

Heterocyclic Compounds

Introduction: Molecular orbital picture and aromatic characteristics of pyrrole, furan, thiophene and pyridine, Methods of synthesis and chemical reactions with particular emphasis on the mechanism of electrophilic substitution. Mechanism of nucleophilic substitution reactions in pyridine. Comparison of basicity of pyridine, piperidine and pyrrole. Condensed Heterocycles: Introduction, Preparation of Quinoline (Skraups Synthesis), Isoquinoline (Bischler - Napirlaski) and Indole (Fischer indole Synthesis).

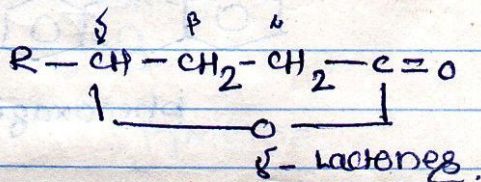
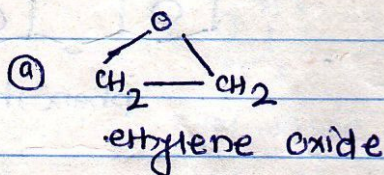
Introduction -

Those cyclic compounds which in addition to carbon contain at least one atom other than carbon i.e heteroatom (Hetero - Greek word; other) within their ring called as heterocyclic compounds. Heteroatom is generally oxygen, nitrogen & sulphur. Some heterocyclic compounds or heterocycles which possess aromatic character or stability are called as aromatic heterocyclic compounds.

These heterocycles may be five membered or six membered compounds contain conjugated system & they obey Huckel rule i.e $(4n+2) \pi$ electrons.

Some compounds like ethylene oxide & δ -lactone possess heteroatom but they are not heterocycles, because ring easily opened (i.e they are not stable), did not show aromatic character.

e.g.



Classification of heterocyclic compounds:-

(a) Five membered heterocyclic compound contain one heteroatom.

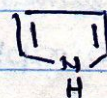
e.g.



furan



Thiophene



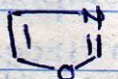
Pyrrole

(b) Five membered heterocycles contain two heteroatoms.

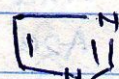
e.g.



Thiazole



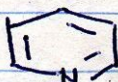
Oxazole



Imidazole

(c) Six membered compounds containing one heteroatom.

e.g.



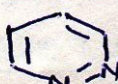
Pyridine



Piperidine

(d) Six membered compound containing two heteroatoms.

e.g.

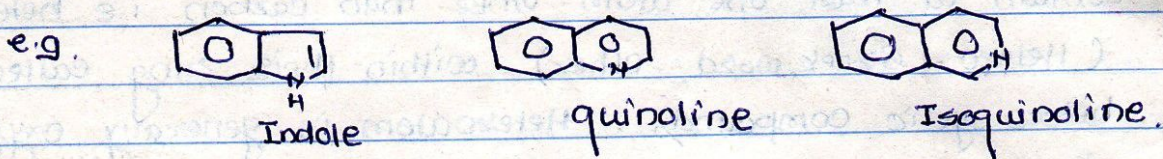


Pyrimidine

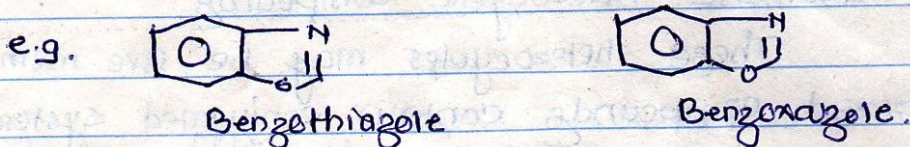


Pyrazine

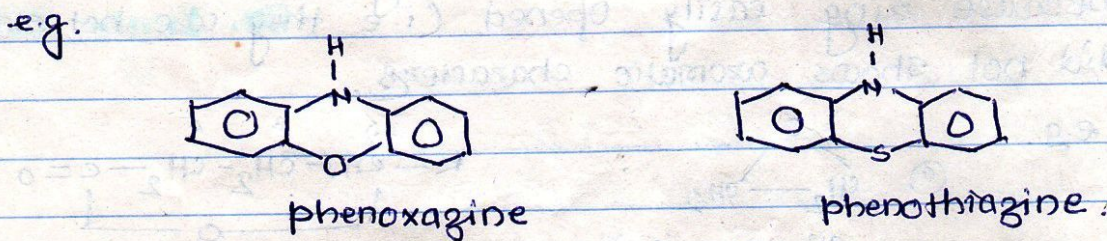
e) Bicyclic compound containing one heteroatom.



f) Bicyclic compound containing two heteroatoms.



g) Polycyclic compounds containing more than two rings & two heteroatoms.







Nomenclature :-

In 1957 IUPAC recommended rules for systematic names for heterocyclic compounds. There is another system implement for names i.e. trivial names or common name systems. For simple heterocycles common name system used, but by IUPAC following some rules.

a) Prefixes are used for the heteroatom, i.e.

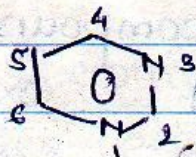
- Oxa for oxygen.
- Sila for silicon.
- Thia for sulphur.
- Phospha for phosphorus.
- Aza for nitrogen.

Structure	Trivial system	IUPAC system.
a) 	fuzan	oxazole.
b) 	Thiophene	Thiazole.
c) 	Pyzrole	Azole.
d) 	Pyridine	Azine.

(B) In a monocyelic compound containing only one hetero atom, numbering starts at this hetero atom.

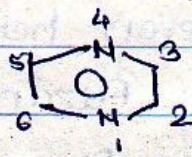
(C) When two or more of the same heteroatoms are present the prefixes di, tri, etc.

e.g.



common - Pyrimidine

IUPAC - 1,3-Diazine.



Pyrazine.

1,4-diazine.

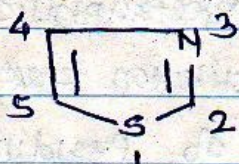
(D) When the ring contains more than one type of hetero-atom then the position 1 (first preference) is given to the element from the highest group number of the periodic table.

e.g. If O & N prefer 1st O (group VI) before N (group V)

If S & N prefer 1st S (group VI) before N (group V).

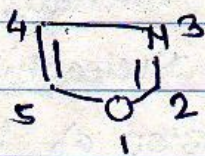
The first preference given to a such element which have a lowest atomic number. If they are in same group

e.g. O (group VI At. No. 08) S (group VI At. No. 16)



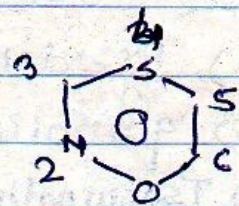
1,3-Thiazole

(1,4 thiazole wrong)



1,3-oxazole

(1,4-oxazole wrong)



1,4,2-oxathia-

azine.

1,4,6-oxathia-azine

Importance of Heterocyclic compounds :-

most of the heterocycles have important applications. Nitrogen heterocycles have a pharmacological application.

e.g. Triazole are used as tranquilliser & sedatives. Some nitrogen heterocycles shows antipyretic; anti-inflammatory & analgesic activity. Quinoline is antiseptic. Some heterocycles used in polymer industry. fused heterocycles i.e. triazolothiazoles are insecticidal & fungicidal agents. Triazolobenzothiazoles & Triazolobenzoxazoles used as plant protective agents & agricultural fungicides.

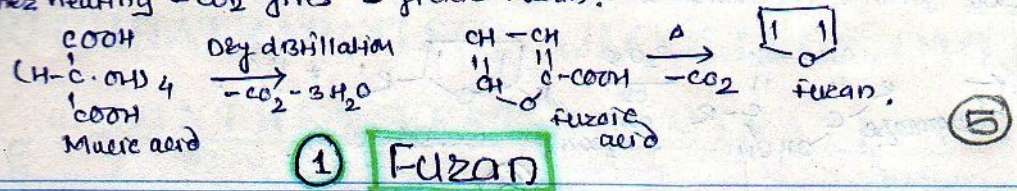
Here seven heterocyclic compounds are included.

- ① Furan C1=CC=CO1 Oxazole
- ② Pyrazole C1=CN=CN1 Azole
- ③ Thiophene C1=CC=CS1 Thiophene
- ④ Pyridine C1=CC=NC=C1 Azine.
- ⑤ Indole C1=CC=C2C(=C1)N=CN2
- ⑥ Quinoline C1=CC=C2C(=C1)N=CN2
- ⑦ Isoquinoline C1=CC=C2C(=C1)N=CN=C2

contents given in new syllabus →

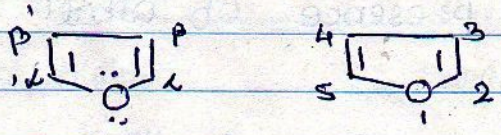
- 1) Pyrazole
 - 2) Furan
 - 3) thiophene
 - 4) pyridine
 - 5) quinoline
 - 6) Isoquinoline - comparison of basicity of pyridine; piperidine & pyrazole.
 - 7) Indole
 - 8) condensed heterocycles - Introdⁿ & synthesis of Isoquinoline by Bischler Napieralski
- * Introduction; M.O. picture & aromatic characteristics of all.
 * Method of synthesis
 Mechanism of electrophilic & nucleophilic substitution reactⁿ in pyridine.

Synthesis of Furan (1) From Maleic Acid - on distillation in dry condⁿ yield furanic acid on further heating - CO₂ gives & yields furan.



1 Furan

Furan is a five membered oxygen contained azomate heterocyclic compound.



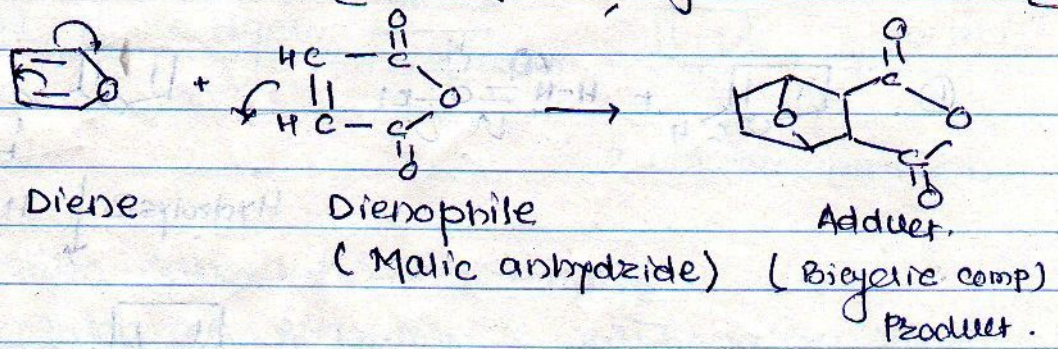
Furan or oxazole.

Properties of furan :- (A) physical properties.

- (1) It is colourless liquid its B.P. 32°C
- (2) It is insoluble in water but soluble in organic solvents like CCl₄; CHCl₃
- (3) Furan resemble like benzene but tends to open or break readily at the oxygen atom.
- (4) It is most reactive five membered heterocycles.

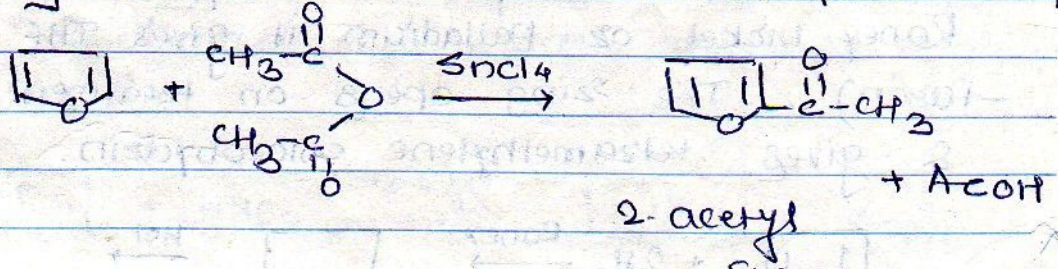
(B) chemical properties of furan. Addition Reactions

(1) Diels-Alder reaction :- furan chemically behaves as an non-aromatic compound but it is less aromatic than pyrazole & thiophene. In this reaction furan acts as diene & other acts dienophile, gives adduct forms.

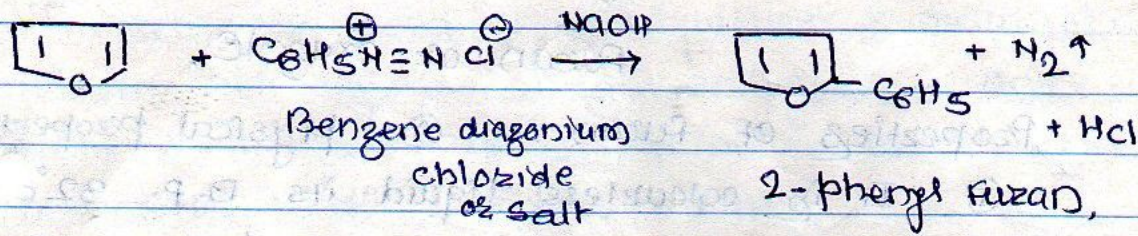


(2) Friedel-Craft reaction! (Electrophilic substitution)

Furan undergoes above reaction in +ve of stannous chloride it reacts with acetyl chloride or acetic anhydride & incoming electrophile comes as 2 or 5-position only

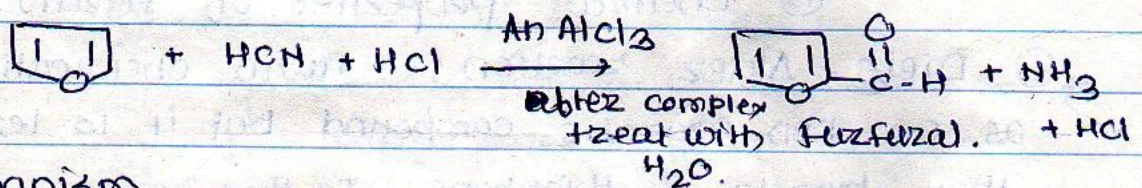


③ Gomberg reaction! - or coupling or Diazotization.
 Furan reacts with benzene diazonium salt or chloride in presence of alkali & gives 2-phenyl furan.

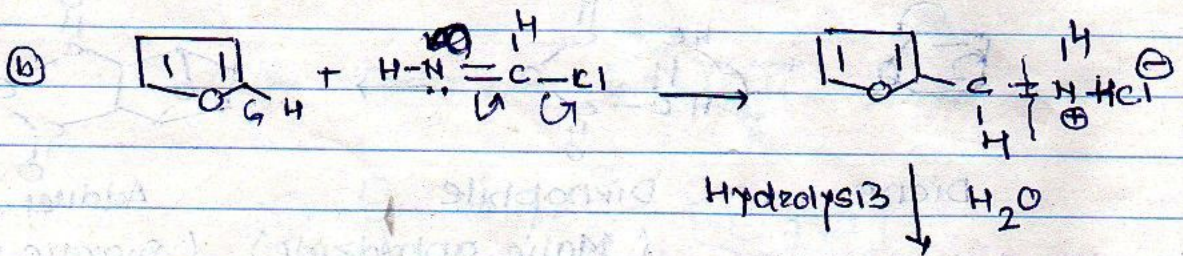
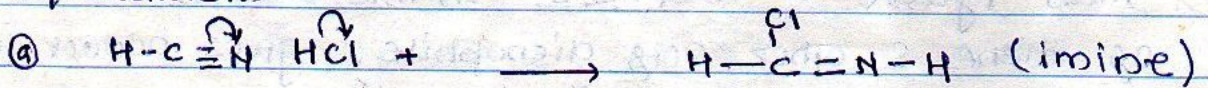


④ Gatterman reaction! -

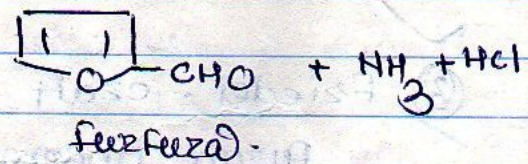
Furan if treated with HCN & HCl in presence of an- AlCl_3 give complex i.e. imine complex which on decomposition with water yields furfural. It is called as Gatterman reaction.



Mechanism

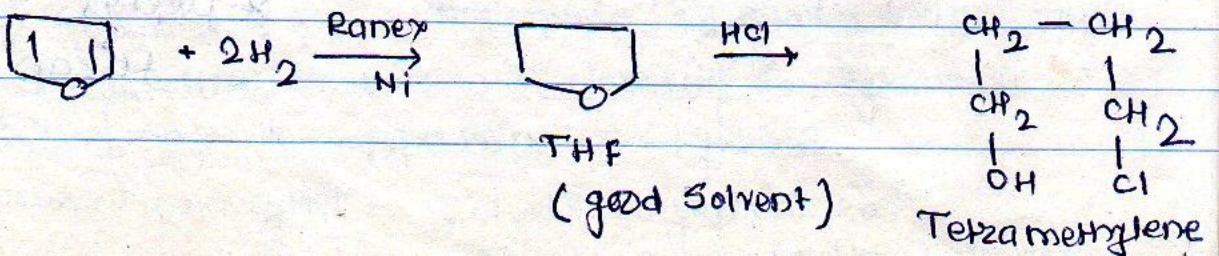


Hydrolysis \downarrow H_2O



⑤ Reduction reaction! -

Furan easily reduced by catalytic redn with Raney nickel or palladium it gives THF (tetrahydrofuran). The ring opens on treatment with HCl & gives tetramethylene chlorohydrin.



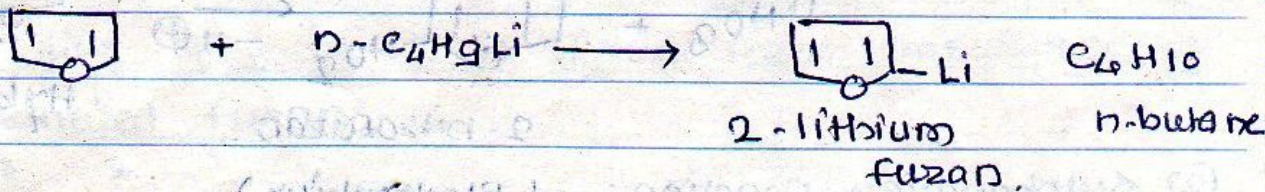
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Nucleophilic Substitution

⑥ Reaction with n-butyl lithium :-

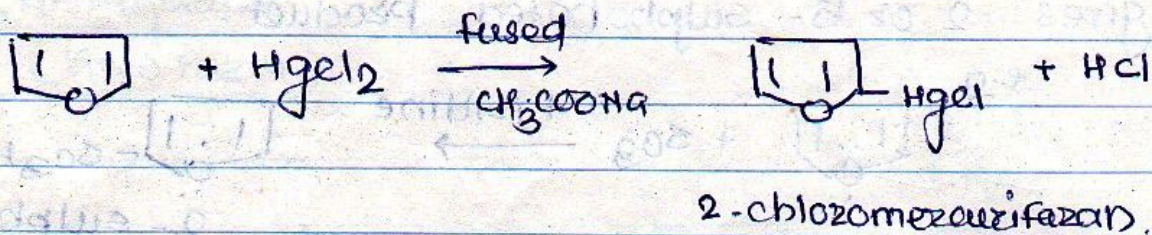
- ① Amination - NaNH_2
- ② Hydroxylation - KOH

Furan reacts with n-butyl lithium & gives 2-lithium furan & hydrocarbon.



⑦ Reaction with Mercuric chloride :-

Furan reacts with HgCl_2 in +nce of fused sodium acetate to form 2-chloromercurifuran.

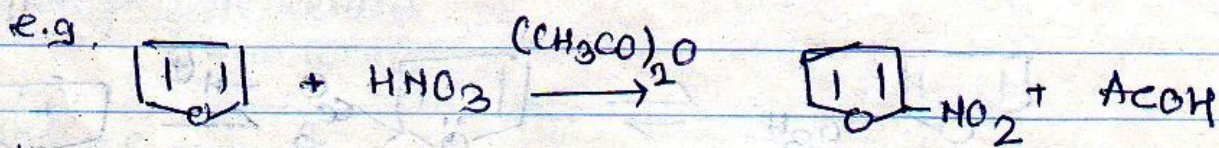


⑧ Electrophilic substitution reactions

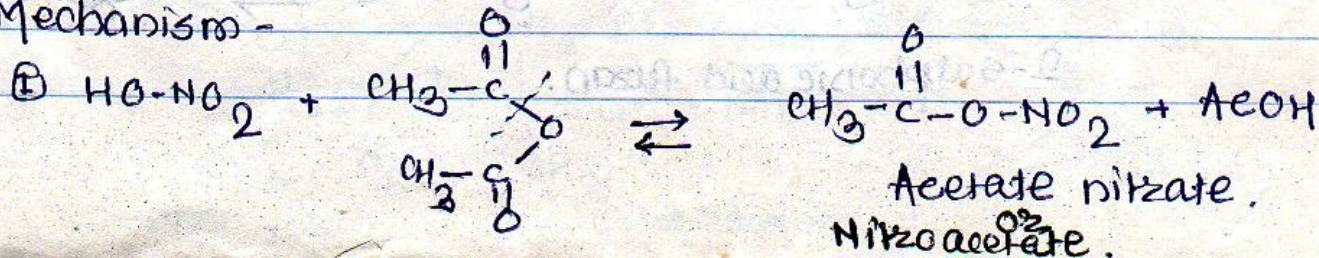
Such as Nitration & Sulphonation reaction.

