UNIT –V Heterocyclic Chemistry Quinoline, Isoquinoline and Indole.

Presentation · May 2018

DOI: 10.13140/RG.2.2.10944.43524

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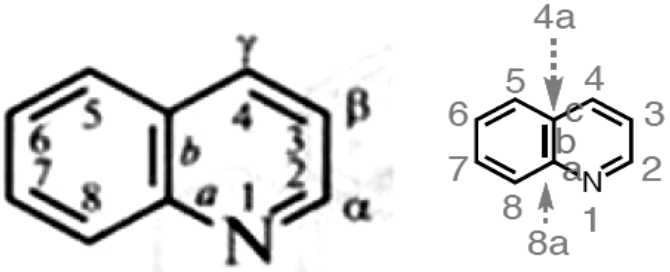
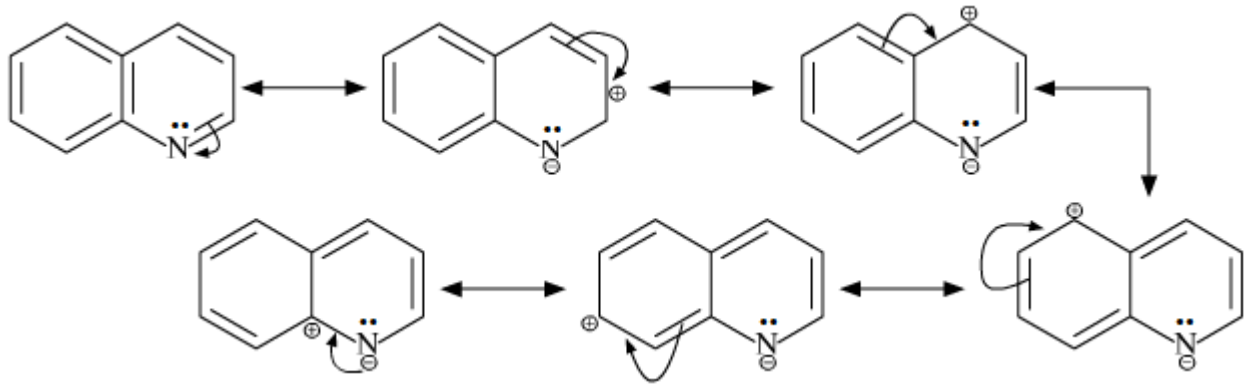
QUINOLINE

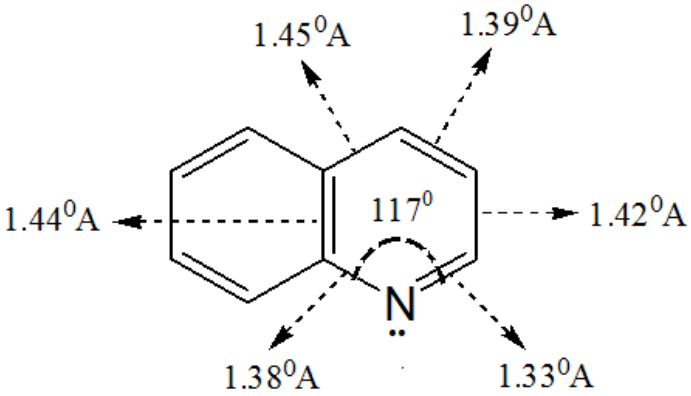
- Quinoline is a heterocyclic aromatic organic compound with the chemical formula C_9H_7N.
- Quinoline (benzo[b]pyridine) is a fused heterocyclic system consisting of a benzene ring fused with pyridine cycle. It can be also considered as the heterocyclic analogue of naphthalene (1-azanaphthalene).
- ***Systematic IUPAC name:*** 1-Benzopyridine; Benzo[b]pyridine; Benzo[b]azine; Benzo[b]azabenzene.
- ***Other names:*** 1-Azanaphthalene; 1-Benzazine; Benzazine; Benzazabenzene; Benzopyridine; Quinolin; Chinoline; Chinoleine; Chinolin; Leucol; Leukol; Leucoline.
- Quinoline is a colourless liquid with an unpleasant odour and boiling point 237^0C. It is miscible with water, ethanol and ether; it may be distilled by steam distillation.



- *Structure of Quinoline:*

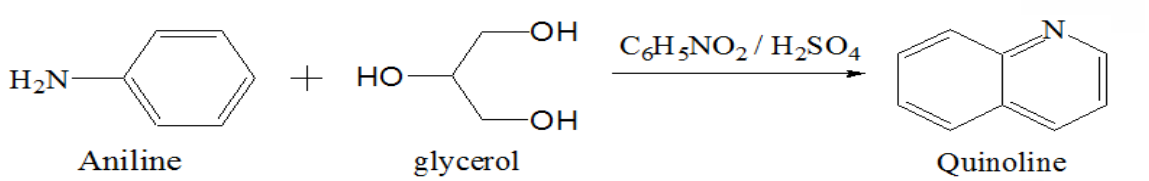
- All ring atoms in Quinoline are SP^2 hybridize.
- The nitrogen lone pair electrons reside in an SP^2 orbital and not involved in the formation of the delocalized **π molecular orbital**.
- It shows aromatic properties because its π orbital contains ten electrons & satisfied the Huckel's rule (n = 2 is 4n+2).
- The resonance of Quinoline:





Bond lengths and angles of Quinoline

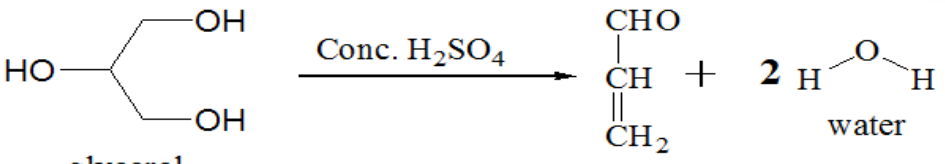
- *Synthesis of Quinoline* (Skraup Synthesis)



