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# **B.PHARMACY IV SEMESTER UNIT – 3 HETEROCYCLIC CHEMISTRY**

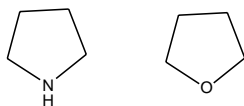
## Heterocyclic Compounds

### 1. DEFINITION:

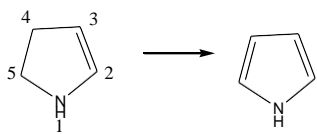
Heterocyclic compounds are organic compounds that contain a ring structure containing atoms in addition to carbon, such as sulfur, oxygen or nitrogen, as the heteroatom. The ring may be aromatic or non-aromatic.

**NOMECLATURE:** The following rules are followed for naming of heterocyclic compounds:

1. Monocyclic compounds containing one or more heteroatom in a 3 to 10 membered ring are named by combining the prefix with a suffix.

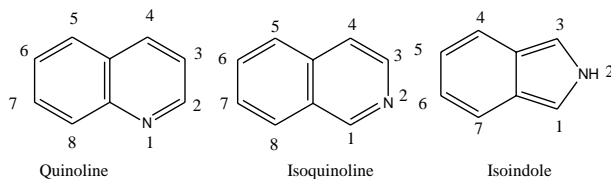


2. The state of hydrogenation is indicated either in suffix or by the prefix dihydro, tetrahydro

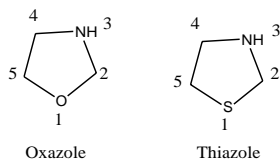


4,5-Dihydroazole

3. When heterocyclic compound contain only one heteroatom the numbering will start from heteroatom exception are isoquinoline and isoindole rings.



4. If more than one heteroatom is present in the ring than numbering will start as preferential series [O, S, Se, N, P, As, Si, B and Hg] and numbering system is selected in which some of the number given to heteroatom is least.

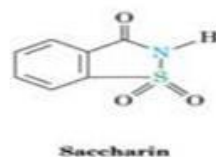
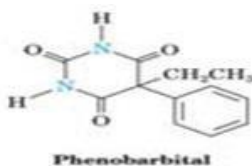
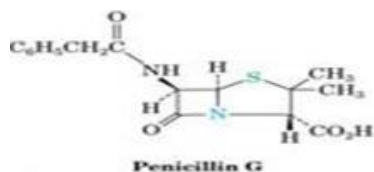


## CLASSIFICATION

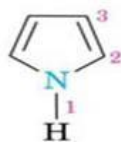
Cyclic organic compounds are carbocycles or heterocycles

- Carbocycle rings contain only carbon atoms
- Heterocycle rings atoms in addition to carbon (N, S, O is common)

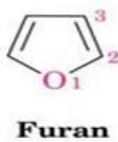
Heterocycles include many important natural materials as well as pharmaceuticals



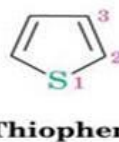
- Pyrrole, furan, and thiophene are common five-membered unsaturated heterocycles
- Each has two double bonds and N, O, or S



Pyrrole

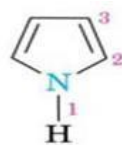


Furan

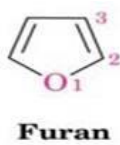


Thiophene:

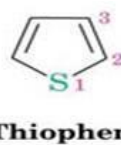
- The main reason for the study of pyrrole came from the work on the structure of haem; the blood respiratory pigment, and the chlorophyll; the green photosynthetic pigment of plants.
- Thiophene does occur in plants in association with polyacetylenes with which they are biogenetically closely linked.
- Furan occurs widely in secondary plant metabolites, especially in terpenoids.
- Unsubstituted pyrrole, furan, and thiophene are usually obtained from petroleum.



