Ministry of Health of the Russian Federation

Volgograd State Medical University

Department of Pharmaceutical and Toxicological Chemistry

SPECIAL PHARMACEUTICAL CHEMISTRY

Pyrimidine derivatives. Uracil and its derivatives

Lesson 4

VII term

Volgograd, 2023

INTRODUCTION

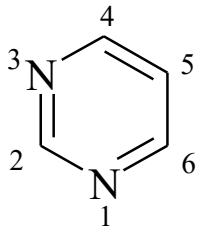
Currently, drugs of heterocyclic compounds constitute up to 70% of the arsenal of all currently used drugs. The biological role of heterocyclic compounds, first of all nitrogen-containing compounds, is determined by their participation in the mechanisms of heredity, metabolism, nerve mediation, functioning of practically all enzymatic systems.

Uracil derivatives occupy the most important place among them. On their basis, numerous and effective drugs for the treatment of infectious and oncologic diseases have been obtained in the last 20 years. However, the spectrum of pharmacological activity of pyrimidine series compounds is not limited only to antiviral and antitumor activity. Along with antiviral activity, a significant number of pyrimidine derivatives exhibit pronounced immunomodulatory, membrane-stabilizing, cardiotropic, anti-inflammatory and antitumor activity, as well as pronounced antidepressant, anxiolytic and nootropic activity.

GENERAL CHARACTERIZATION

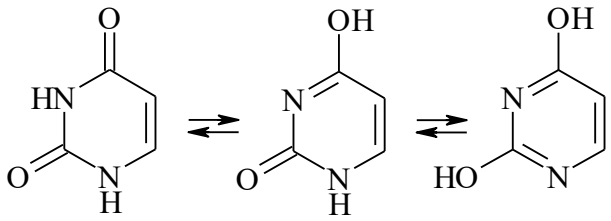
Uracil is a pyrimidine base that is part of RNA. In animal and human organisms uracil is found in the form of N-glycosides of ribose or deoxyribose (nucleosides), which, being esterified by phosphoric acids (nucleoside polyphosphates), play an extremely important role in the biosynthesis of proteins, carbohydrates, fats and other vital substances.

The basis of the uracil molecule is the pyrimidine cycle. Pyrimidine is a six-membered heterocycle with two nitrogen atoms:



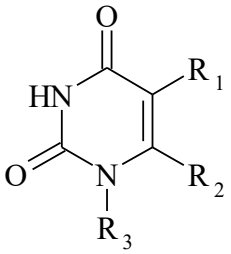
In pyrimidine compared to pyridine, due to the negative inductive effect of nitrogen atoms, the activity of the heterocyclic nucleus in electrophilic substitution is reduced; it is practically inert in these reactions. When the ring is activated by electron-donor substituents, electrophilic substitution reactions take place at the C5 position. Nucleophilic attack occurs at the C2, C4, and C6 positions.

Uracil (1,2,3,4-tetrahydropyridinedione) is characterized by lactim-lactam tautomerism:



It should be noted that the lactam forms predominate in the equilibria.

General formula of uracil derivatives:



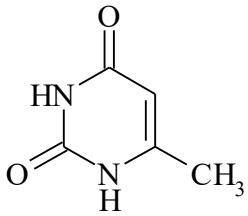
Uracil derivatives may contain fluorine atom (R1), methyl radical (R1 or R2) in the molecule. Some of them are pyrimidine nucleosides - synthetic analogues of pyrimidine base derivatives included in nucleic acids. They contain a monosaccharide residue (R3) in the molecule.

Uracil is included in the structure of very valuable drugs of antitumor action (dopan, fluorouracil, etc.), antithyroid action (methylthiouracil), stimulating leukopoiesis (pentoxyl, methyluracil), antiviral (azidothymidine, lamivudine) and others.

NON-NUCLEOSIDE DERIVATIVES OF URACIL

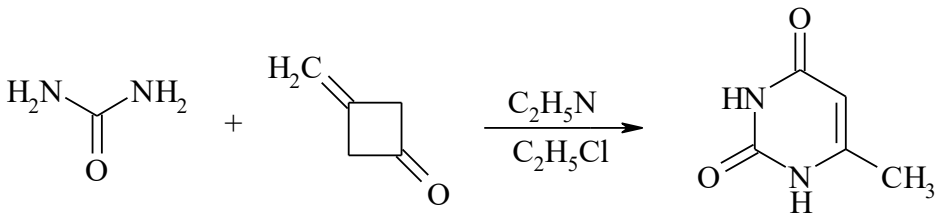
Non-nucleoside derivatives of uracil include ***methyluracil, methylthiouracil, pentoxyl and fluorouracil***. They do not contain a substituent at the N1 position.

METHYLURACIL



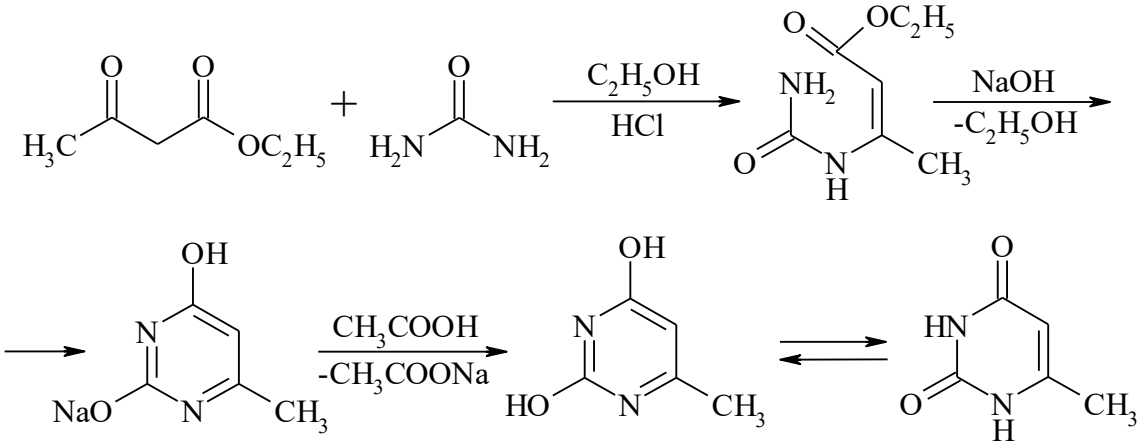
OBTAINING

1. Obtained by heating a mixture of equimolecular amounts of urea and diketene in chlorobenzene in the presence of pyridine (64-65% yield):



urea *diketene* *6-methyluracil*

2. Biltz's method. Urea is acylated with acetoacetic ether in the presence of ethyl alcohol and catalytic amounts of hydrochloric acid. The resulting β-ureidocroton ether is cyclized by treatment with caustic soda solution (48% yield):



PHYSICAL PROPERTIES

White crystalline powder without odor.

Slightly soluble in water and ethanol, practically insoluble in ether and chloroform, easily soluble in alkali and ammonia solutions.

IDENTIFICATION

I. Physicochemical methods

1. Infrared spectrophotometry.

The infrared spectrum of methyluracil in the region 4000 - 400 cm-1 (in disks with potassium bromide) should completely coincide with the spectrum figure attached to the pharmacopoeial article.

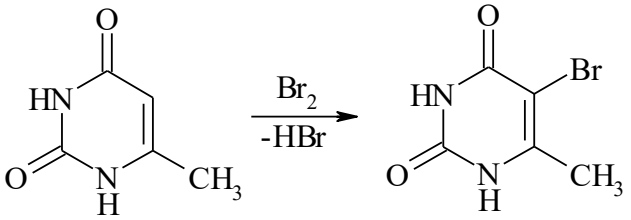
2. UV spectrophotometry.

Uracil derivatives were found to have characteristic UV absorption spectra after dissolution in concentrated sulfuric acid. The absorption maximum for methyluracil is at 275 nm.

