

DEPARTMENT OF CHEMISTRY

V -SEMESTER

ORGANIC CHEMISTRY – I

SUBJECT CODE: BCH 52

(Regulation 2016)

UNIT- V

5.1 Heterocyclic compounds - Huckel's rule – Aromaticity of Heterocyclic compounds - Preparation, Properties, Structure and Uses of Furan, Pyrrole and Thiophene.

5.2 Preparation and properties of Pyridine and Piperidine - Comparative study of Basicity of Pyrrole, Pyridine and Piperidine with Amines – Nucleophilic and Electrophilic substitution reactions of Pyridine.

5.3 Condensed Five and Six Membered Heterocyclic Compounds - Preparation of Indole, Quinoline and Isoquinoline – Fischer-Indole synthesis, Skraup Quinoline synthesis and Bischler-Napieralski synthesis - Electrophilic substitution reactions.

5.1 HETEROCYCLIC COMPOUND

Heterocyclic compound is the class of cyclic organic compounds those having at least one hetero atom (i.e. atom other than carbon) in the cyclic ring system. The most common heteroatoms are nitrogen (N), oxygen (O) and sulphur (S). Heterocyclic compounds are frequently abundant in plants and animal products; and they are one of the important constituent of almost one half of the natural organic compounds known. Alkaloids, natural dyes, drugs, proteins, enzymes etc. are the some important class of natural heterocyclic compounds. Heterocyclic compounds can be easily classified based on their electronic structure. Heterocyclic compounds are primarily classified as saturated and unsaturated. The saturated heterocyclic compounds behave like the acyclic derivatives with modified steric properties. Piperidine and tetrahydrofuran are the conventional amines and ethers of this category. However, unsaturated heterocyclic compounds of 5- and 6- member rings have been studied extensively because of their unstrained nature. The unstrained unsaturated heterocyclic compounds include Pyridine, Thiophene, Pyrrole, Furan and their benzo fused derivatives. Quinoline, Isoquinoline, Indole, Benzothiophene, and Benzofuran are some important example of benzo fused heterocycles. Heterocyclic compounds have a wide application in pharmaceuticals, agrochemicals and veterinary products. Many heterocyclic compounds are very useful and essential for human life. Various compounds such as hormones, alkaloids antibiotic, essential amino acids, hemoglobin, vitamins, dyestuffs and pigments have heterocyclic structure. In the present unit, students would be able to learn about the common five and six membered heterocyclic compounds, such as Pyrrole, Furan, Thiophene, Pyridine and Piperidine etc.

CLASSIFICATION OF HETEROCYCLIC COMPOUNDS:

Based on the structural and electronic arrangement the heterocyclic compounds may be classified into two categories.

- i. Aliphatic heterocyclic compounds
- ii. Aromatic heterocyclic compounds

The aliphatic heterocyclic compounds are the cyclic amines, cyclic amides, cyclic ethers and cyclic thioethers. Aliphatic heterocycles those do not contain double bonds are called saturated heterocycles. The properties of aliphatic heterocycles are mainly

affected by the ring strain. Examples of aliphatic heterocyclic compounds are shown in figure 1.

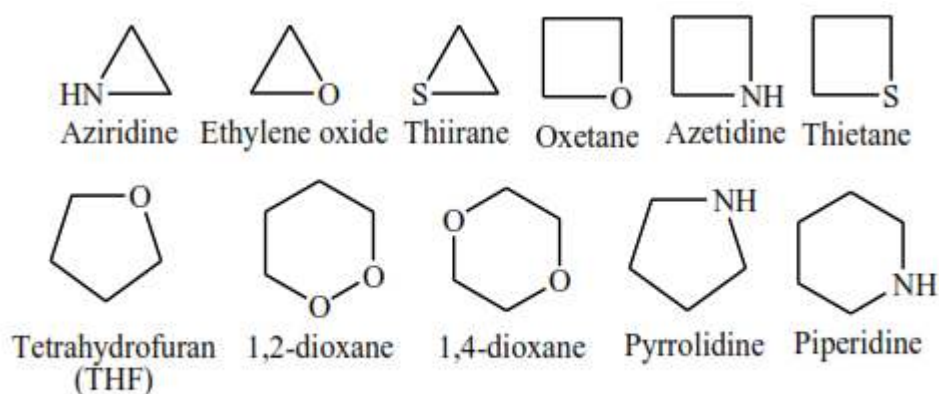


Figure 1. Examples of aliphatic heterocyclic compounds

However, aromatic heterocyclic compounds are analogous of benzene. The aromatic heterocyclic compounds also follow the Huckel's rule. According to Huckel's rule an aromatic compounds must be cyclic in nature with planar geometry due to conjugate double bonds and must have $(4n+2)\pi$ electrons. Examples of aromatic heterocyclic compounds are shown in figure 2.

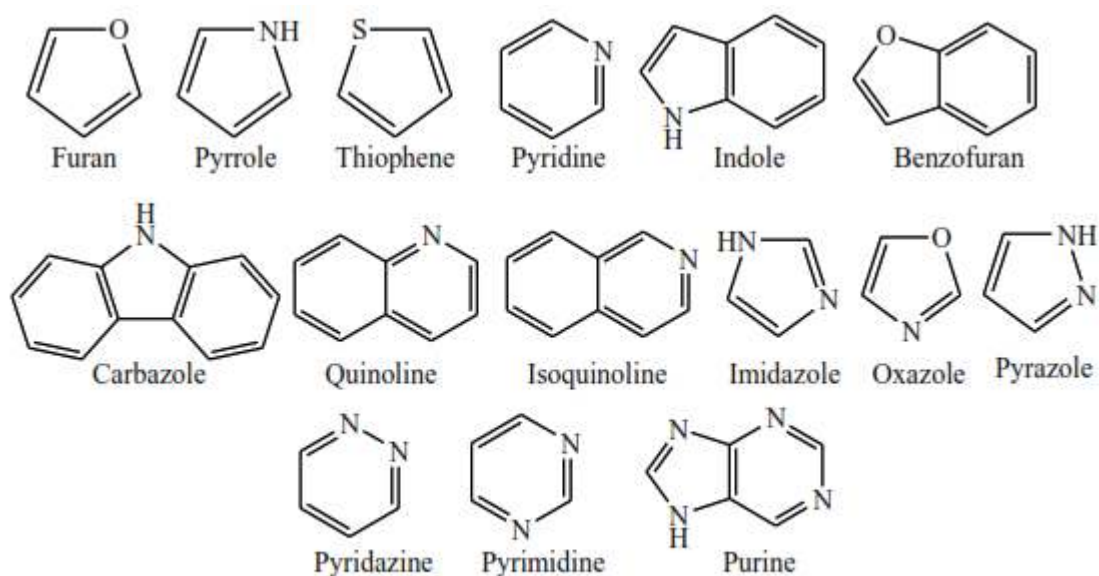


Figure 2. Examples of aromatic heterocyclic compounds

A hetero cyclic ring may comprise of three or more than three atoms, which may be saturated or unsaturated. Also heterocyclic ring may contain more than one heteroatom which may be either similar or different.

Based on the variety of structure, the heterocyclic compounds may also be divided in to three categories.

1. Five membered heterocyclic compounds: These heterocyclic compounds may be considered to be derived from benzene by replacing one C=C bond by a hetero atom with a lone pair of electron. Based on number of hetero atom present in the cyclic ring this class of heterocyclic compounds may be further subdivided in to following categories.

a). Heterocyclic compounds with one hetero atom: Common examples of this class of compounds are furan, thiophene and pyrrole (Figure 3).

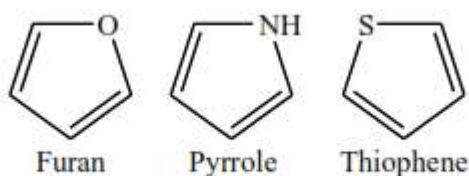


Figure 3. Five member heterocyclic compounds with one hetero atom

b). Heterocyclic compounds with more than one hetero atom: These hetero atoms may be same or different. Common examples of this category of heterocyclic compounds are pyrazole, imidazole, thiazole, oxazole, triazole and tetrazole etc (Figure 4).

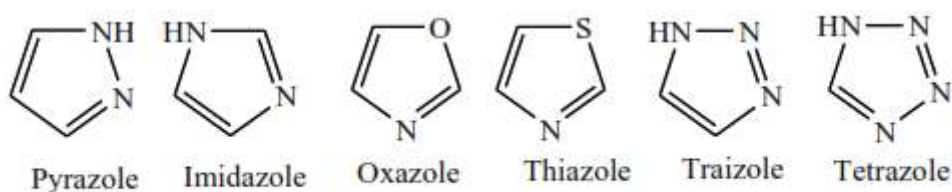


Figure 4. Five member heterocyclic compounds with two hetero atom

2. Six membered heterocyclic compounds: This class of compounds may be considered to be derived from the replacement of a carbon atom of benzene by an iso-electronic atom. Similar to the five membered heterocyclic compounds, the six membered heterocyclic compounds may also be subdivided in to following categories.

a). **Heterocyclic compounds with one hetero atom:** Common examples of this class of compounds are pyridine, pyran, thiopyran etc (Figure 5).

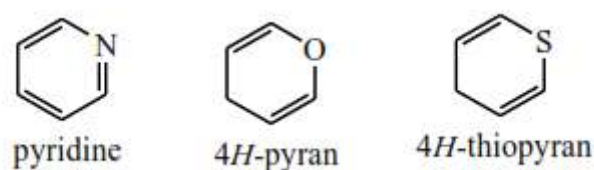


Figure 5. Six member heterocyclic compounds with one hetero atom

b). **Heterocyclic compounds with more than one hetero atom:** Common examples of this class of compounds are pyridazine, pyrimidine, pyrazine etc (Figure 6).

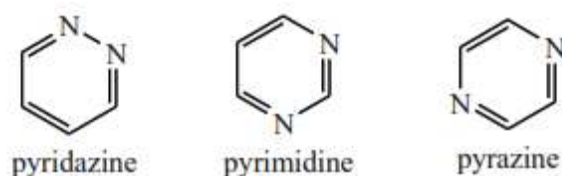


Figure 6. Six member heterocyclic compounds with more than one hetero atom

3. **Fused or condensed heterocyclic compounds:** This class of compound may consist two or more fused rings which may be partly carbocyclic and partly heterocyclic, common examples of this category of heterocyclic compounds are Indole, Quinoine, Isoquionoline, Cabazole etc; or may be completely heterocyclic, common examples of this category of heterocyclic compounds are purine, pteridine etc (Figure 7).

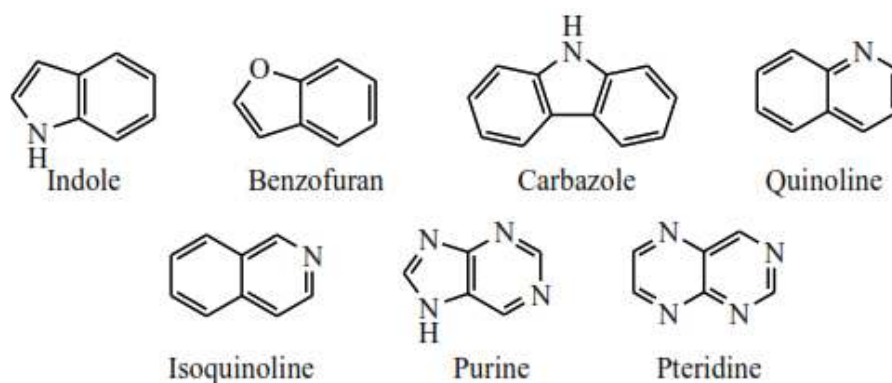


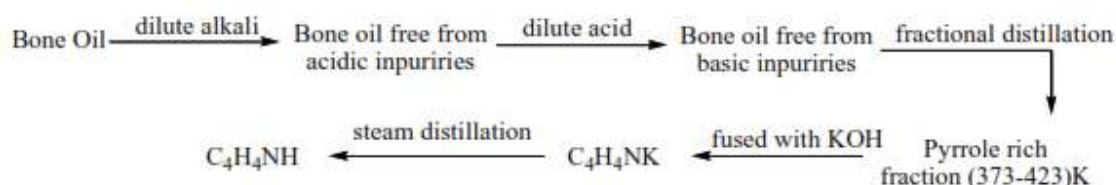
Figure 7. Fused or condensed heterocyclic compounds

METHODS OF PREPARATION AND CHEMICAL REACTIONS

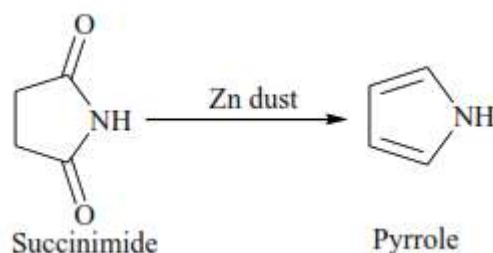
METHODS OF PREPARATION OF PYRROLE:

Following are the general methods of preparation of pyrrole:

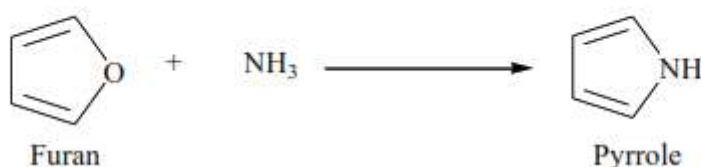
i. **From bone oil:** Bone oil is rich of pyrrole. The basic and acidic impurities of Bone oil are removed by sequential treatment of it with dilute acidic and dilute basic solutions. The treated Bone oil is then subjected for fractional distillation, the fraction obtained between 373K and 423K is collected. The collected fraction is then purified with KOH to obtained potassipyrrole. Steam distillation of potassipyrrole gives pure pyrrole.



