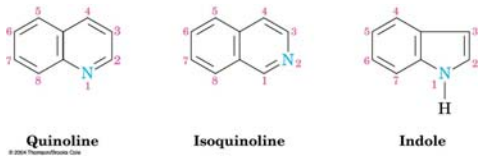
Fused-Ring Heterocycles

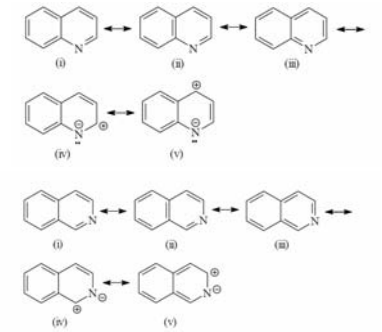
- Quinoline, isoquinoline, and indole are fused-ring heterocycles, containing both a benzene ring and a heterocyclic aromatic ring



Fused-Ring Heterocycles

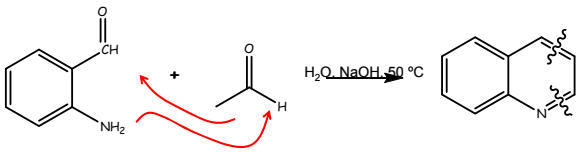
- Quninoline and isoquinoline are two fused heterocycles derived by fusion of pyridine ring with a benzene ring.
- Quinoline is high boiling liquid (b.p. 237°C) and smells like pyridine while isoquinoline is a low melting solid (m.p. 26.5°C, b.p. 243°C).
- Both quinoline and isoquinoline are planar 10π-electron aromatic systems in which all atoms are sp^2 hybridized and contribute one electron each in orthogonal p-orbitals for delocalization over the rings with resonance energies of 198 and 143 KJ/mol respectively

Resonance Structures



Synthesis of Quinoline

Friedländer Synthesis



2-Aminobenzene-carboxaldehyde

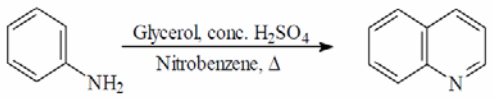
Enolizable carbonyl compound

85%

Paul Friedländer (1857 - 1923)

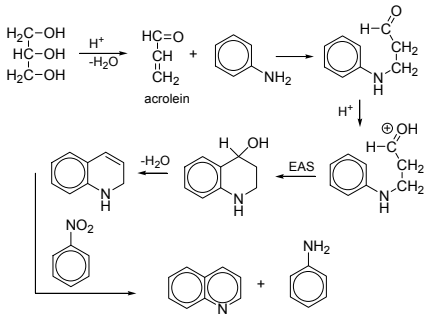
Synthesis of Quinoline

Skraup's Synthesis



Synthesis of Quinoline

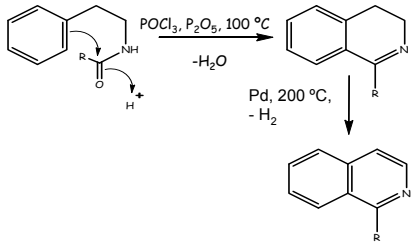
Skraup's Synthesis



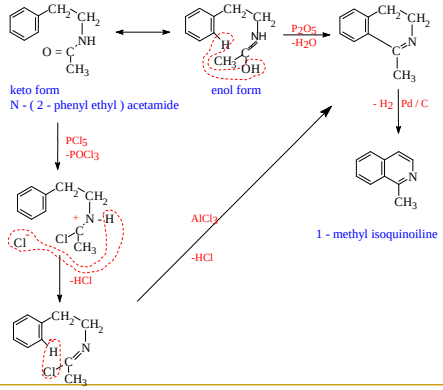
Synthesis of Isoquinoline

Bischler-Napieralski Synthesis

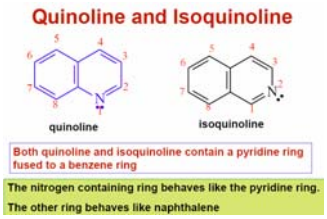
- Acyle derivatives of β- phenyl – ethylamine are cyclized by treatment with acids after (P_2O_5) to yield dihydroisoquinoline ,which can then be aromatized



Bischler-Napieralski Synthesis

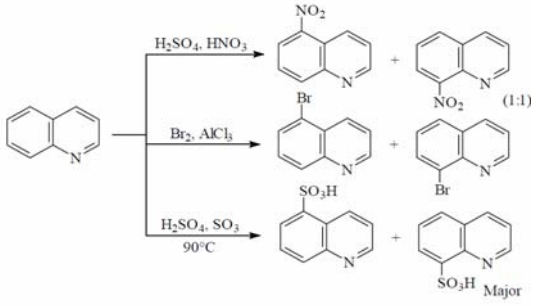


Electrophilic Aromatic Substitution



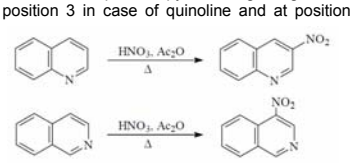
- The nitrogen of the quinoline and isoquinoline has deactivating effect on the ring towards electrophilic substitution as in case of pyridine. However electrophilic substitution of quinoline and isoquinoline requires less vigorous conditions than pyridine.
- Consequently electrophilic aromatic substitution occurs at the benzene ring at positions 5 and 8.

