Ministry of Health of the Russian Federation

Volgograd State Medical University

Department of Pharmaceutical and Toxicological Chemistry

SPECIAL PHARMACEUTICAL CHEMISTRY

Pyrimidine derivatives.

Barbituric acid derivatives.

Lesson 5

VII term

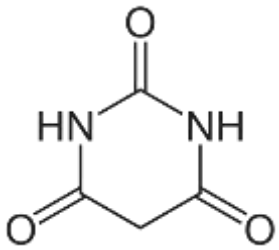
Volgograd, 2023

INTRODUCTION

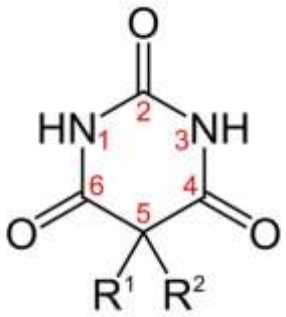
The first barbiturate was discovered in 1862 in Bauer's laboratories in Munich.

Barbiturates were found among many other substances in urine. Many believe that Bauer named them after a woman named Barbara who submitted urine samples (Barbara's urates, Barbiturates). Others claim that the drug was named after the day it was discovered, i.e. St Barbara's Day.

Now the class of drugs called barbiturates has more than two thousand different compounds. But today only about fifty drugs are predominantly used for medical purposes. Since a very large number of barbiturates are still being discovered, usually their common and specific names end with the suffix "-al".

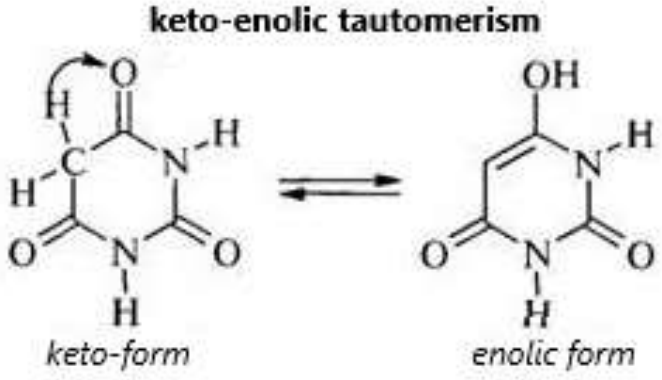


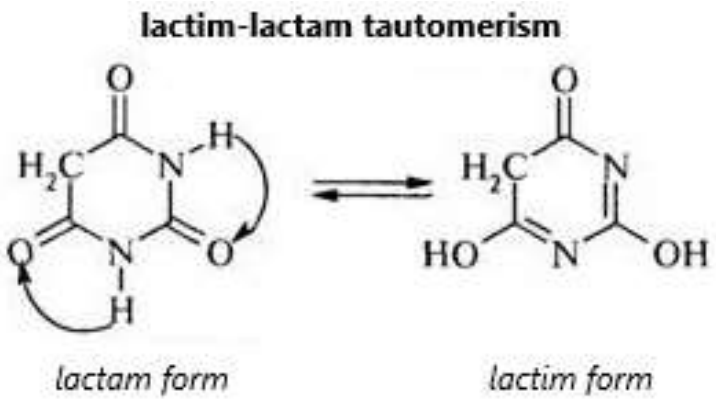
barbituric acid



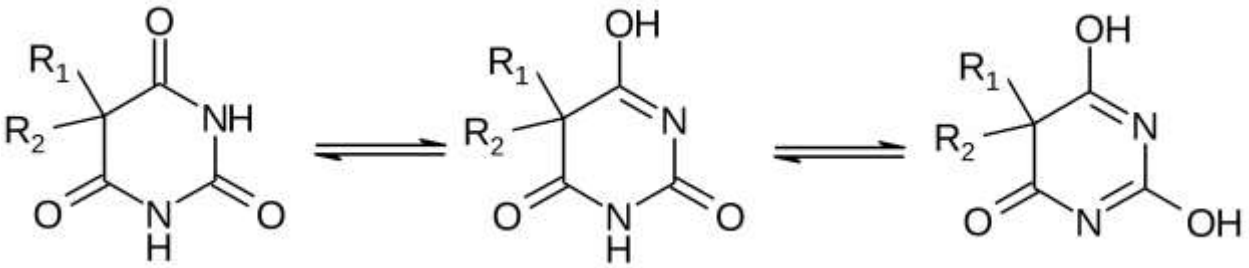
general formula of barbiturates

The acidic properties of barbituric acid are due to the fact that the hydrogen of the imidine (-NH-) and methylene groups, which are in the neighbourhood of carbonyl groups, under their influence acquire greater mobility and can be replaced by metals to form salts. Thus, in the case of barbituric acid, tautomerism can occur, both *ketoenolic* (due to the hydrogen of the methylene group) and *imidoimidolic* (due to the hydrogen of the imide groups):





In the case of barbituric acid derivatives, when the hydrogen of the methylene group is replaced by radicals, only imidoimidol tautomerism is possible:

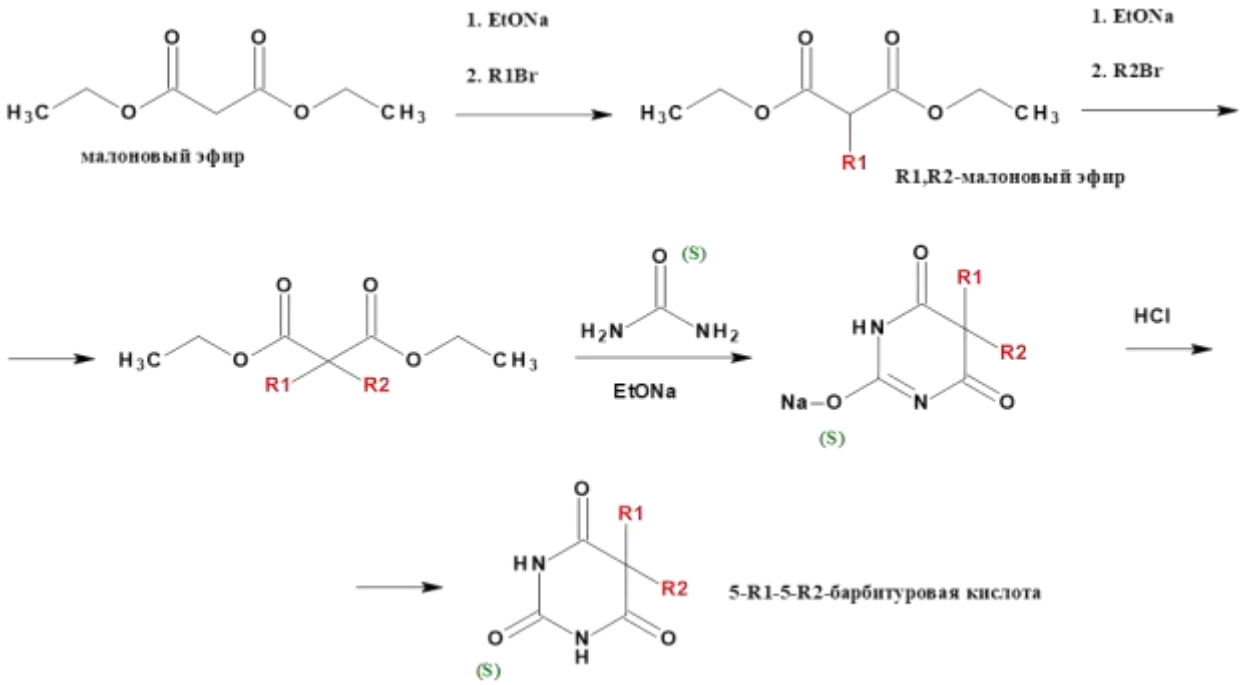


The enolic form of barbituric acid and its derivatives is responsible for their acidic character.

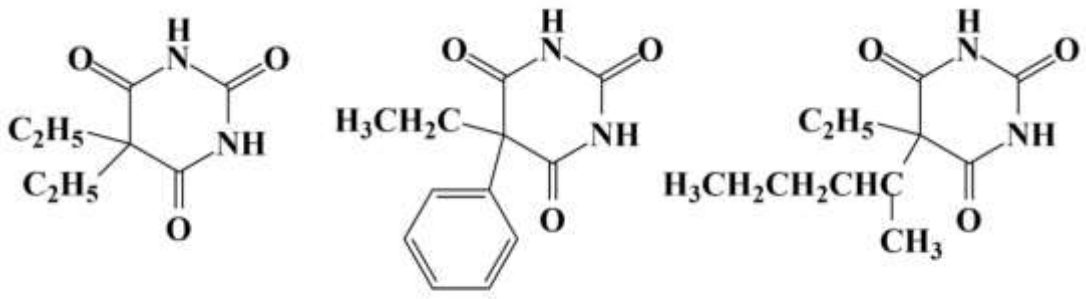
Barbituric acid and its salts have no therapeutic effect and therefore are not medicines. But the ability of the hydrogen of the methylene group to be substituted by various organic radicals makes it possible to obtain a large number of derivatives of this acid (barbiturates), which are successfully used in medicine as drugs with sedative and narcotic effects.

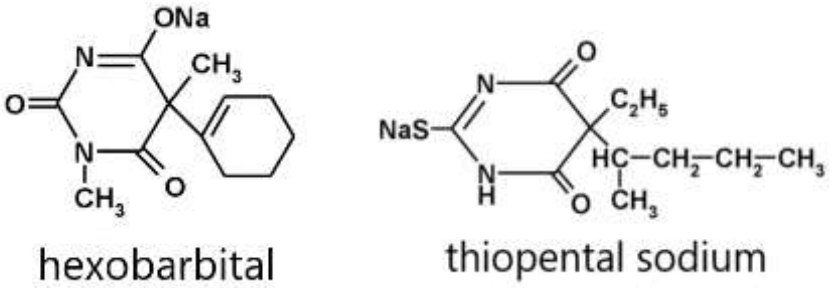
GENERAL METHOD OF OBTAINING

Usually alkylated barbituric acid derivatives are obtained by condensation of urea with the appropriate malonic acid ester. Appropriate substituents (radicals) are introduced into the malonic acid ester beforehand, and then the alkylated ester is condensed with urea:



EXAMPLES OF BARBITURATES





PHYSICAL PROPERTIES

In accordance with their physical properties, barbiturates are white crystalline substances.

