

Al-Mustaqbal University College  
Department of Pharmacy

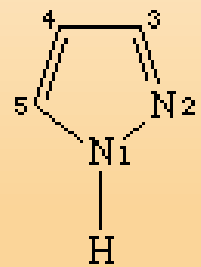


# Organic Chemistry Practical

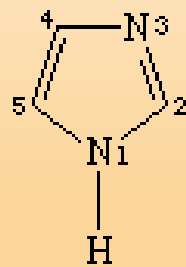
## Lec 7

**Five- and six-membered rings with two or more heteroatoms**

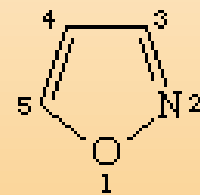
**Dr. Sabrean F. Jawad**



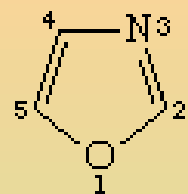
pyrazole



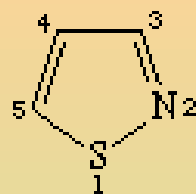
imidazole



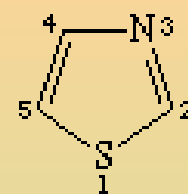
isoxazole



oxazole

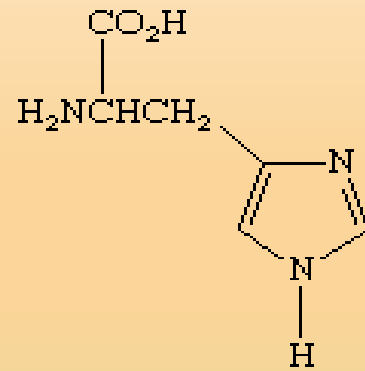


isothiazole

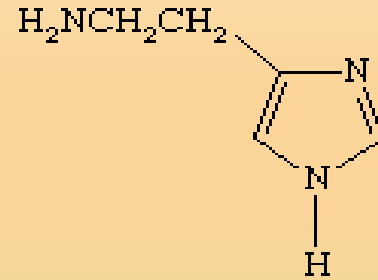


thiazole

Few pyrazoles occur naturally; the compounds of this class are usually prepared by the reaction of hydrazines with 1,3-diketones. Many synthetic pyrazole compounds are of importance as dyes and medicinals. Among them are the fever-reducing analgesic aminopyrine, the anti-inflammatory drug phenylbutazone, used in treating arthritis, the yellow food colour and fibre dye tartrazine, and a series of dyes used as sensitizing agents in colour photography.



histidine



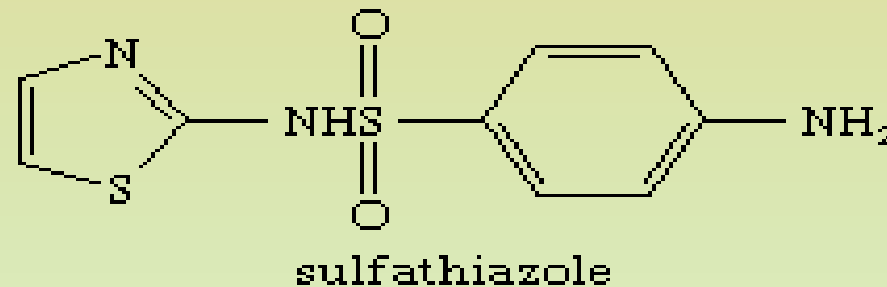
histamine

**Imidazoles** are most important biologically; histidine, for example, is an essential amino acid of particular importance in enzyme reactions. A breakdown product of histidine, called histamine, has a variety of functions in different organisms; in the human body it plays a crucial role in the immune response, including allergic reactions—hence the importance of antihistamine drugs. Histidine and histamine have the structures

Among other naturally occurring compounds with an imidazole nucleus are hydantoin, which is found in beet sap, and allantoin, which is related to the metabolic product uric acid. Hydantoin derivatives, in particular phenytoin, are important antiepileptic drugs. The imidazole ring is also present in the B vitamin biotin (mentioned above for its thiophene unit; *see above* Five-membered rings with one heteroatom).

