SRI AKILANDESWARI WOMEN'S COLLEGE, WANDIWASH

HETEROCYCLIC COMPOUNDS

Class : III UG CHEMISTRY

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Introduction

- **Heterocyclic compound is the class of cyclic organic compounds those having at least one hetero atom (i.e. atom other than carbon) in the cyclic ring system.**
- **The atom of the other element (for example, N , S or O) is called the Hetero atom.**
- **Heterocyclic compounds are frequently abundant in plants and animal products; and they are one of the important constituent of almost one half of the natural organic compounds known.**

Introduction

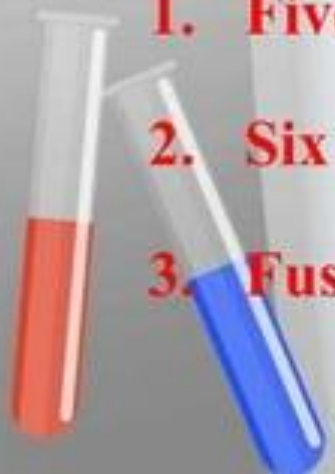
- Alkaloids, natural dyes, drugs, proteins, enzymes etc. are the some important class of natural heterocyclic compounds.
- Heterocyclic compounds are primarily classified as saturated and unsaturated.
- The saturated heterocyclic compounds behave like the acyclic derivatives with modified steric properties. Piperidine and tetrahydrofuran are the conventional amines and ethers of this category.

Introduction

- Heterocyclic compounds have a wide application:
  - Pharmaceuticals,
  - Agrochemicals and veterinary products
- Many heterocyclic compounds are very useful and essential for human life.
- Various compounds such as hormones, alkaloids antibiotic, essential amino acids, hemoglobin, vitamins, dyestuffs and pigments have heterocyclic structure.

Classification of Heterocyclic compound

- Based on the structural and electronic arrangement the heterocyclic compounds may be classified into two categories.
  1. Aliphatic heterocyclic compounds
  2. Aromatic heterocyclic compounds
- Based on the variety of structure, the heterocyclic compounds may also be divided in to:
  1. Five membered heterocyclic compounds
  2. Six membered heterocyclic compounds
  3. Fused or condensed heterocyclic compounds



Structural and electronic Classification

- Based on the structural and electronic arrangement the heterocyclic compounds may be classified into two categories.

1. Aliphatic heterocyclic compounds
2. Aromatic heterocyclic compounds

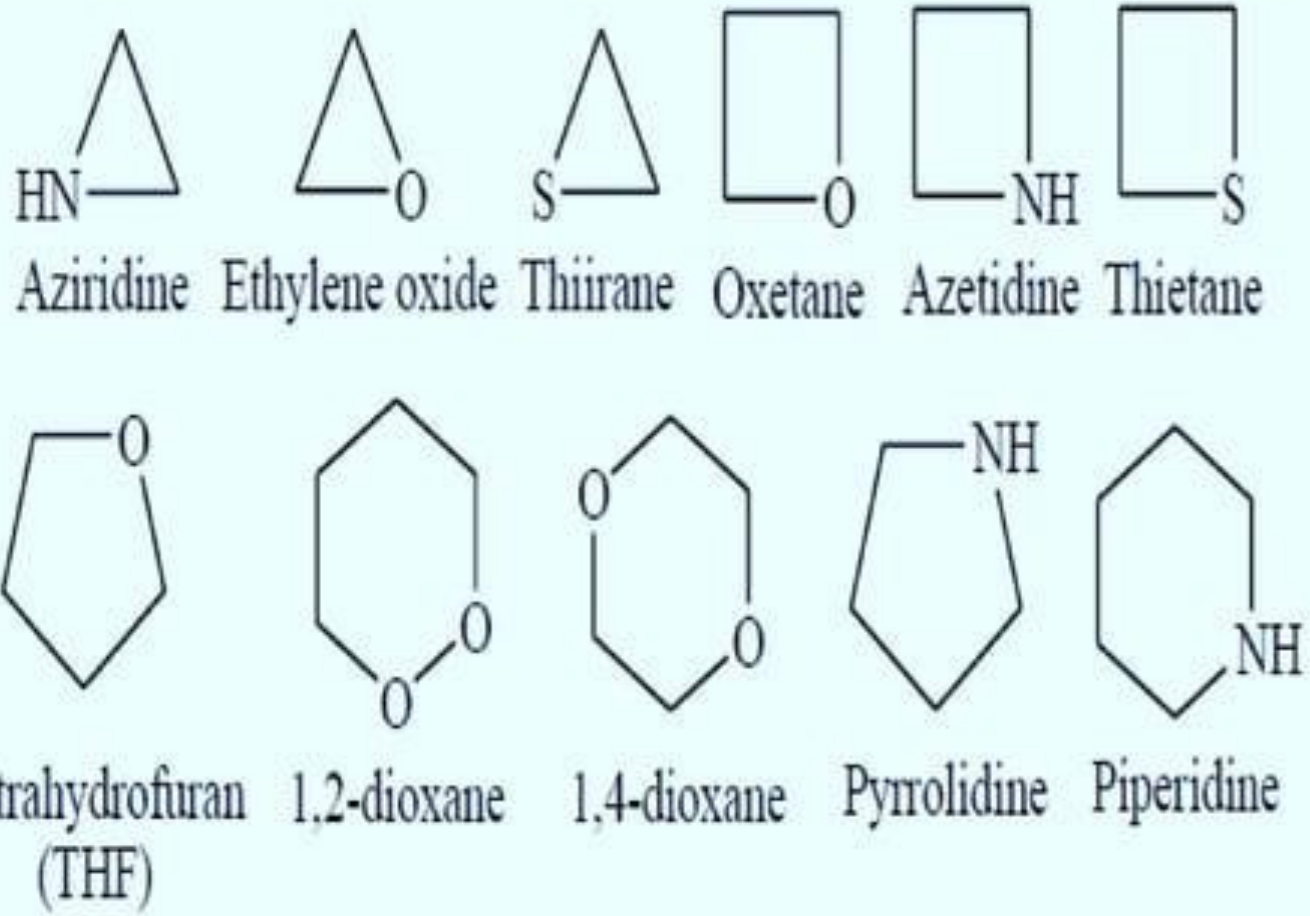
Structural and electronic Classification

1. Aliphatic heterocyclic compounds:

- The aliphatic heterocyclic compounds are the cyclic amines, cyclic amides, cyclic ethers and cyclic thioethers.
- Aliphatic heterocycles those do not contain double bonds are called saturated heterocycles.
- The properties of aliphatic heterocycles are mainly affected by the ring strain

Aliphatic heterocyclic compounds

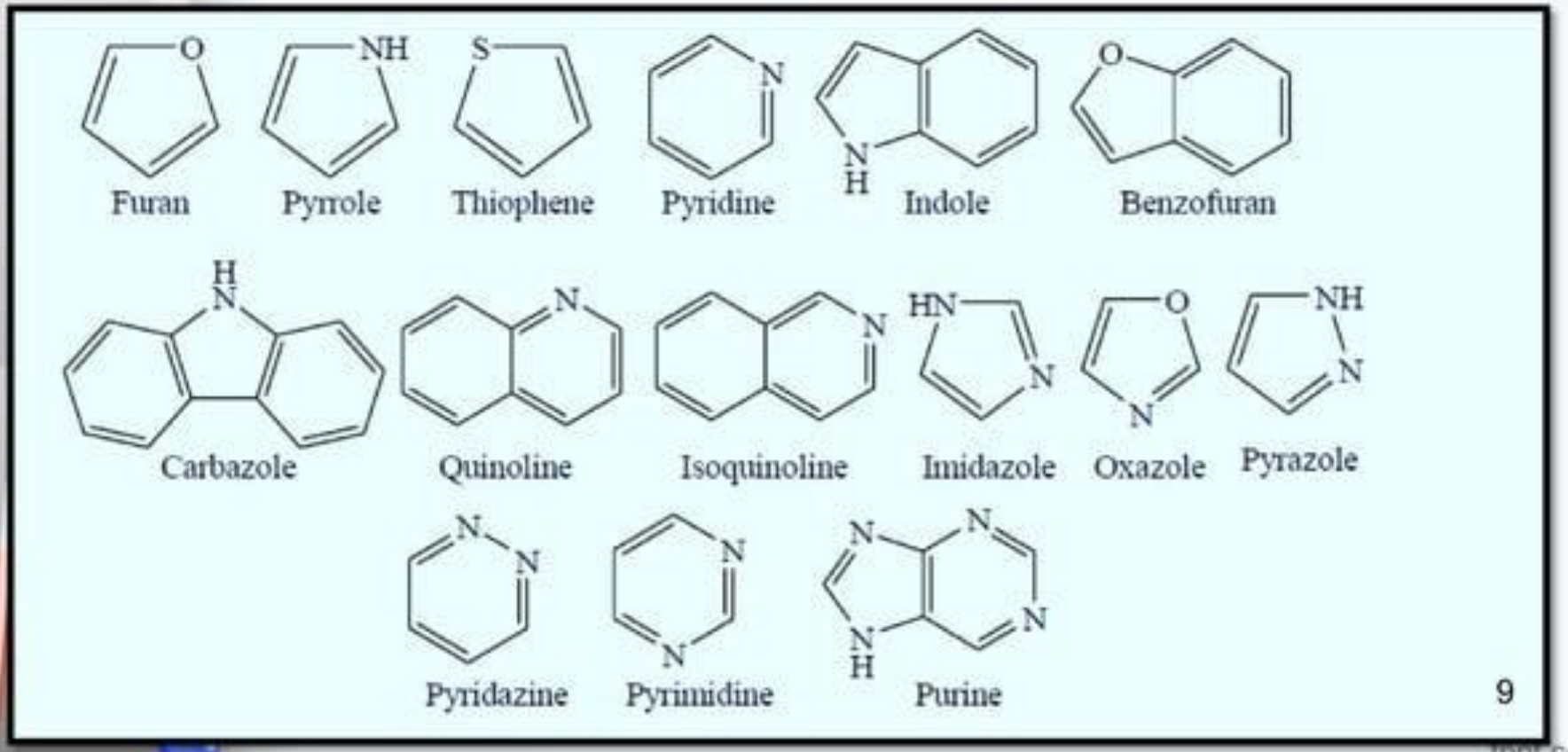
Examples of aliphatic heterocyclic compounds:



Structural and electronic Classification

2. Aromatic heterocyclic compounds:

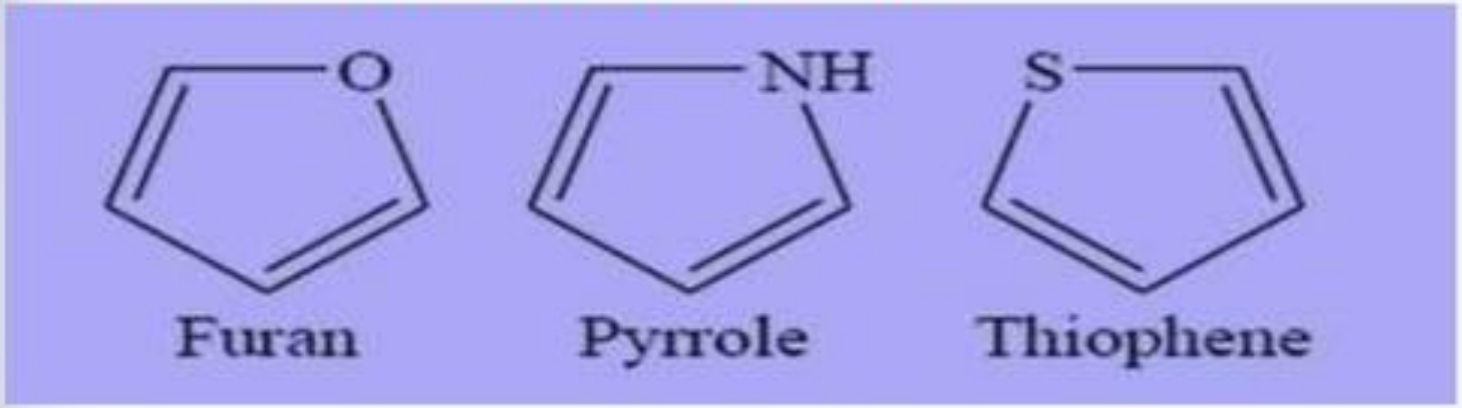
- Aromatic heterocyclic compounds are analogous of benzene.
- Examples of aromatic heterocyclic compounds are:

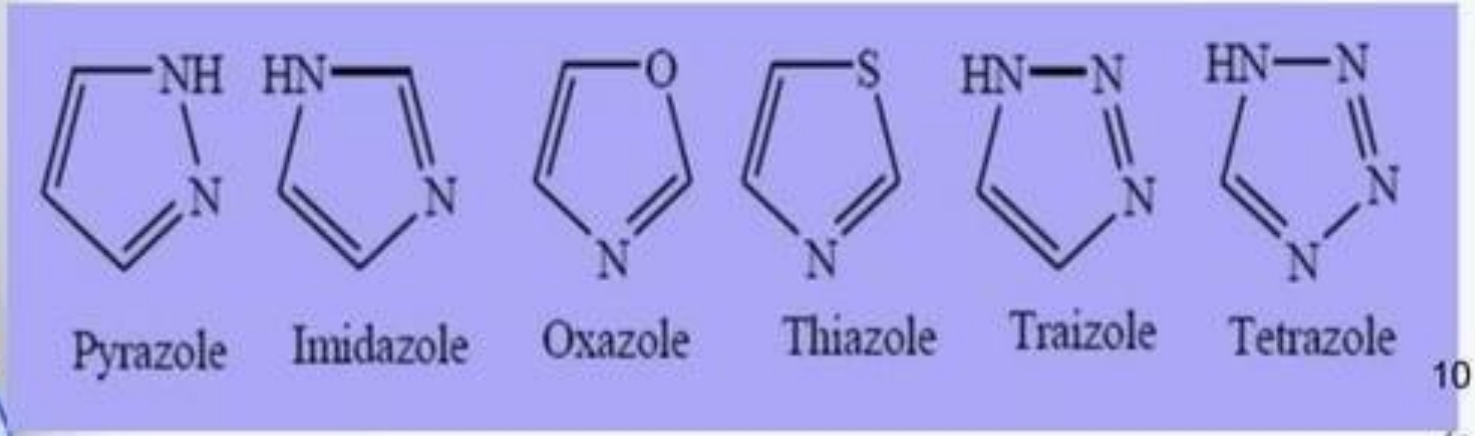


The variety of structure Classification

Based on the variety of structure, the heterocyclic compounds may also be divided in to three categories:

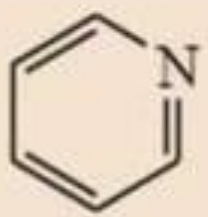
1. Five membered heterocyclic compounds:



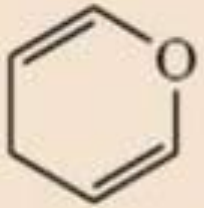


The variety of structure Classification

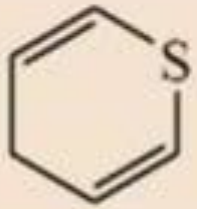
2. Six membered heterocyclic compounds:



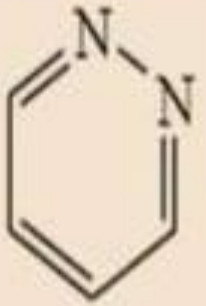
pyridine



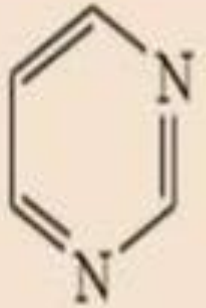
4*H*-pyran



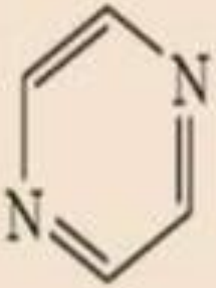
4*H*-thiopyran



pyridazine



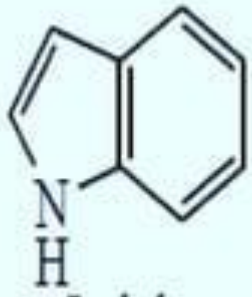
pyrimidine



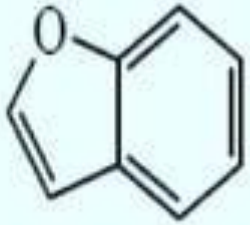
pyrazine

The variety of structure Classification

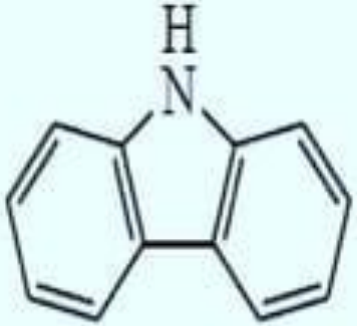
3. Fused or condensed heterocyclic compounds:



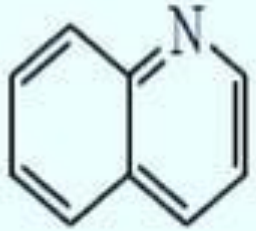
Indole



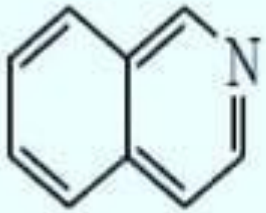
Benzofuran



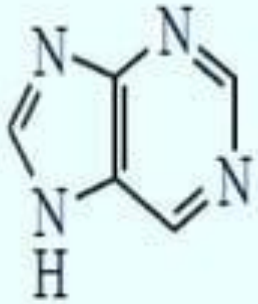
Carbazole



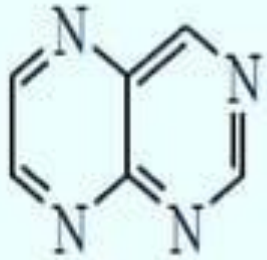
Quinoline



Isoquinoline



Purine



Pteridine

Nomenclature of Heterocyclic Compounds

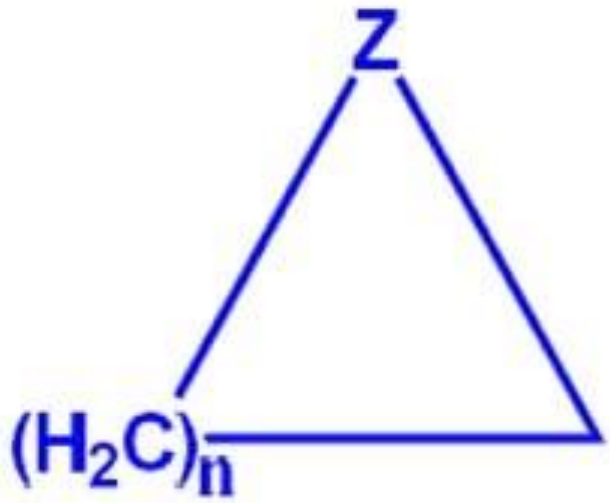
The IUPAC rules allow three nomenclatures.

