→ Heterocyclic compounds:→

- Heterocyclic compounds are the cyclic compounds having more than one type of atoms in the ring. (hetero → other + cyclic)
- Heterocyclic compounds are of great importance to life and occur in nature.

Example:-
- Carbohydrates (Pyranose and furanose)
- Nucleic acid
- Amino acids
- Pepties
- Proteins and alkaloids possess nitrogen containing ring system.

- Many heterocyclic compounds are manfactured by drug industries.

→ Nomenclature:-

- Heterocyclic compounds exist in both simple and condensed ring system.
- Most of heterocyclic compounds have been assigned trivial names which are difficult to replace by systematic names.
- Heterocyclic compounds are named on the basis of size of ring, number, type and positions of heteroatom(s) by providing suitable suffix and prefix to a given system.

1. Size of ring is denoted by stem.

stem	ring size	stem	ring size
ir	3	ep	7
et	4	oc	8
ol	5	on	9
in	6		

2. Following prefixes are used for heteroatoms -

heteroatom	Prefix
O	-oxa
S	- thia
N	- aza
P	- phospha

3. If more than one heteroatoms are present then following sequence is followed for naming.

O > S > N > P

4. Numbering of ring begins with heteroatom and proceeds in such a way that all the substituents get lowest positions.

5. In case of more than one heteroatoms, numbering is done according to the following sequence

O > S > N > P

6. Following suffixes are used for heterocyclic compounds.

Ring size	Stem	With nitrogen		Without nitrogen	
		Unsaturated	Saturated	Unsaturated	Saturated
3	—ir—	—irine	—iridine	—irane	—irane
4	—et—	—ete	—etidine	—ete	—etane
5	—ol—	—ole	—olidine	—ole	—olane
6	—in—	—ine	—inane	—in	—ane
7	—ep—	—epine	—epane	—epine	—epane

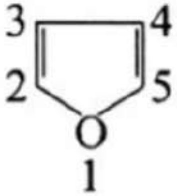
7. Heterocyclic compounds which are partially reduced are often refrred to as dihydro (1 double bond replaced by 2 hydrogens) and tetrahydro (2 double bonds replaced by 4 hydrogens) derivatives of the parent unsaturated compound.

The prefix for saturated nitrogen containing heterocyclic compound is perhydro–

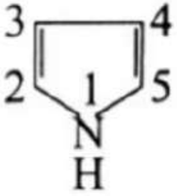
8. When the name contains two vowels coming together, then a of prefix is removed.

Ethylene oxide
(Oxirane)

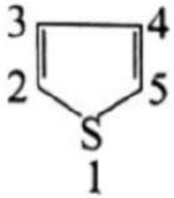
Ethyleneimine
(Aziridine)



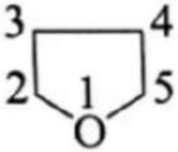
Furan
(Oxole)



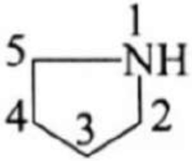
Pyrrole
(Azole)



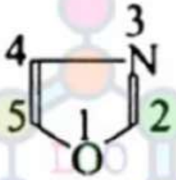
Thiophene
(Thiole)



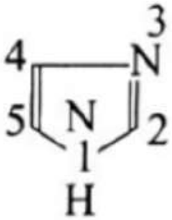
Tetrahydrofuran
(Oxolane)



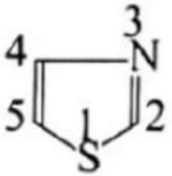
Pyrrolidine
(Azolidine)



Oxazole
(1,3-Oxazole)



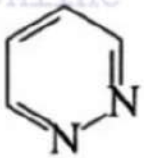
Imidazole
(1,3-Diazole)



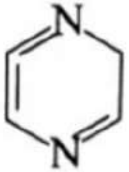
Thiazole
(1,3-Thiazole)

Pyridine
(Azine)

Piperidine
(Perhydroazine)



Pyridazine
(1,2-Diazine)

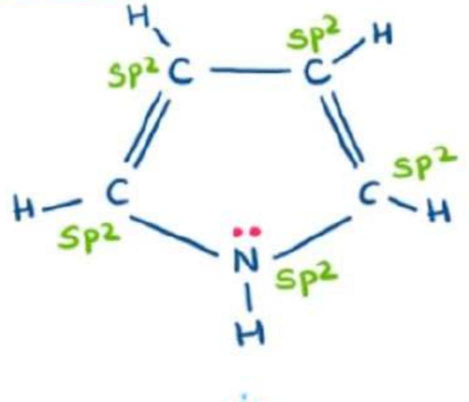


Pyrazine
(1,4-Diazine)

(✱ IUPAC name is given in parantheses)

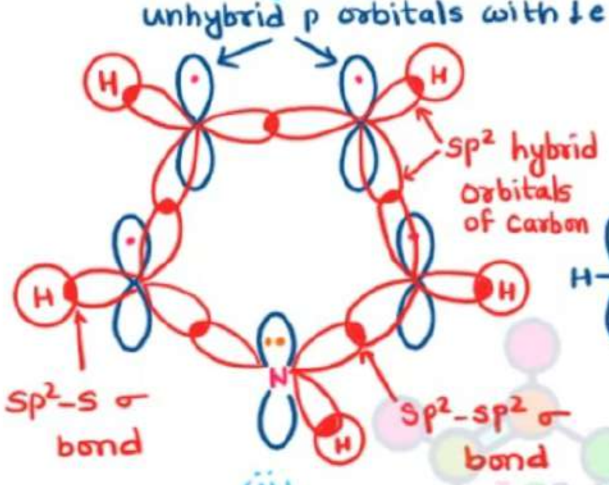
→ Molecular orbital picture of heterocyclic compounds:-

1. Pyrrole :-



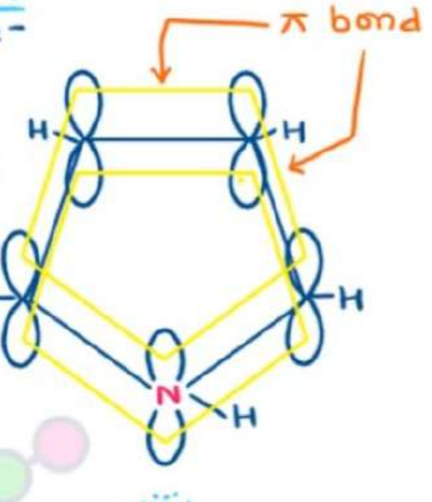
(i)

Pyrrole structure



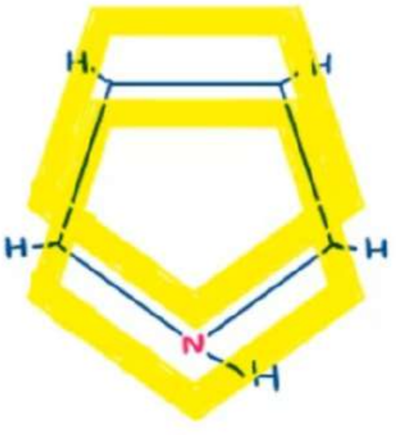
(ii)

formation of σ-bonds by overlapping.



(iii)

formation of π bonds by overlapping

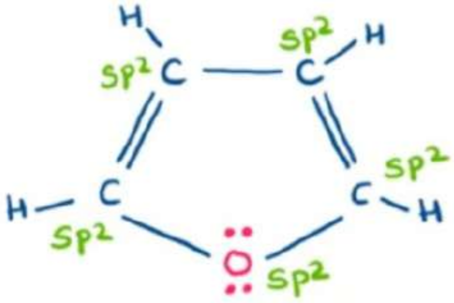


(iv)

π-e⁻ cloud lying above and below the plane of ring

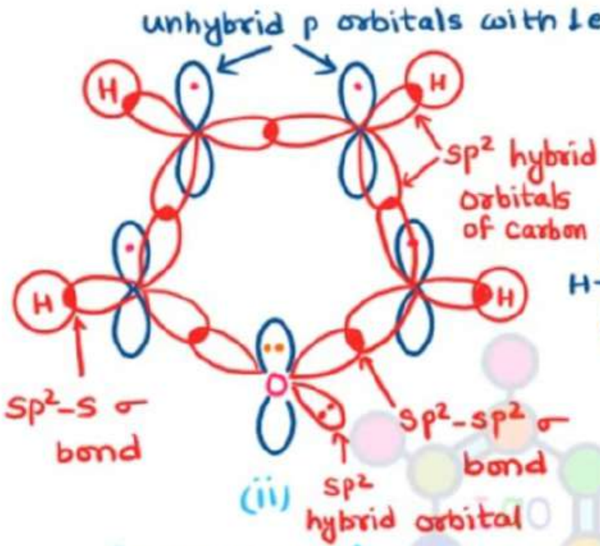
- All carbon atoms - sp²
- Nitrogen atom - sp²
- two adjacent atoms forms sp²-sp² σ bond by overlapping and third sp² hybridised atom forms sp² - s σ bond with hydrogen
- unhybridised p orbitals of C-atoms containing 1 e- are lying perpendicular to plane of ring
- One lone pair of Nitrogen also lying perpendicular to plane of ring.
- unhybridised p-orbitals forms π-bonds by overlapping.
- In π-molecular orbitals 6 π e- are delocalised. (aromatic character)

2. Furan :–



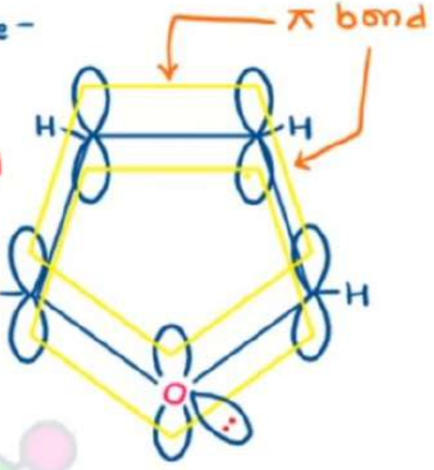
(i)

Furan structure



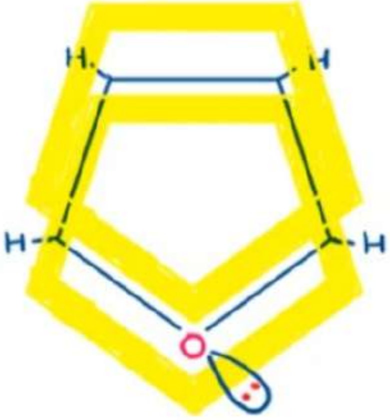
(ii)

formation of σ bonds by overlapping



(iii)

formation of π bonds by overlapping

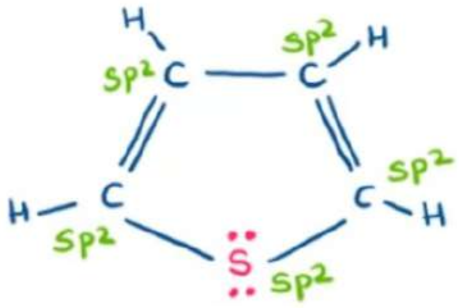


(iv)

π - e⁻ cloud lying above and below the plane of ring

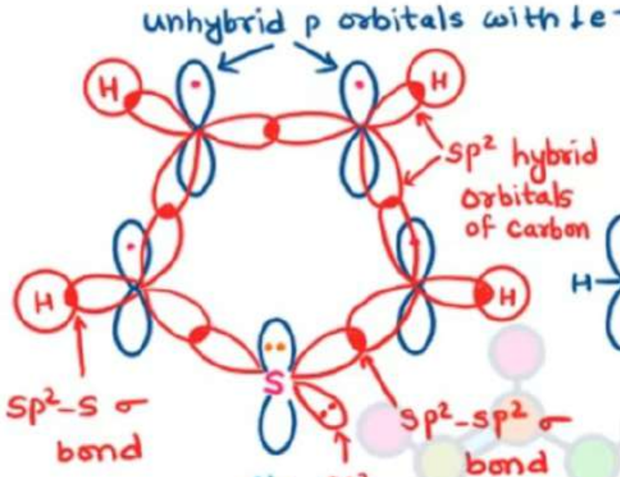
- All carbon atoms - sp^2 – Oxygen atom - sp^2
- two adjacent atoms forms sp^2-sp^2 σ bond by overlapping and third sp^2 hybridised atom forms sp^2-s σ bond with hydrogen
- unhybridised p orbitals of C-atoms containing 1 e⁻ are lying perpendicular to plane of ring
- One unhybridised p-orbital of O containing 1 e⁻ pair lying perpendicular to plane of ring
- one sp^2 hybridised orbital of O containing 1 e⁻ pair lying in the plane of ring.
- unhybridised p-orbitals forms π-bonds by overlapping.
- In π-molecular orbitals 6 π e⁻ are delocalised. (aromatic character)

3. Thiophene :-



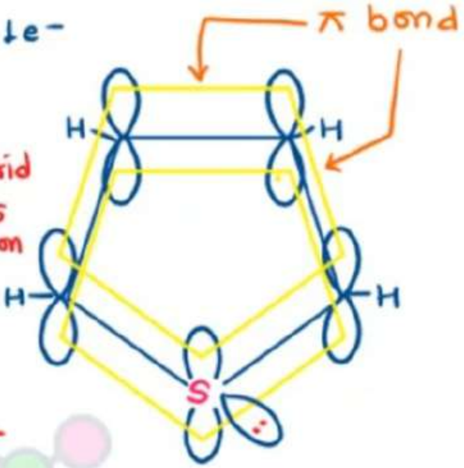
(i)

Thiophene structure



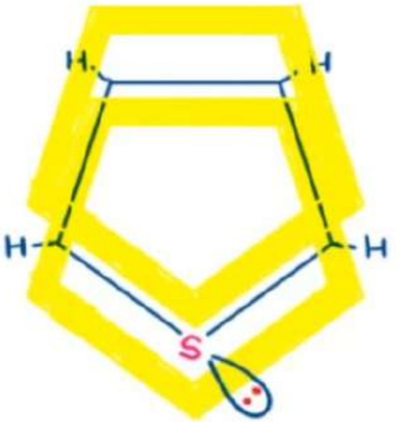
(ii)

formation of σ bonds by overlapping



(iii)

formation of π bonds by overlapping

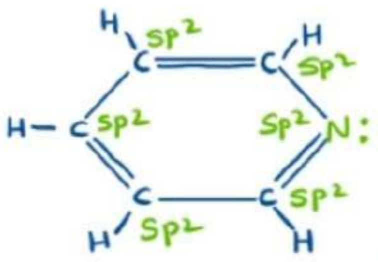


(iv)

π - e⁻ cloud lying above and below the plane of ring

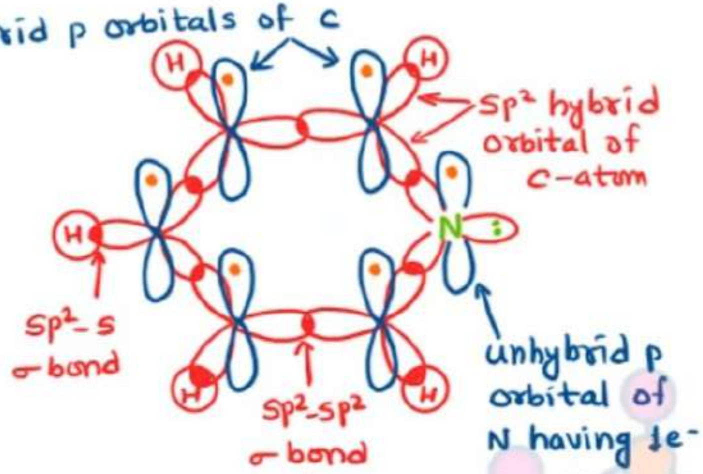
- All carbon atoms - sp² — Sulphur atom - sp²
- two adjacent atoms forms sp²- sp² σ bond by overlapping and third sp² hybridised atom forms sp² - s σ bond with hydrogen
- unhybridised p orbitals of c-atoms containing 1 e⁻ are lying perpendicular to plane of ring
- One unhybridised p-orbital of s containing 1 e⁻ pair lying perpendicular to plane of ring.
- one sp² hybridised orbital of s containing 1 e⁻ pair lying in the plane of ring.
- unhybridised p-orbitals forms π-bonds by overlapping.
- In π - molecular orbitals 6 π e⁻ are delocalised. (aromatic character)

4. Pyridine:-



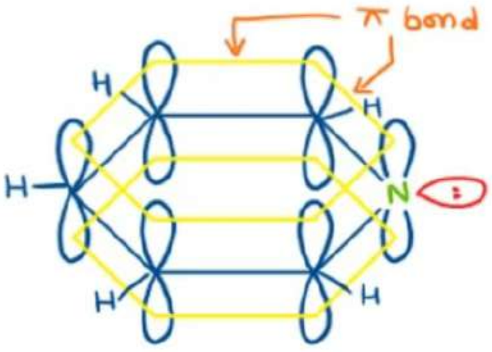
(i)

Pyridine structure



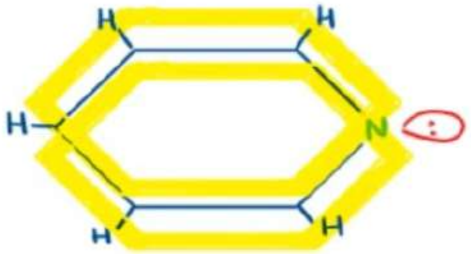
(ii)

σ- bond formation by overlapping



(iii)

π -bond formation by overlapping



(iv)

π - e⁻ cloud lying above and below the plane of ring

- Carbon atom - sp^2 - Nitrogen atom - sp^2
- lone pair of Nitrogen atom lie in the plane of ring i.e. sp^2 hybrid orbitals.
- Six unhybrid p orbitals (5 of carbon + 1 of Nitrogen) are perpendicular to plane of the ring and form π- bonds

→ Aromatic characteristics of heterocyclic compounds:→

→ Pyrrole, Furan and Thiophene (five membered heterocyclic compounds):-

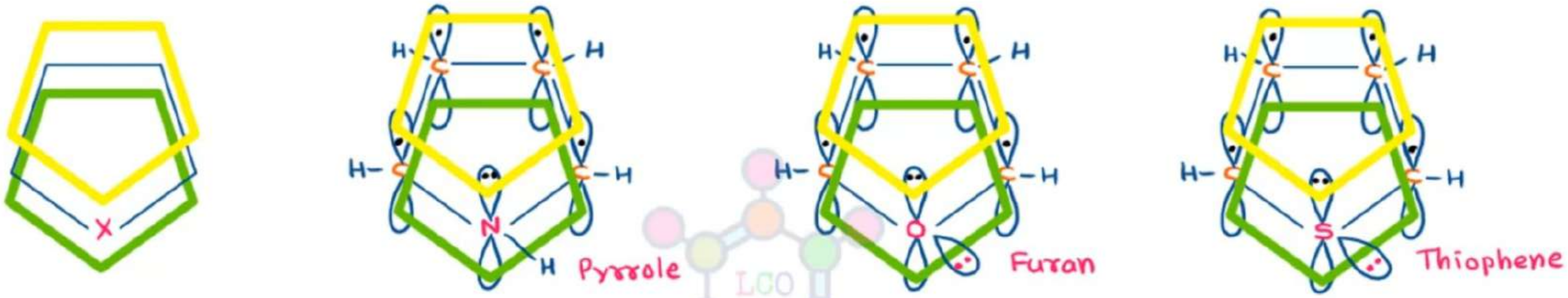


fig:- overlap of unhybridised p-orbitals of Pyrrole, Furan & Thiophene

- The aromatic character of these compounds arises from the delocalisation of four carbon π- electrons and two paired e^- donated by heteroatom (O, N or S), thus forming a sextet of electrons which is characteristic of the aromatic system.
- These compounds follow Huckel's Rule $(4n+2)\pi e^-$, due to 6 delocalised π electrons.
- The π electron cloud of these compounds is lie above and below the plane of the ring.

→ Resonance structures :→

- Pyrrole, Furan and Thiophene molecules are considered as resonance hybrid of the following contributing forms –

1. Pyrrole

2. Furan

3. Thiophene

- These structure have charge separation whereas two resonance structures of benzene do not involve charge separation. Due to charge separation stabilisation energies of these compounds are approximately half of that of benzene.

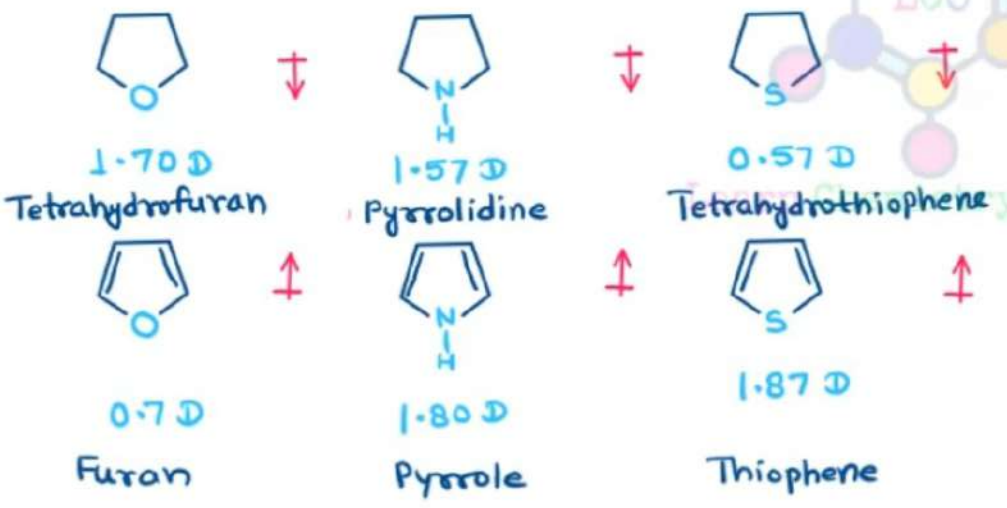
→ Evidence:- There are many evidences which support the above mentioned delocalised structures or resonance structures.

