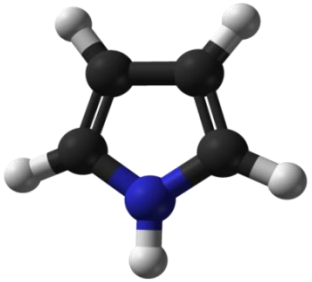


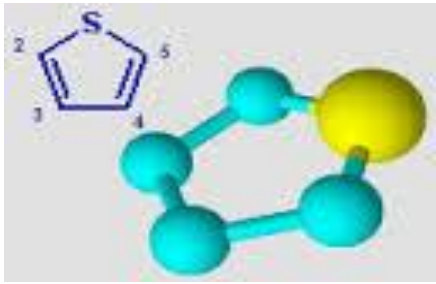
B.Sc. Third Year V Semester

CHEMISTRY

Paper XII [Organic + Inorganic]

Organic Chemistry

HETEROCYCLIC COMPOUNDS



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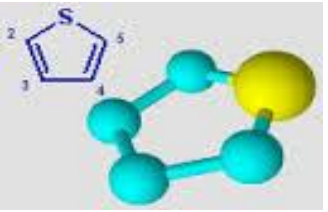
Cell : +919421864138, +918999890115

Email: drsubhashlonkar@gmail.com

HETEROCYCLIC COMPOUNDS

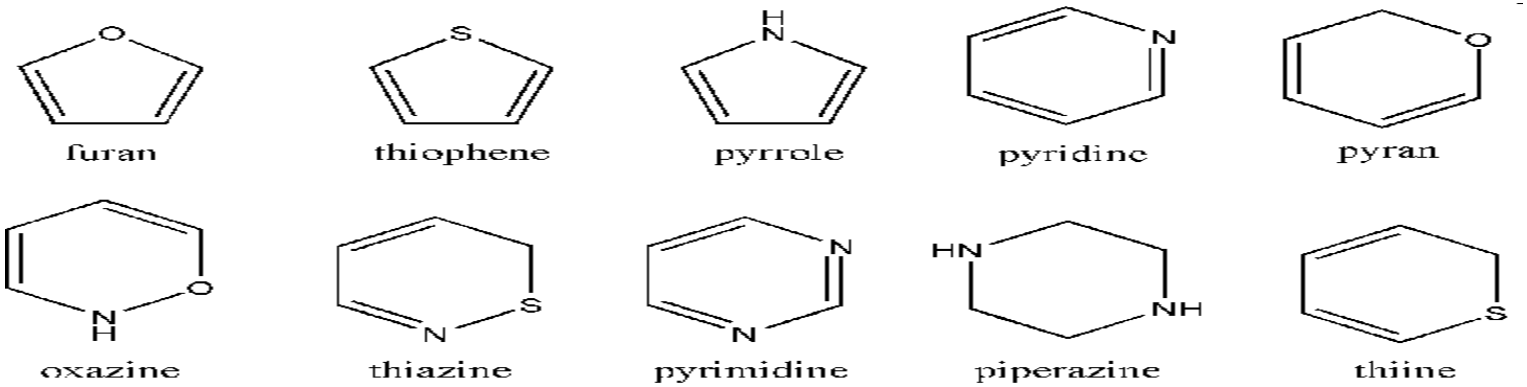


Introduction

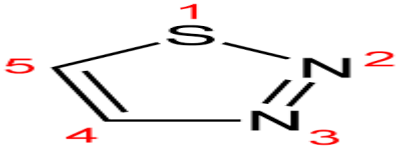
- Heterocyclic compounds are organic compounds that contain ring composed of carbon and other atoms – heteroatoms – in natural heterocycles mostly nitrogen, sulfur and oxygen.

OR

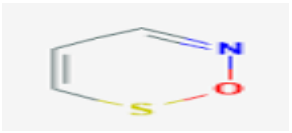
- Heterocyclic compounds are organic compounds that contain a ring structure containing atoms in addition to carbon, such as sulfur, oxygen or nitrogen, as the heteroatom. The ring may be aromatic or non-aromatic.
- Heterocycles exist as *three, four, five, six and multimember* rings.
- Heterocyclic compounds are cyclic compounds in which one or more ring atoms are not carbon (that is *hetero atoms* means *different than carbon).*



- As hetero atom can be N, O, S, B, Al, Si, P, Sn, As, Cu., common are N, O, or S.



1,2,3-Thiadizole



1,4,6-Oxathiazine

Nomenclature of Heterocycles

Common names for many ring systems are accepted by the IUPAC rules:

- ---- Rings with maximum double bonds

  Furan, pyrrole, indole, pyridine etc.

- Saturated ring systems

  either prefixes **dihydro--, tetrahydro--, perhydro--,**

  or in five membered rings **pyrroline, pyrrolidine**

  in six membered rings **piperidine, piperazine**

Systematic names according to **Hantzch-Widman** for monocyclic heterocycles:

prefixes indicating the number of heteroatoms,
stem of the name indicates the type of heteroatom,
endings for number of ring members and saturation.

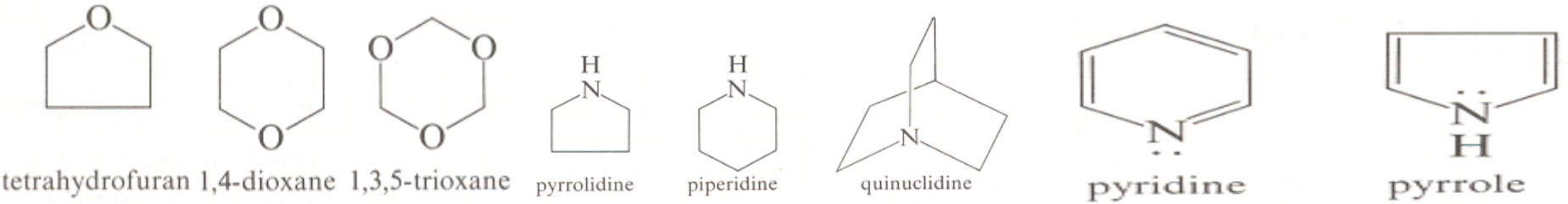
Some examples from the rules (used for some compounds in biochemistry:

Number of heteroatoms	Heteroatom	Number of ring members	Unsaturated	Saturated nitrogenous	Saturated oxygenous	Saturated sulfurous
		1	-irine, -irene	-irane	-irine	
		2	-ete	-etidine	-etane	..
di-	az-	5	**-ole**	**-olidine**	**-olane**	
tri-	thi-	6	**-ine**	(-per-)	**-ane**	
	ox-	7	**-epine**	-epane	-epane	
		8	-ocine	-ocane	..	

Classification of Heterocycles

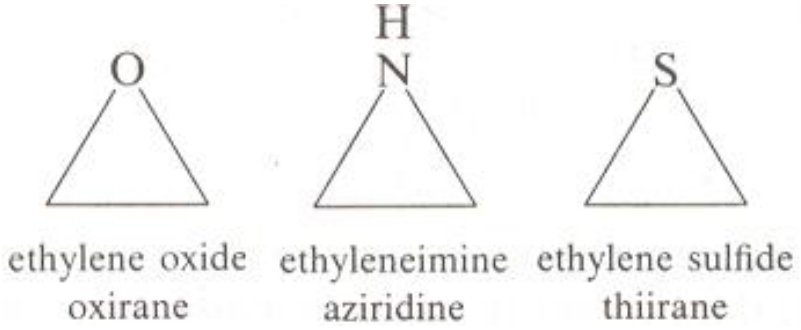
- Heterocycles are conveniently grouped into two classes.

Nonaromatic ***and*** ***Aromatic***



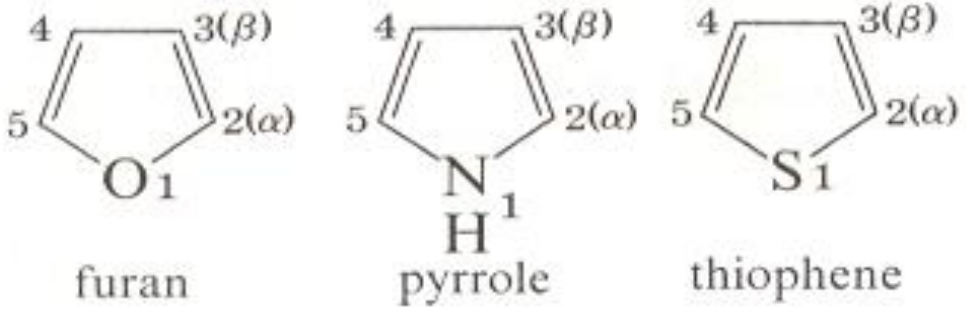
By Size of Ring

Three- membered

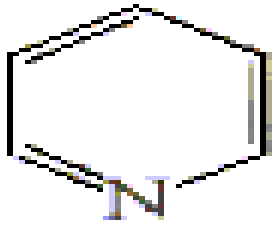


Four- membered

Five- membered

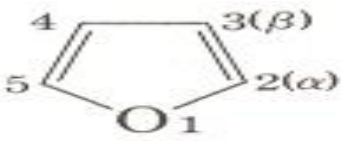


Six- membered

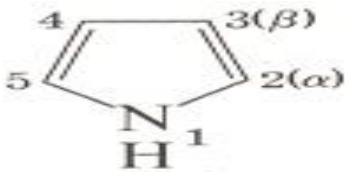


Pyridine

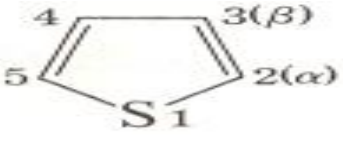
1.Five -Membered Heterocycles contains *one* heteroatom.



furan

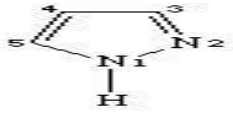


pyrrole

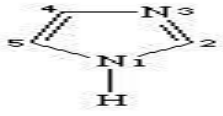


thiophene

2. Five -Membered Heterocycles contains *two* heteroatoms.

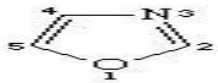


pyrazole

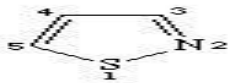


imidazole

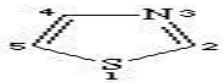
isoxazole



oxazole

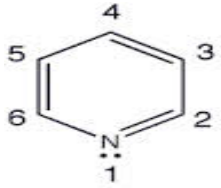


isothiazole

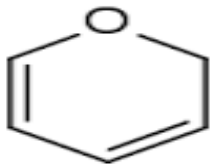


thiazole

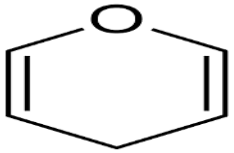
3. Six -Membered Heterocycles contains *one* heteroatom.