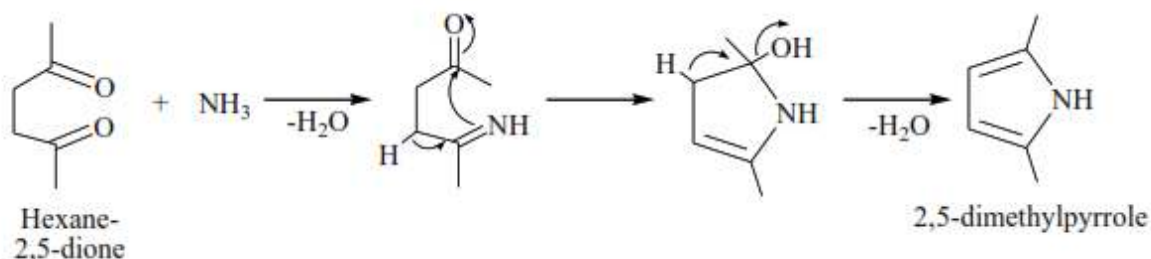
ii. **From succinimide:** Succinimide when is distilled with Zn dust it reduces the succinimide to pyrrole.



iii. **From Furan:** Industrially pyrrole is prepared by passing a mixture of furan and ammonia over alumina over 400° C.



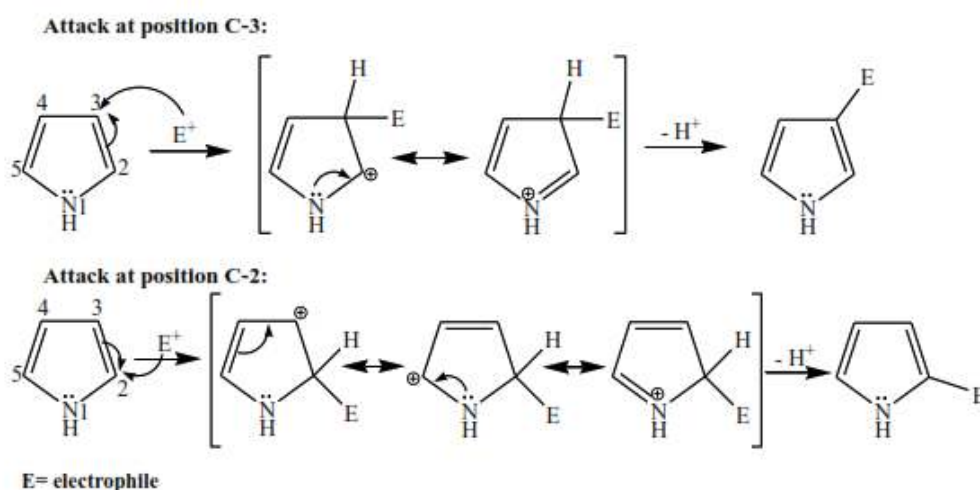
iv. **Pall-Knorr synthesis:** In this method, when a 1,4-diketone is heated with ammonia or a primary amine it gives the corresponding pyrrole derivatives.



PROPERTIES OF PYRROLE:

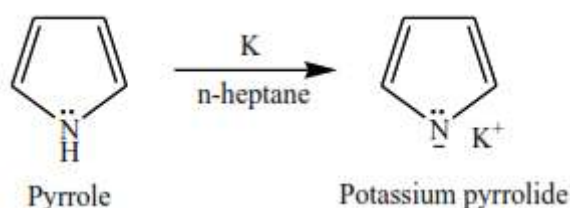
- Physical Properties of pyrrole:** Pyrrole is a colorless liquid with boiling point 131°C . It is highly sensitive to air, when pyrrole is exposed to air it turns brown and gradually resinifies. Pyrrole is slightly soluble in water but completely miscible in ether and ethanol.
- Chemical Properties:** Pyrrole is an aromatic compound and more reactive than benzene. Because of the aromatic nature pyrrole gives all characteristic reactions (electrophilic substitution reactions) of aromatic compounds such as halogenation, nitration, sulphonation, Friedel-Crafts reactions etc.

Pyrrole undergoes electrophilic substitution at the position C-2. Approach of the electrophile at position C-2 leads the formation of three resonating structures; however, only two resonating structures are obtained when the electrophile approaches at position C-3. Thus the intermediate obtained by the approach of electrophile at position C-2 is more stable than the intermediate obtained by the approach of electrophile at position C-3. This is the reason that electrophilic attack occurs at position C-2. Following mechanism is suggested for the electrophilic attack at position C-2.

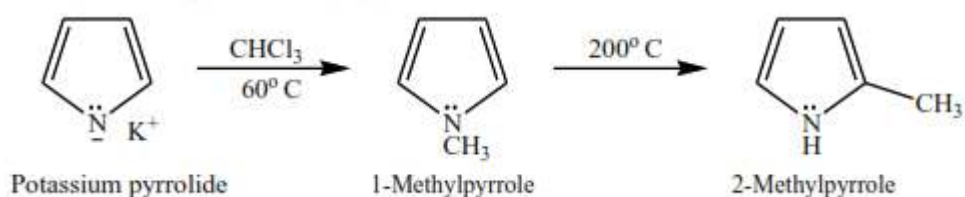


All the electrophilic substitution reactions of pyrrole occur at position C-2 and follow the similar mechanism as shown above.

a) **Acidic Character of Pyrrole:** The lone pair of nitrogen usually participates in resonance and thus makes the pyrrole aromatic. That is the reason, the lone pair of nitrogen could not be available free to react with a proton. However, pyrrole can behave as a weak acid. When pyrrole is heated with potassium in n-heptane as solvent, stable potassium pyrrolide is formed.

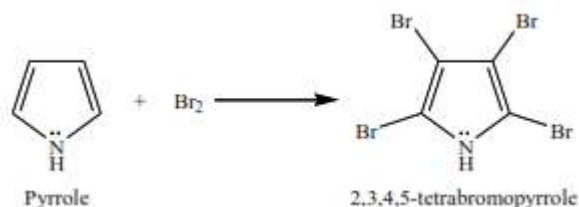


Potassium pyrrolide when reacts with alkyl halide at 60° C to give N-alkyl pyrrole. The N-alkyl pyrrole can easily rearrange to C-alkyl pyrrole.

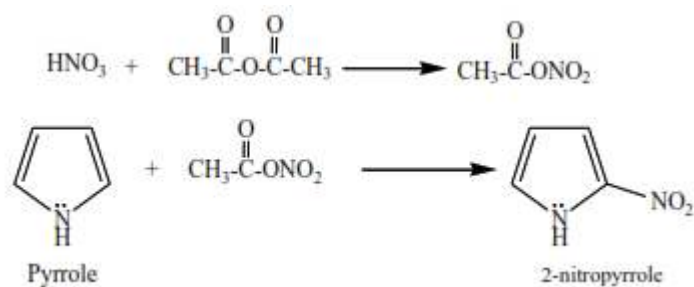


b) **Electrophilic Substitution Reactions of Pyrrole:** Pyrrole undergoes electrophilic substitution reactions at position C-2.

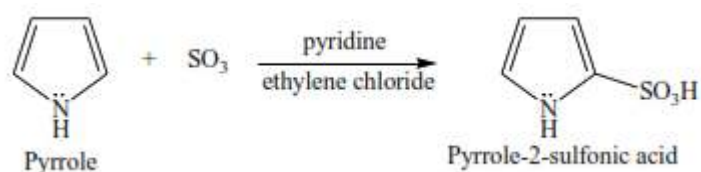
i. **Halogenation:** Pyrrole reacts with halogens [X₂ (X₂ = Cl₂, Br₂ and I₂)] to give tetrahalopyrrole. For example, Reaction of bromine with pyrrole gives tetrabromopyrrole.



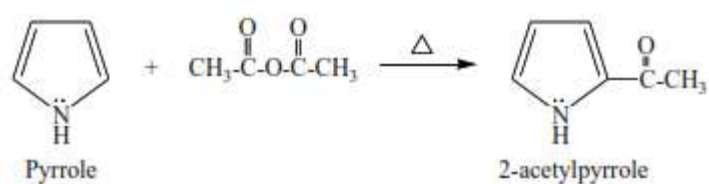
ii. **Nitration:** Nitration of pyrrole is achieved by reacting it with HNO₃ in acetic anhydride. The reaction of HNO₃ and acetic anhydride resulted acetyl nitrate in which –NO₂ acts as an electrophile.



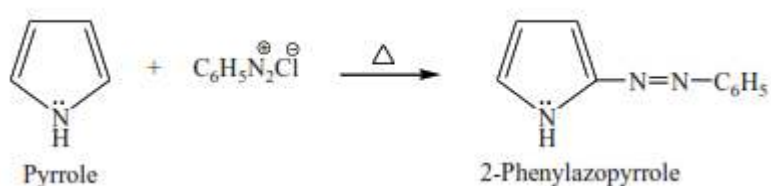
iii. **Sulphonation:** Sulphonation of pyrrole is achieved by reacting it with sulfur trioxide (SO_3) – pyridine mixture in ethylene chloride.



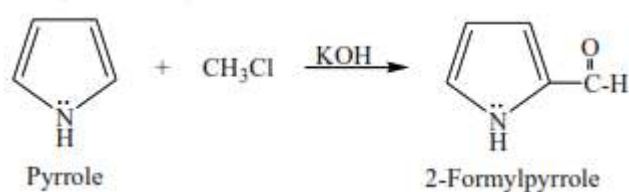
iv. **Friedel-Crafts Acylation:** Reaction of pyrrole with acetic anhydride under condition gives 2-acetylpyrrole.



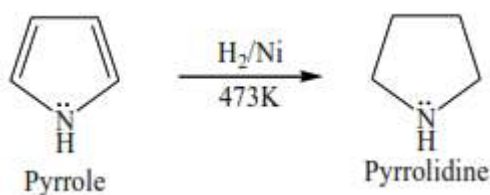
v. **Diazotization:** Pyrrole reacts with benzenediazonium chloride in acidic medium to give 2-phenylazopyrrole.



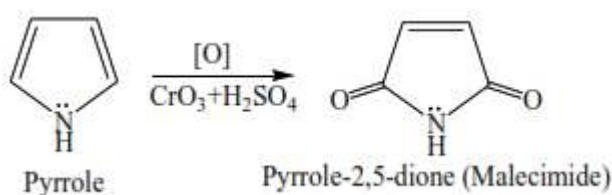
vi. **Reimer-Tiemann Reaction:** Pyrrole reacts with Chloroform in presence of KOH to give 2-Formylpyrrole. This reaction is known as Reimer-Tiemann reaction. It also takes place through electrophilic substitution reaction mechanism.



c) **Reduction:** Pyrrole can be reduced to pyrrolidine (tetrahydropyrrole) by H_2 gas in Raney Ni at very high temperature (473K).

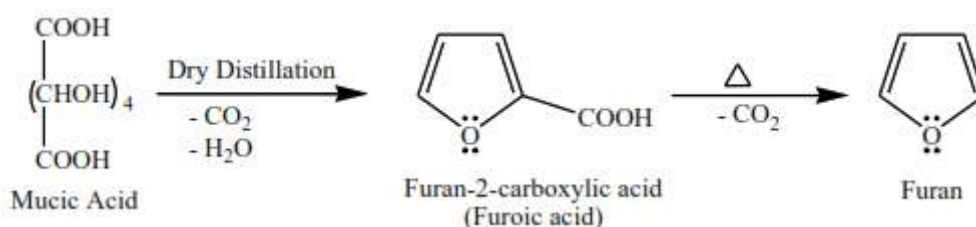


d) **Oxidation:** Pyrrole when oxidized with Chromium trioxide in H_2SO_4 , it gives Malecimide.