Aniline glycerol Quinoline

Mechanism

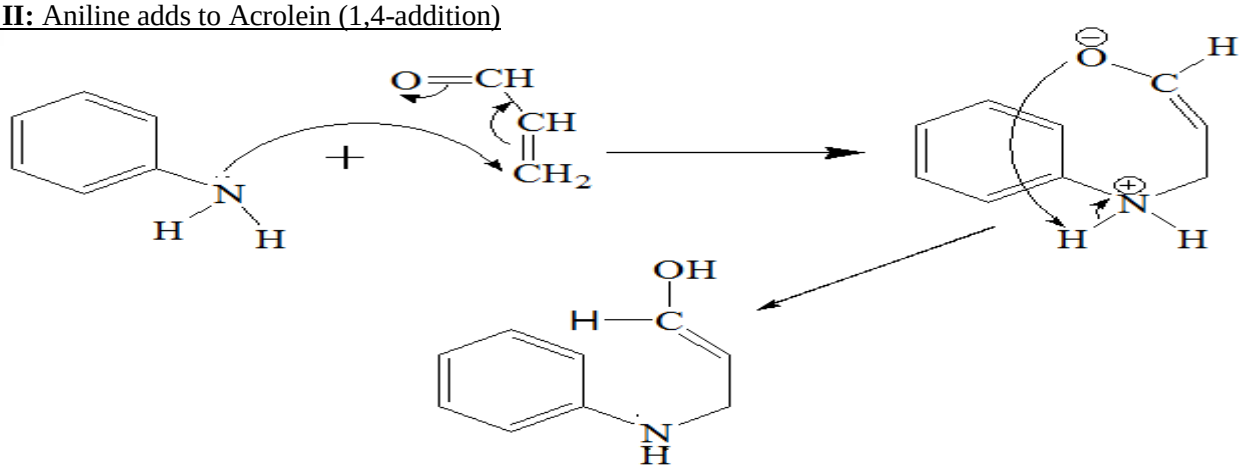
Step I: Glycerol undergoes dehydration with sulfuric acid to give **ACROLEIN**



glycerol water

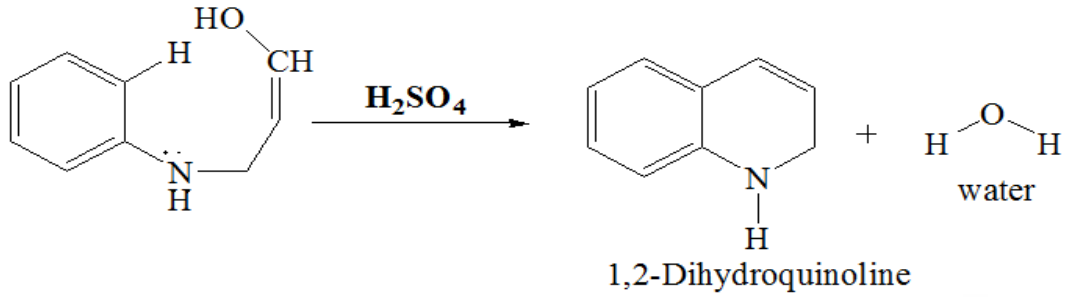
Acrylaldehyde or Acrolein

Step II: Aniline adds to Acrolein (1,4-addition)



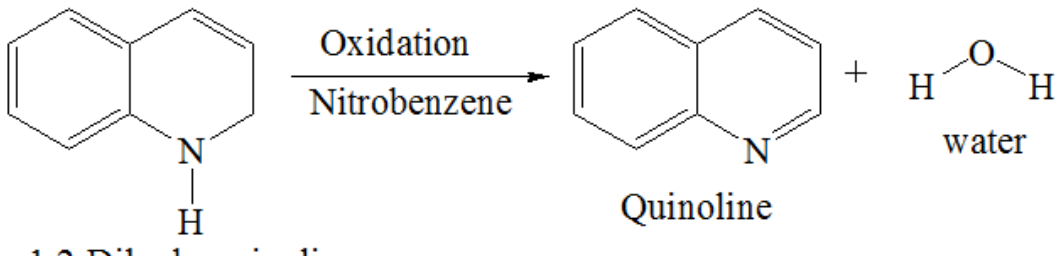
(*E*)-3-(phenylamino)prop-1-en-1-ol

Step III: Undergoes ring closure



1,2-Dihydroquinoline water

Step IV: Oxidation of 1,2-Dihydroquinoline

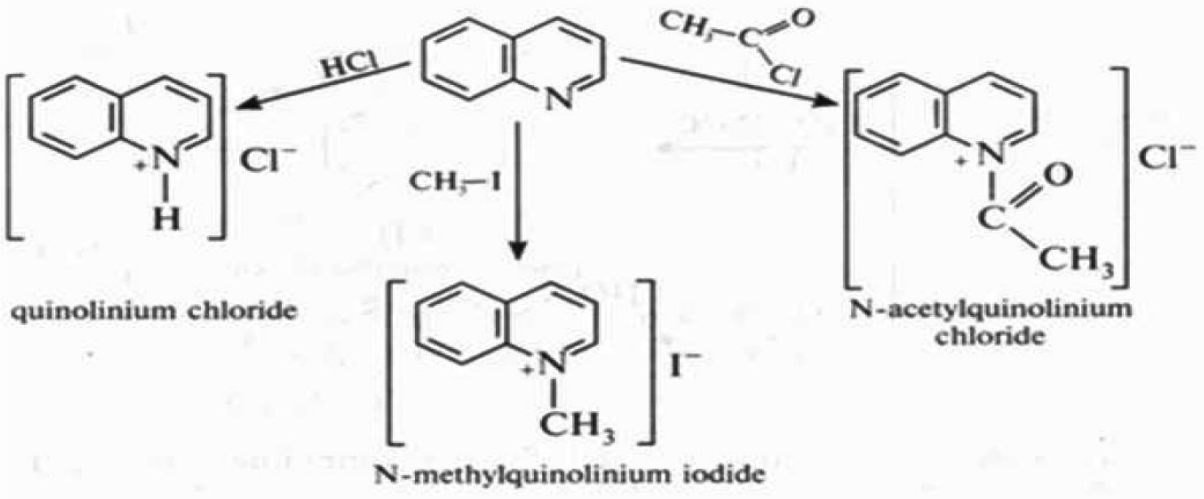


1,2-Dihydroquinoline Quinoline water

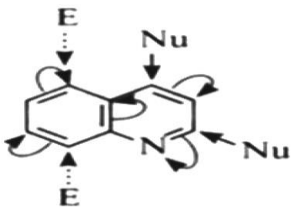
- *Chemical properties of Quinoline*

- The most typical reactions for quinoline are:
  i. Heteroatom reactions
  ii. Electrophilic and nucleophilic substitution reactions;
  iii. Oxidation and reduction.

