Name of Unit	Heterocyclic Compounds
Subject /Course Name	Pharmaceutical Organic Chemistry-III
Subject/Course ID	BP401T
Class: B.Pharm. Semester	4th
Course coordinator	Ms. Sukhwinder Kaur
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Learning Outcome of Module 03

LO	Learning Outcome	Course Outcome Code
LO1.	To gain knowledge about Heterocyclic Compounds.	BP401.1
LO2.	To understand about Nomenclature of Heterocyclic Compounds.	BP401.1
LO3.	To Understand about Classification of Heterocyclic Compounds.	BP401.1
LO4.	To get the knowledge about preparation and reactions associated with heterocycles.	BP401.1
LO5.	To get the knowledge about Medicinal Compounds of these heterocycles.	BP401.3
LO6.	To understand about Relative Aromaticity and Reactivity of these heterocycles	BP401.2

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INTRODUCTION OF HETEROCYCLIC COMPOUND

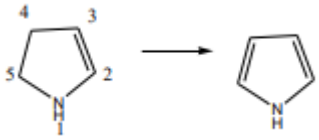
Heterocyclic compounds are organic compounds that contain a ring structure containing atoms in addition to carbon, such as sulfur, oxygen or nitrogen, as the heteroatom. The ring may be aromatic or non-aromatic. Number of drugs in pharmaceutical science are heterocyclic compounds. Hetero cyclic compounds may be of natural origin or synthetically available.

Nomenclature:-

The following rules are followed for naming of heterocyclic compounds:

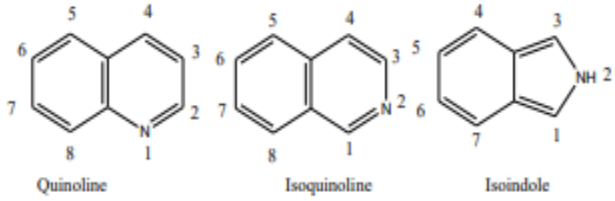
1. Monocyclic compounds containing one or more heteroatom in a 3 to 10 membered ring are named by combining the prefix with a suffix.

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



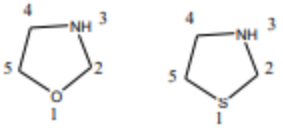
4,5 dihydroazole

3. When heterocyclic compound contain only one heteroatom the numbering will start from heteroatom exception are iso quinoline and iso indole rings.



Quinoline Isoquinoline Isoindole

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 of Heterocyclic Compounds:-

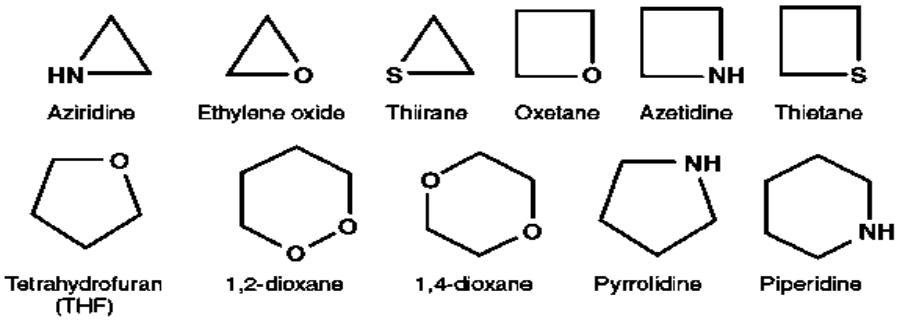
Based on the electronic arrangement, we can classify Heterocyclic compounds into two types:

1.Aliphatic Heterocyclic Compound

2.Aromatic Heterocyclic Compound

1Aliphatic Heterocyclic Compound:- Aliphatic heterocyclic compounds are those cyclic heterocycles that do not contain any double bond. The properties of aliphatic heterocyclic compounds are mainly affected due to ring strain.

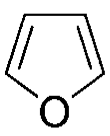
Examples of aliphatic heterocyclic compounds are Aziridine, Ethylene Oxide, Thiirane, Oxetane, Azetidine, Thietane, Tetrahydrofuran (THF), Dioxane, Pyrrolidine, Piperidine, etc.



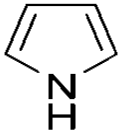
2.Aromatic Heterocyclic Compound:-Aromatic heterocyclic compounds, as the name suggests, are cyclic aromatic compounds. Aliphatic Heterocyclic compounds obey Huckels Rule, i.e.

