Ministry of Health of the Russian Federation

Volgograd State Medical University

Department of Pharmaceutical and Toxicological Chemistry

SPECIAL PHARMACEUTICAL CHEMISTRY

Synthetic pharmaceuticals - pyridine derivatives (part 2)

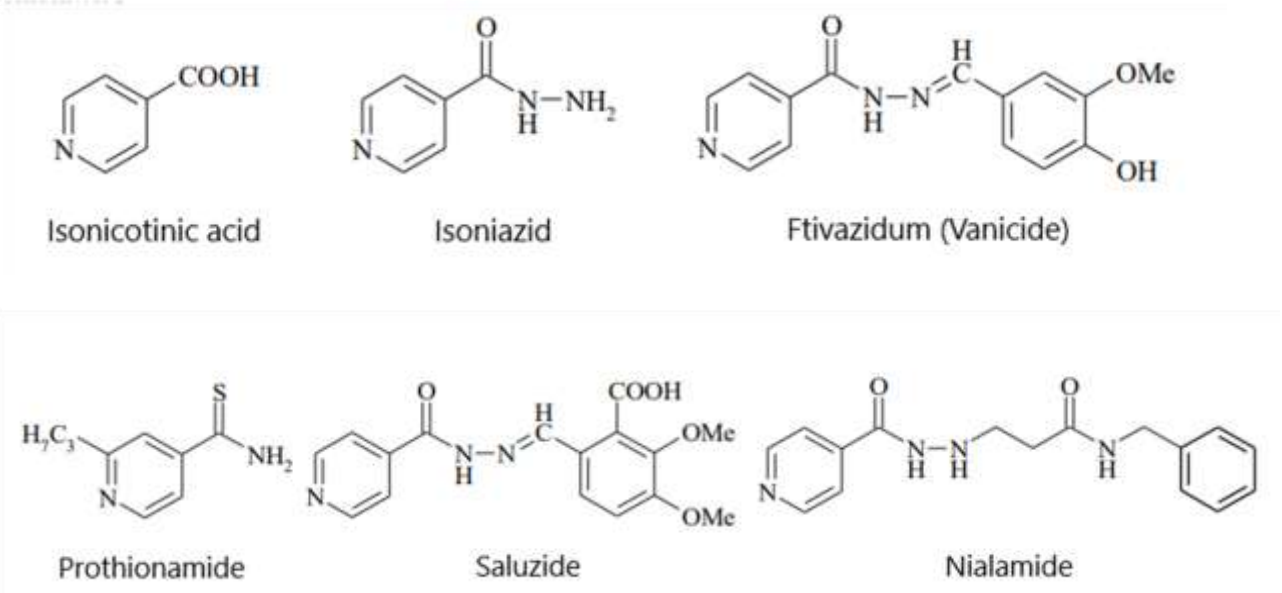
Lesson 1

VII term

Volgograd, 2023

DRUGS DERIVATIVES OF ISONICOTINIC ACID

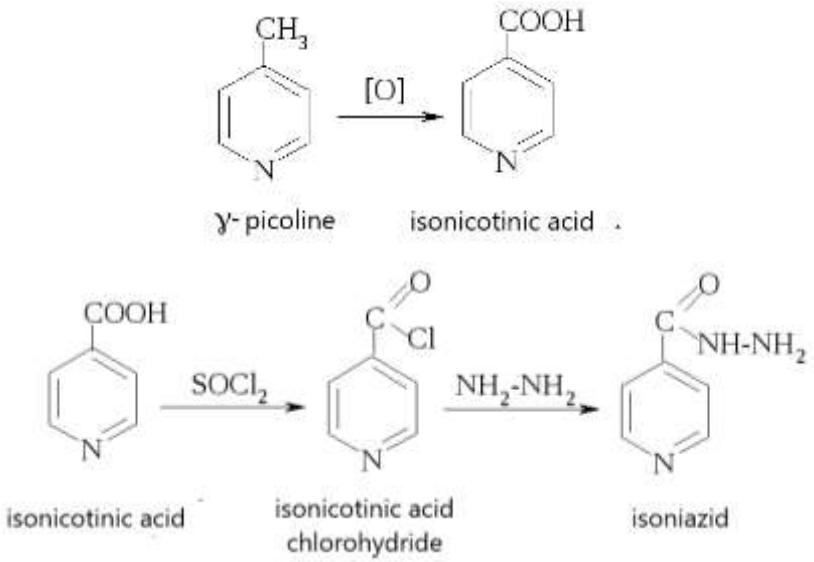
Isonicotinic has served as the basis for the development of antituberculosis drugs such as isoniazid, phthivazide, saluzide, prothionamide, and the antidepressant, nialamide:



ISONIAZID (Изониазид)

OBTAINING

The starting raw material for the production of these compounds is the γ-picoline fraction (140 - 145°C) of coal tar bases. From this fraction γ-picoline is extracted and oxidised to isonicotinic acid.



PHYSICAL PROPERTIES

White crystalline powder, odourless. Melting point 170 - 174°C.

Easily soluble in water, moderately soluble in alcohol, very slightly soluble in chloroform.

IDENTIFICATION

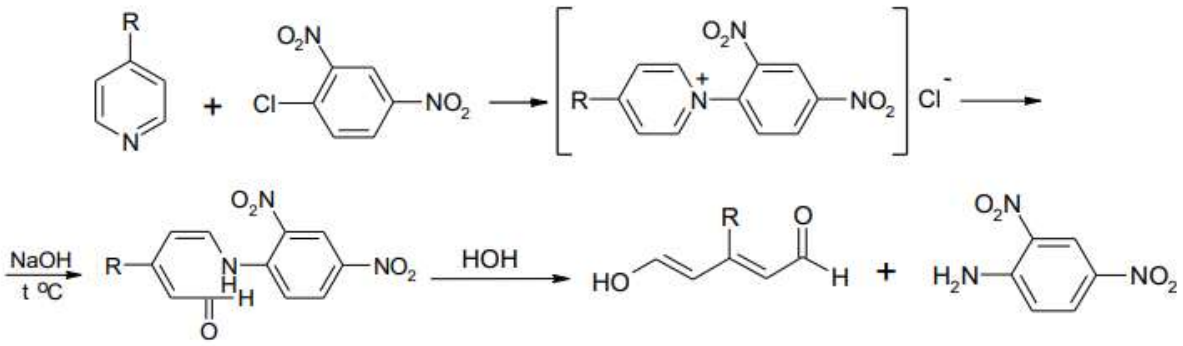
1. Instrumental methods.

IR spectra should have complete coincidence of absorption bands with absorption bands of standard samples in terms of intensity and position of bands.

UV spectra are carried out in alkaline or acidic solutions with coincidence of max and min absorption with the data of the pharmacopoeial article.

2. Formation of a polymethine dye (Zinke reaction)

After boiling the drug substance and 2,4 dinitrochlorobenzene in ethanol, cooling and adding sodium hydroxide solution, a brownish-red colouring appears, changing on standing:

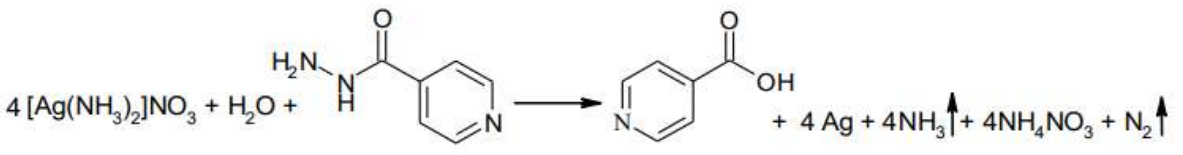


3. Detection of the pyridine cycle

The pyridine cycle is detected by heating in a boiling water bath with acetic anhydride in the presence of citric acid; the reaction mixture becomes cherry-coloured.

