Reactivity of π-Deficient Molecules

by

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Ph.D. of Organic Chemistry

"Synthesis of Hetero Cyclic"

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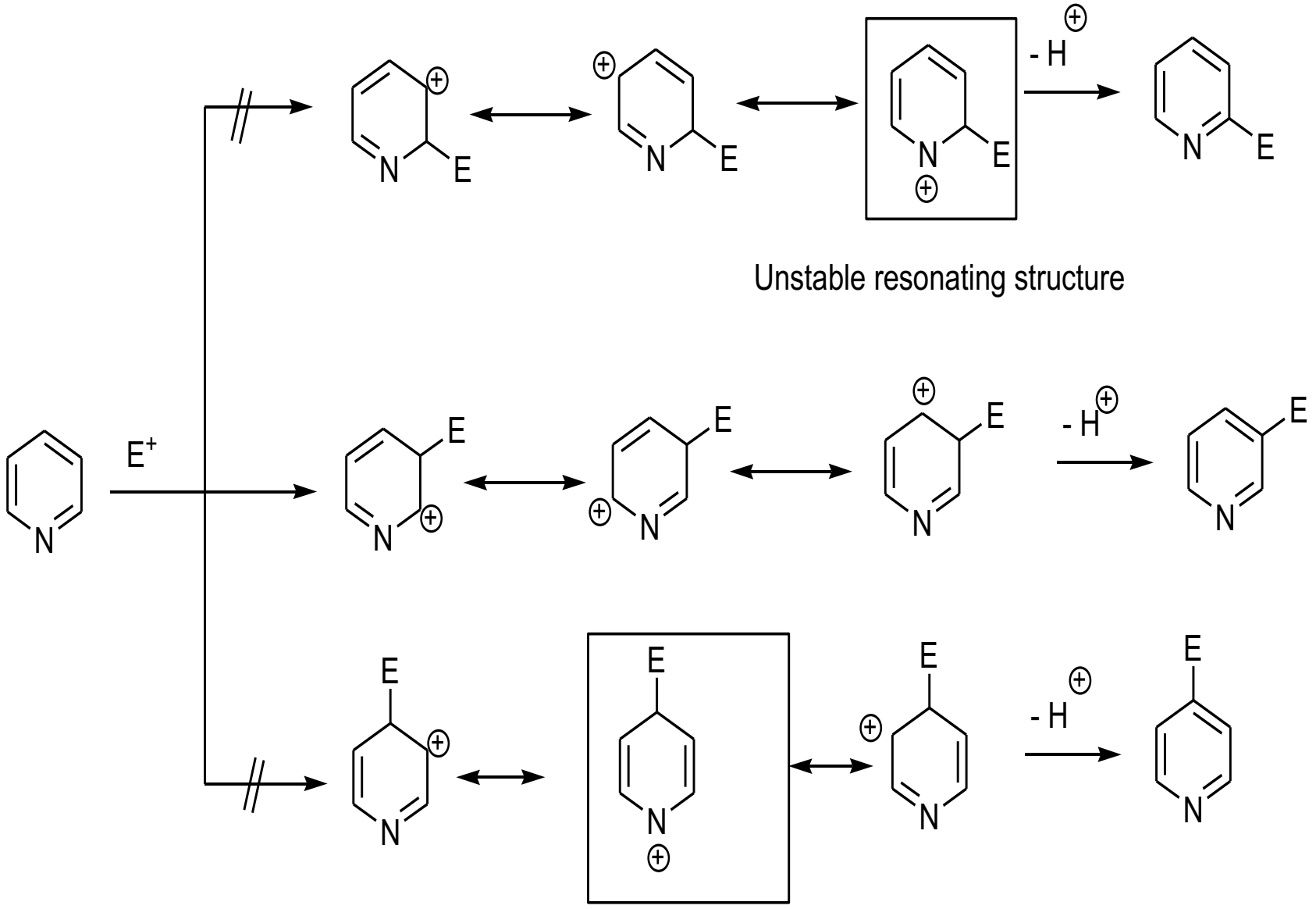
Chemical Reactivity of π-Deficient Molecules

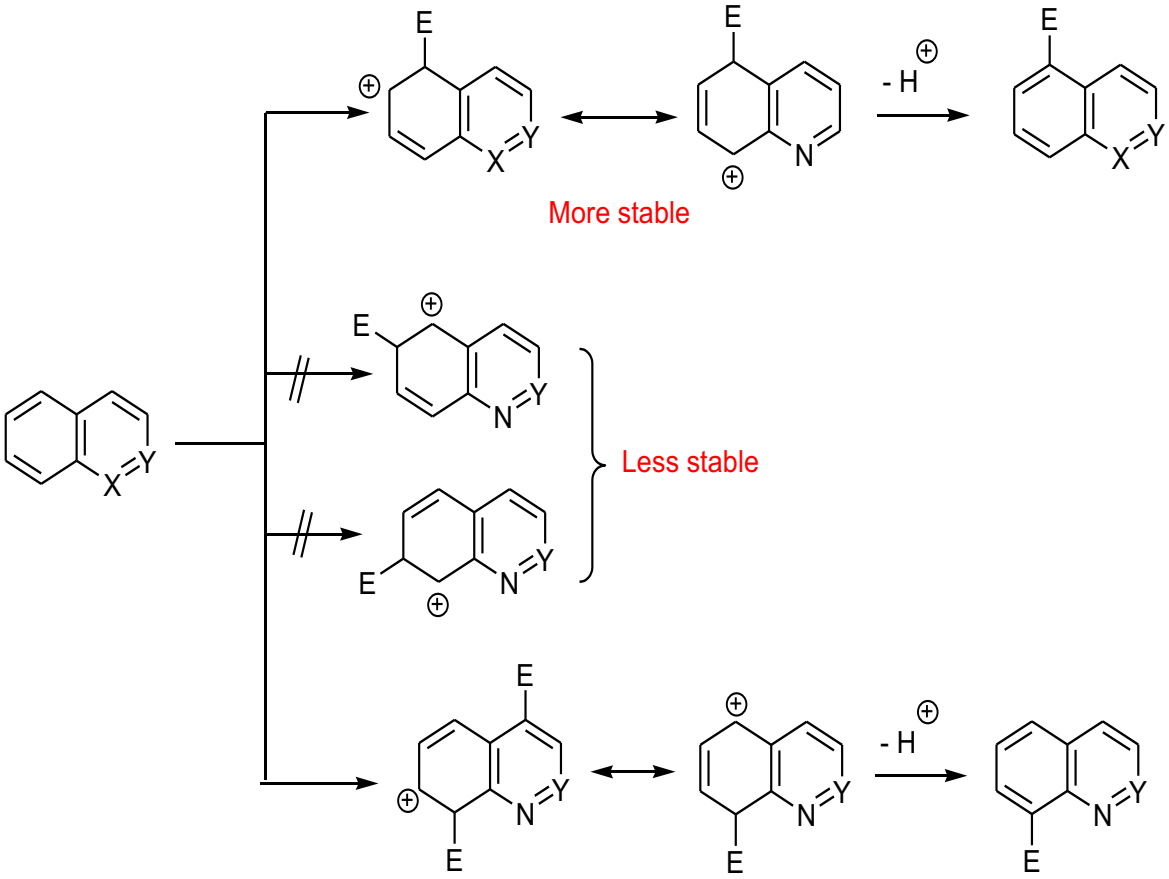
π-Deficient Molecules:

Substitution takes place at C-3 in pyridine as intermediate is the most stable. It has three resonance forms delocalizing +ve charge at carbon corners while in the intermediate for C-2 and C-4 substitution the +ve charge on the heteroatom which has much less tendency for accumulating such charge.

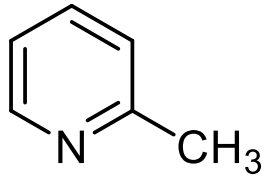

E+
- H
N
E
Unstable resonating structure
Unstable resonating structure

Benzofused π-deficient molecules

Attack take place at benzene ring as it is more electron rich and at position adjacent to the ring junction because the intermediates for substitution at such position is more stabilized by resonance.

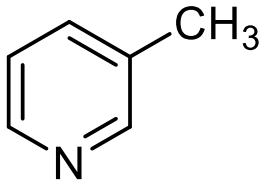


Pyridine is the most important member of the six-membered heterocycles. Its IUPAC name “Azine”. The ring atoms are donated by numerales or Greek letters as idicated bellow



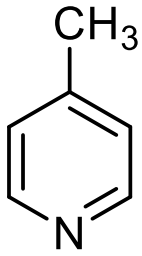
α–Picoline

(2-Picoline)



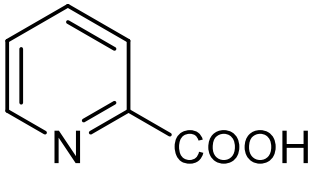
β–Picoline

(3-Picoline)

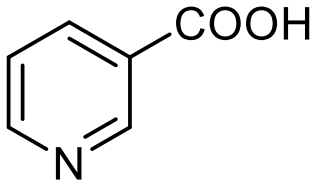


γ–Picoline

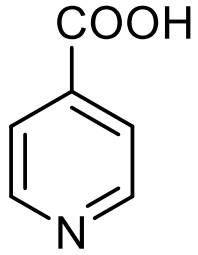
(4-picoline)



Picolinic acid
(Pyridine-2-carboxylic acid)



Nicotinic acid
(Pyridine-3-carboxylic acid)



Isonicotinic acid
(Pyridine-4-carboxylic acid)

Nicotonic acid is a vitamin used in the treatment of pellaara and isonicotinic acid has been used (in the form of its hydrazide) in the treatment of tuberculosis.

Reactions

1- Basic Character

Pyridine as a base with $K_b = 2.3 \times 10^{-9}$. It is a much stronger base than pyrrole ($K_b \sim 2.5 \times 10^{-4}$).

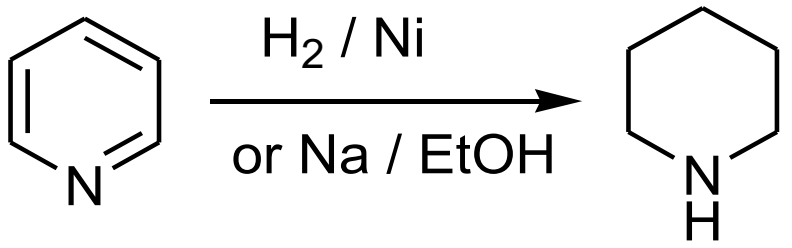
Pyridine has a pair of electrons in an sp^2 orbital that is available for sharing with acid, while pyrrole has not, and can accept an acid only at the expense of the aromatic character of the ring. Since the nitrogen atom in pyridine carriers a negative charge, and the lone pair is completely available for protonation, pyridine would be expected to be a very strong base.

In actual fact pyridine is far less basic than expected, being less basic than aliphatic amines. It is difficult to explain this. Possible explanation is the following:

An electron in a p-orbital is at some distance from the nucleus and is held relatively loosely. However, an electron in an S - orbital is close to the nucleus and is held more tightly. The pair of electrons that gives pyridine its basicity occupies an sp^2 orbital, while the pair of electrons in an aliphatic amine occupied an sp^3 orbital, i.e., the lone pair of pyridine, due its higher S character, is closer to the nucleus and is more tightly held and so is less available for protonation.

2- Reduction

Pyridine is reduced to piperidine by the action of hydrogen in the presence of catalyst, or by sodium metal in ethanol.



$K_b = 2.3 \times 10^{-9}$ $K_b = 2 \times 10^{-3}$

Piperidine K_b = 2 x 10-3) has usual basicity of secondary aliphatic amine since its lone pair occupies an sp3 orbital

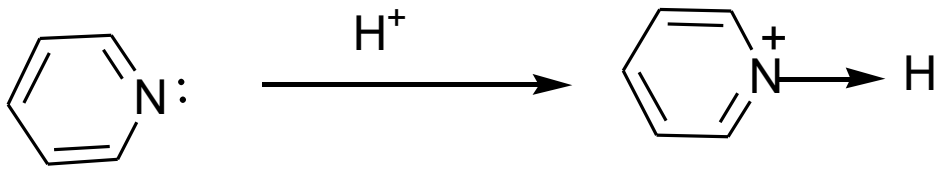
3-Electrophilic substitution

Pyridine resembles a highly deactivated benzene ring (e.g., nitrobenzene) towards electrophilic substitution. It undergoes nitration, sulphonation and halogenation only under very vigorous conditions, and does not undergo the Friedel-Craft's reaction at all.

