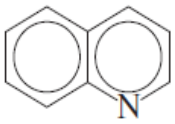
# Fused Ring Heterocycles

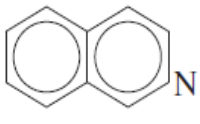
**Prof. Dr. Ayad Kareem**
**Department of Pharmaceutical Chemistry,**
**Collage of Pharmacy, Mustansiriyah University (2022-2023).**

## A) Quinoline and isoquinoline (benzopyridines)

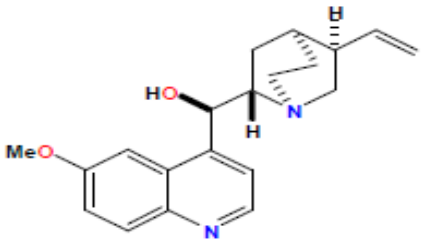
Two isomeric benzopyridines are quinoline and isoquinoline. Quinoline is the benzo[b]pyridine and isoquinoline is the benzo[c]pyridine isomer. These two are very important heterocyclic units because their derivatives widely occur in nature as alkaloids. For example, the antimalarial quinine and the pain reliever morphine.




Quinoline



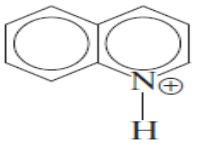

Isoquinoline



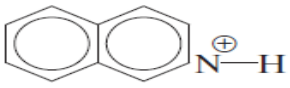

quinine

## General properties

Both of these compounds are basic in nature since the lone pair of electrons on the nitrogen atom is not utilized in the internal resonance for the aromaticity of the compounds. But unlike benzene, the bond lengths of both the compounds are irregular, and both of them possess considerable dipole moment directed toward the nitrogen atom. Both of these compounds react with acids and Lewis acids at the basic nitrogen atom, forming quinolium and isoquinolium salts, respectively.