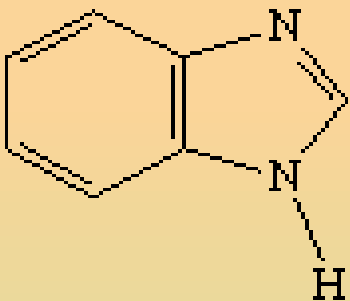
The antibiotic cycloserine, produced by a bacterium, is one of the few naturally occurring isoxazoles. A synthetic isoxazole, hymexazol, has found practical use as soil and seed fungicide.

Thiazoles are of great biological importance. This ring system occurs in thiamin (thiamine, vitamin B<sub>1</sub>), the bacitracin and penicillin antibiotics (from a bacterium and a mold, respectively), and in numerous synthetic drugs, dyes, and industrial chemicals. Synthetic drugs belonging to the thiazole family include the antimicrobial agents sulfathiazole and acinitrazole, the antidepressant pramipexole, and the antiasthmatic drug cinalukast. Sulfathiazole has the structure:



Other thiazole compounds include rhodanine, the dye rhodanine red derived from it, and the yellow dye primuline.

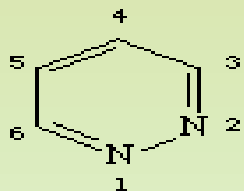
Most bicyclic systems derived from these five-membered rings are named systematically—that is, by use of the prefix benz- or benzo- to indicate the presence of the benzene ring. Benzimidazole, for example, is the name for the compound:



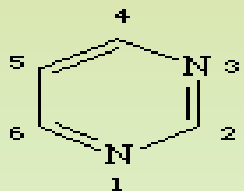
benzimidazole

A benzimidazole unit occurs in vitamin B<sub>12</sub>. Benzothiazole derivatives are used for accelerating the vulcanization of rubber (2-mercaptobenzothiazole), as herbicides (benazolin, mefenacet), and as fungicides and antihelminthic drugs (thiabendazole).

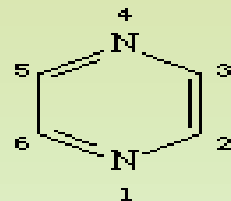
The three monocyclic diazines—six-membered ring compounds with two nitrogen heteroatoms—are named and numbered as shown.



pyridazine

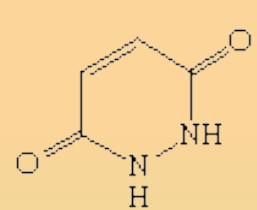


pyrimidine

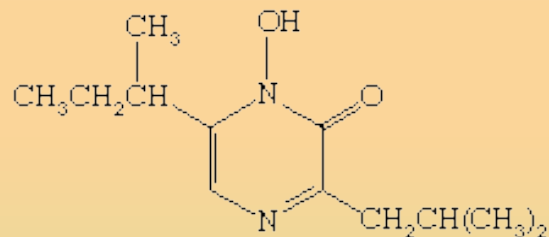


pyrazine

The pyridazine derivative maleic hydrazide is a herbicide, and some pyrazines occur naturally—the antibiotic aspergillilic acid, for example. The structures of the aforementioned compounds are:



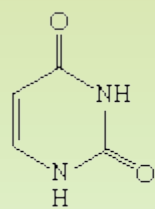
maleic hydrazide



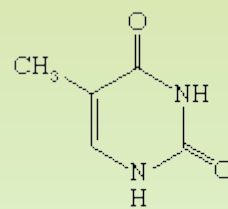
aspergillilic acid

The pyrazine ring is a component of many polycyclic compounds of biological or industrial significance. Important members of the pyrazine family include pteridines, alloxazines, and phenazines, which are discussed below in this section.

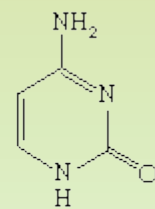
Biologically and pharmacologically, however, the most important diazines are the pyrimidines. Uracil, thymine, and cytosine, for example, with the structures shown, are three of the five nucleotide bases that constitute the genetic code in DNA and RNA.



uracil



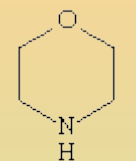
thymine



cytosine

The vitamin thiamin contains a pyrimidine ring (in addition to the five-membered thiazole ring mentioned above), and synthetic barbiturates such as amobarbital (amylobarbitone) are widely used drugs.

