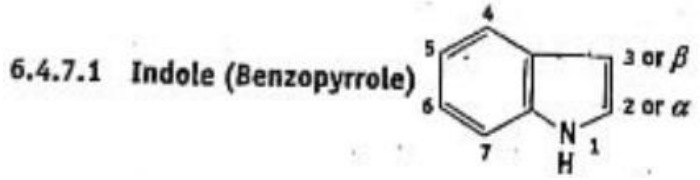
6. Condensed Five and Six-Membered Heterocyclic Systems

Fusion of a benzene ring onto the 2,3-positions of pyridine or pyrrole leads to the formation of bicyclic systems, namely quinoline or isoquinoline or indole. The major effect of this fusion is to alter several chemical properties of the basic heterocyclic system. The stability of these heterocyclic systems depends upon the pair of electrons which the hetero atom contributes to the system. A brief description of indole, quinoline and isoquinoline is given as follows:



6.1.1 Introduction

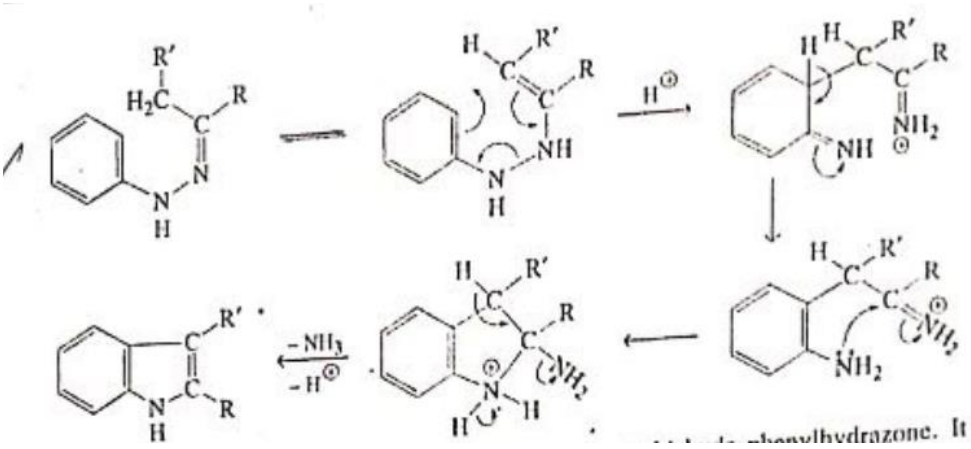
Indole occurs in coal-tar, jasmine flowers and orange blossom oil. Indole and its derivatives hold an important place in organic chemistry because of their wide occurrence in several natural products, alkaloids, amino-acids, indigotin etc. and, therefore, the chemistry of indoles has been investigated much more thoroughly than their oxygen and sulphur analogs.

6.1.2 Methods of Formation of Indole and Its Derivatives

Indole and its derivatives are prepared synthetically by the following methods:

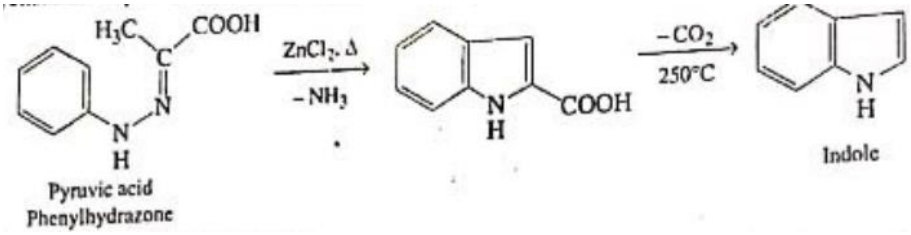
(i) The Fischer-Indole synthesis

The phenylhydrazone of an aldehyde or ketone on heating with an acid catalyst such as boron trifluoride, zinc chloride or polyphosphoric acid, yields indole derivative. The Fischer synthesis of indoles involves rearrangement with the loss of a molecule of ammonia. The probable mechanism is as follows:



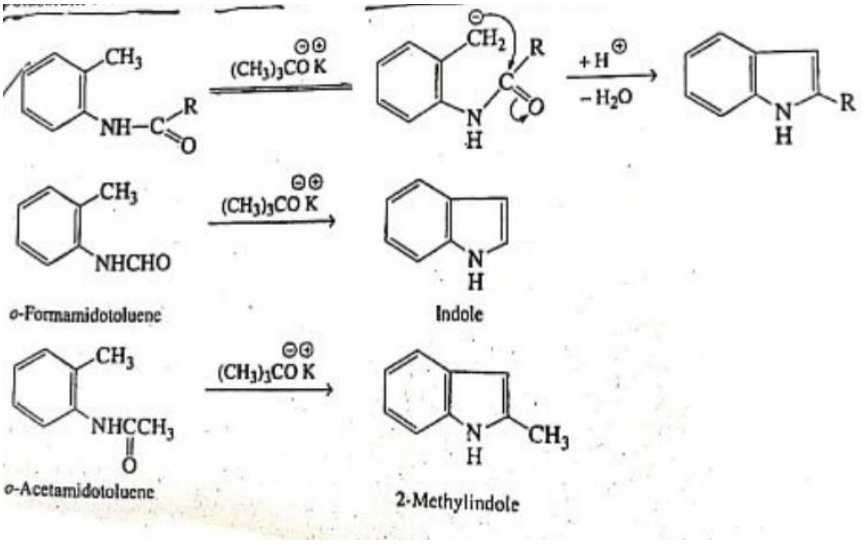
Indole itself cannot be prepared by the cyclization of acetaldehyde phenylhydrazone. It is

conveniently prepared by the decarboxylation of indole-2-carboxylic acid, obtained by the cyclisation of phenylhydrazone of pyruvic acid.



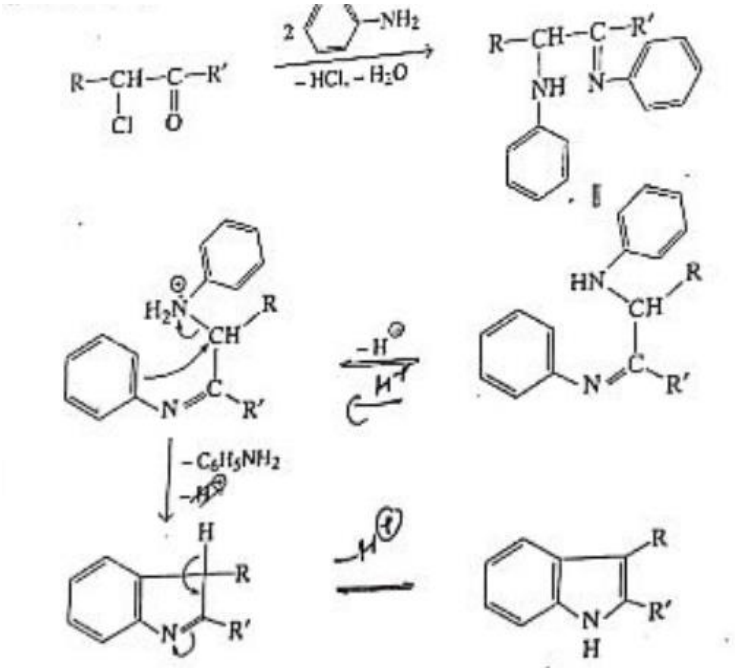
(i) The Madelung indole synthesis

The cyclodehydration of o-formamidotoluene or o-acetamidotoluene with a base such as potassium-t-butoxide or sodamide gives indole or 2-methylindole respectively.



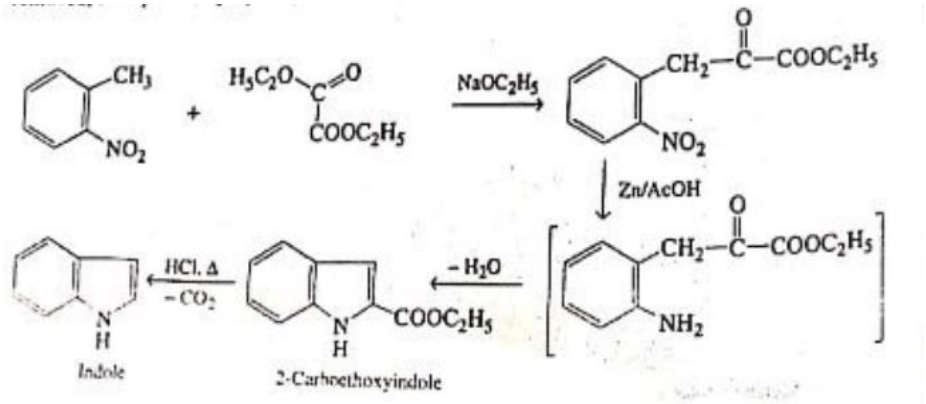
The Bischler synthesis

α-Haloketones on heating with arylamine in presence of acid vields 2-arylindole. The reaction is known as Bischler



(iv) The Retssert Indole synthesis

This synthesis involves the condensation of o-nitrotoluenes with diethyloxalate in the presence of a base to yield o-nitrophenylpyruvic esters. The nitro group of the resulting α-keto ester is reduced to amino to give o-aminophenylpyruvic esters. Cyclodehydration of these esters leads to the formation of indole-2-carboxylic esters. The 2-carboethoxy substituent in the indole may be removed, if required, by hydrolysis and thermal decarboxylation. This is illustrated as follows:

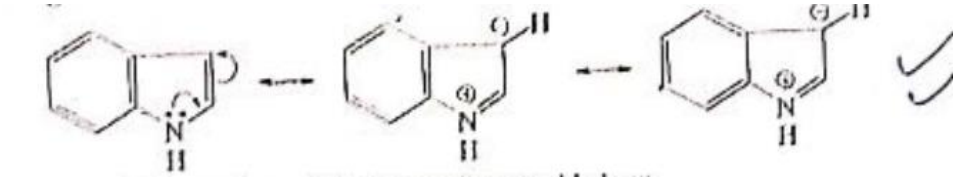


6.1.3 Physical properties

It is a colourless, volatile solid, m.p. 52^0 C. It has strong pleasent odour but in dilule solutions it has flowery odour and is used in perfumery for preperating jasmine and orange blends. Indole is soluble in hot water, alcohol and ether.

6.1.4 Chemical Reactions

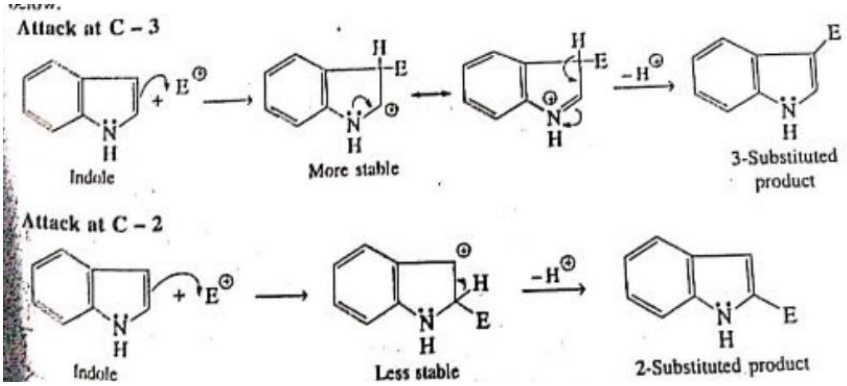
Indole recembles pyrole in general chemical actions but differs considerably from the latter due to the fusion of a benzene ring with the resultl that there are now 10 π- electrons over the cyclic frame work. Indole is a resonating Hybrid of the following principal contributing forms, resonance energy of the system being 47-49 kcal/mol.



