Synthesis and structures of nitroxyalkyl methylphosphonates

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The reactions of ethylene glycol mononitrate and glycerol 1,3-dinitrate with methylphosphonic dichloride afforded new nitroxyalkyl methylphosphonates.

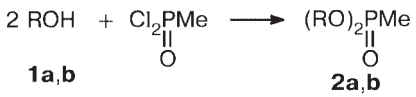
Key words: phosphorylation, nitrates of polyols, nitroxyalkyl methylphosphonates, synthesis, X-ray diffraction analysis, ^{1}H and ^{31}P NMR spectroscopy.

Natural phosphonates containing the fluorine—carbon bond and exhibiting high biological activities were described in the literature.[1] Synthetic phosphonates containing nitrate groups are also of interest as potent biologically active compounds, in particular, as pharmaceuticals used in the treatment of cardiovascular diseases.

Data on the reactions of phosphonic acids and their derivatives with nitroxy-containing compounds are lacking in the literature. Previously,[2] we have reported the synthesis of nitroxyalkyl phosphates. As part of our continuing studies, we examined the reactions of partial nitrates of aliphatic alcohols with methylphosphonic chloride.

Results and Discussion

Phosphorylation of ethylene glycol mononitrate (**1a**) and glycerol dinitrate (**1b**) afforded previously unknown nitroxyalkyl methylphosphonates **2a**,**b**, respectively.



R = $CH_2CH_2ONO_2$ (**a**), $CH(CH_2ONO_2)_2$ (**b**)

The reactions were carried out in anhydrous CH_2Cl_2 in the presence of pyridine at the temperatures of 5—10 °C and −5 °C for several hours to obtain bis(2-nitroxyethyl) methylphosphonate (**2a**) as a colorless oil in 58% yield and bis(1,3-dinitroxyisopropyl) methylphosphonate (**2b**) as crystals in 47% yield.

The compositions and the structures of compounds **2a**,**b** were confirmed by elemental analysis and spectroscopic methods (^{1}H and ^{31}P NMR and IR). In addition, the structure of **2b** was established by X-ray diffraction analysis (Fig. 1; Tables 1 and 2). The IR spectra of compounds **2a**,**b** have stretching vibration bands characteristic of phosphonates and bands corresponding to the nitrate groups (at 1630, 1650, 1280, 1275, and 855 cm^{-1}). The ^{1}H and ^{31}P NMR spectra are in complete agreement with the structures of **2a**,**b** (see the Experimental section).

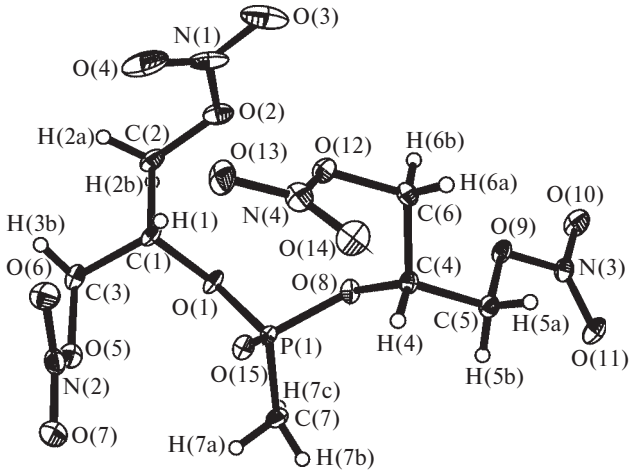


Fig 1. Structure of bis(1,3-dinitroxyisopropyl) methylphosphonate (**2b**).

The CH_2 groups in compound **2b** are nonequivalent due to their diastereotopism,[3] which is additional evidence in support of the proposed structure. The experimental spectral parameters are identical with the calculated values (see the Experimental section).

The molecular structure of **2b**, which was established based on the X-ray diffraction data, is shown in Fig. 1. The coordination environment about the phosphorus atom is a distorted tetrahedron. The bond lengths and bond angles in **2b** are close to the standard values.[4]

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 1, pp. 148—150, January, 2002.

Table 1. Selected geometric characteristics of phosphonate **2b**

Bond	*d*/Å	Angle	ω/deg
P(1)—O(1)	1.586 (2)	O(1)—P(1)—O(8)	102.0(1)
P(1)—C(7)	1.771 (3)	O(8)—P(1)—O(15)	113.4(1)
O(2)—C(2)	1.442 (5)	O(8)—P(1)—C(7)	104.9(1)
O(5)—N(2)	1.415 (4)	P(1)—O(1)—C(1)	121.2(1)
O(7)—N(2)	1.197 (4)	N(2)—O(5)—C(3)	114.4(2)
O(9)—C(5)	1.454 (4)	N(3)—O(9)—C(5)	113.8(2)
O(12)—N(4)	1.399 (4)	O(2)—N(1)—O(3)	111.6(4)
O(14)—N(4)	1.199 (4)	O(3)—N(1)—O(4)	129.4(5)
C(4)—C(6)	1.517 (4)	O(5)—N(2)—O(7)	112.3(3)
P(1)—O(8)	1.599 (2)	O(9)—N(3)—O(10)	112.7(2)
O(1)—C(1)	1.449 (3)	O(10)—N(3)—O(11)	129.1(3)
O(3)—N(1)	1.195 (7)	O(12)—N(4)—O(14)	118.9(3)
O(5)—C(3)	1.433 (4)	O(1)—C(1)—C(2)	107.8(2)
O(8)—C(4)	1.441 (3)	C(2)—C(1)—C(3)	109.6(2)
O(10)—N(3)	1.207 (4)	O(5)—C(3)—C(1)	112.4(2)
O(12)—C(6)	1.442 (3)	O(8)—C(4)—C(6)	108.9(2)
C(1)—C(2)	1.510 (4)	O(9)—C(5)—C(4)	106.1(2)
P(1)—O(15)	1.475 (2)	O(1)—P(1)—O(15)	114.9(1)
O(2)—N(1)	1.412 (5)	O(1)—P(1)—C(7)	103.3(1)
O(4)—N(1)	1.192 (6)	O(15)—P(1)—C(7)	116.8(1)
O(6)—N(2)	1.204 (4)	N(1)—O(2)—C(2)	112.7(3)
O(9)—N(3)	1.395 (3)	P(1)—O(8)—C(4)	120.7(2)
O(11)—N(3)	1.207 (3)	N(4)—O(12)—C(6)	114.0(2)
O(13)—N(4)	1.214 (4)	O(2)—N(1)—O(4)	119.0(4)
C(1)—C(3)	1.518 (4)	O(5)—N(2)—O(6)	117.9(3)
		O(6)—N(2)—O(7)	129.8(3)
		O(9)—N(3)—O(11)	118.2(2)
		O(12)—N(4)—O(13)	112.3(3)
		O(13)—N(4)—O(14)	128.8(3)
		O(1)—C(1)—C(3)	108.0(2)
		O(2)—C(2)—C(1)	111.8(2)
		O(8)—C(4)—C(5)	108.5(2)
		C(5)—C(4)—C(6)	113.0(2)
		O(12)—C(6)—C(4)	110.8(2)

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

Parameter	**3**
Molecular formula	$C_7H_{13}N_4O_{15}P$
Space group	$P\,2_1$
a/Å	8.036(3)
b/Å	9.920(4)
c/Å	10.498(4)
β/deg	95.39(2)
V/Å^3	833.3(5)
Z	2
d_{calc}/g cm^{-3}	1.691
θ—2θ scanning range/deg	2—56
Number of measured reflections	2152
Number of reflections with $I > 4\sigma$	2107
Weighting scheme	$w^{-1}=\sigma^2(F) + 0.0014F^2$
R	0.044
R_w	0.049

Table 3. Anti-ischemic activity and vasodilator action of the compounds synthesized

Compound	LD_{50}/mg kg^{-1}	α* (%)	*N***
Blank test	—	68.0±4.3	—
2a	425	54.5±3.8	1.59
2b	436	61.0±8.5	0.37
Nitroglycerol	108	—	—
Nicorandil	475	42.0±5.4	1

* The ratio between the sizes of the necrotic and ischemic zones.
** The ratio between the concentrations of the compound and nicorandil causing 50% relaxation of the aorta.

The atomic coordinates of compound **2b** were deposited with the Cambridge Structural Database. The selected bond lengths and bond angles of molecule **2b** are listed in Table 1. The crystallographic parameters are given in Table 2.