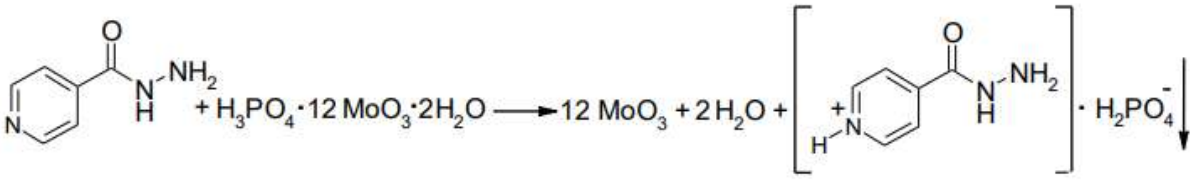
4. *Silver mirror reaction*

For the identification of isoniazid the reducing properties due to the presence of hydrazine in its molecula are used. When the drugs interact with ammonia solution of silver, silver is reduced in the form of grey precipitate, and when heated, silver is deposited on the walls of the vessel in the form of a mirror plaque.



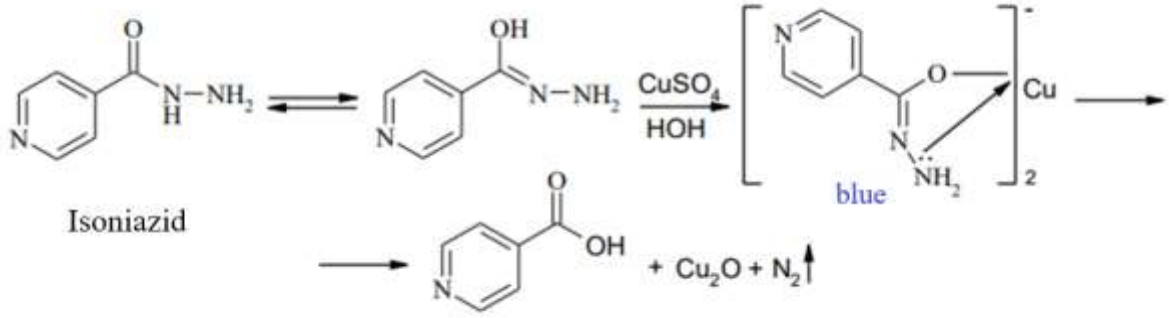
5. Interaction with precipitation reagents

Phosphorus-molybdenum acid is Sonnenstein's reagent. It gives amorphous precipitates of yellowish colour with derivatives of isonicotinic acid, which after some time become blue and green coloured due to the reduction of molybdic acid.



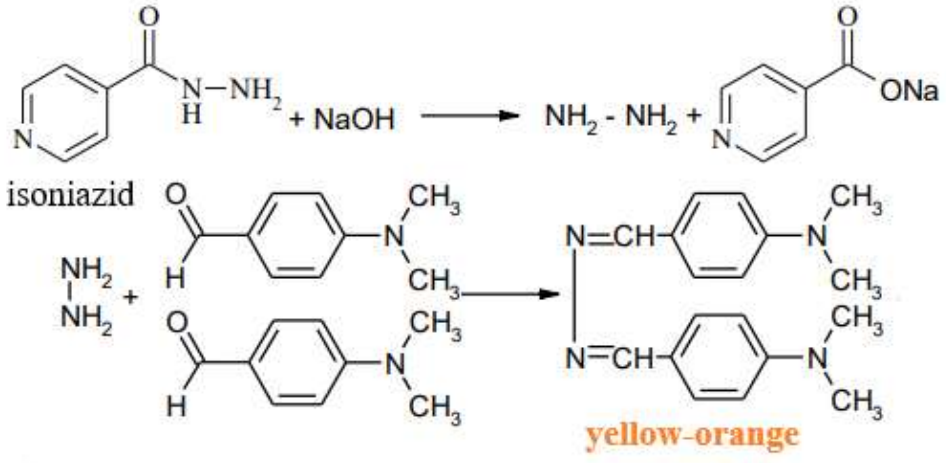
6. Formation of heavy metal salts

When Isoniazid is heated with copper sulphate solution, a blue-coloured copper complex salt of isoniazid is firstly formed. Then the hydrazide is oxidised to molecular nitrogen and the copper (II) ion is reduced to copper (I) oxide. This is accompanied by a change in the colour of the solution from blue to emerald green and dirty yellow:



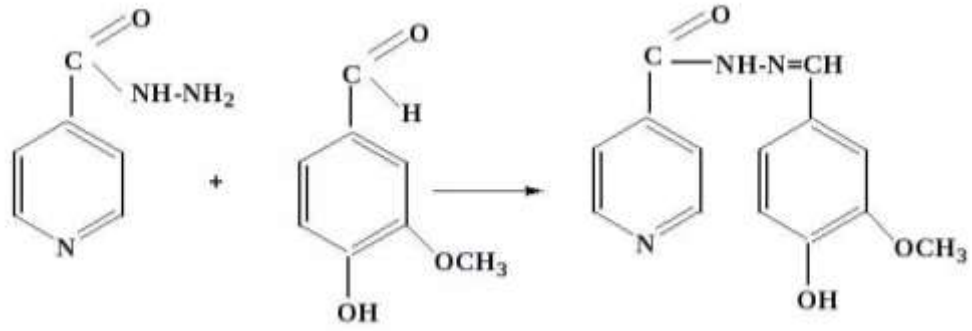
7. Detection of hydrolysis products

Hydrazine formed by alkaline hydrolysis of isoniazid is detected by colour reaction with p-dimethylaminobenzaldehyde in acidic medium. A yellow-orange colour appears.



8. Schiff base formation.

Isoniazid is identified by the formation of phthivazide on addition of hot vanillin solution. The yellow precipitate formed on standing should have a melting point of about 227°C after recrystallization from ethanol and drying.



9. Color reaction with sodium nitroprusside.

Isoniazid gives a colored reaction with an alkaline solution of sodium nitroprusside Na2[Fe(CN)5(NO)]. An orange coloration appears, which changes to cherry color after the addition of hydrochloric acid.

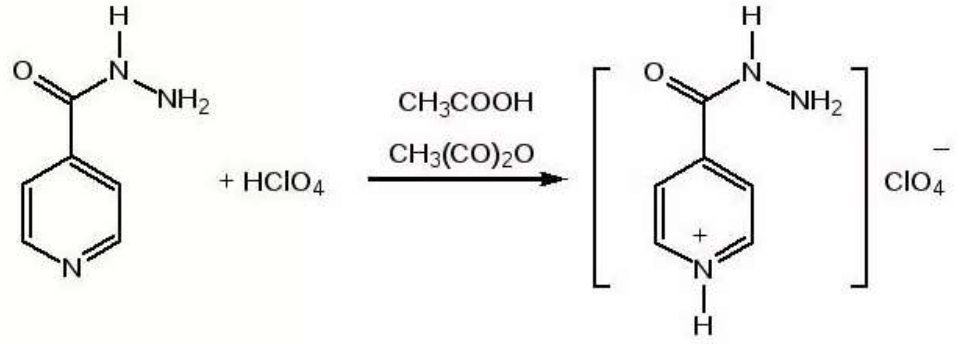
PURITY TEST

In the purity test, the permissible limits of impurities of the starting products of synthesis and hydrolysis are determined.

QUANTIFICATION

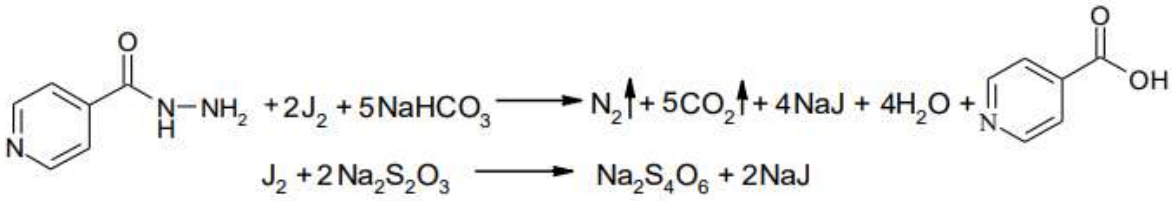
1. Non-aqueous titration.

Quantification of isoniazid is conducted by non-aqueous titration. Titrant 0.1 M chloric acid solution. The indicator is crystal violet. Isoniazid is pre-dissolved in a mixture of glacial acetic acid and acetic anhydride.



