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SAIDOV Sarvar
Institute of the Chemistry of Plant Substances, sarvar-saidov-1989@bk.ru

ABDURAZAKOV Askar
Institute of the Chemistry of Plant Substances, asqar2606@mail.ru

KARIMOV Rikhsibay
Institute of the Chemistry of Plant Substances, rixsiboy.karimov@bk.ru

KHVAN Alla
Institute of the Chemistry of Plant Substances, amkhvan@mail.ru

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HIGH-EFFICIENT AND NEW TECHNOLOGY FOR PRODUCING 5-NITRO-2-ACETYLAMINOBENZIMIDAZOLE

Sarvar SAIDOV[1] (sarvar-saidov-1989@bk.ru), Askar ABDURAZAKOV[1] (asqar2606@mail.ru), Rikhsibay KARIMOV[1] (rixsiboy.karimov@bk.ru), Alla KHVAN[1] (amkhvan@mail.ru), Khasan KADIROV[2] (khasan.kadirov.71@mail.ru)
[1]Institute of the Chemistry of Plant Substances, Tashkent, Uzbekistan
[2]Tashkent Chemical-Technological Institute, Tashkent, Uzbekistan

The aim of this work is to create new veterinary products for agriculture based on local raw materials, to develop a highly efficient technology for their production. Waste from the production of medamine produced in the pilot production of the Institute of Plant Chemistry of the Academy of Sciences of the Republic of Uzbekistan.

The process of synthesis of 5-nitro-2-acetylaminobenzimidazole was studied by one-factor experiments. The structure of the obtained product was investigated by IR, Mass, ^{1}H, ^{13}C NMR spectroscopy. The main factors influencing the process of obtaining 5-nitro-2-acetylaminobenzimidazole were revealed. On the basis of the obtained research results, a technological scheme for the preparation of 5-nitro-2-acetylaminobenzimidazole was developed. Works of selection of equipment, installation of a pilot plant, commissioning and testing of the technology for the production of 5-nitro-2-acetylaminobenzimidazole have been carried out. Experience samples of the product have been received for biological testing.

Keywords: heterocycle, nitration, activated carbon, biologically active, 2-acetylaminobenzimidazole, 5-nitro-2-acetylaminobenzimidazole, filtration, technology

НОВАЯ ВЫСОКОЭФФЕКТИВНАЯ ТЕХНОЛОГИЯ ПОЛУЧЕНИЯ 5-НИТРО-2-АЦЕТИЛАМИНОБЕНЗИМИДАЗОЛА

Сарвар САИДОВ[1] (sarvar-saidov-1989@bk.ru), Аскар АБДУРАЗАКОВ[1] (asqar2606@mail.ru), Риксибай КАРИМОВ[1] (rixsiboy.karimov@bk.ru), Алла ХВАН[1] (amkhvan@mail.ru), Хасан КАДИРОВ[2] (khasan.kadirov.71@mail.ru)
[1]Институт химии растительных веществ, Ташкент, Узбекистан
[2]Ташкентский химико-технологический институт, Ташкент, Узбекистан

Целью данной работы является создание новых лекарственных средств для сельского хозяйства на основе местного сырья, разработка высокоэффективной технологии их получения. В работе использованы отходы производства медамина, выпускаемого на опытном производстве Института химии растительных веществ АН РУз.

Изучены условия синтеза 5-нитро-2-ацетиламинобензимидазола. Структура полученного продукта исследована методами ИК, Масс, ^{1}H, ^{13}C ЯМР спектроскопии. Выявлены основные факторы, влияющие на процесс получения 5-нитро-2-ацетиламинобензимидазола. На основании проведенных исследований разработана технологическая схема получения 5-нитро-2-ацетиламинобензимидазол. Проведён подбор оборудования, монтаж опытной установки, проведены пуско-наладочные работы и отработана технология производства 5-нитро-2-ацетиламинобензимидазола. Получены опытные образцы продукта для биологических испытаний.

