

Heterocycles

Fused ring systems

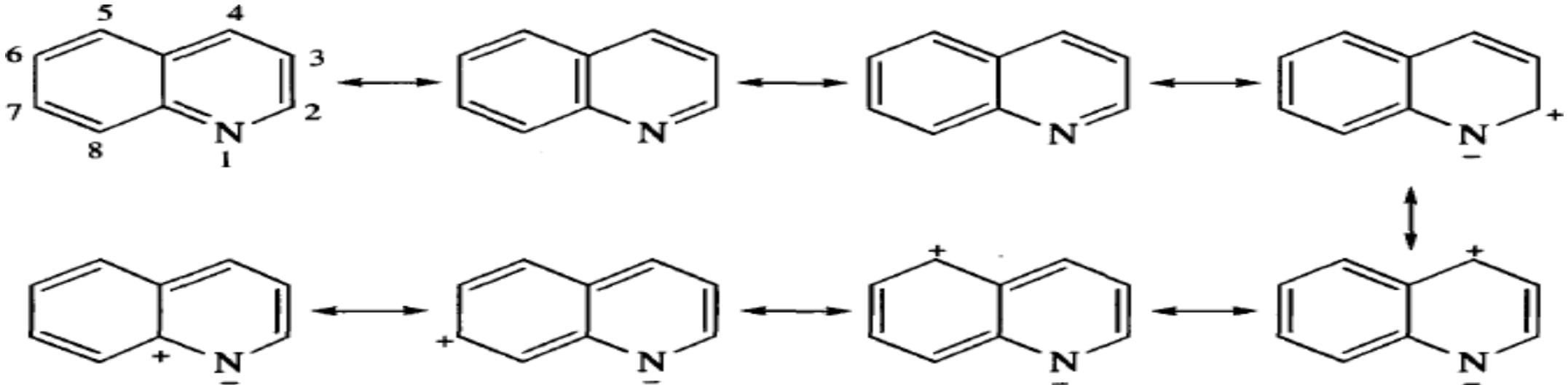
Quinoline — Molecular Formula — C_9H_7N

Quinoline is a Fused aromatic ring system also known as benzo(b)pyridine.

- In quinoline all ring atoms (9 carbons and 1 nitrogen) are SP_2 hybridized.
- Two SP_2 orbitals on each atom overlap with each other to form the **C-C and C-N σ bonds**. The third SP_2 orbital on each **carbon atom** overlaps with an S orbital of hydrogen and forms **C-H σ bonds**.
- The third SP_2 orbital of nitrogen is occupied by the **nitrogen lone pair of electrons**.
- Each ring atom possess **one un hybridized p – orbital** containing one electron and those are perpendicular to the plane containing the **σ bonds**.



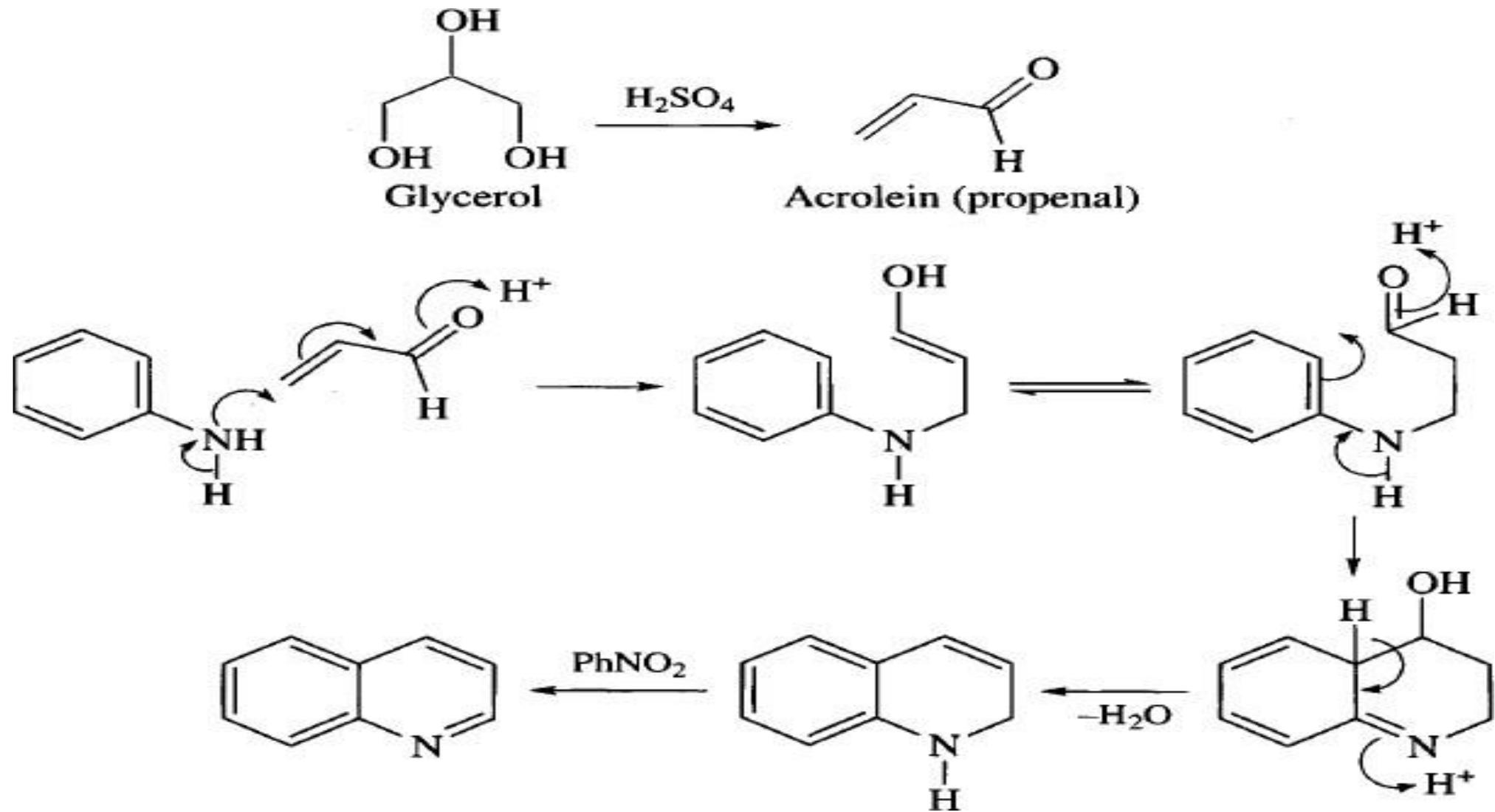
- Overlap of these p – orbitals produces delocalized **π – molecular orbital** containing 10 electrons.
- Quinoline shows aromatic properties because the resulting molecular orbital satisfies the Huckle's rule ($4n+2$ rule).
- The nitrogen lone pair is **not released into the aromatic system** because it is perpendicular to the π system.
- The nitrogen withdraws electrons by resonance, resulting in an **electron-deficient ring system.**



Preparations

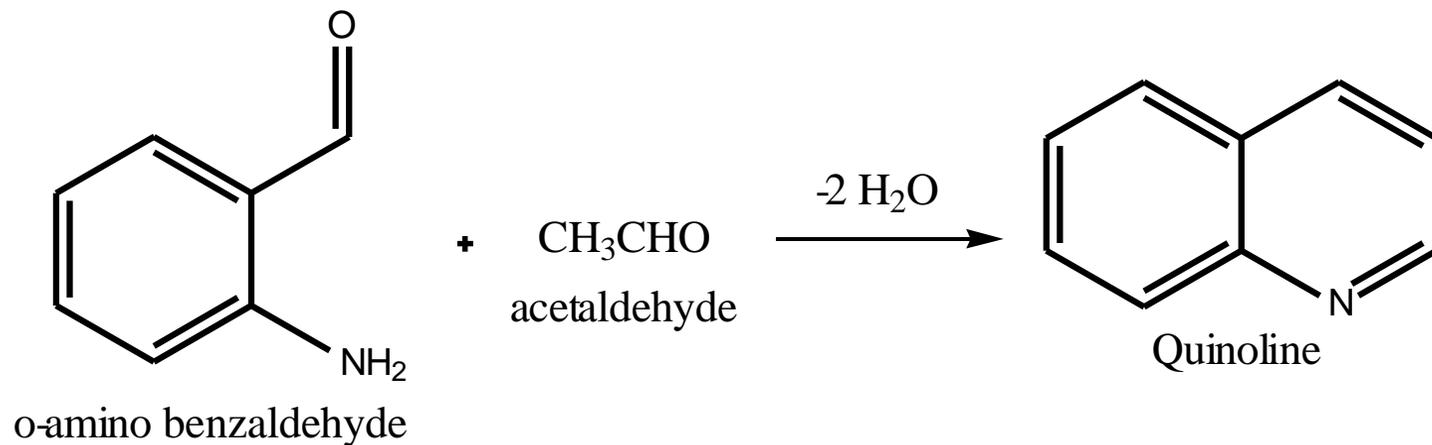
1. Skraup Synthesis:

- ✓ Here a mixture of **glycerol** (propane- 1,2,3-triol), **aniline** (phenylamine), **sulfuric acid**, nitrobenzene and ferrous [iron(II)] sulfate are heated together.
- ✓ The reaction is exothermic and tends to become very violent.
- ✓ **ferrous [iron(II)] sulfate** is added to make the reaction **less violent**.
- ✓ **Nitrobenzene**, or an alternative oxidant (iodine or chloroaniline are often recommended), is required to **convert** the product, 1,2-dihydroquinoline into quinoline.



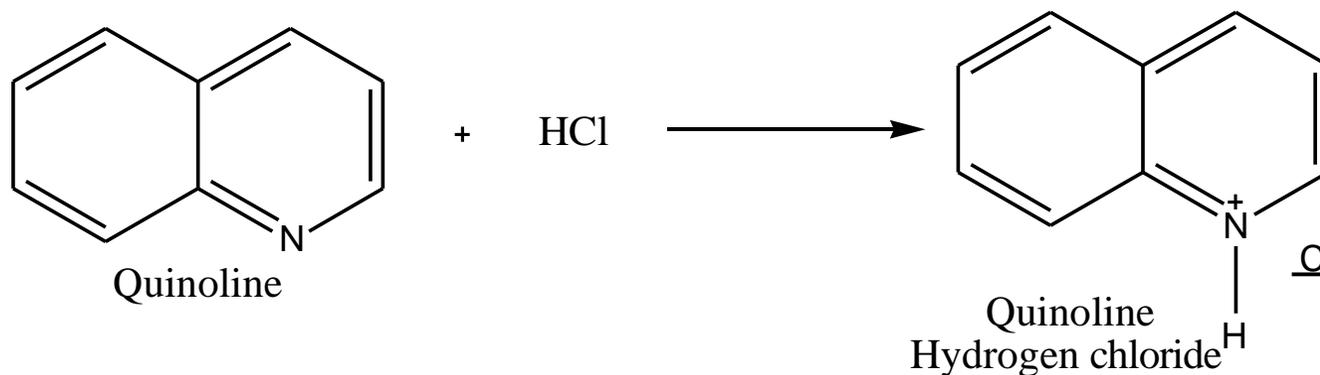
Skraup Synthesis

2. **Friedlander Synthesis:** It involves condensation of o-amino benzaldehyde with acetaldehyde in the presence of an alkali.



Basic Character:

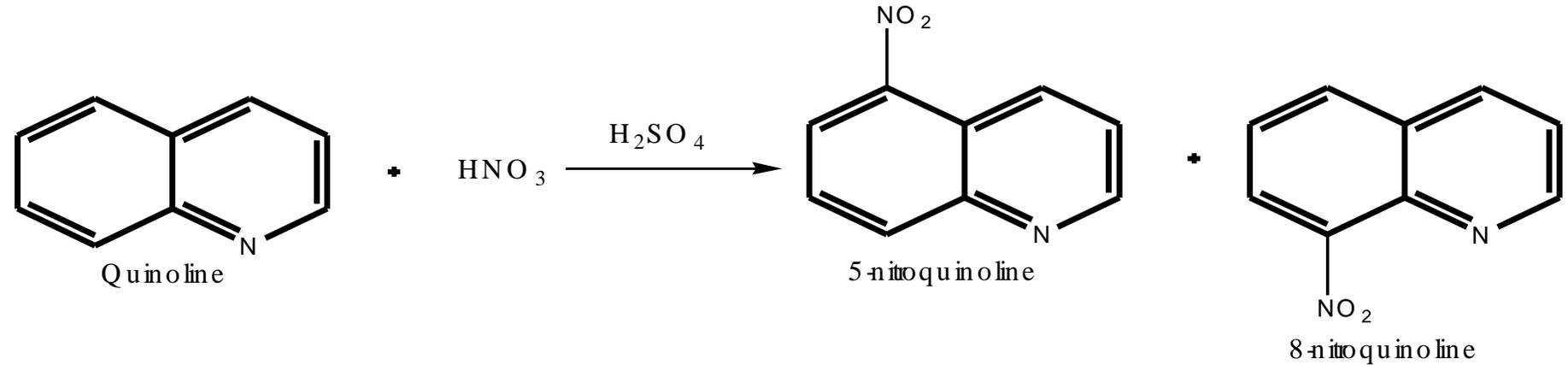
- Quinoline is slightly weaker base than pyridine. It reacts with acids to yield salts which are sparingly soluble in water.



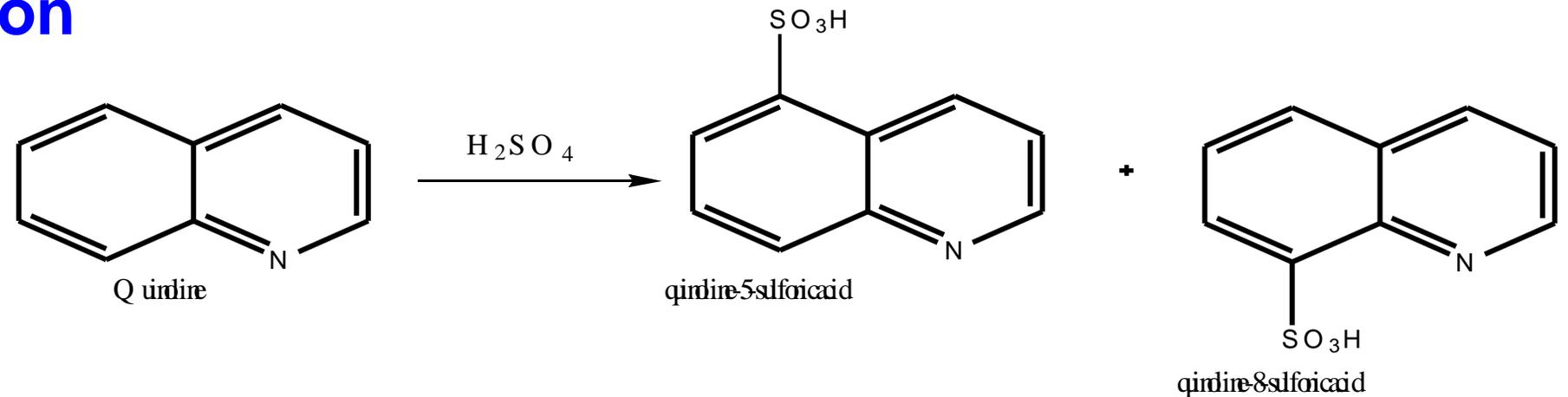
Chemical reactions:

1. **Electrophilic substitution reactions:** Takes at C5 & C8 positions.

a) **Nitration:**

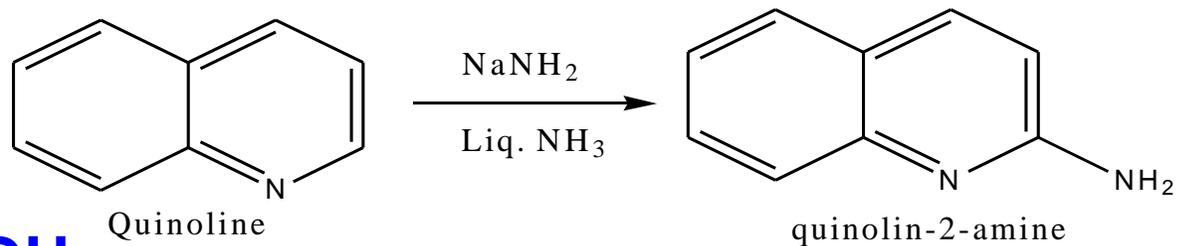


b) **Sulphonation**

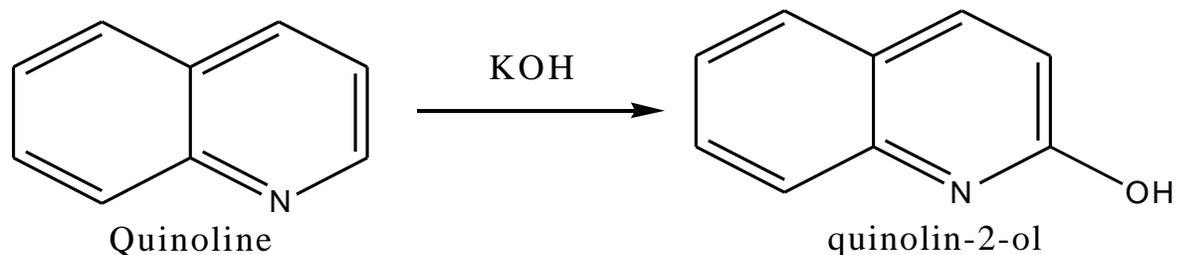


2. Nucleophilic substitution reactions:

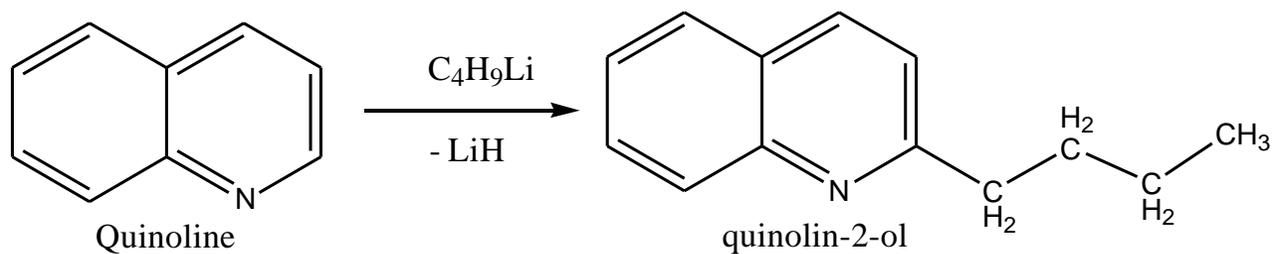
Reaction with sodamide: Substitution mostly happens at C-2 position, if any substitution present at C-2 position then reaction occur at C-4 position.



