}{H} \longrightarrow R{-}\underset{\oplus}{\overset{H}{C}}{-}CH_3$$

2 and 3 [Primarily carbocation intermediate], 1 Duality of mechanism depending on various factors.

(1) Alkyl Halide : $\overset{\delta^+}{R} \longrightarrow \overset{\delta^-}{:\ddot{Cl}:}$

under normal condition it is (R) not sufficient electrophile to cause aromatic substitution

$$R{-}\ddot{\underset{\cdot\cdot}{Cl}}: \xrightarrow[\text{form 1:1 adduct with alkyl halide}]{AlCl_3} [\overset{+}{R}{-}\overset{-}{Cl}{-}AlCl_3] \longrightarrow [\overset{+}{R}.......Cl.........\overset{\ominus}{AlCl_3}] \longrightarrow R^+ + \overset{\ominus}{AlCl_4}$$

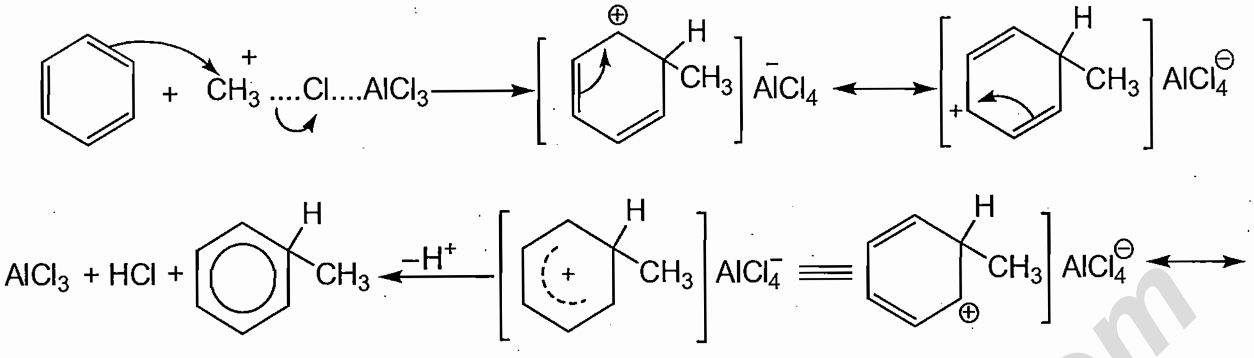
Polarised complex

If it is highly stable carbocation

Donation of electrons to lewis acid makes R-X bond more polar with increase positive charge on R.

With Straight Chain 1° Halide :

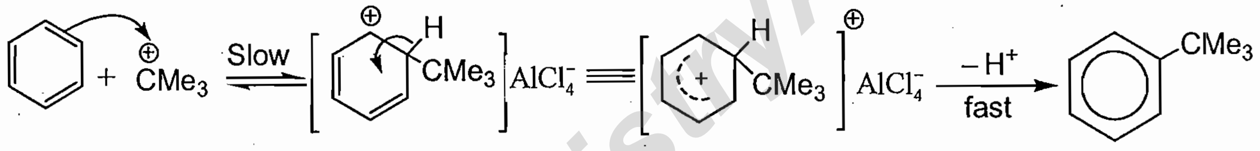
$$CH_3Cl + AlCl_3 \rightleftharpoons [\overset{\delta+}{CH_3}\ldots\ldots\overset{\delta+}{Cl}\ldots\ldots\overset{\delta-}{AlCl_3}]$$



It involves a Nucleophilic attack by the aromatic ring to the alkyl group of the polarised complex. $AlCl_4^-$ is a better leaving group than Cl and the degree of polarization of alkyl halide depends on R and lewis acid.

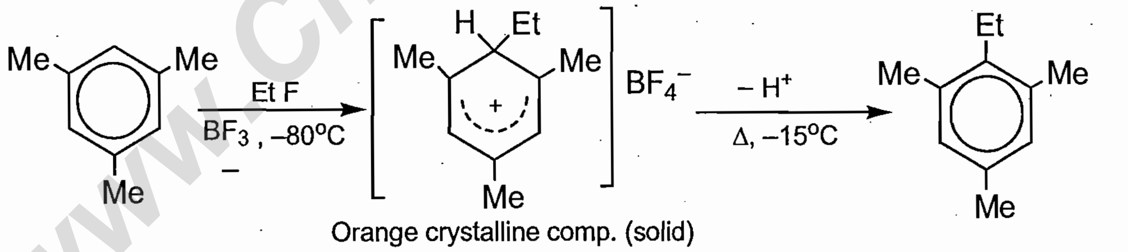
2. With 3° Halide: Carbocation is the actual Electrophile

$$(CH_3)_3-C-Cl + AlCl_3 \xrightleftharpoons{slow} (CH_3)_3\overset{\oplus}{C} + AlCl_4^{\ominus}$$



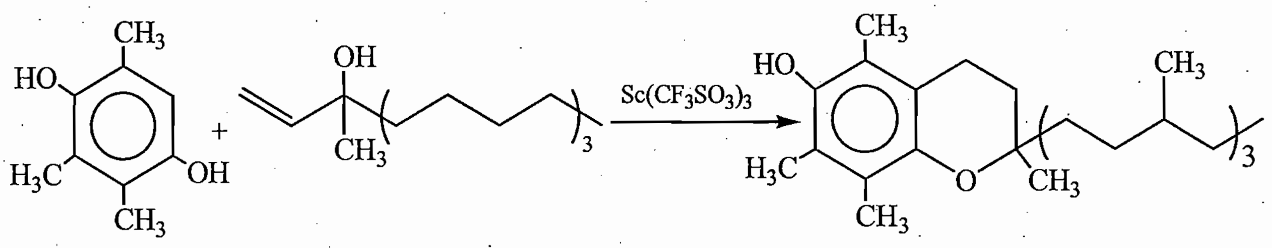
For both Mechanism : Rate law $r = K[Ar-H][Rx][Lewis\ acid]$. While the 3° halide as the carbocation. For all other cases (2° or long chain 1°) it appears that the carbocation mechanism is increasingly favour with increasing branching in the alkyl halide and the strength of the lewis acid.

Evidence: Isolation of Wheland Intermediate

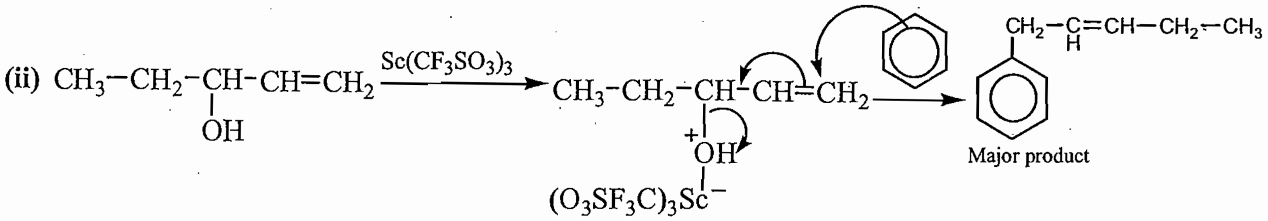


Example:

(i)

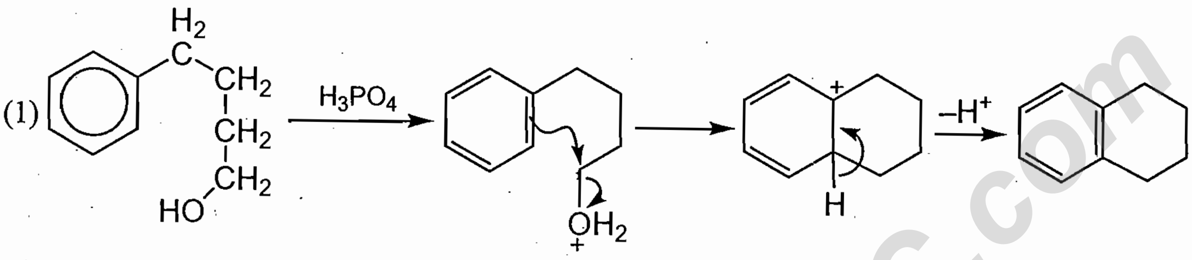


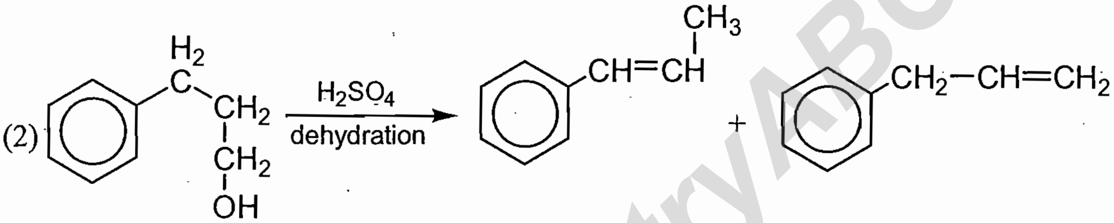
It also give 1, 4-addition.



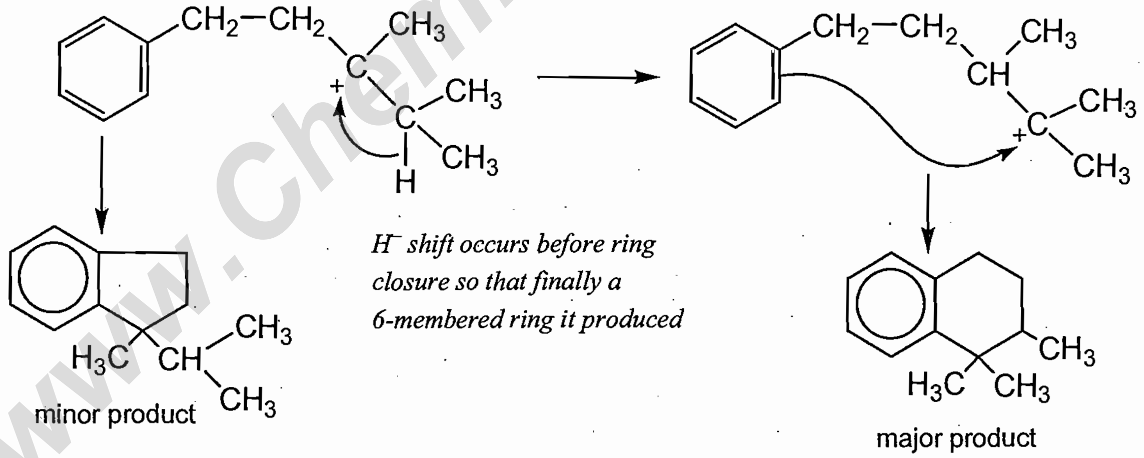
Intramolecular Friedal Craft Alkylation:

In this reaction there is a tendency to produce a six membered ring rather than a five membered ring



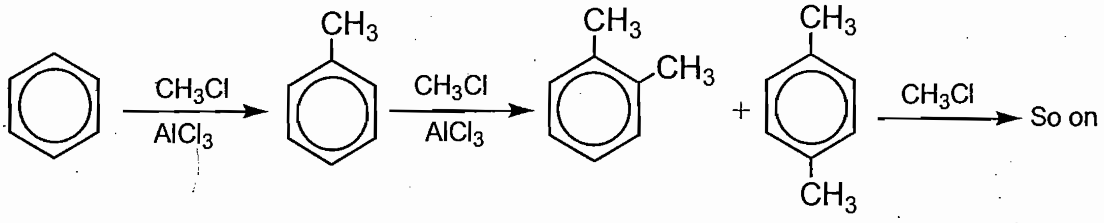


If a potential C^+ intermediate can undergo a hydride or alkyl shift then this will occur in prefrence to cyclize for producing a five membered ring because after shifting the ring closer produces a six membered ring.

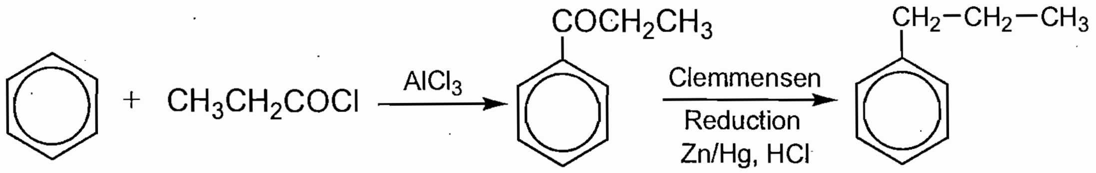

H^- shift occurs before ring closure so that finally a 6-membered ring it produced

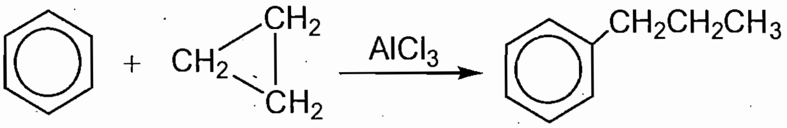
Limitation:

(i) Polyalkylation : Since the alkyl groups are activating the reaction doesn't stop at the mono alkylated stage and di, tri and poly alkylated products are obtained.

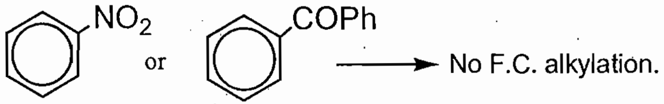


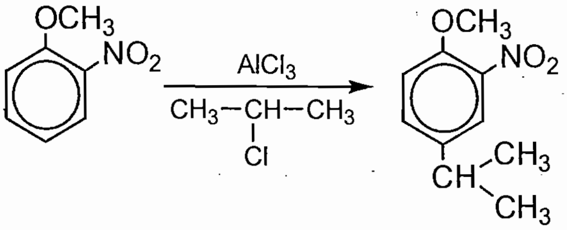
This specially occurs with ethyl and methyl group.
This can explain on the basis of hyperconjugation. *Methyl > ethyl > isopropyl > t-butyl.*
(ii) Rearrangement of C^+ as well as the final end product (migration and disproportionation)
(iii) Two ways to produce n-propyl group.





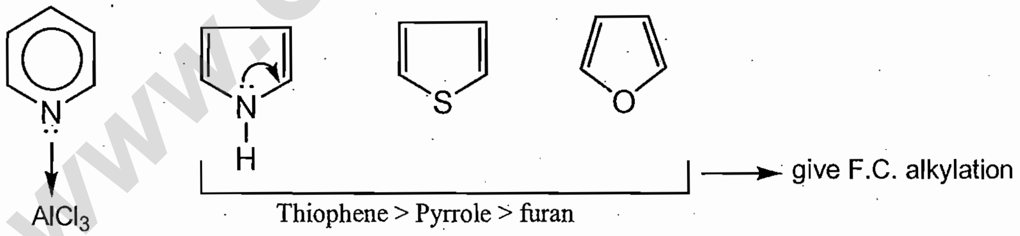
(iv) With electron withdrawing groups: Substrate containing strongly deactivating and e^- withdrawing groups do not undergo F.C. alkylation.



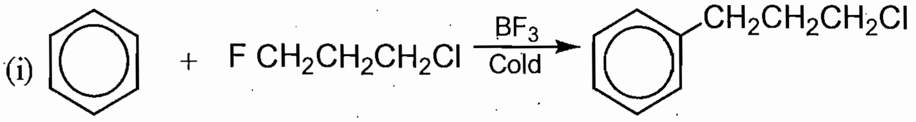


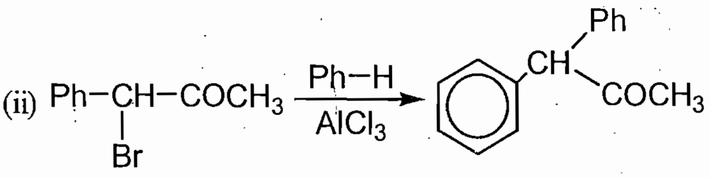
Note: Alkylation is possible if the ring contains one strongly e^- donating group. Nitrobenzene is a preferred solvent because:
(1) It don't undergo Friedal Craft alkylation.
(2) $AlCl_3$ is soluble in nitrobenzene. So a heterogenous reaction is avoided.

Napthalene :
Napthol and pyridine give poor yield with Friedal Craft reagents while certain heterocyclic compounds, like pyrrole, furan, thiophene undergo Friedal Craft alkylation.



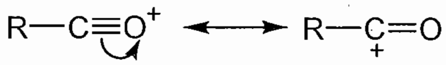
***Example*:**





Friedal Craft Acylation :

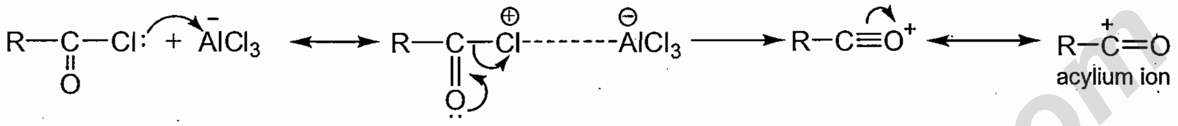
This reaction involves the use of acyl halides and lewis acids like $AlCl_3$, BF_3, SbF_5 etc. to produce alkyl aryl ketones. Acid anhydrides can also be used. The mechanism involves an acylium ion or a polarised complex of acyl chloride and lewis acid. In polar solvent the acyl cation has been detected by IR spectroscopy.

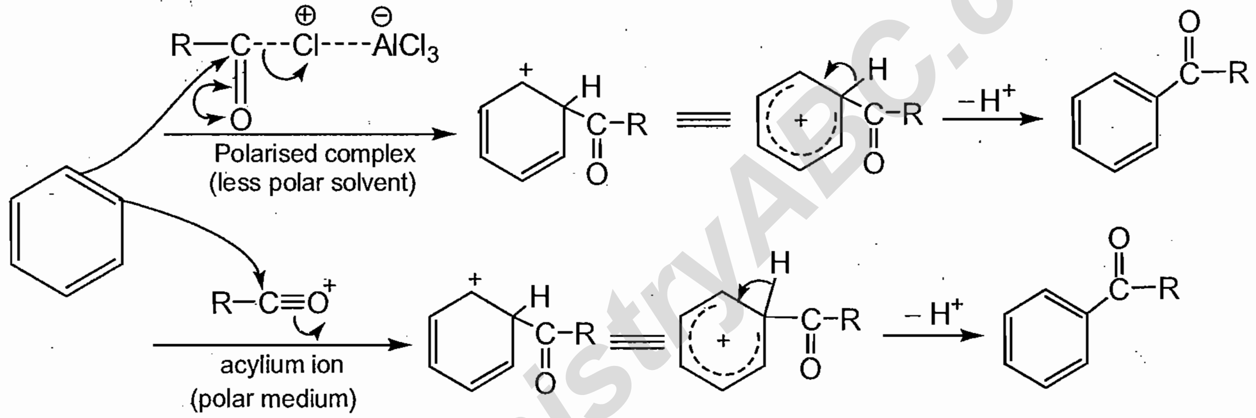


$$R-C\equiv O^{+} \longleftrightarrow R-\underset{+}{C}=O$$

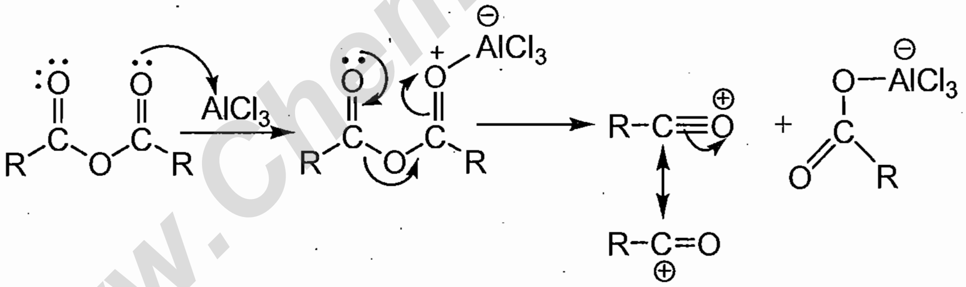
Some complexes like $MeCO^{+}BF_4^{-}$ isolated. In polar solvent when the R group is bulky the mechanism is believe to be proceed via acylium ion. While in less polar solvent and in some other circumstances where the acylium ion is not detected the reaction goes via the polarised complex.

***Mechanism* :**



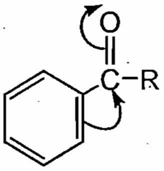


With Anhydride :



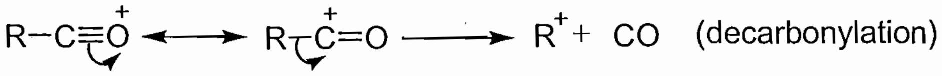
Difference between Alkylation and Acylation:

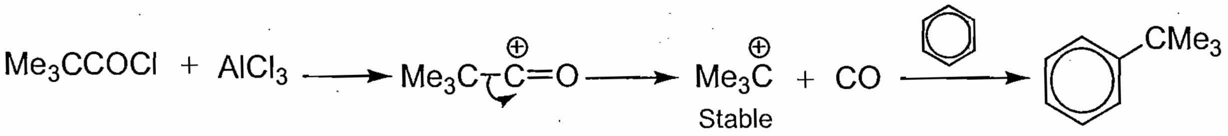
(1) The acyl group withdraws electron from the π system and hence deactivates the ring towards further electrophilic substitution. So the problem of multiple substitution is avoided.



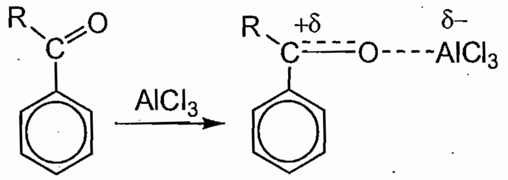
(2) Rearrangement of the initial E^{+} (acylium ion) can't take place as like that of alkylation. So rearrangement products can't be obtained. Under a special circumstance when the R group can form a very stable C^{+} then decarbonylation of acylium ion takes place $\left(R-C\equiv\overset{\oplus}{O}\right)$ to produced a stable C^{+} and the result is alkylation rather than acylation.

Example:

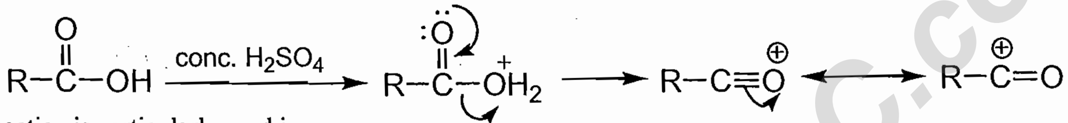




(3) Amount of lewis acid required in acylation is more than the alkylation because in acylation the lewis acid form complex with the product ketone and is thereby removed from further participation in the reaction.



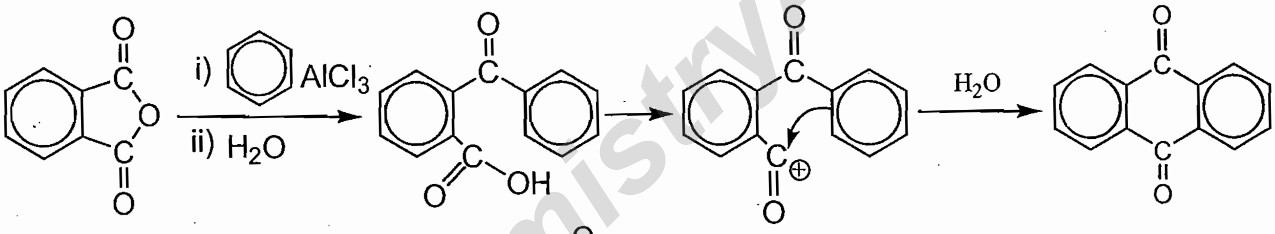
Stable complex



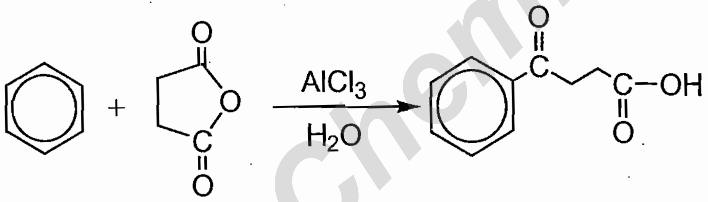
This reaction is particularly used in intramolecular Friedal Craft acylation

Intramolecular Friedal Craft Acylation:

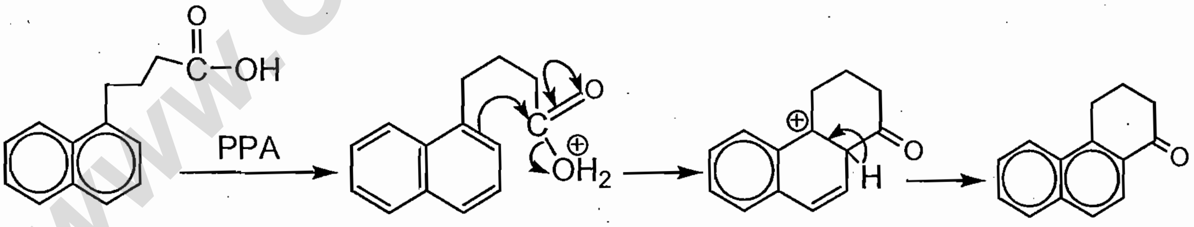
(i)



(ii)

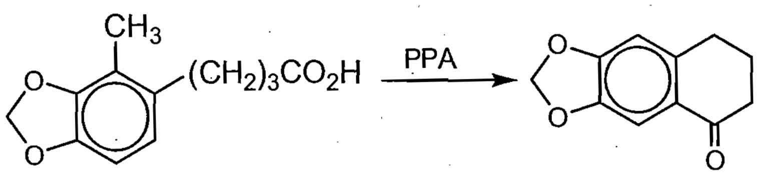


(iii)

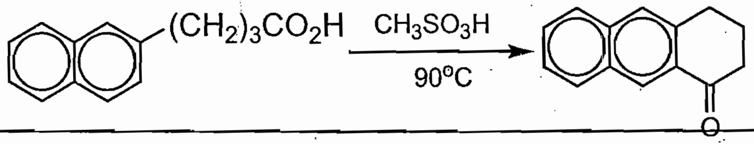


Two Reagents for Intra Molecular Acylation:

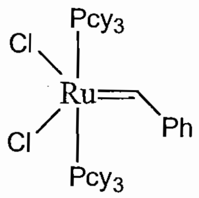
(1) Polyphosphate ester (esterified oligomer of PPA)

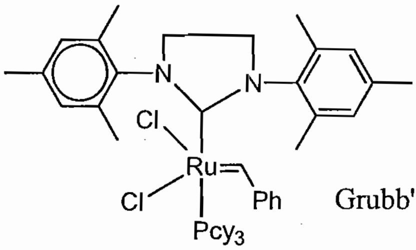


(2) Methane sulphonic acid CH_3SO_3H :

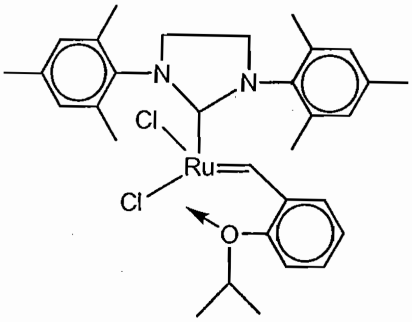


6.17 Grubb's-First Generation Catalyst :

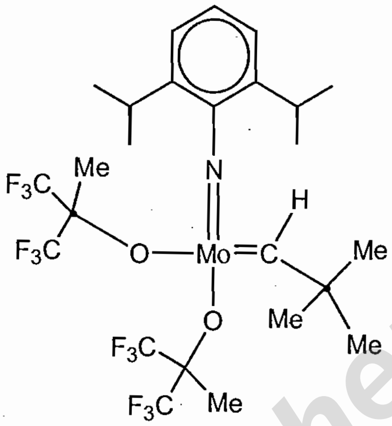




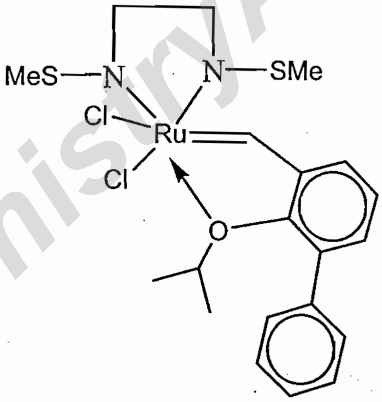
Grubb's 2nd generation catalyst



Hoveyda-Grubb's catalyst

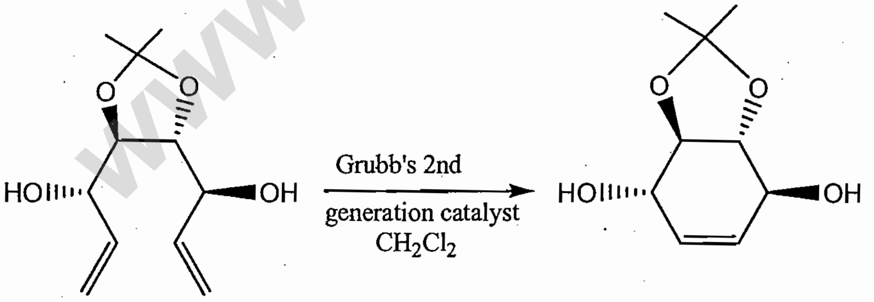


Schrock's catalyst

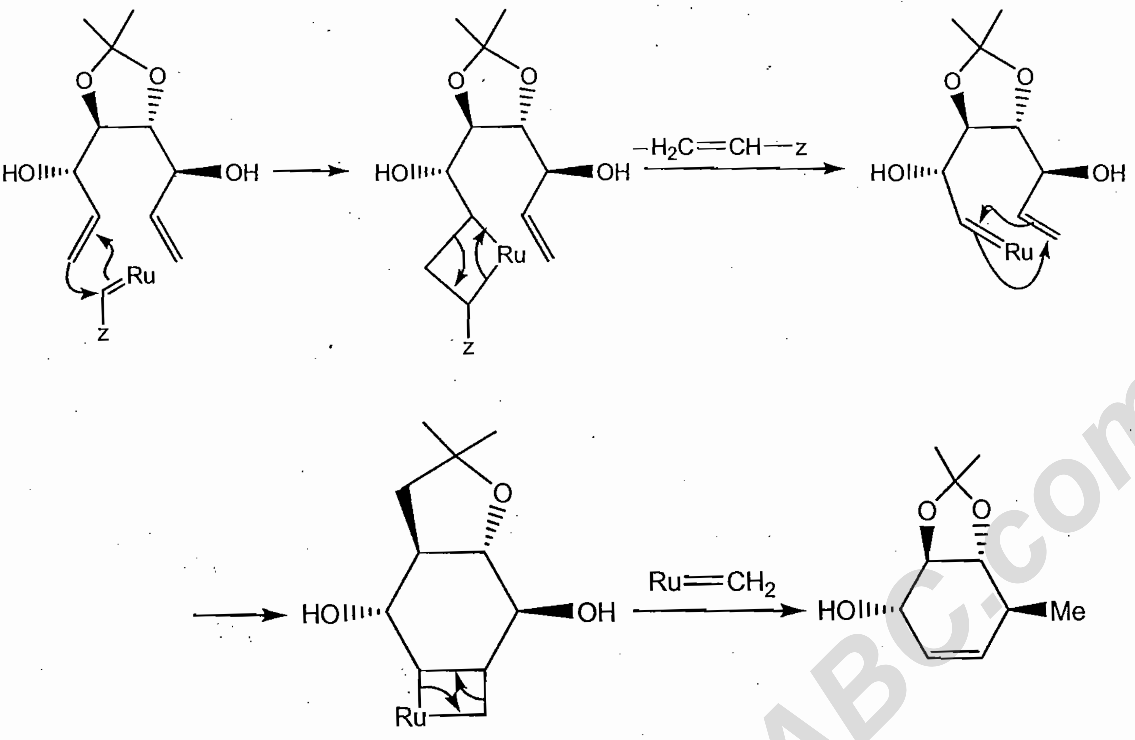


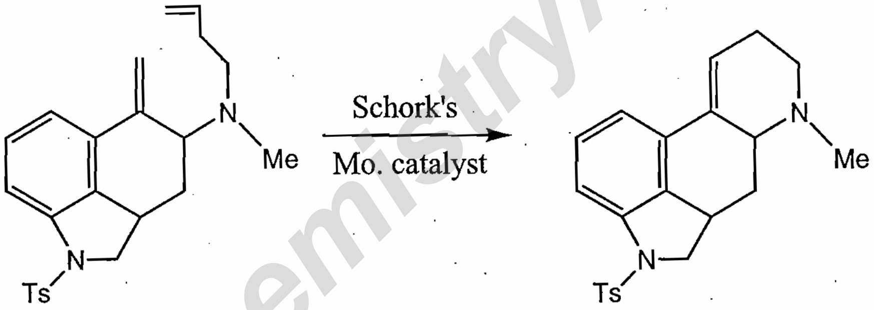
Blechert's catalyst

Ring closing metathesis: (RCM):



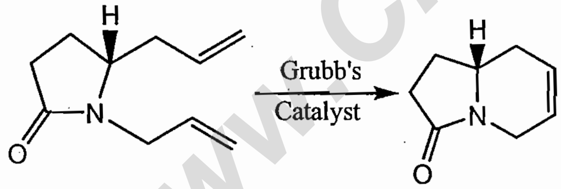
Mechanism:





PROBLEMS

1.



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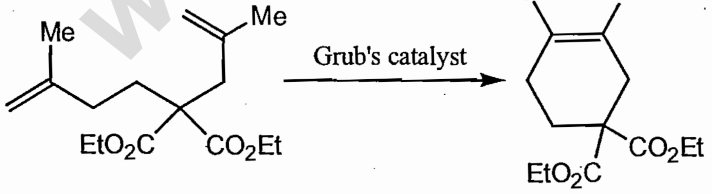

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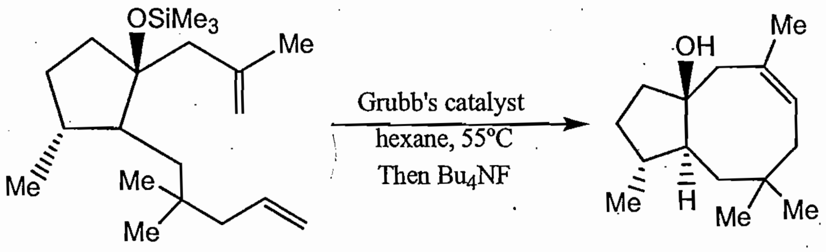
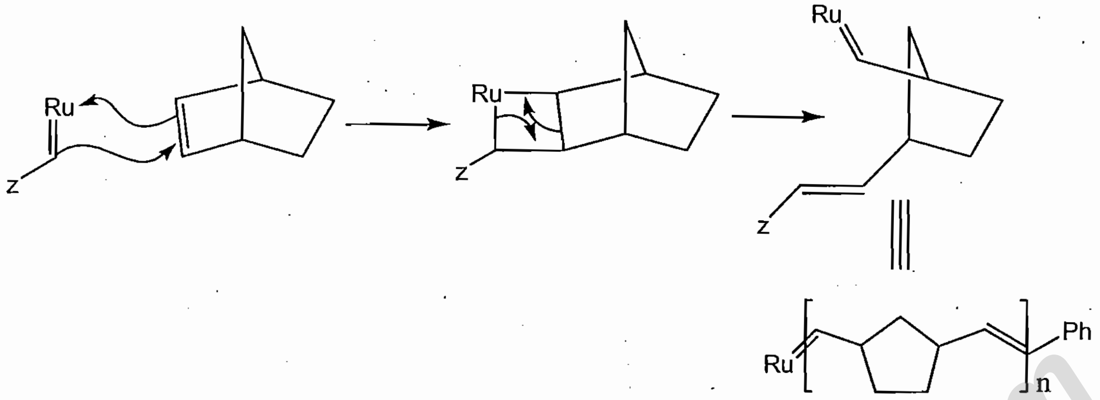


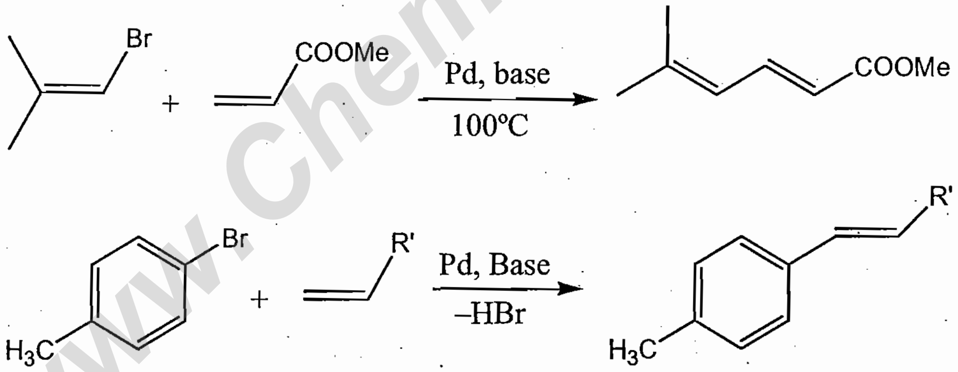
Ring opening metathesis (ROMP) polymerisation.



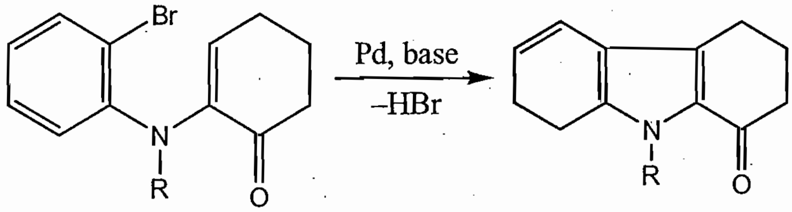
6.18. Heck Reaction

- Heck reaction involves the palladium catalysed substitution of the vinylic hydrogen with a vinyl, aryl or benzyl group.
- Coupling can be intra or intermolecular.
- This coupling reaction is stereoselective with a propensity for trans coupling as the Pd halide group and the bulky organic residue move away from each other in the reaction sequence by bond rotation.
- Typical catalysts are Pd(0)– phosphine complex $Pd(PPh_3)_4$ or in situ catalysts such as $Pd(OAC)_2/PPh_3$.
- Reactions are conducted in polar aprotic solvents like MeCN, DMSO or dimethylacetamide (DMAC)

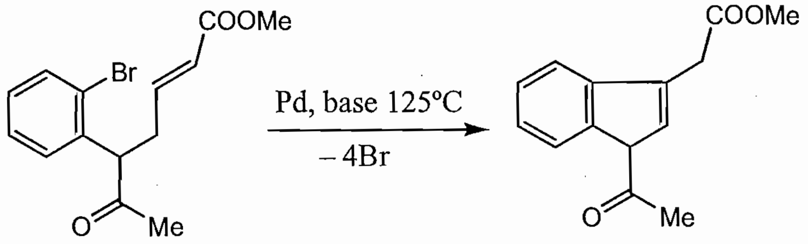
Intermolecular Heck coupling:



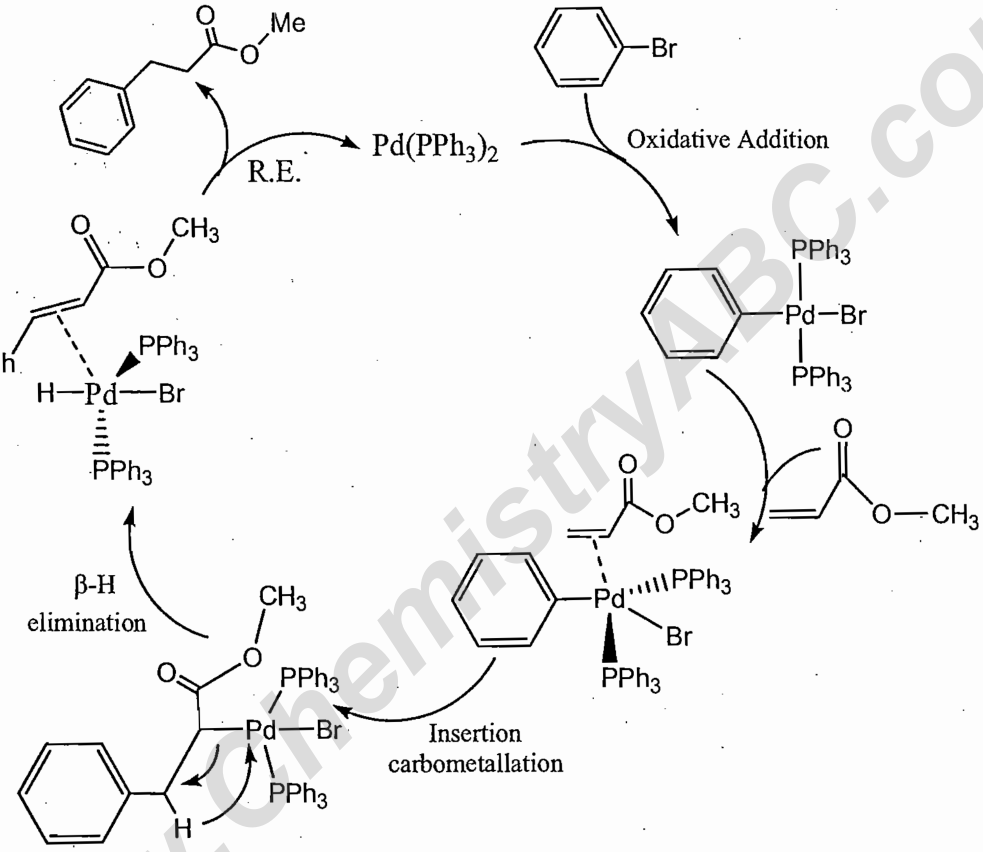
Intramolecular Heck coupling.



Coupling with isomerisation.



6.19. Catalystic cycle for Heck coupling reaction



PROBLEMS

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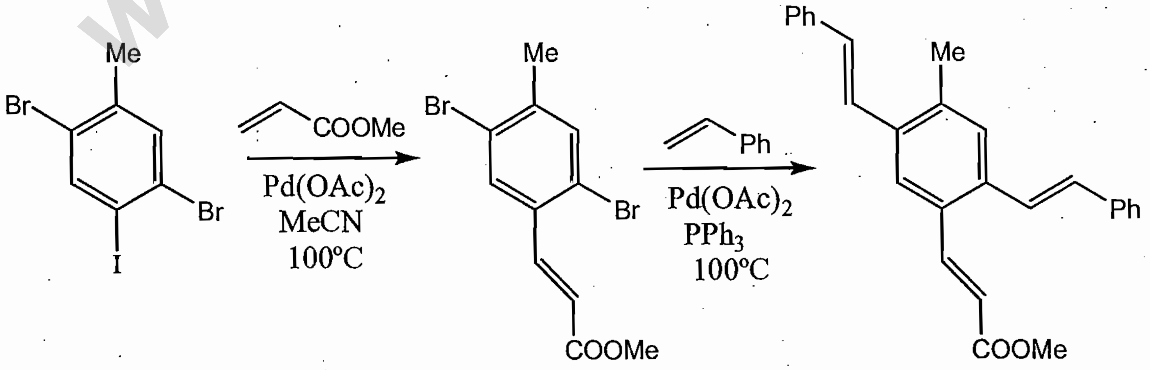
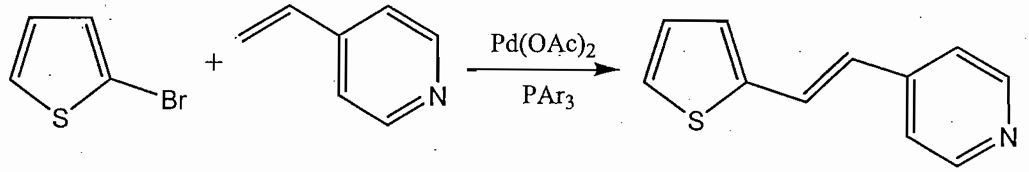
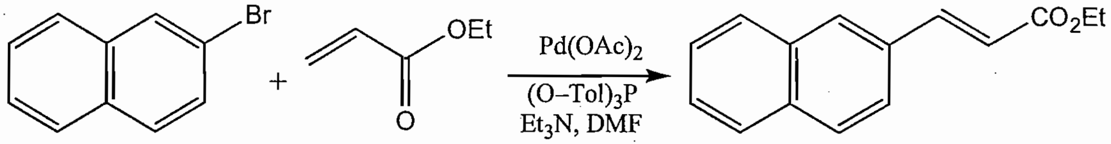
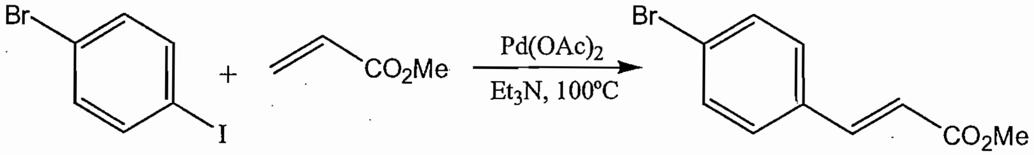
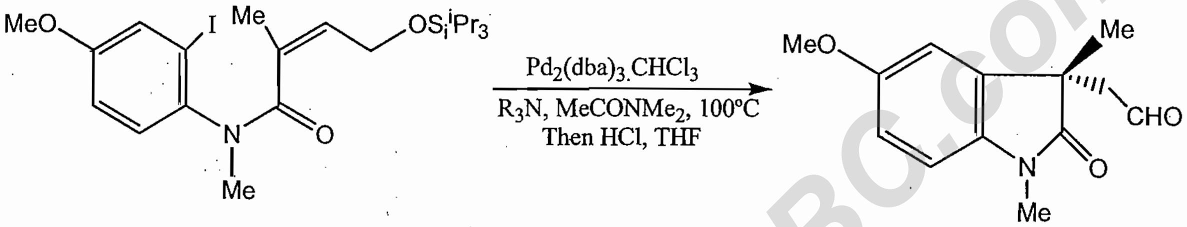
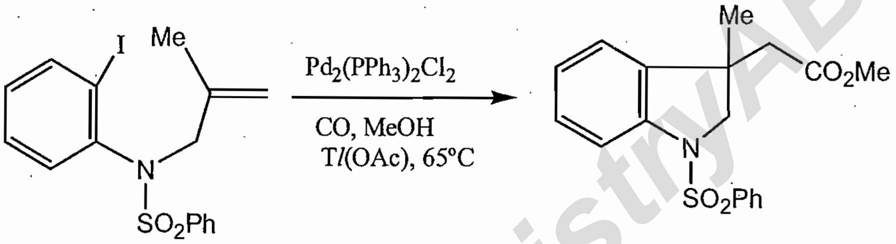




2. 

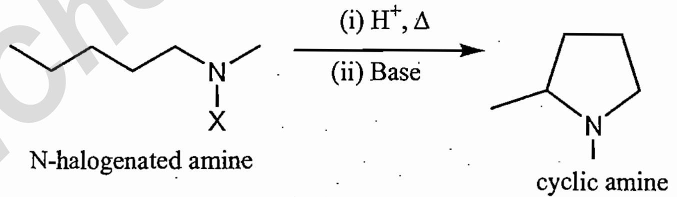
3. 

4. 



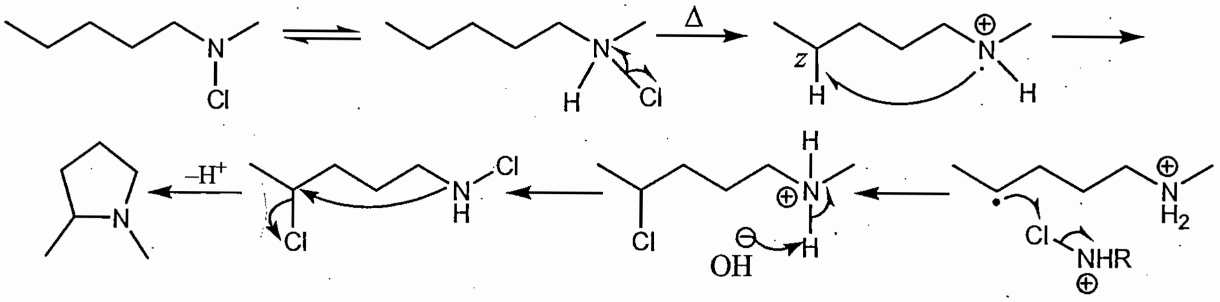
6.20. Hoffmann Loffler Reactions

The Hoffmann Loffler reaction (also refered to as Hoffmann Loffler Freytag reaction) is an organic reaction in which a cyclic amine is generated by thermal or photochemical decomposition of N-halogenated amine in presence of a strong acid.



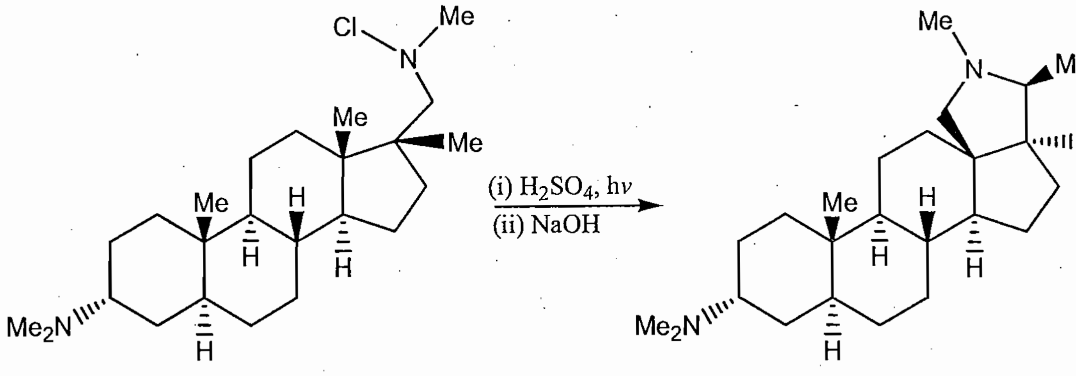
Mechanism: Thermal or photochemical dissociation of the N-chloro ammonium salt formed by protonation of N-chloro amine, is thought to give the reactive ammonium radical species. This abstracts a suitably situated hydrogen atom to give the corresponding carbon radical. This is abstracts a chlorine atom from from another molecule of the N-chloro-ammonium salt, thus propagating the chain and at the same time forming the δ -chloro amine, from which the cyclic amine is obtained.

The mechanism is shown below:

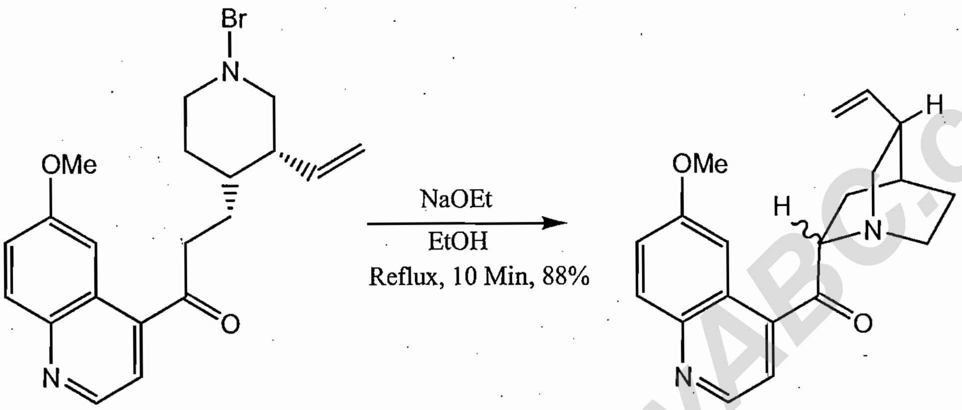


Example:

(i)

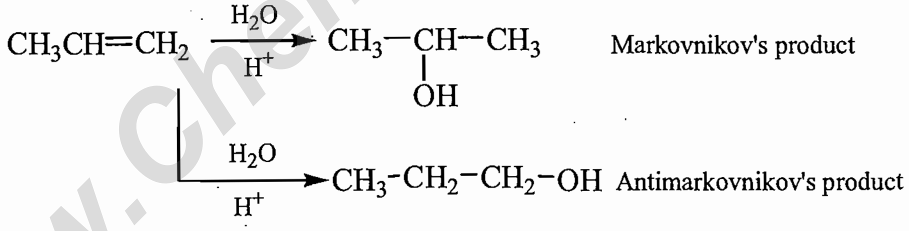


(ii)



6.21. *Hydroboration*

Hydroboration is the process in which alkyl and alkenyl borane are prepared by the addition of borane to olefines and acetylene.



$$CH_3CH{=}CH_2 \xrightarrow[H^+]{H_2O} CH_3{-}\underset{\displaystyle OH}{\underset{|}{CH}}{-}CH_3 \quad \text{Markovnikov's product}$$

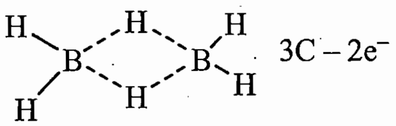
$$\xrightarrow[H^+]{H_2O} CH_3{-}CH_2{-}CH_2{-}OH \quad \text{Antimarkovnikov's product}$$

Alkenes on reaction with diborane (B_2H_6) in ether solution at room temperature produces trialkyl borane (R_3B) which on oxidation with alkaline hydrogen peroxide produces terminal 1° alcohols. This reaction is known as ***Hydroboration - Oxidation***.

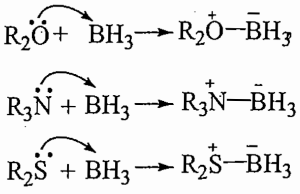
The reaction product seems to be anti markovnikov's addition of H_2O (hydration of alkene) by syn addition.

$$R{-}CH{=}CH_2 \xrightarrow{B_2H_6} (RCH_2CH_2)_3B \xrightarrow[NaOH]{3H_2O_2} 3R{-}CH_2{-}CH_2{-}OH + \underset{\text{Boric acid}}{H_3BO_3 \text{ or } B(OH)_3}$$

(1) This borane BH_3 is a good e^- pair acceptor having only 6 valence e^- around boron. B_2H_6 is a dimer of BH_3 in which the two Hs form a bridge between the boron by a 3C - 2e$^-$ bond.

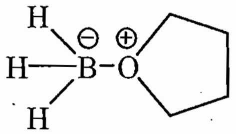


(2) In aprotic solvents that can act as an e⁻ donor to form lewis acid - base adduct with borane. This solvents may be eithers 3° amines or sulphides.

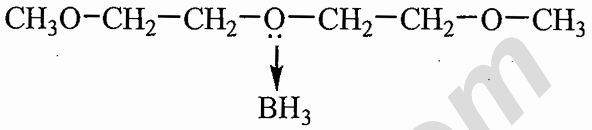


Lewis acid - base adducts.

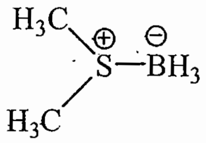
(3) Commonly used reagents is a adduct of BH_3 with THF.

(a) 

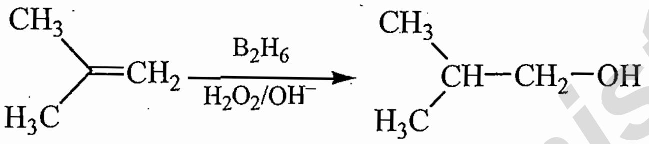
BH_3—THF

(b) With THF 

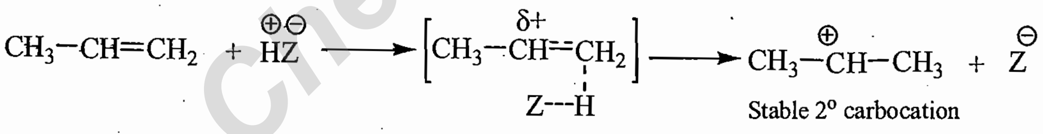
$CH_3O-CH_2-CH_2-\ddot{O}(\rightarrow BH_3)-CH_2-CH_2-O-CH_3$

(c) Dimethyl sulphide adduct. 

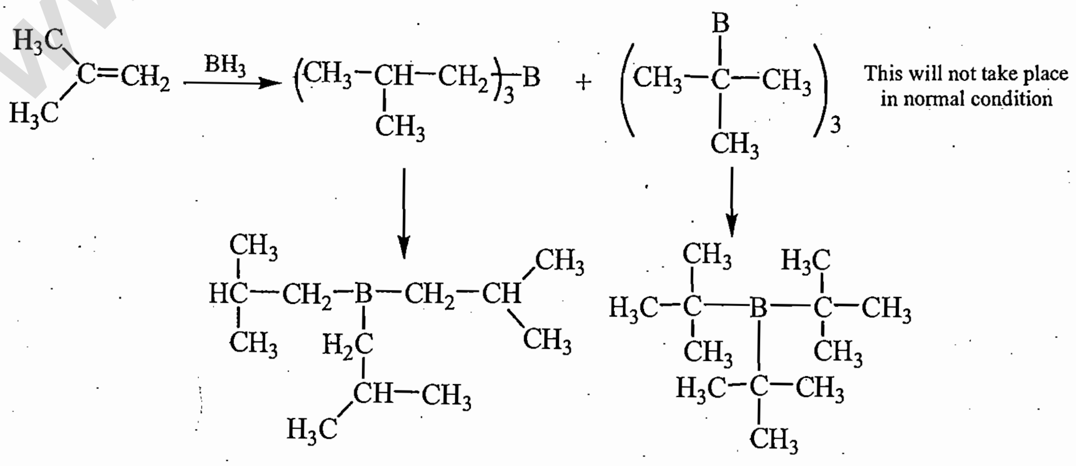
Regioselectivity and Orientation : This reaction is higly regioslective with unsymmetrical alkenes the BH_3 becomes bonded to less substituted carbon of alkene and hydrogen get attached to the other end of the double bond. A combination of steric and e⁻ factors work together to facilitated these orientation. Hence the products are corresponding to anti- markovnikov's of addition of H_2O to C=C.



Electronic Factor: The orientation appears to be unusual because the Hs adds to the opposite end of the double bond. In contrast to the ordinary E^+ addition of hydrogen halide.



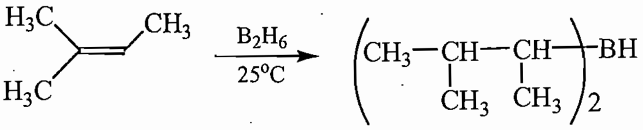
Steric Factor: Steric factors reinforce the electronic factors. i.e. attachment of B takes place more easily or readily to the less crowded carbon of the double bond. The bulkier the substituent on alkene more important is the steric factor, while more strongly electron releasing or electron withdrawing substituent on alkene more important is the electronic factor.



This will not take place in normal condition

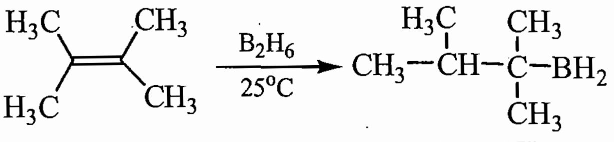
Some Selective Hydroborating Reagents : When the alkene is tri or tetra substituted then give di alkyl & mono alkyl boranes respectively with cyclic di substituted alkene, dialkylated borane is observed. These reagents are less reactive and more selective than borane itself.

(1) Disamyl Borane :



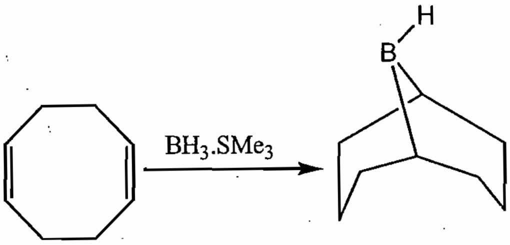
Dialkylated Borane
[Sia_2BH]

(2) Thexyl Borane :



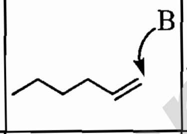
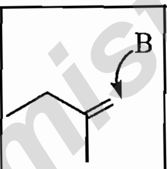
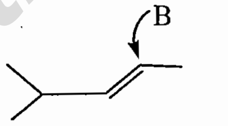
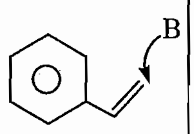
Thex - BH_2

(3) 9–BBN :



Note: It always attack at less hindered carbon

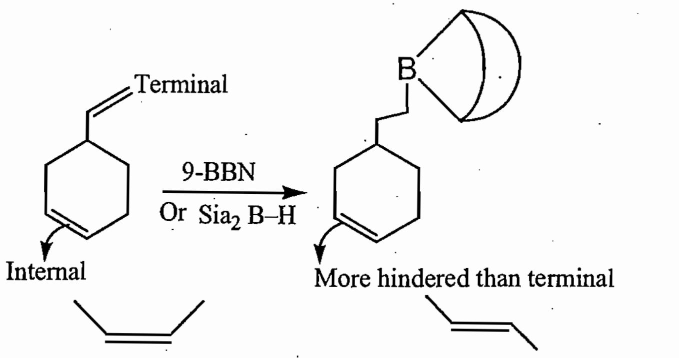
Percent(%) of B added to less hindered / substituted C of alkene :

Hydroborating Reagent					Increasing Regioselecticity ↓
B_2H_6	94	99	57	80	
$(C_5H_{11})_2BH$ (Disamyl borane)	99	99	97	98	
Thexyl chloro - borane(–SMe_2) solvent	99	99	97	99	
9 - BBN	99.9	99.8	99.8	99	

Sia_2BH and 9-BBN are more sensitive to the structure of alkene than borane itself.

Some important Features :

1. Terminal alkenes react more readily than internal alkene.
2. Z alkenes react more readily than E alkene.

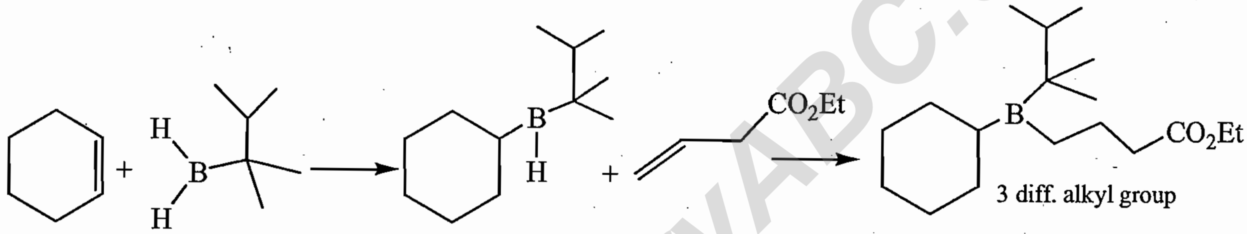


Z - alkene gives faster reaction
Easier to form the T.S.

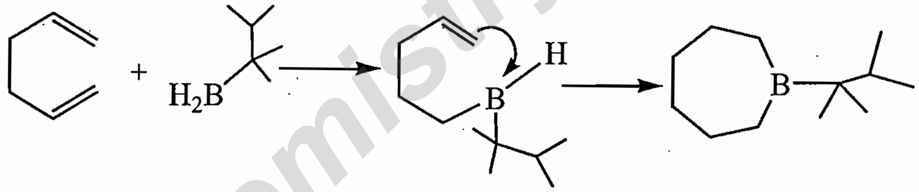
E - alkene give slow reaction
"This is selective hydroboration".

Application:

(1) To prepare boranes with three different alkyl groups : (R, R', R" – B)



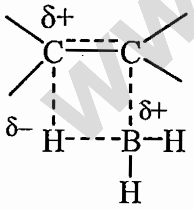
(2) To prepare cyclic boron compounds :



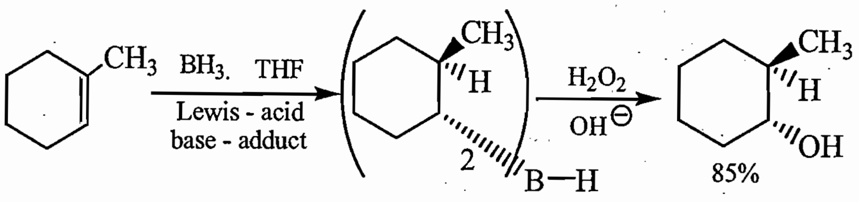
3. Hydroboration is readily affected with alkenes containing many functional groups. When other functional groups are not reduced by borane then hydroboration can be done without any difficulty. The easily reduced carbonyl group must be protected as their acetals and carboxylic acid must be protected as their esters.

Stereospecificity :

Hydroboration is a stereospecific syn addition. The addition accurs through a cyclic 4 membered transition state with essentially simultaneous bonding of alkene to B and H.

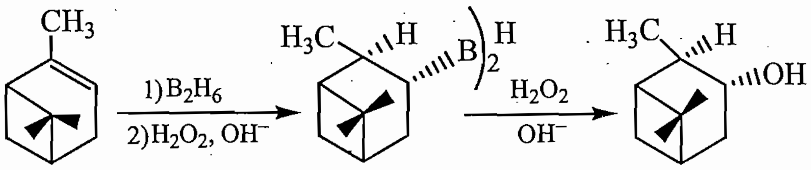


Both the new C–B and C–H bonds are formed from the same side of the double bond so after oxidation in per-oxide both - H and OH appear on the same side.

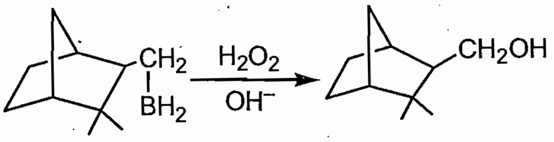


Example:

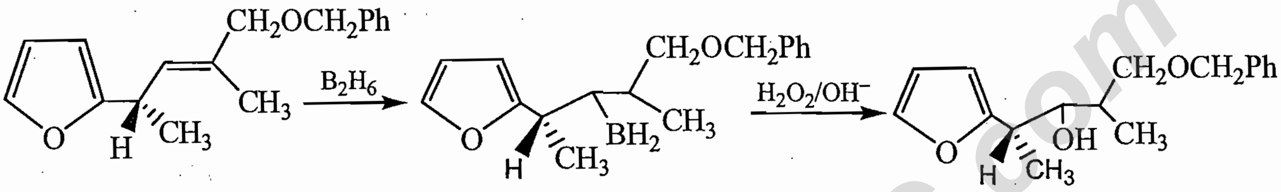
(i)



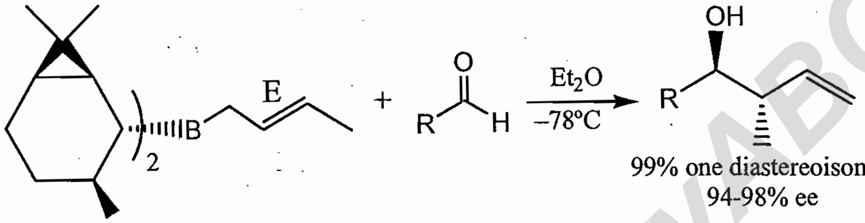
(ii)



(iii)

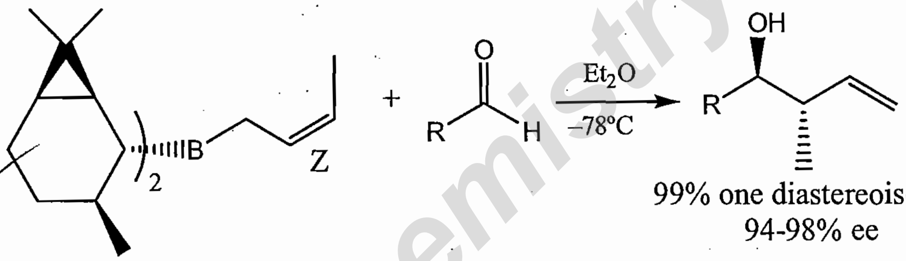


(iv)



99% one diastereoisomer
94-98% ee

(v)

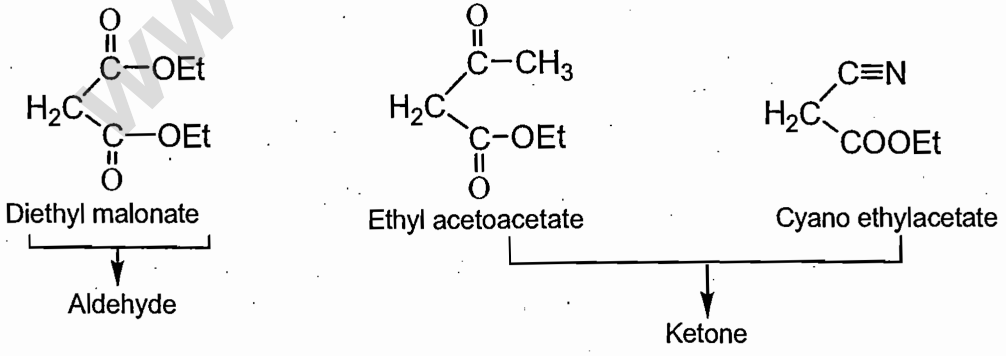


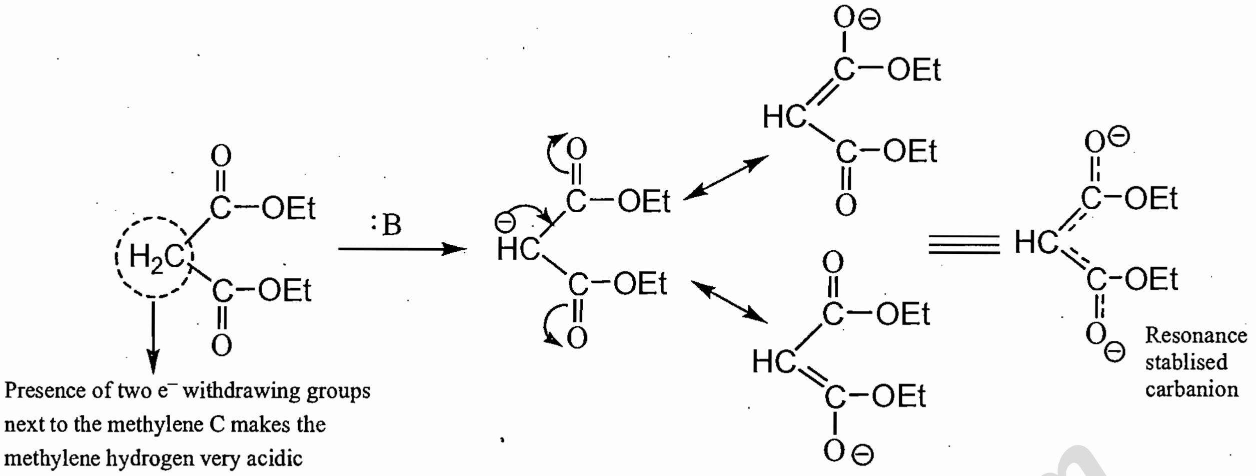
99% one diastereoisomer
94-98% ee

6.22. Knoevenagel Reaction

This is the reaction between aldehyde/ketone and a compound containing active methylene groups in the presence of a organic base to form α, β-unsaturated compounds. The base catalyst which are used generally are NH_3 derivatives like RNH_2, R_2NH, R_3N, Pyridine, piperidine etc.

Active methylene group :



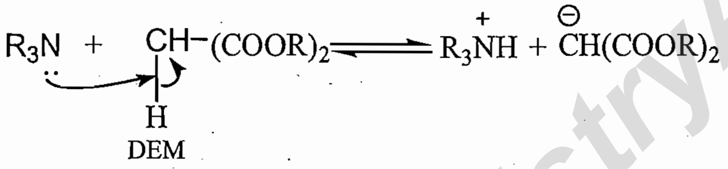


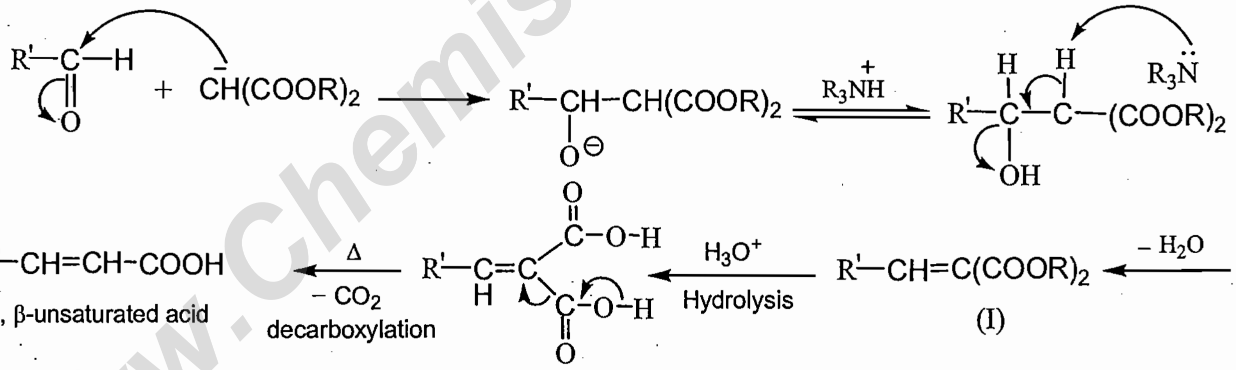
Presence of two e⁻ withdrawing groups next to the methylene C makes the methylene hydrogen very acidic

Mechanism **:**

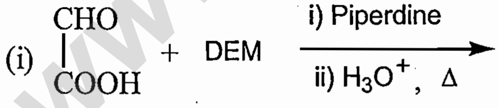
(1) This reaction involves a base catalysed aldol type of reaction with subsequent dehydration, hydrolysis and decarboxylation to produce α, β-unsaturated acid.

(2) High reactivity of the active methylene compounds prevents the self condensation of aldehydes that is aldehydes having α-H do not undergo base catalysed aldol reaction in presence of active methylene compounds because the enolate generated from aldehyde is more reactive compared to the carbanion generated from active methylene compound.



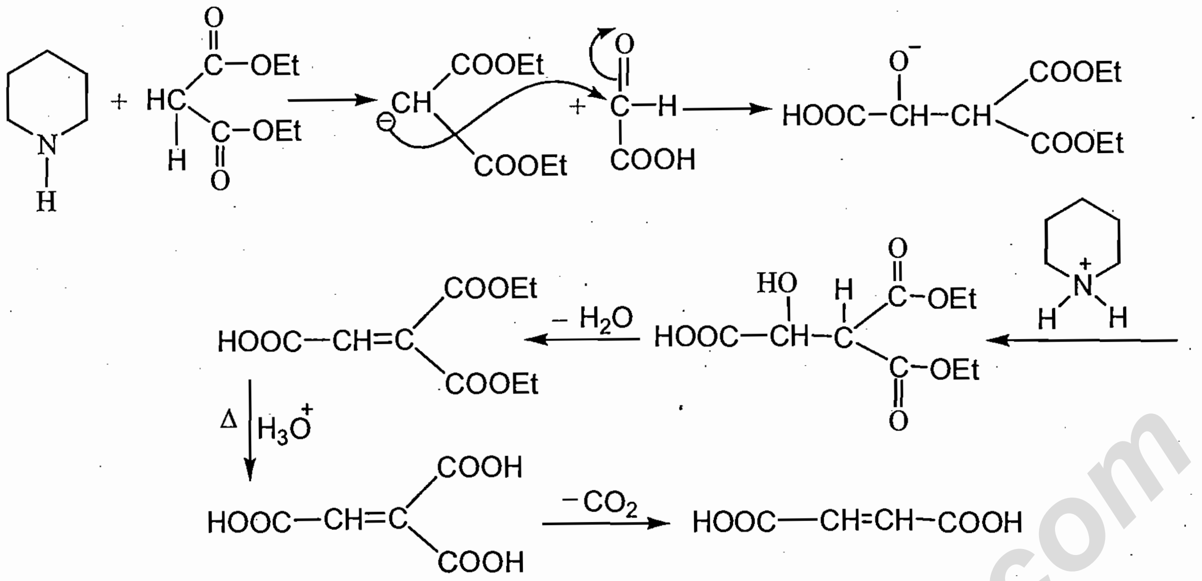


***Example*:**

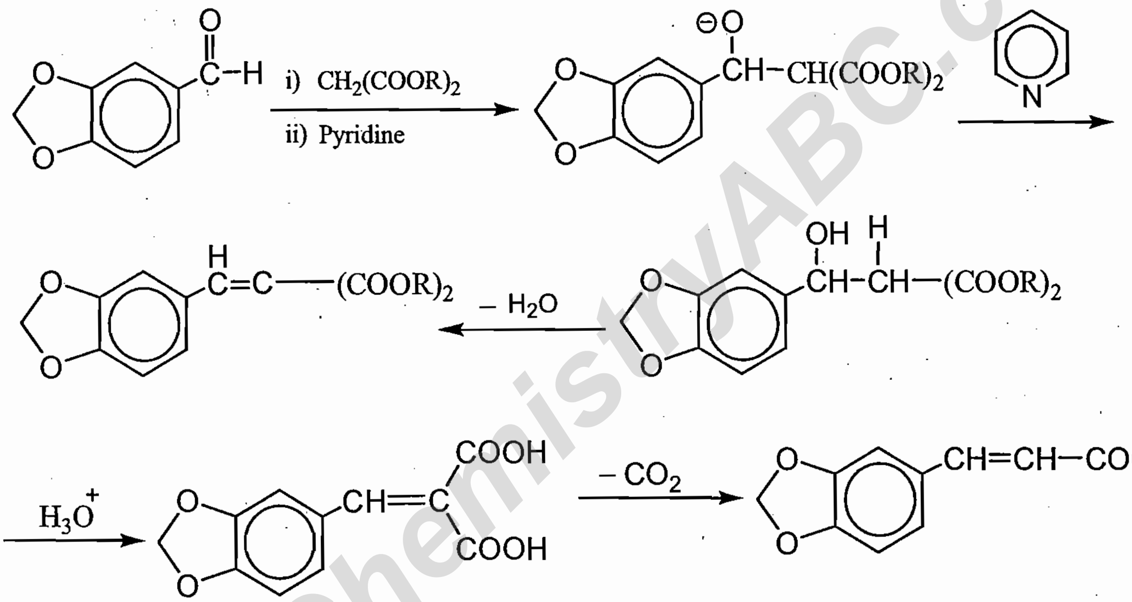
(i) 

$$\overset{\text{CHO}}{\underset{\text{COOH}}{|}} + \text{DEM} \xrightarrow[\text{ii) } H_3O^+,\ \Delta]{\text{i) Piperdine}}$$

Mechanism :



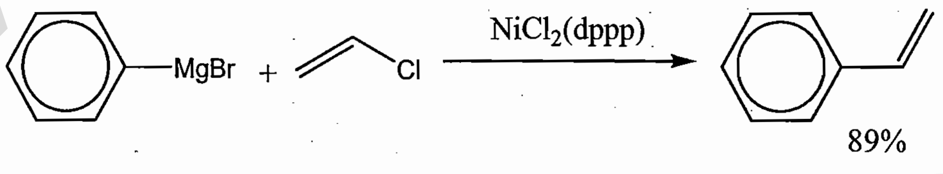
(ii)

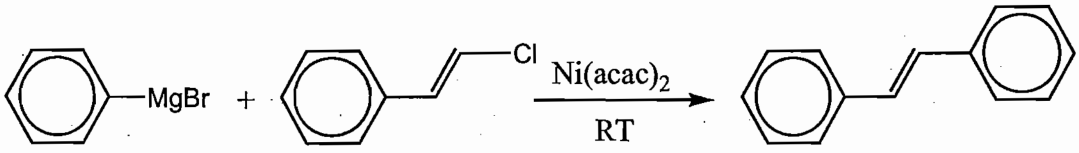


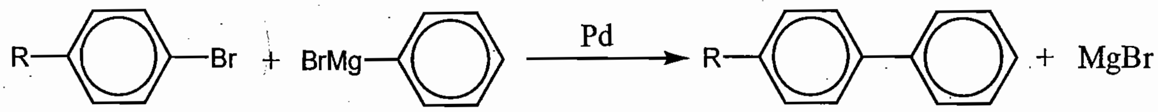
6.23. Kumada Coupling

- Kumada coupling or kumada-corriu coupling is the nickel or Pd catalysed cross coupling reaction between an alkyl, aryl, vinyl halide or triflate and aryl, alkenyl or alkyl Grignard reagents.
- The reactivity of the halides follows the order I > Br > Cl when Pd is used as a catalyst if Ni catalyst, then Cl > I > Br.

For example:



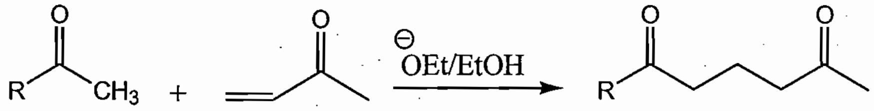




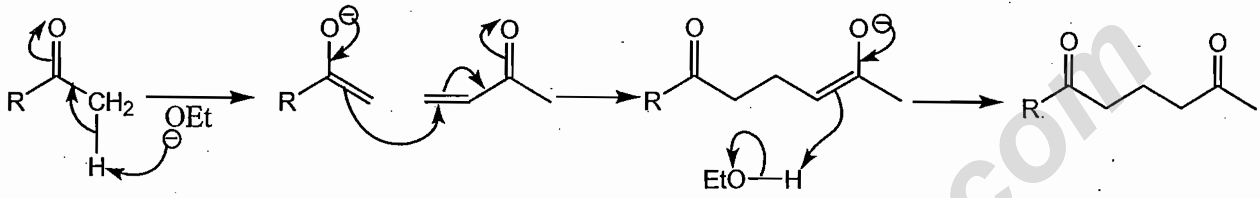
Note: The application of the kumada coupling reaction is somewhat limited because of the incompatibility of Grignard reagent with certain functional group.

6.24. *Michael Reaction*

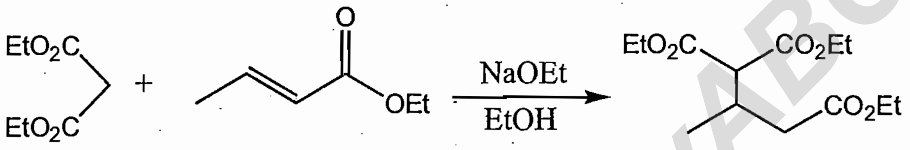
The nucleophilic addition reaction of an nucleophile (generally, enolate) to an α, β -unsaturated carbonyl compound is known as Michael reaction.

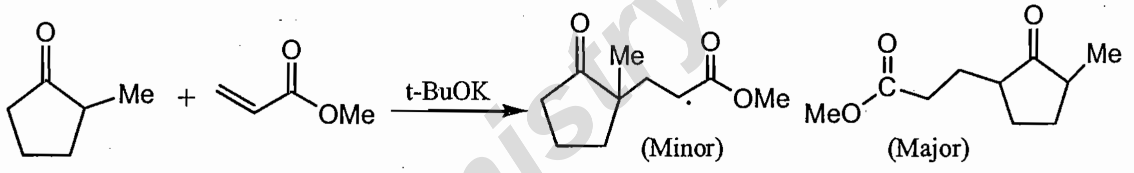


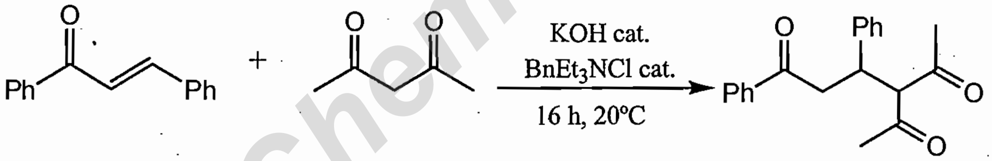
***Mechanism*:**



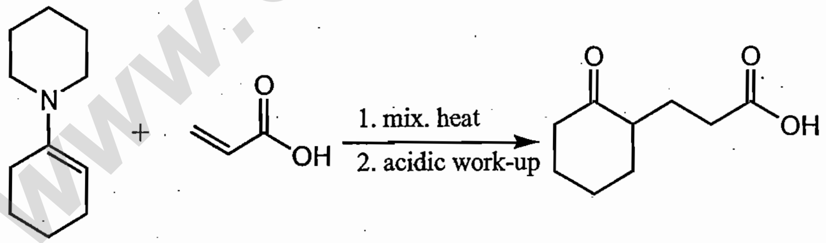
PROBLEMS

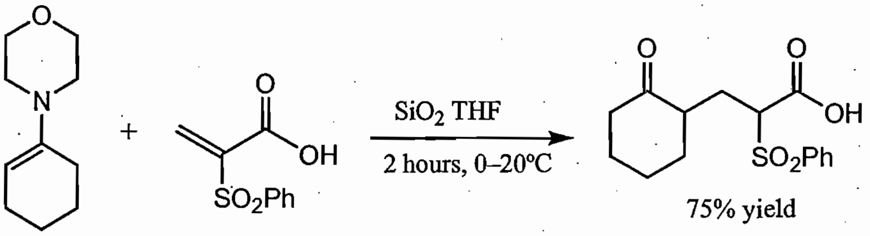
(i)


(ii)


(iii)


77% yield

(iv)


(v)


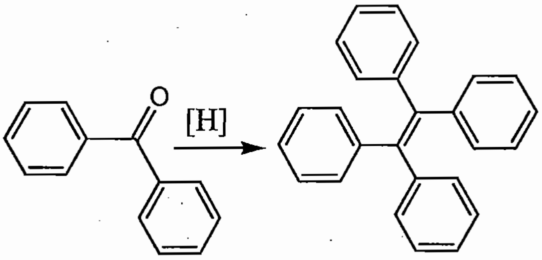
75% yield

morpholine enanmine

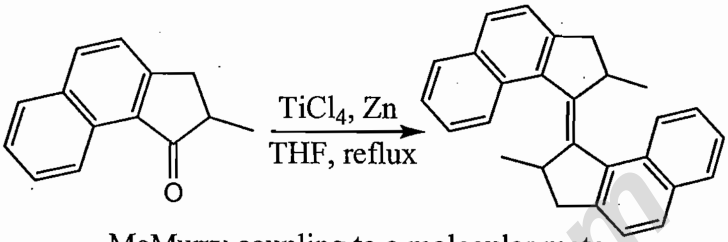
6.25. *Mc-Murry Reaction*

The McMurry reaction is an organic reaction in which two ketone or aldehyde groups are coupled to an alkene using titanium chloride compound such as titanium(III) chloride and a reducing agent. The reaction is named after its co-discoverer, John E. McMurry.

***Example*:**

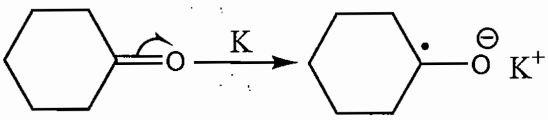


The McMurry reaction of benzophenone

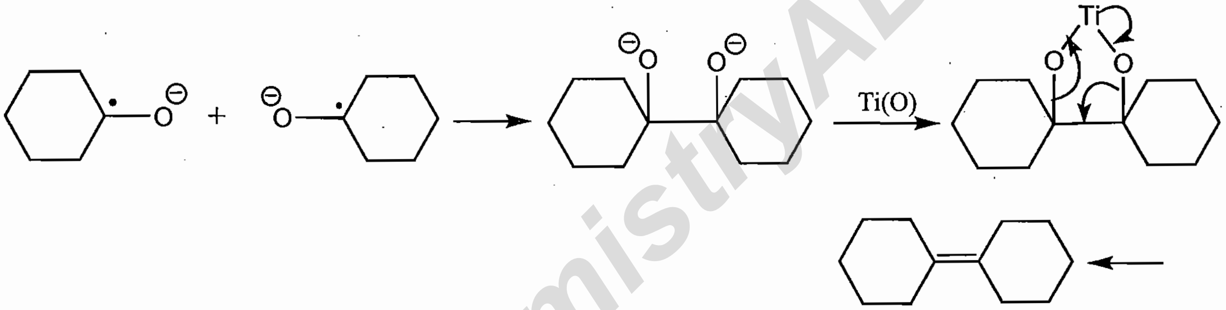


McMurry coupling to a molecular motor

***Mechanism*:**

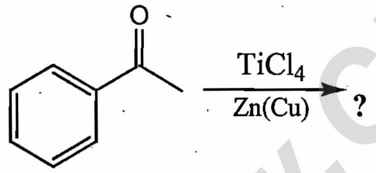


$TiCl_3 + K \longrightarrow Ti^{2+} + KCl$

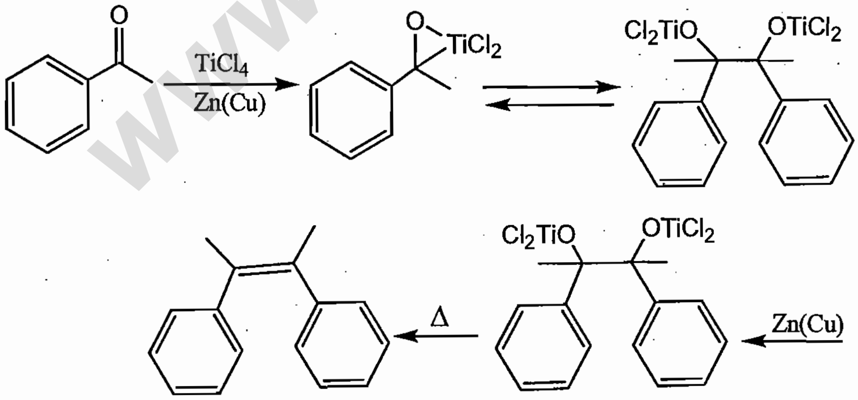


PROBLEMS

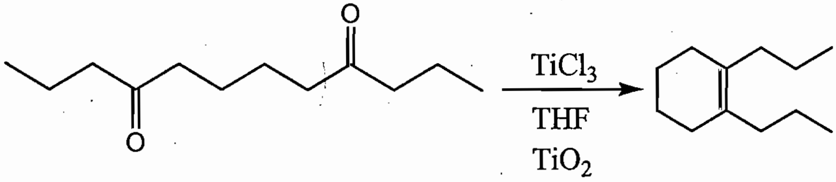
1.



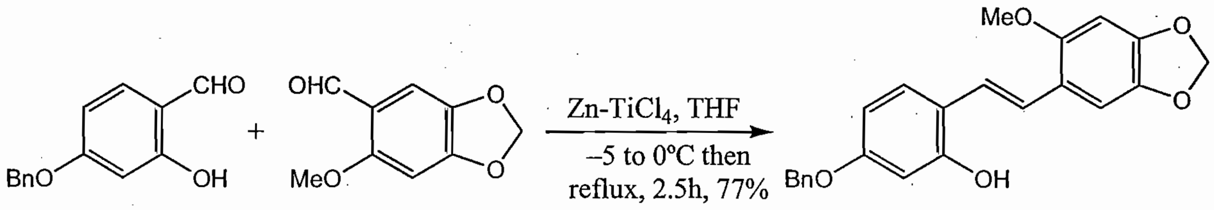
Soln.



2.

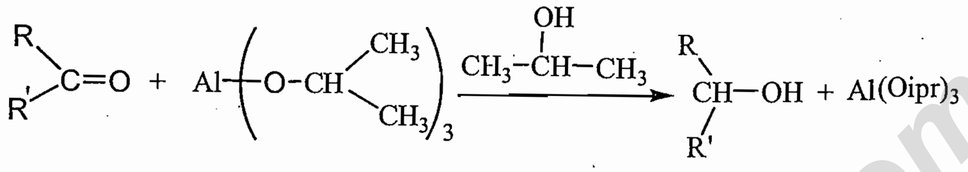


3.



6.26. *Meerwein-Ponndorf Verley Reduction*

The reduction of carbonyl compound to alcohols using aluminium iso propoxide is known as MPV reduction.



$$\underset{R'}{\overset{R}{>}}C=O + Al\left(O-CH\begin{matrix}CH_3\\CH_3\end{matrix}\right)_3 \xrightarrow{CH_3-\overset{OH}{\overset{|}{C}H}-CH_3} \underset{R'}{\overset{R}{>}}CH-OH + Al(Oipr)_3$$

Mechanism **:**

Al t- butoxide is not used in reduction because of absence of H.

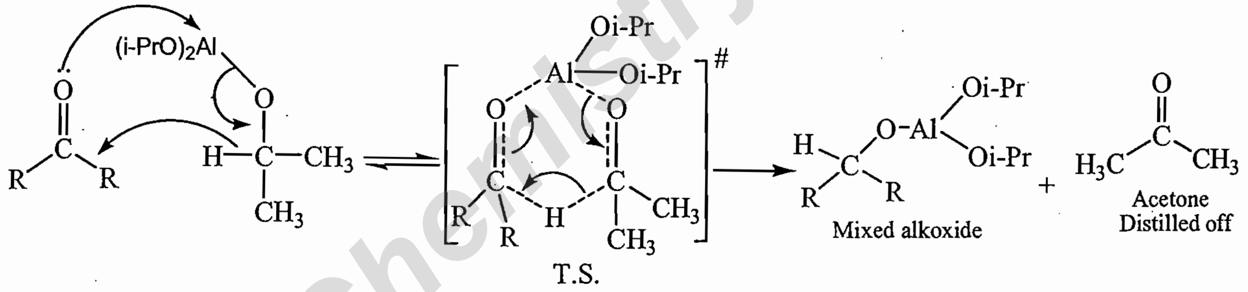
(1) The Ist step involves the transfer of hydride from the aluminium iso propoxide to the carbonyl compound through a six membered cyclic transition state to produce a mixed alkoxide and acetone. The acetone has to be quickly distilled off to take the reaction in the forward direction.

(2) In the 2nd step isopropanol is used which exchanges a proton with the mixed alkoxide to liberate desired alcohol.

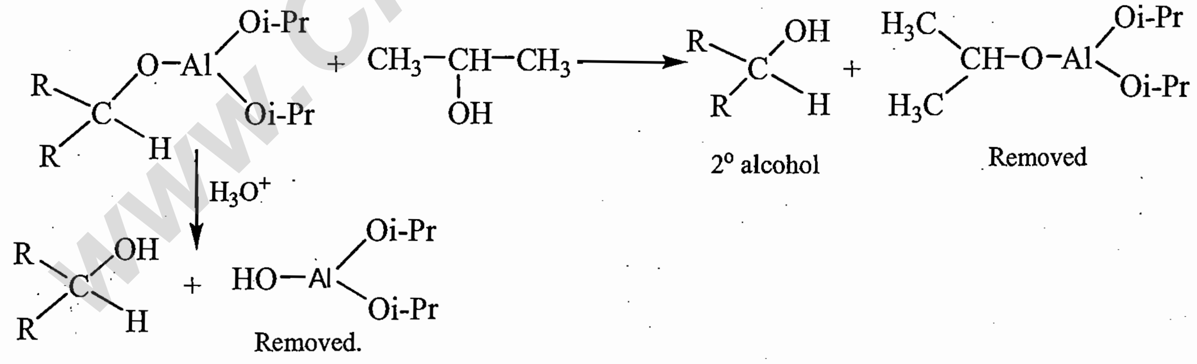
Aldehyde → 1° alcohol; Ketone → 2° alcohol

The second step can also be achieved by protonation.

(1)



(2)



Specificity of Aluminium iso-Propoxide:

(1) It is soluble in both alcohol and hydrocarbon.

(2) Its boiling point is 140°C-160°C. Which allows acetone to be distilled off to shift the equilibrium the forward direction.

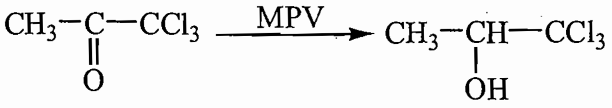
(3) The most important property in the side reaction is that : aluminium alkoxide are much less polar than alkali metal alkoxide. Since Al–O bond is more covalent, it undergoes little dissociation to produce basic alkoxide ions. Which can cause aldol condensation kind of polymerization reaction. So this side reaction is negligible in this reaction condition.

Applications :

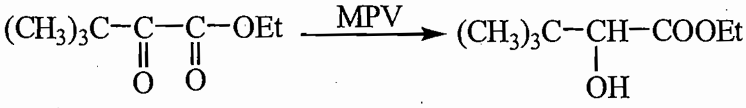
(1) To reduce conversion and α, β - unsaturated carbonyl compounds to α, β– unsaturated alcohols.

$$CH_2=CH-CHO \xrightarrow{MPV} CH_2=CH-CH_2OH$$

(2) Reduction of α-halogenated ketone, keto esters etc.

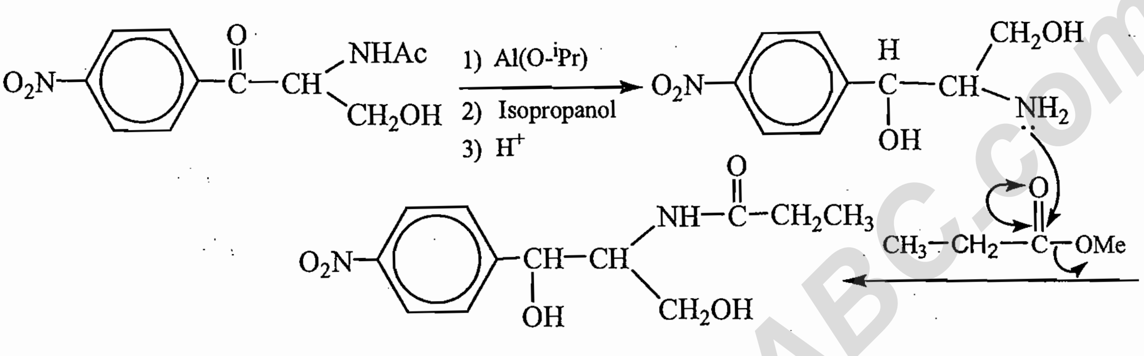


$$CH_3-\underset{\underset{O}{\|}}{C}-CCl_3 \xrightarrow{MPV} CH_3-\underset{\underset{OH}{|}}{CH}-CCl_3$$



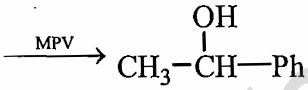
$$(CH_3)_3C-\underset{\underset{O}{\|}}{C}-\underset{\underset{O}{\|}}{C}-OEt \xrightarrow{MPV} (CH_3)_3C-\underset{\underset{OH}{|}}{CH}-COOEt$$

(3) To prepare drugs :

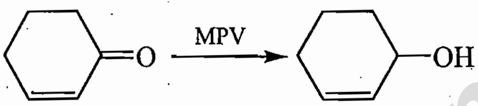


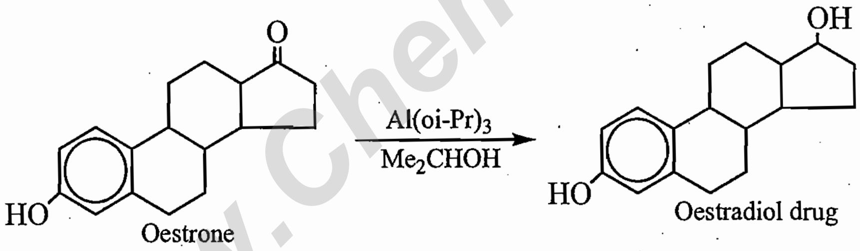
chloromycetin (antibiotic)

***Example*:**

(i) Methyl Phenyl Ketone 

$$\xrightarrow{MPV} CH_3-\overset{\overset{OH}{|}}{CH}-Ph$$

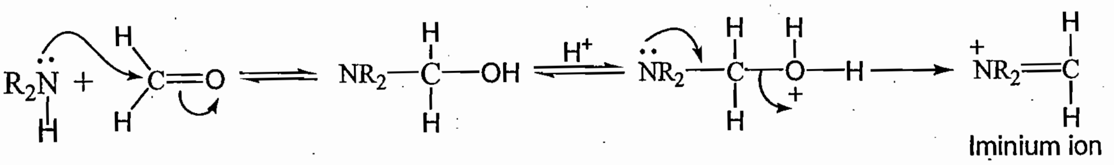
(ii) 

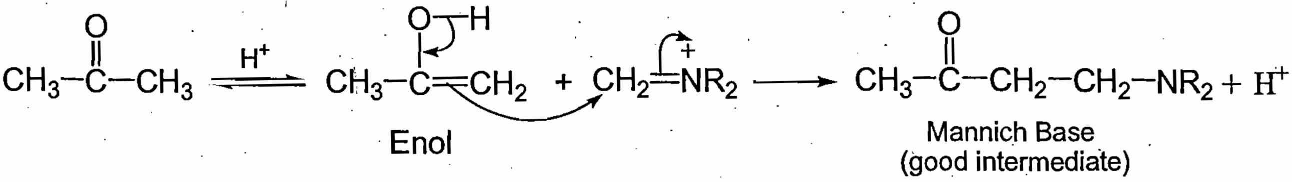
(iii) 

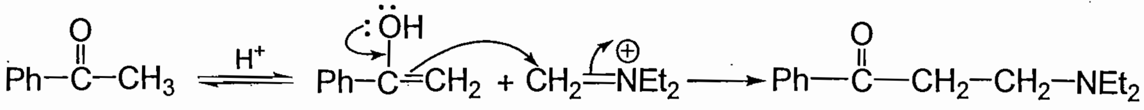
(iv) $CH_3-CH=CH-CHO \xrightarrow{MPV} CH_3-CH=CH-CH_2OH$.

6.27. *Mannich Reaction*

It is the reaction between formaldehyde, primary amine or secondary amine etc. and carbonyl group having active hydrogen in the presence of acid?

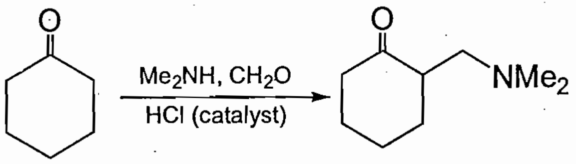




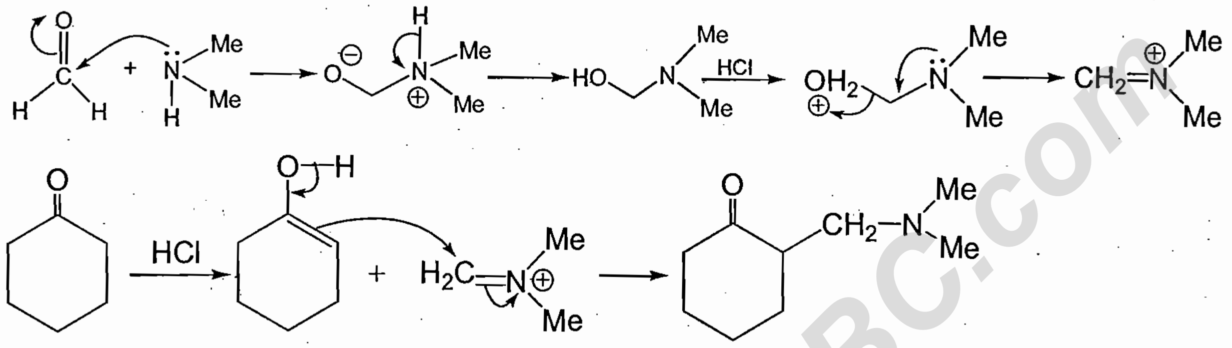


***Examples*:**

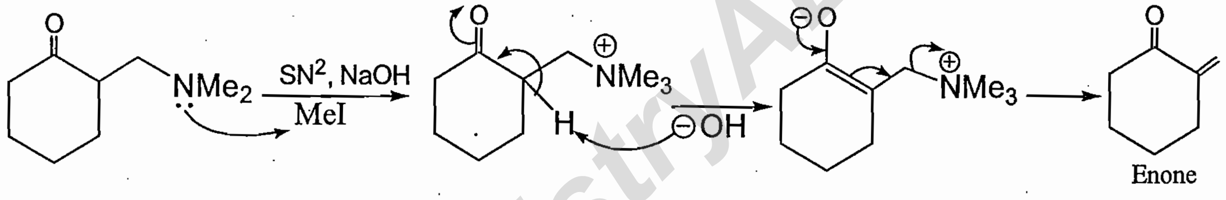
(i)



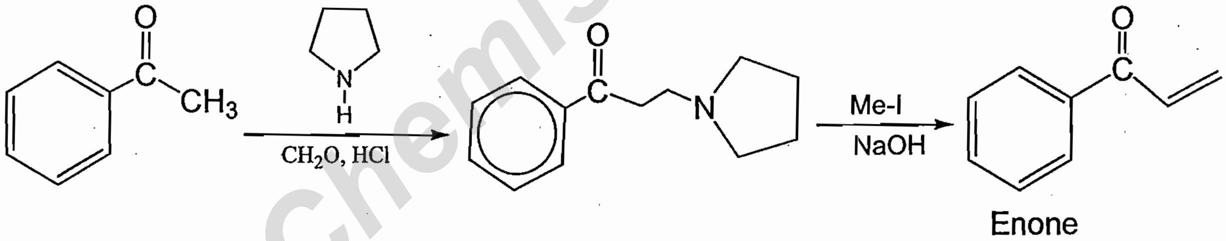
Mechanism:

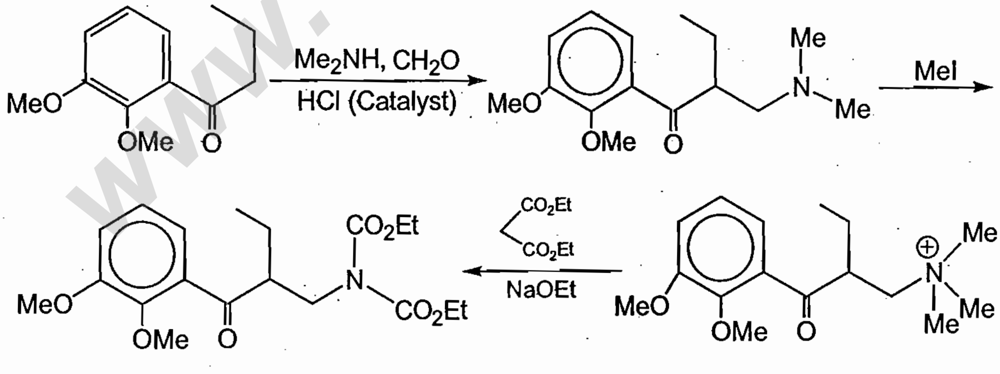


(ii)

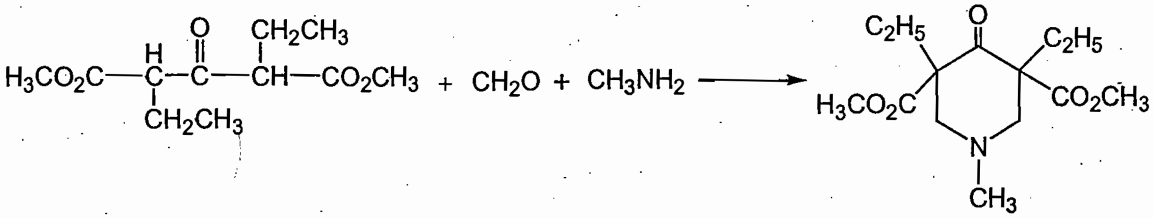


(iii)

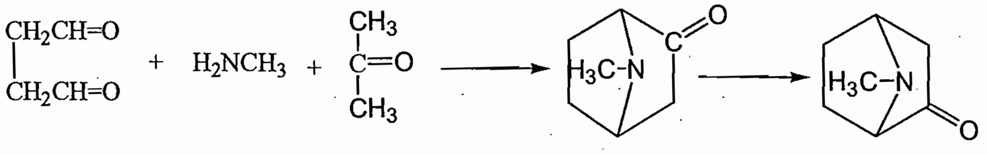




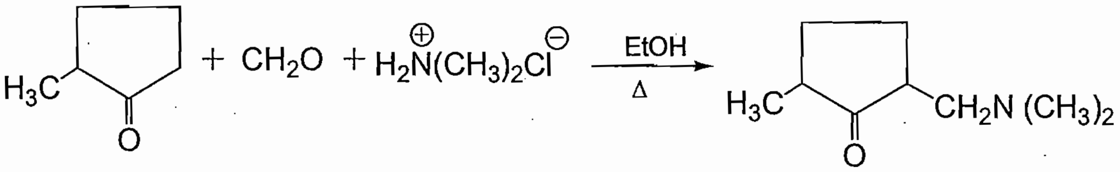
(iv)



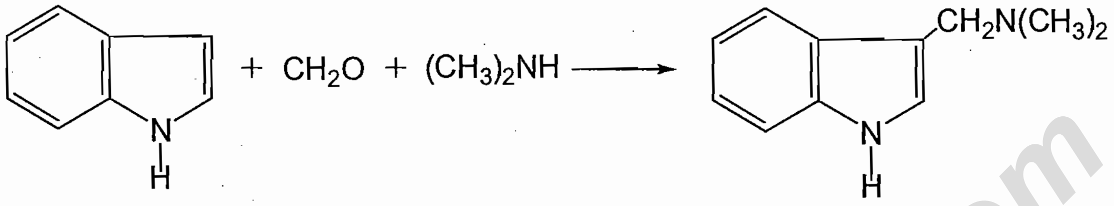
(v)



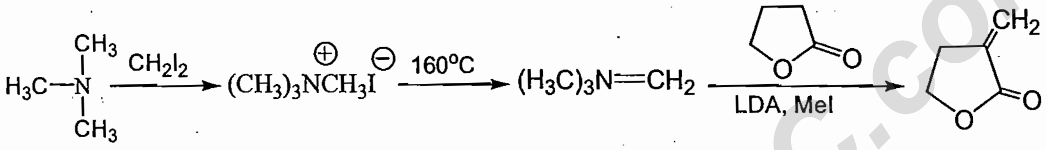
(vi)



(vii)

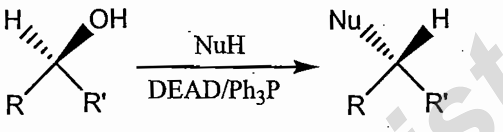


(viii)



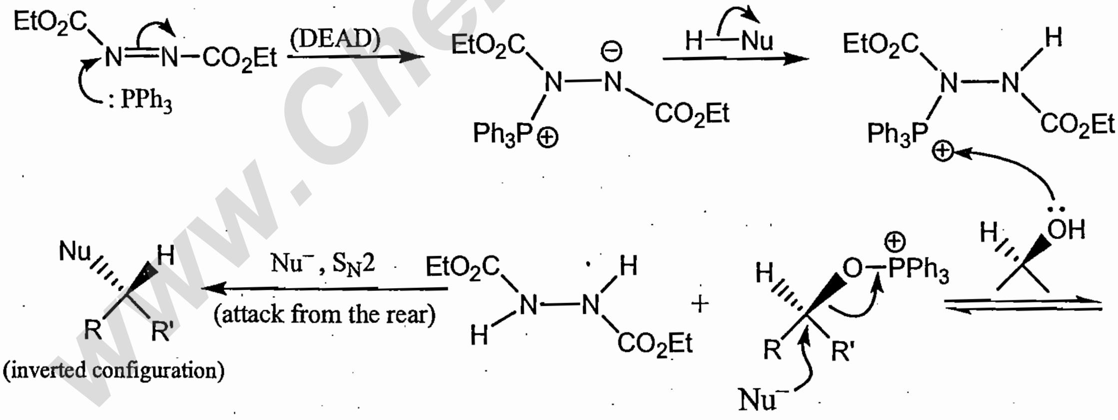
6.28. *Mitsunobu Reaction*

Mitsunobu reaction permits displacement of the –OH group of an alcohol by an incoming nucleophile in the presence of dialkyl azodicarboxylate and triphenyl phosphine.

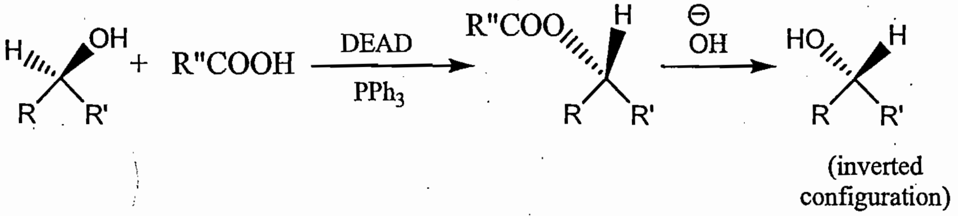


(Nu: nucleophile; DEAD: diethyl azodicarboxylate)

Mechanism:



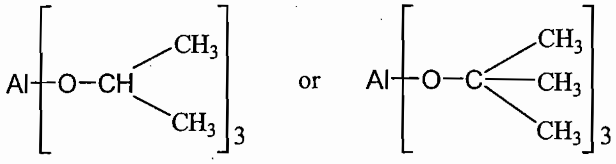
The major application of this reaction is the conversion of a chiral secondary alcohol into an ester having inverted configuration; the ester can be hydrolyzed to yield the inverted alcohol.



6.29. *Oppenauer Oxidation*

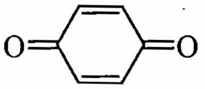
It is the reverse of Meerwein - Pondrof-Verley reduction.

It involves the oxidation of 2° alcohols to ketones with the help of aluminium alkoxides in presence of a hydride acceptor like acetone. Normally used alkoxide are Aluminium tri iso-propoxide or Al-tri tert-butoxide.

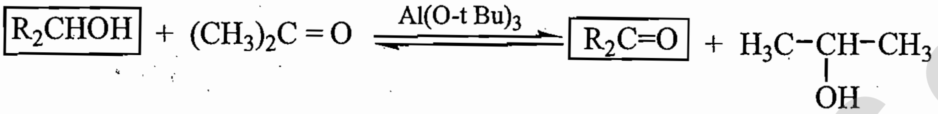


$Al(O\text{-}i\text{-}Pr)_3$ $Al(O\text{-}t\text{-}Bu)_3$

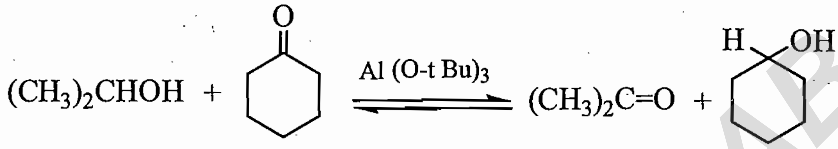
1° alcohols may also be oxidised to aldehydes if acetone is replaced by a better hydrogen acceptor like p-benzoquinone or aromatic ketone.

(i)  p-benzoquinone

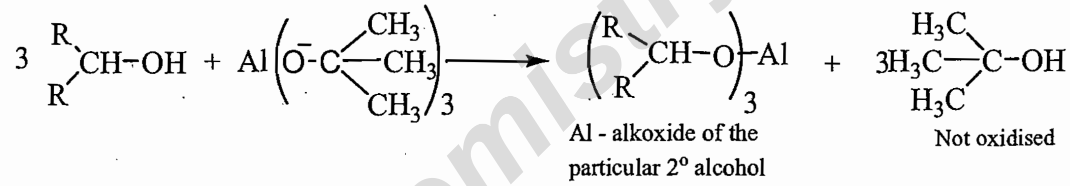
(ii) $2^\circ \text{ alcohol} \underset{\text{MPV reduction}}{\overset{\text{Opp. Oxidation}}{\rightleftharpoons}} \text{Ketones}$

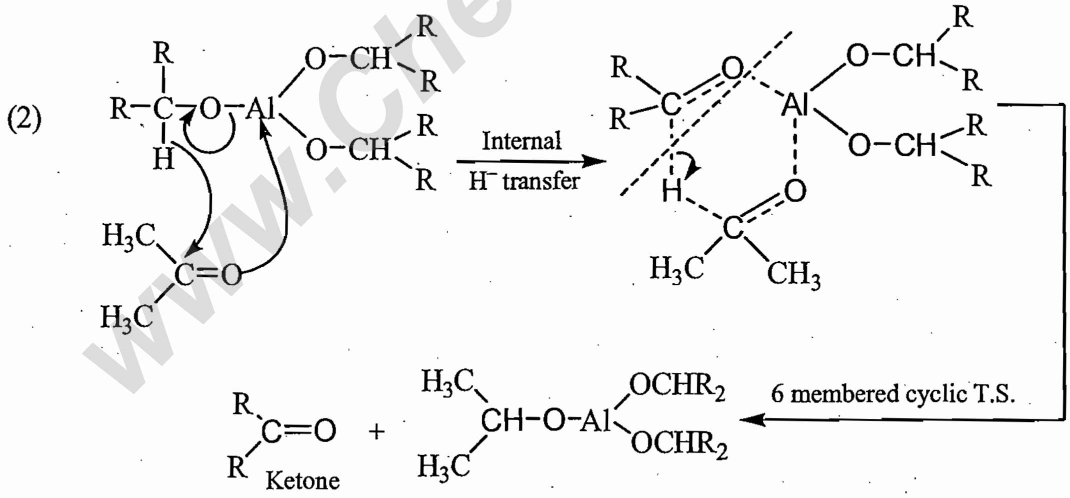
(1) 

$$\boxed{R_2CHOH} + (CH_3)_2C=O \xrightleftharpoons{Al(O\text{-}t\,Bu)_3} \boxed{R_2C{=}O} + H_3C-\underset{\displaystyle OH}{\underset{|}{CH}}-CH_3$$

(2) 

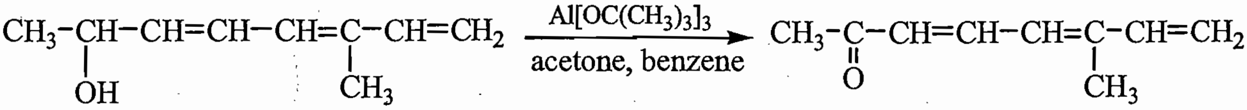
Mechanism : Aluminium alkoxides produce the alkoxide of the particular 2° alcohol which is to be oxidised. This alkoxide of the 2° alcohol alcohol undergoes a internal hydride transfer with acetone forming the desired ketone through a cyclic transition state.

(1) 

(2) 

Applications :

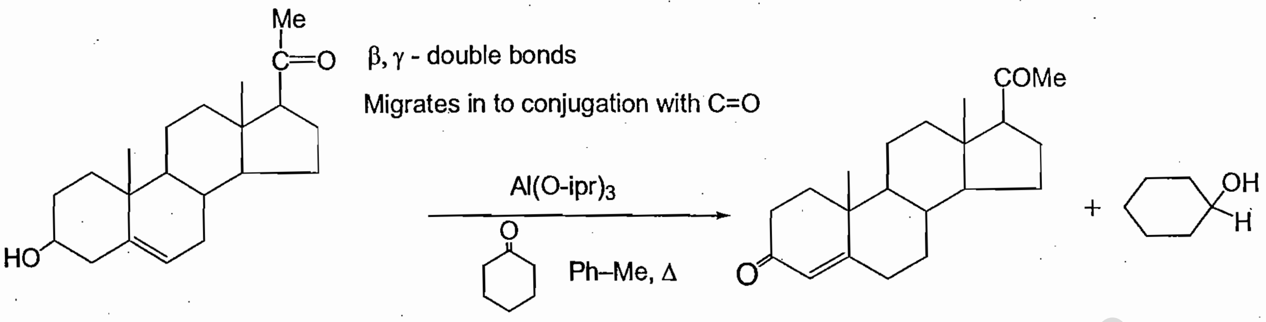
(1) Particularly useful for oxidising unsaturated 2° alcohol. Because double bonds are not affected.



$$CH_3-\underset{\displaystyle OH}{\underset{|}{CH}}-CH=CH-CH=\underset{\displaystyle CH_3}{\underset{|}{C}}-CH=CH_2 \xrightarrow[\text{acetone, benzene}]{Al[OC(CH_3)_3]_3} CH_3-\underset{\displaystyle O}{\underset{\|}{C}}-CH=CH-CH=\underset{\displaystyle CH_3}{\underset{|}{C}}-CH=CH_2$$

For oxidation of steroids :

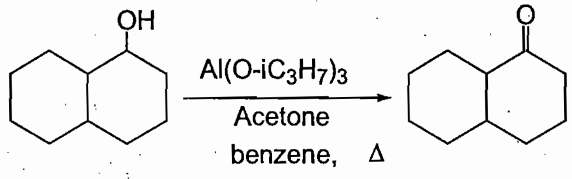
Allylic 2° alcohol ——→ α, β-unsaturated ketone

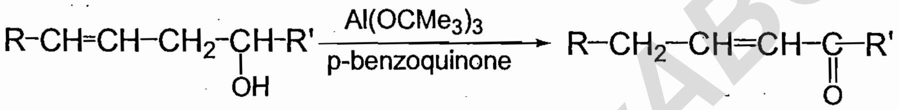


β, γ - double bonds

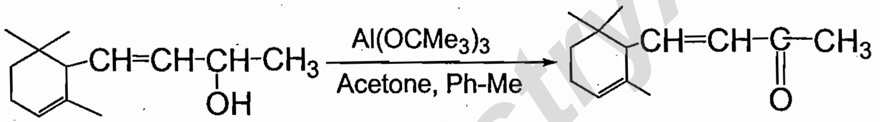
Migrates in to conjugation with C=O

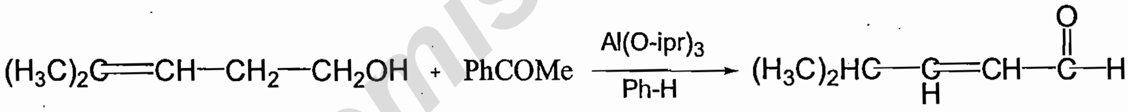
Example:

(i) 



$$R-CH=CH-CH_2-\underset{OH}{CH}-R' \xrightarrow[\text{p-benzoquinone}]{Al(OCMe_3)_3} R-CH_2-CH=CH-\underset{\underset{O}{\|}}{C}-R'$$

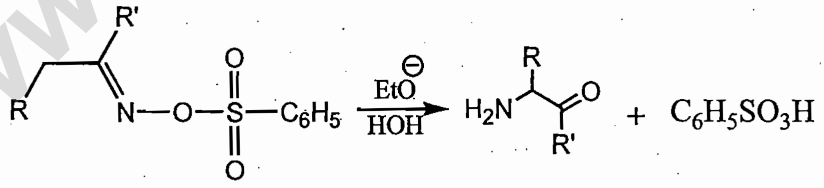
(ii) 

(iii) 

$$(H_3C)_2C=CH-CH_2-CH_2OH + PhCOMe \xrightarrow[\text{Ph-H}]{Al(O\text{-}ipr)_3} (H_3C)_2HC-\underset{H}{C}=CH-\overset{\overset{O}{\|}}{C}-H$$

6.30. The Neber Rearrangement:

This rearrangement is given by ketoxime toluene sulphonates. When the ketoxime tosylate is treated with a base like sodium ethoxide or pyridine, it rearranges to form an α-amino ketone, which is known as Neber rearrangement.

