Ministry of Health of the Russian Federation

Volgograd State Medical University

Department of Pharmaceutical and Toxicological Chemistry

SPECIAL PHARMACEUTICAL CHEMISTRY

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Synthetic pharmaceuticals - pyridine derivatives (part 1)

Lesson 1

VII term

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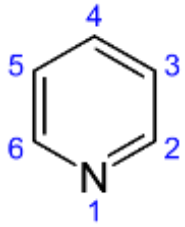
INTRODUCTION

Pyridine is a six-membered heterocycle with one nitrogen atom. It is an aromatic heterocyclic compound. The nitrogen atom exhibits electron acceptor character and therefore the pyridine aromatic system is electron-deficient compared to benzene.

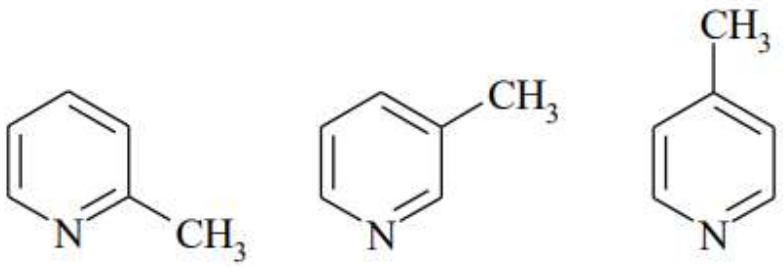


The unshared pair of electrons of the nitrogen atom does not take part in the formation of the π-electron skeleton, but is responsible for manifesting of its basic properties.

Pyridine is a colourless liquid, miscible with water and organic solvents, has a characteristic unpleasant odour. Inhalation of pyridine vapours may cause damage to the nervous system.

Pyridine has a strong bactericidal effect, but due to its high toxicity, it cannot be used in medicine. However, many of its derivatives are not only medicines, but also serve as a source for obtaining a number of synthetic drugs (nicotinic acid, its amide). The pyridine nucleus is part of the molecules of a number of natural compounds, such as alkaloids and vitamins.

Introduction of a carboxyl group into the pyridine ring sharply reduces toxicity. The initial products for the preparation of pyridine carboxylic acids are liquid substances contained in coal tar - picolins.



α-picolin *β-picolin* *γ-picolin*

In medical practice, synthetic drugs are widely used, which are derivatives of nicotinic (3-pyridine-carboxylic) and isonicotinic (4-pyridine-carboxylic) acids.

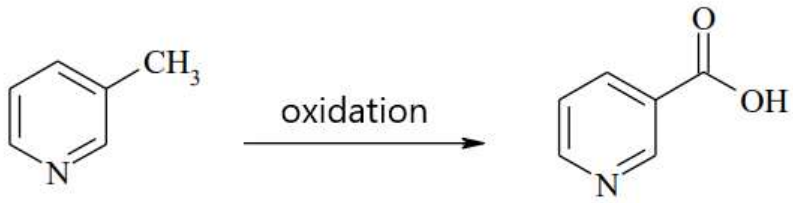
DRUGS - NICOTINIC ACID DERIVATIVES

Nicotinic acid (Никотиновая кислота)

β-Pyridine carboxylic acid, otherwise called nicotinic acid, is known as vitamin PP. It was first was first produced back in 1867.

OBTAINING (ПОЛУЧЕНИЕ)

Various ways of synthesis of nicotinic acid are known, but the method of production from β-picoline is of industrial importance. The picoline fraction is subjected to fractional separation into α- β- and γ-picoline. Then, by oxidation of β-picoline, nicotinic acid is obtained:



PHYSICAL PROPERTIES (ФИЗИЧЕСКИЕ СВОЙСТВА)

White crystalline powder, odourless, slightly acidic taste. Melting point 234 - 238 °C. *Белый кристаллический порошок без запаха, слабокислого вкуса. Температура плавления 234 – 238 °С.*

Difficult to dissolve in water and alcohol, soluble in hot water, very slightly soluble in ether. *Трудно растворим в воде и спирте, растворим в горячей воде, очень мало растворим в эфире.*

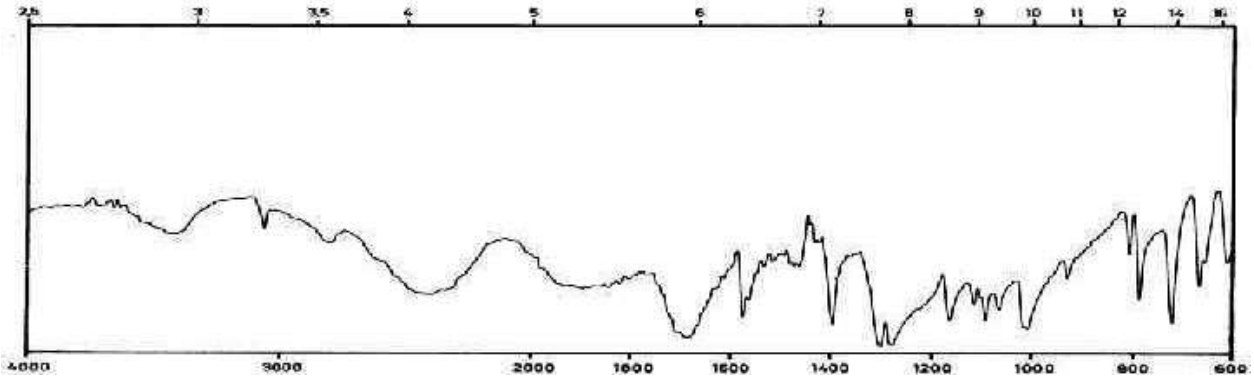
IDENTIFICATION (ПОДЛИННОСТЬ)

Nicotinic acid shows amphoteric properties because of the presence of in its structure of cyclic pridinic nitrogen (basic) and carboxyl group (acidic).

1. Infrared spectroscopy (ИК-спектроскопия)

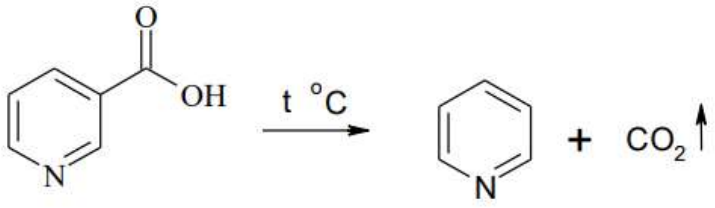
The infrared spectrum of the substance, taken in a disc with KBr, in the region from 4000 to 400 cm^{-1}, according to the position of the absorption bands should correspond to the figure of the spectrum of nicotinic acid.

NICOTINIC ACID



2. Decomposition reaction (Реакция разложения)

When nicotinic acid is heated with crystalline potassium carbonate, it decompose to form pyridine (characteristic odour) and carbon dioxide, which forms an opalescence when passed through lime or barite water:

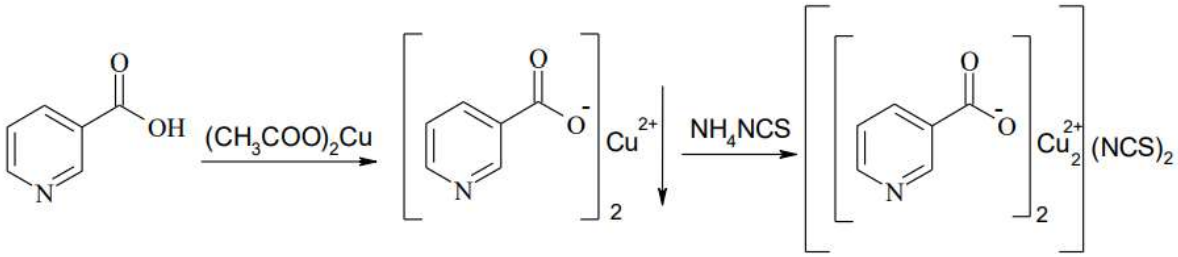


$$CO_2 + Ca(OH)_2 \longrightarrow CaCO_3\downarrow + H_2O$$

При нагревании с кристаллическим карбонатом калия образуется пиридин(характерный запах) и диоксид углерода.

