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Unusual Reaction of 4-[(3-Carboxypropyl)amino]-6-chloro-5-nitrobenzofuroxan with 3-Aminopropane-1,2-diol 1,2-Dinitrate

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Abstract—Reaction of 4-[(3-carboxypropyl)amino]-6-chloro-5-nitrobenzofuroxan with 3-aminopropane-1,2-diol 1,2-dinitrate yielded 6-chloro-5-nitro-4-(2-oxopyrrolidin-1-yl)benzofuroxan instead of the expected 6-chloro-5-nitrobenzofuroxan amino derivative.

Keywords: 4,6-dichloro-5-nitrobenzofuroxan, X-ray diffraction, 3-aminopropane-1,2-diol 1,2-dinitrate, NO-donors

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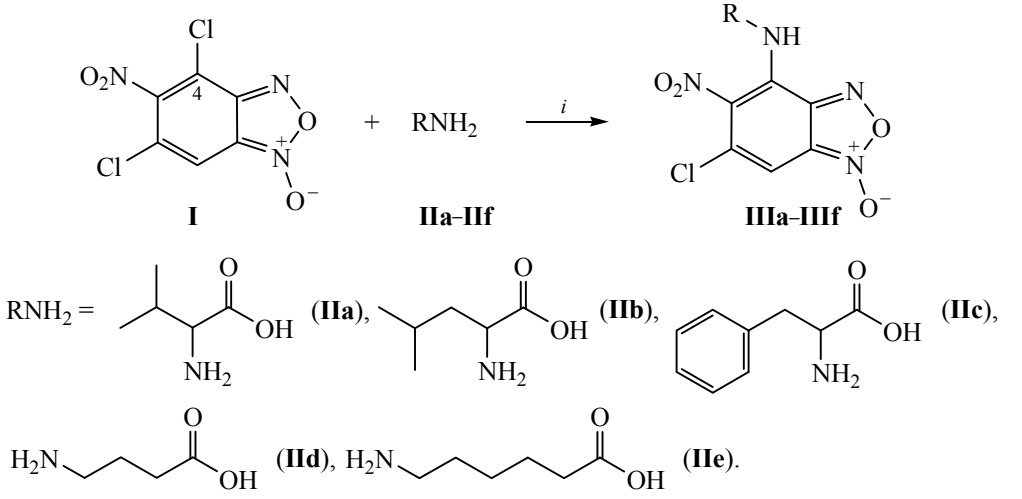
Benzofuroxan derivatives are known for broad range of biological activity [1], including antibacterial [2], herbicidal [3], antiparasitic [4], antileukemic [5], antirheumatic [6], and vasodilator activity [7]. In this regard, benzofuroxans are of interest as synthons for preparation of biologically active heterocyclic compounds, potential NO-generating prodrugs.

We have recently described preparation of some amino derivatives of 6-chloro-5-nitrobenzofuroxan [8] (Scheme 1).

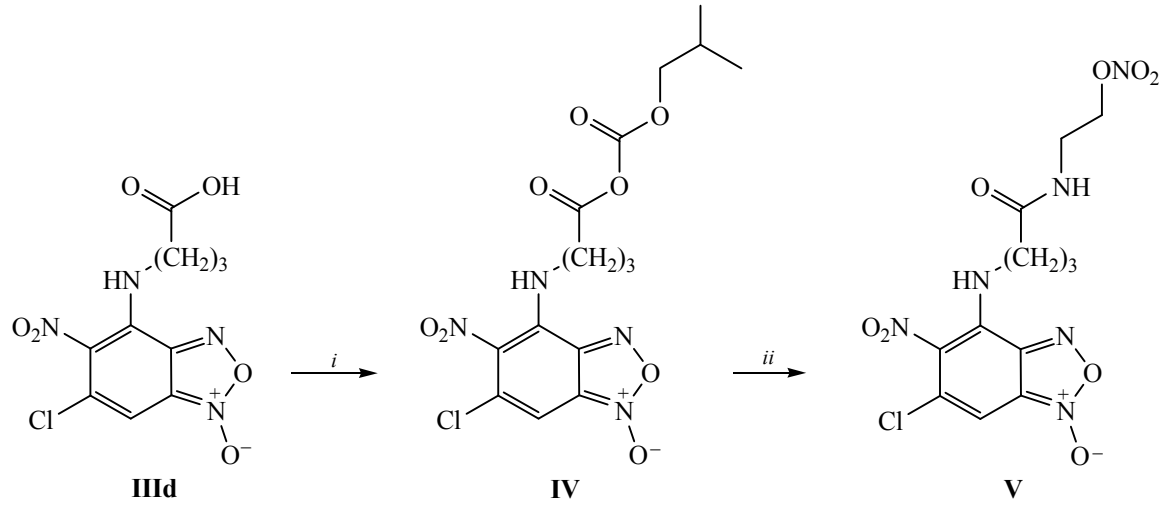
Free carboxyl groups in the molecules of **IIIa**–**IIIe** can serve as linker to introduce additional pharmacophore groups allowing for synthesis of new hybrid

Scheme 1.



i, MeOH, $NaHCO_3$, 60°C, 4 h.