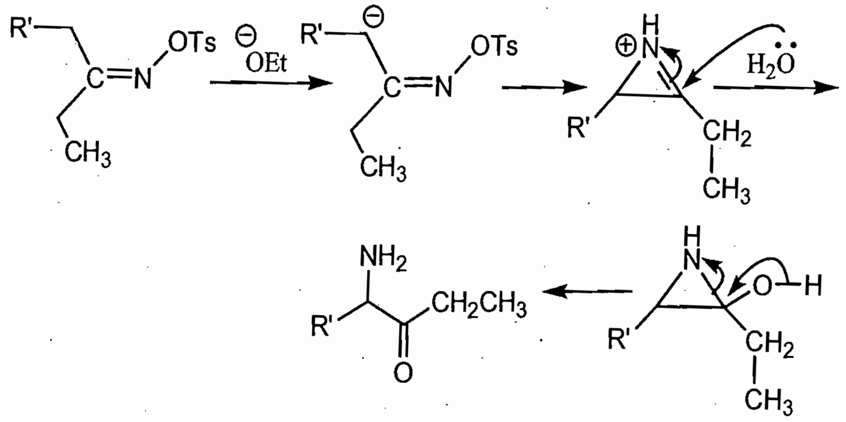


Mechanism: The accepted mechanism is represented as under

(a) The ketoxime tosylate reaction with a base to form an anion

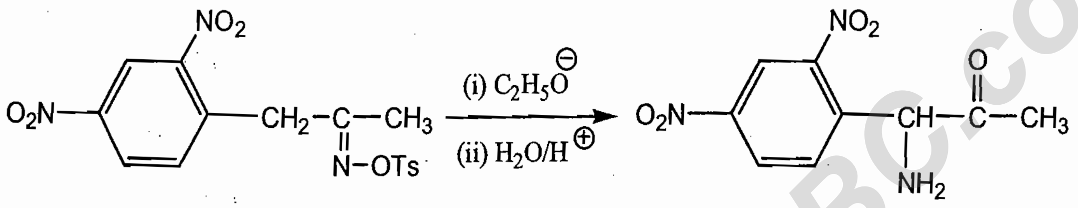
(b) Formation of azirine intermediate followed by the loss of tosylate

(c) Hydrolysis of azirine intermediate forming α-amino ketone.

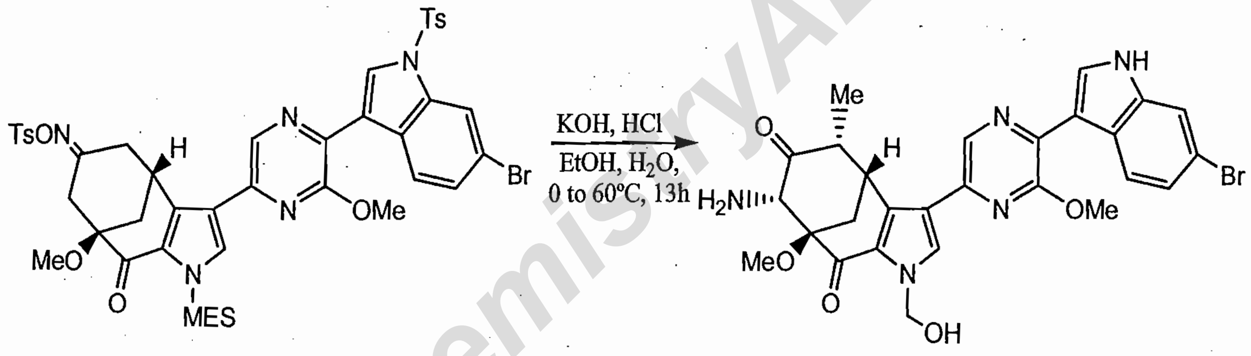


Applications:

1.

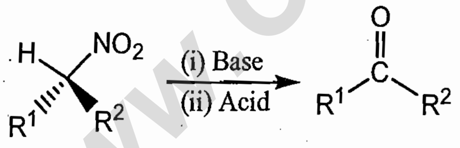


2.



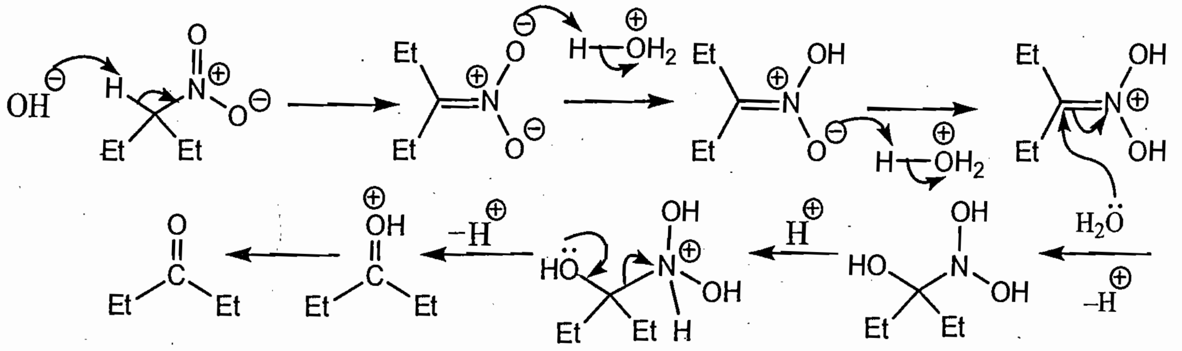
6.31. Nef Reaction:

The conversion of nitro compounds into carbonyls is known as the Nef Reaction.



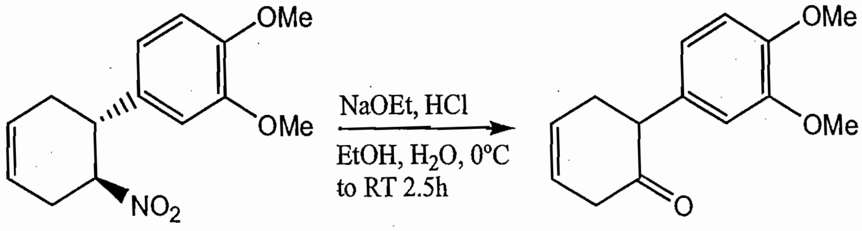
Mechanism:

Nitro alkanes are relatively storng carbon acid and deprotonation leads to nitroate salt. The hydrolysis of this intermediate must takes palce in strong acid to prevent the formation of side products such as aximes or hydroxynitroso compounds.

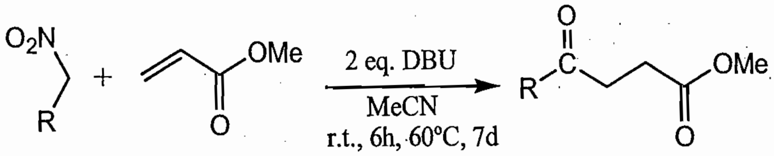


Application:

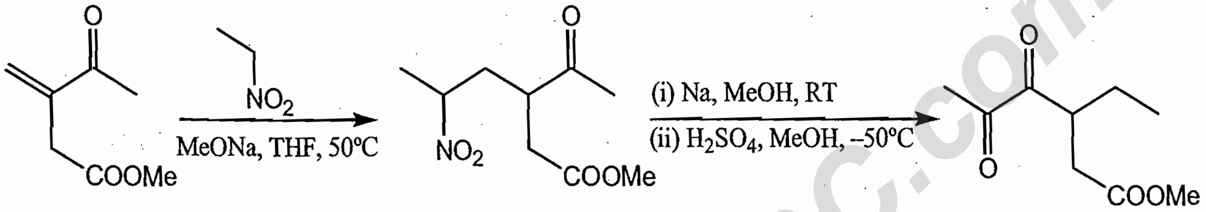
(1)



(2)

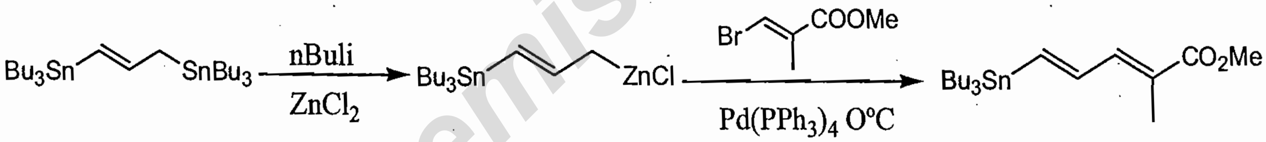


(3)



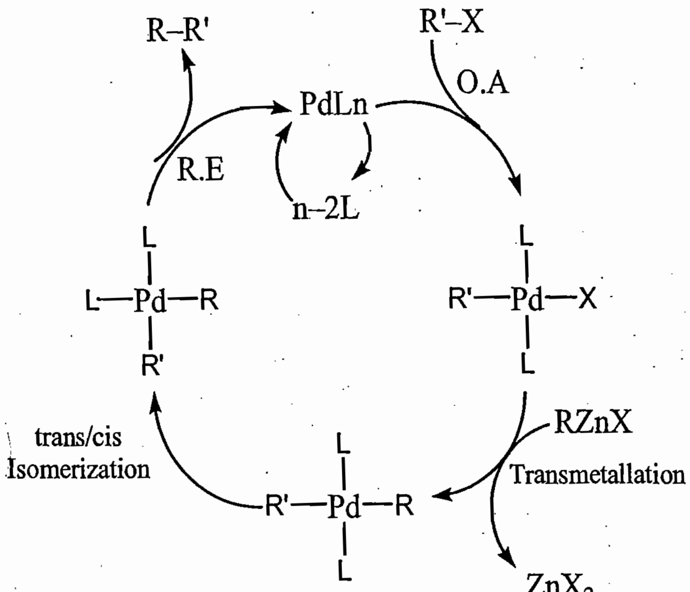
6.32. Negishi Coupling

- The Negishi coupling is a cross coupling reaction that involves an organo zinc compound, an organic halide and a Ni or Pd catalyst and creats a new C–C covalent bond.
- The active catalyst in this reaction is Pd(0) and the reaction in general proceeds through an oxidative addition of the organic halide followed by transmetallation with the Zn compound and finally reductive elimination.

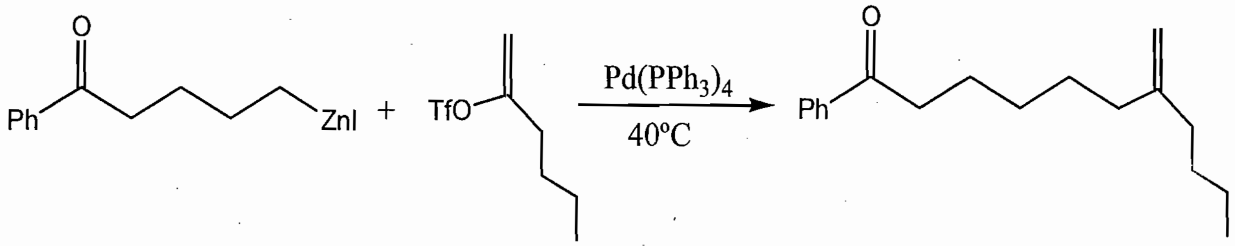


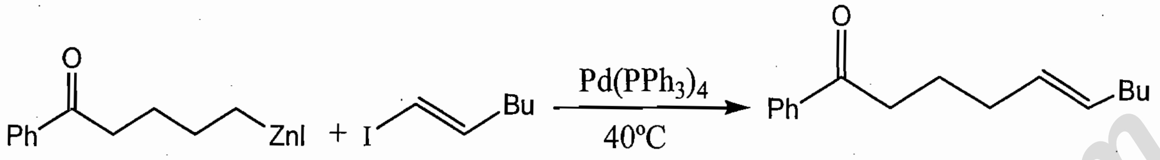
- The mechanism of Negishi coupling and Kumada coupling are quite similar. Both involve oxidative addition of R–X to the Pd/O. Catalyst followed by transmetallation of RZnX or RMgX on the Palladium. Trans to cis isomerisation followed by reductive elimination gives the coupled product.

Catalytic cycle for the Negishi coupling



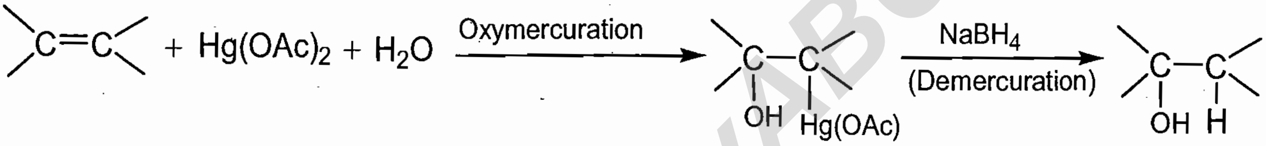
Problem:





6.33. *Oxymercuration - Demercuration*

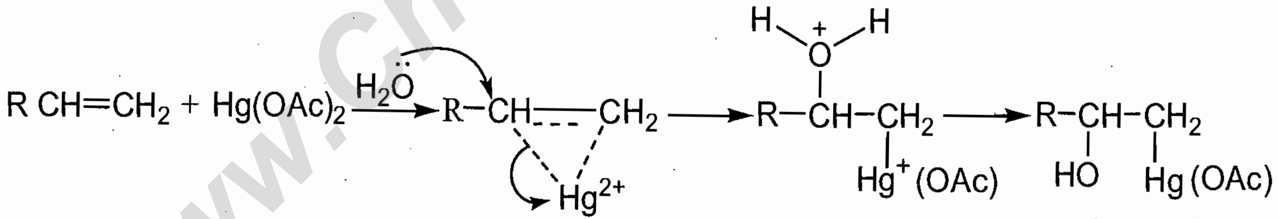
In this reaction alkene reacts with mercuric salts Hg^{2+} (acetate) $Hg(OAc)_2$, $Hg(NO_3)_2$, $Hg(ClO_4)_2$, $Hg(OOCCF_3)$. In presence of H_2O (other Nu^- solvents can also be used) to give hydroxy mercuryl compound. Which on reduction with sodium borohydride ($NaBH_4$) give 2° alcohols.



***Mechanism*:**

In the Ist step(oxymercuration) Hg^{2+} act as a electrophile and attack the C=C forming a cyclic mercurinium ion similar to halonium ion. The addition is competed by the attack of nucleophilic solvent (H_2O) at the more substituted carbon (If the alkene is unsymmetrical to give the addition product) Metal prefers less substituted carbon.

Oxymercuration :



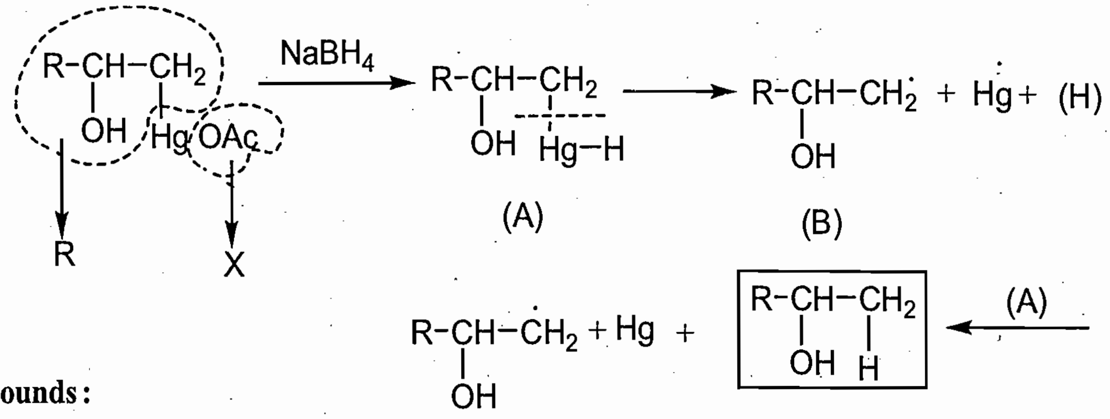
Addition product

Demercuration : After the addition step is completed the Hg is reductively removed by $NaBH_4$ which follows a radical mechanism.

(i) $R{-}HgX + NaBH_4 \longrightarrow R{-}Hg{-}H$

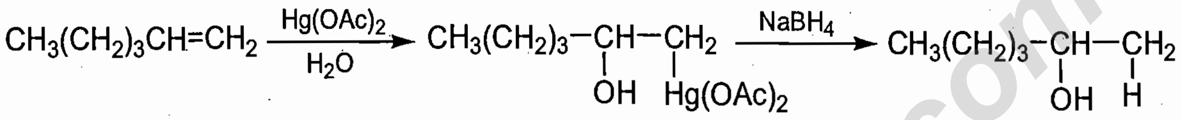
(ii) $R{-}Hg{-}H \longrightarrow R^{\cdot} + Hg^{\cdot}(H)$

(iii) $R^{\cdot} + R{-}Hg{-}H \longrightarrow R{-}H + R^{\cdot} + Hg$

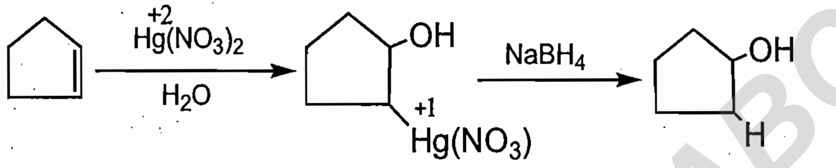


Compounds :

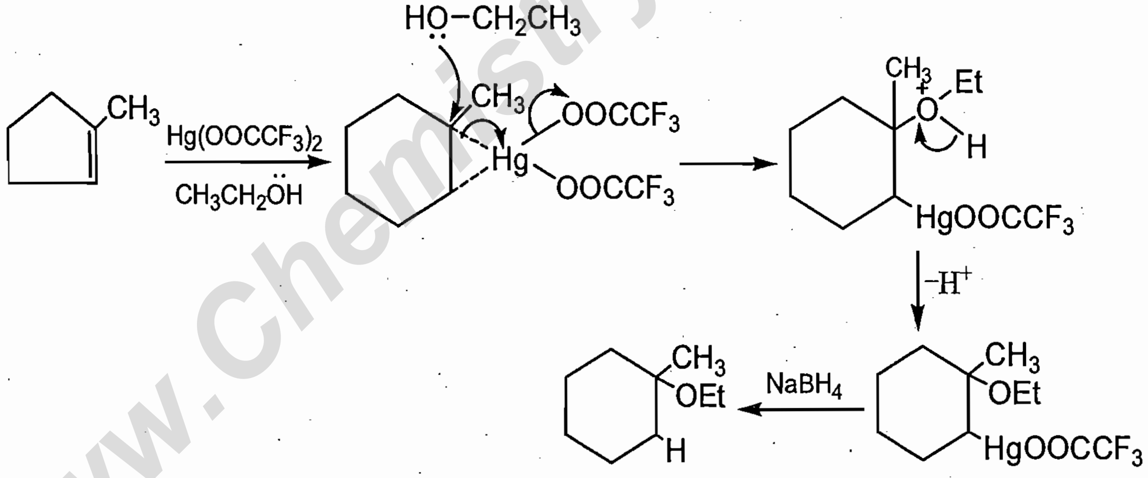
(1) Alcohols :

(a) 

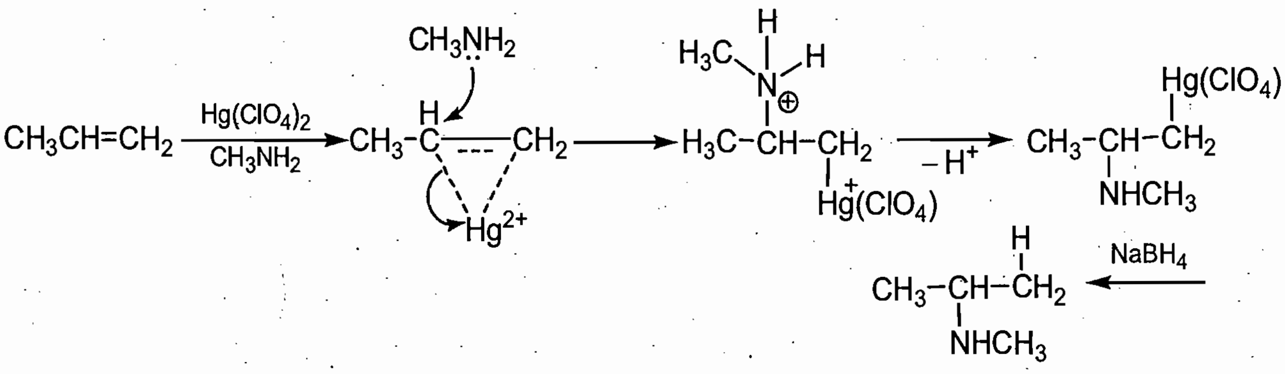
$CH_3(CH_2)_3CH{=}CH_2 \xrightarrow[H_2O]{Hg(OAc)_2} CH_3(CH_2)_3-\underset{OH}{CH}-\underset{Hg(OAc)_2}{CH_2} \xrightarrow{NaBH_4} CH_3(CH_2)_3-\underset{OH}{CH}-\underset{H}{CH_2}$

(b) 

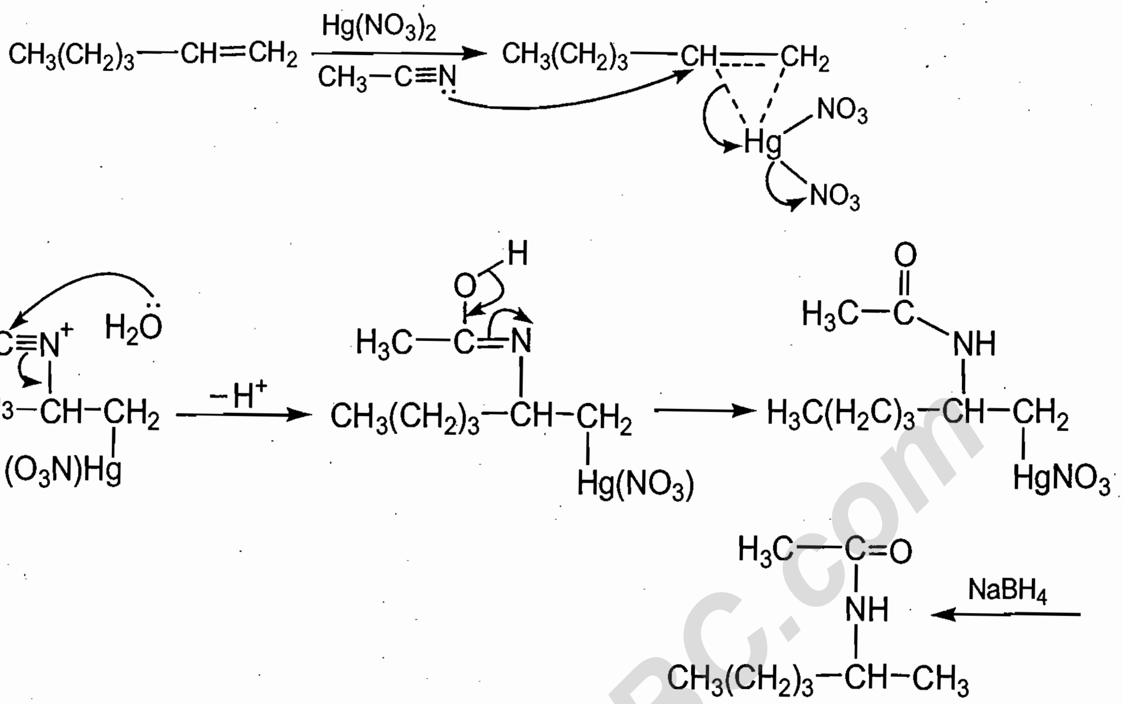
(2) Ethers :

(a) 

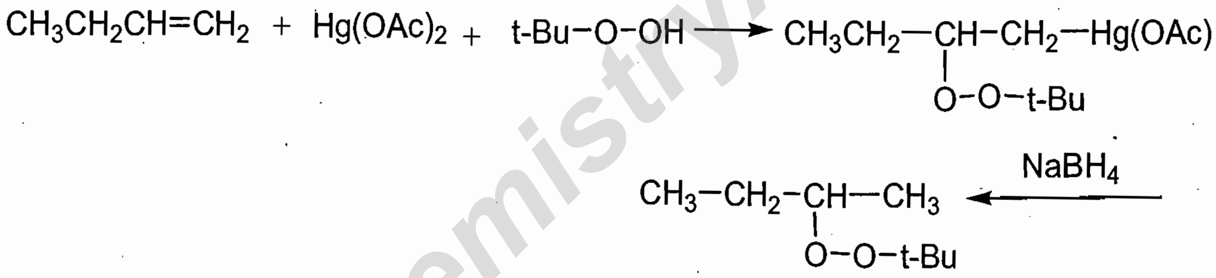
(3) Amines :



(4) Amides :



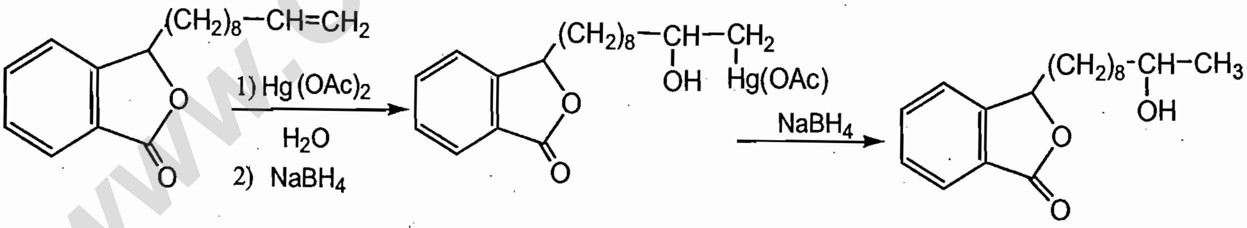
(5) Peroxides :



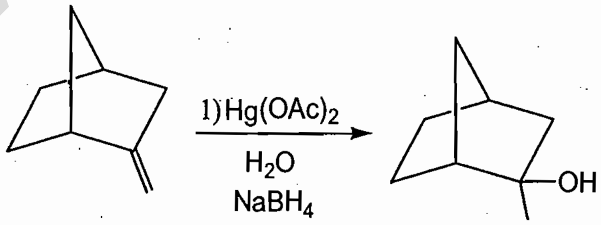
$$CH_3CH_2CH{=}CH_2 + Hg(OAc)_2 + t\text{-}Bu{-}O{-}OH \rightarrow CH_3CH_2{-}\underset{O-O-t\text{-}Bu}{CH}{-}CH_2{-}Hg(OAc) \xrightarrow{NaBH_4} CH_3{-}CH_2{-}\underset{O-O-t\text{-}Bu}{CH}{-}CH_3$$

Example :

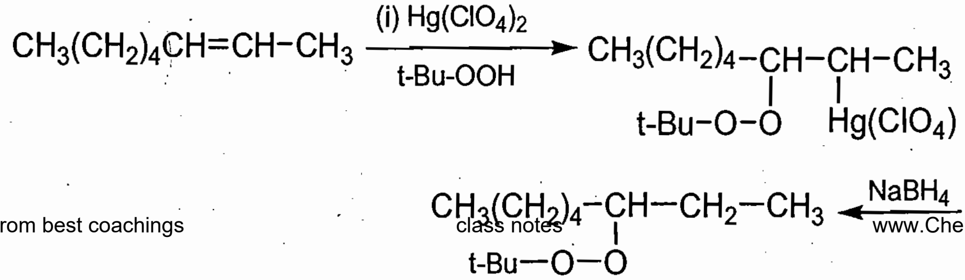
(i)



(ii)



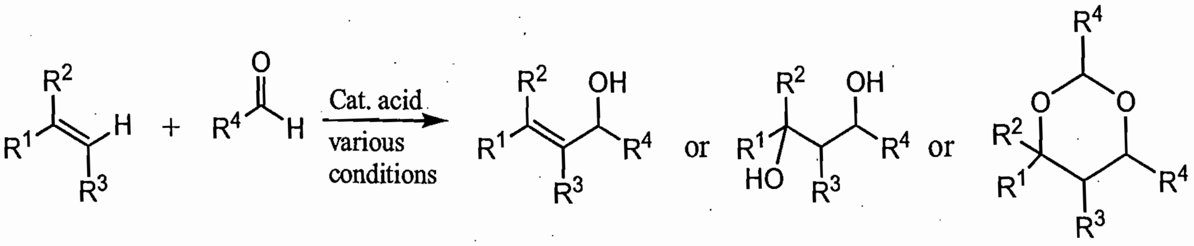
(iii)



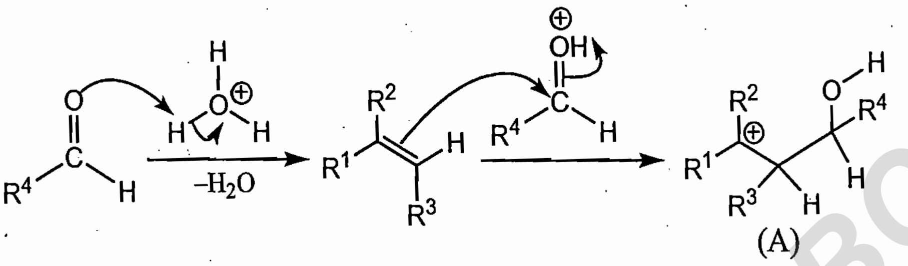
$$CH_3(CH_2)_4CH{=}CH{-}CH_3 \xrightarrow[t\text{-}Bu\text{-}OOH]{(i)\ Hg(ClO_4)_2} CH_3(CH_2)_4{-}\underset{t\text{-}Bu-O-O}{CH}{-}\underset{Hg(ClO_4)}{CH}{-}CH_3 \xrightarrow{NaBH_4} CH_3(CH_2)_4{-}\underset{t\text{-}Bu-O-O}{CH}{-}CH_2{-}CH_3$$

6.34. Prins Reaction:

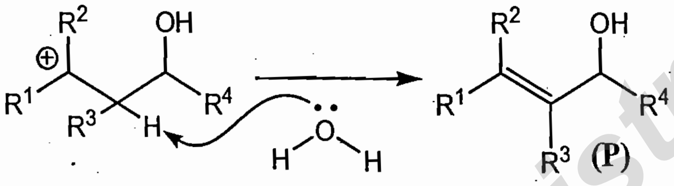
The prins reaction is an organic reaction consisting of an electrophilic addition of an aldehyde or ketone to an alkene or alkyne followed by capture of a nucleophile. The outcome of the reaction depends upon reaction conditions.

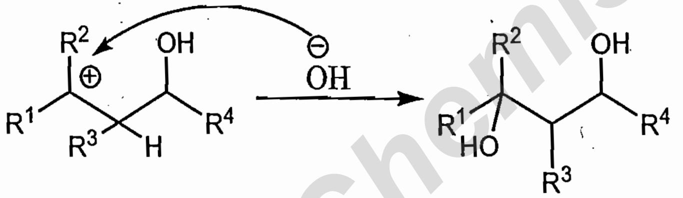


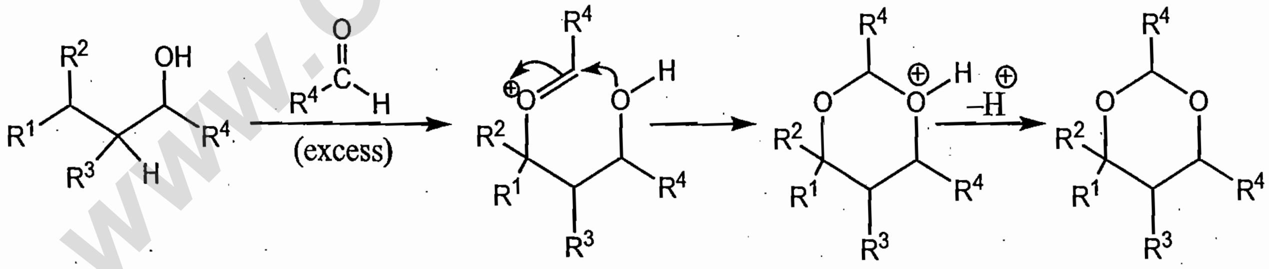
Mechanism:



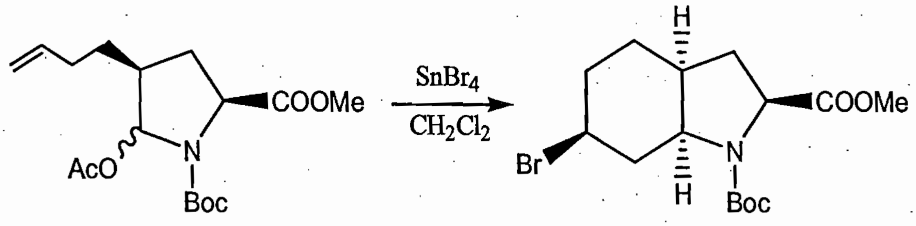
Three possible pathways:

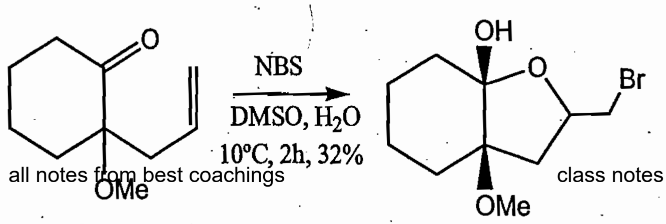
1.


2.


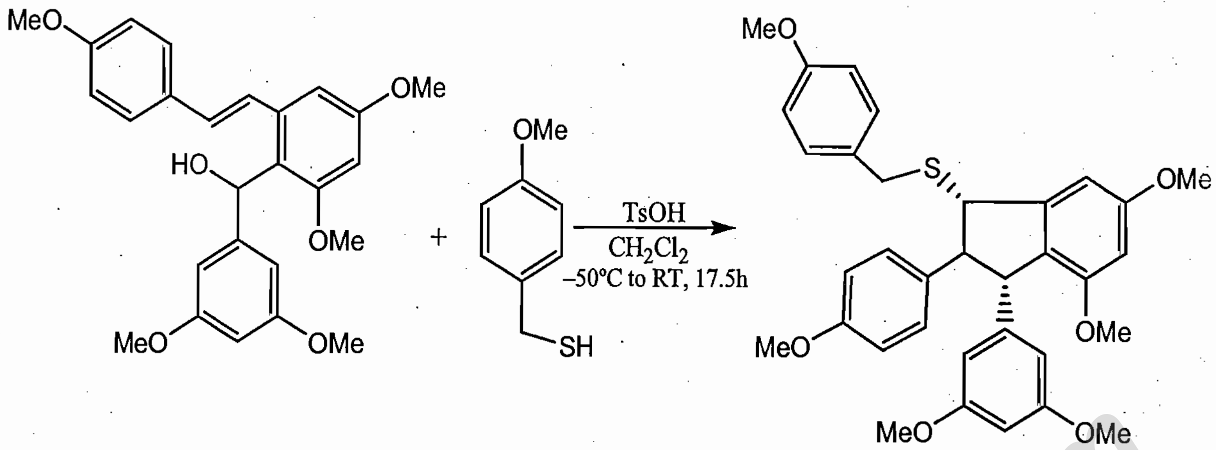
3.


Application:

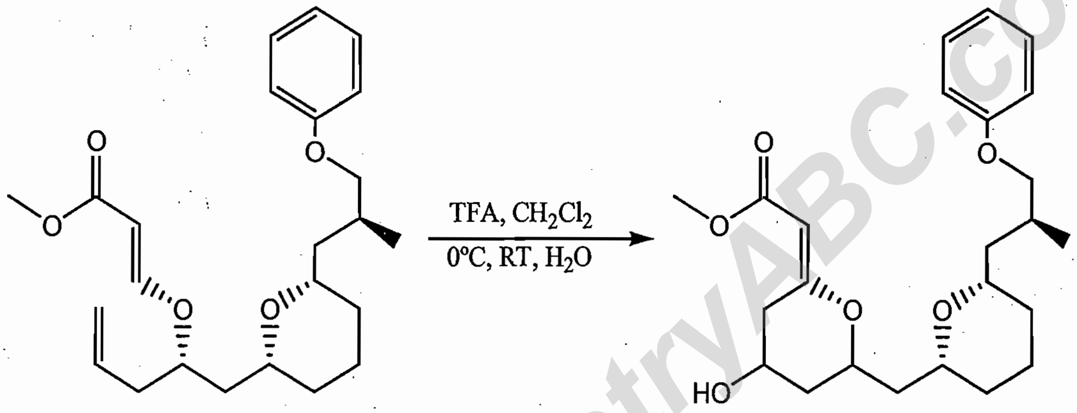
1.


2.


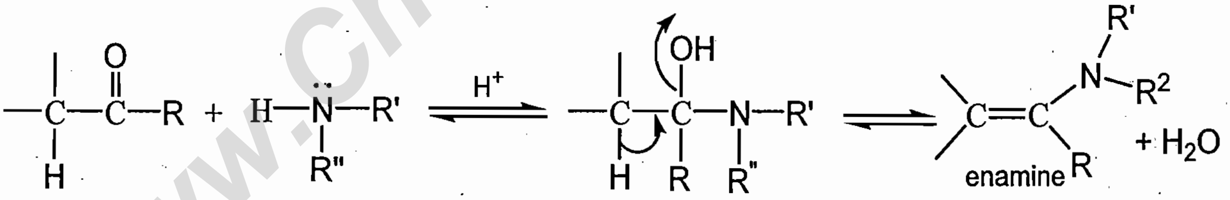
3.



4.

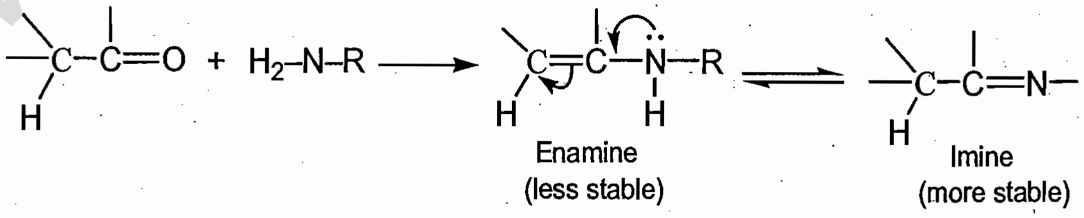


Stork Enamine Synthesis : Any aldehyde or ketone having α – hydrogen react with secondary amine in the presence of acid or dehydrating agent like tolune-p-sulfonic acid to form enamine which is α, β – unsaturated amine.

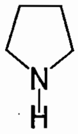


[Where R may be H or any other alkyl group]

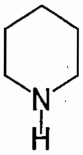
Primary amine can also react with ketone to undergo enamine synthesis.



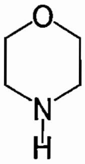
unsymmetric ketone can also undergo the reaction from less substituted side & there are common amine which are used in this type of reaction. For example,



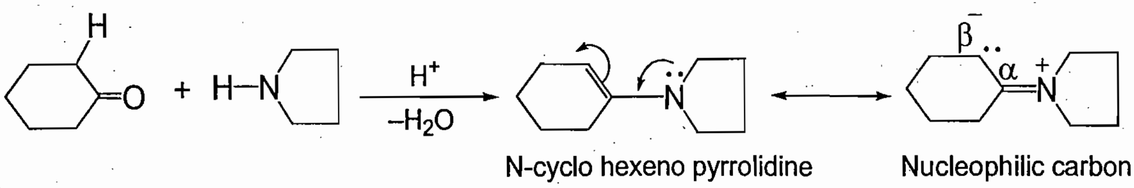
Pyrrolidine



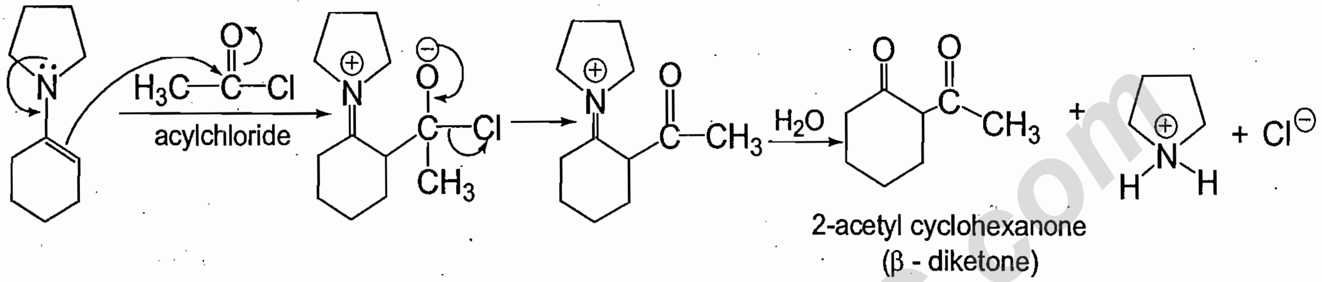
Piperidine



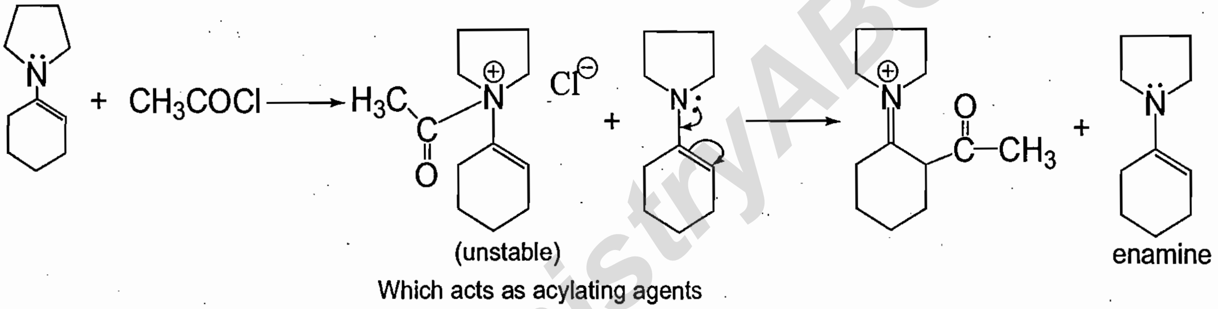
Morpholine



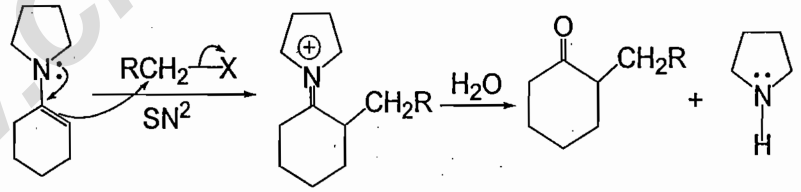
Enamine is very useful intermediate which can be used for alkylation or acylation of aldehyde or ketone at α-position. Stork enamine synthesis is used for monoalkylated reaction. The advantage is
eg. : - (i) acylation reaction : c-acylated is high in yeild.



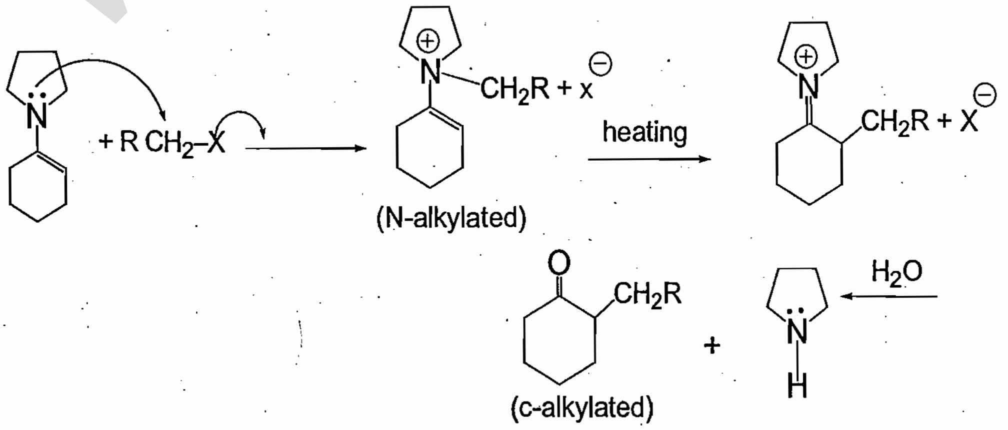
Another Path :



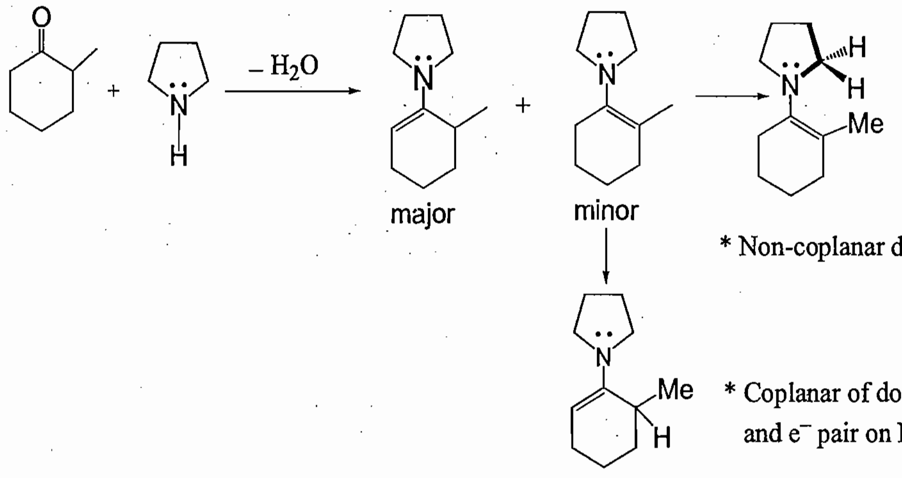
(i) Alkylation: Allylic halide, $(CH_2=CH-CH_2-X)$, Benzylic halide (C_6H_5X), Propargylic halide $(CH_3C\equiv C-X)$ can be used in this reaction.



Sometime like acylation, alkylation can also be at N-atom which undergoes rearrangement on heating to give c- alkylated product.



Enamine formation at less substitued position :

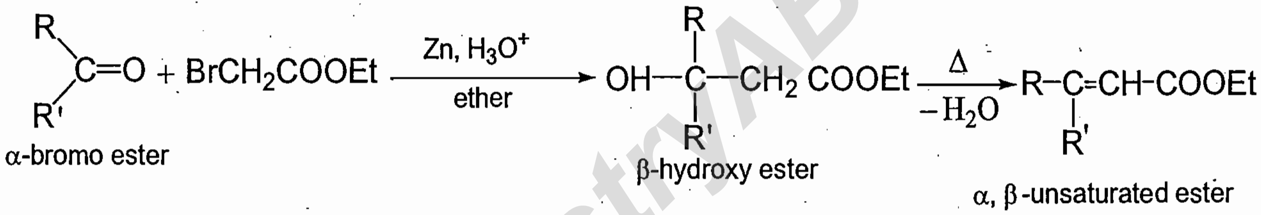


* Non-coplanar due to steric repulsion

* Coplanar of double bond (=) and e⁻ pair on N.

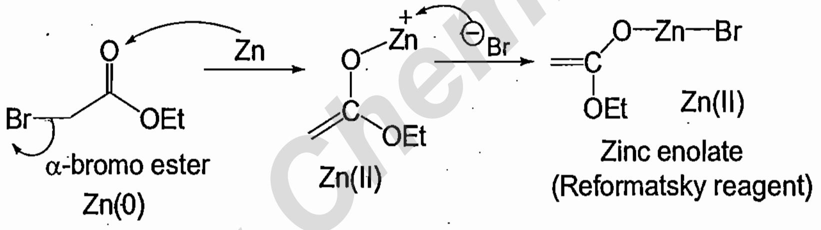
6.34. *Reformatsky Reaction*

The reaction of α-haloester (usually α-bromoester) with carbonyl compounds such as aldehydes and ketones in presence of Zn in an inert solvent (ether benzene to produce β-hydroester. Propagyl bromide and haloamide can be used instead of α-haloester in the reaction.

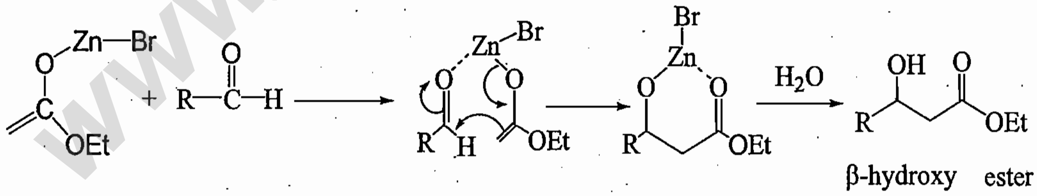


$$R(R')C{=}O + BrCH_2COOEt \xrightarrow[\text{ether}]{Zn,\ H_3O^+} OH-C(R)(R')-CH_2\ COOEt \xrightarrow[-H_2O]{\Delta} R-C(R'){=}CH-COOEt$$

Mechanism :



Reaction with Aldehyde / Ketone :

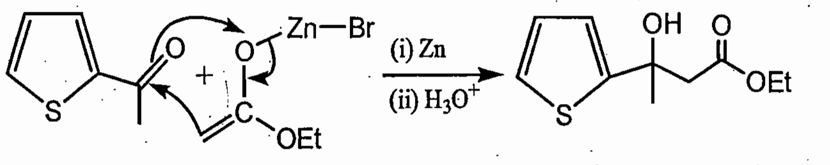


(1) Reformatsky reagent can't be added to highlly substituted sterically hindered ketone. The reaction best proceed with aldehyde, methyl ketones and cyclic ketones.

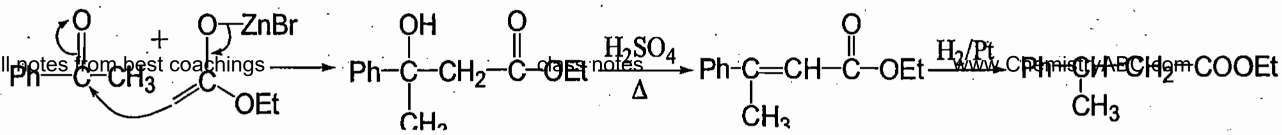
(2) The reactivity order of α-halo ester is: *Iodo* > *Bromo* > *Chloro*

Example:

(i)

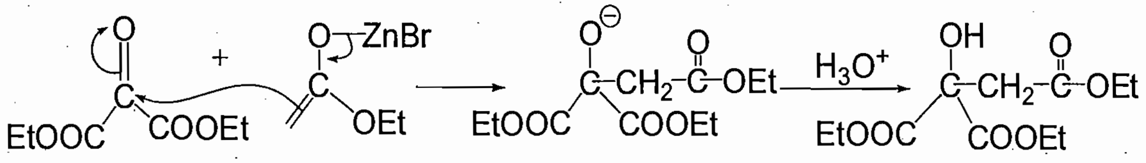


(ii)

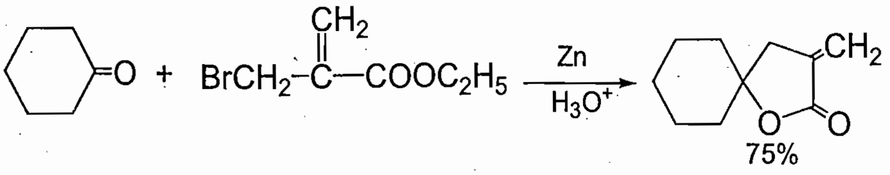


$$Ph-\overset{O}{\overset{\|}{C}}-CH_3 + CH_2{=}C(OEt)-OZnBr \longrightarrow Ph-\underset{CH_3}{\overset{OH}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-OEt \xrightarrow[\Delta]{H_2SO_4} Ph-\underset{CH_3}{C}{=}CH-\overset{O}{\overset{\|}{C}}-OEt \xrightarrow{H_2/Pt} Ph-\underset{CH_3}{CH}-CH_2-COOEt$$

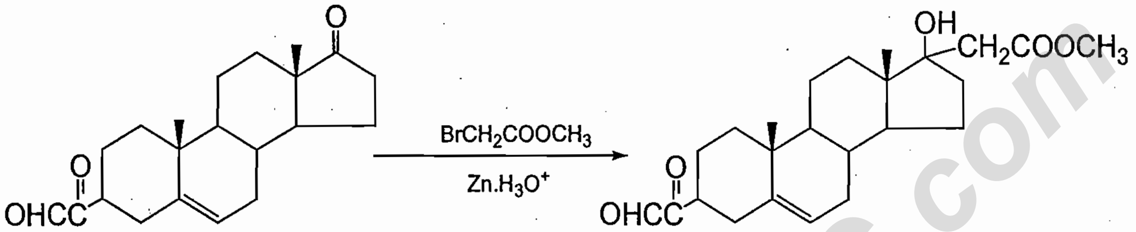
(iii)



(iv)

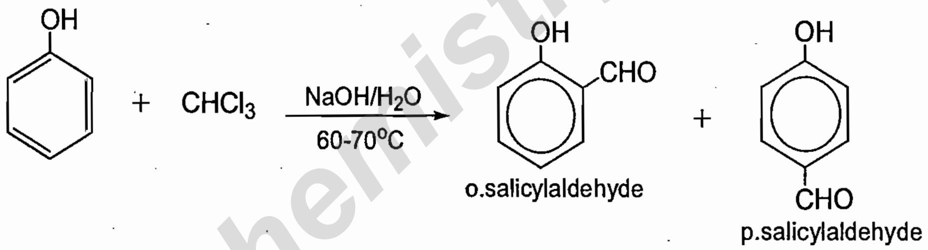


(v)



6.36. *Reimer - Tiemann Reaction*

Phenols react with chloroform in the presence of NaOH to give hydroxy aldehyde. The formyl group is directed to ortho -position unless one of ortho-position or both are occupied in this case, the attack will be at para - position. The reaction goes through carbene intermediate.



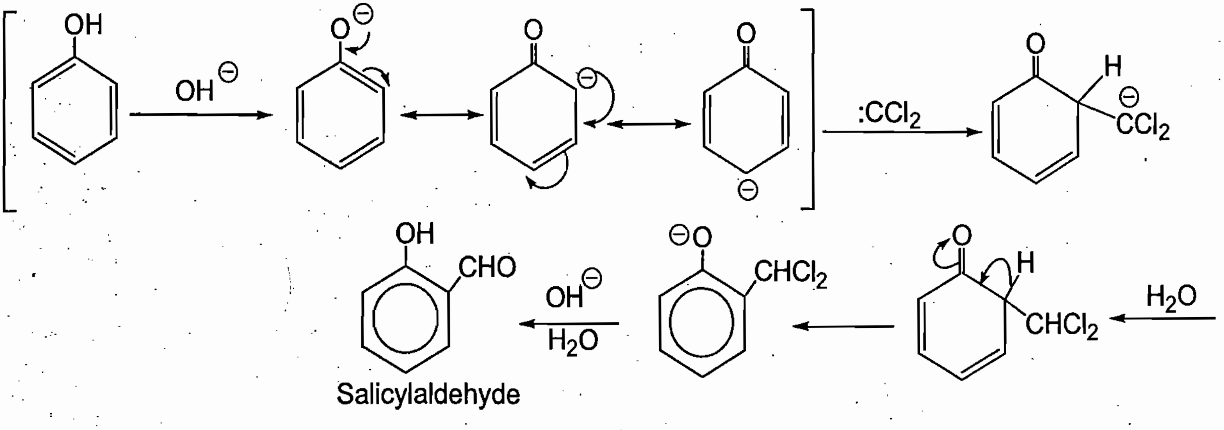
Mechanism : The reaction proceed via dichlorocarbene (:CCl_2), the reaction is basically an Electrophilic substitution on the highly reactive phenoxide ring with the help of : CCl_2 is enough which is generated by action of base on chloroform.

(i) Formation of carbene:

(a) $CHCl_3 \xrightarrow{OH^{\ominus}} \overset{\ominus}{C}Cl_3 + H_2O$ (b) $\overset{\ominus}{C}Cl_3 \xrightarrow{-Cl^{\ominus}} :CCl_2 + Cl^{\ominus}$

dichlorocarbene

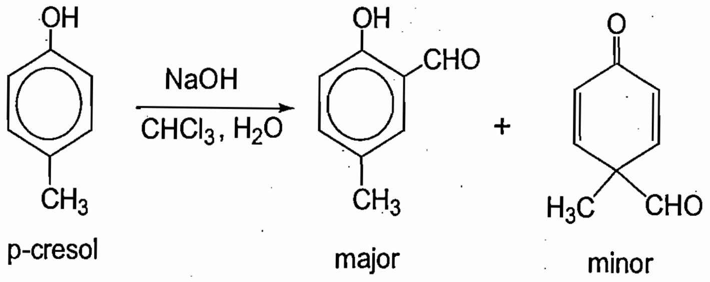
(ii) Electrophilic substitution on phenoxide ion:



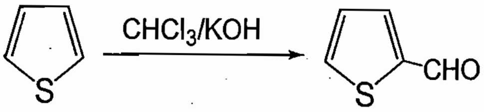
Benzene do not undergo R.T. reaction because :CCl_2 not electrophilic enough to attack the benzene ring.

EXAMPLES

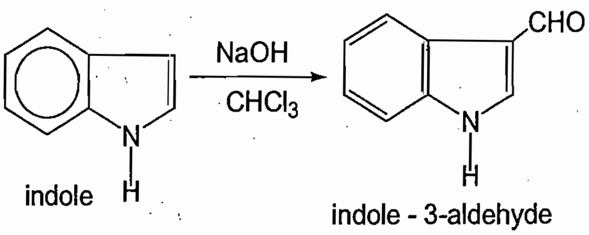
(a)



(b)

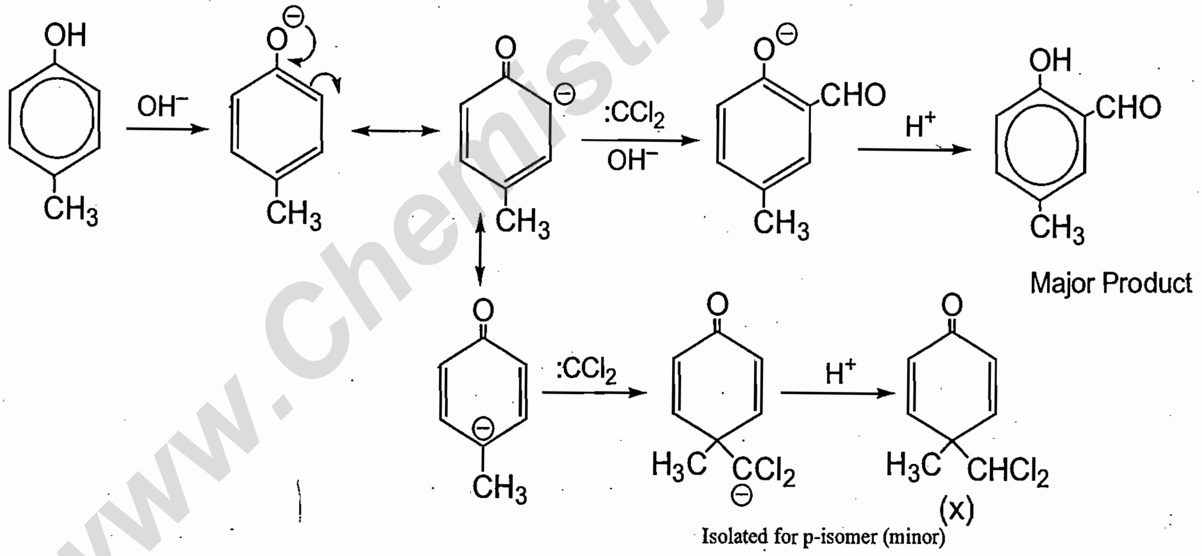


(c)



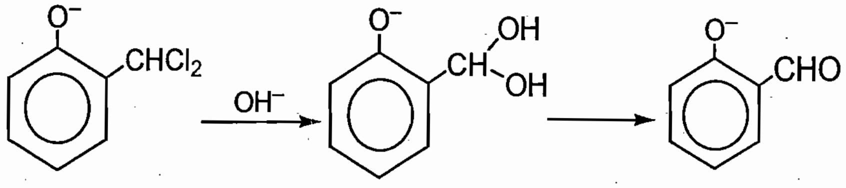
Evidences for the mechanism :

1. When similar reaction is done with p-cresol, intermediates are isolated.



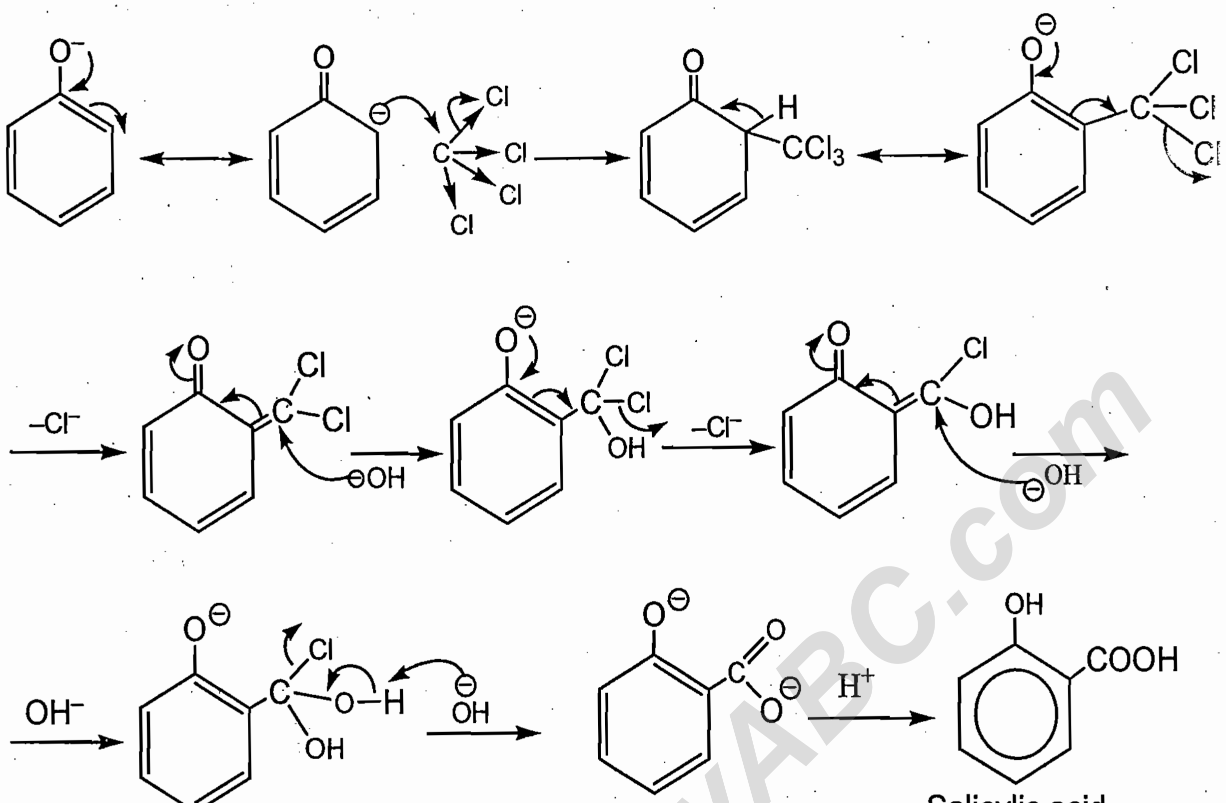
The dichloro compound (x) is resistant to hydrolysis partly due to its insolubility in aq. basic medium and also to the sterically hindered neo pentyl type environment of the Cl atom

[But the other way this is not resistant to hydrolysis.



that is why the (x) has been isolated and it provide a support for the mechanism as an intermediate.

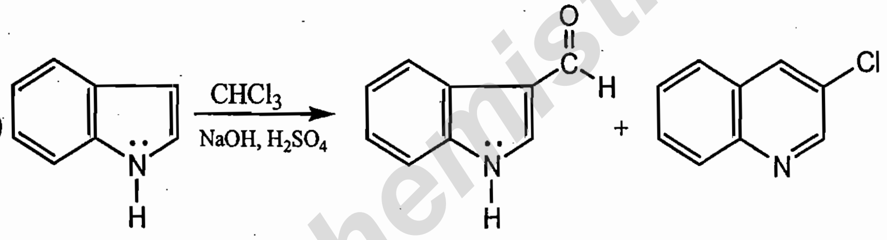
2. Reaction With CCl_4 : Salicylic Acid obtains.



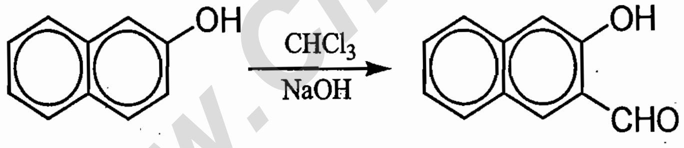
Salicylic acid

Example:

(i)

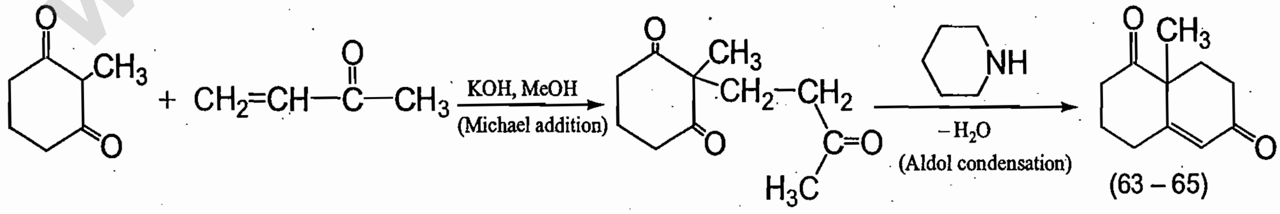


(ii)



6.37. Robinson Annulation

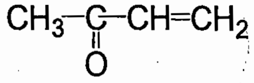
The immediate product of the Michael addition is subjected into an aldol condensation that form a ring.



(63 – 65) % yield

* The basic ingredient in Robinson annulation is α, β-unsaturated compound.

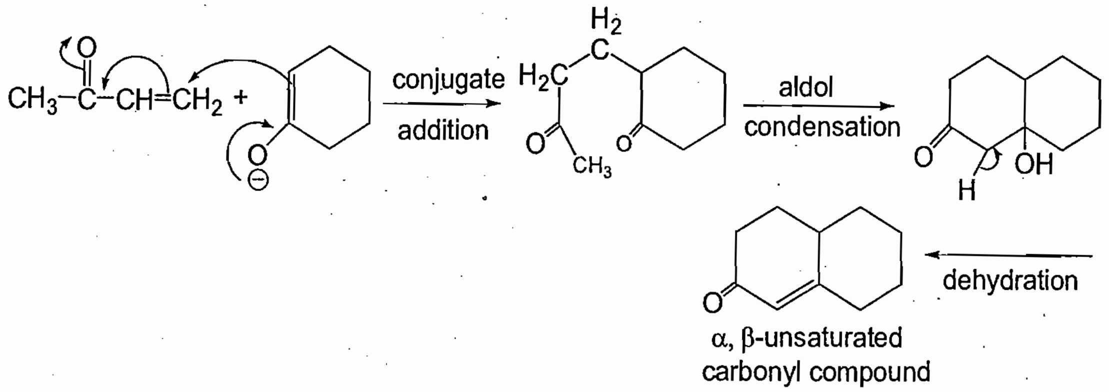
(a)



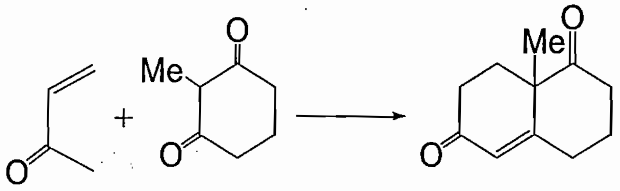
$CH_3-\underset{\|}{\overset{}{C}}-CH=CH_2$ with O below: $CH_3-C(=O)-CH=CH_2$

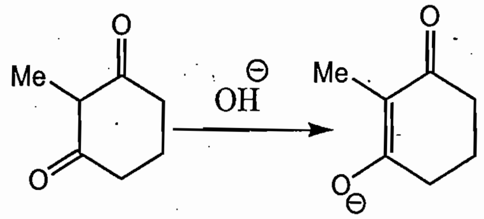
methyl vinyl ketone

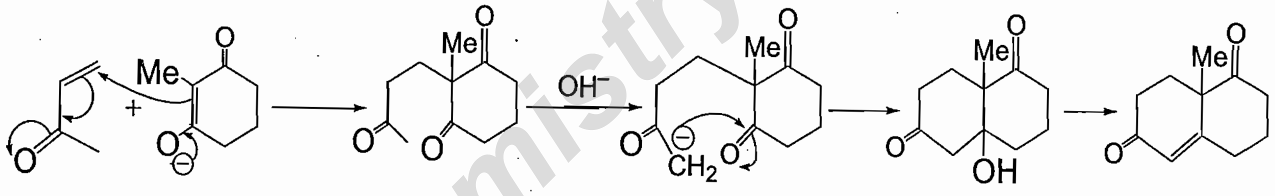
Mechanism :



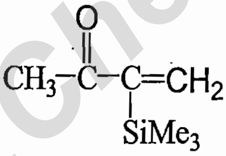
(b)





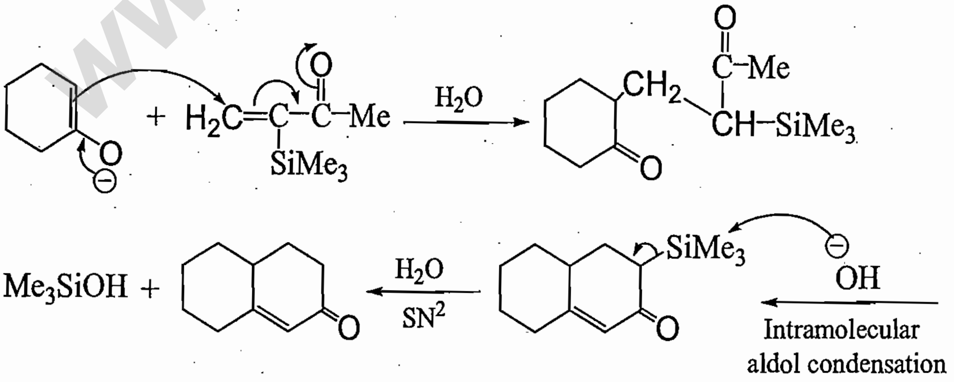


(c) Using methyl - 1- trimethyl silyl vinyl ketone



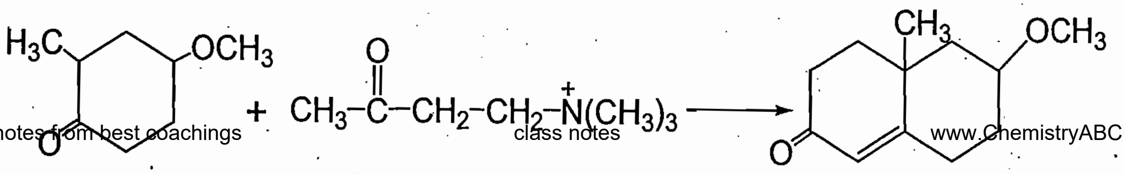
$$CH_3-\overset{O}{\overset{\|}{C}}-\underset{SiMe_3}{\underset{|}{C}}=CH_2$$

Mechanism**:** The role of trimethyl silyl group is to stabilise the enolate form during conjugate addition. The silyl group is then removed during dehydration by using base

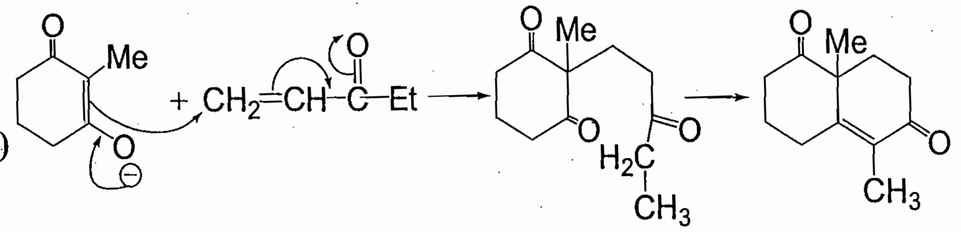


Example**:**

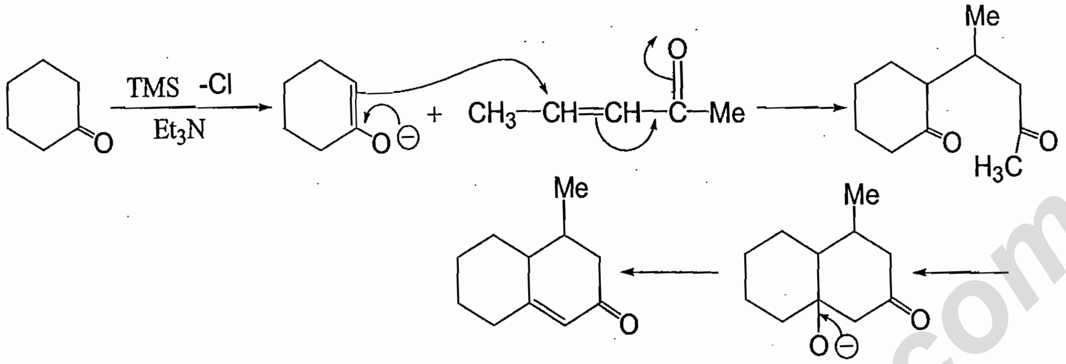
(i)



(ii)

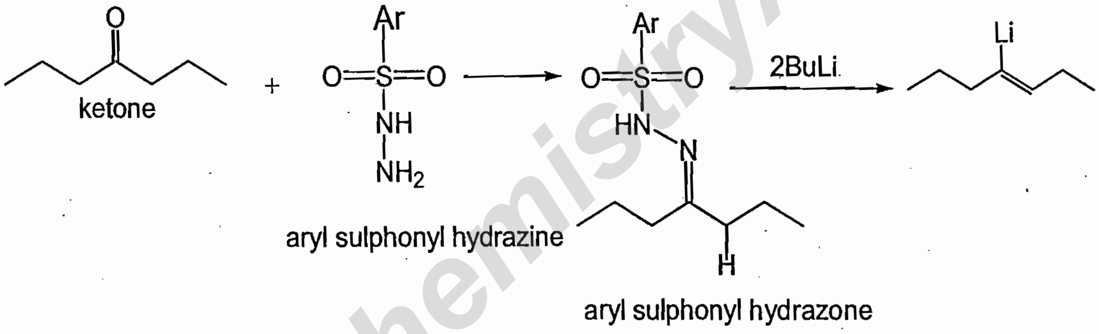


(iii)



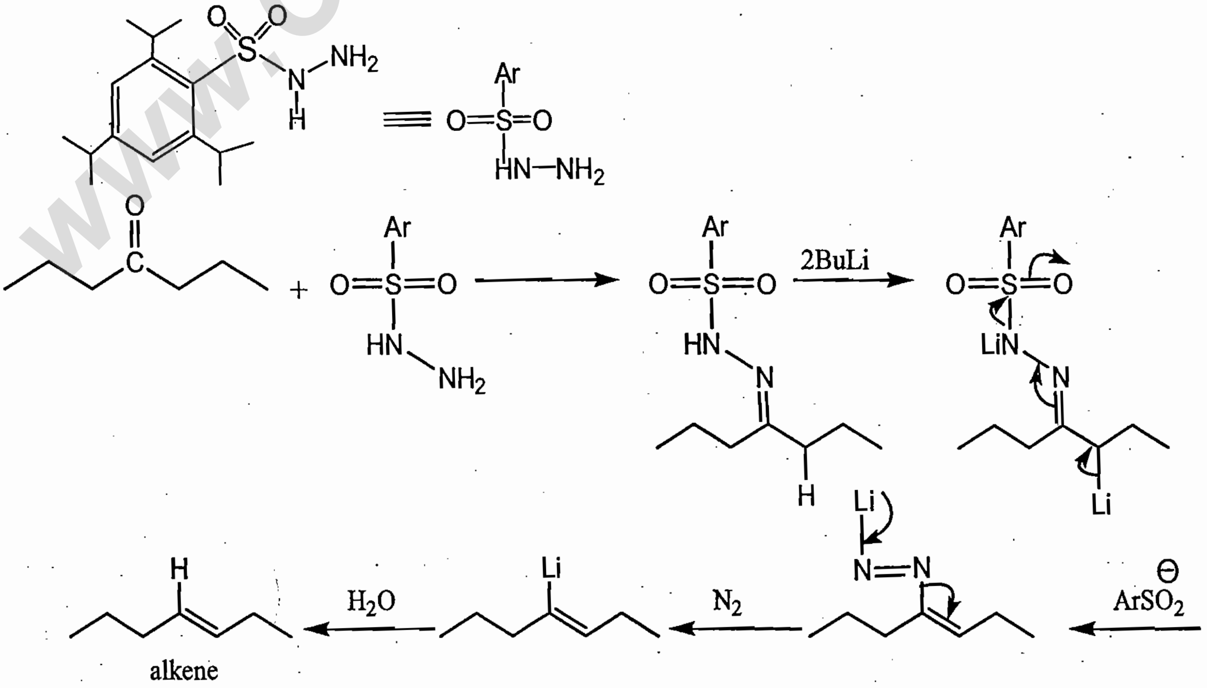
6.38. Shapiro Reaction

The conversion of ketone - p - toluene sulphonyl hydrazone to alkene in the presence of a strong base is called ***shapiro reaction***. The conversion of ketone to aryl sulfonyl hydrazone or p-Toluene sulphonyl hydrazone is taking place, then, addition of base like alkyl lithium converts the reactant to vinyl lithium (alkene), after hydrolysis, it is converted to alkene.

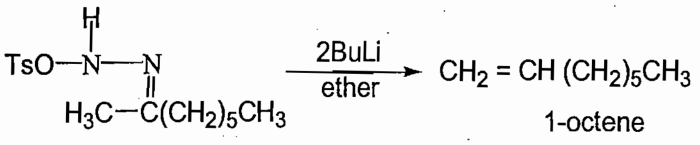


Mechanism:

(i)



Examples:

(i)


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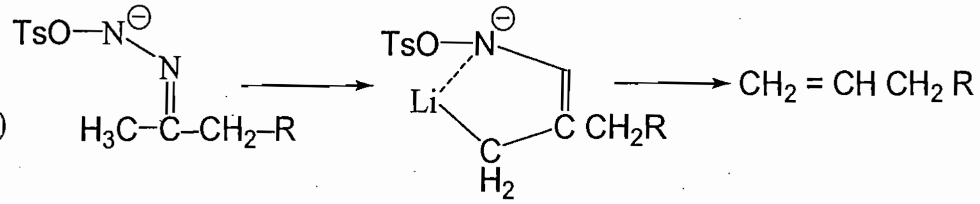

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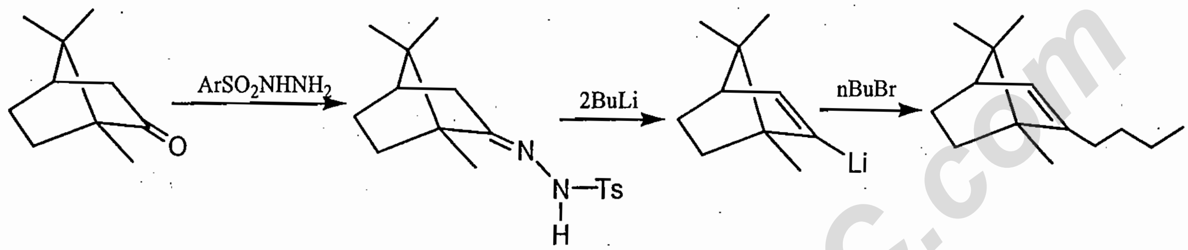
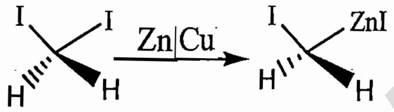


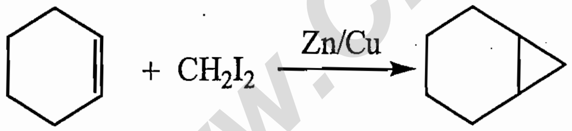
6.39. *Simmons-Smith Reaction*

The Simmons-Smith Reaction is an organic chelotropic reaction involving an argonozinc compound that reacts with an alkane or alkyne to form a cyclopropane. Reagent used in Simmon-Smith reaction is called Simmon-Smith reagent. When an alkene is treated with Simmons-smith reagent, it produces cyclopropane ring and their derivatives.

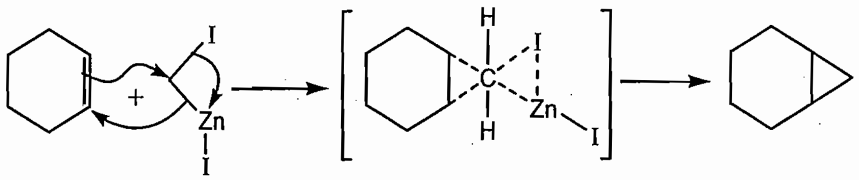
Simmons-Smith reagent



Structure of Simmons-Smith reagent



Mechanism: The mechanism of this reaction appears to be carbene transfer from the metal to the alkene without any free carbene being released.



SOLVED PROBLEMS

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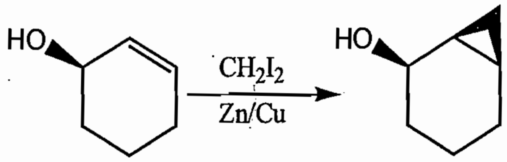

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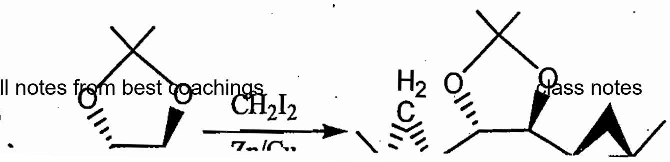

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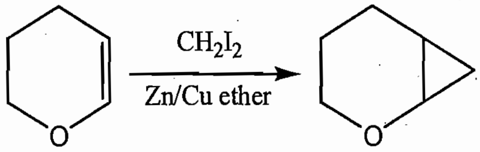

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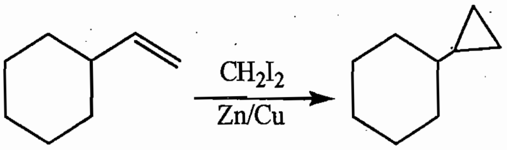

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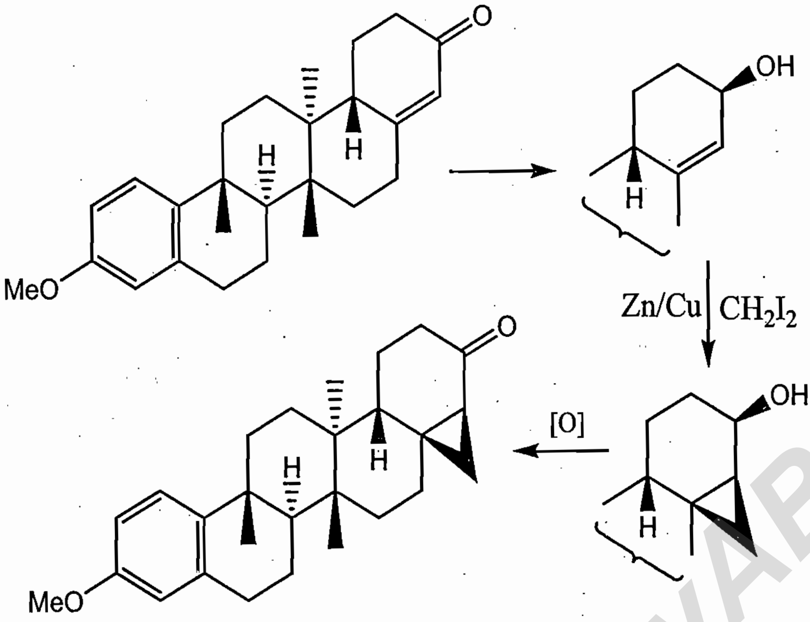
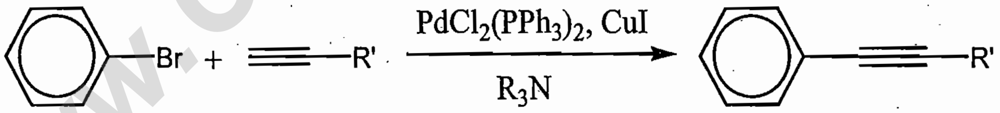
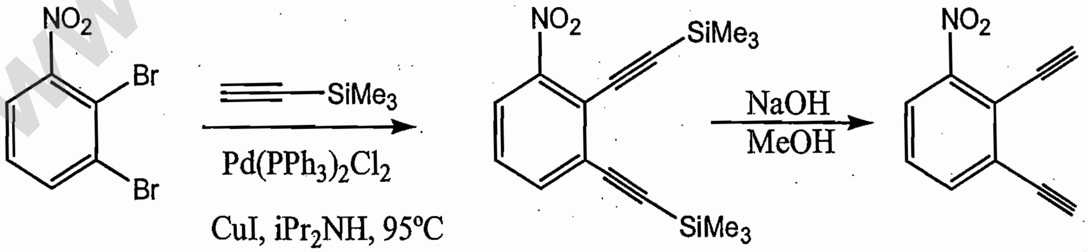


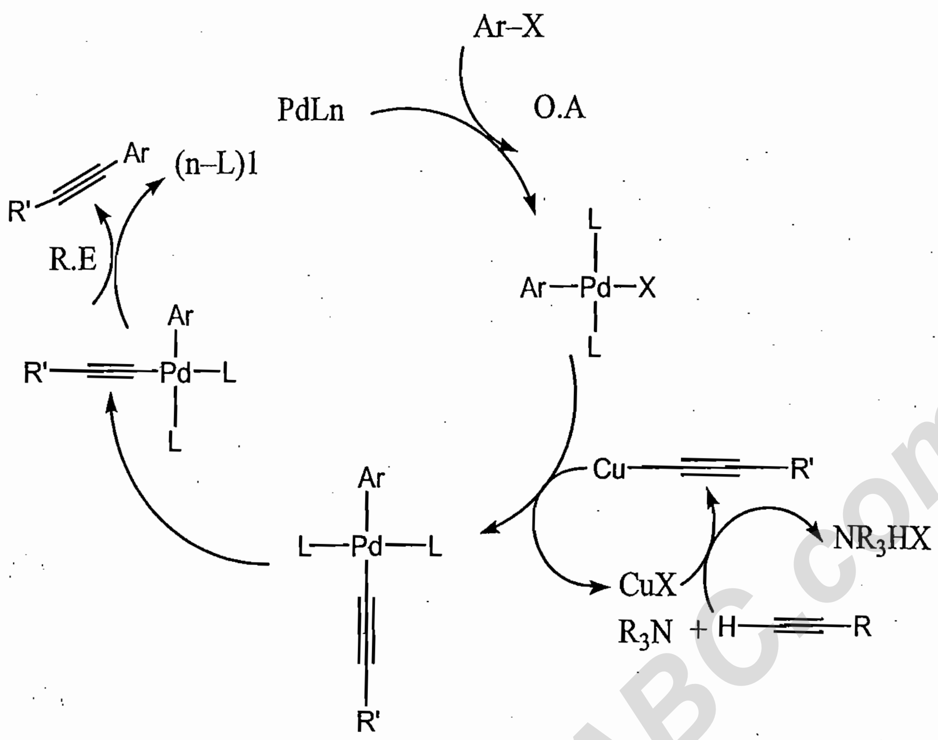
6.40. Sonogashira coupling

- Coupling of terminal alkynes with aryl or vinyl halides.
- Performed with a Pd catalyst, a Cu(1) Co catalyst and an amine base.
- The Sonogashira reaction usually use mild condition, often room temperature and therefore it can tolerate the presence of a large number of functional groups.
- Sonogashira coupling of trimethylsilyl alkyne followes by treatment with a strong base or a fluoride source is a common strategy used for introducing terminal alkyne.

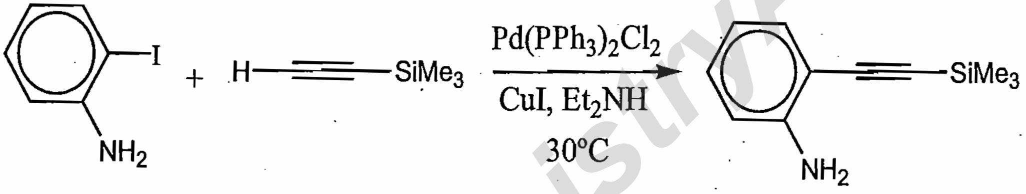


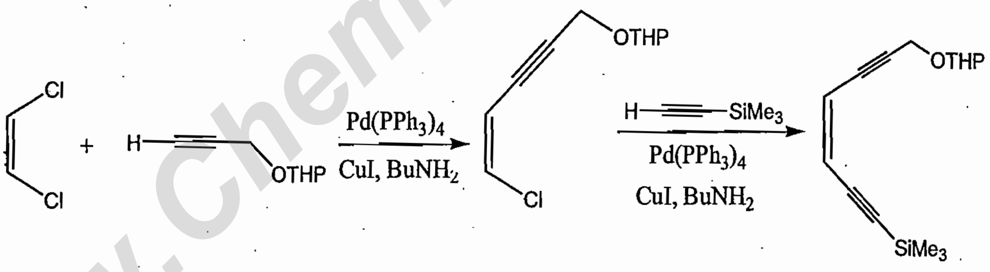


Catalytic cycle for sonogashira coupling



Problem:

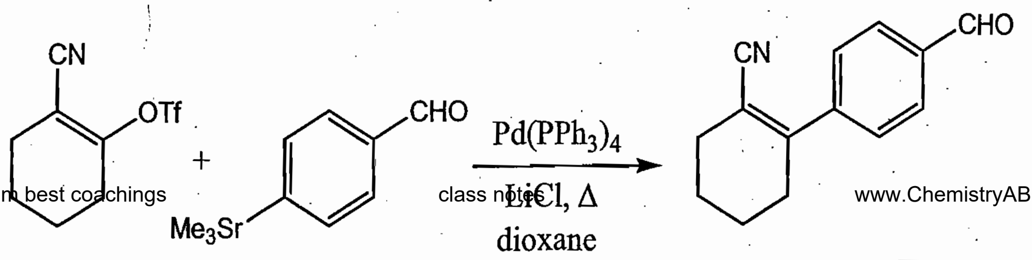


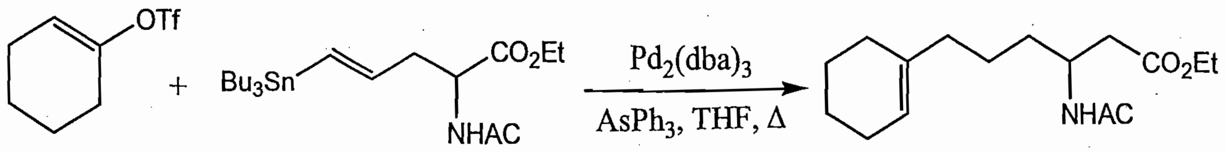


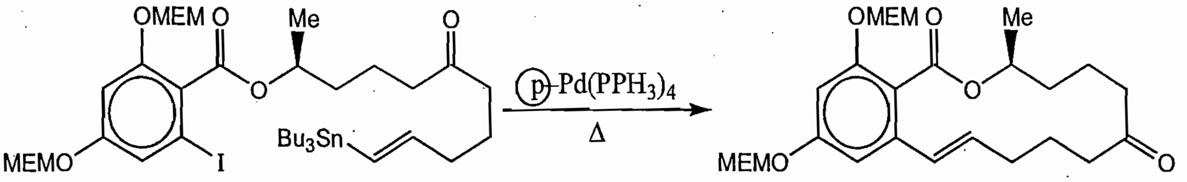
6.41. Stille coupling

- Pd catalysed cross coupling reactions involving organotin based reagents and organohalides are referred to as stille coupling reaction.
- The toxicity of the tin compounds used and their poor solubility in water due to their low polarity are the main drawbacks of this reaction compared to suzuki coupling.
- No base is required for this reaction.
- A wide range of functional group tolerance is also observed and the halide substrate with NO2, CN, OMe, COOR, COOH and even CHO group are tolerated.

Problem:



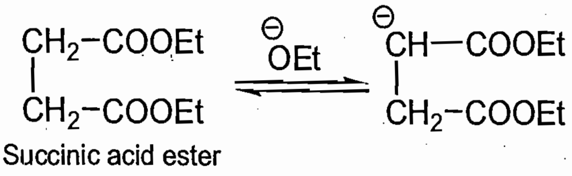




6.42. *Stobbe Condensation*

It is reaction between dialkyl succinate and aldehyde or ketone in the presence of NaH or $K\left(t-BuO^-\right)$ or $NaOC_2H_5$ to form salt of α, β-unsaturated half ester. This reaction is limited to α-ω diester ester group at Ist carbon and last carbon.

(1) The reaction goes via a lactone intermediate which on subsequent base catalysed elimination causes almost irreversible ring opening to produce salt of unsaturated esters. The lactone intermediate has been isolated and provides the support for the mechanism.

(2) 

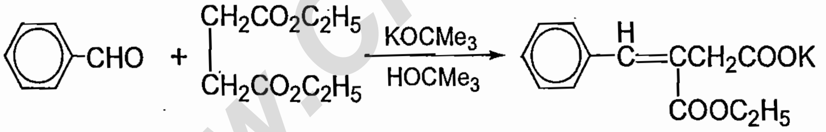
$$\begin{array}{l} CH_2-COOEt \\ | \\ CH_2-COOEt \end{array} \underset{}{\overset{\overset{\ominus}{O}Et}{\rightleftharpoons}} \begin{array}{l} \overset{\ominus}{C}H-COOEt \\ | \\ CH_2-COOEt \end{array}$$

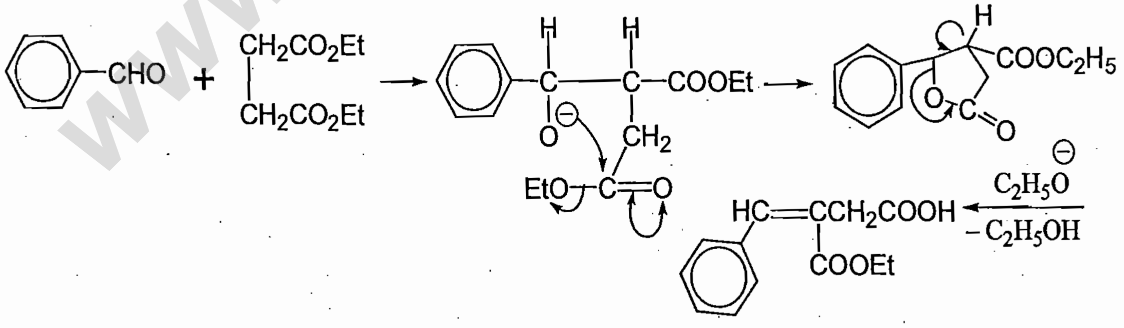
Succinic acid ester

This kind of esters where only one α-hydrogen is present can not undergo irreversible ring opening at the last step, which actually drives the reaction in the forward direction. In case of these esters only the lactone intermediate has been isolated.

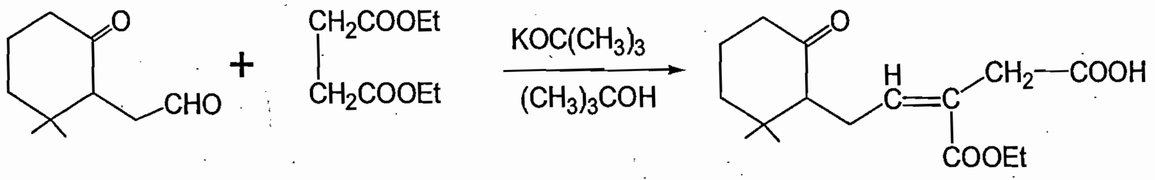
3. If only one α carbon has two α-hydrogens then reaction can proceed to the last step.

Mechanism **:**

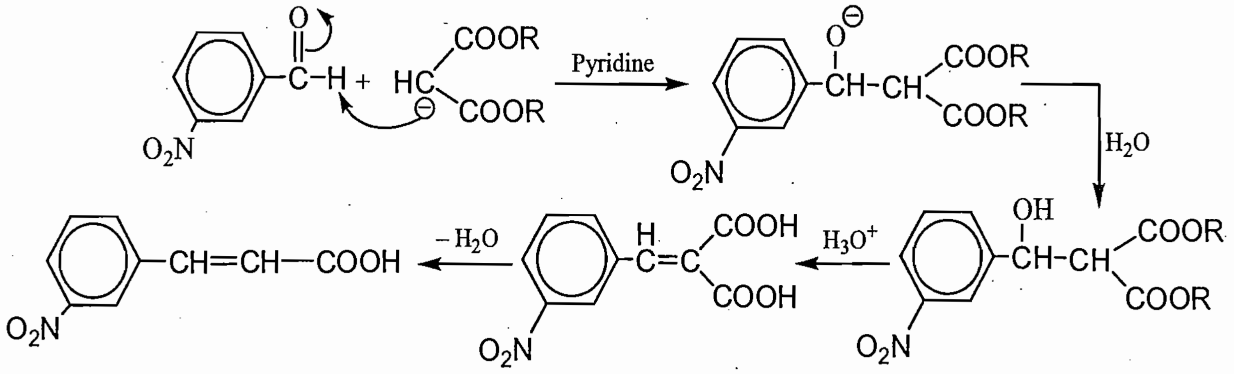




***Example*:**

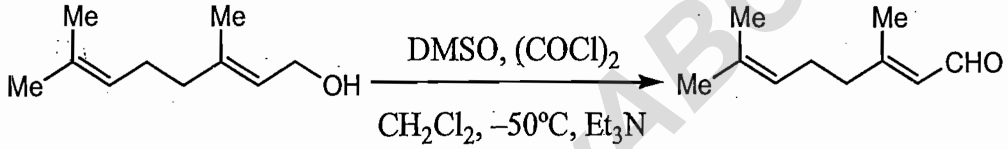
(i) 

(ii)



6.43. *Swern Oxidation*

- By reaction with dimethyl sulfoxide and oxalyl chloride, followed by treatment of the resulting aloxysulfonium salt with base, usually triethyl amine, many different alcohols have been converted into the corresponding carbonyl compounds in high yield under mild conditions.
- It is effective for almost all of primary and secondary alcohol.
- No enolization takes place so stereochemistry is maintained.



PROBLEM

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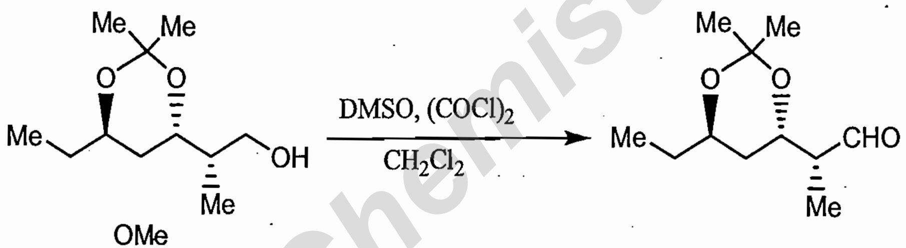

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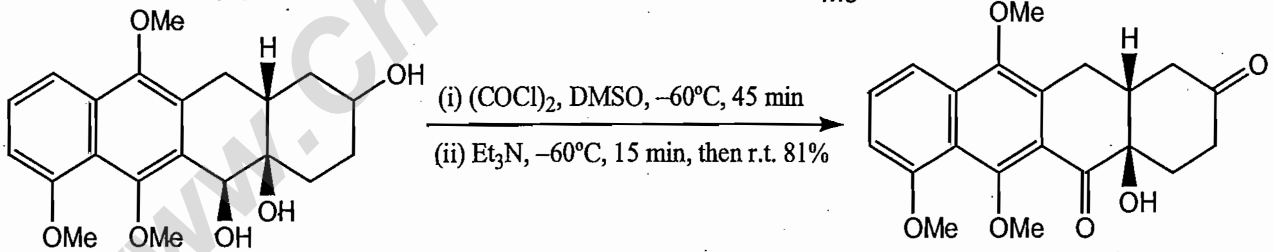

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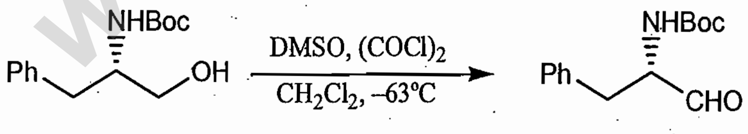
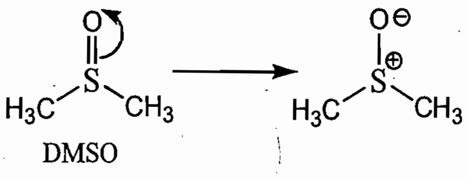
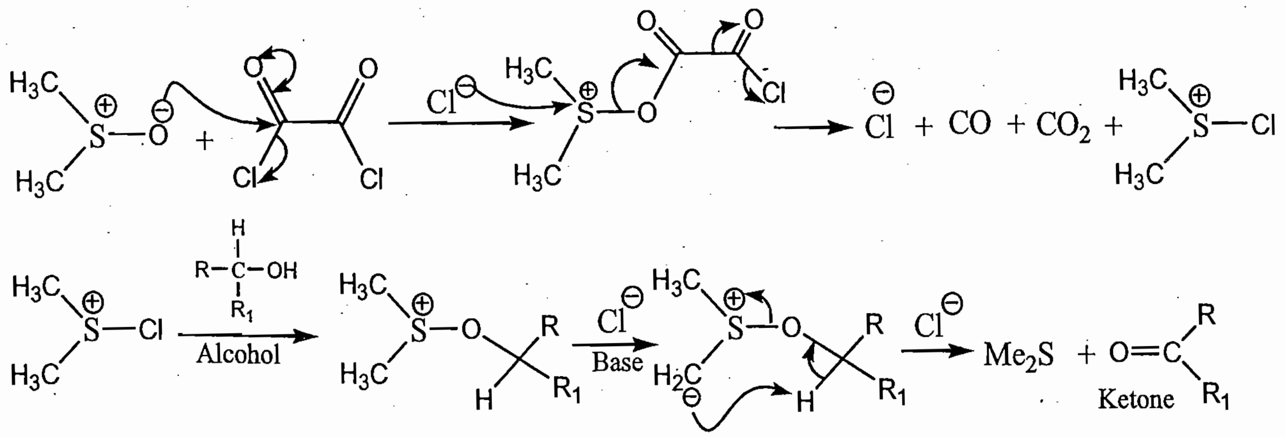


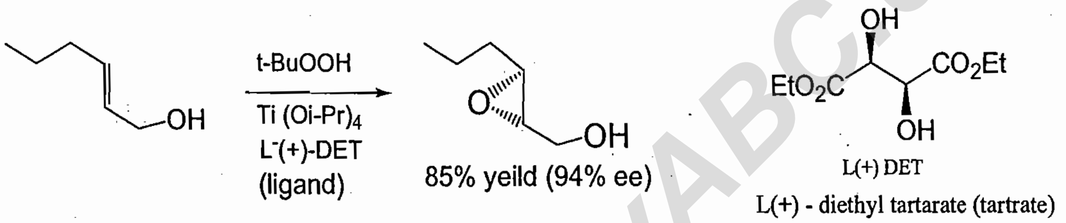
***Mechanism*:**



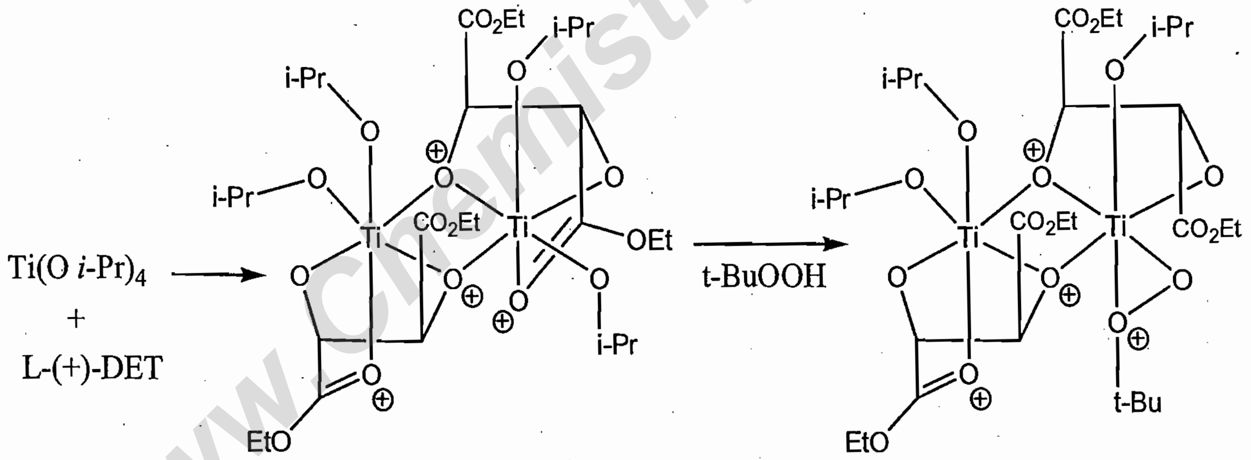


6.44. *Sharpless Reaction*

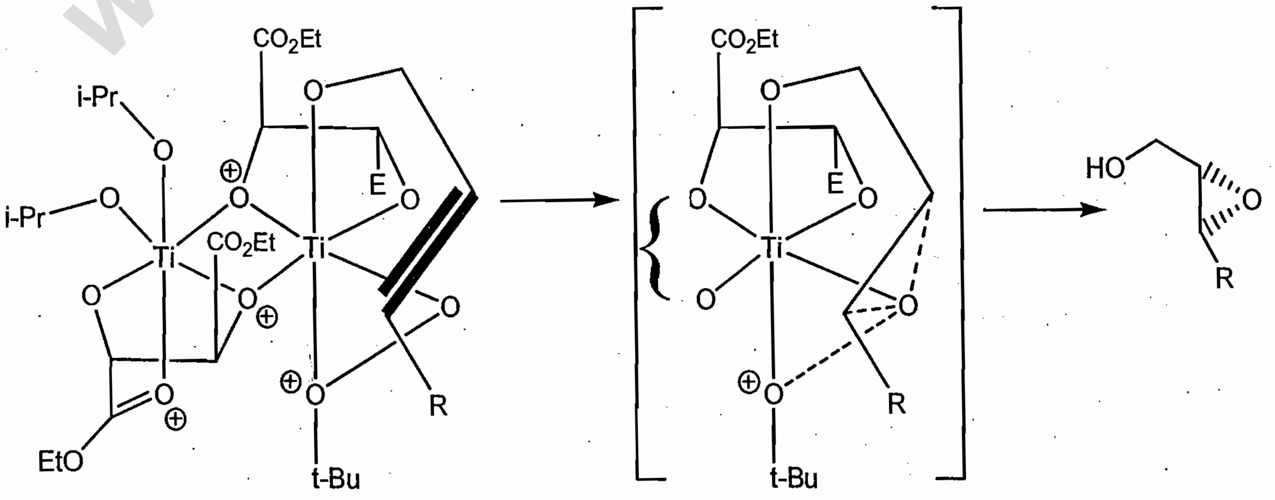
Sharpless assymmetric epoxidation : Transition metal catalysed epoxidation of allylic alcohol in the presence of ligand and t-BuOOH. (t-Butyl hydroperoxide). Sharpless was awarded by Nobel Prize in 2001.



***Mechanism*:**

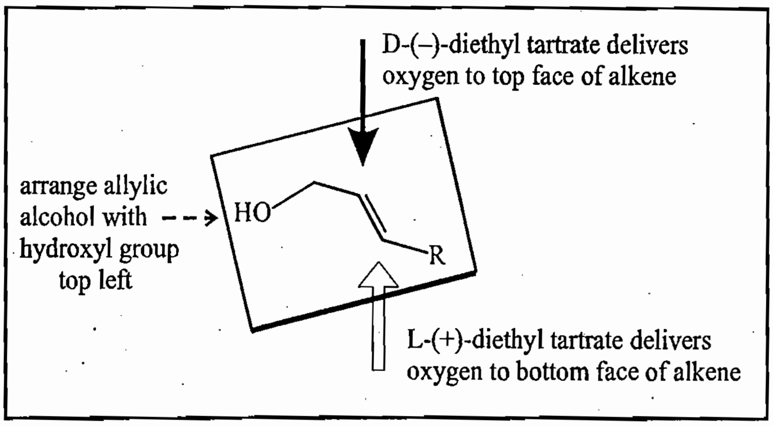


When the oxidising agent(t-BuOOH) is added to the mixture, it displaces one of the remaining isopropoxide ligands and one of the tartrate carbonyl groups.



CO_2Et group at back simplified to 'E' for chirality

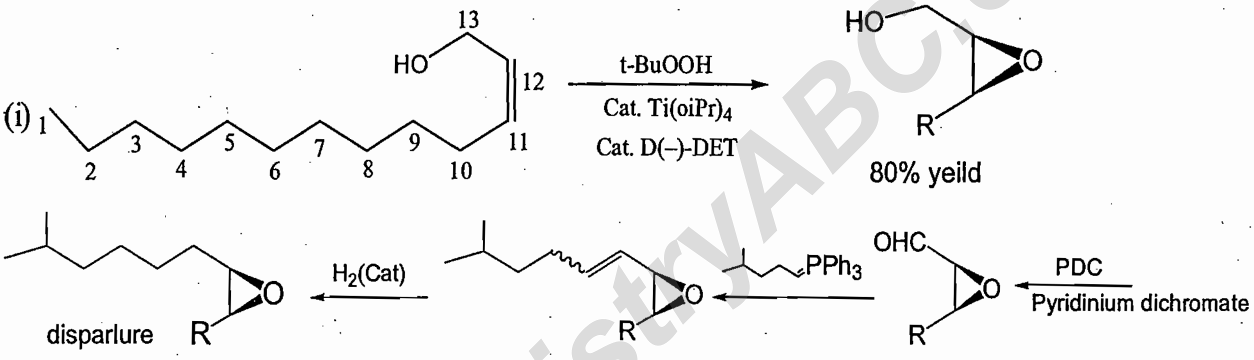
- **Enantioselectivity in the Sharpless asymmetric epoxidation**



Sharpless reaction is only for allylic alcohol and discovered in 1981. K.B. sharpless (1941) found that the reaction works with only a catalytic amount of titanium - tartrate complex.

***Examples*:**

(i)



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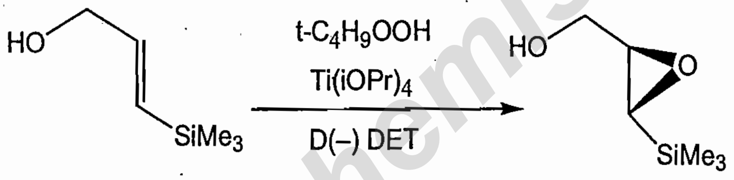

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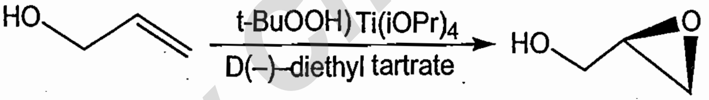

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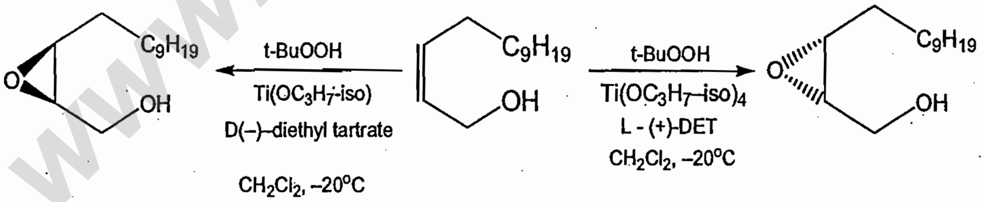

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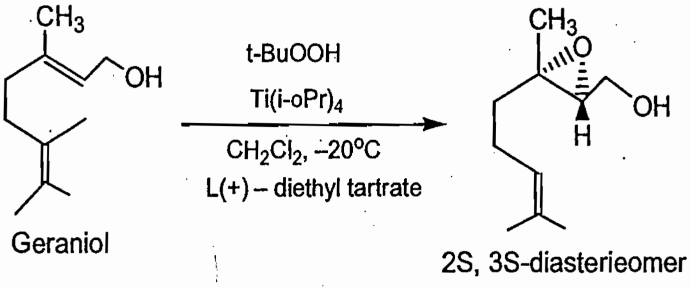

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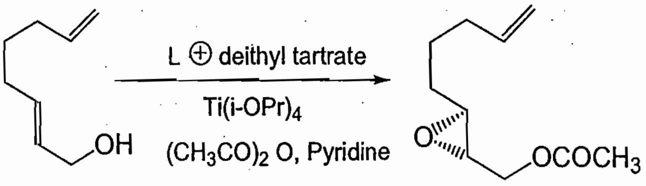

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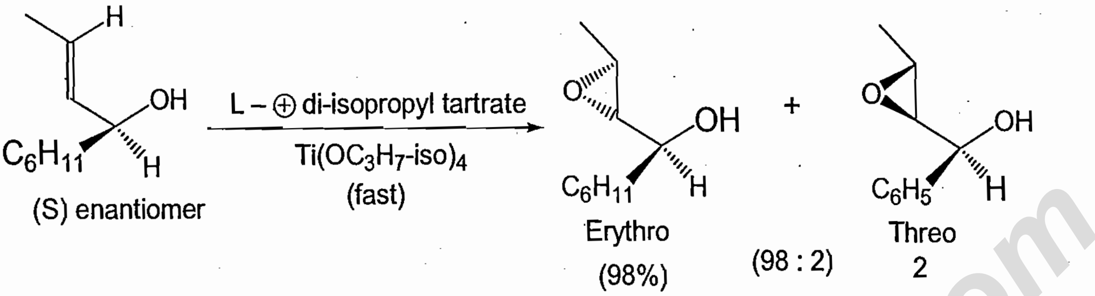

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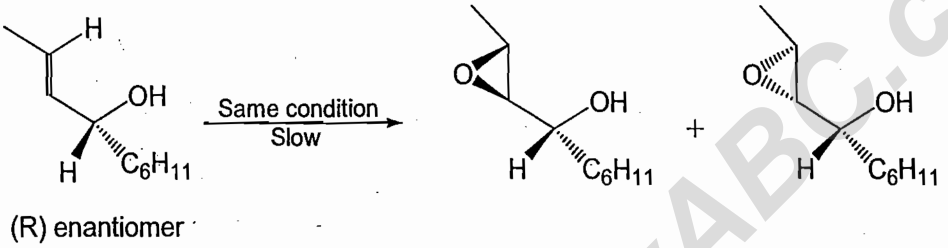
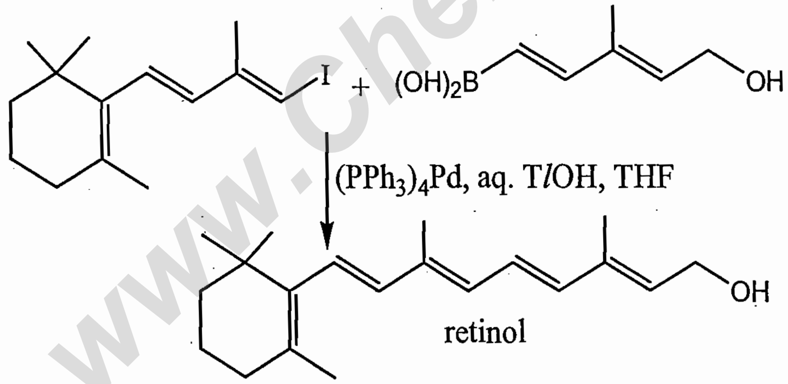


6.45. Suzuki Reaction:

- This is one of the most powerful reaction in synthetic organic chemistry for C–C bond formation.
- Suzuki reaction requires conditions milder than that for Heck reaction.
- Boronic acid are air and water stable as well as non-toxic.
- Suzuki coupling has been utilised in the synthesis of retinol.



PROBLEMS

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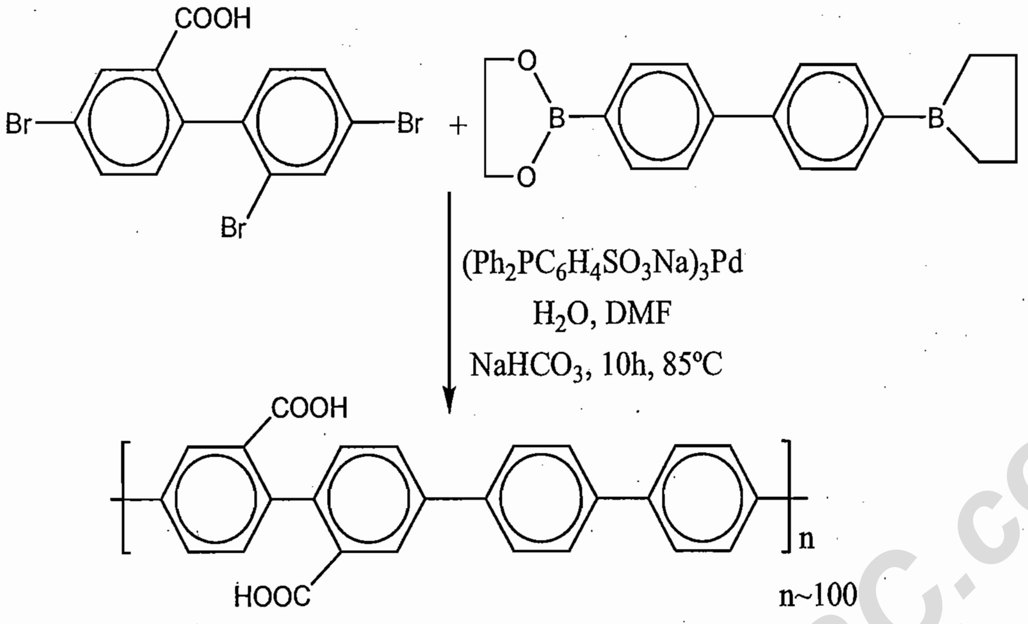
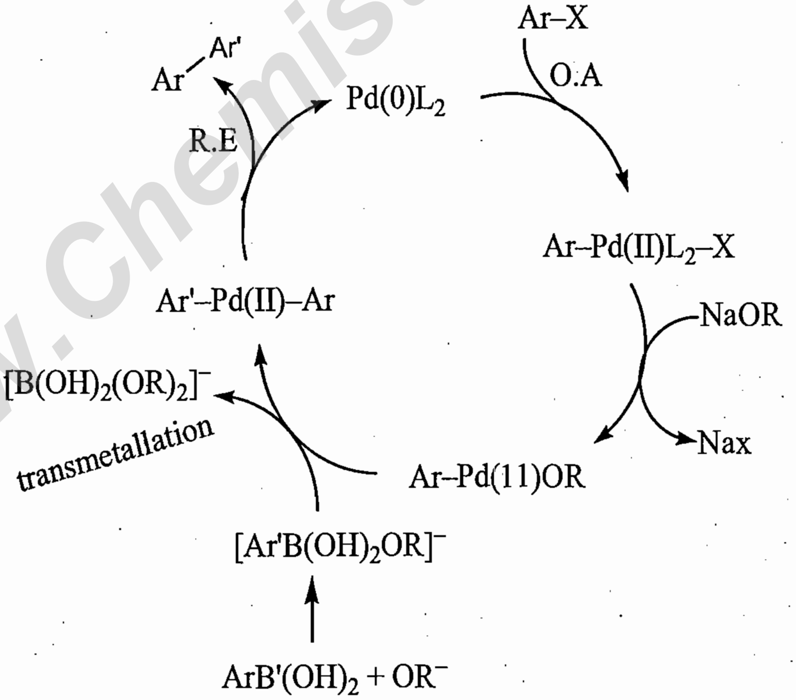


poly p-phenylene(LED)

Catalytic cycle for suzuki coupling



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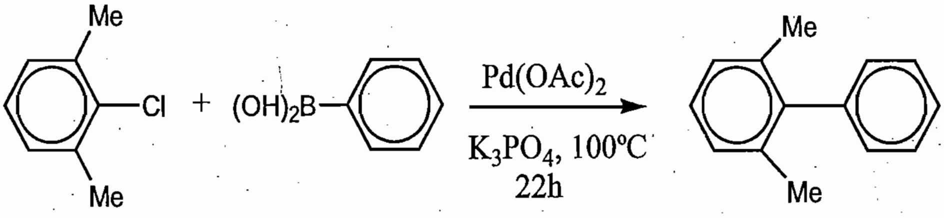

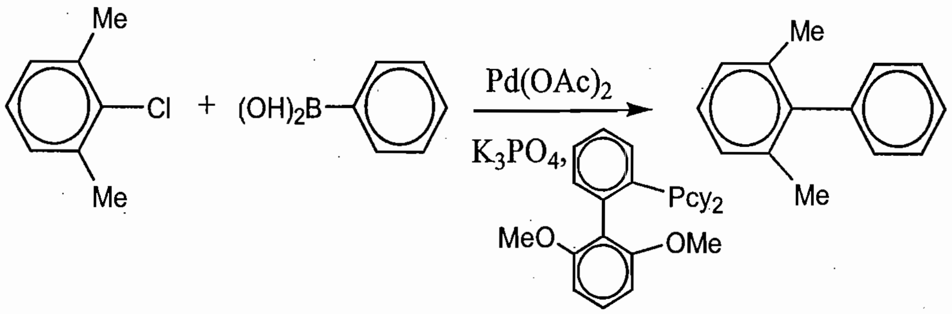

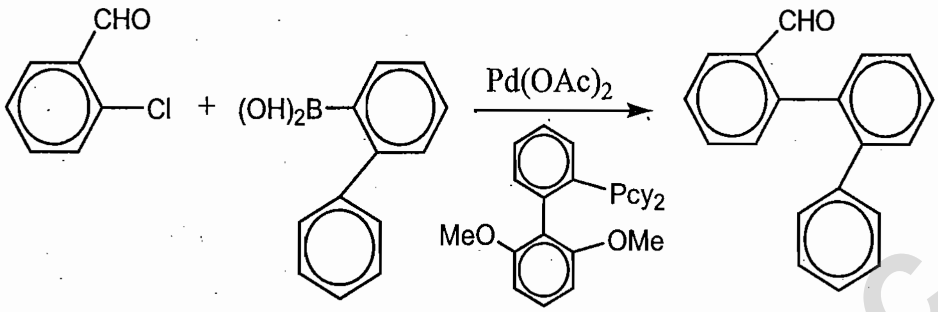

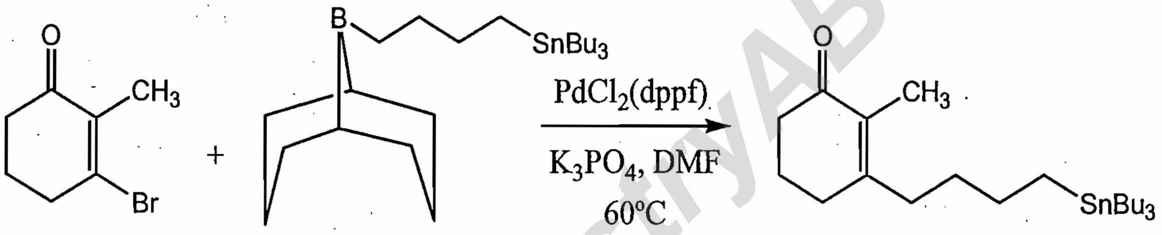

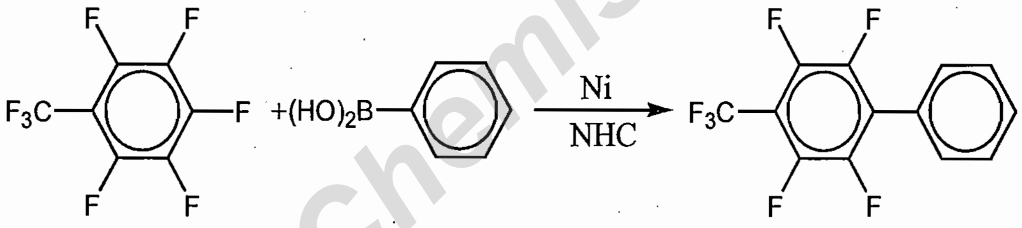

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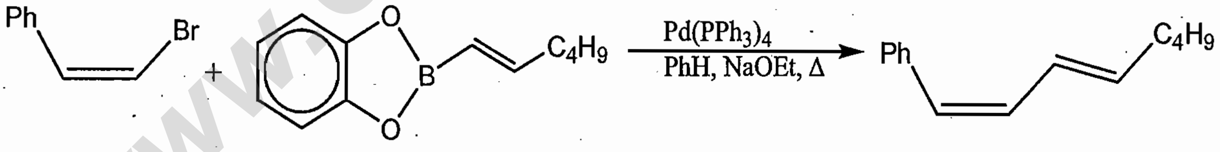

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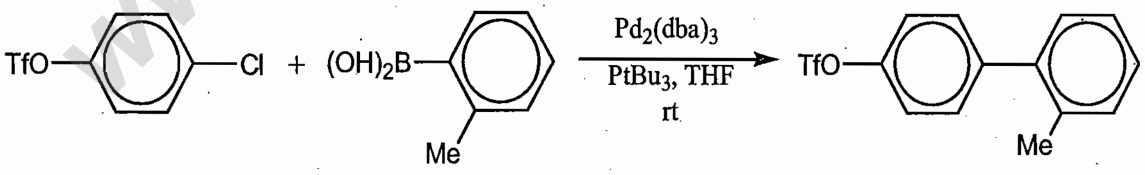
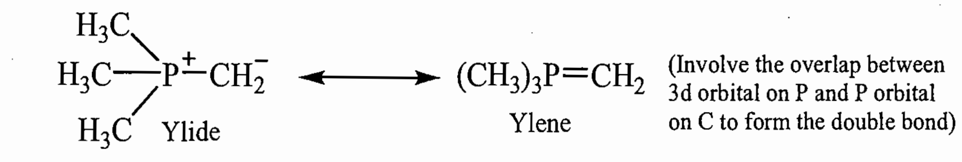


6.46. *Wittig Reaction*

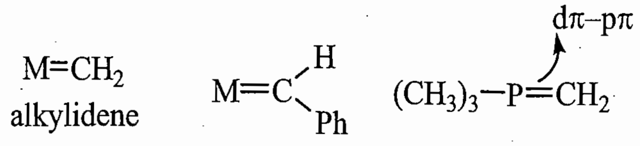
Reaction is discovered by George Wittig (1979 - Noble prize) The reaction between aldehyde, ketone and phosphorous ylide also called phosphonium ylide to produce an alkene and phosphine oxide ($R_3P{=}O$) is known as wittig reaction.

