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# REACTION OF 4,5-DINITROIMIDAZOLE WITH ETHYLENEDIAMINE AND SOME TRANSFORMATIONS OF THE OBTAINED 5-(2-AMINOETHYLAMINO)-4-NITRO-1H-IMIDAZOLE

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*The nitro group at position 5 in 4,5-dinitroimidazole was substituted by reaction with ethylenediamine with the formation of 5-(2-aminoethylamino)-4-nitro-1H-imidazole. The acylation of the compound was studied; a new bicyclic derivative of imidazole containing a benzothiazole fragment was obtained.*

**Keywords:** benzothiazole, bifunctional amines, dinitroimidazole, imidazolylthioureides, nitro group, ethylenediamine, acylation.

It is well known that the nitro group at position 5 of 4,5-dinitroimidazole (**1**) has high mobility and is easily substituted during the action of nucleophiles such as halide ions, aliphatic amines, CH-active compounds, and sodium sulfide and sulfite with the formation of the respective 5-substituted 4-nitroimidazoles [1].

The aim of the present work was to study the reaction of the imidazole **1** with ethylenediamine and also the reactions of the obtained amino derivative with acylating agents and aldehydes, which could be expected to result in the formation of five-, six-, or seven-membered heterocycles or products with linear structures.

During the reaction of the imidazole **1** with ethylenediamine under conditions similar to those described earlier [1] it was possible to isolate compound **2a** – a salt of the dinitroimidazole **1** and the amine. Its structure was confirmed by the data from $^1$H NMR spectroscopy (Table 1) and by the presence of a molecular ion peak at 158 in its mass spectrum. The nitro group in the imidazole **1** was substituted under harsher conditions, i.e., as a result of reaction with the ethylenediamine, which was used as solvent, at 60°C. The structure of the obtained 5-(2-aminoethylamino)-4-nitro-1H-imidazole (**3**) was confirmed by $^1$H NMR spectroscopy (Table 1) and by the presence of a molecular ion peak 171 in its mass spectrum.

To obtain evidence for the presence of a free β-amino group in compound **3** it was brought into reaction with aromatic aldehydes in acetic acid. As a result the Schiff bases **4a**,**b** were isolated. Their structures were proved by $^1$H NMR spectroscopy, and their individuality was established by elemental analysis (Tables 1 and 2).

During the reaction of the imidazolylethylenediamine **3** with ethyl chlorocarbonate and with acetic anhydride it could be expected that derivatives of imidazolyltriazepine, imidazolyl-5-imidazoline, or the products from acylation of the amino group of the ethylenediamine fragment of the molecule would be obtained. As a result of the reaction only the N-acyl derivatives **5a**,**b** were isolated, and their structures were proved by $^1$H NMR spectroscopy. Thus, in the $^1$H NMR spectrum of compound **5a** there are two broad one-proton singlets for the NH groups and signals for the ethyl group in the form of a quartet and a triplet at 3.96 and 1.14 ppm (Table 1). Correspondingly, in the $^1$H NMR spectrum of compound **5b** there is a broad singlet for the NH protons

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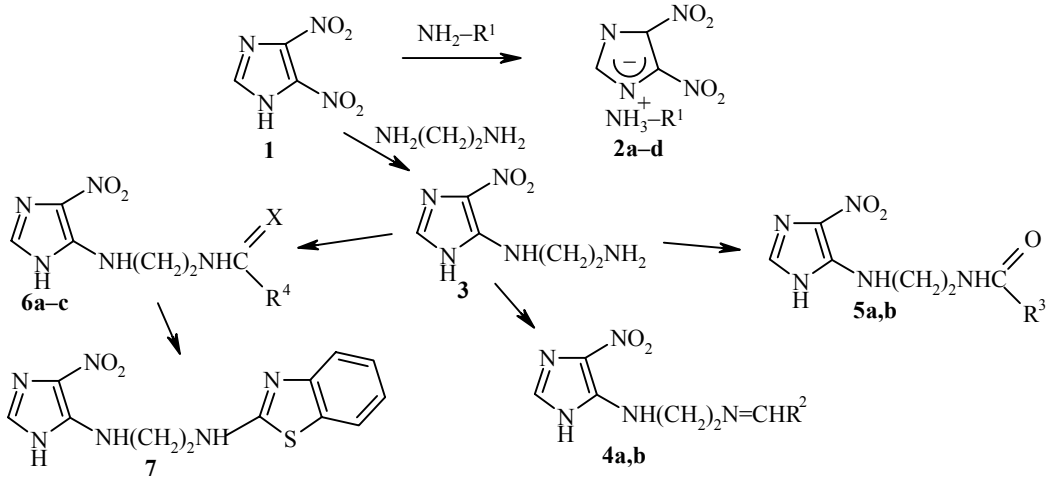
of the imidazole ring at 12.19 ppm, signals for the NH protons of ethylenediamine fragment in the form of two triplets at 7.99 and 7.72 ppm on account of their splitting at the adjacent protons of the $–CH_2CH_2–$ groups, and a three-proton singlet for the acetyl fragment at 1.92 ppm (Table 1). During attempts at the cyclization of compounds **5a**,**b** in the presence of a 1% alcohol solution of potassium hydroxide, alkali metal alcoholates, phosphorus oxychloride, and concentrated sulfuric acid resinification of the reaction mixture was observed, and a multitude of chromatographically inseparable products was formed.