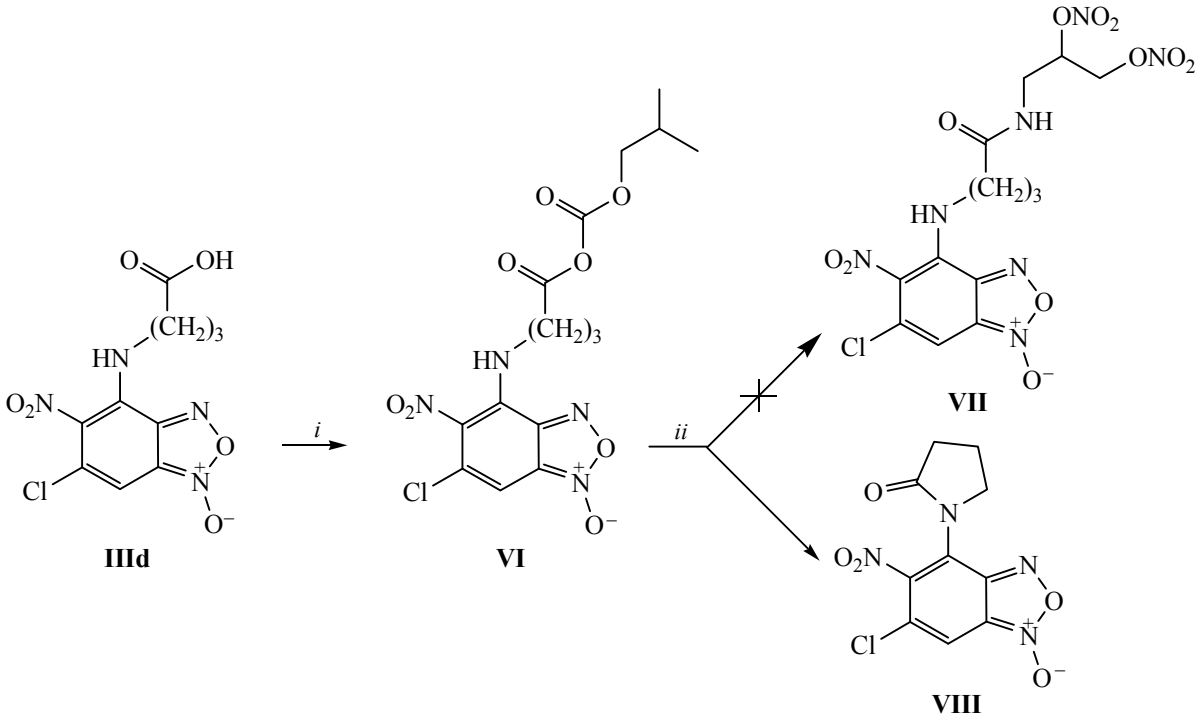
Scheme 2.



IIId **IV** **V**

i, isobutyl chloroformate, EtOAc, Et_3N, 0–4°C, 30 min; *ii*, 2-aminoethylnitrate, EtOAc, Et_3N, 20°C, 1 h.

Scheme 3.



IIId **VI** **VII** **VIII**

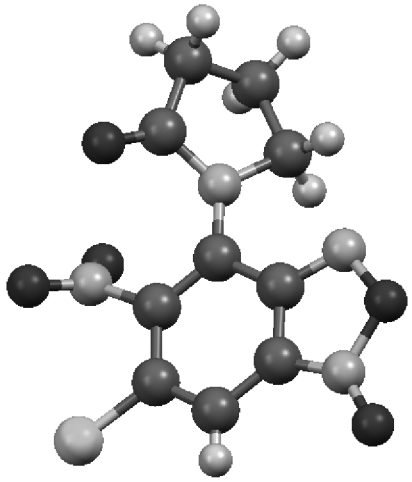
i, isobutyl chloroformate, EtOAc, Et_3N, 0–4°C, 30 min; *ii*, 3-aminopropane-1,2-diol 1,2-dinitrate, EtOAc, Et_3N, 20°C, 1 h.

drugs. Such opportunity has been demonstrated in [8] with reaction of **IIId** with 2-aminoethylnitrate (Scheme 2).

