

## Heterocyclic Chemistry

By Dr Vipul Kataria

**Definition:** A heterocyclic compound or ring structure is a cyclic compound that has atoms of at least two different elements (N, O, S, P) as members of its ring.

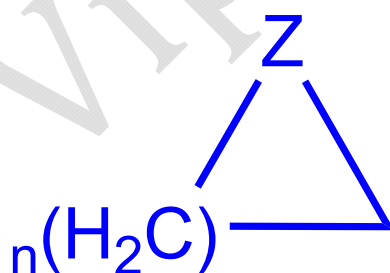
### Introduction:

- Heterocyclic compounds may be defined as cyclic compounds having as ring members atoms of at least two different elements. It means the cyclic compound has one another atom different than carbon.
- Heterocyclic compounds have much importance in organic chemistry because of abundant presence of heterocyclic compounds in present pharmaceutical drugs.
- Like other organic compounds, there are several defined rules for naming heterocyclic compounds.

### IUPAC rules for nomenclature of heterocyclic systems

(SPU 2012, 2 Marks)

- The system for nomenclature for heterocyclic systems was given by Hantzsch and Widman.



Where  $n = 1, 2, 3, \dots$   
 $Z = \text{N, O, S, P, \dots}$

- The Hantzsch-Widman nomenclature is based on the type (Z) of the heteroatom; the ring size (n) and nature of the ring, whether it is saturated or unsaturated.
- This system of nomenclature applies to monocyclic 3-to-10-membered ring heterocycles.
- **Type of the heteroatom:** The type of heteroatom is indicated by a prefix as shown below for common heteroatoms.

Heteroatom	Prefix
O	Oxa
N	Aza
S	Thia
P	Phospha

- When two or more of the same heteroatoms are present, the prefix di, tri, tetra... are used. e.g. dioxa, triaza, dithia.
- If the heteroatoms are different their atomic number in that group is considered. Thus order of numbering will be O, S, N, P, Si.
- Ring size: The ring size is indicated by a suffix according to Table I below. Some of the syllables are derived from Latin numerals, namely **ir** from **tri**, **et** from **tetra**, **ep** from **hepta**, **oc** from **octa**, **on** from **nona**, **ec** from **deca**.

Table I: Stems to indicate the ring size of heterocycles

Ring size	Suffix	Ring size	Suffix
3	ir	7	ep
4	et	8	oc
5	ol	9	on
6	in	10	ec

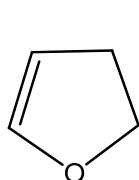
- The endings indicate the size and degree of unsaturation of the ring.

Table II: Stems to indicate the ring size and degree of unsaturation of heterocycles.

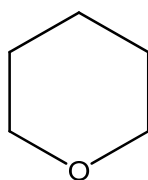
Ring size	Saturated	Unsaturated	Saturated (With Nitrogen)
3	-irane	-irine	-iridine
4	-etane	-ete	-etidine
5	-olane	-ole	-olidine
6	-inane	-ine	
7	-epane	-epine	
8	-ocane	-ocine	
9	-onane	-onine	
10	-ecane	-ecine	

\*Heterocycles 6-10 membered saturated (with N) is named using prefix perhydro to the name of the corresponding unsaturated compound.

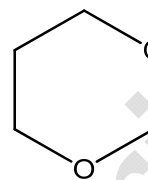
- In a monocyclic compound, numbering starts from hetero atom ( $O > S > N$ ).
- The state of hydrogenation is indicated by the prefixes dihydro, tetrahydro etc. or by prefixing the name of the parent unsaturated compound with the symbol H proceeded by number indicating the position of saturation.



2,3-dihydrofuran

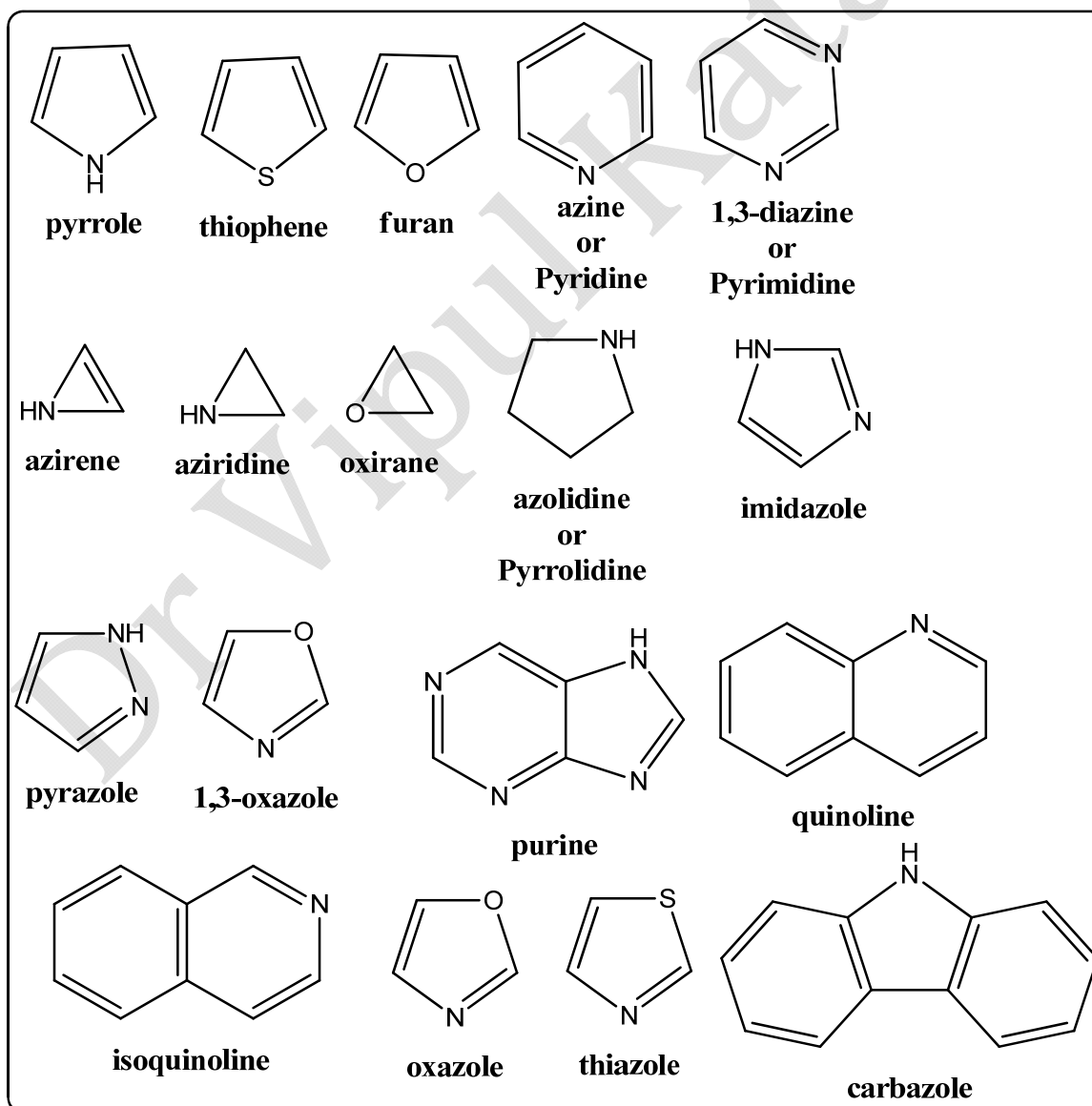


tetrahydro-2H-pyran



1,3-dioxane

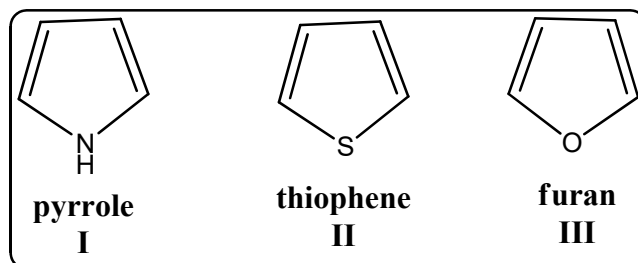
### Examples



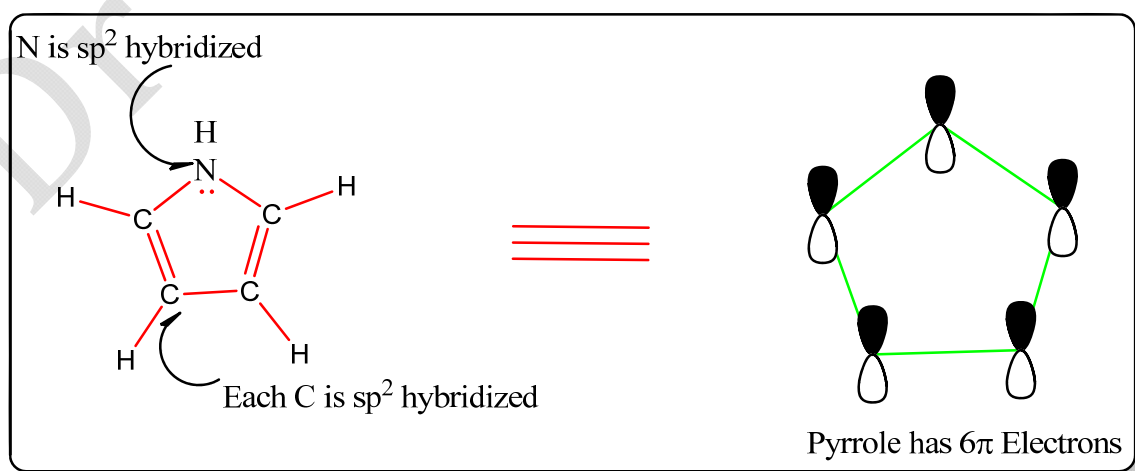
## Structure of Pyrrole, Furan and Thiophene

(SPU 2013, 2014, 2017 2 Marks, VP 2018 2 Marks)

- Pyrrole, furan and thiophene represent simplest five membered heterocyclic ring systems having single heteroatom.

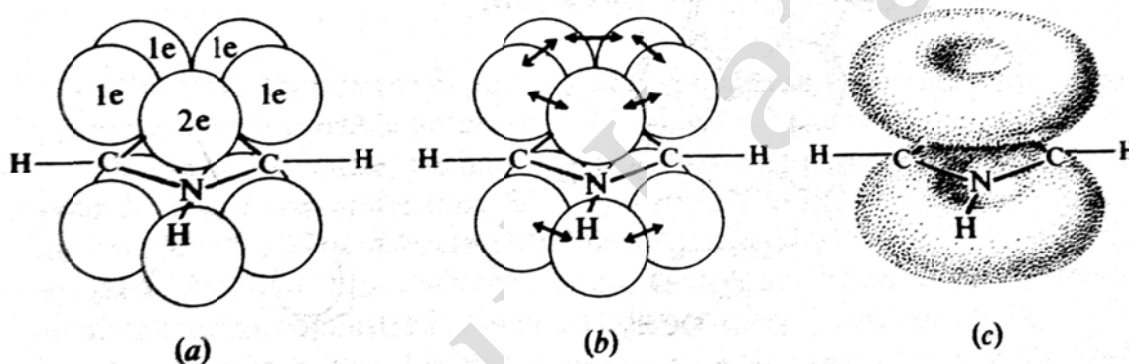


- Upon examination of structures, we can judge that these all structures might have properties of conjugated dienes and of an amine, ether and sulphide.
- However, except for certain properties like tendency to undergo addition reactions these heterocycles do not have expected properties.
- Thiophene does not undergo sulphide like oxidation.
- Pyrrole does not exhibit basicity like secondary amine.
- These heterocycles typically undergo electrophilic substitution reaction like benzene. viz. nitration, sulphonation, halogenation FCRs etc.
- Upon looking at heat of combustion values it is known that these molecules have resonance energy of 22-28 Kcal/mole which is slight lesser than benzene (36 Kcal/Mole) but much higher than conjugated diene (2-6 Kcal/Mole).
- So, these structures are aromatic in this sense.
- It is also proved upon seeing their orbital picture diagram



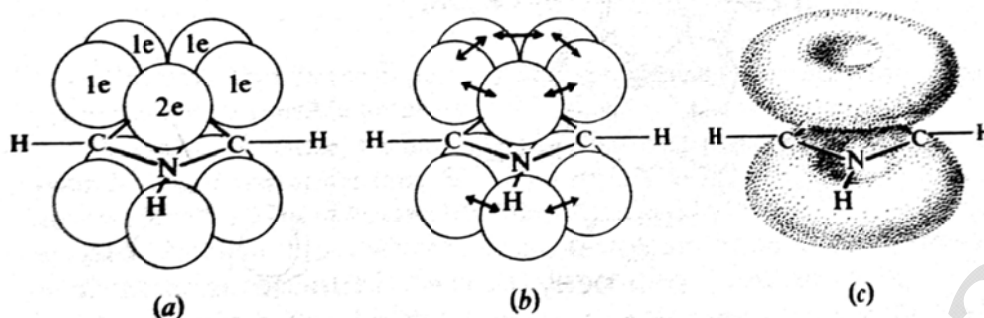
- Each atom of the ring either carbon or nitrogen is bonded via  $\sigma$  bond with other three atoms of the ring. For this bonding this atom uses  $sp^2$  orbital that lie in plan and at  $120^\circ$  apart.
- After formation of  $\sigma$  bond each carbon atom has left one more electron and nitrogen has left two more electron that forms  $\pi$  - clouds above and below of the ring.
- This  $\pi$  - cloud contains six electrons. *Aromatic sextet.*

Discuss aromatic character of five membered heterocyclic compounds containing one heteroatom.