1. Bond length:→

- The bonds of these compounds are intermediate in length between the normal single and double bond lengths for C–C, C–N, C–S and C–O bonds.

2. Dipole moment :→

- If we compare dipole moments of these compounds with suitable reference compounds then this indicates delocalisation of e⁻ pair into the ring.



Direction of normal dipole moments of C–X bond

Direction of the dipole moments due to delocalisation

→ Relative aromatic character :-

- The electronegativities of the heteroatoms are in the order O > N > S.
- This means that oxygen has the least tendency to donate the e^- pair to the aromatic sextet. so the aromatic character should be least in case of furan, followed by pyrrole and maximum for thiophene.

Furan < Pyrrole < Thiophene

Furan < Pyrrole < Thiophene < Benzene.

- These compounds undergo electrophilic substitution reactions rather than addition reactions due to aromatic character.

→ Pyridine (six membered heterocyclic compound) :-

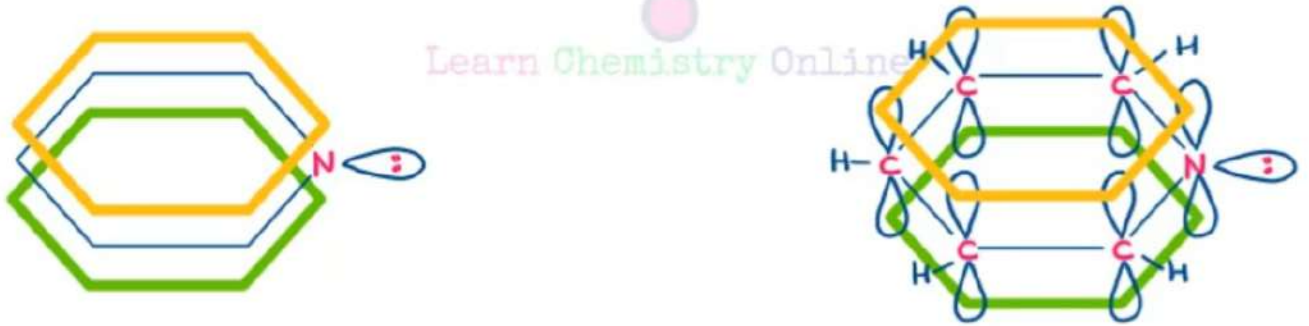


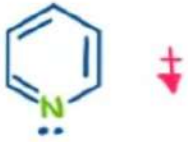
fig:- overlape of unhybridised p-orbitals of Pyridine

- The aromatic character of pyridine arises from the delocalisation of five carbon π e⁻ and one e⁻ of N heteroatom. Thus forming a sextet of electrons which is characteristic of the aromatic system.

→ Resonance structure:-

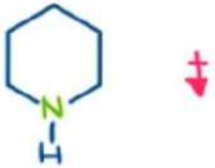
- Pyridine is described as a resonance hybrid of the following contributing forms :-

- The resonance hybrid structure of pyridine not only explains the stability of pyridine ring but is also supported by the bond length data.
- Dipole moment value of pyridine is more than piperidine.



Dipole moment = 2.26 D

Pyridine



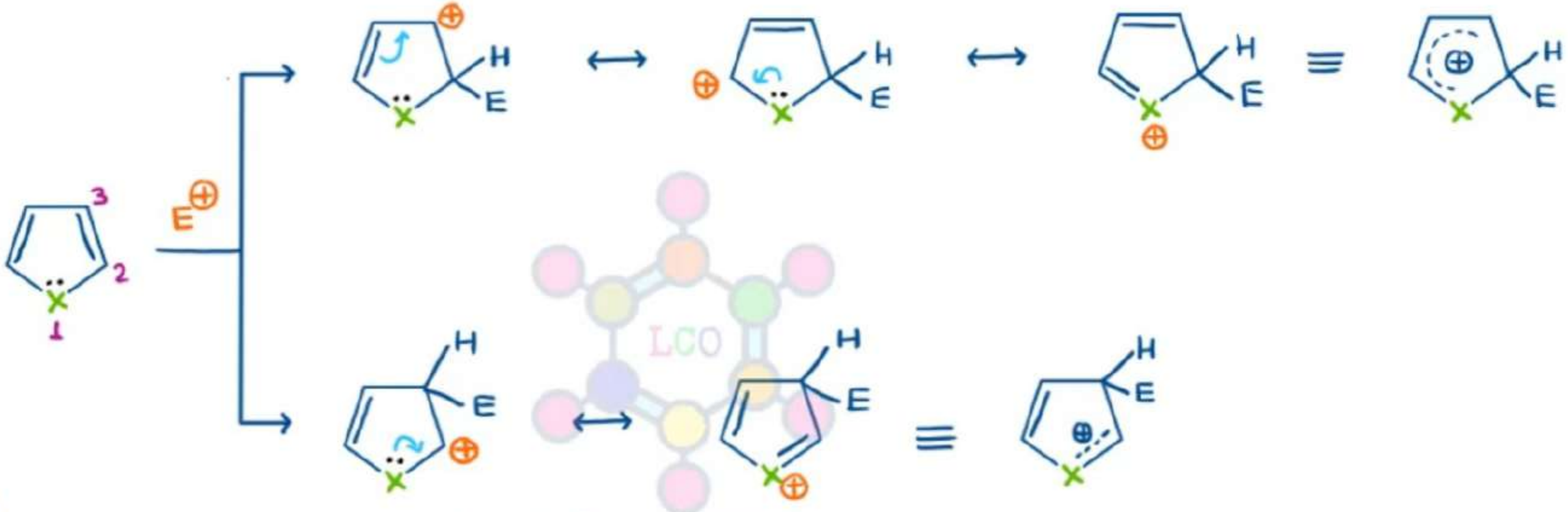
Dipole moment = 1.17 D

piperidine

- In case of pyridine, electronegative nitrogen produces deficiency of electron density in the ring whereas in pyrrole, ring carbons acquire increased electron density. Thus the nitrogen atom in pyridine causes the deactivation ring.

→ Orientation and relative rates of electrophilic substitution in five membered heterocyclic compounds:→

- Consider the attack of an electrophile at positions 2 and 3 of five membered heterocyclic compounds -



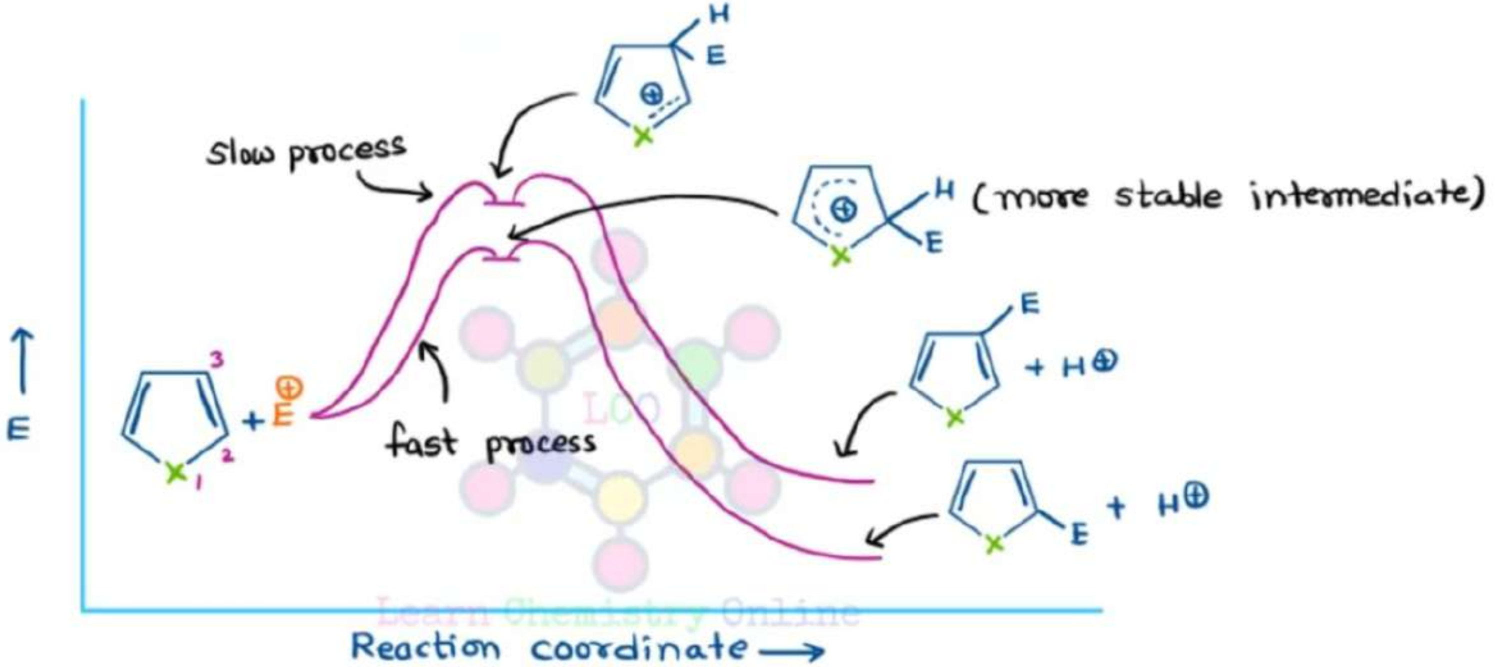
X = O, NH, S

$E^{\oplus}$ = Electrophile

- The above resonance structures show that attack at position 2 will be prefered due to extra stabilisation caused by the contribution of an additional structure.

→ Energy profile diagram:-

- Energy profile diagram shows that a reaction involving a more stable intermediate should be faster.



- The reactivity order of Pyrrole, furan and Thiophene towards electrophilic substitution reaction is

→ Pyrrole :→

- Azole, C_4H_5N ,

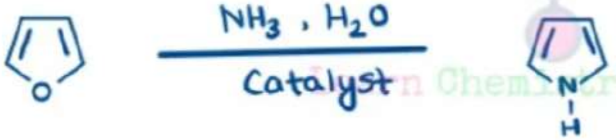
- Pyrrole is found in many naturally - occuring substances such as chlorophyll or alkaloids.
- It occurs in coal-tar and bone oil as well.

→ Methods of formation :→

1. Isolation from bone oil :→

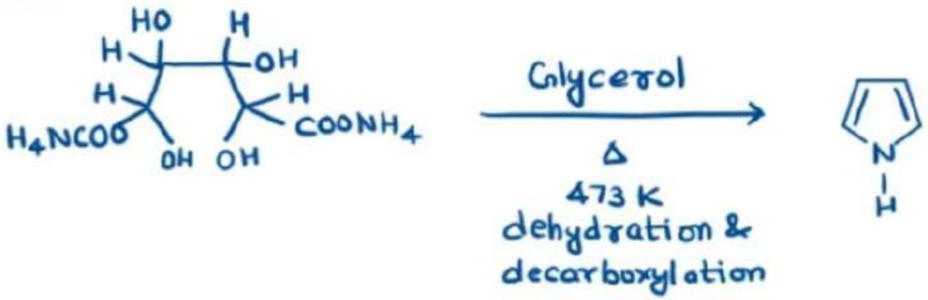
- Pyrrole is prepared commercially by fractional distillation of bone oil which itself obtained from dry distillation of horns, hoofs and bones of animals.

2. From furan :→

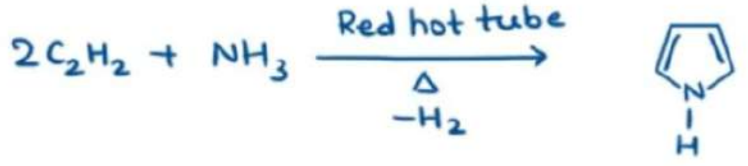


3. From ammonium mucate :→

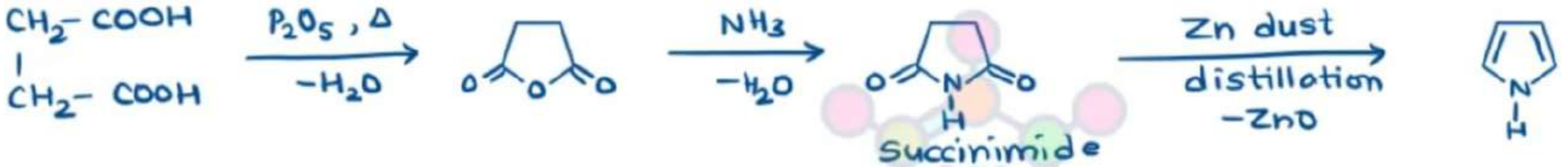
$H_4NOO(CHOH)_4COONH_4 \equiv$



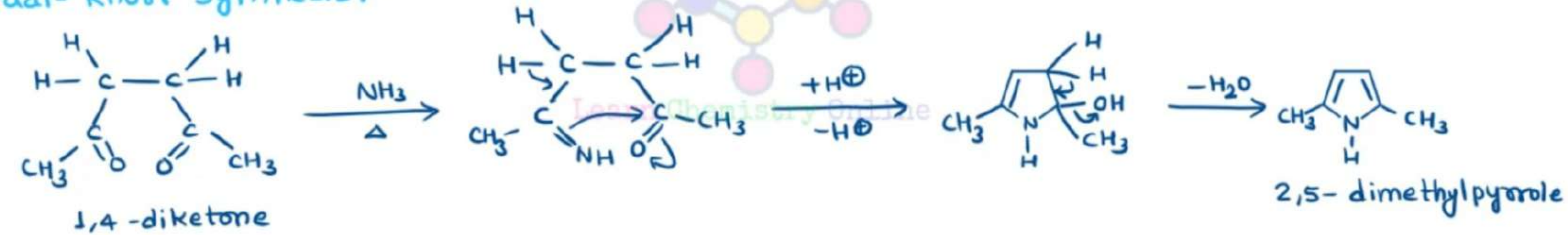
4. From acetylene:-



5. From succinic acid:→

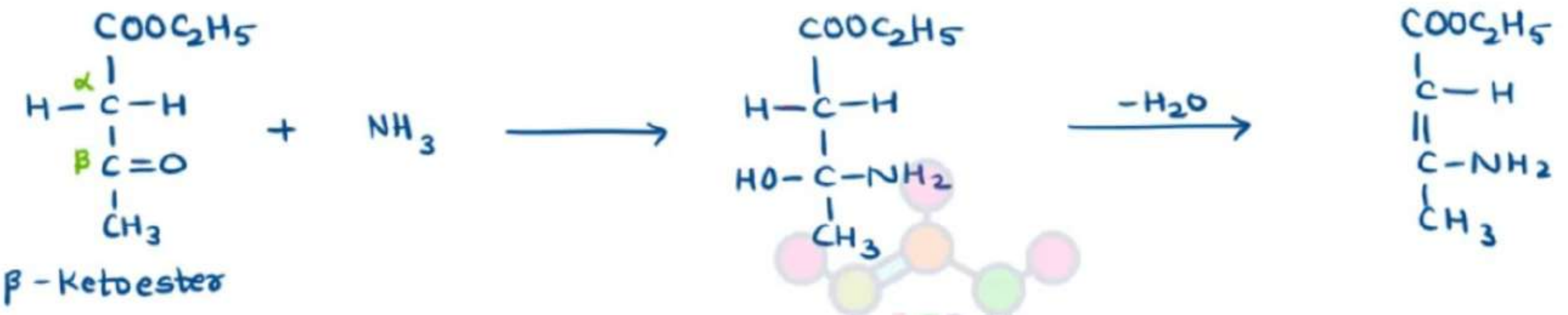


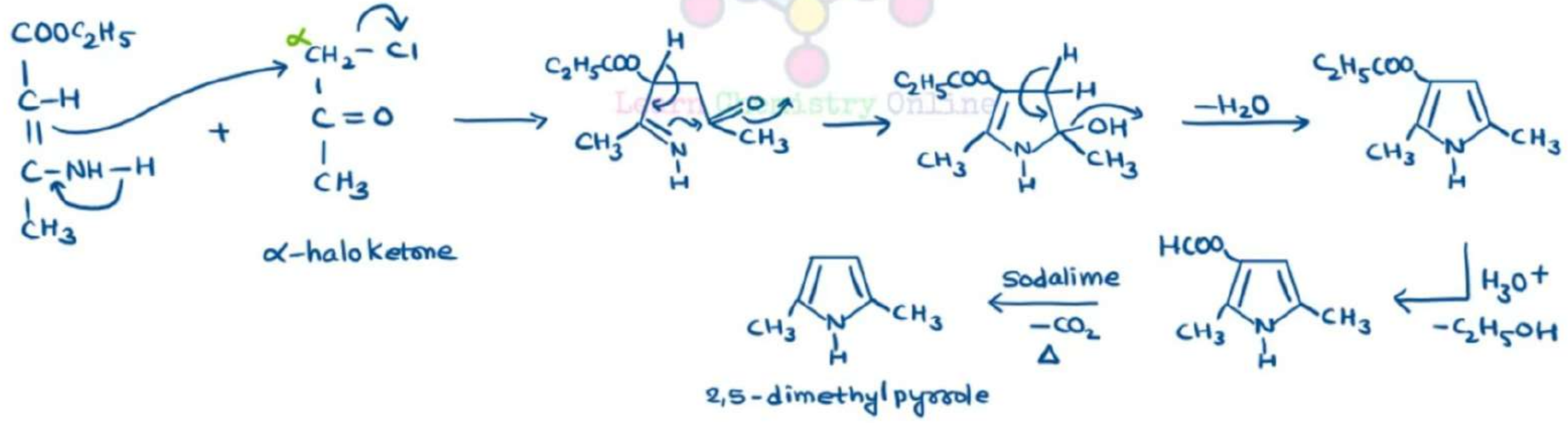
6. Paal- knorr synthesis:-



7. The Hantzsch - pyrrole synthesis:-

- This reaction involves condensation of an α-haloketone with a β-ketoester in presence of ammonia or primary amine.





8. The Knorr-pyrrole synthesis:-

- This method is widely use for synthesis of pyrrole derivatives.
- In this reaction, an α- aminoketone is condensed with β-Ketoester in the presence of acetic acid.

2,4-dicarbethoxy-3,5-dimethylpyrrole

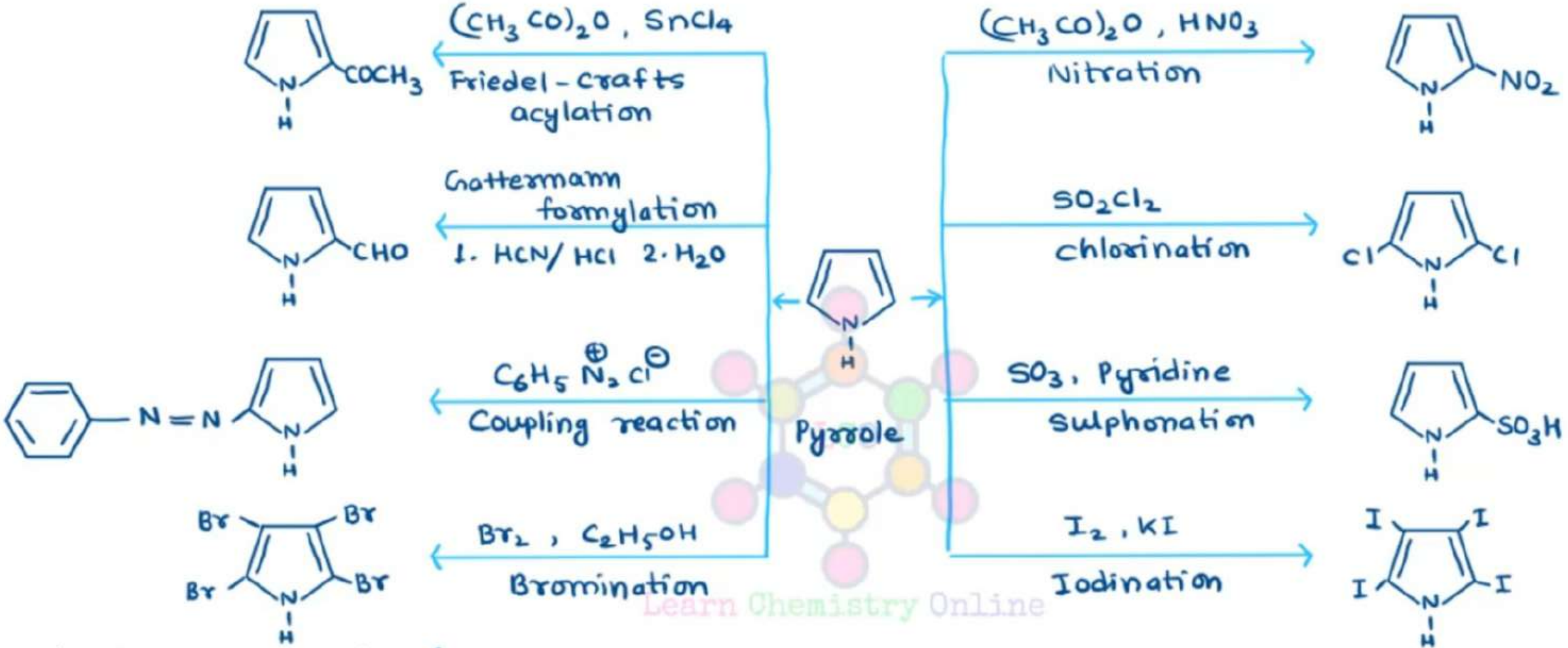
→ Physical properties:-

- Pyrrol is a colourless liquid, which turns brown on exposure to air.
- b.p.- 404 K
- It smells like chloroform.
- It is inosoluble in water but dissolves in alcohol and ether.
- It is extremely weak base because lone pair of nitrogen is used in delocalisation.