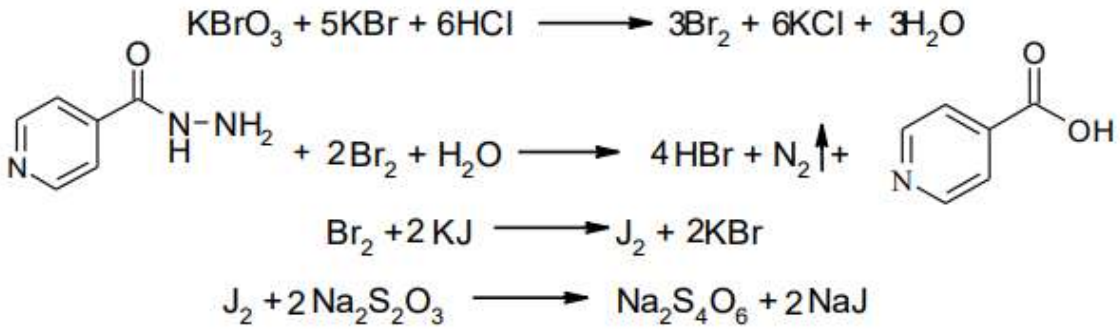
2. Iodometry.

Oxidation is conducted with iodine in a slightly alkaline medium, excess iodine is titrated with sodium thiosulfate in the presence of starch indicator:



3. Bromatometric method.

This method is also one of the redox methods by which isoniazid can be determined. The reverse titration is carried out in hydrochloric acid. Excess bromine is titrated iodometrically:



STORAGE

Isonicotinic acid derivatives are stored in well closed containers, in a cool, protected from light, dry place.

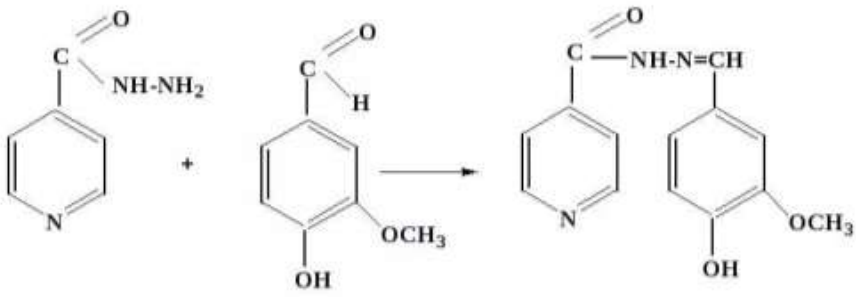
MEDICAL USE

It is used as an antitubercular agent.

PHTHIVAZIDE (Фтивазид)

OBTAINING

In order to obtain phthivazide, it is necessary to condense isoniazid with vanillin:



PHYSICAL PROPERTIES

Light yellow or yellow fine crystalline powder, with a slight odor of vanillin. Melting point melting point 128 - 131°C.

Practically insoluble in water, easily soluble in mineral acids, soluble in solutions of caustic alkalis.

IDENTIFICATION

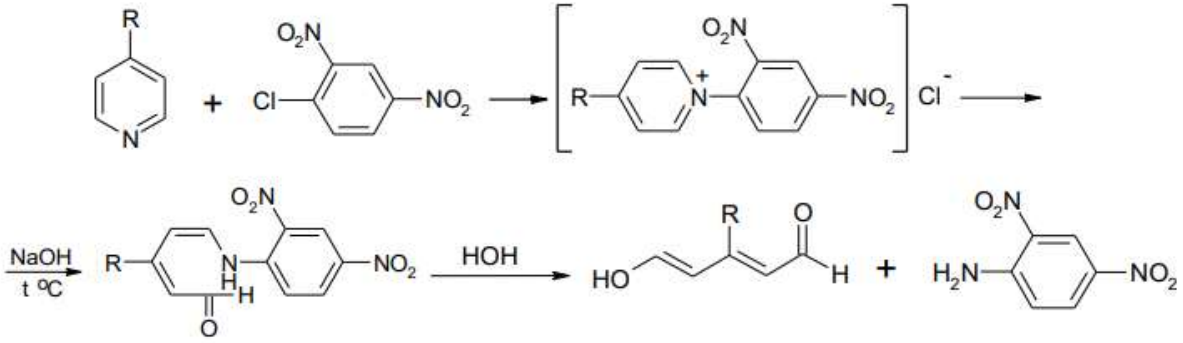
1. Instrumental methods.

IR spectra should have complete coincidence of absorption bands with absorption bands of standard samples in terms of intensity and position of bands.

UV spectra are carried out in alkaline or acidic solutions with coincidence of max and min absorption with the data of the pharmacopoeial article.

2. Formation of a polymethine dye (Zinke reaction)

After boiling the drug substance and 2,4 dinitrochlorobenzene in ethanol, cooling and adding sodium hydroxide solution, a brownish-red colouring appears, changing on standing:



3. Detection of the pyridine cycle

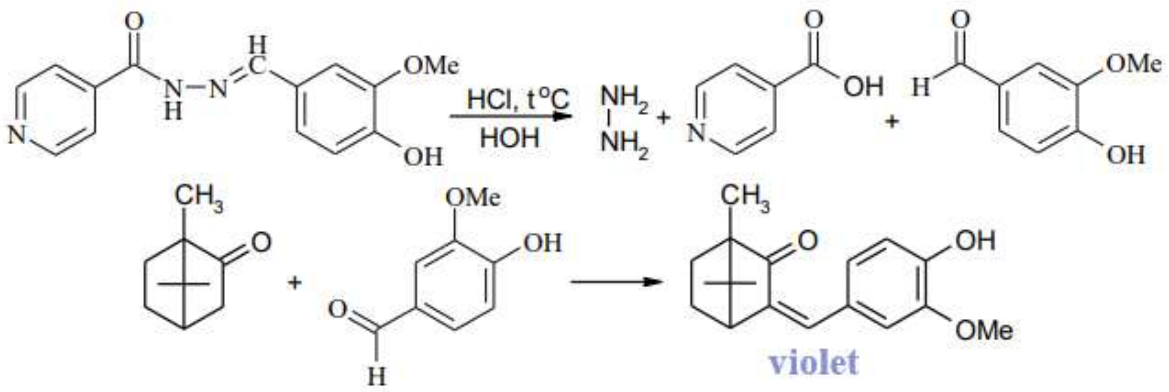
The pyridine cycle is detected by heating in a boiling water bath with acetic anhydride in the presence of citric acid; the reaction mixture becomes cherry-coloured.

4. Interaction with precipitation reagents.

Phosphorus-molybdenum acid is Sonnenstein's reagent. It gives amorphous precipitates of yellowish colour with derivatives of isonicotinic acid, which after some time become blue and green coloured due to the reduction of molybdic acid.

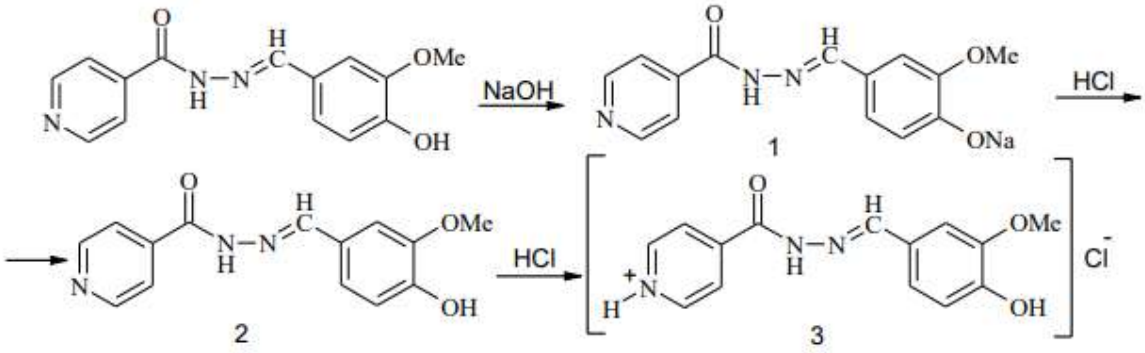
5. Detection of hydrolysis products.

