№ 34. HETEROCYCLIC COMPOUNDS – DEFINITION, CLASSIFICATION AND CHARACTERIZATION. FIFE-MEMBERED HETEROCYCLES WITH ONE HETEROATOM. PYRROLE, INDOLE AND THEIR DERIVATIVES.

Objectives to learn in Theme “Heterocyclic compounds”

- structure of five and six-membered heterocycles
- reaction scheme of five-membered heterocycles
- S_EAr reactions (refresh also other mechanisms)
- reaction scheme of pyridine
- S_EAr and S_NAr reactions
- condensed heterocyclic compounds
- bases of nucleic acids, nucleosides and nucleotides
- primary and secondary structure of DNA

I. Heterocyclic compounds – definition, classification and characterization.

Cyclic compounds that contain only carbon atoms in their ring are called **carbocyclic compounds**. Many substances have structures in which an atom other than carbon is present in a ring. Such atom different than carbon or hydrogen is called **heteroatom**. A ring that contains at least one heteroatom is called **heterocycle**, and a substance based on a heterocyclic ring is a **heterocyclic compound**. Organic compounds whose molecules contain a ring built from carbon and other atoms are called heterocyclic compounds.

Heterocycles can contain a wide variety of elements in the ring, including N, O, S, P, B, Si, Al, Cu etc. The most common heterocycles are those containing oxygen, nitrogen, and sulfur in the ring. It is also common to find more than one heteroatom in a ring. In such compounds, the heteroatoms may be the same or they may differ.

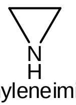
Some heterocyclic (mostly aliphatic) compounds are formed from polyfunctional derivatives – lactones, lactams or are cyclic analogs of major classes of compounds, e.g. cyclic amines, ethers, sulfides. The characteristics of the latter are similar to those of the open-chain parent compounds. Of particular interest are heterocyclic aromatic compounds. (Refresh your knowledge on aromatic hydrocarbons: benzene, naphthalene, anthracene, phenanthrene, benzo[a]pyrene.)

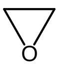
The classification of heterocycles is :

- According to the nature of their heteroatom – nitrogen, sulfur, phosphorus, etc. and their number.
- According to the ring size – small (3,4), medium (5-8), large
- According to the chemical bonding – saturated, unsaturated, aromatic.

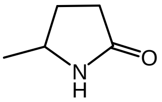
Depending on the number of atoms building the ring, heterocyclic compounds are tri-, tetra-, penta-, hexa-atomic, or even lager. They are roughly grouped as small rings (3 or 4 atoms), medium-sized rings (5 or 6 atoms) and large rings (more than 6 atoms). Naturally found compounds contain most often five- or six-membered heterocycles. This is so because such rings are the most stable ring systems.

Depending on the types of bonds between atoms in the ring, the heterocyclic compounds may be divided into: saturated (containing single bonds only in the ring), unsaturated (containing also double, or very rarely – triple, bonds in the ring), and aromatic heterocyclic compounds. The latter group has most important representatives in Nature.


ethyleneimine
(aziridine)


ethylene oxide
(oxirane)


ethylenesulfide
(thiirane)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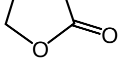
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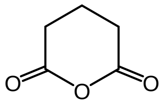
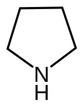
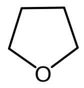
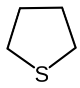
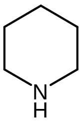
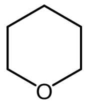

glutaric anhydride

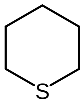

pyrrolidine


tetrahydrofuran


tetrahydrothiophene


piperidine


tetrahydropyran

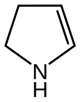

tetrahydrothiopyran

The saturated heterocyclic compounds include cyclic (secondary or tertiary) amines, cyclic ethers and sulfides, lactones, lactams and cyclic anhydrides (from dicarboxylic acids). Examples and the names of some saturated heterocycles are given to the right.