Ключевые слова: гетероцикл, нитрование, активированный уголь, биологически активный, 2-ацетиламинобензимидазол, 5-нитро-2-ацетиламинобензимидазол, фильтрация, технология

5-NITRO-2-ASETILAMINOBENZIMIDAZOL ISHLAB CHIQARISHNING YUQORI SAMARALI YANGI TEXNOLOGIYASI

Sarvar SAIDOV[1] (sarvar-saidov-1989@bk.ru), Askar ABDURAZAKOV[1] (asqar2606@mail.ru), Rixsibay KARIMOV[1] (rixsiboy.karimov@bk.ru), Alla XVAN[1] (amkhvan@mail.ru), Xasan KADIROV[2] (khasan.kadirov.71@mail.ru)
[1]O'simlik moddalari kimyosi instituti, Toshkent, O'zbekiston
[2]Toshkent kimyo-texnologiya instituti, Toshkent, O'zbekiston

Ushbu ishning maqsadi qishloq xo'jaligida mahalliy xom ashyo asosida yangi veterinary vositalar yaratish va ularni olish uchun yuqori samarali texnologiyasini ishlab chiqishdir. Ishda O'zbekiston Respublikasi Fanlar akademiyasining O'simliklar kimyosi institutida tajriba asosida ishlab chiqarilgan medamin ishlab chiqarish chiqindilari ishlatilgan.

5-nitro-2-asetilaminobenzimidazol sintezi jarayonlarini bir faktorli natijalar bilan o'rganilган. Olingan mahsulotning tuzilishi IQ, Mass, ^{1}H, ^{13}C YaMR spektroskopik usullari bilan tadqiq qilingan. 5-nitro-2-atsetilaminobenzimidazolni olish jarayoniga ta'sir qiluvchi asosiy omillar aniqlanган. O'tkazilgan tadqiqotlar asosida 5-nitro-2-asetilaminobenzimidazolni tayyorlashning texnologik sxemasi ishlab chiqildi. Uskunani tanlash, tajriba zavodini o'rnatish, 5-nitro-2-asetilaminobenzimidazol ishlab chiqarish texnologiyasini ishga tushirish va sinovdan o'tkazish. Biologik sinovlar uchun mahsulotning tajriba namunalari olingi.

Kalit so'zlar: geterotoxalqa, nitrollash, faollashtirilgan ko`mir, biologik faol, 2-atsetilaminobenzimidazol, 5-nitro-2-atsetaminobenzimidazol, filtrlash, texnologiya

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Introduction

According to the diversity of biological activity, heterocyclic compounds occupy almost the first place among other classes of organic compounds [1]. Benzimidazole and its derivatives are of interest both theoretically and practically. The fields of application of these compounds are very diverse. Benzimidazole derivatives are a wide and chemically diverse class of compounds.

Their biological activity is not limited to action against helminths, but extends to pathogenic fungi, viruses and bacteria [2]. Various benzimidazole derivatives have received wide practical application over the past 30 years as herbicides, fungicides, acaricides and anthelmintic drugs [3]. Thus, 2-methoxycarbonylaminobenzimidazole exhibits high anthelmintic activity against helminthiasis fasceliosis [4].

2-Acetylaminobenzimidazole (2-ACB) effectively affects fascioliasis and moniesioses, which are widespread among farm animals and annually cause enormous damage in animal husbandry [5]. In this work, we set the task of studying the nitration reaction of 2-acetylaminobenzimidazole in order to optimize and develop a technology for obtaining 5-nitro-2-acetylamibenzimidazole from 2-methoxycarbonylaminobenzimidazoles, which includes an acylation step followed by a nitration step of the acyl derivative and the identification of the biological activity of the products [6].

Further nitration of the acyl derivative leads to the expansion of a number of benzimidolyl derivatives with a wide spectrum of biological activity [7]. In addition, nitro derivatives are also interesting from the point of view of further reduction to amino derivatives [8], since amino groups are an active and convenient reaction center, in particular, for the addition of various physiologically active compounds [9].

