Ministry of Health of the Russian Federation

Volgograd State Medical University

Department of Pharmaceutical and Toxicological Chemistry

SPECIAL PHARMACEUTICAL CHEMISTRY

Neuroleptic agents – phenothiazine derivatives acyl phenothiazine derivatives

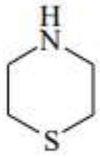
Lesson 7

VII term

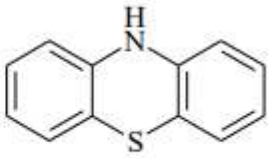
Volgograd, 2023

NEUROLEPTICS PHENOTHIAZINE DERIVATIVES

Phenothiazine is a condensed heterocyclic system consisting of a six-membered thiazine heterocycle and two benzene nuclei.

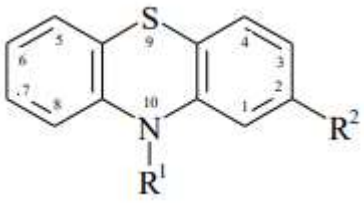


Thiazine



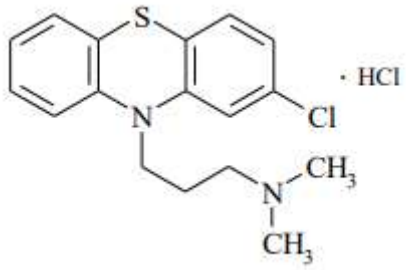
Phenothiazine

A large number of phenothiazines have been synthesized, the general formula of which is:

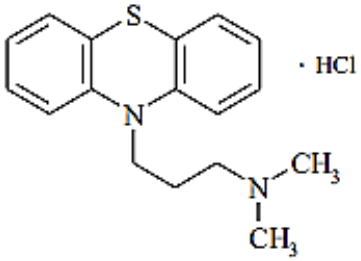


Of the large number of drugs of this group, 5 drugs are used in medicine. Let's consider four of them: aminazine, propazine, etacizine, etmozine.

