SYNTHESIS OF 9-(2-PHOSPHINOMETHOXYETHYL)ADENINE AND RELATED COMPOUNDS

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Alkyl 2-chloroethoxymethyl(diethoxymethyl)phosphinates *VII* and *XIII* were prepared by reaction of silyl esters of dialkoxymethylphosphinic acid with 2-chloroethyl chloromethyl ether. Adenine was alkylated with *VII* and *XIII* to give [2-(adenin-9-yl)ethoxy]methyl(diethoxymethyl)phosphinates *VIII* and *XIV*, bearing the dialkoxymethyl protecting group on the phosphorus atom. Acid hydrolysis of compounds *VIII* and *XIV* afforded 9-(2-phosphinoethoxymethyl)adenine (*X*). Alkyl dialkoxymethylphosphinates *V* and *XI* reacted with paraformaldehyde to give hydroxymethylphosphinates *XV* and *XIX* which were converted into the synthons *XVI*, *XVII* and *XVIII* capable of introducing a protected hydroxymethylphosphino group on a hydroxy or amino group.

Phosphonate derivatives represent important analogs with modified phosphate functionality. Particularly important are phosphonomethoxy derivatives of acyclic nucleosides among which a series of extraordinarily biologically active compounds has been found[1]. In these compounds the phosphomonoester bond, present in nucleotides, is replaced by the chemically as well as enzymatically very stable P–C bond. They possess high inhibitory activity also against mutants or strains of DNA viruses that are resistant toward nucleoside antivirals due e.g. to reduced activity of some phosphorylation enzymes.

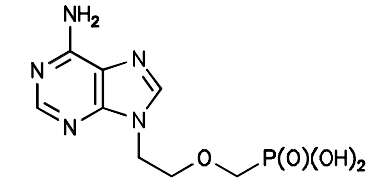
Within the framework of our studies of potential prodrugs of 9-(2-phosphonomethoxyethyl)adenine[2] (PMEA, *I*), which is recently undergoing clinical tests[3] against AIDS, we tried to prepare derivatives of the corresponding acyclic nucleoside analogs *II* in which the phosphonate group is replaced by the phosphinate group. These compounds, analogous to nucleoside phosphites with respect to the oxidation state of the phosphorus atom, have not been described so far in the chemistry of nucleic acid analogs. Nucleoside phosphites[4,5] are widely used in the synthesis of oligonucleotides[6] or other nucleotide esters[7]. Phosphites of some nucleoside analogs are biologically active[8]. The chemical reactivity, together with the possible activation of phosphinate analogs, could lead to new synthetic approach to nucleoside phosphonates, in analogy with methods using nucleoside phosphites in the phosphate series.

The simplest approach to the desired compounds could consist in reduction of derivatives of compound *I* by some of the methods applied already to aliphatic phosphonates[9]. However, the reduction of diethyl ester of compound *I* with lithium aluminium hydride or sodium bis(2-methoxyethyl)aluminium hydride (Synhydride) leads directly to the phosphine intermediate which is cleaved under the reaction conditions to give 9-(2-hydroxyethyl)adenine *III* as the sole reaction product. The corresponding phosphonochloridate (generated from the phosphonate group by thionyl chloride) is reduced under milder conditions with $NaBH_4$, as described for alkyl phosphonates[10]. In the case of compound *I*, however, even this reaction failed.

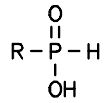
Another possibility how to obtain compound *II* consists in using a suitable phosphorus derivative that bears structural elements of the target phosphonate and a protecting group which upon removal affords the P–H bond. This method is recently used in the chemistry of phosphonopeptides[11]; it was also employed by Hata and Sekine in the synthesis of nucleoside phosphites[12] or optically active dinucleoside phosphothioates[13]. Of groups with suitable properties we chose the dialkoxymethyl group which can be removed from the phosphorus atom by acid hydrolysis[14]. In the series of PME derivatives, 2-chloroethyl chloromethyl ether[15] (*IV*) is the most accessible compound capable of forming the required skeleton between the phosphorus atom and the amino nitrogen. This ether easily undergoes Arbuzov reaction with trivalent phosphorus compounds[16]. By treatment of the ether *IV* with silylated ethyl diethoxymethylphosphinate *VI* we prepared synthon *VII* containing a halogen-activated alkyl moiety with protected phosphinate functionality (see Scheme 1). The required silyl ester was prepared according to a described procedure[14] by reaction of phosphorous acid with triethyl orthoformate, catalyzed with trifluoroacetic acid, and subsequent silylation of the arising phosphonite *V* with hexamethyldisilazane[17]. Compound *VII* is sufficiently stable in anhydrous alkaline as well as weakly acidic media and can be used for alkylation of corresponding bases under formation of phosphinates *VIII*. However, alkylation of sodium salt of adenine at elevated temperatures resulted mainly in undesired alkylation of adenine with the ester-bonded ethyl group. Thus, under standard conditions[2] (at 100 °C in dimethylformamide in the presence of potassium carbonate), the reaction gave predominantly 9-ethyladenine (*IX*). In spite of this, we also isolated the desired ethyl [2-(adenin-9-yl)ethoxymethyl]phosphinate (*VIII*) in 10% yield. As expected, on heating in 80% trifluoroacetic acid this compound lost the dialkoxymethyl group to give 9-(2-phosphinomethoxyethyl)adenine [(2-(adenin-9-yl)ethoxymethylphosphinic acid) (*X*)].