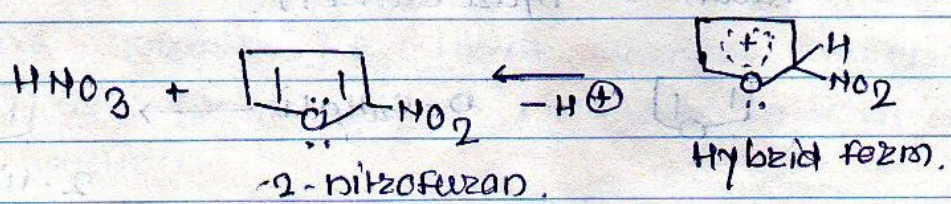
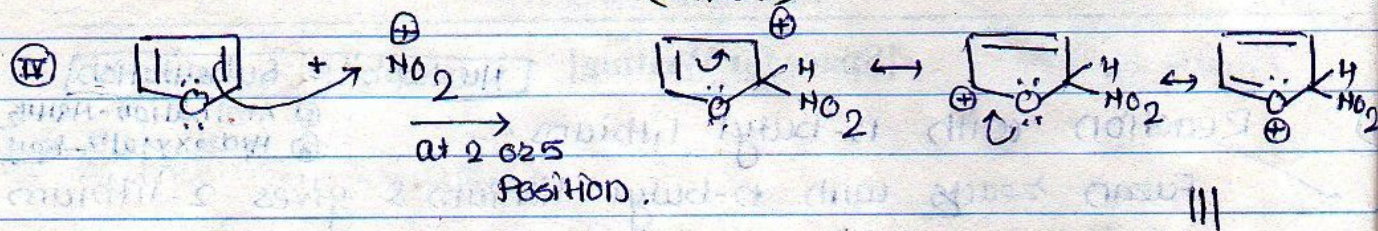
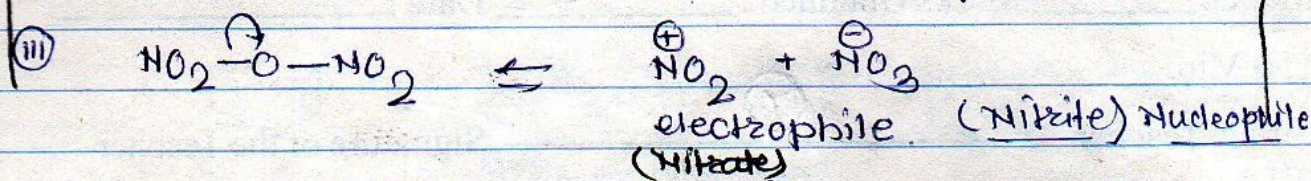
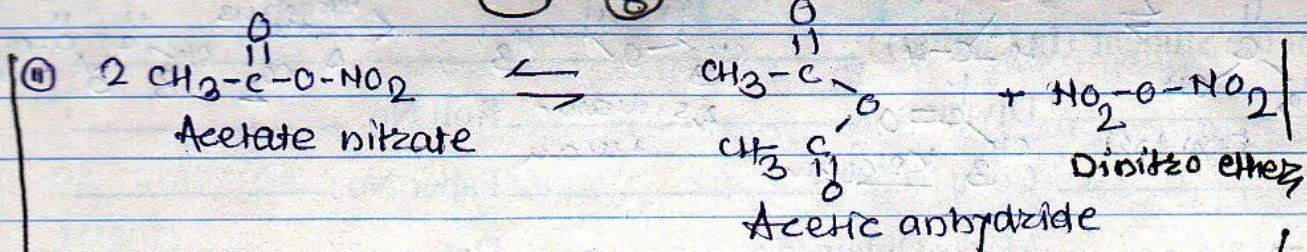
(Electrophilic) & Friedel-Crafts Acylation

① Nitration Reaction :- Furan direct nitration reaction not occurs it gives polymerisation if treated with conc- HNO_3 or nitrating mixture. so that nitration carried out with nitric acid in +nce of acetic anhydride to gives 2-nitro furan.



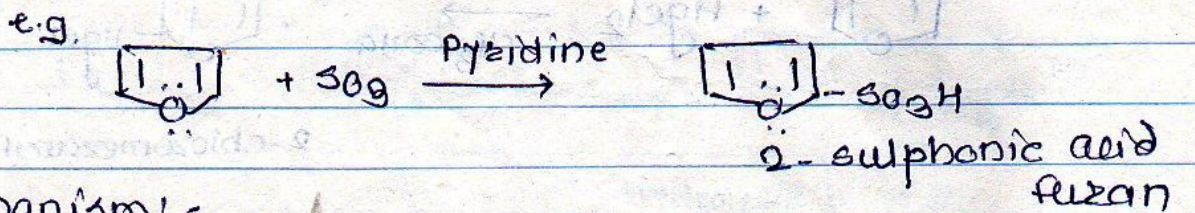
Mechanism -





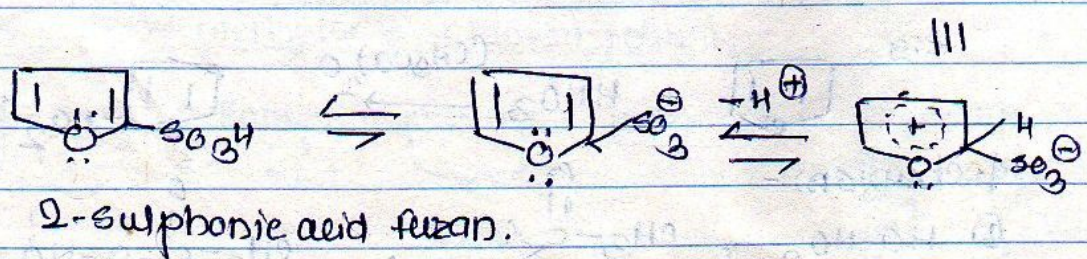
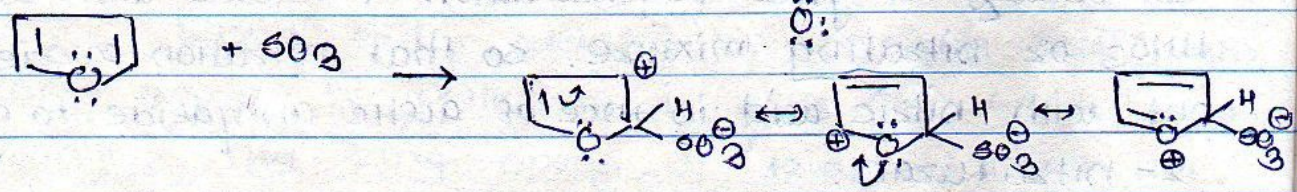
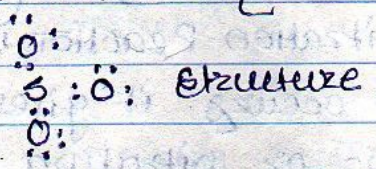
② Sulphonation Reaction:- (Electrophilic)

Furazan get decomposed if it reacts with conc. H_2SO_4 or other strong acid, so that sulphonation carried in +ve of SO_3 gas passing in +ve of pyridine gives 2 or 5-sulphonated product.



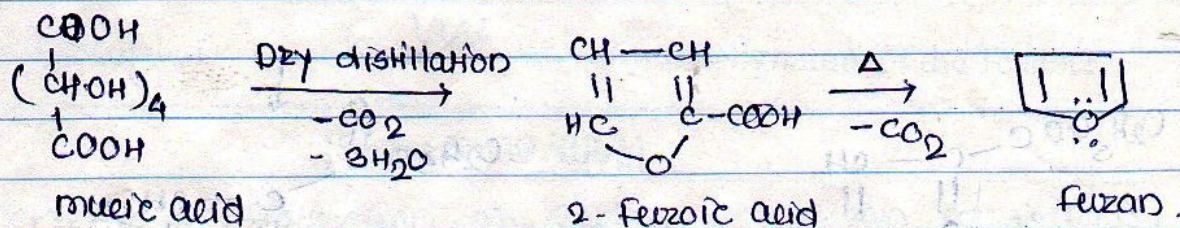
Mechanism:-

SO_3 is a electron deficient neutral molecule (Lewis acid) Hence acts as electrophile. Pyridine & SO_3 reacts first to form 1-protopyridium sulfonate which acts as a source of electrophile i.e SO_3 .



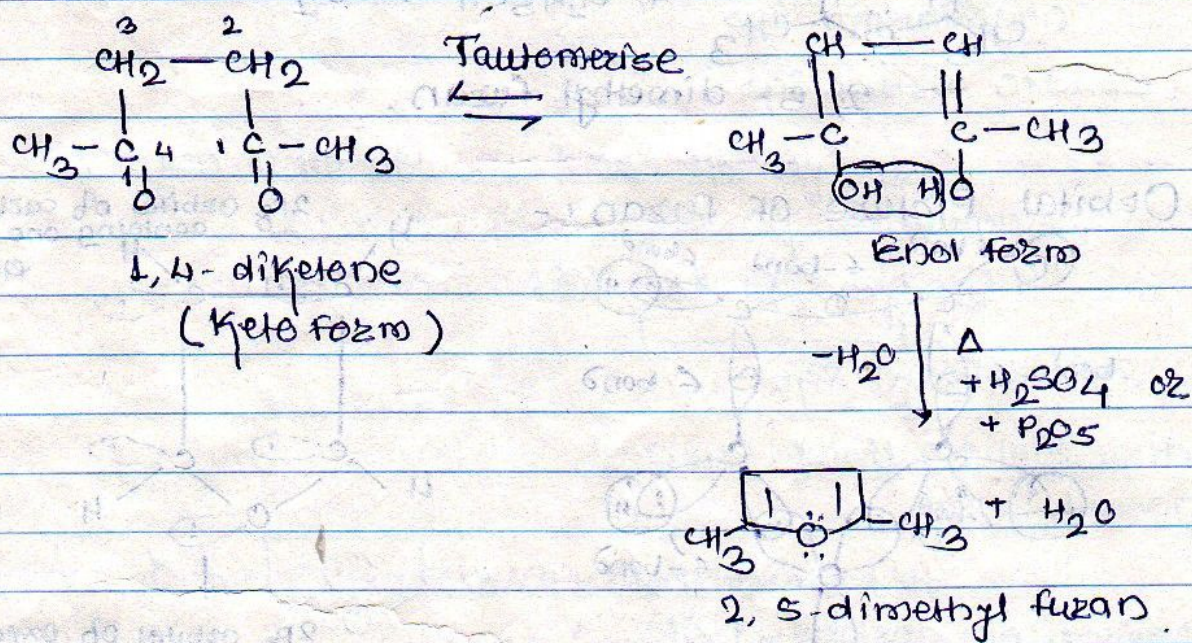
Preparation of furan :-

(a) From Mucic acid :- Mucic acid on distillation under dry condition gives 2-furoic acid on heating at its B.P. decarboxylation occurs & gives furan.



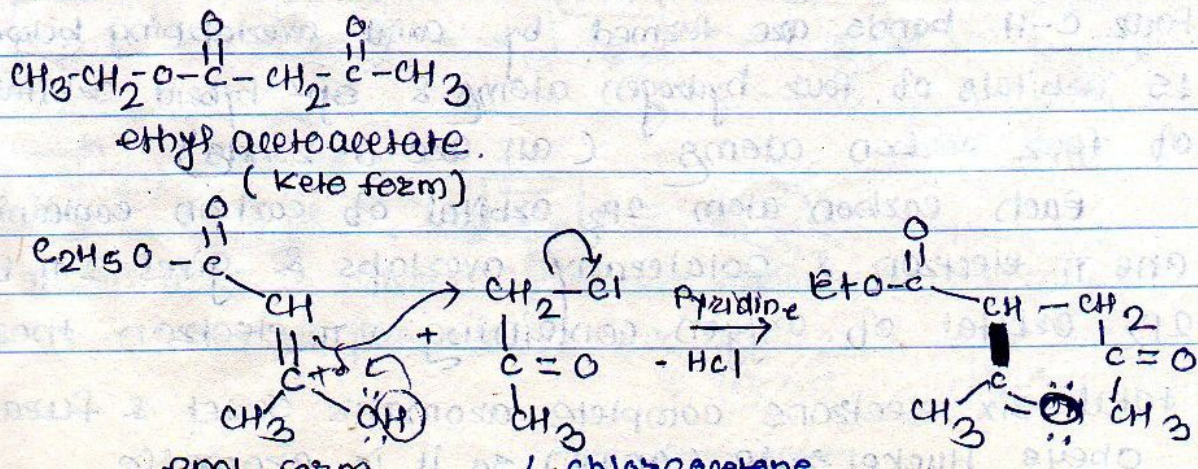
(b) From 1,4-Diketones or 1,4-dialdehyde :-

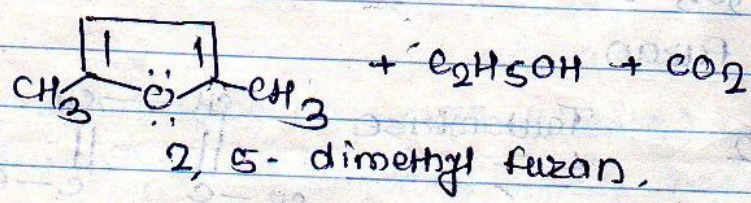
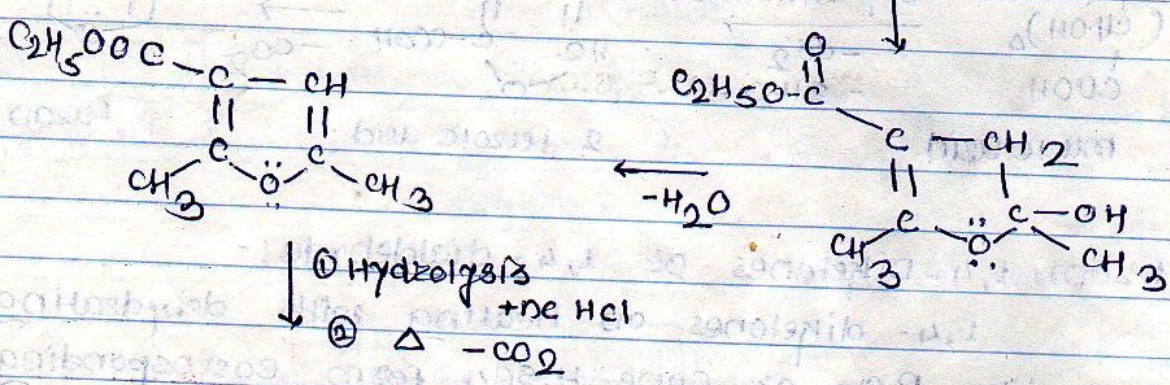
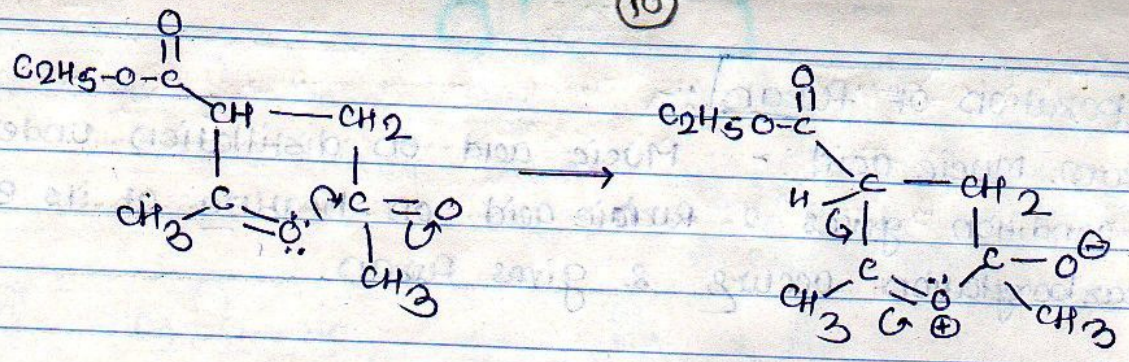
1,4-diketones on heating with dehydrating agent like P_2O_5 or conc H_2SO_4 form corresponding substituted furan.



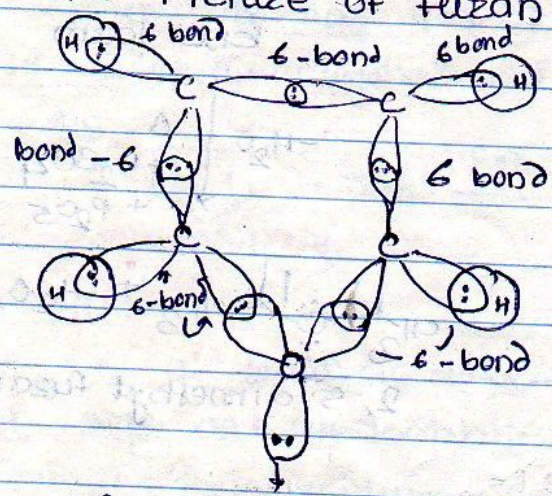
(c) From ethyl acetoacetate :-

when α -chloroacetone & β -ketoester or ethylacetoacetate condensed with each other in +nce of pyridine gives substituted furan.

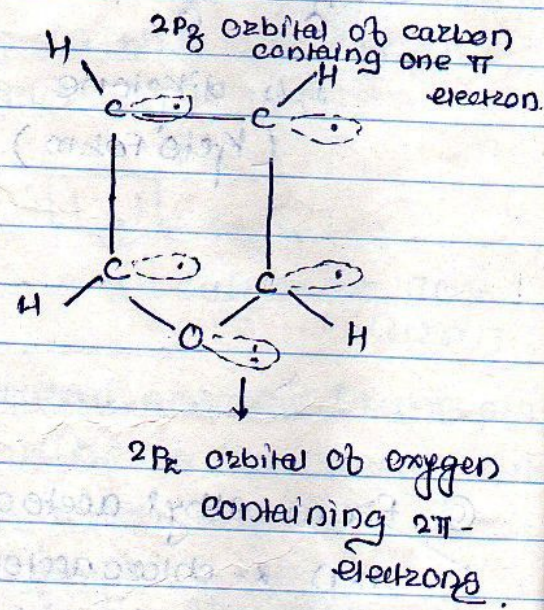




Orbital Picture of furan :-



sp^2 hybrid orbital of oxygen containing unshared pair of electron.

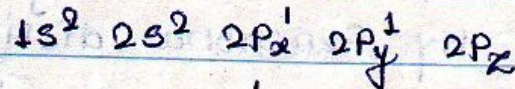


Four C-H bonds are formed by axial overlapping between 1s orbitals of four hydrogen atoms & sp^2 hybrid orbitals of four carbon atoms (all are σ -bonds)

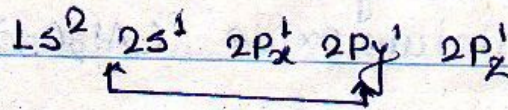
Each carbon atom $2p_z$ orbital of carbon containing one π electron & collaterally overlaps & gives 2π bonds. $2p_z$ orbital of oxygen containing 2π electron these total six electrons complete aromatic sextet & furan

Electronic configuration of carbon & oxygen as follows;

Carbon At. No. 06



↓ Excitation.

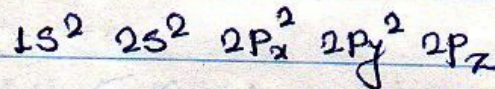


03

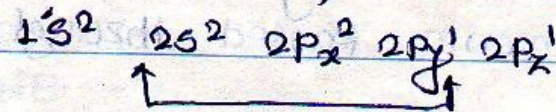
sp² hybridization

sp² hybrid orbitals.

Oxygen At. No. 08

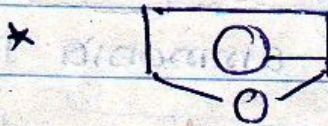


↓ excitation.



sp² hybridization.

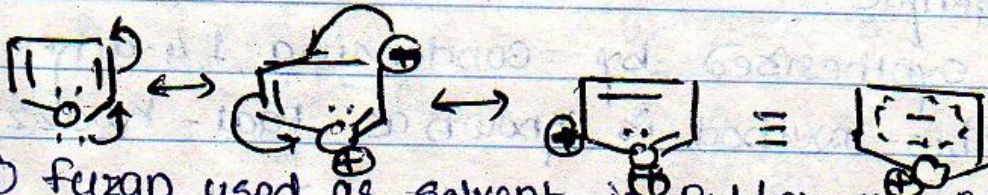
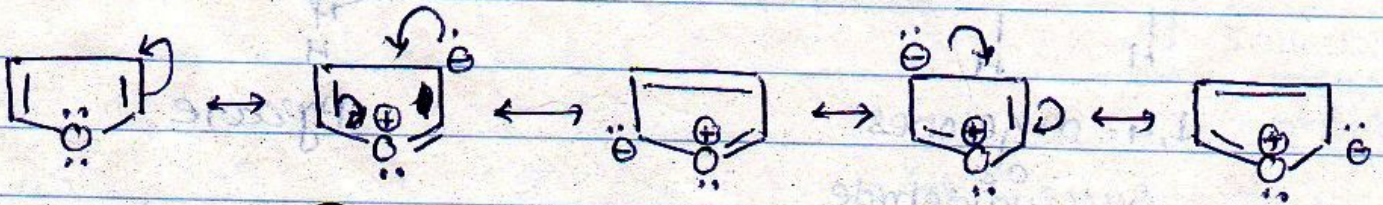
3 sp² hybrid orbitals with four electrons.



π - electron cloud of

six p_z electron so it aromatic

Resonance Structure of furan as follows;



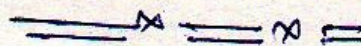
III

① furan used as solvent in Rubber manufacture.

② It is used as preservative for leather & wood.

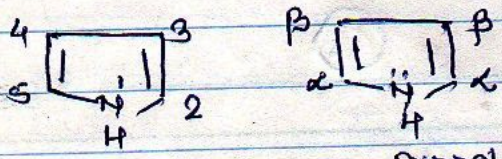


Hybrid forms.



② Pyrazole

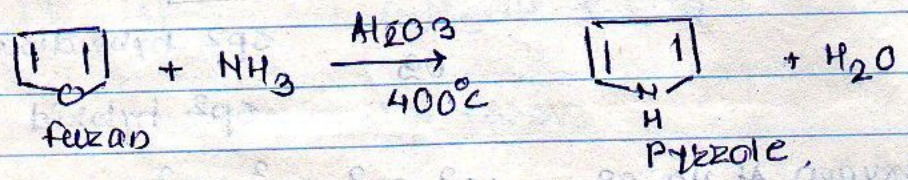
It is important five membered heterocyclic compound it contains nitrogen as heteroatom. Many natural compounds like chlorophyll; haematin; alkaloid etc contain pyrazole ring, it also occurs in coal tar & bone oil.



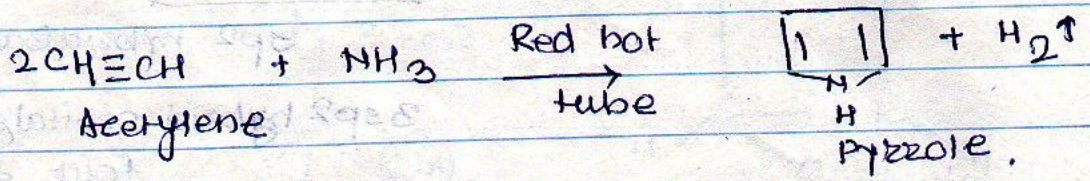
Azole or Pyrazole.