AMINAZINE and PROPAZINE



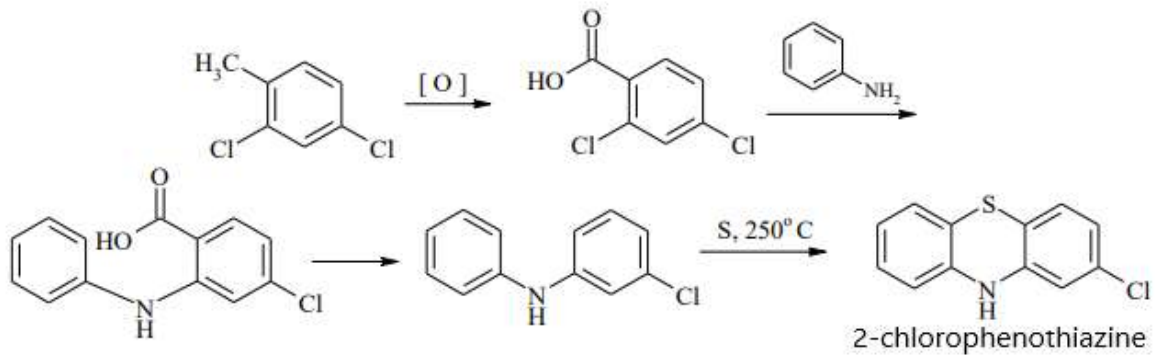
Aminazine



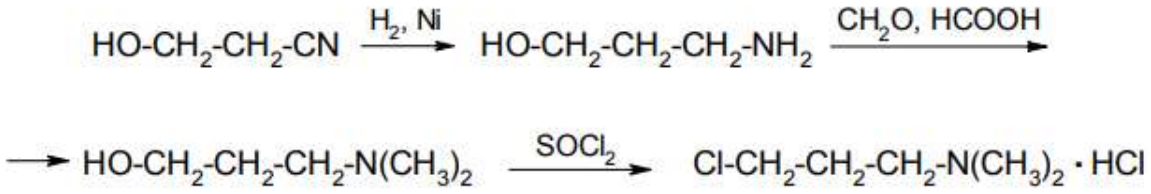
Propazine

OBTAINING

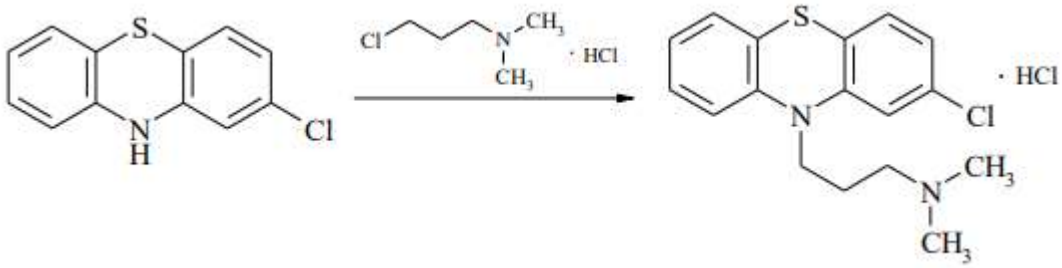
Synthesis of ***aminazine*** was first carried out in France. For the synthesis of aminazine, 2-chlorophenothiazine is obtained from 2,4-dichlorotoluene. Phenothiazine can be obtained by the interaction of sulfur with diphenylamine in the presence of a catalyst, iodine or aluminum chloride. The reaction takes place at a temperature of 180-250°C.



3-dimethylaminopropyl chloride is obtained according to the scheme:



Third synthesis step: condensation of 2-chlorophenothiazine and 3-dimethylaminopropyl chloride hydrochloride:



Propazine is synthesized according to an analogous scheme. The starting point for the synthesis is ortho-chlorotorluene, from which o-chlorobenzoic acid is obtained by oxidation and condensed with aniline to yield the phenothiazine nucleus

PHYSICAL PROPERTIES

Aminazine is a white or slightly yellowish tinged crystalline substance. The melting point of aminazine is 195-198°C. Oxidizing in air it changes color to red.

Propazine is a white or slightly yellowish tinted crystalline substance. The melting point of propazine is 177-181°C. Oxidizing in air it changes color to blue-green.

Aminazine and Propazine are well soluble in water, ethyl alcohol and chloroform, practically insoluble in diethyl ether.

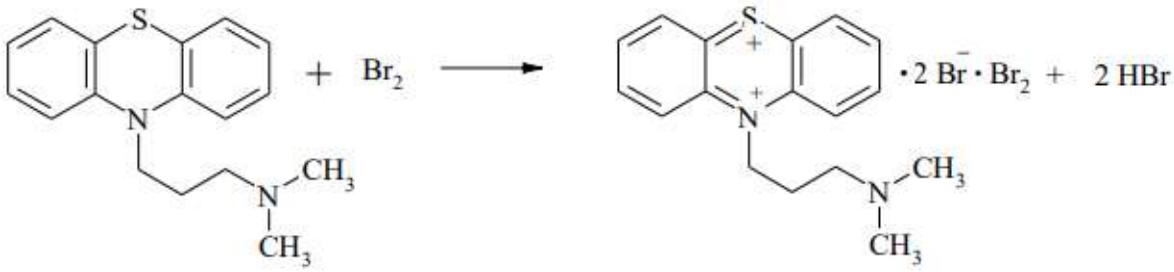
IDENTIFICATION

1. *Oxidation of the phenothiazine core.*

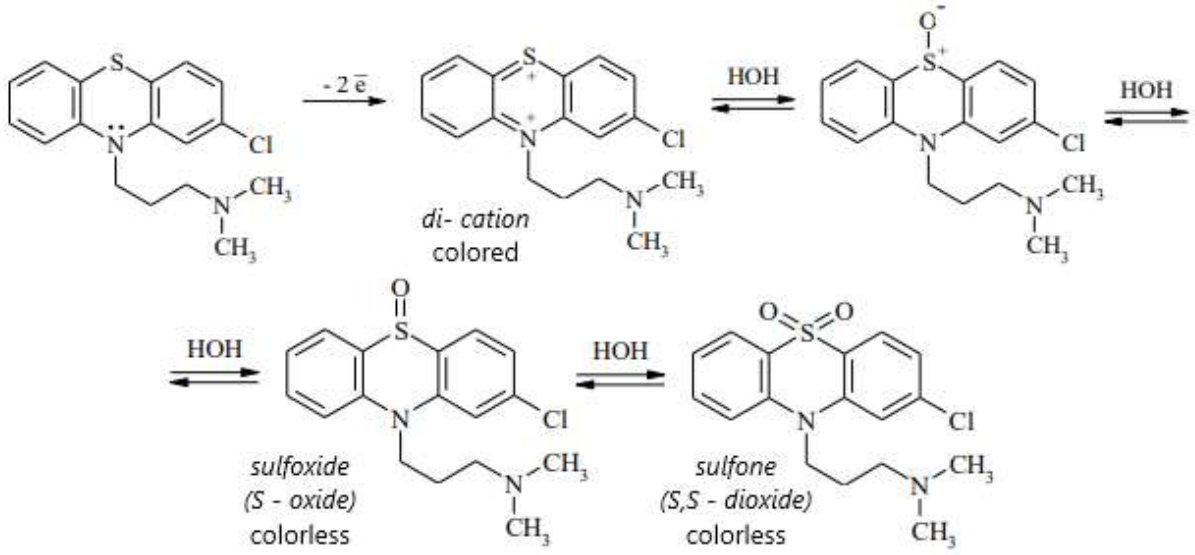
The ability of preparations to oxidize readily to form colored products is used for authenticity testing. Bromine water, nitric acid, iron (III) chloride, hydrogen peroxide, concentrated sulfuric acid can be used as oxidizing agents. Oxidation products with red, cherry-red, red-orange, crimson coloring are formed.