- It should be cyclic.
- It should be planar.
- It should not contain any sp3 hybridised atoms.
- It must have (4n+2) **π** electrons.
- Aromatic Heterocyclic compounds are analogous to Benzene.
- Examples: Furan, Pyrrole, Thiophene, Indole, Benzofuran, Carbazole, Quinoline, Isoquinoline, Imidazole, Oxazole, Pyrazole, Pyridazine, Pyrimidine, Purine, etc.

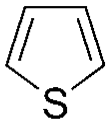
(a) 5-Membered Heterocyclic Compounds Having One Hetero Atom :-



FURAN

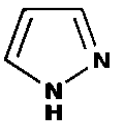


PYRROLE

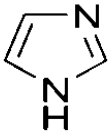


THIOPHENE

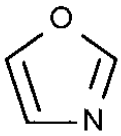
(b) 5-Membered Heterocyclic Compounds Having More Than One Hetero Atom:-



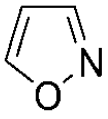
PYRAZOLE



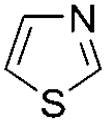
IMIDAZOLE



OXAZOLE

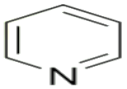


ISOXAZOLE

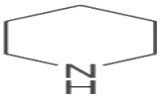


THIAZOLE

(c) 6- Membered Heterocyclic Compounds Having One Hetero Atom:-

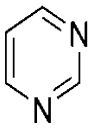


PYRIDINE

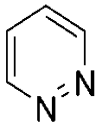


PIPERIDINE

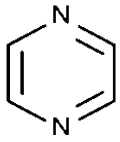
(d) 6- Membered Heterocyclic Compounds Having One or more Hetero Atom:-



PYRIMIDINE

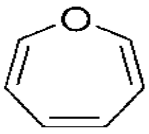


PYIRIDAZINE

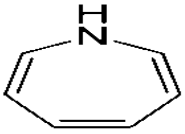


PYRAZINE

(e)7-Membered Heterocyclic Compounds Having One Hetero Atom:-

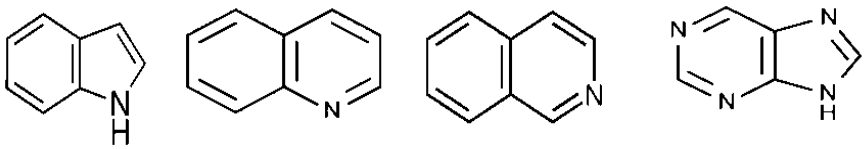


OXEPINE



1-H-AZEPINE

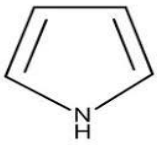
(f) Condensed Heterocyclic Compounds:-



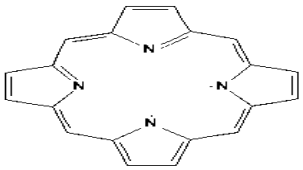
INDOLE QUINOLINE ISOQUINOLINE PURINE

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.



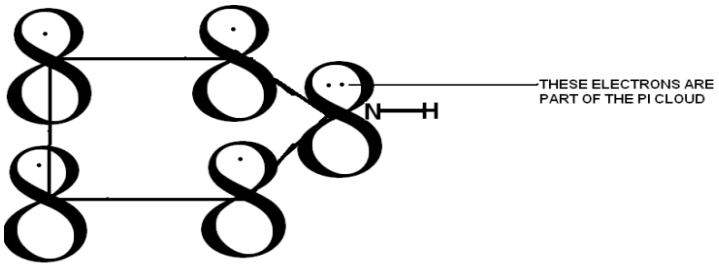
The essential structural feature of chlorophyll and heme is porphyrin which consists of four pyrrole rings held together by bridges. Pyrrole is obtained commercially by distillation of coal tar.