A distinction should be made between acid barbiturates (barbital, phenobarbital) and barbiturate salts (medinal, hexenal, barbamyl, etc.).

Acidic forms of barbiturates are slightly soluble in water, insoluble in acids, but easily soluble in solutions of caustic alkalis and in sodium carbonic acid solution. They are also soluble in some organic solvents (diethyl ether, alcohol, chloroform, ethyl ether of acetic acid), the best of which is ethyl acetate. They have definite melting points which characterise the individuality of each drug.

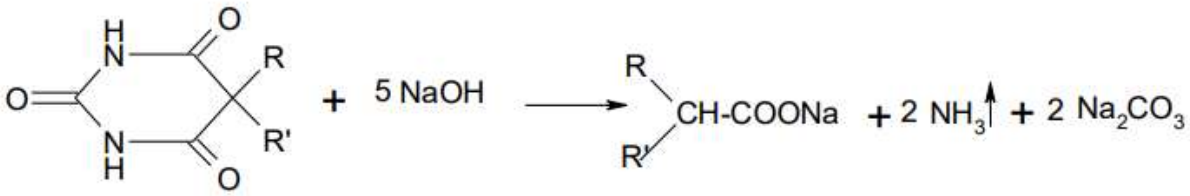
Barbiturate salts are well soluble in water. When heated, barbiturates ignite without decomposing.

The acidic forms of barbituric acid derivatives are stable in storage, and their sodium salts decompose relatively easily under the influence of carbon dioxide and air moisture with the release of the acid form of barbiturate.

GENERAL IDENTITY REACTIONS

1. Melting with alkalis

All barbiturates (as well as barbituric acid) break down when melted with caustic alkalis, releasing ammonia (a decomposition product of urea):

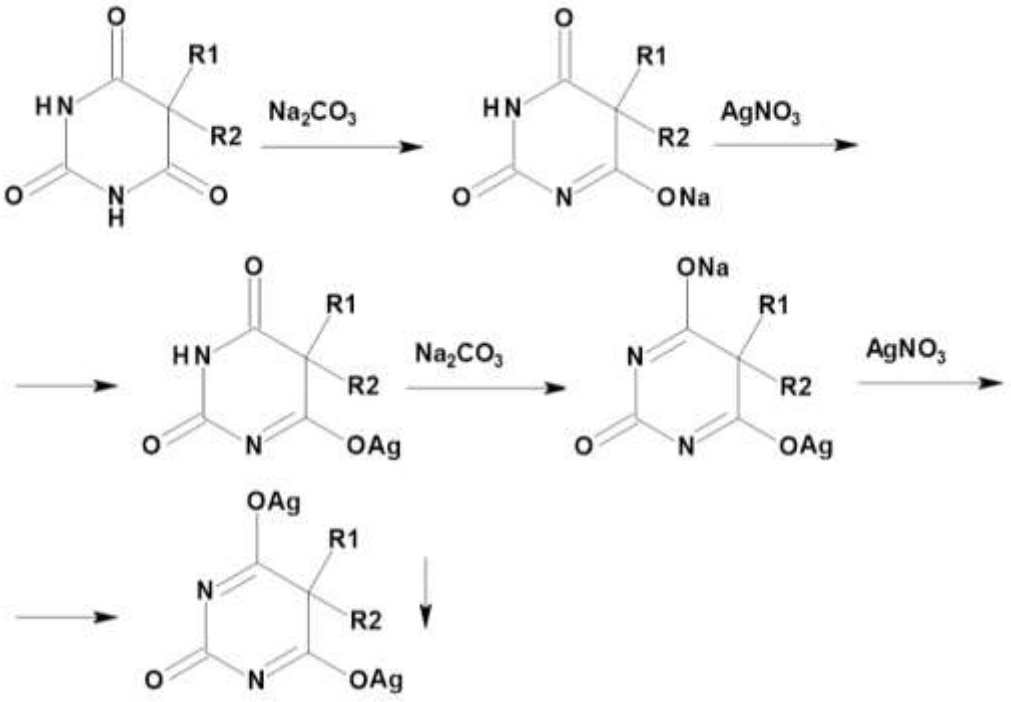


If the resulting reaction products are acidified, gas bubbles (CO_2) will be released and the odour of the corresponding fatty acid will be sensed:

$$Na_2CO_3 + 2HCl = 2NaCl + CO_2 + H_2O$$

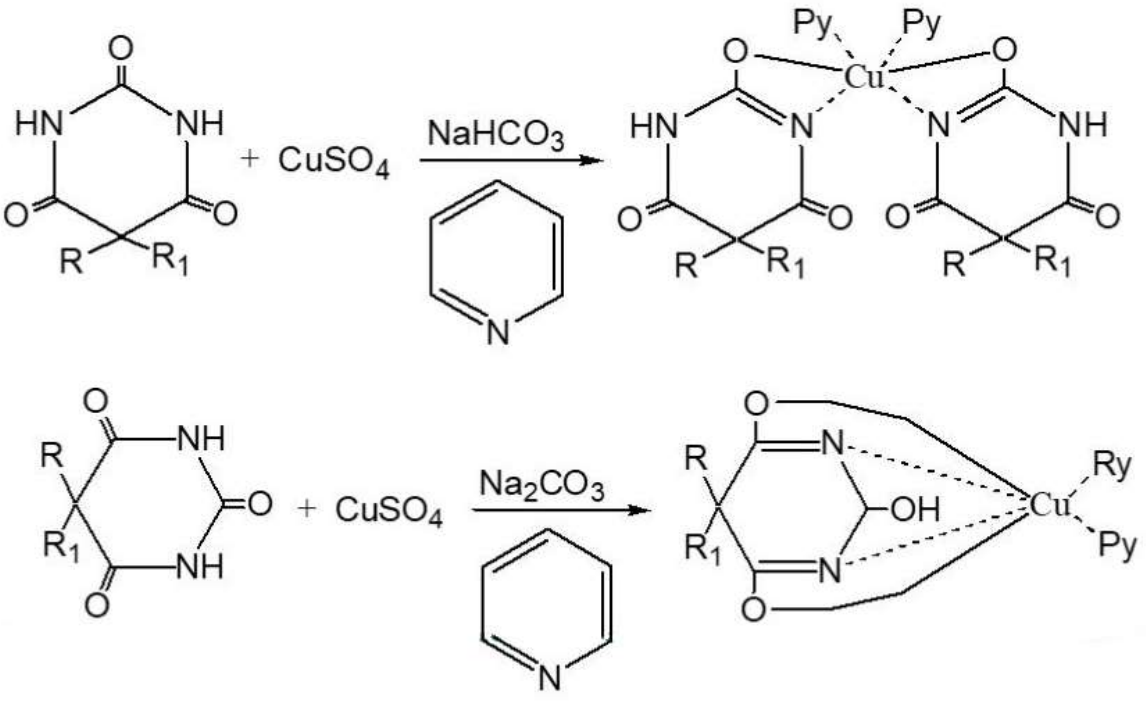
2. Interaction with silver nitrate

With their acidic properties, barbiturates are capable of forming two kinds of silver salts: monosubstituted (water-soluble) and disubstituted (water-insoluble):

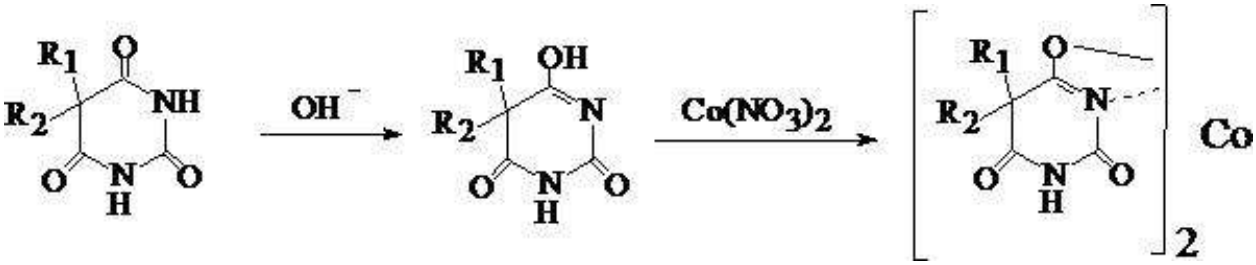


3. Interaction with copper salts in the presence of pyridine.

With salts of divalent copper in the presence of pyridine, barbiturates form one- and two-substituted complexes coloured lilac.



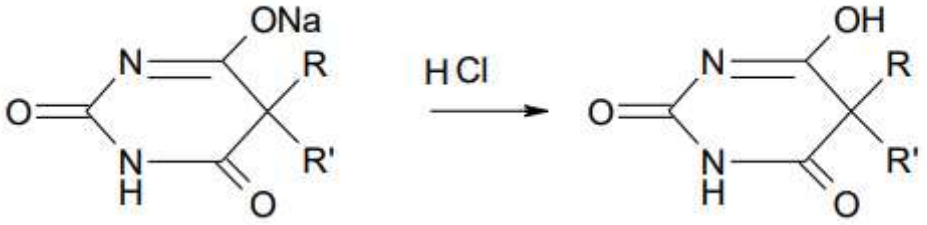
4. Reaction with cobalt nitrate and calcium chloride in the presence of one drop of 10% alkali solution.



A blue-violet colouring appears.