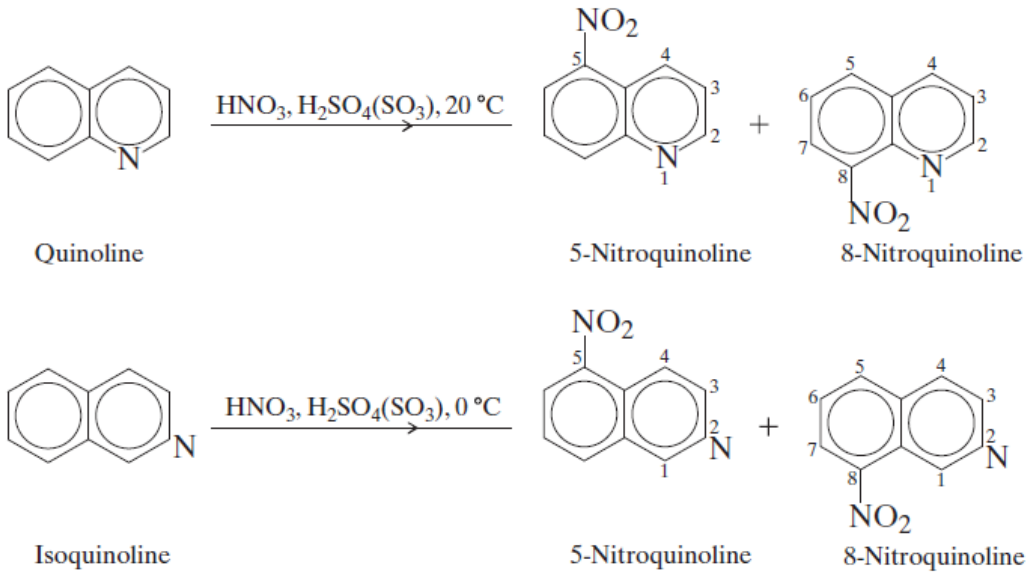

Quinolium ion



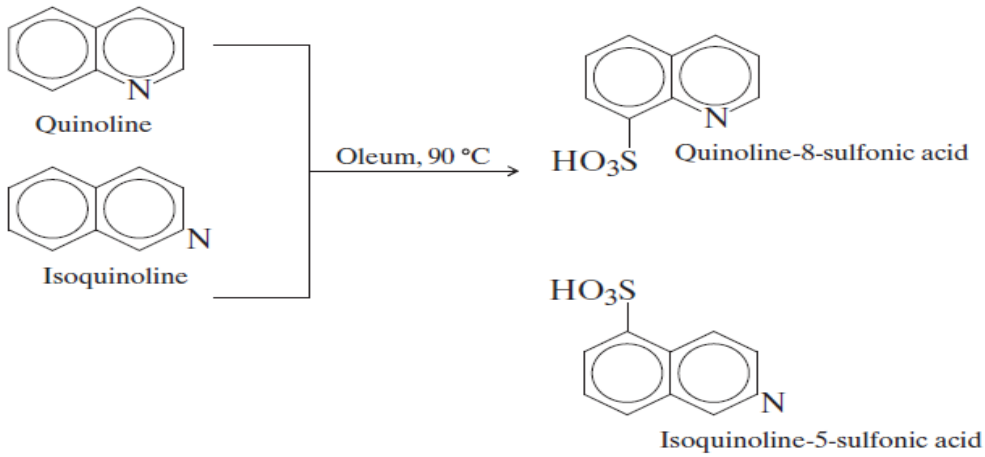

Isoquinolium ion

Therefore, the products of **electrophilic substitution** of the compounds depend on the nature of the reagent used for the reaction. Since the electron density of the pyridine ring is lower than that of the benzene ring, the electrophilic substitutions of both quinoline and isoquinoline take place in the benzene ring. For example,

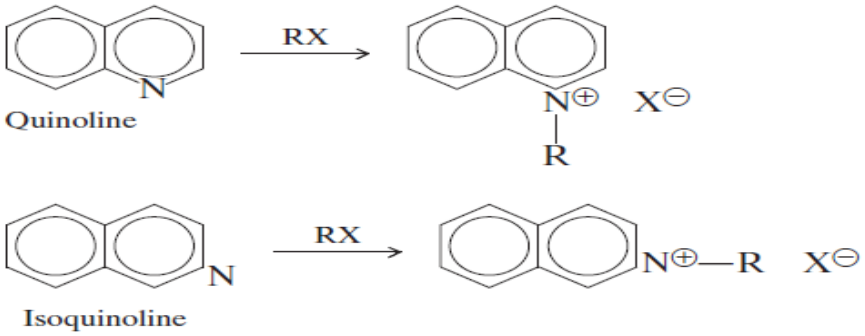
1. The nitration of quinoline with fuming nitric acid in concentrated (conc.) sulfuric acid containing $SO_3$ at room temperature gives a mixture of 5-nitro-and 8-nitroquinolines, whereas isoquinoline reacts with same reagent at 0°C to give a mixture of 5- and 8-nitroisoquinolines.



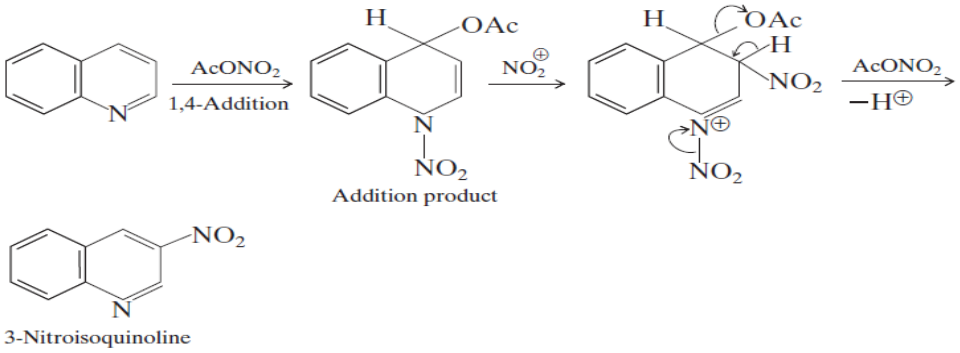

2. Sulfonation of quinoline with oleum at 92°C gives mainly quinoline-8- sulfonic acid. But, isoquinoline under similar condition gives isoquinoline-5- sulfonic acid.