Porphyrin

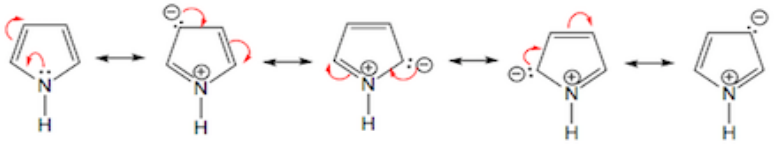
Structure of Pyrrole:-

Pyrrole has three pairs of delocalized π electrons. Two of the pairs are shown as π bonds and third pair is shown as a pair of nonbonding electrons on the heteroatom. These non-bonding electrons are in a sp2 hybrid orbital perpendicular to the p-orbitals. Since it is cyclic, planar molecule with three pairs of delocalized π electrons, fulfils the criteria for aromaticity. Pyrrole is less aromatic than thiophene and more aromatic than furan. The ***molecular orbital of pyrrole*** is:



Resonance Structure of Pyrrole:-

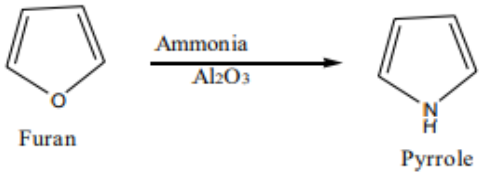
According to the resonance theory, Pyrrole is considered as a resonance hybrid of the following contributing structures.



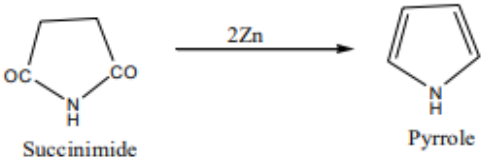
Among the resonance contributing structures 1. 2, and 3 are the main contributing structures to the resonance hybrid and hence resonance hybrid has a larger electron density at positions 2 and 5 than at 3 and 4.

Preparation Methods of Pyrrole:-

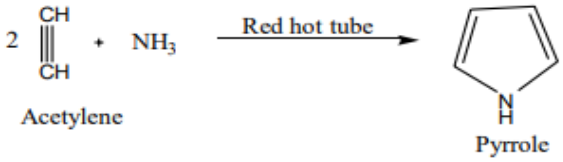
1. Furan on heating with ammonia in presence of alumina gives pyrrole.



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.



Physical Properties of Pyrrole:-

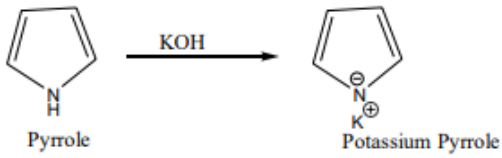
1.Pyrrole is a colorless liquid sparingly soluble in water but easily soluble in organic solvents.

2.It boils at 131°C.

3.Pyrrole behaves both as a weak acid and a weak base and exhibits chemical reactions.

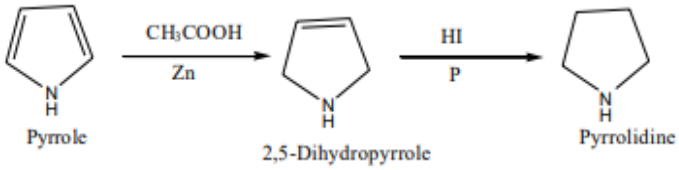
Amphoteric Properties:-

Pyrrole is a weak base because the lone pair of electrons of nitrogen atom contributes to the (4n+2)π-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.

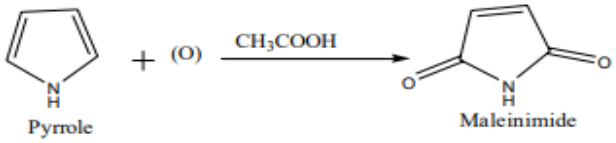


Chemical Properties of Pyrrole:-

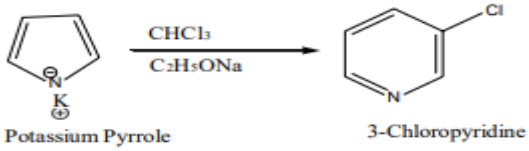
1.Reduction:- Pyrrole on reduction with zinc and acetic acid gives 2,5-dihydropyrrole which on reduction with HI and red phosphorus gives pyrrolidine.



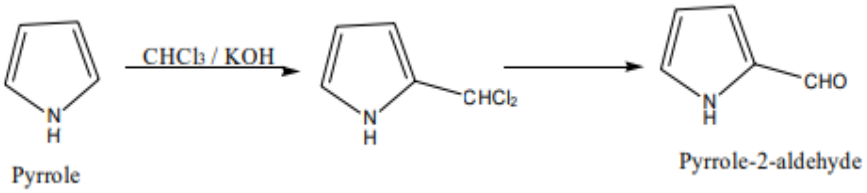
2. Oxidation:- Pyrrole is oxidized to maleinimide with chromium trioxide in acetic acid.



