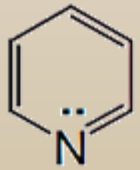
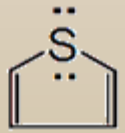
4.0 Heterocyclic compounds and their derivatives

Cyclic compounds that have one or more of atoms other than carbon, e.g. N, O or S (hetero-atoms), in their rings are called *heterocyclic compounds* or *heterocycles*, e.g. pyridine, tetrahydrofuran, thiophene and so on.



Pyridine
N is the hetero-atom

Tetrahydrofuran
O is the hetero-atom

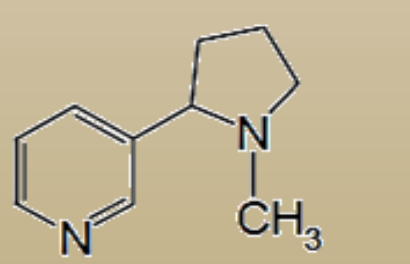


Thiophene
S is the hetero-atom

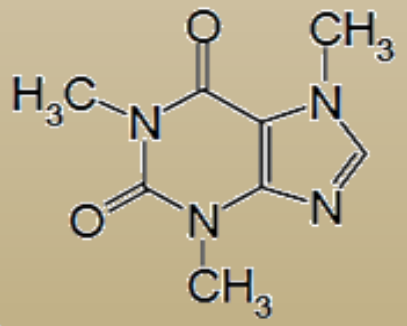
Among the heterocyclic compounds, there are aromatic, e.g. pyridine, as well as nonaromatic, e.g. tetrahydrofuran, compounds. Similarly, there are saturated (e.g. tetrahydrofuran) and unsaturated (e.g. pyridine) heterocyclic compounds. Heterocycles also differ in their ring sizes, e.g. pyridine has a six-membered ring, whereas tetrahydrofuran is a five-membered oxygen-containing heterocyclic compound.

4.1 Medicinal importance of heterocyclic compounds

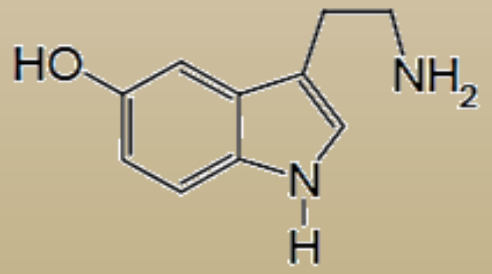
More than 50% of all known organic compounds are *heterocyclic compounds*. They play important roles in medicine and biological systems. A great majority of important drugs and natural products, e.g. caffeine, nicotine, morphine, penicillins and cephalosporins, are heterocyclic compounds. The purine and pyrimidine bases, two nitrogenous heterocyclic compounds, are structural units of RNA and DNA. Serotonin, a neurotransmitter found in our body, is responsible for various bodily functions.



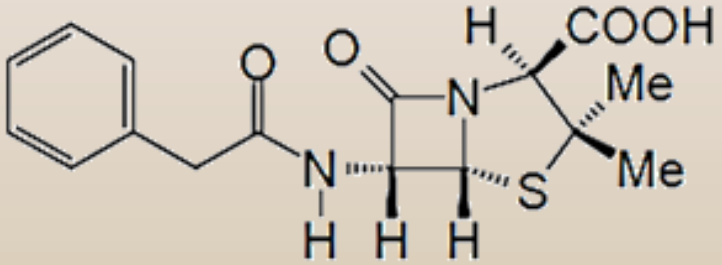
Nicotine
An alkaloid found in tobacco leaves



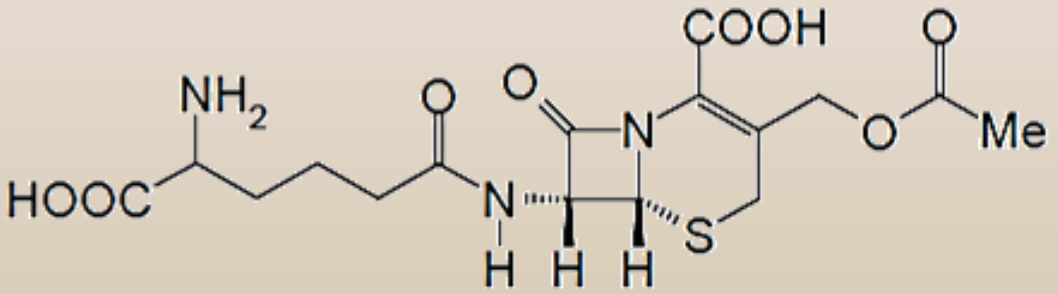
Caffeine
A natural stimulant found in
tea leaves, coffee beans and cola nuts



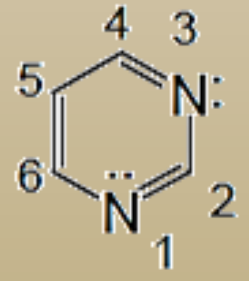
Serotonin
A natural neurotransmitter



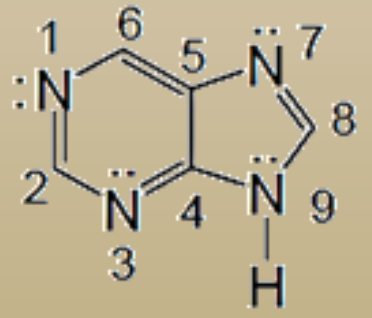
Penicillin G
An antibiotic



Cephalosporin C
An antibiotic



Pyrimidine
A structural unit of RNA and DNA



Purine
A structural unit of RNA and DNA

4.2 Nomenclature of heterocyclic compounds

Most of the heterocycles are known by their trivial names, e.g. pyridine, indole, quinoline, thiophene and so on. However, there are some general rules to be followed in a heterocycle, especially in the use of suffixes to indicate the ring size, saturation or unsaturation as shown in the following table. For example, from the name, *pyridine*, where the suffix is -*ine*, one can understand that this heterocyclic compound contains nitrogen, has a six-membered ring system and is unsaturated.

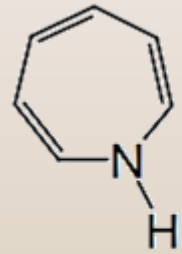
	Ring with nitrogen		Ring without nitrogen	
Ring size	*Maximum unsaturation*	*Saturation*	*Maximum unsaturation*	*Saturation*
3	irine	iridine	irene	irane
4	ete	etidine	ete	etane
5	ole	olidine	ole	olane
6	ine	–	ine	ane
7	epine	–	epine	epane
8	ocine	–	ocine	ocane
9	onine	–	onine	onane
10	ecine	–	ecine	ecane

Monocyclic heterocycles containing three to ten members, and one or more hetero-atoms, are named systematically by using a prefix or prefixes to indicate the nature of the hetero-atoms as presented in the following table. For example, ***thia*cyclobutane** contains the hetero-atom sulphur (S).

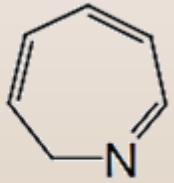
Element	Prefix	Element	Prefix	Element	Prefix
O	oxa	P	phospha	Ge	germa
S	thia	As	arsa	Sn	stanna
Se	selena	Sb	stiba	Pb	plumba
Te	tellura	Bi	bisma	B	bora
N	aza	Si	sila	Hg	mercura

Two or more identical hetero-atoms are indicated by use of the multiplying prefixes *di*-, *tri*- or *tetra*-. When more than one distinct hetero-atom is present, the appropriate prefixes are cited in the name in descending order of group number in the periodic table, e.g. *oxa*- takes precedence over *aza*-. If both lie within the same group of the periodic table, then the order is determined by increasing atomic number, e.g. *oxa*- precedes *thia*-.

