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DEVELOPMENT OF A NEW TECHNOLOGY FOR OBTAINING THE SUBSTANCE OF THE DRUG ACETAMIZOLE

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DEVELOPMENT OF A NEW TECHNOLOGY FOR OBTAINING THE SUBSTANCE OF THE DRUG ACETAMIZOLE

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Abstract: The main goal of this work is to obtain a preparation of acetamizole based on local raw materials by a more convenient method of acylation of 2-methoxycarbonylamino benzimidazole with glacial acetic acid, this synthesis method is proposed for the first time. On the basis of the conducted experiments, favorable conditions for the reaction were found, the influence of the nature of the acid, the temperature, the duration of the reaction and other factors on the course of the reaction was studied, the technology was developed and implemented at the experimental production of "IHRV AN RUz". Based on experiments conducted by scientists of the Institute of Veterinary Research of Uzbekistan in experiments, it was determined that the received batches of the drug "Acetamizole" showed 100% effectiveness against gastrointestinal strongylates, fasciolosis and moniesia at a dose of 100-150 mg/kg. The structure of the obtained 2-acetylaminobenzimidazole was studied by IR, Mass, ¹H, ¹³C NMR spectroscopy, and the structures of the synthesized compounds were studied and established.

Key words: benzimidazole, acetamizole, synthesis, acylation, substances, technologies, antihelminth, fasciolosis, moniesiosis, biotest, *Xanthomonas mivacurium*, *fusarium oxysporum*.

Аннотация: Ушбу ишнинг асосий мақсади, қулай усулда ацетамизол препаратини маҳаллий хом-ашёлар асосида 2-метоксикарбониламинобензимидазолни музли сирка кислотаси билан қулай усулда ациллашдан иборат бўлиб, мазкур синтезлаш усули биринчи марта таклиф этилмоқда. Олиб борилган тажрибалар асосида реакция боришининг қулай шaroитлари аниқланган, бунда кислота табиати, ҳарорат, реакция давомийлиги ҳамда реакциянинг боришига таъсир этувчи бошқа омиллар ўрганилган ва технологияси ишлаб чиқилган ва ЎМКИ тажриба ишлаб чиқариши корхонасида ишлаб чиқаришига тадбиқ этилган. "Ацетамизол" препаратининг янги технология асосида олинган намуналари Ўзбекистон Ветеринария илмий-тадқиқот институти олимлари томонидан олиб борилган тажрибалар асосида, мазкур препарат 100-150 мг/кг дозада ошқазон-ичак стронгилятлари, фациола ва мониезиялар каби гижжа турларига қарши 100 % гельминтлардан холис қилиши тажрибаларда аниқланган. Олинган 2-ацетиламинобензимидазолнинг тузилиши IQ, Mass, 1H, 13C YAMR спектроскопияси усуллари билан ўрганилган ва синтезланган бирикманинг тузилиши аниқланган.

Таянч сўзлар: бензимидазол, ацетамизол, синтез, ациллаш, субстанция, технология, антигельминт, фациоллёз, мониезиоз, биотест, *Xanthomonas mivacurium*, *fusarium oxysporum*.

Аннотация: Основная цель работы состоит в получении препарата ацетамизола на основе местного сырья более удобным способом ацилирования 2-метоксикарбониламинобензимидазола с ледяной уксусной кислотой: этот метод синтеза предлагается впервые. На основе проведенных экспериментов были найдены благоприятные условия протекания реакции, изучен влияние природы кислоты, температуры, продолжительности реакции и других факторов, на ход реакции, разработана технология и внедрена на опытном производстве "ИХРВ АН РУз". На основании экспериментов, проведенных учеными Института ветеринарных исследований Узбекистана, было определено, что полученные партии препарата "Ацетамизол" показали 100% эффективность против желудочно-кишечных стронгилатов, фациоллёз и мониезия в дозе 100-150 мг/кг. Структура полученный 2-ацетиламинобензимидазола установлена методами ИК, Масс, ¹H, ¹³C ЯМР-спектроскопии.

Ключевые слова: бензимидазол, ацетамизол, синтез, ацилирования, субстанции, технологии, антигельминт, фациоллѐз, мониезиоз, биотест, *Xanthomonas mivacurium*, *fusarium oxysporum*.

