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Hydrolysis of Bisbicyclophosphite and Related Thionophosphate, Derivatives of Tripentaerythritol. Arbuzov Alkylation of the Bisbicyclophosphite

M. A. Malenkovskaya, O. V. Vyunskovskaya, L. K. Vasyanina, D. A. Predvoditelev, and E. E. Nifant'ev

Moscow State Pedagogical University, Nesvizhskii per. 3, Moscow, 119021 Russia
e-mail: chemdept@mtu-net.ru

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Abstract—The first data on the study of hydrolysis of bisbicyclophosphite and related thionophosphates of tripentaerythritol series in acidic and basic media are presented. Arbuzov alkylation of bisbicyclophosphite with methyl iodide was studied.

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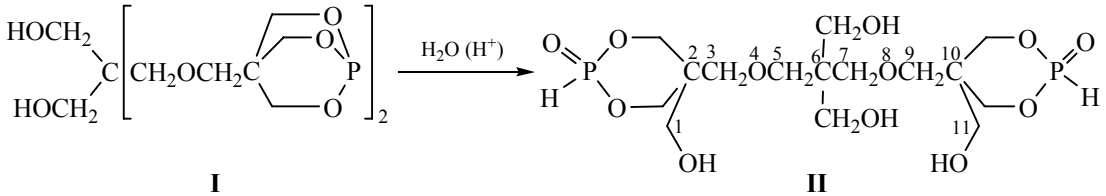
Recently in our laboratory the first representatives of new systems with phosphoric framework systems were obtained based on tripentaerythritol, and a study was initiated of chemical properties of these complex polyol compounds [1]. Extending this research, in the present work we studied the hydrolysis of bisbiphosphorus(III) cyclic tripentaerythritol derivatives as well as the hydrolysis of related bisphoshorus(IV) cyclanes. Another line of this work was to study the Arbuzov alkylation of trivalent phosphobicycle by methyl iodide.

The first part of this work concerning the hydrolysis was the study of the acid hydrolysis of bisbiphosphorus(III) bicycle (**I**).



I **II**

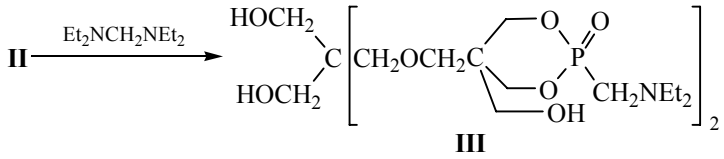
The reaction of bisbicycle **I** with acidified water (pH 5) in dioxane was carried out for 12 h. Note the importance of maintaining a special temperature regime of this process. The reaction should be carried out at gradual raising the temperature from 20°C to 110°C. An attempt of direct hydrolysis at elevated temperature led to a sharp decrease in the yield of the desired product **II**, probably due to the limited solubility of phosphite **I** in conventional organic solvents, including dioxane. Hydrolysis of phosphite **I** led to the opening of two frame structures and to the formation of hydroxy-functionalized bishydrophosphoryl compound **II**. The target product **II** was isolated by precipitation from solution in dioxane into hexane. The yield of the chromatographically pure hydrophosphite **II** was 45%.[1] A low yield of hydrophosphite **II** in this reaction is apparently due to the limited solubility of initial phosphodiol **I** in dioxane.

The ^{31}P NMR spectrum of compound **II** contains a signal at δ_P 3.54 ppm, $^1J_{PH}$ 624.45 Hz. Note that the hydrophosphite derived from dipentaerythritol bisbicyclophosphite **I** was characterized by a signal at δ_P 3.67 ppm and $^1J_{PH}$ 628.84 Hz [2]. The ^{1}H NMR spectrum of compound **II** contains characteristic

[1] Here and hereinafter the individuality of obtained compounds was determined by TLC, MALDI-TOF mass spectrometry, and ^{31}P, ^{1}H and ^{13}C NMR spectroscopy.

signals of all groups of protons. The protons of the hydrophosphoryl function appear as a doublet signal at δ 7.60 ppm, $^{1}J_{PH}$ 626.9 Hz due to spin-spin coupling with the phosphorus nuclei, and signals of the protons of 1,3-dioxane fragments of the molecule are observed as multiplets at δ 3.85 and δ 4.85 ppm for equatorial and axial protons, respectively. In addition, the spectrum contains singlet signals of methylene protons of hydroxymethyl groups at δ 4.15 ppm, and of the molecule frame at δ 4.20 ppm

The hydrophosphite **II** was used for the synthesis on its basis of a new type aminomethylenephosphonate (**III**).



III

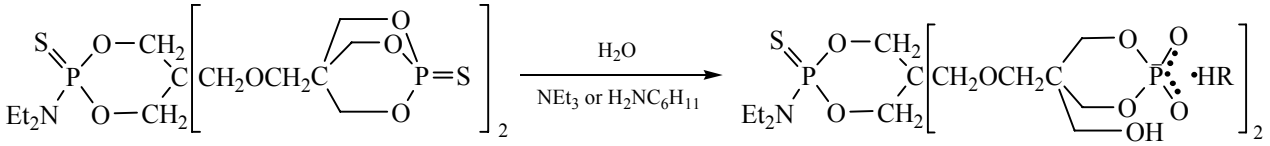
The reaction with tetraethylmethylenediamine was carried out for 6 h at 100°C in dioxane. In the ^{31}P NMR spectrum there is a singlet signal with δ_P 24.00 ppm. In the ^{1}H NMR spectrum of compound **III** the signals of the main structure of the molecule remained and the signals appeared of the protons of *N*-ethyl groups as broad multiplets in the regions of δ 1.01 and 2.49 ppm. In addition, the spectrum contained a typical doublet signal characteristic of the group of atoms PCH_2N with $^{2}J_{PH}$ 11.05 Hz.

The structure of compound **III** was further confirmed by the data of ^{13}C NMR spectroscopy (see Experimental). The assignment of signals was performed using two-dimensional heteronuclear correlation (HETCOR ^{1}H–^{13}C).

Thus, we have synthesized a new tripentaerythritol hydrophosphite **II** which can serve as a convenient starting compound for obtaining different types of organophosphorus compounds using the methods of phosphite chemistry.

The next stage of hydrolysis part of this work was the study of the hydrolysis of a series of tripentaerythritol bisbiphosphobicycles in the presence of organic bases triethylamine and cyclohexylamine. Note that previously we published the data on the study of chemical reactions of bisbiphospho(IV)cyclic tripentaerythritol derivatives involving the unprotected hydroxy groups in their structure [2] . This mode of performance was apparently due to the poor solubility of the above bisbiphosphocyclanes in traditional organic solvents (benzene, dioxane, acetonitrile, etc.), so the reaction should be carried out in pyridine. The choice in this work of the modified phosphorus compounds of the same type but with protected hydroxy groups, readily soluble in acetonitrile, gave an opportunity to expand significantly the chemical experiments in a homogeneous environment.

For such study we selected as a starting compound the bisthionophosphocyclane **IV** containing in its composition, along with the bisphosphobicyclic fragment, the central thionodioxaphosphorinane ring. The hydrolysis of the trichalcogenic product **IV** was carried out in acetonitrile solution in the presence of 20-fold excess of triethylamine (120°C, 10 h) or cyclohexylamine (140°C, 12 h). After the hydrolysis the terminal compounds **V, VI** were obtained in the form of ammonium salts. Their yields reached 65%.



IV **V, VI**

R = $-\overset{+}{N}HEt_3$ (**V**), $-\overset{+}{N}H_2C_6H_{11}$ (**VI**).

