Heterocyclic Compounds

Lec. 01

المركبات الحلقية غير المتجانسة

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No.	Lecture title	hours
1	Heterocyclic system: classes of heterocyclic systems, general structures, properties, occurrences in nature and in medicinal products	5
2	Five membered ring heterocyclic compounds, pyrrole, furan, and thiophen.	3
3	Source of pyrrole, furan and thiophen.	2
4	Electrophilic substitution in pyrrole, furan and thiophen: Reactivity and orientation.	5
5	Six-membered ring heterocyclic compounds: Structure & reactions of pyridine.	4
6	Saturated five-membered heterocyclic compounds.	6
7	Heterocyclic of five & six member rings with two & three heteroatoms.	5

Classification	Sub-Class
Heterocyclic system	Classes of heterocyclic systems including small hetrocyclic rings (epoxides)
	general structures and nomenclature
	properties
	Occurrence in nature and in medicinal products
Five-membered ring heterocyclic compounds	pyrrole, benzo[b]pyrrole (Indole)
	furan
	thiophen
Source of Five-membered ring heterocyclic compounds	pyrrole
	furan
	thiophen
Electrophilic substitution (Reactivity and orientation)	pyrrole,
	furan
	thiophen
Six-membered ring heterocyclic compounds	Structure, source and basicity of pyridine
	reactions of pyridine
	benzopyridines (Quinoline and isoquinoline)
Saturated five-membered heterocyclic rings.with one heteroatom	pyrrolidine
	tetrahydrofuran
	tetrahydrothiophen

Heterocyclic systems

Heterocyclic compounds are those where one or more atom(s) of the ring are heteroatoms, for example, N, O, S, P, As, Se, B, and so on (Greek word "heteros" means different). More than half of the known organic compounds are heterocyclic compounds. These are widely distributed in nature, and many of them are of fundamental importance for life processes. For example, nucleic acid bases containing purines and pyrimidines; hemoglobin and chlorophyll containing porphyrin rings; essential dietary ingredients containing vitamins B_1, B_2, B_3, B_6, and ascorbic acid; the three essential amino acids, namely, histidine, proline, and tryptophan; almost all the drugs and pharmaceuticals; and many natural products like alkaloids, carbohydrates, and plant pigments. All these compounds contain hetero ring(s) in their molecules. These are the reasons why a great deal of recent research work is concerned with the methods of synthesis of hetero rings and studying their properties.

Importance of heterocyclic compounds:

- A large number of heterocyclic compounds, both synthetic and natural, are pharmacologically active and are in clinical use.
- Several heterocyclic compounds have applications in agriculture as insecticides, fungicides, herbicides, pesticides etc.
- They also find applications as sensitizers, developers, antioxidants, copolymers etc.
- They are used as vehicles in the synthesis of other organic compounds.
- Chlorophyll-photosynthesizing and hemoglobin-oxygen transporting pigments are also heterocyclic compounds.
- Heterocyclic compounds include many of the biochemical material essential to life. For example, nucleic acids, the chemical substances that carry the genetic information controlling inheritance, consist of long chains of heterocyclic units held together(DNA is composed of heterocyclic bases-pyrimidines and purines).
- Many naturally occurring pigments, vitamins, and antibiotics are heterocyclic compounds.

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- Because the biological properties of heterocycles in general make them one of the prime interests of the pharmaceutical and biotechnology industries.
- A selection of just six biologically active pyridine or piperidine derivatives. It includes four natural products (nicotine, pyridoxine, cocaine and morphine) and two synthetic compounds (nifedipine and paraquat).

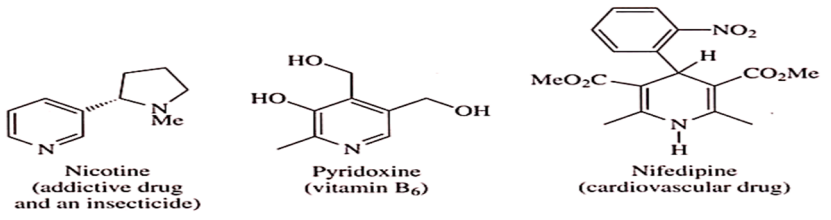

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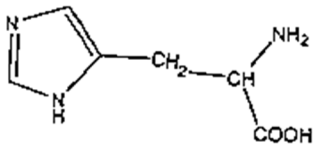
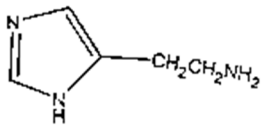
Table 31.1 HETEROCYCLIC COMPOUNDS

