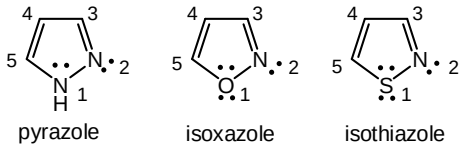
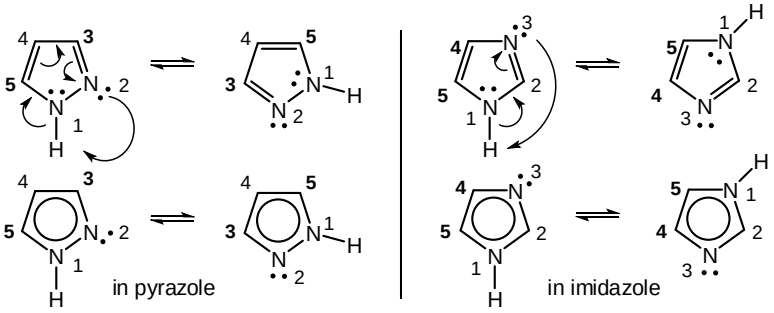
№ 36. FIVE-MEMBERED HETEROCYCLES WITH TWO HETEROATOMS. PYRAZOLE AND IMIDAZOLE. ANALGESIC AND OTHER DERIVATIVES.

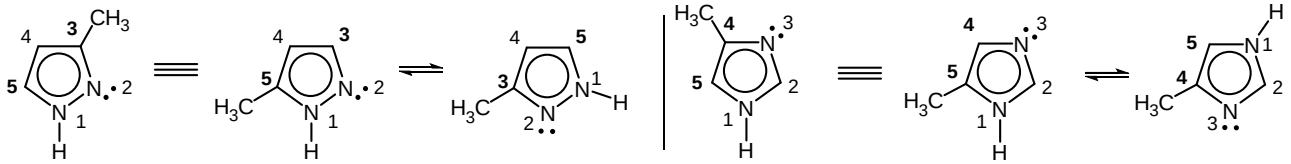
A group of heterocyclic aromatic compounds can be described as derived from pyrrole by replacing one of the ring carbons by second heteroatom. Such five-membered ring heterocycles with two heteroatoms, one of them nitrogen, are called azoles. The group name is retained as base for five-membered aromatic heterocycles with two nitrogen atoms. The combination of heteroatoms nitrogen–oxygen gives oxazoles, and nitrogen–sulfur – thiazoles. These compounds are aza-analogs of pyrrole, furan, and thiophene. The heteroatoms can be adjacent or separated by one -CH= unit, as shown.



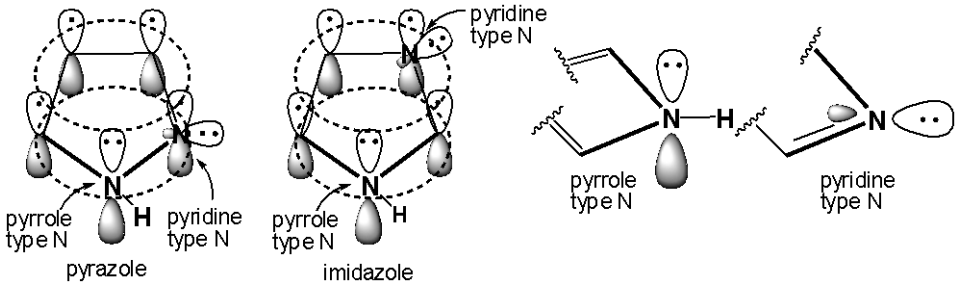
The correct numbering begins from more saturated heteroatom which in the case of azoles is NH of pyrrole type or from higher priority atom (O, S) to the second heteroatom, such as to get lowest number of the second heteroatom. Therefore, the pyridine type N in azoles (-N=) can have either number 2 or number 3. When one of the nitrogen atoms is substituted in pyraloze and imidazole derivatives, it is the starting point for numbering of the ring. Substitution at position C(2) of imidazole does not change the numbering system because of its symmetrical location in respect to the nitrogens. For the same reason, there is unambiguous number assignment in C(4) substituted pyrazoles. Position C(4) in pyrazole and C(2) in imidazole are unique. Positions C(3), C(5) in pyrazole and C(4), C(5) in imidazole seem different but there are one isomer of each monosubstituted at these positions pyrazole and imidazole. The mentioned positions are equivalent due to symmetry arising from tautomerism.