In the ^{31}P NMR spectra of salts **V** and **VI**, together with the signals at δ_P 75 ppm related to phosphoamide phosphorus atom, appeared the signals characteristic of dialkylenethionophosphates at δ_P 54 ppm with a ratio of integral intensities 1:2. In the ^{1}H NMR spectra of compounds **V** and **VI** remained the signals of the protons of basic frame of the molecule and appeared the signals characteristic of the protons of ammonium

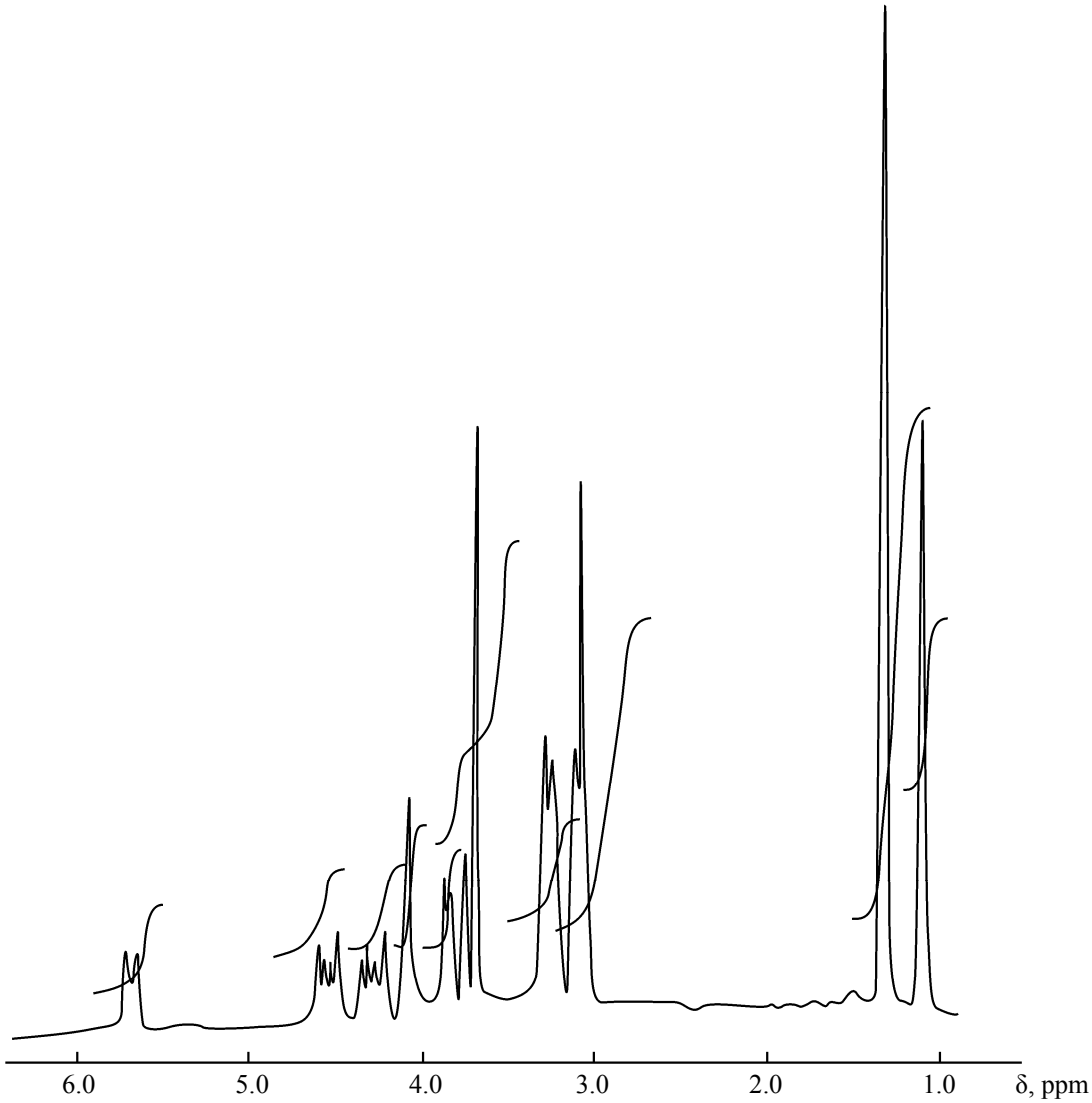
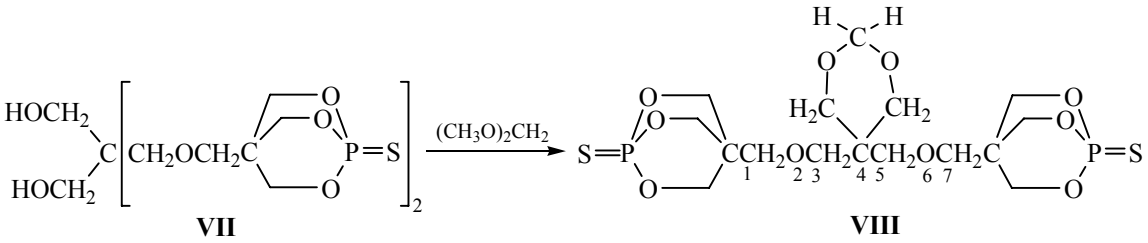


Fig. 1. ^{1}H NMR spectrum of 2',2'-bishydrotriethylammonium-1,7-bis(1',3',2'-dihydroxy-2'-thio-2-oxaphosphonylhydroxymethyl-5')-4-(2-diethylamino-2"-thio-1",3",2"-dioxaphosphonyl)-2,6-dioxaheptane (**V**).

groups. In the case of salt **V** there are an extra triplet (δ 1.37 ppm) and quartet (δ 3.09 ppm) of the methyl and methylene protons of triethylammonium group (Fig. 1), and in the case of salt **VI**, a multiplet signal (δ 1.21–2.05 ppm) of axial and equatorial methylene protons and a multiplet (δ 3.10 ppm) of methine proton in the cyclohexyl fragment of the molecule. The downfield signals at δ 5.71 ppm (**V**) and 5.69 ppm (**VI**) belong to the protons of the hydroxy groups. The chemical shift of methine proton in the cyclohexane fragment of compound **VI** is consistent with the published data [2] for the equatorial position. The ^{13}C NMR spectra also fully confirm the structure of salts **V** and **VI** (see Experimental).

Continuing the studies of hydrolysis in a basic medium of a series of framework bisbicyclothionophosphates soluble in common organic solvents we synthesized a bisbicyclothionophosphate **VIII** containing in its composition 1,3-dioxane ring. For the synthesis of such acetal a reaction of diol **VII** was performed with dimethoxymetane excess in the presence of *p*-toluenesulfonic acid.

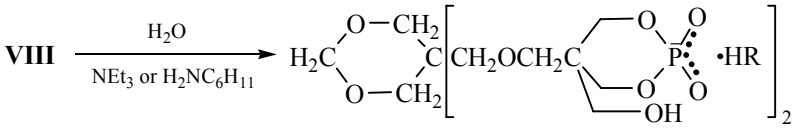
The process was carried out at 100–115°C for 12 h. Yield of the chromatographically pure compound **VIII** was 50%. The target product **VIII** was an oily compound, which crystallized at room temperature within several days. In its ^{31}P NMR spectrum a singlet



VII **VIII**

signal (δ_P 57.2 ppm) remained, as in the case of the parent bisthionophosphate **VII**. In the ^{1}H NMR spectrum of the phosphocyclane **VIII** instead of the signals of protons of the diol system of starting compound **VII** a singlet signal (δ 4.77 ppm) appeared of the methylene protons of acetal groups and multiplets of 1,3-methylene protons of dioxane ring (δ 3.35 and 3.70 ppm). In the spectrum also the signals were observed of other protons in the structure **VIII** (see Experimental). The composition of the phosphoacetal **VIII** was confirmed also by the data of MALDI-TOF mass spectrometry.

The bisphosphocyclic compound **VIII** was hydrolysed in acetonitrile in the presence of nitrogen bases.