Phthivazide in acidic medium is hydrolysed to isonicotinic acid and vanillin, which is detected by a specific odour and by the formation of violet colouring when interacting with camphor:



6. Reaction of an alcoholic solution of phthivazide on medium

Phthivazide, having amphoteric properties, dissolves both in hydroxide solutions (due to the presence of phenolic hydroxyl in the molecule) and in acids (due to tertiary nitrogen). The salts formed, have different coloring. This property is used to test its authenticity. Thus, an alcoholic solution of phthivazide from the addition of alkali solution acquires orange-yellow coloring (1). Subsequent gradual addition of hydrochloric acid solution leads first to weakening (2), and then to strengthening of coloring to orange-yellow (due to the formation of quaternary salt with nitrogen atom (3) in the pyridine cycle):



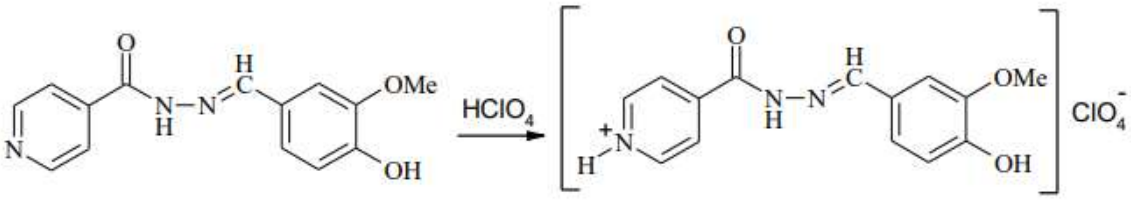
PURITY TEST

In the purity test, the permissible limits of impurities of the starting products of synthesis and hydrolysis are determined.

QUANTIFICATION

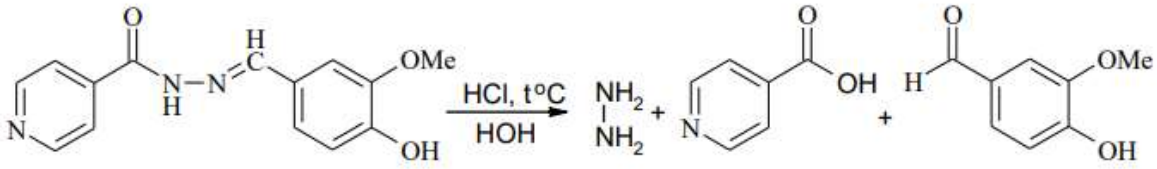
1. Non-aqueous titration.

Quantification of phthivazid is conducted by non-aqueous titration. Titrant 0.1 M chloric acid solution. The indicator is crystal violet. Phthivazid is pre-dissolved in a mixture of formic acid and acetic anhydride.



2. Iodatometry

Phthivazide is quantified by the iodatometric method after preliminary hydrolysis in hydrochloric acid medium. Hydrazine released during hydrolysis is oxidised with potassium iodate in the presence of chloroform. The resulting iodine is extracted with chloroform. Titration with potassium iodate solution is carried out until the pink colouring of the chloroform layer disappears (chloroform is added at the end of titration):



$$5NH_2\text{-}NH_2 + 4KJO_3 + 4HCl \longrightarrow 5N_2 + 2J_2 + 4KCl + 12H_2O$$

$$5KJO_3 + 2J_2 + 6HCl \longrightarrow 5JCl + KCl + 3H_2O$$

STORAGE

Isonicotinic acid derivatives are stored in well closed containers, in a cool, protected from light, dry place.

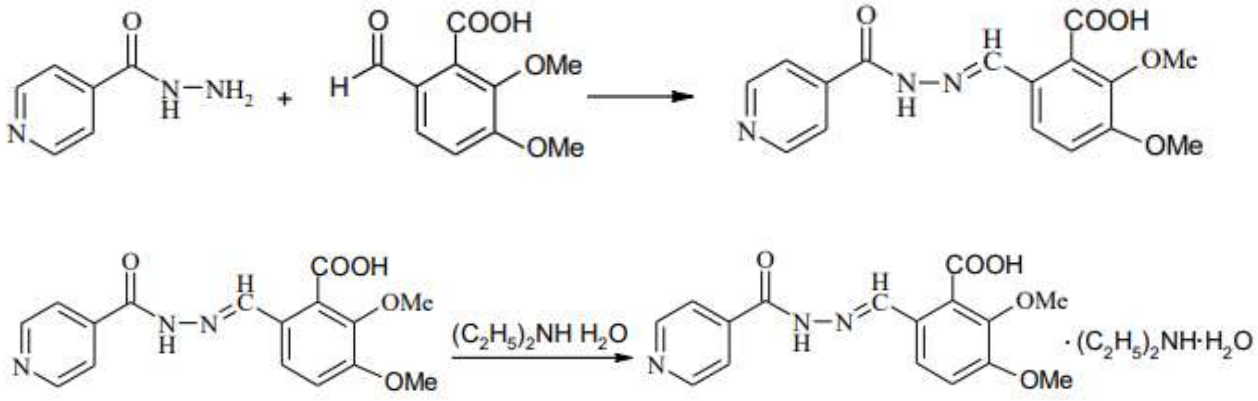
MEDICAL USE

It is used as an antitubercular agent.

SALUZIDE (Салюзид)

OBTAINING

Saluzide is a condensation product of isoniazid and opiate acid (2-carbonyl-4,5-dimethoxybenzoic acid). In medical practice, soluble saluzide, a salt of saluzide with diethylamine monohydrate, is used:



PHYSICAL PROPERTIES

Greenish-yellow fine-crystalline powder.

Easily soluble in alkalis and mineral acids. Insoluble in water, alcohol and insoluble in ether and chloroform.

IDENTIFICATION

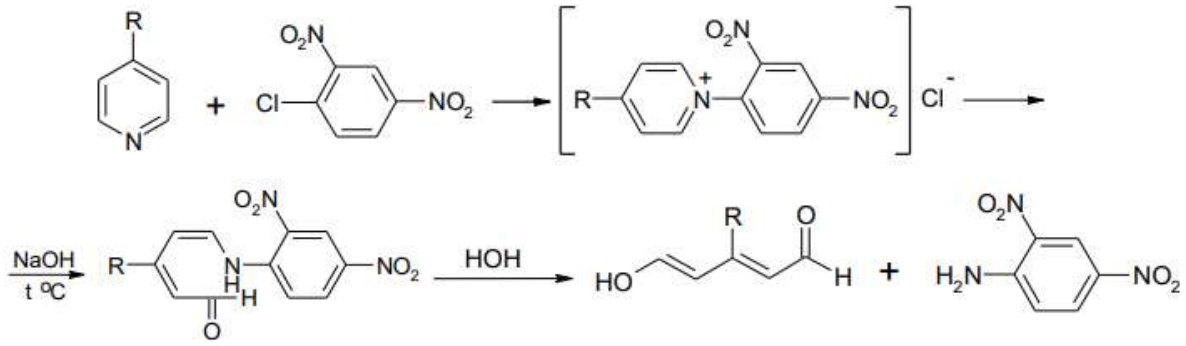
1. Instrumental methods.

IR spectra should have complete coincidence of absorption bands with absorption bands of standard samples in terms of intensity and position of bands.

UV spectra are carried out in alkaline or acidic solutions with coincidence of max and min absorption with the data of the pharmacopoeial article.

2. Formation of a polymethine dye (Zinke reaction)

After boiling the drug substance and 2,4 dinitrochlorobenzene in ethanol, cooling and adding sodium hydroxide solution, a brownish-red colouring appears, changing on standing:



3. Detection of the pyridine cycle

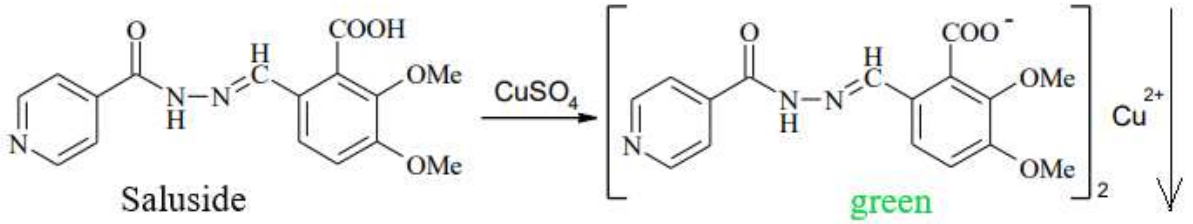
The pyridine cycle is detected by heating in a boiling water bath with acetic anhydride in the presence of citric acid; the reaction mixture becomes cherry-coloured.