**2 a** $R^1 = (CH_2)_2NH_2$, **b** $R^1 = (CH_2)_2OH$, **c** $R^1 = (CH_2)_3COOH$, **d** $R^1 = C_6H_4NH_2$-*o*; **4 a** $R^2 = C_6H_4$–Cl-*p*, **b** $R^2 = C_6H_4$–Cl-*o*;
**5 a** $R^3$ = OEt, **b** $R^3$ = Me; **6 a** $R^4 = NH_2$, X = O, **b** $R^4 = NHC_6H_4$–Cl-*p*, X = O, **c** $R^4$ = NHPh, X = S

TABLE 1. The $^1$H NMR Spectra of the Synthesized Compounds

| Com-pound | Chemical shifts, δ, ppm, CCSS, *J* (Hz) |
|---|---|
| **2a** | 6.93 (1H, s, 2-H); 5.18 (5H, br. s, $NH_3^+$, $NH_2$); 2.78 (4H, s, $CH_2CH_2$) |
| **2b** | 7.60 (3H, br. s, $NH_3^+$); 6.94 (1H, s, 2-H); 3.52 (2H, t, $J$ = 4.91, $CH_2$); 2.80 (2H, t, $J$ = 4.91, $CH_2$) |
| **2c** | 8.28 (3H, br. s, $NH_3^+$); 6.94 (1H, s, 2-H); 2.80 (2H, t, $J$ = 7.00, $CH_2$); 2.33 (2H, t, $J$ = 7.28, $CH_2$); 1.62 (2H, dt, $J_1$ = 7.28, $J_2$ = 7.00, $CH_2$) |
| **2d** | 9.28 (5H, br. s, $NH_3^+$, $NH_2$); 7.80 ( 4H, m, $H_{arom}$); 7.07 (1H, s, 2-H) |
| **3** | 12.25 (1H, br. s, NH); 7.31 (1H, br. s, NH); 6.94 (1H, s, 2-H); 5.39 (2H, br. s, $NH_2$); 3.49 (2H, m, $CH_2$); 2.99 (2H, t, $J$ = 5.99, $CH_2$) |
| **4a** | 12.15 (1H, s, NH); 8.85 (1H, s, CH); 7.93-7.49 (4H, m, $H_{arom}$); 7.70 (1H, t, $J$ = 5.95, NH); 7.43 (1H, s, 2-H); 3.92 (2H, t, $J$ = 5.80, $CH_2$); 3.72 (2H, dt, $J_1$ = 5.95, $J_2$ = 5.80, $CH_2$) |
| **4b** | 12.05 (1H, s, NH); 8.66 (1H, s, CH); 7.88-7.39 (4H, m, $H_{arom}$); 7.75 (1H, t, $J$ = 5.91, NH); 7.36 (1H, s, 2-H); 3.89 (2H, t, $J$ = 5.79, $CH_2$); 3.68 (2H, dt, $J_1$ = 5.91, $J_2$ = 5.79, $CH_2$) |
| **5a** | 12.20 (1H, br. s, NH); 7.72 (1H, s, 2-H); 7.48 (1H, br. s, NH); 7.16 (1H, br. s, NH); 3.96 (2H, q, $J$ = 7.02, $CH_2$); 3.46-3.20 (4H, m, $CH_2CH_2$); 1.14 (3H, t, $J$ = 7.02, $CH_3$) |
| **5b** | 12.19 (1H, s, NH); 7.99 (1H, t, $J$ = 5.17, NH); 7.72 (1H, t, $J$ = 5.82, NH); 7.47 (1H, s, 2-H); 3.43 (2H, dt, $J_1$ = 5.17, $J_2$ = 7.33, $CH_2$); 3.28 (2H, dt, $J_1$ = 5.82, $J_2$ = 7.33, $CH_2$); 1.92 (3H, s, $CH_3$) |
| **6a** | 12.21 (1H, br, s, NH); 7.70 (1H, t, $J$ = 6.21, NH); 7.36 (1H, s, 2-H); 6.13 (1H, t, $J$ = 5.30, NH); 5.56 (2H, s, $NH_2$); 3.41 (2H, dt, $J_1$ = 6.21, $J_2$ = 6.04, $CH_2$); 3.21 (2H, dt, $J_1$ = 5.30, $J_2$ = 6.04, $CH_2$) |
| **6b** | 12.10 (1H, br. s, NH); 8.67 (1H, s, NH); 7.76 (1H, t, $J$ = 5.36, NH); 7.49-7.22 (4H, m, $H_{arom}$); 7.39 (1H, s, 2-H); 6.30 (1H, t, $J$ = 5.68, NH); 3.45 (2H, dt, $J_1$ = 5.68, $J_2$ = 6.00, $CH_2$); 3.35 (2H, dt, $J_1$ = 5.36, $J_2$ = 5.99, $CH_2$) |
| **6c** | 12.22 (1H, br. s, NH); 9.56 (1H, s, NH); 7.95 (2H, br. s, 2NH); 7.46 (1H, s, 2-H); 7.37-7.08 (5H, m, $C_6H_5$); 3.76 (2H, m, $CH_2$); 3.59 (2H, m, $CH_2$) |
| **7** | 12.23 (1H, s, NH); 8.83 (1H, br. s, NH); 7.93 (1H, br. s, NH); 7.76-7.09 (4H, m, $H_{arom}$); 7.53 (1H, s, 2-H); 3.66 (4H, m, $CH_2CH_2$) |