The low reactivity of pyridine towards electrophilic substitution is due to two reasons.

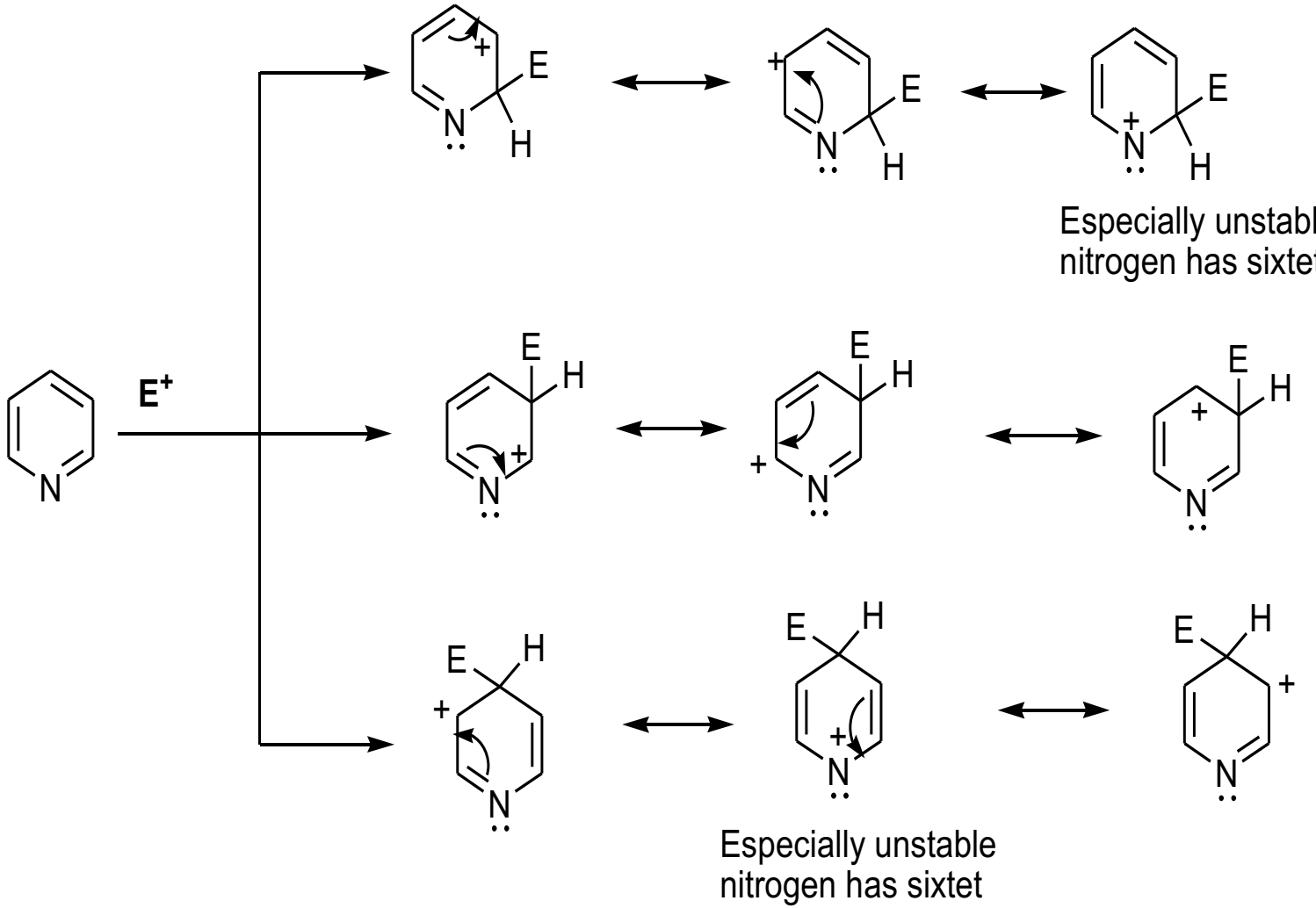
(1)Because of the greater electronegativity of nitrogen atom it decreases the electron density (-I effect) of the ring thereby deactivating it.

(2) In acid medium , the nitrogen atom is protonated forming a pyridinium ion with a positive charge on nitrogen. The positively charged nitrogen attracts electrons to greater extent and results in greater deactivation of the ring.



Pyidinium ion

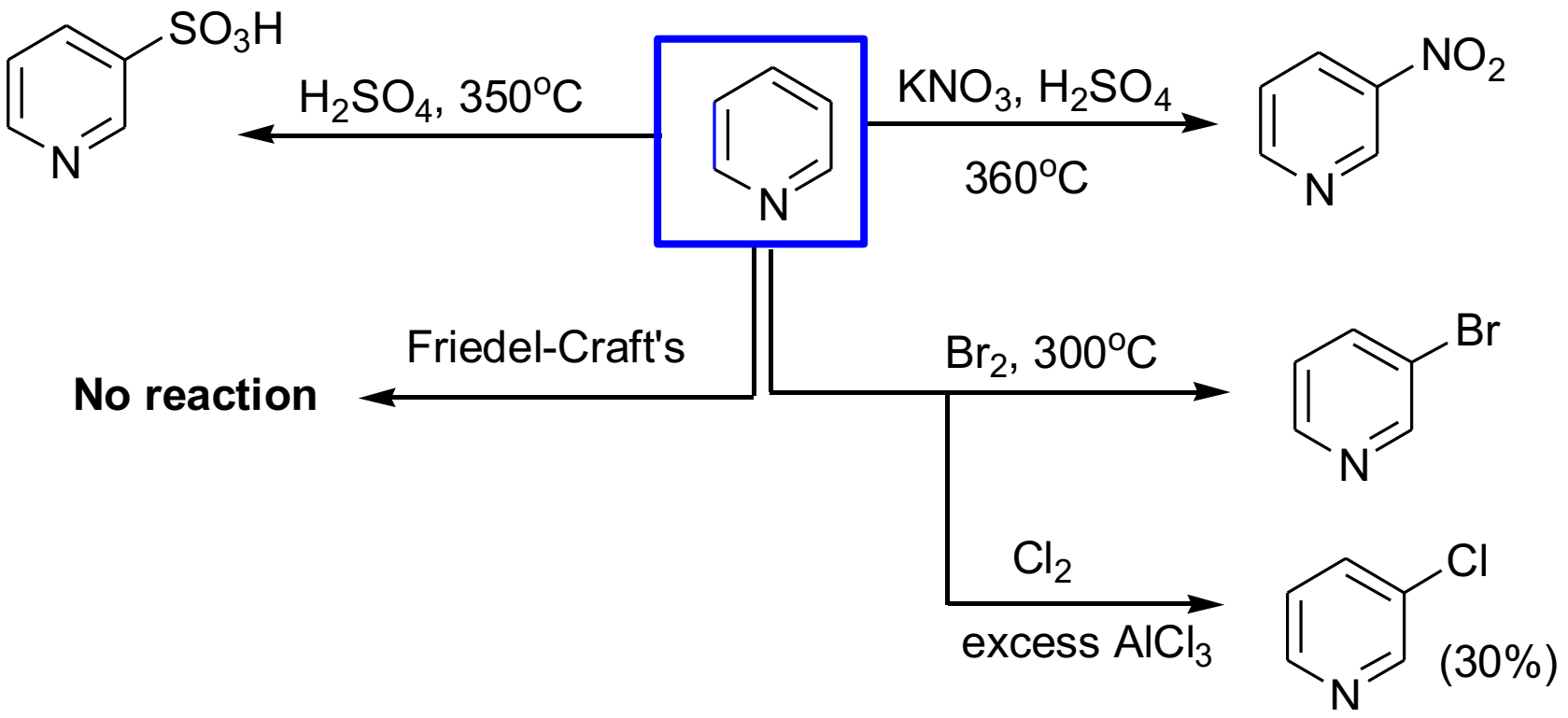
The position of substitution may be considered from the point of view of the stabilities of the intermediate carbocations.



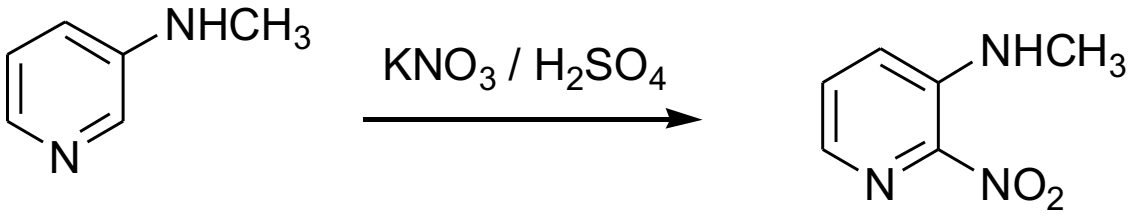
It is clear that, there are three resonating structures for 2-, 3- and 4- substitution.

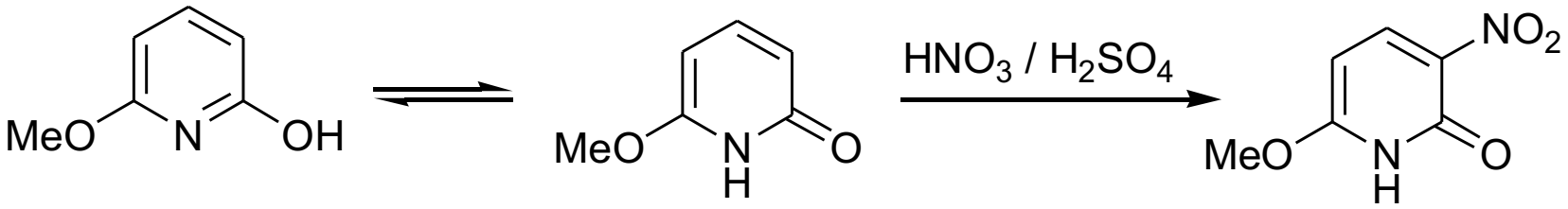
In case of electrophilic attack at position 2 as well as 4, there is one structure which is especially unstable since the electronegative nitrogen atom has only a sixtet of electrons. For this reason electrophilic attack takes place predominantly at position 3

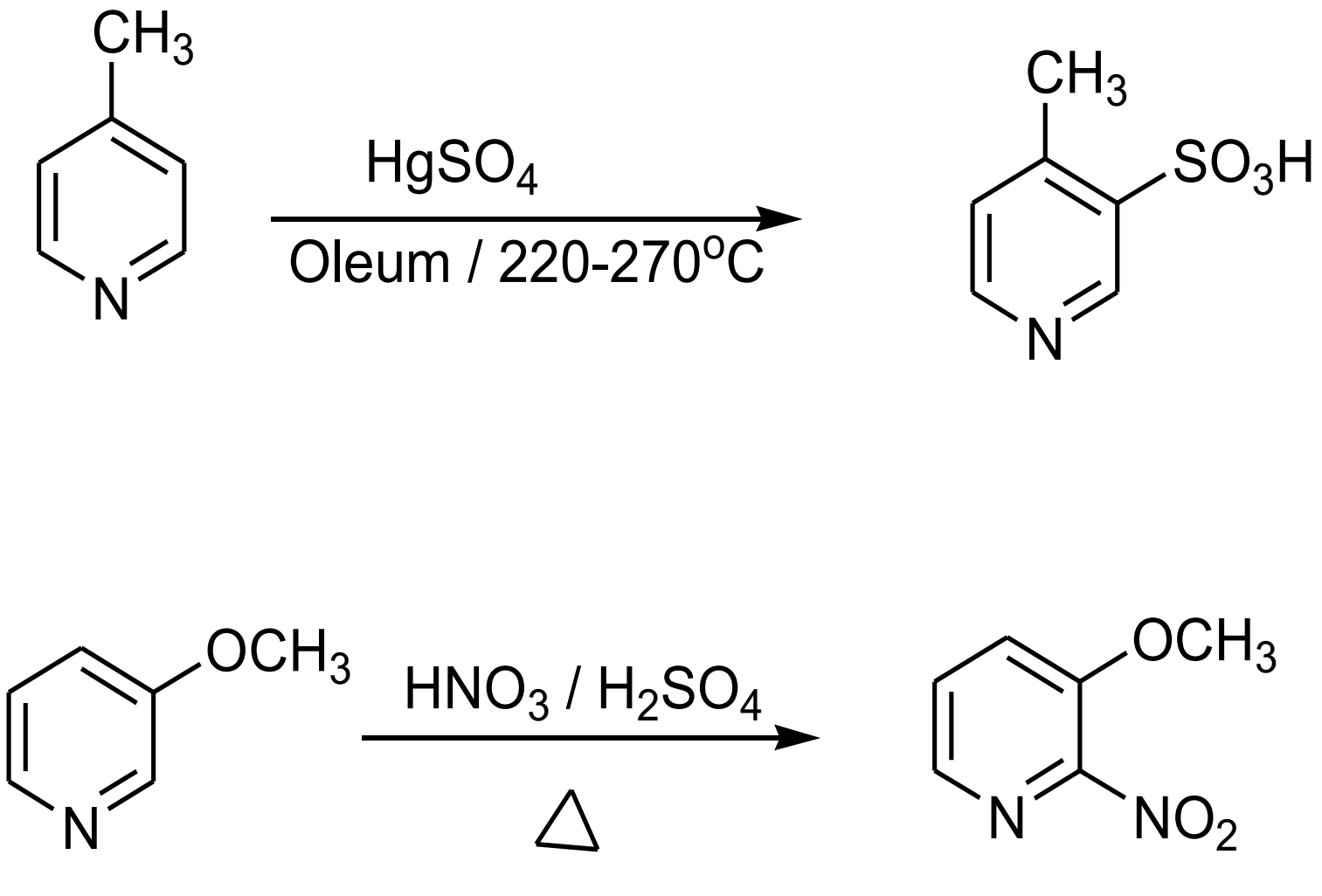
We have seen that position -3 is characterized by highest electron density and consequently it is the preferred position for electrophilic attack.



