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Synthesis and Structure of Bis-phosphorylated 1,4:3,6-Dianhydro-D-mannitol Derivatives

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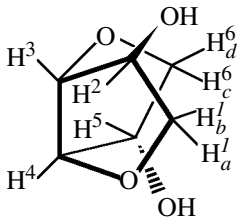
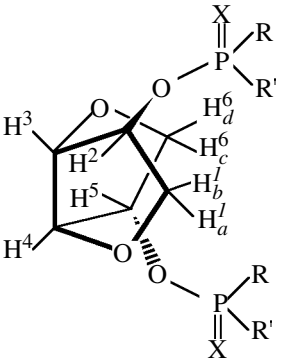
Abstract — A number of bis-phosphorylated 1,4:3,6-dianhydro-D-mannitol derivatives were synthesized. The increased steric loading of the phosphorus-containing residues in the compounds prepared gives rise to complicated ^{1}H and ^{31}P NMR spectra and magnetic nonequivalence of structurally similar molecular fragments.

We previously reported on the synthesis of new phosphorus-containing cyclic systems on the basis of 1,4:3,6-dianhydro-D-mannitol (**I**) and phosphorous amides. We found that the formation of such complex molecular structures is possible only when fine details of spatial compatibility of the initial amides and ring-closing reagents is taken into account [1, 2]. Furthermore, the compounds thus obtained were used for design of new chelating ligands; transition metal complexes derived from these ligands are promising stereoselective catalysts in homogeneous reactions (see structure **A**, where X is an unshared electron pair [3, 4]).



I



A

With the above in mind, we have continued studies in the field of synthesis of new bis-phosphorylated derivatives of diol **I**, which attract interest from the viewpoint of creation of molecular cavities and other 3D structures. As a separate problem, we examined the effect of steric loading of the phosphorus atom on the steric structure of the products. It should be noted that the C^2–O and C^5–O bonds in phosphorylated derivatives like **A** are oriented inside the fused bicyclic system; therefore, a certain steric interaction between the phosphorus-containing fragments should exist. This interaction should lead to dephosphorylation (see [3]) and change of usual spectral parameters, e.g., complication of ^{1}H NMR spectra and nonequivalence of phosphorus nuclei in ^{31}P NMR spectra [1, 2].

We have started our study with the synthesis of phosphorous amides **II**–**VII** from diol **I** and examination of their spectral parameters. Compounds **II**–**VII** can be regarded as a series of type **A** derivatives with successively increasing steric loading of the phosphorus-containing moieties. Compounds **II** and **III** were obtained in 35 and 50% yield, respectively, by heating of diol **I** with 2 equiv. of the corresponding phosphorous triamide at 80°C under a weak stream of nitrogen with continuous removal (by distillation) of the released dialkylamine. Compounds **II** and **III** readily take up sulfur to give phosphinothioyl derivatives **IV** and **V**. On the other hand, we succeeded in synthesizing analogous *P*-phenyl derivative **VI** and the corresponding phosphine sulfide **VII** only by treatment of diol **I** with chloro(diethylamino)phenylphosphine in benzene at 20°C in the presence of triethylamine as hydrogen chloride acceptor. The progress of formation of P(III) derivative **VI** was monitored by ^{31}P NMR spectroscopy. When the reaction was complete, product **VI** was converted into bis-sulfide **VII** without isolation from the reaction mixture (see Experimental). Our attempts to synthesize bis(tetrapiperidino)phosphine under analogous conditions resulted in formation of a mixture of products which were difficult to separate.

