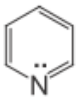
# Heterocyclic compounds and their derivatives

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

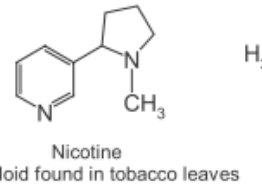
Tetrahydrofuran
O is the hetero-atom

Thiophene
S is the hetero-atom

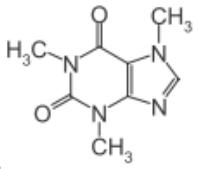
Among the heterocyclic compounds, there are aromatic, e.g. pyridine, as well as nonaromatic, e.g. tetrahydrofuran, compounds. Similarly, there are saturated (e.g. tetrahydrofuran) and unsaturated (e.g. pyridine) heterocyclic compounds. Heterocycles also differ in their ring sizes, e.g. pyridine has a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

## 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.

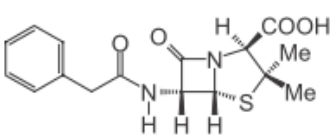


Nicotine
An alkaloid found in tobacco leaves

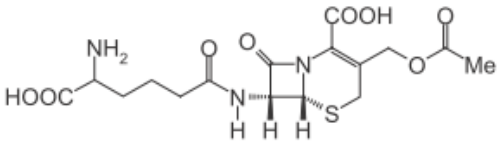


Caffeine
A natural stimulant found in
tea leaves, coffee beans and cola nuts

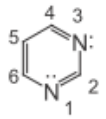
Serotonin
A natural neurotransmitter



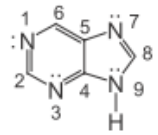
Penicillin G
An antibiotic



Cephalosporin C
An antibiotic



Pyrimidine
A structural unit of RNA and DNA



Purine
A structural unit of RNA and DNA

## 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, pyrid*ine*, where the suffix is *-ine*, one can understand that this heterocyclic compound contains nitrogen, has a six-membered ring system and is unsaturated.

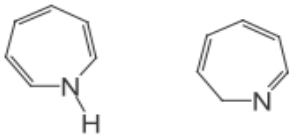
| | Ring with nitrogen | | Ring without nitrogen | |
|---|---|---|---|---|
| *Ring size* | *Maximum unsaturation* | *Saturation* | *Maximum unsaturation* | *Saturation* |
| 3 | irine | iridine | irene | irane |
| 4 | ete | etidine | ete | etane |
| 5 | ole | olidine | ole | olane |
| 6 | ine | – | ine | 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 |

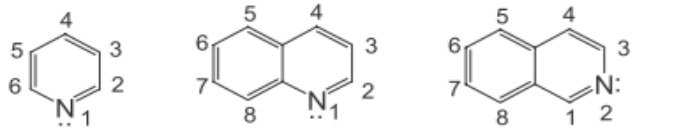
Two or more identical hetero-atoms are indicated by use of the multiplying prefixes *di-*, *tri-* or *tetra-*. When more than one distinct hetero-atom is present, the appropriate prefixes are cited in the name in descending order of group number in the periodic table, e.g. *oxa-* takes precedence over *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.

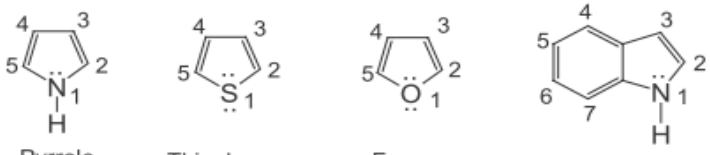


1H-Azepine 2H-Azepine

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

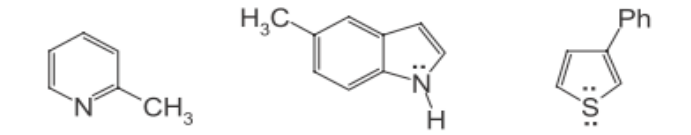


Pyridine Quinoline Isoquinoline



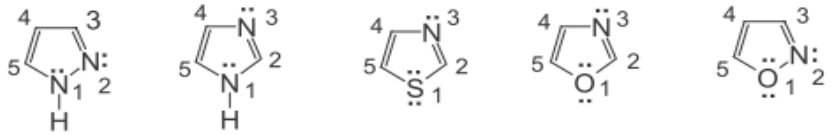
Pyrrole Thiophene Furan Indole

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.