II. Chemical methods

1. Oxidation with bromine water

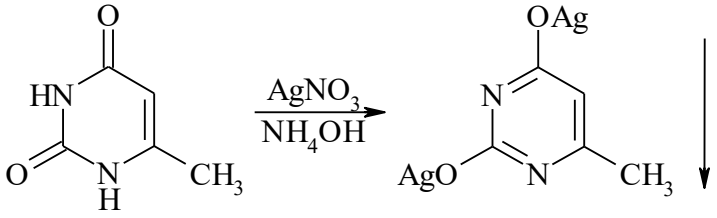
When heated with bromine water, discoloration of the solution occurs:



2. Interaction with salts of heavy metals

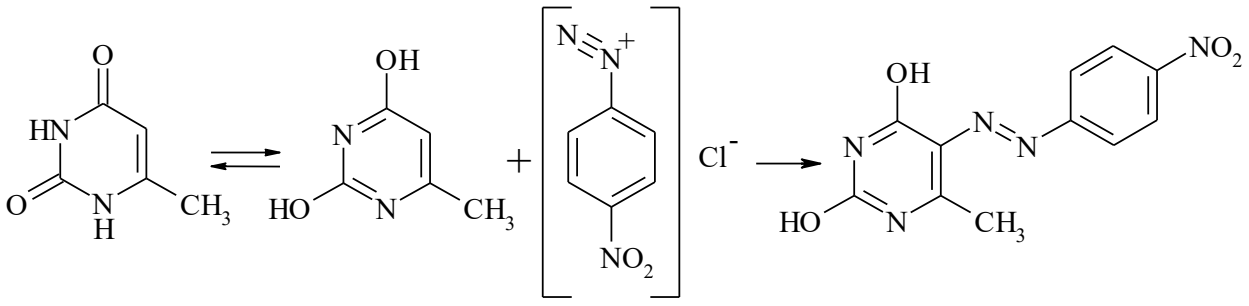
Methyluracil solution in ethanol after heating, subsequent cooling, addition of alcoholic solution of cobalt nitrate and ammonia solution acquires violet coloring.

In the presence of ammonia solution it forms white precipitates with silver nitrate and mercury dichloride solution:



3. Formation of azo dye

When azo-combination with p-nitrodiazobenzene chloride in sodium carbonate solution, a red-orange coloration appears and a precipitate of the same color is formed:



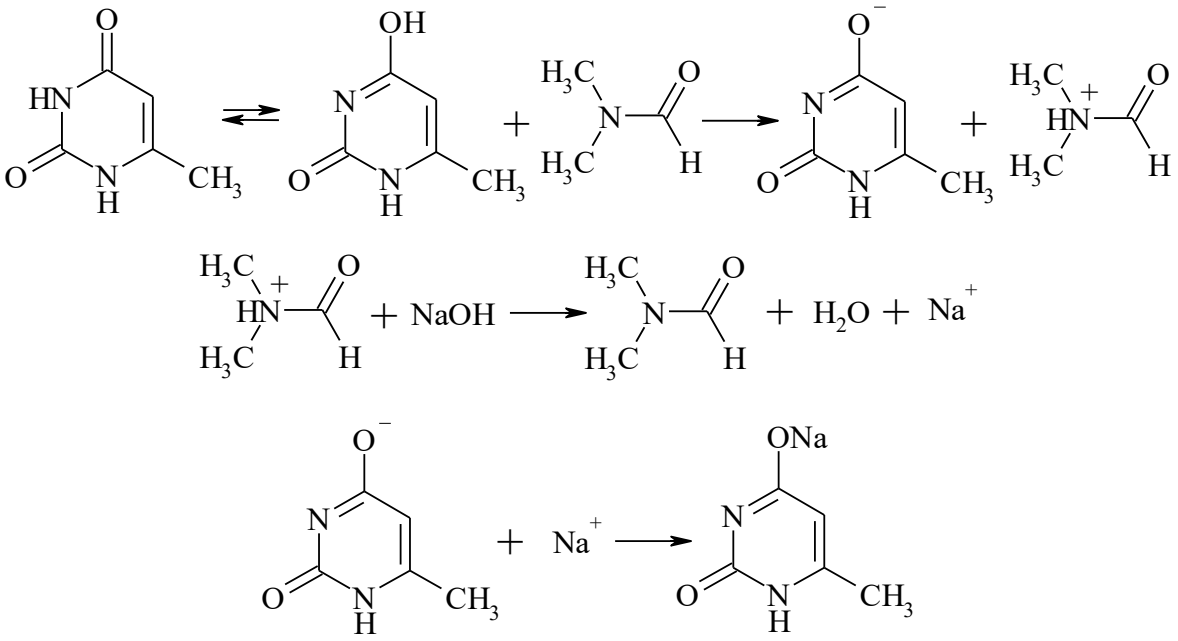
PURITY TEST

The product should be free of sulfates, chlorides, sulfur. Arsenic should be within the standard. In addition, the weight loss on drying is determined.

QUANTIFICATION

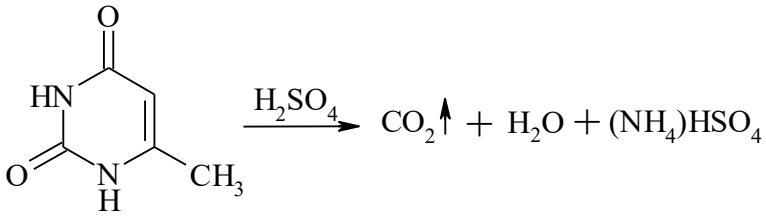
1. Non-aqueous titration

A sample of the drug is dissolved in dimethylformamide and titrated with 0.1M sodium hydroxide solution in a mixture of methanol and benzene. The indicator is a solution of thymol blue in dimethylformamide.



2. Kjeldahl's method

A suspension of the preparation is heated with concentrated sulfuric acid:



As a result, the organically bound nitrogen is converted to ammonium hydrosulfate, which is treated with sodium hydroxide and the resulting ammonia is distilled off into a receiver:

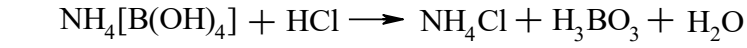
$$(NH_4)HSO_4 + 2OH^- \longrightarrow NH_3\uparrow + 2H_2O + SO_4^{2-}$$

Ammonia interacts with boric acid to form ammonium tetrahydroxyborate:

$$H_3BO_3 + H_2O \longrightarrow H[B(OH)_4]$$

$$NH_3 + H[B(OH)_4] \longrightarrow NH_4[B(OH)_4]$$

Which is then titrated with 0.1M hydrochloric acid solution:



A control experiment is carried out in parallel.

3. Spectrophotometry

The drug is dissolved in 0.1M sodium hydroxide solution and determined at 260 nm wavelength.

STORAGE

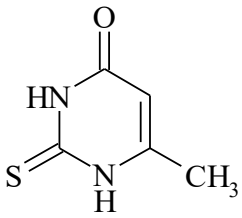
Methyluracil is stored in a dry place protected from light.

MEDICAL USE

It is a stimulator of hematopoiesis, has anabolic activity, stimulates leukopoiesis, accelerates wound healing, has anti-inflammatory effect. Used in leukopenia, agranulocytic angina, sluggish-healing wounds, burns, bone fractures, peptic ulcer and duodenal ulcer, benzene intoxication, radiation lesions, trophic ulcers.

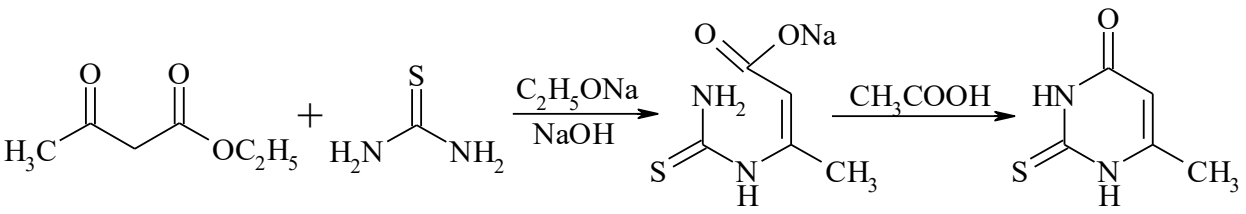
Forms of release: powder, tablets of 0.05 g, suppositories of 0.5 g, ointment 10%, and as part of ointments "Levomikol", "Levosin", sponge "Meturacol".

METHYLTHIOURACIL



OBTAINING

It is obtained by condensation of acetoacetic ester with thiourea in the presence of sodium ethylate or caustic alkali under heating; the resulting β-thioureidocrotonate sodium is subjected to cyclization:



PHYSICAL PROPERTIES

White or white with slightly yellowish tinge, odorless crystalline powder.