I. The Hantzsch-Widman Nomenclature.

II. Common Names

III. The Replacement Nomenclature

I. Hantzsch-Widman Nomenclature



n = 1,2,3, ...

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 three-to-ten-membered ring heterocycles.

I. Type of the heteroatom

The type of heteroatom is indicated by a prefix as shown below for common hetreroatoms:

Hetreroatom	Prefix
O	Oxa
N	Aza
S	Thia
P	Phospha

II. Ring size (n)

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

Table I : Common Prefix for Heteroatoms (arranged in the preferential order)

Sl No	Heteroatom	Symbol	Prefix
1	Oxygen	O	Oxa
2	Sulphur	S	Thia
3	Selenium	Se	Selena
4	Nitrogen	N	Aza
5	Phosphorous	P	Phospha
6	Arsenic	As	Arsa
7	Antimony	Sb	Stiba
8	Bismuth	Bi	Bisma
9	Silicon	Si	Silia
10	Tin	Sn	Stanna
11	Lead	Pb	Plumba
12	Boron	B	Bora
13	Mercury	Hg	Mercura

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	

According to this system heterocyles are named by combining appropriate prefix/prefixes with a stem from Table II. The letter "a" in the prefix is omitted where necessary.

Each suffix consists of a ring size root and an ending intended to designate the degree of unsaturation in the ring.

It is important to recognize that the saturated suffix applies only to completely saturated ring systems, and the unsaturated suffix applies to rings incorporating the maximum number of non-cumulated double bonds.

Systems having a lesser degree of unsaturation require an appropriate prefix, such as "dihydro"or "tetrahydro".

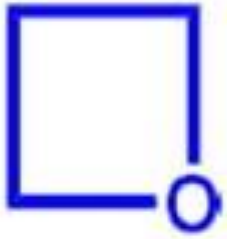
Saturated 3, 4 & 5-membered nitrogen heterocycles should use respectively the traditional "iridine", "etidine" & "olidine" suffix.

Examples

Oxa+irane= Oxirane

Thia+irane= Thiirane

Aza+iridine= Aziridine



Oxa+etane=Oxetane

Thia+etane=Thietane

Aza+etidine=Azetidine

Oxa+olane= Oxolane

Thia+olane= Thiolane

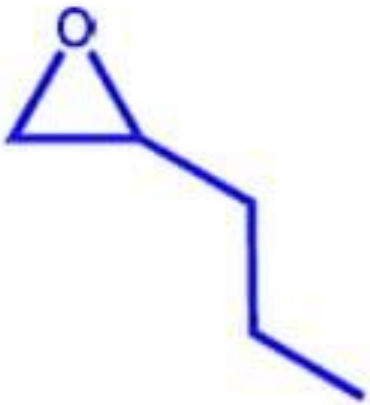
Aza+olidine= Azolidine

Azinane

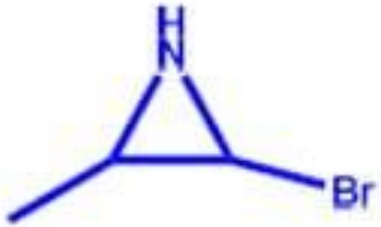
Azine

Pyridine

In case of substituents, the heteroatom is designated number 1, and the substituents around the chain are numbered so as to have the lowest number for the substituents.



2-Propyloxirane



2-Bromo-3-methylaziridine

2-Bromo-4-ethylthiolane

The compound with the maximum number of noncumulative double bonds is regarded as the parent compound of the monocyclic systems of a given ring size.

Oxirine

Azirine

Azepine

Azocine

Partial Unsaturation

Use fully unsaturated name with dihydro, tetrahydro, etc

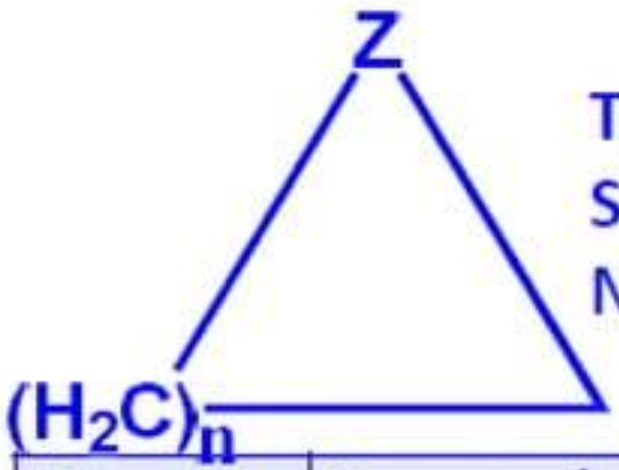
Azepine

2,3-Dihydroazepine

4,5-Dihydroazepine

2,5-Dihydroazepine

Revision



Type (Z) - Prefix

Size (n) - Suffix

Nature of ring - Ending

Hetreroatom	Prefix
O	Oxa
N	Aza
S	Thia
P	Phospha

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	

Rings With More Than One Heteroatom

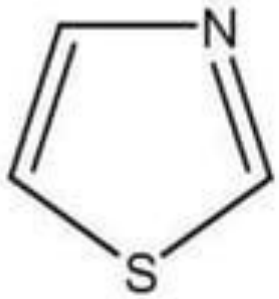
Two or more similar atoms contained in a ring are indicated by the prefixes '*di-*', '*tri*', *etc.*

1,3,5-Triazine

1,2,4 - Triazole

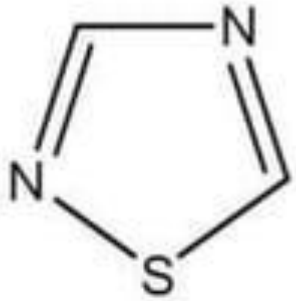
If more than one hetero atom occur in the ring, then the heterocycle is named by combining the appropriate prefixes with the ending in Table I in order of their preference, O > S > N.

When two or more heteroatoms of the same type are present, then the prefixes, di-, tri-, etc. are used and placed before the prefix used for the heteroatom.



1,3-Thiazole

1,2-Oxathiolane

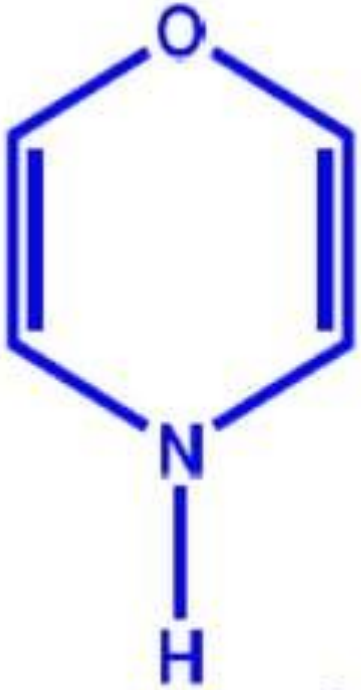


1,2,4-Thiadiazole

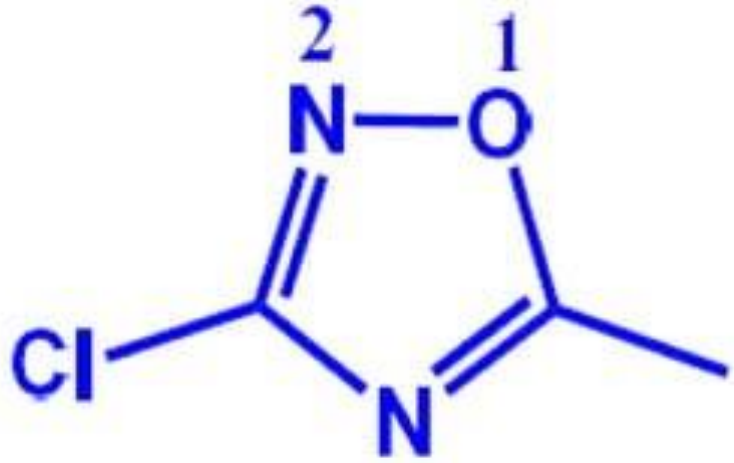
Oxaziridine

1,3-Thiazole
(Thiazole)