Compounds **II**, **III**, and **IV** were described previously. They are characterized by symmetric arrangement of the phosphorus-containing fragments with respect to the dianhydro-D-mannitol cavity, which

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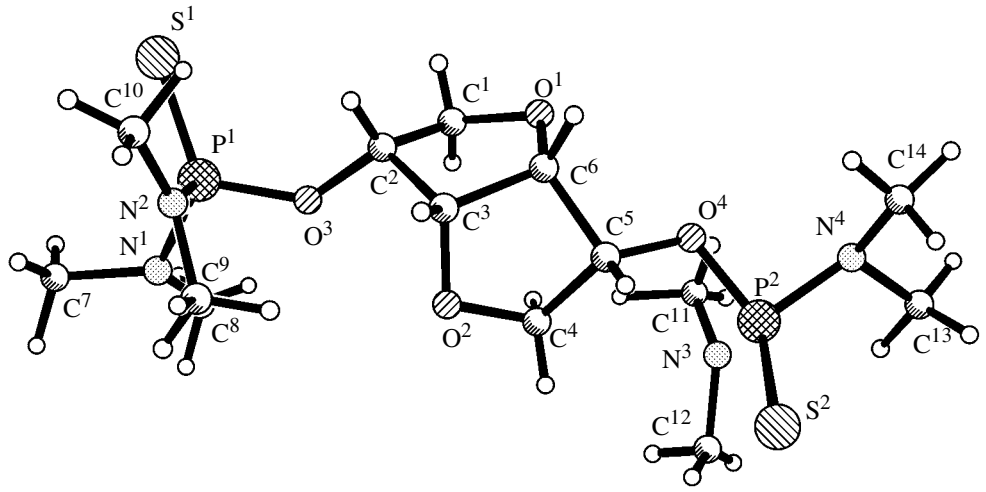
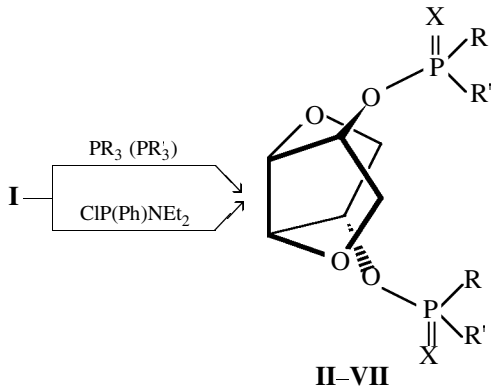


Structure of compound **IV** according to the X-ray diffraction data.

gives rise to the corresponding ^{1}H NMR spectra and similar signals from two equivalent phosphorus nuclei in the ^{31}P NMR spectra [3]. However, the spectral pattern becomes more complicated on addition of sulfur (compound **V**) or introduction of bulkier substituents (compounds **VI** and **VII**).



II–**VII**

II, **IV**, R = R' = NMe_2; **III**, **V**, R = R' = NEt_2; **VI**, **VII**, R = NEt_2, R' = Ph; **II**, **III**, **VI**, X = unshared electron pair; **IV**, **V**, **VII**, X = S.

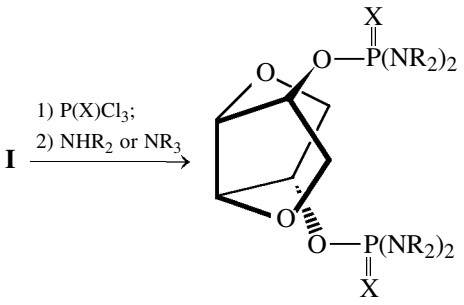
According to the TLC data, compound **V** is a mixture of two isomers **Va** and **Vb** at a ratio of ~2 : 1. Isomer **Va** is a symmetric product; it shows in the ^{31}P NMR spectrum a singlet at δ_P 80 ppm, and the 1-H/6-H, 2-H/5-H, and 3-H/4-H protons of the dianhydro-D-mannitol skeleton are equivalent in pairs. Unsymmetrical isomer **Vb** gives two equal-intensity singlets in the ^{31}P NMR spectrum, δ_P 79.9 and 80 ppm, and the ^{1}H NMR spectral pattern is more complicated due to nonequivalence of the above listed dianhydro-D-mannitol protons and phosphorus-containing moieties (see Experimental). Isomers **Va** and **Vb** are characterized by similar chromatographic mobilities, and we failed to separate them completely by column chromatography. Therefore, the assignment of their ^{1}H NMR signals given in Experimental was based on analysis of the spectra of the corresponding chromatographic fractions.