Oxidation of propazine with bromine water.

The more specific of the listed reagents for phenothiazine nucleus is bromine water. This reagent is used to distinguish drugs from each other (the drug solution is heated to boiling with bromine water). In this case, *propazine* forms a transparent *brownish-red solution*, while *aminazine* forms a transparent *light crimson solution*. Colored products obtained by heating phenothiazine derivatives with bromine water are due to the formation of perbromo derivatives of phenothiazonium cation. *Phenothiazine* forms *red-colored* perbromophenothiazonium when oxidized with bromine:



Instead of unstable and toxic reagent - bromine water was proposed to test the authenticity of phenothiazine derivatives *1% aqueous solution of potassium bromate in the presence of 0.15 ml of dilute hydrochloric acid*. Aqueous or aqueous-alcoholic 0.1% solutions *of aminazine and propazine* acquire a *pink or pink-orange coloration, gradually changing to crimson or brown*.



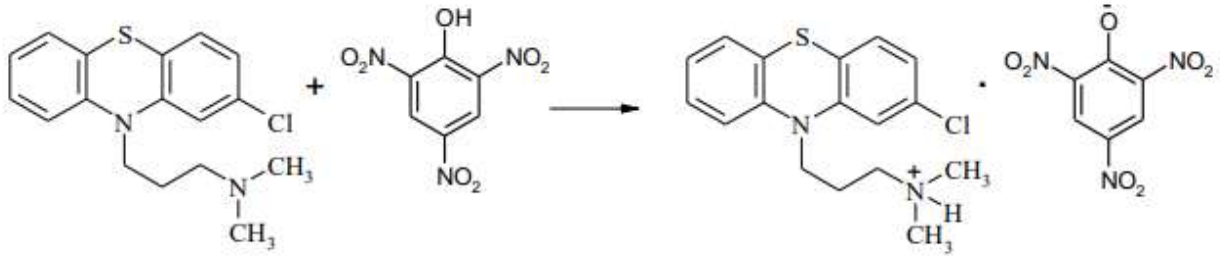
2. ***Interaction with methylene blue.***

   Methylene blue in the presence of concentrated sulfuric acid forms colored reaction products with drugs. *Aminazine* acquires a *poupure* coloration, *proprazine - light brown*.

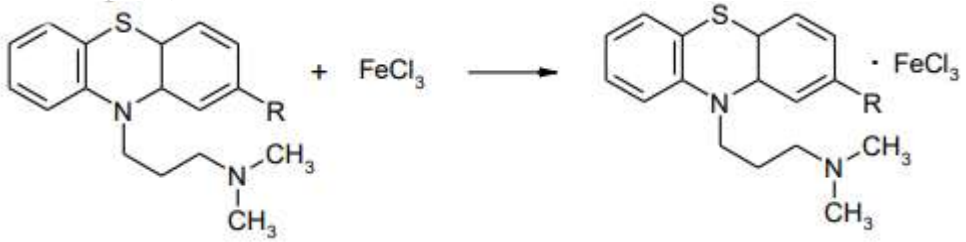
3. ***Condensation with maleic anhydride.***

   Acetone solution of maleic anhydride is a group reagent for phenothiazine derivatives. The reaction products acquire a *yellow-orange coloration*.

