Letters to the Editor

Nitroxyalkyl phosphates

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The biological effect of esters of phosphorous acids is commonly known.[1] However, phosphates with nitroxyalkyl groups have not been described to date, although they could be of interest as potential physiologically active compounds.

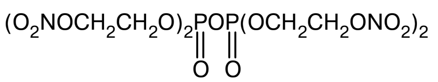
We synthesized for the first time nitroxyalkyl phosphates by the reactions of ethylene glycol mononitrate (**1a**) and glycerol 1,3-dinitrate (**1b**) with $POCl_3$ in an organic solvent in the presence of a base.

$$\underset{\mathbf{1a,b}}{3\ ROH} + POCl_3 \rightarrow \underset{\mathbf{2a,b}}{(RO)_3PO}$$

1,2: R = $CH_2CH_2ONO_2$ (**a**), $CH(CH_2ONO_2)_2$ (**b**)

Alcohols **1a**,**b** were phosphorylated at −5÷+5 °C in anhydrous CH_2Cl_2 in the presence of Py or Et_3N as acceptors of HCl. Compounds **2a,b** are transparent liquids.

The reaction of $POCl_3$ with alcohol **1a** in the presence of water affords tetrakis(2-nitroxyethyl) pyrophosphate (**3**) along with phosphate **2a**



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Monitoring of the reaction by ^1H NMR spectroscopy showed that the yield of pyrophosphate **3** depended on the amount of water. The yield of **3** in the reaction mixture is a maximum in the presence of 4% H_2O (**3** : **2a** = 3 : 2). Compound **3** was not isolated, it was identified in the reaction mixture based on the NMR spectral data.

The assay of compounds **2a,b** by the published method[2,3] showed that they possessed anti-ischemical activity. In addition, compounds **2a,b** were subjected to acute toxicity tests. The tests were performed with mice by intra-abdominal injection of the chemicals as solutions in 15% aqueous ethanol. The LD_{50} values of compounds **2a**,**b** were 625 and 385 mg per kg. The toxicity of these compounds is lower than that of nitroglycerol for which LD_{50} = 108 mg kg^{-1}.

^1H NMR spectra were obtained on an NMR spectrometer (developed at the Institute of Problems of Chemical Physics of the RAS) with the superconducting magnet (294 MHz). IR spectra were recorded on a Specord-M82 spectrophotometer. Solvents were dried according to standard procedures.[4] Ethylene glycol mononitrate **1a** and glycerol 1,3-dinitrate **1b** were prepared by known procedures[5]; for compound **1a**, b.p. 55—57 °C (2 Torr), n_D^{20} 1.348; for **1b**, b.p. 73—75 °C (0.5 Torr), n_D^{20} 1.469.

Tris(2-nitroxyethyl) phosphate (2a). Ethylene glycol mononitrate **1a** (3.21 g, 30 mmol) was dissolved in anhydrous CH_2Cl_2 (20 mL), the solution was cooled to −2 °C, and freshly distilled pyridine (2.53 g, 32 mmol) was added dropwise with stirring. Thirty min after, $POCl_3$ (1.53 g, 10 mmol) was added dropwise at −2 to +5 °C, and stirring was continued for ~3 h. The reaction mixture was gradually brought to ~20 °C and left overnight. Then the solution was washed with water, 3% HCl,

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5% $NaHCO_3$, and water again. The organic layer was dried with $MgSO_4$, concentrated and the residue was chromatographed on SiO_2 (eluent hexane—acetone, 2 : 1). Compound **2a** (2.2 g, 61%), n_D^{20} 1.4601. Found (%): C, 20.1; H, 2.9; N, 11.2; P, 8.2. $C_6H_{12}N_3O_{13}P$. Calculated (%): C, 19.74; H, 3.31; N, 11.51; P, 8.48. IR (KBr), ν/cm^{-1}: 2966, 2900, 1373 (CH_2); 1652, 1286, 854 (ONO_2); 1252 (P=O); 1067 (P—O—C). ^{1}H (CD_3CN), δ: 4.31 (m, 2 H, CH_2OP); 4.69 (m, 2 H, CH_2ONO_2).

A mixture of tris(2-nitroxyethyl) phosphate (2a) and tetrakis(2-nitroxyethyl) pyrophosphate (3). Similarly to the synthesis of compound **2a**, ethylene glycol mononitrate **1a** (3.34 g, 30 mmol) reacted with $POCl_3$ (1.53 g, 10 mmol) in the presence of pyridine (2.53 g, 32 mmol) containing H_2O (0.13 g, 7.2 mmol) in anhydrous CH_2Cl_2 (20 mL) to give a mixture (2.0 g) of **2a** and **3**, n_D^{20} 1.4630.

The ratio **2a** : **3** = 2 : 3 was determined from ^{1}H NMR spectrum. IR (KBr), ν/cm^{-1}: 2969, 2900, 1373 (CH_2); 1652, 1637, 1289, 1283, 857, 851 (ONO_2); 1238 (P=O); 1064 (POC); 986 (POP). ^{1}H NMR (CD_3CN), δ: 4.31 (m, 2 H, CH_2OP, **2a**); 4.46 (m, 2 H, CH_2OP, **3**); 4.69 and 4.70 (m, CH_2ONO_2, **2a**+**3**). ^{31}P NMR {^{1}H} (CD_3CN), δ: −0.63 (s, **2a**); −12.44 (s, **3**).

Tris(1,3-dinitroxyisopropyl) phosphate (2b). Glycerol dinitrate **1b** (5.46 g, 30 mmol) was dissolved in anhydrous CH_2Cl_2 (30 mL), the solution was cooled to −2 °C, and triethylamine (3.24 g, 32 mmol) was added dropwise with stirring. Then $POCl_3$ (1.53 g, 10 mmol) was added dropwise at −5 to 2 °C. The mixture was stirred for 1 h at the same temperature, then the temperature was gradually raised to ~20 °C, the mixture was left overnight. The solution was washed with water, 5% aqueous solution of H_2SO_4, 5% $NaHCO_3$, and water again. The organic layer was dried with $MgSO_4$ and concentrated to yield compound **2b** (3.7 g, 63%) in the chemically pure state without additional purification, n_D^{20} 1.4855. Found (%): C, 18.1; H, 2.4; N, 14.4; P, 5.1. $C_9H_{15}N_6O_{22}P$. Calculated (%): C, 18.31; H, 2.56; N, 14.24; P, 5.25.

IR (KBr), ν/cm^{-1}: 845, 1280, 1646 (ONO_2); 1067 (POC); 1280 (P=O). The band of P=O overlaps with the absorption band of the ONO_2 fragment. The frequency of the band of the stretching vibration of P=O at 1294 cm^{-1} in a solution of CH_3CN was found by quantitative IRS analysis.

^{1}H NMR (Me_4Si, CD_3CN), δ: 4.75 (m, 12 H, CH_2, AB-part of the ABMXA′B′-type spectrum $\Delta\nu$ = 48.1, ^2J = 12.7 Hz, J_{AM} = 7.67 Hz, $^3J_{BM}$ = 3.2 Hz, $^5J_{M-X}$ = 1.3 Hz); 5.03 (3 H, CH, M is a part of the ABMXA′B′ spectrum, J_{HP} = 7.67 Hz).

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