Strongly electron-donating substituents in pyridine facilitate the electrophilic substitution and control the site of substitution.

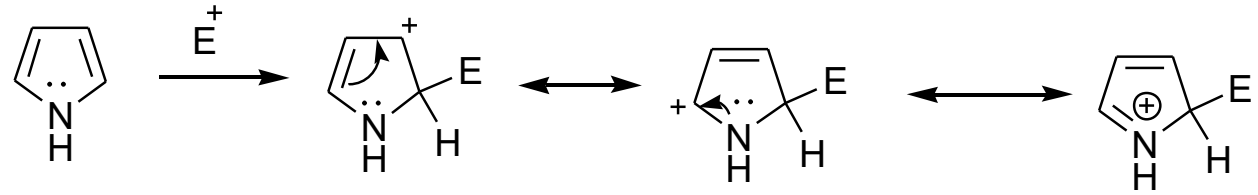




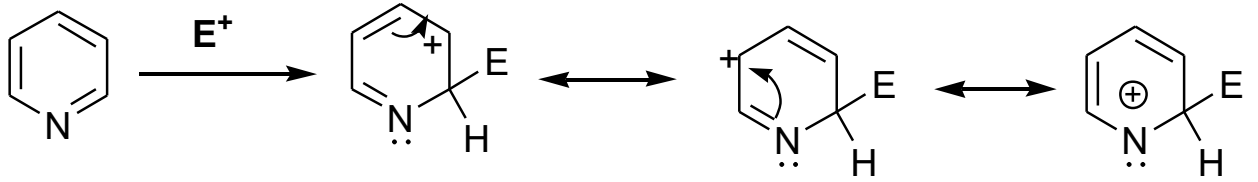

CH3
N
HgSO4
Oleum / 220-270°C
CH3
SO3H
N
OCH3
N
HNO3 / H2SO4
OCH3
N
NO2

It is very important to see the difference between substitution in pyridine and substitution of pyrrole.

In case of pyrrole the structure in which nitrogen carries a positive charge especially stable because nitrogen has an octet of electrons, while in pyridine the structure with a positively charged nitrogen is especially unstable, since nitrogen has only a sixtet of electron



Especially stable
Nitrogen has octet



Especially unstable
nitrogen has sixtet

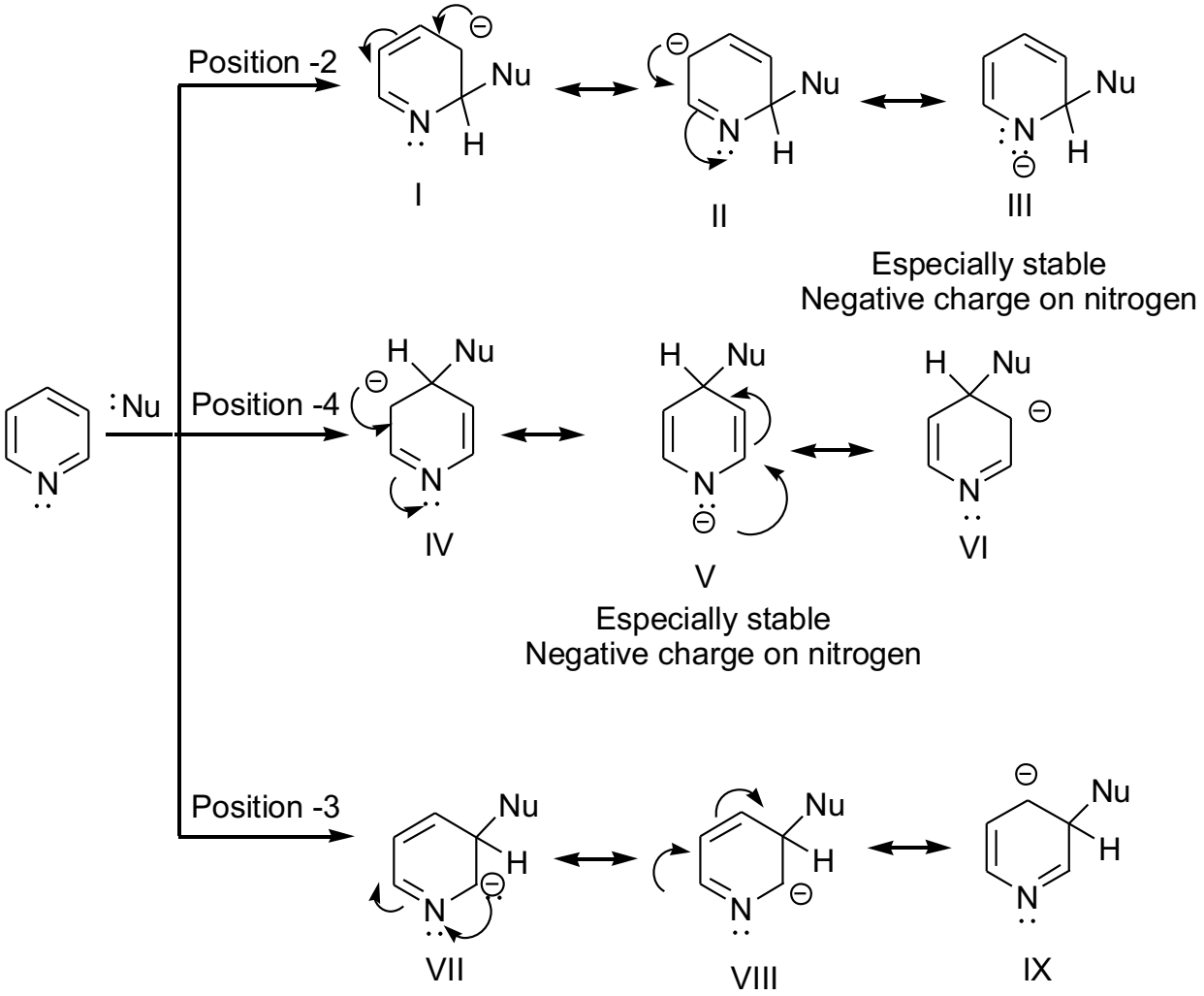
Nucleophilic Substitution

Pyridine is very reactive towards nucleophilic and resembles a benzene ring that contains strongly electron-withdrawing groups.

We have seen that the π-electron density is less than one in position -2 and position -4, and more than one in position -3, it follows that nucleophilic substitution takes place at electron-deficient position -2 and -4 and more readily at the more electron-defcient position -2 (the electron densities being 0.866 and 0.932 at position -2 and -4, respectively).

The reactivity of pyridine towards nucleophilic substitution is so great that even the powerfully basic ion ($:H^-$) can be displaced.

The position of nucleophilic substitution may be also been considered from the point of view of the stabilities of the intermediate carbanions.



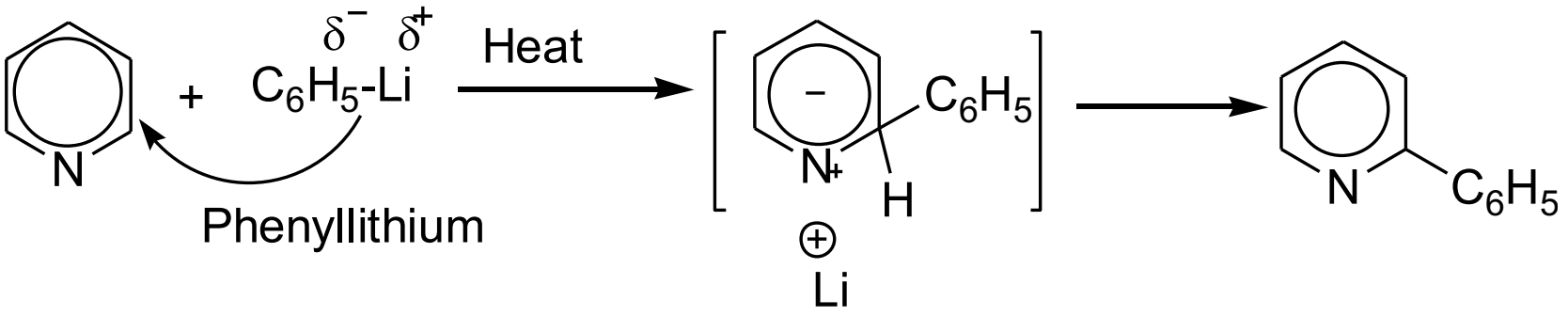
All these structures are more stable than corresponding ones for nucleophilic attack on a benzene derivative because of the electron-withdrawing property of the nitrogen atom stabilizes the carbanion.

- Thus, nuclophilic attack occurs more rapidely on pyridine ring than benzene and more readily on position -2 and -4 than position -3.

The electronegativity of nitrogen that makes pyridine unreactive towards electrophilic substitution makes it highly reactive towards nucleophilic substitution.