In unsaturated heterocycles, if the double bonds can be arranged in more than one way, their positions are defined by indicating the N or C atoms that are not multiply bonded, and consequently carry an ‘extra’ hydrogen atom, by 1H-, 2H- and so on, for example 1H-azepine and 2H-azepine.

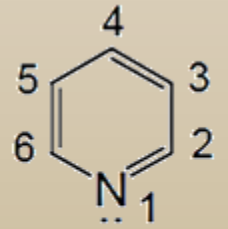


1H-Azepine

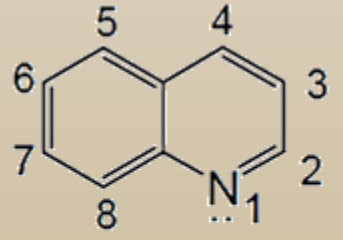


2H-Azepine

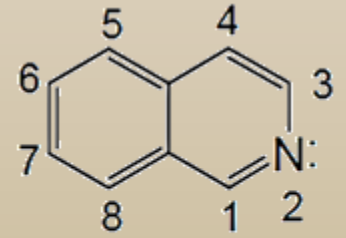
Important aromatic heterocycles that contain a single hetero-atom include pyridine, quinoline, isoquinoline, pyrrole, thiophene, furan and indole.



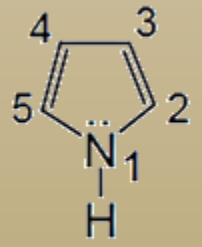
Pyridine



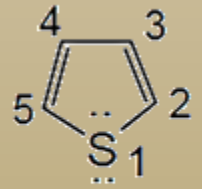
Quinoline



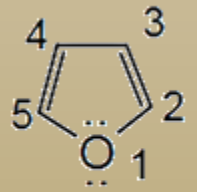
Isoquinoline



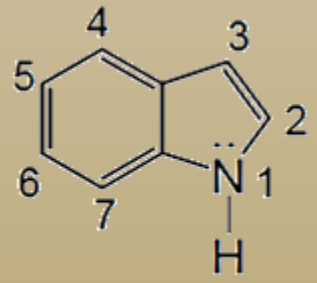
Pyrrole



Thiophene

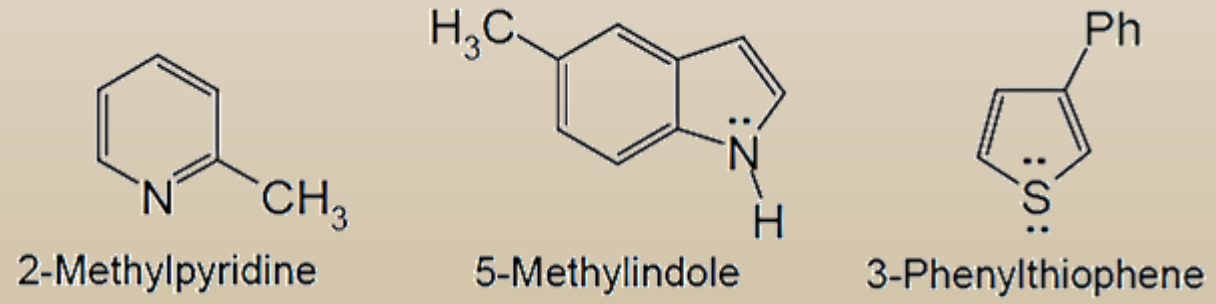


Furan



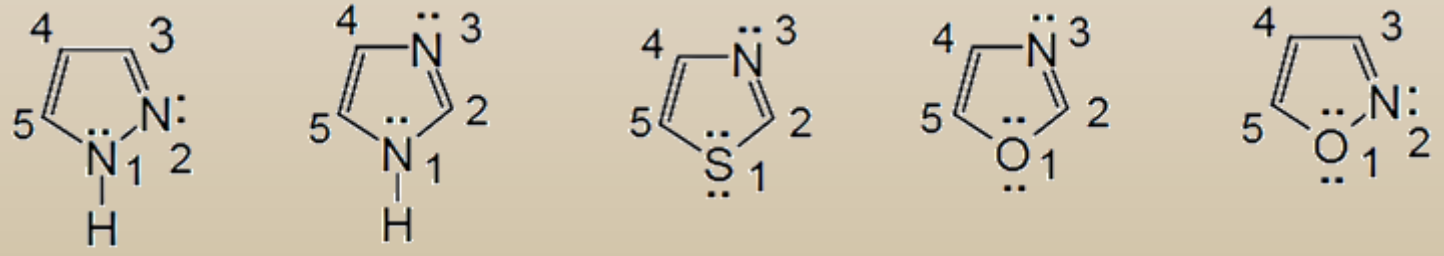
Indole

Derivatives of these heterocyclic compounds are named in the same way as other compounds, by adding the name of the substituent, in most cases as a prefix to the name of the heterocycle, and a number to indicate its position on the ring system, e.g. 2-methylpyridine, 5-methylindole and 3-phenylthiophene.

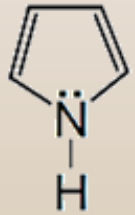
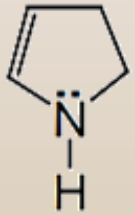
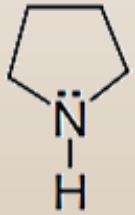
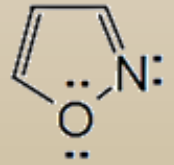
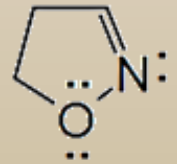
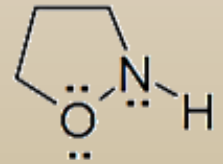
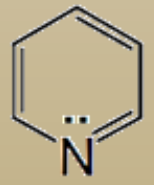
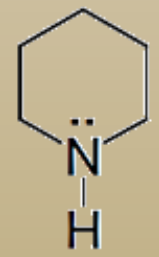


Heterocyclic aromatic compounds can also have two or more hetero-atoms. If one of the hetero-atoms is a nitrogen atom, and the compound has a five membered system, their names all end in -*azole*, and the rest of the name indicates other hetero-atoms. For example, pyrazole and imidazole are two isomeric heterocycles that contain two nitrogen atoms in the ring, thiazole has a sulphur atom and a nitrogen atom in the ring, and oxazole contains an oxygen atom and a nitrogen atom.

In imidazole and oxazole, two heteroatoms are separated by a carbon atom, whereas in their isomers, pyrazole and isoxazole, the hetero-atoms are directly linked to each other. The six-membered aromatic heterocycles with two nitrogens can exist in three isomeric forms, the most important being pyrimidine.



There are a number of fully saturated nonaromatic heterocycles. For example, pyrrolidine, tetrahydrofuran, isoxazolidine and piperidine are fully saturated derivatives of pyrrole, furan, isoxazole and pyridine, respectively. Partially saturated derivatives, e.g. 2-pyroline, 2-isoxazoline and 1,4-dihydropyridine, are also known.