Introduction

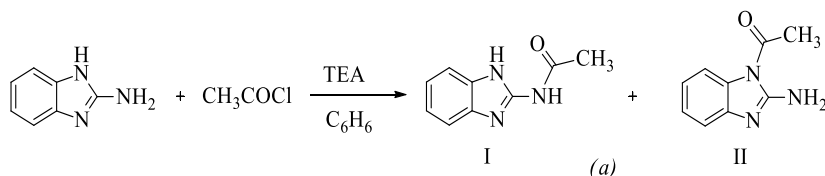
Solutions for global environmental problems are aimed at developing waste processing technologies [1]. Everyone knows that helminths are causing enormous damage in animal husbandry. One of the main objects of helminthic diseases is farm animals.

Today, there is a rapid increase in the number of multidrug-resistant infections that cause various public health problems. Among the benzimidazole derivatives, the search for fungicides, insecticides, and other pesticides used in agriculture was carried out [2]. Therefore, the creation of drugs based on local natural and synthetic raw materials is especially relevant. Benzimidazoles and its derivatives play an important role in the processes of drug discovery, which are of significant chemical importance and biological activity [3]. Benzimidazoles are used for the synthesis of a wide range of heterocyclic compounds and raw materials for the synthesis of drugs, and are also crucial for the theoretical development of heterocyclic chemistry and organic synthesis [4]. Benzimidazoles and its derivatives have been described with a wide range of biological potential: anthelmintic, anticancer, antiviral, antimicrobial, anti-inflammatory, analgesic, antioxidant and antimalarial, and others [5]. Many well-known drugs are imported from foreign countries because Uzbekistan does not have the production of domestic drugs of this series [6].

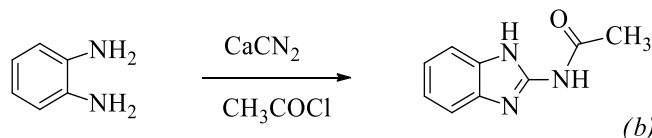
2-Acetylaminobenzimidazole, a local drug developed at the Institute of Chemical Chemistry of the Academy of Sciences of the Republic of Uzbekistan, is used against the disease of fascioliasis and moniesiasis, which is widespread among animals. Earlier, instructions were developed for the use of asetamizole in animal husbandry and poultry farming as a remedy against helminthiasis.

According to the literature, a number of N-acyl (aryl) -aminobenzimidazoles are obtained by two methods: by acylation of 2-aminobenzimidazole with acid chlorides in the presence of triethylamine, in dry benzene (method a) and cyclization of o-phenylenediamine with acyl (aryl) - cyanamides (method "b").

According to the "a" method, both the endocyclic heteroatom in position I and the nitrogen of the exocyclic amino group can be subjected to electrophilic attack, that is, the formation of two isomers (I, II) is possible:

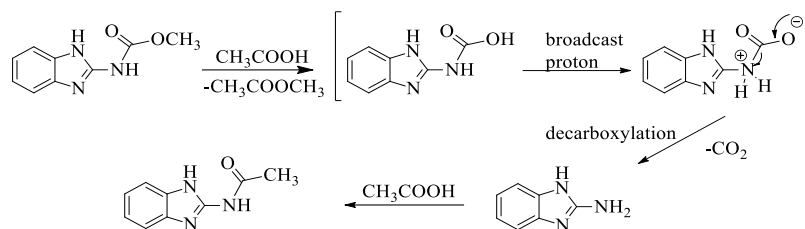


Method "b" as an alternative method for the synthesis of 2-acetylaminobenzimidazole was proposed a method using o-phenylenediamine, calcium cyanamide and acetyl chloride according to the following scheme



At present, due to the fact that the initial reagents used to carry out these reactions are not produced in our republic, we propose the following synthesis method.

The purpose of this work is the development of a new technology for producing the anthelmintic drug 2-acetylaminobenzimidazole is economically viable. The one-step method for carrying out the acylation reaction of 2-methoxycarbonylamino benzimidazole isolated from waste with glacial acetic acid is very convenient. The mechanism of the acylation reaction of 2-methoxycarbonylamino benzimidazole with glacial acetic acid proceeds as follows:



According to the reaction mechanism, the decarboxylation process first proceeds, then the formed intermediate product 2-aminobenzimidazole interacts with glacial acetic acid to form the final target product 2-acetylaminobenzimidazole.