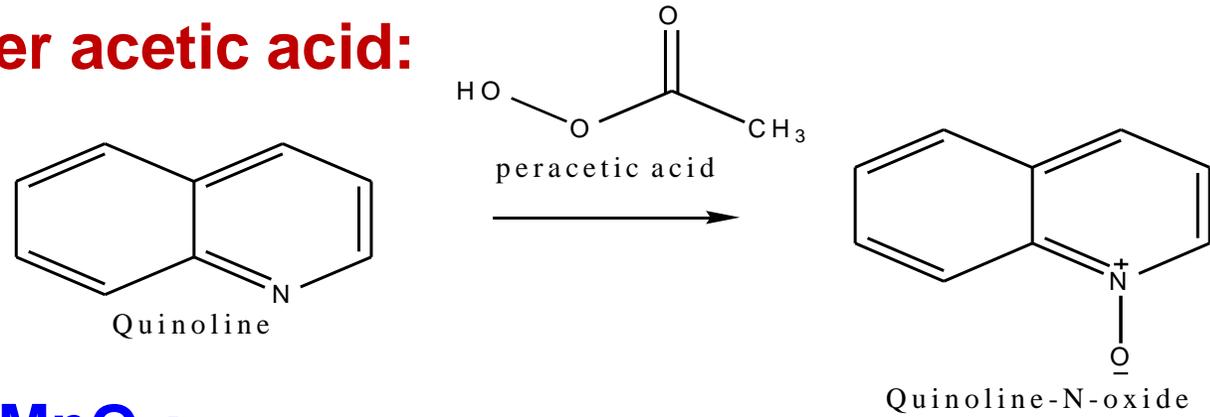
3. Reaction with KOH:



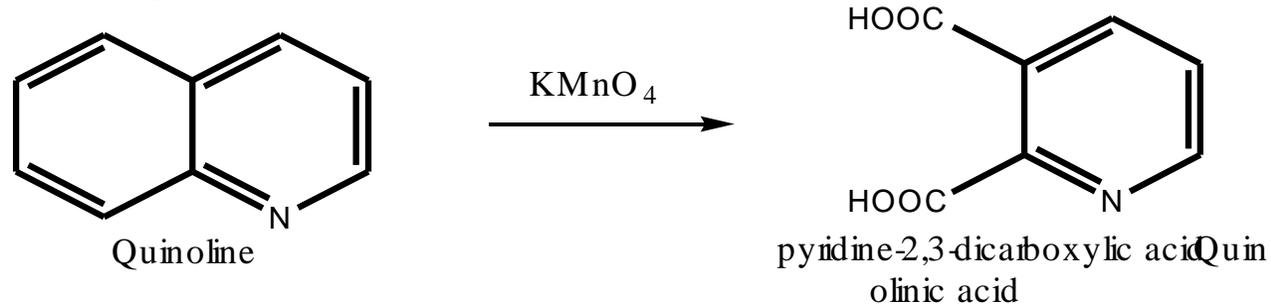
4. Reaction with n-butyl lithium



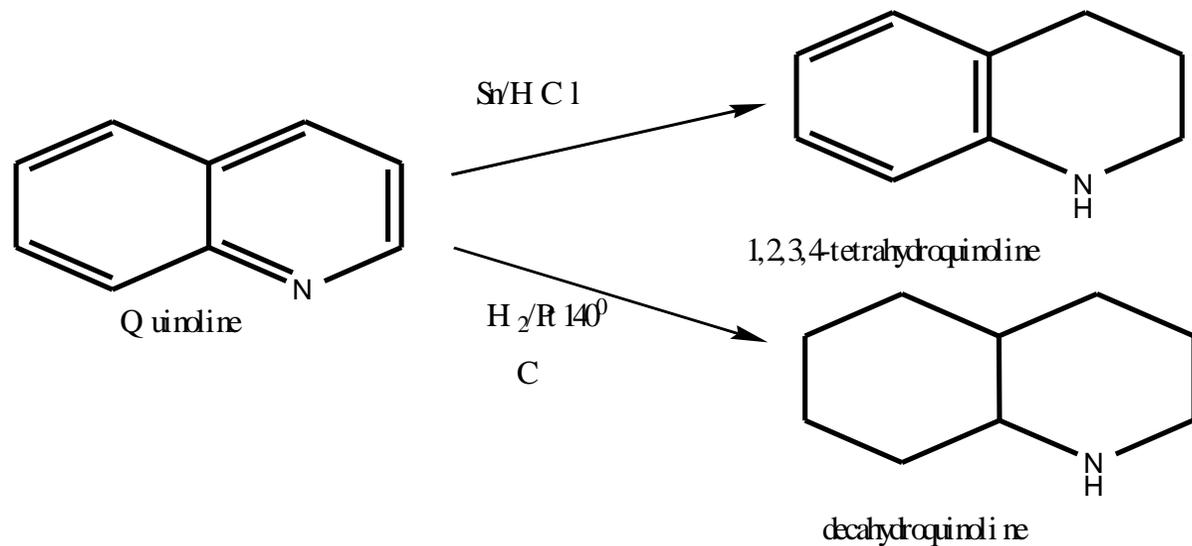
5. Reaction with per acetic acid:



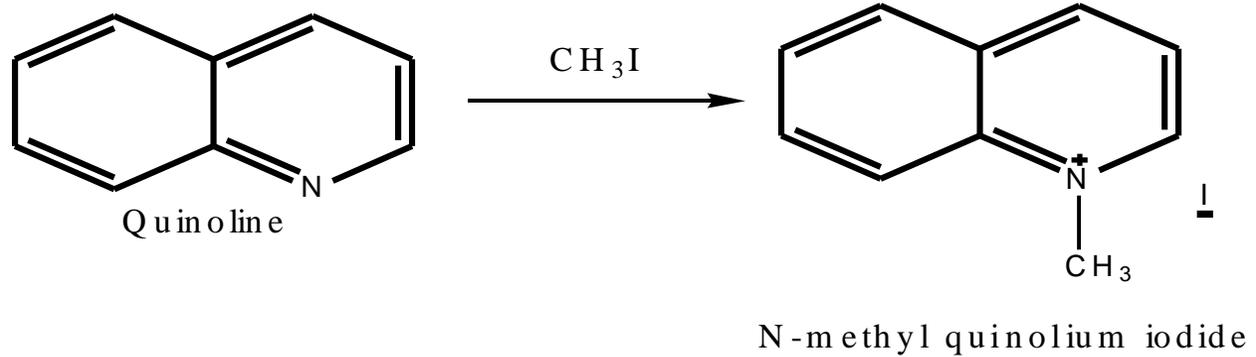
6. Reaction with KMnO_4 :



7. Reduction:



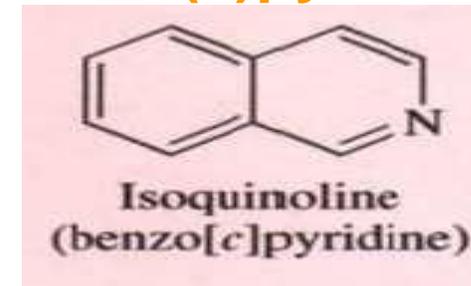
8. Reaction with alkyl halides:



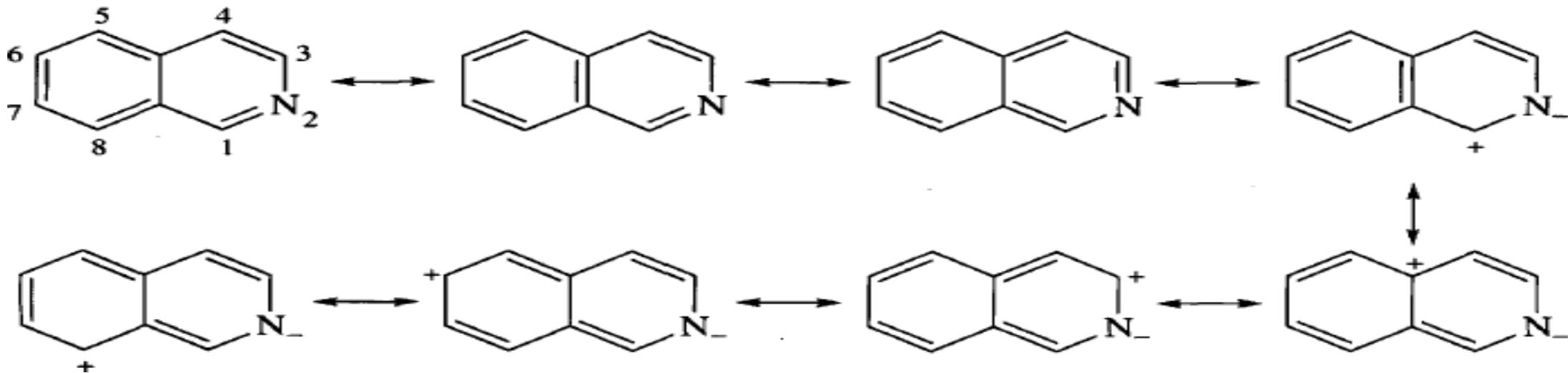
Isoquinoline — Molecular Formula — C_9H_7N

Isoquinoline is a Fused aromatic ring system also known as benzo(c)pyridine.

- In isoquinoline all ring atoms (9 carbons and 1 nitrogen) are SP_2 hybridized.
- Two SP_2 orbitals on each atom overlap with each other to form the **C-C and C-N σ bonds**. The third SP_2 orbital on each **carbon atom** overlaps with an S orbital of hydrogen and forms **C-H σ bonds**.
- The third SP_2 orbital of nitrogen is occupied by the **nitrogen lone pair of electrons**.
- Each ring atom possess **one un hybridized p – orbital** containing one electron and those are perpendicular to the plane containing the **σ bonds**.



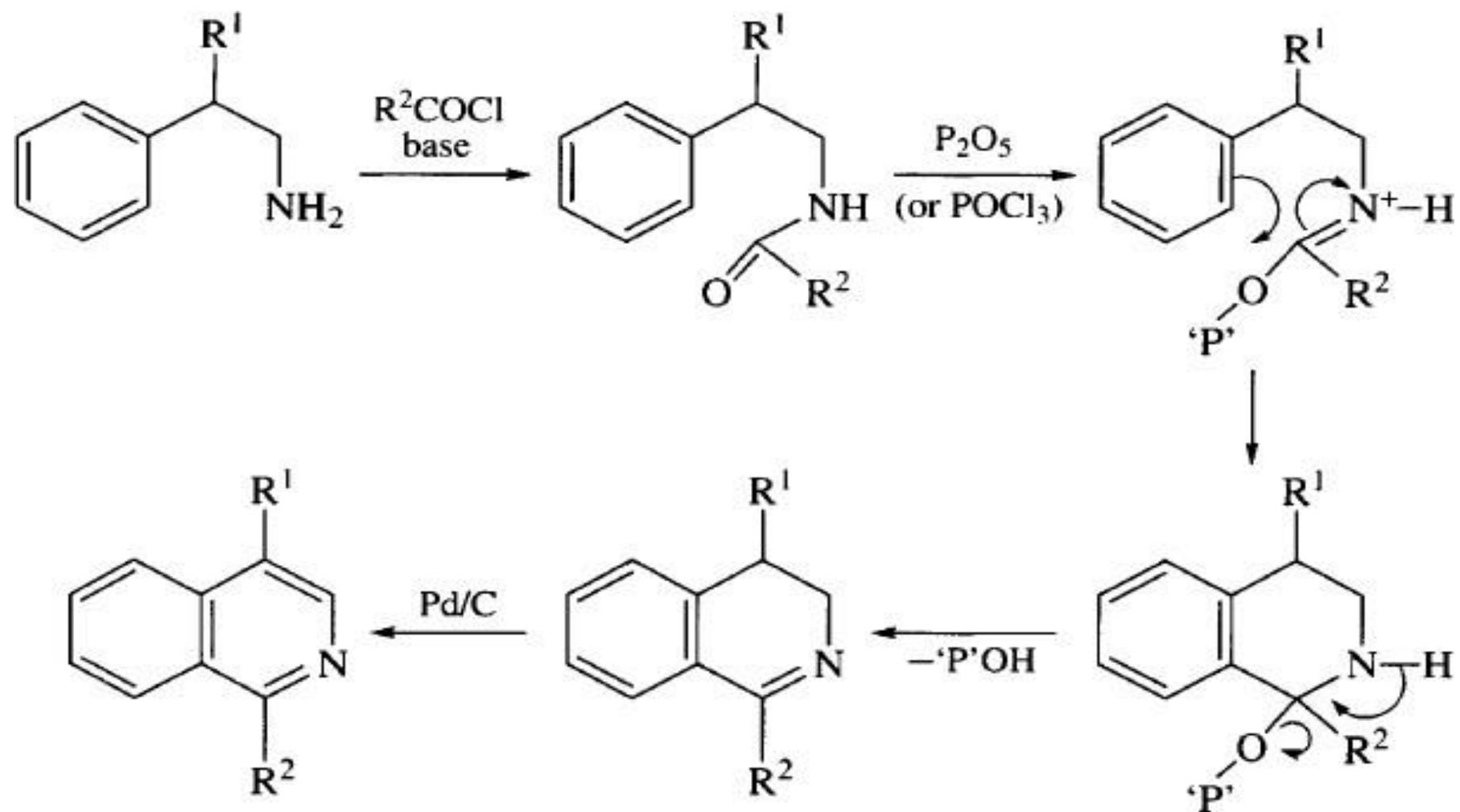
- Overlap of these p – orbitals produces delocalized **π – molecular orbital** containing 10 electrons.
- Isoquinoline shows aromatic properties because the resulting molecular orbital satisfies the Huckle's rule ($4n+2$ rule).
- The nitrogen lone pair is **not released into the aromatic system** because it is perpendicular to the π system.
- The nitrogen withdraws electrons by resonance, resulting in an **electron-deficient ring system.**



Preparations

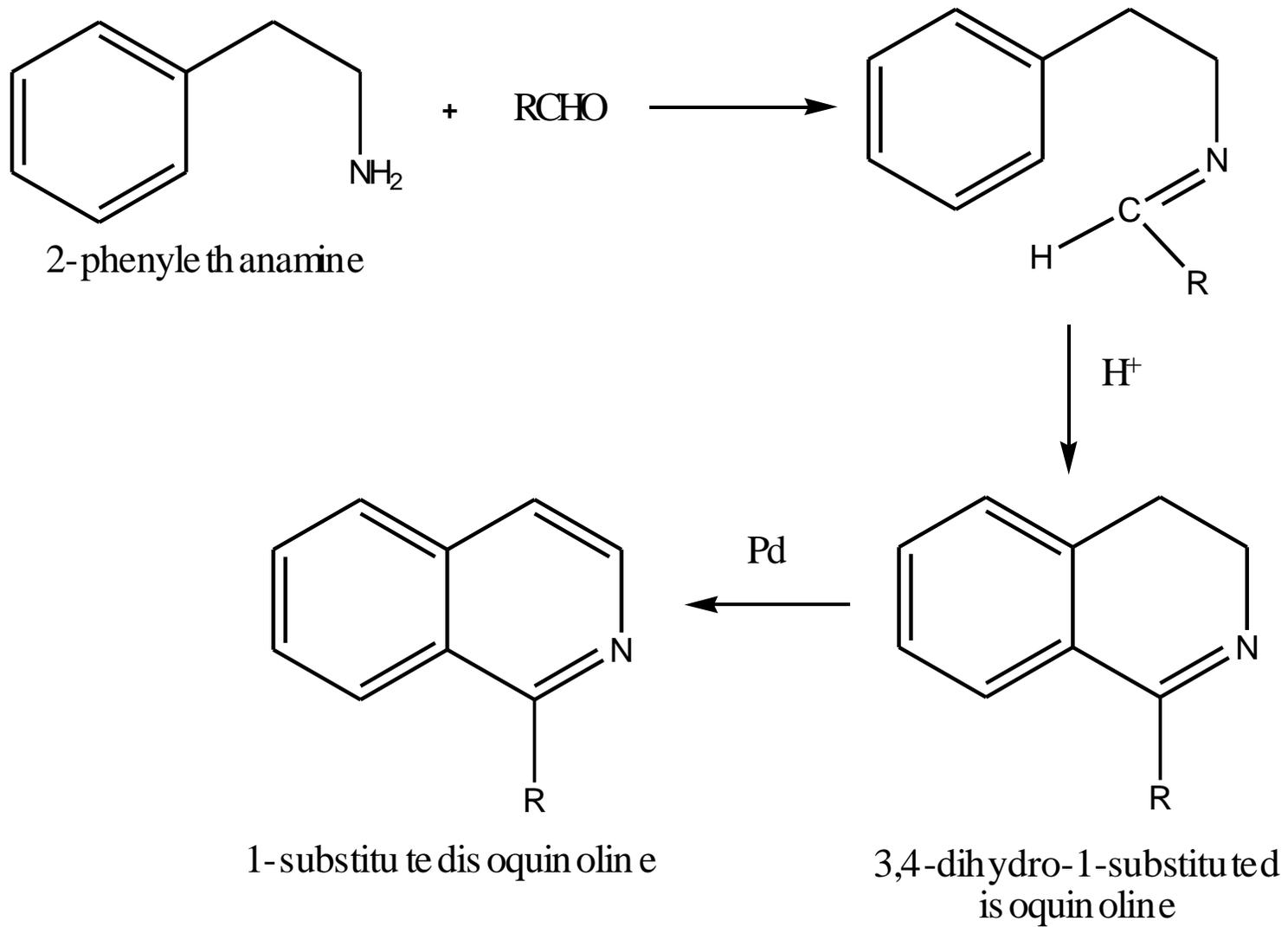
1. Bischler-Napieralski Synthesis:

- ✓ This method is very useful for the construction of 1-substituted 3,4-dihydroisoquinolines, which if necessary can be oxidized to isoquinolines.
- ✓ β -phenylethylamine is reacted with an acyl chloride and a base to give the corresponding amide ($R^1 = H$) and then this is cyclized to a 3,4-dihydroisoquinoline by treatment with either phosphorus pentoxide or phosphorus oxychloride. Finally, aromatization is accomplished by heating the 3,4-dihydroisoquinoline over palladium on charcoal.



