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SYNTHESIS OF ISOMERIC ALKYL DERIVATIVES IN THE 2-METHYL-5-CHLOROBENZIMIDAZOLE SERIES

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Abstract

Origin of the problem. Currently, benzimidazoles and their derivatives are of great importance from theoretical and practical points of view among heterocyclic compounds. The presence in their molecule of a benzene and imidazole ring and an ambifunctional fragment containing a secondary nitrogen atom leads to their existence in various tautomeric forms and allows regioselective reactions of alkylation, acylation, arylsulfonylation and chlorosulfonylation at one or another center.

It should be noted that among benzimidazoles and their derivatives there are quite highly effective drugs that are successfully used in agriculture, medicine, pharmaceuticals and other industries. For example, Veliparib (ABT-888) is a potential anticancer drug that acts as a PARP *(poly(ADP-ribose) polymerase)* inhibitor. Veliparib during radiation therapy causes the whole brain to work effectively against brain metastases from non-small cell lung cancer *(NSCLC – –Non-small-cell lung cancer).* Additionally, Lerisetron (F-0930-RS) is a drug that acts as an antagonist (namely, it kills the virus) at the 5-HT3 receptor, which is a potent antiemetic and is being used in clinical trials to treat nausea associated with cancer chemotherapy.

Thanks to scientific research, the synthesis and introduction into practice of various pharmacologically active drugs is becoming important for restoring the health of many patients. The synthesis of new derivatives of heterocyclic compounds, the study of possible reaction mechanisms, and the implementation of targeted synthesis of biologically active substances are also important.

Therefore, the study of alkylation reactions of benzimidazoles and their derivatives, identification of the main factors influencing the course and direction of reactions, and the search for biologically active substances among synthesized compounds is an urgent task.

Purpose of the work. Synthesis of N^{endo}-protected 2-methyl-5-chlorobenzimidazoles (N-alkyl derivatives), determination of the type and ratio of isomers, determination of factors influencing the course of the reaction and study of the structure of the resulting compounds (IR, ^{1}H and ^{13}C NMR spectroscopy).

Methodology. Carrying out reactions of introducing an alkyl group into the 2-methyl-5-chlorobenzimidazole molecule with alkyl halides in a protic solvent (alcohol) in the presence of alkalis and studying the proposed mechanism. Studying the structure of substances using IR,^{1}H and^{13}C NMR spectroscopy methods.

Scientific novelty. Taking into account the main factors influencing the course of reactions, new isomeric 1,2-dialkyl derivatives were synthesized under various conditions and an optimal method for obtaining the target products was developed.

Results obtained. The synthesis of new dialkyl isomers in the series of benzimidazoles containing various alkyl groups has been carried out. The structure of the substances was analyzed based on IR,^{1}H and^{13}C NMR spectroscopy data and their correspondence to the proposed structures was proven.

Keywords: *2-methyl-5-chlorobenzimidazole, alkylation, isomers, alkyl halides, electrophilic substitution, column chromatography*

Peculiarities:

— effective methods for the synthesis of 2-methyl-5-chlorobenzimidazole, 1,2-dialkyl-5-chlorobenzimidazoles have been created;

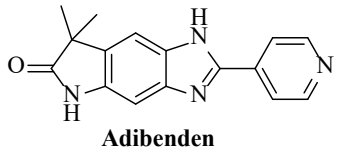
— by the alkylation reaction of 2-methyl-5-chlorobenzimidazole in an alkaline medium, methods have been developed for the preparation of isomeric 1,2-dialkylbenzimidazoles in high yields;

— the reliability of the research results is confirmed on the basis of data obtained using modern methods of IR,^{1}H and^{13}C NMR spectroscopy, chromatography (TLC, column) and others.

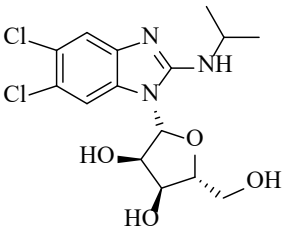
Introduction

Currently, many studies are being carried out on the basis of heterocyclic compounds, in particular benzimidazoles. The reason is that there are numerous pharmacological and biologically active substances among the five-membered imidazole ring compounds containing two nitrogen atoms.

Previously synthesized substances still attract the attention of organic chemists and pharmacists due to their high biological activity and low toxicity. In particular, one of the important issues is the successful use of benzimidazole derivatives in agriculture and medicine against various diseases.



Adibenden
(Phosphodiesterase inhibitor)



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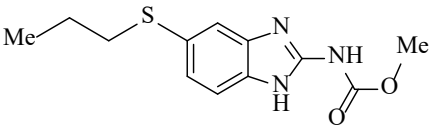
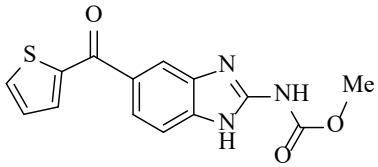
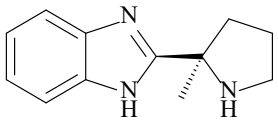
(antiviral agent)



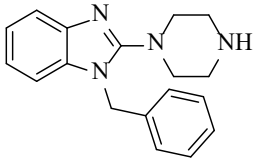
Albendazole
(Anthelmintic)