In the reactions of the imidazole **3** with sodium isocyanate, *p*-chlorophenyl isocyanate, and phenyl isothiocyanate only products with linear structures were isolated, i.e., the 4-nitroimidazolyl-5-ureido and 4-nitroimidazolyl-5-thioureido derivatives **6a-c**. The $^1$H NMR spectra of compounds **6b**,**c** contain signals for the aromatic protons and singlets for the NHAr protons, while the signals for the NH groups of the ethylenediamine fragment are superimposed on each other, forming a broad two-proton singlet at 7.95 ppm (Table 1).

Examples of the oxidative cyclization of thioamides [2] and imidazolylthioureides [3] are known from the literature. It could be expected that during treatment of compound **6c** with bromine cyclization would take place with the participation of only one of the nitrogen atoms or of the benzene ring of the substituent (synthesis of benzothiazoles according to Hugershoff) [4]. When the reaction was conducted in glacial acetic acid the individual compound was isolated and characterized. The presence of only four aromatic protons in the region of 7.76-7.09 ppm in its $^1$H NMR spectrum made it possible to assign the compound the structure of the benzothiazole **7**.

Thus, in the reaction of compound **3** with acylating agents the formation of only linear derivatives was observed, and it was not possible to detect the products from cyclization involving the nitrogen atoms. In order to check the discovered features of the behaviour of the imidazole **3** we tried to produce other nitroaminoimidazoles by substitution of the nitro group in compound **1** by bifunctional amines. For the latter we chose ethanolamine, γ-aminobutyric acid, and *o*-phenylenediamine. In the reaction of the dinitroimidazole **1** with these compounds only their salts **2b-d** were isolated, as demonstrated by the molecular peaks 158 in the mass spectra of these compounds, corresponding the molecular mass of 4,5-dinitroimidazole. In the $^1$H NMR spectra of the products from the reaction of the dinitroimidazole **1** with bifunctional amines signals are observed for the protons of the introduced amines, and at the same time there are no signals for the NH protons of the imidazole ring. In contrast to the reaction with ethylenediamine the reactions of the imidazole **1** with above-