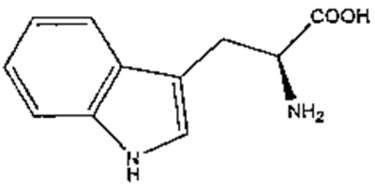
Name	M.p., °C	B.p., °C	Name	M.p., °C	B.p., °C
Furan	− 30	32	Pyridine	− 42	115
Tetrahydrofuran	−108	66	α-Picoline	− 64	128
Furfuryl alcohol		171	β-Picoline		143
Furfural	− 36	162	γ-Picoline		144
Furoic acid	134		Piperidine	− 9	106
Pyrrole		130	Picolinic acid	137	
Pyrrolidine		88	Nicotinic acid	237	
Thiophene	− 40	84	Isonicotinic acid	317	
			Indole	53	254
			Quinoline	− 19	238
			Isoquinoline	23	243



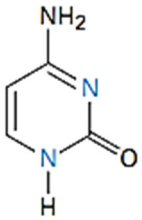
Histidine



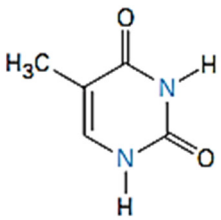
Histamine



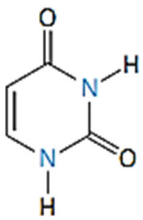
Tryptophan



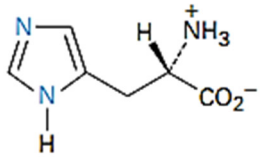
Cytosine (in DNA and RNA)



Thymine (in DNA)



Uracil (in RNA)



Histidine (an amino acid)

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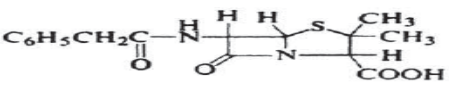
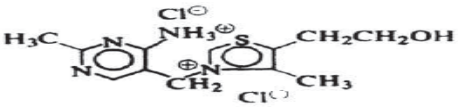
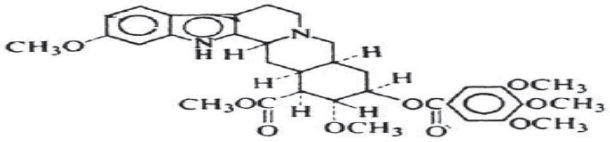


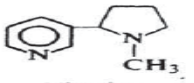
Penicillin G
Antibiotic



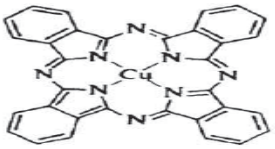
Thiamine
Vitamin B_1
Anti-beriberi factor



Reserpine
A tranquilizing drug



Nicotine
A tobacco alkaloid



Copper phthalocyanine
A blue pigment

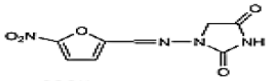
Chlorophyll a
Green plant pigment: catalyst for photosynthesis