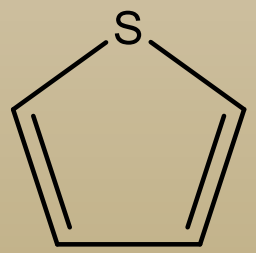
Unsaturated	Partially saturated	Fully saturated
 Pyrrole	 2-Pyrroline	 Pyrrolidine
 Isoxazole	 2-isoxazoline	 Isoxazolidine
 Pyridine	 1,4-Dihydropyridine	 Piperidine

4.3 Physical properties of heterocyclic compounds

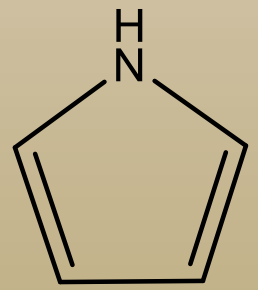
A large number of structurally diverse compounds belong to the class *heterocycles*. This makes it extremely difficult to generalize the physical properties of these compounds, because they vary significantly depending on the saturation–unsaturation status, aromatic–nonaromatic behaviour, ring sizes and type and number of hetero-atoms present. Saturated heterocycles, known as *alicyclic heterocycles*, containing five or more atoms have physical and chemical properties typical of acyclic compounds that contain the same hetero-atoms. These compounds undergo the same reactions as their open chain analogues. On the other hand, aromatic heterocycles display very characteristic and often complex reactivity. However, aromatic heterocycles show general patterns of reactivity associated with certain ‘molecular fragments’ such that the reactivity of a given heterocycle can be anticipated. Physical and chemical properties of selected important heterocyclic compounds are discussed under each compound sub-heading.

4.4 Pyrrole, Furan and Thiophene: Five-membered unsaturated heterocycles

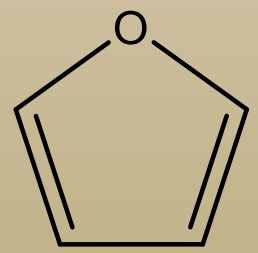
Pyrrole is a nitrogen-containing unsaturated five-membered heterocyclic aromatic compound. It shows aromaticity by delocalization of a lone pair of electrons from nitrogen. In pyrrole, there are four π electrons, two short of the Huckel criteria for aromaticity. The nitrogen atom is sp^2-hybridized, formally containing a lone pair of electrons in the *p* orbital at right angles to the ring. However, the system delocalizes and pushes the lone pair of electrons into the ring to complete the sextet required for aromaticity. The nonbonding electrons on the nitrogen atom become a part of the aromatic sextet.



thiophene



pyrrole



furan

4.4.1 Physical properties of pyrrole, furan and thiophene

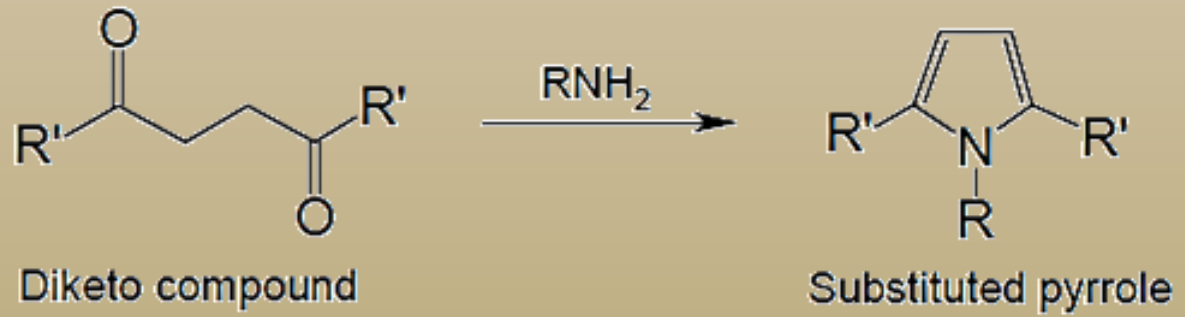
Pyrrole is a weakly basic compound. However, as the nonbonding electrons on the nitrogen atom are part of the aromatic sextet.

Furan and thiophene are both clear and colorless liquids at room temperature. While furan is extremely volatile and highly flammable with a boiling point close to room temperature (31.4 ^{o}C), the boiling point of thiophene is 84 ^{o}C. Thiophene possesses a mildly pleasant odor.

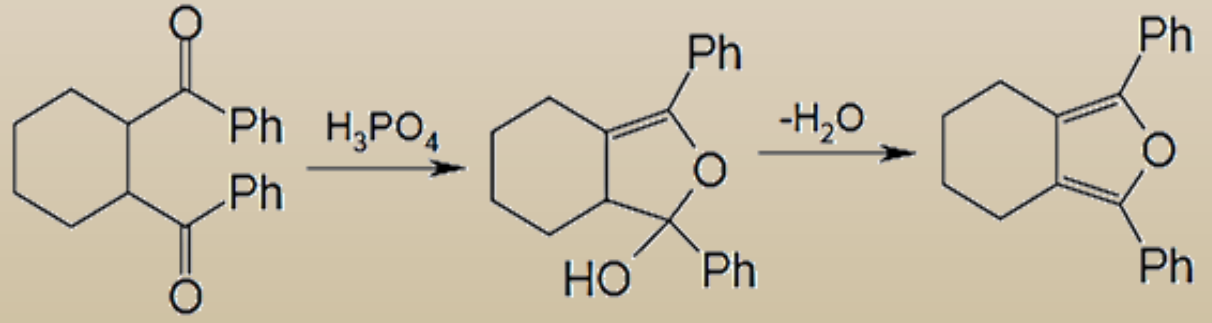
4.4.2 Preparation of pyrrole, furan and thiophene

A general way of synthesizing heterocyclic compounds is by cyclization of a dicarbonyl or diketo compound using a nucleophilic reagent that introduces the desired hetero-atom.

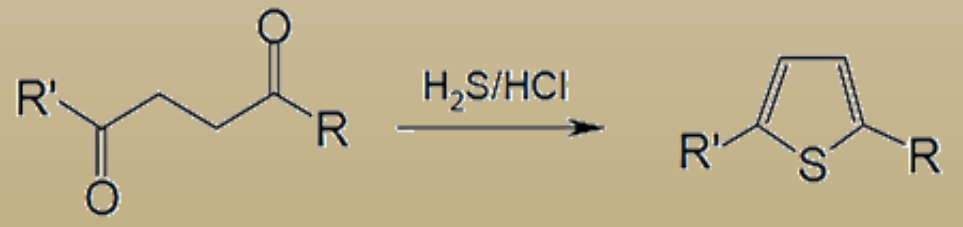
Paal–Knorr synthesis: It is a useful and straightforward method for the synthesis of five-membered heterocyclic compounds, e.g. pyrrole, furan and thiophene. However, necessary precursors, e.g. dicarbonyl compounds, are not readily available. Ammonia, primary amines, hydroxylamines or hydrazines are used as the nitrogen component for the synthesis of pyrrole.



Paal–Knorr synthesis can also be used to synthesize furan and thiophene ring systems. A simple dehydration of a 1,4-dicarbonyl compound provides the furan system, whereas thiophene or substituted thiophenes can be prepared by treating 1,4-dicarbonyl compounds with hydrogen sulphide (H_2S) and hydrochloric acid (HCl).