In connection with the above, this work posed the task of studying the process of nitration of 2-acetylaminobenzimidazole in order to develop a technology for producing 5-nitro-2-acetylaminobenzimidazole using 2-methoxyca-rbonylaminobenzimidazole as a feed-

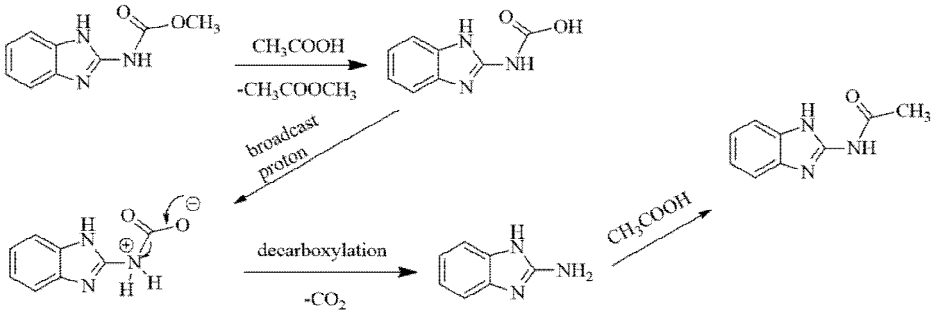

Figure 1. The reaction mechanism of obtaining 2-acetylaminobenzimidazole.

stock through the acylation step. The product 2-acetylaminobenzimidazole was obtained at the laboratory facility of the Academy of Sciences of the Republic of Uzbekistan Institute of Chemistry of Plant Substances.

Results and discussion

We have previously developed a convenient and simple method for the synthesis of 2-acetylaminobenzimidazole by acylation of 2-methoxycarbonylaminobenzimidazole with glacial acetic acid.

We have optimized the acylation process for 2-methoxycarbonylaminobenzimidazole. It was found that the optimal conditions are: process temperature 118 °C, quantitative ratio of starting materials (mol) 2-methoxycarbonylaminobenzi-midazole/glacial acetic acid, 1/13, reaction time 8 hours. The yield of the product of 2-acetylaminobenzimidazole under laboratory conditions is 97% with a purity of at least 98% of the main substance. The product 2-acetylaminobenzimidazole was also obtained at the experimental laboratory unit of the Institute of Chemistry of Plant Substances of the Academy of Sciences of the Republic of Uzbekistan. Received 5 series of samples of 2 kg. The unit yield was 97.8% with a purity of 98% [10].

2-Acetylaminobenzimidazole. The substance was recrystallized from 96% ethyl alcohol. The reaction product is an odorless white crystalline substance. The product yield is 95%. $C_9H_9N_3O$. Melting temperature= 282-284 °C (recrystallization from ethanol). 2-ACB was characterized by IR spectroscopy. In the IR spectra of 2-ACB, stretching vibrations of the C = O group appear in the region of 1688 cm-^{1}, and (N-H) - in the region of 3321 cm-^{1}. In the region of 1638 cm-^{1}, absorption bands of (C = N) groups are visible, the 1584 cm-^{1} band belongs to (CN) groups, (C = C) group absorbs at 1524 cm-^{1} and the 1456 cm-^{1} band belongs to (CH_3) group. ^{1}H NMR spectrum of ACB (400 MHz, solvent CD_3COOD has bands: 11.55 (1H, s, NH), 7.6-7.56 ppm (2H, AA`BB` -type, H-4.6), 7.32-7.28 m d. (2H, AA`BB`-type, H-5.7), 2.27 ppm (3H, s, CH_3). Methyl protons appear in the region of 2.27 ppm (3H singlet), and aromatic protons appear in the range of 7.6-7.28 ppm. ^{13}C NMR spectrum (400 MHz, solvent CD_3COOD) (d, ppm) is characterized by: 176.71, 154.94, 136.94, 136.49, 119.85, 119.52, 111.84, 111.28, 26.52 [11]. that the number of protons corresponds to the protons of 2-acetylaminobenzimidazole.