- Each atom of the ring either carbon or nitrogen is bonded via  $\sigma$  bond with other three atoms of the ring. For this bonding this atom uses  $sp^2$  orbital that lie in plan and at  $120^\circ$  apart.
- After formation of  $\sigma$  bond each carbon atom has left one more electron and nitrogen has left two more electron that forms  $\pi$  - clouds above and below of the ring.
- This  $\pi$  - cloud contains six electrons. *Aromatic sextet.*
- Delocalization of  $\pi$  electrons stabilizes the ring. Due to this Pyrrole has an abnormally lower heat of combustion value.
- As a result, it undergoes substitution reactions in place of addition reactions.
- The Pyrrole molecule clearly obeys huckel rule for aromaticity.
- It is planar structure. It has  $\pi$  electron cloud above and below of the structure. It has  $(4n + 2) \pi e$ .
- It shows properties like benzene in place of conjugated diene or amine.

**Pyrrole is extremely weak base having  $K_b = 2.5 \times 10^{-14}$  explain.**



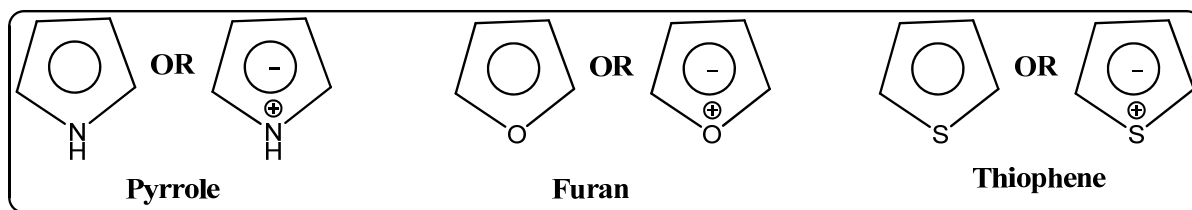
- Upon examination of structures, we can judge that Pyrrole might have properties of conjugated dienes and of an amine. However, except for certain properties like tendency to undergo addition reactions these heterocycles do not have expected properties.
- Amines are basic as lone pair of nitrogen is available for acid however in case of pyrrole it has different properties.
- Nitrogen's lone pair of electron that is responsible for usual basicity is part of aromatic sextet.
- The lone pair of electron is part of  $\pi$  - cloud and is not available for acid.
- In contrast to other amines, pyrrole is extremely weak base having  $K_b = 2.5 \times 10^{-14}$
- Due to  $\pi$  electron cloud above and below of the ring it generates high electron density and makes it more like benzene that undergoes electrophilic substitution reactions.
- The lone pair of electron is only available for acid if pyrrole loses its aromaticity that is not possible in normal conditions.
- As a result, pyrrole is extremely weak base.

**Pyrrole, furan and thiophene undergo electrophilic substitution reaction, Explain.**

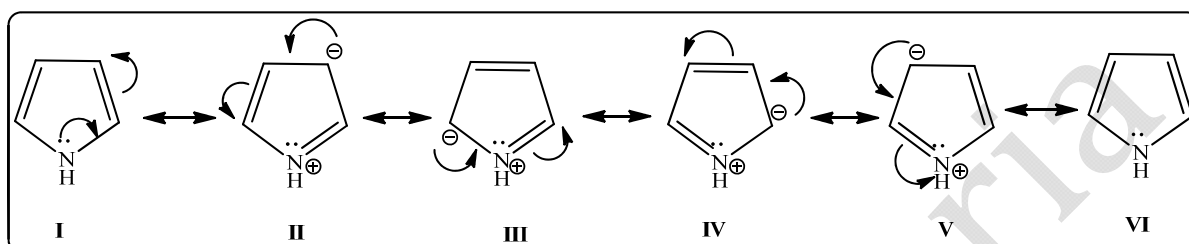
Or

**Pyrrole is extremely reactive than benzene**

- The structure of pyrrole, furan and thiophene can be represented as under.



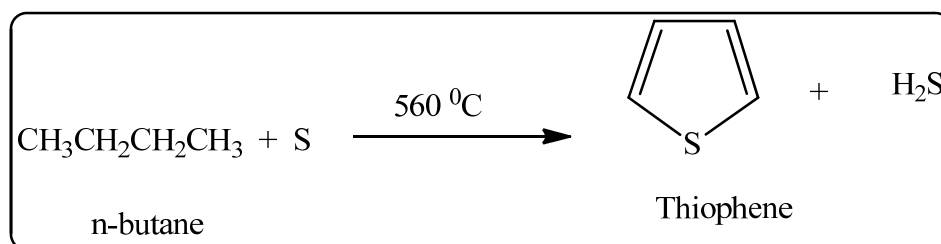
- The resonance structure for pyrrole can be represented as below.



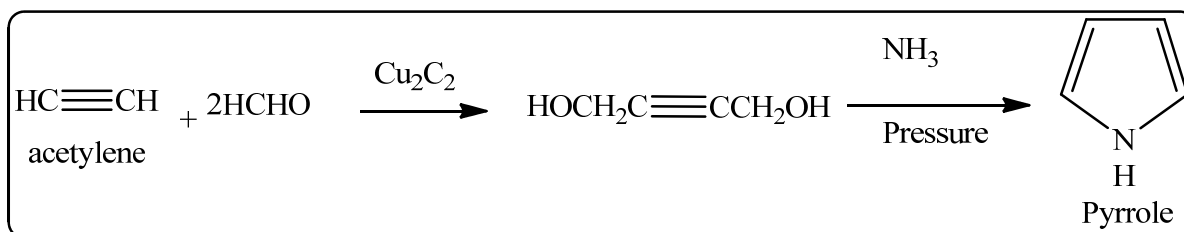
- Pyrrole is hybrid structure of above all the structures in which nitrogen possesses positive charge and ring possesses negative charge.
- Furan and thiophene also have structures analogues to pyrrole. Pyrrole contains H atom whereas furan and thiophene contains one more lone pair of electron.
- These structures become aromatic as lone pair of electrons is a part of aromatic sextet.
- These compounds have somewhat less resonance energy than benzene makes them more reactive than benzene.
- Like benzene, these compounds give electrophilic substitution reactions in place of addition reactions.

### Sources of pyrrole, furan and thiophene

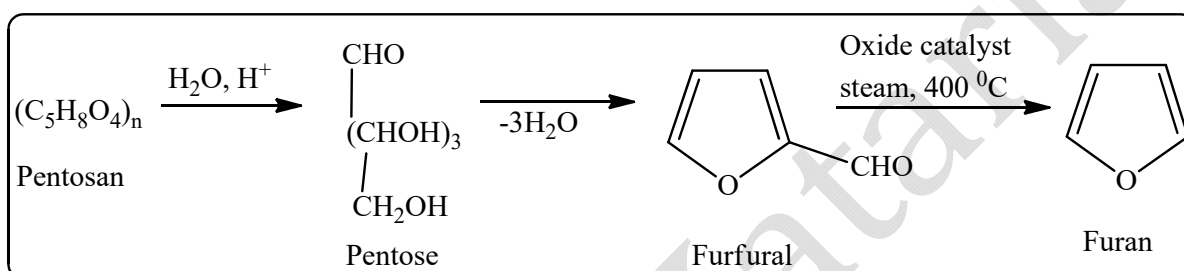
- Pyrrole and thiophene are found in small amounts in coal tar.
- During fractional distillation of coal tar, thiophene (B.P. 84°C) is collected along with the benzene.
- Thiophene can be synthesized on industrial scale by heating n-butane with sulphur at higher temperature (560 °C).



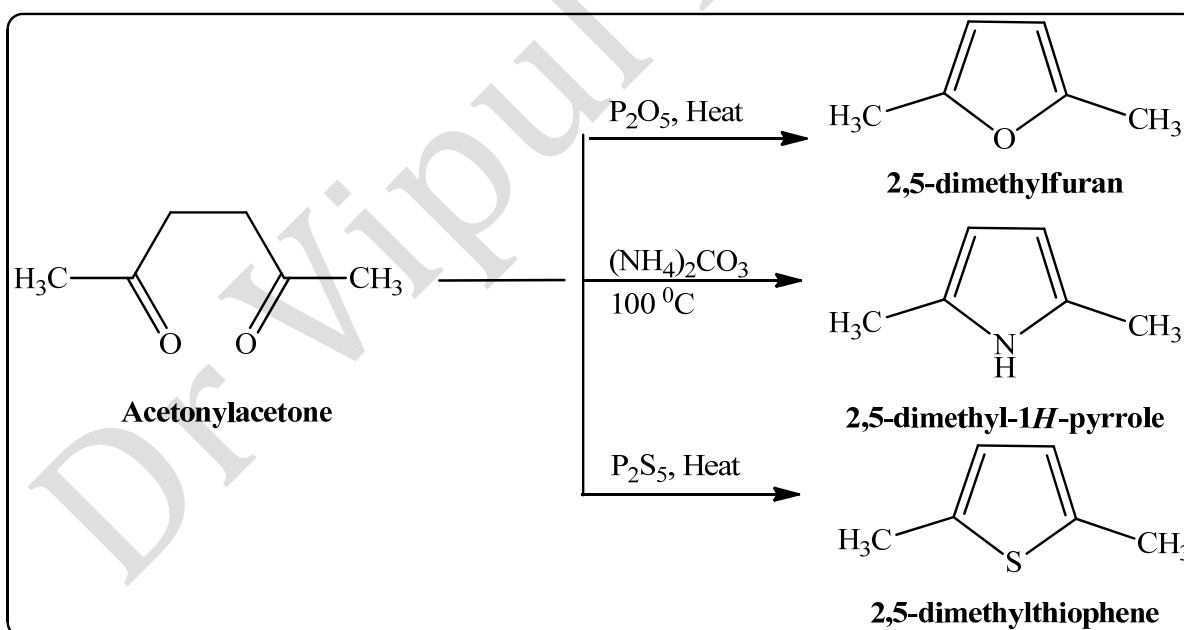
- Pyrrole can be synthesized by following method.



- Pyrrole is also a part of chlorophyll and haemoglobin.
- Furan is most readily prepared by decarbonylation of furfural. (VP 2013, 2018 2 Marks)



- Many substituted pyrrole, furan and thiophene can be prepared by ring closure reaction of 1,4-diketone compounds.

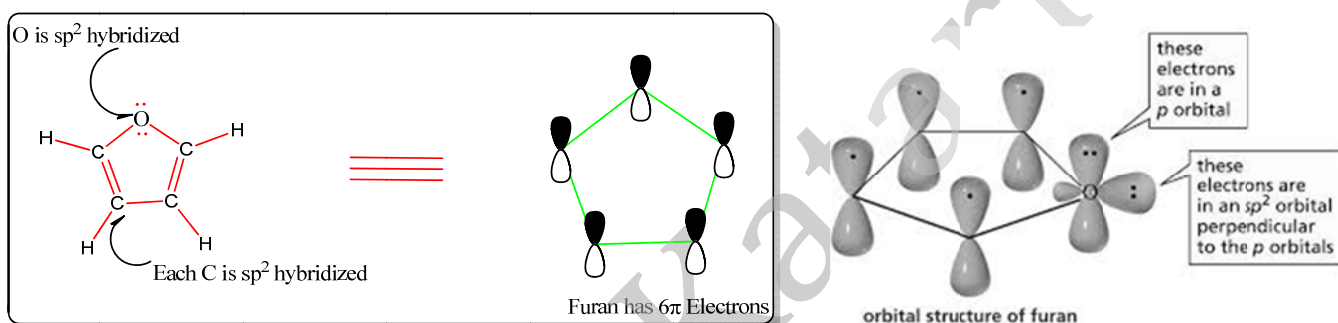


### Structure of Furan (VP 2012 2 Marks)

- Furan is planar pentagonal structure in which four carbon atom and one oxygen atom are in sp<sup>2</sup> hybridized state.



- The  $sp^2$  hybridized orbitals overlap with each other and with S-orbital of hydrogen to form carbon-carbon, carbon-oxygen and carbon-hydrogen bonds.
- Two lone pairs of electrons on oxygen are in different orbitals, one lone pair of electron is in  $sp^2$  hybridized orbital while other is in p-orbital.
- Four  $\pi$ -orbitals of four carbon atoms (each containing one electron) and  $\pi$ -orbital of oxygen atom (with lone pair) are parallel to each other and are perpendicular to the plane of the ring.
- The lateral overlapping of  $\pi$ -orbitals produces a  $\pi$ -molecular orbital containing six  $\pi$ -electrons.



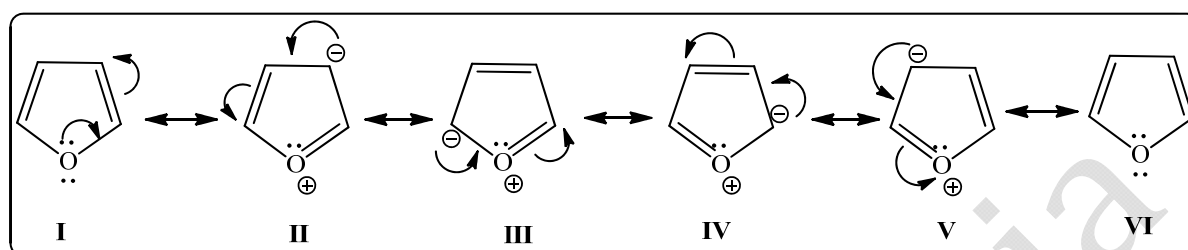
- The bonding in furan is same as in pyrrole only difference is H-atom in pyrrole is replaced by lone pair of electron in furan. This lone pair of electron does not take part in aromatic sextet.