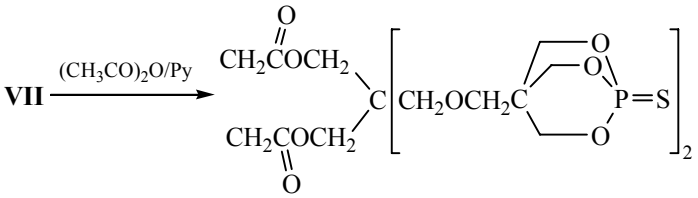
IX, X

$R = -\overset{+}{N}Et_3$ (**IX**), $-\overset{+}{N}H_2C_6H_{11}$ (**X**).

New target compounds **IX** and **X** were isolated as ammonium salts in yields up to 63%. Salts **IX** and **X** are oily substances, stable at storage. In the ^{31}P NMR spectra of salts **IX, X** in the region of δ_P 52–54 ppm singlet signals appeared characteristic of the cyclic dialkylenethionophosphates. In the ^{1}H NMR spectra of compounds **IX, X** except for the signals of the basic structure of the molecules the signals appeared characteristic of protons of ammonium group like in the case of salts **V** and **VI** containing a phosphamide fragment. Note that the methine proton of the cyclohexyl fragment of salt **X** is located in the equatorial position (δ 3.03 ppm), as in salt **VI**. The structure of compounds **IX, X** was further confirmed by ^{13}C NMR spectra, and of salt **IX**, by MALDI-TOF mass spectrometry (see Experimental).

It is important that at the synthesis of salts **V**, **VI**, **IX**, and **X** under the above conditions of the hydrolysis the phosphorinane and dioxane rings remained intact.

We also studied the hydrolysis of bisbiphospho(IV) bicycles **XI** containing in their composition an acyclic ester fragment. For the synthesis of such substances we studied acylation of diol **VIII** with acetic anhydride.



XI

The acetylation of bisbicyclothionophosphate **VII** was carried out at room temperature for 50 h. The yield of the desired product **XI** isolated by column chromatography was 65%.

The ^{31}P NMR spectrum of compound **XI** contains a singlet signal (δ_P 57.53 ppm) in the same area as the signal of the parent bisbicycle **VII**. In the ^{1}H NMR spectrum instead of the signal of protons of hydroxy

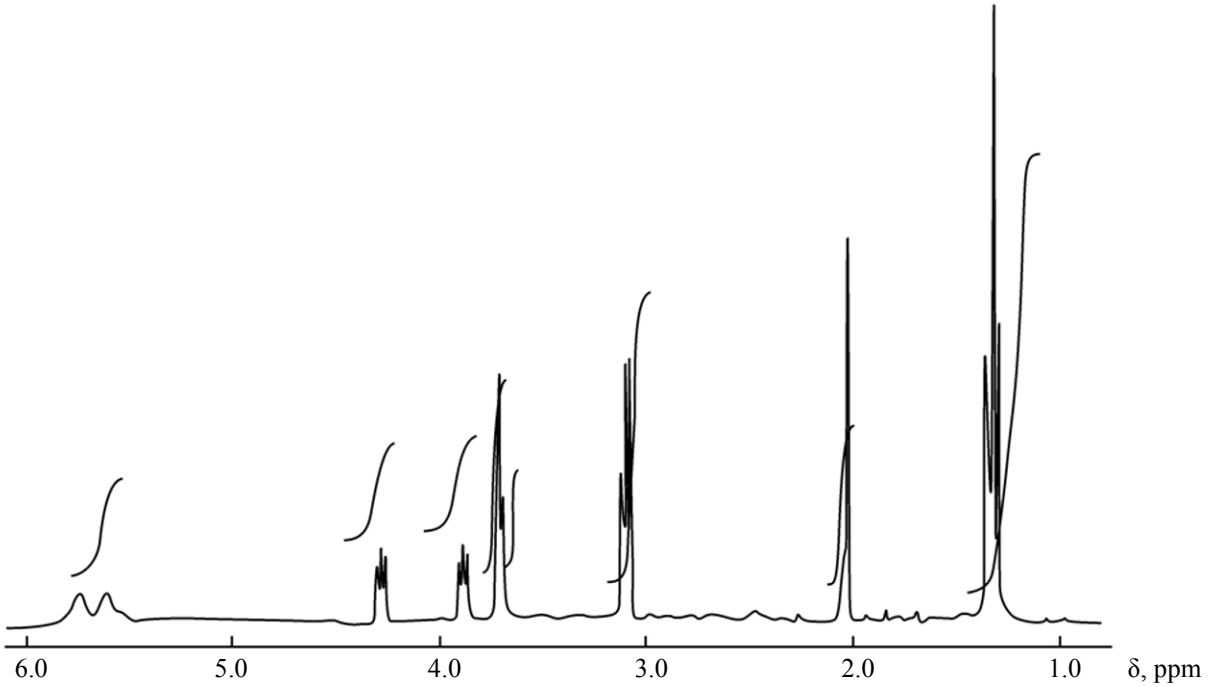
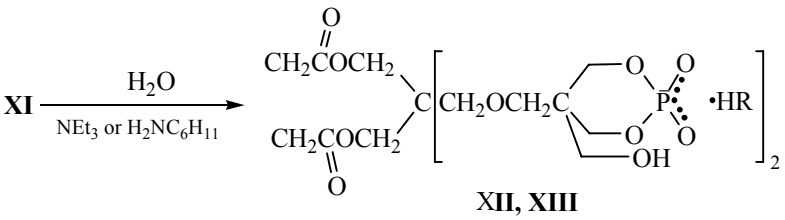


Fig. 2. ^{1}H NMR spectrum of 2',2'-bishydrotriethylammonium-1,7-bis(1',2',3'-dihydroxy-2'-thio-2'- oxaphosphonylhydroxymethyl-5')-4,4-bisacetomethyl-2,6-dioxaheptane (**XII**).

groups a singlet signal was observed corresponding to the methyl protons of acyl group (δ 2.06 ppm). In addition, the signal of methylene protons in $CH_3C(O)\cdot OCH_2$ fragment was shifted downfield compared with the related signal of the initial compound **VII**. Other signals in the spectra correspond approximately to the parent bicycle **VII**.

The correlation of signals of carbon atoms of ester **XI** in ^{13}C NMR spectrum with the signals of protons in the ^{1}H NMR spectrum was revealed using the two-dimensional heteronuclear spectroscopy (HETCOR ^{1}H–^{13}C). In the ^{13}C NMR spectrum singlet signals of methyl (δ_C 20.88 ppm) and methylene (δ_C to 61.15 ppm) groups, and carbonyl carbons (δ_C 170.36 ppm) in the $CH_3C(O)OCH_2$ fragment of the molecule **XI** were detected. Other signals in the spectrum confirm completely the structure of compound **XI** (see Experimental).

The resulting diacyl derivative **XI** was also subjected to hydrolysis in the presence of nitrogen bases (120–140°C, 48–56 h).



XII, XIII

R = $-\overset{+}{N}Et_3$ (**XII**), $-\overset{+}{N}H_2C_6H_{11}$ (**XIII**).

The obtained ammonium salts **XII** and **XIII** were isolated in 65% yield. Salt **XII** is an oily compound, salt **XIII** is a crystalline compound. The individuality and the structure of salts **XII**, **XIII** obtained for the first time were proved by the above-mentioned traditional physicochemical methods (see Experimental). The chemical shift δ 2.87 ppm in the ^{1}H NMR spectrum of compound **XIII** indicates the axial position of the methine proton in the cyclohexyl fragment of the molecule [2]. Figure 2 shows the ^{1}H NMR spectrum of compound **XII**, which fully confirms the structure of the diacyl salt.