Preparation Method or synthesis of pyrazole :-

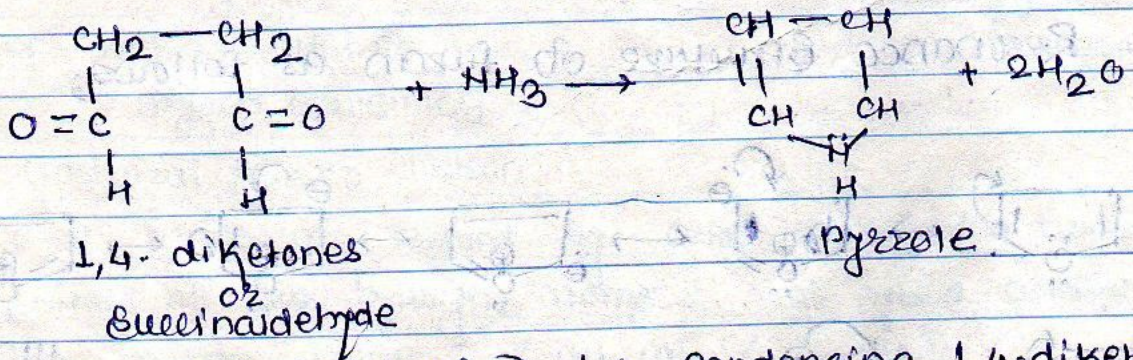
① Fractional Distillation - generally pyrazole found in coal tar, by fractional distillation it is isolated. The commercially pyrazole prepared by treating furan & NH_3 with Aluminium oxide (Al_2O_3) as a catalyst at 400°C



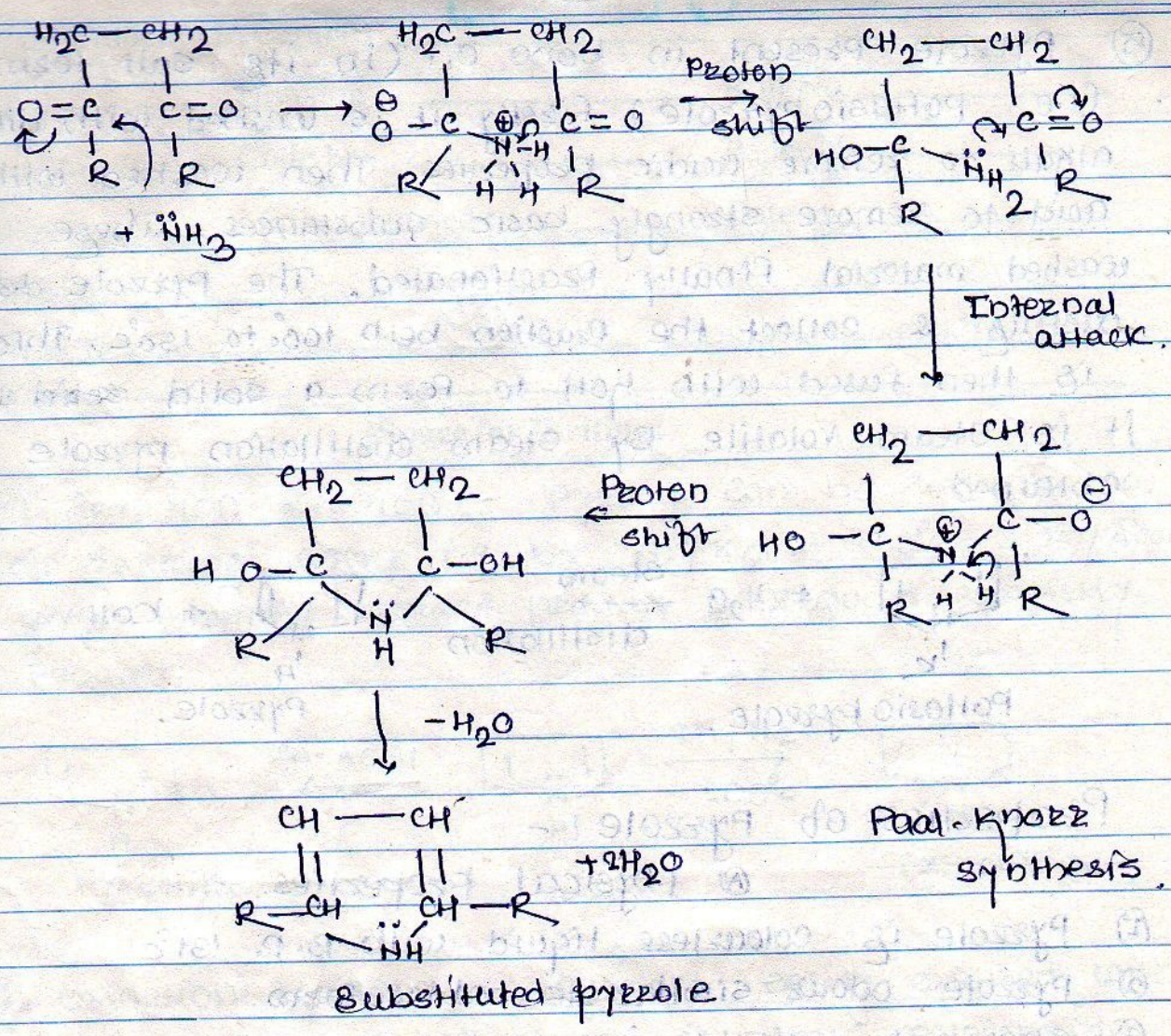
② It can be synthesised by passing acetylene gas with ammonia passed through red hot tube.



③ Succinaldehyde when reacts with ammonia it yields pyrazole but yield is poor.

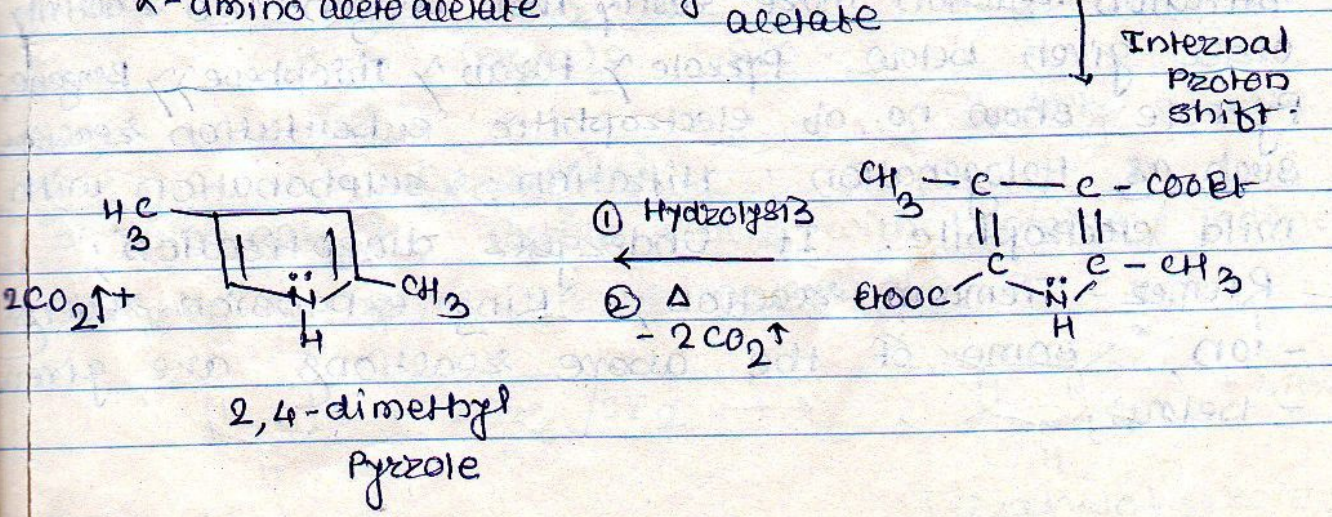
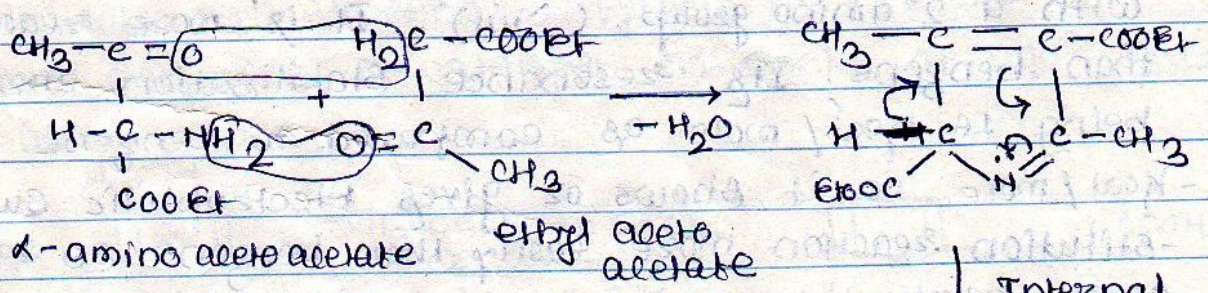


Pyrazole can be synthesised by condensing 1,4-diketones with ammonia. This method is known as Paal-Knorr synthesis.

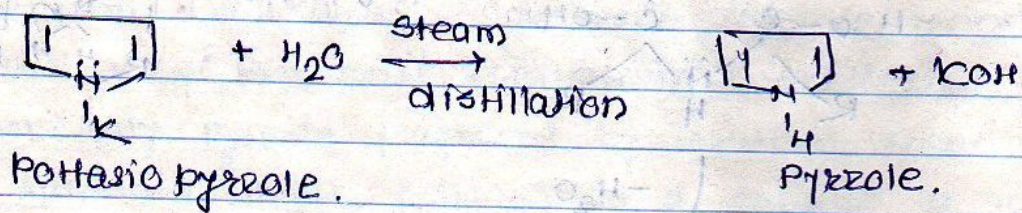


④ From ethyl acetoacetate (-)

The condensation between α -amino ethyl acetoacetate & ethyl acetoacetate gives substituted pyrazole, It is also known as Knorr-pyrazole synthesis.



⑤ Pyrrazole present in bone oil (in its salt form) (i.e. potassium pyrrazole) firstly it is washed with dil-alkali to remove acidic properties. Then washed with acid to remove strongly basic substances. These washed material finally fractionated. The pyrrazole distills distilling & collect the fraction betw 100°C to 150°C. This is then fused with KOH to form a solid salt. It is steam volatile by steam distillation pyrrazole obtained.



Properties of Pyrrazole :-

① Physical properties.

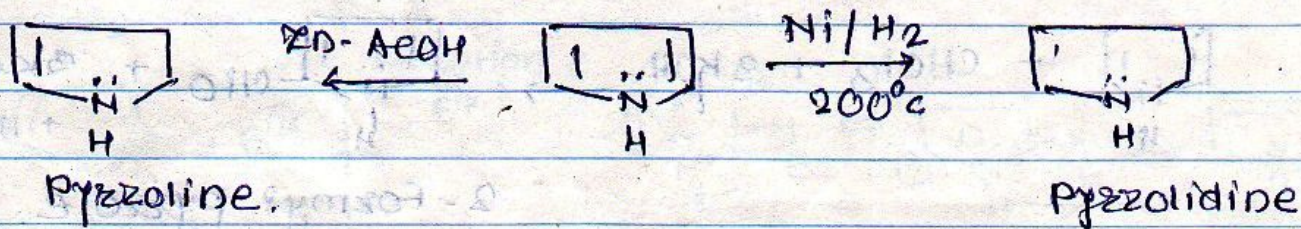
- ① Pyrrazole is colourless liquid with B.P. 131°C
- ② Pyrrazole odour similar to chloroform.
- ③ sparingly soluble in H₂O but freely soluble in cold
- ④ It rapidly turns brown when exposed to air.

② Chemical properties.

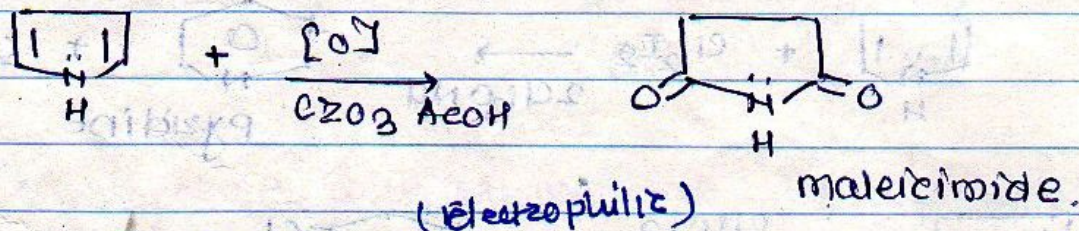
Pyrrazole has a heterocyclic compound or ring system with a 2° amino group (>NH). It is more reactive than benzene. Its resonance stabilisation energy being 16 kcal/mole as compared to benzene 36 kcal/mole so it shows or gives electrophilic substitution reaction more easily than benzene so reactivity order given below, Pyrrazole > furan > Thiophene > Benzene. Pyrrazole show no. of electrophilic substitution reaction such as Halogenation; Nitration; sulphonation with mild electrophile. It undergoes diazotisation; Riemez - Tiemann reaction; Ring expansion reaction; some of the above reactions are given below;

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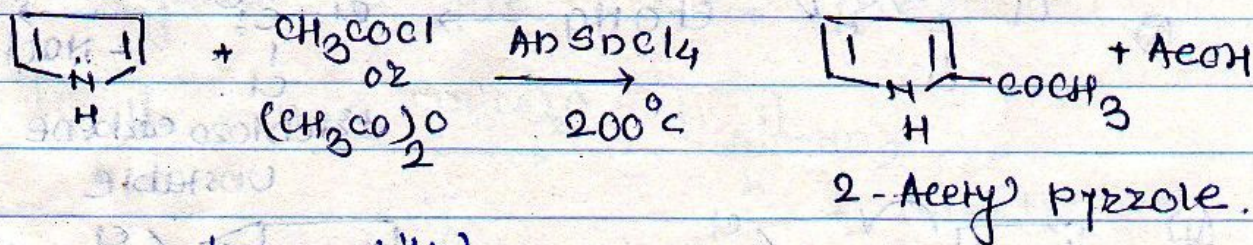
① Reduction Reaction: - Pyrrzole can be reduced no. of reducing agent i.e by Ni/H_2 at $200^\circ C$ & $Zn/AcOH$ gives partially reduced product & reduced completely product.



② Oxidation reaction: - Pyrrzole easily oxidized with Cr_2O_3 in presence of H_2SO_4 it gives maleimide.

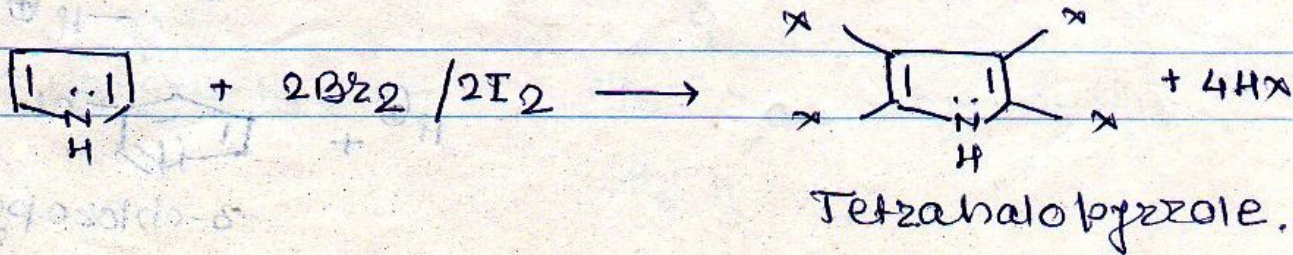


③ Friedel-Craft Reaction: - Pyrrzole in presence of acetic anhydride & catalyst $Al- SnCl_4$ at $200^\circ C$ gives 2-acetyl pyrrzole.

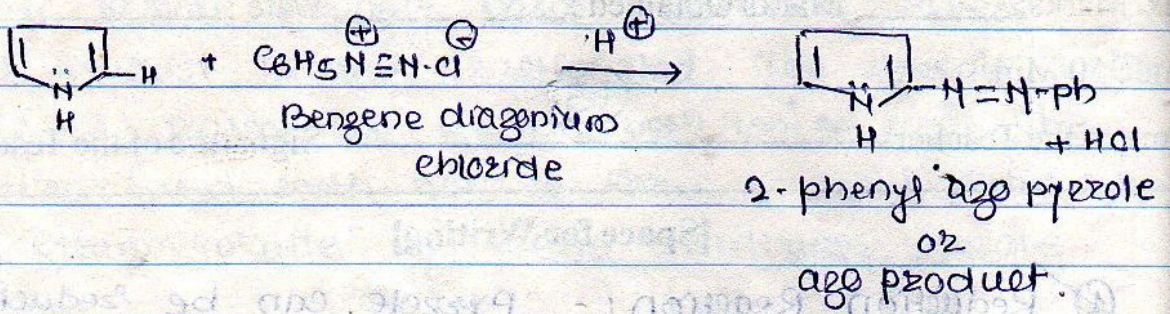


(Electrophilic)

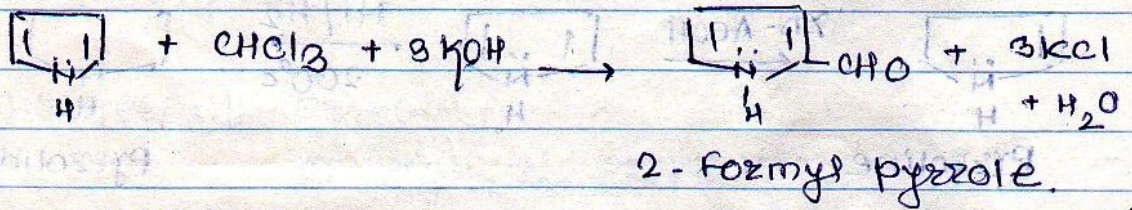
④ Halogenation: - Pyrrzole reacts with bromine / iodine solution it gives tetrahalopyrrzole.



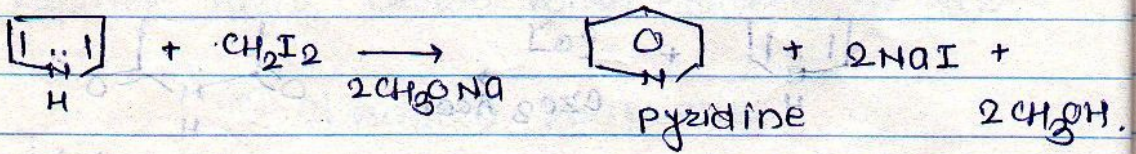
⑤ Diazotisation or coupling Reaction:- pyrazole reacts with benzene diazonium chloride in presence of acid soln & gives coupled product.



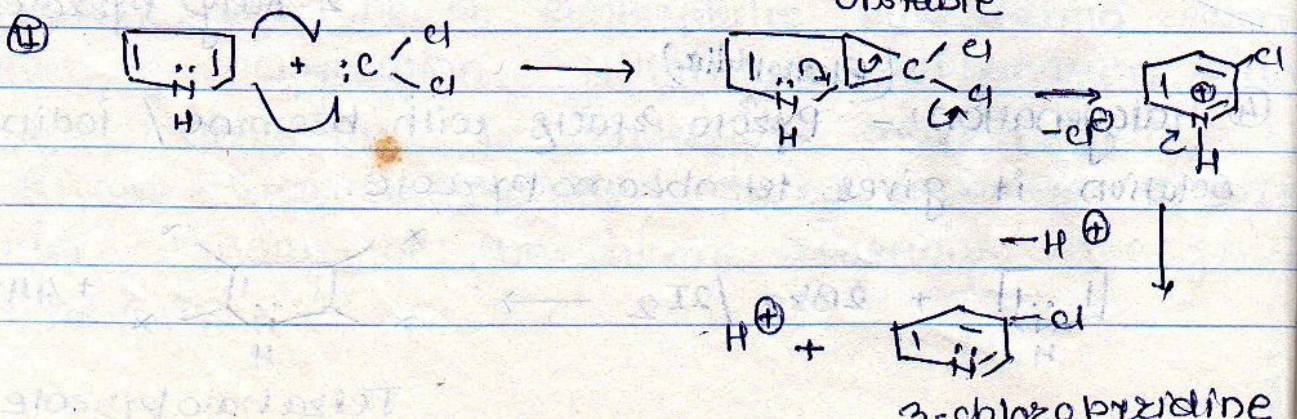
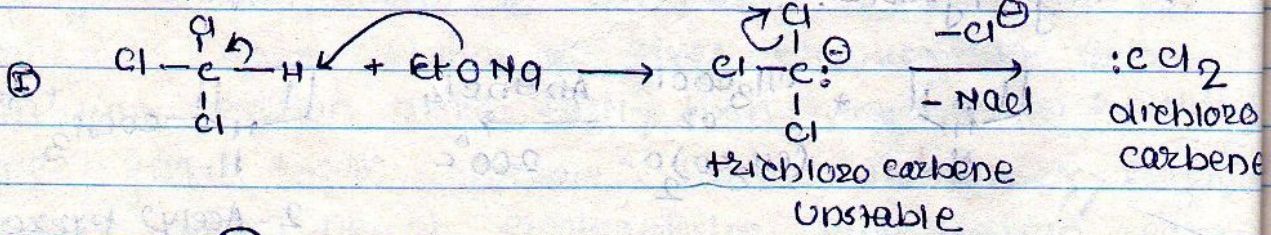
⑥ Reimer-Tiemann Reaction:- Pyrazole in presence of alkali soln (KOH or NaOH) reacts with chloroform to give 2-aldehyde pyrazole.



⑦ Ring expansion:- Pyrazole on heating with ethylmagnesium chloride & chloroform or methylene iodide gives ring expansion.



Mechanism:

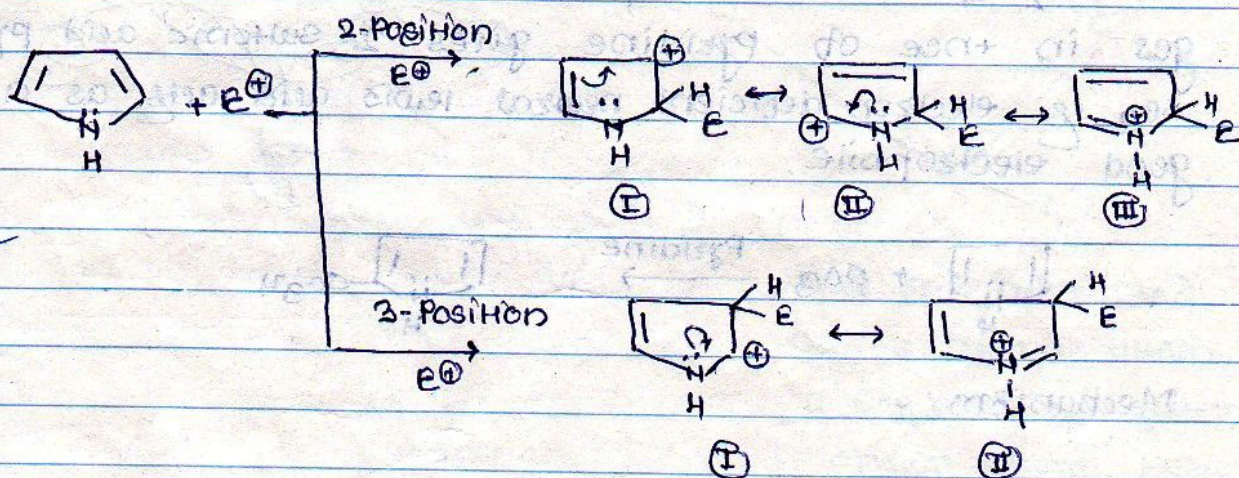


Electrophilic Substitution Reaction of Pyrrazole:-

Pyrrazole undergoes electrophilic substitution reaction which are characteristic of aromatic compounds. In pyrrazole attack of electrophile at 2 or 3 position of pyrrazole ring

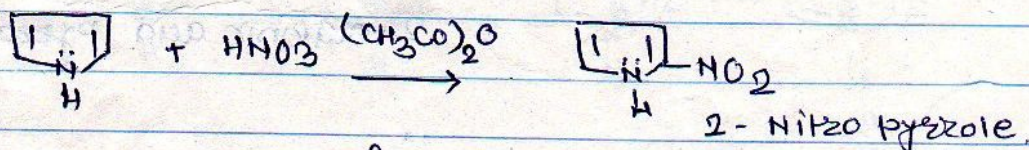
why 2 & 5 position preferred for attack than the position of 3 & 4 position in pyrrazole ring. It will be clear by forming a no. of resonating structure. If attack at 2 or 5 position it gives three stable resonating form / structure, & if at 3 or 4 position it gives only two stable resonating form / structures.