2-Acetylaminobenzimidazole is an odorless, white, off-white powder. The product is readily soluble in glacial acetic acid, slightly soluble in chloroform and acetone, and very slightly soluble in water and in 96% alcohol [7].

Research methods and results obtained

Procedure for the synthesis of 2-acetylaminobenzimidazole. The experiments were carried out in a three-necked flask equipped with a mechanical stirrer and reflux condenser. 2-methoxycarbonylaminobenzimidazole 10 g (0.05 mol) was added glacial acetic acid ($\rho = 1.0498 \text{ g / cm}^3$) 36 ml (0.6 mol). The reaction mixture was heated in an oil bath. Then 15 ml (0.25 mol) of glacial acetic acid was distilled off and the remainder of the reaction mixture was left for 10 hours at room temperature. The precipitated crystals were filtered off and dried to obtain 5.7 g of 2-acetylaminobenzimidazole (yield 61.9%). The filtrate was distilled off to dryness, the residue was additionally purified by recrystallization in ethyl alcohol in the presence of activated carbon. An additional 3.3 g of 2-acetylaminobenzimidazole was obtained (35.9% yield). The overall maximum yield was 9 g (97.8%). For a qualitative and quantitative assessment of the influence of a number of factors on the studied reaction, a mathematical model was created using the Box-Wilson method [8], with the help of which the optimal conditions for obtaining the product were determined.

Based on the research results, the main factors were selected, the levels and intervals of variation, presented in the table, were established [9].

Table

Factor levels and variation intervals

№	Variation levels	-	0	+
1	X_1	102	110	118
2	X_2	7	8	9
3	X_3	1/12	1/13	1/14

X_1 – reaction temperature, °C;

X_2 – reaction time, hour;

X_3 – the quantitative ratio of the starting materials (mol).

According to the experimental data, the regression equation was calculated:

$$Y = 91,8 - 1,43x_1 + 4,21x_2 - 1,18x_3$$

The results of the statistical analysis showed that the mathematical model is adequate and the significant coefficient is $-b_2$.

Thus, based on the optimization of the process, it was found that the main factor influencing the synthesis of 2-acetylaminobenzimidazole is a temperature of 118 °C and a reaction time of 8 hours. The found optimal conditions were reproduced in a large laboratory setup. In the process of obtaining medamine, a number of wastes are formed: activated carbon and mother liquors with a high content.

2-Methoxycarbonylaminobenzimidazole, for which it was necessary to develop methods for their utilization and regeneration. We have developed a method for the isolation of 2-methoxycarbonylaminobenzimidazole from this waste and its application for the synthesis of the target product [10].

Technological part

Isolation of 2-acetylaminobenzimidazole from waste of medamine production; The prepared medamine is fed into a glass container G-1 for cooling, then filtered on a F-2 suction filter. The filtered part is sent for drying, and the mother part is collected in the G-3 glass container. The acidic mother liquor obtained after filtration of medamine is poured into a container E-4. While cooling from the measuring tank M-4, add 25% ammonia solution to pH 8. The precipitate of 2-methoxycarbonylaminobenzimidazole is filtered on a F-6 suction filter, washed with water until neutral and dried in a Dr-14 drying oven at 60 °C until moisture content not more than 1.5%. Then they are transferred to the B-16 bunker to obtain a new preparation of 2-acetylaminobenzimidazole.

The activated carbon used in the preparation of medamine, along with the balance substances, adsorbs a certain amount of 2-methoxycarbonylaminobenzimidazole. Used coal is loaded into a heat-exchange reactor with a R-8 thermometer, a 5% hydrochloric acid solution is poured from the M-7 measurer and boiled for an hour. Then the mixture is fed to the F-9 suction filter, where the coal is filtered, the filtrate is placed in the G-10 glass container and, after cooling, is sent to the K-12 container. The purified activated carbon is sent to the B-15 bunker to purify the Acetamizole substance. In vessel K-12, the mother liquor containing 2-methoxycarbonylaminobenzimidazole from the measuring vessel M-11 is made alkaline with 25% ammonia solution to pH 8. The precipitate formed is filtered on a F-13 suction filter, washed with water to a neutral medium, dried in a Dr-14 drying oven at temperature 6 °C to a moisture content of not more than 1.5%. The resulting precipitate of 2-methoxycarbonylaminobenzimidazole can be used to obtain a new substance of the drug Acetamizole.