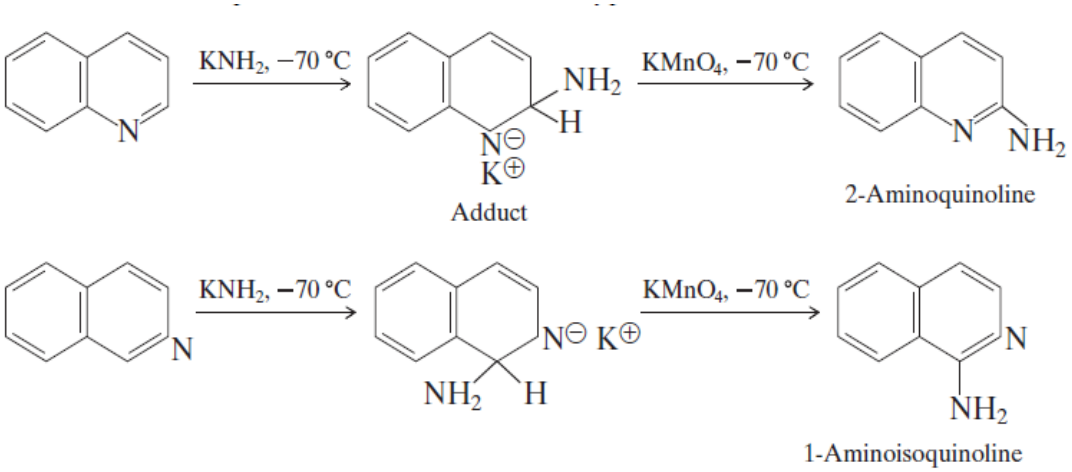
3. Alkyl and acyl halides react directly with the basic nitrogen atom of both the compounds to give quaternary salts.




However, with acetyl nitrate at 20°C, quinoline undergoes an addition-substitution reaction to give 3-nitroquinoline. Isoquinoline undergoes no such reaction in the pyridine ring.



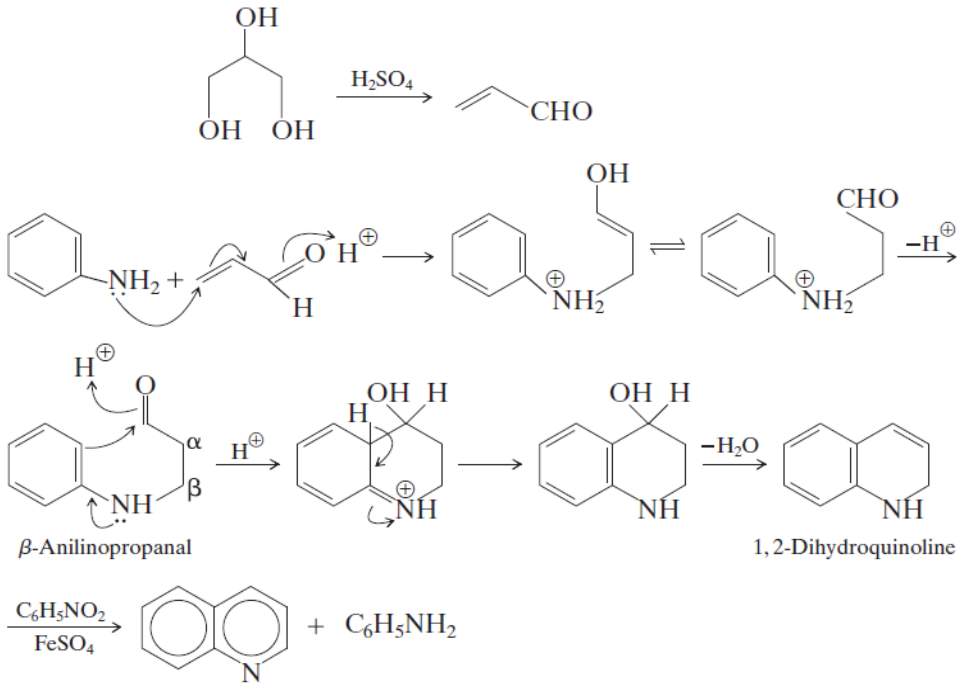

The C=N bond of the pyridine ring in both of these compounds undergoes **nucleophilic addition** at low temperature with $KNH_2$, and the adduct on oxidation with $KMnO_4$ at low temperature gives 2-aminoquinoline and 1-aminoisoquinoline in a Chichibabin-type reaction.



## Synthesis of benzopyridines

### 1. *Synthesis of quinoline*: Skraup synthesis

A mixture of glycerol, amiline, sulfuric acid, nitrobenzene, and ferrous sulfate and heating gives quinoline. Glycerol is dehydrated by sulfuric acid to acrolein. Aniline undergoes a Michael-type addition with acrolein in an acid-promoted reaction to form *β*-anilinopropanal that, in turn, undergoes an acid-catalysed cyclization to give 1,2-dihydroquinoline. Nitrobenzene aromatizes this dihydro compound to quinoline and itself is reduced to aniline. Ferrous sulfate moderates this last exothermic step.

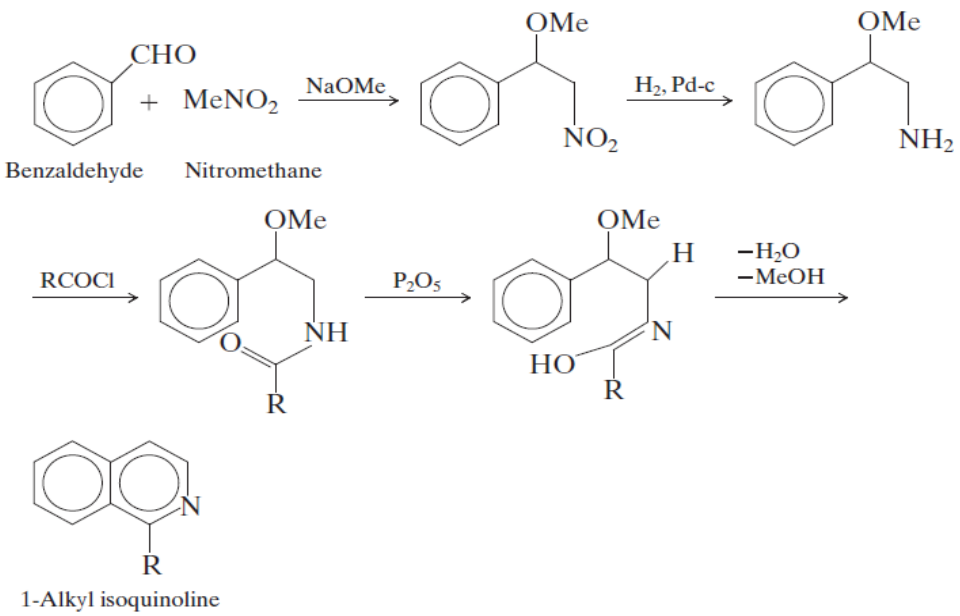



This method can be applied to synthesize benzene ring-substituted quinoline provided the substituents are not strongly deactivating in nature.

## 2. *Synthesis of isoquinoline*

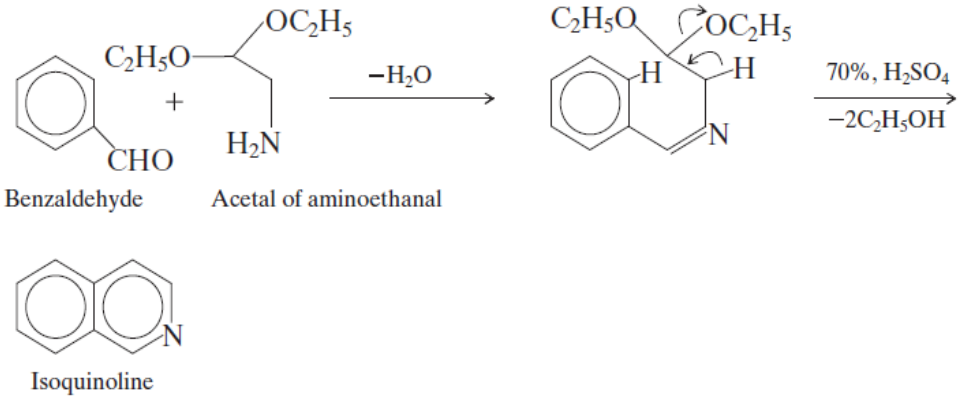
### a) Bischler–Napieralski synthesis.