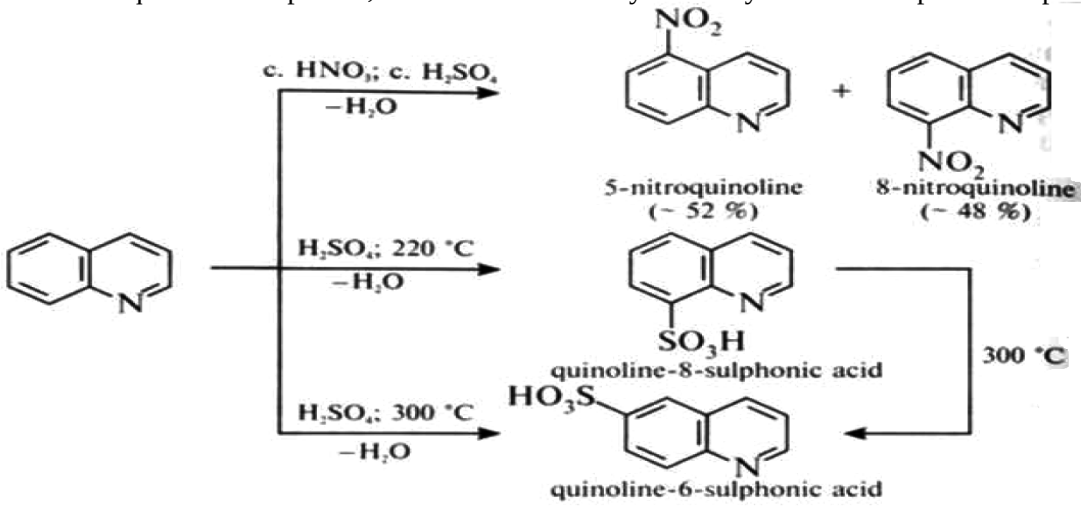
1. **Heteroatom reactions: T**he nitrogen in Quinoline, which undergoes protonation, alkylation, acylation, etc. Quinoline is a weaker base than pyridine. ($pKBH^+$ of quinoline in H_2O is 4.94)



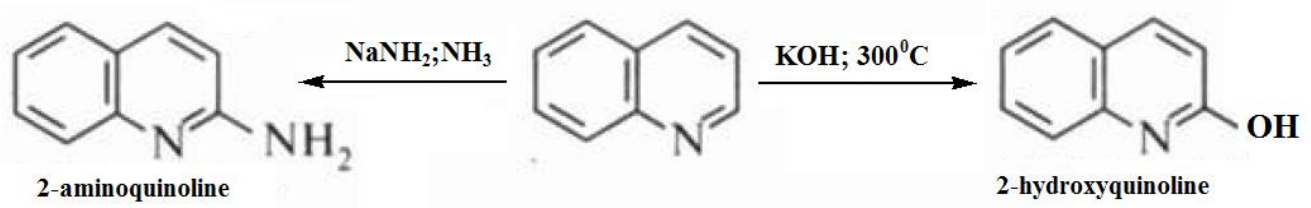
2. **Electrophilic and nucleophilic substitution reactions:**
   - ✓ *Electrophilic substitution* reactions occur on the ring **C-atoms**, mainly on those of the more activated benzene moiety. Nucleophilic substitution of quinoline occurs in the electron deficient pyridine ring, as a rule in the position 2 or 4.



   - ✓ *Electrophilic substitution reactions* occur in **positions 5 and 8 of quinoline**. Treatment of quinoline with nitrating mixture results in 5and 8-nitroquinolines. Sulphonation of quinoline produces different products depending on the reaction temperature. At 220°C quinoline8sulphonic acid is formed predominantly; At 300°C, quinoline6sulphonic acid is the sole product. When heating to 300°C quinoline8sulphonic acid is converted into quinoline6sulphonic, which is the thermodynamically favoured Sulphonation product.

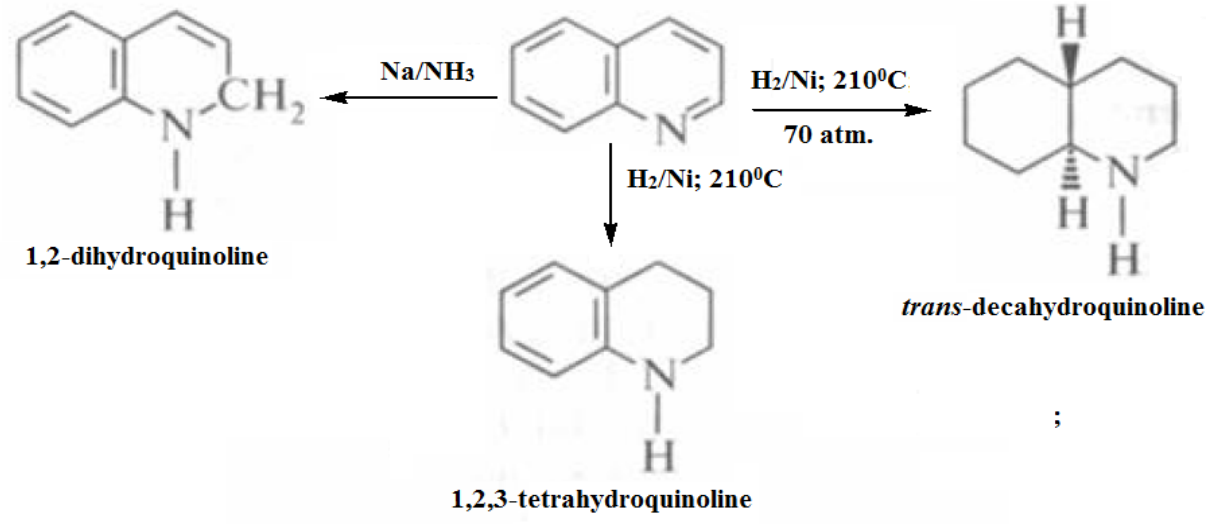


- ✓ ***Nucleophilic substitution*** proceeds faster in quinoline than in pyridine. Nucleophilic substitution of quinoline occurs in the heterocyclic ring, as a rule in the **position 2**.



