Cyclic sulfates of pentaerythritol dinitrate

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New mixed nitric and sulfuric esters of pentaerythritol, *viz.*, 5,5-bis(nitroxymethyl)-1,3-dioxa-2-thiacyclohexane 2,2-dioxide and 5,11-bis(nitroxymethyl)-1,3,7,9-tetraoxa-2,8-dithiacyclododecane 2,2,8,8-tetroxide, were synthesized by the reaction of pentaerythritol dinitrate with sulfuryl chloride (followed by alkaline treatment) and bis(chlorosulfonyl)pentaerythritol dinitrate, respectively.

Key words: 5,5-bis(nitroxymethyl)-1,3-dioxa-2-thiacyclohexane 2,2-dioxide, pentaerythritol dinitrate, bis(chlorosulfonyl)pentaerythritol dinitrate, 5,11-bis(nitroxymethyl)-1,3,7,9-tetraoxa-2,8-dithiacyclododecane 2,2,8,8-tetroxide, X-ray diffraction analysis.

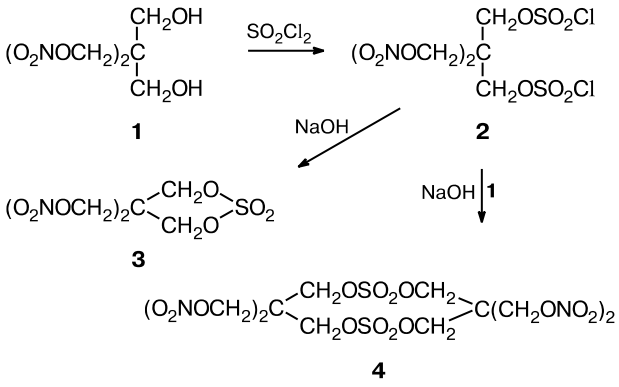
The biological activity of pentaerythritol tetranitrate is well known.[1] Other pentaerythritol nitro derivatives, for example, 3,3-bis(hydroxymethyl)oxetane dinitrate, also possess physiological activity. In combination with certain cytostatics, the latter compound (as a nitrogen monoxide donor) exhibits powerful antimetastatic activity.[2,3] The spectrum of physiological activities of pentaerythritol nitro derivatives can be extended by modifications, for example, by introduction of sulfonyl groups. In this context, the aim of the present study was to develop approaches to the synthesis of pentaerythritol derivatives with nitrate and sulfonyl groups.

Mixed nitric and sulfuric esters of polyhydric alcohols can be prepared by the reactions of alcohols, for example, of pentaerythritol,[4] with a mixture of sulfuric and nitric acids. The resulting acid esters remain in the acidic solution and can be isolated as salts. Pentaerythritol sulfates containing also the nitrate group are unknown.

The mixed ester was synthesized by the known reaction of alcohols with sulfuryl chloride.[5] The reaction of pentaerythritol dinitrate (**1**) with SO_2Cl_2 (1 : 2) afforded bis-sulfonylation product **2** (Scheme 1), which could be isolated from the reaction mixture. Alkaline hydrolysis of compound **2** is accompanied by elimination of one chlorosulfonyl fragment to give 5,5-bis(nitroxymethyl)-1,3-dioxa-2-thiacyclohexane 2,2-dioxide (**3**) in ~25% yield.

X-ray diffraction study demonstrated that molecule **3** (Fig. 1, Table 1) contained the dinitrate fragment $(O_2NOCH_2)_2C$ (O=N, 1.187(3)—1.197(3) Å; N—O, 1.394(3) and 1.398(3) Å) and a six-membered ring formed

Scheme 1



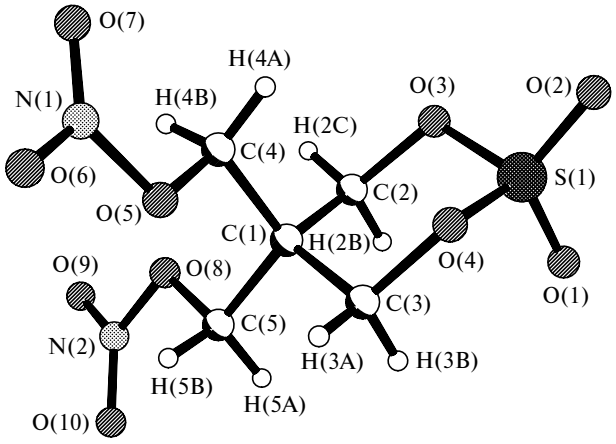


Fig. 1. Molecular structure of compound **3**.