Pyridine

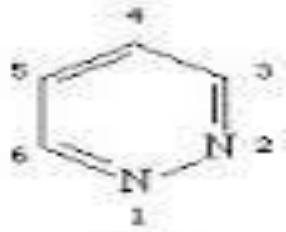


α-Pyrane

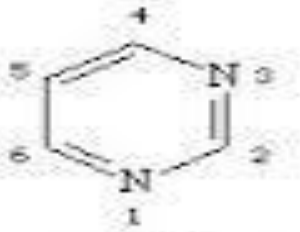


ϒ-Pyrane

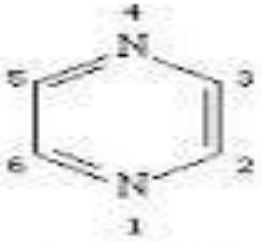
4. Six -Membered Heterocycles contains *two* heteroatoms.



pyridazine

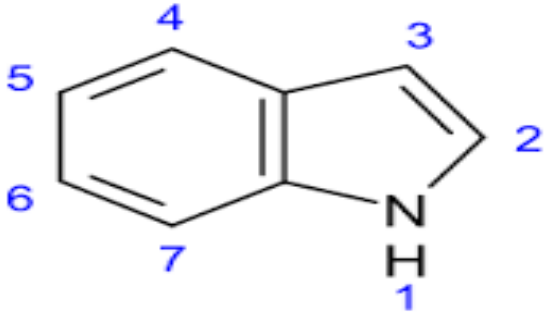


pyrimidine

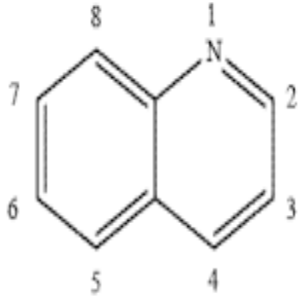


pyrazine

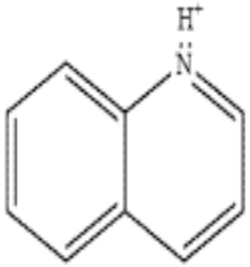
5. Bicyclic Heterocycles contains *one* heteroatom.



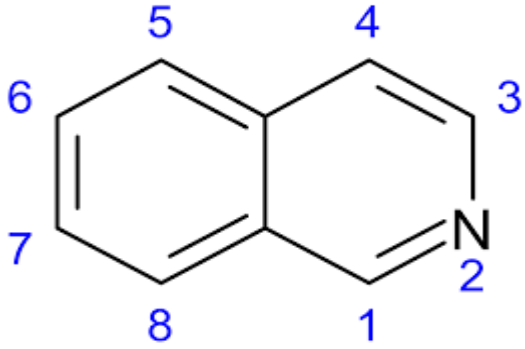
Indole



quinoline (base)

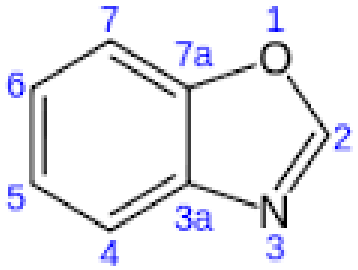


quinolinium ion
(conjugated acid)

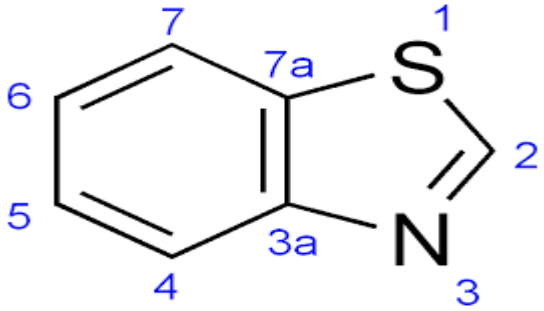


Isoquinoline

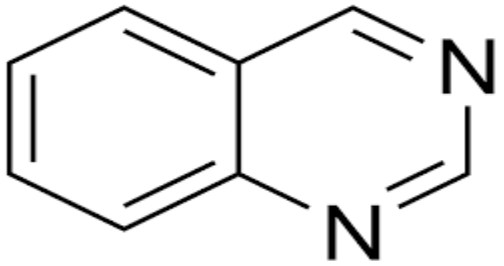
6. Bicyclic Heterocycles contains *two* heteroatoms.



Benzoxazole

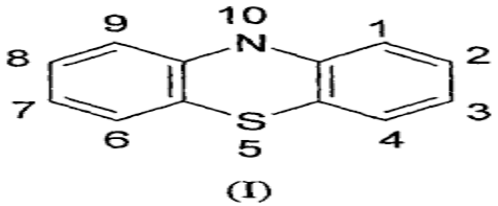


Bezothiazole



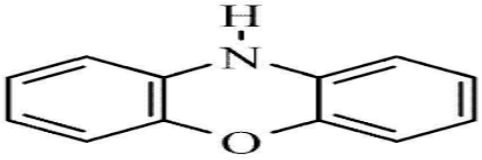
Quinazoline

7. Polycyclic Heterocycles contains *two / more* heteroatoms.

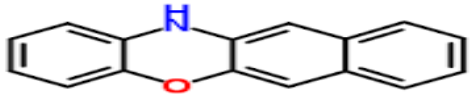


(I)

Phenothiazine



Phenoxazine

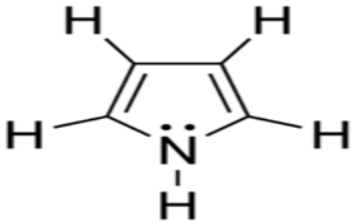


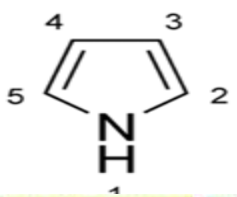
Benzophenoxazole

Section A: A. Five Membered Heterocycles: Pyrrole [Azole]

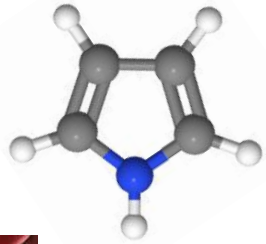
M.F. C_4H_5N

S.F.



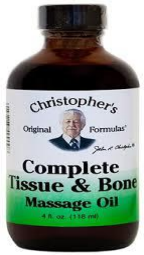


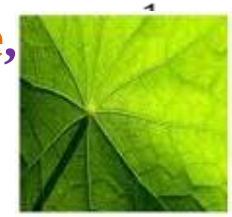
3D Structure



Occurrences:

Chlorophyll, Haemin (Blood) , Nicotine, Vitamin B_{12}, Coal tar & Bone oil

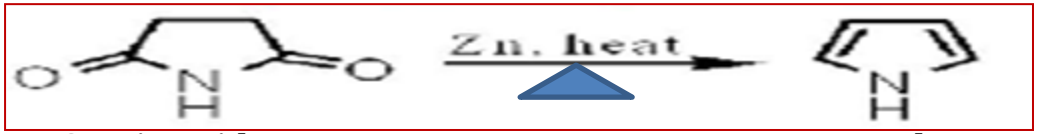




Synthesis of Pyrrole [Azole]

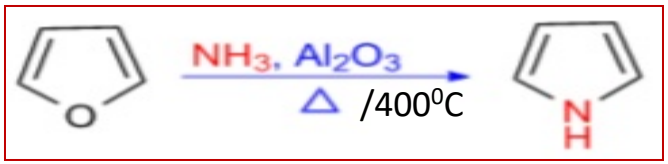
1. **Runge** (1934) From Coaltar & Bone oil. Pyrros = Red like fire & oleum = Oil

2. **From Succinamide:**



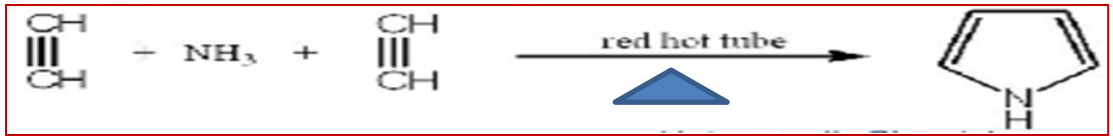
Succinamide **Pyrrole**

3. **From Furan:**



Furan **Pyrrole**

4. **From Acetylene:**



Acetylene **Pyrrole**

➢ **Physical Properties:** **Colourless liquid, B.P. 131⁰C, Sparingly in water, Soluble in organic solvents, Smell resemblance with chloroform & Shows basic property.**

Molecular Orbital Picture of Pyrrole

- Pyrrole is a five membered aromatic heterocycles contains one nitrogen and four carbon atoms in its cyclic structure.

