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# Reaction of 2-Chloro-5(6)-nitrobenzimidazole with Cloromethylthiirane and Isomeric Composition of the Products

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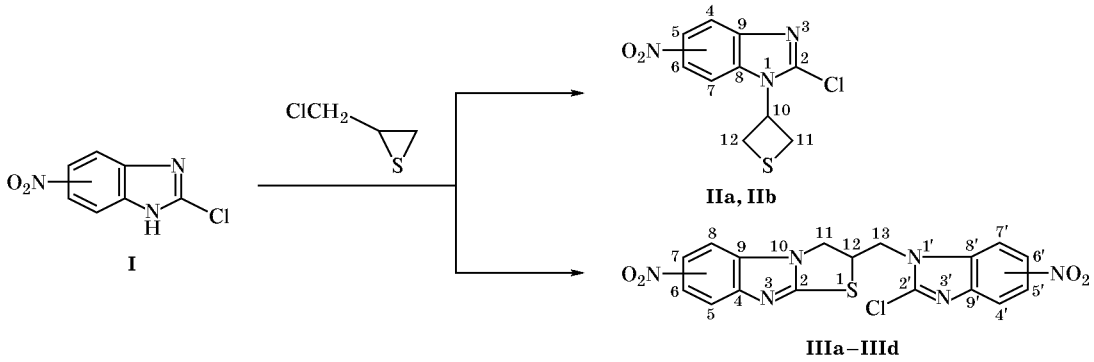
**Abstract**—The alkylation of 2-chloro-5(6)-nitrobenzimidazole with 2-chloromethylthiirane was studied for the first time. Depending on the conditions, isomeric mixtures of nitro-substituted 2-chloro-1-(thietan-3-yl)-benzimidazoles and dihydrothiazolo[3,2-*a*]benzimidazoles were obtained.

Benzimidazole derivatives occupy an importnant place among synthetic medical preparations due to wide spectrum of their pharmacological activity [1]. The goal of the present study was to obtain nitrobenzimidazole derivatives with a chemically modified heterocyclic fragment and to examine their isomeric composition. For this purpose, we performed alkylation of 2-chloro-5(6)-nitrobenzimidazole (**I**) with 2-chloromethylthiirane. We have found that the reaction direction is determined by the reactant ratio and solvent nature [2]. The alkylation of **I** with an equimolar amount of 2-chloromethylthiirane gave chromatographically pure products in a high yield. In protic solvents, the products were 2-chloro-5- and 6-nitro-1-(thietan-3-yl)benzimidazoles **IIa** and **IIb**.

The possibility for thiirane–thietane rearrangement [3] was studied by carrying out the reaction in aprotic solvents which are incapable of specifically solvating benzimidazolate anion [4]. Under these conditions, isomeric 2-[2-chloro-(5(6)-nitrobenzimidazol-1-ylmethyl]-6(7)-nitro-2,3-dihydrothiazolo[1,2-*a*]benzimidazoles **IIIa**–**IIId** were obtained in quantitative yield (Scheme 1).

The structure of the products was confirmed by elemental analysis and spectral data. The isomeric composition of the products was examined using $^{1}H$ and $^{13}C$ NMR spectroscopy. The experimental NMR spectra were compared with those simulated by the ACD Labs 3.0 program and by the additivity scheme. The $^{13}C$ NMR spectrum of product mixture **IIa**/**IIb**

**Scheme 1.**

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contained signals corresponding to 2-chloro-5-nitro-1-(thietan-3-yl)benzimidazole (**IIa**) and 2-chloro-6-nitro-1-(thietan-3-yl)benzimidazole (**IIb**). A reliable criterion for the assignment of isomers **IIa** and **IIb** was the chemical shift of $C^7$. The $C^7$ signal of 6-nitro isomer **IIb** appears at $\delta_C$ 107.0 ppm, for the $C^7$ nuclei suffers from two negative β-effects of nitrogen atoms (the signal is displaced upfield). The corresponding signal of isomer **IIa** is located at $\delta_C$ 110.40 ppm; in this case, shielding effects are observed for the $C^4$ atom, $\delta_C$ 116.40 ppm against 120.20 ppm for isomer **IIb**. The ratio of isomers **IIa** and **IIb** was estimated at 1:3 from the $^{13}C$ signal intensities.