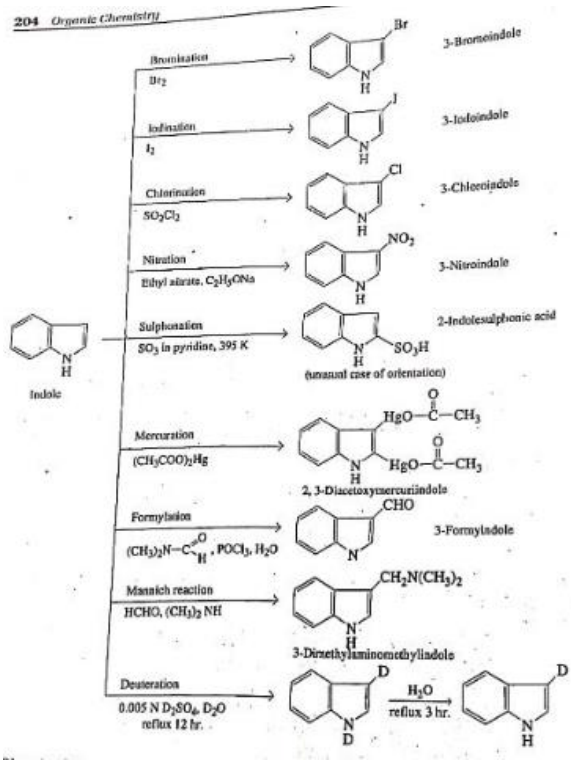
Some important chemical reactions of indole are illustrated below:

(1) Electrophilic substitution

The major effect of fusing a benzene ring onto the 2,3-positions of pyrrole is to alter the position of greatest electron density of the pyrrole ring from position 2. to position-3. Thus, the electrophilic substitution in indole occurs at position 3. If the position 3 is occupied, the substitution takes place at position 2. However, if both 2- and 3-positions are occupied, substitution occurs at position 6. The formation of 3-substituted derivative is explained by taking into consideration the carbocations formed by the attack of electrophile at C-3 and C-2 positions, as illustrated below:

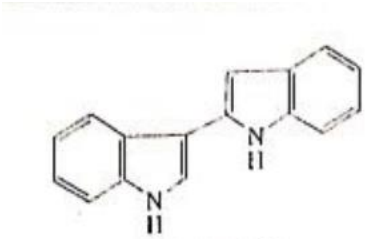


there are two resonating forms possible for the intermediate cation formed from attack at whereas only one such form is possible for substitution at C-2. Therefore, the substitution occurs preferentially at position-3. Some important electrophilic substitution reaction of indole are depicted below:



(ii) Dimerization

Indole forms the dimer when treated with hydrogen chloride in aprotic solvents, whereas in aqueous acid an equilibrium is established between indole and its dimer. its trimer, and their salts.

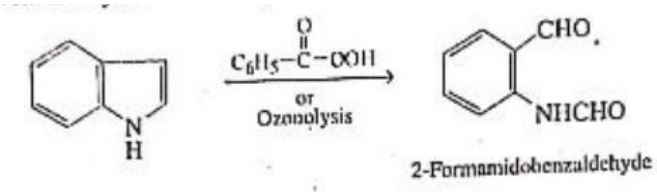


Dimer of indole

It is of interest to emphasize the fact that indole, in contrast to pyrrole which polymerizes under these conditions, does not self-condense beyond the trimer stage.

(iii) Oxidation

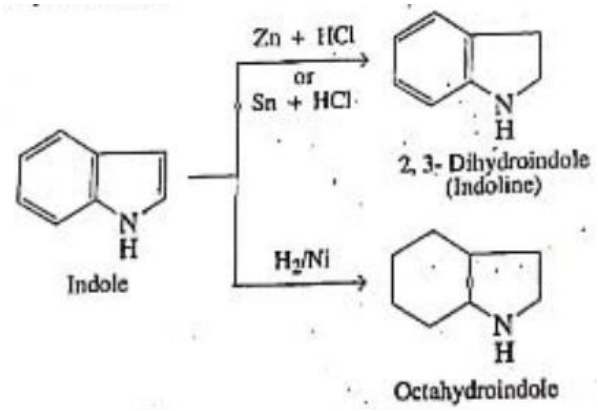
The pyrrole ring of indele opens up on oxidation with perbenzoic acid or ozone to yield 2-formamido benzaldehyde.



2-Formamidobenzaldehyde

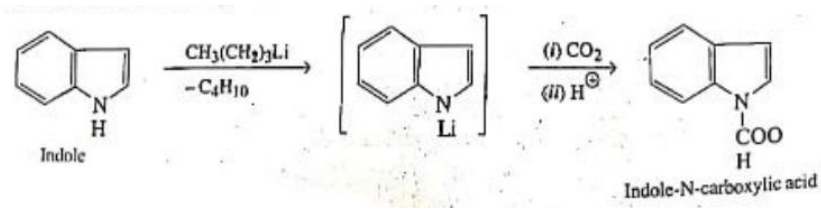
(iv) Reduction

Zinc or tin and hydrochloric acid reduces indole to 2,3-dihydroindole. However, catalytic hydrogenation yields octahydroindole.

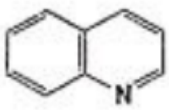


(v) Reaction with n-Butyllithium (Acidic character)

The N-H proton of indole, being sufficiently acidic, may be replaced by lithium, when treated with n-butyllithium. This provides a method for the synthesis of indole-N-carboxylic acid, as illustrated in the following reaction.



6.4 Quinoline



Quinoline is a bicyclic heterocyclic system in which benzene ring is fused with a pyridine ning in 2. 3.positions. Quinoline was first isolated from coal tar and was obtained by the distillation of quinine alkaloid with alkali. The quinoline nucleus is present in a number of alkaloids (quinine and me antimalarials (chloroquine) and analgesics (uricophen).

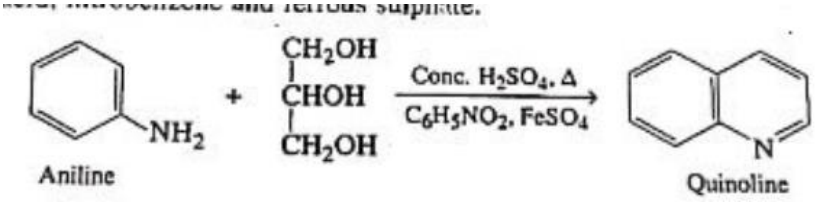
6.2.1 Methods of Formation of Quinoline and its Derivatives

Quinoline and its derivatives are prepared by the following methods:

(i) Skraup synthesis

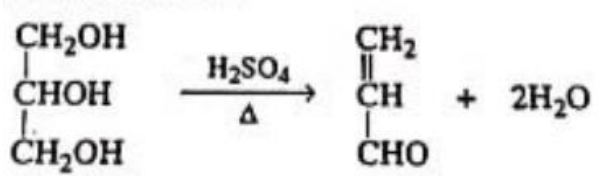
This is the commercial method for the preparation of quinoline and many of its derivatives. It consists of heating a primary aromatic amine, containing at least one vacant ortho position, with

an α,β-unsaturated carbonyl compound (or its precursor, generally glycerol) in the presence of a condensing agent (concentrated sulphuric acid) and nitrobenzene which acts as a mild oxidising agent. Ferrous sulphate is generally added to the reaction mixture to make it less violent. Quinoline, for example, may be prepared by heating a mixture of aniline, glycerol, concentrated sulphuric acid, nitrobenzene and ferrous sulphate.