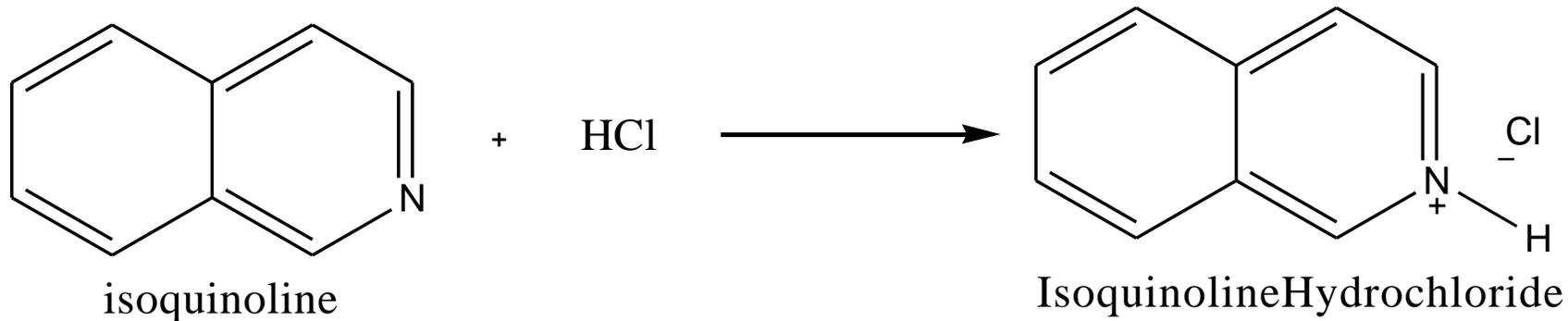
2. Pictet-Spengler Synthesis:

β -phenylethylamine react with an aldehyde, the reaction intermediate is an imine which, provided the benzene ring contains electron donating groups, often ring closes under very mild acidic conditions. Indeed, cyclization can occur under physiological conditions, and in Nature this is an important step in the biosynthesis of many tetrahydroisoquinoline alkaloids. This tetrahydroisoquinoline can be dehydrogenated by palladium to form 1-substituted isoquinoline.



Basic Character:

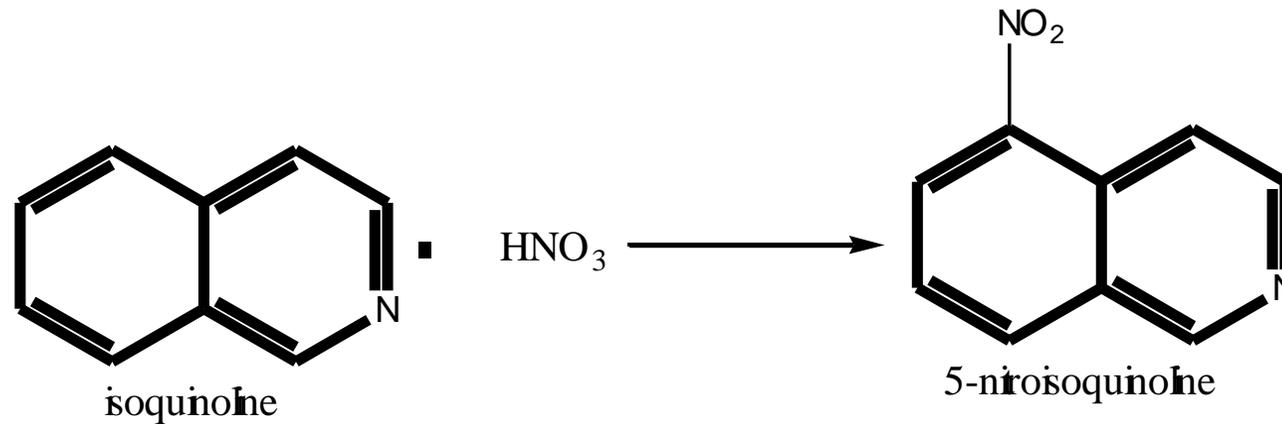
- Isoquinoline is slightly weaker base, It reacts with acids to yield salts which are sparingly soluble in water.



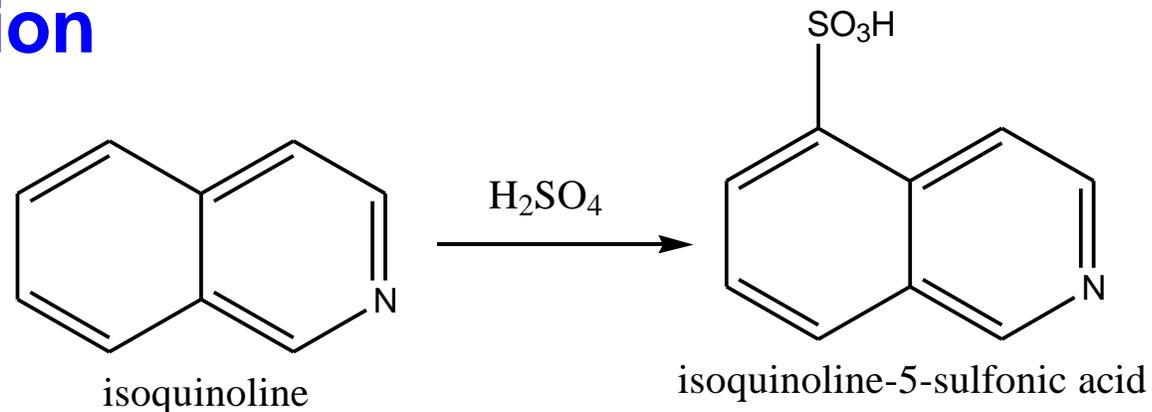
Chemical reactions:

1. **Electrophilic substitution reactions:** It takes place at the position 5.

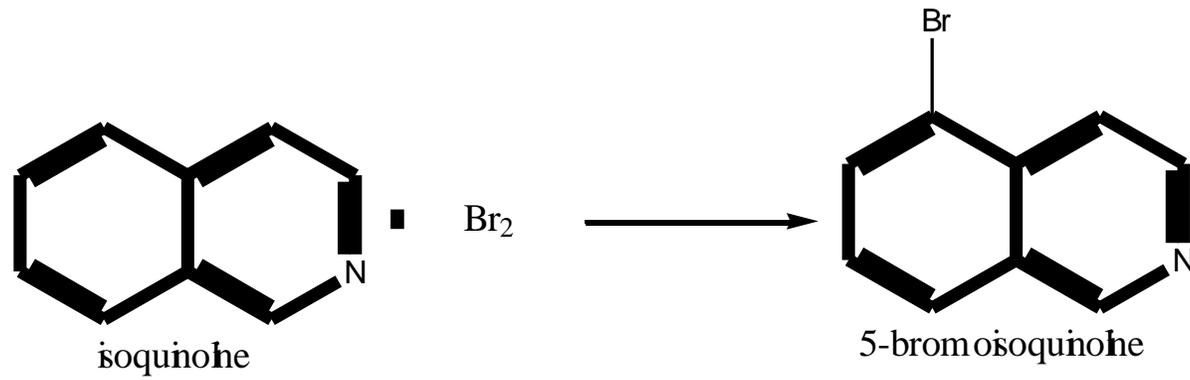
a) **Nitration:**



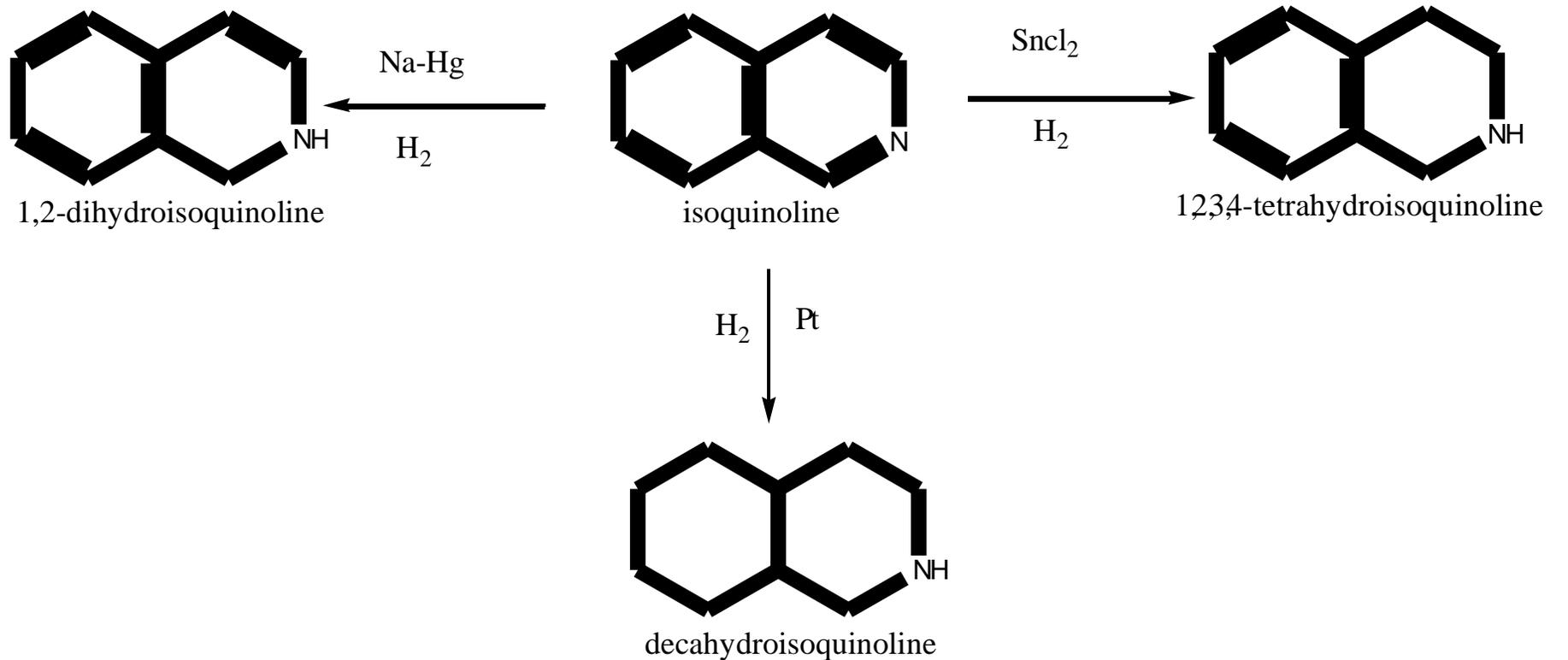
b) **Sulphonation**



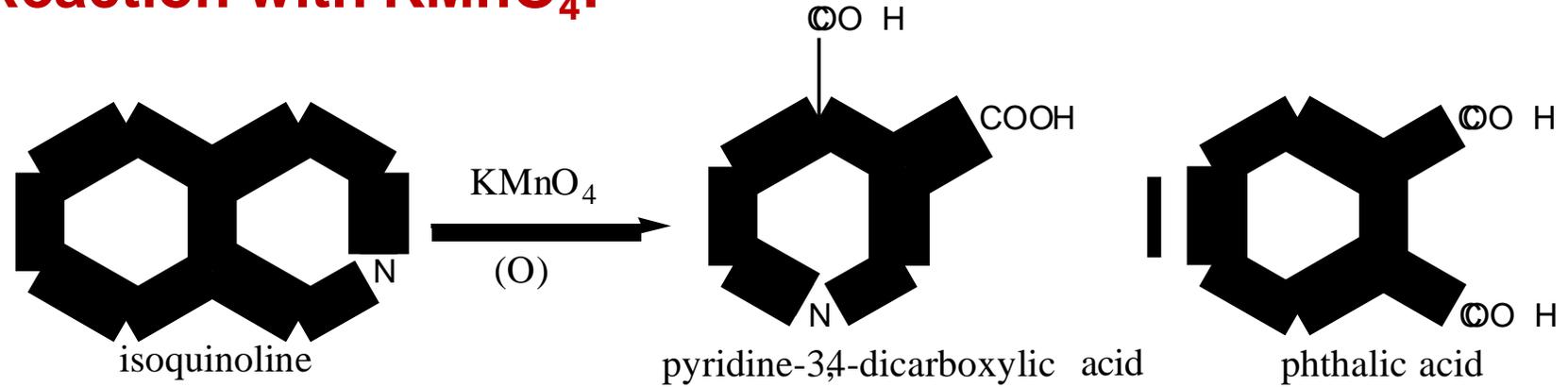
c. Bromination:



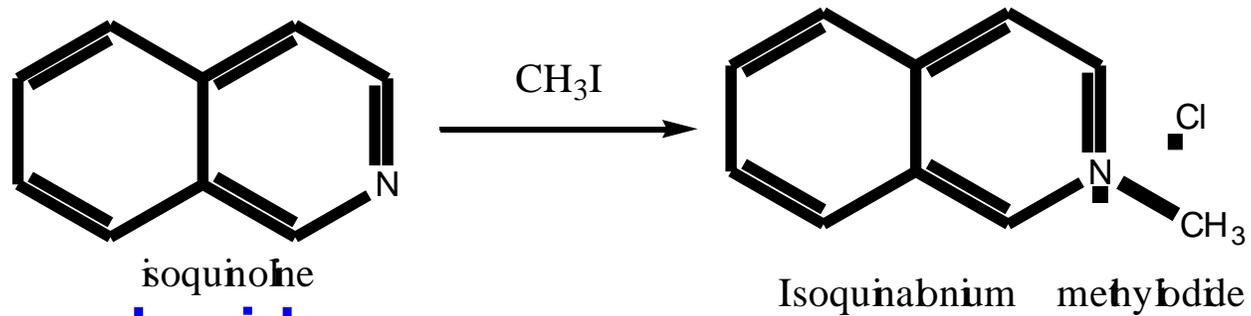
2. Reduction:



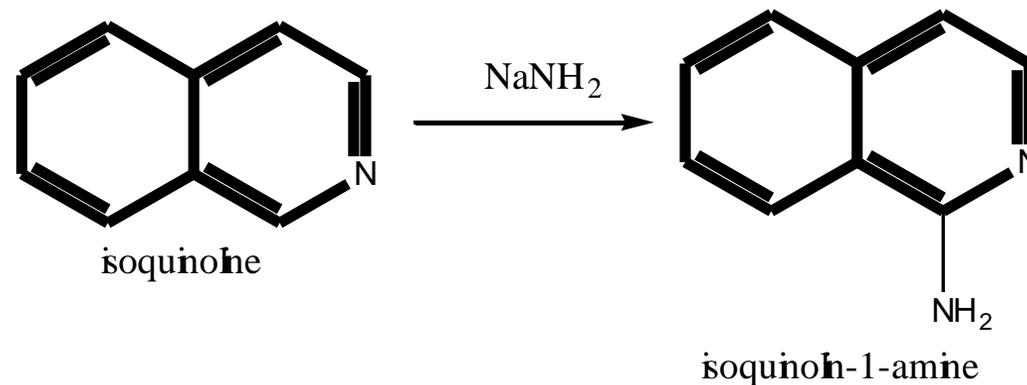
3. Oxidation / Reaction with KMnO_4 :



4. Reaction with alkyl halide:



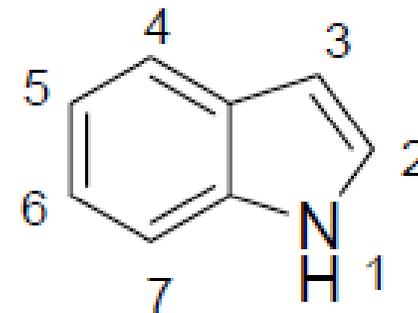
5. Reaction with sodamide:



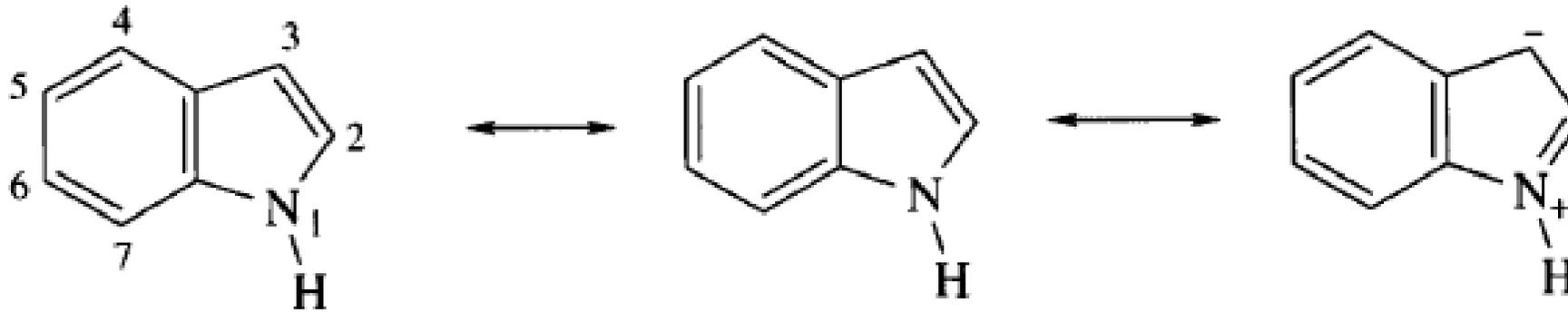
Indole — Molecular Formula — C_8H_7N

Indole is a Fused aromatic ring system also known as benzo(b)pyrrole.