1,4,2 - Dithiazine

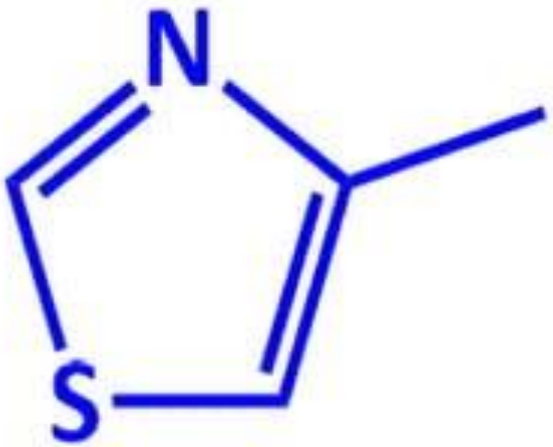


1,4-Oxazine



3-chloro-5-methyl-1,2,4-oxadiazole

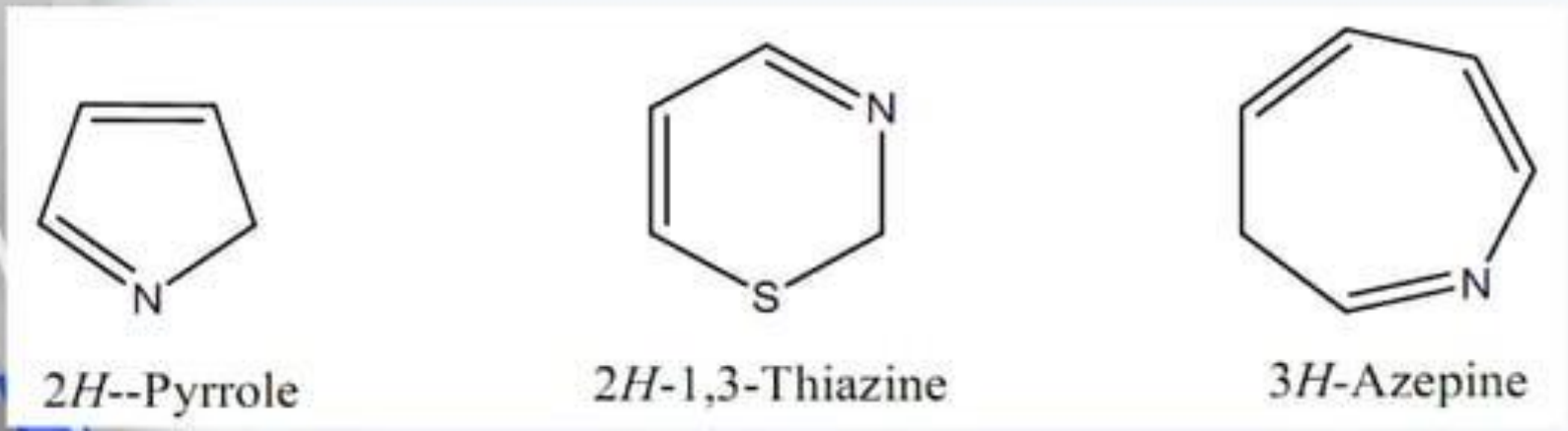
The ring is numbered from the atom of preference in such a way so as to give the smallest possible number to the other hetero atoms in the ring. As a result the position of the substituent plays no part in determining how the ring is numbered in such compounds.



4-Methyl-1,3-thiazole

Presence of saturated atom (indicated hydrogen)

- When heterocyclic ring with maximum number of noncumulative double bonds contains a saturated atom, its position is given the lowest possible locant and is numerically indicated by an italic capital *H* before the name of heterocyclic ring system.



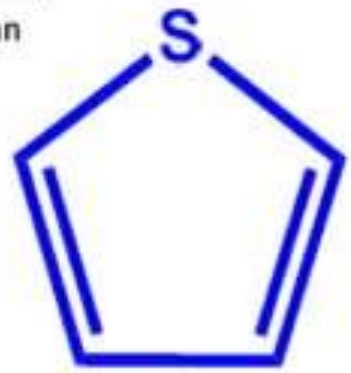
2*H*--Pyrrole 2*H*-1,3-Thiazine 3*H*-Azepine

II. Common Names

There are a large number of important ring systems which are named widely known with their non-systematic or common names.

Pyran

Furan

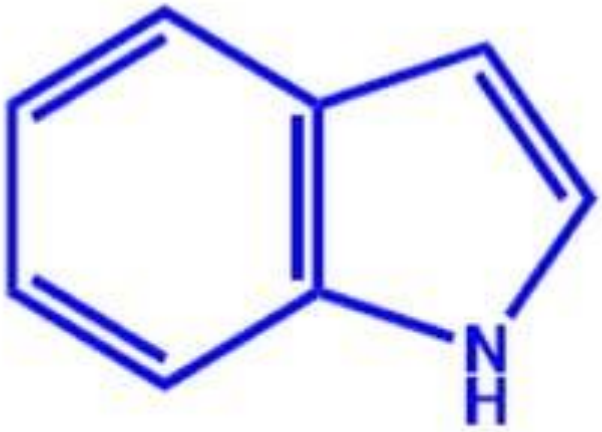


Thiophene

Pyrrole

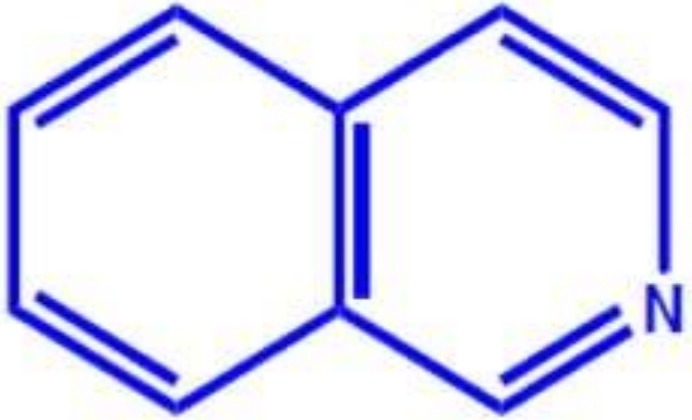
Pyridine

Pyridazine

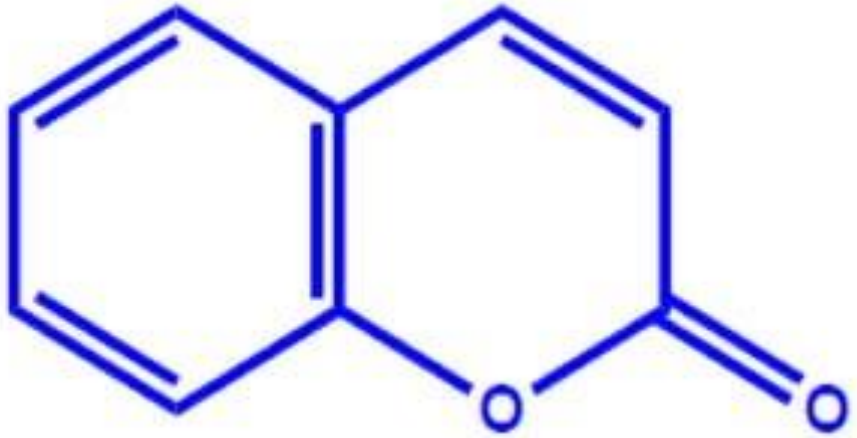


Indole

Quinoline

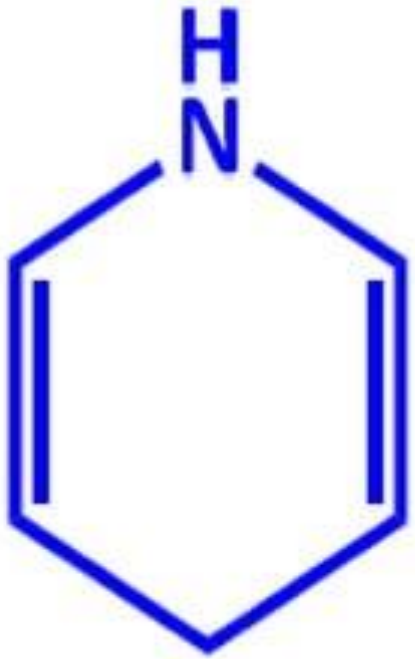


Isoquinoline



Coumarin

Pyridine



1,4-Dihydropyridine

2,3-Dihydropyridine

Naming of fused ring systems

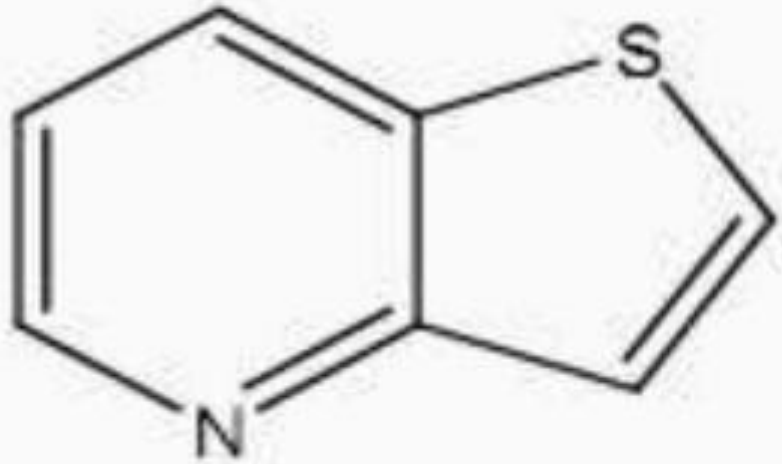
- The fused heterocyclic system is considered to be constructed by the combination of two or more cyclic structural units.
- The cyclic structural units contain maximum number of non-cumulative double bonds and are fused in such a way that each structural unit has one bond common with other.