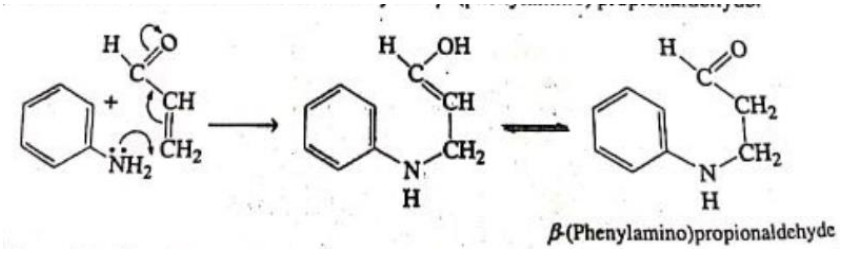


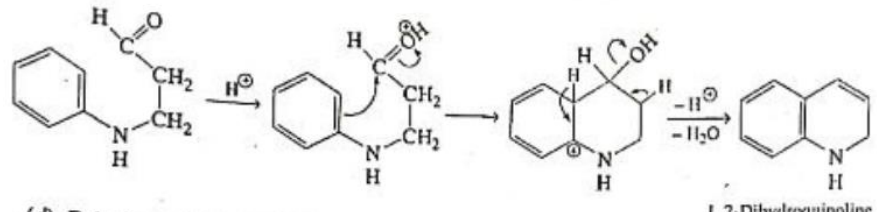
The mechanism of the reaction involves the following sequence of steps:

(a) Dehydration of glycerol to acrolein

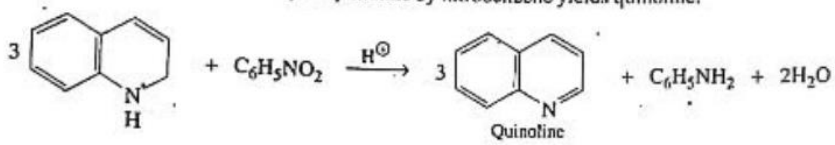


(b) Michael addition of aniline to acrolein yields β-(phenylamino) propionaldehyde.





(d) Dehydrogenation of 1, 2-dihydroquinoline by nitrobenzene yields quinoline.

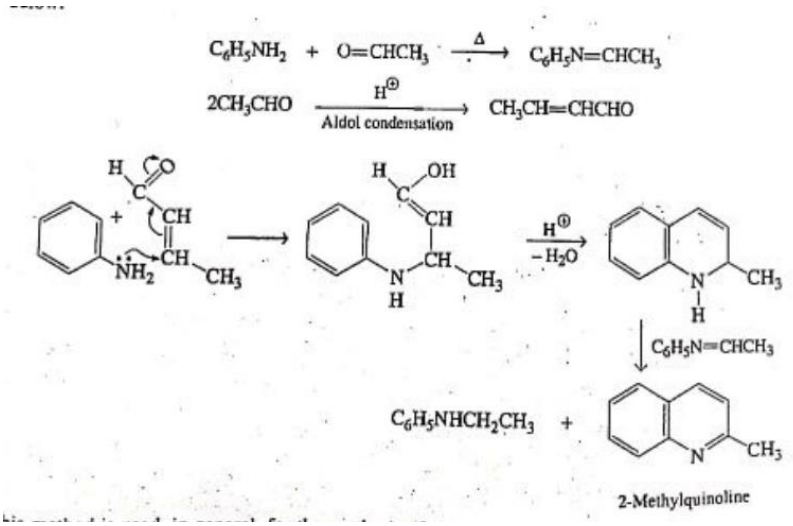


In Skraup synthesis, acrolein as such is not used since it polymerises under the reaction conditions. However, it is a general method for the preparation of quinoline derivatives starting with

appropriately substituted anilines**.**

(ii) The Doebner-Miller synthesis

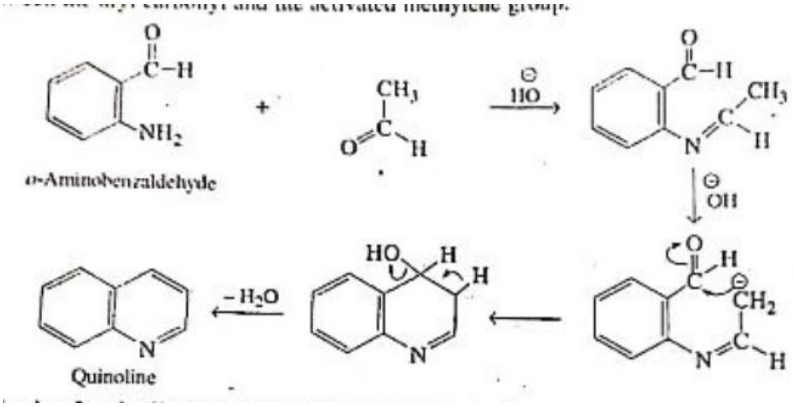
This synthesis is a modification of Skraup's synthesis and involves condensation of a primary amine on heating with an aldehyde in the presence of hydrochloric acid to yield the initial formation of a β-unsaturated aldehyde. The accepted mechanism involves self-condensation of the aldehyde to an β- unsaturated aldehyde which reacts with the aromatic amine, as illustrated below:



This method is used, in general, for the synthesis of quinoline homologues.