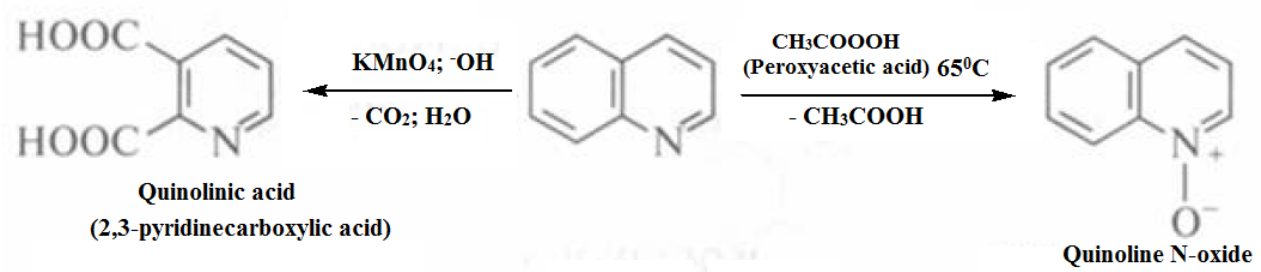
3. ***Oxidation and reduction reactions.***

- ✓ The pyrimidine ring is hydrogenated prior to the benzene ring of quinoline. The product of reduction depends much upon the reaction conditions.



;

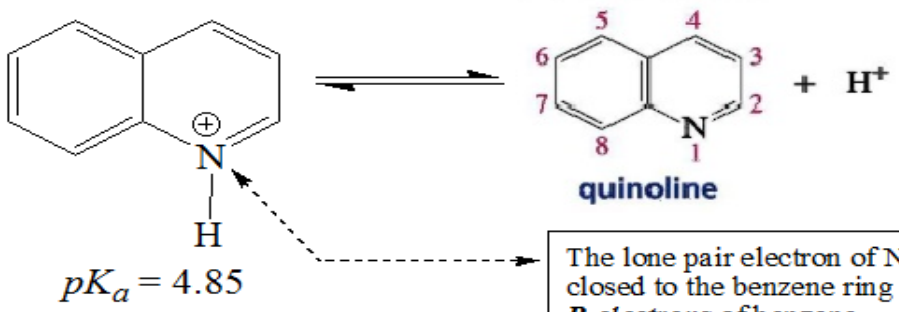
- ✓ The alkaline permanganate solution causes oxidative cleavage of the benzene ring in quinoline to give quinolinic acid (pyridine 2,3-dicarboxylic acid). The reaction of quinoline with peroxycarboxylic acids leads to its N-oxide.



- *Basicity of Quinoline & Isoquinoline*

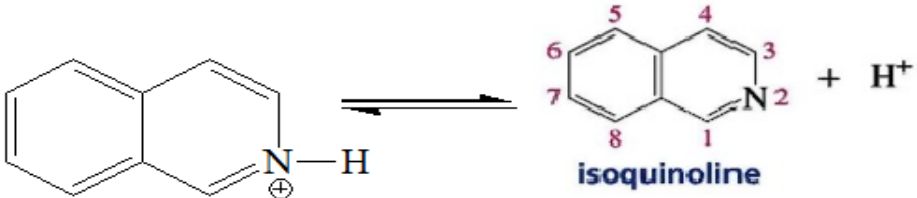
✓ Isoquinoline is a stronger base than quinoline

N-atom of Quinoline & Isoquinoline are SP^2 hybridize



$pK_a = 4.85$

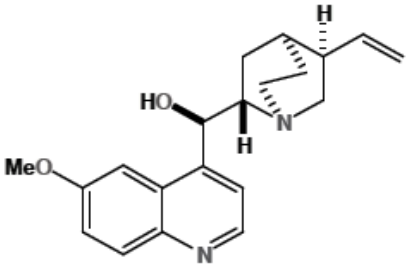
The lone pair electron of N-atom of Quinoline are closed to the benzene ring & thus get involved with ***P-electrons*** of benzene.
(Just a kids play with neighbor kid)



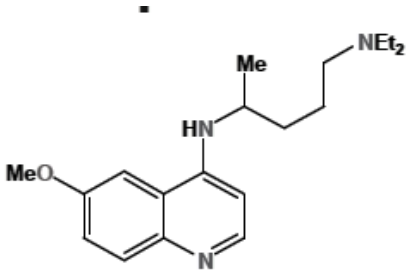
$pK_a = 5.14$

The lone pair electron of N-atom of Isoquinoline are far from the benzene ring & thus get not involved with ***P-electrons*** of benzene.
(no neighbor kids to play with)

- *Bioactive Quinoline & Isoquinoline*

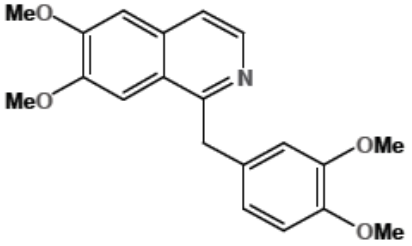


quinine



chloroquine

- Quinine is an anti-malarial natural product isolated from the bark of the *Cinchona* tree
- Chloroquine is a completely synthetic anti-malarial drug that has the quinoline system found in quinine – parasite resistance is now a problem

