

**Classification and nomenclature, Structure,
aromaticity in 5 & 6 membered rings containing
one heteroatom
Pyrrole**

Heterocyclic compounds

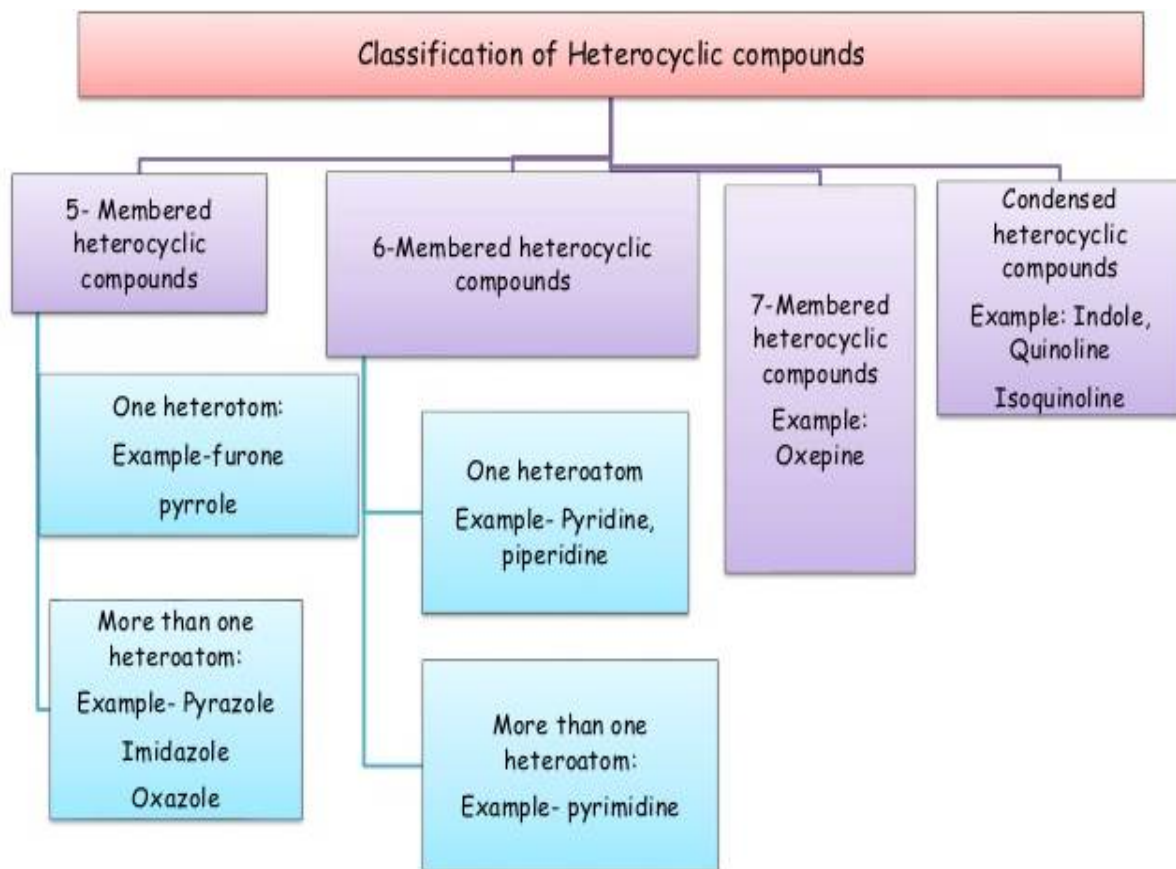
HETEROCYCLIC COMPOUNDS

➤ A cyclic organic compound containing all carbon atoms in ring formation is referred to as a carbocyclic compound.

➤ **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.

➤ Number of drugs in pharmaceutical science are heterocyclic compounds.

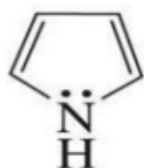
➤ Heterocyclic compounds may be of natural origin or synthetically available.



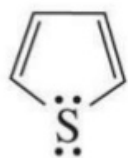
➤ 5- Membered heterocyclic compound having one heteroatom:



furan

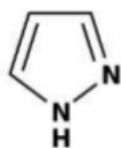


Pyrrole

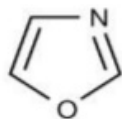


Thiophene

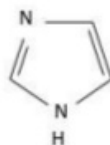
➤ 5- Membered heterocyclic compound having more than one heteroatom



Pyrazole



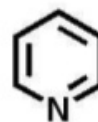
Oxazole



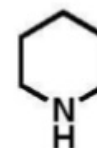
Imidazole

6

➤ 6- Membered heterocyclic compounds having one heteroatom:

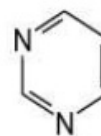


Pyridine

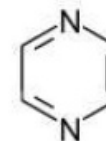


Piperidine

➤ 6- Membered heterocyclic compounds having more than one heteroatom:



Pyrimidine

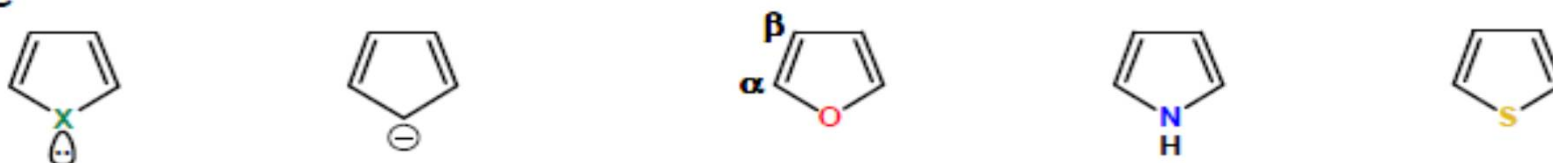


Pyrazine

7

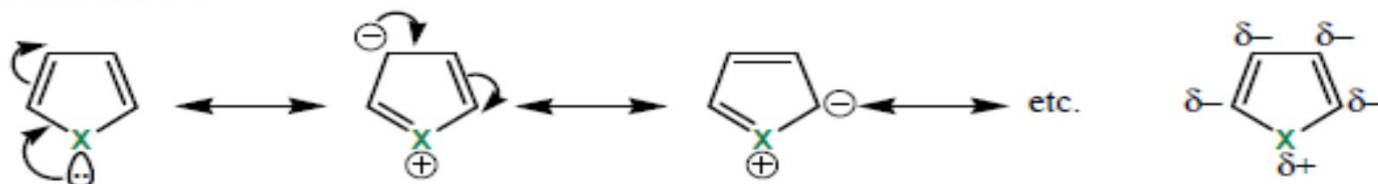
Furans, Pyrroles and Thiophenes – Structure