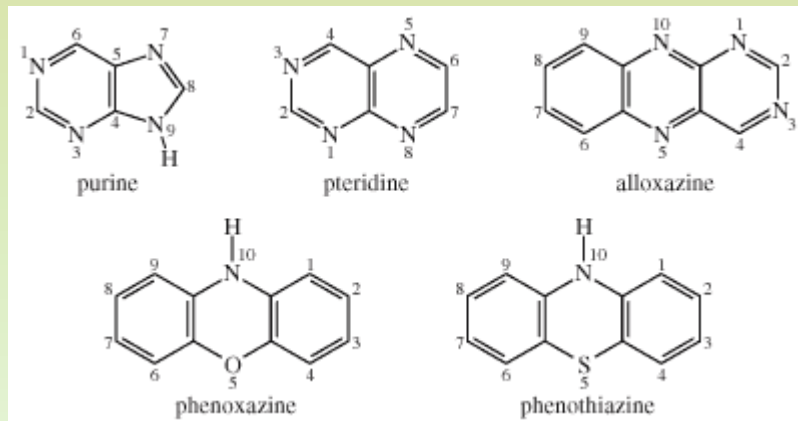
Various oxazine and thiazine derivatives are known, but monocyclic thiazines are as yet of little importance. The parent tetrahydro-1,4-oxazine, commonly called morpholine, is produced on a large scale for use as a solvent, corrosion inhibitor, and fungicide. The morpholine ring is also present in the sedative-hypnotic drug trimetozine and in some fungicides such as tridemorph and fenpropimorph. The structural formula for morpholine is:



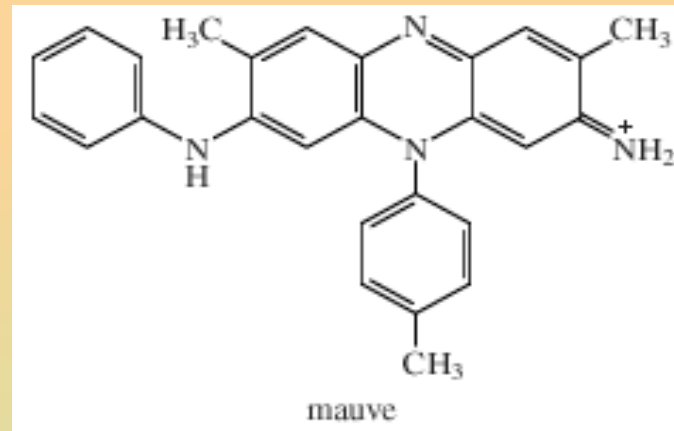
morpholine

The benzodiazines are polycyclic compounds containing one or more benzene rings fused to a diazine ring. Many have common names—e.g., cinnoline, quinazoline, and phenazine.

Five other polycyclic systems in this general family are of significance, their names, structures, and numbering systems being:

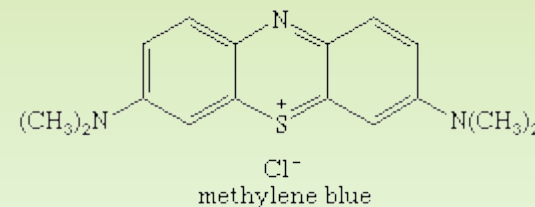


Quinoxaline alkaloids exist, and there are some phenazine natural products. Phenazine dyes are used for fabrics (for example, indanthrones and anthraquinone vat dyes; *see* anthraquinone dye) and for inks and printer toners (nigrosines). The first synthetic phenazine dye, mauve (aniline purple), is historically important; its structure is:



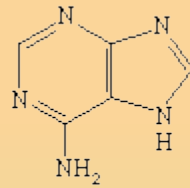
The phenoxazine system is a chromophoric (colour-imparting) part of the molecular structures of the naturally occurring actinomycin antibiotics, which are yellow-red in colour. Many polycyclic compounds containing a phenoxazine ring are used as biological stains, fabric dyes, and light-emitting materials in dye lasers (e.g., cresyl violet and nile blue).

