Mono- and bis(5-*O*-nitro-1,4:3,6-dianhydro-D-sorbit-2-yl) phosphates: synthesis and reactions with hydroxy- and amino-containing compounds

L. T. Eremenko,[a] G. V. Oreshko,[a] G. V. Lagodzinskaya,[a]★ G. G. Aleksandrov,[b] and I. L. Eremenko[b]

[a]*Institute of Problems of Chemical Physics, Russian Academy of Sciences, 1 prosp. Akad. Semenova, 142432 Chernogolovka, Moscow Region, Russian Federation. Fax: +7 (496) 515 5420. E-mail: lago@icp.ac.ru*
[b]*N. S. Kurnakov Institute of General and Inorganic Chemistry, Russian Academy of Sciences, 31 Leninsky prosp., 119991 Moscow, Russian Federation. Fax: +7 (495) 954 1279. E-mail: ilerem@igic.ras.ru*

The reaction of 1,4:3,6-dianhydro-D-sorbitol 5-nitrate with $POCl_3$ afforded mono- and bis(5-*O*-nitro-1,4:3,6-dianhydro-D-sorbit-2-yl) phosphorochloridates, whose hydrolysis resulted in phosphoric acid mono- and diesters. The subsequent treatment of these compounds with bases gave sodium and cyclohexylammonium salts. The reactions of phosphorochloridates with phenol, pentaerythritol dibromohydrin, and ethylenimine in the presence of organic bases afford mixed phosphates and phosphoramidates.

Key words: phosphorylation, 1,4:3,6-dianhydro-D-sorbitol 5-nitrate, mono- and bis(5-*O*-nitro-1,4:3,6-dianhydro-D-sorbit-2-yl) phosphates, bis(5-*O*-nitro-1,4:3,6-dianhydro-D-sorbit-2-yl) phosphoramidate, ^1H, ^{31}P, and ^{13}C NMR spectroscopy, X-ray diffraction study.

Primary and secondary phosphates play an important role in the chemistry of living cells. For example, adenosine 5′-monophosphate[1] is a component of certain coenzymes regulating redox processes and is involved in the exchange of amino acids, lipids, and carbohydrates. Nitroxyalkyl phosphates were described[2] as donors of nitric oxide, which serves as a neuromediator and reacts in organisms with various compounds, such as thiols, proteins, sugars, protein hemes, *etc*.

The pharmacological activity of 1,4:3,6-dianhydro-D-sorbitol 5-nitrate (**1**) (isosorbide mononitrate), which has found use in the medical practice, is attributed to its ability to *in vivo* release nitric oxide.

Earlier,[3] we have demonstrated that the phosphorylation of **1** with $POCl_3$ in the presence of organic bases affords tris(5-*O*-nitro-1,4:3,6-dianhydro-D-sorbit-2-yl) phosphate (**2**). In the present study, we examined the possibility of the synthesis of mono- (**3**) and bis(5-*O*-nitro-1,4:3,6-dianhydro-D-sorbit-2-yl) phosphates (**4**) as precursors of hybrid drugs[4] combining fragments of phosphoric acid, 1,4:3,6-dianhydro-D-sorbitol 5-nitrate, and other compounds in one molecule.

Several approaches to the synthesis of mono- and diphosphates were developed[5—8] based on the use of phosphorus oxyhalides, dialkyl phosphorochloridates, alkyl chlorophosphoramidates, *etc*.

The reaction of compound **1** with an equimolar amount of $POCl_3$ in dioxane in the absence of hydrogen chloride acceptors yields 80% of dichloride **3** (Scheme 1). The reaction of **1** with $POCl_3$ in a molar ratio of 2 : 1 in dioxane in the presence of 2 equiv. of pyridine afforded monochloride **4** in 52% yield. Phosphorochloridates **3** and **4** are highly reactive compounds and are hydrolyzed to mono- and bis(5-*O*-nitro-1,4:3,6-dianhydro-D-sorbit-2-yl) phosphates **5** and **6**, respectively, even under conditions of spectroscopic analysis.

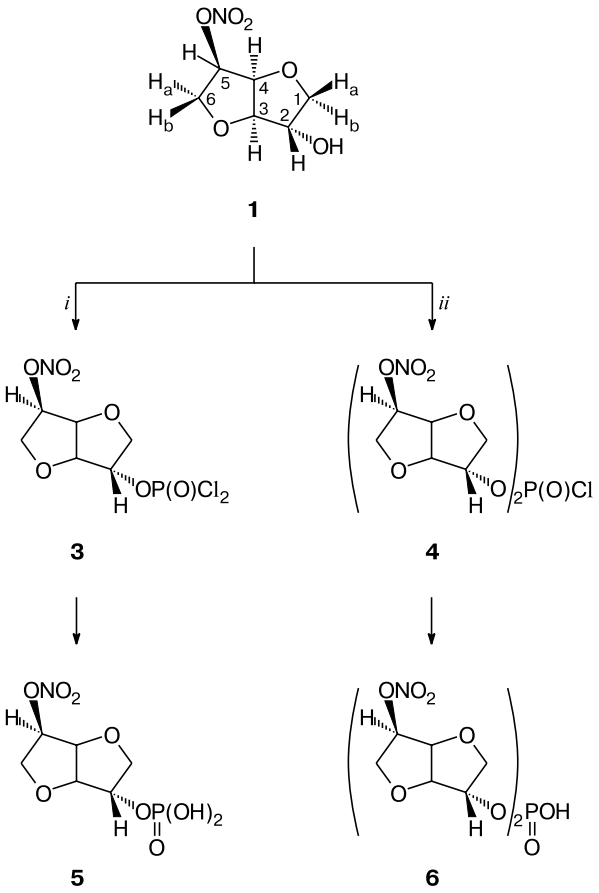
The IR spectra of phosphates **5** and **6** show a broad diffuse band at 2250—3000 cm^{-1} corresponding to hydroxy groups involved in hydrogen bonding. The absorption from 1205 to 1235 cm^{-1} is assigned to vibrations of phosphoryl groups.

The structures of phosphates **5** and **6** were established by ^1H, ^{31}P, and ^{13}C NMR spectroscopy. Table 1 gives the ^1H and ^{31}P NMR spectroscopic parameters for compounds **5** and **6** in comparison with the data for phosphate **2** synthesized earlier.[3]

The ^1H NMR spectra of compounds **2**, **5**, and **6** in solution show multiplets for eight nonequivalent coupled protons of the isosorbide moiety, whose parameters are analogous to those observed for isosorbide mononitrate derivatives devoid of phosphoryl groups.[9] The multiplets for H(2) and H_a(1) are characterized by an additional splitting with the spin-spin coupling constants of 7.0 and 1.5 Hz, respectively, due to coupling with ^{31}P. In the proton-coupled ^{31}P NMR spectra, the multiplets are broadened due to long-range interactions (in compounds **5** and **6**, due apparently also to the insufficiently fast proton exchange in P(O)OH); however, the predominant cou-

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 10, pp. 2026—2032, October, 2007.

Scheme 1



Reagents and conditions: *i*. $POCl_3$: **1** = 1 :1, 75 °C; *ii*. $POCl_3$: **1** : Py = 1 : 2 : 2, ~20 °C.

