Heterocyclic Organic Chemistry CHEM 341

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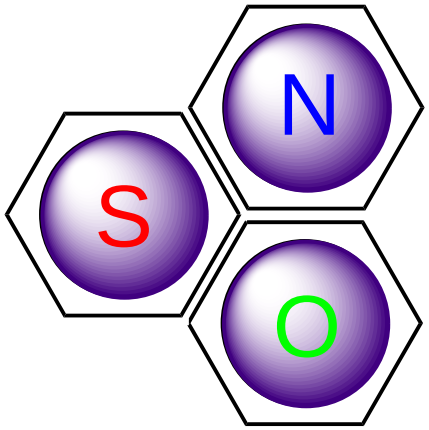
GOALS & OBJECTIVES

- Name heterocyclic, carbohydrates, amino acids, peptides, protein and lipids of organic compounds using IUPAC and COMMON naming system, their occurrence in nature, physical properties.
- Identify, classify, synthesis and reactions of the major functional groups the above compounds.
- Understanding the reaction of functional groups and families of these organic compounds.
- The practical uses of these organic compounds as drugs, food additives, pesticides, plastics, and other products, as well as their occurrence in nature.

Quick LOOK!



Topics will be Covered:

- Heterocyclic compounds.
- Carbohydrates.
- Amino acids, peptide and protein, lipids.

Schedule of Assessment Tasks for Students During the Semester

	Assessment task (i.e., essay, test, quizzes, group project, examination, speech, oral presentation, etc.)	Week Due	Proportion of Total Assessment
1	Major exam I	Week 6	20%
2	Major exam II	Week 12	20%
3	Quiz and activities	Week 1-15	20%
4	Final Exam	Week 16	40%

List Required Textbooks

- Heterocyclic chemistry, J.A. Joule and K. Mills, and G. F. Smith.4th ed., Blackwell Publishing 2000.
- Heterocyclic Chemistry (Oxford Primer Series) – T. Gilchrist.
- Aromatic Heterocyclic Chemistry – D. T. Davies.
- http://www.acdlabs.com/iupac/nomenclature/

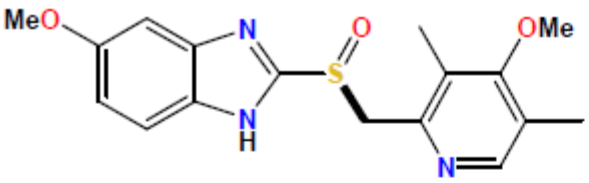
Introduction

- **Cyclic organic compounds are carbocycles or heterocycles**
  - Carbocycle rings contain only carbon atoms
  - Heterocycle rings atoms in addition to carbon (N,S,O are common)
- **Heterocycles include many important natural materials as well as pharmaceuticals.**
- **Heterocyclic systems are important building-blocks for new materials possessing interesting electronic, mechanical or biological properties.**

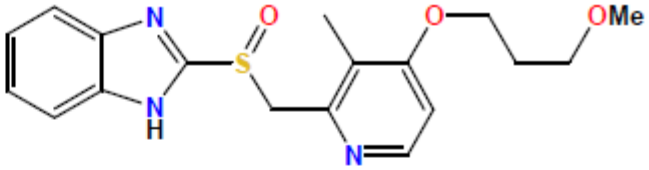
carbocycle

heterocycles – X, Y, Z are usually O, N or S

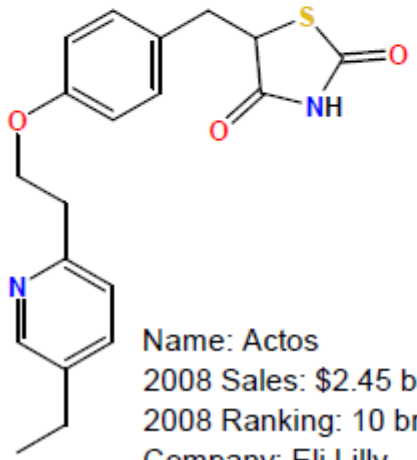
Drugs Containing Heterocycles



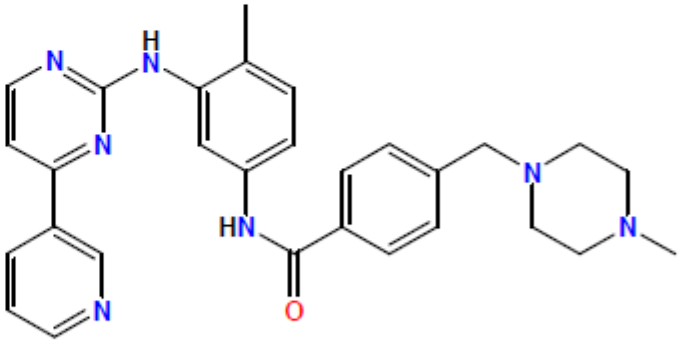
Name: Nexium
2008 Sales: $4.79 billion
2008 Ranking: 2 branded
Company: AstraZeneca
Disease: Acid reflux



Name: Aciphex
2008 Sales: $1.05 billion
2008 Ranking: 34 branded
Company: Eisai
Disease: Duodenal ulcers and acid reflux

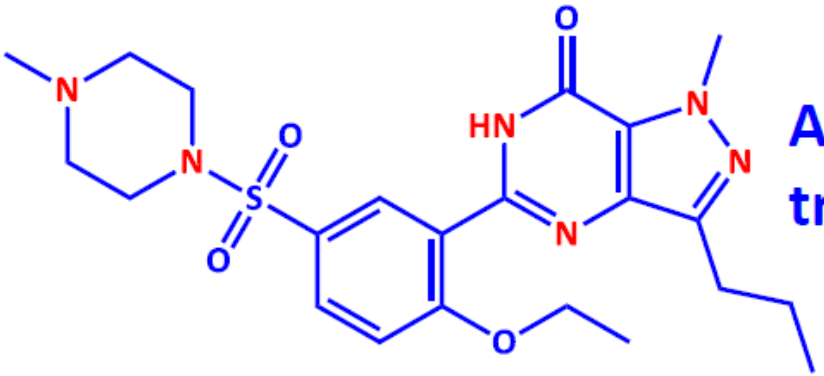


Name: Actos
2008 Sales: $2.45 billion
2008 Ranking: 10 branded
Company: Eli Lilly
Disease: Type 2 diabetes



Name: Gleevec
2008 Sales: $0.45 billion
2008 Ranking: 87 branded
Company: Novartis
Disease: Chronic myeloid leukemia

Drugs Containing Heterocycles



Viagra

Approved in 1997 for treatment of male impotence.

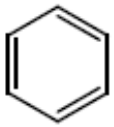
Sildenafil (initially studied for use in **hypertension** (high blood pressure) and angina pectoris, but that it could induce marked **penile erections**.