1-Alkyl isoquinolines can be synthesized by this method, which involves the following steps:



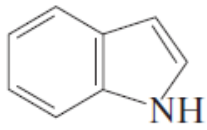

### b) Pomeranz–Fritsch reaction.

The parent compound, that is, isoquinoline can be synthesized by this reaction, which is as follows:



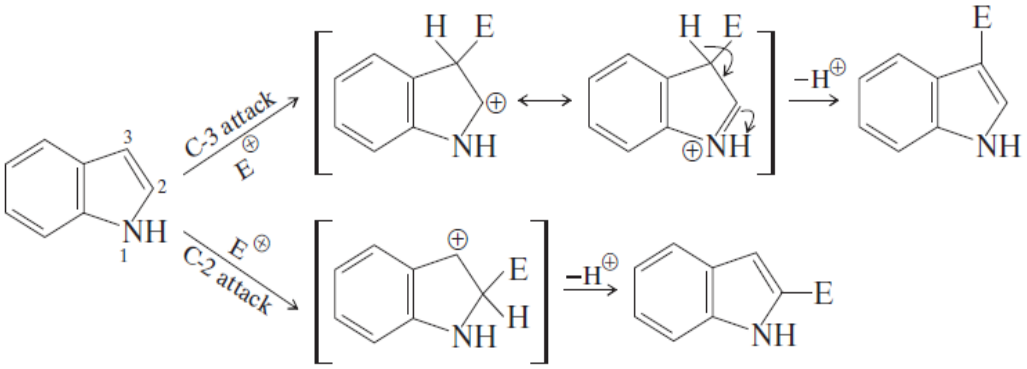
## B) Indole (benzo[b]pyrrole)

Indole ring occurs widely in nature as alkaloids. The alkaloids have medicinal values. In these compounds, a benzene ring is fused with a pyrrole ring and hence behaves as an aromatic heterocyclic compound. Because of the aromatic stability of the benzene ring, the most important contributing structure of indole to its resonance hybrid is its enamine form.

