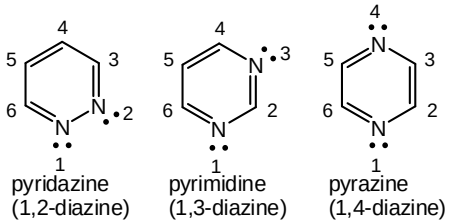
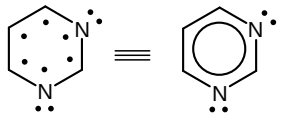
№ 38. SIX- AND SEVEN-MEMBERED HETEROCYCLES WITH TWO HETEROATOMS – PYRIMIDINE, DIAZEPINE AND THEIR DERIVATIVES.

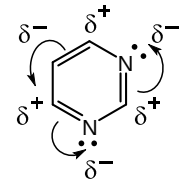
The group of aromatic six-membered heterocycles with two nitrogen atoms is called diazines. The three isomeric diazines are **pyridazine, pyrimidine, and pyrazine**. The numbering system in these diazines begins from one nitrogen atom and runs to the second so as to obtain lowest numbers to the second.



I. **Pyrimidine**. Pyrimidine nucleus is found in many biologically important compounds. Pyrimidine is a six-membered aromatic heterocycle. Its electronic structure is similar to that of benzene and pyridine. The distinguishing feature of this structure is π-electron sextet. Both nitrogen atoms are sp^2 hybridized. The lone electron pairs on the nitrogens are on hybrid sp^2 orbitals, therefore the nitrogens are described as of pyridine type. Each carbon atom and each nitrogen atom provides one electron on non-hybridized $2p_z$ orbital to the π-electron sextet. The lone pairs on both nitrogen atoms in all diazines are out of the aromatic system. Therefore the nitrogen atoms are basic.

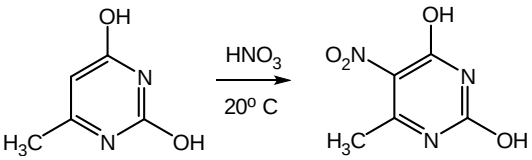


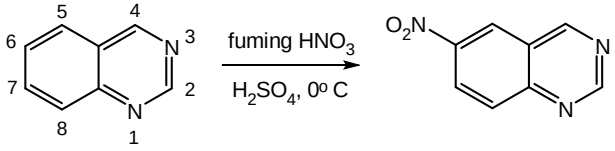
Due to the higher electronegativity of nitrogen in comparison to carbon, the electron density is shifted towards the nitrogen atoms in diazines. Their ring is even further deactivated towards electrophilic aromatic substitution reactions (S_EAr), relative to pyridine. These S_EAr are not typical reactions for diazines.



∴ S_EAr on C-5
S_NAr on C-2

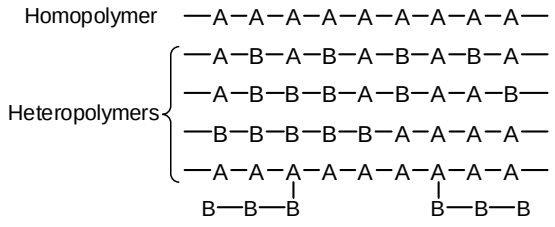
In some pyrimidine derivatives that are specifically substituted with groups that are strong electron donors, like phenolic hydroxyl groups, the activation of the ring is enough to allow S_EAr reaction, e.g nitration. When diazine ring is fused to benzene ring, the benzodiazines react in S_EAr reactions in the benzene ring which is not that strongly deactivated.





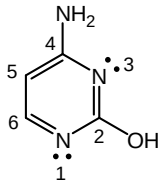
II. Pyrimidine derivatives. 1. Pyrimidines.