Very slightly soluble in water, slightly soluble in ethanol and ether, practically insoluble in benzene and chloroform, easily soluble in alkali and ammonia solutions.

IDENTIFICATION

I. Physicochemical methods

1. Infrared spectrophotometry.

Objective constants confirming the authenticity of uracil derivatives are maxima and minima of light absorption in the region of 220 - 300 nm in acid and alkali solutions. The IR spectrum of methylthiouracil in the region 4000 - 400 cm-1 (in disks with potassium bromide) should completely coincide with the spectrum figure attached to the pharmacopoeial article.

2. UV spectrophotometry.

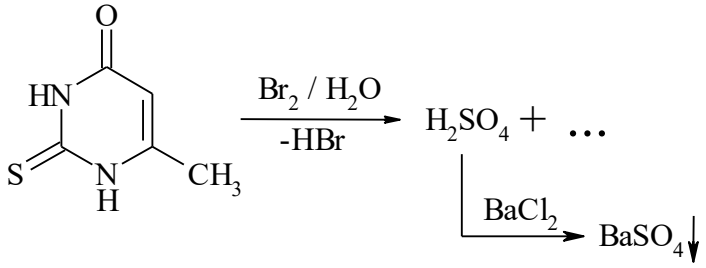
The uracil derivatives were found to have characteristic UV absorption spectra after dissolution in concentrated sulfuric acid.

II. Chemical methods

1. Oxidation with bromine water

When the drug is heated with bromine water, it is discolored.

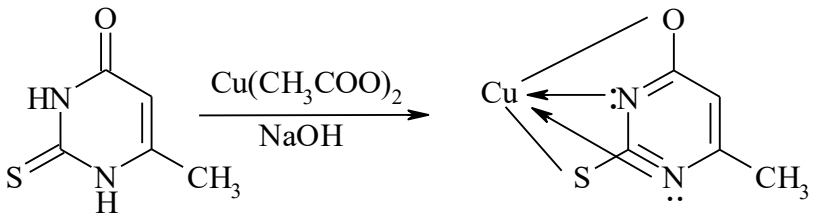
The resulting solution gives a positive reaction for sulfate ion. When barium chloride solution is added, a white precipitate insoluble in acids is formed:



2. Interaction with salts of heavy metals

a) With silver nitrate solution in the presence of ammonia solution forms a white gelatinous precipitate, insoluble in excess ammonia.

b) When interacting with copper acetate in the presence of sodium hydroxide, bright red fluorescence is observed in ultraviolet light:

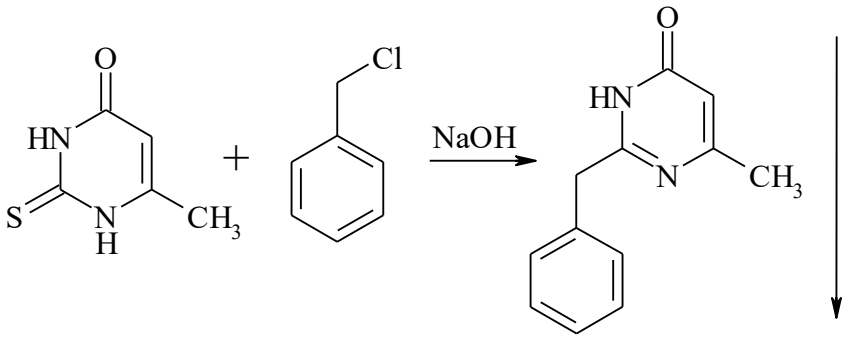


3. Interaction with sodium nitroprusside

Sodium nitroprusside, hydroxylamine chlorohydrate and sodium carbonate added to a hot solution of the drug causes greenish blue coloration.

4. Interaction with benzyl chloride

When benzyl chloride acts on the drug in the presence of alkali, a white crystalline precipitate of benzyl derivative is released:



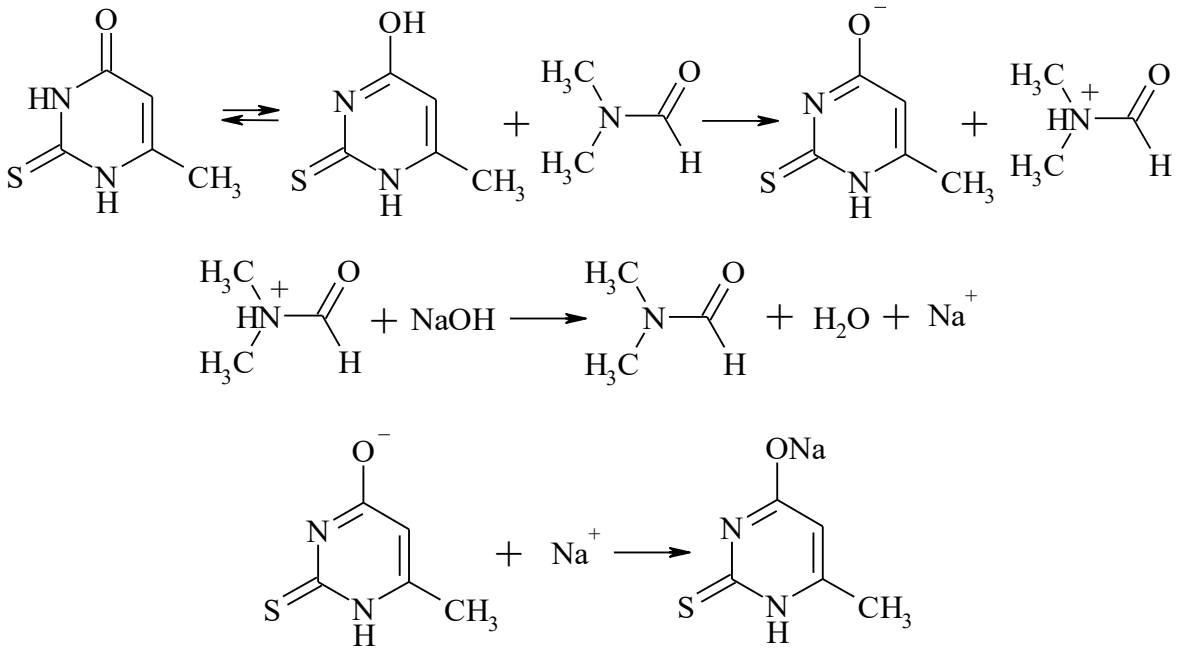
PURITY TEST

The purity of the preparation is determined by transparency and color of the alkaline solution (should be colorless and transparent), acidity. Organic impurities, sulfate ash and heavy metals should be within the standard. Loss in mass during drying should not exceed 0.5%. The preparation should be free of thiourea, which is determined by reaction with sodium acetate and silver nitrate.

QUANTIFICATION

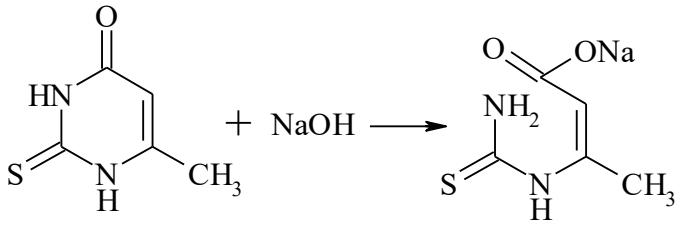
1. Non-aqueous titration

The preparation is dissolved in dimethylformamide, previously neutralized by 1% solution of thymol blue in dimethylformamide, and titrated with 0.1M sodium methylate solution until blue staining. The indicator is thymol blue.



2. Neutralization

Determination is based on hydrolysis of the alcoholic solution of the preparation with 0.1M sodium hydroxide solution on heating in the presence of thymolphthalein indicator to blue coloring.



STORAGE

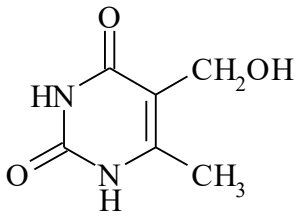
Methylthiouracil in well sealed containers protected from the action of light.

MEDICAL USE

It is an antithyroid drug. But due to high toxicity it was taken out of production in 1982.

