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[1,4]Dithiino[2,3-*c*:5,6-*c′*]bis[1,2,5]oxadiazole di-*N*-oxide: synthesis and oxidation to mono- and bis-*S*-oxides

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[1,4]Dithiino[2,3-*c*:5,6-*c′*]bis[1,2,5]oxadiazole di-*N*-oxide being an equilibrium mixture of two isomers was synthesized from 1,4-dithiane-2,3,5,6-tetraone tetraoxime and nitric acid; its oxidation to mono- and bis-*S*-oxides gave one isomer of each derivative.

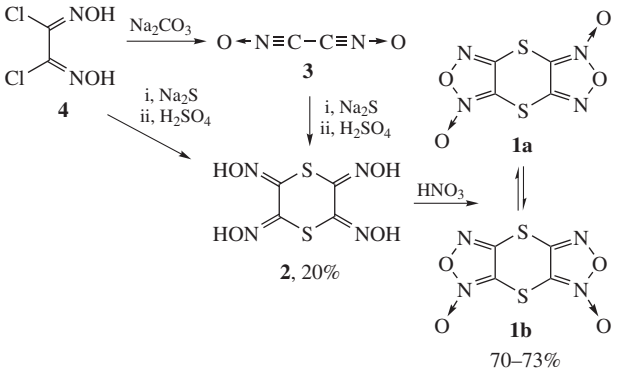
1,2,5-Oxadiazole *N*-oxides (furoxans) attract undiminishing interest due to their application in medicine and industry.[1–4] Apart from antiinfective, anticancer, platelet antiaggregatory and vasodilating properties, the nitric oxide (NO) releasing capacity of furoxans is the most studied pharmacological property for these compounds in the last years.[5–7]

Leading positions in the chemistry and application of furoxans are occupied by the group of Professor Alberto Gasco (Dipartimento di Scienza e Tecnologia del Farmaco, Universita de Torino, Italy, see his latest papers[8–10]) and Professor Nina Makhova (N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Moscow, Russian Federation, see her latest papers[11–13]). The particular attention had recently been paid to the compounds with the combination of a furoxanyl or a fused furoxanyl moiety with another pharmacologically active substructure in a single molecule, called as hybrid drugs.[6,14]

Fused furoxans are insufficiently investigated as potential drugs.[6,15–17] In 4,7-dimethyl-1,2,5-oxadiazolo[3,4-*d*]pyridazine 1,5,6-trioxide, both heterocycles exert a synergetic effect with enhanced biological activity.[18] Sulfide, sulfoxide and sulfone-containing furoxans showed one of the most powerful platelet antiaggregatory activity compared to other furoxans.[6,19–21] Herein we report the synthesis of [1,4]dithiino[2,3-*c*:5,6-*c′*]bis[1,2,5]oxadiazole di-*N*-oxide **1** and the study of its oxidation to *S*-oxides and *S*-sulfones. These compounds can be considered as potentially useful NO-donors.

According to the literature data one of the general furoxan synthesis is the oxidation of vicinal dioximes (glyoximes).[1] This method on using NaOCl as an oxidant was successfully employed for the preparation of only known dithiinofuroxan representative, namely, 5,6-dihydro[1,4]dithiino[2,3-*c*][1,2,5]oxadiazole 1-oxide.[22] 1,4-Dithiane-2,3,5,6-tetraone tetraoxime **2**, which can be a starting material for the preparation of difuroxan **1**, is known,[21] however, its synthesis is inconvenient and dangerous because of using unstable and explosive ethanedinitrile 1,2-dioxide **3** as an intermediate. We have elaborated a one-step synthesis of dithiane-2,3,5,6-tetraone tetraoxime **2** from dichloroglyoxime **4** by its treatment with sodium sulfide at 0–5 °C. Tetraoxime **2** was obtained in 20% yield which is better than in two-step synthesis (14%) through ethanedinitrile 1,2-dioxide **3** (Scheme 1).[23]

Tetraoxime **2** on oxidation with NaOCl, N_2O_4 and $K_3Fe(CN)_6$, which are usually used for the preparation of furoxans from glyoximes,[1] gave complex hardly separable mixtures where difuroxan **1** was detected in traces only. Treatment of tetraoxime **2** with nitric acid, which is rarely used in furoxan synthesis, afforded difuroxan **1** in high yields; remarkably that for this purpose nitric acid of various concentrations (from 25 to 100%) can be employed with no influence on the yield of the product (see Scheme 1).†