→ Chemical properties:-

1. Electrophilic substitution :-

- Pyrrole is very reactive towards electrophilic substitution reactions and substitution takes place at 2-position.

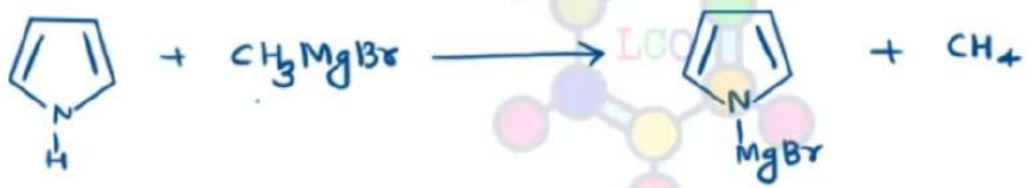


- Due to high reactivity of pyrrol ring, milder reagents/reaction conditions are used. e.g.- Friedel-crafts acylation is carried out with $SnCl_4$ which is weaker lewis acid than anhy. $AlCl_3$.
- As pyrrole polymerises in concn acid solution, nitration is carried out with HNO_3 in acetic acid. similarly sulphonation is carried out with SO_3 in pyridine at 373 K.
- Chlorination is carried out with SO_2Cl_2, bromination with Br_2 in ethanol and iodination with I_2 in KI sol. Bromination and iodination of pyrrole gives tetrasubstituted products.

2. Acidic character:-

- On heating with solid KOH, the imino hydrogen of pyrrole is replaced by potassium showing the acidic character of the substance.

- Further due to the acidic nature, pyrrole reacts with Grignard reagents to form pyrrolylmagnesium halide.

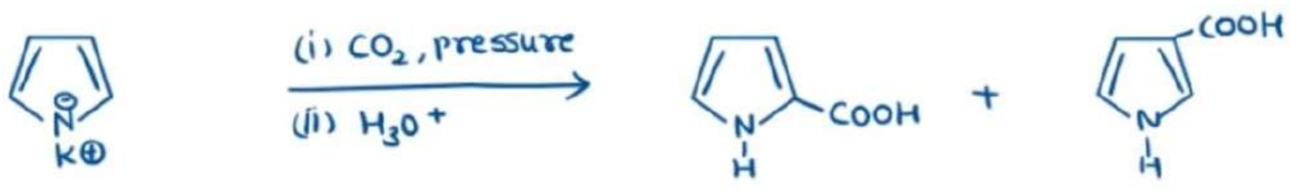


- The acidic character of pyrrole is due to resonance stablised pyrrole anion.

- Due to presence of negative charge on position 2 and 3, pyrrole anion undergo electrophilic substitution reactions at 2 and 3 positions.

- **Example:-**

(i) Kolbe Schmidtt reaction:-

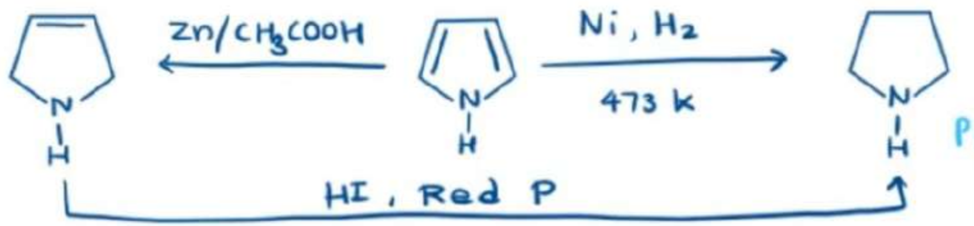


(ii) Reimer- Tiemann reaction:-

3. Basic character:-

- Pyrrole can act as a base by gaining a proton or by combining with a Lewis acid at the hetero atom. but the heteroatom in pyrrole contributes a lone pair of electrons to the $\pi - e^-$ clouds constituting the aromatic sextet.
- As a result, pyrrole cannot readily accept a proton and hence does not possess significant basic character. ($K_b = 2.5 \times 10^{-14}$).

4. Reduction:-



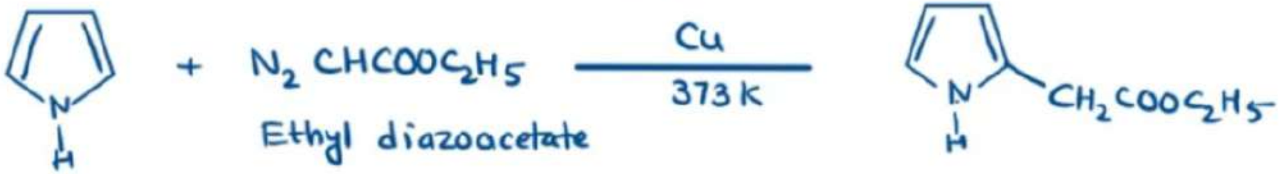
Pyrrolidine (properties similar to 2° aliphatic amine)

5. Reaction with Maleic anhydride:-

- A substitution product is formed.

6. Reaction with carbene:→

- Electrophilic substitution product is formed.



7. Ring cleavage reaction:-

- Pyrrole ring is not cleaved readily by acids and bases. However, when pyrrole is refluxed with an ethanolic solution of hydroxyl amine hydrochloride, the ring cleavage takes place.

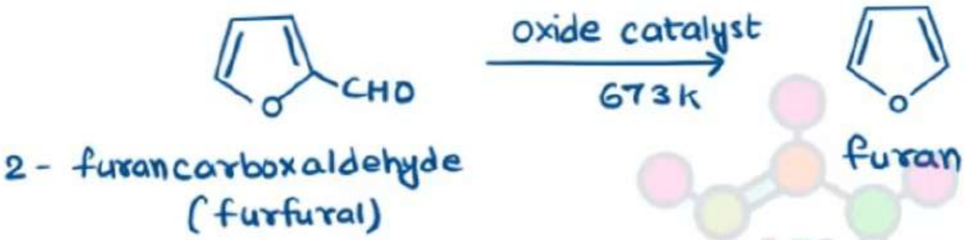
Succinialdehyde dioxime.

→ Furan :→

– Oxole , C_4H_4O , 

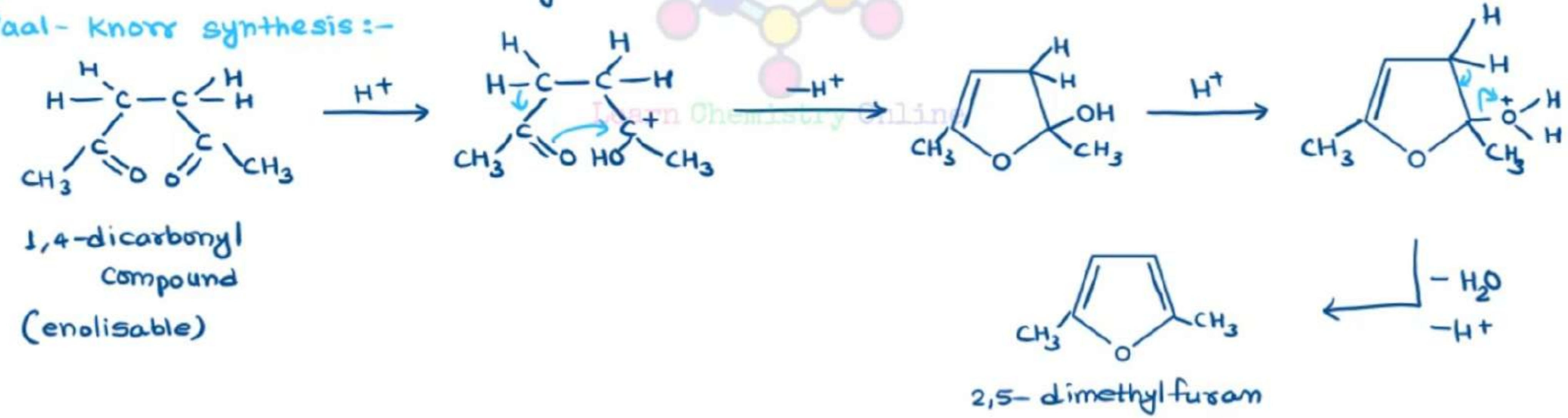
→ Methods of formation :→

1. Commercial method : Decarbonylation of furfural →



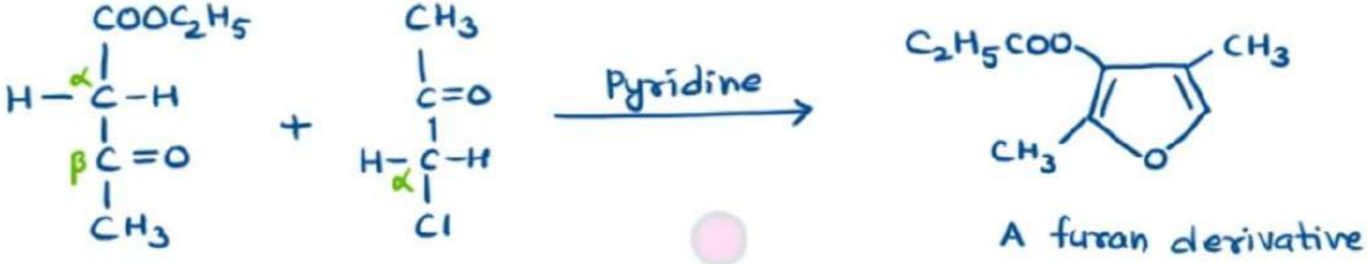
– Furfural is obatiamed from polysaccharides.

2. Paal- Knorr synthesis :-



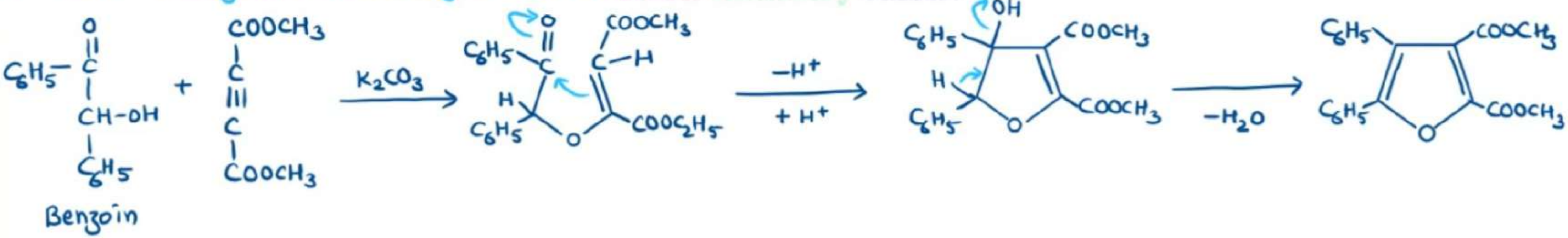
3. Fiest Benary synthesis:-

- β-Ketoester and α-haloketone condensed in the presence of pyridine.



4. From mucic acid:-

5. From acetylene dicarboxylic esters:-



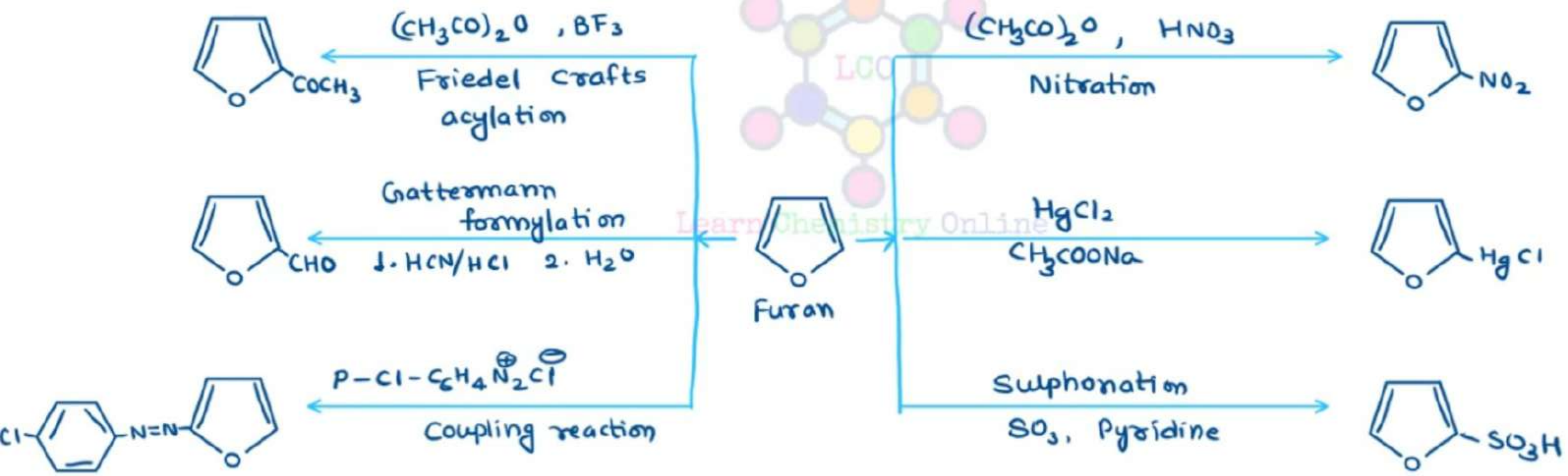
→ Physical properties:→

- Furan is a colourless liquid
- b.p. 305 K
- Odour similar to chloroform.
- Slightly soluble in water but dissolves in alcohol and ether.

→ Chemical reactions:-

1. Electrophilic substitution:-

- Electrophilic substitution takes place at 2-position.



Some important features of electrophilic substitution reactions are-

ⓐ Since acidic conditions leads to polymerisation of furan, care must be taken in selecting appropriate reaction conditions.

<u>Example</u>:- Nitration of furan is perfomed with nitronium acetate, $CH_3CO\overset{\ominus}{O}\overset{\oplus}{N}O_2$ $[(CH_3CO)_2O + HNO_3]$, as the usual nitration mixture ($HNO_3 + H_2SO_4$) cause polymerisation of furan.

ⓑ Similarly furan-2-sulphonic acid is prepared by the action of SO_3 and pyridine on furan.

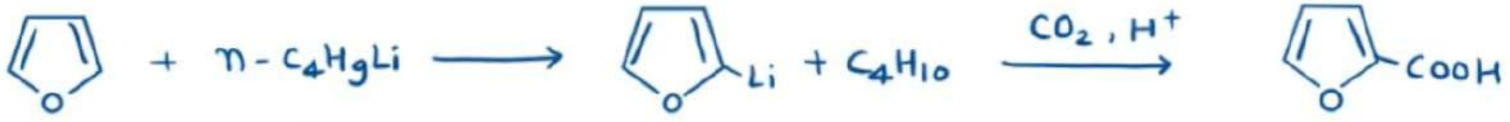
ⓒ Since, halogen acids liberated during halogenation of furan cause polymerisation, therefore halogenated furans are obtained by indirect route.

Furoic acid

2-Bromofuran

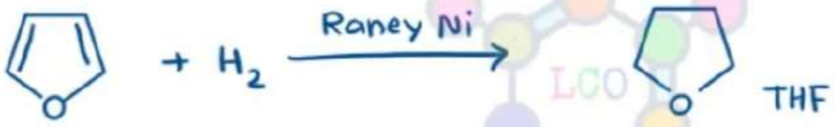
ⓓ 2-chloromercurifuran is a useful synthetic intermediate as the mercury group is a good leaving group.

ⓔ Furoic acid is obtained by treating furan with n-butyllithium followed by the carboxylation of organolithium compound.



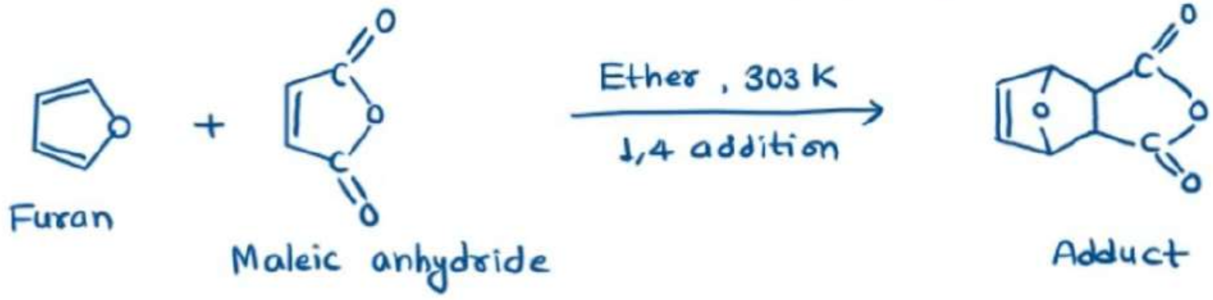
ⓕ like benzaldehyde, furfural on treatment with aq- NaOH undergoes Cannizzaro reaction and on treatment with alcoholic KCN, it undergoes Benzoin condensation.

2. Reduction:-

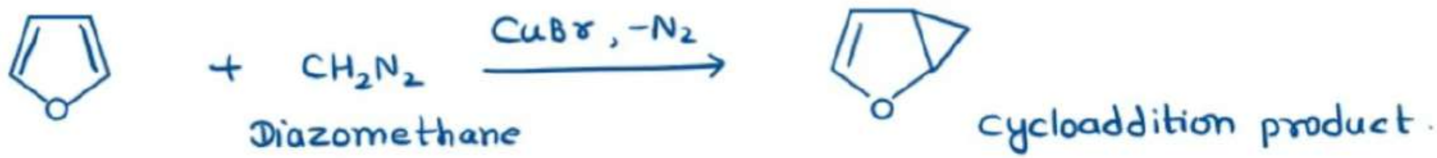


3. Diels-Alder reaction:-

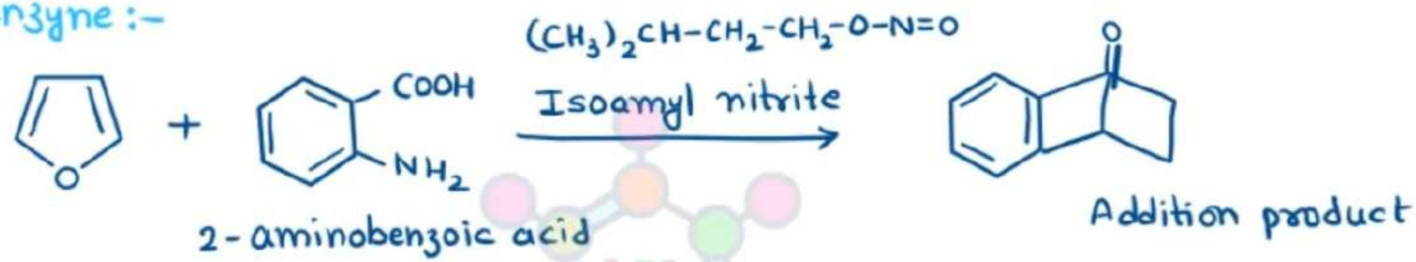
- furan behave as diene due to less aromatic character



4. Reaction with carbene :-

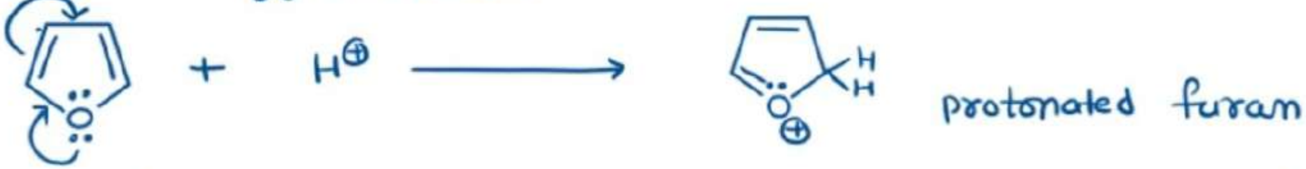


5. Reaction with benzyne :-



6. Basic properties:-

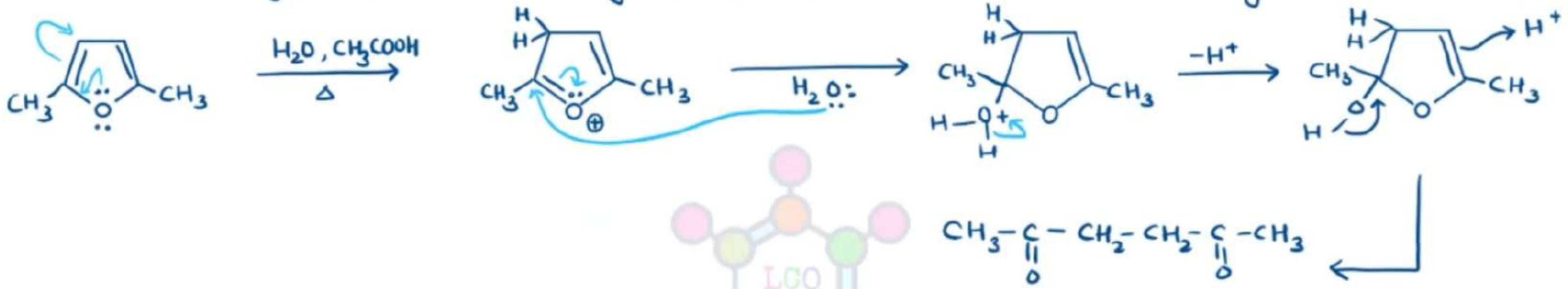
- On treatment with acids, protonation takes place at the ring carbons rather than at oxygen. because if protonation takes place at oxygen, then it inhibit the resonance. As a result stabilisation energy decreases.