In this work, we used 3-amino-1,2-diol 1,2-dinitrate as pharmacophore group consisting of additional NO-donor moiety. However, attempts to obtain 6-chloro-5-nitrobenzofuroxan derivative **VII** by analogy with compound **V** [8] failed. 6-Chloro-5-nitro-4-(2-oxopyrrolidin-1-yl)benzofuroxan **VIII** was obtained as the major reaction product (Scheme 3).

The structure of **VIII** was confirmed by NMR spectroscopy and X-ray diffraction. The NMR spectra contained two sets of broadened signals corresponding to two tautomers in the 7 : 3 ratio.

According to the X-ray diffraction (see Figure), the unit cell of compound **VIII** contained two independent molecules, differing in arrangement of the C^{13} and C^{14} atoms in the oxopyrrolidine fragment. The bond lengths were close to the usual values. Intermolecular interactions led to formation of complex three-dimensional structure.



General view of the molecule of compound **VIII**.

EXPERIMENTAL

^{1}H NMR spectra were recorded with the Bruker AVANCE-600 spectrometer (600.13 MHz) relative to the signals of residual solvent protons (acetone-d_6). Melting point was determined with the Boetius apparatus and reported uncorrected. TLC was performed using Silufol UV 254 plates (Kavalier).

X-Ray diffraction study was carried out at 150 K with the Bruker Smart APEX II CCD automatic diffractometer [graphitic monochromator, λ(MoK_α) = 0.71073 Å, ω-scanning, 2θ < 54°, R_{int} 0.021]. Crystals of **VIII** were monoclinic, $C_{10}H_7ClN_4O_5$, M 298.65. The unit cells parameters were as follows: a 18.992(2), b 15.552(2), c 7.932(1) Å, β 94.259(1)°, V 2336.3(5) Å^3, Z 8, space group $P2_1/c$, d_{calc} 1.698 g cm^{-3}, μ 0.356 mm^{-1}, F(000) 1216. Intensity of 19452 reflections was measured {5085 independent, 4629 observed [$I > 2\sigma(I)$]}. Final refinement parameters: values of the divergence factors: R 0.0282, wR_2 0.0772, GOF 0.91. Absorption was corrected for in SADABS software [9]. The structure was solved by direct methods (SIR [10]) and refined in the isotropic-anisotropic approximation (SHELXL-97 [11]). Parameters of the hydrogen atoms were refined using the *rider* model. All calculations were performed using WinGX [12] and APEX2 [13] software. Figures and analysis of intermolecular contacts were performed taking advantage of PLATON software [14]. Crystallographic data for **IX** were deposited at the Cambridge Structural Database (CCDC 1001192).

X-Ray diffraction analysis of single crystals of compound **VIII** was performed at Department of X-ray diffraction studies, Center for Collective Use, Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Center, Russian Academy of Sciences.

6-Chloro-5-nitro-4-(2-oxopyrrolidin-1-yl)benzofuroxan (VIII). A mixture of 2 mL of ethyl acetate, 0.080 g (0.25 mmol) of benzofuroxan **IIId**, 0.035 mL (0.25 mmol) of triethylamine and 0.035 mL (0.25 mmol) of isobutyl chloroformate was stirred during 30 min at 0–4°C. Then the solvent was removed in vacuum, and the residue was dissolved in 2 mL of ethyl acetate. A solution of 3-aminopropane-1,2-diol 1,2-dinitrate, prepared from 55 mg (0.30 mmol) of 2,3-bis(nitrooxy)propylammonium nitrate and 45 μL of triethylamine in 2 mL of ethyl acetate, was added to a solution of **VI** in ethyl acetate. The reaction mixture was stirred at room temperature during 1 h, and then washed sequentially with water, hydrochloric acid, and saturated aqueous solution of NaCl. The organic layer was separated, dried over anhydrous Na_2SO_4, and evaporated in vacuum. The residue was purified by chromatography on silica gel (Merck, Germany) eluting with the benzene–EtOAc mixture. Yield 74%, mp 110–112°C (hexane). ^{1}H NMR spectrum, δ, ppm: 2.35 s (2H, H^{13}), 2.55 s (2H, H^{12}), 3.78 d (2H^{14}_{minor}, 68.3 Hz), 4.11 s (2H, H^{14}), 7.99 s (1H, H^7), 8.28 s (1H^7_{minor}). ^{13}C NMR spectrum, δ_C, ppm: 19.71 (C^{13}), 30.08 (C^{12}), 50.02 (C^{14}), 50.33 (C^{14}_{minor}), 110.85 (C^9_{minor}), 113.73 (C^7, C^8), 119.49 (C^7_{minor}), 122.77 (C^4_{minor}), 125.06 (C^4, C^6), 128.75 (C^6_{minor}), 147.10 (C^5), 148.64 (C^9, C^5_{minor}), 150.91 (C^8_{minor}), 174.58 (C^{11}), 175.46 (C^{11}_{minor}).

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