4. Interaction with precipitation reagents.

Phosphorus-molybdenum acid is Sonnenstein's reagent. It gives amorphous precipitates of yellowish colour with derivatives of isonicotinic acid, which after some time become blue and green coloured due to the reduction of molybdic acid.

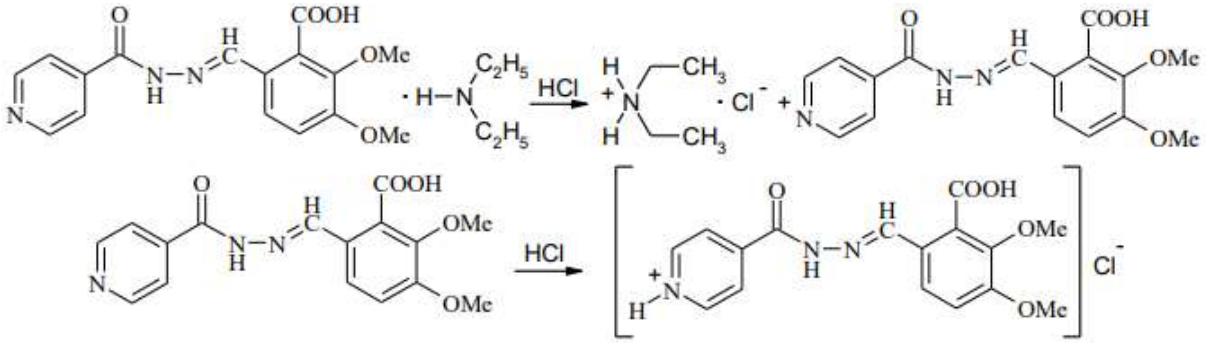
5. Formation of heavy metal salts.

Saluside forms a curd-like precipitate of green colour when interacting with CuSO4 solution:



6. Interaction with hydrochloric acid

When saluside is exposed to soluble hydrochloric acid, a precipitate of saluside precipitates; with excess hydrochloric acid, the precipitate dissolves as saluside hydrochloride is formed:.



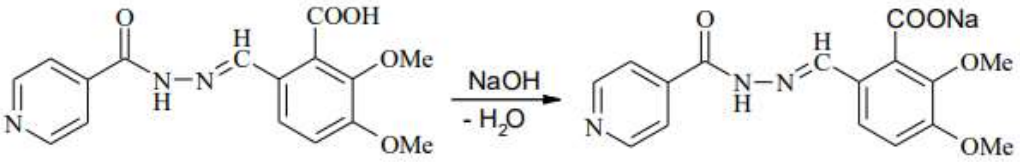
PURITY TEST

In the purity test, the permissible limits of impurities of the starting products of synthesis and hydrolysis are determined.

QUANTIFICATION

Neutralisation.

Saluside in is determined by the neutralisation method. Titrant - 0.1 N NaOH solution. The indicator is methyl red; at the equivalence point the solution changes colour from red to yellow. Titration proceeds according to the scheme:



STORAGE

Isonicotinic acid derivatives are stored in well closed containers, in a cool, protected from light, dry place.

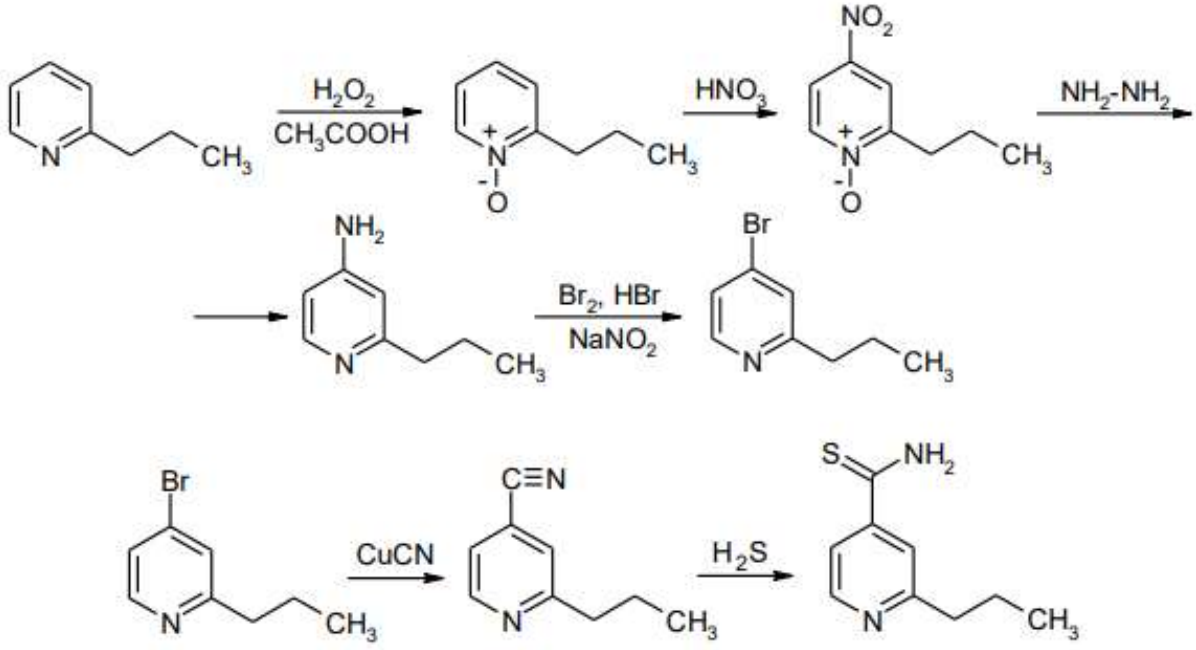
MEDICAL USE

It is used as an antitubercular agent.

PROTIONAMIDE (Протионамид)

OBTAINING

The starting material for the synthesis of protionamide is 2-propylpyridine.



PHYSICAL PROPERTIES

Small yellow crystals or yellow crystalline powder with a slight sulfide odor. Melting point 158 - 164°C.

Practically insoluble in water, soluble in ethanol and methanol, slightly soluble in ether and chloroform.

IDENTIFICATION

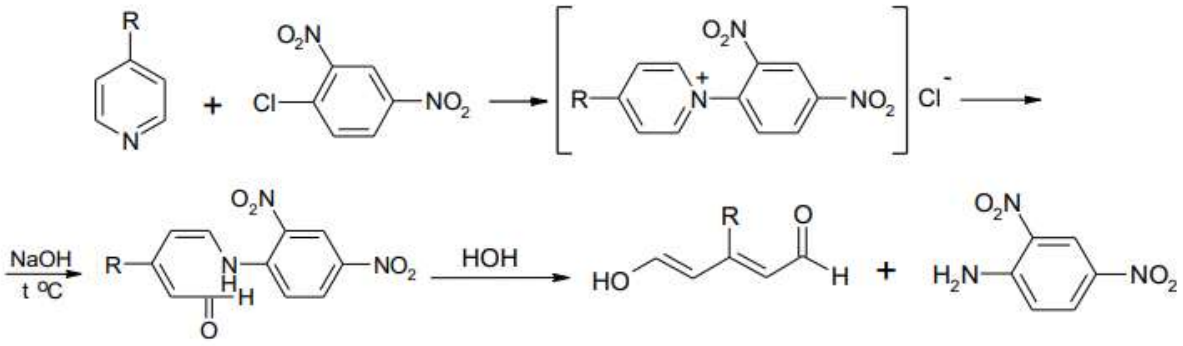
1. Instrumental methods.

IR spectra should have complete coincidence of absorption bands with absorption bands of standard samples in terms of intensity and position of bands.

UV spectra are carried out in alkaline or acidic solutions with coincidence of max and min absorption with the data of the pharmacopoeial article.