Ylide : It is neutral compound An ylide is a molecule that has a contributing lewis structure with opposite charges on adjacent atom, each of which have a octet of electron. In phosphonium ylide P is next to carbon and contains positive charge and carbon contains the negative charge, $\overset{\oplus}{P}-\overset{\ominus}{C}$.

Negative charge of carbon allow the ylides to act as nucleophile in reaction.



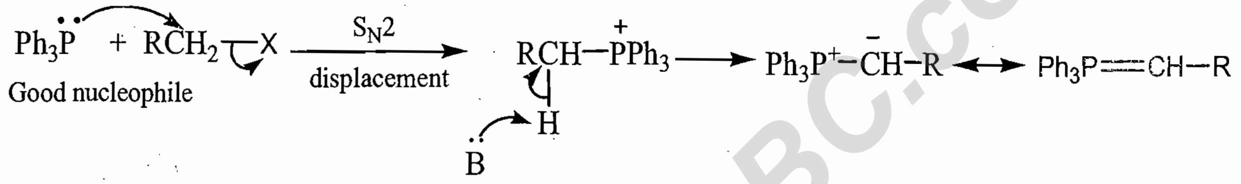
(Trimethyl phosphonium methylide)



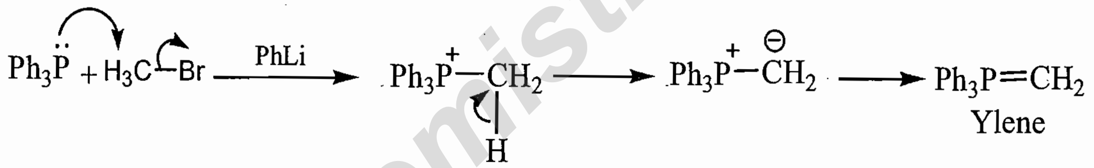
The dπ-pπ is not stable

NMR studies ^1H, ^{13}C, ^{31}P are consistent with the dipolar ylide structure and suggest only a minor contribution from ylene. (weaker dπ–Pπ bond)

Preparation of Ylide :



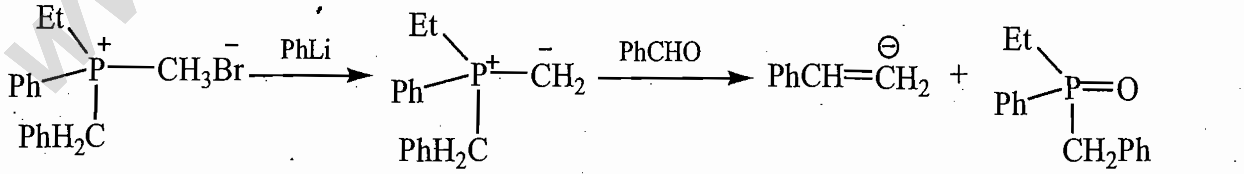
B = BuLi, NH_2^-, LiHMDS etc (strong bases)
X = I, Br, Cl
RX should be (1°/2°)

1\. 

2\. $CH_2=CH-CH_2Cl + Ph_3P \xrightarrow{NH_2^-} Ph_3P=CH-CH=CH_2$

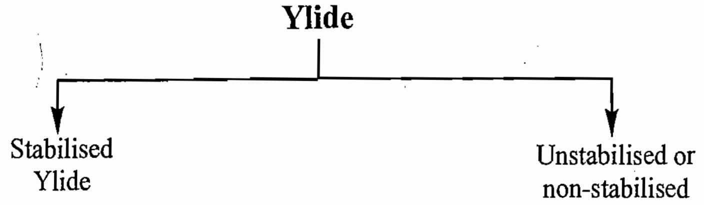
Evidences :

1. Currently accepted mechanism is that the initial addition is normally concerted giving directly the observed oxaphosphetane intermediate by NMR at low temperature.
2. Optically active phosphonium salt reacts to produced a phosphine oxide with retention of configuration.



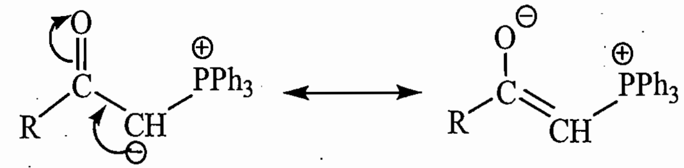
Geometry around P is preserved during the reaction

Types of Ylides :



Stabilised Ylide : If in a ylide the substituents on carbon are electron withdrawing, (ester, amide) then the negative charge on the ylide carbon can be delocalised in the substituent. This type of ylide with conjugated and anion stablizing substituents on adjacent to the negative charge is known as stabilised ylide.

As a result of delocalization, the nucleophilicity as well as reactivity of the ylide decreases. So stabilised ylide are stable but less reactive.

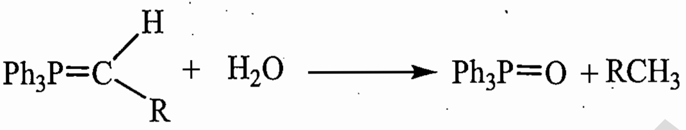


Nu⁻ Character decreases

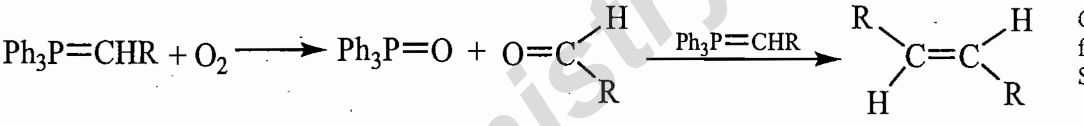
Non Stabilised Ylide :

Alkyl, (H) substituted phosphorous ylides with no electron withdrawing substituent on anionic carbon are known as unstabilised ylide. They react very readily or quickly with carbonyl and other polar groups, (rapidly with aldehyde and ketones).

Note: Reaction involving non-stabilised ylides must be done under anhydrous condition and in inert atmosphere to get the desired product because highly reactive unstabilised ylides also react with H_2O and oxygen.



$$Ph_3P{=}C(H)(R) + H_2O \longrightarrow Ph_3P{=}O + RCH_3$$

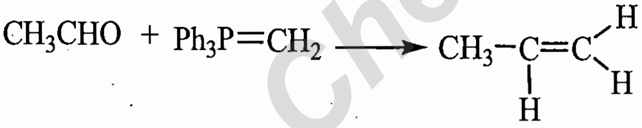


$$Ph_3P{=}CHR + O_2 \longrightarrow Ph_3P{=}O + O{=}C(H)(R) \xrightarrow{Ph_3P{=}CHR} RHC{=}CHR$$

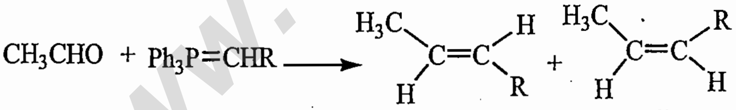
Symmetrical alkene

Good method for producing Syn alkene

Stereoselectivity of Wittig Reaction :



$$CH_3CHO + Ph_3P{=}CH_2 \longrightarrow CH_3{-}CH{=}CH_2$$

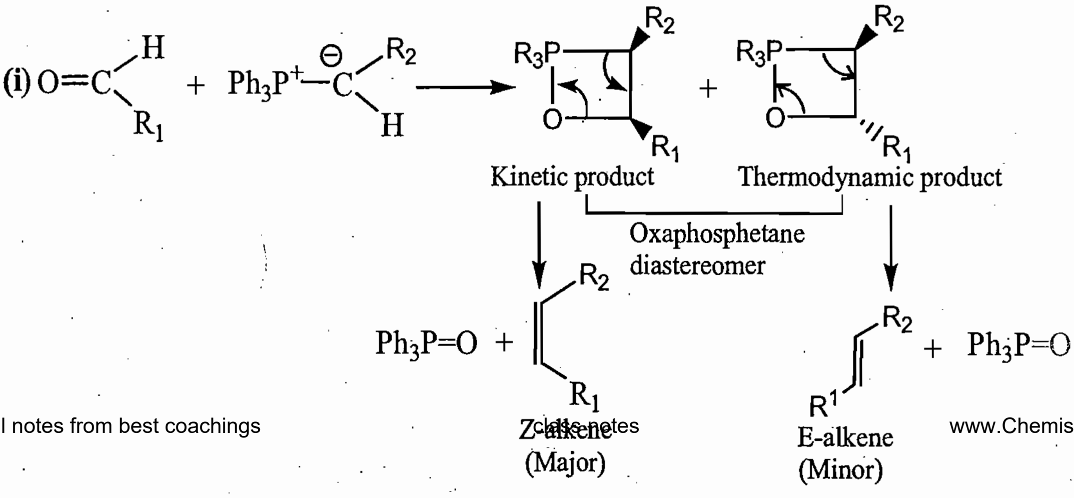


$$CH_3CHO + Ph_3P{=}CHR \longrightarrow H_3C(H)C{=}C(H)R + H_3C(H)C{=}C(R)H$$

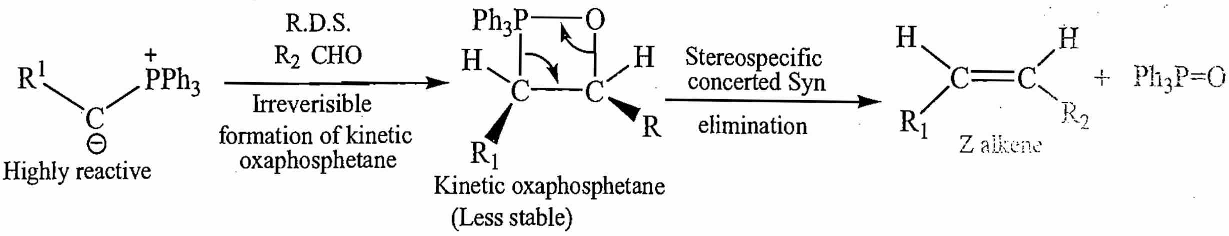
E-alkene Z-alkene

Non stabilised ylides predominantly give = Z-alkene. Stabilised ylides predominantly give = E-alkene

EXAMPLES



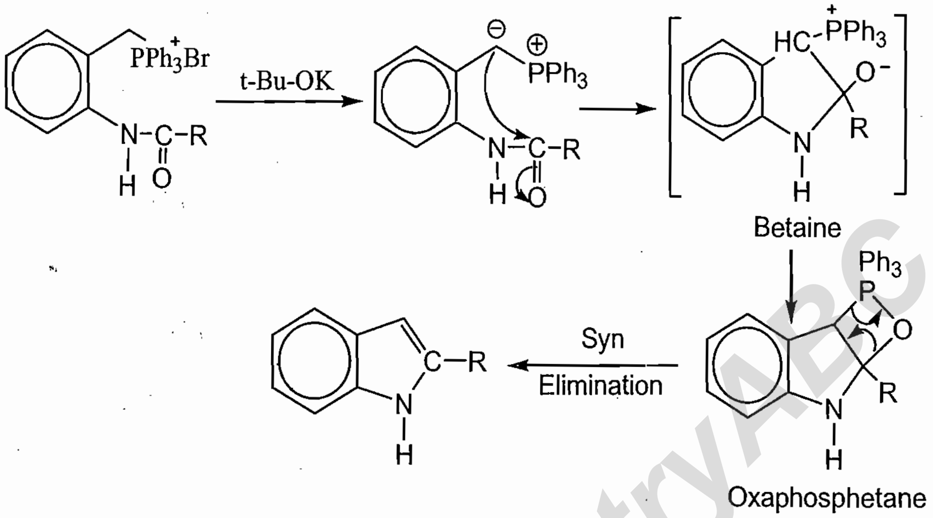
(ii)



Intramolecular Wittig Reaction :

To prepare alkenes:

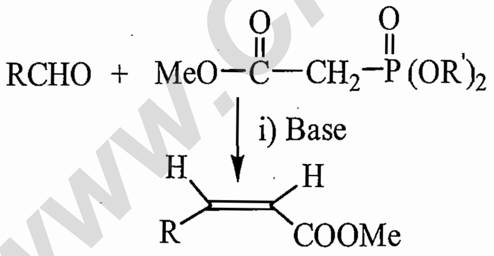
1. Mainly with stabilised ylide electrophile and nucleophile both are present in same compound.



Advantages :

1. Mainly useful with stabilised ylide and used to prepare α, β-unsaturated esters and other conjugated compound.
2. It has high selectivity for E-alkene and the E selectivity can be enhanced by using bulkier bis(isopropyl) phosphonate ester.

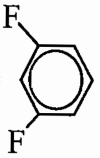
Exceptions: The modified phosphonate esters show Z-stereoselectivity in W-E reaction.



$$RCHO + MeO-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{P}}(OR')_2 \xrightarrow{\text{i) Base}} \text{(Z)-}RCH=CHCOOMe$$

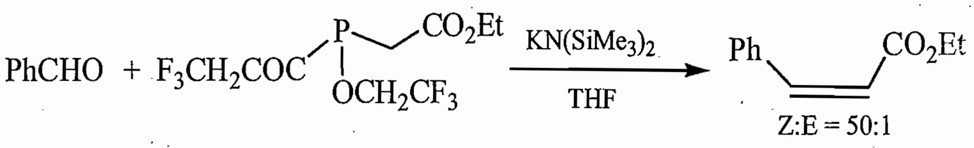
$R' = -CH_2CF_3$ (Trifluoroethyl)

$R' = -Ph$ (Phenyl)

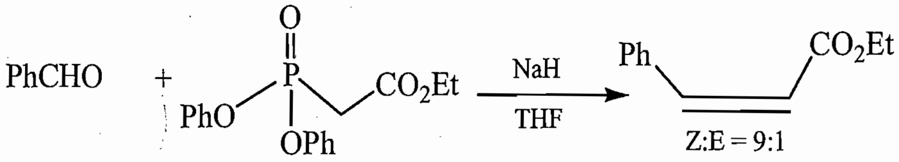
R' =  2, 6-difluoro phenyl

Examples:

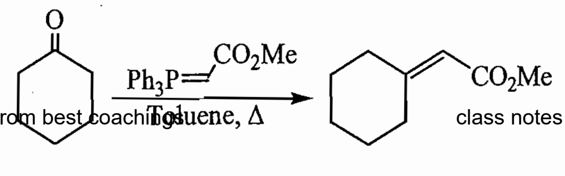
(i)



(ii)

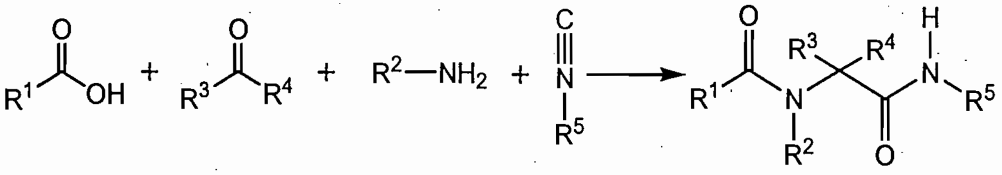


(iii)

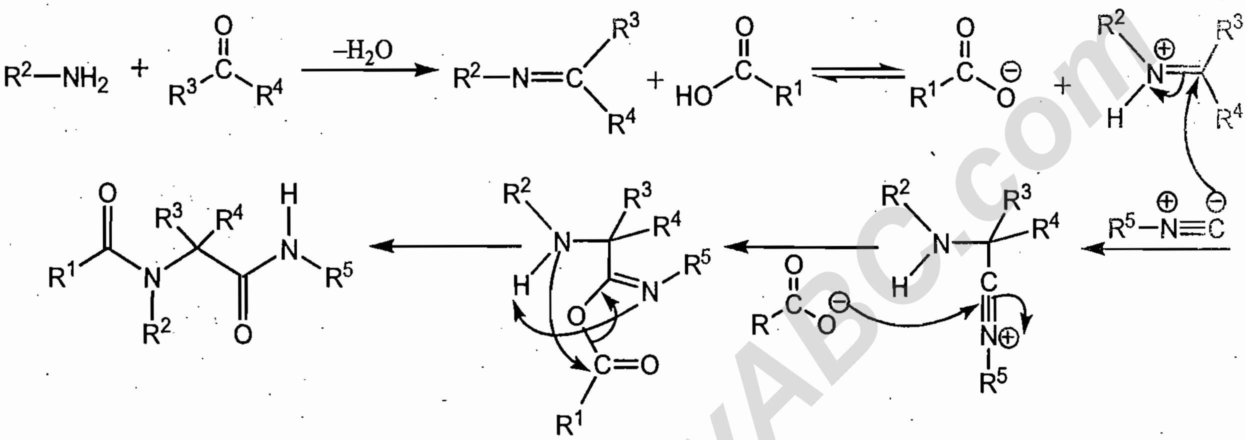


6.47. Ugi Reaction:

It is a multicomponent reaction occuring between an aldehyde, an amine, a carboxylic acid and an isocyanate which allows the rapid preparation of α -amino acyl amide derivatives.

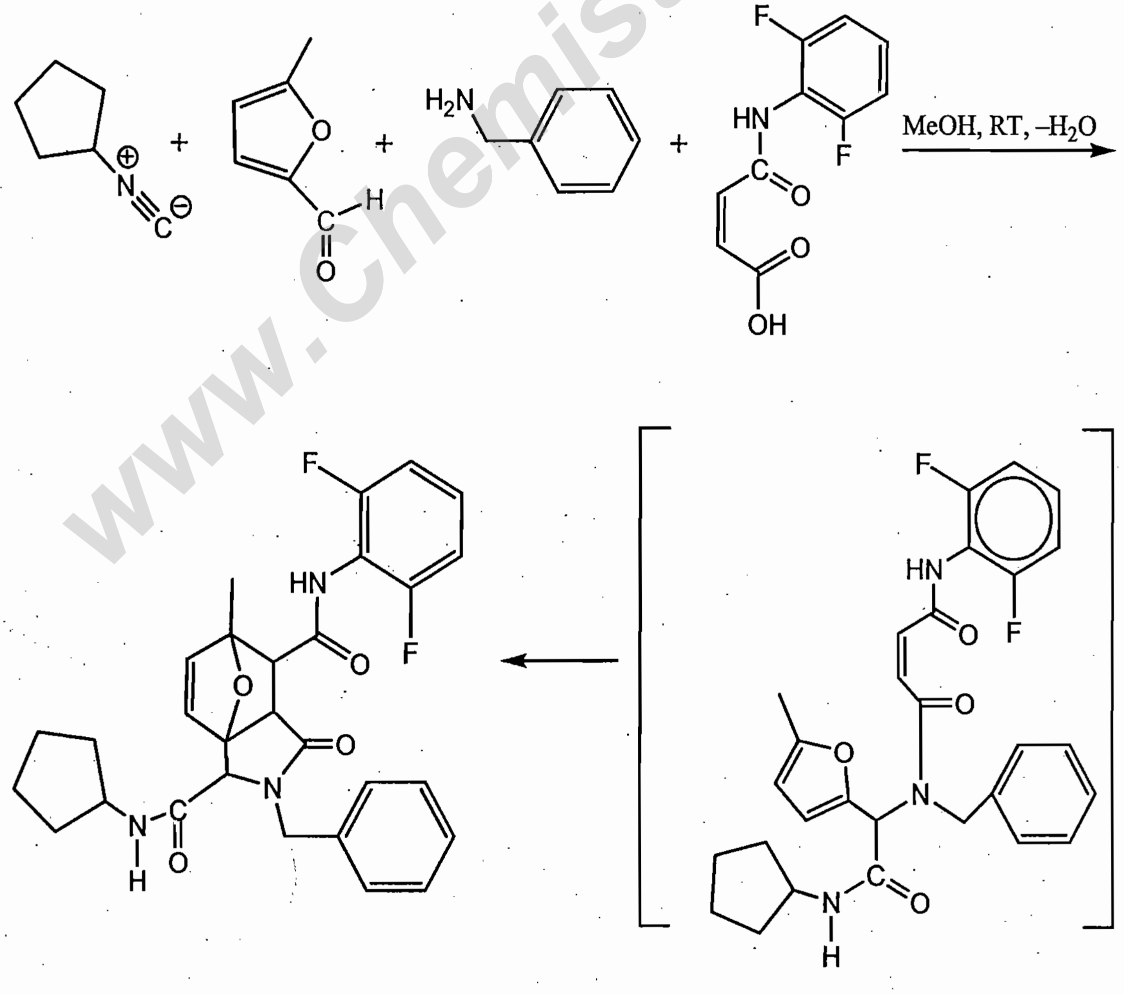


Mechanism:

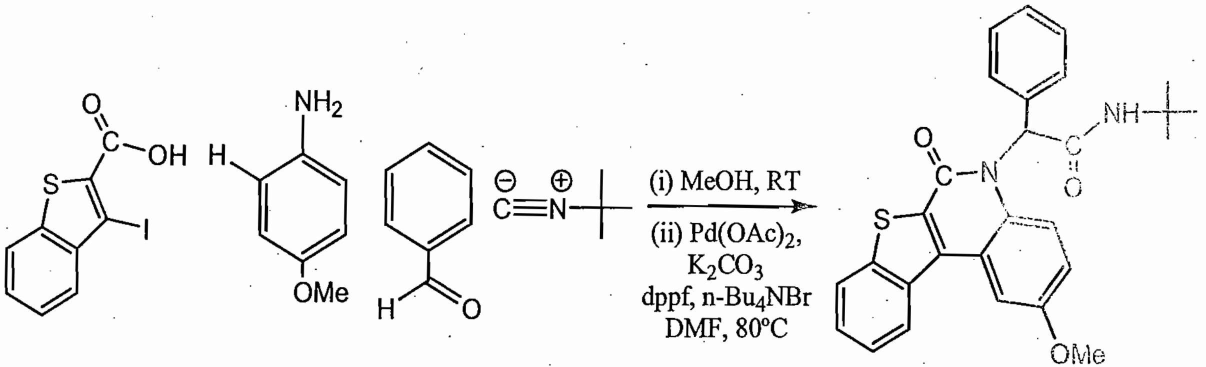


Examples:

1.

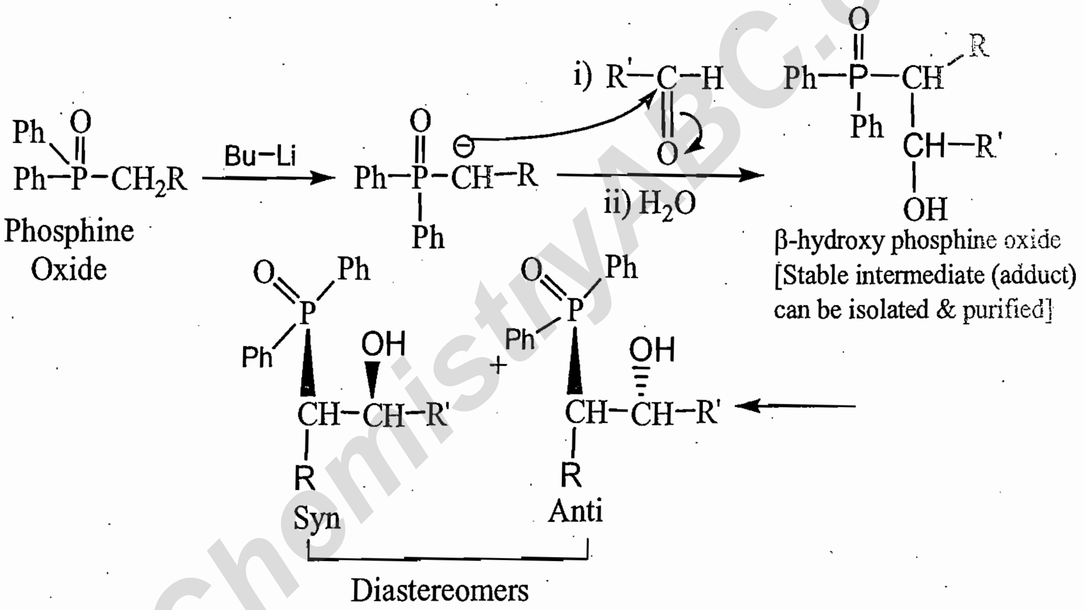


2.



6.48. Wittig - Horner Reaction

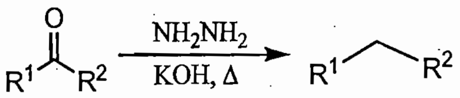
To overcome the problem of stereochemical outcome this reaction has been formulated. It uses carbanions derive from phosphine oxide to react with carbonyl compounds. The adducts (Intermediates) are stable which can be isolated and purified. The elimination is stereospecific which occurs by a syn pathway using 4 membered cyclic transition state just like that of wittig reaction. So the stereochemistry of the alkene depends on the stereochemistry of the intermediate adduct.



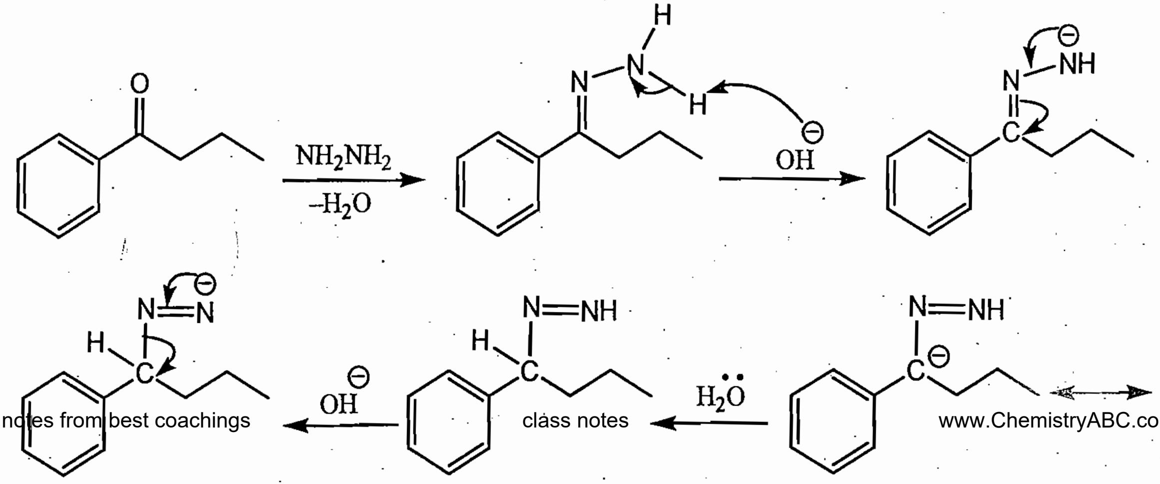
Anti - product – Z-alkene
Syn - product – E-alkene

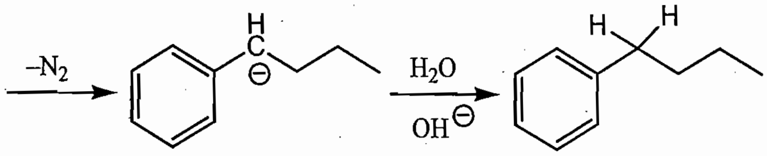
Wolff Kishner Reduction:

The Wolf Kishner Reduction is an organic reaction used to convert an aldehyde or ketone to an alkene using hydrozine, base and thermal conditions.



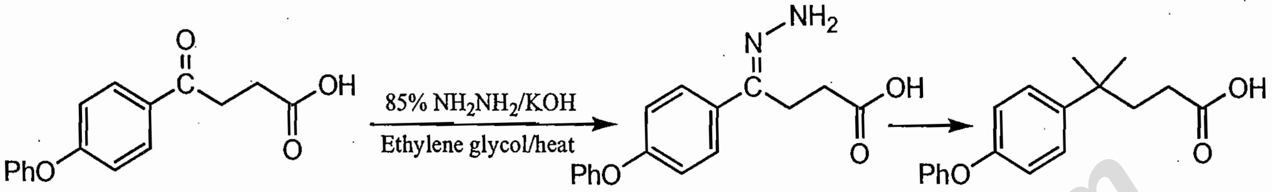
Mechanism:



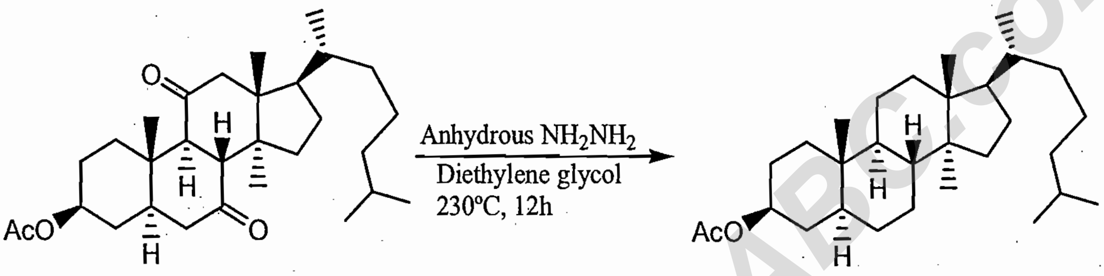

–N2
H2O
OH⊖

Example:

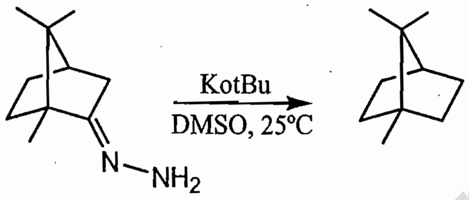
1\.


85% NH2NH2/KOH
Ethylene glycol/heat
PhO

2\.


Anhydrous NH2NH2
Diethylene glycol
230°C, 12h
AcO

3\.

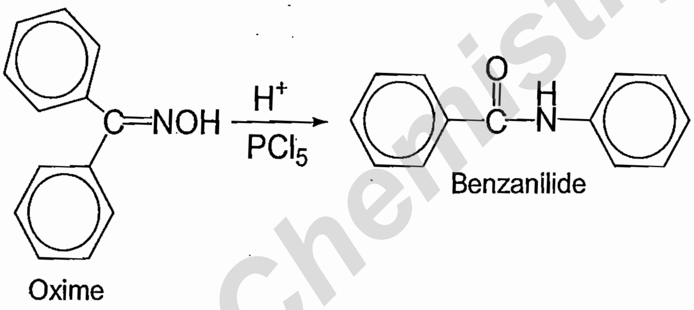

KotBu
DMSO, 25°C

CHAPTER 7

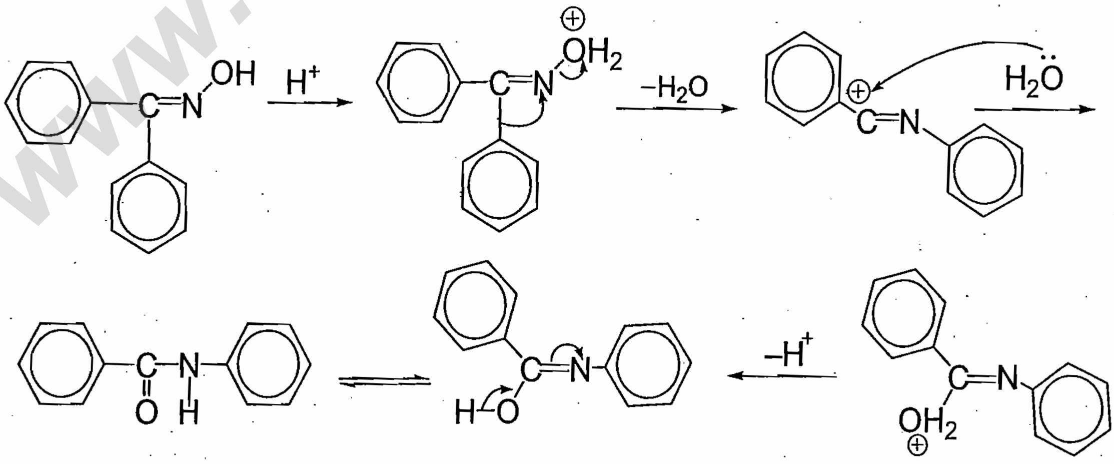
Rearrangement Reactions

7.1. *Beckmann Rearrangement*

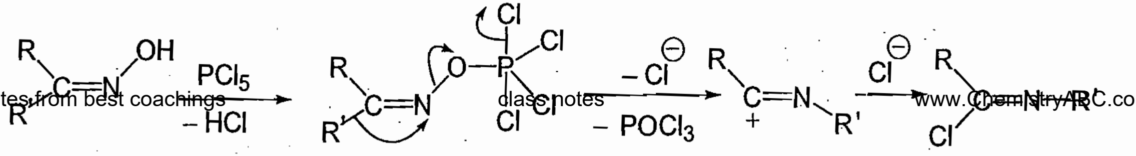
The rearrangement of oxime under the influence of a variety of acidic reagent to N-substituted amide. PCl_5 is commonly used as a catalyst in Beckmann Rearrangement but conc. H_2SO_4, polyphosphoric acid, formic acid, thionyl chloride, silica etc. have been used successfully. e.g.: Benzophenone oxime is converted into benzanilide in the presence of PCl_5. The role of these catalyst is to convert the hydroxyl group into a better leaving group.

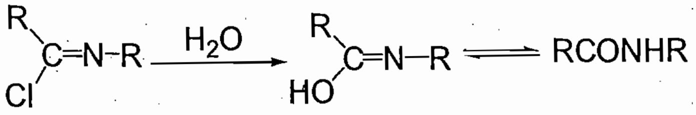


***Mechanism*:**

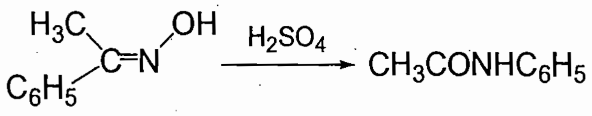


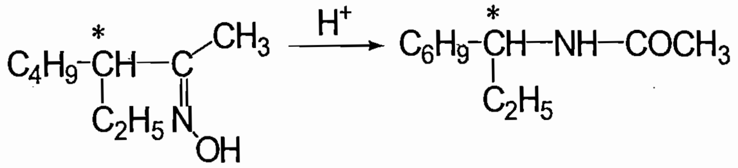
* It has been found that the electron withdrawing substituents (–R group) attached to the migrating aryl group retard the rate of reaction. The presence of electron donating group (+R group), on the otherhand, has an accelerating influence.





* This rearrangement is highly stereospecific that is the group anti to the oxime hydroxyl group always migrates regardless of relative migratory aptitude of the two groups. The chiral group migrate with retention of configuration.

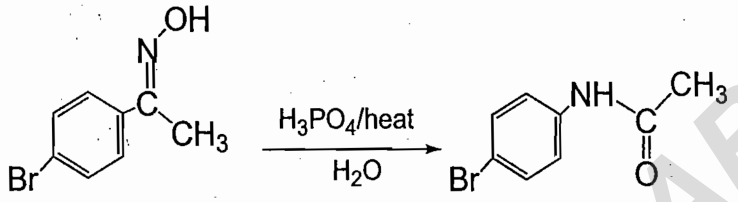




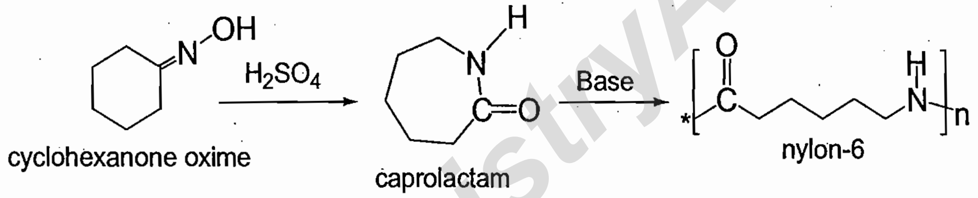
methyl - 3 - heptyl ketoxime 3 - acetamidoheptane (Retention)

***Examples*:**

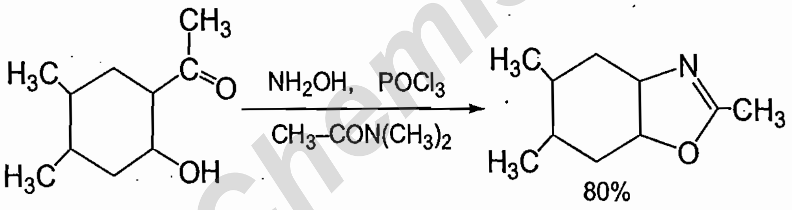
(i)

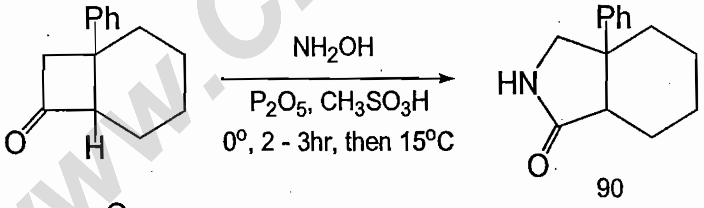


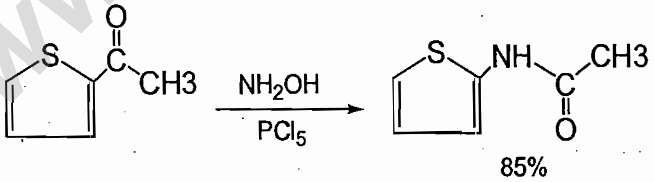
(ii)



(iii)



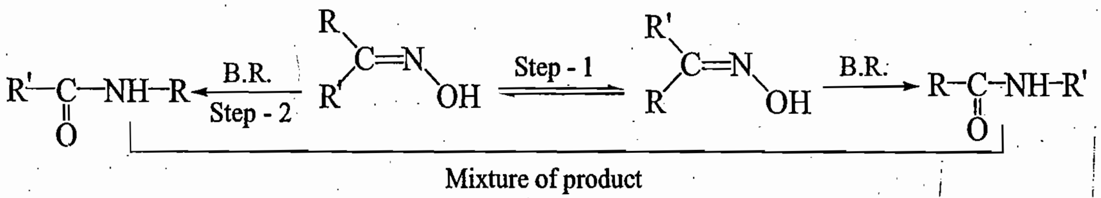




Drawbacks :

(1) Anti - Syn isomerisation of oxime. (2) Beckmann fragmentation

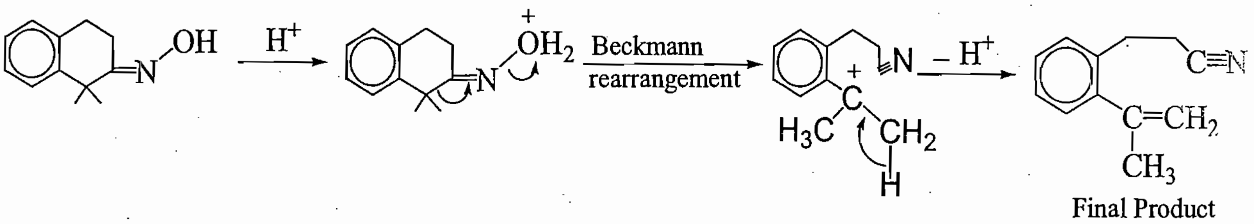
1. **Anti - syn isomerisation :** Some reaction condition can lead to syn-anti isomerization of the oxime occuring at the rate faster than the Beckmann rearrangement then a mixture of product will be obtained.

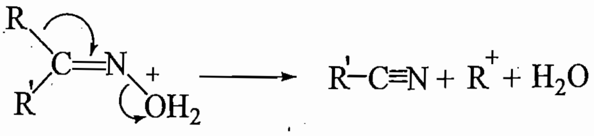


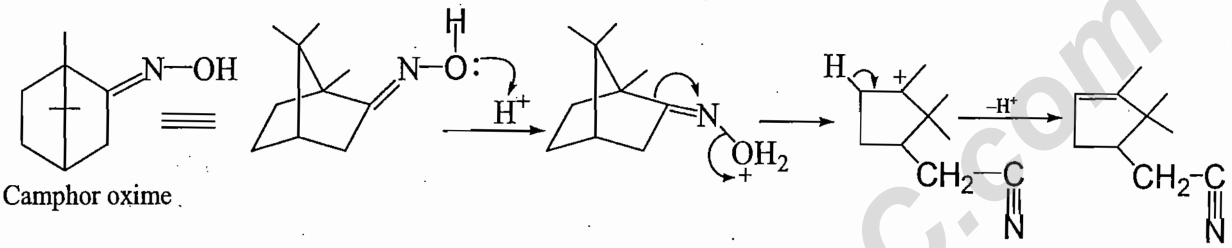
Rate (Step 1 > Step 2) – Product mixture

Rate (Step 2 > Step 1) – Pure product

2. **Fragmentation :** A fragmentation reaction occurs if one of the oxime substituent can give rise to a very stable carbocation and subsequent formation of nitrile (C≡N)

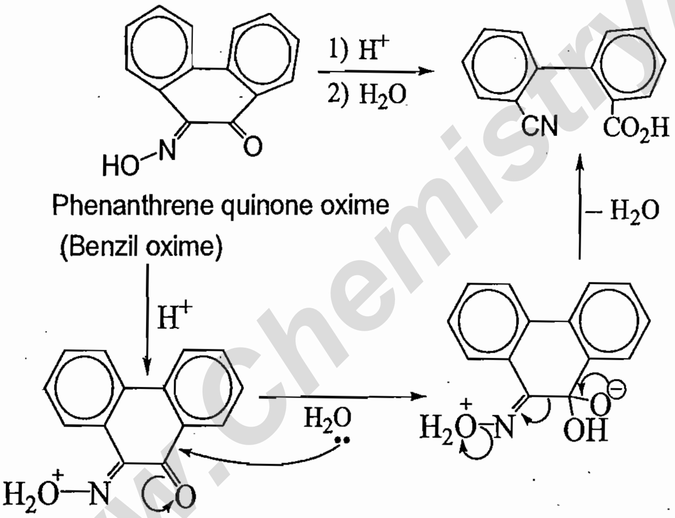






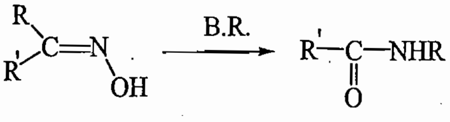
Fragmentation is favoured by reagents like PCl_5, $SOCl_2$, strong acids. While aryl sulphonyl chloride in pyridine or aquous alkali encourage rearrangement over fragmentation.

***Example*:**

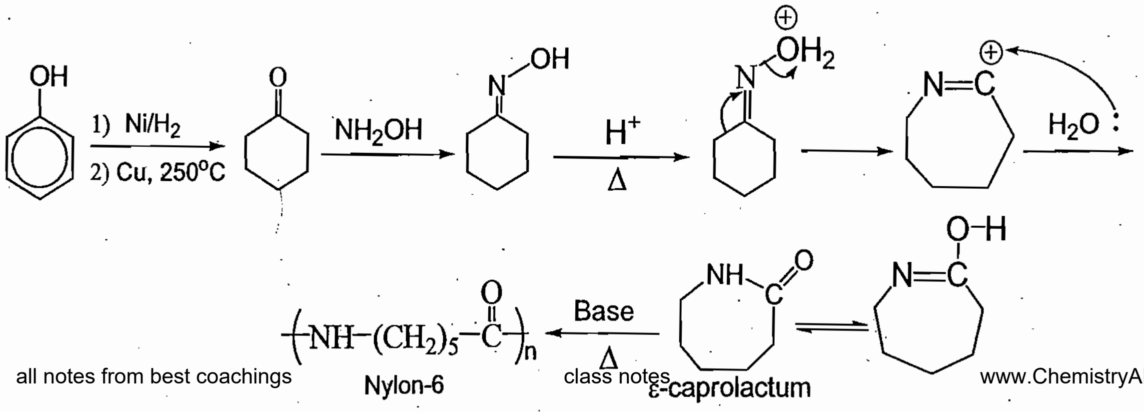


Application:

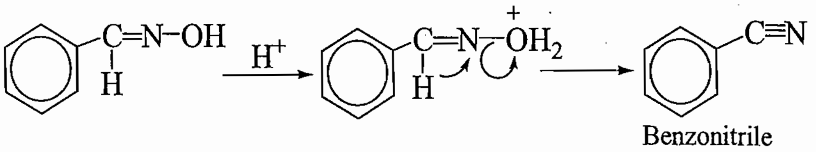
1. Configuration of ketoxime can be obtained.



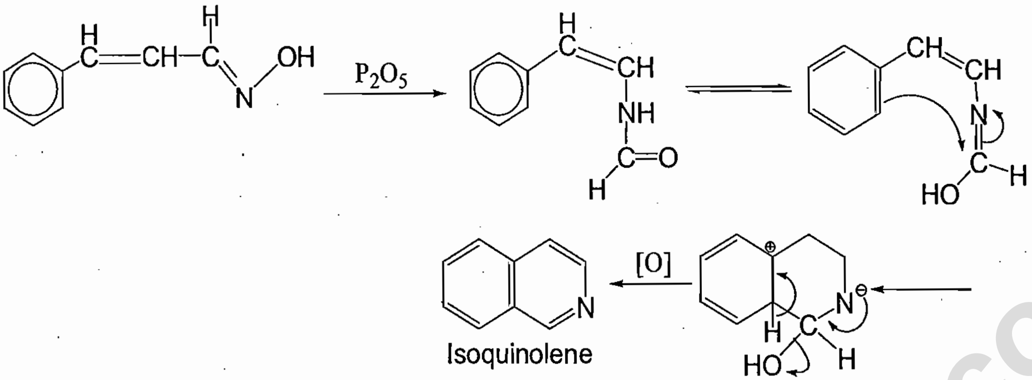
2. Synthesis of polymer – Nylon 6



3. Aldoxime under Beckmann rearrangement condition may dehydrate to nitriles

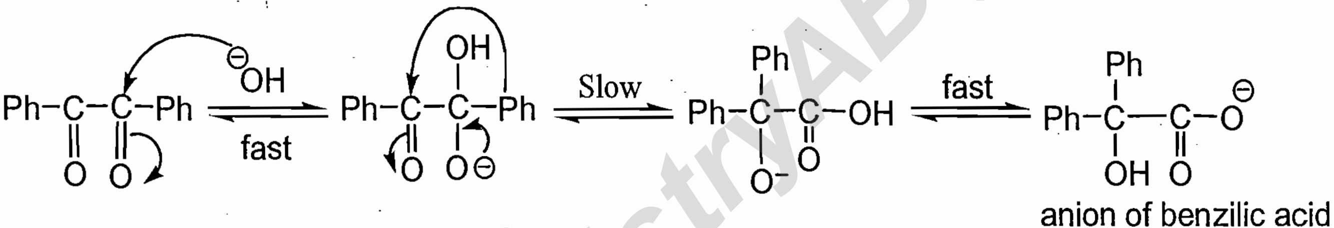


4. Synthesis of isoquinoline :

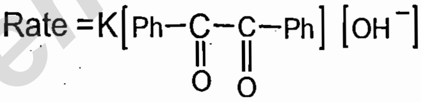


7.2. Benzil-benzilic acid Rearrangement

The base catalysed rearrangement of benzil (obtained from oxidation of benzoin) to produce the anion of a a-hydroxy acid known as benzilic acid is known as Benzil-Benzilic Acid Rearrangement.



Nucleophilic addition reaction of $Ph^{\ominus}$ on C=O



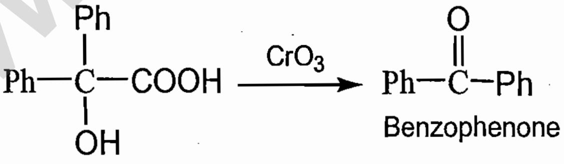
$$\text{Rate} = K\left[\mathrm{Ph{-}\underset{O}{\underset{\|}{C}}{-}\underset{O}{\underset{\|}{C}}{-}Ph}\right]\left[OH^{-}\right]$$

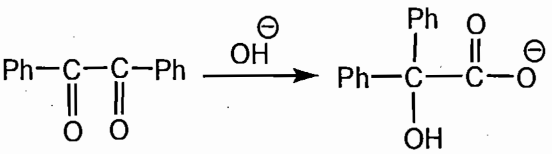
Second order reaction

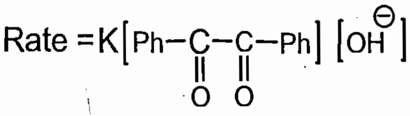
Properties of Benzilic Acid:

Melting point : 150°C

Oxidation :

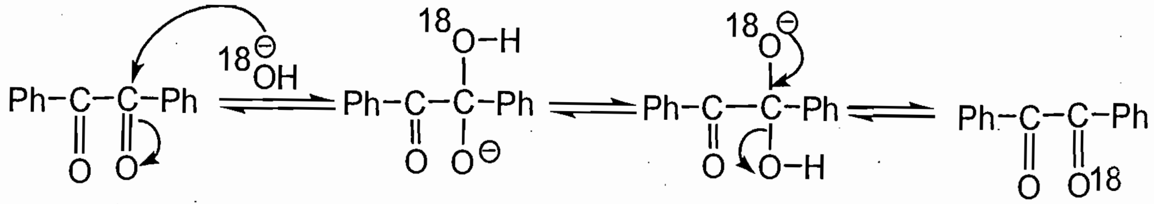






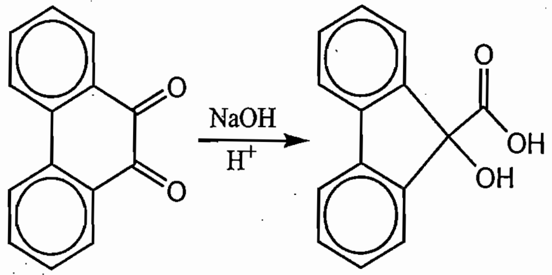
$$\text{Rate} = K\left[\mathrm{Ph{-}\underset{O}{\underset{\|}{C}}{-}\underset{O}{\underset{\|}{C}}{-}Ph}\right]\left[OH^{\ominus}\right]$$

It has been found that when reaction is carried out in $\left(H_2O^{18} \rightarrow {}^{18}OH^{-}\right)$ then the benzil exchanges ^{18}O faster than the rearrangement that is why it has been suggested that a fast reverrisible nucleophilic attack occurs at the carbonyl carbon in the initial step which is followed by rate determining migration of the aryl group.

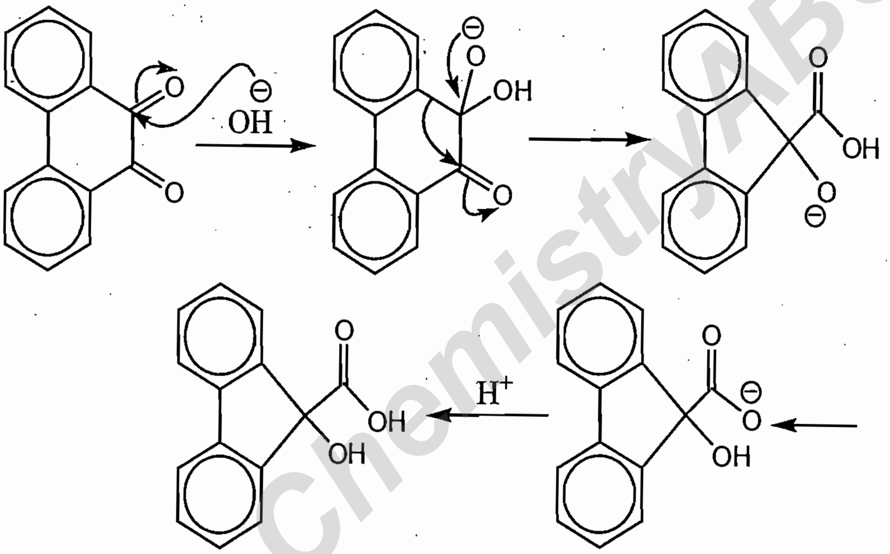


exchange of ^{18}O Showing that rearrangement is a slow step

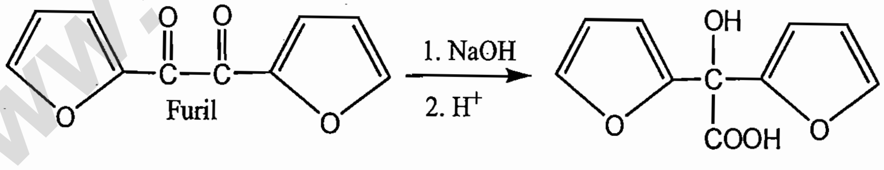
Problem:



Mechanism: $NaOH \longrightarrow Na^+ + OH^-$

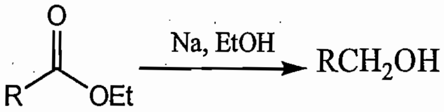


Problem:



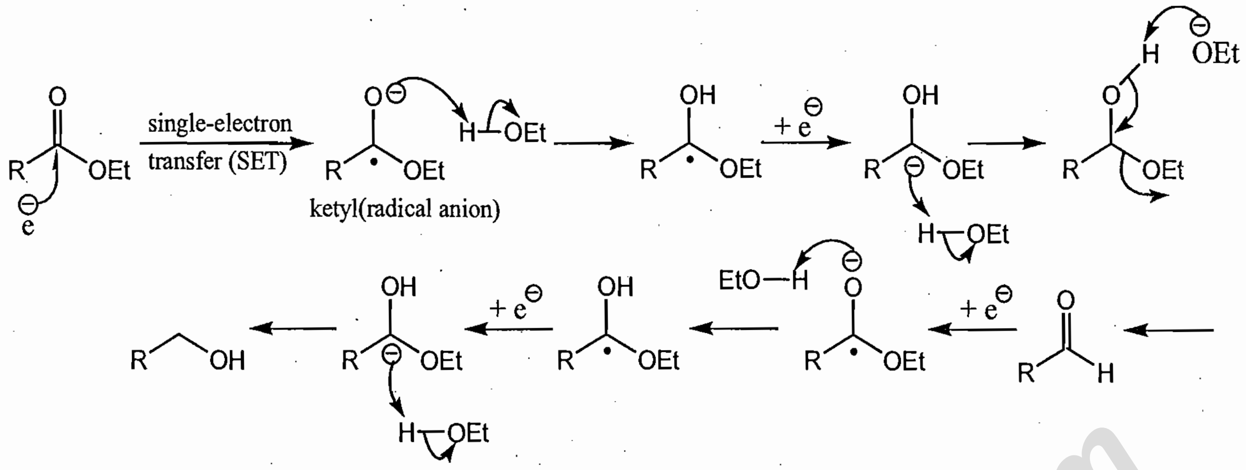
7.3. *Bouveault-Blanc Reduction*

The conversion of esters to the corresponding alcohols using sodium in an alcoholic solvent is known as Bouveault Blanc reduction.

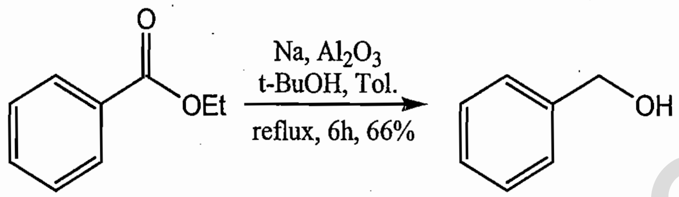


$$RCOOEt \xrightarrow{Na,\ EtOH} RCH_2OH$$

Mechanism:

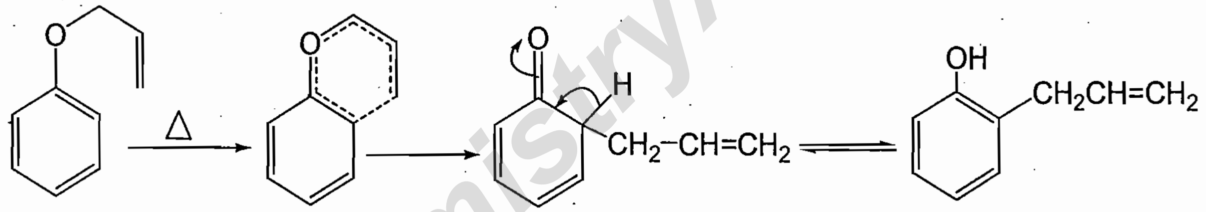


Example:

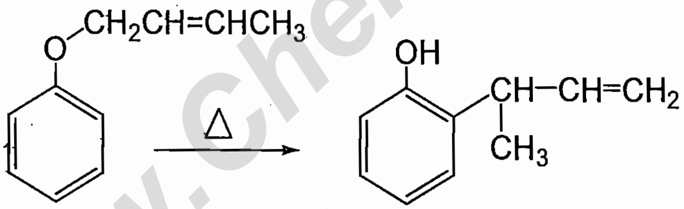


7.4. Claisen Rearrangement

Rearrangement of allyl aryl ether into *o* or *p*-allyl phenol through sigmatropic rearrangement. The allyl group migrate from oxygen to the ring preferably at ortho position.

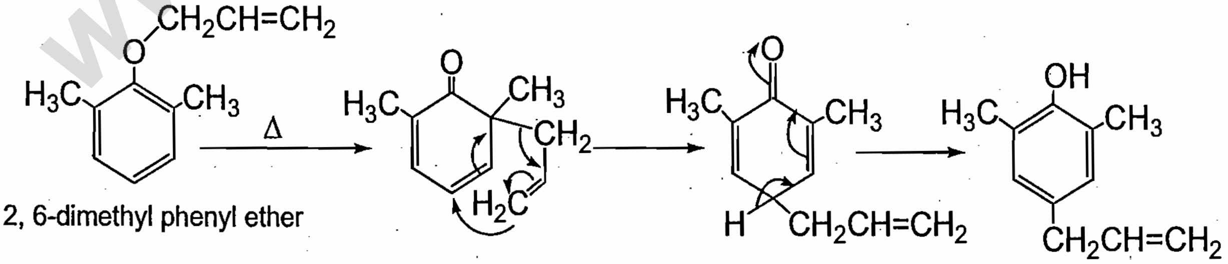


2-allyl phenyl ether cyclic transition state cyclohexadienone o-allylphenol



2-butenyl phenyl ether 2-(1-methyl(-2-propenyl) Phenol

Mechanism:

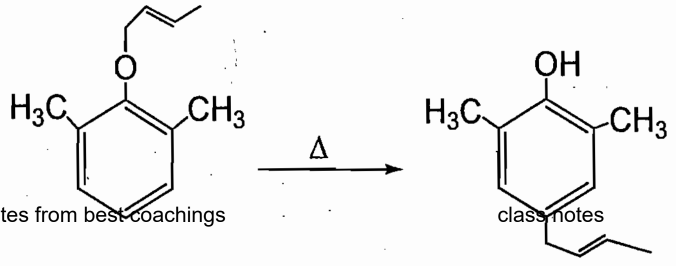


2, 6-dimethyl phenyl ether

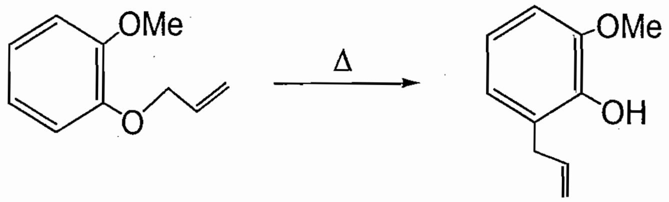
4-allyl (2, 6-dimethyl phenol)

Example:

(i)

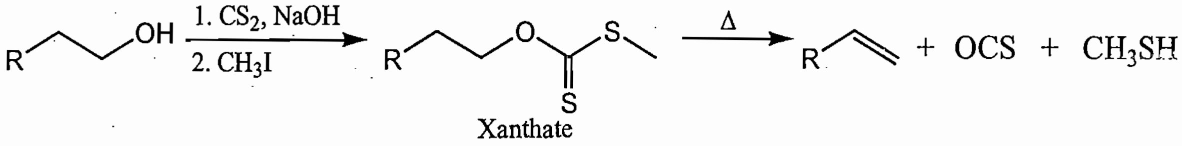


(ii)

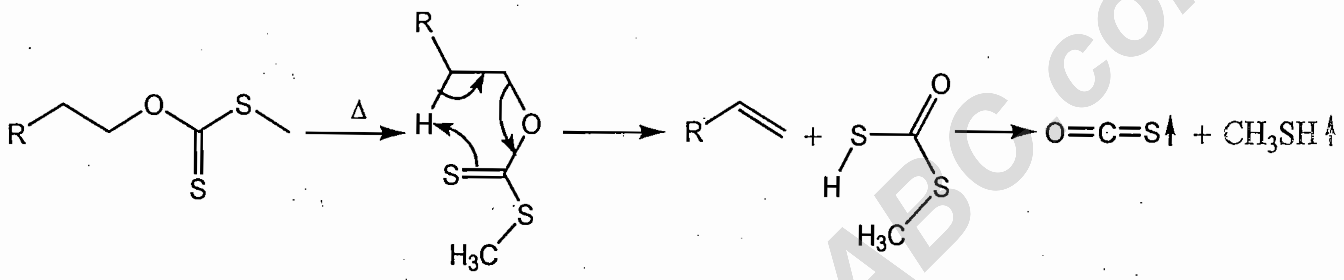


7.5. *Chugaev Elimination*

Thermal elimination of xanthates to olefins is known as Chugaev elimination.

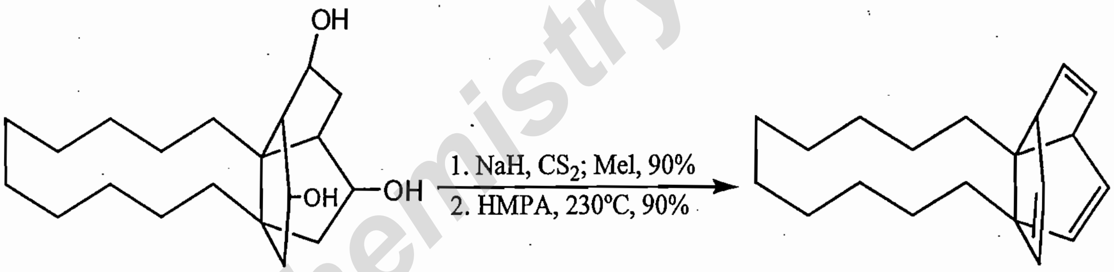


Mechanism:

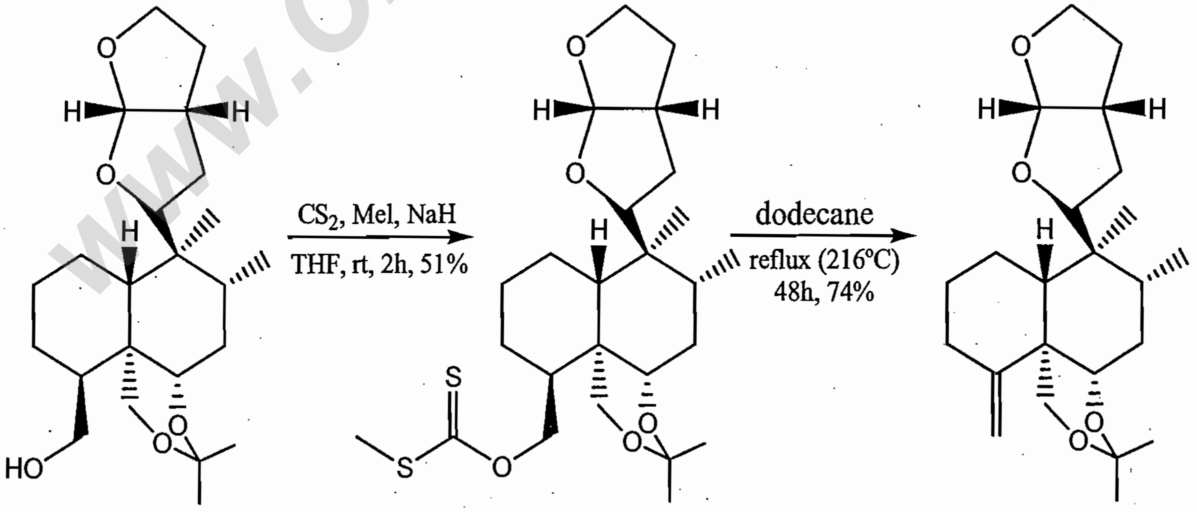


EXAMPLES

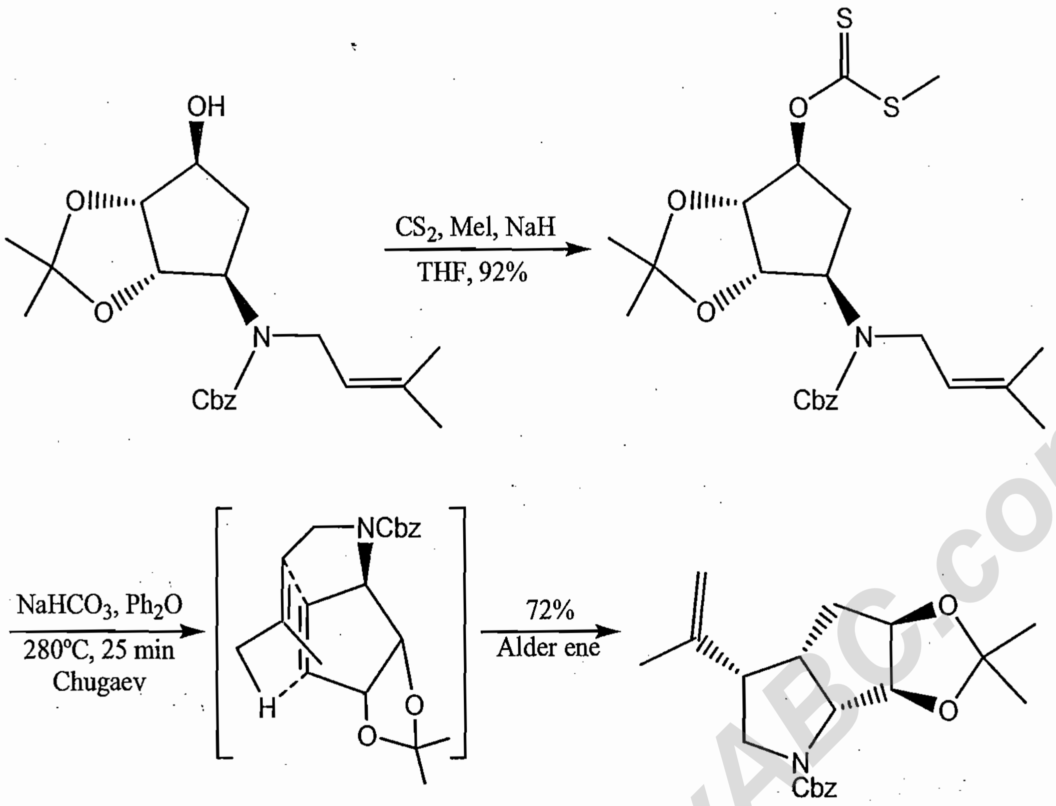
1.



2.

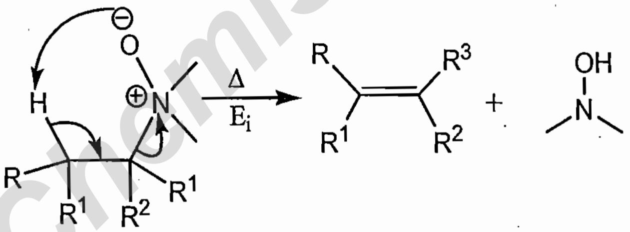


3. This reaction is an example of Chugaev syn-elimination is followed by an intramolecular ene reaction.



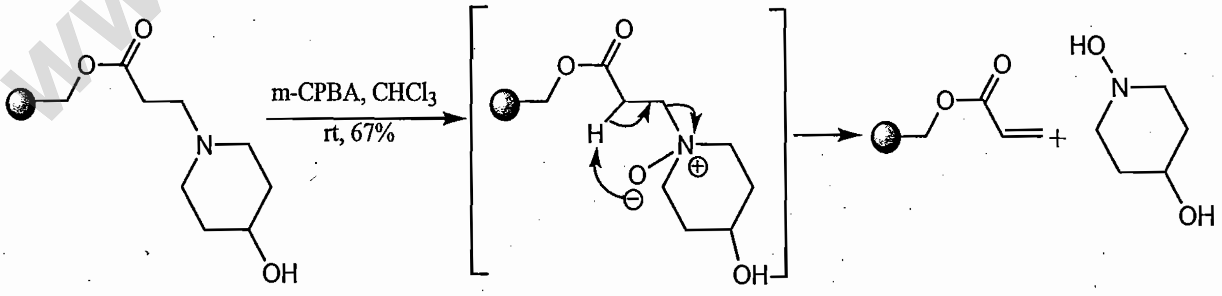
7.6. *Cope Elimination Reaction*

This reaction includes thermal elimination of N-oxides to olefines and N-hydroxyl amines.

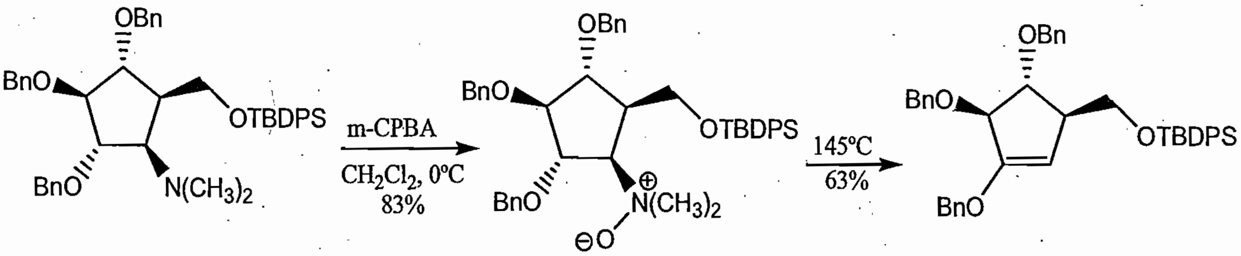


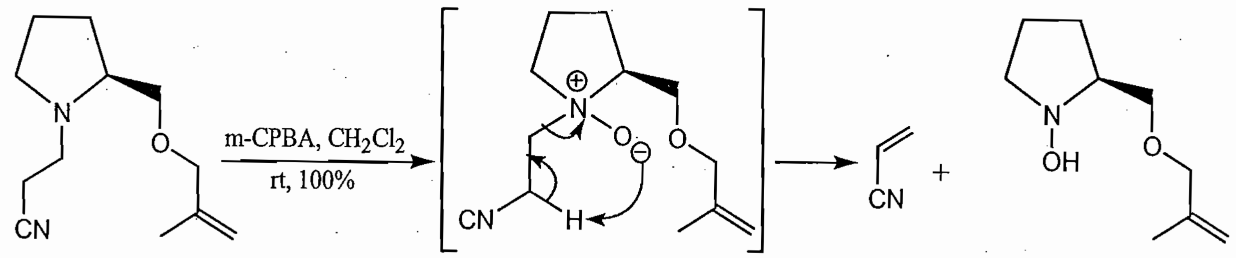
PROBLEMS

1. Solid-phase Cope elimination.

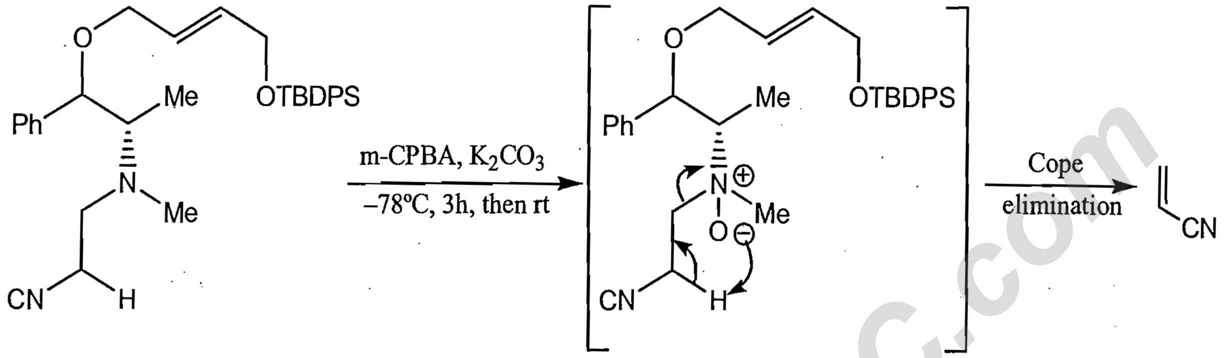


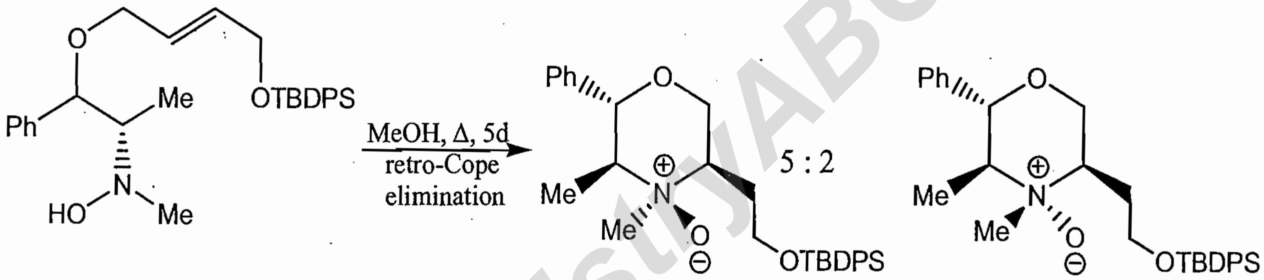
2.



3. 

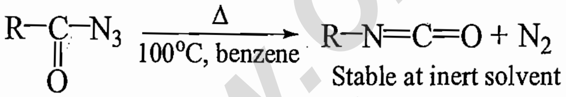
4. Retro-Cope elimination:





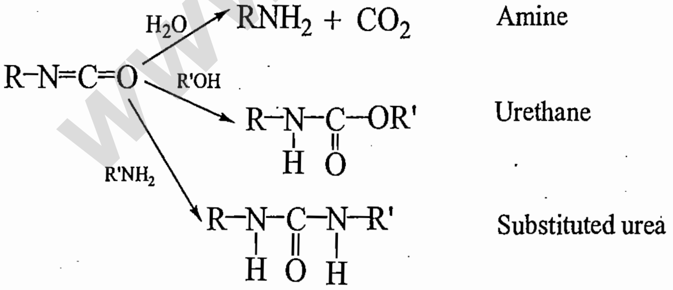
7.7. *Curtius Rearrangement*

It involves the decomposition of acyl azides in an inert solvent (benzene) by heating to isocyanate; the temperature required is around 100°C. The isocyanate can be converted to amine by adding H_2O, to urethane by adding alcohol and to substituted urea by adding amine. The conversion of acyl azide to isocyanates uses curtius rearrangement followed by conversion to amines, urethanes, etc. is known as curtius rearrangement.



$$R-\underset{\underset{O}{\|}}{C}-N_3 \xrightarrow[100^\circ C,\ benzene]{\Delta} R-N=C=O + N_2$$

Stable at inert solvent

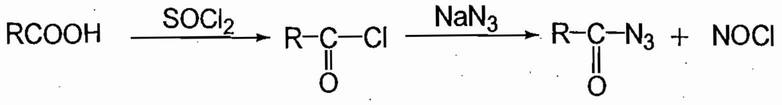


Ester of carbonic acid is called urethane.

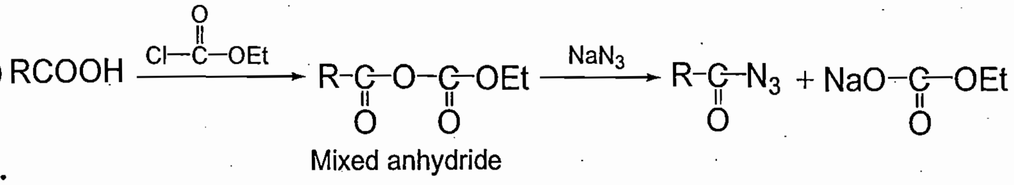
The reaction is general and can be applied to aliphatic, aromatic, heterocyclic and unsaturated acids. The other functional group remain unaffected during the reaction.

1. **Acyl azide preparation :** Reacting sodium azide (NaN_3) with a reactive acylating agent made from acid.

$$NaN_3 = Na-\overset{\ominus}{N}-\overset{+}{N}\equiv N$$

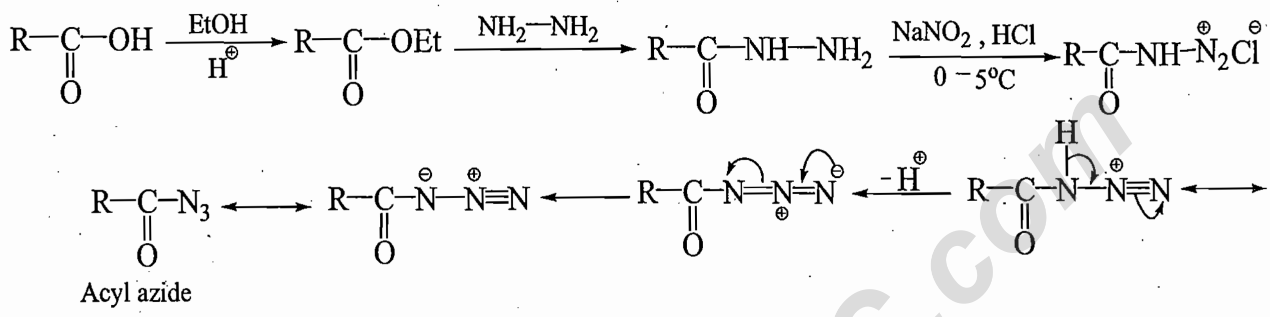
(i)


$$\mathrm{RCOOH} \xrightarrow{SOCl_2} R{-}\underset{\underset{O}{\|}}{C}{-}Cl \xrightarrow{NaN_3} R{-}\underset{\underset{O}{\|}}{C}{-}N_3 + NOCl$$

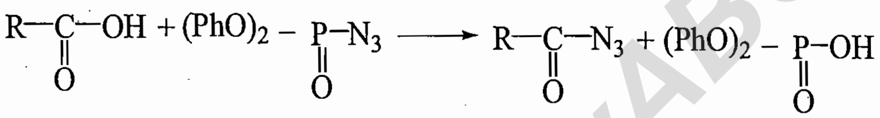
(ii)


$$\mathrm{RCOOH} \xrightarrow{Cl-\overset{\overset{O}{\|}}{C}-OEt} R{-}\underset{\underset{O}{\|}}{C}{-}O{-}\underset{\underset{O}{\|}}{C}{-}OEt \xrightarrow{NaN_3} R{-}\underset{\underset{O}{\|}}{C}{-}N_3 + NaO{-}\underset{\underset{O}{\|}}{C}{-}OEt$$

2. **By diazotisation of acyl hydrazide :**



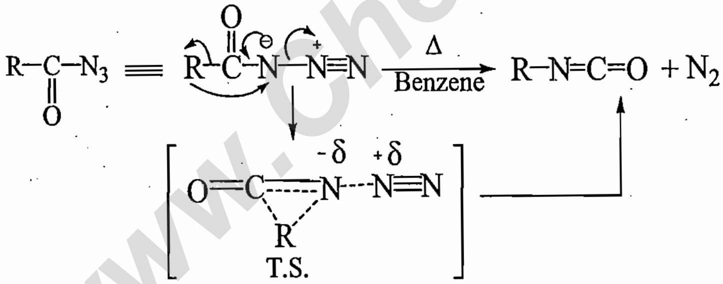
3. **Using diphenyl phosphoryl azide :**

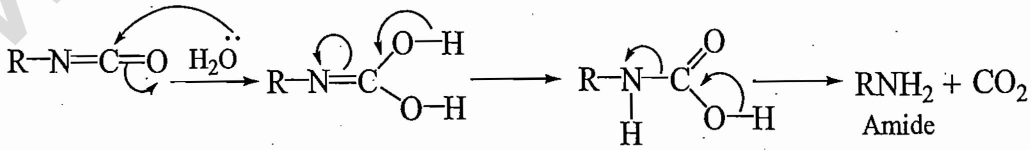


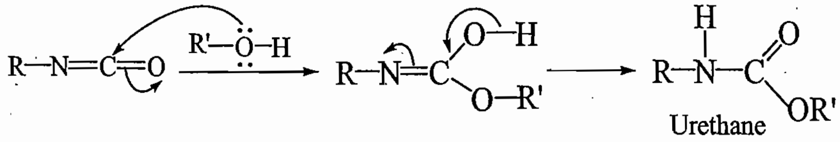
$$R{-}\underset{\underset{O}{\|}}{C}{-}OH + (PhO)_2 - \underset{\underset{O}{\|}}{P}{-}N_3 \longrightarrow R{-}\underset{\underset{O}{\|}}{C}{-}N_3 + (PhO)_2 - \underset{\underset{O}{\|}}{P}{-}OH$$

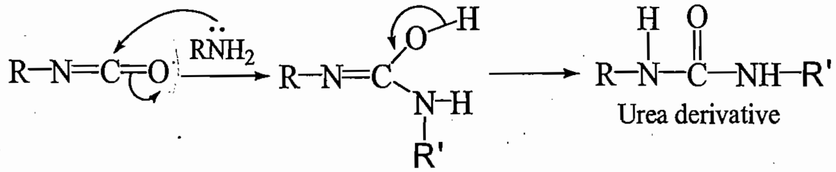
***Mechanism* :**

The rearrangement is a concerted process in which the migration of the R group is accompanied by the loss of N_2. So removal of N_2 is driving force and also derives the reaction forward. The migrating group retains the stereochemical consideration (If chiral during the rearrangement. like that of Hoffinann rearrangement) No cross over products are obtained suggesting that it is strictly intramolecular process. Since there is no evidence for the formation of the $R{-}\underset{\underset{O}{\|}}{C}{-}\ddot{N}$, hence the rearrangement step is concerted.



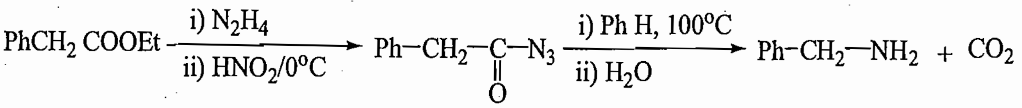
(a)


(b)


(c)


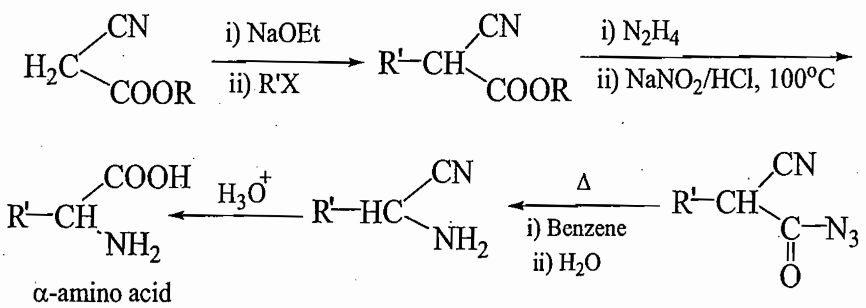
Applications :

1. **Synthesis of 1° amine:**

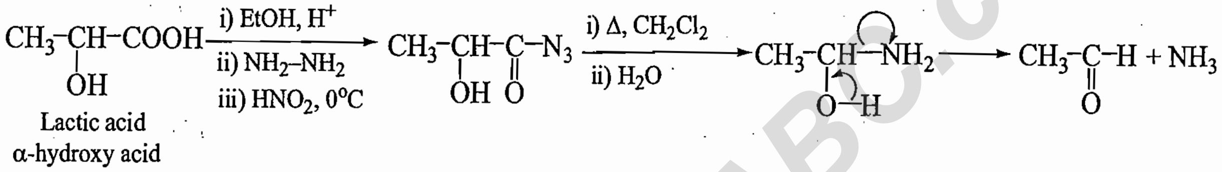


$$PhCH_2COOEt \xrightarrow[\text{ii) } HNO_2/0^\circ C]{\text{i) } N_2H_4} Ph-CH_2-\underset{\underset{O}{\|}}{C}-N_3 \xrightarrow[\text{ii) } H_2O]{\text{i) Ph H, } 100^\circ C} Ph-CH_2-NH_2 + CO_2$$

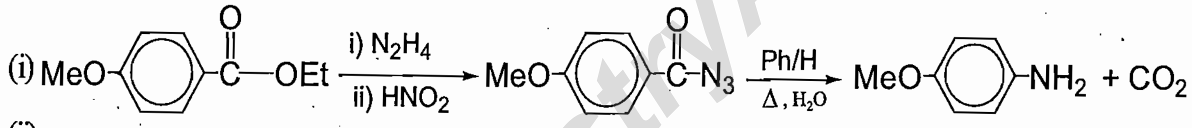
2. **Synthesis of a-amino acids:**



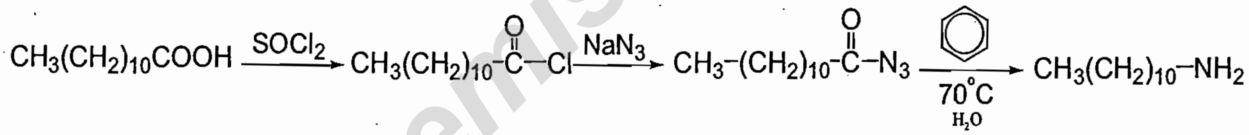
3. **Synthesis of Aldehydes :**

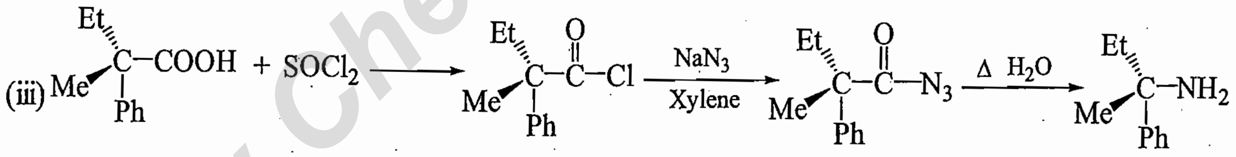


***Example*:**



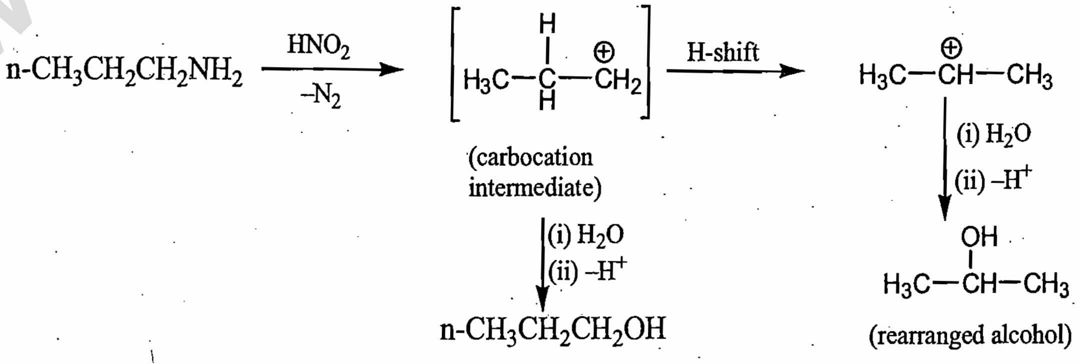
(ii)



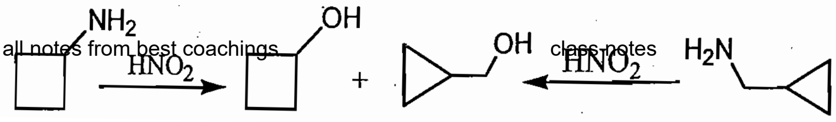


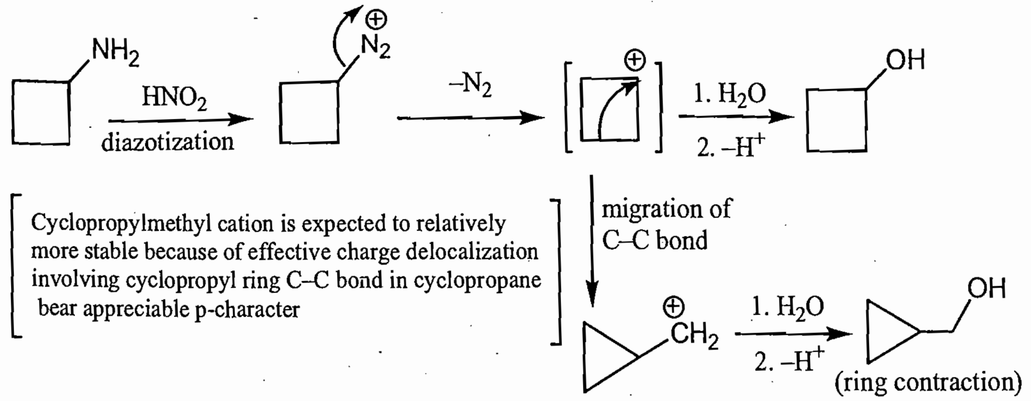
7.8. *Demjanov Rearrangement*

Rearrangement reaction of carbocations formed by diazotization of primary amines leading to the formation of rearranged alcohols is termed as Demjanov rearrangement. Thus, n-propylamine on treatment with nitrous acid yields minor amount of n-propyl alcohol together with a major proportion of isopropyl alcohol.

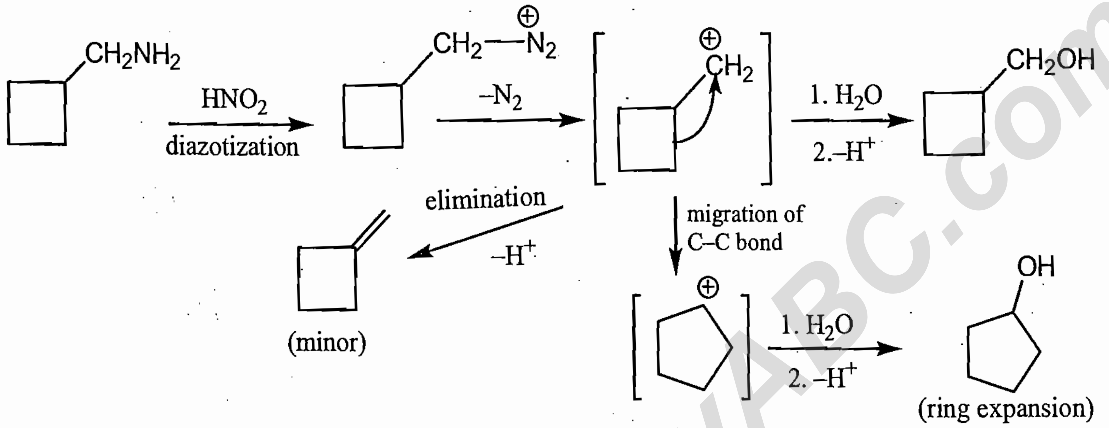


This reaction makes the basis of Demjanov's method of contracting and expanding alicyclic ring systems. Ring contraction takes place when a positive charge is formed on an alicyclic carbon, and ring expansion occurs when the positive charge is placed on a carbon α to an alicylic ring.



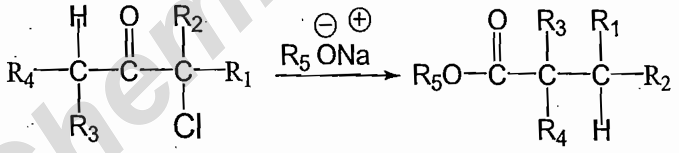


Cyclopropylmethyl cation is expected to relatively more stable because of effective charge delocalization involving cyclopropyl ring C–C bond in cyclopropane bear appreciable p-character



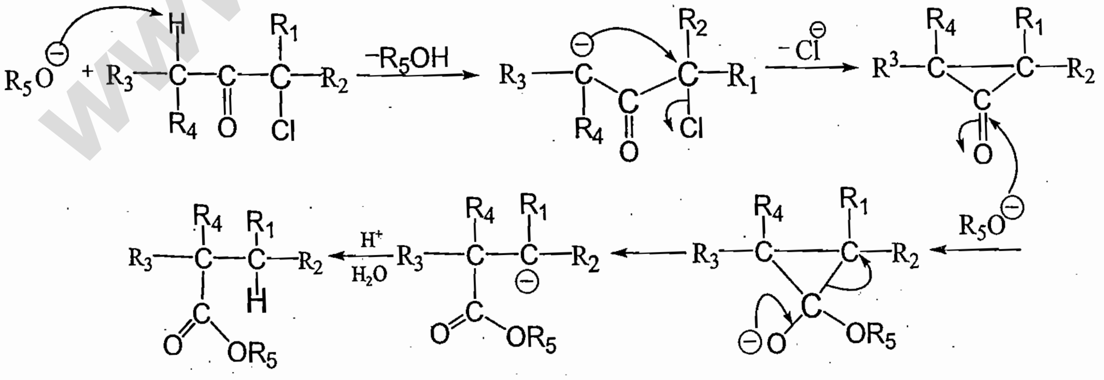
7.9. *Favorskii Rearrangement*

The base - catalysed rearrangement of α -halo ketone (chloro/bromo) to carboxylic acid derivative is known as Favorskii rearrangement.



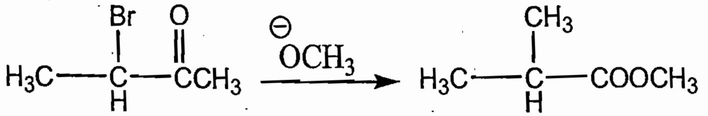
$$R_4-\overset{H}{\underset{R_3}{C}}-\overset{O}{\overset{\|}{C}}-\overset{R_2}{\underset{Cl}{C}}-R_1 \xrightarrow{R_5\overset{\ominus}{O}\overset{\oplus}{Na}} R_5O-\overset{O}{\overset{\|}{C}}-\overset{R_3}{\underset{R_4}{C}}-\overset{R_1}{\underset{H}{C}}-R_2$$

Mechanism:



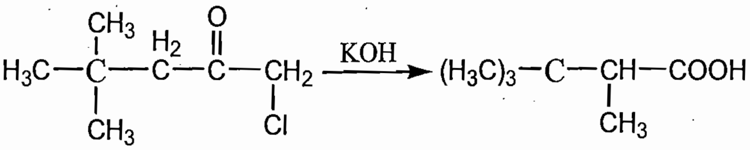
PROBLEMS

(i)



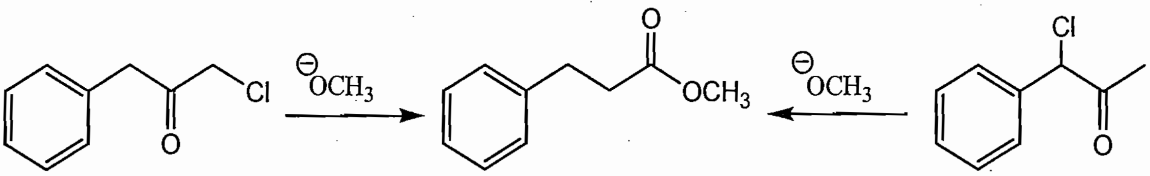
$$H_3C-\overset{Br}{\underset{H}{C}}-\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow{\overset{\ominus}{O}CH_3} H_3C-\overset{CH_3}{\underset{H}{C}}-COOCH_3$$

(ii)

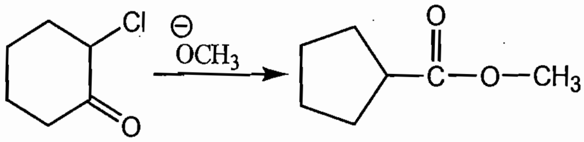


$H_3C-C(CH_3)_2-CH_2-CO-CH_2Cl \xrightarrow{KOH} (H_3C)_3-C-CH(CH_3)-COOH$

(iii)

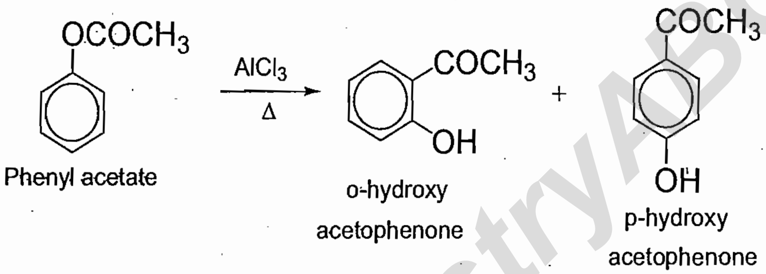


(iv)



7.10. *Fries Rearrangement*

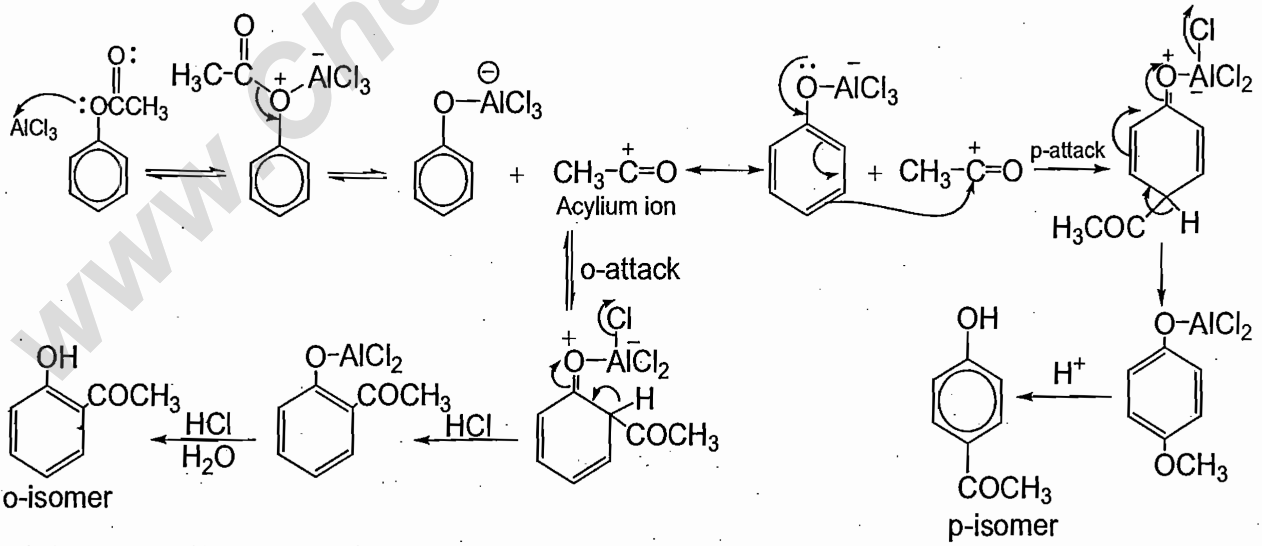
Ester of phenol can undergo rearrangement on heating with anhydrous aluminium chloride [lewis acid] to form phenolic ketone.



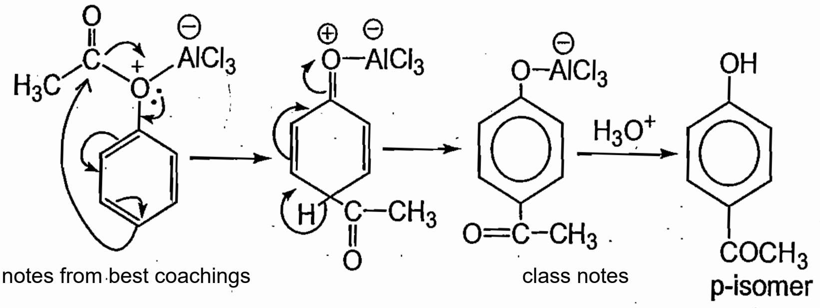
Mechanism :

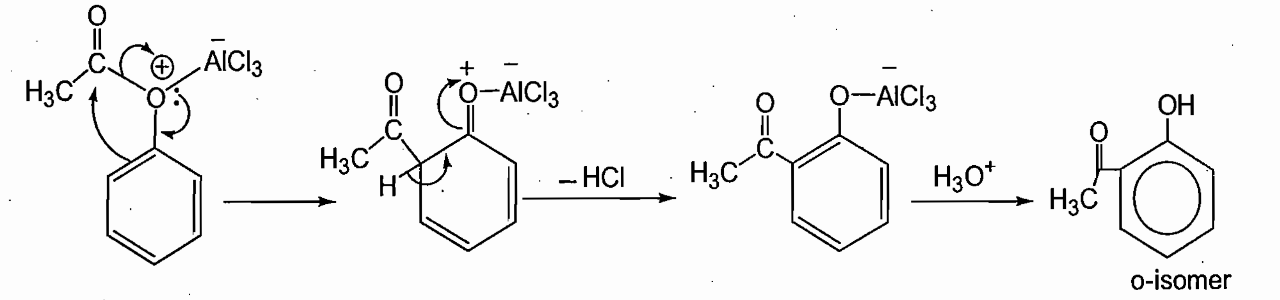
Evidences for both the intermolecular & intramolecular have been found suggesting that both mechanism operates simultaneously.

(1) Intermolecular Mechanism :



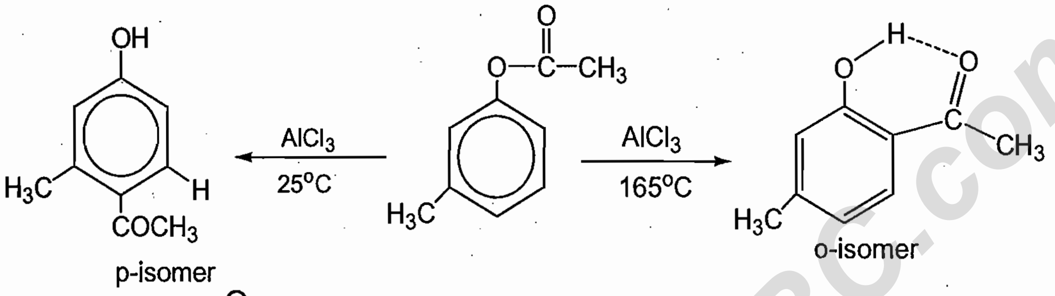
(2) Intramolecular Mechanism :



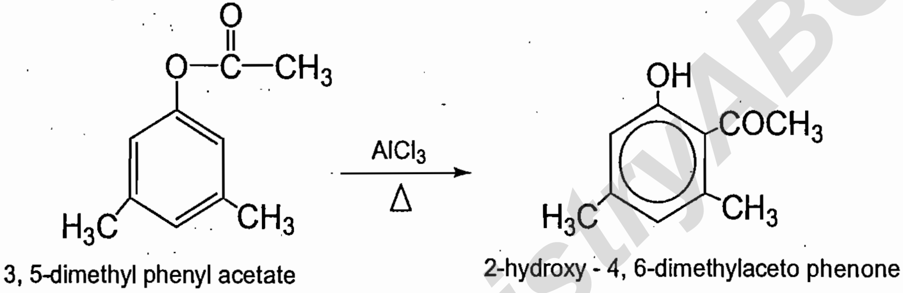


- In general, low temperature (<160°C) favour the formotion of p-isomers and higher temperature (> 160°C) favour the formation of the o-isomer. The mixture of o and p-isomer resulting from fries rearrangement can be repeated by steam distillation o-isomers are intramolecular hydrogen bonded and have greater volatility.

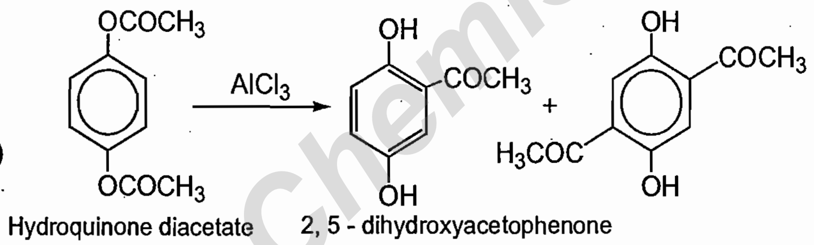
(i)



(ii)



(iii)



Evidences:

1. Evidence for intramolecular process has been obtained from trapping experiments while cross-over experiments support the intermolecular path way.

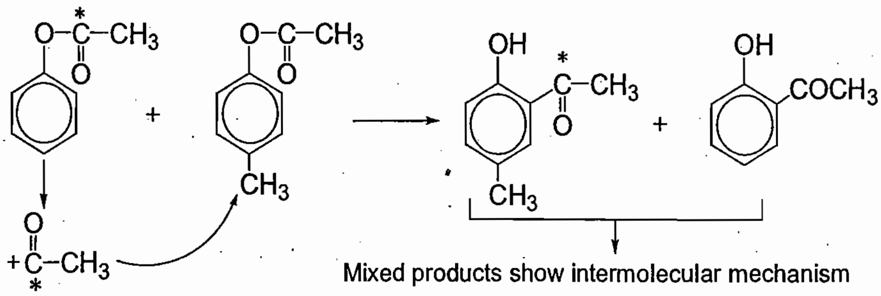
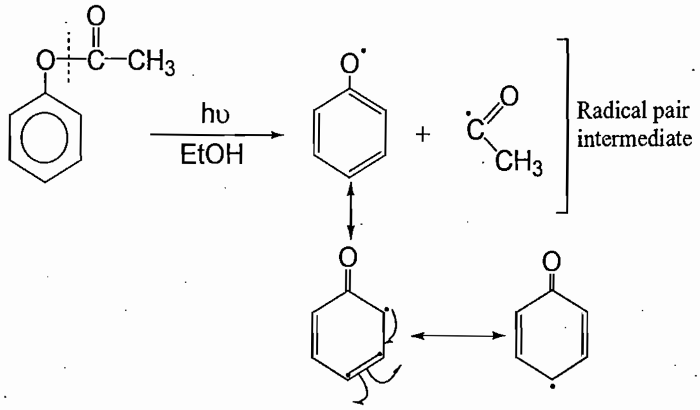
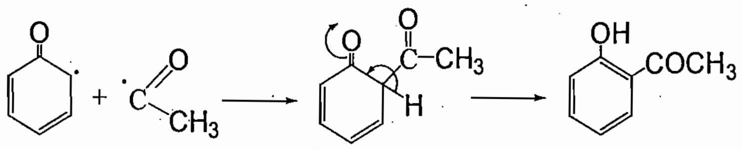


Photo Fries Rearrangement:

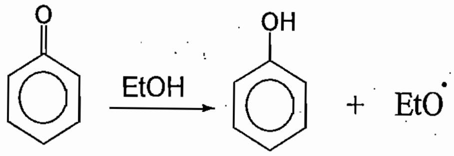
The fries rearrangement which is catalysed by light is known as photo fries rearrangement. It involves a homolytic cleavage of the acyl oxygen bond to form a radical pair intermediate. The coupling of the radicals then produce the stable product.



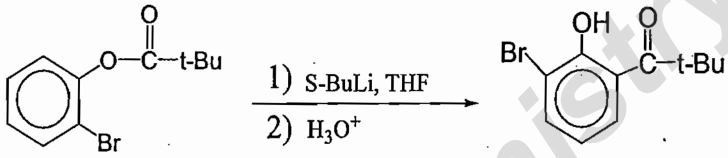
Coupling :



Phenol is obtained as a side product.

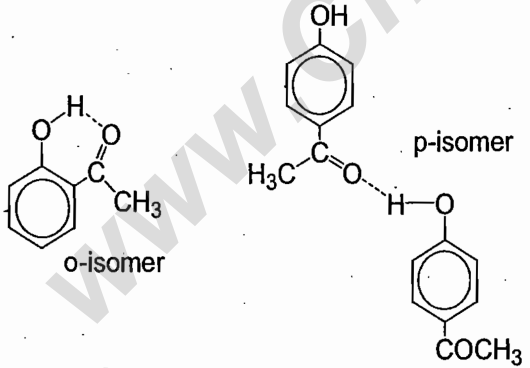


Metal promoted fries rearrangement is also reported.



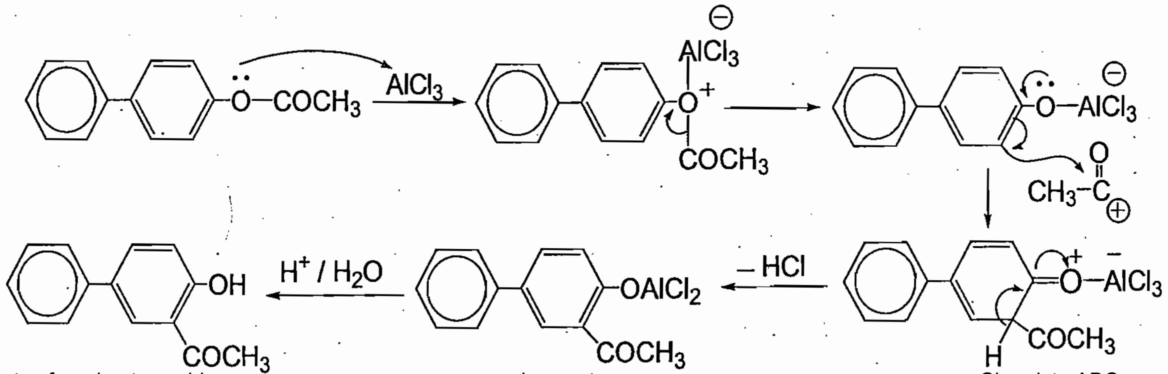
o-bromo phenyl esters.

Advantages: The o-product is intramolecular hydrogen bonded so boiling point is less and the p-product is intermolecular hydrogen bonded so boiling point is high.

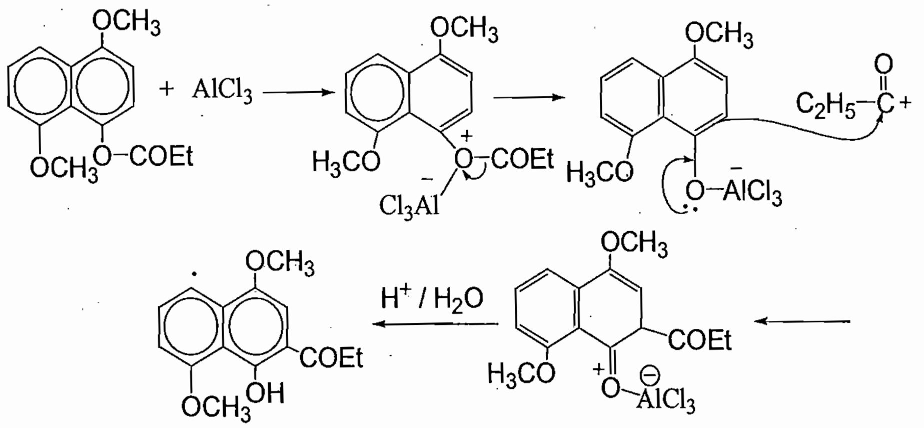


***Example*:**

(i)



(ii)



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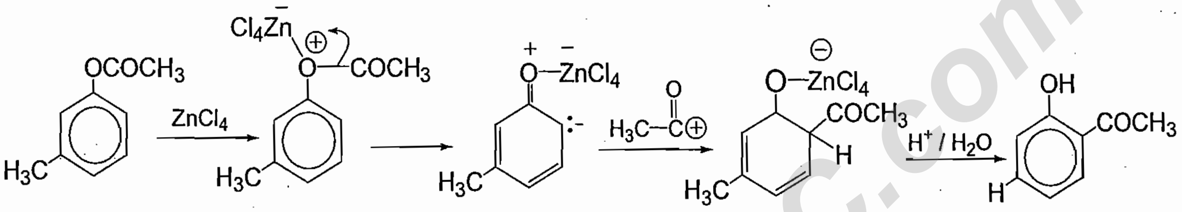
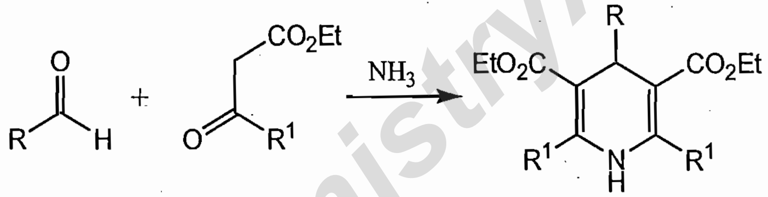
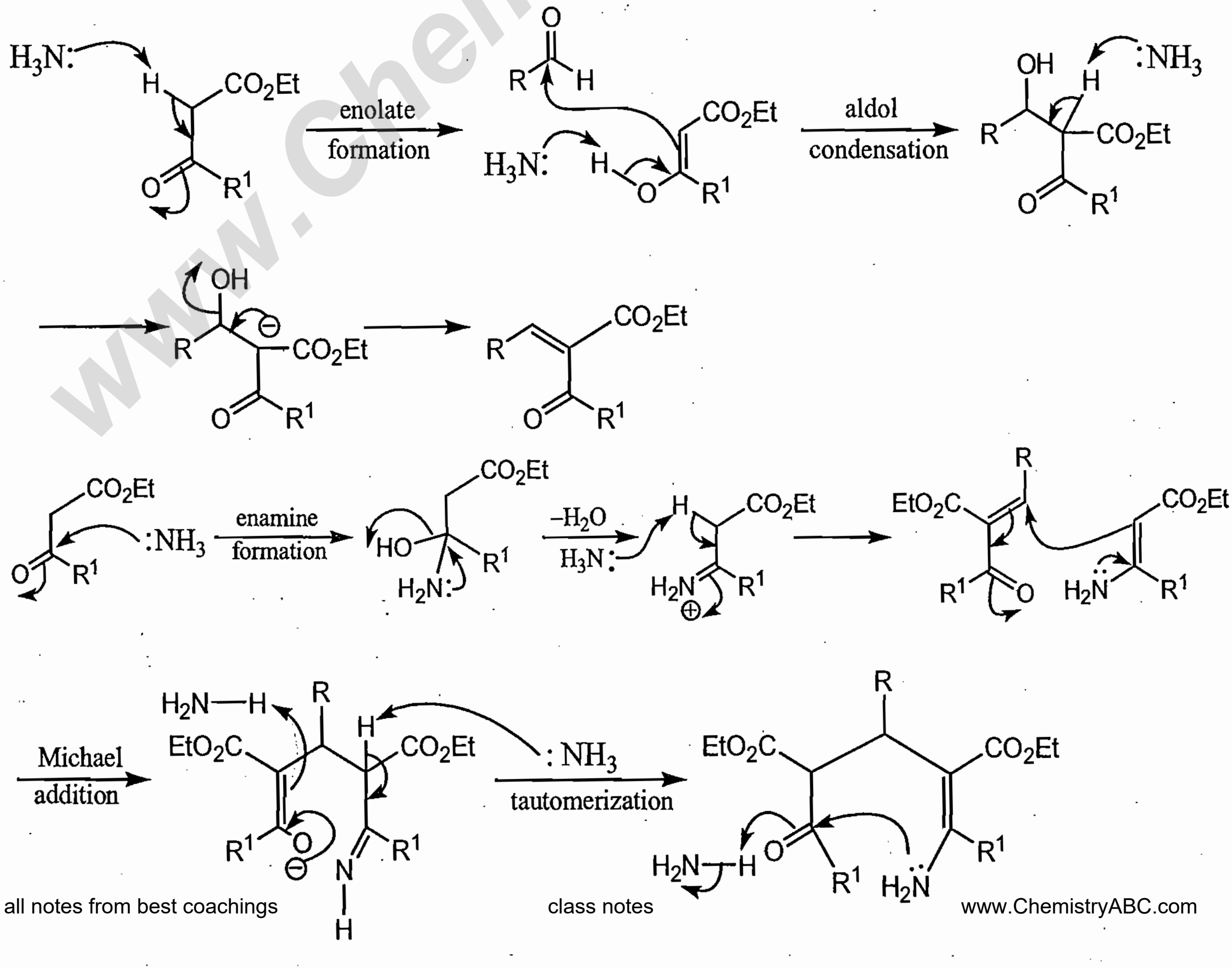


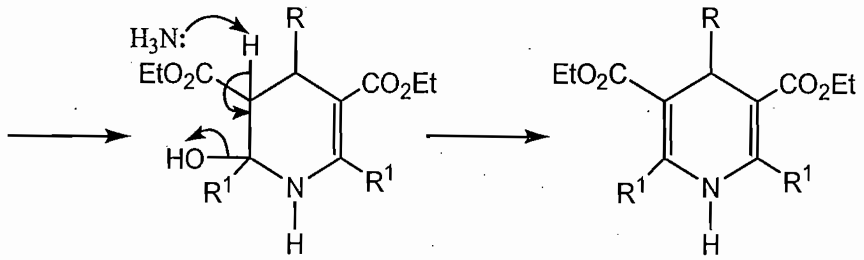
7.11. *Hantszch Dihydrophyridine Synthesis*

Hantzsch 1, 4-dihydropyridines are popular reducing reagents in organocatalysis. It can be synthesized from the condensation of aldehyde, b-ketoester and ammonia.



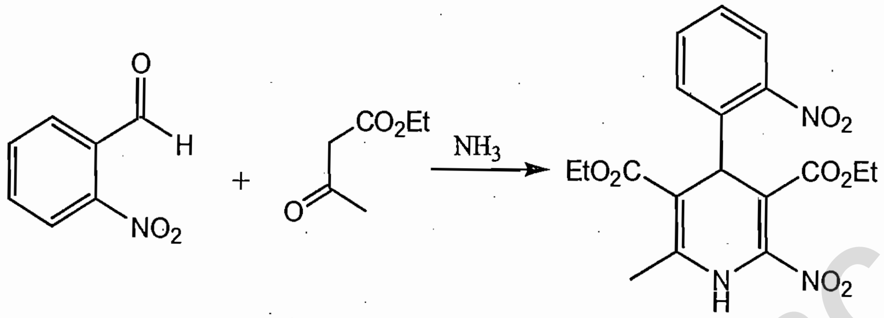
Mechanism:





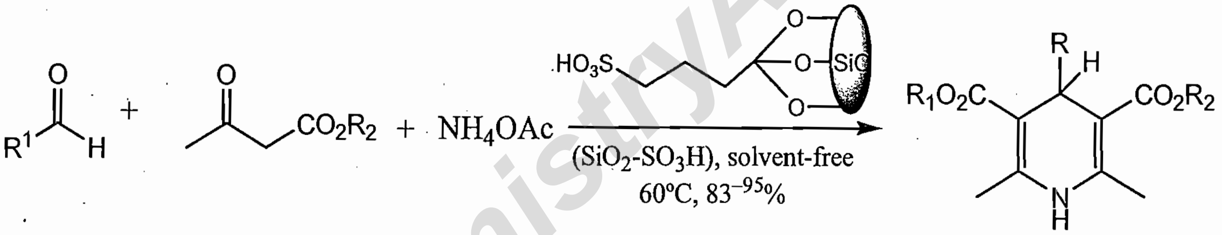
EXAMPLES

1.

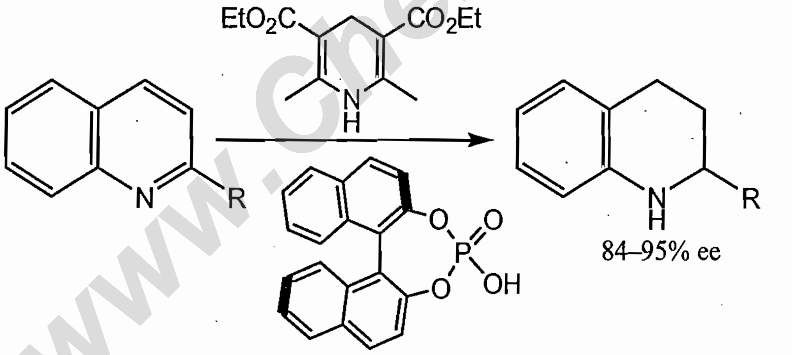


nifedipine

2.