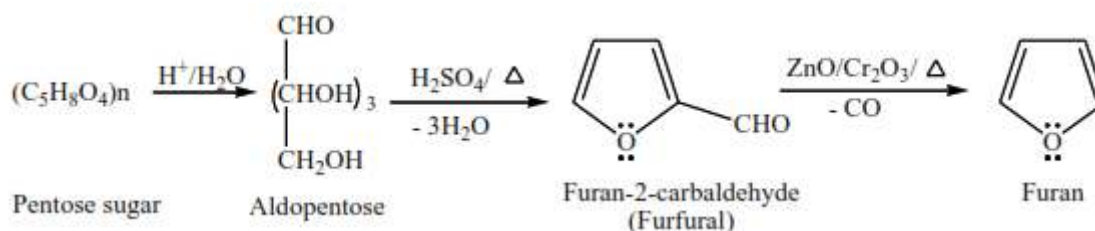


METHODS OF PREPARATION OF FURAN:

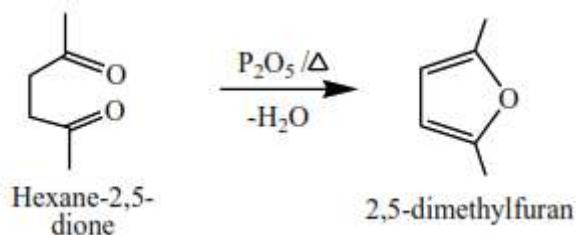
Following are the general methods of preparation of Furan: i. From Mucic acid: Dry distillation of mucic acid first gives Furoic acid which on decarboxylation by heating gives Furan.



ii. **From Furfural:** Furan is synthesized from furfural which is obtained by acid-hydrolysis of pentose sugars.



iii. **Paal-Knorr Synthesis:** Dehydration of 1,4-diketone with P_2O_5 (phosphorous Pentaoxide) gives derivatives of Furan.

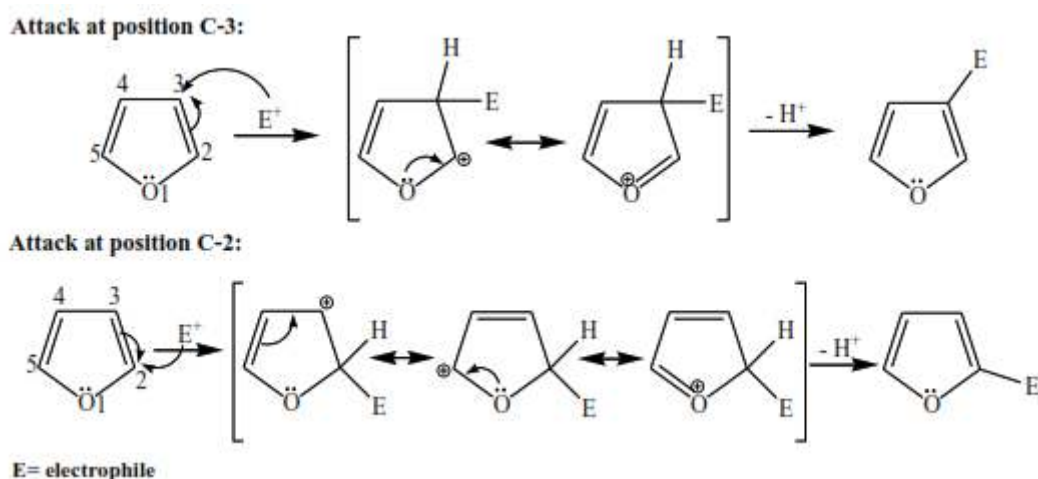


PROPERTIES OF FURAN:

i. **Physical Properties of Furan:** Furan is colourless liquid. Its boiling point is 31.4°C . It has an odour similar to Chloroform. It is insoluble in ether but soluble in most of the organic solvents.

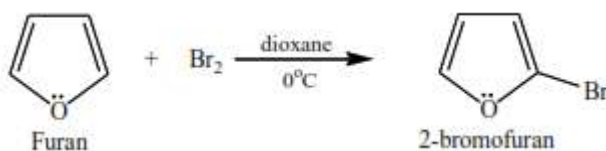
ii. **Chemical Properties of Furan:** furan is an aromatic compound and more reactive than benzene. Because of the aromatic nature, furan gives all characteristic reactions (electrophilic substitution reactions) of aromatic compounds such as halogenation, nitration, sulphonation, Friedel-Crafts reactions etc.

Similar to pyrrole, furan also undergoes electrophilic substitution at the position C-2. Approach of the electrophile at position C-2 leads the formation of three resonating structures; however, only two resonating structures are obtained when the electrophile approaches at position C-3. Thus the intermediate obtained by the approach of electrophile at position C-2 is more stable than the intermediate obtained by the approach of electrophile at position C-3. This is the reason that electrophilic attack occurs at position C-2. Following mechanism is suggested for the electrophilic attack at position C-2.

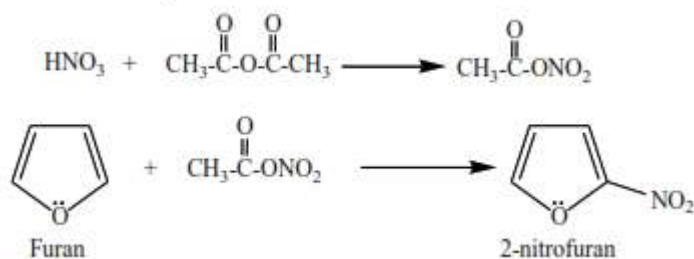


a) **Electrophilic Substitution Reactions of Furan:** Furan undergoes electrophilic substitution reactions at position C-2.

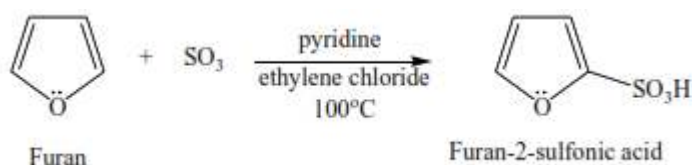
i. **Halogenation:** Furan reacts with halogens [X_2 ($X_2 = Cl_2, Br_2$ and I_2)] to give 2-halofuran. For example, reaction of bromine with Furan gives 2-bromofuran.



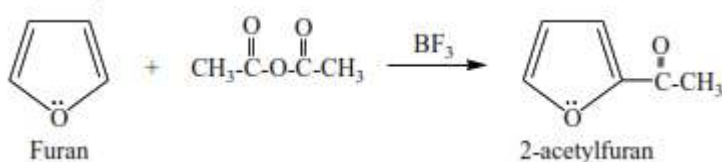
ii. **Nitration:** Nitration of furan is achieved by reacting it with HNO_3 in acetic anhydride. The reaction of HNO_3 and acetic anhydride resulted acetyl nitrate in which $-NO_2$ acts as an electrophile.



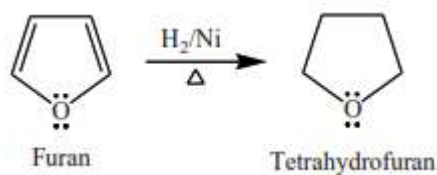
iii. **Sulphonation:** Sulphonation of Furan is achieved by reacting it with sulfur trioxide (SO_3) – pyridine mixture in ethylene chloride at $100^\circ C$.



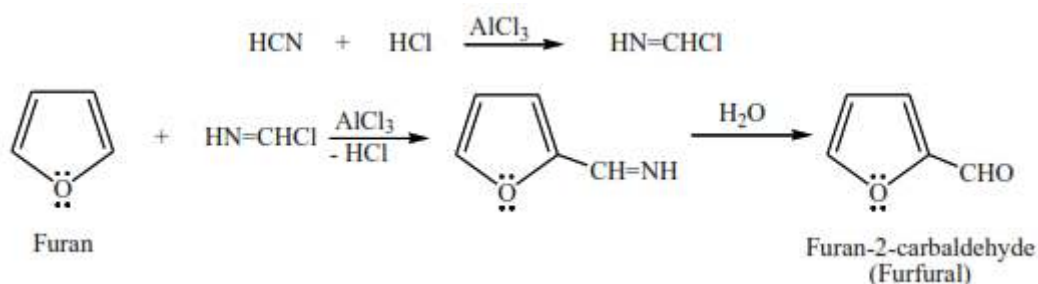
iv. **Friedel-Crafts Acylation:** Reaction of furan with acetic anhydride in presence of BF_3 gives 2-acetylfuran.



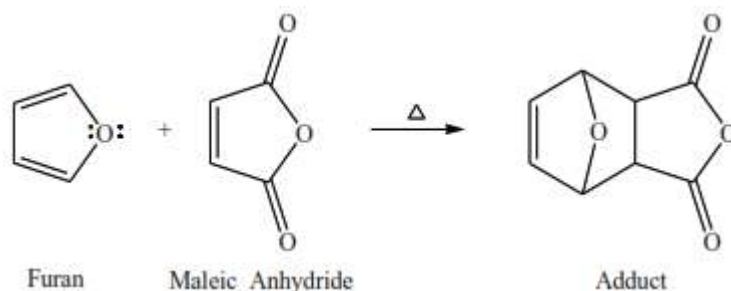
b) **Reduction:** On catalytic hydrogenation of furan, the tetrahydrofuran (THF) is obtained. THF is used as a solvent in place of ether in the Grignard reactions.



c) **Gattermann Koch Synthesis:** When furan is treated with a mixture of HCN and HCl in the presence of Lewis acid catalyst AlCl_3 , furfural is obtained as final product.



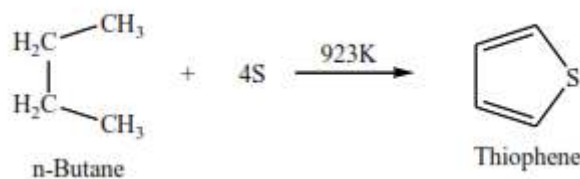
d) **Diels-Elder Reaction:** Furan is the only heterocyclic compound which undergoes Diels-Elder reaction. Diels-Elder reaction is a cycloaddition reaction of 4π -system to 2π -system.



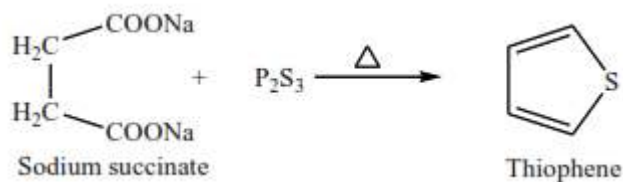
METHODS OF PREPARATION OF THIOPHENE:

Following are the general methods of preparation of thiophene

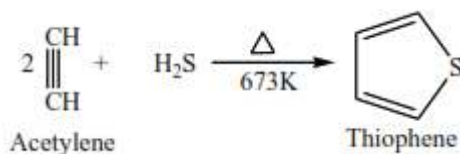
i. **From n-Butane:** Thiophene is obtained when n-butane is heated with elemental sulphur at very high temperature (923K).



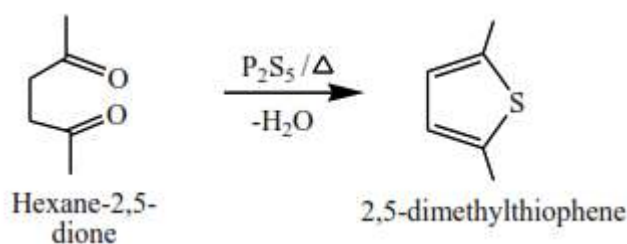
ii. **Laboratory Method:** When sodium succinate is heated with phosphorous sulphide, thiophene is obtained.



iii. **Industrial Method:** Industrially, thiophene is prepared by passing a mixture of acetylene and hydrogen sulphide through a tube containing alumina (Al₂O₃) at 673K.



iv. **Pall-Knorr synthesis of thiophene derivatives:** In this method, dehydration of 1,4-diketone with P₂S₅ (phosphorous Pentasulphide) gives derivatives of thiophene.



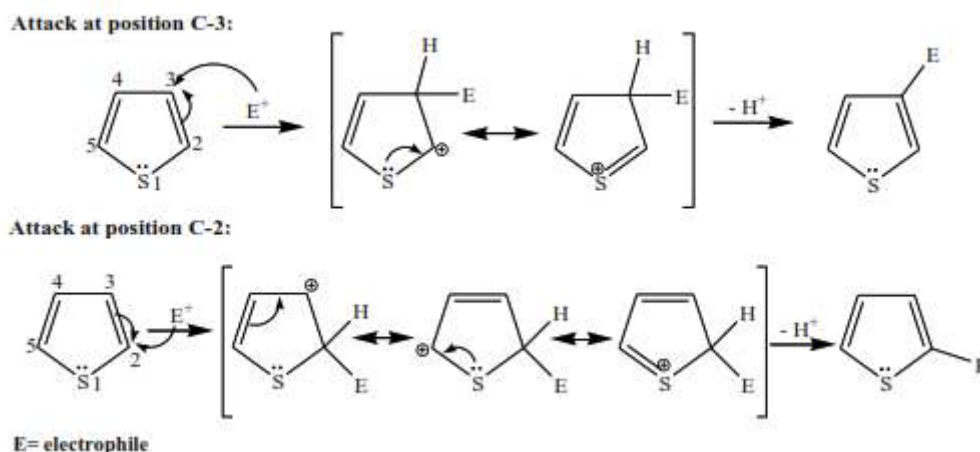
PROPERTIES OF THIOPHENE:

i. **Physical Properties of thiophene:** Thiophene is colorless liquid. Boiling point of thiophene is 357 K. It smells like benzene. It is soluble in alcohol and ether but insoluble in water.

ii. **Chemical Properties of thiophene:** Thiophene is an aromatic compound and more reactive than benzene. Because of the aromatic nature, thiophene gives all characteristic reactions (electrophilic substitution reactions) of aromatic compounds such as halogenation, nitration, sulphonation, Friedel-Crafts reactions etc.