Structure

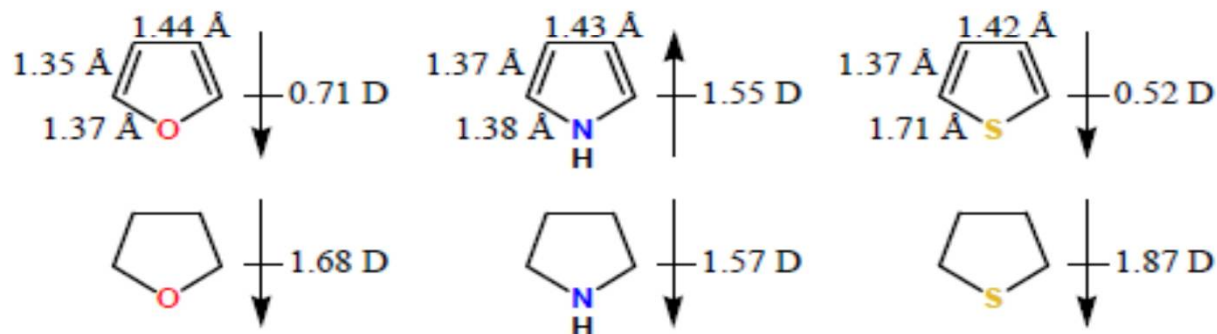


- 6 π electrons, planar, aromatic, isoelectronic with cyclopentadienyl anion

Resonance Structures

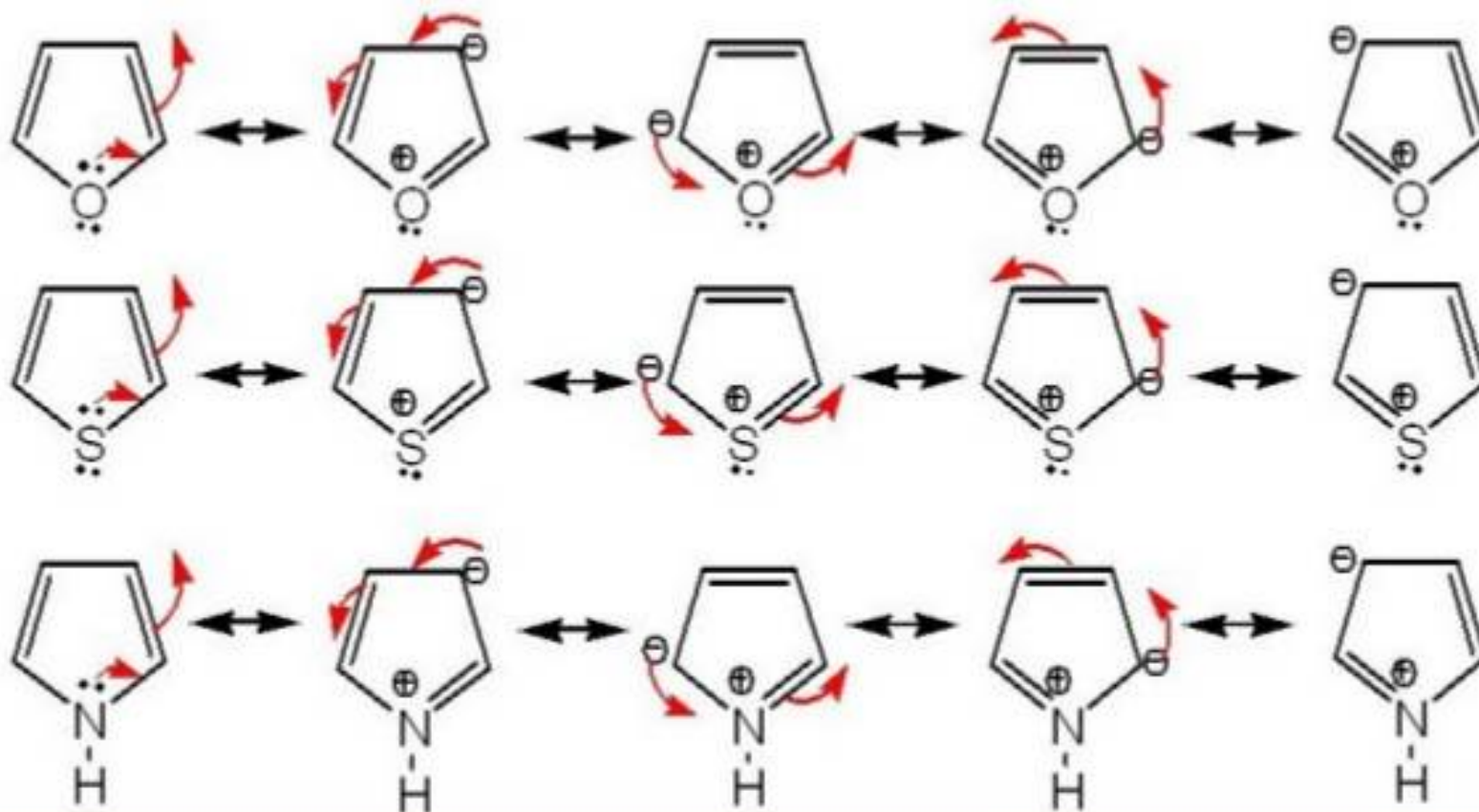


- Electron donation into the ring by resonance but inductive electron withdrawal



- O and S are more electronegative than N and so inductive effects dominate

Resonance structures of furan Thiophene and Pyrrole



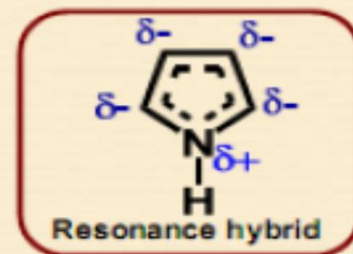
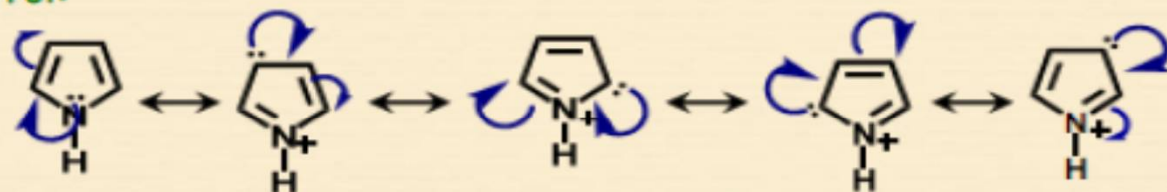
π -EXCEDENT AROMATIC HETEROCYCLES



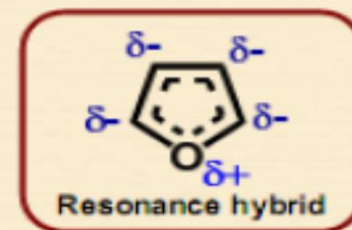
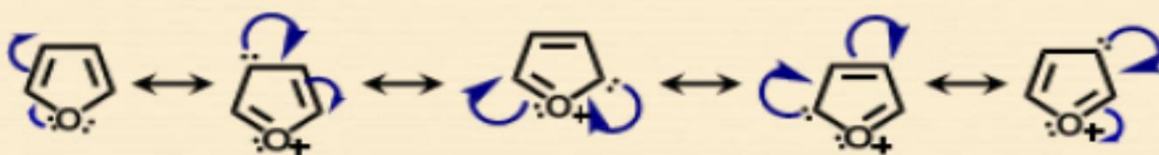
ELECTRON DENSITY MAP