Therefore, derivatives of these azoles can be written in two ways using double bonds representations, e.g for the amino acid histidine. This is illustrated with 3-methyl-pyrazole, that is identical to "5-methyl-pyrazole" and with 4-methylimidazole that is identical to "5-methylimidazole". Naturally, the nomenclature names must contain the lower numbers.



The molecular orbital description of the electronic structure of azoles is similar to that of simpler aromatic heterocycles. Each carbon in imidazole and its nitrogen atom may be considered as sp^2 hybridized. One nitrogen in imidazole participates in two sp^2 - sp^2 σ-bonds to carbon and one sp^2 - s σ-bond to hydrogen. This nitrogen atom provides lone pair on non-hybridized $2p_z$ orbital to the aromatic sextet. This nitrogen is of pyrrole type. The other nitrogen has its lone pair on sp^2 hybrid orbital and provides one π-electron to the sextet. This nitrogen is of pyridine type.

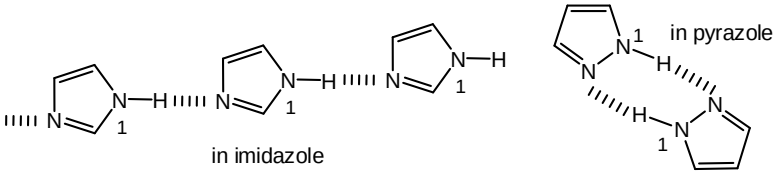


Notice the shape of orbitals on the two types of nitrogens.

The π-orbital system in both heterocycles is made up from the p_z orbital from each ring atom. Each of the three carbon atoms and one of the nitrogens (pyridine type) provides one electron and the second nitrogen (pyrrole type) provides two electrons to form the stable, aromatic π-electron sextet, according to the Hückel's rule. The π-electron system of both pyrazole and imidazole consists of six electrons delocalized on five atoms. Therefore, both

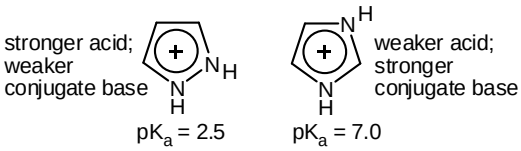
heterocycles are electron richer in comparison to benzene. This fact has consequences in the reactivity of these electron-rich compounds.

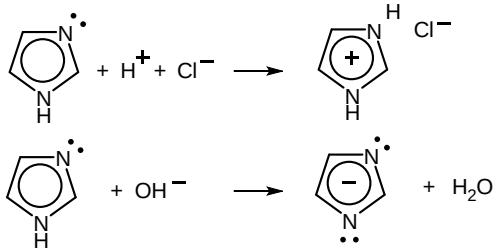
Physical properties. Pyrazole and imidazole are solids at room temperature. Both compounds have anomalously high boiling points. The boiling points are much lower in C(1)-methyl derivatives, but are not significantly affected by methyl groups at C(3), or C(5) in pyrazole and at C(4), or C(5) in imidazole. These facts show that the hydrogen atom on the pyrrole type nitrogen is, to a certain degree, responsible for the observed high boiling points of pyrazole and imidazole. The higher boiling points are explained with intermolecular hydrogen bonding. For imidazole, such hydrogen bonding is realized in a linear fasion, and for pyrazole in dimeric structures.



Imidazole is a highly polar compound, as evidenced by a calculated dipole of 3.61D, and is entirely soluble in water.