3. Ring Expansion Reaction:- Pyrrole ring expands on heating potassium pyrrole with chloroform and sodium ethoxide.

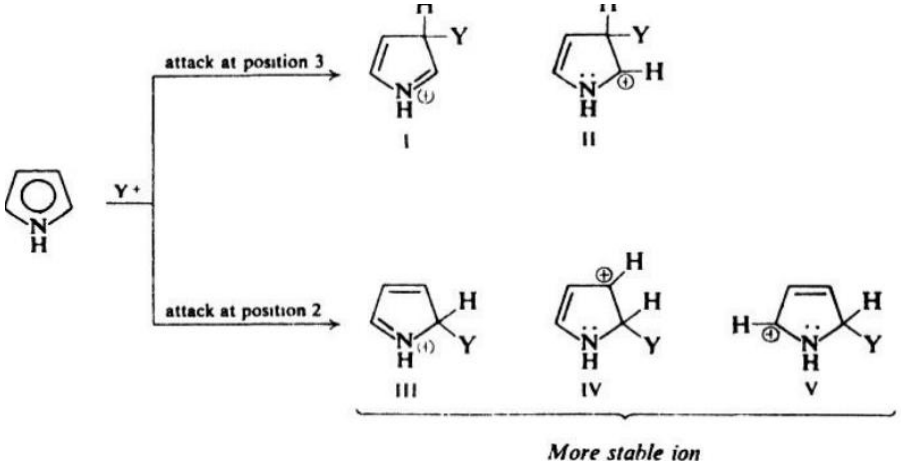


4. Reimer-Tiemann Reaction:- In presence of a strong base and chloroform pyrrole undergoes Reimer-Tiemann reaction to form pyrrole-2-aldehyde.

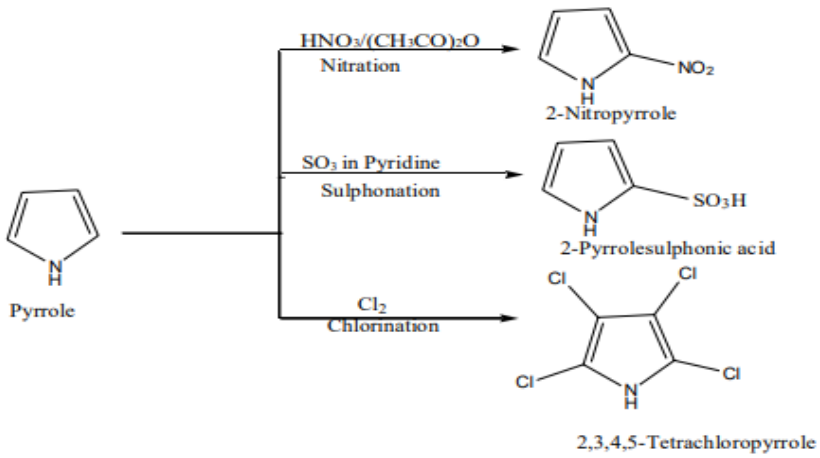


5. Electrophilic Aromatic Substitution Reactions:- Pyrrole undergoes electrophilic aromatic substitution more readily at C-2 than C-3 position.

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:



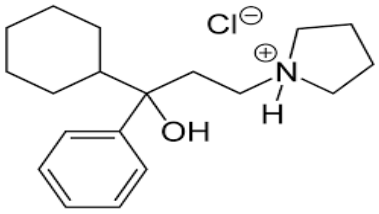
- Substitution occurs preferentially at C–2 because the intermediate carbocation obtained by putting a substituent at this position is more stable than the intermediate carbocation obtained by placing a substituent at C-3.
- The intermediate resulting from C-2 substitution has 3 resonance contributors; they both have a positive charge on a relatively stable secondary allylic carbon.
- The intermediate resulting from c-3 Substitution has only 2-resonance contributors and has positive charge on a primary carbon, which is unstable. Thus substitution at C-2 predominates.



Medicinal Compounds:-

The following medicinal compounds possess pyrrole heterocyclic ring system.

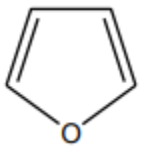
1.Procyclidine:- Chemically procyclidine is **α-cyclohexyl, α- phenyl-l-pyrrolidine propanol.**



It is an anti-muscarinic drug used in the treatment of parkinsonism.