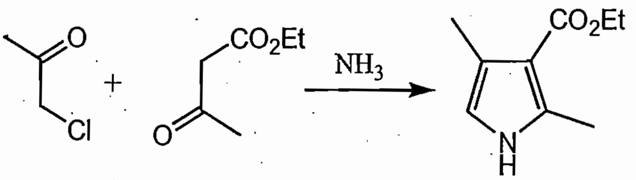


3. Hantzsch 1, 4-dihydropyridine can also be used as a hydrogen donor.

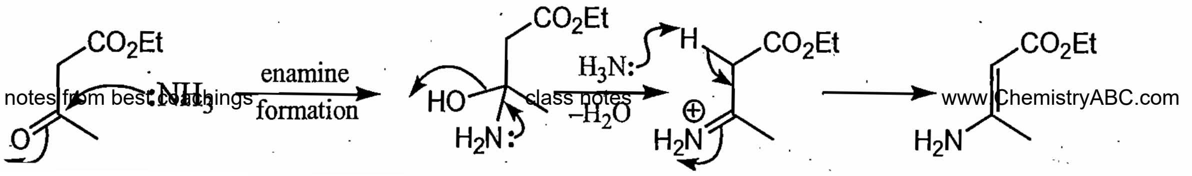


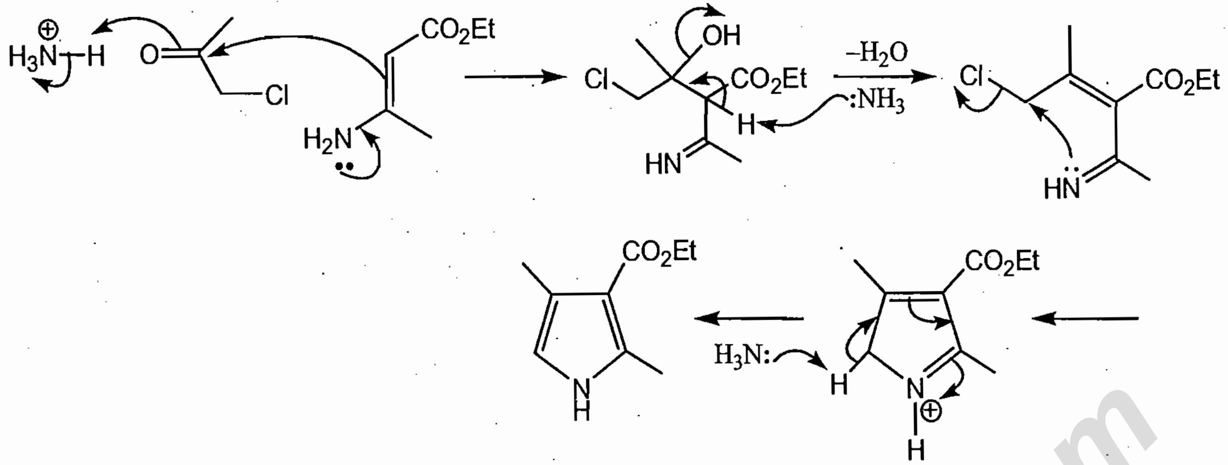
7.12. *Hantzsch Pyrrole Synthesis*

Synthesis of pyrroles by the reaction of a-chloromethyl ketones with b-ketoester and ammonia is known as Hantzsch pyrrole syntheses.



***Mechanism*:**





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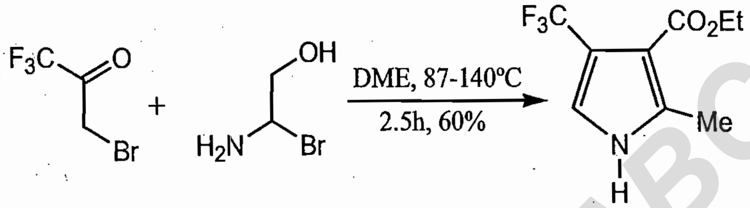

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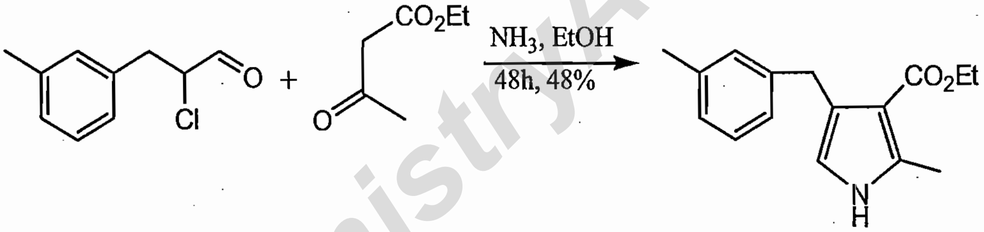
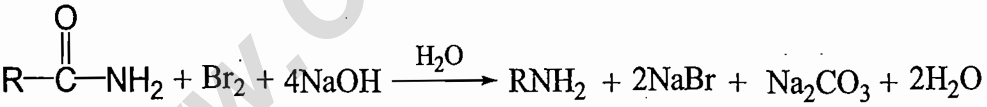


7.13. *Hoffmann Rearrangement*

The conversion of amide with no substituent on the nitrogen to an amine containing one carbon less by the action of alkaline hypobromite. It involves the migration of an alkyl or aryl group with its electron pair to electron deficient N from adjacent carbon. The reaction involves the intermediate of isocyanate (R-N=C=O)

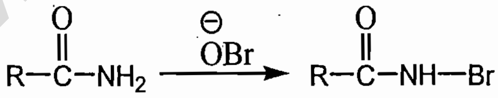


$$R-\overset{\overset{O}{\|}}{C}-NH_2 + Br_2 + 4NaOH \xrightarrow{H_2O} RNH_2 + 2NaBr + Na_2CO_3 + 2H_2O$$

Mechanism :

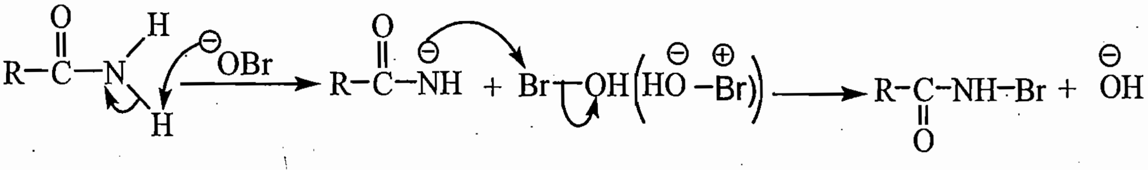
It is SN^2 intramolecular substitution reaction: $Br_2 + OH^- \rightarrow OBr^-$ Hypobromite

Step-I:

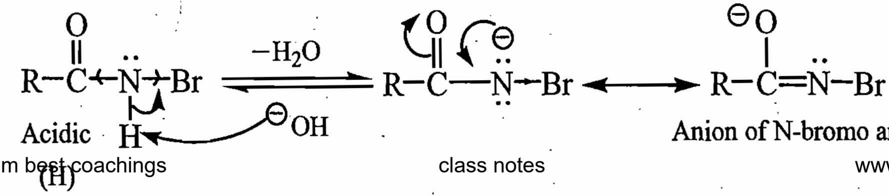


$$R-\overset{\overset{O}{\|}}{C}-NH_2 \xrightarrow{\overset{\ominus}{O}Br} R-\overset{\overset{O}{\|}}{C}-NH-Br$$

N-bromoamide (A)

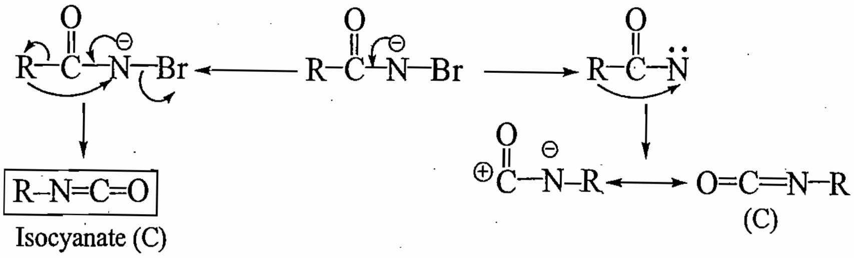


Step-II:

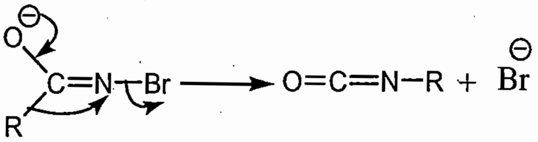


Anion of N-bromo amide (B)

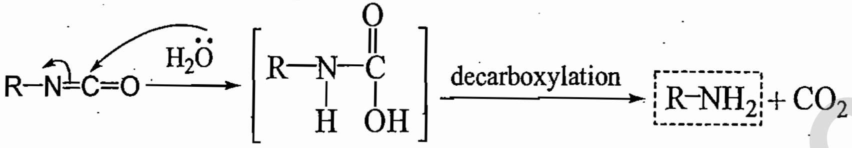
STEP-III:



The second step (B) can be :

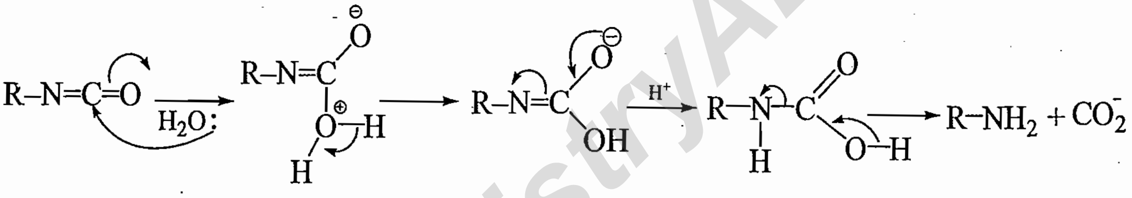


STEP -IV: Attack of H_2O on isocyanate : (Nucleophilic Solvent)



N-alkyl carbonic acid
(unstable)

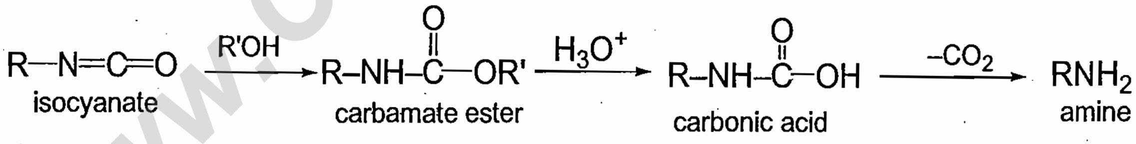
Second way



$$CO_2 + 2KOH \longrightarrow \underset{(CO_3)^{2-}}{K_2CO_3} + H_2O$$

CO_2 is exists as a carbonate because basic medium is used.

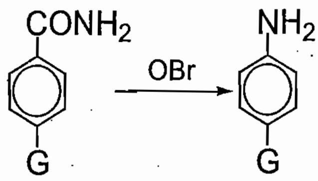
* when acyl azide is decomposed in the presence of alcohol, the isocyanate react with alcohol to form a carbonate ester hydrolysis of carbonate ester gives the corresponding amine.



$$\underset{\text{isocyanate}}{R–N=C=O} \xrightarrow{R'OH} \underset{\text{carbamate ester}}{R–NH–\overset{O}{\overset{\|}{C}}–OR'} \xrightarrow{H_3O^+} \underset{\text{carbonic acid}}{R–NH–\overset{O}{\overset{\|}{C}}–OH} \xrightarrow{-CO_2} \underset{\text{amine}}{RNH_2}$$

Migrating aptitude in aromatic groups :

- Presence of electron releasing groups increase the rate of reaction.
- Presence of electron withdrawing groups decrease the rate of reaction.

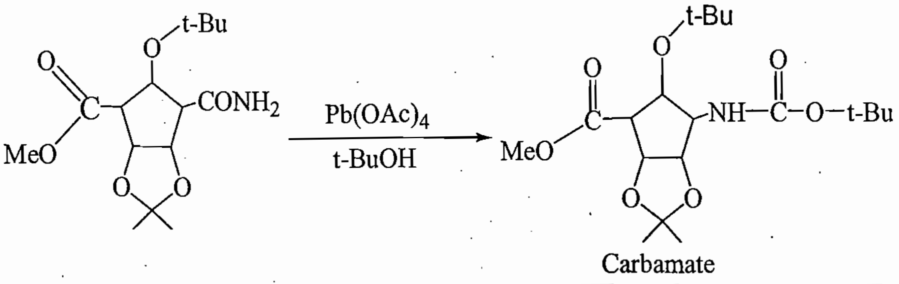


Rate : $–OCH_3 > –CH_3 > –H > –Cl > –NO_2$

Side-Products :

1. $\underset{\text{(If R group contain more than 8C)}}{R–CONH_2} \xrightarrow{H.R.} \underset{\text{Nitrile}}{R–C{\equiv}N} \xrightarrow{[H]} \underset{\text{(ammine having same no. of C as that of amide)}}{R–CH_2–NH_2}$

2. Direct oxidation of amides can also lead to Hoffinann type of rearrangement with the formation of amine or Carbamate



EXAMPLES

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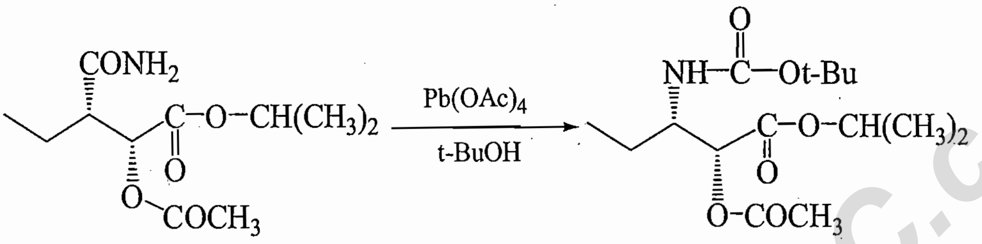

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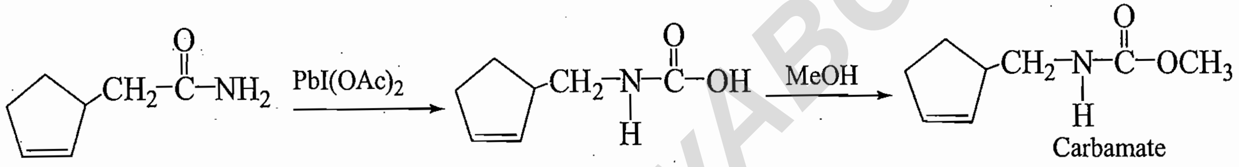

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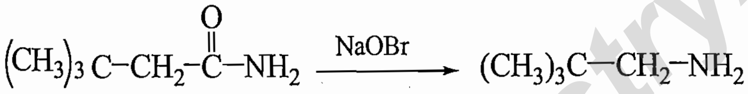
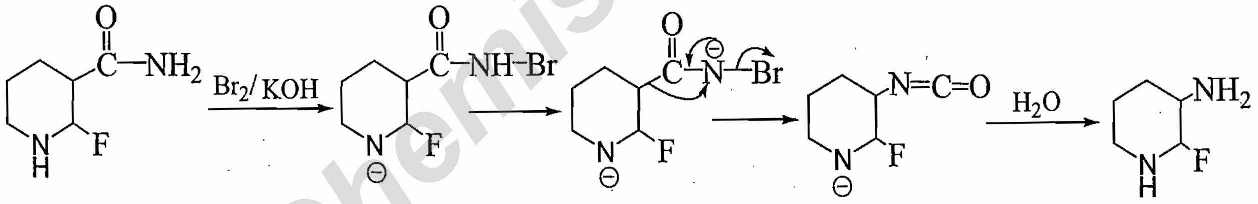


$$(CH_3)_3C-CH_2-\overset{O}{\overset{\|}{C}}-NH_2 \xrightarrow{NaOBr} (CH_3)_3C-CH_2-NH_2$$

(4)


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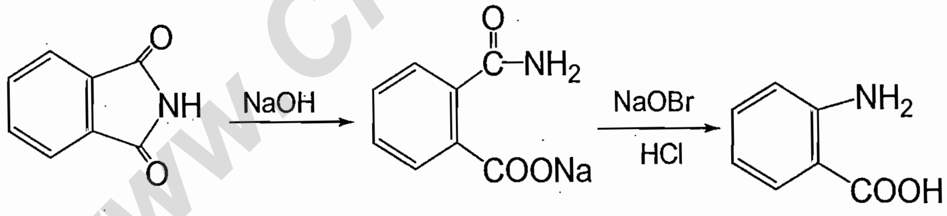

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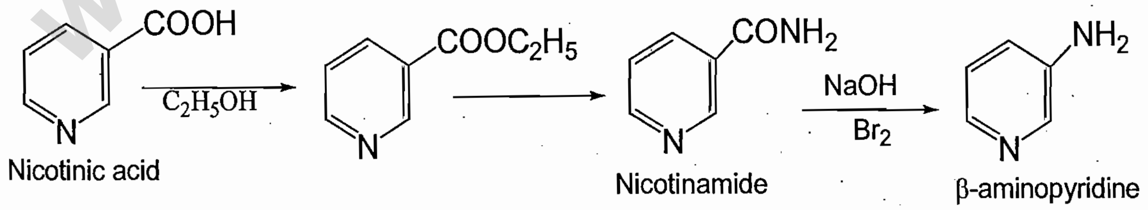

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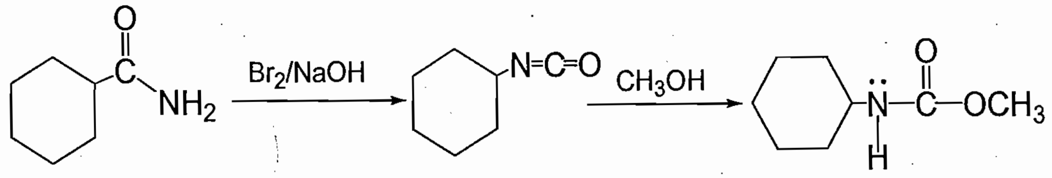
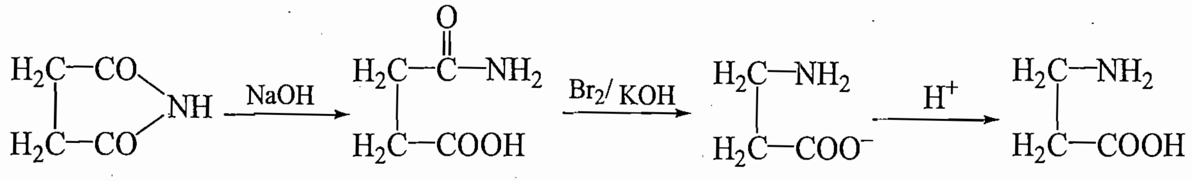


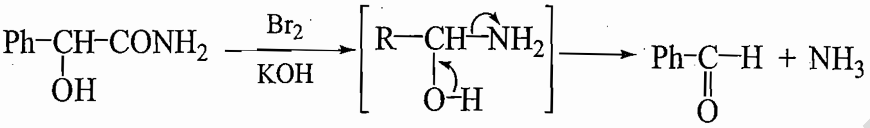
Applications :

(i) Formation of amines (ii) Synthesis of amino acid



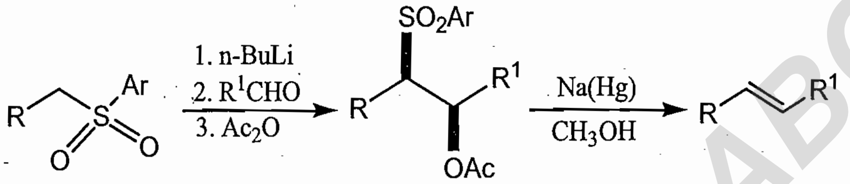
Succinimide β-alanine (AA)

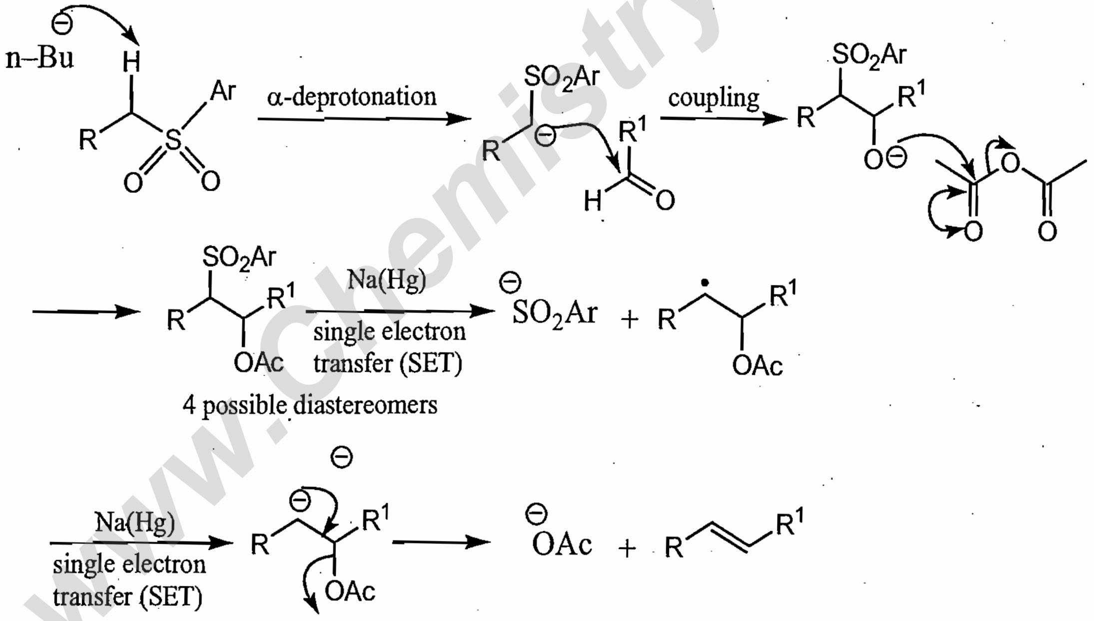
3. **Aldehydes from hydroxy - acid amides :**



7.14. Jullia-Lythgoe Olefination

(E)-Olefines from sulfones and aldehydes.





EXAMPLES

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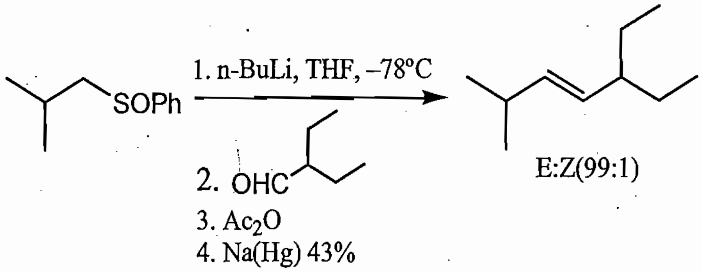

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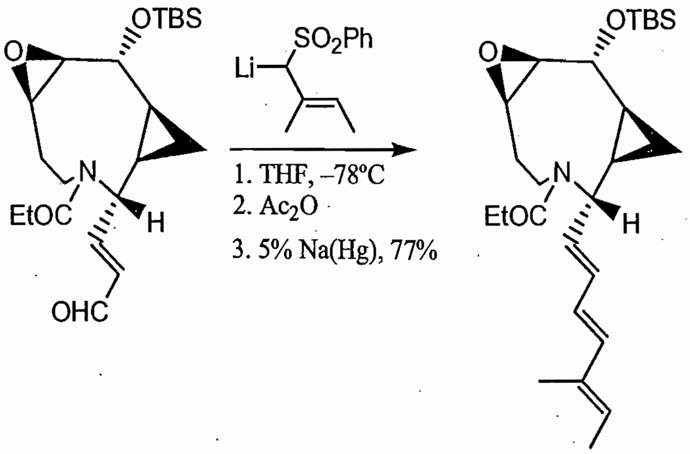

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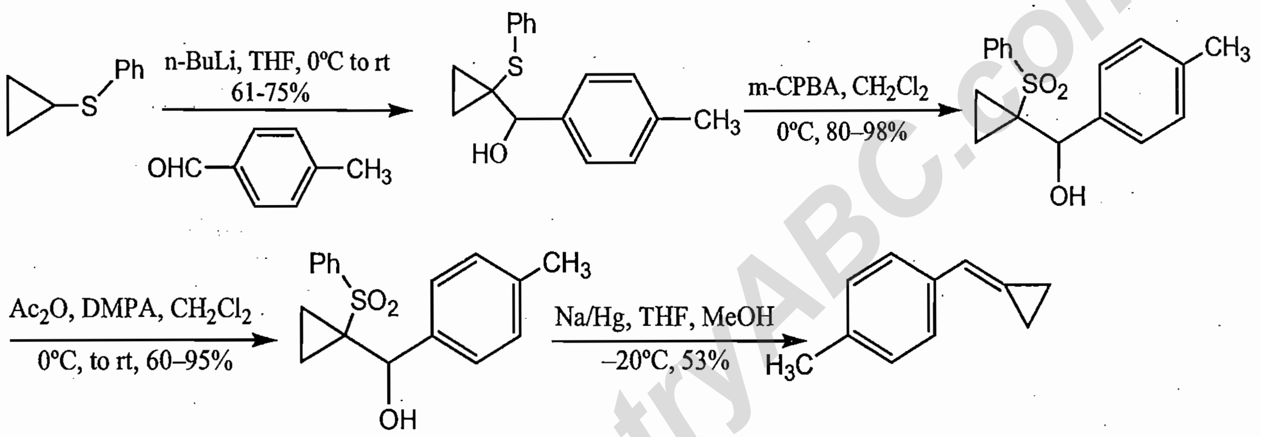

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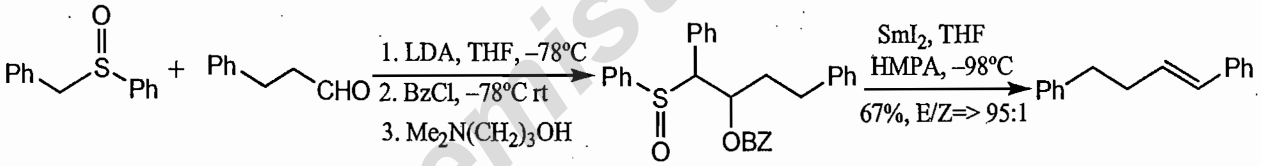
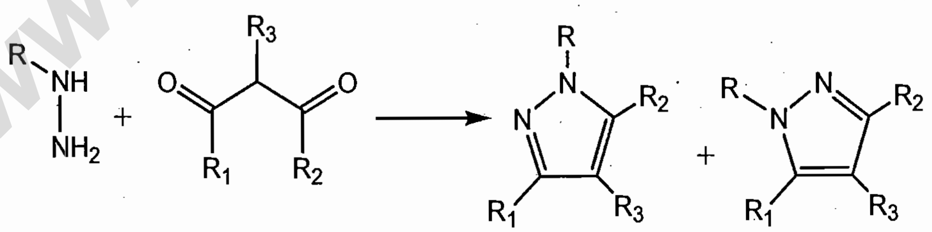


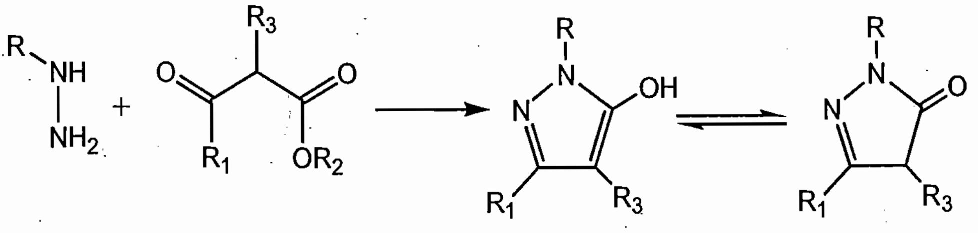
7.15. *Knorr Pyrazole Synthesis*

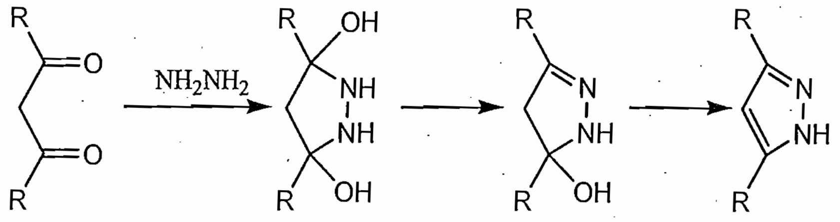
The reaction of hydrazine or substituted hydrazine with 1, 3-dicarbonyl compounds to produce the pyrazole or pyrazolone ring system is known as knorr pyrazole synthesis.



R=H, Alkyl, Aryl,Het-aryl, Acyl, etc.

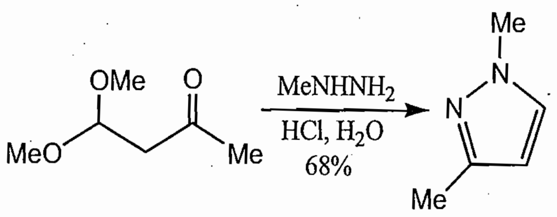
***Mechanism*:**





EXAMPLES

1.



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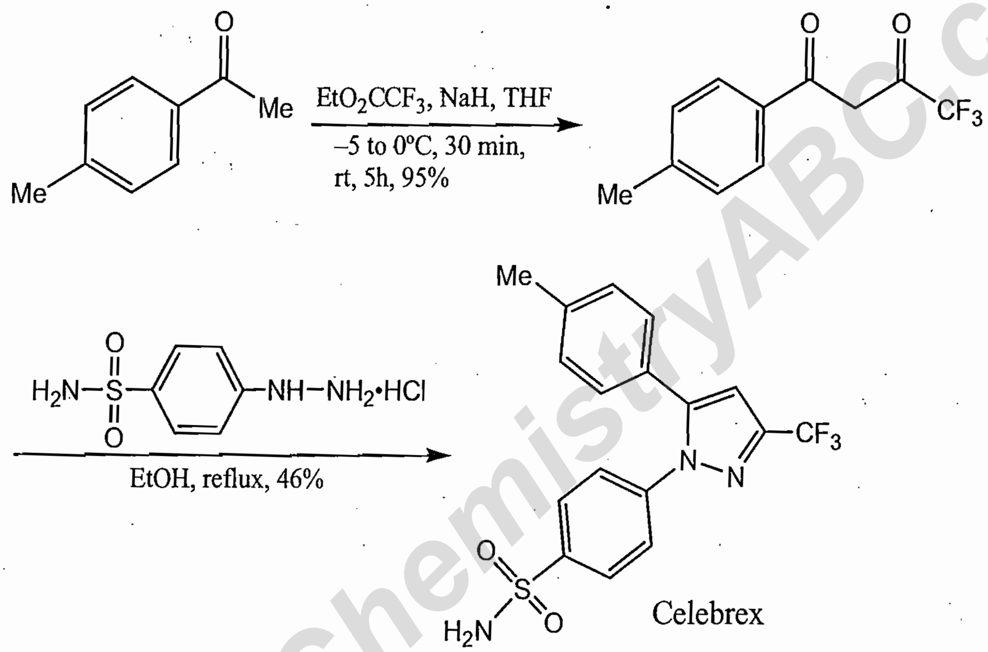
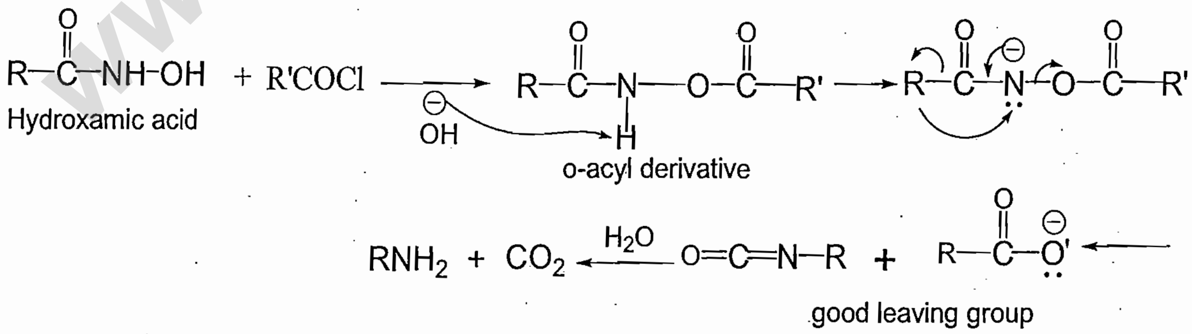


Celebrex

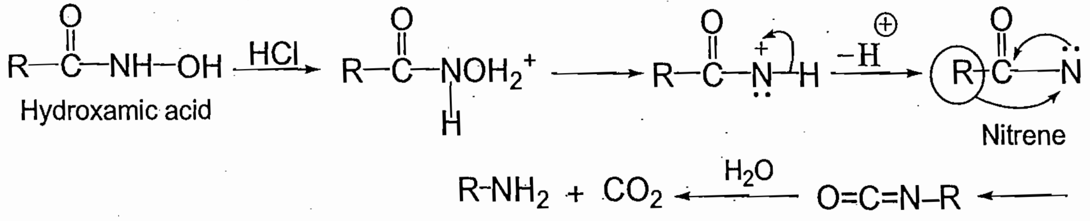
7.16. *Lossen Rearrangement*

The rearrangement of acyl derivative of hydroxamic acid to isocyanate followed by hydrolysis of isocyanate to this corresponding amine is known as lossen rearrangement.



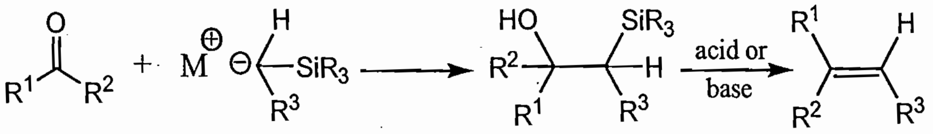
The concerted nature of the rearrangement is supported by the fact that not only is the reaction facilitated by electron donating groups on R but also through electron withdrawing groups R^1 in the leaving group in the rate determining step.

* Hydroxamic acid itself may undergo the lossen rearrangement by the action of strong inorganic acids to primary amine.



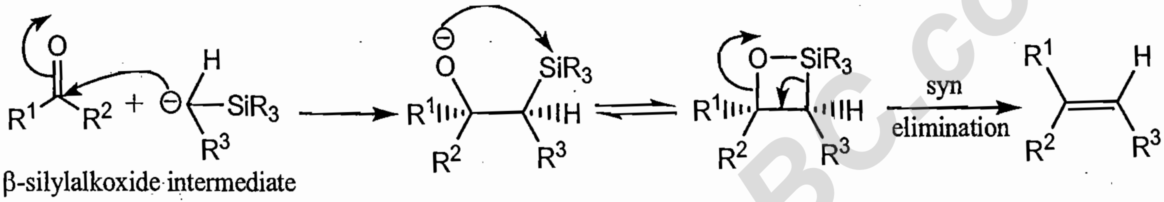
7.17. *Peterson Olefination*

Preparation of alkenes from a-silyl carbanions and carbonyl compounds. It is also known as the sila-wittig reaction.

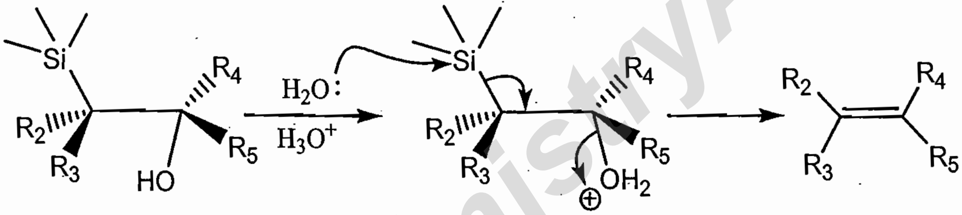


***Mechanism*:**

(a) Basic conditions:



(b) Acidic conditions:



EXAMPLES

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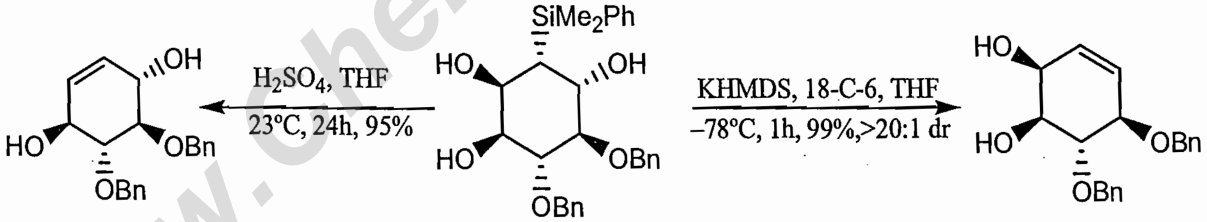

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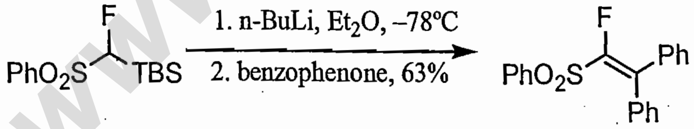

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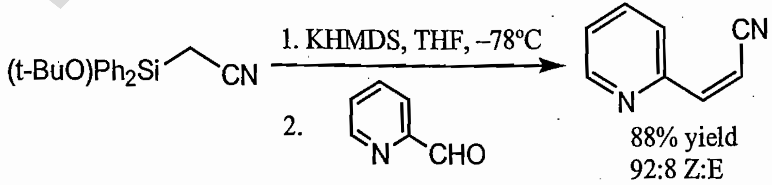

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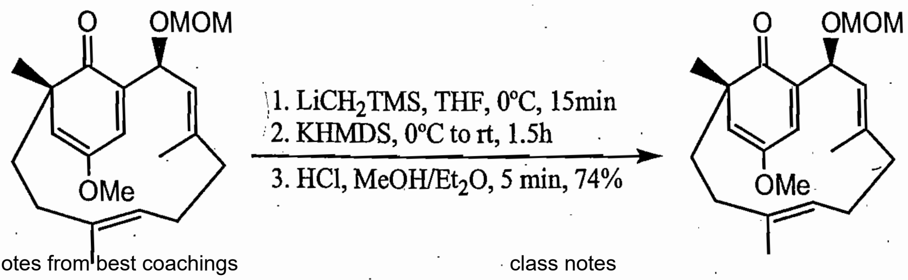
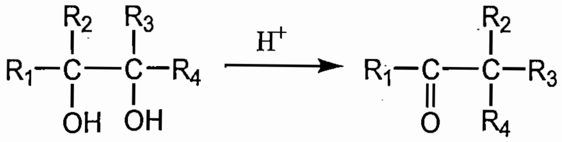


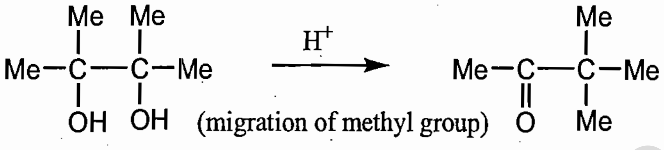
7.18. *Pinacol-pinacolone Rearrangement*

The acid-catalyzed rearrangement of vic-diols (1, 2-glycols) to aldehydes or ketones is called the pinacol rearrangement.



(R=alkyl, aryl or hydrogen)

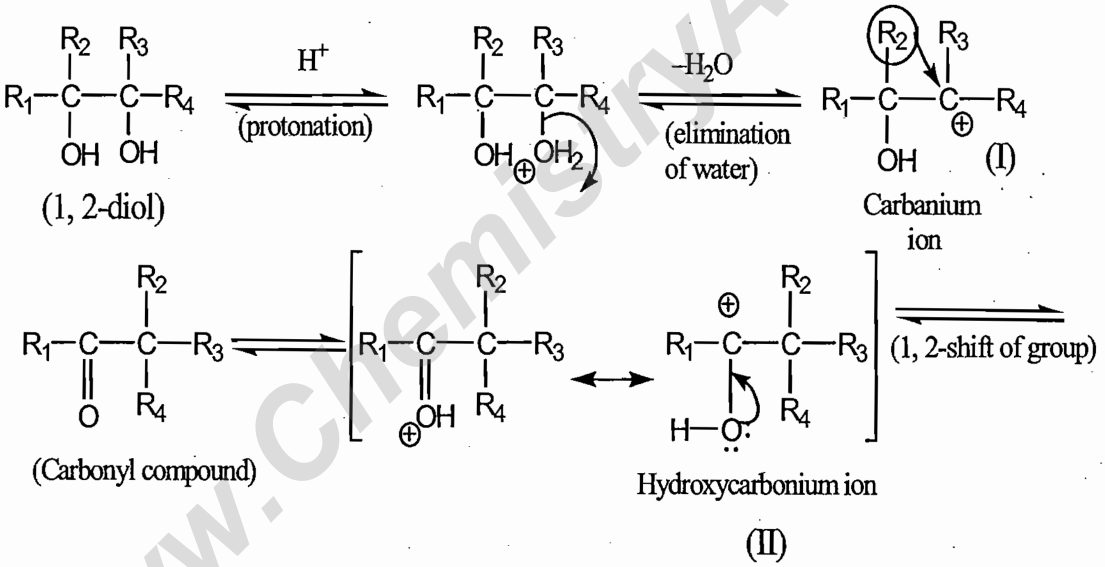
The name is originated from the classical example of conversion of pinacol to pinacolone.



(Pinacol) (Pinacolone)

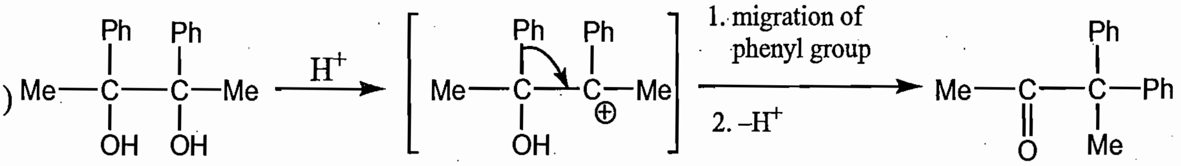
The migrating group may be alkyl, aryl, hydrogen, and even ethoxycarbonyl (COOEt)$_3$. However, elimination of water to yield alkene – the normal reaction of alcohols– may be observed as a side-reaction.

***Mechanism*:**



Critical Views:

(a) Migratory aptitude: It is necessary to get an idea about the migratory aptitude of groups in the cases where glycols contain four different groups. Various experimental observations suggest the realtive aptitude of groups in pinacol-type rearrangement as in the order of aryl > 3°-alkyl > 2°-alkyl-> 1°-alkyl.

(1)


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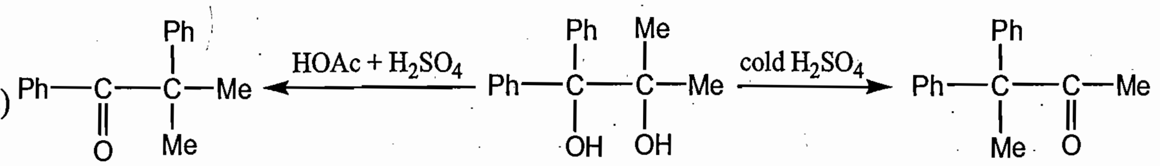
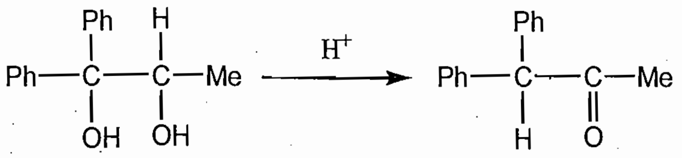
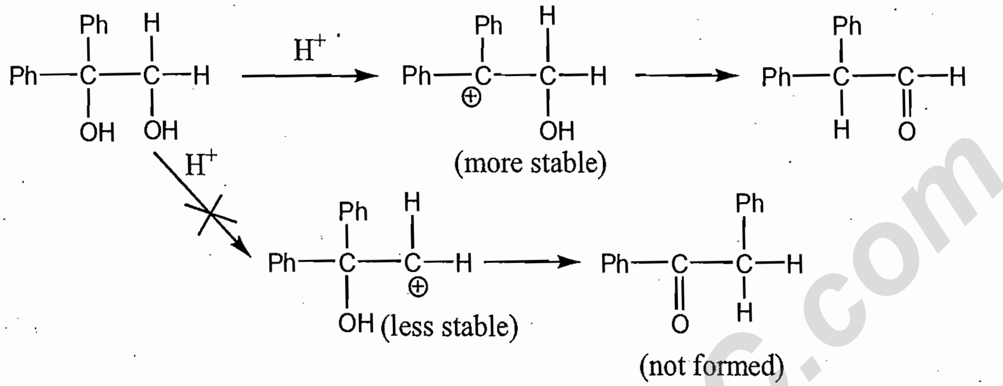
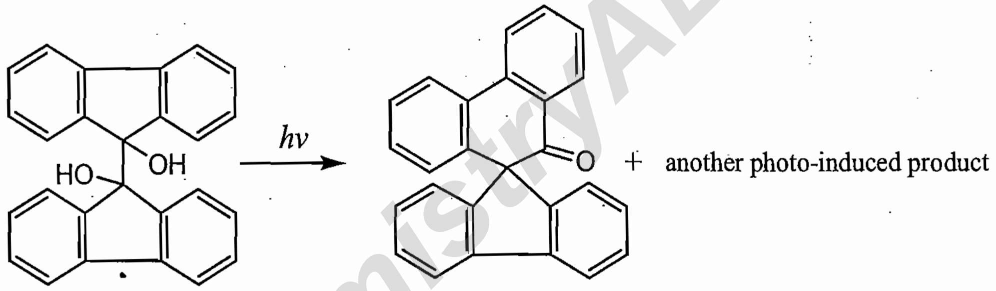




(b) In the case of unsymetrically substituted glycols, the –OH that becomes protonated and ultimately is eliminated is the one whose loss gives rise to the more stable carbonium ion.



(c) Piancol rearrangement may also be catalyzed photochemically.

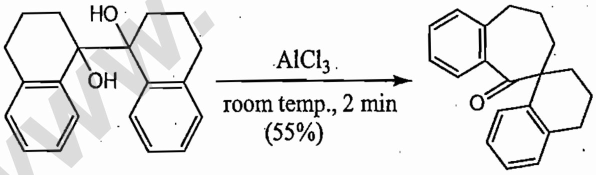


pinacol-rearranged product

(d) Pinacol rearrangement can also be accomplished in the solid state.

$PhCH(OH)CH(OH)Ph \xrightarrow[\text{room temp., 2 min}]{AlCl_3} PhCOCH_2Ph$ (87%)

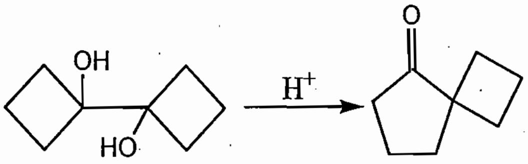
$(\rho-MeOC_6H_4)CH(OH)C(OH)Ph_2 \xrightarrow[\text{room temp., 2 min}]{AlCl_3} (\rho-MeOC_6H_4)CHPhCOPh$ (94%)



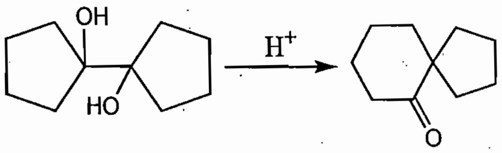
Applications: The pinacol rearrangement reaction is a useful alternative tool to the standard methods for synthesis of aldehydes and ketones.

$Me_2C(OH)CH_2OH \xrightarrow{H^+} Me_2CHCHO$

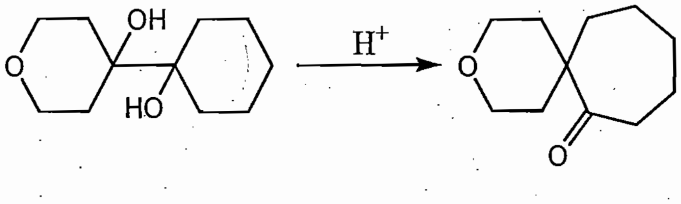
(i)



(ii)

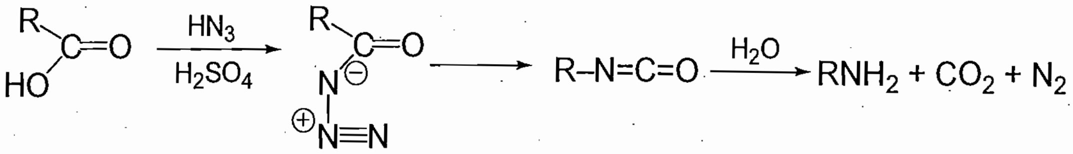


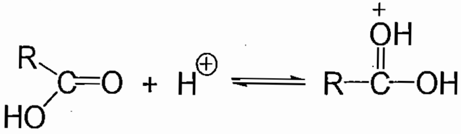
(iii)



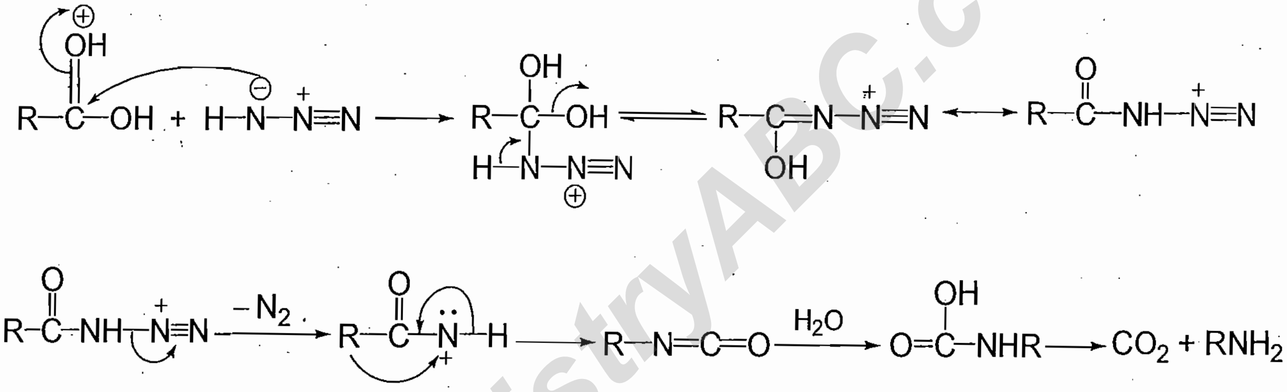
7.19. Schmidt Rearrangement

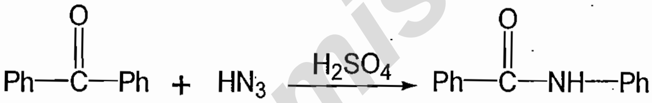
The conversion of carboxylic acid into primary amine having one carbon less is schmidt rearrangement reaction. This reaction can be done by reacting carboxylic acid with hydrazoic acid in presence of H_2SO_4 through one step procedure but hydrazoic acid is toxic and explosive & hence it is generated in situ by adding azide gradually to the carboxylic acid in the presence of sulphuric acid





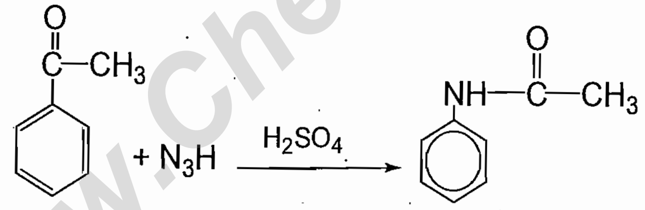
Mechanism :





$$\text{Ph}-\overset{\overset{\displaystyle O}{\|}}{C}-\text{Ph} + HN_3 \xrightarrow{H_2SO_4} \text{Ph}-\overset{\overset{\displaystyle O}{\|}}{C}-NH-\text{Ph}$$

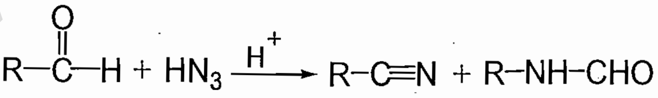
Example: Benzophenone → Benzanilide



acetophenone acetanilide

* Since the hydrolysis of amide gives amine.

* aldehyde gives mainly mixture of nitrile and N formyl derivative

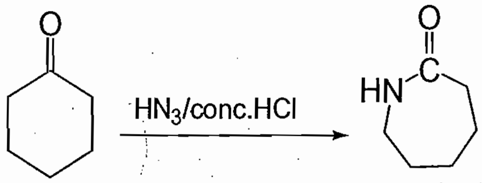


$$R-\overset{\overset{\displaystyle O}{\|}}{C}-H + HN_3 \xrightarrow{H^+} R-C\equiv N + R-NH-CHO$$

Nitrile N formyl amine

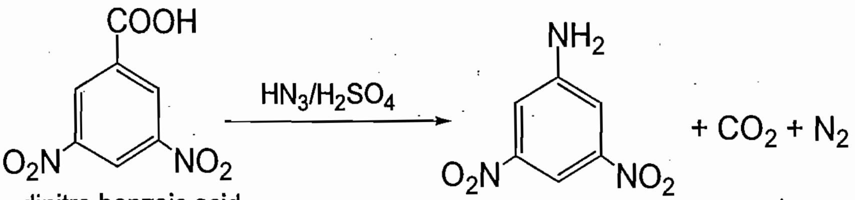
* Cyclic ketones undergo a ring enlargement to give lactams this schmidt reaction provide a synthetic alternative to the Beckmann rearrangement.

(i)



cyclohexanone caprolactam

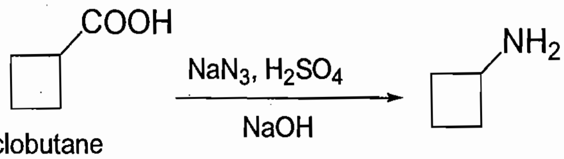
(ii)



3, 5 - dinitro benzoic acid

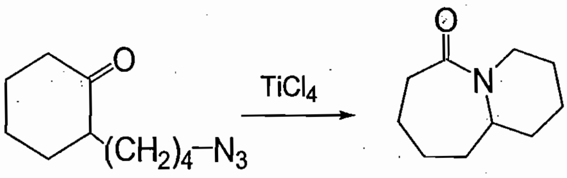
3, 5 - nitroaniline

(iii)

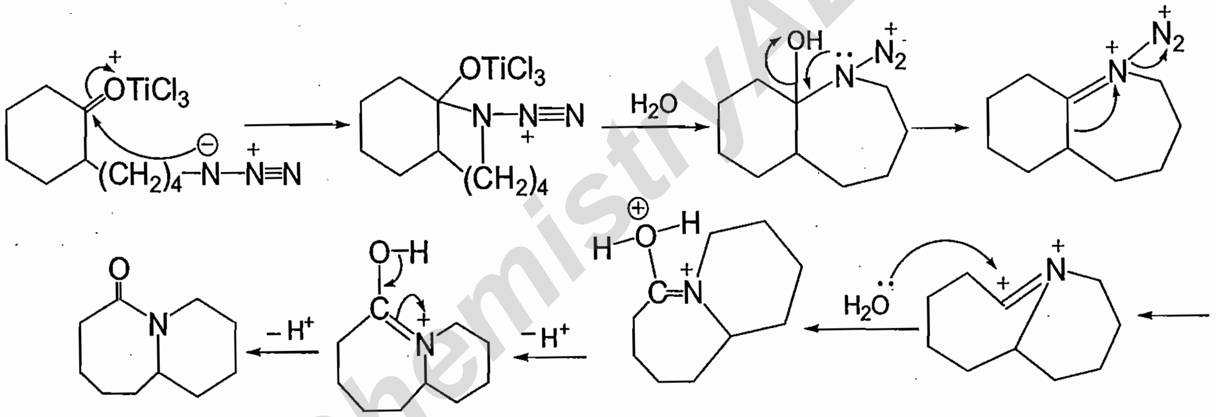


cyclobutane carboxylic acid

Intramolecular Schmidt Reaction:



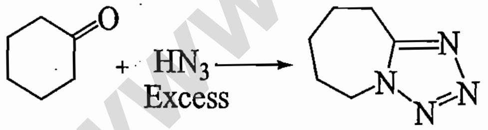
Mechanism :



Applications:

(1) Production of amine from acid

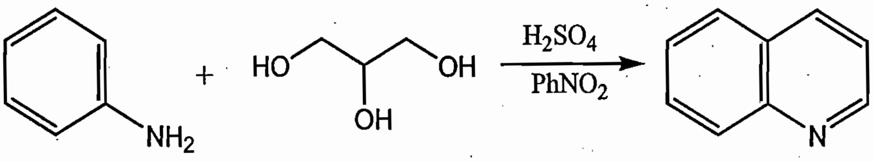
(2) With excess HN_3 ⟶ Tetrazole derivative obtain



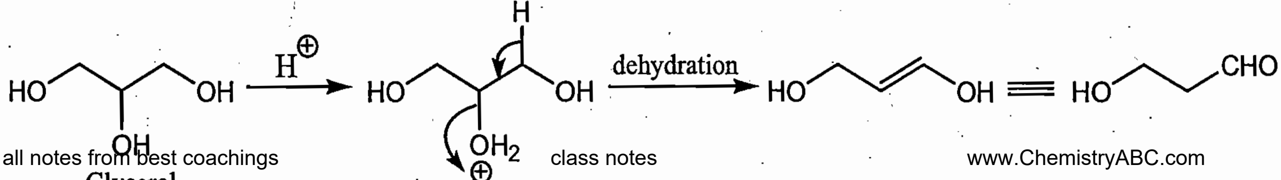
Cardiazole (Heart stimulant)

7.20. *Skraup Quninoline Synthesis*

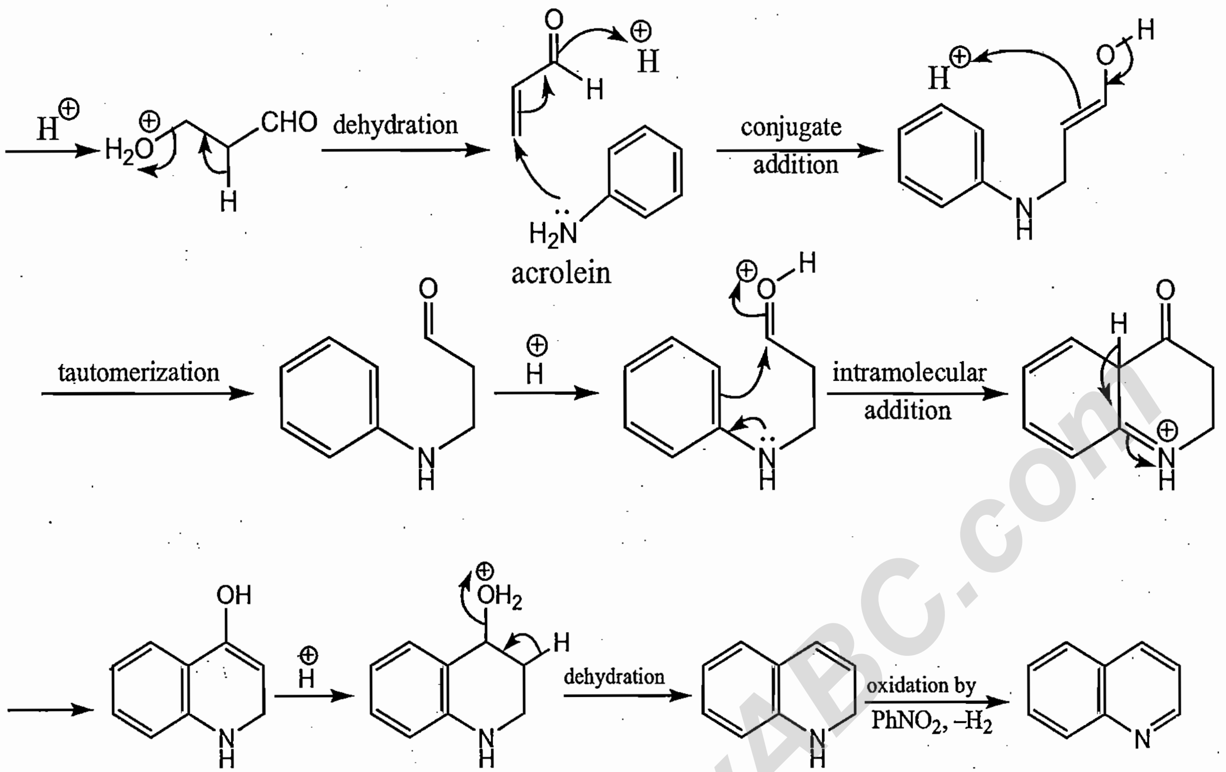
Preparation of quinoline from aniline, glycerol, sulfuric acid and oxidizing agent (e.g. $PhNO_2$).



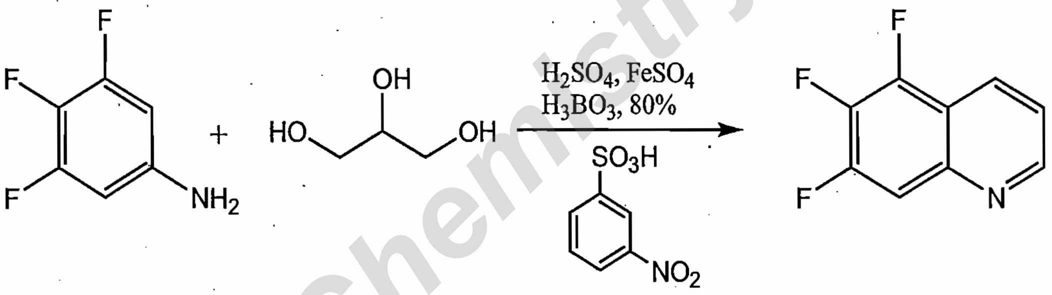
Mechanism:



Glycerol

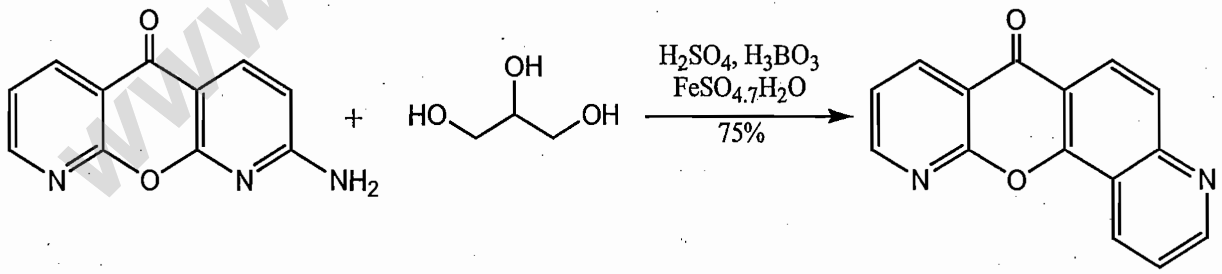


For an alternative mechanism, see that of the Doebner-von Miller reaction.

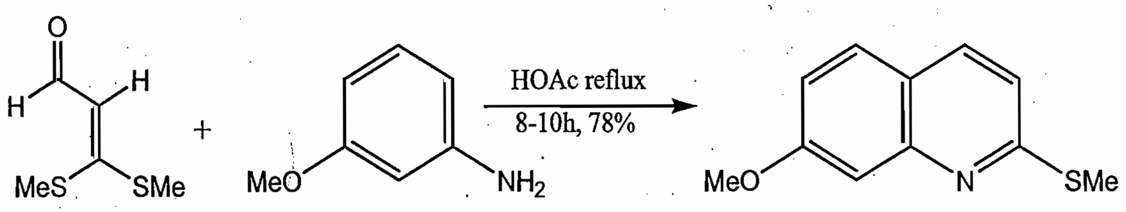


EXAMPLES

1.



2. A modified Skraup quinoline synthesis.



7.21. *Wagner Meerwein Rearrangement*

Wagner-Meerwein rearrangement was **first discovered in the bicylic terpenes** and most of the early development of this reaction was with these compounds.

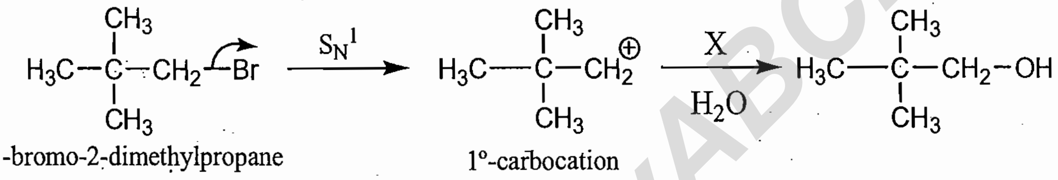
The term Wagner-Meerwein rearrangement is generally taken to describe a 1, 2-migration of a ring carbon atom in a bridged polycyclic molecule. Some chemists have expanded the co-notation to include all **1, 2-migrations of hydrogen alkyl or aryl groups from b-carbon to carbocationic carbon.**

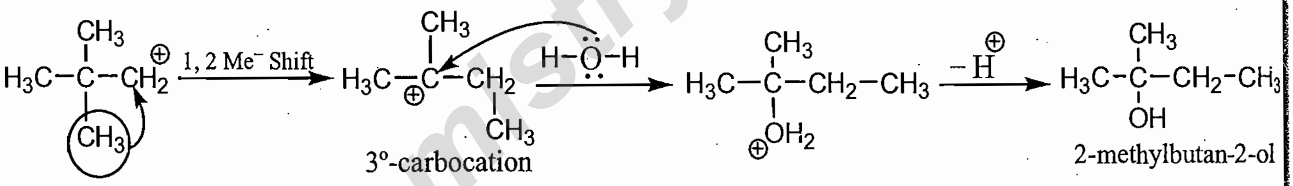
Driving force for the Wagner-Meerwein Rearrangement:

1. Wagner-Meerwein rearrangement will occur if it leads to the new carbocation being more stable than the original.
2. Stability of carbocations, 3° > 2° > 1°.

Evidences for Wagner Meerwein Rearrangement:

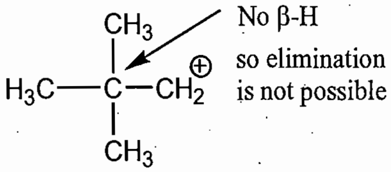
When hydrolysis of 1-bromo-2, 2-dimethyl propane (neopentyl bromide) is carried out under conditions favouring the S_N1 mode the product alcohol is found to be 2-methyl butan-2-ol and not the expected 2, 2-dimethylpropanol (neopentylalcohol).

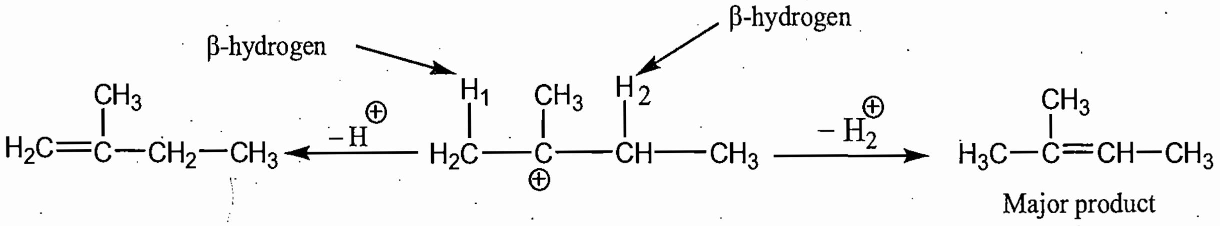




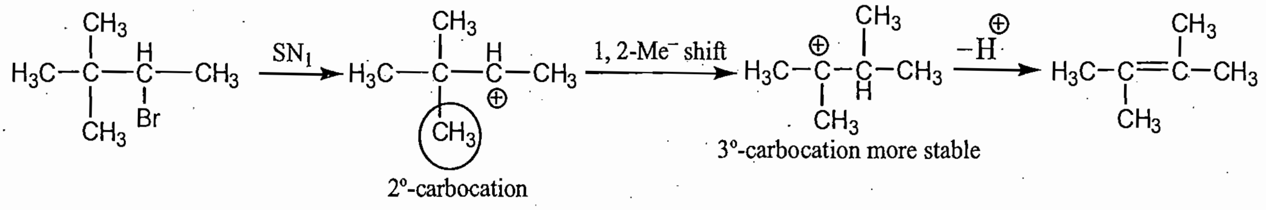
Conclusion: The greater stability of the 3°-carbocation, compared with the initial primary carbocation, provides the driving force for the C—C bond-breaking involved in migration of the methyl groups with it electron pair such changes in carbon skeleton-involving carbocations are known collectively as Wagner-Meerwein rearrangement.

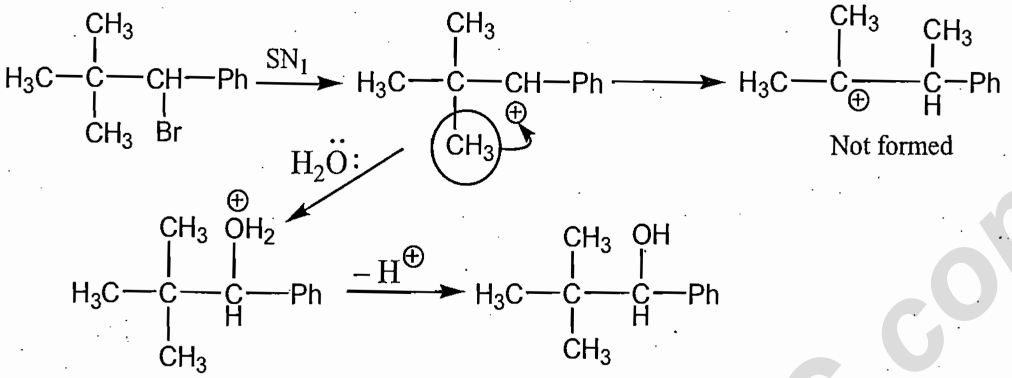
Further confirmation of the involvement of 3°-carbocation is the simultaneous formation of the alkene, 2-methyl-but-2-ene by loss of proton a product not obtained from 1°-carbocation because it has not b-hydrogen as we know b-hydrogen is necessary for b-H elimination reaction.





Note: While the neopentyl-type bromide undergoes rearragement during S_N1 hydrolysis, no such rearrangement takes place with its phenyl analogue.

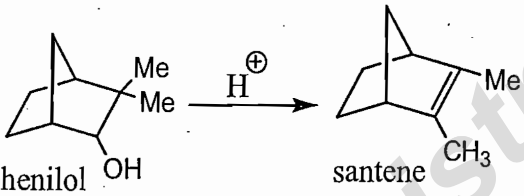




- Terpene chemists call the migration of a methyl group the Nametkin rearrangement.

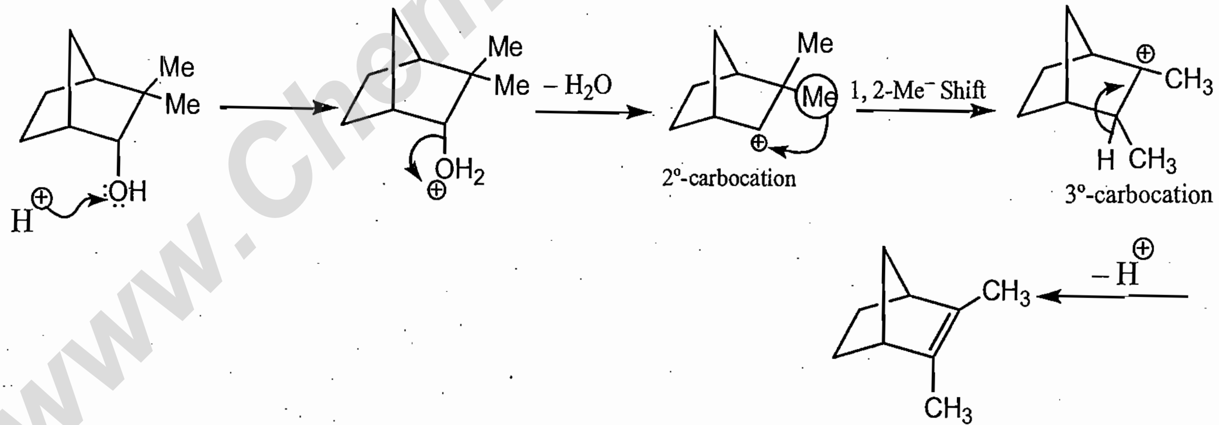
Examples of Wagner Meerwein rearragement:

1. Acid catalysed dehydration of the natural product camphenilol gives the alkene santene.

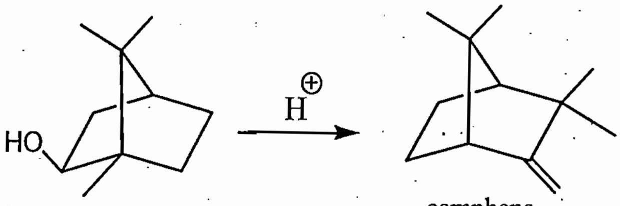


camphenilol santene

Mechanism:

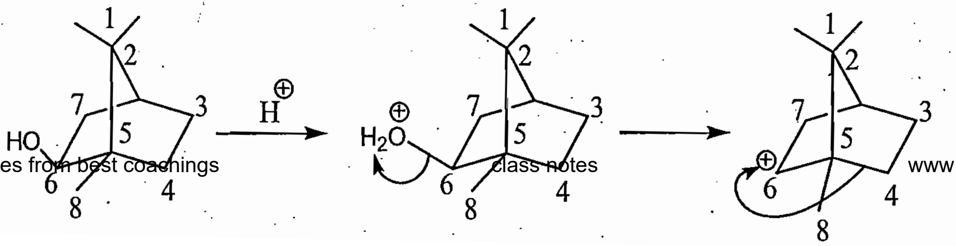


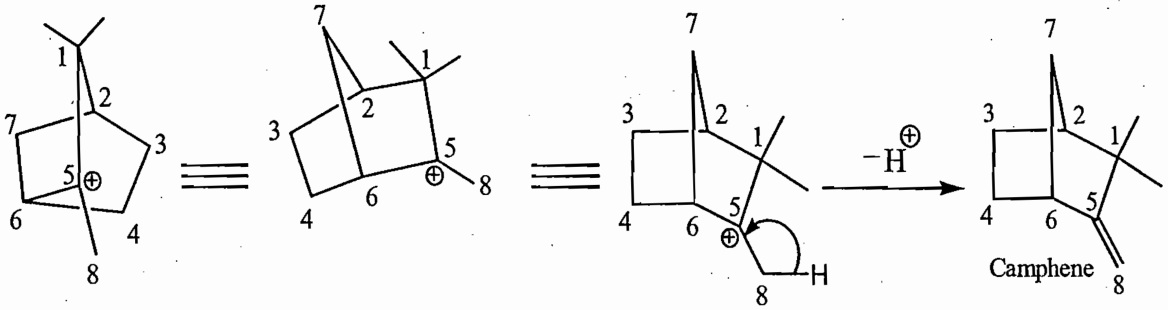
2. Acid catalysed dehydration of isoborneol to camphene.



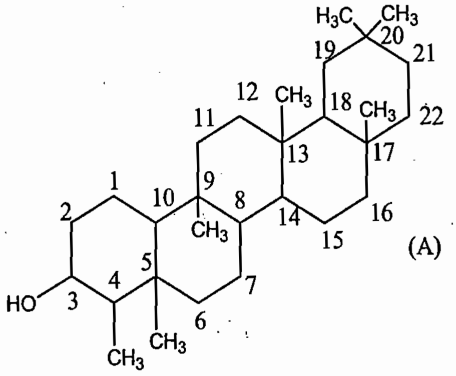
camphene

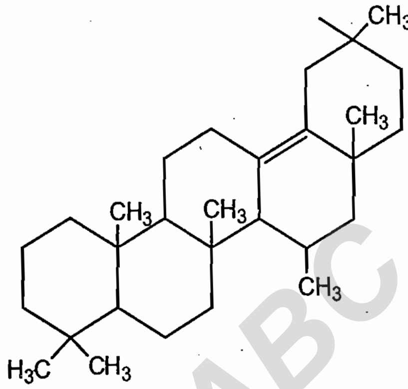
Mechanism:





Some times several of these rearrangements occur in one molecule, either simultaneously or in rapid sucession.
***Example*:**


(A)


(B)

When this compound is treated with acid C_{13}–C_{18} olefin is formed

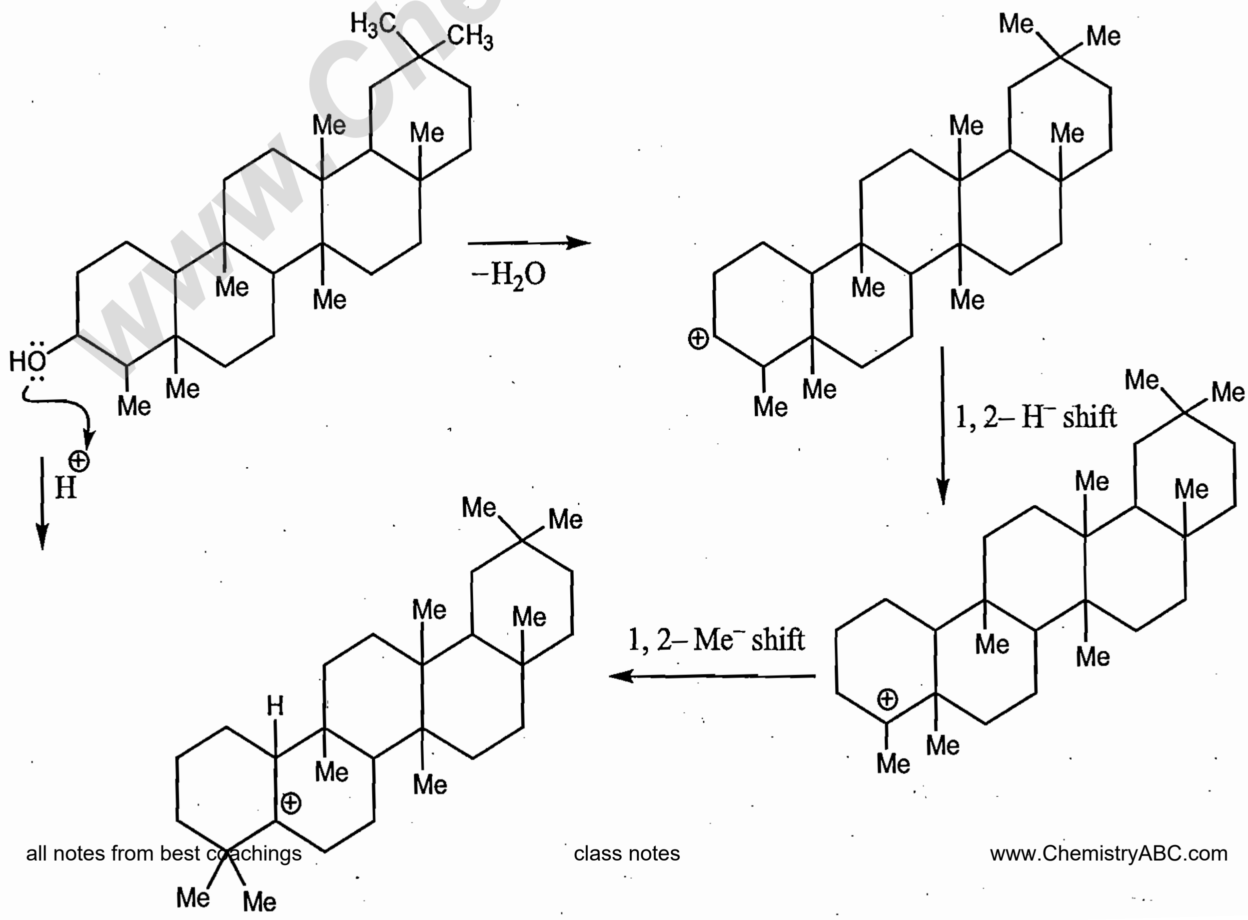
In this case seven 1, 2-shift, takes place. One removal of H_2O from position '3' to leave a positive charge, the following shifts occur

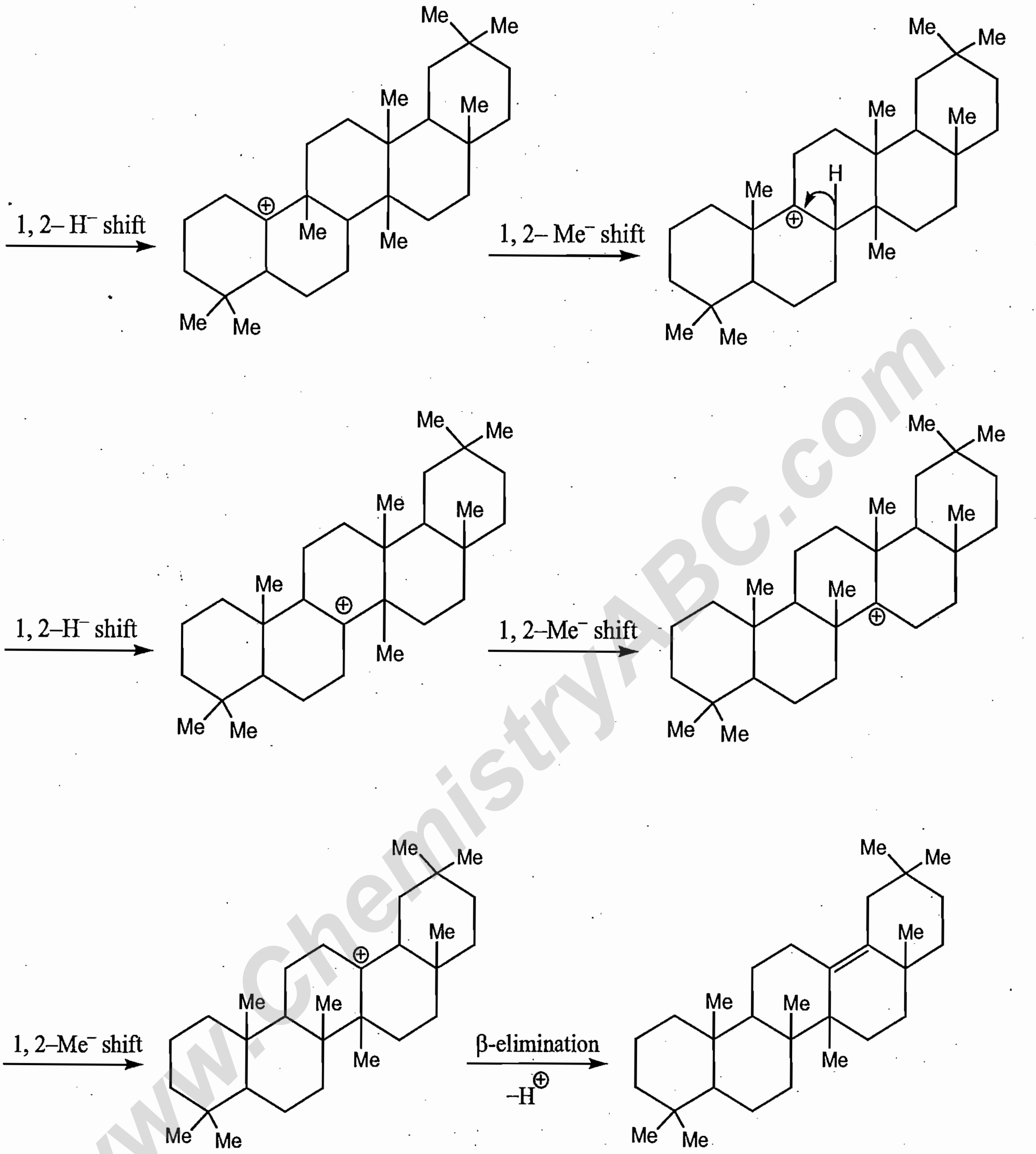
4 ⟶ 3 ⟶ hydride shift ; 5 ⟶ 4 ⟶ methyl shift ; 10 ⟶ 5 ⟶ hydride shift

9 ⟶ 10 ⟶ methyl shift ; 8 ⟶ 9 ⟶ hydride shift ; 14 ⟶ 8 ⟶ methyl shift

13 ⟶ 14 ⟶ methyl shift

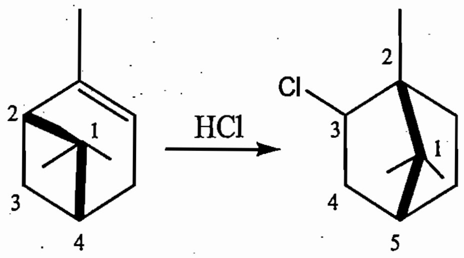
This leaves a positive charge at position 13, which is stabilized by loss of the proton at 18-position to give (B).





Note: Alkyl migrations occur in order to make a carbocation more stable.
A cation can be made more stable if they become less strained.

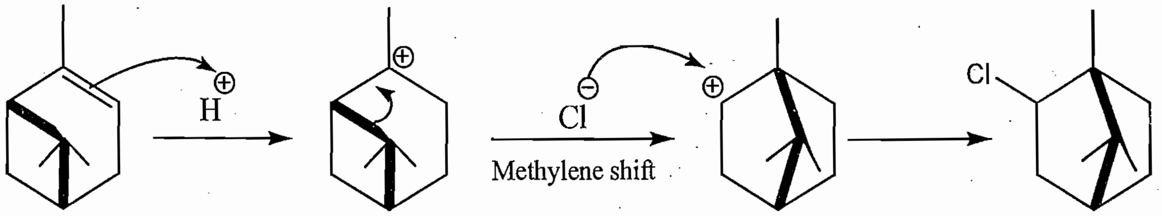
For example **:** Four-membered rings adjacent to cations readily rearrange to five memebred rings in order to relieve ring strain.



Four membered ring 5-membered ring.

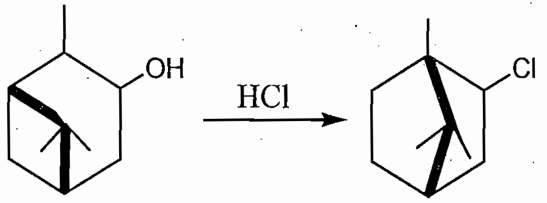
Mechanism:

$$H-Cl \longrightarrow H^{\oplus} + Cl^{\ominus}$$



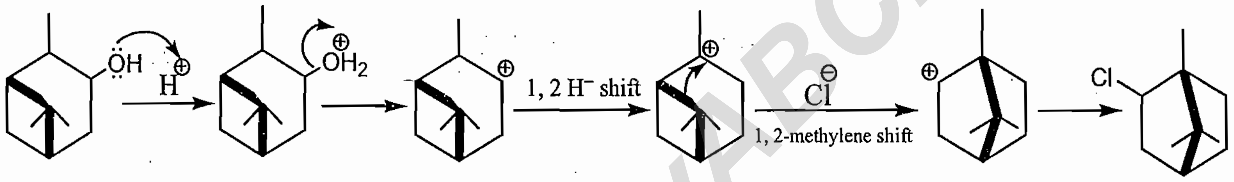
In order to relive the ring strain

Problem:

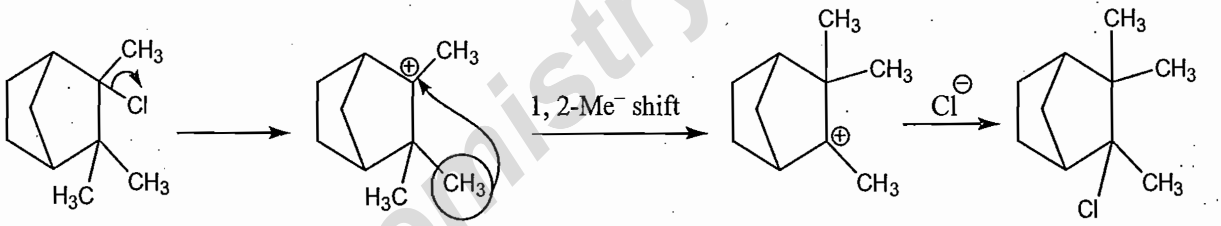


Mechanism:

$$H-Cl \longrightarrow H^{\oplus} + Cl^{\ominus}$$



Problem: The racemisation of camphene hydrochloride (Nemetkin rearrangement)



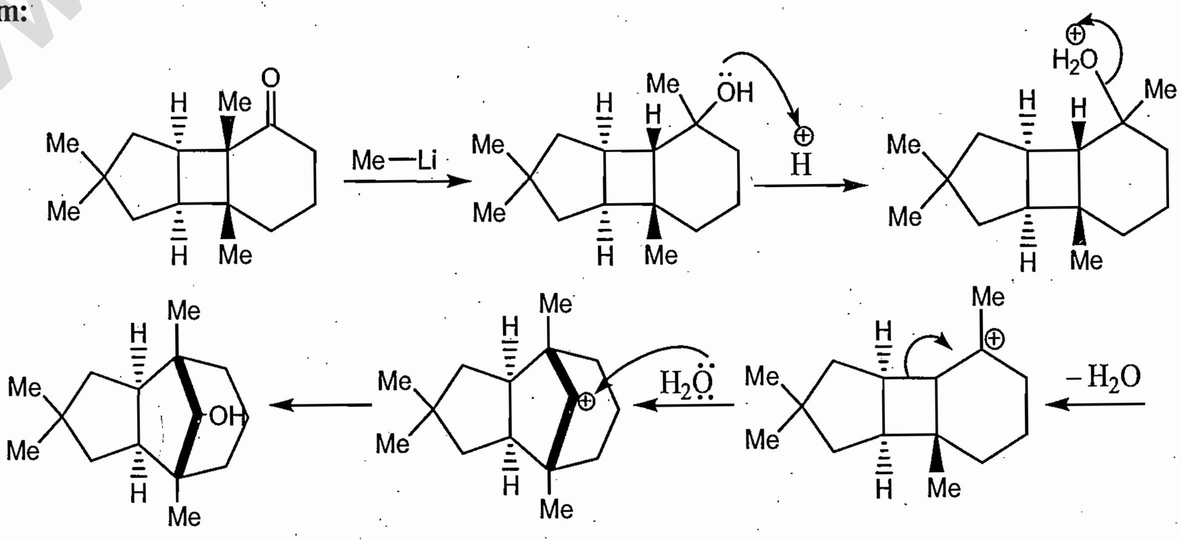
Remark:

1. The rate of the rearrangement was found to 1st order and rate depends on the nature of the solvent, the rate being faster the greater the ionising power of the solvent. The order observed for some solvents was:

$$SO_2 > MeNO_2 > Me-CN > Ph-\overset{O}{\overset{\|}{C}}-Me > Ph-OMe > PhBr > PhH > Et_2O$$

2. Meerwein also found that the rearrangment was strongly catalysed by lewis acids such as stannic chloride ($SnCl_4$), ferric chloride ($FeCl_3$) etc.

Problem:

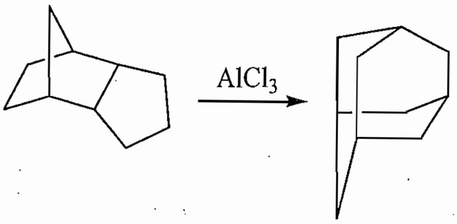


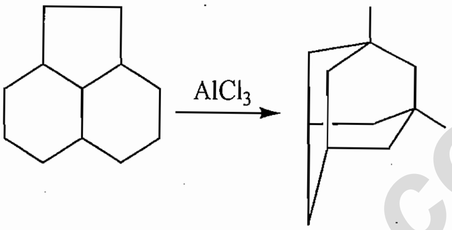
driving force of the reaction is relives in strain in the 4 membered ring.

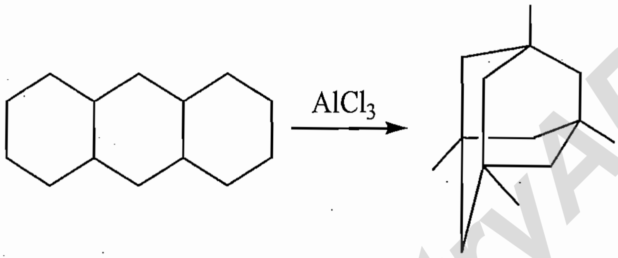
- Even alkanes undergo Wagner-Meerwein rearrangment if treated with lewis acids and a small amount of the inatiator.
  An interesting application of this reaction is the conversion of tricyclic molecule to adamantane and its derivative.

It has been found that all tricyclic alkanes containing 10 carbons are converted to adamantane by treatment Lewis acid such as $AlCl_3$.

If the substrate contains more than 10 carbons, alkyl substituted adamantanes are produced. The IUPAC name for these reaction is **Schleyer adamantization.**





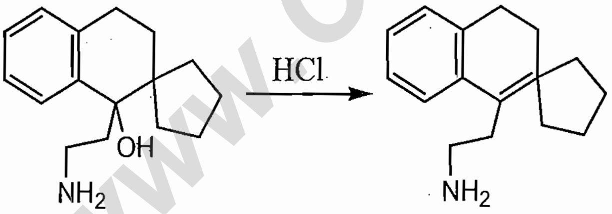


If 14 or more carbons are present, the product may be diamantane or a susbtituted diamantane.

Note: These reactions are successful because the high thermodynamic stability of adamantane, diamantane, and similar diamond-like molecule. Best yields are obtained by the use of **"Sludge"** catalyst (i.e. mixture of AlX_3 and t-butyl bromide or sec-butyl bormide.

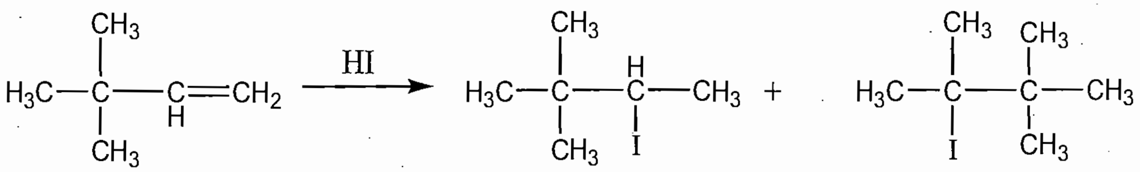
PROBLEMS

1.



When the alkene 3, 3-dimethyl -1-butene is treated with hydrogen iodide there is a mixture of products obtained.

2.

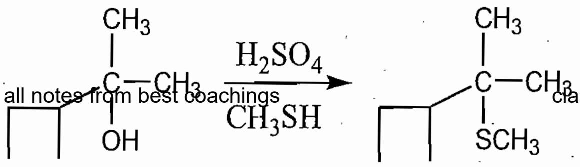


$$H_3C-\underset{CH_3}{\overset{CH_3}{C}}-\underset{H}{C}=CH_2 \xrightarrow{HI} H_3C-\underset{CH_3}{\overset{CH_3}{C}}-\underset{I}{\overset{H}{C}}-CH_3 + H_3C-\underset{I}{\overset{CH_3}{C}}-\underset{CH_3}{\overset{CH_3}{C}}-CH_3$$

3, -dimethyl-1-butene 3-iodo-2, 2-dimethylbutane 3-iodo-2, 3-dimethyl butane

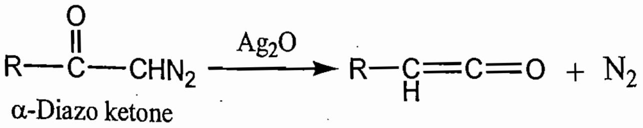
propose a likely mechanism for this reaction.

3.



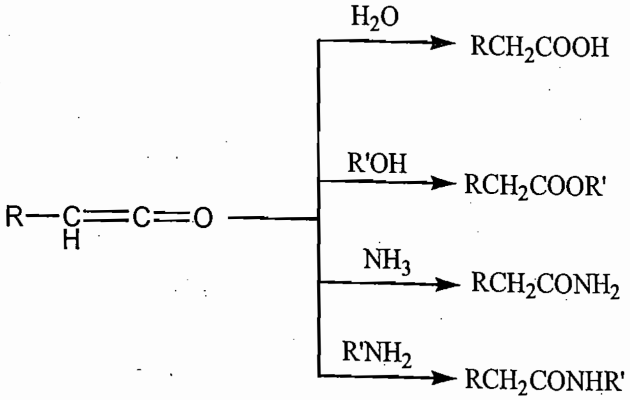
7.22. Wolff Rearrangement

α-Diazo ketones on treatment with solid silver oxides split off nitrogen and rearrangement to ketene. This is known as Wolff rearrangement.



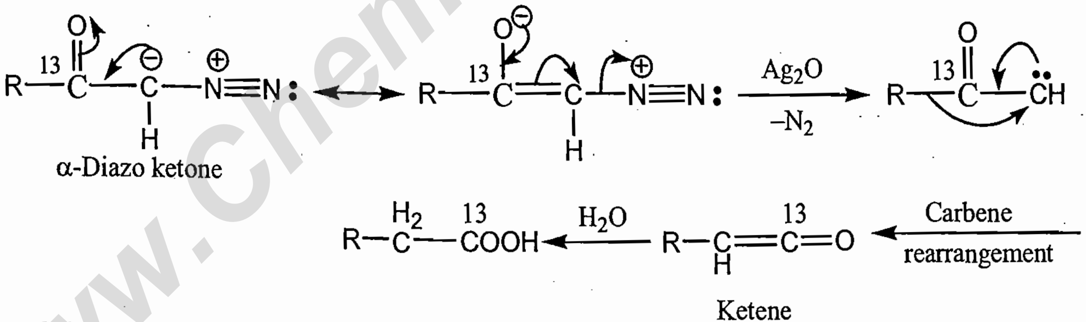
$$R-\overset{O}{\overset{\|}{C}}-CHN_2 \xrightarrow{Ag_2O} R-\underset{H}{C}=C=O + N_2$$

The rearrangement may also occur on irradiation or on heating. When the reaction is carried out in the presence of water, alcohol, ammonia or amine, the highly reactive ketene readily reacts with the nucleophiles present, e.g., H_2O, ROH etc. to give respectively acids, esters, amides or substituted amides of the next higher homologue of the acid from which the α – Diazo ketone is prepared.



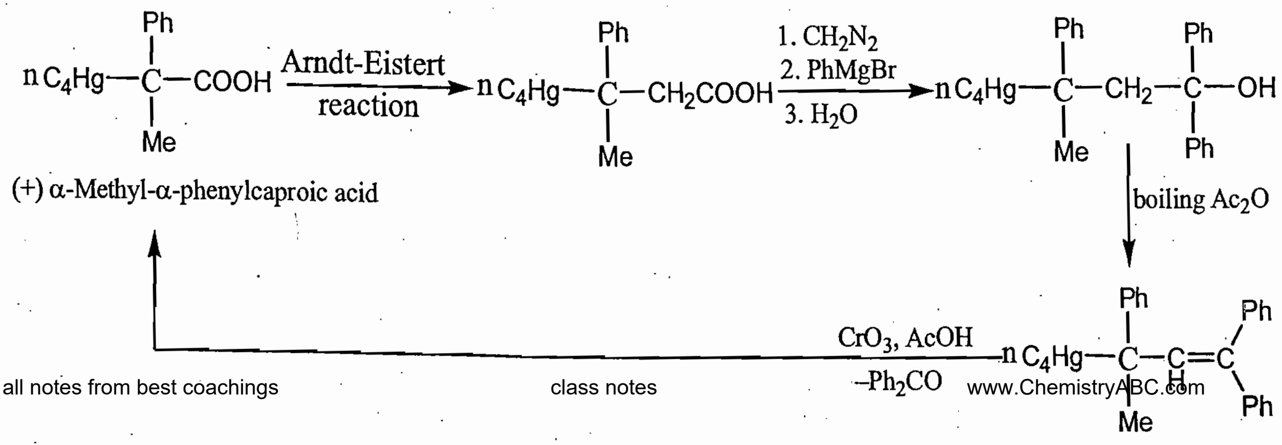
where R= aliphatic, aromatic, heterocyclic and alicyclic

Mechanism: It has been shown isotopically labelled carbon (^{13}C) in a series of transformations that the carbonyl carbon of α – Diazo ketone is present in the resulting acid as the carboxyl carbon when the reaction is carried out in the presence of water. Obviously, migration must have occured during the rearrangement. On the basis of this, the following mechanism has been suggested.



Splitting of nitrogen and migration of R group may be concerted. In some cases ketenes have been isolated. The group R migrates with retention of configuration. This has been confirmed by the following observation.

A higher homologue of an optically active and (i) obtained by Arndt-Eistert-Wolff rearrangement on degradation by Barbier-Wieland method gave the original acid with the same configuration(Lane and Walls).



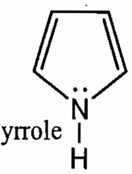
CHAPTER

8

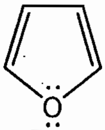
Heterocyclic Chemistry

The atoms other than carbon and hydrogen are known as hetero atom. The compound containing hetero atom[such as N, S, O etc], is known as heterocyclic compound.

Monocyclic compounds with one hetero atom:
Some of the important heterocyclic compounds containing one hetero atom are:
(i) 5-membered heterocyclic compounds:

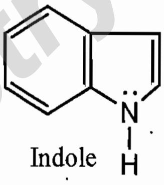


Pyrrole



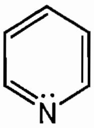
Furan

Thiophene

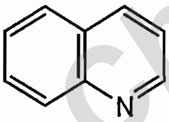


Indole

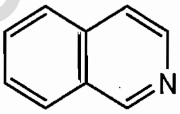
(ii) 6-membered heterocyclic compounds:



Pyridine



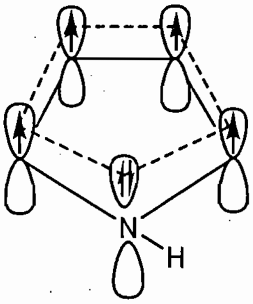
Quinoline



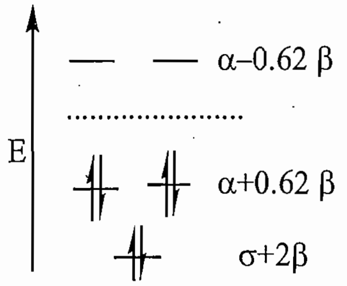
Isoquinoline

8.1. PYRROLE

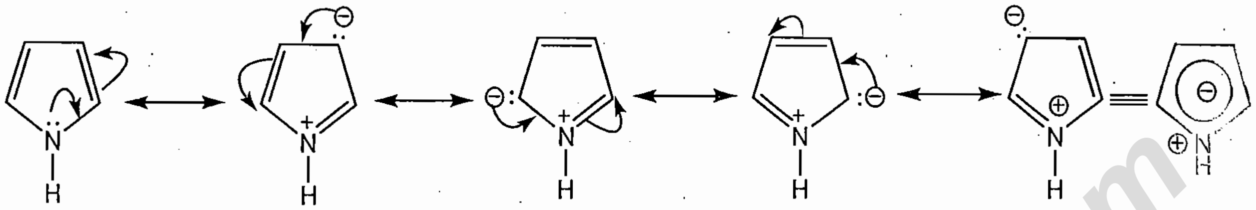
(A) General characteristics:
(1) Molecular formula C_4H_5N. Resonance Energy is 21 Kcal/mole, pKa = 16.5
(2) The pyrrole ring system is important as it is found in many natural products including hemoglobin, chlorophyll and alkaloids.
(3) Molecular orbital picture:



The ring has five 'p' orbitals that can overlap to create five new orbitals, three bonding and two antibonding molecular orbitals, there are six electrons for these orbitals. The four 'p' orbitals of the double bonds each contribute one and the filled orbital contribute the other two electrons. The six electrons occupy the bonding orbitals and constitute an aromatic sextet.



(4) **Resonance structure:**

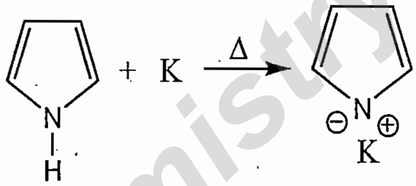


(5) **Pyrrole is a weak base:**

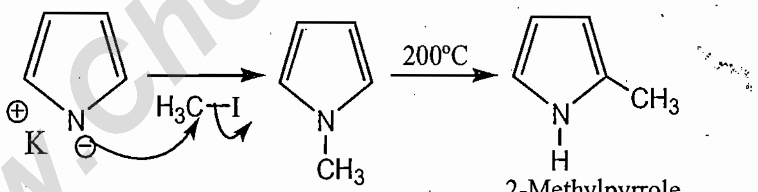
Pyrrole is an extremely weak base because the pair of electrons shown as non bonding electrons is part of the p cloud. When pyrrole is protonated its aromaticity is destroyed. Therefore the conjugate acid of pyrroledine is a very strong acid pKa = –3.8.

$$K_b \sim 2.5\times10^{-14}$$

(6) **Acidic character pyrrole:** Pyrrole is a very weak acid, its acidity is about the same as that of acetylene. **Example:** If pyrrole is heated with metallic potassium in n-heptane as solvents, stable potassium pyrrolide is formed.



Potassium pyrollidine reacts with alkyl halides at 60°C to give N-alkyl pyrroles. On heating to 200°C these readily rearrange to C-alkyl pyrroles



1-Methylpyrrole 2-Methylpyrrole

(7) **Physical properties:**

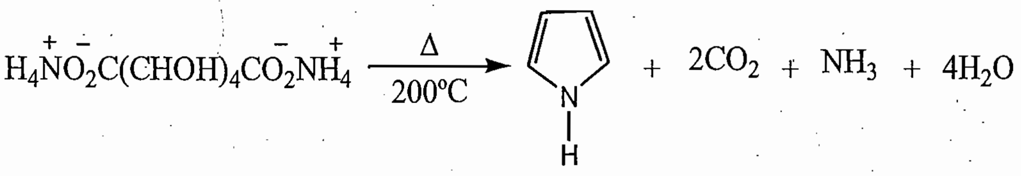
- Pyrrole is a colourless liquid.
- Boiling point 131°C.
- It turns brown in the air and gradually resinifies.
- It is only slightly soluble in water but totally miscible with ether or ethanol.

(B) Synthesis of Pyrrole:

(1) By passing a mixture of acetylene and ammonia through red hot tube.

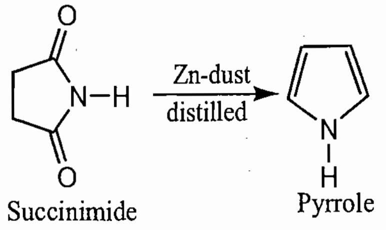
$$2C_2H_2 + NH_3 \longrightarrow C_4H_5N + H_2$$

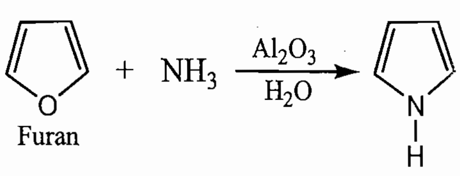
(2) By distilling a mixture of ammonium mucate and glycerol at 200°C.



$$\overset{+}{H_4N}\overset{-}{O_2}C(CHOH)_4C\overset{-}{O_2}\overset{+}{NH_4} \xrightarrow[200°C]{\Delta} C_4H_5N + 2CO_2 + NH_3 + 4H_2O$$

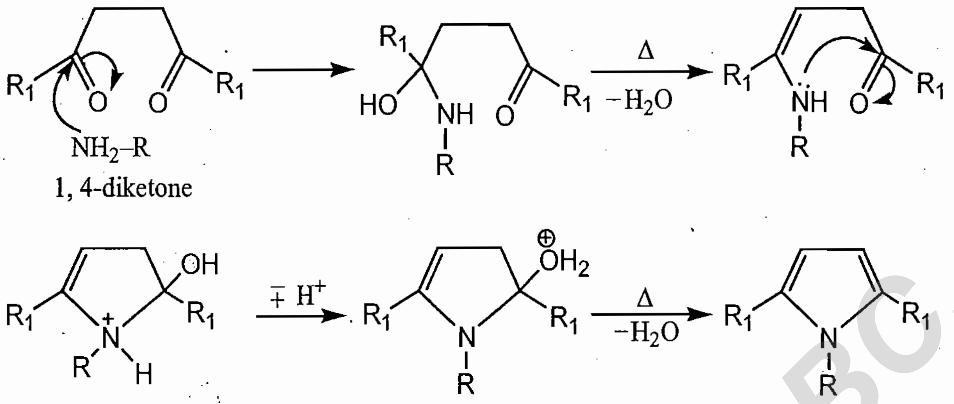
(3) From Succinamide (4) From Furan





(5) Paal-Knorr synthesis:

By treating 1, 4-diketone with ammonia, primary amine or hydrazine etc.

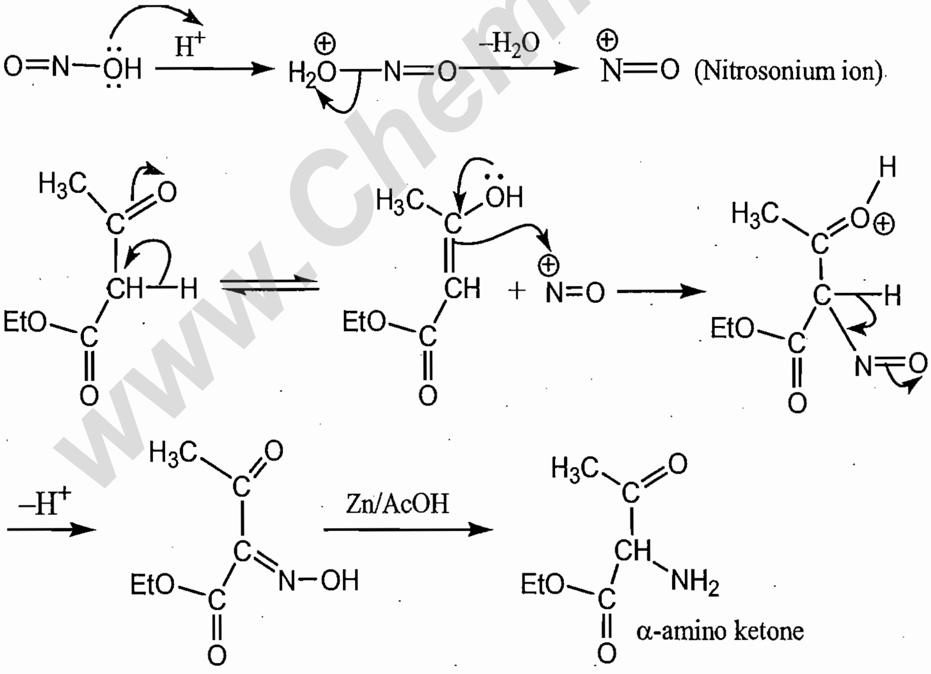


(6) Knorr Pyrrole synthesis:

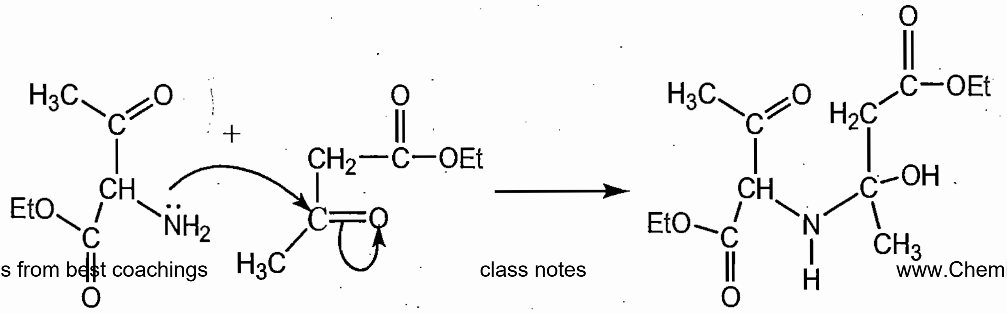
It involves the condensation between an α – amino ketone and a β – diketone or β – ketoester which produces derivative of pyrrole.

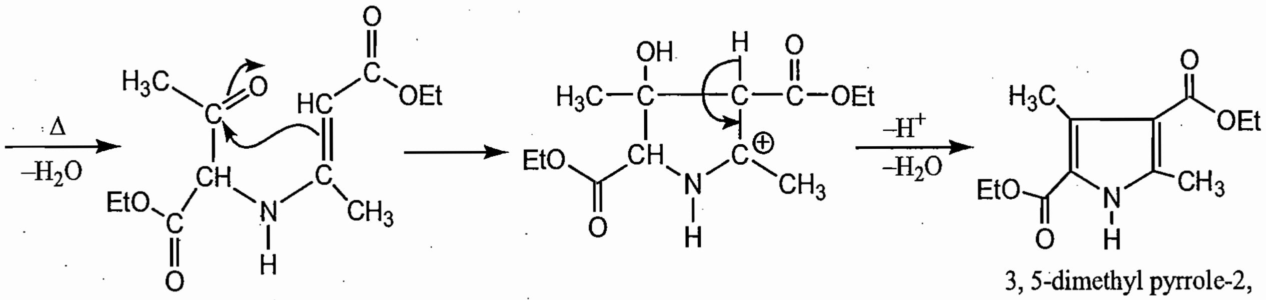
$HNO_2 \longrightarrow H^+ + NO_2^-$

Mechanism:



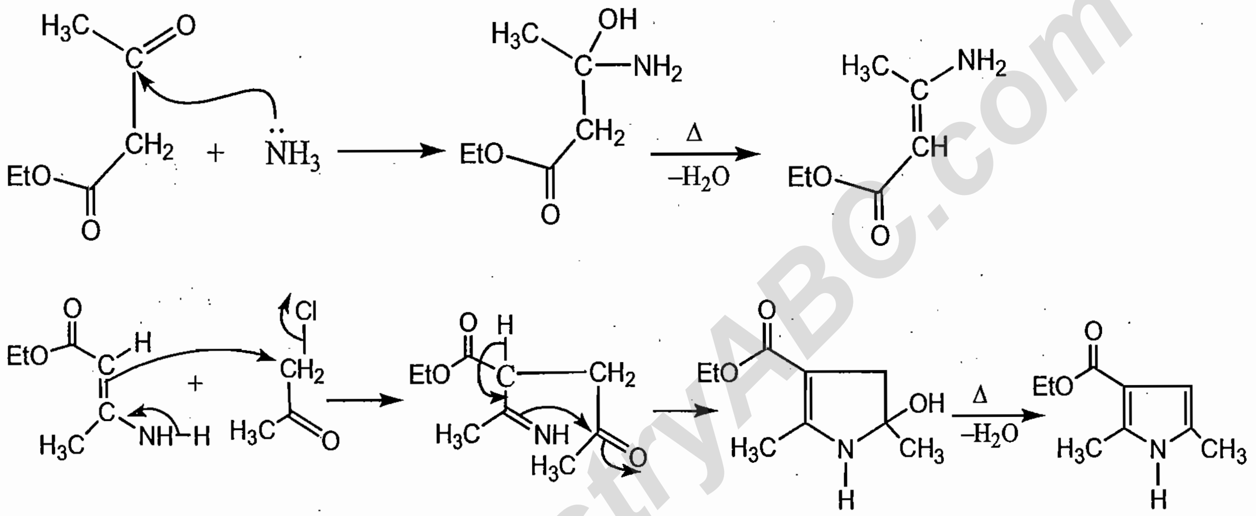
Now,





3, 5-dimethyl pyrrole-2, 4-dicarboxylic ester

(7) Hantzsch synthesis: Condensation between chloroacetone, a β – ketoester and primary amine.

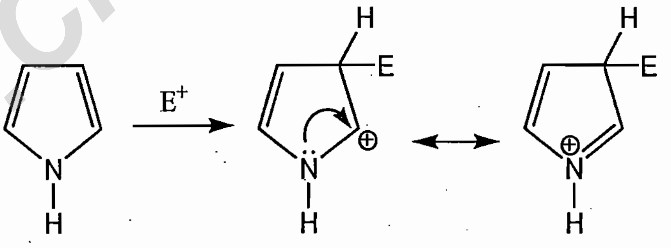


(C) Chemical Properties:

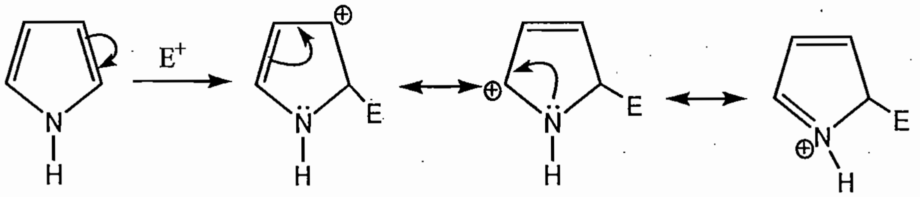
- Pyrrole is aromatic and more reactive than benzene.
- It gives electrophilic substitution reaction.

Preferential position for the attack of E$^+$:

Case 1: Electrophilic attack at 3-position.

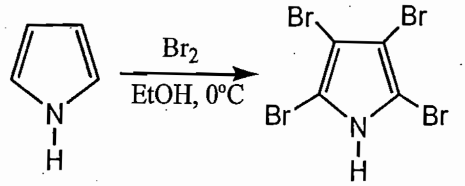


Case 2: Electrophilic attack at 2-position.

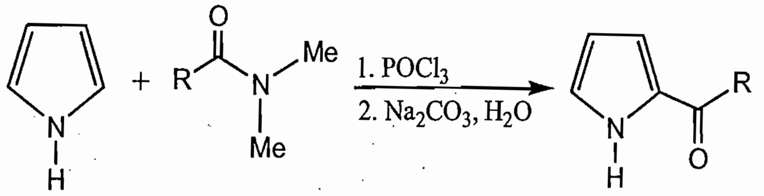


Since intermediate formed after the attack of E$^+$ at 2-position is more stable (due to more resonating structure) than that of intermediate formed after electrophilic attack at 3-position so, electrophilic substitution are favorably occured at 2-position rather than three. If the 2-position is occupied then next substitution will be at 5-carbon if both position 2 and 5 are occupied then substitution can be possible at 3-position.

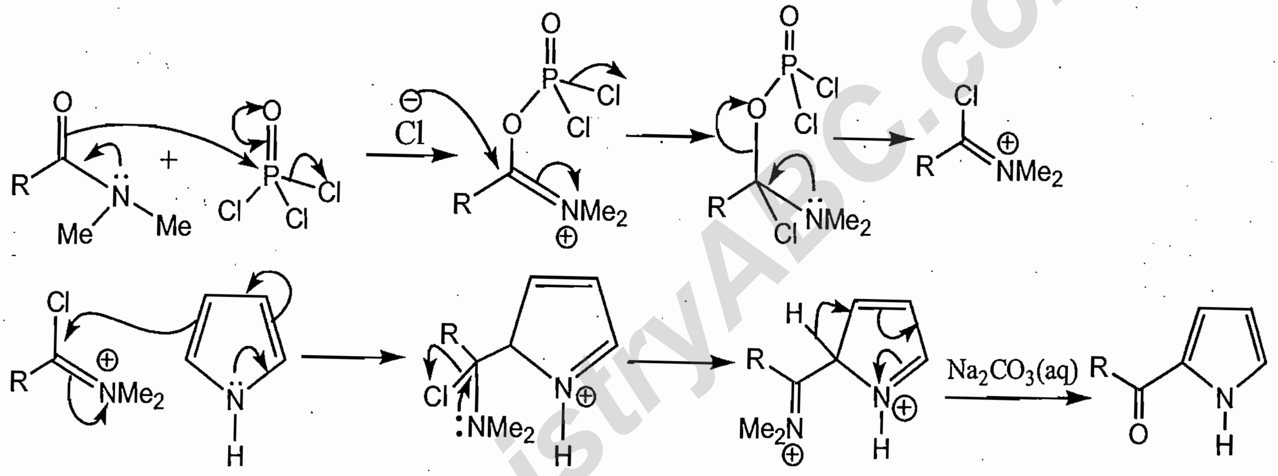
(1) Reaction with Br$_2$: Reaction with bromine requires no Lewis acid and leads to substitution at all four free positions.



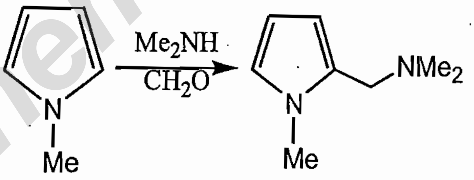
(2) Vilsmeier reaction: Combination of an N, N–dimethylamide and $POCl_3$ in the absence of strong acid or Lewis acid.



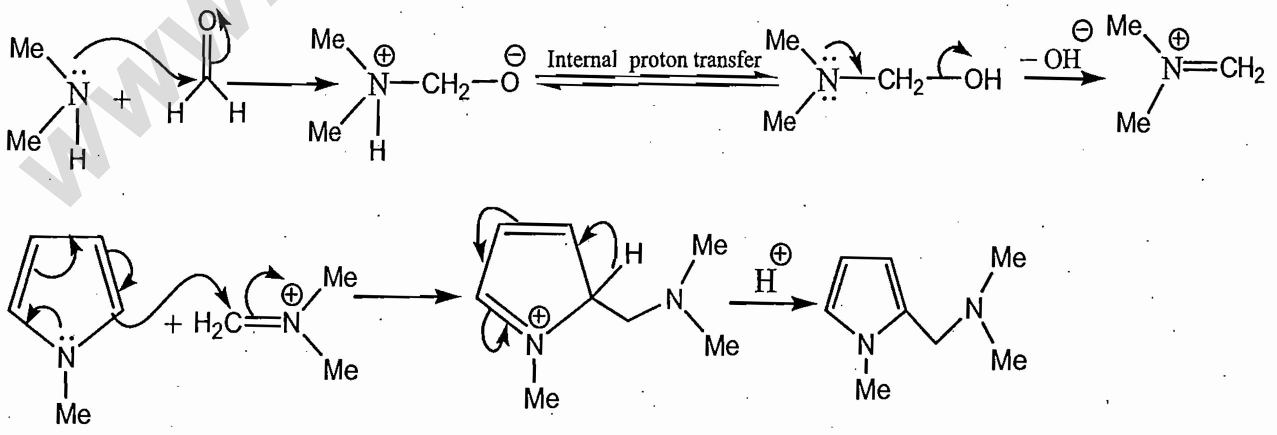
***Mechanism*:**



(3) Mannich reaction:

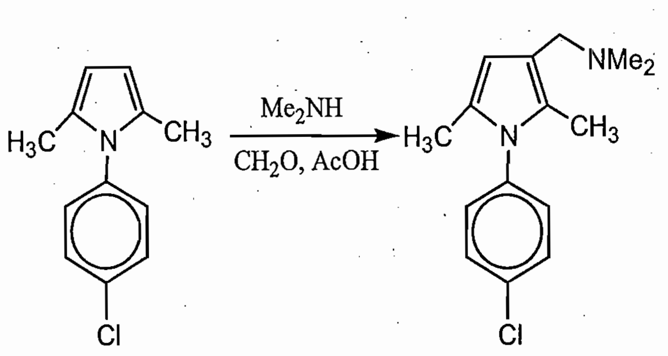


***Mechanism*:**

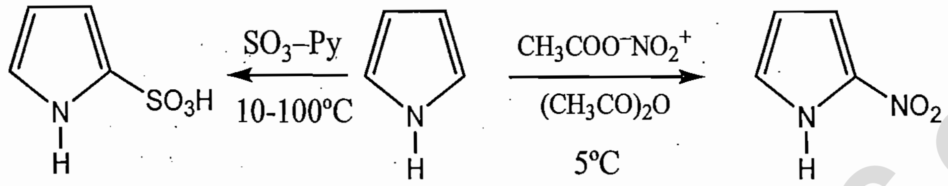


Remark: Though all positions react with reagents like bromine, more selective reagents usually go for the 2- (or 5) position and attack the (3 or 4) positions only if the 2 and 5 positions are blocked.