Pyrrole



Furan



Thiophene:

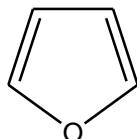
## AROMATIC HETEROCYCLES

- Aromatic heterocyclic compounds are those have a heteroatom in a ring and behave in a manner similar to benzene in some of their properties (i.e. react by electrophilic aromatic substitution).
- Furthermore, these compounds comply with the general rule proposed by Huckel.
- Erich Hückel, a German physical chemist recognized in the early 1930s through molecular orbital calculations that cyclic planar molecules with a closed loop of 2,6,10,14,18,22.....  $\pi$ -electrons in a fully conjugated system should be **aromatic**.
- This finding is called the  $(4n+2) \pi$ -electron rule. Conversely, monocyclic planar molecules with  $4n \pi$ -electrons are said to be **antiaromatic**.

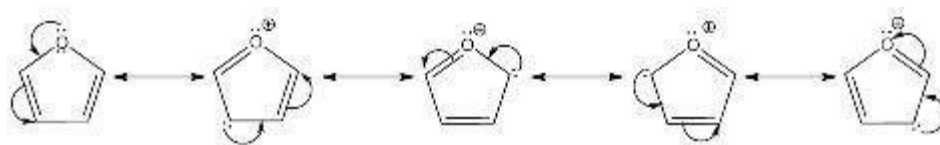
## 2. Synthesis, reactions and medicinal uses of following compounds/ derivatives Pyrrole, Furan and Thiophene

### Furan:

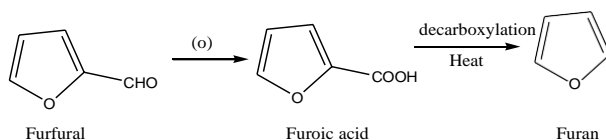
Furan is five membered heterocyclic compound containing oxygen as hetero atom. The molecular formula of furan is  $C_4H_4O$ .



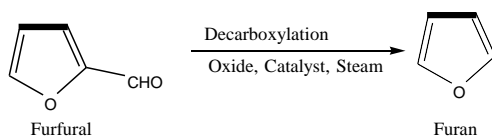
Furan has three pairs of delocalized  $\pi$ -electrons. Two of the pairs are shown as  $\pi$ -bonds and one pair is shown as a pair of nonbonding electrons on the heteroatom. Furan has a third pair of nonbonding electrons that are not part of the  $\pi$ -cloud. These electrons are in a  $sp^2$  hybrid orbital perpendicular to the  $\pi$ -orbitals. Since furan is cyclic, planar molecule with three pairs of delocalized  $\pi$ -electrons fulfils the criteria for aromaticity.



**Preparation:** 1. Furfural on oxidation gives furoic acid which on heating at  $200^\circ\text{C}$  in quinoline and copper powder yield furan.



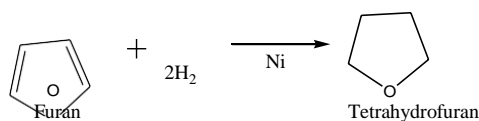
2. Catalytic decomposition of furfural in steam gives furan



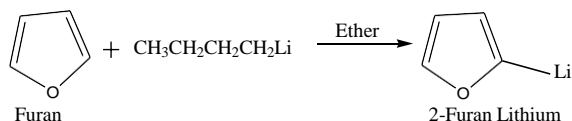
**Physical Properties:** Furan is a colourless liquid and having chloroform like odour. It is insoluble in water but easily soluble in common organic solvents. Furan boils at  $31.4^\circ\text{C}$

### Chemical Properties:

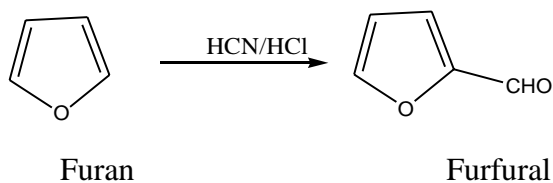
1. **Reduction:** Furan on treatment with hydrogen gas in presence of nickel, platinum or palladium gives tetrahydro furan.



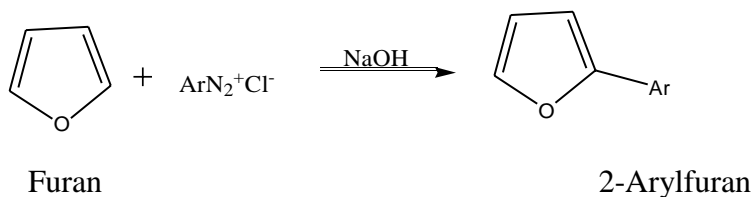
2. Furan reacts with n-butyl lithium in ether and gives 2-lithium furan.