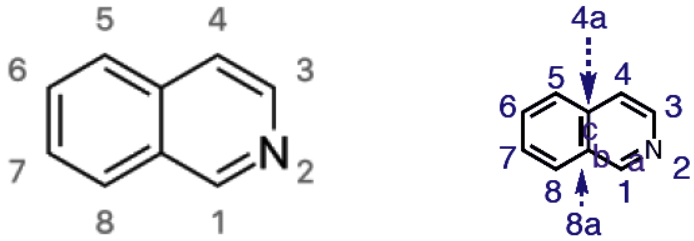


papaverine

- Papaverine is an alkaloid isolated from the opium poppy and is a smooth muscle relaxant and a coronary vasodilator

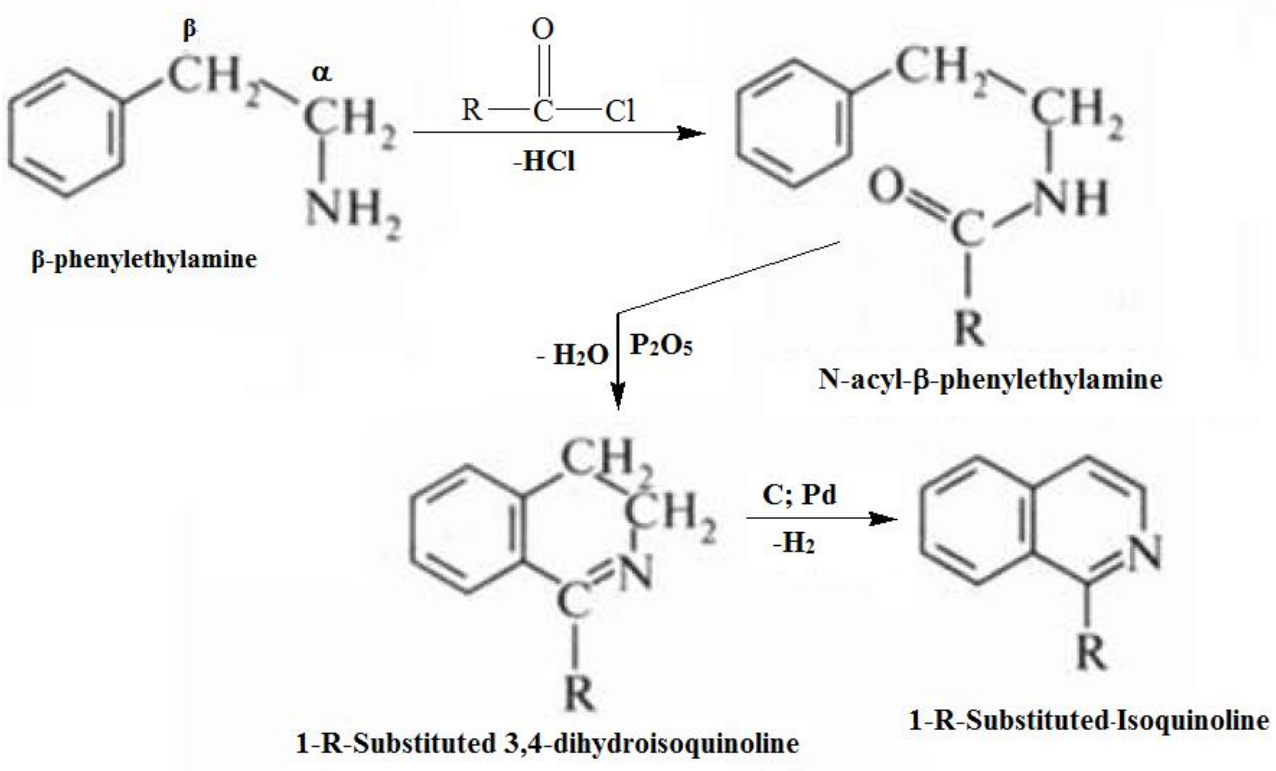
ISOQUINOLINE

- Isoquinoline is a heterocyclic aromatic organic compound. It is a structural isomer of quinoline. Isoquinoline and quinoline are benzopyridines, which are composed of a benzene ring fused to a pyridine ring.



(IUPAC name Isoquinoline; other names: 2-azanaphtalene, Benzo[*c*]pyridine, 2-benzanine)

- ***Properties***
  - Isoquinoline is a colorless hygroscopic liquid at room temperature.
  - It crystallizes platelets that have a low solubility in water but dissolve well in ethanol, acetone, diethyl ether, carbon disulfide, and other common organic solvents. It is also soluble in dilute acids as the protonated derivative.
  - Isoquinoline is a crystalline substance with a quinoline like odour; Its melting point is 24.6°C.
- ***Synthesis of Isoquinoline***
  - In the ***Bischler-Napieralski*** reaction a β-phenylethylamine is acylated and cyclodehydrated by a Lewis acid, such as phosphoryl chloride or phosphorus pentoxide.