Example:

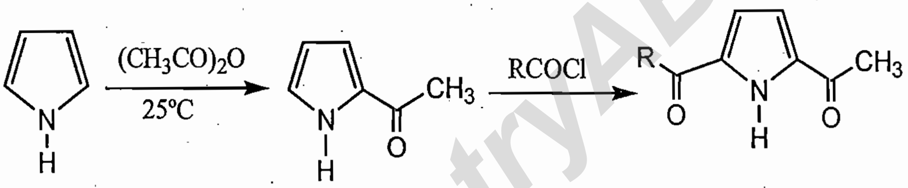


(4) Nitration and sulphonation:

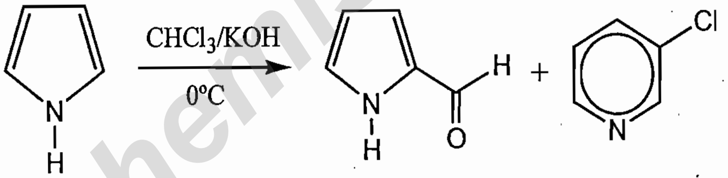


2-nitropyrrole

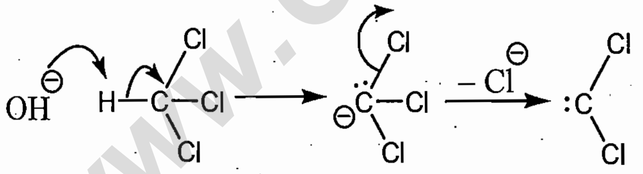
(5) Friedel Craft acylation:



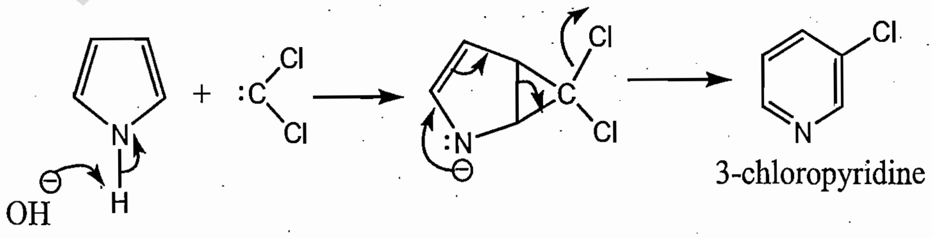
(6) Riemer - Tiemann reaction:



Mechanism:

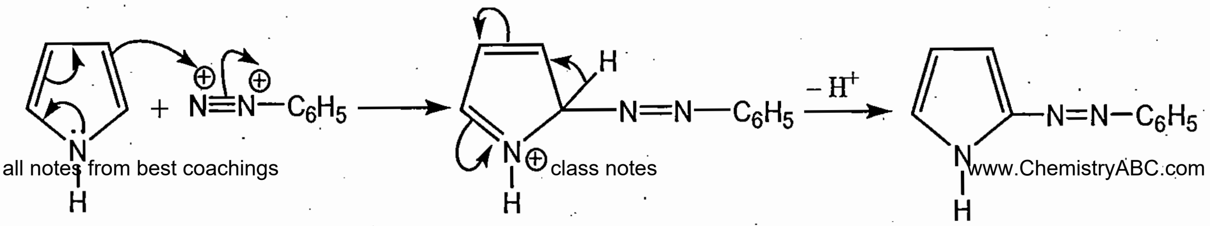


dichlorocarbene



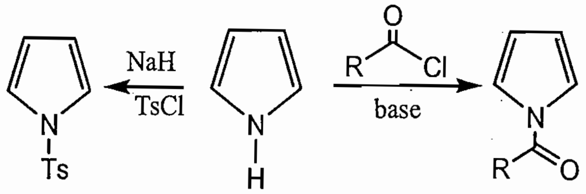
3-chloropyridine

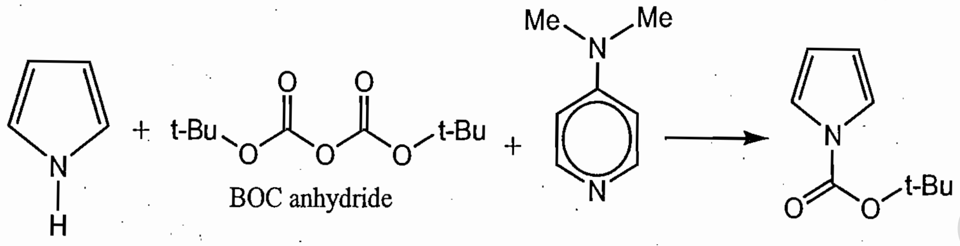
(7) Diazotisation:



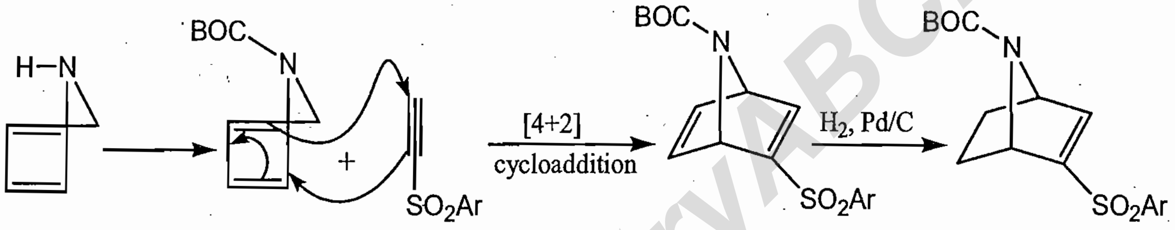
(8) N-acylation of pyrrole:

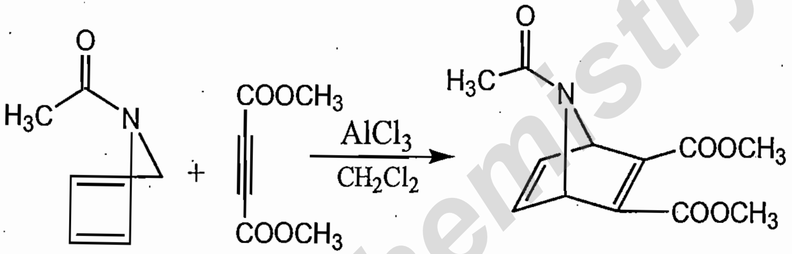
- N-acylated derivatives can be made.
- Commonly used base is NaH.
- Anions of pyrrole react with electrophiles at the nitrogen atom.



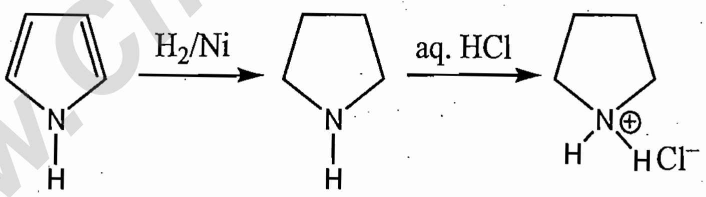


(9) Diels Alder reaction:





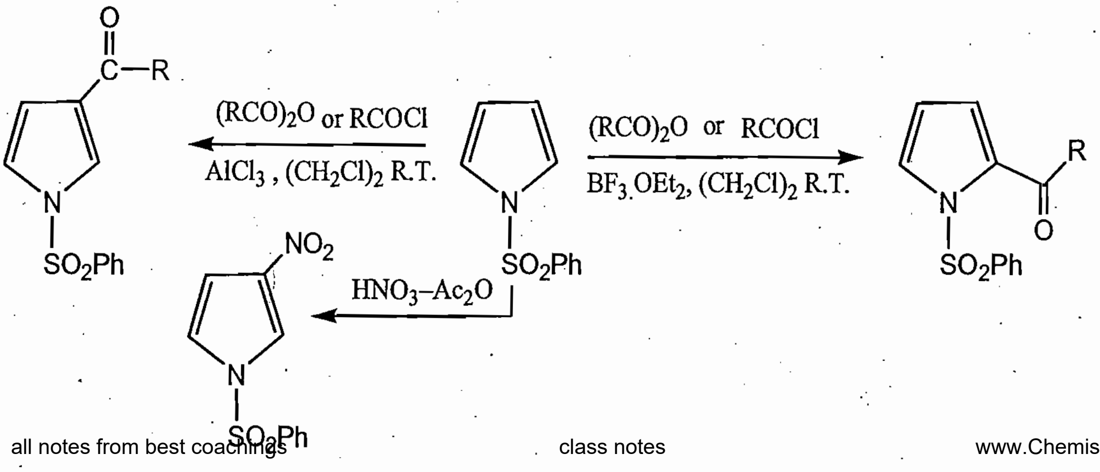
Reduction:



pyrrolidine

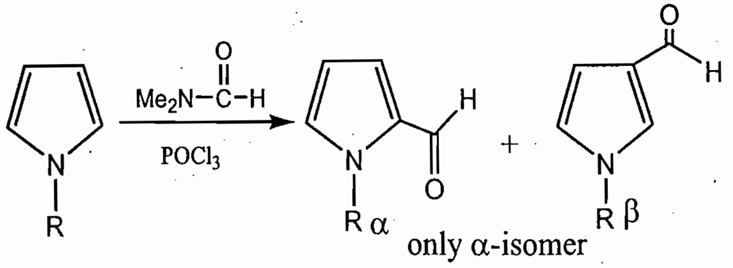
(10) Role of nature of reagents:

In presence of $AlCl_3$ the 3-acyl substituted derivative is obtained while reaction in preference of BF_3 etherate gives the 2-isomer.

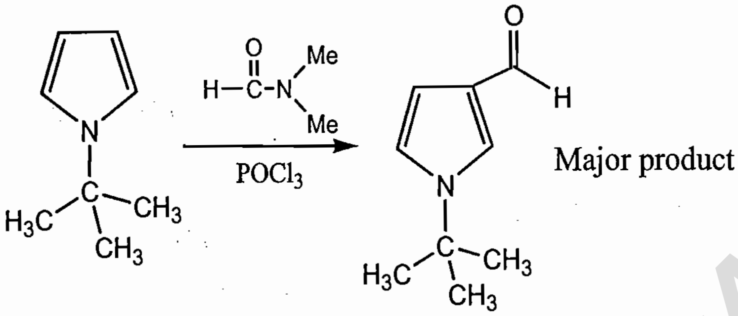


(11) Steric factor: The a:b ratio is influenced by steric requirement of a substituent at the N-atom.

Formylation of N-alkylpyrrole:

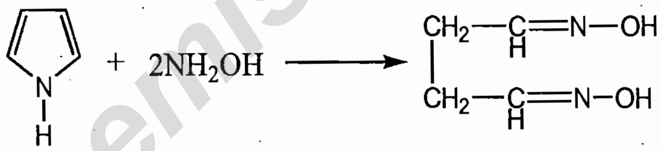


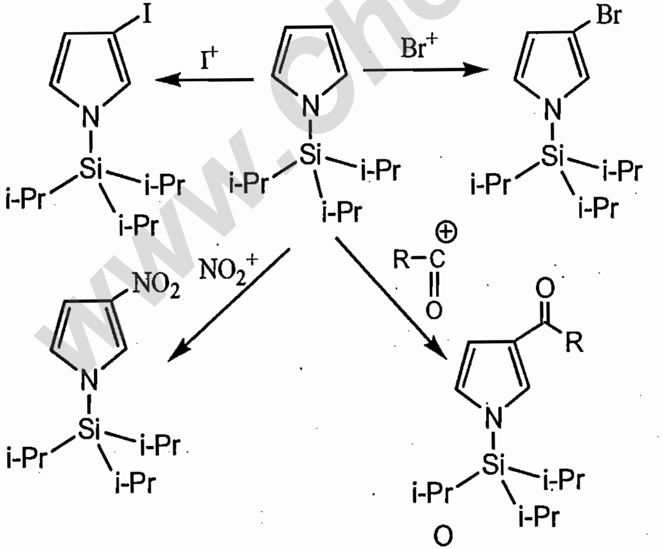
R	a	b
Et	11.5	1
i-Pr	1.9	1
t-Bu	1	14

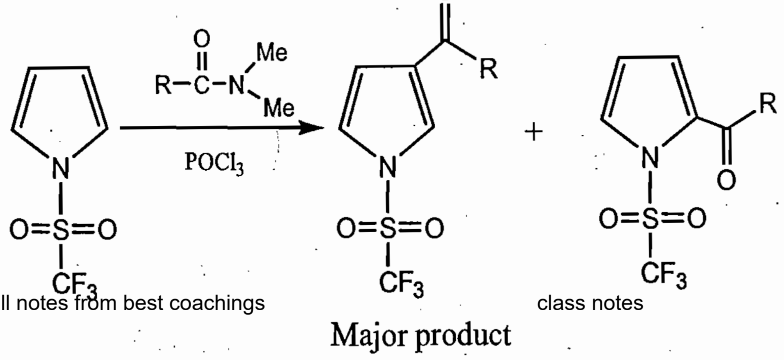


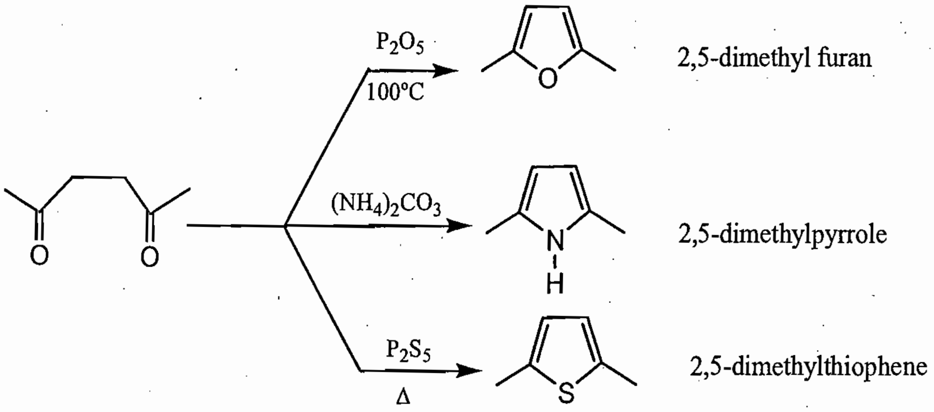
b-substituted derivative on formylation of N-alkyl pyrrole in the sequence.
Me < Et < i–Pr < t–Bu.

When pyrrole is refluxed with an ethanolic solution of hydroxyl amine, the ring is opened and succinaldehyde dioxime is formed.



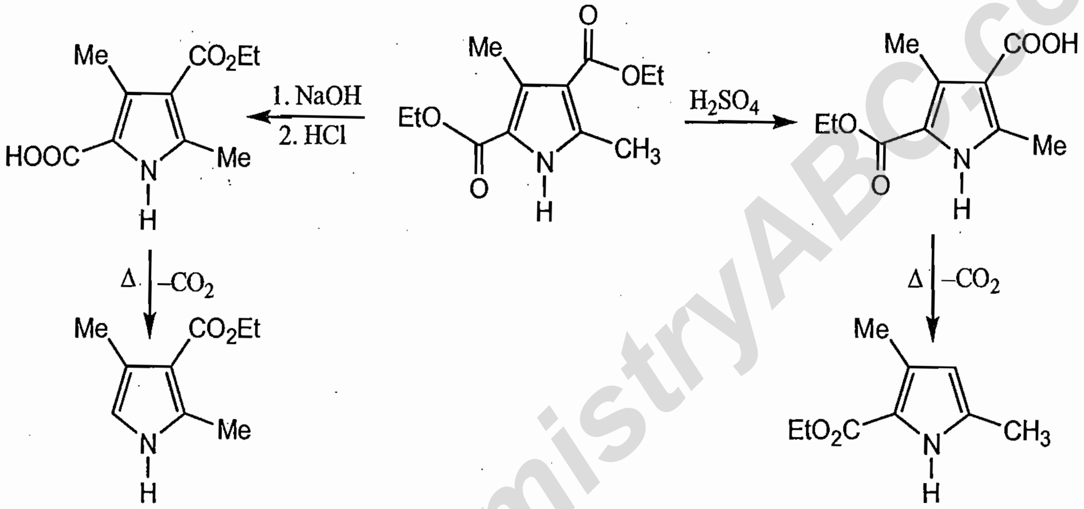






PROBLEMS

1.



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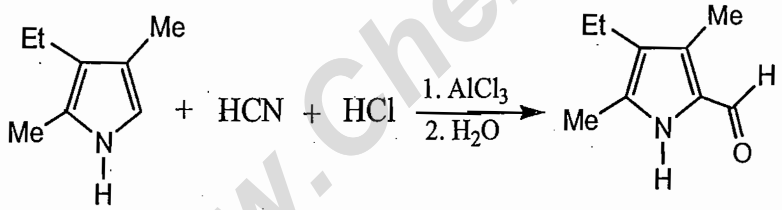

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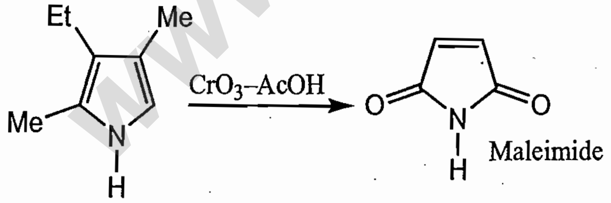

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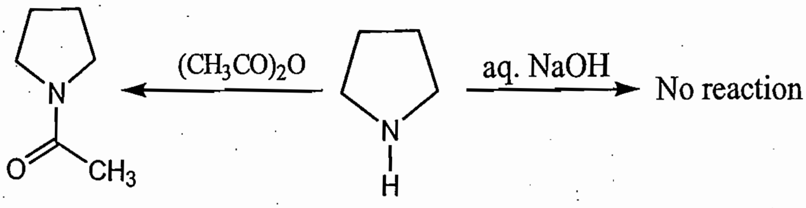
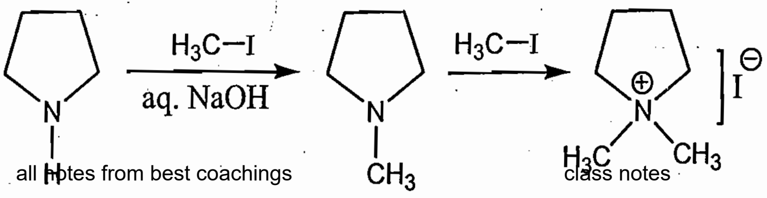
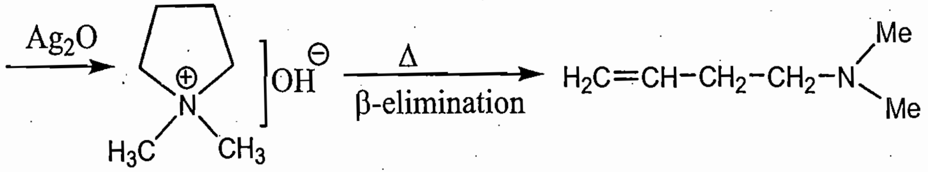


5.

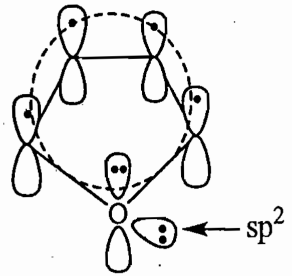




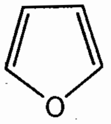
8.2. FURAN

(A) General Characteristics:

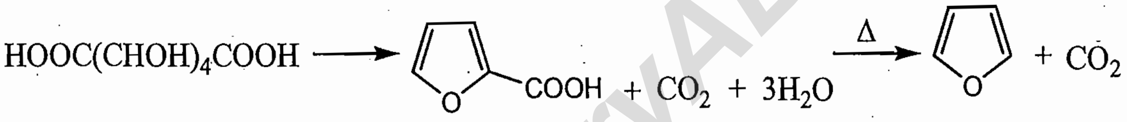
Furan is a colourless, flammable, highly volatile liquid with boiling point close to room temperature. It is toxic may be carcinogenic.

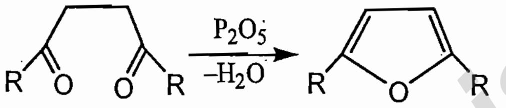


Molecular orbital picture

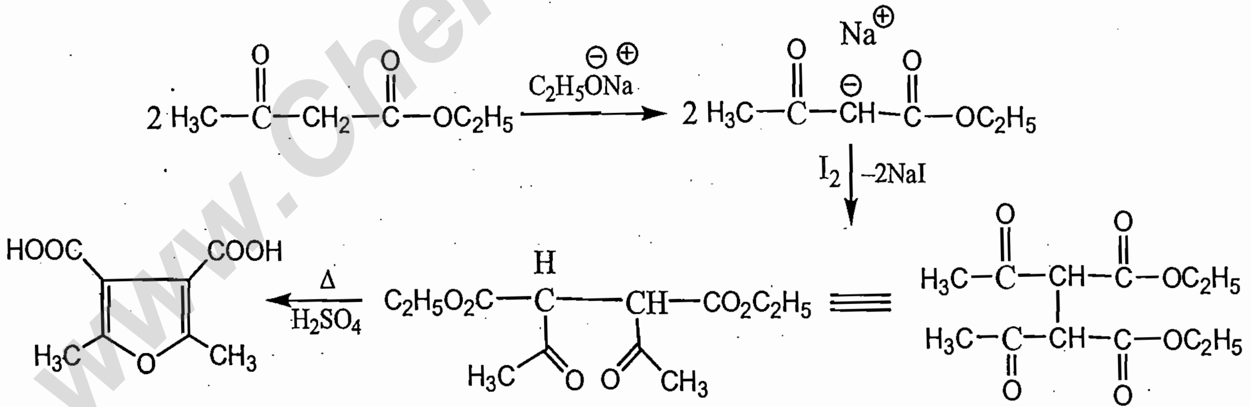


(B) Synthesis of furan:

(1) 

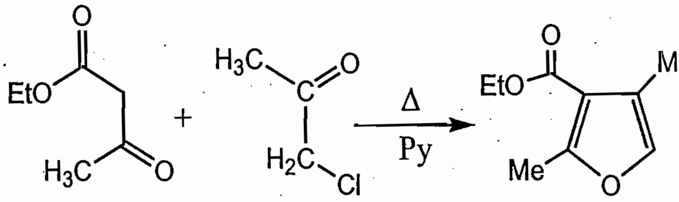
(2) 

(3) From ethyl acetoacetate:



(4) Feist-Benary synthesis:

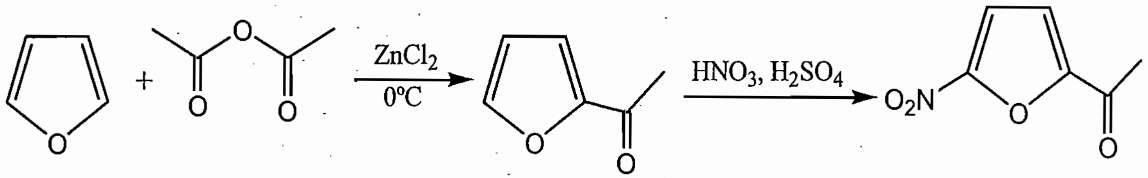
Condensation between α – chloro ketone with a β – keto ester of pyridine.



(C) Chemical Properties:

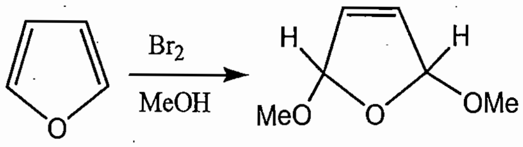
Electrophilic substitution reaction: Preferred position for electrophilic attack is similar to pyrrole i.e. at position 2 and 5 mainly and at 3 if 2 and 5 both are blocked.

(1) Friedel craft acylation reaction:

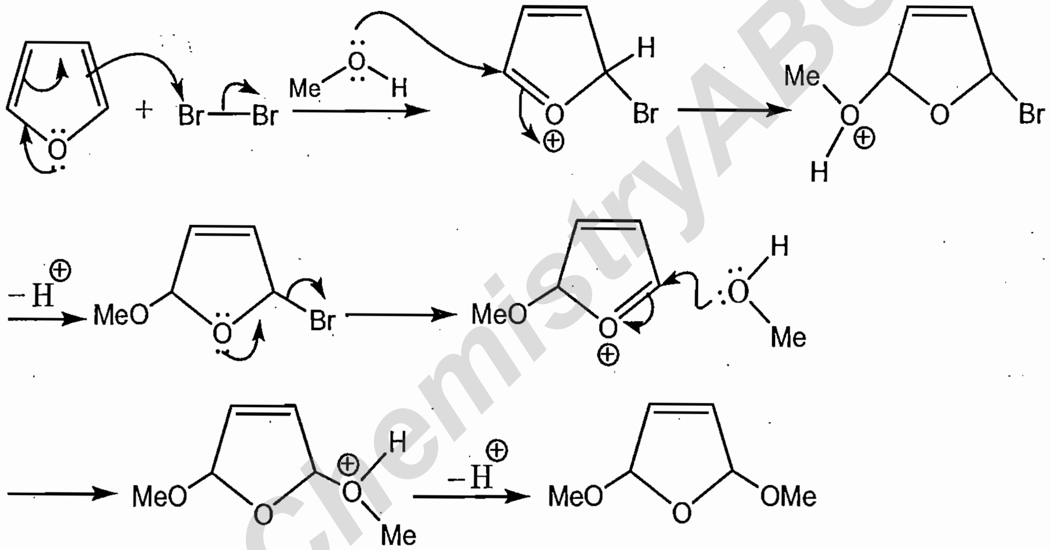


(2) Reaction of Br$_2$/MeOH:

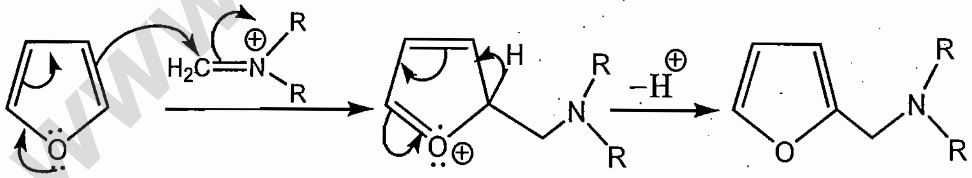
- Furan is not very aromatic and if there is the prospect of forming stable bond such as C–O single bonds by additions
- This may be preferred to substitution.



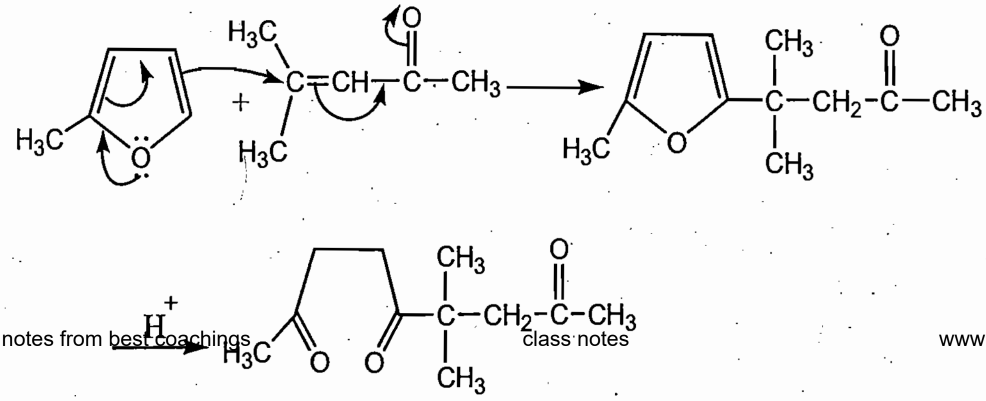
bromination must start in the usual way but a molecule of methonal captures the first formed cation in a 1, 4-addition to furan.



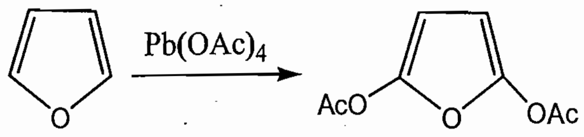
(3) Mannich reaction:



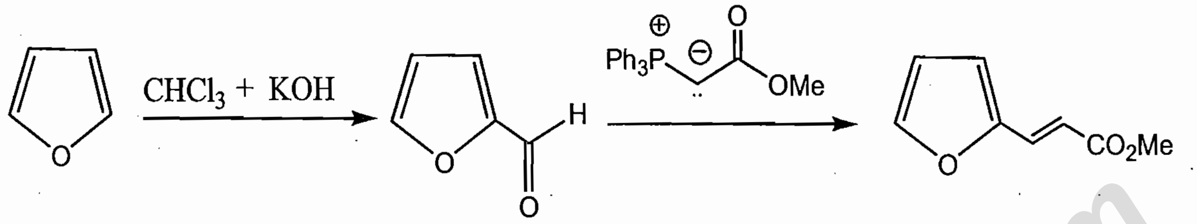
(4) Michael addition:



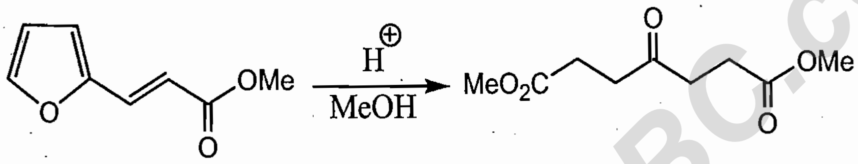
(5) Reaction with $Pb(OAc)_4$:



(6) Riemer Tiemann reaction:

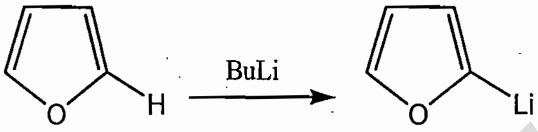


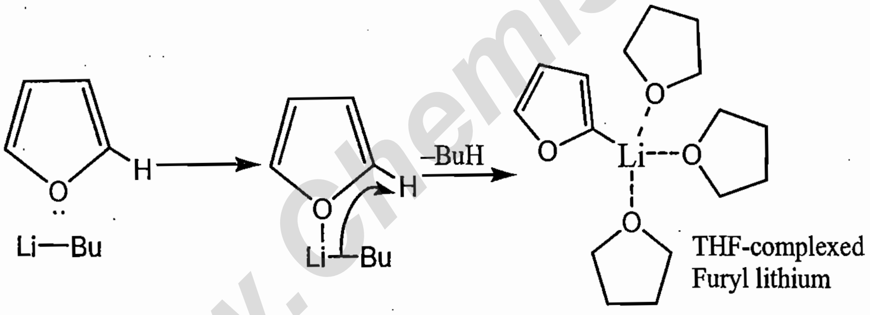
treatment of this furan with acidic methanol gives a white crystalline compound having two -1, 4-dicarbonyl relationship.

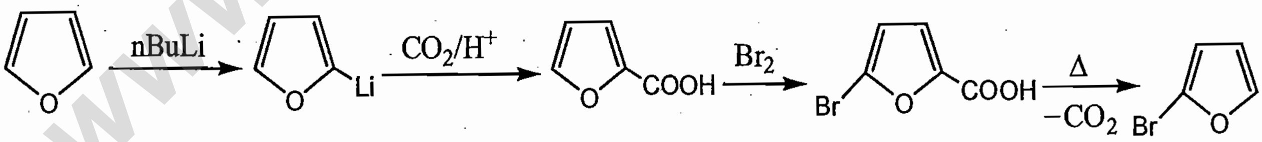


1, 4-dicarbonyl compound

(7) Lithiation of furan:

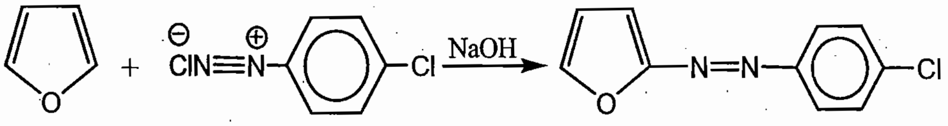






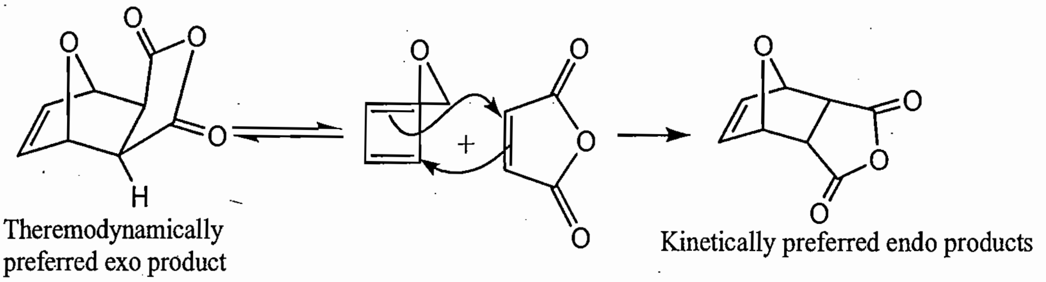
This method is used indirectly for Bromination of furan.

(8) Diazocoupling reaction is:



(9) Diels Alder reaction:

Furan is particularly good at Diels Alder reaction but it gives thermodynamic product, the exo adduct because with this aromatic diene the reaction is reversible.



Theremodynamically preferred exo product

Kinetically preferred endo products

PROBLEMS

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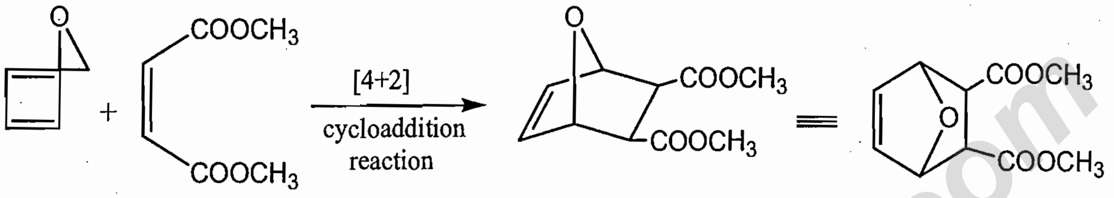

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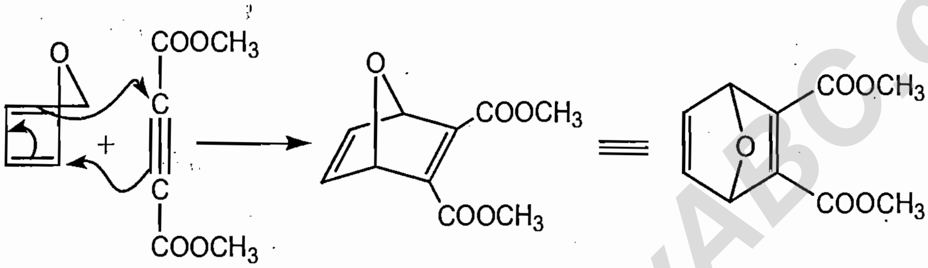

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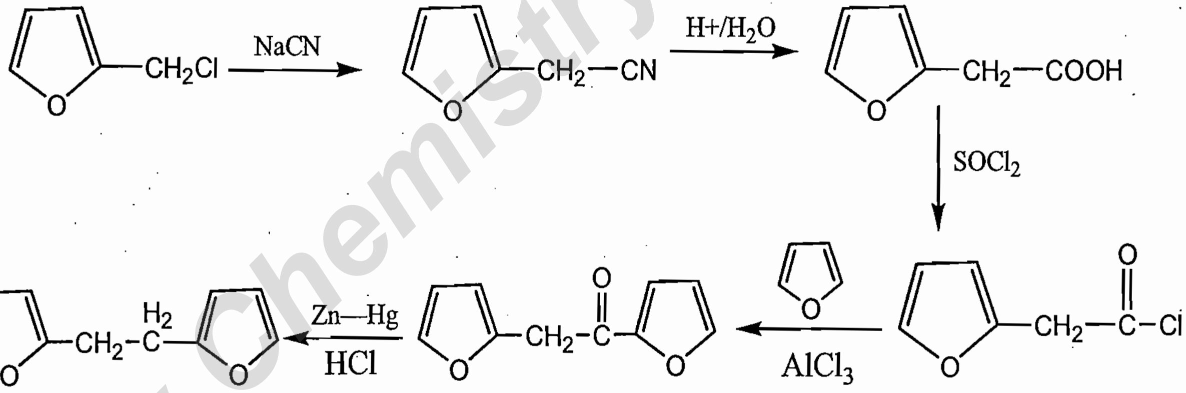

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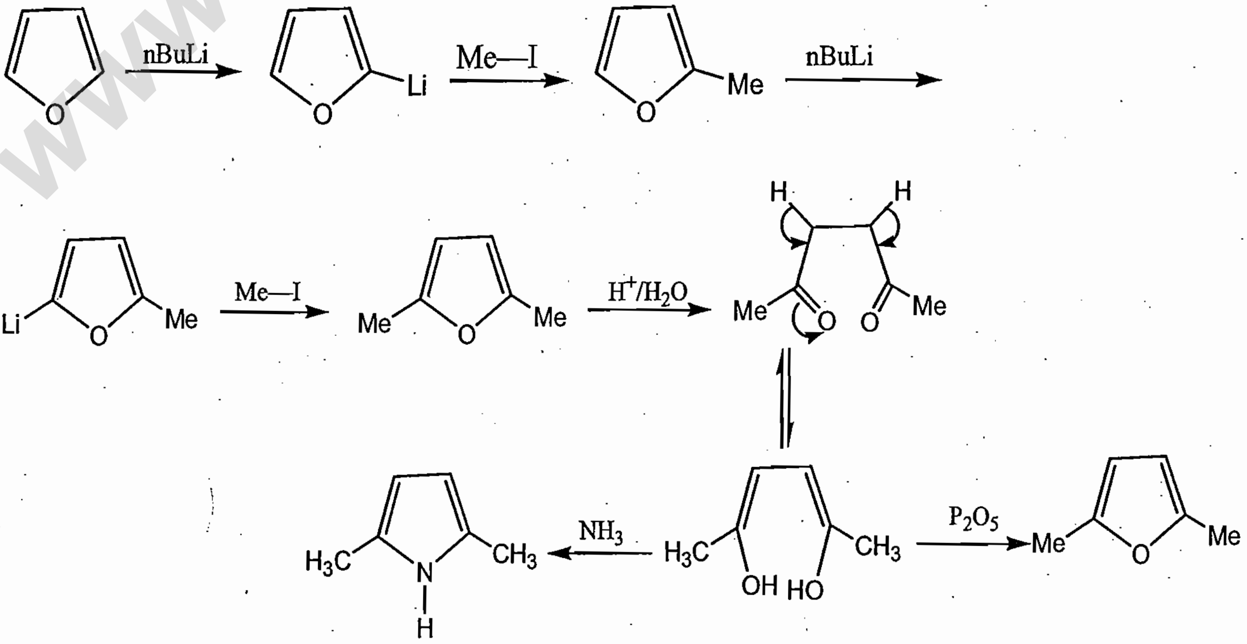
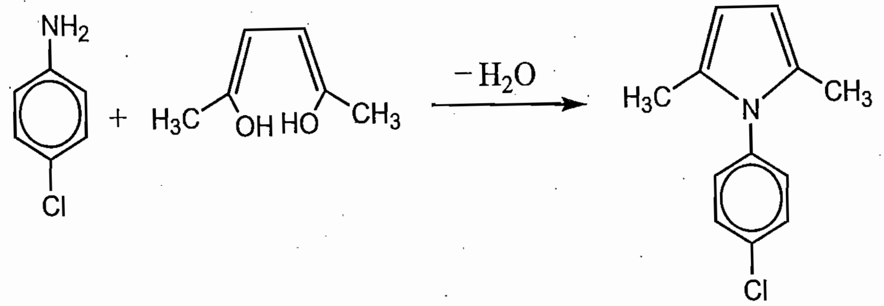
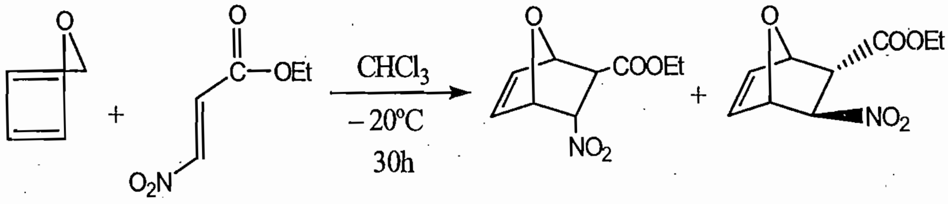
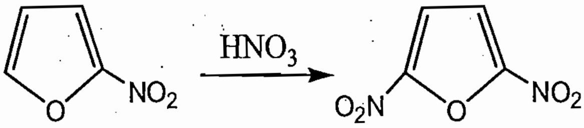


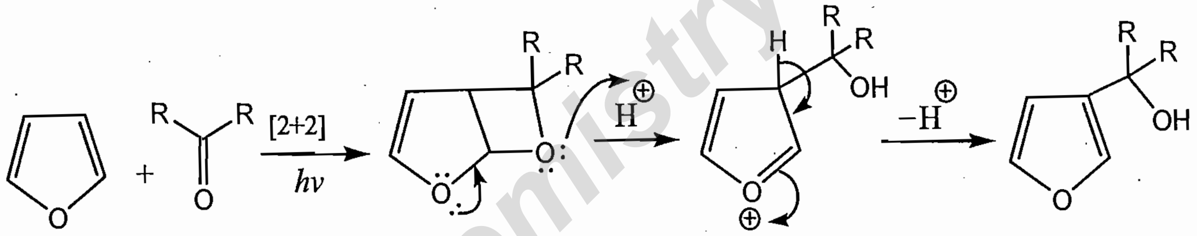
5. 

6. 

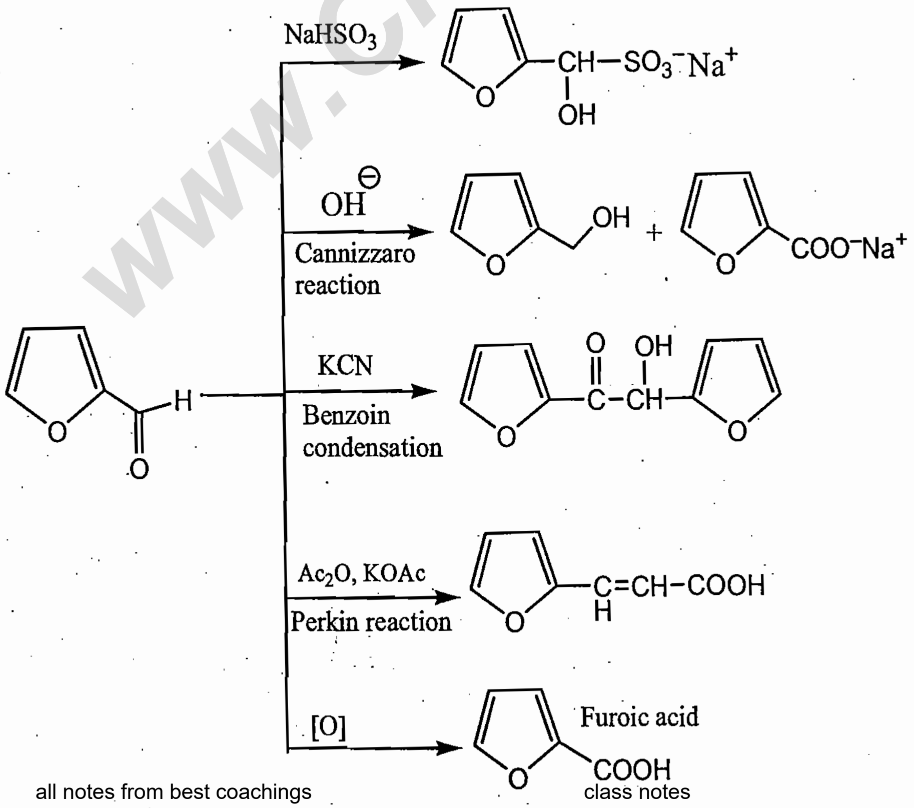
7. 

2, 5-dinitrofuran

(10) Photochemical cycloaddition reaction:



Some other important cycloaddition reaction of furan can be summarised as:



PROBLEMS

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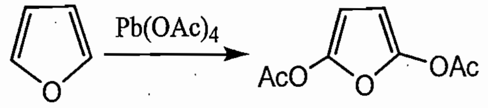

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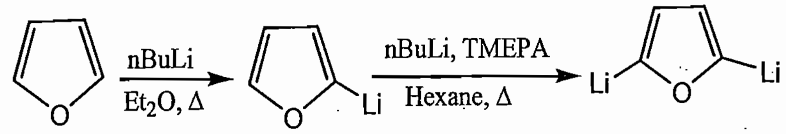

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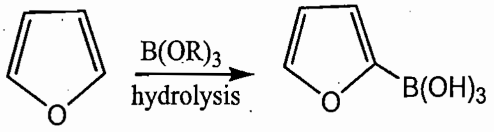

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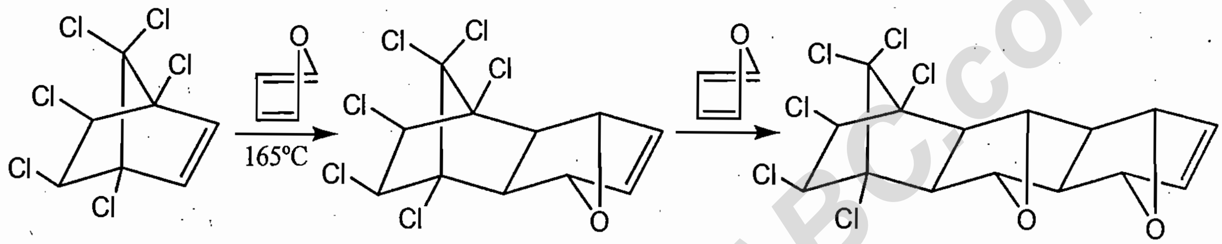

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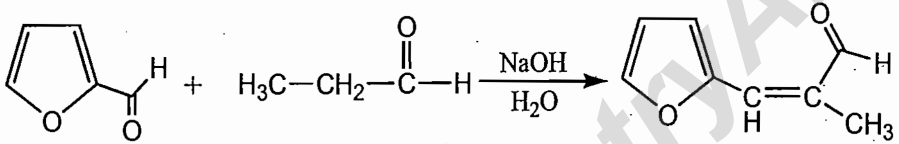

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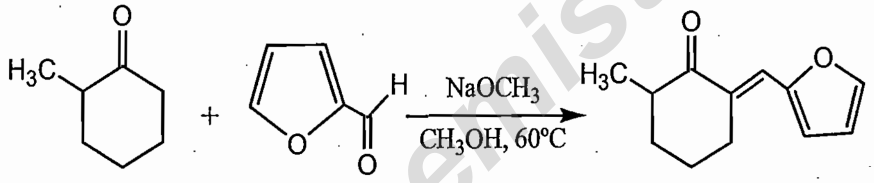

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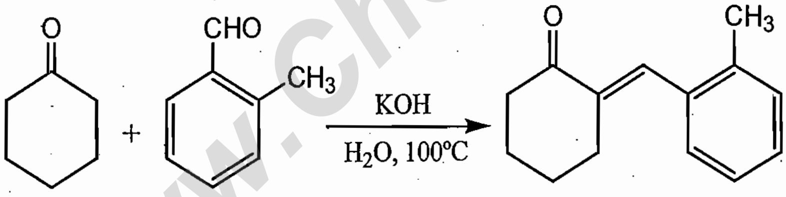

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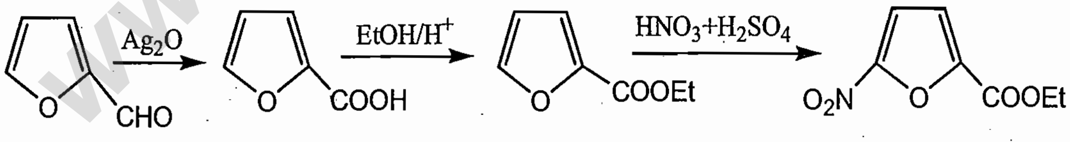

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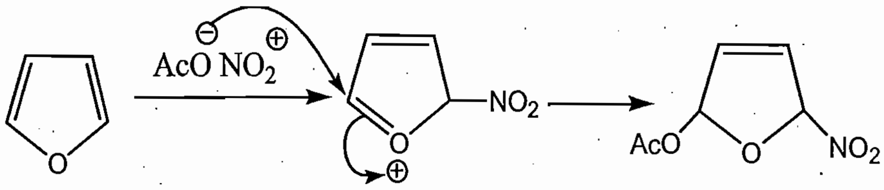

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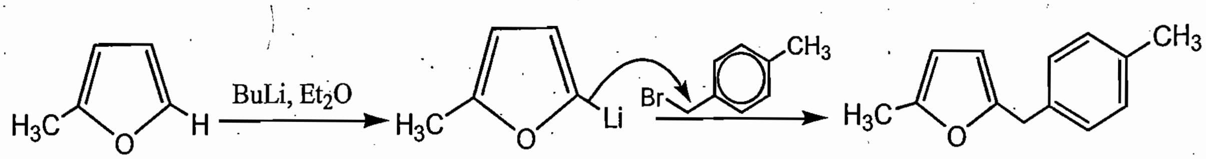

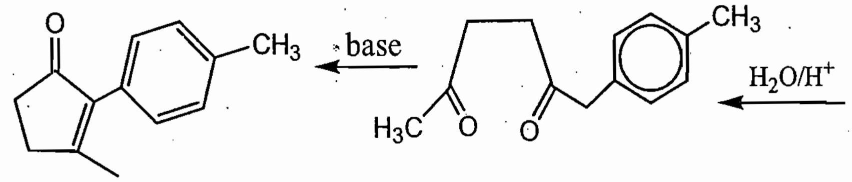

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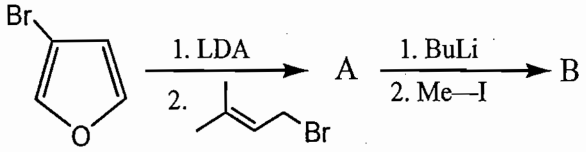
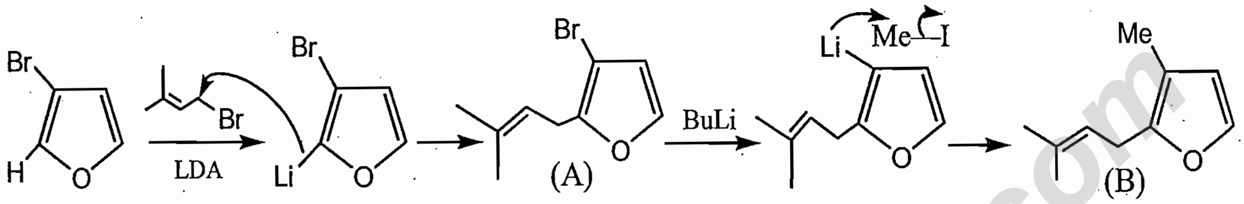
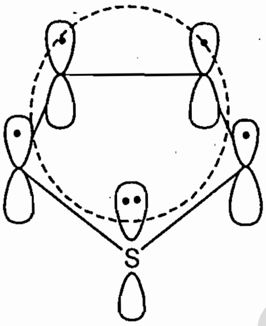


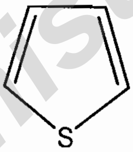


8.3. THIOPHENE (C_4H_4S)

(A) General Characteristics:

(1) Molecular orbital picture.





Molecular formula C_4H_4S, **Molecular orbital picture**

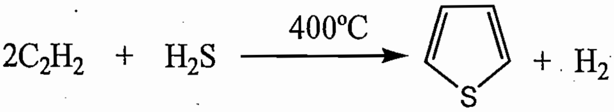
(2) Thiophene is a colourless liquid.having boiling point 84°C

(3) It is insoluble in water but freely soluble in ethanol, ether and acetone.

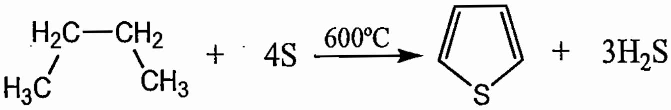
Thiophene is much more reactive than benzene. Thus thiophene undergoes the electrophilic substitution reaction like benzene under moderate condition.

(B) Synthesis of Thiophene:

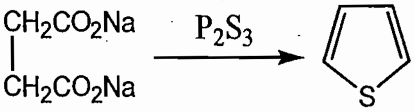
(1) By passing a mixture of acetylene and hydrogen sulfide through tube containing alumina at 400°C.



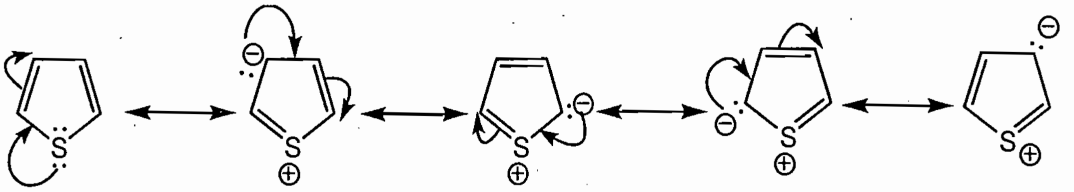
(2) Reaction between n-butane and sulfur in the vapour phase



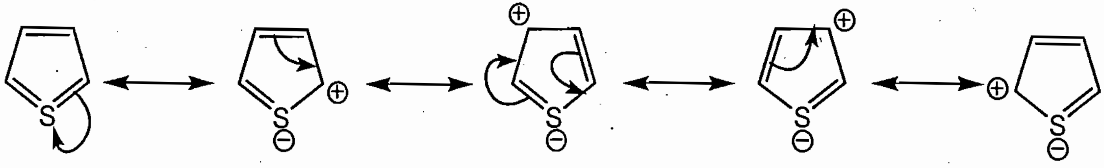
(3) Thiophene may also be prepared by heating sodium succinate with phosphorus trisulphide.



Resonating structure of Thiophene can be shown as.

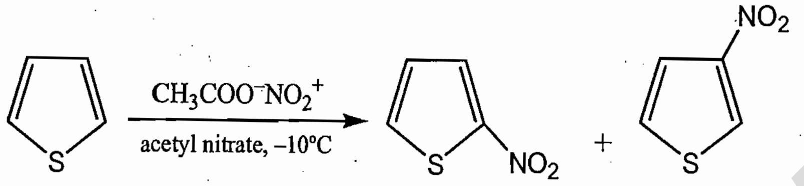


If the sulfur use d-orbital for resonating structure



(C) Chemical Properties:

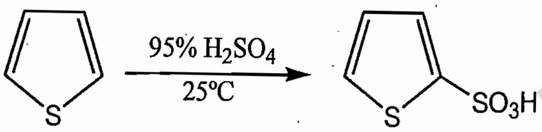
(1) Nitration:



70% 2-nitrothiophene

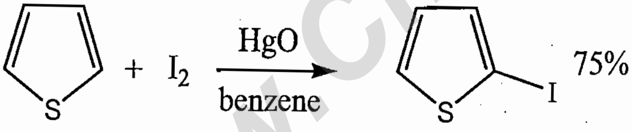
5% 3-nitrothiophene

(2) Sulphonation:



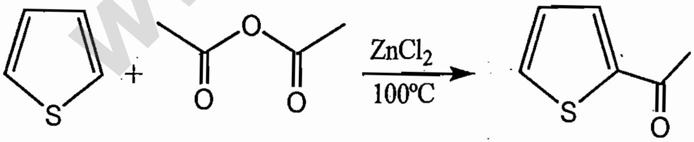
(69-76%)
Thiophene -2-sulfonic acid.

(3) Iodination:



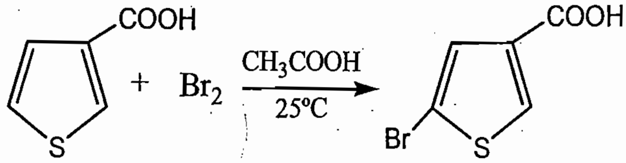
2-Iodothiophene

(4) Acylation:

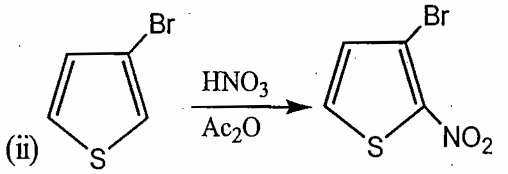


When the substituent is electron attracting meta directing reaction occurs at the non adjacent α-position (i.e. meta to the group present)

(i)

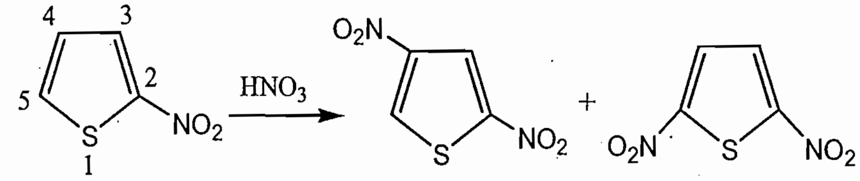


5-Bromo-3-thiophene carboxylic acid.

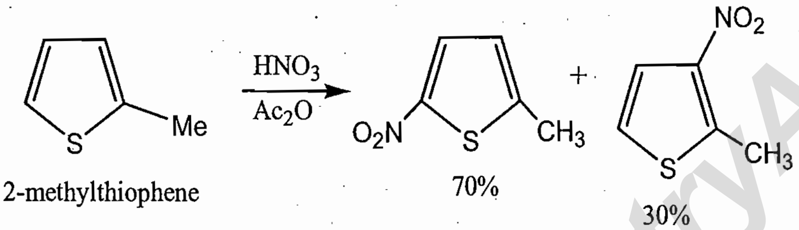


55-60%
3-bromo-2-nitrothiophene

When the 3-substituent is electron donating (ortho, para directing) susbtitution occurs at the adjacent a-position. With 2-susbtituted pyrroles and thiophenes attack can occur at C–4 or C–5 when the group present is metadirecting or at C–3 and C–5 when the group present is ortho, para directing.



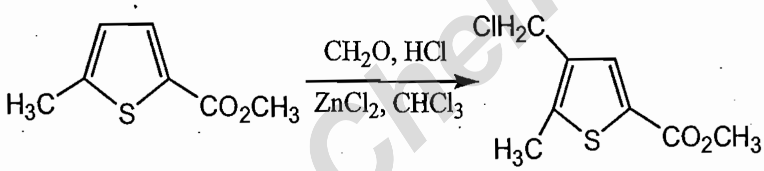
2-nitrothiophene
85%
2,4-dinitrothiophene

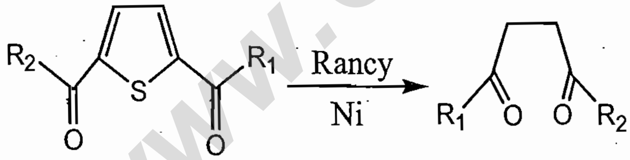


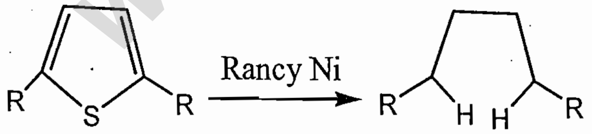
2-methylthiophene
70%
30%

(6) Reduction:

When both α -positions are occupied further susbtitution occurs at a β -position.
The direction of attack being governed by the directing effect of the two group present.

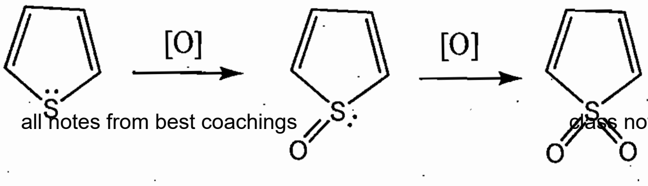


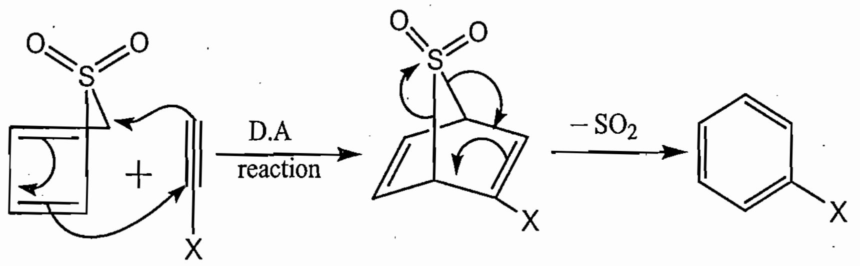




(6) Diels Alder reaction:

Aromaticity prevents thiophene taking part in Diels-Alder reaction, but oxidation to the sulfene destroys the aromaticity because both lone pairs become involved in bonds to oxygen, the sulfone is unstable and reacts with itself but will also do Diels Alder reaction with dienophiles. If the dienophile is an alkyne loss of SO_2 gives a substituted benzene derivative.





PROBLEMS

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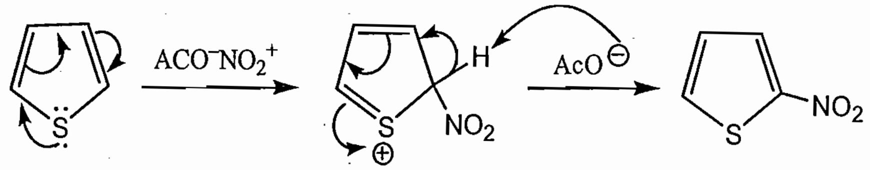

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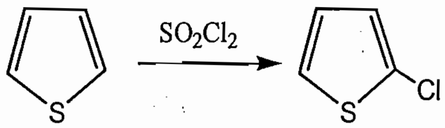

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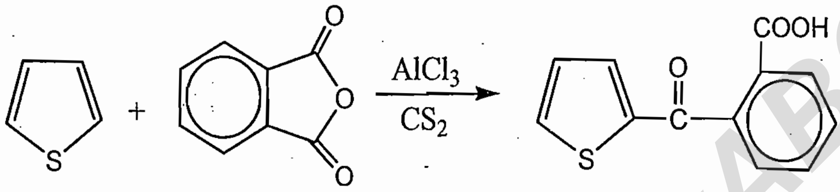

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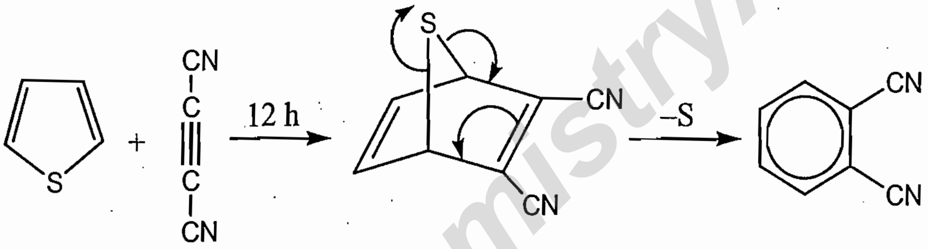

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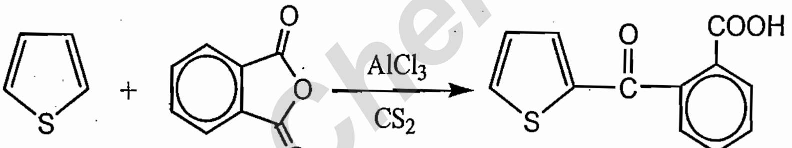

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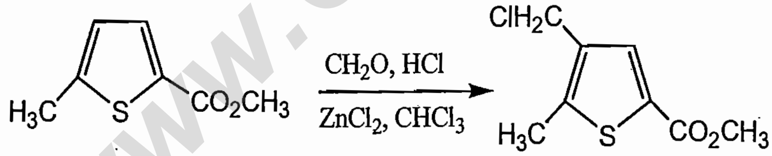

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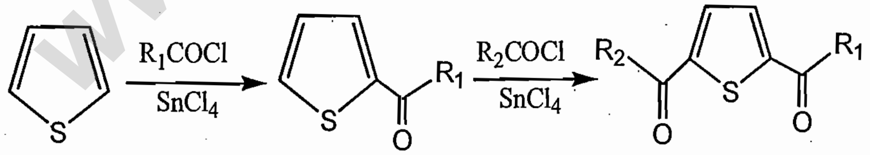
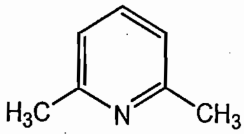


8.4. PYRIDINE

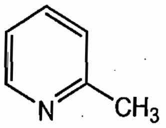
(A) General characteristics:

(i) Pyridine occurs in coal tar and in the distillate from bones (bone oil) and has been produced industrially from these sources.

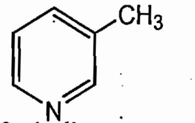
Derivatives of pyridine:



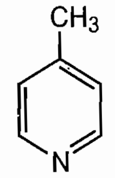
2, 6-Lutidine
b.p. 144°C

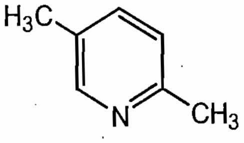


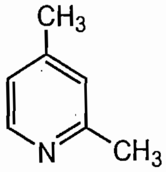
α-picoline
b.p. 128°C

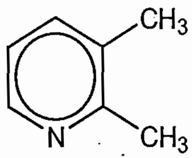


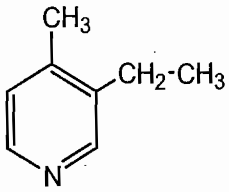
β-picoline
b.p. 144°C

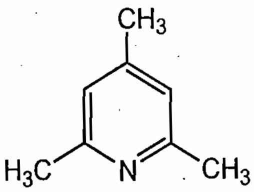

γ-picoline

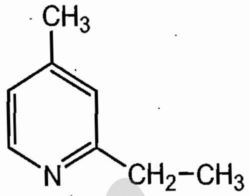

2,5–Lutidine
b.p. 157°C


2,4-Lutidine
b.p. 187°C

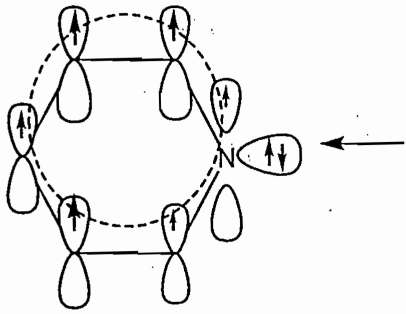

2, 3-Lutidine


β-collidine
b.p. 196°C


Symmetrical-collidine
b.p. 170°C

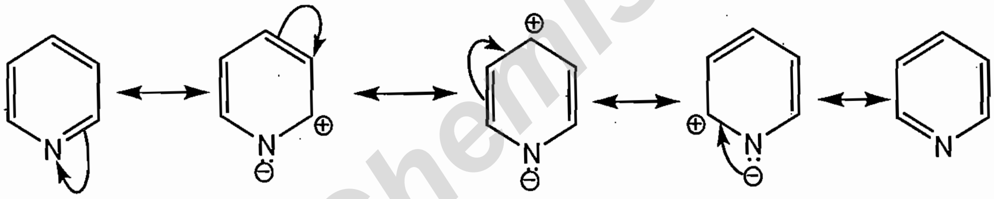

α-collidine
b.p. 179°C

(ii) Molecular orbital diagram:


The lone pair in sp^2 orbital at right angles to p-orbitals in ring no interaction between orthogonal orbitals.

(iii) Resonating structure of pyridine:

According to the resonance theory, pyridine is considered to be hybrid of the following resonance structure.



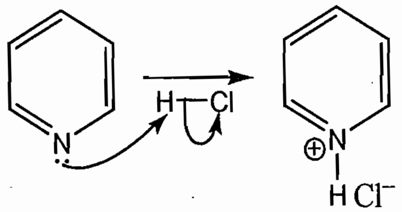
(iv) Physical properties:

- Pyridine is a colourless liquid.
- Boiling point 115.5°C.
- Having a characteristic unpleasant odour.
- It is soluble in water and most organic solvents.

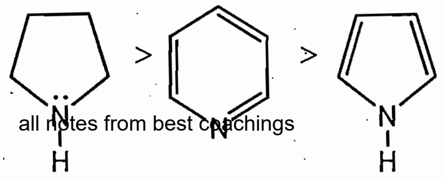
(v) Basic characteristic of pyridine:

Pyridine is basic $pK_b = 8.75$

- It react with strong acid to form salt.

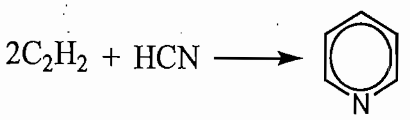

Pyridinium chloride

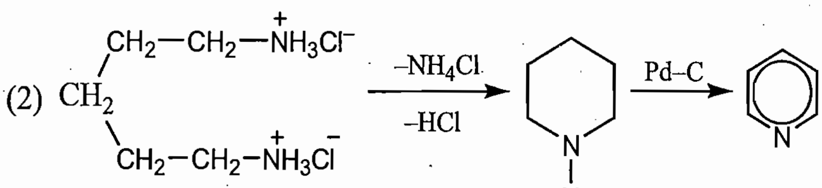
basic strength among following compounds.



(B) Synthesis of pyridine:

(1) By passing a mixture of acetylene and hydrogen cyanide through red hot tube.

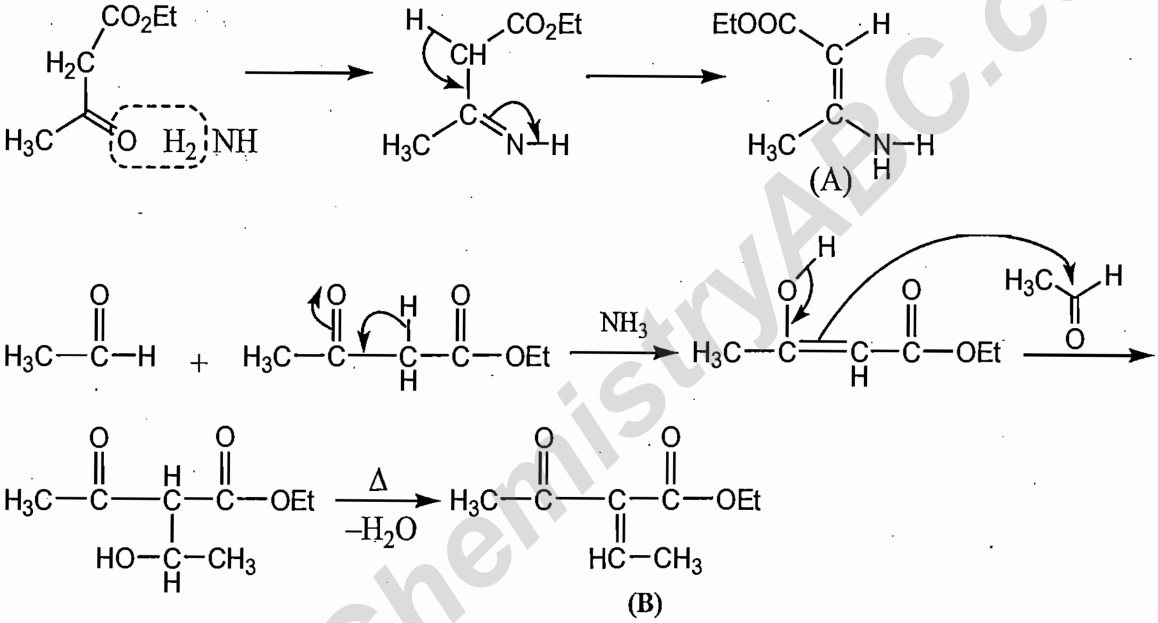




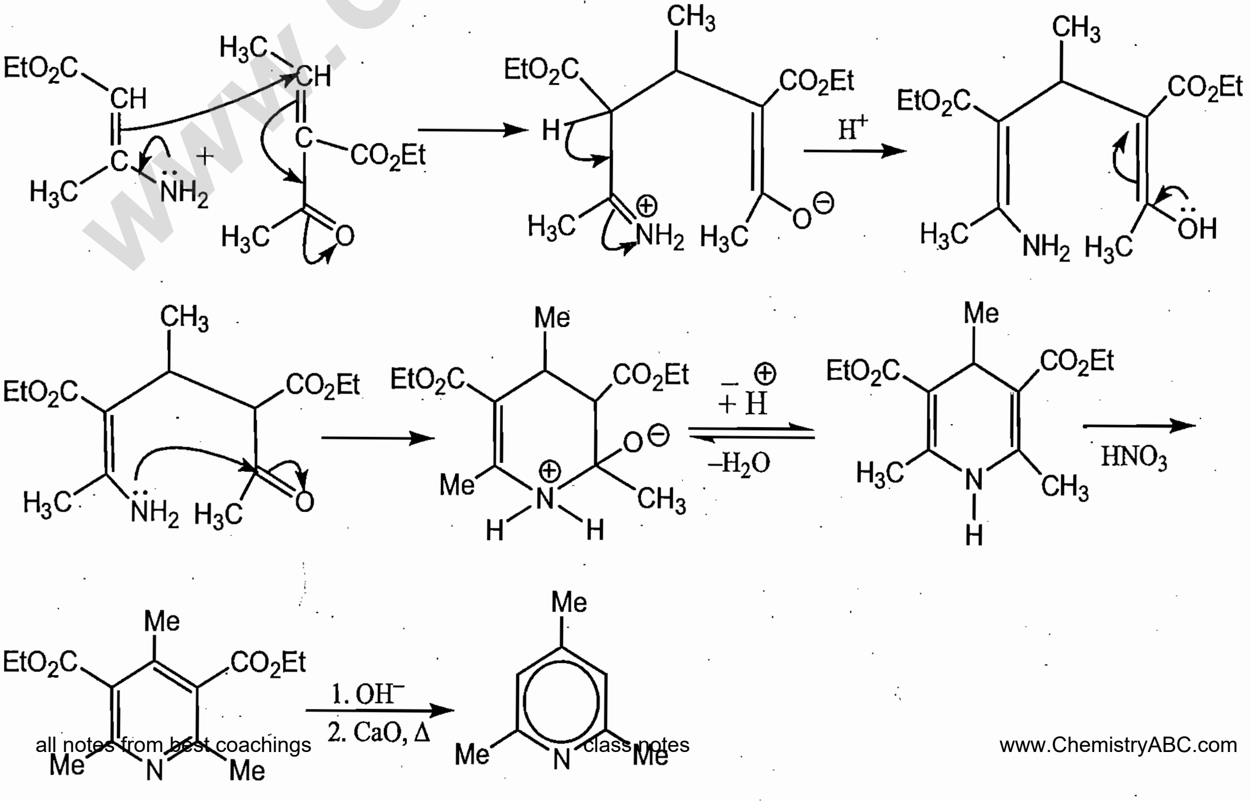
Pentamethyl diamine hydrochloride

(3) Hantzsch synthesis:

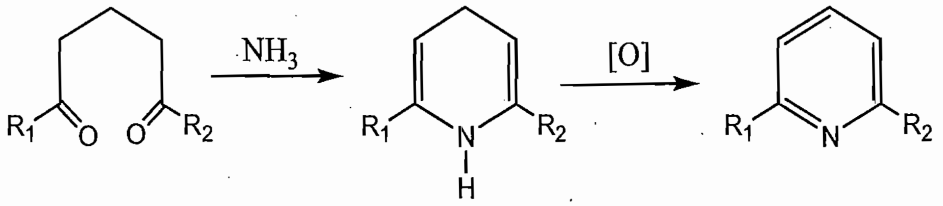
Two molecules of β – dicarbonyl compound are condensed with one molecule of aldehyde and one molecule of ammonia.



Now interaction between (A) and (B)



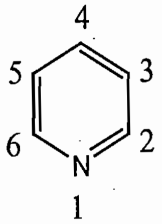
(4)



(i) Electrophilic substitution of pyridine:

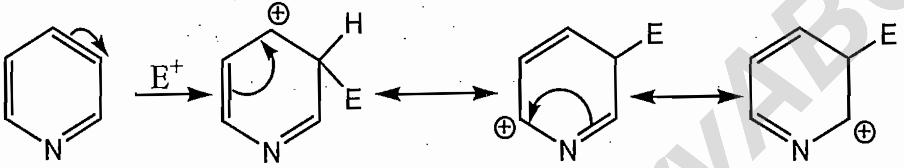
According to the resonance structure of pyridine. The electronegativity of the p-system is more localised on N-atom as compared to the carbon atom in the ring due to electronegativity difference between N and C atom. Therefore it shows some reluctance or some resistance towards the electrophilic substitution reaction.

Orientation of Electrophilic substitution:

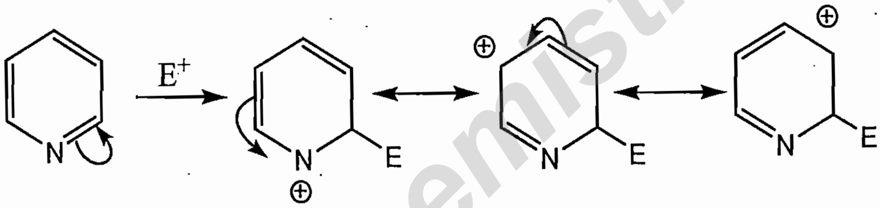


position
2 = 6
3 = 5
4 = → unique

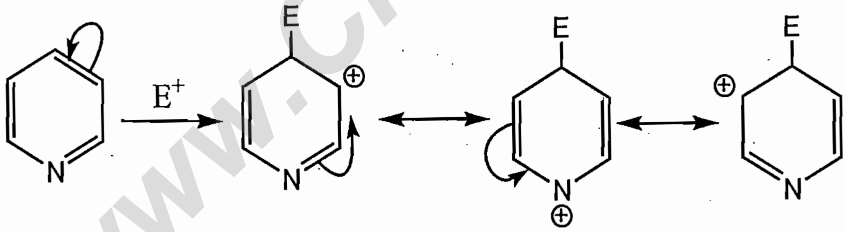
Case I: Electrophilic attack at 3 position.



Case II: Electrophilic attack at position 2.



Case III: Electrophilic attack at position 4.



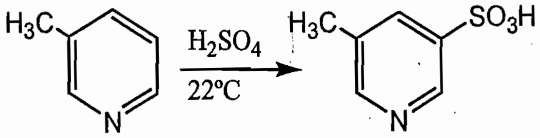
Conclusion:

- Pyridine undergoes electrophilic substitution reaction at the 3-position which is energetically favourable and when third position is already blocked then next incoming electrophile will attack at position -5.

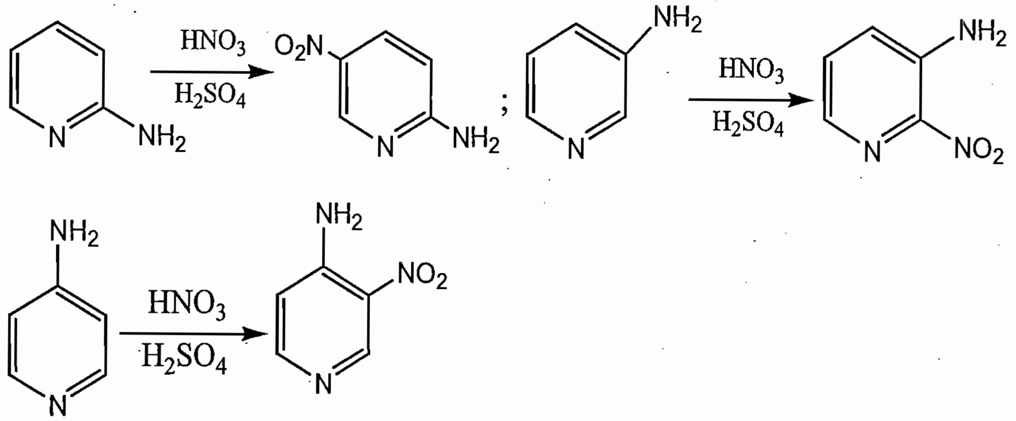
Whenever 2 and 4 positions are having chance to be attack by electrophile the 2-position is more preferable rather than four.

- Alkyl group activates the pyridine ring towards the electrophilic substitution reaction.
- Amino group also activates the ring and direct incoming electrophile to ortho and para position.

***Example*:**

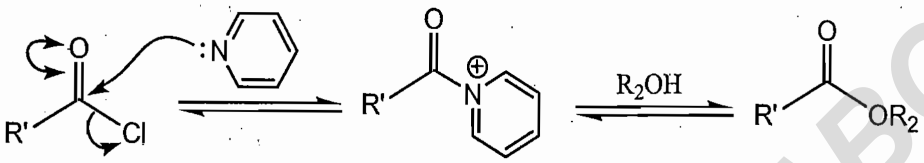


Methyl group does not direct the incoming group direction will be directed by pyridine itself.



So, 2-amino pyridine direct at 5, 3 - amino pyridine direct at 2, 4- amino pyridine direct at 3.

- Pyridine is a reasonable nucleophile for carbonyl group and is often used as nucleophilic catalyst in acylation reaction. Esters are often made in pyridine solution from alcohols and acid chloride.

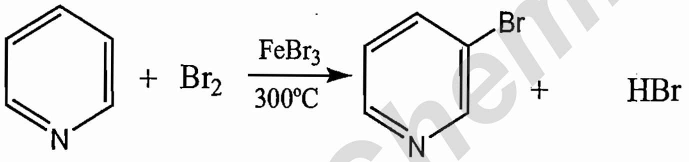


acylpyridinium ion
reactive intermediate

(ii) Disadvantages in using pyridine as a solvent:

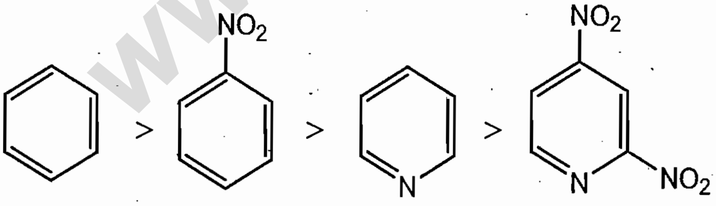
Pyridine is toxic and has a foul smell. So, there are disadvantages in using pyridine as a solvent but it is cheap and remains a popular solvent inspite of the problem.

Reaction of pyridine:

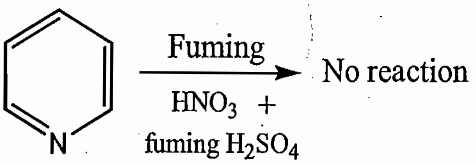


Note: Pyridine has electron-withdrawing nitrogen causes the ring to have significantly less electron density than benzene. Pyridine therefore less reactive than benzene towards electrophilic aromatic substitution. It is even less reactive than nitrobenzene.

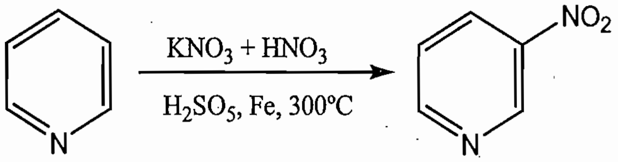
Relative reactivity towards electrophilic aromatic substitution.



So, pyridine undergoes electrophilic substitution reactions only under vigorous conditions and the yields of these reactions are often quite low. If the nitrogen becomes protonated under the reaction conditions, the reactivity is further decreased because a positively charged nitrogen is more electron withdrawing than a neutral nitrogen.

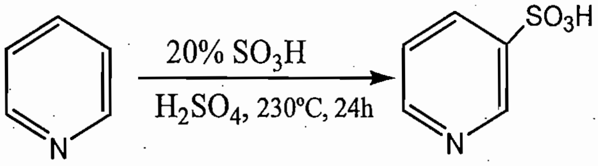


Substitution is achieved only under the most drastic conditions, for example



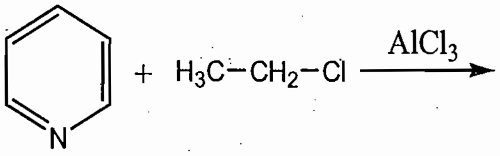
22% 3-nitropyridine

(a) Sulfonation:



71% Pyridine–3-sulfonic acid

(b) Friedel - Craft reaction: As we know deactivated benzene does not undergo Friedel crafts alkylation or acylation reaction. Therefore, pyridine, whose reactivity is similar to that of a highly deactivated benzene, does not undergo these reactions.

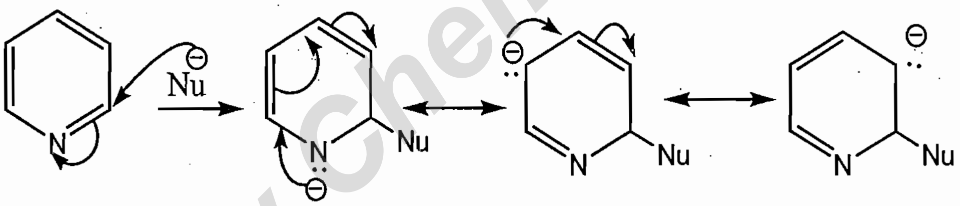


No electrophilic aromtic substitution reactions

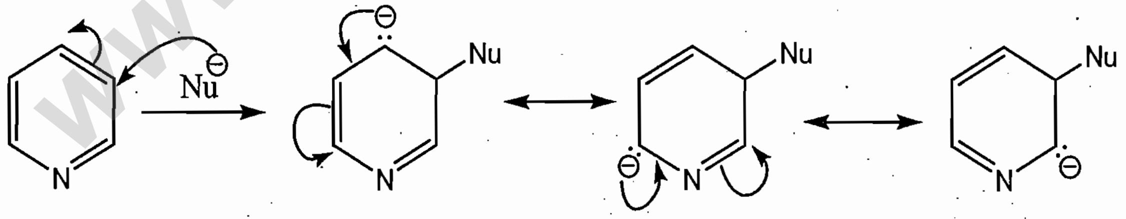
(ii) Nucleophilic Substitution Reaction

Pyridine can also undergo nucleophilic subtitution reaction through addition - elimination mechanism or elimination addition mechanism.

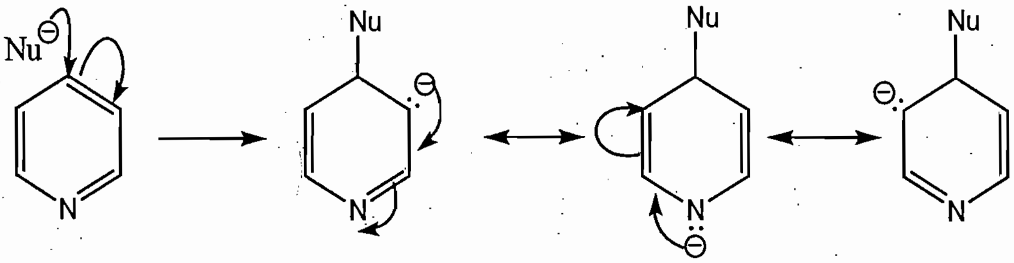
(a) Nucleophilic attack at position-2:



(b) Nucleophilic attack at position-3:

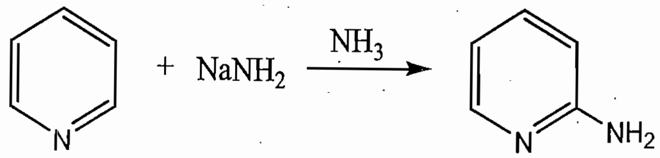


(c) Nucleophilic attack at position -4:



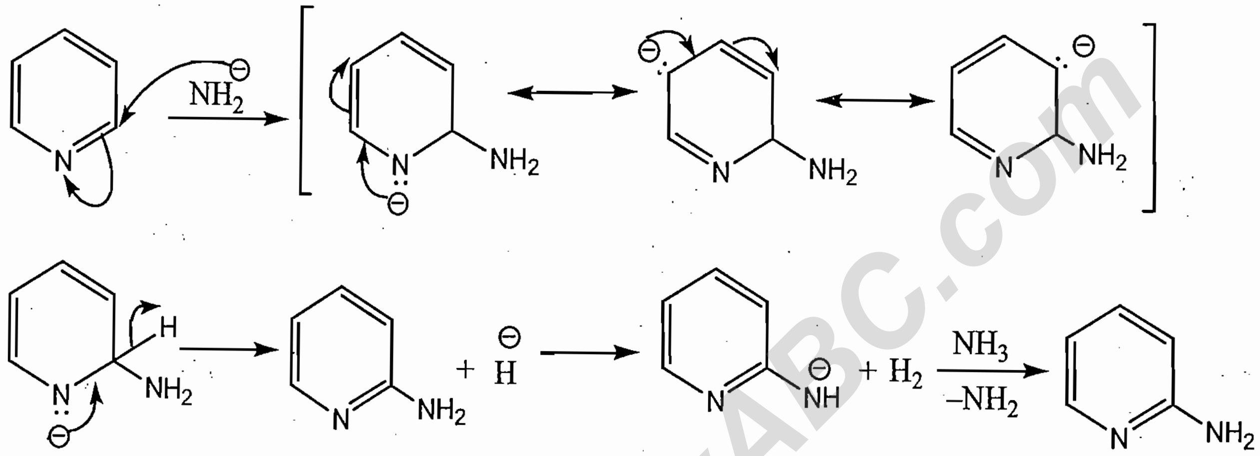
So, due to the stability of resulting carbanion intermediate. The nucleophilic substitution can be taken place at 4-position and 2-position but in practice, nucleophilic attack occur exclusively at 2-position. This is due to electron-withdrawing effect of the ring nitrogen which is strongest at 2-position.

(i) Reaction of pyridine with sodamide: (*Chichibabin reaction*)

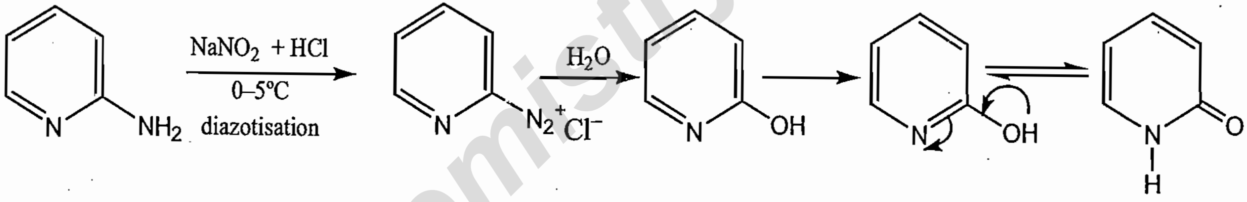


***Mechanism*:**

$$NaNH_2 \longrightarrow \overset{\oplus}{Na} + \overset{\ominus}{NH_2}$$

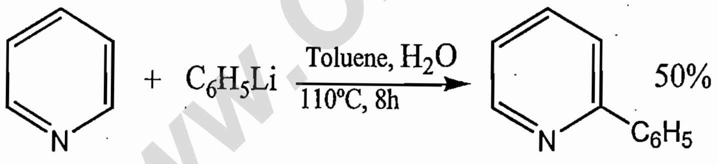


***Example*:**



α-pyridone

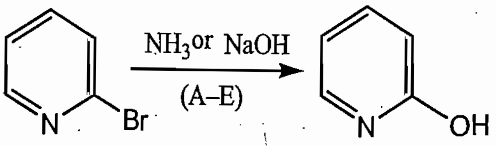
- **Chichibabin** like reactions are also observed with organolithium compounds.



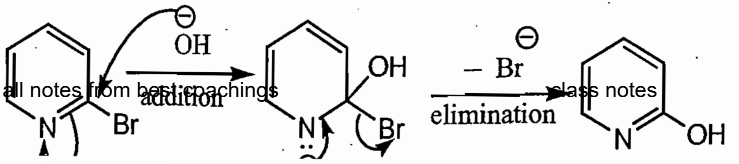
2-phenyl pyridine

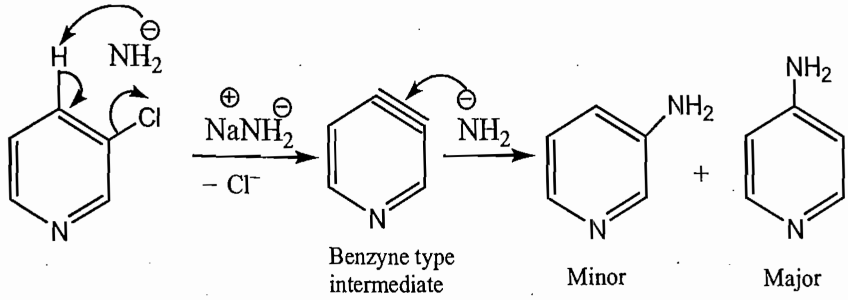
Note: If the good leaving groups are present in the pyridine then the substituted pyridine can easily undergo nucleophilic substitution reaction generally 2 or 4 substituted pyridine undergo nucleophilic substitution exclusively by addition elimination mechanism. However, 3-substituted pyridine gives 3 and 4-substituted product through elimination - addition mechanism.

***Example*:**

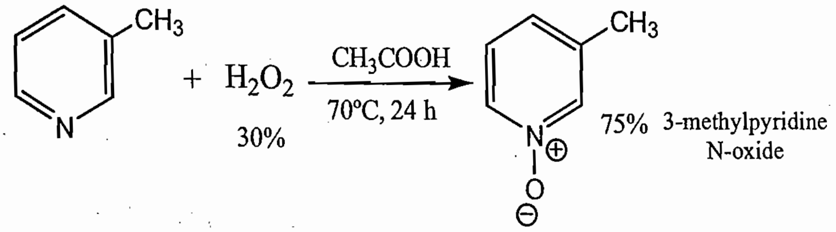


***Mechanism*:**

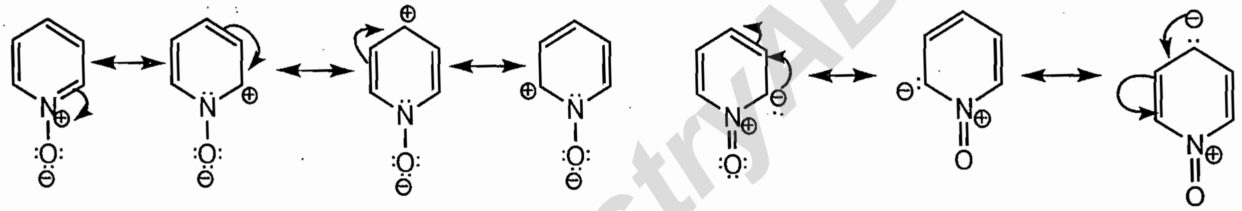




- Under proper conditions, the nitrogen is oxidized to the N-oxide as are other tertiary amines.

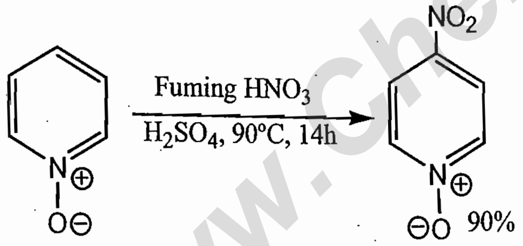


Pyridine N-oxides are important synthetic intermediates. The electronic structure may be described by the following resonance forms.

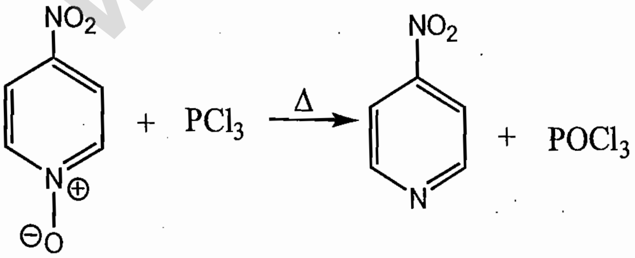


- Pyridine N-oxide undergo electrophilic substitution some what more readily.
- Reaction generally occurs at C–4.

Example:

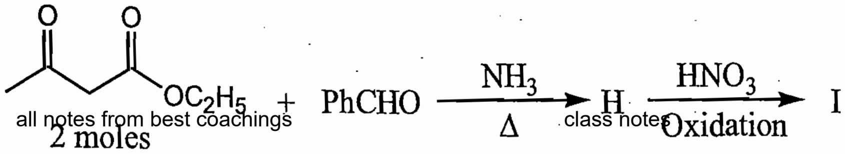


The N-oxide can often used as an activated form of pyridine, treatment of the substituted N-oxide with PCl_3 results in deoxygenation.

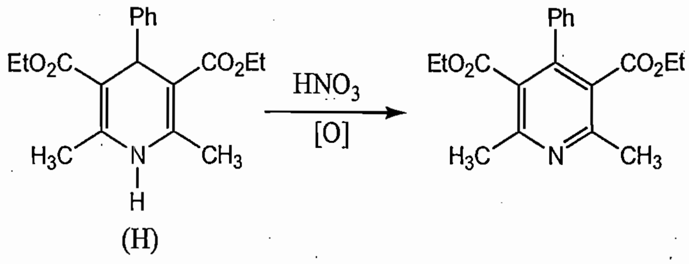


PROBLEMS

1. Indentify H and I in the reaction below.



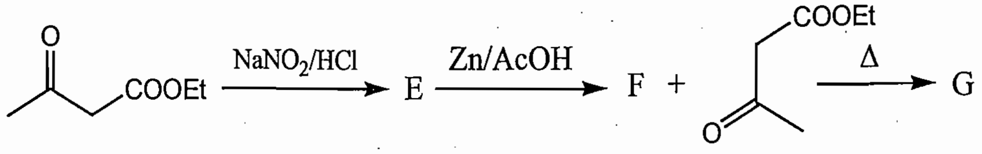
Soln.



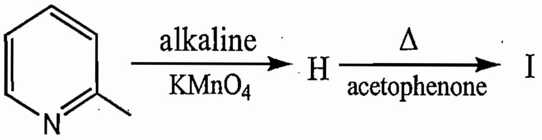
(H)

2. Complete the following reaction with appropriate structure for E, F, H and I.

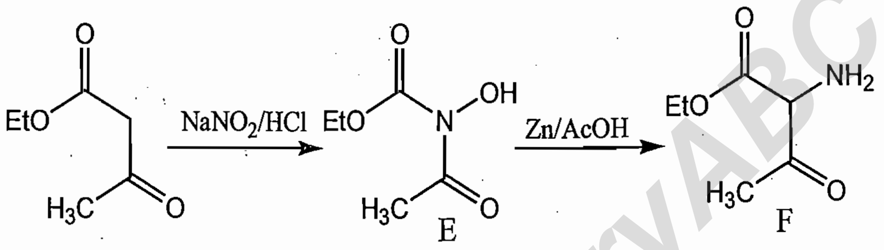
(a)



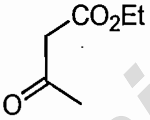
(b)

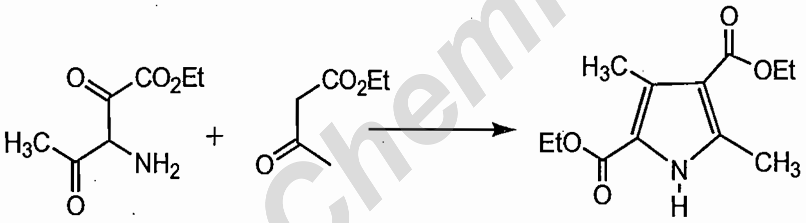


Soln. (a)

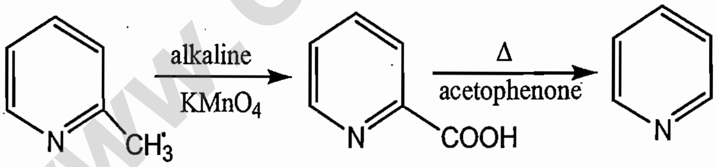


Now, interaction between F and

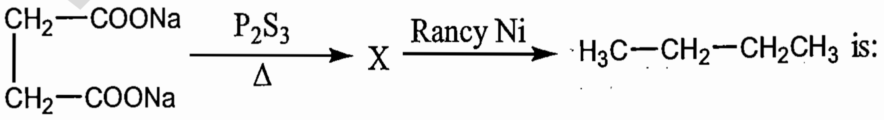




(b)

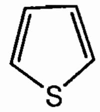


3. The Compound (x) in the reaction sequence

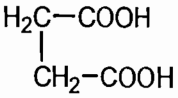


$$\begin{array}{l} CH_2-COONa \\ | \\ CH_2-COONa \end{array} \xrightarrow[\Delta]{P_2S_3} X \xrightarrow{\text{Rancy Ni}} H_3C-CH_2-CH_2CH_3 \text{ is:}$$

(a)

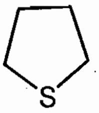


(b)

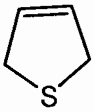


$$\begin{array}{l} H_2C-COOH \\ | \\ CH_2-COOH \end{array}$$

(c)

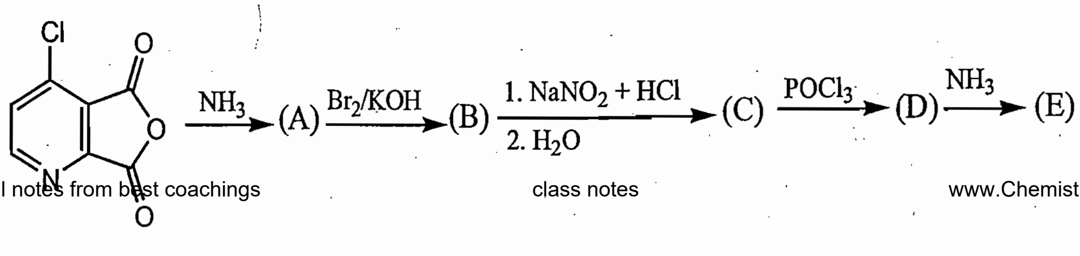


(d)

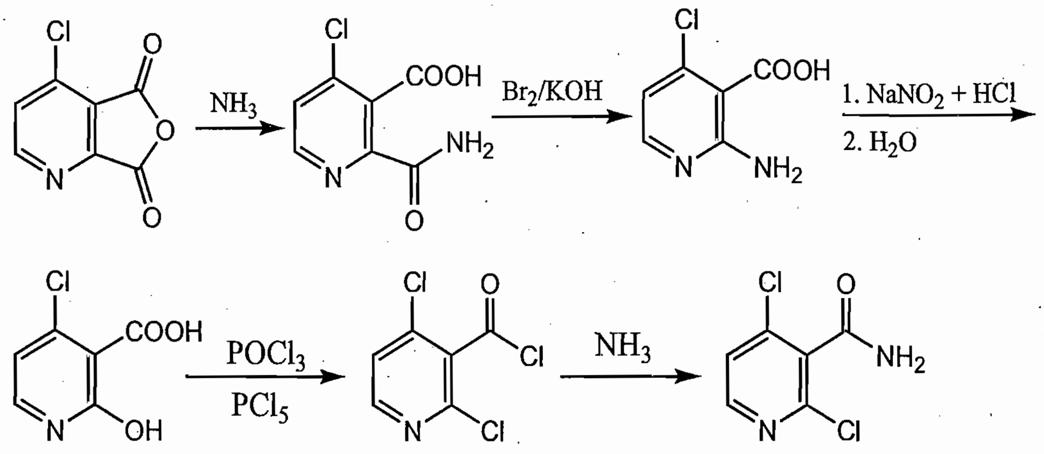


Soln. (a)

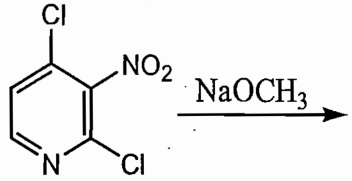
4.



Soln.

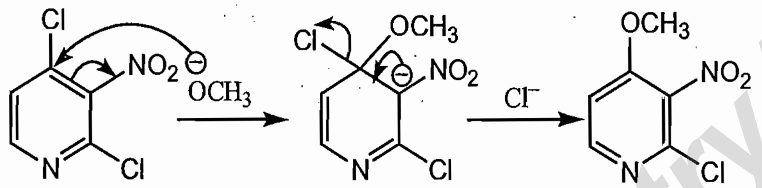


5.

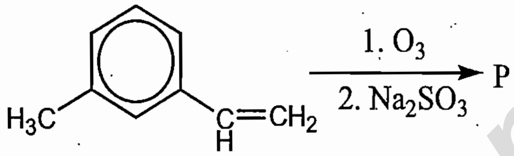


(A). Find the major product (A) in the above reaction.

Soln.

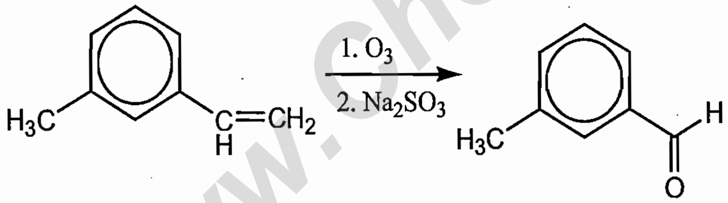


6.

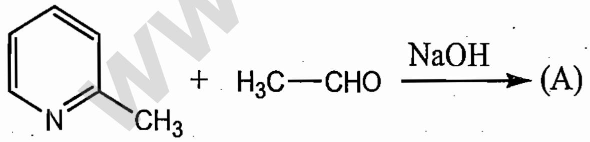


The major product (A) in the above reaction is:

Soln.

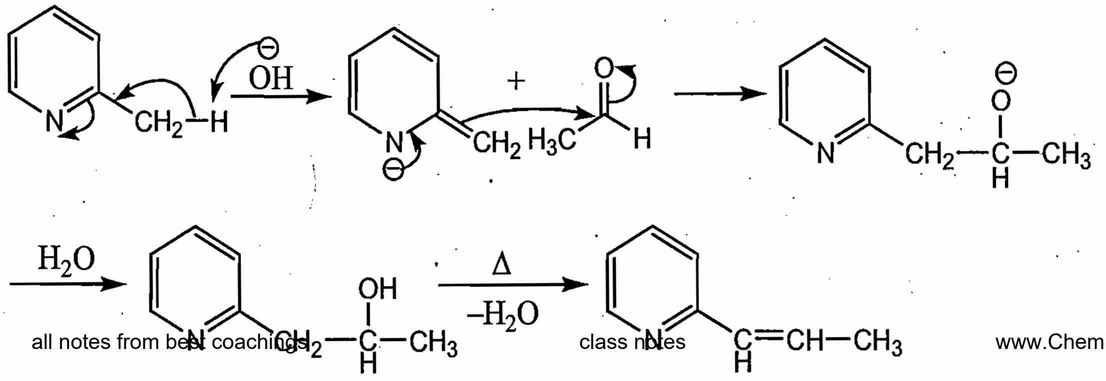


7.

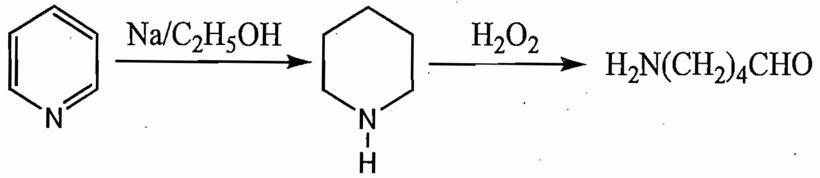


Find the major product (A) in the above reaction.

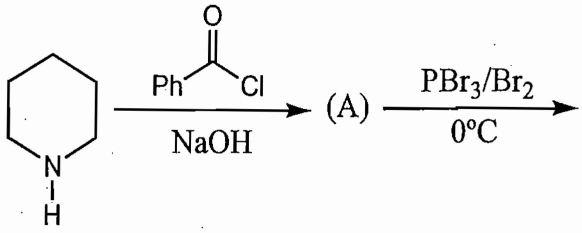
Soln. $NaOH \longrightarrow Na^+ + OH^-$



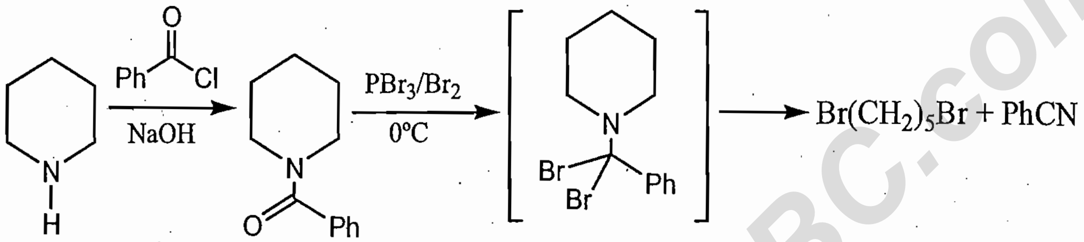
8.



9.

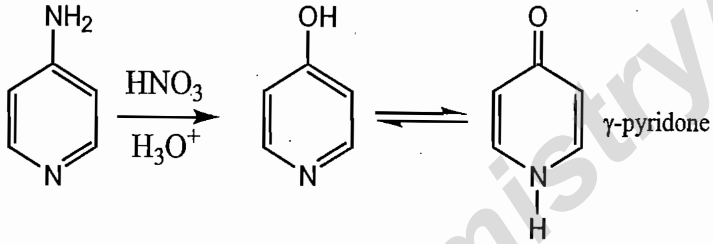


(B). Find the major product (A) and (B) in the above reaction.

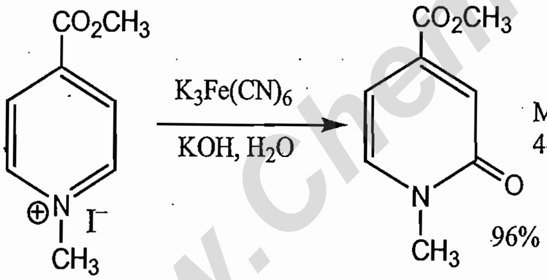


This method for ring opening is known as *Von Braun's method* for ring opening.

10.



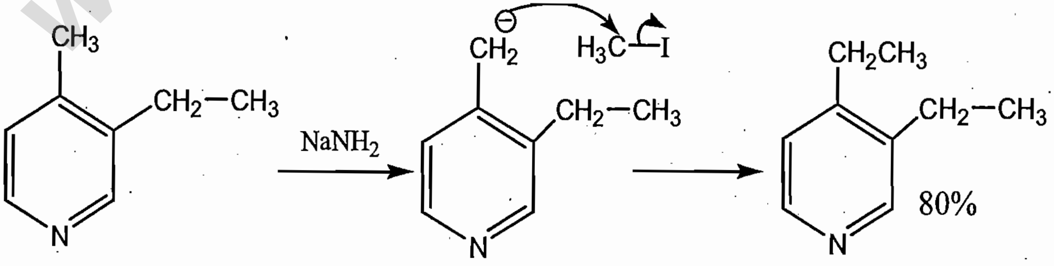
11.



Methyl N-methyl-2-pyridone 4-carboxylate.

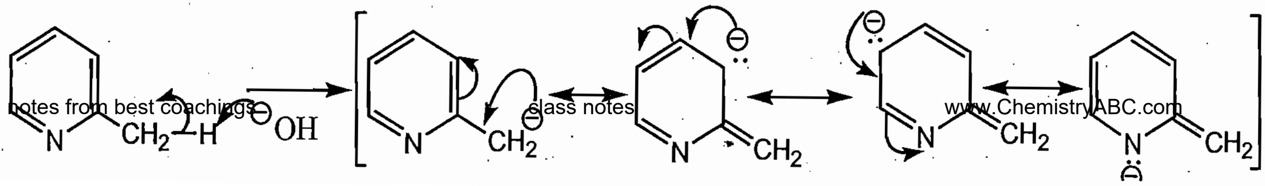
Note: The methyl groups in a and g picoline are comparable in acidity to methyl ketones and readily undergo base - catalyzed reactions.

***Example*:**

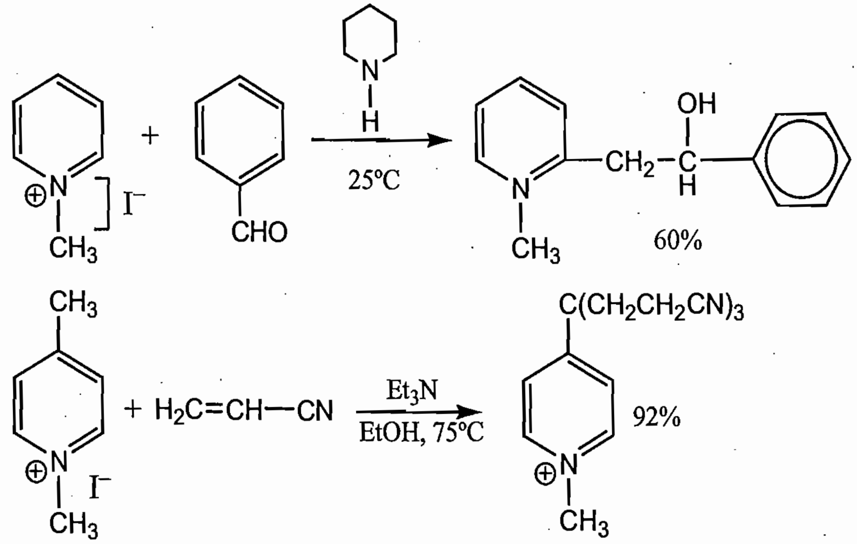


3, 4-diethylpyridine

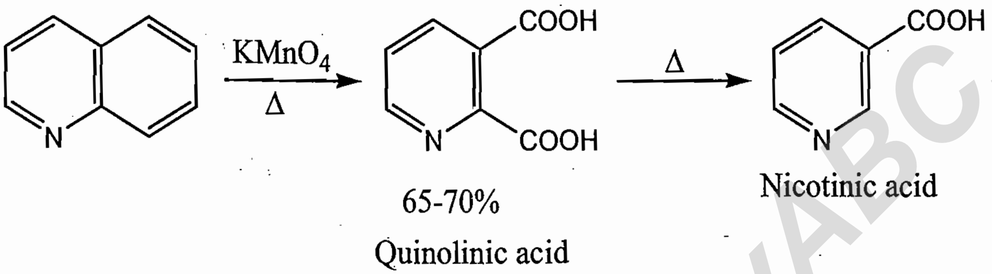
Remark: The enhanced acidity at these positions is again attributed to delocalization of negative charge in intermediate anion into the ring and especially onto the nitrogen.



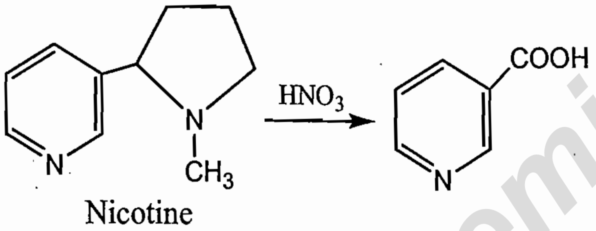
12.


⊕N
I⁻
CH₃
+
CHO
N
H
25°C
OH
CH₂
C
H
N
CH₃
60%
CH₃
+ H₂C=CH—CN
Et₃N
EtOH, 75°C
C(CH₂CH₂CN)₃
92%
⊕N
I⁻
CH₃

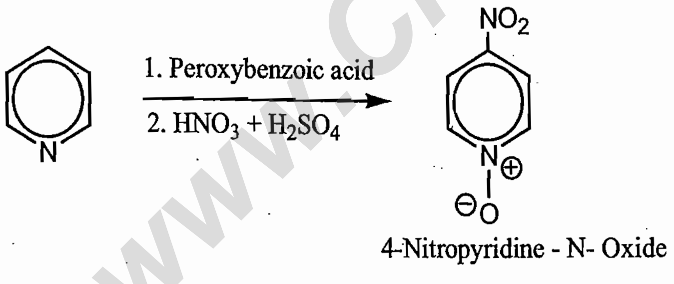
13.


N
KMnO₄
Δ
COOH
COOH
N
Δ
COOH
N
Nicotinic acid
65-70%
Quinolinic acid

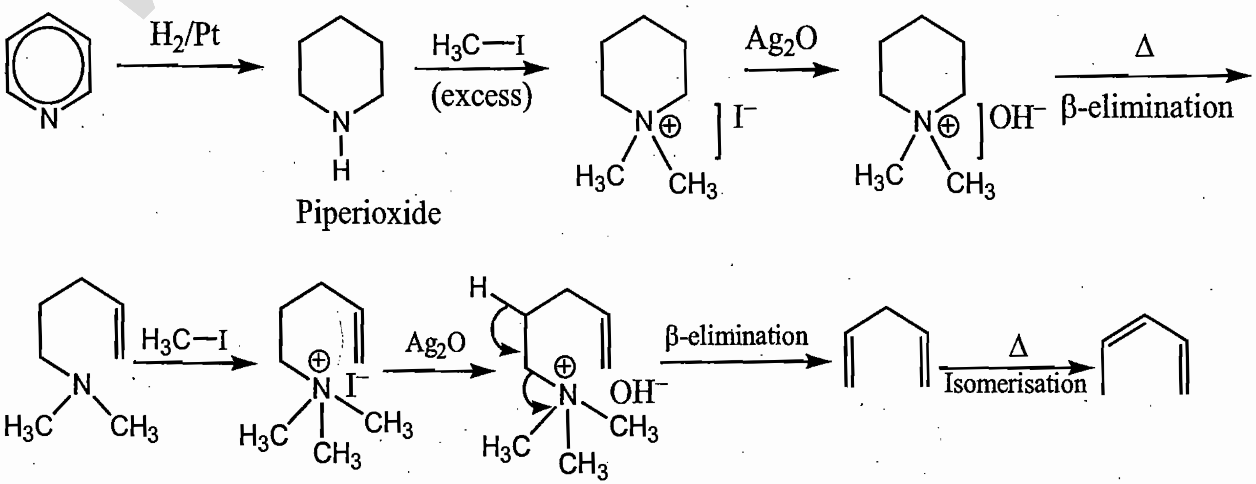
14.


N
N
CH₃
Nicotine
HNO₃
COOH
N

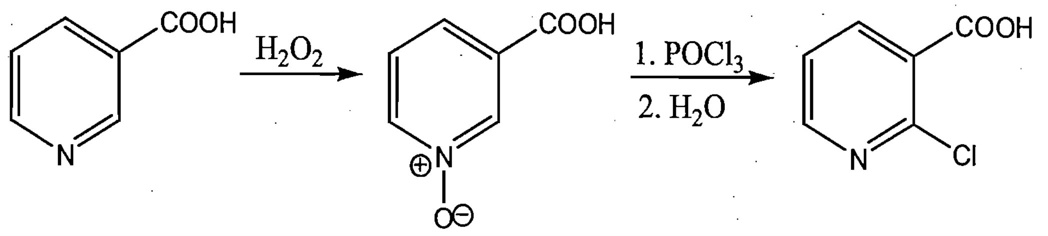
15.


N
1. Peroxybenzoic acid
2. HNO₃ + H₂SO₄
NO₂
N⊕
⊖O
4-Nitropyridine - N- Oxide

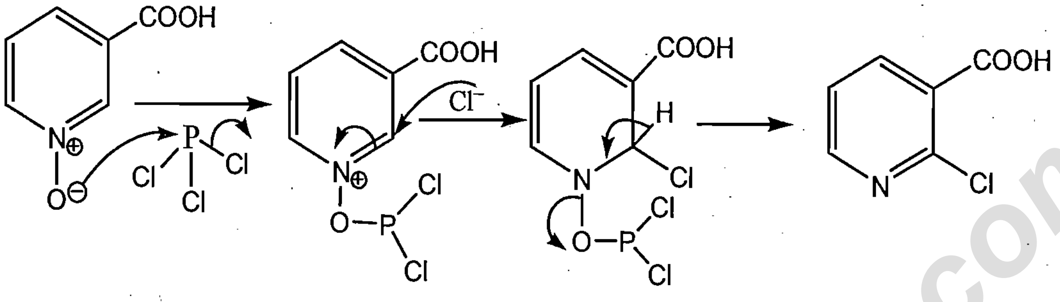
16.


N
H₂/Pt
N
H
Piperioxide
H₃C—I
(excess)
N⊕
I⁻
H₃C
CH₃
Ag₂O
N⊕
OH⁻
H₃C
CH₃
Δ
β-elimination
N
H₃C
CH₃
H₃C—I
⊕
N
I⁻
H₃C
CH₃
CH₃
Ag₂O
H
⊕
N
OH⁻
H₃C
CH₃
CH₃
β-elimination
Δ
Isomerisation

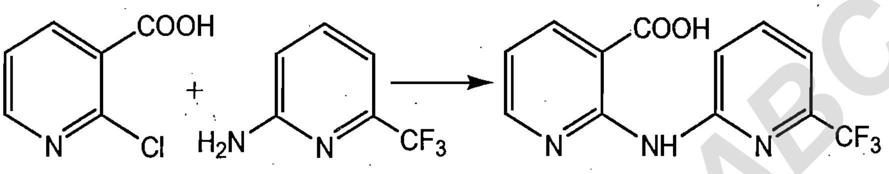
17.



***Mechanism*:**

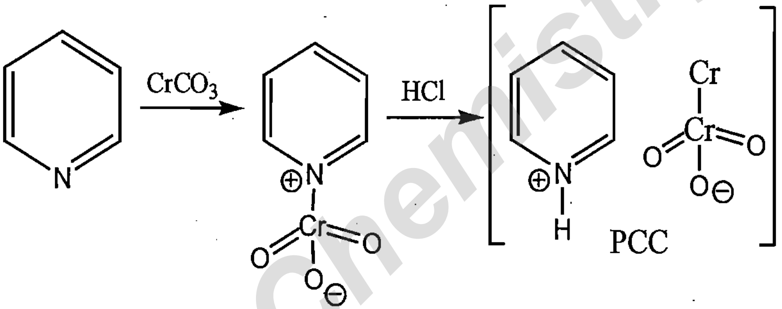


18.

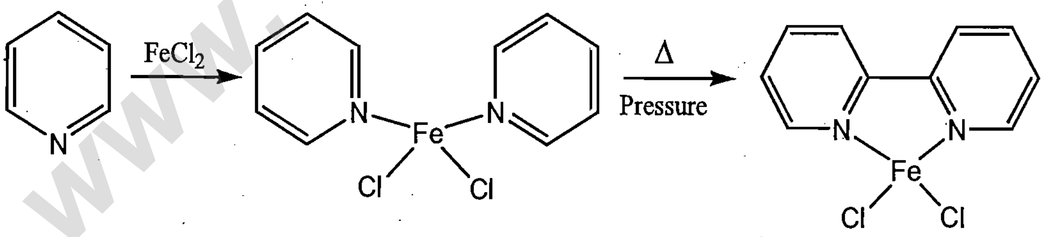


Niflumic acid (analgesic)

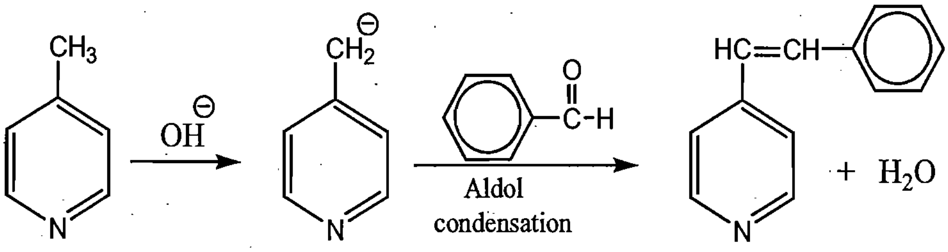
19.



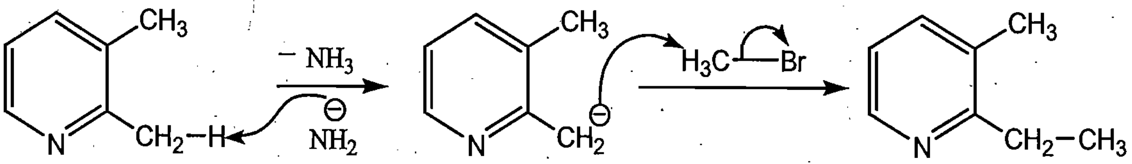
20.



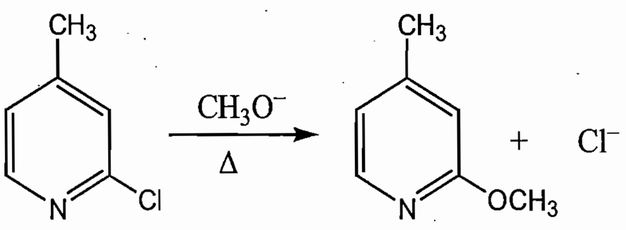
21.