TABLE 2. The Characteristics of the Synthesized Compounds

| Compound | Empirical formula | Found, % / Calculated, % | | | mp, °C | Yield, % |
|---|---|---|---|---|---|---|
| | | C | H | N | | |
| **2a** | $C_3H_2N_4O_4 \cdot C_2H_8N_2$ | 27.78 / 27.52 | 4.81 / 4.59 | 38.70 / 38.53 | 199-201 | 93 |
| **2b** | $C_3H_2N_4O_4 \cdot C_2H_7NO$ | 27.76 / 27.39 | 4.38 / 4.11 | 31.80 / 31.96 | 191-193 | 75 |
| **2c** | $C_3H_2N_4O_4 \cdot C_4H_9NO_2$ | 32.42 / 32.18 | 4.51 / 4.21 | 26.59 / 26.82 | 162-164 | 80 |
| **2d** | $C_3H_2N_4O_4 \cdot C_6H_8N_2$ | 40.80 / 40.60 | 3.52 / 3.76 | 31.80 / 31.58 | 220-222 | 51 |
| **3** | $C_5H_9N_5O_2$ | 35.39 / 35.08 | 4.94 / 5.26 | 40.62 / 40.93 | 121-120 | 43 |
| **4a** | $C_{12}H_{12}ClN_5O_2$ | 49.31 / 49.06 | 4.28 / 4.09 | 23.74 / 23.85 | 160-161 | 65 |
| **4b** | $C_{12}H_{12}ClN_5O_2$ | 48.89 / 49.06 | 3.94 / 4.09 | 24.25 / 23.85 | 148-150 | 61 |
| **5a** | $C_8H_{13}N_5O_4$ | 39.78 / 39.51 | 5.66 / 5.35 | 29.02 / 28.81 | 179-181 | 59 |
| **5b** | $C_7H_{11}N_5O_3$ | 39.24 / 39.44 | 5.46 / 5.16 | 33.08 / 32.86 | 190-192 | 82 |
| **6a** | $C_6H_{10}N_6O_3$ | 33.99 / 33.64 | 5.00 / 4.67 | 39.51 / 39.25 | 184-186 | 61 |
| **6b** | $C_{12}H_{13}ClN_6O_3$ | 44.66 / 44.37 | 4.22 / 4.01 | 25.73 / 25.88 | 229-231 | 55 |
| **6c** | $C_{12}H_{14}N_6O_2S$ | 47.46 / 47.06 | 4.34 / 4.58 | 27.77 / 27.45 | 210-212 | 75 |
| **7** | $C_{12}H_{12}N_6O_2S$ | 47.21 / 47.37 | 4.12 / 3.95 | 28.01 / 27.63 | 228-229 | 48 |

mentioned bifunctional amines, heated in the range of 60-90°C, led to resinification of the reaction mass, which only contained a mixture of products with close chromatographic mobility, as a result of which it was not possible to isolate the individual compounds.

## EXPERIMENTAL

The $^1$H NMR spectra were recorded on a Bruker WM-250 instrument at 250 MHz in DMSO-$d_6$ solution with TMS as internal standard. The reaction and the individuality of the products were monitored by TLC on Sorbfil UV-254 plates in the 1:2:1 butanol–acetic acid–water system. The mass spectra were recorded on a Varian MAT-311A instrument (accelerating potential 3 kV, ionization energy 70 eV). The melting points were not corrected. The characteristics of the synthesized compounds are given in Tables 1 and 2.

**2'-Aminoethylammonium Salt of 4,5-Dinitro-1H-imidazole (2a).** To a solution of the dinitroimidazole **1** (1 g, 6.3 mmol) in ethanol (15 ml) we added ethylenediamine (1.27 ml, 18.99 mmol). The reaction mixture was kept at room temperature for 15 min. The precipitated dinitroimidazole salt was filtered off, washed on the filter with ethanol (5 ml), and dried. We obtained 1.28 g of the salt **2a**.

**2'-Hydroxyethylammonium Salt of 4,5-Dinitro-1H-imidazole (2b).** The compound was obtained similarly to compound **2a**.

**3'-Carboxy-*n*-propylammonium Salt of 4,5-Dinitro-1-H-imidazole (2c).** The compound was obtained similarly to compound **2a**.