Example 1:

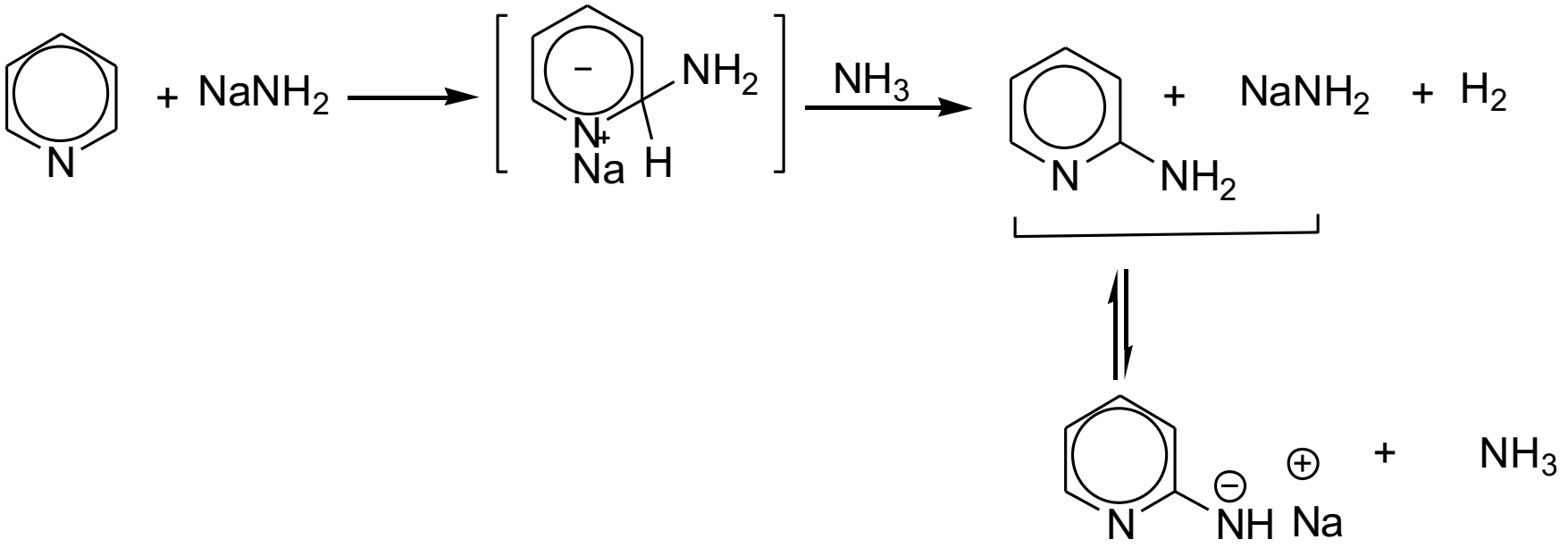
Alkylation or arylation by organolithium compounds



Example 2

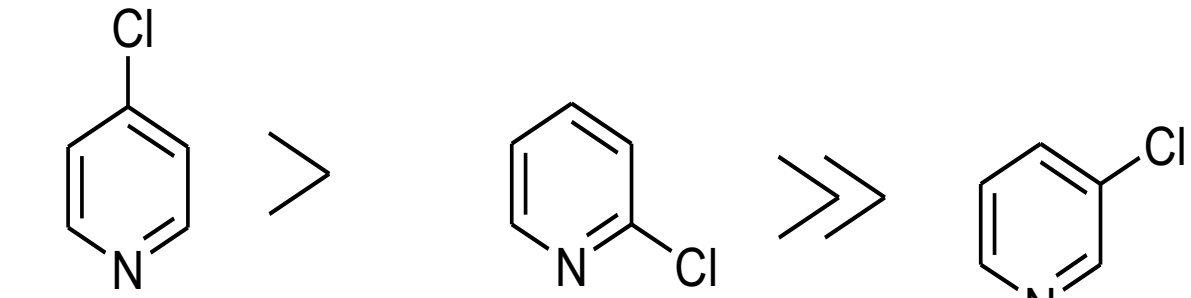
Amination by sodium amide ($NaNH_2$)(Chichibabin Reaction)

When pyridine is heated with sodium amide in liquid ammonia, 2-aminopyridine is obtained.



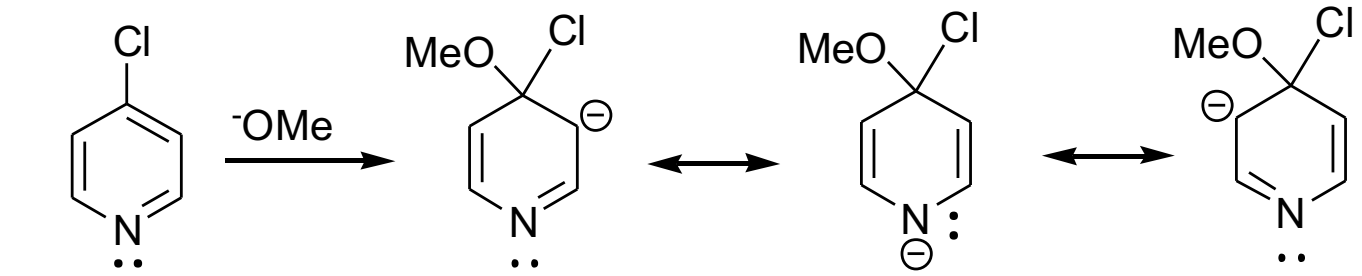
Nucleophilic Substitution of Halogenopyridine

Most nuclophilic substitutions on pyridine involve the replacement of halogen. The reactivites of the reaction of methoxide ion "-OCH_3" with 2-, 3-, 4-chloropyridine is in the following order:



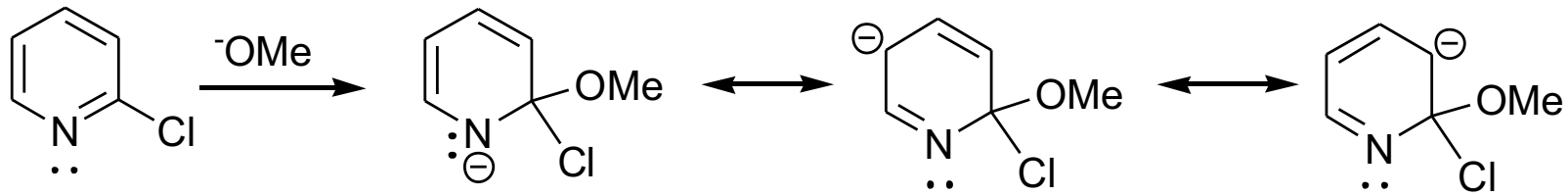
4-Chloropyridine > 2-Chloropyridine >> 3-Chloropyridine

3-Chloropyridine is 10,000 times less reactive the 2-chloropyridine and about 100,000 times less reactive than 4-chloropyridine. This could be explained by relative stabilities of the intermediate carboanions



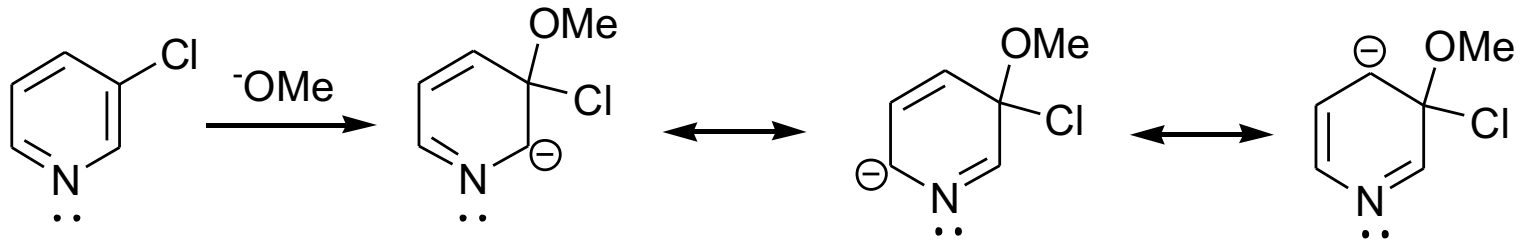
4-Chloropyridine

Especially stable



2-Chloropyridine

Especially stable

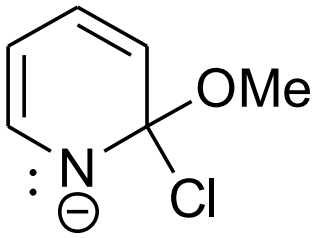


3-Chloropyridine

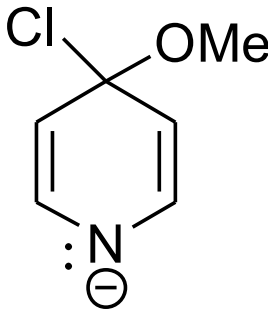
It is clear that the resonance stabilizing forms in which nitrogen is negatively charged are present only in case 4- and 2-chloropyridines.

It was expected that position -2 in pyridine is more favored than position -4 in nucleophilic attack due to lower π-electron density. The unexpected fact that 4-chloropyridine is more reactive than 2-chloropyridine can be explained by examination of the most stable two Wheland complexes I and II.

It is clear that structure "I" is less stable because the negative charge is closer to chlorine and methoxy group which withdraw electrons by their –I effect.