5. Interaction with mineral acids

Barbiturate salts, when mineral acid is added to their aqueous solution, produce an acid form that is insoluble in water and therefore precipitates:



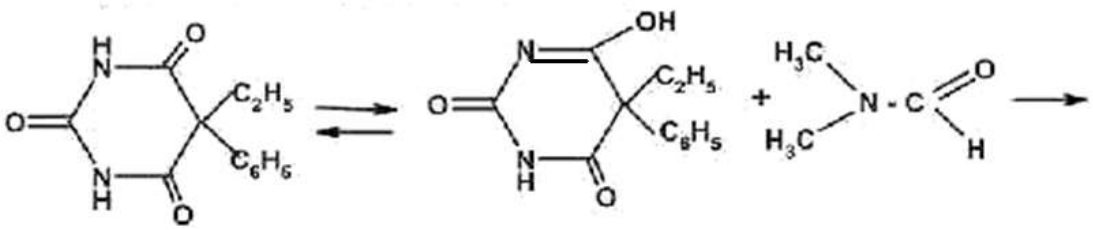
GENERAL METHODS OF QUANTIFICATION

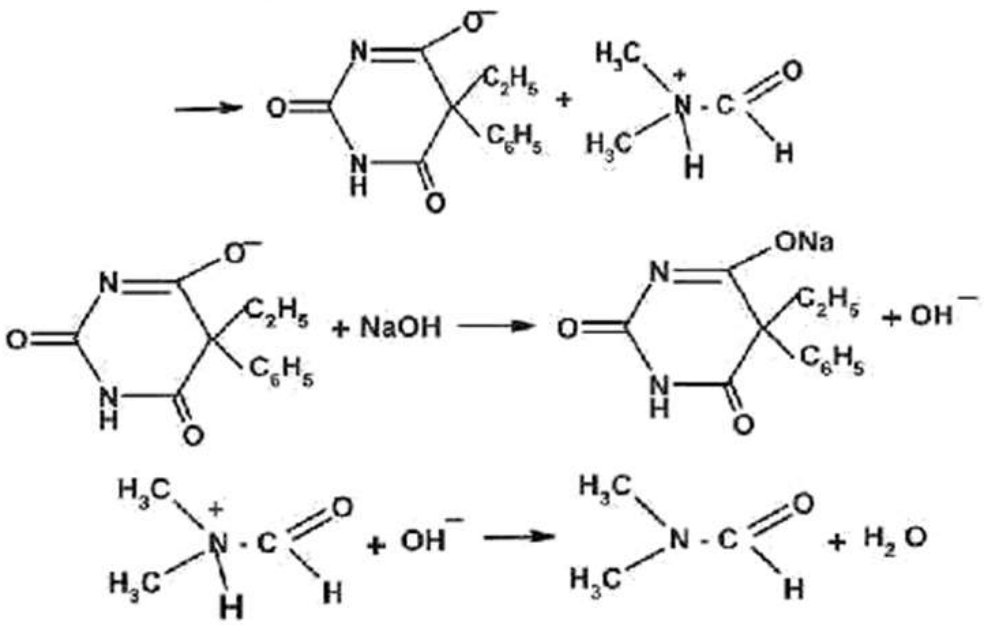
1. Gravimetry

The acidic forms of barbiturates are extracted with ether from the acidic medium. The ether is then distilled off, the residue is dried and weighed. This method is usually used for the determination of the sodium salts of barbiturates and for the analysis of drug mixtures.

2. Non-aqueous titration (for acid forms)

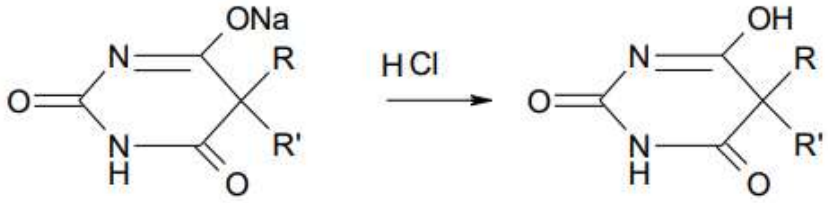
Barbiturate is titrated with sodium methylate in DMFA or caustic potassium in alcohol or acetone, indicator - thymolphthalein.





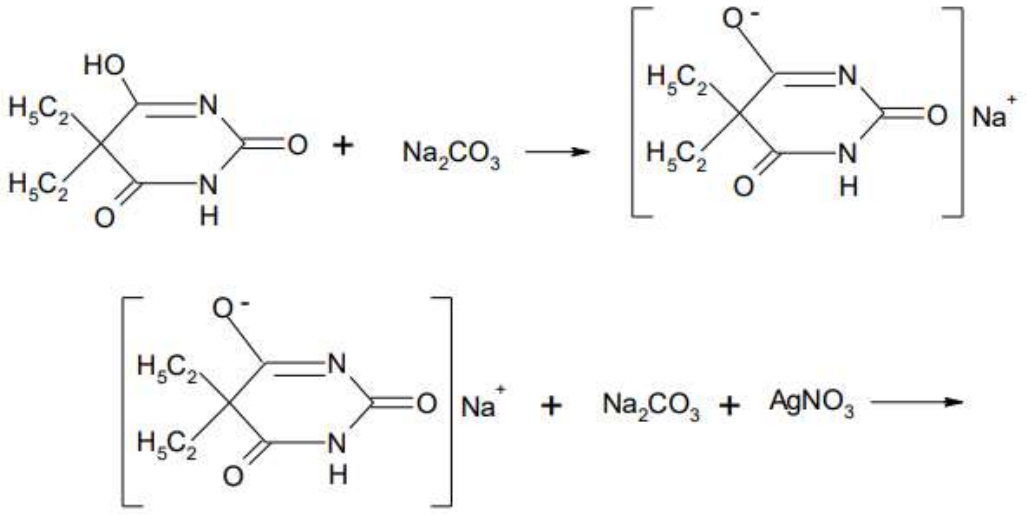
3. Acidometry (for salt forms)

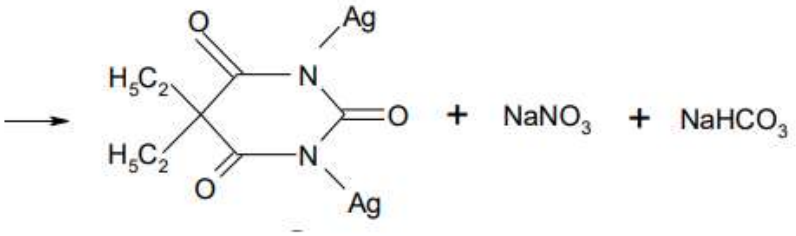
Barbiturate is titrated with mineral acid in the presence of diethyl ether, indicator - methyl red.



4. Argentometry

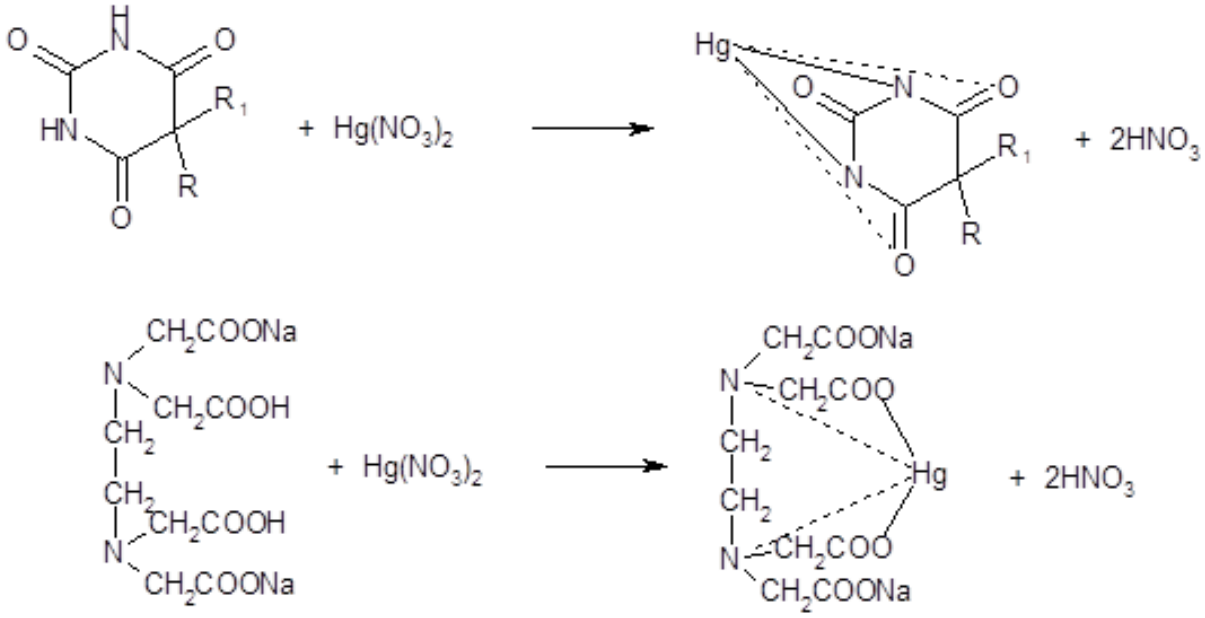
For acidic forms of barbiturates without substituents at nitrogen atoms, the direct argentometry method is used for titration in carbonate medium without indicator.