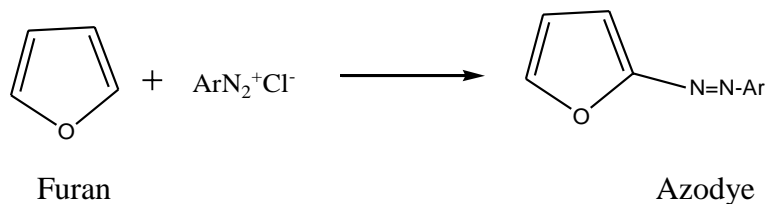
3. **Gattermann-Koch reaction:** Furan on heating with hydrogen cyanide (HCN) and HCl forms furfural.



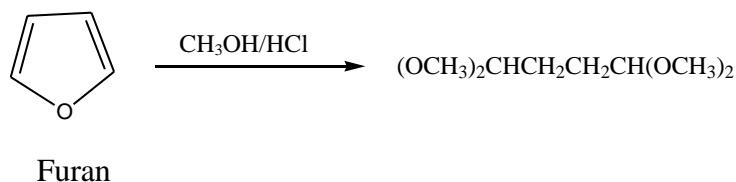
4. **Gomberg's reaction:** Furan on treatment with diazonium salts in alkaline solution 2-aryl furan is formed.



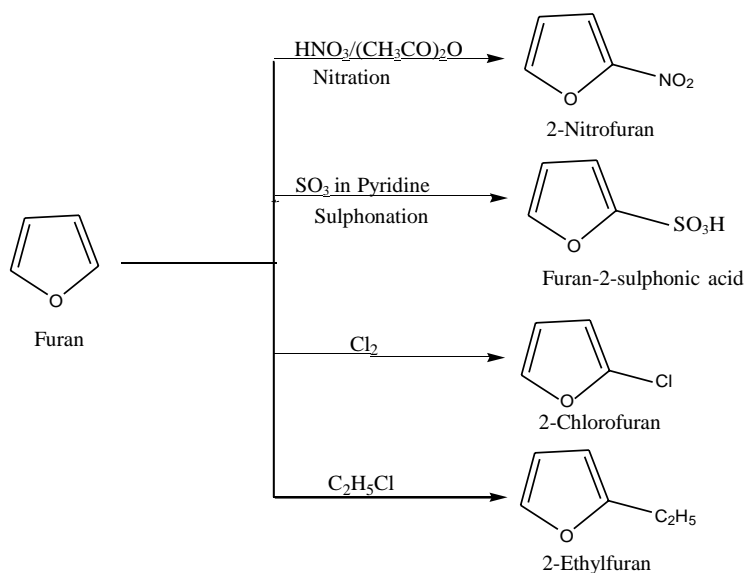
5. **Coupling reaction:** Furan on reaction with diazonium salts yields azodyes.



6. **Ring opening reaction:** Furan gives 1,4-dioxo compounds on treatment with methanol and HCl.



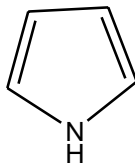
**Electrophilic Aromatic Substitution Reaction:** Furan is aromatic compound hence undergo electrophilic aromatic substitution reactions.



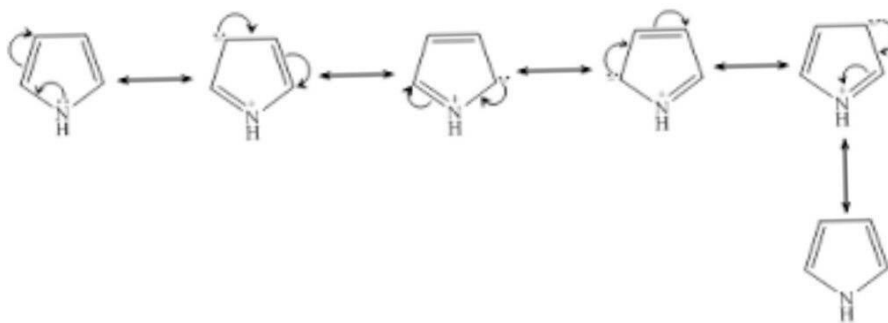
**Medicinal Uses:** Furan and its derivatives show various pharmacological activities as Antidepressant, Analgesic, Anti-inflammatory, Muscle relaxant, Antihypertensive, Antimicrobial, Antiulcer and antidiuretic.

