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LETTERS TO THE EDITOR

Benzofuroxans Containing NO-Generating Fragment

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Currently, one of the promising direction of medicinal chemistry is to create a hybrid multitarget pharmaceuticals by introducing into the known drug molecule the fragment, which is a generator of nitric oxide (NO) [1]. Nitric oxide is an endogenous signaling molecule with a wide range of biological activities and plays an important role. This biological mediator formed in the organism from the amino acid arginine including several types of NO-synthases, an important regulator of many physiological processes through a mechanism involving activation of cytosolic guanidylcyclase [2].

Furoxans, derivatives of 1,2,5-oxadiazole *N*-oxide, are heterocyclic thermally stable compounds, which are capable to slowly generate NO for a long time and which do not cause development of nitrate tolerance [3]. Also they are of great interest as possible potential NO-generating prodrugs.

We synthesized new derivatives of 6-chloro-5-nitro- and 4,6-dinitrobenzofuroxans containing additional NO-donor fragment. Nitroxy group was used as this fragment, which was introduced into the benzofuroxan molecule using amino alcohol as a linker.

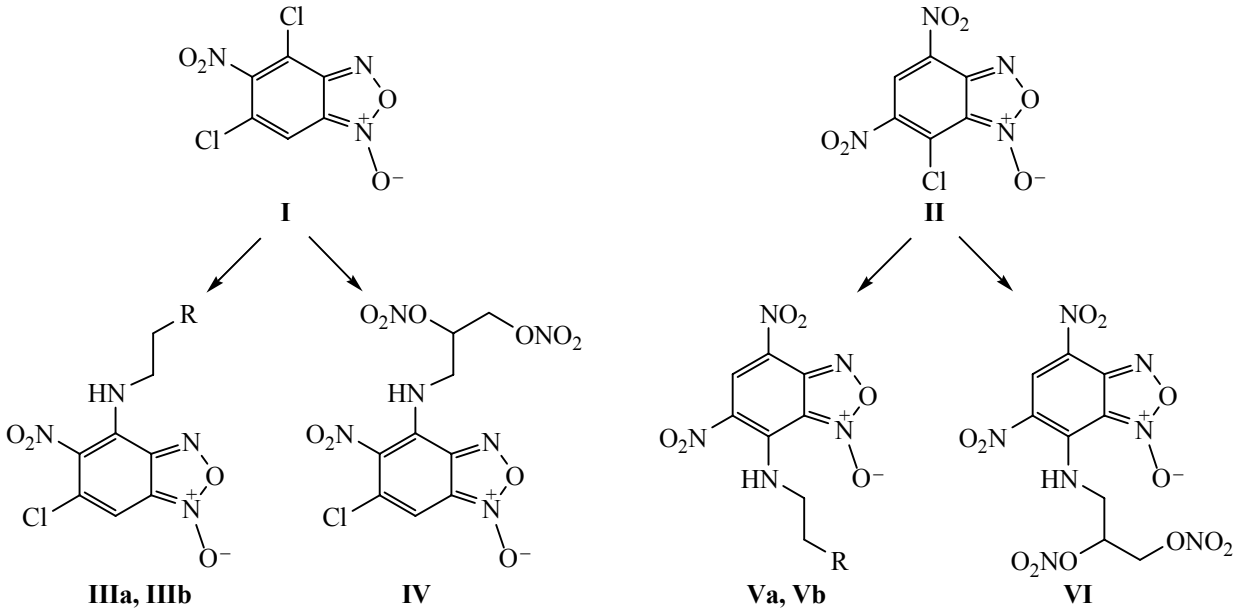
The initial 4,6-dichloro-5-nitro- **I** and 4,6-dinitro-7-chlorobenzofuroxans **II** were synthesized from *p*-nitroaniline [4] and 2-nitro-4-chloroaniline [5]. *O*-Nitrates of aminoalcohols, nitroethanolamine and 3-aminopropanediol-1,2-dinitrate, were obtained by nitration of the appropriate amino alcohol with nitric acid in methylene chloride [6]. The reaction of nitroaminoalcohol with nitrobenzofuroxan was carried out in methanol in the presence of sodium bicarbonate. Note that 4,6-dichloro-5-nitrobenzofuroxan interacts with the amino group of nitroaminoalcohol only with the participation of the chlorine atom in the position 4 of aromatic ring [7] to form only the monosubstituted products.

Attempts to synthesize 6-chloro-5-nitro-4-{[2-(nitroxy)ethyl]amino}benzofuroxan **IIIb** via the nitration of 6-chloro-4-[(2-hydroxyethyl)amino]-5-nitrobenzofuroxan **IIIa** failed. The nitration of alcohol **IIIa** by nitric acid results in degradation of the starting compound.

Preliminary study of the biological activity of the synthesized benzofuroxans showed that in experiments with yeast-like fungi *Candida albicans* the activity of compound **IIIb** is comparable to the reference ketoconazole (7.8 and 3.9 mg ml^{-1}, respectively). In experiments with Gram-positive bacteria *Staphylococcus aureus* the activity of compound **IIIb** is several times exceed Chloramphenicol (15.6 and 62.5 mg ml^{-1}, respectively).