3. Complexation reaction (Реакция комплексообразования)

When copper (II) acetate acts on a solution of nicotinic acid, copper nicotinate, a blue-coloured precipitate, is formed. When ammonium thiocyanate is added, a ternary complex compound of green colour:



Blue (синий) *green (зеленый)*

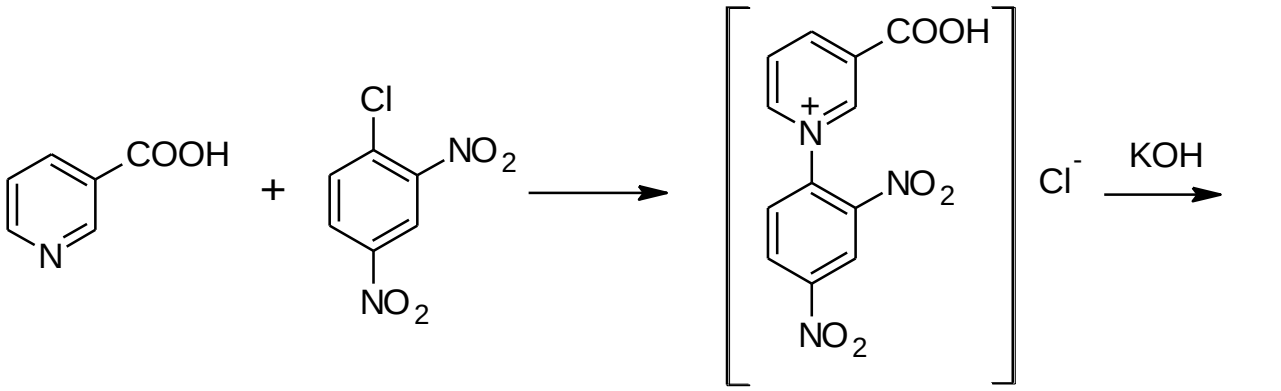
4. Formation of polymethine dye (Zinke reaction)

Образование полиметинового красителя (реакция Цинке)

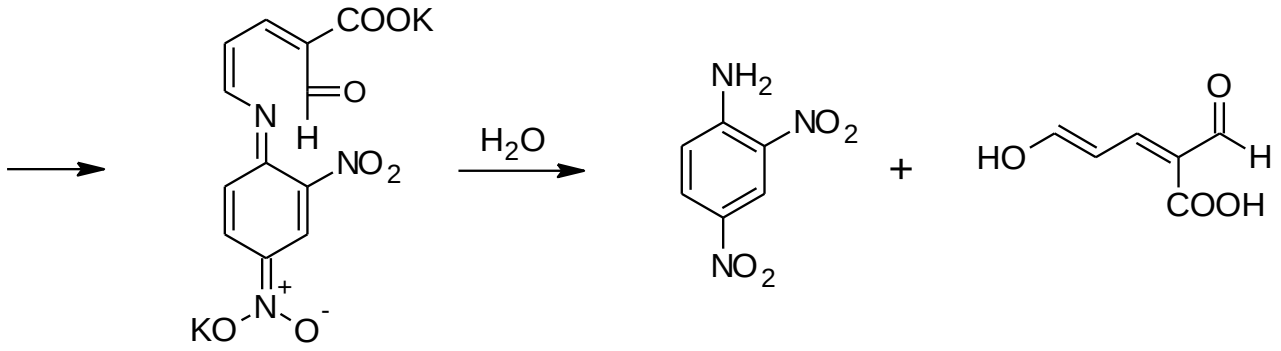
When 2,4-dinitrochlorobenzene is reacted in an alcoholic alkali solution, the pyridine cycle is cleaved.

First, a colourless pyridinium salt is formed (1) *(бесцветная соль)*, which under the action of alkali opens the pyridine cycle to form a glutaconic aldehyde derivative (polymethine base), coloured brown or red *(бурый или красный цвет)* (2).

Glutaconic aldehyde derivatives are unstable compounds susceptible to hydrolysis in alkaline media. They are cleaved to glutaconic aldehyde (4) and 2,4-dinitroaniline (3):



1

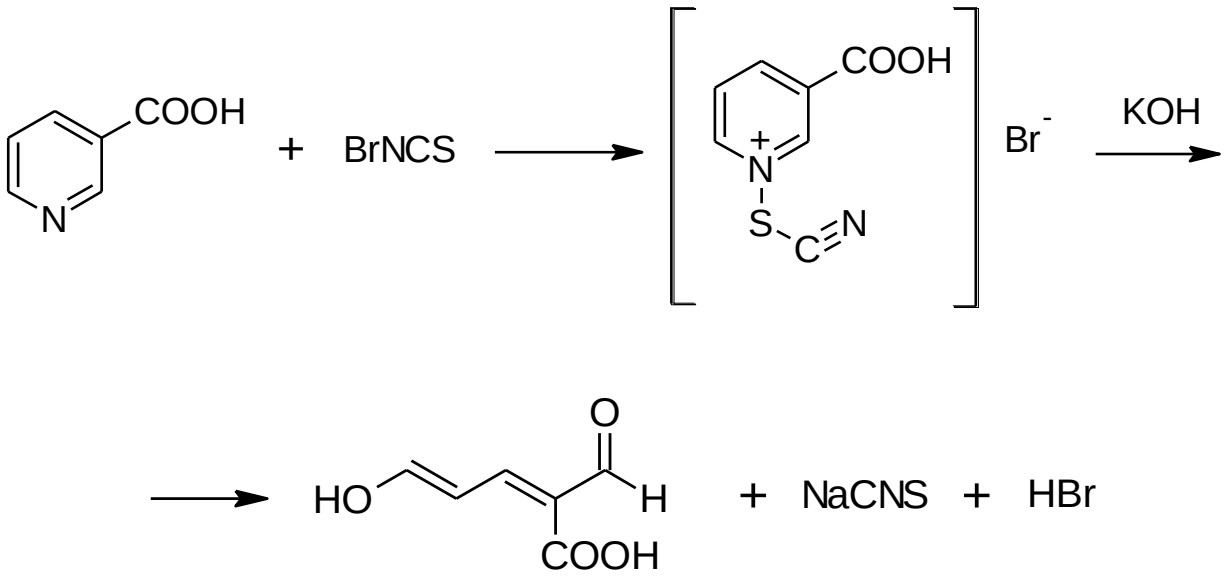


2 *3* *4*

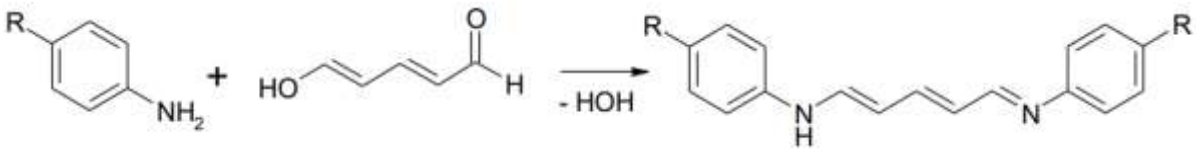
Glutaconic aldehyde has a yellow colour *(желтая окраска)* in alkaline medium.