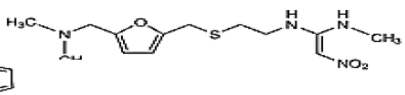
Examples of drugs

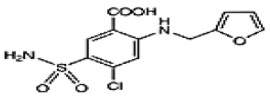
Five membered with one heteroatom

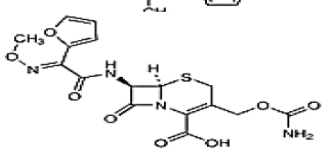
Furan derivatives

- Nitrofurantoin
- Ranitidine
- Furosemide
- Cefuroxime



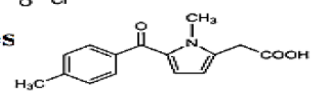






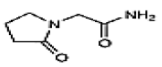
Pyrrole derivatives

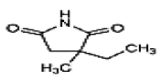
- Tolmetin



Pyrrolidine derivatives

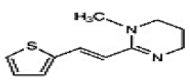
- Piracetam
- Ethosuximide

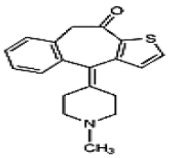




Thiophene derivatives

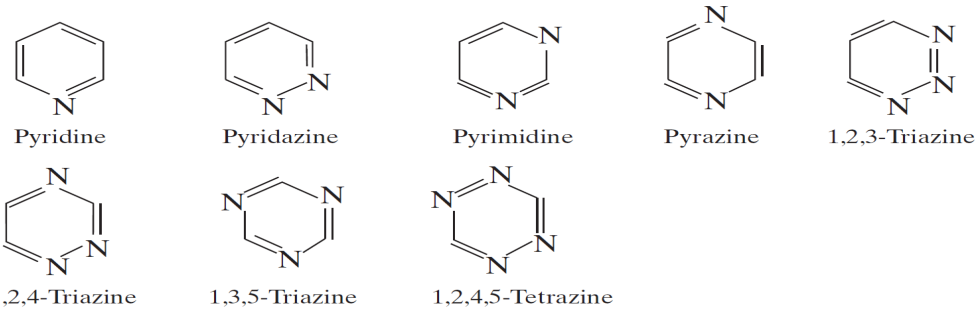
- Pyrantel
- Ketotifen





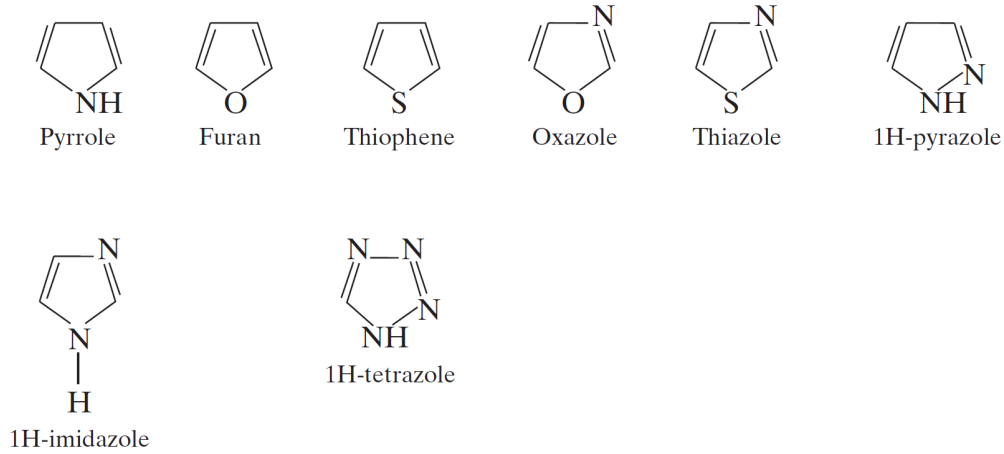
Common structural types of heterocycles

The heterocycles with the structures analogous to that of benzene but with a heteroatom replacing at least one carbon atom of the benzene ring are called aromatic heterocycles, for example, pyridine. There are other analogous heterocycles where more than one carbon atom of the benzene ring are replaced by heteroatoms, for example, pyridazine, pyrimidine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, and 1,2,4,5-tetrazine.

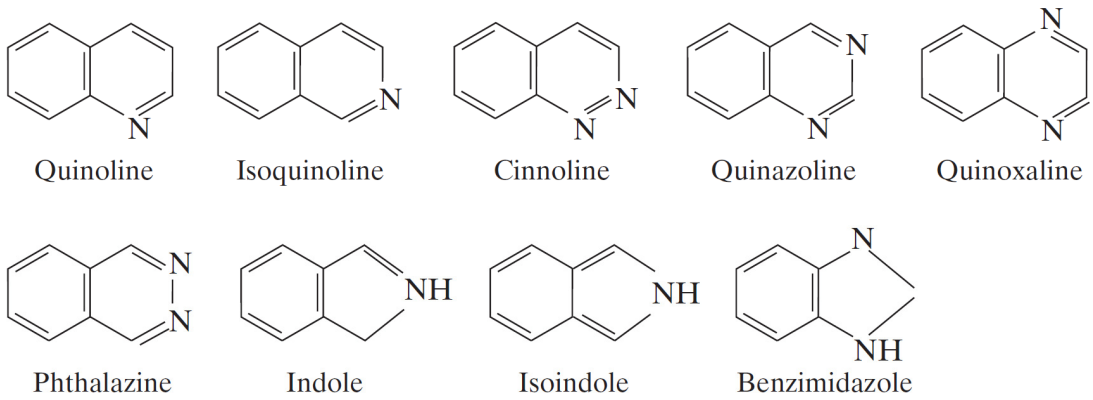


All of the above heterocycles are six-atom, six-π-electron aromatic heterocycles.

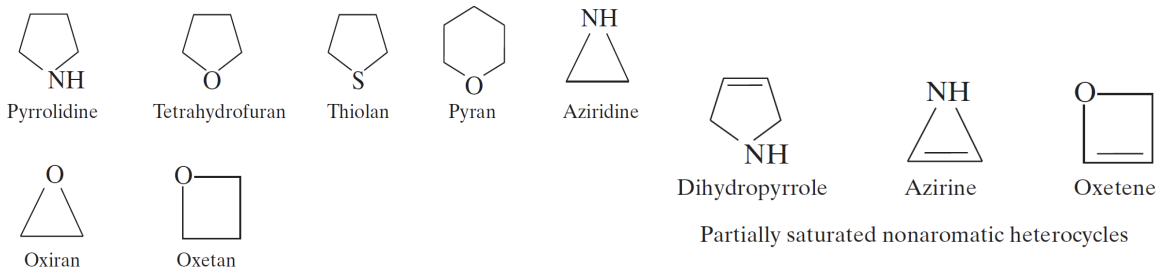
There are five-atom, six-π-electron aromatic heterocycles, for example, pyrrole, furan, and thiophene contain only one heteroatom in the ring system, and oxazole, thiazole, isothiazole, 1H-pyrazole, 1H-imidazole, and 1H-tetrazole contain two heteroatoms in the ring.