It should be noted that, according to the TLC and NMR (^{1}H and ^{31}P) data, the previously reported compound **III** possessing two tetraethyldiaminophosphino groups is an individual substance [3]. More sterically loaded phosphorus(III) derivative **VI** is also an individual substance, but the phosphorus-containing moieties therein are nonequivalent: Two signals are observed in the ^{31}P NMR spectrum at δ_P 132.9 and 135.2 ppm. Like compound **V**, phosphorus(V) derivative **VII** exists as two conformers at a ratio of about 1 : 1. According to the ^{1}H and ^{31}P NMR spectra, isomers **VIIa** and **VIIb** are, respectively, symmetric and unsymmetric products (cf. **Va** and **Vb**). We succeeded in isolating by column chromatography only symmetric isomer **VIIa**; the spectra of isomer **VIIb** were analyzed using its mixture with **VIIa**. Presumably, the lack of symmetry in structures **Vb** and **VIIb** results from restricted rotation of the phosphorus-containing groups about the O–P bonds which are extensions of the *endo*-oriented C^2–O and C^5–O bonds.

Phosphorus(V) derivative **IV** was isolated as individual crystalline substance, and its structure was determined by X-ray analysis (see figure). The furanose rings in the bicyclic framework have a nearly planar structure: Only the oxygen atoms deviate from the plane by 0.35 Å. Essential differences are observed for the *endo*- and *exo*-substituents on C^1, C^2, C^5, and C^6. The C^2–O and C^5–O bonds, which connect the anhydromannitol skeleton with phosphorus-containing fragments, are oriented *endo*, and

they form angles of 111.5 and 113.8°, respectively, with the furanose planes. The bond angles at the oxygen atoms are 109.7 and 111.0° (see table), indicating their sp^3 hybridization. The phosphorus atoms are tetrahedral: The average bond angle is 109.2°. The larger bond angles involving sulfur atom (SPO, SPN) suggest repulsion between electrons of the P=S bond (which is characterized by increased electron density), on the one hand, and P–O and two P–N bonds, on the other. Therefore, the angles between the latter are on the average 103.3°.

By reaction of diol **I** with phosphoryl chloride and thiophosphoryl chloride we synthesized P(V) derivatives **VIII**–**XI**. The reactions were carried out in dioxane at 20°C in the presence of excess diethylamine (compound **VIII**), diisopropylamine (**IX**), or triethylamine (**X**, **XI**) as hydrogen chloride acceptor. The progress of the reactions was monitored by ^{31}P NMR spectroscopy.



VIII–**XI**

VIII, R = Et; **IX**, R = *i*-Pr; **X**, **XI**, R_2N = piperidino; **VIII**, **IX**, **X**, X = O; **XI**, X = S.

Compounds **VIII**–**XI** were isolated in 65–85% by reprecipitation (**VIII**, **X**) or by column chromatography (**IX**, **XI**). They are viscous, difficultly crystallizable oily substances. According to the TLC and NMR (^1H and ^{31}P) data, compounds **VIII**, **X**, and **XI** exist as a single isomer, whereas sterically loaded bis(tetraisopropyldiamidophosphate) **IX** is a mixture of two isomers (TLC data) with very close chromatographic mobilities (we failed to separate them by column chromatography). Compound **IX** showed double sets of signals in the ^1H and ^{31}P NMR spectra.

The reaction of dianhydro-D-mannitol **I** with thiophosphoryl chloride was not complete under the given conditions. Separation of the reaction mixture by column chromatography, apart from the expected product **XI** (yield 50%), gave 25% of mono(dipiperidophosphate) **XII**. This is a specific feature of phosphorylation of diol **I** with phosphorus(V) chlorides. The reaction with P(III) derivatives (both chlorides and amides) involves both hydroxy groups of **I** simultaneously even at an equimolar reactant ratio [3].