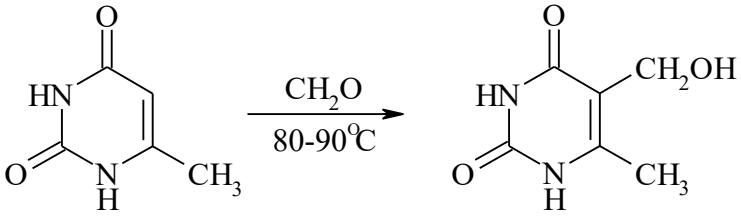
Forms of release: powder, tablets.

PENTOXYL



OBTAINING

It is obtained by heating 6-methyluracil with 40% aqueous formaldehyde solution:



PHYSICAL PROPERTIES

White microcrystalline powder with faint odor of formaldehyde, bitter taste.

Insoluble in ethanol, slightly soluble in water and acids, soluble in alkali and ammonia solutions.

IDENTIFICATION

I. Physicochemical methods

1. Infrared spectrophotometry.

Objective constants confirming the authenticity of uracil derivatives are maxima and minima of light absorption in the region of 220 - 300 nm in acid and alkali solutions.

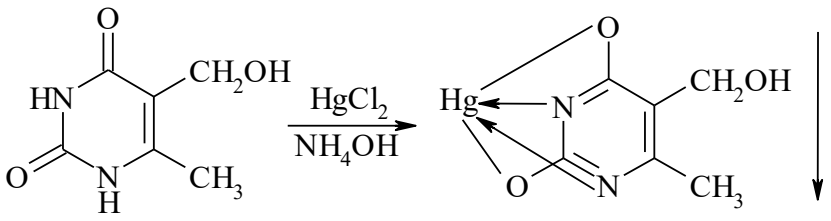
2. UV spectrophotometry.

The uracil derivatives were found to have characteristic UV absorption spectra after dissolution in concentrated sulfuric acid.

II. Chemical methods

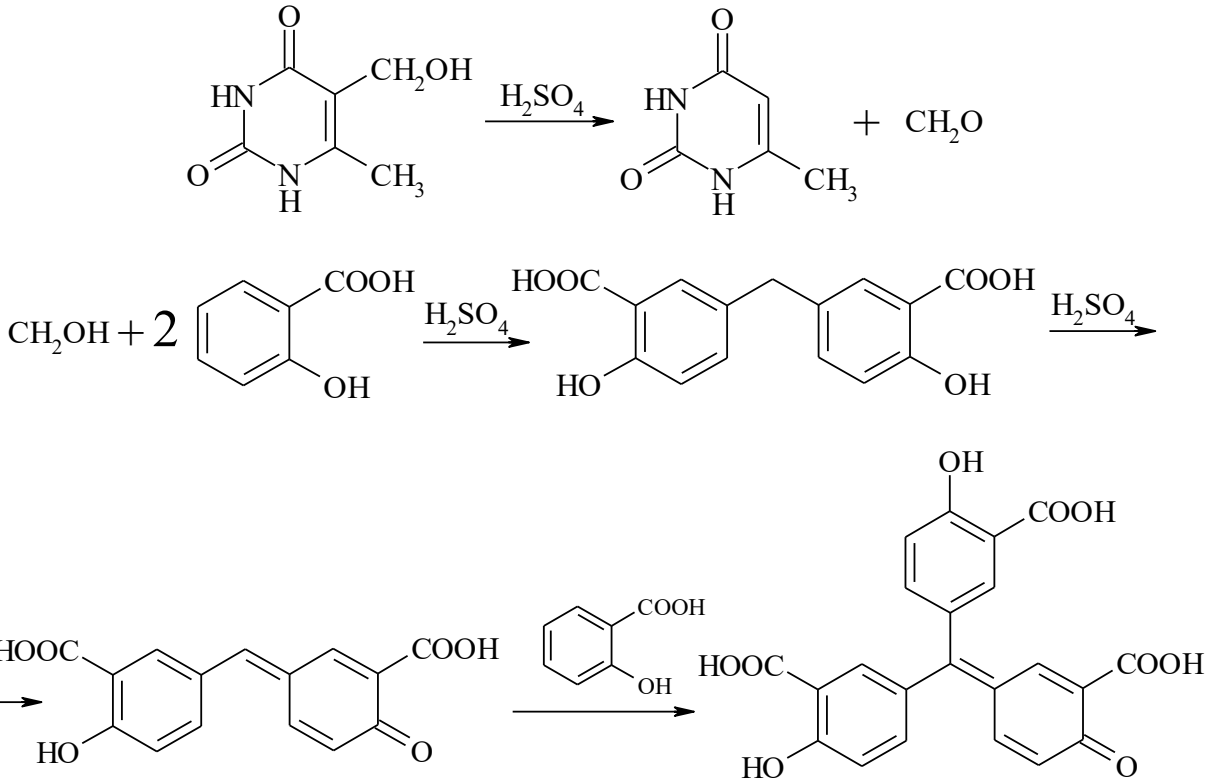
1. Interaction with salts of heavy metals

In the presence of ammonia solution forms white precipitates with silver nitrate and mercury dichloride solution:



2. Formation of auric dye

When heated with salicylic acid in the presence of concentrated sulfuric acid, a red coloration appears:



PURITY TEST

The purity of the drug is determined by the absence of impurities of arsenic, heavy metals and volatile substances (when dried for 3 hours at 50-60ºC the weight loss should not exceed 1%).

QUANTIFICATION

1. Non-aqueous titration

A sample of the preparation is dissolved in dimethylformamide and titrated with 0.1M sodium hydroxide solution in methanol until blue coloring. The indicator is thymol blue. (*Write down the reaction*s).

2. Kjeldahl method

The determination is carried out in the same way as for methyluracil. (*Write down the reactions*).

STORAGE

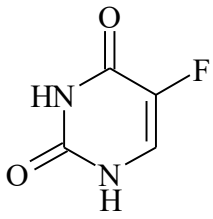
Pentoxyl is stored in well sealed containers protected from light.

MEDICAL USE

It is a stimulator of leukopoiesis, has anti-inflammatory effect. Used for trophic ulcers, burns, fistulas, bone fractures, peptic ulcer, chronic pancreatitis, infectious-inflammatory diseases of the respiratory tract, occurring with neutropenia and inhibition of phagocytosis.

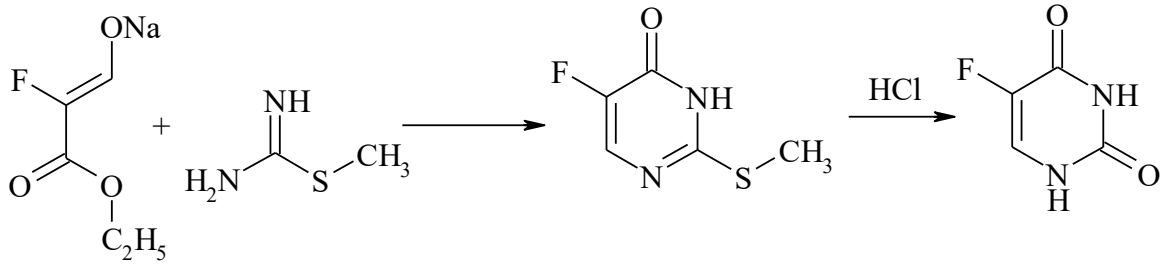
Forms of release: powder, coated tablets, 0.025 and 0.2 g in a package of 10 pieces.