There are fused-ring system aromatic heterocycles. For example, quinoline, isoquinoline, cinnoline, quinazoline, quinoxaline, phthalazine, indole, isoindole, and benzimidazole.



Besides the above fully unsaturated aromatic heterocycles, there are other nonaromatic small-ring heterocyclic compounds that may be either partially or fully saturated. In these heterocyclic compounds, there is no possibility of cyclic delocalization of *p*-electrons for which they lack any aromatic character and these small-ring heterocycles suffer from considerable angle strain. For example, pyrrolidine, tetrahydrofuran, thiolan, pyran, aziridine, oxiran, azetidine, oxetan, and so on, are fully saturated heterocycles and dihydropyrrole, azirine, oxetene, and so on, are partially saturated heterocycles.



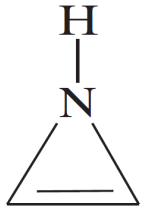
Nomenclature of heterocyclic compounds

Monocyclic compounds are named by prefixing the name that indicates the nature of the heteroatom. For example, nitrogen → aza, sulfur → thia, oxygen → oxa, silicon → sila, phosphorus → phospha, and boron → bora.

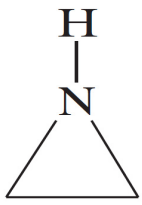
The size of the ring of monocyclic compounds is indicated by appropriate suffixing for each ring size.

The suffixing depends on the nature of the heteroatom—nitrogen-containing heterocycles and heterocycles without nitrogen are suffixed in different but distinct ways. The suffixing of aromatic (fully unsaturated) and nonaromatic (fully or partially saturated) heterocycles have different but related suffixes.

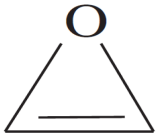
An example will help to understand the method of naming a heterocyclic compound.



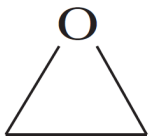
Azirine
Prefix: az-
Suffix: -irine
(fully unsaturated nitrogen-containing three-membered heterocycle)



Aziridine
Prefix: az-
Suffix: -iridine
(fully saturated nitrogen containing three-membered heterocycle)

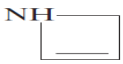
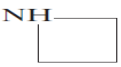
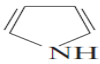


Oxiren
Prefix: ox-
Suffix: -iren
(fully unsaturated three-membered heterocycle without a nitrogen atom)



Oxiran
Prefix: ox-
Suffix: -iran
(fully saturated three-membered heterocycle without a nitrogen atom)

Naming of fully unsaturated and fully saturated monocyclic heterocycles is shown below:

	Nitrogen present		Nitrogen absent	
Number of ring members	Fully unsaturated (suffix)	Fully saturated (suffix)	Fully unsaturated (suffix)	Fully saturated (suffix)
3	-irine	-iridine	-iren	-iran
	 Azirine	 Aziridine	 Oxiren	 Oxiran
4	-ete	-etidine	-et	-etan
	 Azete	 Azetidine	 Oxet	 Oxetan
5	-ole	-olidine	-ole	-olan
	 Azole	 Azolidine	 Thiole	 Thiolan
6	-ine	-perhydro.....ine	-in	-ane
	 Azine	 Perhydroazine	 Oxin	 Oxane

1. The heteroatom is given a name and is used as a prefix: N, aza-; O, oxa-; S, thia-; P, phospha-; As, arsa-; Si, sila-; Se, selena-, B, bora, and so on. The "a" ending is dropped if the next syllable starts with a vowel. Thus "aza-irine" is properly written "azirine."
2. Ring size is designated by stems that follow the prefix: 3-atoms,-ir-; 4-atoms, -et-; 5-atoms, -ol-; 6-atoms, -in-; 7-atoms, -ep-; 8-atoms, -oc-; 9-atoms, -on-; and so on.
3. If fully unsaturated, the name is concluded with a suffix for ring size: 3-atoms, -ene (except -ine- for N); 4-, 5-, and 6-atoms, -e; 7-, 8-, and 9- atoms, -ine.
4. If fully saturated, the suffix is -ane for all ring sizes, except for N, which uses -idine for rings of 3-, 4-, or 5-atoms, and for 6-atoms, a prefix of hexahydro- is used. Also, the name oxane, not oxinane, is used for the 6-membered ring with O present. Other exceptions exist for P, As, and B rings, but they will not be given here.

