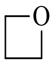
# B.Sc. VI Semester
# Paper: I Organic Synthesis-B
# Unit: VII Heterocyclic Compounds

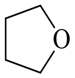
Organic cyclic compounds having one atom other than carbon in their ring formation are designated as “heterocyclic compounds”. Now a day various heterocyclic compounds containing nitrogen, sulphur, oxygen and other hetero atoms are known. The organic compounds having heterocycles nucleus in central position perform biological activities in several agrochemical and pharmaceutical areas.

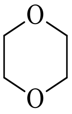
**Classification:** According to chemical behavior, heterocyclic compounds have been classified into following categories.

**1. Non-aromatic or aliphatic heterocyclic compounds:** If alicyclic compounds having one or more heteroatom in their rings are called non-aromatic or aliphatic heterocyclic compounds. These heterocyclic compounds do not have double bond. Hence, it is also called saturated heterocyclic compounds. Some examples are as follows.


oxirane


oxetane

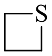

tetrahydrofuran

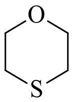

1,4-dioxane

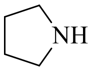

aziridine

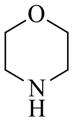

azetidine

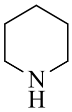

thiirane


thietane


1,4-oxathiane


pyrrolidine

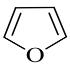

morpholine

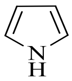

piperidine

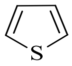
**2. Aromatic heterocyclic compounds:** If aromatic ring contains one or more heteroatom in their ring is called aromatic heterocyclic compounds.

On the basis of size of ring aromatic heterocyclic compounds are classified into following categories.

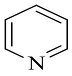
i. Five membered heterocyclic compounds containing one heteroatom: For example,


Furan

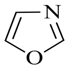

Pyrrole

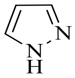

Thiophene

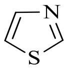
ii. Six membered heterocyclic compounds containing one heteroatom: For example,

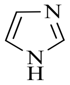

Pyridine

iii. Five membered heterocyclic compounds containing two heteroatoms: For example,

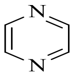

Oxazole

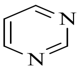

1H-Pyrazole

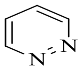

Thiazole


1H-Imidazole

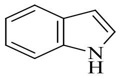
iv. Six membered heterocyclic compounds containing two heteroatoms: For example,

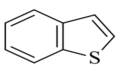

Pyrazine

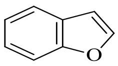

Pyrimidine

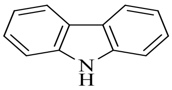

Pyridazine

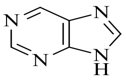
v. Five membered heterocyclic rings condensed with benzene ring: For example,


Indole

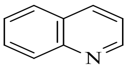

Benzo[β]thiophene

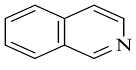

Benzofuran


Carbazole


Purine

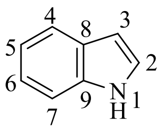
vi. Six membered heterocyclic rings condensed with benzene ring: For example,


Quinoline


Isoquinoline

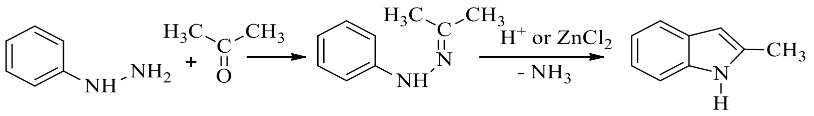
## Condensed five membered heterocyclic systems

**Indole:** Indole was first prepared by Baeyer in 1866 by zinc dust distillation of oxindole. It occurs in coal-tar, jasmine flowers etc. Indole is the parent substance of indigotin. The IUPAC name of indole is 1H-benzo [b] pyrrole, it being the b-face benzo-fused isomer. The numbering starts from heteroatom (N) and going anticlockwise direction around the two condensed rings.