C_6: Electronic configuration

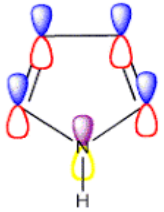
G.S. $1S^2$ $2S^2$ $2p_x^1, 2p_y^1, 2p_z^0$

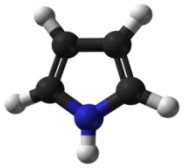
E.S. $1S^2$ $2S^1$ $2p_x^1, 2p_y^1, 2p_z^1$

N_7: Electronic configuration

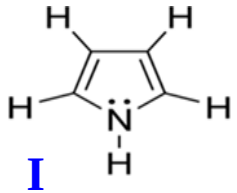
G.S. $1S^2$ $2S^2$ $2p_x^1, 2p_y^1, 2p_z^1$

E.S. $1S^2$ $2S^1$ $2p_x^1, 2p_y^2, 2p_z^1$





- In Carbon, hybridization– three Sp^2 hybrid orbital's contain single electron in each, (Sp^2 hybridization, $2S^1$ $2p_x^1$, $2p_y^1$) and $2p_z^1$ unhybridized orbital.
- In Nitrogen, hybridization– three Sp^2 hybrid orbital's, two hybrid orbital's contain single electron in each and third hybrid orbital contains two electrons, (Sp^2 hybridization, $2S^1$ $2p_x^1$, $2p_y^2$) and $2p_z^1$ unhybridized orbital.



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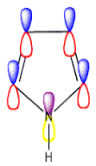
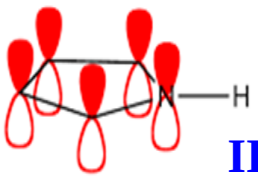
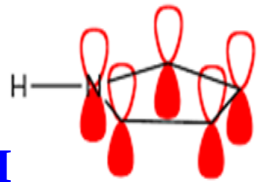
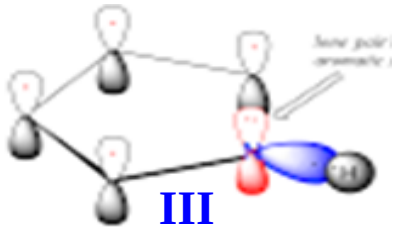


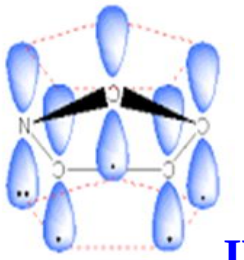


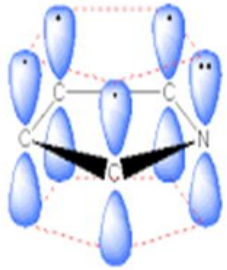
II



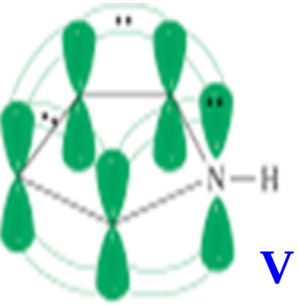


III

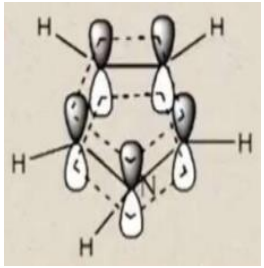




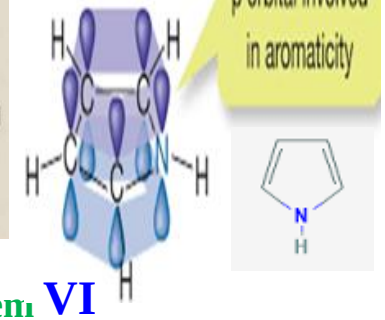
IV



V



Pyrrole Pi System

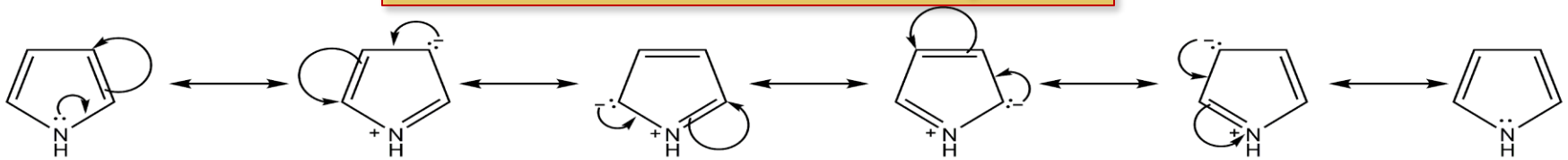


VI

The pyrrole nitrogen atom SP^2 hybridized with a loan pair of electrons in the p orbital. This p orbital overlaps with the p orbital of the carbon Atoms to form continuous ring.

Pyrrole is a aromatic because its has six pi electrons (n=1)

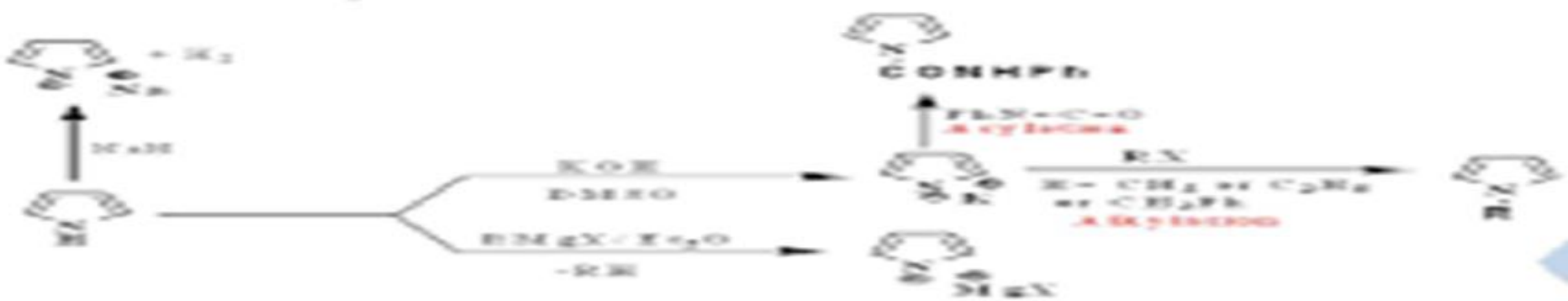
Resonance Structure of Pyrrole



Resonating Structures of Pyrrole

- Resonance contribute of pyrrole provide insight to reactivity of compound like furan and Thiophene. Pyrrole is more reactive than benzene towards electrophilic aromatic substitution reaction because it is able to stabilized +ve charge of intermediate carbonations.
- The loan pair on nitrogen is in the p orbital so it is involved in the 6 pi-electron aromatic system. Hence pyrrole is not very nucleophilic and is only weakly basic at nitrogen. Looking at of pyrrole the lobes are much bigger at the 2- and 5- positions, this indicate that the reactions are most likely to take place at these positions.

Acidic Properties of Pyrrole



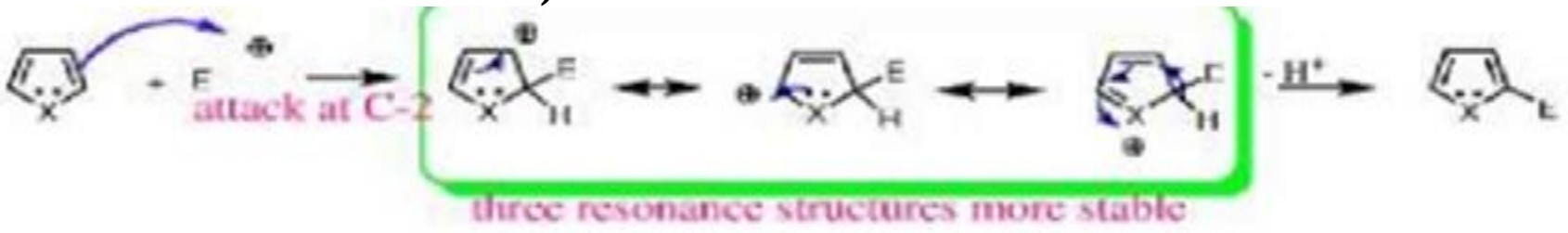
- Due to participation of N loan in aromaticity, Pyrrole has exceptionally strong acidic properties for a secondary amine for instance it can react with strong bases or Grignard reagent or potassium metal in inert solvents, and with sodamide in liquid ammonia to give salt like compounds which can be used to alkylate or acylate the nitrogen atom as shown above.