Pfizer therefore decided to **market** it for **erectile dysfunction** rather than for **angina**. annual sales of Viagra in the period **1999–2001** exceeded **$1 billion**

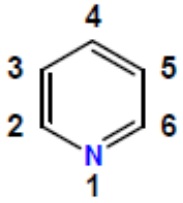
Classification of heterocycles

A) Classification – Aromatic Six-Membered

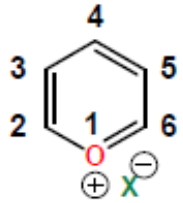
Isoelectronic carbocycle



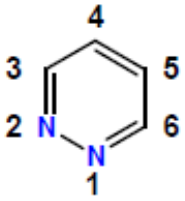
Heterocycles



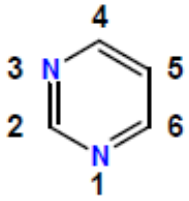
pyridine



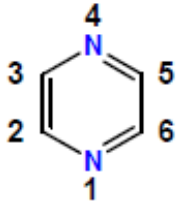
pyrylium



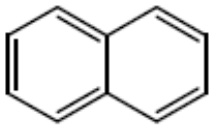
pyridazine

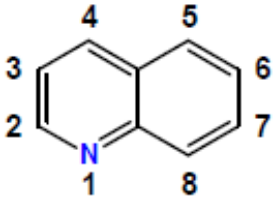


pyrimidine

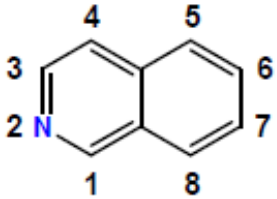


pyrazine





quinoline

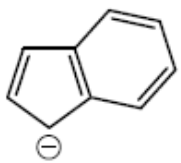


isoquinoline

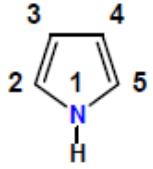
Classification of heterocycles

B) Classification – Aromatic Five-Membered

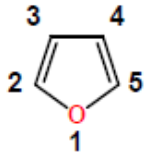
Isoelectronic carbocycle



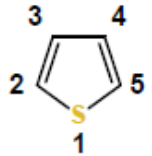
Heterocycles



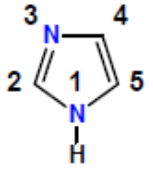
pyrrole



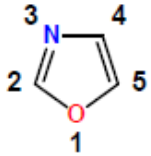
furan



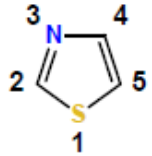
thiophene



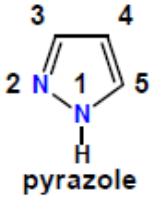
imidazole



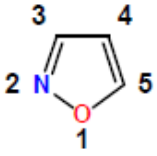
oxazole



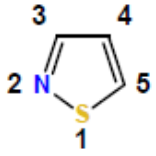
thiazole



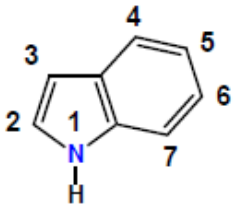
pyrazole



isoxazole



isothiazole

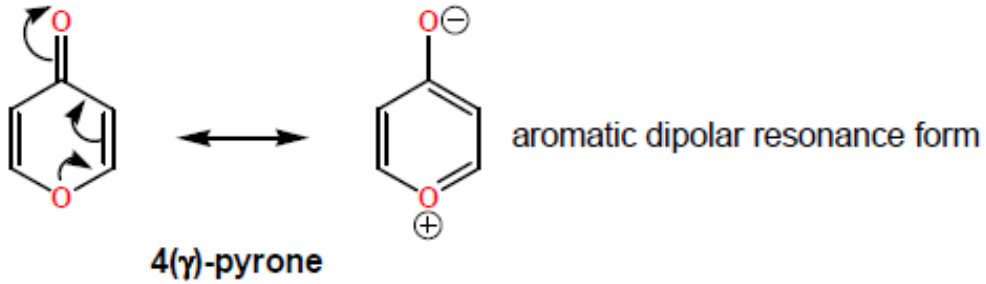


indole

Classification of heterocycles

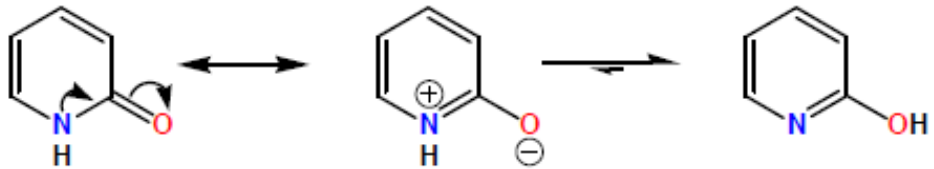
Classification – Unsaturated / Saturated

Unsaturated



aromatic dipolar resonance form

4(γ)-pyrone

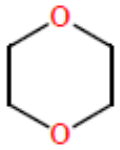


2-pyridone

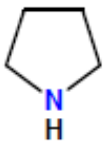
Saturated

ethylene oxide

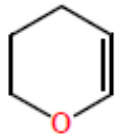
THF



1,4-dioxan



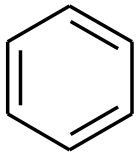
pyrrolidine



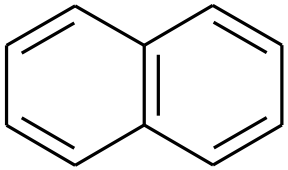
dihydropyran

Structure and Aromaticity

- **For a molecule to be aromatic it must:**
  - Be cyclic
  - Have a *p*-orbital on every atom in ring
  - Be planar
  - Posses 4n+2 p electrons (n = any integer)