Rules for naming fused heterocyclic rings

- The fused heterocyclic system is dissected into its components in which one is base component and the other(s) is attached component(s).
- The components are given their recognized trivial names (if possible) else, systematic name is used.
- The base component should always be a heterocyclic system. If there is a choice, it is determined by order of preference.

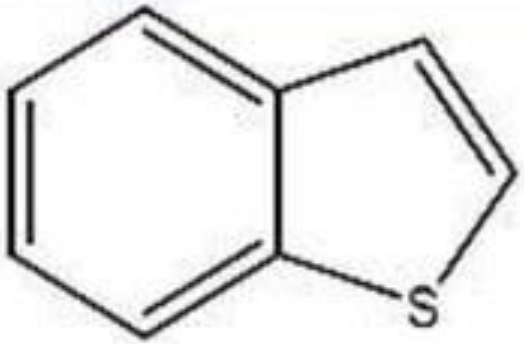
Selection of base component

- **Nitrogen containing component: a nitrogen containing component is selected as base component.**

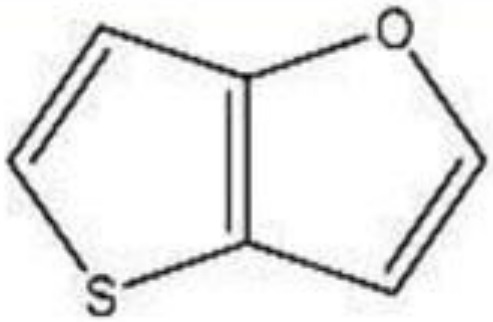


Base component : Pyridine

•If nitrogen is absent, then ring with other heteroatom(s) is selected as base component (order of preference as in the table)

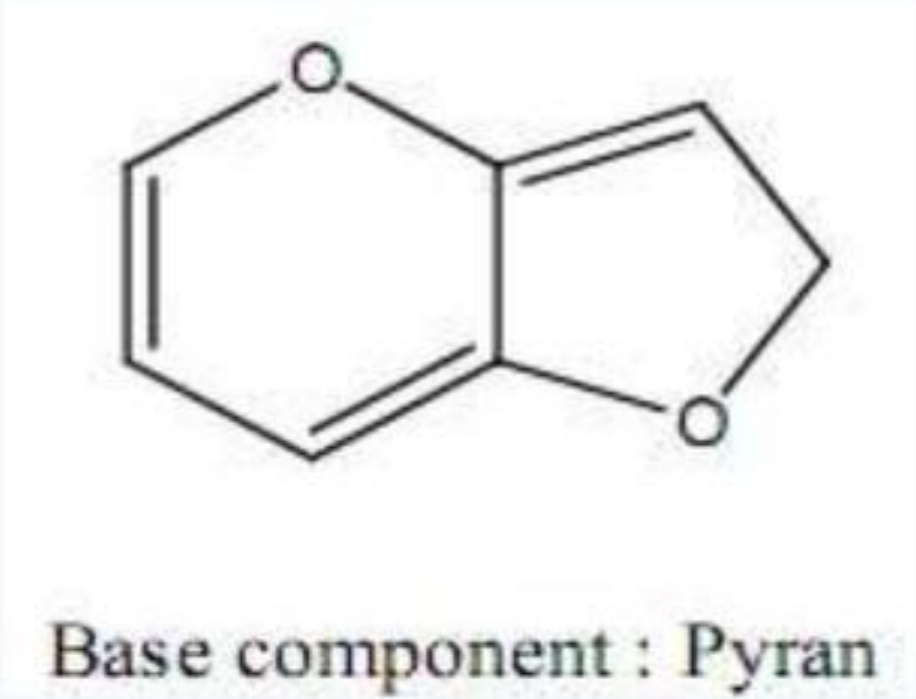


Base component : Thiphene



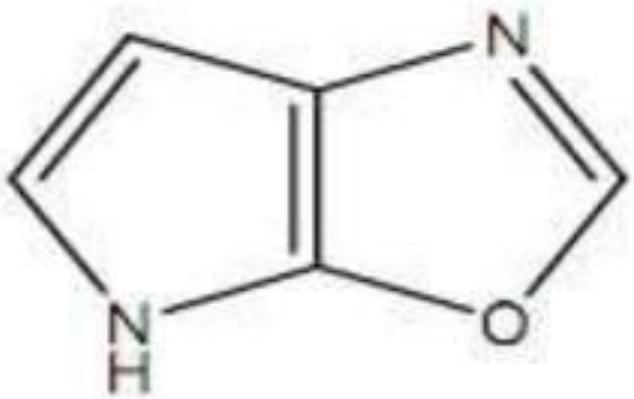
Base component : Furan

- **If rings of unequal size are present, then the one with largest size of the ring is selected.**



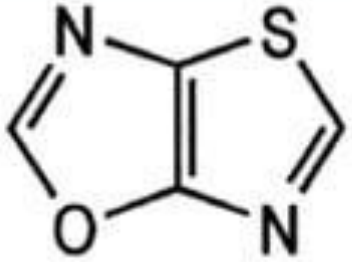
Base component : Pyran

- If rings or equal size with different number of heteroatoms are present, then the ring with greater number of heteroatoms of any kind is considered as a base component.



Base component : Oxazole

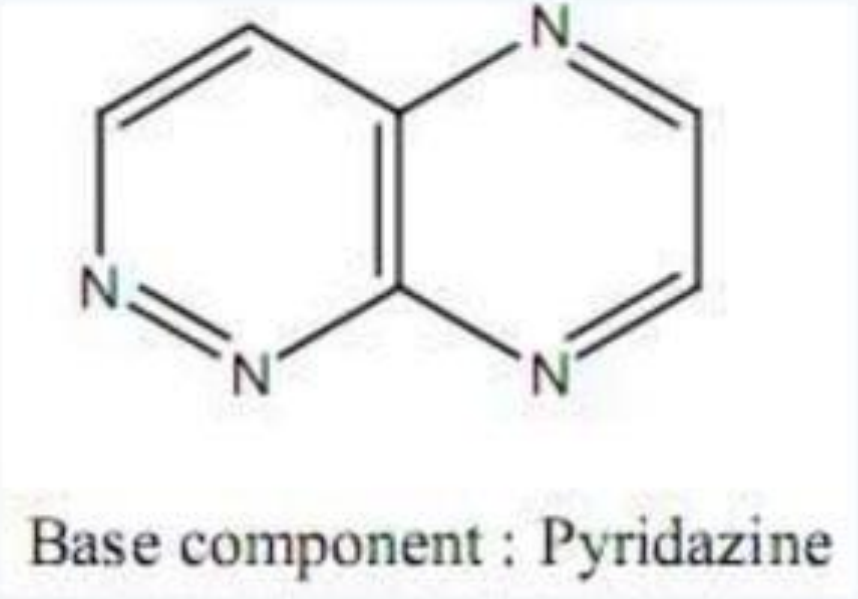
- **If two heteroatoms of the same group are present, then components containing heteroatoms appearing first in table is preferred.**



Base component : Oxazole

Heteroatom	Symbol (Valence)	Prefix
Oxygen	O(II)	Oxa
Sulfur	S(II)	Thia
Selenium	Se(II)	Selena
Tellurium	Te(II)	Tellma
Nitrogen	N(III)	Aza
Phosphorus	P(III)	Phospha
Arsenic	As (iII)	Arsa
Antimony	Sb(III)	Stiba
Bismuth	Bi(III)	Bisma
Silicon	Si(IV)	Sila
Gennanium	Ge(IV)	Genna
Tin	Sn(IV)	Stanna
Lead	Pb(IV)	Plwnba
Boron	B(III)	Bora
Mercury	Hg(II)	Mercura

•If rings of same size with same numbers and same kinds of heteroatoms are present, then the component containing the ring with heteroatoms which have lowest locant numbers is preferred.



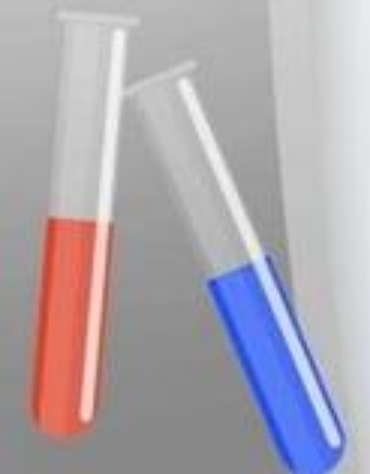
Base component : Pyridazine

- The attached component (second component) is added as a prefix to the name of the base component. The prefix designating an attached component is formed by changing terminal 'e' of a trivial or Hantzsch Widman name of a component into 'o'.

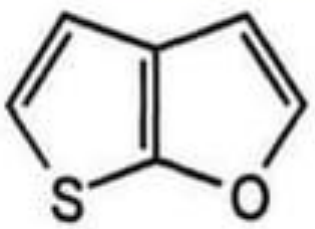
Pyrazine	Pyrazino
Pyrazole	Pyrazolo
Thiazole	Thiazolo

- **However, there are some exceptions to this rule. The prefixes for some common heterocycles used in the fused nomenclature are presented in below Table.**

Heterocyclic compound	Prefix
Pyridine	Pyrido
Quinoline	Quino
Isoquinoline	Isoquino
Furan	Furo
Thiophene	Thieno
Imidazole	Imidazo-

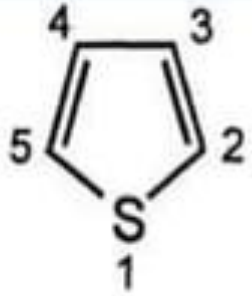


- The bonds of the base component are alphabetized with consecutive italic letters starting with *'a'* for 1,2- bond, *'b'* for 2,3-bond, *'c'* for 3,4-bond *'d'* for 4,5-bond and so on.
- The atoms of ring system of second component (attached component) are numbered in the normal way; 1,2,3,4,5, *etc.*, observing the principle of the lowest possible numbering.
- The atoms common to both rings (side of fusion) are indicated by the appropriate letters and numbers and are enclosed in a square bracket and placed immediately after the prefix of the attached component. The numbers (positions of attachment) of the second component are placed in the sequence in which they are attached to the base component.