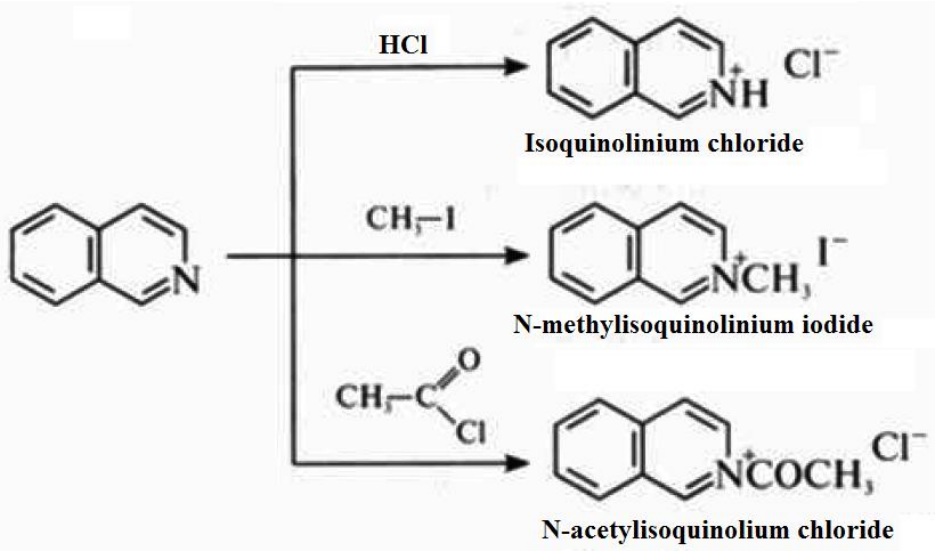


E-mail: logonchemistry@yahoo.co.in; chloroform@hotmail.com

- ***Chemical properties***

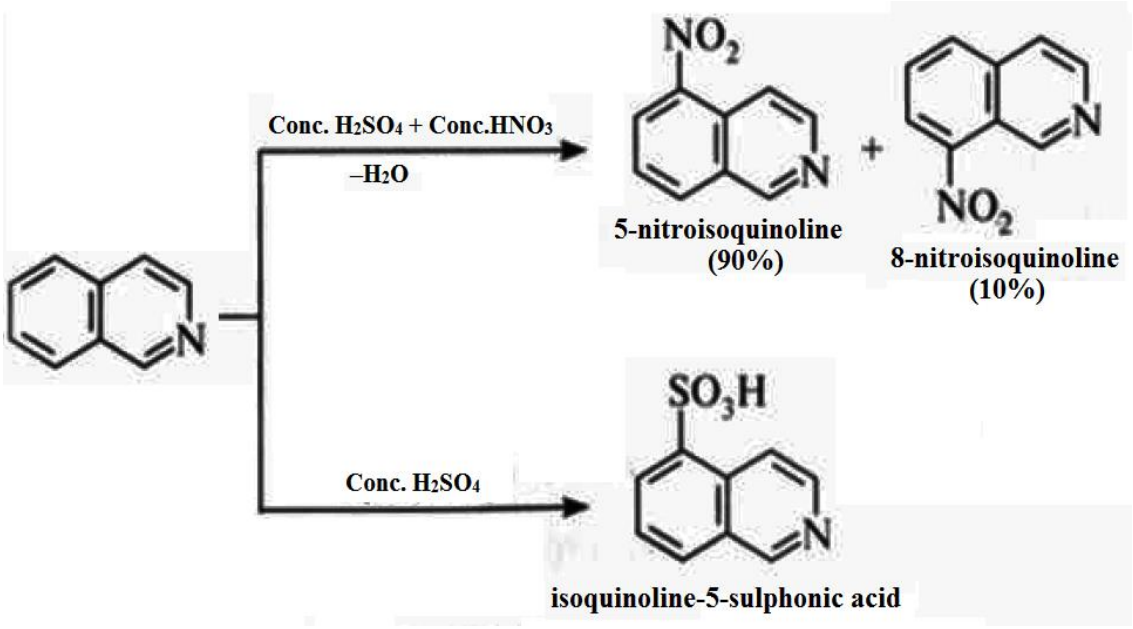
- The reactions of isoquinoline are closely parallel to those of quinoline.
- Isoquinoline reacts with strong mineral acids to form salts. Isoquinoline is a stronger base than quinoline.

1. Alkylation and acylation occur on nitrogen

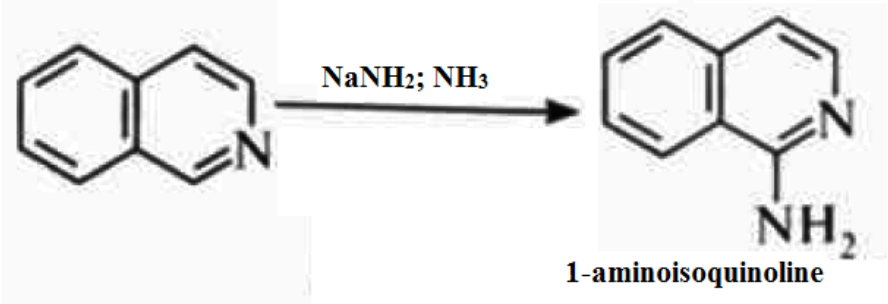


2. Reactions of electrophilic and nucleophilic substitution:

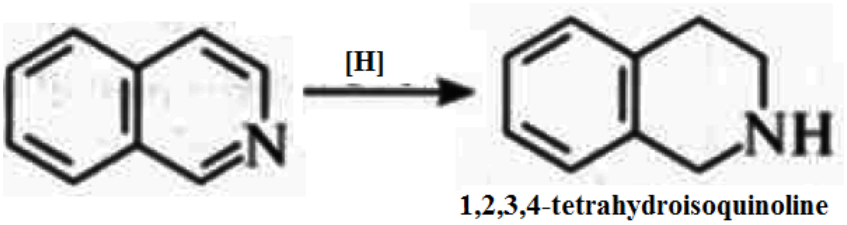
- Similarly to quinoline electrophilic substitution reactions occur mainly in the **5**or **8 position** of isoquinoline.



- Nucleophilic reactions take place on the heterocyclic ring, prefer ably in the **1-position**.

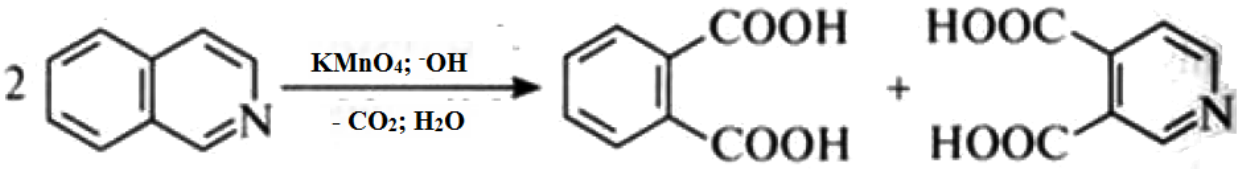


3. ***Reduction reactions:*** Reduction of isoquinoline is more complicated than those for quinoline.