Bond Length (Å)		Bond Angle (°)
O - C <sub>2</sub> = 1.362		C <sub>2</sub> -O-C <sub>5</sub> = 106.50
C <sub>2</sub> - C <sub>3</sub> = 1.361		O-C <sub>2</sub> -C <sub>3</sub> = 110.65
C <sub>3</sub> - C <sub>4</sub> = 1.430		C <sub>2</sub> -C <sub>3</sub> -C <sub>4</sub> = 106.07
C <sub>2</sub> - H = 1.075		O-C <sub>2</sub> -H = 115.98
C <sub>3</sub> - H = 1.077		C <sub>2</sub> -C <sub>3</sub> -H = 127.83

## Electrophilic reactions in furan occur at carbon atom and not on heteroatom.

(Write accordingly for pyrrole or thiophene)

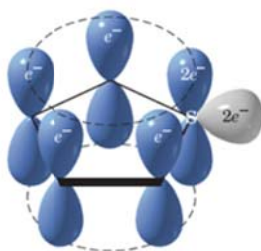
- Furan is considered to be resonance hybrid of the following resonating structures.



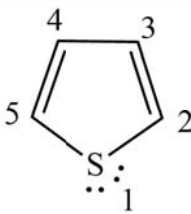
- Lone pair of the oxygen ring is delocalized around the ring.
- The positively charged trivalent oxygen atom makes dipolar structures less stable because of high electronegativity of oxygen atom therefore contributing less to the resonance hybrid of furan.
- Upon examination of the resonating structures it is clear that ring bears negative charge whereas oxygen atom bears positive charge.
- Hence, electrophilic reactions will occur at carbon atom instead of heteroatom.

## Structure of Thiophene

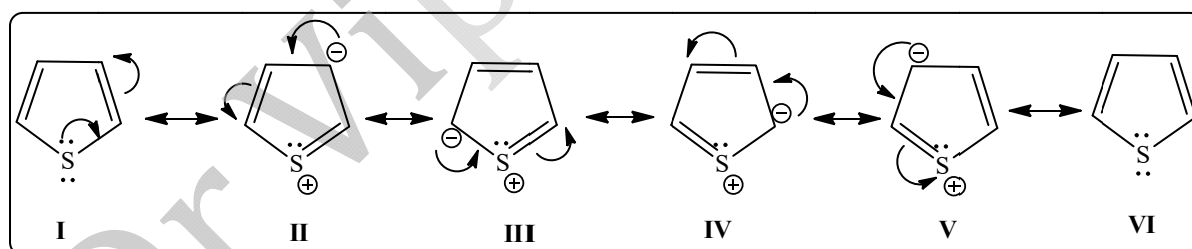
- Thiophene is planar pentagonal structure in which four carbon atom and one sulphur atom are in  $sp^2$  hybridized state.
- The  $sp^2$  hybridized orbitals overlap with each other and with S-orbital of hydrogen to form carbon-carbon, carbon-oxygen and carbon-hydrogen bonds.
- Two lone pairs of electrons on sulphur are in different orbitals, one lone pair of electron is in  $sp^2$  hybridized orbital while other is in p-orbital.
- Four  $\pi$ -orbitals of four carbon atoms (each containing one electron) and  $\pi$ -orbital of sulphur atom (with lone pair) are parallel to each other and are perpendicular to the plane of the ring.
- The lateral overlapping of  $\pi$ -orbitals produces a  $\pi$ -molecular orbital containing six  $\pi$ -electrons.



- The bonding in thiophene is same as in pyrrole only difference is H-atom in pyrrole is replaced by lone pair of electron in furan. This lone pair of electron does not take part in aromatic sextet.

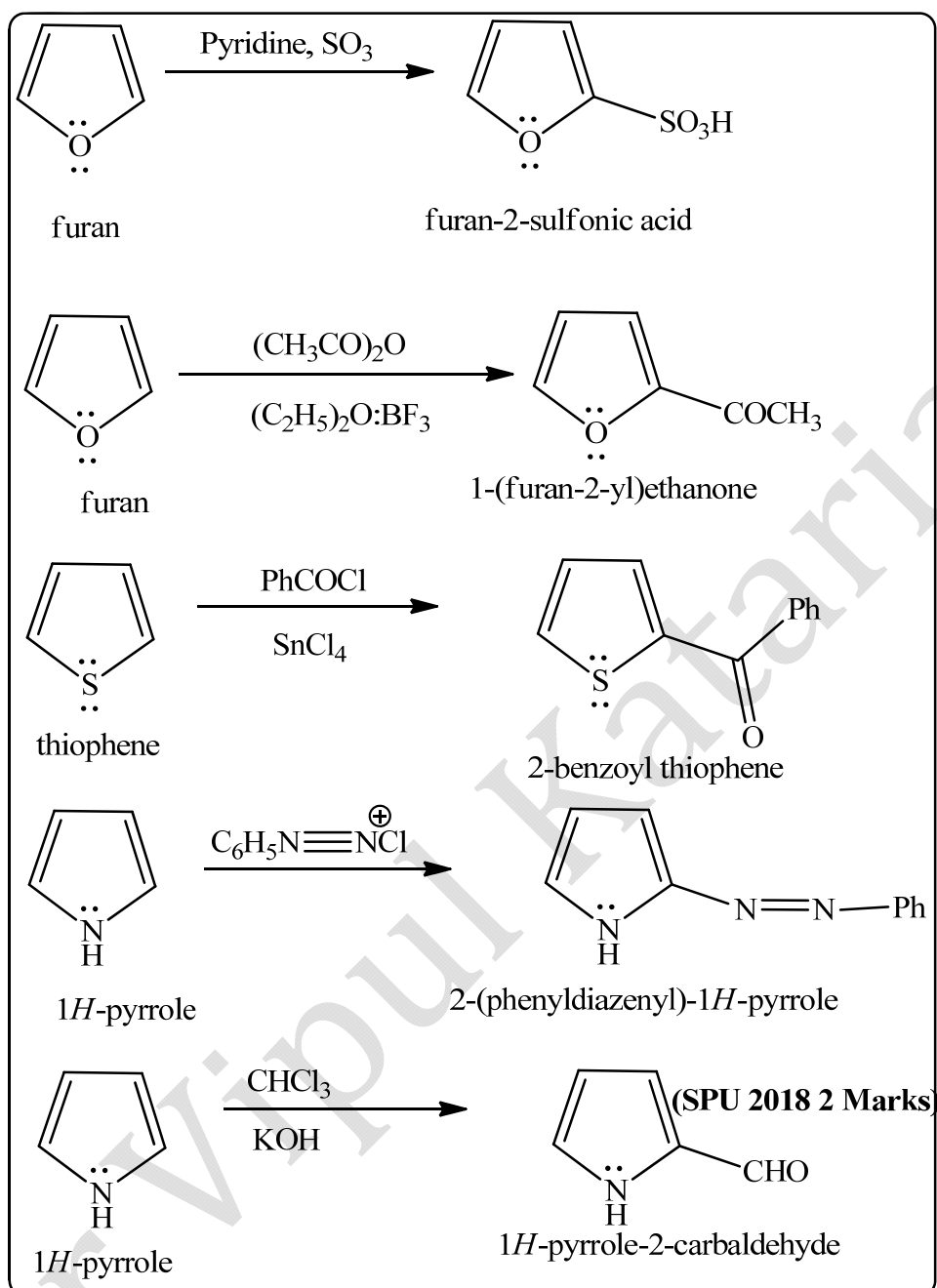
Bond Length (Å)		Bond Angle (°)
S - C <sub>2</sub> = 1.714		C <sub>2</sub> -S-C <sub>5</sub> = 92.17
C <sub>2</sub> - C <sub>3</sub> = 1.370		S-C <sub>2</sub> -C <sub>3</sub> = 111.47
C <sub>3</sub> - C <sub>4</sub> = 1.423		C <sub>2</sub> -C <sub>3</sub> -C <sub>4</sub> = 112.45
C <sub>2</sub> - H = 1.078		C <sub>2</sub> -C <sub>3</sub> -H = 123.28
C <sub>3</sub> - H = 1.081		

- Thiophene is uniquely  $\pi$ -successive aromatic heterocycles and has the highest resonance stabilization energy among the five membered heterocycles.
- The resonance energy is attributed to the expansion of valence shell by using d-orbitals in hybridization. The resonating structures for thiophene are as under.



### Electrophilic substitution in pyrrole, furan and thiophene

- Like other aromatic compounds, these five membered heterocyclic compounds undergo nitration, sulphonation, halogenation, and FCRs.
- They are much more reactive than benzene and resemble the most reactive benzene derivatives (amine and phenols) in undergoing such reactions as the reimer-tiemann reaction, nitrosation and coupling with diazonium salts.
- The electrophilic reaction takes place predominantly at the 2-position.



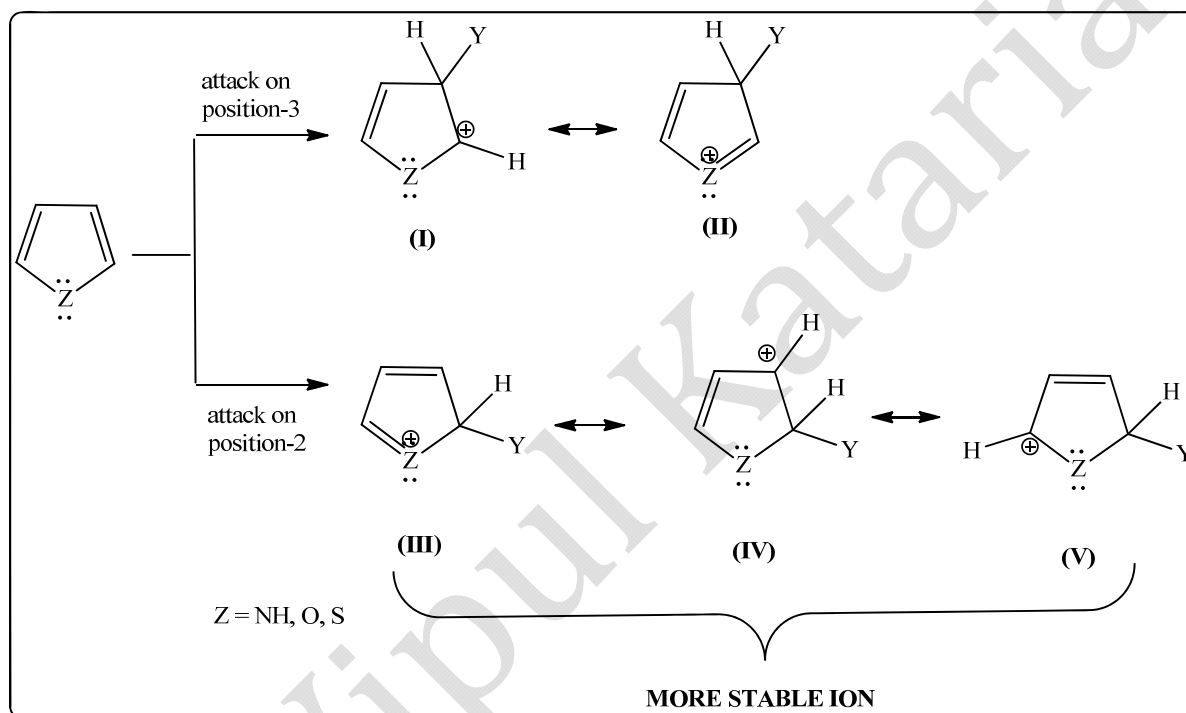
- The high reactivity of these compounds makes it possible to use mild reagent or mild reaction conditions.
- FCR of thiophene can be carried out using weak lewis acid like stannic chloride.

**Electrophilic reactions in five membered heterocycles exclusively occur at position-2 not at position-3**

**(SPU 2012 (2 Marks), 2015 (4 Marks), 2017 (3 Marks), VP 2013, 2018 3 Marks )**

(write your answer according to pyrrole, furan thiophene)

- Let us consider following resonating structures for five membered heterocycles attacked by electrophile at position-2 and 3.

