Heterocyclic Compounds

Assist. Prof. Dr. Ayad Kareem

Department of Pharmaceutical Chemistry,

Collage of Pharmacy, Al-Mustansiriyah University (2019-2020).

References Text Book:

1. J. McMurry "Organic Chemistry" 9th ed. Cengage Learning, USA (**2016**).
2. R.T. Morrison, R.N. Boyd and S.K. Bhattacharjee "Organic Chemistry" 7th ed. Pearson Education Inc. India (**2011**).
3. P. Y. Bruice "Organic Chemistry" 8th ed. Pearson Education Inc., USA (**2016**).

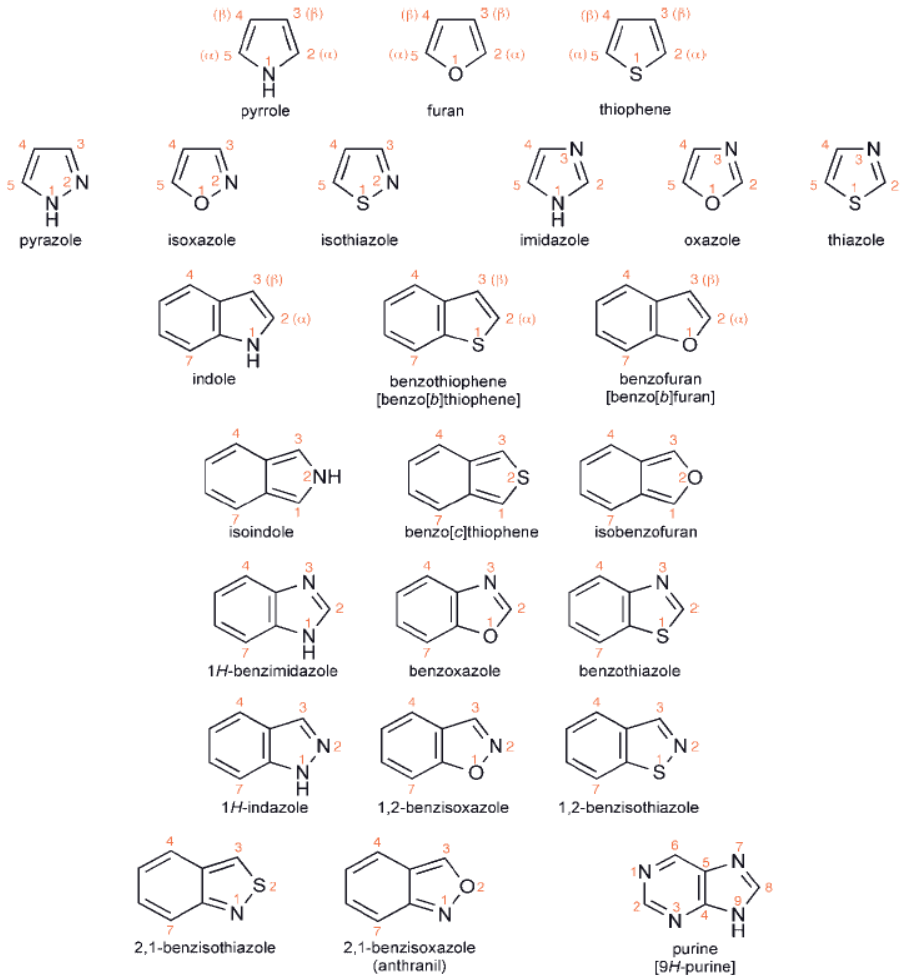
Heterocyclic systems

A cyclic organic compound that contains atoms of two or more elements in its ring is a called a ***heterocycle*** or ***heterocyclic* compound** is one that contains a ring made up of more than one kind of atom.

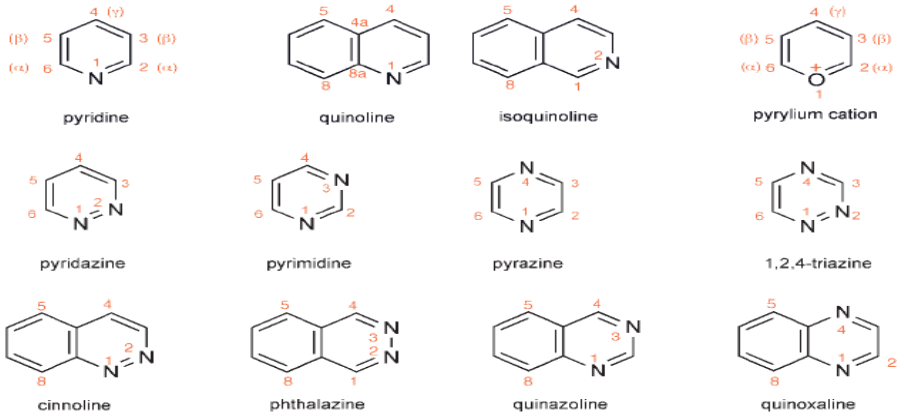
In most of the cyclic compounds that we have studied so far benzene, naphthalene, cyclohexanol, cyclopentadiene the rings are made up only of carbon atoms; such compounds are called ***homocyclic*** or ***alicyclic*** or ***carbocyclic*** compounds.

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

But there are also rings containing, in addition to carbon, other kinds of atoms, most commonly nitrogen, oxygen, or sulfur. For example:



Five-membered aromatic heterocycles



Six-membered aromatic heterocycles

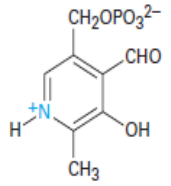
We notice that in the numbering of ring positions, hetero atoms are generally given the lowest possible numbers.