Can be understood in terms of resonance structures

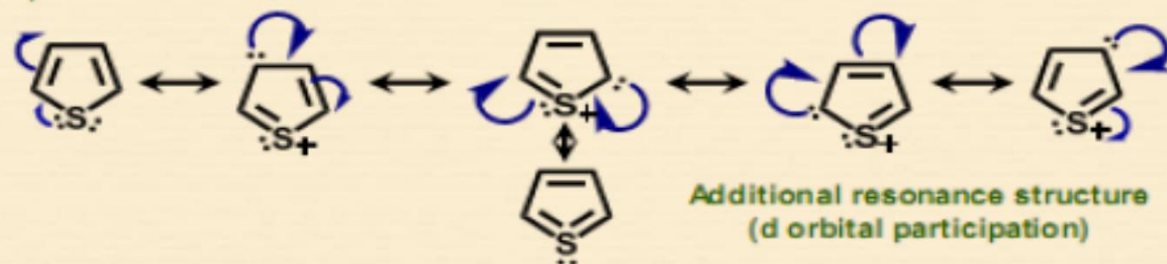
→ **Pyrrrol:**



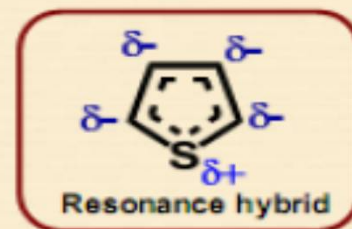
→ **Furane:**



→ **Thiophene:**



Additional resonance structure
(d orbital participation)



- Thiophene has a **more aromatic** character (contribution of additional resonance structure without charge separation)
- Furane has **the less aromatic character** (unstability of resonance structures with a positively charged oxygen atom)

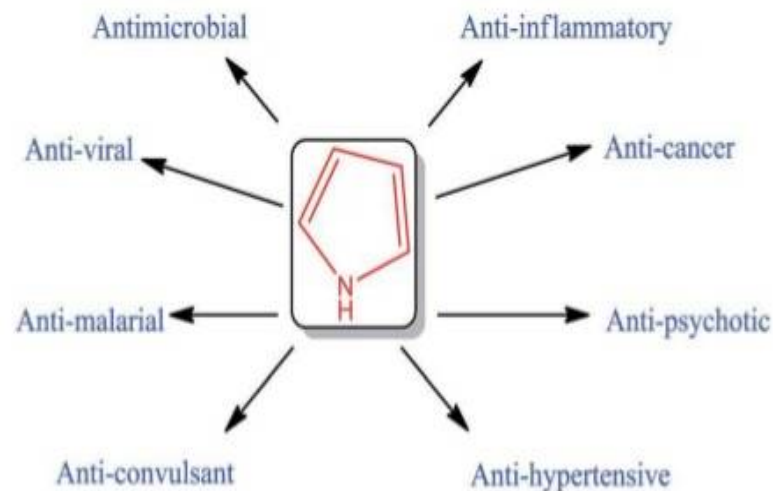
PYRROLE

HISTORY



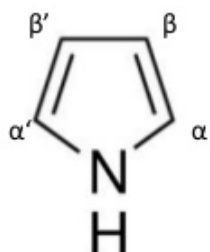
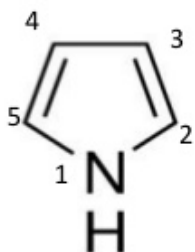
| | | |
|------|----------|--|
| 1834 | Runge | Distillation of coal tar, bone oil, and other product derived from proteins gave unknown product in ammonia & dipped in HCl, called PYRROLE |
| 1857 | Anderson | Obtained pure compound from bone oil distillate and synthesized by the pyrolysis of ammonium mucate which is commercially used. |

- Pyrrole is the 5- membered ring containing N-atom replacement with C-atom.
- the pyrrole ring system soon become of great interest, as it was found in many compounds widely distributed in nature.
- Pyrrole rings are present in a number of natural products for eg. alkaloids and synthetic pharmaceuticals.
- Pyrroles having a following therapeutical activity



Nomenclature

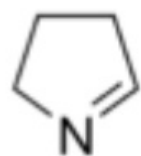
- In naming pyrrole and its derivatives, the nitrogen atom is assigned position-1.



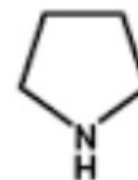
- The position of the substituent may be specified in Arabic numerals or in Greek letters.

- Five - membered heterocycles containing nitrogen general end with 'ole'

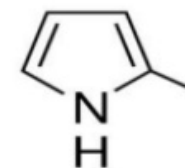
- Three dihydropyrroles or pyrrolines are theoretically possible and tetrahydropyrrole is called pyrrolidine. The pyrrole ring, when considered as a substituent in another structure is called pyrryl.



Pyrroline

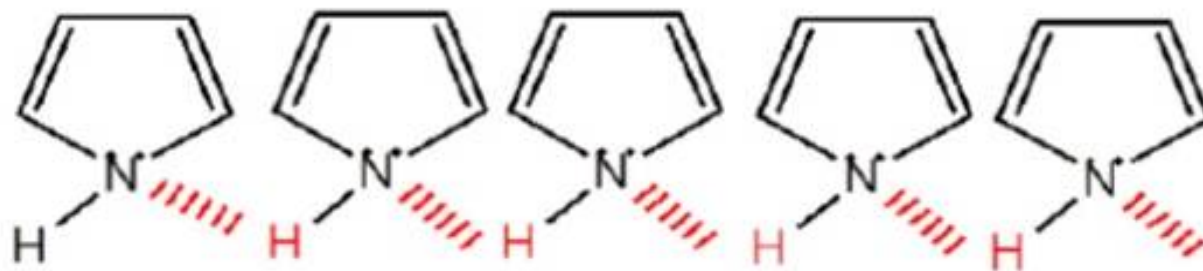


Pyrrolidine



Pyrryl

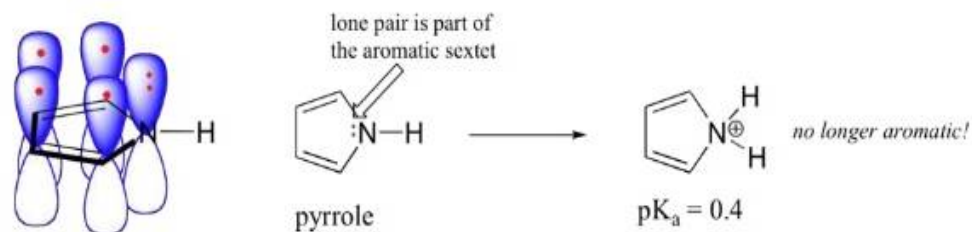
- It is a colourless volatile liquid.
- It's boiling point is 131°C and melting point is -23°C .
- It turns brown in the air and gradually resinifies.
- Only slightly soluble in water but it is totally miscible with ether and ethanol.
- Pyrrole is weakly basic in nature.
- Pyrrole has a relatively high boiling point as compared to furan and thiophene, this is due to the presence of intermolecular hydrogen bonding in pyrrole.



