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2-Hydroxymethyl-2-propylpropane-1,3-diol in the Synthesis of Acetal-Like and Phosphacyclic Lipids

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Abstract—New acetal-like and phosphacyclic lipids were synthesized on the basis of 2-hydroxymethyl-2-propylpropane-1,3-diol. The initial triol was initially treated with higher aldehydes to obtain the corresponding acetals, which were phosphorylated with chlorobis(diethylamino)phosphine. Intermediate phosphorodiamidites were oxidized (without isolation) with phenyliodane oxide or subjected to sulfurization or selenization. Bicyclic phosphite derived from 2-hydroxymethyl-2-propylpropane-1,3-diol was acylated with hexadecanoyl chloride to give 2-chloro-4-propyl-1,3,2-dioxaphosphinan-4-ylmethyl hexadecanoate, and methanolysis of the latter, followed by sulfurization, afforded 2-methoxy-5-propyl-2-thioxo-1,3,2λ^5-dioxaphosphinan-5-ylmethyl hexadecanoate as a new phosphacyclic lipid.

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Natural phospholipids and their synthetic analogs are subjects of various biophysical studies; therefore, development of new methods for their synthesis is an important problem in modern organic and bioorganic chemistry [1]. The present work continues our previous studies on the synthesis of non-glycerol polyol phospholipids based on 2-hydroxymethyl-2-propylpropane-1,3-diol [2, 3]. It was aimed at synthesizing new acetal-like phospholipids and their chalcogen-containing analogs, as well as phosphacyclic lipids. The new phospholipids differ from naturally occurring ones by structural organization of their molecules which contain a 2-hydroxymethyl-2-propylpropane-1,3-diol moiety instead of glycerol; in addition, they are derivatives of not only phosphoric acid but also thio- and selenophosphoric acids. Acetal-like lipids contain long-chain alkylidene fragments instead of fatty acid residues. The above specificities of the synthesized phosphatides ensured their successful application in membrane, enzymological, and other biophysical and pharmacological studies.

Scheme 1.

I **II**, **III** **IV**, **V**

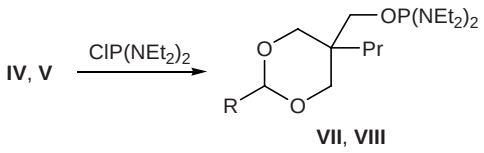
II, **IV**, R = C_9H_{19}; **III**, **V**, R = $C_{11}H_{23}$.

In the first step of our study, readily accessible 2-hydroxymethyl-2-propylpropane-1,3-diol (**I**) was treated with higher aldehydes **II** and **III** to obtain the corresponding cyclic acetals **IV** and **V** (Scheme 1). As the aldehyde components we used decanal (**II**) and dodecanal (**III**) whose hydrocarbon chains are comparable with those of natural fatty acid residues. The reactions were carried out by heating equimolar amounts of triol **I** and aldehyde **II** or **III** in boiling anhydrous benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid with simultaneous removal of liberated water as azeotrope (Dean–Stark trap; 12–15 h). No appreciable difference in the reactivities of aldehydes **II** and **III** toward triol **I** was observed. Acetals **IV** and **V** were purified by column chromatography on silica gel, and their yields attained 80%. The structure of **IV** and **V** was proved by elemental analyses and ^{1}H NMR spectroscopy. Unlike initial triol **I**, the ^{1}H NMR spectra of **IV** and **V** contained signals in the regions δ 0.84–1.50 and 4.26 ppm due to protons in the long-chain alkyl radical.

Acetals **IV** and **V** were then subjected to phosphorylation using chlorobis(diethylamino)phosphine (**VI**) [4]; as a result, the corresponding phosphorodiamidites **VII** and **VIII** were obtained (Scheme 2). The reactions were carried out in anhydrous diethyl ether on cooling to –10°C; the reactant mixture was thoroughly stirred over a period of 2 h in the presence of triethylamine as hydrogen chloride acceptor. The

formation of phosphorylated compounds **VII** and **VIII** was monitored by ^{31}P NMR spectroscopy. The ^{31}P NMR spectra of the reaction mixtures contained a singlet at δ_P 134 ppm, which is typical of phosphorodiamidites [5]. We previously used hexaethylphosphorous triamide to effect phosphorylation of protected polyols [3, 6, 7]. Reagent **VI** was selected for phosphorylation of compounds **IV** and **V**, taking into account its accessibility and high reactivity, as well as sufficient stability of the phosphorylation products (compounds **VII** and **VIII**); therefore, we were able to carry out the process under mild conditions.