Similar to pyrrole and furan; thiophene also undergoes electrophilic substitution at the position C-2. Approach of the electrophile at position C-2 leads the formation of three resonating structures; however, only two resonating structures are obtained when the electrophile approaches at position C-3. Thus the intermediate obtained by the approach of electrophile at position C-2 is more stable than the intermediate obtained by the

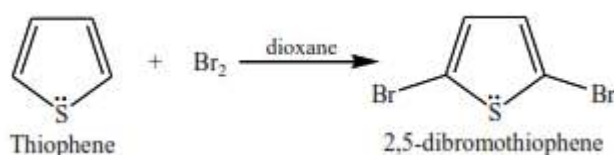
approach of electrophile at position C-3. This is the reason that electrophilic attack occurs at position C-2. Following mechanism is suggested for the electrophilic attack at position C-2.



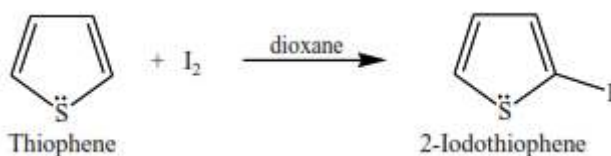
a) **Electrophilic Substitution Reactions of Thiophene:** Thiophene undergoes electrophilic substitution reactions at position C-2.

i. **Halogenation:** Thiophene reacts with halogens [X_2 ($X_2 = Cl_2, Br_2$ and I_2)] to give 2-halofuran.

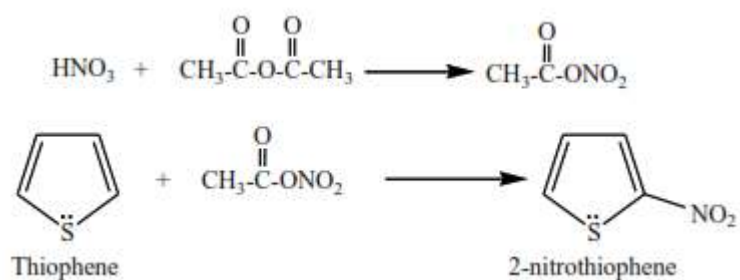
For example, reaction of bromine with Thiophene in absence of any halogen carrier gives 2,5-dibromothiophene.



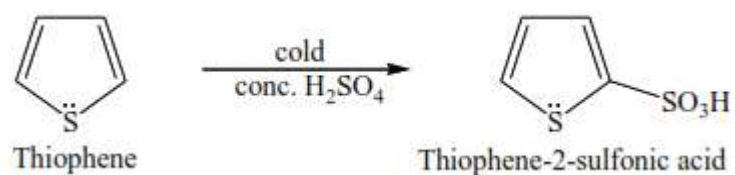
However, Iodination of thiophene in presence of yellow mercuric oxide gives 2-iodothiophene.



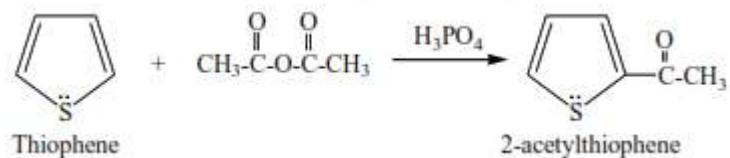
ii. **Nitration:** 2-Nitrothiophene is obtained when nitration of thiophene is performed by reacting it with fuming HNO_3 in acetic anhydride. The reaction of HNO_3 and acetic anhydride resulted acetyl nitrate in which $-NO_2$ acts as an electrophile.



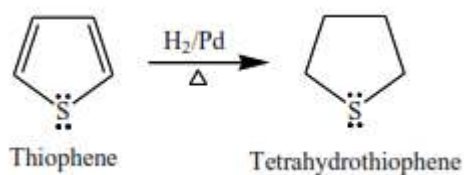
iii. **Sulphonation:** Sulphonation of thiophene is achieved by reacting it with cold concentrated H_2SO_4 . Thiophene-2-sulphonic acid is obtained as product.



iv. **Friedel-Crafts Acylation:** Reaction of thiophene with acetic anhydride in presence of H_3PO_4 gives 2-acetylthiophene.



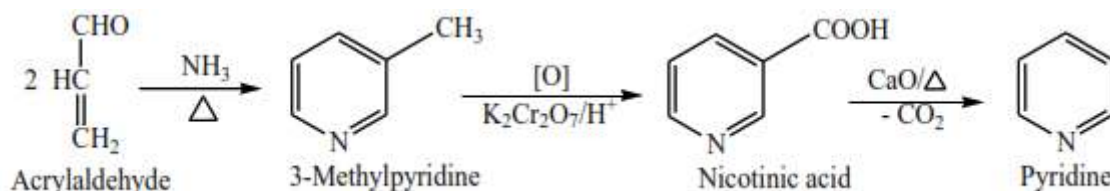
b) **Reduction:** On catalytic hydrogenation of thiophene, the tetrahydrothiophene (Thiophane) is obtained.



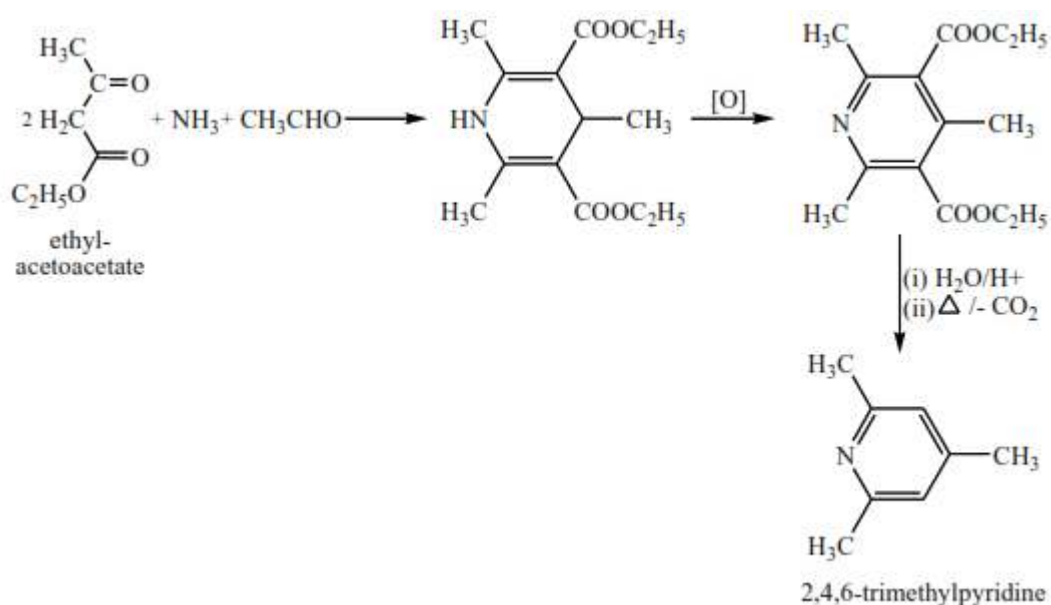
5.2 METHODS OF PREPARATION OF PYRIDINE:

Following are the general methods of preparation of pyridine:

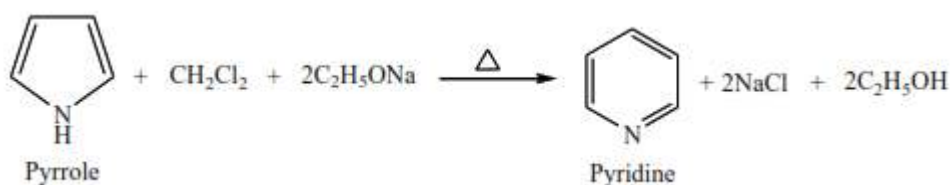
i. **From acrolein:** Pyridine can be prepared by the reaction of acrolein and ammonia according to following reaction steps.



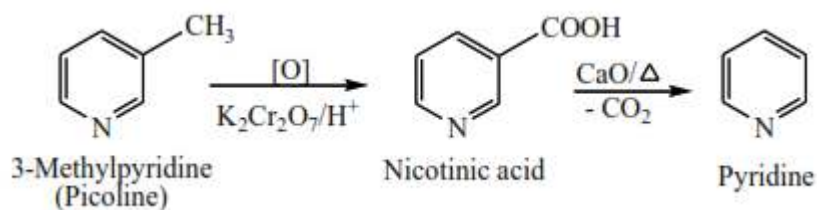
ii. **Hantzsch Synthesis (1882):** In this method, the condensation of a beta-dicarbonyl compound, ammonia and an aldehyde lead the formation of 1,4-dihydropyridine derivative. The 1,4-dihydro pyridine derivative on oxidation with HNO_3 yields the formation of pyridine derivative.



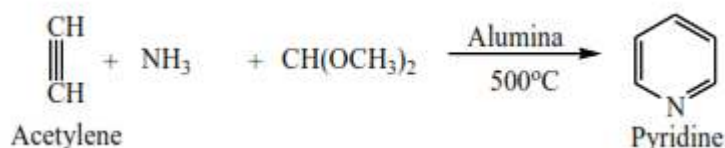
iii. **From pyrrole:** Pyrrole when heated with methylene chloride in presence of sodium methoxide, pyridine is formed.



iv. **From Picoline:** Beta-picoline on oxidation with potassium dichromate and sulphuric acid gives nicotinic acid, which on decarboxylation with calcium oxide gives pyridine.



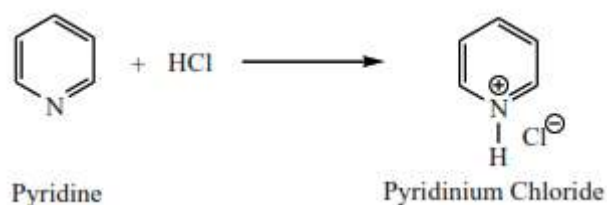
v. **Industrial Method:** Industrially pyridine is prepared by heating the acetylene, ammonia and formaldehyde dimethylacetal in the presence of alumina at 500° C.



PROPERTIES OF PYRIDINE:

- i. **Physical Properties of Pyridine:** Pyridine is a colourless liquid. Its boiling point is 115.5° C. It has a characteristic unpleasant odor. It is soluble in water and most organic solvents.
- ii. **Chemical properties of Pyridine:** Chemical properties of pyridine are discussed as follow:

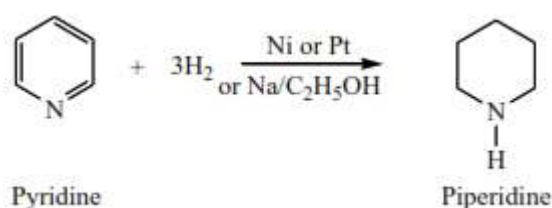
a. **Basic character of pyridine:** Pyridine is basic in nature. Its pK_b is 8.75. It reacts with strong acids to form salts.



The basic nature of pyridine is due to the freely available lone pair of electrons in sp² hybridized orbital pyridine, which does not participate in the formation of delocalized π - molecular orbital. Pyridine is less basic in comparison to aliphatic amines whereas, it is more basic than aniline and pyrrole. This is because the lone pair of electrons in aliphatic

amines exists in sp^3 hybridized orbital, however, in case of pyridine the lone pairs of electrons exists in sp^2 hybridized orbital. Electrons are held more tightly by the nucleus in a sp^2 hybridized orbital than an sp^3 hybridized orbital. Hence the lone pair of electrons in pyridine is less available for protonation. The less basicity of pyrrole and aniline can be explained in terms of non-availability of these lone pair of electrons on nitrogen atom. These lone pair of electrons is involved in the formation of delocalized π -molecular orbital.

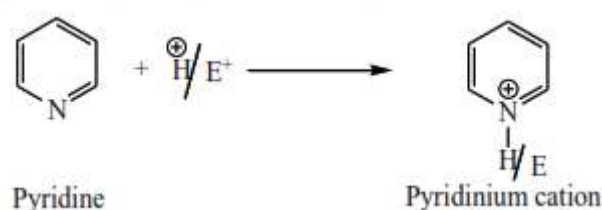
b. Reduction: Under catalytic hydrogenation of pyridine hexahydropyridine is formed. It is also known as Piperidine.