### Pyrrole

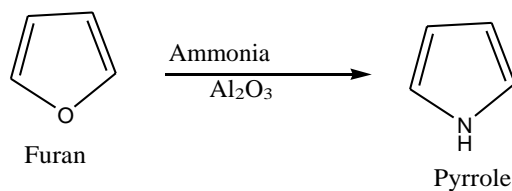
**Pyrrole:** Pyrrole is an important five-membered heterocyclic compound possessing a nitrogen atom as hetero atom. Pyrrole plays an important role in the chemistry of living organisms. The essential structural feature of chlorophyll and heme is porphyrin which consists of four pyrrole rings held together by bridges. Pyrrole is obtained commercially by distillation of coal tar.



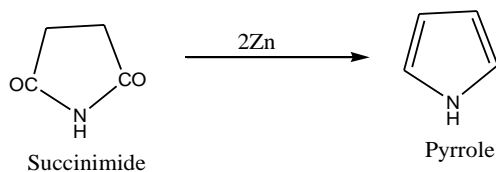
Pyrrole has three pairs of delocalized  $\pi$  electrons. Two of the pairs are shown as  $\pi$  bonds and third pair is shown as a pair of nonbonding electrons on the heteroatom. These non-bonding electrons are in a  $\text{sp}^2$  hybrid orbital perpendicular to the p-orbitals. Since it is cyclic, planar molecule with three pairs of delocalized  $\pi$  electrons, fulfils the criteria for aromaticity. Pyrrole is less aromatic than thiophene and more aromatic than furan.



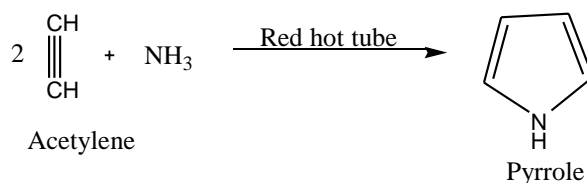
**Preparation:** 1. Furan on heating with ammonia in presence of alumina gives pyrrole.



2. Pyrrole is also obtained by the distillation of succinimide with zinc dust.

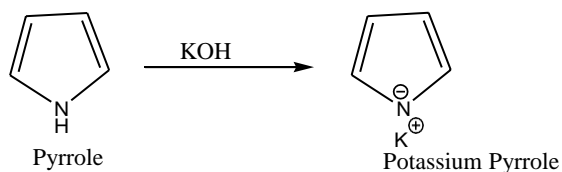


3. Pyrrole can also be prepared by passing acetylene and ammonia through a red hot tube.



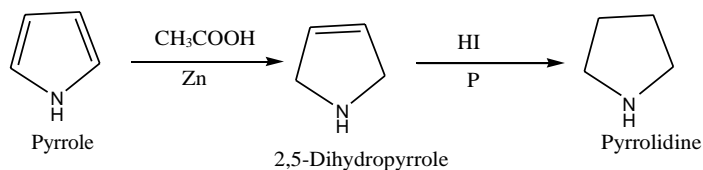
**Properties:** Pyrrole is a colourless liquid sparingly soluble in water but easily soluble in organic solvents. It boils at 131°C. Pyrrole behaves both as a weak acid and a weak base and exhibits chemical reactions.

**Amphoteric properties:** Pyrrole is a weak base because the lone pair of electrons of nitrogen atom contributes to the  $(4n+2)\pi$ -electron cloud. Hence the availability of these electrons is decreased and consequently it is a very weak base. Pyrrole also exhibit weak acidic properties. The weak acidic property is due to its formation of potassium pyrrole with potassium hydroxide.