- In indole all ring atoms (8 carbons and 1 nitrogen) are SP_2 hybridized.
- Two SP_2 orbitals on each atom overlap with each other to form the **C-C and C-N σ bonds**. The third SP_2 orbital on each **ring atom** overlaps with an S orbital of hydrogen and forms **C-H and N-H σ bonds**.
- The **un hybridized p – orbital** of nitrogen is occupied by the **nitrogen lone pair of electrons**.
 - Each carbon atom in ring possess **one un hybridized p –orbital** containing one electron and those are perpendicular to the plane containing the **σ bonds**.



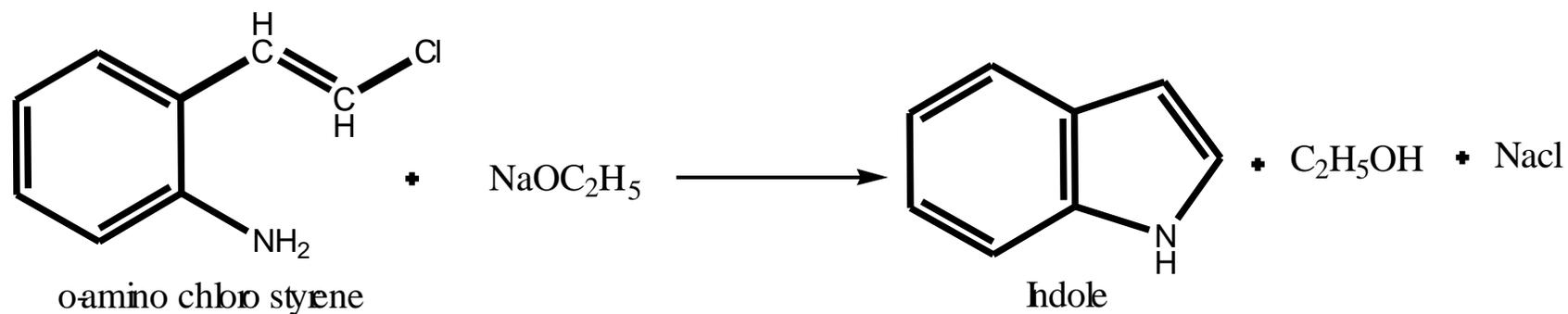
- Overlap of these p – orbitals produces delocalized π – **molecular orbital** containing 10 electrons. **(8 electrons from 8 carbons and lone pair of electrons from nitrogen)**
- Indole shows aromatic properties because the resulting molecular orbital satisfies the Huckle’s rule ($4n+2$ rule).
- The nitrogen lone pair is **released into the aromatic system.**



Preparations

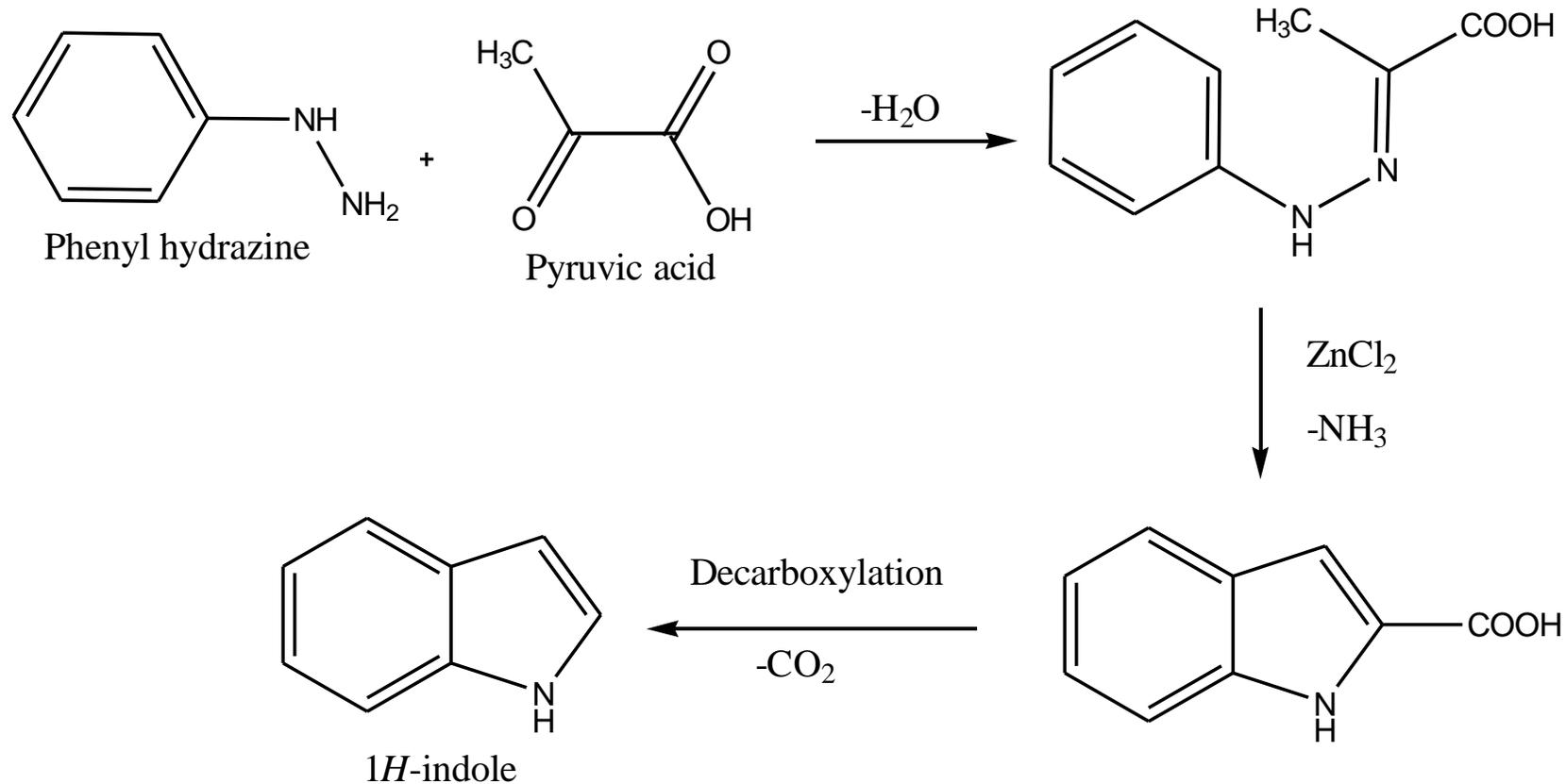
1. Lipp Synthesis:

- ✓ In this method o-amino chlorostyrene is heated with sodium ethoxide at 160-170°C.



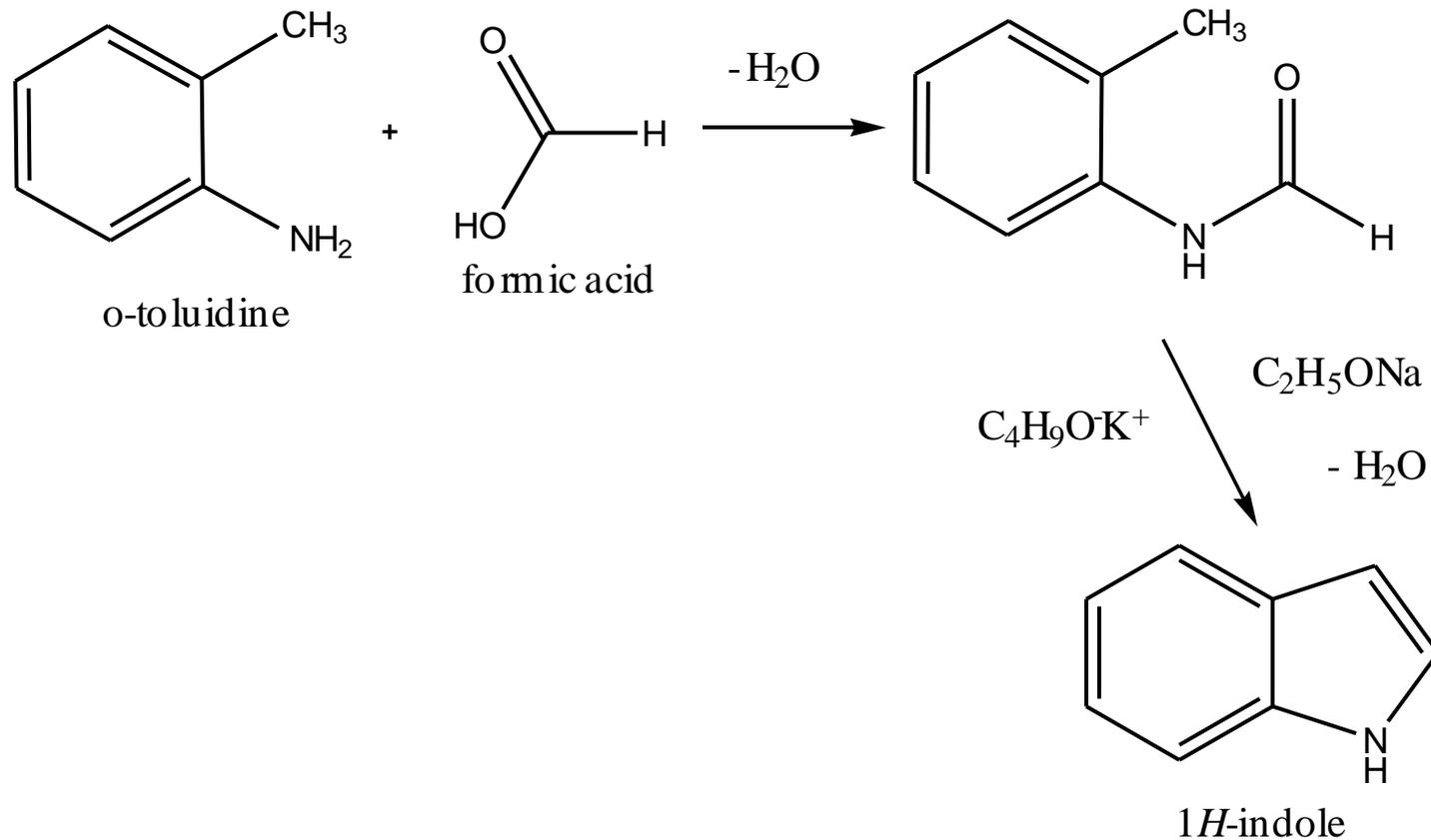
2. Fisher indole synthesis:

- ✓ Pyruvic acid is first treated with phenyl hydrazine to form the corresponding phenyl hydrazone.
- ✓ Then the hydrazone is heated with anhydrous zinc chloride or poly phosphoric acid to give indole-2-carboxylic acid, which upon decarboxylation yields indole.



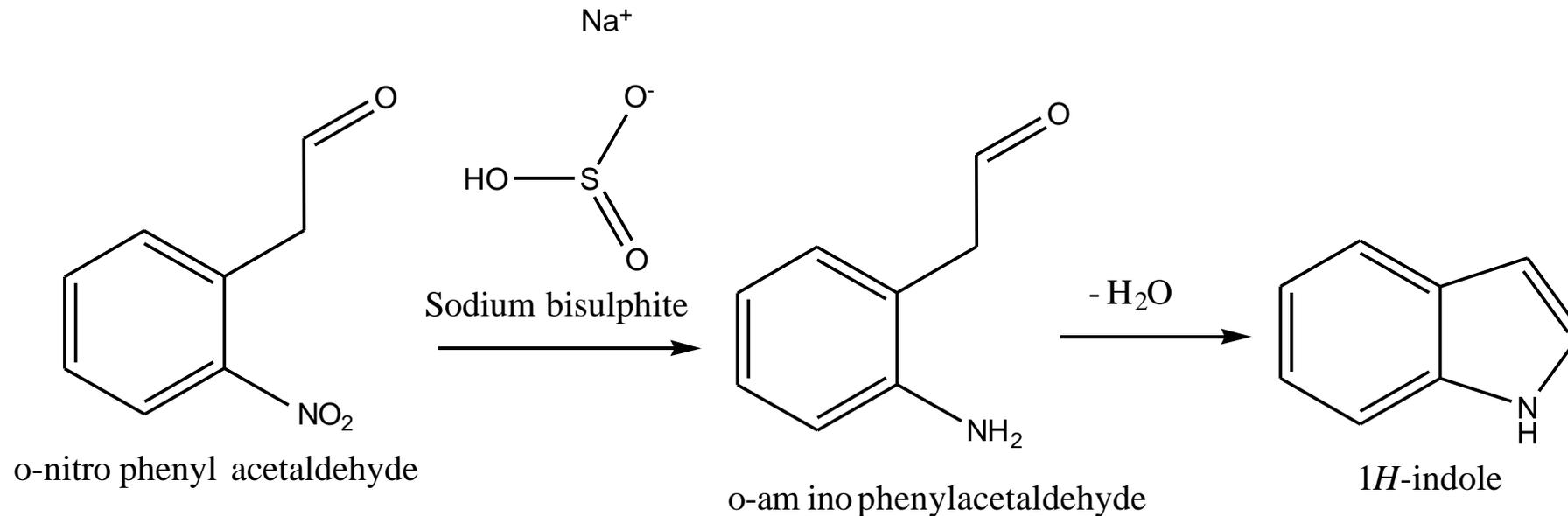
3. Madelung synthesis:

- ✓ O-toluidine is react with formic acid to form N-formyl o-toluidine. This undergoes dehydration on heating with sodium ethoxide or potassium t-butoxide to yield indole.



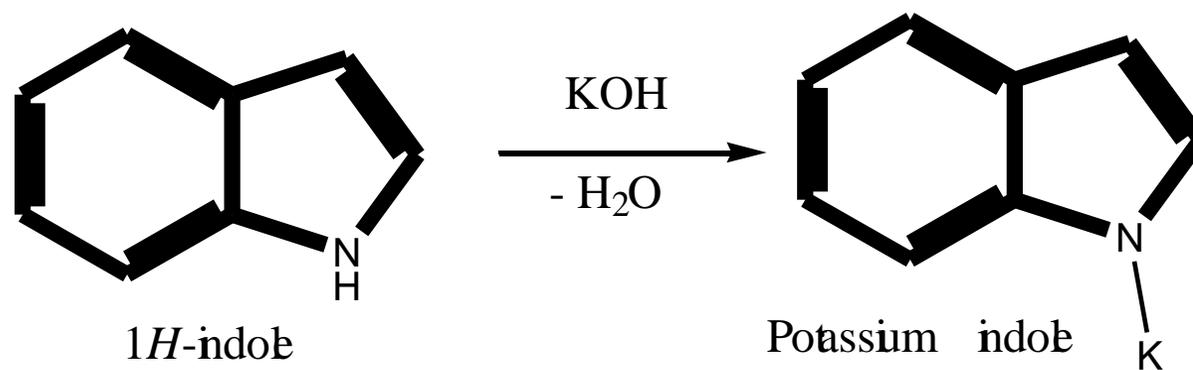
4. From o-nitro phenyl acetaldehyde:

- ✓ This involves reduction of o-nitro phenyl acetaldehyde with iron powder and sodium bisulphite to give o-amino phenyl acetaldehyde, which cyclizes spontaneously to yield indole.



Basic Character & Acidic character:

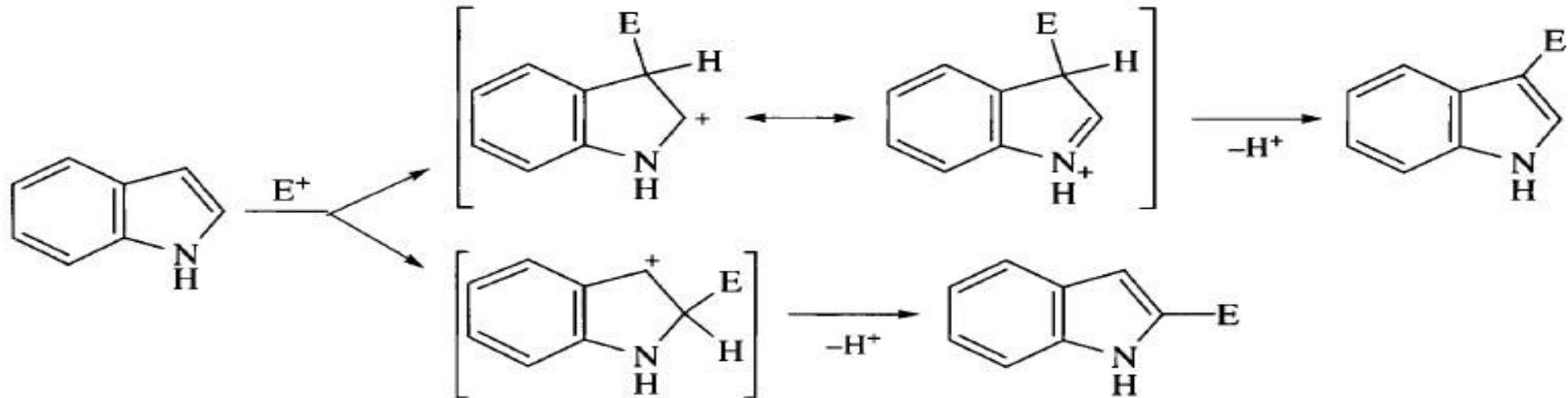
- Indole is a weak base and also a weak acid as like pyrrole.
- Indole is a weak base since the lone pair of electrons of nitrogen atom contributes to the $4n+2$ π electron cloud (aromatic sextet). Thus, the availability of these lone pair of electrons is decreased.
- Indole also exhibit weak acidic properties, the weak acidic property is because of its formation of potassium indole with KOH.