Table 2.2 shows the application of the above rules to several N, O, and S rings. However, it is preferable and acceptable to use the common names in some cases, and these are included in parentheses.

The naming system easily accommodates the case of partial saturation of the double bonds by designating with numbers the positions on the ring where hydrogen has been added. For this purpose, the heteroatom is designated position 1 on the ring, and the numbering proceeds through the site of hydrogenation. If one double bond is removed, the prefix dihydro- is used; with two double bonds removed, it is tetrahydro-. The following examples will make this system clear.

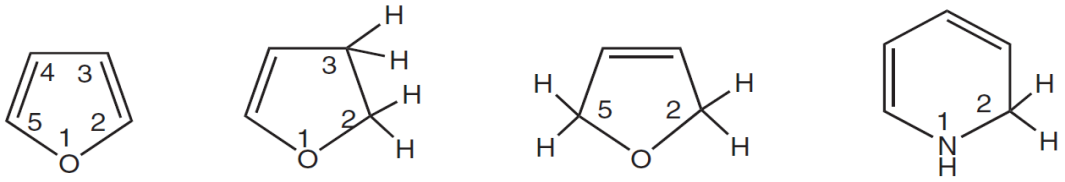


Table 2.2. IUPAC and Common Names for Monocyclic Heterocycles

A. Nitrogen Heterocyclic Parents

azirine, azete, azole (pyrrole), azine (pyridine), azepine

B. Oxygen Heterocyclic Parents

oxirene, oxete, oxole (furan), γ-pyran (1,4-pyran), α-pyran (1,2-pyran)

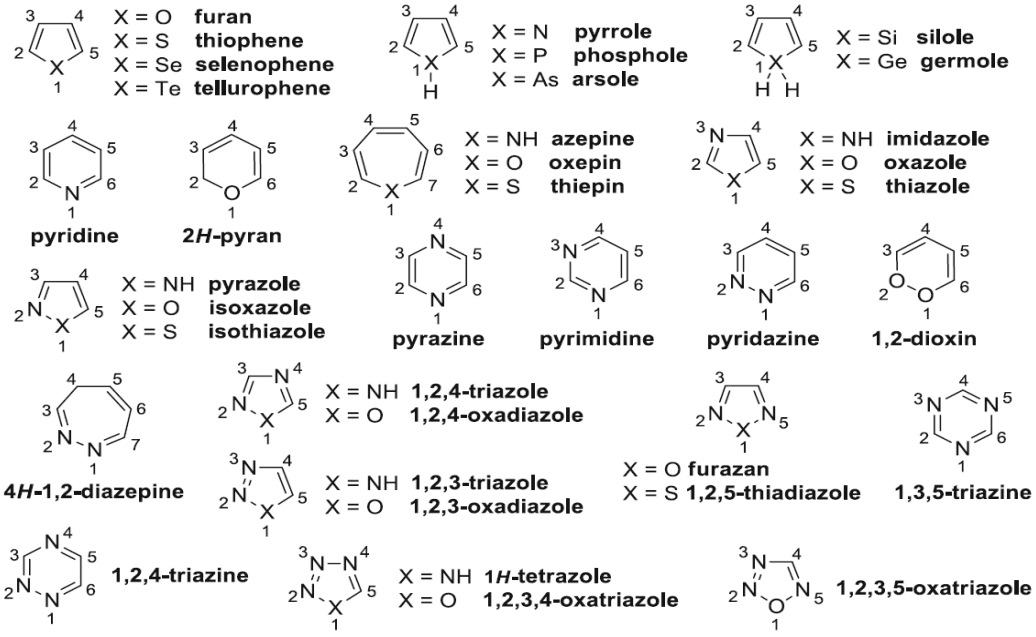
C. Sulfur Heterocyclic Parents

thiirene, thiete, thiole (thiophene), γ-thiopyran

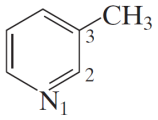
D. Some Saturated Rings

aziridine (ethyleneimine), azetidine, azolidine (pyrrolidine), hexahydropyridine (piperidine)

oxirane (ethylene oxide), oxetane, oxolane (tetrahydrofuran), oxane (tetrahydropyran)



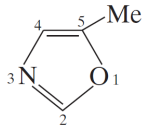
In a monocyclic compound, numbering starts from the heteroatom and moves in the direction where the substituent gets lower location. For example,



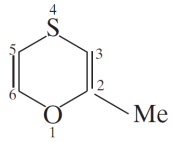
3-Methylazine

For monocyclic compounds having more than one heteroatom, the priority of the heteroatoms is decided as follows:

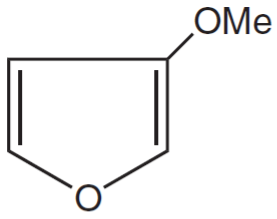
1. If the group number of the heteroatoms are different, the atom of the higher group number gets higher preference, for example, O (Gr. vi) > N (Gr. v)
2. If the group number of the heteroatoms are same, then the lighter atom is preferred, for example, O (atomic mass 16) > S (atomic mass 32)