Nocodazole
(anti-cancer drug)



Vleparib
(anti-cancer drug)



Lerisetron
(antihistamine)

Research into the development of heterocyclic compounds began much earlier, and research is currently being conducted in many countries around the world based on this class of compounds. Among the compounds containing the benzimidazole heterocycle, many drugs have been found that are effectively used in medical practice and agriculture (veterinary medicine). This is due to the fact that the benzimidazole ring is a pharmacophore ring that is included in various drugs. It should be noted that previ-

ous studies have identified among benzimidazoles anticancer (Tahlan S., Kumar S., Narasimhan B., 2019; Tahlan S. et al., 2019), anticholinesterase inhibitors (Tahlan S., Ramasamy K., Lim S. M., Shah S. A.A., Mani V., Narasimhan B., 2019), as well as anthelmintic (Alpan A. S. et al., 2013), anti-inflammatory (Andrzejewska M. et al., 2004), antimalarial (Shaharyar M. et al., 2017), antiviral (Yoon Y. K. et al., 2015) and antimicrobial (Tahlan S. et al., 2019) drugs:

Information on the use of benzimidazoles in medicine and agriculture, and their analogues (benzoxazoles, benzothiazoles) is given in the following articles (Kakkar S. et al. 2018; Tahlan S., Kumar S., Narasimhan B., 2019; Prajapat P., 2018), published in foreign journals. Among them are benzimidazoles, an important class of heterocyclic compounds, the research of which began many years ago and is expanding every year. In the synthesis of benzimidazoles, readily available o-phenylenediamine and its various derivatives (amidines, acyl products) substituted in the benzene ring and amino group are used as the main starting material. On the other hand, aliphatic and aromatic aldehydes, as well as carboxylic acids, are widely used as electrophilic reagents. To increase the efficiency of reactions, cyclization is usually carried out in the presence of catalysts.

Methods and materials

Solvents: hexane, cyclohexane, chloroform, methyl alcohol, ethyl alcohol, acetone, acetic acid were dried and purified by traditional distillation. IR spectra of the compounds were obtained on a Perkin-Elmer IR-Fourier 2000 spectrometer in tablets with KBr, mass spectra on MS-30 (Kratos), and 1H and 13C NMR spectra were obtained on JNM-ECZ 400 and JNM- ECZ 600 (JEOL, Japan) (internal standard TMC, in δ-scale) with an operating frequency of 400 and 600 MHz in solutions of deuterochloroform ($CDCl_3$), deuteromethanol (CD_3OD) and deuterium oxide (D_2O). Thin layer chromatography (TLC) analysis was carried out on Sorbfil (Russia) and Whatman® UV-254 (Germany) plates. The melting point of the synthesized compounds was determined using Boetius (Germany) and MEL-TEMP (USA) instruments.

Synthesis of 2-methyl-5-chlorobenzimidazole (1) (improved method)

24.7 g (0.17 mol) of 4-chloro-2-nitroaniline, 24 g (0.43 mol) of Fe powder and 48.9 ml (51.4 g) of ice-cold AcOH and 142.8 ml of HCl (32%) were placed in a 1-liter flask. The mixture was heated to 60–70 °C and boiled (105––110 °C) for 2 hours. The mixture is cooled, and the resulting precipitate is filtered and dried at 20–25 °C. The product was neutralized with NaOH solution and then treated with ethanol. The solution was filtered, the ethanol filtrate was diluted with water, and the resulting precipitate was filtered and dried. As a result, 19.5 g (83.4%) of substance (**1**) was synthesized, melting point 205–206 °C, Rf=0.38 (benzene: methanol – 5:1).^{1}H NMR spectrum (CD_3OD, δ, ppm, J/Hz, 400 MHz): 2.56 (3H, s, CH_3), 7.17 (1H, dd, J=1.6, 8.4, H-6), 7.43 (1H, d, J=8.4, H-7), 7.47 (1H, d, J=1.8, H-4).

Synthesis of isomers of 1,2-dimethyl-5-chlorobenzimidazole (2) and 1,2-dimethyl-6-chlorobenzimidazole (3)

Method A *(in the presence of acetone and potash)*: 1.665 g (0.01 mol) of mebinol, 1.5 ml (d = 2.28 g/ml, 2.84 g, 0.01 mol) methyl iodide, 1 g (0.0072 mol) of dried potash, 80 ml of acetone were placed in a one-neck flask with a volume of 250 ml. water bath through reflux for 6 hours and leave overnight. The solvent was then distilled off and the product was recrystallized from cyclohexane (30 ml). As a result, we obtained 1.03 g (62%) a mixture of isomeric products (2.3) with a melting point of 99–100 °C, Rf = 0.34 (benzene: methanol – 5:1) (or: Rf = 0.81 (chloroform: methanol – 10:1)).