Note. The atomic numbering scheme presented for compound **1** is used in the description of the NMR spectra.

pling with H(2) is pronounced in all cases. As a result, the proton-coupled ^{31}P NMR spectra unambiguously showed that compounds **2**, **5**, and **6** have three, one, and two isosorbide fragments, respectively. The similarity of the chemical shifts and the coupling constants for the isosorbide fragments in all three compounds indicates that their conformations remain unchanged in spite of the use of different solvents. A substantial change in the ^{31}P chemical shift is observed only for monophosphate **5**.[10] The observed chemical shifts are typical of phosphates. For compounds **2** and **6**, the chemical shifts and coupling constants given in Table 1 were calculated with the use of the gNMRdemo program by varying the calculated spectra until the coincidence with the experimental data was achieved. The calculations for ^{1}H were carried out for the nine-spin system consisting of eight nonequivalent protons of one of the equivalent substituents (1,4:3,6-dianhydro-D-sorbitol 5-nitrate) and the phosphorus nucleus. The ^{31}P multiplet was simulated by the spin system containing, in addition to the phosphorus nucleus, the phosphorus-coupled H(1) and H(3) protons of these three and two substituents, respectively. For compound **5**, the calculations were not performed; however, taking into account the form of the multiplets, the coupling constants for compounds **2**, **5**, and **6** are the same within 0.2—0.3 Hz.

The ^{13}C NMR spectra of compounds **2** and **6** are also similar and show signals for six nonequivalent carbon atoms (two CH_2 groups and four CH groups, $^{13}C\{^{1}H\}$DEPT135 data). Taking into account that the structure of tris-phosphate **2** was established by X-ray diffraction, the NMR spectroscopic data completely confirm the structures of compounds **5** and **6**.

Compound **6** was found to undergo disproportionation in the course of NMR experiments in DMSO. Heating of compound **6** in MeOH in the presence of Et_3N

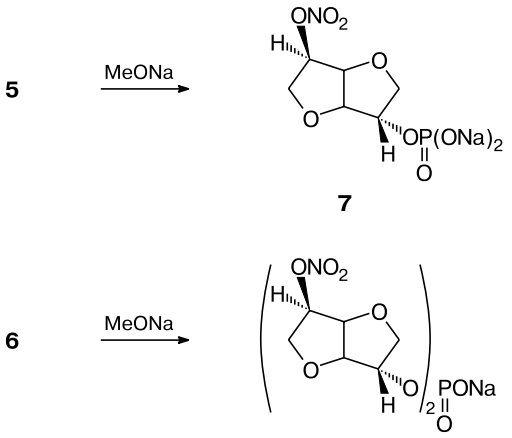
Table 1. ^{1}H and ^{31}P NMR spectroscopic data (δ, *J*/Hz) for phosphates **2**, **6** (calculations with the use of the gNMRdemo program), and **5**

Compound	$H_a(1)$	$H_b(1)$	H(2)	H(3)	H(4)	H(5)	$H_a(6)$	$H_b(6)$	^{31}P
2	3.75 (ddd, $\lvert J_{H_a(1),H_b(1)}\rvert$ = 10.4, $J_{H_a(1),H(2)}$ = 2.0, $J_{H_a(1),P}$ ≈ 1.5)	4.03 (m, $\lvert J_{H_a(1),H_b(1)}\rvert$ = 10.4, $J_{H_b(1),H(2)}$ ≈ 0)	4.84 (dd, $J_{H(2),H_a(1)}$ = 2.0, $J_{H(2),P}$ ≈ 7.0, $J_{H(2),H_b(1)}$ ≈ 0, $J_{H(2),H(3)}$ ≈ 0)	4.53 (d, $J_{H(3),H(4)}$ = 5.0, $J_{H(3),H(2)}$ ≈ 0)	5.00 (t, $J_{H(4),H(5)}$ ≈ $J_{H(4),H(3)}$ ≈ 5.0)	5.50 (dt, $J_{H(5),H(4)}$ ≈ $J_{H(5),H_a(6)}$ ≈ 5.0, $J_{H(5),H_b(6)}$ = 2.2)	3.87 (dd, $\lvert J_{H_a(6),H_b(6)}\rvert$ = 11.7, $J_{H_a(6),H(5)}$ = 5.0)	3.93 (dd, $\lvert J_{H_a(6),H_b(6)}\rvert$ = 11.7, $J_{H_b(6),H(5)}$ ≈ 2.2)	−3.08 (dd, $J_{H(2),P}$ ≈ 7.0, $J_{H_a(1),P}$ ≈ 1.5)
5	3.85 (m)	4.10 (m)	4.79 (m)	4.61 (m)	5.02 (m)	5.41 (m)	3.85 (m)	3.95 (m)	0.03 (br.d, $J_{P,H(2)}$ ≈ 7.0)
6	3.74 (ddd, $\lvert J_{H_a(1),H_b(1)}\rvert$ = 10.4, $J_{H_a(1),H(2)}$ ≈ 2.4, $J_{H_a(1),P}$ = 1.5)	4.00 (d, $\lvert J_{H_b(1),H_a(1)}\rvert$ = 10.4, $J_{H_b(1),H(2)}$ ≈ 0)	4.68 (dd, $J_{H(2),H_a(1)}$ = 2.4, $J_{H(2),P}$ = 7.1, $J_{H(2),H_b(1)}$ ≈ 0, $J_{H(2),H(3)}$ ≈ 0)	4.52 (d, $J_{H(3),H(4)}$ = 5.0, $J_{H(3),H(2)}$ ≈ 0)	4.99 (t, $J_{H(4),H(5)}$ = $J_{H(4),H(3)}$ = 5.0)	5.50 (dt, $J_{H(5),H(4)}$ = $J_{H(5),H_a(6)}$ = 5.0, $J_{H(5),H_b(6)}$ = 2.0)	3.87 (dd, $\lvert J_{H_a(6),H_b(6)}\rvert$ = 11.7, $J_{H_a(6),H(5)}$ = 5.0)	3.97 (dd, $\lvert J_{H_a(6),H_b(6)}\rvert$ = 11.7, $J_{H_b(6),H(5)}$ = 2.0)	−2.05 (dd, $J_{P,H(2)}$ = 7.1, $J_{P,H_a(1)}$ = 1.5)

afforded compounds **2** and **5**, which is consistent with the published data.[11]

Sodium salts **7** and **8** were synthesized by the reactions of acids **5** and **6** with MeONa in MeOH (Scheme 2).

Scheme 2



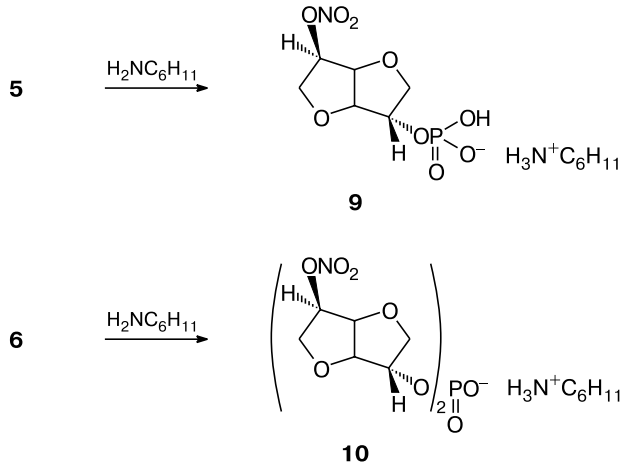
The structures of salts **7** and **8** were determined based on the ^{1}H and ^{31}P NMR spectra. The form and the chemical shifts of the multiplets for eight nonequivalent protons of the isosorbide fragments in compounds **7** and **8** are similar to those of **5** and **6**, except for the fact that the multiplet for H(2) in compounds **7** and **8** is shifted upfield by ~0.2 ppm due to the presence of a negative charge on this proton, which is indicative of the replacement of the OH groups by ONa. This is also evident from narrowing of the lines of the multiplets in the ^{31}P NMR spectra (the absence of exchange broadening caused by OH groups) showing a distinct doublet and triplet with $J \approx 8$ Hz due to the presence of one and two isosorbide fragments, respectively.