Due to more resonating form attack only at 2 or 5 position in pyrrazole ring; furan; thiophene etc.

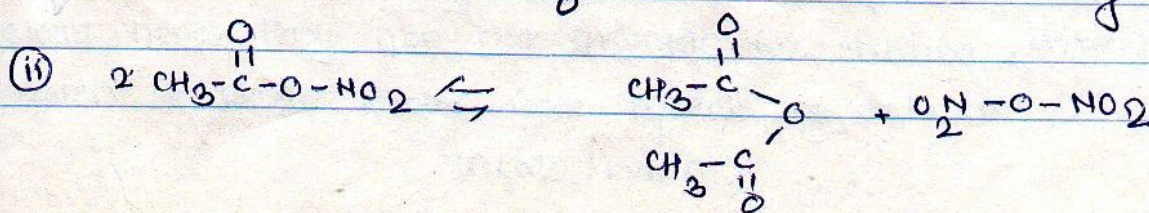
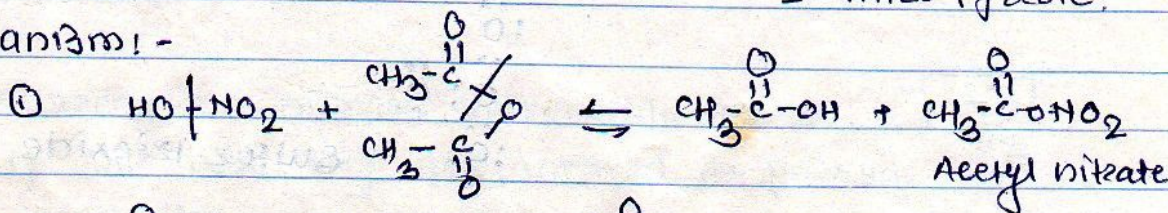


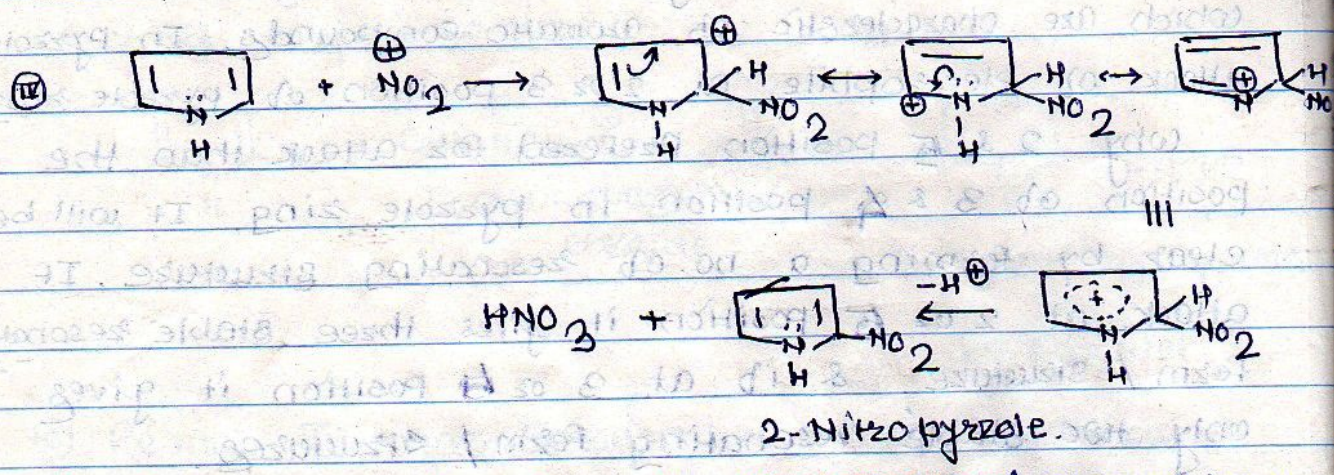
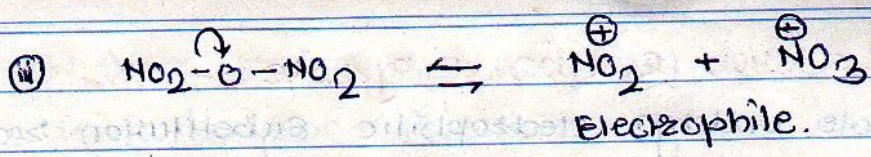
Nitration of Pyrrazole with Mechanism:- (Electrophilic)

Direct nitration of pyrrazole is not possible it gives polymerisation product on treatment with conc- HNO_3 or mixture of nitrating mixture. If nitration carried in presence of acetic anhydride to give 2-nitro pyrrazole.



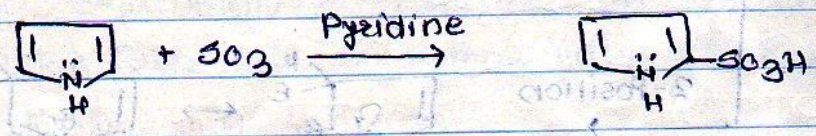
Mechanism:-



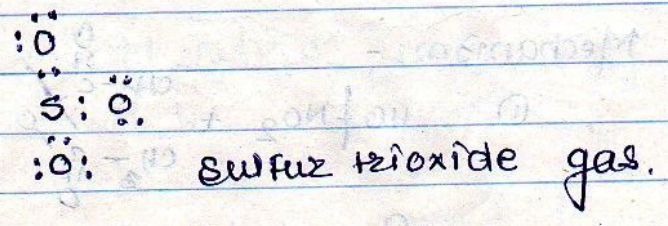
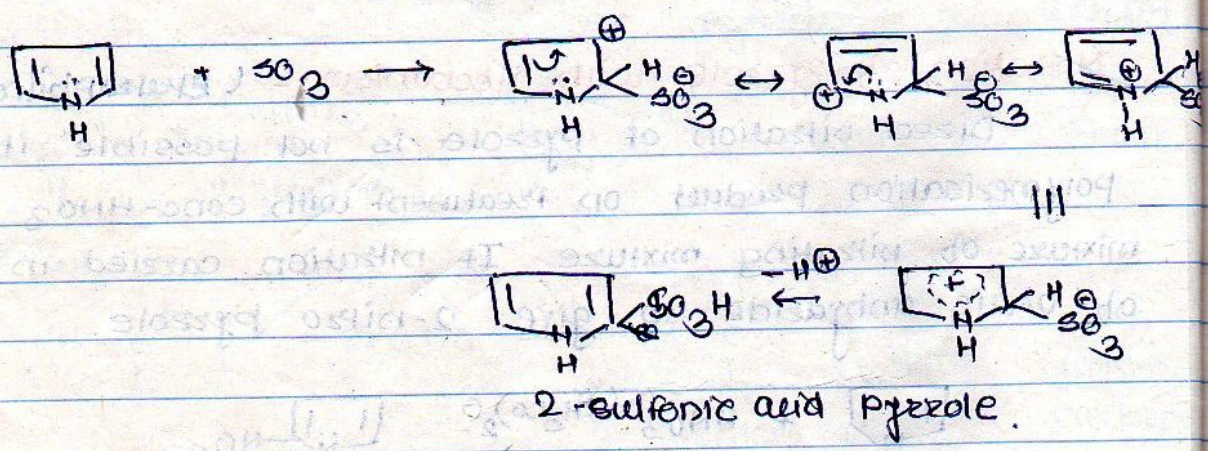


Sulfonation of pyrazole with Mechanisms: (Electrophilic)

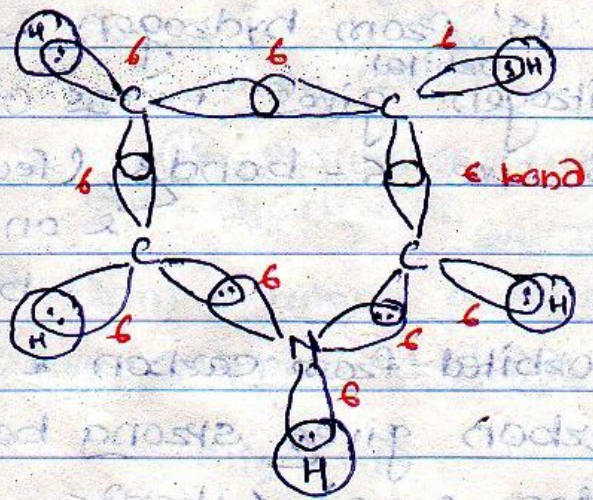
Pyrazole decomposed if directly treated with conc- H_2SO_4 . So that sulphonation carried out by SO_3 gas in presence of pyridine gives 2-sulfonic acid pyrazole. SO_3 is electron deficient neutral Lewis acid acts as a good electrophile.



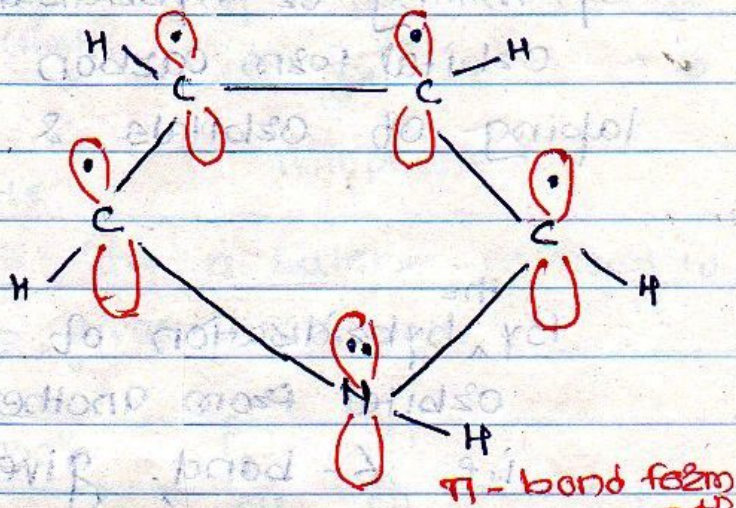
Mechanism:-



Molecular orbital picture of pyrrazole:-



6-bond formation



π -bond form

four sp^2 hybridized

carbon atoms sustain

a 6π electron system

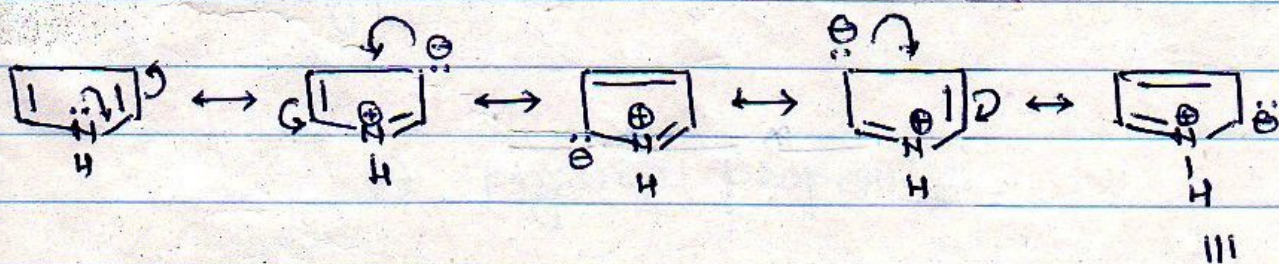
shown above. Here

nitrogen lone pair involve

in aromatic sextet,

and available for protonatⁿ.

Resonating structure of pyrrazole:-



Two electrons on nitrogen responsible for basicity but here they are involved in p-electron cloud hence they are not available for sharing



Hybrid form.

proton or acid. There fore pyrrazole is extremely weak base.

Electronic configuration for carbon & nitrogen.

Carbon At. No. 06 $1s^2 2s^1 2p_x^1 2p_y^1 2p_z^1$
 3 sp^2 hybridisation

sp^2 hybrid orbitals.

Nitrogen At. No. 07 $1s^2 2s^2 2p_x^1 2p_y^1 2p_z^1$

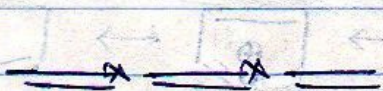
3 sp^2 hybridisation.

By mixing $2s$ hybridisation $1s^1$ from hydrogen & sp^2 orbital from carbon & nitrogen gives excess $2s$ overlap of orbitals & gives five σ -bonds, (four C-H & one N-H bonds)

By the hybridisation of sp^2 orbital from carbon & sp^2 orbital from another carbon gives strong bond i.e. σ -bond, gives (three C-C) σ -bonds.

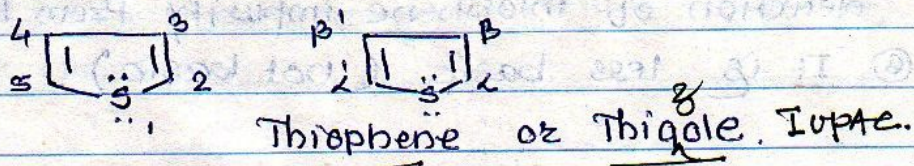
The Hybridisation of sp^2 orbital from carbon & sp^2 orbital from nitrogen gives C-N strong σ -bond (two C-N bonds).

The co-lateral overlapping of unhybridized P-orbitals of carbon & lone pair of electron from nitrogen gives aromatic sextet or π electrons.



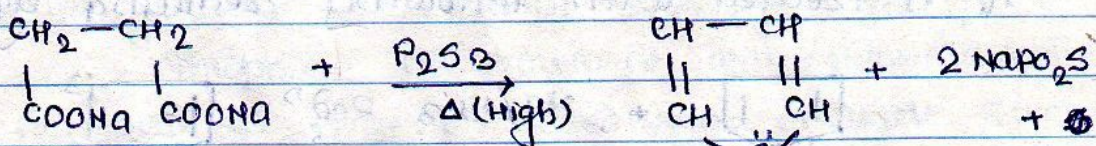
③ Thiophene

Thiophene is a five membered sulphur contained hetero-cyclic compound. It is found in coal tar & petroleum.



Preparation Methods of thiophene.

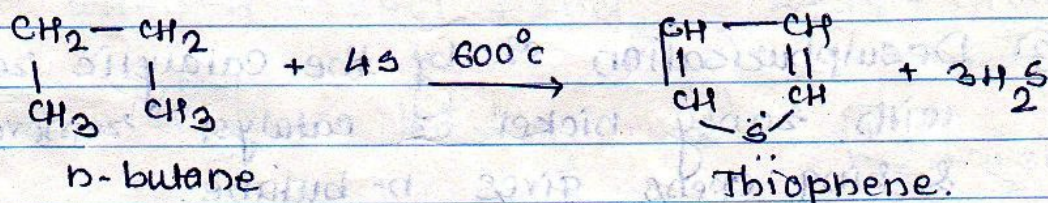
① From sodium succinate :- Thiophene prepared by heating sodium succinate with phosphorus trisulphide yield 83%.



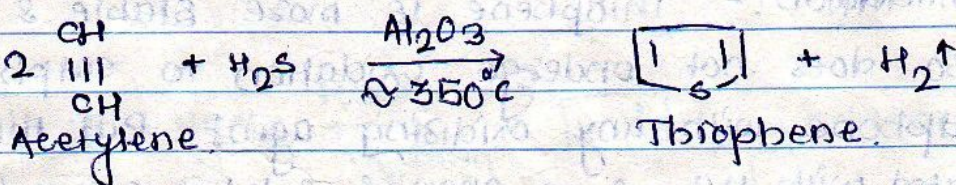
② Sodium succinate
OHC - CH₂ - CH₂ - CHO Succinaldehyde.

Thiophene

② From n-butane & sulphur :- The n-butane allowed to react sulphur at high temp gives thiophene.



③ From acetylene :- Thiophene manufactured on large scale by passing acetylene gas & hydrogen sulphide through red hot tube over Al₂O₃ at 350°C



Properties of thiophene :-

① physical properties.

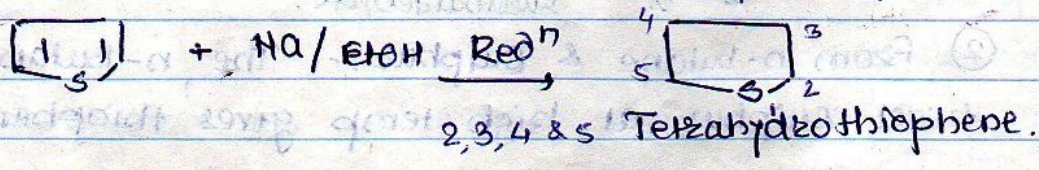
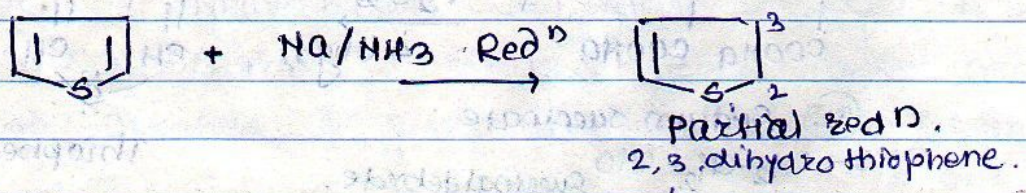
- ① It is colourless liquid b.p. 84°C.
- ② Its odour similar to that of benzene.
- ③ It is insoluble in water freely soluble in organic solvents (CHCl₃; CCl₄; ether).
- ④ It is flammable & slightly toxic.

- ⑤ Thiophene treated with isatin & conc. H₂SO₄ develops blue colour. This test is Endophenin test used for the detection of thiophene impurity from benzene.
- ⑥ It is less basic (not basic).

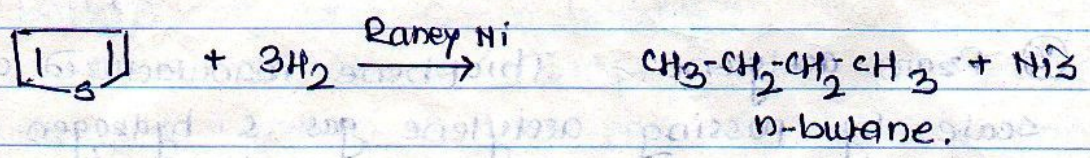
Chemical properties.

① Reduction Reaction:-

Thiophene can be reduced by no. of ways if it treated with following reducing agents,



- ② Desulphurisation or by the catalytic reduction with Raney nickel as catalyst removal of sulphur & ring opens, gives n-butane.

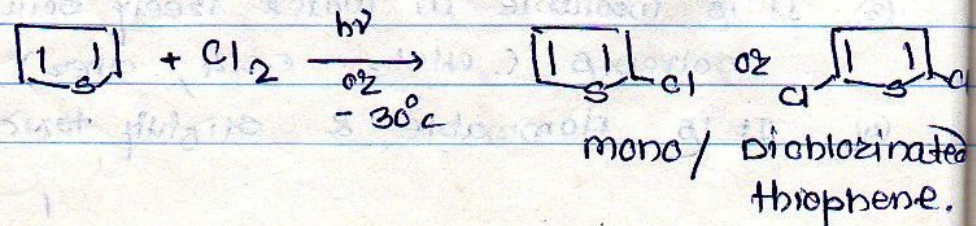


- ③ Oxidation:- Thiophene is more stable & aromatic so does not undergo oxidation to sulphoxide or sulphone with any oxidizing agent. But thiophene if treated with H₂O₂ ring open & sulphur converts or oxidise to H₂SO₄.

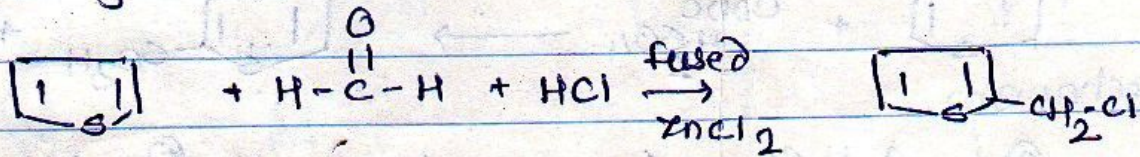


④ Chlorination or Halogenation:- (Electrophilic)

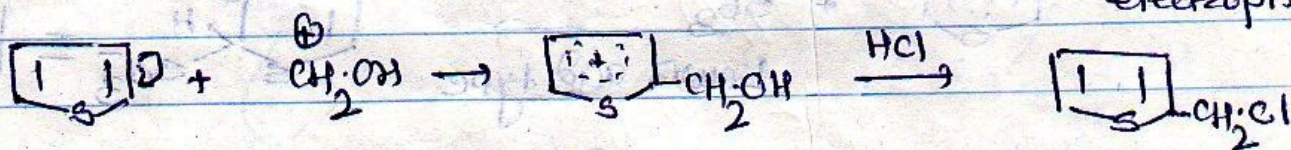
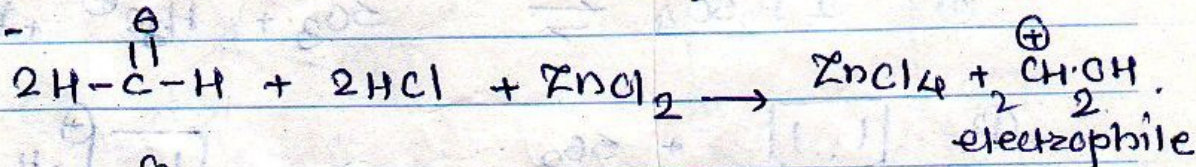
Thiophene on chlorination with Cl₂ gas at 30°C or in +nce of uv light gives chlorination



⑤ chloromethylation :- oz / (Arzant ester synthesis type) - Thiophene on treatment with formaldehyde & dry HCl gas in +nce of fused zinc chloride gives 2-chloromethyl thiophene.