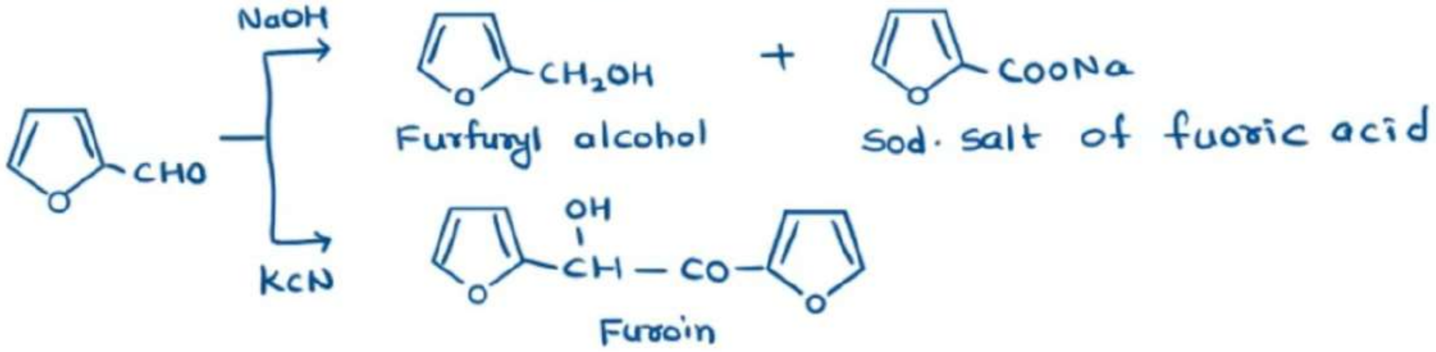
- The protonated furan forms polymeric products by attack on other furan molecule.

7. Ring cleavage:-

- Under careful conditions, furan and its derivatives may undergo ring-opening reactions to give 1,4-dicarbonyl compounds which are useful synthetic intermediates.



- Furfural or furfuroldehyde (furan derivative) is widely used for the preparation of dyes, plastics and as an industrial solvent.
- Furfural gives Cannizzaro reaction, Benzoin condensation and perkin reaction.



→ Thiophene :→

- Thiazole, C_4H_4S, 
- Also called Thiole.
- Thiophene occurs naturally in the benzene fraction of coal-tar. Since its b.p. (357 K) is close to that of benzene (353 K), it is not possible to separate these compounds by fractional distillation.
- Thiophene and benzene are separated by reacting with conc. H_2SO_4. Thiophene forms water soluble compound with acid while benzene forms water insoluble compound with acid.

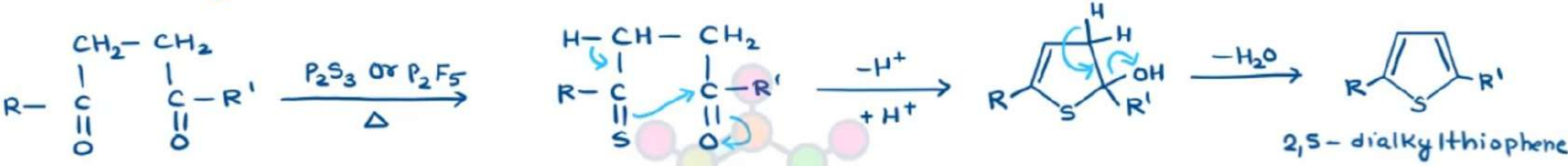
→ Methods of formation:→

1. From n-butane:-

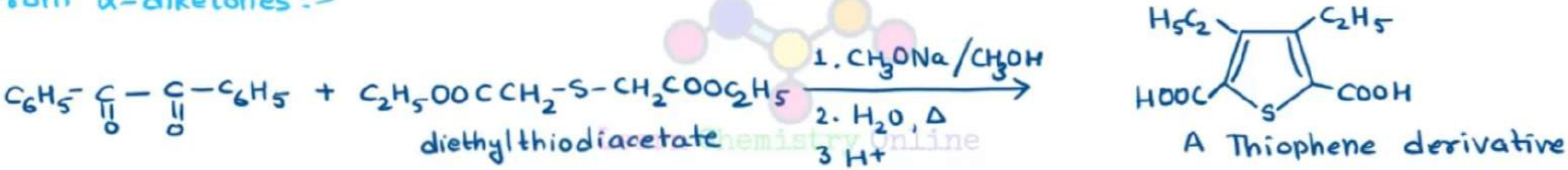
2. From acetylene:-

3. From sodium succinate :→

4. Paal-Knorr synthesis :-



5. From α-diketones :-



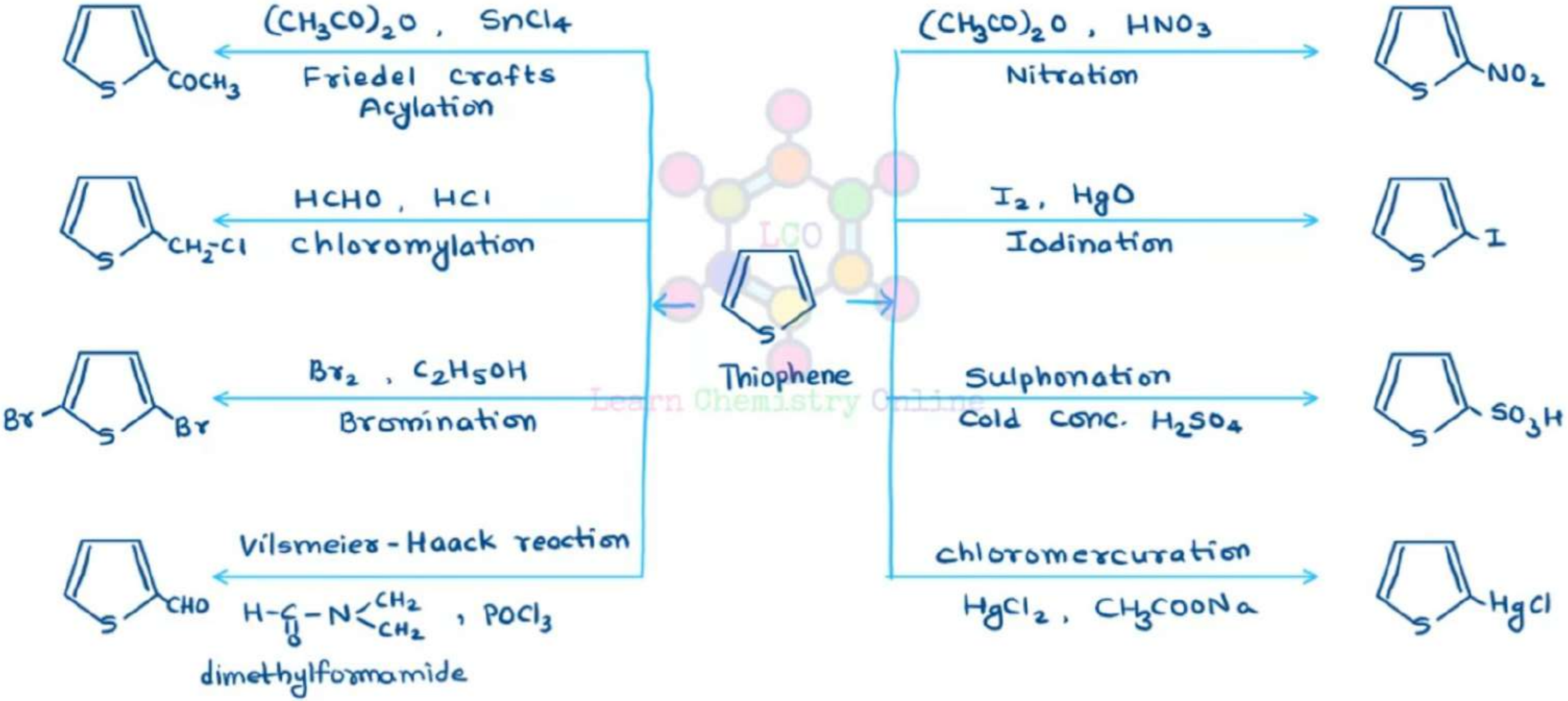
→ Physical Properties :- -

- Thiophene is a colourless liquid.
- b.p. 357K
- Benzene like smell
- Insoluble in water but soluble in alcohol and ether.

→ Chemical properties:-

- Thiophene is less reactive than Furan and pyrrole.

1. Electrophilic substitution:-



– Some important features of electrophilic substitution reactions –

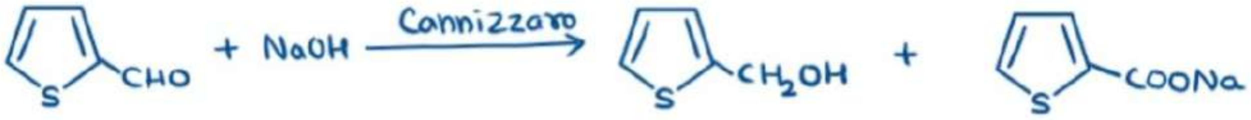
ⓐ On chlorination 2-chloro- and 2,5-dichlorothiophenes are formed.

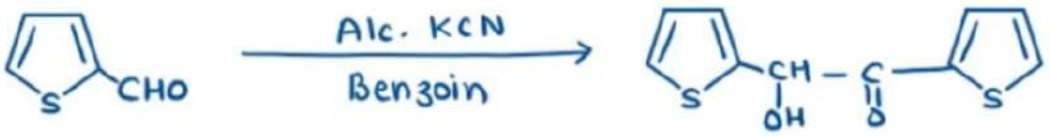
ⓑ Br_2 reacts in benzene solution to form 2,5-dibromothiophene.

ⓒ Monohalo derivatives of thiophene are prepared only under special conditions.

ⓓ Since, thiophene is quite stable towards acids, its reactions such as nitration and sulphonation can be carried out relatively more easily.

ⓔ Thiophene-2-carboxaldehyde like furfural and benzaldehyde undergoes Cannizzaro as well as benzoin condensation.



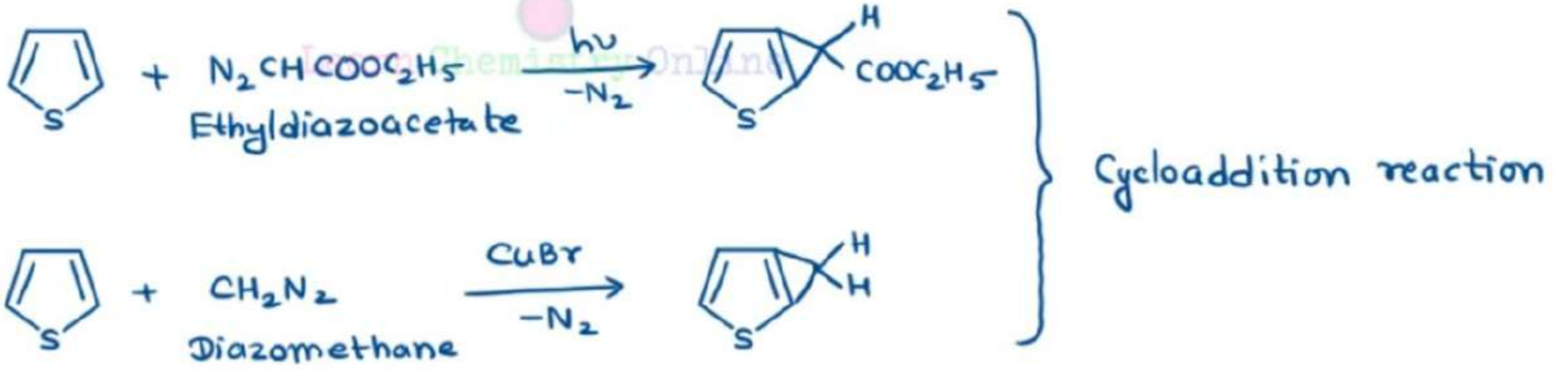


① Thiophene does not undergo Diels-Alder reaction.

2. Reduction:-

- However, catalytic reduction of thiophene with Raney Ni results in the removal of sulphur to give n-butane.

3. Reaction with carbene:→

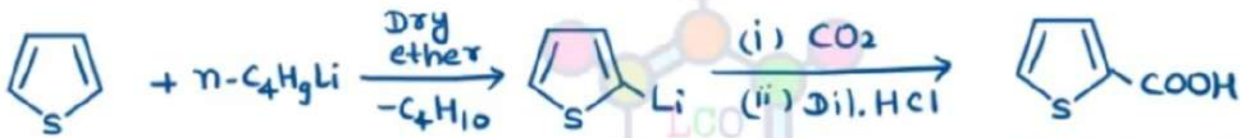


4. Radical substitution:-

o-nitrobenzenediazoniumchloride
(Radical source)

2-(2-nitrophenyl) thiophene

5. Reaction with n-butyllithium:-



Thiophene -2- carboxylic acid

→ Pyridine:→

- Pyridine is a six membered heterocyclic compound.
- Azine, C_5H_5N,

- Pyridine is an important solvent and raw material for preparation of large number of industrially important substances.
- It forms basic skeleton for a number of naturally occuring substances such as alkaloids, vitamins and many synthetic drugs.

→ Structure:-

- The structure of pyridine is similar to that of benzene.
- The molecule has planar structure with bond angle of 120°.
- The C–C and C–N bond lengths are intermediate between those known for the single and double bonds.

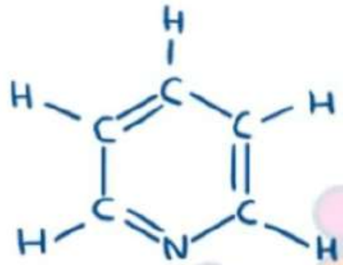
C–C bond length in pyridine = 139 pm   C–C (154 pm), C=C (134 pm)

C–N bond length in pyridine = 137 pm   C–N (147 pm), C=N (128 pm)

- Similar to benzene, pyridine shows aromatic behaviour and undergoes electrophilic substitution reactions such halogenation, nitration and sulphonation.

- Korner's formula:-

- On the basis of chemical and aromatic behaviour, korner suggested the structure of pyridine which is analogous to the kekule structure of benzene.



→ Methods of Formation:-

1. Isolation from light oil:-

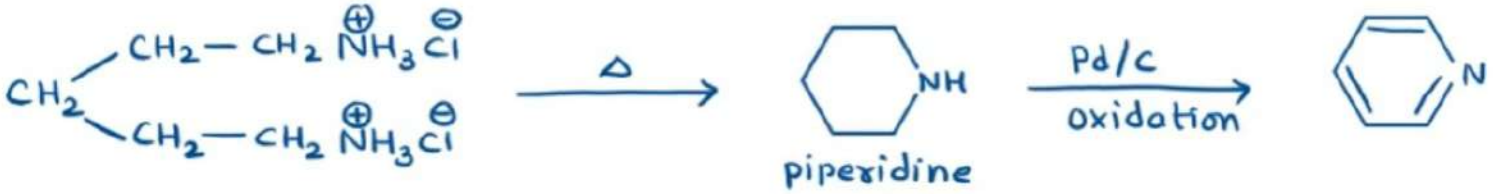
light oil of Coal tar (low b.p. oil) $\xrightarrow[H_2SO_4]{dil}$ Acid layer of pyridine + other basic substances $\xrightarrow{NaOH}$ Neutral pyridine + other basic substances

Repeated fractional distillation → Pure pyridine

2. From Acetylene:-

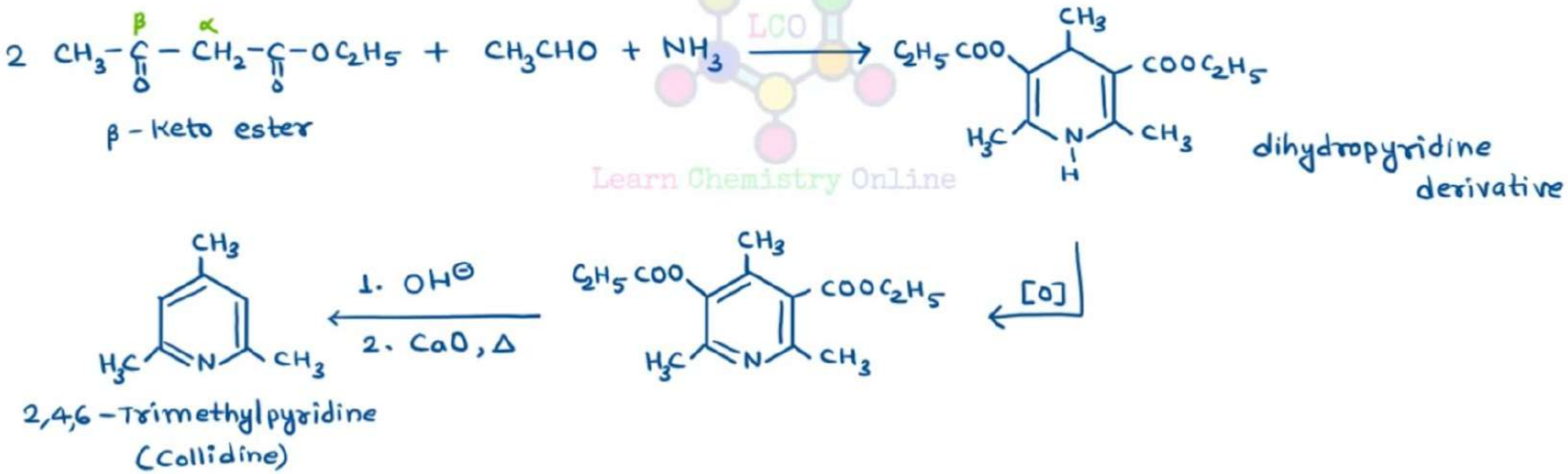
$2C_2H_2 + HCN \xrightarrow{\text{Red hot tube}}$

3. From pentamethylenediamine hydrochloride :-



4. Hantzsch synthesis :-

- This reaction is used to synthesis various pyridine derivatives.
- This reaction involves condensation of a β-keto ester, an aldehyde and ammonia.



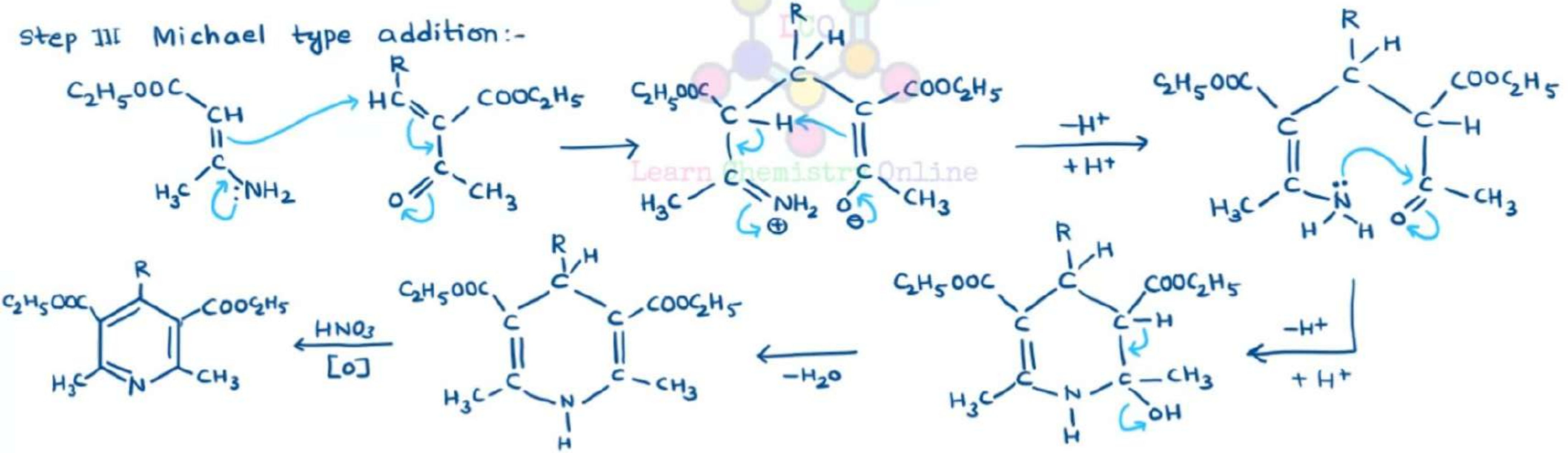
→ Mechanism:→

step-I Formation of β-amino-α,β unsaturated carbonyl compound (enamine)

$$CH_3COCH_2COOC_2H_5 + NH_3 \xrightarrow[-H_2O]{} \overset{\beta}{CH_3\underset{NH_2}{\underset{|}{C}}}=\overset{\alpha}{C}HCOOC_2H_5$$

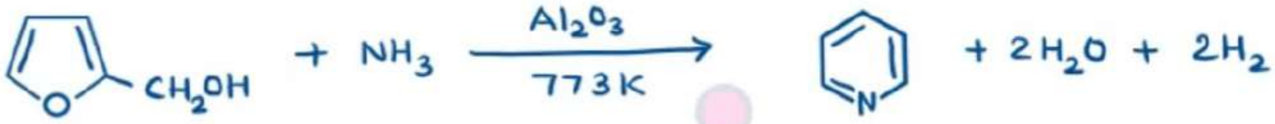
Step-II Formation of alkylidine 1,3 dicarbonyl compound.

step III Michael type addition:-



5. From aldehydes or ketones:-

6. From tetrahydrofurfuryl alcohol:-



7. From pyrrole:-

→ Physical properties:→

- Pyridine is a colourless hygroscopic liquid.
- b.p. 388K
- unpleasent smell
- Miscible with water and many organic solvents.
- Used as solvent for organic compounds.