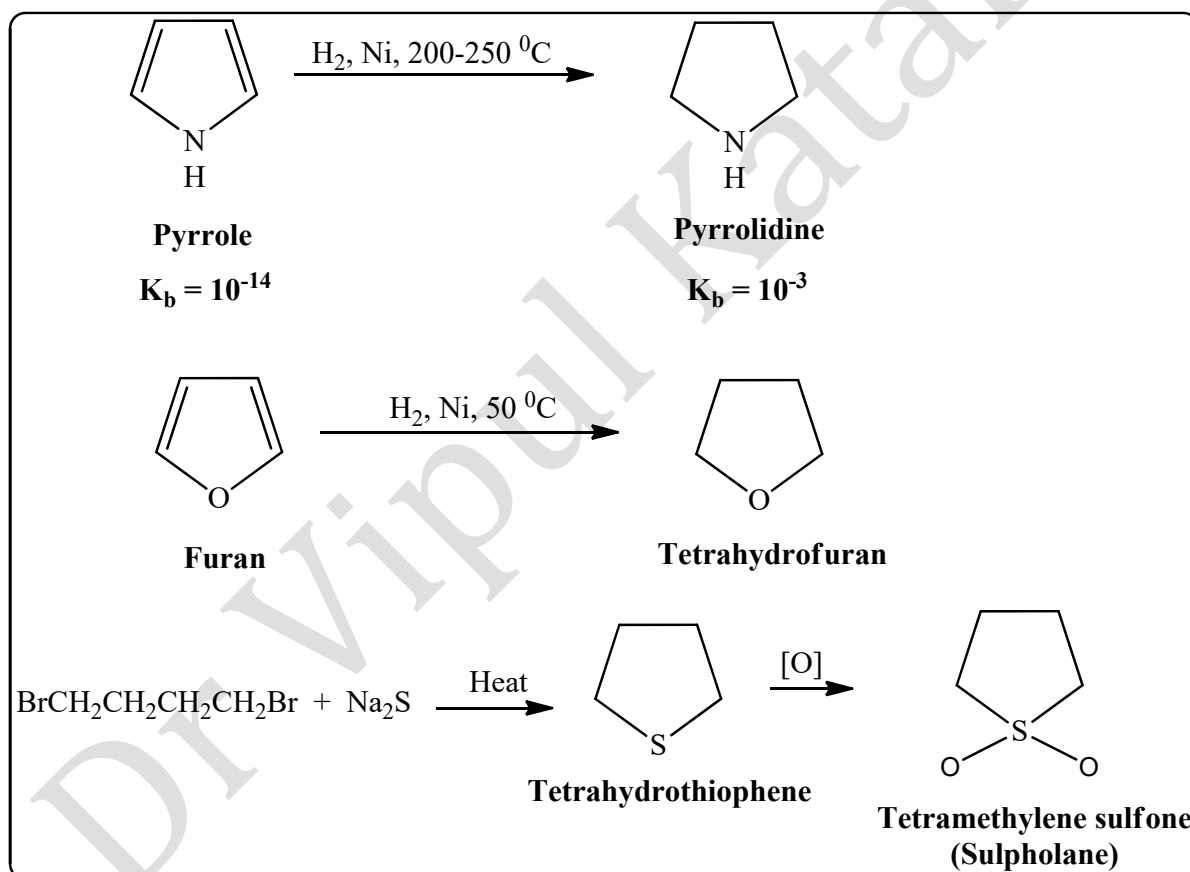


- Upon examination of above resonating structures, it is clear that attack on position-3 yields two resonating structures while attack on position-2 would yield three resonating structures.
- The extra resonating structure for attack at position-2 would make it more stable position.
- Moreover, the structure III has all the atoms with its octet of electrons that makes it more stable.
- The heteroatom (N, S, O) possesses positive charge simply by sharing four pairs of electrons.
- Therefore, in five membered heterocyclic compounds position-2 is more reactive than position-3.

- In case of position-2 is occupied, the electrophilic reaction will occur at position-5 (identical to position-2).
- If both the positions are occupied then electrophilic reaction would occur on position-3 or 4.

### Saturated five membered heterocycles

- Pyrrole and furan upon catalytic hydrogenation (reduction) produces pyrrolidine and tetrahydrofuran respectively.
- Tetrahydrothiophene is prepared from open chain compound as thiophene poisons most of the catalysts.



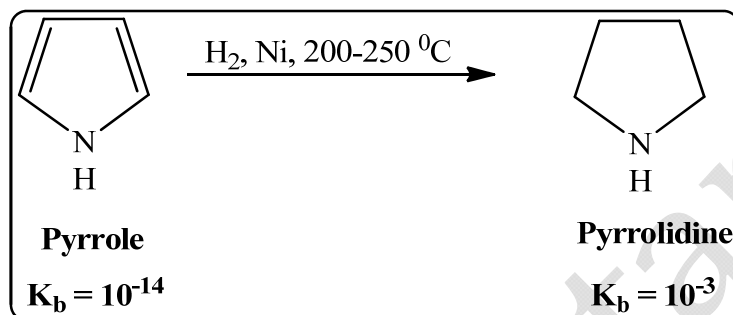
- Saturation of these rings destroys their aromatic character and aromatic properties.
- Pyrrole, furan and thiophene upon saturation yield expected properties of secondary aliphatic amine, an aliphatic ether and aliphatic sulphide respectively.
- Furan upon hydrogenation yields tetrahydrofuran that is very good organic solvent especially used in reduction with lithium aluminium hydride in preparation of aryl magnesium chlorides and in hydroboration.

- Tetrahydrothiophene upon oxidation yields sulpholane is also a very good aprotic solvent.

**Hydrogenation of pyrrole increases its base strength by a factor of  $10^{11}$ .**

**(SPU 2014, 2016 2 Marks)**

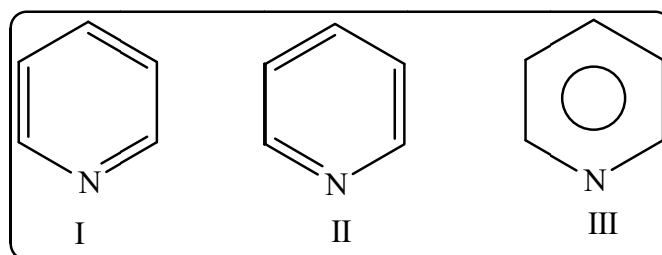
- Pyrrole upon hydrogenation gives pyrrolidine.



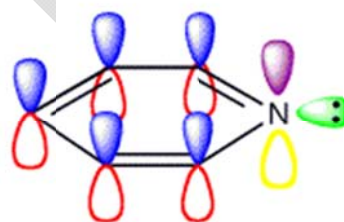
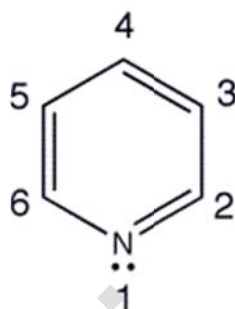
- Pyrrole is aromatic in nature and the lone pair of nitrogen is not available for acid therefore pyrrole is extremely weak base with  $K_b$  of  $10^{-14}$ .
- Upon hydrogenation pyrrole loses its aromaticity and aromatic properties.
- The pyrrolidine yields properties same like aliphatic amine.
- The lone pair of pyrrolidine is freely available for acid as the molecule is no more aromatic.
- It behaves like aliphatic amine so it is much more basic than pyrrole.
- The  $K_b$  for pyrrolidine is  $10^{-3}$  that is  $10^{11}$  times higher than pyrrole.

**Structure of Pyridine (VP 2013 2 Marks)**

- Pyridine is six membered heterocyclic compound having N as heteroatom.
- It is planar and hexagonal.
- It is aromatic due to its properties.
- It has bond angle of  $120^\circ$ .
- All four C-C bonds are equal and two C-N bonds are equal.
- It undergoes electrophilic substitution reaction and resist to addition reaction.
- Its resonance energy is 23 Kcal/mol.



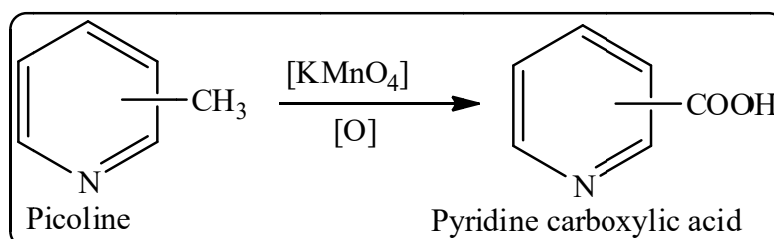
- Pyridine is hybrid of structure I and II and can be represented by III in which ring signifies aromatic sextet.
- The electronic configuration of nitrogen of pyridine is quite different from nitrogen of pyrrole.
- In pyridine, nitrogen is bonded to two other atoms of the ring by the use of  $sp^2$  orbitals and provides one electron for the  $\pi$ -cloud.
- The third  $sp^2$  orbital of carbon is bonded with hydrogen.
- The nitrogen has lone pair of electron available for acid (make it more basic than pyrrole).



- Due to such electronic configuration of the nitrogen atom pyridine is much stronger base than pyrrole.

### Sources of Pyridine

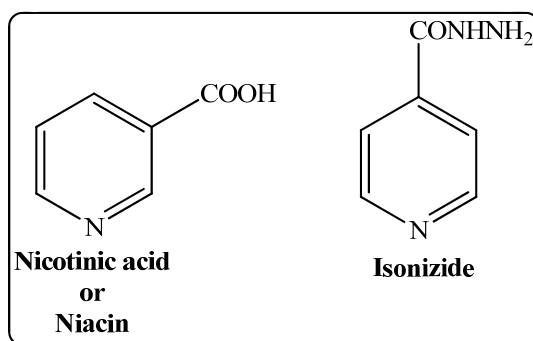
- Pyridine is found in coal tar.
- It is also found as methyl pyridines among which most important is monomethyl pyridine known as picolines.



- Oxidation of the picolines yields pyridine carboxylic acid.



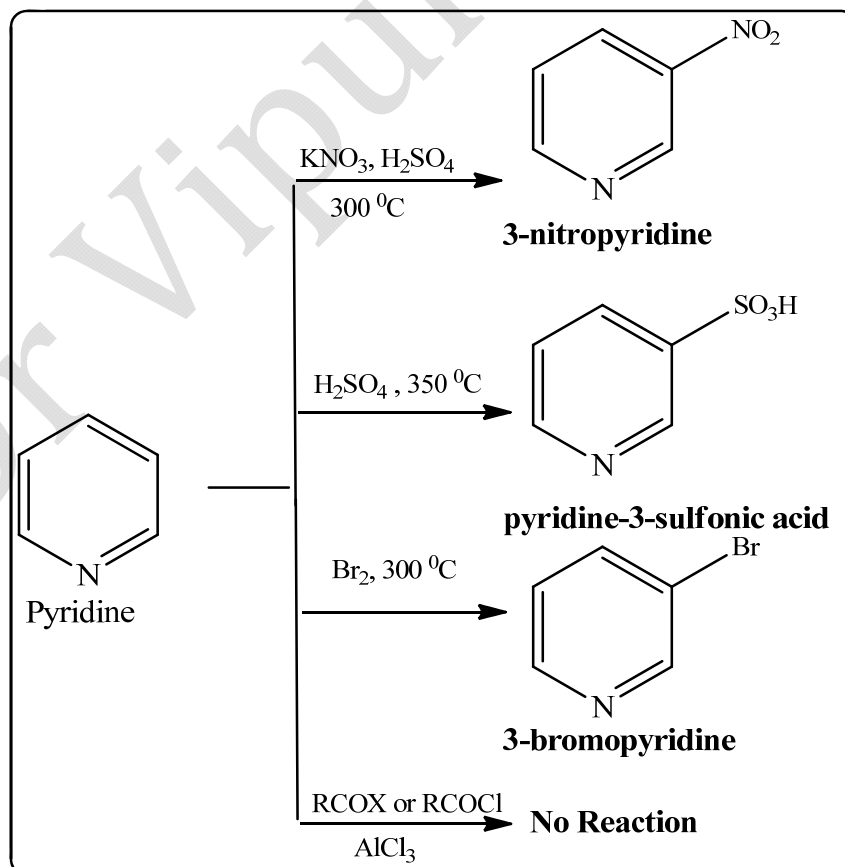
- Pyridine-3-carboxylic acid is called niacin (vitamin) or nicotinic acid.



- Hydrazide of pyridine-4-carboxylic acid is known as isoniazid (antitubercular drug).

### Electrophilic substitution reaction of pyridine

- Pyridine undergoes electrophilic substitution reaction just like other aromatic molecules.
- It resembles highly deactivated benzene for electrophilic substitution reactions.
- It undergoes nitration, sulphonation and halogenation at very vigorous reaction conditions and it does not undergo FCR at all.



- Electrophilic substitution chiefly occurs at position-3.

Explain: Electrophilic substitution reaction occurs chiefly at position-3 in pyridine.

or

Explain: Pyridine undergoes electrophilic substitution slower than benzene.

or

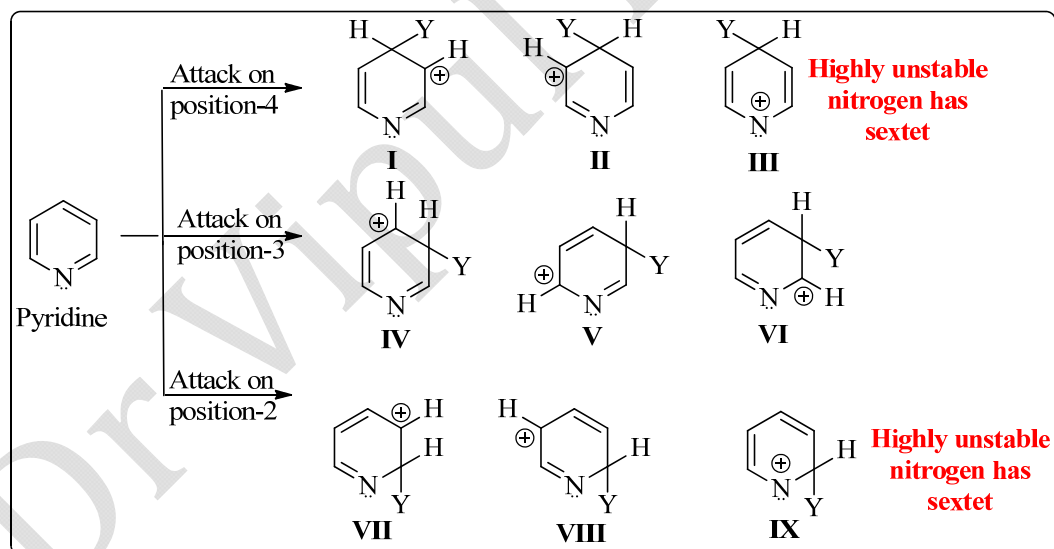
Explain: Pyridine undergoes electrophilic substitution reaction at position-3 and not at position-2 or 4.

or

How does electrophilic substitution reaction take place at different positions in pyridine?

(SPU 2014, 2016 3 Marks, 2015 4 Marks, VP 2018 4 Marks)

- Let us consider electrophilic attack at different positions in pyridine.