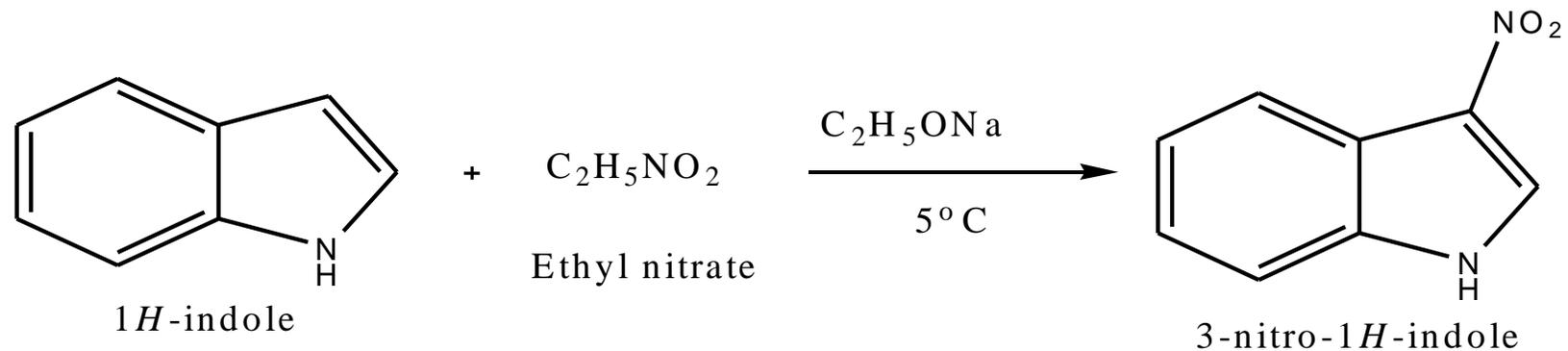
Chemical reactions:

Electrophilic Substitution reactions (C-3 versus C-2):

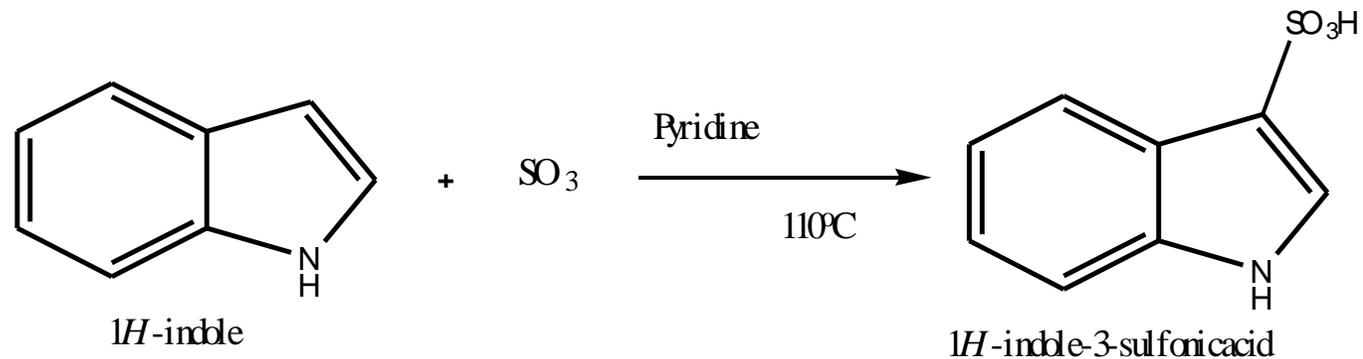
- ✓ Electrophiles attack indole at **C-3**, rather than at **C-2**.
- ✓ This is the opposite result to that observed for pyrroles, but can be explained if the intermediates for each type of reaction are considered.
- ✓ For a reaction at **C-3**, the energy of activation of the intermediate is lowered because it is possible to delocalize the positive charge through resonance involving the nitrogen lone pair of electrons.
- ✓ This favourable situation is not possible in the corresponding intermediate for attack at **C-2**. Any attempt to delocalize the positive charge would now disrupt the 6π electrons system of the benzene ring.



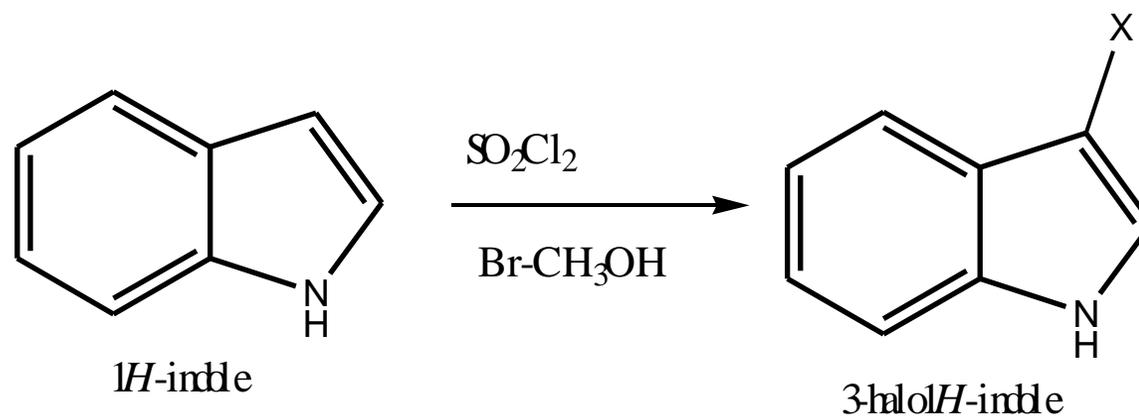
a) Nitration:



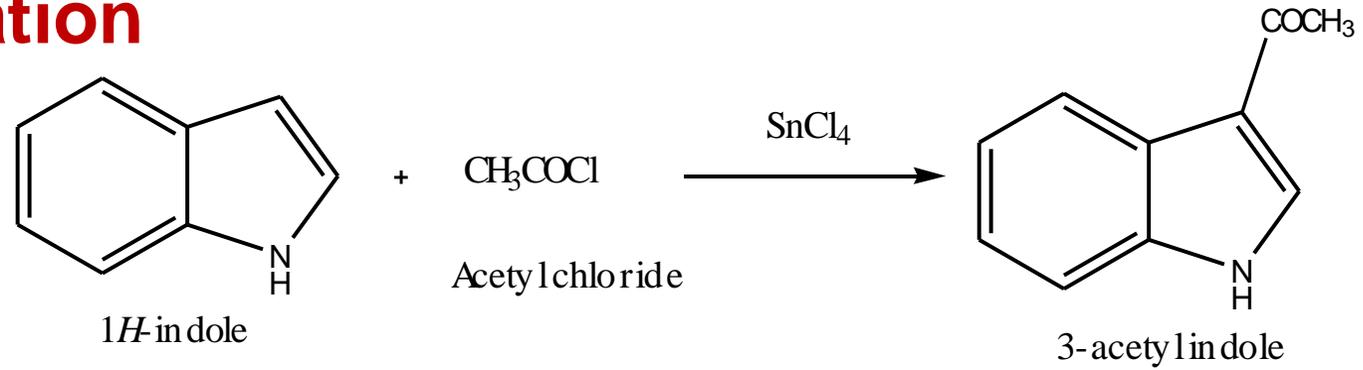
b) Sulphonation



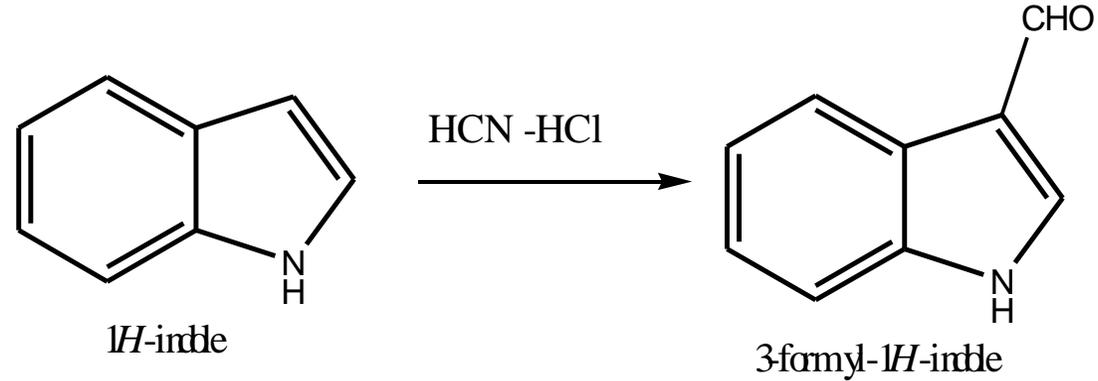
c) Halogenation



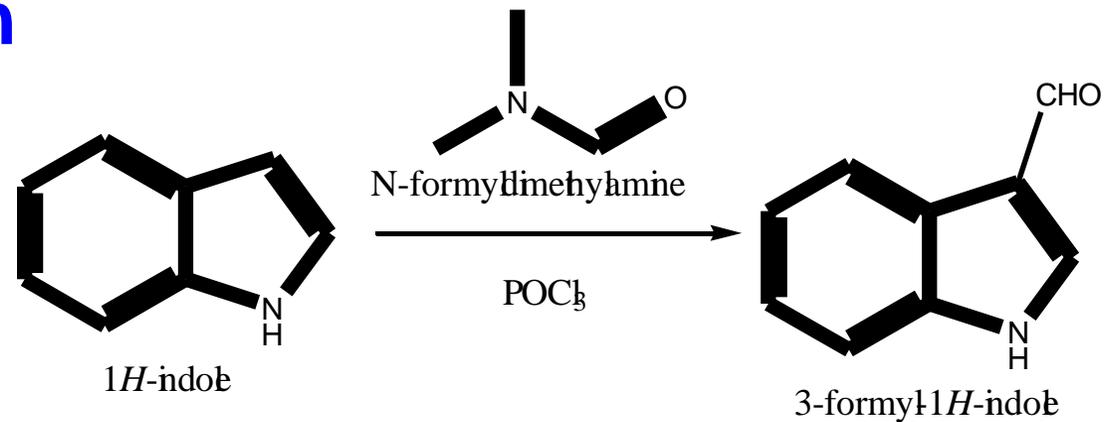
d) Friedel-Craft acylation



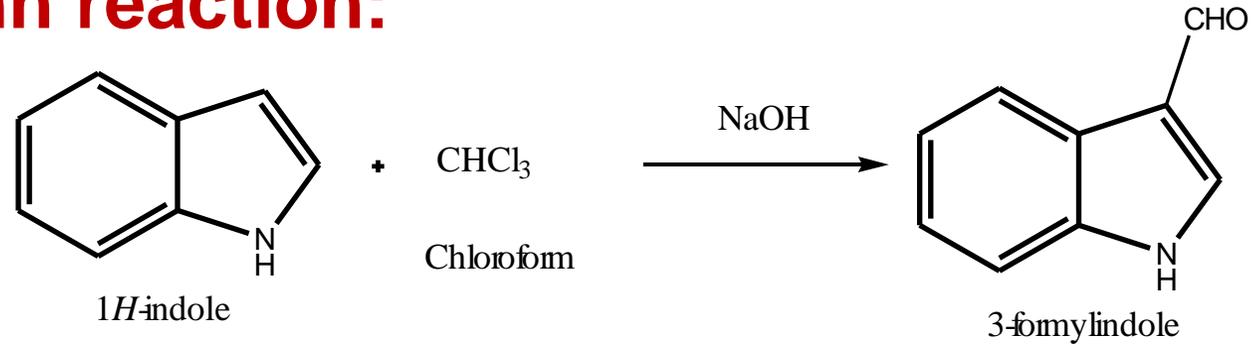
e) Formylation



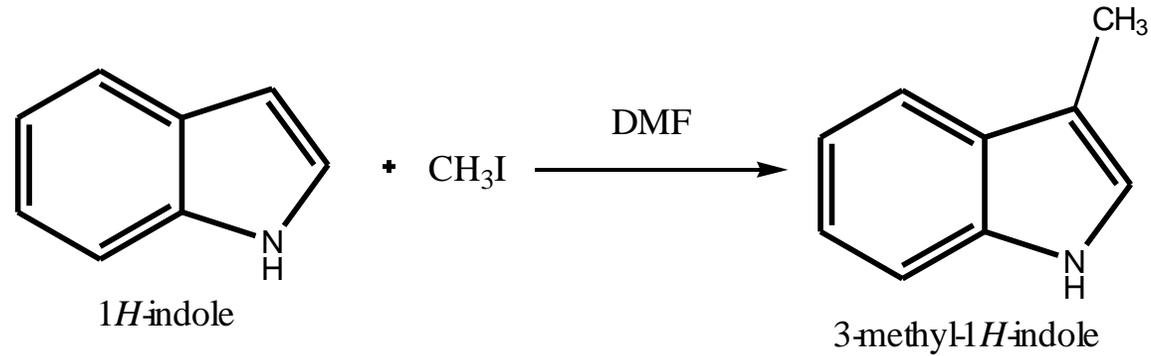
f) Vilsmeier reaction



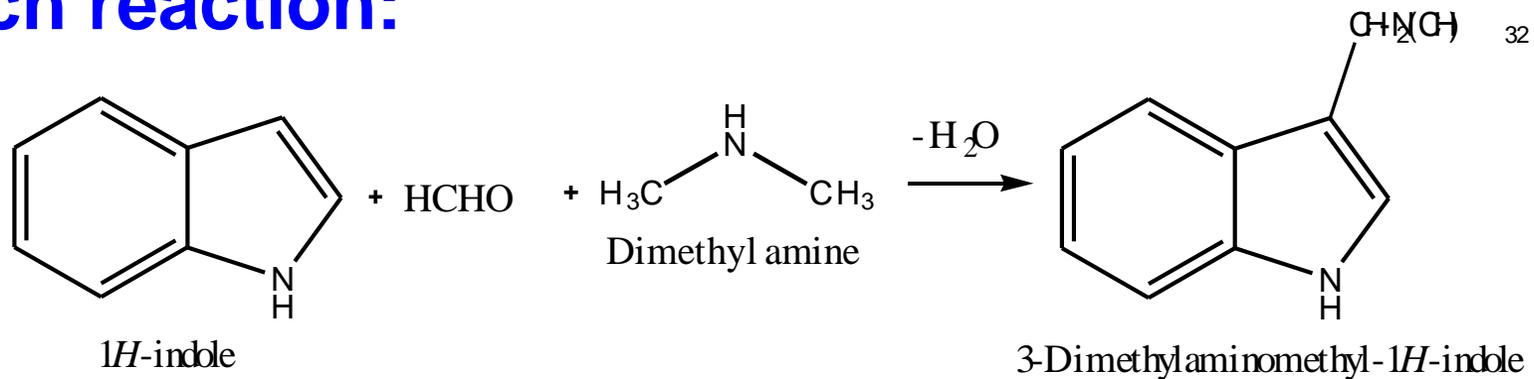
g) Reimer – tiemann reaction:



h) Alkylation



i) Mannich reaction:



Acridine — Molecular Formula – $C_{13}H_9N$

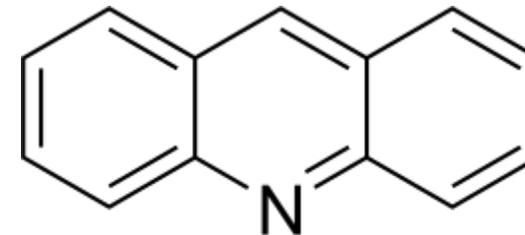
Acridine is a Fused aromatic ring system also known as **Dibenzo[b,e]pyridine** / **2,3-Benzoquinoline**

- In acridine all ring atoms (13 carbons and 1 nitrogen) are SP_2 hybridized.

- Two SP_2 orbitals on each atom overlap with each other to form the **C-C and C-N σ bonds**. The third SP_2 orbital on each **carbon atom** overlaps with an S orbital of hydrogen and forms **C-H σ bonds**.

- The **third SP_2 orbital of nitrogen** is occupied by the **lone pair of electron of nitrogen**.