Method B *(in the presence of alcohol and alkali)*: 4.995 g (0.03 mol) mebinol, 3.74 ml (d = 2.28 g/ml, 8.52 g, 0.06 mol) methyl iodide, 1.2 g (0.03 mol) were poured into a 500 ml one-neck flask. sodium hydroxide and 80 ml of alcohol, connecting a reflux refrigerator, the mixture was boiled in a water bath for 7 hours and left overnight. The solution was then filtered and the filtrate was diluted with 50 ml of water, then extracted with 30 ml of chloroform (2 times) and the extract was washed with 300 g of 5% NaOH (3 times). The chloroform solution was dried over anhydrous Na_2SO_4 and filtered. The solvent was distilled off and recrystallized from cyclohexane (40 ml)

using a hot filter. As a result, 4.09 g (81.8%) of a mixture of isomeric products (**2,3**) was obtained, melting point 99–100 °C, Rf=0.64 (chloroform: methanol – 20:1).

Compound 2: ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz, 400 MHz): 2.58 (3H, s, 2-CH_3, 3.67 (3H, s, N-CH3), 7.15 (1H, dd, J=8.5, J=0.6, H-7), 7.19 (1H, dd, J=8.5, J=1.9, H-6), 7.25 (1H, br.d, J=2.0, H-4)^{13}C NMR ($CDCl_3$, δ, ppm, 100 MHz): 13.97 (2-). CH_3), 30.09 (N-CH3), 109.19 (C-7), 118.89 (C-4), 122.47 (C-6), 127.47 (C-5), 134.54 (C-7a), 141.28 (C-4a), 152.84 (C-2).

Compound 3: ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz, 400 MHz): 2.58 (3H, s, 2-CH_3), 3.69 (3H, s, N-CH_3), 7.18 (1H, dd, J=8.5, J=1.8, H-5), 7.25 (1H, br.d, J=2.0, H-7), 7.56 (1H, dd, J=8.6, J=0.5, H-4).^{13}C NMR ($CDCl_3$, δ, ppm, 100 MHz): 14.00 (2-CH_3), 30.12 (N-CH_3), 109.68 (C-4), 119.88 (C-7), 123.55 (C-5), 127.83 (C-6), 136.53 (C-4a), 143.46 (C-7a), 153.26 (C-2).

The ratio of isomers **2** and **3** based on the integrated intensity of proton signals in the ^{1}H NMR spectra was 51.3%: 48.7%, respectively.

Preparation of isomers of 1-ethyl-2-methyl-5-chlorobenzimidazole (4) and 1-ethyl-2-methyl-6-chlorobenzimidazole (5)

In a one-neck flask with a volume of 500 ml, 3.33 g (0.02 mol) of 2-methyl-5-chlorobenzimidazole, 4.5 ml (d = 1.47 g/ml, 6.54 g, 0.06 mol) ethyl bromide, 0.8 g (0.02 mol) sodium hydroxide, 60 ml were placed alcohol and boiled through reflux in for 6 hours and the reaction mixture was left overnight. The solution was filtered and the filtrate was extracted with 30 ml chloroform (2 times), then washed with 300 g 5% NaOH (3–4 times) and 50 ml water (3 times). The extract was dried over anhydrous Na_2SO_4 and filtered. The solvent was distilled off, and the dry residue was recrystallized from 30–40 ml of cyclohexane. As a result, 2.6 g (78%) mixture of isomeric products (4.5) was synthesized, melting point 104–105 °C, Rf = 0.81 (chloroform: methanol – 15:1), Rf = 0.66 (chloroform: methanol – 20:1).^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz, 400 MHz): 1.39 (3H, t, J=7.2, CH_2CH_3), 2.58 (3H, s, 2-CH_3), 4.12 (2H, quartet, J=7.3, CH_2CH_3), 7.18 (2H, d, J=8.2, H-6.7), 7.65 (1H, d, J=1.2, H-4).^{13}C NMR spectrum ($CDCl_3$, δ, ppm, 100 MHz): 13.90 (N-CH_2CH_3), 14.99 (2-CH_3), 38.78 (N-CH_2CH_3), 109.24 (C-7), 109.75 (C-4), 118.98 (C-6), 127.41 (C-5), 133.46 (C-7a), 143.69 (C-4a), 152.55 (C-2).

The ratio of isomers **4** and **5** based on the integrated intensity of proton signals in the NMR spectra was 95%: 5%, respectively.

Synthesis of isomers of 1-butyl-2-methyl-5-chlorobenzimidazole (6) and 1-butyl-2-methyl-6-chlorobenzimidazole (7) and preparation of their hydrochlorides (8,9)

4.995 g (0.03 mol) of 2-methyl-5-chlorobenzimidazole (mebinol), 6.5 ml (d= 1.276 g/ml, 8.22 g, 0.06 mol) butyl bromide, 1.2 g (0.03 mol) caustic were placed in a round-bottomed one-neck flask with a volume of 500 ml sodium and 90 ml alcohol and the mixture was refluxed for 7–8 hours and left overnight. The solution in the flask was washed with 200 g NaOH (5%) (2–3 times), extracted with 40 ml chloroform (2 times) and washed with 50 ml water (3 times) until pH=7–8. The chloroform solution was dried over anhydrous Na_2SO_4 and filtered. The solvent was distilled completely in vacuum (on a rotary evaporator). As a result, a mixture of oily isomer was obtained: 1-butyl-2-methyl-5-chlorobenzimidazole (**6**) and 1-butyl-2-methyl-6-chlorobenzimidazole (**7**) with a yield of 67%. The purity of the oily product was examined by TLC (Rf=0.69, chloroform: methanol – 20:1) and was determined to be pure (one spot).