Electrophilic Substitution Reactions of Pyrrole

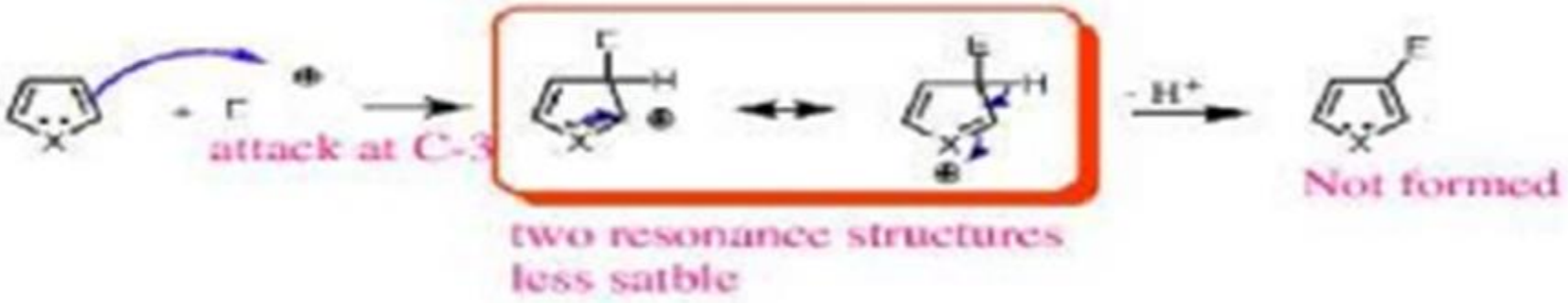
- Pyrrole is reactive towards electrophilic substitution reaction. It is more reactive than benzene of the resonance that pushes away the electron density from nitrogen towards carbon, thus making the ring electron rich. The substitution is easier and mild reagents can be used.

Reactivity in electrophilic substitution.

- Electrophilic substitution occurs at carbons (the ring) not nitrogen.
- Preferable position is C_2, the carbon next to the heteroatom.
- If there is an already substitution on C_2 then C_3.
- The first substitution is on C_2 because it has more stable intermediates (it stabilizes three resonance structures).



- The intermediate resulted from C_3 attack is stabilizes by two resonance structures.



General Mechanism of Electrophilic Substitution Reactions of Pyrrole

- Pyrrole undergoes electrophilic aromatic substitution more readily at **C-2** than **C-3** position
- Mechanism of electrophilic aromatic substitution: electrophilic aromatic substitution of pyrrole, involves the following steps:

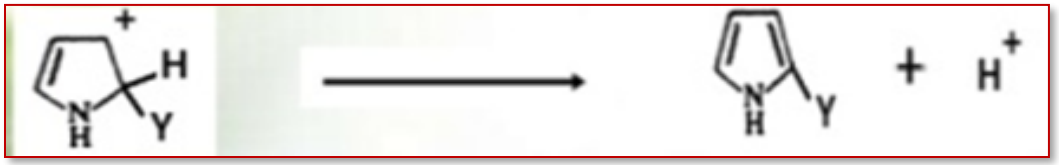
Step: 1. Generation of electrophile:

Electrophile

Step: 2. Attachment of electrophile to the aromatic ring to form intermediate carbocation:

Pyrrole **Electrophile** **Intermediate carbocation**

Step: 3. Elimination of proton from carbocation to form substitution product:



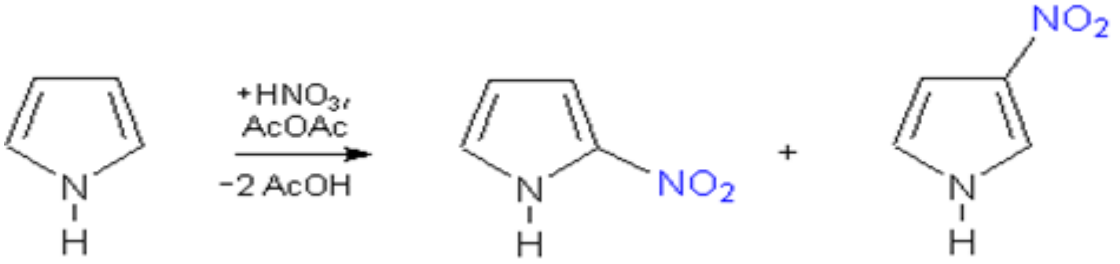
Intermediate carbocation **Substitution product** **Proton**

Where N = Heteroatom = N/S/O

Y^+=E^+ = NO_2^+/SO_3^+/Br^+/CH_3CO^+/$CHCl_3$/HCN/$C_6H_5N_2$ [E^+ = Electrophiles]

Electrophilic Substitution Reactions of Pyrrole

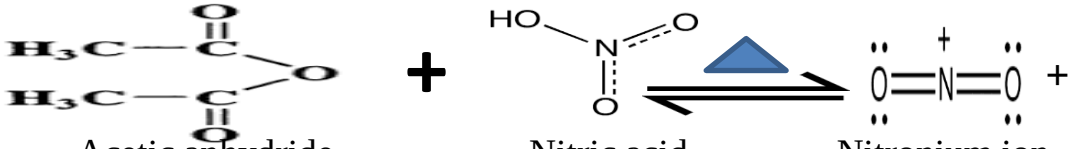
Nitration Reaction of Pyrrole



Pyrrole — 2-Nitropyrrole — 3-Nitropyrrole

Mechanism:

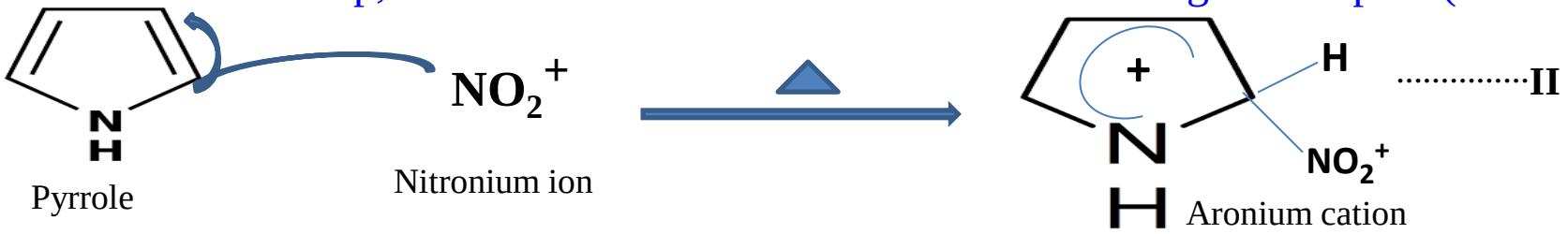
❑ 1st Step, Generation of Nitronium ion [NO_2^+]



Acetic anhydride — Nitric acid — Nitronium ion

$+ CH_3COOH + CH_3COO^-$ I

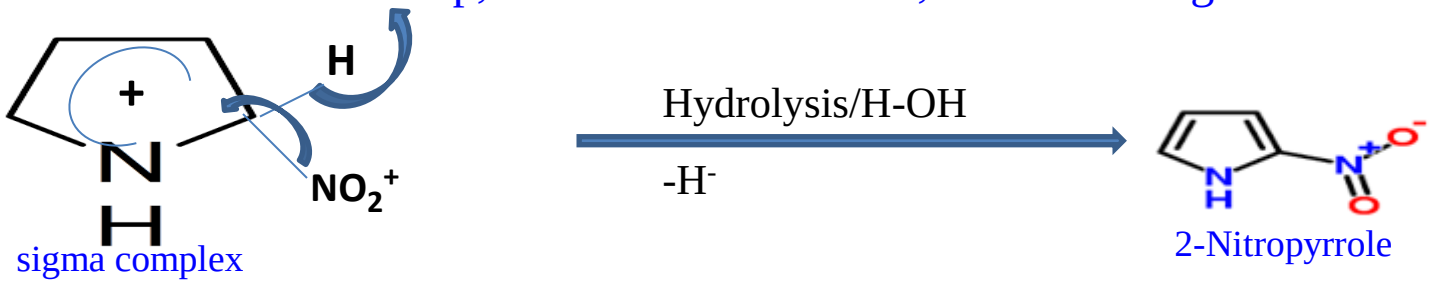
❑ 2nd Step, Attack of Nitronium ion and formation of sigma complex (aronium cation)



Pyrrole — Nitronium ion — Aronium cation

.....II

❑ 3rd Step, Elimination of H^+ ion, stabilized ring structure to form 2-nitropyrrole.