MS (70-eV) m / z (%) 175 (14) [M] +, 134 (3.2), 133 (100) [M-$COCH_2$] +, 105 (10.4) ESI-HRMS: calculated for $C_9C_9N_3O$: 175.0746, found 175.0755 MW 175.187. Rf-0.53 (acetone: benzole 3: 2 system).

In this work, we investigated the nitration reaction of 2-acetylaminobenzimidazole. The nitration reaction proceeds according to the classical mechanism of electrophilic substitution in the benzene nucleus under the action of a nitrating mixture, fuming nitric and concentrated sulfuric acids to form 5-nitro-2-acetylaminobenzimidazole. Below is a scheme for the nitration reaction of 2-acetylaminobenzimidazole:

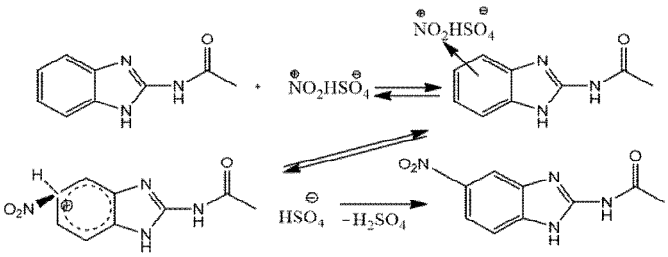

Figure 2. The reaction mechanism of 5-nitro-2-acetylaminobenzimidazole.

The nitration reaction was carried out under various conditions for 3-5 hours at a temperature of 5-30 ^{0}C and the quantitative ratio of the starting materials. (Table 1).

It can be seen from the table that at temperatures below 30 °C and a reaction time of less than 5 hours, the nitration process of 5-nitro-2-acetylaminobenzimidazole is less than 78%. In experiment No. 9, the reaction was carried out for 5 hours at a temperature of 30 °C and a quantitative ratio of 1: 6: 9 of the starting substances, the product yields up to 78.2% is observed. It also follows from table 1 that the main factors affecting the yield of the product are the temperature and the quantitative ratio of the starting materials.

The established optimal conditions were reproduced in a large laboratory setup.

To optimize the technological conditions of this process, we carried out a qualitative and quantitative assessment of the influence of a number of factors using the experiment planning matrix using the Box-Wilson method. On the basis of the optimization of the process, it has been established that the main factor influencing the process is the process temperature and the quantitative ratio