Product (**6,7**) was dissolved in 20–30 ml of absolute cyclohexane, HCl (NaCl + H_2SO_4 (conc.)) gas was continuously passed into the product solution for 30 minutes, the resulting precipitate was filtered, washed with cyclohexane (2 times, 10–15 ml) and dried. The resulting hydrochloride (**8,9**) of the isomers 1-butyl-2-methyl-5-chlorobenzimidazole and 1-butyl-2-methyl-6-chlorobenzimidazole was isolated in the form of white crystals with a yield of 3.8 g (76%), melting point 166–168 °C, Rf=0.8 (chloroform: methanol – 20:1).

Compound 8: ^{1}H NMR spectrum (D_2O, δ, ppm, J/Hz, 400 MHz): 0.99 (3H, t, J=7.2, $(CH_2)_3$-CH_3), 1.41–1.48 (2H, m, CH-$_2CH_2CH_2CH_3$), 1.84–1.93 (2H, m, CH_2CH-$_2CH_2CH_3$), 2.91 (3H, s, 2-CH_3), 7.53 (2H, dd, J=2.1, J=8.4, H-4.6), 7.86 (1H, d, J=8.4, H-7).

Compound 9: ^{1}H NMR spectrum (D_2O, δ, ppm, J/Hz, 400 MHz): 0.98 (3H, t, J=7.2, $(CH_2)_3$-CH_3), 1.41–1.48 (2H, m, CH-$_2CH_2CH_2CH_3$), 1.84–1.93 (2H, m, CH_2CH-$_2CH_2CH_3$), 2.91 (3H, s, 2-CH_3), 7.66–7.76 (3H, m, H-4,5,7).

Compounds 8 and 9: ^{13}C NMR spectrum (D_2O, δ, ppm, 100 MHz): 11.62, 13.42, 19.90, 30.81, 30.89, 45.63, 112.97, 114.10, 114.17, 115.40, 126.61, 127.09, 129.02, 130.87, 131.04, 131.62, 131.85, 132.90.

Synthesis of 1-benzyl-2-methyl-5-chlorobenzimidazole and 1-benzyl-2-methyl-6-chlorobenzimidazole (10, 11)

In a one-neck flask with a volume of 500 ml, 4.995 g (0.03 mol) of mebinol (**1**), 6.9 ml (d = 1.1 g/ml, 7.59 g, 0.06 mol) benzyl chloride, 1 g (0.025 mol) NaOH and 60 ml of ethanol were placed, the mixture was boiled 8 hours through reflux and left for 24 hours. Then the solution in the flask was filtered and the filtrate was treated with 5% (250 g) NaOH (3 times), then extracted with chloroform 2 times (30 ml each), then washed 2–3 times (50 ml each) with water to neutral pH. The extract was dried over anhydrous Na_2SO_4 and filtered. The solvent was distilled to dryness, and the residue was recrystallized from 30 ml of hexane. A 4.09 g (81.8%) mixture of isomeric products was obtained; after purification by CC, individual substances **10** (9.1%) and **11** (72.7%) were isolated.

- **10:** Melting point 101–102 °C, Rf=0.77 (chloroform: methanol – 20:1). ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz, 600 MHz): 2.56 (3H, s, 2-CH_3), 5.30 (2H, s, CH_2-Ph), 7.02 (2H, m, H–2',6'), 7.30 (3H, m, H-3',4',5'), 7.11 (1H, d, J=8.5, H-7), 7.16 (1H, dd, J=8.5, 1.9, H-6), 7.69 (1H, d, J=1.9, H-4).
- **11:** Melting point 98–100 °C, Rf= 0.73 (chloroform: methanol – 20:1). ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz, 600 MHz): 2.56 (3H, s, 2-CH_3), 5.28 (2H, s, CH_2-Ph), 7.03 (2H, m, H–2',6'), 7.32 (3H, m, H-3',4',5'), 7.19 (1H, d, J=1.9, H-7), 7.21 (1H, dd, J=8.5, 1.9, H-5), 7.62 (1H, dd, J=8.2, H-4).

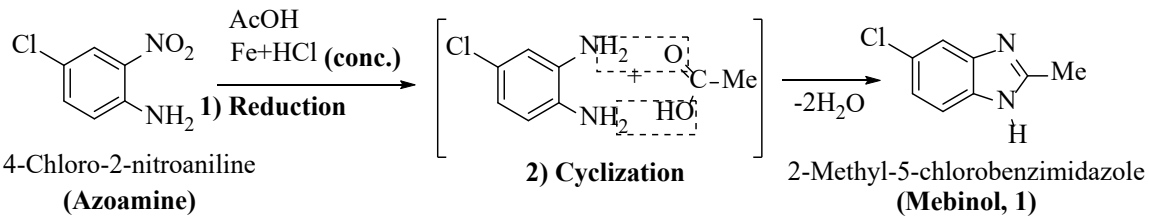
Results obtained and their discussion

The object of study, 2-methyl-5-chlorobenzimidazole (mebinol), is of great interest both theoretically and practically among heterocyclic compounds. The presence of benzene and imidazole rings and the N-H group in it allow various exchange and condensation reactions to occur with high yields. The dialkyl products obtained from this basis are mainly used in medicine, agriculture and pharmaceuticals.

