Synthesis and study of organic nitrates of heterofunctional series

5.* Synthesis of 3,3-bis(hydroxymethyl)oxetane mono- and dinitrates and 2,2-bis(hydroxymethyl)propane-1,3-diol (pentaerythritol) mono- and dinitrates

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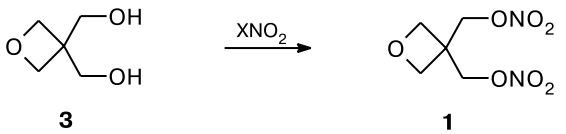
New procedures were developed for the synthesis of 3,3-bis(hydroxymethyl)oxetane dinitrate (**1**) by *O*-nitration of the corresponding glycol (**3**) or its mononitrate (**6**), which were prepared by the reactions of 2,2-bis(hydroxymethyl)propane-1,3-diol (pentaerythritol) (**2**) mono- (**4**) and dinitrates (**5**), respectively, with alkali. A new method was devised for the synthesis of compounds **4** and **5** by the reaction of tetraol **2** with concentrated HNO_3 in dichloroethane. The structures of compounds **1** and **6** were established by X-ray diffraction analysis.

Key words: 3,3-bis(hydroxymethyl)oxetane, 3,3-bis(hydroxymethyl)oxetane mono- and dinitrates, *O*-nitration, 2,2-bis(hydroxymethyl)propane-1,3-diol (pentaerythritol), 2,2-bis(hydroxymethyl)propane-1,3-diol (pentaerythritol) mono- and dinitrates, heterocyclization, X-ray diffraction analysis, IR, ^1H and ^{13}C NMR spectra.

3,3-Bis(hydroxymethyl)oxetane dinitrate (**1**), which is a heterofunctional derivative of 2,2-bis(hydroxymethyl)propane-1,3-diol (pentaerythritol, **2**), is used as an active monomer in the synthesis of energetic polymeric composites.[2,3] Besides, it was found that this compound exhibits cardiovascular[4] and antitumor[5—8] activities.

The aim of the present study was to develop new rational approaches to the synthesis of compound **1**. Known procedures for the preparation of **1** are based on *O*-nitration of 3,3-bis(hydroxymethyl)oxetane (**3**)[9,10] (Scheme 1).

Scheme 1

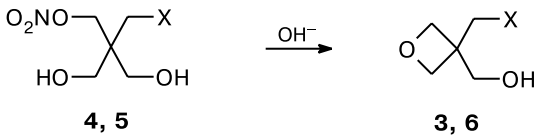


3 **1**

X = NO_3, AcO

Recently,[11] we have devised a new procedure for the synthesis of glycol **3** by the reaction of pentaerythritol mononitrate (**4**) with alkali, which extends the possibilities of preparing compound **1**. Besides, the study of this reaction (intramolecular heterocyclization) using pentaerythritol dinitrate (**5**) as an example is of interest for the synthesis of yet another possible starting compound, *viz.*, of the previously unknown 3,3-bis(hydroxymethyl)oxetane mononitrate (**6**) (Scheme 2).

Scheme 2



4, 5 **3, 6**

X = OH (**3, 4**); ONO_2 (**5, 6**)

The available methods for the synthesis of mononitrates **4** and **5** are rather complicated.[12,13] Hence, another aim of the present study was to simplify these procedures.

* For Part 4, see Ref. 1.

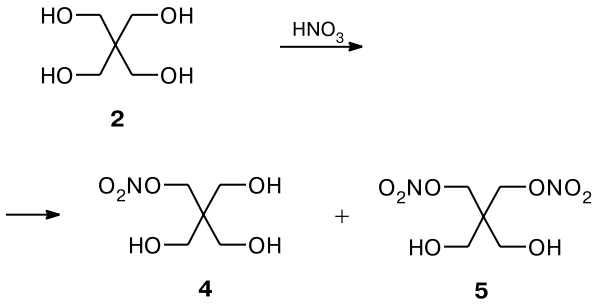
Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 8, pp. 1763—1767, August, 2003.