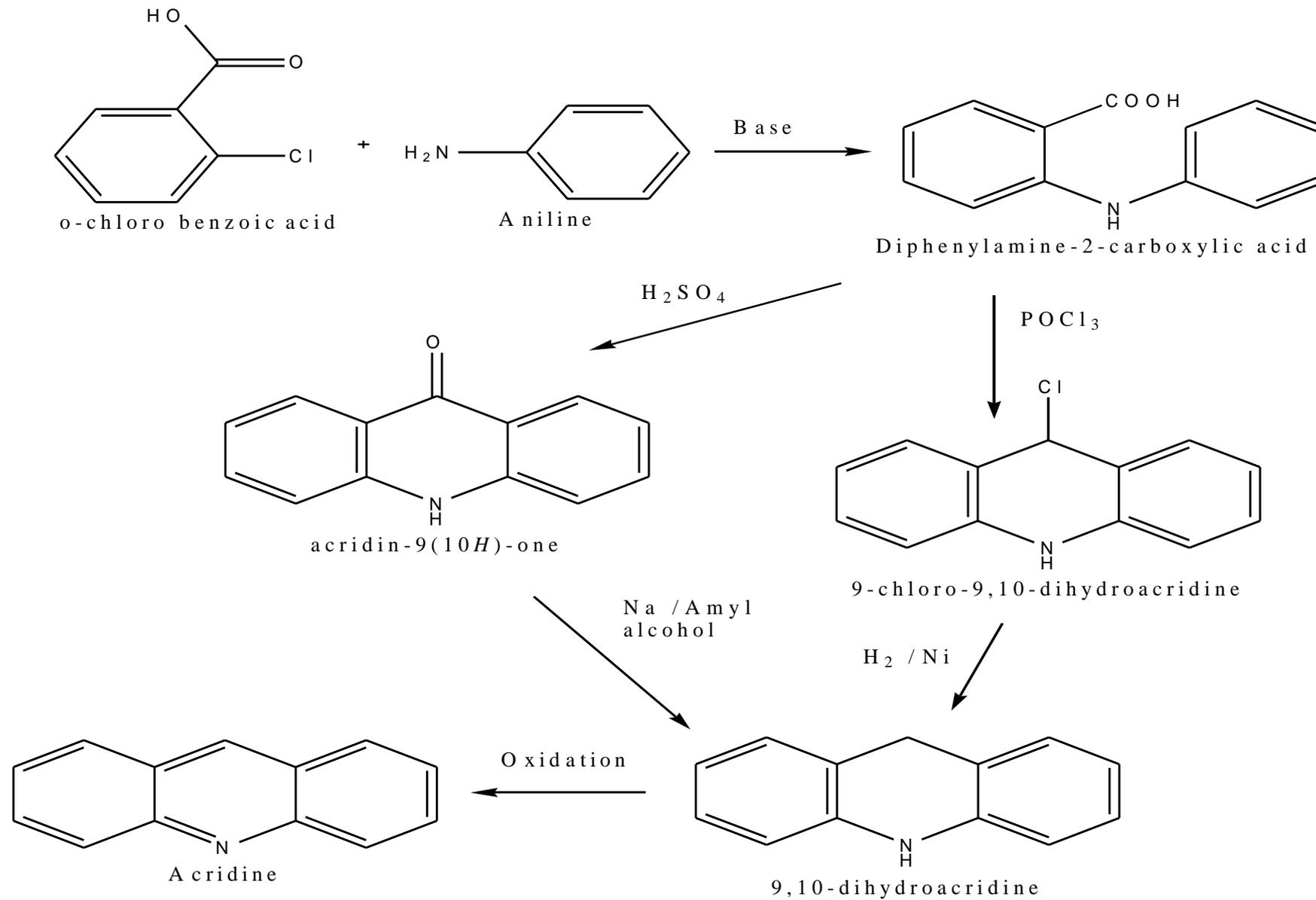
- Each **ring atom** in ring possess **one un hybridized p – orbital** containing one electron and those are perpendicular to the plane containing the **σ bonds**.



- Overlap of these p – orbitals produces delocalized **π – molecular orbital** containing 14 electrons.
- Acridine shows aromatic properties because the resulting molecular orbital satisfies the Huckle’s rule ($4n+2$ rule).
- The nitrogen lone pair is **not released into the aromatic system.**
- It is a planar molecule that is structurally related to anthracene with one of the central CH group is replaced by nitrogen.

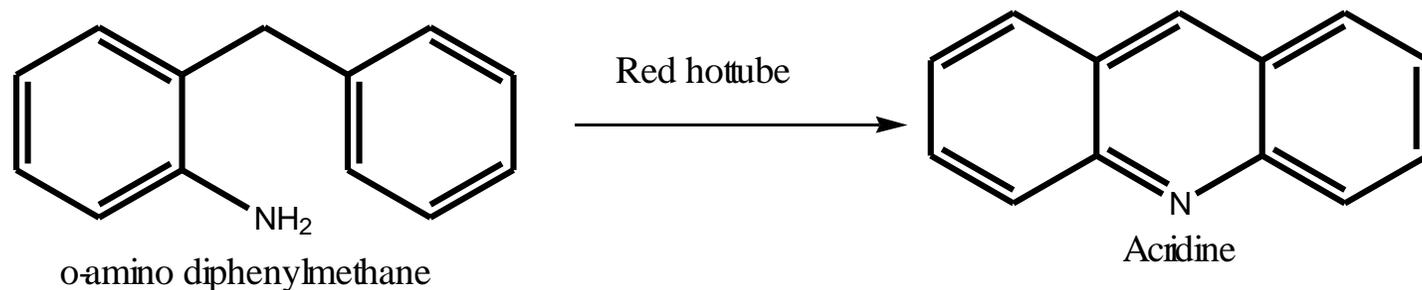
Preparations

1. From diphenyl amine-2-carboxylic acid:



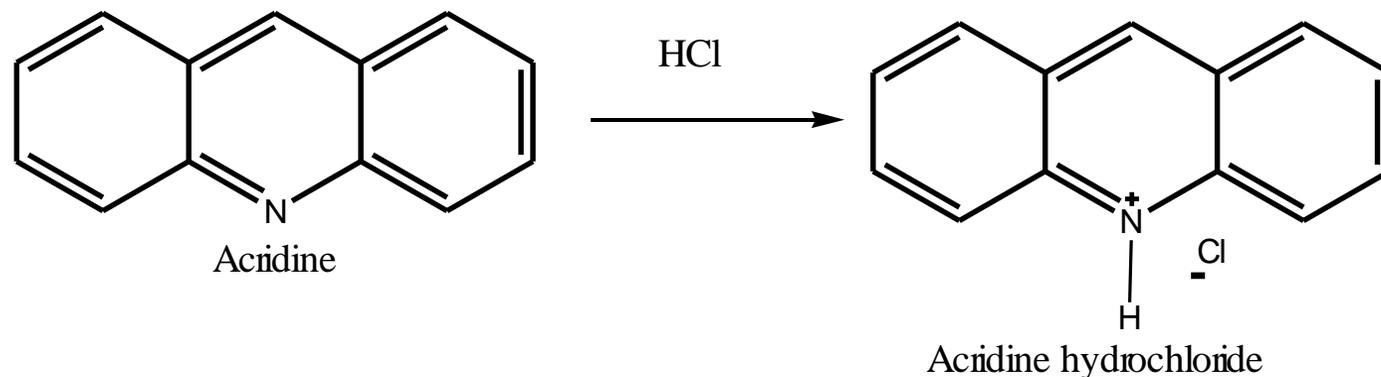
2. From o-amino diphenyl methane:

Acridine is also prepared by passing o-amino diphenyl methane through a red hot tube.



Basic character:

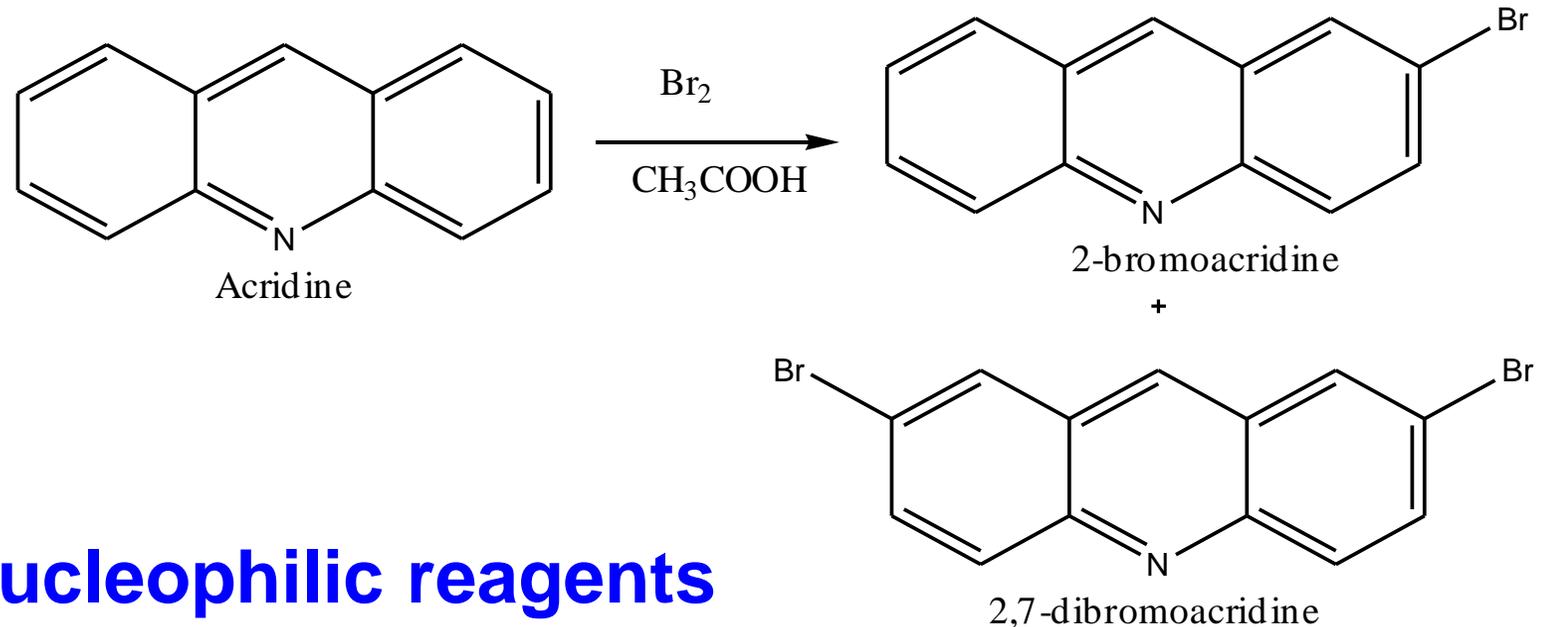
Acridine is a weak base but it forms soluble salts with mineral acids.



Chemical reactions:

1. Electrophilic substitution reactions:

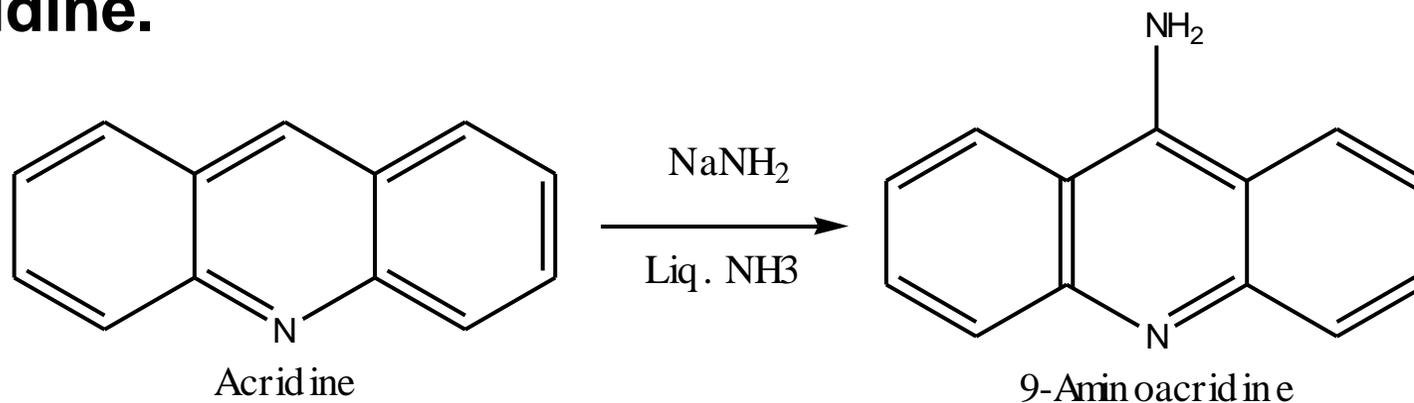
Halogenation:



2. Reaction with nucleophilic reagents

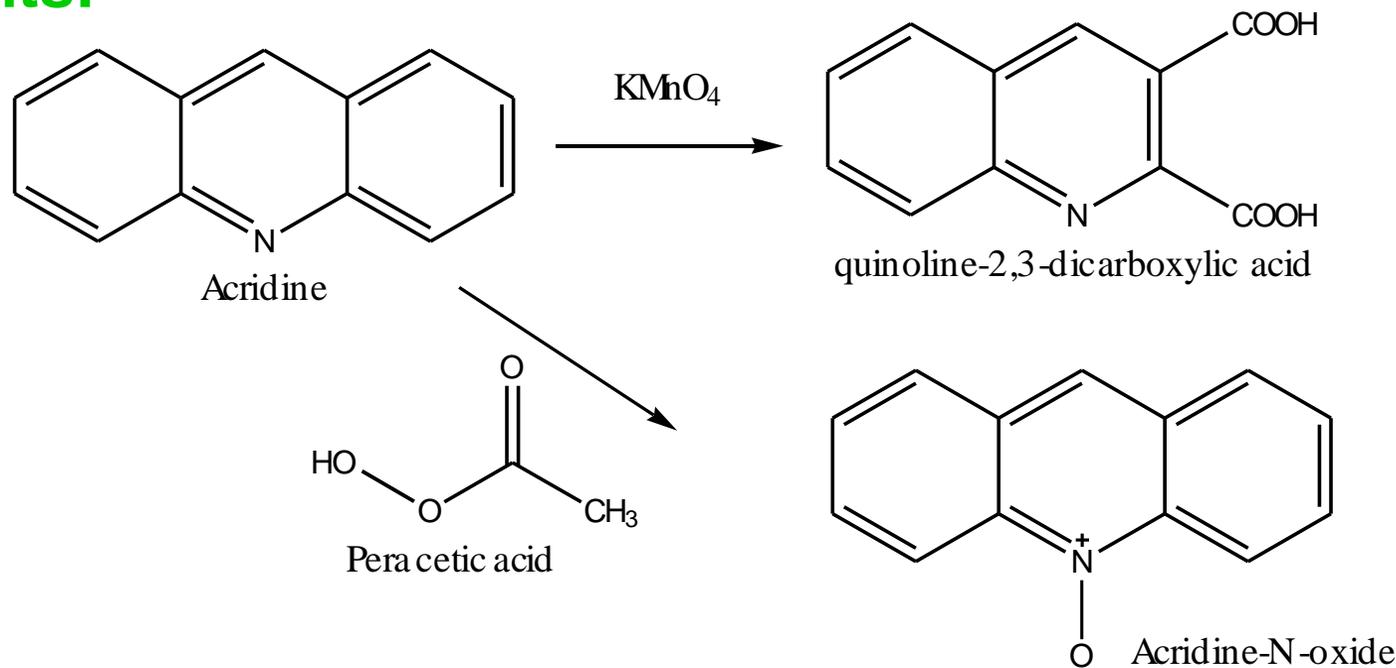
- ✓ Acridine easily reacts with nucleophilic reagents.
- ✓ Nucleophilic attack takes place at 9-position, because the electron density is decreased at this position when compared to 1,2,3 and 4th positions.

- ✓ So, Acridine easily reacted with sodamide in liq. Ammonia, it gives 9-amino acridine.

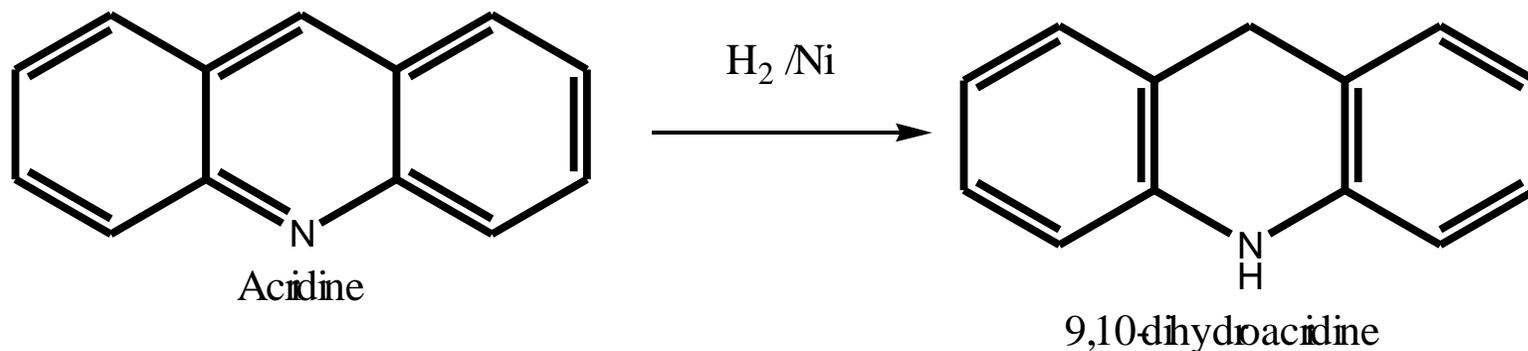


3. Reaction with oxidizing agents:

Acridine is very stable ring system towards oxidizing agents. But in the presence of per acids acridine easily converted to N-oxide.