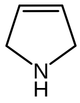
The three-membered rings (ethyleneimine, ethylene oxide and ethylene sulfide) have significant deviation from the normal valence angles and, therefore, are very highly strained. These compounds are extremely reactive and difficult to work with.

Many heterocycles have properties like those of similar open-chain compounds, such as ethers and secondary amines. The properties of lactams (cyclic amides) and of lactones (cyclic esters) are similar to those of amides and esters, although the strained lactams and lactones (three- and four-membered rings) are more reactive than their unstrained or open-chain counterparts.

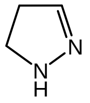
Unsaturated heterocycles, such as pyrroline, pyrazoline and dihydrothiophene are less stable compounds and possess high reactivity, often to achieve aromatic stability.



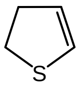
2-pyrroline



3-pyrroline



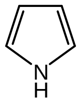
pyrazoline



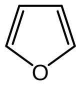
2,3-dihydro-
thiophene

Those heterocyclic compounds that possess aromatic electronic system and aromatic stability are called heterocyclic aromatic compounds. They include, among many others, pyridine, where nitrogen replaces one CH group in benzene, and pyrrole, where the aromatic π-system is formed from four electrons of the two double bonds and the lone electron pair on nitrogen. Some aromatic heterocyclic compounds may contain more than one heteroatom, and many others contain fused aromatic rings (some of them could be carbocyclic, but still the compound is regarded as heterocyclic). Examples that will be shown in more details include also pyrazole, imidazole, indole, and purine. All heterocyclic aromatic compounds resemble in their stability benzene rather than corresponding alkenes. For this reason, some heterocyclic systems can contain charged heteroatoms.

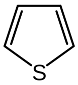
Some examples of more important aromatic heterocyclic compounds, with their names and IUPAC numbering system used in naming derivatives) are shown:



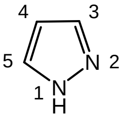
pyrrole



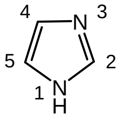
furan



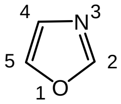
thiophene



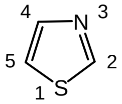
pyrazole



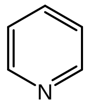
imidazole



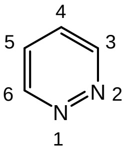
oxazole



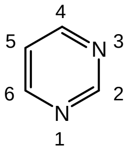
thiazole



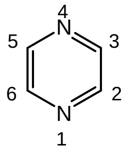
pyridine



pyridazine

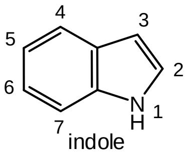


pyrimidine

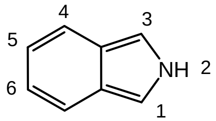


pyrazine

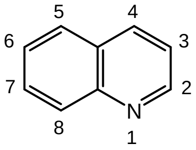
Heterocycles with condensed (fused) rings are viewed as formally derived by fusion with other rings, either carbocyclic or heterocyclic. They have a variety of common and systematic names. For example, with the benzo-fused unsaturated nitrogen heterocycles, pyrrole provides indole or isoindole depending on the nitrogen orientation. The pyridine analogs are quinoline or isoquinoline. Similarly, the compounds with two benzene rings fused to the central heterocycle are carbazole, acridine.



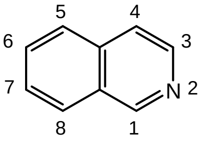
indole



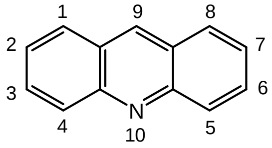
isoindole



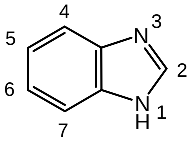
quinoline



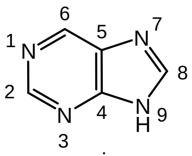
isoquinoline



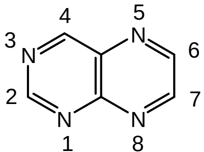
acridine



benzimidazole



purine



pteridin

Nomenclature

The IUPAC nomenclature of heterocycles is complex but often allows use of old, trivial names. The systematic nomenclature is based on:

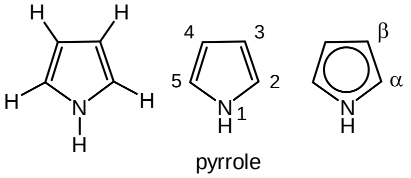
- Size of the ring
- Nature of heteroatoms and their number
- Unsaturation degree.