Analysis of the $^{13}C$ NMR spectra of nitro derivatives **III** of dihydrothiazolo[1,2-*a*]benzimidazole showed the presence of all possible isomers. Signals from quaternary carbon atoms at $\delta_C$ 162.80 and 162.67 ppm belong to $C^2$. Their chemical shifts could differ only due to different positions (at $C^6$ or $C^7$) of the nitro group in the dihydrothiazolo[1,2-*a*]benzimidazole fragment. The region $\delta_C$ 106–111 ppm contains eight signals from four pairs of methylene carbon atoms. The signals at $\delta_C$ 106.44 and 106.51 ppm belong to $C^{7'}$ in the benzimidazole fragment of the 6′-nitro isomer. The $C^8$ atoms of the 7-nitro isomers give signals at $\delta_C$ 107.74 and 107.94 ppm, and those at $\delta_C$ 109.83 and 109.96 ppm should be assigned to $C^{7'}$ of the 5′-nitro isomers. The signals at $\delta_C$ 111.58 and 111.78 ppm arise from $C^8$ of the 6-nitro isomers. Each pair of signals is characterized by an intensity ratio of about 3:1; the same intensity ratio is observed for the following pairs of signals: $\delta_C$ (ppm) 106.44 and 106.51 to 109.70 and 109.9, 111.70 and 111.50 to 107.70 and 107.90 ppm. Hence, 2-[2-chloro-(5(6)-nitrobenzimidazol-1-ylmethyl]-6(7)-nitro-2,3-dihydrothiazolo[1,2-*a*]benzimidazole isomers **IIIa**–**IIId** may be arranged in the following series which corresponds to decrease in their fraction: (1) 2-(2-chloro-6-nitrobenzimidazol-1-ylmethyl)-6-nitro-2,3-dihydrothiazolo-[1,2-*a*]benzimidazole (**IIIa**); (2) 2-(2-chloro-5-nitrobenzimidazol-1-ylmethyl)-6-nitro-2,3-dihydrothiazolo-[1,2-*a*]benzimidazole (**IIIb**); (3) 2-(2-chloro-6-nitrobenzimidazol-1-ylmethyl)-7-nitro-2,3-dihydrothiazolo-[1,2-*a*]benzimidazole (**IIIc**); and (4) 2-(2-chloro-5-nitrobenzimidazol-1-ylmethyl)-7-nitro-2,3-dihydrothiazolo[1,2-*a*]benzimidazole (**IIId**). Their concentration ratio is 9:3:3:1 (**a**:**b**:**c**:**d**).

## EXPERIMENTAL

The $^1H$ and $^{13}C$ NMR spectra were measured on a Bruker AM-300 spectrometer operating at 300 and 75 MHz, respectively. The $^{13}C$ NMR spectra were recorded with complete decoupling from protons and with modulation of CH coupling. The $^{13}C$ chemical shifts were measured relative to the middle line of the DMSO-$d_6$ signal ($\delta_C$ 39.43 ppm). The IR spectra were recorded on a UR-20 instrument from samples dispersed in mineral oil or hexachlorobutadiene. The progress of reactions was monitored by TLC on Silufol UV-254 plates.