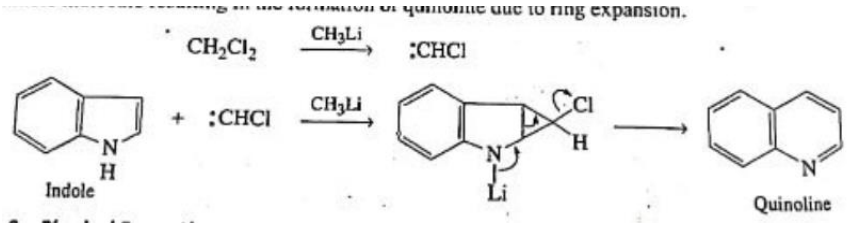
(ii) The Friedlander synthesis

This method involves the alkaline condensation of aminobenzaldehyde with a carbonyl compound containing a reactive methylene group . The mechanism of the rection involves the initial formation of Schiff base followed by an internal aldol-type condensation between the aryl carbonyl and the activated methylene group.



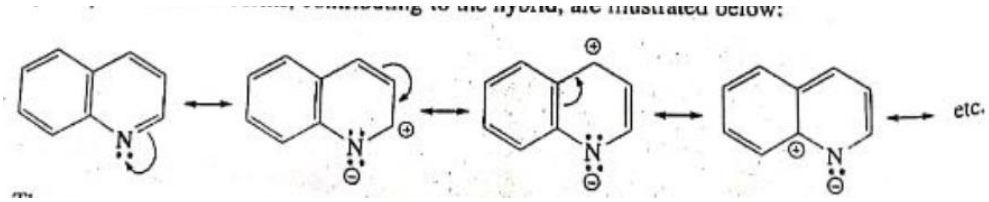
(iv) Synthesis of quinoline from indole (Ring expansion)

Quinoline may be synthesised from indole by treating it with methyllithium in methylene chloride solution. The mechanism involves the initial formation of chloromethylene which adds to the indole molecule resulting in the formation of quinoline due to ring expansion.



6.2.2 Physical Properties

Quinoline is a colourless liquid, b.p. 238°C, having an unpleasant odour and volatile in steam. It is sparingly soluble in water but miscible with ether and alcohol.Quinoline is a planar molecule with a conjugated system of 10 π electrons and obeys Huckel rule. The principle resonance forms, contributing to the hybrid, are illustrated below:



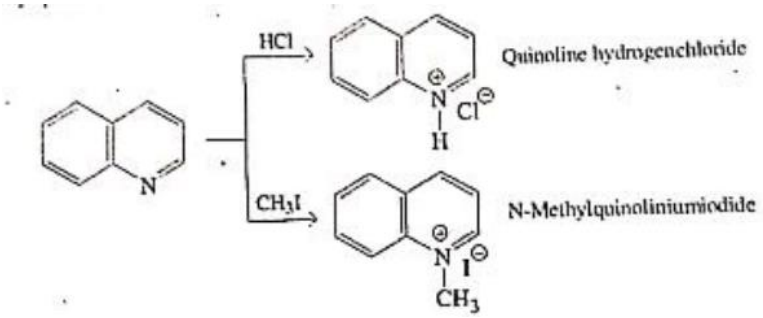
The resonance energy of the system is 47.3 kcal/mole.

6.2.3 Chemical Reactions

Quinoline exhibits the reactions of both pyridine and benzene. Some important reactions are as Follows:

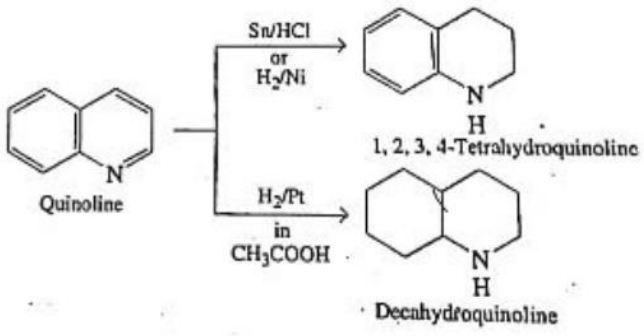
(i)Basic character

Quinoline contains a pair of 2p electrons on nitrogen, located orthogonally to the molecular cloud, which is not required for aromatic stabilization. Thus, quinoline is a tertiary base and forms quaternary salts on treatment with inorganic acids and reacts with methyl iodide to yield N-methylquinolinium iodide.



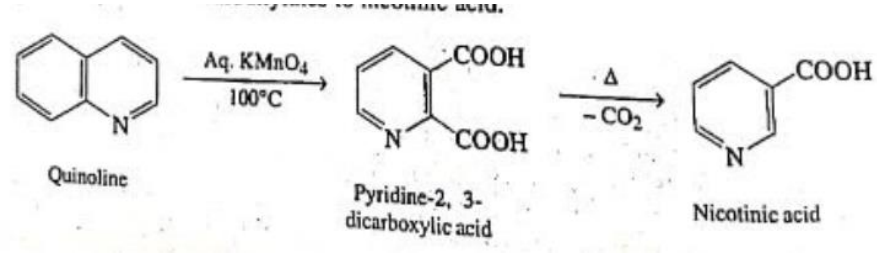
(ii) Reduction

Catalytic reduction with tin and hydrochloric acid or with H/Ni yields 1,2,3,4-tetrahydroquinoline. However, catalytic reduction with H /Pt in acetic acid yields decahydroquinoline.

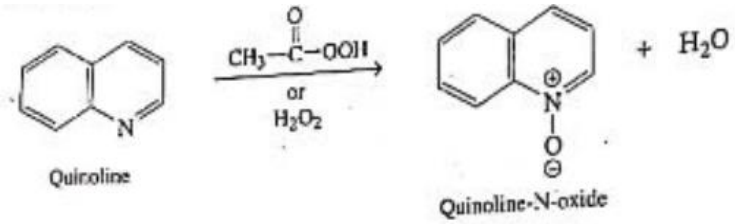


(iii) Oxidation

(a) Vigorous oxidation with potassium permanganate yields quinolinic acid (pyridine-2, 3-dicarboxylic acid) which decarboxylates to nicotinic acid.