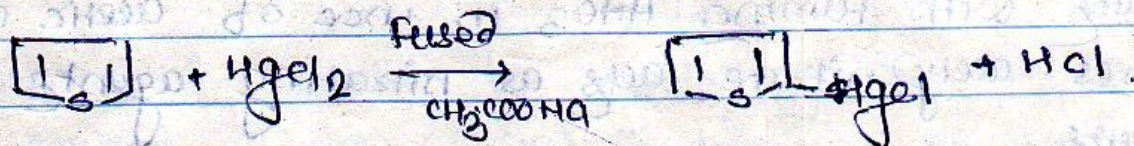
Mechanism:-



2-chloromethyl thiophene.

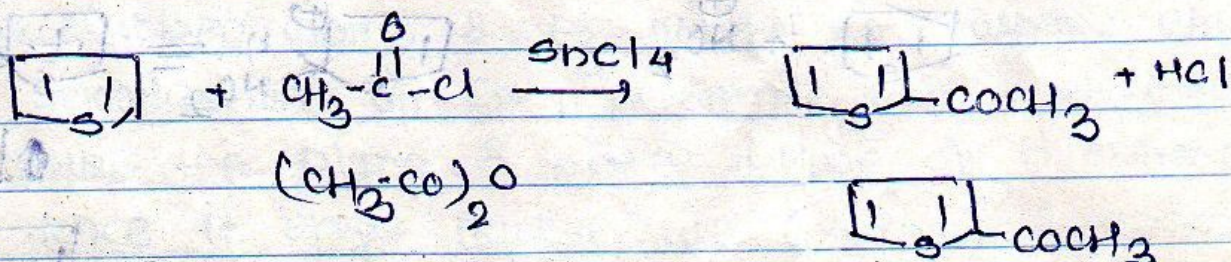
⑥ Mercurization:-

Thiophene reacts with mercuric chloride in +nce of sodium acetate catalyst gives 2-mercuric chloride thiophene.



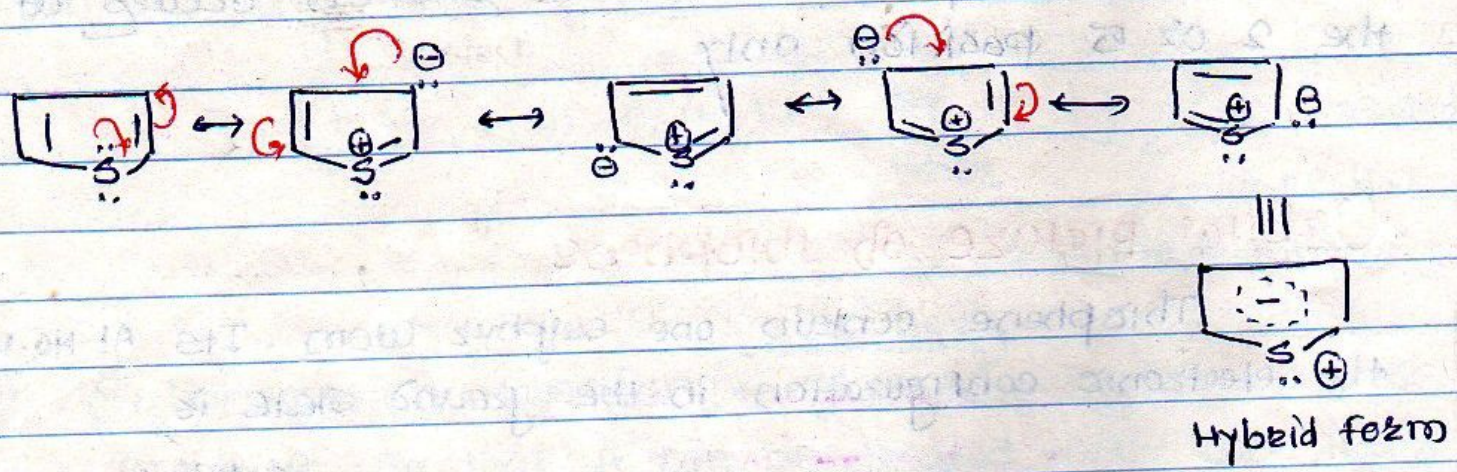
2-chloromercuric chloride.

⑦ Friedel-Craft reaction: - Thiophene treated with acetyl chloride or acetic anhydride in +nce of Lewis acid.



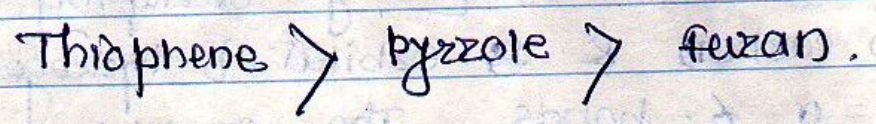
2-Acetyl thiophene + AcOH

Structure of thiophene can be represented as a resonance hybrid of the following structure;



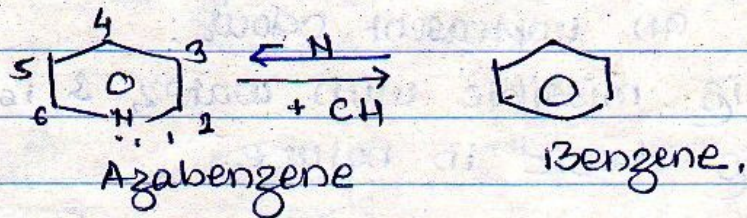
More resonating structure for thiophene are possible than furan & pyrrole. Hence thiophene is more stable than furan & pyrrole. The electronegativity consideration the sulphur is less electronegative as compare to the nitrogen & oxygen. Hence the electron on sulphur in thiophene ring are readily available for electrophilic attack.

In pyrrole & furan due to presence of H & O most electronegative atom present. so the π -electron cloud in both compound shifts towards H & O atoms. Hence attack of electrophile becomes slower. These -like thiophene readily undergo electrophilic substitution reaction. so it is more aromatic than pyrrole & furan. Order of aromaticity for these compounds



④ **Pyridine**

Pyridine is six membered heterocyclic compound with one nitrogen in the ring its name is azabenzene.

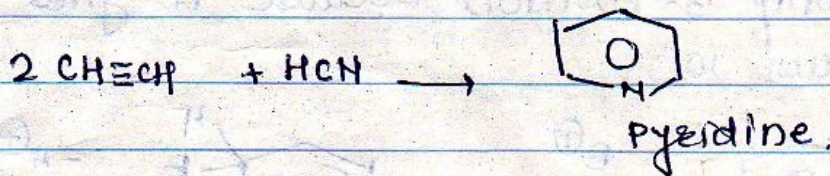


It is present in coal tar & in bone oil; by decomposition of several alkaloids gets azabenzene.

Preparation of pyridine :-

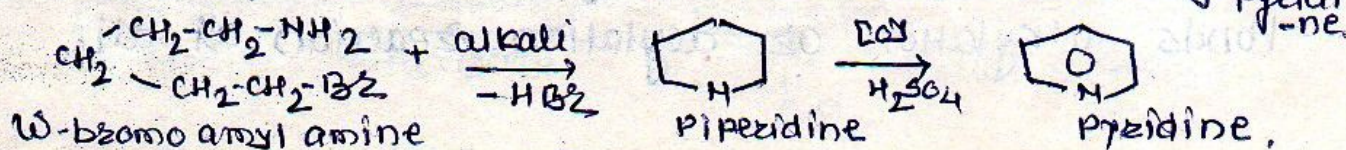
① From coal tar :- The light oil fraction is treated with dil. H_2SO_4 this dissolves the pyridine & other basic substances, the acid layer is neutralized with NaOH lastly this repeatedly fractionated.

② From acetylene :- Pyridine can be prepared by passing a mixture of acetylene & hydrogen cyanide through a red hot tube.

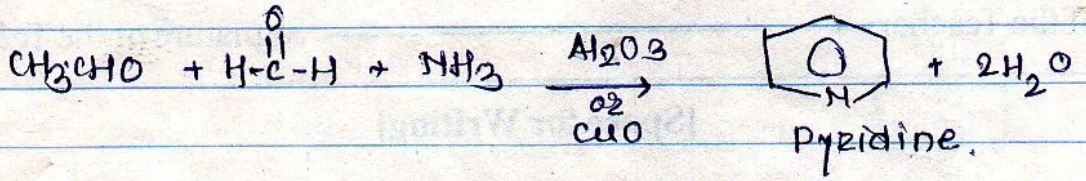


③ From ω-bromo pentamethylene diamine or Pentamethylene diamine.

when ω-bromopenta / aeryl amine is heated with alkali to form piperidine which is oxidized by H_2SO_4 & get pyridine.



④ Hantzsch synthesis :- In 1970 adequate quantities of pyridine prepared by synthetic method have come in the market. A mixture of acetaldehyde, formaldehyde & ammonia is passed over a dehydration catalyst such as CuO or Alumina.



Properties of pyridine:-

Ⓐ physical properties

- ① pyridine is colourless liquid its b.p. 115.5°C having an unpleasant odour.
- ② It is miscible with water, & is hygroscopic.
- ③ It is basic in nature.

Ⓑ chemical properties.

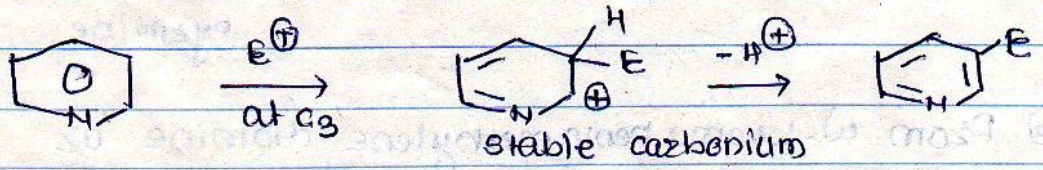
Pyridine has the same delocalised 6π electron system as like benzene



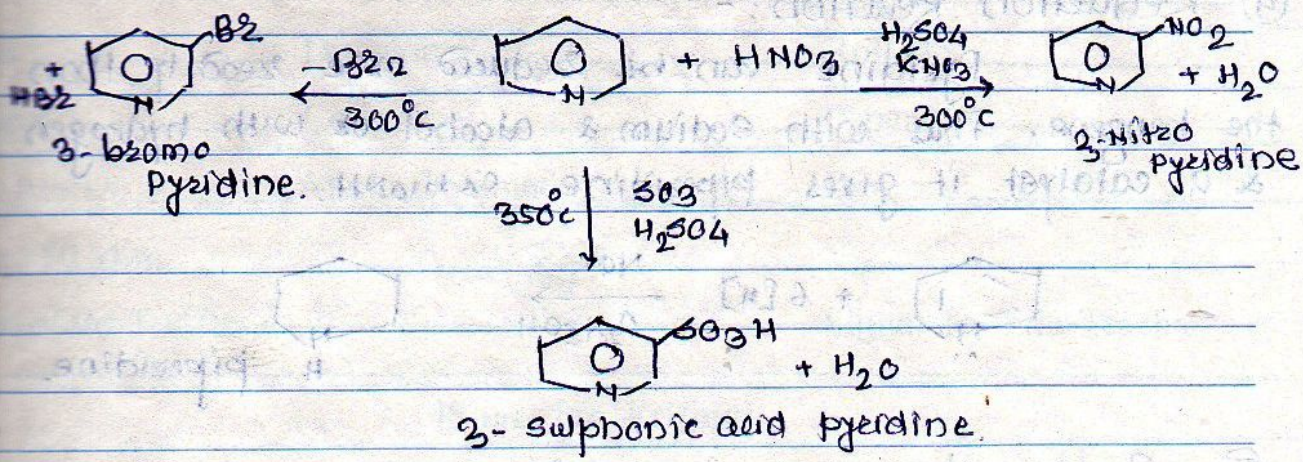
Thus it gives electrophilic substitution reaction like benzene & also behaves as a tertiary base at the N atom.

Ⓘ Ⓐ Electrophilic substitution in pyridine, at 3 position

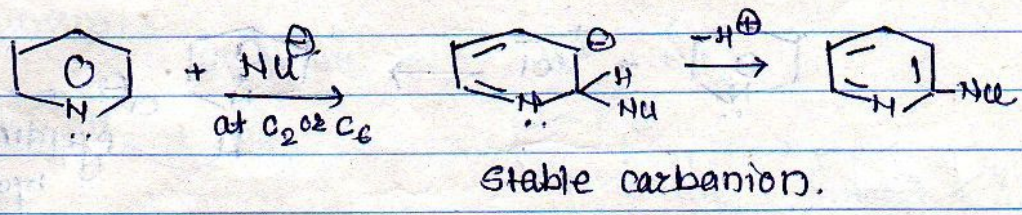
The electrophilic substitution in pyridine take place only under difficult condition because Nitrogen is high electro-negatively atom withdraws electron from whole ring & deactivates the ring. If electrophilic substitution carried out at only 3-position because it gives more stable carbonium ion.



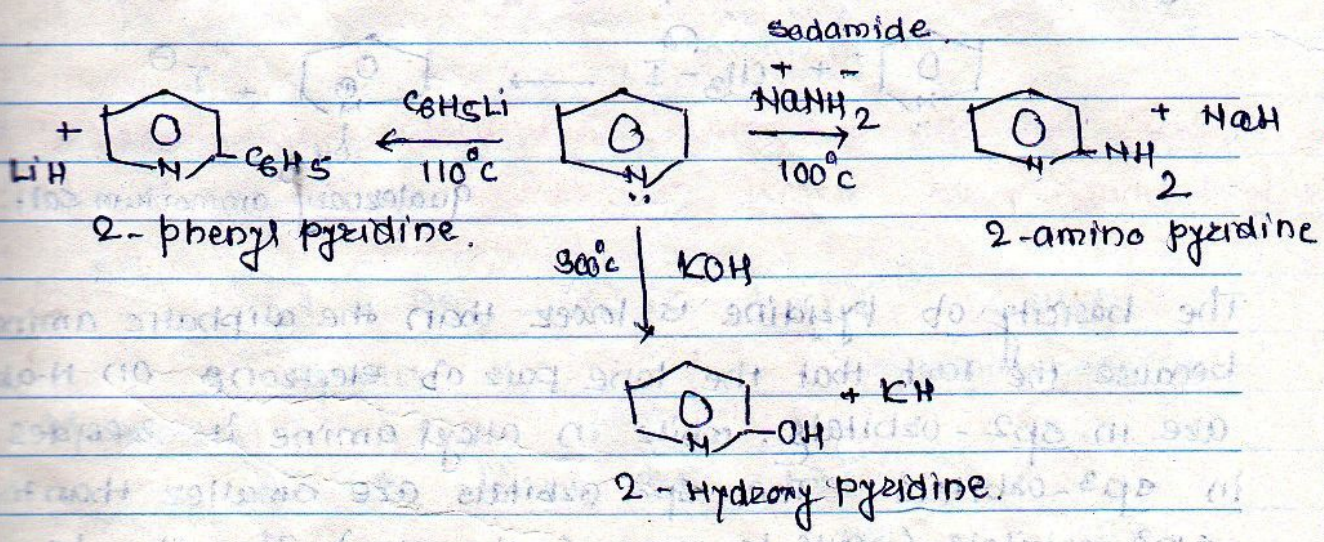
Some electrophilic substitution examples are given below, like nitration, sulphonation, Halogenation etc. at 3-position at vigorous condn. It does not res-ponds alkylation or acylation reaction at all.



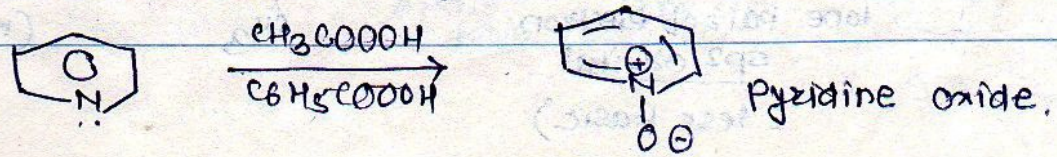
II (b) Nucleophilic substitution in pyridine. - (at 2 position)
 Nucleophilic substitution occurs at 2 or 6-position only because of the electronegativity character by the nitrogen atom.



Some nucleophilic substitution examples in pyridine are given below. Generally pyridine reacts with strong nucleophile at 2 or 6 position only.

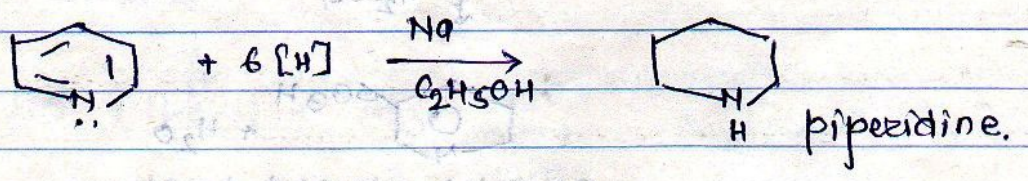


III Oxidation Reaction:-
 Pyridine does not react with chromic acid or nitric acid, but it is oxidized by peracetic acid or perbenzoic acid & forms pyridine oxide.



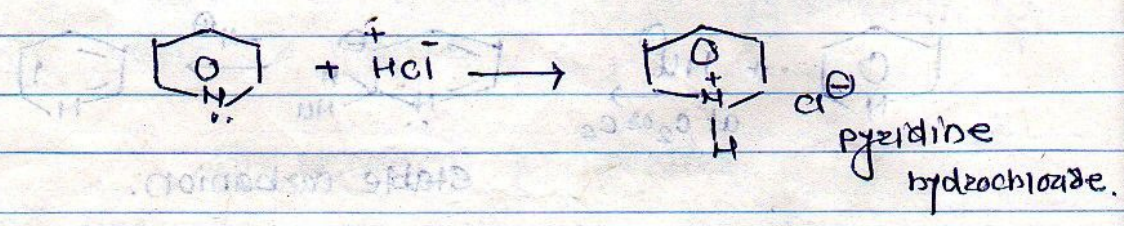
④ Reduction Reaction:-

Pyridine can be reduced more readily than the benzene. Thus with sodium & alcohol or with hydrogen & a catalyst it gives piperidine $C_6H_{10}NH$.



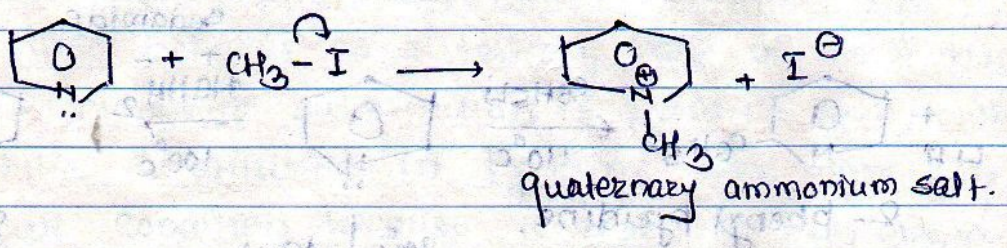
⑤ Basic character of pyridine:-

Pyridine is much less basic $K_b = 1.78 \times 10^{-9}$ than the alkyl amine e.g. trimethyl amine $K_b = 4.4 \times 10^{-4}$. However it is sufficiently strong base because it forms salts with mineral acids.

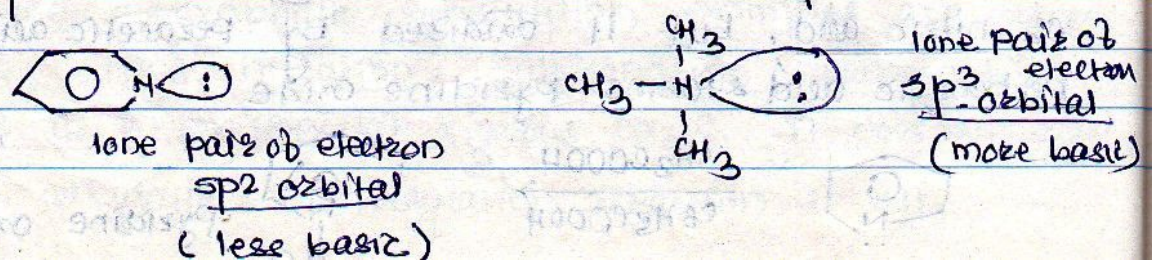


Reaction with alkyl halide;

As a tertiary amine, pyridine reacts with alkyl halide to form quaternary ammonium salts.

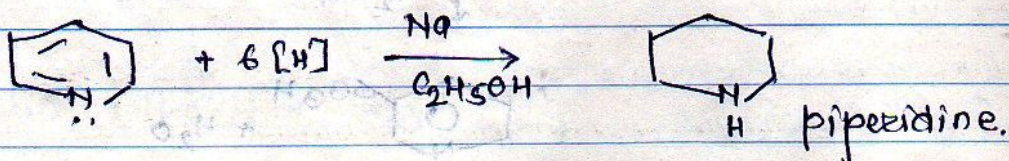


The basicity of pyridine is lower than the aliphatic amines because the fact that the lone pair of electrons on N-atom are in sp^2 -orbitals. while in alkyl amine it resides in sp^3 -orbitals. The sp^2 orbitals are smaller than the sp^3 orbitals (due to more s character). Thus the lone pair of electron in pyridine being closer is more tightly held & is less available for protonation.



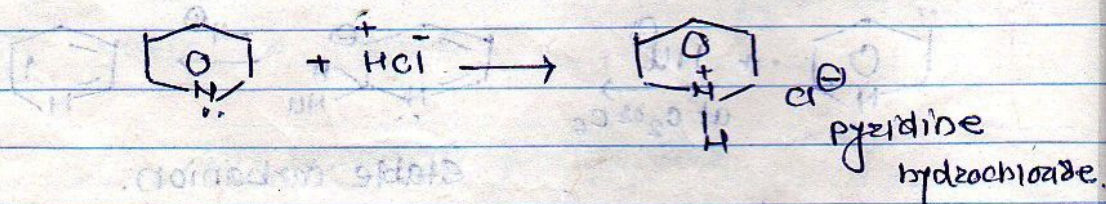
④ Reduction Reaction:-

Pyridine can be reduced more readily than the benzene. Thus with sodium & alcohol or with hydrogen & a catalyst it gives piperidine $C_6H_{11}NH$.