**2-Chloro-5(6)-nitro-1-(thietan-3-yl)benzimidazoles IIa and IIb.** 2-Chloro-5(6)-nitrobenzimidazole, 9.9 g (0.05 mol), was dissolved in 22 ml of a 10% aqueous solution of sodium hydroxide. The solution was warmed to 30–35°C, 5.45 g (0.05 mol) of 2-chloromethylthiirane was added, and the mixture was stirred for 1 h. Crystals precipitated and were filtered off, washed with diethyl ether and water, and dried at 60°C. Yield 2.29 g (85%), mp 181–183°C (from aqueous ethanol, 1:1). IR spectrum, ν, $cm^{-1}$: 762 (C–$NO_2$), 845 (C–$NO_2$), 1040 (C–S), 1345 ($NO_2$), 1523 ($NO_2$), 1495 (C=N). $^1H$ NMR spectrum ($CDCl_3$), δ, ppm: 3.6–3.7 m (2H, $SCH_2$), 4.12–4.23 m (2H, $SCH_2$), 5.9–6.1 m (1H, NCH), 7.7–8.7 m (3H, $H_{arom}$). $^{13}C$ NMR spectrum ($CDCl_3$), $\delta_C$, ppm: **IIa**: 32.57 ($C^{11}$, $C^{12}$), 51.73 ($C^{10}$), 110.40 ($C^7$), 116.40 ($C^4$), 119.30 ($C^6$), 132.83 ($C^8$), 141.30 ($C^2$), 144.0 ($C^9$), 144.20 ($C^5$); **IIb**: 32.77 ($C^{11}$, $C^{12}$), 51.81, ($C^{10}$) 107.10 ($C^7$), 119.0 ($C^5$), 120.2 ($C^4$), 137.65 ($C^9$), 141.30 ($C^2$), 143.90 ($C^8$), 146.10 ($C^6$). Found, %: C 44.15; H 3.3; N 13.85; S 12.04. $C_{10}H_8ClN_3O_2S$. Calculated, %: C 44.52; H 2.96; N 15.58; S 11.80.

**2-[2-Chloro-5(6)-nitrobenzimidazol-1-ylmethyl]-6(7)-nitro-2,3-dihydrothiazolo[1,2-*a*]benzimidazoles IIIa–IIId.** Potassium carbonate, 1.38 g (0.01 mol), was added to a solution of 1.98 g (0.01 mol) of 2-chloro-5(6)-nitrobenzimidazole in 30 ml of acetone. The mixture was heated for 30 min, 1.09 g (0.01 mol) of 2-chloromethylthiirane was added in one portion, and the mixture was heated for 3 h under reflux. It was then cooled to 5–10°C and poured into water. The precipitate was filtered off, washed with acetone and water, and dried at 60°C. Yield 3.31 g (77%). $^1H$ NMR spectrum (DMSO-$d_6$), δ, ppm: 4.3–4.5 m (2H, 13-$H_2$), 4.85–4.9 m (2H, 12-$H_2$), 5.15–5.20 m (1H, SCH), 7.6–8.5 m (6H, $H_{arom}$). $^{13}C$ NMR spectrum (DMSO-$d_6$), $\delta_C$, ppm: **IIIa**: 47.43 ($C^{11}$), 47.14 ($C^{13}$), 51.60 ($C^{12}$), 106.51 ($C^{7'}$), 111.80 ($C^8$), 162.79 ($C^2$); **IIIb**: 47.43 ($C^{11}$), 48.84 ($C^{13}$), 51.24 ($C^{12}$), 109.80 ($C^{7'}$), 111.80 ($C^8$), 162.79 ($C^2$); **IIIc**: 47.14

($C^{13}$), 47.31 ($C^{11}$), 51.60 ($C^{12}$), 106.44 ($C^{7'}$), 107.94 ($C^{8}$), 162.67 ($C^{2}$); **IIId**: 47.31 ($C^{11}$), 48.84 ($C^{13}$), 51.24 ($C^{12}$), 107.74 ($C^{8}$), 109.70 ($C^{7'}$), 162.67 ($C^{2}$); other carbon signals: 113.37, 114.62, 117.27, 117.47, 117.62, 118.0, 118.20, 118.54, 118.97; quaternary carbon signals: 132.95, 133.04, 134.34, 139.19, 139.29, 140.0, 141.76, 142.25, 143.22, 143.36, 144.19, 145.21, 145.30, 153.0. Found, %: C 47.3; H 2.4; N 19.7; S 7.4. $C_{17}H_{11}N_6SO_4$. Calculated, %: C 47.4; H 2.56; N 19.5; S 7.43.

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