Because of the mentioned alkylation side-reaction, tris(2-propyl) orthoformate was converted analogously into synthon *XIII* which on reaction with adenine afforded phosphinate *XIV* without any side reaction. Also the derivative *XIV* was hydrolyzed into the free phosphinate *X*.

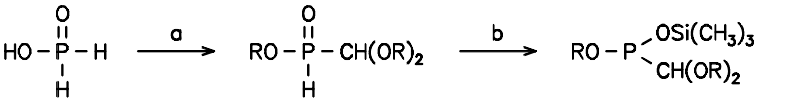
As alternative synthons for attaching of the mentioned phosphinomethyl ether functionality to hydroxy or amino groups in other compounds, we also prepared the



I



II

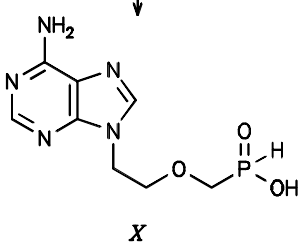


V, R = C_2H_5
XI, R = $CH(CH_3)_2$

VI, R = C_2H_5
XII, R = $CH(CH_3)_2$

VIII, R = C_2H_5
XIV, R = $CH(CH_3)_2$

VII, R = C_2H_5
XIII, R = $CH(CH_3)_2$

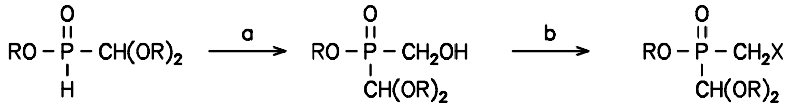


X

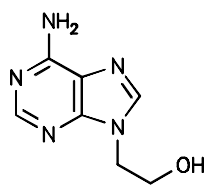
a) $(RO)_3CH$, TFA; b) HMDS; c) $ClCH_2OCH_2CH_2Cl$ (*IV*);
d) adenine, NaH/DMF; e) TFA, H_2O

SCHEME 1

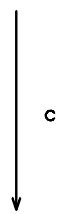
tosyl- or methanesulfonyloxymethylphosphinates *XVI*, *XVII* and *XVIII* (Scheme 2). Base-catalyzed reaction of ethyl diethoxymethylphosphinate (*V*) with paraformaldehyde afforded the corresponding hydroxymethyl derivative *XV* which was then smoothly converted into the tosyl or mesyl derivative (*XVI* and *XVII*, respectively). Reaction of these compounds with 9-(2-hydroxyethyl)adenine in the presence of three equivalents of sodium hydride in dimethylformamide at room temperature[2] afforded compound *VIII* in an acceptable yield. The corresponding methanesulfonyl derivative of the 2-propyl ester, *XVIII*, reacted with *N*-benzoyl-9-(2-hydroxyethyl)adenine to give phosphinate *XIV* in very good yield.



V, R = C_2H_5 *XV*, R = C_2H_5 *XVI*, R = C_2H_5; X = OTs
XI, R = $CH(CH_3)_2$ *XIX*, R = $CH(CH_3)_2$ *XVII*, R = C_2H_5; X = OMs
XVIII, R = $CH(CH_3)_2$; X = OMs



III



VIII, R = C_2H_5
XIV, R = $CH(CH_3)_2$

a) $(CH_2O)_n$, $(C_2H_5)_3N$; b) MsCl or TsCl, $(C_2H_5)_3N$, CH_2Cl_2;
c) *III*, NaH; d) TFA, H_2O

SCHEME 2

Compounds *XVI*, *XVII* and *XVIII*, containing a sulfonyl group-activated hydroxymethylphosphinate moiety, represent universal synthons suitable for preparation of analogous phosphinates derived from other alcohols.

According to preliminary results, compound *X* exhibits neither antiviral[18] nor antitumor activity.

EXPERIMENTAL

Unless stated otherwise, the solvents were evaporated at 40 °C/2 kPa and the products were dried over phosphorus pentoxide at 13 Pa. Analytical samples were dried at 25 °C and 6.5 Pa for 8 h. Melting points were determined on a Kofler block and are uncorrected.