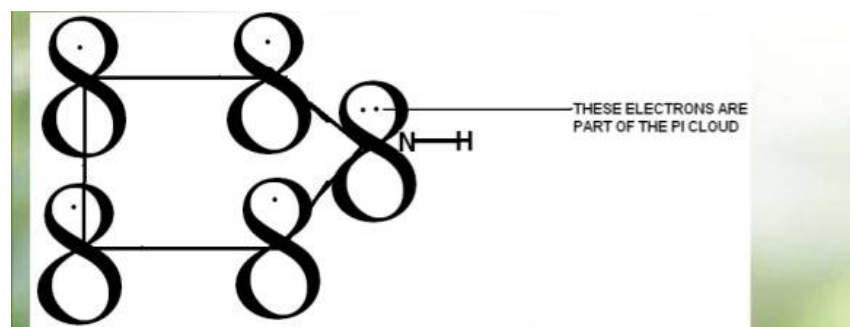
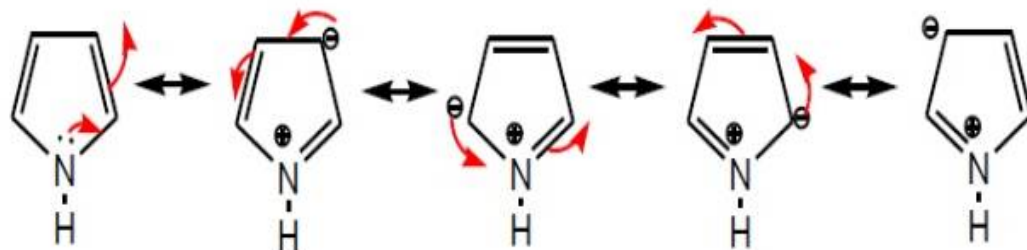
Aromaticity of pyrrole

- Pyrrole itself is completely planar and has molecular dimensions.
- The 5 sp^2 hybridised C-atoms sustained 6π electron system. From the molecular orbital standpoint it is consisting of planar pentagon with sp^2 hybridised C-atoms.
- Each of the 4 C-atoms has one electron remaining in a p_z orbital. The N-atom has 2 electrons in p orbital.
- These p orbitals overlap to give a total of six electrons in π system and this shell provides stability.
- Pyrrole is an extremely weak base because its pair of non-bonding electrons are part of the π -cloud ($K^b = 2.5 \times 10^{-14}$). Therefore, if pyrrole is protonated, it loses its aromaticity.

Pyrrole is less aromatic than thiophene and more aromatic than furan. Therefore the total orbital diagram of Pyrrole is:



- They tend to react by electrophilic substitution due to appearance of -ve charge on carbon atoms.
- Due to delocalization of electrons as shown in the following resonance structures.



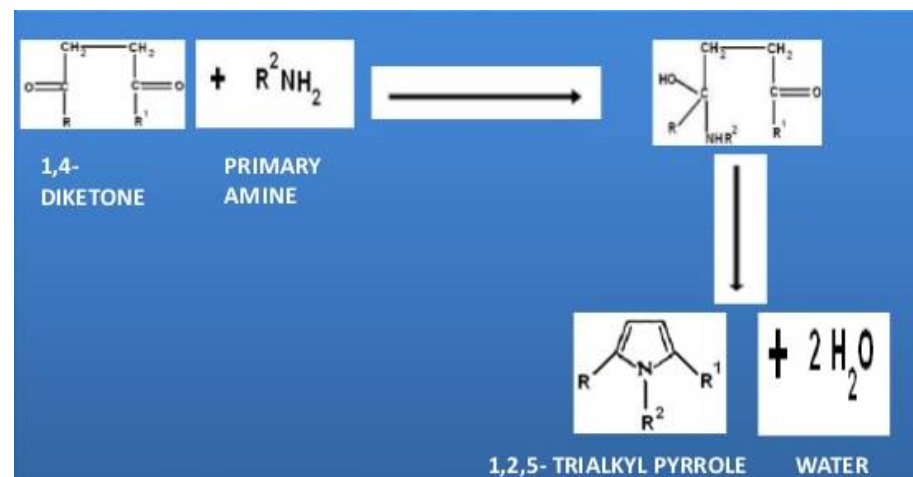
Synthesis of Pyrrole

1. Paal-Knorr synthesis

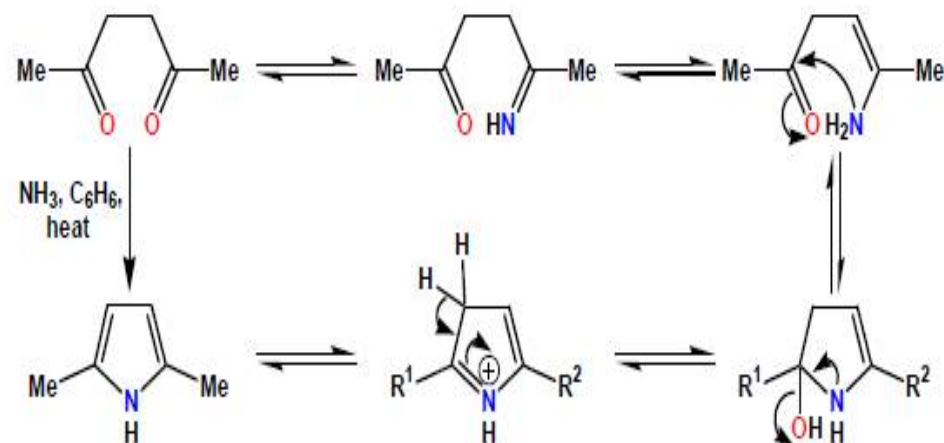
➤ Generally Substituted pyrrole may be synthesized through the cyclization of 1,4-diketones in combination with ammonia (NH₃) or amines.

➤ The ring-closure is proceeded by dehydration (condensation), which then yields the two double bonds and thus the aromatic π system.

➤ The formation of the energetically favored aromatic system is one of the driving forces of the reaction.



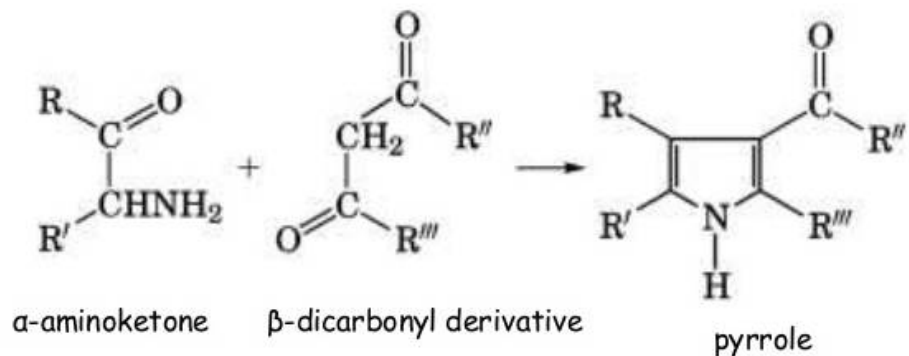
Paal Knorr Synthesis ("4+1")