Electrophilic Aromatic Substitution



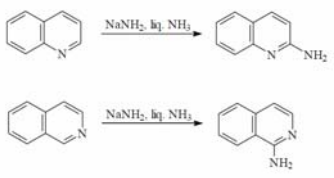
Electrophilic Aromatic Substitution

- However, nitration can take place at pyridine ring using nitric acid and acetic anhydride at position 3 in case of quinoline and at position 4 in case of isoquinoline



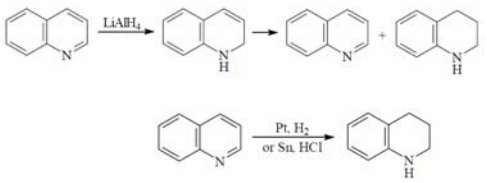
Nucleophilic Aromatic Substitution

- Quinoline and isoquinoline undergo facile nucleophilic substitution as in pyridine.
  - Quinoline undergoes Chichibabin reaction to give 2-amino- quinoline while
  - Isoquinoline undergoes Chichibabin reaction to give 1-amino isoquinoline .
    - Isoquinoline undergoes substitution faster than quinoline.
    - The reaction proceeds in a manner analogues to pyridine.



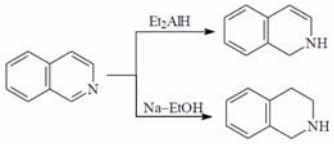
Reduction of Quinoline

- The pyridine ring is more easily reduced
  - Quinoline can be selectively reduced at 1,2-bond by reaction with lithium aluminium hydride but the 1,2-dihydro quinolines are unstable and disproportionate easily to give quinoline and 1,2,3,4-tetrahydroquinoline.
  - Quinoline can be converted to 1,2,3,4-tetrahydroquinoline by catalytic hydrogenation or with tin and hydrochloric acid



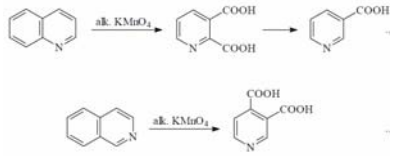
Reduction of Isoquinoline

- The pyridine ring is more easily reduced
  - Isoquinoline can also be converted to 1,2-dihydro or 1,2,3,4-tetrahydroisoquinoline with diethyl aluminium hydride and sodium-ethanol, respectively



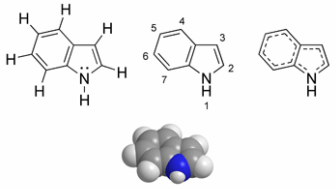
Oxidation

- Quinoline and isoquinoline undergo oxidative cleavage with alkalian potassium permangnate to give pyridine-2,3-dicarboxylic acid and pyridine-3,4-dicarboxylic acid respectively.
  - However, pyridine-2,3-dicarboxylic acid is not stable and undergoes decarboxylation to give nicotinic acid.
  - Quinoline and isoquinoline both form N-oxides when treated with hydrogen peroxide in acetic acid or with organic peracids.

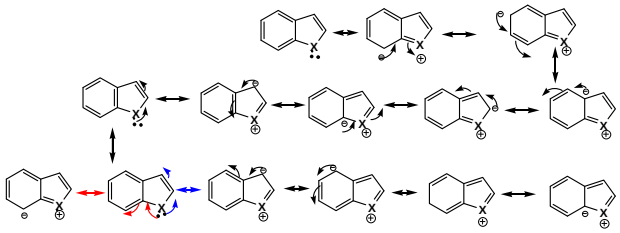


Indole

- **Indole** is an aromatic heterocyclic organic compound. It has a bicyclic structure, consisting of a six-membered benzene ring fused to a five-membered nitrogen-containing pyrrole ring.