Scheme 1

According to ^{13}C NMR data, compound **1** exists as a mixture of two isomers in practically equal ratio; this ratio did not depend on the concentration of HNO_3 used in the synthesis of **1**. In an

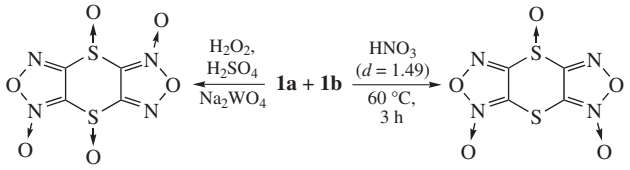
† New compounds were characterised by elemental analysis, ^1H, ^{13}C and ^{15}N NMR, mass and IR spectra.

1,4-Dithiane-2,3,5,6-tetraone tetraoxime **2**. 1,2-Dichloroglyoxime **4** (47.1 g, 0.3 mol) was added portionwise to a solution of $Na_2S·9H_2O$ (172.8 g, 0.72 mol) in H_2O (300 ml) at 0–5 °C within 0.5 h. The reaction mixture was stirred for 1 h at this temperature and then allowed to reach room temperature, after which it was acidified with 20% H_2SO_4 to pH 4. The precipitate was filtered and dissolved in diethyl ether. The mother liquids were extracted with Et_2O (3×30 ml), the extracts were combined, dried with $CaCl_2$ and evaporated under reduced pressure. The residue was washed with $CHCl_3$ and CF_3CO_2H. Yield 7.14 g (20 %), mp 225 °C (lit.,[23] mp 225–230 °C). ^1H NMR (DMSO-d_6) δ: 12.91 (br.s, 4H, OH). ^{13}C NMR (DMSO-d_6) δ: 138.5. IR (KBr, ν/cm^{-1}): 3190 (OH), 2950, 2800, 1570, 1545, 1350, 1200, 1170, 980, 910.

[1,4]Dithiino[2,3-c:5,6-c′]bis[1,2,5]oxadiazole di-N-oxide **1**. Tetraoxime **2** (118 mg, 0.5 mmol) was added to HNO_3 (3 ml, d = 1.36 g cm^{-3}) at room temperature and the mixture was stirred for 40 min. Ice water (10 ml) was added, the mixture was extracted with CH_2Cl_2 (2×10 ml), extracts were washed with H_2O, dried with $CaCl_2$ and evaporated under reduced pressure. Yield 85 mg (73%), mp 155.5–157.5 °C (CCl_4). ^{13}C NMR (DMSO-d_6): 109.5 and 109.8 [C=N(O)O], 149.4 and 150.1 (C=N–O). ^{15}N NMR (DMSO-d_6): –33.2 and –33.6 [C=N(O)O], –16.0 and –15.4 (C=N–O). IR (KBr, ν/cm^{-1}): 1580 (C=N), 1440, 1380, 1330, 1230, 1050, 1025, 980, 800, 720. MS (EI, 70 eV), *m/z* (%): 232 (M^+, 40), 216 (M^+ – O, 5), 202 (M^+ – NO, 5), 186 (M^+ – 2O – NO, 5), 172 (M^+ – 2NO, 10), 156 (M^+ – O – 2NO, 7). Found (%): C, 20.57; N, 24.47; S, 27.35. Calc. for $C_4N_4O_4S_2$ (%): C, 20.69; N, 24.13; S, 27.62.

attempt to change the ratio of isomers and to obtain one single isomer, thermal behaviour of **1** was investigated. Heating it in chlorobenzene (130 °C, 4 h) or neat at mps temperature left the ratio of isomers **1a** and **1b** unchanged; heating in DMSO at 100 °C for 0.5 h led to decomposition of difuroxan **1**. We suppose that isomers **1a** and **1b** are in thermodynamic equilibrium.