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Table 1. Selected bond lengths (*d*) and bond angles (ω) in molecule **3**

Bond	*d*/Å	Angle	ω/deg
S(1)—O(2)	1.4037(17)	O(2)—S(1)—O(1)	120.66(11)
S(1)—O(4)	1.5574(16)	O(1)—S(1)—O(4)	110.13(10)
O(3)—C(2)	1.469(2)	O(1)—S(1)—O(3)	108.84(11)
O(5)—N(1)	1.398(2)	C(2)—O(3)—S(1)	114.94(14)
O(6)—N(1)	1.197(3)	N(1)—O(5)—C(4)	113.64(18)
O(8)—N(2)	1.394(2)	O(7)—N(1)—O(6)	130.1(2)
O(9)—N(2)	1.195(3)	O(6)—N(1)—O(5)	111.4(2)
C(1)—C(2)	1.526(3)	O(9)—N(2)—O(8)	112.95(18)
C(1)—C(4)	1.529(3)	C(2)—C(1)—C(5)	109.75(16)
S(1)—O(1)	1.4175(18)	C(5)—C(1)—C(4)	112.44(17)
S(1)—O(3)	1.5616(17)	C(5)—C(1)—C(3)	105.22(15)
O(4)—C(3)	1.458(2)	O(3)—C(2)—C(1)	110.29(17)
O(5)—C(4)	1.446(3)	O(5)—C(4)—C(1)	105.43(16)
O(7)—N(1)	1.187(3)	O(2)—S(1)—O(4)	107.25(10)
O(8)—C(5)	1.447(2)	O(2)—S(1)—O(3)	107.05(10)
O(10)—N(2)	1.197(2)	O(4)—S(1)—O(3)	101.13(8)
C(1)—C(5)	1.528(3)	C(3)—O(4)—S(1)	114.07(12)
C(1)—C(3)	1.533(3)	N(2)—O(8)—C(5)	112.98(15)
		O(7)—N(1)—O(5)	118.5(2)
		O(9)—N(2)—O(10)	128.9(2)
		O(10)—N(2)—O(8)	118.14(19)
		C(2)—C(1)—C(4)	107.75(17)
		C(2)—C(1)—C(3)	109.49(17)
		C(4)—C(1)—C(3)	112.17(17)
		O(4)—C(3)—C(1)	110.19(15)
		O(8)—C(5)—C(1)	106.10(15)

by the $C(CH_2)_2$ (C—C, 1.526(3) and 1.533(3) Å) and O_2S (O—S, 1.5574(16) and 1.5616(17) Å) fragments. The ring adopts a chair conformation. The S—O distances in the ring are essentially larger than the S=O bond lengths (1.4037(17) and 1.4175(18) Å, respectively).

Alkaline hydrolysis of bis(chlorosulfate) **2** in dioxane in the presence of an excess of diol **1** occurs with retention of both sulfonyl fragments to give compound **4** as a condensation product of compounds **1** and **2** (see Scheme 1). Compound **4** was characterized by IR and NMR spectroscopy.

Therefore, the above-described procedure of chemical assembly of pentaerythritol esters holds promise and can be used to synthesize this class of compounds.

Experimental

The starting pentaerythritol dinitrate (**1**) was prepared according to a known procedure.[6] The IR spectra were recorded on a Specord M-82 spectrometer in KBr pellets. The ^{1}H NMR spectra were measured on a cryogenic spectrometer (294 MHz), which was designed and built at the Institute of Problems of Chemical Physics in Chernogolovka of the Russian Academy of Sciences. The ^{13}C NMR spectrum was recorded on a Bruker DXP-200 spectrometer. Melting points were determined on a Boetius RNMK-05 hot-stage apparatus.

Di-*O*-chlorosulfonylpentaerythritol dinitrate (2). Dinitrate **1** (31.2 g, 0.138 mol) was added with vigorous stirring to SO_2Cl_2 (19.5 mL, 0.24 mol) at 30—32 °C. The reaction mixture was kept at this temperature for 20—25 min and then cooled to 20 °C, after which ethanol (60 mL) was added. After thorough stirring, the white precipitate that formed was filtered off, washed on a filter with ethanol (2×20 mL), and dried in air. Compound **2** was obtained in a yield of 27.3 g (47.7%) as a crystalline product, m.p. 76.6 °C. Found (%): C, 14.18; H, 1.89; Cl, 16.78; N, 6.62; S, 15.13. $C_5H_8Cl_2N_2O_{12}S_2$. Calculated (%): C, 14.35; H, 2.15; Cl, 16.90; N, 6.54; S, 15.02. IR, ν/cm^{-1}: 3030 v.w, 2984 v.w, 2914 v.w, 1464 w (CH_2); 1644 v.s, 1281 s, 859 s, 847 sh (ONO_2); 1413 s, 1194 s (OSO_2); 620 m, 605 m, 594 m (S—Cl).

5,5-Bis(nitroxymethyl)-1,3-dioxa-2-thiacyclohexane 2,2-dioxide (3). Dinitrate **1** (33.6 g, 0.149 mol) was added with vigorous stirring to SO_2Cl_2 (21 mL, 0.26 mol) at 30—35 °C. The reaction mixture was kept at this temperature for 20 min and then cooled to 20 °C, after which ethanol (60 mL) was added. After the addition of water (150 mL) to the reaction mixture, an oily product sedimented. This was separated by decantation and washed with water. Then acetone (150 mL) was added. A solution of NaOH (15 g, 0.375 mol) in water (25 mL) was added to the acetone solution at 60 °C. The reaction mixture was diluted with water (150 mL) and the solid precipitate that formed was filtered off and dried. The yield of compound **3** was 9.6 g (25%), m.p. 131.5 °C. Found (%): C, 20.83; N, 9.72; S, 11.11. $C_5H_8N_2O_{10}S$. Calculated (%): C, 21.09; N, 9.90; S, 11.32. IR, ν/cm^{-1}: 2943 v.w, 2908 v.w, ~2850 sh, 1444 w, 1456 w (CH_2); 1647 v.s, 1288 s, 1279 s, 876 s, 870 sh (ONO_2); 1413 s, 1401 s, 1200 s (OSO_2). ^{1}H NMR (DMSO-d_6), δ: 4.73 (s, 4 H, CH_2ONO_2 or CH_2OS); 4.82 (s, 4 H, CH_2OS or CH_2ONO_2).

5,11-Bis(nitroxymethyl)-1,3,7,9-tetraoxa-2,8-dithiacyclododecane 2,2,8,8-tetroxide (4). To a solution of bis-chlorosulfate **2** (1 g, 2.3 mmol) in dry dioxane (10 mL), dinitrate **1** (2 g, 9 mmol) and a solution of NaOH (0.24 g, 6 mmol, 18% excess) in dry MeOH (7 mL) were added at 25 °C. The reaction mixture was kept at this temperature for 1 h. The precipitate that formed was filtered off and the filtrate was concentrated to dryness. The residue was washed with diethyl ether and recrystallized from dioxane. The yield of compound **4** was 0.4 g (29.4%), m.p. 169—170 °C (with decomp.). Found (%): C, 20.86; N, 9.78; S, 11.14. $C_{10}H_{16}N_4O_{20}S_2$. Calculated (%): C, 21.84; N, 9.72; S, 11.13. IR, ν/cm^{-1}: 2942 w, 2908 sh, 2868 sh, 1471 m (CH_2); 1646 v.s, 1284 v.s, 983 s, 862 s, 755 m (ONO_2); 1416 s, 1200 v.s (OSO_2O). ^{1}H NMR (DMSO-d_6), δ: 4.51 (s, 8 H, CH_2ONO_2 or CH_2OS); 4.70 (s, 8 H, CH_2OS or CH_2ONO_2).

X-ray diffraction study of compound 3. Crystals suitable for X-ray diffraction study were prepared by slow concentration of a solution in CH_2Cl_2. The X-ray diffraction data were collected on an automated Bruker AXS SMART diffractometer equipped with a CCD detector (graphite monochromator, 110 K, scan step was 0.3°, frames were exposed for 30 s) according to a standard procedure.[7] The crystallographic parameters and details of structure refinement are given in Table 2. The structure of compound **3** was solved by direct methods and refined by the full-matrix least-squares method with anisotropic displacement parameters for all nonhydrogen atoms. The H atoms were localized from a difference Fourier synthesis and refined isotropically.

Table 2. Crystallographic parameters of compound **3**

Parameter	**3**
Molecular formula	$C_5H_8N_2O_{10}S$
Space group	$P2_1/n$
a/Å	8.190(2)
b/Å	10.916(3)
c/Å	12.157(3)
β/deg	101.51(2)
V/Å^3	1065.0(5)
Z	4
d_{calc}/g cm^{-3}	1.797
μ/cm^{-1}	0.360
Radiation	Mo-Kα (λ = 0.71073 Å)
Number of measured reflections	3505
Number of reflections with $I > 2\sigma(I)$	2969
R_1	0.0397
wR_2	0.0984

All calculations were carried out using the SHELX97 program package.[8] Selected geometric parameters of compound **3** are given in Table 1.

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