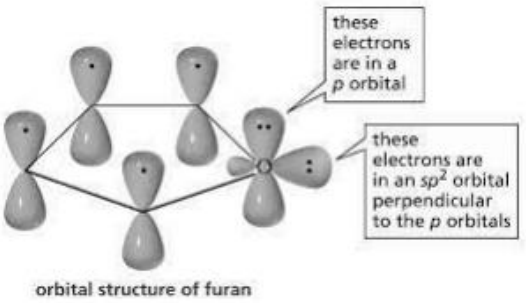
Furan

Furan is a five membered heterocyclic compound containing **oxygen as hetero atom**. The molecular formula is C_2H_4O.



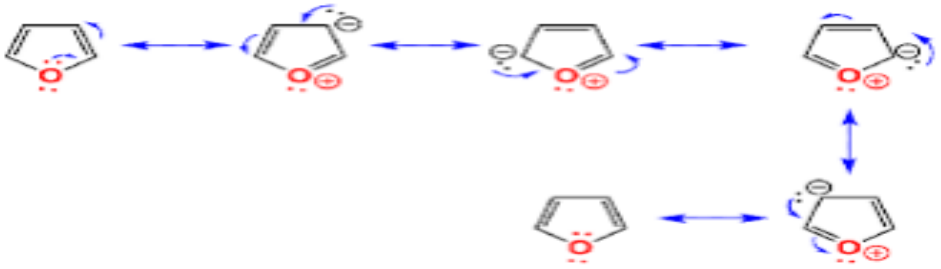
Molecular Orbital Structure of Furan (Aromaticty):-

Furan has three pairs of delocalized π-electrons. Two of the pairs are shown as π-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 π-cloud. These electrons are in a sp2 hybrid orbital perpendicular to the π-orbitals. Since furan is cyclic, planar molecule with three pairs of delocalized π-electrons fulfils the criteria for aromaticity.



orbital structure of furan

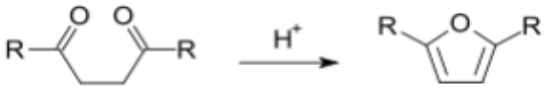
Resonance Structure of Furan:-



In contributing resonance hybrid structures have 1,3,4 larger electron density at positions 2,5 than 3and 4.

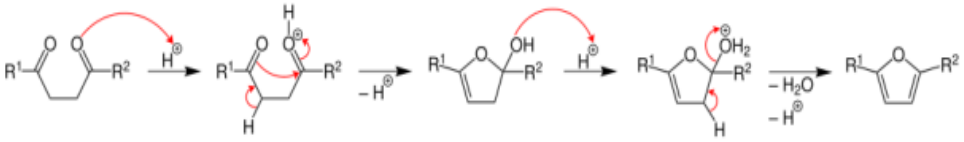
Methods of Preparation of Furan:-

1.Paal Knorr Synthesis:- (Dehydration of 1,4 Dicarbonyl Compound) :-This synthesis involves the action of dehydrating agent like P2O5,ZnCl2 or H2SO4 on a 1,4 -Dicarbonyl compound which can undergo enolization.

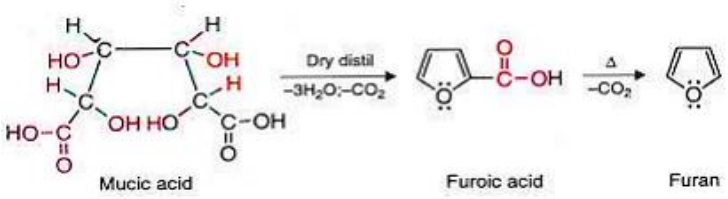


Mechanism :-

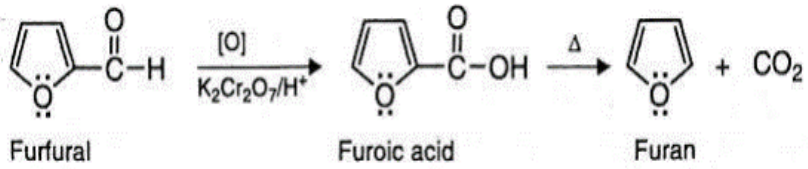
The acid catalyzed furan synthesis proceeds by protonation of one carbonyl which is attacked by the forming enol of the other carbonyl. Dehydration of the hemiacetal gives the resultant furan.