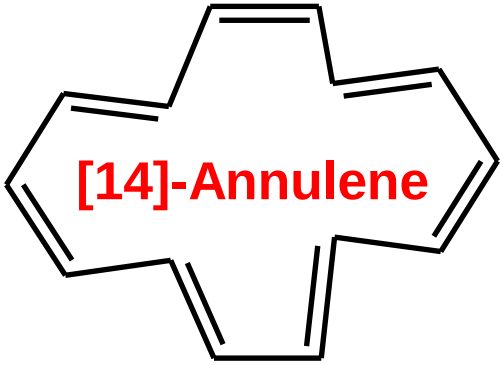


benzene



naphthalene

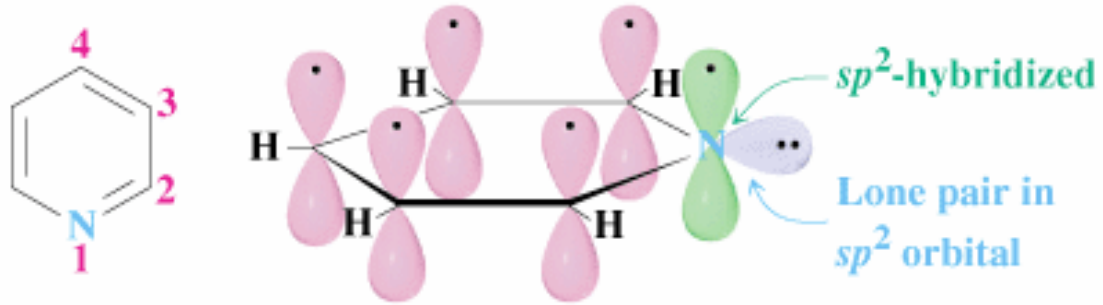
cyclopropenyl cation

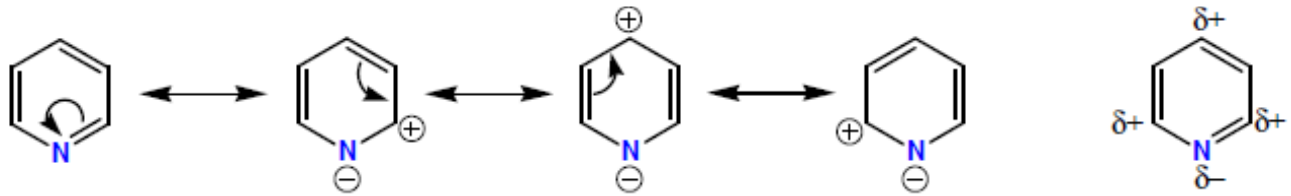


Erich Hückel

Electronic structure of pyridine

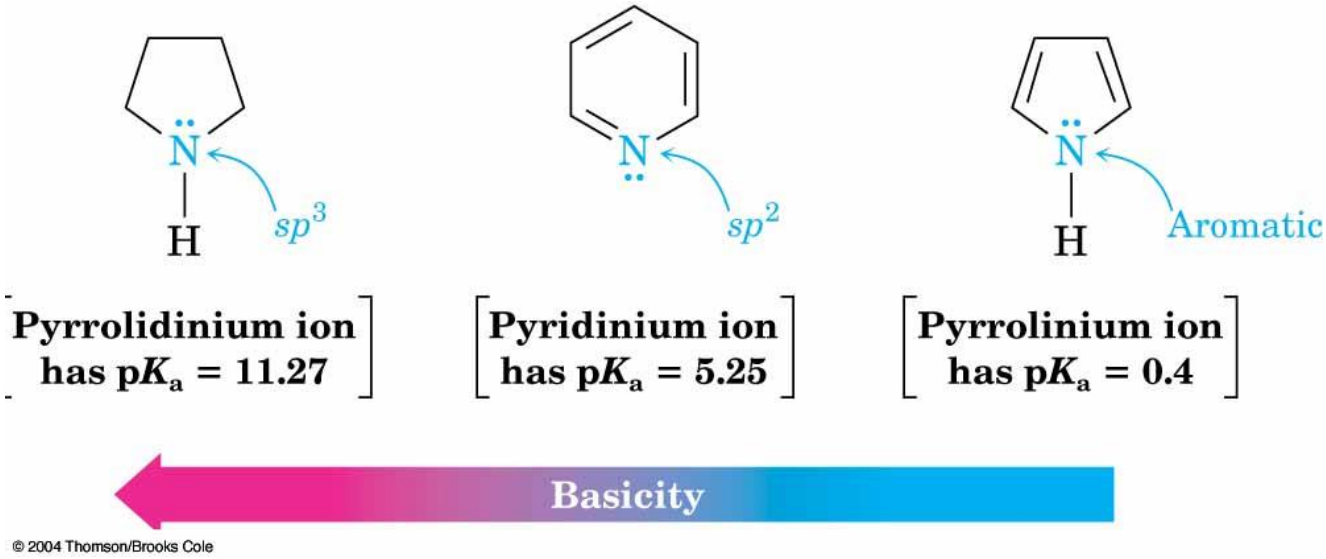
- Pyridine is basic in nature; it reacts with water and acids.
- The nitrogen atom is more electronegative as compared with the carbon itself. It pulls electron density from the ring.
- Therefore, the system with the pyridine nitrogen is called π -deficiency.





Electronic structure of pyridine

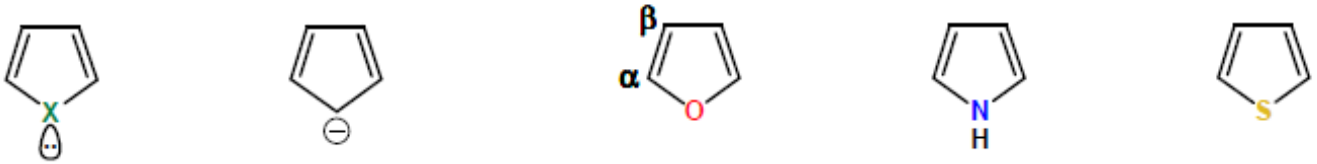
- Pyridine is a stronger base than pyrrole but a weaker base than alkylamines.
- The sp^2-hybridized N holds the lone-pair electrons more tightly than the sp^3-hybridized nitrogen in an alkylamine.
- Electrophilic aromatic substitution is **difficult.**
- Nucleophilic aromatic substitution is **easy.**



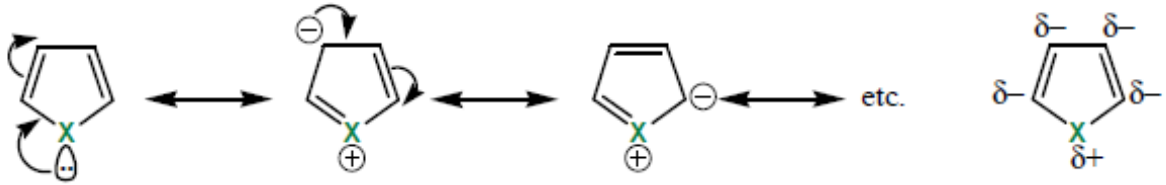
Furans, Pyrroles and Thiophenes – Structure

- Aromatic: Thus, 6π electrons Sp^2 hybridised and planar
- Lone pair tied up in aromatic ring
- Pyrrole is π-electron excessive
- Thus, Electrophilic Aromatic Substitution is Easy.
- Nucleophilic Substitution is Difficult.

Structure



Resonance Structures



Nomenclature of Heterocyclic Compounds

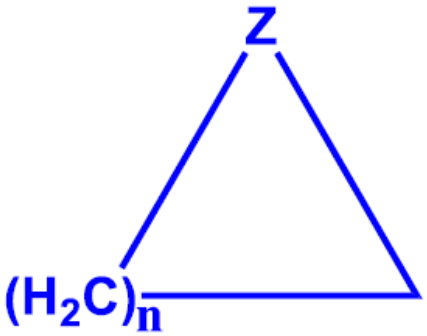
The IUPAC rules allow three nomenclatures.