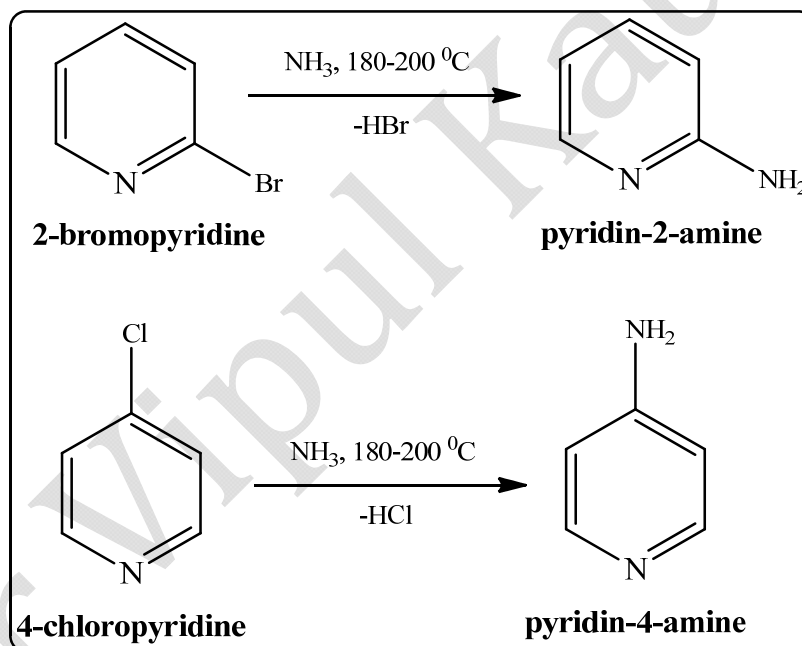


- It is important to understand that all the above structures are unstable when compared to the same attack on benzene due to the electron-withdrawing property of the nitrogen atom.
- As a result of this, pyridine undergoes electrophilic substitution reaction slower than benzene.
- Upon examination of the above structures, it is clear that structures III and IX are especially unstable as the nitrogen atom has a sextet.

- Due to this reason, electrophilic substitution occurs predominantly at position-3 as compare to position-4 or 2.
- It is also important to understand electrophilic substitution pattern in pyrrole and pyridine as in case of pyrrole nitrogen also bear positive charge however all the atoms in that case has an octet of electron and nitrogen accommodates positive charge simply by sharing four pairs of electrons.
- Whereas in case of pyridine, the structures in which nitrogen bears positive charge are especially unstable as nitrogen has sextet.

### Nucleophilic substitution reaction in pyridine

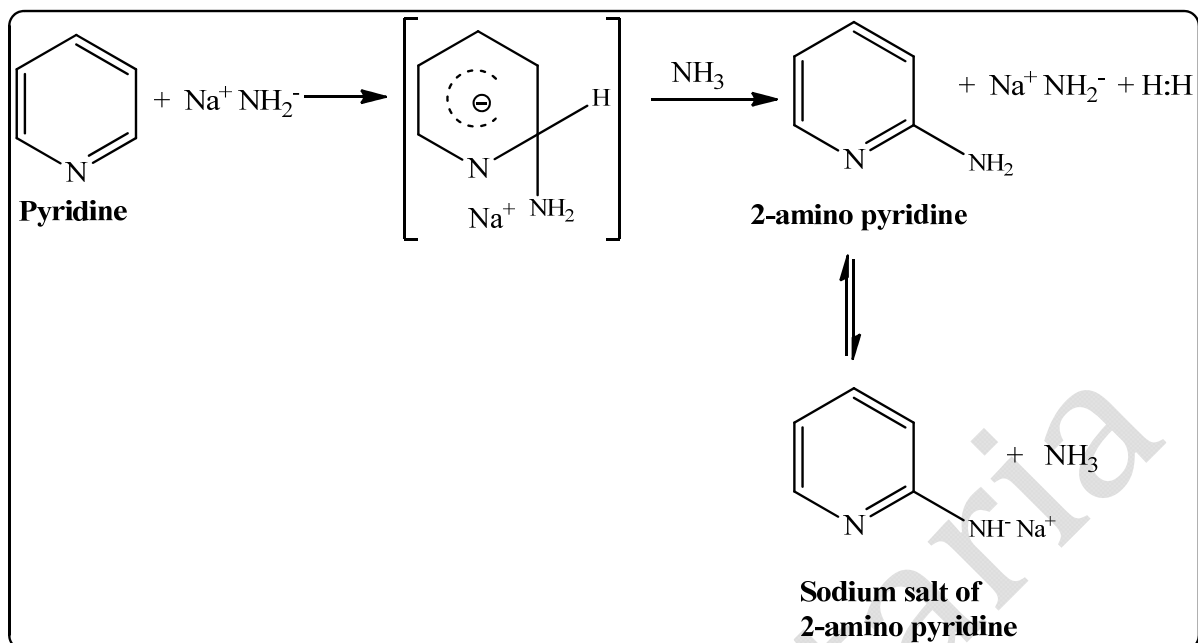
- As in case of electrophilic reactions pyridine resembles to highly deactivating benzene ring, it undergoes nucleophilic reactions readily.



- Pyridine undergoes nucleophilic reactions so easily that even powerful basic hydride ( $\text{H}^-$ ) ion can be displaced.

### Chichibabin Reaction (SPU 2013, 2015, 2016, 2017 2 Marks)

- The Chichibabin reaction is a method for producing 2-aminopyridine derivatives by the reaction of pyridine with sodium amide.
- The direct amination of pyridine with sodium amide takes place in liquid ammonia. Following the addition elimination mechanism first a nucleophilic  $\text{NH}_2^-$  is added while a hydride ( $\text{H}^-$ ) is leaving.



- Chichibabin reaction predominantly occurs at position-2.

Explain: pyridine undergoes nucleophilic reaction faster than benzene.

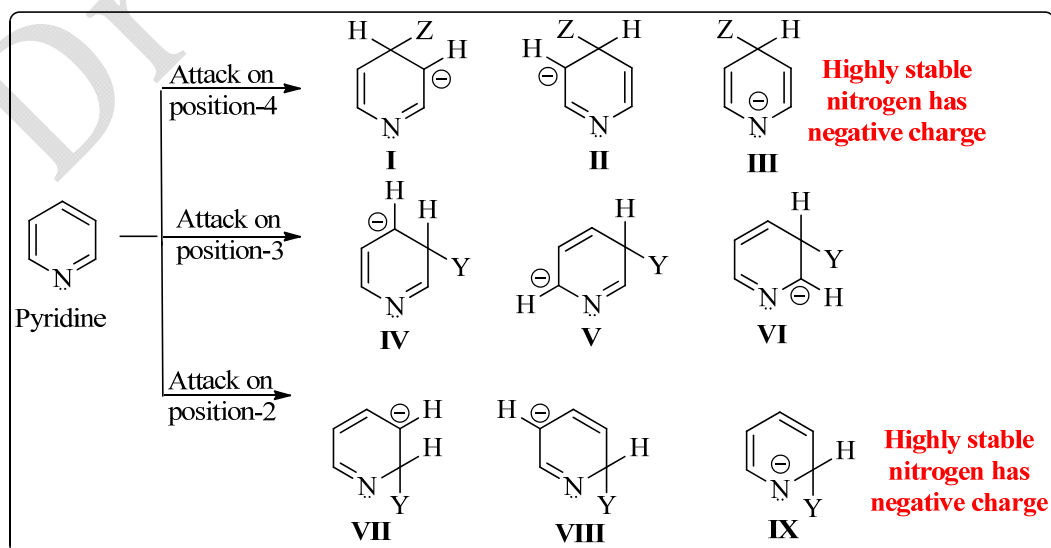
or

Explain: Nucleophilic substitution reaction occurs chiefly at position-2 and 4 and not at position-3.

or

How does nucleophilic substitution reaction take place at different positions in pyridine? (SPU 2012, 2017 3 Marks, VP 2013, 2016 3 Marks)

- Let us consider nucleophilic attack on various positions for pyridine.



- All the above structures are more stable than corresponding attack on benzene due to electron withdrawal nature of nitrogen.
- As a result of this, pyridine undergoes nucleophilic substitution reaction faster than benzene.
- Upon examination of above structures, it is clear that structure III and IX are especially stable as nitrogen possesses negative charge.
- Due to this reason, electrophilic substitution occurs predominantly at position-2 or 4 as compare to position-3.
- The same electronegativity of nitrogen that makes pyridine unreactive towards electrophilic substitution makes pyridine highly reactive towards nucleophilic substitution reactions.

Arrange the following compounds in the increasing order of basicity and justify your answer.

(1) Methyl amine ( $\text{CH}_3\text{NH}_2$ )  $K_b = 2 \times 10^{-3}$  (2) Pyrrole  $K_b = 2.5 \times 10^{-14}$  (3) Pyridine  $K_b = 2.3 \times 10^{-9}$

Or

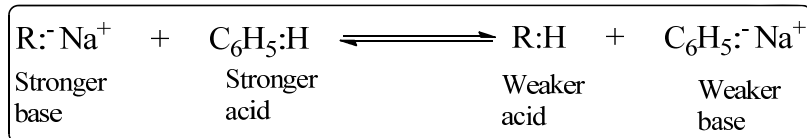
Explain: Pyridine is stronger base than pyrrole but weaker base than aliphatic amines.

Or

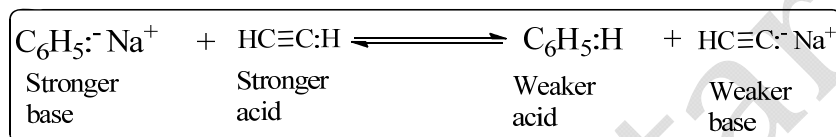
Arrange the relative basicity of anions of acetylene, benzene and alkane and justify your answer. (SPU 2012, 2015, 2016, 2017, 2018 4 Marks, VP 2012 3 Marks)

- Pyridine ( $K_b = 2.3 \times 10^{-9}$ ) is more basic than pyrrole ( $K_b = 2.5 \times 10^{-14}$ ) but less basic than aliphatic amine ( $K_b = 2 \times 10^{-3}$ ).
- Pyridine has lone pair of electron in  $sp^2$  orbital is readily available for sharing with acid whereas in case of pyrrole the lone pair of electron is part of aromatic sextet and is only available for acid if it loses its aromaticity.
- The fact that pyridine is weaker base than aliphatic amine is more difficult to account for however it can be understood by concept of acidity of hydrocarbons and basicity of their anions.

- Relative acidity:  $\text{H-C}\equiv\text{C-H} > \text{C}_6\text{H}_5\text{:H} > \text{R:H}$
- Relative basicity:  $\text{H-C}\equiv\text{C}^- > \text{C}_6\text{H}_5\text{:}^- > \text{R:}^-$
- Benzene is stronger acid than alkane as it can displace an alkane from its salt therefore we can say that phenyl anion is a weaker base than alkyl anion.



- In a same way, acetylene is a stronger acid than benzene and the acetylide ion is a weaker base than the phenyl anion.

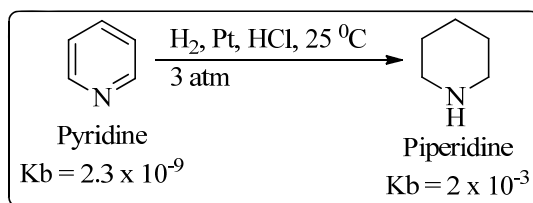


- The possible explanation is found in the electronic configuration of the carbanions.
- In alkyl, phenyl and acetylide anions, the unshared pair of electrons occupies in  $sp^3$ ,  $sp^2$  and  $sp$  orbital respectively.
- The availability of this unshared electron pair for acids determines the extent of basicity.
- The electron in p orbital is bound loosely as compare to electron in s orbital.
- Among the three anions the alkyl anion is strongest base since its pair of electron is held most loosely ( $sp^3$ ). The acetylide ions is weakest base since its pair of electron is held most tightly ( $sp$ ).
- Pyridine has same relationship with aliphatic amine as the phenyl anion has with alkyl anion.
- Pyridine is  $sp^2$  hybridized and aliphatic amine is  $sp^3$  hybridized so electron pair of aliphatic amine is more readily available as compare to pyridine.

### Reduction of pyridine Or Explain: Piperidine is stronger base than pyridine.

(SPU 2015 2 Marks, VP 2018 2 Marks)

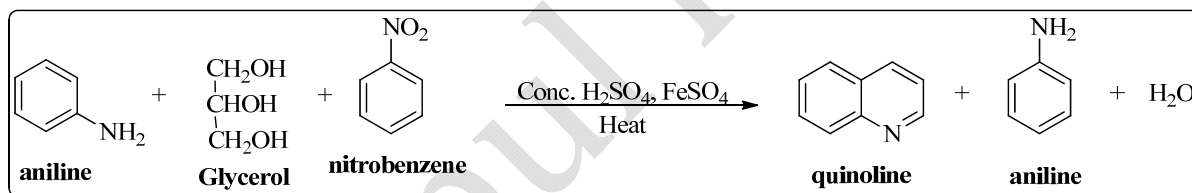
- Catalytic hydrogenation (reduction) of pyridine yields the aliphatic heterocyclic compound known as piperidine.



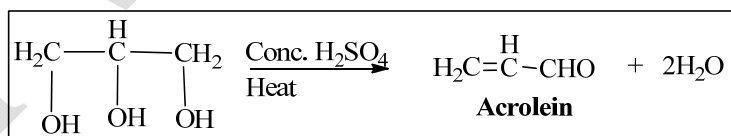
- Piperidine has usual basicity as of aliphatic amine much higher than pyridine.
- Piperidine is used as basic catalyst in many organic reactions.
- Here increase in basicity can be explained by the change in structure.
- Pyridine is planar structure whereas piperidine resembles to chair confirmation of the cyclohexane.
- Piperidine is found in a number of alkaloids including nicotine, strychnine, cocaine and reserpine.