Bromine thiocyanate can be used as a cleavage agent. Bromine thiocyanate is obtained by adding to bromine water ammonium thiocyanate to bromine water until discolouration:

$$Br_2 + NH_4NCS \longrightarrow BrNCS + NH_4Br$$



The subsequent addition of primary aromatic amines (aniline, novocainamide, sodium sulphacyl) leads to a condensation reaction with glutaconic aldehyde to form Schiff bases coloured intensely yellow, orange or red *(основаня Шиффа, окрашенные в интенсивно желтый, оранжевый или красный цвет)*:



5. Reaction with citric acid and acetic anhydride

Interaction with citric acid and acetic anhydride produces a red-violet colouration when heated.

При взаимодействии с лимонной кислотой и уксусным ангидридом при нагревании образуется красно-фиолетовая окраска.

PURITY TEST (ДОБРОКАЧЕСТВЕННОСТЬ)

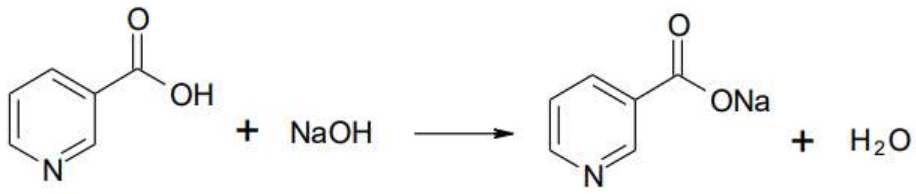
In the purity test, the permissible impurity content of the initial products of synthesis or decomposition is determined. In nicotinic acid the permissible content of 2,6- and 2,5-pyridindicarboxylic acids is determined using a standard.

При проверке чистоты определяется допустимое содержание примесей в исходных продуктах синтеза или разложения. В никотиновой кислоте с помощью эталона определяют допустимое содержание 2,6- и 2,5-пиридиндикарбоновых кислот.

QUANTIFICATION (КОЛИЧЕСТВЕННОЕ ОПРЕДЕЛЕНИЕ)

1. Alkalimetry (Алкалиметрия)

Aqueous solutions of nicotinic acid have acidic properties. A suspension of nicotinic acid is dissolved in hot water and titrated with 0.1 N sodium hydroxide solution to the formation of sodium salt (indicator phenolphthalein - colour change from colourless to pink):

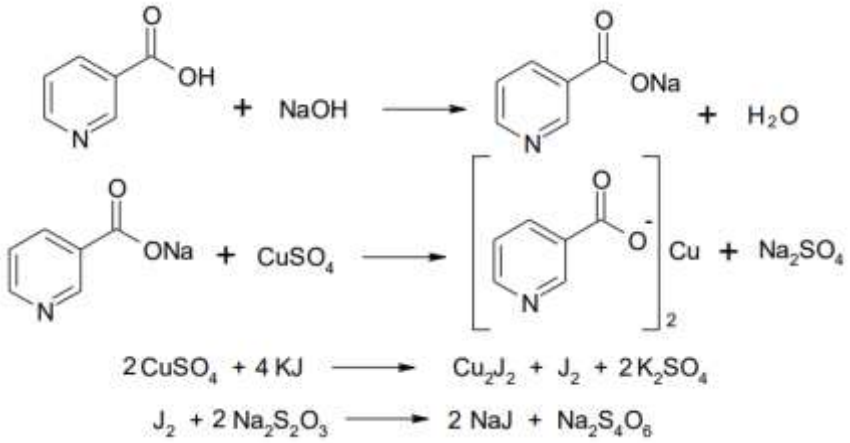


Титрант натрия гидроксид, индикатор фенолфталеин. Переход окраски с бесцветного до розового)

2. Iodometric titration (after precipitation of copper nicotinate)

Йодометрия после осаждения никотината меди

Nicotinic acid is treated with an excess of titrated copper (II) sulphate solution in alkaline medium. Then excess working solution is titrated iodometrically in the presence of indicator - starch:



Никотиновую кислоту обрабатывают избытком титрованного раствора сульфата меди (II) в щелочной среде. Затем избыток рабочего раствора титруют йодометрически в присутствии индикатора – крахмала.

STORAGE (ХРАНЕНИЕ)

Nicotinic acid is stored in well sealed containers protected from light in a dry place protected from light.

Никотиновую кислоту хранят в хорошо закупоренной таре, защищенной от света, в сухом, защищенном от света месте.

MEDICAL USE (ПРИМЕНЕНИЕ)

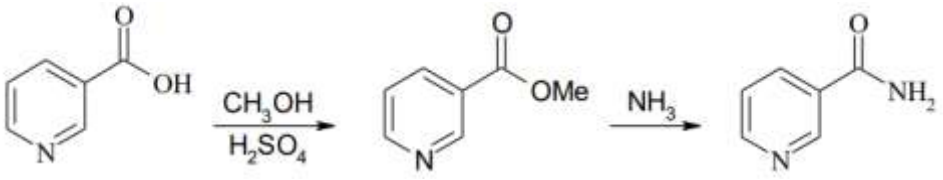
Nicotinic acid is a vitamin, hypolipidaemic and specific antipellagic agent. In the body, nicotinic acid is converted into nicotinamide, which binds to hydrogen transfer codehydrogenase I and II coenzymes (NAD and NADPH), participates in the metabolism of fats, proteins, amino acids, purines, tissue respiration, glycogenolysis, biosynthesis processes, and, most importantly, reduces the level of lipoprotein and triglyceride, which clog blood vessels and contribute to high blood pressure.

Никотиновая кислота применяется как витаминное, гиполипидемическое и антипеллагрическое средство.

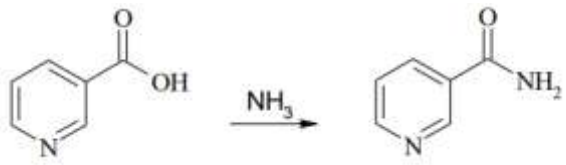
Nicotinamide (НИКОТИНАМИД)

OBTAINING (ПОЛУЧЕНИЕ)

Nicotinamide is synthesised from nicotinic acid. The intermediate product of the synthesis is nicotinic acid methyl ester:



A better and more economical way to synthesise nicotinamide is by passing ammonia gas into a mixture of nicotinic acid and aqueous ammonia solution at 180-185 °C:



PHYSICAL PROPERTIES (ФИЗИЧЕСКИЕ СВОЙСТВА)

A white, fine crystalline powder, with very faint odour, bitter taste. Melting point 128 - 131 °C.

Белый мелкокристаллический порошок с очень слабым запахом, горьким вкусом. Температура плавления 128 - 131 °C.