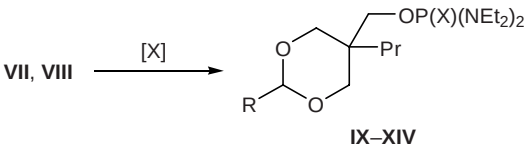
Scheme 2.



IV, **VII**, R = C_9H_{19}; **V**, **VIII**, R = $C_{11}H_{23}$.

Compounds **VII** and **VIII** were converted (without additional purification) into the corresponding phosphorus(V) derivatives **IX**–**XIV** by treatment with phenyliodane oxide [8, 9], sulfur [10, 11], and selenium [11, 12] (Scheme 3). The reactions were performed by heating the reactants in boiling anhydrous benzene over a period of 6 h, and products **IX**–**XIV** were purified by column chromatography on silica gel. The yield of phosphates **IX** and **XII** was 40%, and of thio- and selenophosphates **X**, **XIII** and **XI**, **XIV**, 62–63% (calculated on the initial acetal **IV** or **V**). The purity of phospholipid analogs **IX**–**XIV** was checked by thin-layer chromatography, and their structure was confirmed by the ^1H and ^{31}P NMR spectra. Compounds **IX**–**XIV** showed in the ^1H NMR spectra signals from protons in the ethyl groups (δ 1.08 and 3.06 ppm). The ^{31}P NMR spectra of **IX**–**XIV** contained singlets at δ_P 17 (**IX**, **XII**), 79 (**X**, **XIII**), and 81 ppm (**XI**, **XIV**). In addition, selenophosphates **XI** and **XIV** displayed in the ^{31}P NMR spectra satellites due to spin–spin coupling ^{31}P–^{77}Se ($^1J_{P,Se}$ = 850 Hz).

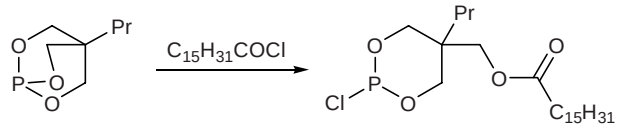
Scheme 3.



VII, **IX**–**XI**, R = C_9H_{19}; **VIII**, **XII**–**XIV**, R = $C_{11}H_{23}$; **IX**, **XII**, X = O; **X**, **XIII**, X = S; **XI**, **XIV**, X = Se.

Along the other line of our study, we used in the synthesis of phospholipids a neutral phosphite derived from 2-hydroxymethyl-2-propylpropane-1,3-diol, 4-propyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane (**XV**). Initially, bicyclic phosphite **XV** was treated with hexadecanoyl chloride. According to spectral data, the acylation occurred at one of the oxygen atoms with formation of cyclic phosphorochloridite **XVI** rather than at the phosphorus atom with formation of α-keto phosphonate [13, 14] (Scheme 4). The reaction was carried out by heating equimolar amounts of the reactants in a sealed ampule for 36 h at 130–140°C. The progress of the reaction was monitored by ^{31}P NMR spectroscopy, following accumulation of product **XVI** which gives rise to a singlet at δ_P δ 149 ppm.

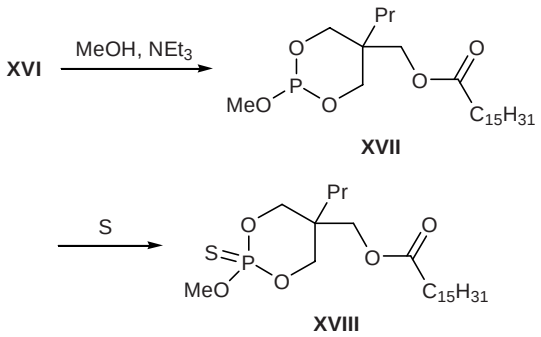
Scheme 4.