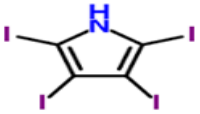


sigma complex — 2-Nitropyrrole

..... III

Electrophilic Substitution Reactions of Pyrrole

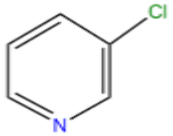
Iodination



Tetraidopyrrole

$4I_2/KI$

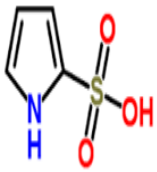
Ring Expansion



3-Chloropyridine

$CHCl_3/C_2H_5ONa$

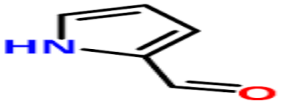
Sulphonation Reaction



Pyrrole-2-sulphonic acid

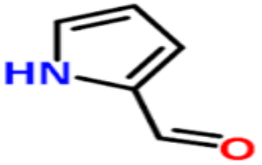
SO_3/H_2SO_4

Getterman Reaction



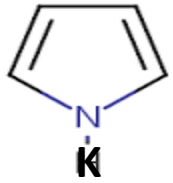
2-Formyl pyrrole

HCN/ HCl Lewis. Acid



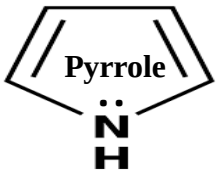
2-Formyl pyrrole

$CHCl_3/KOH$

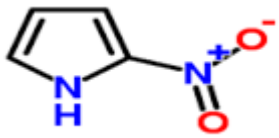


Potasiopyrrole

KOH



Pyrrole

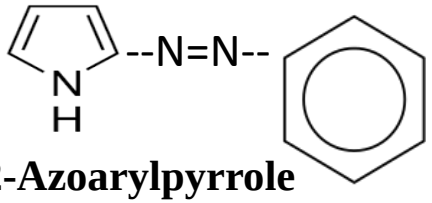


2-Nitro pyrrole

$HNO_3/(CH_3CO)_2O$

Nitration Reaction

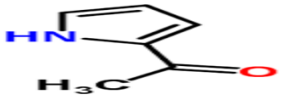
$C_6H_5N_2Cl$/ Acid



2-Azoarylpyrrole

Coupling Reaction

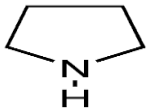
$(CH_3CO)_2O$ Lewis. Acid



2-Acetyl pyrrole

Friedel Craft Acylation

$H_2/Pt/$



Pyrrolidine

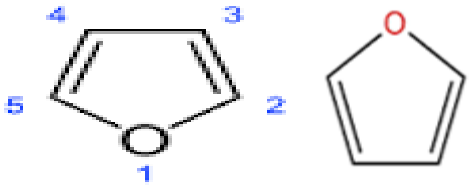
Reduction

Reimer- Timann Reaction

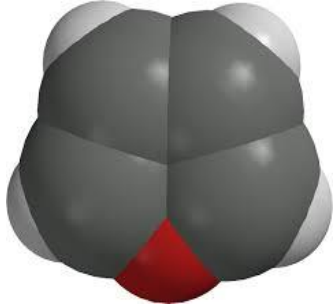
B. Five Membered Heterocycles: Furan [Oxole]

M.F. C_4H_4O

S.F.



3D Structure

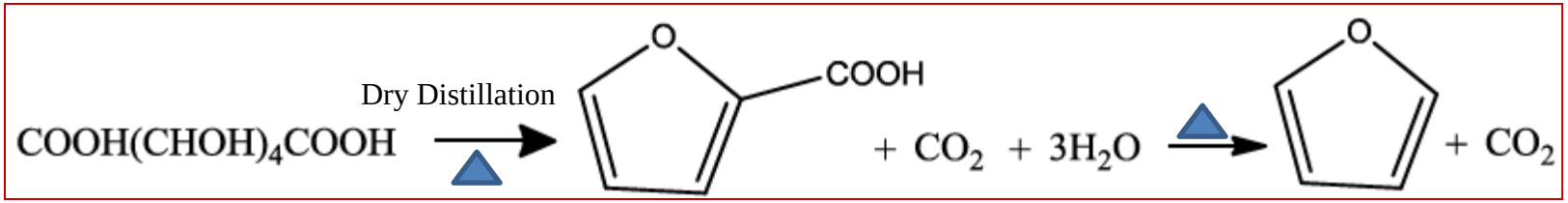


Occurrences:

- Coal tar
- Grain husk
- Pine wood tar
- Barn (branch of tree)

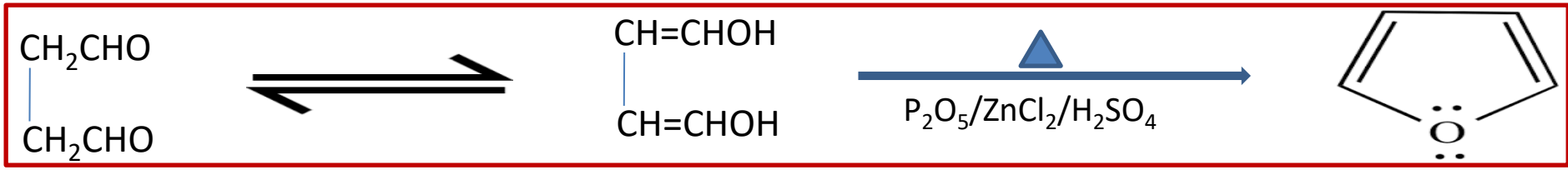
Synthesis of Furan [Oxole]

1. Mucic acid:



Mucic acid **Furoic cid** **Furan**

2. Succinaldehyde:



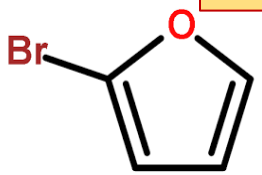
Keto **Enol** **Furan**

➢ **Physical Properties of Furan**

- ❑ Colourless liquid, B.P. 32^0C, Insoluble in water, Soluble in alcohol & ether.
- ❑ Smell resemblance with benzene, Donot shows basic property.

Electrophilic Substitution Reactions of Furan

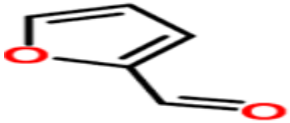
Bromination Reaction



2-Bromofuran

Br_2/Dioxane

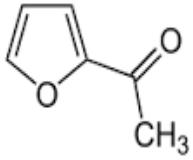
Getterman Koch Reaction



2-Formyl furan

CO/ HCl Lewis. Acid

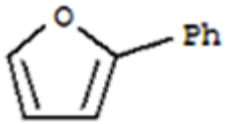
Friedel Craft Acylation



2-Acetylfuran

$(CH_3CO)_2O/SnCl_2$

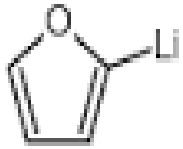
Coupling Reaction



2-phenylfuran

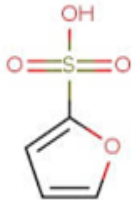
Ph.diz.cl./NaOH

n- Butyllithium



2-Lithiumfuran

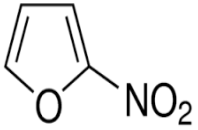
Sulphonation Reaction



Furan-2-sulphonic acid

SO_3/pyridine

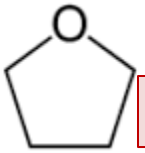
$HNO_3/(CH_3CO)_2O$



2-nitrofuran

Nitration Reaction

H_2 /Pt/



Reduction

Tetrahydrofuran

Diel's-Alder Reaction

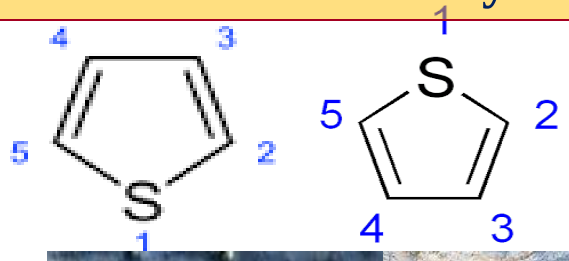
Furan + Maleic anhydride → Adduct

7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride

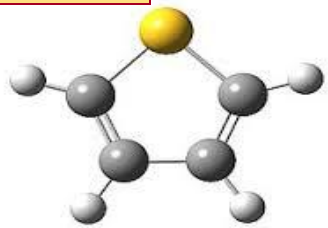
C. Five Membered Heterocycles: Thiophene [Thiole]

M.F. C_4H_4S

S.F.



3D Structure



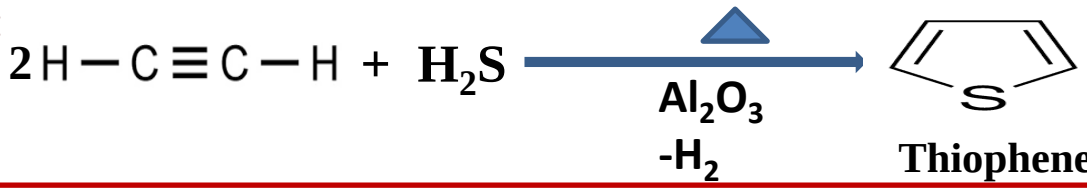
Occurrences:

- **Coaltar**
- **Shale oil**
- **Rock formed in thin layers**

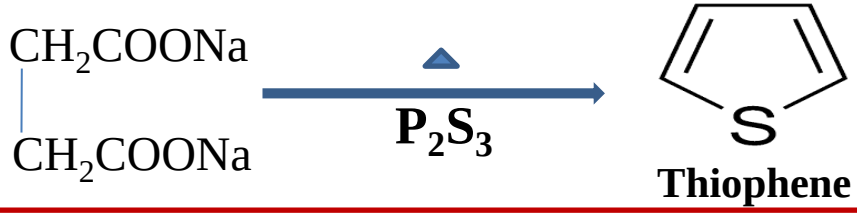
Synthesis of Thiophene [Thiole]

Victor Meyer(1882), firstly synthesized thiophene by Fractional distillation of Coal tar.

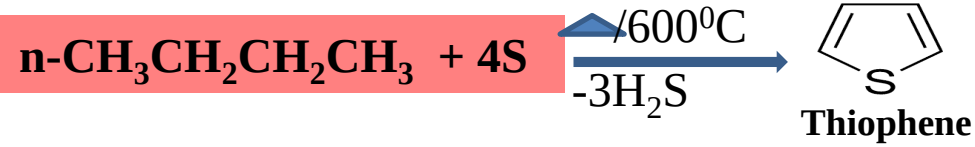
1. Acetylene:



2. Sodium Succinate:



3. n-Butane:

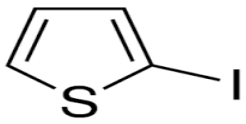


➢ Physical Properties:

- Colourless liquid.
- B.P. 84^0C.
- Insoluble in water.
- Soluble in organic solvents.
- Smell resemblance with benzene.
- It is stable in aq. acid & doesn't shows basic property.