We initially conducted studies on a one-step reduction-cyclization reaction in the presence of acetic acid, azoamine, and iron powder and prepared the resulting heterocyclic product for use in the synthesis of dialkyl derivatives needed for our main experiments.

For this purpose, reactions of 2-methyl-5-chlorobenzimidazole [12] with alkyl halides in K_2CO_3/acetone or NaOH/alcohol were carried out under optimal conditions and temperatures, and the expected substances were synthesized in high yields. Homological changes in the obtained dialkyl products and some physicochemical properties were analyzed and an appropriate production procedure was developed.

2-methyl-5-chlorobenzimidazole (**1**) was synthesized using an improved initial reaction method. To do this, using 4-chloro-2-nitroaniline (azoamine), glacial acetic acid and iron powders in appropriate molar proportions, concentrated hydrochloric acid was diluted in a ratio of 5:1 and heated in a water bath at 70–80 °C for 2 hours until the release of H_2 gas stops. The mixture was then left at this temperature for 1 hour and again heated at 90–100 °C for 2 hours. A 20% solution of sodium hydroxide was added until the pH of the medium reached 9–10, then the precipitate that formed was filtered:

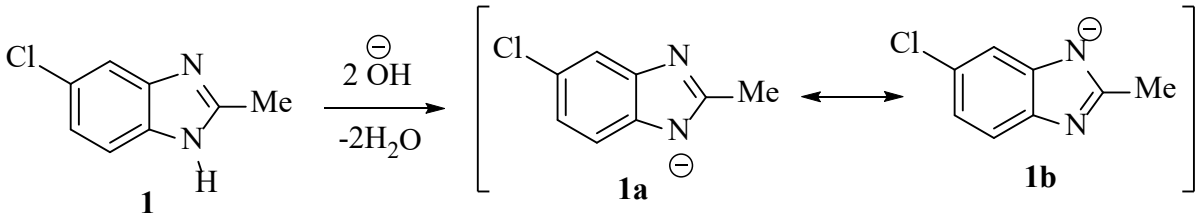


4-Chloro-2-nitroaniline **(Azoamine)**

2-Methyl-5-chlorobenzimidazole **(Mebinol, 1)**

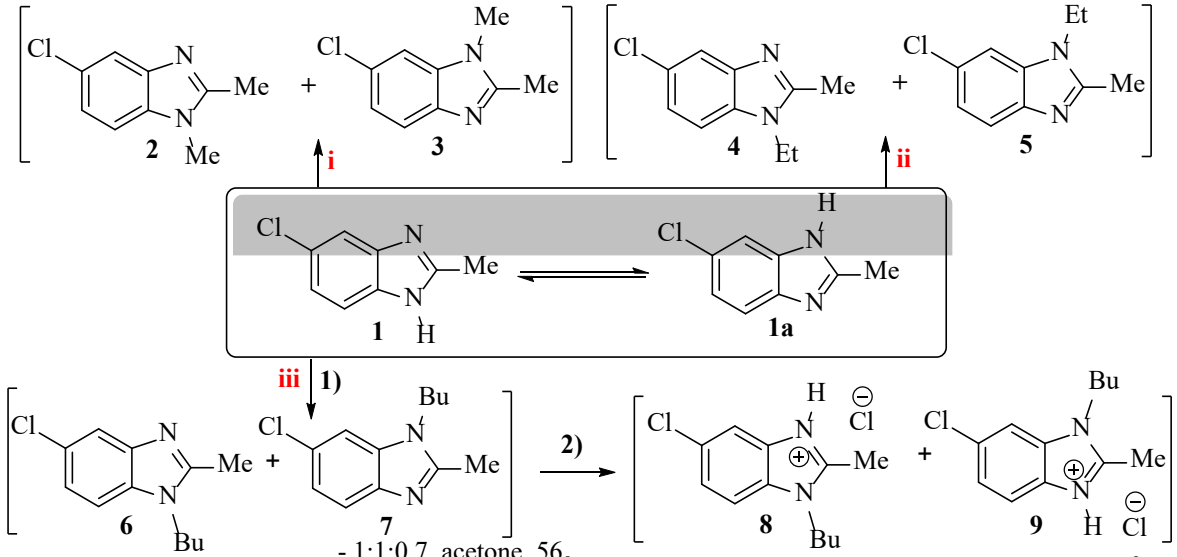
The reaction mixture was washed with water until neutral, alcohol was added, the mixture was heated for 1 hour and filtered hot. Alcohol was distilled from the filtrate, 3 times more water was added to the remaining residue (in a ratio of 1:3, by volume), and the precipitate that formed was filtered off. At the end of the reaction, the product was purified by recrystallization from 30% alcohol to obtain 2-methyl-5-chlorobenzimidazole (**1**) in 83.4% yield. It is noteworthy that this reaction was carried out using the "one-pot synthesis" method. During the reaction, reduction and cyclization reactions occur; in this case, an intermediate reduction product, 2-amino-4-chloroaniline, is first formed, which then reacts with carboxylic acids and the corresponding 2-methyl-5-chlorobenzimidazole (**1**) is released in high yield. The hydrogen atom of the N-H group, the imidazole ring of benzimidazole, is active and readily undergoes electrophilic substitution in the presence of alkyl halides. Therefore, alkylation reactions of the resulting 2-methyl-5-chlorobenzimidazole (**1**) were carried out under various conditions.