2. Formation of a polymethine dye (Zinke reaction)

After boiling the drug substance and 2,4 dinitrochlorobenzene in ethanol, cooling and adding sodium hydroxide solution, a brownish-red colouring appears, changing on standing:



3. Detection of the pyridine cycle

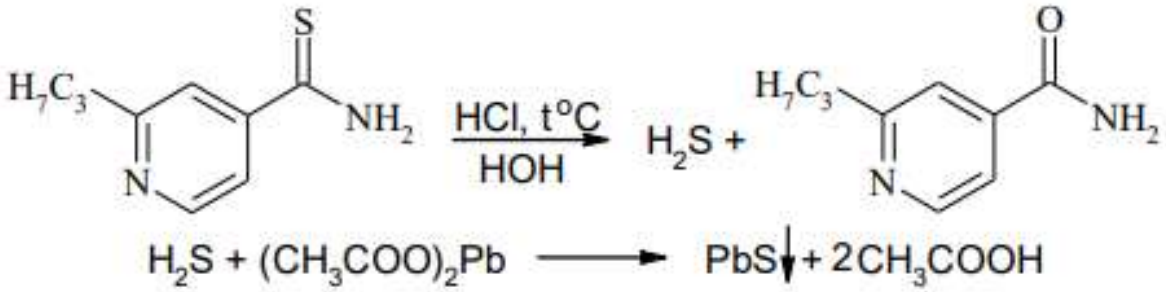
The pyridine cycle is detected by heating in a boiling water bath with acetic anhydride in the presence of citric acid; the reaction mixture becomes cherry-coloured.

4. Interaction with precipitation reagents.

Phosphorus-molybdenum acid is Sonnenstein's reagent. It gives amorphous precipitates of yellowish colour with derivatives of isonicotinic acid, which after some time become blue and green coloured due to the reduction of molybdic acid.

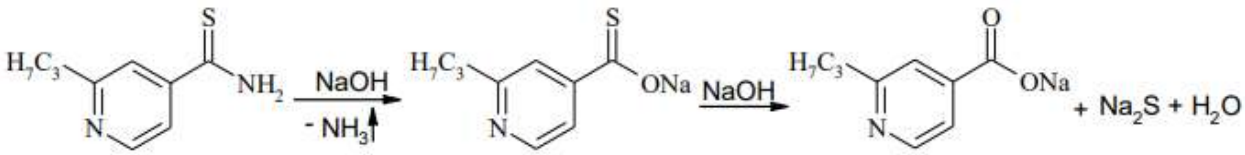
5. Sulfur detection.

When prothionamide is heated with hydrochloric acid, the emitted hydrogen sulfide vapor stains black the paper soaked in lead acetate solution:



6. Interaction with sodium hydroxide solution.

When prothionamide is heated with sodium hydroxide solution, ammonia and fustafide ion are formed. Ammonia has a sharp odor and stains wet, red litmus paper blue. The sulfide ion is detected with sodium nitroprusside solution (red-violet coloring):



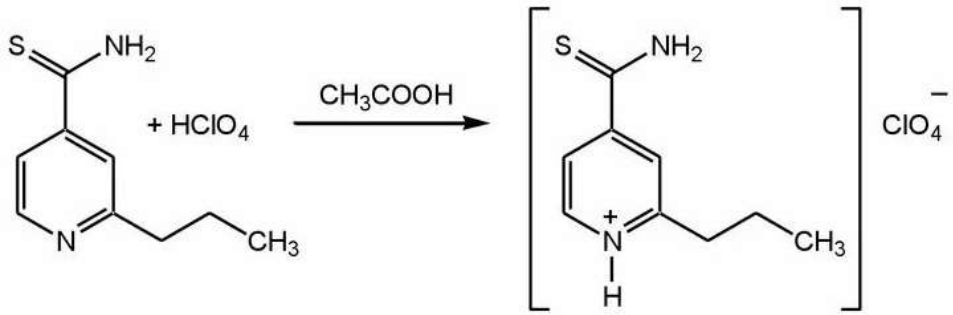
PURITY TEST

In the purity test, the permissible limits of impurities of the starting products of synthesis and hydrolysis are determined.

QUANTIFICATION

Non-aqueous titration.

Titrant 0.1 M chloric acid solution. The indicator is crystal violet. For prothionamide, glacial acetic acid is used as a solvent.



STORAGE

Isonicotinic acid derivatives are stored in well closed containers, in a cool, protected from light, dry place.

MEDICAL USE

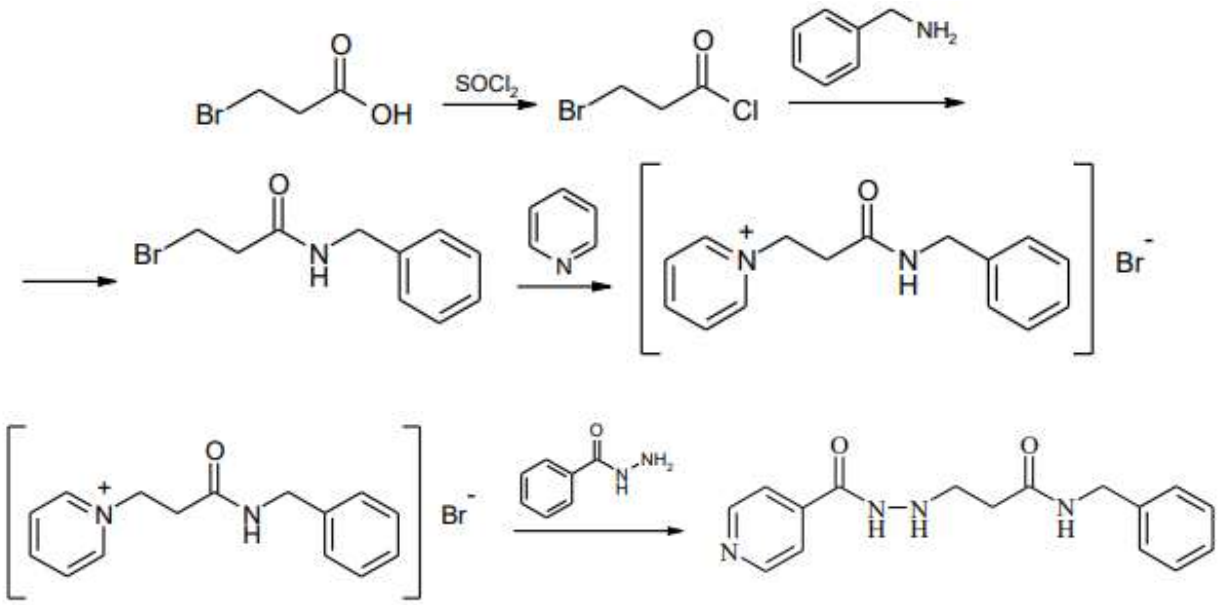
It is used as an antitubercular agent.

NIALAMIDE (Ниаламид)

OBTAINING

A two-step synthesis scheme is used for the preparation of nialamide:

- ✓ Synthesis of 2-(benzylcarbomail-ethyl)pyridinium bromide.
- ✓ Condensation of carbomail derivative with isoniazid.



PHYSICAL PROPERTIES

White fine-crystalline powder, odorless. Melting point 151 - 153°C.

Slightly soluble in water and chloroform, moderately soluble in alcohol, readily soluble in mineral acids.

IDENTIFICATION

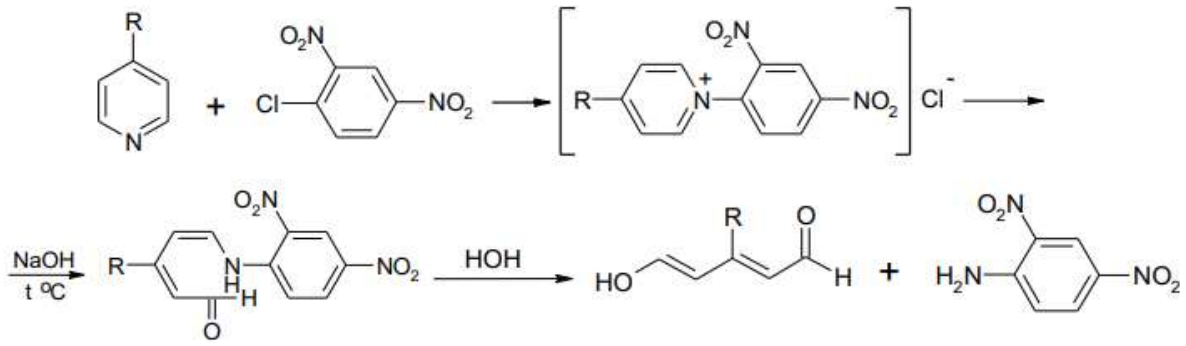
1. Instrumental methods.

IR spectra should have complete coincidence of absorption bands with absorption bands of standard samples in terms of intensity and position of bands.