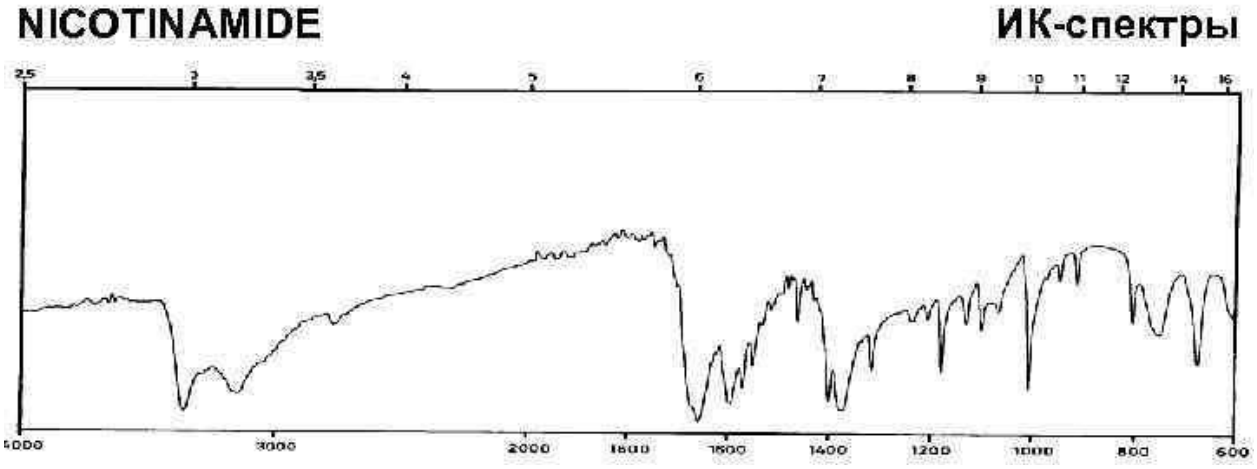
Easily soluble in water and in alcohol, soluble in glycerine, very slightly soluble in ether and chloroform.

Легко растворим в воде и спирте, растворим в глицерине, очень слабо растворим в эфире и хлороформе.

IDENTIFICATION (ПОДЛИННОСТЬ)

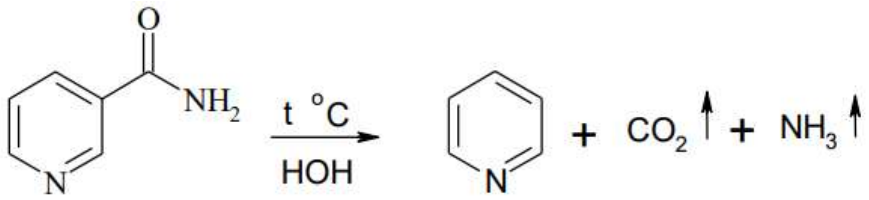
1. Infrared spectrometry (ИК-спектрометрия)

The infrared spectrum of the substance, taken in a disc of potassium bromide, in the region from 4000 to 400 cm-1 in the position of the absorption bands shall correspond to the spectrum of a standard sample of nicotinamide or to the following figure.



2. Decomposition reaction (Реакция разложения)

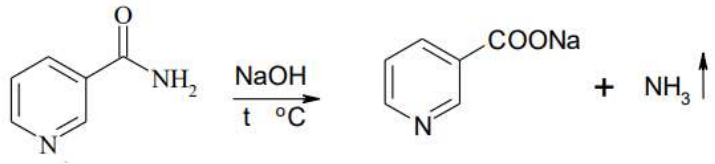
When nicotinamide is heated with crystalline potassium carbonate, it decomposes to form pyridine (characteristic odour), ammonia (blueing of wet red litmus paper) and carbon dioxide, which forms an opalescence when it is passed through lime or barite water:



При нагревании никотинамида с кристаллическим карбонатом калия он разлагается с образованием пиридина (характерный запах), аммиака (посинение влажной красной лакмусовой бумаги) и углекислого газа, который при пропускании через известковую или баритовую воду образует опалесцирующее вещество.

3. Alkaline hydrolysis (Щелочной гидролиз)

When nicotinamide is heated in solutions of alkali metal hydroxides, hydrolysis products are formed: nicotinic acid and ammonia. The effect of the reaction: sharp odour and blueing of wet red litmus paper.



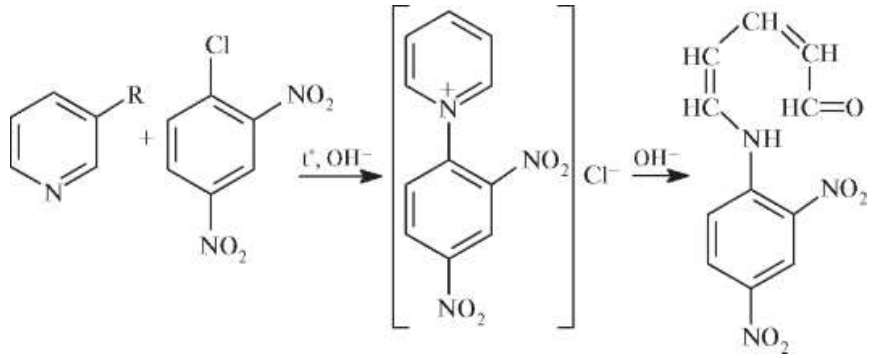
Эффект реакции: резкий запах и посинение влажной красной лакмусовой бумаги

4. Formation of a polymethine dye (Zinke reaction)

Образование полиметинового красителя (реакция Цинке)

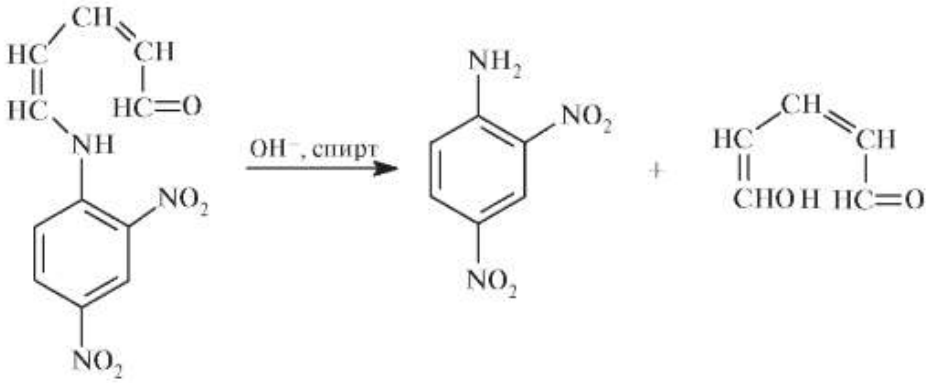
The reaction proceeds similarly to nicotinic acid.

a) With 2,4-dinitrochlorobenzene



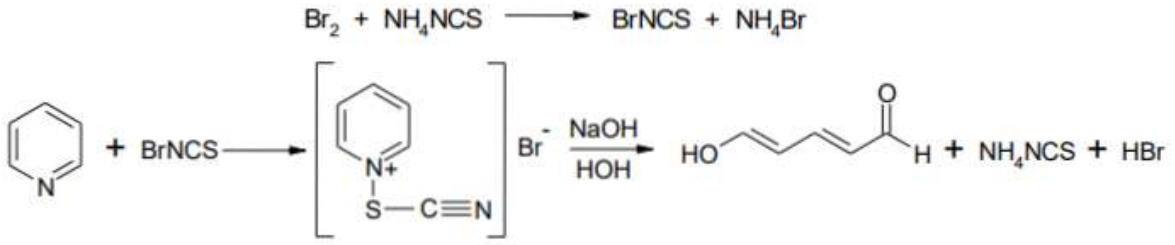
brown or red colour

бурый или красный цвет

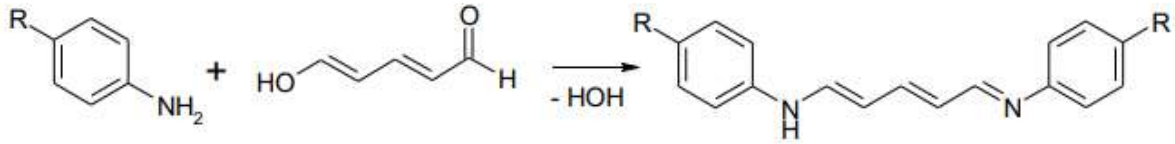


yellow colour (желтый)

(b) with bromine thiocyanate



yellow colour (желтый)



intense yellow, orange or red colour

интенсивный желтый, оранжевый или красный цвет

5. Reaction with citric acid and acetic anhydride

Реакция с лимонной кислотой и уксусным ангидридом

Interaction with citric acid and acetic anhydride produces a red-violet colouration when heated.