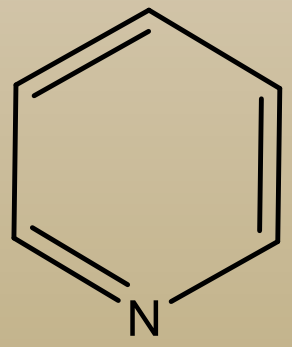
Substituted dihydrofuran system Substituted furan system



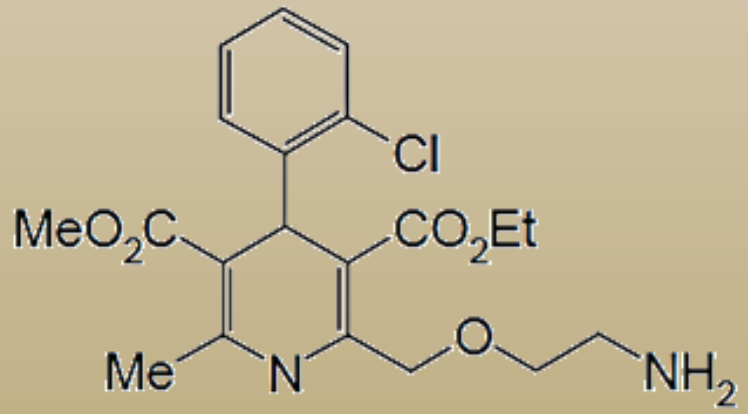
Diketo compound Substituted thiphene

4.5 Pyridine

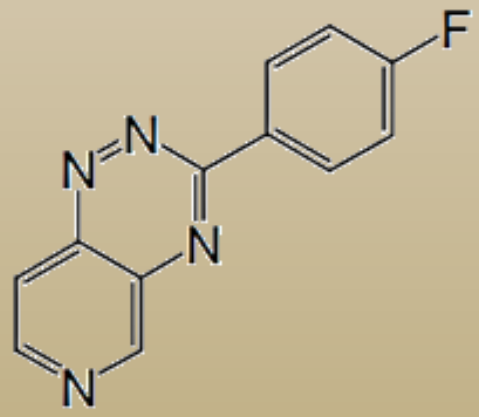
Pyridine (C_5H_5N) is a nitrogen-containing unsaturated six-membered heterocyclic aromatic compound. It is similar to benzene, and conforms to Huckel's rule for aromaticity. Pyridine, a tertiary amine, has a lone pair of electrons instead of a hydrogen atom, but the six π electrons are essentially the same as benzene. A number of drug molecules possess pyridine or a modified pyridine skeleton in their structures, e.g. the antihypertensive drug amlodipine and the antifungal drug pyridotriazine.



pyridine



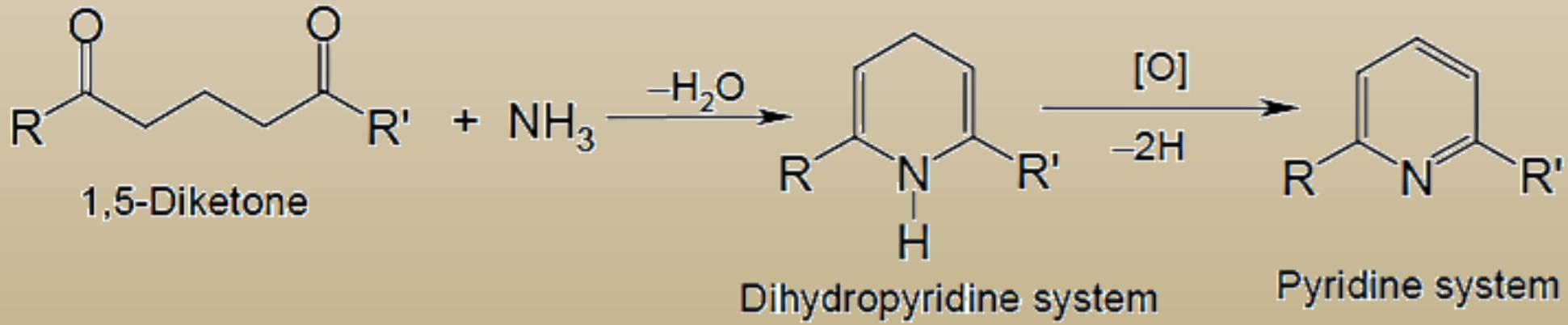
Amlodipine
An antihypertensive agent



Pyridotriazine
An antifungal drug

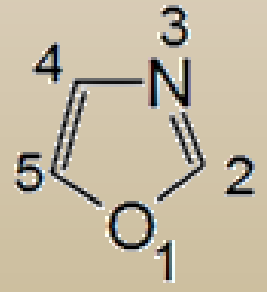
Preparation of pyridine

Cyclization of 1,5-diketones The reaction between 1,5-diketones and NH_3 produces dihydropyridine systems, which can easily be oxidized to pyridines.



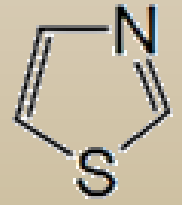
4.6 Oxazole, imidazole and thiazole

Oxazole, imidazole and thiazole systems contain a five-membered ring and two hetero-atoms, one of which is a nitrogen atom. The hetero-atoms are separated by a carbon atom in the ring. The second hetero-atoms are oxygen, nitrogen and sulphur for oxazole, imidazole and thiazole systems, respectively.



Oxazole

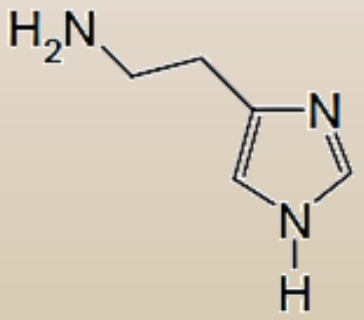
Imidazole



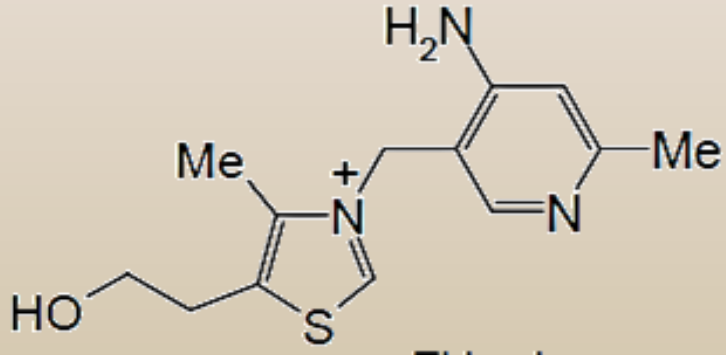
Thiazole

These compounds are isomeric with the 1,2-azoles, e.g. isoxazole, pyrazole and isothiazole. The aromatic characters of the oxazole, imidazole and thiazole systems arise from delocalization of a lone pair of electrons from the second hetero-atom.

Histamine, an important mediator of inflammation, gastric acid secretion and other allergic manifestations, contain an imidazole ring system. Thiamine, an essential vitamin, possesses a quaternized thiazole ring.

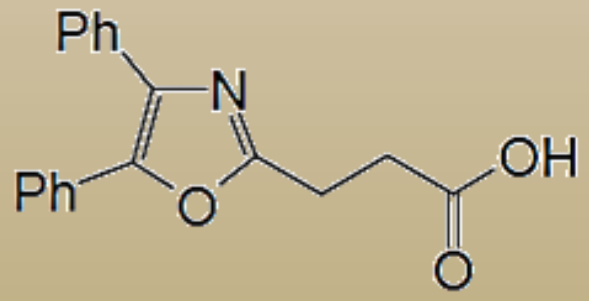


Histamine



Thiamine

Apart from some plant and fungal secondary metabolites, the occurrence of oxazole ring system in nature is rather limited. However, the following anti-inflammatory drug contains an oxazole ring system.