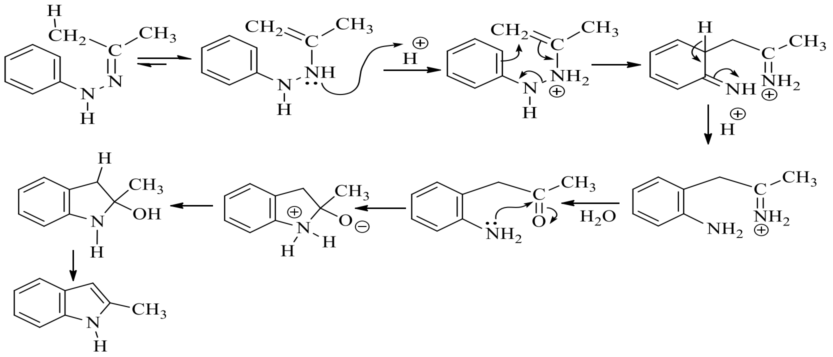


**Synthetic Methods of Indole:**

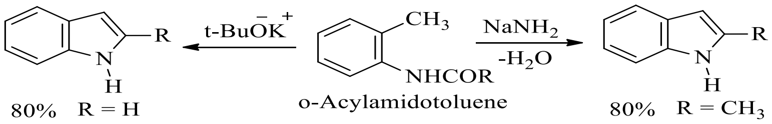
**1. Fischer's Indole synthesis:** Indole is prepared by heating the phenyl hydrazone or substituted phenylhydrazone of an appropriate aldehyde and ketone with zinc chloride, polyphosphoric acid, sulphuric acid in ethanol etc.



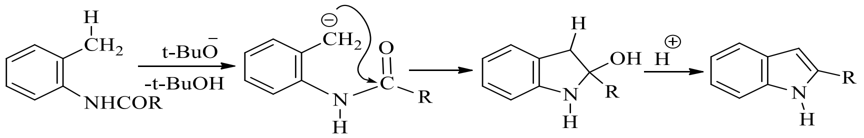
**Mechanism:**



**2. Madelung Synthesis:** o-acylamidotoluene treated with strong base such as potassium tert-butoxide or sodamide, it produces 2-alkylindoles.



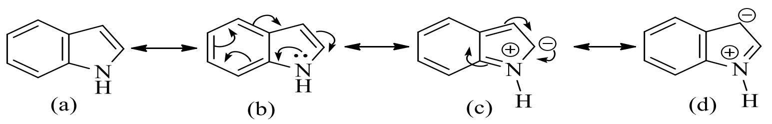
**Mechanism:**



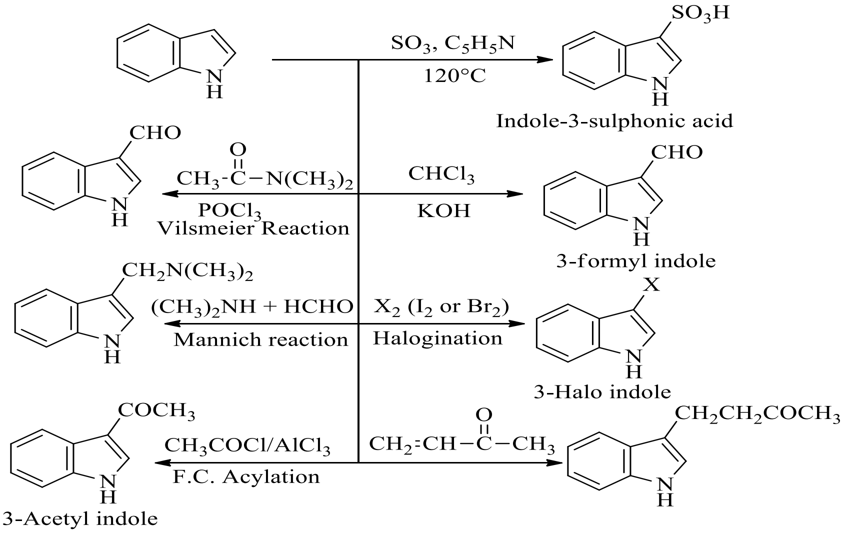
**Properties:** It is a crystalline solid with a pleasant smell. Its melting point 52°C.