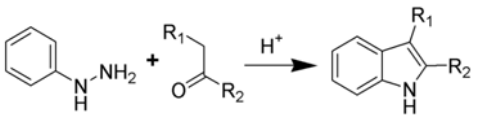
Resonance structures of Indole



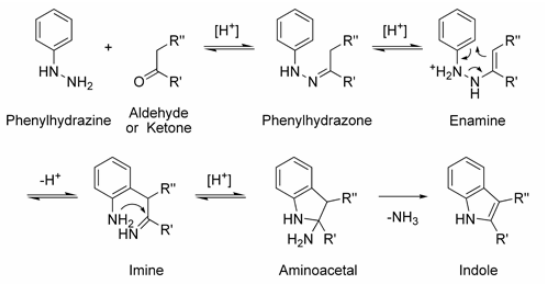
- It appears from these resonance structures that all C atoms bear – ve. charge while the hetero atom bears + ve. charge

Fischer Indole synthesis

- The Fischer indole synthesis is a chemical reaction that produces the aromatic heterocycle indole from a (substituted) phenylhydrazine and an aldehyde or ketone under acidic conditions
  - The reaction was discovered in 1883 by Hermann Emil Fischer.

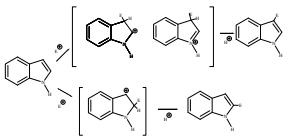


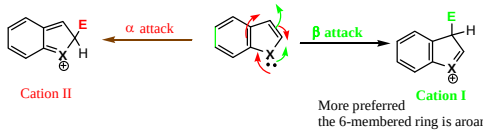
Fischer Indole synthesis



Regioselectivity in Electrophilic Substitution

- Electrophiles attack indole at C-3, rather than C-2. The energy of activation of the intermediate in C-3 is lowered because it is possible to delocalize the positive charge through resonance.

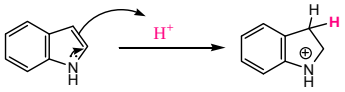




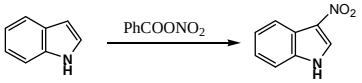
More preferred the 6-membered ring is aroamtic

Electrophilic Substitution Reactions

- Protonation

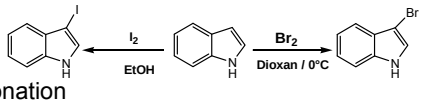


- Nitration

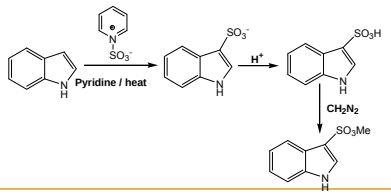


Electrophilic Substitution Reactions

- Halogenation

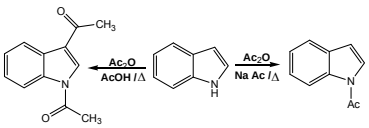


- Sulphonation

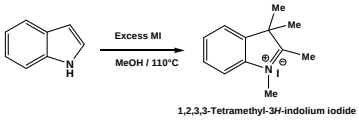


Electrophilic Substitution Reactions

- Acylation

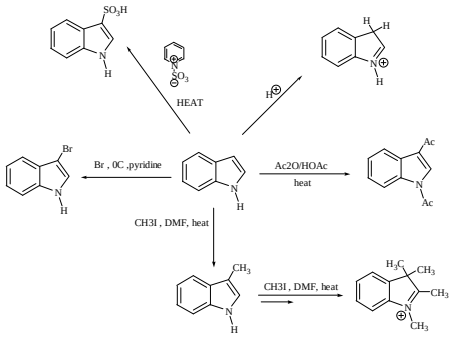


- Alkylation

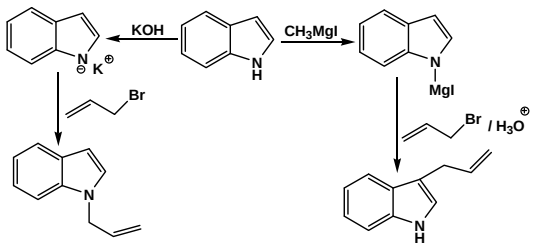


1,2,3,3-Tetramethyl-3*H*-indolium iodide

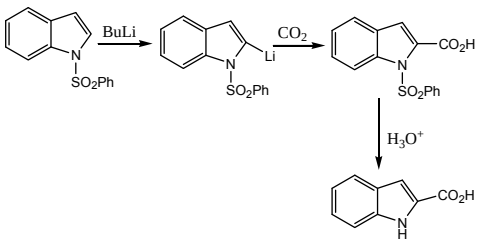
Electrophilic Substitution Reactions



Nucleophilic Substitution Reactions

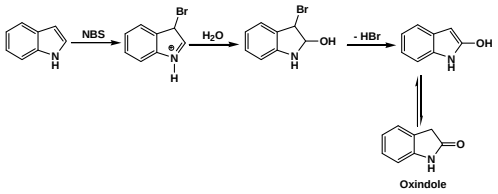


Nucleophilic Substitution Reactions



Oxidation of Indole

- Due to the electron-rich nature of indole, it is easily oxidized .
  - Simple oxidants such as *N*-bromosuccinimide will selectively oxidize indole to oxindole .



Reduction of Indole