Table 1. Heterocyclic Compounds

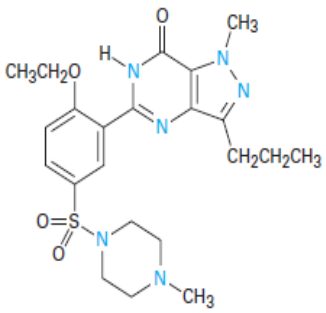
Name	M.p., °C	B.p., °C	Name	M.p., °C	B.p., °C
Furan	− 30	32	Pyridine	− 42	115
Tetrahydrofuran	−108	66	α-Picoline	− 64	128
Furfuryl alcohol		171	β-Picoline		143
Furfural	− 36	162	γ-Picoline		144
Furoic acid	134		Piperidine	− 9	106
Pyrrole		130	Picolinic acid	137	
Pyrrolidine		88	Nicotinic acid	237	
Thiophene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

Significance

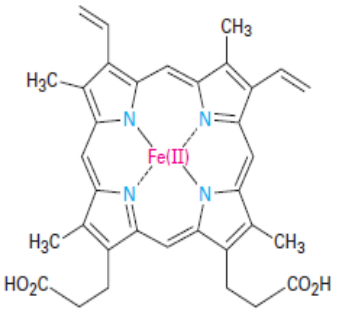
Two thirds of all organic compounds are aromatic heterocycles. Most pharmaceuticals are heterocycles. Heterocyclic amines are particularly common, and many have important biological properties. Pyridoxal phosphate, a coenzyme; sildenafil (Viagra), a well-known pharmaceutical; and heme, the oxygen carrier in blood, are a few examples.



Pyridoxal phosphate
(a coenzyme)



Sildenafil
(Viagra)



Heme

Most heterocycles have the same chemistry as their open-chain counterparts. Lactones and acyclic esters behave similarly, lactams and acyclic amides behave similarly, and cyclic and acyclic ethers behave similarly. In certain cases, however, particularly when the ring is unsaturated, heterocycles have unique and interesting properties.

Actually, we have already encountered numerous heterocyclic compounds: ***cyclic anhydrides*** and ***cyclic imides***, for example: ***lactones*** and ***lactams***; ***cyclic acetals*** of dihydroxy alcohols; the solvents ***dioxane*** and ***tetrahydrofuran***.

In all these, the chemistry is essentially that of their open-chain analogs.

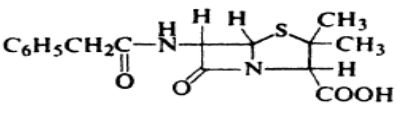
We have encountered three-membered heterocyclic rings which, because of ring strain, are highly reactive: ***epoxides*** and ***aziridines***; the fleeting but important intermediates, ***cyclic halonium ions*** and ***cyclic sulfonium ions***.

Heterocyclic intermediates are being used more and more in synthesis as protecting groups, readily generated and, when their job is done, readily removed. We have seen two examples of this: the temporary incorporation of the carboxyl group into a ***2-oxazoline*** ring and the temporary formation of ***tetrahydropyranyl (THP)*** esters, resistant toward alkali but extremely easily cleaved by acid.

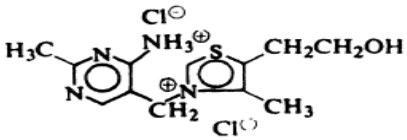
In the biological world carbohydrates are heterocyclic; so are chlorophyll and hemin, which make leaves green and blood red and bring life to plants and animals. Heterocycles form the sites of reaction in many enzymes and coenzymes.

Heredity comes down, ultimately, to the particular sequence of attachment of a half-dozen heterocyclic rings to the long chains of nucleic acids.

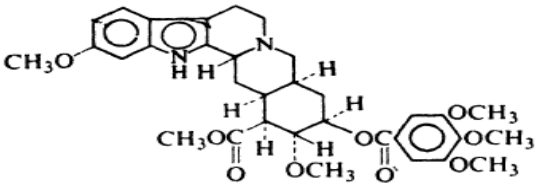
We can get some idea of the importance as well as complexity of heterocyclic systems from the following examples. Some others are ***hemin, nicotinamide adenine dinucleotide***, and ***oxytocin***.



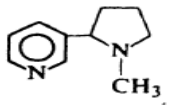
Penicillin G
Antibiotic



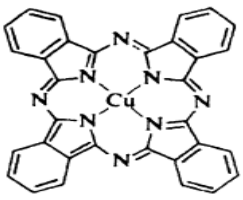
Thiamine
Vitamin B_1
Anti-beriberi factor



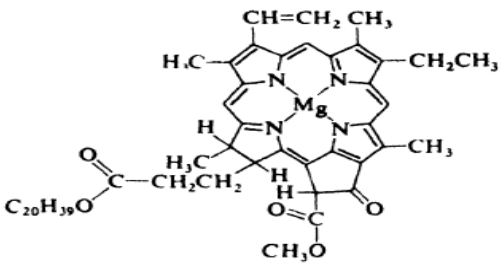
Reserpine
A tranquilizing drug



Nicotine
A tobacco alkaloid



Copper phthalocyanine
A blue pigment



Chlorophyll a
Green plant pigment: catalyst for photosynthesis

Naming Heterocyclic amines

Compounds in which the nitrogen atom occurs as part of a ring are also common, and each different heterocyclic ring system has its own parent name. The heterocyclic nitrogen atom is always numbered as position 1.