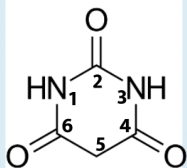


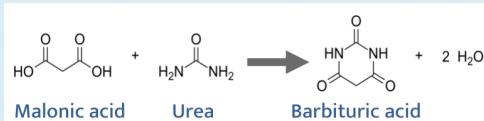
Barbituric acid and Barbiturates

Molar Mass : 128.09 g mol⁻¹

Melting point : 245 °C

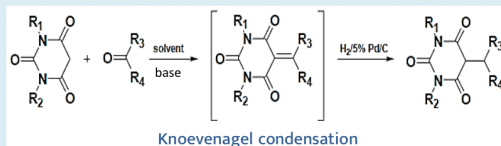


Barbituric acid (also known as malonyl urea) is a white, crystalline, organic compound. This compound is highly acidic (pKa = 4.0) due to a highly active methylene group, whose deprotonation produces an anion that is very stable due to resonance.



This anion can react with aldehydes and ketones to produce mono- or di-substituted barbiturates. Barbituric acid is synthesized by reaction between malonic acid and urea. It is soluble in water, alcohol and ether.

The Knoevenagel condensation reaction is one of the important methods for synthesis and modification of barbiturate compounds. This reaction involves a nucleophilic addition of an active methylene compound to a carbonyl group followed by elimination of a water molecule.



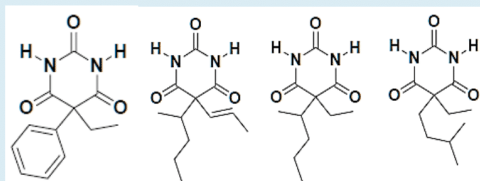
General reaction for synthesis of mono- C-5 alkylated barbiturates

Structure of Barbiturates

Barbiturates are synthesized by making modifications in the structure of Barbituric acid. These modifications can be of three types:

5,5-disubstitution

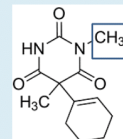
Here the hydrogens in position 5 are substituted with two other functional groups. eg. alkyl or aryl groups.



Phenobarbital Secobarbital Pentobarbital Amobarbital

Substitution on Nitrogen

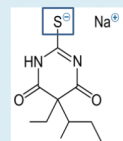
Here alkyl groups replace the imide hydrogens at positions 1 or/and 3.



Hexobarbital

Replacement of Oxygen

In this type, the Oxygen at position 2 is replaced with Sulphur.



Sodium thiopental

Synthesis of Barbiturates

1864



Adolf von Baeyer

Barbituric acid was first synthesized by the German Chemist Adolf von Baeyer, in the year 1864. It did not exhibit any therapeutic properties.

1902



Emil Fischer

In the year 1902, Baeyer's student Emil Fischer and Joseph von Mering synthesized the first barbiturate, Barbital.

On studying the pharmacological properties of Barbital, they found that this new compound could induce sleep. By 1903, Baeyer's company made Barbital available in the market under the name 'Veronal'.

In 1912, Phenobarbital, the second barbiturate drug was synthesized and marketed as 'Luminal' for treatment of seizures, and sleep disorders.

Barbiturates were widely used till mid 20th century after which physicians reduced prescription of barbiturates owing to its harmful side effects

Josep von Mering

Commonly used barbiturates

Barbiturates are used as sedatives, pain killers and anxiolytics (anxiety reducing medication). Over the years, more than 2500 barbiturates were synthesized but only around 50 of them were used clinically. Though barbiturates did not have standard colours, they were commonly known by names based on colours of specific barbiturate capsules produced by famous brands. Currently, very few barbiturates are prescribed for treatment of physical/ mental ailments.

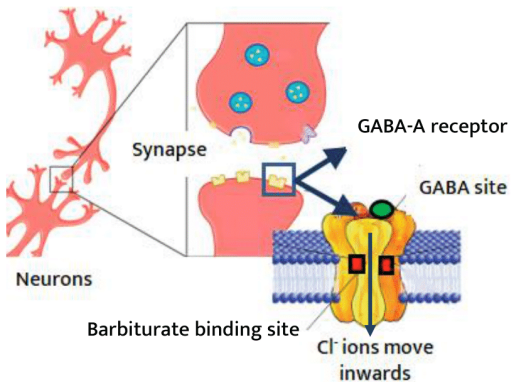


Barbiturates are classified as long-acting, intermediate, short and ultra-short based on i) how long their effects last and ii) their speed of action.

Some barbiturates show anticonvulsant properties and are used to treat epilepsy eg. Phenobarbital. Short-acting barbiturates are used in anesthesia. Others are used to treat insomnia, migraines etc. Use of barbiturates for treating anxiety and insomnia has decreased overtime.

Effect of barbiturates on the CNS

The neurons or the brain cells have ion channels that open or close depending on binding of the neurotransmitter gamma-aminobutyric acid (GABA) at a specific receptor site classed GABA-A receptor. The binding of the GABA to the receptor opens the ion channel and allows the flow of chloride ions into the neuron. The increase in negatively charged chloride ions inside the neurons prevent it from sending signals. As a consequence, the central nervous system calms down and eases stress, anxiety etc.



Binding of barbiturates to the GABA-A receptor keeps the channel open for more time thereby increasing the uptake of Chloride ions. At higher concentrations barbiturates may give rise to opening of the GABA-A receptor channels even in the absence of GABA.

Do you know?

Barbiturates like sodium thiopental and amobarbital are used as 'truth serum' in narcoanalysis. These compounds can make defendants uninhibited and cooperative during police interrogation. However, the reliability of the statements provided under the influence of such drugs are debatable.

Narcoanalysis is illegal in many countries. Previously, it has been used in some notable cases in India.

Detection of Barbiturates

Prolonged use/ over dose of barbiturates can lead to various harmful effects. Therefore, this should be used only under close supervision of medical experts.

Barbiturates or its metabolites can be detected in blood, urine, saliva and even hair follicle samples of users for medical, forensic and drug tests. Barbiturates Drug Testing devices which can display preliminary qualitative results within a few minutes are also available in market, but for such tests the amount of drug present in the sample must exceed a specific cut off level. However, for precise identification and quantitative results methods like gas chromatography/mass spectrometry and liquid chromatography/tandem mass spectrometry (LC/MS/MS) are used.

Other applications of Barbiturates



Barbiturates are used as sedatives and anesthetics in veterinary medicine. Some barbiturates are also used as pH buffers in biological research.

References and Further Reading (Accessed in August, 2020)

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Now, can you find?

- Which barbiturates are under international control and in which categories are they classified? For more questions, refer Indian National Chemistry Olympiad questions (2017 paper): Problem 1-<https://olympiads.hbcse.tifr.res.in/>

