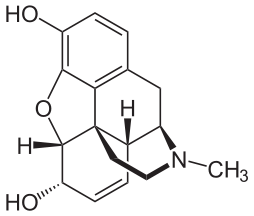
**Heterocyclic Chemistry**

**Lecture Notes ( Phar. 226 )**



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**Preface**

This heterocyclic chemistry was designed for pharmacy students, and assuming that students have a good background in organic chemistry.

The importance of heterocyclic compounds as a functioning part of drug molecules is highly appreciated by the medicinal chemists. The principles of heterocyclic chemistry that will be discussed in this course can help in the understanding of the mechanism of action of such compounds.

The course starts with an introduction, to understand the structure, nomenclature, use, and general properties of heterocyclic compounds. The second part includes synthesis and reactions of aliphatic heterocyclic compounds, with emphasis on three and four member ring compounds. The third part deals with the properties and synthesis of five and six member aromatic heterocyclic compounds, in addition to some medicinally important fused ring compounds.

I would like to thank Dr. AmjadQandil for reading the manuscript, for his valuable suggestions, and his assistance in drawing chemical structures.

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**PART 1**

**1**

**Definitions and Classifications**

**Definitions and Classifications**:

Organic compounds can be divided into two main groups; **acyclic**, these are compounds in which their atoms are attached together to form chains. The other group is **cyclic**, in these compounds the atoms are joined together to form a ring. Cyclic compounds can be subdivided further into: **isocyclic** , the atoms in the cycle are one kind, and called **carbocyclic** if it consists of carbon atoms only in the ring formation; **heterocycle** , these constitute compounds that are cyclic with more than one element as part of the ring structure.

In organic heterocyclic compounds, at least one carbon atom should be present, and any atom other than carbon is called **heteroatom**. Almost any element in the periodic table can be part of the ring structure. The most common heteroatoms are nitrogen then oxygen and sulfur; less common atoms include phosphorous, silicon, germanium, boron, and lead. The smallest ring size is three and there is no upper limit, but the most common are 5 or 6 membered ring structures.

Heterocyclic compounds stability and reactivity can be determined, in principle, by comparison to their carbocyclic analogues, which can be divided into:

1- Saturated, as in piperidine and 1,4-dioxane, they behave as their acyclic analogous (secondary amines).



2- Partially unsaturated, with at least one double bond as part of the ring structure as in the following examples:



The first compound behaves as an alkene and ether, and the next two compounds behave as an imine.

3- Compounds with the maximum number of non cumulated# double bonds, for example: azete, furan, and pyridine



#. Polyenes can be divided into three classes according to the arrangement of the double bonds.

1. Conjugated. Double bonds alternating with single bonds, such as 1,3-butadiene and benzene.



2. Isolated. Double bonds that are separated by more than one single bond, such as 1,4-pentadiene and 1,4-cyclohexadiene.



3. Cumulated. Double bonds that share a carbon, such as 1,2-propadiene and 1,2-cyclohexadiene



Cyclic compounds with cumulated double bonds or compounds containing alkyne functional groups are not included, because of the large angle strain, especially in the small (3-4) and normal (5-7) ring size heterocycles.

Heterocyclic compounds may be divided into two main types

**1- Aliphatic**. These are the cyclic analogues of ethers, amines, sulfides, esters, amides, etc. They have many properties in common with their acyclic analogues, but they have unique properties in small ring structures (3 and 4), which is affected by the strain in the ring.



**2-Aromatic**. These are compounds which have a heteroatom in their ring structure and have some of the properties of benzene.

The properties of benzene include:

a. Benzene is stable and inert compared to a typical alkene. It undergoes electrophilic aromatic substitutions instead of the expected addition reactions typical for an alkene.

b. The heat of hydrogenation is much less than expected. The difference between bond energy of benzene and that of a theoretical cyclohexatriene is called resonance energy (obtained experimentally from the heat of hydrogenation).

c. The bond lengths are between those of a double and that of a single bond. All are equivalent.