Compounds **2a**,**b** were tested for acute toxicity, anti-ischemic, and vasodilator activities (Table 3). In the tests for acute toxicity, solutions of the corresponding compound in 5% aqueous ethanol were once introduced intraperitoneally into male mice (with weights of 19—21 g) of the BDF line. The toxicity of compounds **2a**,**b** is much lower than that of nitroglycerol. The anti-ischemic activity was estimated according to the integral method from the change in the ratio between the necrotic and ischemic zones within 4 h after occlusion of the coronary artery.[5,6] The studies were carried out at the All-Russian Research Center on Safety of Biologically Active Compounds. The myocardial infarction was induced in non-line white rats with weights of 250—350 g.

The vasodilator action of compounds **2a**,**b** was estimated from relaxation of rat isolated aorta upon the cummulative addition of the compounds after aorta contracture with noradrenaline.[7] The efficiency was assessed as the concentration of the compound under study (μmol L^{-1}), which caused 50% relaxation, related to the concentration of nicorandil having the same effect. The vasodilator action of phosphonates **2a**,**b** depends on the type of the nitroxyalkyl substituent at the phosphorus atom. Compound **2b** exhibits the highest vasodilator activity. The concentration ratio for this compound was 0.37, *i.e.*, according to the results of this test, compound **2b** proved to be 2.7 times more active than *N*-(2-nitroxyethyl)nicotinamide (nicorandil), which is presently the most efficient drug (of all esters of nitric acid) for the treatment of stenocardia.

Experimental

The IR spectra were recorded on a Specord M-82 spectrometer. The NMR spectra were measured on a cryogenic NMR

spectrometer (operating at 294 MHz for ^{1}H), which was developed and built at the Institute of Problems of Chemical Physics in Chernogolovka of the Russian Academy of Sciences, and on a Bruker CXP 200 spectrometer (200 MHz for ^{1}H and 81 MHz for ^{31}P) relative to the signals for the residual protons of deuterated solvents (^{1}H) and 85% aqueous H_3PO_4 (^{31}P). The δ and *J* parameters were determined by simulating the experimental spectra with the use of the gNMR program (Cherwell, demo version). The melting point of compound **2b** was determined on a Boetius RWMK-05 stage. Methylphosphonic dichloride (98%, Fluka) was used without additional purification. Pyridine, the solvents, and the inorganic reagents were of chemically pure grade. Column chromatography was carried out with the use of silica gel 60 (Fluka). Pyridine and CH_2Cl_2 were dried according to standard procedures.[8] Ethylene glycol mononitrate **1a** and glycerol dinitrate **1b** were prepared according to known procedures.[9] For compound **1a**, b.p. 55—57 °C (2 Torr), n_D^{20} 1.348; for compound **1b**, b.p. 73—75 °C (0.5 Torr), n_D^{20} 1.469.

Bis(2-nitroxyethyl) methylphosphonate (2a). Methylphosphonic dichloride (4.0 g, 30 mmol) was dissolved in anhydrous CH_2Cl_2 (20 mL) and cooled to 5 °C. A solution of ethylene glycol mononitrate (6.4 g, 60 mmol) in anhydrous CH_2Cl_2 (20 mL) was cooled to 0 °C and added to freshly distilled pyridine (4.8 g, 60 mmol). The resulting solution was added dropwise with stirring to the solution of methylphosphonic dichloride at 5—10 °C. The reaction mixture was stirred for ~3 h, gradually warmed to ~20 °C, and stirred for ~6 h. Then $C_5H_5N \cdot HCl$ that formed was filtered off. The solution was successively washed with ice water, a 5% H_2SO_4 solution, a 5% $NaHCO_3$ solution, and water. The organic layer was dried with $MgSO_4$, the solvent was removed, and the residue was chromatographed on SiO_2 (a 3 : 1 heptane—acetone mixture as the eluent). Compound **1a** was obtained in a yield of 4.8 g (58%), n_D^{20} 1.4625. Found (%): C, 21.7; H, 4.2; N, 10.3; P, 11.1. $C_5H_{11}N_2O_9P$. Calculated (%): C, 21.91; H, 4.05; N, 10.22; P, 11.30. IR (KBr), ν/cm^{-1}: 2966 (Me); 2896 (CH_2); 1630, 1280, 855 (ONO_2); 1240 (P=O); 1020 (POC). ^{1}H NMR (CD_3CN), δ: 1.50 (d, 3 H, MeP(O), $^2J_{P-H}$ = 17.7 Hz); 4.26 (m, 4 H, OCH_2, AB portion of the spectrum of the ABK_2X type; δ_A = 4.24, δ_B = 4.27; $^2J_{AB} \approx {}^3J_{CH_2-OP}$ = 8.6 Hz; $^3J_{CH_2-CH_2}$ = 4.0 and 4.5 Hz); 4.67 (dd, 4 H, CH_2ONO_2, $^3J_{CH_2-CH_2}$ = 4.0 and 4.5 Hz). ^{31}P NMR (CD_3CN), δ: 33.58 (m, 1 P, P(O), $^2J_{P-Me}$ = 17.7 Hz, $^3J_{P-OCH_2}$ = 8.6); in the ^{31}P{^{1}H} mode, singlet.