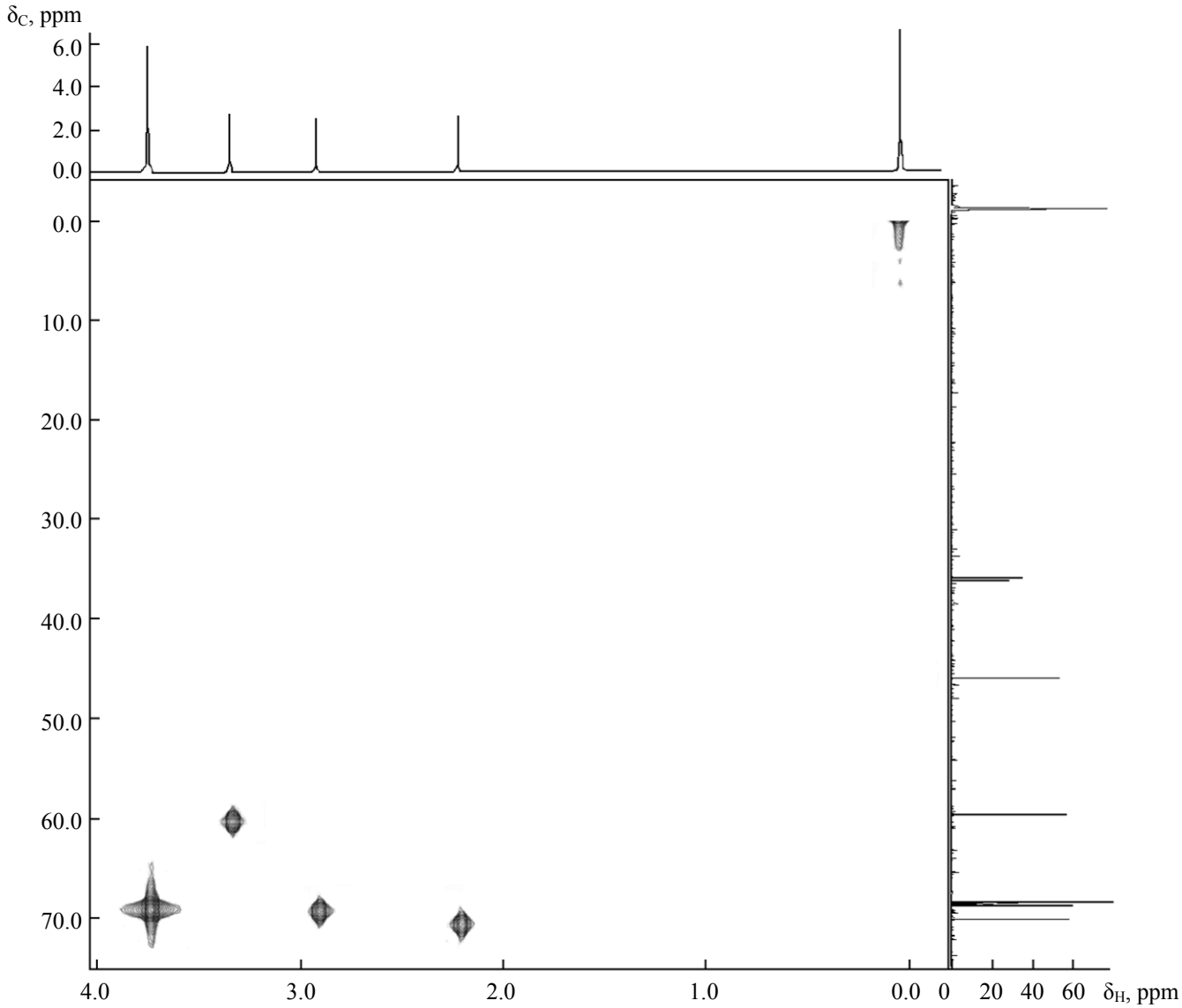
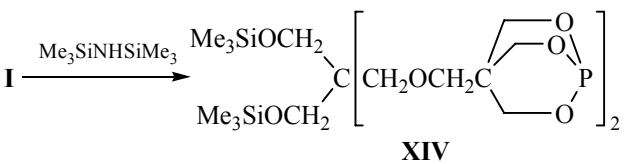


Fig. 3. Two-dimensional spectrum of 1,7-bis(2',6',7'-trioxa-1'-thio-1-phosphabicyclo[2.2.2.]-octyl-4')-4,4-trimethylsiloxymethyl-2,6 -dioxaheptane (**XIV**).

Study of the hydrolysis of the tripentaerythritol bisbiphospho(IV)cycles in the presence of nitrogen bases made it possible to develop an effective method of synthesis of new salts of six-membered heterophosphocyclanes. Thus, the mentioned hydrolytic syntheses form the basis for obtaining new products **V**, **VI**, **IX**, **X**, **XII**, and **XIII** with acyclic fragments fixed at the central carbon atom C^4.

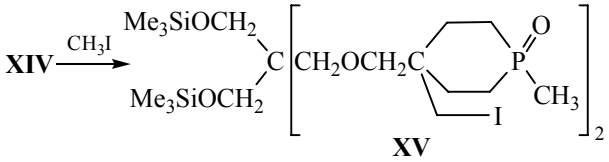
Besides the studies of hydrolysis of the tricoordinated bisbiphosphocyclane **I**. we studied Arbuzov alkylation of such systems. Unfortunately, we were unable to use directly the bisbiphospho(III) cyclane **I** as a substrate in this process due to the limited solubility of this substance in many organic solvents (benzene, dioxane, acetonitrile, etc.). Therefore, for preparative convenience, in the alkylation was used the bistrimethylsilyl ester **XIV** prepared from the phosphodiol **I**. Synthesis of silyl derivative was carried out by a reaction of the phosphodiol **I** with hexamethyldisilazane at 160°C for 1 h.



XIV

The yield of disilyl derivative **XIV** after separation on a silica gel column was 32%. In the ^{31}P NMR spectrum, as in the case of the parent compound **I**, there is a singlet signal (δ_P 94.39 ppm) characteristic of the bisbicyclophosphites of phosphorinane–phosphorinane structure [1]. The ^1H NMR spectrum of phosphocyclane **XIV** differs from the spectrum of the starting compound **I** by the presence of singlet signals of methyl (δ 0.02 ppm) and methylene (δ 3.32 ppm) protons of the protecting $CH_2OSi(CH_3)_3$ groups. The structure of compound **XIV** was further confirmed by ^{13}C NMR spectrum. The assignment of signals in the spectrum was performed using two-dimensional hetero-nuclear correlation spectroscopy HETCOR ^1H–^{13}C (Fig. 3).

The resulting disilyl derivative **XIV** was alkylated with iodmethane by Arbuzov reaction with the destruction of the bicyclic system and the formation of the methylphosphonate **XV**.



XV

The reaction of the phosphocycle **XIV** with methyl iodide was carried out in benzene solution in a sealed ampoule at 90°C for 12 h. We note the importance of thorough drying of benzene for this reaction, as well as maintaining the indicated temperature of the process. The yield of methylphosphonate **XV** was 27%. The ^{31}P NMR spectrum of compound **XV** includes a singlet signal in the phosphonate region (δ_P 27.9 ppm), which allows an effective identification of the phosphonate **XV**. In the ^1H NMR spectrum of compound **XV** there is a clearly visible doublet of protons of methyl groups associated with phosphorus at δ 1.1 ppm, with the geminal spin–spin coupling constnt $^2J_{PH}$ 17.44 Hz. The spectrum also contains a singlet of methylene protons of CH_2I groups at δ 3.14 ppm. Other signals completely confirm the structure (see Experimental).

The result of this work is a convincing demonstration of broad synthetic performance of the bisbiphosphobicyclic tripentaerythritol structures in obtaining by the hydrolysis and alkylation reactions of new phosphorus compounds, whose synthesis by other synthetic methods is difficult or impossible.