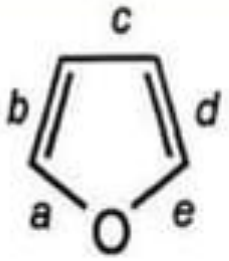
Thieno[2,3-*b*]furan

=

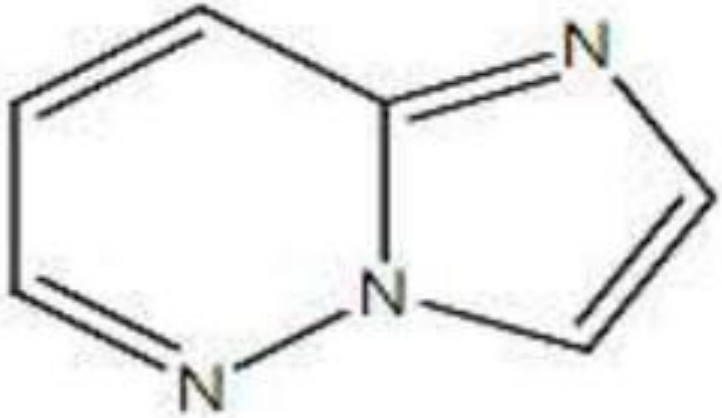


Thiophene
(attached component)

+



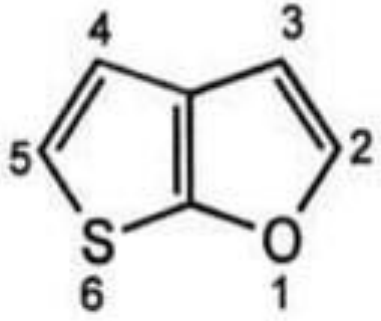
Furan
(base component)



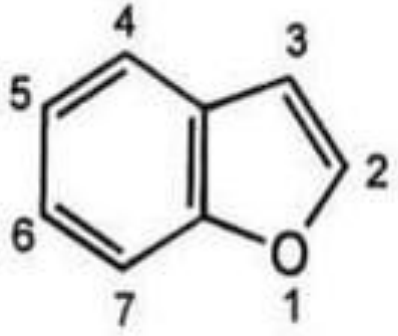
Imidazo[1,2-*b*]pyridazine

Numbering of fused heterocyclic system

- **Fused heterocyclic system is numbered independently of the combining components (base and attached components). The numbering is started from the atom adjacent to the bridgehead position with the lowest possible locant(s) to the heteroatom(s). If there is choice, the heteroatom appearing highest in Table 1 is preferred.**



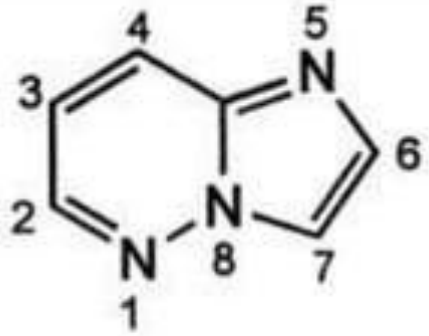
Thieno[2,3-*b*]furan



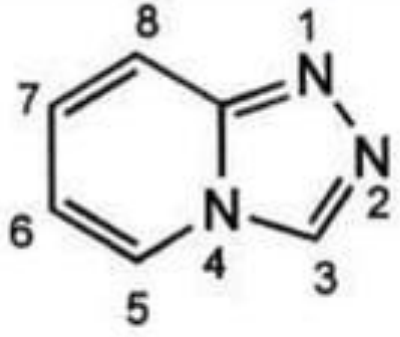
Benzo[*b*]furan

Numbering of fused heterocyclic system

- **Carbon atom common to two rings is given the lowest possible position, but not numbered. However, the heteroatom at a position of fusion of two rings (common heteroatom) is numbered.**



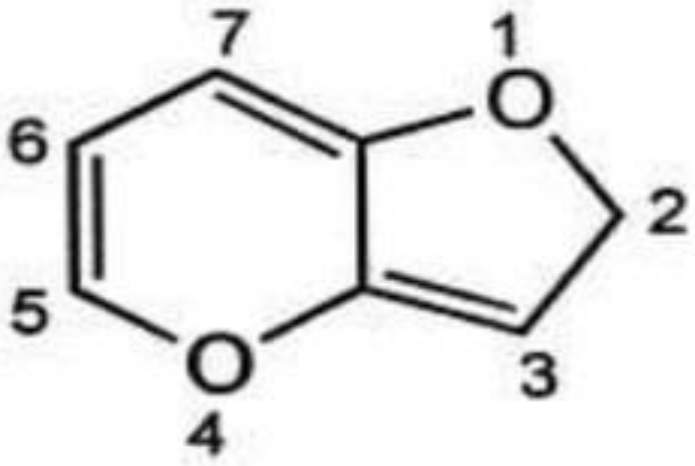
Imidazo[1,2-*b*]pyridazine



1,2,4-Triazolo[4,3-*a*]pyridine

Numbering of fused heterocyclic system

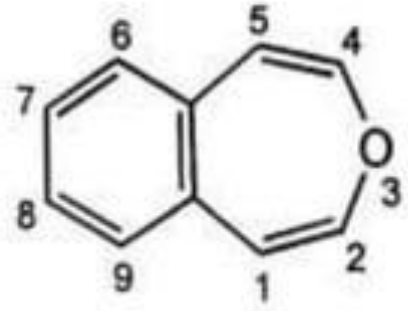
- **The position of a saturated atom is indicated by an italic hydrogen and is given the lowest possible number locant.**



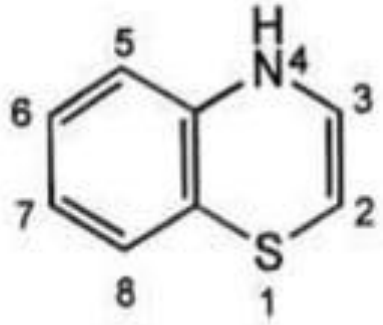
2*H*-Furo[3,2-*b*]pyran

Benzo fused heterocycles

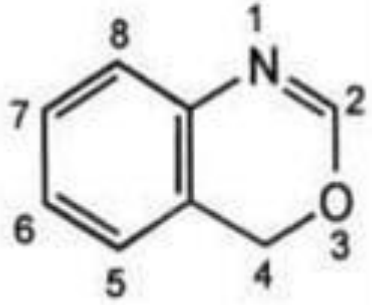
- **If a benzene ring is fused to the heterocyclic ring, the compound is named by placing number(s) indicating position(s) of the heteroatom(s) before the prefix benzo- (from benzene) followed by the name of the heterocyclic component.**



3-Benzoxepin



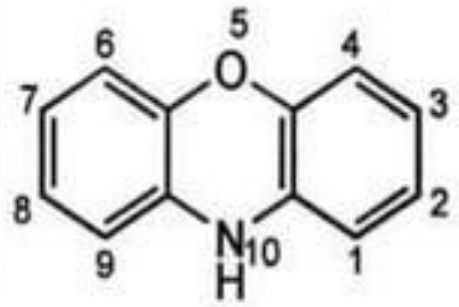
4*H*-1,4-Benzothiazine



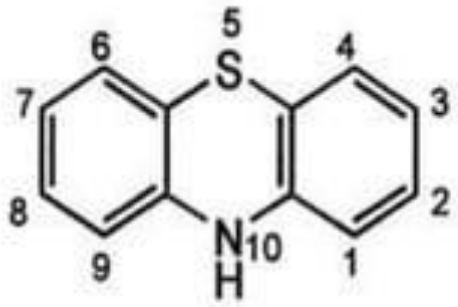
4*H*-3,1-Benzoxazine

Benzo fused heterocycles

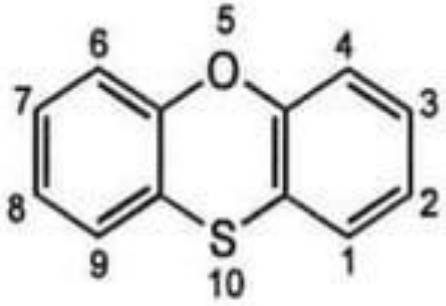
- **If two benzene rings are ortho-fused to a six-membered 1,4-diheteromonocyclic ring containing different heteroatoms, the heterocyclic system is named by adding the prefix 'pheno-' to the Hantzsch-Widman name of the heteromonocycle.**



10*H*-Phenoxazine



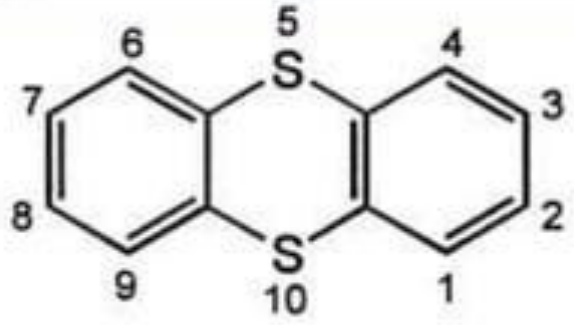
10*H*-Phenothiazine



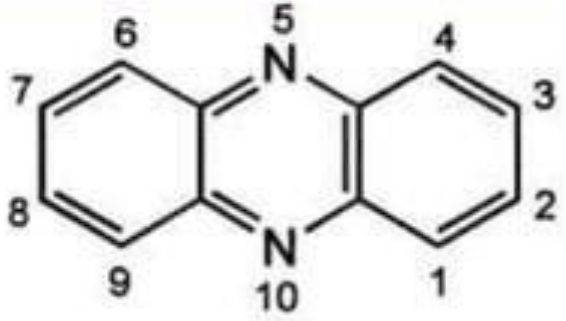
Phenoxathiine

Benzo fused heterocycles

- However, the heterocyclic system in which two benzene rings are orthofused to a six-membered 1,4-diheteromonocycle containing the same heteroatoms are named by adding the replacement prefix for the heteroatom (Table 1) to the term '-anthrene' with elision of an 'a'.