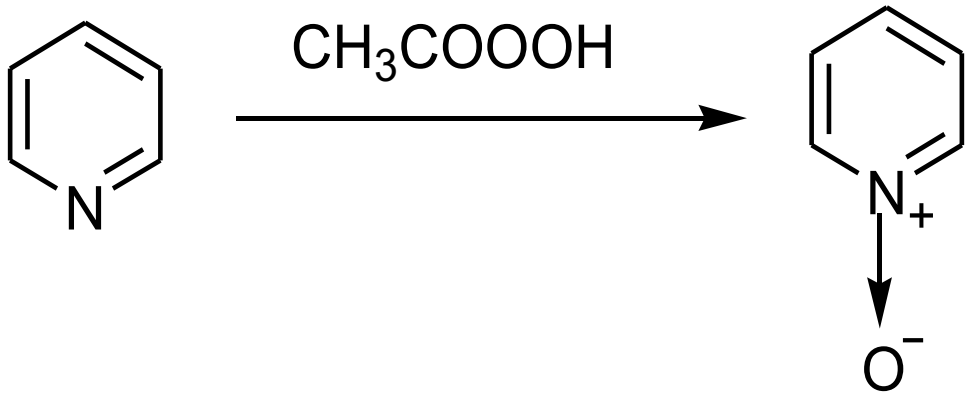
I

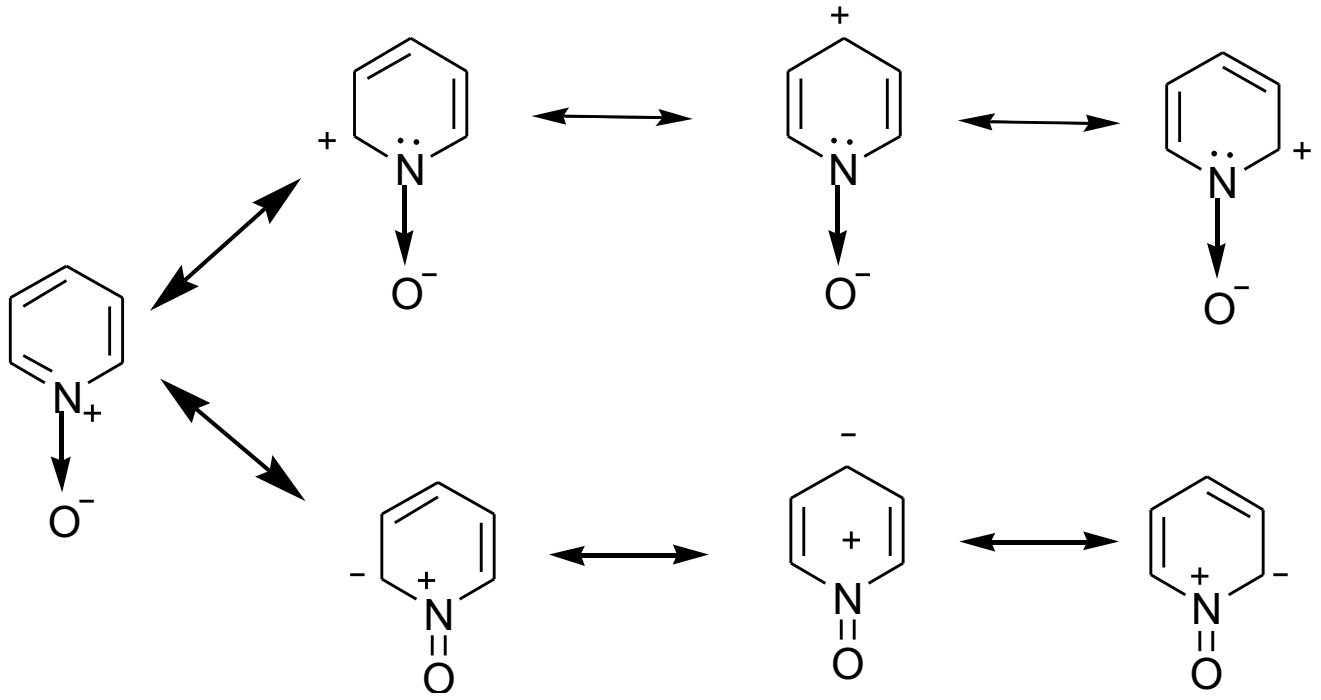


II

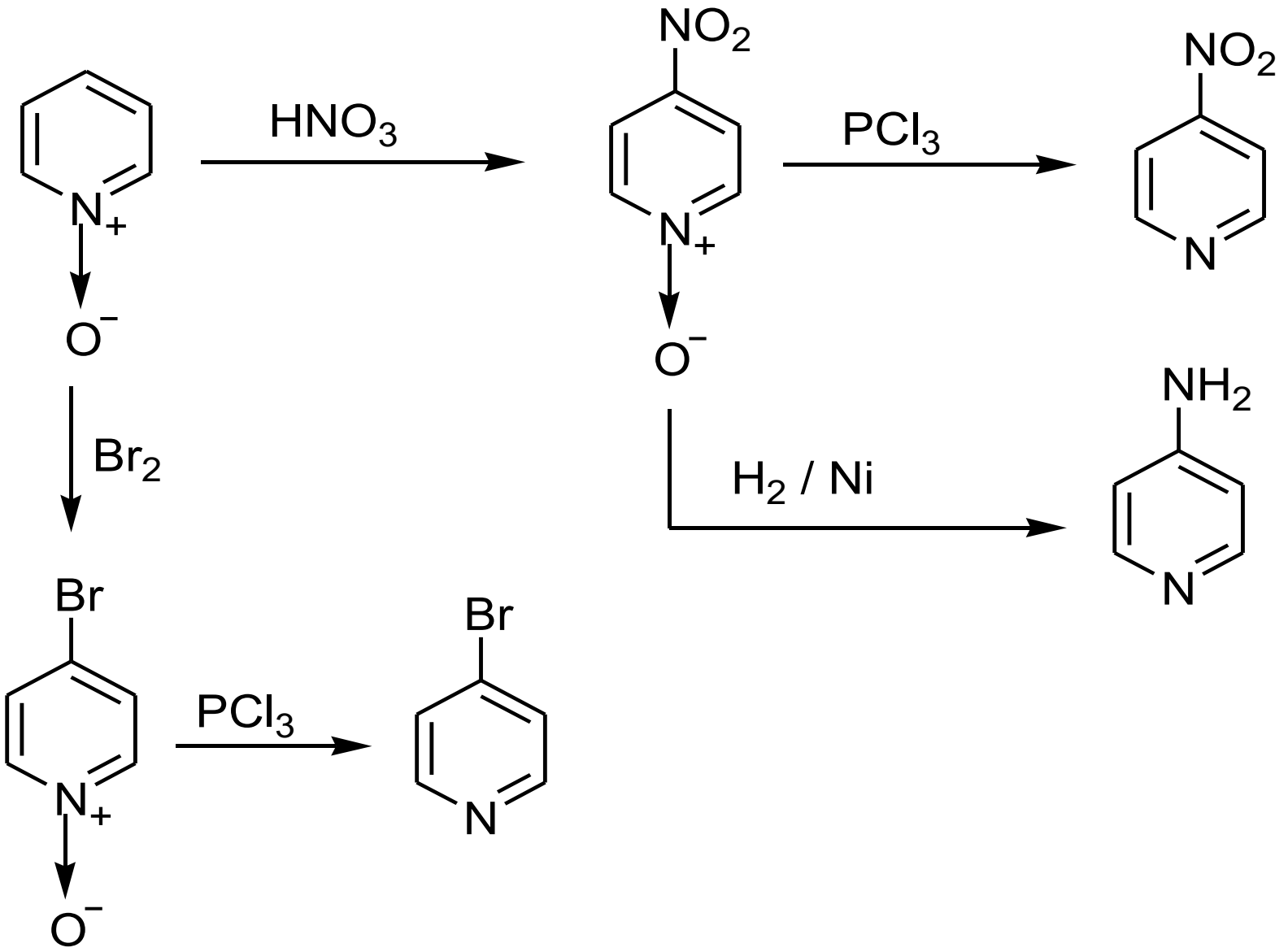
5- Oxidation

Like any other tertiary amine, pyridine is oxidized by peracids (e.g., peracetic acid perbenzoic acid) to its N-oxide





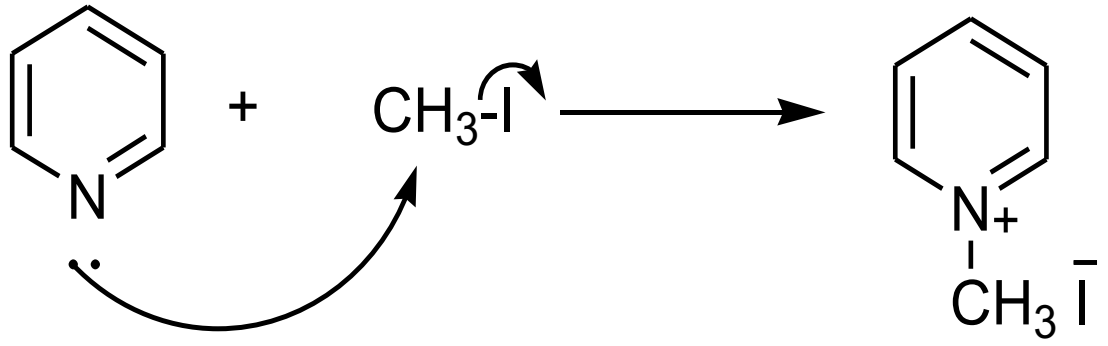
It is clear from these forms that there are positive charges at position 2- and 4-, as well as negative charges at the same positions. Thus, pyridine –N-oxide is more reactive towards both electrophilic and nucleophilic reagents than pyridine itself. In practice it occurs predominantly at Position -4, and since oxygen atom can be readily removed by PCl_3, this offers a means of preparing pyridine derivatives that are difficult to prepare by other methods.


HNO3
NO2
PCl3
NO2
N+
O−
N
Br2
H2 / Ni
NH2
Br
PCl3
Br
N

6-Pyridine as a Nucleophile

(Reaction with Alkyl Halide)

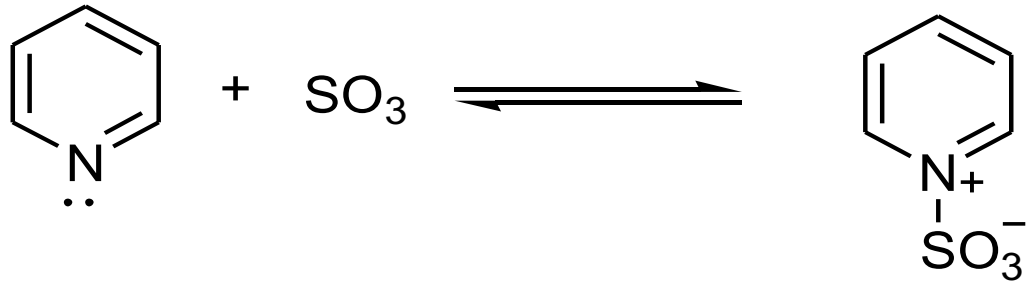
Like other amines, pyridine has nucleophilic properties, and reacts with alkyl halides to form quaternary ammonium salts.



N-Methylperidinium iodide
(Pyridine methiodide)

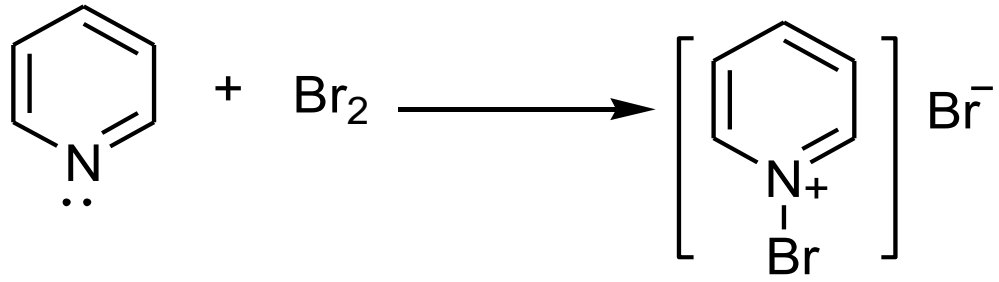
Reaction with Sulphur Trioxide

It reacts with sulphur trioxides to form a salt that is used in the sulphonation of acid sensitive aromatic compounds, e.g., pyrrole and furan.



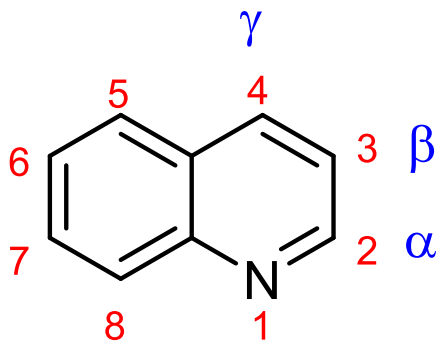
Reaction with Halogen

Pyridine reacts with halogen in the cold to form 1-hlogenopyridinium halides.



Fused Rings Containing Six-Membered Heterocycles

Quinoline contains a benzene ring and a pyridine ring fused as shown. Generally, its properties are those expected from pyridine and naphthalene. The numbering in quinoline has the same sequence of naphthalene where N atom takes number 1.

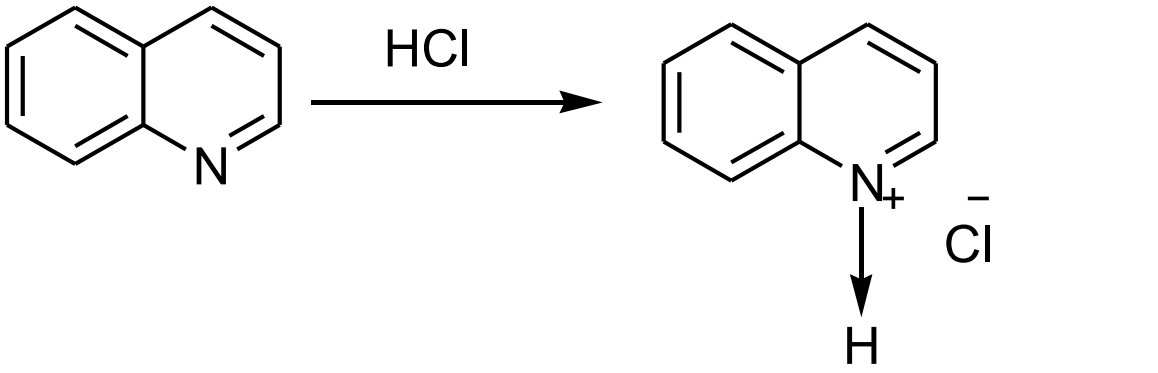


$K_b = 3 \times 10^{-10}$

The reactions of quinoline are those expected from pyridine and naphthalene.

1-Basic nature

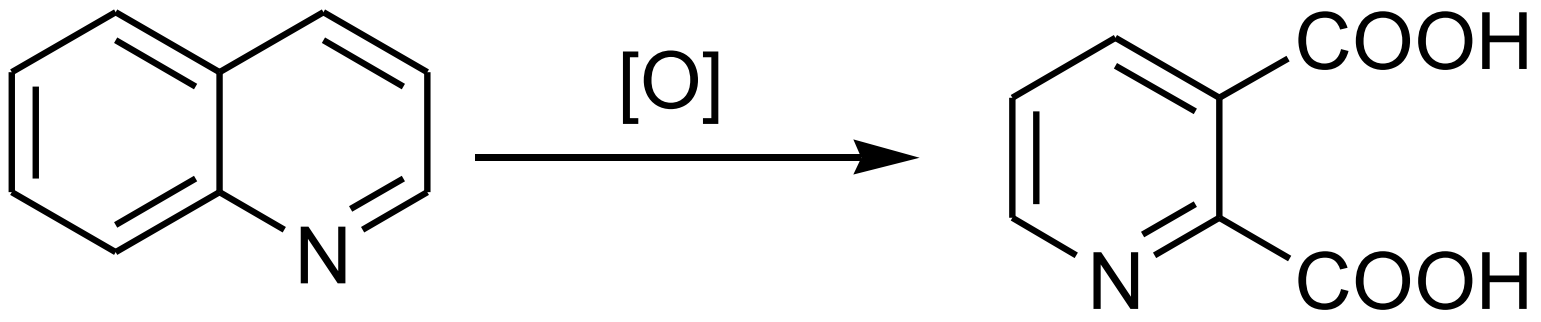
Quinoline is a monoacid tertiary base comparable in strength to pyridine (Kb = $3x10^{-10}$).