With the aim to obtain *S*-oxides and *S*-sulfones of compound **1**, its oxidation with various agents was studied. Organic and inorganic peroxy acids,[24–26] nitric acid[27,28] and other reagents were usually employed for the oxidation of 1,4-dithiines. In fact, NaOCl and N_2O_4 did not react with difuroxan **1**, which was practically fully recovered. Treatment with 100% HNO_3 at 60 °C for 3 h gave mono-*S*-oxide **5** in good yield (Scheme 2).† Surprisingly ^{13}C NMR spectrum of this compound showed only one isomer of mono-*S*-oxide, apparently due to sterical hindrance of *N*- and *S*-oxide groups. More powerful oxidizing agents such as trifluoroperoxyacetic acid and a mixture of conc. H_2O_2, H_2SO_4 and Na_2WO_4 produced di-*S*-oxide **6**. Treatment with CF_3CO_3H provided low yield of di-*S*-oxide **6** contaminated with side products, while reaction with Caro's acid in the presence of Na_2WO_4 at 10–15 °C for 2 h afforded compound **6** in moderate yield (see Scheme 2). According to ^{13}C NMR spectrum di-*S*-oxide exists as one, probably, centrosymmetric isomer **6**. The structure of *S*-oxides was confirmed by IR (specific band at 1080–1100 cm^{-1})[29] and mass spectra which contained along with peaks of molecular ions, intensive peaks of one and two oxygen atoms removal from *S*-oxide group.



6, 47% **5**, 72%

Scheme 2

Further treatment of di-*S*-oxide **6** with conc. H_2O_2, H_2SO_4 and Na_2WO_4 gave a complex mixture which, according to IR spectra, did not contain sulfone derivatives (absence of intense bands at 1335–1360 and 1170–1160 cm^{-1}).

In conclusion, previously unknown [1,4]dithiino[2,3-*c*:5,6-*c*′]-bis[1,2,5]oxadiazole di-*N*-oxide **1** has been synthesized. It exists as a thermodinamic mixture of two tautomers. Selective oxidation of difuroxan **1** to mono- and bis-*S*-oxides has been developed.

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We dedicate this study to the memory of Professor Lenor I. Khmel'nitskii who was our colleague and co-author for many years.

[1,4]Dithiino[2,3-c:5,6-c′]bis[1,2,5]oxadiazole 1,4,7-trioxide **5**. A mixture of difuroxan **1** (232 mg, 1 mmol) and conc. HNO_3 (1 ml, d = 1.49 g cm^{-3}) was heated at 55–60 °C for 3 h, cooled to room temperature, and diluted with ice water (20 ml). The resulting precipitate was filtered and dissolved in CH_2Cl_2, mother liquids were extracted with CH_2Cl_2 (2×10 ml). Combined extracts were washed with H_2O, dried with $CaCl_2$ and evaporated under reduced pressure. Yield 179 mg (72%), mp 169–170 °C ($CHCl_3$). ^{13}C NMR (DMSO-d_6): 117.6 [C=N(O)O], 147.3 (C=N–O). IR (KBr, ν/cm^{-1}): 1580 (C=N), 1360, 1330, 1220, 1080 (S=O), 1050, 1010, 960, 790, 700. MS (EI, 70 eV), *m*/*z* (%): 248 (M^+, 25), 232 (M^+ – O, 12), 218 (M^+ – NO, 22), 216 (M^+ – 2O, 18), 202 (M^+ – O – NO, 15), 200 (M^+ – 3O, 29), 188 (M^+ – 2NO, 35). Found (%): C, 19.38; N, 22.66; S, 25.42. Calc. for $C_4N_4O_5S_2$ (%): C, 19.36; N, 22.57; S, 25.84.

[1,4]Dithiino[2,3-c:5,6-c′]bis[1,2,5]oxadiazole 1,4,5,8-tetraoxide **6**. Reagents $Na_2WO_4 \cdot 2H_2O$ (330 mg, 1 mmol), conc. H_2SO_4 (2 ml) and difuroxan **1** (160 mg, 0.7 mmol) were added in turn to conc. (85%) H_2O_2 at 10–15 °C. The mixture was stirred at room temperature for 2 h, and diluted carefully with ice water (50 ml). The resulting precipitate was filtered, washed with H_2O and dried. Yield 80 mg (44%), mp 161–162 °C (1,2-dichloroethane–heptane). ^{13}C NMR (DMSO-d_6) δ: 113.6 [C=N(O)O], 148.8 (C=N–O). IR (KBr, ν/cm^{-1}): 1600 (C=N), 1430, 1320, 1220, 1180, 1080 (S=O), 960, 780. MS (EI, 70 eV), *m*/*z* (%): 264 (M^+, 27), 248 (M^+ – O, 15), 232 (M^+ – 2O, 22), 216 (M^+ – 3O, 18), 202 (M^+ – 2O – NO, 30), 186 (M^+ – 3O – NO, 35). Found (%): C, 18.39; N, 21.34; S, 24.28. Calc. for $C_4N_4O_6S_2$ (%): C, 18.18; N, 22.21; S, 24.24.

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