→ **Pyridine:-**

→ **chemical reactions:-**

1. Basic nature:-

- Pyridine is behave as base due to lone pair present on nitrogen atom.
- $K_b = 2.3 \times 10^{-9}$
- Pyridine can accept a proton to form the corresponding conjugate acid, the pyridinium Ion.

- Pyridine v/s pyrrole :-
- Pyridine is a much stronger base than pyrrole. because pyridine nitrogen has a electron pair, which is not required for stabilisation of aromatic system. while the electron pair on nitrogen atom in pyrrole is not available for sharing with the acid.
- Pyridine v/s aliphatic amines:-
- Pyridine < aliphatic amine

	$R-\ddot{N}H_2$
- sp^2 hybridised N-atom	- sp^3 hybridised N-atom
- More s-character (33.3%)	- less s-character (25%)
- diffcult to share e^- pair to accept proton	- easily shares e^- pair to accept proton

2. Electrophilic substitution:-

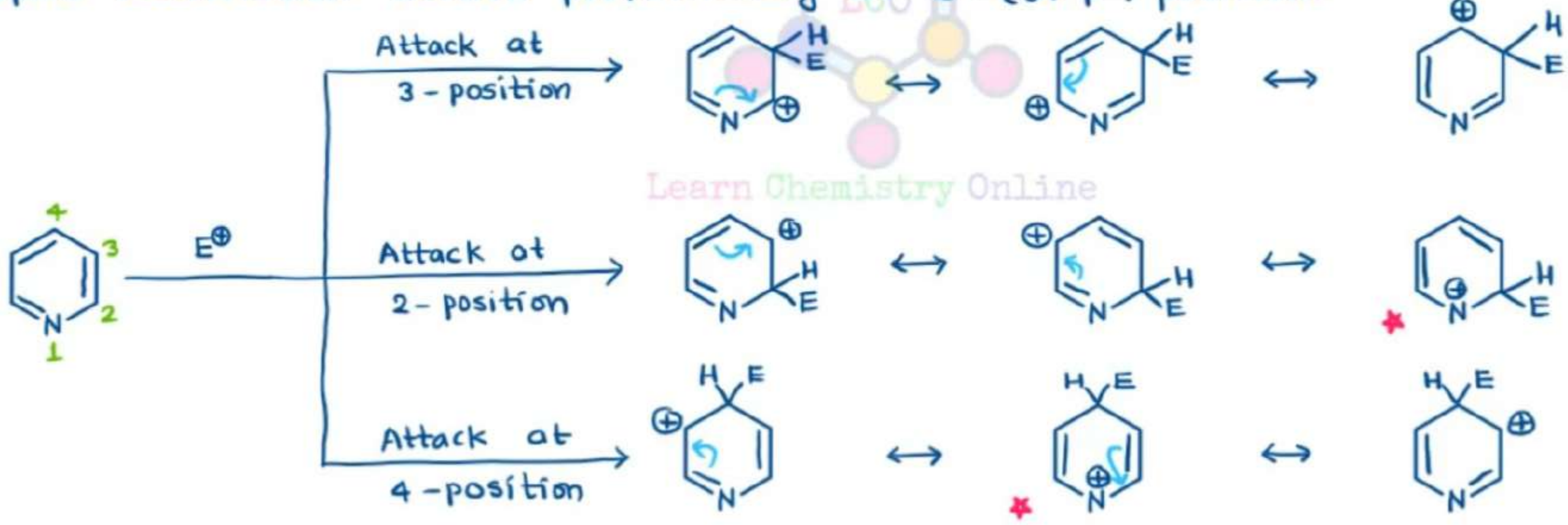
- The pyridine molecule is less reactive towards electrophilic substitution reactions due to following reasons-

(i) Due to high electronegativity of nitrogen, electron density decreases in the ring. This causes deactivation of ring and hence pyridine does not undergo Friedel-Craft reaction

(ii) In acidic conditions, pyridine converts into pyridinium ion, which has +ve charge on it. This +ve charge makes attack of electrophile more difficult. Thus pyridine shows less reactivity in sulphonation and nitration reactions.

- Orientation:-

- Electrophic substitution occurs preferentially at 3- (or β-) position.



- The tranistion state leading to substitution at 3-position is energetically more favourable.
- When electrophile attaks on position 2- or 4-, then there are resonance structures marked ✱ with positive charge on the electronegative nitrogen atom. This would increase the energy of transition state relative to 3-substitution pathway where no such situation arises.
- However, the carbocation intermediate resulting from attak at position-3 in pyridine is less stable than the carbocation intermediate formed in case of benzene. Due to this pyridine is less reactive than benzene towards electrophilic substitution reactions.
- Mechanism:-

(i) Generation of electrophile:-

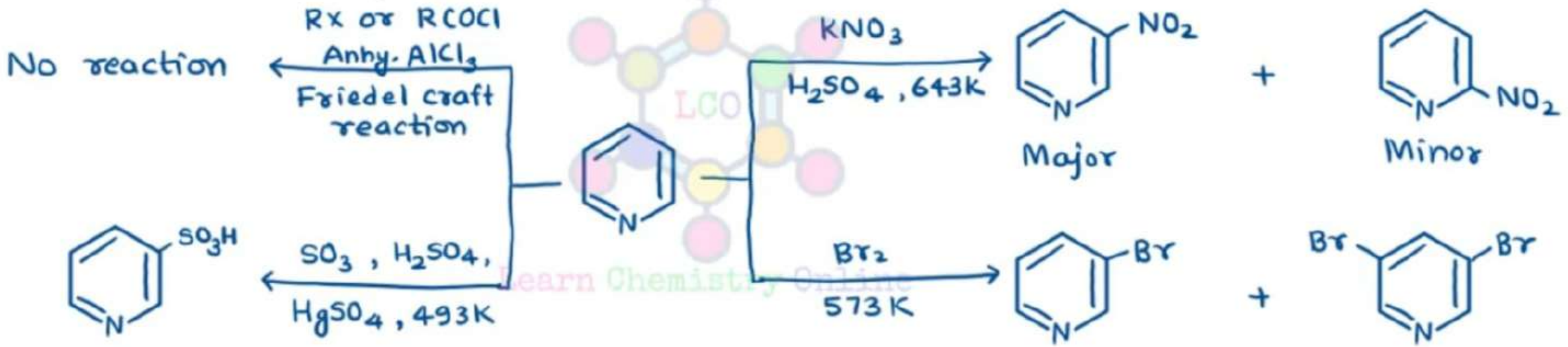
$$\underset{\text{Reagent}}{\text{E}\overset{\curvearrowright}{-}\text{Nu}} \longrightarrow \underset{\text{Electrophile}}{\text{E}^{\oplus}} + \underset{\text{Nucleophile}}{\text{Nu}^{\ominus}}$$

(ii) Formation of the resonance stablised carbocation:-

- This step is slow and hence is the rate-determining step of the reaction.

(iii) Removal of a proton to give substituted product

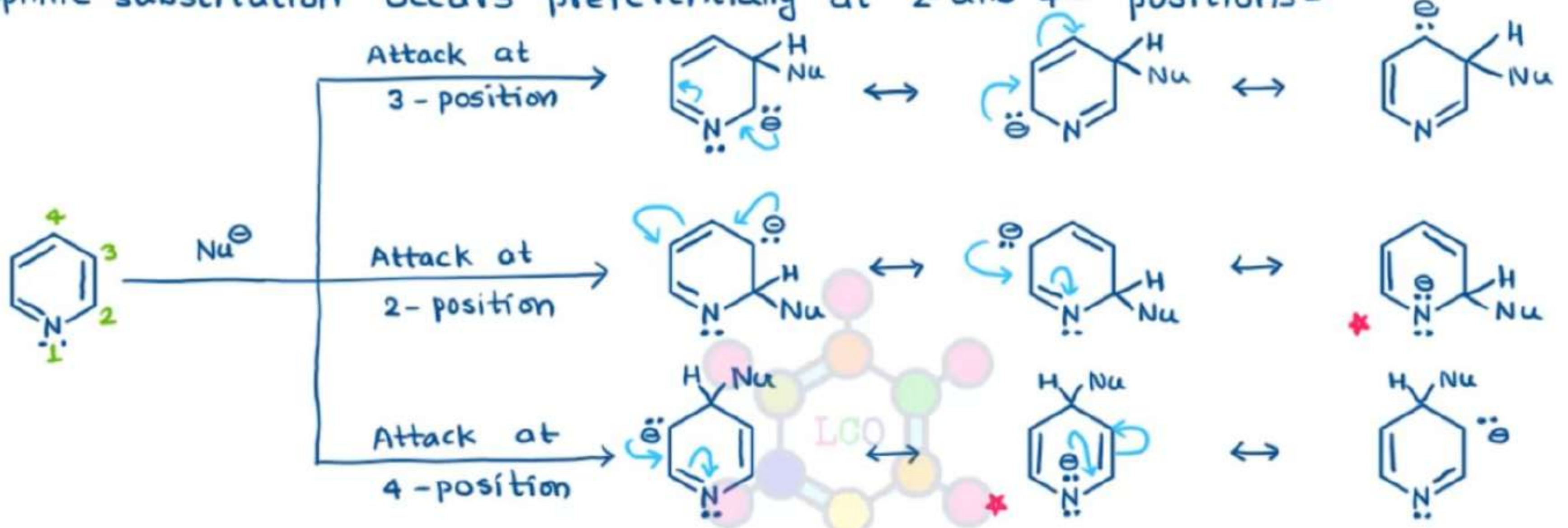
- This step is fast and hence does not affect the rate of reaction.
- The electrophilic substitution reactions of pyridine are performed under drastic conditions due to deactivation of ring.



3. Nucleophilic substitution:-

- Due to electron withdrawing effect of ring nitrogen, pyridine ring show similarity with benzene ring containing strongly electron-withdrawing groups and shows nucleophilic substitution reactions.

- Orientation:-
- Nucleophilic substitution occurs preferentially at 2-and 4- positions-

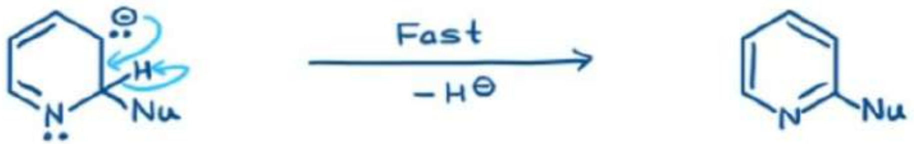


- When nucleophile attacks on positions 2-and 4- then -ve charge is resides on nitrogen rather than on carbon (★) i.e. a stable intermediate carbanion is formed. It is therefor nucleophile attaks on positions 2- and 4-

- Mechanism:-

(i) Attack of the nucleophile

(ii) Removal of hydride ion:-

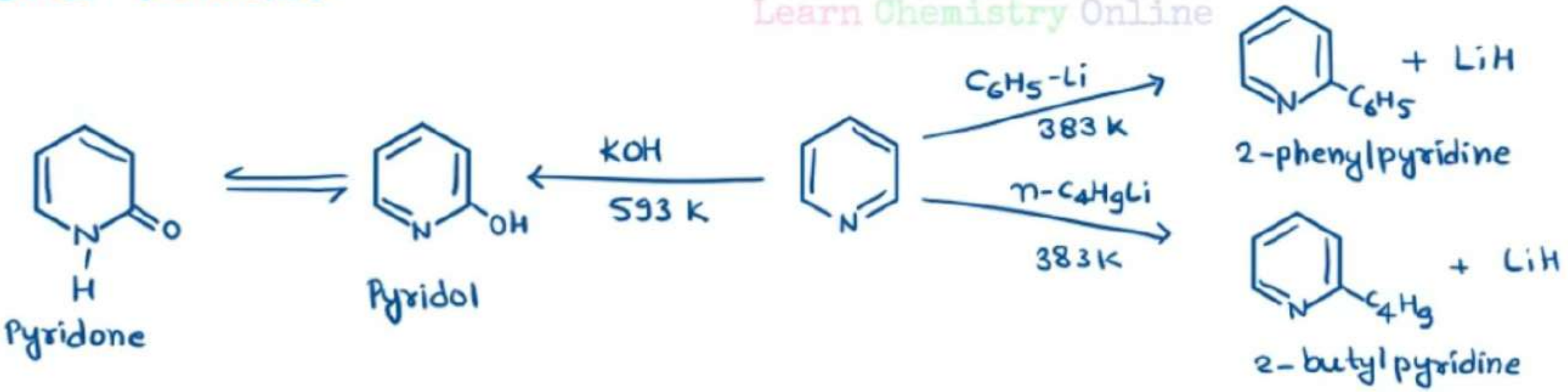


- Some important nucleophilic substitution reactions are-

(i) Tschitschibabin reaction:-

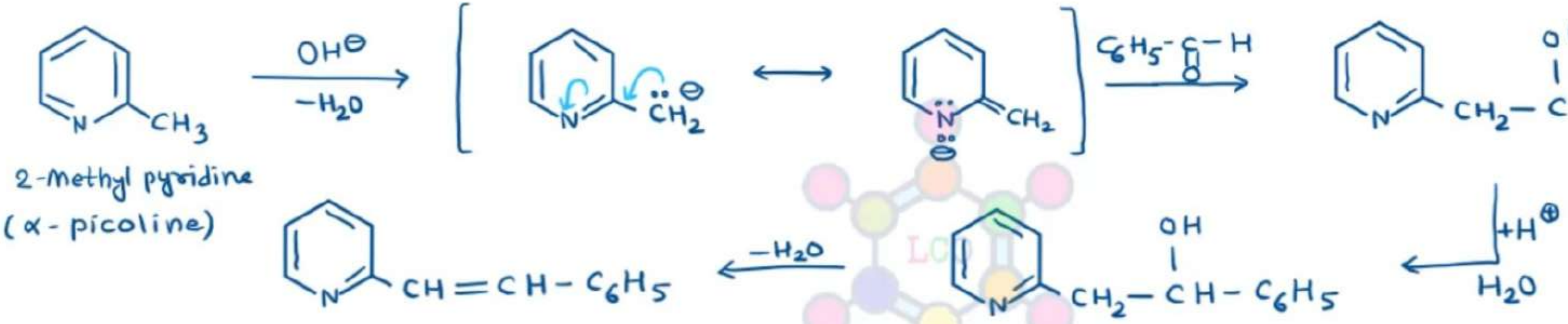
- Amination reaction

(ii) other reactions:-



4. Side chain reactivity:-

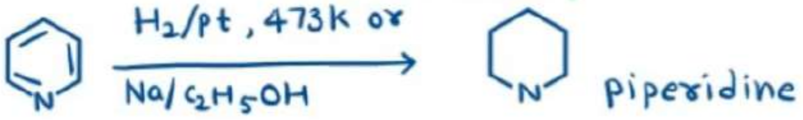
- Due to high electronegativity of nitrogen atom, the methyl hydrogen are acidic in 2- and 4- methyl pyridine and such pyridines undergoes aldol-type condensation with aldehyde in the presence of a base.



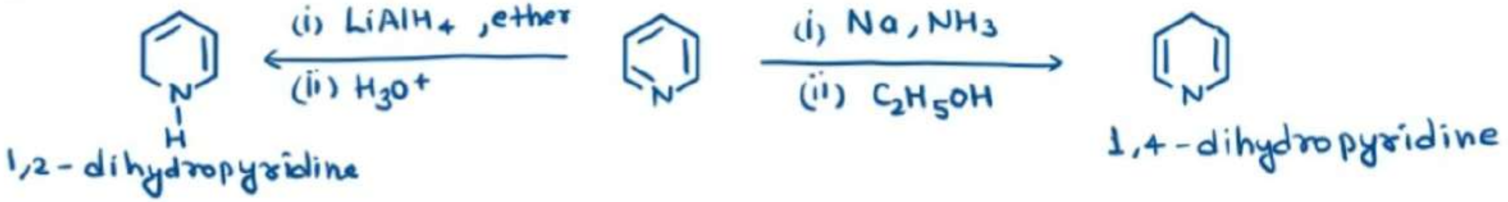
2-Methyl pyridine
(α-picoline)

5. Reduction:-

(i) Hydrogenation



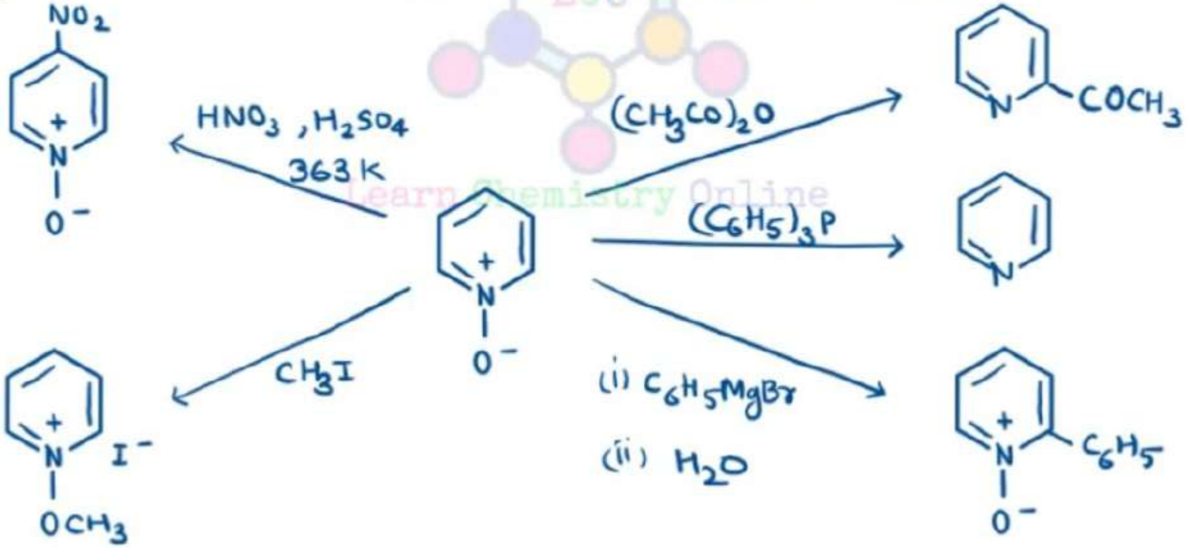
(ii) Birch reduction



6. Oxidation:-

- Upon treatment with peracids such as peracetic or perbenzoic acids, pyridine is converted into pyridine N-oxide.

- Pyridine N-oxide is more reactive towards electrophilic and nucleophilic substitution reactions than pyridine. It is due to polarization effect.



→ Comparison of basicity of pyridine, piperidine and pyrrole :→

- The order of basicity is as follows-

Pyrrole < **Pyridine** < **Piperidine**

Very weak base < Mild base < Very strong base

$pK_b \sim 14$ < $pK_b \sim 8.7$ < $pK_b \sim 2.7$

Pyrrole

- sp^2 – Hybridised orbital
- No lone pair available for protonation

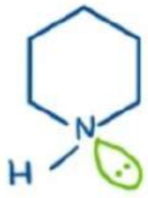
<

Pyridine

- sp^2 – Hybridised orbital
- A lone pair available for protonation

<

Piperidine



- sp^3 – Hybridised orbital
- A lone pair available more easily for protonation

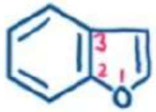
- In pyrrole, the nitrogen lone pair is contributed towards the π-electron cloud and hence is not available for protonation at all. Therefore pyrrole is a very weak base. It is so weak that in presence of a strong base like potassium metal, it behave as a weak acid to give potassiopyrrole.
- In pyridine, the lone pair present in sp^2- orbital while in piperidine, it is present in a sp^3- orbital. Due to less electronegativity of sp^3- orbital, the electron in piperidine are more easily available for protonation than in pyridine. Hence piperidine is a stronger base than pyridine.

- In aniline, the nitrogen atom carrying the lone pair of electron is directly attached to the benzene ring and hence delocalised in the ring. hence lone pair is less easily available for protonation. Therefore, aniline is weaker base than pyridine.