2. From Mucic Acid:- Mucic acid upon dry distillation produces furoic acid which when heated at, its boiling point, it undergoes decarboxylation to give furan.



3.From Furfural:- Oxidation of furfural with potassium dichromate give furoic acid .Further on heating ,it undergoes decarboxylation to give furan.



Physical Properties of Furan:-

1.Furan is a colorless liquid and having chloroform like odor.

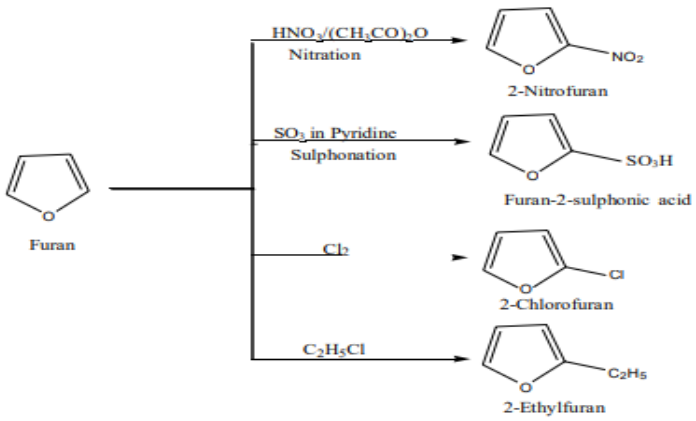
2.It is insoluble in water but easily soluble in common organic solvents.

3.Furan boils at 31.4° C.

Chemical Properties of Furan:-

The following are various chemical reactions of furan are

1.Electrophilic Aromatic Substituation Reactions:- Furan is aromatic compound hence undergo electrophilic aromatic substitution reactions.



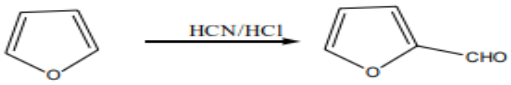
2. Reduction:- On reduction, in the presence of NICKLE Or PLATINUM, furan gives tetrahydrofuran.

Furan Tetrahydrofuran

3. Diels-Alder Reaction:- Furan undergoes Diels-Alder reaction with dienophile such as maleic anhydride to form addition product.

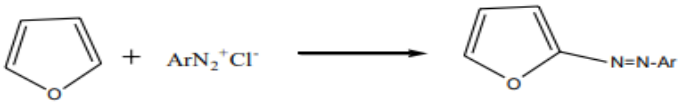
Furan maleic anhydride adduct

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



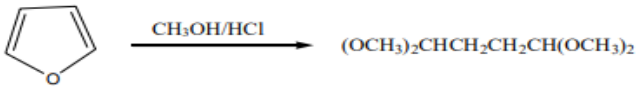
Furan Furfural

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



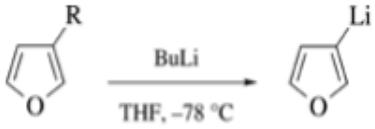
Furan Azodye

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



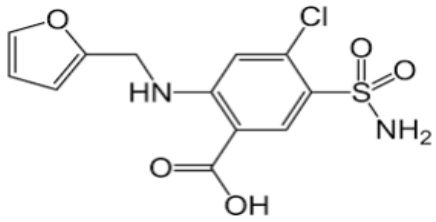
Furan

7.Reaction With n-Butyl Lithium:- Furan reacts with n-butyl lithium in the presence of ether to form 2-lithium furan.

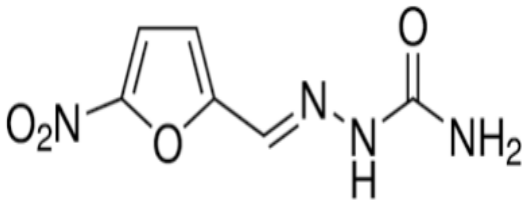


Medicinal Compounds:-

A. FRUSEMIDE:- Chemically frusemide is 4-chloro-N-furfuryl-5-sulphamoylanthranilic acid. It is used as a high ceiling diuretic and anti- hypertensive agent.



B. NITROFURAZONE :- Chemically nitrofurazone is hydrazine carboxamide,5-nitro-2-furaldehyde semi-carbazone. It is used as a local antibacterial agent. It is also used in the management of infections of eye, ear nose.