Pyrimidine and purine, described later, are heterocyclic fundamental structural components of a major class of biomolecules - the nucleic acids. The nucleic acids, **deoxyribonucleic acid (DNA)** and **ribonucleic acid (RNA)**, are the chemical carriers of a cell's genetic information. Coded in a cell's DNA is all the information that determines the nature of the cell, controls cell growth and division, and directs biosynthesis of the enzymes and other proteins required for all cellular function. The molecules of DNA and RNA are very large molecules. They are **biopolymers**. A polymer is simply a large molecule -sometimes *very* large- molecule (macromolecule) built up by repetitive bonding together of many smaller molecules. These repeating structural units typically connected by covalent chemical bonds are called monomers. One or several different monomers (A, B) can be connected in different ways, as schematically shown. If the polymer contains identical monomeric units, it is a **homopolymer**. When the polymer is constructed by various monomeric units, it is a **heteropolymer**. The arrangement of monomeric units in a heteropolymer may be rather different: regular, irregular, block of identical units attached to block of other unit kind, branched.

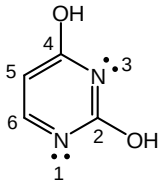


The biopolymers are proteins, carbohydrates, and nucleic acids. Complex carbohydrates can be composed of many various sugar units, proteins - of 20 different amino acid units, and DNA, RNA of 4 different units. From viewpoint of a chemist, DNA and RNA are the simplest biopolymers. They are linear and have random but strictly determined by an organism primary structure, i.e. the order of attachment of monomeric units. Of the three classes biopolymers, only carbohydrates can be branched.

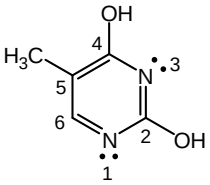
Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) consist of two very long polymers of simple units called **nucleotides**, with backbones made of sugars and phosphate groups joined by ester bonds. Attached to each sugar is one of four types of molecules called nitrogen bases or simply **bases**. Some are **pyrimidine bases**, and some – **purine bases**. The pyrimidine bases are **cytosine**, **uracil**, and **thymine**.



Cytosine (C)
4-amino-2-hydroxypyrimidine
in RNA and DNA



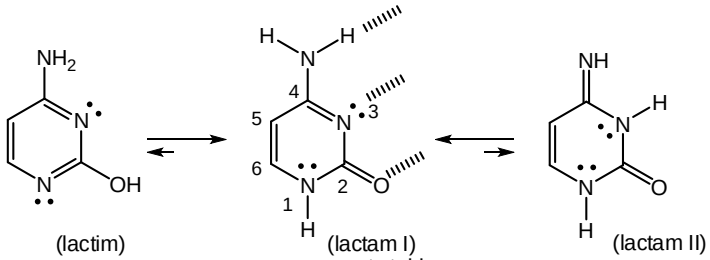
Uracil (U)
2,4-dihydroxy-pyrimidine
in RNA



Thymine (T)
2,4-dihydroxy-5-methylpyrimidine
in DNA

The bases are usually abbreviated using one letter code corresponding to the first letter of the name: **C**, **U**, **T**. All three are aromatic systems which prefer lactam, that is the cyclic amide tautomeric form.

Cytosine is a pyrimidine substituted with an amino group at position C(4) and a **keto group at position C(2)** (at neutral pH). From the three shown tautomers of cytosine, the most stable in physiological conditions is the keto-amino form. Cytosine can be found as part of DNA, RNA, or as a part of a nucleotide. As cytidine triphosphate (CTP), it can act as a co-factor to enzymes, and can transfer a phosphate in conversion of adenosine diphosphate (ADP) into adenosine triphosphate (ATP). In DNA and RNA, **cytosine is paired with guanine** using three hydrogen bonds. These bonds are indicated with dashed lines in the biochemically relevant structures and the pairing pattern will be discussed also later. Cytosine can change into uracil by spontaneous deamination. This change can lead to a point mutation.

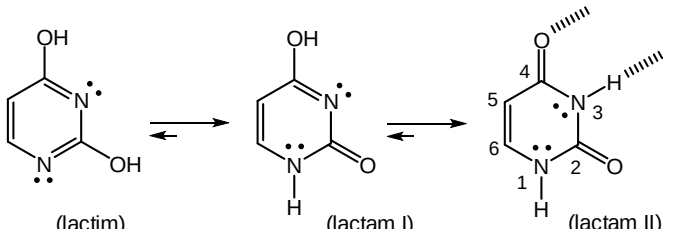


(lactim) (lactam I) most stable (lactam II)

Cytosine tautomers (4-aminopyrimidin-2(1*H*)-one)

Uracil has pyrimidine core substituted with **two keto groups at C(2) and C(4)**. All three tautomeric structures shown are aromatic. Uracil is found in RNA only. It base **pairs with adenine** using two hydrogen bonds (dashed lines) and replaces thymine during DNA transcription. It turns into thymine to protect the DNA and to improve the efficiency of DNA replication. The amide tautomer (designated as lactam II) is predominant at pH = 7 to imidic acid tautomer (the lactim structure).