Thianthrene



Phenazine
(exception to this rule)

III. The Replacement Nomenclature

In replacement nomenclature, the heterocycle's name is composed of the carbocycle's name and a prefix that denotes the heteroatom.

Thus, "aza", "oxa", and "thia" are prefixes for a nitrogen ring atom, an oxygen ring atom, and a sulfur ring atom, respectively.

Notice that heterocyclic rings are numbered so that the heteroatom has the lowest possible number.

Azacyclopropane

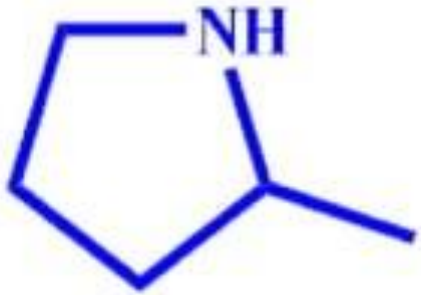
or

Aziridine

Azacyclobutane

or

Azetidine



2-Methylazolidine

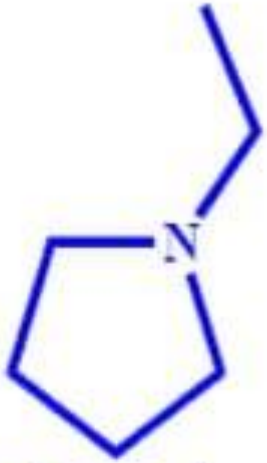
or

2-Methylazacyclopentane

2-Methylazacyclohexane

or

2-Methylpiperidine

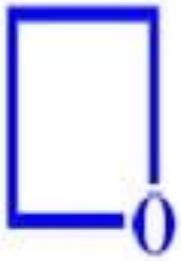


N-Ethylazacyclopentane

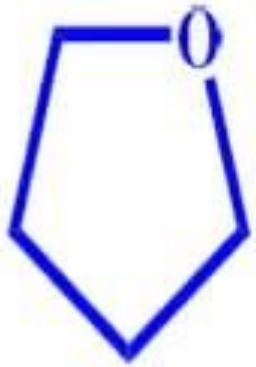
or

N-Ethylpyrrolidine

Oxacyclopropane
or
Oxirane
or
Ethyleneoxide



Oxacyclobutane
or
oxetane



Oxacyclopentane
or
Tetrahydrofuran

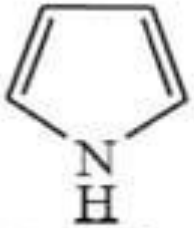
Thiacyclopropane
or
Thiirane

Structure & Aromaticity of Pyrrole

- **Structure and aromaticity of pyrrole can be discussed according to following points.**

✓ **The molecular weight determination method and related analytical studies revealed that the molecular formula of Pyrrole would be C_4H_5N.**

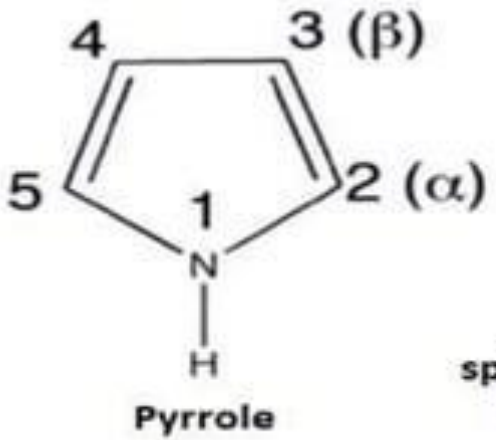
✓ **The possible structure of pyrrole can be given by considering the tetravalency of carbon and tri valency of nitrogen, and it is shown below:**



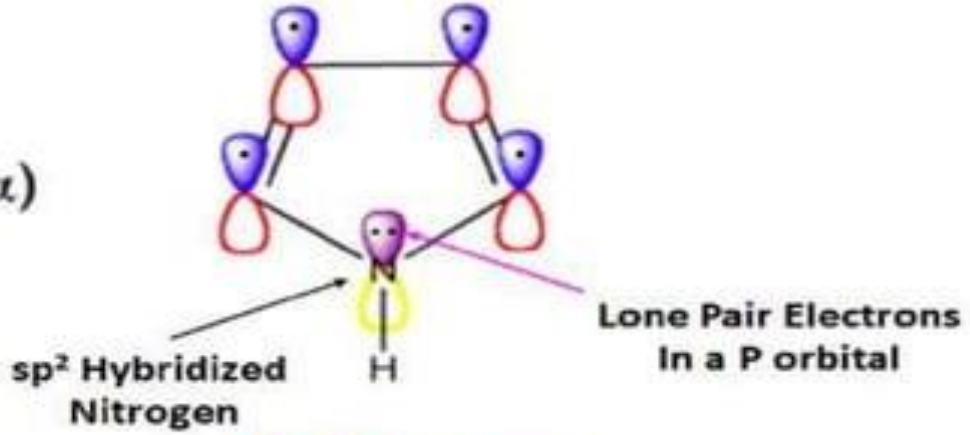
Pyrrole

Structure & Aromaticity of Pyrrole

- ✓ Pyrrole is cyclic and conjugated (that lone pair on nitrogen can contribute to the pi-system).There are two pi bonds and one lone pair of electrons that contribute to the pi system and it follows the Huckel's aromaticity rules (4n+2 electron rule).
- ✓ All rings atom in pyrrole (4 Carbons + 1 Nitrogen) are sp^2 hybridized.



Pyrrole

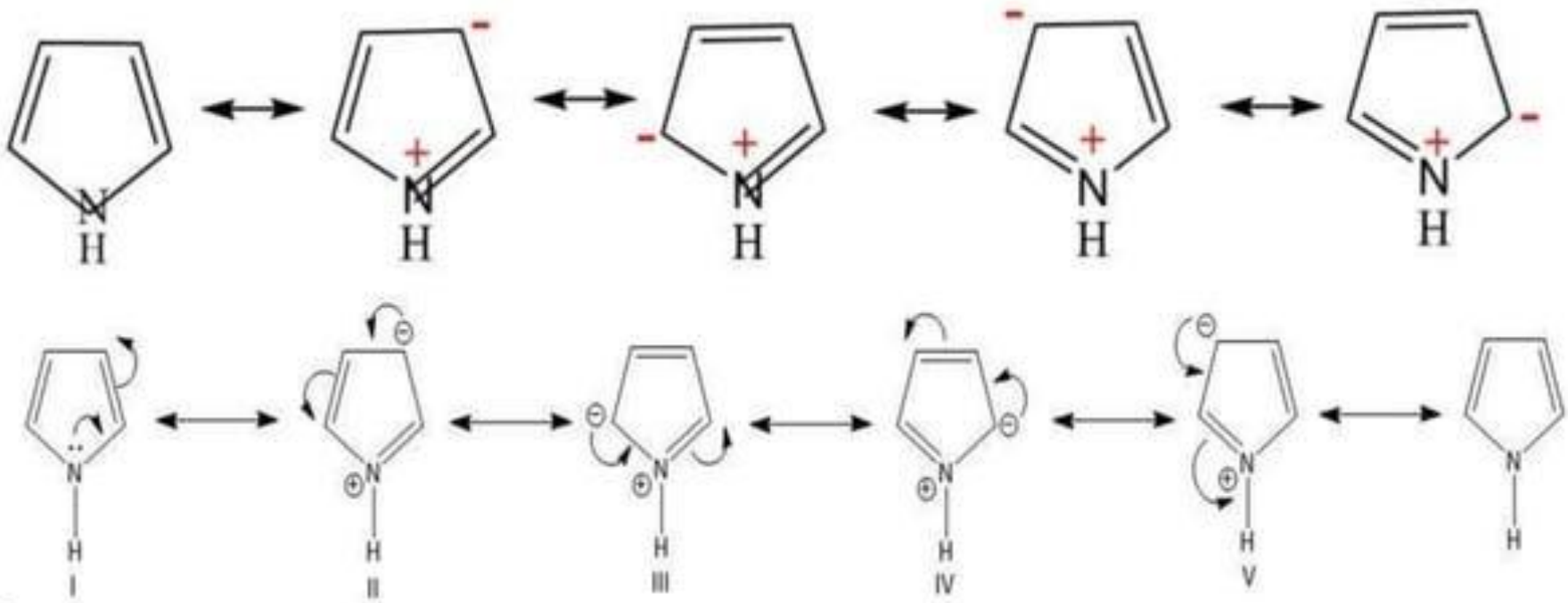


6 Π Electrons

Structure & Aromaticity of Pyrrole

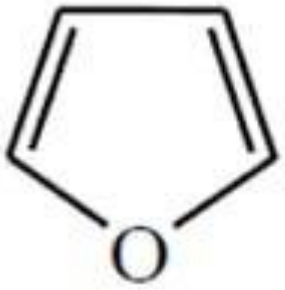
- **The aromatic nature and extra-stability of pyrrole can also be supported by the formation of its different resonating structures as shown in below figure.**