Bond lengths (*d*, Å) and bond angles (ω, deg) in the molecule of compounds **IV**

Bond	*d*	Bond	*d*
S^1–P^1	1.912(3)	N^1–C^8	1.421(14)
S^2–P^2	1.930(3)	N^1–C^7	1.446(14)
P^1–O^3	1.577(5)	N^2–C^9	1.427(13)
P^1–N^2	1.621(8)	N^3–C^{11}	1.45(2)
P^1–N^1	1.655(8)	N^3–C^{12}	1.463(13)
P^2–O^4	1.592(6)	N^4–C^{14}	1.455(13)
P^2–N^3	1.612(8)	N^4–C^{13}	1.460(14)
P^2–N^4	1.654(7)	C^1–C^2	1.513(14)
O^1–C^1	1.422(13)	C^2–C^3	1.551(14)
O^1–C^4	1.435(12)	C^3–C^4	1.513(12)
O^2–C^6	1.420(10)	C^6–C^5	1.507(13)
O^2–C^3	1.431(10)	C^5–C^4	1.509(12)
O^3–C^2	1.419(10)	N^2–C^{10}	1.414(13)
O^4–C^5	1.434(9)		
Angle	**ω**	**Angle**	**ω**
$O^3P^1N^2$	108.6(4)	$C^{10}N^2P^1$	125.9(8)
$O^3P^1N^1$	97.9(4)	$C^{11}N^3C^{12}$	113.8(12)
$N^2P^1N^1$	103.8(4)	$C^{11}N^3P^2$	121.8(9)
$O^3P^1S^1$	114.3(3)	$C^{12}N^3P^2$	124.3(9)
$N^2P^1S^1$	112.3(3)	$C^{14}N^4C^{13}$	111.6(10)
$N^1P^1S^1$	118.5(3)	$C^{14}N^4R^2$	117.9(7)
$O^4P^2N^3$	106.1(4)	$C^{13}N^4P^2$	114.6(7)
$O^4P^2N^4$	97.4(3)	$O^1C^1C^2$	105.8(10)
$N^3P^2N^4$	105.8(4)	$O^3C^2C^1$	110.8(9)
$O^4P^2S^2$	114.4(2)	$O^3S^2S^3$	112.2(8)
$N^3P^2S^2$	113.1(3)	$S^1S^2S^3$	102.6(9)
$N^4P^2S^2$	118.3(3)	$O^2S^3S^4$	106.7(7)
$C^1O^1C^4$	111.0(7)	$O^2S^3S^2$	109.0(8)
$C^6O^2C^3$	109.7(7)	$S^4S^3S^2$	103.8(9)
$C^2O^3P^1$	121.6(5)	$O^2S^6S^5$	103.3(7)
$C^5O^4P^2$	119.8(5)	$O^4S^5S^6$	115.7(7)
$C^8N^1C^7$	115.6(12)	$O^4S^5S^4$	111.9(7)
$C^8N^1P^1$	112.0(8)	$S^6S^5C^4$	102.4(8)
$C^7N^1P^1$	114.3(8)	$O^1C^4C^5$	112.3(8)
$C^9N^2C^{10}$	112.8(10)	$O^1C^4C^3$	107.0(9)
$C^9N^2P^1$	121.1(7)	$C^5C^4C^3$	102.3(7)

Thus the structure of bis-phosphorylated 1,4:3,6-dianhydro-D-mannitol derivatives strongly depends on the nature and steric loading of the phosphorus-containing moieties.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker WP-250 spectrometer at 250 MHz, and the ^{31}P–{^{1}H} NMR spectra were obtained on a Bruker WP-80 instrument operating at 32.4 MHz, respectively. The chemical shifts were measured relative to tetramethylsilane (^{1}H, internal reference) and 85% phosphoric acid (^{31}P, external reference).

Thin-layer chromatography was performed on Silufol UV-366 plates using the following solvent systems as eluent: benzene–dioxane, 5 : 1 (A); benzene–dioxane, 3 : 1 (B); acetone–ethanol, 3 : 1 (C); chloroform–ethanol, 3 : 1 (D); acetone–ethanol, 10 : 1 (E); dioxane–ethanol, 10 : 1 (F); chloroform–ethanol, 3 : 2 (G); hexane–dioxane, 1 : 1 (H).