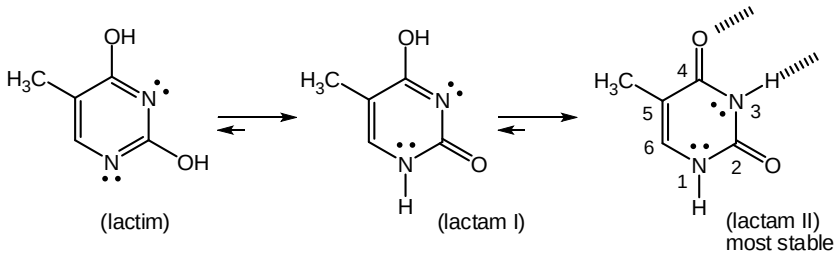
In a 2009 article, NASA scientists reported production of uracil from pyrimidine by exposing it to ultraviolet light under space-like conditions. This fact suggests one possible natural original source for uracil.



(lactim) (lactam I) (lactam II) most stable

Uracil tautomers (Pyrimidin-2,4(1*H*,3*H*)-dione)

Thymine is one of the four nucleobases in DNA. Thymine is similar to uracil having one additional methyl group at C(5), therefore sometimes is referred to as 5-methyluracil. The most stable in physiological conditions is the bis-lactam tautomer with pyrimidine core substituted with two keto groups at C(2) and C(4). All three tautomeric forms are aromatic systems. **Thymine pairs with adenine** through two hydrogen bonds (dashed lines) which stabilize the nucleic acid structure.



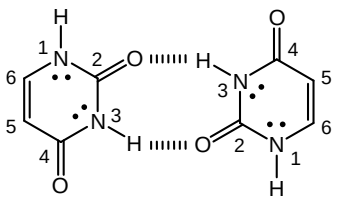
(lactim) (lactam I) (lactam II) most stable

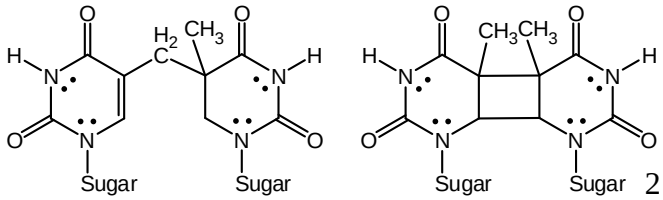
Thymine tautomers (5-Methylpyrimidin-2,4(1*H*,3*H*)-dione)

One of the common mutations of DNA involves two adjacent thymines or cytosine, which, under exposure to ultraviolet light, may form thymine dimers, causing "kinks" in the DNA molecule that inhibit normal function. Such mutation is responsible for melanoma formation (type of skin cancer).

Notice! – all oxygenated pyrimidines in the nucleobases exist in keto forms.

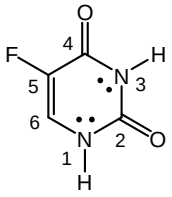
The presence of heteroatoms (N, O) that can donate electron pair and hydrogen atoms (bonded to electronegative nitrogen atom) that can accept an electron pair renders cytosine, uracil and thymine ideal participants in intermolecular hydrogen bonding. Such bonding is responsible for dimer formation *in vitro*, for instance in uracil. These type of dimers are weaker and can be disrupted. They are in equilibrium with the corresponding monomers. On the contrary, the pyrimidine dimers mentioned above, *in vivo* are molecular lesions





Sugar Sugar Sugar Sugar

formed from thymine or cytosine bases in DNA via photochemical reactions. Ultraviolet light induces the formation of covalent linkages by reactions localized on the C=C double bonds in pyrimidine ring.