An anti-inflammatory drug

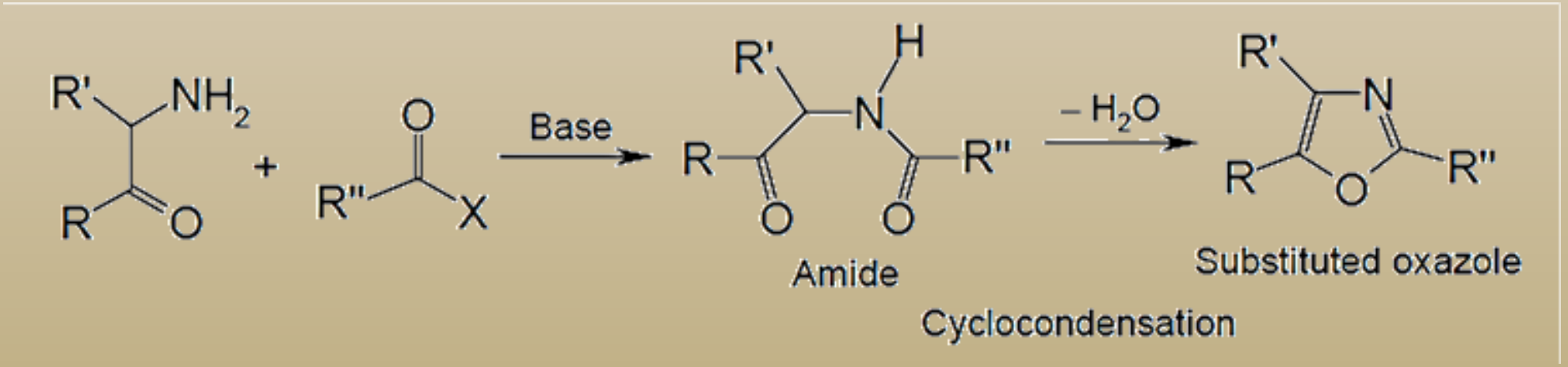
Physical properties of oxazole, imidazole and thiazole

Among these 1,3-azoles, imidazole is the most basic compound. The increased basicity of imidazole can be accounted for from the greater electron-releasing ability of two nitrogen atoms relative to a nitrogen atom and a hetero-atom of higher electronegativity. Some of the physical properties of these compounds are presented below.

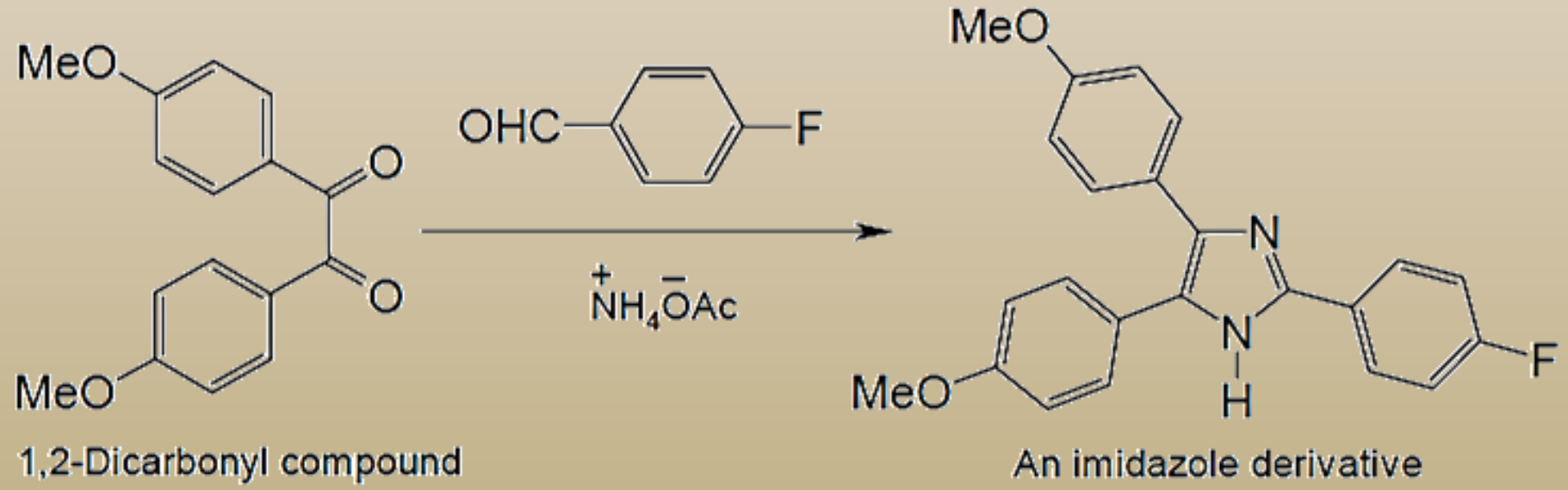
1,3-azoles	pK_a	b.p. (°C)	Water solubility	Physical state
Oxazole	0.8	69–70	Sparingly soluble	Clear to pale yellow liquid
Imidazole	7.0	255–256	Soluble	Clear to pale yellow crystalline flake
Thiazole	2.5	116–118	Sparingly soluble	Clear to pale yellow liquid

Preparation of oxazole, imidazole and thiazole

Preparation of oxazole Cyclocondensation of amides, through dehydration, leads to the formation of corresponding oxazoles. This synthesis is known as Robinson-Gabriel synthesis. A number of acids or acid anhydrides, e.g. phosphoric acid, phosphorus oxychloride, phosgene and thionyl chloride, can bring about this dehydration.



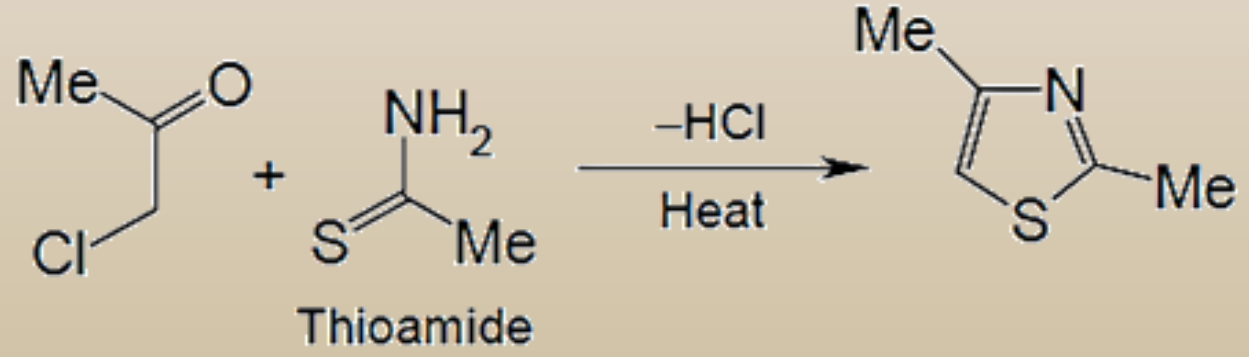
Preparation of imidazole The condensation of a 1,2-dicarbonyl compound with ammonium acetate and an aldehyde results in the formation of an imidazole skeleton.