При взаимодействии с лимонной кислотой и уксусным ангидридом при нагревании образуется красно-фиолетовая окраска.

PURITY TEST (ДОБРОКАЧЕСТВЕННОСТЬ)

In the purity test, the permissible impurity content of the initial products of synthesis or decomposition is determined. Related impurities are determined by HPLC method.

При проверке чистоты определяется допустимое содержание примесей в исходных продуктах синтеза или разложения. Сопутствующие примеси определяются методом ВЭЖХ.

QUANTIFICATION (КОЛИЧЕСТВЕННОЕ ОПРЕДЕЛЕНИЕ)

1. Kjeldahl method (Метод Кьельдаля)

The Kjeldahl method is used to quantify nicotinamide in two ways:

(a) after alkaline hydrolysis;

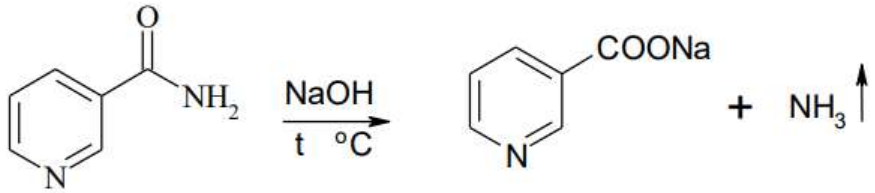
(b) after boiling in 50% sulphuric acid solution.

Метод Кьельдаля используется для количественного определения никотинамида двумя способами:

(a) после щелочного гидролиза;

(b) после кипячения в 50% растворе серной кислоты.

(a) Alkaline hydrolysis of nicotinamide yields ammonia, which are quantitatively distilled off into a receiver containing boric acid solution:



Boric acid in water forms tetrahydroxyboronic acid, which interacts with ammonia. The forming ammonium salts are titrated with 0.1 M hydrochloric acid solution in the presence of methyl red or methyl orange indicator:

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

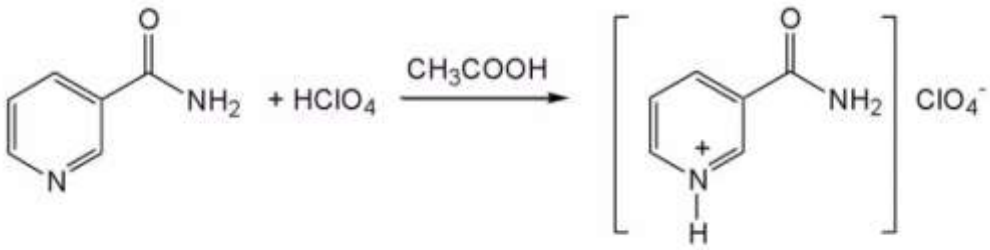
$$NH_3 + H[B(OH)_4] \longrightarrow NH_4[B(OH)_4]$$

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

(b) After boiling nicotinamide in 50% sulphuric acid solution, all organically bound nitrogen is converted to ammonia. It is distilled off into a receiver containing boric acid solution. The resulting ammonium tetrahydroxoborate is titrated with 0.1 M hydrochloric acid solution in the presence of methyl red or methyl orange indicator (chemistry above).

2. Non-aqueous titration (Неводное титрование)

The basic properties of nicotinamide are enhanced in the presence of glacial acetic acid or acetic anhydride. Titrant 0.1 M is chloric acid solution. The indicator is crystal violet.



Среда - ледяная уксусная кислота или уксусный ангидрид. Титрант 0,1 М - раствор хлорной кислоты. Индикатор - кристаллический фиолетовый.

STORAGE (ХРАНЕНИЕ)

Nicotinamide is stored in well sealed containers protected from light in a dry place protected from light.

Никотинамид хранят в хорошо закрытой таре, защищенной от света, в сухом, защищенном от света месте.

MEDICAL USE (ПРИМЕНЕНИЕ)

Nicotinamide is used as a vitamin preparation (vitamin PP). It is a specific antipellagic agent and also has a vasodilating effect.

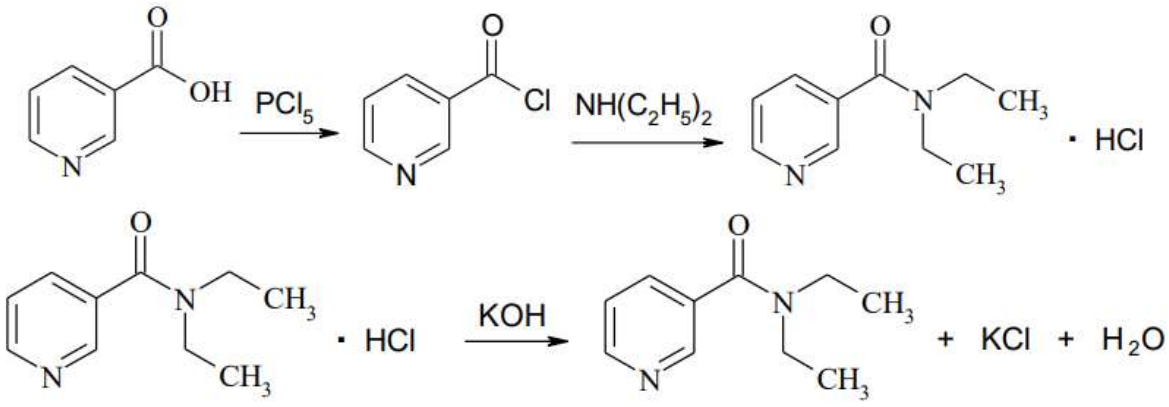
Никотинамид используется в качестве витаминного препарата (витамин PP). Он является специфическим противопеллагическим средством, а также обладает сосудорасширяющим действием.

Nicotinic acid diethylamide (Nikethamide)

Диэтиламид никотиновой кислоты (Никетамид)

OBTAINING (ПОЛУЧЕНИЕ)

Nicotinic acid diethylamide is prepared by acting on nicotinic acid with diethylamine diethylamine in the presence of phosphorus (V) chloroxide or phosphorus pentachloride. The intermediates are nicotinic acid chlorohydride and nicotinic acid diethylamide hydrochloride:



PHYSICAL PROPERTIES (ФИЗИЧЕСКИЕ СВОЙСТВА)

Colourless or slightly yellow oily liquid with weak specific odour.

Solidification temperature 20 - 25 °C. Density 1.058 - 1.066. Refractive index 1.524 - 1.526.

Miscible with water, alcohol, ether and chloroform in all ratios.

Бесцветная или слегка желтая маслянистая жидкость со слабым специфическим запахом.