EXPERIMENTAL

^1H, ^{13}C, and ^{31}P NMR spectra were obtained on a JEOL ECX-400 instrument (400 MHz), chemical shifts for ^1H and ^{13}C were related to TMS, for ^{31}P related to 85% phosphoric acid; assignment of proton signals was carried with the use of double magnetic resonance and heteronuclear correlation spectroscopy (HETCOR ^1H–^{13}C).

The mass-spectral studies were performed on a Bruker Ultra Flex instrument with TOF detector by the method of matrix-assisted laser desorption and ionization (MALDI) (λ 337 nm) using trihydroxyanthracene as a matrix.

Elemental analyses were performed on a Perkin-Elmer 2400 analyzer.

All syntheses involving compounds of trivalent phosphorus were carried out in an atmosphere of dry argon. The adsorption chromatography was performed on a column of 10 mm diameter with silica gel L 100-250 mm. The R_f values were identified by TLC on Silufol UV-254 plates. The eluents used are as follows: methanol-water, 3:1 (A), chloroform-methanol, 3:1 (B), benzene-ethyl acetate, 3:1 (C), benzene-dioxane, 3:1 (D), benzene-dioxane, 1:1 (E), hexane-dioxane, 3:1 (F), and benzene-ethanol, 3:1 (G).

The melting points were determined in sealed capillary tubes, heating rate 1 K min^{-1}.

1,7-Bis(2',6',7'-trioxa-1'-phosphabicyclo[2.2.2]-octyl-4')-4,4-bishydroxy-methyl-2,6-dioxaheptane (I), 1,7-bis(2',6',7'-trioxa-1'-thio-1'-phosphabicyclo [2.2.2]octyl-4')-4-(2-diethylamino-2"-thio-1",3",2"-dioxaphosphonyl)-2,6-dihydroxyheptane (IV) and 1,7-bis(2',6',7'-trioxa-1'-thio-1'-phosphabicyclo [2.2.2]octyl-4')-4,4-bishydroxymethyl-2,6-dioxaheptane (VII) were synthesized by the described method [1]. The compounds obtained had the constants consistent with published data.

1,7-Bis(2'-hydro-2'-oxo-5'-hydroxymethyl-1',3',2'-dioxaphosphorinyl)-4,4-di(hydroxymethyl)-2,6-oxaheptane (II). A suspension of 0.2 g of bisbicyclophosphite **I** (δ_P 94.25 ppm) and 0.03 g of water (pH 5) (molar ratio 1:3) in 3 ml of anhydrous dioxane was heated in a sealed ampule for 12 h at 100–110°C. The solution was decanted, and hydrophosphite **II** was precipitated by hexane and washed with the same solvent (2×2 ml). The target product was kept for 3 h at 50°C (1 mm Hg). Yield of compound **II** 0.1 g (45%), mp 152–155°C, R_f 0.55 (A). ^1H NMR spectrum (C_5D_5N), δ, ppm: 3.85 m ($4H_e$) and 4.85 m ($4H_a$) (CH_2OP), 4.15 s (8H, CH_2OH), 4.20 s (8H, CH_2OCH_2), 7.60 s [2H, P(O)H, $^1J_{PH}$ 626.9 Hz]. ^{31}P

NMR spectrum (dioxane), δ_P, ppm: 3.5 s, $^1J_{PH}$ 624.45 Hz. Found, %: C 38.98, H 6.73, P 13.54. $C_{15}N_{30}O_{12}P_2$. Calculated, %: C 38.80, H 6.51, P 13.34. *M* 464.

1,7-Bis(2'-diethylaminomethyl-2'-oxo-5'-hydroxymethyl-1',3',2'-dioxaphosphornyl)-4,4-di(hydroxymethyl)-2,6-oxaheptane (III). 0.1 g of hydrophosphite **II** and equimolar amount (0.07 g) of tetraethylmethylenediamine in 20 ml of dioxane was heated in a flask with a reflux condenser for 6 h at 110°C. The solvent and volatile reaction products were removed in a vacuum, and the remaining oil was washed with hexane (2×2 ml). Target phosphonate **III** was kept for 3 h at 40°C (1 mm Hg). Yield of compounds **III** 0.08 g (55%), n_D^{20} 1.4425, R_f 0.85 (B). ^{1}H NMR spectrum (C_5D_5N), δ, ppm: 1.01 br.m (12H, $NCH_2C\underline{H}_3$), 2.49 br.m (8H, $NC\underline{H}_2CH_3$, $^3J_{HP}$ 4.5 Hz), 2.92 br.q (4H, PCH_2N, $^2J_{HP}$ 11.05 Hz), 3.62 br.s (4H, $C^{3,9}H_2$), 3.74 br.m (4H$_e$) and 4.75 br.m (4H$_a$) ($OCH_2C^{2,10}CH_2O$), 4.01 br.s (4H, $C^{5,7}H_2$), 4.24 br.s (8H, CH_2OH). The ^{13}C NMR spectrum (C_5D_5N), δ_C, ppm: 13.37 s (4C, $NCH_2\underline{C}H_3$), 29.86 s (2C, $C^{2,10}$), 39.38 s (1C, C^6), 44.77 d (4C, $N\underline{C}H_2CH_3$, $^3J_{CP}$ 15.4 Hz), 63.36 d (2C, $P\underline{C}NCH_2CH_3$, $^1J_{CP}$ 11.4 Hz), 67.50 s (4C, CH_2OH), and 75.51 s 82.25 s (4C, $C^{3,5,7,9}$), 85.39 d (4C, $OCH_2C^{2,10}\underline{C}H_2O$, $^2J_{CP}$ 11.5 Hz). ^{31}P NMR spectrum (dioxane), δ_P, ppm: 24.00 s. Found, %: C 47.52, H 8.51, P 9.93. $C_{25}H_{52}N_2O_{12}P_2$. Calculated, %: C 47.31, H 8.26, P 9.76. *M* 635.

2',2'-Bishydrotriethylammonium-1,7-bis(1',3',2'-dihydroxy-2'-thio-2'-oxaphosphonylhydroxymethyl-5')-4-(2-diethylamino-2"-thio-1",3",2"-dioxaphosphonyl)-2,6-dioxaheptane (V). A solution of 0.1 g of amidocyclothionophosphate **IV** (δ_P 59.5 and 75.5 ppm with the ratio of integral intensities 2:1), 0.06 g of water, and 0.32 g of triethylamine (molar ratio 1:20:20) in 5 ml of acetonitrile (pH > 10) was heated in a sealed ampule at 120°C for 10 h. Acetonitrile, triethylamine, and water were removed in a vacuum, and the remaining oily substance was dissolved in 3 ml of dioxane and reprecipitated with hexane (2×3 ml). The salt **V** was kept for 4 h at 80°C (1 mm Hg). Yield of compound **V** 0.08 g (60.5%), n_D^{20} 1.5098, R_f 0.45 (B). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.23 t (6H, $NCH_2C\underline{H}_3$, $^3J_{HH}$ 7.1 Hz), 1.37 t {18H, $[HN(CH_2C\underline{H}_3)_3]^+$, $^3J_{HH}$ 7.3 Hz}, 3.09 q {12H, $[HN(C\underline{H}_2CH_3)_3]^+$, $^3J_{HP}$ 12.2 Hz}, 3.25 q (4H, $NC\underline{H}_2CH_3$, $^3J_{HP}$ 11.0 Hz), 3.71 s (8H, $C^{3,9}H_2OC^{5,7}H_2$), 3.74 m (4H$_e$) and 4.29 m (4H$_a$) [$OCH_2C^{2,10}CH_2O$, $^2J(H_aH_e)$ 11.0 Hz], 4.09 m (4H$_e$) and 4.33 m (4H$_a$) [$OCH_2C^6CH_2O$, $^2J(H_aH_e)$ 11.33 Hz, $^3J_{HP}$ 6.01 Hz], 4.28 s (4H, CH_2OH), 5.68 br.s (4H, NH, OH). ^{31}P NMR spectrum (chloroform), δ_P, ppm: 53.9 s and 75.5 s at the ratio of integral intensities 2:1. Found, %: C 43.35, H 8.04, P 10.93. $C_{31}H_{68}N_3O_{12}P_3S_3$. Calculated, %: C 43.09, H 7.93, P 10.76. *M* 864.