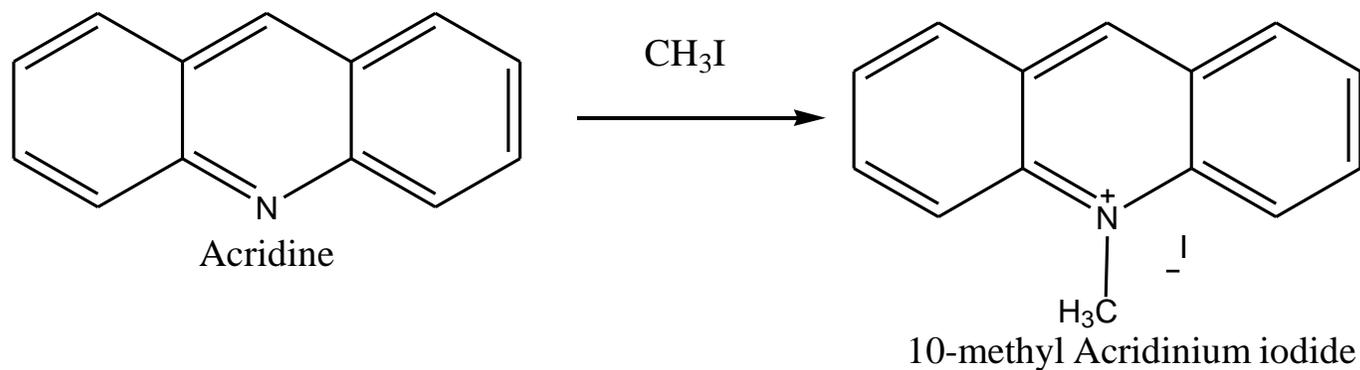


4. Reaction with reducing agents:



5. Reaction with alkyl halides:

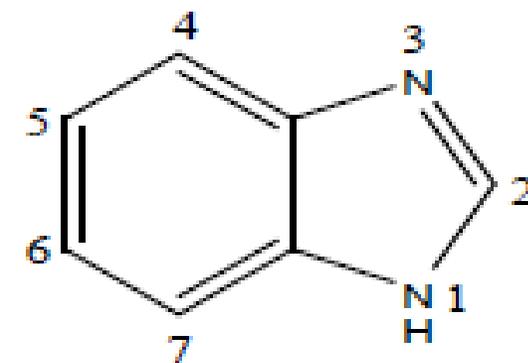
Acridine readily reacts with alkyl halides for example with methyl iodide it gives N-methyl acridinium iodide.



Benzimidazole — Molecular Formula – $C_7H_6N_2$

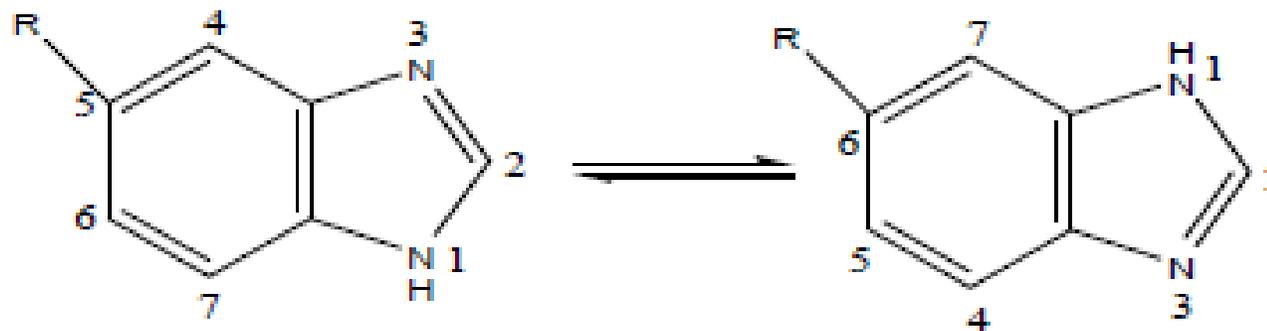
Benzimidazole is a Fused aromatic ring system fusion of benzene and imidazole.

- In Benzimidazole all ring atoms (7 carbons and 2 nitrogens) are SP_2 hybridized.
- Two SP_2 orbitals on each atom overlap with each other to form the **C-C and C-N σ bonds**.
- The third SP_2 orbital on each **carbon atom and one nitrogen atom** overlaps with an S orbital of hydrogen and forms **C-H and N-H σ bonds**.
- The **third SP_2 orbital of second nitrogen** is occupied by the **lone pair of electrons**.
- Each **carbon atom** in ring possess **one un hybridized p – orbital** containing one electron and those are perpendicular to the plane containing the **σ bonds**.



Benzo(d)imidazole

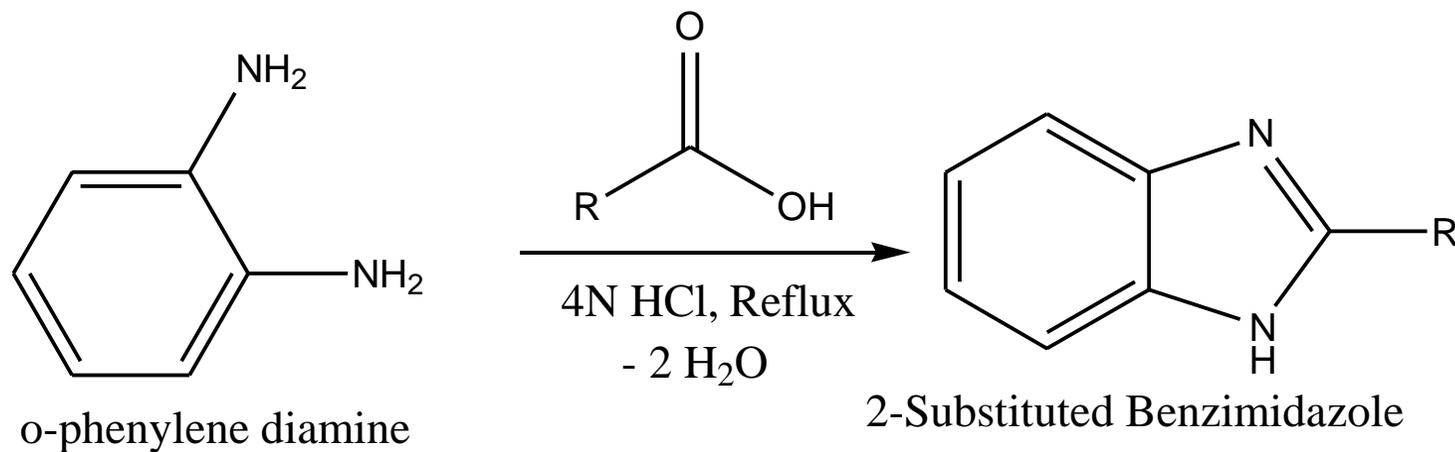
- One of the nitrogen in benzimidazole having lone pair of electrons are **released into the aromatic system**.
- Overlap of these p – orbitals, lone pair of electrons from **one nitrogen** produces delocalized **π – molecular orbital** containing 10 electrons.
- Benzimidazole shows aromatic properties because the resulting molecular orbital satisfies the Huckle's rule ($4n+2$ rule).
- benzimidazoles display annular tautomerism in solution, e.g.



Preparations

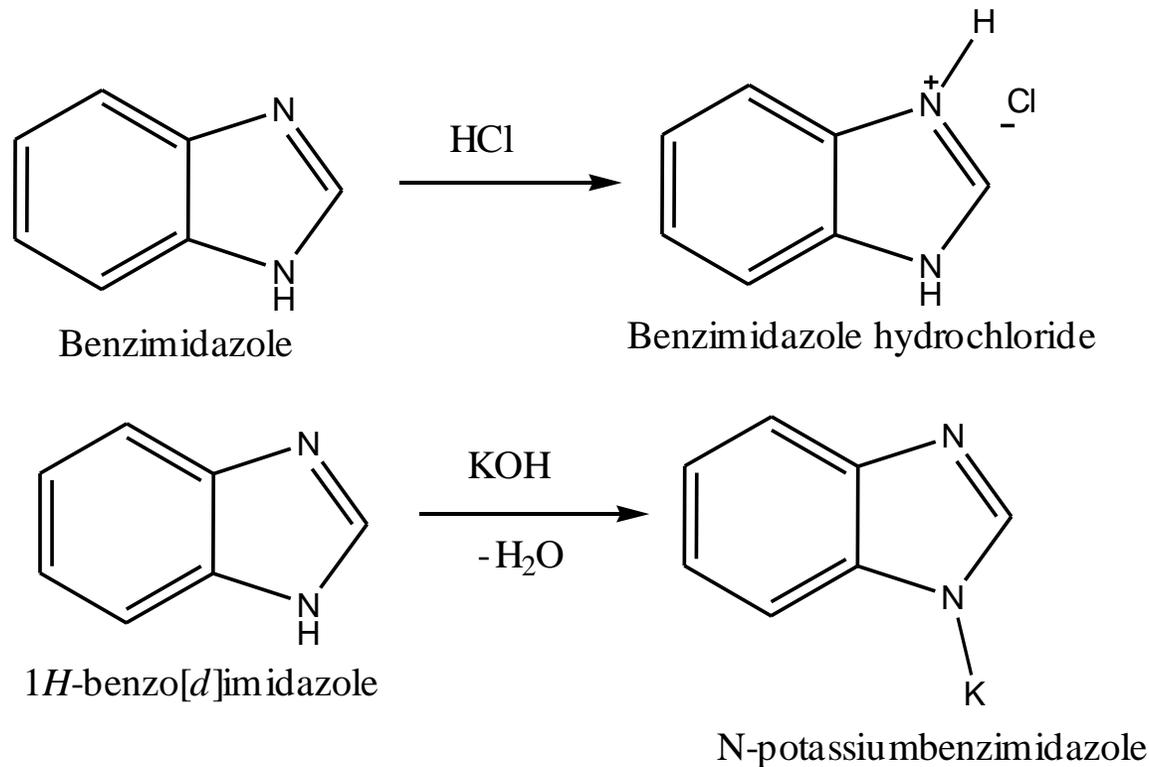
1. From o-phenylenediamine / Phillips reaction:

It is the most important method of preparing benzimidazole by refluxing o-phenylenediamine with a carboxylic acid in 4N HCl.



Basic Character & Acidic character:

- Benzimidazole is a **weak base and also a weak acid**.
- Benzimidazole is a weak base because due to the presence of lone pair of electrons on one of the nitrogen atom.
- Benzimidazole also exhibit weak acidic properties, the weak acidic property is because of its formation of potassium phenothiazine with KOH.

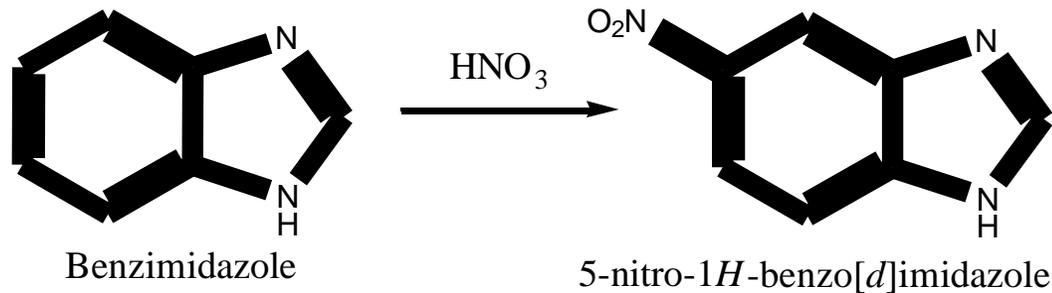


Chemical reactions:

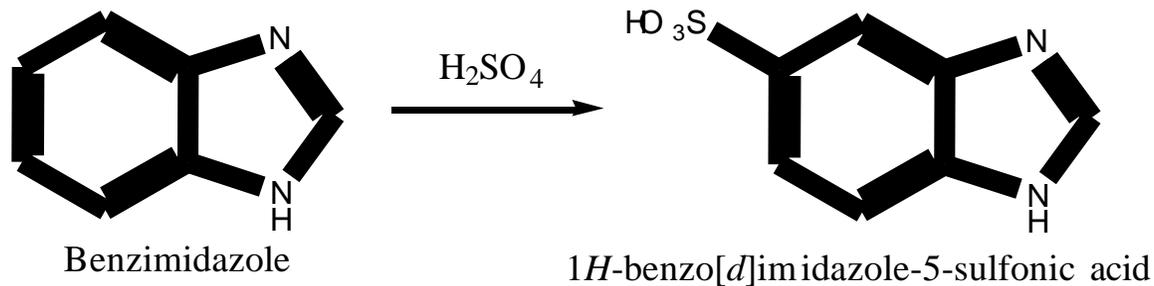
Electrophilic Substitution reactions:

- ✓ Electrophiles attack in benzimidazole take place preferentially at the 5- or 6-position. However, the electrophile may also enter the 4- or 7-position if the 5- or 6-position is blocked.

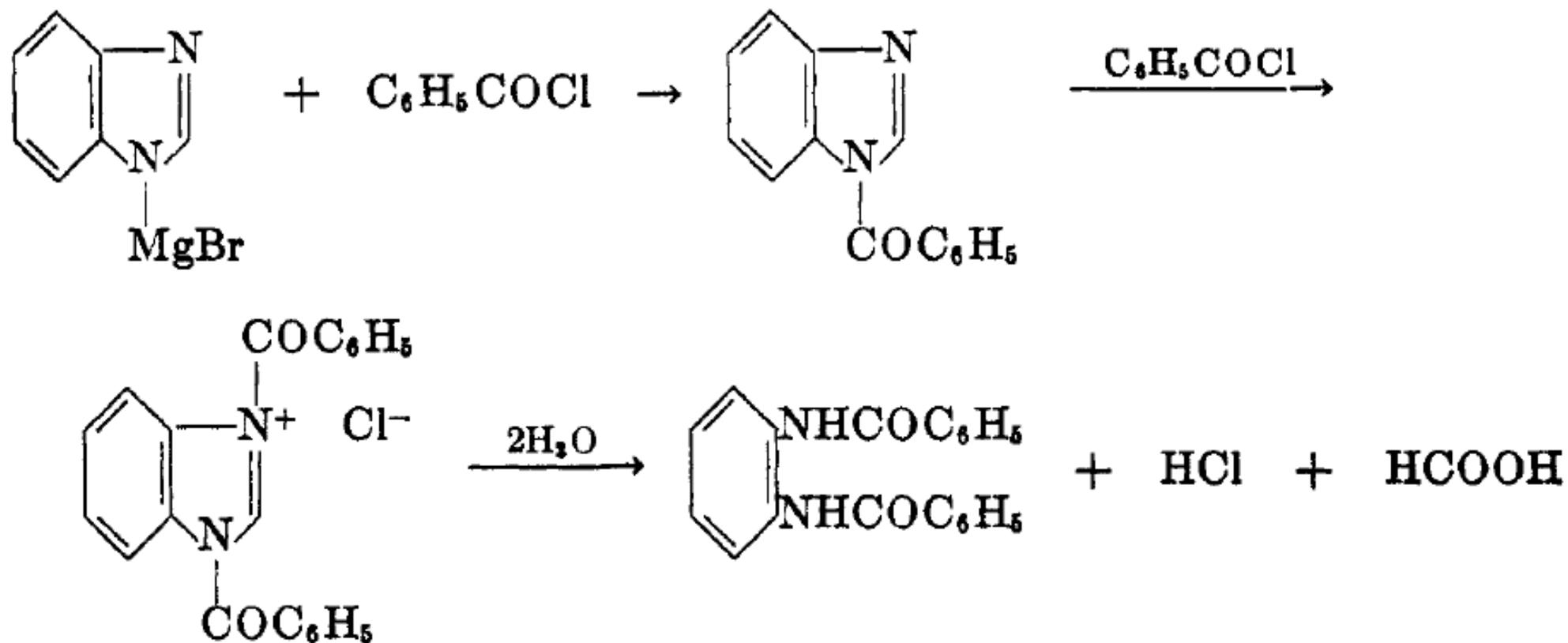
Nitration:



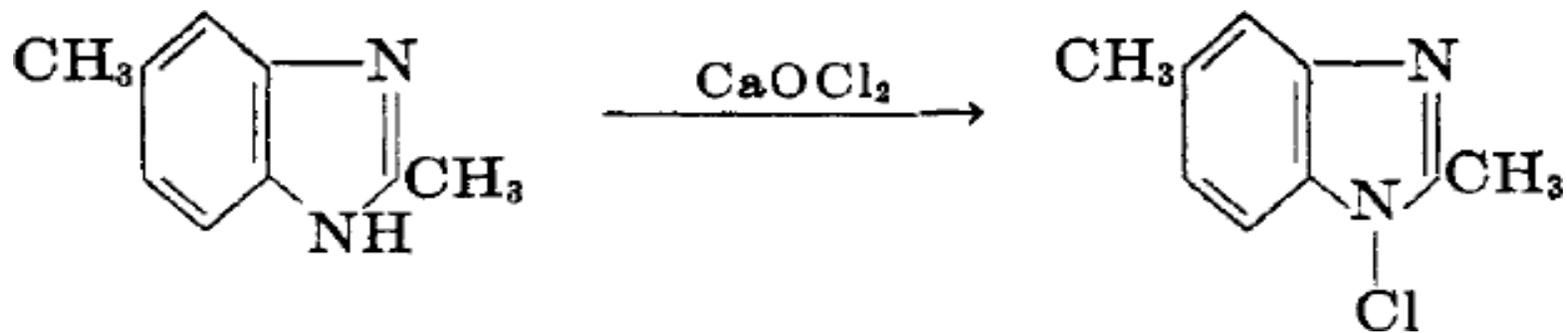
Sulphonation:



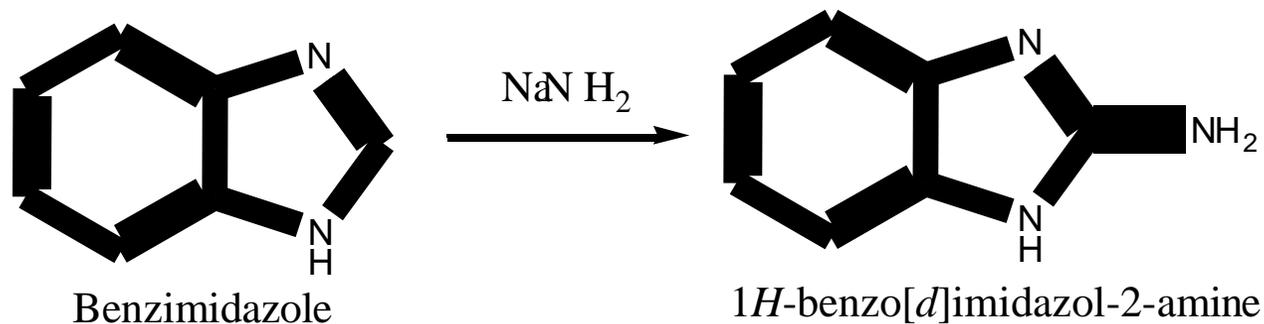
By treatment with acid anhydrides: 1-benzimidazolmagnesium bromide when treated with benzoyl chloride in ether solution gives mostly *N,N'*-dibenzoylbenzimidazole and the rupture of the imidazole ring has been postulated by hydrolysis.