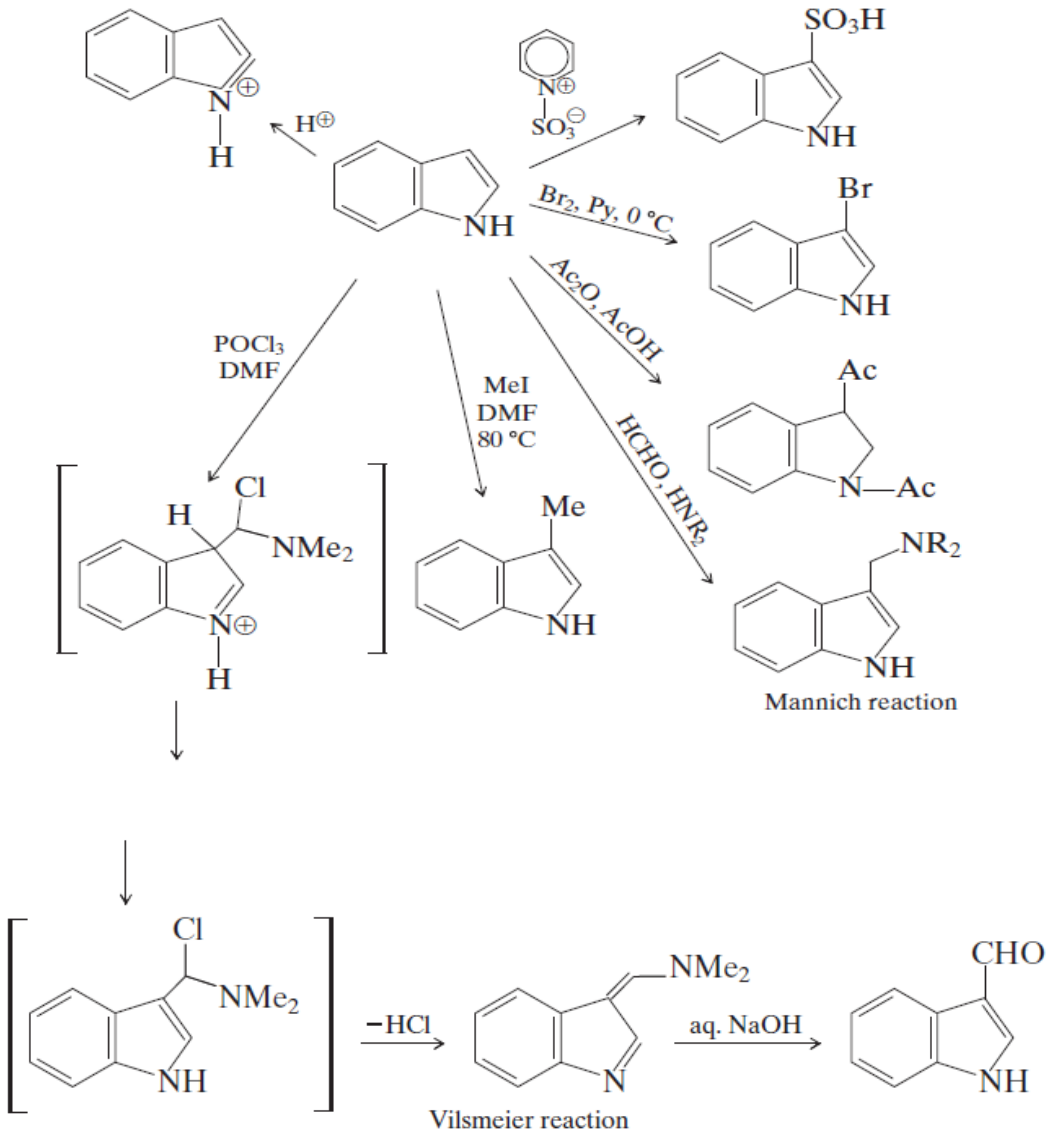



Indole in the enamine form

Because of the higher electron density in the heteroring, indole undergoes electrophilic substitution at C-2 in the pyrrole ring and regioselectively at C-3 due to higher resonance stabilization of the intermediate formed by C-3 attack.




However, indole easily undergoes protonation to give indolenium cation for which the electrophilic substitutions of indole cannot be carried out under the similar conditions as are used in benzene series. For example, indole is sulfonated at C-3 with pyridinium–*N*-sulfonate, brominated at C-3 with bromine in pyridine at 0°C, acetylated at C-1 and C-3 to give diacetyl derivative with acetic anhydride in acetic acid, methylated at C-3 with methyl iodide in DMF at 80°C, formylated at C-3 with $POCl_3$ and DMF at 5°C followed by alkaline hydrolysis (Vilsmeier reac tion), and amino methylated at C-3 with HCHO and amines (Mannich reaction).


H⊕
SO3H
Br2, Py, 0 °C
Br
Ac2O, AcOH
Ac
N—Ac
POCl3
DMF
MeI
DMF
80 °C
HCHO, HNR2
NR2
Me
Cl
H
NMe2
Mannich reaction
−HCl
aq. NaOH
CHO
Vilsmeier reaction

## Synthesis of indole (Fischer's indole synthesis)

Phenylhydrazones having an α-methylene group on treatment with a mineral acid undergoes ring closure through a [3,3] sigmatropic shift with the loss of ammonia. The reaction is known as Fisher's indole synthesis.