5. Mercurimetry

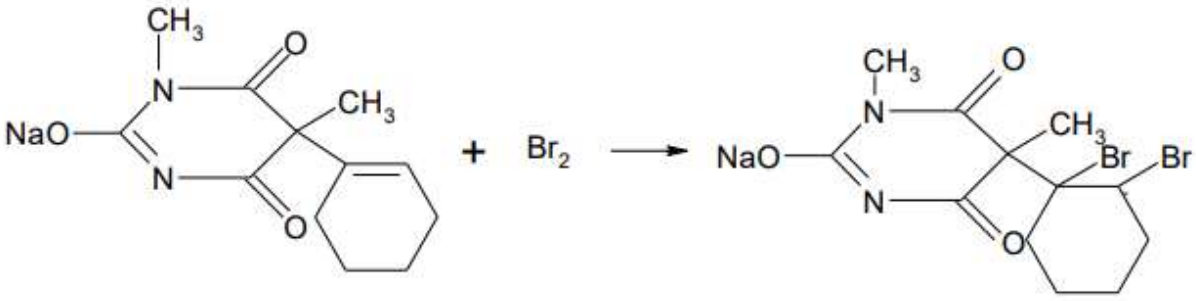
An excess of mercury (II) nitrate solution is added to the barbiturate. The resulting precipitate of mercury barbiturate is filtered off. The unreacted excess of mercury nitrate is titrated with trilon B.



6. Bromatometry

This method is used for the quantification of barbiturates having an unsaturated bond in the molecule (e.g. hexenal).

$$KBrO_3 + 5KBr + 6HCl \longrightarrow 3Br_2 + 6KCl + 3H_2O$$

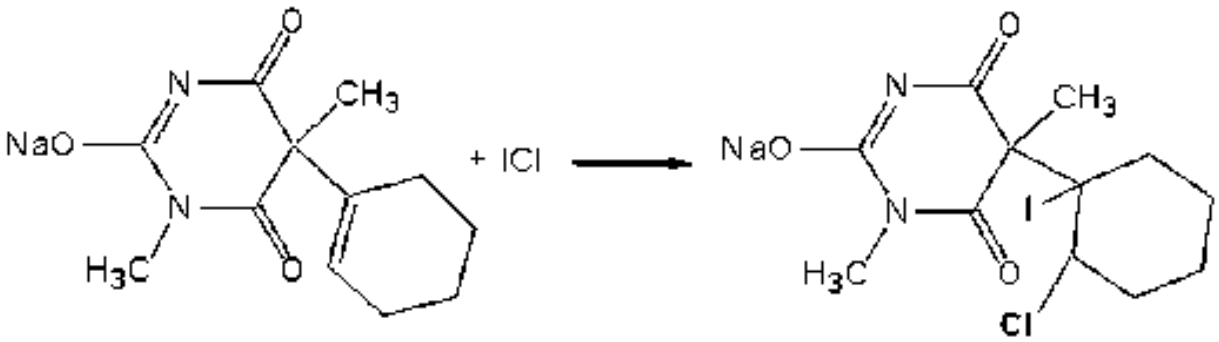


$$Br_2 + 2KI \longrightarrow I_2 + 2KBr$$

$$I_2 + 2Na_2S_2O_3 \longrightarrow 2NaI + Na_2S_4O_6$$

7. Iodochlorometry

The iodochlorometric method can also be used for the quantification of unsaturated barbiturates. Iodine chloride will attach at the double bond site and excess iodine is determined iodometrically.



$$ICl + KI \longrightarrow I_2 + KCl$$

$$I_2 + 2Na_2S_2O_3 \longrightarrow 2NaI + Na_2S_4O_6$$

8. Spectrophotometry

In biological fluids, barbiturates are determined spectrophotometrically by the formation of coloured copper or cobalt complexes.

RELATIONSHIP BETWEEN CHEMICAL STRUCTURE, NARCOTIC AND ANTICONVULSANT ACTION IN A SERIES OF BARBITURATES

In studying the relationship between the structure of barbiturates and their action on the body, it was possible to establish some regularities.

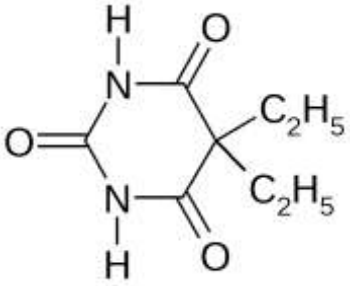
1. Lengthening the chain of the alkyl substituent at C^5 to 5-6 carbon atoms increases sedative and sleeping effects. Further increasing the chain decreases the activity of the substance and stimulates convulsions.
2. The introduction of an aromatic substituent at the C^5 position increases activity and gives anticonvulsant properties.

3. Branching the chain of the alkyl substituent at C^5 increases activity and decreases duration of action.
4. The introduction of halogens or a double C=C bond in the substituent at C^5 increases the activity.
5. Substitution at one nitrogen atom decreases the duration of action, substitution at both nitrogen atoms gives a convulsive effect.
6. Thiobarbiturates have a shorter duration of action than similarly structured barbiturates.

BARBITAL

BARBITALUM

5,5-Diethylbarbituric acid



Barbital (Veronal) is one of the first sleeping pills from the group of barbituric acid derivatives. It was first obtained in 1881 and has been used in medicine since 1905.

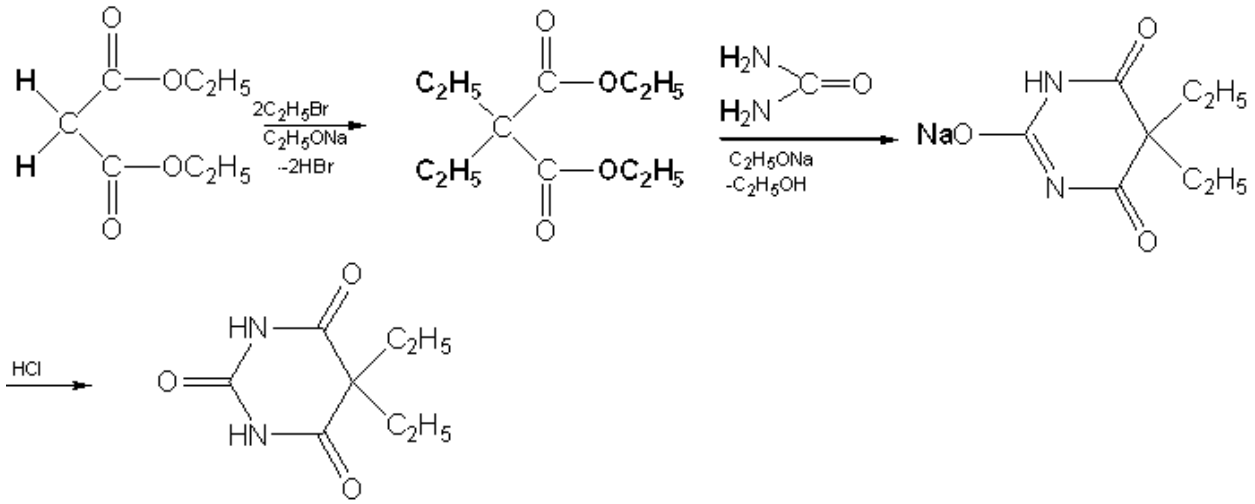
OBTAINING

The production of barbital consists of the following steps:

1. Obtaining of diethyl ether of diethylmalonic acid

2.Condensation of diethyl ether of diethylmalonic acid with urea

3.Purification of the technical product



PHYSICAL PROPERTIES

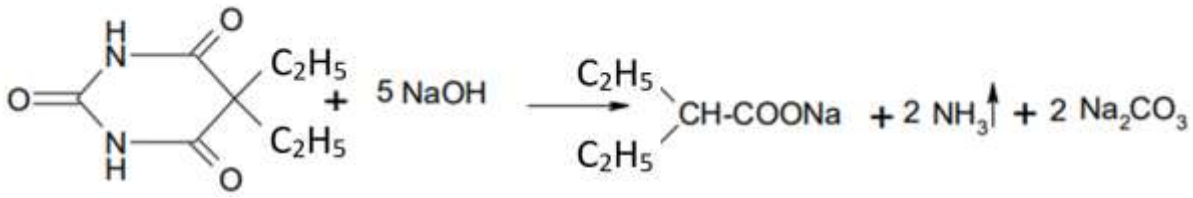
White crystalline powder of slightly bitter taste, odourless. Melting point is 191°C.

Difficult to dissolve in cold water, easier to dissolve in hot water, forming a liquid with acidic reaction. Being an acid, barbital dissolves in alkalis, easily dissolves in some organic solvents: alcohol, ether.

IDENTIFICATION

1. Alloying with alkali (General reaction)

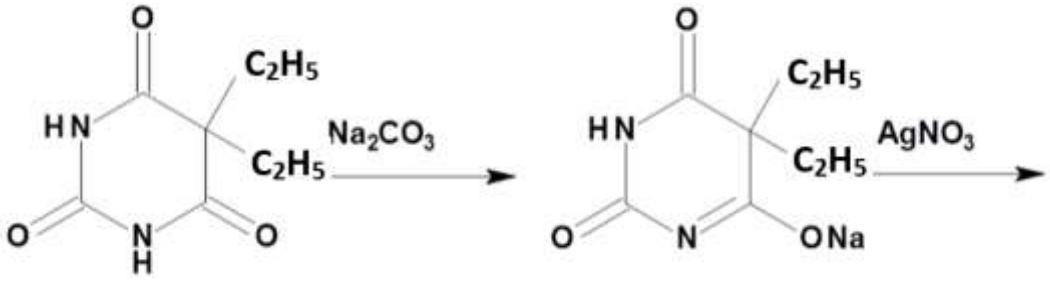
Barbital breaks down when melted with alkali, and an odour of ammonia is sensed. On following acidification, the release of gas bubbles (CO2) is observed and a specific odour of diethylacetic acid is sensed.