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 .

I. Hantzsch-Widman Nomenclature

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 heteroatoms:

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

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".

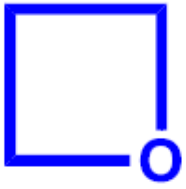
Saturated 3,4 & 5 membered nitrogen heterocycles should use respectively the traditional "iridine", "etidine" & "olidine" suffix.

Examples

Oxa+irane= Oxirane

Thia+irane= Thiirane

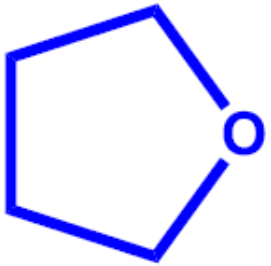
Aza+iridine= Aziridine



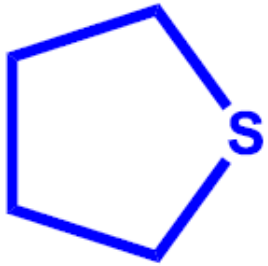
Oxa+etane=Oxetane

Thia+etane=Thietane

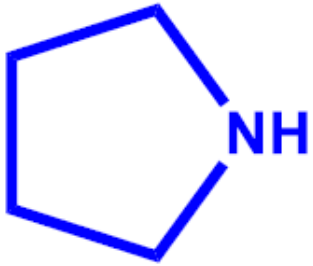
Aza+etidine=Azetidine



Oxa+olane= Oxolane

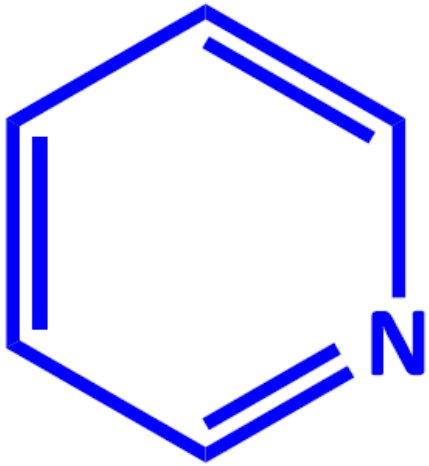


Thia+olane= Thiolane



Aza+olidine= Azolidine

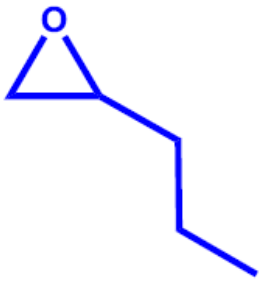
Azinane



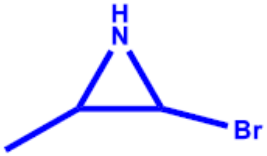
Azine

Pyridine

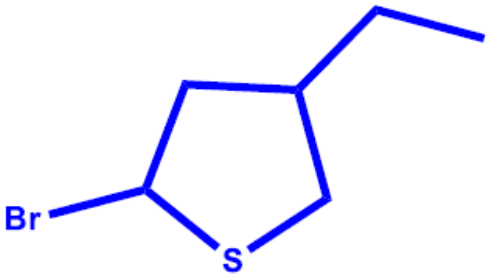
In case of substituents, the heteroatom is designated number 1, and the substituents around the chain are numbered so as to have the lowest number for the substituents.



2-Propyloxirane



2-Bromo-3-methylaziridine



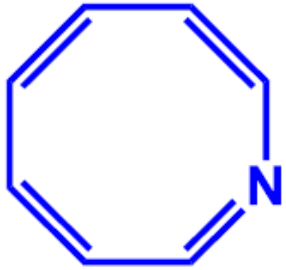
2-Bromo-4-ethylthiolane

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

Oxirine

Azirine

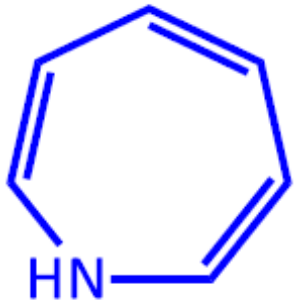
Azepine



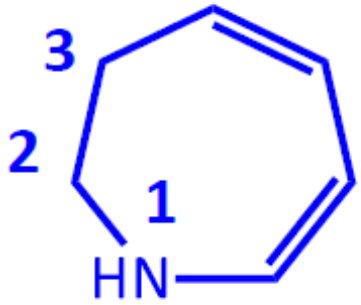
Azocine

Partial Unsaturation

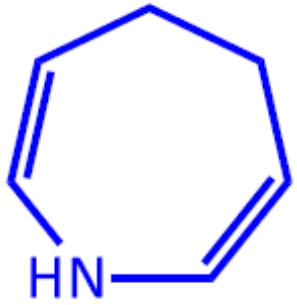
Use fully unsaturated name with dihydro, tetrahydro, etc



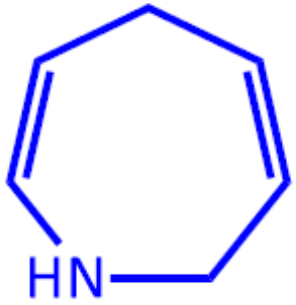
Azepine



2,3-Dihydroazepine

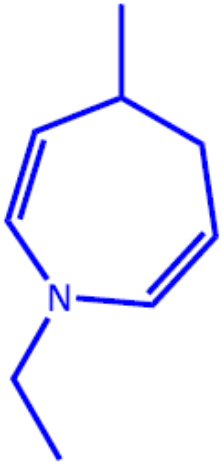


4,5-Dihydroazepine

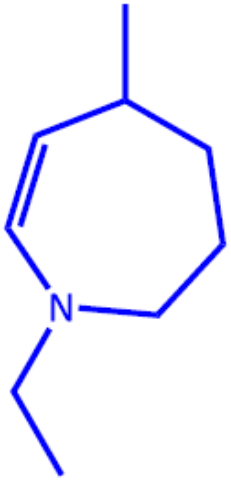


2,5-Dihydroazepine

When numbering give priority to saturated atoms.