FLUOROURACIL

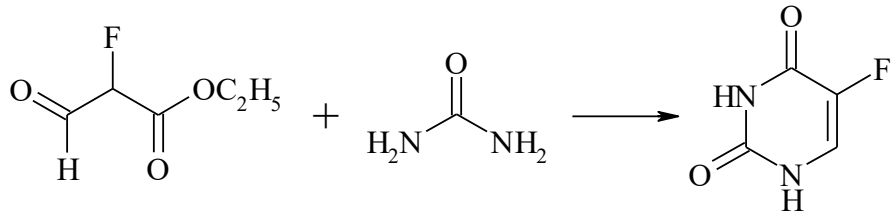


OBTAINING

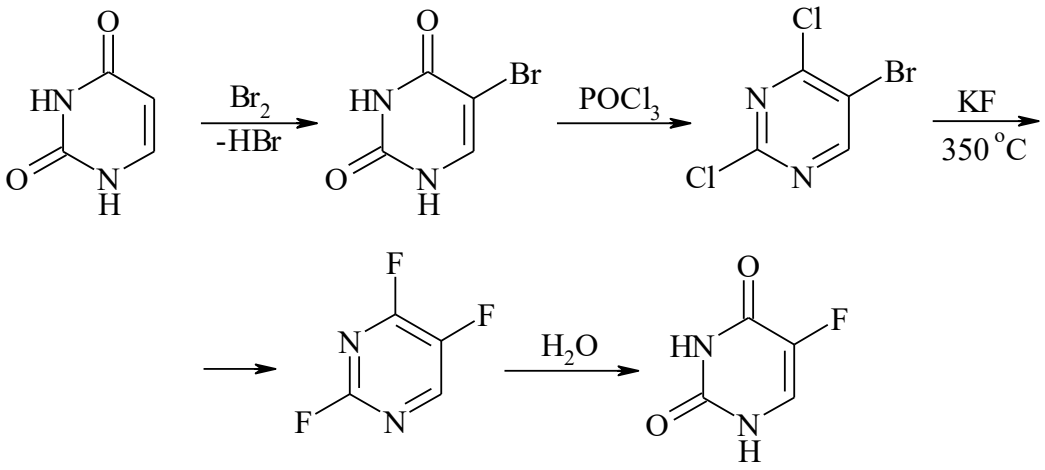
1. Condensation of sodiumformylfluoroacetic ester and 5-methyliso-thiourea. The resulting 2-methylthio-5-fluorouracil is converted to 5-fluorouracil by hydrolysis in hydrochloric acid solution:



2. Condensation of the ethyl ester of formylfluoroacetic acid with urea:



3. Obtained from uracil according to the scheme:



PHYSICAL PROPERTIES

White or white with yellowish tinge crystalline powder.

It is slightly soluble in water and ethanol, moderately soluble in alkali and ammonia solutions, slightly soluble in 0.1 M hydrochloric acid solution.

IDENTIFICATION

I. Physicochemical methods

1. Infrared spectrophotometry.

Objective constants confirming the authenticity of uracil derivatives are maxima and minima of light absorption in the region of 220 - 300 nm in acid and alkali solutions. Fluorouracil has absorption maximum at a wavelength of 265 nm. The specific absorption index of fluorouracil (0.001% solution in 0.1 M hydrochloric acid solution) is in the range from 530 to 550.

2. UV spectrophotometry.

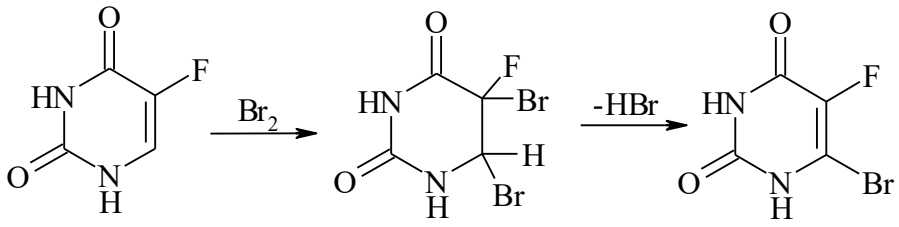
The uracil derivatives were found to have characteristic UV absorption spectra after dissolution in concentrated sulfuric acid. Two absorption bands (256 and 290 nm) appear in the spectrum of fluorouracil.

II. Chemical methods

1. Oxidation reactions

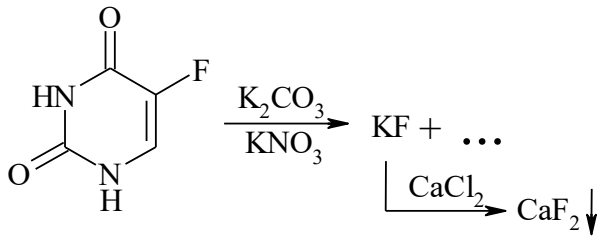
a) Interaction with potassium permanganate in alkaline medium. The product of the reaction is colored green.

b) Discoloration of bromine water:



2. Discovery of fluoride ion

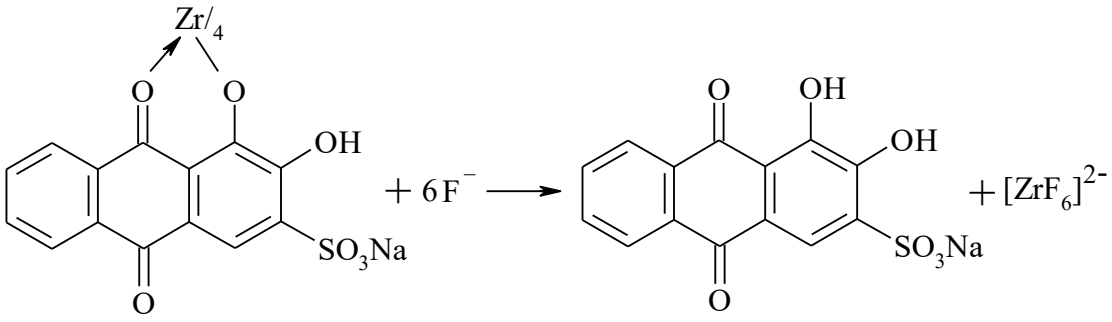
a) Preliminary mineralization with sintering mixture (K_2CO_3 and KNO_3). Then the residue is dissolved and acted on with calcium chloride solution at pH 4.0-5.0. A white opalescence appears:



b) The preparation is burned in a flask with oxygen in the presence of hydrogen peroxide. The fluoride ions formed decolorize the blood-red coloring of the added ferric thiocyanate solution, binding it into a strong complex ion:

$$6F^- + Fe(SCN)_3 \longrightarrow [FeF_6]^{-3} + 3SCN^-$$

c) After mineralization, the fluoride ion can be detected using a 1% alcohol solution of alizarinate, which is previously mixed with a 2% solution of zirconium nitrate in 5% hydrochloric acid. Zirconium alizarinate has a red-violet coloration, which disappears when adding a solution containing fluoride ions. The coloring changes to yellow due to the release of free alizarin:



3. Interaction with chloroform

When the preparation is heated in the presence of chloroform or chloral hydrate, orange-red coloration appears.

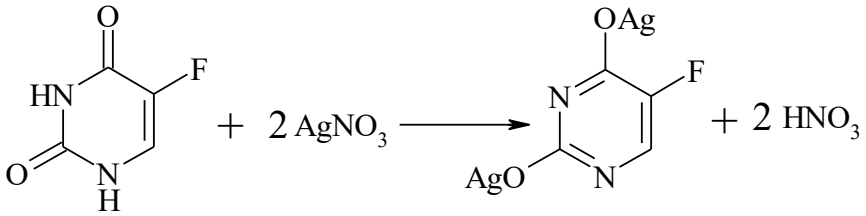
PURITY TEST

The degree of purity is checked by the TLC method using Silufol UV-254 chromatographic plates. Fluorouracil should not contain impurities of intermediate products of synthesis: methylthiofluorouracil and thiofluorouracil. Impurity of uracil (not more than 0.16%) is detected by HPLC method, and the content of impurity of free fluoride ions (not more than 0.005%) is determined using fluoroselective electrode.

QUANTIFICATION

1. Indirect neutralization

A suspension of the preparation is dissolved in water and 0.1M silver nitrate solution is added. The equivalent amount of nitric acid is then titrated with 0.1M sodium hydroxide solution:

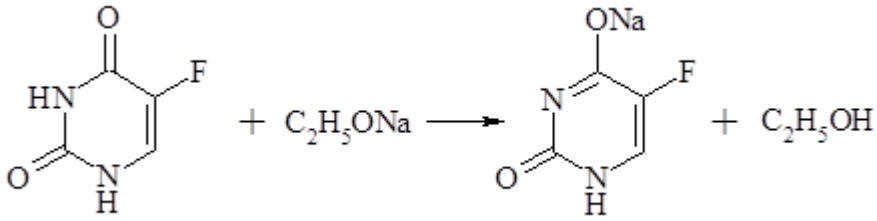


$$HNO_3 + NaOH \longrightarrow NaNO_3 + H_2O$$

The indicator is phenol red.