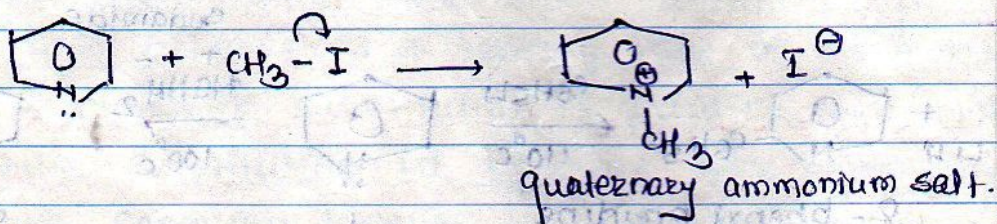
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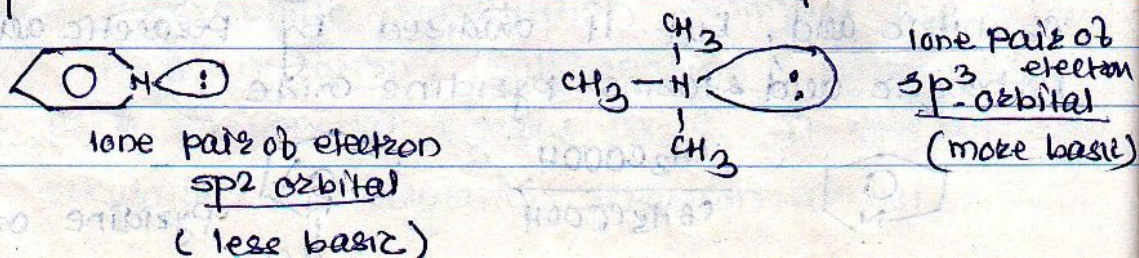


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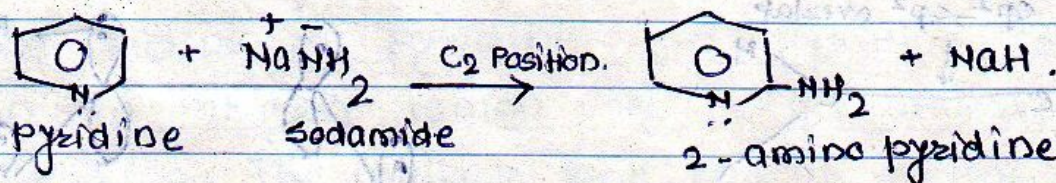


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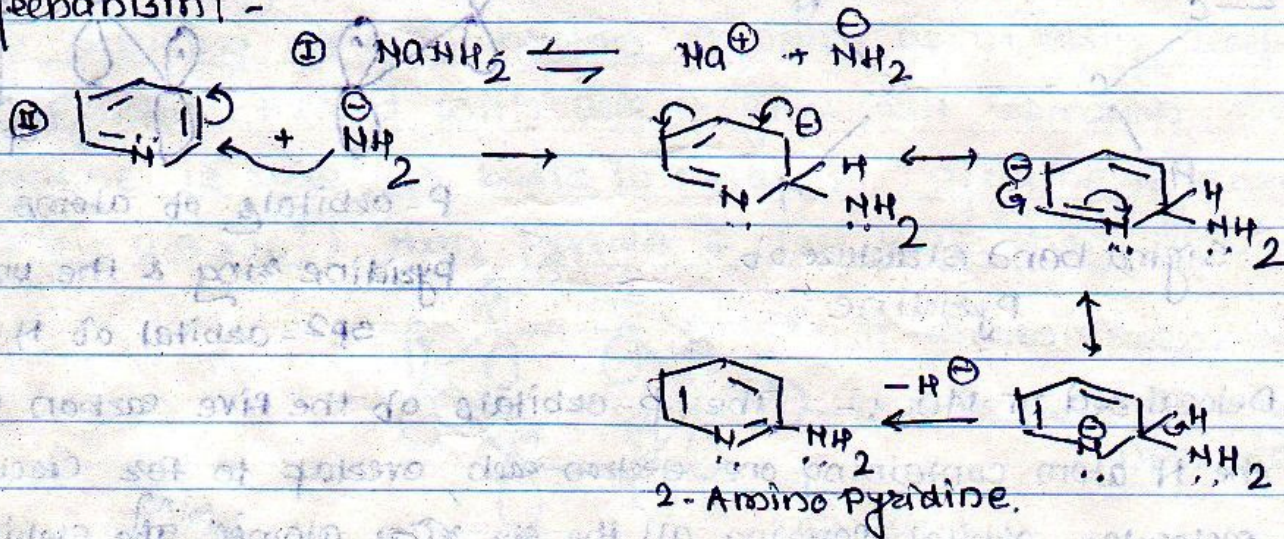


Representative Mechanism for pyridine :-

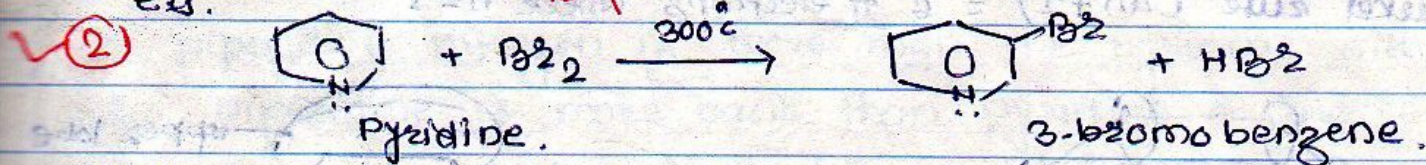
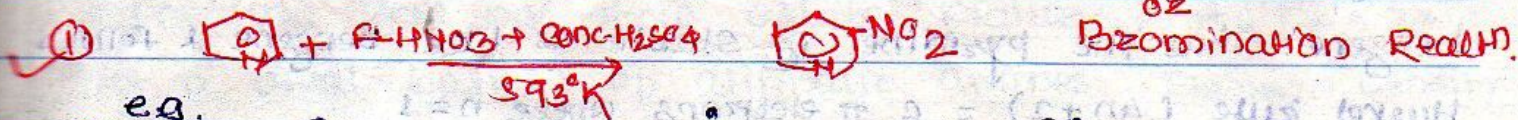
I) Nucleophilic substitution reaction or Amination Reaction.



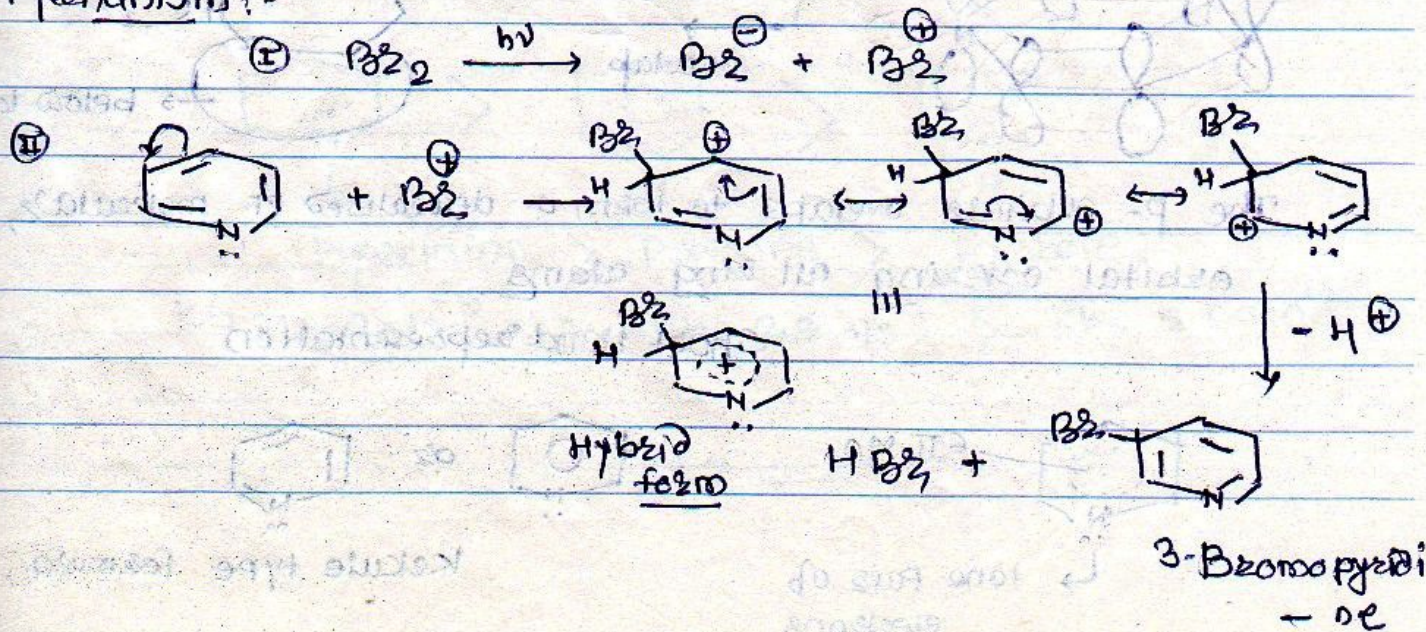
Mechanism -



II) Electrophilic substitution reaction or Nitration Reaction :-

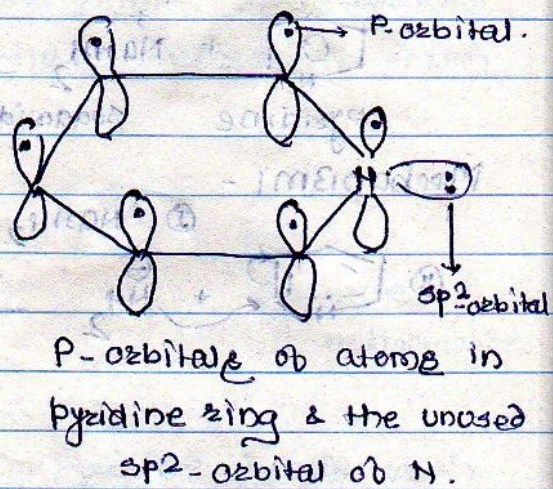
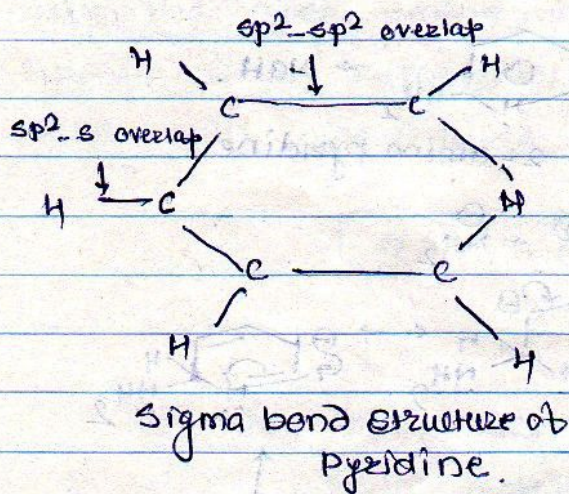


Mechanism -

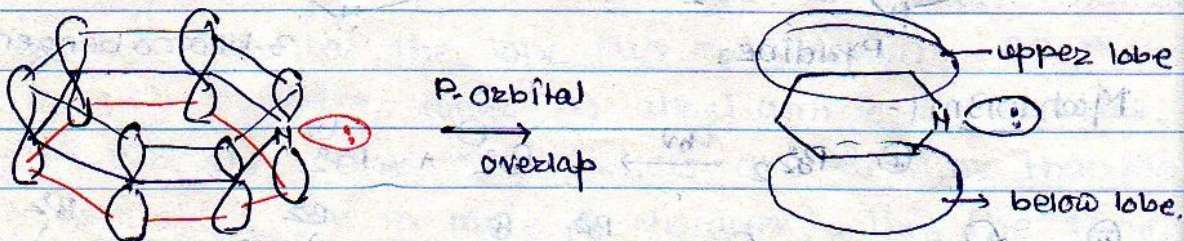


Orbital Model for Pyridine :-

(I) sigma framework or σ -bonds :- The five carbon atoms & the nitrogen atom of the pyridine ring are sp^2 hybridized. Each of these atoms has three sp^2 orbitals in the same plane & one p-orbital at right angle to it. The ring is constructed by the overlap of the two sp^2 orbitals of the adjacent carbon & nitrogen atoms. The third sp^2 orbital of each carbon overlaps with an s-orbital of a hydrogen atom. But the third sp^2 orbital of N atom containing a lone pair of electrons remains unused & lies in the plane of the ring.

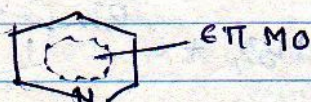


(II) Delocalized π MO :- The p-orbitals of the five carbon atoms & the N atom containing one electron each, overlap to form circular π molecular orbital covering all the six ring atoms. The stabilization energy due to delocalization of π -electrons is almost the same as benzene. Thus the pyridine is stable as like benzene & follows Hückel rule $(4n+2) = 6$ π electrons where $n=1$.

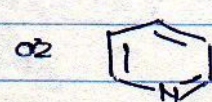


The p-orbitals overlaps to form a delocalized π molecular orbital covering all ring atoms.

Short Hand Representation



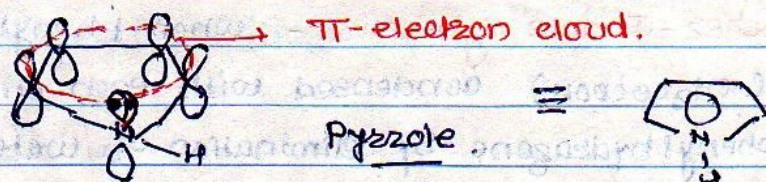
↳ lone pair of



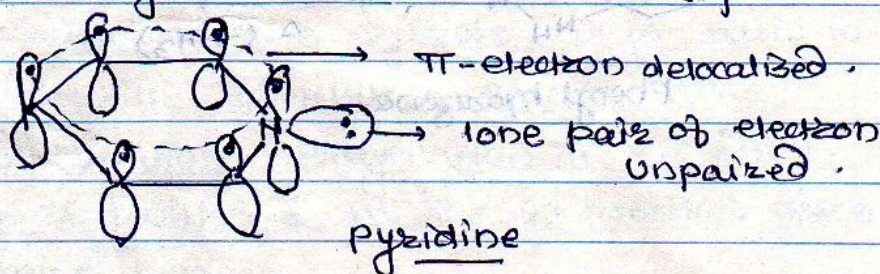
Kekule type formula.

Comparison of basicity of Pyrazole; pyridine & piperidine.

Orbital picture of pyrazole shows that the lone pair of electron on nitrogen which are responsible for basicity. The π electron delocalized over pyrazole ring to form π -electron cloud & hence are not available for acceptance of proton. Hence pyrazole is extremely weak base ($K_b = 2.5 \times 10^{-14}$) & weaker base than pyridine & piperidine.

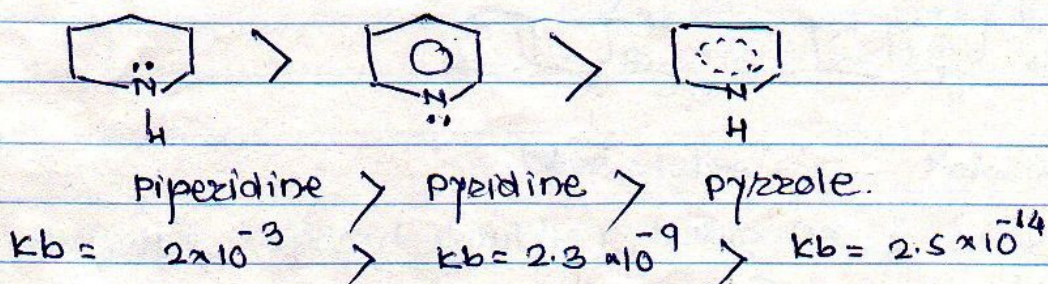


Orbital picture of pyridine, in pyridine lone pair of electron on nitrogen, which does not get delocalized over pyridine ring. The available lone pair of electron is available for sharing with proton of acid. or it easily accept proton. If pyridine treated with acid it gives salt formation, so that pyridine is base (or basic in nature). pyridine is more basic ($K_b = 2.3 \times 10^{-9}$) than pyrazole & less basic than piperidine.



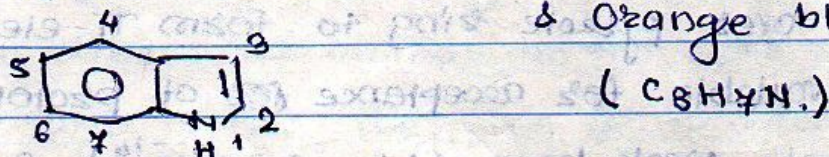
Piperidine does not show orbital picture. its $K_b = 2 \times 10^{-3}$ has a usual basicity of aliphatic amines. Electron density on piperidine nitrogen is more than the pyridine nitrogen. so piperidine is more basic than pyridine & pyrazole.

The order of basicity given below,



(5) Indole (Benzopyrrole)

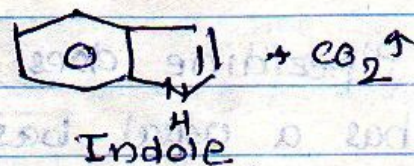
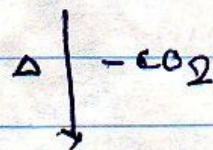
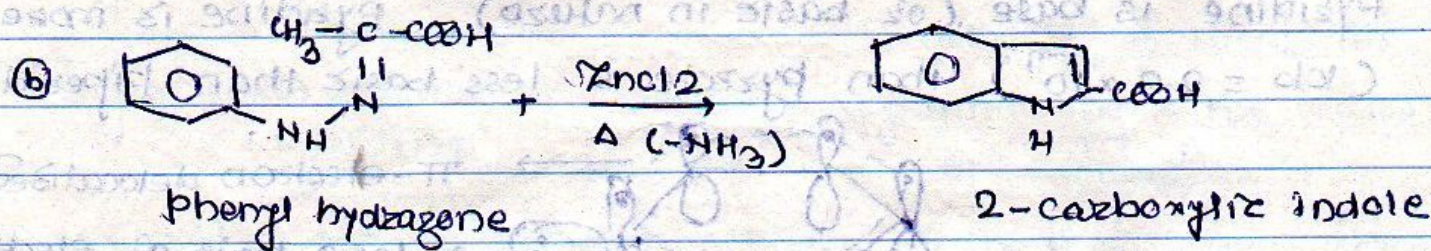
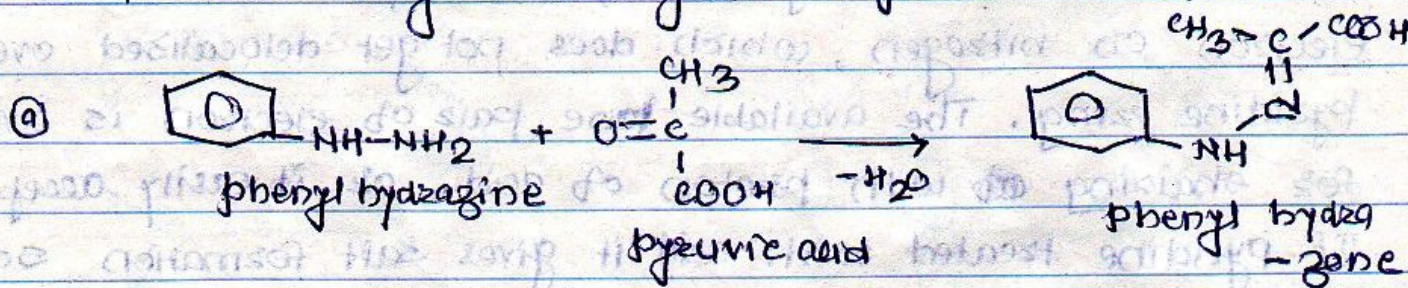
Indole is a bicyclic nitrogen heterocycle. Benzene ring is fused with pyrrole ring called as indole & its IUPAC name is benzopyrrole. It occurs in cowhage, Jasmine flower & Orange blossom oil.



Benzopyrrole.

Preparation Method for Indole:-

(I) Fischer-Indole synthesis:- when phenylhydrazine & pyruvic acid (CH₃COCOOH) condensed with each other gives a pyruvic acid phenylhydrazone by elimination of water. The phenylhydrazone is heated with ZnCl₂ as catalyst it give 2-indole-2-carboxylic acid which lastly decarboxylate & yields indole.



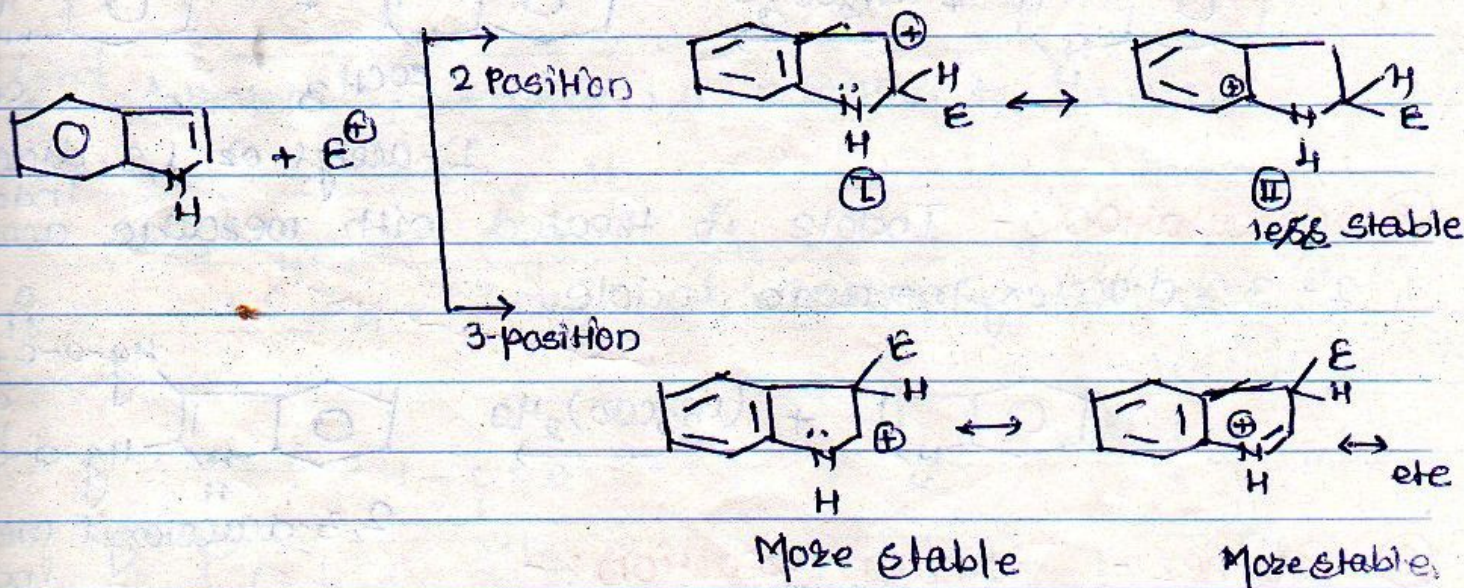
Properties of Indole :-

(A) Physical properties.

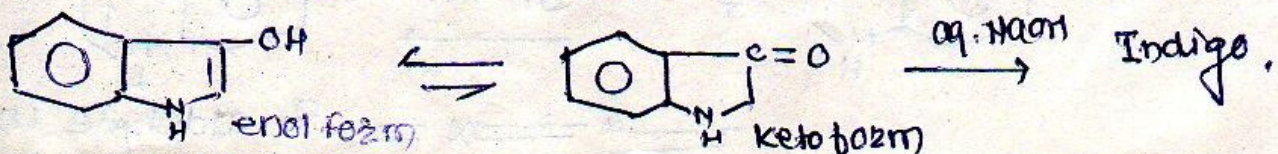
- (a) Indole is colourless crystalline solid its M.P. = 52.5°C
- (b) Indole is soluble in hot water, ether & alcohol.
- (c) It has a strong fecal odour, curiously enough in dilute form it has flowery odour & is used in perfumery for preparing Jasmine & Orange blends.