An analogous path of reaction between neutral phosphites and acid chlorides was reported by us in [15], where O-acylation of bicyclic phosphite derived from 2-ethyl-2-(hydroxymethyl)propane-1,3-diol was studied; it was then confirmed by direct acylation of bicyclic phosphite derived from 2-butyl-2-(hydroxymethyl)propane-1,3-diol [11]. Therefore, the described O-acylation of bicyclic phosphites may be regarded as general reaction.

Compound **XVI** was converted (without isolation) into phosphite **XVII** by treatment with methanol, and crude phosphite **XVII** was subjected to sulfurization to obtain thiophosphate **XVIII** (Scheme 5).

Scheme 5.



Compound **XVIII** was isolated from the reaction mixture by column chromatography on silica gel. Its

yield was 35% with respect to initial phosphite **XV**. Thiophosphate **XVIII** may be regarded as an analog of neutral phosphacyclic lipids.

EXPERIMENTAL

The ^{1}H and ^{31}P NMR spectra were recorded on a Varian Mercury 300 spectrometer (300 MHz for ^{1}H and 121.47 MHz for ^{31}P). The proton signals were assigned on the basis of double-resonance spectra, and ^{31}P chemical shifts were measured relative to 85% phosphoric acid as external reference. Column chromatography was performed on silica gel L 40/100 μm. Silufol UV-254 plates were used for thin-layer chromatography; benzene–dioxane (5:1, A) and hexane–dioxane (5:1, B) were used as eluents; phosphorus-containing compounds were detected by treatment with Molybdenum Blue [16], and sulfur-containing compounds, by treatment with a 1% aqueous solution of silver nitrate [17], as well as by calcination.

All syntheses involving tervalent phosphorus compounds were carried out under dry argon. The progress of reactions was monitored by TLC and NMR spectroscopy.

2-Nonyl-5-propyl-1,3-dioxan-5-ylmethanol (IV). A mixture of 3.7 g (25 mmol) of triol **I**, 3.9 g (25 mmol) of decanal (**II**), and 10 mg of *p*-toluenesulfonic acid in 100 ml of anhydrous benzene was heated under reflux in a flask equipped with a Dean–Stark trap until water no longer separated (12 h). The mixture was treated with a saturated solution of sodium carbonate, the organic layer was separated and dried over anhydrous calcium chloride, the solvent was distilled off, and the residue was subjected to column chromatography on silica gel using benzene as eluent. Yield 5.73 g (80%), n_D^{20} = 1.4610, R_f 0.6 (A). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.84 t [3H, $(CH_2)_8CH_3$], 0.97 t [3H, $CH_3(CH_2)_2$], 1.22 m [18H, $CH_3(CH_2)_2$, $(CH_2)_7CH_3$], 1.52 m (2H, 2-CH_2), 2.90 br.s (1H, OH), 3.23 d and 3.75 d (4H, CH_2O), 3.64 s (2H, 5-CH_2), 4.26 t (1H, 2-H). Found, %: C 71.15; H 12.03. $C_{17}H_{34}O_3$. Calculated, %: C 71.28; H 11.96.

5-Propyl-2-undecyl-1,3-dioxan-5-ylmethanol (V) was synthesized in a similar way from 3.7 g (25 mmol) of triol **I** and 4.6 g (25 mmol) of dodecanal (**III**) (reaction time 15 h). Yield 6.17 g (78.5%), n_D^{20} = 1.4590, R_f 0.6 (A). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.85 t [3H, $(CH_2)_{10}CH_3$], 0.95 t [3H, $CH_3(CH_2)_2$], 1.24 m [22H, $CH_3(CH_2)_2$, $(CH_2)_9CH_3$], 1.56 m (2H, 2-CH_2), 3.30 br.s (1H, OH), 3.25 d and 3.77 d (4H, CH_2O), 3.68 s (2H, 5-CH_2), 4.30 t (1H, 2-H). Found, %: C 72.40; H 12.12. $C_{19}H_{38}O_3$. Calculated, %: C 72.56; H 12.18.

2-Nonyl-5-propyl-1,3-dioxan-5-ylmethyl tetraethylphosphorodiamidite (VII). A solution of 4.21 g (20 mmol) of phosphine **VI** in 50 ml of anhydrous diethyl ether was cooled to –10°C, a mixture of 5.74 g (20 mmol) of acetal **IV** and 2.1 g of triethylamine in 50 ml of anhydrous diethyl ether was added under vigorous stirring, and the mixture was kept for 1 h at room temperature, filtered, and evaporated. Compound **VII** was used in further syntheses without preliminary purification. R_f 0.3 (A). ^{31}P NMR spectrum (C_6H_6): δ_P 133.9 ppm, s.