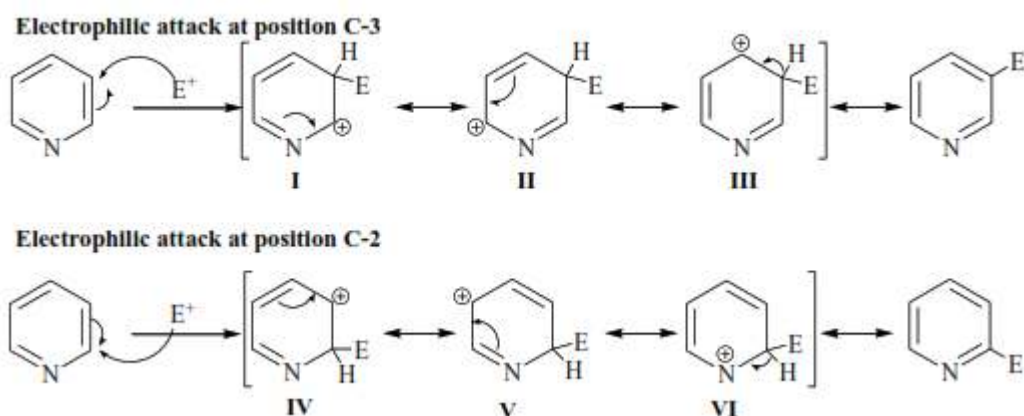
c. Electrophilic substitution Reactions: Pyridine is also an aromatic compound. It is less aromatic than benzene and pyrrole. Pyridine usually considered a highly deactivated aromatic nucleus towards electrophilic substitution reactions. Therefore highly vigorous reaction conditions should be used for these reactions to take place. The low reactivity of pyridine towards the electrophilic substitution reactions is due to the following reasons:

- The higher electro negativity of nitrogen atom reduces electron density on the ring, thus deactivate the ring.
- Pyridine is highly sensitive to acidic medium; it readily forms pyridinium cation with a positive charge on nitrogen atom. Similarly, electrophile itself may also react with pyridine to form corresponding pyridinium ion. This positive charge on nitrogen atom decreases electron density on nitrogen atom, consequently, the electron density on ring also decreases.

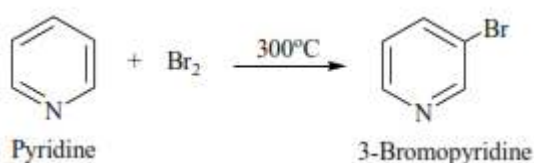
However, the effect of such deactivation is comparatively lower at position C-3. The position C-3 is thus, comparatively, the position of highest electron density in pyridine.



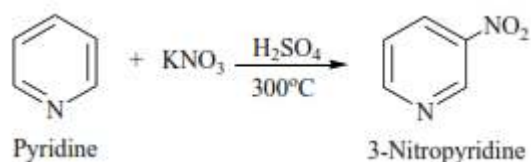
This is the reason that the pyridine undergoes electrophilic substitution at position C-3. Pyridine also gives electrophilic substitution like halogenation, nitration and sulphonation only under drastic conditions. Pyridine does not give Friedel-Crafts reaction. Approach of the electrophile at position C-3 leads the formation of three resonating structures (I, II and III); similarly, approach of electrophile at position C-2 also leads the formation of three resonating structures (IV, V and VI). However, out of the three contributing resonating structures for the intermediate ion resulting from the attack of electrophile at position C-2, structure VI is considered as an unstable resonating form because in resonating structure VI the more electronegative nitrogen atom bears a +ve charge. Because of the unstable nature of one of the resonating structures of the intermediate ion formed during the attack of electrophile at position C-2 than that of the intermediate ion formed during the attack of electrophile at position C-3, the electrophilic substitution in pyridine at position C-3 is always favoured. Following mechanism is suggested for the electrophilic attack at position C-3.



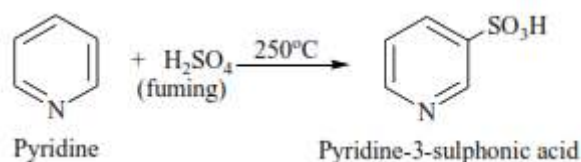
- i. **Bromination:** Pyridine reacts with Bromine at high temperature to give 3-Bromopyridine.



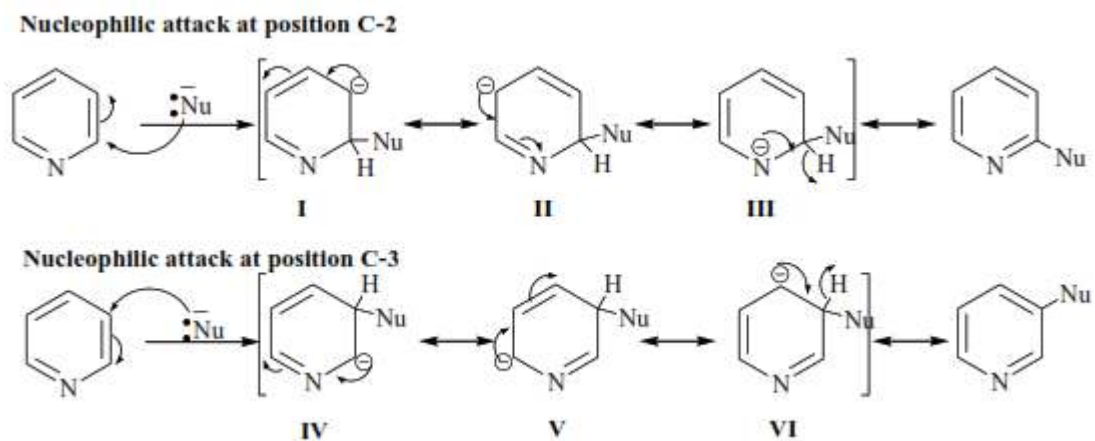
- ii. **Nitration:** 3-Nitropyridine is obtained when nitration of pyridine is performed by reacting it with KNO₃ in concentrated H₂SO₄ at 300°C. The reaction of KNO₃ and concentrated H₂SO₄ resulted—NO₂ which acts as an electrophile.



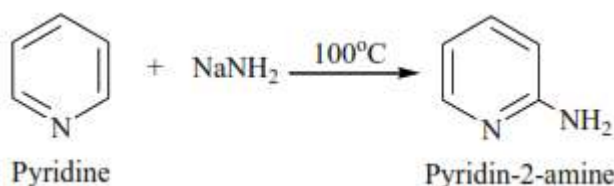
- iii. **Sulphonation:** Sulphonation of pyridine is achieved by reacting it with fuming H_2SO_4 at 250°C . Pyridine-3-sulphonic acid is obtained as product.



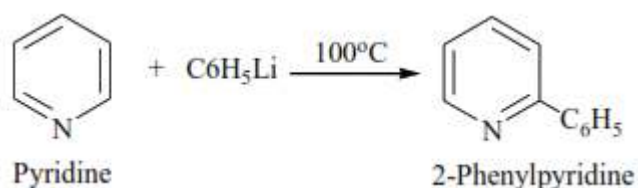
d. Nucleophilic Substitution Reactions: As we have discussed in previous section that pyridine generally deactivated the aromatic ring towards electrophilic substitution reaction. The deactivation of aromatic ring towards electrophilic substitution resulted due to the electron withdrawing nature of nitrogen atom. Due to such deactivation, pyridine also gives nucleophilic substitution reaction. Nucleophilic substitution in pyridine ring occurs at position C-2. Approach of the nucleophilic at position C-2 leads the formation of three resonating structures (I, II and III); similarly, approach of nucleophilic at position C-3 also leads the formation of three resonating structures (IV, V and VI). The resonating structures for intermediate resulting from the attack of nucleophile at position C-2 are more stable than those of position C-3, since more electronegative nitrogen atom hold –ve charge in one of the resonating structure (III) obtained from the attack of nucleophile at position C-2. Hence, the nucleophilic substitution in pyridine at position C-2 is always favored. Following mechanism is suggested for the electrophilic attack at position C-2.



- i. Reaction with Sodium amide: Pyridine reacts with sodium amide to give 2-aminopyridine via nucleophilic substitution.

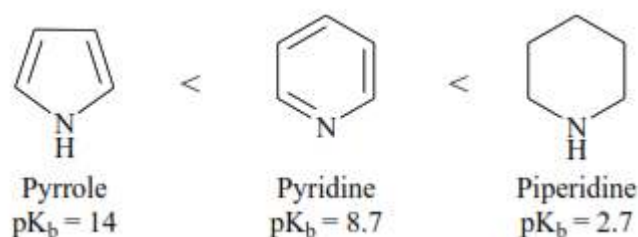


- ii. Reaction with Phenyllithium: Pyridine reacts with phenyllithium (an organometallic compound) to give 2-phenylpyridine.



COMPARISON OF BASICITY OF PYRROLE, PYRIDINE AND PIPERIDINE

From experimental studies it is observed that the pK_b values of pyrrole, pyridine and Piperidine are ~ 14 , ~ 8.7 and ~ 2.7 , respectively. Based on the suggested pK_b values the piperidine is found as a stronger base than pyridine and pyrrole. Pyrrole is the weakest base among these three heterocyclic bases. The order of basicity of pyrrole, pyridine and piperidine is as given below:



The above order of basicity of pyrrole, pyridine and piperidine can be justified in terms of the structure of these compounds. As we know that the basicity of nitrogen compounds depends upon the availability of lone pair of electron on nitrogen atom. In pyrrole, the lone pair of electron on nitrogen atom exists in the sp^2 hybridized orbital of nitrogen and participates in the delocalization, hence does not freely available to cause the basic character of pyrrole. Similar to pyrrole, the lone pair of electron on nitrogen atom of pyridine also exists in the sp^2 hybridized orbital; however, it does not participate in the delocalization and available freely to cause the basic character. Although the lone pair

of electron on nitrogen atom of pyridine available freely but due to more electronegative character of sp^2 hybridized nitrogen atom (50% s-character) this lone pair is tightly bonded with nucleus, hence, less available for protonation. However, in piperidine, the lone pair of electron of nitrogen atom lies in sp^3 hybridized orbital of nitrogen. These electrons are less tightly bonded with nucleus. Therefore, these electrons are readily available for protonation. Thus, piperidine is the strongest base among the three.

5.3 PREPARATION AND REACTIONS OF INDOLE QUINOLINE AND ISOQUINOLINE

Heterocyclic rings systems that are formally derived by fusion with other rings, either carbocyclic or heterocyclic, have a variety of common and systematic names. For example, with the benzo-fused unsaturated nitrogen heterocycles, pyrrole provides Indole or isoindole depending on the orientation. Various other important examples of benzofused heterocyclic compounds are Quinoline, Isoquinoline, Benzothiophene, Benzazepine, Dibenzazepine Carbazole, Acridine, and Benzofuran. Figure 1 shows the structural representation of various important 5 and 6 membered benzofused heterocyclic compounds.

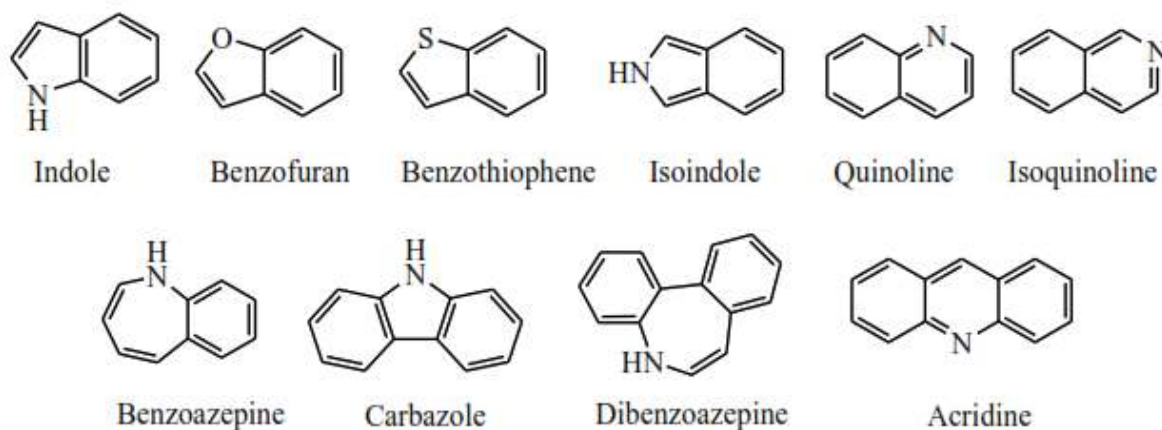


Figure 1: Examples of various important benzo fused heterocyclic compounds

In the present unit, students would be able to learn about the most important five and six membered benzo fused heterocyclic compounds, such as Indole, Quinoline and Isoquinoline.