### Quinoline (Skraup Synthesis) (SPU 2017 4 Marks, VP 2013 3 Marks)

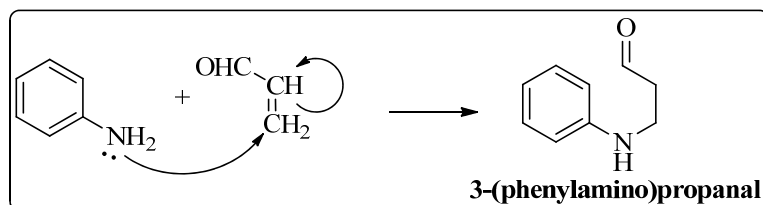
- Aniline reacts with glycerol in presence of conc.  $\text{H}_2\text{SO}_4$ , nitrobenzene and ferrous sulphate to give quinoline.



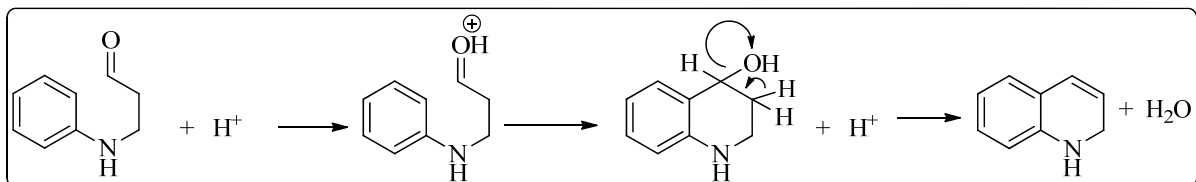
- The plausible reaction mechanism is as under.
- Dehydration of glycerol in presence of hot concentrated sulphuric acid yields acrolein (propenal).



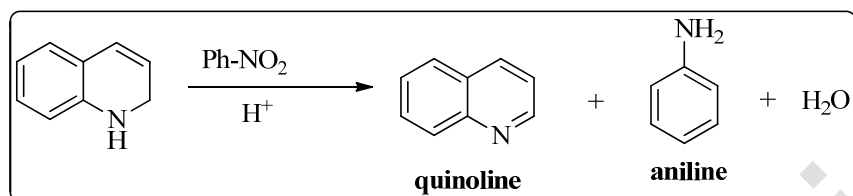
- Nucleophilic addition of aniline to acrolein to yield 3-(phenylamino) propanal.



- Ring closing step by electrophilic attack on the aromatic ring by electron efficient carbonyl carbon.

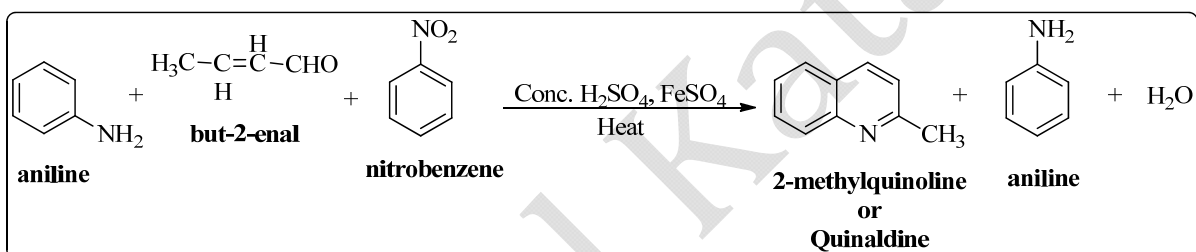


➤ Oxidation by nitrobenzene that aromatize the newly formed quinolone structure.

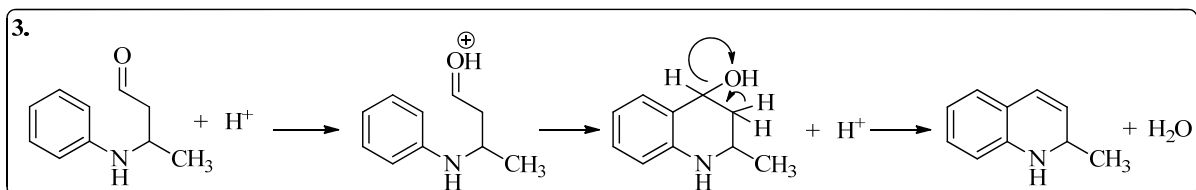
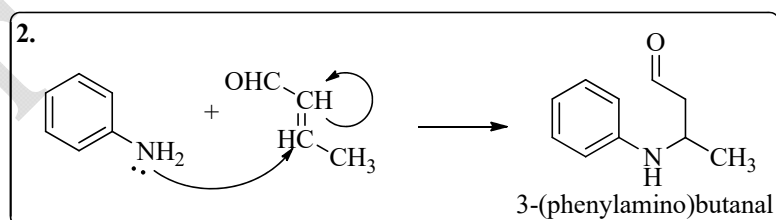
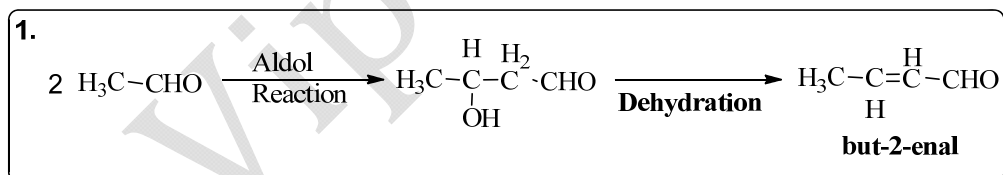


➤ Ferrous sulphate is used to control the oxidation process.

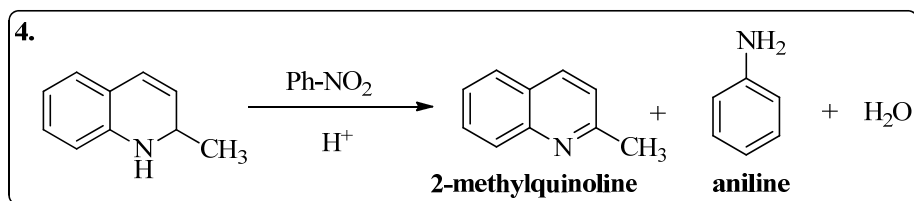
### Quinaldine (2-methyl Quinoline) (SPU 2015 3 Marks)



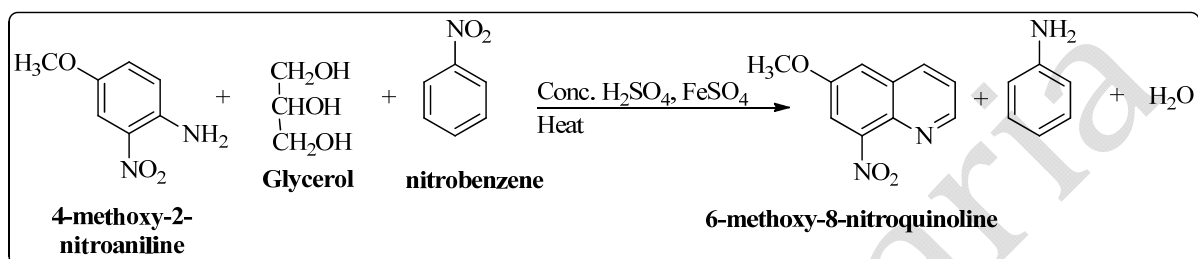
Following steps are involved in reaction mechanism.



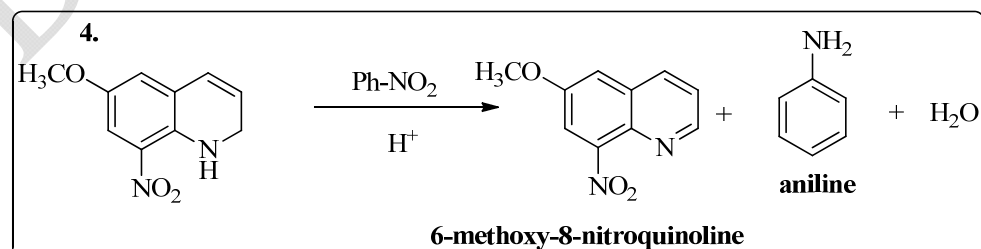
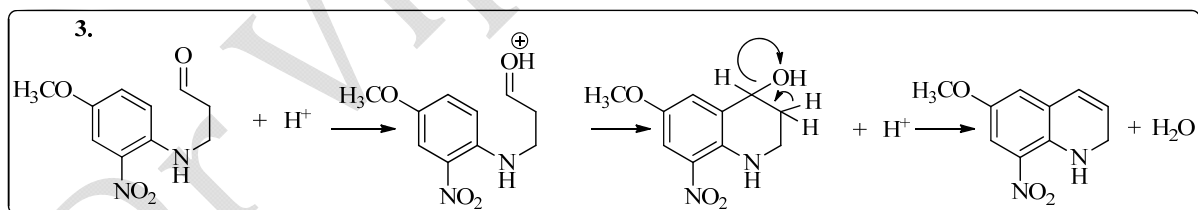
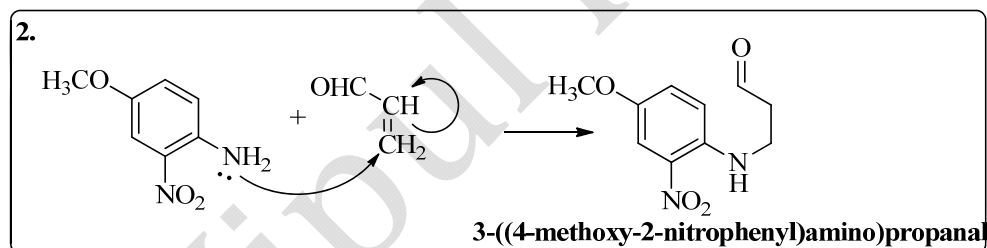
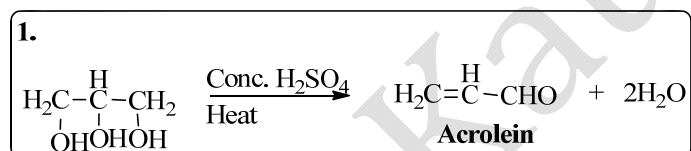




### 6-methoxy-8-nitro quinoline

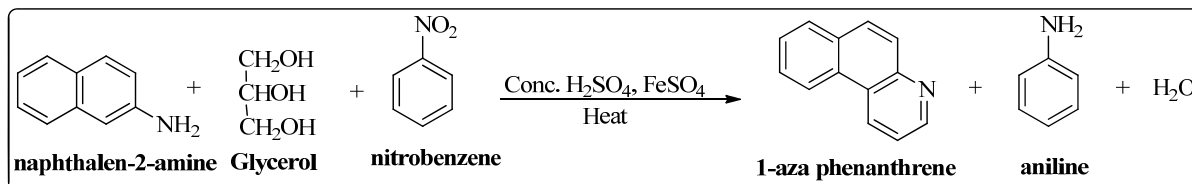


Following steps are involved

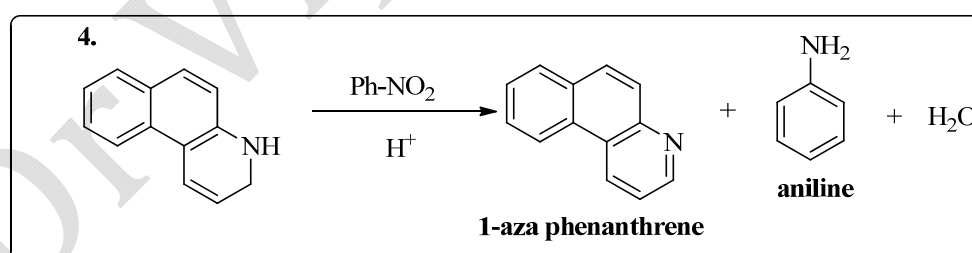
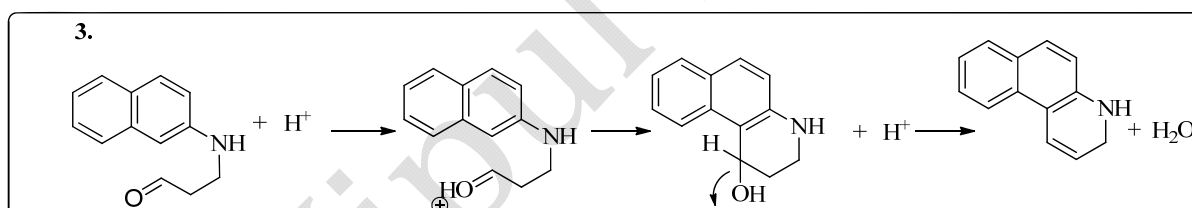
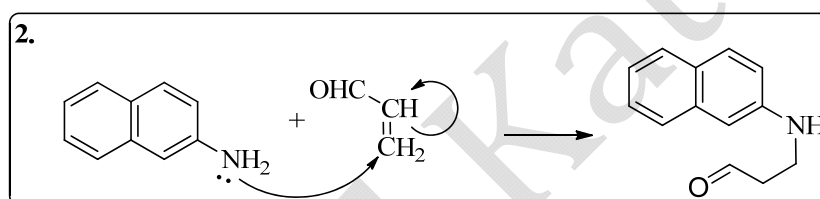
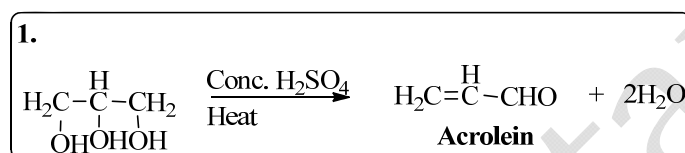


Give the detail stepwise reaction for synthesis of 1-azaphenanthrene or 5,6-benzoquinone by skraup synthesis.