The treatment of compounds **5** and **6** with cyclohexylamine yields salts **9** and **10**, respectively (Scheme 3).

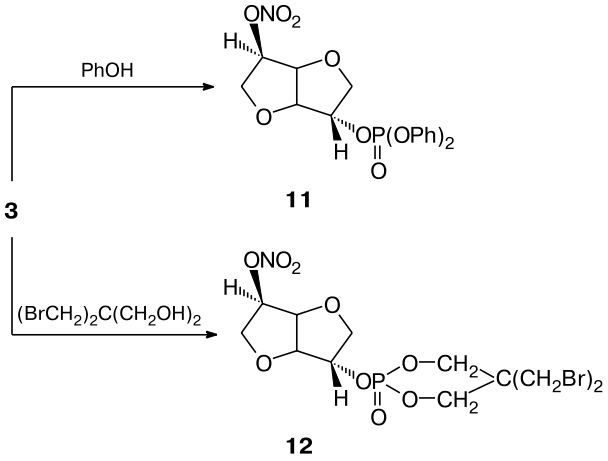
The structures of salts **9** and **10** were established based on the ^{1}H and ^{31}P NMR spectra. The chemical shifts and the coupling constants for the multiplets for the protons of the isosorbide fragments in compounds **9** and **10** are similar to those observed for **5** and **6**. In the spectra of **9** and **10**, the multiplet for H(2) is also shifted upfield by ~0.2 ppm, analogously to that observed in the spectra of salts **7** and **8**. The chemical shifts and the multiplicities of the signals in the ^{31}P NMR spectra correspond to phosphates and the numbers of the isosorbide substituents in compounds **9** (doublet) and **10** (triplet).

The reactivities of phosphorochloridates **3** and **4** in the reactions with nucleophiles were studied using phenol, pentaerythritol dibromohydrin, and ethylenimine (Schemes 4 and 5).

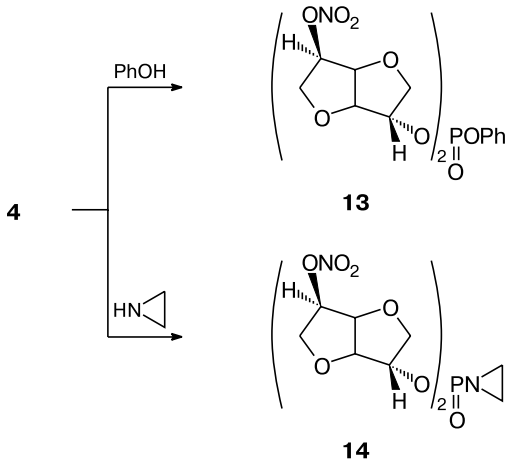
Scheme 3



Scheme 4



Scheme 5



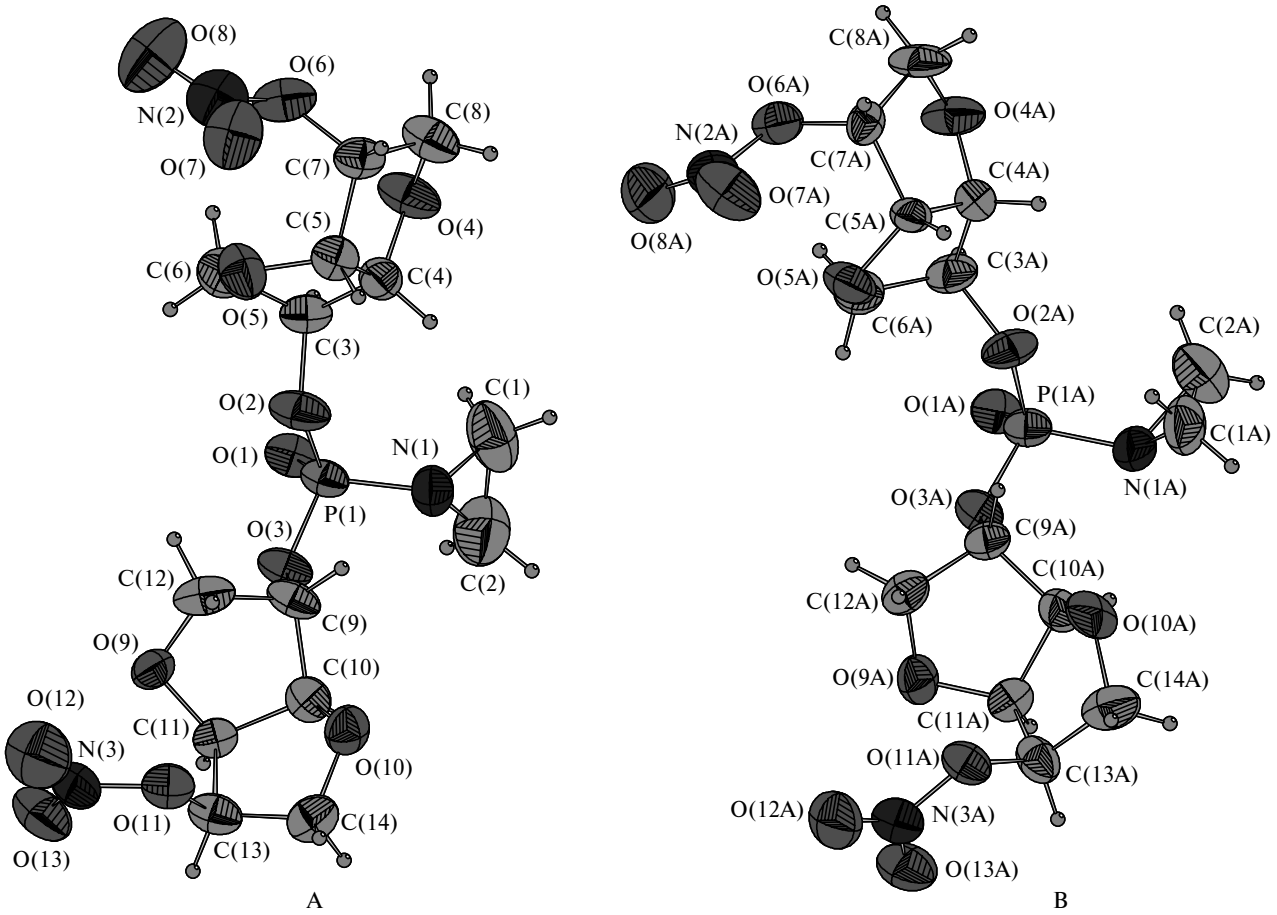


Fig. 1. Structures of two independent molecules in the crystal structure of **14**.

The compositions and structures of compounds **11**—**14** were confirmed by elemental analysis and ^{1}H and ^{31}P NMR spectroscopy. The structure of phosphoramidate **14** was established by X-ray diffraction (Fig. 1, Table 2).

The ^{1}H and ^{31}P NMR spectra of compounds **11** and **13** unambiguously confirm their structures. These spectra contain all multiplets for eight nonequivalent protons characteristic of isosorbide; the ratio between the integrated intensities of the signals for the protons of the Ph groups and the isosorbide fragments is 10 : 8 and 5 : 16 in **11** and **13**, respectively. The ^{31}P NMR spectra show the coupling constants $^{3}J_{P,H(2)} \approx 7$ Hz characteristic of isosorbide derivatives. It is known[10] that the ^{31}P signal of each Ph residue in phenyl phosphates is shifted upfield by ~5 ppm. This is observed in the spectra under consideration: **11**, δ −11.54 (br.d, $^{3}J_{P,H(2)} \approx 6.9$ Hz); **13**, δ −7.32

Table 2. Selected bond lengths (*d*) and bond angles (ω) in compound **14**

Bond	*d*/Å	Bond	*d*/Å	Angle	ω/deg	Angle	ω/deg
P(1)—O(1)	1.466(6)	P(1)—O(2)	1.581(6)	O(1)—P(1)—O(2)	115.3(4)	O(1)—P(1)—O(3)	111.7(4)
P(1)—O(3)	1.552(6)	P(1)—N(1)	1.620(8)	O(1)—P(1)—N(1)	117.6(4)	O(2)—P(1)—O(3)	102.6(3)
O(6)—N(2)	1.41(1)	O(7)—N(2)	1.19(1)	O(2)—P(1)—N(1)	103.6(4)	O(3)—P(1)—N(1)	104.4(4)
O(8)—N(2)	1.23(2)	O(11)—N(3)	1.38(1)	O(6)—N(2)—O(7)	118(1)	O(6)—N(2)—O(8)	110(1)
O(12)—N(3)	1.21(1)	O(13)—N(3)	1.20(1)	O(7)—N(2)—O(8)	132(1)	O(11)—N(3)—O(12)	111.3(9)
P(1A)—O(1A)	1.465(6)	P(1A)—O(2A)	1.581(6)	O(11)—N(3)—O(13)	121.1(9)	O(12)—N(3)—O(13)	128(1)
P(1A)—O(3A)	1.575(6)	P(1A)—N(1A)	1.619(8)	O(1A)—P(1A)—O(2A)	115.2(4)	O(1A)—P(1A)—O(3A)	110.2(3)
O(6A)—N(2A)	1.40(1)	O(7A)—N(2A)	1.20(1)	O(1A)—P(1A)—N(1A)	113.8(4)	O(2A)—P(1A)—O(3A)	104.8(3)
O(8A)—N(2A)	1.20(1)	O(11A)—N(3A)	1.38(1)	O(2A)—P(1A)—N(1A)	106.1(4)	O(3A)—P(1A)—N(1A)	105.9(4)
O(12A)—N(3A)	1.19(1)	O(13A)—N(3A)	1.22(1)	O(6A)—N(2A)—O(7A)	117.3(9)	O(6A)—N(2A)—O(8A)	114.4(9)
				O(7A)—N(2A)—O(8A)	128(1)	O(11A)—N(3A)—O(12A)	115.6(9)
				O(11A)—N(3A)—O(13A)	116.9(8)	O(12A)—N(3A)—O(13A)	127(1)

(br.t, $^3J_{P,H(2)} \approx 6.5$ Hz) compared to δ −2.05 (m, $^3J_{H(2),P} \approx$ 7.1 Hz) for diester **6**. It is of note that the shifts characteristic (and informative) of the presence of the phenyl substituents are observed in the ^{1}H NMR spectrum as well; this shift is most substantial for the multiplet of the H(2) proton, which is shifted downfield to δ 5.16 in the spectrum of **11** compared to δ 4.7—4.8 in the spectra of the acids.

Compounds **12** and **14** were characterized also by NMR spectra, which convincingly confirmed their structures. For example, the ^{1}H NMR spectrum of compound **12** shows, along with multiplets of the isosorbide fragment, a complex multiplet for the protons of the 1,3,2-dioxaphosphinane ring. The geminal protons in the OCH_2 groups are nonequivalent and their coupling constants with ^{31}P are strongly different. One of these constants (apparently, $J^1_{P,H_{eq}}$) is ~20 Hz (due to the *trans* arrangement of the P and H atoms in the chair conformation), and it is this constant that is clearly observed in the ^{31}P NMR spectrum showing a triplet splitting. Another coupling constant, $J^2_{P,H_{ax}}$, being a few Hertz (due to the *gauche* arrangement), together with $J_{P,H(2)}$, which is approximately equal to $J^2_{P,H_{ax}}$, is responsible for the fact that each line of this triplet appears as a broadened quartet with the splitting of ~5—7 Hz. The chemical shift δ_P −8.21 suggests the involvement of the phosphorus atom in the ring.[10] Compared to the spectra of **12**, the spectra of compound **14** are much more simple. Thus, the ^{1}H spectrum shows, in addition to the multiplets typical of isosorbide, a doublet for the equivalent protons of ethylenimine with $J_{H,P} = 16$ Hz, which confirms the presence of the P—N covalent bond. This is also evidenced by a large positive ^{31}P chemical shift (δ_P 15.46).

It should be noted that the isosorbide fragments are equivalent in the NMR spectra of compounds **2**, **6**, **8**, and **10**, whereas these fragments in the spectra of compounds **13** and **14** are nonequivalent. Their diastereotopicity[12] associated with the asymmetry of the molecule is manifested at 200 MHz as a pronounced doubling of the multiplet for H(2) adjacent to the center of asymmetry and a broadening of the lines of the other multiplets.

The structure of compound **14** was established by X-ray diffraction. There are two independent molecules per asymmetric unit (see Fig. 1). In both independent molecules, the phosphorus atom is bound to the phosphoryl oxygen atom, the ethylenimine nitrogen atom, and two O atoms of two 5-*O*-nitro-1,4:3,6-dianhydro-D-sorbitol fragments. The absolute configurations of all asymmetric C atoms correspond to the D configuration. Both independent molecules are not diastereomers. They are, in fact, rotational isomers characterized by different angles of rotation of the isosorbide fragments about the P—O and O—C bonds and of the ethylenimine ring about the P—N bond (Fig. 2). The torsion angles describing the orientation of the dianhydrosorbitol fragments in molecules A and B are given in Table 3.

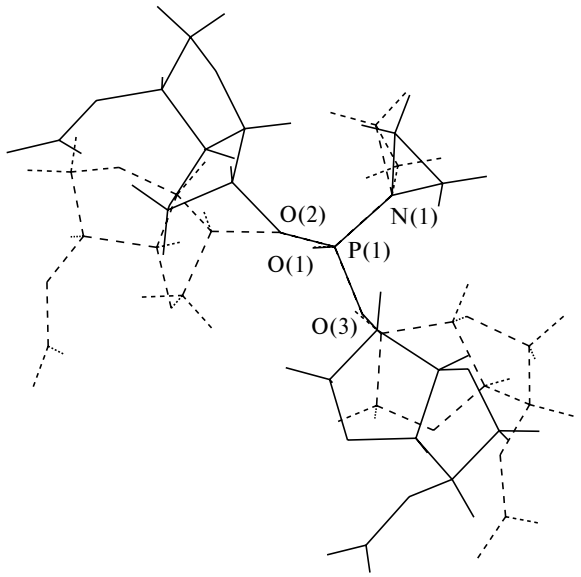


Fig. 2. Projection of two molecules in the structure of **14** (the P, O(1), O(2), O(3), and N(1) atoms are superimposed; the second molecule (labeled by B) is shown by dashed lines).

Table 3. Selected torsion angles (φ) in two independent molecules of compound **14**

Angle	φ/deg	
	A	B
C(3)—O(2)—P(1)—O(1)	−43.8	10.8
C(9)—O(2)—P(1)—O(1)	−169.0	−173.3
C(3)—O(2)—P(1)—N(1)	85.9	137.4
C(9)—O(2)—P(1)—N(1)	63.3	63.4

A substantial difference in the orientation of these groups is apparently associated with the crystal packing effects. As in the tris(5-*O*-nitro-1,4:3,6-dianhydro-D-sorbit-2-yl) phosphate molecule studied earlier,[3] the *cis*-fused oxolane rings adopt conformations intermediate between an envelope and a *twist* form. The bond lengths and bond angles in compound **14** (see Table 2) are similar to those in the dinitro derivative of 1,4:3,6-dianhydro-D-sorbitol studied earlier.[13]

To conclude, we synthesized mono- and bis(5-*O*-nitro-1,4:3,6-dianhydro-D-sorbit-2-yl) phosphates and studied their transformations. The vasodilator activity of compound **6*** is of the same order of magnitude as the efficiency of the drug nicorandil.

* The vasodilator activity was determined from the relaxation of isolated rat aorta contracted with noradrenaline; the investigation was carried out in the Laboratory of Receptor and Biochemical Pharmacology at the All-Russian Research Center for Safety of Biologically Active Compounds.

Experimental

The ^1H (200.13 MHz), ^{31}P (81 MHz), and ^{13}C (50.3 MHz) NMR spectra were recorded on a Bruker DPX-200 spectrometer relative to Me_4Si as the internal standard for ^1H and ^{13}C and relative to 85% aqueous H_3PO_4 as the external standard for ^{31}P. Different NMR experiments were carried out for the same freshly prepared samples using a DMSO-d_6—25 vol.% CCl_4—0.1 vol.% Me_4Si mixture as the solvent. The assignment of the signals was made based on a comparative analysis of our results[3] and the data published in the literature[9] for the related compounds, the forms of multiplets, integrated intensities, and $^{13}C\{^1H\}$DEPT experiments.

The IR spectra were recorded on a Specord M-82 spectrometer. The melting points were determined on a Boetius RWMK-05 instrument. Isosorbide 5-mononitrate (Acros), $POCl_3$ (99%, Aldrich), Py, Et_3N, solvents, and inorganic reagents of reagent grade were used. Pyridine, Et_3N, and the solvents were dried according to standard procedures.[14]

(5-*O*-Nitro-1,4:3,6-dianhydro-D-sorbit-2-yl) phosphorodichloridate (3) and **(5-*O*-nitro-1,4:3,6-dianhydro-D-sorbit-2-yl) phosphate (5).** Phosphorus oxychloride (0.88 g, 5.74 mmol) was added with stirring to a solution of compound **1** (1 g, 5.23 mmol) in anhydrous dioxane (15 mL) at ~20 °C. The reaction mixture was stirred at ~20 °C for 30 min. Then the temperature was gradually raised to 75 °C for 1 h. After cooling of the mixture to ~20 °C, volatile components were removed *in vacuo*. The residue was dissolved in anhydrous acetone (10 mL) and poured into anhydrous diethyl ether (15 mL). The oil that formed was separated and dried *in vacuo*. Compound **3** was obtained in a yield of 1.3 g (81%) as a colorless oil, n_D^{20} 1.587. Found (%): C, 23.61; H, 2.88; Cl, 22.87; N, 4.72; P, 10.21. $C_6H_8Cl_2NO_7P$. Calculated (%): C, 23.40; H, 2.62; Cl, 23.02; N, 4.55; P, 10.06. The recording of the IR and NMR spectra was accompanied by hydrolysis of phosphorodichloridate **3**.

Compound **3** (1.3 g, 4.2 mmol) was dissolved in aqueous acetone (10 mL). The reaction mixture was stirred for 3 h and kept for 20 h. Then anhydrous $MgSO_4$ was added, the mixture was filtered, the solvent was removed *in vacuo*, and the residue was additionally dried in a vacuum desiccator over P_2O_5. Compound **5** was obtained in a yield of 1.1 g (96%), n_D^{20} 1.5045. Found (%): C, 26.65; H, 3.91; N, 5.26; P, 11.24. $C_6H_{10}NO_9P$. Calculated (%): C, 26.65; H, 3.72; N, 5.17; P, 11.42. IR, ν/cm^{-1}: 1650, 1280, 958, 855 (ONO_2); 1005 (POC); 1205 (P=O). ^1H NMR ($CDCl_3$—CD_3CN), δ: 3.70—4.08 (m, 4 H, $H_a(1)$, $H_b(1)$, $H_a(6)$, $H_b(6)$); 4.61 (m, 1 H, H(3)); 4.79 (m, 1 H, H(2)); 5.02 (m, 1 H, H(4)); 5.41 (m, 1 H, H(5)); 7.34 (br.s, 2 H, OH). ^{31}P NMR ($CDCl_3$—CD_3CN), δ: 0.03 (br.d, P(O), $^3J_{P,H(2)}$ = 5.0 Hz). $^{31}P\{^1H\}$ NMR: singlet.

Bis(5-*O*-nitro-1,4:3,6-dianhydro-D-sorbit-2-yl) phosphorochloridate (4) and **bis(5-*O*-nitro-1,4:3,6-dianhydro-D-sorbit-2-yl) phosphate (6).** A solution of $POCl_3$ (0.77 g, 5.0 mmol) in anhydrous dioxane (5 mL) was added to a solution of compound **1** (1.9 g, 10 mmol) and Py (0.8 g, 10.1 mmol) in anhydrous dioxane (10 mL) at 8—10 °C. The reaction mixture was stirred at 8—10 °C for 1 h and then at 18—20 °C for 2 h. The precipitate that formed was filtered off, and the solvent was removed *in vacuo*. The residue was treated with a 1 : 1 acetone—diethyl ether mixture (2×5 mL), the solvent was removed, and the residue was dried in a vacuum desiccator over P_2O_5. Compound **4** was obtained in a yield of 1.2 g (52%) as a colorless oil, n_D^{20} 1.571. Found (%): C, 31.20; H, 3.65; Cl, 7.42; N, 6.18; P, 6.44. $C_{12}H_{16}ClN_2O_{13}P$. Calculated (%): C, 31.15; H, 3.48; Cl, 7.66; N, 6.05; P, 6.69. The identification of the IR and NMR spectra was accompanied by hydrolysis of phosphorochloridate.

Compound **4** (1.2 g, 2.6 mmol) was dissolved in dichloromethane (10 mL). The reaction mixture was washed with water (3×5 mL), the solvent was removed *in vacuo*, and the residue was recrystallized from acetone. Compound **6** was obtained as hydrate in a yield of 1.0 g (83%), m.p. 93—94 °C. Found (%): C, 31.46; H, 4.28; N, 6.31; P, 6.47. $C_{12}H_{17}N_2O_{14}P \cdot H_2O$. Calculated (%): C, 31.28; H, 4.14; N, 6.06; P, 6.70. IR, ν/cm^{-1}: 1638, 1280, 965, 855 (ONO_2); 1026 (POC); 1256 (P=O). ^1H NMR (DMSO-d_6—CCl_4), δ: 3.74 (m, $H_a(1)$, $|^2J_{H_a(1),H_b(1)}|$ = 10.4 Hz, $^3J_{H_a(1),H(2)}$ = 2.4 Hz, $^4J_{H_a(1),P} \approx$ 1.5 Hz); 3.87 (m, $H_a(6)$, $|^2J_{H_a(6),H_b(6)}|$ = 11.7 Hz, $^3J_{H_a(6),H(5)}$ = 5.0 Hz); 3.97 (m, $H_b(6)$, $|^2J_{H_a(6),H_b(6)}|$ = 11.7 Hz, $^3J_{H_b(6),H(5)} \approx$ 2.0 Hz); 4.00 (m, $H_b(1)$, $|^2J_{H_a(1),H_b(1)}|$ = 10.4 Hz, $^3J_{H_b(1),H(2)} \approx$ 0 Hz); 4.38 (s, P(O)OH + H_2O); 4.52 (d, H(3), $^3J_{H(3),H(4)}$ = 5.0 Hz, $^3J_{H(3),H(2)} \approx$ 0 Hz); 4.68 (m, H(2), $^3J_{H(2),H_a(1)}$ = 2.4 Hz, $^3J_{H(2),H(3)} \approx$ 0 Hz, $^3J_{H(2),P} \approx$ 7.1 Hz); 4.99 (m, H(4), $^3J_{H(4),H(5)} = {}^3J_{H(4),H(3)} \approx$ 5.0 Hz); 5.50 (m, H(5), $^3J_{H(5),H(4)} \approx {}^3J_{H(5),H_a(6)} \approx$ 5.0 Hz, $^3J_{H(5),H_b(6)}$ = 2.0 Hz). ^{31}P NMR (DMSO-d_6—CCl_4), δ: −2.05 (m, P(O), $^3J_{H(2),P} \approx$ 7.1 Hz, $^4J_{H_a(1),P} \approx$ 1.5 Hz). $^{31}P\{^1H\}$ NMR: singlet. $^{13}C\{^1H\}$ and $^{13}C\{^1H\}$DEPT135(+,−) NMR (DMSO-d_6—CCl_4), δ: 87.48 (+) (d, C(3), $^3J_{C(3),P}$ = 6.0 Hz); 83.18 (+) (s, C(4) or C(5)); 82.11 (+) (s, C(5) or C(4)); 79.90 (+) (d, C(2), $^2J_{C(2),P}$ = 5.0 Hz); 74.35 (−) (d, C(1), $^3J_{C(1),P}$ = 5.0 Hz); 69.81 (−) (s, C(6)).

Sodium mono- and bis(5-*O*-nitro-1,4;3,6-dianhydro-D-sorbit-2-yl) phosphates (7 and 8). A methanolic solution of compound **5** or **6** was added with stirring to a methanolic solution of MeONa. The reaction mixture was stirred at ~20 °C for 15 min and kept in a refrigerator at 5—10 °C for 12 h. The salt was filtered off, washed with diethyl ether, and dried in a vacuum desiccator over P_2O_5. Diethyl ether (1 : 4) was added to the filtrate, and an additional amount of the sodium salt was obtained.

Disodium (5-*O*-nitro-1,4:3,6-dianhydro-D-sorbit-2-yl) phosphate (7). The reaction of compound **5** (2.71 g, 10 mmol) in MeOH (5 mL) and sodium methoxide (prepared from Na (0.46 g, 20 mmol)) in MeOH (10 mL) afforded compound **7** in a yield of 2.60 g (82.5%), t.decomp. 203—205 °C. Found (%): C, 21.41; H, 3.22; N, 4.40. $C_6H_8Na_2NO_9P \cdot H_2O$. Calculated (%): C, 21.63; H, 3.03; N, 4.21. IR, ν/cm^{-1}: 1632, 1280, 988, 872 (ONO_2); 1056 (POC); 1164 (P=O). ^1H NMR (DMSO-d_6—CCl_4—$(CD_3)_2C$=O), δ: 3.60—4.40 (m, 4 H, $H_a(1)$, $H_b(1)$, $H_a(6)$, $H_b(6)$, H_2O); 4.51 (m, 2 H, H(3), H(2)); 4.90 (m, 1 H, H(4)); 5.46 (m, 1 H, H(5)). ^{31}P NMR (DMSO-d_6—CCl_4—$(CD_3)_2CO$), δ: 1.11 (br.d, P(O), $^3J_{P,H(2)} \approx$ 7.9 Hz). $^{31}P\{^1H\}$ NMR: singlet.

Sodium bis(5-*O*-nitro-1,4:3,6-dianhydro-D-sorbit-2-yl) phosphate (8). The reaction of compound **6** (2.31 g, 5 mmol) in MeOH (5 mL) and sodium methoxide (prepared from Na (0.12 g, 5 mmol) in MeOH (10 mL)) afforded compound **8** in a yield of 2.05 g (84.5%), t.decomp. 186—188 °C. Found (%): C, 29.53; H, 3.26; N, 5.57. $C_{12}H_{16}NaN_2O_{14}P \cdot H_2O$. Calculated (%): C, 29.76; H, 3.75; N, 5.78. IR, ν/cm^{-1}: 1636, 1281, 966, 854 (ONO_2); 1090 (POC); 1241 (P=O). ^1H NMR (DMSO-d_6—CCl_4), δ: 3.55—4.00 (m, 8 H, $H_a(1)$, $H_b(1)$, $H_a(6)$, $H_b(6)$); 4.34—4.54 (m, 4 H, H(2), H(3)); 4.89 (t, 2 H, H(4));

5.44 (m, 2 H, H(5)). ^{31}P NMR (DMSO-d_6—CCl_4), δ: −1.41 (br.t, P(O), $^3J_{P,H(2)} \approx 7.6$ Hz).

Cyclohexylammonium (5-*O*-nitro-1,4:3,6-dianhydro-D-sorbit-2-yl) phosphate (9). A solution of compound **5** (2.7 g, 10 mmol) in MeOH (10 mL) was added with stirring to a solution of cyclohexylamine (2.0 g, 20 mmol) in MeOH (15 mL) at 5—10 °C. The reaction mixture was stirred for 2 h, the temperature being gradually raised to ~20 °C. Diethyl ether (25 mL) was added, and the salt was filtered off, washed with diethyl ether, and dried in a vacuum desiccator over P_2O_5. Compound **9** was obtained as hydrate in a yield of 2.9 g (85.3%), t.decomp. 171—173 °C. Found (%): C, 37.30; H, 6.63; N, 6.94; P, 7.71. $C_{12}H_{23}N_2O_9P \cdot H_2O$. Calculated (%): C, 37.12; H, 6.49; N, 7.21; P, 7.98. IR, ν/cm^{-1}: 1640, 1280, 960, 855 (ONO_2); 1100 (POC); 1250 (P=O). ^{1}H NMR (DMSO-d_6—CCl_4—$(CD_3)_2CO$), δ: 1.00—2.00 (m, 10 H, C_5H_{10}); 2.83 (unresolved m, 1 H, NCH); 3.10—7.00 (br.s, 3 H, POH + NH_2); 3.60—4.00 (m, 4 H, $H_a(1)$, $H_b(1)$, $H_a(6)$, $H_b(6)$); 4.51 (m, 2 H, H(2), H(3)); 4.89 (m, 1 H, H(4)); 5.48 (m, 1 H, H(5)). ^{31}P NMR (DMSO-d_6—CCl_4—$(CD_3)_2CO$), δ: 0.06 (br.d, $^3J_{P,H(2)} \approx 6.8$ Hz). ^{31}P{^{1}H} NMR: singlet.

Cyclohexylammonium bis(5-*O*-nitro-1,4:3,6-dianhydro-D-sorbit-2-yl) phosphate (10). A solution of compound **6** (2.2 g, 5 mol) in acetone (10 mL) was added with stirring to a solution of cyclohexylamine (1.0 g, 10 mmol) in acetone (10 mL) at 0—5 °C. The reaction mixture was stirred for 1 h, the temperature being gradually raised to 18—20 °C. Then the mixture was cooled to 0 °C, and diethyl ether (25 mL) was added. The salt that precipitated was filtered off, washed with cold methanol and diethyl ether, and dried in a vacuum desiccator. Compound **10** was obtained in a yield of 5 g (90%), t.decomp. 183—184 °C. Found (%): C, 38.73; H, 5.92; N, 7.65; P, 5.30. $C_{18}H_{30}N_3O_{14}P \cdot H_2O$. Calculated (%): C, 38.51; H, 5.74; N, 7.48; P, 5.52. IR, ν/cm^{-1}: 1647, 1281, 975, 852 (ONO_2); 1076 (POC); 1207 (P=O). ^{1}H NMR (DMSO-d_6—CCl_4), δ: 1.00—2.00 (m, 10 H, C_5H_{10}); 2.83 (m, 1 H, NCH); 3.10—7.00 (br.s, 3 H, POH + NH_2); 3.60—4.00 (m, 8 H, $H_a(1)$, $H_b(1)$, $H_a(6)$, $H_b(6)$); 4.42 (m, 4 H, H(2), H(3)); 4.89 (m, 2 H, H(4)); 5.46 (m, 2 H, H(5)). ^{31}P NMR (DMSO-d_6—CCl_4), δ: −2.44 (br.t, P(O)). ^{31}P{^{1}H} NMR: singlet.

(5-*O*-Nitro-1,4:3,6-dianhydro-D-sorbit-2-yl)diphenyl phosphate (11). A solution of compound **3** (3.1 g, 10 mmol) in anhydrous dioxane (10 mL) was added with stirring to a solution of phenol (1.9 g, 20 mmol) and Et_3N (2.2 g, 22 mmol) in anhydrous dioxane (15 mL) at ~20 °C. The reaction mixture was stirred for 30 min, the temperature being gradually raised to 50—55 °C. Then the mixture was kept at 50—55 °C for 1 h and at ~20 °C for 20 h. The precipitate that formed was filtered off, the solvent was distilled off *in vacuo*, and the residue was dissolved in CH_2Cl_2 (30 mL). The resulting solution was washed with water, 5% aqueous H_2SO_4, a 5% aqueous $NaHCO_3$ solution, and water and dried over $MgSO_4$. After removal of the solvent *in vacuo*, compound **11** was obtained in a yield of 2.4 g (57%) as a colorless oil, n_D^{20} 1.5408. Found (%): C, 51.30; H, 4.42; N, 3.18; P, 7.21. $C_{18}H_{18}NO_9P$. Calculated (%): C, 51.07; H, 4.20; N, 3.31; P, 7.32. IR, ν/cm^{-1}: 1644, 1281, 957, 852 (ONO_2); 1026 (POC); 1261 (P=O). ^{1}H NMR (DMSO-d_6—CCl_4), δ: 3.78—4.21 (m, 4 H, $H_a(1)$, $H_b(1)$, $H_a(6)$, $H_b(6)$); 4.60 (m, 1 H, H(3)); 5.04 (m, 1 H, H(4)); 5.16 (m, 1 H, H(2)); 5.46 (m, 1 H, H(5)); 7.10—7.50 (m, 10 H, C_6H_5O). ^{31}P NMR (DMSO-d_6—CCl_4), δ: −11.54 (br.d, P(O), $^3J_{P,H(2)} \approx 6.9$ Hz). ^{31}P{^{1}H} NMR: singlet.

5,5-Bis(bromomethyl)-2-(5-*O*-nitro-1,4:3,6-dianhydro-D-sorbit-2-yloxy)-2-oxo-1,3,2-λ^5-dioxaphosphinane (12). A solution of compound **3** (3.08 g, 10 mmol) in anhydrous dioxane (10 mL) was added with stirring to a solution of pentaerythritol dibromohydrin (2.62 g, 10 mmol) and Py (1.6 g, 20.2 mmol) in anhydrous dioxane (15 mL) at 25—30 °C. The reaction mixture was stirred for 3 h and kept at ~20 °C for 20 h. The precipitate that formed was filtered off, the solvent was distilled off *in vacuo*, and the residue was treated with water. The reaction product was filtered off, washed with water, dried in air, and recrystallized from aqueous acetone. Compound **12** was obtained in a yield of 3.3 g (64%), m.p. 148—150 °C. Found (%): C, 25.86; H, 3.81; Br, 31.18; N, 2.65; P, 5.86. $C_{11}H_{16}Br_2NO_9P \cdot H_2O$. Calculated (%): C, 25.65; H, 3.52; Br, 31.03; N, 2.72; P, 6.01. IR, ν/cm^{-1}: 1648, 1284, 1004, 868 (ONO_2); 1024 (POC); 1241 (P=O); 664 (CBr). ^{1}H NMR (DMSO-d_6—CCl_4), δ: 3.52 (s, 2 H, CH_2Br); 3.60—4.50 (m, 8 H, $H_a(1)$, $H_b(1)$, $H_a(6)$, $H_b(6)$ + 2 OCH_2); 3.81 (s, 2 H, CH_2Br); 4.61 (m, 1 H, H(3)); 4.80 (m, 1 H, H(2)); 5.06 (m, 1 H, H(4)); 5.51 (m, 1 H, H(5)). ^{31}P NMR (DMSO-d_6—CCl_4), δ: −8.21 (br.tq, P(O), $^3J^{(1)}_{P,H} \approx 20$ Hz, $^3J^{(2)}_{P,H} \approx {}^3J^{(3)}_{P,H(2)} \approx 4$—6 Hz). ^{31}P{^{1}H} NMR: singlet.