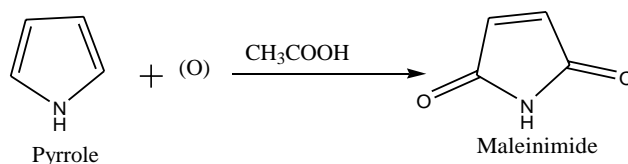


## Chemical Properties:

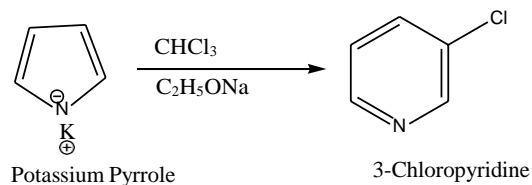
1. **Reduction:** Pyrrole on reduction with zinc and acetic acid gives 2,5-dihydropyrrole which on reduction with HI and red phosphorus gives pyrrolidine.



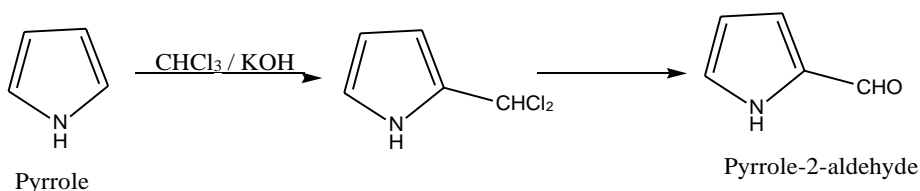
2. **Oxidation:** Pyrrole is oxidized to maleinimide with chromium trioxide in acetic acid.



3. **Ring expansion reaction:** Pyrrole ring expands on heating potassium pyrrole with chloroform and sodium ethoxide.

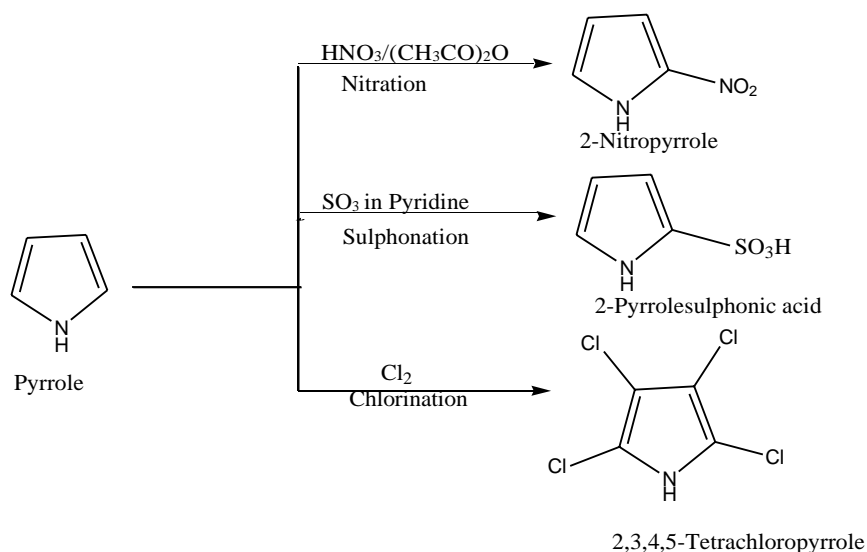


4. **Reimer-Tiemann Reaction:** In presence of a strong base and chloroform pyrrole undergoes Reimer-Tiemann reaction to form pyrrole-2-aldehyde.



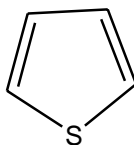
5. **Electrophilic Aromatic Substitution Reactions:** Pyrrole undergoes electrophilic aromatic substitution more readily at C-2 than C-3 position.