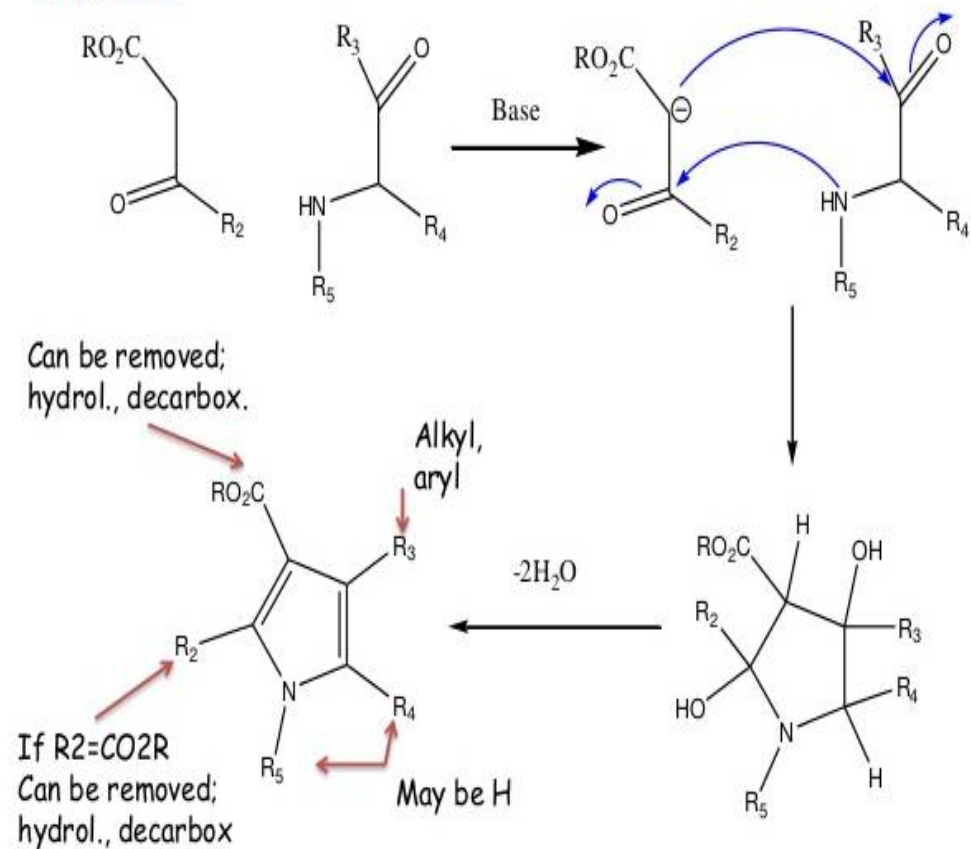
• Ammonia or a primary amine can be used to give the pyrrole or *N*-alkyl pyrrole

2. Knorr Pyrrole synthesis

- Condensation of an α -aminoketone with a carbonyl compound was first reported by Knorr.
- This reaction and its modifications are among the most important and widely used methods for the synthesis of pyrroles.

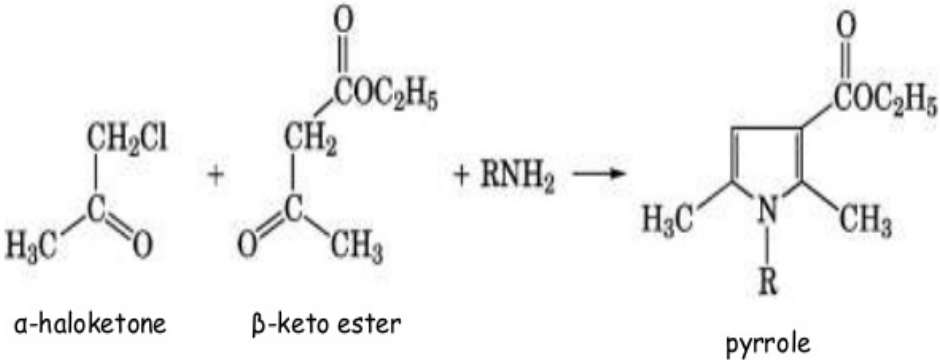


Mechanism

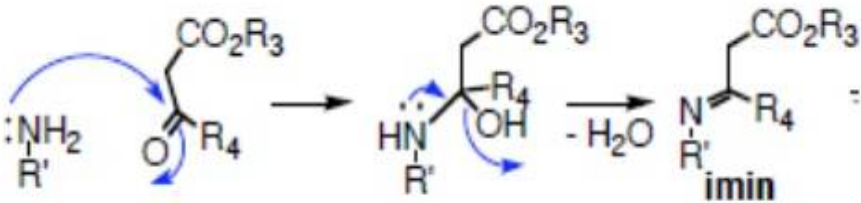


3. Hantzsch synthesis

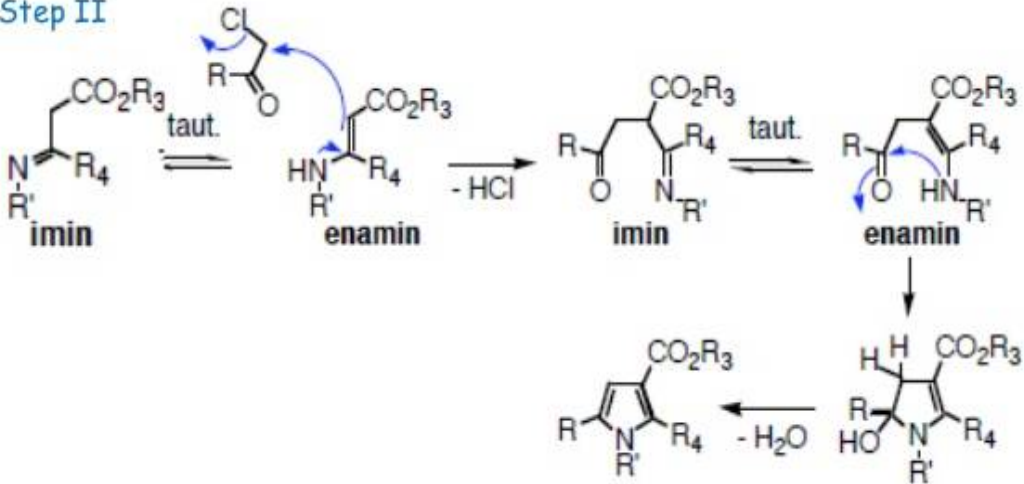
> The Hantzsch synthesis of pyrroles involves condensation of an α -haloketone with a β -keto ester in the presence of ammonia or an amine.



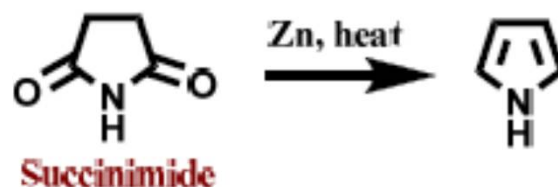
Step I



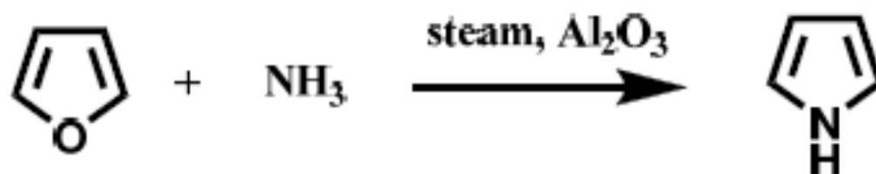
Step II



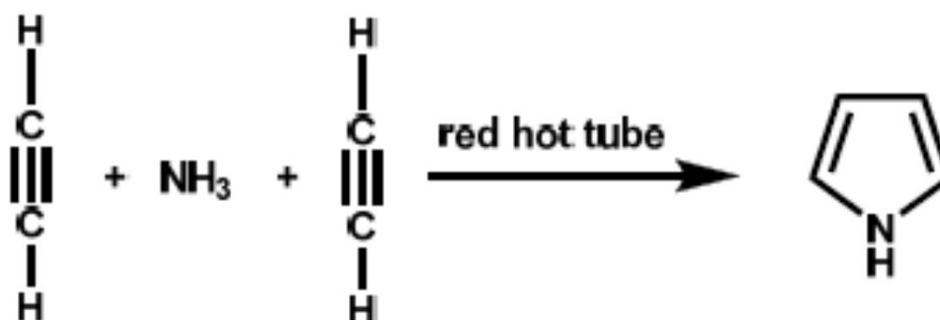
4. Pyrrole is obtained by distillation of succinimide over zinc dust.