1066-5285/03/5208-1859 $25.00

Results and Discussion

Presently, mono- (**4**) and dinitrates (**5**) are prepared from **2** either with the use of methods involving the preliminary protection of the hydroxy groups in **2** [12] or by the synthesis of pentaerythritol tetranitrate (powerful explosive, PETN) followed by its stepwise denitration.[13] We developed a one-pot method for the synthesis of compounds **4** and **5** by direct incomplete *O*-nitration of **2** with concentrated HNO_3 in dichloroethane (Scheme 3).

Scheme 3



The isolation of compounds **4** and **5** in individual form is based on the difference in their solubility in water and organic solvents.

Using a procedure devised by us earlier,[11] oxetane glycol **3** was prepared from mononitrate **4** in ~70% yield, which is as good as that obtained according to known procedures.[14,15] The study of heterocyclization of dinitrate **5** demonstrated that the reaction of **5** with an ethanolic solution of an equimolar amount of alkali afforded mononitrate **6** in ~55% yield. The latter is the first representative of incomplete nitrates of the oxetane series. The composition and structure of **6** were established by elemental analysis, spectroscopic methods (IR, ^1H NMR), and X-ray diffraction analysis (Fig. 1, Table 1).

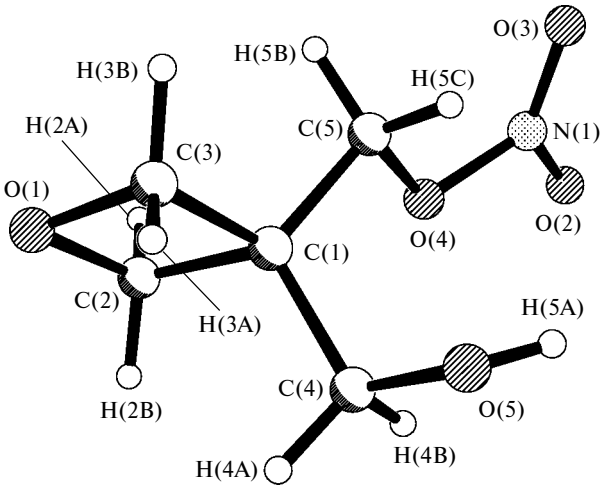


Fig. 1. Molecular structure of **6**.

Table 1. Selected geometric parameters of molecule **6**

Bond	*d*/Å	Bond angle	ω/deg
O(1)—C(2)	1.459(3)	C(2)—O(1)—C(3)	91.39(17)
O(1)—C(3)	1.459(3)	N(1)—O(4)—C(5)	113.41(17)
O(2)—N(1)	1.207(3)	O(3)—N(1)—O(2)	128.4(2)
O(3)—N(1)	1.203(3)	O(3)—N(1)—O(4)	118.77(18)
O(4)—N(1)	1.386(3)	O(2)—N(1)—O(4)	112.80(19)
O(4)—C(5)	1.455(3)	C(5)—C(1)—C(4)	113.1(2)
O(5)—C(4)	1.425(3)	C(5)—C(1)—C(3)	112.4(2)
C(1)—C(5)	1.513(3)	C(4)—C(1)—C(3)	114.4(2)
C(1)—C(4)	1.514(3)	C(5)—C(1)—C(2)	115.3(2)
C(1)—C(3)	1.536(3)	C(4)—C(1)—C(2)	113.64(19)
C(1)—C(2)	1.545(3)	C(3)—C(1)—C(2)	85.31(18)
		O(1)—C(2)—C(1)	91.32(17)
		O(1)—C(3)—C(1)	91.67(18)
		O(5)—C(4)—C(1)	111.90(19)
		O(4)—C(5)—C(1)	105.18(18)

Molecule **6** contains the virtually planar four-membered ring C_3O (H_2C—O, 1.459(3) Å; $R^1R^2C(1)$—$C(2)H_2$, 1.545(3) Å; $R^1R^2C(1)$—$C(3)H_2$, 1.545(3) Å) in which the carbon atom located opposite to the O atom bears two nonequivalent substituents, *viz.*, CH_2OH (C—O, 1.425(3) Å) and CH_2ONO_2 (C—O, 1.455(3) Å; O—N, 1.386(3) Å; N—O(3) and N—O(2), 1.203(3) and 1.207(3) Å, respectively). There is an intramolecular hydrogen bond between the proton of the hydroxy group and one of the terminal oxygen atoms of the nitrate fragment (H...O, 1.914(9) Å).