Bis(5-*O*-nitro-1,4:3,6-dianhydro-D-sorbit-2-yl)phenyl phosphate (13). A solution of compound **4** (2.31 g, 5 mmol) in anhydrous dioxane (10 mL) was added with stirring to a solution of phenol (0.47 g, 5 mmol) and Et_3N (0.61 g, 6 mmol) in anhydrous dioxane (10 mL) at 20—25 °C. The reaction mixture was stirred at 45—50 °C for 3 h and kept at ~20 °C for 20 h. The precipitate that formed was filtered off, anhydrous diethyl ether (25 mL) was added to the filtrate, and an additional amount of the precipitate was filtered off. The organic layer was washed with ice water, 5% aqueous H_2SO_4, a 5% aqueous $NaHCO_3$ solution, and water and dried over $MgSO_4$. After removal of the solvent *in vacuo*, compound **13** was obtained in a yield of 1.5 g (58%) as a colorless oil, n_D^{20} 1.5120. Found (%): C, 41.32; H, 4.31; N, 5.60; P, 5.76. $C_{18}H_{21}N_2O_{14}P$. Calculated (%): C, 41.55; H, 4.07; N, 5.38; P, 5.95. IR, ν/cm^{-1}: 1639, 1281, 960, 852 (ONO_2); 1027 (POC); 1238 (P=O). ^{1}H NMR (DMSO-d_6—CCl_4), δ: 3.71—4.16 (m, 8 H, $H_a(1)$, $H_b(1)$, $H_a(6)$, $H_b(6)$); 4.51 and 4.58 (both m, 1 H each, H(3)); 4.85—5.12 (m, 4 H, H(2), H(4)); 5.48 (m, 2 H, H(5)); 7.10—7.50 (m, 5 H, C_6H_5O). ^{31}P NMR (DMSO-d_6—CCl_4), δ: −7.32 (br.t, OP(O), $^3J_{P,H(2)} \approx 6.5$ Hz). ^{31}P{^{1}H} NMR: singlet.

Aziridinobis(5-*O*-nitro-1,4:3,6-dianhydro-D-sorbit-2-yl) phosphate (14). A solution of compound **4** (4.6 g, 10 mmol) in anhydrous dioxane (20 mL) was added with stirring to a solution of ethylenimine (0.5 g, 11.6 mmol) and Et_3N (1.2 g, 11.8 mmol) in anhydrous dioxane (10 mL) at 15—20 °C. The reaction mixture was stirred at ~20 °C for 3 h and kept for 20 h. The precipitate that formed was filtered off, the solvent was distilled off *in vacuo*, and the residue was recrystallized from chloroform. Compound **14** was obtained in a yield of 2.2 g (45.8%), m.p. 100—101 °C. Found (%): C, 35.58; H, 4.57; N, 8.72; P, 6.46. $C_{14}H_{20}N_3O_{13}P$. Calculated (%): C, 35.83; H, 4.30; N, 8.95; P, 6.60. IR, ν/cm^{-1}: 1636, 1276, 956, 856 (ONO_2); 1024 (POC); 1248 (P=O). ^{1}H NMR (DMSO-d_6—CCl_4), δ: 2.15 (d, 4 H, NCH_2, $^3J_{H,NP}$ = 16.0 Hz); 3.70—4.10 (m, 8 H, $H_a(1)$, $H_b(1)$, $H_a(6)$, $H_b(6)$); 4.52 (m, 2 H, H(3)); 4.82 (m, 2 H, H(2)); 5.00 (m,

2 H, H(4)); 5.50 (m, 2 H, H(5)). ^{31}P NMR (DMSO-d_6—CCl_4), δ: 15.46 (m, P(O)). $^{31}P\{^1H\}$ NMR: singlet.

X-ray diffraction study. X-ray diffraction data were collected on an Enraf-Nonius CAD-4 automated diffractometer (λ(Mo-Kα), graphite monochromator, ω scanning technique, T = 293 K, $2\theta_{max}$ = 50.2°, 3497 independent reflections, of which 1500 reflections were with $F^2 > 2\sigma(I)$). The structure was solved by direct methods and refined by the least-squares method using the SHELXS97[15] and SHELXL97[16] program packages with anisotropic displacement parameters for nonhydrogen atoms (isotropic displacement parameters for H atoms) to R = 0.0375 (wR_2 = 0.067) based on 1500 reflections with $F^2 > 2\sigma(I)$; the goodness-of-fit GOOF = 1.000. Crystals of **14** are triclinic, a = 6.535(2) Å, b = 9.179(2) Å, c = 16.046(3) Å, α = 102.96°, β = 95.26(2)°, γ = 95.06(2)°, Z = 2, d_{calc} = 1.586 g cm^{-3}, μ = 0.217 mm^{-1}, V = 982.8(4) Å^3, space group $P\bar{1}$. The Flack parameter is –0.00(17).

This study was financially supported by the Russian Foundation for Basic Research (Project No. 06-03-32482) and the Presidium of the Russian Academy of Sciences (Program of Fundamental Research No. 08P).

References

1. M. D. Mashkovskii, *Lekarstvennye sredstva* [*Drugs*], Novaya Volna, Moscow, 2005, 1206 pp. (in Russian).
2. V. G. Granik and N. B. Grigor´ev, *Vestn. RFFI*, 2002, **30**, No. 4, 49 [*RFBR Information Bulletin*, 2002, **30**, No. 4 (Engl. Transl.)].
3. L. T. Eremenko, G. V. Oreshko, G. V. Lagodzinskaya, G. G. Aleksandrov, and I. L. Eremenko, *Izv. Akad. Nauk, Ser. Khim.*, 2006, 380 [*Russ. Chem. Bull., Int. Ed.*, 2006, **55**, 393].
4. V. G. Granik and N. B. Grigor´ev, *Izv. Akad. Nauk, Ser. Khim.*, 2002, 1268 [*Russ. Chem. Bull., Int. Ed.*, 2002, **51**, 1375].
5. E. Fischer, *Ber.*, 1914, **47**, 3193.
6. M. Gulland and G. I. Hobday, *J. Chem. Soc.*, 1940, 746.
7. P. T. Gilham and H. G. Khorana, *J. Am. Chem. Soc.*, 1958, **80**, 6212.
8. H. A. C. Montgomery and J. H. Turnbull, *J. Chem. Soc.*, 1958, 1963.
9. H. Hayashi, J. Ikeda, T. Kuroda, K. Kubo, T. Sano, and F. Suzuki, *Chem. Pharm. Bull.*, 1993, **41**, 1091.
10. E. E. Nifant´ev, *Khimiya fosfororganicheskikh soedinenii* [*Chemistry of Organophosphorus Compounds*], Izd-vo MGU, Moscow, 1971, 352 pp. (in Russian).
11. *Phosphorus-31 NMR: Principles and Applications*, Ed. D. G. Gorenshtein, Academic Press, New York, 1984, 604 pp.
12. K. Mislow and M. Raban in *Topics in Stereochemistry*, Eds N. L. Allinger and E. L. Eliel, Intersci. Publ.—Wiley and Sons, New York, 1967.
13. J. A. Kanters, A. Schouten, G. J. Sterk, and M. H. de Jomg, *J. Mol. Struct.*, 1993, **298**, 113.
14. A. J. Gordon and R. A. Ford, *The Chemists Companion. A Handbook of Practical Data, Techniques and References*, J. Wiley and Sons, New York—London, 1972.
15. G. M. Sheldrick, *SHELXS97, Program for the Solution of Crystal Structures*, University of Göttingen, Germany, 1997.
16. G. M. Sheldrick, *SHELXL97, Program for the Refinement of Crystal Structures*, University of Göttingen, Germany, 1997.

Received October 2, 2006;
in revised form April 3, 2007