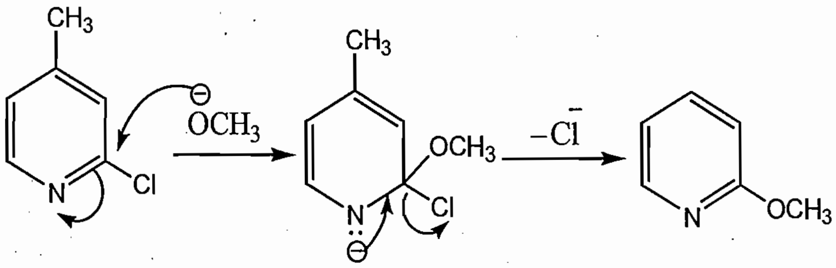
22.



23.



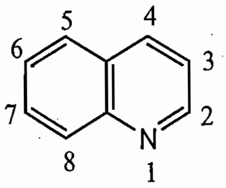
***Mechanism*:**



8.5. QUINOLINE

(A) General Characteristics:

Quinoline is present in coal tar and bone-oil.

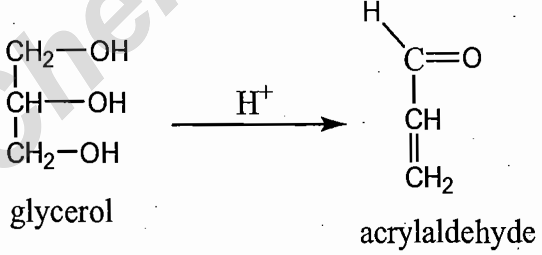


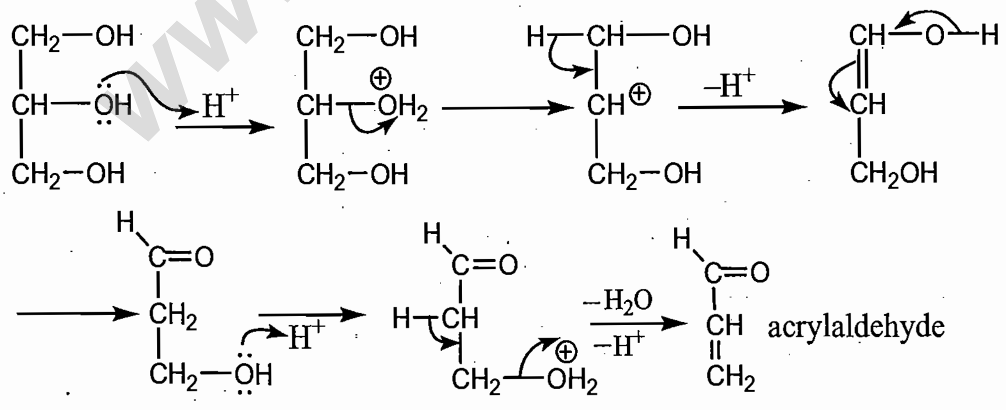
B.P. = 238°C

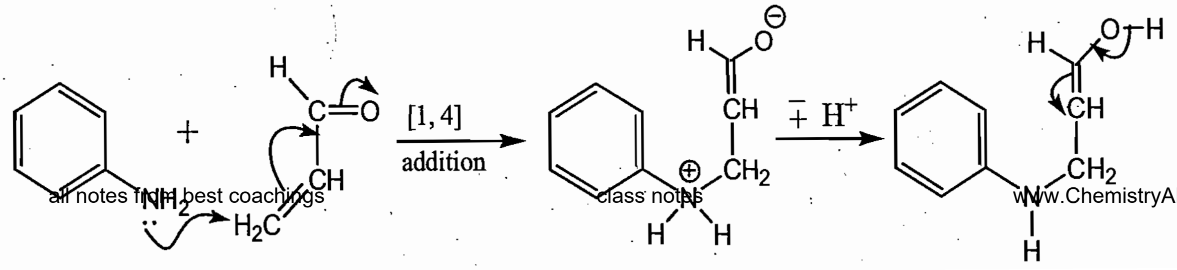
(B) Synthesis of quinoline.

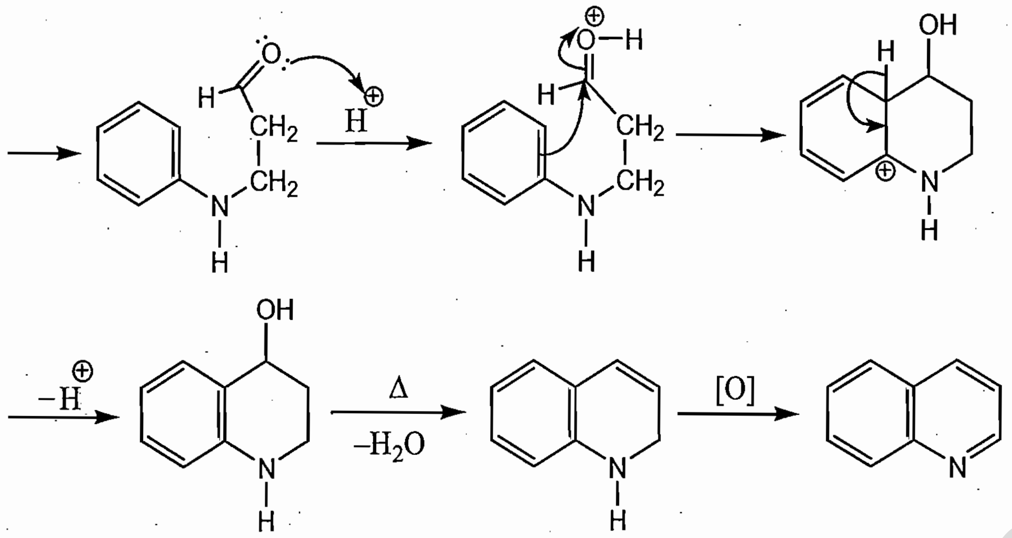
(i) Skraup synthesis. By heating a mixture of aniline, nitrobenzene, glycerol conc. H_2SO_4 and ferrous sulphate.

In this reaction nitrobenzene acts as an oxidising agent whereas $FeSO_4$ makes the reaction less violent.

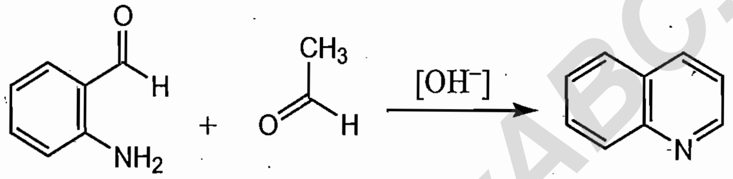




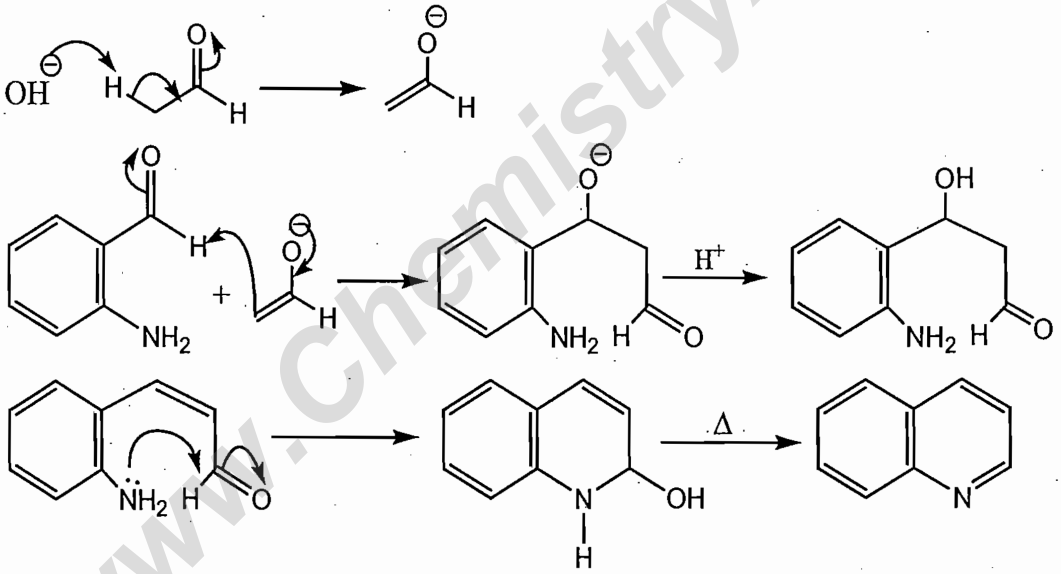




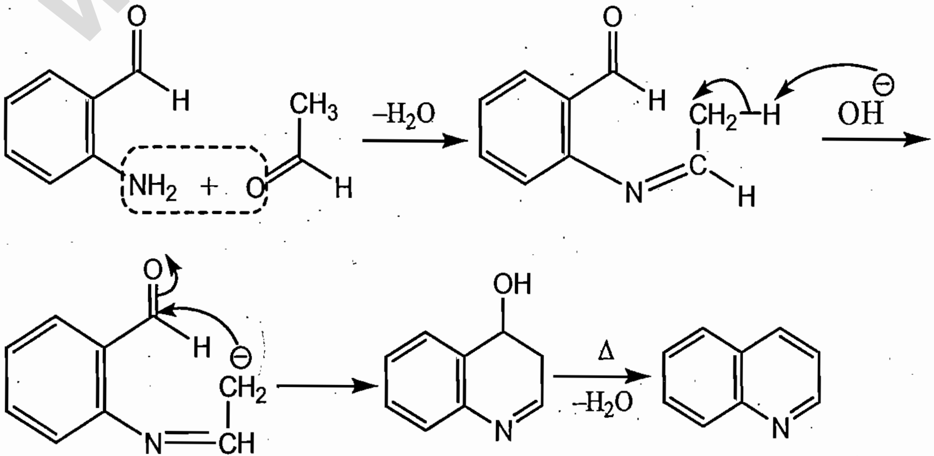
(ii) **Friedlander synthesis:** When o-aminobenzaldehyde is condensed with acetaldehyde in aqueous sodium hydroxide, quinoline is formed.



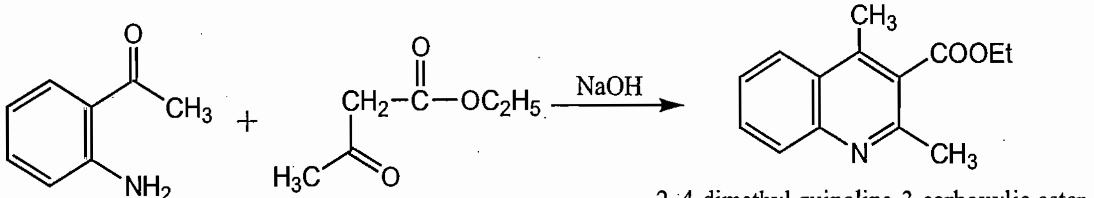
Mechanism:



Alternative mechanism:

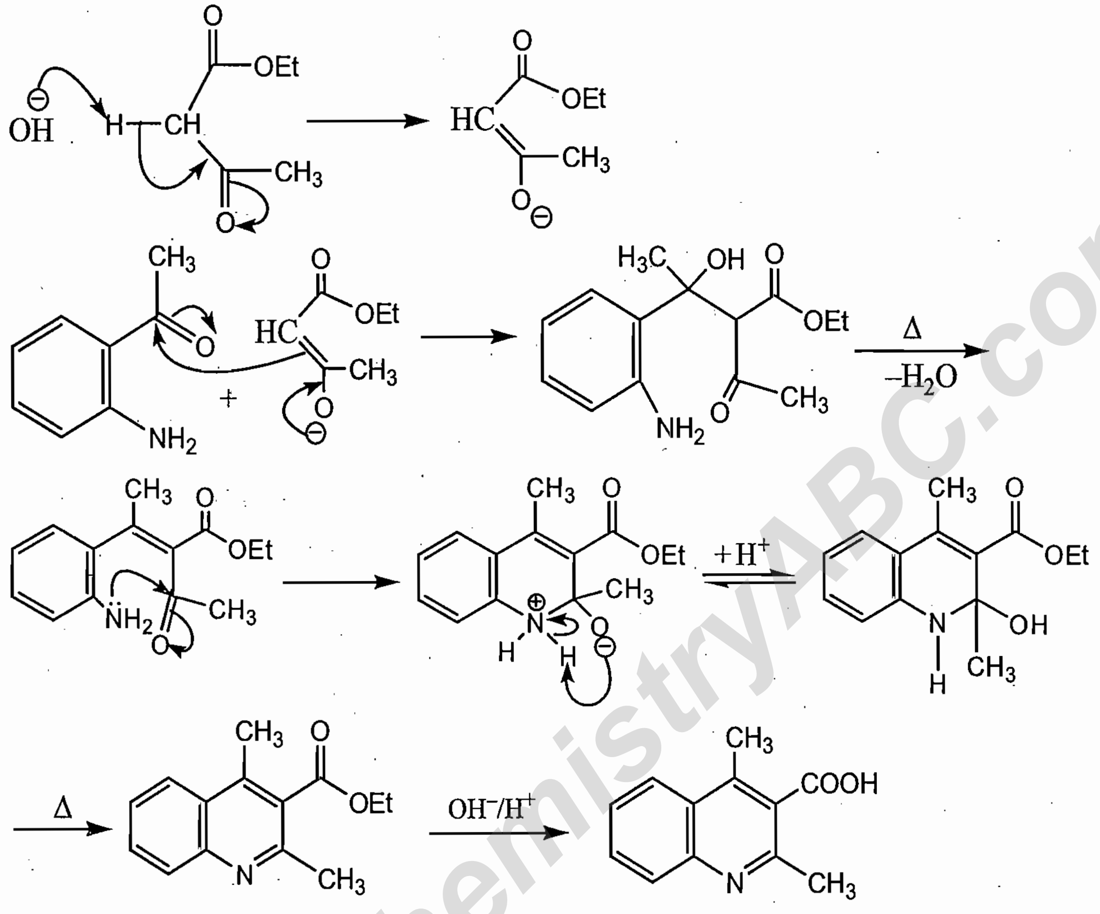


Quinoline



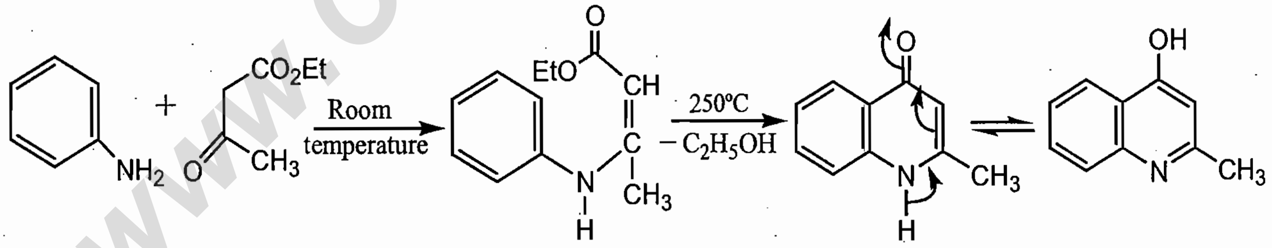
2, 4-dimethyl quinoline-3-carboxylic ester

Mechanism:

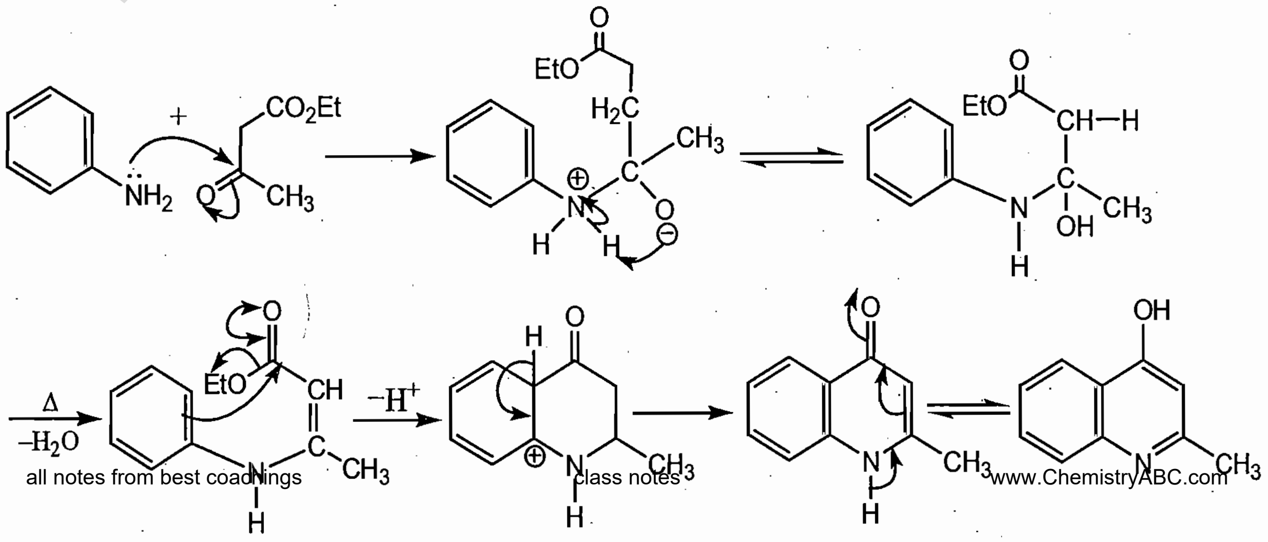


2, 4-dimethyl quinoline carboxylic ester

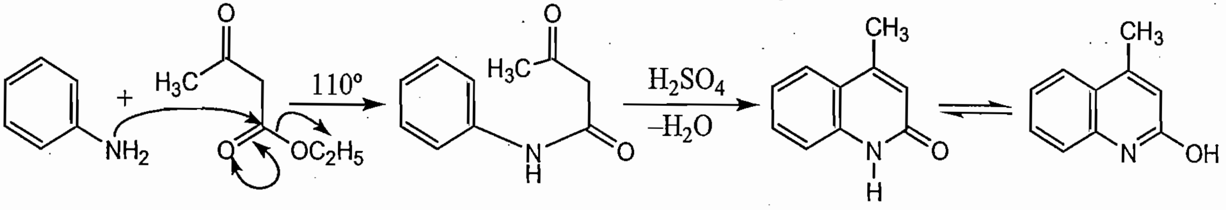
(iii) Conard-limpach synthesis:



Mechanism:



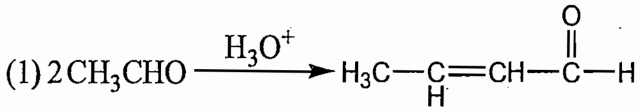
(iv) Knorr quinidine synthesis:



Note: In the above mentioned two synthesis, the nature of the product will depend upon the condition of reaction.

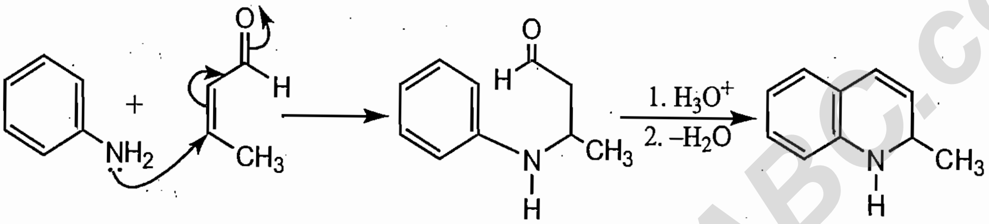
(v) Doebner-miller synthesis:

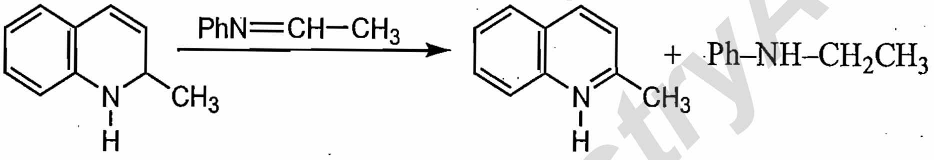
With two molecules of acetaldehyde by using aldol condensation reaction we can obtain.



$$(1)\ 2CH_3CHO \xrightarrow{H_3O^+} H_3C-\underset{H}{C}=CH-\overset{O}{\overset{\|}{C}}-H$$

(2)

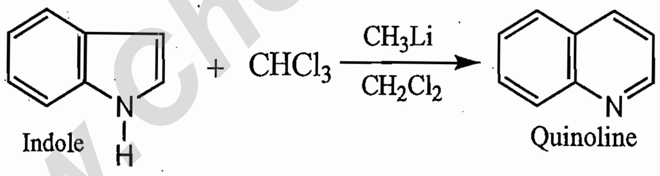




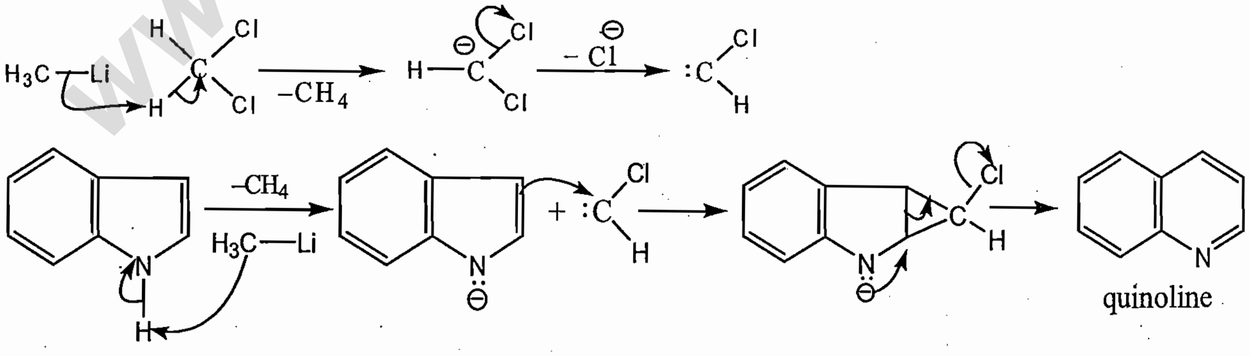
Note: In this synthesis no oxidising agent is added, and the final dehydrogenation is believed to occur by the action of schiff base produced by aniline and acetaldehyde.

$$PhNH_2 + O=\overset{H}{\overset{|}{C}}-CH_3 \longrightarrow PhN=CH-CH_3 \text{ (Schiff base)}$$

Problem.

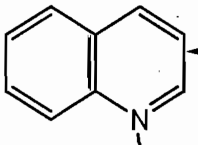


***Mechanism*:**

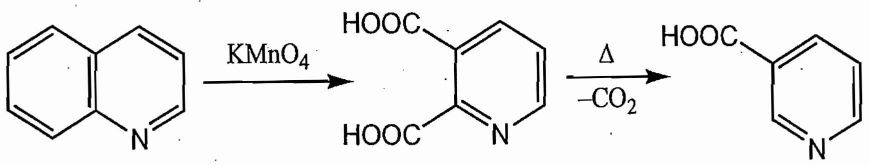


(C) Chemical reaction of quinoline:

(i) *Oxidation of quinoline.*



N atom withdraws electron density towards itself, and it deactivates the ring towards electrophile, while nucleophilic substitution preferentially occurs at this ring.

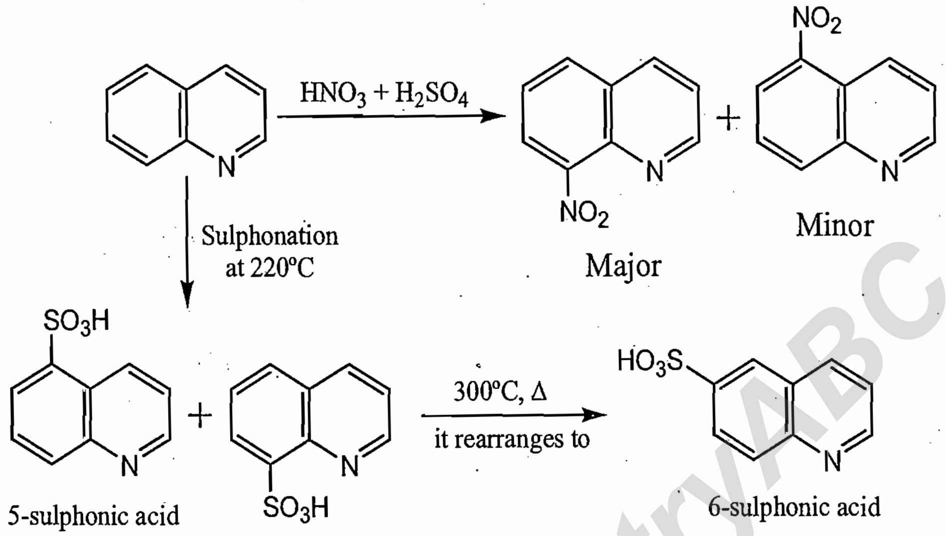


quinolinic acid
or, pyridine-2,3-dicarboxylic acid

nicotinic acid

Remark: Electrophilic substitution preferentially occurs at position-8 by elecrophilic reagent, and position 2 and 4 by nucleophilic reagent.

(ii) Electrophilic substitution reactions.



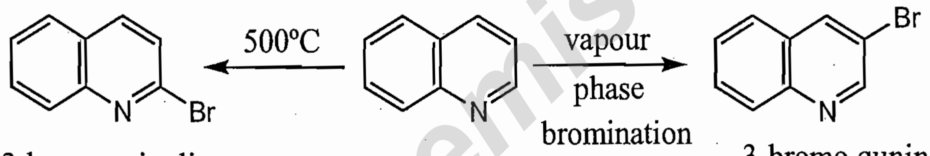
Major

Minor

5-sulphonic acid minor product

8-sulphonic acid

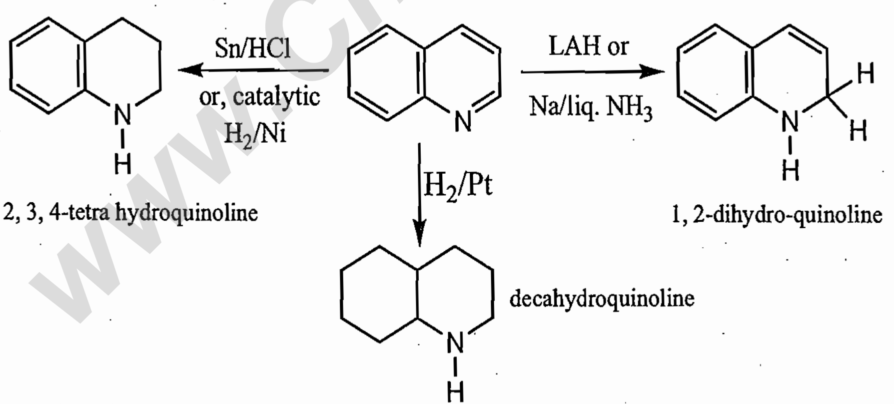
6-sulphonic acid



2-bromoquinoline

3-bromo quninoline

(iii) Reduction of quinoline:

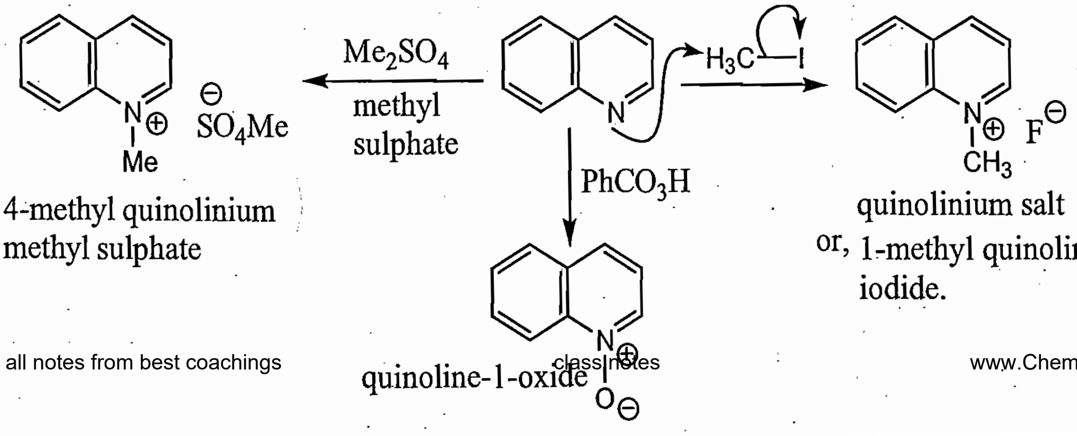


1, 2, 3, 4-tetra hydroquinoline

1, 2-dihydro-quinoline

decahydroquinoline

Reaction due to N-atom:

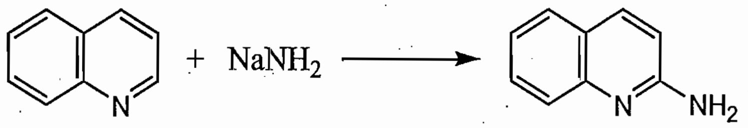


4-methyl quinolinium methyl sulphate

quinolinium salt
or, 1-methyl quinolinium iodide.

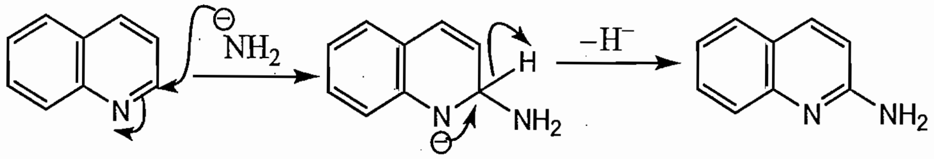
quinoline-1-oxide

Chichibabin reaction:

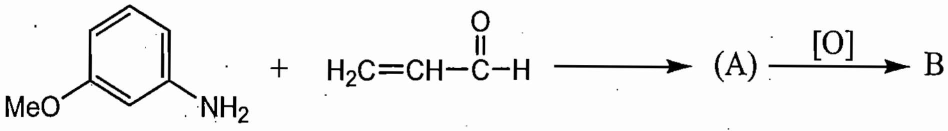


2-aminoquinoline

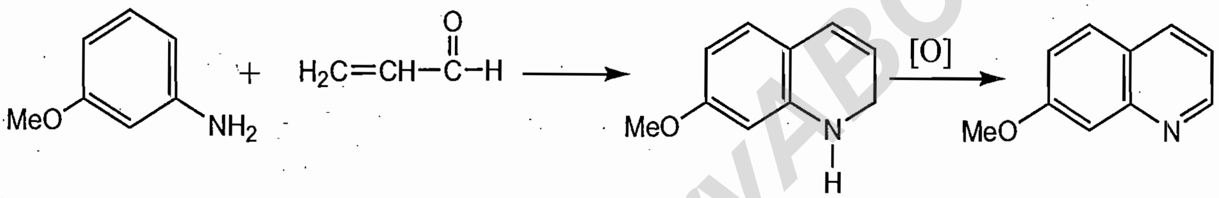
$$NaNH_2 \longrightarrow \overset{\oplus}{Na} + \overset{\ominus}{N}H_2$$

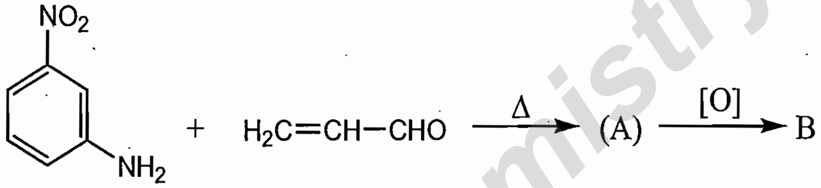


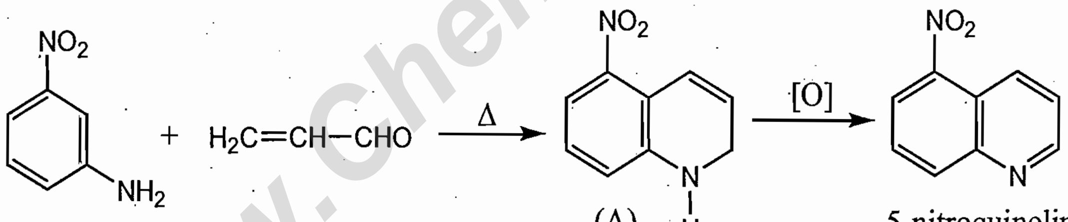
PROBLEMS

1. 

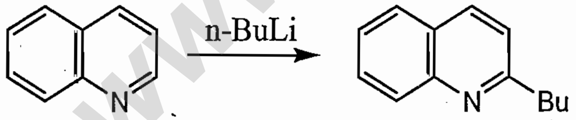
Find (A) and (B).

Soln. 

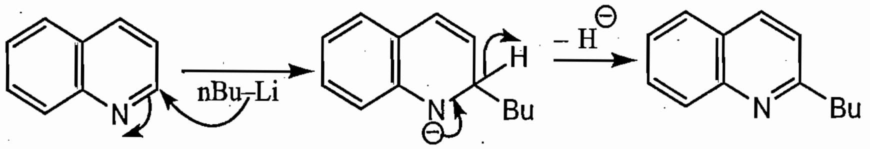
2. 

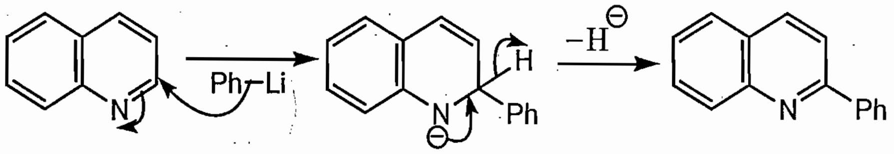
Soln. 

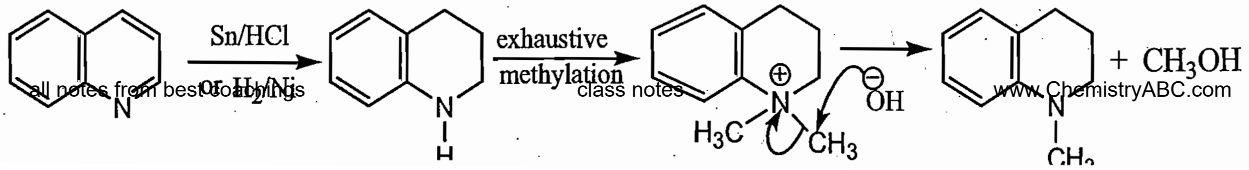
(A) 5-nitroquinoline

3. 

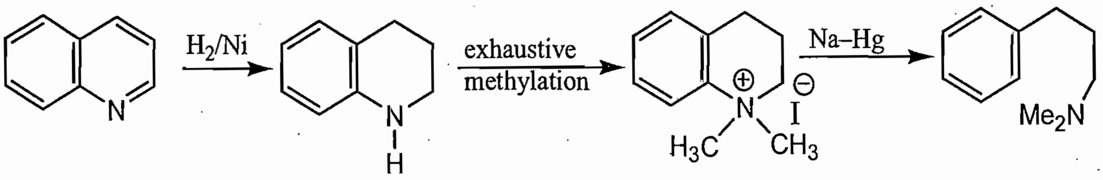
***Mechanism*:**



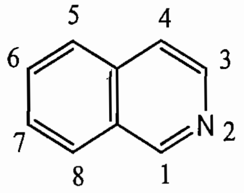
4. 

5. 

The exhaustive methylation fails with tetrahydroquinoline however, the heterocylic ring is opened by emde degradation.



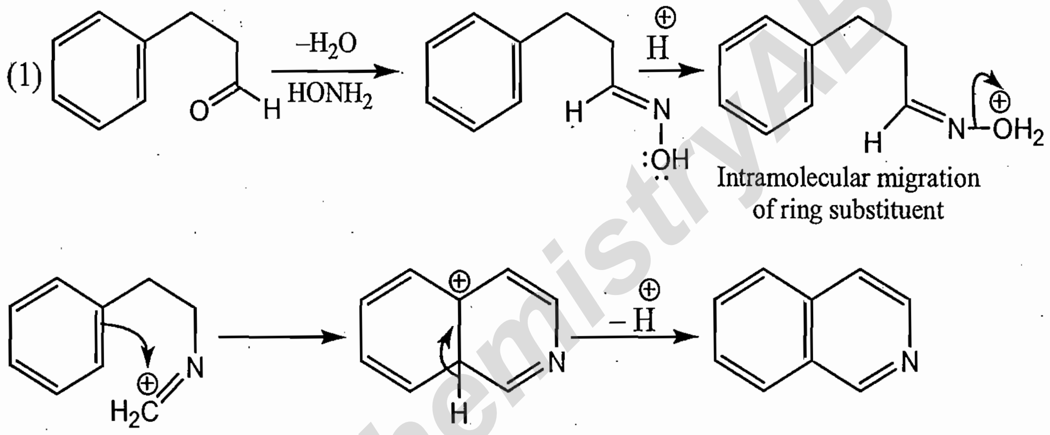
8.6. ISOQUINOLINE



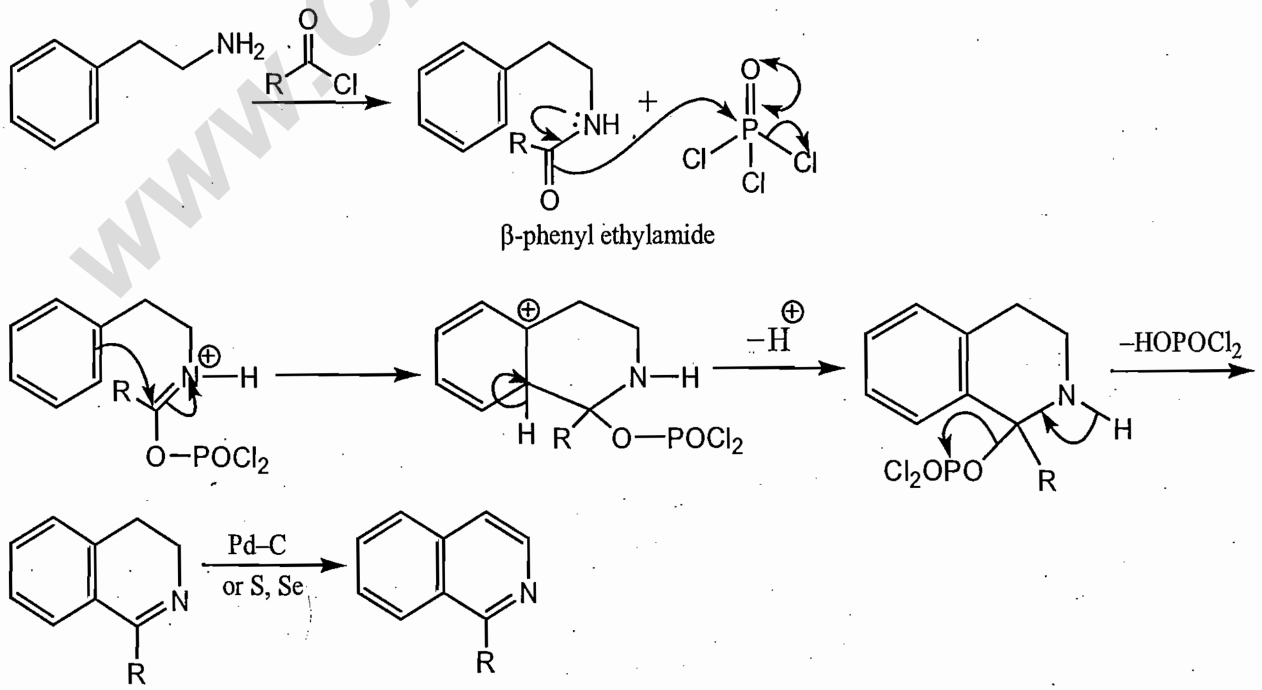
Isoquinoline is present with quinoline in coal tar and bone oil, and is a decompositional product of many alkaloid.

(A) Synthesis of isoquinoline.

(1)

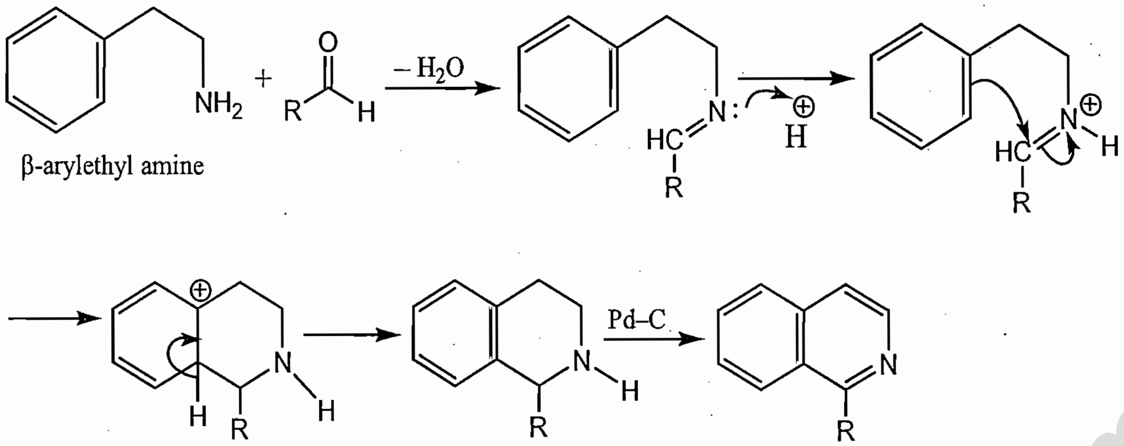


(ii) Bischler-Napieralski reaction:

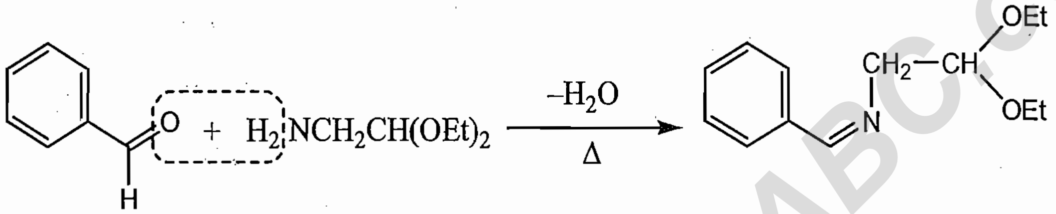


(iii) Pictet-Spengler reaction:

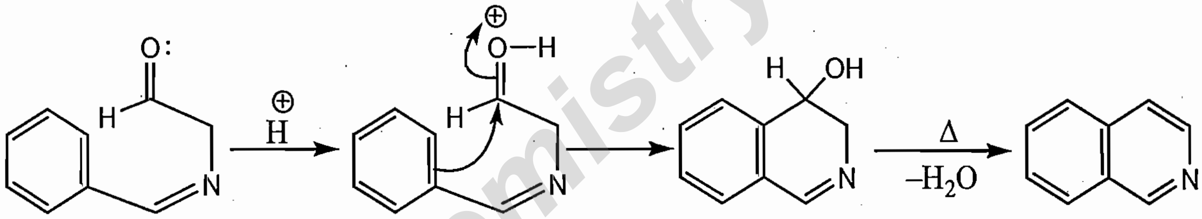
It is a condensation between β-arylethylamine and an aldehyde in the presence of a large excess HCl at 100°C produces to a 1, 2, 3, 4-tetrahydro Isoquinoline.



(iv) Pomeranz-Fritsch reaction:

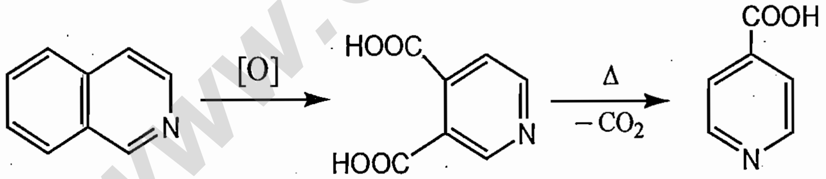


Benzaldehyde



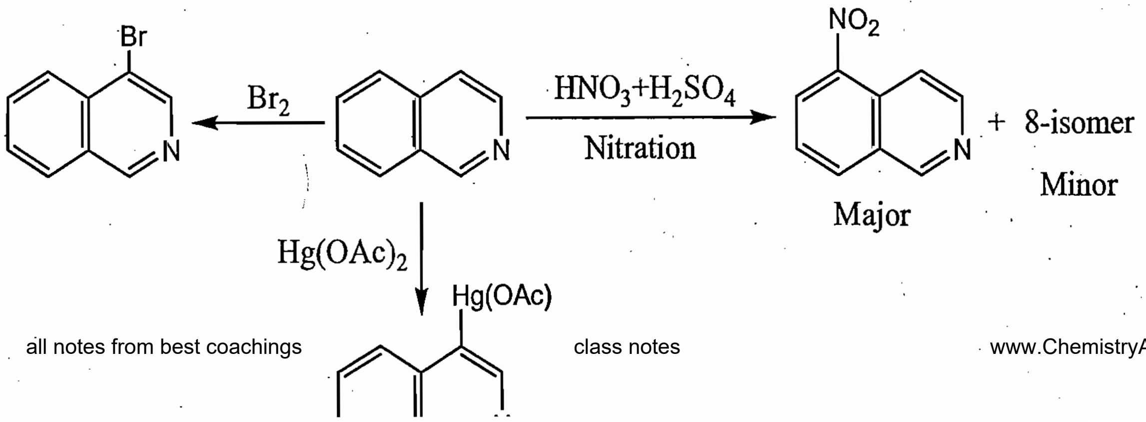
(B) Chemical Reaction:

(i) Oxidation of isoquinoline:

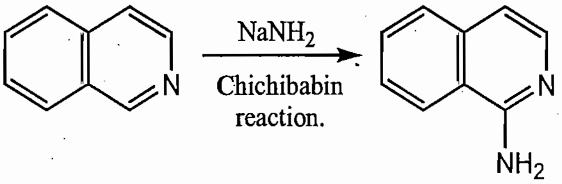


Cinchomeronic acid Isonicotinic acid

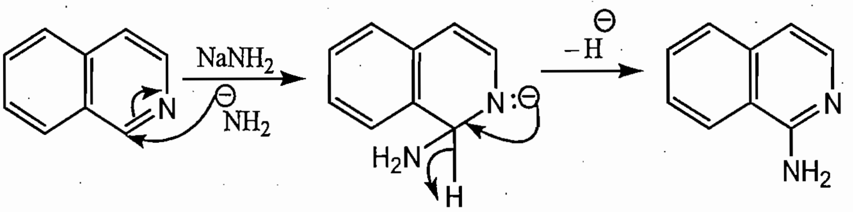
Electrophilic substitution occurs predominantly at position 5 and position 8. But bromination mainly occur at 4 position.



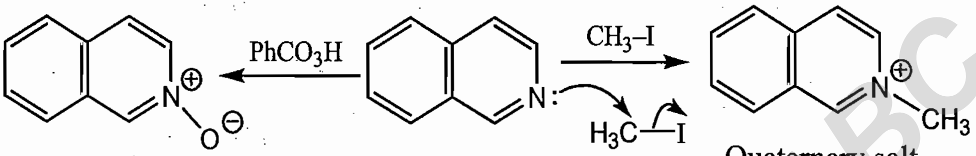
Nucleophilic substitution occurs at position-1.



***Mechanism*:**

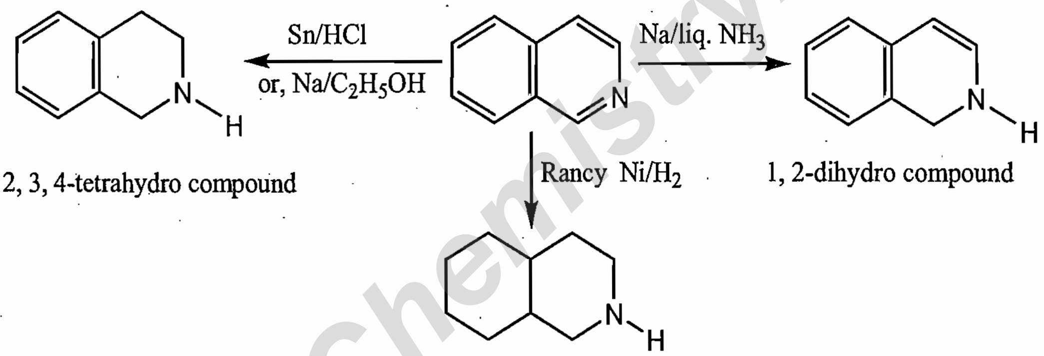


Reaction due to N–atom.



Quaternary salt

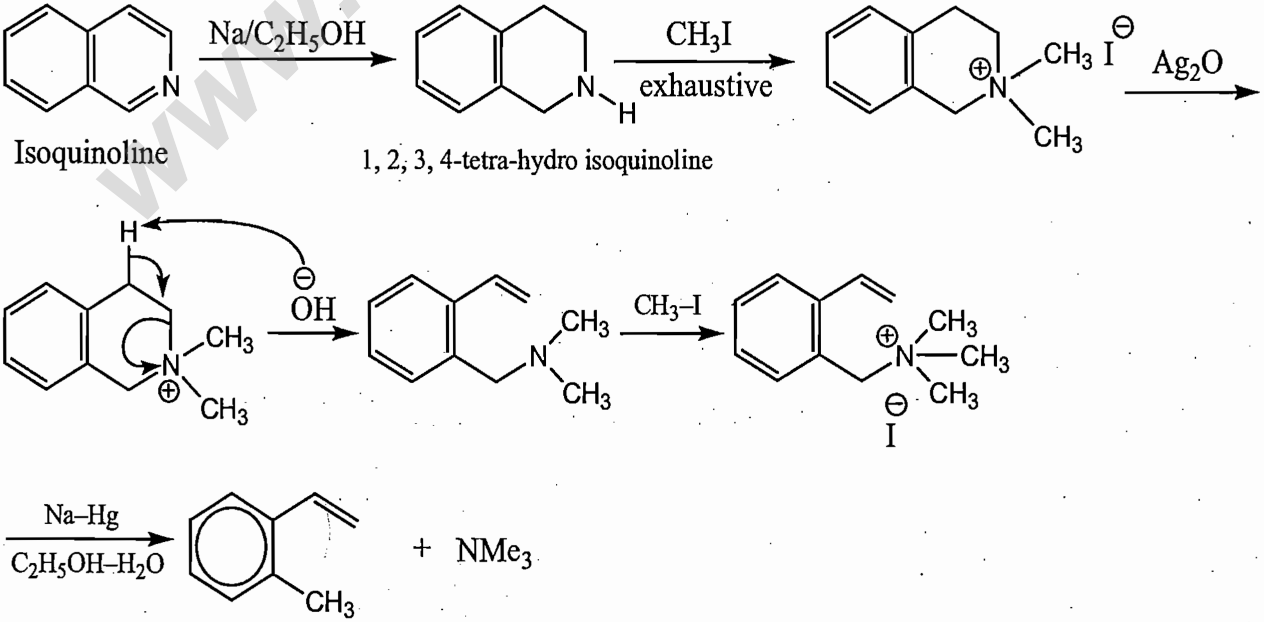
(ii) Reduction of isoquinoline:



1, 2, 3, 4-tetrahydro compound

1, 2-dihydro compound

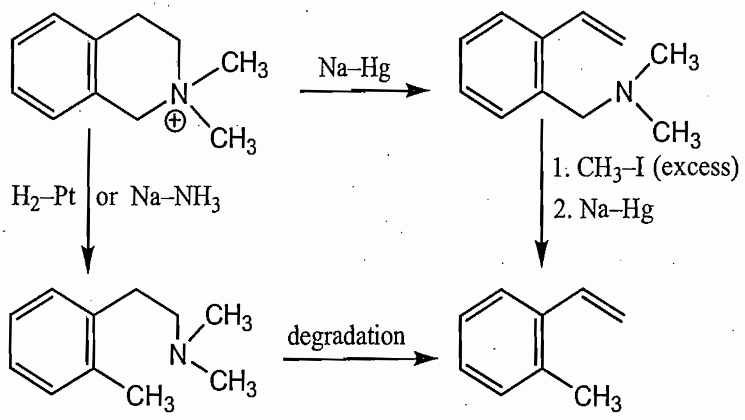
Exhaustive methylation of isoquinoline.



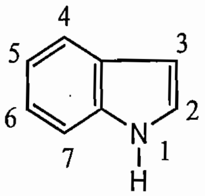
Isoquinoline

1, 2, 3, 4-tetra-hydro isoquinoline

Emde degradation on tetrahydro Isoquinoline.



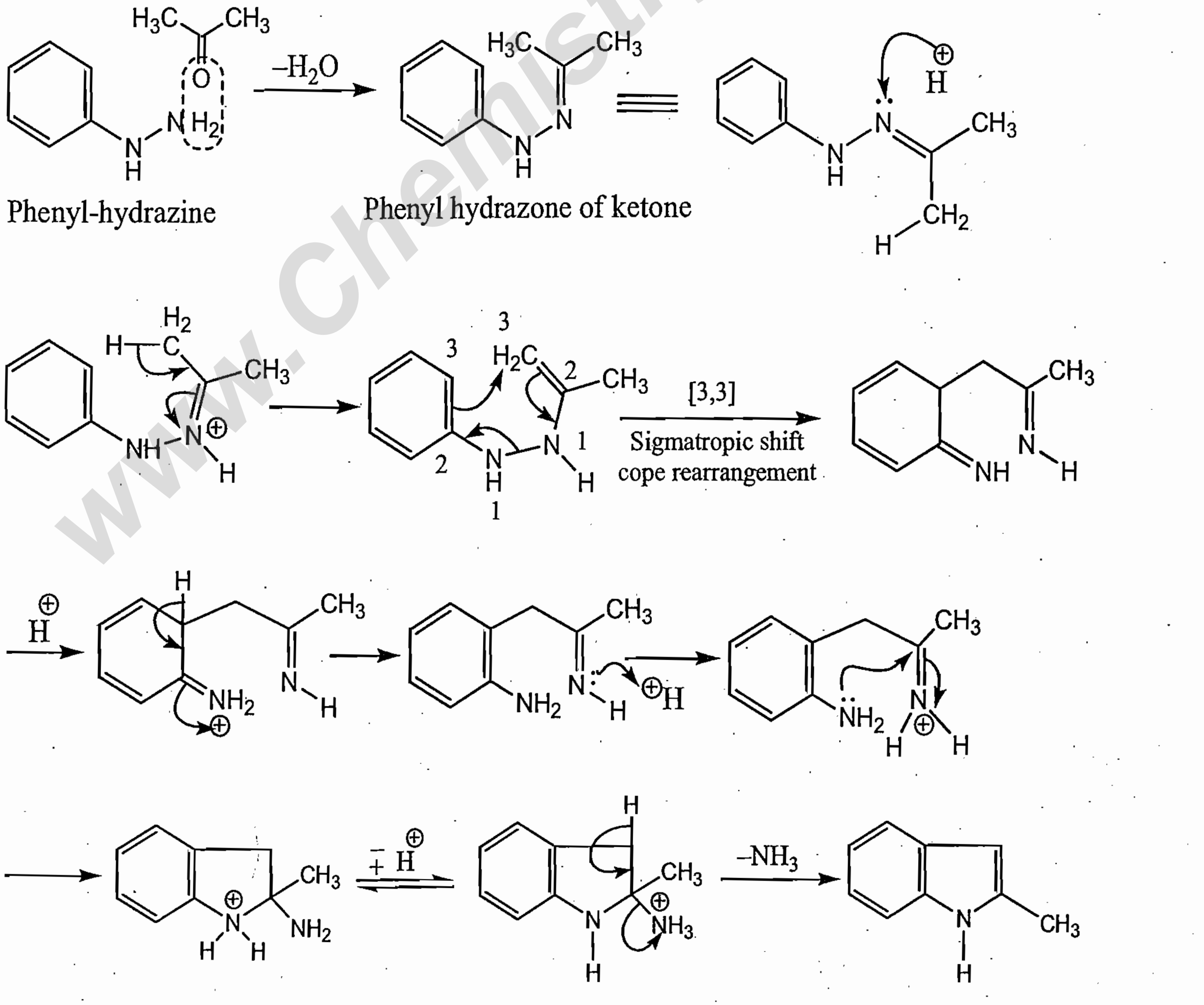
8.7. INDOLE



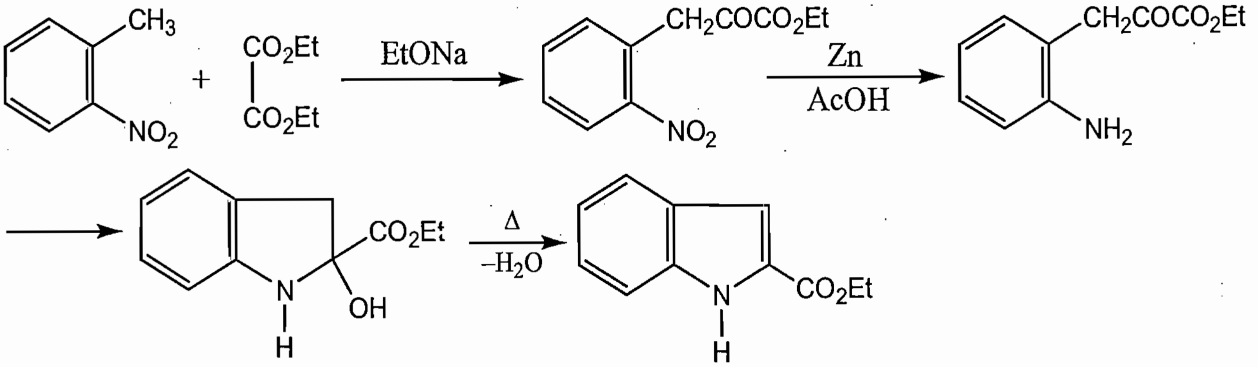
It is also called benzo pyrrole. Indole occurs in coal tar, Jasmine flower and orange blossoms.

(A) Synthesis of indole:

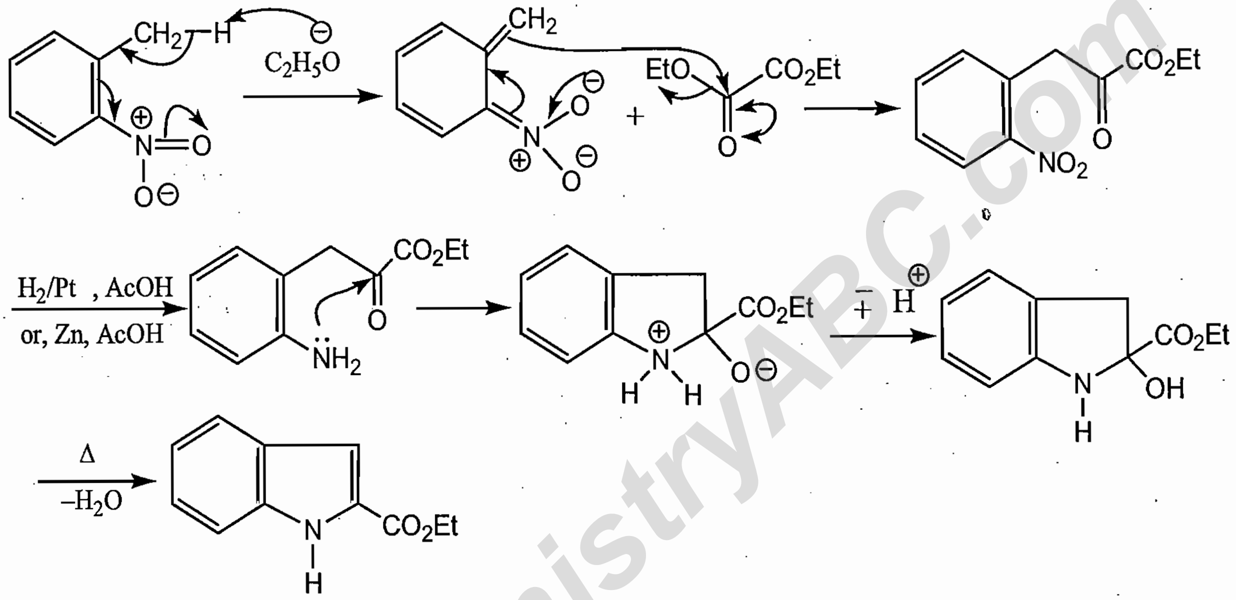
(i) Fischer Indole synthesis:



(ii) Reissert synthesis: Reissert synthesis is carried out with o-nitrotoluene and ethyl oxalate.

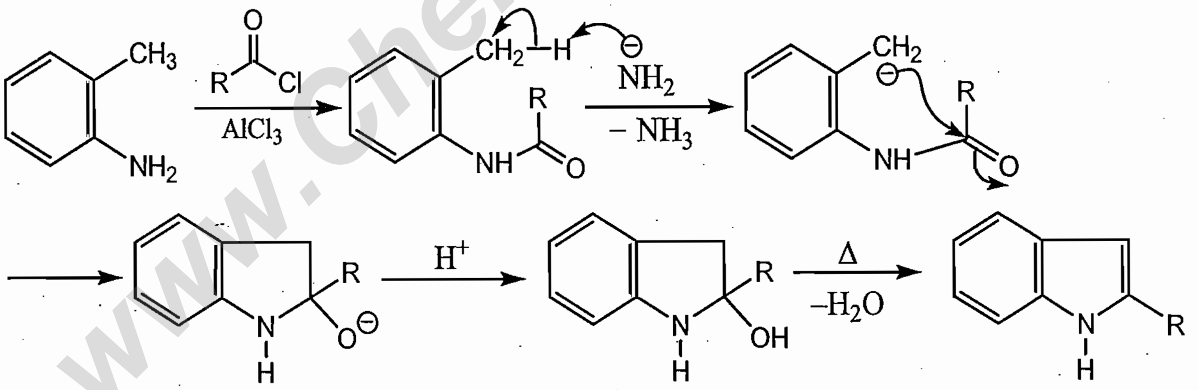


***Mechanism*:**



(iii) Madelung synthesis:

Madelung synthesis involves the cyclisation of an o-acyl amidotoluene by means of strong base.

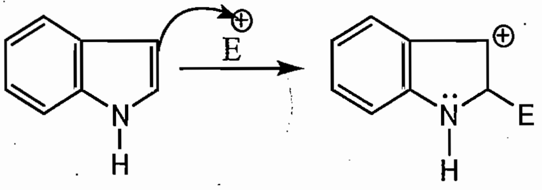


(B) Chemical reaction of Indole:

Electrophilic substitution generally occurs at position 3.

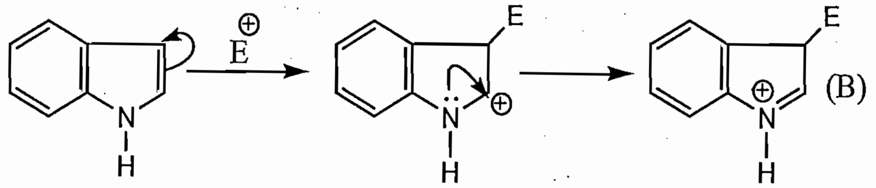
Illustration.

Let us consider electrophilic attack at position 2.

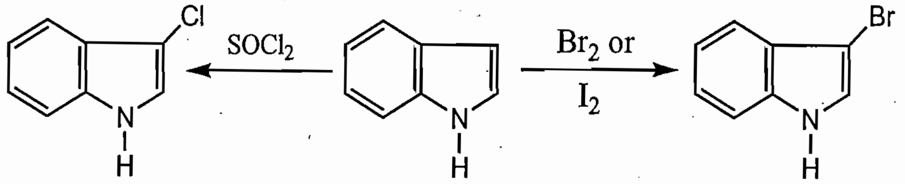


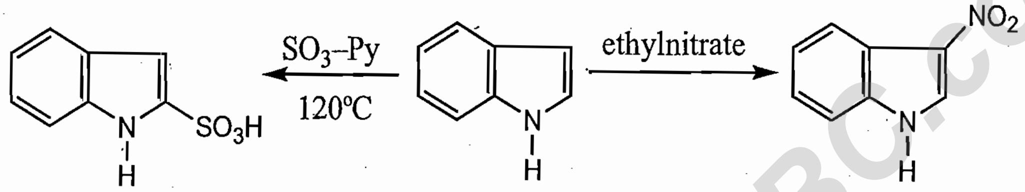
(A)

electrophilic attack at position 3.

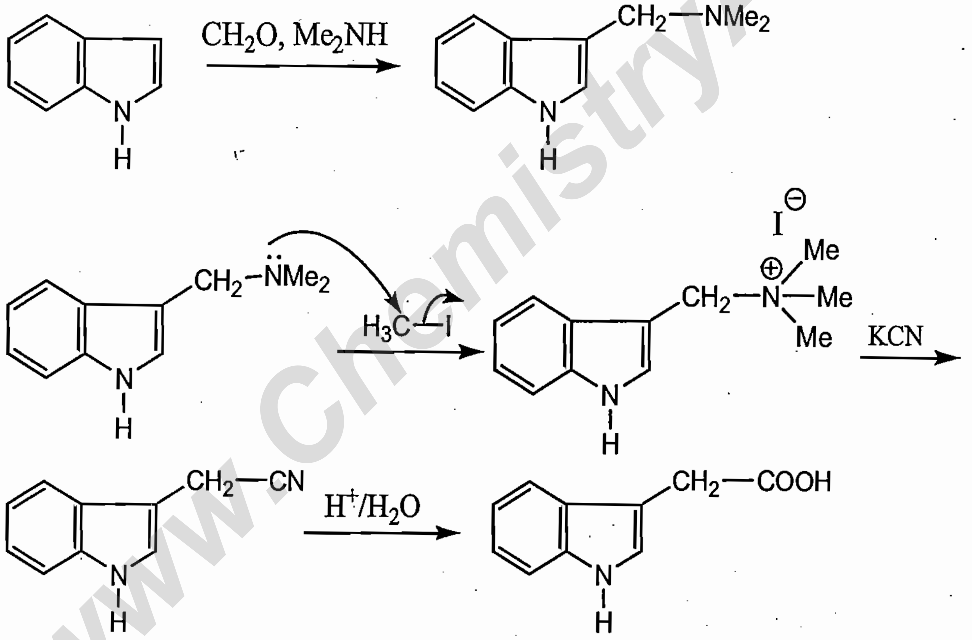


Hence, the intermediate (B) is more stable than that of intermediate (A). So, electrophilic substitution preferentially occurs at position 3. However, if the position-3 is occupied then the substitution occurs at position 2. If both 2 and 3 positions are blocked, then, substitutent will be attached in the benzene ring is attached at the 6 position.

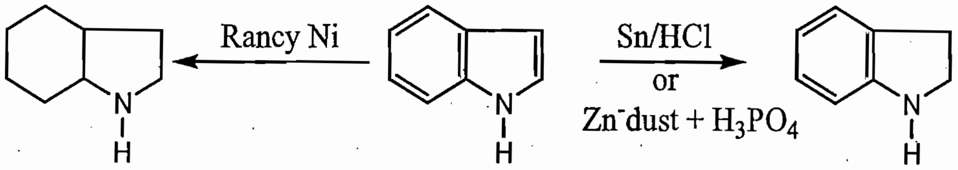




(B) Mannich reaction on indole.



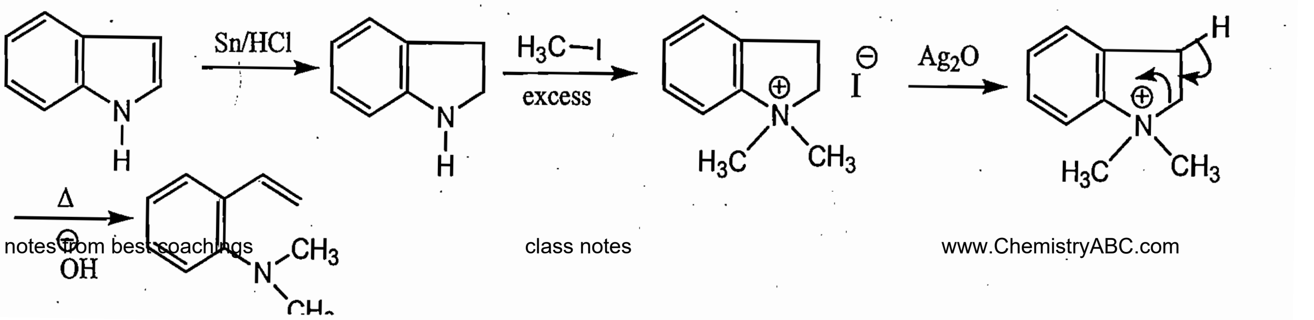
(C) Reduction of indole:



2, 3-dihydro indole
or, indoline

PROBLEMS

1.



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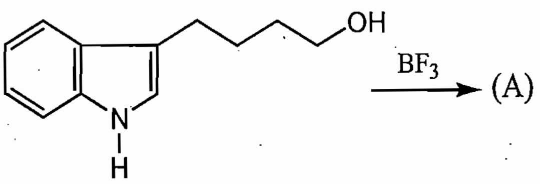
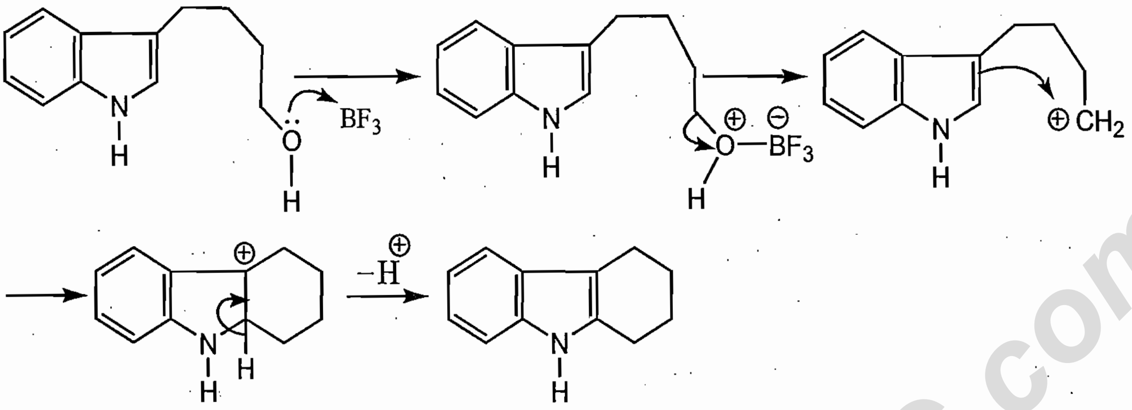


Find the major product (A) in the above reaction.

Soln.



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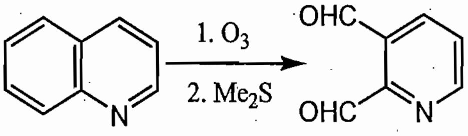
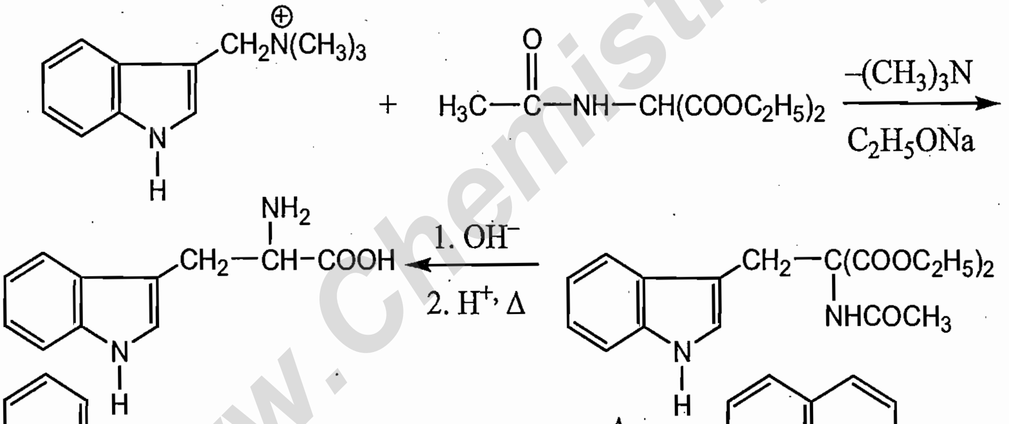


4. Synthesis of tryptophan, The amino acid, tryptophan is synthesized from the quaternary salt of gramine and acetamido malonic ester.



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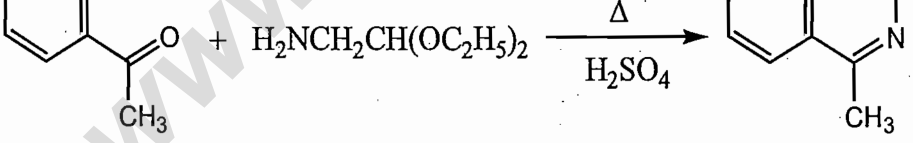

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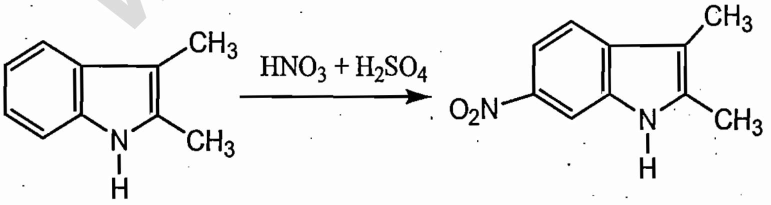
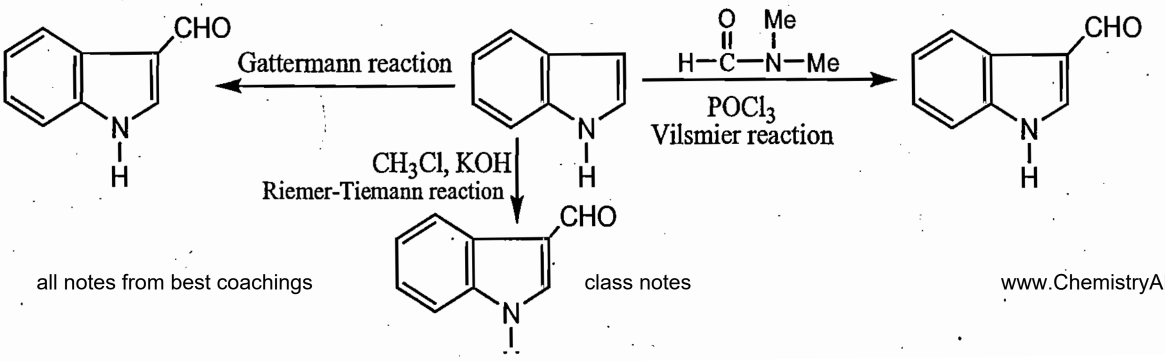
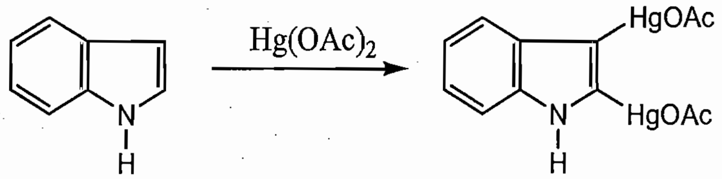




Mercuration with mercuric acetate lead to 2, 3-diacetoxy mercuri-indole.



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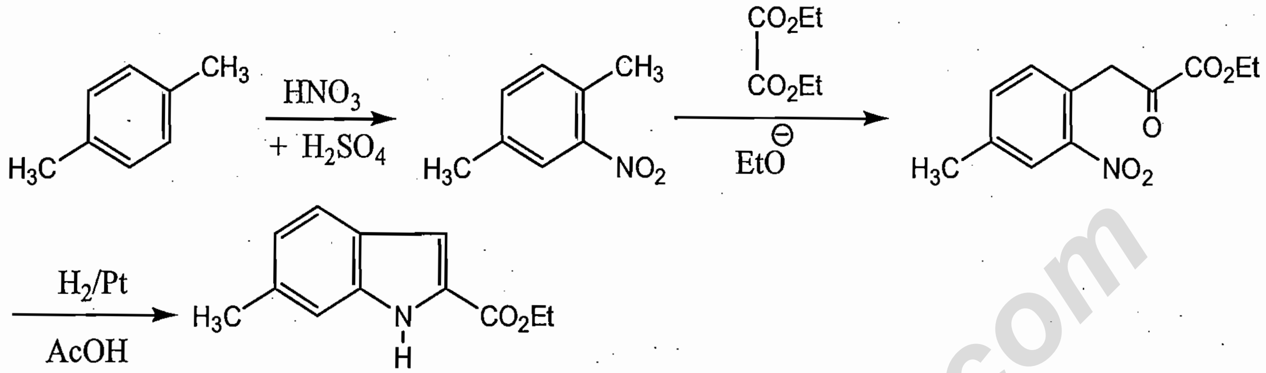
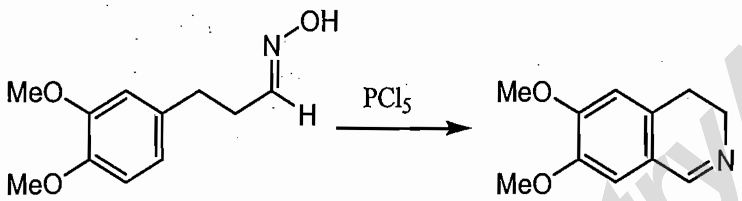
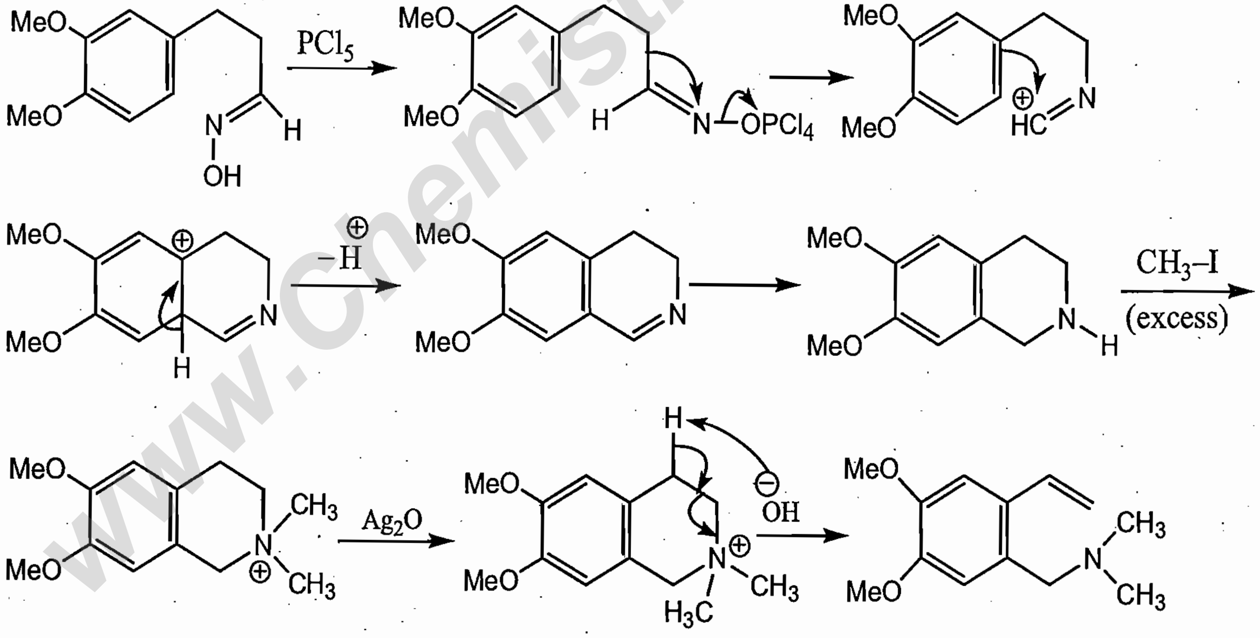


8. Account for the following transformation with an appropriate mechanism. Give the structure of the Hofmann exhaustive methylation product of 1, 2-dihydro derivative of X.



Soln.



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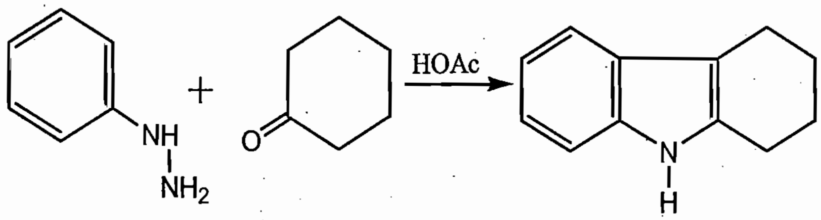

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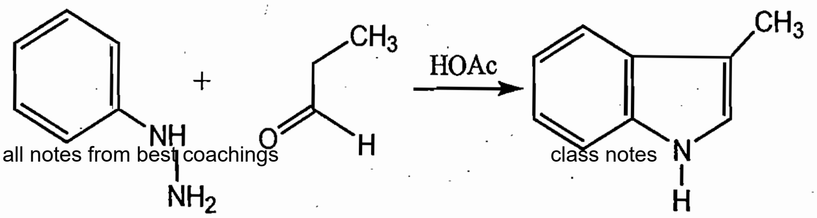

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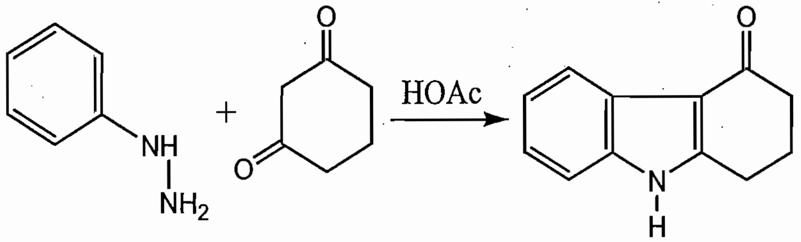
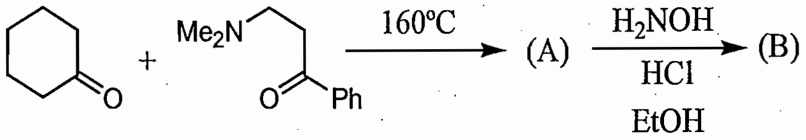


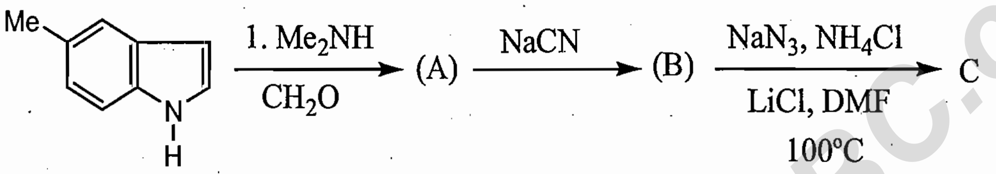
PRACTICE QUESTIONS

1.

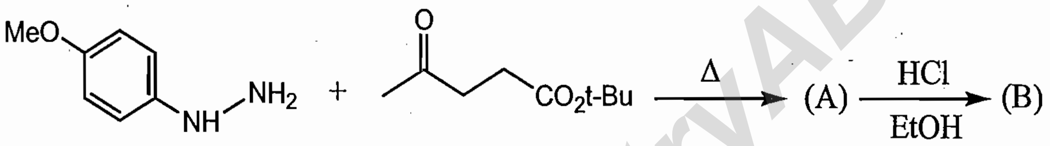


Find the major product (A) and (B) in the above reaction.

2.



3.



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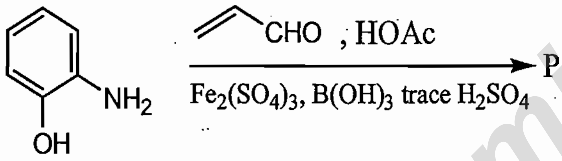
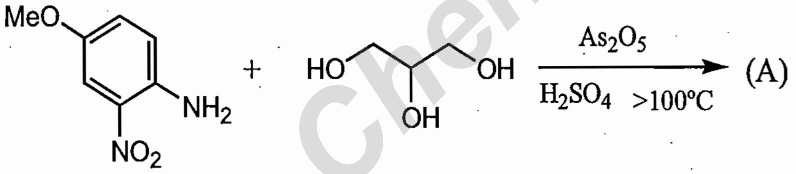


. The major product 'P' is:

5.



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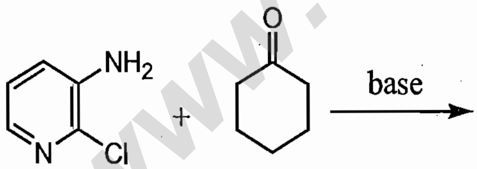
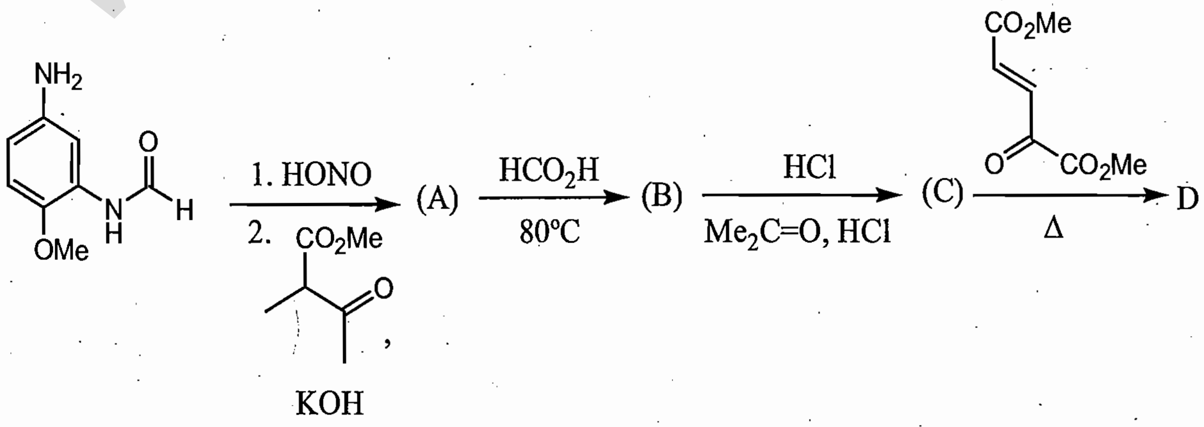
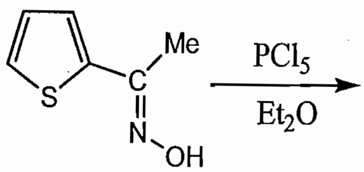


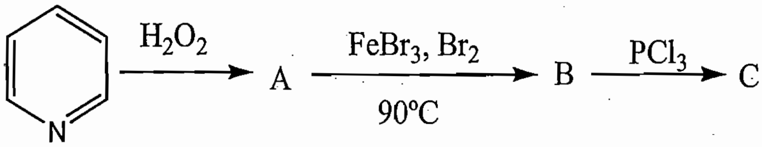
(A) Find A.

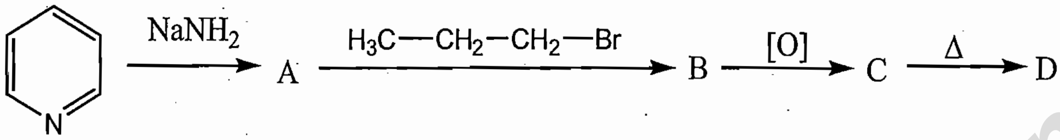
7.

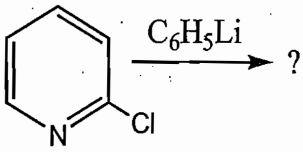


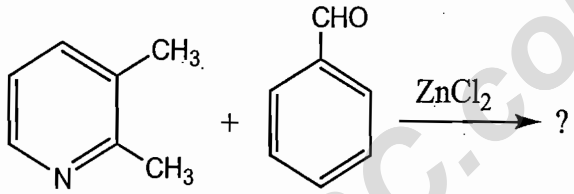
In the above reaction sequence find $A \to D$.

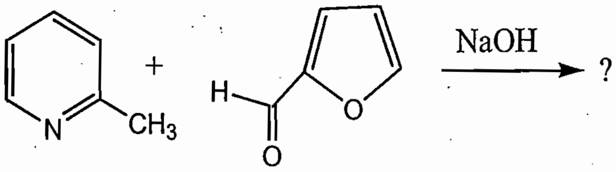
8. 
P. Find the product P.

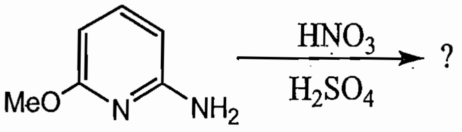
9. 

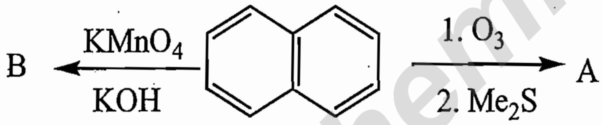
10. 

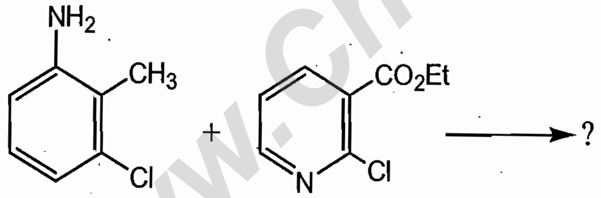
11. 

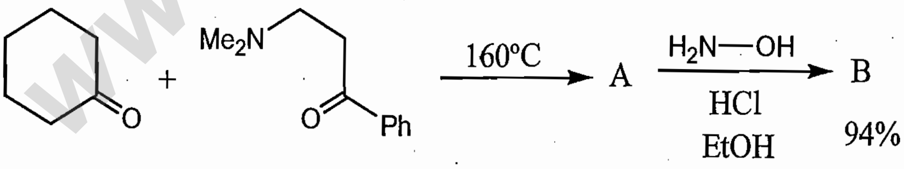
12. 

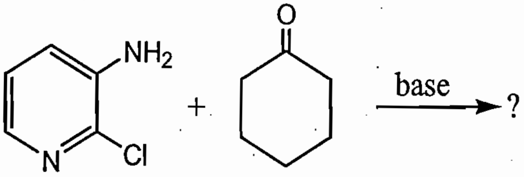
12. 

13. 

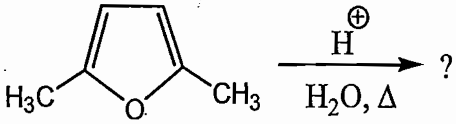
14. 

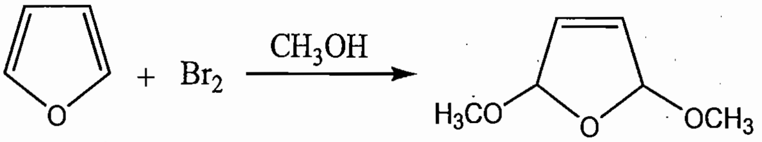
15. 

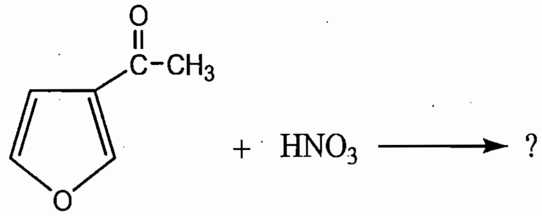
16. 

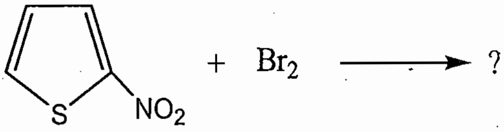
17. 

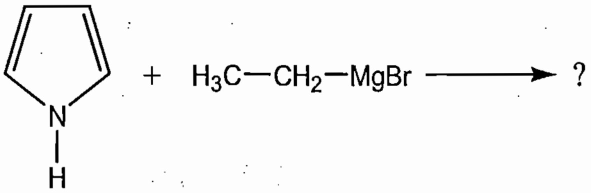
18. Propose a mechanism for each of the following reaction.

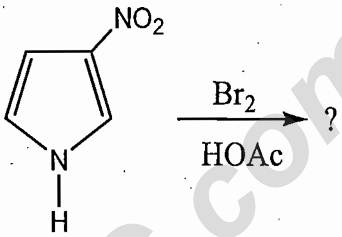
(a) 

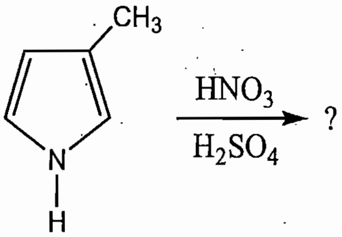
(b) 

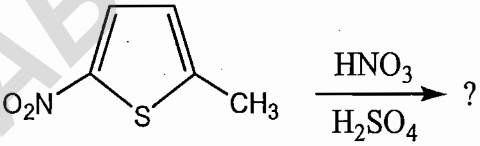
19. 

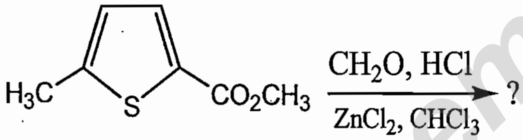
20. 

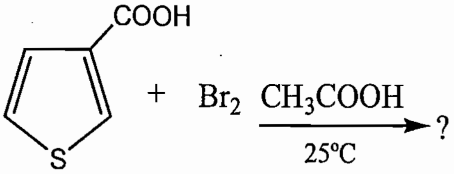
21. 

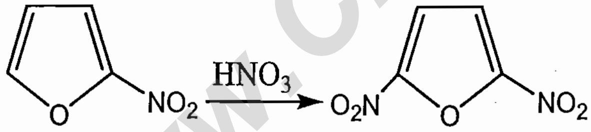
22. 

23. 

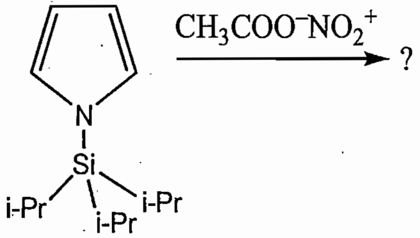
24. 

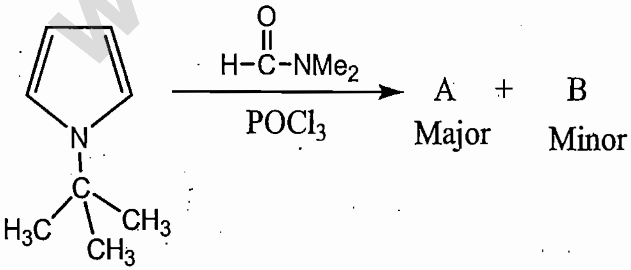
25. 

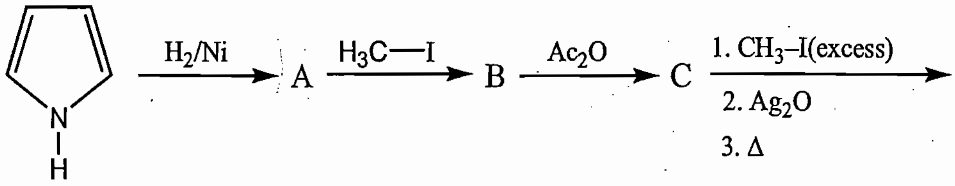
26. 

27. 

2-nitrofuran

28. 

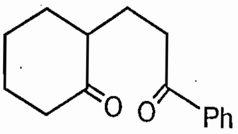
29. 

30. 

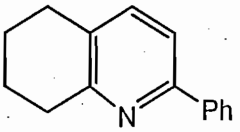
31. Upon treatment with HCHO and acid, ethyl 2, 4-dimethyl-3-pyrrole carboxylate is converted into a compound of formulae $C_{19}H_{26}O_4N_2$. What is most likely structure of the product.

SOLUTIONS

1. (A)



(B)



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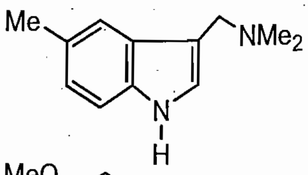

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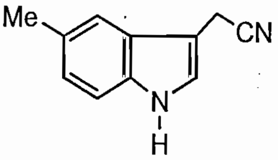

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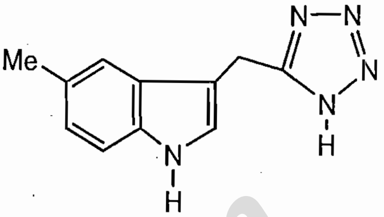

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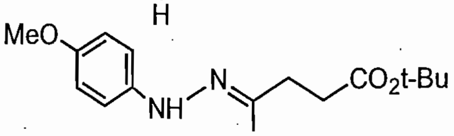

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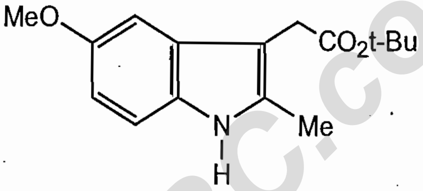

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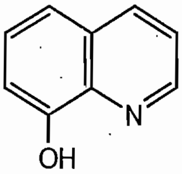

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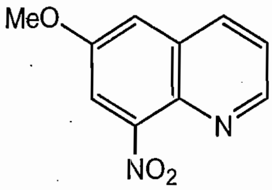

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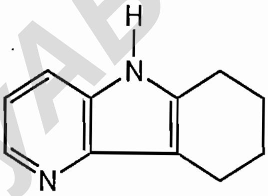
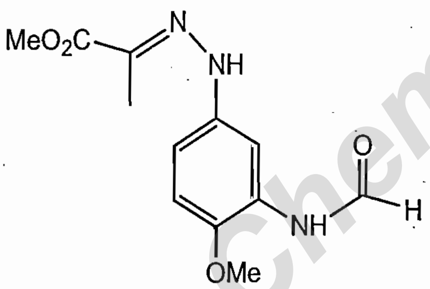


7. (A)



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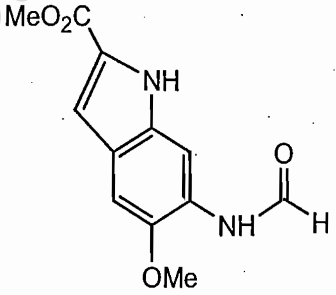
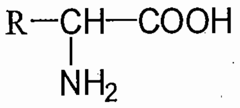


CHAPTER 9

Natural Products

9.1. Amino Acid :

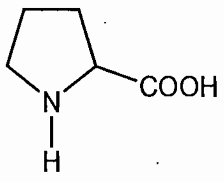
The amino acid is an organic acid containing both NH_2 and COOH group called as amino-acid.

Basic structure of α – amino-acid is 

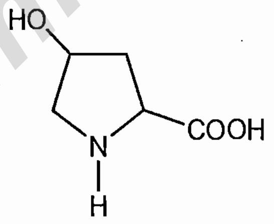
$$R-\underset{\displaystyle NH_2}{\underset{|}{CH}}-COOH$$

There are 20 amino acids in human body out of these two amino acids are α-Imino - acid viz.

(1) Proline



(2) Hydroxyproline

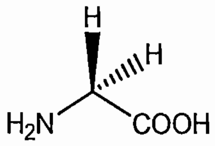
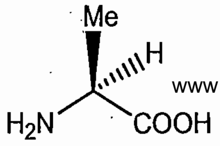


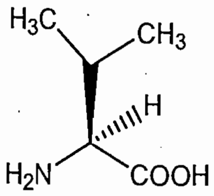
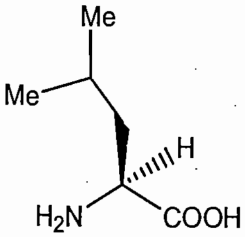
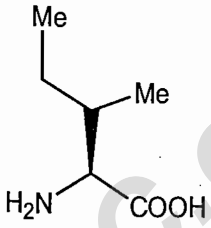
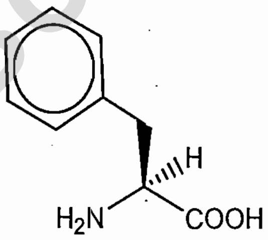
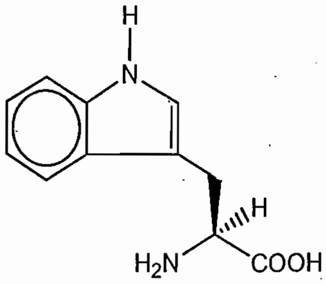
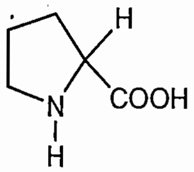
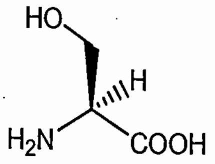
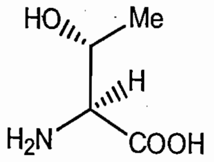
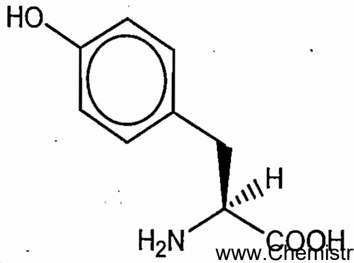
- All α-amino acid are chiral except glycine.
- They are optically active
- All amino-acid are L-Amino acid and their standard unit is serine.
- All amino-acid are S-configuration except cysteine which have R-configuration.

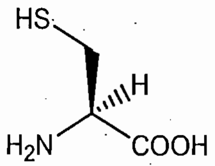
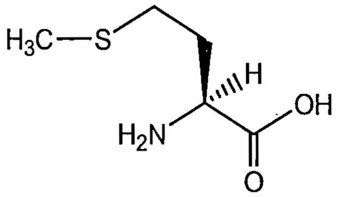
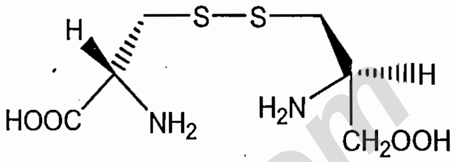
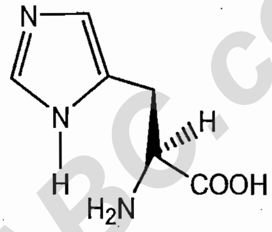
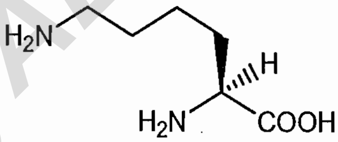
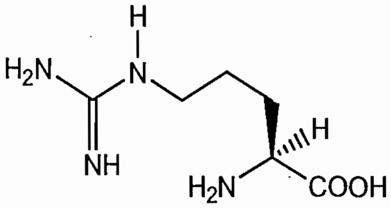
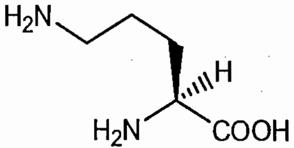
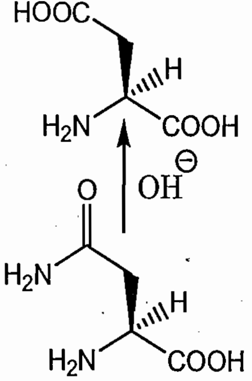
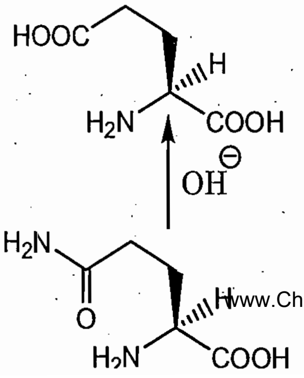
Classification on the basis of NH_2 and COOH group:

1. Neutral Amino acid → $-NH_2 = -COOH$
2. Acidic Amino acid → $-COOH > -NH_2$
3. Basic Amino acid → $-NH_2 > -COOH$

Amino Acid:

Name	Three Letter Symbol	Structure
Glycine	Gly	
Alanine	Ala	

Valine	Val	
Isoleucine	ILe	
Leucine	Leu	
Phenylalanine	Phe	
Tryptophan	Trp	
Proline	Pro	
Serine	Ser	
Threonine	Thr	
Tyrosine	Tyr	

Cysteine	Cys	
Methionine	Met	
Cystine	Cys-cys	
Histidine	His	
Lysine	Lys	
Arginine	Arg	
Ornithine	Orn	
Aspartic acid	Asp	
Asparagine	Asn	
Glutamic acid	Glu	
Glutamine	Gln	

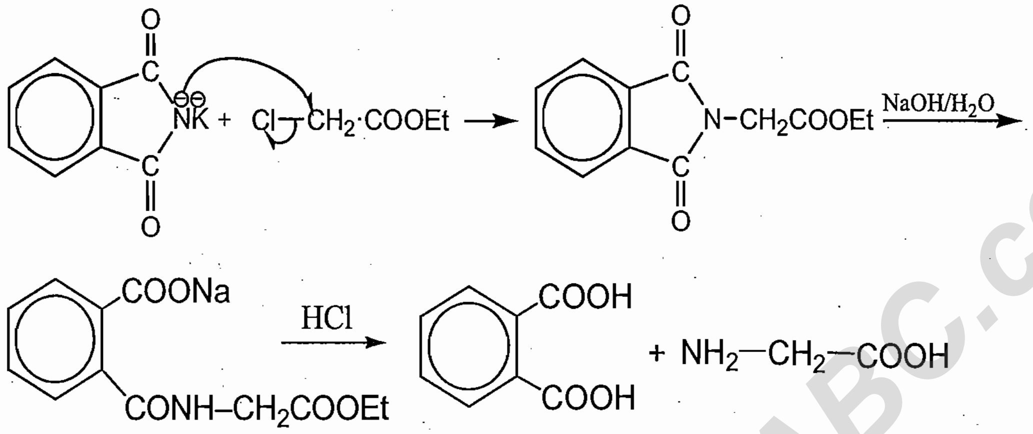
- **Amino acid with aromatic side chain:** Phe, Tyr, Trp

Essential and Non - Essential Amino acid :

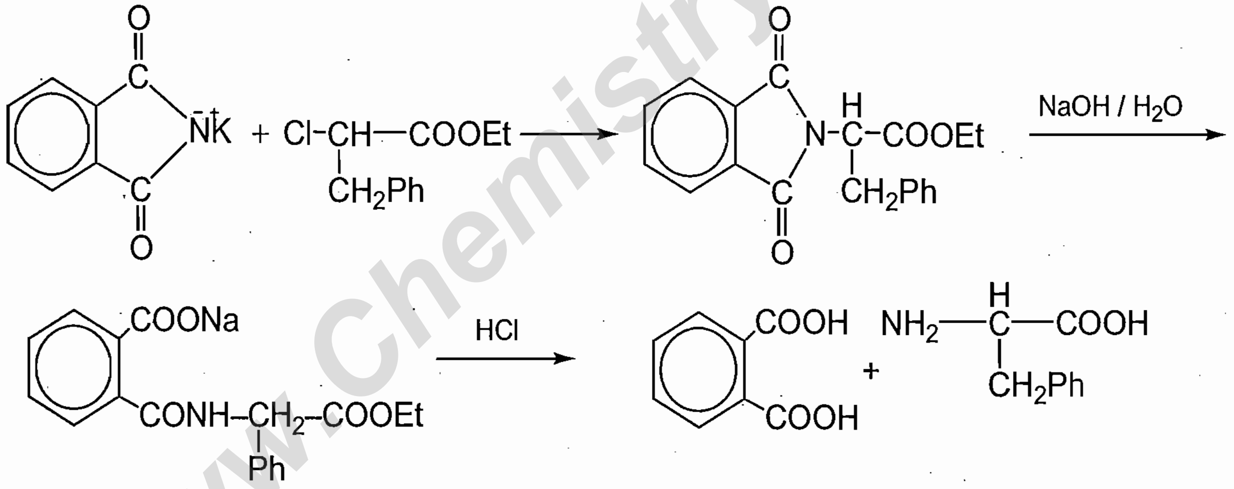
Those amino acid that can't synthesised in the body and has to be provided from out side by food called as essential amino acid. There are ten essential amino acid such as Phe, Val, Trp, Tyr, ILeu, Met, His, Arg, Leu and Lys.

Synthesis of Amino ACid :

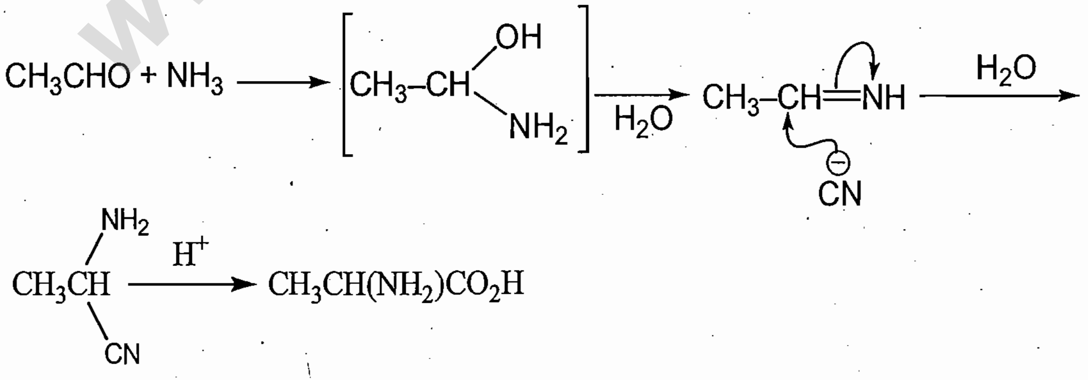
1. Gabriel Phthalimide Synthesis :



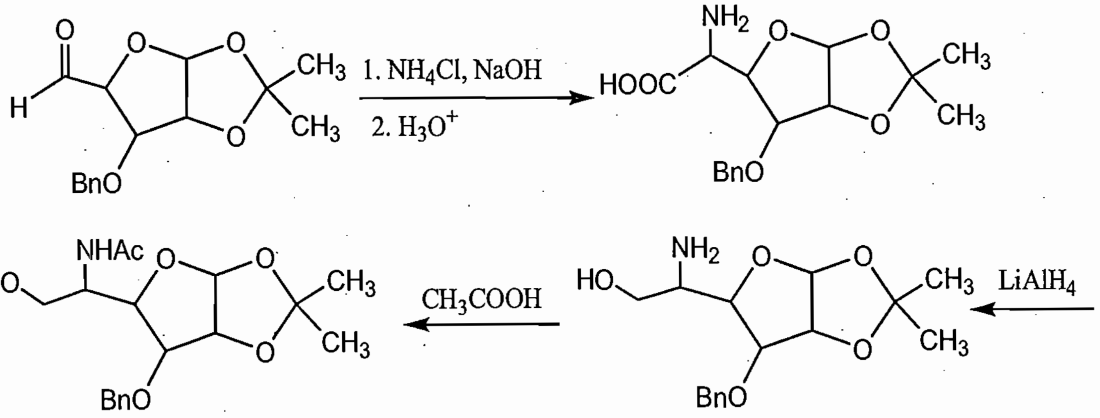
Synthesis of phenyl alanine by Gabriel phthalimide method:



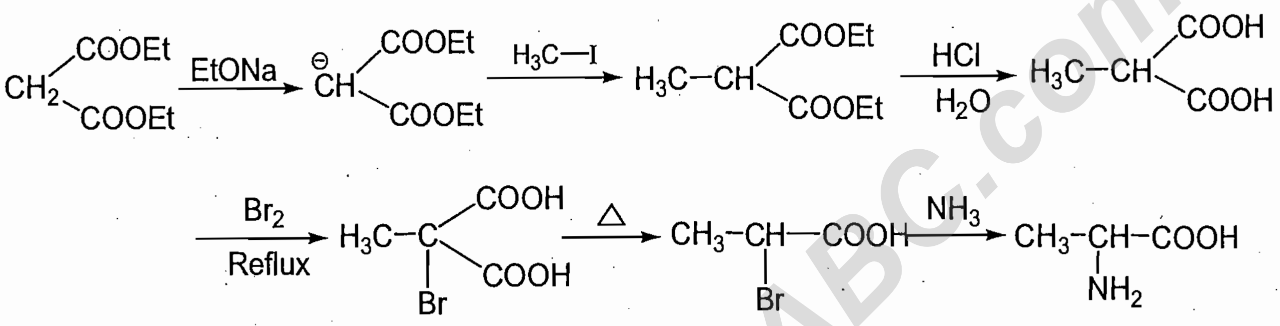
2. Strecker Synthesis:



Problem:



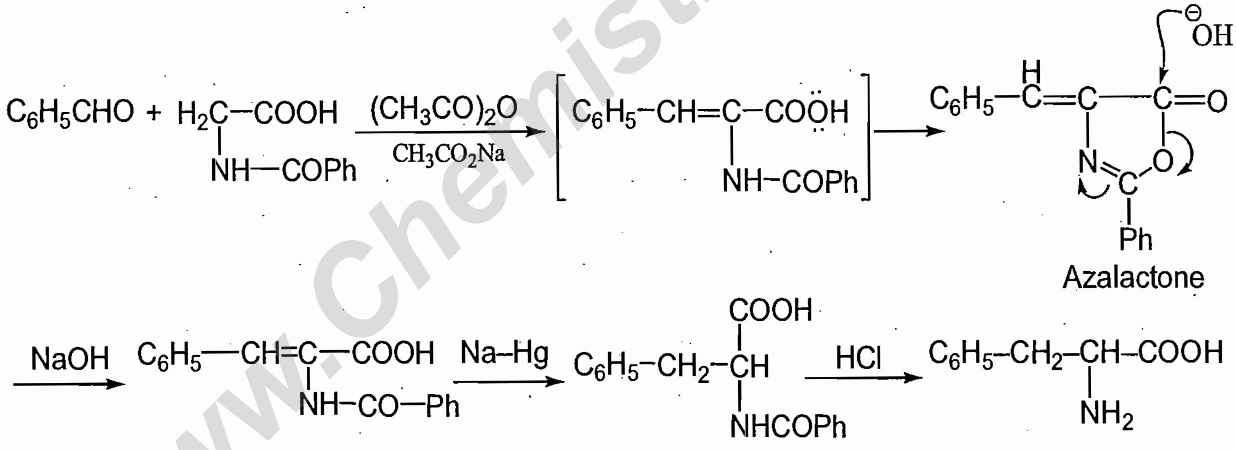
3. Malonic Ester Synthesis :



- By these methods we can prepare the following amino acids.

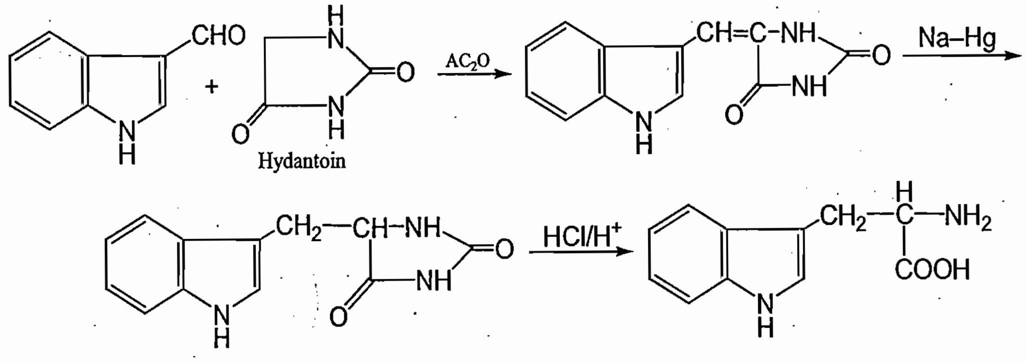
Phe, Pro, Tyr, Cys, Ser, Asp, Met and Lys.

4. Erlenmeyer Azalactone Synthesis :



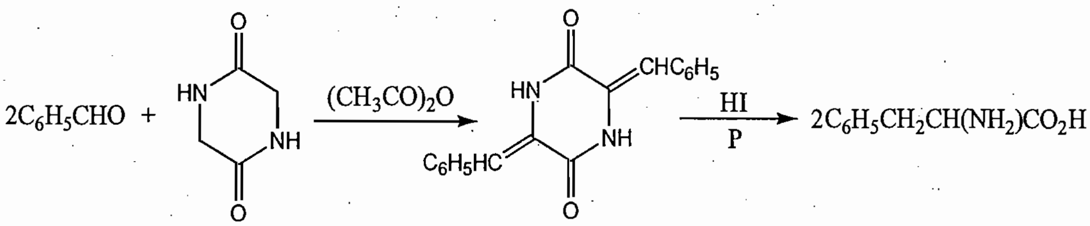
This method is best for the synthesis of Phe, Tyr, Try and thyroxine.

5. Hydantoin Synthesis:



This method may be used for the preparation of Phe, Tyr, Try and Met.

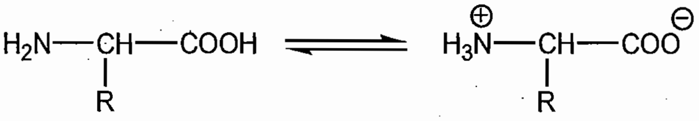
6. Aromatic aldehydes may be condensed with diketonpiperazine, and the product converted into an amino acid by heating with hydriodic acid and red phosphorus for example,



Physical Properties :

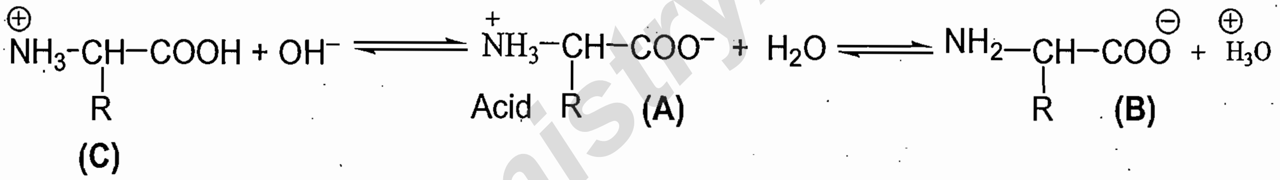
1. The amino acids are colourless crystalline compounds which are soluble in water and sparingly soluble in organic solvent.
2. The acidity and basicity are very low.
3. They have very high melting point > 200°C.
4. They have high dipole moment.

The amino acids exist in ***Zwitter ion*** form such as



$$H_2N-\underset{\underset{R}{|}}{CH}-COOH \rightleftharpoons \overset{\oplus}{H_3N}-\underset{\underset{R}{|}}{CH}-COO^{\ominus}$$

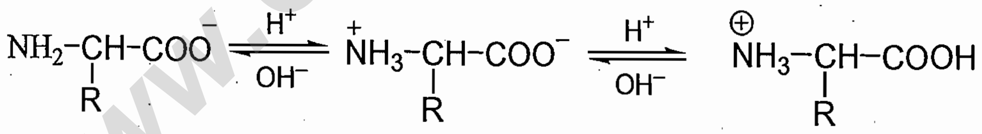
The properties shown by amino acid suggest that they exist as dipolar ion by internal proton transfer known as Zwitter ion because of the Zwitter ionic structure. The acidity in amino acid is due to NH_3^+ group and basicity is due to COO^-.



$$\overset{\oplus}{N}H_3-\underset{\underset{\underset{(C)}{R}}{|}}{CH}-COOH + OH^- \rightleftharpoons \underset{\text{Acid}}{\overset{+}{N}H_3}-\underset{\underset{R}{|}}{CH}-\underset{(A)}{COO^-} + H_2O \rightleftharpoons NH_2-\underset{\underset{R}{|}}{CH}-\underset{(B)}{COO^{\ominus}} + \overset{\oplus}{H_3O}$$

$$K_a = \frac{\left[H_3O^+\right][B]}{[A][H_2O]},\quad K_b = \frac{[C]\left[OH^-\right]}{[A][H_2O]}$$

Isoelectric Point :



$$NH_2-\underset{\underset{R}{|}}{CH}-COO^- \underset{OH^-}{\overset{H^+}{\rightleftharpoons}} \overset{+}{N}H_3-\underset{\underset{R}{|}}{CH}-COO^- \underset{OH^-}{\overset{H^+}{\rightleftharpoons}} \overset{\oplus}{N}H_3-\underset{\underset{R}{|}}{CH}-COOH$$

Conjugate base (–ve charge)
(High pH)
migrate towards anode
in electric field

Zwitter ion
Don't migrate

Conjugate acid (+ ve charge)
(Low pH)
migrates towards cathode
in electric field

At high pH the amino acid migrates towards anode because of negative charge and at low pH they will migrate to cathode because of +ve charge whereas at a particular pH the amino acid molecule will exist in zwitter ionic form which has neutral structure and will not migrate to any of the electrode, this pH is known as isoelectric point of that amino acid

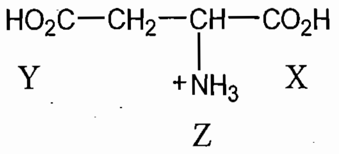
Neutral	Amino acid	~ 5.5 – 6.3
Acidic	Amino acid	~ 3
Basic	Amino acid	~ 9 – 10

PROBLEMS

1. Arrange the following in increasing order of their isoelectric point (P_I)
Arg, Tyr, Asp

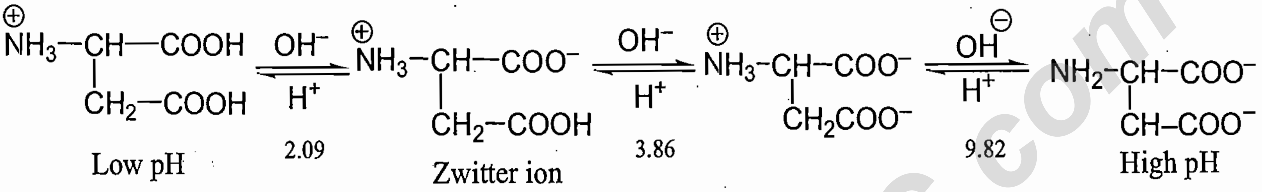
Soln. Asp < Tyr < Arg

2. The pKa values for the three ionisable group X, Y and Z of aspartic acids are 2.09, 3.86 and 9.82 respectively. The isoelectric point for the amino acid is:



$$\underset{Y}{HO_2C}-CH_2-\underset{\underset{Z}{^+NH_3}}{CH}-\underset{X}{CO_2H}$$

Soln.

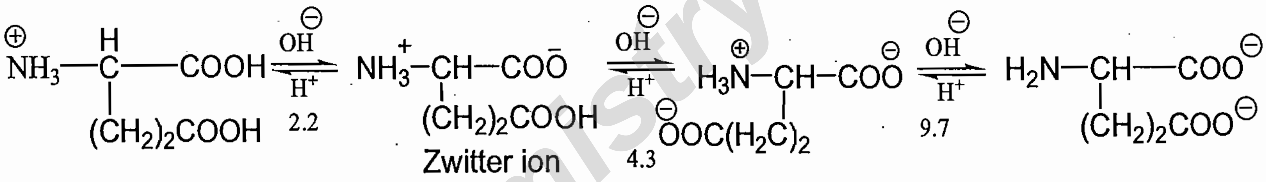


Isoelectric point is the average of two pKa value of the right and left hand side of the zwitter ion.

$$pH_i = \frac{p_{K_1} + p_{K_2}}{2} = \frac{2.09 + 3.86}{2} = 2.97$$

3. The pK_a value for the three ionisable groups x, y, z of glutamic acid are 4.3, 9.7 and 2.2 calculate the isoelectric point.

Soln.



$$pH_i = \frac{2.2 + 4.3}{2} = 3.25$$

Remark: Amino acid molecule show least solubility at its isoelectric point.