Bis(1,3-dinitroxyisopropyl) methylphosphonate (2b). A solution of pyridine (5.14 g, 6.5 mmol) in CH_2Cl_2 (20 mL) was added with stirring and cooling (−5 °C) to a solution of compound **1b** (10.92 g, 60 mmol) in CH_2Cl_2 (30 mL). Then methylphosphonic dichloride (4.0 g, 30 mmol) was added at the same temperature. The reaction mixture was stirred at −5 °C for ~6 h. The precipitate of $C_6H_5N \cdot HCl$ that formed was filtered off and washed with CH_2Cl_2. The washing liquid was combined with the filtrate. The filtrate was successively washed with water, a 5% aqueous solution of $NaHCO_3$, and water. The resulting solution was dried with $MgSO_4$ and the solvent was evaporated *in vacuo*. Compound **2b** was obtained in a yield of 6.0 g (47%), m.p. 46—47 °C (from $CHCl_3$—CCl_4). Found (%): C, 19.6; H, 3.3; N, 13.3; P, 7.1. $C_7H_{13}N_4O_{15}P$. Calculated (%): C, 19.82; H, 3.09; N, 13.21; P, 7.30. IR (KBr), ν/cm^{-1}: 1650, 1275, 855 (ONO_2), 1018 (POC); 1244 (P=O). ^{1}H NMR (CD_3CN, Me_4Si), δ: 1.58 (d, 3 H, (O)PMe, $^2J_{P-H}$ = 18.6 Hz); 4.50—4.90 (m, 8 H, superposition of AB portions of the ABX spectra from two nonequivalent CH_2ONO_2 groups in the equivalent $CH(CH_2ONO_2)_2$ fragments; the parameters: 4.595 and 4.625, $CH_{A(1)}$ and $CH_{A(2)}$; 4.778 and 4.790 Hz, $CH_{B(1)}$ and $CH_{B(2)}$; $^2J_{A(1)B(1)} = {}^2J_{A(2)B(2)}$ = 12.7 Hz, $^3J_{A(1)X} = {}^3J_{A(2)X}$ = 6.70 Hz, $^3J_{B(1)X} = {}^3J_{B(2)X}$ = 3.20 Hz); 5.03 (m, 2 H, (O)POCH, $^3J_{CH-P}$ = 10.0 Hz). ^{31}P NMR (CD_3CN), δ: 35.20 (m, 1 P, P(O); $^2J_{P-Me}$ = 18.5 Hz, $^3J_{P-OCH}$ = 9.8 Hz; in the ^{31}P{H} mode, singlet).

X-ray diffraction study. The X-ray diffraction data for compound **2b** were collected on an automated four-circle Siemens R3/PC diffractometer (λMo-Kα = 0.71074 Å, *T* = −120 °C). The unit cell parameters were determined and refined using 24 equivalent reflections with 2θ < 22—26°. Three strong reflections with 0 < χ < 65° were used as the standards and were measured after each 100 reflections. The intensities of the standard reflections showed no decrease in the course of data collection, and therefore, corrections were not applied. The crystallographic parameters and details of the structure refinement are given in Table 2.

The structure was 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 located from the difference Fourier synthesis and refined isotropically. All calculations were carried out using the SHELXTL PLUS program package (PC version).[10]

This study was financially supported by the International Science and Technology Center (Project Nos. 123 and 1550).

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Received January 4, 2001;
in revised form August 6, 2001