Dinitrate **1** was prepared in ~15% yield by the reaction of pentaerythritol trinitrate with alkali.[16] A comparison of the yields of the intramolecular heterocyclization products prepared starting from pentaerythritol mono- (**4**), di- (**5**), and trinitrates demonstrated that the yield increases as the number of the nitrate groups in the molecules decreases.

Of known methods for the preparation of the target compound **1**, *O*-nitration of diol **3** with an HNO_3—Ac_2O mixture at −10 °C is the method of choice.[10] This reaction gave rise to the desired product in 73% yield. However, in the study[10] glycol **3** was used as a dilute solution (~8 wt.%) in CH_2Cl_2 to which a cooled nitrating mixture was added. This complicated the procedure for mixing the reagents. Besides, the quality of compound **1** was estimated only with respect to its ability to undergo polymerization. We developed a new procedure for the preparation of compound **1** in a nearly quantitative yield by *O*-nitration of diol **3** with an HNO_3—Ac_2O mixture. The characteristic feature of the new method is that the starting glycol **3**, which is insoluble in usual chloroalkanes, is nitrated as a more concentrated solution in glacial AcOH (~40 wt.%) in the presence of a higher molar HNO_3 con-

tent (60 mol.%) in the HNO_3—Ac_2O system at higher temperature (with a rise from −5 to ~20 °C). In this process, a solution of the substrate is added to the nitrating mixture in $CHCl_3$. An increase in the concentration of HNO_3 to 80—85 mol.% leads to a sharp decrease in the yield of **1**. Apparently, this is associated with the appearance of N_2O_5, which is a more severe nitrating agent, in the nitrating mixture.[17]

The study of mononitrate **6** as the starting compound for the synthesis of **1** demonstrated that *O*-nitration with an HNO_3—Ac_2O mixture also afforded the target product in a nearly quantitative yield. The better solubility of mononitrate **6** (compared to diol **3**) in organic solvents, including haloalkanes, substantially simplifies the synthesis of **1**.

Dinitrate **1** is a colorless crystalline compound with m.p. 93.5—94 °C, which is higher than that published in the literature[9,16,18,19] (89—92 °C). The composition and structure of dinitrate **1** were established by spectroscopic methods (^1H and ^{13}C NMR, IR) and X-ray diffraction analysis (Fig. 2, Table 2).

It should be noted that the anomalies observed in the IR spectrum of compound **1**,[19] which was prepared as a crystalline film (low intensity of a band corresponding to the stretching antisymmetric vibration of the ONO_2 group and its large splitting, $\Delta\nu = 53$ cm^{-1}), are absent in the IR spectrum measured for compound **1** in a KBr pellet (Fig. 3).