Ouinoline hydrochloride

2-Oxidation

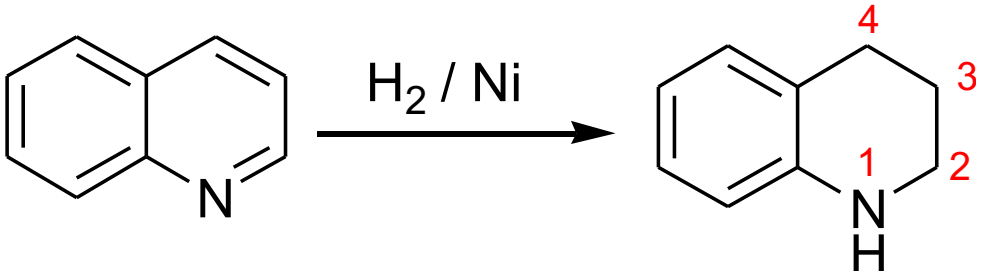
Qunioline is stable compound resistant to oxidising agents, but vigorous oxidation with potassium permanganate yields quinoline acid (α,β-pyridine dicarboxylic acid). Preferential oxidation of the benzene ring has been explained by its comparatively lowers stability than the pyridine ring (compare the resonance structures of pyridine and benzene).



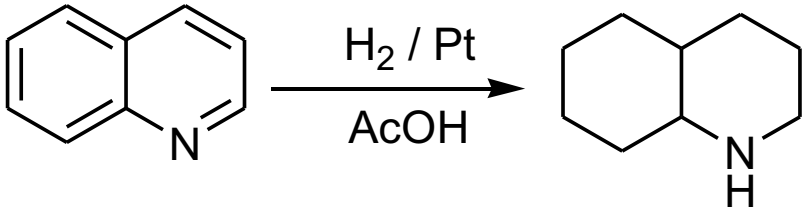
Quinolinic acid

3-Reduction

The pyridine ring is more easily reduced than the benzene ring. Thus, catalytic reduction of quinoline yields 1,2,3,4-tetrahydroquinoline



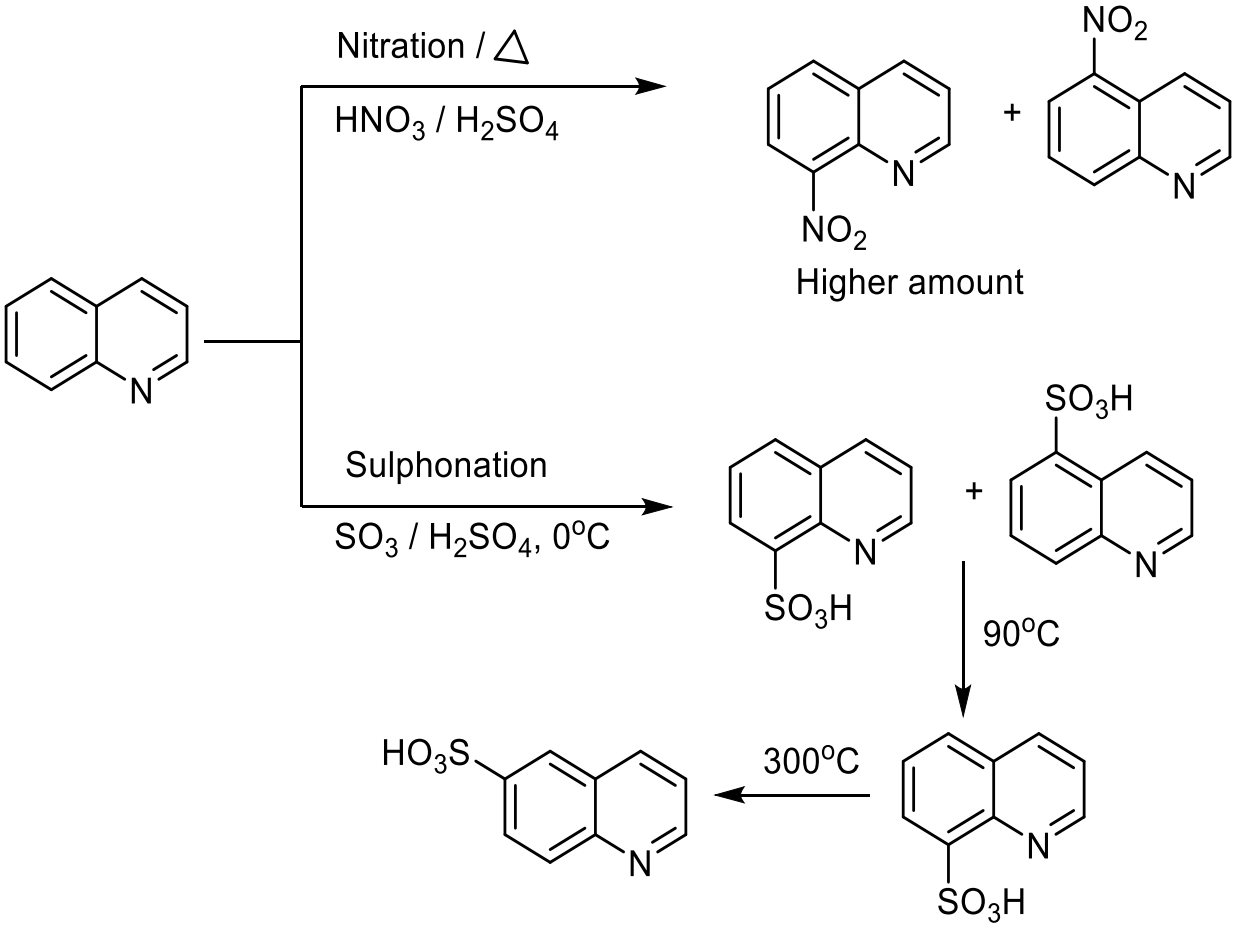
Complete reduction to decahydroquinoline is comparatively more difficult and is achieved by using platinum catalyst in acetic acid



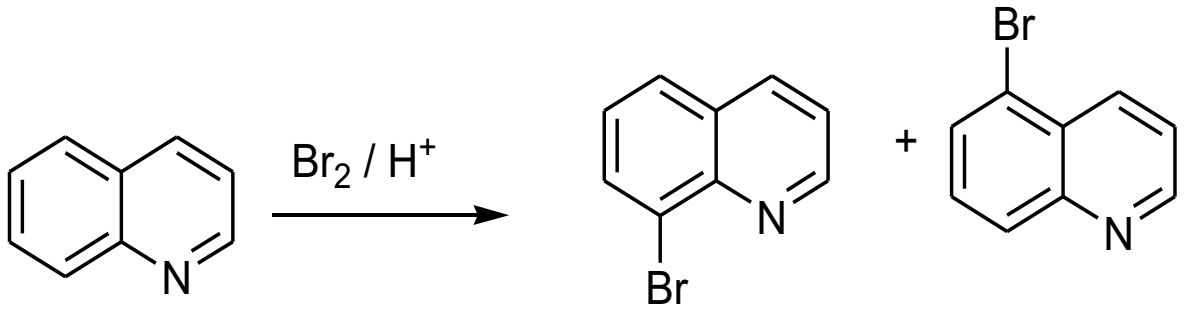
Decahydroquinoline

4-Electrophilic Substitution

As the nitrogen atom deactivates the pyridine, electrophilic substitution occurs in the benzene ring (at position -5 and -8). Postion-8 is more preferred. Quinoline undergoes electrophilic substitution, e.g., nitration, sulphonation and halogenation.

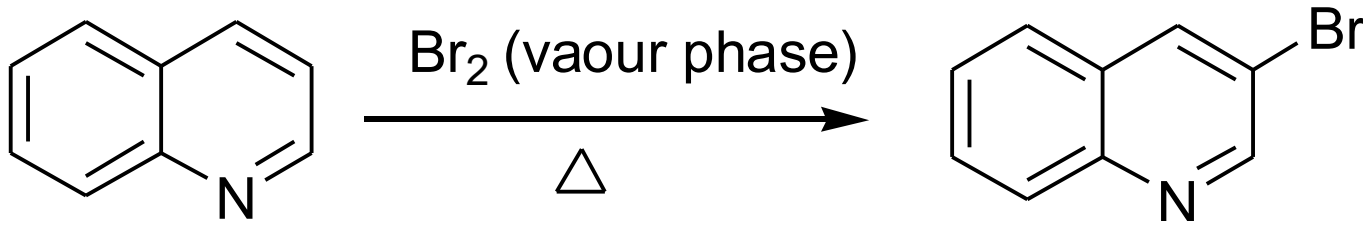


Under condition of high acidity bromination occurs normally at position -5 and -8



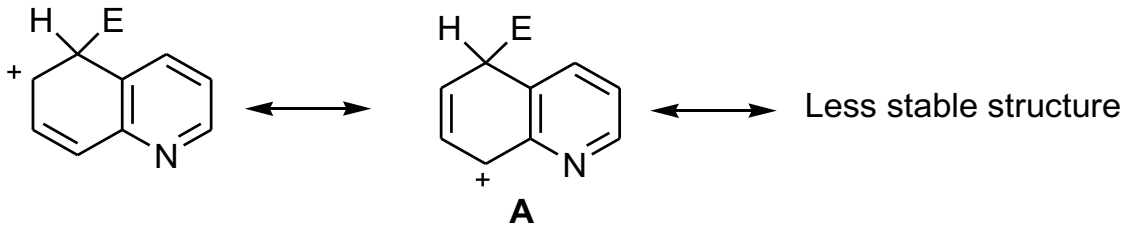
Main product

However, vapor bromination (which is carried out under drastic condition) results in bromination of the less reactive pyridine ring to yields 3-bromoquinoline. This is comperable to the bromination of pyridine to give 3-bromo pyridine



The position of electrophilic substitution in the benzene ring of quinoline is indicted by considering the stabilites of the intermediate carbocations

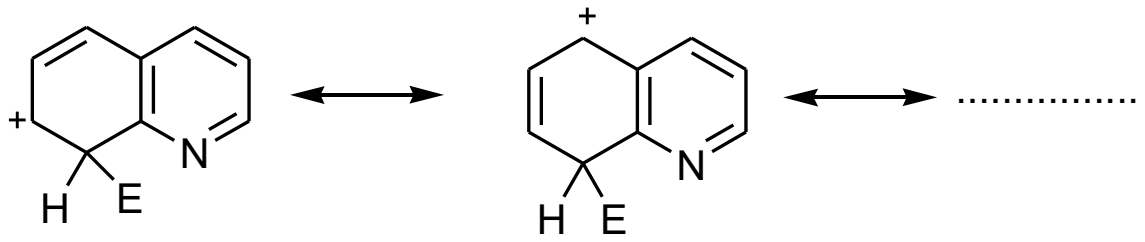
Attack at position -5



A

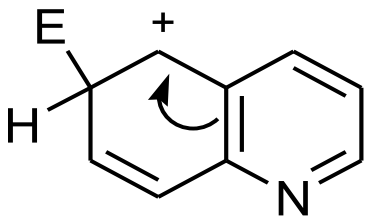
Less stable due to electron deficientat 8a of quinoline