5. Pyrrole is obtained by heating a mixture of furan, ammonia and steam over alumina catalyst.



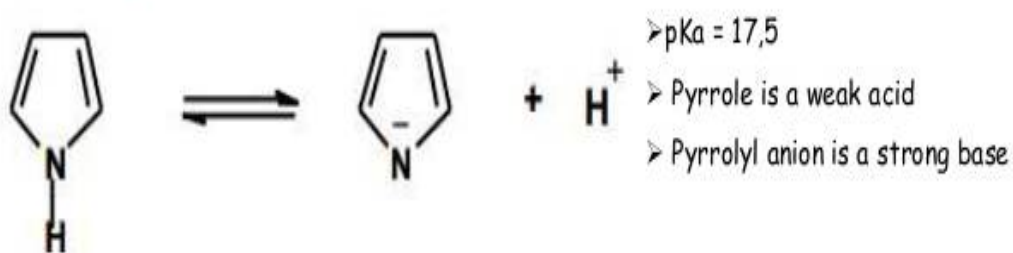
6. By passing a mixture of acetylene and ammonia over red hot tube



REACTIONS OF PYRROLE

- Pyrrole is aromatic and more reactive than benzene.
- It gives electrophilic substitution reactions such as halogenation, nitration, etc.
- It also undergoes diazotization and Reimer-Tiemann reactions, while benzene does not.

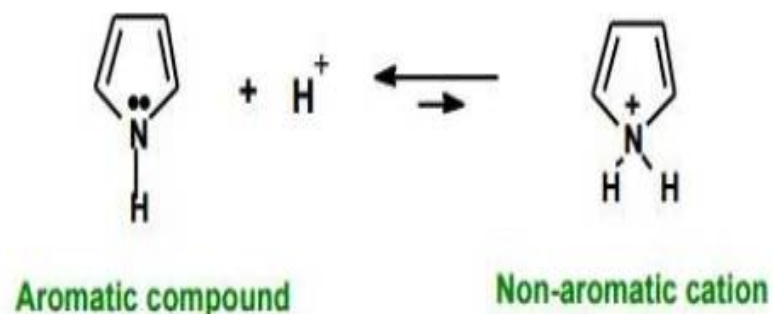
➤ Acidity



Resonance energy is 21.6 Kcal/mole. It reacts violently with conc, acids or even hot dilute acids to form dark coloured polymeric product because of the preferential addition of a proton to a double bond. The positive ion adds to another molecule of pyrrole and a repetition of the reaction leads to a polymer.

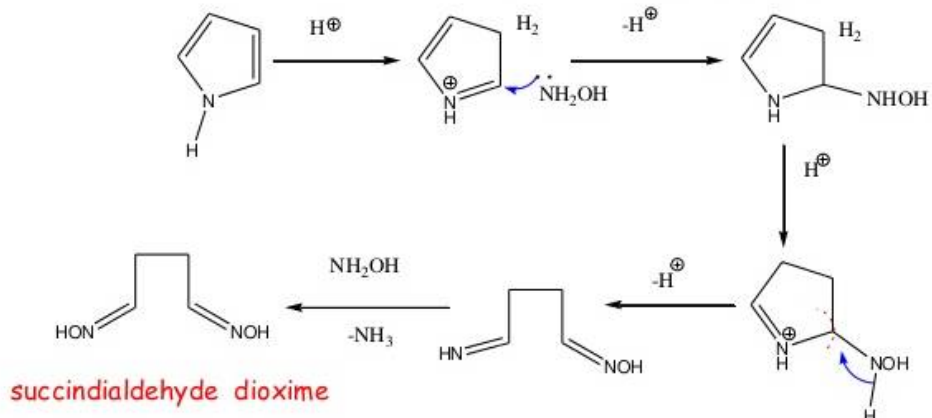
➤ Basicity

Pyrrole is a weak base: Protonation breaks aromaticity (lone pair participates in conjugation) and thus it is not readily available

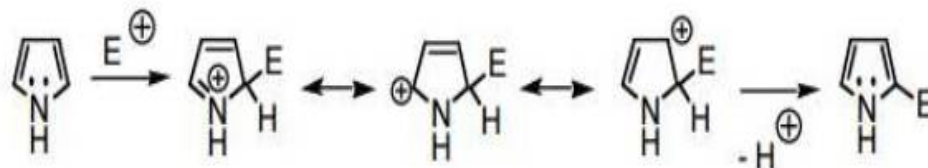


1. Opening of the pyrrole ring:

➤ The pyrrole ring is not readily opened by acids or alkalis, but boiling with **alcoholic hydroxylamine hydrochloride** causes rupture, with the formation of **succindialdehyde dioxime**.



2. Reaction with electrophiles



- for example

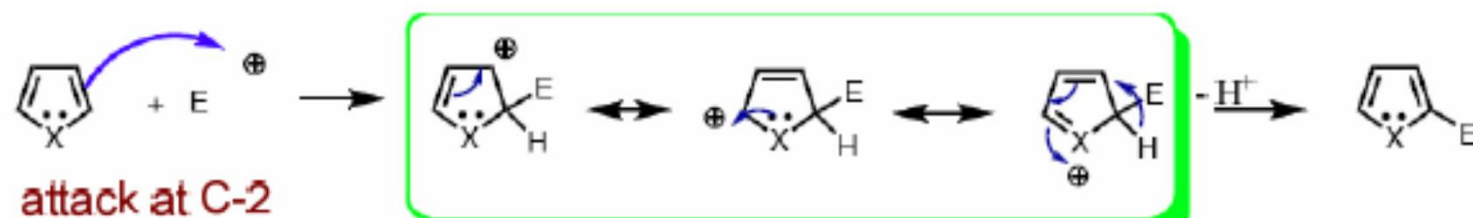
- ✓ Nitration
- ✓ Sulfonation
- ✓ Halogenation

➤ The ozonolysis of pyrrole and derivatives at $-60\text{ }^\circ\text{C}$ in chloroform breaks the ring.

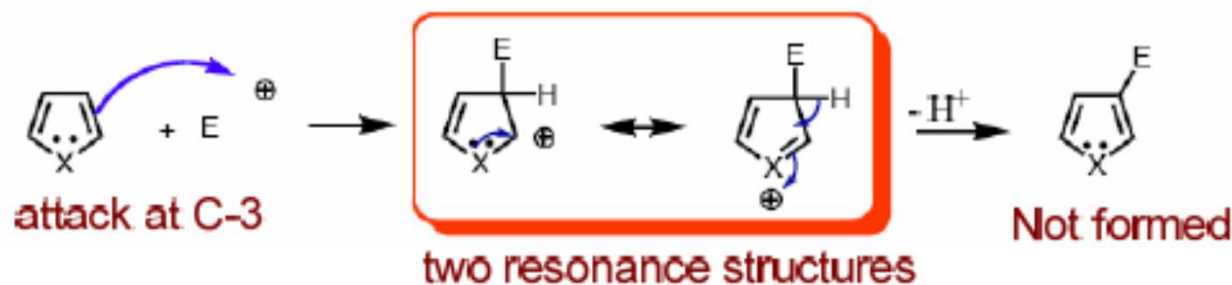
➤ Pyrrole in aq. Silver nitrate is broken down by ultrasonic vibration into acetylene and cyanide ion.