Chemical properties. Acid-base properties. Pyrazole is a weak base. As in pyridine, the nitrogen lone pair is on sp^2-hybrid orbital. The greater *s*-character, in comparison to aliphatic amines, is associated with greater stability and lower basicity. This accounts for a decrease of basicity by several powers of ten. In pyrazole, the basicity is further reduced by the presence of adjacent electronegative nitrogen. In sharp contrast, imidazole appears as abnormally basic for a compound with sp^2-hybridized nitrogen. Imidazole is approximately 100 times more basic (pK_a = 7.0) than pyridine. This enhanced basicity is presumably due to symmetry of the conjugate acid and its stability.

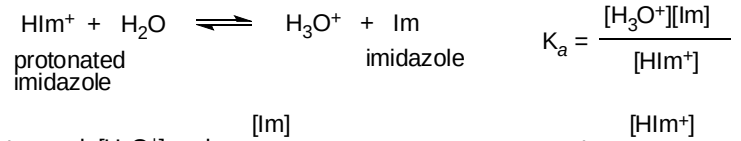




Both pyrazole and imidazole behave as ampholites – they can react as proton donors and proton acceptors. Imidazole amphoteric properties are more pronounced due to greater distance between the nitrogen atoms.

Imidazole has amphoteric character. In the cation and anion, shown to the left, the N atoms are undistinguishable, as indicated by the circles used for depiction of the aromatic sextet.

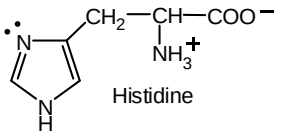
The value of pK_a of 7.0 of imidazolium ion means that half of imidazole is protonated in neutral water. This conclusion can be obtained from the expression for the acidity constant of imidazole in a protonation equilibrium, as shown.



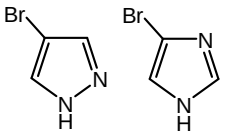
$$\lg K_a = \lg[H_3O^+] + \lg \frac{[Im]}{[HIm^+]} \quad \text{or} \quad pK_a = pH + \lg \frac{[HIm^+]}{[Im]}$$

Having $pK_a = 7$ and at $pH = 7$, follows $\lg \frac{[HIm^+]}{[Im]} = 0$ or $\mathbf{[HIm^+] = [Im]}$

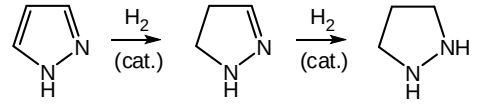
As a result of this basicity, imidazole in the amino acid histidine is often involved in proton transfer reactions at the active site of enzymes. Such proton transfers are fast and often the term for imidazolium involved in them is "proton shuttle".



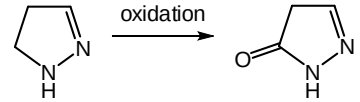
Pyrazole and imidazole react in electrophilic aromatic substitutions. They are less reactive than pyrrole in such reactions. Their lower reactivity in S_EAr is due to the presence of second electronegative nitrogen atom in the ring which decreases the available for an electrophile electron density of the π-system. The C(4) position is more reactive in both pyrazole and imidazole, e.g. major products in S_EAr bromination are 4-bromopyrazole and 4-bromoimidazole.



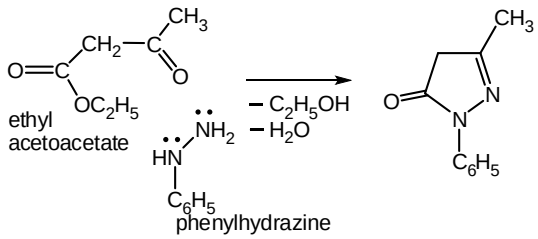
Both pyrazole and imidazole are stable aromatic systems and for this reason, the hydrogenation and oxidation reactions are not typical. The stepwise hydrogenation of pyrazole affords pyrazoline and the saturated heterocycle pyrazolidine which can be viewed as cyclic hydrazine.



The oxidation of pyrazoline gives 5-pyrazolone which is the basic structure of numerous

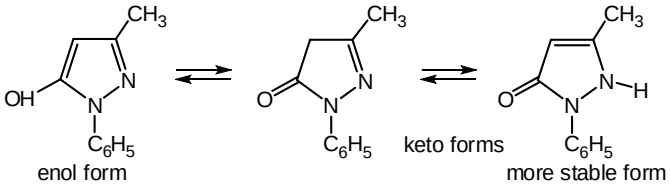


pharmaceuticals.