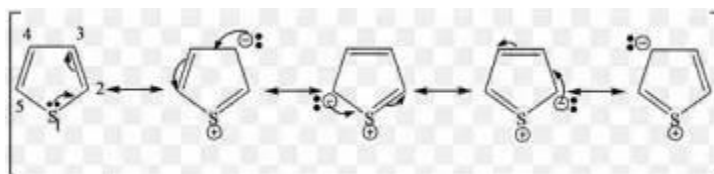


**Medicinal uses:** Pyrrole and its derivatives are actively used as fungicide, antibiotics, anti-inflammatory agents, cholesterol reducing drugs, antitumor agents.

**Thiophene:** Thiophene is a 5-membered heterocyclic ring system containing sulphur as the hetero atom. It occurs in coal tar and shale oil along with benzene.

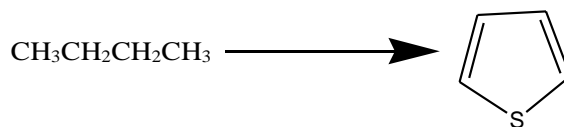


Thiophene has three pairs of delocalized  $\pi$ -electrons. Two of the pairs are shown as  $\pi$ -bonds and one pair is shown as a pair of nonbonding electrons on the heteroatom. Thiophene has a third pair of nonbonding electrons that are not part of the  $\pi$ -cloud. These electrons are in a  $\text{sp}^2$  hybrid orbital perpendicular to the  $\pi$ -orbitals. Since furan is cyclic, planar molecule with three pairs of delocalized  $\pi$ -electrons fulfils the criteria for aromaticity.

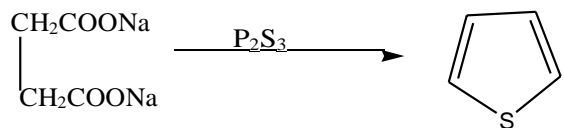


**Preparation:** 1. Thiophene naturally occurs in the benzene fraction of coal-tar distillation. Thiophene is separated from benzene by shaking the mixture with cold concentrated sulphuric acid. Thiophene form thiophene sulphonic acid as it can be easily sulphonated than benzene. Finally thiophene is obtained from thiophene sulphonic acid by heating with steam.

2. Thiophene is prepared by the reaction of n-butane and sulphur in the vapor phase.

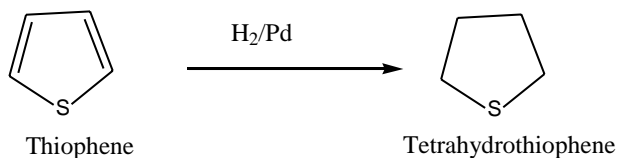


3. Thiophene can also be prepared by heating sodium succinate with phosphorous trisulphide.

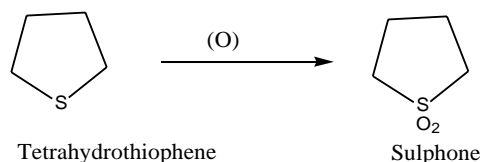


**Properties:** 1. Thiophene is a colourless liquid having benzene like odour. It is insoluble in water but soluble in organic solvents and boils at 84°C.