Attack at position -8

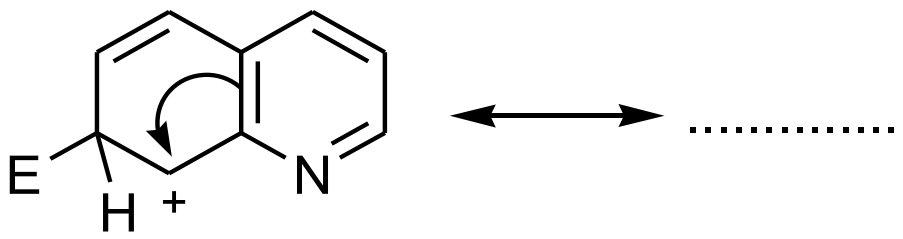


B

Attack at position -6



Attack at position -7



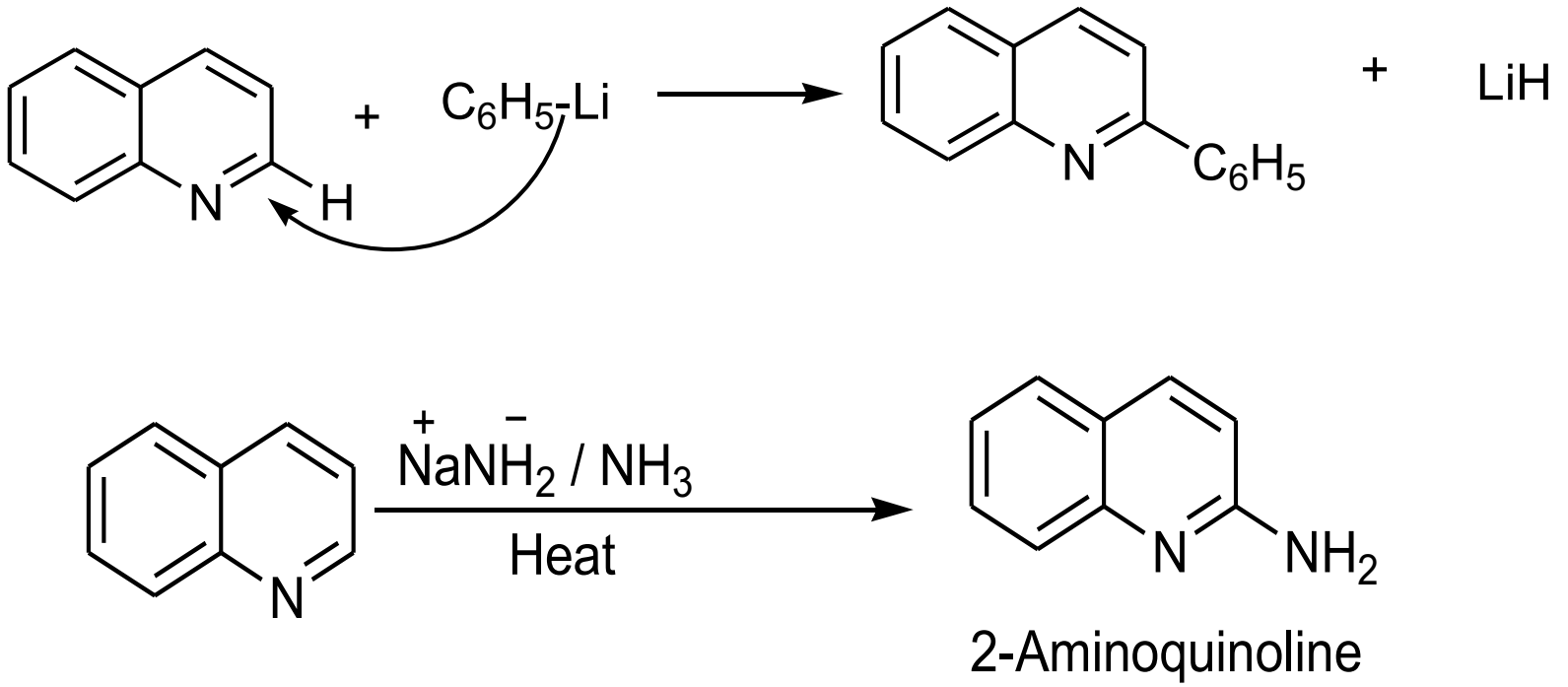
It is clear that attack at position 8 (or 5) yields two more stable resonance structures in which the aromatic sixtet of the pyridine ring is preserved, while attack at position 6 (or 7) yields one structure only in which the aromatic sixtet is preserved.

Position 8 is preferred than position 5 due to the less stability of resonating structure **A** in comparison to **B**.

Other resonance structures are unimportant. They are particularly unstable because the aromatic sixtet is disrupted.

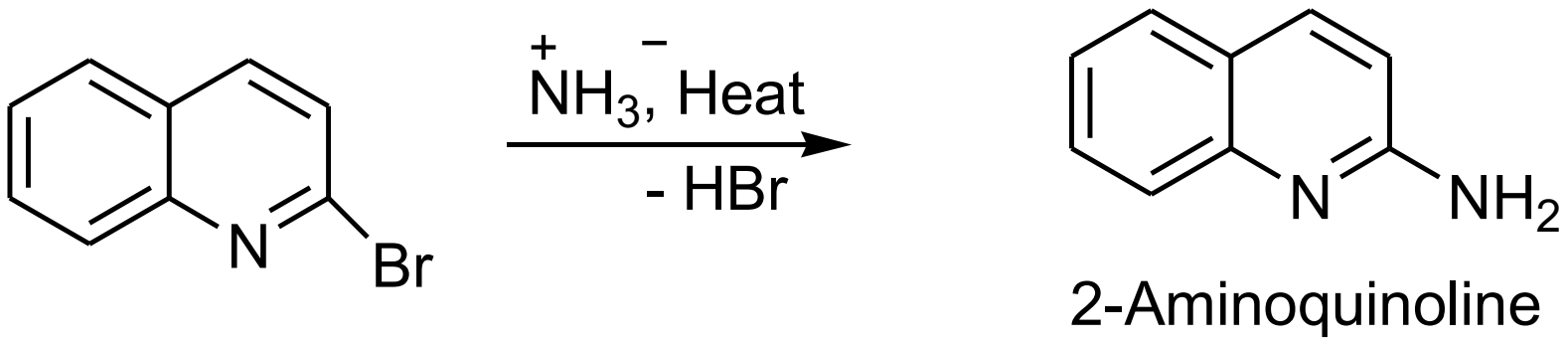
5-Nuclophilic Substitution

The presence of the electron-withdrawing nitrogen atom activates the pyridine ring towards nucleophilc substitution. The preferred position are 2 and 4. Like pyridine itself, the pyridine ring in quinoline is so reactive that even the powerfully basic hydride ion can be displaced as idicated by alkylation (or arylation) by organolithium compound and amination by sodium amide (Chichibabin reaction)



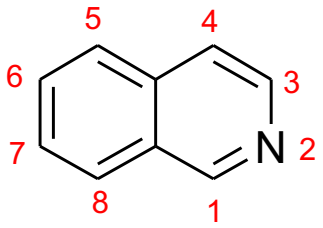
Nucleophilic Substitution of Halogen

Like pyridine, the halogen atom in position 2 and 4 are readily displaced by nuclophile



2-Aminoquinoline

Isoquinoline



K_b =- 1.1 x 10^{-9}

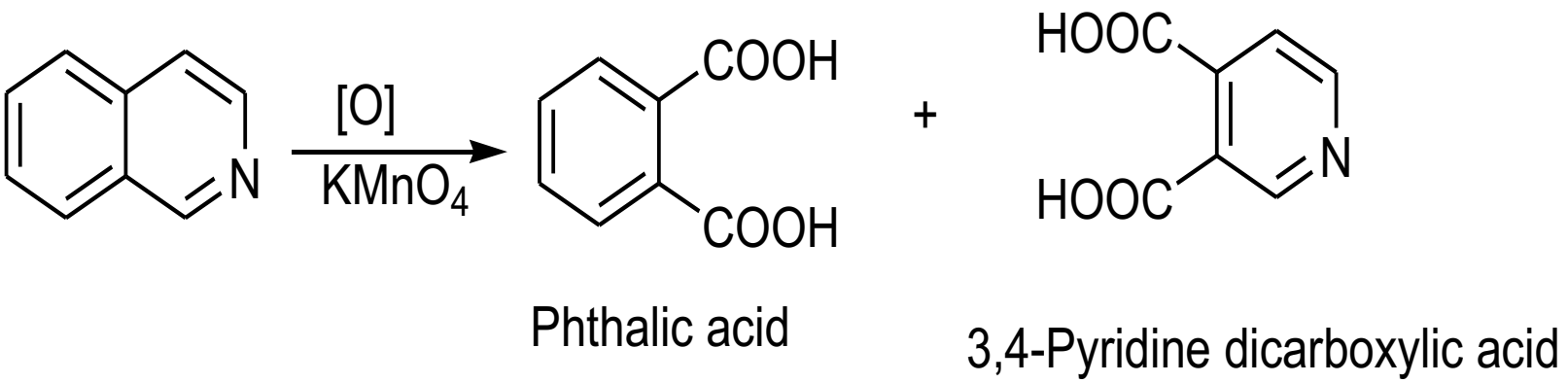
Isoquinoline contain a benzene ring and a pyridine ring fused as indicted above. Isoquinoline is one of the very few heterocyclic compounds in which numbering does not start with the heteroatom. The objective of this exceptional feature is to make the numbering of substitutions in isoquinoline in the same sequence as in quinoline and naphthalene.

Isoquinoline, like quinoline has the properties we would except from pyridine and naphthalene.

Reactions

1- Oxidation

It resembles quinoline in its reactions. Thus, it is a monoacid tertiary base. It undergoes oxidation to phthalic acid and 3,4-pyridinedicarboxylic acid.