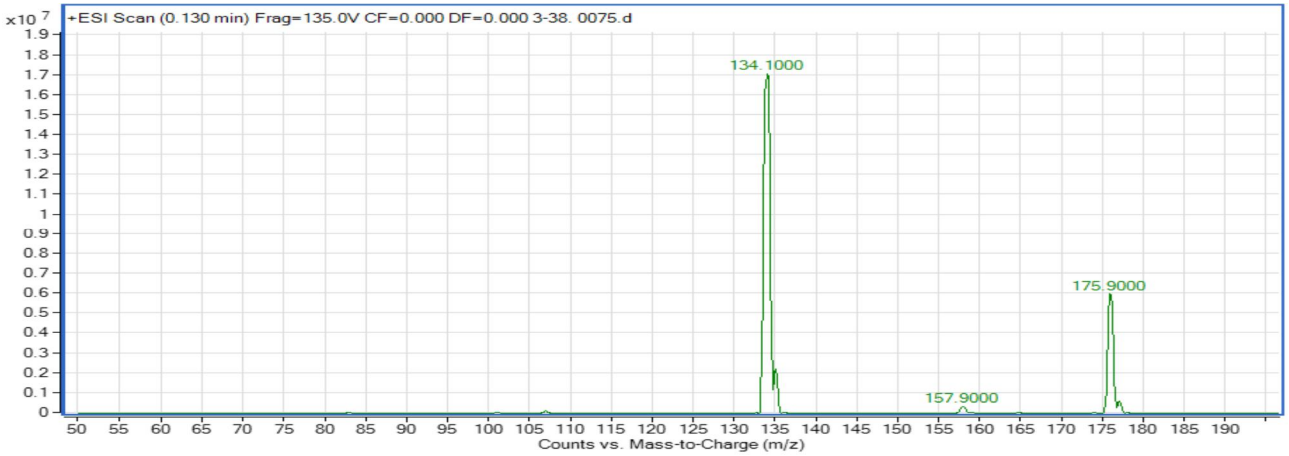

Figure 3. Mass spectrum of 2-acetylaminobenzimidazole.

Table 1

Influence of temperature, reaction time, quantitative ratio of starting materials of nitration of 5-nitro-2-acetylaminobenzimidazole

Experiment №	Temperature ^{0}C	Time hours.	Quantitative ratio of starting materials (mol) 2-ACB/HNO_3/H_2SO_4	Exit product %
1	5	3	1:4:7	61,1
2	15	3	1:4:7	68,2
3	30	3	1:4:7	72,4
4	5	4	1:5:8	63,0
5	15	4	1:5:8	74,0
6	30	4	1:5:8	76,4
7	5	5	1:6:9	70,5
8	15	5	1:6:9	76,3
9	30	5	1:6:9	78,2

Table 2

Solubility of 5-nitro-2-acetylaminobenzimidazole

№	Solvent	Conditional terms	The amount of solvent (ml) required to dissolve 1 g of the substance
1	Water	Very little soluble	3000
2	Ethanol	Very little soluble	1800
3	Methyl alcohol	Very little soluble	1400
4	Acetone	Slightly soluble	800
5	Chloroform	Slightly soluble	700
6	acetic acid	Dissolve	26

of the starting materials. The found optimal conditions were reproduced in a large laboratory setup, where 5-nitro-2-acetylaminobenzimidazole was obtained in 78% with a content of at least 98% of the basic substance [12].

5-nitro-2-acetylaminobenzimidazole.

The substance was recrystallized from 96% ethyl alcohol. The reaction product is an odorless white crystalline substance. $C_9H_8N_4O_3$. Melting temperature= 344-346 °C (recrystallization from ethanol).

In the IR spectrum, stretching vibrations of the NH group are found, which appear in the region of 3406.85 cm-^{1}. There are also bands (CN) at 2924.36 cm-^{1}, (C = O) at 1696.81 cm-^{1}, (C = N) 1630.76 cm-^{1}, (C-NO_2) 1529.81 cm-^{1}, (CH_3) 1465.73 cm-^{1}.

The ^{1}H NMR spectrum (400 MHz, solvent DMSO) of the product contains bands: 8.84 (1H, s, NH), 7.6-7.56 ppm. (2H, AA`BB`-type, H-4,6), 7.32-7.28 ppm (2H, AA`BB`-type, H-5,7), 2.27 ppm (3H, s, CH_3). Methyl protons appear at 2.27 ppm. (3H singlet), and aromatic protons appear in the 7.6-7.28 ppm region. M / z calculated for [M + H]: 220.185 found 221.185. Molecular weight 220.185. Rf -0.58 (acetone: benzene 3: 2 system).

Research methods

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

Results and discussion

Based on the results of our studies and optimization of the acylation process and subsequent nitration, a technological scheme for obtaining 5-nitro-2-acetylaminobenzimidazole was developed [12], including the 1-st stage - acylation of 2-methoxycarbonylaminobenzimidazole, the 2-nd stage - nitration of 2-acetylaminobenzimidazole (Figure 6): 3600 ml (ρ = 1.0498 g / cm^3) of glacial acetic acid is poured into the reactor (Glass. Vertical, cylindrical with a jacket, with a bottom drain, anchor stirrer, rotation speed - 75 rpm.