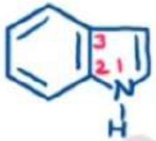
- Solubility of pyrrole, pyridine and piperidine:-
- Due to availability of e⁻ pair of N-atom in pyridine, it forms H-bond with water and hence, pyridine is water soluble.
- The electrons in piperidine are more easily available for protonation than in pyridine. Hence, piperidine is more soluble than pyridine.
- In case of pyrrole, the lone pair is contributed towards the aromatic sextet of the ring and hence not available for H-bonding with water. Therfore, pyrrole is water insoluble.

→ Condensed five membered heterocyclic compounds:-

- These are the compounds in which five membered heterocyclic compounds are condensed or fused with benzene ring at 2-3 position.
- Examples:-



Benzofuran

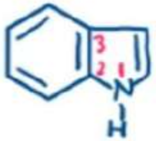


Benzopyrrole (indole)

Benzothiophene

→ Indole, Benzopyrrole:-

- Benzazole, C_8H_7N,



- Indole is found in coal-tar, orange blossoms, Jasmine blossoms, alkaloids and indigo dye.

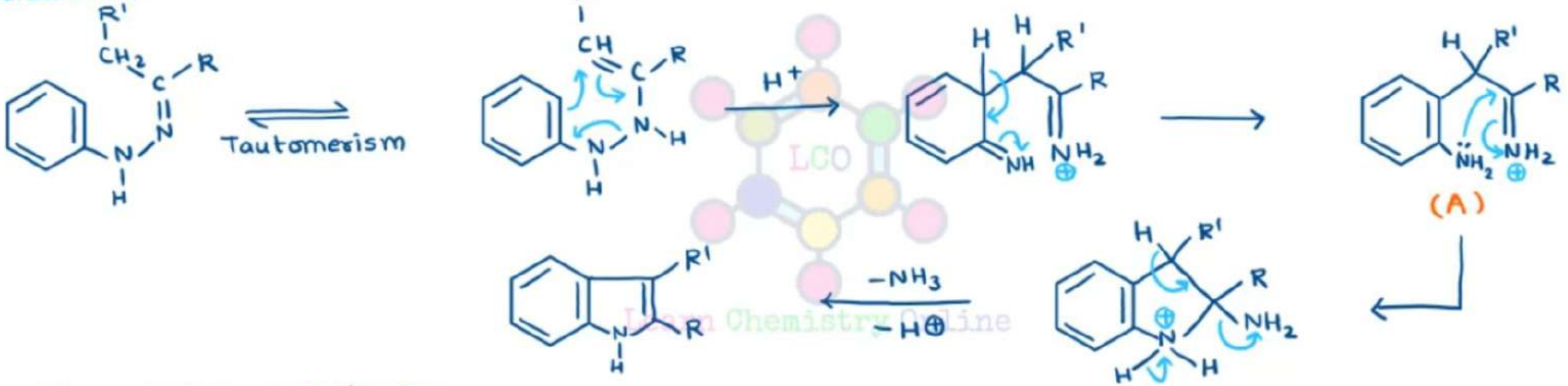
- Methods of formation:-

1. Fischer indole synthesis:-

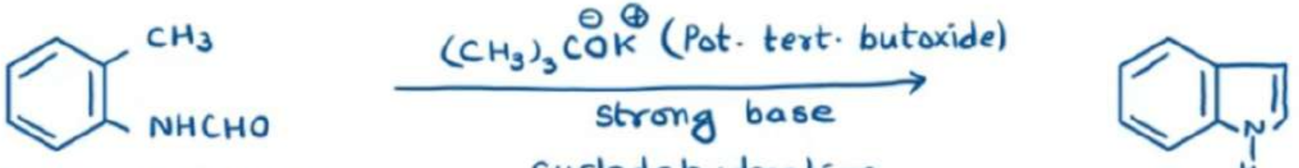
- This method is one of the most important method for synthesis of indole derivatives.
- This method involves heating of arylhydrazones of aldehyde and ketones with catalysts such as polyphosphoric acid (PPA, $H_3PO_4 + P_2O_5$), $ZnCl_2$ or BF_3.

Phenyl or arylhydrazone of ketone
(Phenylhydrazine + ketone)

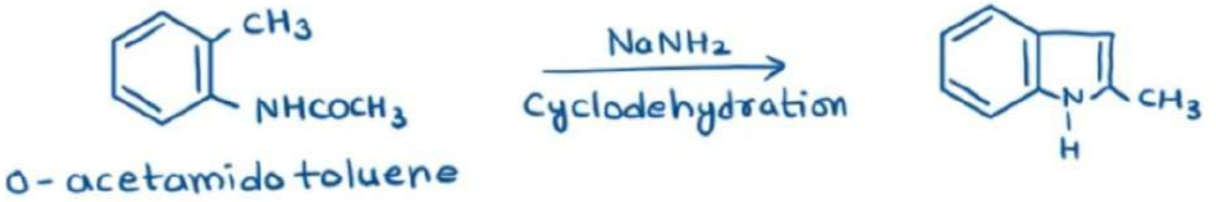
- Mechanism:-



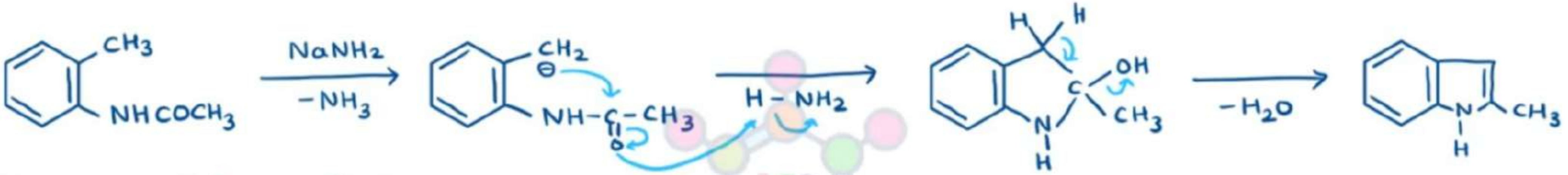
2. Madelung indole synthesis:-



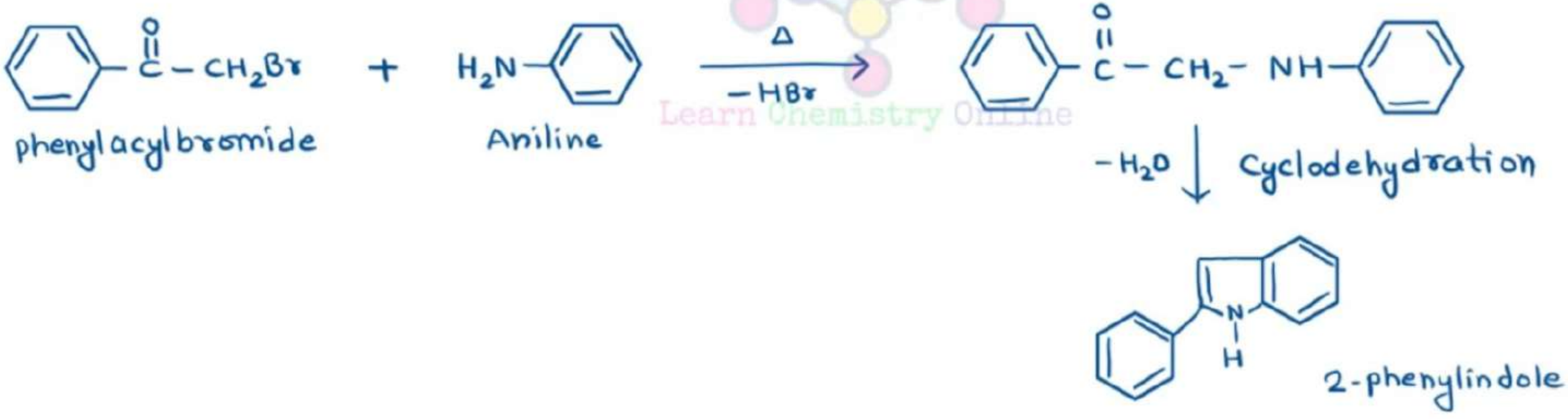
o-formomidotoluene



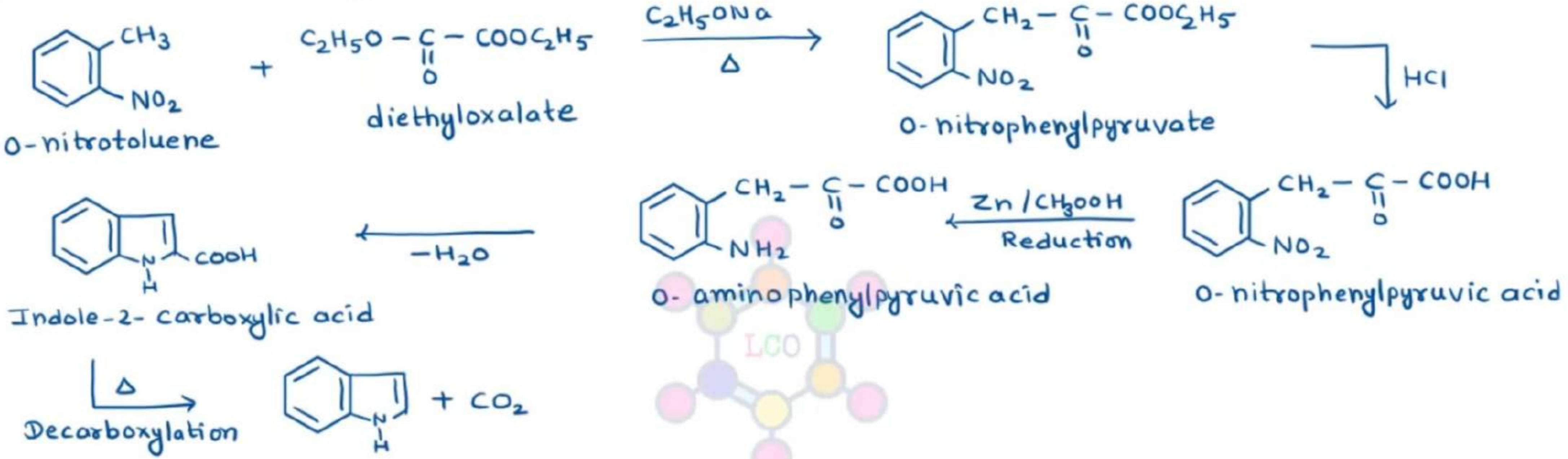
- Mechanism:-



3. Bischler indole synthesis :-



4. The Reissert indole synthesis:-



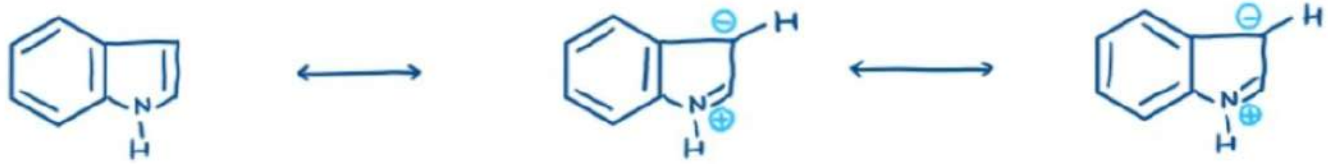
→ Physical properties:-

- Indole is a colourless crystalline solid.
- m.p. 325 K

→ chemical reactions:-

- Indole shows some similar reactions of pyrrole but shows some different reactions due to fusion of benzene ring.
- Pyrrole has 6 π electrons while Indole has 10 π electrons.

- The resonance energy of indole is 188-196 KJ/mole.
- Indole is a resonance hybrid of three resonance structures.



1. Electrophilic substitution:-

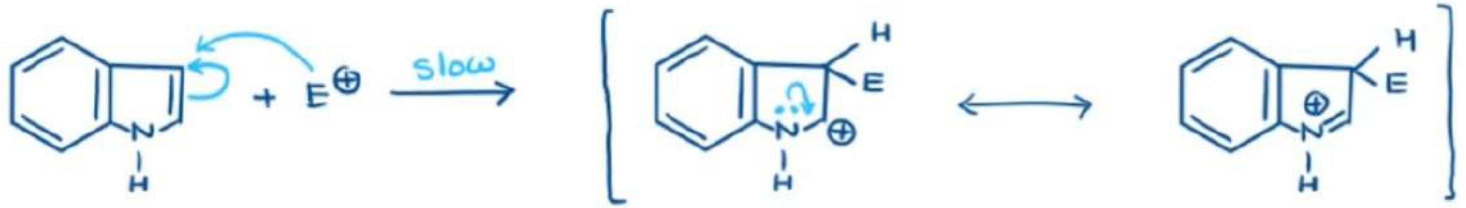
- Due to fused benzene ring the electron density is shifted from position 2- to position 3-. Therefore, electrophilic substitution occurs at position 3- and if this position is occupied, then the substitution occurs at postion 2-.
- The reactivity of Indole towards electrophilic substitution is less than that of pyrrole. It is due to fact that because of fusion, one double bond of pyrrole ring becomes part of the more stable benzene ring.

- Mechanism:-
- The mechanism of electrophilic substitution reactions of indole is similar to that of pyrrole which involves following steps-

(i) Generation of electrophile

$$\underset{\text{Reagent}}{\text{E}-\text{Nu}} \longrightarrow \underset{\text{Electrophile}}{\text{E}^{\oplus}} + \underset{\text{Nucleophile}}{\text{Nu}^{\ominus}}$$

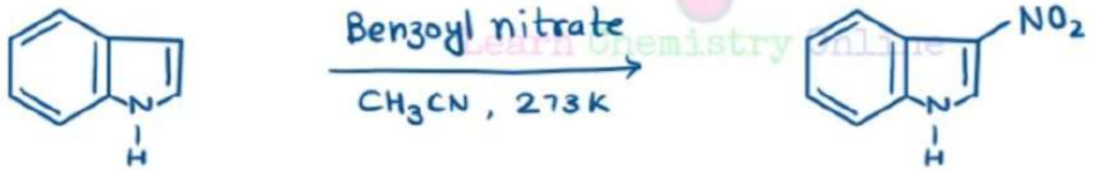
(ii) Formation of resonance stablised carbocation



(iii) Removal of proton to give final product

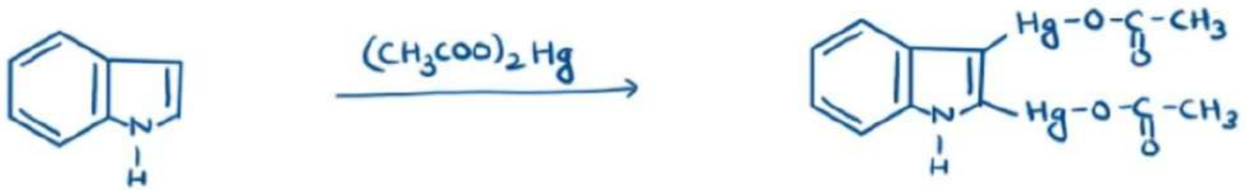
– some electrophilic substitution reactions of Indole:-

ⓐ Nitration:-



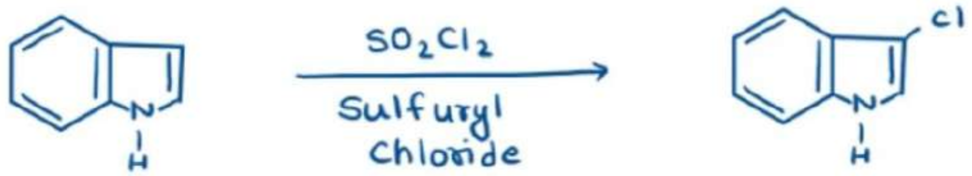
3-nitroindole

ⓑ Mercuration:-



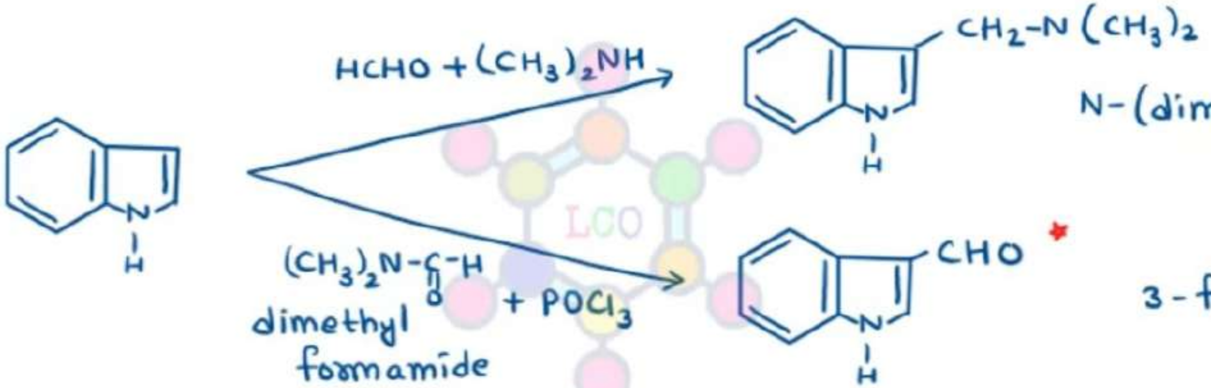
2,3-diacetoxymercuriindole

ⓒ Halogenation:-



3-chloroindole

ⓓ Mannich Reaction:-

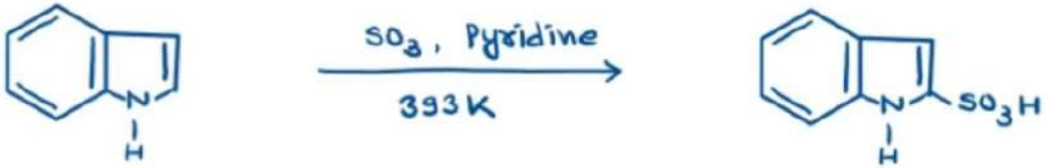


N-(dimethylaminomethyl) indole

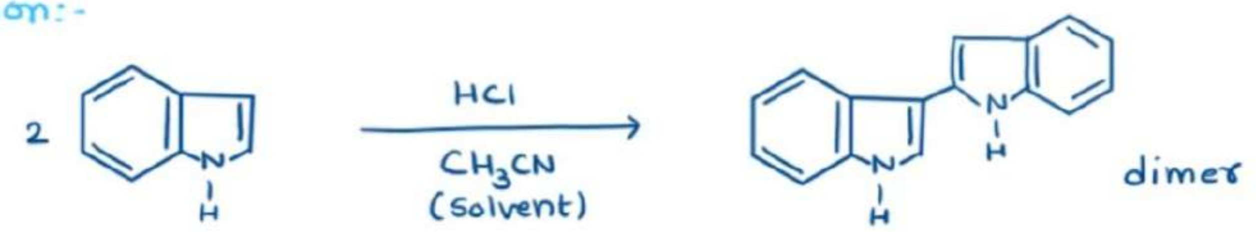
3-formylindole *

* The presence of formyl group act as electron withdrawing group and deactivates the ring towards further substitution. so the further substitution takes place at benzene ring.

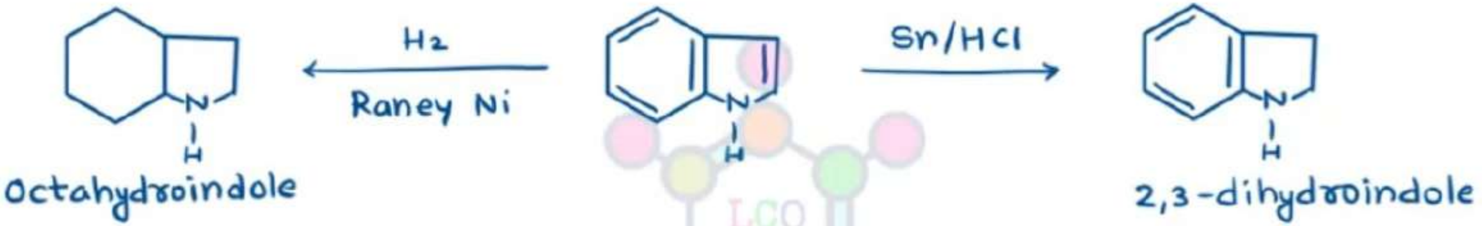
ⓔ Sulphonation:- It is exceptional case, in which substitution takes place at 2-position.