2. Non-aqueous titration

A suspension of the drug is dissolved in dimethylformamide. The titrant is 0.1M sodium methylate or tetrabutylammonium hydroxide solution. The indicator is thymol blue.



3. Spectrophotometry

The drug is dissolved in 0.1M hydrochloric acid solution and the determination is carried out (at 265 nm wavelength).

4. Photocolorimetry

It is based on the determination of the optical density of solutions of products of color reactions. For example, interaction with potassium permanganate.

STORAGE

Fluorouracil is stored in a cool place protected from light.

MEDICAL USE

It has antitumor, cytostatic effect. It is used in cancer of the colon, breast, pancreas, tumors in the head and neck region. Toxicity of the drug is significant. The drug depresses hematopoiesis.

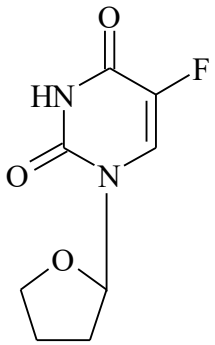
Forms of release: 2.5% and 5% solutions for infusion in ampoules or vials of 5, 10, 20 or 40 ml.

URACIL NUCLEOSIDE DERIVATIVES

It is known that the cells of microorganisms, plant and animal tissues contain nucleosides that are not components of nucleic acids. These substances have antibiotic activity. Structurally, they are similar to ordinary nucleosides, so they play the role of antimetabolites in the body. Antimetabolites - synthetic nucleosides with antiviral and antitumor activity - were created on the basis of nucleosides included in nucleic acids. The mechanism of action is based on inhibition of nucleic acid replication.

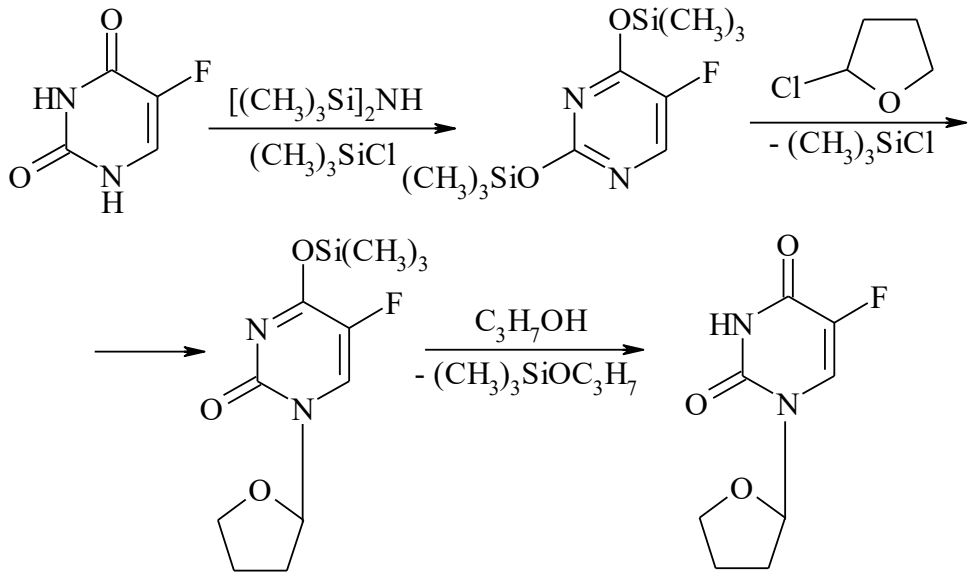
Nucleosides contain a sugar residue in the N1 position. Most often they are various pentoses.

TEGAFUR



OBTAINING

The starting compound fluorouracil is subjected to O-silylation with hexamyldisilazane, then the obtained pyrimidine derivative is alkylated with 2-chlorotetrahydrofuran and the silyl protection is removed by crystallization of the ester from propanol:



PHYSICAL PROPERTIES

White crystalline odorless powder. Tpl 165 - 171ºC

Moderately soluble in water, slightly soluble in ethanol, practically insoluble in chloroform and ether.

IDENTIFICATION

I. Physicochemical methods

1. Infrared spectrophotometry

The IR spectra of the preparations should be in complete agreement with the spectrum figure attached to the pharmacopoeial article. Tegafur at wavelength of 220-300 nm has minimum at 248 nm and maximum at 270 nm.

2. UV spectrophotometry

Tegafur has an intense absorption band at 290 nm and a small shoulder at 258-263 nm.

3. Chromatography

TLC, GC, HPLC and HPLC methods are used to determine the authenticity of nucleosides. Rf (Rs) and retention time are determined (the difference between the test substance and the standard sample should not exceed 2%).

4. Other methods

NMR^{1}H spectroscopy is also used (compare the obtained spectra with the figure of the spectrum in the pharmacy article), derivatography, X-ray diffractography.

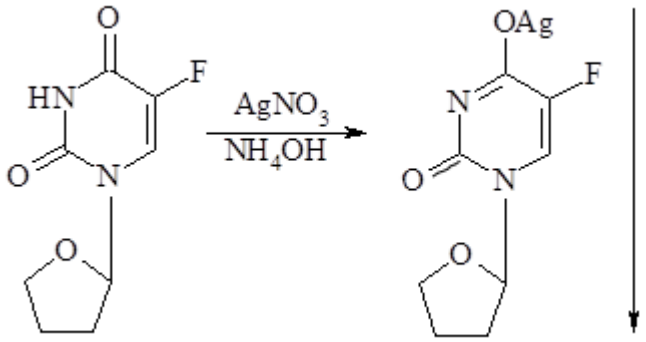
II. Chemical methods

1. Interaction with chloroform (chloral hydrate)

When heated with chloroform or chloral hydrate, an orange-red coloration appears.

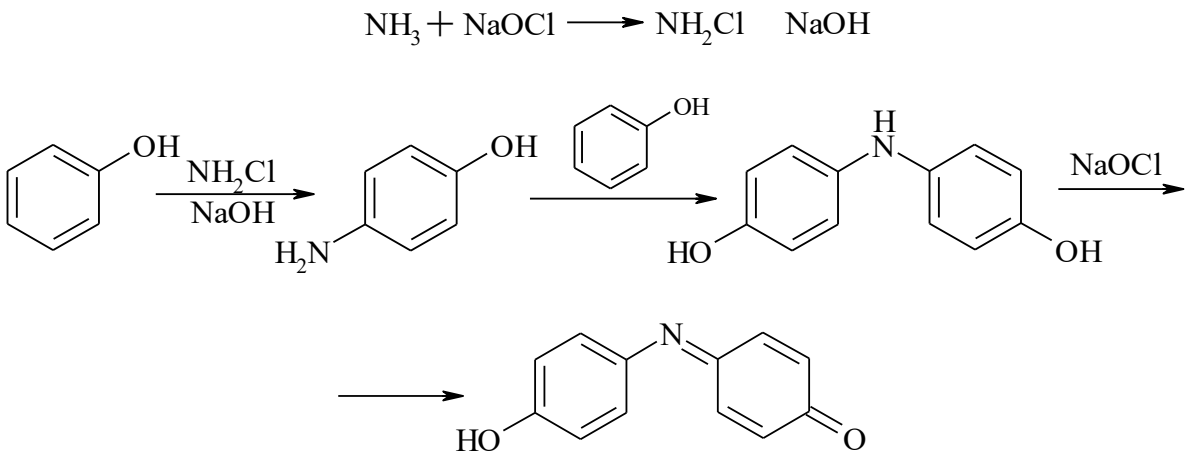
2. Interaction with salts of heavy metals.

Tegafur forms a violet-colored compound with cobalt salts, white precipitates with solutions of silver nitrate and mercury dichloride:



3. Formation of indophenol.

When a solution of the drug is heated in a 30% solution of sodium hydroxide in the presence of zinc dust, ammonia is released. If then phenol and sodium hypochloride are added to the reaction mixture, the released ammonia, interacting with them, forms monochloramine and then indophenol (at pH 11), which has a characteristic blue color:



4. Fluoride-ion detection.

After mineralization, fluoride-ion detection is carried out similarly to fluorouracil.

PURITY TEST

The degree of purity of tegafur is checked by TLC method using Silufol UV-254 chromatographic plates. The preparation should not contain 5-fluorouracil and other extraneous impurities. The content of free fluoride ions impurity is determined using fluoroselective electrode.