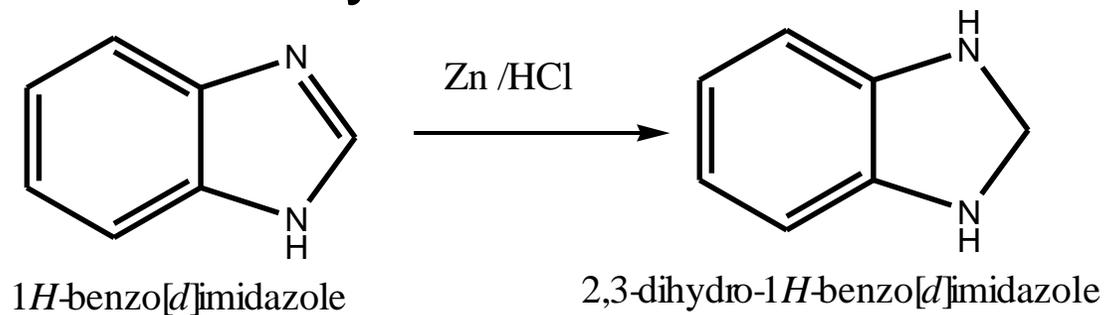
Halogenation: When 2,5 (or 2,6)-dimethylbenzimidazole in an aqueous acid solution is treated with a saturated solution of bleaching powder at 0 to 5°C, 1-chloro-2,5(or 2,6)-dimethylbenzimidazole is obtained.



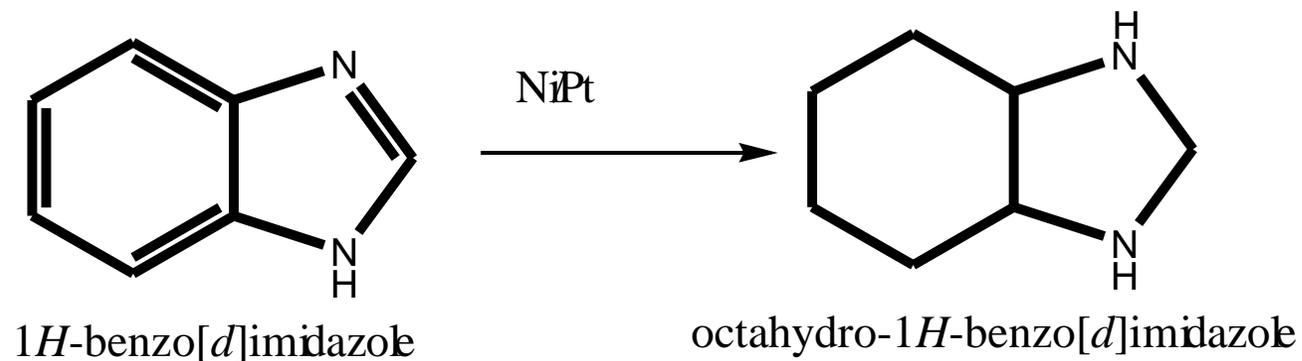
Nucleophilic substitution reaction:
Reaction with sodamide:



Reduction: Mild reduction by Zn & HCl.



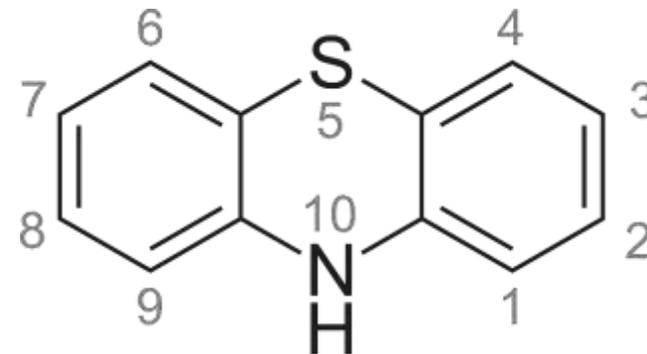
But catalyst Ni / Pt reduces both rings and forms octa hydro indole.



Phenothiazine — Molecular Formula – C₁₂H₉NS

Phenothiazine is a Fused aromatic ring system also known as Dibenzothiazine

- In phenothiazine all ring atoms (12 carbons and 1 nitrogen and 1 sulphur) are SP₂ hybridized.
- Two SP₂ orbitals on each atom overlap with each other to form the **C-C and C-N and C-S σ bonds**.
- The third SP₂ orbital on each **carbon atom and nitrogen atom** overlaps with an S orbital of hydrogen and forms **C-H and N-H σ bonds**.
- The **third SP₂ orbital of sulphur** is occupied by the **lone pair of electrons**.
- Each **carbon atom** in ring possess **one un hybridized p – orbital** containing one electron and those are perpendicular to the plane containing the **σ bonds**.

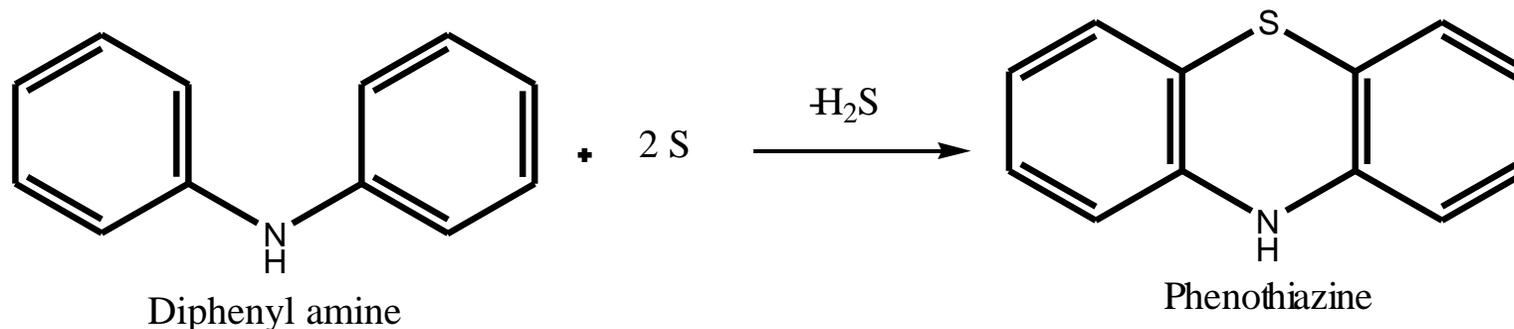


- Overlap of these p – orbitals, lone pair of electrons from Sulphur and nitrogen produces delocalized **π – molecular orbital** containing 14 electrons.
- Phenothiazine shows aromatic properties because the resulting molecular orbital satisfies the Huckle's rule ($4n+2$ rule).
- The nitrogen and Sulphur lone pair are **released into the aromatic system.**

Preparations

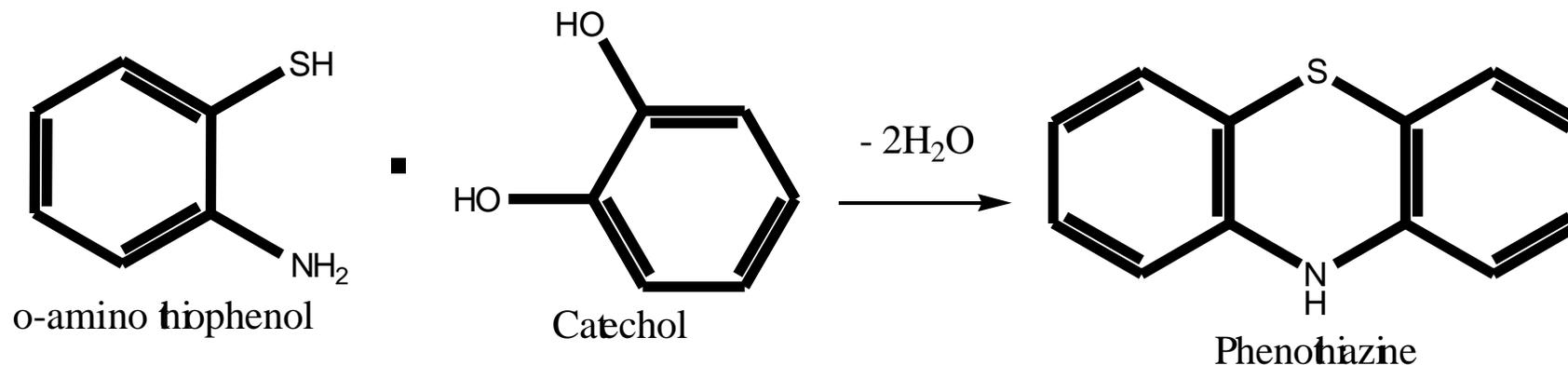
1. From diphenyl amine:

It is prepared by fusing diphenyl amine with Sulphur.



2. From o-amino thiophenol:

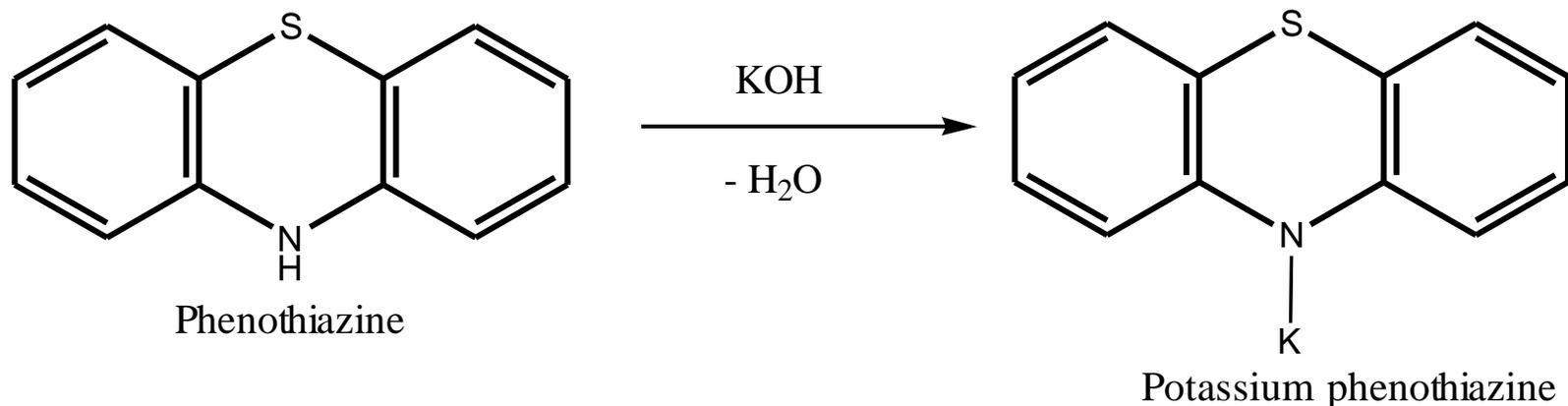
It is prepared by heating o-amino thiophenol with catechol.



Basic Character & Acidic character:

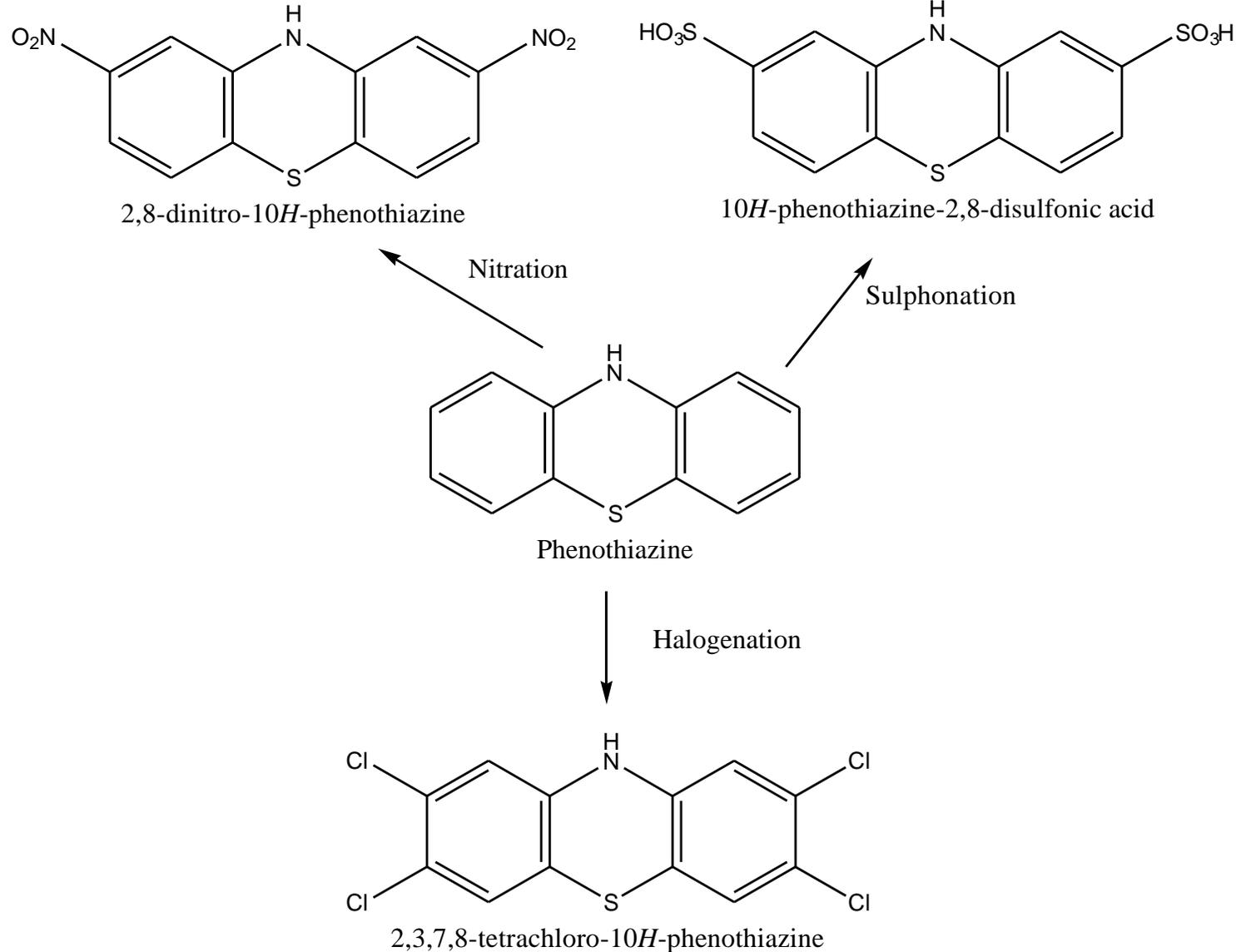
Phenothiazine is a **weak base and also a weak acid**.

- Phenothiazine is a weak base since the lone pair of electrons of nitrogen atom contributes to the $4n+2 \pi$ electron cloud. Thus, the availability of these lone pair of electrons is decreased.
- Indole also exhibit weak acidic properties, the weak acidic property is because of its formation of potassium phenothiazine with KOH.

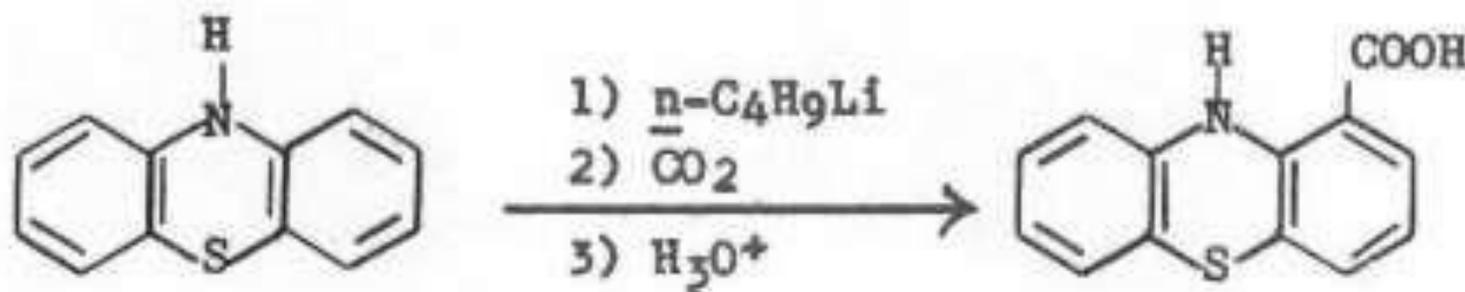


1. Electrophilic substitution reactions:

Mostly the electrophilic substitution reactions happens at 2, 3, 7 and 8 th positions.



2. Reaction of phenothiazine and n-butyl lithium followed by the addition of solid carbon dioxide to the mixture and gives 1-carboxy phenothiazine.



3. Nucleophilic substitution reactions:

Mostly happens at 1 or 9th positions.

Reaction with sodamide:

