Tris(5-*O*-nitro-1,4:3,6-dianhydro-D-sorbit-2-yl) phosphate: synthesis and structure

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The reaction of 1,4:3,6-dianhydro-D-sorbitol 5-nitrate with phosphorus oxychloride afforded tris(5-*O*-nitro-1,4:3,6-dianhydro-D-sorbit-2-yl) phosphate, whose structure was confirmed by X-ray diffraction and ^{1}H, ^{31}P, and ^{13}C NMR spectroscopy.

Key words: phosphorylation, 1,4:3,6-dianhydro-D-sorbitol 5-nitrate, synthesis, X-ray diffraction study, ^{1}H, ^{31}P, and ^{13}C NMR spectroscopy.

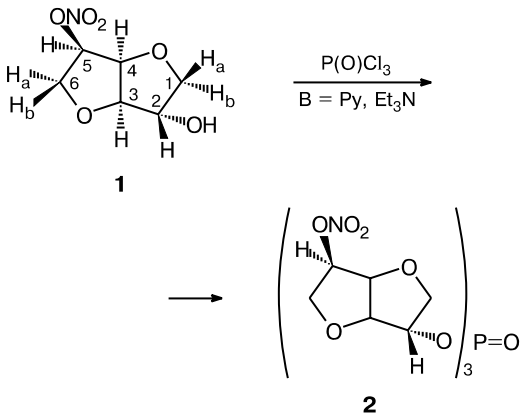
1,4:3,6-Dianhydro-D-sorbitol 5-nitrate (or isosorbide mononitrate **1**) is used as a drug.[1] Since the mid-1980s, this drug has found use[2] in antianginal therapy for the treatment of ischemic diseases. We plan to use this compound in the directed approach to the synthesis of other pharmaceuticals. The phosphorylation method is of interest because certain organophosphorus drugs (cocarboxylase, phosphaden, *etc.*) are used for improvement of myocardial metabolism.[3] In the treatment with antianginal drugs, it is particularly important to obey the requirements of pharmacotherapy, *i.e.*, to maintain a rather high drug concentration in blood for a long period of time.[2] Prolonged-action drug forms of isosorbide mononitrate used for this purpose[4] are unavailable on the Russian pharmaceutical market.

A change in the chemical structure of a drug by introducing new chemical groups can give rise to a prolonged-action pharmaceutical. The use of compound **1** in biomedical studies was documented.[5]

Earlier,[6] we have reported the synthesis of biologically active nitroxyalkyl phosphates. In continuation of our studies, we made an attempt to extend this method to the synthesis of partially nitrated 1,4:3,6-dianhydro-D-sorbitol with the aim of preparing phosphate. Phosphorylation of unsubstituted 1,4:3,6-dianhydro-D-mannitol at one[7] or both[8,9] hydroxy groups with trivalent phosphorus acid chlorides followed by oxidation gave mono- and bis-phosphates, respectively.

Phosphorylation of **1** with phosphorus oxychloride afforded tris(5-*O*-nitro-1,4:3,6-dianhydro-D-sorbit-2-yl) phosphate (**2**) (Scheme 1).*

Scheme 1



1 **2**

Experiments were carried out in different solvents (CH_2Cl_2, dioxane, and MeCN) in the presence of an organic base. The course of the reaction was monitored by ^{31}P NMR spectroscopy based on the appearance of the signal of the corresponding tris-phosphate derivative **2**. Triethylamine proved to be the most efficient amine for this reaction, and dioxane is the solvent of choice.

The structure of compound **2** as a solvate with a water molecule (which is, apparently, generated in the reaction), which is disordered over two equivalent positions with occupancies of ~0.5, was established by X-ray diffraction (Fig. 1). In the crystal structure, the water molecule is linked to the phosphate molecule through weak hydrogen bonds.

In the tris(5-*O*-nitro-1,4:3,6-dianhydro-D-sorbit-2-yl) phosphate molecule (**2**), the phosphorus atom has a distorted tetrahedral configuration formed by the phosphoryl O(19) atom (P=O, 1.467(6) Å) and three O atoms of

* The atomic numbering scheme of C atoms used for the description of the NMR spectra of compound **2** is identical to that given for compound **1**.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 2, pp. 380—382, February, 2006.

1066-5285/06/5502-0393

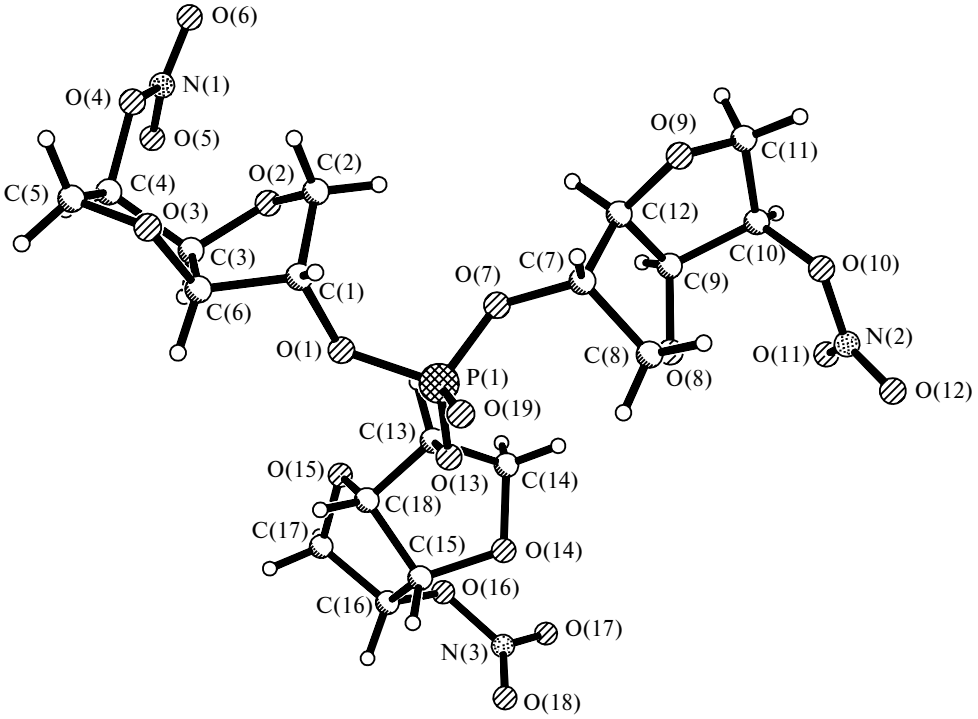


Fig. 1. Molecular structure of compound **2**.

three dianhydro-D-sorbitol groups (P—O, 1.584(7), 1.587(7), and 1.598(7) Å). The *cis*-fused five-membered oxalan rings in the 1,4:3,6-dianhydro-D-sorbitol fragments adopt envelope conformations with the C(1), C(7), and C(13) atoms and the O(3), O(9), and O(15) atoms deviating from the planes through the other four atoms of the corresponding five-membered rings (deviations vary from 0.50 to 0.60 Å). The main geometric parameters of the molecule are typical of fused furan systems.[10]

Compound **2** was tested in the Laboratory of Receptor and Biochemical Pharmacology of the All-Russian Scientific Center for the Safety of Biologically Active Compounds for antiischemic activity by relaxation of isolated rat aorta after contracture with noradrenaline. The coronary dilatory capacity of compound **2** determined after 4 h was lower than that of isosorbide mononitrate, which is apparently indicative of retarded release of an active substance. We believe that compound **2** holds promise for the prolongation of the therapeutic effect of isosorbide mononitrate and plan to continue these studies.

Experimental

The ^{1}H (200.13 MHz), ^{31}P (81 MHz), and ^{13}C NMR (50.3 MHz) spectra were recorded on a Bruker DPX-200 spectrometer with the use of Me_4Si as the internal standard for ^{1}H and ^{13}C and 85% aqueous H_3PO_4 as the external standard for ^{31}P. The NMR experiments on different nuclei were carried out with the use of the same sample in a DMSO-d_6—CCl_4 (25 wt.%)—Me_4Si solvent system (0.1 wt.%). The ^{1}H and ^{31}P NMR spectroscopic parameters were determined by calculating the spectra with the use of the gNMR program. Calculations for ^{1}H NMR were performed for a nine-spin system consisting of eight nonequivalent protons of one of three equivalent 1,4:3,6-dianhydro-D-sorbitol-5-nitrate substituents and the phosphorus nucleus; the ^{31}P multiplet was modeled by a spin system containing, along with the phosphorus nucleus, the phosphorus-coupled $H_a(1)$ and H(2) protons of all three 1,4:3,6-dianhydro-D-sorbitol-5-nitrate substituents.

The IR spectra were recorded in KBr pellets on a Specord M-82 spectrometer. The melting point was measured on a Boetius RWMK-05 instrument. Isosorbide 5-mononitrate (Acros) and phosphorus(V) oxychloride (99%, Aldrich) were used. Pyridine, Et_3N, solvents, and inorganic reagents were of reagent grade. Pyridine, Et_3N, and solvents were dried according to standard procedures.[11]

Tris(5-*O*-nitro-1,4:3,6-dianhydro-D-sorbit-2-yl) phosphate (2). A solution of $POCl_3$ (0.5 g, 3.3 mmol) in anhydrous dioxane (10 mL) was added with stirring to a solution of a mixture of compound **1** (1.7 g, 9 mmol) and Et_3N (1.0 g, 10 mmol) in anhydrous dioxane (10 mL) at 8—10 °C. The reaction mixture was stirred for 30 min, the temperature being gradually raised to 18—20 °C. After 12 h, the reaction mixture was heated to 30 °C, stored for 1 h, and kept at ~20 °C for 20 h. Then $Et_3N \cdot HCl$ that precipiated was filtered off, the solvent was distilled off *in vacuo*, and the residue was recrystallized from acetone or CH_2Cl_2. Compound **2** was obtained in a yield of 0.9 g (49%), m.p. 100—101 °C. Found (%): C, 33.90; H, 4.30; N, 6.50; P, 4.80. $C_{18}H_{24}N_3P \cdot H_2O$. Calculated (%): C, 34.03; H, 4.12; N, 6.61; P, 4.87. IR, ν/cm^{-1}: 1636, 1281, 965, 852 (ONO_2); 1029 (POC); 1238 (P=O); 2989, 2937, 2884,1458, 1348 (CH_2, CH).

^{1}H NMR, δ: 3.75 (m, 3 $H_a(1)$, 3 H, $|^2J_{H_a(1),H_b(1)}| = 10.4$ Hz, $^3J_{H_a(1),H(2)} = 2.0$ Hz, $^4J_{H_a(1),P} \cong 1.5$ Hz); 3.87 (m, 3 $H_a(6)$, 3 H,

$|^2J_{H_a(6),H_b(6)}| = 11.7$ Hz, $^3J_{H_a(6),H(5)} = 5.0$ Hz); 3.93 (m, 3 H_b(6), 3 H, $|^2J_{H_a(6),H_b(6)}| = 11.7$ Hz, $^3J_{H_b(6),H(5)} \cong 2.2$ Hz); 4.03 (m, 3 H_b(1), 3 H, $|^2J_{H_a(1),H_b(1)}| = 10.4$ Hz, $^3J_{H_b(1),H(2)} \cong 0$ Hz); 4.53 (dd, 3 H, 3 H(3), $^3J_{H(3),H(4)} = 5.0$ Hz, $^3J_{H(2),H(3)} \approx 0$ Hz); 4.84 (dd, 3 H, 3 H(2), $^3J_{H(2),H_a(1)} = 2.0$ Hz, $^3J_{H(2),P} \approx 7.0$ Hz); 5.00 (dd, 3 H, 3 H(4), $^3J_{H(4),H(5)} \approx {}^3J_{H(4),H(3)} \approx 5.0$ Hz); 5.50 (ddd, 3 H, 3 H(5), $^3J_{H(5),H(4)} \approx {}^3J_{H(5),H_a(6)} = 5.0$ Hz, $^3J_{H(5),H_b(6)} = 2.2$ Hz). ^{31}P NMR, δ: −3.08 (qq, P(O), $^3J_{H(2),P} \approx 7.0$ Hz, $^4J_{H_a(1),P} \cong 1.5$ Hz); in $^{31}P\{^1H\}$ NMR, singlet. ^{13}C NMR, δ: 86.26 (d, 3 C, C(3), $^3J_{C(3),P} = 6.0$ Hz); 81.91 (s, 3 C, C(4) or C(5)); 81.21 (s, 3 C, C(5) or C(4)); 80.39 (d, 3 C, C(2), $^2J_{C(2),P} = 5.0$ Hz); 73.13 (d, 3 C, C(1), $^3J_{C(1),P} = 5.5$ Hz); 68.99 (s, 3 C, C(6)).

Crystals suitable for X-ray diffraction study were grown by slow evaporation of a solution of **2** · H_2O in CH_2Cl_2.

X-ray diffraction study. X-ray diffraction study was carried out in the Center of X-ray Diffraction Studies (A. N. Nesmeyanov Institute of Organoelement Compounds of the Russian Academy of Sciences) on a Bruker AXS SMART 1000 diffractometer[12,13] equipped with a CCD detector (Mo-Kα, graphite monochromator, 110 K, ω scanning technique with a step of 0.3°, exposure time per frame was 30 s, $2\theta_{max} = 56°$). The structure was solved by direct methods and refined by the full-matrix least-squares method with anisotropic displacement parameters for all nonhydrogen atoms (the positions of the hydrogen atoms were calculated geometrically and refined using a riding model). The calculations were performed with the use of the SHELX97 program package.[14] Crystals of **2** are orthorhombic, $a = 6.923(2)$, $b = 18.836(5)$, $c = 21.390(6)$ Å; $V = 2790(1)$ Å^3, $\rho_{calc} = 1.513$ g cm^{-3}, $\mu = 0.192$ mm^{-1}, $Z = 4$, space group $P2_12_12_1$. A total of 8874 reflections were measured, of which 3597 reflections were with $I > 2\sigma(I)$, $R_1 = 0.0599$ and $wR_2 = 0.1210$ for 1887 independent reflections with $I > 2\sigma(I)$.

This study was financially supported by the International Science and Technology Center (ISTC, Grant No. 1550).

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Received June 30, 2005;
in revised form December 6, 2005