ELECTROPHILIC AROMATIC SUBSTITUTION

- Electrophilic aromatic substitution normally occurs **at carbon atoms** instead of at the nitrogen.
- Also it occurs preferentially at **C-2** (the position next to the heteroatom) rather than at C-3 (if position 2- is occupied it occurs at position 3).
- This is because attack at C-2 gives a more stable intermediate (it is stabilized by three resonance structures) than the one resulted from C-3 attack (it is stabilized by two resonance structures) .



three resonance structures





PYRROLE

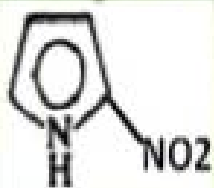
$\text{HNO}_3 / (\text{CH}_3\text{CO})_2\text{O}$
10⁺ NITRATION

SO_3 ,
PYRIDINE, 100°C
SULPHONATION

SO_2Cl_2 0°C
CHLORINATION

$\text{I}_2 / \text{Aq. KI}$
IODINATION

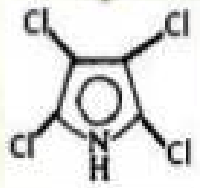
$(\text{CH}_3\text{CO})_2\text{O} / \text{SnCl}_4$
200 °c



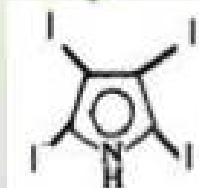
2-NITRO
PYRROLE



2-PYRROLE
SULPHONIC ACID



2,3,4,5TETRACHLORO
PYRROLE

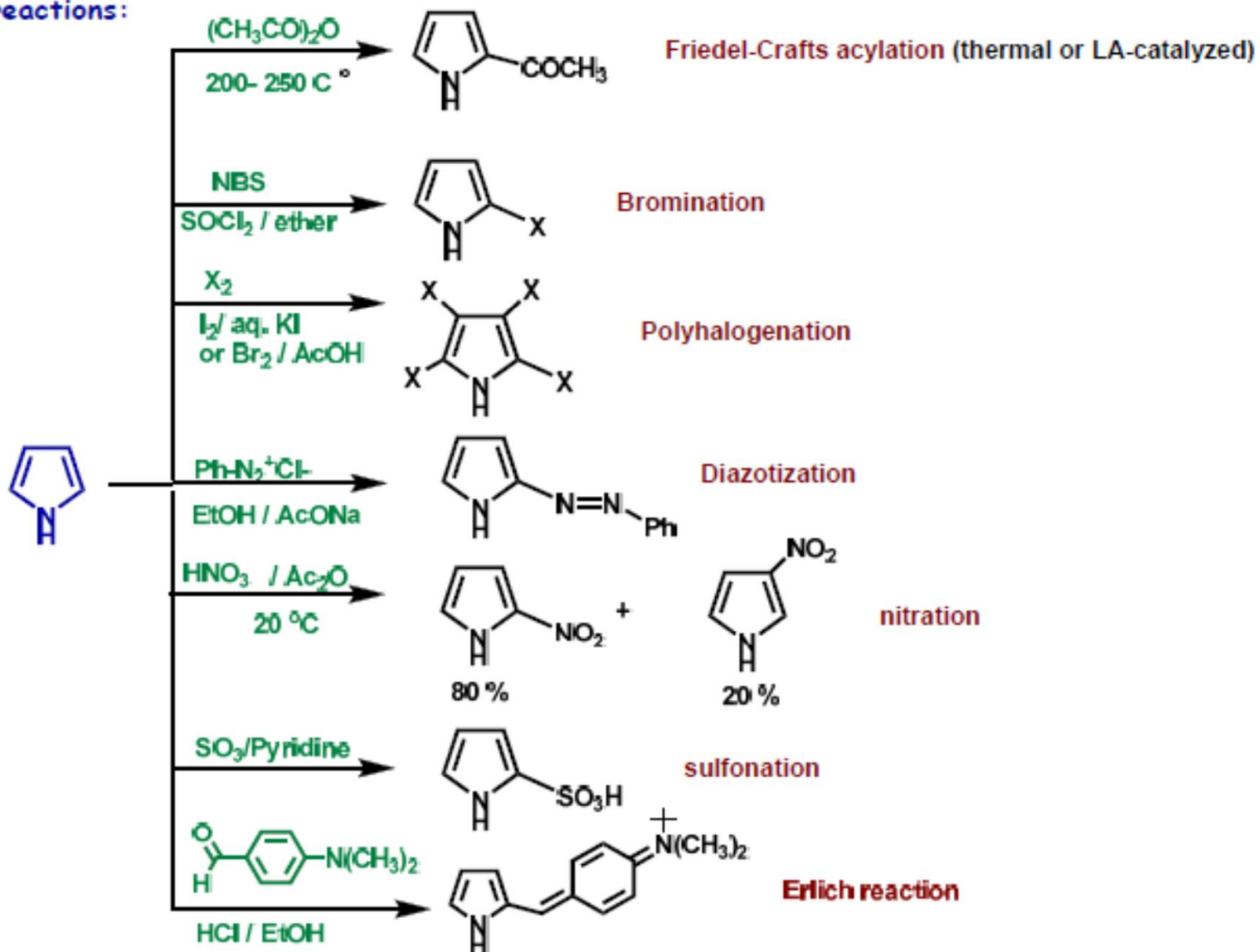


2,3,4,5TETRAIDO
PYRROLE



2-ACETYL PYRROLE

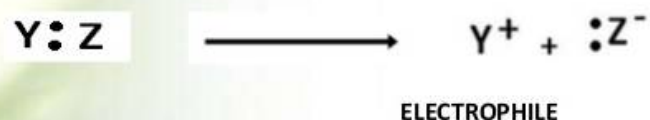
Other reactions:



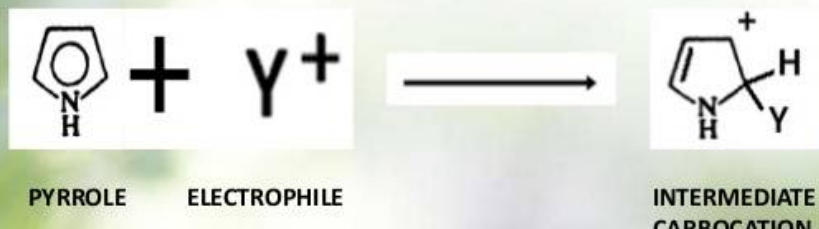
➤ pyrrole undergoes electrophilic aromatic substitution more readily at C-2 than C-3 position.

➤ Mechanism of electrophilic aromatic substitution : electrophilic aromatic substitution of pyrrole, involves the following steps:

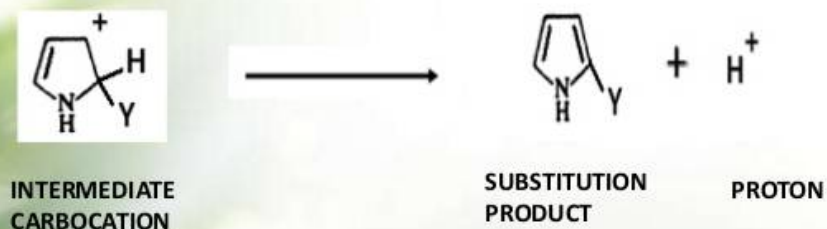
Step-01) Generation of electrophile :