The numbering usually begins from the heteroatom, in the direction of other heteroatoms (if present), in order to obtain smallest numbers.

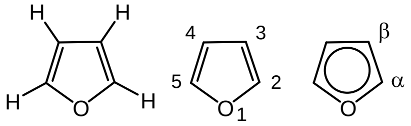
When the heterocycle contains more than one heteroatom, the priority for naming and numbering of complex heterocycles is oxygen > sulfur > nitrogen (oxaza for (O,N), thiaza for (S,N)), as seen in the example **ox**azole . The prefixes indicating heteroatoms are: for O – oxa; S – thia; N – aza. The prefixes are preceded for multiple heteroatoms by: di-; tri- etc., e.g diaza- for two N. Five-membered heterocycles, containing one nitrogen are –**azoles**, and six-membered with one N are-**azines**.

When two identical heteroatoms are present in the same ring, the numbering begins with the more saturated – see pyrazole and imidazole. Carbon atoms lacking attached hydrogens are not included in the numbering system with exception of purine.

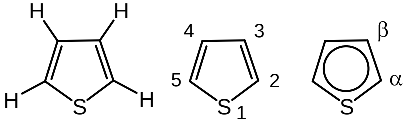
II. Five-membered heterocycles with one heteroatom. Pyrrole. Furan. Thiophene. These three compounds are members of a family aromatic five-membered heterocycles with one heteroatom. They are building units of more complex compounds with biological importance.



pyrrole



furan



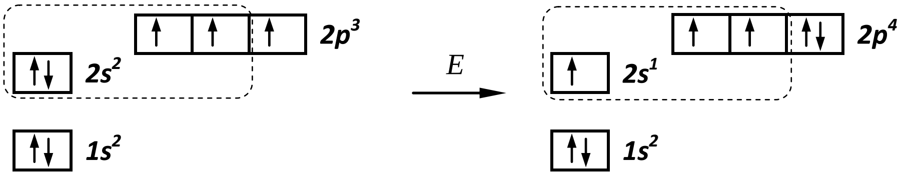
thiophene

Notice! – different ways of writing the structures. Usually the hydrogen atoms are omitted. The heteroatoms N, O, or S are always in ring, not besides it!

These three heterocyclic compounds can interconvert between each other at high temperature and in the presence of catalyst, using source of a heteroatom - water, ammonia or hydrogen sulfide. Pyrrole is prepared industrially by treatment of furan with ammonia in the presence of solid acid catalysts.

The presented structures of pyrrole, furan, and thiophene, using double bonds, suggest diene character, and the presence of lone pair(s) of electrons on the heteroatoms – basic character. However, like benzene, these compounds have chemical properties that are not typical of dienes. The most profound is their participation in electrophilic aromatic substitution reactions rather than in addition reactions. This and other characteristics are associated with the aromaticity.

All three heterocycles are planar, aromatic systems containing 6π electrons. Four of them are supplied by four *sp*^{2} hybridized C atoms and a pair is on p_z non-hybrid orbital on the heteroatom. Thus, six π electrons are delocalized over five atoms giving electron rich systems. Therefore they are more reactive than benzene in general in S_EAr reactions (bromination, acylation, nitration).