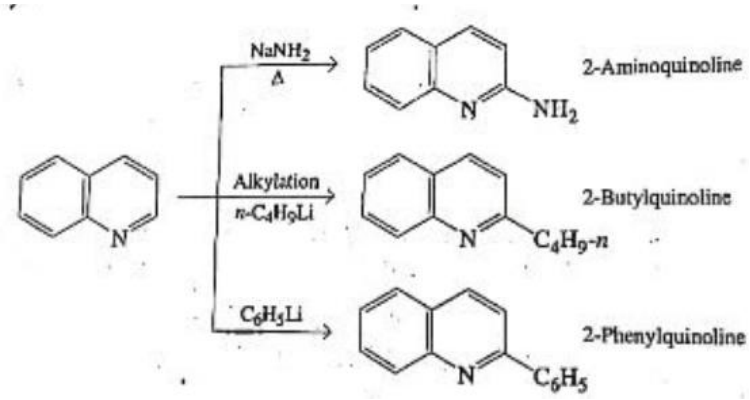


(b) Oxidation with peracids or hydrogen peroxide, however, yields quinoline-N-oxide.



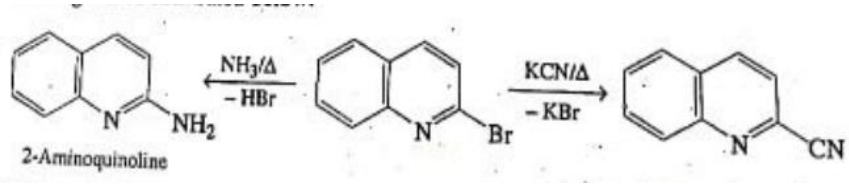
(iv) Nucleophilic substitution reactions

(a) Quinoline on heating with sodamide yields 2-aminoquinolines (Chichibabin reaction), with phenyllithium and ЛI-butyllithium, it gives 2-phenylquinoline and 2-butylquinoline respectively.



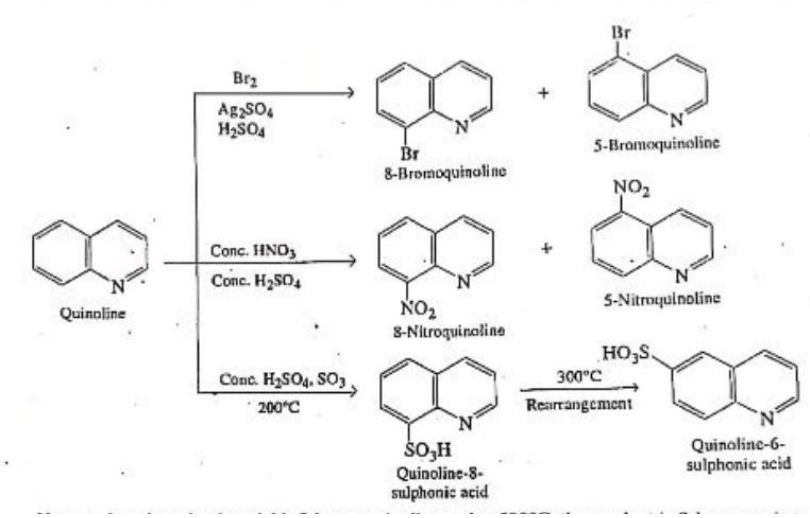
(b) Nucleophilic substitution of halogens in haloquinolines

Halogen atoms when present in 2 or 4-position of quinoline are readily replaced by nucleophilic reagents as illustrated below.

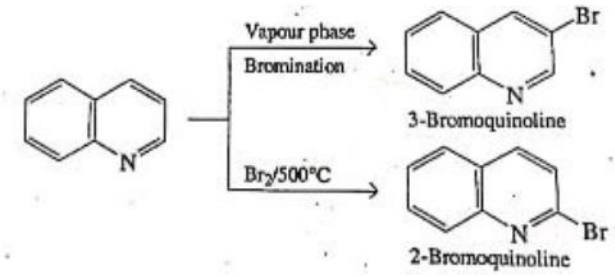


(v) Electrophilic substitution

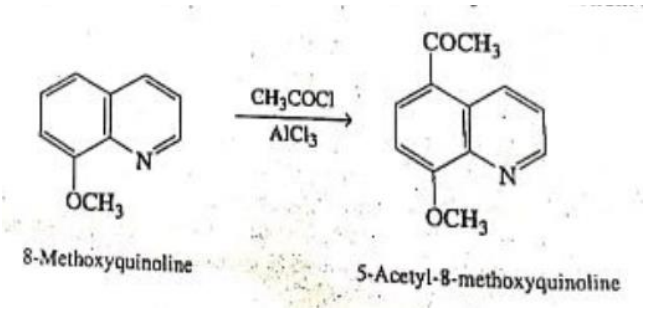
Quinoline undergoes electrophilic substitution reactions like halogenation, nitration, sulphonation and Friedel-Crafts reactions. Since nitrogen atom deactivates the pyridine ring for electrophilic substitution, the substitution occurs in the benzene ring preferably at 8-position to yield 8-substituted derivative together with small amounts of 5-substituted product.



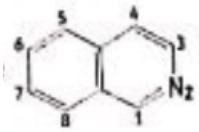
Vapour phase bromination yields 3-bromoquinoline and at 500°C, the product is 2-bromoquinoline.



Quinoline bearing the activated group displays friedel craft acylation reaction. For example,



6.3 Isoquinoline



6.3.1 Introduction

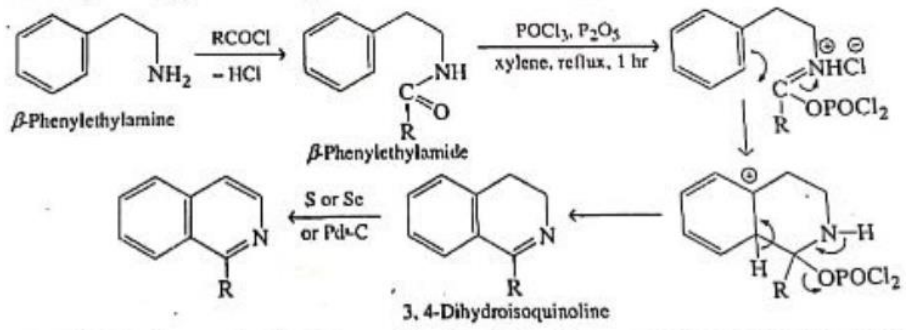
The benzene ring in isoquinoline is used with pyridine at its β,γ-position and hence is designed as β,γ- benzopyridine. Isoquinoline is one of the very few heterocyclic compounds in which numbering of the ring does not start with the hetero alom. Isoquinoline is the decomposition products of many alkaloids (papaverine, narcotine, etc.) and is obtained commercially from coal tar and bone oil.