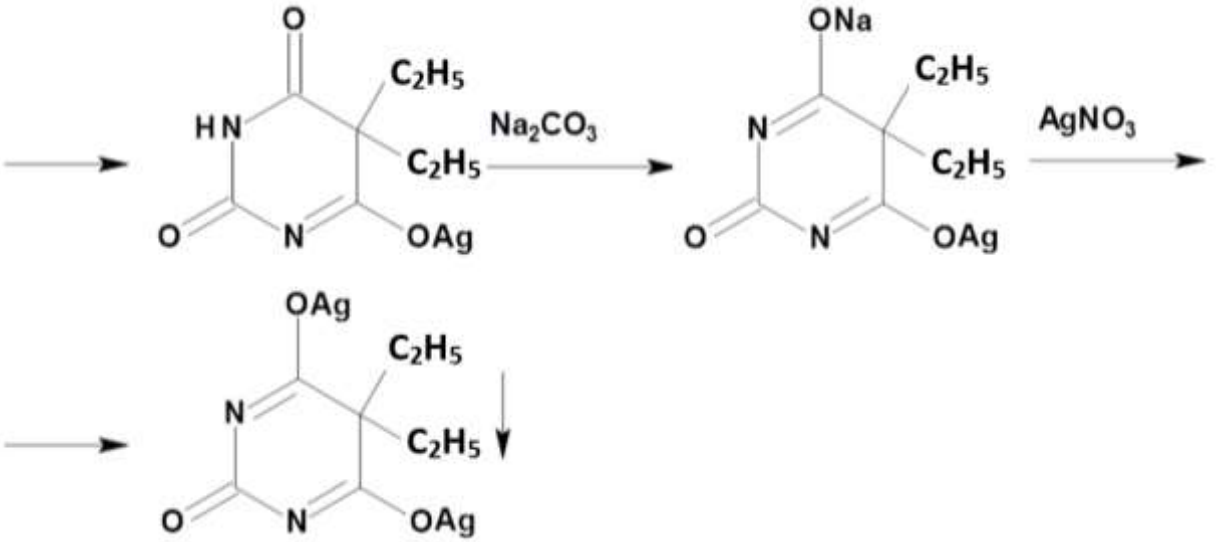


$$Na_2CO_3 + 2HCl = 2NaCl + CO_2 + H_2O$$

2. Interaction with silver nitrate (General reaction)

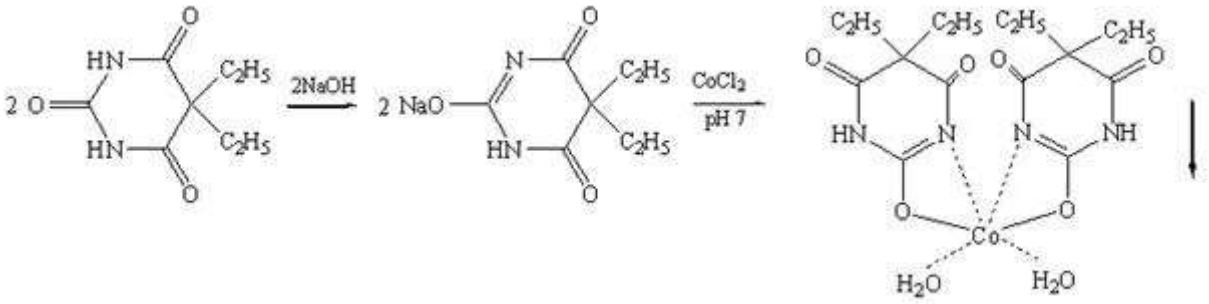
If a dilute solution of AgN03 is added to an alkaline solution of barbital, a white precipitate of doubly substituted silver salt falls out.





3. Interaction with cobalt salts (General reaction)

Barbital gives a blue-violet colouring when solutions of cobalt chloride or cobalt nitrate are added to it.

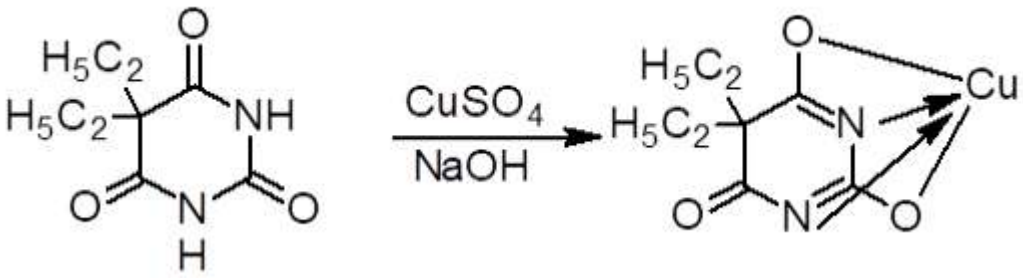


4. Interaction with copper salts in the presence of pyridine (General reaction)

Form complexe coloured lilac.

5. Interaction with copper sulphate (Specific reaction)

A blue colouration appears, followed by the formation of a reddish purple precipitate.



6. Reaction with calcium oxide (Specific reaction)

A mixture of calcium oxide and barbital is heated in a porcelain cup. At first ammonia vapours are released, then a brick-red colouring appears on the surface of the reaction mass.

PURITY TEST

Diethylbarbituric acid, diethylacetylurea and other organic impurities are determined.

QUANTIFICATION

1. *Non-aqueous titration*
2. *Argentometry*
3. *Mercurimetry*
4. *Gravimetry*

STORAGE

In well sealed containers, in a dry place.

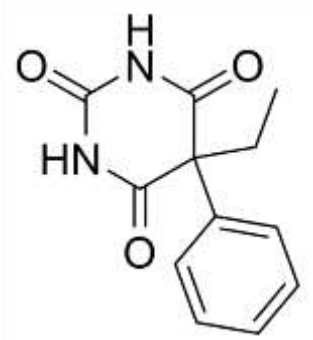
MEDICAL USE

Barbital is used as a sleeping pill in powders and tablets

PHENOBARBITAL ((LUMINAL)

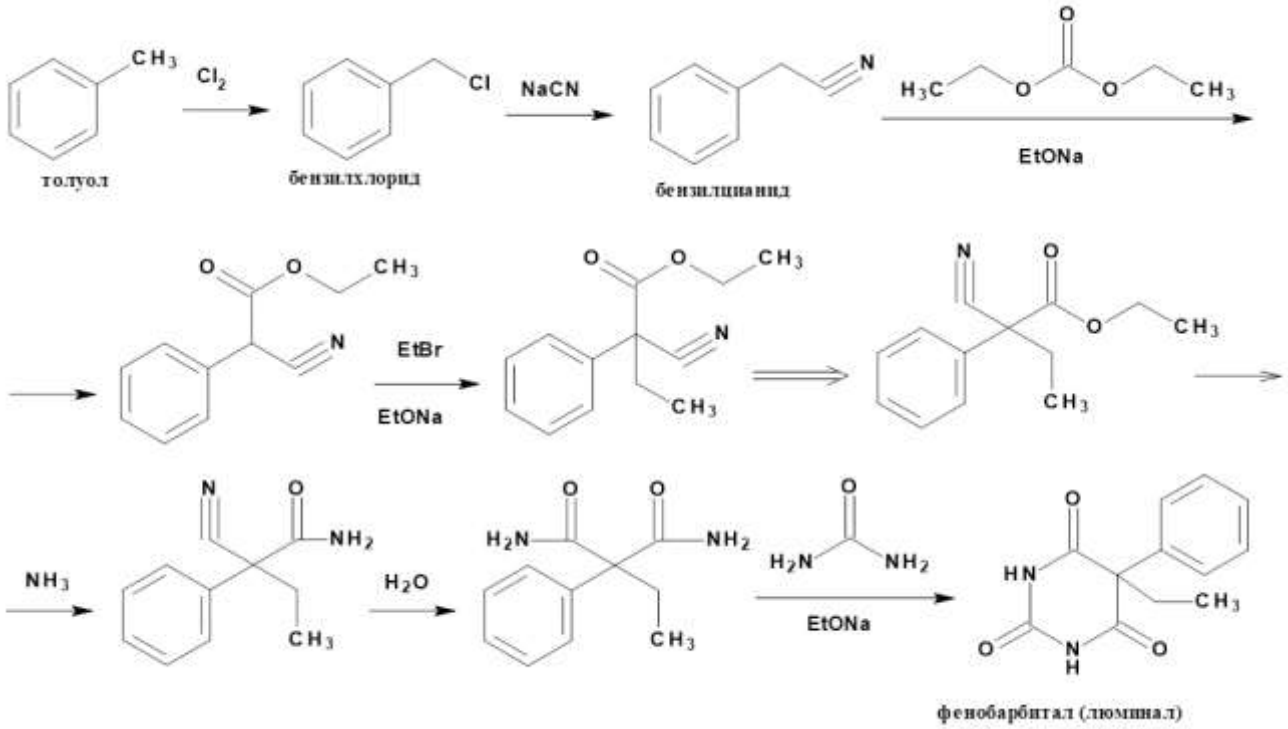
PHENOBARBITALUM

5-Phenyl-5-ethylbarbituric acid



Bayer released ***phenobarbital*** for sale in 1912 under the trade name ***Luminal***. The new barbiturate was synthesised by German chemist Emil Fischer in 1904, 2 years after the synthesis of the first barbiturate, barbital. Luminal remained a common sedative and sleeping pill until the advent of benzodiazepines in the 1950s.

OBTAINING



PHYSICAL PROPERTIES

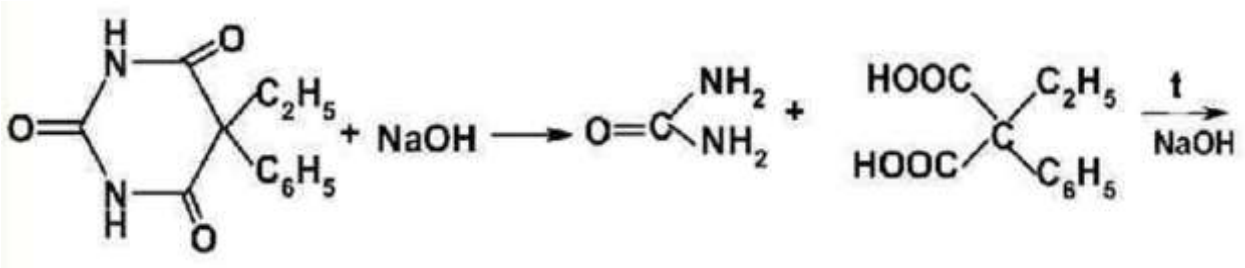
White crystalline powder without odour. Melting point 175-179 C.°

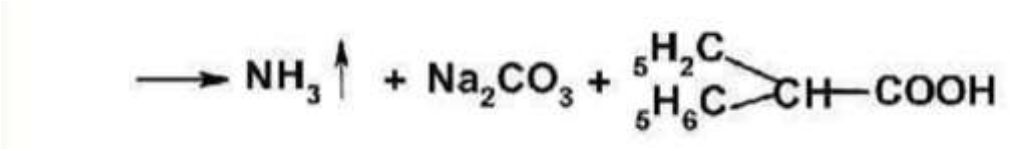
Very slightly soluble in cold water, hardly soluble in boiling water and chloroform, easily soluble in 95% alcohol and alkali solutions, soluble in ether.

IDENTIFICATION

1. Alloying with alkali (General reaction)

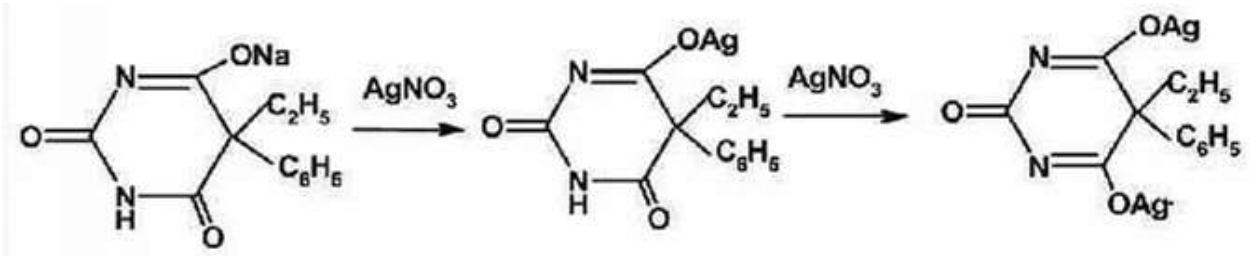
Phenobarbital breaks down when melted with alkali, and an odour of ammonia is sensed. On following acidification, the release of gas bubbles (CO2) is observed and a specific odour of phenylacetic acid is sensed.





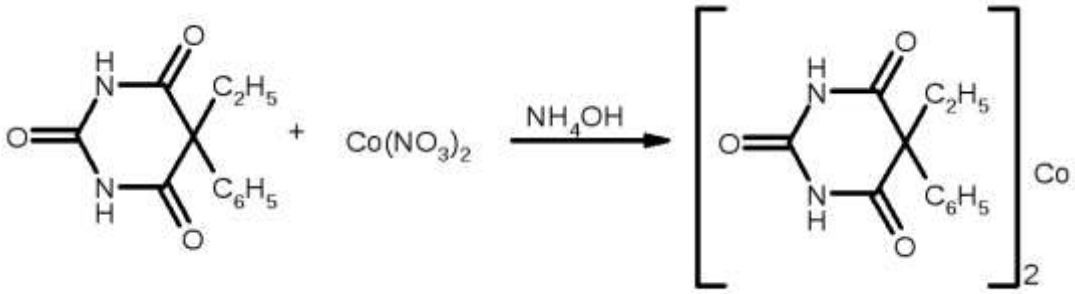
2. Interaction with silver nitrate (General reaction)

If a dilute solution of AgN03 is added to an alkaline solution of phenobarbital, a white precipitate of doubly substituted silver salt falls out.



3. Interaction with cobalt salts (General reaction)

Phenobarbital gives a blue-violet colouring when solutions of cobalt chloride or cobalt nitrate are added to it.

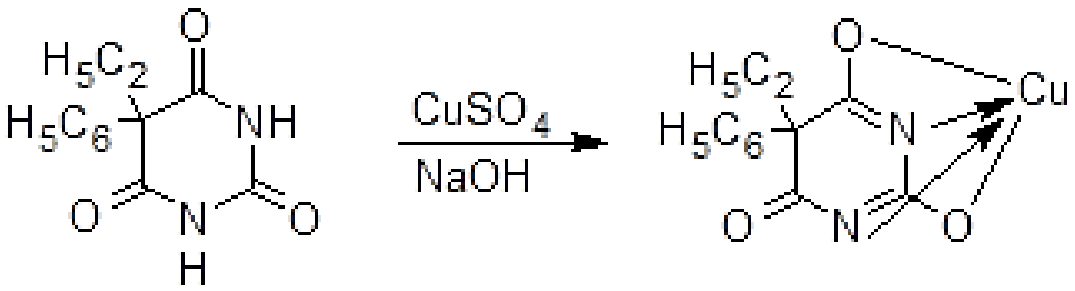


4. Interaction with copper salts in the presence of pyridine (General reaction)

Form complexe coloured lilac.

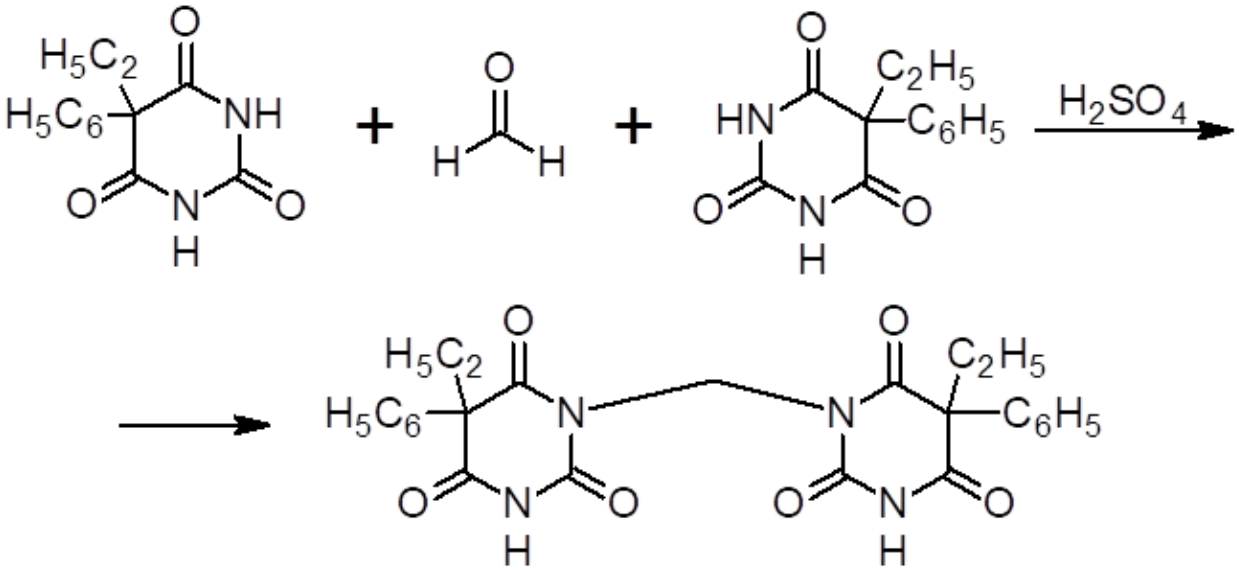
5. Interaction with copper sulphate (Specific reaction)

The reaction produces a pale lilac coloured precipitate.



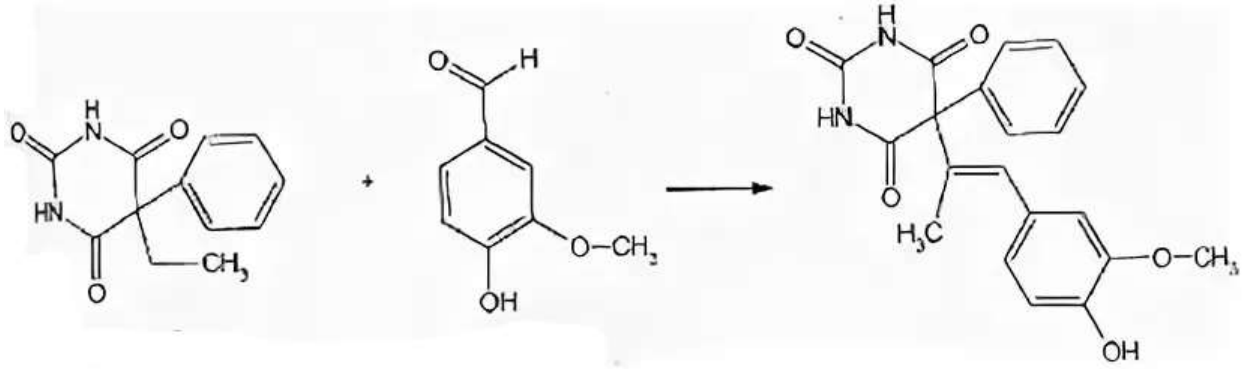
6. Reaction with formaldehyde solution and sulphuric acid (Specific reaction)

A small amount of phenobarbital is dissolved by heating in a formaldehyde solution in a water bath. Then concentrated H2SO4 is carefully poured over the walls of the test tube and the mixture is heated again. A pink ring is formed at the boundary of the two liquids.



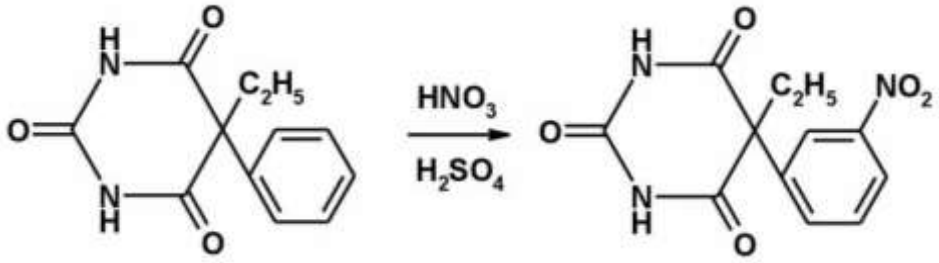
6. Interaction with vanillin (Specific reaction)

When phenobarbital is boiled with vanillin in the presence of concentrated sulphuric acid, cherry colouring appears, changing to blue-violet colouring.



7. Nitration reaction of the aromatic ring (Specific reaction)

When a nitrating mixture (concentrated HNO3 and H2SO4) is added to phenobarbital and heated, a yellow colouration is formed:



PURITY TEST

Determine the content of phenylbarbituric acid and other organic impurities.

QUANTIFICATION

1. *Non-aqueous titration*
2. *Argentometry*
3. *Mercurimetry*
4. *Gravimetry*

STORAGE

Store in dark glass jars in a place protected from light.

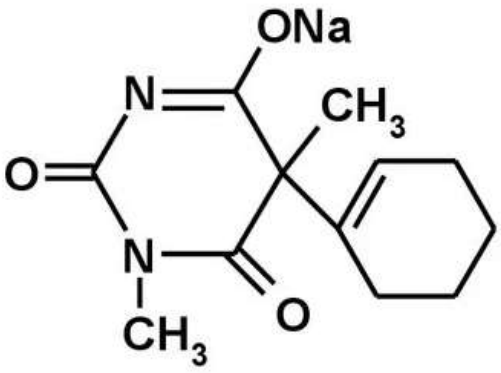
MEDICAL USE

Phenobarbital is a long-acting sedative; it also slightly reduces arterial blood pressure and stops epileptic attacks.

HEXENAL

HEXENALUM

1,5-Dimethyl-5-cyclohexene-1'-yl-barbiturate sodium



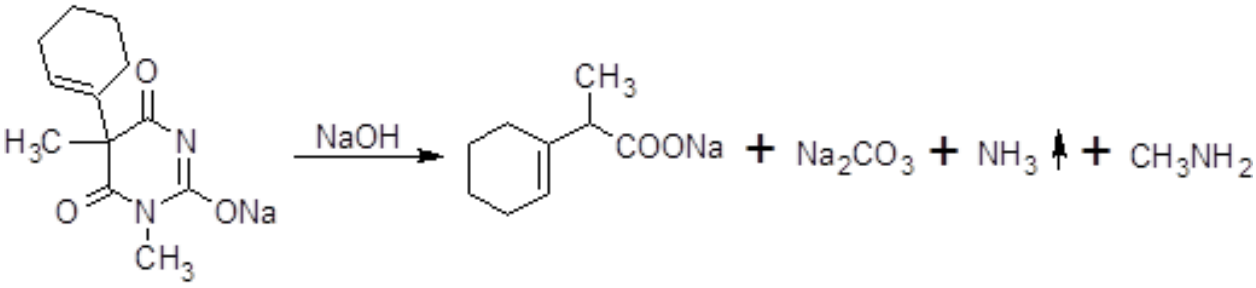
PHYSICAL PROPERTIES

White or slightly yellowish crystalline powder of slightly bitter taste. Easily soluble in water and alcohol, insoluble in ether.

IDENTIFICATION

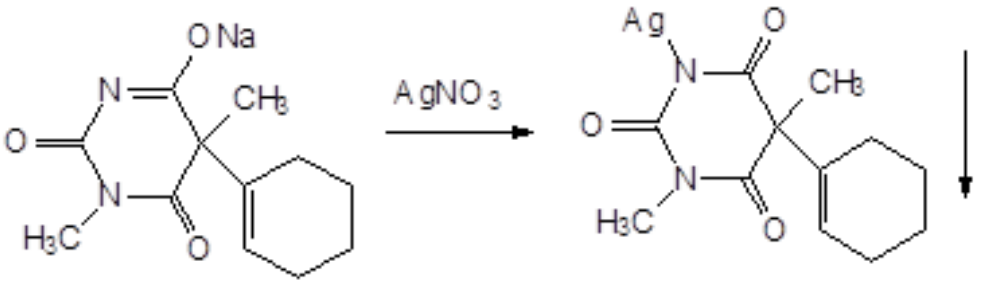
1. Alloying with alkali (General reaction)

Hexenal breaks down when melted with alkali, and an odour of ammonia is sensed. On following acidification, the release of gas bubbles (CO2) is observed and a specific odour of acid is sensed.



2. Interaction with silver nitrate (General reaction)

If a dilute solution of AgN03 is added to an alkaline solution of Hexenal, a white precipitate of single-substituted silver salt falls out.



3. Interaction with cobalt salts (General reaction)

Hexenal gives a blue-violet colouring when solutions of cobalt chloride or cobalt nitrate are added to it.

4. Interaction with copper salts in the presence of pyridine (General reaction)

Form complexe coloured lilac.

5. *Interaction with copper sulphate (Specific reaction)*

A blue colouration appears, changing to bright blue, followed by a white precipitate.

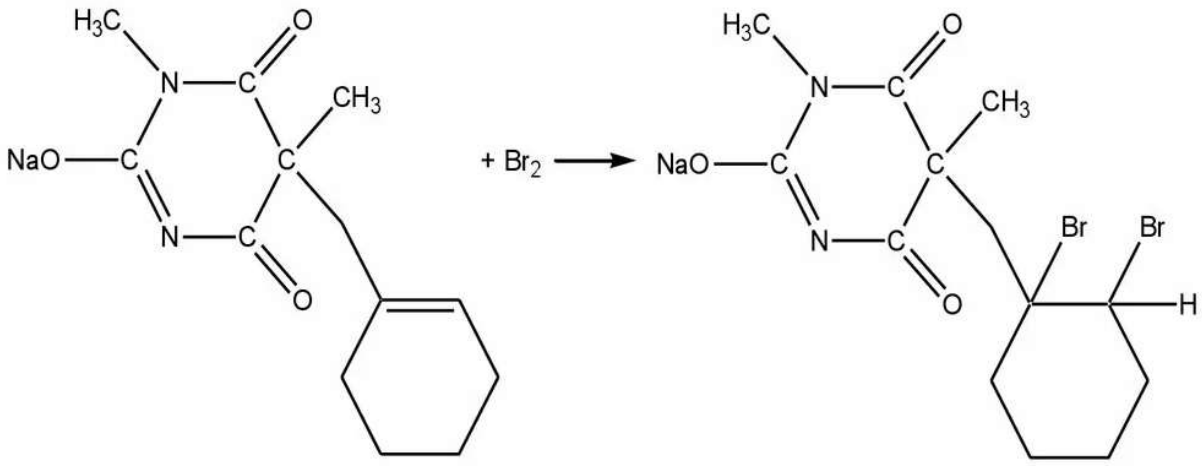
6. Reaction with formaldehyde solution and sulphuric acid (Specific reaction)

A small amount of Hexenal is dissolved by heating in a formaldehyde solution in a water bath. Then concentrated H2SO4 is carefully poured over the walls of the test tube and the mixture is heated again. A dark red ring appears at the boundary between the two liquids and green fluorescence appears above the ring.

7. Interaction with potassium permanganate (Specific reaction).

Discolouration of the solution is observed.

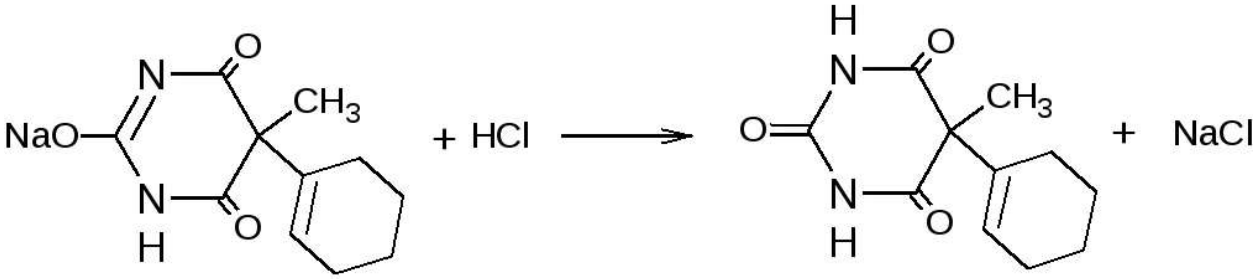
8. Interaction with bromine water (Specific reaction).



Discolouration of the solution is observed

9. Interaction with acids (General reaction).

When acid is added, a precipitate of the acidic form of barbiturate precipitates.



10. Detection of sodium (Specific reaction).

a) The presence of Na+ in the molecule causes the yellow colour of the flame when a grain of the drug is introduced into it.
b) Interaction with zincuranyl acetate. A yellow crystalline precipitate is formed.

$$Na^+ + Zn[(UO_2)_3(CH_3COO)_8] + CH_3COO^- + 9H_2O \rightleftarrows$$
$$\rightleftarrows NaZn(UO_2)_3(CH_3COO)_9 \cdot 9H_2O$$

QUANTIFICATION

1. *Gravimetry*
2. *Acidometry*
3. *Argentometry*
4. *Mercurimetry*
5. *Bromatometry*
6. *Iodochlorometry*

STORAGE

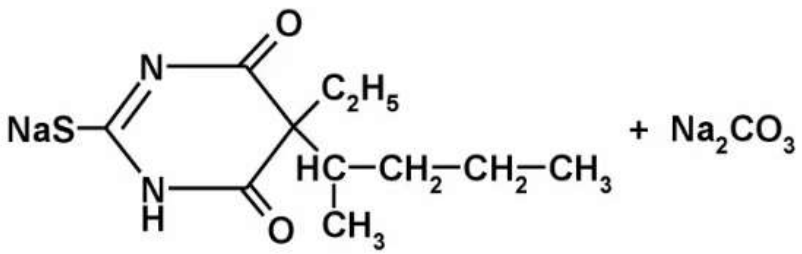
Hexenal is not stable in the presence of moisture and C02 of air. Moisture promotes hydrolysis of the drug, therefore solutions of hexenal should not be prepared in advance.

Non-stability of hexenal in the presence of moisture and air CO2 determines its storage conditions - in sealed ampoules at moderate temperature.

MEDICAL USE

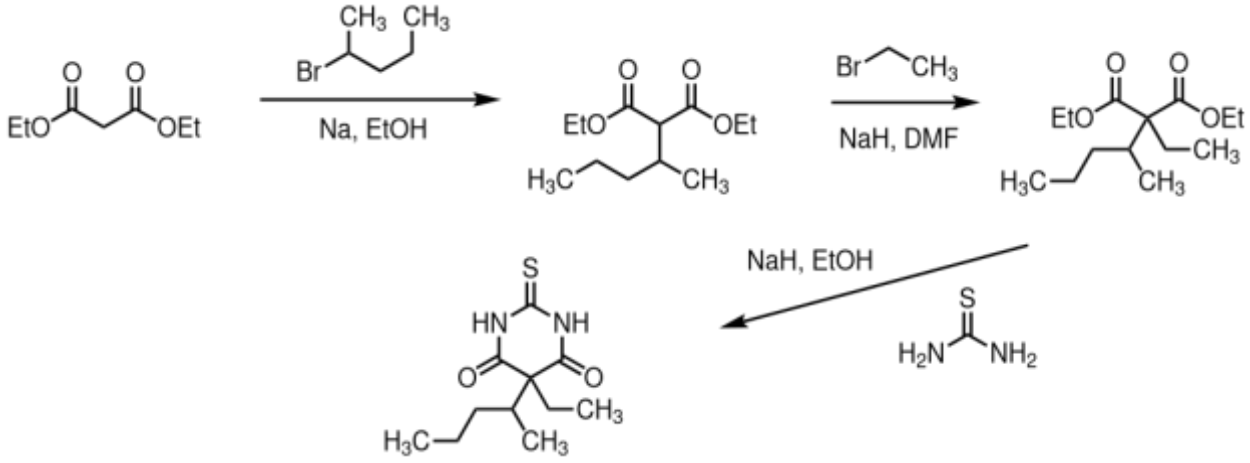
Hexenal is used as a narcotic sedative, intravenously, intramuscularly, subcutaneously, most commonly used for preoperative anaesthesia.

SODIUM THIOPENTAL



Sodium thiopental, also known as Sodium Pentothal (a trademark of Abbott Laboratories), thiopental, thiopentone, or Trapanal (also a trademark), is a rapid-onset short-acting barbiturate general anesthetic.

OBTAINING



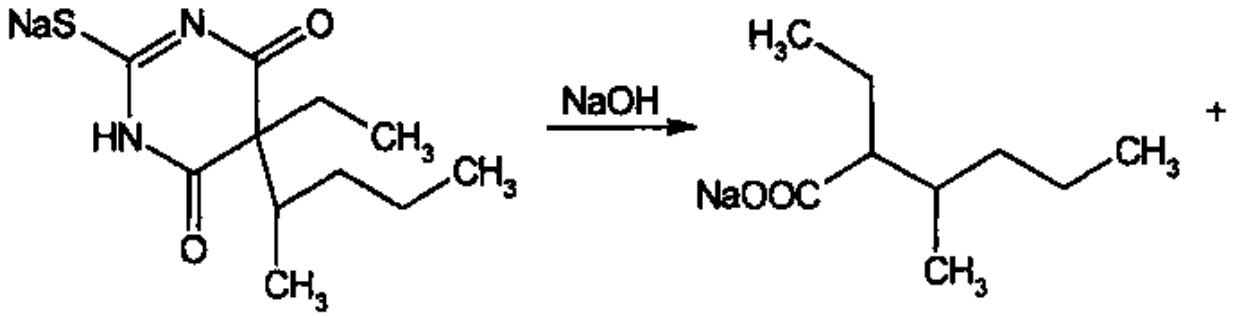
PHYSICAL PROPERTIES

Dry porous mass or powder of yellowish (yellowish-greenish) color with peculiar odor. Easily soluble in water. Aqueous solutions have alkaline reaction (pH about 10.0), not stable (prepare immediately before use).

IDENTIFICATION

1. Melting with alkalis (general reaction)

When fused with alkalis, a red-colored melt is formed and ammonia is released.

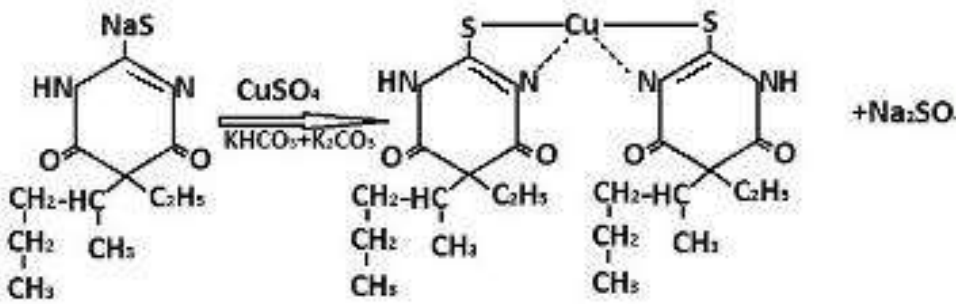


2. Interaction with silver nitrate (general reaction)

3. Interaction with copper sulfate in the presence of pyridine (general reaction)

4. Interaction with cobalt nitrate (general reaction)

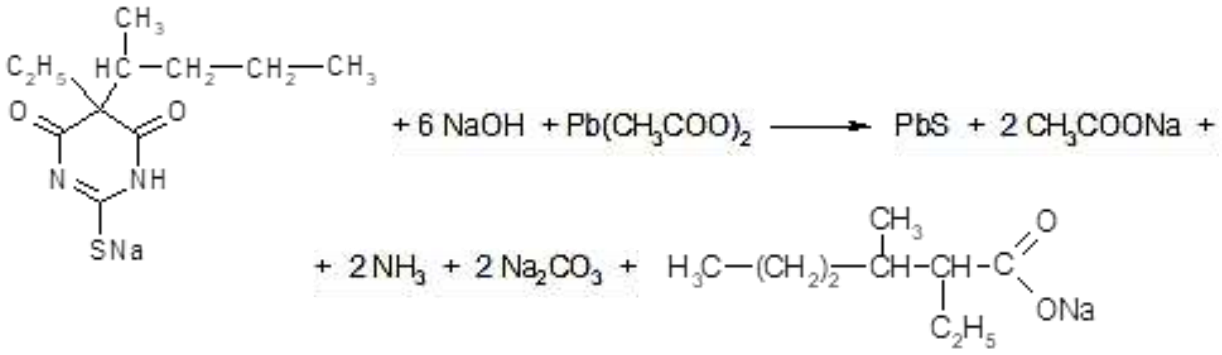
5. Interaction with copper sulfate (specific reaction)



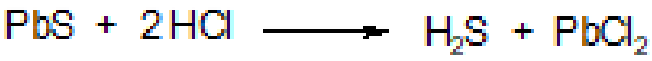
A yellow-green coloration is formed.

6. Sulfur detection (specific reaction)

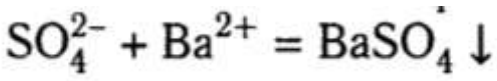
- ✓ When sodium thiopental is boiled with lead acetate in an alkaline medium, a black precipitate of lead sulfide is formed.



Subsequent acidification with dilute hydrochloric acid produces hydrogen sulfide.



- ✓ When the drug is mineralized with a sintering mixture (mixture of Na_2CO_3 and $NaNO_3$), sulfur is converted to SO_4^{2-} anions, which are detected with $BaCl_2$ solution:



white precipitate

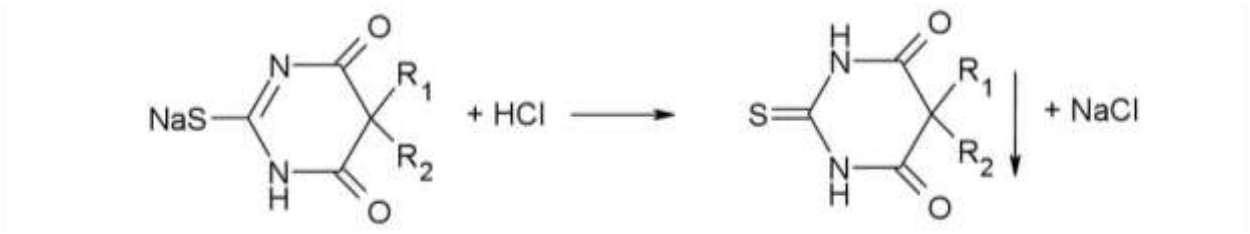
7. Determination of sodium cation (specific reaction)

- ✓ Yellow coloration of the flame.
- ✓ Interaction with zincuranyl acetate.

QUANTIFICATION

Gravimetry

A solution of sodium thiopental is acidified with hydrochloric acid.



The resulting acidic form is extracted with chloroform. The chloroform is distilled off, the resulting precipitate is dried and weighed.

STORAGE

In a place protected from light, at a temperature not exceeding 25ºC.

MEDICAL USE

Used for induction anesthesia. As an additional agent for basic anesthesia (with subsequent use of analgesics and myorelaxants).

As an additional agent for treatment of convulsive states of various etiologies, including those caused by local anesthetics.

To reduce intracranial pressure in patients with increased intracranial pressure, if artificial ventilation is provided.