Resonance structures of pyrrole



Structure & Aromaticity of Furan

- The molecular weight determination method and related analytical studies revealed that the molecular formula of Furan would be C_4H_4O.
- The possible structure of Furan can be given by considering the tetravalency of carbon and bivalency of oxygen, and it is shown below:

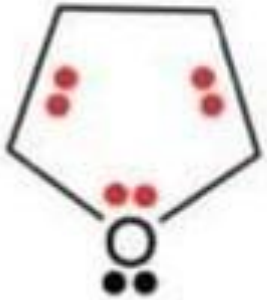


Furan

Structure & Aromaticity of Furan

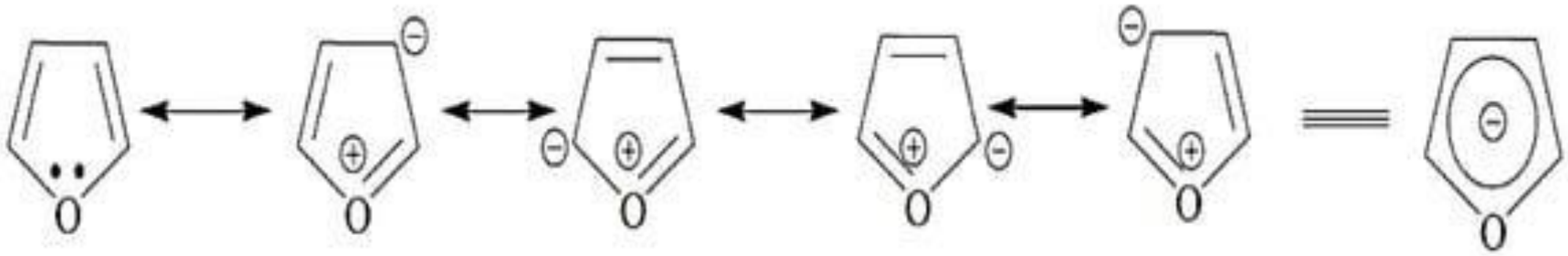
- The proposed structure of furan is also considered as an aromatic compound since it follows the Huckel's aromaticity rules (4n+2 electron rule).
- All atoms in these structures are sp2 hybridized. So , all the four carbon atoms and the heteroatom are in the same plane.

Furan



Structure & Aromaticity of Furan

- **The aromatic nature and extra-stability of furan is also supported by the formation of its different resonating structures as shown in below figure.**



Structure & Aromaticity of Thiophene

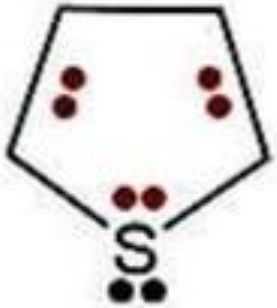
- The molecular weight determination method and related analytical studies revealed that the molecular formula of Thiophene would be C_4H_4S.
- The possible structure of Thiophene can be given by considering the tetravalency of carbon and bivalency of sulphur, and it is shown below:

Thiophene

Structure & Aromaticity of Thiophene

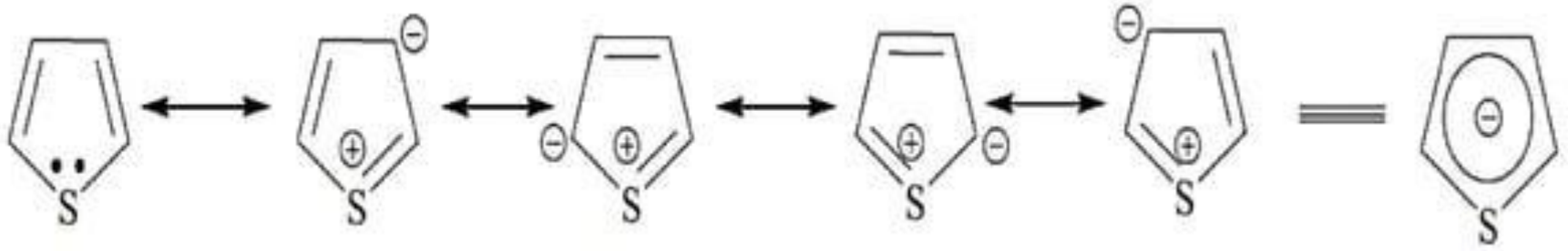
- The proposed structure of thiophene is also considered as an aromatic compound since it follows the Huckel's aromaticity rules (4n+2 electron rule).
- All atoms in these structures are sp2 hybridized. So , all the four carbon atoms and the heteroatom are in the same plane.

Thiophene



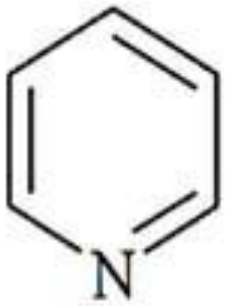
Structure & Aromaticity of Thiophene

- **The aromatic nature and extra-stability of thiophene is also supported by the formation of its different resonating structures as shown in below figure.**



Structure & Aromaticity of Pyridine

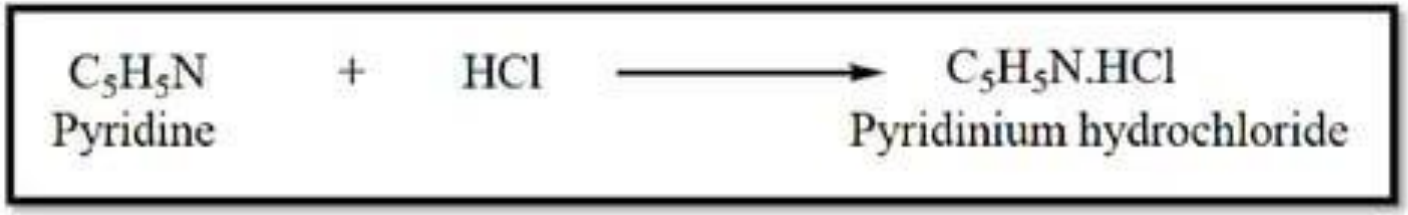
- The molecular weight determination method and related analytical studies revealed that the molecular formula of Pyridine as C_5H_5N.
- The possible structure of Pyridine can be given by considering the tetravalency of carbon and trivalency of nitrogen, and it is shown below:



pyridine

Structure & Aromaticity of Pyridine

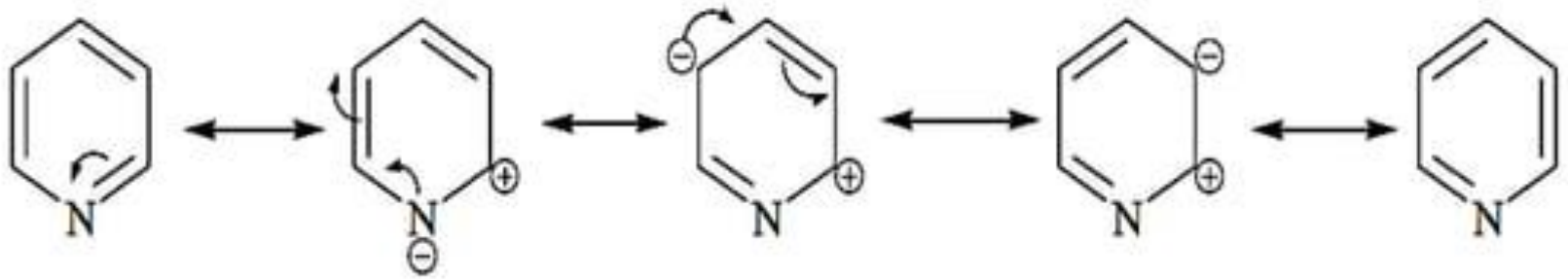
- **Pyridine was found to be basic in nature since it forms salt with acids.**



- **All the carbon, nitrogen and hydrogen atoms lie in the same plane all the carbon and nitrogen atoms of pyridine are sp2 hybridized.**
- **Pyridine shows aromatic properties or aromaticity because the pi molecular orbitals satisfies the Huckel's aromaticity rules (4n+2 electron rule).**

Resonance Structure of Pyridine

- **The structure of Pyridine is considered to be the resonance hybrid of the following structures.**



METHODS OF PREPARATION AND CHEMICAL REACTIONS

PYRROLE, FURAN, THIOPHENE AND PYRIDINE

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