Electrophilic Substitution Reactions of Thiophene

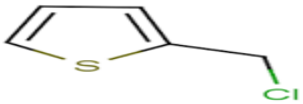
Iodination Reaction



2-iodothiophene

I_2/HgO

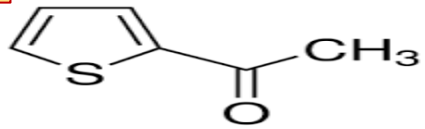
Chloro Methylation Reaction



2-chloromethyl Thiophene

HCHO/ HCl Lewis. Acid

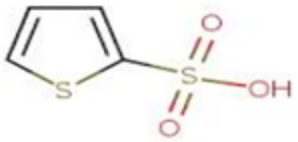
Friedel Craft Acylation



2-acetylthiophene

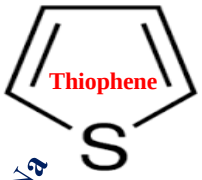
$(CH_3CO)_2O/SnCl_2$

Sulphonation Reaction

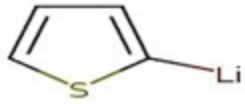


Thiophene-2-sulphonic acid

SO_3/H_2SO_4



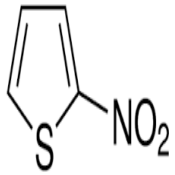
n- Butyllithium /Dry ether



2-Lithiothiophene

$HNO_3/ (CH_3CO)_2O$

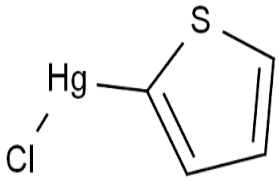
Nitration Reaction



2-nitrothiophene

$HgCl2/CH3COONa$ -HCl

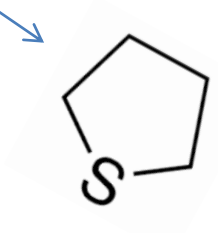
Mercuration



2-Mercuric chloride Thiophene

H_2 /Pt/

Reduction

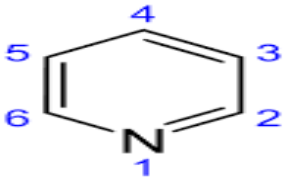


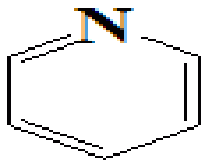
Tetrahydrothiophene

Section B: Six Membered Heterocycles: Pyridine [Azine]

M.F. C_5H_5N

S.F.

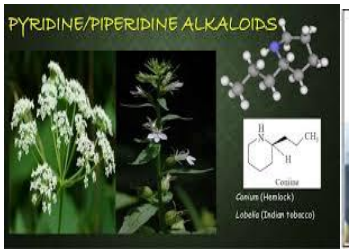


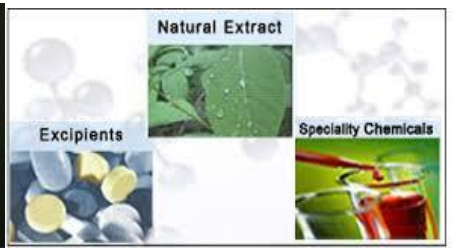


3D Structure

Occurrence:

- **Coaltar**
- **Bone oil**
- **Along with pyrrole bone oil**
- **Several alkaloids**

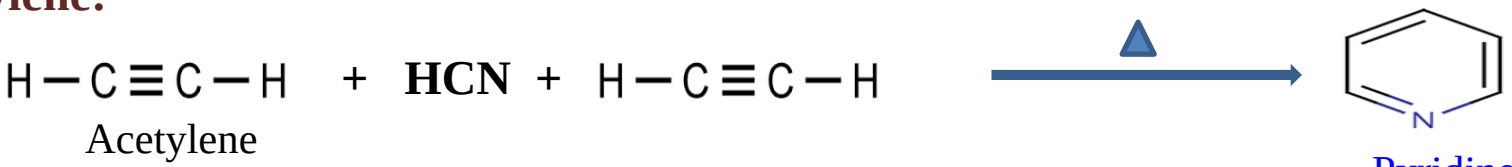




❑ Pyridine is not abundant in nature. In daily life, trace amounts of pyridine are components of The volatile organic compounds that are produced in roasting and canning processes, roasted Coffee, potato chips, sunflower honey.

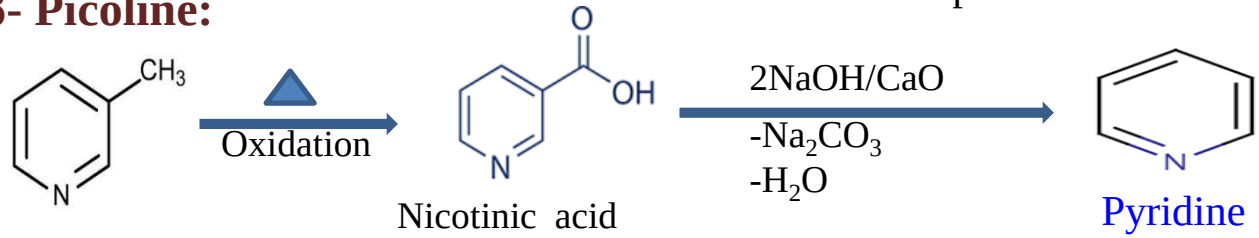
Synthesis of Pyridine [Azine]

1. Acetylene:



2. Pentamethylenediamine:

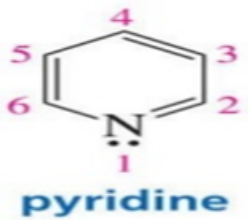
3. β- Picoline:



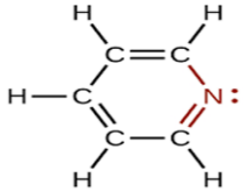
➢ **Physical Properties:** Colourless liquid, B.P. 115^0C , Miscible in water & Hygroscopic.

- Soluble in organic solvents, Characteristics unpleasant smell, It shows basic property.

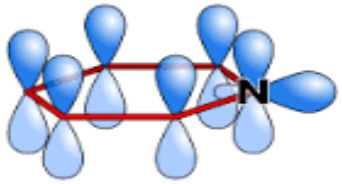
Molecular Orbital Picture of Pyridine



I



II



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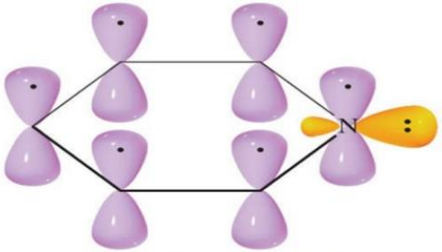

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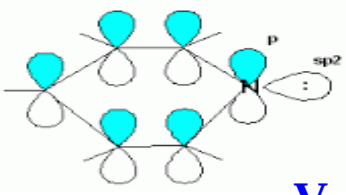
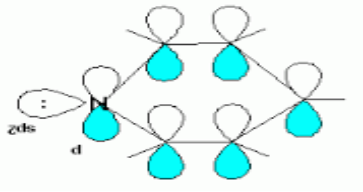
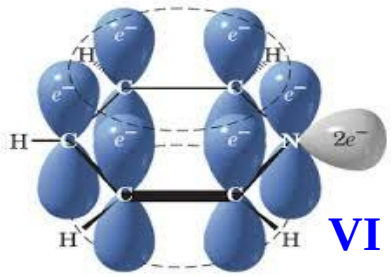


V





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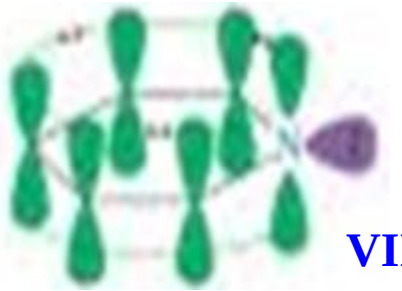
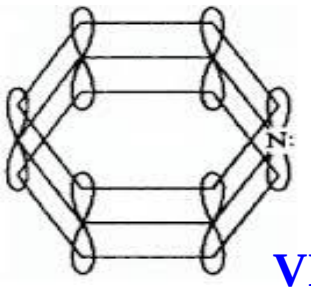


VII



VIII

IX

Resonance Structure of Pyridine

Resonance contribution structures of Pyridine

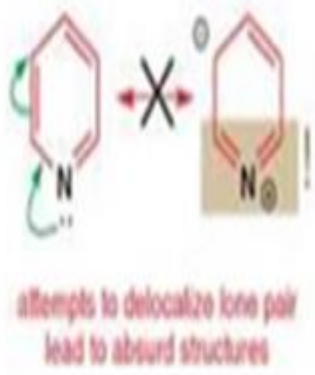
Basic Property of Pyridine

- The nitrogen center of pyridine features a basic loan pair of electrons. Because this loan pair is not part of the aromatic ring, pyridine is abase, having chemical properties similar to those of tertiary amines.
- Pyridine can act as Lewis base, donating it's pair of electron to a Lewis acid as in the sulfur trioxide pyridine complex.

- **Pyridine is strong base than pyrrole**

Pyridine as Nucleophile

- Pyridine is a nucleophile as NITROGEN because its lone pair is not delocalized.