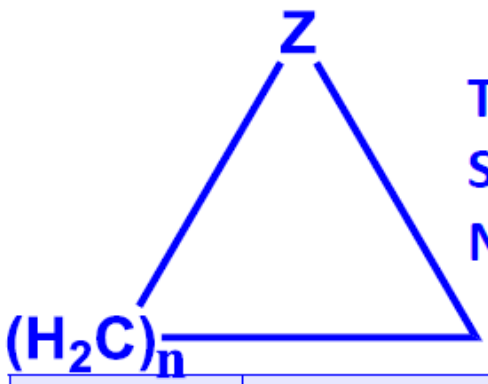


1-Ethyl-4-methyl-4,5-dihydroazepine



1-Ethyl-5-methyl-2,3,4,5-tetrahydroazepine

Revision



Type (Z) - Prefix

Size (n) - Suffix

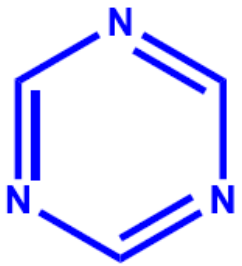
Nature of ring - Ending

Hetreroatom	Prefix
O	Oxa
N	Aza
S	Thia
P	Phospha

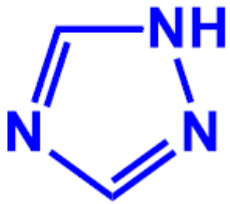
Ring size	Saturated	Unsaturated	Saturated (With Nitrogen)
3	-irane	-irine	-iridine
4	-etane	-ete	-etidine
5	-olane	-ole	-olidine
6	-inane	-ine	
7	-epane	-epine	
8	-ocane	-ocine	
9	-onane	-onine	
10	-ecane	-ecine	

Rings With More Than One Heteroatom

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



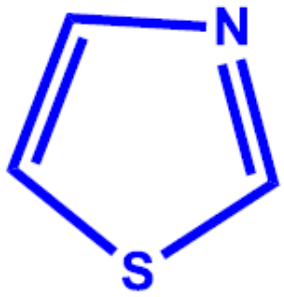
1,3,5-Triazine



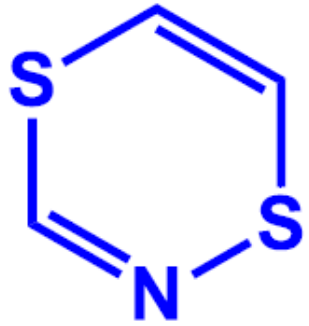
1,2,4 - Triazole

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.

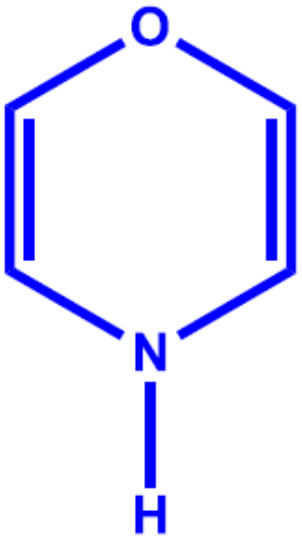
Oxaziridine



1,3-Thiazole
(Thiazole)



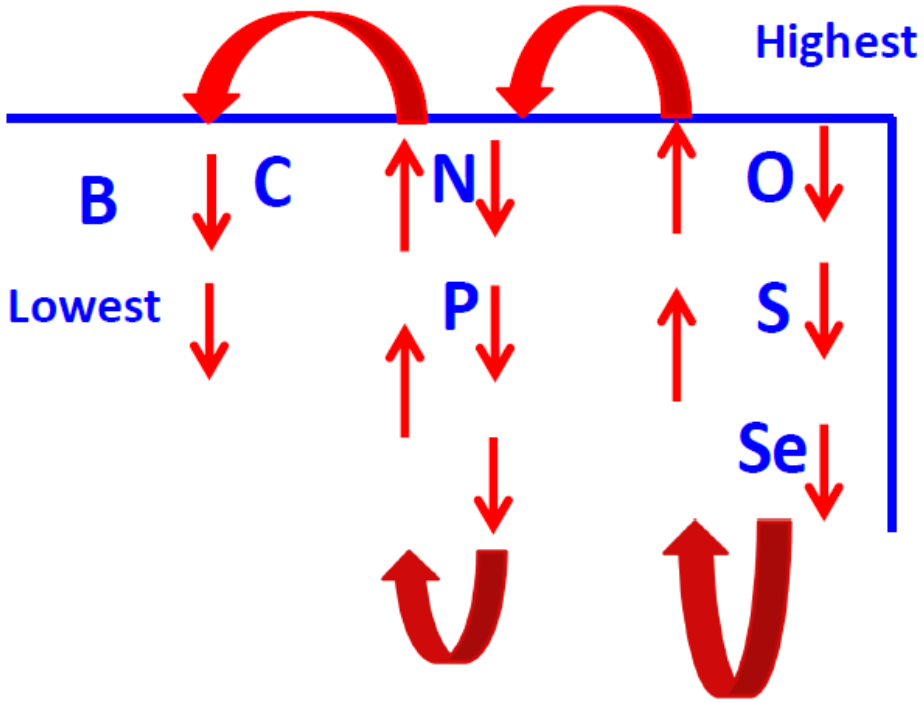
1,4,2 - Dithiazine



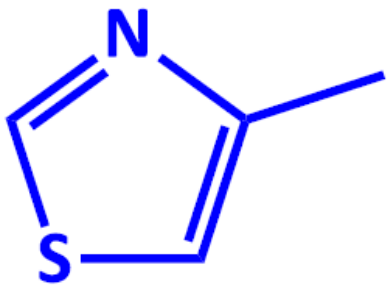
1,4-Oxazine

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

Priority of heteroatoms for numbering purposes:

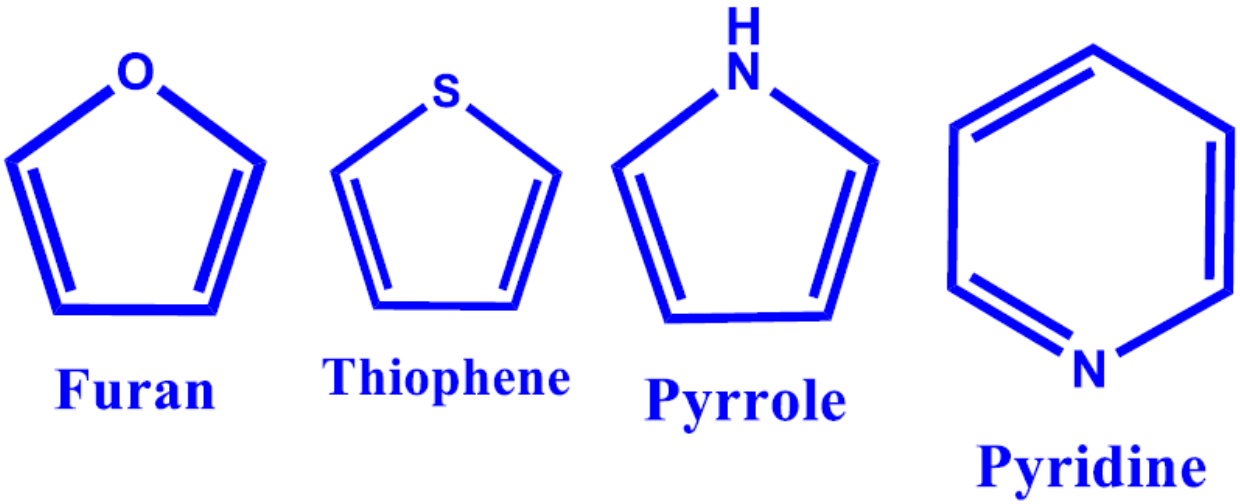


The ring is numbered from the atom of preference in such a way so as to give the smallest possible number to the other hetero atoms in the ring. As a result the position of the substituent plays no part in determining how the ring is numbered in such compounds.