The bond length for C---C single bond is 1.54Ao , C=C double is 1.34Aoand in benzene it is 1.4Ao.

Structurally, for any compound to be considered aromatic, it must fulfill all of the following structural requirements below:

1- To be cyclic and planar

2- Each carbon atom in the cycle must have a P orbital, or a heteroatom (N, O, S) if it is not involved with a double bond,it must have a P orbital and two electrons, and parallel with the rest of Porbitals.

3- It must follow Huckel rule of 4n + 2 ( where n is an integer n=0,1,2,3…), which determines the total number of electrons in the overlapping P orbitals that form the electron cloud of the delocalized electrons, and it should be any of these number of electrons 2,6,10,14, etc.

Aromatic heterocyclic compounds are not limited to a certain ring size, but the most important examples are:



Five-membered rings with one heteroatom, or more than one as in the following examples.



Six or more membered ring structures include:



Fused ring heterocyclic structures as in the examples:



Compounds with similar structure as benzene, but has 4n electrons, will be destabilized by delocalization and these compounds are called anti-aromatic. These compounds are unstable, very reactive, and their heat of hydrogenation is higher than expected for an alkene.

Examples on anti-aromatic compounds are:



Seven membered unsaturated ring structures with N, O, or S as the heteroatom are expected to be anti-aromatic,but it was shown that these compounds are not planar and hence similar in properties to polyenes.



Aromatic heterocyclic compounds are considered to be analogous to carbocyclic compounds and can be divided into three types

**1- π -deficient heterocycles**

These are obtained by substituting a heteroatom or more for a carbon in the carbocyclic aromatic compound.

For example, if we substitute one carbon in benzene with nitrogen it produces pyridine, or if two nitrogen atoms, three compounds can be obtained; as shown below.



When naphthalene is selected as the carbocyclic reference the following few examples are obtained



The electronegativity of nitrogen will cause localization of the electron density on the heteroatom(s) resulting in loss of the electron density from the carbon atoms. Because of the decreased electron density on carbon atoms, it is expected that electrophilic aromatic substitution is more difficult than π-neutral compounds.

The π-deficient compounds as in pyridine, exhibit greater dipole moment than piperidine.



This confirms the importance of the resonance structures 3, 4, and 5.



Nucleophilic aromatic substitution reactions, on the other hand, are expected to be easier, due to the decreased electron density on the carbon atoms compared to the neutral aromatic compound (benzene).

**2- π -Excessive heterocycles.**

These are derived by replacing C=C in the carbocyclic aromatic analogue by a heteroatom as in pyrrole, furan, and thiophene or fused derivatives such as indole, benzofuran and benzothiophene.



The heteroatom must have a P orbital, with two electrons, to replace the two π-electrons of the double bond. The 4n + 2 electrons are delocalized over atoms decreased by one (6 carbons in benzene becomes 5; as in pyrrole, furan and thiophene) i.e the electron density on carbon atoms increases.

In π-exessive heterocycles, because of the increased electron density on all carbon atoms, electrophilic aromatic substitutions are expected to be accomplished more readily than their carbocyclic aromatic analogues.

In contrast, nucleophilic aromatic substitution on π-excessive systems is difficult.

Dipole moments of the π-excessive systems should be less in the direction of the heteroatom than the corresponding saturated derivative since the electrons are withdrawn from the heteroatom towards the ring as shown in the following resonance structures.





In pyrrole the direction of the dipole moment is reversed compared to the saturated analogue pyrrolidine.



The large difference reflects the acidic character of NH bond

**3- Mixed aromatic heterocycles**.

In these systems both operations of π-deficient and π-excessive are carried out in the same compound i.e. substituting a carbon for a heteroatom and C=C for another heteroatom.



Imidazole is an example of this kind with properties in between the above two systems in electrophilic or nucleophilic substitutions.

Other examples of mixed systems are the following:

