Ministry of Health of the Russian Federation

Volgograd State Medical University

Department of Pharmaceutical and Toxicological Chemistry

SPECIAL PHARMACEUTICAL CHEMISTRY

Drugs - Benzothiazine derivatives, Benzothiadiazine, Chlorobenzene sulfonic acid

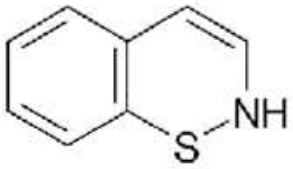
Lesson 6

VII term

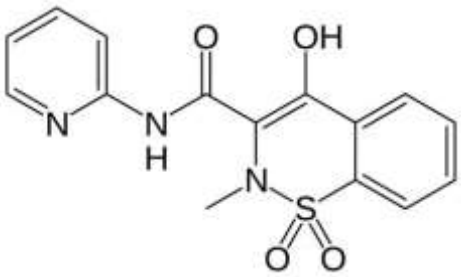
Volgograd, 2023

BENZOTHIAZINE DERIVATIVES

Benzothiazine is a heterocyclic compound consisting of a benzene ring attached to the 6-membered heterocycle thiazine . This name applies to both the 2H- and 4H-isomers of the molecule.

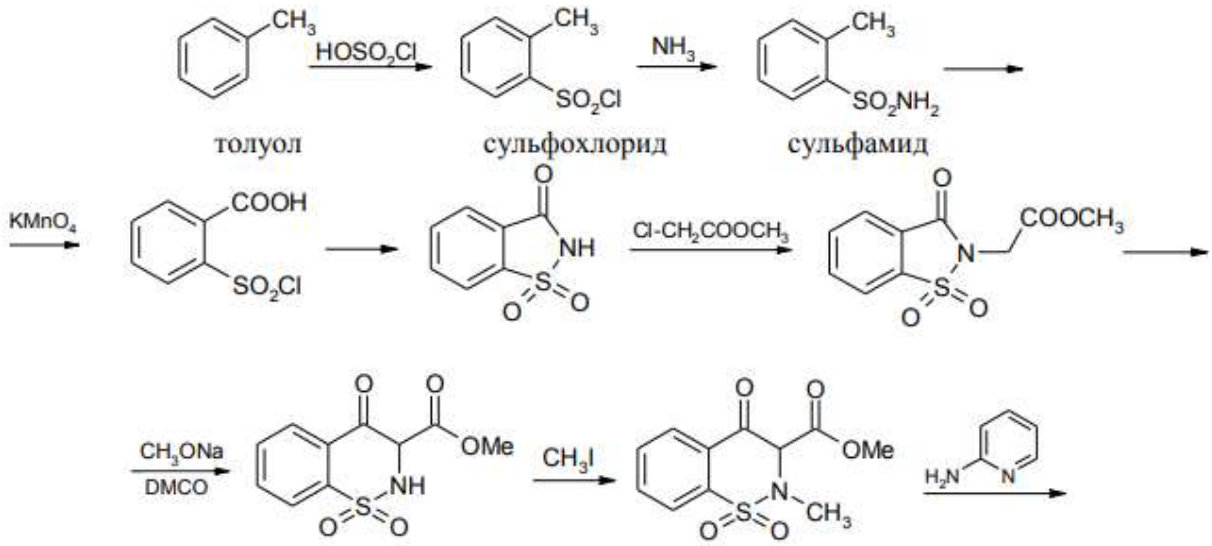


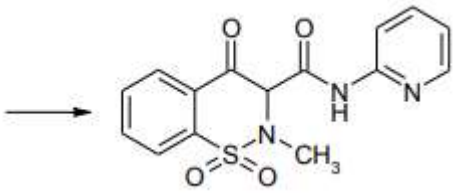
PYROXICAM



OBTAINING

Synthesis of piroxicam is carried out by successively obtaining sulfamide from toluene, then saccharine, which is alkylated with chloroacetic acid ester. After that under the action of sodium methylate there is a recyclization with the formation of benzothiazine ring. At the last stages of the synthesis N-methylation and conversion of the ester group into N-(2-pyridyl)amide group are carried out:





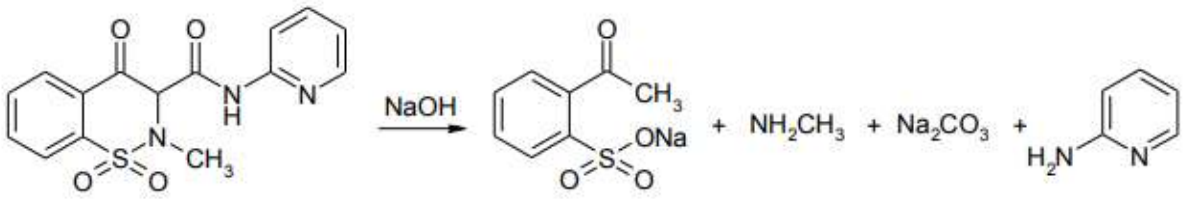
IDENTIFICATION

I. Instrumental methods

The authenticity of piroxicam is established by the ***IR spectrum*** taken in vaseline oil and ***UV spectrum*** of a solution in 0.01 M hydrochloric acid (compared with the standard). The ***TLC method*** is also used, establishing the identity of the Rf value of the main stain of solutions of the test substance and the witness in a mixture of chloroform and methanol (1:1).

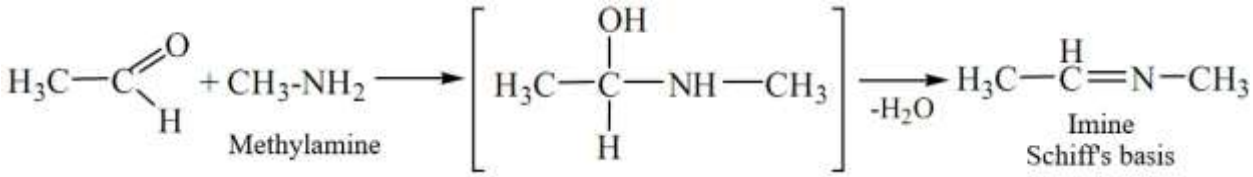
II. Chemical methods

1. Hydrolysis



a) Detection of methylamine:

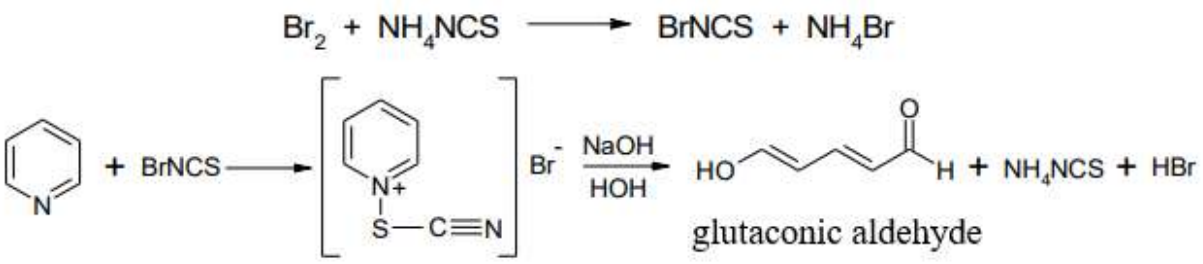
Methylamine is a colorless gas with an ammonia odor. It colors wet red litmus paper blue. Reactions with aldehydes and acetals lead to Schiff bases.



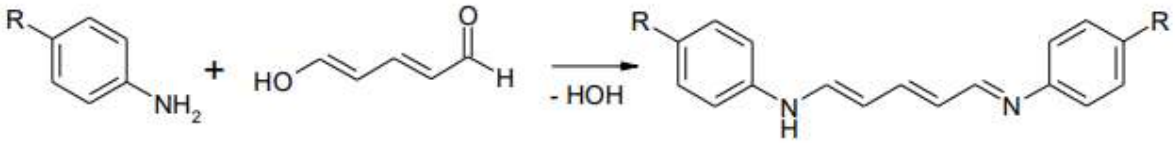
b) Detection of aminopyridine after hydrolysis of piroxicam (production of glutaconic aldehyde)

Glutaconic aldehyde in alkaline medium has yellow coloring. Bromine thiocyanate (bromorodane) or chlorine thiocyanate (chlororodane), bromine cyanide, chloroform, chloral hydrate can be used as a cleavage agent.

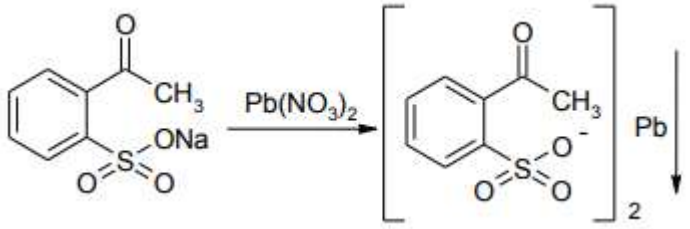
Bromorodane is obtained by adding ammonium thiocyanate to bromine water until discolored:



The subsequent addition of primary aromatic amines (aniline, novocainamide, sodium sulfacyl) leads to the reaction of their condensation with glutaconic aldehyde to form Schiff bases colored intensely yellow, orange or red:

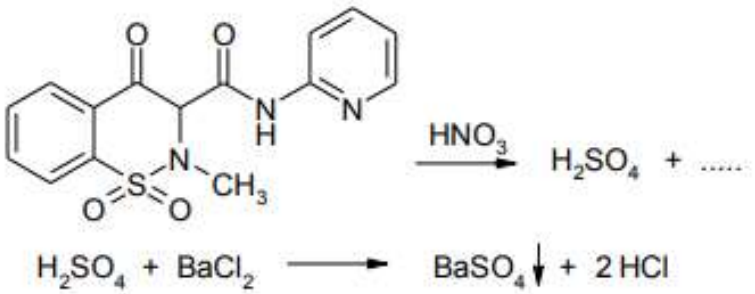


c) *Formation of complex salts with heavy metal ions after hydrolysis of piroxicam:*



2. Detection of sulfate ion

after boiling with concentrated nitric acid:



PURITY TEST

For the detection of 2-aminopyridine impurity (not more than 1%) in piroxicam, the TCA method is also used, establishing the identity of the Rf value of the main stain of the solutions of the test substance and the witness in a mixture of chloroform and methanol (1:1).

QUANTIFICATION

The quantitative determination of piroxicam is carried out by HPLC, on a liquid chromatograph with UV detector relative to a standard sample in a mobile phase consisting of buffer solution with methanol (55:45). The responses for the main peak are measured and the content is calculated (97- 103%). Detect at a wavelength of 254 nm.

STORAGE

The drug should be stored in a place protected from light at a temperature of 15° to 25°C.

MEDICAL USE

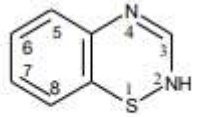
Piroxicam belongs to the number of non-steroidal anti-inflammatory drugs. Prescribed for pain after surgical, orthopedic, gynecological, dental interventions; post-traumatic conditions (pain syndrome in sprains, dislocations, fractures); gout; dysmenorrhea, adnexitis, cystitis.

Used in rheumatism, arthritis, arthrosis tablets (capsules) of 0.01 g once a day or injected intramuscularly 2% solutions of 2 ml.

Helps relieve pain syndrome, symptoms of inflammation in any method of application. In joint syndrome weakens or eliminates inflammation and pain in the joints at rest and during movement, reduces morning stiffness and swelling of the joints.

BENZOTHIADIAZINE DERIVATIVES

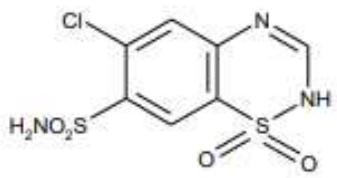
Benzothiadiazine is a condensed system consisting of benzene and dihydropyrimidine cycles with a sulfur atom at position 1.



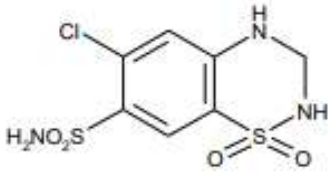
1,2,4-benzothiadiazine

Benzothiadiazine derivatives have diuretic (saluretic) action. These drugs are used in the treatment of various types of edema, as well as in hypertensive disease.

The ancestor of this group of derivatives is chlorthiazide (6-chloro-7-sulfamido-1,2,4-benzothiadiazide-1,1-dioxide), which was first obtained in 1954 by Novello and Spragomme. However, more pronounced diuretic effect has 3,4-dihydro derivative of chlortiazide - dichlothiazide (hypothiazide), which is 10 times more active than chlortiazide.



Chlortiazide

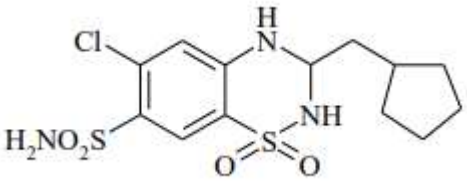


Dichlothiazide

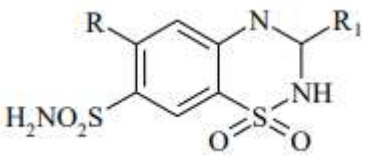
In a study of benzothiadiazine derivatives, it was found that the diuretic effect is seen in compounds that have:

- ✓ have a sulfamide group at the 7 position,
- ✓ nitro-, chloro- or fluoromethyl groups in the 6 position.
- ✓ introduction of a substituent at position 4 or 8 completely removes the activity,
- ✓ the presence of a substituent at position 2 increases the activity several times.
- ✓ The presence of a substituent at position 3 is particularly important. If it is an alkyl radical and its length is up to 5 carbon atoms, the activity is increased, and if the carbon radical increases, the activity decreases.
- ✓ Chain branching has no effect on pharmacological action.
- ✓ Introduction of a halogen into the radical increases the diuretic effect several times.
- ✓ If a cycloalkyl group connected to the heterocycle by a methylene fragment at position 3 is introduced, the diuretic effect is significantly increased.

  For example cyclometazide: 100 times more active than dichlothiazide



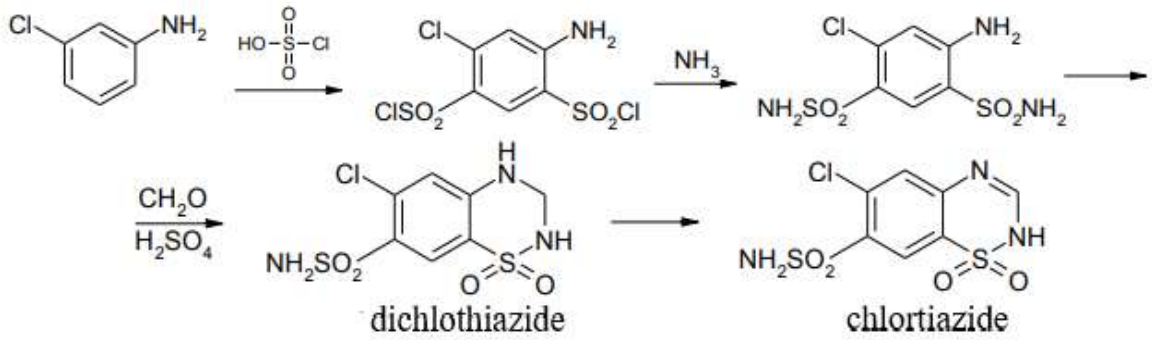
and 1000 times more active than chlorthiazide. Thus, the general formula of benzothiadiazine derivatives preparations is as follows:



CHLORTIAZIDE
DICHLOTHIAZIDE

OBTAINING

The drug dichlothiazide used in medical practice was obtained in 1958 by Stevens by condensation of 6 chloro-4-amino-1,3- benzoldisulphanilamide with formaldehyde in the presence of sulfuric acid. Currently, the starting material for the synthesis of dichlothiazide is m-chloroaniline**.**



PHYSICAL PROPERTIES

Dichlothiazide is a white crystalline powder, bitter tasting, odorless. Its melting point is 257-262° C. It is slightly soluble in water and ethanol, but well in alkaline solutions, forming salts. The alkaline solution is well hydrolyzed to form the original product.

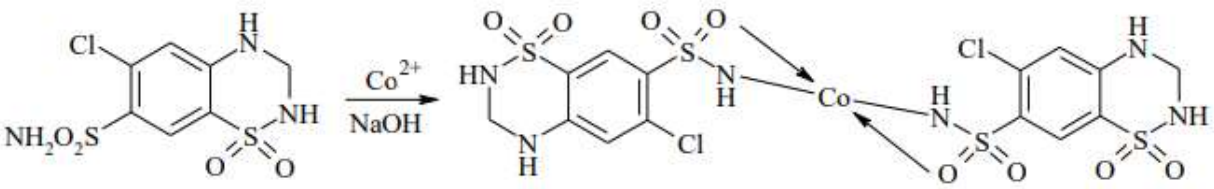
IDENTIFICATION

1. ***UV spectrophotometry***

   Dichlothiazide solution at pH=10 has maximum light absorption at 275 nm.

2. ***Interaction with heavy metal salts***

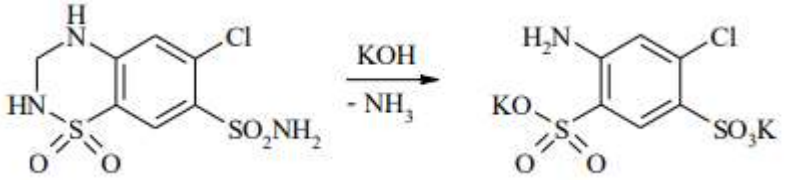
   When dichlothiazide alkaline solution interacts with solutions of heavy metal salts (the most characteristic reaction with cobalt chloride solution), colored precipitates are formed:



   The precipitate is a dirty greenish-blue color.

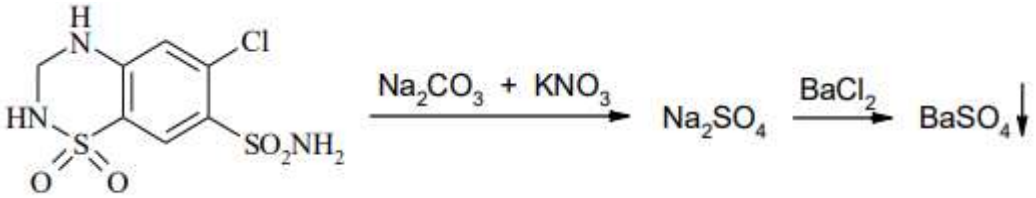
3. *Melting with alkalis.*

When fused with potassium hydroxide crystals, ammonia is released, which can be detected by the strong odor and the blueing of wet red litmus paper:



4. *Detection of sulfur and chlorine after mineralization*

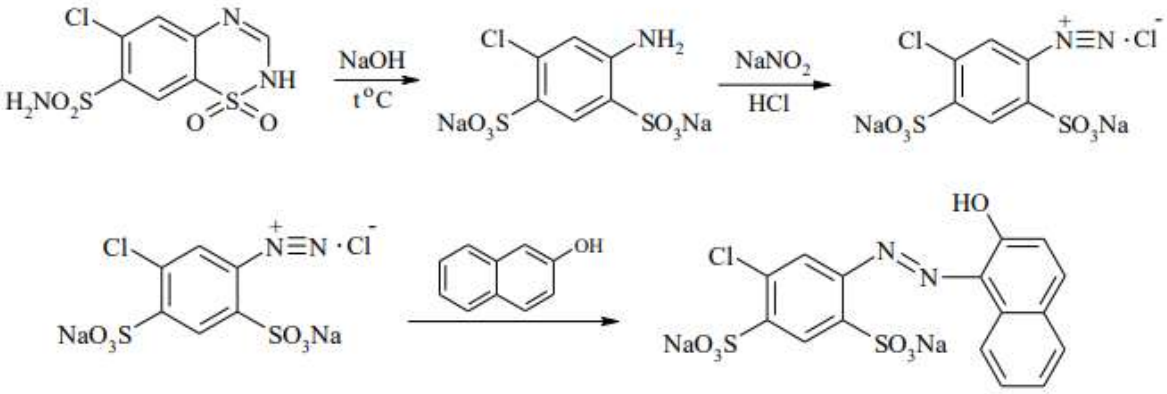
When the preparation is boiled with concentrated nitric acid or fused with 10 times potassium nitrate, the sulfur mineralizes to sulfate ion:



The sulfate ion formed is opened with barium chloride solution to form a white precipitate of barium sulfate.

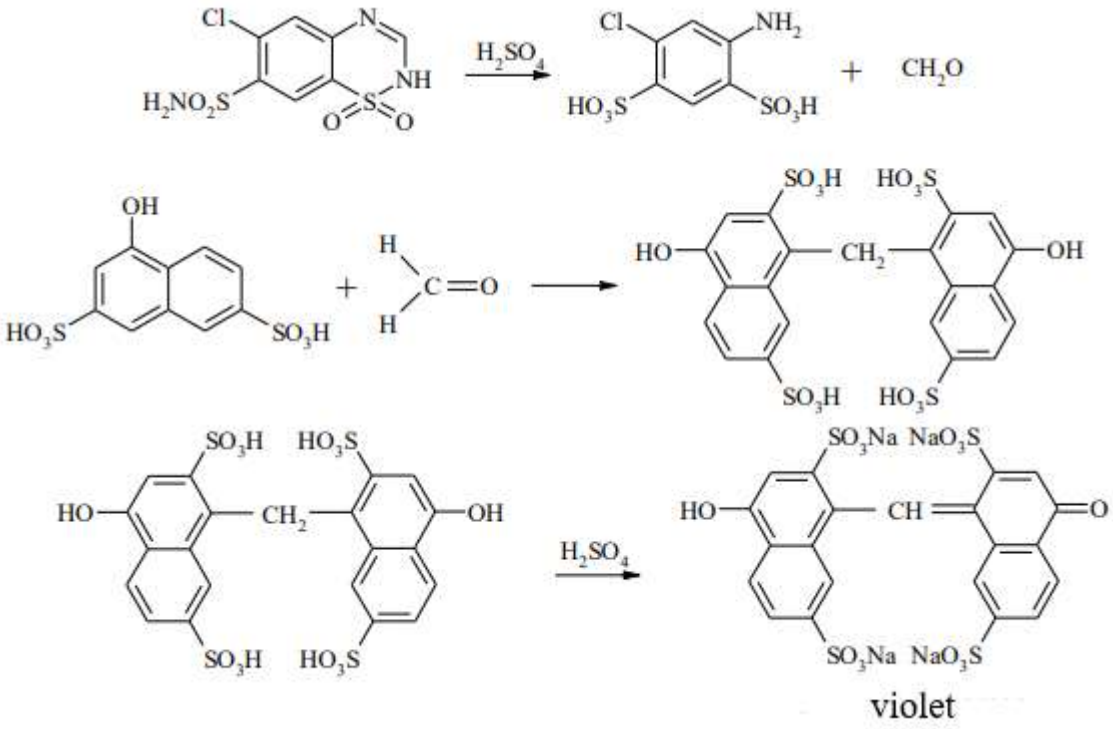
5. *Formation of azo dye after alkaline hydrolysis.*

The drug (chlorothiazide or dichlothiazide) is boiled with caustic soda solution, thus 6-chloro-4-amino1,3-benzene disulfamide is formed, which is acidified with hydrochloric acid, sodium nitrite is added: diazonium salt is obtained. A freshly prepared alkaline solution of β-naphthol is added to it. An azo dye of dark red color is formed:



6. *Detection of formaldehyde after acid hydrolysis*

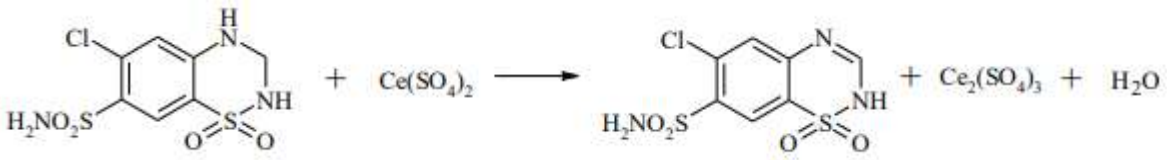
When chlorothiazide is heated with 15 M sulfuric acid solution, the drug decomposes to form formaldehyde. If chromotropic acid is added to the reaction mixture after decomposition, violet coloration appears due to the formation of a compound of *para*-quinoid structure:



QUANTIFICATION

1. *Cerimetric method*

The cerimetric method is based on the oxidation of dichlothiazide by cerium sulfate to chlorthiazide:



Excess cerium sulfate is titrated iodometrically:

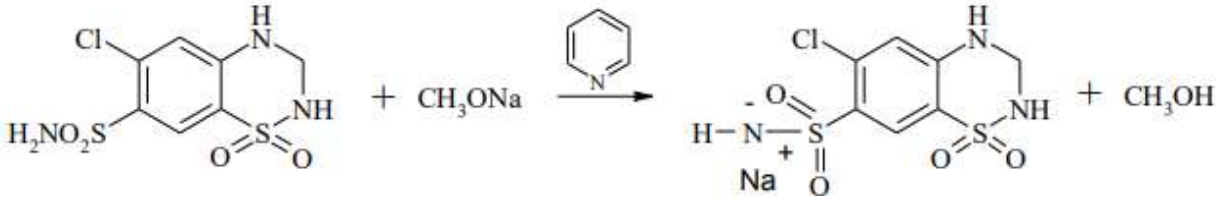
$$2\,Ce(SO_4)_2 + 2\,KI \longrightarrow I_2 + Ce_2(SO_4)_3 + K_2SO_4$$

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

The released iodine is titrated with sodium thiosulfate in the presence of the indicator - starch. At the equivalence point there is a color change from dark blue to colorless.

2. ***Non-aqueous titration***

The method of titration in the medium of non-aqueous solvents is based on the presence of weak acidic properties of dichlothiazide (intensified in the medium of *dimethylformamide*), which are due to the presence of a sulfamide group in the molecule. Titration is conducted by 0.1 M *potassium hydroxide* solution in benzene-propanol mixture (or *sodium methanol* in the medium of pyridine or 1-butylamine); the indicator is a solution of *azofiolet* in benzene:



STORAGE

Dichlothiazide (hydrochlorothiazide) in the presence of moisture undergoes hydrolysis, therefore dichlothiazide is stored in well-corked containers, in a dry place protected from light.

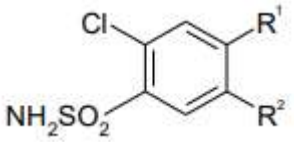
MEDICAL USE

Dichlothiazide is used as a diuretic. It is highly active when administered orally. It is used in congestion associated with cardiovascular insufficiency, liver cirrhosis, premenstrual conditions accompanied by congestion. It is rapidly absorbed and diuretic effect develops quickly.

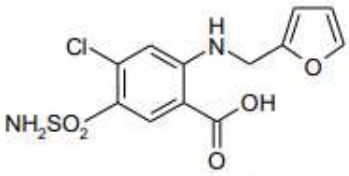
ACYCLIC BENZOTHIADIAZINE ANALOGS

CHLOROBENZENESULFONIC ACID AMIDE DERIVATIVES

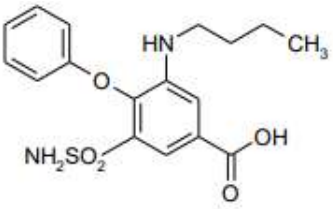
The chemical structure of benzothiadiazine derivatives is similar to that of benzothiadiazine derivatives in the molecule of which amide of chlorobenzenesulfonic acid is contained, having a common formula:



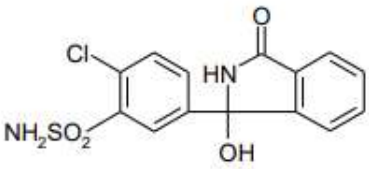
and exhibit active diuretic and hypertensive action. The most widely used of this group of drugs are furosemide, bufenox (bumetanide) and oxodoline (chlortolidone).



Furosemide



Bufenox



Oxodoline

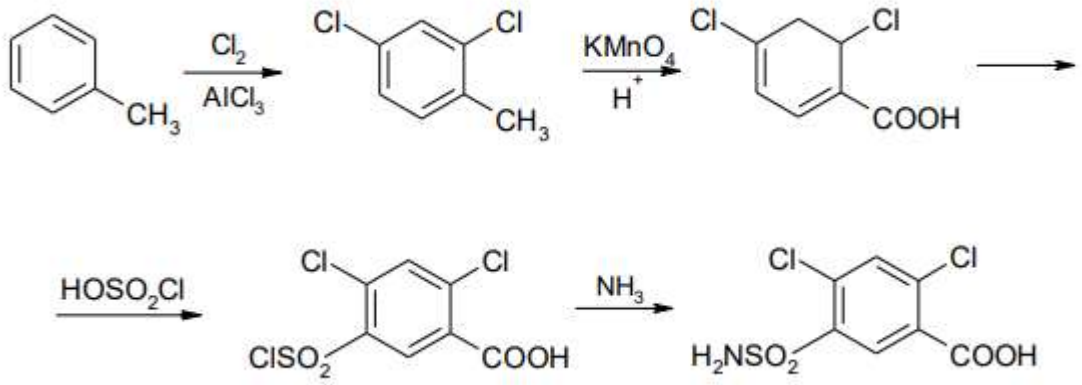
FUROSEMIDE

OBTAINING

Furosemide is produced in three stages.

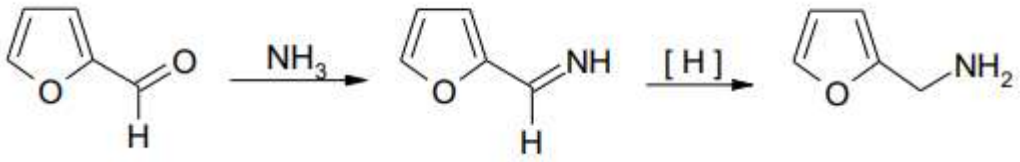
1. *Synthesis of 2,4-dichloro 5 benzoic acid sulfonamide.*

   The starting point for the synthesis is toluene, which is chlorinated in the presence of Lewis acid. The methyl group is then oxidized with potassium permanganate in acidic medium to form 2,4-dichlorobenzoic acid. The resulting product is treated sequentially with chlorosulfonic acid and ammonia:



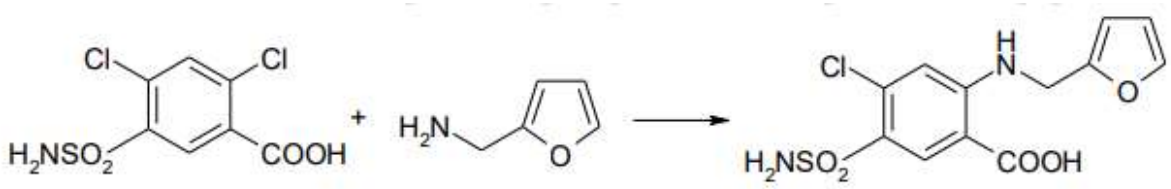
2. *Synthesis of α-methylaminofuran*

   The starting material for methylaminofuran is furfural, which condenses with ammonia to form imine and is then reduced:



3. *Condensation of the obtained substances:*

   Furfurylamine and 2,4-dichloro-5-benzoic acid sulfonamide are fused together at 130°C to form furosemide:



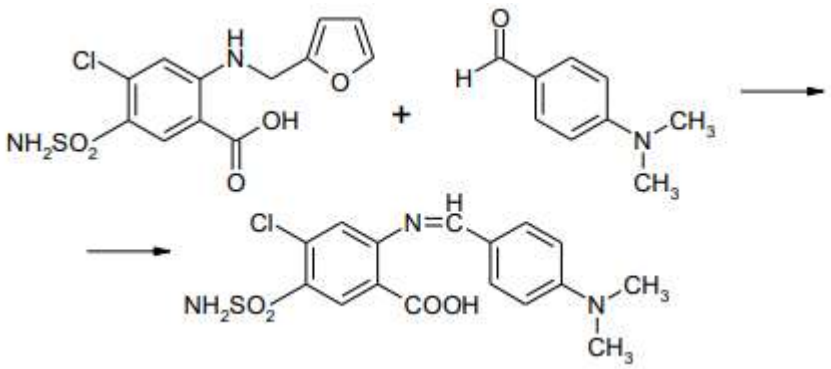
PHYSICAL PROPERTIES

Furosemide is a white (or with a faint cream color) crystalline substance, practically insoluble in water, hardly or slightly in ethanol, easily soluble in sodium hydroxide solutions.

IDENTIFICATION

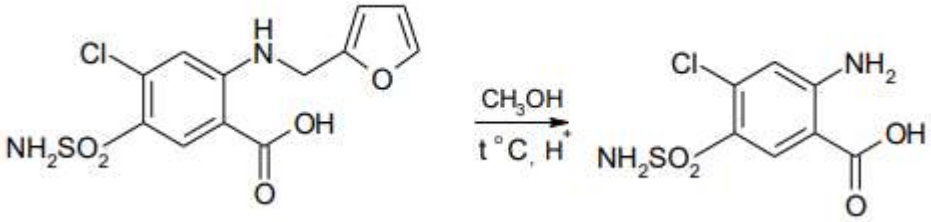
1. *Formation of Schiff's base*

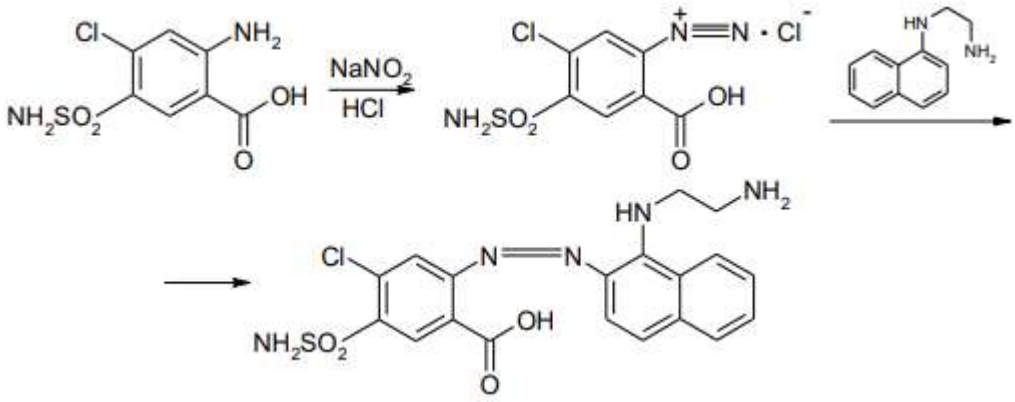
A solution of furosemide in ethanol after addition of *p*-imethylaminobenzaldehyde acquires a green coloration changing to dark red:



2. *Formation of an azo dye*

If a solution of furosemide in ethanol is hydrolyzed by heating in an acidic medium, the resulting primary aromatic amine can be prodiazotized and azo-combined with N-(1-naphthyl)ethylenediamine in an alkaline medium. an azo dye of red-violet color is formed:





3. *Determination of ionized chlorine*

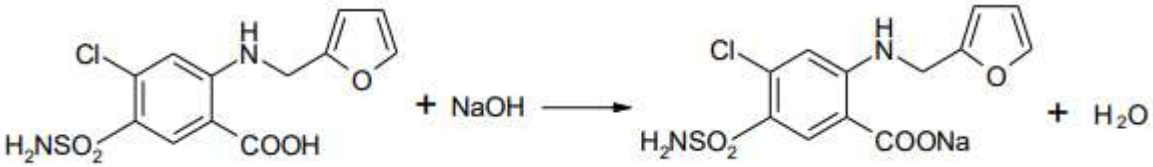
After combustion or fusion with alkali of a sample of the preparation, chlorine is ionized. By dissolving the combustion products in water, the ionized chlorine can be determined by interaction with silver nitrate solution:

$$NaCl + AgNO_3 \longrightarrow AgCl\downarrow + NaNO_3$$

A white precipitate of silver chloride is formed.

4. *Determination of sulphate ion*

The presence of sulphur atom in drug is detected by mineralization of sulphate ion after boiling in nitric acid and precipitation with solutions of barium salts:



$$H_2SO_4 + BaCl_2 \longrightarrow BaSO_4 + 2\,HCl$$

5. *Ammonia detection*

When the drug is boiled with an alkali solution, ammonia is released. It can be detected by a strong smell and blueing of wet red litmus paper.

6. *Interaction with dimethylaminobenzaldehyde*

A solution of furosemide in ethanol after addition of dimethylaminobenzaldehyde acquires a green coloration that turns dark red.

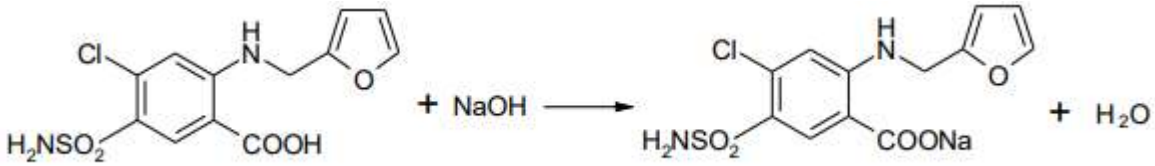
PURITY TEST

In the purity test, the presence of impurities of primary aromatic amines (intermediate products of synthesis) is determined in furosemide. The test is based on the formation of azo dye with N-(1-naphthyl)ethylenediamine hydrochloride in dimethylformamide. The optical density should not be higher than 0.15 (at a wavelength of 530 nm).

QUANTIFICATION

Acid-base titration

Quantitative determination of furosemide is based on its acidic properties. The working solution is 0.1 M sodium hydroxide solution. The indicator is bromthymol blue. Furosemide titration is carried out in dimethylformamide medium. Furosemide is titrated as a mono-basic acid:



STORAGE

The drug is stored in a dry place, protected from light, in tightly closed containers.

MEDICAL USE

Furosemide is used as a diuretic for congestion due to cardiac insufficiency in the small and large circle of blood circulation and various, including severe forms of hypertension, liver cirrhosis, chronic and acute renal failure, barbiturate poisoning.

OXODOLINE

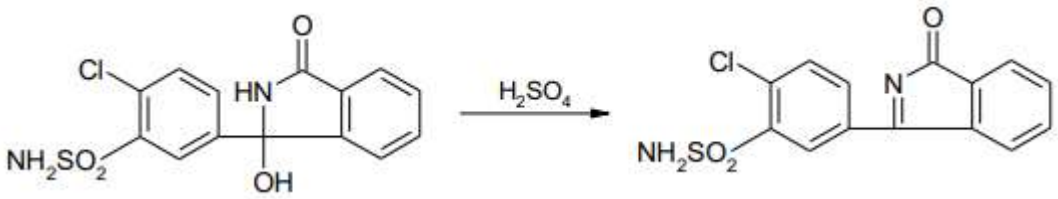
PHYSICAL PROPERTIES

Oxodoline is a white (or with a faint cream color) crystalline substance, practically insoluble in water, hardly or slightly in ethanol, easily soluble in sodium hydroxide solutions.

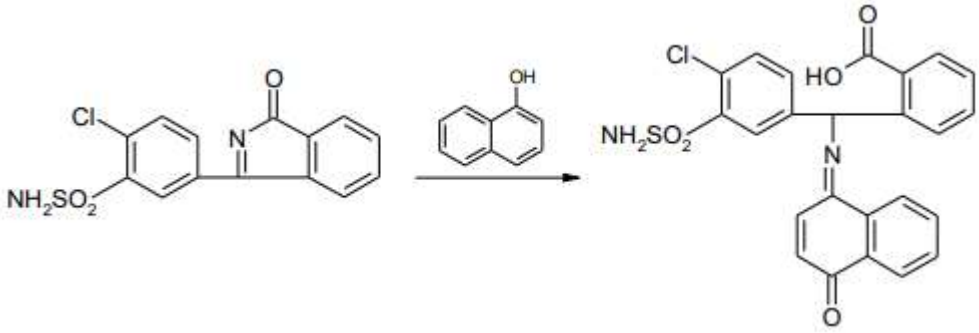
IDENTIFICATION

1. ***Color reaction of oxodoline with sulfuric acid***

   A solution of oxodoline in sulfuric acid has an intense yellow coloration:



After heating in a water bath and adding α-naphthol, the color changes to red-violet:



2. ***Determination of ionized chlorine***

After combustion or fusion with alkali of a sample of the preparation, chlorine is ionized. By dissolving the combustion products in water, the ionized chlorine can be determined by interaction with silver nitrate solution:

$$NaCl + AgNO_3 \longrightarrow AgCl\downarrow + NaNO_3$$

A white precipitate of silver chloride is formed.

3. ***Determination of sulphate ion***

The presence of sulphur atom in drug is detected by mineralization of sulphate ion after boiling in nitric acid and precipitation with solutions of barium salts:

$$H_2SO_4 + BaCl_2 \longrightarrow BaSO_4 + 2\,HCl$$

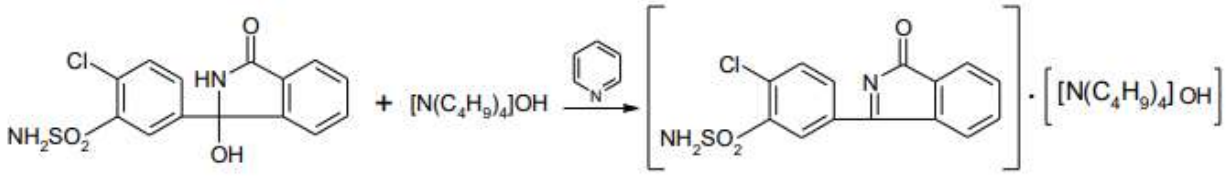
4. ***Ammonia detection***

When the drug is boiled with an alkali solution, ammonia is released. It can be detected by a strong smell and blueing of wet red litmus paper.

QUANTIFICATION

Non-aqueous titration

Oxodoline is determined by the non-aqueous titration method. *Pyridine* is taken as a solvent; the working solution is *tetrabutylammonium hydroxide*. The equivalence point is determined *potentiometrically*:



STORAGE

The drug is stored in a dry place, protected from light, in tightly closed containers.

MEDICAL USE

Furosemide is used as a diuretic for congestion due to cardiac insufficiency in the small and large circle of blood circulation and various, including severe forms of hypertension, liver cirrhosis, chronic and acute renal failure, barbiturate poisoning.