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Organic Chemistry

Study of the Cyclization Reaction of Adamantyldiaminobenzene in Order to Obtain New Derivatives of 5(6)-(1-Adamantyl)-1*H*-2-R-Benzimidazoles

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In order to synthesize new derivatives of 5(6)-(1-adamantyl)-1*H*-2R-benzimidazole, the cyclization reaction of 4-(1-adamantyl)-1,2-diaminobenzene dihydrochloride with various substituted aromatic carbonic acids were studied. Cyclization reactions with aromatic carboxylic acids: salicylic acid, 3,5-dibromalsalicylic acid, 3,5-diiodosalicylic acid, 3-aminobenzoic and 4-aminobenzoic acids were carried out in polyphosphoric acid (PPA) or phosphorus oxychloride ($POCl_3$). The structures of synthesized compounds were confirmed by IR, ^1H, ^{13}C NMR, and Mass-spectrum analysis.

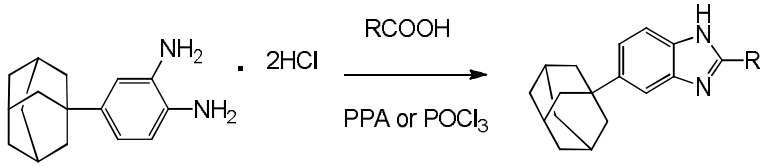
Adamantane, benzimidazole, adamantylbenzimidazole, condensation, cyclization

Adamantane is a widely used compound in synthesis and applications of new drug delivery systems. It is used in the production of antiviral, antibacterial, anticytotoxic drugs as well as treatment of Parkinson's disease. The remarkable properties of adamantane containing drugs can be explained by the unique structure of adamantane and are the basis of their wide range of therapeutic activity [1-6]. Benzimidazole is well known for its anti-viral, spasmolytic, antimicrobial, anthelmintic and fungicide capabilities. Based on them, highly effective drugs used in medicine, veterinary medicine and agriculture are obtained [7-11]. Therefore, the synthesis of adamantane-containing benzimidazoles is relevant and of interest in the search of new compounds with a wide range of biological effects.

Previously, we described the synthesis and properties of 5(6)-(1-adamantyl)-1*H*-benzimidazole and 2-(1-adamantyl)-1*H*-benzimidazole derivatives [12-15].

The present work aims to study the cyclization reaction of 4-(1-adamantyl)-1,2-diaminobenzene dihydrochloride with some aromatic carboxylic acids.

The condensation reaction of 4-(1-adamantyl)-1,2-diaminobenzene dihydrochloride (1) with carboxylic acids in PPA or $POCl_3$ medium was conducted. It was found that by heating a mixture of 4-(1-adamantyl)-1,2-diaminobenzene dihydrochloride with aromatic acids (salicylic-, dibromo-, and diiodsalicylic-, 3-amino- and 4-aminobenzoic acids) in a ratio of 1: 1, 1: 2 in the presence of PPA, the corresponding benzimidazoles **2, 5, 6** were isolated in different yields, but isolation of benzimidazole derivatives **3** and **4** with dibromo- and diiodosalicylic acids under the same conditions failed, due to the grinding of the reaction mixture and the removal of iodine and bromine. Preparation of benzimidazoles **3, 4, 7** were possible by heating the reaction mixture in $POCl_3$ medium (107°C) (As shown in Scheme and the Table).



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R=*o*-C_6H_4OH (**2**), 2–OH-3,5-$Br_2C_6H_2$ (**3**), 2-OH-3,5-$I_2C_6H_2$ (**4**), 4-$NH_2C_6H_4$ (**5**), 3-$NH_2C_6H_4$ (**6**), 3-$C_6H_5CONHC_6H_4$ (**7**)

Scheme. Synthesis of 5(6)-(1-adamantyl)-1*H*-2-R-benzimidazoles (**2 - 7**).

Table. Synthesis of 5(6)-(1-adamantyl)-1*H*-2-R-benzimidazoles (2 - 7)

Entry	R	Cat.	Temp. (°C)	Time (h)	Yield (%)
2	*o*-C_6H_4OH	PPA	190 - 195	4	50
5	4-$NH_2C_6H_4$	PPA	205 - 210	8	50
6	3-$NH_2C_6H_4$	PPA	200 - 205	4	65
3	2–OH-3,5-$Br_2C_6H_2$	$POCl_3$	107	2	96
4	2-OH-3,5-$I_2C_6H_2$	$POCl_3$	107	5	82
7	3-$C_6H_5CONHC_6H_4$	$POCl_3$	107	8	95

The molecular structure of the synthesized compounds was established by spectroscopy analysis, including IR, UV, ^1H, ^{13}C NMR and HRMS.

Experimental Part

IR spectra of the synthesized compound were recorded in the range of 400 - 4000 cm^{-1} with a Thermo Nicolet Avatar 370 (USA) spectrometer using Vaseline oil, hexachlorobutadiene and Varian 660 FT-IR Spectrometer using KBr pellets. UV spectra were recorded on Agilent 8453 and HP 8452 spectrometer using methanol. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-400 spectrometer (400 and 100 MHz, respectively) using tetramethylsilane (TMS) as internal standard and Dimethylsulfoxide (DMSO-d_6) as a solvent. The high-resolution mass spectral analysis (HRMS) data were measured on a Finnigan MAT 95, CI (gas – reagent – methane). All chemicals were of reagent grade and used as commercially purchased without further purification. All reactions were monitored by thin-layer chromatography (TLC) on silica gel Al-foils and Silufol UV 254 plates using UV light and iodine as visualizing agent (if applicable), and as eluent was used CCl_4–Me_2CO, 2:1; melting points were determined on a Boethius instrument with a PHMKO5 visual device.

5(6)-(1-Adamantyl)-2-(2-hydroxyphenyl)-1*H*-benzimidazole (2). A mixture of 4-(1-adamantyl)-1,2-diaminobenzene (1) dihydrochloride (1.57 g, 5 mmol), salicylic acid (1.38 g, 10 mmol) and PPA (20 g) was heated at 190–195°C for 4 h. The mixture was poured into ice water. The formed precipitate was filtered off, and worked up with 10% $NaHCO_3$ aqueous solution to pH 8 (to remove excess salicylic acid) and left overnight. The formed precipitate from the weak alkaline solution was filtered off, washed with water until neutral and until the salicylic acid was completely removed. The precipitate was dissolved in 10% NaOH aqueous solution and 10% HCl solution was added dropwise to pH 7 - 6, then it was extracted with diethyl ether; the ether solution was washed with water until neutral, dried over Na_2SO_4, evaporated on a rotary evaporator and added hexane. The precipitate formed from hexane was filtered and dried in vacuum. The cream-coloured crystals of compound 2 were obtained. After column chromatography (adsorbent: silica gel 100/400, eluent: hexane – ether, 5: 1) white crystals was obtained, Yield: 50%. mp 264-265°C ($CHCl_3$), R_f 0.66. UV spectrum, λ max, nm (log ε): 217 (4.69), 294 (4.38), 319 (4.60), 333 (4.56). IR spectrum, (HCBD, Vaseline oil), ν, cm^{-1}: 3300-3200 (NH), 3270 (O-H), 3083, 3018 (C-H Ar), 2893, 2847 (C-H Ad), 1640 (C-N). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, ppm): δ 13.13 (1H, s, NH), 13.12 (1H, s, OH), 8.02 (1H, dd, *J*=1.2, *J*=7.8 Hz, H-6); 7.58-7.56 (2H, m, H Ar), 7.39-7.34 (2H, m, H Ar), 7.04-6.99 (2H, m, H Ar), 2.11-2.07 (3H, m, H Ad), 1.97–1.93 (6H, m, H Ad), 1.79-1.75 (6H, m, H Ad). ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 157.85 (C-OH), 151.47 (1C Ar), 149.01 (1C Ar), 145.81 (1C Ar), 140.47 (1C Ar), 131.41 (1C Ar), 125.90 (2C Ar), 118.94 (2C Ar), 117.03 (2C Ar), 112.63 (1C Ar), 42.99 (3C Ad), 36.14 (3C Ad), 35.82 (1C Ad), 28.35 (3C Ad). HRMS: m/z Calculated, for $C_{23}H_{24}N_2O$: 344.1889; found: 344.1882 $[M]^+$.

5(6)-(1-Adamantyl)-2-(2-hydroxy-3,5-dibromophenyl)-1*H*-benzimidazole (3). To a mixture of 4-(1-adamantyl)-1,2-diaminobenzene dihydrochloride (945 mg, 3 mmol) and 3,5-dibromosalicylic acid (890 mg, 3 mmol), $POCl_3$ (5 mL) was added. The reaction mixture was stirred at room temperature for 30 min and then boiled at 107°C for 2 h. The mixture was cooled, cold water was added, the formed precipitate was filtered off and transferred to a beaker, 10% $NaHCO_3$ aqueous solution was added by dropwise to pH 8 and left overnight. The formed precipitate was filtered, washed with water until neutral and dried in vacuum. As yellow crystals of compound **3** was obtained. Yield: 96%; mp 280-282°C ($CHCl_3$). R_f 0.57 (CCl_4–Me_2CO, 10:1). UV spectrum, λ max, nm (log ε): 221 (4.34), 299 (3.87), 306 (3.98), 333 (4.04), 348 (4.05). IR spectrum (HCBD, Vaseline oil), ν, cm^{-1}**:** 3401 (OH), 3317 (NH), 3047 (C-H Ar), 2908, 2847 (C-H Ad), 1612 (CN), 686 (C-Br). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, ppm): δ 13.76 (1H, s, NH), 8.31 (1H, s, OH), 8.29 (1H, d, *J*=2.4 Hz, H Ar), 7.89 (1H, d, *J*=2.4 Hz, H Ar), 7.63 (1H, d, *J*=8.6 Hz, H-7), 7.57 (1H, s, H-4); 7.42 (1H, dd, *J*=1.6, *J*=8.6 Hz, H-6), 2.10-2.06 (3H, m, Ad), 1.97-1.92 (6H, m, Ad), 1.79-1.74 (6H, m, Ad). ^{13}C NMR (100 MHz, DMSO - d_6, ppm): δ 154.56 (C-OH), 151.15 (1C Ar), 147.12 (1C Ar), 144.20 (1C Ar), 139.28 (1C Ar), 125.22 (1C Ar), 115.99 (1C Ar), 114.28 (1C Ar), 110.37 (1C Ar), 109.83 (1C Ar), 105.95 (1C Ar), 97.84 (1C Ar), 86.02 (1C Ar), 42.91 (3C Ad), 36.10 (3C Ad), 35.90 (1C Ad), 28.33 (3C Ad). HRMS: m/z Calculated, for $C_{23}H_{22}Br_2N_2O$: 502.0078; found: 502.0111 $[M]^+$.

5(6)-(1-Adamantyl)-2-(2-hydroxy-3,5-diiodophenyl)-1*H*-benzimidazole (4). To a mixture of 4-(1-adamantyl)-1,2-diaminobenzene dihydrochloride (950 mg, 3 mmol) and 3,5-diiodosalicylic acid (1.17 g, 3 mmol) was added $POCl_3$ (5 mL). The reaction mixture was stirred at room temperature for 30 min and then boiled in $POCl_3$ (107°C) for 5 h. The reaction mixture was cooled, cold water was added and the precipitate was filtered off, transferred to a beaker and 10% $NaHCO_3$ aqueous solution was added dropwise to pH 8 and left overnight. The formed precipitate was filtered off, washed with water until neutral, dried

in vacuum. As yellow crystals of compound **4** was obtained. Yield: 82%; mp 208 – 210°C ($CHCl_3$). R_f 0.62 (CCl_4-Me_2CO, 5:1). UV spectrum, λ max, nm (log ε): 221 (4.34), 298 (3.86), 306 (3.96), 333 (4.01), 348 (4.03). IR spectrum, (HCBD, Vaseline oil), ν, cm^{-1}**:** 3500 - 3300 (N-H), 3402 (O-H), 3062 (C-H Ar), 2908, 2846 (C-H Ad), 1612 (C-N), 663 (C-I). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, ppm): δ 13.79 (1H, brs, NH), 8.39 (1H, s, H Ar), 8.31 (1H, s, OH), 8.10 (1H, s, H Ar), 7.59 (1H, d, *J* = 8.4 Hz, H-7), 7.55 (1H, s, H-4), 7.40 (1H, d, *J*=8.4 Hz, H-6), 2.09-2.04 (3H, m, H Ad), 1.95-1.90 (6H, m, H Ad), 1.79–1.74 (6H, s, H Ad). ^{13}C NMR spectrum (100 MHz, DMSO-d_6, ppm): δ 171.10 (C-OH), 157.00 (1C Ar), 149.26 (1C Ar), 147.03 (1C Ar), 146.66 (1C Ar), 146.63 (1C Ar), 134.88 (1C Ar), 133.76 (1C Ar), 114.48 (1C Ar), 112.77 (1C Ad), 88.27 (1C Ar), 81.47 (1C Ar), 80.22 (1C Ar), 42.91 (3C Ad), 36.11 (3C Ad), 35.88 (1C Ad), 28.33 (3C Ad). HRMS: m/z Calculated, for $C_{23}H_{22}I_2N_2O$: 595.9821; found: 595.9798 $[M]^+$.

5(6)-(1-Adamantyl)-2-(4-aminophenyl)-1*H*-benzimidazole (5). A mixture of 4-(1-adamantyl)-1,2-diaminobenzene dihydrochloride (630 mg, 2 mmol), 4-aminobenzoic acid (280 mg, 2 mmol) and PPA (20 g) was slowly heated to 205-210°C for 8 h. The mixture was poured into water; activated carbon was added, heated, boiled and filtered. The filtrate was cooled, diluted with cold water, 10% NaOH aqueous solution was added by dropwise to pH of 8-9 and left overnight. The formed precipitate was filtered off, washed with water until neutral, dried in vacuum. Cream-coloured crystals of compound **5** were obtained. Yield: 50%; mp 197-199°C ($CHCl_3$). R_f 0.38 (CCl_4-Me_2CO, 1:1). UV spectrum, λ max, nm (log ε): 218 (3.90), 328 (3.91). IR spectrum, (KBr), ν, cm^{-1}: 3485, 3387 (NH_2), 3206 (N-H), 3052 (C-H Ar), 2903, 2849 (C-H Ad), 1619 (NH_2 deform., C-N). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, ppm): δ 12.45 (1H, s, NH), 8.32 (1H, s, H Ar), 7.80 (2H, d, *J*=8.6 Hz, H Ar), 7.48-7.40 (2H, m, H Ar), 6.65 (2H, d, *J*=8.6 Hz, H Ar), 5.65 (2H, s, NH_2), 2.25-2.17 (6H, m, H Ad), 2.15-2.05 (3H, m, H Ad), 1.80-1.70 (6H, m, H Ad). ^{13}C NMR spectrum (100 MHz, DMSO-d_6, ppm): δ 153.92 (1C Ar), 150.77 (1C Ar), 148.96 (1C Ar), 141.62 (1C Ar), 138.70 (1C Ar), 127.79 (2C Ar), 127.72 (1C Ar), 125.29 (1C Ar), 116.82 (1C Ar), 116.65 (1C Ar), 113.41 (2C Ar), 39.96 (3C Ad), 37.39 (1C Ad), 36.18 (3C Ad), 28.42(3C Ad). HRMS: m/z Calculated, for $C_{23}H_{25}N_3$: 343.2048; found: 343.2033$[M]^+$.

5(6)-(1-Adamantyl)-2-(3-aminophenyl)-1*H*-benzimidazole (6). A mixture of 4-(1-adamantyl)-1,2-diaminobenzene dihydrochloride (950 mg, 3 mmol), 3-aminobenzoic acid (410 mg, 3 mmol) and PPA (20 g) was heated at 200-205°C for 4 hours. The mixture was poured into ice water and 10% NaOH aqueous solution was added to pH 8–9 and left overnight. The formed precipitate was filtered off, washed with water until neutral and dried in vacuum. Cream-coloured crystals of compound **6** were obtained.; mp 207-209°C ($CHCl_3$). R_f 0.38. UV spectrum, λ max, nm (log ε): 228 (3.81), 309 (3.66). IR spectrum, (KBr), ν, cm^{-1}: 3480, 3332 (NH_2), 3200 (N-H), 3067 (C-H Ar), 2902, 2847 (C-H Ad), 1618 (NH_2 def., C-N). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, ppm): δ 12.34 (1H, brs, NH), 7.56-7.47 (2H, m, Ar), 7.43-7.36 (1H, m, Ar), 7.33-7.22 (2H, m, Ar), 7.22-7.14 (1H, m, Ar) 6.70 (1H, td, *J*=1.2, *J*=7.6 Hz, H Ar); 3.48 (2H, s, NH_2), 2.23 (3H, s, H Ad), 2.12-2.06 (3H, m, H Ad), 1.95-1.90 (3H, m, H Ad), 1.80-1.70 (6H, m, H Ad). ^{13}C NMR spectrum (100 MHz, DMSO-d_6, ppm): δ 153.36 (1C Ar), 148.92 (1C Ar), 139.45 (1C Ar), 134.88 (1C Ar), 130.17 (1C Ar), 129.36 (1C Ar), 129.30 (1C Ar), 125.98 (1C Ar), 119.88 (1C Ar), 115.74 (1C Ar), 113.98 (1C Ar), 111.76 (1C Ar), 109.99 (1C Ar), 43.04 (3C Ad), 37.49 (1C Ad), 36.16 (3C Ad), 28.36 (3C Ad). HRMS: m/z Calculated, for $C_{23}H_{25}N_3$: 343.2048; found, m/z: 343.2061 $[M]^+$.

5(6)-(1-Adamantyl)-2-(3-benzoylaminophenyl)-1*H*-benzimidazole (7). To a mixture of 4-(1-adamantyl)-1,2-diaminobenzene dihydrochloride (945 mg, 3 mmol) and 3-benzoylaminobenzoic acid (724 mg, 3 mmol) $POCl_3$ (5 mL) was added. The reaction mixture was stirred at room temperature for

30 min and then boiled at $POCl_3$ boiling point (107°C) for 8 h. The reaction mixture was cooled, transferred into ice water and 10% NaOH aqueous solution was added to pH 8 and left overnight. The formed precipitate was filtered off, washed with water until neutral, dried in vacuum. White crystals of compound **7** were obtained. Yield: 95%; mp 188 - 190°C ($CHCl_3$). R_f 0.63. UV speqtrum, λ max, nm (log ε): 207 (4.47), 244 (3.95), 308 (4.29). IR spectrum, (KBr), ν, cm^{-1}: 3400 - 3201(N-H), 3063, 3040 (C-H Ar), 2903, 2848 (C-H Ad), 1656 (NH-C=O). ^{1}H NMR spectrum (400 MHz, DMSO - d_6, ppm): δ 12.74 (1H, brs, NH), 10.45 (1H, s, NHCO), 8.15 (2H, d, *J* = 7.2 Hz, H Ar), 7.61 - 7.38 (8H, m, H Ar), 7.28 (2H, dd, *J*=1.2, *J* = 8.4 Hz, H Ar), 2.08 - 2.04 (3H, m, H Ad), 1.96 - 1.88 (6H, m, H Ad), 1.80 - 1.71 (6H, m, H Ad). ^{13}C NMR spectrum (100 MHz, DMSO-d_6, ppm): δ 166.07 (C=O), 153.13 (1C Ar), 150.94 (1C Ar), 150.90 (1C Ar), 145.48 (1C Ar), 145.38 (1C Ar), 143.44 (1C Ar), 130.08 (1C Ar), 129.64 (1C Ar), 129.62 (1C Ar), 128.91 (2C Ar), 128.83 (1C Ar), 126.22 (2C Ar), 126.12 (1C Ar), 119.53 (1C Ar), 119.52 (1C Ar), 113.43 (1C Ar), 109.49 (1C Ar), 43.07 (3C Ad), 36.18 (3C Ad), 35.73 (1C Ad), 28.37 (3C Ad). HRMS: m/z Calculated, for $C_{30}H_{29}N_3O$: 447.2311; found: 447.2289 $[M]^+$.

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ორგანული ქიმია

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5(6)-(1-ადამანტილ)-1*H*-2R-ბენზიმიდაზოლის ახალი წარმოებულების სინთეზის მიზნით შესწავლილია 4-(1-ადამანტილ)-1,2-დიამინობენზოლის დიჰიდროქლორიდის ციკლიზაციის რეაქცია სხვადასხვა ჩანაცვლებულ არომატულ კარბონმჟავებთან. ციკლიზაციის რეაქციები

არომატულ კარბონმჟავებთან: სალიცილის მჟავა, 3,5-დიბრომსალიცილის მჟავა, 3,5-დიიოდ-სალიცილის მჟავა, 3-ამინობენზოის და 4-ამინობენზოის მჟავებთან ჩატარებულია პოლი-ფოსფორმჟავასა (პფმ) და ფოსფორის ოქსიქლორიდში ($POCl_3$). სინთეზირებული 5(6)-(1-ადამანტილ)-2-(3-ამინოფენილ)-1*H*-ბენზიმიდაზოლის (6) კონდენსაციით სალიცილის ალდე-ჰიდსა და ბენზოილქლორიდთან მიღებულია შესაბამისად შიფის ფუძე და ამიდი. სინთეზი-რებული ნაერთების სტრუქტურა დადასტურებულია იწ, უი, ^1H, ^{13}C ბმრ და მას-სპექტრების მონაცემებით.

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