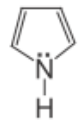
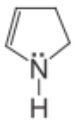
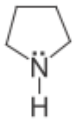
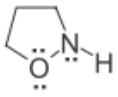
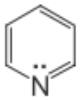
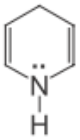
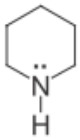
2-Methylpyridine 5-Methylindole 3-Phenylthiophene

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 hetero-atoms 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.



Pyrazole Imidazole Thiazole Oxazole Isoxazole

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 |

### Physical properties of heterocyclic compounds

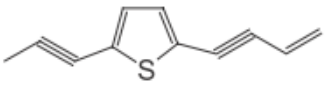
A large number of structurally diverse compounds belong to the class *heterocycles*. This makes it extremely difficult to generalize the physical properties of these compounds, because they vary significantly depending on the saturation–unsaturation status, aromatic–nonaromatic behaviour, ring sizes 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.

## Pyrrole, furan and thiophene: five-membered unsaturated heterocycles

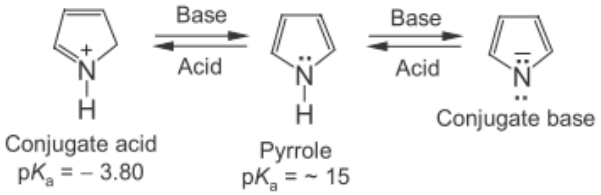
*Pyrrole* is a nitrogen-containing unsaturated five-membered heterocyclic aromatic compound. It shows aromaticity by delocalization of a lone pair of electrons from nitrogen. In pyrrole, there are four π electrons, two short of the Hückel criteria for aromaticity. The nitrogen atom is $sp^2$-hybridized, 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. A small number of simple pyrroles occur in nature. However, biologically more significant natural pyrroles are rather less simple; they are tetrameric pyrrole derivatives, known as porphyrins, e.g. chlorophyll-a and haem.

*Furan*, also known as furane and furfuran, is an oxygen-containing five-membered aromatic heterocyclic compound that is usually produced when wood, especially pine wood, is distilled. The highly electronegative oxygen holds on the electron density tightly. Although it has a lone pair of electrons, these electrons cannot delocalize easily, and so the system is generally considered to be almost nonaromatic or weakly aromatic.

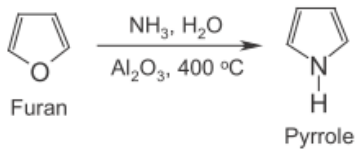
*Thiophene* is a sulphur-containing five-membered unsaturated heterocycle. The lone pair electrons of the sulphur are in the 3*s* orbital, and are less able to interact with the π electrons of the double bonds. Therefore, thiophene is considered weakly aromatic. Acetylenic thiophene is found in some higher plant species. However, the thiophene ring is present in many important pharmaceutical products.




Acetylenic thiophene



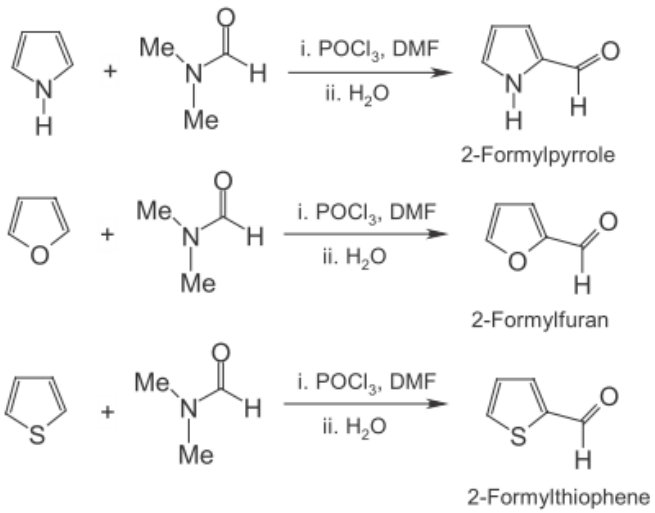

**Commercial preparation of pyrrole, furan and thiophene** Pyrrole is obtained commercially from coal tar or by treating furan with $NH_3$ over an alumina catalyst at 400 °C.