2',2'-Bishydrocyclohexylammonium-1,7-bis(1',3',2'-dihydroxy-2'-thio-2'-oxaphosphonylhydroxymethyl-5')-4-(2-diethylamino-2"-thio-1",3",2"-dioxaphosphonyl)-2,6-dioxaheptane (VI) was prepared by analogy with salt **V** from 0.05 g of the bisbicycle **IV** (δ_P 59.7 and 75.5 ppm with a ratio of integral intensities 2:1), 0.03 g of water, and 0.16 g of cyclohexylamine (molar ratio 1:20:20) in 5 ml of acetonitrile (pH > 10) at 140°C for 12 h. Then acetonitrile, cyclohexylamine, and water were removed in a vacuum and the residue was washed with hexane (2×2 ml). Salt **VI** was kept for 4 h at 80°C (1 mm Hg). Yield 0.05 g (65%), 1.5890, R_f 0.35 (B). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.12 t (6H, $NCH_2C\underline{H}_3$, $^3J_{HH}$ 7.12 Hz), 1.21 m [2H, s, $NCH(CH_2CH_2)_2C\underline{H}_2$], 1.24 m [4H$_e$, $NCH(CH_2C\underline{H}_2)_2CH_2$], 1.38 m [4H$_e$, $NCH(C\underline{H}_2CH_2)_2CH_2$], 1.60 m [2H$_a$, $NCH(CH_2CH_2)_2C\underline{H}_2$, $^2J(H_aH_e)$ 10.8 Hz], 1.76 m [4H well, $NCH(CH_2\ CH_2)_2\ CH_2$, $^2J(H_aH_e)$ 11.0 Hz], 2.05 m [4H well, $NCH(CH_2\cdot CH_2)_2\ CH_2$, $^2J(H_aH_e)$ 11.8 Hz], 3.1 m (2H, H_3N + CH), 3.29 q (4H, NCH_2CH_3, $^3J_{HP}$ 11.64 Hz), 3.32 s and 3.62 s (4H, $C^{3,9}H_2$), 3.49 s and 3.52 s (4H, $C^{5,7}$, H_2), 3.74 s (4H, CH_2 OH), 3.88 m (2H, s) and 4.35 m (2H, a) [$ROCH_2C^2$, $^2J(H_aH_e)$ 5.5 Hz, $^3J_{HP}$ 5.5 Hz], 4.10 m (2H, s) and 4.52 m (2H$_a$) [C^6H_2OR, $^2J(H_a\ H_e)$ 11.5 Hz, $^3J_{HP}$ 4.2 Hz], 5.69–6.31 br.s (8H, OH, H_3N^+). The ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.48 s (2C, NCH_2CH_3), 24.95 s [2C, $NCH(CH_2\underline{C}H_2)_2CH_2$], 25.61 s [2C, $NCH\cdot(\underline{C}H_2CH_2)_2CH_2$], 29.78 s (2C, $C^{2,10}$), 31.53 s [2C, $NCH\cdot(CH_2CH_2)_2\underline{C}H_2$], 34.02 d (2C, $N\underline{C}H_2CH_3$, $^3J_{PC}$ 5.73 Hz), 40.46 s (1C, C^6), 50.74 s [2C, $N\underline{C}H(CH_2CH_2)_2CH_2$], 60.35 s (2C, $C^{1,11}$), 68.72 br.s (2C, $C^{3,5}$), 70.11 br.s (2C, $C^{7,9}$), 70.75 d (4C, $C^6\underline{C}H_2$, $^2J_{CP}$ 10.85 Hz). ^{31}P NMR spectrum (chloroform), δ_P, ppm: 53.04 s and 74.9 s at the ratio of integral intensities 2:1. Found, %: C 43.51, H 7.79, P 11.01. $C_{31}H_{64}N_3O_{12}P_3S_3$. Calculated, %: C 43.29, H 7.50, P 10.80. *M* 860.

1,7-Bis(2',6',7'-trioxa-1'-thio-1-phosphabicyclo-[2.2.2.]-octyl-4')-4-(4,4-*O*-methylene-4,4-dihydroxymethylene)-2,6-dioxaheptane (VIII). To a solution of 0.3 g of bicyclothionophosphate **VII** (δ_P 57.2 ppm) in 3 ml of pyridine was added 3 ml of methylal and 0.01 g of *p*-toluenesulfonic acid, and the mixture was heated in a sealed ampule at 110–115°C for 12 h. The excess pyridine and methylal was removed in a vacuum and the residue was dissolved in 1 ml of a

mixture of benzene–acetonitrile, 10:1, and the solution was applied to a column with silica gel (10 g) filled with benzene. Compound **VIII** was eluted with benzene–acetonitrile, 5:1. Solvents were removed in a vacuum and the residue was kept for 2 h at 80°C (1 mm Hg). Yield of compound **VIII** 0.14 g (46.7%), mp 234–235°C, R_f 0.6 (C). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.23 s (4H, C^1H_2), 3.65 s (4H, $C^{3,5}H_2$), 3.35 m (2H$_e$) and 3.70 m (2H$_a$) [CH_2OC^4, $^2J(H_aH_e)$ 8.98 Hz], 4.52 d (12H, CH_2OR, $^3J_{HP}$ 6.71 Hz), 4.77 s (2H, OCH_2O, $^2J_{HH}$ 6.9 Hz). The ^{13}C NMR spectrum (C_5D_5N), δ_C, ppm: 38.21 d (2C, $CH_2O\underline{C}$, $^3J_{CP}$ 3.81 Hz), 39.71 s (1C, C^4), 68.26 s (2C, $O\underline{C}H_2C^4$), 68.99 s (2C, $C^{1,7}$), 70.64 s (2C, $C^{3,5}$), 76.20 d (6C, CH_2OP, $^2J_{CP}$ 7.69 Hz), 94.25 s (1C, OCH_2O). ^{31}P NMR spectrum (chloroform), δ_P, ppm: 57.2 s. Found, %: C 38.33, H 5.29, P 12.41. $C_{16}H_{26}O_{10}P_2S_2$. Calculated, %: C 38.13, H 5.20, P 12.29. *M* 504. Mass spectrum, *m/e* (%). Found, *M* (^{12}C): 527.175 (100) $[M + Na]^+$. Calculated, *M* (^{12}C): 527.29 $[M + Na]^+$.