N (ground state) N* (excited state)

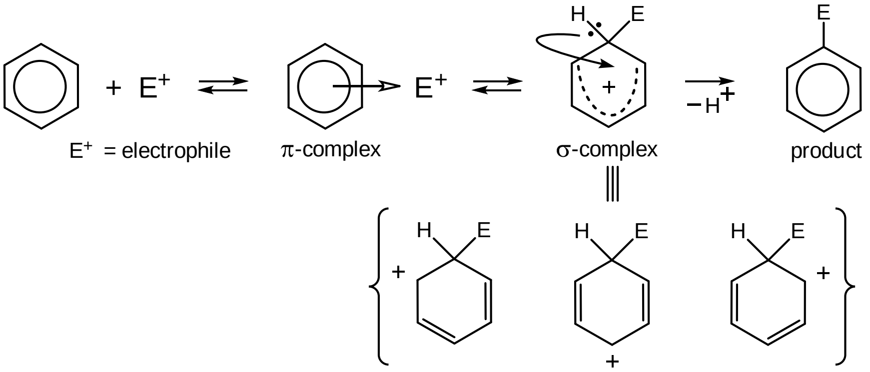
pyridine nitrogen, *sp*^{2} pyrrole nitrogen, *sp*^{2}

The participation of the pyrrole nitrogen in the aromatic system can be described with excited state of N which is in *sp*^{2} hybrid state. The three hybrid orbitals form the sigma bonds (two to *sp*^{2} hybridized carbons and one to hydrogen). The non-hybrid orbital on nitrogen has two electrons that delocalize together with four electrons from carbons to form the π system of pyrrole. The resulting π electron sextet is similar to the one in benzene ring.

Pyrrole, furan, and thiophene fulfill Hückel's rule for aromaticity which states: aromaticity is obtained in cyclic, conjugated and planar systems containing (4n+2) π electrons. The aromatic stabilization results in a diminished tendency of the molecule to react by addition but a larger tendency to react by substitution in which the aromatic ring remains intact. Pyrrole, furan, and thiophene react in S_EAr and not in electrophilic addition, except for hydrogenation and polymerization. Positions 2 and 5 (α) are more reactive than 3 and 4 (β) in S_EAr. Examples of electrophilic substitution reactions on benzene are shown in the Table.

Reaction		Reagent		Product	Electrophile
Halogenation:	C_6H_6	+ Cl_2 (heat and $FeCl_3$ catalyst)	→	C_6H_5Cl + HCl Chlorobenzene	$Cl^{(+)}$ or $Br^{(+)}$
Nitration:	C_6H_6	+ HNO_3 (heat and H_2SO_4 catalyst)	→	$C_6H_5NO_2$ + H_2O Nitrobenzene	$NO_2^{(+)}$
Sulfonation:	C_6H_6	+ H_2SO_4 + SO_3 (heat)	→	$C_6H_5SO_3H$ + H_2O Benzenesulfonic acid	$SO_3H^{(+)}$
Alkylation: Friedel-Crafts	C_6H_6	+ R-Cl (heat and $AlCl_3$ catalyst)	→	C_6H_5-R + HCl An Arene - alkylbenzene	$R^{(+)}$
Acylation: Friedel-Crafts	C_6H_6	+ RCOCl (heat and $AlCl_3$ catalyst)	→	C_6H_5COR + HCl An Aryl Ketone	$RCO^{(+)}$

The mechanism of electrophilic aromatic substitution in benzene proceeds according the scheme:

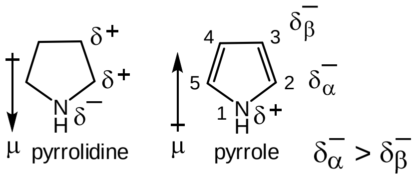


This mechanism involves intermediate positively charged σ-complex where the aromatic system is destroyed. Following elimination of a proton restores the aromatic system and this is the driving force to obtain the product.

Groups attached to the ring that stabilize the positive charge in the σ-complex are activating and the reaction proceeds faster and easier. Such groups are electron donors. Usually the donation occurs from a heteroatom as shown in the following Chart.