The ring as Nucleophile:

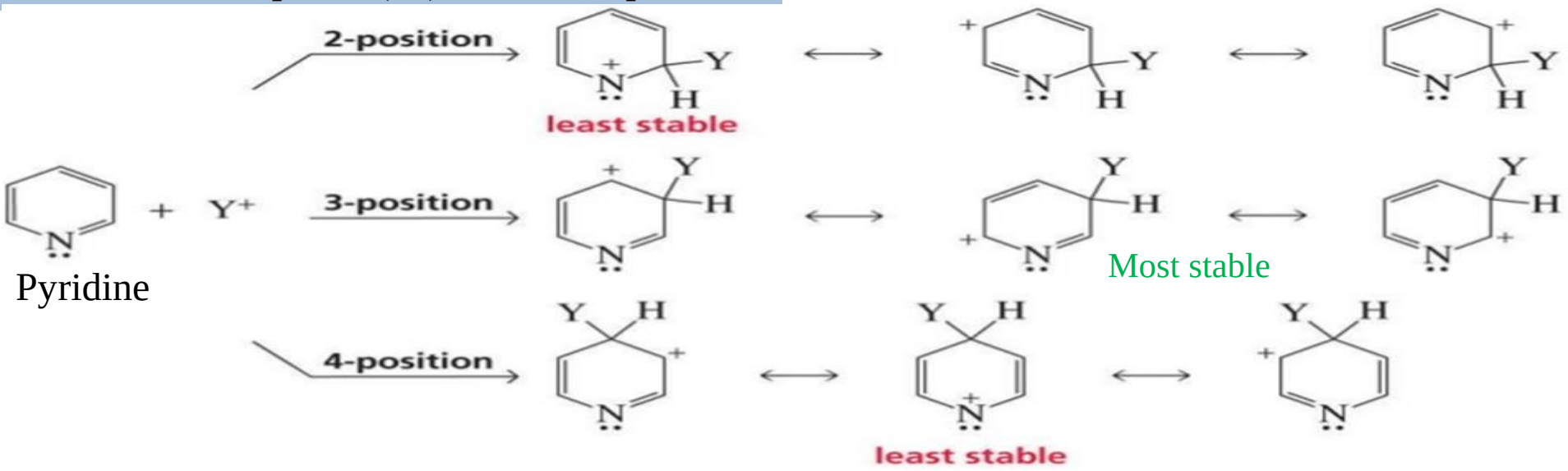
- Electronegative atom like nitrogen lowers the energy of the ring, this means a less reactive nucleophile.

The ring as Electrophile:

But LUMO means a more reactive ELECTROPHILE

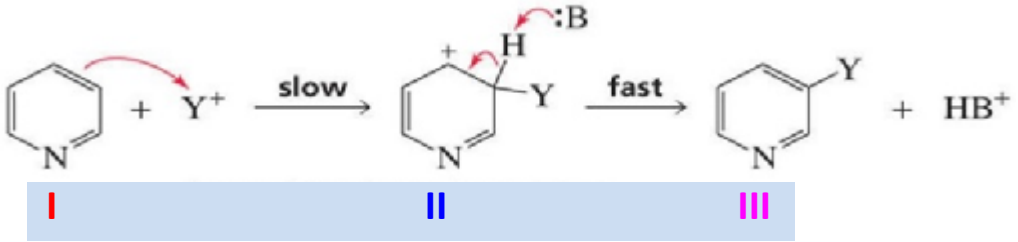
Electrophilic Substitution Reactions of Pyridine

Attack of Electrophiles (Y^+) at different positions



General Mechanism of Electrophilic Substitution Reactions of Pyridine

Mechanism:



- **I. Generation of Electrophile (y^+).**

$$Y\text{ --- }Z \rightleftharpoons y^+ + Z^-$$

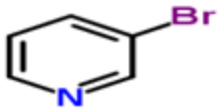
- **II. Formation of sigma complex.**
- **III. Loss of proton to form stable compound.**

Where Y^+ [Electrophiles]= $NO_2^+/SO_3^+/Br^+$

- Many electrophilic substitutions on pyridine either do not proceed or proceed only partially they lead only to the additional at the nitrogen atom.

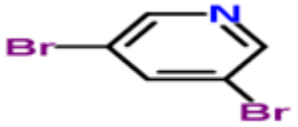
Electrophilic Substitution Reactions of Pyridine

Bromination

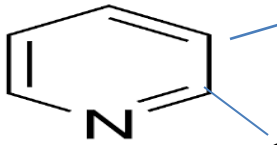


3-Bromopyridine

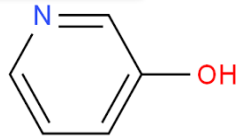
+



3,5-Dibromopyriidine

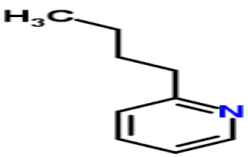


KOH/300°C



Pyridol

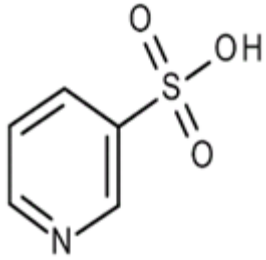
300°C
Br_2/Charcoal



2-n-butylpyridine

n- Butyllithium
100 °C

Sulphonation

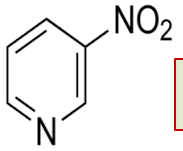


Pyridine-3-sulphonic acid

SO_3/H_2SO_4

Pyridine

HNO_3/Conc. H_2SO_4

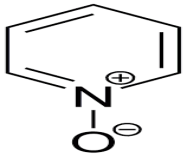


Nitration

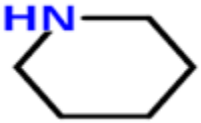
3-nitropyridine

Perbenzoic acid/peroxide

H_2 /Na/ EtOH
3.atm.pressure



Pyridine oxide



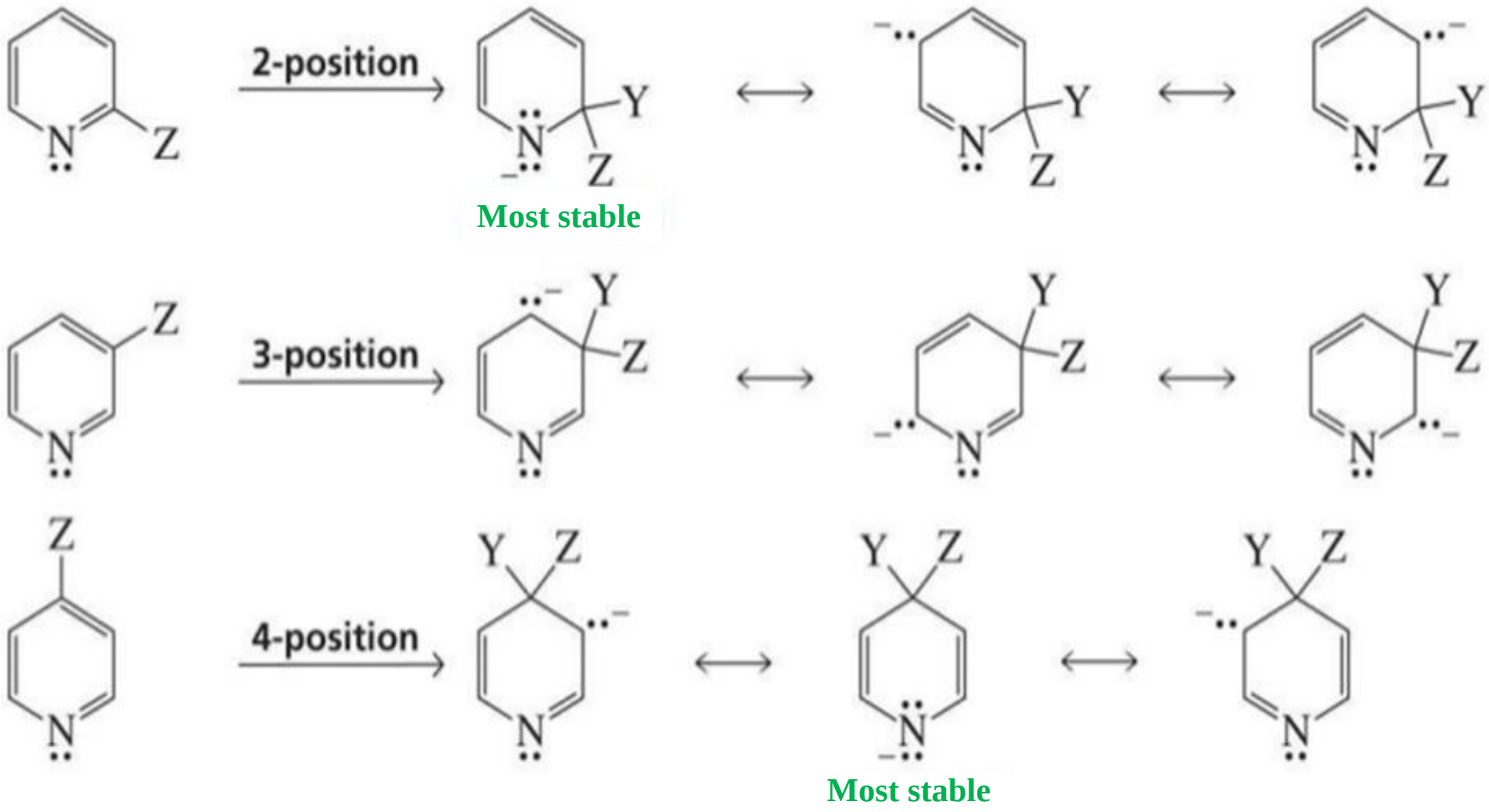
Piperidine

Reduction

Oxidation

Nucleophilic Substitution Reactions of Pyridine

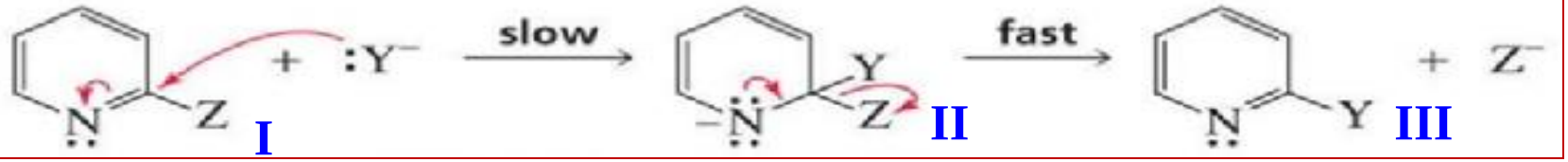
Attack of Neuclophile (Y^-) at different positions