**Chemical Properties:** The chemical properties of indole are similar to pyrrole.

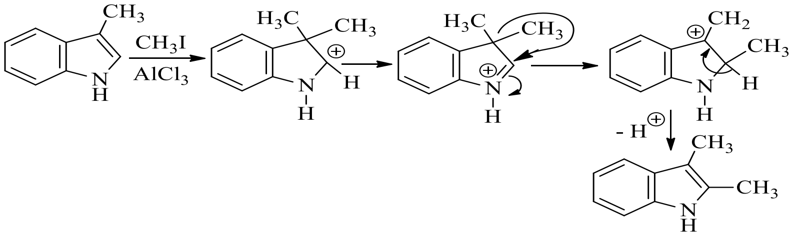
**1. Electrophilic Substitution:** Indole is a planar molecule with a conjugated system of 10$\pi$-electrons, two from the nitrogen and eight from the carbon atoms and is thus $\pi$-excessive molecule. It is considered a resonance hybrid of the following canonical forms.



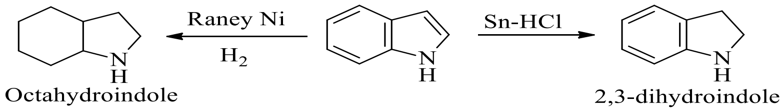
Its resonance energy is about 47 kcal/mole. From the resonance structures it may be noted that structures (a), (b) and (d) are the only ones in which the benzenoid 6$\pi$-system is preserved. Presence of high electron density at the 3-position indicates that electrophilic substitution occurs at 3-position.



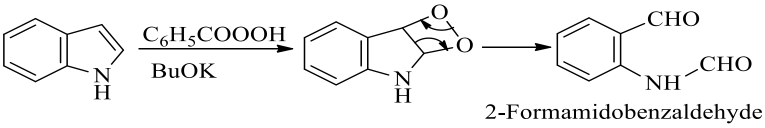
If position-3 of indole is substituted then electrophilic substitution occurs at position-2 through 3,3-disubstitution.



**2. Reduction:** Indole on reduction with Sn-HCl and $H_2$/raney Ni gives dihydro and octahydroindole respectively.

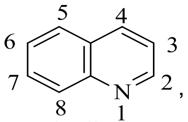


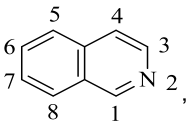
**3. Oxidation:** Indole on oxidation with perbenzoic acid in potassium butoxide gives 2-formamidobenzaldehyde.

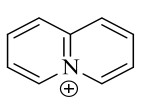


## Condensed Six membered Heterocyclic compounds

When benzene ring fused with six-memberd heterocyclic ring called condensed six membered heterocyclic compounds e.g. pyridine fused with benzene in different position in quinolone, isoquinoline and quinolzenium salt.

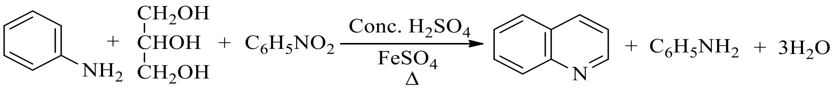

Quinoline


Isoquinoline

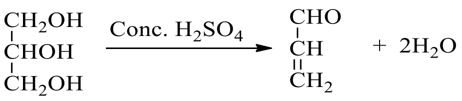

Quinolizinium salt

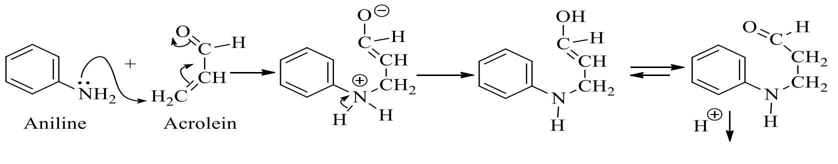
**Quinoline: or ($\alpha,\beta$-Benzopyridine)**: In quinoline, benzene ring is fused with pyridine ring at $\alpha,\beta$-positions. It occurs in coal tar, bone oils etc. and its nucleus is also present in natural antimalarial alkaloid-quinine and cinconine, in synthetic antimalarials-chloroquine and pamaquine, in analgesisc drug-cinchopen.

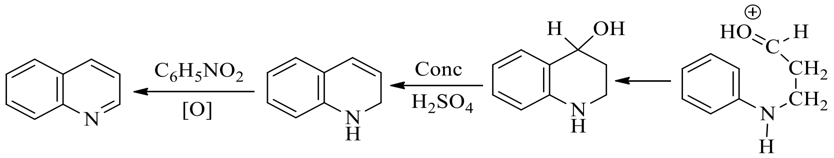
**1. Skraup Synthesis:** In this method, the preparation of quinoline is carried out by heating mixture of aniline, glycerol and concentrate sulphuric acid in presence of nitrobenzene and ferrous sulphate.