QUANTIFICATION

1. Chromatography

HPLC method is used for quantitative determination of nucleoside preparations. Calculations are performed by simple normalization by the peak area of the main substance and the standard sample.

2. Spectrophotometry

Used for the quantitative determination of tegafur. The drug is dissolved in 0.1M hydrochloric acid solution and determined at 270 nm.

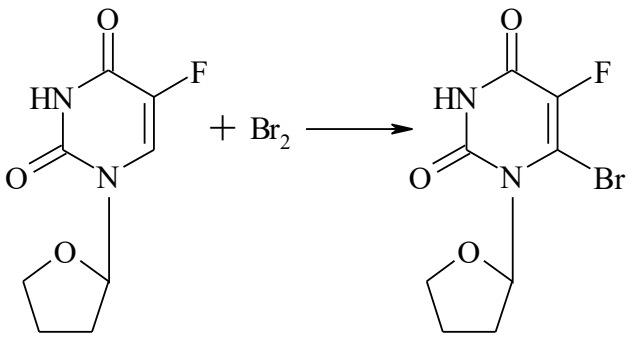
3. Photocolorimetry

Color reactions (e.g., complex formation with cobalt ion) are used for photocolorimetric determination.

4. Bromide bromatometry

Used for the determination of tegafur. The titrant is potassium bromate:

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



Excess titrant is determined iodometrically:

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

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

The indicator is starch.

STORAGE

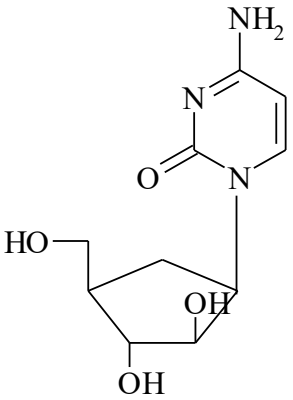
Tegafur is stored according to List A in a dry place protected from light.

MEDICAL USE

Used in malignant tumors of the stomach, colon, sigmoid and rectum, breast cancer, skin lymphomas, as well as diffuse neurodermatitis.

Forms of release: 4% solution of sodium salt in ampoules of 10 ml; capsules of 0.4 g in a package of 100 pieces.

CYTARABINE

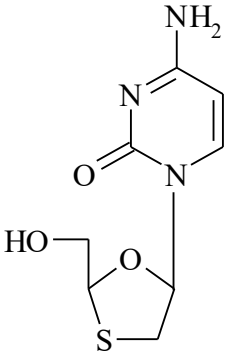


White or whitish crystalline odorless powder. Soluble in water, slightly soluble in ethanol and chloroform.

Used in acute myeloblastic leukemia in children and adults, in acute lymphoblastic leukemia, erythroleukosis, non-Hodgkin's lymphoma.

Forms of release: lyophilized powder or porous mass in vials of 0.1 and 0.5 g with solvent; 2% solution for injection and infusion in ampoules of 5 ml.

LAMIVUDINE

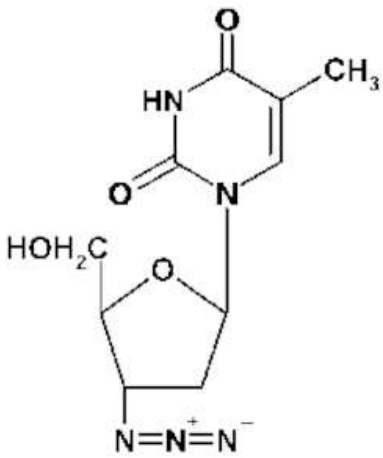


White or whitish crystalline powder. Soluble in water, very slightly soluble in chloroform and ether.

It is ***used*** mainly in the complex therapy of AIDS. It is an inhibitor of HIV reverse transcriptase.

Forms of release: lamivudine tablets (0.15 g) with zidovudine (0.3 g) are available under the name Combivir.

ZIDOVUDINE (AZIDOTHYMIDINE)



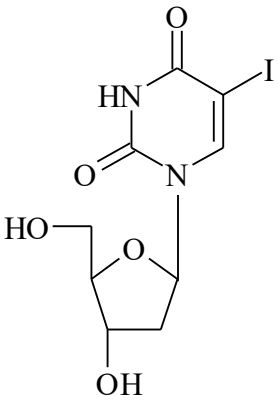
White or white with yellowish tinge odorless crystalline powder. Tpl 120 - 123ºC. Specific rotation from +58 to +62 (1% solution in methanol).

Moderately soluble in water, soluble in ethanol and methanol, slightly soluble in chloroform, very little in ether.

Used in the complex therapy of AIDS. The drug inhibits the replication of retroviruses.

Forms of release: 0.1 and 0.25 g capsules; 1% syrup; 2% solution for infusion in 20 ml vials.

IODOXURIDINE



White or white with yellowish tinge, odorless crystalline powder.

Moderately soluble in water, slightly soluble in chloroform and ether.

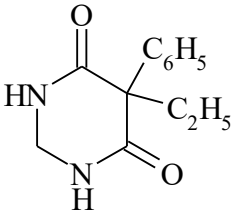
It has a selective inhibitory effect on replication of some viruses. It is **used** in ophthalmologic practice as a topical antiviral agent in keratitis caused by Herpes simplex or vaccinia virus.

Forms of release: 0.1% solution (eye drops) in 10 ml vials.

PYRIMIDINE-4,6-DIONE DERIVATIVES

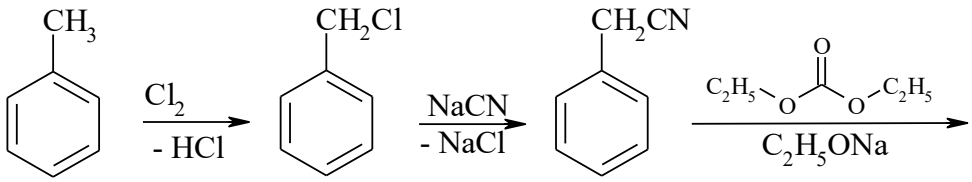
The drug hexamidine belongs to this group of medicines. By chemical structure, hexamidine is close to phenobarbital, but is not a barbiturate, as its molecule lacks a urea fragment. The modification of the molecule led to the creation of a drug with a pronounced anticonvulsant effect and a lower sleeping effect than phenobarbital.

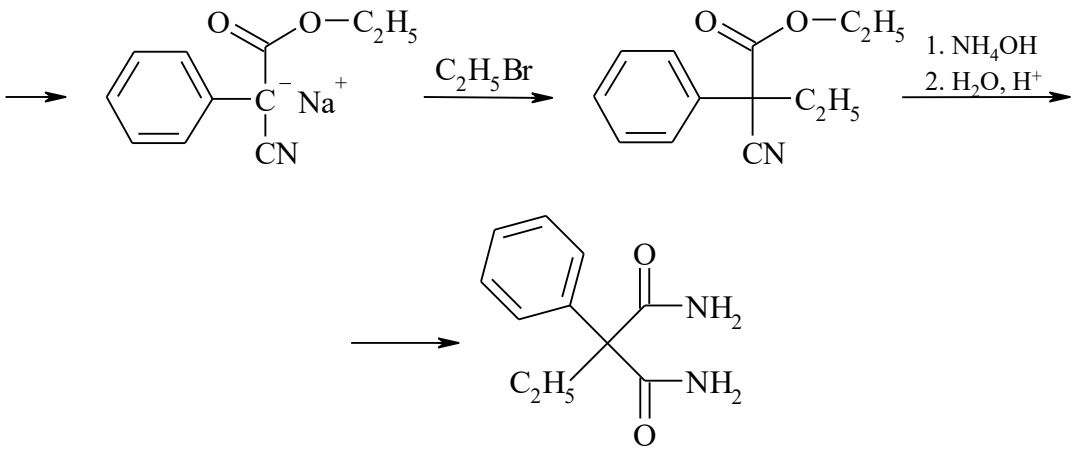
HEXAMIDINE



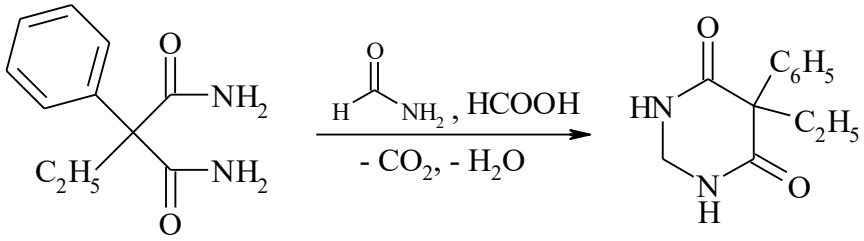
OBTAINING

The starting compound is toluene:





The resulting phenylethylmalonic acid diamide is condensed with formamide at 192-195°C:



PHYSICAL PROPERTIES

White crystalline powder without odor. Melting point 280 - 284ºC

Practically insoluble in water, ether and benzene, slightly soluble in 95% ethanol and acetone.