(B) Chemical properties :-

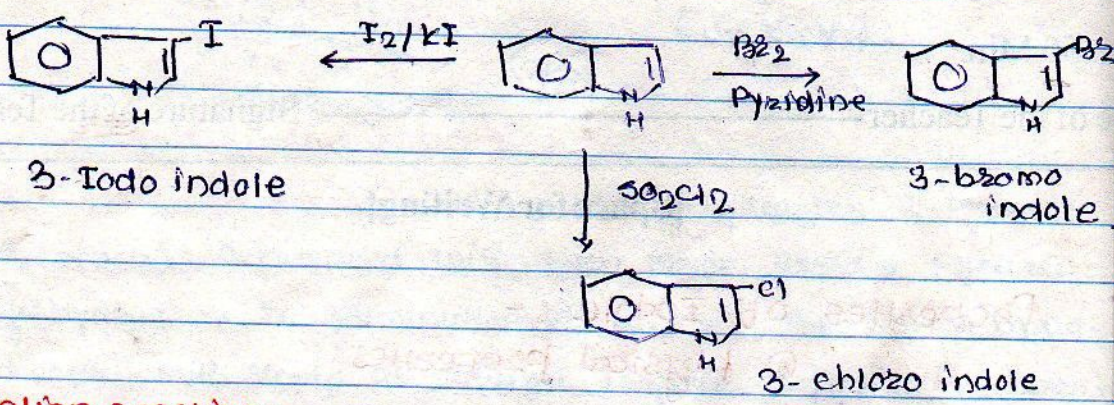
Chemically indole resembles like pyrrole. It is basic in nature & gives electrophilic substitution reaction like, Nitration; Sulphonation; Halogenation at 3-position. Why at only 3-position & not for 2-position ~~given~~ clarification given below,



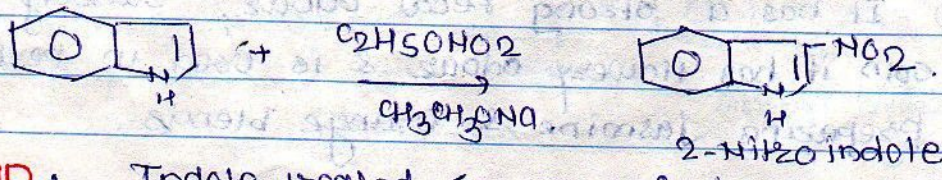
Indole derivative (Indoxyl exhibits) tautomerism & behaves like phenol. Indoxyl in aq. NaOH readily oxidized by air & gives insoluble blue dye i.e. indigo.



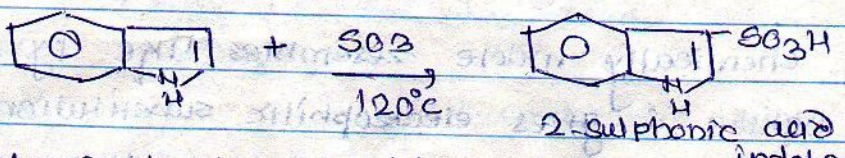
(1) Halogenation reaction:- chlorination by sulphuryl chloride, bromination in dioxane or pyridine & iodination in aq. KI at 3-position only.



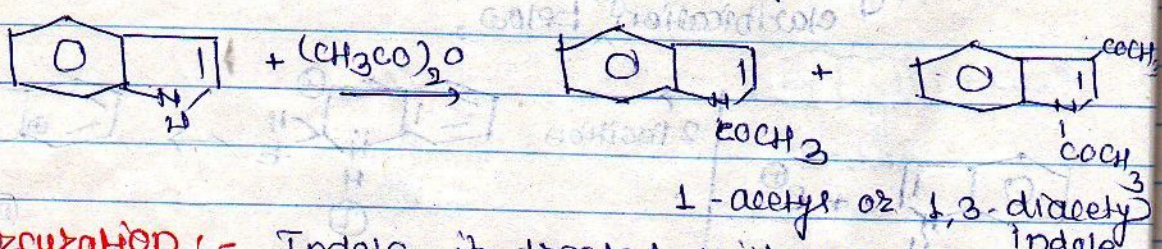
(2) Nitration reaction:- Indole on treatment with ethyl nitrate in presence of sodium ethoxide form 3-nitroindole.



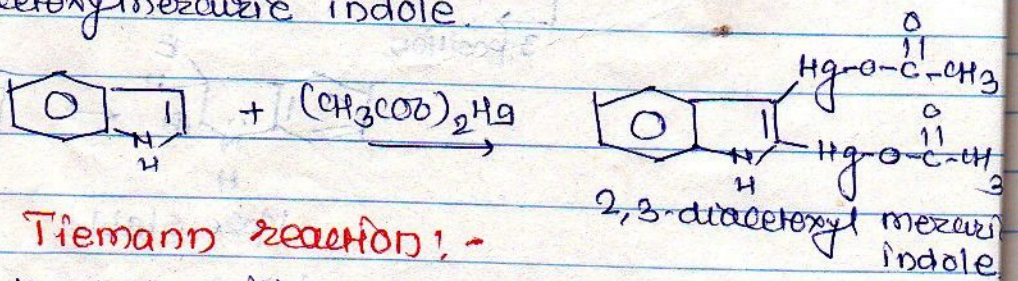
(3) Sulphonation:- Indole treated SO₃ at 120°C it gives 3-sulphonic acid indole



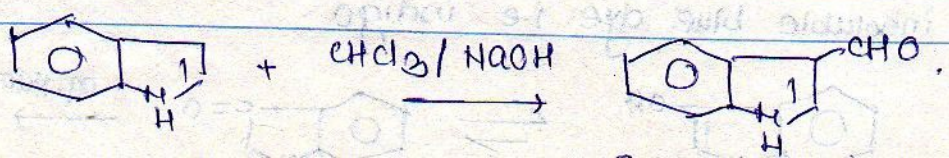
(4) Acylation:- Indole on treatment with acetic anhydride it gives a mixture of 1 & 1,3-diacetyl indole.



(5) Mercurization:- Indole is treated with mercuric acetate 2,3-diacetoxymercuric indole.

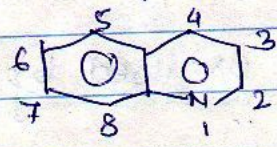


(6) Reimer-Tiemann reaction:- Indole treated with chloroform & NaOH it gives 3-aldehyde indole.



(6) Quinoline.

Quinoline is a bicyclic nitrogen heterocyclic compound it is present in coal tar - bone oil, Actually in quinoline two rings are fused, i.e. benzene fused with pyridine, it is called as 1-azaphthalene. (IUPAC name)

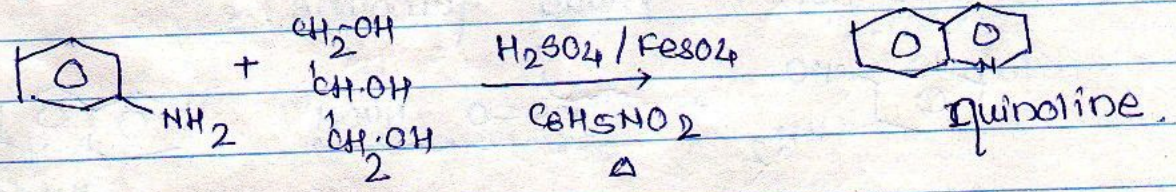


Common name - Quinoline
IUPAC Name - 1-Azabenzene.

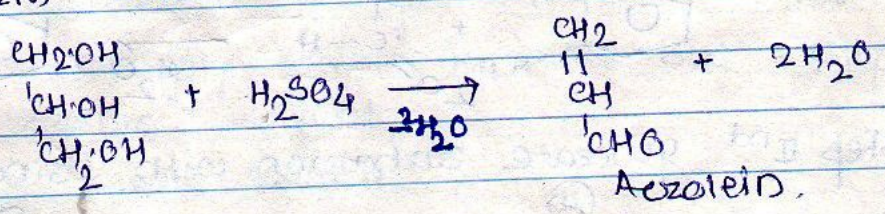
Preparation of quinoline :- Quinoline can be prepared by no. of method, but some are popular methods ;

(I) Skraup synthesis :-

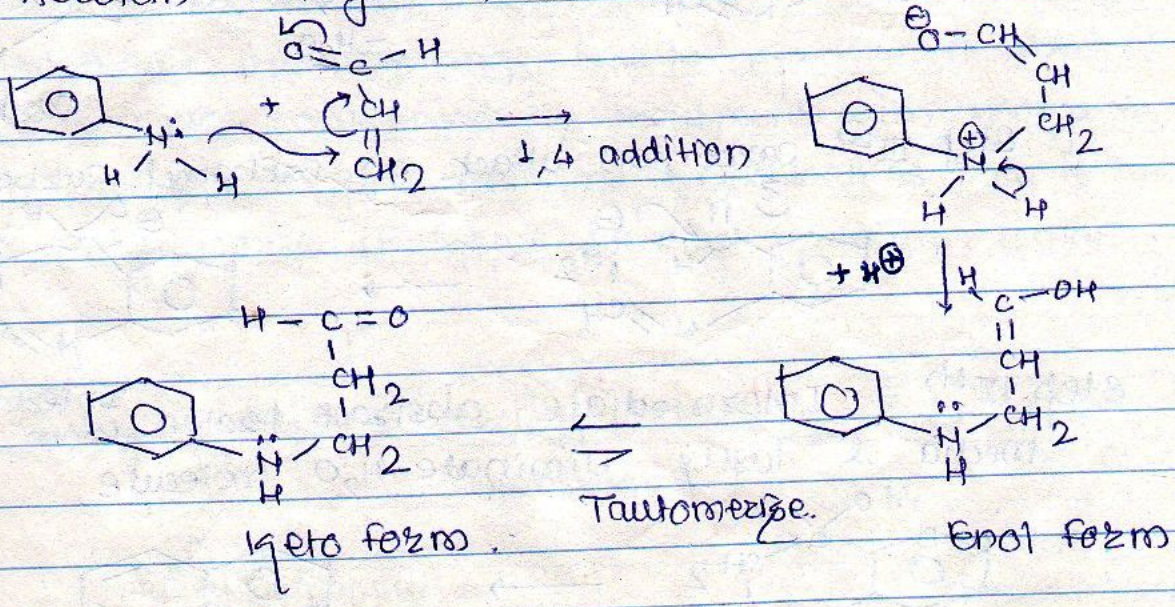
A mixture of aniline, glycerol & H_2SO_4 is heated in the presence of mild oxidizing agent such as nitrobenzene. The reaction being exothermic tend to be violent & $FeSO_4$ is also added as moderator.



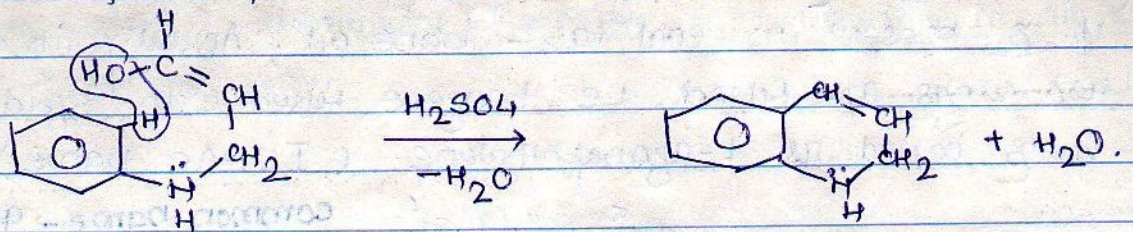
Mechanism :- In 1st step glycerol dehydrates with H_2SO_4 to form acrolein.



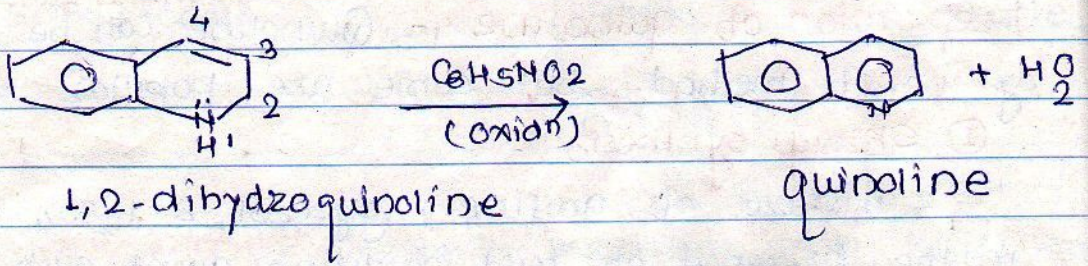
2nd Acrolein undergoes 1,4-addition to aniline.



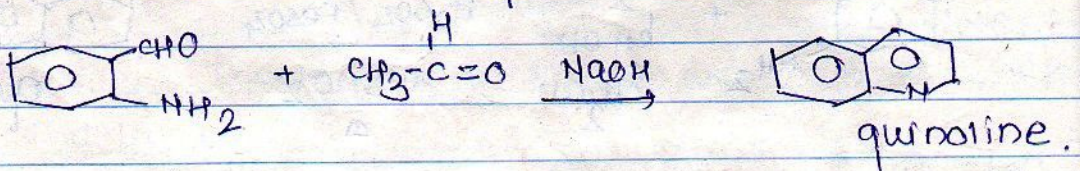
IIIrd step dehydration or elimination of H₂O.



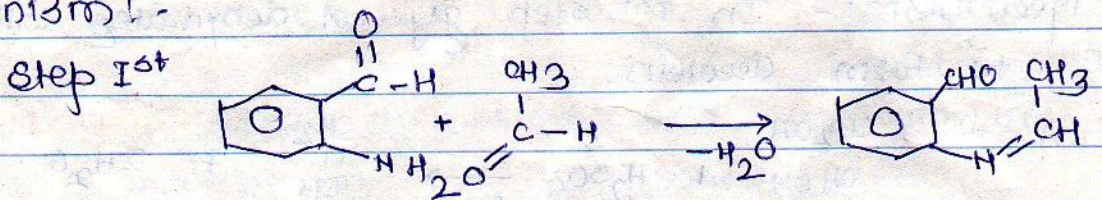
IVth step above product oxidized by K₂Cr₂O₇ gives quinoline.



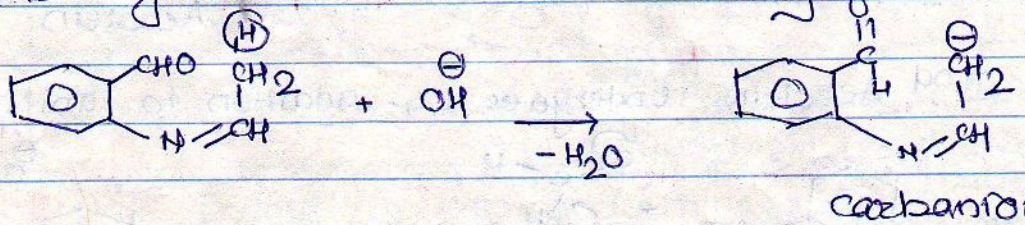
② **Friedlander synthesis** :- In 1882 by condensation of o-aminobenzaldehyde with acetaldehyde in the presence of NaOH solution it yields quinoline.



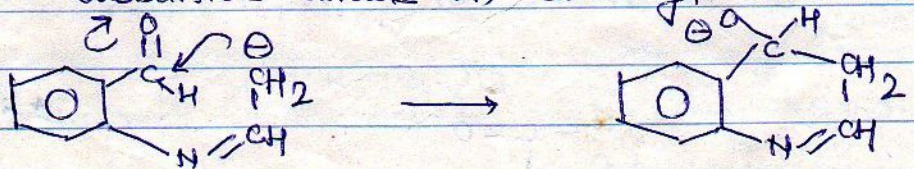
Mechanism :-



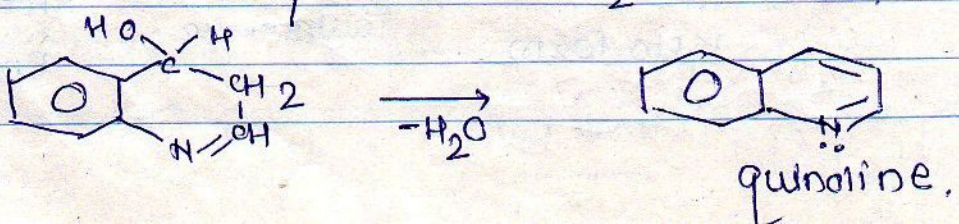
Step IInd generate carbanion with using base.



Step IIIrd carbanion attack on carbonyl carbonium ion

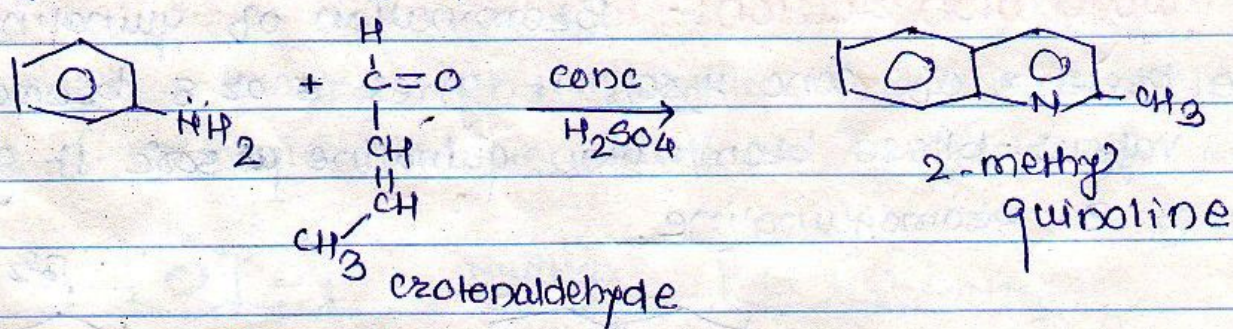


Step IVth - Intermediate abstract proton from solvent media & lastly eliminate H₂O molecule.



③ Doebner-Miller synthesis:-

In this method aniline is heated with unsaturated aldehyde like crotonaldehyde in presence of conc. H_2SO_4 to give 2-methyl quinoline.



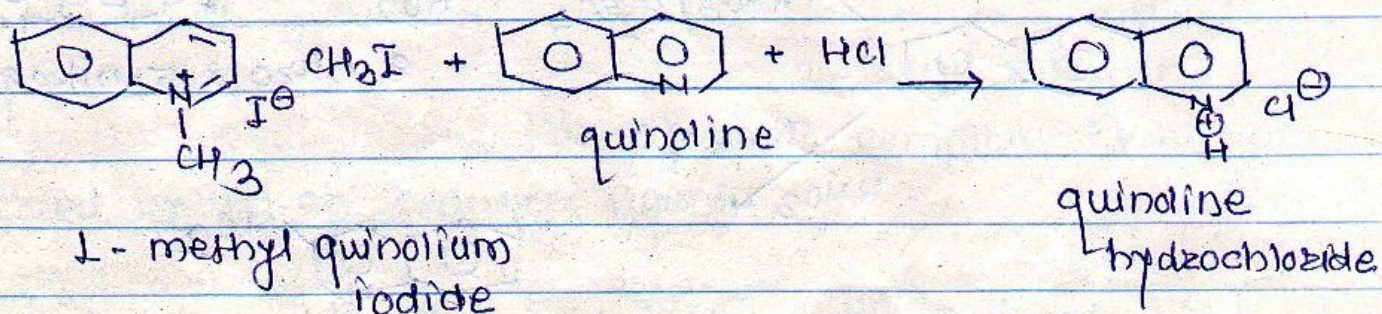
Properties of quinoline:-

(i) Physical properties.

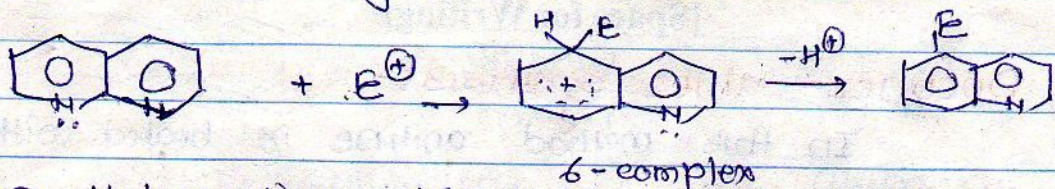
- ① It is colourless oily liquid its B.P. = $238^\circ C$
- ② It is sparingly soluble in water but easily soluble in organic solvent.
- ③ It is steam volatile.

(ii) Chemical properties.

Quinoline acts as a base because it fused product of benzene + pyridine ring. Due to pyridine it shows basic character confirmed by treatment with inorganic acid like HCl it gives quinoline hydrochlorides. If it treat with methyl iodide it forms 1-methyl quinolinium iodide.

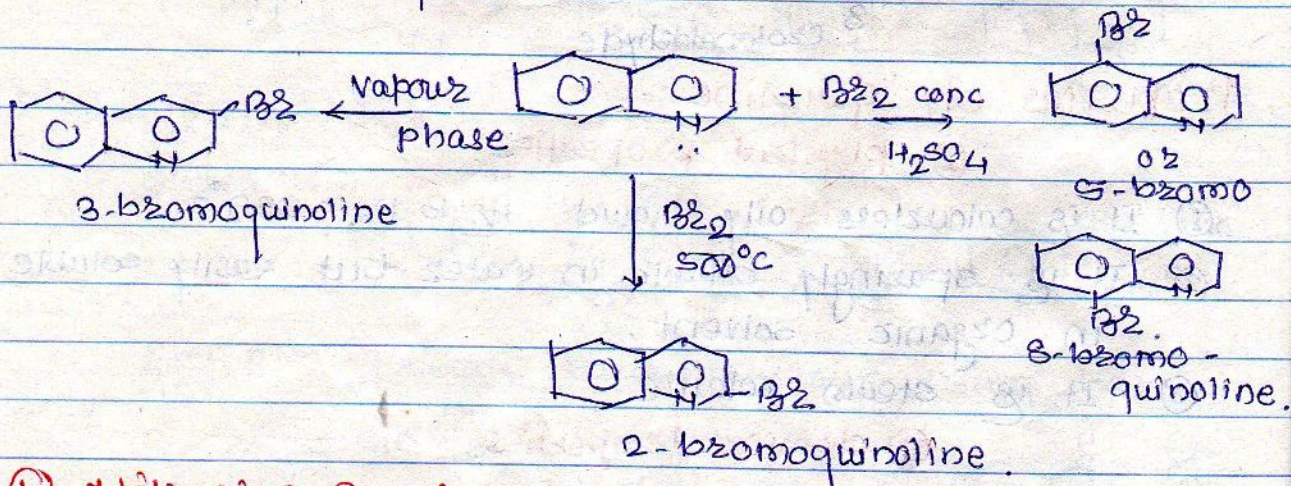


② Electrophilic substitution Reaction :- (at 5 or 8 - position)
 quinoline undergoes the electrophilic substitution but the attack of electrophile at 5 or 8 position only because electron withdrawing nitrogen atom withdraw electron towards so the pyridine ring deactivate for the electrophilic attack so it attack ~~at~~ on benzene ring at 5 or 8 position only.