It is known that 2-substituted benzimidazoles can undergo prototropic tautomerism under alkaline conditions, therefore, in S_E reactions, isomeric 5/6-substituted benzimidazoles can be formed:



Selective alkylation reactions of 2-methyl-5-chlorobenzimidazole (**1**) were carried out in acetone/potash or alcohol/alkali systems. However, in acetone the reaction does not proceed to completion, and the yield is relatively low. It was found that the alcohol/alkali system was a more suitable condition for the synthesis of dialkyl products in high yields.

It was initially concluded that the reaction produced only one isomeric dialkyl product. Indeed, the resulting alkyl products give one spot on TLC and have a small melting range, which indicate that a single substance is formed. However, doubling the amounts of proton and carbon atom signals in the ^1H and ^{13}C NMR spectra and their manifestation in very close regions confirms the formation of a mixture of isomers.



i: Method A: 1:MeI:K_2CO_3 - 1:1:0.7, acetone, 56^0C, 6 h; **Method B: 1**:MeI:NaOH - 1:2:1, ethanol, 78^0C, 7 hours.

ii: 1: EtBr:NaOH - 1:3:1, ethanol, 78^0C, 6 h.

iii: 1) Method B: 1: BuBr:NaOH - 1:2:1, ethanol, 78^0C, 7-8 hours; **2)** Cyclohexane, HCl (gas) [NaCl + H_2SO_4].

Methyl iodide, ethyl bromide, butyl bromide and benzyl chloride were selected as alkyl halides. Initially, the reactions were carried out in two ways with methyl iodide, ethyl and butyl bromides. It is noteworthy that in methylation reactions a mixture of two isomers (**2,3**) was obtained with a yield of 62% in the acetone/potash system and 81.8% in the alcohol/alkali system:

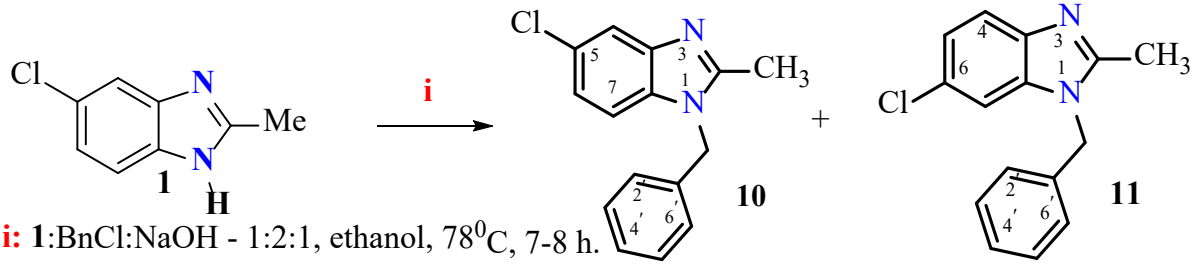
Therefore, in subsequent studies we used the alcohol/alkali system. In particular, the ethylation reaction was also carried out according to this system and isomeric products (**4,5**) were obtained with a yield of 78%. The bottling reaction was also carried out according to method **B**, in which oily alkyl products (**6,7**) are formed with a yield of 67% (Rf = = 0.69, chloroform: methanol-20:1) [13]. However, this mixture of isomers also produces one spot on TLC. To obtain their hydrochlorides (**8,9**), dry gaseous HCl was passed through a solution of substances (**6,7**) in the form of a base in absolute cyclohexane (yield of hydrochloride (**8,9**) 76%, Rf=0.8, chloroform: methanol – 20:1). The structures of the obtained compounds were determined using spectral and X-ray diffraction analysis (XRD) (Juraev B., Oxunxo'jayeva Z., Tojiboev A., Bobakulov Kh., Turgunov K., Elmuradov B., Zokhidov K., 2023).

Table 1. *Some physicochemical data of compounds (1-11)*

Compound	Brutto formula	Melting point,^{0}C	Rf (system)	Yield, %
1	$C_8H_7N_2Cl$	205–206	0.38 (**A**)	83.4
2,3 (isomer)	$C_9H_9N_2Cl$	99–100	0.34 (**A**); 0.81 (**B**)	62 (method A) 81.8 (method B)
4,5 (isomer)	$C_{10}H_{11}N_2Cl$	104–105	0.39 (**A**); 0.88 (**C**)	58 (method A) 78 (method B)
6,7 (isomer)	$C_{12}H_{15}N_2Cl$	oil	0.69 (**D**)	67
8,9 (isomer)	$C_{12}H_{16}N_2Cl_2$	166–168	0.8 (**D**)	76
10	$C_{15}H_{13}N_2Cl$	101–102	0.77 (**D**)	9.1
11	$C_{15}H_{13}N_2Cl$	98–100	0.73 (**D**)	72.7

System: *benzene: methanol – 5:1 (**A**); chloroform: methanol – 10:1 (**B**); chloroform: methanol – 15:1 (**C**); chloroform: methanol – 20:1 (**D**)*