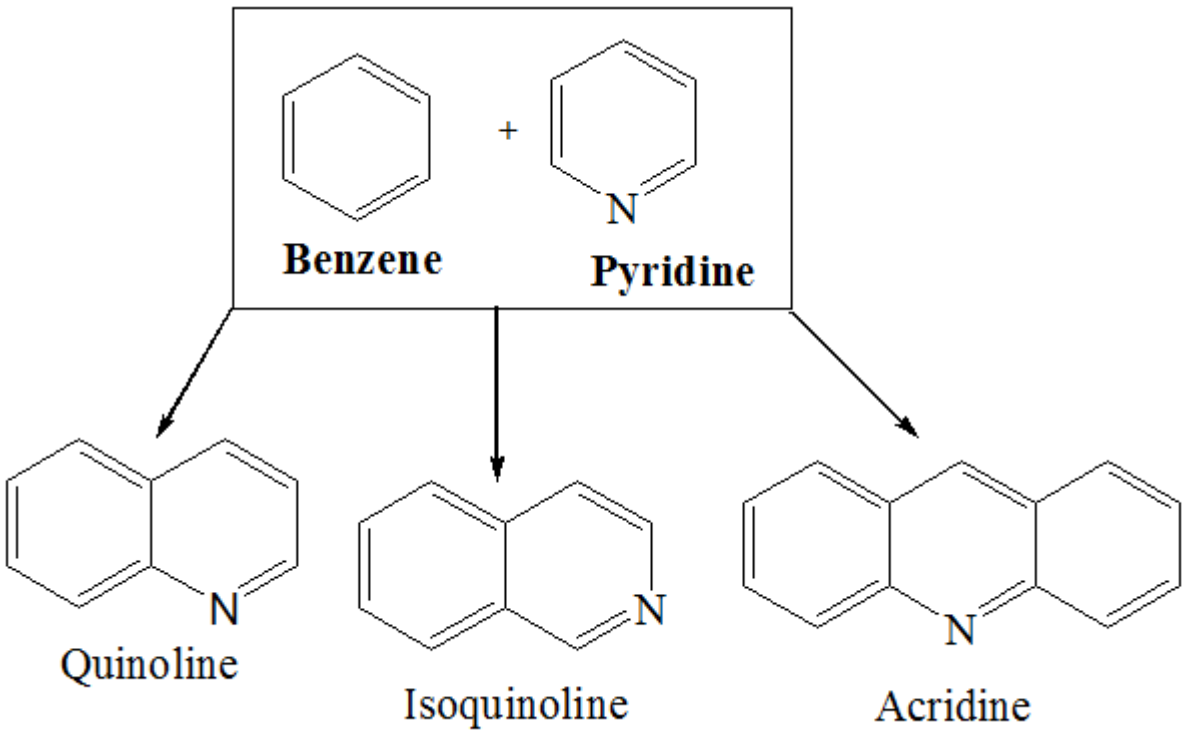


1,2,3,4-tetrahydroisoquinoline

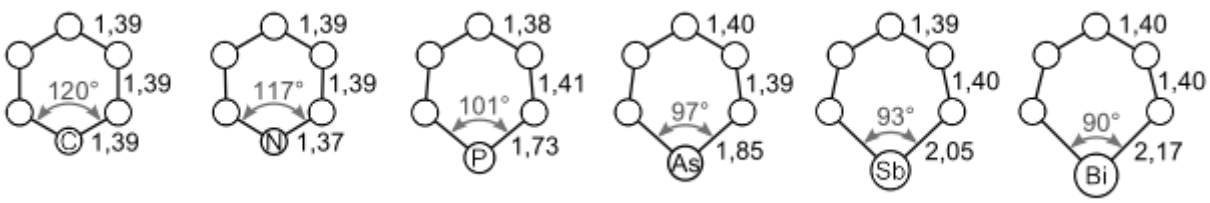
❖ ***Oxidation reactions:*** Oxidation of isoquinoline with alkaline permanganate solution yields a mixture of *phthalic acid* and *pyridine3,4-dicarboxylic acid*.



Phthalic acid **Pyridine-3,4-dicarboxylic acid**



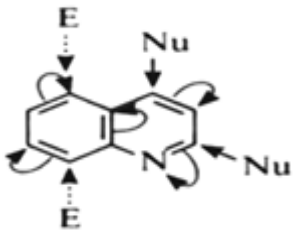
Bond length (^{0}A) & Bond angle (^{0})



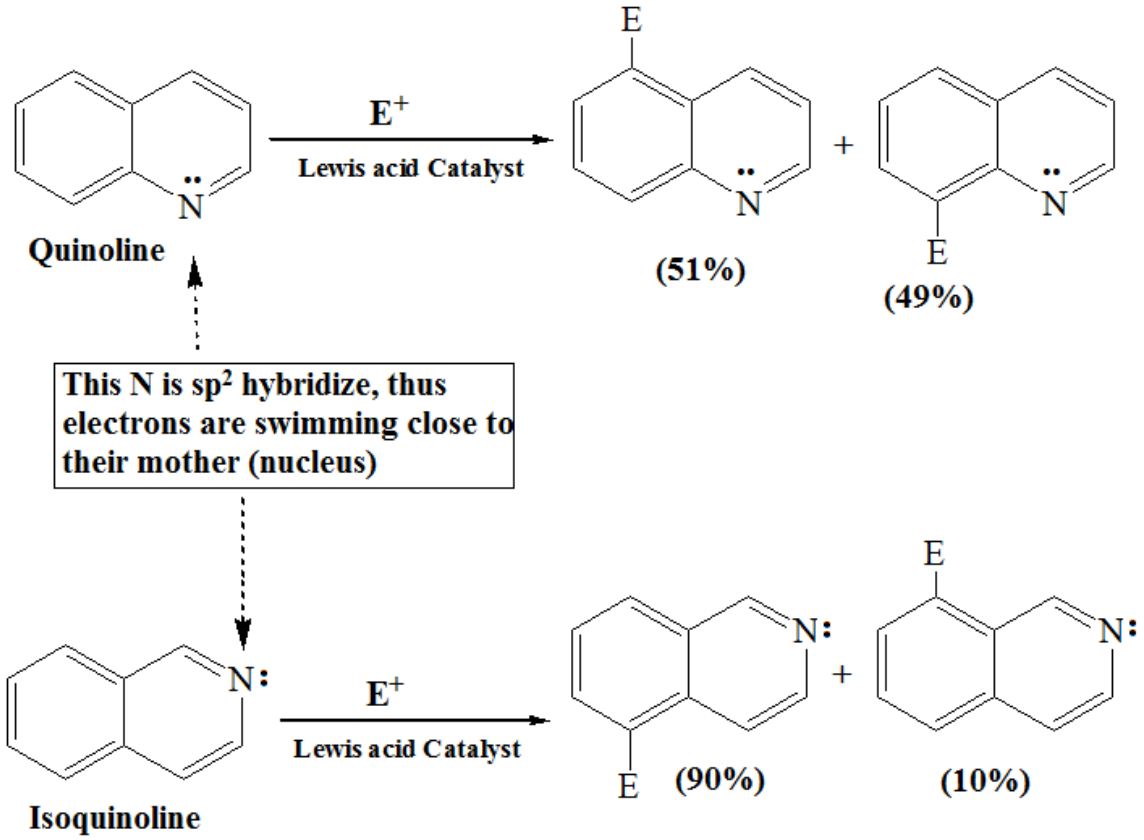
E-mail: logonchemistry@yahoo.co.in; chloroform@hotmail.com