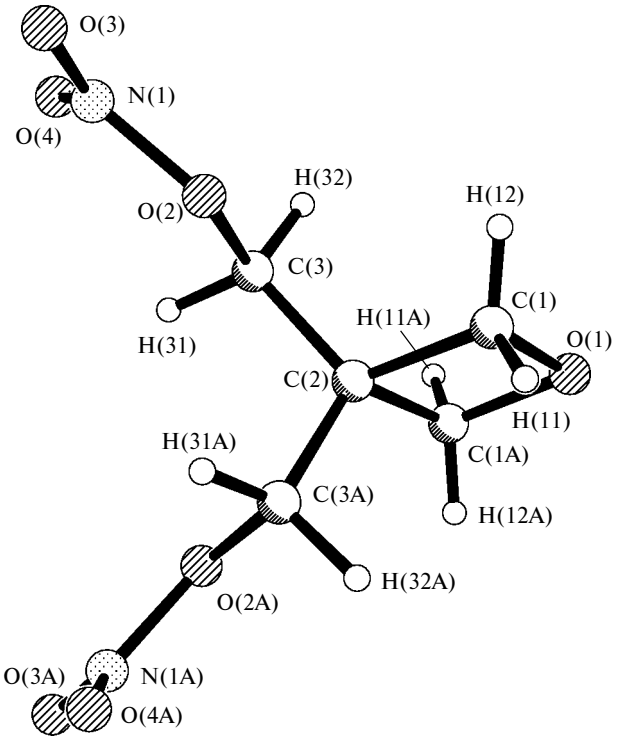


Fig. 2. Molecular structure of **1**.

Table 2. Selected geometric parameters of molecule **1**

Bond	d/Å	Bond angle	ω/deg
O(1)—C(1)	1.446(2)	C(1)—O(1)—C(1A)	92.03(18)
O(2)—N(1)	1.387(2)	N(1)—O(2)—C(3)	113.33(15)
O(2)—C(3)	1.454(2)	O(4)—N(1)—O(3)	128.28(19)
O(3)—N(1)	1.203(2)	O(4)—N(1)—O(2)	119.61(15)
O(4)—N(1)	1.199(2)	O(3)—N(1)—O(2)	112.11(17)
C(1)—C(2)	1.545(2)	O(1)—C(1)—C(2)	91.67(14)
C(2)—C(3)	1.511(2)	C(3)—C(2)—C(3A)	112.0(2)
		C(3)—C(2)—C(1)	115.79(12)
		C(3)—C(2)—C(1A)	113.10(12)
		C(1)—C(2)—C(1A)	84.63(19)
		O(2)—C(3)—C(2)	104.12(14)

The cardiovascular and antitumor activities of dinitrate **1**[4—8] were examined using samples prepared by the new methods.

Experimental

The IR spectra were recorded on a Specord M-82 spectrometer. The ^1H 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. The melting points were determined on a Boetius RNMK-05 stage.

2,2-Bis(hydroxymethyl)propane-1,3-diol mono- (4) and dinitrates (5). Powdered compound **2** (37.5 g, 0.275 mol) was rapidly added with vigorous stirring and cooling to a solution of concentrated HNO_3 (d_4^{20} 1.510) (103 mL, 2.46 mol) in 1,2-dichloroethane (DCE) (525 mL), the temperature being maintained at ~5 °C. After additional stirring at ~5 °C for 1 h, water (115 mL) was slowly added to the reaction mixture at 20 °C. The aqueous layer was separated and neutralized with Na_2CO_3 at ~20 °C. The neutralized solution was extracted with Et_2O (50 mL×3) and then with a 1 : 1 Et_2O—Me_2CO mixture (50 mL×2) by adding first Me_2CO (25 mL) and then Et_2O (25 mL). The combined extracts were concentrated to dryness

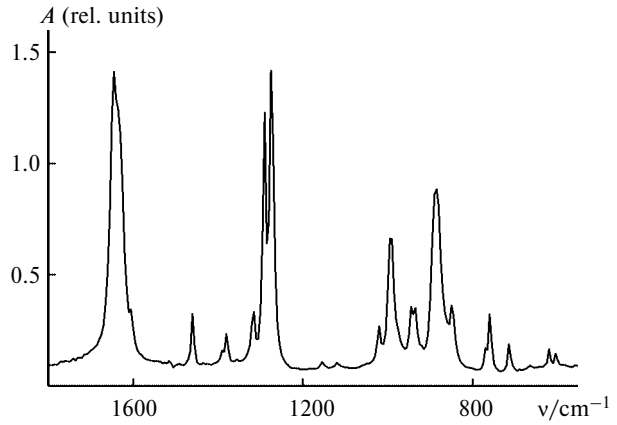


Fig. 3. IR spectrum of compound **1**.