Continuing the research, we studied benzylation in the presence of alkali in alcohol by boiling a mixture of reagents in the ratio: **1**: BnCl: NaOH – 1:2:1 for 7–8 hours (78^{o}C). After the mixture of reaction products (**10,11**) was separated by extraction ($CHCl_3$), washed with an aqueous (5%) NaOH solution and dried over Na_2SO_4 (anhydrous), then the solvent (chloroform) was distilled. It should be emphasized that the resulting mixture of isomers forms two spots in TLC, which are separated by column chromatography. Thus, a mixture of 1-benzyl-2-methyl-5-chlorobenzimidazole (**10**, 9.1%) and 1-benzyl-2-methyl-6-chlorobenzimidazole (**11**, 72.7%) was obtained in the form of light yellow crystals with a total yield of 81.8%:



i: **1**:BnCl:NaOH - 1:2:1, ethanol, 78^{0}C, 7-8 h.

The results of ^{1}H NMR spectroscopy show that the ratio of isomeric benzyl products (**10:11**) is ~1:9. The spectra of individual isomers (**10** and **11**), isolated in pure form by column chromatography, are presented in Figures 1 and 2. In particular, in the spectrum of substance 10 (Figure 1), obtained in $CDCl_3$, in the region of 2.56 ppm. chemical

shifts are observed in the form of a three-proton singlet (3H, s), belonging to the CH_3 group, at 5.30 ppm. two-proton singlet (2H, c) of the aliphatic protons of the benzyl group.

Figure 1. *^{1}H NMR spectrum of 1-benzyl-2-methyl-5-chlorobenzimidazole (10) in $CDCl_3$*

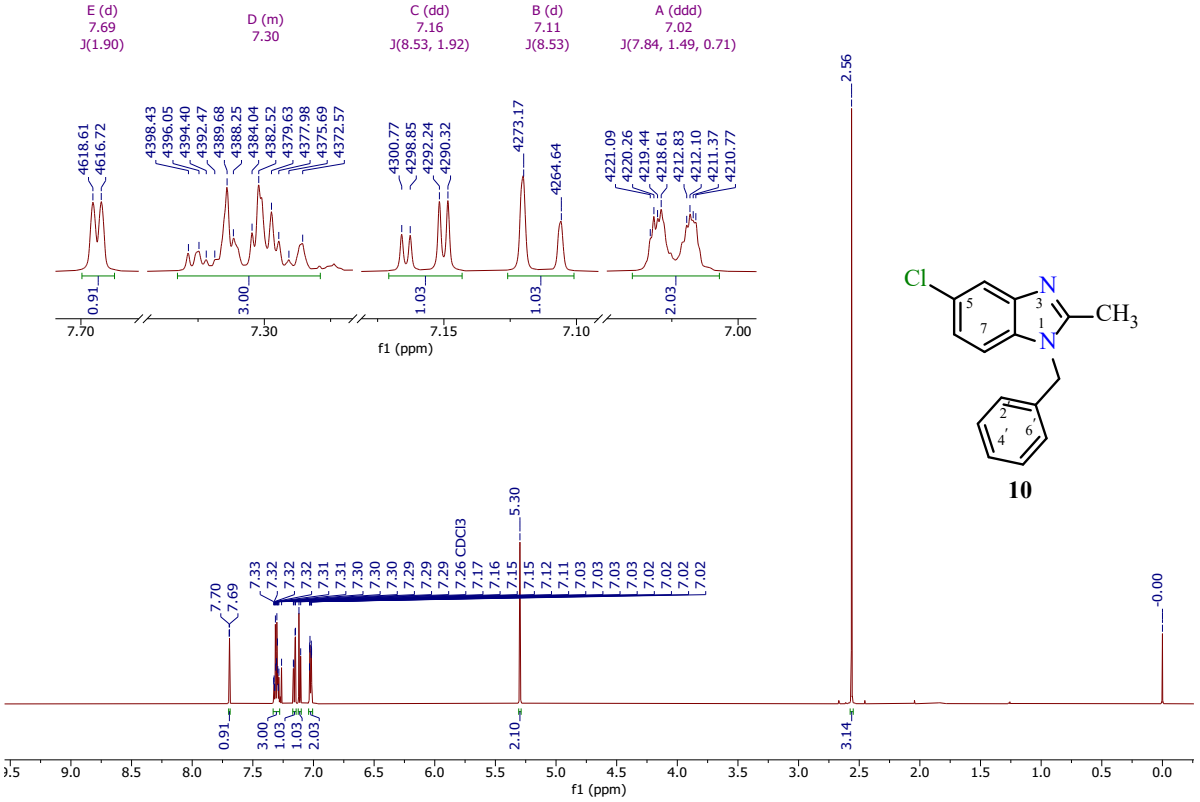
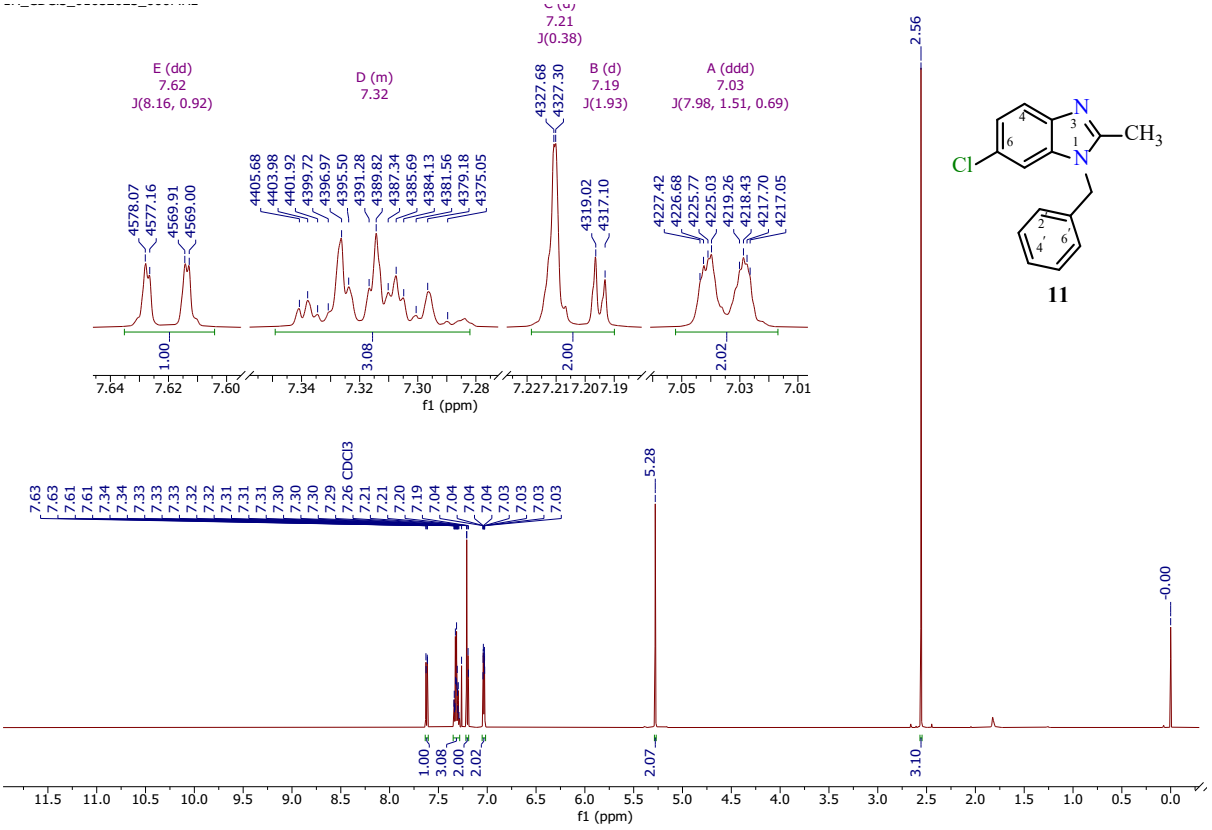