Phenothiazine has been used as a worming agent for livestock and as an insecticide. Drugs of the phenothiazine type include the antipsychotic agents chlorpromazine and thioridazine, the long-acting antihistamine promethazine, and ethopropazine, used in treatment of parkinsonism. A large group of dyes have the phenothiazine structure, including methylene blue, a substance widely used as a biological stain and an oxidation-reduction indicator. The structure of methylene blue is:

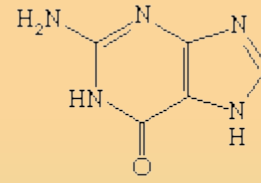




Biologically, the purines and pteridines are the most important polycyclic diazines. Purine itself is not common, but the purine structure is present in many natural substances. Two purine nucleotide bases, adenine and guanine, occur together with the pyrimidine bases in DNA and RNA mentioned above.

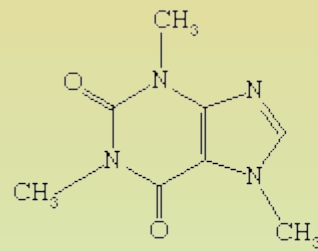


adenine

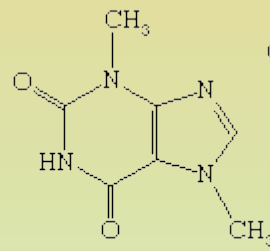


guanine

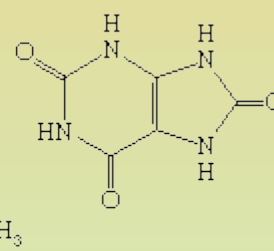
Other natural purines include the alkaloids xanthine and caffeine (found in tea, coffee, and cocoa), the alkaloid theobromine (found in cocoa), and uric acid. The structures of caffeine, theobromine, and uric acid are:



caffeine

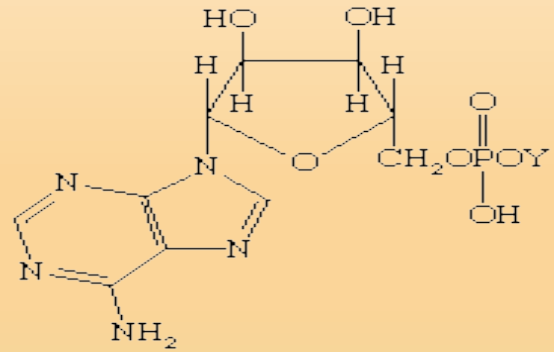


theobromine



uric acid

Adenosine monophosphate, diphosphate, and triphosphate (AMP, ADP, and ATP, respectively) are important participants in energy processes in the living cell. Each of the compounds is composed of the nucleotide base adenine linked to the sugar ribose, which in turn is linked to a linear “tail” of one, two, or three phosphate groups, respectively, as shown.

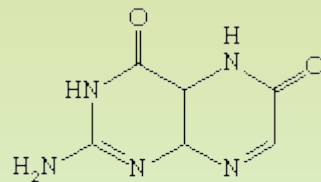


adenosine monophosphate: Y = H

adenosine diphosphate: Y = PO<sub>3</sub>H<sub>2</sub>

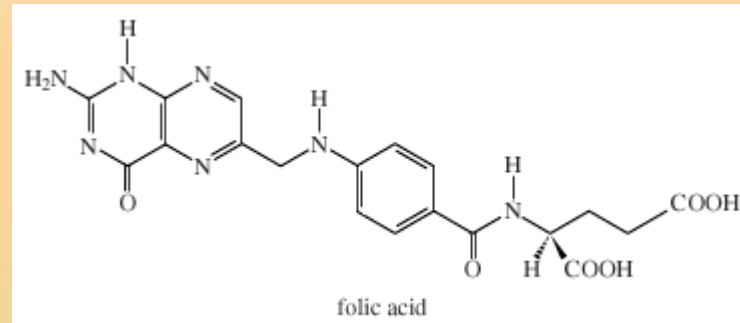
adenosine triphosphate: Y = P<sub>2</sub>O<sub>6</sub>H<sub>3</sub>

The biological significance of pteridine compounds (from Greek *pteron*, “wing”) has become apparent since the first known members of the group were discovered as pigments of butterfly wings. One example is the yellow pigment 2-amino-4,6-pteridinedione (xanthopterin).



2-amino-4,6-pteridinedione

Folic acid, also a pteridine, is a B-complex vitamin and an important growth factor.



Riboflavin, or vitamin B<sub>2</sub>, is a derivative of alloxazine.