and the resulting product was dissolved in a sixfold (by weight) excess of water. The aqueous solution was extracted with Et_2O (50 mL×4) and the ethereal solution was dried with $MgSO_4$. After removal of the solvent, compound **5** was obtained in a yield of 26.8 g (43%), n_D^{20} 1.4934 (*cf.* lit. data[12]: n_D^{20} 1.4936). Found (%): C, 26.58; H, 4,55; N, 12.30. $C_5H_{10}N_2O_8$. Calculated (%): C, 26.56; H, 4,46; N, 12.39. The aqueous solution was concentrated to dryness to prepare compound **4** in a yield of 8.1 g (16.2%), m.p. 78—79 °C (from DCE) (*cf.* lit. data[12]: 79 °C). Found (%): C, 33.21; H, 6,24; N, 7.65. $C_5H_{11}NO_6$. Calculated (%): C, 33.15; H, 6.12; N, 7.73. The neutralized aqueous solution was concentrated to dryness, the residue was extracted with Me_2CO (25 mL×4), and the solution in acetone was dried with $MgSO_4$. After removal of the solvent, compound **4** was obtained in a yield of 4.1 g (8.2%), m.p. 78—79 °C (from DCE). A mixture with a sample prepared as described above did not give a melting point depression.

3,3-Bis(hydroxymethyl)oxetane (3) was prepared from a solution of compound **4** (18.1 g, 100 mmol) and KOH (6.5 g, 115 mmol) in anhydrous EtOH according to a procedure described earlier.[11] The yield was 8.25 g (70%), b.p. 132—134 °C (1 Torr) (*cf.* lit. data[11]: 132—134 °C (1 Torr)).

3,3-Bis(hydroxymethyl)oxetane mononitrate (6). A solution (7.9 mL) of KOH (0.6 g, 10.6 mmol) in anhydrous EtOH was added with stirring to a solution of compound **5** (2.40 g, 10.6 mmol) in anhydrous EtOH (8 mL). The reaction mixture was refluxed for 3 h, the precipitate that formed was filtered off, the filtrate was concentrated, and the residue was fractionated. Compound **6** was obtained in a yield of 0.96 g (55.5%), b.p. 117—119 °C (1 Torr), m.p. 39—40 °C. Found (%): C, 36.72; H, 5.69; N, 8.44. $C_5H_9NO_5$. Calculated (%): C, 36.81; H, 5.56; N, 8.59. IR (capillary film), ν/cm^{-1}: 3409, 1047 (OH); 1636, 1629, 1281, 872, 844 sh (ONO_2); 980 (oxetane ring); 2960, 2884, 1461, 1379 (CH_2). ^1H NMR (DMSO-d_6), δ: 3.63 (s, 2 H, CH_2OH); 4.35 (m, 4 H, OCH_2, AB, $^2J_{AB} \approx 6.0$; $\Delta\nu_{AB} \approx 11.9$ Hz); 4.71 (s, 2 H, CH_2ONO_2); ~5.00 (br.s, 1 H, OH).