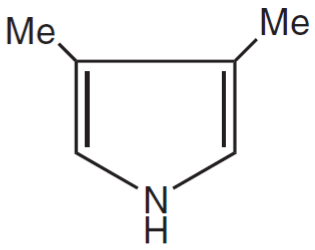
5-Methyl-1,3-oxazole



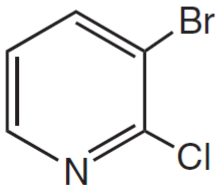
2-Methyl-1,4-thiaoxin



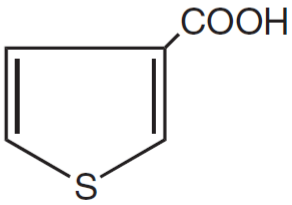
3-methoxyfuran



3,4-dimethyl-1H-pyrrole

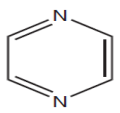


3-bromo-2-chloropyridine

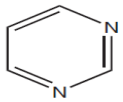


thiophene-3-carboxylic acid

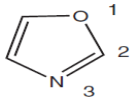
Table 2.3. Some Multiheteroatom Systems



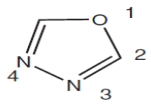
1,4-diazine (pyrazine)



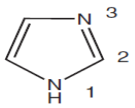
1,3-diazine (pyrimidine)



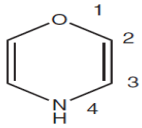
1,3-oxazole



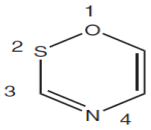
1,3,4-oxadiazole



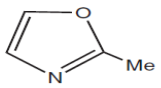
1H-1,3-diazole (imidazole)



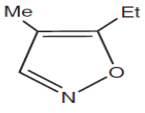
4H-1,4-oxazine



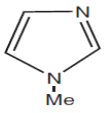
1,2,4-oxathiazine



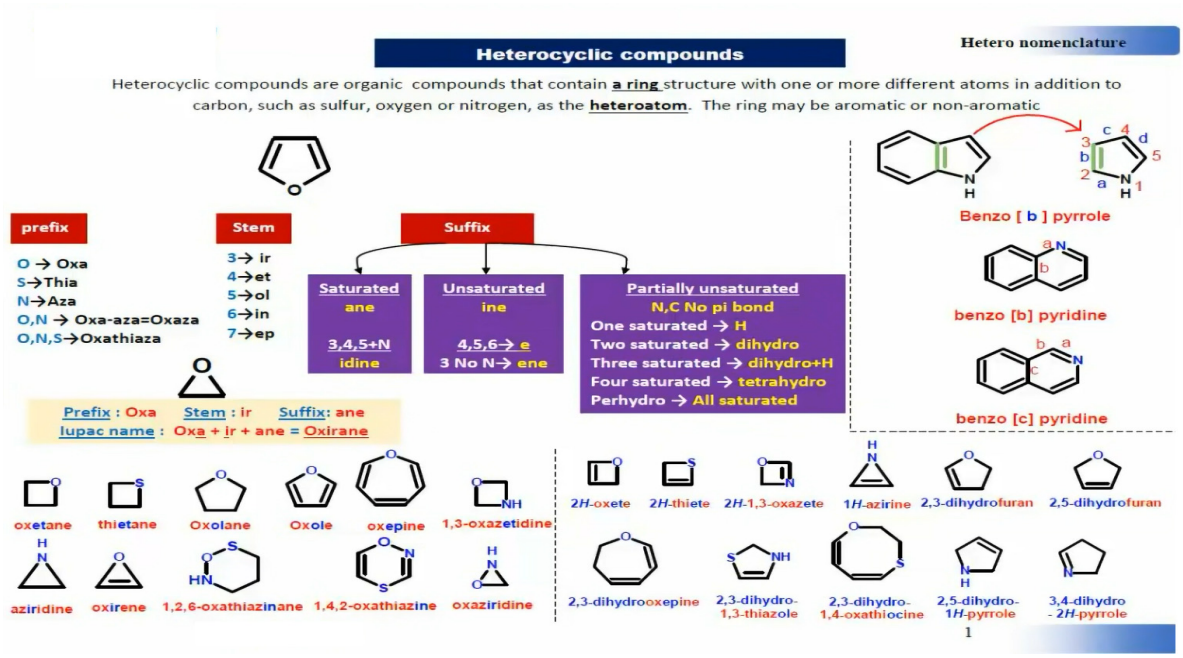
2-methyl-1,3-oxazole



5-ethyl-4-methyl-1,2-oxazole



1-methyl-1H-1,3-diazole (N-methylimidazole)