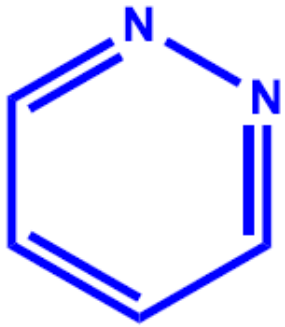


4-Methyl-1,3-thiazole

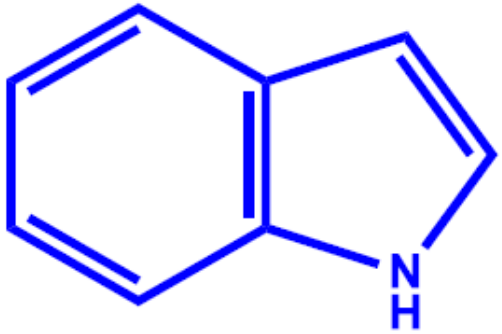
There are a large number of important ring systems which are named widely known with their non-systematic or common names.



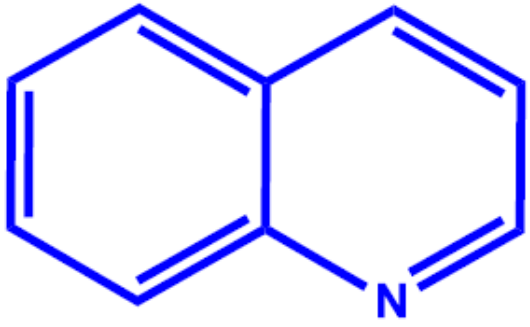
Furan Thiophene Pyrrole Pyridine



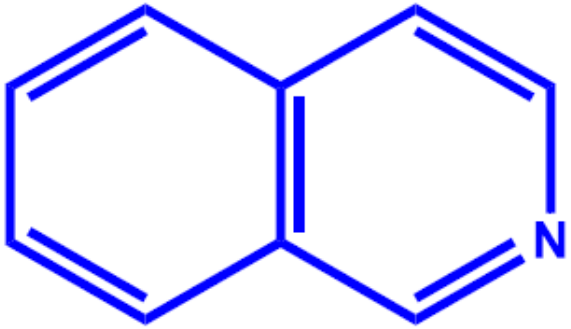
Pyridazine



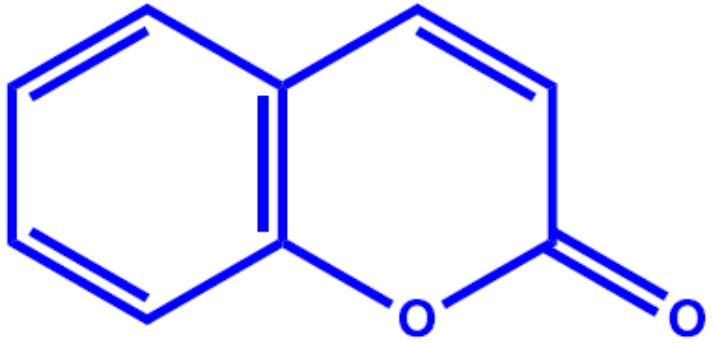
Indole



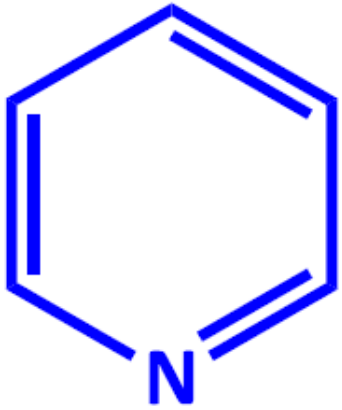
Quinoline



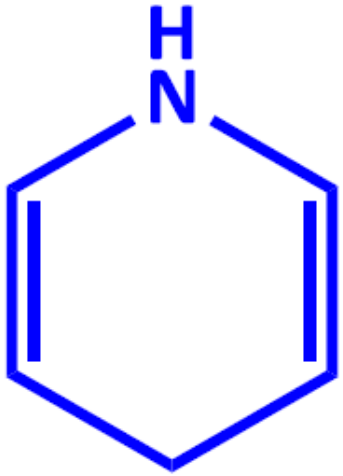
Isoquinoline



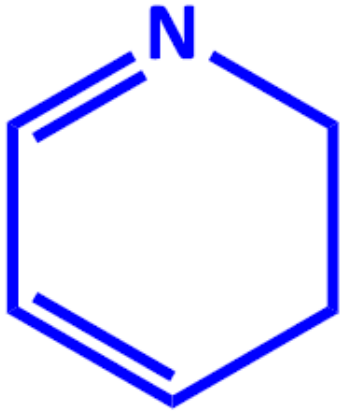
Coumarin



Pyridine



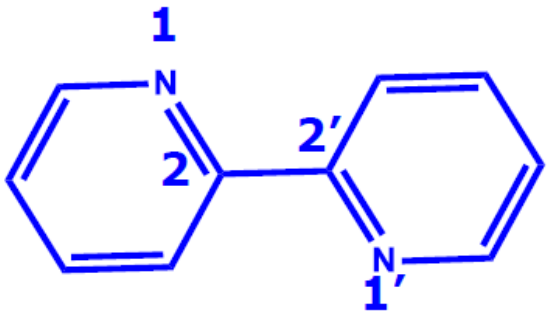
1,4-Dihydropyridine



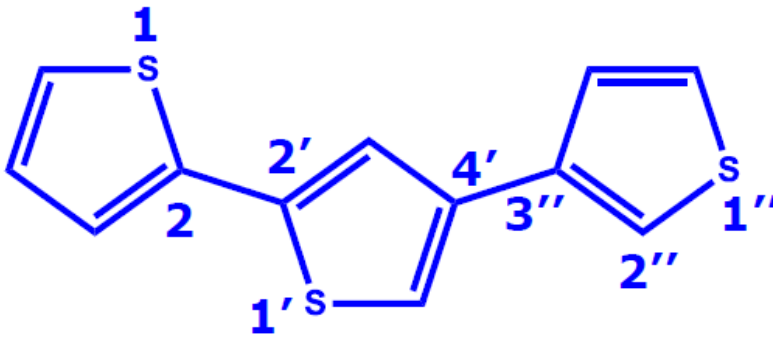
2,3-Dihydropyridine

Identical systems connected by a single bond

Such compounds are defined by the prefixes bi-, tert- , quater-, etc., according to the number of systems, and the bonding is indicated as follows:



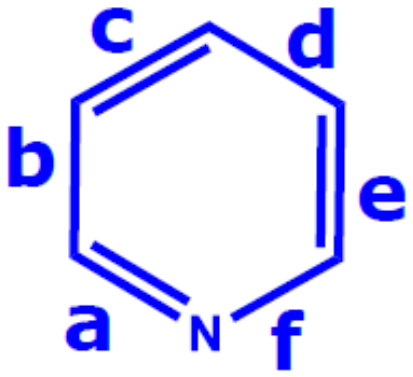
2,2' - Bipyridine



2,2': 4',3'' - Terthiophene

Naming Hetrocycles with fused rings

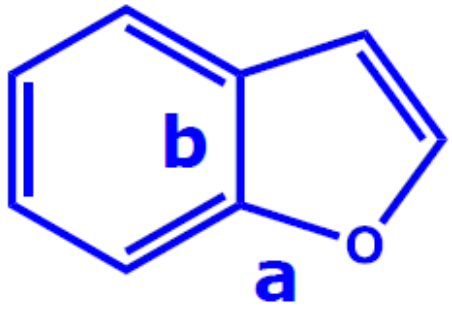
When naming such compounds the side of the heterocyclic ring is labeled by the letters a, b, c, etc., starting from the atom numbered 1. Therefore side '*a*' *being between atoms 1 and 2, side 'b' between atoms 2 and 3*, and so on as shown below for pyridine.



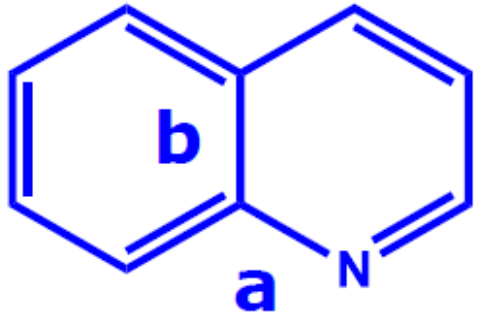
Pyridine

Naming Hetrocycles with fused rings

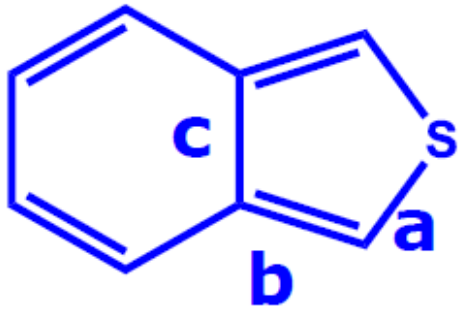
The name of the heterocyclic ring is chosen as the parent compound and the name of the fused ring is attached as a prefix. The prefix in such names has the ending '*o*', *i.e.*, *benzo*, *naphtho* and so on.



Benzo [b] furan

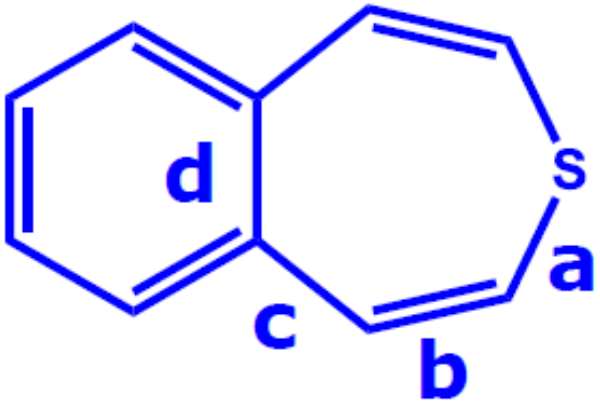


Benzo [b] pyridine



Benzo [c] thiophene

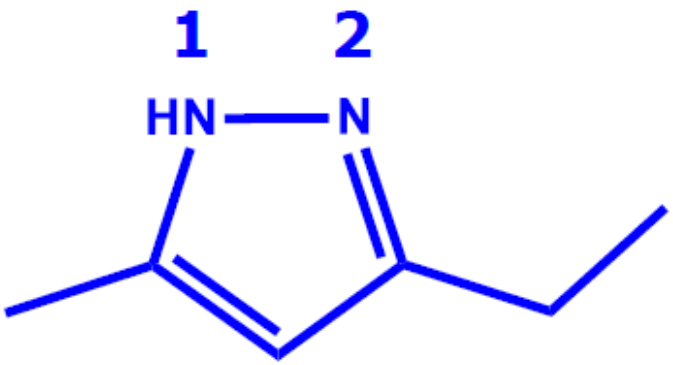
Naming Hetrocycles with fused rings



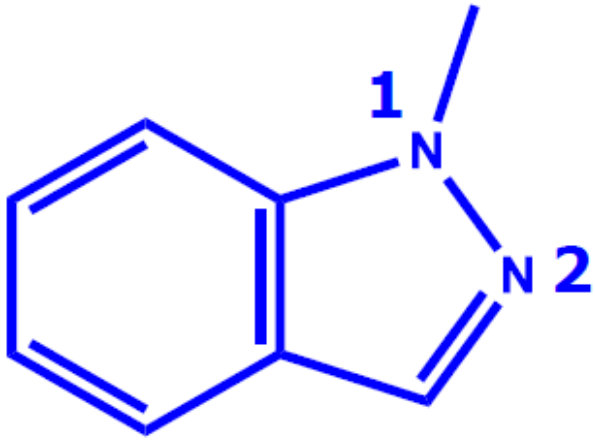
Benzo [d] thiepine

Naming Hetrocycles with fused rings

In a heterocyclic ring, other things being equal, numbering preferably commences at a saturated rather than at an unsaturated hetero atom.



3-Ethyl-5-methylpyrazole



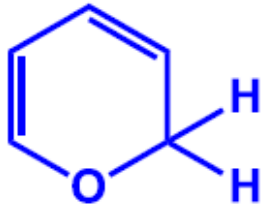
1-Methylindazole

Handling the "Extra Hydrogen"

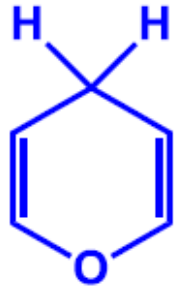
Heterocycles with maximum number of double bonds which can be arranged in more than one way.