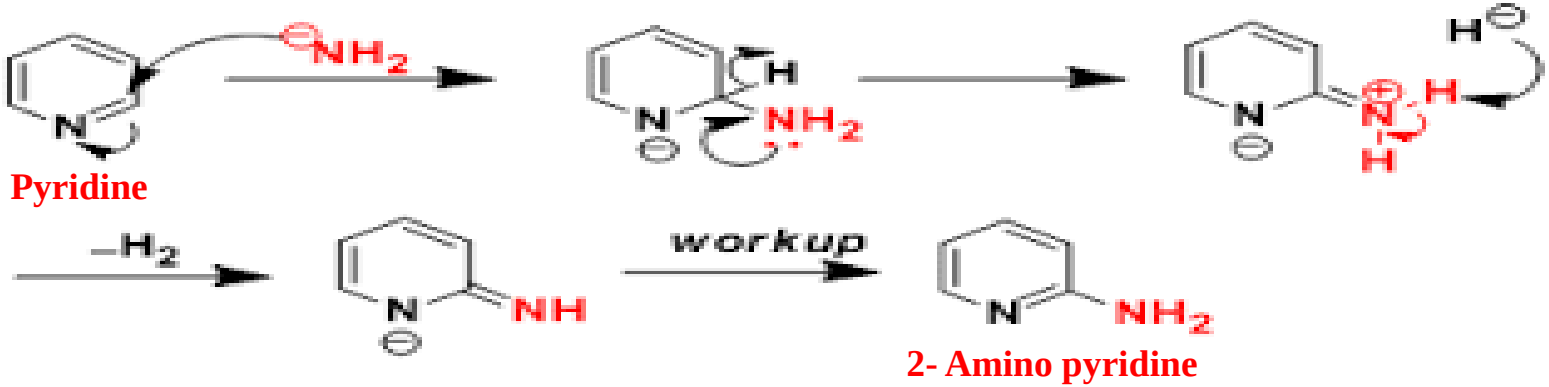
Nucleophilic Substitution Reactions of Pyridine

❑ Chichibabin Reaction

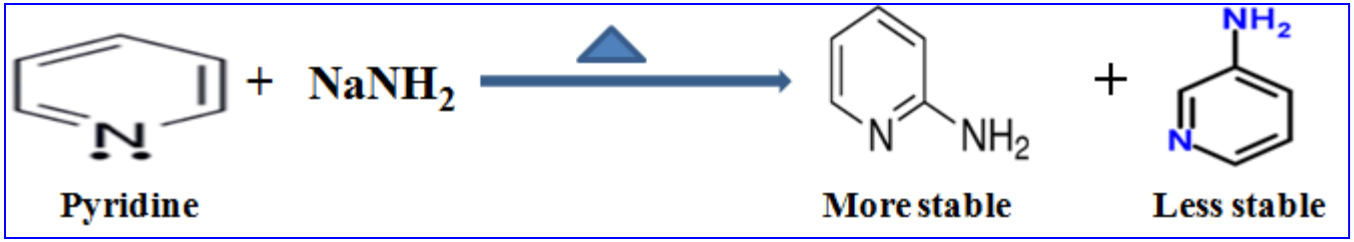
When pyridine is heated with sodamide, an-NH_2 group is introduced directly into the pyridine nucleus mainly at 2- position & small amount of 4- position is formed at the same time called as Chichibabin Reaction.



General Mechanism:



❑ Amination Reaction:



Mechanism of Amination Reaction of Pyridine

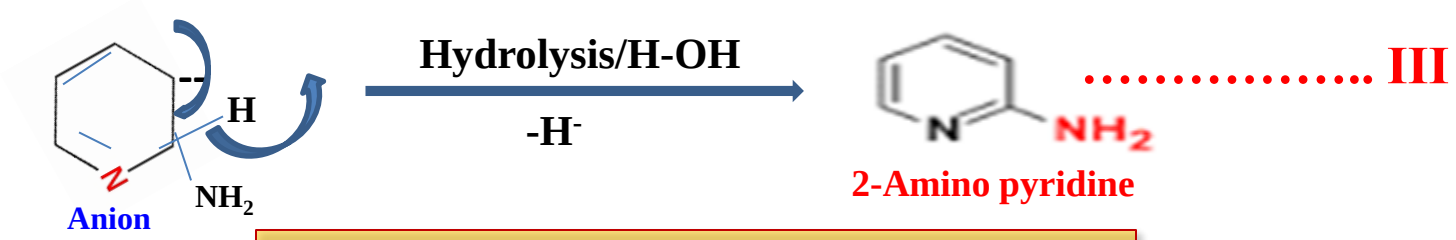
Mechanism :

I. Generation of Neuclophile .

$$NaNH_2 \rightleftharpoons Na^+ + NH_2^- \text{.....} \quad \text{I}$$

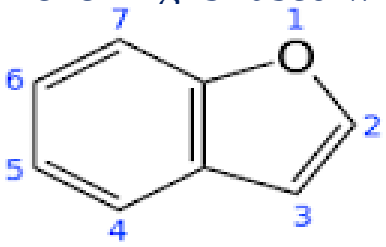
II. Formation of carbanion (anion).

III. Loss of hydride (H^-) to form stable compound.

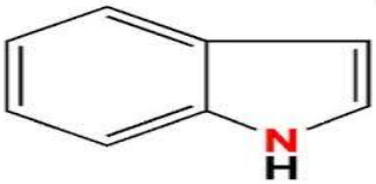


Condensed Heterocyclic Compounds

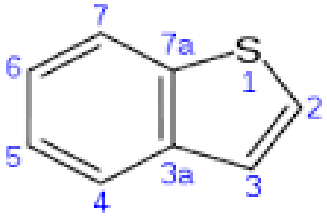
- Benzene ring is fused with Furan, Pyrrole & Thiophene at 2,3 positions to get fused compounds.



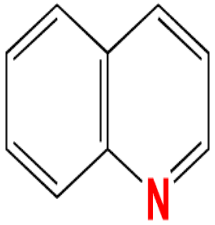
Benzofuran



Indole



Benzothiophene



Benzopyridine

1. Friedlander's Quinoline Synthesis

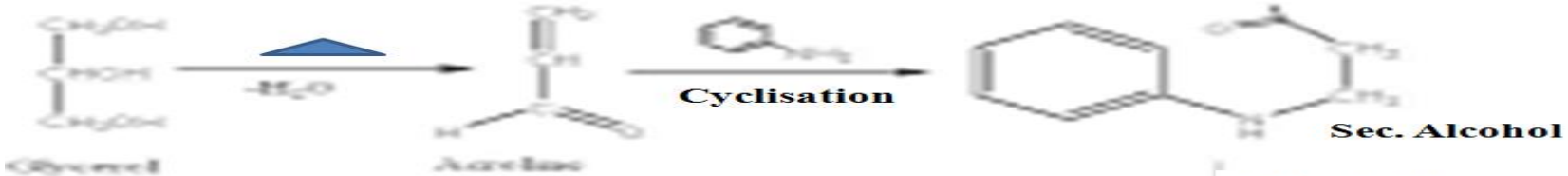
Friedlander

2-aminobenzene carbaldehyde Enolizable carbonyl compound Quinoline

2. Skraup's Quinoline Synthesis

Aniline Quinoline

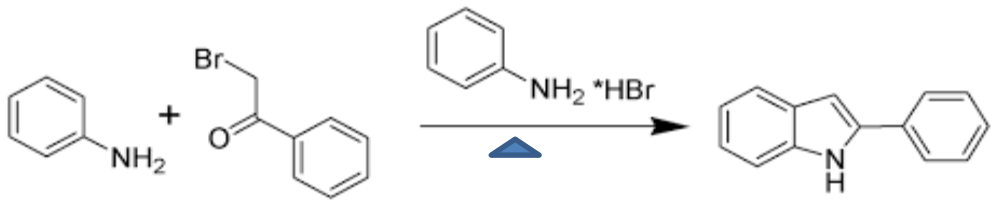
Skraup



Bischler

Quinoline 1,2-Dihydroquinoline

❑ Bischler's Indole Synthesis



Aniline Phenacyl bromide 2-Phenyl Indole

.....SUGGESTIONS

Created by, Dr. Subhash Lonkar