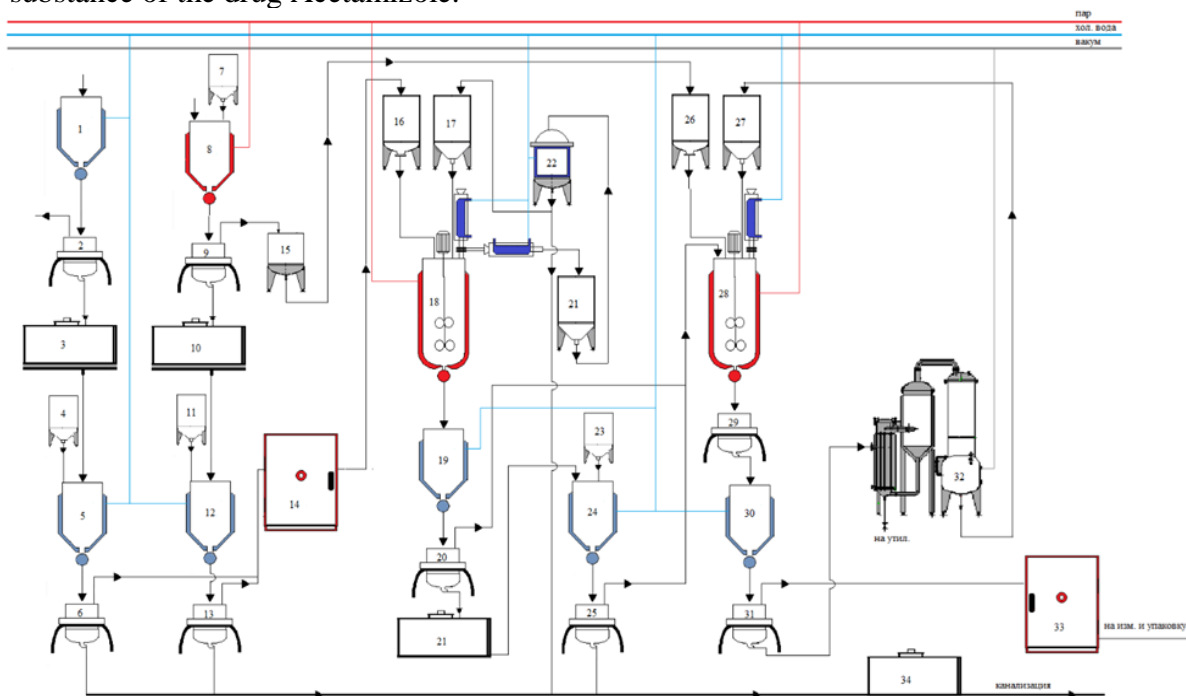


Fig. Technological scheme for the production of 2-acetylaminobenzimidazole.

1,5,8,12,19,24,30-glass container for cooling; 2,6,9,13,20,25,29,31-nutsch filters; 3,10,21,34- containers; 4,7,11,17,21,23,27-measurers; 14,33-oven for drying the finished product; 15,16,26- bunkers; 18,28-glass reactors; 22-refrigerator; 32-vacuum-circulation evaporator.