6.3.2 Methods of Formation of Isoquinoline and Its Derivatives

Isoquinoline may be prepared by the following methods:

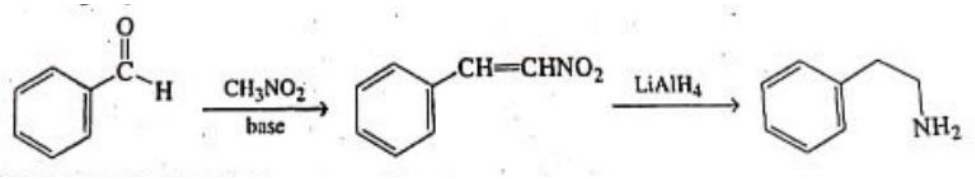
(i) The Bischler-Napieralski synthesis

The cyclodehydration of acyl derivative of □-phenylamine, usually effected by heating with a dehydrating agent in an inert solvent, results in the formation of 3. 4-dihydroisoquinoline which is dehydrogenated with sulphur or selenium to yield isoquinoline derivative. The mechanism involves an intramolecular electrophilic substitution of the aromatic ring induced by initial attack of the dehydrating agent at the oxygen atom of the amide linkage.



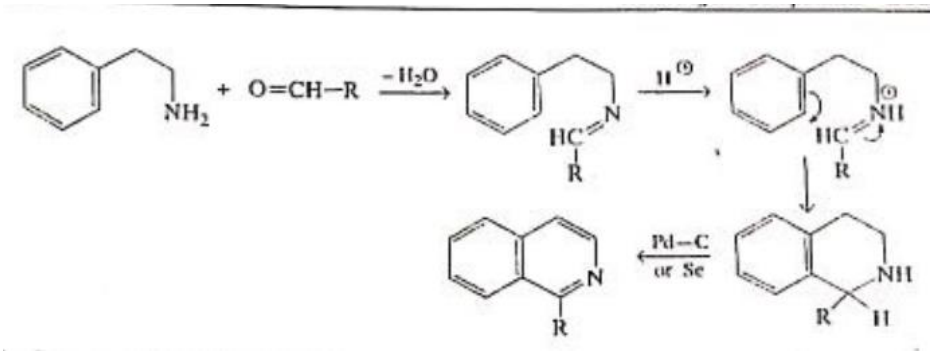
□-Phenylethylamine, required for the reaction, is obtained from aromatic aldehydes as per the

following sequence:



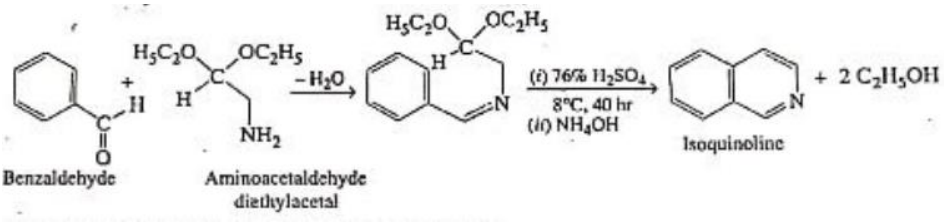
(ii) Pictet-Spengler reaction

The synthesis involves the condensation of a □-arylethylamine with an aldehyde in presence hydrochloric acid at 100°C to yield 1, 2, 3, 4-tetrahydroisoquinoline which upon dehydrogenation with palladium-charcoal or selenium gives isoquinoline. The mechanism involves initial formation of an imine which is protonated and subsequently undergoes intramolecular electrophilic substitution as in the case of Bischler Napieralski synthesis.



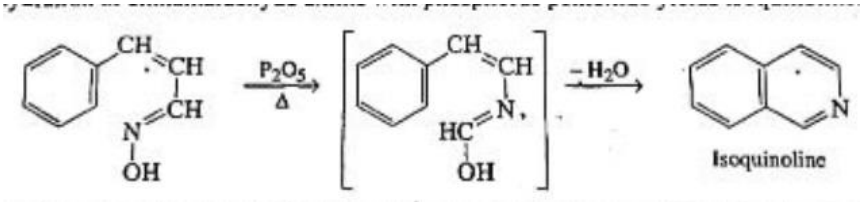
(iii) The Pomeranz-Fritsch synthesis

This represents a direct synthesis of isoquinoline ring and involves the condensation of an aromatic aldehyde with an aminoacetal to yield a Schiff base, followed by cyclization with a suitable acidic catalyst.



(iv) By the dehydration of cinnamaldehyde oxime

Dehydration of cinnamaldehyde oxime with phosphorus pentoxide yields isoquinoline.

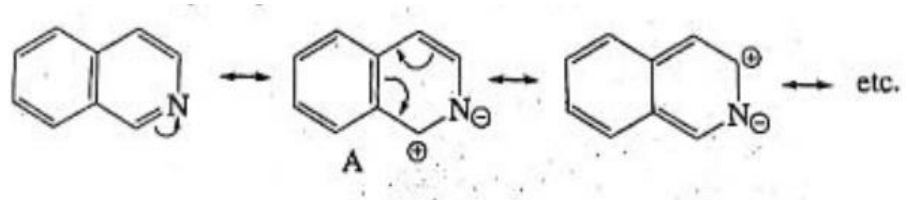


The formation of isoquinoline is explained by assuming that oxime first undergoes Beckmann

rearrangement followed by ring closure.