X-Ray diffraction study of a single crystal of compound **IV** was performed on a CAD-4 diffractometer (MoK_α radiation, λ = 0.71073 Å). Crystals suitable for the analysis were obtained by slowly cooling a saturated solution of **IV** in hexane. Orthorhombic crystals with the following unit cell parameters: a = 7.2790(1), b = 12.307(2), c = 25.257(5) Å; Z = 4; space group $P2_12_12_1$. Total of 2371 reflections were measured, 817 of which were unique [R(int) = 0.0170]. The structure was solved by the direct method and was refined by the full-matrix least-squares procedure in anisotropic approximation for non-hydrogen atoms to R = 0.024. The positions of hydrogen atoms were determined from the difference synthesis and were partially included in the refinement. The bond lengths and bond angles are given in table. The X-ray diffraction study was performed with participation of K.L. Anfilov.

All syntheses were carried out under dry nitrogen in anhydrous solvents. The procedures for preparation of compounds **II**–**IV** were described by us previously [3].

1,4:3,6-Dianhydro-D-mannitol 2,5-bis(tetraethyldiamidophosphorothioate) (Va/Vb). Finely powdered sulfur, 0.064 g, was added to a mixture of 0.5 g of compound **III** and 5 ml of benzene. The mixture was stirred for 40 min at 60–65°C, filtered from excess sulfur, and evaporated under reduced pressure. The residue was subjected to column chromatography on aluminum oxide (activity grade II) using solvent system B as eluent.

Isomer **Va**. Yield 0.29 g (52%), R_f 0.8 (B). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz): 1.05–1.15 m (24H, NCH_2CH_3), 3.09–3.11 m (16H, NCH_2CH_3), 3.68 d.d (2H, 1-H$_a$, 6-H$_c$, $^2J_{a,b} = {}^2J_{c,d}$ = 8.8), 4.07 d.d (2H, 1-H$_b$, 6-H$_d$, $^2J_{a,b} = {}^2J_{c,d}$ = 8.8), 4.52–4.58 m (2H, 3-H, 4-H), 4.84–4.98 m (2H, 2-H, 5-H). ^{31}P NMR spectrum (C_6H_6): δ_P 80 ppm. Found, %: C 47.38; H 8.79; P 10.87. $C_{22}H_{48}N_4O_4P_2S_2$. Calculated, %: C 47.29; H 8.65; P 11.08.

Isomer **Vb**. Yield 0.19 g (35%), R_f 0.77 (B). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz): 1.03–1.13 m (24H, NCH_2CH_3); 2.95–3.19 m (16H, NCH_2CH_3); 3.55 d.d, 3.67 d.d, 3.94 d.d, 4.08 d.d (4H, 1-H$_a$, 6-H$_c$, 1-H$_b$, 6-H$_d$, $^2J_{a,b}$ = 9.5, $^2J_{c,d}$ = 8.3); 4.21–4.31 m, 4.48–4.54 m (2H, 3-H, 4-H); 4.41–4.47 m, 4.87–5.01 m (2H, 2-H, 5-H). ^{31}P NMR spectrum (C_6H_6), δ_P, ppm: 79.9, 80.0 (intensity ratio 1 : 1). Found, %: C 48.16; H 8.57; P 10.98. $C_{22}H_{48}N_4O_4P_2S_2$. Calculated, %: C 47.29; H 8.65; P 11.08.

1,4:3,6-Anhydro-D-mannitol 2,5-bis(*N*,*N*-diethyl-*P*-phenylphosphonamidothioate) (VIIa/VIIb). A solution of 8.75 g of diethylamine and 13.3 g of triethylamine in 50 ml of hexane was added over a period of 1.5 h while stirring at 0°C to a solution of 21.4 g of dichlorophenylphosphine in 200 ml of hexane. The mixture was stirred for 20 h at 20°C, filtered from triethylamine hydrochloride, and evaporated under reduced pressure. The residue was distilled in a vacuum. Yield of chloro(diethylamino)-phenylphosphine 20.6 g (80%), bp 96–98°C (1 mm). ^{31}P NMR spectrum (C_6H_6): δ_P 140 ppm.