**2'-Aminophenylammonium Salt of 4,5-Dinitro-1H-imidazole (2d).** To a solution of dinitroimidazole **1** (1 g, 6.33 mmol) in butyric acid (7 ml) we added *o*-phenylenediamine (2.05 g, 18.99 mmol). The mixture was kept at 100°C for 4 h. The reaction mixture was poured onto ice, and the precipitated salt **2d** was filtered off, crystallized from ethanol, and dried. Yield of the salt **2d** 0.86 g.

**5-(2-Aminoethylamino)-4-nitro-1H-imidazole (3).** To dinitroimidazole **1** (1 g, 6.33 mmol) we added ethylenediamine (2.53 ml, 37.98 mmol). The reaction mixture was kept at 60°C for 4 h and was then diluted with ethanol and cooled. The precipitate was filtered off, washed on the filter, and dried. We obtained 0.46 g of compound **3**.

**5-[2-(4-Chlorobenzylideneamino)ethylamino]-4-nitro-1H-imidazole (4a).** To a solution of compound **3** (0.2 g, 1.17 mmol) in a mixture of ethanol (5 ml) and acetic acid (2 ml) we added 4-chlorobenzaldehyde (0.18 g, 1.28 mmol). The solution was boiled for 3.5 h and cooled. The precipitated compound **4a** was filtered off, crystallized from 70% aqueous ethanol, and dried. Yield 0.22 g.

**5-[2-(2-Chlorobenzylideneamino)ethylamino]-4-nitro-1H-imidazole (4b).** The compound was obtained similarly to compound **4a**.

**5-(2-Ethoxycarbonylaminoethylamino)-4-nitro-1H-imidazole (5a).** To a suspension of compound **3** (0.2 g, 1.17 mmol) in DMF (2 ml) at 5°C we added in portions ethyl chlorocarbonate (0.12 ml, 1.28 mmol) and triethylamine (0.18 ml, 1.28 mmol). The obtained solution was kept for 30 min. The solvent was evaporated to dryness, and the residue was crystallized from 70% aqueous ethanol and dried. We obtained 0.21 g of compound **5a**.

**5-(2-Acetylaminoethylamino)-4-nitro-1H-imidazole (5b).** A solution of compound **3** (0.2 g, 1.17 mmol) in acetic anhydride (4 ml) was kept at room temperature for 30 min. The precipitated compound **5b** was filtered off, washed on the filter with ethanol, and dried. Yield 0.20 g.

**5-(2-Aminocarbonylaminoethylamino)-4-nitro-1H-imidazole (6a).** To a solution of compound **3** (0.2 g, 1.17 mmol) in a mixture of ethanol (5 ml) and acetic acid (2 ml) we added potassium isocyanate (0.1 g, 1.28 mmol). The solution was boiled for 3.5 h and cooled. The precipitated compound **6a** was filtered off, crystallized from 70% aqueous ethanol, and dried. Yield 0.15 g.

**5-[2-(4-Chlorophenylaminocarbonylamino)ethylamino]-4-nitro-1H-imidazole (6b).** To a solution of *p*-chlorophenyl isocyanate (0.19 g, 1.28 mmol) in chloroform (15 ml) we added compound **3** (0.2 g, 1.17 mmol) and acetic acid (0.1 ml). The obtained suspension was boiled for 2 h and cooled. The precipitated imidazole **6b** was filtered off, crystallized from 70% aqueous ethanol, and dried. Yield 0.21 g.

**4-Nitro-5-(2-phenylaminothiocarbonylaminoethylamino)-1H-imidazole (6c).** To a solution of compound **3** (0.2 g, 1.17 mmol) in a mixture of ethanol (5 ml) and acetic acid (2 ml) we added phenyl isothiocyanate (0.15 ml, 1.28 mmol). The solution was boiled for 4.5 h and cooled. The precipitated imidazole **6c** was filtered off, crystallized from 70% aqueous ethanol, and dried. Yield of the imidazole **6c** 0.26 g.

**5-(2-Benzothiazol-2-ylaminoethylamino)-4-nitro-1H-imidazole (7).** To a solution of compound **6c** (0.2 g, 0.65 mmol) in acetic acid (10 ml) at 70°C we added bromine (0.09 ml, 1.96 mmol). The reaction mixture was kept at this temperature for 30 min. It was then cooled, and the precipitated imidazole **7** was filtered off, crystallized from ethanol, and dried. Yield 0.09 g.

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