Synthesis of benzofuroxan derivatives III–VI *(general procedure).* A mixture of 0.4 mmol of (nitro)-aminoalcohol, 68 mg (0.8 mmol) of $NaHCO_3$, and 0.4 mmol of benzofuroxan in 2 ml of methanol was stirred for 1 h at 60°C, then diluted with 4 ml of water and 20 ml of ethyl acetate. The organic layer was separated, washed with water and saturated aqueous NaCl, dried over anhydrous Na_2SO_4. The solution was filtered and evaporated in a vacuum. The residue was purified by column chromatography on silica gel L (100–250 μm) eluting with benzene.

6-Chloro-4-[(2-hydroxyethyl)amino]-5-nitrobenzo-[*c*][1,2,5]oxadiazol 1-oxide (IIIa). Yield 89%, mp



R = OH (**a**), ONO_2 (**b**).

110–112°C (hexane). ^{1}H NMR spectrum, (DMSO-d_6), δ_H, ppm, (*J*, Hz): 3.79 t (2H, C$\underline{H}_2$OH, $^3J_{HH}$ 6.2), 4.15 q (2H, C$\underline{H}_2$NH, $^3J_{HH}$ 6.2), 7.22 s (1H, Ar), 9.17 t (1H, NH, $^3J_{HH}$ 6.1).

6-Chloro-5-nitro-4-{[2-(nitroxy)ethyl]amino}benzo[*c*][1,2,5]oxadiazol 1-oxide (IIIb). Yield 94%, mp 103–105°C (hexane). ^{1}H NMR spectrum ($CDCl_3$), δ_H, ppm (*J*, Hz): 4.45 q (2H, C$\underline{H}_2$NH, $^3J_{HH}$ 8.1), 4.78 t (2H, C$\underline{H}_2$ONO$_2$, $^3J_{HH}$ 5.0), 6.77 s (1H, Ar), 7.98 br. s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm (*J*, Hz): 44.16 (CH_2NH), 71.32 (CH_2ONO_2), 92.95 (C^6), 101.14 (C^7), 112.88 (C^3), 129.57 (C^4), 136.85 (C^5), 147.29 (C^8).

6-Chloro-5-nitro-4-{[3-(nitroxy)-2-(nitrosoperoxy)propyl]amino}benzo[*c*][1,2,5]oxadiazol 1-oxide (IV). Yield 82%, mp 115–117°C (hexane). ^{1}H NMR spectrum ($CDCl_3$), δ_H, ppm (*J*, Hz): 4.10–4.30 m (1H, C$\underline{H}_2$NH), 4.55–4.75 m (2H, C$\underline{H}_2$NH+C$\underline{H}_2$ONO$_2$), 4.94 d. d (1H, C$\underline{H}_2$ONO$_2$, $^3J_{HH}$ 3.40, 13.0), 5.55–5.75 m (1H, C$\underline{H}$), 6.81 s (1H, Ar), 7.75–7.90 m (1H, NH).

7-[(2-Hydroxyethyl)amino]-4,6-dinitrobenzo[*c*][1,2,5]oxadiazol 1-oxide (Va). Yield 78%, mp 140–142°C (hexane). ^{1}H NMR spectrum (DMSO-d_6), δ_H, ppm (*J*, Hz): 3.76 t (2H, C$\underline{H}_2$OH, $^3J_{HH}$ 5.2), 3.91 t (2H, C$\underline{H}_2$NH, $^3J_{HH}$ 6.0), 9.43 s (1H, Ar), 11.70–1.85 m (1H, NH).

4,6-Dinitro-7-{[2-(nitroxy)ethyl]amino}benzo[*c*][1,2,5]oxadiazol 1-oxide (Vb). Yield 68%, orange oil. ^{1}H NMR spectrum (acetone-d_6), δ_H, ppm (*J*, Hz): 4.83 q (2H, C$\underline{H}_2$NH, $^3J_{HH}$ 5.5), 5.09 t (2H, C$\underline{H}_2$ONO$_2$, $^3J_{HH}$ 4.9), 8.85 s (1H, Ar), 10.93 br. s (1H, NH).

4,6-Dinitro-7-{[(3-(nitroxy)-2-(nitrosoperoxy)propyl]amino}benzo[*c*][1,2,5]oxadiazol-1-oxide (VI). Yield 73%. ^{1}H NMR spectrum (acetone-d_6), δ_H, ppm (*J*, Hz): 4.60–4.80 m (3H, C$\underline{H}_2$NH + C$\underline{H}_2$ONO$_2$), 5.25 d. d (1H, C$\underline{H}_2$ONO$_2$, $^3J_{HH}$ 3.4, 13.0), 6.00–6.25 m (1H, C$\underline{H}$), 8.84 s (1H, Ar), 10.92 br. s (1H, NH).

The NMR spectra were recorded on a Bruker CXP-200 instrument (Germany) relative to Me_4Si from $CDCl_3$, acetone-d_6 and DMSO-d_6 solutions. Melting points were determined on a Boethius heating block and reported correction. TLC was performed on Silufol UV 254 plates (Kavalier, Czechoslovakia). Column chromatography was carried out using Kieselgel 60 silica gel (Merck, Germany).

Bacteriostatic and fungiostatic properties were studied by the method of serial dilutions in a liquid medium according to [8, 9]. Stock solution should contain 500 μg ml^{-1} of the test sample.

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