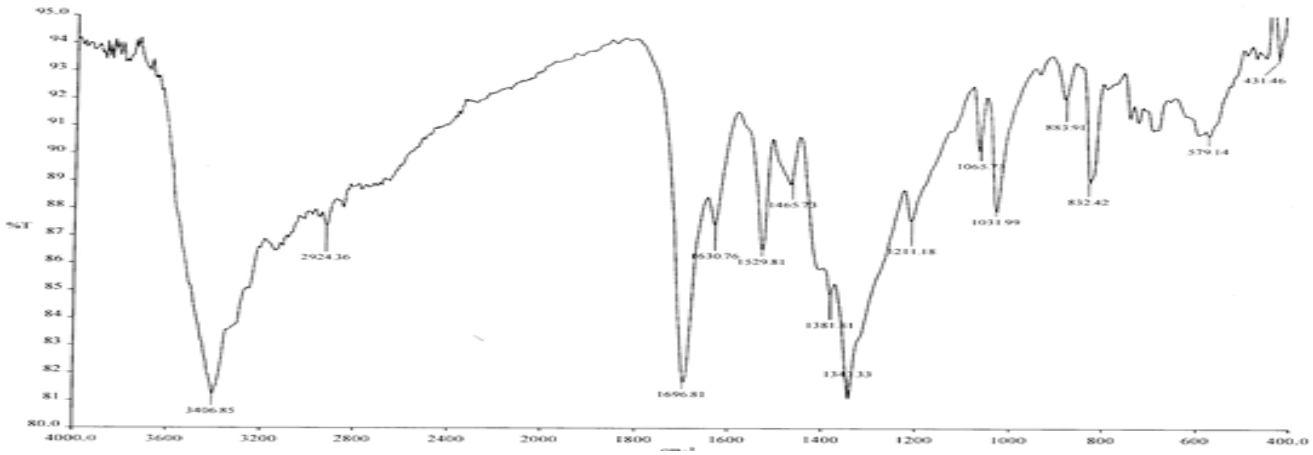

Figure 4. IR - spectrum of 5-nitro-2-acetylaminobenzimidazole.

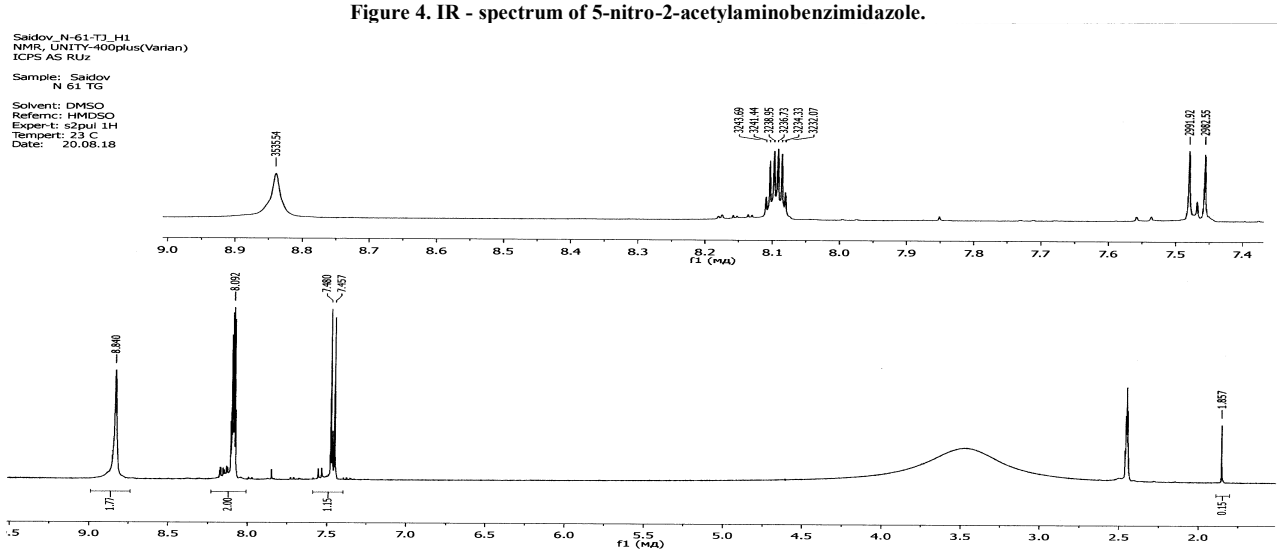

Figure 5. NMR ^{1}H spectrum of 5-nitro-2-acetylaminobenzimidazole.