UV spectra are carried out in alkaline or acidic solutions with coincidence of max and min absorption with the data of the pharmacopoeial article.

2. Formation of a polymethine dye (Zinke reaction)

After boiling the drug substance and 2,4 dinitrochlorobenzene in ethanol, cooling and adding sodium hydroxide solution, a brownish-red colouring appears, changing on standing:



3. Detection of the pyridine cycle

The pyridine cycle is detected by heating in a boiling water bath with acetic anhydride in the presence of citric acid; the reaction mixture becomes cherry-coloured.

4. Interaction with precipitation reagents.

Phosphorus-molybdenum acid is Sonnenstein's reagent. It gives amorphous precipitates of yellowish colour with derivatives of isonicotinic acid, which after some time become blue and green coloured due to the reduction of molybdic acid.

5. Silver mirror reaction.

For the identification of nialamide, the reducing properties due to the presence of hydrazine in their molecules are used. When the drug interact with ammonia solution of silver, silver is reduced in the form of grey precipitate, and when heated, silver is deposited on the walls of the vessel in the form of a mirror plaque.

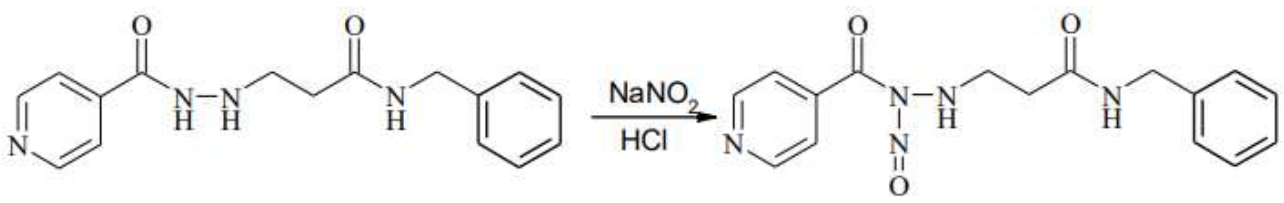
PURITY TEST

In the purity test, the permissible limits of impurities of the starting products of synthesis and hydrolysis are determined.

QUANTIFICATION

Nitritometry.

Quantification of nialamide is conducted by the nitritometric method, using an internal indicator - a mixture of tropheolin 00 and methylene blue. The determination is based on the formation of a nitroso derivative of nialamide:



STORAGE

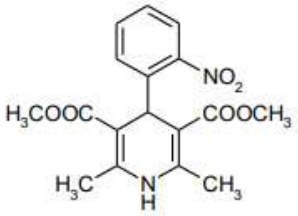
Isonicotinic acid derivatives are stored in well closed containers, in a cool, protected from light, dry place.

MEDICAL USE

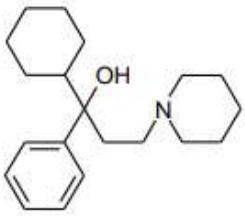
Nialamide is used in psychiatric practice for depressive conditions various forms.

DRUGS HYDROGENATED PYRIDINE DERIVATIVES

A number of pyridine-derived drugs include drugs containing fully or partially saturated pyridine cycle. These drugs include nifedipine and cyclodol.



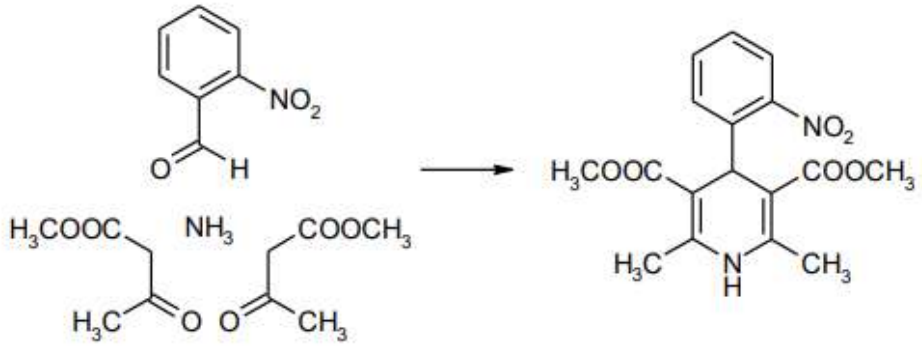
Nifedipine



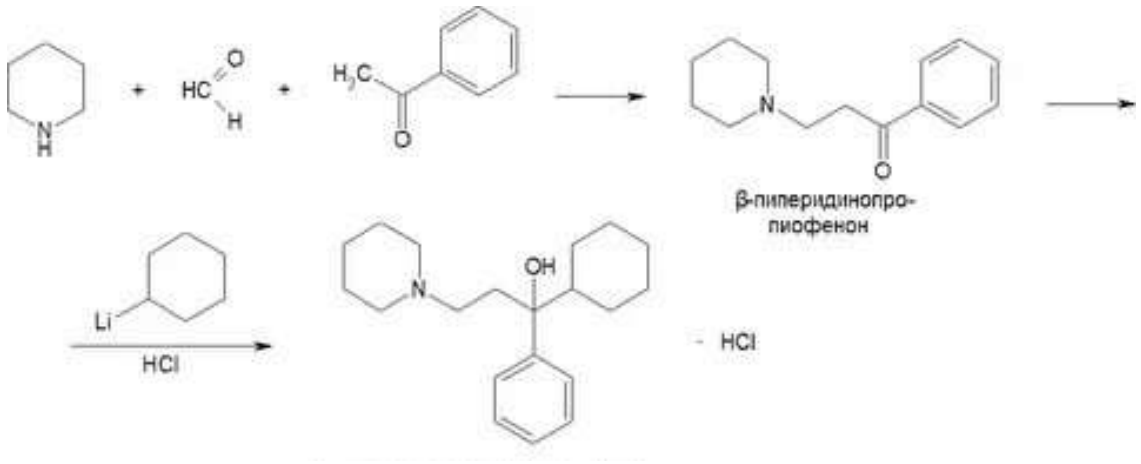
Cyclodol

OBTAINING

The starting materials for the synthesis of ***nifedipine*** (phenigdine) are: onitrobenzaldehyde and acetoacetic acid methyl ester. The synthesis is carried out in the presence of ammonium salts. Nifedipine is formed as a result of the condensation reaction:



The starting point for the preparation of ***cyclodol*** is piperidine, which is condensed with acetophenone and formaldehyde:



PHYSICAL PROPERTIES

Nifedipine Yellow crystalline powder, decomposable in light, odourless. Melting point 170-174 °C.

Practically insoluble in water, slightly soluble in ethanol, soluble in chloroform, easily in acetone, very easily in ether.

Cyclodolol White, fine-crystalline powder, odourless. Melting point 249.5 oC (with decomposition).

Slightly soluble in water, easily soluble in methanol, ethanol, chloroform, practically insoluble in ether.

IDENTIFICATION

1. Spectral methods

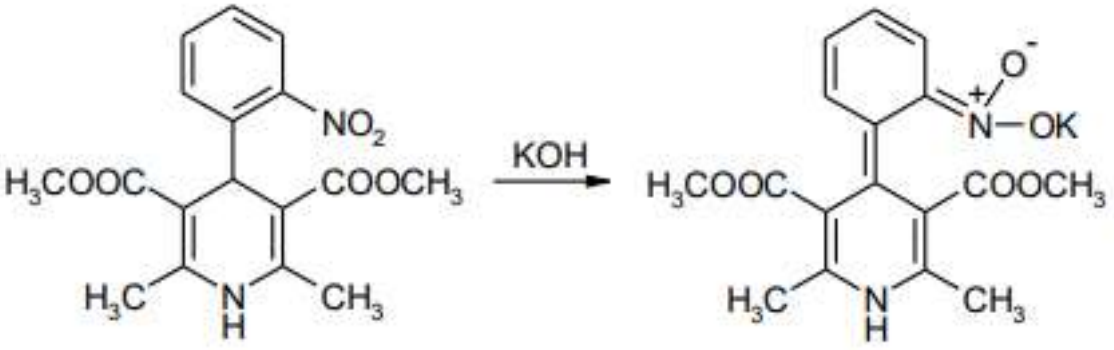
The IR spectra should correspond to the spectra of the standard samples.