2',2'-Bishydrotriethylammonium-1,7-bis(1',3',2'-dihydroxy-2'-thio-2'-oxaphosphonylhydroxymethyl-5')-4-(4,4-*O*-methylene-4,4-dihydroxymethyl)-2,6-dioxaheptane (IX) was prepared similarly to salt **V** from 0.04 g of compound **VIII**, 0.03 g of water, and 0.16 g of triethylamine (molar ratio 1:20:20) in 2 ml of acetonitrile (pH > 10) at 120–125°C for 52 h. Acetonitrile, triethylamine, and water were removed in a vacuum and the residue was washed successively with hexane and benzene (2×2 ml). Salt **IX** was dissolved in 2 ml of chloroform and heated with activated charcoal for 15 min. The solution was filtered off, chloroform was removed in a vacuum and the residue was kept for 2 h at 80°C in a vacuum (1 mm Hg). Yield 0.03 g (57%), 1.4498, R_f 0.55 (C). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.28 m (18H, $NCH_2C\underline{H}_3$, $^3J_{HH}$ 6.94 Hz), 2.86 q and 3.22 q (12 H, $NC\underline{H}_2CH_3$, $^3J_{HP}$ 12.81 Hz), 3.44 m (12H, $C^{1,7}H_2OC^{3,5}H$, $2OCH_2C^4\cdot CH_2O$), 3.68 s (4H, CH_2OH), 3.95 m (4H$_e$) and 4.33 m (4H$_a$) [$ROCH_2$, $^2J(H_aH_e)$ 5.1 Hz, $^3J_{HP}$ 11.00 Hz], 4.52 s (2H, OCH_2O), 8.5 br.s (2H, OH), 9.04 br.s (2H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 11.42 s (2C, $NCH_2\underline{C}H_3$), 29.78 s (2C, $\underline{C}CH_2O$), 41.45 s (1C, C^4), 44.88 d (2C, $N\underline{C}H_2CH_3$, $^2J_{CP}$ 5.55 Hz), 58.03 s (2C, CH_2OH), 67.30 s (2C, $C^{1,7}$), 71.14 s (2C, $C^{3,5}$), 96.89 s (1C, OCH_2O). ^{31}P NMR spectrum (chloroform), δ_P, ppm: 54.5 s. Found, %: C 45.43, H 8.03, P 8.49. $C_{28}H_{60}N_2O_{12}P_2S_2$. Calculated, %: C 45.26, H 8.20, P 8.34. *M* 743. Mass spectrum, *m/e* (%): Found, *M*(^{12}C): 743.956 (100) $[M + H]^+$. Calculated, *M*(^{12}C): 743.588 $[M + H]^+$.

2',2'-Bishydrocyclohexylammonium-1,7-bis(1',3',2'-dihydroxy-2'-thio-2'-oxaphosphonylhydroxymethyl-5')-4-(4,4-*O*-methylene-4,4-dihydroxymethyl)-2,6-dioxaheptane (X) was prepared similarly to the salt **V** from 0.02 g of compound **VIII**, 0.01 g of water and 0.08 g of cyclohexylamine (molar ratio 1:20:20) in 2 ml of acetonitrile (pH > 10) at 115–125°C for 56 h. Acetonitrile, cyclohexylamine, and water were removed in a vacuum, and the remaining oil was washed successively with hexane and benzene (2×2 ml). Target product **X** was kept for 2 h at 80°C in a vacuum (1 mm Hg). Yield 0.02 g (63%), 1.4573, R_f 0.42 (B). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.15 t [2H$_e$, NCH $(CH_2CH_2)_2C\underline{H}_2$], 1.26 m [4H$_e$, $NCH(CH_2C\underline{H}_2)_2CH_2$] 1.43 m [4H$_e$, $NCH(C\underline{H}_2CH_2)_2H_2$], 1.59 m [2H$_a$, $NCH\cdot(CH_2CH_2)_2C\underline{H}_2$, $^2J(H_aH_e)$ 11.9 Hz], 1.77 m [4H$_a$, $NCH\cdot(CH_2C\underline{H}_2)_2CH_2$, $^2J(H_aH_e)$ 12.4 Hz], 2.07 m [4H$_a$, $NCH\cdot(C\underline{H}_2CH_2)_2CH_2$, $^2J(H_aH_e)$ 10.5 Hz], 3.03 m (2H, H_3N^+CH), 3.29 s (4H, $C^{1,7}H_2$), 3.45 s (4H, $OCH_2\cdot C^4CH_2O$), 3.47 s (4H, CH_2OH), 3.61 s (4H, $C^{3,5}H_2$), 3.97 m (4H$_e$) and 4.31 m (4H$_a$) [$POCH_2$, $^2J(H_aH_e)$ 6.5 Hz, $^3J_{HP}$ 7.1 Hz], 4.54 s (2H, OCH_2O), 7.25 br.s (8H, OH, H_3N^+). The ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 23.5 s [2C, $NCH(CH_2\underline{C}H_2)_2CH_2$], 24.86 s [2C, $NCH\cdot(\underline{C}H_2CH_2)_2CH_2$], 31.06 s (2C, $\underline{C}C^{1,7}$), 33.17 s [2C, $NCH(CH_2CH_2)_2\underline{C}H_2$], 41.58 s (1C, C^4), 50.61 s [2C, $N\underline{C}H(CH_2CH_2)_2CH_2$], 62.61 s (2C, CH_2OH), 67.11 s (2C, $C^{1,7}$), 70.46 s (2C, $C^{3,5}$), 96.81 s (1C, OCH_2O). ^{31}P NMR spectrum (chloroform), δ_P, ppm: 52.5 s. Found, %: C 45.39, H 7.47, P 8.21. $C_{28}H_{56}N_2O_{12}P_2S_2$. Calculated, %: C 45.50, H 7.64, P 8.38. *M* 739.

1,7-Bis(2',6',7'-trioxa-1'-thio-1-phosphabicyclo-[2.2.2]-octyl-4')-4,4-bisacetoxymethyl-2,6-dioxaheptane (XI). To a solution of 0.15 g of bisthionophosphate (**VII**) (δ_P 57.2 ppm) in 5 ml of pyridine at 5°C was added 0.062 g of freshly distilled acetic anhydride. The temperature was raised to room temperature and the reaction mixture was stirred at this temperature for 50 h. The pyridine solution was poured into ice water (0–1°C), the precipitated oily substance was decanted and washed with cold water (2×10 ml). The oily substance was dissolved in chloroform, filtered from insoluble impurities, and the solution was dried over anhydrous K_2CO_3 for 2 h. The solvent was removed in a vacuum, compound **XI** was purified by chromatography on a column with silica gel (10 g) filled with benzene. Compound **XI** was eluted with 25 ml of benzene–dioxane mixture, 1:1. The solvents were removed in a vacuum, the residue was kept for 2 h at 40°C (1 mm Hg). Yield of compound **XI** 0.11 g (65%), n_D^{20} 1.5564, R_f 0.00 (D), 0.45 (E). ^{1}H NMR spectrum

($CDCl_3$), δ, ppm: 2.06 s [6H, $CH_3(O)$], 3.21 s (4H, $C^{3,5}H_2$), 3.29 s (4H, $C^{1,7}H_2$), 4.04 s [4H, $CCH_2OC(O)$], 4.51 d (12H, CH_2OR, $^3J_{HP}$ 6.4 Hz). The ^{13}C NMR spectrum($CDCl_3$), δ_C, ppm: 20.88 s [2C, $CH_3(O)$], 37.79 d (2C, $\underline{C}C^{1,7}$, $^3J_{CP}$ 3.6 Hz), 43.95 s (1C, C^4), 61.15 s [2C, $\underline{C}H_2C(O)$], s 68.80 (2C, $C^{1,7}$), 70.24 s (2C, $C^{3,5}$), 75.64 d (6C, $POCH_2$, $^2J_{CP}$ 7.43 Hz), 170.36 s (2C, C=O). ^{31}P NMR spectrum (chloroform), δ_P, ppm: 57.53. Found, %: C 39.68, H 5.39, P 10.91. $C_{19}H_{30}O_{12}P_2S_2$. Calculated, %: C 39.55, H 5.24, P 10.74. *M* 577.