Weight 23 kg; overall dimensions H-1m, d-0.8m. Manufacturer: China) R-2 with a capacity of 10 l, equipped with an electric stirrer, a heat exchanger, a thermometer, and 10 kg of 2-methoxycarbony-laminobenzimidazole is loaded from the bunker (Stainless steel. Vertical, cylindrical. The lid and bottom are spherical. Manufacturer: China) B-1 at working mixer. The reaction mixture is heated, stirred for 8 hours at 118 °C, after which the mixture is fed from the reactor into a glass container (Stainless steel. Vertical, cylindrical with bottom outlet. The lid and bottom are spherical. Manufacturer: China) G-4, the reaction mixture is left for 10 hours at room temperature. The dropped-out crystals are fed from the container to the F-5 suction filter (Stainless steel. Vertical, cylindrical, capacity - 50 l, diameter 400 mm, height - 750 mm, filtration area - 0.25 m2, filter material - belting. Manufacturer: China). The filtrate is sent for processing. The product 2-acetylaminobenzimidazole is fed into the reactor R-6 equipped with an electric stirrer, for recrystallization 50 l of ethyl alcohol are added from the measuring tank (Stainless steel. Vertical, cylindrical with bottom outlet. The lid and bottom are spherical. Manufacturer: China) M-7, 500 g of activated carbon from the bunker B-8 and heated for another 0.5 hour. Then the solution is filtered on the F-9 suction filter, the filtrate is sent to the C-10 crystallizer and left for a day. A day later, the formed precipitate of 2-acetylaminobenzimidazole is filtered on an F -11 suction filter, the filtrate is sent to a vacuum-circulating evaporator Vac-23. The precipitate of 2-acetylaminobenzimidazole is dried in a Dr-24 drying oven at temperature 60 ^{0}C to moisture content not more than 0.5%. The total yield of 2-acetylaminobenzimidazole is 842.9 g (92%). The dried product is fed to the R-12 nitration reactor.

In the reactor R-12, equipped with a mechanical stirrer, a reflux condenser and a thermometer, 16.8 l of concentrated sulfuric acid is loaded through a measuring vessel M-13.

Then the reactor R-12 is charged with 10 kg of 2-acetylaminobenzimidazole and dissolved in concentrated sulfuric acid at room temperature for 1 hour. Then, a nitrating mixture (12.6 l of nitric acid and 4.2 l of concentrated sulfuric acid) is added dropwise to the solution with vigorous stirring from a measuring vessel M-14. The reaction mixture is stirred for another 3 hours, maintaining the temperature not higher than 5°C. Then add dropwise 800 ml of nitric acid in a measuring vessel M-14 at the end of the loading of the components, the reaction mass is stirred while cooling for 1 hour. The reaction mass is poured into a container C-15 with chilled water and left for 24 hours, then filtered on an F-16 suction filter, the filtrate is sent to the drainage tank Dr-26 and, after neutralization, is sent to the sewer.