5-fluorouracil

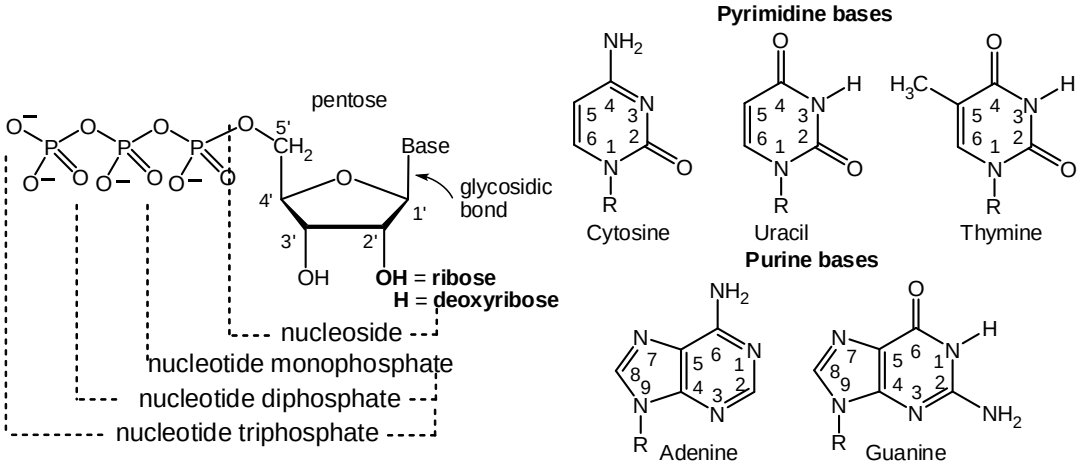
Thymine biosynthesis is the target for actions of **5-fluorouracil** in cancer chemotherapy. 5-Fluorouracil is a drug that is a pyrimidine analog which is used in the treatment of cancer. As a pyrimidine analog, it is transformed inside the cell into different cytotoxic metabolites which are then incorporated into DNA and RNA. Substitution of these analogs inhibits DNA synthesis in actively-dividing cells (hopefully - selectively in cancer cells), finally inducing cell cycle arrest and cell death.

2. Pyrimidine nucleosides and nucleotides.

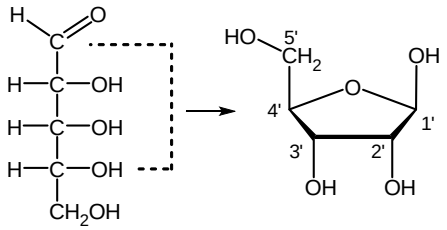
Nucleosides are glycosylamines consisting of a **nucleobase** (often referred to as simply *base*) **bound to a ribose or deoxyribose** sugar via a **beta-glycosidic linkage**. Pyrimidine nucleosides are **cytidine**, **uridine**, and **thymidine**.

A **nucleotide** is composed of a **nucleobase**, a **five-carbon sugar** (either ribose or 2'-deoxyribose), **and one to three phosphate groups**. A nucleoside connected to phosphate groups represents nucleotide.

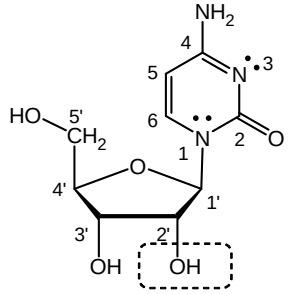
Nucleotides are the monomeric molecules that, when joined together, make up the structural units of RNA and DNA. The general structure of nucleoside, nucleotide, and structures of the bases with the attachment position to the pentose are shown:

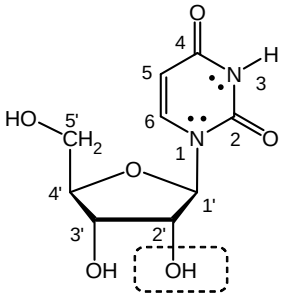


Ribose and deoxyribose exist in five-membered cyclic hemiacetal form. Its presence is indicated in a systematic name, e.g. D-ribofuranose and by the sugar name as a substituent - "furanosyl". Sugar cyclization creates a new stereogenic center called anomeric carbon (1') which is the former aldehyde carbon atom in ribose and deoxyribose. The configuration of the newly created hydroxyl group is designated as α- or β-configuration, depending on spatial OH position relative to the ring's midplane. All nucleosides and nucleotides have their bases attached at β-position. That means, in the usually written projection formulas, **the base is above the furanose plane**.