5-Propyl-2-undecyl-1,3-dioxan-5-ylmethyl tetraethylphosphorodiamidite (VIII) was synthesized in a similar way from 4.21 g (20 mmol) of phosphine **VI** and 6.3 g (20 mmol) of acetal **V** in the presence of 2.1 g of triethylamine. It was used in further syntheses without preliminary purification. R_f 0.3 (A). ^{31}P NMR spectrum (C_6H_6): δ_P 134 ppm, s.

2-Nonyl-5-propyl-1,3-dioxan-5-ylmethyl *N,N,N′,N′*-tetraethylphosphorodiamidate (IX). Finely powdered phenyliodane oxide, 1.32 g (6 mmol), was added to 2.3 g (5 mmol) of crude compound **IV** in 50 ml of anhydrous benzene. The mixture was heated for 6 h under reflux and cooled, excess phenyliodane oxide was filtered off, the solvent was distilled off from the filtrate, and the residue was purified by column chromatography on silica gel using benzene as eluent. Yield 0.96 g (40%), colorless oily liquid, R_f 0.55 (A). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.84 t [3H, $(CH_2)_8CH_3$], 0.96 t [3H, $CH_3(CH_2)_2$], 1.08 t (12H, CH_3CH_2N), 1.22 m [18H, $CH_3(CH_2)_2$, $(CH_2)_7CH_3$], 1.53 m (2H, 2-CH_2), 3.06 m (8H, CH_2N, $^3J_{HP}$ = 11.9 Hz), 3.28 d and 3.77 d (4H, CH_2O), 3.94 d (2H, CH_2OP, $^3J_{HP}$ = 4.8 Hz), 4.29 t (1H, 2-H). ^{31}P NMR spectrum (C_6H_6): δ_P 17 ppm, s. Found, %: C 62.82; H 11.19; N 5.90. $C_{25}H_{53}N_2O_4P$. Calculated, %: C 62.99; H 11.21; N 5.88.

***O*-(2-Nonyl-5-propyl-1,3-dioxan-5-ylmethyl) *N,N,N′,N′*-tetraethylphosphorodiamidothioate (X)** was synthesized in a similar way from 2.3 g (5 mmol) of crude compound **IV** and 0.16 g (5 mmol) of finely powdered sulfur. Yield 1.53 g (62%), colorless oily liquid, R_f 0.7 (A). The ^{1}H NMR spectrum of **X** was similar to that of **IX**. ^{31}P NMR spectrum (C_6H_6): δ_P 79 ppm. Found, %: C 60.81; H 10.80; N 5.72.

$C_{25}H_{53}N_2O_3PS$. Calculated, %: C 60.93; N 10.84; N 5.69.

***O*-(2-Nonyl-5-propyl-1,3-dioxan-5-ylmethyl) *N,N,N′,N′*-tetraethylphosphorodiamidoselenoate (XI)** was synthesized in a similar way from 2.3 g (5 mmol) of crude product **IV** and 0.4 g (5 mmol) of finely powdered selenium. Yield 1.7 g (63%), colorless oily liquid, R_f 0.7 (A). The ^{1}H NMR spectrum of **XI** was similar to that of **IX**. ^{31}P NMR spectrum (C_6H_6): δ_P 80.9 ppm, s; $^1J_{P,Se}$ = 850.8 Hz (satellites). Found, %: C 55.46; H 9.87; N 5.21. $C_{25}H_{53}N_2O_3PSe$. Calculated, %: C 55.65; H 9.90; N 5.19.

5-Propyl-2-undecyl-1,3-dioxan-5-ylmethyl *N,N,N′,N′*-tetraethylphosphorodiamidate (XII) was synthesized in a similar way from 2.45 g (5 mmol) of crude product **V** and 1.32 g (6 mmol) of finely powdered phenyliodane oxide. Yield 1 g (40%), colorless oily liquid, R_f 0.55 (A). The ^{1}H NMR spectrum of **XII** was similar to that of **IX**. ^{31}P NMR spectrum (C_6H_6): δ_P 17.05 ppm, s. Found, %: C 64.12; H 11.39; N 5.57. $C_{27}H_{57}N_2O_4P$. Calculated, %: C 64.24; H 11.38; N 5.55.