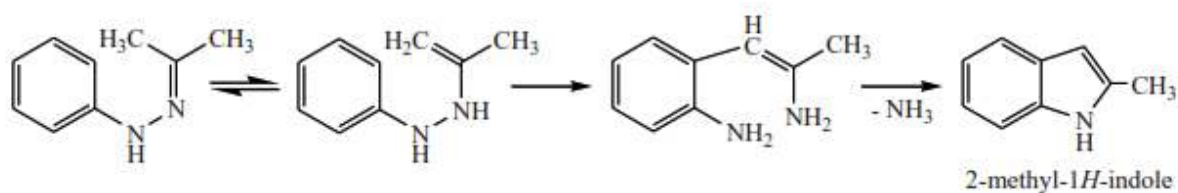
INDOLE

Indole is an aromatic heterocyclic organic compound with formula C_8H_7N . It has a bicyclic structure, consisting of a six-membered benzene ring fused to a five membered nitrogen-containing pyrrole ring. Chemistry of Indole was developed with the study of the dye indigo. Indigo can be converted to Isatin and then to Oxindole. Indole was first synthesized in 1866, when Adolf von Baeyer reduced Oxindole to Indole using zinc dust. The name Indole is a combined name of the words indigo and oleum, since Indole was first isolated by treatment of the indigo dye with oleum. Indole is widely distributed in the natural environment and can be produced by a variety of bacteria. As an intercellular signal molecule, it regulates various aspects of bacterial physiology, including spore formation, plasmid stability, drugs resistance, bio-film formation, and virulence. The amino acid tryptophan is an Indole derivative and the precursor of the neurotransmitter serotonin.

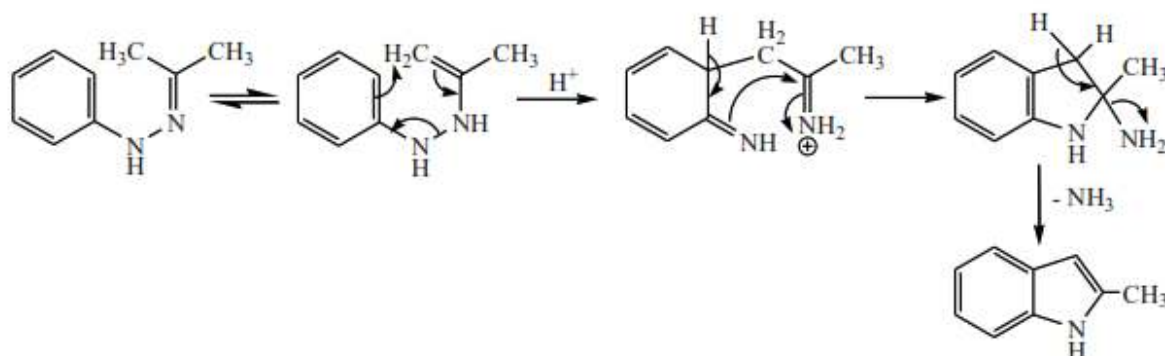
Certain Indole derivatives were important dyestuffs until the end of the 19th century. In the 1930s, interest in Indole intensified when it became known that the Indole substituent is present in many important alkaloids (e.g., tryptophan and auxins), and it remains an active area of research today. Indole is found in coal tar and in essential oils (Jesamine oil, orange oil) of many plants. It also occurs in amino acids as a plant growth hormone in alkaloids.

Synthesis or preparation of Indole: There are different methods available for the synthesis of Indole and its derivatives. These methods differ in their range of applicability. However, a number of general methods are also known in which the pyrrole ring formed through the ring closure reactions.

The Fisher-Indole synthesis: This is the most widely used method for the synthesis of Indole. It involves an acid (Lewis acid) catalyzed rearrangement of a phenylhydrazone of an aldehyde or ketone, with the elimination of a molecule of ammonia. The conventional catalysts used in this process are zinc chloride, polyphosphoric acid or a Lewis acid (BF_3). Synthesis of 2-methyl indole can be achieved by taking the phenylhydrazone of acetone. The reaction is as shown below.



Mechanism: Fisher–Indole synthesis is supposed to take place through the acid catalyzed rearrangement of the tautomeric form of the starting phenylhydrazone as shown below.



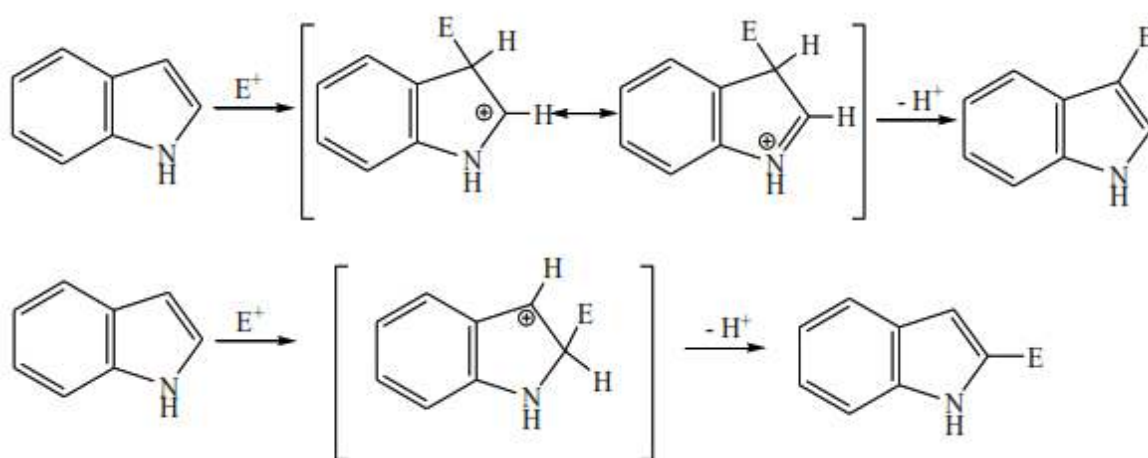
PHYSICAL PROPERTIES OF INDOLE: Indoles and simple alkyl Indoles are colourless crystalline solids. The melting point of Indole is 52°C and boiling point is 254°C. Indole is soluble in most of the organic solvents. The pure form of Indole has very pleasant smell and this is the reason it is used as a perfumery base, however, the impure Indole has very unpleasant smell. The main commercial source of Indole comes from the 220-260°C fraction of coal tar distillation.

The ^1H NMR spectra of Indole feature all the resonances for the hydrogen in the aromatic region. The upfield shift observed for H3 and C3 in the ^1H and ^{13}C NMR indicate the higher electron density around C3.

CHEMICAL PROPERTIES OF INDOLE

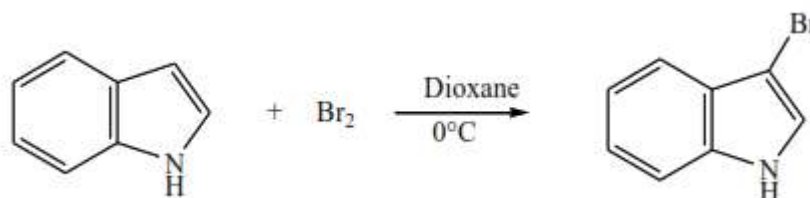
Electrophilic substitution reactions: Indole is a π -excessive aromatic heterocycles with ten π -electron. Indole is an aromatic compound. It involves the $4n+2$ π electrons and hence follows the Huckel rule of aromaticity. The lone pair of sp^2 hybridized nitrogen atom participates in the delocalization process and thus helps to complete the ten π -electron across the ring. Like pyrrole, the π excessive nature of the aromatic ring governs the reactivity and chemical properties of Indole. Indole is a weak base ($\text{pK}_a = -2.4$). In presence of a strong acid protonation of the nitrogen atom would disrupt the aromaticity of the five-

membered ring. Like other aromatic compounds, Indole also gives the electrophilic substitution (the characteristic reactions of aromatic compounds). However, unlike pyrrole, electrophilic substitution in Indole takes place preferentially at C3. A simple explanation for this can be made by analysis of the Wheland intermediates resulting from the attack of an electrophile at C3 and C2 positions. For a reaction at C-3, the energy of activation of the intermediate is lowered because it is possible to delocalize the positive charge through resonance involving the nitrogen lone pair of electrons. This favourable situation is not possible in the corresponding intermediate for attack at C-2.



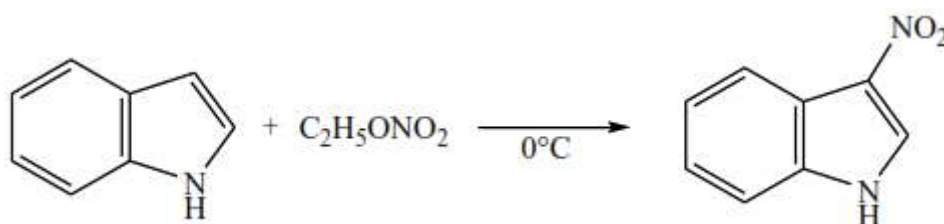
The intermediate of the attack at C3 is stabilized by delocalization of the positive charge. However, no delocalization is possible in the intermediate derived from attack at C2 position without disrupting the aromaticity of the six membered rings. The common electrophilic substitution reactions of Indole are discussed as follow.

1. **Bromination:** Indole undergoes bromination at very low temperature (0°C) in dioxane. The bromination occurs at C3 position.

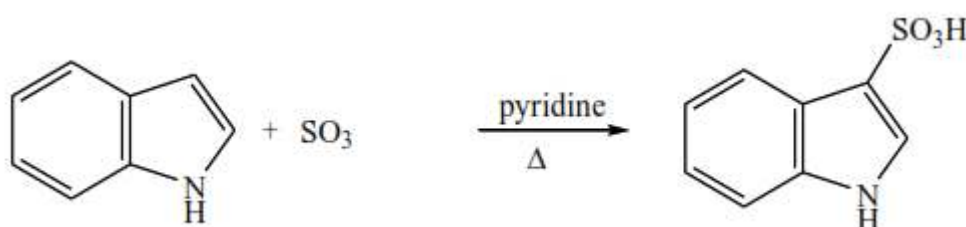


The mechanism of bromination is similar as discussed above the general mechanism of electrophilic substitution. In above mechanism the E can be replaced by Br.

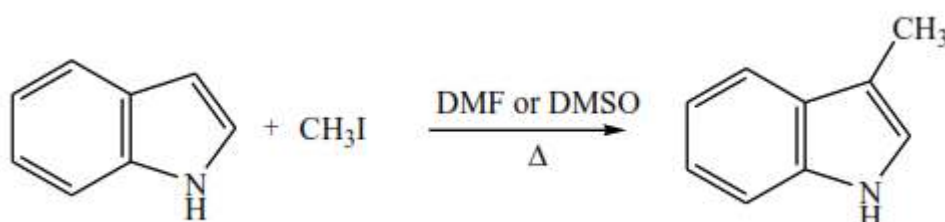
2. **Nitration:** Indole undergoes nitration in presence of ethyl nitrate at low temperature (0 - 5°C). Nitration of Indole also occurs at C3 with the similar mechanism as discussed above.



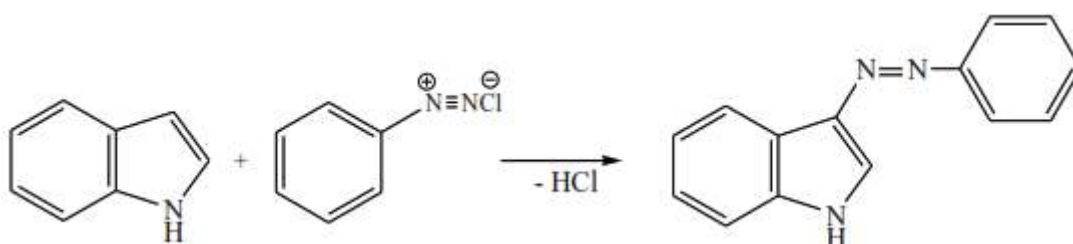
3. **Sulphonation:** Sulphonation of Indole is carried out only under milder conditions using pyridine-sulphur trioxide complex in order to minimize the acidity of the reagent.



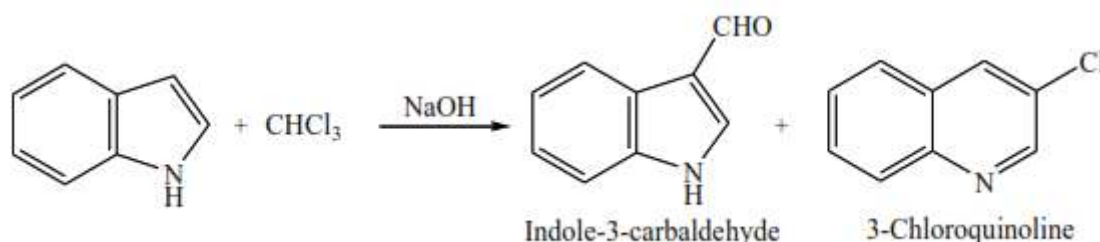
4. **Friedel crafts alkylation:** Indole undergoes alkylation at C3 position with alkyl iodide in N,N-dimethyl formamide (DMF) or dimethyl sulphoxide (DMSO) as solvent.