❖ Reactivity of Quinoline & Isoquinoline

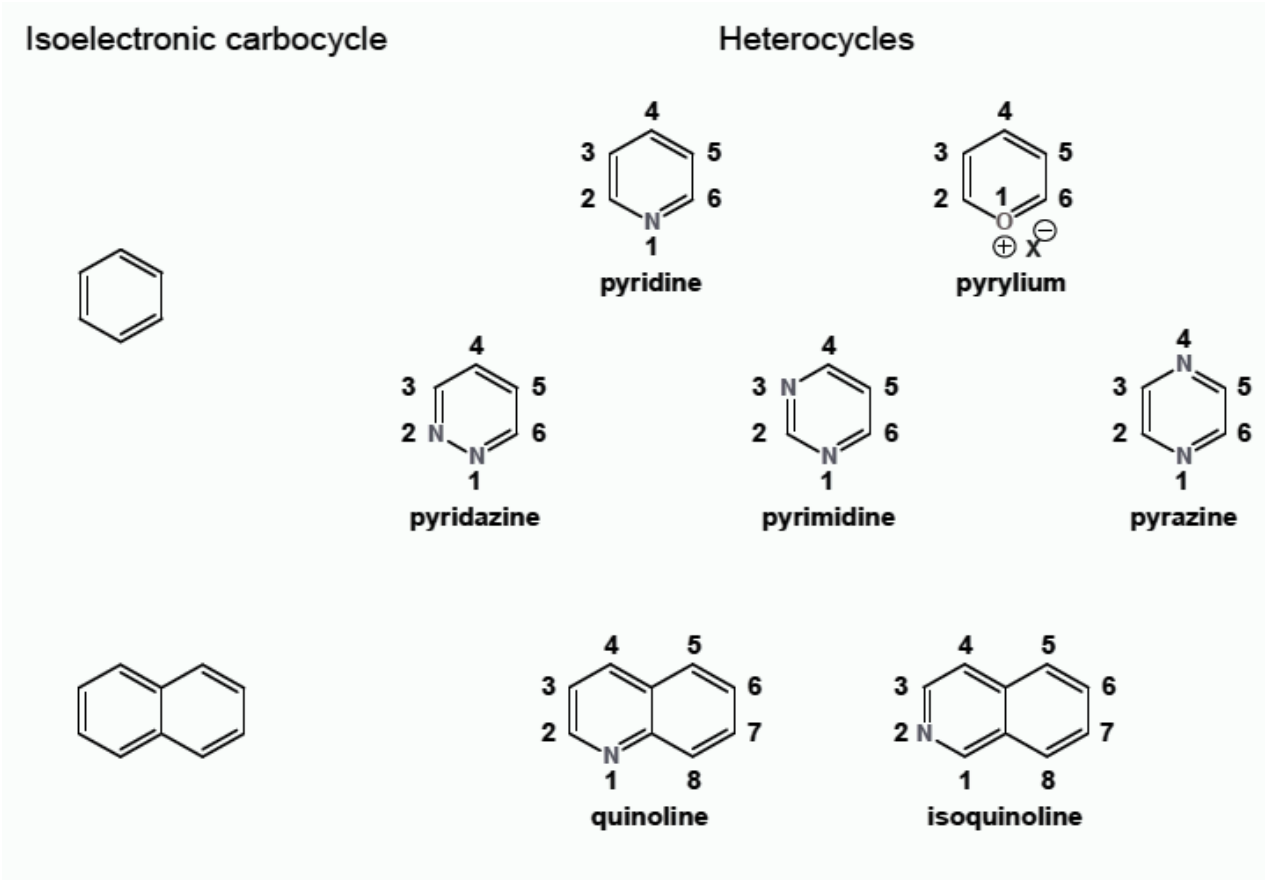
- Quinoline & Isoquinoline both have
  i. Have basic, pyridine like nitrogen atoms, which undergo electrophilic substitutions.
  ii. Are less reactive toward electrophilic substitution than benzene because of the nitrogen atom that withdraws electrons from the ring.
  iii. Electrophilic substitution occurs on the benzene ring rather than on the nitrogen-containing pyridine ring and a mixture of substitution products is obtained.



- In quinoline and isoquinoline the **N-atom** withdrawn electron in **pyridine ring** thus few are available for Electrophilic Aromatic Substitution (EAS), therefore $\mathbf{E}^+$ prefers to go to **benzene**.



❖ Classification-Aromatic Six-Membered



❖ Classification – Aromatic Five-Membered