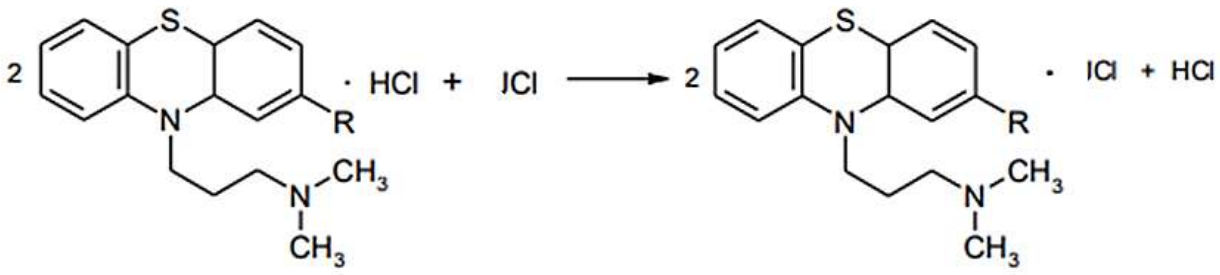
4. ***Interaction with common alkaloid reagents. Formation of picrates.***
   Aminazine with picric acid solution forms a precipitate having a melting point of 177 °C:



5. ***Formation of colored complexes with metal salts.***
   Red-colored complex compounds with phenothiazine derivatives form iron (III), mercury (II), cobalt, and silver ions.

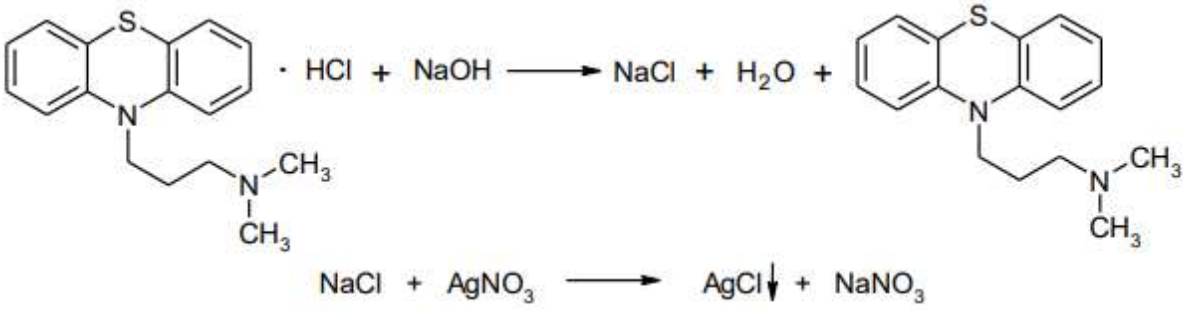


6. ***Interaction with iodimonochloride.***
   When iodimonochloride solution interacts with propazine or aminazine, a *brown precipitate* is formed. On subsequent addition of saturated aqueous solution of sulfanilic acid and ethanol, *propazine acquires green and aminazine purple coloring.*



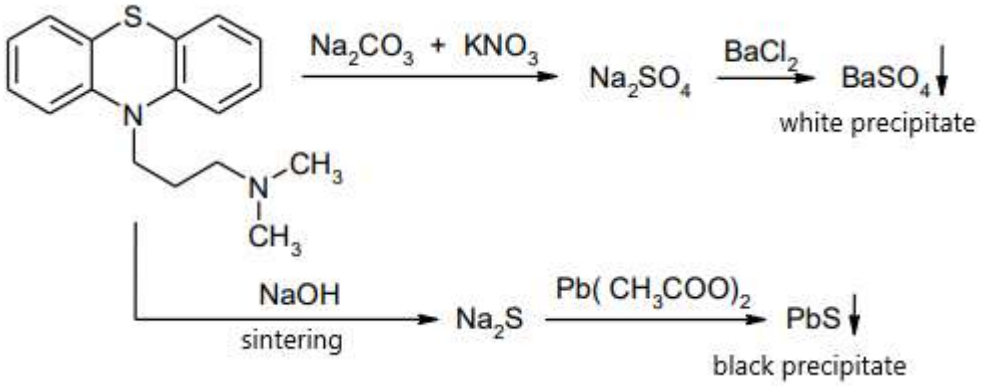
7. ***Determination of aminazine base and chloride ions.***

On the action of an alkali solution on the salt form of aminazine or propazine, the base precipitates, which is separated, washed, dried and the melting point determined, and chloride ions are detected in the filtrate:



8. ***Detection of organically bound sulfur***

The presence of sulfur atom in the molecules of phenothiazine derivatives is established by calcination with sodium carbonate and potassium nitrate. The resulting sulfate ion is detected in the filtrate using barium chloride solution as a reagent:

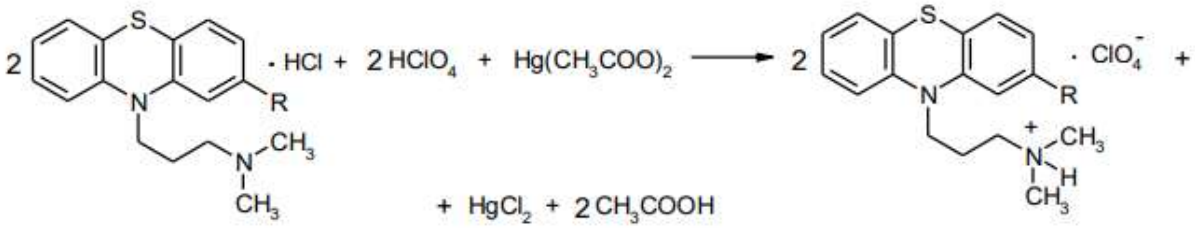


If the preparation is sintered with alkali, after dissolution of the ash in the solution, the sulfide ion can be detected with lead acetate. In this case a black precipitate falls out.

QUANTIFICATION

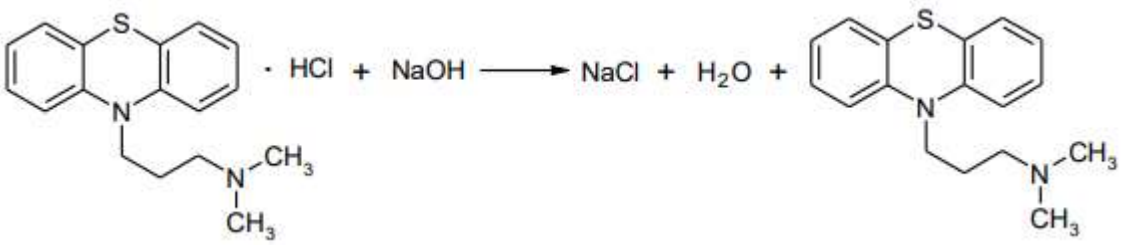
1. **Non-aqueous titration.**

The titrant is a solution of perchloric acid. Glacial acetic acid is used as a solvent and crystal violet is used as an indicator. Since both preparations are hydrochloride salts, mercury acetate is added to the titrated solution to accurately determine the equivalence point (to bind chloride ions). The titration proceeds according to the scheme:



2. ***Neutralization. Alkalimetric titration.***

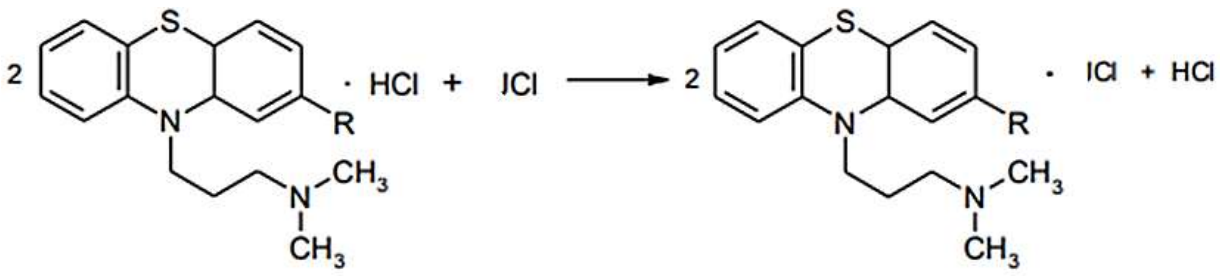
Titrated with 0.1 M aqueous sodium hydroxide solution. The indicator is phenolphthalein. In order that the base precipitate does not interfere with the determination it is extracted into the organic phase by adding chloroform to the test solution. The determination proceeds according to the scheme:



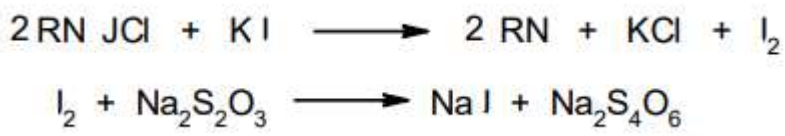
3. ***Iodometric, bromatometric and iodochlorometric titration.***

Iodometric determination of phenothiazine derivatives is based on the formation of polyiodides. In bromatometric determination, a solution of a drug suspension in 2 M hydrochloric acid solution in the presence of potassium bromide is titrated with 0.1 M potassium bromate solution until discoloration of the appearing red color.

Iodochlorometric titration of preparations consists in precipitation of the complex of preparations with iodine monochloride, its separation by filtration and subsequent decomposition.