Diol **I**, 0.20 g, was added with stirring at 20°C to a solution of 0.6 g chloro(diethylamino)phenylphosphine (prepared as described above) and 0.31 g of triethylamine in 15 ml of benzene. The mixture was stirred for 20 h at 20°C and filtered from triethylamine hydrochloride; R_f 0.8 (B). ^{31}P NMR spectrum of the reaction mixture (compound **VI**), δ_P, ppm: 132.9 and 135.2 (intensity ratio 1 : 2).

Finely powdered sulfur, 0.17 g, was added to the mixture obtained as described above. The resulting mixture was stirred for 1 h at 80°C, filtered from excess sulfur, and evaporated under reduced pressure. The residue (compound **VII**) was purified by column chromatography on aluminum oxide (activity grade II) using solvent system B as eluent.

Isomer **VIIa**. Yield 0.1 g (22%), light yellow thick oily substance, R_f 0.7 (A). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz): 1.01–1.10 m (12H, NCH_2CH_3, $^3J_{HH}$ = 6.9), 3.12–3.32 m (8H, NCH_2CH_3, $^3J_{PH}$ = 12.4), 3.87 d.d (2H, 1-H$_a$, 6-H$_c$, $^2J_{a,b} = {}^2J_{c,d}$ = 8.5), 4.12 d.d (2H, 1-H$_b$, 6-H$_d$), 4.59 d.d (2H, 3-H, 4-H, $^3J_{3,4}$ = 4.7), 4.96–5.16 m (2H, 2-H, 5-H), 7.44 s (6H, H$_{arom}$), 7.74–7.92 m (4H, H$_{arom}$). ^{31}P NMR spectrum (C_6H_6): δ_P 82 ppm. Found, %: C 54.99; H 6.76; P 10.98. $C_{26}H_{38}N_2O_4P_2S_2$. Calculated, %: C 54.91; H 6.74; P 10.89.

Isomer mixture **VIIa/VIIb**. Yield 0.22 g (51%), light yellow thick oily substance, R_f 0.7, 0.5 (A). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.02–1.10 m (NCH_2CH_3), 3.12–3.34 m (NCH_2CH_3), 3.74–4.00 m (1-H_a, 6-H_c), 4.02–4.22 m (1-H_b, 6-H_d), 4.48–4.68 m (3-H, 4-H), 4.97–5.16 m (2-H, 5-H), 7.44 br.s (H_{arom}), 7.75–7.94 m (H_{arom}). ^{31}P NMR spectrum (C_6H_6), δ_P, ppm: 81, 82 (intensity ratio 1 : 2). Found, %: C 55.12; H 6.95; P 10.78. $C_{26}H_{38}N_2O_4P_2S_2$. Calculated, %: C 54.91; H 6.74; P 10.89.

1,4:3,6-Dianhydro-D-mannitol 2,5-bis(tetraethyldiamidophosphate) (VIII). A mixture of 1.46 g diol **I** and 2.23 g of triethylamine in 25 ml of dioxane was added with stirring at 10°C to a solution of 3.06 g of phosphoryl chloride in 20 ml of dioxane. The mixture was stirred for 20 h at 20°C and filtered from triethylamine hydrochloride. ^{31}P NMR spectrum of the reaction mixture: δ_P 7 ppm.

A solution of 6.44 g of diethylamine in 40 ml of dioxane was added to the above mixture over a period of 1 h while stirring at 20°C. The mixture was stirred for 2 h at 75°C, filtered from diethylamine hydrochloride, and evaporated under reduced pressure. The residue was dissolved in 20 ml of benzene, 10 ml of hexane was added, the mixture was stirred, and oily product **VIII** was separated. Yield 4.48 g (85%), R_f 0.8 (C), 0.4 (D). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.92–0.98 m (24H, NCH_2CH_3, $^3J_{HH}$ = 7.3), 2.88–2.98 m (16H, NCH_2CH_3, $^3J_{PH}$ = 11.1), 3.57 d.d (2H, 1-H_a, 6-H_c, $^2J_{a,b} = {}^2J_{c,d}$ = 8.5, $^3J_{a,2}$ = 8.5), 3.90 d.d (2H, 1-H_b, 6-H_d, $^2J_{a,b} = {}^2J_{c,d}$ = 8.5, $^3J_{b,2}$ = 6.4), 4.39 d.d (2H, 3-H, 4-H, $^3J_{3,4}$ = 3.8, $^3J_{3,2}$ = 1.3), 4.55–4.61 m (2H, 2-H, 5-H, $^3J_{HP}$ = 6.3). ^{31}P NMR spectrum ($CHCl_3$): δ_P 18 ppm. Found, %: C 50.49; H 9.39; P 11.61. $C_{22}H_{48}N_4O_6P_2$. Calculated, %: C 50.18; H 9.19; P 11.76.