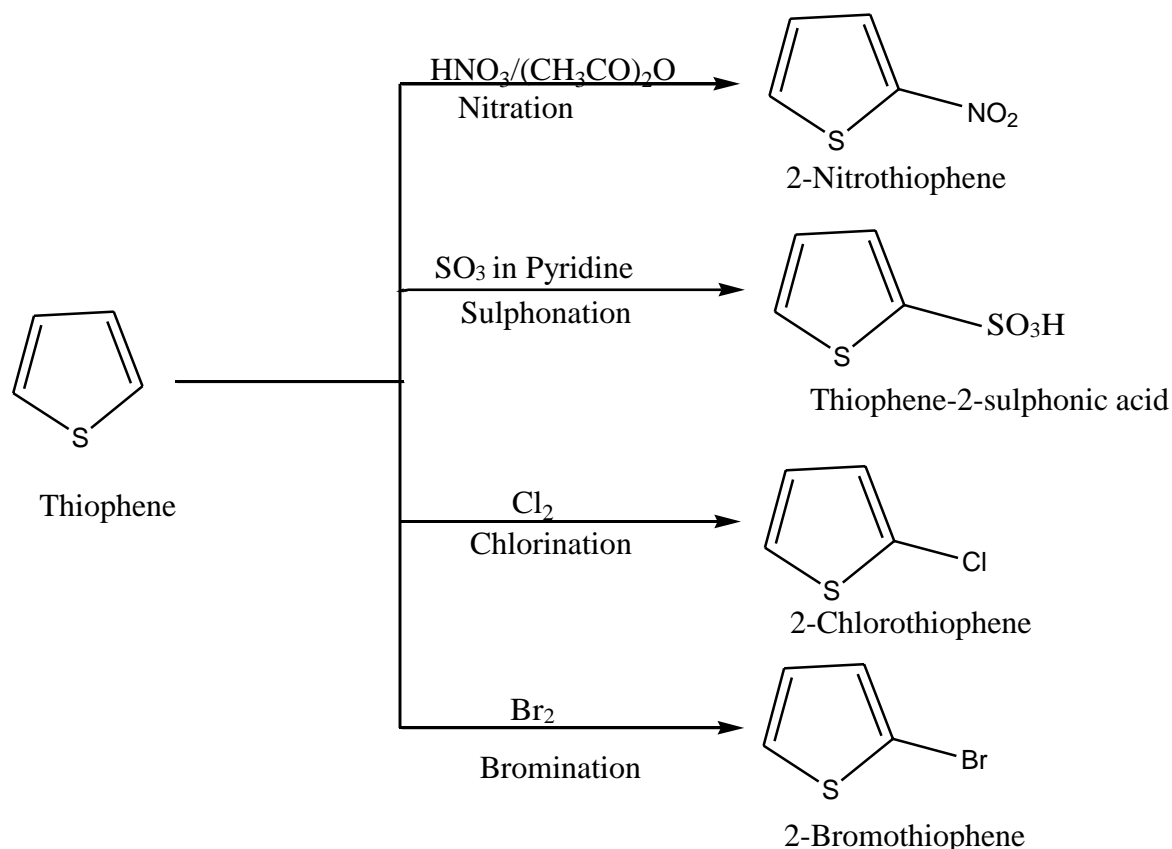
**2. Reduction:** Thiophene is reduced to tetrahydrothiophene on reaction with hydrogen and large amount of catalyst but on reduction of thiophene with nickel gives n-butane by the removal of sulphur.



**3. Oxidation:** Thiophene is not oxidized but tetrahydrothiophene is oxidized to sulphone.



**4. Electrophilic aromatic substitution reactions:** Thiophene is an aromatic compound hence undergoes electrophilic aromatic substitution reactions at C-2 because the intermediate obtained by putting a substituent at this position is more stable than the intermediate obtained by putting a substituent at C-3. The following are some electrophilic substitution reactions of thiophene:



**Medicinal Uses:** Antimicrobial agents, Anticancer activity, Antiinflammatory effect, CNS activity, Antihypertensive activity, Anticoagulant activity.

### 3.0 Relative aromaticity of Pyrrole, Furan and Thiophene

Furan, Pyrrole and thiophene each consists of a flat ring of four carbon atoms and a hetero atom with a cyclic electron cloud of six delocalized  $\pi$ -electrons. So according to Huckel rule, all these compound shows aromatic character.

All the three compounds have five contributing structure in which there is only one structure in each case which does not involve charge separation. The relative aromaticity of Pyrrole, Thiophene and Furan depends upon the electronegativities of the hetero atoms present in pyrrole, furan and thiophene and it is in the order as follows:



It means oxygen has very less tendency to release or donate its pair of electrons to the aromatic sextet. So number of ionic resonating structure should be least in case of Furan followed by Pyrrole and should be maximum in case of Thiophene. So the order of aromaticity will be





All these heterocycles are less aromatic than benzene as all the resonating structures of benzene are uncharged and equally stable and involves no separation of +ve and -ve charges. The resonance energies of these heterocycles is less than that of benzene. So the aromatic character of these heterocycles relatives to benzene decreases in order as

Benzene>Thiophene>Pyrrole>Furan