Температура застывания 20 - 25 °С. Плотность 1,058 - 1,066. Показатель преломления 1,524 - 1,526.

Смешивается с водой, спиртом, эфиром и хлороформом во всех соотношениях.

IDENTIFICATION (ПОДЛИННОСТЬ)

1. Infrared spectrometry (ИК-спектрометрия)

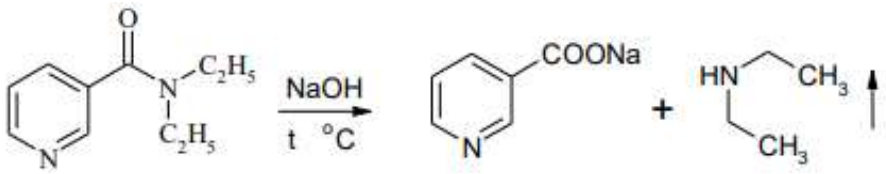
The infrared spectrum of the substance, taken in a disc of potassium bromide, in the region from 4000 to 400 cm-1 in the position of the absorption bands should correspond to the spectrum of a standard sample of nikethamide.

2. UV- Spectrophotometry (УФ-спектрофотометрия)

The absorption spectrum of a 0.0015% solution of the substance in 0.01 M hydrochloric acid solution at wavelengths from 230 to 350 nm in a quartz cuvette with a layer thickness of 2 cm should have a maximum at 263 nm with a specific absorption index of about 285.

3. Alkaline hydrolysis (Щелочной гидролиз)

When heated in solutions of alkali metal hydroxides, hydrolysis products are formed: nicotinic acid and diethylamine (rotten fish smell):

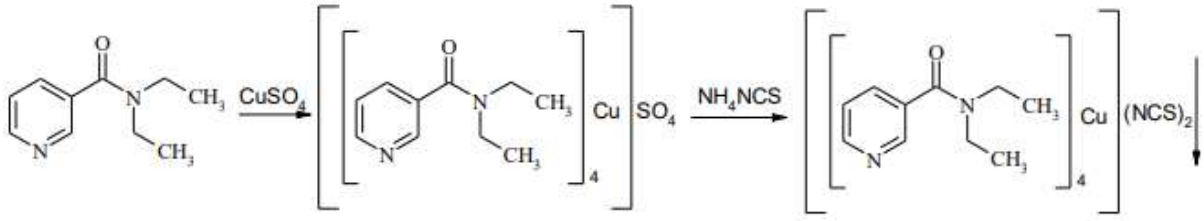


При нагревании в растворах гидроксидов щелочных металлов образуются продукты гидролиза: никотиновая кислота и диэтиламин (запах тухлой рыбы).

4. Formation of insoluble salts with heavy metal ions

Образование нерастворимых солей с ионами тяжелых металлов

When copper (II) acetate acts on a solution of nicotinic acid diethylamide, copper nicotinate, a blue precipitate, is formed. If ammonium thiocyanate is added, a triple complex compound of green colour is formed:



blue (синий) green (зеленый)

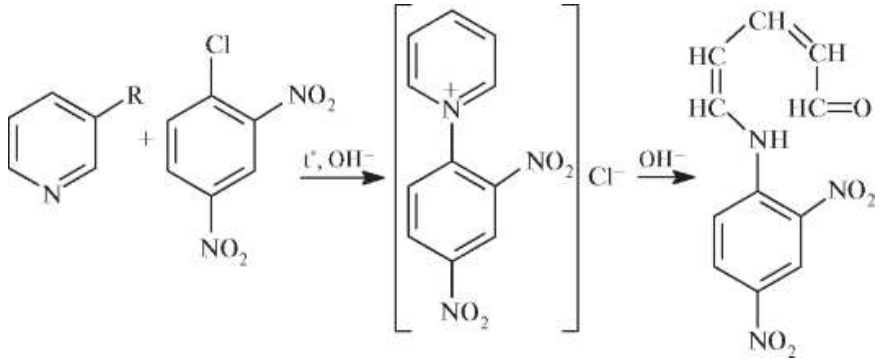
5. Formation of a polymethine dye (Zinke reaction)

Образование полиметинового красителя (реакция Цинке)

The reaction proceeds similarly to nicotinic acid.

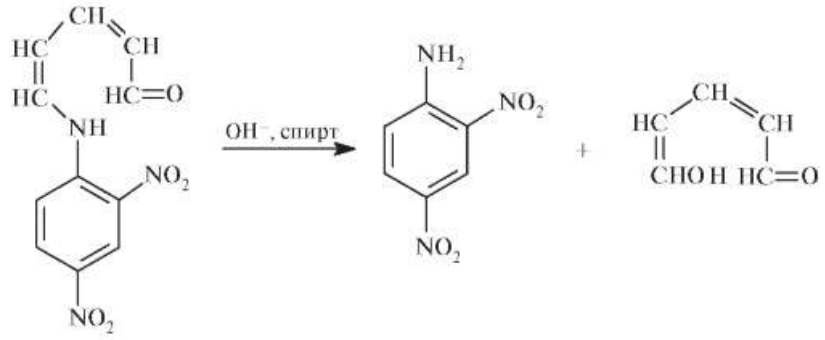
(a) With 2,4-dinitrochlorobenzene

Dissolve niketamide and 2,4-dinitrochlorobenzene in alcohol at boiling; the solution should turn yellow. After cooling and addition of sodium hydroxide a violet colouring appears, which gradually changes to brownish-red on further addition of sodium hydroxide solution.



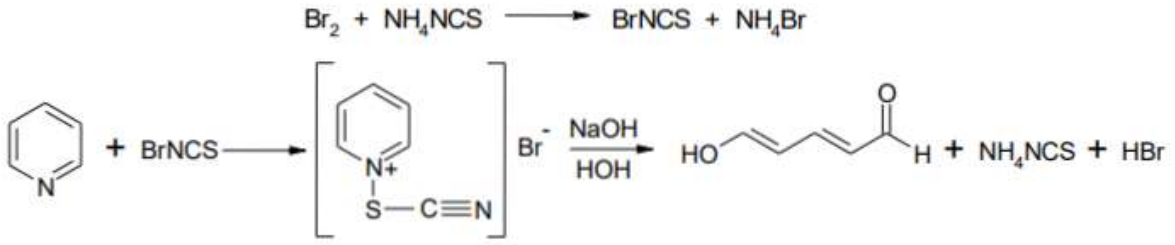
brownish-red

буро-красный

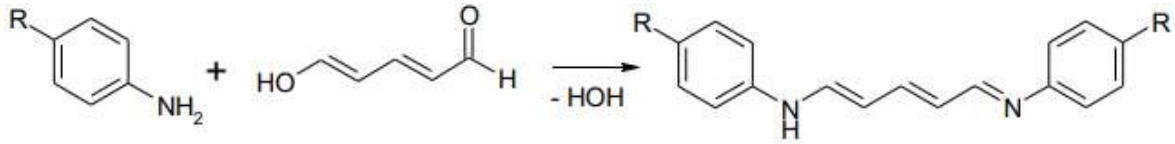


yellow (желтый)

(b) with bromine thiocyanate



yellow colour (желтый)



intense yellow, orange or red colour

интенсивный желтый, оранжевый или красный цвет

4. Reaction with citric acid and acetic anhydride

Реакция с лимонной кислотой и уксусным ангидридом

Interaction with citric acid and acetic anhydride produces a red-violet colouration when heated.