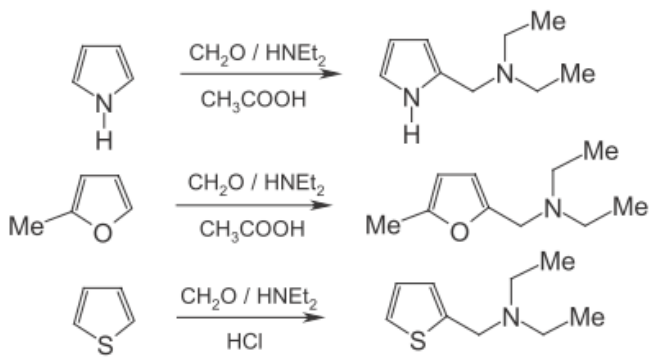
### *Reactions of pyrrole, furan and thiophene*

Pyrrole, furan and thiophene undergo electrophilic substitution reactions. However, the reactivity of this reaction varies significantly among these heterocycles. The ease of electrophilic substitution is usually furan > pyrrole > thiophene > benzene. Clearly, all three heterocycles are more reactive than benzene towards electrophilic substitution. Electrophilic substitution generally occurs at C-2, i.e. the position next to the hetero-atom.

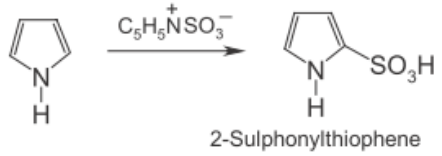
**Vilsmeier reaction** Formylation of pyrrole, furan or thiophene is carried out using a combination of phosphorus oxychloride ($POCl_3$) and *N*, *N*-dimethylformamide (DMF). This reaction proceeds by formation of the electrophilic Vilsmeier complex, followed by electrophilic substitution of the heterocycle. The formyl group is generated in the hydrolytic workup.



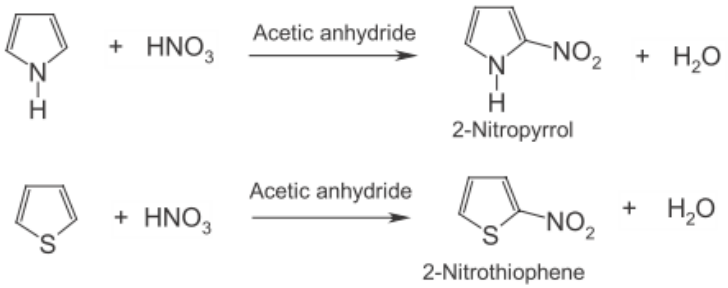

**Mannich reaction** Pyrrole and alkyl substituted furan undergo the *Mannich reaction*. Thiophene also undergoes this reaction, but, instead of acetic acid, hydrochloric acid is used.



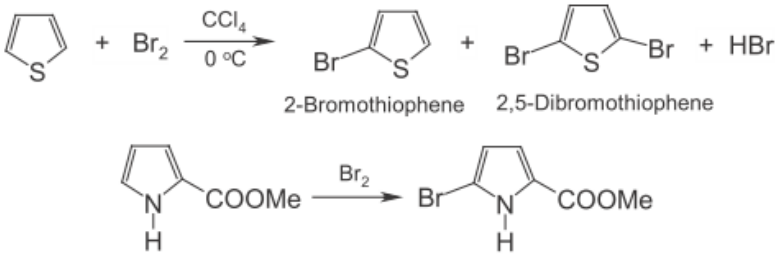
**Sulphonation** Pyrrole, furan and thiophene undergo sulphonation with the pyridine–sulphur trioxide complex ($C_5H_5N^+SO_3^-$).



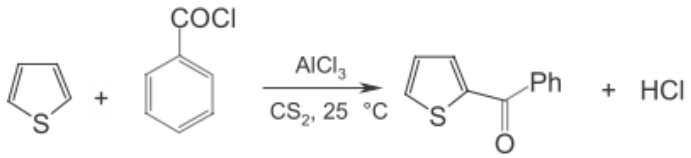

**Nitration** Instead of a mixture of nitric acid and sulphuric acid, nitration of these three heterocycles is carried out with acetyl nitrate (formed from nitric acid and acetic anhydride). Nitration is in place mainly at one of the carbon atoms next to the hetero-atom.




**Bromination** The five-membered aromatic heterocycles are all more reactive toward electrophiles than benzene is, and the reactivity is similar to that of phenol. These compounds undergo electrophilic bromination. However, reaction rates vary considerably, and for pyrrole, furan and thiophene the rates are $5.6 \times 10^8$, $1.2 \times 10^2$ and 1.00, respectively. While unsubstituted five-membered aromatic heterocycles produce a mixture of bromo-derivatives, e.g. bromothiphenes, substituted heterocycles produce a single product.