**Mechanism:**


$$\begin{array}{l}CH_2OH\\ |\\ CHOH\\ |\\ CH_2OH\end{array} \xrightarrow{\text{Conc. } H_2SO_4} \begin{array}{l}CHO\\ |\\ CH\\ \|\\ CH_2\end{array} + 2H_2O$$





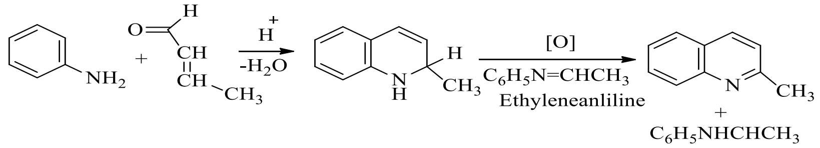
**2. Doebner-Miller synthesis:** This method is similar to Skraup synthesis. In this method, crotonaldehyde is used in place of acrolein. Crotonaldehyde is obtained through aldol condensation. In such reaction ethyleneaniline is formed by reaction of aniline and acetaldehyde, which is used for oxidation.

$$2CH_3CHO \xrightarrow[\Delta]{NaOH} CH_3-CH=CH-CHO$$

But-2-enal (Crotonaldehyde)

$$CH_3CHO + C_6H_5NH_2 \xrightarrow[\Delta]{\overset{+}{H}} C_6H_5-N=CH-CH_3$$

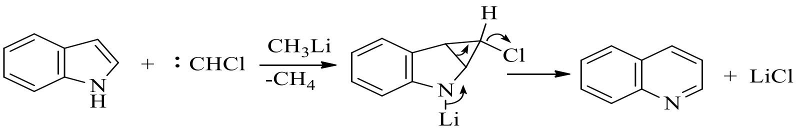
N-Ethylideneaniline



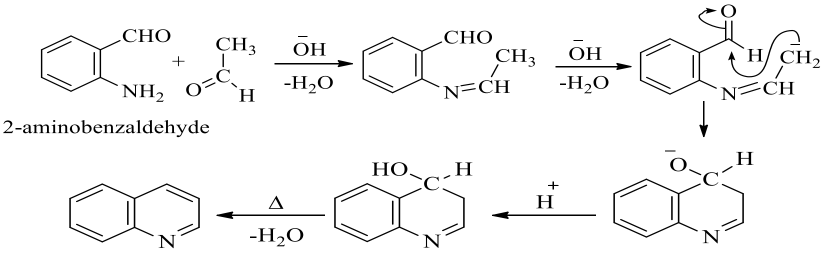
**3. From indole:** When indole is added into mixture of dichloromethane and methyl lithium, it gives quinoline.

$$CH_2Cl_2 + CH_3Li \longrightarrow :CHCl + LiCl + CH_4$$

Chloromethylene

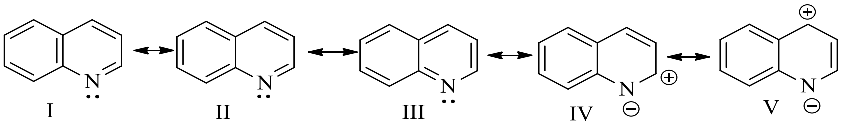


**4. Friedlander's synthesis:** When o-aminobenzaldehyde or ketone condenses with an aliphatic aldehyde or ketone having active methylene group adjacent to carbonyl group in presence of aqueous base to produce quinoline and its derivatives.



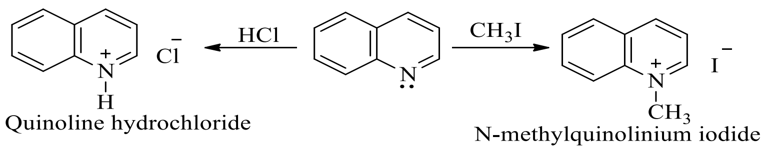
**Properties:** It is a colourless, volatile liquid with unpleasant smell. It is sparingly soluble in water but soluble in organic solvent like alcohols, ethers etc.