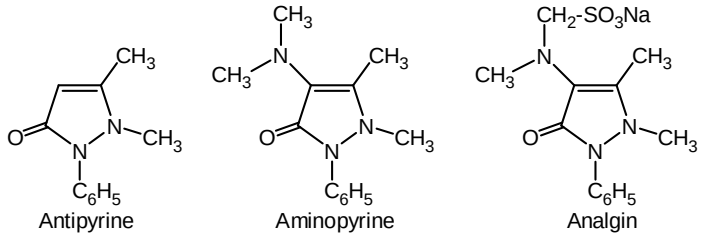
Pyrazole derivatives. Particularly important are 3-methyl-1-phenyl-5-pyrazolones. In practice these type of compounds are synthesized by ring closing reaction between a β-ketoester and substituted hydrazine. The highly reactive β-keto group condenses with the NH_2 with release of water to form a Schiff's base intermediate. It forms a ring by cyclization through nucleophilic attack of the second nitrogen on the ester carbonyl group.

5-Pyrazolones bearing substituents at C(1) and C(3) exhibit keto-enol type of tautomerism where one of the forms is usually most stable.



Some representatives of the 3-methyl-1-phenyl-5-pyrazolone family with use in medicine are Antipyrine, Aminopyrine, and Analgin (trade names).

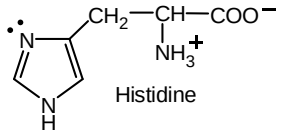
Antipyrine (Phenazone, 2,3-dimethyl-1-phenyl-5-pyrazolone) is the first antipyretic drug. It reduces high body temperature in fevers. The compound has also analgesic action (painkiller, relieves pain).



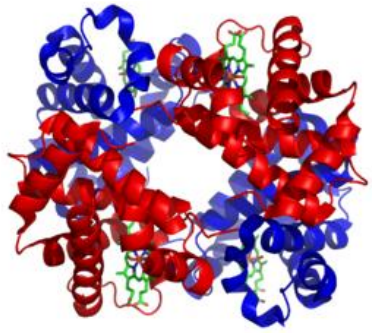
Aminopyrine (Aminophenazone, pyramidone) has analgesic, anti-inflammatory, and antipyretic properties. Its antirheumatic action is better than that of salicylate. Aminopyrine is more active than antipyrine and has longer time of action.

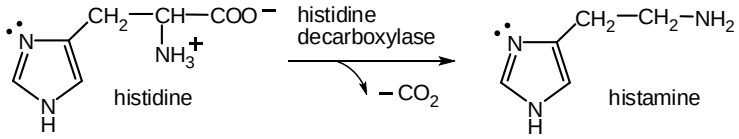
Analgin (Metamizole sodium) is a non-steroidal anti-inflammatory drug (NSAID), commonly used in many countries as a powerful analgesic and antipyretic. Because of the sulfonic acid salt group in the molecule analgin has higher solubility in water and better action profile.

Imidazole derivatives. **Histidine**. Histidine is an essential amino acid. It plays acid-base catalytic role in the active center of many enzymes. In catalytic triads at enzyme active site, the basic nitrogen of histidine is used to abstract a proton from either amino acid serine, threonine or cysteine in order to activate it as a nucleophile. In a histidine proton shuttle, histidine is used to quickly shuttle protons, it can do this by abstracting a proton with its basic nitrogen to make a positively-charged intermediate and then use another molecule, a buffer, to take the proton from its acidic nitrogen. In enzymes such as carbonic anhydrases, a histidine proton shuttle is utilized to rapidly shuttle protons away from a zinc-bound water molecule to quickly regenerate the active form of the enzyme. Proteases (enzymes that break down proteins) begin protein catabolism by hydrolysis of peptide bonds. The mechanism used to cleave a (relatively strong) peptide bond involves making an amino acid residue that has cysteine and threonine (peptidases) or a water molecule nucleophilic so that it can attack the peptide carbonyl group. One way to make a nucleophile is by a catalytic triad, where a histidine residue is used to activate serine, cysteine, or threonine as a nucleophile.