3,3-Bis(hydroxymethyl)oxetane dinitrate (1). ***A.*** A solution of compound **3** (2.36 g, 20 mmol) in glacial AcOH (3.6 mL) was added with stirring to a solution of a mixture of concentrated HNO_3 (d_4^{20} 1.513) (3.2 mL, 80 mmol) and Ac_2O (4.7 mL, 50 mmol) in $CHCl_3$ (20 mL) at −5—0 °C. The reaction mixture was stirred for 20 min with a gradual increase in the temperature to 18—20 °C and then stirred at ~20 °C for 40 min, after which it was poured into ice water. The organic layer was separated, washed with water, a 10% aqueous $NaHCO_3$ solution, and again with water, and then dried with $MgSO_4$. After removal of the solvent, compound **1** was obtained in a yield of 4.04 g (97%) as colorless crystals, m.p. 93.5—94 °C (from 1,2-dichloroethane) (*cf.* lit. data: m.p. 89—91[16] и 90—92 °C[9,18,19]). Found (%): C, 28.86; H, 4.02; N, 13.50. $C_5H_8N_2O_7$. Calculated (%): C, 28.85; H, 3.87; N, 13.46. IR (KBr), ν/cm^{-1}: 1645, 1638, 1292, 1274, 848 (ONO_2), 993 (oxetane ring); 2972, 2896, 1461, 1382 (CH_2). ^1H NMR ($CDCl_3$), δ: 4.54 (s, 4 H, OCH_2); 4.75 (s, 4 H, CH_2ONO_2). ^{13}C NMR (DMSO-d_6+CCl_4), δ: 73.78 (s, 2 C(CH_2ONO_2 or OCH_2)); 73.08 (s, 2 C(OCH_2 or CH_2ONO_2)); 39.91 (s, 1 C (C_{quat})).

B. A solution of compound **6** (417 mg, 2.55 mmol) in $CHCl_3$ (2.5 mL) was added with stirring to a mixture of concentrated HNO_3 (d_4^{20} 1.513) (0.22 mL, 5.1 mmol) and Ac_2O (0.48 mL, 5.1 mmol) at ~0 °C. The reaction mixture was stirred for 20 min with a gradual increase in the temperature to 20 °C and then stirred at ~20 °C for 40 min, after which the reaction mixture was diluted with $CHCl_3$ (3 mL) and poured into ice water. The organic layer was separated, washed with water, a 10% aqueous $NaHCO_3$ solution, and again with water, and then dried with $MgSO_4$. After removal of the solvent, compound **1** was obtained in a yield of 525 mg (99%) as colorless crystals, m.p. 93.5—94 °C (from DCE). A mixture with a sample prepared according to the procedure *A* did not give a melting point depression. The IR spectra of these samples are identical.

Table 3. Crystallographic parameters of compounds **1** and **6**

Parameter	**1**	**6**
Molecular formula	$C_5H_8N_2O_7$	$C_5H_9NO_5$
Molecular weight	208.14	163.13
Space group	$C2/c$	$P2_1/n$
a/Å	15.020(2)	8.285(9)
b/Å	6.0553(9)	9.306(9)
c/Å	11.2392(16)	9.259(6)
β/deg	123.613(3)	95.21(10)
V/Å^3	851.3(2)	710.8(11)
Z	4*	4
ρ_{calc}/g cm^{-3}	1.624	1.524
μ/mm^{-1}	0.155	0.138
Radiation	Mo-Kα (λ = 0.71073 Å)	
θ-2θ Scan range/deg	3.26—30.03	3.11—30.02
Number of measured reflections	1048	3127
Number of reflections with $I \geq 2\sigma(I)$	873	1496
R_1	0.0693	0.0601
${}_wR_2$	0.1851	0.1362

* The molecule is located on a crystallographic twofold axis.

X-ray diffraction study. The X-ray diffraction data sets for compounds **1** and **6** were collected on an automated Bruker AXS SMART 1000 diffractometer equipped with a CCD detector (graphite monochromator, 110 K, ω scanning technique, scan step was 0.3°, frames were exposed for 30 s) according to a standard procedure.[20] The crystallographic parameters and details of the structure refinement of both structures are listed in Table 3.

The structures of both compounds were solved by direct methods and refined by the full-matrix least-squares method with anisotropic thermal parameters for all nonhydrogen atoms. The positions of the hydrogen atoms were calculated geometrically and refined using the riding model. All calculations were carried out using the SHELX97 program package.[21,22] The selected geometric parameters of the compounds are given in Tables 1 and 2.

We thank the Head and staff of the Center of X-ray Diffraction Studies (A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences) for giving us the possibility to collect the X-ray data on a Smart diffractometer.

This study was financially supported by the International Science and Technology Center (ISTC, Grant 1550).

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Received April 10, 2003