6.4.7.3.3 Physical Properties

Isoquinoline is a colourless liquid, b.p. 243°C, sparingly soluble in water but miscible with alcohol and ether. It is volatile in steam and has an unpleasant odour. It is fairly basic (PK, = 6.1). The various resonating forms contributing to hybrid are illustrated below:



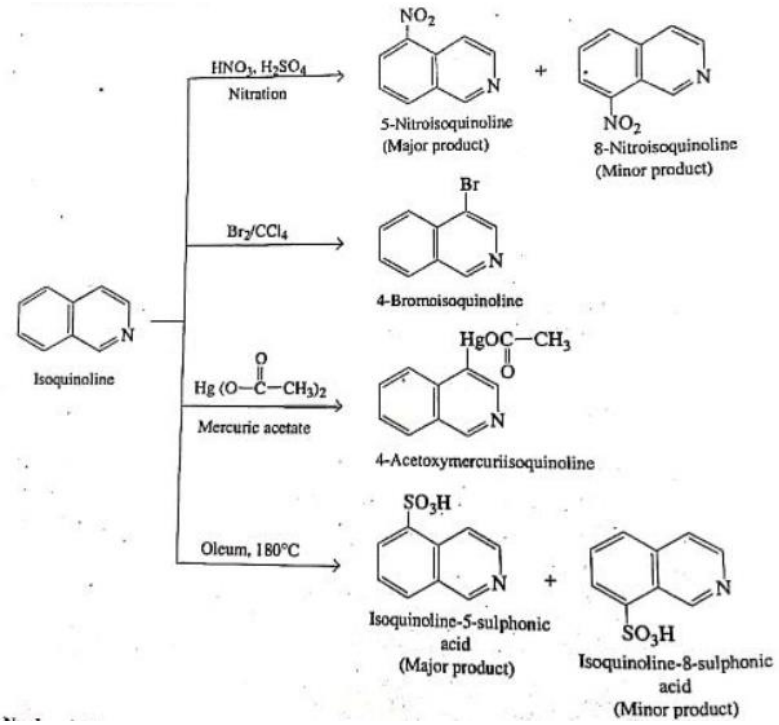
The form A contributes to greater extent, as in the other forms the benzenoid character is lost.

6.4.7.3.4 Chemical Reactions

Isoquinoline resembles quinoline in its chemical properties. Some important reactions of isoquinoline are illustrated below:

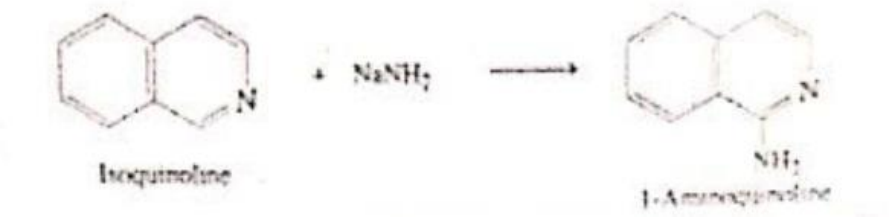
(1) Electrophilic substitution

Analogous to quinoline, the electrophilic attack in isoquinoline takes place in the benzene ring due to the deactivation of the pyridine ring because of protonation. Electrophilic attack occurs mainly at 5-position though a small amount of 8-substituted product is also obtained. For example, nitration and sulphonation yield predominantly 5-substituted product. However, mercuration (with mercuric acetate) and bromination (with Br_2/CCl_4) yield the 4-substituted product.



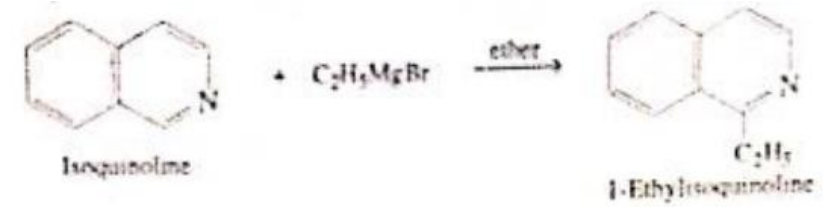
(ii) Nucleophilic substitution

Nucleophilic substitution in isoquinoline occurs mainly at position-1. Thus. 1-aminoisoquinoline is obtained on heating with sodamide (Chichibabin reaction).



Isoquinoline

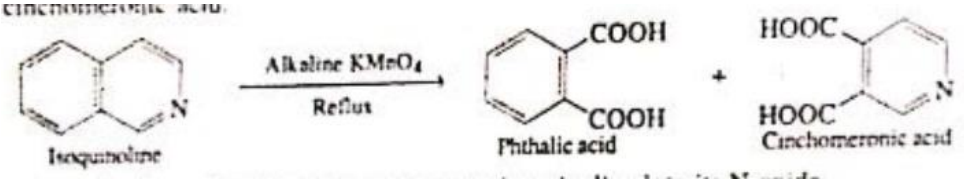
Similarly, 1-alkyl derivativee are obtained by treating isoquinoline with Grignard reagent.



Isoquinoline

(iii)Oxidation

Oxidation of isoquinoline with alkaline potassium permanganate yields a mixture of phthalic acid and cinchomeronic acid



Isoquinoline

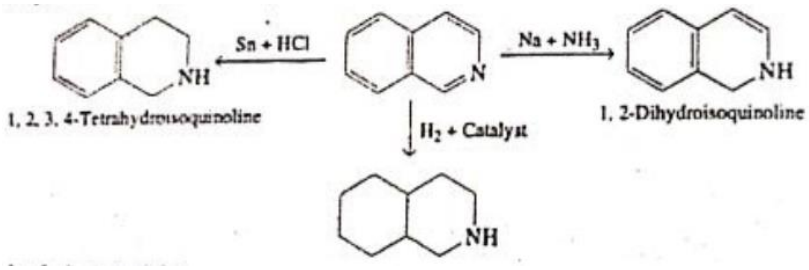
Phthalic acid

Cinchomeronic acid

The action of perbenzoic acid, however, converts isoquinoline to its N-oxide.

(iv) Reduction

Isoquinoline on reduction with sodium in liquid ammonia yields 1,2-dihydroisoquinoline. With tin and hydrochloric acid, the product obtained is 1. 2. 3. 4-tetrahydroisoquinoline whereas catalytic reduction gives octahydroisoquinoline.



(v) Side-chain reactivity

Like other heterocycles, alkyl groups at ortho or para position to the ring nitrogen atom exhibit acidic character and hence undergo typical reactions. For example, l-methylisoquinoline reacts with benzaldehyde to yield styryl derivative.