(SPU 2014,2016, 2017 4 Marks, VP 2012, 2013 3 Marks)

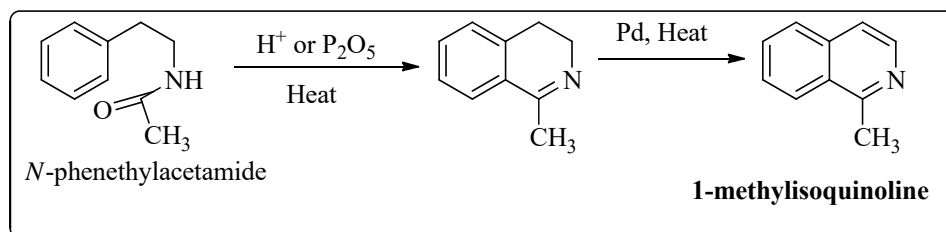


Following steps are involved.

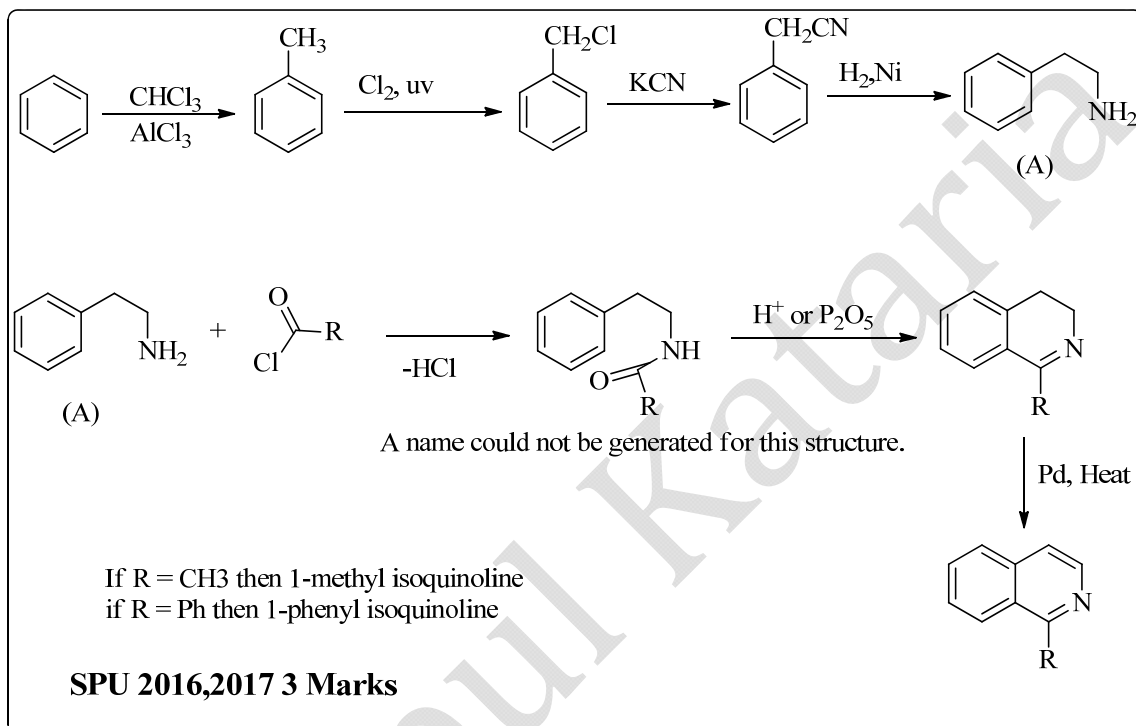


### Isoquinoline (Bischler-Napieralski Synthesis)

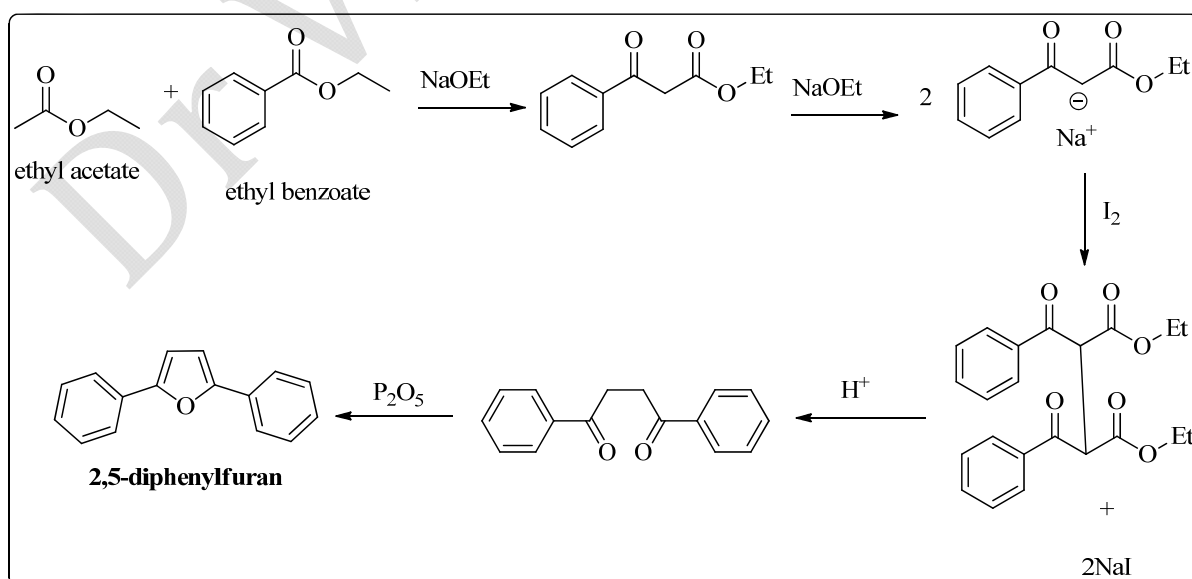
- Isoquinoline contains a benzene ring fused with pyridine ring as shown below.
- Isoquinoline derivative can be synthesized using Bischler-Napieralski Synthesis.
- Acyl derivative of  $\beta$ -phenyl ethyl amine is cyclized using acid or P2O5 to yield dihydroisoquinoline that can be aromatized to 1-methyl isoquinoline.



➤ Following steps are involved in reaction.

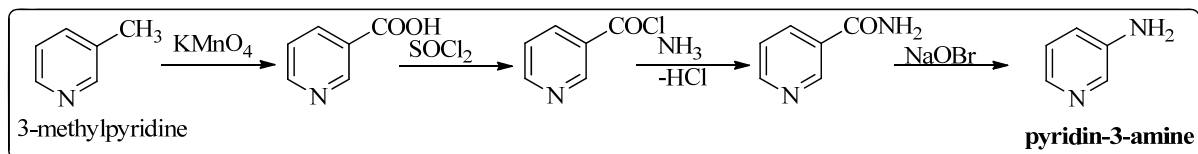


Outline synthesis of 2,5-diphenylfuran from ethyl benzoate and ethyl acetate

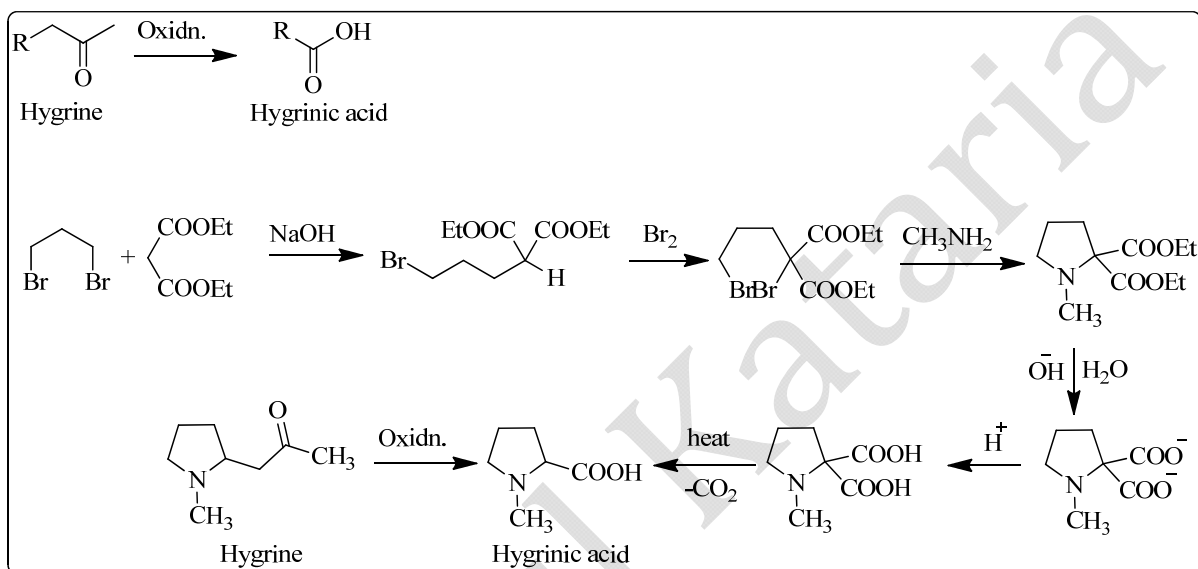


### Outline synthesis of 3-amino pyridine from $\beta$ -picoline

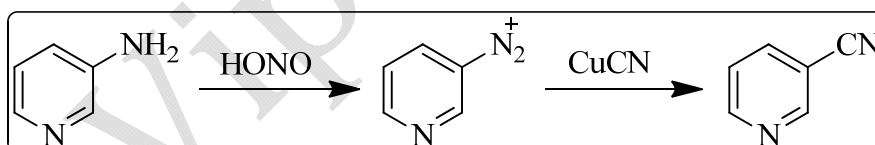
(SPU 2013, 2014 2 Marks, VP 2012, 2016 2 Marks)



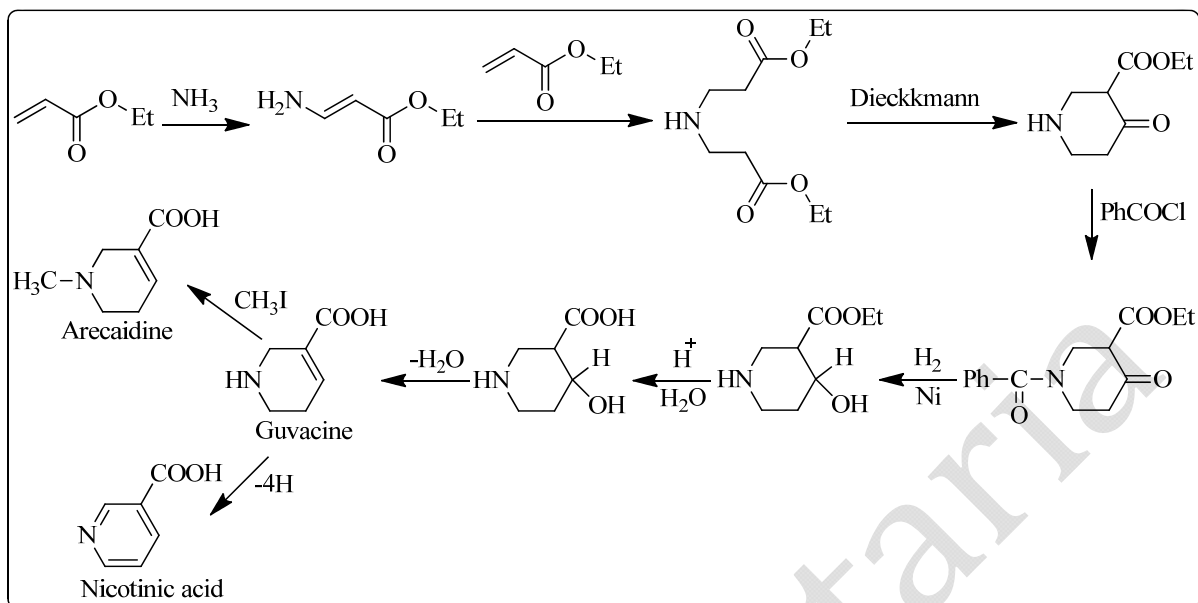
### Outline synthesis of Hygrine (SPU 2016 3 Marks, VP 2018 3 Marks)