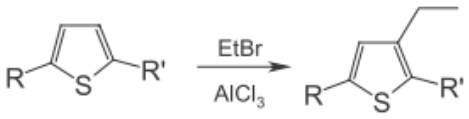



**FC acylation and alkylation** As pyrroles and furans are not stable in the presence of Lewis acids, which are necessary for FC alkylations and acylations, only thiophene, which is stable in Lewis acids, can undergo these reactions. Thiophene reacts with benzoyl chloride in the presence of aluminium chloride to produce phenyl 2-thienyl ketone.

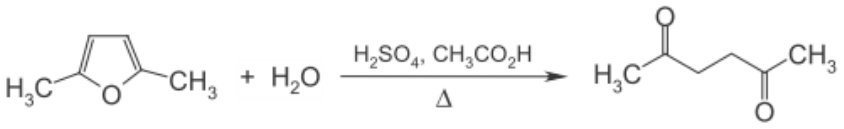



Phenyl 2-thienyl ketone

Alkylthiophene reacts with bromothane in the presence of a Lewis acid to bring in 3-ethyl substituent on the ring.

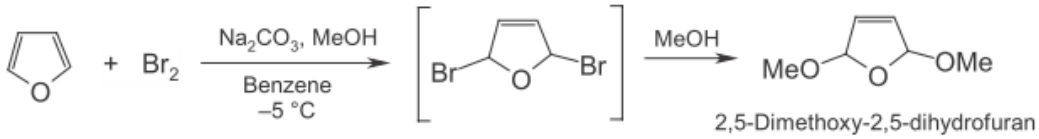



**Ring opening of substituted furan** Furan may be regarded as a cyclic hemi-acetal that has been dehydrated, and is hydrolysed back to a dicarbonyl compound when heated with dilute mineral acid.



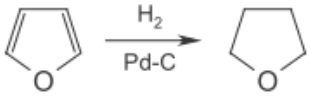

2,5-Dimethylfuran 2,5-Hexanedione (86%)

**Addition reaction of furan** Furan reacts with bromine by 1,4-addition reactions, not electrophilic substitution. When this reaction is carried out in methanol (MeOH), the isolated product is formed by solvolysis of the intermediate dibromide.




2,5-Dimethoxy-2,5-dihydrofuran

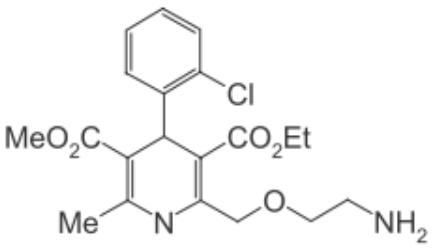
**Catalytic hydrogenation of furan** Catalytic hydrogenation of furan with a palladium catalyst gives tetrahydrofuran, which is a clear, low-viscosity liquid with a diethyl-ether-like smell.



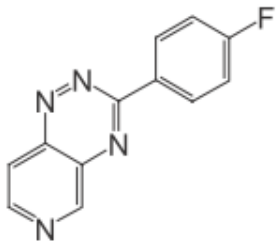

Tetrahydrofuran

## Pyridine

Pyridine ($C_5H_5N$) is a nitrogen-containing unsaturated six-membered heterocyclic aromatic compound. It is similar to benzene, and conforms to Hückel'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.