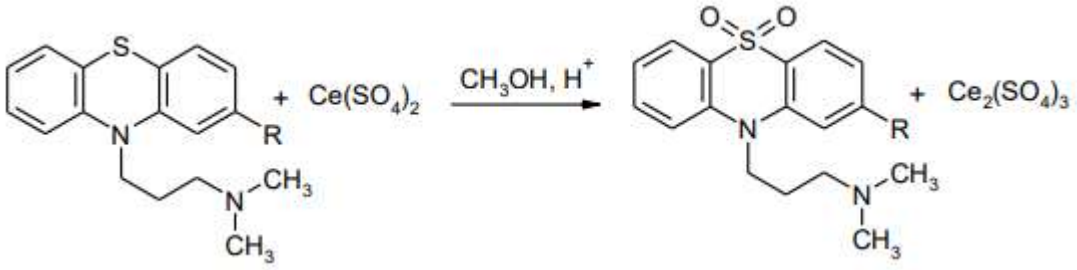


The released equivalent amount of iodine is titrated with sodium thiosulfate in the presence of starch indicator:



4. ***Cerimetric method.***

The preparation is dissolved by heating in methanol, then cooled, dilute sulfuric acid is added and titrated with working solution of cerium (IV) sulfate until the disappearance of coloration after the addition of the first drop of titrant. Titration is carried out without indicator.



STORAGE

Aminazine darkens with prolonged exposure to air. It breaks down even in the dark in a humid atmosphere. Propazine also oxidizes in air with discoloration. Both drugs are stored in dark glass jars, tightly sealed with corks filled with paraffin, in a dry place protected from light.

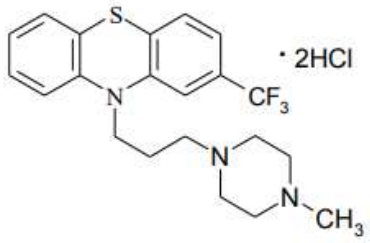
Phenothiazine derivatives have the ability to penetrate into the body through the respiratory tract, skin and mucous membrane. At the same time they cause allergic reaction. Strictly observe safety precautions in work, excluding the possibility of contact with skin and mucous membranes.

MEDICAL USE

Aminazine and propazine are used as neuroleptic and sedative agents. They are prescribed in psychiatric diseases. In the occurrence of psychomotor agitation in patients with schizophrenia. Aminazine and propazine enhance the effect of narcotics, sleeping pills, analgesics and local anesthetics. The effect of anticonvulsants under the influence of aminazine is enhanced, but in some cases may cause seizures. The drug has a strong antiemetic effect and soothes hiccups.

After taking amnazine, allergic phenomena may be observed (itching, swelling of mucous membranes, skin of hands, decreased blood pressure, depression, etc.) Propazine is less toxic and less likely to cause allergic reactions. It is used orally, intramuscularly and intravenously.

TRIPHTAHZINE

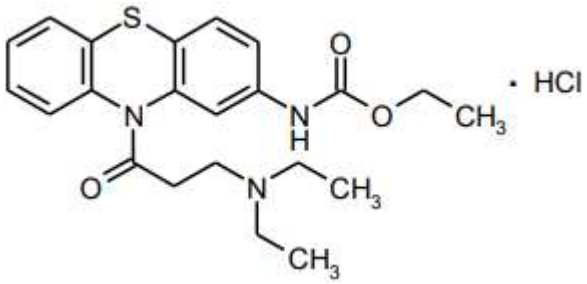


Unlike aminazine trifluoperazine has a weak adrenolytic effect, almost no hypotensive effect. Less potentiates the effect of sleeping pills; does not have antihistamine, antispasmodic and anticonvulsant activity. It has a strong cataleptogenic effect.

ACYL DERIVATIVES OF PHENOTHIAZINE

ETHACIZINE

Ethacizine belongs to the acyl derivatives of phenothiazine. It has an N-dimethylaminopropionyl radical at position 10, and p. 2 is an ethoxycarbomine group:

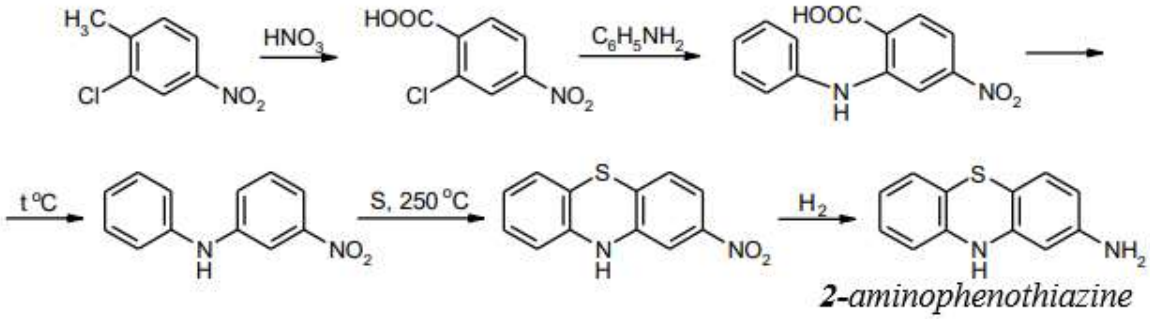


OBTAINING

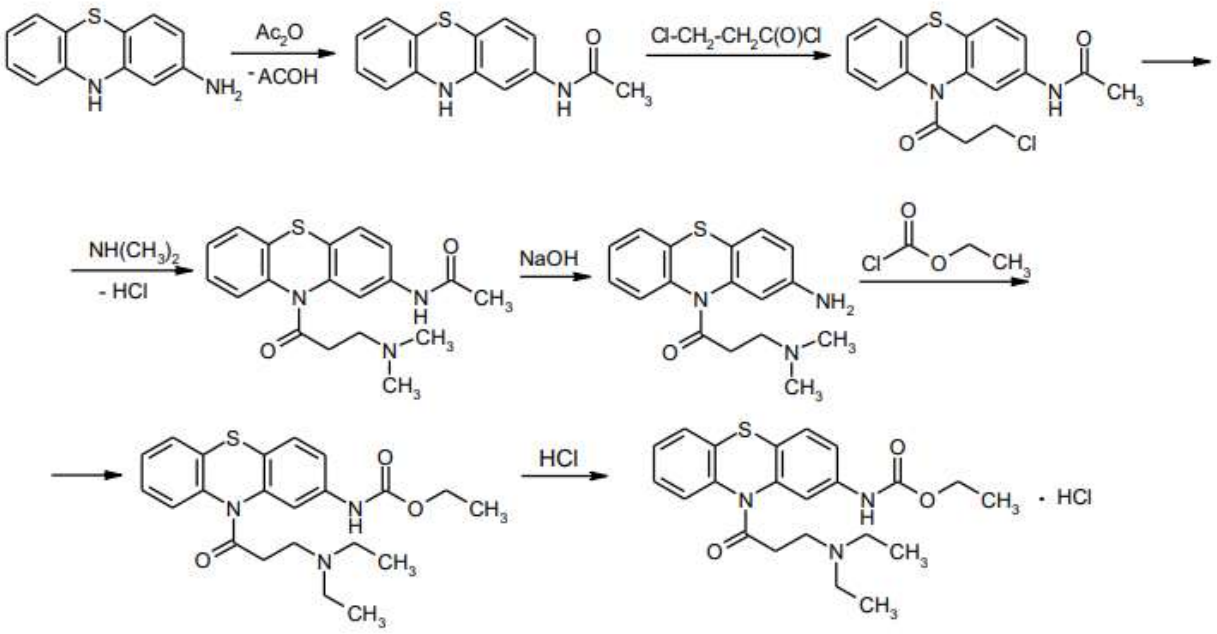
The synthesis proceeds in two stages.

1. ***Synthesis of 2-aminophenothiazine.***

   The starting point for obtaining the phenothiazine ring is 2-chloro-4-nitrotoluene, in which the methyl radical is oxidized and the resulting product (2-chloro-4-nitrobenzoic acid) is condensed with anayiline and then sintered with sulfur at 250 °C:



2. Acylation of cyclic and exocyclic nitrogen by acid chlorangdrides.



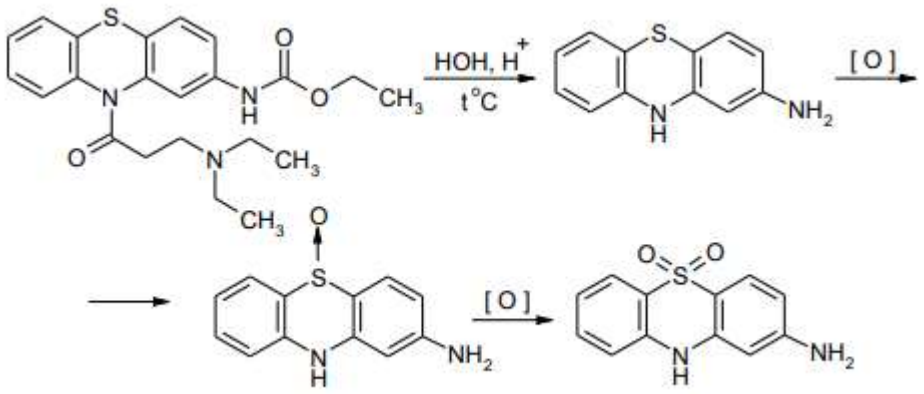
PHYSICAL PROPERTIES

Ethacizine is a white crystalline powder, Tpl 199-208°C. It is slightly soluble in water, soluble in ethanol, very well in chloroform.