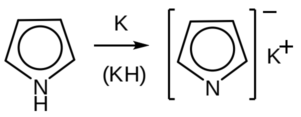
Activating Substituents ortho & para-Orientation		Deactivating Substituents meta-Orientation		Deactivating Substituents ortho & para-Orientation
$-O^{(-)}$	$-NH_2$	$-NO_2$	$-CO_2H$	$-F$
$-OH$	$-NR_2$	$-NR_3^{(+)}$	$-CO_2R$	$-Cl$
$-OR$	$-NHCOCH_3$	$-PR_3^{(+)}$	$-CONH_2$	$-Br$
$-OC_6H_5$	$-R$	$-SR_2^{(+)}$	$-CHO$	$-I$
$-OCOCH_3$	$-C_6H_5$	$-SO_3H$	$-COR$	$-CH_2Cl$
		$-SO_2R$	$-CN$	$-CH{=}CHNO_2$

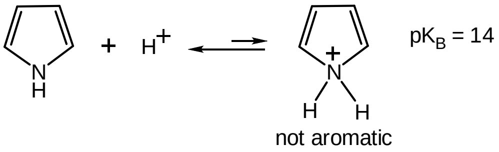
Very similar arguments explain the high reactivity of pyrrole, furan, and thiophene in electrophilic aromatic substitution reactions. The significant difference from substituted benzenes is that the activation of the aromatic system is due to increased electron density provided by the heteroatom in the ring.

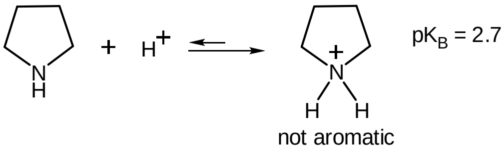


The delocalization of the lone electron pair away from the nitrogen atom in pyrrole can be inferred by the dipole moments of pyrrole and its nonaromatic, saturated counterpart – pyrrolidine. In the saturated compound, the higher electronegativity of nitrogen causes withdrawal of electron density from the ring bonds. The nitrogen atom is at the negative end of the dipole. In contrast, the pyrrole nitrogen is at the positive end of the dipole due to the donation of lone pair to the aromatic system. The dipole moment of pyrrole is rather large, 1.8 D (more polar than ammonia) and the electron density is increased more on the α-carbons. This fact explains the higher reactivity of carbons 2 and 5 in S_EAr substitution reactions.

Since pyrrole lone pair is engaged in the aromatic sextet, the nitrogen does not exhibit basic properties (this is significant difference from tertiary amines and pyridine). Due to the polarization of N-H bond pyrrole is even slightly acidic. Therefore, very strong bases are necessary in order to remove the hydrogen from a pyrrole nitrogen (to deprotonate it). The resulting anion can be alkylated on N or C.