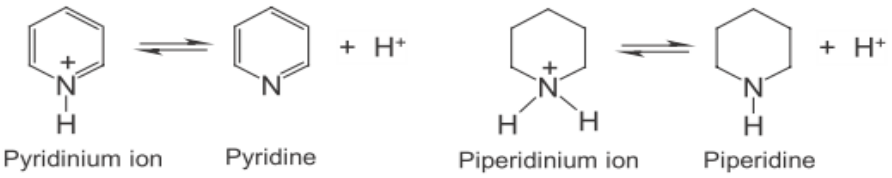

Amlodipine
An antihypertensive agent




Pyridotriazine
An antifungal drug

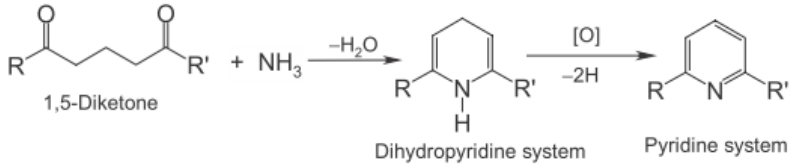
### *Physical properties of pyridine*

Pyridine is a liquid (b.p. 115 °C) with an unpleasant smell. It is a polar aprotic solvent and is miscible with both water and organic solvents. The dipole moment of pyridine is 1.57 D. Pyridine is an excellent donor ligand in metal complexes. It is highly aromatic and moderately basic in nature, with a p$K_a$ 5.23, i.e. a stronger base than pyrrole but weaker than alkylamines. The lone pair of electrons on the nitrogen atom in pyridine is available for bonding without interfering with its aromaticity. Protonation of pyridine results in a pyridinium ion (p$K_a = 5.16$), which is a stronger acid than a typical ammonium ion (e.g. piperinium ion, p$K_a = 11.12$), because the acidic hydrogen of a pyridinium ion is attached to an $sp^2$-hybridized nitrogen that is more electronegative than an $sp^3$-hybridized nitrogen.




Pyridinium ion Pyridine Piperidinium ion Piperidine

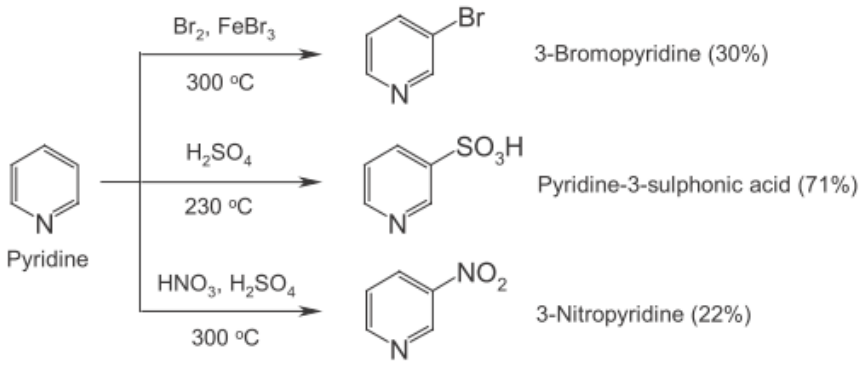
### *Preparation of pyridine*




1,5-Diketone Dihydropyridine system Pyridine system

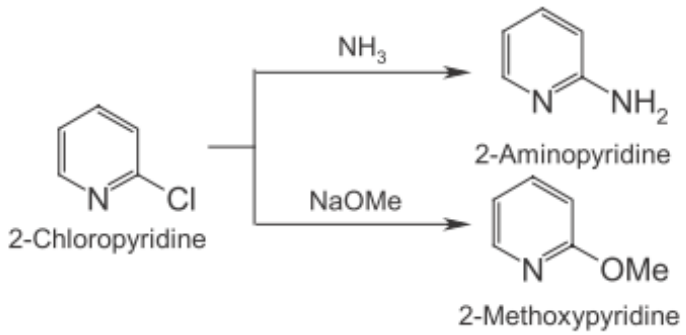
### *Reactions of pyridine*

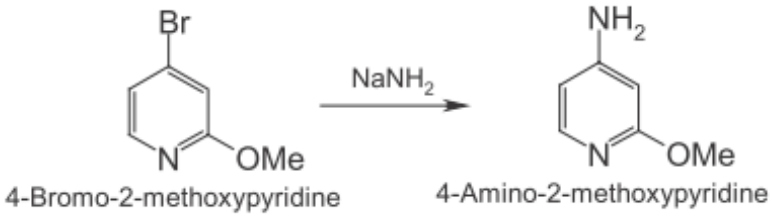
**Electrophilic substitutions** Pyridine's electron-withdrawing nitrogen causes the ring carbons to have significantly less electron density than the ring carbons of benzene. Thus, pyridine is less reactive than benzene towards electrophilic aromatic substitution. However, pyridine undergoes some electrophilic substitution reactions under drastic conditions, e.g. high temperature, and the yields of these reactions are usually quite low. The main substitution takes place at C-3.