При взаимодействии с лимонной кислотой и уксусным ангидридом при нагревании образуется красно-фиолетовая окраска.

PURITY TEST (ДОБРОКАЧЕСТВЕННОСТЬ)

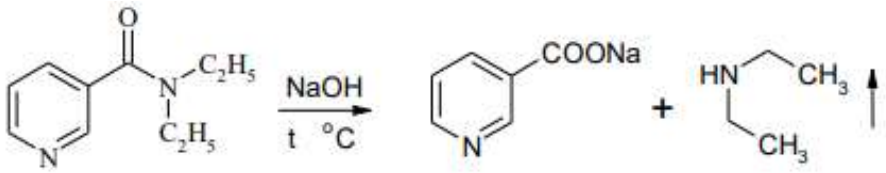
In the purity test, the permissible impurity content of the initial products of synthesis or decomposition is determined. Related impurities are determined by HPLC method.

При проверке чистоты определяется допустимое содержание примесей в исходных продуктах синтеза или разложения. Сопутствующие примеси определяются методом ВЭЖХ.

QUANTIFICATION (КОЛИЧЕСТВЕННОЕ ОПРЕДЕЛЕНИЕ)

1. Kjeldahl method (Метод Кьельдаля)

After alkaline hydrolysis the diethylamine, which is quantitatively distilled off into a receiver containing boric acid solution:



Boric acid in water forms tetrahydroxyboronic acid, which interacts with diethylamine. The resulting salt diethylamine is titrated with 0.1 M hydrochloric acid solution in the presence of the indicator methyl red or methyl orange:

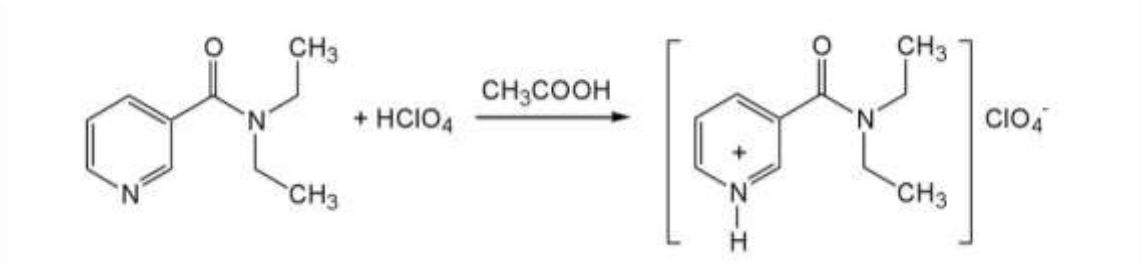
$$H_3BO_3 + H_2O \longrightarrow H[B(OH)_4]$$

$$NH(C_2H_5)_2 + H[B(OH)_4] \longrightarrow [NH_2(C_2H_5)_2][B(OH)_4]$$

$$[NH_2(C_2H_5)_2][B(OH)_4] + HCl \longrightarrow NH(C_2H_5)_2 + H_3BO_3 + H_2O$$

2. Non-aqueous titration (Неводное титрование)

The basic properties of nicotinic acid diethylamide are enhanced in the presence of glacial acetic acid or acetic anhydride. Titrant 0.1 M is chloric acid solution. The indicator is crystal violet.



Среда - ледяная уксусная кислота или уксусный ангидрид. Титрант 0,1 М - раствор хлорной кислоты. Индикатор - кристаллический фиолетовый.

STORAGE (ХРАНЕНИЕ)

Nicetamide is stored in orange glass bottles in a place protected from light.

Никетамид хранят во флаконах оранжевого стекла в защищенном от света месте.

MEDICAL USE (ПРИМЕНЕНИЕ)

Nicetamide in the form of 25% water-alcohol solution is used in medical practice under the name "Cordiaminum" - cordiamine as a central nervous system stimulant and analeptic agent.

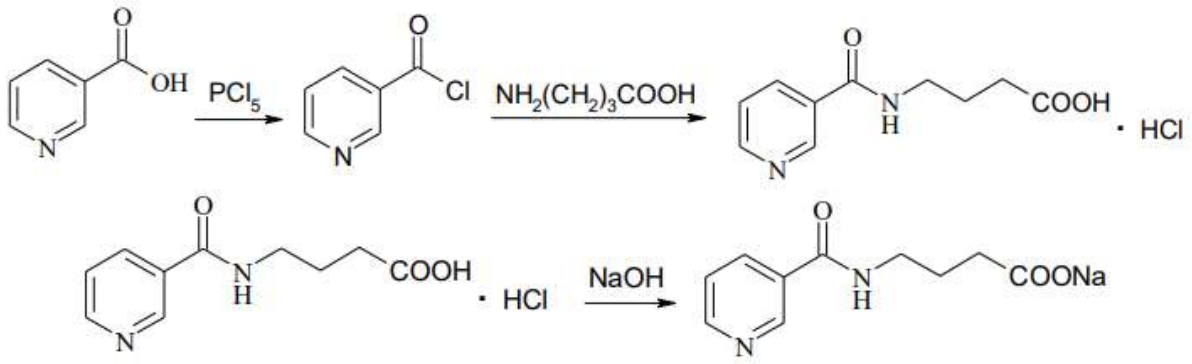
Никетамид в виде 25% водно-спиртового раствора используется в медицинской практике под названием "Cordiaminum" - кордиамин в качестве стимулятора центральной нервной системы и аналептического средства.

Picamilon

Пикамилон

OBTAINING (ПОЛУЧЕНИЕ)

Picamilon can be obtained by acting on nicotinic acid chlorohydride with γ-aminobutyric acid:



PHYSICAL PROPERTIES (ФИЗИЧЕСКИЕ СВОЙСТВА)

White crystalline powder, odourless, hygroscopic.

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

Белый кристаллический порошок, без запаха, гигроскопичен.

Легко растворим в воде, умеренно растворим в спирте, очень слабо растворим в эфире и хлороформе.

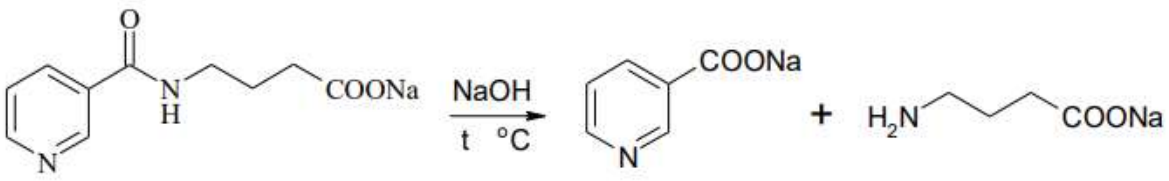
IDENTIFICATION (ПОДЛИННОСТЬ)

1. IR and UV spectrophotometry

- IR spectra should have complete coincidence of absorption bands with the standard samples.
- UV spectra are conducted in alkaline or acidic solutions with max and min absorbance matching with the data of the pharmacopoeial article