1,4:3,6-Dianhydro-D-mannitol 2,5-bis(tetraisopropyldiamidophosphate) (IX). A mixture of 1 g of diol **I** and 1.54 g of triethylamine in 10 ml of dioxane was added with stirring at 10°C to a solution of 2.1 g of phosphoryl chloride in 10 ml of dioxane. The mixture was stirred for 20 h at 20°C and filtered from triethylamine hydrochloride. ^{31}P NMR spectrum of the mixture: δ_P 7 ppm.

A solution of 6.05 g of diisopropylamine in 20 ml of dioxane was added over a period of 1 h to the above mixture while stirring at 20°C. The mixture was stirred for 20 h at 20°C and filtered from diisopropylamine hydrochloride. Product **IX** was purified by column chromatography on aluminum oxide (activity grade II) using solvent system E as eluent. Yield 2.70 g (65%), R_f 0.9, 0.8 (E), 0.6, 0.5 (F). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.24–1.32 m [48H, $NCH(CH_3)2$], 3.50–3.78 m [8H, $NCH(CH_3)_2$], 3.80–3.92 m (2H, 1-H_a, 6-H_c, $^2J_{a,b} = {}^2J_{c,d}$ = 8.3, $^3J_{a,2}$ = 8.3), 4.13 d.d (2H, 1-H_b, 6-H_d, $^2J_{a,b} = {}^2J_{c,d}$ = 8.3, $^3J_{b,2}$ = 6.2), 4.59–4.71 m (2H, 3-H, 4-H), 4.86–5.02 m (2H, 2-H, 5-H). ^{31}P NMR spectrum ($CHCl_3$), δ_P, ppm: 13.3, 13.9. Found, %: C 56.49; H 10.39; P 9.63. $C_{30}H_{64}N_4O_6P_2$. Calculated, %: C 56.41; H 10.10; P 9.70.

1,4:3,6-Dianhydro-D-mannitol 2,5-bis(dipiperididophosphate) (X). A mixture of 1 g of diol **I** and 1.54 g of triethylamine in 10 ml of dioxane was added with stirring at 10°C to a solution of 2.10 g of phosphiryl chloride in 10 ml of dioxane. The mixture was stirred for 20 h at 20°C and filtered from triethylamine hydrochloride. ^{31}P NMR spectrum of the mixture: δ_P 7 ppm.

A solution of 2.32 g of piperidine and 3.03 g of triethylamine in 20 ml of dioxane was added over a period of 1 h to the mixture prepared as described above while stirring at 10°C. The mixture was stirred for 20 h at 20°C, filtered from triethylamine hydrochloride, and evaporated under reduced pressure. The residue was dissolved in 10 ml of dioxane, 5 ml of diethyl ether was added, and oily product **X** was separated. Yield 3.20 g (82%), R_f 0.4 (D), 0.5 (G). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.34–1.68 m [24H, $N(CH_2)_2(CH_2)_3$], 2.86–3.24 m [16H, $N(CH_2)_2(CH_2)_3$, $^3J_{PH}$ = 8.9, $^3J_{PH}$ = 7.3], 3.71 d.d (2H, 1-H_a, 6-H_c, $^2J_{a,b} = {}^2J_{c,d}$ = 8.5, $^3J_{a,2}$ = 8.5), 4.07 d.d (2H, 1-H_b, 6-H_d, $^2J_{a,b} = {}^2J_{c,d}$ = 8.5), 4.52 d (2H, 3-H, 4-H), 4.68–4.80 m (2H, 2-H, 5-H). ^{31}P NMR spectrum (C_6H_6): δ_P 15 ppm. Found, %: C 54.59; H 8.39; P 10.51. $C_{26}H_{48}N_4O_6P_2$. Calculated, %: C 54.34; H 8.42; P 10.78.