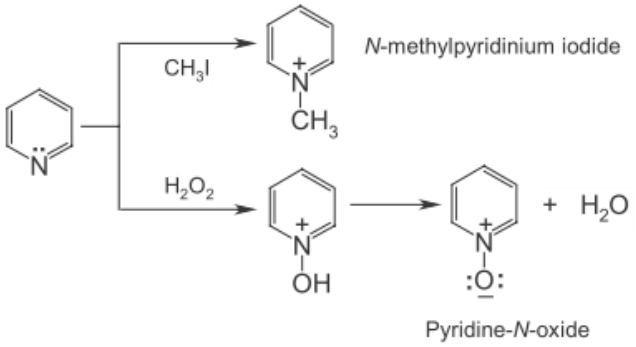

**Nucleophilic aromatic substitutions** Pyridine is more reactive than benzene towards nucleophilic aromatic substitutions because of the presence of electron-withdrawing nitrogen in the ring. Nucleophilic aromatic substitutions of pyridine occur at C-2 (or C-6) and C-4 positions.


These nucleophilic substitution reactions are rather facile when better leaving groups, e.g. halide ions, are present. Reaction occurs by addition of the nucleophile to the C=N bond, followed by loss of halide ion from the anion intermediate.



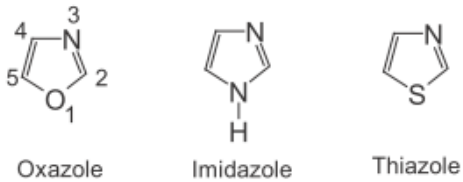




**Reactions as an amine** Pyridine is a tertiary amine, and undergoes reactions characteristic to tertiary amines. For example, pyridine undergoes $S_N2$ reactions with alkyl halides, and it reacts with hydrogen peroxide to form an *N*-oxide.



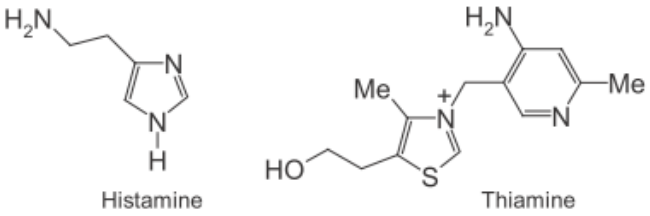

## Oxazole, imidazole and thiazole

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.




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.



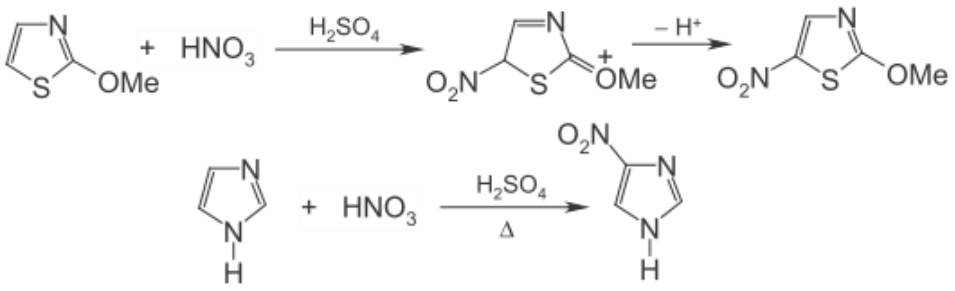

### *Physical properties of oxazole, imidazole and thiazole*

| 1,3-azoles | p$K_a$ | 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 |

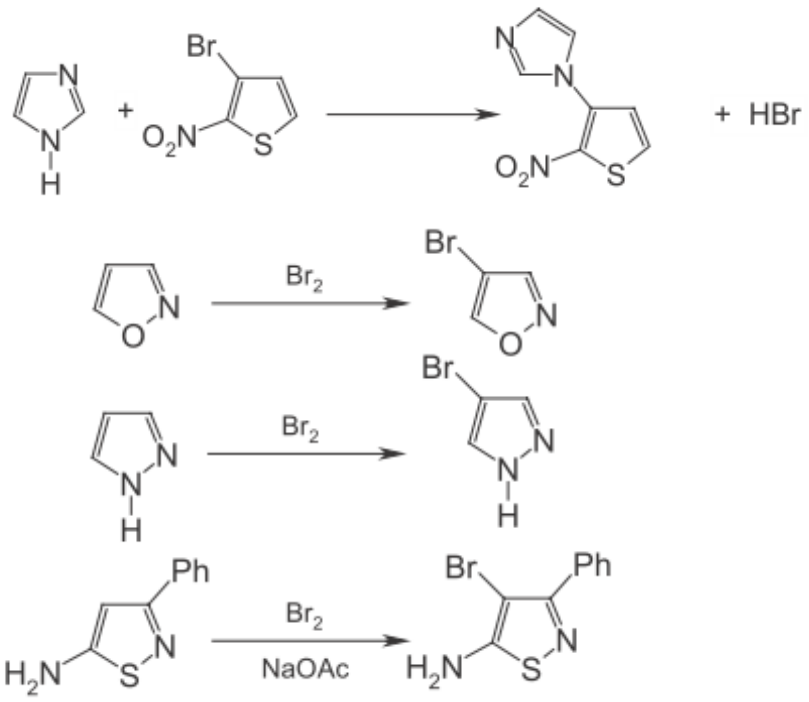
### *Reactions of oxazole, imidazole and thiazole*