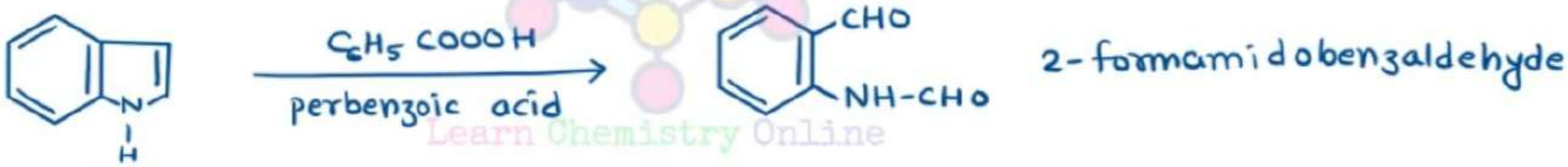
2. Addition reaction:-



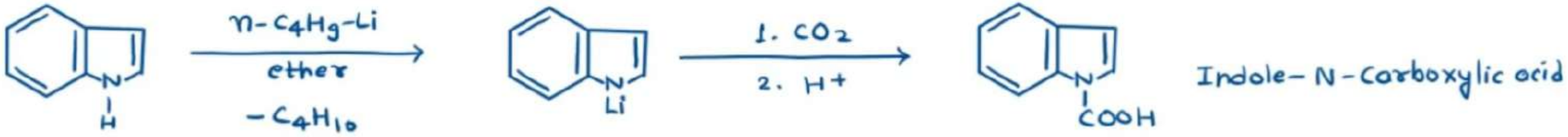
3. Reduction:-



4. Oxidation:-



5. Acidic properties:- (Reaction with organometallic compounds)



→ Condensed six membered heterocyclic compounds:-

- In these compounds, benzene ring is condensed or fused with six membered heterocylic ring.
- Example:-

Quindine

Isoquinoline

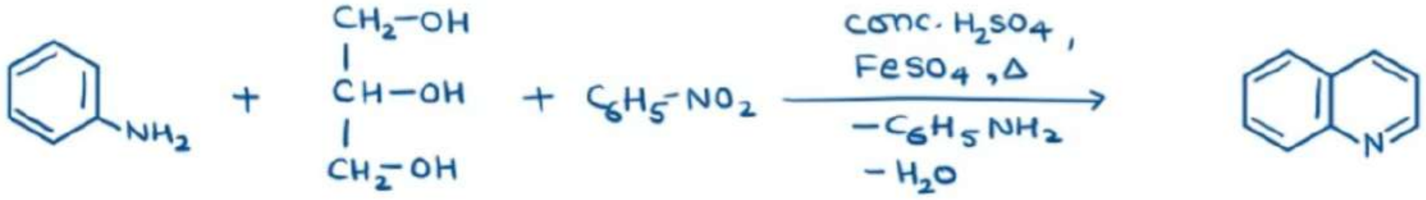
→ Quinoline:-

- Quinoline was initially obtained as one of the degradation product of the alkaliod quinine (used to treat malaria).
- It is also obtained from coal-tar and bone oil.

→ Methods of formation:-

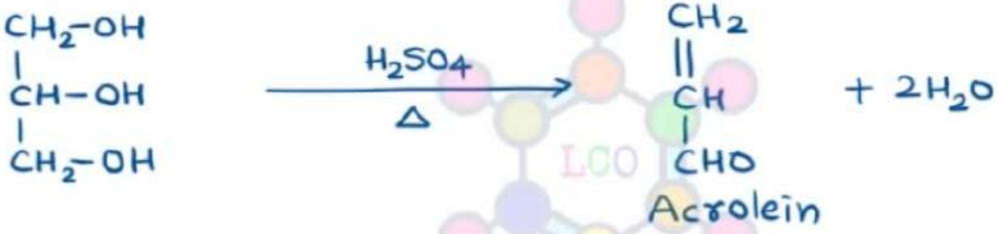
1. The Skraup synthesis:-

- This method is widely used for the synthesis of quinoline and its derivatives.
- Quinoline is obtained by heating a mixture of aniline, nitrobenzene (oxidant), glycerol, conc. H_2SO_4 (condensing agent) and $FeSO_4$.
- $FeSO_4$ is used to make reaction less violent.

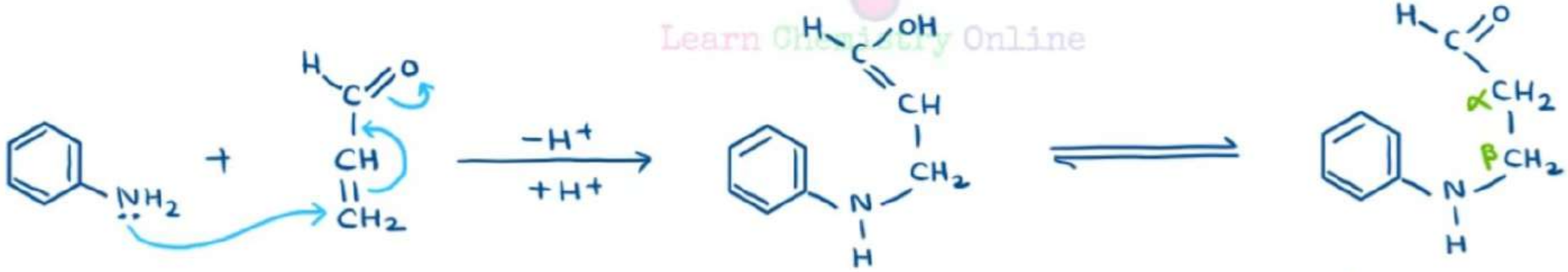


– Mechanism:-

(i) The dehydration of glycerol to acrolein.

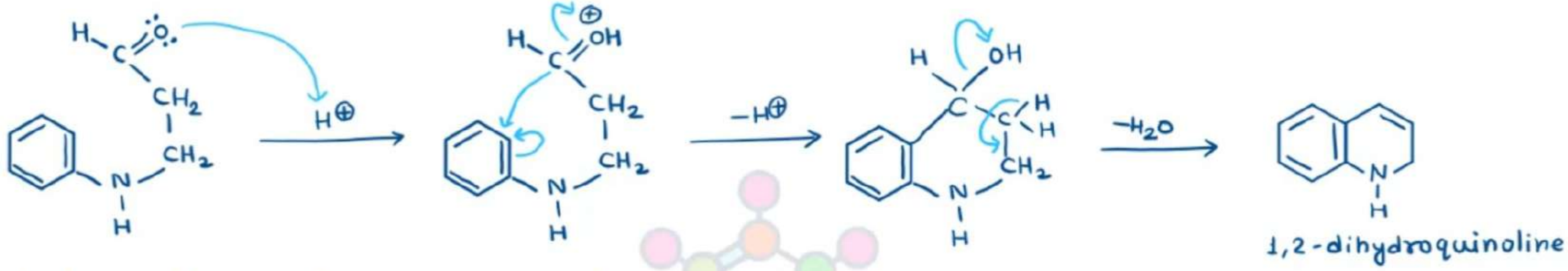


(b) Michael addition of aniline and acrolein to give β-(phenylamino) propionaldehyde.



β-(phenylamino)propionaldehyde

(c) Intramolecular electrophilic substitution upon the aromatic ring by protonated aldehyde followed by dehydration.



(d) Dehydrogenation of 1, 2-dihydroquinoline by nitrobenzene.

2. The Doebner - Miller synthesis :→

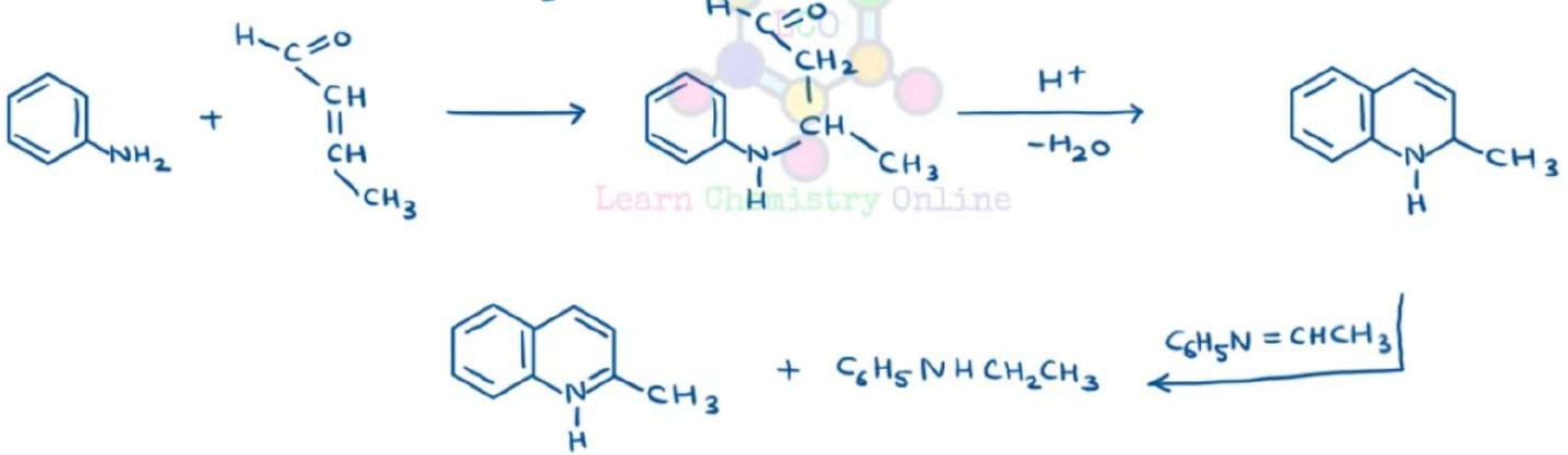
- This is a modification of Skraup synthesis in which aldehyde, ketone or mixture of both are taken in place of glycerol.
- There is initial formation of an α,β-unsaturated carbonyl compound (In situ, Aldol condensation) and then reaction follows the usual mechanistic path.

- In this reaction no oxidising agent is added because the anil (Schiff base compound) formed between the starting aldehyde / ketone and the primary amine acts as oxidising agent.
- If aldehyde is used, the product from aniline is 2- methylquinoline.

$$C_6H_5NH_2 + O{=}CHCH_3 \xrightarrow{H^+} C_6H_5N{=}CHCH_3$$

Ethylideneaniline (An anil)

$$CH_3CHO \xrightarrow[\text{1. Aldol condensation}\ \text{2. } H_2O]{H^+} CH_3CH{=}CHCHO$$



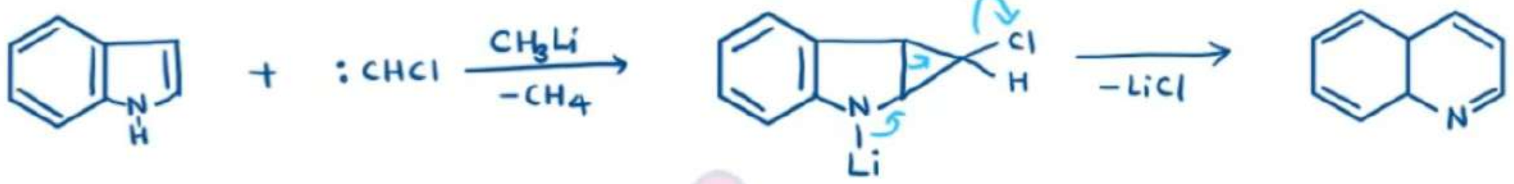
2-methylquinoline

3. From indole by ring expansion :→

$$CH_2Cl_2 + CH_3Li \longrightarrow :CHCl + CH_4 + LiCl$$

Methylene chloride

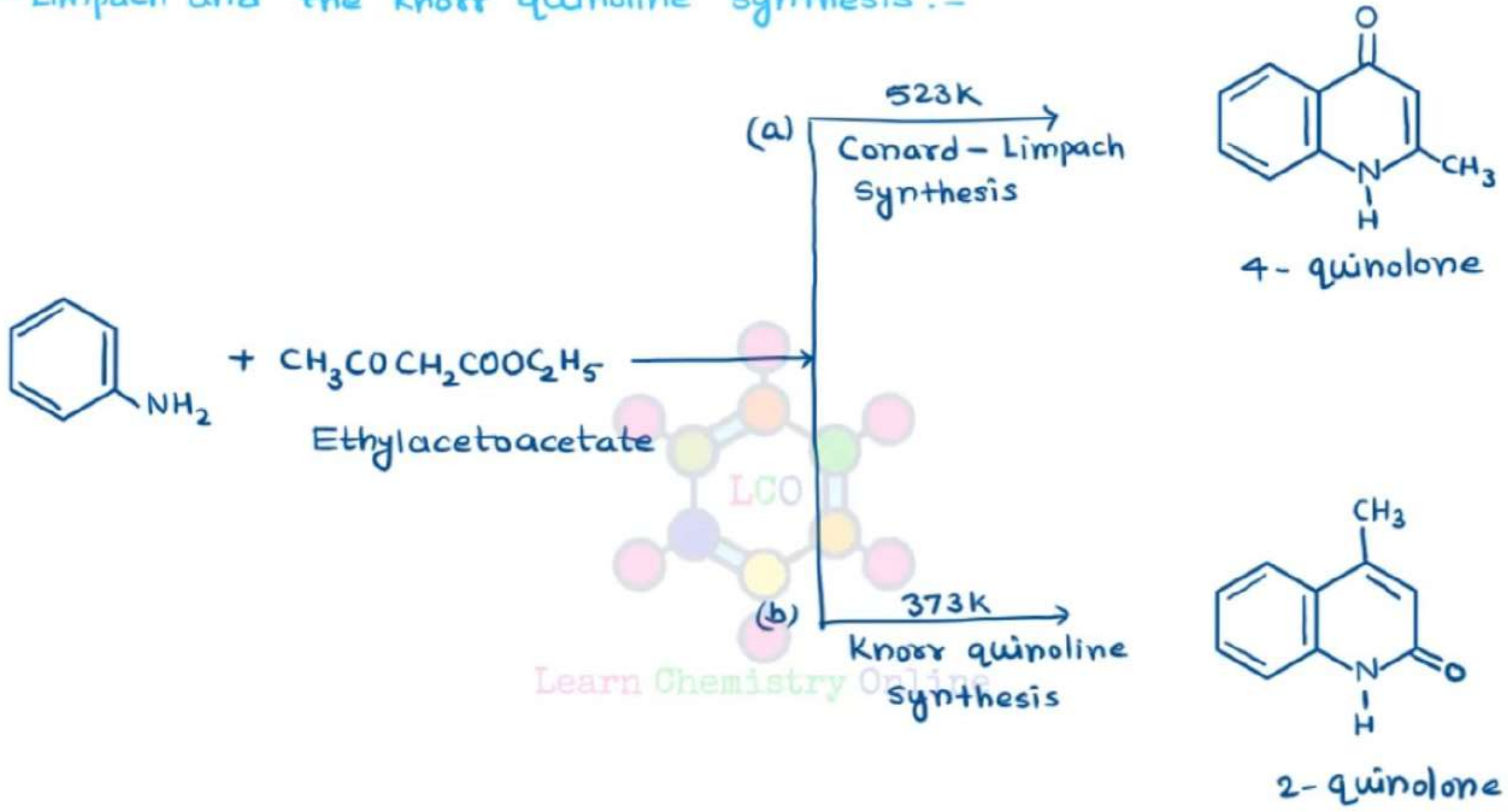
Chloromethylene



4. Friedlander synthesis:→

- Condensation reaction of o-amino aldehyde or ketone with a carbonyl compound having the group $-CH_2CO$.

5. The Conard - Limpach and the knorr quinoline synthesis :-



→ Quinoline :-

- Physical properties:-
- Quinoline is a colourless liquid.
- b.p. 511 K
- The resonance energy of quinoline is 249.6 kJ/mole.
- Chemical reactions:-

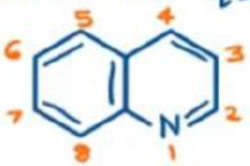
1. Basic nature:-

- The lone pair of heteroatom N is not contributed in aromatic stabilisation. Due to availability of this lone pair nitrogen, quinoline forms quaternary salt on treatment with alkyl halides.

1-methylquinolinium iodide

2. Electrophilic substitution:-

- Nitrogen containing ring is similar to pyridine whereas the carbocyclic ring is similar to benzene. so the quinoline easily shows electrophilic substitution reactions.
- The electrophilic substitution takes place in quinoline at 5- and 8- positions.



- Mechanism and orientation:-

(i) Generation of electrophile :-

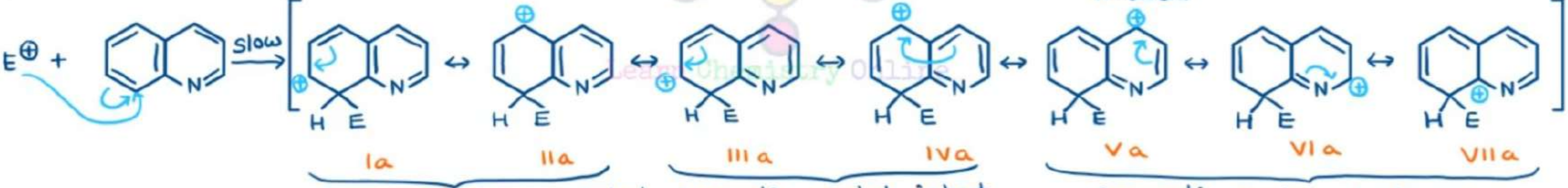
$$\underset{\text{Reagent}}{E - \overset{\frown}{Nu}} \longrightarrow \underset{\text{Electrophile}}{E^{\oplus}} + Nu^{\ominus}$$

(ii) Formation of resonance stabilsed carbocation intermediate:-

ⓐ At position 5

Aromatic sextet intact (more stable | Aromatic sextet intact (more stable) | Highly unstable +ve charge on N-atom | Aromic sextet destroyed (less stable)

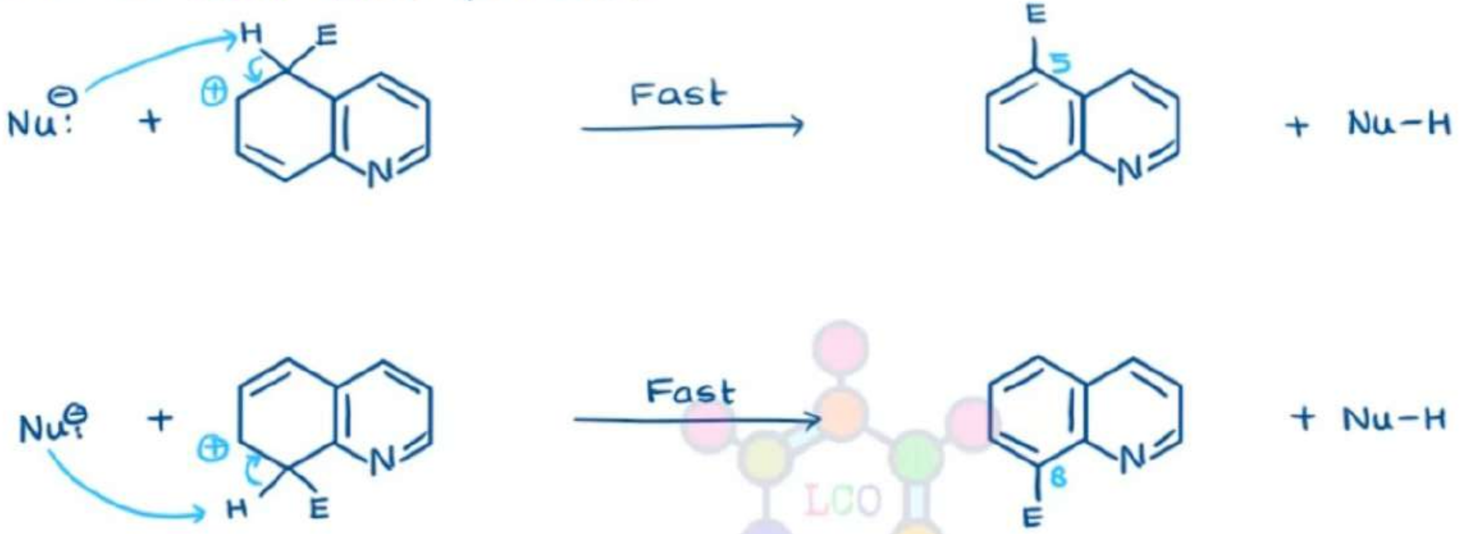
ⓑ At position 8



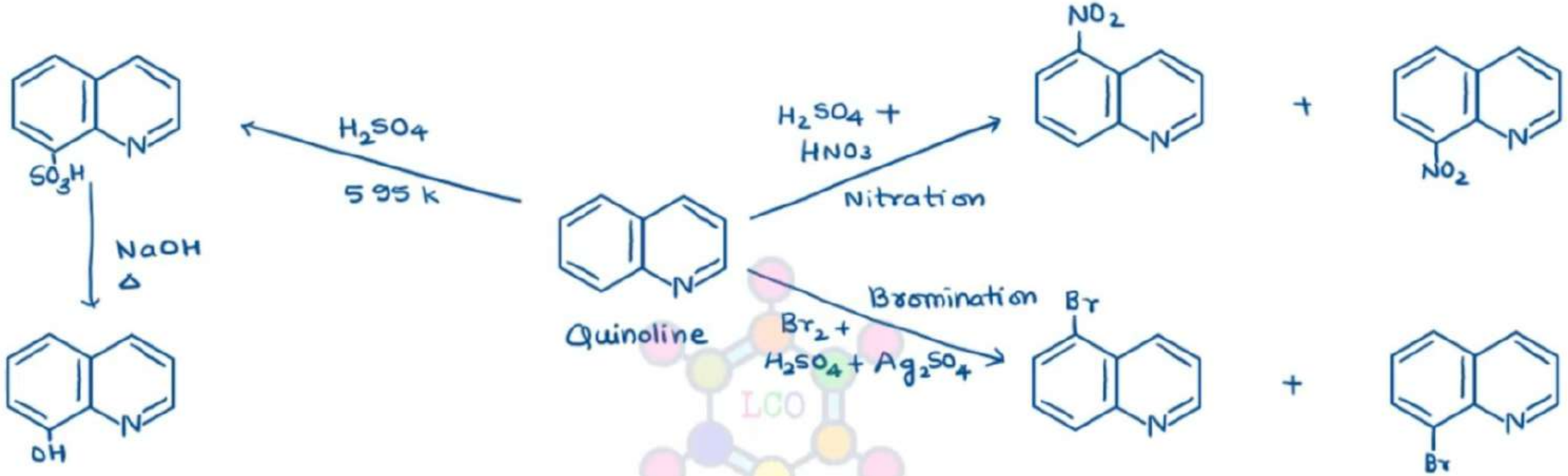
Aromatic sextet intact (more stable | Aromatic sextet intact (more stable) | Aromatic sextet destroyed (less stable)

- If electrophile attaks on position 6-or 7-, then the carbocation intermediate is stabilised by only two resonance structures. In all other resonance structures, aromatic sextet of pyridine ring is destroyed.