Examples

Pyrans



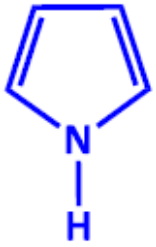
Double bonds @ 2 and 4

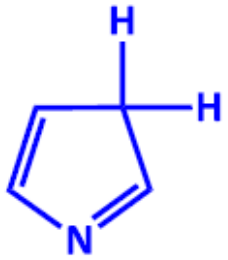


Double bonds @ 2 and 5

Pyrroles

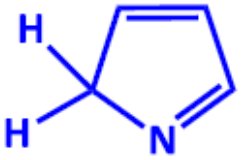
Double bonds @ 2 and 4





Double bonds @ 1 and 4

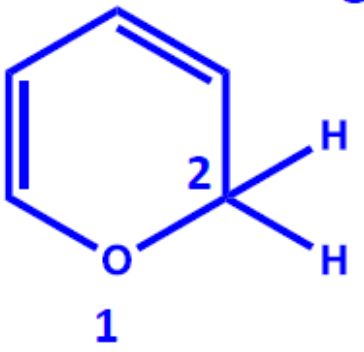
Double bonds @ 1 and 3



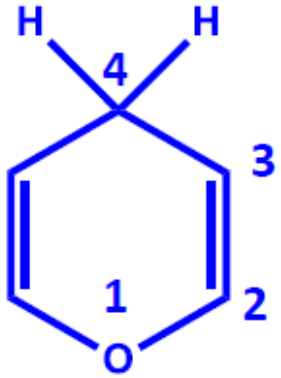
Therefore, should have different names.

Handling the "Extra Hydrogen"

This is a special problem resulting from isomerism in the position of the double bonds which is sometimes referred to as "extra-hydrogen" and this can be addressed by simply adding a prefix that indicates the number of the ring atom that possesses the hydrogen using *italic capital '1H' '2H' '3H', etc. The* numerals indicate the position of these atoms having the extra hydrogen atom.



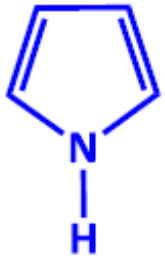
2*H*-Pyran



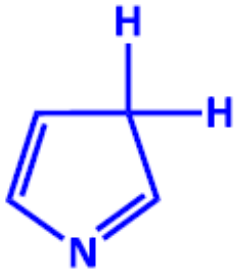
4*H*-Pyran

The saturated position takes priority in numbering.

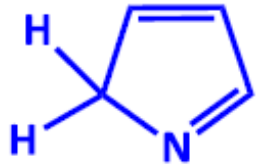
Handling the "Extra Hydrogen"



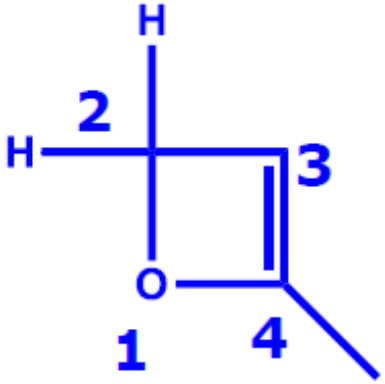
1*H*-Pyrrole
(Pyrrole)



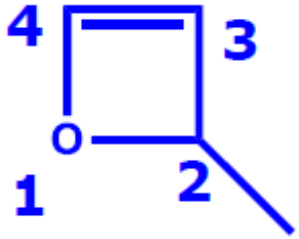
3*H*-Pyrrole



2*H*-Pyrrole

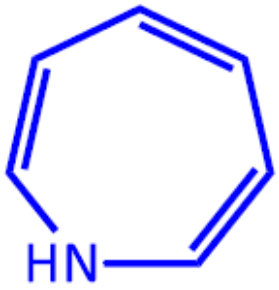


4-Methyl-*2H*-oxete

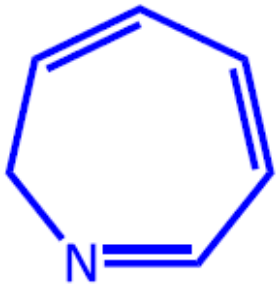


2-Methyl-*2H*-oxete

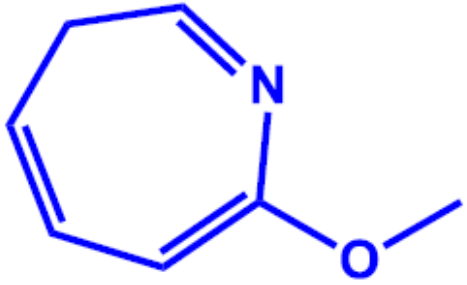
Handling the "Extra Hydrogen"



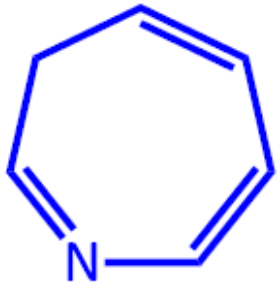
Azepine



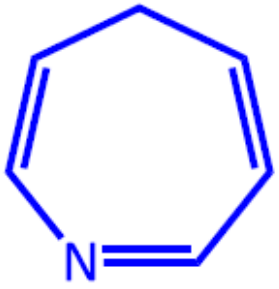
2*H*-Azepine



7-Methoxy-3*H*-azepine



3*H*-Azepine



4*H*-Azepine

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.

III. The Replacement Nomenclature

Azacyclopropane

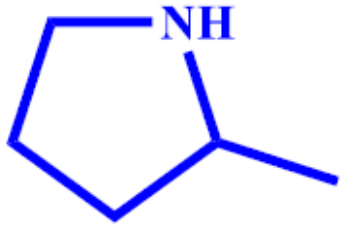
or

Aziridine

Azacyclobutane

or

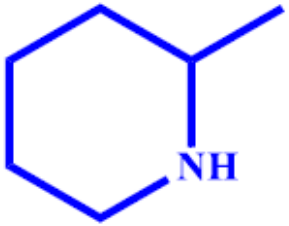
Azetidine



2-Methylazolidine

or

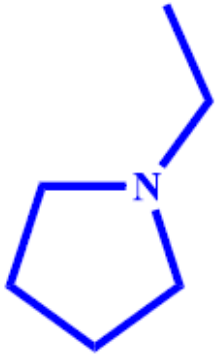
2-Methylazacyclopentane



2-Methylazacyclohexane

or

2-Methylpiperidine



N-Ethylazacyclopentane

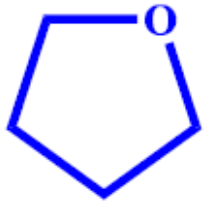
or

N-Ethylpyrrolidine

III. The Replacement Nomenclature

Oxacyclopropane
or
Oxirane
or
Ethyleneoxide

Oxacyclobutane
or
oxetane



Oxacyclopentane
or
Tetrahydrofuran

Thiacyclopropane
or
Thiirane