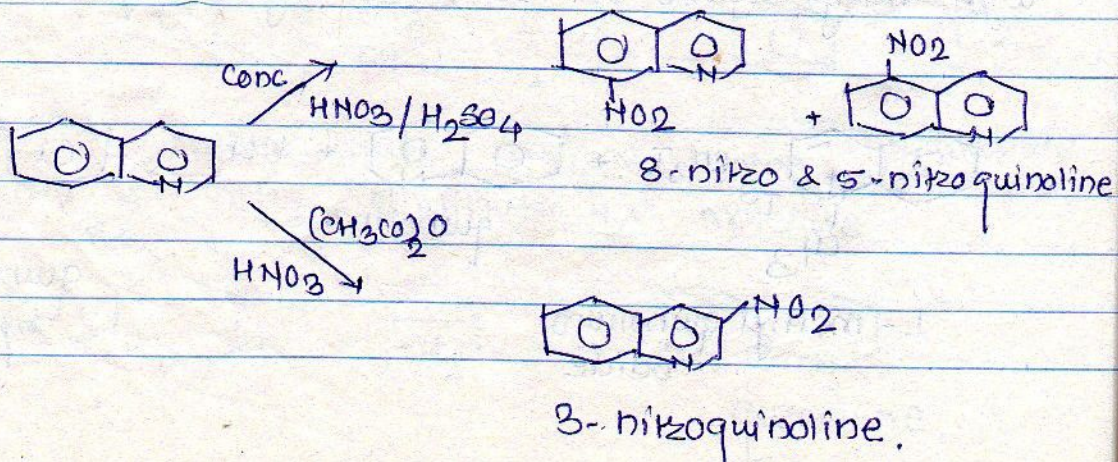


e.g. Halogenation; Nitration; Sulphonation etc.

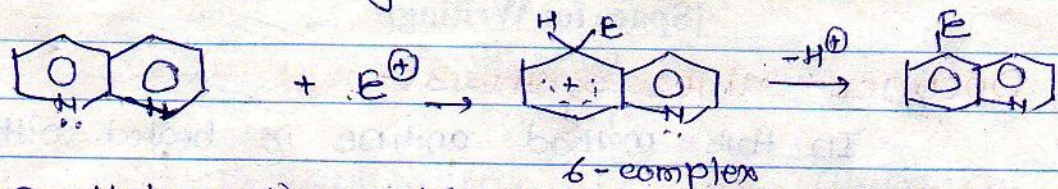
① Halogenation reaction :- Bromination of quinoline in the presence of conc H_2SO_4 it gives 5 or 8-bromoquinoline. If vapour-phase bromination quinoline at $500^\circ C$ it gives 2 or 3-bromoquinoline.



② Nitration Reaction :- quinoline on nitration with the nitrating mixture forms a mixture of 5 or 8-nitroquinoline. But it treated with HNO_3 -acetic anhydride offered at 3-nitroquinoline.

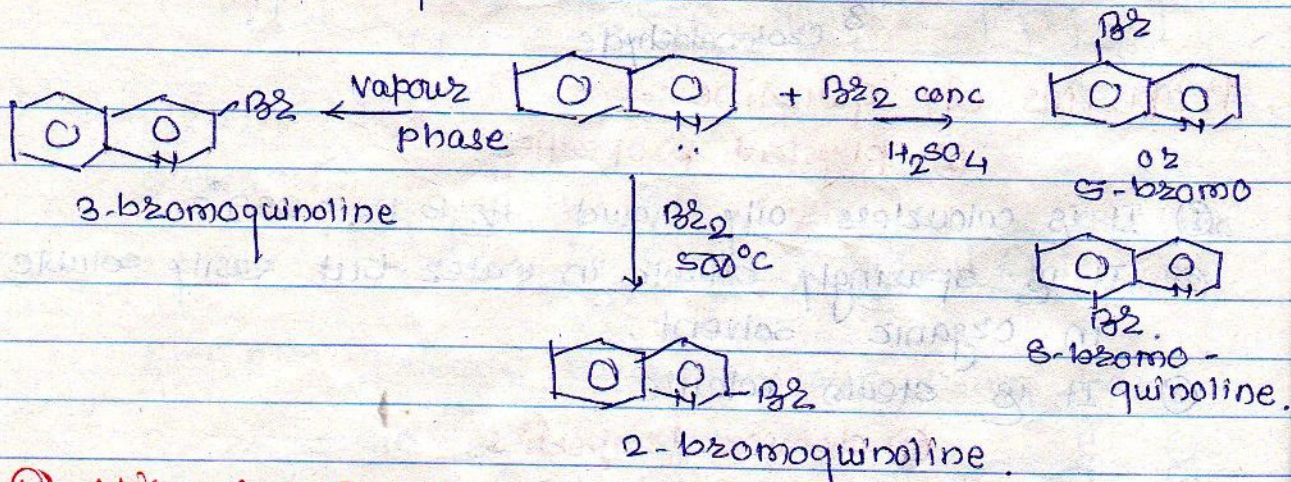


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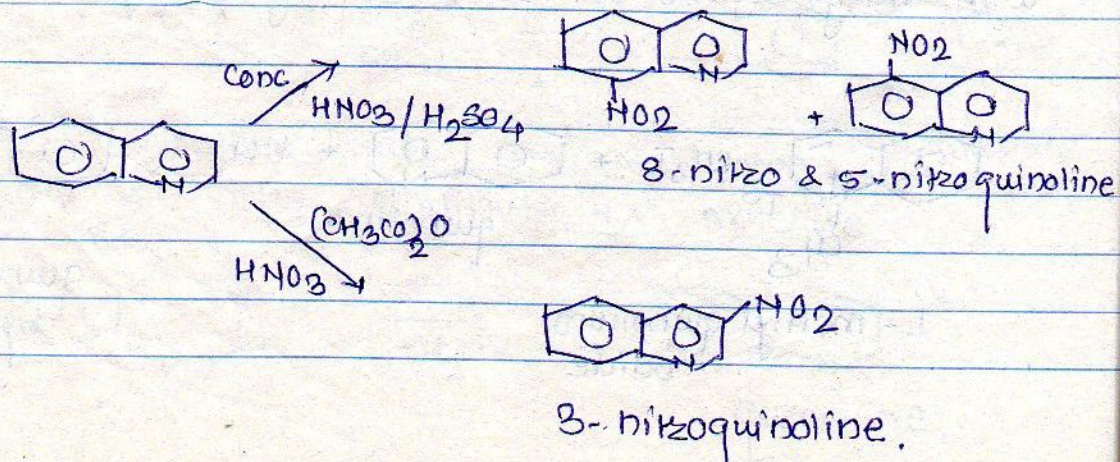


e.g. Halogenation; Nitration; Sulphonation etc.

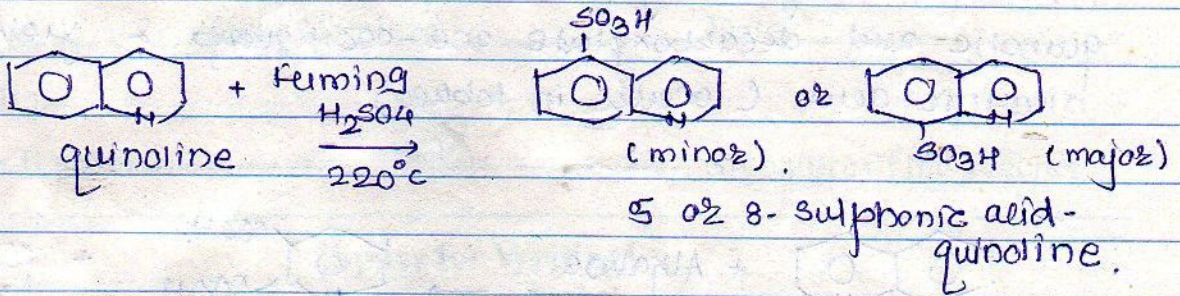
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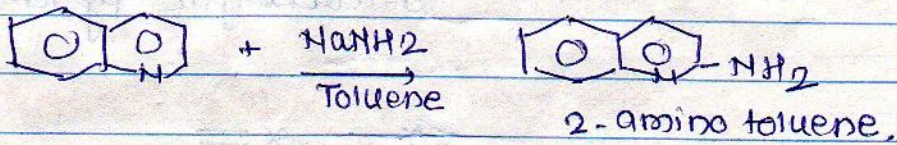
© **Sulphonation Reaction**:- quinoline on sulphonation at 220°C gives 8 or 5-sulphonic acid quinoline as follows



Nucleophilic Substitution Reaction:- (at 2-position only)
quinoline readily gives nucleophilic substitution reaction at 2-position by strong nucleophile. e.g. NH_2^- , OH^- , $n-C_4H_9^-$

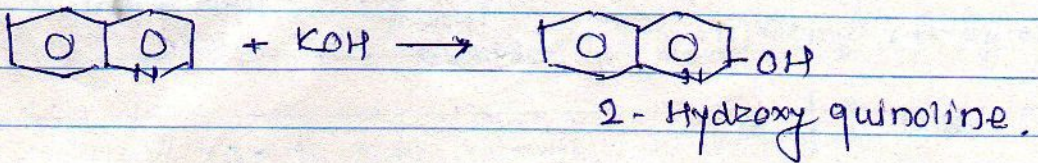
① **Amination or Reaction with sodamide**:-

quinoline heating with sodamide in toluene as solvent gives 2-aminoquinoline is called as Tschitschibabin reaction.



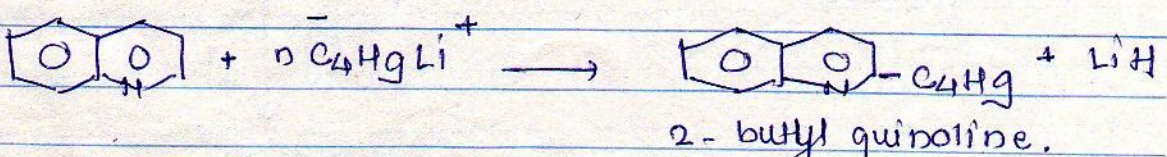
② **Hydroxylation or Reaction with NaOH or KOH**.

quinoline treated with strong alkali i.e KOH it gives 2-Hydroxy quinoline.

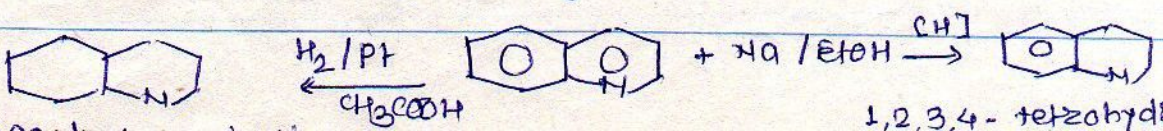


③ **Reaction with n-butyl lithium or alkylation**:-

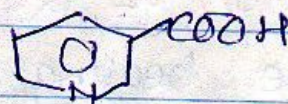
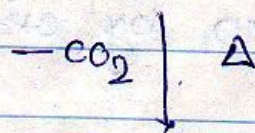
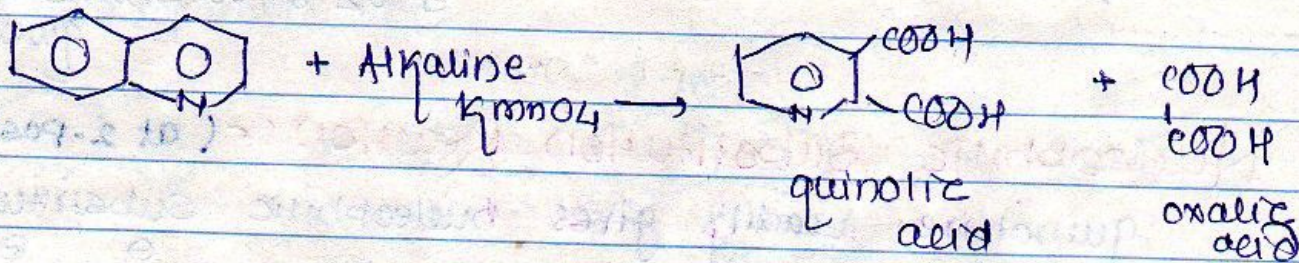
Reaction with n-butyl lithium it gives 2-butyl quinoline.



④ **Reduction reaction**:- partial and complete reduction carried by no. of reducing agent.



(e) Oxidation Reaction! - quinoline vigorously oxidized by alkaline potassium permanganate ($KMnO_4$) it yields 2,3-dicarboxylic pyridine (quinolic acid) on heating quinolic acid decarboxylate one $-COOH$ group & yields the nicotinic acid (occurs in tobacco).

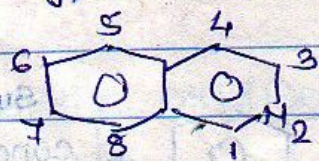


Nicotinic acid

3-carboxylic^{o2} pyridine.

7 Isoquinoline

Isoquinoline is generally occurs in many alkaloids it is fused or bicyclic compound.

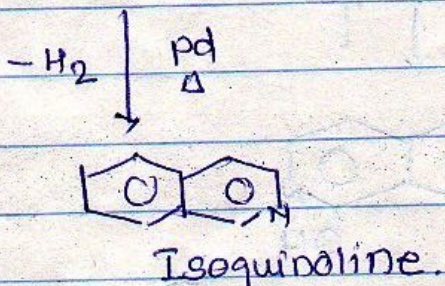
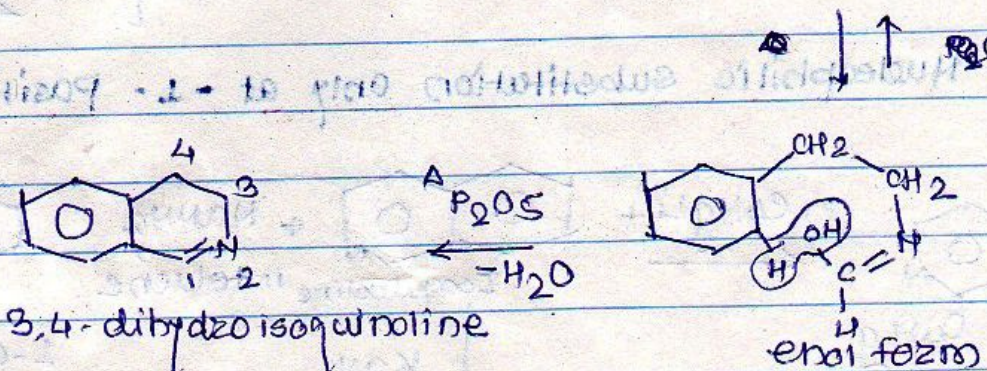
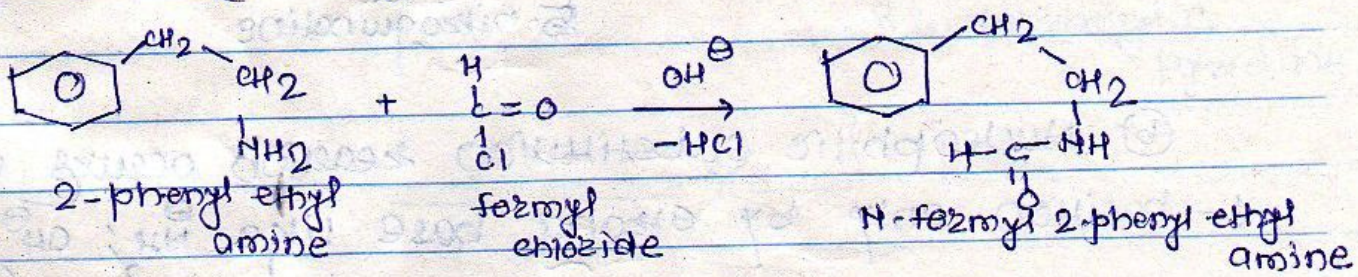


2-Azaphthalene
or
Isoquinoline.

Preparation methods of Isoquinoline:-

(a) Bischler-Napieralski synthesis:-

Isoquinoline is easily prepared from 2-phenyl ethylamine by following steps.



Properties of Isoquinoline:-

I Physical properties.

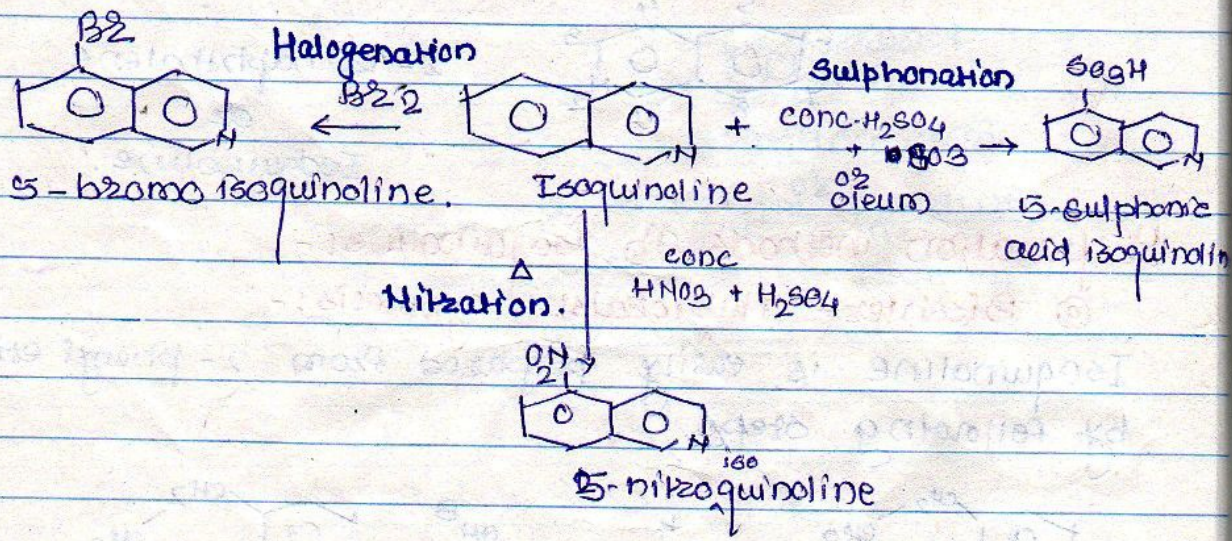
- ① Isoquinoline is colourless solid or liquid M.P 23°C b.p. 243°C
- ② It is insoluble in water but easily soluble in organic solvents.

II chemical properties:-

In chemical properties it is closely resembles like quinoline it gives substitution reaction like -

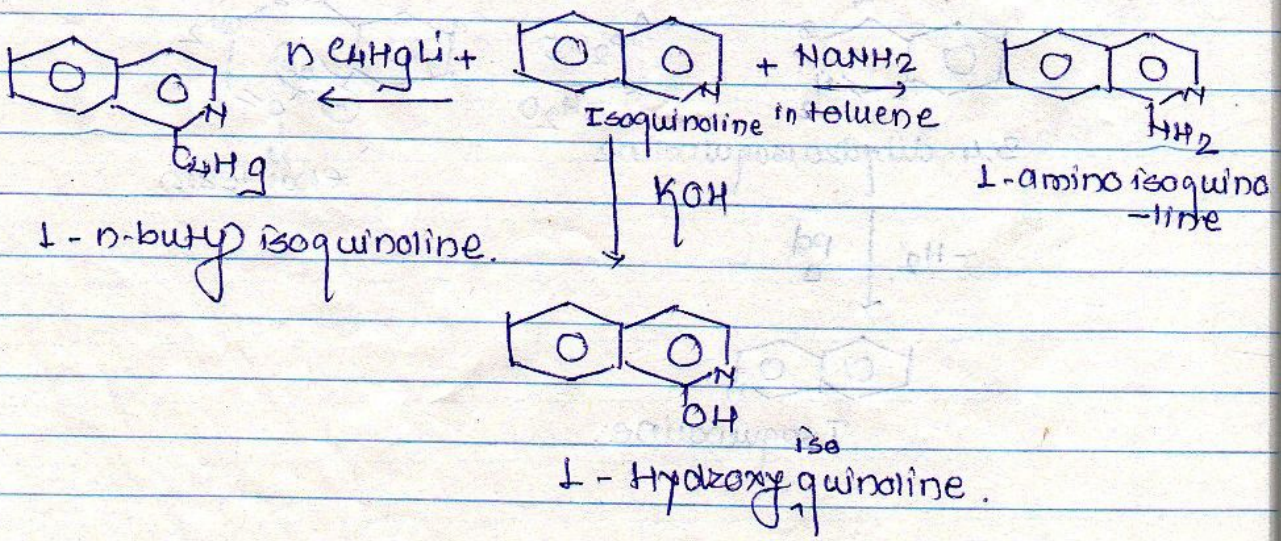
① Electrophilic substitution reaction occurs at 5-position only like Nitration; Sulphonation & Halogenation

* Electrophilic substitution only at 5-position.

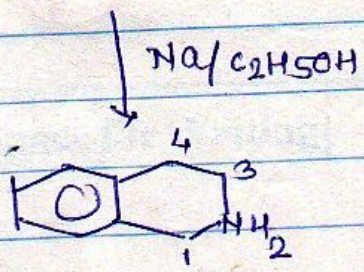
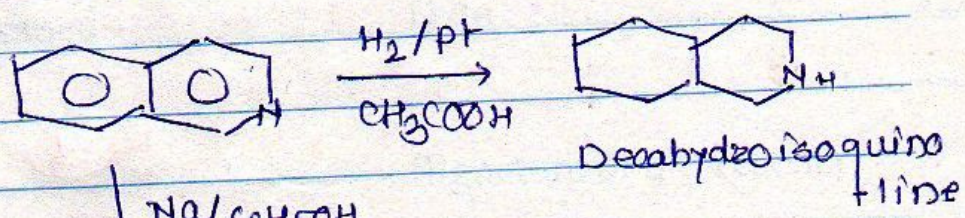


② Nucleophilic substitution reaction occurs at 1-position only by strong base like NH_2^- ; OH^- ; $C_4H_9^-$

* Nucleophilic substitution only at -1- position only.



ⓑ Reduction Reaction:- Isoquinoline can be reduced by no. of reducing agent partially or completely as follows



1,2,3,4-tetrahydroisoquinoline.

Ⓒ Oxidation Reaction:- Isoquinoline with alkaline $KMnO_4$ vigorously oxidized & it gives phthalic acid & cinchomezoic acid.