### Outline synthesis of $\beta$ -cynopyridine from $\beta$ -picoline

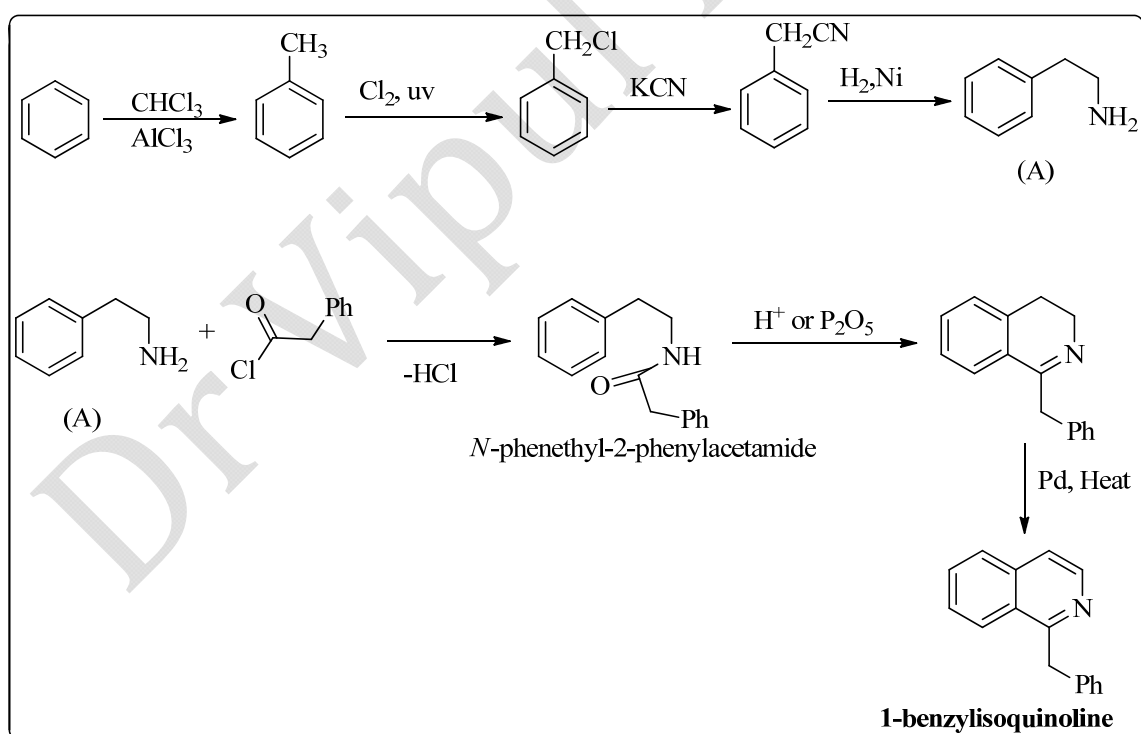


## Outline synthesis of Nicotine



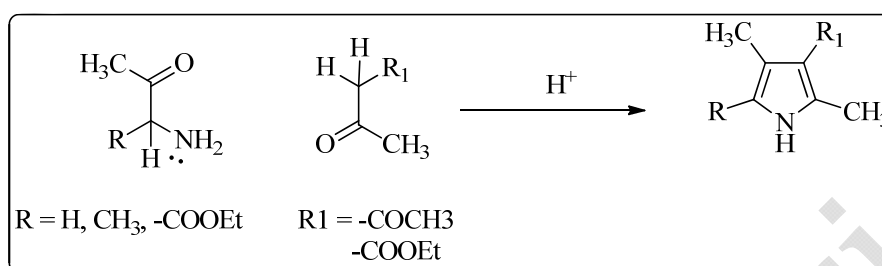
## Outline synthesis of 1-benzyl isoquinoline from benzene

(SPU 2016 2 Marks)

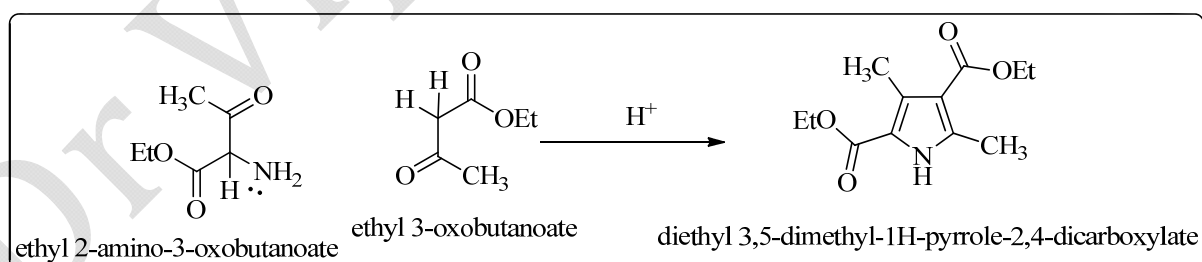
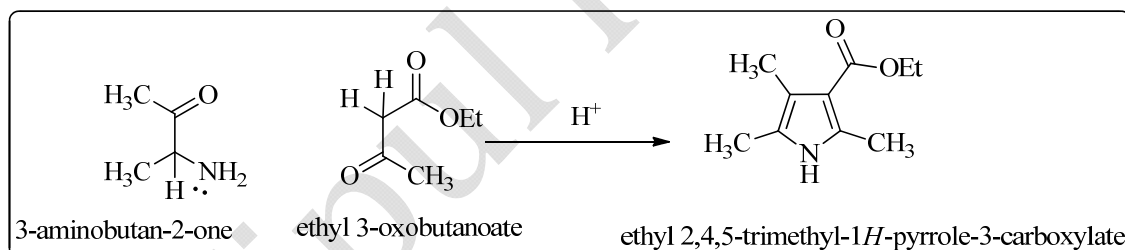
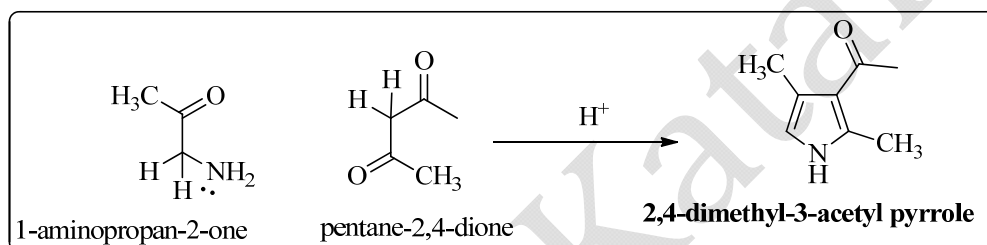


## Knorr Pyrrole Synthesis (SPU 2016, 2017 3 Marks, VP 2013 3 Marks)

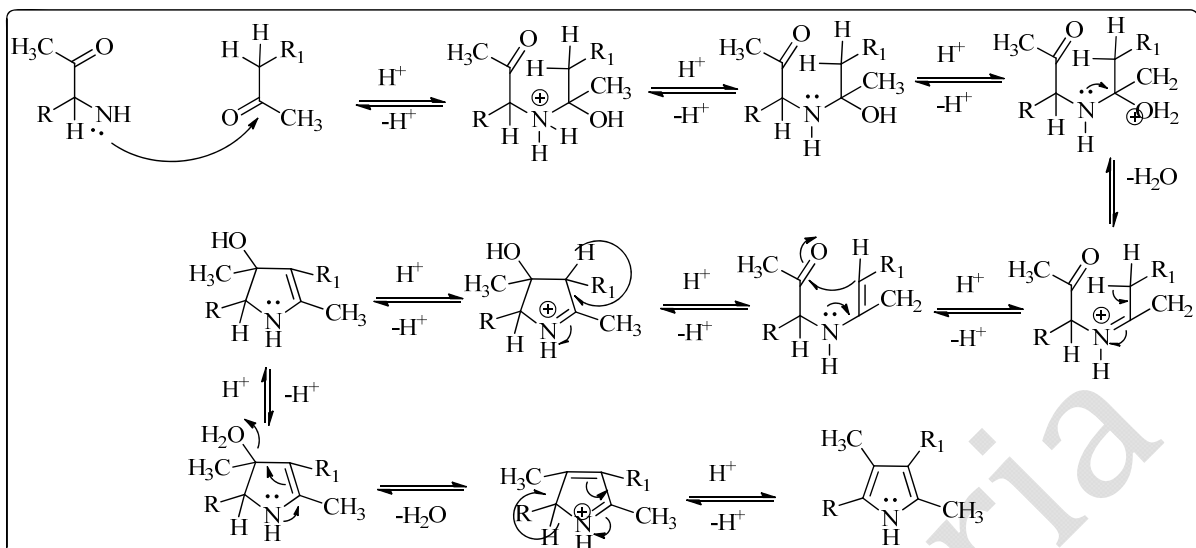
- This is most widely used method to synthesize pyrrole derivatives.
- It involves cyclization condensation of  $\alpha$ -amino ketones or  $\alpha$ -amino- $\beta$ -ketoesters with  $\beta$ -keto esters.



- Various examples can be illustrated as under.

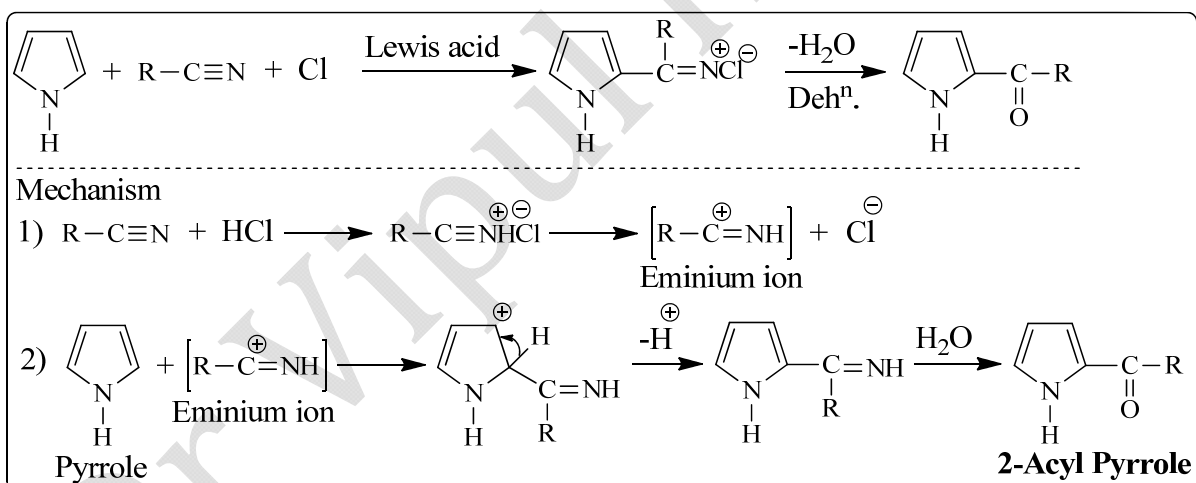


- The reaction proceeds via following steps.
- The reaction is considered to proceed with the formation of enamine intermediate involving attack of nucleophilic amino group of  $\alpha$ -amino- $\beta$ -ketoester on the electrophilic carbonyl carbon of  $\beta$ -ketoester.

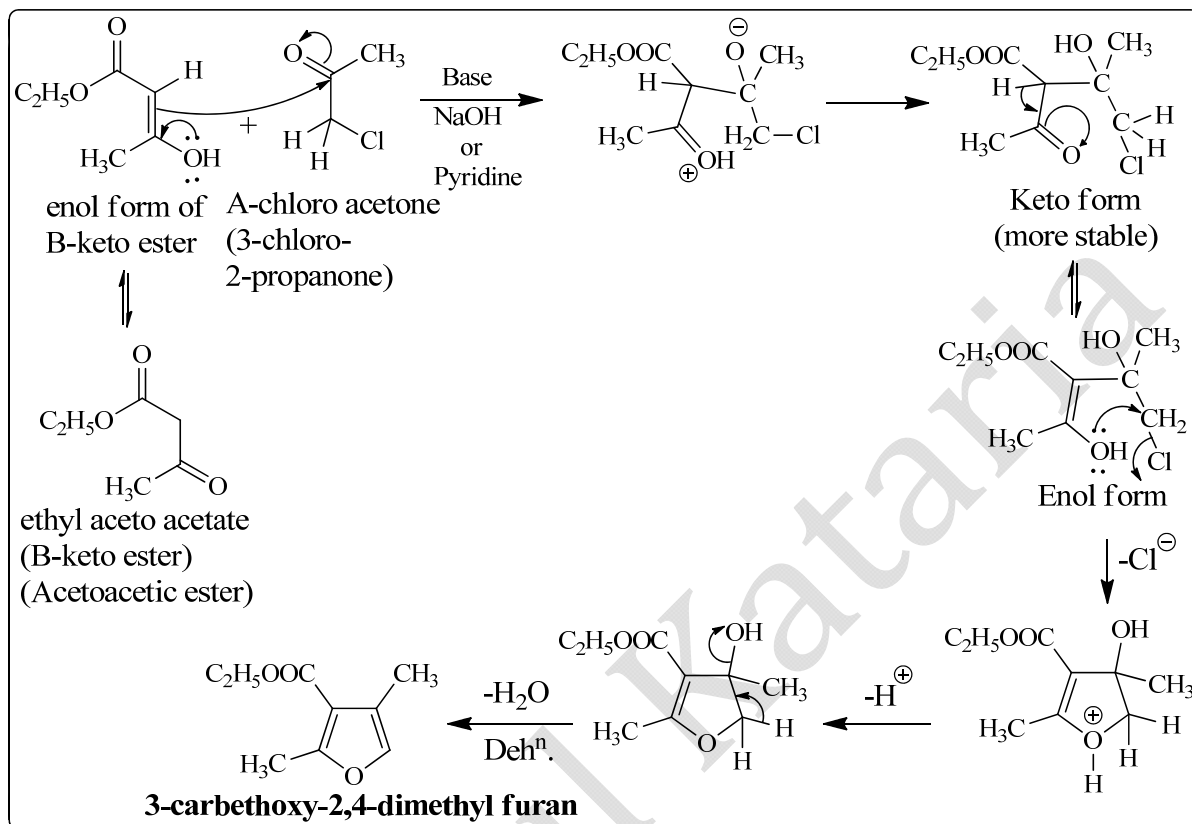


- Subsequent cyclization takes place with the nucleophilic attack of  $\beta$ -carbon of enamine on the electrophilic carbon of carbonyl group of  $\alpha$ -amino ketone.

### Hauben-Hoesch Reaction



### Feist-Benary Reaction (SPU 2016 3 Marks, VP 2018 4 Marks)



*I have work hard preparing this material.....*

*You also work hard preparing from this material!!!!*

*Best Luck....*