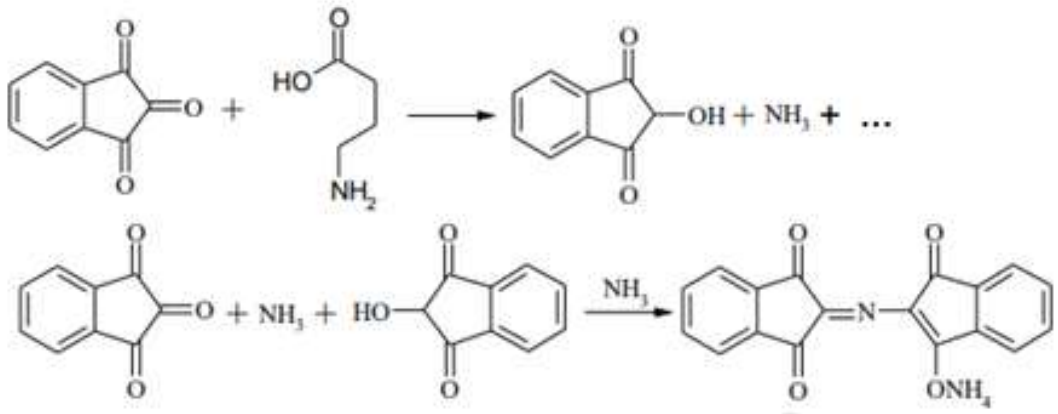
2. Alkaline hydrolysis (Щелочной гидролиз)

When Picamilon is heated in solutions of alkali metal hydroxides, hydrolysis products are formed: nicotinic acid and the sodium salt of γ-aminobutyric acid:



γ-Aminobutyric acid can be detected in two ways:

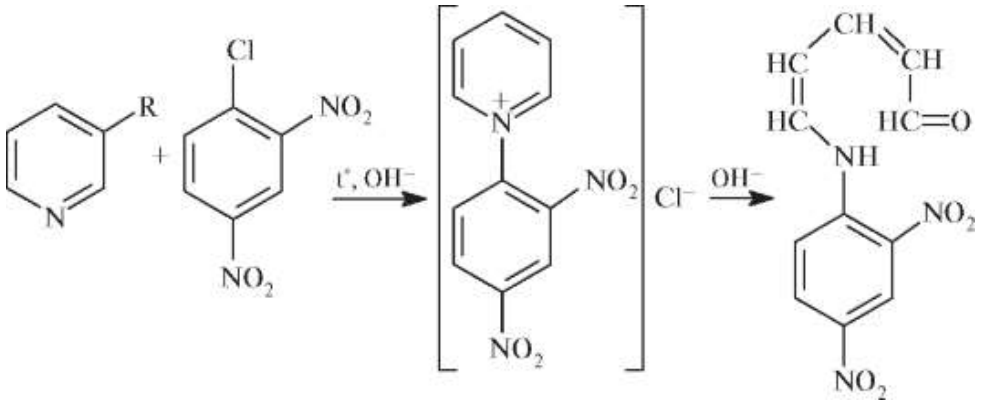
1. When acidification occurs, oil droplets appear on the surface of the solution.
2. When ninhydrin is added, a violet colouring appears:



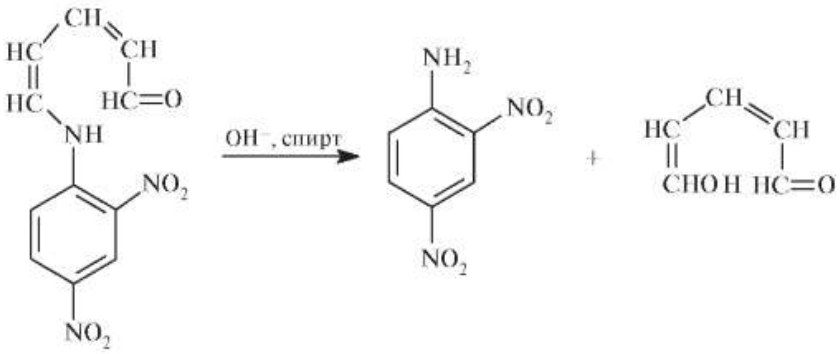
3. Formation of a polymethine dye (Zinke reaction)

Образование полиметинового красителя (Реакция Цинке)

Upon action of 2,4 dinitrochlorobenzene in alcoholic alkali solution the pyridine cycle is cleaved. First, a colourless pyridinium salt is formed. This salt under the action of alkali opens the pyridine cycle with the formation of glutaconic aldehyde derivative (polymethine base), coloured brown or red. Glutaconic aldehyde derivatives are unstable compounds prone to hydrolysis in alkaline media. They are cleaved to glutaconic aldehyde and 2,4-dinitroaniline:



brownish-red



yellow

Glutaconic aldehyde has a yellow colour in alkaline medium.

4. Reaction with citric acid and acetic anhydride (Реакция с лимонной кислотой и уксусным ангидридом)

A common reaction for pyridine derivatives is the reaction with citric acid in acetic anhydride. It produces a violet colouration.

Общей реакцией для производных пиридина является реакция с лимонной кислотой в уксусном ангидриде. При этом возникает фиолетовое окрашивание.

5. Detection of sodium ion (Обнаружение иона натрия)

Picamilon gives a characteristic reaction to sodium ion:

- yellow colouring of the flame;
- interaction with zinccuranyl acetate. A yellow coloured fine crystalline precipitate is formed:

$$Na^+ + Zn[(UO_2)_3(CH_3COO)_8] + CH_3COOH + 9H_2O \longrightarrow$$
$$\longrightarrow NaZn[(UO_2)_3(CH_3COO)_9]\cdot 9H_2O\downarrow + H^+$$

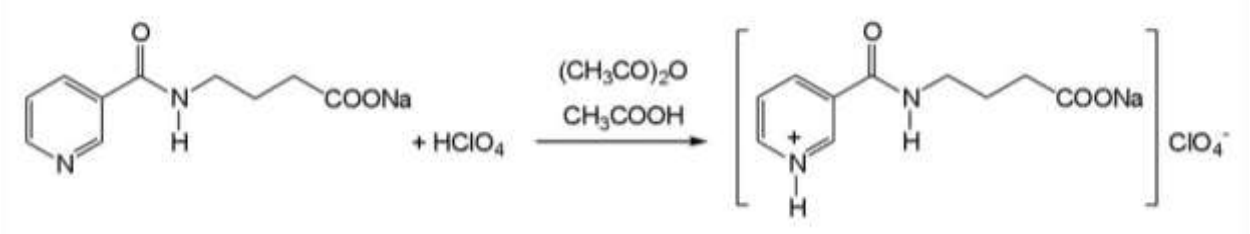
PURITY TEST (ДОБРОКАЧЕСТВЕННОСТЬ)

The purity test establishes the permissible impurity content of the starting products of synthesis or decomposition.

QUANTIFICATION (КОЛИЧЕСТВЕННОЕ ОПРЕДЕЛЕНИЕ)

Non-aqueous titration

Picamilon is quantified by non-aqueous titration. Its basic properties are enhanced in the presence of glacial acetic acid or acetic anhydride. Titrant 0.1 M is chloric acid solution. The indicator is crystal violet.



STORAGE (ХРАНЕНИЕ)

Picamilon is stored in well-corked containers protected from light in a dry place protected from light.

Пикамилон хранят в хорошо укупоренной таре, защищенной от света, в сухом, защищенном от света месте.

MEDICAL USE (ПРИМЕНЕНИЕ)

Picamilon is a vasoactive and nootropic agent. It is prescribed in acute disorders or chronic insufficiency of cerebral blood circulation, vegetovascular dystonia, as well as to increase resistance to physical exertion.

Пикамилон - вазоактивное и ноотропное средство. Назначается при острых нарушениях или хронической недостаточности мозгового кровообращения, вегетососудистой дистонии, а также для повышения устойчивости к физическим нагрузкам.