RINGS WITH MORE THAN ONE HETEROATOM

Now we have to consider the common case where more than one heteroatom is present in the ring. The usual rules for stems to indicate ring size and suffixes for degree of saturation are used, as are the prefixes for the various heteroatoms. They are listed in the following order of priorities, derived from the main groups of the Periodic System, and then within each group by increasing atomic number: Group VI (O > S > Se > Te) > Group V (N > P > As) > Group IV (Si > Ge) > Group III (B). This listing can be simplified greatly by taking out the most commonly found heteroatoms in their order, which gives O > S > N > P. Each heteroatom is then given a number as found in the ring, with that of highest priority given position 1. Some additional points include the following (examples in Table 2.3 will illustrate these points):

- A saturated heteroatom with an extra-hydrogen attached is given priority over an unsaturated form of the same atom, as in 1H-1,3-diazole (see the following discussion).
- The numbers are grouped together in front of the heteroatom listings (thus, 1,3-oxazole, not 1-oxa-3-azole).
- The heteroatom prefixes follow the numbers in the priorities given previously.

- Punctuation is important; in the examples to follow, a comma separates the numbers and a dash separates the numbers from the heteroatom prefixes.
- A slight modification is used when two vowels adjoin; one is deleted, as in the listing for "oxaaza," which becomes simply "oxaza."
- As for monohetero systems, substituents on the ring are listed alphabetically with a ring atom number for each (not grouped together).

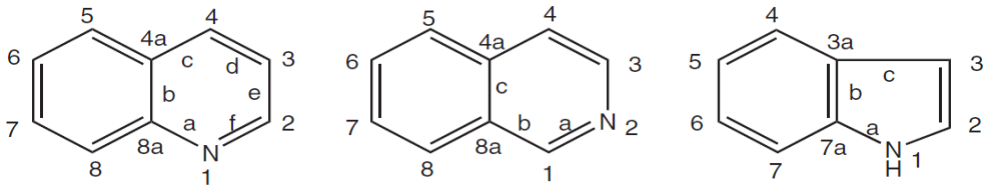
BICYCLIC COMPOUNDS

We have now seen rules that will allow the naming of *any* monocyclic heterocycle. We next consider systems where two rings share a common single or double bond, which are said to be fused rings. A common case is where a benzene ring is fused to a heterocyclic ring. The name begins with the prefix "benzo." The point of attachment is indicated by a letter that defines the "face" of the heterocycle involved. Thus, the 1,2- position on the heterocyclic ring is always the "a-face," 2,3- is the "b-face," 3,4- is the "c-face," and so on. After the name is established, the ring atoms are given new numbers for the entire bicycle. In Table 2.4 and in subsequent examples, the letters for the faces of the monocycle are placed inside the ring, and the numbers for ring positions of the bicycle taken as a whole are shown on the outside. Note that the final numbering always begins at a position next to the benzo group and that the heteroatoms are given the lowest numbers possible, observing the O > S > N > P rule. The positions of ring fusion bear the number of the preceding ring atom with the letter "a" attached. Brackets are used around the face letter, and the name is put together without spaces, except that a dash separates the bracket from ring numbers if present, as in benzo[d]-1,3-thiazole. A convention frequently followed is to write the structure with the heteroring on the right and with its heteroatom at the bottom.

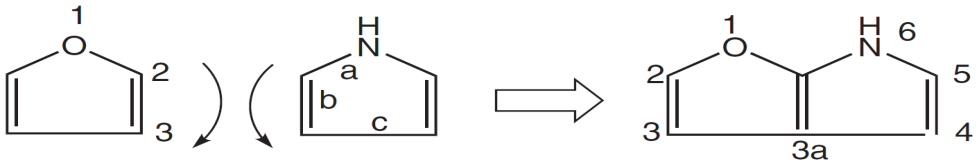
If two heterocyclic rings are fused, additional rules are required. A parent ring is selected, and the other ring is considered fused on, as was observed for benzene fusion. Some rules are as follows:

- If one ring contains N, it is considered the parent, and its name is placed last in the compound's name.