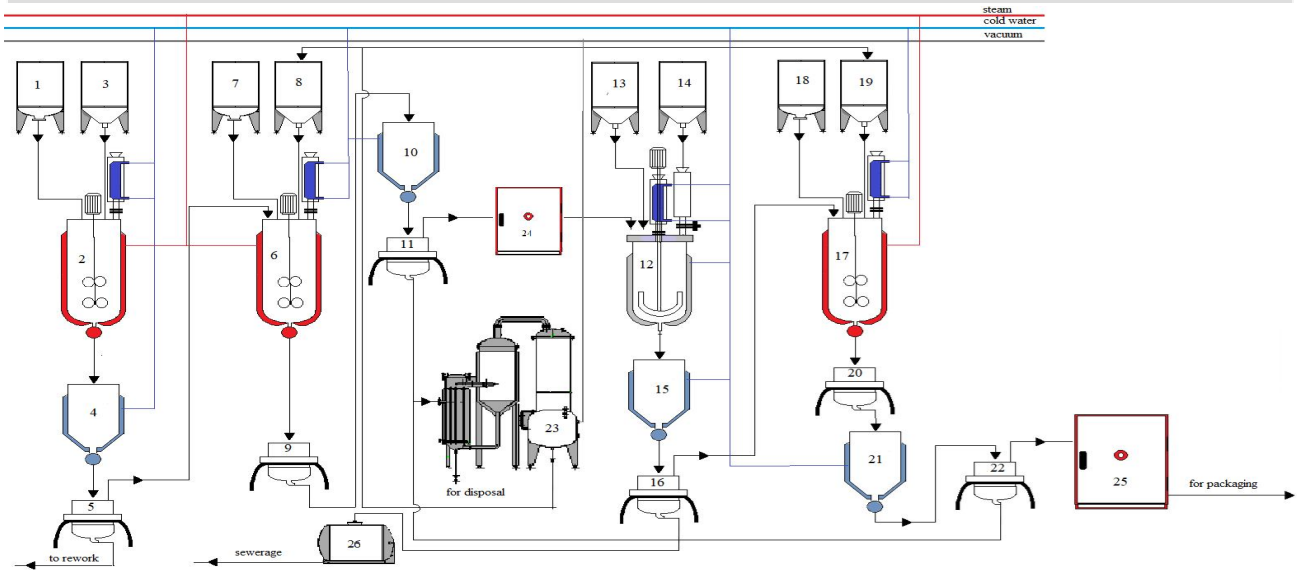

Figure 6. The technological scheme for the production of *5-nitro-2-acetylaminobenzimidazole*. 1,7,18-bins; 2.6.17-glass reactors; 3,8,13,14,19-merniks; 4,10,15,21-glass container for cooling; 5.9, 11, 16, 20, 22-filters; 12-glass nitration reactors; 23-vacuum-circulation evaporator; 24.25-oven for drying the finished product; 26-drainage tank.

The technical precipitate of 5-nitro-2-acetylaminobenzimidazole is washed with chilled water and sent to the R-17 reactor (equipped with an electric stirrer) for recrystallization, 50 l of ethanol is added from the M-19 meter and 500 g of activated carbon from the B-18 hopper are then heated further 0.5 hours. The reaction mixture is filtered on a F-20 suction filter, the filtrate is sent to a crystallizer K-21 and left for a day. After a day, the formed precipitate is filtered on a suction filter F-22, the filtrate is directed to a vacuum-circulating evaporator Vac-23.

The distillation of ethyl alcohol is sent to the measuring tanks M-8 and M-19, and the distillation residue for disposal. The 5-nitro-2-acetylaminobenzimidazole precipitate is dried in an Dr-25 drying oven at a temperature of 60°C to a moisture content of no more than 0.5%. The total yield of 5-nitro-2-acetylaminobenzimidazole is 9.8 kg (78%) with a content of at least 98% of the basic substance. The dried product is ground in a mill and sent to packaging.

Conclusion

Thus, a method for the synthesis of 5-nitro-2-acetylaminobenzimidazole has been developed. The structure of the synthesized compounds was proved by IR, Mass, ^{1}H ^{13}C NMR spectroscopy. A technological scheme for the preparation of 5-nitro-2-acetylaminobenzimidazole using 2-methoxycarbonylaminobenzimidazole as a starting material has been developed. A pilot plant for the production of 5-nitro -2-acetylaminobenzimidazole has been created. The product 5-nitro-2-acetylaminobenzimidazole was obtained in 78% yield.

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