***O*-(5-Propyl-2-undecyl-1,3-dioxan-5-ylmethyl) *N,N,N′,N′*-tetraethylphosphorodiamidothioate (XIII)** was synthesized in a similar way from 2.45 g (5 mmol) of crude product **V** and 0.16 g (5 mmol) of finely powdered sulfur. Yield 1.61 g (62%), colorless oily liquid, R_f 0.7 (A). The ^{1}H NMR spectrum of **XIII** was similar to that of **IX**. ^{31}P NMR spectrum (C_6H_6): δ_P 79.1 ppm. Found, %: C 62.10; H 11.00; N 5.40. $C_{27}H_{57}N_2O_3PS$. Calculated, %: C 62.26; H 11.03; N 5.38.

***O*-(5-Propyl-2-undecyl-1,3-dioxan-5-ylmethyl) *N,N,N′,N′*-tetraethylphosphorodiamidoselenoate (XIV)** was synthesized in a similar way from 2.45 g (5 mmol) of crude product **V** and 0.4 g (5 mmol) of finely powdered selenium. Yield 1.78 g (63%), colorless oily liquid, R_f 0.7 (A). The ^{1}H NMR spectrum of **XIV** was similar to that of **IX**. ^{31}P NMR spectrum (C_6H_6): δ_P 81.1 ppm, s; $^1J_{P,Se}$ = 849 Hz (satellites). Found, %: C 56.98; H 10.09; N 4.95. $C_{27}H_{57}N_2O_3PSe$. Calculated, %: C 57.12; H 10.12; N 4.93.

2-Methoxy-5-propyl-2-thioxo-1,3,2λ^5-dioxaphosphinan-5-ylmethyl hexadecanoate (XVIII). A mixture of 1.76 g (10 mmol) of bicyclic phosphite **XV** and 2.75 g (10 mmol) of hexadecanoyl chloride was heated in a sealed ampule for 36 h at 130–140°C. Compound **XVI** thus obtained was then used in further syntheses without preliminary purification. ^{31}P NMR spectrum (C_6H_6): δ_P 149 ppm, s. Crude compound **XVI**, 2.26 g (5 mmol), was dissolved in 50 ml of anhydrous diethyl ether, the solution was cooled to –10°C, and a mixture of 0.16 g (5 mmol) of methanol and 0.5 g (5 mmol) of triethylamine in 20 ml of anhydrous diethyl ether was added under vigorous stirring. The mixture was kept for 1 h at room temperature and filtered, the solvent was distilled off from the filtrate, and the residue [phosphite **XVII**; δ_P 125.8 ppm, s (C_6H_6)] was subjected to sulfurization without additional purification. Crude phosphite **XVII**, 2.23 g (5 mmol), was dissolved in 50 ml of anhydrous benzene, 0.16 g (5 mmol) of finely powdered sulfur was added, and the mixture was heated for 6 h under reflux. The solvent was distilled off, and the residue was purified by column chromatography on silica gel using benzene as eluent. Yield 0.84 g (35%), mp 45–46°C, R_f 0.5 (B). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.83 t [3H, C**H**$_3$(CH$_2$)$_{12}$], 0.94 t [3H, C**H**$_3$(CH$_2$)$_2$], 1.21 m [28H, CH$_3$(C**H**$_2$)$_2$, CH$_3$(C**H**$_2$)$_{12}$], 1.56 m [2H, C(O)CH$_2$C**H**$_2$], 2.23 t [2H, C(O)CH$_2$], 3.76 d (3H, OCH$_3$, $^3J_{HP}$ = 14 Hz), 3.98 m and 4.30 m (4H, CH$_2$O), 4.10 s (2H, 5-CH$_2$). ^{31}P NMR spectrum (C_6H_6): δ_P 64.1 ppm, s. Found, %: C 60.05; H 9.87; P 6.46. $C_{24}H_{47}O_5PS$. Calculated, %: C 60.22; H 9.90; P 6.47.

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