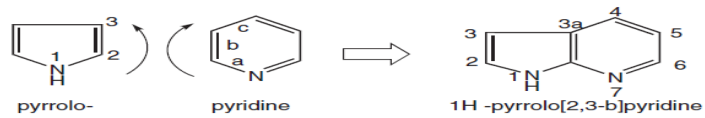
Table 2.4. Benzo-Fused Systems



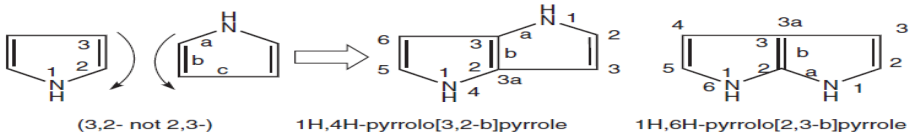
- If both rings contain N, the larger ring is the parent.
- If both rings are of the same size, that with the most N atoms is the parent, or if the same number of N atoms is present, that fusion of the rings that gives the smallest numbers for N when the bicycle is numbered is chosen.
- If no N is present, O has priority over S over P, and then the above rules are applied.
- The ring fused onto the parent has the suffix "o"; common names are used (with modification) where possible to simplify the name. Some examples are pyrido for pyridine, pyrrolo for pyrrole, thieno for thiophene, furo for furan, imidazo for imidazole, pyrimido for pyrimidine, pyrazino for pyrazine, among others.
- The face letter of the parent ring where the fusion occurs is placed in brackets preceding the name of that ring. The position numbers of the fused ring are placed inside the brackets before the face letter of the parent ring, separated by a comma. The proper numbers for the fused ring are those that are encountered as one goes around the ring in the same direction as going alphabetically around the faces of the parent. (One can liken this to the meshing of two gears.) These need not be in numerical order. Some examples will illustrate the two possible situations. Thus, fusing the 2,3-bond of furan onto the b-face of pyrrole, taken as the parent, results in the name 6H-furo[2,3-b]pyrrole.



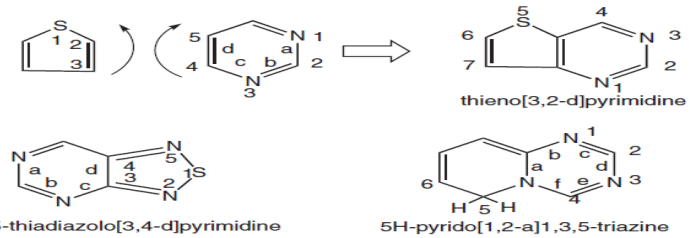
Similarly, fusing the 2,3-bond of pyrrole onto the b-face of pyridine results in a pyrrolo[2,3-b]pyridine. Note that numbering for the atoms in the overall fused compound is assigned from the rule that the heteroatoms should be given the lowest numbers possible, and where there is a choice of the numbering sequence, the site of an extra-hydrogen is given priority. Thus, in pyrrolo[2,3]pyridine, numbering could begin from either N as position one, because the numbers would be 1,7 starting from either N, but NH has priority.



An example where the numbers are in reverse order is pyrrolo[3,2-b]pyrrole. Note that the numbering technique clearly distinguishes between isomers of pyrrolopyrrole.



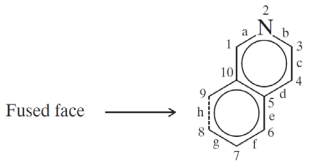
Some other examples are as follows:



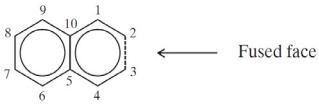
For fused-ring heterocycles, the heterocyclic ring having maximum number of rings with a simple name is chosen. If more than one heterorings are present, then the nitrogen containing ring is given preference. For heterorings having no nitrogen, the order of preference is decided by the above mentioned two rules (1) and (2). When the parent heteroring is chosen, its name is prefixed by the name of the ring fused with it, for example, benzo-, naphtho-.

The structure is now written with the greatest number of rings in horizontal position, and the other nonhorizontal rings are written at the right of the horizontal row and above it.

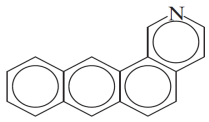
To distinguish isomers, the peripheral sides of the parent compound are lettered as a, b, c …, and so on, beginning with "a" for the side C_1—C_2, "b" for C_2—C_3 …, and so on. The numbering of the parent ring is done in such a way that the side undergoing fusion gets the *lowest alphabet*. For example heterocycle isoquinoline ring should be numbered as follows:



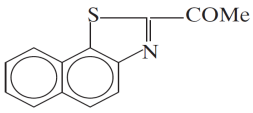
The naphthalene ring is numbered as follows:



Therefore, the name of the isomer



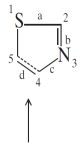
is naphtho[3,2-h]isoquinoline. Another example is given below.



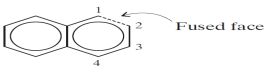
In the above compound, the heteroring is

which is called 1,3-Thiazole.

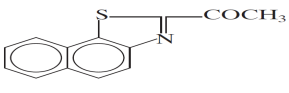
The compound is, therefore, naphthothiazole. To identify the fused side, the lettering is done as follows:



The fused face is d.
The naphthalene ring is numbered as follows:



So, the name of the compound



is 2-ethanoyl naphtho[2,1-d]-1,3-thiazole.