Figure 2. *^{1}H NMR spectrum of 1-benzyl-2-methyl-6-chlorobenzimidazole (11) in $CDCl_3$*



There are also signals in the region of 7.02 ppm. in the form of a two-proton multiplet (2H, m), belonging to the equivalent hydrogens of the benzyl fragment in positions 2′ and 6′, signals at 7.30 ppm. in the form of a three-proton multiplet (3H, m) were assigned to the H-3′,5′ protons (Fig. 1).

Furthermore, the presence of proton signals at 7.69, 7.11, and 7.16 ppm of aromatic hydrogen benzymidazole fragments at positions C-4, C-6, and C-7 manifests as a single-proton doublet (J=1.9, H-4; J=8.5, H-6) and doublet (J=8.5, 1.9, H-7). These data confirm the structure of compound **10** (Fig. 1).

The ^{1}H NMR spectrum of compound **11** (Fig. 2) also shows the presence of three-proton signals at H 2.56 and 5.28 ppm, belonging to the CH_3 group, and two-proton singlet signals specific to the methylene group of the benzene fragment.

Along with signals in the form of two-proton (2H, m, H-2′, H-6′) multiplets at δ 7.03 and 7.32 ppm, and in the form of three-proton multiplets (H-3′, H-4′, H-5′) corresponding to the aromatic hydrogens of the benzyl group, as well as at 7.19, 7.62 and 7.21 ppm, signals of benzimidazole aromatic hydrogens appear as a doublet (d, J=1.9, H-7; J=8.2, H-4) and a doublet of doublets (J=8.5, 1.9, H-5). These data confirm our understanding of the structure of this molecule (Pic. 2).

Conclusions

The alkylation reactions of 2-methyl-5-chlorobenzimidazole with various alkyl halides were carried out under different conditions: acetone/potassium carbonate and ethanol/alkali. Studies have shown that when using the ethanol/alkali system, alkylation products are formed with relatively high yields.

It was established that upon alkylation with methyl iodide, ethyl bromide, butyl bromide, and benzyl chlorides, a mixture of isomers is formed. It should be noted that with an increase in the alkyl chain length in the series of alkyl halides, the melting point of the products decreases, and in some cases (during butylation), oily isomeric products are formed. The ratio of isomers formed in the methylation, ethylation, and butylation reactions was determined based on the analysis of ^{1}H NMR spectra. For the first time, it was possible to separate the benzylation products into individual isomers using column chromatography. The obtained products serve as raw materials for further research.

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