D-ribose β-D-ribofuranose

The structure, numbering system, and names of nucleosides corresponding to RNA and DNA are shown.

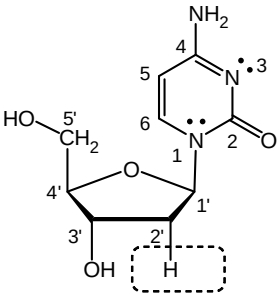

Cytidine (RNA)
1-β-D-ribofuranosylcytosine


Uridine (RNA)
1-β-D-ribofuranosyluracil

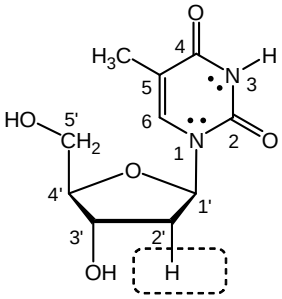
It is important for describing RNA, DNA structures that the ribose or deoxyribose numbers are 1', 2', 3' etc. Using primes (') distinguishes them from the atom numbering in pyrimidine ring. The ribose is a substituent on N(1) of the pyrimidine base, therefore the sugar name ends on "ribofuranosyl". The linkage sugar-base is via β-glycosidic bond to the anomeric carbon C(1').

The names of DNA nucleosides are formed in similar way, using the term deoxyribose instead of ribose, for instance, the cytidine nucleoside of 2-

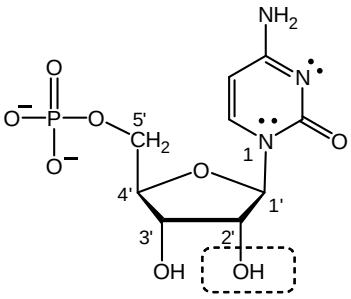
deoxyribose is named 2-deoxycitidine or 1-β-D-2'-deoxyribofuranosylcytosine.



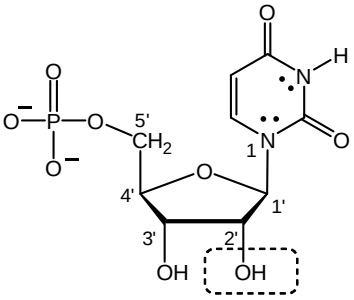
2'-Deoxycytidine (DNA)
1-β-D-2'-deoxyribofura-
nosylcytosine



Thymidine (DNA)
1-β-D-2'-deoxyribofura-
nosylthymine



5'-Cytidine monophosphate
(CMP, cytidylic acid)



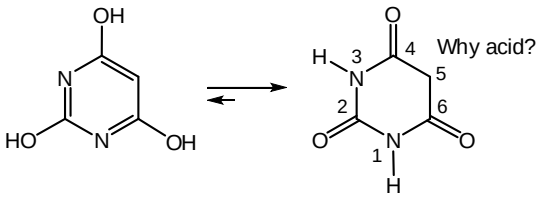
5'-Uridine monophosphate
(UMP, uridylic acid)

Nucleotides are phosphorylated nucleosides. Typically the C(5') sugar hydroxyl group of each nucleoside ribofuranoside or deoxyribofuranoside is esterified with phosphoric acid. **Cyclic nucleotides** are also biochemically important. They are formed when the phosphate group is bound to two of the sugar's hydroxyl groups. Triphosphates are of particular importance – CTP is **cytidine triphosphate**; UTP is **uridine triphosphate**.

At physiological pH the hydroxyl groups on the phosphoric acid residue are ionized.