The presence of the pyridine-like nitrogen deactivates the 1,3-azoles toward electrophilic attack, and increases their affinity towards nucleophilic attack.

**Electrophilic substitutions** Although oxazole, imidazole and thiazoles are not very reactive towards aromatic electrophilic substitution reactions, the presence of any electron-donating group on the ring can facilitate electrophilic substitution. For example, 2-methoxythiazole is more reactive than thiazole itself. Some examples of electrophilic substitutions of oxazole, imidazole and thiazoles and their derivatives are presented below.

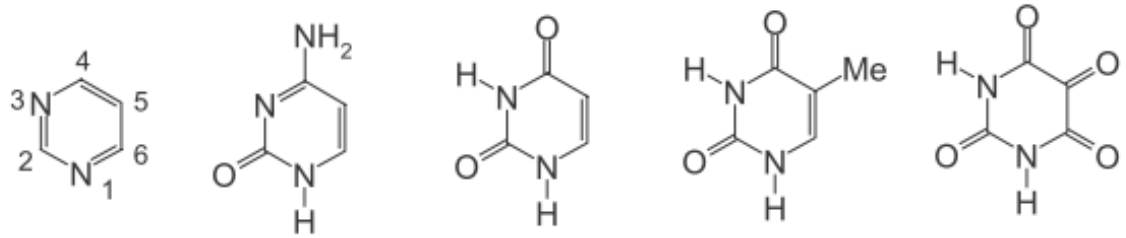



**Nucleophilic aromatic substitutions** 1,3-azoles are more reactive than pyrrole, furan or thiaphene towards nucleophilic attack. Some examples of nucleophilic aromatic substitutions of oxazole, imidazole and thiazoles and their derivatives are given below. In the reaction with imidazole, the presence of a nitro-group in the reactant can activate the reaction because the nitro-group can act as an electron acceptor.



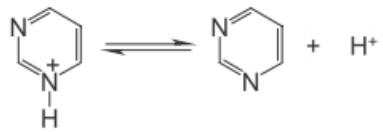

## Pyrimidine

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.



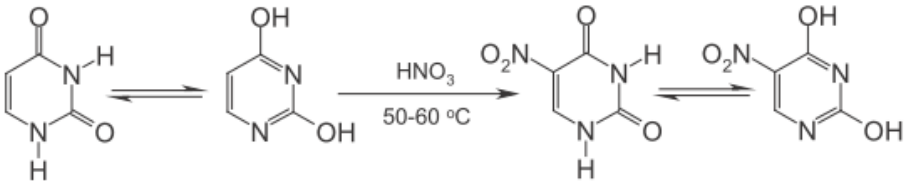

### *Physical properties of pyrimidine*

Pyrimidine is a weaker base than pyridine because of the presence of the second nitrogen. Its conjugate acid is a much stronger acid ($pK_a = 1.0$). The $pK_a$ values of the *N*-1 hydrogen in uracil, thymine and cytosine are 9.5, 9.8 and 12.1, respectively. Pyrimidine is a hygroscopic solid (b.p. 123–124 °C, m.p. 20–22 °C) and soluble in water.