5. **Diazocoupling or Diazotization reaction:** Indole reacts with benzene diazonium chloride to give 3-phenylazoindole, a diazotized coupled product.



6. **Reimer Tiemann formylation:** Indole, like other aromatic compounds, reacts with Chloroform (CHCl_3) in presence of alkali to give formylated product at C3 position. This reaction proceeds via carbene intermediate. In general two products are obtained in this reaction, first, the C3 formylated product (Indole-3-carbaldehyde) and second, the rearranged product (3-Chloroquinoline).



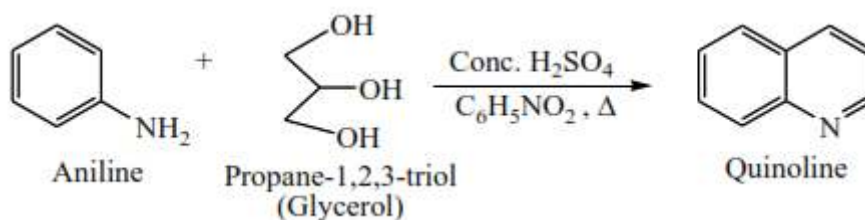
APPLICATIONS OF INDOLE AND ITS DERIVATIVES

Indole and its derivatives are being extensively used in medicinal and pharmaceutical industry. Indole derivative Indigo is also used as a dyestuff called in Textile industry.

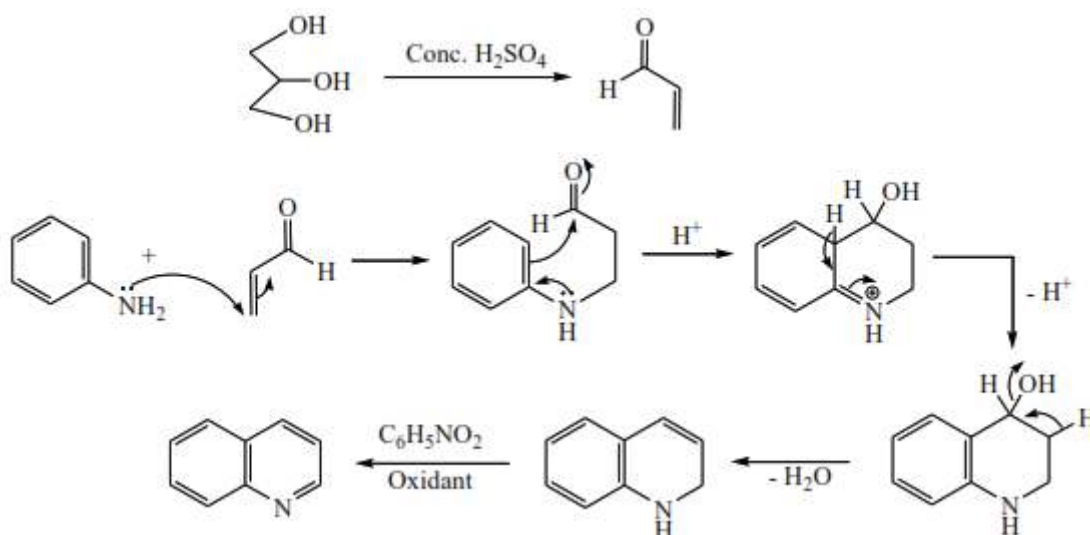
QUINOLINE

Synthesis or preparation of Quinoline: There are different methods available for the synthesis of quinoline and its derivatives. These methods may differ in their range of applicability. However, a number of general well known methods have been used for the preparation of quinoline. The important methods for the synthesis of quinoline are discussed below.

The Skraup synthesis: This is one of the most important methods for the preparation of quinoline. In this method the aniline and its derivatives having vacant ortho position is when heated with glycerol, concentrated H_2SO_4 and an oxidizing agent the resultant product is obtained as quinoline or its derivatives. The nitrobenzene is generally used as mild oxidizing agent in Skraup synthesis. Glycerol when heated with concentrated H_2SO_4 it gives the acrolein after dehydration. Condensation of acrolein thus obtained with aniline or its derivatives followed by oxidation gives the quinoline. The reaction is shown as follow.



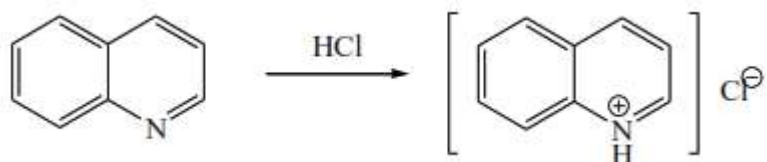
Mechanism: The step wise mechanism of Skraup synthesis of quinoline is given as follow.



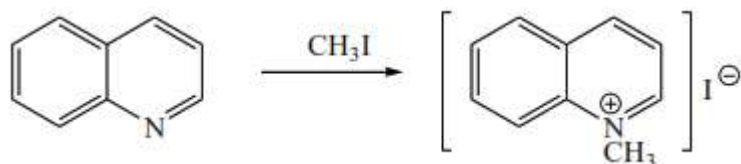
PHYSICAL PROPERTIES OF QUINOLINE: Quinoline is colourless hygroscopic liquid. Its boiling point is 237 °C. It has a characteristic smell similar to that of pyridine. On exposure to air quinoline turns in to yellow coloured. It is miscible in organic solvents. Quinoline is highly aromatic in nature and it has resonance energy 47.3 kcal/mole. Quinoline is a weak base having pKa 4.94. The basicity of quinoline is intermediate between aniline (pKa 4.58) and pyridine (pKa 5.17).

CHEMICAL PROPERTIES OF QUINOLINE: The important chemical properties of quinoline are discussed as follow.

1. **Basicity:** Due to availability of lone pair of electrons on nitrogen, quinoline acts as a base and forms salts with acids and quaternary salts with alkyl halides.
 - a. Reaction with acids:

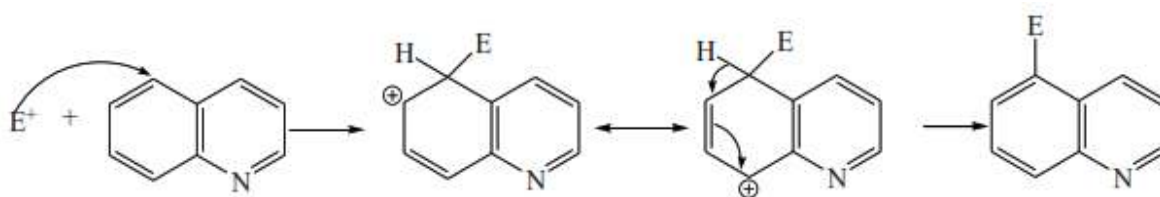


b. Reaction with methyl iodide:

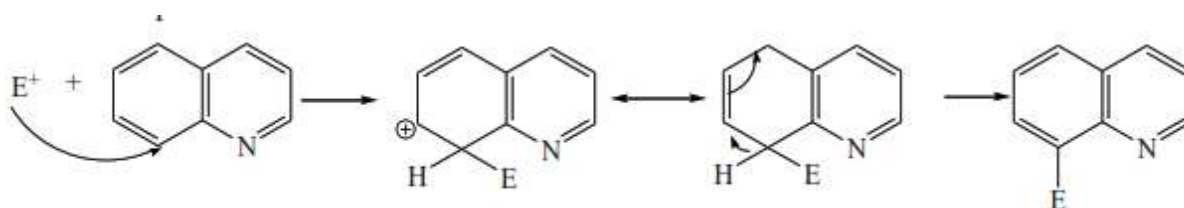


2. **Electrophilic substitution:** Out of the two fused rings in quinoline, the carbocyclic (benzene) ring is relatively more electron rich and resembles benzene ring while the nitrogen containing ring (less electron rich) resembles with pyridine ring. Therefore the electrophilic substitution in quinoline takes place more readily at benzene ring (at position 5 and 8 of benzene ring) rather than the pyridine ring. Thus if both the positions in benzene ring are vacant than mixture of substituted product is obtained. The general mechanism of electrophilic substitution on quinoline is shown below.

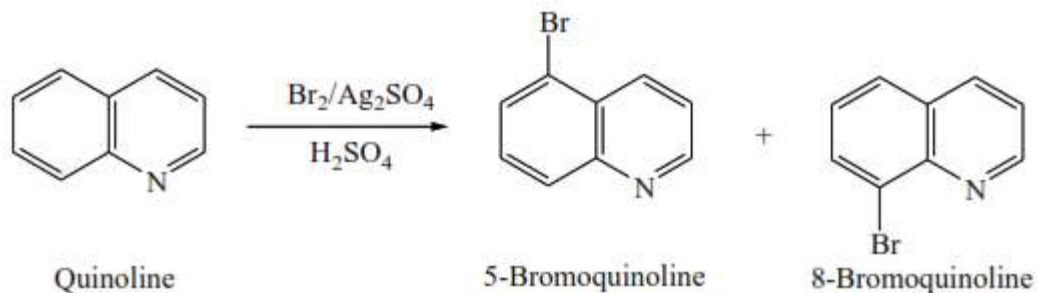
a) At position 5



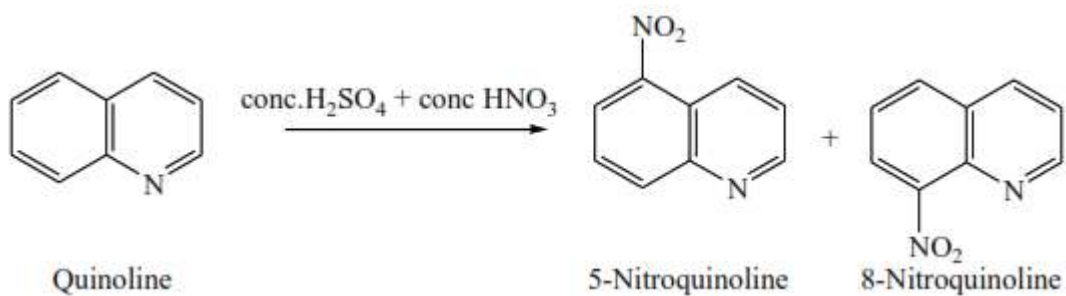
b) At position 8



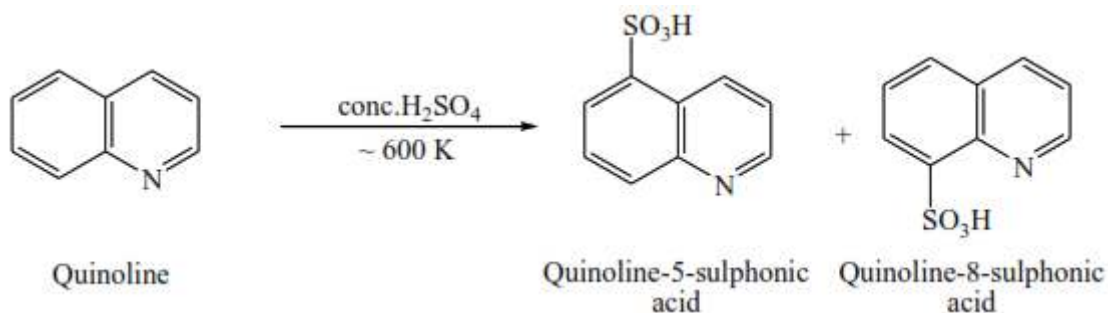
- I. **Bromination:** Quinoline undergoes bromination with Br_2 in presence of silver sulphate (Ag_2SO_4) and H_2SO_4 . Bromination occurs at position 5 and 8 hence mixture of products is formed.



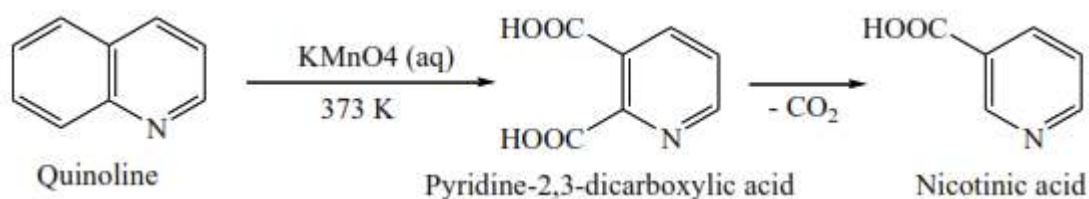
- II. **Nitration:** Quinoline can undergo nitration by reacting with the well known nitrating agent (Conc. H_2SO_4 + conc. HNO_3). Nitration of quinoline occurs at position 5 and 8.



- III. **Sulphonation:** In presence of Conc. H_2SO_4 at high temperature ($\sim 600\text{K}$) sulphonation of quinoline takes place. Like nitration or bromination, the sulphonation of quinoline occurs at position 5 and 8.