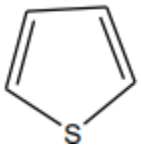
C. Geiparvarin is a coumarin derivative having furan moiety and has a good antidepressant activity.

D. Furazolidone is an antibacterial and used in the treatment of diarrhoea.

Furan and its derivatives shows various pharmacological activities as Antidepressant, Analgesic, Anti-inflammatory, Muscle relaxant, Antihypertensive, Antimicrobial, Antiulcer and antidiuretic.

Thiophene

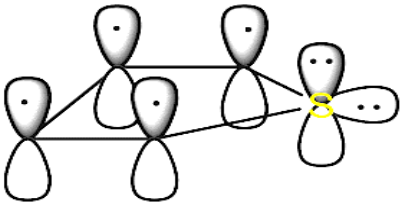
Thiophene: Thiophene is a 5-membered heterocyclic ring system containing **sulphur as the hetero atom.** It occurs in coal tar and shale oil along with benzene.



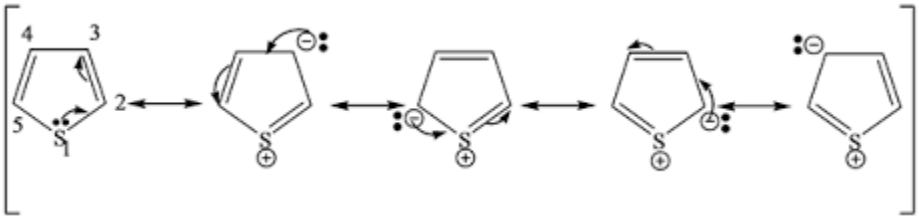
Molecular Orbital Structure of Thiophene:-

Thiophene has three pairs of delocalized π-electrons. Two of the pairs are shown as π-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 π-cloud. These electrons are in a sp2 hybrid

orbital perpendicular to the π-orbitals. Since furan is cyclic, planar molecule with three pairs of delocalized π-electrons fulfils the criteria for aromaticity.



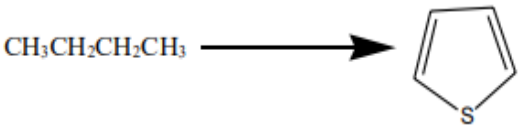
Resonance Structure of Thiophene:-



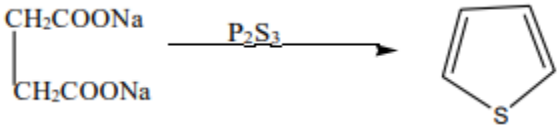
Preparation Methods of Thiophene:-

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.

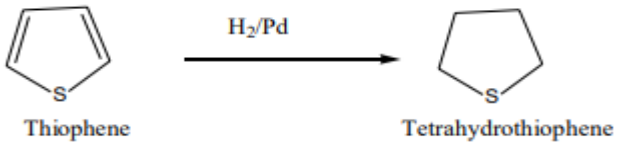


Physical Properties of Thiophene:-

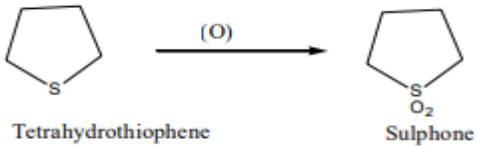
1. Thiophene is a colorless liquid having benzene like odor.
2. It is insoluble in water but soluble in organic solvents.
3. It boils at 84°C.

Chemical Properties of Thiophene:-

1.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.

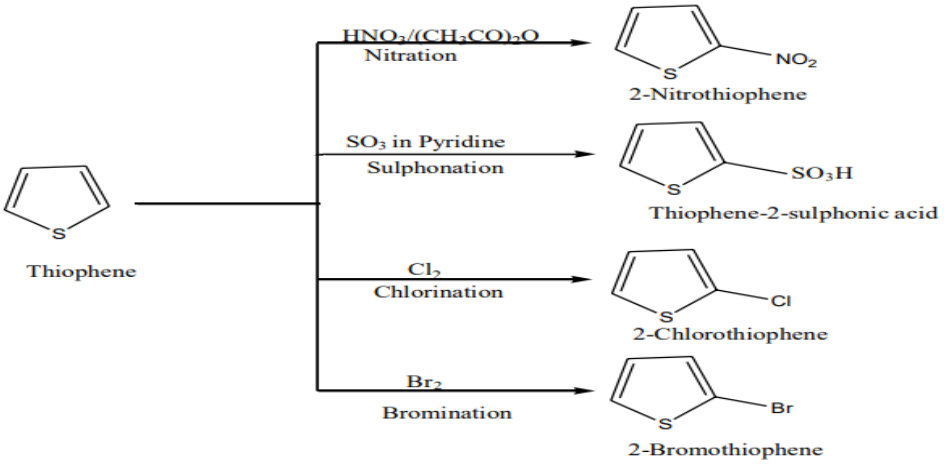


2.Oxidation:- Thiophene is not oxidized but tetrahydrothiophene is oxidized to sulphone.