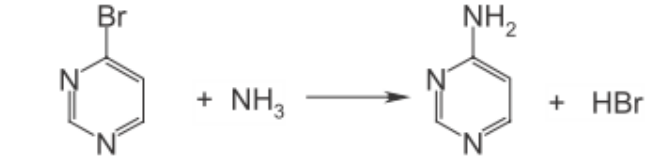

Conjugate acid of pyrimidine

## *Reactions of pyrimidine*



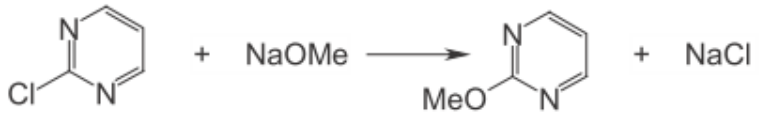

Keto-enol tautomeric forms of uracil

2,4-Dihydroxy-5-nitropyrimidine
(5-Nitrouracil)




4-Bromopyrimidine

4-Aminopyrimidine

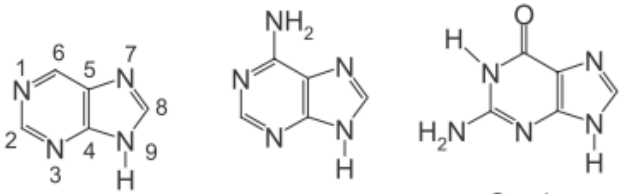



2-Chloropyrimidine

4-Aminopyrimidine

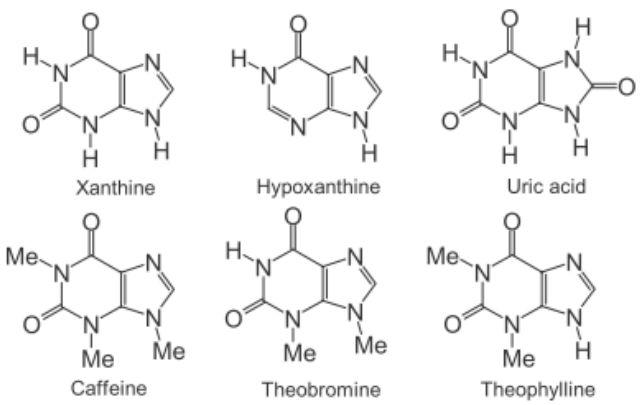
## Purine

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.



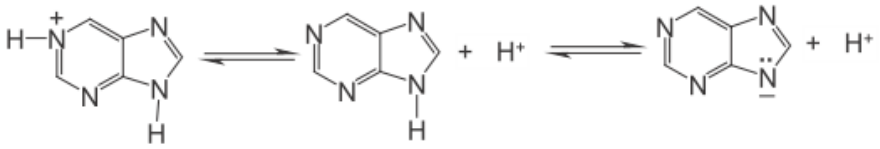
Purine Adenine Guanine

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.



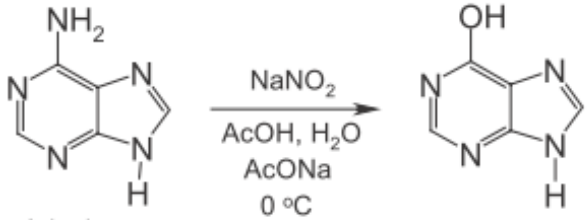
Xanthine Hypoxanthine Uric acid

Caffeine Theobromine Theophylline



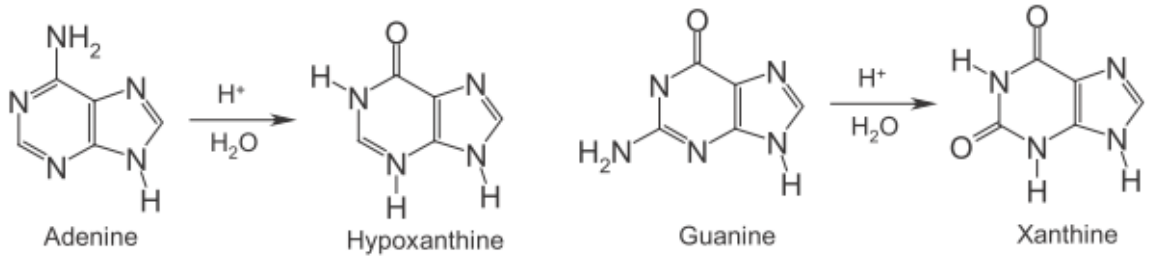
## *Reactions of purine*

**Nucleophilic substitutions**




Adenine

**Deamination of aminopurines**




Adenine Hypoxanthine Guanine Xanthine

## Literature:

**1.** Sarker, Satyajit D. Chemistry for pharmacy students: general, organic, and natural product chemistry / Satyajit D. Sarker, Lutfun Nahar. John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex PO19 8SQ, England