Thin-layer chromatography was performed on Silufol UV 254 sheets (Kavalier, The Czech Republic) in the systems: S1, 2-propanol–concentrated ammonia–water (7 : 1 : 2); S2, chloroform–methanol (9 : 1); S3, chloroform–methanol (4 : 1). Compounds were detected by (i) UV light at 254 nm, (ii) spraying with 2% solution of 4-(*p*-nitrobenzyl)pyridine in ethanol, followed by heating and exposure to ammonia vapour (for compounds capable of alkylation), and (iii) carbonization.

Analytical high performance liquid chromatography was carried out on 250 × 4 mm columns packed with Separon SGXC18 (5 μm or 10 μm; Laboratorni pristroje, Prague, The Czech Republic). Preparative reversed-phase chromatography was performed on a 20 × 500 mm octadecylsilica gel column (20 μm, Laboratorni pristroje, Prague); detection at 254 nm with a Uvicord 4 701 instrument (LKB, Sweden).

Mass spectra were measured on a ZAB-EQ (VG Analytical) instrument using the EI (electron energy 70 eV) and FAB (ionization with Xe, accelerating voltage 8 kV) techniques.

^{1}H NMR spectra were taken on Varian UNITY 200 (200.01 MHz) and Varian UNITY 500 (499.8 MHz) spectrometers in hexadeuteriodimethyl sulfoxide with tetramethylsilane (TMS) as internal standard. Free phosphonates and monoesters were measured in D_2O with sodium disilapentasulfonate (DSS) as internal standard. ^{13}C NMR spectra were obtained with a Varian UNITY 200 instrument (50.31 MHz); the signals were referenced to the solvent signal, $\delta(^{13}C) = 39.7$, or to dioxane as external standard, $\delta(^{13}C)$ (dioxane) = 66.86, for solutions in D_2O.

Electrophoresis was performed on a Whatman No. 3 MM paper at 20 V/cm (1 h) in 0.1 M triethylammonium hydrogen carbonate (TEAB).

Phosphorous acid, sodium hydride, tris(2-propyl) phosphite, hexamethyldisilazane and dimethylformamide were obtained from Janssen (Belgium), adenine and 4-(*p*-nitrobenzyl)pyridine from Fluka (Switzerland).

Ethyl 2-Chloroethoxymethyl(diethoxymethyl)phosphinate (*VII*)

A mixture of ethyl diethoxymethylphosphinate[11] (*V*) (8.9 g, 45.3 mmol) and hexamethyldisilazane (7.5 g, 46 mmol) was heated under nitrogen at 120 – 130 °C for 3 h. Distillation under diminished pressure afforded 10 g of silylated intermediate *VI*, boiling at 55 – 60 °C/13 Pa. This fraction was heated with 2-chloroethyl chloromethyl ether (5.16 g, 40 mmol) at 90 °C for 3 h under nitrogen. Chromatography on silica gel (200 g) in chloroform afforded 9.4 g (72%) of product *VII* as a colourless viscous syrup which was used in the next step. ^{1}H NMR spectrum: 1.15 t, 3 H, $J(CH_3,CH_2)$ = 7.1 (CH_3); 1.16 t, 3 H, $J(CH_3,CH_2)$ = 7.1 (CH_3); 1.24 t, 3 H, $J(CH_3,CH_2)$ = 7.1 (CH_3); 3.62 dq, 1 H and 3.63 dq, 1 H, J(gem) = 9.5, $J(CH_2,CH_3)$ = 7.1 (OCH_2); 3.72 – 3.82 m, 6 H ($ClCH_2$, 2 × OCH_2); 3.83 dd, 1 H, J(gem) = 13.9, J(P,CH) = 5.6 (PCH_2); 3.87 dd, 1 H, J(gem) = 13.9, J(P,CH) = 6.1 (PCH_2); 4.09 p, 2 H, $J(CH_2,CH_3)$ = 7.1, J(P,OCH) = 7.1 ($POCH_2$); 4.83 d, 1 H, J(P,CH) = 8.1 (PCH). ^{13}C NMR spectrum: 15.32 s (CH_3); 15.36 s (CH_3); 16.62 d, J(C,P) = 4.5 (CH_3); 43.37 s ($ClCH_2$); 61.37 d, J(C,P) = 6.1 ($POCH_2$); 64.56 d, J(C,P) = 105.3 (PCH_2); 64.79 d, J(C,P) = 9.2 ($PCOCH_2$); 65.12 d, J(C,P) = 9.2 ($PCOCH_2$); 72.75 d, J(C,P) = 9.2 (OCH_2); 99.08 d, J(C,P) = 145.0 (PCH).