1,4:3,6-Dianhydro-D-mannitol 2,5-bis(dipiperididophosphorothioate) (XI) and 1,4:3,6-dianhydro-D-mannitol 2-dipiperididophosphorothioate (XII). Diol **I**, 0.73 g, and a solution of 1.11 g of triethylamine in 10 ml of dioxane were added with stirring at 20°C to a solution of 1.69 g of thiophosphoryl chloride in 10 ml of dioxane. The mixture was stirred for 20 h at 20°C and filtered from triethylamine hydrochloride. ^{31}P NMR spectrum of the mixture, δ_P, ppm: 59 (product), 33 (unreacted thiophosphoryl chloride); intensity ratio 2 : 1.

A solution of 1.7 g of piperidine and 2.23 g of triethylamine in 20 ml of dioxane was added over a period of 1 h to the mixture prepared as described above while stirring at 20°C. The mixture was stirred for 20 h at that temperature, filtered from triethylamine hydrochloride, and evaporated under reduced pressure. Products **XI** and **XII** were separated by

column chromatography on aluminum oxide (activity grade II) using solvent system B as eluent.

Compound **XI**. Yield 1.52 g (50%), R_f 0.6 (B), 0.5 (H). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.46–1.56 m [24H, $N(CH_2)_2(CH_2)_3$], 2.94–3.12 m [16H, $N(CH_2)_2(CH_2)_3$, $^3J_{PH}$ = 6.8, $^3J_{PH}$ = 7.5], 3.69 d.d (2H, 1-H$_a$, 6-H$_c$, $^2J_{a,b} = {}^2J_{c,d}$ = 8.5, $^3J_{a,2}$ = 8.5), 4.01 d.d (2H, 1-H$_b$, 6-H$_d$, $^2J_{a,b} = {}^2J_{c,d}$ = 8.5, $^3J_{b,2}$ 6.8), 4.50 d.d (2H, 3-H, 4-H, $^3J_{3,4}$ = 4.5, $^3J_{3,2}$ = 1.5), 4.83–4.99 m (2H, 2-H, 5-H). ^{31}P NMR spectrum (C_6H_6): δ_P 78 ppm. Found, %: C 51.92; H 7.99; P 10.17. $C_{26}H_{48}N_4O_4P_2S_2$. Calculated, %: C 51.47; H 7.97; P 10.21.

Compound **XII**. Yield 0.47 g (25%), R_f 0.9 (B), 0.7 (H). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.43–1.63 m [12H, $N(CH_2)_2(CH_2)_3$], 2.93–3.17 m [8H, $N(CH_2)_2(CH_2)_3$, $^3J_{PH}$ = 6.6, $^3J_{PH}$ = 6.9], 2.61–2.69 br.s (1H, OH, $^3J_{HH}$ = 5.5), 3.61 d.d (1H, 6-H$_c$, $^2J_{d,c}$ = 9.4, $^3J_{5,6}$ = 6.8), 3.74 d.d (1H, 1-H$_a$, $^2J_{a,b}$ = 8.1, $^3J_{b,2}$ = 8.1), 3.95 d.d (1H, 6-H$_d$), 4.06 d.d (1H, 1-H$_b$), 4.23–4.31 m (1H, 5-H), 4.45 d.d (1H, 4-H, $^5J_{4,5}$ = 4.7, $^5J_{3,4}$ = 4.7), 4.52 d.d (1H, 3-H, $^5J_{2,3}$ = 4.9, $^5J_{3,4}$ = 4.7), 4.87–5.07 m (1H, 2-H). ^{31}P NMR spectrum (C_6H_6): δ_P 78 ppm. Found, %: C 51.29; H 7.89; P 8.21. $C_{16}H_{29}N_2O_4PS$. Calculated, %: C 51.05; H 7.76; P 8.23.

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