**Chemical Properties:** It gives the properties of both benzene and pyridine. The resonance structure of quinoline is as follow:

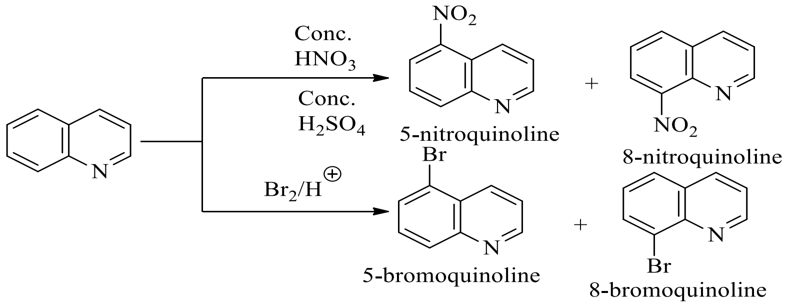


The pyridine ring has $\pi$-electron deficiency (IV and V) due to presence of more electronegative N-atom than benzene ring. Therefore, electrophilic substitution reactions occur on benzene ring and nucleophilic substitution reactions occur in pyridine ring.

**1. Basic Character:** As like pyridine, the quinoline is basic in nature because its nitrogen has easily available lone pair of electrons for protonation. It reacts with acid to form salts and quaternary salts with alkyl halide.

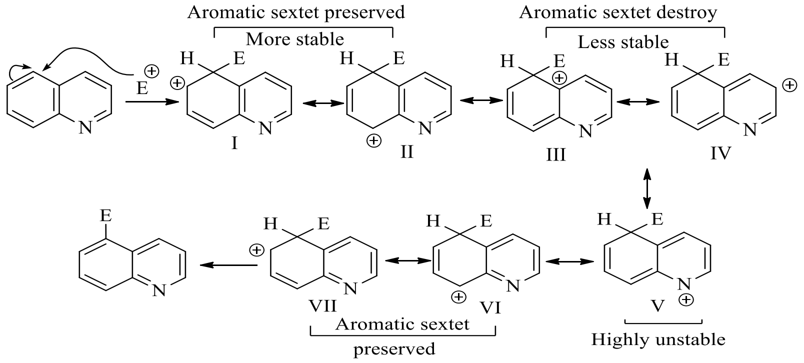


**2. Electrophilic substitution:**

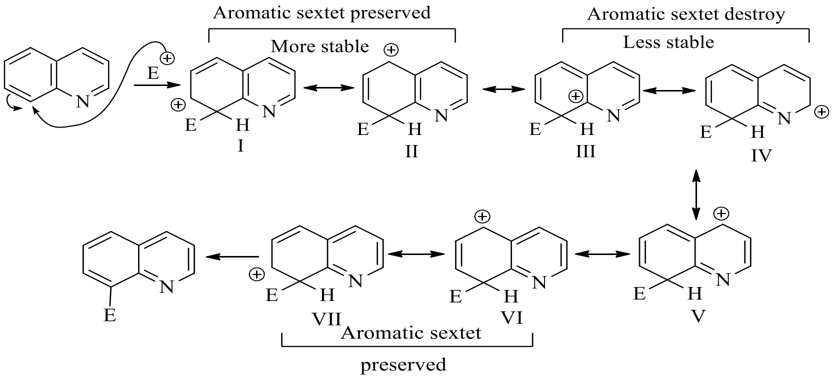


It is clear that from above reaction, the next incoming electrophile attached at benzene ring rather than pyridine ring. This is due to the pyridine ring is particularly deactivated by nitrogen atom. It is also seen that the substituents attach at C-5 and C-8 position in benzene ring. This can be explained by comparing the relative stabilities of intermediate carbocation formed when electrophile $(E^+)$ attacks at different position.