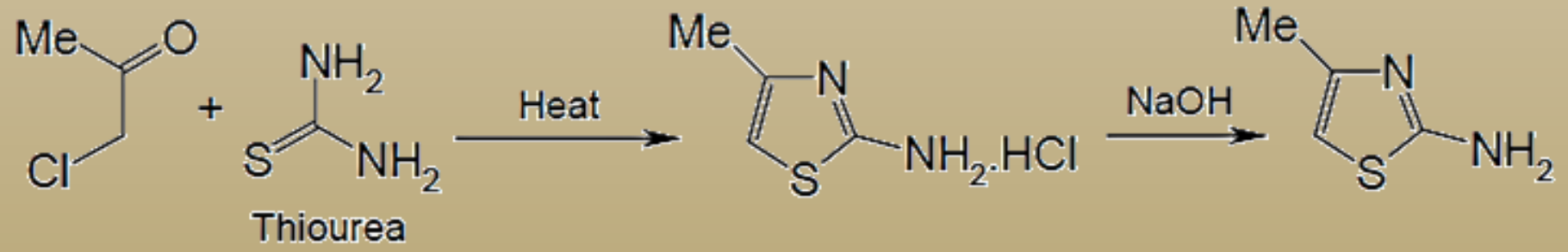
1,2-Dicarbonyl compound

An imidazole derivative

Preparation of thiazole *Hantzsch synthesis* can be applied to synthesize the thiazole system from thioamides. The reaction involves initial nucleophilic attack by sulphur followed by a cyclocondensation.

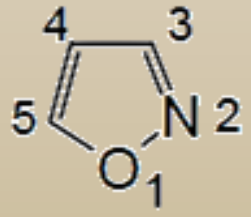


A modification of the above method involves the use of thiourea instead of a thioamide.

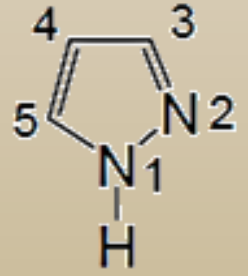


4.7 Isoxazole, pyrazole and isothiazole

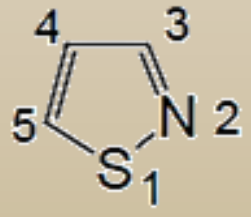
Isoxazole, pyrazole and isothiazole constitute the 1,2-azole family of heterocycles that contain two hetero-atoms, one of which is a nitrogen atom. The second hetero-atom is oxygen, nitrogen or sulphur, respectively, for isoxazole, pyrazole and isothiazole. The aromaticity of these compounds is due to the delocalization of a lone pair of electrons from the second hetero-atom to complete the aromatic sextet.



Isoxazole

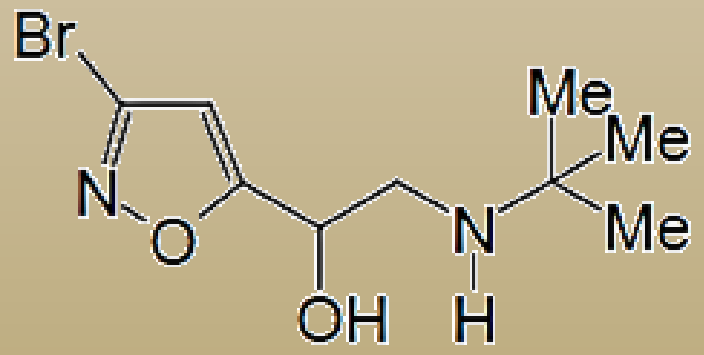


Pyrazole



Isothiazole

The 1,2-azole family of heterocycles is important in medicine. For example, the following drug used in the treatment of bronchial asthma possesses a substituted isoxazole system.



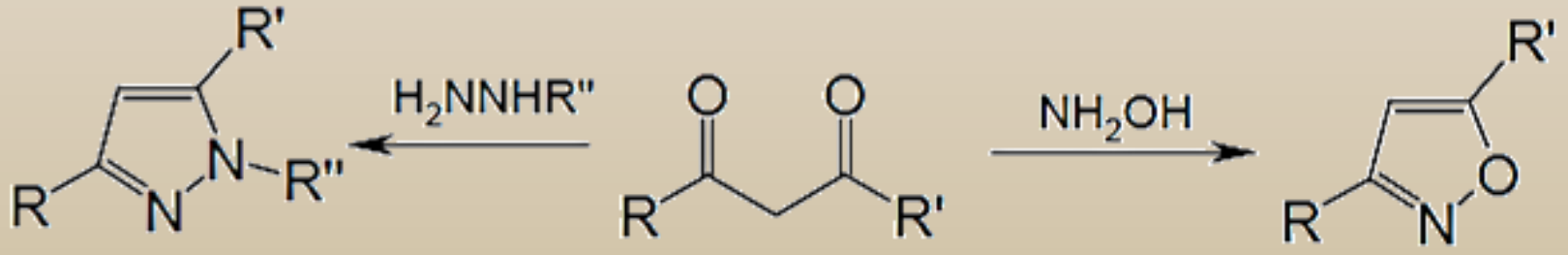
Physical properties of isoxazole, pyrazole and isothiazole

The 1,2-azoles are basic compounds because of the lone pair of electrons on the nitrogen atom, which is available for protonation. However, these compounds are much less basic than their isomers, 1,3-azoles, owing to the electron-withdrawing effect of the adjacent hetero-atom. Some of the physical properties of these compounds are as follows.

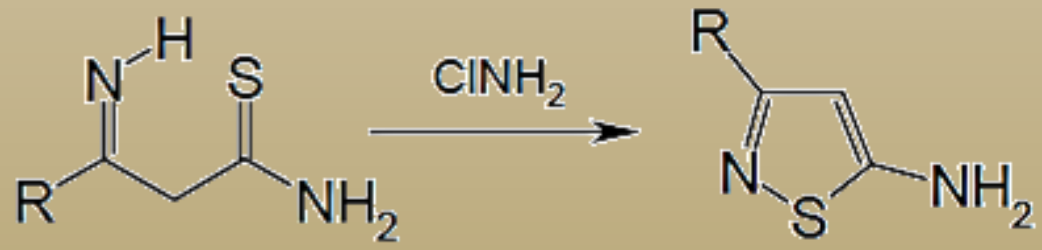
1,2-azoles	pK_a	b.p. (°C)	m.p. (°C)	Physical state
Isoxazole	−2.97	95	–	Liquid
Pyrazole	2.52	186–188	60–70	Solid
Isothiazole	–	114	–	Liquid

Preparation of isoxazole, pyrazole and isothiazole

Isoxazole and pyrazole synthesis While 1,3-diketones undergo condensation with hydroxylamine to produce isoxazoles, with hydrazine they yield corresponding pyrazoles.