(iii) Loss of proton to form final product:-



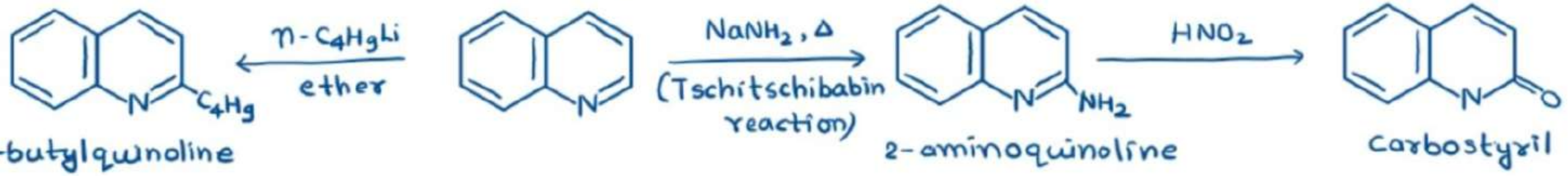
- Some important electrophilic substitution reactions are:-



- Vapour phase bromination gives 3-bromoquinoline while bromination at 773 K gives 2-bromoquinoline.
- Nitration with nitric acid and acetic anhydride gives 3-nitroquinoline.

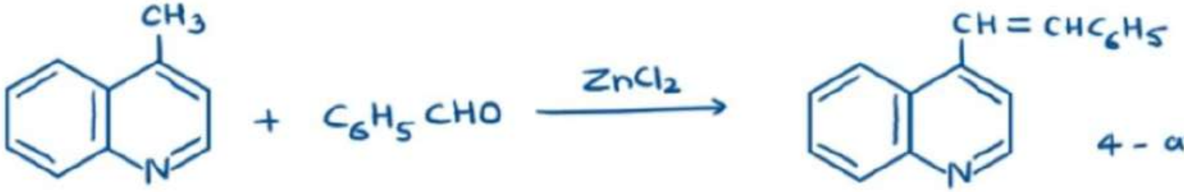
3. Nucleophilic substitution:-

- like pyridine, quinoline also undergoes nucleophilic substitution.



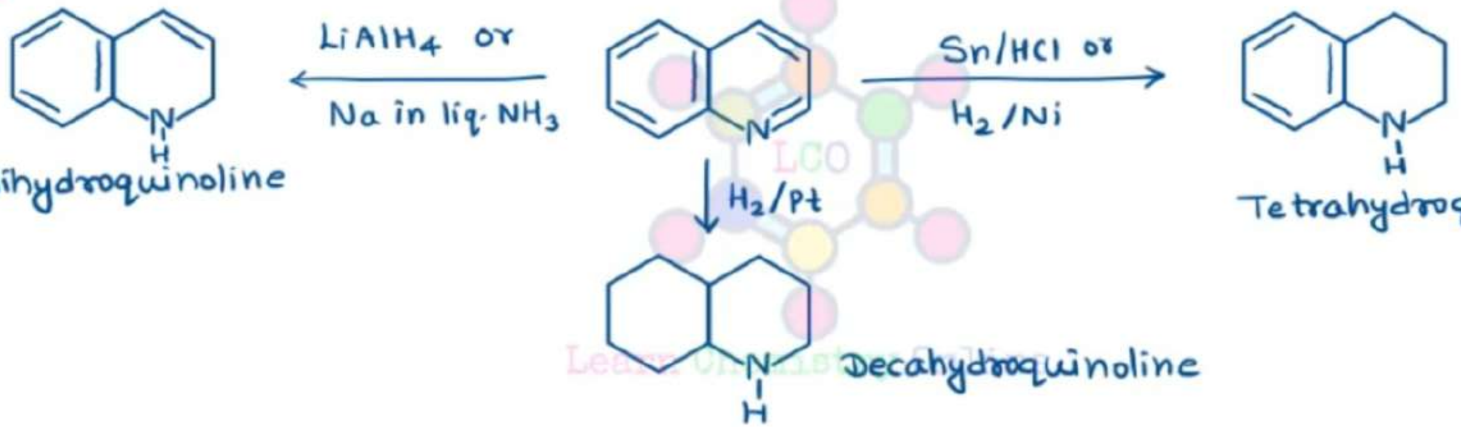
4 Side chain reactivity:-

- like pyridine, alkyl groups attached to ortho or para to the ring nitrogen are show acidic nature.



4 - arylethenyl quinoline

5. Reduction:-

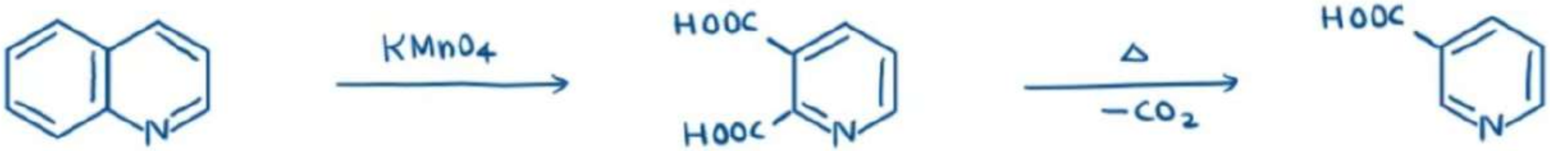


1,2-dihydroquinoline

Tetrahydroquinoline

Decahydroquinoline

6. Oxidation:-

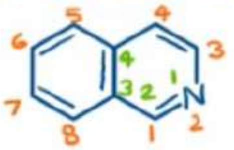


quinoline

2,3-pyridine corboxylic acid

Nictonic acid

→ Isoquinoline:-

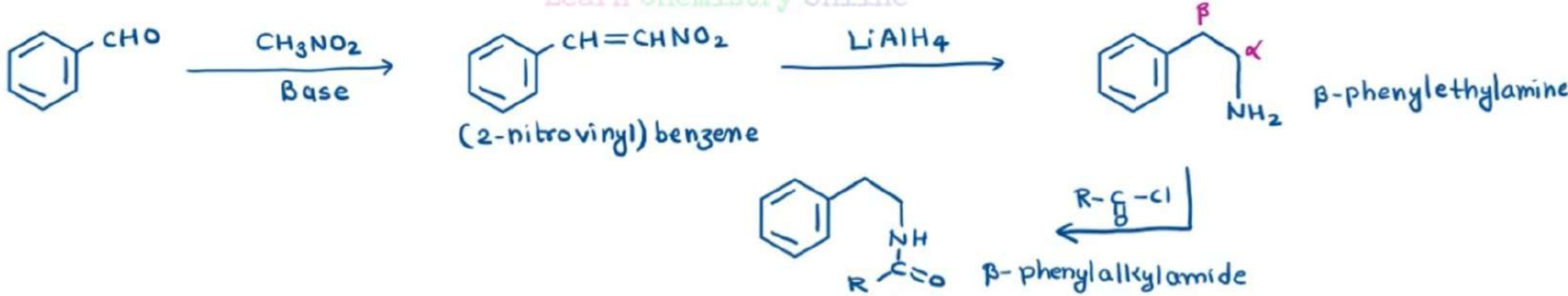
- 2-Benzazine, 3,4-Benzopyridine, β-γ-Benzopyridine
- 

- Isoquinoline is a decomposition product of many alkaloids.
- Commercially it is obtained from Coal-tar.
- Synthetically it is obtained by various cyclisation procedures.

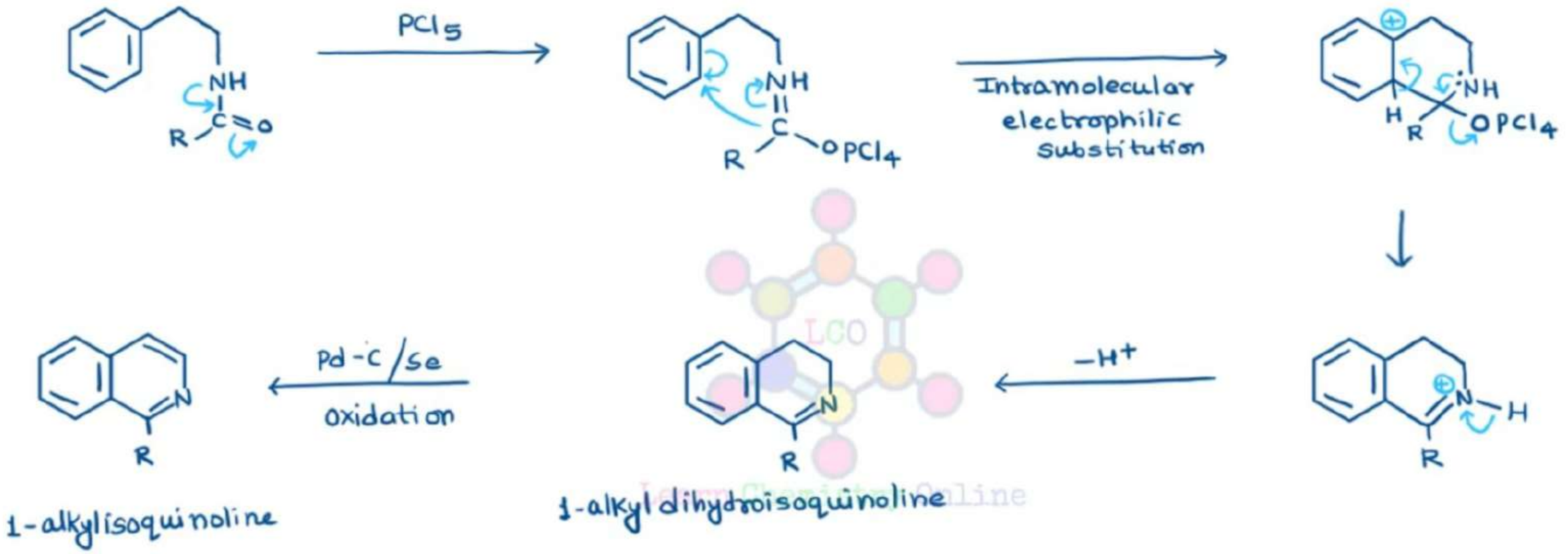
→ Methods of formation:-

1. The Bischler-Napieralski synthesis:-

- In this procedure, acyl derivatives of β-phenylethylamine are cyclodehydrated by heating with acid reagents
- Formation of β-phenylalkylamide (acyl derivative of β-phenylethylamine).

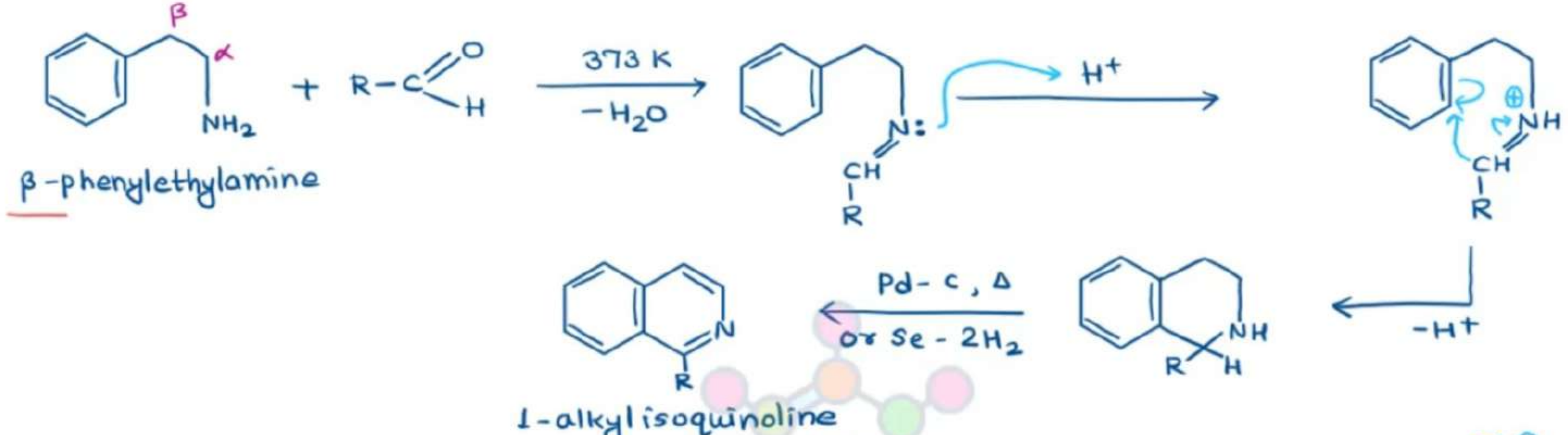


- Formation of isoquinoline from β-phenylalkyl amide.

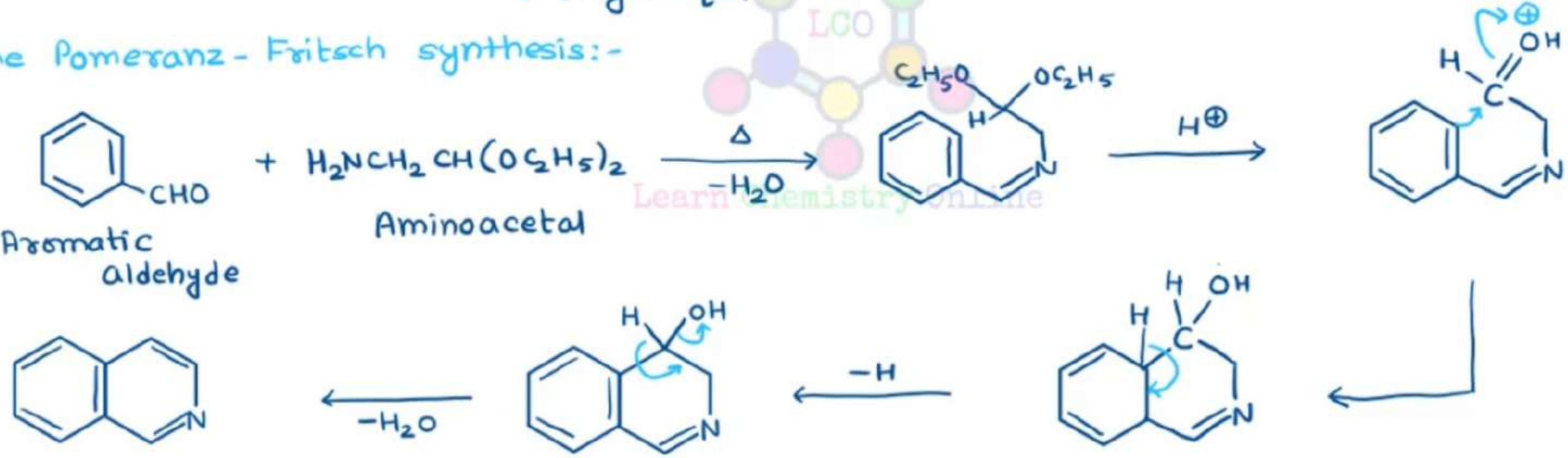


2. The Pictet-Spengler synthesis:-

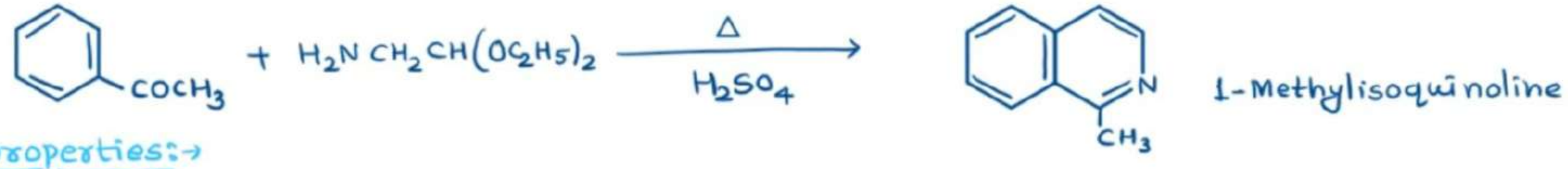
- This synthesis involves condensation of a β-arylethylamine with an aldehyde in the presence of excess acid.



3. The Pomeranz-Fritsch synthesis:-



- If an aromatic ketone is used then the product is 1- substituted isoquinoline



- Physical properties:→
- Isoquinoline is a colourless liquid.
- b.p. 516 K
- Chemical reactions:-

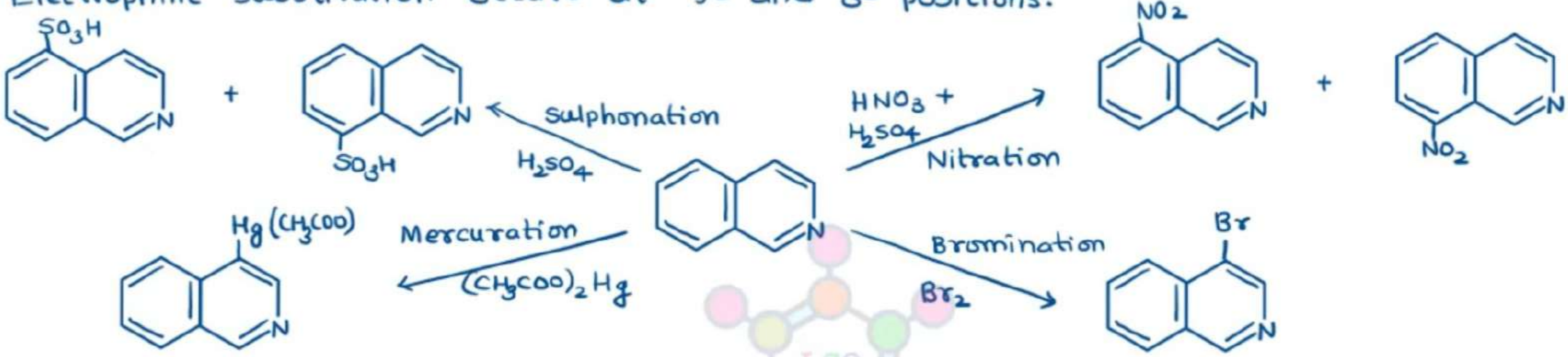
1. Basic nature:-

- Due to availability of lone pair of N- atom, isoquinoline shows basic character and form quaternary salts when reacts with acids or alkyl halides.

- Isoquinoline is a strong base than quinoline because in quinoline the N-atom is directly attached to the benzene ring due to which its lone pair is delocalised on the ring and hence is less available for protonation. On the other hand, in isoquinoline, N-atom is not directly attached to the benzene ring due to which its electrons are easily available for protonation.

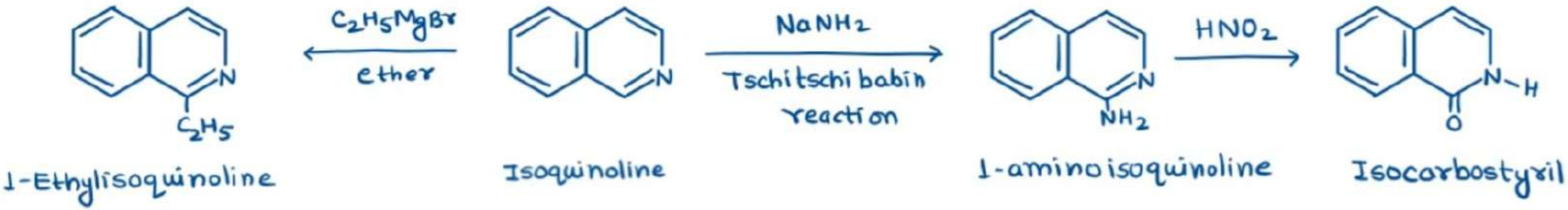
2. Electrophilic substitution:-

- Electrophilic substitution occurs at 5- and 8- positions.



3. Nucleophilic substitution:-

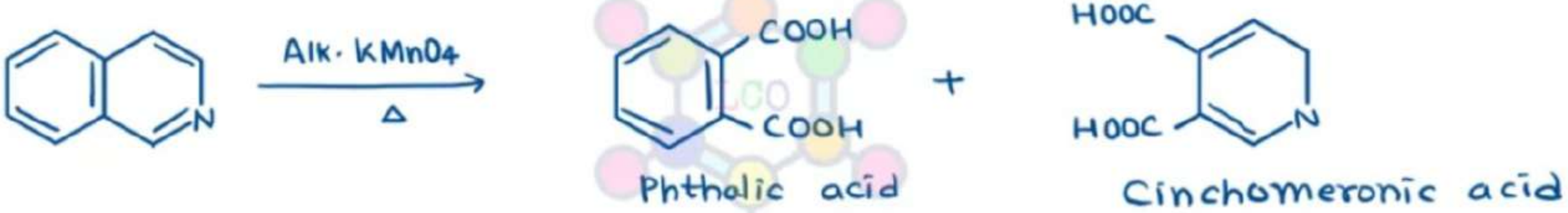
- Nucleophilic substitution occurs at 1- position



4. Side chain reactivity:-

- Alkyl group present ortho or para position to N-atom shows acidic nature.

5. Oxidation:-



6. Reduction:-