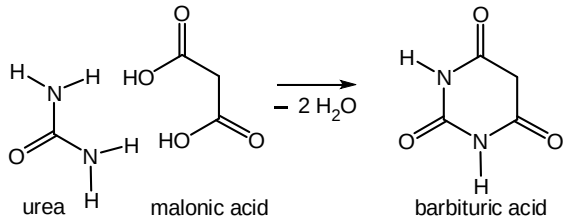
The structures of nucleotides based on deoxyribose are constructed in a similar way. 5'-Deoxycytidine monophosphate (or deoxycytidilic acid) is similar to CMP, except for the pentose which is 2-deoxyribose. Deoxythymidine 5'-monophosphate is nucleotide containing thymidine where the pentose is 2-deoxyribose.

III. Barbituric acid. Barbiturates. Although barbituric acid may be described as 2,4,6-trihydroxypyrimidine (6-hydroxyuracil) it exists in bis-lactam-keto form. The compound was discovered by the German chemist Adolf von Baeyer in 1864, on the day of the feast of Saint Barbara who gave the compound its namesake. The chemical synthesis is simply by combining urea and malonic acid in a condensation reaction with release of 2 moles of water. Barbituric acid is an odorless powder soluble in water.



(6-hydroxyuracil,
2,4,6-trihydroxypyrimidine)

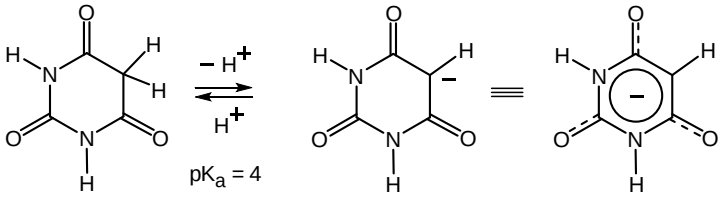
barbituric acid
most stable form



urea malonic acid barbituric acid

Barbituric acid is the parent compound of barbiturate drugs but barbituric acid itself is not pharmacologically active. Barbiturates are classified as sedative-hypnotic agents. They are drugs that act as CNS depressants (decreasing the responsiveness of central nervous system and promoting sleep). By virtue of this, they produce a wide spectrum of effects, from mild sedation to total anesthesia. They are also effective as hypnotics and as anticonvulsants. Many barbiturates are known pharmaceuticals because the parent compound has several available positions for substitution variety. The derivatives of barbituric acid that are disubstituted at C(5),C(5) carbon are most useful.

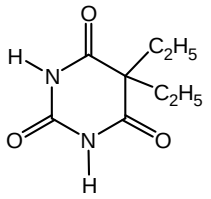
The easy synthesis of C(5),C(5) disubstituted derivatives has its roots in the relatively strong C-H acidity of barbituric acid. It transfers proton from C(5) (deprotonates) even by some weak bases such as acetate ion. The resulting barbiturate anion is stable. The stabilization is due to aromaticity and delocalization of the negative charge on three oxygens. Thus, the anion can be alkylated in one step with two identical groups or stepwise with two different reagents.

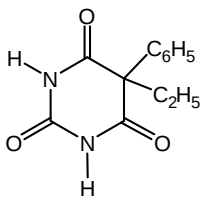


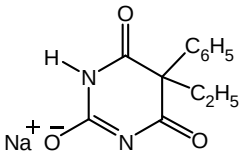
C-H acidity

Barbiturates like Pentobarbital (which is oxygen analog of Thiopental) and Phenobarbital were long used as anxiolytics (for treatment of anxiety) and hypnotics. Ultrashort barbiturates such as Thiopental

produce unconsciousness within about a minute of IV injection. This can be used in preparation of patient for surgery. These compounds are mild tranquilizers.

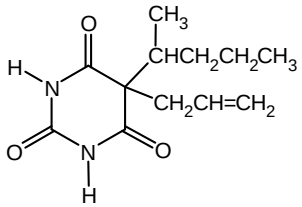

5,5-diethylbarbituric acid
(Barbital, Veronal)

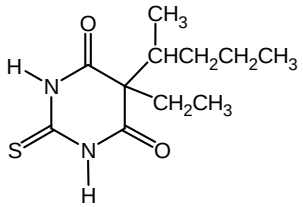

5-ethyl-5-phenylbarbituric acid
(Phenobarbital, Luminal)


Phenobarbital sodium
or Luminal sodium

Long-acting barbiturates such as Luminal and Mephobarbital when taken at bedtime, they help treat insomnia (so called "sleeping pills"), and when taken during the day they have sedative effects that can aid in the treatment of tension and anxiety.