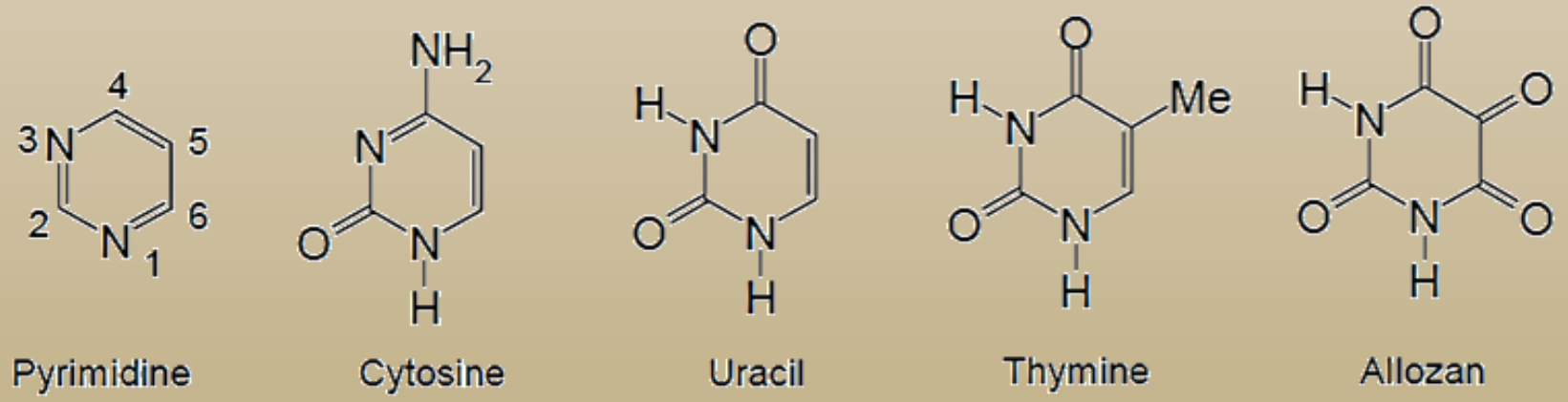


Isothiazole synthesis Isothiazole can be prepared from thioamide in the following way.

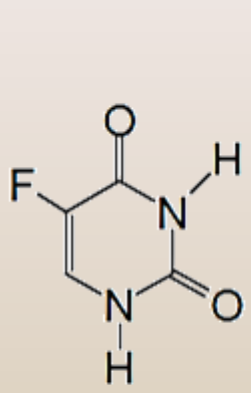


4.8 Pyrimidine

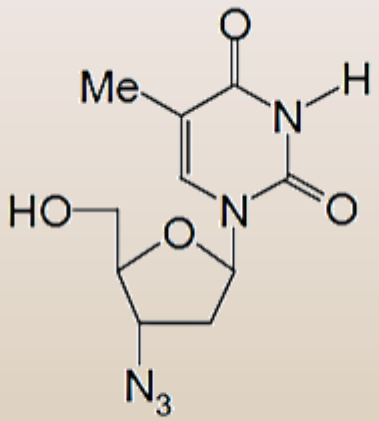
Pyrimidine is a six-membered aromatic heterocyclic compound that contains two nitrogen atoms, separated by a carbon atom, in the ring. Nucleic acids, DNA and RNA, contain substituted purines and pyrimidines. Cytosine, uracil, thymine and alloxan are just a few of the biologically significant modified pyrimidine compounds, the first three being the components of the nucleic acids.



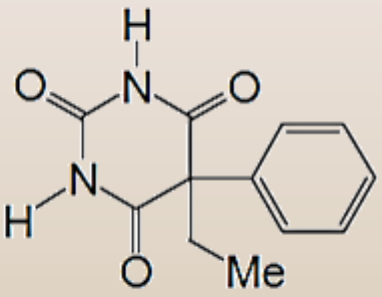
A number of drug molecules contain a modified pyrimidine skeleton, the best known examples being the anticancer drug 5-fluorouracil, which is structurally similar to thymine, the antiviral drug AZT, currently being used in the treatment of AIDS, and phenobarbital, a well known sedative.



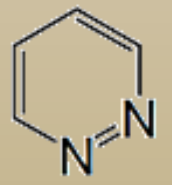
5-Fluorouracil
An anticancer drug



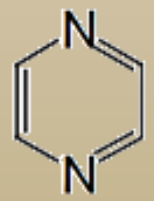
AZT
An antiviral drug



Phenobarbital
A sedative



Pyridiazine

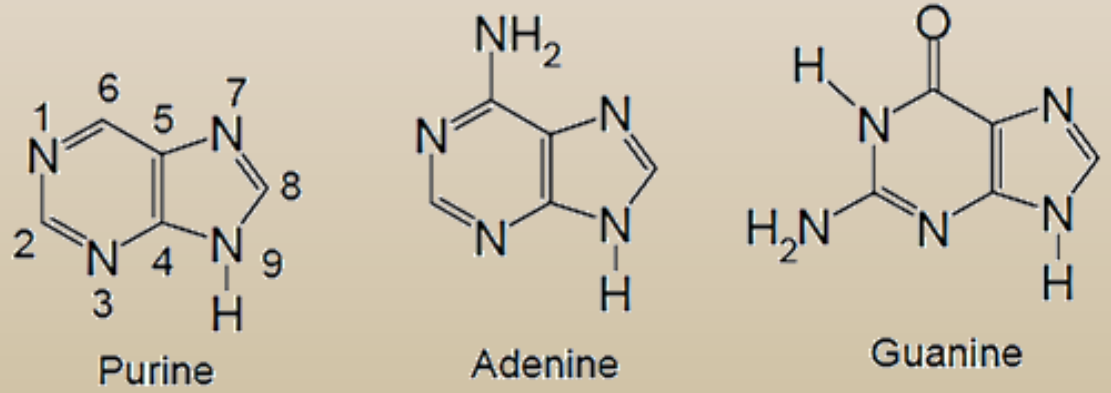


Pyrazine

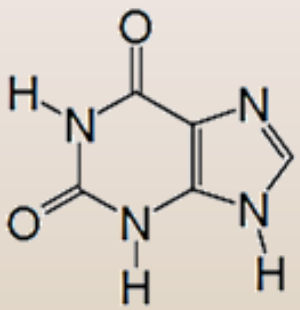
Two positional isomers of pyrimidine are pyridiazine and pyrazine, which only differ Structurally from pyrimidine in terms of the position of the nitrogen atoms in the ring. These three heterocycles together with their derivatives are known as diazines.

4.9 Purine

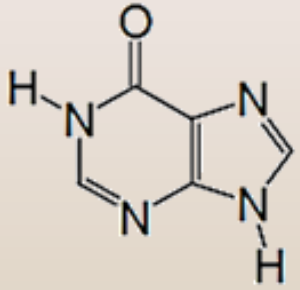
Purine contains a pyrimidine ring fused with an imidazole nucleus. Guanine and adenine are two purine bases that are found in nucleic acids, DNA and RNA.



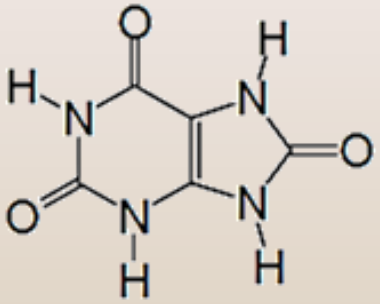
Several purine derivatives are found in nature, e.g. xanthine, hypoxanthine and uric acid. The pharmacologically important (CNS-stimulant) xanthine alkaloids, e.g. caffeine, theobromine and theophylline, are found in tea leaves, coffee beans and coco. The actual biosynthesis of purines involves construction of a pyrimidine ring onto a pre-formed imidazole system.