4. Find the isoelectric point of glycine whose pK_1 and pK_2 values are 2.4 and 9.6 respectively.

Soln. $pH_i = \frac{2.4 + 9.6}{2} = 6.0$

The values of isoelectric point for few important amino acids are listed below:

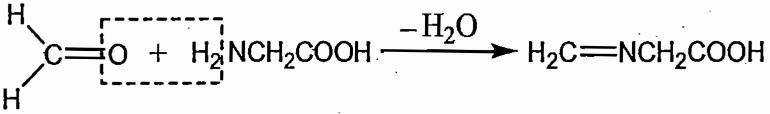
Acid	Symbol	Isoelectric point
Glycine	Gly	6.0
Alanine	Ala	6.1
Valine	Val	6.0
Leucine	Leu	6.0
Isoleucine	Ileu	6.0
Phenylalanine	Phe	5.9
Tyrosine	Tyr	5.6
Serine	Ser	5.7
Cysteine	CySH	5.1
Cystine	CySSCy	5.0
Threonine	Thr	5.7
Methionine	Met	5.7
Tryptophan	Try	5.9
Proline	Pro	6.3
Hydroxyproline	Hypro	5.8
Aspartic acid	Asp	3.0
Asparagine	$AspNH_2$	5.4
Glutamic acid	Glu	3.1
Glutamine	$GluNH_2$	5.7
Arginine	Arg	10.8
Lysine	Lys	9.5
Histidine	His	7.6

5. Arrange the following amino acids in decreasing order of pH_i.
Asp, Tyr, Ala, Arg.

Soln. Arg > Ala > Tyr > Asp.

Sorensen Formol Titration:

In order to titrate the carboxylic group with alkali, the amino group must be 'masked'. Thus when a formalin solution is added to glycine, methylene-glycine is formed. For example

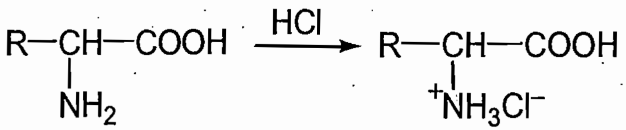


Hence the carboxylic group is free which can be titrated by alkali. This method of titrating amino acid with alkali is known as "Sorensen Formol Titration".

Reaction of Amino Acid:

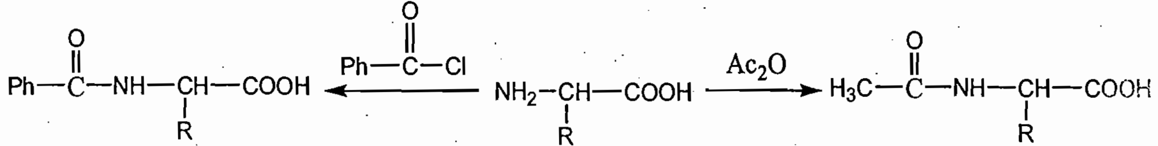
1. Reaction due to NH_2 group :

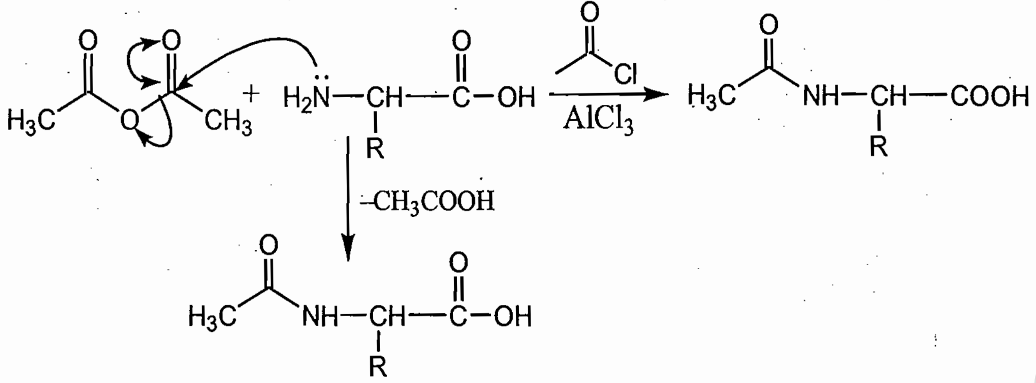
(i) Salt formation:



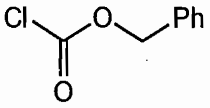
$$R{-}\underset{\displaystyle NH_2}{\underset{|}{CH}}{-}COOH \xrightarrow{HCl} R{-}\underset{\displaystyle {}^{+}NH_3Cl^{-}}{\underset{|}{CH}}{-}COOH$$

(ii) **Acetylation of NH_2 group:** Amino acid may be acetylated of means of acetyl chloride or acetic anhydride

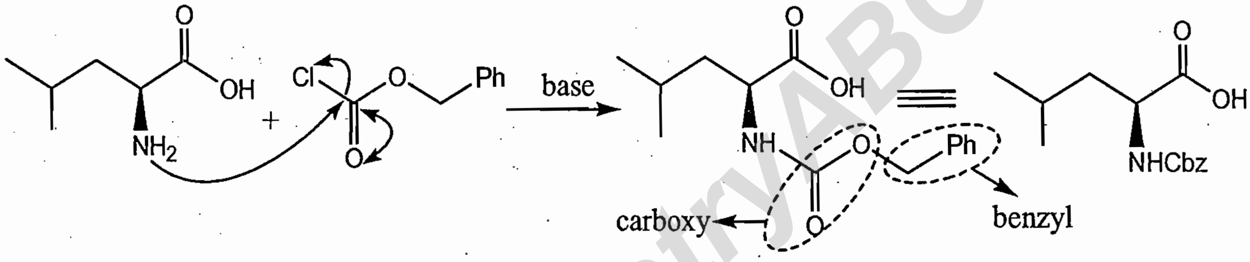




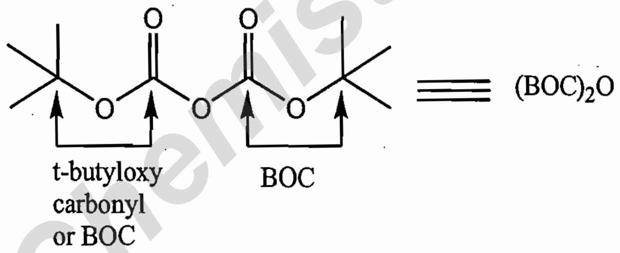
Reaction with Cbz-Cl:

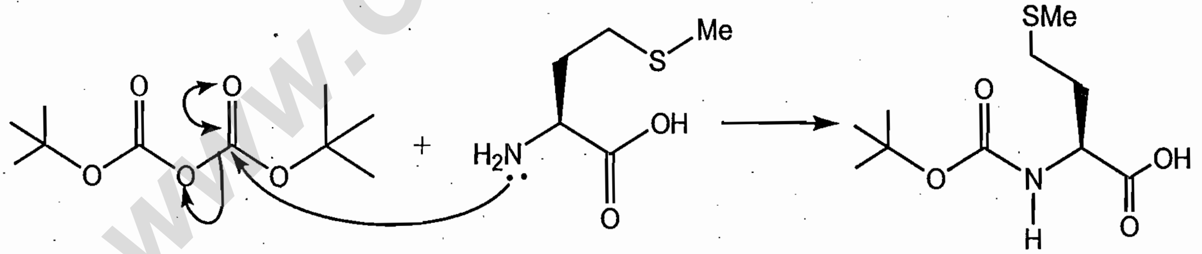


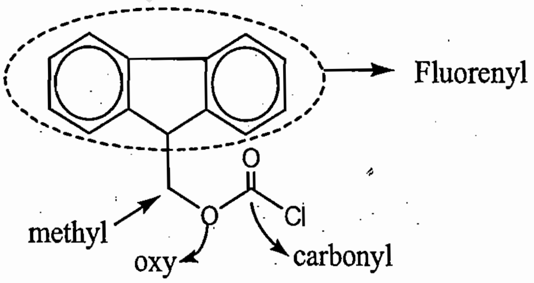
(BnOCOCl)

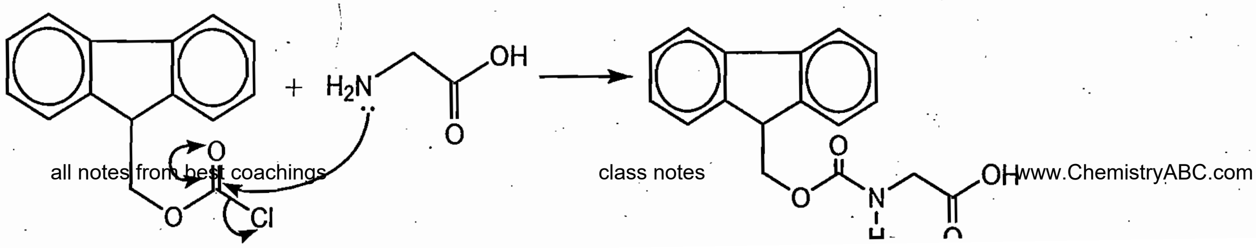


Reaction with $(BOC)_2O$:

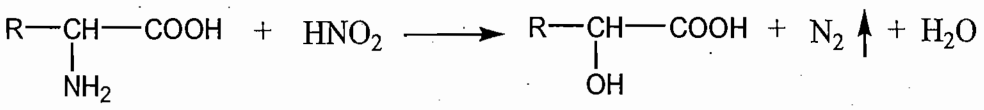








(iii) Reaction with Nitrous acid:

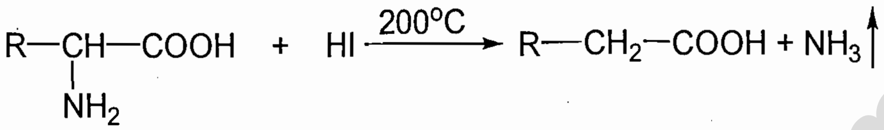


$$R-CH(NH_2)-COOH + HNO_2 \longrightarrow R-CH(OH)-COOH + N_2\uparrow + H_2O$$

It is a quantitative method for the determination of number of amino acid in a mixture and the evolution of nitrogen is the basis of "van Slyke method" for analysing mixtures of amino acid.

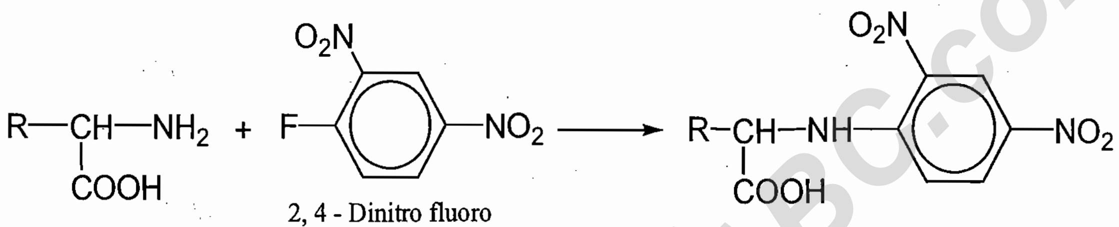
Number of N_2 molecule released ≡ Number of amino acid in the mixture.

(iv) Reaction with Hydriodic acid:



$$R-CH(NH_2)-COOH + HI \xrightarrow{200^\circ C} R-CH_2-COOH + NH_3\uparrow$$

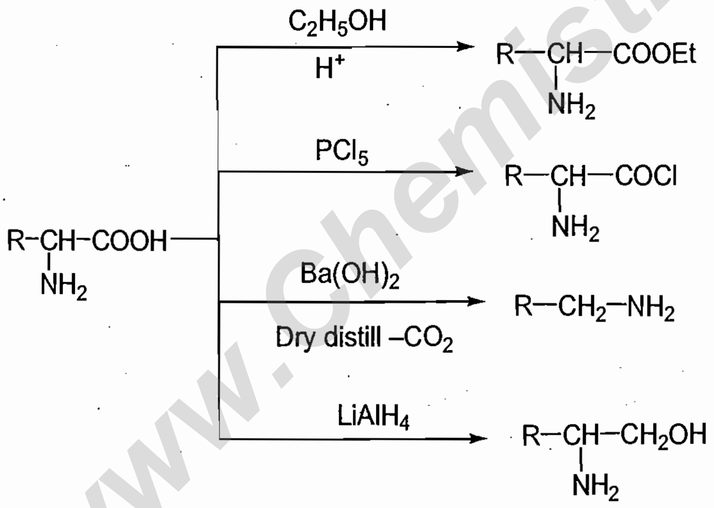
(v) Reaction with Sanger's Reagent :



2, 4 - Dinitro fluoro benzene (DNFB)
(Sanger Reagent)

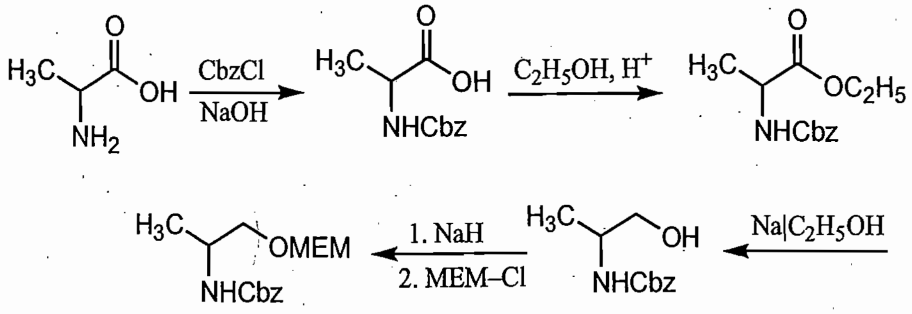
Labelled amino acid
yellow coloured

2. Reaction due to carboxylic group:

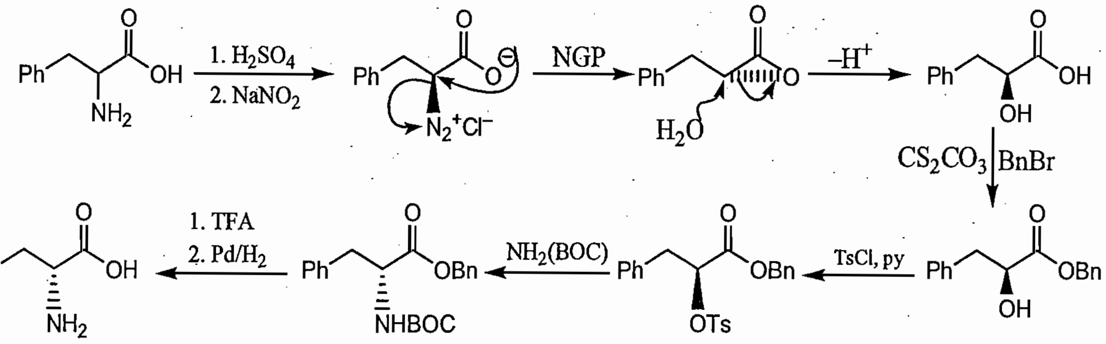


PROBLEMS

1.

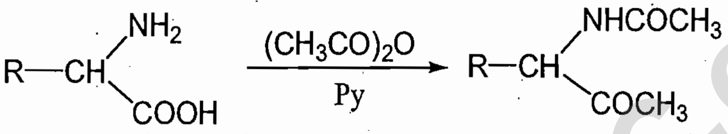


2.

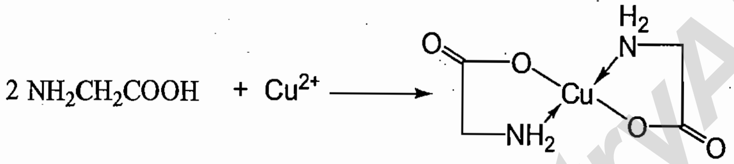


3. **Reaction with both NH_2 and COOH group :**

(i) Dakin-West reaction: When the amino acid is heated with acetic anhydride in pyridine solution, it is converted into methyl α-acetamidoketones, this reaction is known as Dakin-West reaction.



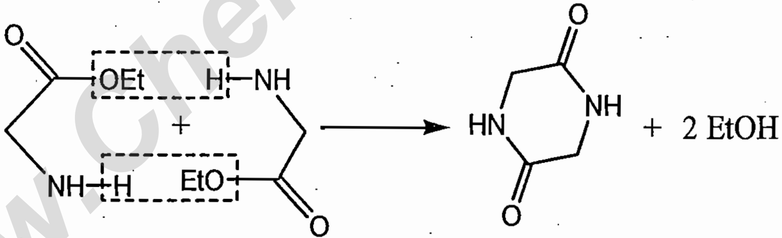
(ii) Chelate Complex : The copper salt of glycine is formed by heating copper oxide with an aqueous solution of glyline.



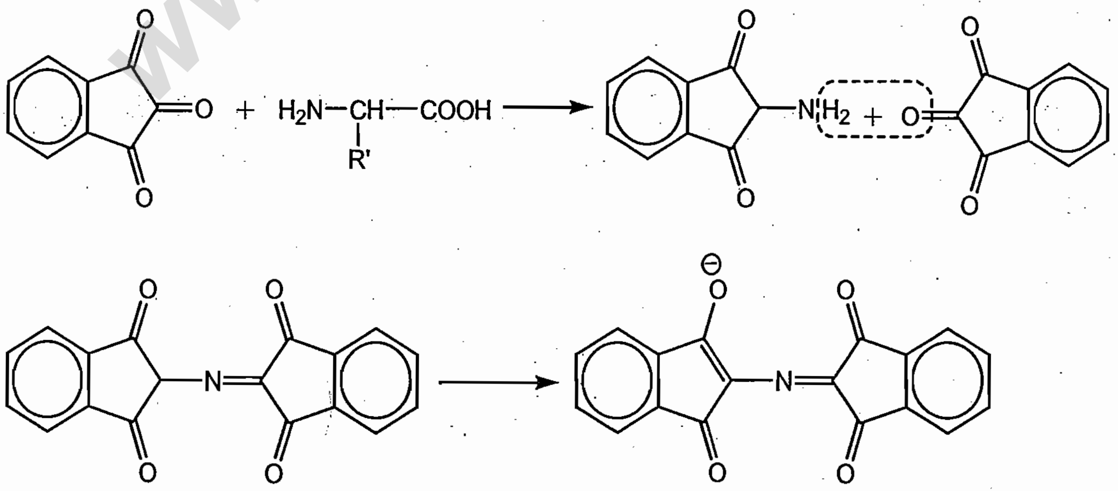
Deep blue needles

The amino acid may be liberated from the alkali salts by treatment in ethanolic solution with ethyloxyminocyanoacitate.

(iv) Action of Heat: When the α-amino acids are heated it forms 2, 5-diketopiperazines.



(v) Test for amino acid (Ninhydrin Reaction) :



Purple-coloured product

All α – amino acid reacts with two molecule of ninhydrin to yield an intensely coloured product whereas with proline and hydroxy proline it gives yellow colour.

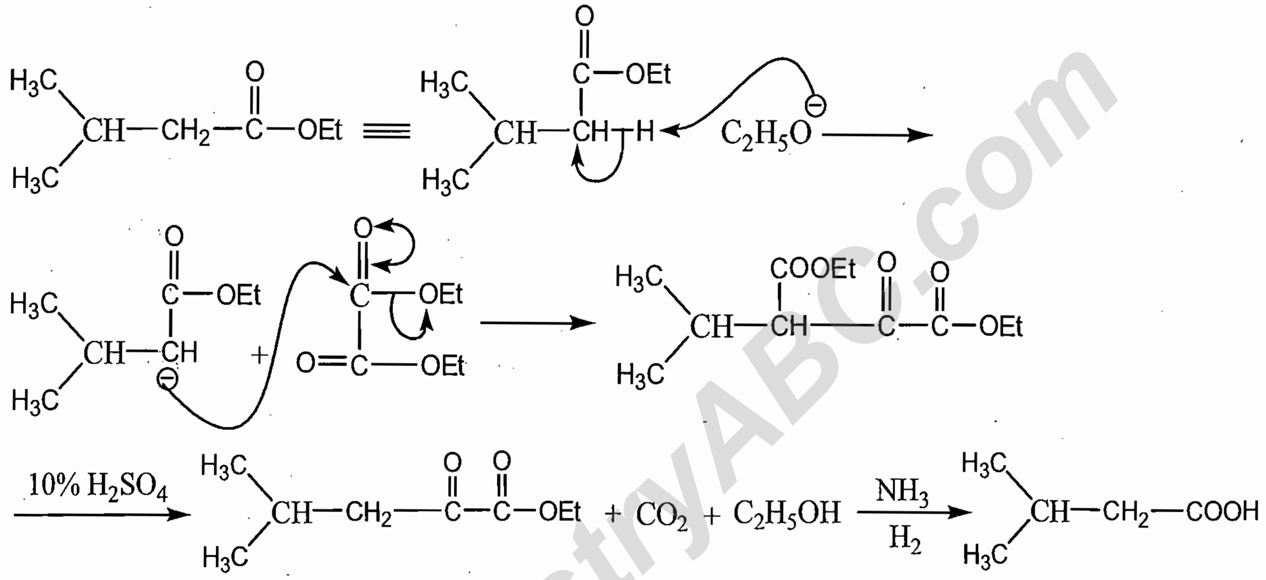
4. Synthesis of amino acids by reductive amination is illustrated by the following synthesis of leucine:

$$\text{Ethyl isovalerate} + \text{ethyl oxalate} \xrightarrow{NaOC_2H_5} A\left(C_{11}H_{18}O_5\right)$$

$$A + 10\%H_2SO_4 \xrightarrow{\text{boil}} B\left(C_6H_{10}O_3\right) + CO_2 + C_2H_5OH$$

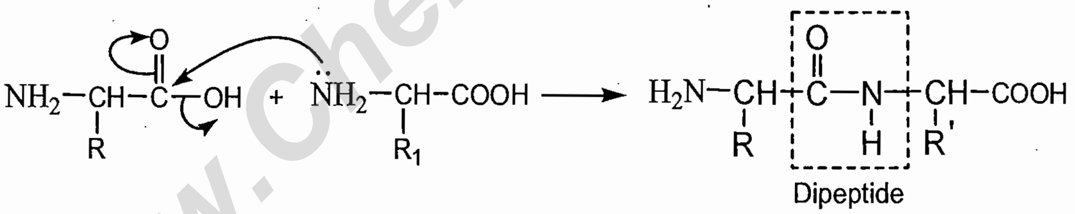
$$B + NH_3 + H_2 \xrightarrow{\text{Pd. heat}} \text{leucine}$$

Soln.



9.2 Peptide :

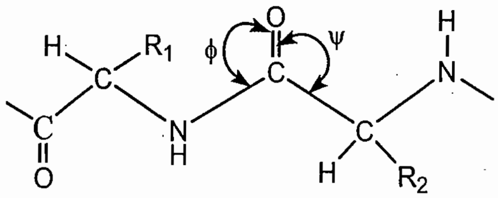
Amino acids are covalently linked by amide bonds the resulting molecules are called 'Peptides' and 'Proteins'. Peptide are the combination of minimum of two or more amino acid, connected by the peptide bond.



The amino group of one amino acid combined with the –COOH group of the other amino acid and remove one molecule of H_2O to form the peptide bond. Peptides are condensation polymers.

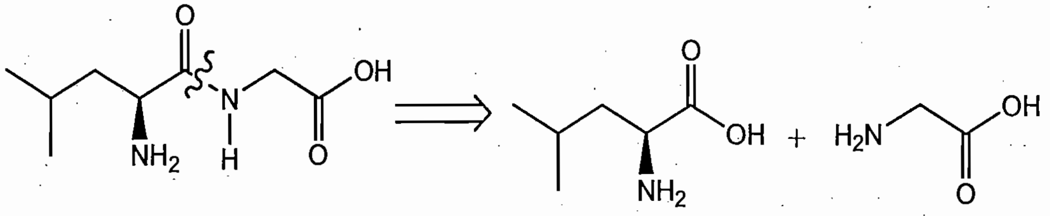
Features of Peptide Bonds:

- The peptide bonds are usually inert.
- There is a restricted rotation about the amide bond.

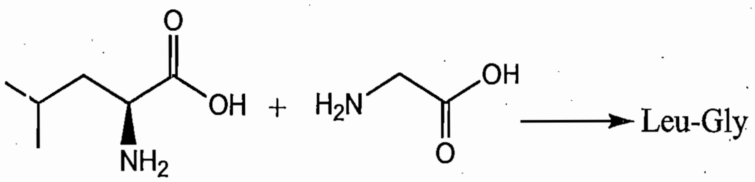


- The atom in the group –CONH–, are planar and the O and H are trans.
- Since the peptide C–N bond length (1.32 Å) is shorter than the usual C–N bond length (~1.47Å), it means that the peptide bond has some double bond character.

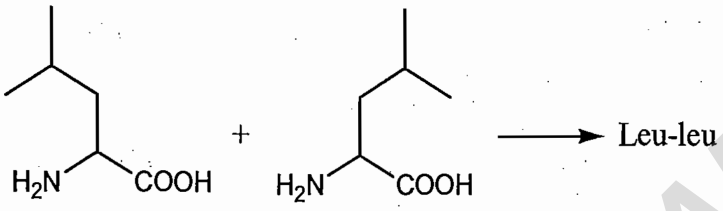
Synthesis of peptide



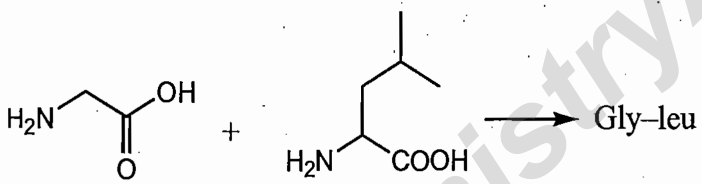
Possibilities-1:



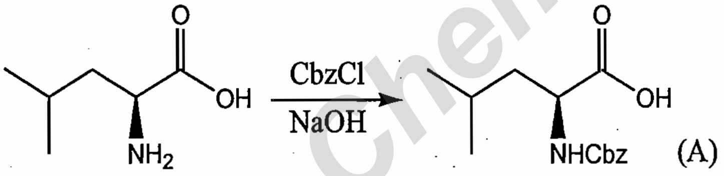
Possibilities-2:

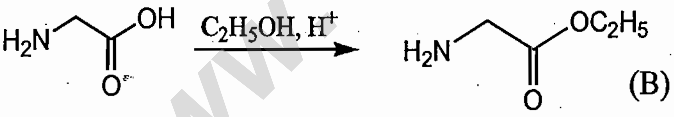


Possibilities-3:

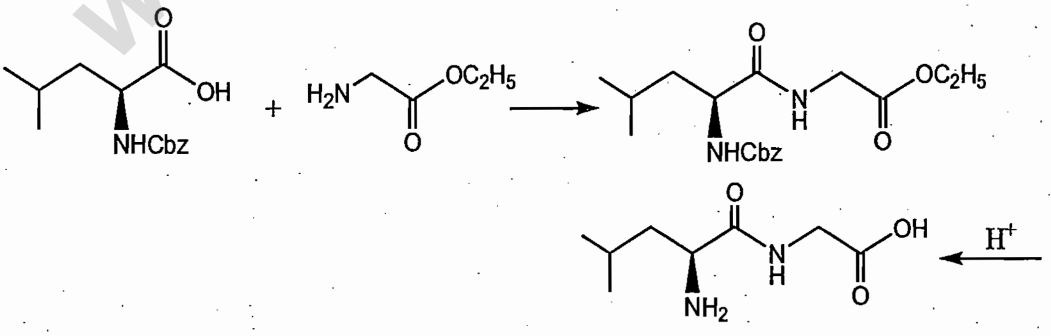


So, one can use protecting group strategy.

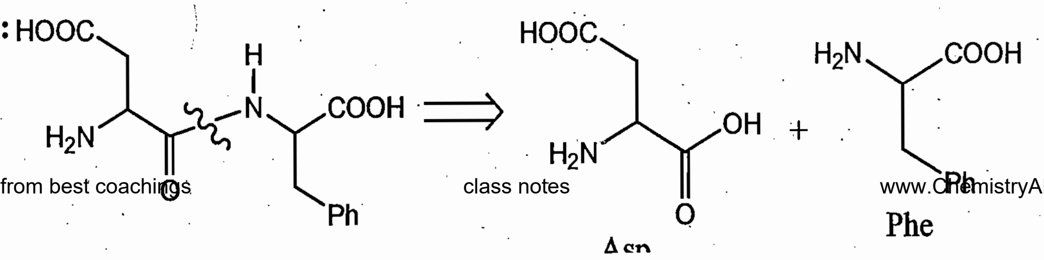


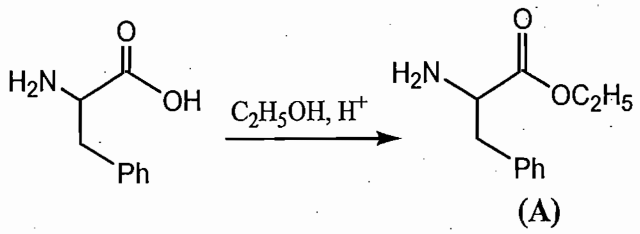


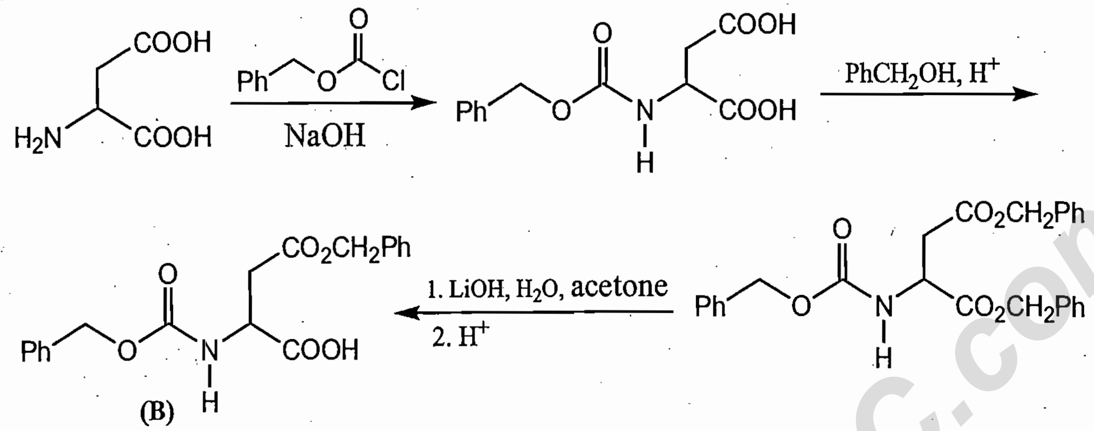
Now, coupling between (A) and (B)



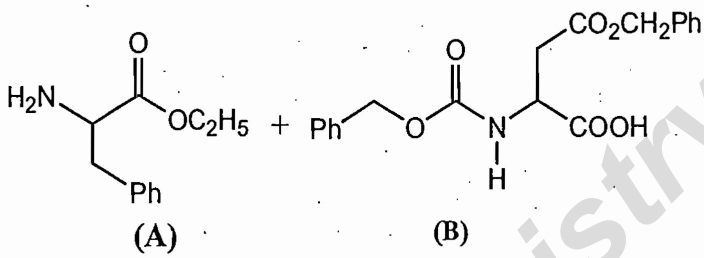
Problem:

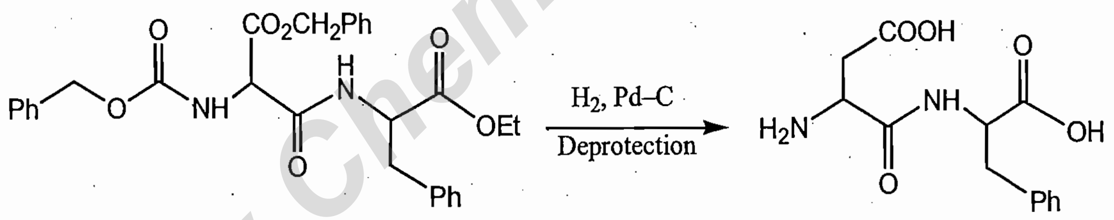






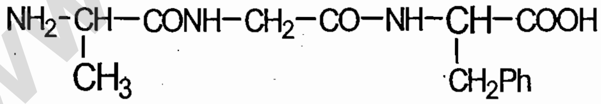
Coupling between (A) and (B).





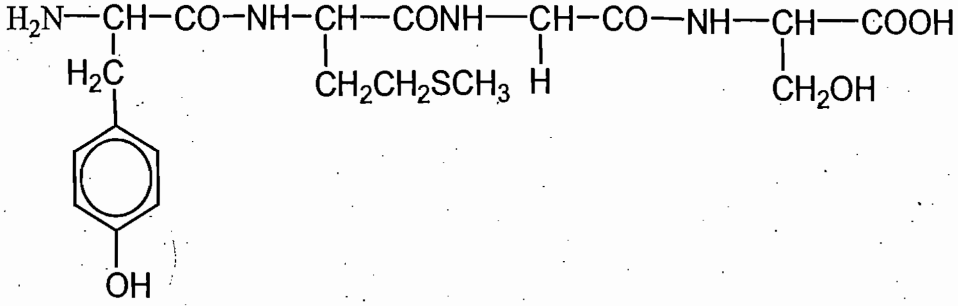
Structure of Peptide:

1. **Ala – Gly – Phe**



$$\mathrm{NH_2{-}\underset{\substack{|\\ CH_3}}{CH}{-}CONH{-}CH_2{-}CO{-}NH{-}\underset{\substack{|\\ CH_2Ph}}{CH}{-}COOH}$$

2. **Tyr – Met - Gly - Ser**



Determination of Sequence of amino acid in Peptide :

1. **Enzymatic Hydrolysis :**

(a) Carboxypeptidase: It cut at C-terminal of peptide with one amino acid at once.

$$A-B-C \wr D \xrightarrow{\text{CBA}} A-B-C+D \qquad \text{CBA} = \text{Carboxypeptidase}$$

For example: $\text{Phe}-\text{Gly}-\text{Lys} \xrightarrow{\text{CBA}} ?$

Soln. $\text{Phe}-\text{Gly}+\text{Lys}$

2. **Leucine - aminopeptidase (or Aminopeptidase) : Cut at N- terminal at once**

$$A \wr B-C-D \xrightarrow{\text{LAP}} A+B-C-D \qquad \text{LAP} = \text{Leucine-aminopeptidase}$$

For example

$$\text{Gly-Arg-Phe-Ala} \xrightarrow{\text{LAP}} \text{Gly} + \text{Arg}-\text{Phe}-\text{Ala}$$

3. **Trypsin :** It cut at the C-terminal / or right side of basic amino acid : Lys, Arg.

$$\text{Ala}-\text{Gly}-\text{Lys} \wr \text{Asp}-\text{Met} \xrightarrow{\text{Trypsin}} \text{Ala}-\text{Gly}-\text{Lys}+\text{Asp}-\text{Met}$$

4. **Chymotrypsin :** It cut at the C-terminal / or right side of amino acid having aromatic side chain: Trp, Tyr, Phe.

$$\text{ALa}-\text{Gly}-\text{Phe}-\text{Met}-\text{ALa} \xrightarrow{\text{Chymotrypsin}} \text{ALa}-\text{Gly}-\text{Phe}+\text{Met}-\text{ALa}$$

5. **Pepsin :** N–side of Leu, Asp, Glu
6. **Papain :** C– side of Gly, Lys, Arg
7. **Cyanogen Bromide :** It is a chemical method and cut at the C-terminal / or right side of methionine.

For example:

$$\text{Gly}-\text{Arg}-\text{Met} \wr \text{Ala} \xrightarrow{\text{CNBr}} \text{Gly}-\text{Arg}-\text{Met}+\text{Ala}$$

PROBLEMS

1. **Phe - Gly – Lys – Glu – Met – Tyr – Leu – Asp – Arg – Trp – Ala**

Trypsin: Phe – Gly – Lys + Glu – Met – Tyr – Leu – Asp – Arg + Trp – Ala

Chymotrypsin : Phe + Gly – Lys – Glu – Met – Tyr + Leu – Asp – Arg – Trp + Ala

Pepsin : Phe – Gly – Lys + Glu – Met – Tyr + leu + Asp – Arg – Trp – Ala

CNBr + HCOOH : Phe –Gly–Lys–Glu – Met + Tyr – Leu – Asp – Arg – Trp – Ala

2. **The peptide has been treated with trypsin to give fragments A and B. Which are respectively reacted with chymotrypsin & CNBr + HCOOH. Deduce the ulimate fragment.**

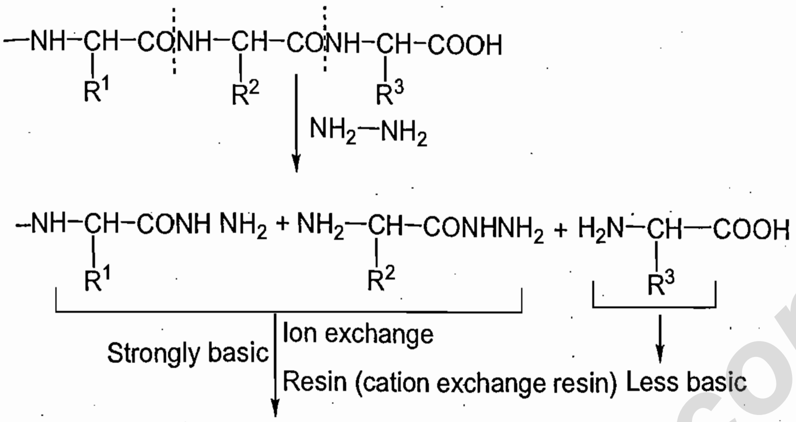
$$\begin{tikzcd}
\text{Asp-Phe-Val-Ser-Lys-Met-Gly-Ala} \arrow[r] & \underset{(A)}{\text{Asp-Phe-Val-Ser-Lys}} \arrow[d, "\text{Chymotrypsin}"] & + & \underset{(B)}{\text{Met-Gly-Ala}} \arrow[d, "\text{Cyanogen bromide}"] \\
 & \text{Asp-Phe + Val-Ser-Lys} & & \text{Met + Gly-Ala}
\end{tikzcd}$$

1. **End Group Analysis:** C – Termination Determination

(i) Carboxypeptidase : It cut at C-terminal of peptide with one amino acid at once.

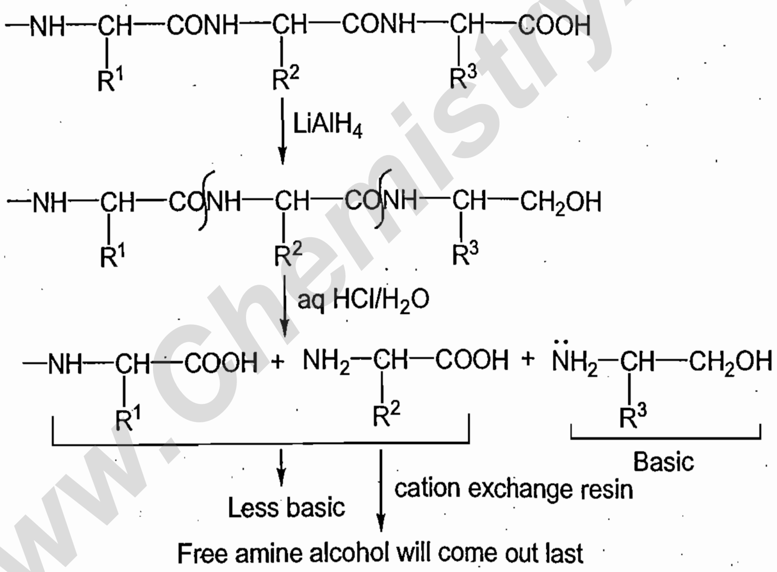
$$A-B-C \wr D \xrightarrow{\text{CBA}} A-B-C+D$$

(ii) Hydrazenolysis: The peptides (or protein) is heated with anhydrous hydrazine at 100°C. This converts all amino acids residues except the C-terminal one into amino acid hydrazides. The mixture of products is subjected to chromatography on a column of a strong cation exchange resin. On elution the strongly basic hydrazides are retained, but the free amino acid is eluted and can be identified.



Strongly basic fragments will be retained and less basic amino acid will come out first.

(ii) Reduction by Lithium borohydride or lithium aluminium hydride:
The lithium borohydride converts the free terminal carboxyl group to a primary alcoholic group. The hydrolysis produces a mixture of amino acids and amino alcohol, the amino alcohol being separated and identified by paper chromatography.



2. N- Terminal Determination :

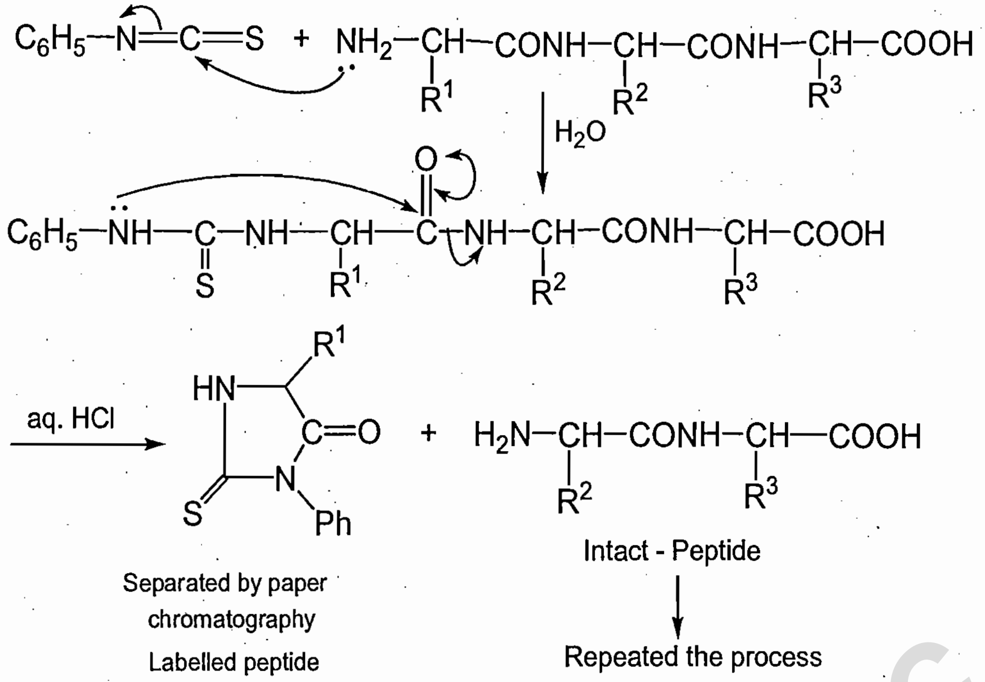
(i) Edman Method / Degradation : It is based on reaction between the peptide and phenyl isothio cyanate $(Ph-N=C=S)$ to form phenyl thio carbonyl (PTC) peptide in the presence of dilute base. The N–terminal end react with phenyl isothio cyanate.

On treatment with acid the N-terminal end gets converted to phenyl thio hydantoin (PTH) and the peptide is degraded by one unit from N–terminal site. PTH is separated by paper chromatography.

Advantage :

(i) It breaks only one amino acid from N-terminal site and keeps the rest of the peptide intact. So the process can be repeated again.

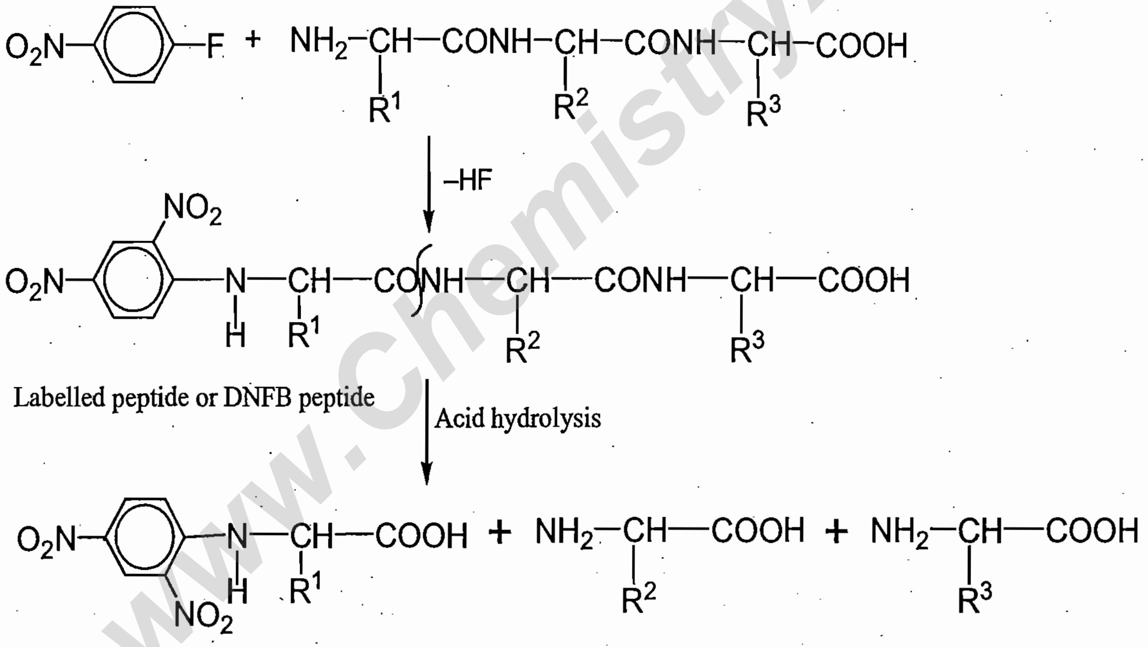
(ii) This process is automatic and less time consuming



2. **Amino Peptidase :** Cut one amino acid from N-Side.

$$A \wr B - C - D \xrightarrow{LAP} A + B - C - D$$

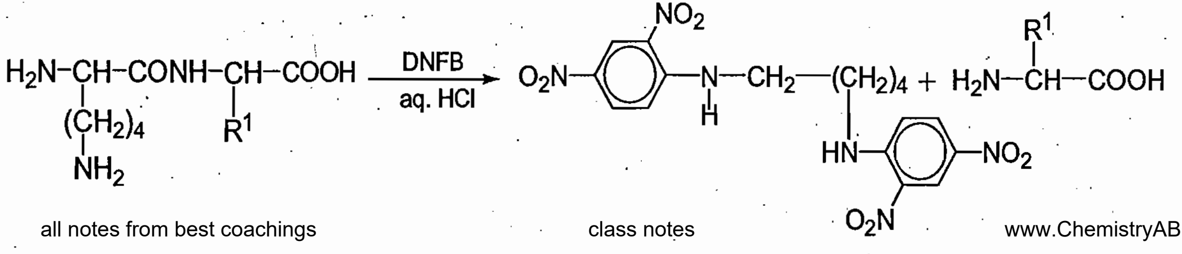
3. **Sanger's Method :**



DNFB derivatives are formed with any free NH_2 group the basic amino acid like Lys and Arg will react with DNFB even if it is not N-terminal acid. Besides NH_2 the –OH group of Tyr, SH group of Cys and OH group of Ser and imidazole nucleus of Histidine also react with DNFB slowly.

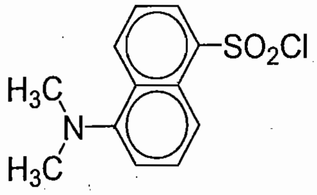
If the basic amino acid is not in the N terminal it will form mono DNFB derivative. If it is N-terminal it will form di DNFB derivatives. The DNFB derivatives are isolated and identified by TLC (thin layer chromatography)

For example: If Lys is in N-Terminal

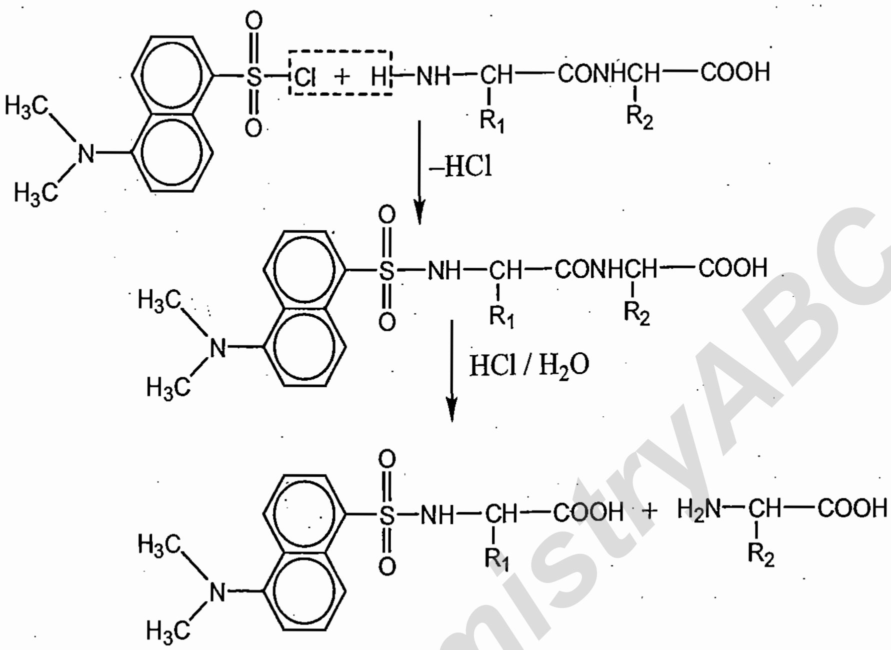


Di-DNFB derivatives

4. **Dansyl Method:** A recent modification of DNP method is use of 5-dimethylaminonaphthalene-1-sulphonylchloride 'dansyl' chloride (DNS-Cl), in place of DNFB. This modificication is called Dansyl method. The Dansyl method is being used because the dansyl group is highly fluorescent permits the detection and estimation of dansyl amino acids in minute amount by fluorometric methods.



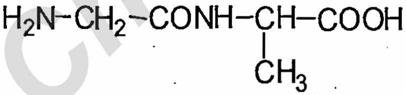
Dansyl group (Highly fluorescent) chloride



Synthesis of Peptides:

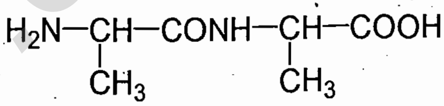
1. Glycyl - Glycine : $H_2N-CH_2-CONH-CH_2-COOH$

2. Glycyl alanine :



$$H_2N-CH_2-CONH-\underset{CH_3}{\underset{|}{CH}}-COOH$$

3. Alanyl alanine :

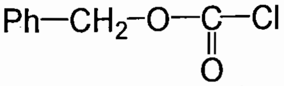


$$H_2N-\underset{CH_3}{\underset{|}{CH}}-CONH-\underset{CH_3}{\underset{|}{CH}}-COOH$$

Protection Method:

Protecting group – For NH_2 group.

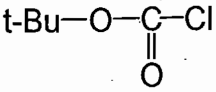
1. Benzyl oxy carbonyl :



$$Ph-CH_2-O-\underset{O}{\underset{||}{C}}-Cl$$

(carbobenzyloxy)

2. t - butyl oxy carbonyl :



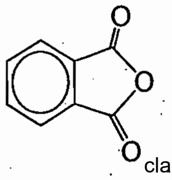
$$t\text{-}Bu-O-\underset{O}{\underset{||}{C}}-Cl$$

(BOC)

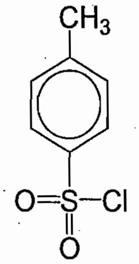
3. Trityl : $(C_6H_5)_3C-$

(Triphenyl methyl)

4. **Phthaloyl**

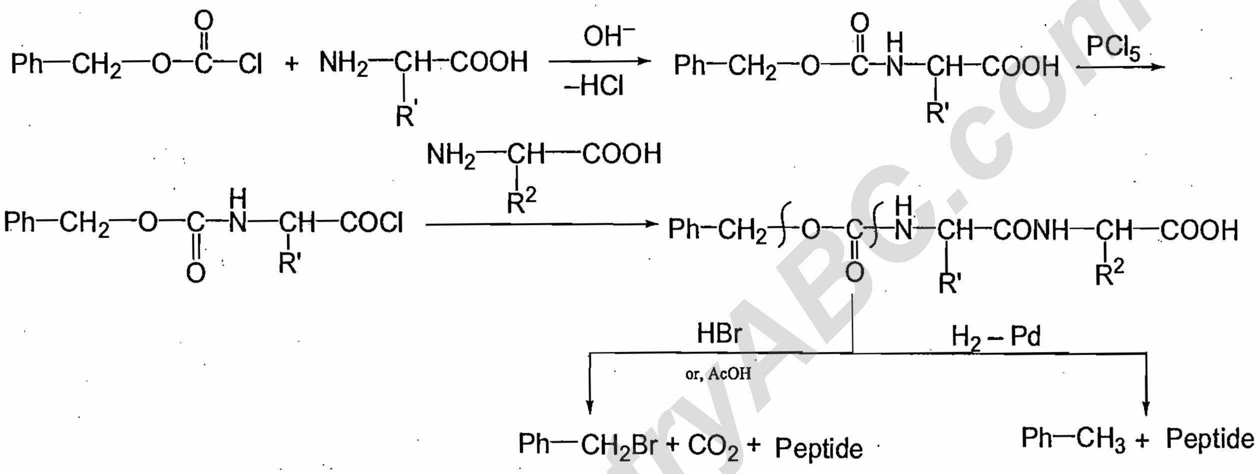


5. **Tosyl**

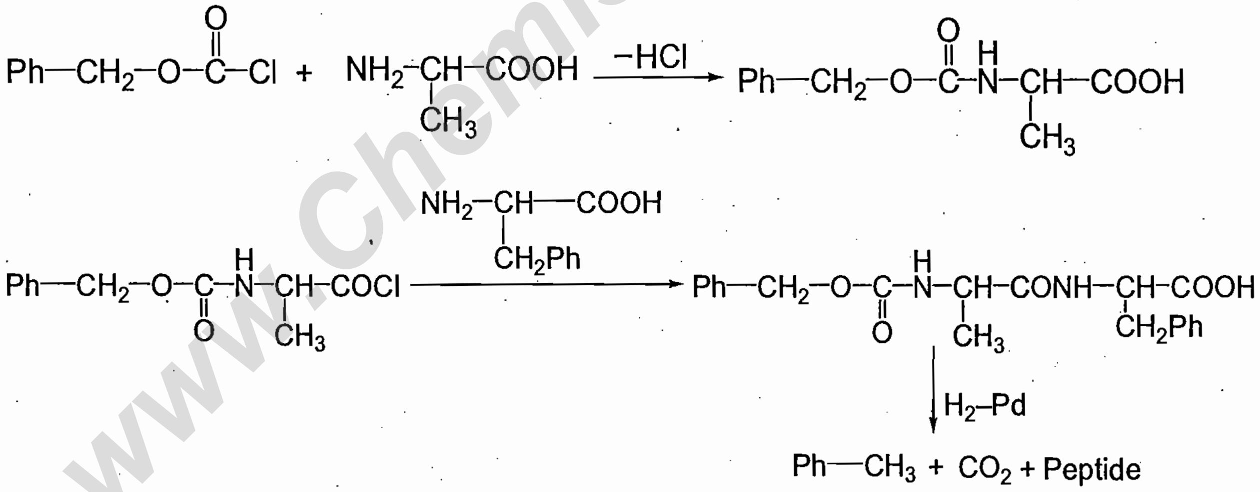


Protecting group for COOH : Esterification
Activation group for COOH: Acid choride, acid azide, p-nitrophenyl ester.
DCC (Dehydrating agent): Direct combination of NH_2 and COOH.
Dicyclo hexyl carbo-di-imide $C_6H_{11}N{=}C{=}N{-}C_6H_{11}$

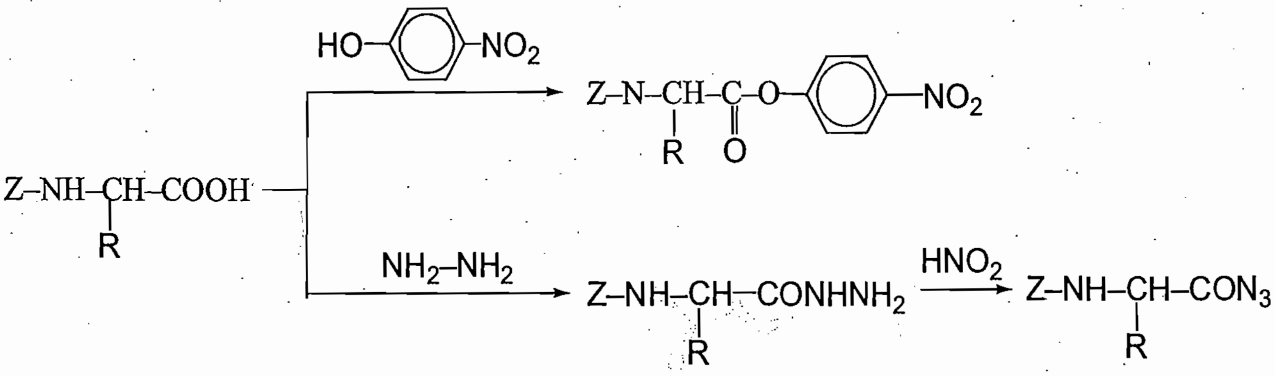
1. **From Benzyl –Oxy Carbonyl :**



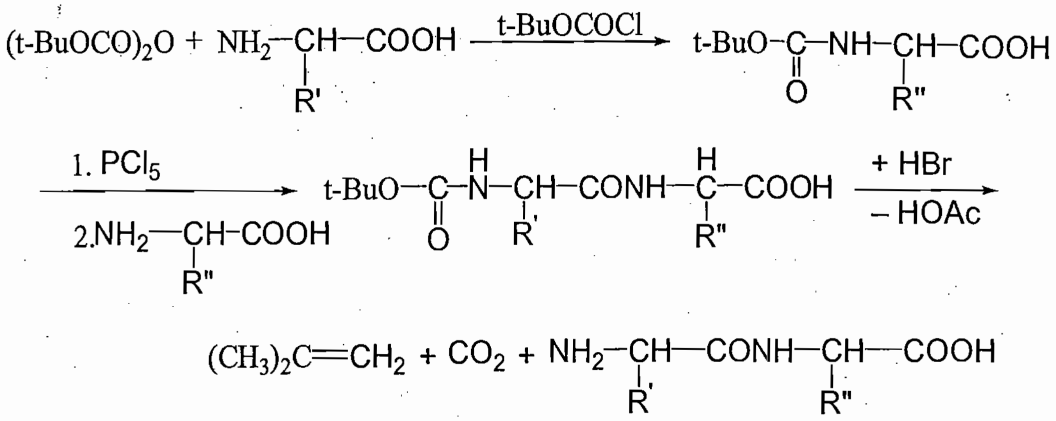
Alanyl Phenylaline :



Activation of – COOH :



2. FROM BOC METHOD :

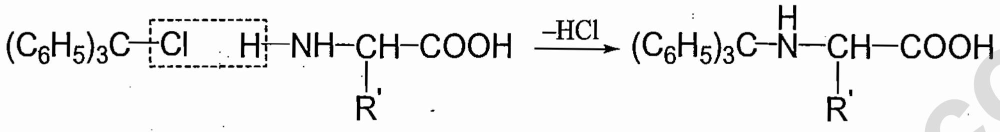


$$(t\text{-BuOCO})_2O + NH_2-\underset{R'}{\underset{|}{CH}}-COOH \xrightarrow{t\text{-BuOCOCl}} t\text{-BuO}-\underset{O}{\underset{\|}{C}}-NH-\underset{R''}{\underset{|}{CH}}-COOH$$

$$\xrightarrow[2.\,NH_2-\underset{R''}{\underset{|}{CH}}-COOH]{1.\,PCl_5} t\text{-BuO}-\underset{O}{\underset{\|}{C}}-\overset{H}{N}-\underset{R'}{\underset{|}{CH}}-CONH-\overset{H}{\underset{R''}{\underset{|}{C}}}-COOH \xrightarrow[-\,HOAc]{+\,HBr}$$

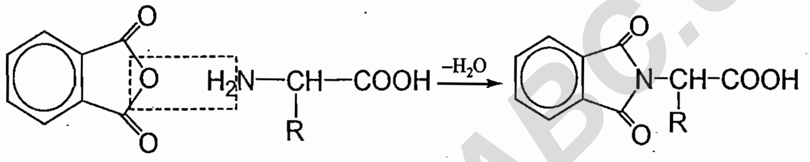
$$(CH_3)_2C{=}CH_2 + CO_2 + NH_2-\underset{R'}{\underset{|}{CH}}-CONH-\underset{R''}{\underset{|}{CH}}-COOH$$

3. FROM TRITYL CHLORIDE:

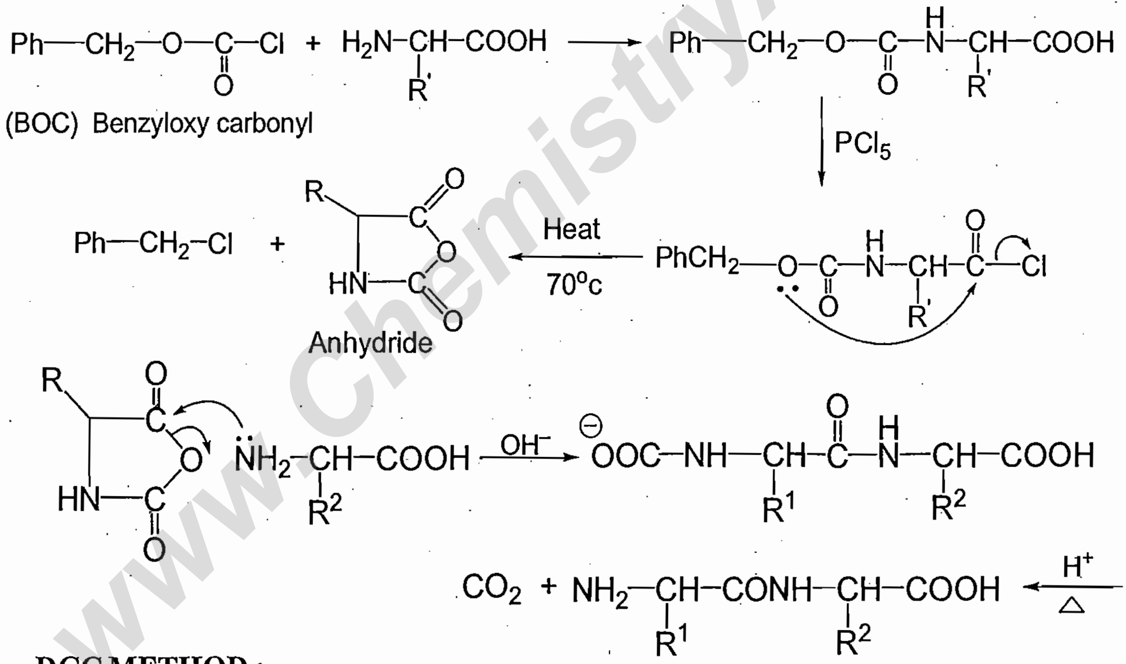


$$(C_6H_5)_3C-\boxed{Cl\quad H}-NH-\underset{R'}{\underset{|}{CH}}-COOH \xrightarrow{-HCl} (C_6H_5)_3C-\overset{H}{N}-\underset{R'}{\underset{|}{CH}}-COOH$$

4. From Phthalayl :

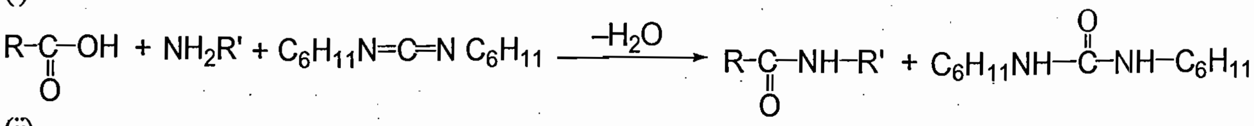


3. ANHYDRIDE METHOD :



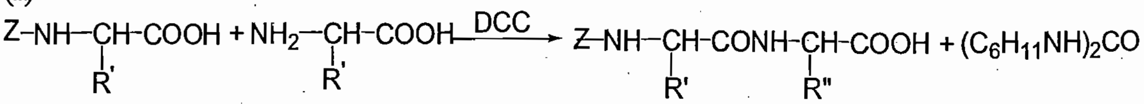
4. DCC METHOD :

(i)



$$R-\underset{O}{\underset{\|}{C}}-OH + NH_2R' + C_6H_{11}N{=}C{=}N\,C_6H_{11} \xrightarrow{-H_2O} R-\underset{O}{\underset{\|}{C}}-NH-R' + C_6H_{11}NH-\overset{O}{\overset{\|}{C}}-NH-C_6H_{11}$$

(ii)

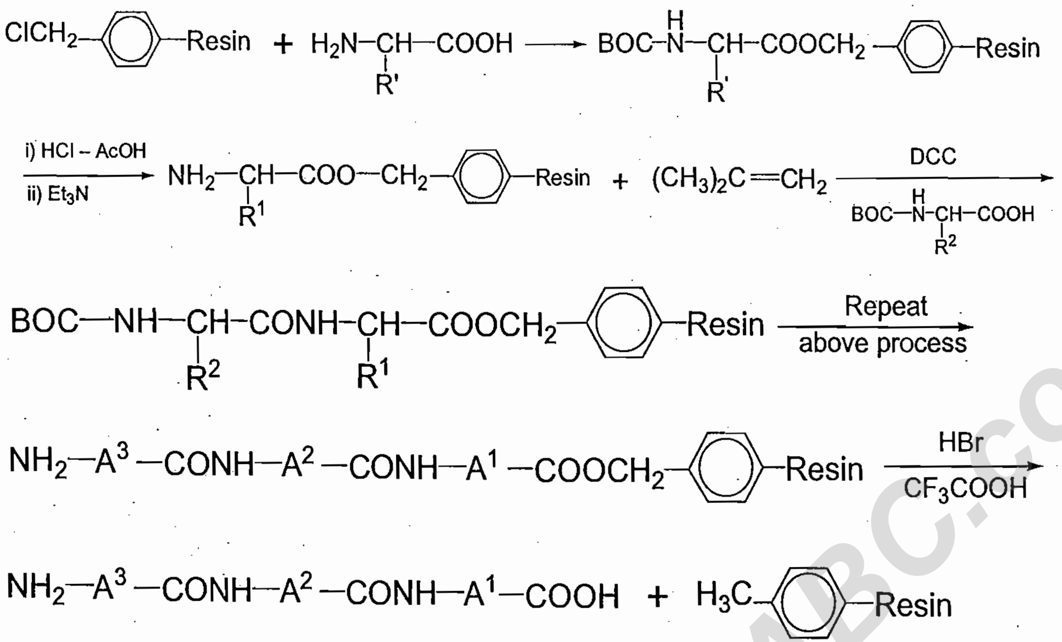


$$Z-NH-\underset{R'}{\underset{|}{CH}}-COOH + NH_2-\underset{R'}{\underset{|}{CH}}-COOH \xrightarrow{DCC} Z-NH-\underset{R'}{\underset{|}{CH}}-CONH-\underset{R''}{\underset{|}{CH}}-COOH + (C_6H_{11}NH)_2CO$$

SOLID PHASE SYNTHESIS :

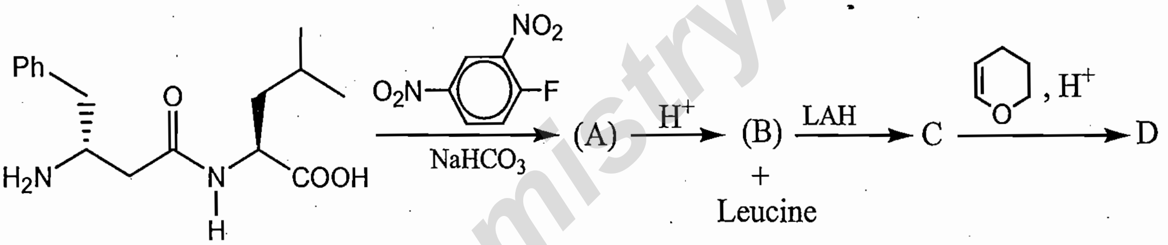
Given by Bruce Merryfield. In this method amino acid or a peptide is bound chemically to a insoluble synthetic resin and the peptide chain is build up by adding one amino acid at a time at the free end. When the required peptide is synthesised it is liberated and removed from the solid support. The resin which is commonly used is a co-polymer of styrene and divinylbenzene.

The biggest advantage of this method is that the purification of product is not neccessory because of the use of insoluble solid support. Excess reagent or side product are simply removed by washing with suitable solvent. The process is less time consuming & give excellent yield. The process is now automated that is each addition of appropriate amino acid is carried out automatically at the predetermined time.



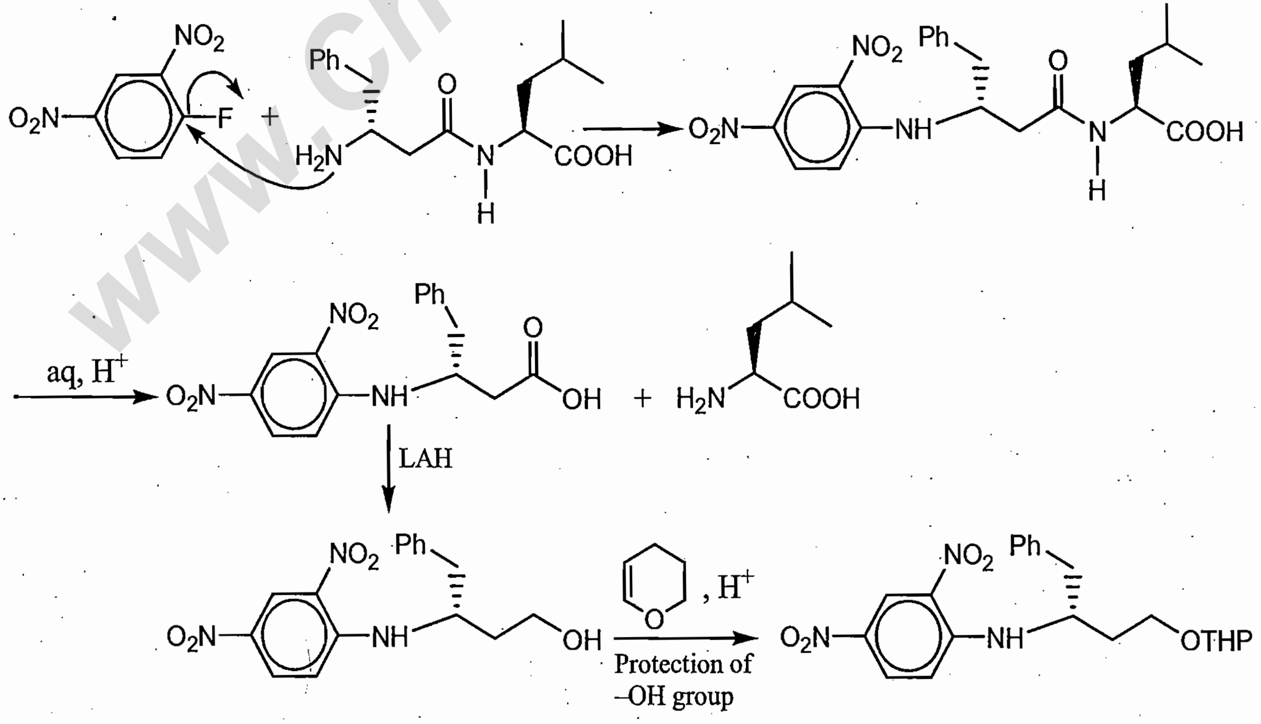
PROBLEMS

1.

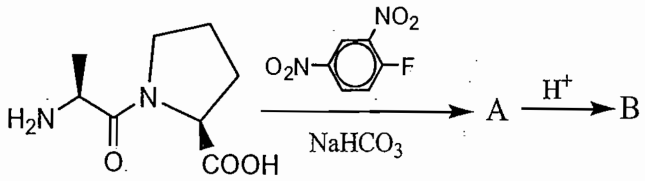


Find, A → D

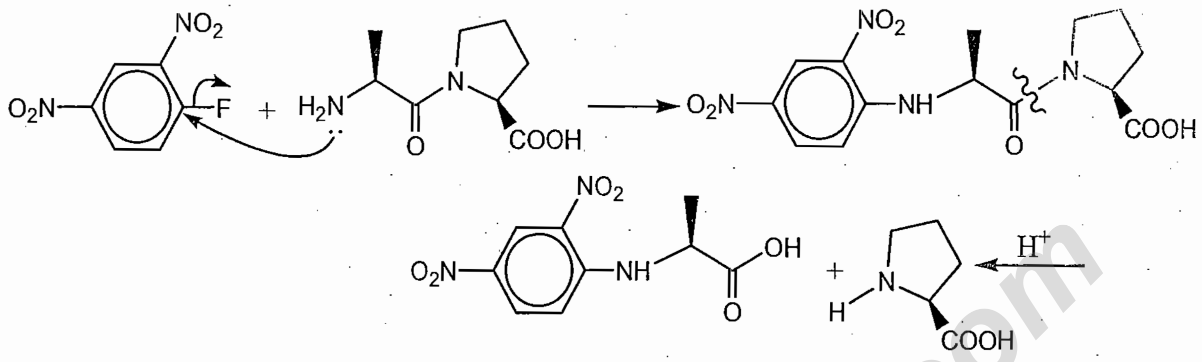
Soln.



2.



Soln.

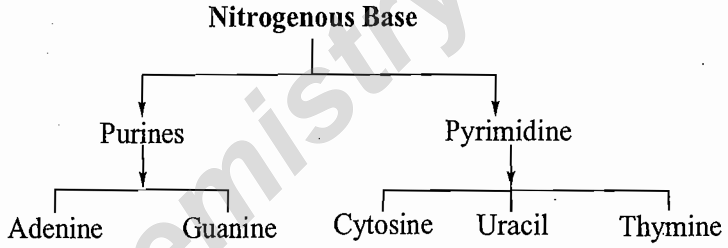


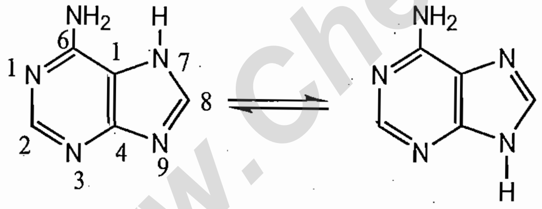
9.3. Nucleic Acid :

Nucleic acids are colourless solids which contain: Carbon, hydrogen, oxygen, nitrogen and phosphorus. There are three components of the nucleic acid such as

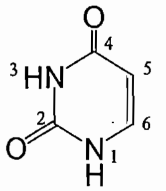
(1) Nitrogenous Base (2) Sugar/Carbohydrate (3) Phosphate group $PO_4^{3-}(H_3PO_4)$.

1. There are two types of bases which occurs in nucleic acids: purines and pyrimidines. The most common purine bases are adenine and guanine whereas the most common pyrimidine bases are uracil, thymine and cytosine.

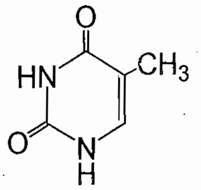




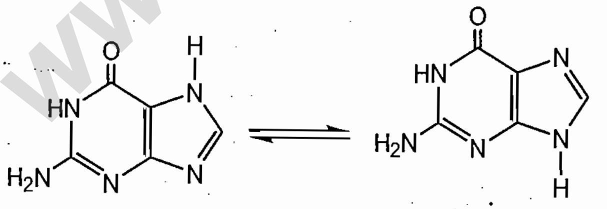
Adenine



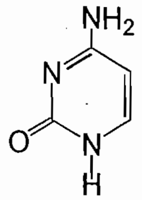
Uracil



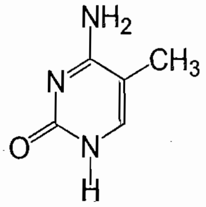
Thymine



guanine

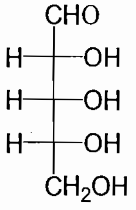


Cytosine

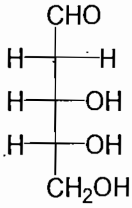


5-methylcytosine

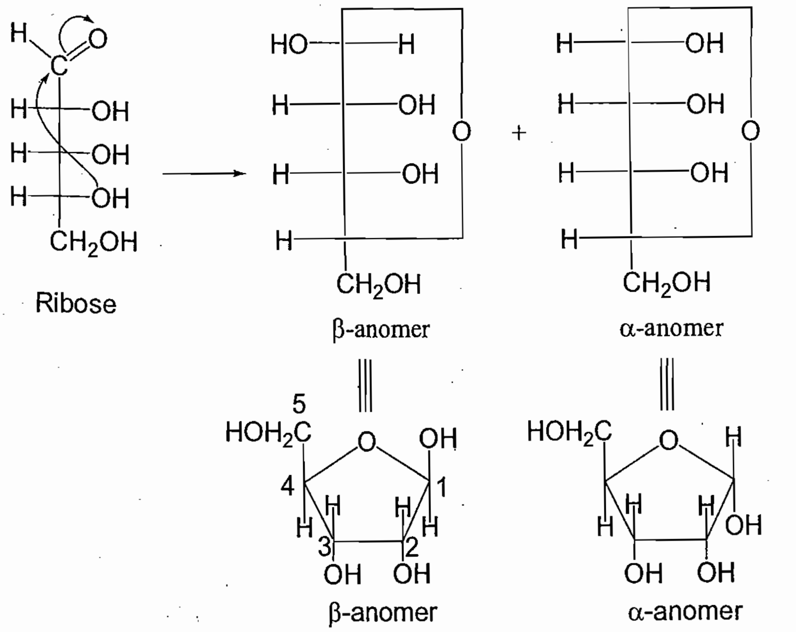
2. **Sugars:** The sugar present in the nucleic acids are pentoses: D(–)-ribose and 2-deoxy-D-(–)-ribose.



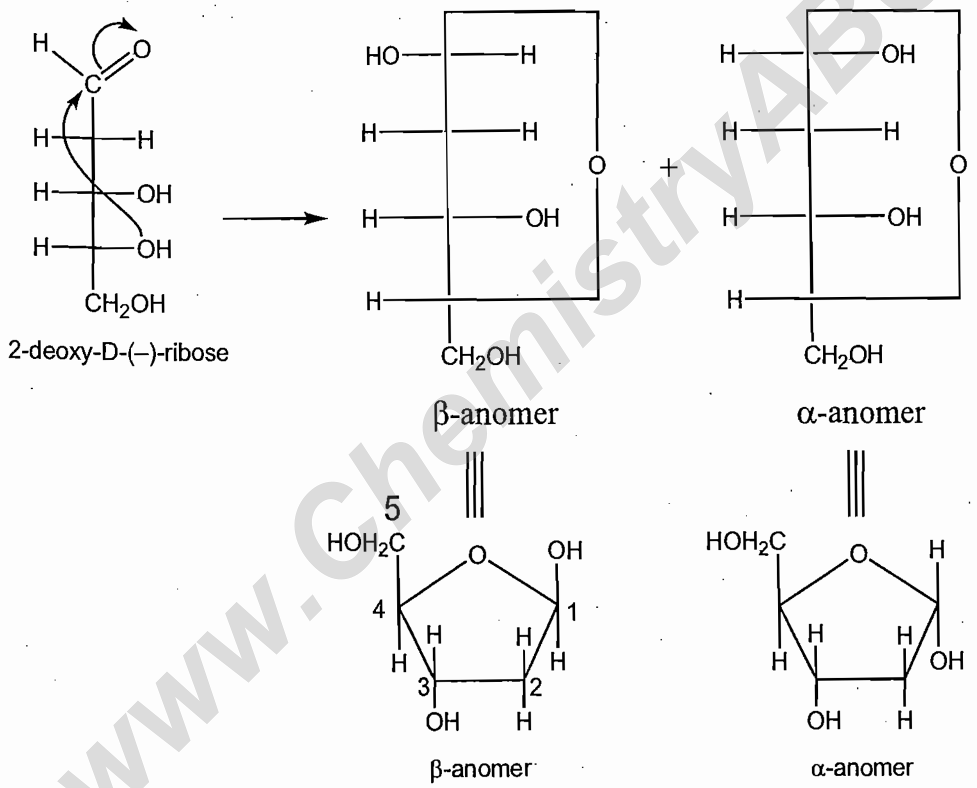
D(–)-ribose



2-deoxy-D-(–)-ribose

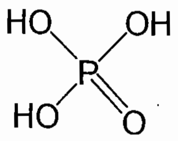


3. Deoxy Ribose:



Remark: In nucleic acid sugars are in β-anomeric, furanose form and it is hemiacetal.

4. Phosphate Group :



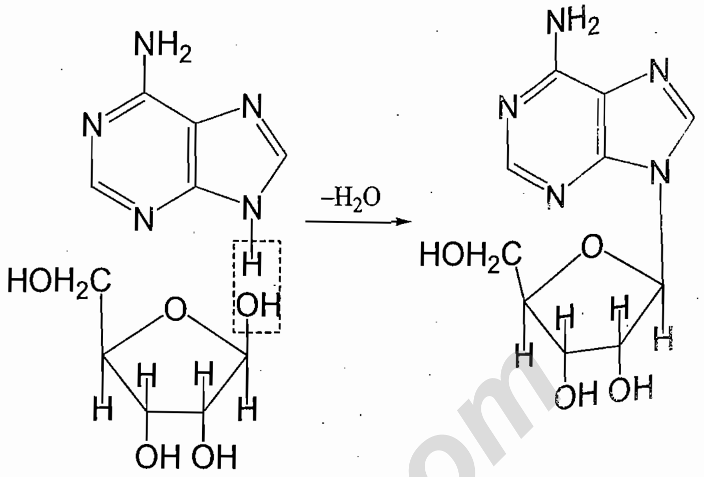
$H_3PO_4 \rightleftharpoons H^+ + H_2PO_4^-$;

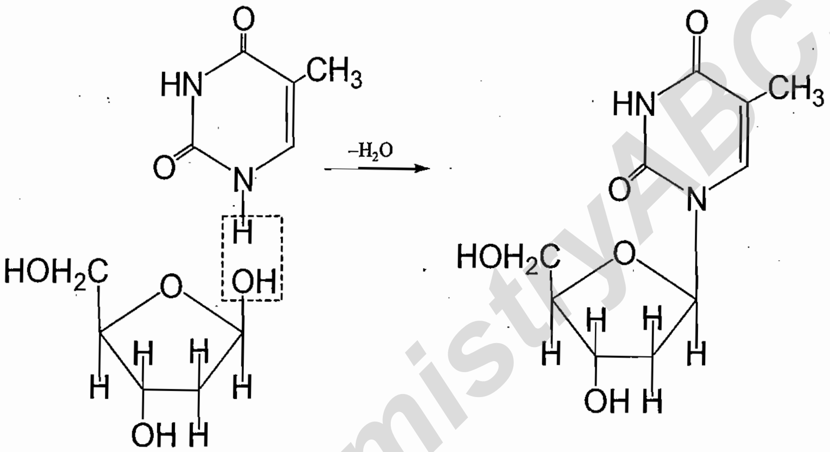
$H_2PO_4^- \rightleftharpoons H^+ + HPO_4^{2-}$;

$HPO_4^{2-} \rightleftharpoons H^+ + PO_4^{3-}$

Nucleoside: The combination of a base (either a purine or pyramidine with a sugar(ribose or deoxyribose) are called nucleosides. For example

Adenine + Sugar	→	Adenosine
Guanine + Sugar	→	Guanosine
Cytosine + Sugar	→	Cytidine
Thymine + Sugar	→	Thymidine
Uracil + Sugar	→	Uridine

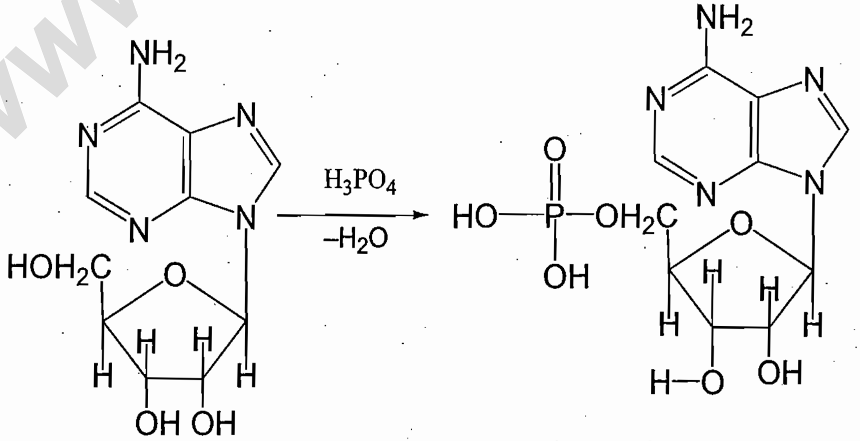




Nucleotide:

Nucleotides are the combination of a nucleoside and phosphoric acid i.e. nucleotides are nucleosides phosphate. For example

Adenosine	+	phosphate	→	Adenylic acids
Guanosine	+	phosphate	→	Guanylic acids
Cytidine	+	phosphate	→	Cytidylic acids
Uridine	+	phosphate	→	Uridylic acids



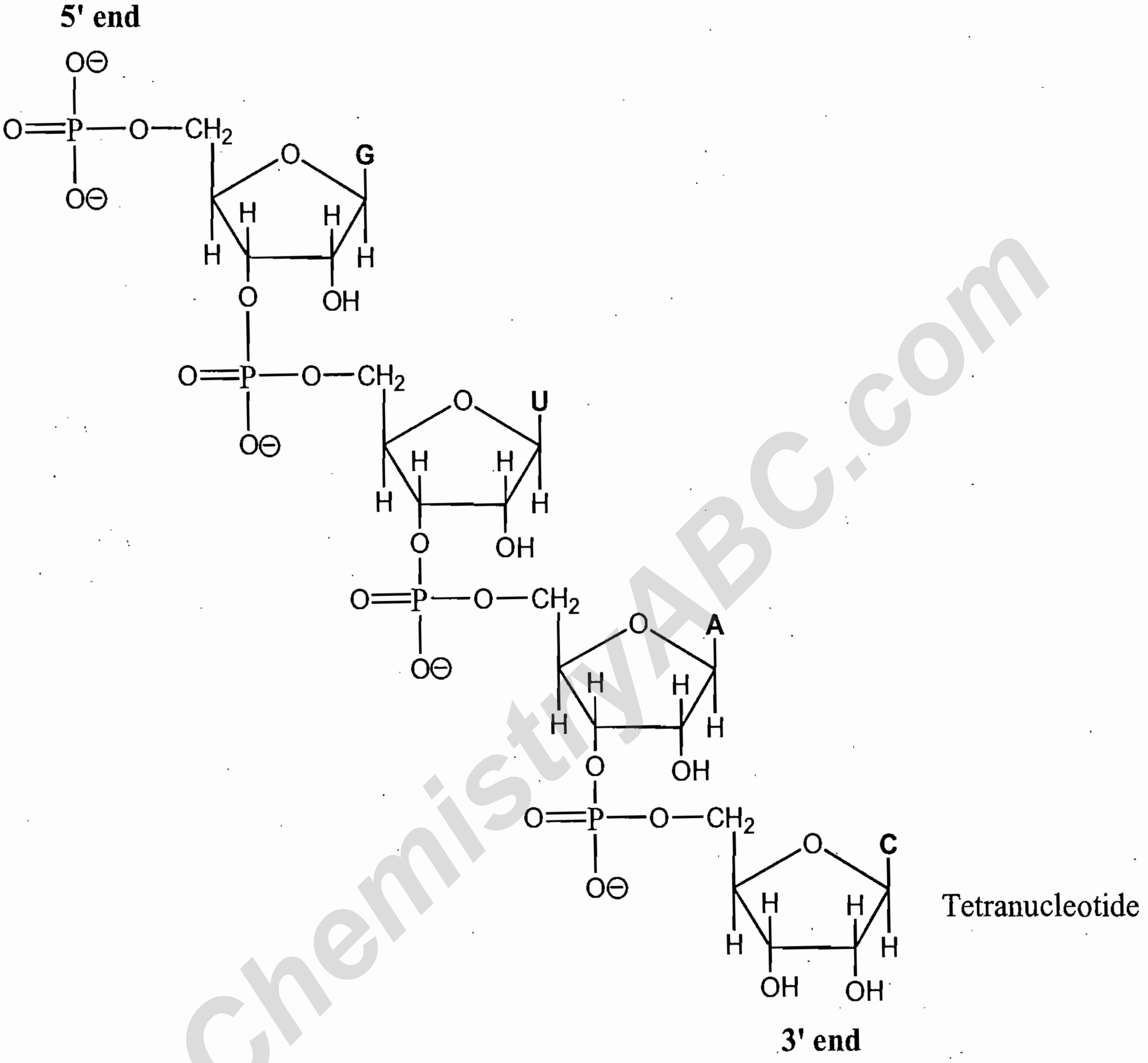
On the basis of sugar present in the nucleic acid, it can be classified into two parts: Ribonucleic acids (RNA) and the deoxyribonucleic acid (DNA).

Ribonucleic Acids(RNA):

- RNA is a polymer of ribonucleotides.
- The individual ribonucleotides are linked together by phosphodiester bonds.
- The attachment of the phosphate is at the 3'–position in the ribose molecules.

- The common bases in RNAs are adenine, guanine, uracil and cytosine.
- According to the source of nucleic acid there are three types of nucleic acid: Ribosomal RNA (r–RNA), Transfer RNA(t–RNA) and Messenger RNA (m–RNA).

Primary Structure of RNA:

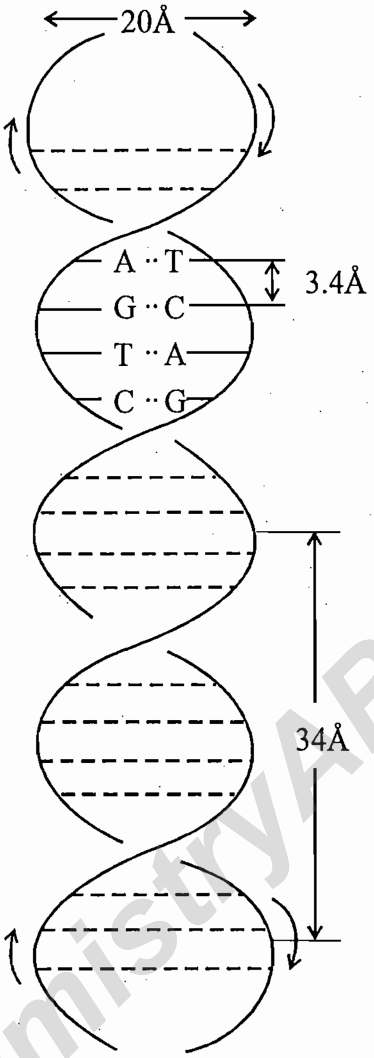


The secondary structure of RNA has been investigated and it appears that RNAs exist as a single strands which contain helical segments established by hydrogen bond.

Deoxyribonucleic acid:

- DNA are polymers of the deoxyribonucleotides and hydrolysis by certain enzymes result in a mixture of monomers.
- The common bases DNAs are Adenine(A), Guanine (G), Thymine (T) and Cytosine (C).

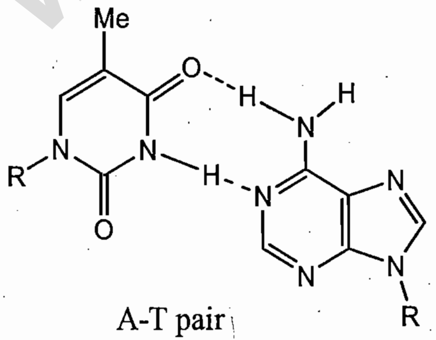
Secondary Structure of DNA: (Double helix model by Watson & Crick):



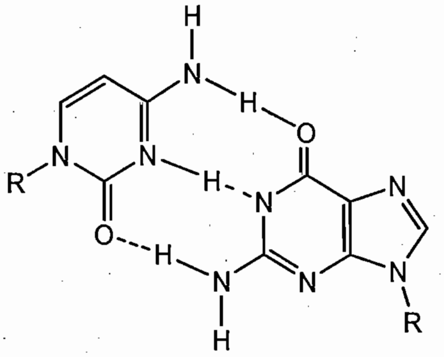
(a)

- Two strands are antiparallel.
- The X-ray studies have shown that the pairs are planar and that the hydrogen bonds are almost collinear, their lengths lying between 2.8 and 2.9 Å.
- Each turn of the helix contains ten nucleotide pairs and the diameter of the helix is about 20 Å.
- The spacing between adjacent pair is 3.4 Å.

Base pairing in DNA.
Adenine always paired with thymine by double H-bond.
Guanine always paired with cytosine by triple H-bond.

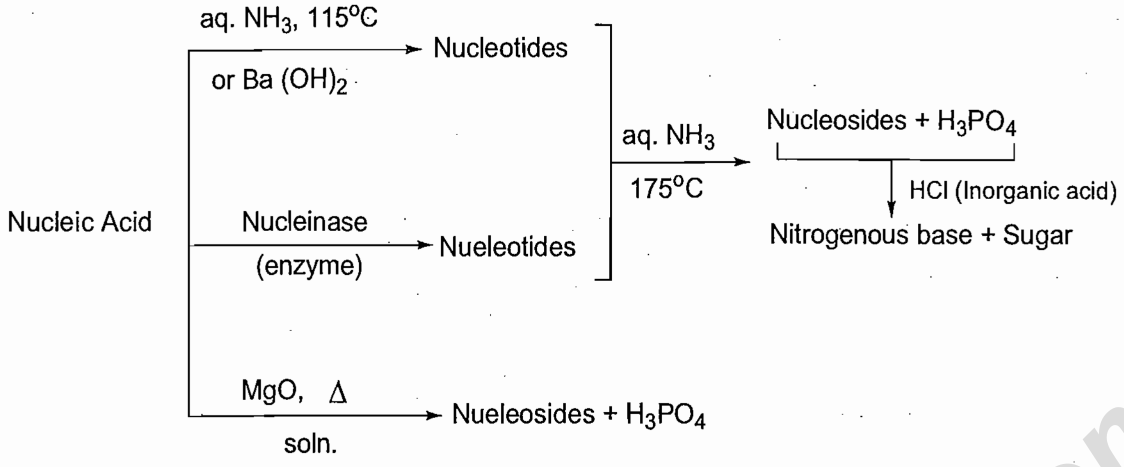


A-T pair



G-C pair

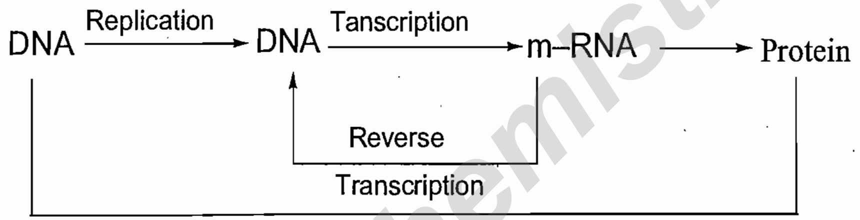
Hydrolysis of Nucleic Acid :



$$\underset{\text{(Nucleotides)}}{\text{AMP}} \xrightarrow[175^{\circ}\text{C}]{\text{aq.NH}_3} \text{Adenosine} + H_3PO_4$$

Problem: $\text{RNA} \xrightarrow{?} \text{CMP} \xrightarrow[175^{\circ}\text{C}]{\text{aq.NH}_3} X \xrightarrow{\text{HCl}} Y$

Soln. $\text{RNA} \xrightarrow[115^{\circ}\text{C}]{\text{aq.NH}_3} \text{CMP} \xrightarrow[175^{\circ}\text{C}]{\text{aq.NH}_3} \underset{\text{(cytidine)}}{\text{Nudeoside}} \xrightarrow{\text{HCl}} \underset{\substack{\text{(Cytosine + Sugar)} \\ \text{Ribose}}}{\text{N base + Sugar}}$

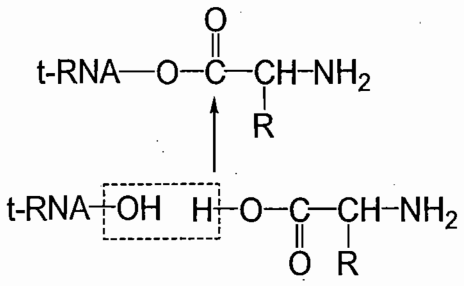


The whole process is known as central Dogma (flow of genetic information)

Site of protein synthesis in cell : Ribosomes r - RNA provide a template / base or the site where protein synthesis occur.

r-RNA : It provide a template / base or support on which protein synthesis takes place in Ribosome.
It consist Protein & RNA.

t-RNA : They bring the amino acid to the site where protein synthesis occurs each amino acid has its own specific t-RNA and the bonding with t-RNA accurs line.



m-RNA :
It brings the information regarding the sequence of amino acid to the ribosomes. The four base in m-RNA exist in form triplet called as CODON with code for one specific amino acid. (a amino acid can have more than one codon).
eg. : UCU → serine → GCA + AGC (more than 1 codon is used for 1 amino acid)

9.4. Proteins :

- Proteins are nitrogenous substances which occurs in protoplasm of all animal and plants cells. Their composition varies with the source: carbon, 46-55%; hydrogen, 6-9%; oxygen, 12-30%; nitrogen, 10-32%; sulphur, 0.2-0.3%. Other elements may also be present, for example phosphorus (nucleoproteins), iron(homeoglobin).
- Proteins can be broken down into smaller and smaller fragments until, the final products are amino acids.

$$\text{Protein} \rightarrow \text{polypeptides} \rightarrow \text{peptides} \rightarrow \text{amino acids.}$$

- There are no sharp dividing lines between peptides, polypeptides and proteins. Generally–

  If the molecular weight above $\sim 10,000$ = Proteins.

  If the molecular weight below $\sim 10,000$ = Peptide and polypeptide.
- The physical and chemical properties of proteins and peptides are different.
- Proteins are amphoteric in nature.
- All proteins are optically active, and may be coagulated and precipitated from aqueous solution by heat, the addition of acids, alkalies, salts, organic solvents miscible with water.
- Proteins in precipitated state are called denatured and the process of reaching this state, denaturation occurs most readily near the isoelectric point.
- Denaturation is generally irreversible, but in many cases the process has been reversed this reversal of denaturation is called renaturation.

Classification of proteins:

(A) Simple Proteins **(B) Conjugated Proteins**

(A) Kind of simple proteins:

(i) Albumins: These are soluble in water, acids and alkalis. It is coagulated by heat.

(ii) Globulins: These are insoluble in water, but are soluble in dilute salt solution and in dilute solutions of strong inorganic acids and alkali.

(iii) Prolamins: These are insoluble in water or salt solution but are soluble in dilute acids and alkalies.

(iv) Glutelins: These are insoluble in water or dilute salt solution, but are soluble in dilute acids alkalies. They are coagulated by heat, glutelins are rich in arginine, proline and glutamic acids.

(v) Scleroproteins: These are insoluble in water or salt solution, but are soluble in concentrated acid. For example: keratin(from hair, hoof), fibroin (from silk).

(vi) Basic Proteins: These are strongly basic, and are of the two kinds: (a) Histones (b) Protamines

(B) Conjugated proteins: These are proteins which contains a non-protein group(i.e. a compound not containing amino acid residues) attached to the protein part. The non protein group is known as prosthetic group and it may be separated from the protein part by careful hydrolysis.

Kinds of conjugated proteins.

(i) Nucleoproteins: In nucleoproteins the prosthetic group is a nucleic acid.

(ii) Chromoproteins: Their prosthetic group are coloured. For example, chlorophyll and haemoglobin.

(iii) Glycoproteins: In glycoproteins the prosthetic group contains a carbohydrates or a derivative of carbohydrate. It is also known as mucoproteins.

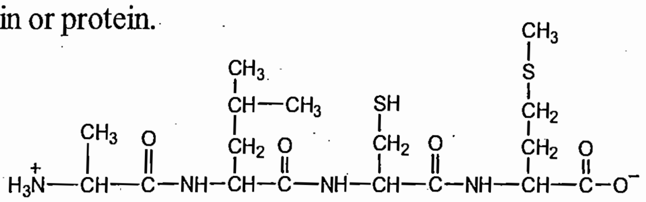
(iv) Phosphoproteins: In phosphoproteins the prosthetic group contains phosphoric acids.

(v) Lipoproteins: In lipoproteins the prosthetic group is lecithin, kephalin etc.

(vi) Metalloproteins: The metalloproteins contain metal which is an integral part of the structure.

Structure of Proteins:

1. **Primary Structure:** The primary structure of proteins are the particular sequence of amino acids ,that is the backbone of a peptide chain or protein.

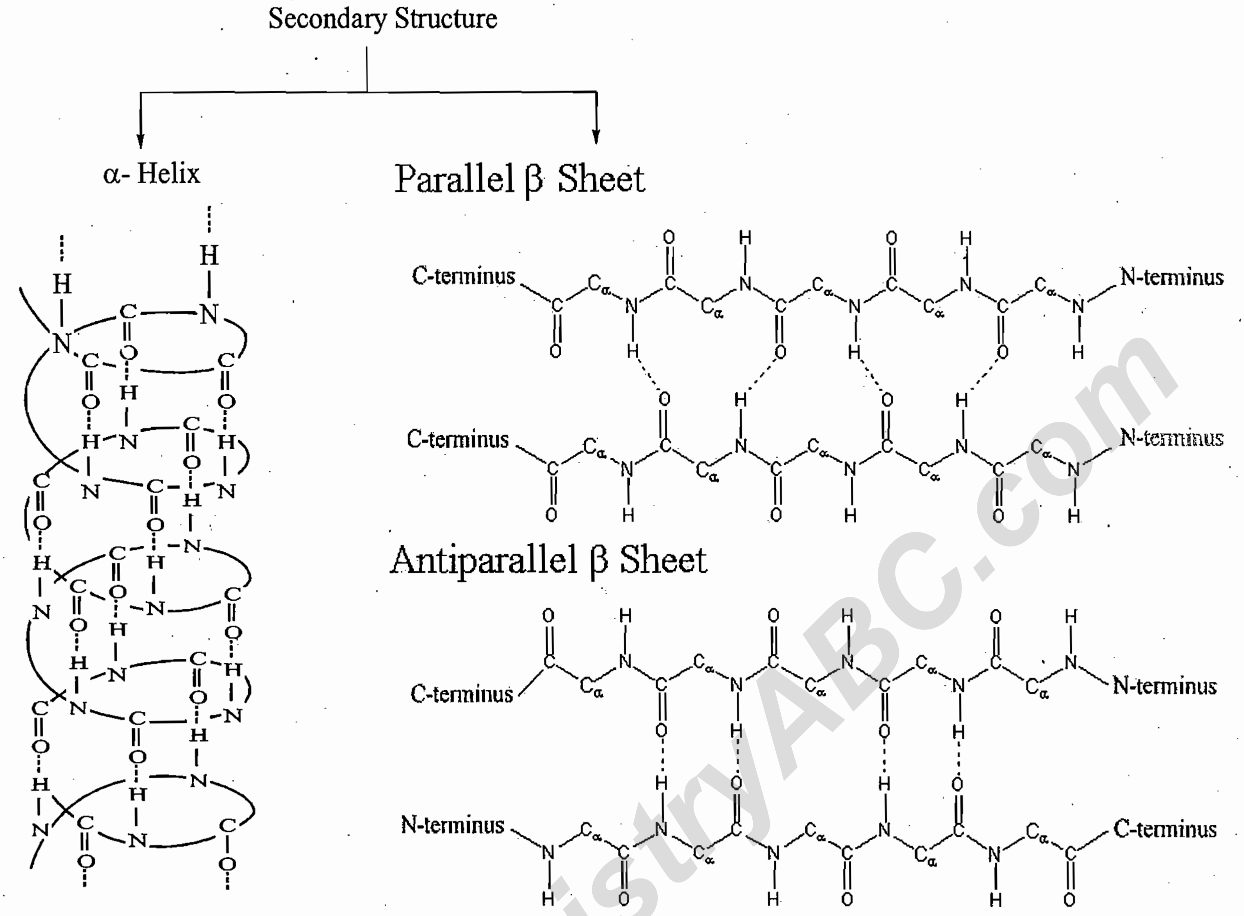


Ala – Leu — Cys — Met

2. **Secondary structure:**

- In secondary structures polypeptide chains are arranged side by side.

- Hydrogen bonds form between chains.
- R groups of the amino acid extend above and below the sheet.



The α – helix model for the conformation of protein was proposed by Pauling and it suggest that:

(i) The peptide group is planar

(ii) Hydrogen bonding stabilises the conformation and the strength of this bond is a maximum, when the atoms concerned $(C{=}O{-}H{-}N)$ are collinear or, failing this ideal situation do not deviate by more than 30°.

The β – conformation, was proposed by Pauling. In this, the Pauli peptide chain is extended and chains are held together by inter molecular hydrogen bonds. There are two types of β -conformation(Pleated sheet): parallel and anti-parallel.

3. Tertiary Structure :

- The tertiary structure of protein deals with folding of entire molecule which envolves hydrogen bonding, ionic, chemical and hydrophobic bonds.
- The tertiary structure that a protein assumes under the normal condition of temperature and pH will be its most stable arrangement. This has been refered to as the native conformation of that protein.
- There are two major molecular shapes of naturally occuring proteins: Globular and fibrous.
- Fibrous proteins have a large helical content and are essentially rigid molecules of rod-like shape.
- Globular proteins have a peptide chain which consist partly or helical section and folded about the random coil section to give a spherical shape.
- In globular proteins most polar groups lies on the surface of the molecule and most hydrofobic side change lies inside the molecules.
- The tertiary structure of protein have been elucidated by X-ray analysis, viscosity measurements, diffusion, light-scattering, ultracentirifuge methods and electromicroscopy.
- When a protein undergoes denaturation, the changes that occur involve changes in secondary and/or tertiary structure of proteins.

9.5. Carbohydrate :

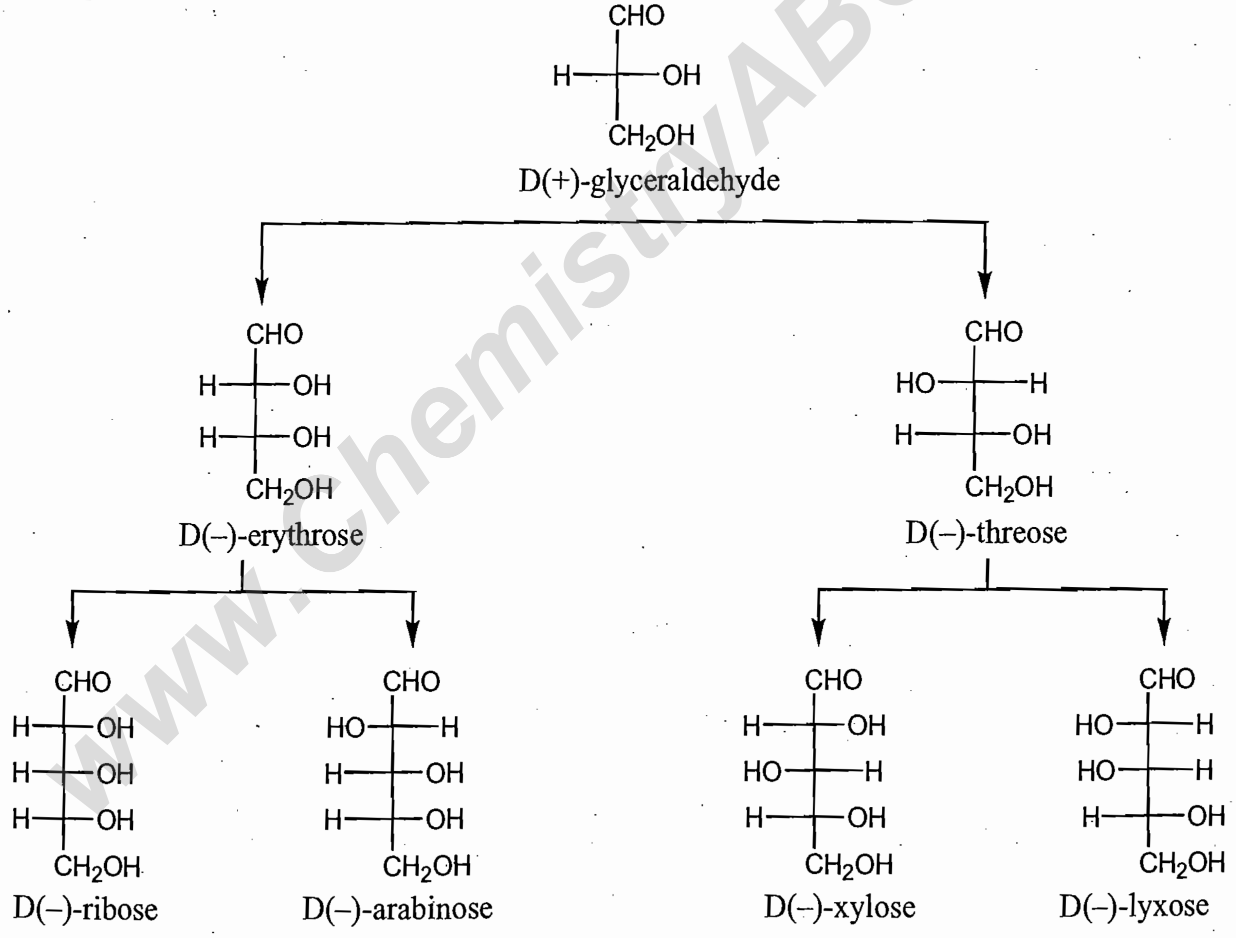
Carbohydrates are polyhydroxy aldehydes, polyhydroxy ketones or compound that can be hydrolyzed to them. Carbohydrates are the ultimate source of most of the food.

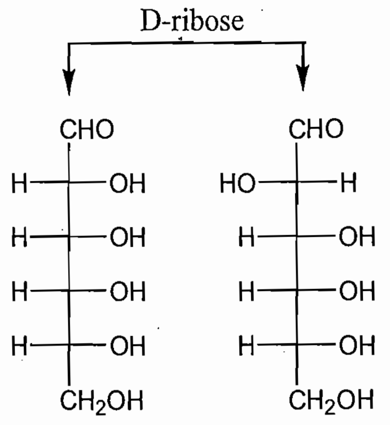
Classifications of Carbohydrate:
(i) Monosaccharide (ii)Disaccharide (iii) Polysaccharide

(i) Monosaccharide: Carbohydrate that can not be hydrolyzed to simpler compounds is said to be monosaccharide. For example: Glucose, Fructose etc.
(ii) Disaccharide: A carbohydrate that can be hydrolyzed to two monosaccharide molecule is said to be disaccharide. For example: Lactose, Maltose, Sucrose, Cellobiose etc.
(iii) Polysaccharide: A carbohydrate that can be a hydrolyzed to many monosaccharide molecules is said to polysaccharide. For example: Starch, Amylose, Amylopectin, Cyclodextrine, Cellulose etc.

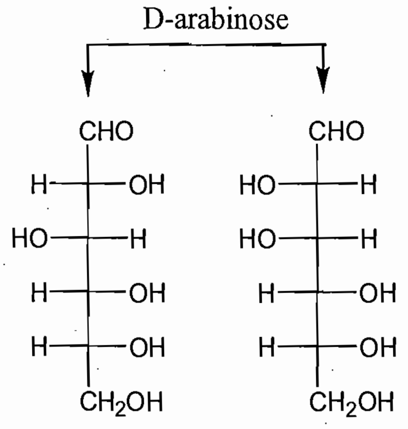
Monosaccharide may be further classified as aldoes, if it contain aldehyde and ketose, if contains ketonic group. On the basis of numbers of carbon atoms monosaccharides are also classified as: triose, tetrose, pentose, hexose and so on.

Reducing and Non-Reducing: Carbohydrate that reduce Fehling's solution (or Benedict's solutions) Tollen's are known as reducing sugar. All monosaccharide whether aldoes or ketose are reducing sugars. Most disaccharides are reducing sugars, for example lactose, maltose, cellobiose etc. except sucrose which is non-reducing sugar.

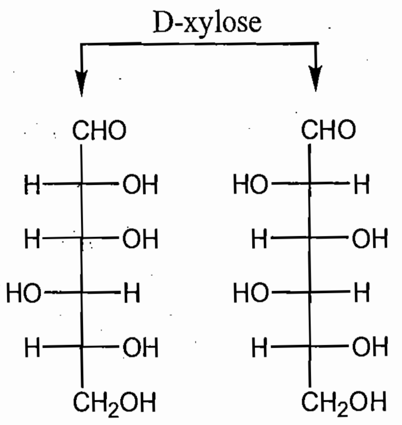




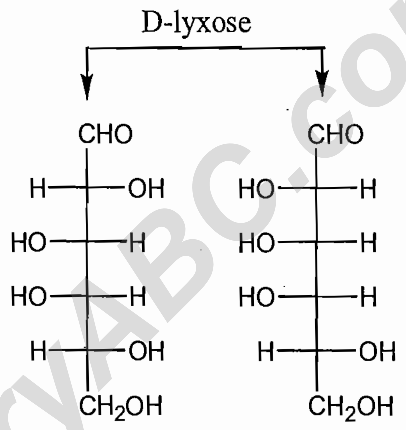
D(+)–allose D(+)–altrose



D(+)–glucose D(+)–mannose



D(+)–glyose D(+)–idose



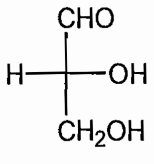
D(+)–galactose D(+)–talose

1. **Mono Saccharides :**

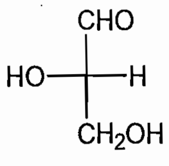
These are the sugars which can't be hydrolysed in to smallar molecules. $C_nH_{2n}O_n$ (n = 2 – 6)

$$C_6H_{12}O_6 \xrightarrow[H^+]{H_2O} \text{No Reaction}$$

Configuration : In carbohydrates configurational differences are associated with different spatial arrangement of tetrahedrally disposed ligands attached to chiral carbon atoms. The presence of asymmetric carbon makes possible the formation of stereo isomers. Glycer aldehyde [CHO–CHOH–CH_2OH] is selected as the standard of reference to assign the configuration of carbohydrate because it is the simplest carbohydrate which is capable of optical isomerism. It is a aldose triose.



D(+)–glyceraldehyde

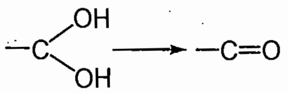


L(–)-glyceraldehyde

All natural sugars are D-sugars D(+) glyceraldehyde taken as standard.

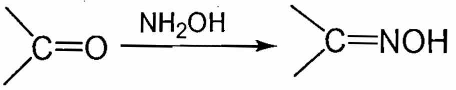
Structure elucidation of glucose :

1. Molecular Weight determination showed formula $C_6H_{12}O_6$
2. When glucose is treated with $(CH_3CO)_2O$ / Py → Pentaacetate formed showing presence of five –OH group.
3. As glucose is not easily dehydrated, so –OH group are vicinal

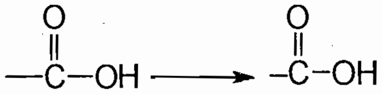


Don't occur

4. Glucose reacts with one mole of HCN to form cyanohydrin and with NH_2OH to form oxime. This indicate presence of a carbonyl group.



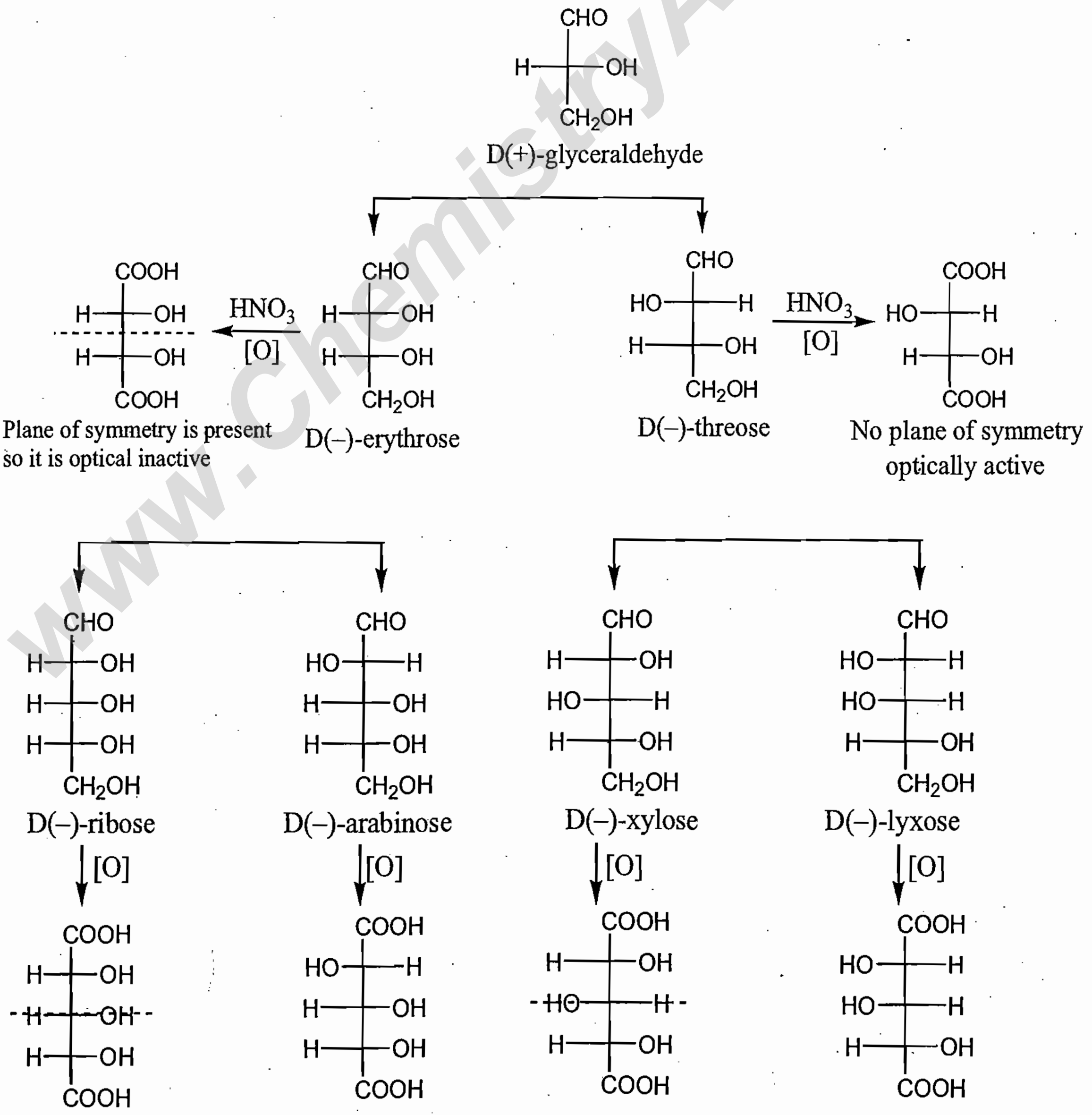
5. Oxidation of glucose with Br_2/H_2O give gluconic acid having same number of carbon atom as that of glucose. $(C_6H_{12}O_7)$. This indicates that carbonyl group is on –CHO (aldehyde) group (keto group containing sugars give acid with less C-atoms).



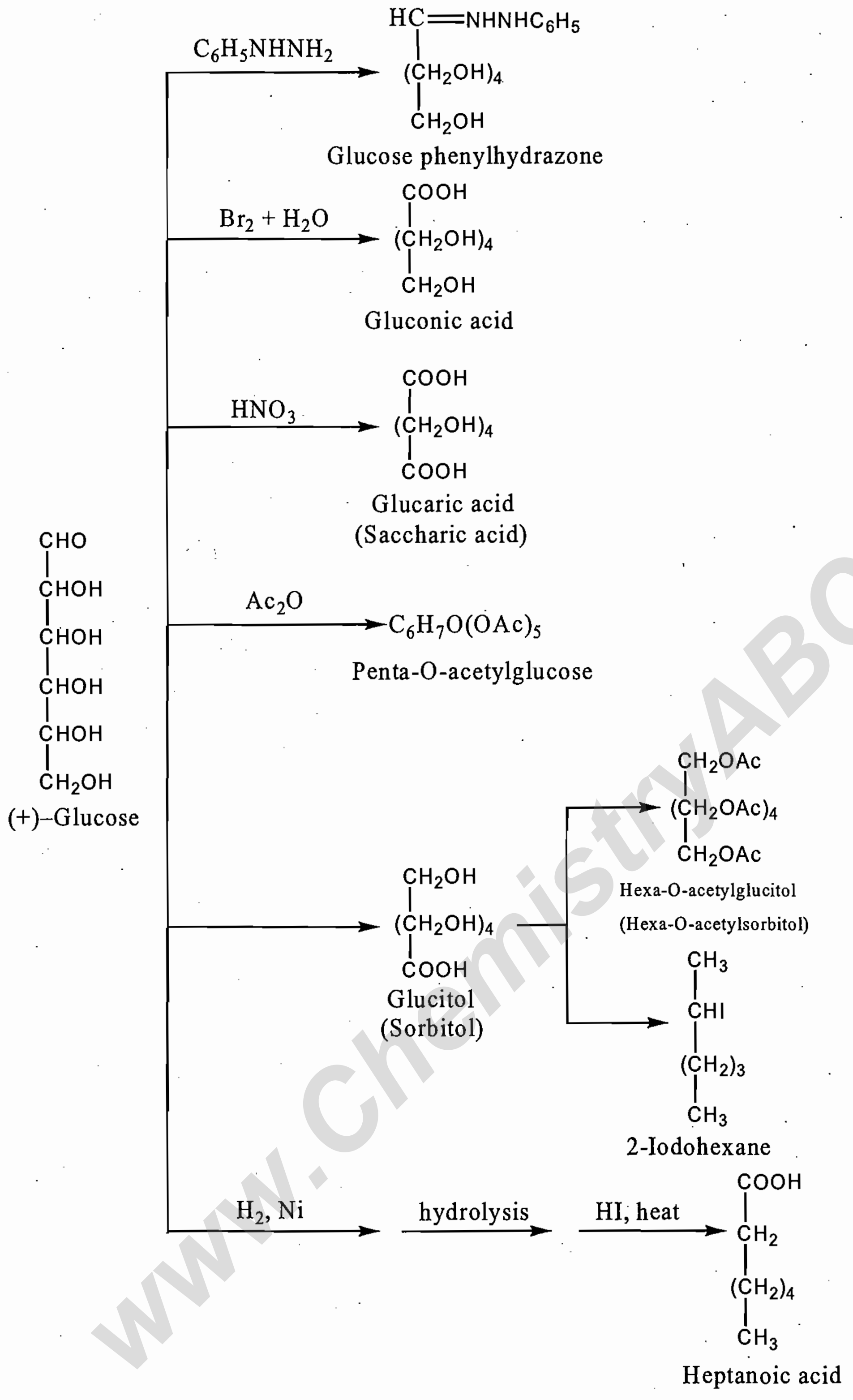
$$-\overset{O}{\overset{\|}{C}}-OH \longrightarrow -\overset{O}{\overset{\|}{C}}-OH$$

6. Oxidation of gluconic acid with HNO_3 produces a dicarboxylic acid (Gluceric acid) with molecular formula $C_6H_{10}O_8$. This indicates a presence of alcohol group (CH_2OH) an oxidation occures with loss of 2Hs and gain of one oxygen atom.
7. Glucose dissolve in H_2O to produce a neutral solution shows that it don't contain –COOH.
8. Glucose on reduction with H_2/Ni, produces a hexa-hydric alcohol (Glucitol) (–CHO –CH_2OH). This on reaction with HI/red P first yield 2-iodohexane at 100°C and then n-hexane on prolonged heating.
It indicate that all six C atoms in glucose are in a straight chain.
9. Glucose on reaction with HCN, form cyanohydrin, which on hydrolysis and followed by reduction with HI/red phosphorus yields n-heptanoic acid which indicates the presence of six C atoms in straight chain.
10. Periodate or $Pb(CH_3COO)_4$ oxidation of Glucose produces five molecule of HCOOH and HCHO group.