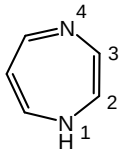
Barbiturates can be used as either the free acid or for better bioavailability as salts of sodium, calcium, potassium, magnesium, lithium, etc. Such salt is Luminal sodium. Sodium Thiopental is sometimes used as a "truth serum". It can decrease inhibitions, making subjects more likely to be caught off guard when questioned.

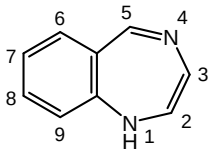

(Secobarbital, Seconal)


(Thiopental, Pentothal)

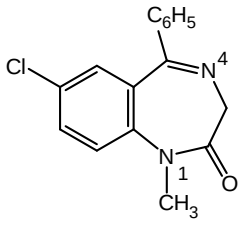
Barbiturates can be abused like ethanol. Barbiturates are intoxicating and produce similar effects during intoxication. Individuals who constantly use these drugs require larger and larger doses to achieve the desired state of "drunkenness". Thus barbiturates have addiction potential, both physical and psychological. Combining alcohol and barbiturates enhances the tranquilizing effect of each. Such synergistic effect might be lethal from overdose.

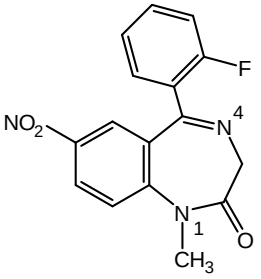
IV. **Diazepines**. The group name diazepines designates compounds that contain seven-membered heterocyclic ring with two nitrogen atoms. The nitrogens can be arranged in 1,2-, 1,3- or 1,4- fashion. The 1,4-diazepine is the core segment in the structure of benzodiazepines which contain also fused benzene ring.

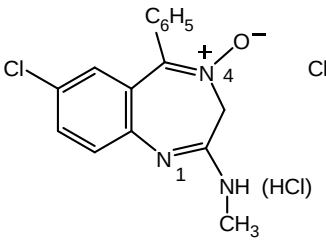

1,4-diazepine

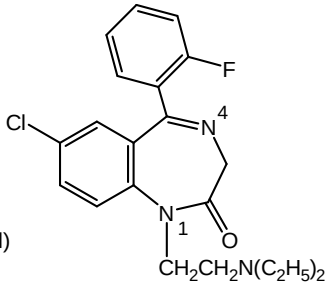

1,4-benzodiazepine

Thousands of derivatives of 1,4-benzodiazepins have been prepared and tested for pharmacological activity although the entire class of compounds is relatively new. The first successful compound from this group was Librium (1960 on the market) that showed very strong sedative, anticonvulsant and muscle relaxant effects. Following Librium, diazepam was marketed in 1963 under the brand name Valium, and for a while the two were the most commercially successful drugs. The introduction of benzodiazepines led to a decrease in the prescription of barbiturates for sedative and hypnotic uses. Barbiturates have now largely been replaced by benzodiazepines in routine medical practice – for example, in the treatment of anxiety and insomnia – mainly because benzodiazepines are significantly less dangerous in overdose. In general, benzodiazepines are psychoactive drugs which possess sedative (act as tranquilizers), hypnotic, anxiolytic, anticonvulsant, muscle relaxant and amnesic (loss of memory) actions


Diazepam (Valium)


Flunitrazepam (Rohypnol)


Chlordiazepoxide (Librium)


Flurazepam (Dalmane)

Flunitrazepam is an intermediate acting benzodiazepine derivative prescribed for the treatment of severe insomnia. It is potent hypnotic and powerful sedative drug, one of the most effective on a dose bases.

Flurazepam is widely prescribed for mild to moderate insomnia of patients having difficulty falling asleep, frequent awakening, early awakenings or a combination of each. Flurazepam is a long acting benzodiazepine and is sometimes used in patients who have difficulty in maintaining sleep. Effects start approximately 1/2 to 1 hour after oral administration but last long time.