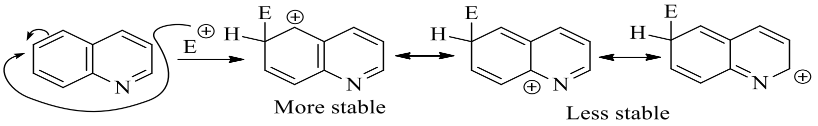
**Attack at 5-Position:**



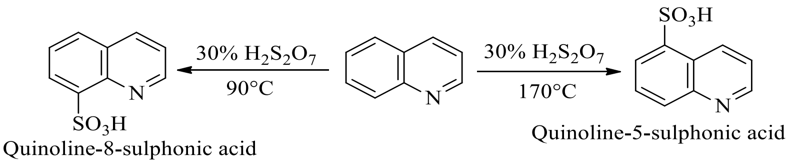
**Attack at 8-Position:**



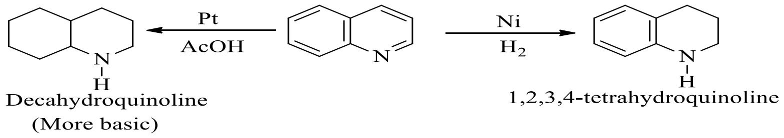
Similar, attack at 6- and 7-positions gives only one stable intermediate carbocation's in each case and remaining unstable structures. Thus, preferential attack takes place at 5- and 8- position.



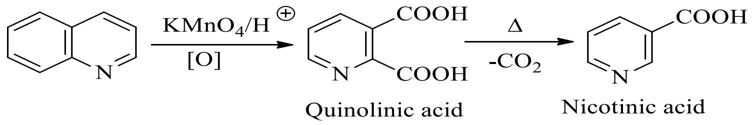
**Sulphonation:** Sulphonation of quinoline gives rise to different mono substituted products depending on the reaction temperature.



**3. Reduction:** On catalytic reduction, the pyridine ring is reduced to form tetrahydroquinoline. Benzene ring is difficult to reduce but on reduction with platinum in acetic acid complete reduction occurs.

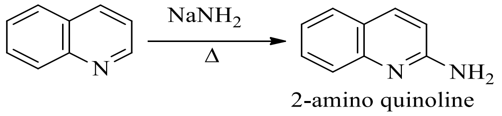


**4. Oxidation:** On vigorous oxidation with potassium permanganate, it can be oxidized to quinolinic acid which on heating gives nicotinic acid. The benzenes ring being less stable than pyridine undergoes oxidation.

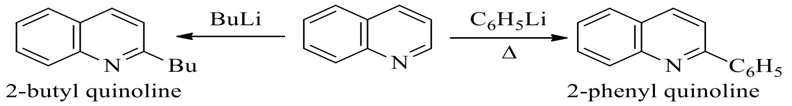


**5. Nucleophilic substitution:** As like pyridine, quinoline gives nucleophilic substitution reactions at position-2 e.g.

**Amination (Chichibabin reaction):** Quinoline on heating with sodamide gives 2-amioquinoline.

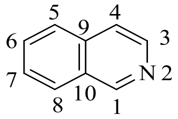


**Alkylation and arylation:** 2-Akyl or phenyl quinolone is formed on heating quinoline with alkyl or phenyl lithium.



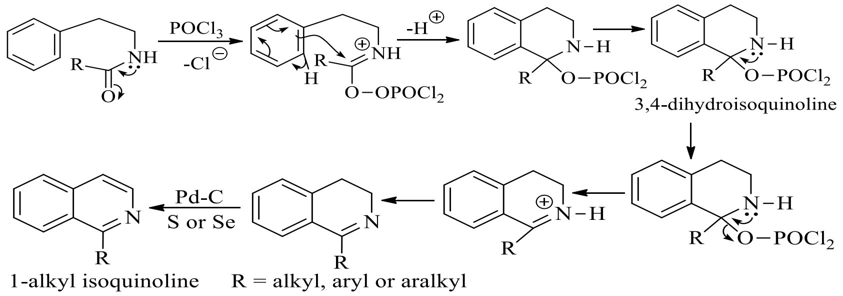
## Isoquinoline

Isoquinoline is structural isomer of quinoline. It is present in number of alkaloids like paperverine (opium alkaloid), norcotine etc. It is called 2-azanaphthalene or benzo [b] pyridine.