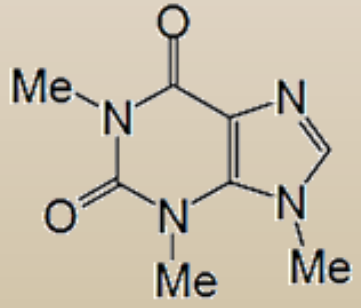
Xanthine



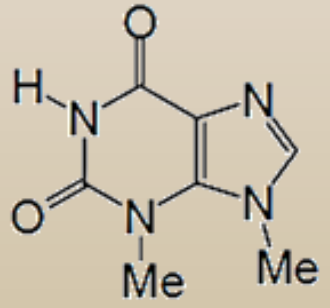
Hypoxanthine



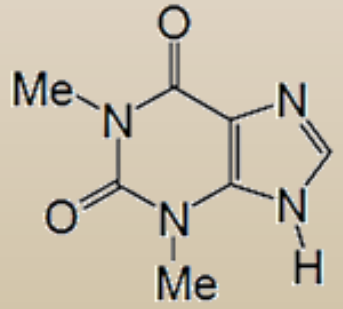
Uric acid



Caffeine



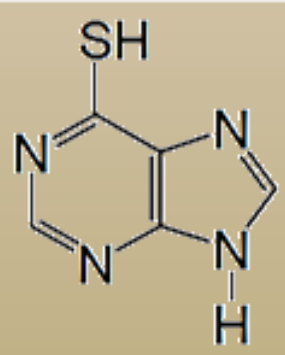
Theobromine



Theophylline

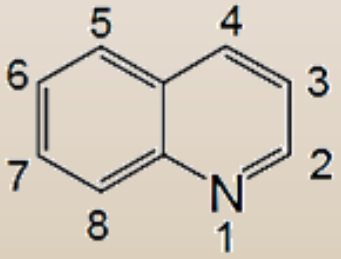
The purine and pyrimidine bases play an important role in the metabolic processes of cells through their involvement in the regulation of protein synthesis. Thus, several synthetic analogues of these compounds are used to interrupt the cancer cell growth.

One such example is an adenine mimic, 6-mercaptopurine, which is a well known anticancer drug.



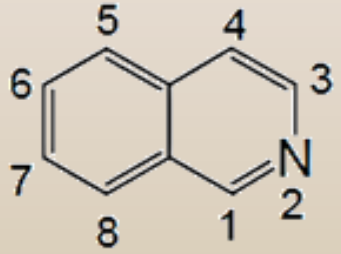
6-Mercaptopurine
An anticancer drug

4.10 Quinoline and isoquinoline



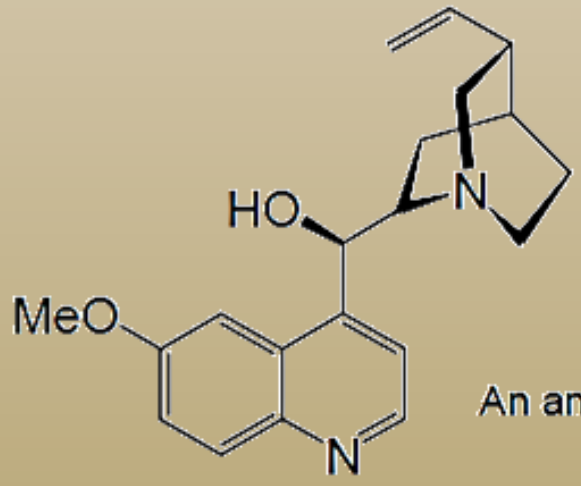
Quinoline

Quinoline and isoquinoline, known as benzopyridines, are two isomeric heterocyclic compounds that have two rings, a benzene and a pyridine ring, fused together.
In quinoline this fusion is at C2/C3, whereas in isoquinoline this is at C3/C4 of the pyridine ring. Like benzene and pyridine, these benzopyridines are also aromatic in nature.



Isoquinoline

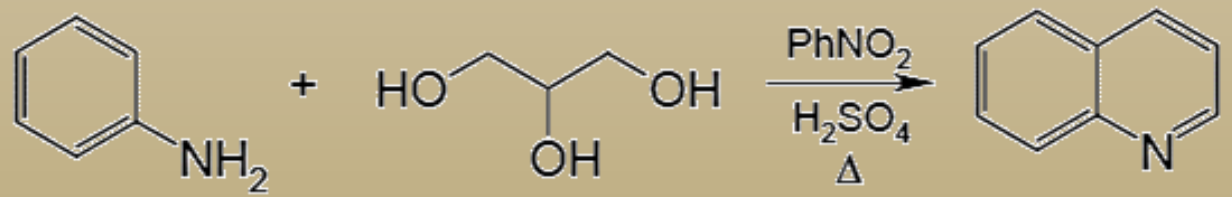
A number of naturally occurring pharmacologically active alkaloids possess quinoline and isoquinoline skeleton. For examples, papaverine from *Papaver somniferum* is an isoquinoline alkaloid and quinine from *Cinchona* barks is a quinoline alkaloid that has antimalarial properties.



Quinine
An antimalarial drug

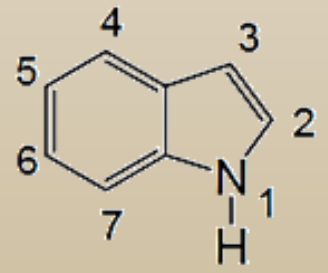
Preparation of quinoline and isoquinoline

Quinoline synthesis *Skraup synthesis* is used to synthesize the quinoline skeleton by heating aniline with glycerol, using sulphuric acid as a catalyst and dehydrating agent. Ferrous sulphate is often added as a moderator, as the reaction can be violently exothermic. The most likely mechanism of this synthesis is that glycerol is dehydrated to acrolein, which undergoes conjugate addition to the aniline. This intermediate is then cyclized, oxidized and dehydrated to give the quinoline system.

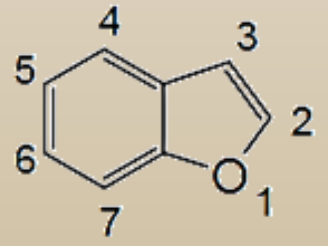


4.11 Indole

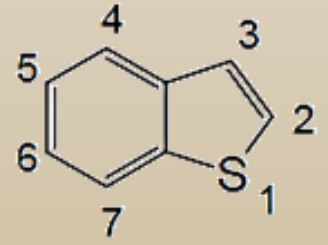
Indole contains a benzene ring fused with a pyrrole ring at C-2/C-3, and can be described as benzopyrrole. Indole is a ten p electron aromatic system achieved from the delocalization of the lone pair of electrons on the nitrogen atom. Benzofuran and benzothiaphene are very similar to benzopyrrole (indole), with different hetero-atoms, oxygen and sulphur respectively.



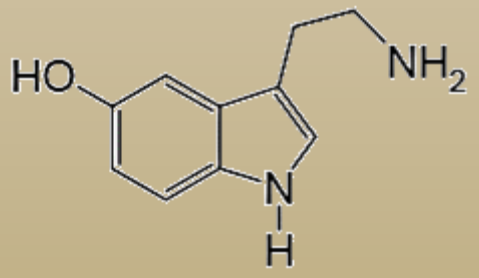
Benzopyrrole
Indole



Benzofuran



Benzothiophene



Serotonin
(5-Hydroxytryptamine)
A neurotransmitter

The indole group of compounds is one of the most prevalent groups of alkaloids found in nature. A number of important pharmacologically active medicinal products and potential drug candidates contain the indole system. For example, serotonin, a well known neurotransmitter, has a substituted indole system.