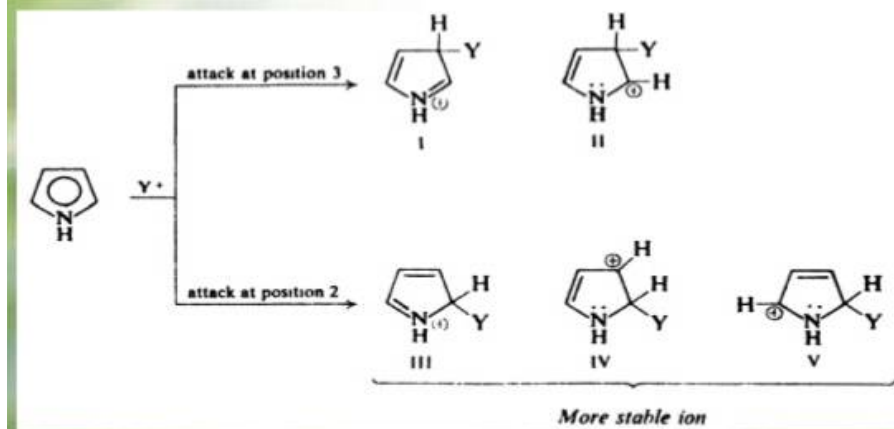
Step-02) Attachment of electrophile to the aromatic ring to form intermediate carbocation :



Step-03) Elimination of proton from carbocation to form substitution product :



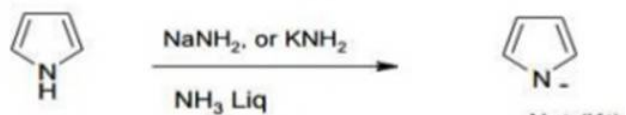
In Pyrrole Electrophilic Substitution takes place at 2 or 5 positions. If these positions are filled substitution takes place at 3 or 4 positions. This can be explained as follows :



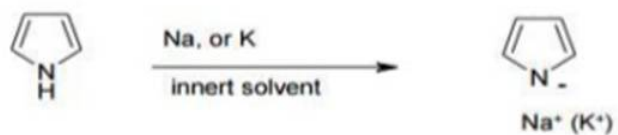
3. Substitution reaction

Substitution at nitrogen:

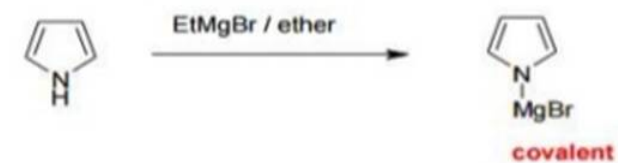
A) Metallation of Pyrrole



ionic



ionic

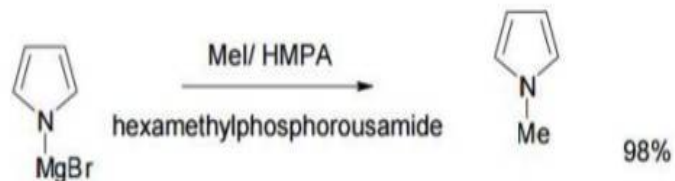
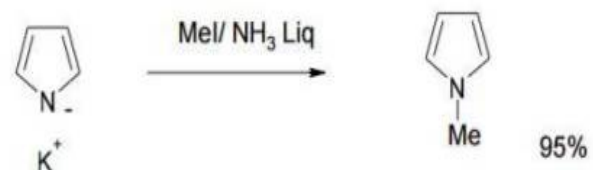


covalent



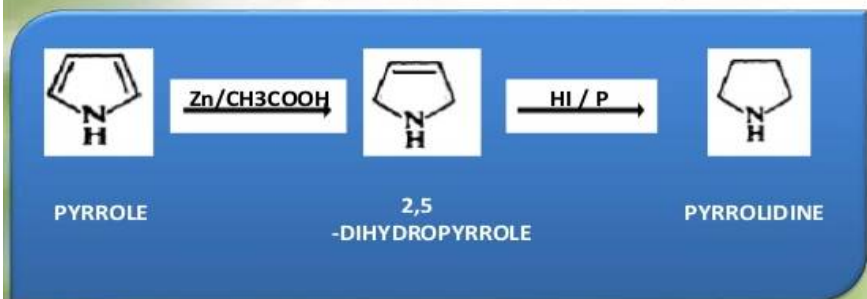
covalent

B) Formation of N-substituted pyrrole



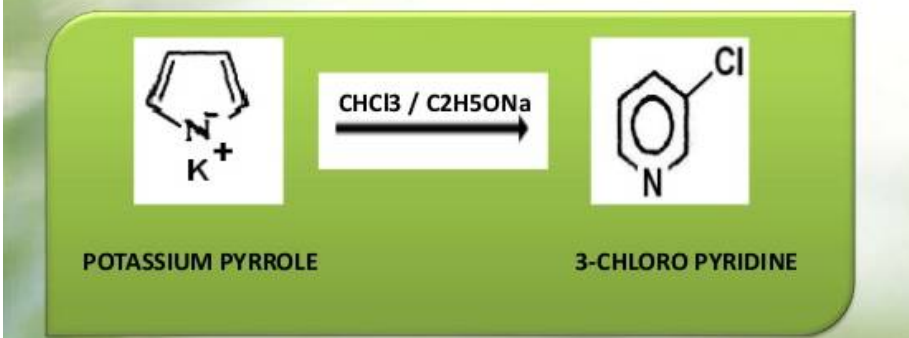
a. Reduction reaction.

Pyrrole on reduction with Zinc and Acetic acid gives 2,5-dihydropyrrole which on reduction with HI and Red phosphorus gives Pyrrolidine.



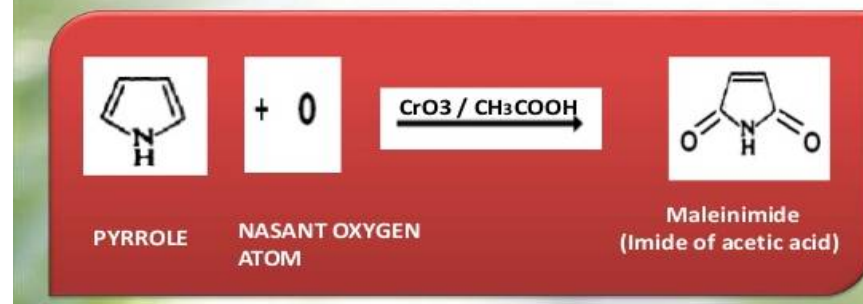
c. Ring expansion reaction.

Pyrrole ring expands on heating Potassium Pyrrole with Chloroform and Sodium Ethoxide.



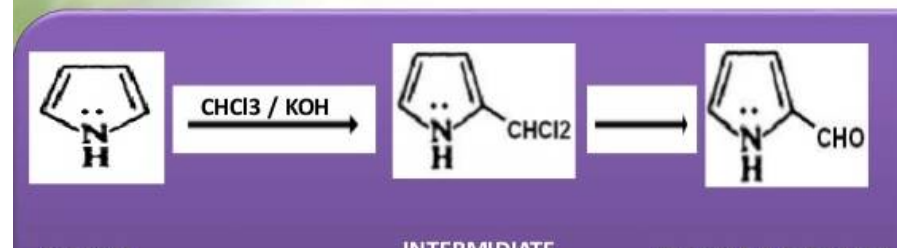
b. Oxidation reaction.

Pyrrole is oxidized to Maleinimide (Imide of acetic acid) with chromium tri oxide in Acetic acid.



d. Reimer-Tiemann reaction.

In presence of a strong base and Chloroform Pyrrole undergoes Reimer-Tiemann reaction to form Pyrrole-2-aldehyde.



Condensation with carbonyl comps