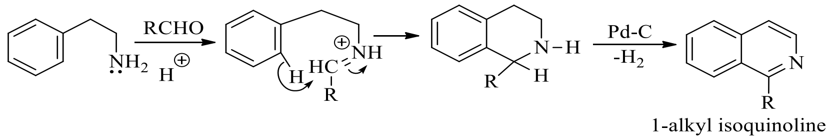


**Synthetic Methods:**

**1. Bischler-Napieralski synthesis:** In this method, acyl derivative of $\beta$-phenyl ethylamine is heated with phosphoryl chloride in boiling xylene afford 3, 4-dihydroisoquinoline derivatives which after dehydrogenation give the isoquinoline and its derivatives.

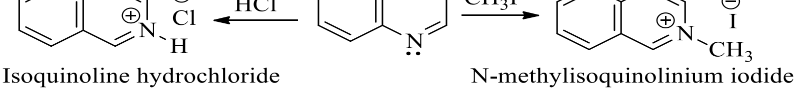


**2. Pictet-Spengler synthesis:** $\beta$-aryl ethylamine condenses with an aldehyde in presence of excess HCl at 373K to form 1,2,3,4-tetrahydroisoquinoline which after subsequent dehydrogenation give the isoquinoline and its derivatives.

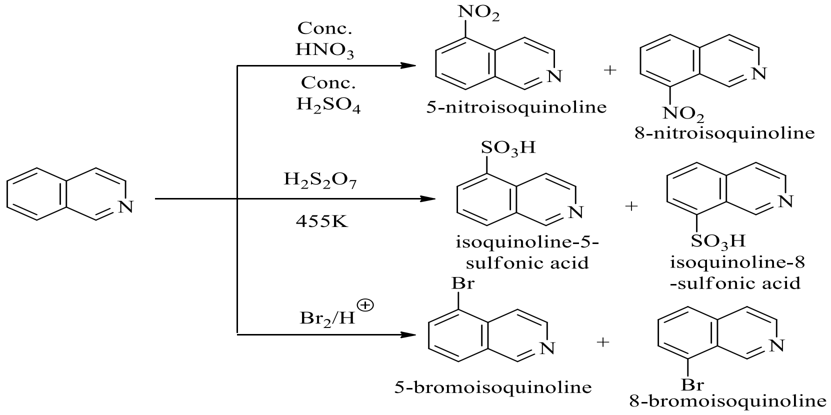


**Chemical Properties:** It resembles quinoline in most of its chemical properties viz. basic character, reduction and electrophilic substitution reactions.

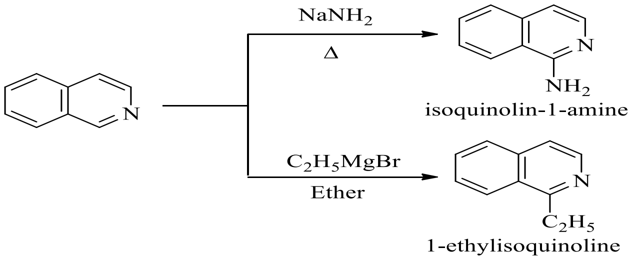
**1. Basic Character:** As like pyridine or quinoline, isoquinoline acts as base due to the availability of a lone pair of electrons on nitrogen atom. It reacts with acid to form salts and quaternary salts with alkyl halide.



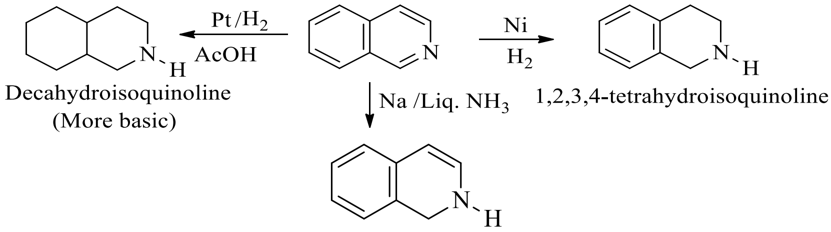
**2. Electrophilic substitution reactions:**



**3. Nucleophilic substitution reactions:** Isoquinoline predominantly gives nucleophilic substitution reaction at position-1 as like pyridine and quinoline.



**4. Reduction:** As like quinoline, the pyridine is reduced readily with sodium in liquid ammonia or Ni/$H_2$ than the benzene ring. Strong reducing agent such as Pt/$H_2$ reduces both rings to give octahydroisoquinoline.



**5. Oxidation:** Unlike quinoline, however, it is oxidized to give a mixture of phthalic acid and cinchomeronic acids.