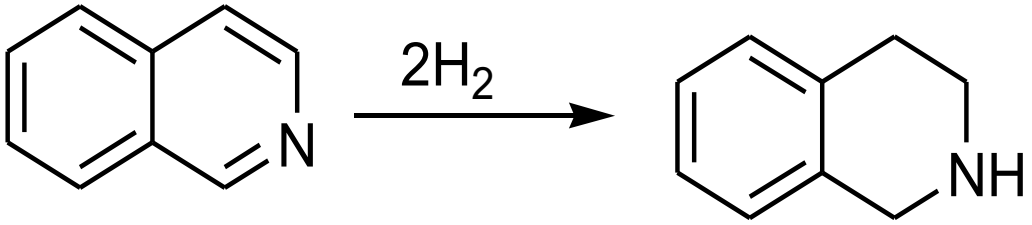


Phthalic acid

3,4-Pyridine dicarboxylic acid

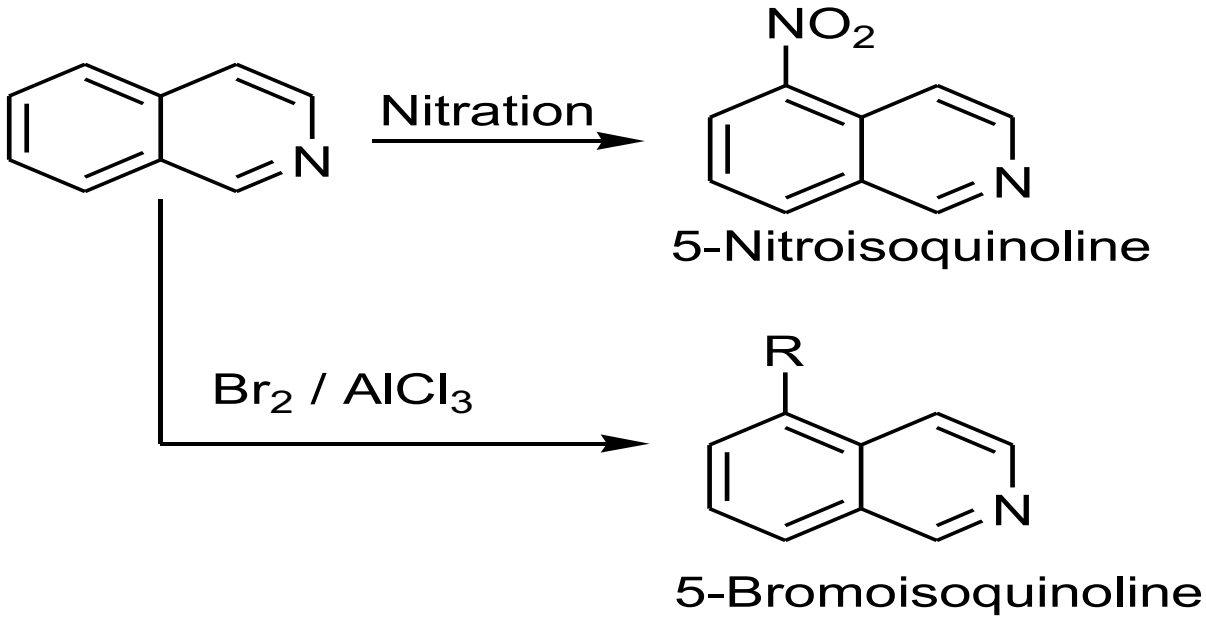
2- Reduction

Upon reduction 1,2,3,4-tetrahydroisoquinoline is obtained

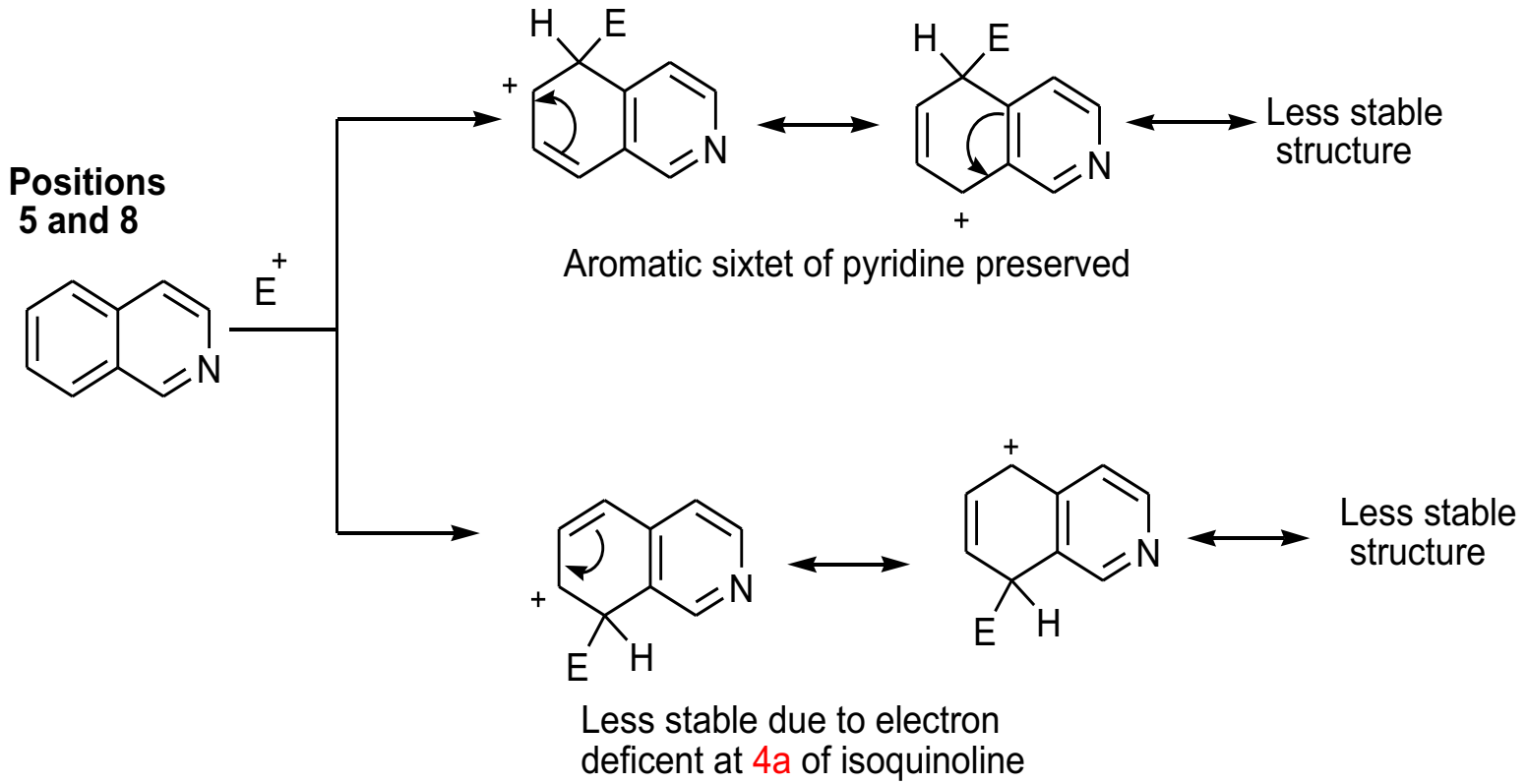


3-Electrophilic Substitution

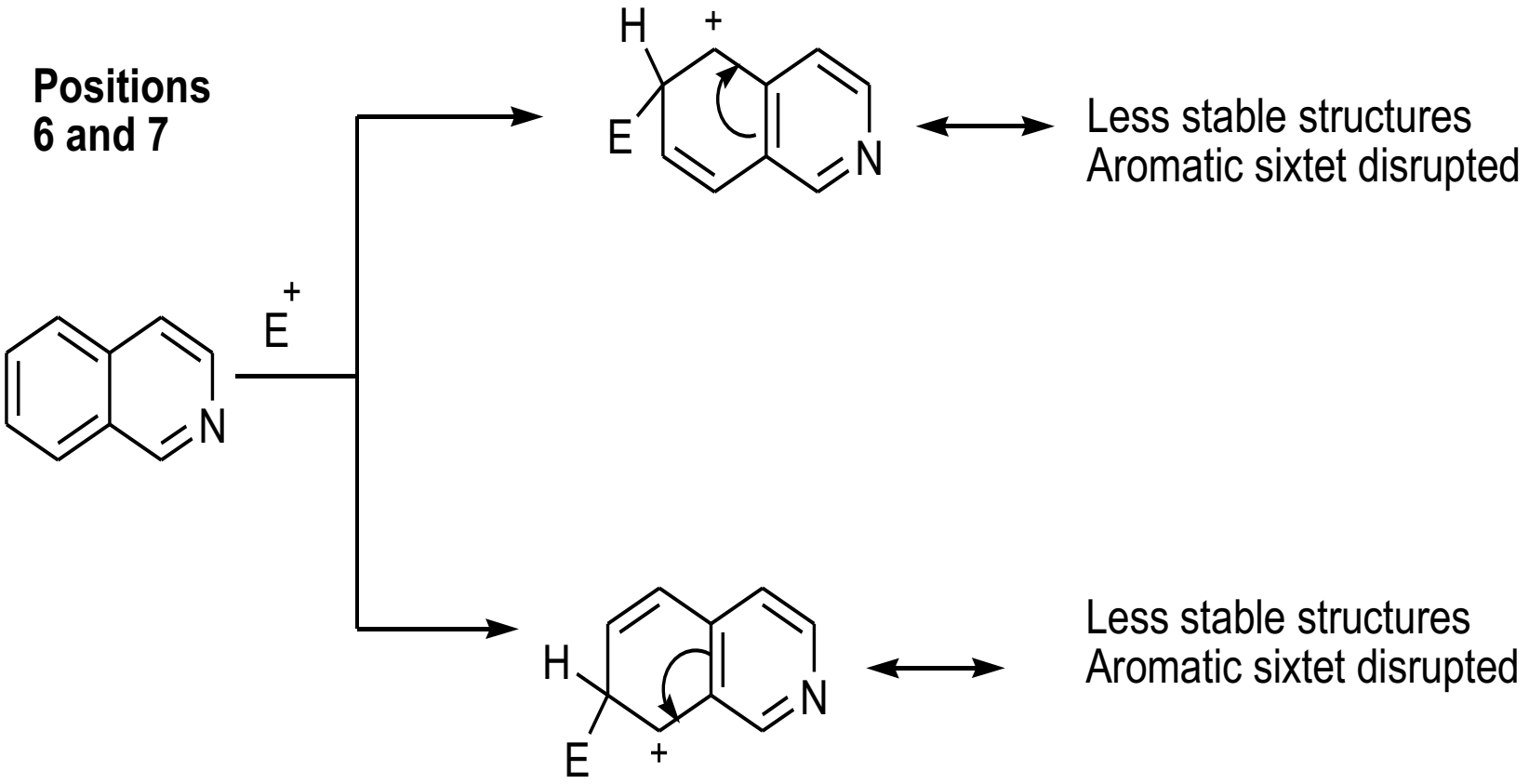
Like quinoline, isoquinoline undergoes electrophilic substitution in benzene ring.



Position 5 is preferred position for electrphilic attack since it results in two more stable resonance structures in which the aromatic sixtet of the pyridine ring is preserved, while attack at positions 6 and 7 yields one structure only in which the aromatic sixtet is presented.

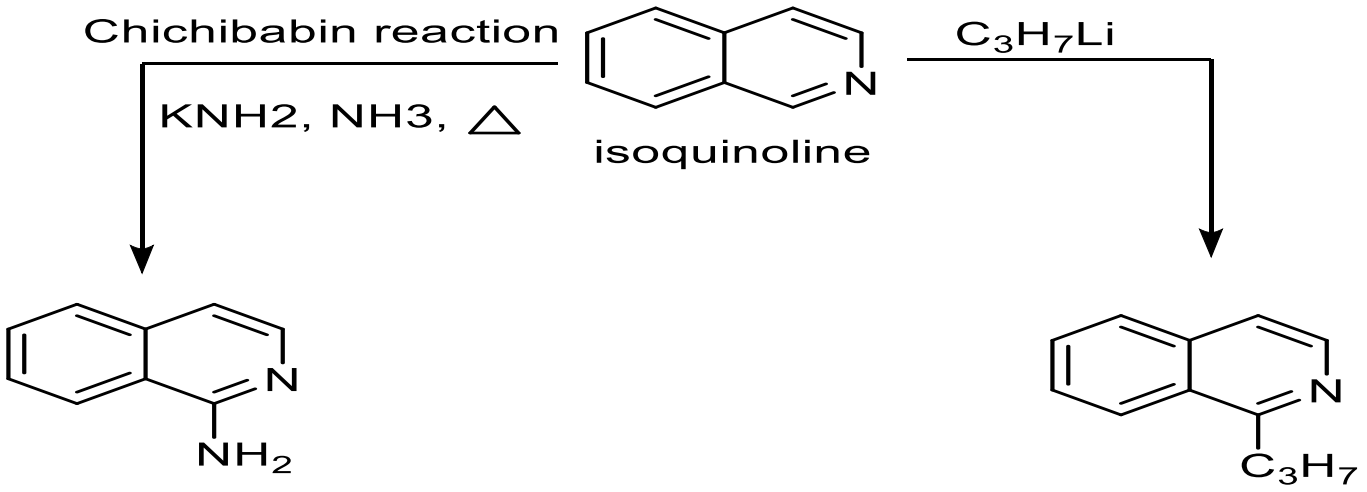


Positions 6 and 7



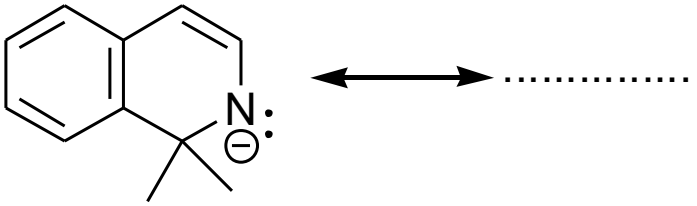
4-Nucleophilic Substitution

The pyridine ring in isoquinoline is also very reactive towards nucleophilic displacement.



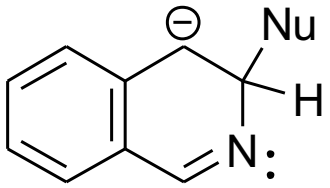
Nuclophilic attack takes place at position 1 as it is the only position which yields a resonance structure in which the aromatic sixtet is presented and nitrogen carriers a negative charge

Attack at position **1**

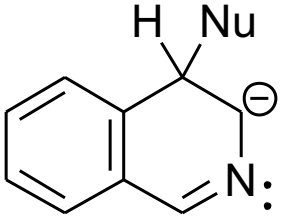


Prartically stable, aromatic sixtet of benzene preserved; nitrogen carries a negative charge

Attack at position **3**

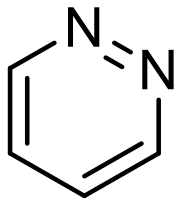


Attack at position **4**



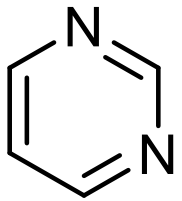
Diazines

There are three isomeric diazine



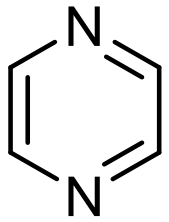
1,2-Diazine

Pyridazine



1,3-Diazine

Pyrimidine

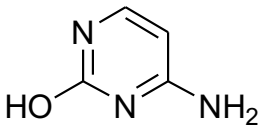


1,4-Diazine

Pyrazine

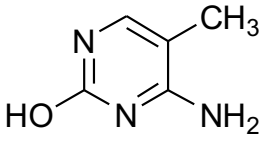
Pyrimidines

Pyrimidines are particularly important since the pyrimidine nucleus occurs in purines, nucleic acid, and synthetic barbiturates. Compounds containing the pyrimidine ring are present in all livingingcells. Hydrolysis of nucleic acids yield the pyrimidines: Cytosine, 5-methylcytosine, uracil and 5-methyluracil (thymine), as well as purines and other product.

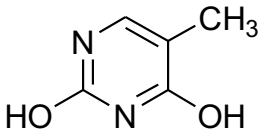


Cytosine

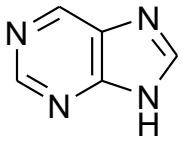
4-amino-2-hydroxypyrimidine



5-Methylcytosine



Thymine
(5-Methyuracil)



Purine

(Fused pyrimidine

and imidazole rings)