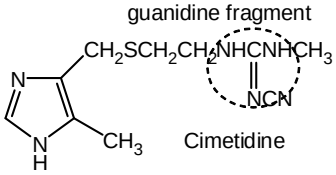
Histidine is a ligand of heme in hemoglobin. In most humans, the hemoglobin molecule is an assembly of four globular protein subunits - two α-subunits and two β-subunits. Each subunit is composed of a protein chain tightly associated with a non-protein heme group. Each protein chain arranges into a set of alpha-helix structural segments connected together in a globin fold arrangement, so called because this arrangement is the same as in myoglobin. This folding pattern contains a pocket that strongly binds the heme group. The heme iron (2+) is bound strongly to the globular protein via the imidazole ring of the histidine residue on one side of the porphyrin ring. A sixth position on the other side of the ring can reversibly bind oxygen by a coordinate covalent bond.





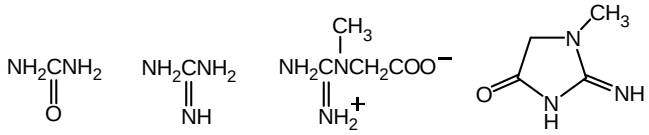
Histamine is derived from histidine by enzymatic decarboxylation. It is a biogenic amine, powerful vasodilator normally present in tissue. It is formed in excessive amounts in condition known as traumatic shock. Histamine is involved in local immune responses. Excess of histamine in the synapses triggers allergic reaction with pain, sneezing, and itching. Histamine is responsible for many of the symptoms associated with hay fever and other allergic states.

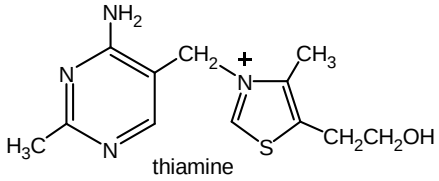
Antihistamines are substances that relieve the allergic symptoms by blocking the histamine action. A histamine antagonist (antagonist is a chemical agent, drug that prevents the physiological effect of other substance) is an agent that serves to inhibit the release or action of histamine. The antihistamines' action is due to competitive binding and occupying sites of the receptor, normally taken by histamine. Classical antihistamines act upon the H1 histamine receptor. H1 histamine receptor antagonists produce also sleep. Sedation is their common side effect, and some H1 antagonists are also used to treat insomnia.



Cimetidine (Tagamet) is a histamine H2-receptor antagonist that inhibits the production of acid in the stomach. This synthetic drug is largely used in the treatment of heartburn and peptic ulcers. Besides the imidazole ring, cimetidine contains a group, called guanidine that is nitrogen analog of urea.

Urea serves an important role in the metabolism of nitrogen-containing compounds by animals and is the main nitrogen-containing substance in the urine of mammals. Urea is synthesized in the body as part of the urea cycle, either from the oxidation of amino acids or from ammonia. The handling of urea by the kidneys is a vital part of human metabolism. Guanidine is also found in urine as a normal product of protein metabolism. Creatine is a nitrogen-containing organic acid that occurs naturally in vertebrates and helps to supply energy to all cells in the body, primarily muscle, by increasing the formation of adenosine triphosphate (ATP). Creatine is naturally produced in the human body from amino acids primarily in the kidney and liver. In solution, creatine is in equilibrium with **creatinine** which is dehydrated, cyclic amide with an imidazolidinone ring. In chemical terms, creatinine is a spontaneously formed cyclic derivative of creatine. Creatinine is chiefly filtered out of the blood by the kidneys. Blood concentration of creatinine and urea is clinically important parameter for kidneys' function. When kidneys do not function properly, hemodialysis removes most of blood urea and creatinine.





Thiazole ring is found in Vitamin B1 (thiamine). Thiamine pyrophosphate is a coenzyme in the catabolism of sugars and amino acids.

Penicillins are β-lactams with condensed thiazolidine ring. Penicillin antibiotics are historically significant because they are the first drugs that were effective against many previously serious diseases such as syphilis and *Staphylococcus* infections.