2. Chromatography.

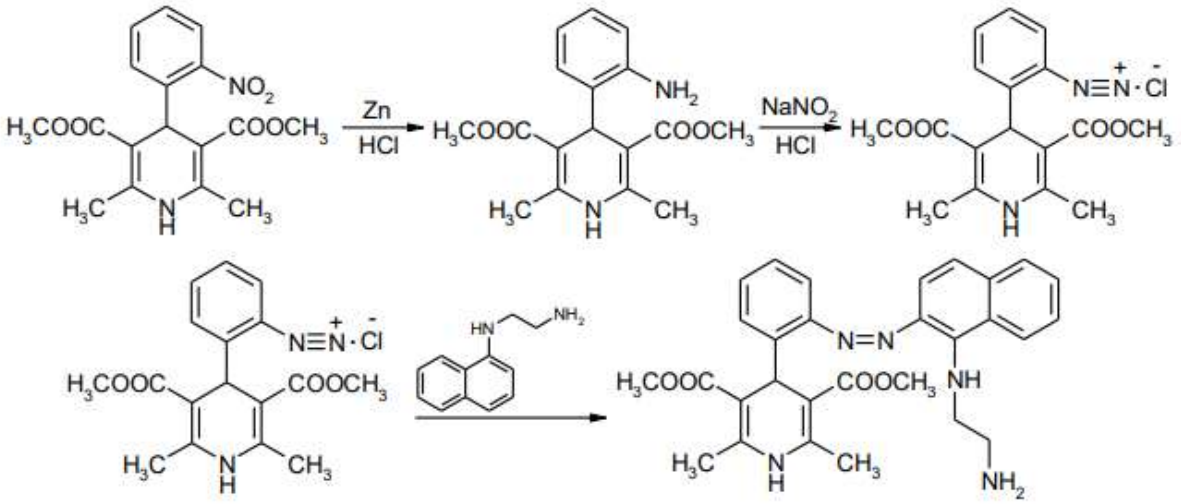
The identity of nifedipine is confirmed by TLC and HPLC methods

3. Detection of nitro group.

Nifedipine solution in dimethylformamide becomes red coloured after addition of alcoholic potassium hydroxide solution:

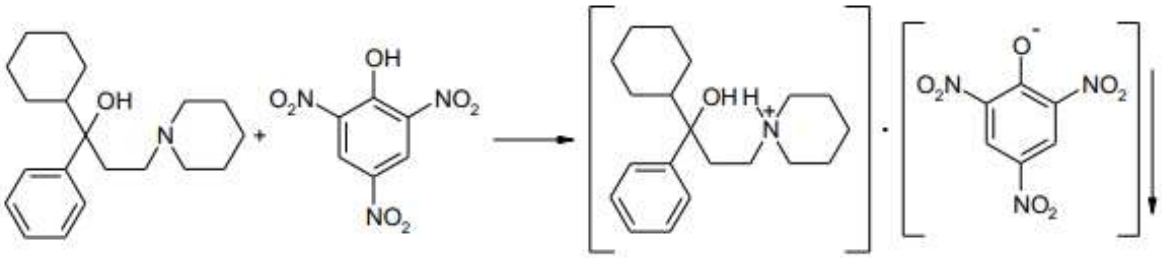


To test the identity of nifedipine, the reaction of hydrogenation of the nitro group to an amino group (by zinc in the presence of hydrochloric acid) followed by the formation of an azo dye is used:



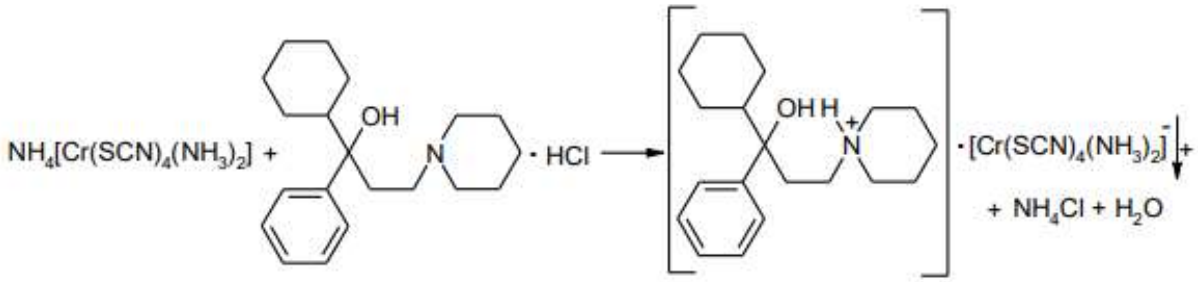
4. Reaction with common alkaloid reagents.

Precipitation reactions based on the presence of a tertiary nitrogen atom in the molecules are used to test the identity of nifedipine and cyclodolol. For example, the reaction with picric acid goes like this:



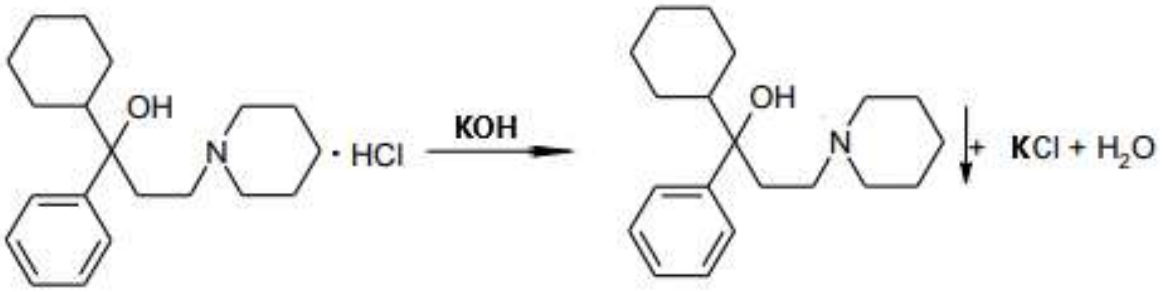
5. Reaction with ammonium reynecate for cyclodol

a light pink precipitate forms



6. Precipitation of the organic base of cyclodiol

Cyclodol has a salt form with hydrochloride. The base is precipitated from its solution by the action of sodium hydroxide, extracted with ether, which is then distilled off. Then the melting point of the cyclodol base is established (114-116 °C).



7.Cyclodol gives a positive reaction to chloride ions.

$$Ag^{+} + Cl^{-} = AgCl\downarrow$$

PURITY TEST

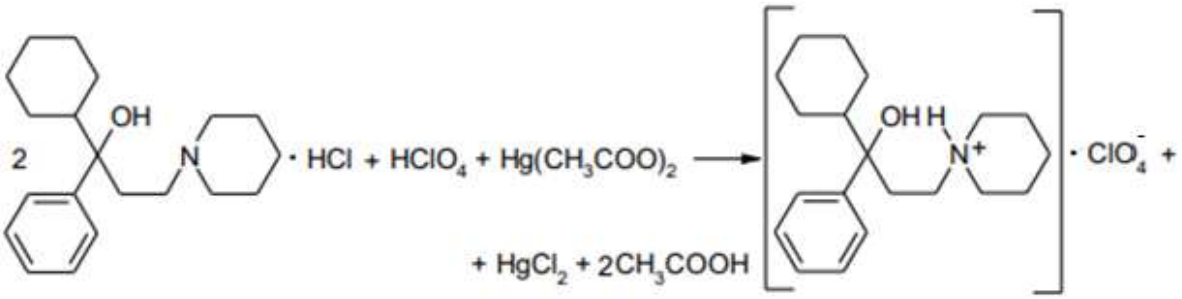
The presence of foreign impurities is determined by TLC and HPLC, and the content of residual solvents is determined by GLC.

QUANTIFICATION

1. Spectrophotometric determination.

2. Non-aqueous titration.

Cyclodol is determined in a mixture of formic acid and acetic anhydride. The indicator is crystal violet, the titrant is perchloric acid.



STORAGE

Nifedipine and cyclodol are stored in well-closed jars, in a dry, dark place protected from light, at room temperature. Cyclodol is stored according to the rules established for narcotic analgesics.

MEDICAL USE

Nifedipine is a calcium ion antagonist, dilates coronary and arterial vessels, reduces myocardial oxygen demand, has hypotensive effect. Ciclodol is a cholinolytic and is used for treatment of parkinsonism.