IDENTIFICATION

1. ***Spectrophotometry in the UV region.***
2. ***High-performance liquid chromatography HPLC.***
3. ***Oxidation in acidic medium.***

   For identification of 10-acyl derivatives of phenothiazine, 1% potassium bromate solution is used as an oxidizing agent after preliminary hydrolysis of the drug with dilute hydrochloric acid (heating for 15 minutes). Oxidation products have *pink coloring*:



4. ***Boiling in hydrochloric acid medium.***

   When ethacisin is boiled with hydrochloric acid, its solution is colored lilac.

5. ***Precipitation of ethacisin base.***

   The authenticity reaction is the precipitation of ethacisin base and determination of its melting point (199-208°). In aqueous solution, chloride ion is determined by interacting it with silver nitrate.

6. ***Phenothiazine core reactions.***

   In addition, all qualitative reactions of the phenothiazine cycle, are also intrinsic to ethacisin. These are reactions with methylene blue. With acetone solution of maleic anhydride, with sodium cobaltonitrite in the presence of acetic anhydride (red staining), with thiacyanatoacidocomplexes of Fe, Co, Ni (colored precipitates) and with thiacyanatoacidocomplexes of Zn and Cd (white precipitates).

7. ***Detection of the sulfur atom. (See above.)***

QUANTIFICATION

Quantitative methods for the determination of 10-acyl derivatives duplicate methods for the quantification of 10-alkyl derivatives of phenothiazine (aminazine, propazine) (*write reactions*).

1. ***Non-aqueous titration.***
2. ***Neutralization. Alkalimetric titration.***
3. ***Iodometric, bromatometric and 4. Iodochlorometric titrations.***
4. ***Iodochlorometric titration.***
5. ***The cerimetric method.***

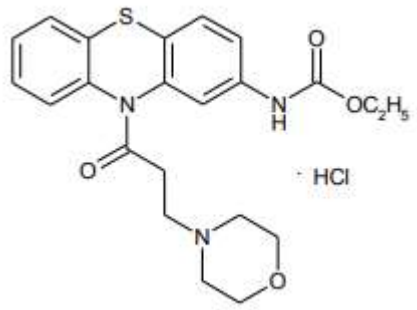
STORAGE

Ethacizin, taking into account its hygroscopicity and ability to oxidize easily, is stored in dark glass jars, tightly corked, filled with paraffin, in a dry place protected from light.

MEDICAL USE

Etacyzine has antiarrhythmic effect. It is used for ventricular and supraventricular extrasystoles, tachycardia. It is also prescribed in myocardial infarction complicated by heart rhythm disturbances. It is administered orally and intravenously, Intravenously administered to control tachycardia attacks.

ETMOSIN



It is used in atrial and ventricular extrasystole, paroxysmal tachycardia, paroxysmal atrial fibrillation, arrhythmia against overdose of cardiac glycosides.

Laboratory work

IDENTIFICATION OF "AMINAZINE"

The drug aminazine is a dragee containing 25 mg of the active ingredient (aminazine), enclosed in a cell pack of 10 pieces.

The identification of aminazine is established by the following reactions:

1. ***Release of bases by the action of alkaline solutions***: 40 mg of the drug dissolved in 5 ml of water (if necessary, filtered) and added 0.5 ml of 10% NaOH precipitate. After 5 minutes the precipitate is filtered through a thick paper filter. The filtrate gives a characteristic reaction for chlorides.
2. ***Picrate formation***: 25 mg of aminazine is dissolved in 5 ml of H20 and 3 ml of 1% solution of picric acid in 95% alcohol is added. A yellow colored precipitate precipitates out.
3. ***Oxidation reaction***: 10 mg of aminazine is dissolved in 1 ml of water and 3 drops of 1% aqueous solution of potassium bromate (or potassium iodate) and 3 drops of dilute hydrochloric acid are added. The solution acquires a crimson-pink coloration.