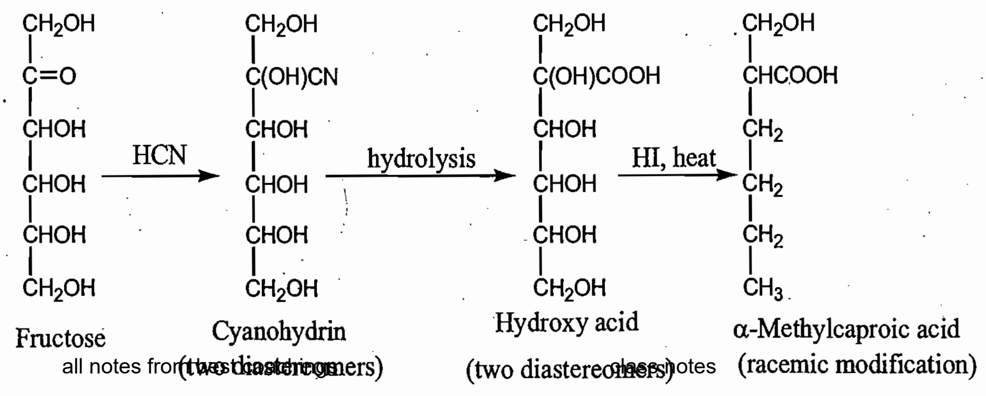
Optical activity in monosaccharide:

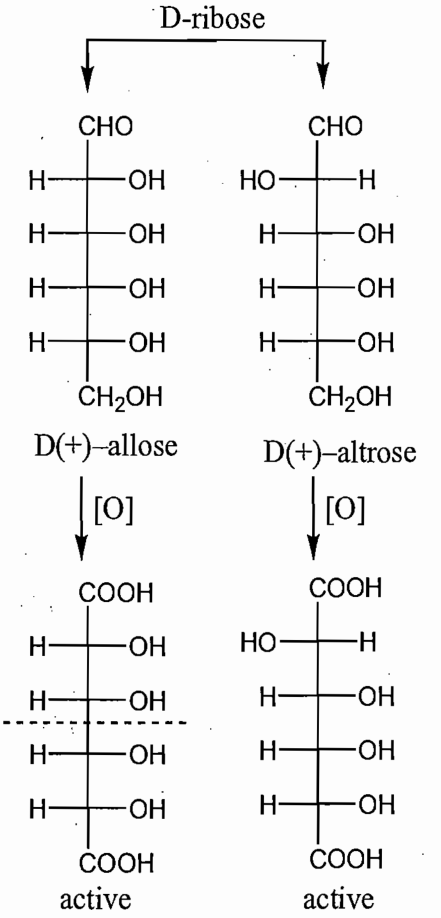


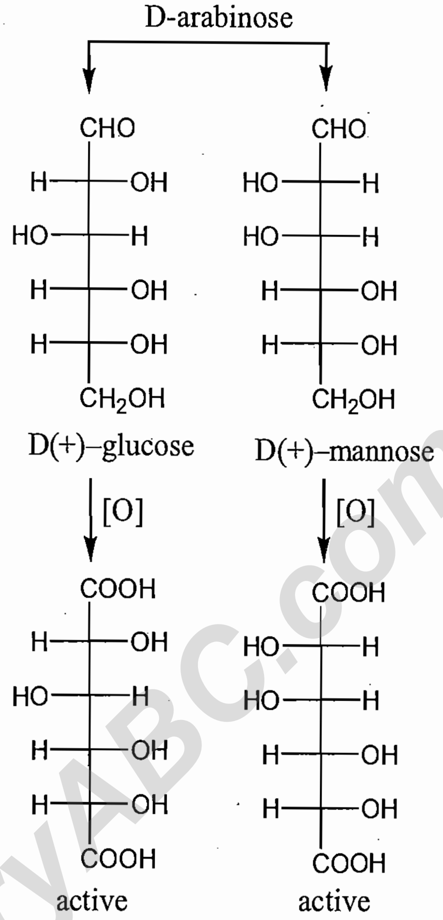
Reactions of Aldohexose:

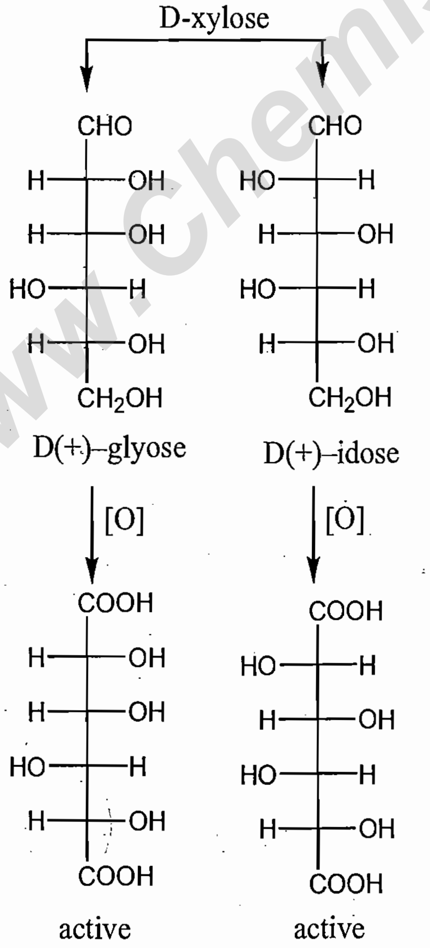


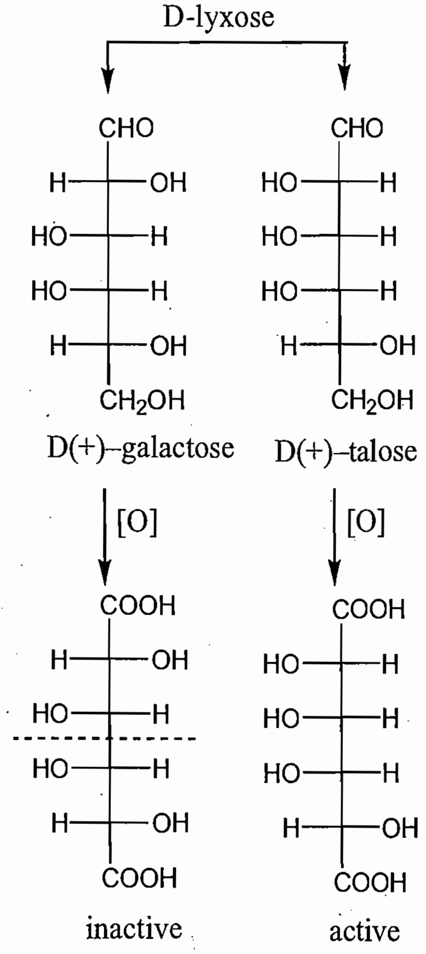
Reactions of Fructose:



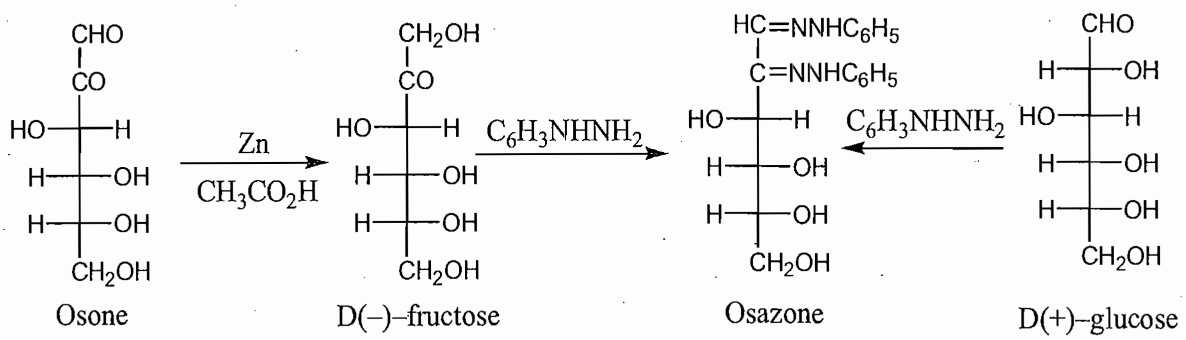

D-ribose
D(+)–allose
D(+)–altrose
[O]
[O]
active
active


D-arabinose
D(+)–glucose
D(+)–mannose
[O]
[O]
active
active

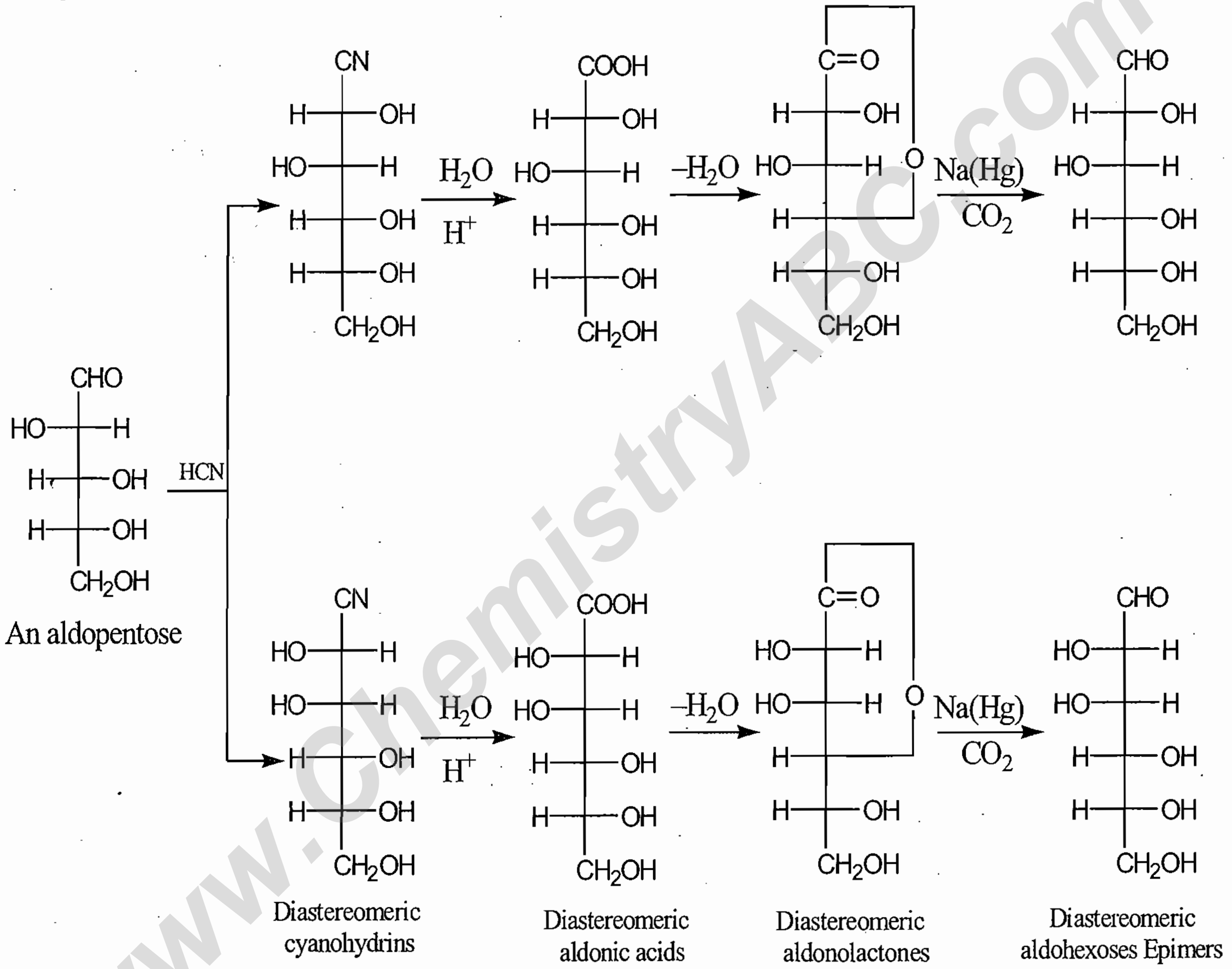

D-xylose
D(+)–glyose
D(+)–idose
[O]
[O]
active
active


D-lyxose
D(+)–galactose
D(+)–talose
[O]
[O]
inactive
active

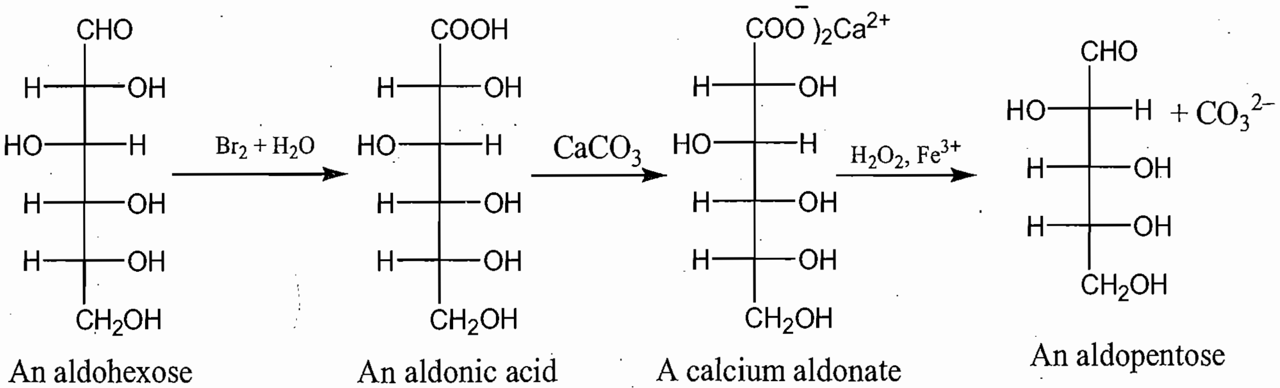
OSAZONE FORMATION OF KETOSE AND HEXOSE:



Lengthening the carbon chain of aldose. The Killiani-Fischer synthesis:

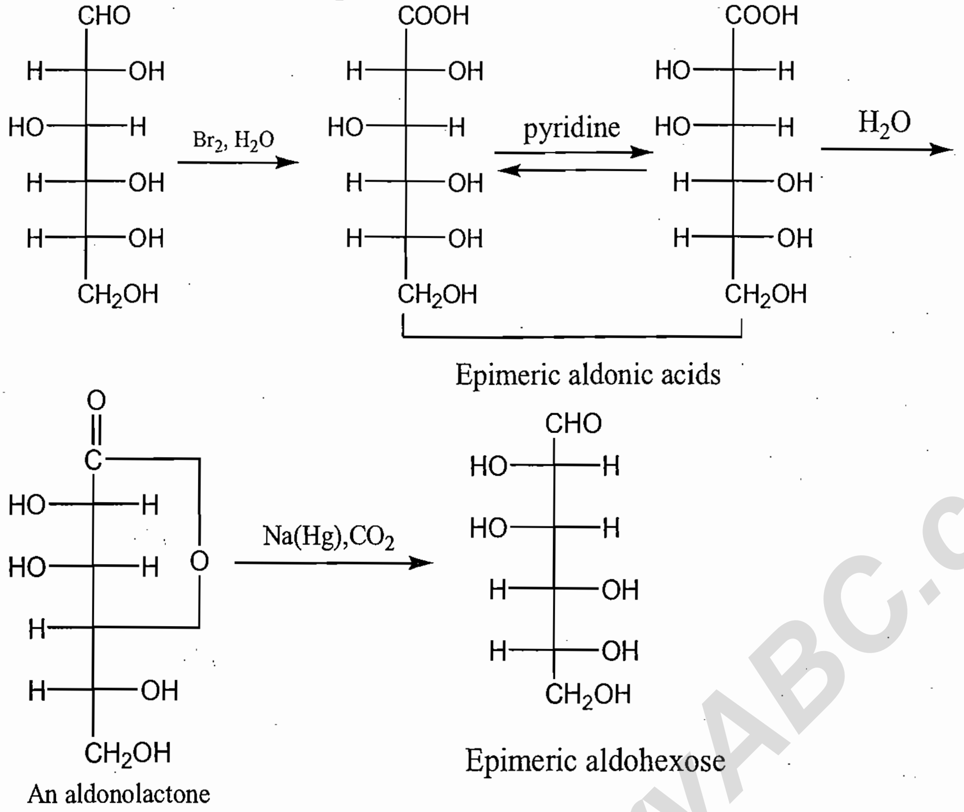


Shortening the carbon chain of Aldose: Ruff degradation:



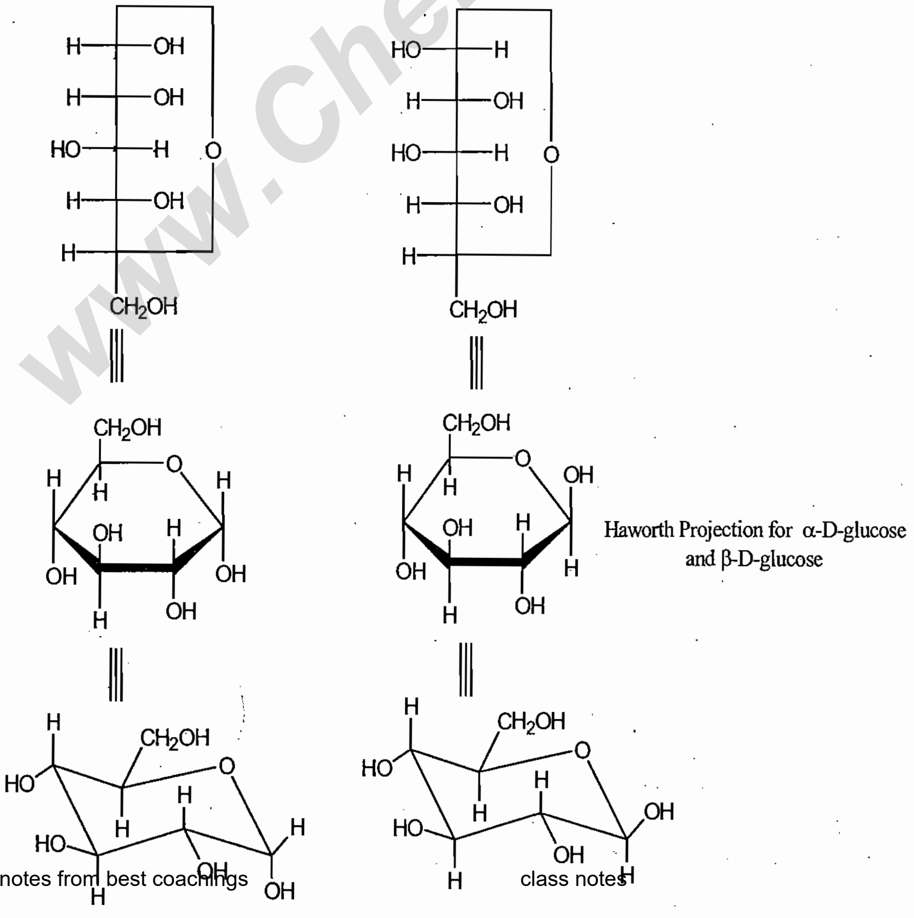
Conversion of glucose into mannose:

Glucose and Mannose are epimers at carbon number two.



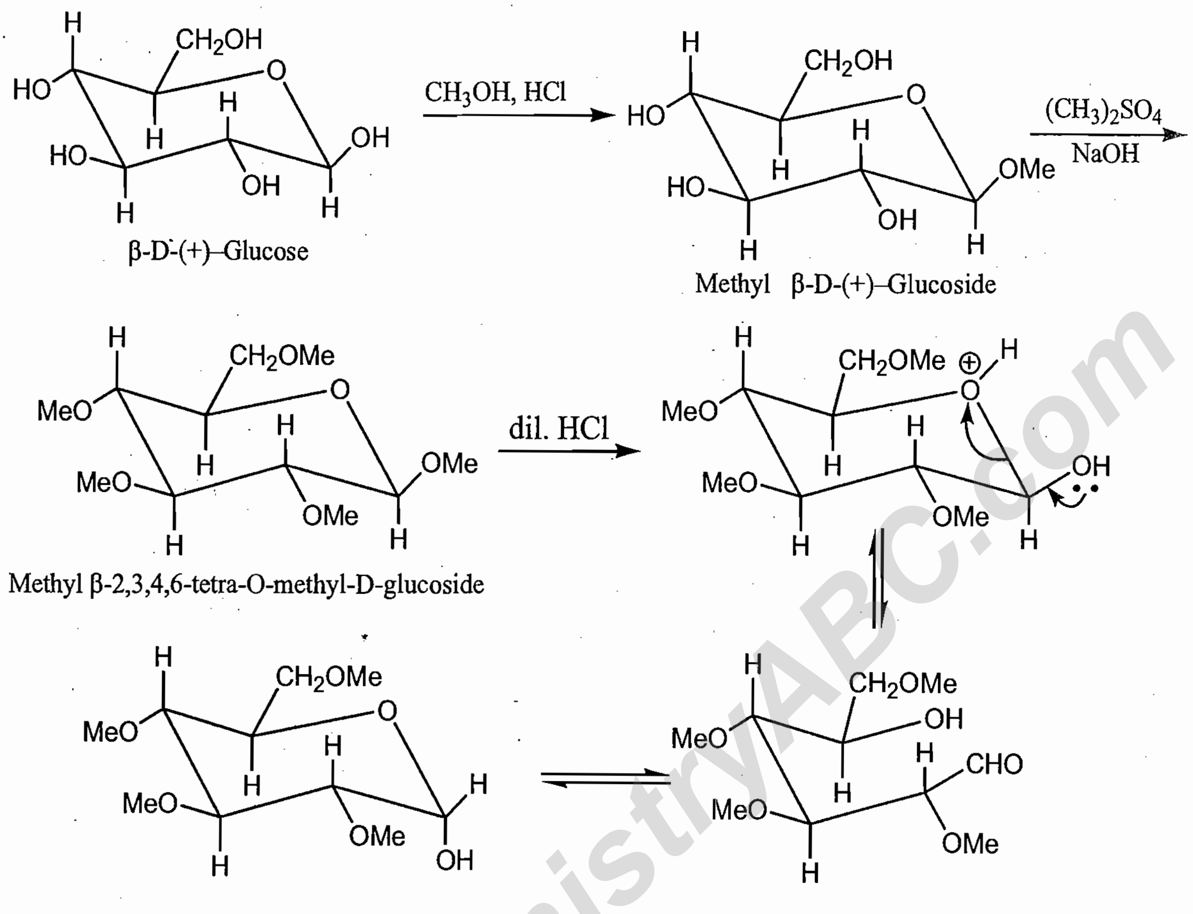
Cyclic structure of D(+)–glucose: Formation of glucosides:

- D(+)-glucose fails to undergo certain reactions typical of aldehydes. For example it gives a negative Schiff test and does not form bisulfite addition product.
- D(+)-glucose exists in two isomeric forms which undergo mutarotations.
- D(+)-glucose forms two isomeric methyl D-glucosides.



Haworth Projection for α-D-glucose and β-D-glucose

Problem:



β-D-(+)-Glucose

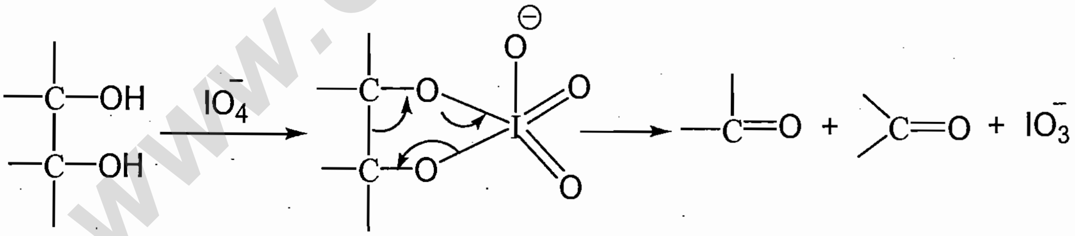
Methyl β-D-(+)-Glucoside

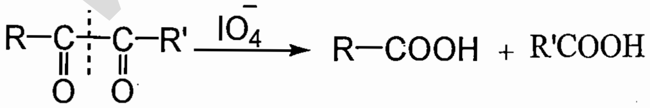
Methyl β-2,3,4,6-tetra-O-methyl-D-glucoside

α-2, 3,4,6-Tetra-O-methyl-D-glucose

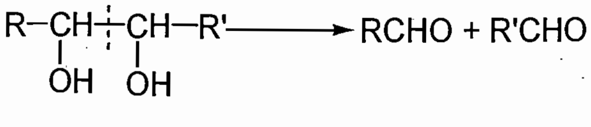
HIO_4:

On treatment with HIO_4 aquous solution or $Pb(OAc)_4$ in organic solvent compounds containing two or more C=O or C–OH groups adjacent to each other undergo oxidation with cleavage of the C–C bond.

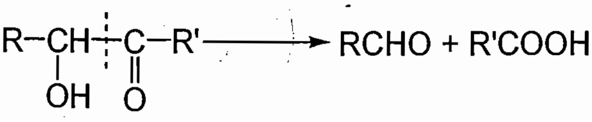




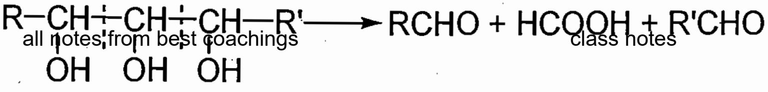
$$\mathrm{R-\underset{\underset{O}{\|}}{C}\,\vdots\,\underset{\underset{O}{\|}}{C}-R'} \xrightarrow{IO_4^-} \mathrm{R-COOH + R'COOH}$$



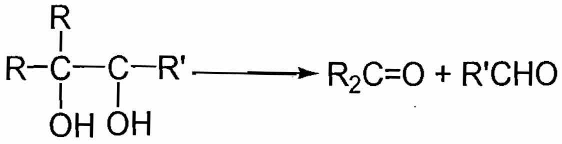
$$\mathrm{R-\underset{\underset{OH}{|}}{CH}\,\vdots\,\underset{\underset{OH}{|}}{CH}-R'} \longrightarrow \mathrm{RCHO + R'CHO}$$



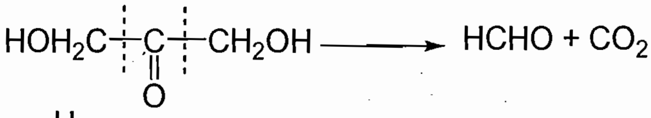
$$\mathrm{R-\underset{\underset{OH}{|}}{CH}\,\vdots\,\underset{\underset{O}{\|}}{C}-R'} \longrightarrow \mathrm{RCHO + R'COOH}$$



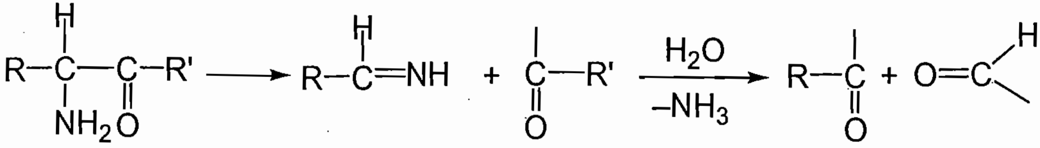
$$\mathrm{R-\underset{\underset{OH}{|}}{CH}\,\vdots\,\underset{\underset{OH}{|}}{CH}\,\vdots\,\underset{\underset{OH}{|}}{CH}-R'} \longrightarrow \mathrm{RCHO + HCOOH + R'CHO}$$



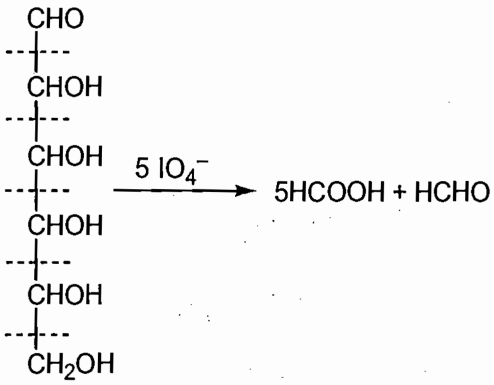
$$R-\underset{OH}{\overset{R}{C}}-\underset{OH}{C}H-R' \longrightarrow R_2C=O + R'CHO$$

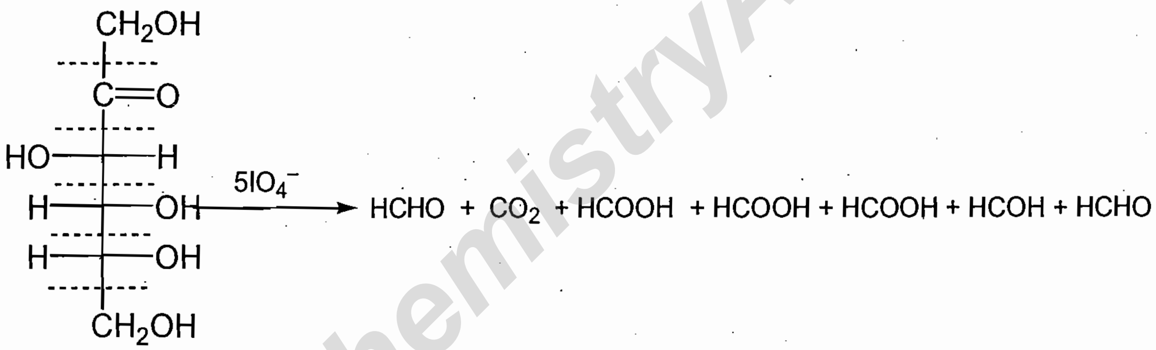


$$HOH_2C-\underset{\underset{O}{\|}}{C}-CH_2OH \longrightarrow HCHO + CO_2$$



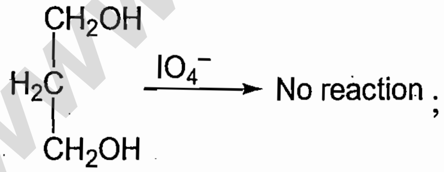
$$R-\underset{NH_2}{\overset{H}{C}}-\underset{\underset{O}{\|}}{C}-R' \longrightarrow R-\overset{H}{C}=NH + \underset{\underset{O}{\|}}{C}-R' \xrightarrow[-NH_3]{H_2O} R-\underset{\underset{O}{\|}}{C} + O=C\langle^{H}$$

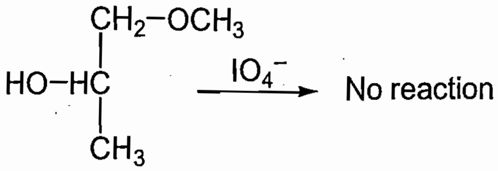




Limitation:

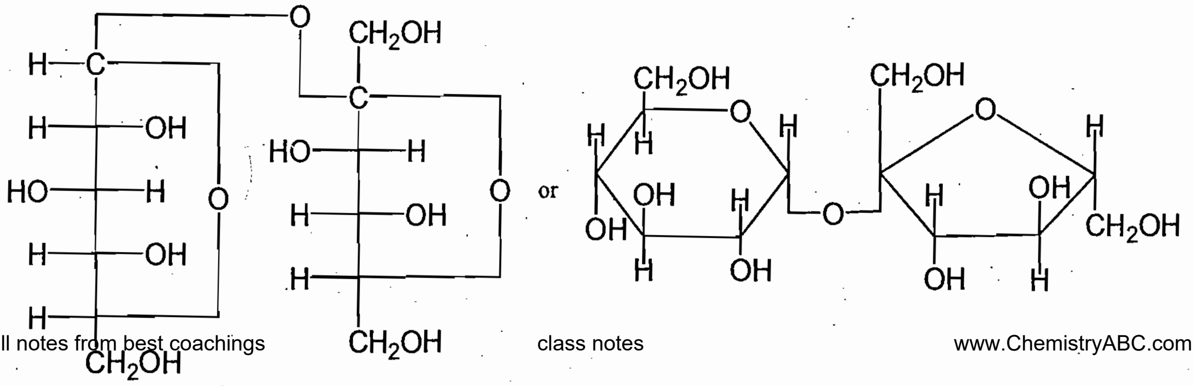
Periodate oxidation don't occur in which – OH group or C=O group are separated by a CH_2 group. It also do not cleave the compounds in which OH group is adjacent to a ether or acetyl group.



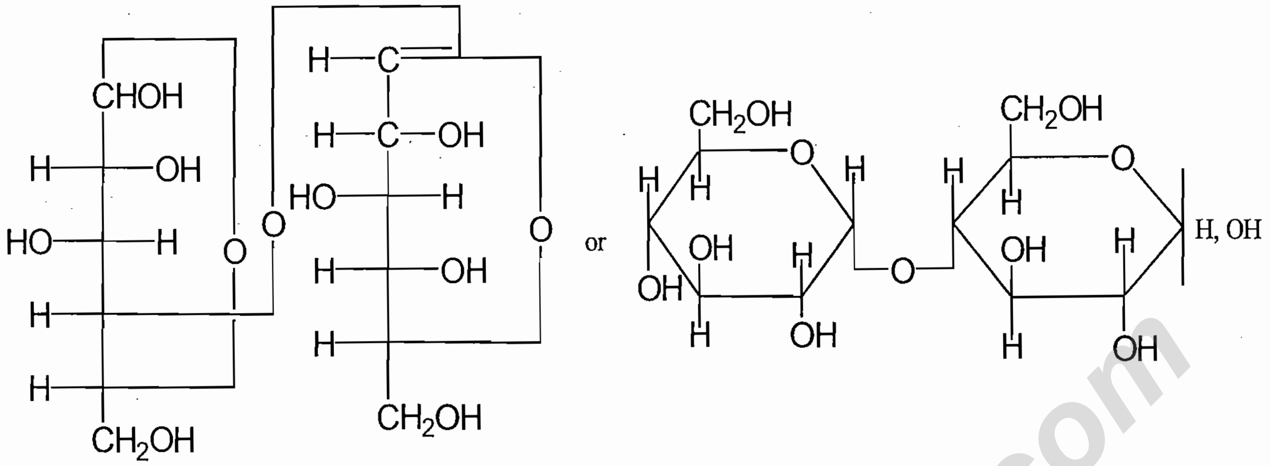


Disaccharides:

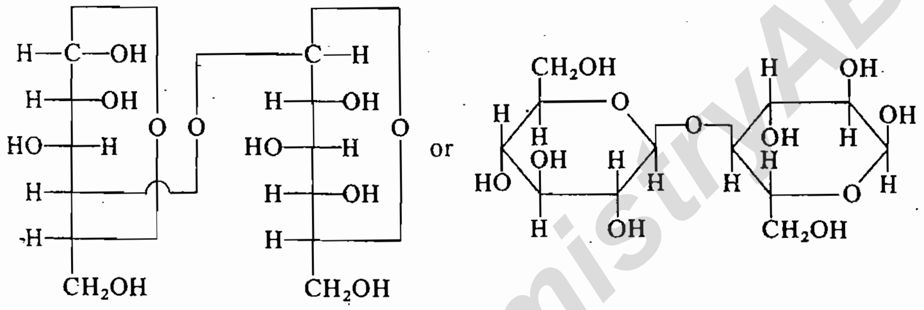
Sucrose: Sucrose is a non-reducing sugar. Upon hydrolysis with dilute acids or by enzyme invertase it gives an equimolar mixture of D-glucose and give fructose.

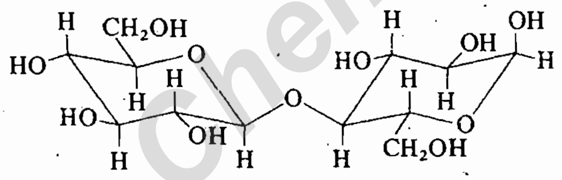


Maltose: Maltose is 4-O-α-D-glucopyranosyl-D-glucopyranose. It is hydrolyzed by dilute acids and gives two molecules of D-glucose. Maltose is reducing sugar and it is hydrolyzed by enzyme maltase. The glycosidic link of the non-reducing half of the molecule is α-linkage.

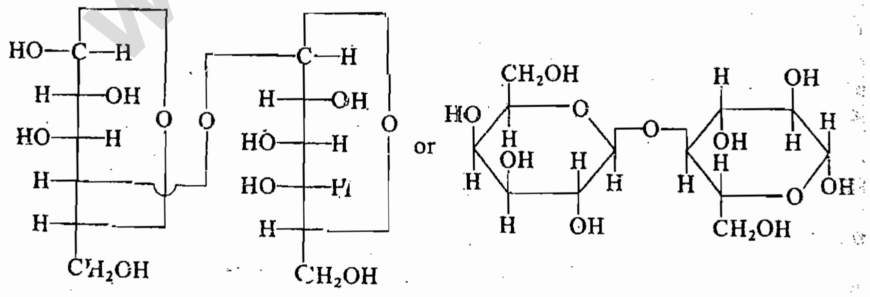


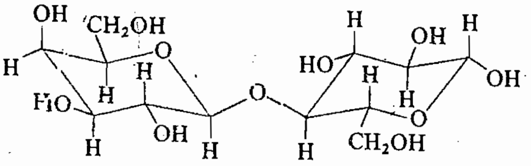
Cellobiose: The Cellobiose is 4-O-β-D-glucopyranosyl-D-glucopyranose. Cellobiose upon hydrolysis with dilute acid gives two molecules of D-glucose. Since this hydrolysis is effected by emulsin, the glycocidic link must be beta. Cellobiose is reducing sugar.





Lactose: Lactose is 4-O-β-D-galactopyranosyl-D-glucopyranose. Lactose is reducing sugar and it is hydrolyzed by dilute acids and gives one molecules of D-glucose and another molecule of D-galactose. Since the lactose is also hydrolyzed by an enzyme lactase, it means that the glycosidic linkage is β.





9.6. Terpenoids :

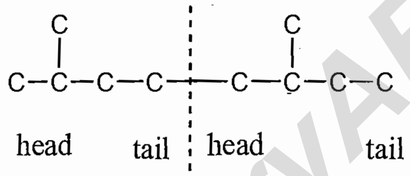
The terpenoids form a group of compounds, the majority of which occur in plant kingdom.
Most natural terpenoid hydrocarbons have a the molecular formula $(C_5H_8)_n$, where n = number of carbon atom. The value of 'n' is used as a basis for classification.

Number of carbon atoms	Value of n	Class
10	2	Monoterpenoids $(C_{10}H_{16})$
15	3	Sesquiterpenoids $(C_{15}H_{24})$
20	4	Diterpenoids $(C_{20}H_{32})$
25	5	Sesterterpenoids $(C_{25}H_{40})$
30	6	Triterpenoids $(C_{30}H_{48})$

Note: The name 'terpene' is inappropriate to include compounds such as alcohols, aldehydes, ketones etc. So, There is a tendency to use the more general name terpenoids.

Isoprene rule: The thermal decomposition of almost all terpenoids gives isoprene as one of the products so, this indicates that the skeleton structures of all naturally occuring terpenoids can be buit-up of isoprene units, this is known as the Isoprene rule.

- The isoprene unit in natural terpenoid is joined head to tail fashion.

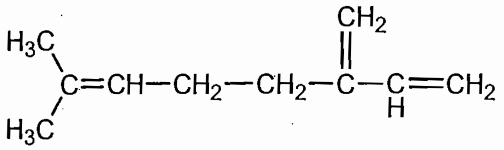


Monoterpenoids: The monoterpenoids may be subdivided into three groups
(1) Acyclic (2) Monocyclic (3) Bicyclic

9.7. Acyclic Monoterpenoids :

Myrcene: Molecular formula – $C_{10}H_{16}$, B.P. 166–168°C

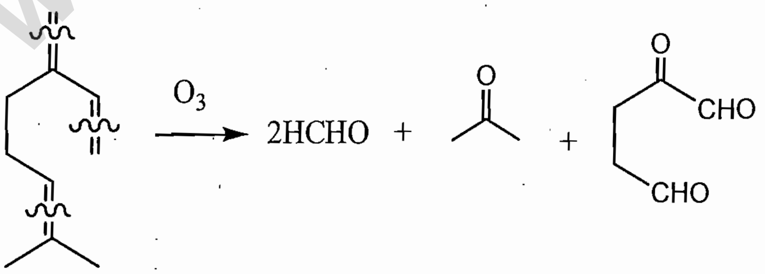
- This is an acyclic monoterpenoid hydrocarbons.
- Occurs in verbena and bay oils.
- Myrcene contains three double bond two of which are in conjugation.



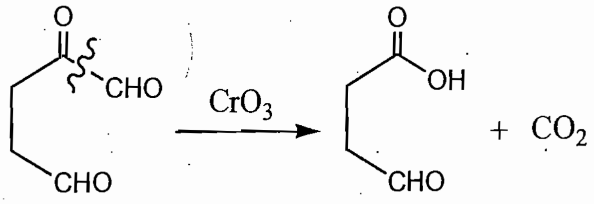
$$(H_3C)_2C{=}CH{-}CH_2{-}CH_2{-}C({=}CH_2){-}CH{=}CH_2$$

- Ozonolysis of myrcene produces acetone, formaldehyde and ketodialdehyde

(i)

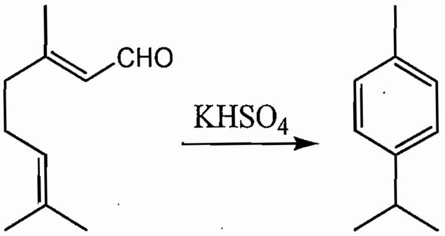


(ii)

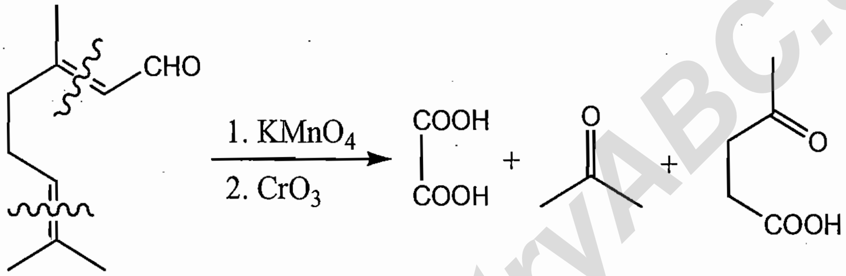


Citral: Molecular formula: $C_{10}H_{16}O$

- Most important member of the acyclic monoterpenoids.
- It occurs in Lemon grass oil
- Citral is a liquid which has the smell of Lemons.
- On heating with $KHSO_4$, citral forms p-cymere.

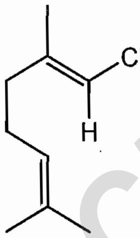


- Citral can be reduced by sodium amalgam to an alcohol, geraniol.
- Oxidation of citral with alkaline permanganate followed by chromic acid, gives acetone, oxalic acid and Laevulic acids.

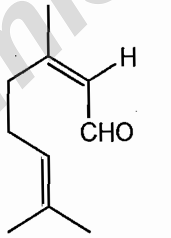


- Citral shows two geometrical isomers.

The functional group (aldehyde) is trans or cis with respect to the methylene group of the main chain.

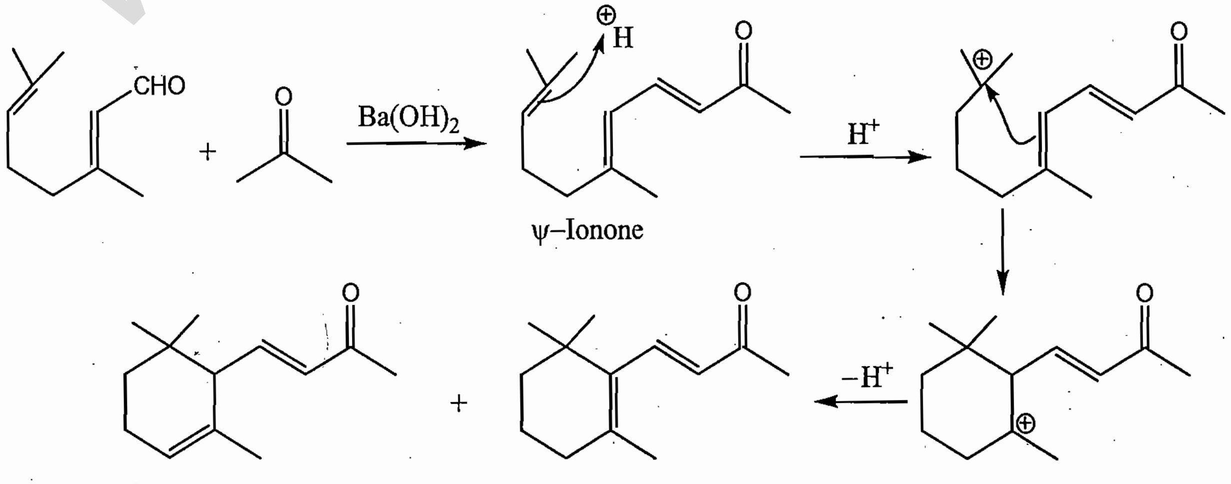


trans-(or E) form
Citral-a, geranial



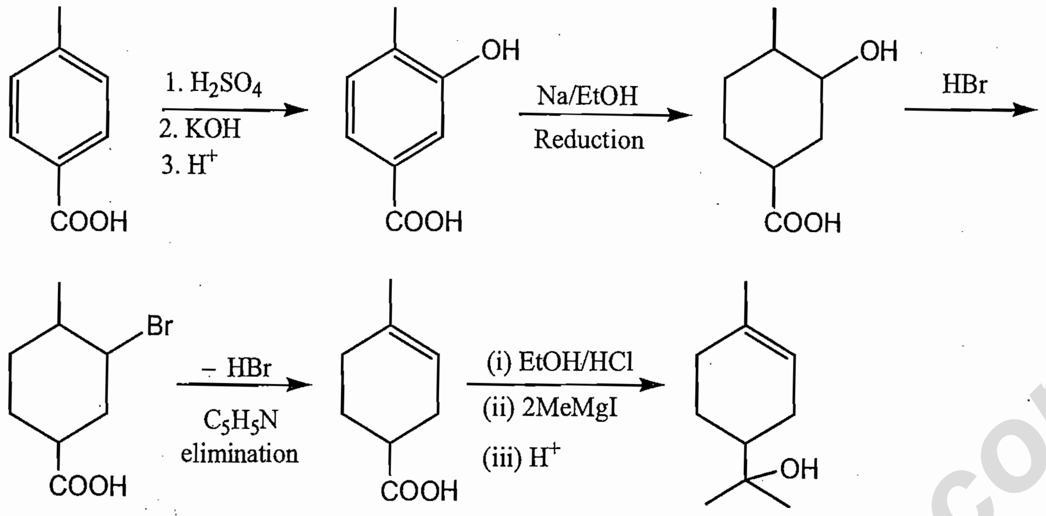
Cis-(or Z) form
Citral-b. neral.

- When citral is condensed with acetone in the presence of $Ba(OH)_2$, ψ-ionone is formed and this, on heating with dilute H_2SO_4 in the presence of glycerol forms a mixture of α and β-ionones.

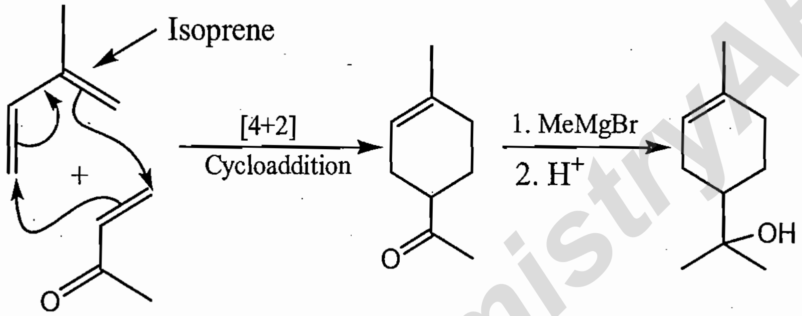


9.8. Monocyclic Monoterpenoids :

Synthesis of α-terpineol: Carried out by Perkin, Junior(1904).



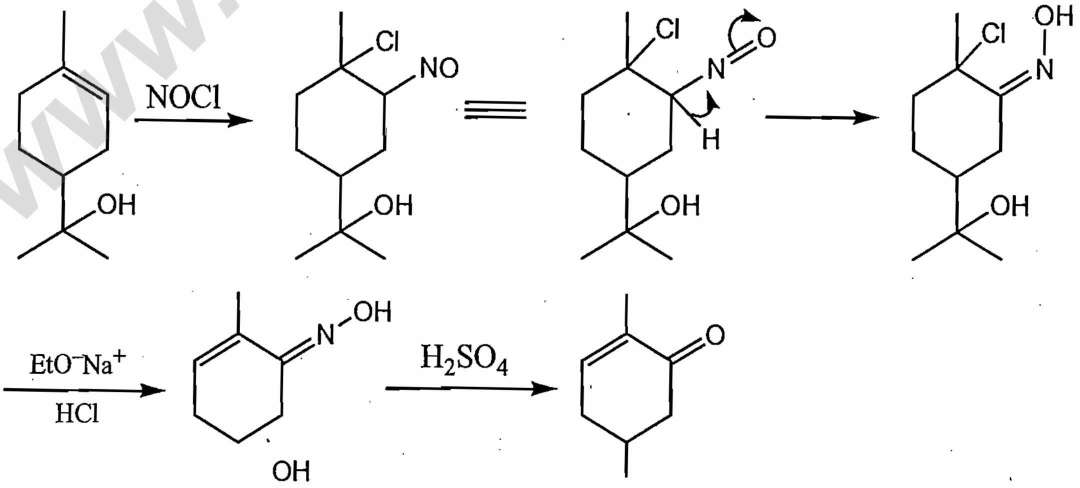
A much simpler synthesis of α-terpineol has been carried out by Alder and Vogt (1949) by using Diels-Alder reaction:



9.9. Carvone :

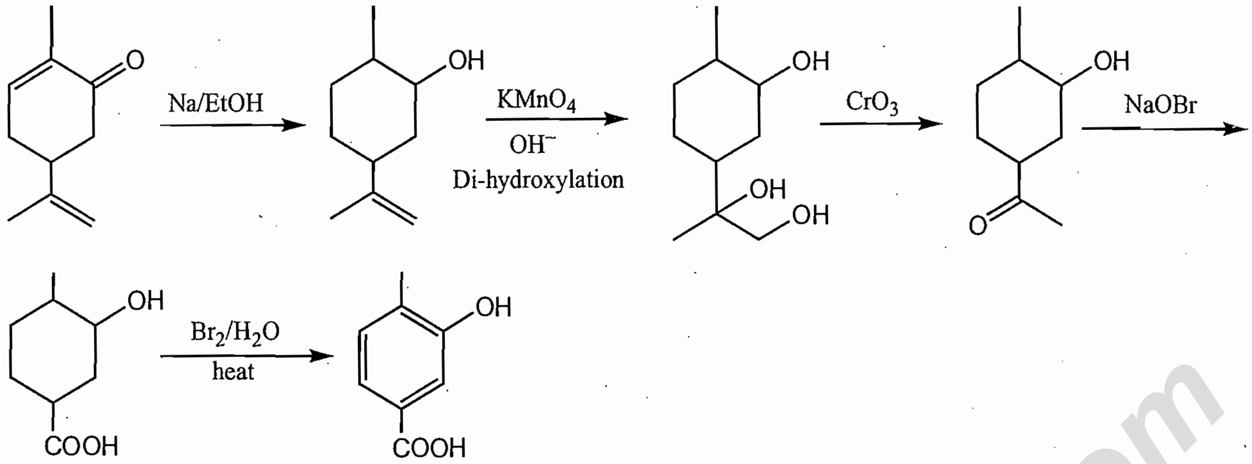
Molecular formula – $C_{10}H_{14}O$, B.P. = 230°C/755 mm.

- Occurs in essential oils eg → spearmint and Caraway oil.
- Preparation of carvone from α-terpineol.



- **Reaction of Carvones:**

1.



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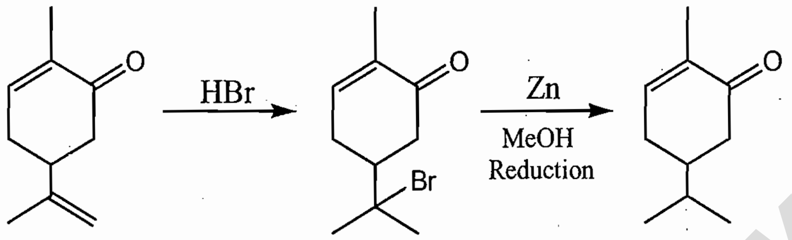
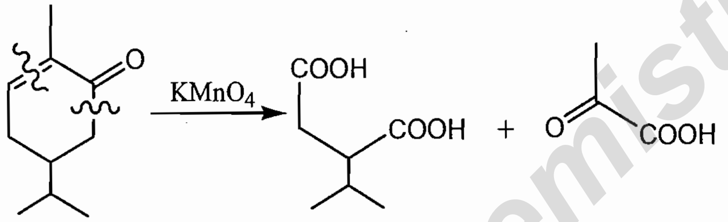
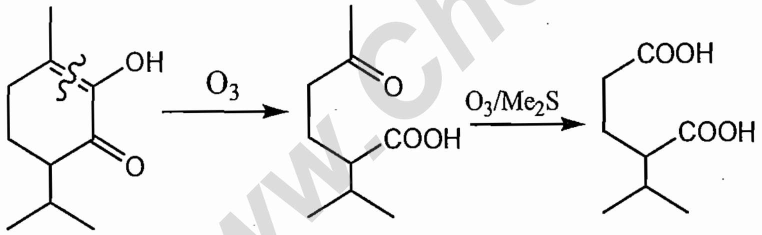




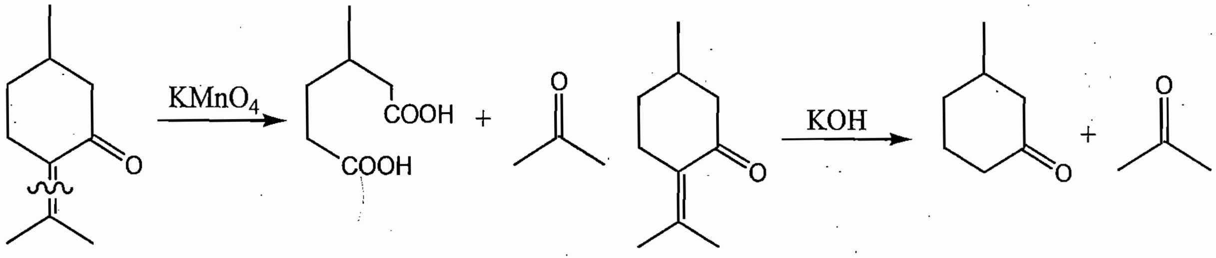


2-Isopropyl-glutaric acid

9.10. Pulegone :

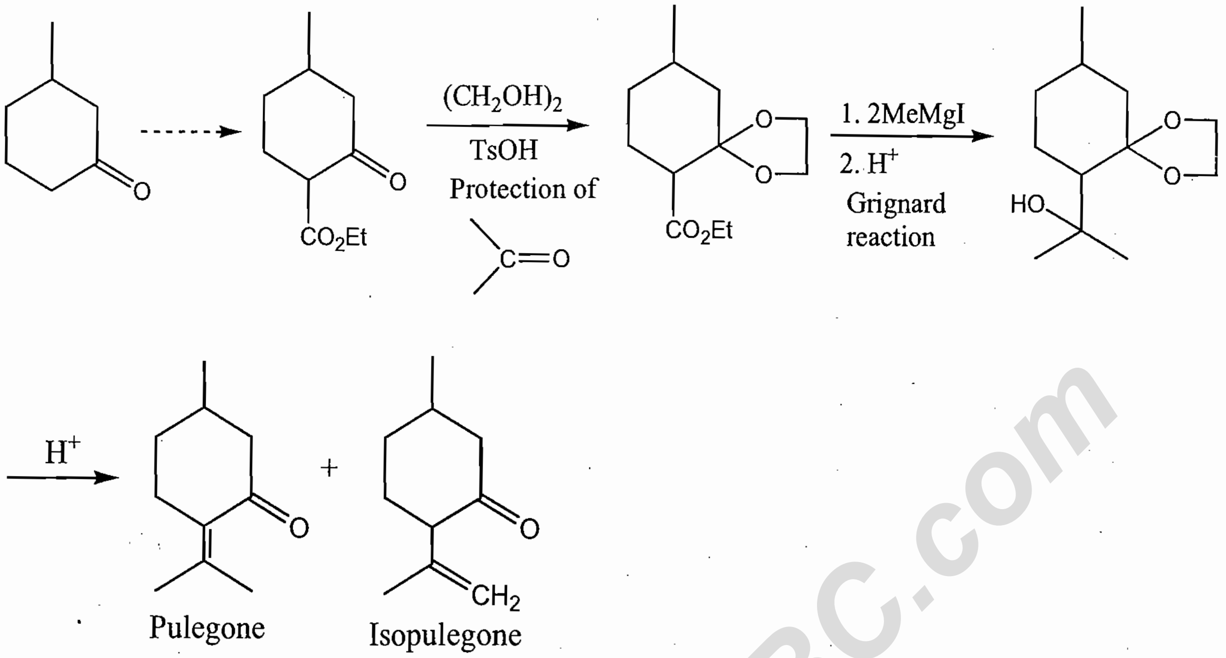
Molecular formula $C_{10}H_{16}O$, B.P.= 221–222°C

- It contains double bond, and behaves as ketone.
- On reduction pulegone first gives menthone and this on further reduction gives menthol.



Pulegone

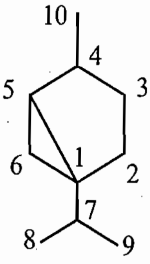
Synthesis of Pulegone:



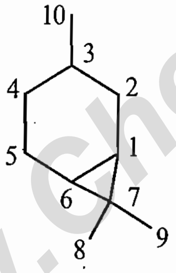
9.11. Bicyclic Monoterpenoids :

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

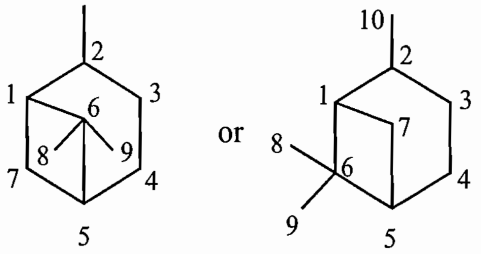
Class - I: **(6 + 3– membered ring)** **Class 2: (6 + 4)**



Thujane

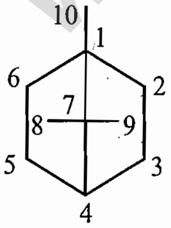


Carane

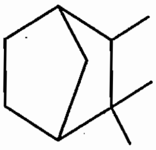


Pinane

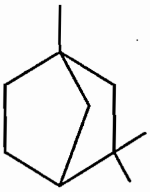
Class 3: (6+5)



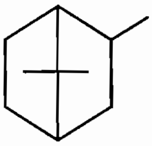
Bornane
(Camphane)



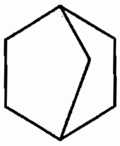
Norbornane derivative
(Isocamphane)



Norbornane derivative
(Fenchane)



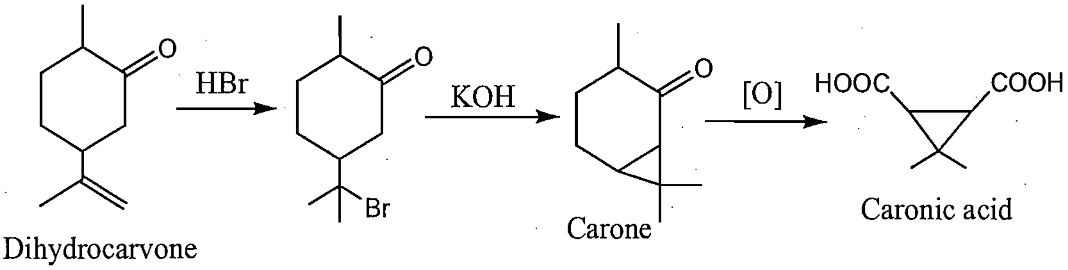
Norbornane derivative
(Isobornylane)

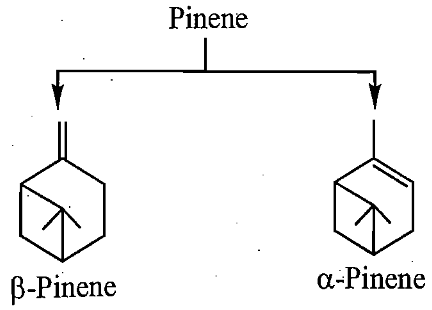


Norbornane derivative

- The two rings do not lie in one plane but are almost perpendicular to each other.

Carone: B.P. = 99–100°C/15 min.

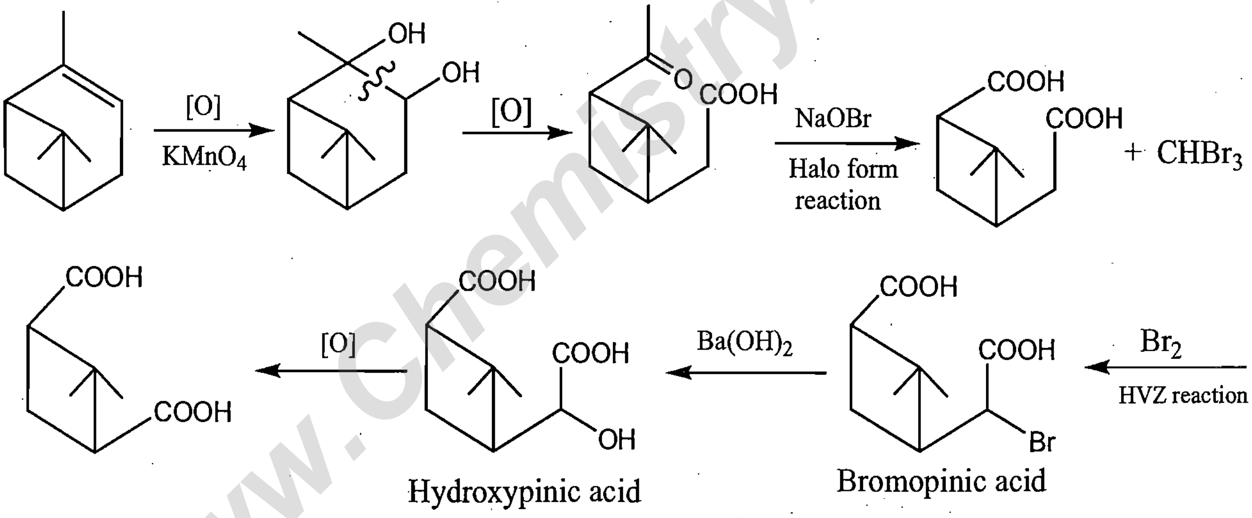




α- pinene: B.P. = 156° C

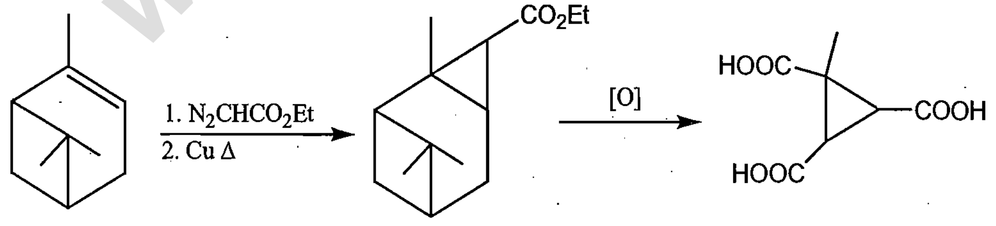
- The most important member of pinane class.
- It occurs in both the (+) and (–) forms in all turpentine oils.

Reactions:



PROBLEMS

1.



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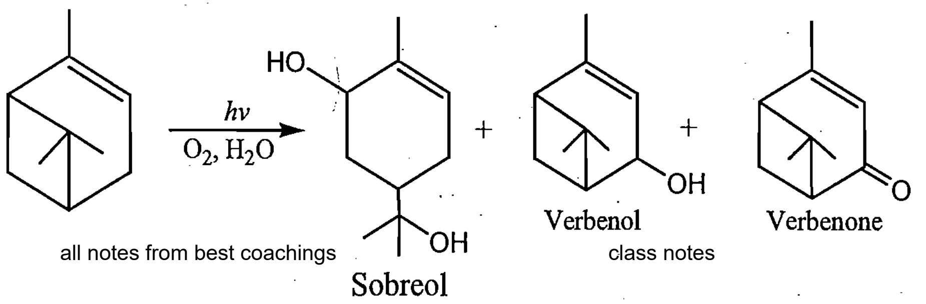
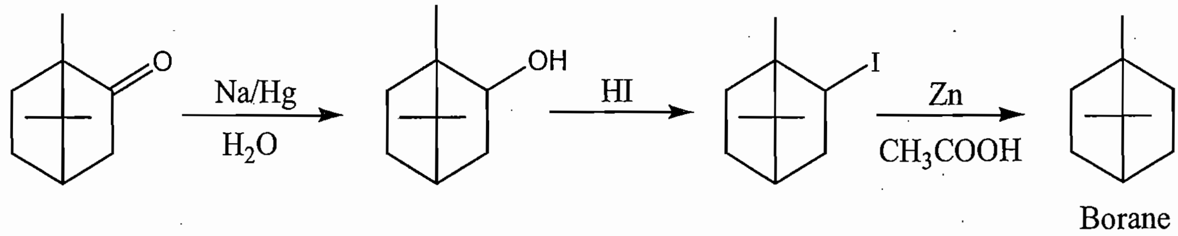


9.12. Camphane:

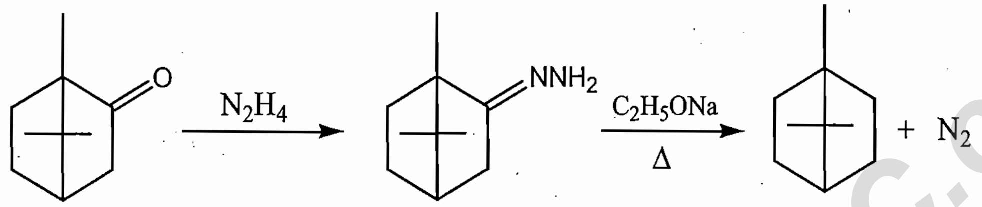
Borane (Camphane): Molecular formula – $C_{10}H_{18}$, solid, m.p. = 156° C.

Preparation of Camphane.

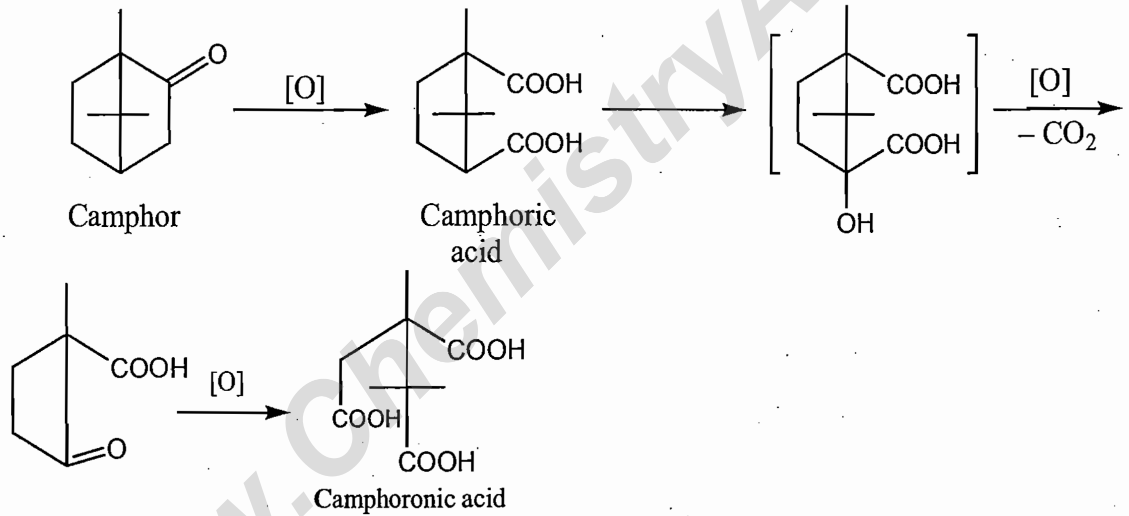
(i)



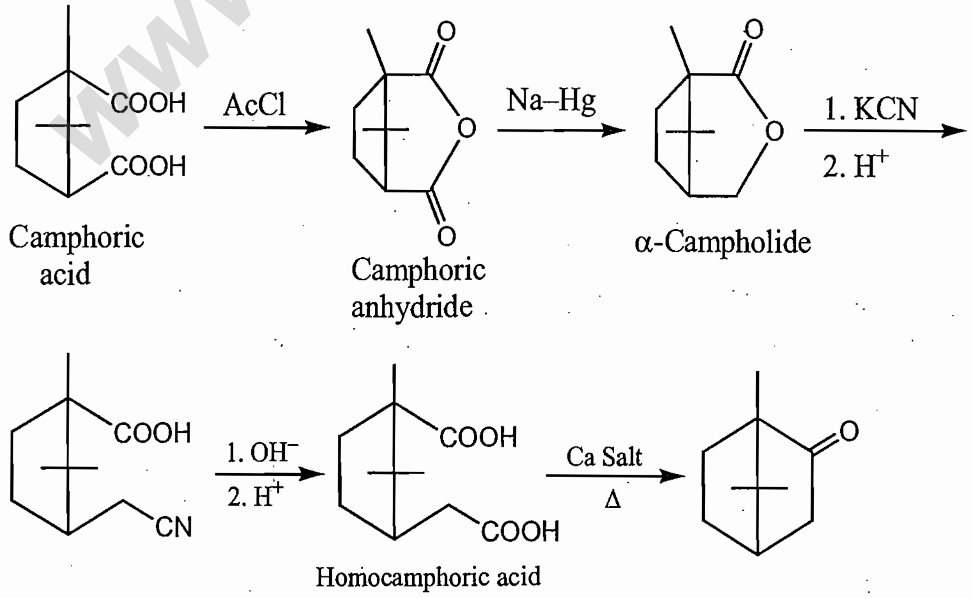
(ii) By Wolff-Kishner reduction:



Camphor : Molecular formula – $C_{10}H_{16}O$, solid, m.p. 180°C, optically active, the (+) and (–) forms occur naturally and so, does racemic comphor, which is the usual form of synthetic camphor.



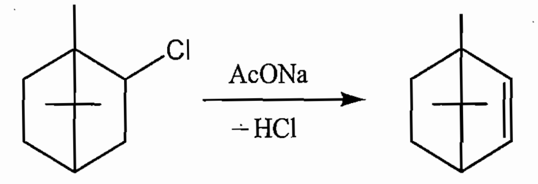
Synthesis of camphor:



Camphene:

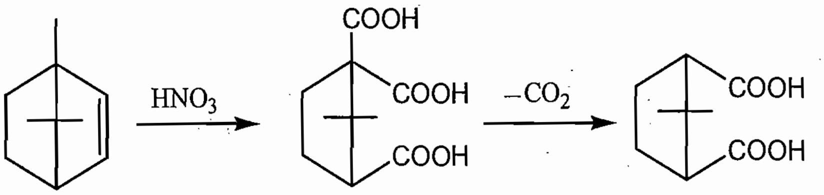
- Molecular formula – $C_{10}H_{10}$, M.P. 51-52°C
- Naturally occur in the (+), – (–) and (±) form

Preparation:



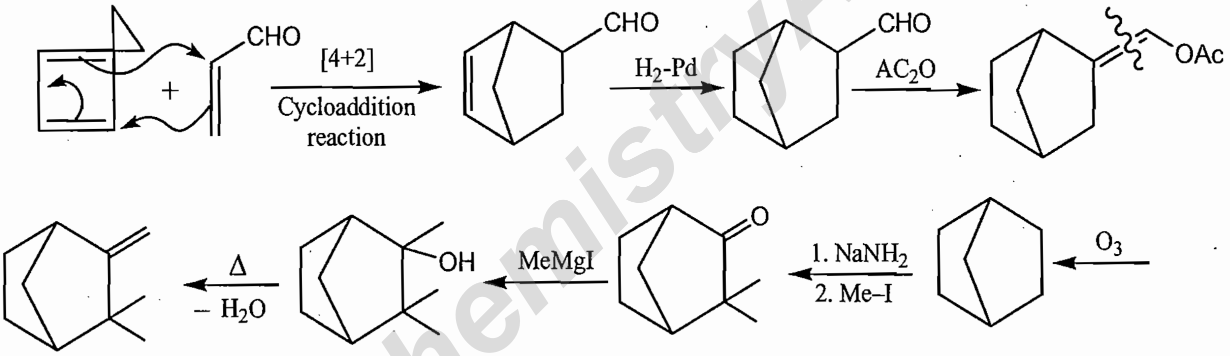
Bornyl chloride Camphene

- Oxidation of camphene with dilute HNO_3 produces carboxy apcamphoric acid.



Camphene Carboxy apocamphoric acid Apocamphoric acid

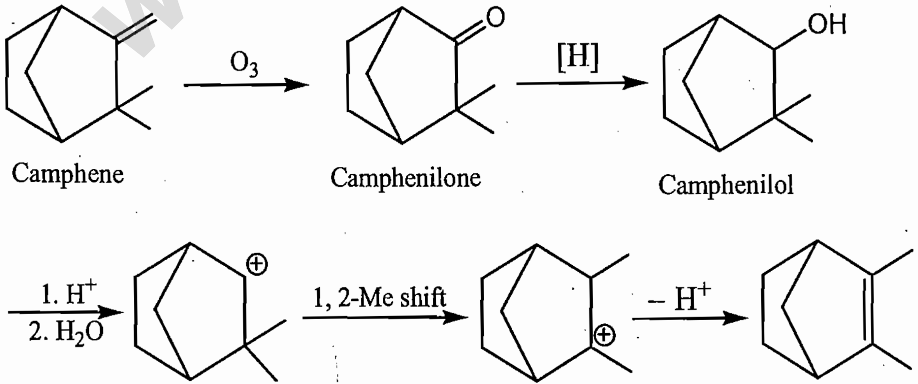
Synthesis of camphene:



Structurally related to Camphene is the compound santene.

Santene:

- Molecular formula – C_9H_{14}, B.P. = 142°C.
- Occurs in east india Sandal wood oil.



Camphene Camphenilone Camphenilol

Santene

Sesquiterpenoids:

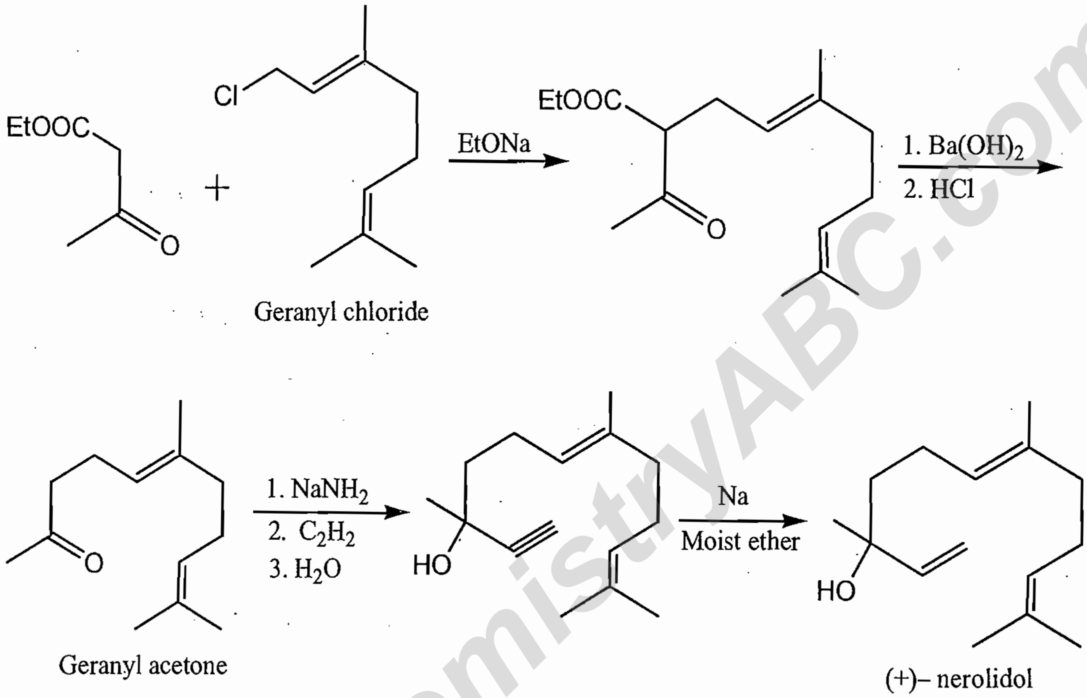
The sesquiterpenoids are classfied into four groups according to the number of ring present. The nature of the sesquiterpenoid skeleton is also characterized by the number of double bonds present in the molecule.

Class of sesquiterpenoids	No. of double bonds	Molecular refraction.
Acyclic	4	69.5
Monocyclic	3	67.8
Bicyclic	2	66.1
Tricyclic	1	64.4

Nerolidol:

- Molecular formula – $C_{15}H_{26}O$, B.P. = 125– 127°C /4.5 mm.
- Occur in the oil of neroli

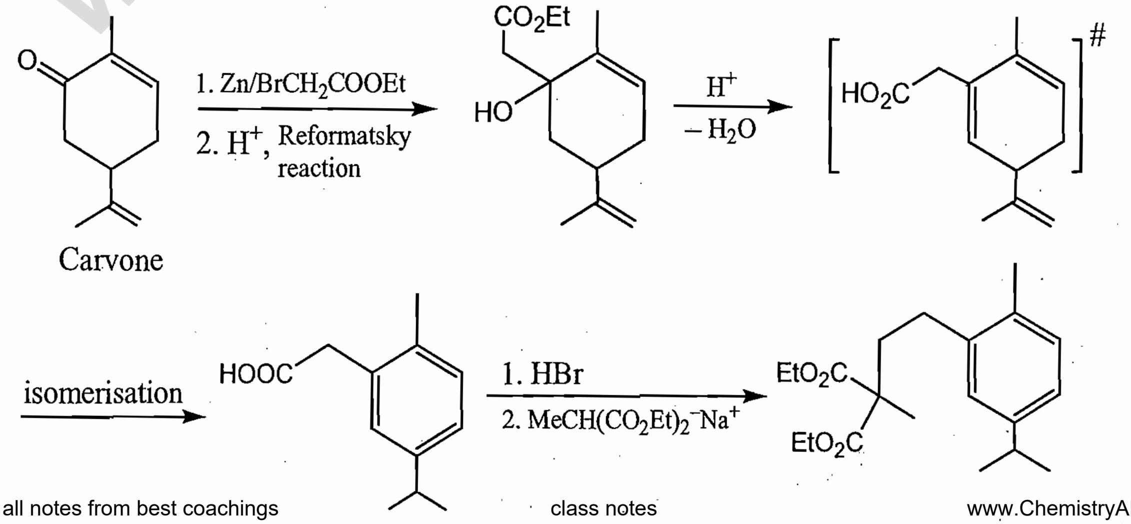
Synthesis of Nerolidol:

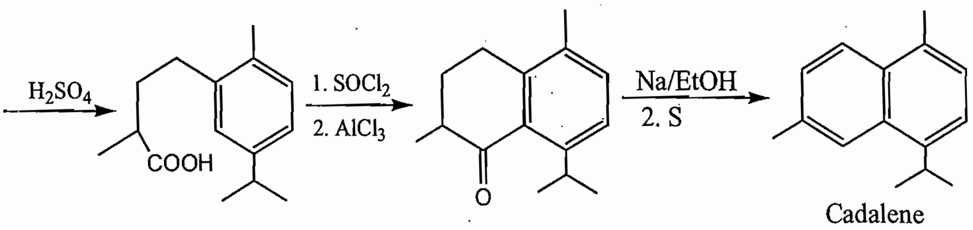


9.13. Bicyclic Sesquiterpenoids :

α-Cadinene:

- Molecular formula is $C_{15}H_{24}$, B.P. 134–136°C/11 mm.
- Occurs in the (–) form is oil of cubebs.
- On dehydregenation with sulfur, cadinene forms cadalene $C_{15}H_{18}$.
- Cadalane does not add on bromine, and form a picrate, this led to the belief that cadalene was an an aromatic compound.





9.14. Diterpenoids:

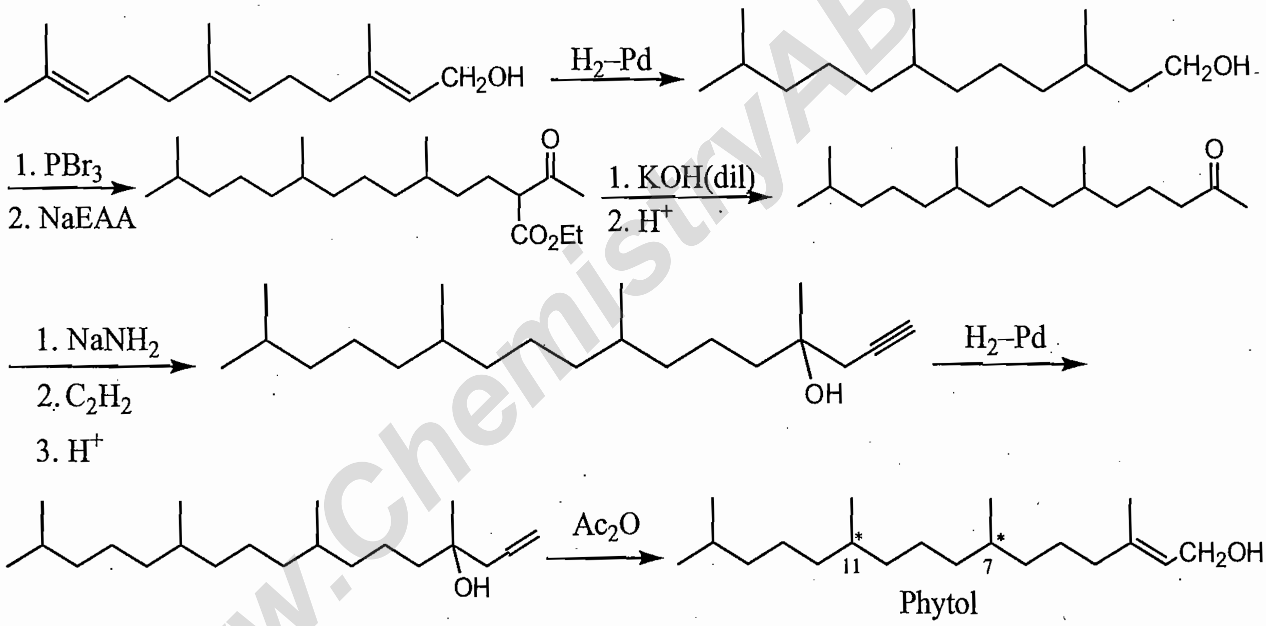
Phytol:

Molecular formula – $C_{20}H_{40}O$, B.P. – 145°C

- Acyclic diterpenoid.
- Produced form the hydrolysis of chlorophyll
- It also forms part of the molecule of vitamins E and K.
- It is a primary alchol.
- It contains double bond.
- Ozonolysis of phytol gives glycoaldehyde and a saturated ketone.

$$C_{18}H_{36}{=}CH{-}CH_2{-}OH \xrightarrow{O_3} C_{18}H_{36}O + OCHCH_2OH$$

Synthesis:



- The phytol molecule contain two chiral centres (7 and 11).

9.15. Alkaloids :

Originally the name alkaloid (which means alkali - like) was given to all organic bases isolated from plants. Alkaloids are very poisonous, but are used medicinally in very small quantities. Thus the basic properties, usually complex structures, physiological action and plant origin are the main characters which define plant alkaloids.

Sources of alkaloids:

Alkaloids are usually found in the seeds, root leaves, or bark of the plant, and generally occur as salts of various plant acids eq. acetic acid, oxalic acid, citric acid, malic acid and tartaric acid etc. Most alkaloids are obtained from natural sources, but a few synthesised commercially e.g. ephedrine and papaverine.

General properties of alkaloids:

Generally colourless, crystalline non volatile solids which are insoluble in water, but are soluble in ethanol, ether, chloroform etc.

Some alkaloids are liquids which are soluble in water, For example: Coniine and nicotine and few are coloured, berberine is yellow.

The alkaloids form insoluble precipitates with solutions of phosphotungstic acid, phosphomolybdic, picric acid, potassium mercuric-iodide, etc.

Classification of the Alkaloids:

According to the nature of nucleus present in the molecules.

1. Phenyl ethyl amine group.	2. Pyrrolidine group
3. Pyridine and piperidine groups	4. Pyrrolidine-pyridine group
5. Quinoline group.	6. Isoquinoline group.
7. Phenanthrene group.	8. Indole group

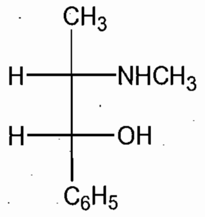
Phenyl ethylamine group: Many compounds of this group are known, some natural and others synthetic. **Their outstanding physiological action is to increase the blood-pressure, hence they are often referred to as** the **pressor drugs.**

β-phenylethyl amine:

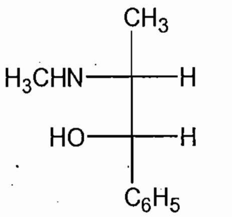
- This is the parent substance of this group of alkaloids

$$C_6H_5CH_2Cl + KCN \longrightarrow C_6H_5CH_2CN \xrightarrow[C_2H_5OH]{Na} C_6H_5CH_2CH_2NH_2$$

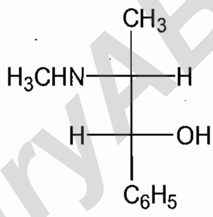
D(–)–Ephenrine: Ephedrine is one of the most important drugs in Ma Huang (a chinese drug). It has also been used in the treatment of Hay fever, chronchial asthama etc.



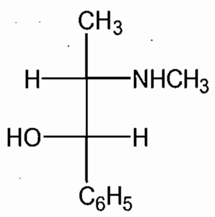
D(–)–ephedrine



L(+)–ephedrine

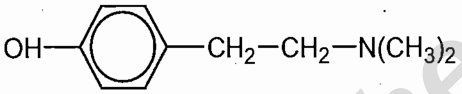


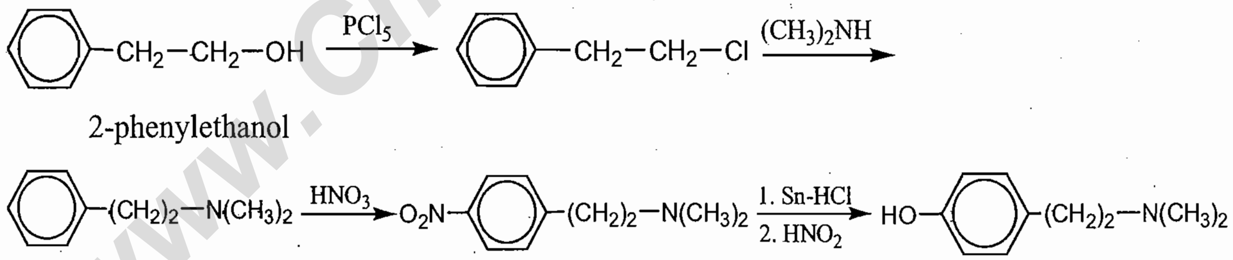
D(–)–ψ–ephedrine



L(+)–ephedrine

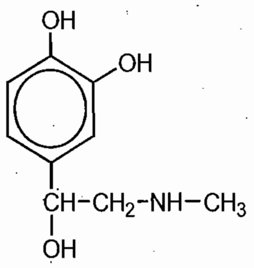
Hordenine: M.P. 117–118 °C.





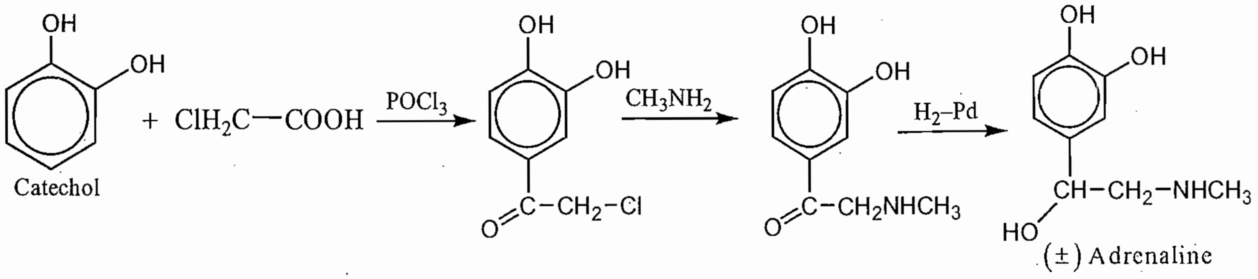
Adrenaline:

- Molecular formula $C_9H_{13}NO_3$.
- Non-steroid hormone.
- Ist hormone to be isolated in a cystalline form.
- It raises the blood-pressure, and is used locally to stop haemorrhage.



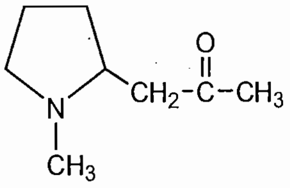
(±) Adrenaline

Synthesis:



9.16. Pyrrolidine Group :

Hygrine: Molecular formula is $C_8H_{15}NO$, B.P. 193–195° C.



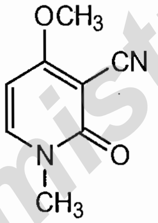
(±) Hygrine

Pyridine and piperidine groups:

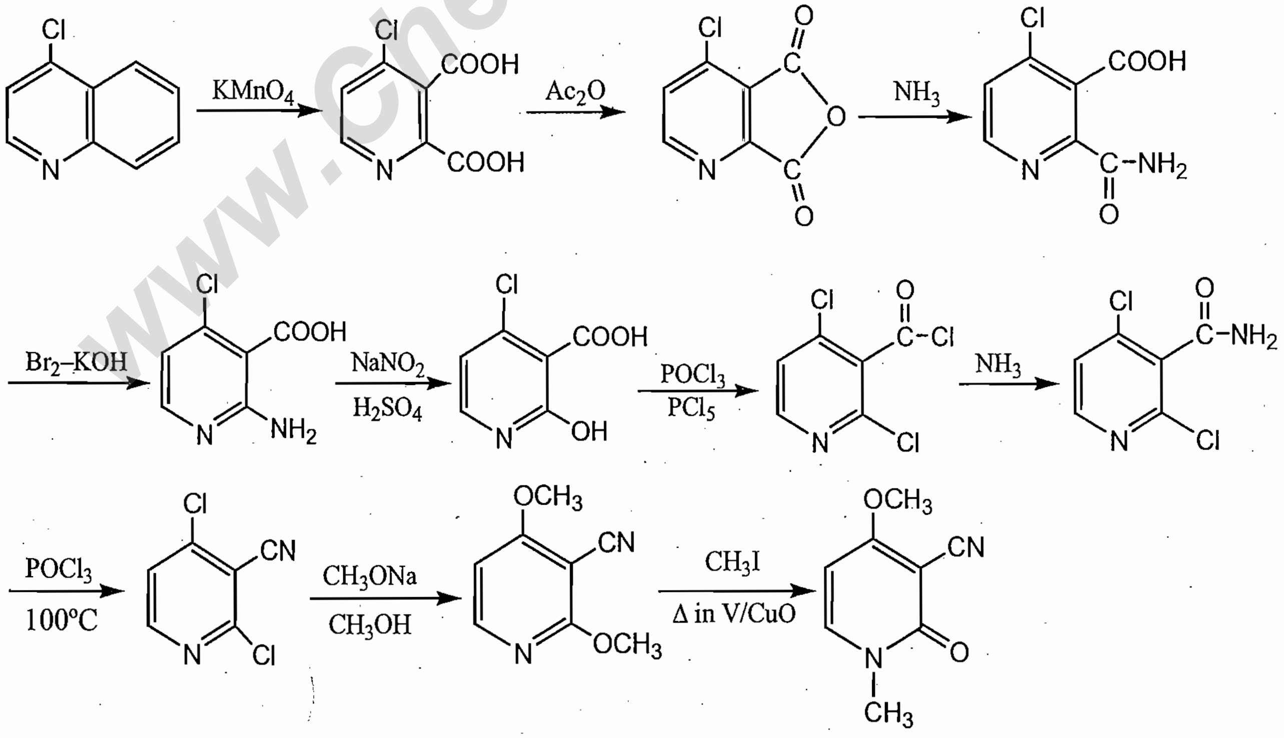
Ricinine: Molecular formula – $C_8H_8N_2O_2$, M.P. 201.5° C

- Isolated from castor-oil seed. It is not a very toxic alkaloid.

Structure of Ricinine:



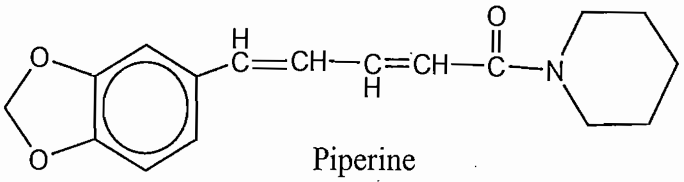
Synthesis of Ricinine:



Piperine:

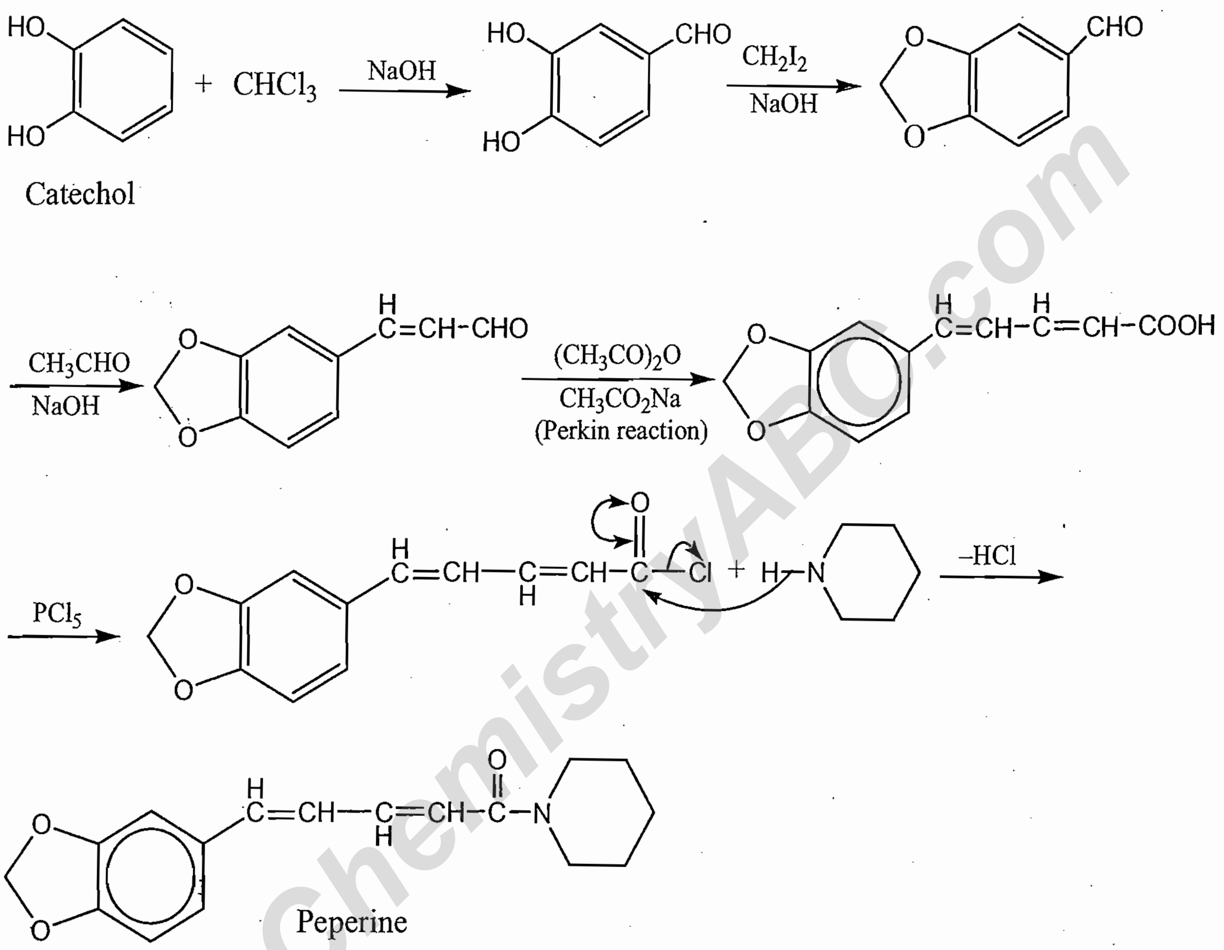
Molecular formula – $C_{17}H_{19}NO_3$, M.P. 128–129.5°C

- This occur in papper, especially black papper.



Piperine

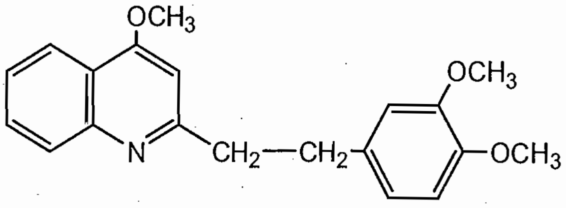
Synthesis:



9.17. Guinoline Group :

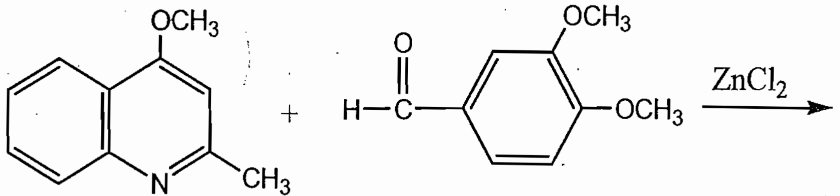
Galipine:

Molecular formula $C_{20}H_{21}NO_3$, M.P. 113°C.

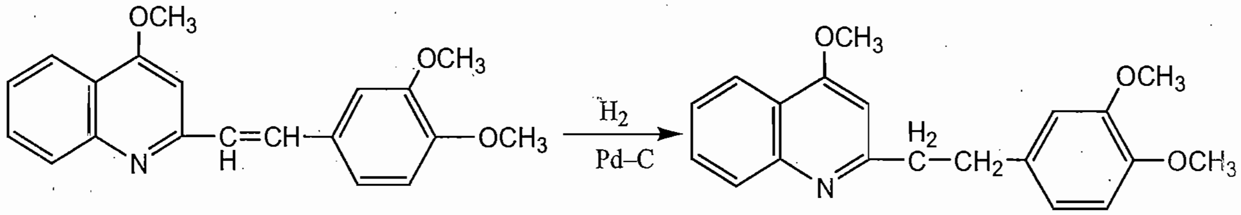


Galipine

Synthesis:



Vertraldehyde



Galipine

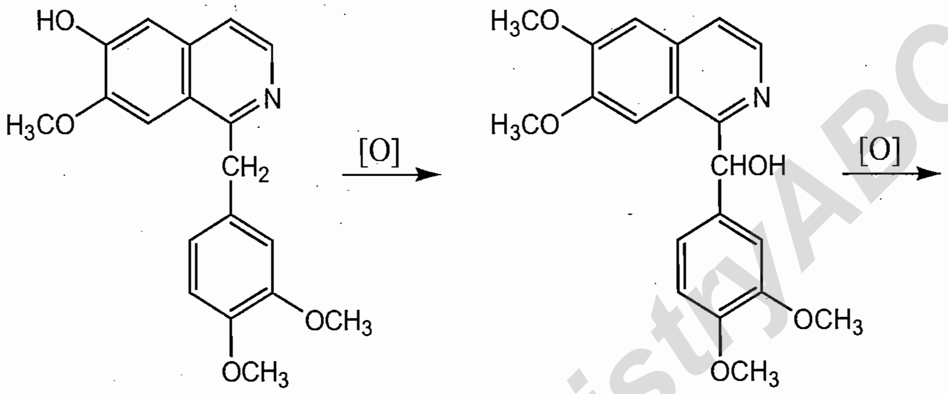
9.18. Isoquinoline Group :

Opium Alkaloids: Many alkaloids have been isolated from opium, and they are divided into two groups according to the nature of their structure.

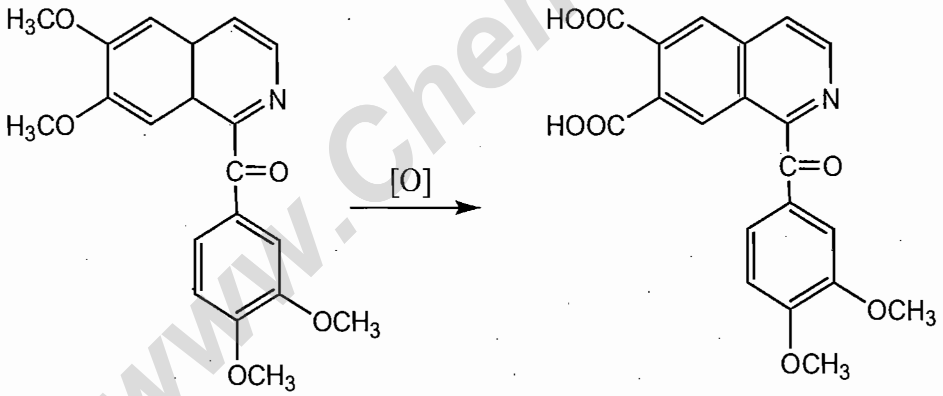
(i) Isoquinoline group, for example Papaverine, Laudanosine etc.

(ii) Phenanthrene group, for example morphine.

Papaverine: Molecular formula $C_{20}H_{21}NO_4$, M.P. 147°C.
Optically inactive alkaloids, does not contain any chiral centre.



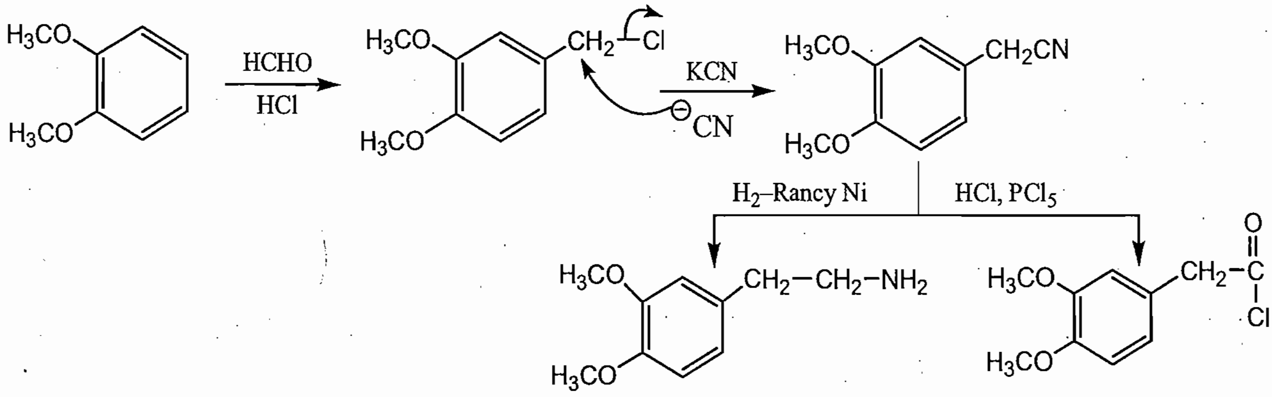
Papaverine

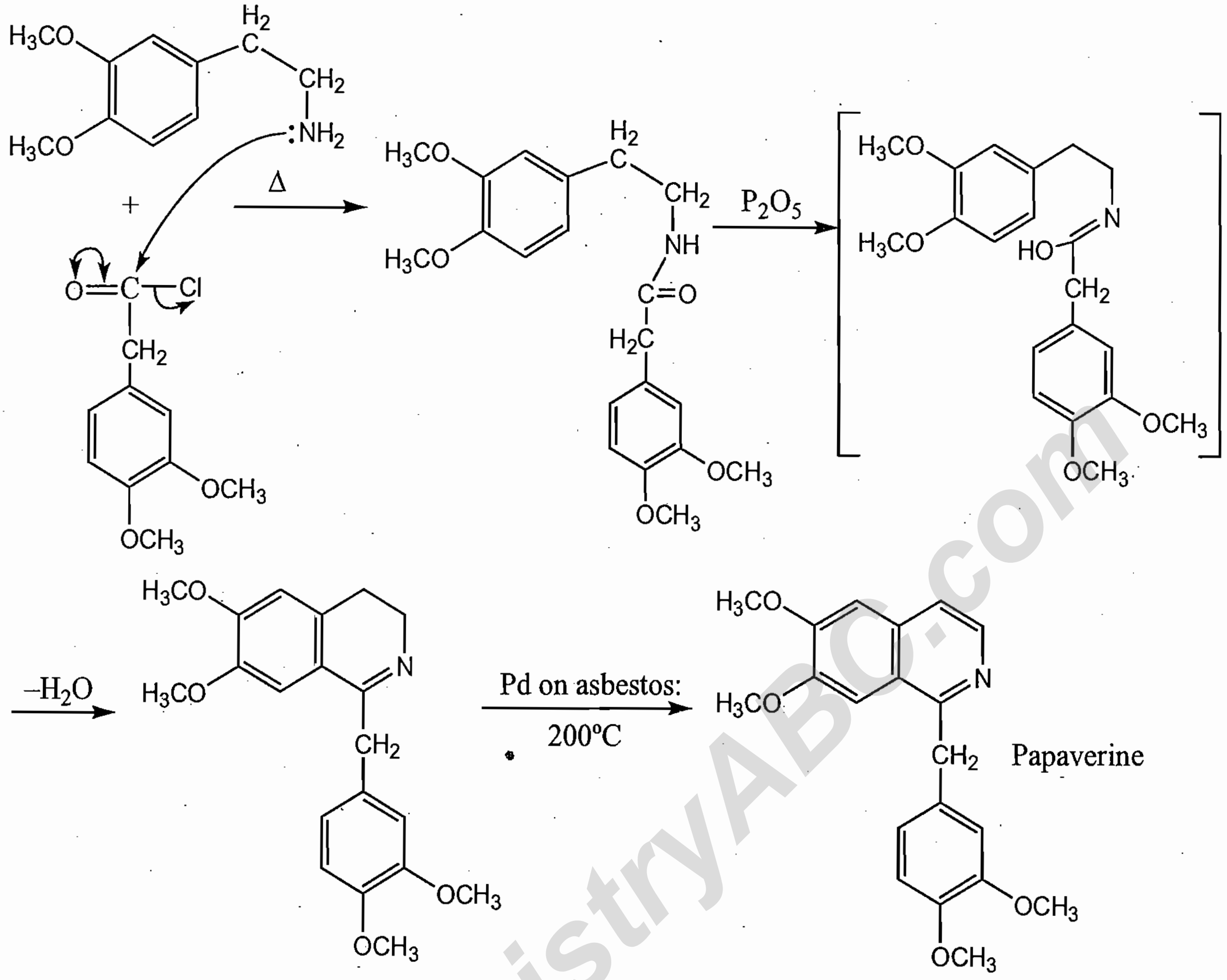


Papaveraldine

Papaverinic acid

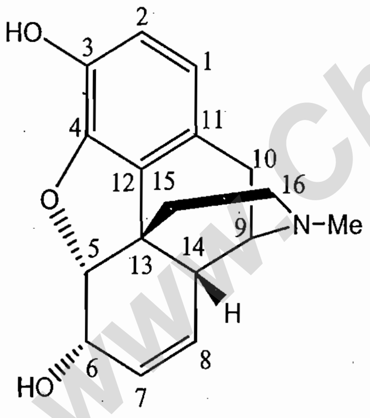
Synthesis:



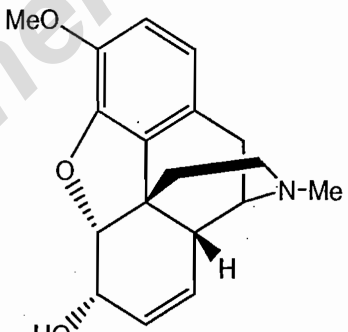


Papaverine

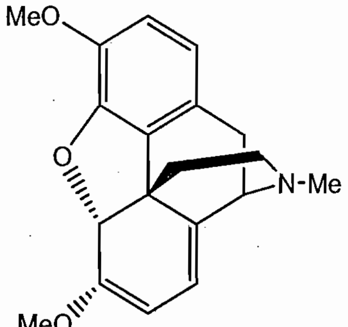
Phenanthrene group:
Morphine, Codeine and Thebaine:



Morphine



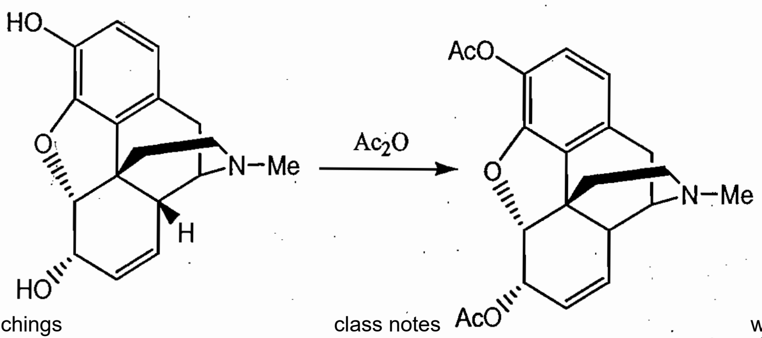
Codeine



Thebaine

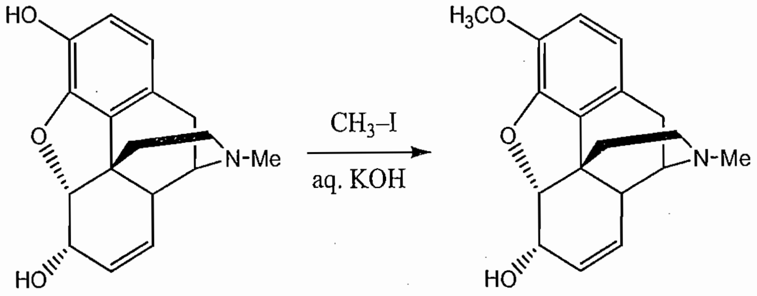
Morphine: Molecular formula $C_{17}H_{19}NO_3$, M.P. 254°C

- Morphine is the chief alkaloid in opium.
- The diacetyl derivative of morphine is known as Heroin.



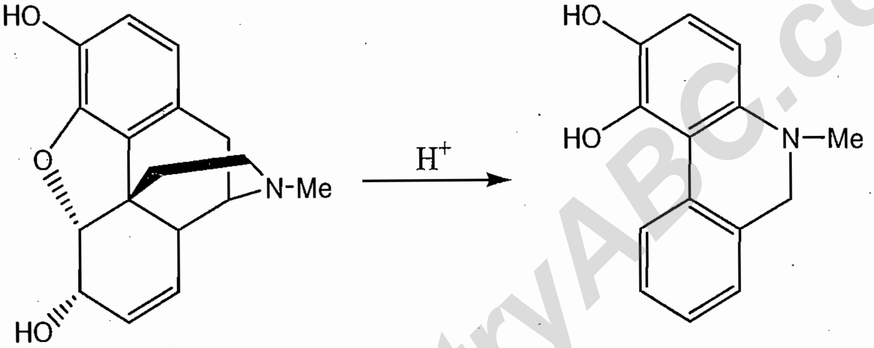
Heroine (diacetyl derivative of morphine)

- When heated with methyl iodide in the presence of aqueous potassium hydroxide, morphine methylated to give codeine.



Codeine

- Morphine when heated with concentrated hydrochloride undergoes rearrangement to form apomorphine. This rearrangement occurs with the loss of the elements of water $(C_{17}H_{19}NO_3 \rightarrow C_{17}H_{17}NO_3)$

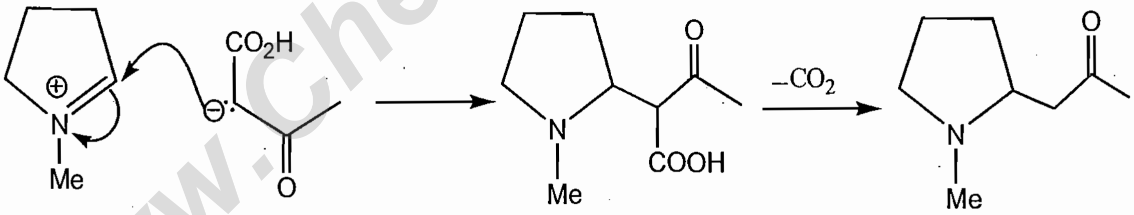


Morphine

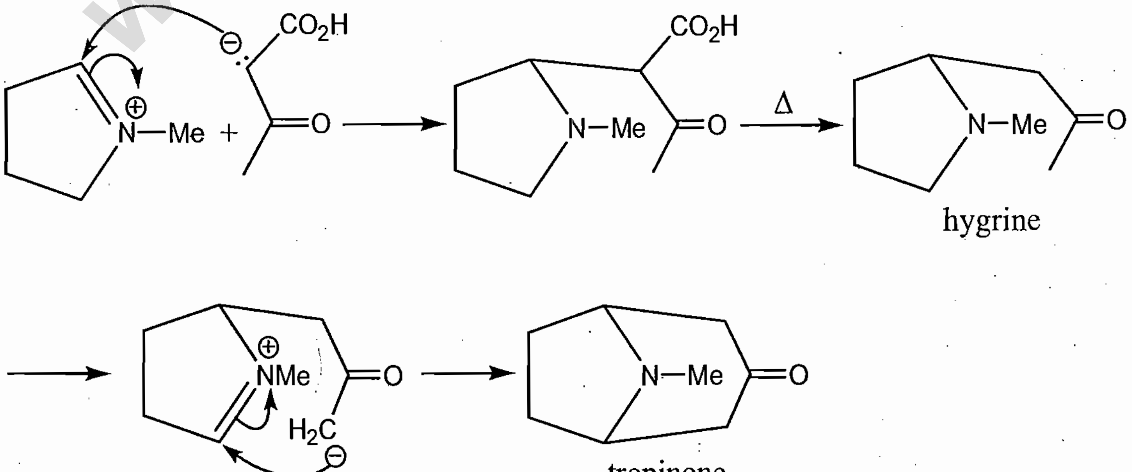
Apomorphine

The details of the mechanism for morphine apomorphine is uncertain.

9.19. Pyrrolidine Alkaloids :



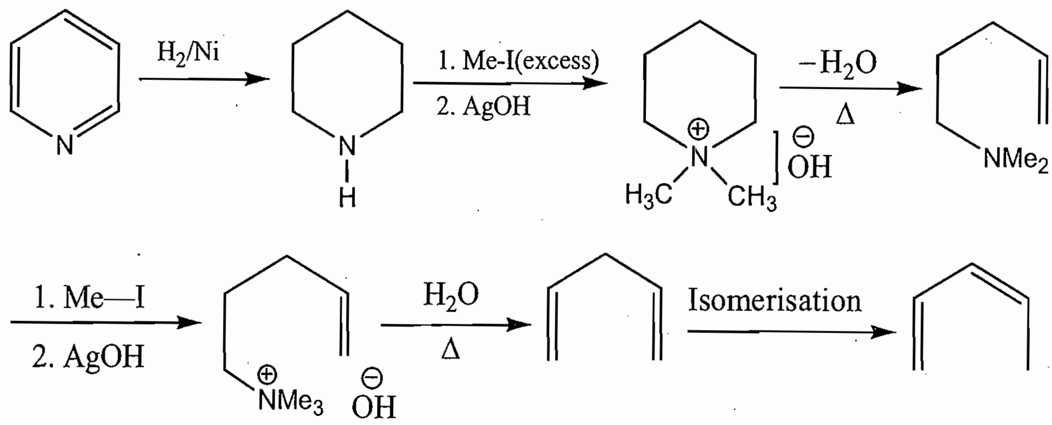
Tropane alkaloids:

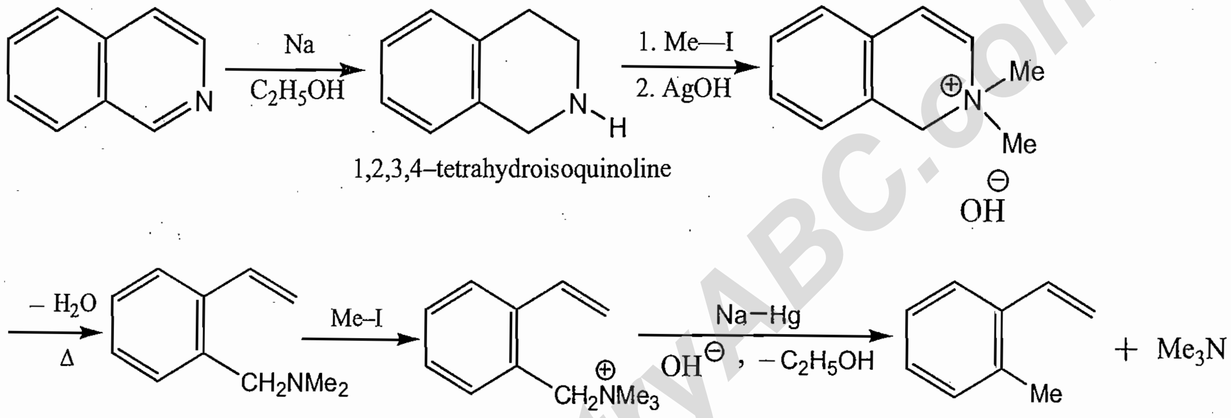


hygrine

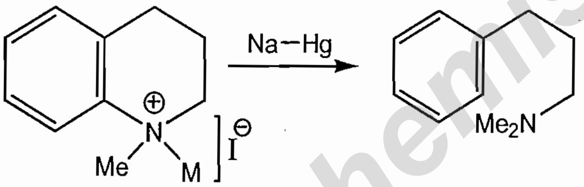
tropinone

Hofmann's exhaustive methylation of alkaloids:

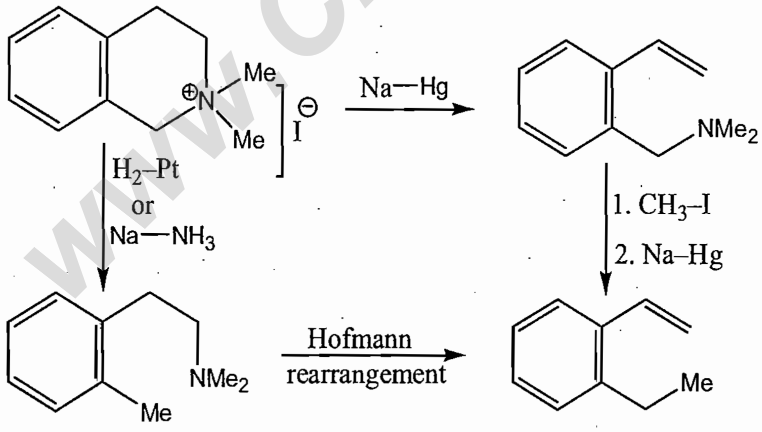




The exhaustive methylation fails with tetrahedroquinoline. However, the heterocyclic ring is opened by the Emde degradation.



The Emde degradation on tetrahydroisoquinoline is also interesting.



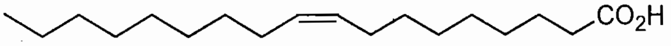
9.20. Fatty Acids :

Fatty acids: refer to long, straight - chain saturated and unsaturated acids, typically from C_{12}—C_{20}.
Saturated fatty acids:

$CH_3(CH_2)_nCO_2H$

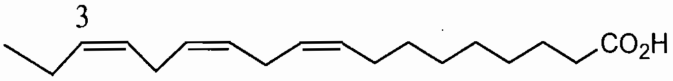
n = 10, lauric acid (C_{12})
n = 12, myristic acid (C_{14})
n = 14, palmitic acid (C16)
n = 16, steric acid (C_{18})

unsaturated fatty acid.

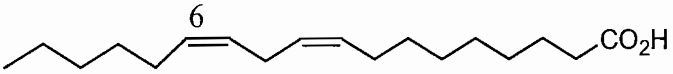


C_{18}, oleic acid

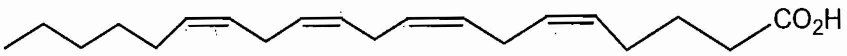
Polyunsaturated fatty acids.



C_{18}, linolenic acid (18:3)

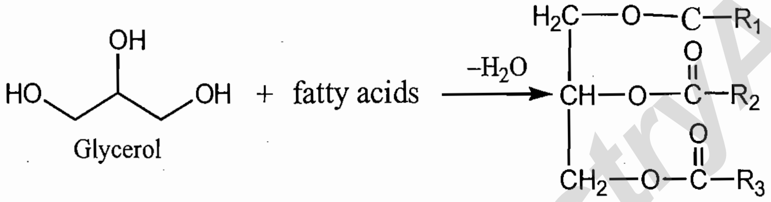


C_{18}, linoleic acid (18:4)

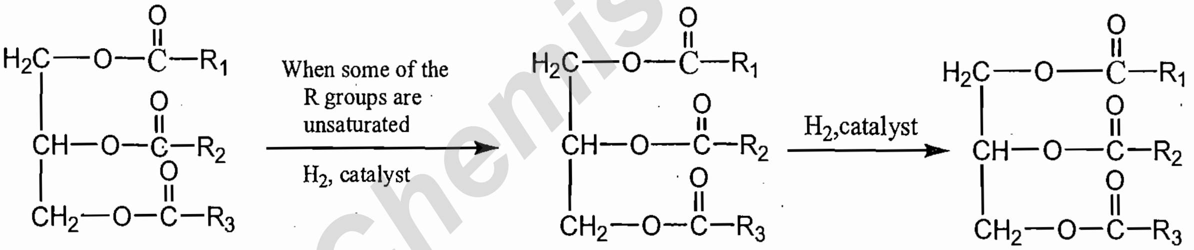


C_{20}, arachidonic acid (20:4)

Fats and Oils: Triglycerides (triacylglycerols) are tri-esters of glycerol (1, 2, 3-trihydroxypropane) and fatty acids.



The R groups can be saturated or unsaturated the same or different.



Partially hydrogenated, some cis double bond are isomerized to trans double bonds.

Hydrogenated- only saturated fatty acids.