2',2'-Bishydrotriethylammonium-1,7-bis(1',3',2'-dihydroxy-2'-thio-2'-oxaphosphonylhydroxymethyl-5')-4,4-bisacetomethyl-2,6-dioxaheptane (XII) was prepared like salt **V** from 0.1 g of compound **XI**, 0.06 g of water, and 0.35 g of triethylamine (molar ratio 1:20:20) in 5 ml of acetonitrile (pH > 10) at 100–110°C for 30 h. Acetonitrile, triethylamine, and water were removed in a vacuum, and the residue was washed successively with hexane and benzene (2×2 ml). Salt **XII** was dissolved in 5 ml of chloroform and heated with charcoal for 10 min. The solution was filtered off, chloroform was removed in a vacuum, and the residue was kept for 2 h at 80°C (1 mm Hg). Yield of **XII** 0.07 g (52%), 1.4564, R_f 0.65 (B). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.34 t (18H, $NCH_2C\underline{H}_3$, $^3J_{HH}$ 7.30 Hz), 2.04 s [6H, $CH_3(O)$], 3.09 q (12H, $NC\underline{H}_2CH_3$, $^3J_{HP}$ 11.33 Hz), 3.69 s (4H, $C\underline{H}_2OH$), 3.71 s (8H, $C^{1,3,5,7}H_2$), 3.79 s [4H, $CH_2OC(O)$], 3.85 m (4H_e) and 4.29 m (4H_a) [$POCH_2$, $^2J(H_aH_e)$ 6.51 Hz, $^3J_{HP}$ 11.15 Hz], 5.63 br.s (2H, OH), 5.77 br.s (2H, HN^+). ^{31}P NMR spectrum (chloroform), δ_P, ppm: 53.9. Found, %: C 45.53, H 8.12, P 7.85. $C_{31}H_{64}N_2O_{14}P_2S_2$. Calculated, %: C 45.68, H 7.92, P 7.60. *M* 815.

2',2'-Bishydrocyclohexylammonium-1,7-bis(1',3',2'-dihydroxy-2'-thio-2'-oxaphosphonylhydroxymethyl-5')-4,4-bisacetomethyl-2,6-dioxaheptane (XIII) was prepared like salt **V** from 0.1 g of compound **XI**, 0.06 g of water, and 0.34 g of cyclohexylamine (molar ratio 1:20:20) in 5 ml of acetonitrile (pH > 10) at 140°C for 48 h. Acetonitrile, cyclohexylamine, and water were removed in a vacuum, and the remaining oily substance was washed successively with hexane and benzene (2×2 ml). Salt **XIII** was kept for 3 h at 80°C (1 mm Hg). Yield 0.09 g (65%), mp 104–105°C, R_f 0.5 (B). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.07 m [2H_e, $NCH(CH_2CH_2)_2C\underline{H}_2$], 1.24 m [4$H_e$, $NCH(CH_2C\underline{H}_2)_2CH_2$], 1.31 m [4$H_e$, $NCH(C\underline{H}_2CH_2)_2CH_2$], 1.63 m [2$H_a$, $NCH\cdot(CH_2CH_2)_2C\underline{H}_2$, $^2J(H_aH_e)$ 9.85 Hz], 1.67 m [4H_a, $NCH\cdot(CH_2C\underline{H}_2)_2CH_2$, $^2J(H_aH_e)$ 10.25 Hz], 1.90 m [4H_a, $NCH(C\underline{H}_2CH_2)_2CH_2$, $^2J(H_aH_e)$ 9.95 Hz], 1.93 s [6H, CH_3(O)], 2.87 br.s (2H, $H_3N^+C\underline{H}$), 3.37 br.s (4H, $C^{1,7}H_2$), 3.51 br.s (4H, $C\underline{H}_2OH$), 3.61 s (4H, $C^{3,5}H_2$), 3.67 s [4H, $CH_2OC(O)$], 3.95 m, 4.21 m (4H_e) and 4.46 m, 4.71 m (4H_a) [$POCH_2$, $^2J(H_aH_e)$ 6.75 Hz, $^3J_{HP}$ 7.05 Hz], 5.89 br.s (6H, H_3N^+), 6.25 br.s (2H, OH). ^{31}P NMR spectrum (chloroform), δ_P, ppm: 52.6. Found, %: C 45.79, H 7.39, P 7.53. $C_{31}H_{60}N_2O_{14}P_2S_2$. Calculated, %: C 45.91, H 7.46, P 7.64. *M* 811.

1,7-Bis(2',6',7'-trioxa-1'-thio-1-phosphabicyclo-[2.2.2.]-octyl-4')-4,4-trimethylsiloxymethyl-2,6-dioxaheptane (XIV). 0.4 g of bisbicyclophosphite **I** (δ_P 94.25 ppm) and 4 ml of hexamethyldisilazane in 4 ml of dioxane was heated in a flask with a reflux condenser for 1 h at 160°C. Dioxane and excess hexamethyldisilazane were removed in a vacuum, and compound **XIV** was purified by chromatography on a silica gel column (20 g) filled with hexane. Target product **XIV** was eluted with 25 ml of a mixture of hexane-dioxane, 5:1. The solvents were removed in a vacuum, and the residue was kept for 2 h at 60°C (1 mm Hg). Yield 0.17 g (31.8%), mp 118–120°C, R_f 0.9 (D), 0.60 (E). ^1H NMR spectrum (C_6D_6), δ, ppm: 0.02 s [18H, $Si(CH_3)_3$], 2.2 s (4H, $C^{1,7}H_2$), 2.9 s (4H, $C^{3,5}H_2$), 3.3 s (4H, CH_2OSi), 3.7 d (12H, CH_2OR, $^3J_{HP}$ 1.8 Hz). The ^{13}C NMR spectrum(C_6D_6), δ_C, ppm: –0.89 s [6C, $Si(CH_3)_3$], 36.52 d (2C, $\underline{C}C^{1,7}H_2$, $^3J_{CP}$ 2.3 Hz), 46.38 s (1C, C^4), 59.90 s (2C, CH_2Si), 68.8 g (6C, CH_2OR, $^2J_{CP}$ 6.8 Hz), 69.02 s (2C, $C^{1,7}$), 70.45 s (2C, $C^{3,5}$). ^{31}P NMR spectrum (benzene), δ_P, ppm: 94.39. Found, %: C 43.91, H 7.24, P 10.75. $C_{21}H_{42}O_{10}P_2Si_2$. Calculated, %: C 44.04, H 7.39, P 10.82. *M* 573.

1,7-Bis(2'-methyl-5'-iododmethyl-2'-oxo-1',3',2'-dioxaphosphorinyl)-4,4-trimethylsiloxymethyl-2,6-dioxaheptane (XV). 0.05 g of bisbicyclodisilylphosphite **XIV** and 2 ml of iodomethane in 2 ml of anhydrous benzene was heated in an ampule at 90°C for 12 h. The formation of phosphonate **XV** was monitored by ^{31}P NMR (benzene): δ_P: 27.43 ppm. The oil precipitated, and the solution was decanted. Benzene

and iodomethane excess were removed in a vacuum, and the residue was washed with hexane (2×2 ml) and kept for 3 h at 60°C (1 mm Hg). Yield of methylphosphonate **XV** 0.02 g (27%), n_D^{20} 1.4981, R_f 0.65 (F). ^{1}H NMR spectrum (C_6D_6), δ, ppm: 0.05 s [18H, Si(CH_3)$_3$], 1.1 d (6H, PCH_3, $^3J_{HP}$ 17.44 Hz), 2.5 s (4H, $C^{1,7}H_2$), 2.95 s (4H, $C^{3,5}H_2$), 3.25 s (4H, CH_2OSi), 3.65 m (4H$_e$) and 4.15 m (4H$_a$) (CH_2OP, $^2J_{HH}$ 11.74 Hz, $^3J_{HP}$ 5.46 Hz). ^{31}P NMR spectrum (benzene), δ_P, ppm: 27.43. Found, %: C 32.20, H 5.61, P 7.18. $C_{23}H_{48}O_{10}P_2Si_2I_2$. Calculated, %: C 32.25, H 5.65, P 7.23. *M* 857.

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