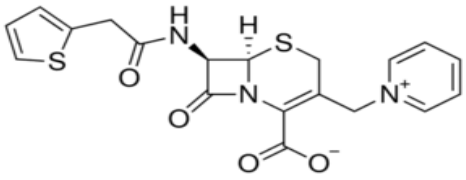
3.Electrophilic Aromatic Substitution Reactions:- Thiophene is an aromatic compound hence undergoes electrophilic aromatic substitution reactions at C-2 because the intermediate obtained by putting a substituent at this position is more stable than the intermediate obtained by putting a substituent at C-3.

The following are some electrophilic substitution reactions of thiophene:

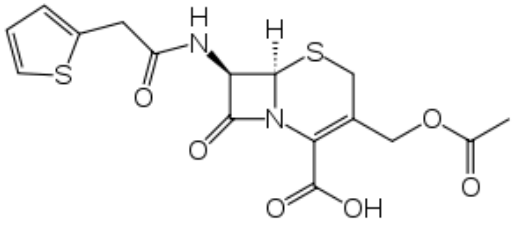


Medicinal Uses:-

1.Cephaloridine:- It is used to treat Staphylococcal infections.



2.Cephalothin:- It is used to treat the infections caused by Staphylococci.



Thiophene and its derivatives is used as Antimicrobial agents, Anticancer activity, Anti inflammatory effect, CNS activity, Antihypertensive activity, Anticoagulant activity.

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 π-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:

O> N> S

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

Furan<Pyrrole<Thiophene

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

Relative Reactivity of Pyrrole, Furan and Thiophene:-

These compounds Furan, Pyrrole and thiophene are certainly more reactive than Benzene. Out of these, Pyrrole being most aromatic, followed by Furan. Furan is comparatively less reactive

because O-atom (in furan) can accommodate accommodate a positive charge less readily at N-atom (in Pyrrole).

Thiophene is being followed by these two and is least reactive. It is so because +M-effect of sulphur is weaker than that of oxygen because overlap of 2p-orbitals of carbon and 3-p orbitals of sulphur is less than 2p -orbitals of C and O -atoms.

That's why order of reactivity is something like that, as you mentioned.

Pyrrole>Furan> Thiophene>Benzene.

Questions carrying 2 marks

1.Why are Pyrrole, Thiophene and Furan are aromatics?

2. Draw Orbital structure of Pyrrole.

3. What are Heterocyclic Compounds? Give three examples along with their common and IUPAC name.

4. What are Condensed Ring Heterocycles? Give three examples along with common name.

5. Pyrrole is acidic like phenol. Explain.

6. Why is thiophene more aromatic in nature than Furan.

7. Explain why pyrrole is more reactive in Electrophilic Substitution than benzene?

8. Give two preparation methods of Pyrrole.

9. Give two preparation methods of Furan.

10.Give two preparation methods of Thiophene.

11. Explain the aromatic character of Furan.

12. Explain the aromatic character of Thiophene.

13. Give the Classification of Heterocyclic Compounds.

14. Give medicinal uses of Pyrrole.

15. Give medicinal uses of Furan.

16. Give medicinal uses of Thiophene.

Questions carrying 5 marks

1. Give Synthesis methods of Pyrrole.

2. Give Synthesis methods of Furan.

3. Give Synthesis methods of Thiophene.

4. Discuss Electrophilic Substitution Reaction of Thiophene.

5. Discuss Electrophilic Substitution Reaction of Furan.

6. Discuss Electrophilic Substitution Reaction of Pyrrole.

7.Comment on relative aromaticity of Pyrrole, Furan and Thiophene.

Questions carrying 10 marks

1.Explain relative reactivity and aromaticity of Pyrrole, Furan and Thiophene.

2.Write a detailed note on Pyrrole.

3.Write a detailed note on Furan.

4. Write a detailed note on Thiophene.