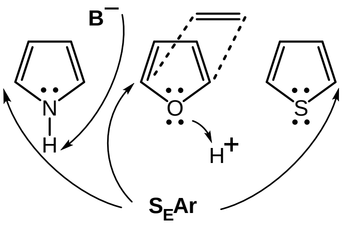




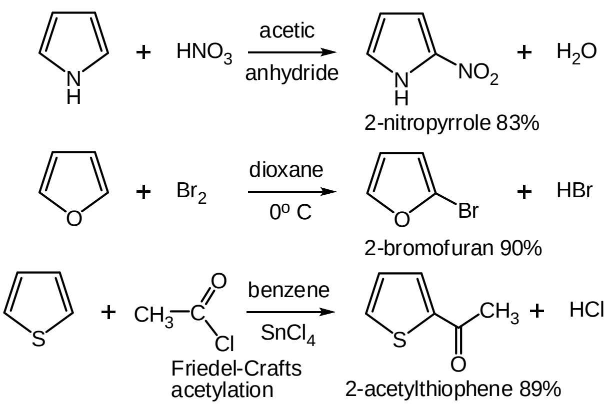


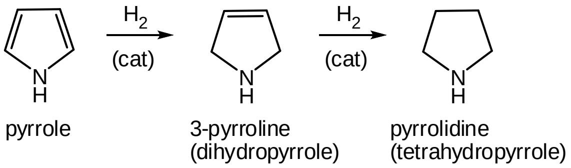
Pyrrole is much less basic and nucleophilic than non-aromatic secondary amines. In order to react as a base or a nucleophile, pyrrole's lone electron pair should leave the aromatic sextet to form a new bond. This is a disadvantageous process because the product is no longer aromatic. Comparison can be made by the basicity constants: protonation of pyrrolidine is preferable to protonation of pyrrole, as the pK_B of pyrrolidine is typical for a secondary amine but pK_B of pyrrole is much smaller.

The general reaction scheme of five-membered aromatic heterocycles – pyrrole, furan, and thiophene is:



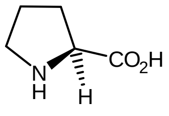
Examples of electrophlic aromatic substitution reactions in pyrrole, furan, and thiophene are shown. The scheme shows that the yields are high and the experimental conditions are much milder than for corresponding reactions with benzene. For all such reactions is essential to use special reagents and mild conditions because of the increased reactivity of these five-membered aromatic heterocycles, e.g. the bromination often leads also to dibromo-derivative.

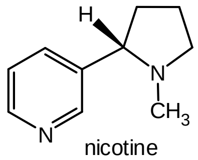


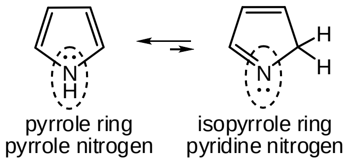


The aromatic system of pyrrole, furan and thiophene is not as stable as that of benzene. Therefore, they are hydrogenated easier and they can participate as a dien in concerted cycloaddition reactions to an alkene. The hydrogenation of pyrrole results in dihydropyrrole (pyrroline), and tetrahydropyrrole, usually called pyrrolidine. In pyrrolines and pyrrolidine, the N lone pair is not in aromatic sextet and these compounds have basic properties.

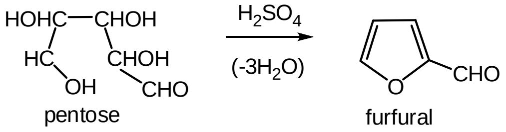
Two examples of natural products containing pyrrolidine ring are proline and nicotine. **Proline** is the only proteinogenic α-amino acid that is a secondary amine (the N atom is in a ring). **Nicotine** is a familiar tobacco alkaloid. Alkaloid is a general name for naturally occurring compound containing basic nitrogen atoms.


L-proline

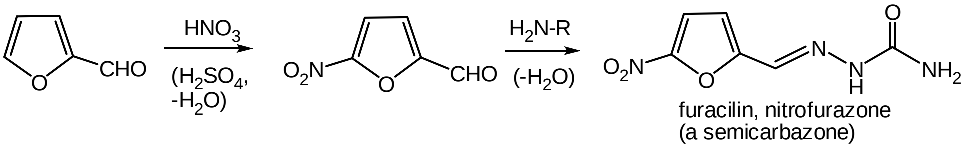

nicotine



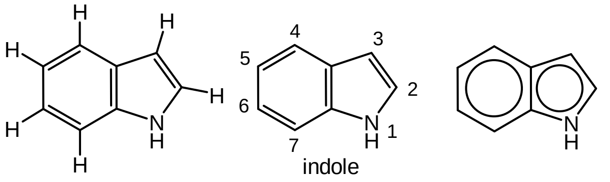
Tautomerism in pyrrole. Two tautomeric forms of pyrrole can be recognized in some specific compounds. In common pyrrole derivatives, the stable tautomer is with the typical pyrrole structure (N lone pair in aromatic system). The isopyrrole structure (N lone pair out of the aromatic sextet) can be recognized in some natural pyrrole pigments, like biliverdin, where conjugation stabilizes such tautomer.