Glacial acetic acid ($\rho = 1.0498 \text{ g / cm}^3$) is poured into the reactor equipped with a stirrer, a heat exchanger, a R-18 thermometer with a capacity of 100 liters, and 10 kg of 2-methoxycarbonylaminobenzimidazole is charged from the M-17 measuring tank ($\rho = 1.0498 \text{ g / cm}^3$). with the stirrer running. The reaction mixture is heated, stirred for 8 hours at $118 \text{ }^\circ\text{C}$, while 15 liters of glacial acetic acid are distilled off in a container K-21 and then sent to the refrigerator Rg-22 for cooling to $16 \text{ }^\circ\text{C}$. After that, the mixture is fed from the R-18 reactor into a glass container G-19, the reaction mixture is left for 10 hours at room temperature. The crystals that have fallen out are fed from the G-19 glass container to the F-20 suction filter. The acidic mother liquor filtrate is sent to the C-21 container, obtained after filtration of 2-acetylaminobenzimidazole, is poured into the G-24 glass container. When cooled, a 25% ammonia solution is added from the M-23 measuring tank to pH 8 and filtered into the F-25 suction filter, the filtrate is sent to the K-34 container for neutralization and sent to the sewer. The precipitate formed in the F-25 suction filter is sent to the R-28 reactor for recrystallization, 70 liters of ethyl alcohol are added for recrystallization from the M-27 meter, and 0.5 kg of activated carbon from the B-26 hopper and heated for another 30 minutes. Then the solution is filtered on the F-29 suction filter, the filtrate is sent to the G-30 tank for crystallization and left for a day. A day later, the formed precipitate of 2-acetylaminobenzimidazole is filtered on an F-31 suction filter, the filtrate is sent to a Vac-32 vacuum circulating evaporator to distill alcohol. The precipitate of 2-acetylaminobenzimidazole is dried in a Dr-33 drying oven at a temperature of $60 \text{ }^\circ\text{C}$ to a moisture content of no more than 1.5%. The total yield of 2-acetylaminobenzimidazole is 8.43 kg (92%). The dried product is sent to packaging.

Results and their discussion

Biotests for *Xanthomonas malvecearum* showed that the compound 2-acetylaminobenzimidazole has a weak bactericidal activity, the zone of no growth was within 4 mm. At the same time, the investigated essential fungicidal activity in relation to *Fusarium oxysporum*, the zone of no growth on the 5th day of cultivation was 16 mm [7].

The results of these experiments showed that 2-Acetylaminobenzimidazole at doses of 25 and 50 mg / kg against gastrointestinal strong-gilatoses, fascioliasis and moniesiasis are not effective, and at doses of 100 and 150 mg / kg, 100% death of helminths is observed [10].

IR spectra were recorded on a System 2000 IR Fourier spectrometer in KBr tablets, ^1H ^{13}C NMR spectra - on a Unity-400 + instrument (operating frequency 400 MHz, internal TMS standard, δ scale) solvent CD_3COOD . The melting point of the synthesized compound was determined on a BOETIUS heating table (Germany). Electrospray ionization mass spectrometry (ESI-MS) was recorded using a 6420 Triple Quad LC / MS mass spectrometer (Agilent Technologies, USA). The purity of the product and the progress of the reaction were monitored by TLC Silufol UV-254. Rf-0.53 (system: acetone-benzene 3: 2)

The resulting product 2-Acetylaminobenzimidazole was also characterized by IR spectroscopy. IR spectrum (ν , cm^{-1}): 3150, 3400 (NH, NH_2), 1688 (C=O), 1638 (C=N), 1584 (C-N), 1456 (CH_3), 1524 (C=C). ^1H NMR - range (δ , м.д., Гц, CD_3COOD): 11.55 (1H, c, -HN-C=O), 7.56-7.60 (2H, AA`BB`- a type, H-4,6), 7.28-7.32 (2H, AA`BB`- a type, H-5,7), 2.27 (3H, c, CH_3). ^{13}C NMR (400 МГц, solvent CD_3COOD) (d, ppm): 176.71, 154.94, 136.94, 136.49, 119.85, 119.52, 111.84, 111.28, 26.52. From these data follows IR, NMR ^1H , ^{13}C - spectra that the number of protons corresponds to the protons of 2-acetylaminobenzimidazole. Melting point $282\text{-}284 \text{ }^\circ\text{C}$. M / z calculated for [M + H]: 175.187, found 175.900. Molecular weight 175.187.

Conclusions

Thus, an original method for the synthesis of 2-acetylaminobenzimidazole has been developed.

The structures of the synthesized compounds have been studied and established by IR, ^1H NMR spectroscopy. For the qualitative and quantitative analysis of the target product, a TLC method has been

developed. The optimal reaction conditions were found by the method of mathematical planning of the experiment.

On the basis of the research, an industrial technological scheme was developed for obtaining the substance of the anthelmintic drug 2-acetylaminobenzimidazole based on the production waste of the medamine drug. At the same time, the issues of disposal of waste from the production of medamine and the production of 2-acetylaminobenzimidazole by the original method were resolved.

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