IDENTIFICATION

I. Physicochemical methods

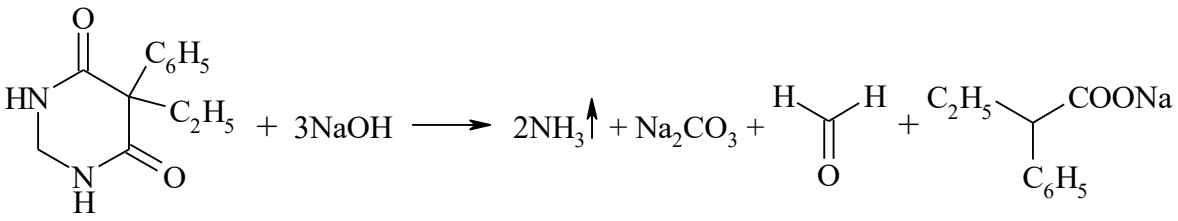
UV spectrophotometry

The UV spectrum of a solution of hexamidine in ethanol should have three absorption maxima, at 252, 258, 264 nm.

II. Chemical methods (authenticity reactions)

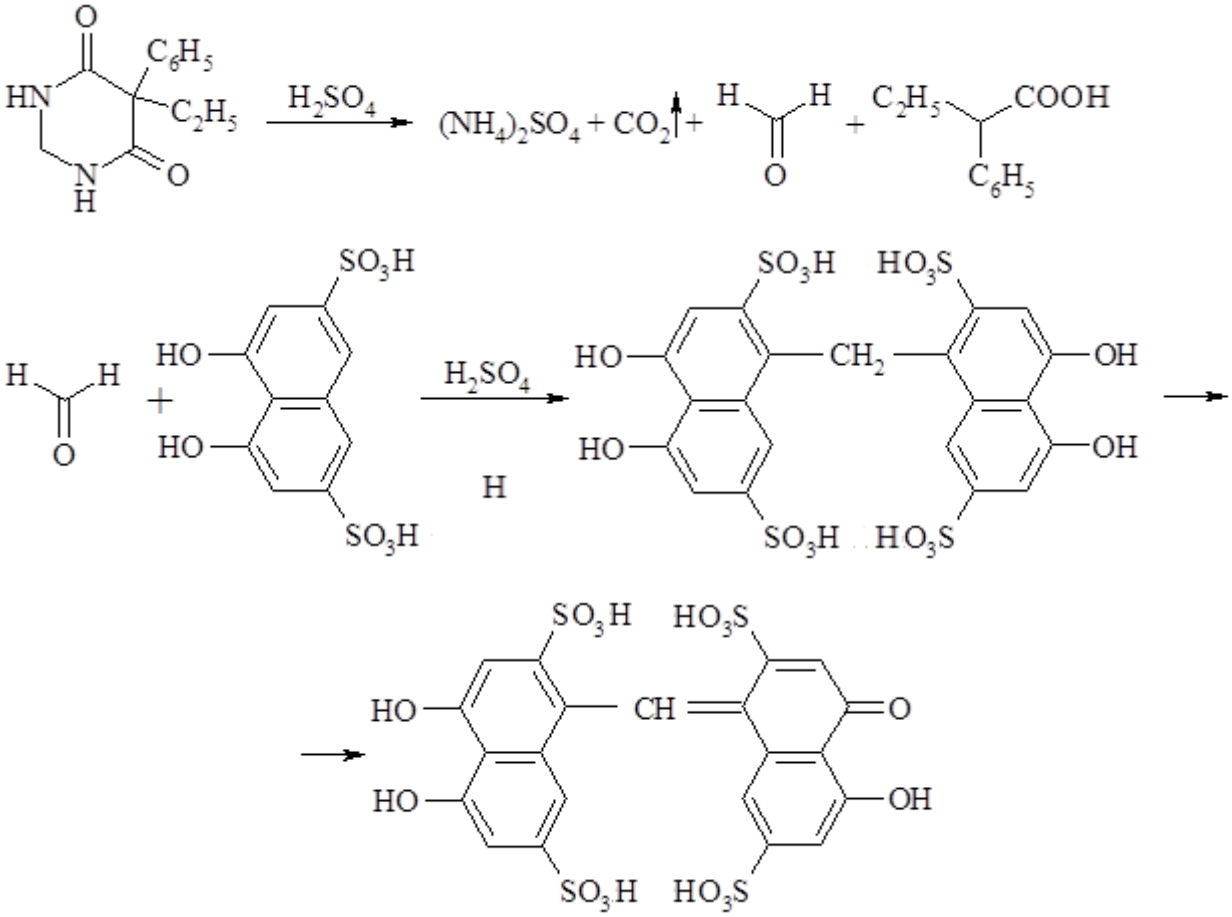
1. Fusion with alkali

When fused with crystalline sodium hydroxide, ammonia is released, which is detected by the blueing of red litmus paper:



2. Interaction with chromotropic acid in the presence of concentrated sulfuric acid

When the preparation is heated with the chromotropic acid in the presence of concentrated sulfuric acid, a lilac coloration appears (condensation product of released formaldehyde with chromotropic acid):



3. Interaction with chloramine B and copper sulfate

When boiling a solution of the drug with chloramine B and copper sulfate, an aromatic odor appears, a blue precipitate falls out, and the solution is colored red-violet.

PURITY TEST

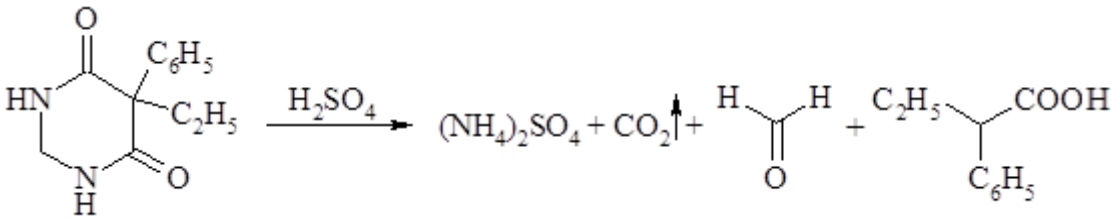
Determine loss in weight on drying (not more than 0.5%), sulphate ash (not more than 0.1%) and heavy metal impurities. Chlorides and sulfates should be within the

standard. For the determination of organic impurities use thin-layer chromatography.

QUANTIFICATION

1. Kjeldahl method

A suspension of the preparation is heated with concentrated sulfuric acid:



As a result, the organically bound nitrogen is converted to ammonium hydrosulfate, which is treated with sodium hydroxide and the resulting ammonia is distilled off into a receiver:

$$(NH_4)_2SO_4 + 2OH^- \longrightarrow 2NH_3\uparrow + 2H_2O + SO_4^{2-}$$

Ammonia interacts with boric acid to form ammonium tetrahydroxyborate:

$$H_3BO_3 + H_2O \longrightarrow H[B(OH)_4]$$

$$NH_3 + H[B(OH)_4] \longrightarrow NH_4[B(OH)_4]$$

Which is then titrated with 0.1M hydrochloric acid solution:

$$NH_4[B(OH)_4] + HCl \longrightarrow NH_4Cl + H_3BO_3 + H_2O$$

A control experiment is carried out in parallel.

STORAGE

Stored according to list B in well sealed containers.

MEDICAL USE

The drug has a strong anticonvulsant effect. Unlike phenobarbital, it does not produce pronounced sleeping effect. Hexamidine is used mainly in large convulsive seizures. It is less effective in mild abortive seizures.

Forms of release: tablets 0.125 and 0.25 in a package of 50 pieces.