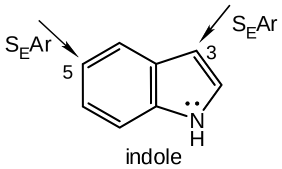
Furfural is 2-furanaldehyde that is obtained from a variety of agricultural byproducts, including corncobs, oat, wheat bran, and sawdust. The production of furfural requires hydrolysis of hemicellulose to xylose which along with other pentoses dehydrates (-3H$_2$O). A derivative of furfural has bactericidal properties and was used as an antibiotic most commonly in the form of ointments.



III. Indole and its derivatives. Indole (benzopyrrole) is heterocyclic compound having fused rings, i.e. rings that share two adjacent ring atoms and the bond between them. Most often the indole structure is represented with double bonds omitting hydrogen atoms (the numbered structure). Indole is an aromatic heterocyclic organic compound. Its structure consists of a six-membered benzene ring fused to a five-membered nitrogen-containing pyrrole ring. Indole is a popular component of fragrances and the precursor to many pharmaceuticals.

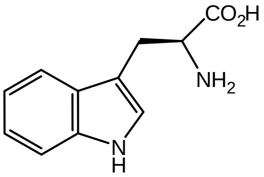


Indole does not possess basic properties due to the engagement of N lone pair in the aromatic system of 10 π electrons. Electrophilic aromatic substitution is preferred at positions C(3) and C(5). The electronic system is activated towards S_EAr reactions for the same reason as for pyrrole. The polar N-H bond determines weakly acidic properties (indolylpotassium). The bond C(2)−C(3) is prone to addition reactions (hydrogenation).



indole

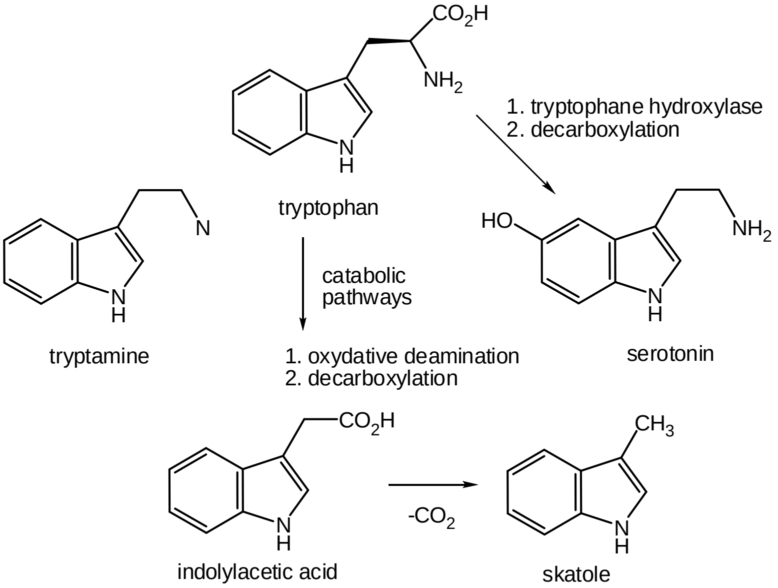
Many natural products and drugs possess indole structures. Indole derivative with greatest importance is the essential amino acid tryptophan.



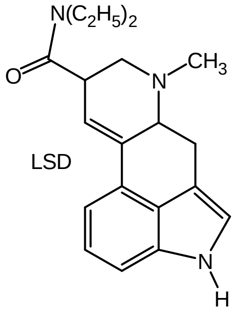
tryptophan

The proteinogenic amino acid **tryptophan** is biochemical precursor for **serotonin** (a calming neurotransmitter when present in moderate levels), **tryptamine** (found in trace amounts in the brains of mammals and is believed to play a role as a neuromodulator or neurotransmitter), and indolylacetic acid (auxin, plant growth substance).

The last compounds in tryptophan catabolism (degradation) are indolylacetic acid and **skatole**.



Indole portion can be recognized in lysergic acid diethylamide, commonly known as LSD. LSD is very potent psychoactive compound and hallucinogen.



LSD

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