- IV. **Oxidation:** In presence of KMnO_4 quinoline get oxidized to pyridine-2,3-dicarboxylic acid which on decarboxylation gives nicotinic acid.



Applications of Quinoline: Quinoline is used

- As a high boiling basic solvent in organic reactions
- Quinoline is used in the manufacture of dyes, the preparation of hydroxyquinoline sulfate and niacin. It is also used as a solvent for resins and terpenes.
- Quinoline is mainly used as in the production of other specialty chemicals.
- Its principal use is as a precursor to 8-hydroxyquinoline, which is a versatile chelating agent and precursor to pesticides.
- Its 2- and 4-methyl derivatives are precursors to cyanine dyes.
- Oxidation of quinoline affords quinolinic acid (pyridine-2,3-dicarboxylic acid), a precursor to the herbicide sold under the name "Assert".
- The reduction of quinoline with sodium borohydride in the presence of acetic acid is known to produce Kairolin A.
- The piperazine antidepressant quipazine is also leucomine based.

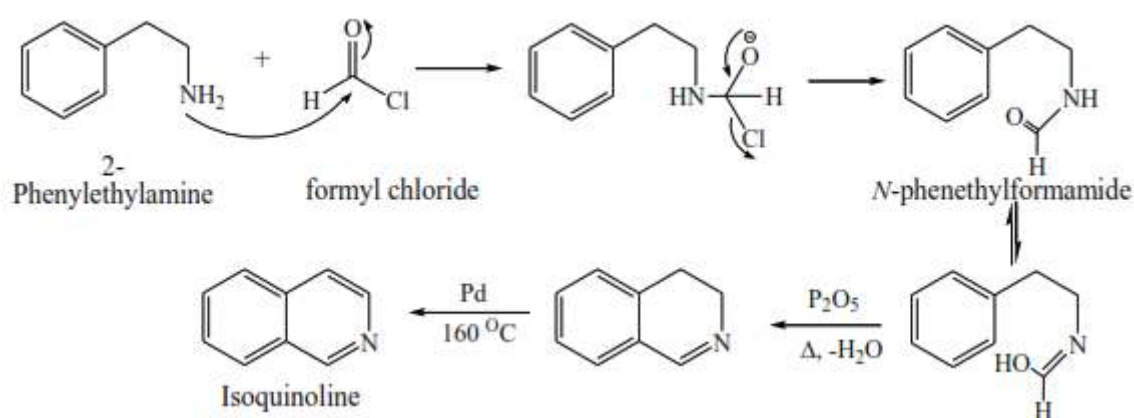
ISOQUINOLINE



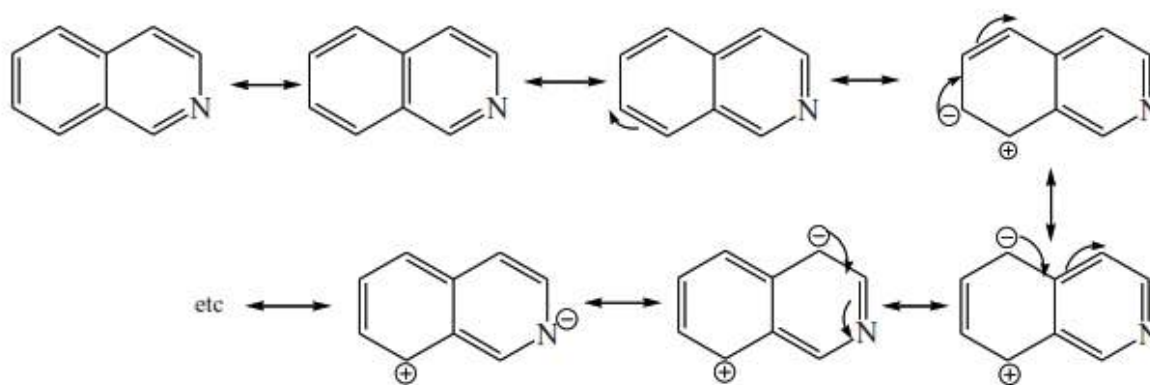
Isoquinoline is a heterocyclic aromatic organic compound. It is a structural isomer of quinoline. Isoquinoline is also obtained by ring fusion of pyridine and with a benzene ring. It was first isolated by Hoogewerff and Drop from the quinoline fraction of coal

tar in 1885. Several derivatives of Isoquinoline also occur in coal tar. Isoquinoline does not occur free in nature but is found frequently in several alkaloids. It is called 2-azanaphthalene or benzo[b]pyridine. The numbering of the atoms in Isoquinoline is similar as followed in quinoline; however, the nitrogen atom is assigned position-2. Isoquinoline has close similarities in the structure with quinoline; therefore both have a close relationship in their physical and chemical properties.

The Bischler Napieralski synthesis: This synthesis was first suggested by the Bischler and Napieralski and has been subjected to a number of improvements later on. This method involves the cyclodehydration of an acyl derivative of B-phenylethylamine to give 3,4-dihydroisoquinoline, in the presence of Lewis acids such as polyphosphoric acid, zinc chloride or phosphorous pentoxide. The 3,4-dihydroisoquinoline is then dehydrogenated by Pd at 160 °C to Isoquinoline. It must be noted that the yields of this reaction are excellent if electron donating groups are present on benzene ring however if the electron withdrawing groups are present on benzene ring the yields are very poor. This is because of the electrophilic ring closure nature of the ring.



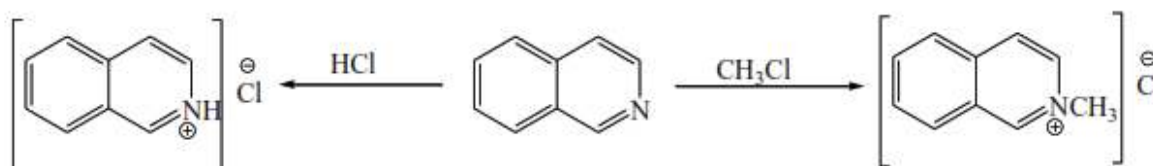
PHYSICAL PROPERTIES OF ISOQUINOLINE: Isoquinoline is a colourless solid with melting point 243°C . It has a smell resembling that of Benzaldehyde. It is steam volatile and sparingly soluble in water but soluble in most of the organic solvents such as ethanol, acetone, diethyl ether, carbon disulfide, and other common organic solvents. It is also soluble in dilute acids as the protonated derivative. Isoquinoline is highly aromatic and may be considered a resonance hybrid of following structures. Similar to pyridine the lone pair of electrons on the nitrogen atom is not conjugated with the ring and therefore, Isoquinoline behaves as weak base.



The pKa of Isoquinoline is 5.14 in compare to quinoline (pKa 4.94). It gets protonated to form salts upon treatment with strong acids, such as HCl. It forms adducts with Lewis acids, such as BF₃.

CHEMICAL PROPERTIES OF ISOQUINOLINE: The important chemical properties of Isoquinoline are discussed as follow.

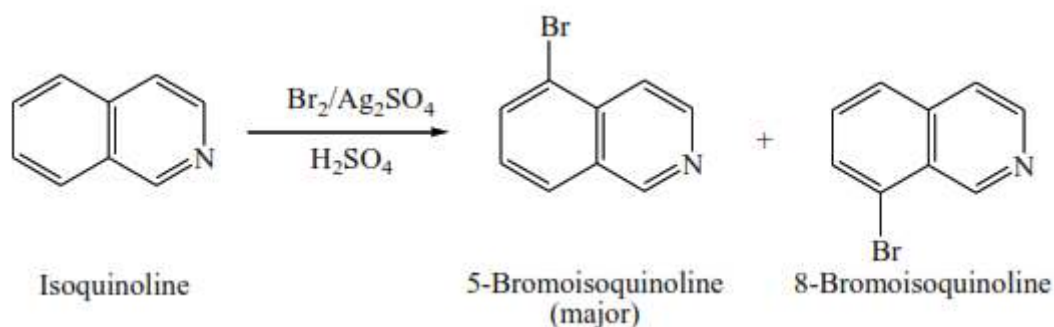
1. **Basicity:** Isoquinoline is moderately basic compound. It reacts with protic acid to form salts, and with alkyl halides to form quaternary ammonium salt.



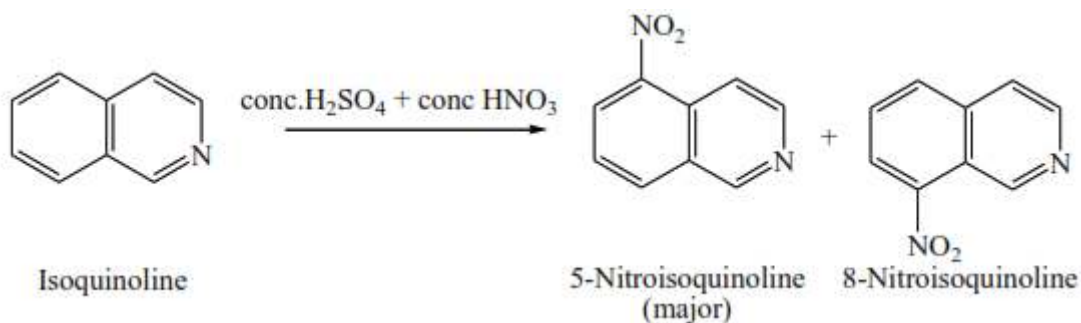
2. **Electrophilic substitution:** Isoquinoline also gives electrophilic substitution like quinoline. Electrophilic substitution on Isoquinoline takes place more preferentially at position 5 however small amount of substitution also occurs at position 8. The different types of electrophilic substitution reactions of Isoquinoline are discussed as follow.

- i. **Bromination:** Isoquinoline undergoes bromination with Br₂ in presence of silver sulphate (Ag₂SO₄) and H₂SO₄. Bromination occurs preferentially at

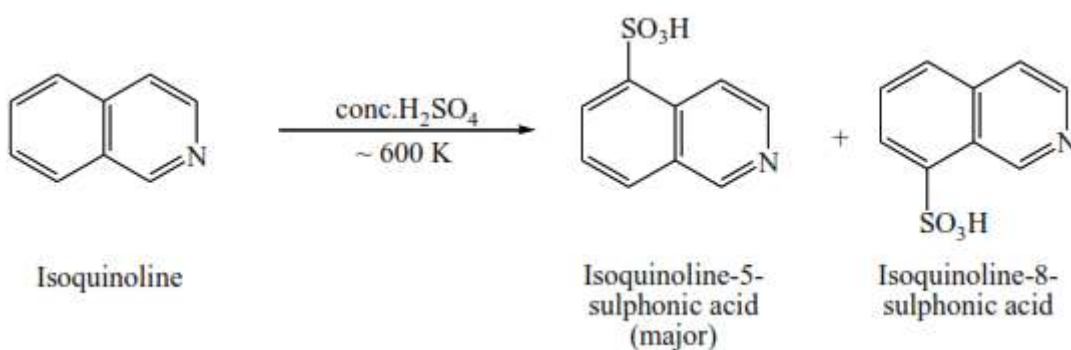
position 5; small amount of product is also formed with substitution at position 8.



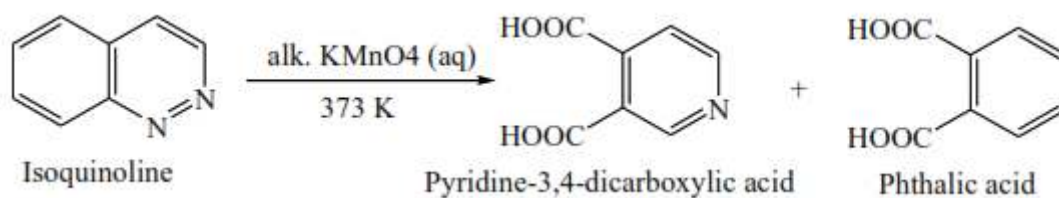
- ii. **Nitration:** Isoquinoline can undergo nitration by reacting with the well known nitrating agent (Conc. H_2SO_4 + conc. HNO_3). Nitration of Isoquinoline occurs preferentially at position 5; small amount of product is also formed with substitution at position 8.



- iii. **Sulphonation:** In presence of Conc. H_2SO_4 at high temperature ($\sim 600\text{K}$) sulphonation of Isoquinoline takes place. Like nitration or bromination, the sulphonation of Isoquinoline occurs preferentially at position 5; small amount of product is also formed with substitution at position 8.



- iv. **Oxidation:** In presence of alkaline KMnO_4 Isoquinoline get oxidized to equimolar mixture of phthalic acid and pyridine-3,4-dicarboxylic acid.



Applications of Isoquinoline: Isoquinolines have various applications as:

1. Isoquinoline and its derivatives are used in the manufacture of dyes, paints, insecticides, disinfectants, anesthetics, antihypertension agents and antifungal agents.
2. It is also used as a solvent for the extraction of resins and terpenes, and as a corrosion inhibitor.