Ethyl [2-(Adenin-9-yl)ethoxymethyl](diethoxymethyl)phosphinate (*VIII*)

Procedure A. A mixture of adenine (200 mg, 1.48 mmol), potassium carbonate (500 mg), compound *VII* (350 mg, 1.21 mmol) and dimethylformamide (5 ml) was heated at 100 – 110 °C for 12 h

under exclusion of moisture. The mixture was concentrated and chromatographed on silica gel (20 g) in the system S4. Crystallization from ethyl acetate–light petroleum afforded 55 mg (10%) of product *VIII*. For $C_{15}H_{26}N_5O_5P$ (387.4) calculated: 46.51% C, 6.77% H, 18.08% N, 8.00% P; found: 46.60% C, 6.92% H, 18.3% N, 7.80% P. ^{1}H NMR spectrum: 1.06 t, 3 H, $J(CH_3,CH_2)$ = 7.1 (CH_3); 1.07 t, 3 H, $J(CH_3,CH_2)$ = 7.1 (CH_3); 1.15 t, 3 H, $J(CH_3,CH_2)$ = 7.1 (CH_3), 3.40 dq, 1 H and 3.44 dq, 1 H, J(gem) = 9.5, $J(CH_2,CH_3)$ = 7.1 (OCH_2); 3.63 dq, 1 H and 3.67 dq, 1 H, J(gem) = 9.5, $J(CH_2,CH_3)$ = 7.1 (OCH_2); 3.77 dd, 1 H, J(gem) = 13.7, J(P,CH) = 5.6 (PCH_2); 3.82 dd, 1 H, J(gem) = 13.7, J(P,CH) = 6.8 (PCH_2); 3.87 t, 2 H, $J(CH_2,CH_2)$ = 5.1 (OCH_2); 3.97 p, 2 H, $J(CH_2,CH_3)$ = 7.1, J(P,OCH) = 7.1 ($POCH_2$); 4.32 t, 2 H, $J(CH_2,CH_2)$ = 5.1 (NCH_2); 4.55 d, 1 H, J(P,CH) = 8.1 (PCH); 7.18 bs, 2 H (NH_2); 8.1 s, 1 H (H-base); 8.13 s, 1 H (H-base). ^{13}C NMR spectrum: 15.25 s (CH_3); 15.30 s (CH_3); 16.56 d, J(C,P) = 4.4 (CH_3); 40.75 s (NCH_2); 61.25 d, J(C,P) = 7.6 ($POCH_2$); 64.46 d, J(C,P) = 105.6 (PCH_2); 64.85 d, J(C,P) = 7.6 ($PCOCH_2$); 65.08 d, J(C,P) = 9.9 ($PCOCH_2$); 70.80 d, J(C,P) = 10.7 (OCH_2); 98.97 d, J(C,P) = 143.4 (PCH); 118.79 s (C-5, base); 152.52 s (C-2, base); 156.12 s (C-6, base).

The mixture further afforded 128 mg (53%) of 9-ethyladenine *IX*, m.p. 195 °C (reported[16] m.p. 195 – 197 °C).

Compounds *VIII* and *IX* exhibit similar chromatographic mobility on Silufol and in the systems S2 (R_F 0.6) and S3 (R_F 0.35) were not separated. The separation was achieved only by repeated developing in S4. Compound *VIII* can be detected by spraying with 2% solution of *p*-nitrobenzylpyridine followed by heating and exposure to ammonia vapour. Compound *IX* was not detected by this procedure.

Procedure B. A mixture of adenine (200 mg, 1.48 mmol), 60% sodium hydride suspension (60 mg, 1.5 mmol) and dimethylformamide (10 ml) was heated at 80 °C for 30 min. Compound *VII* (350 mg, 1.21 mmol) was added at 60 °C and the mixture was stirred at this temperature for 24 h under exclusion of moisture. The mixture was neutralized with a drop of acetic acid, concentrated and the residue was chromatographed on silica gel (20 g) in solvent system S4; yield 275 mg (48%) of product, identical with compound *VIII* obtained by procedure *A*.

Procedure C. Sodium hydride (60% suspension; 80 mg, 2 mmol) was added at 0 °C to a mixture of compound *XVIII* (305 mg, 1 mmol), 9-(2-hydroxyethyl)adenine[19] (283 mg, 1.1 mmol) and dimethyl sulfoxide (5 ml). After stirring at ambient temperature for 48 h under exclusion of moisture, the mixture was neutralized with acetic acid. The solvent was evaporated and the residue was chromatographed on silica gel (150 ml) in solvent system S4. Yield 175 mg (45%) of product identical with compound *VIII* obtained by procedure *A*.

Procedure D. Sodium hydride (60% suspension; 0.12 mg, 3 mmol) was added at 0 °C to a mixture of compound *XVIII* (305 mg, 1 mmol), N^6-benzoyl-9-(2-hydroxyethyl)adenine (283 mg, 1 mmol) and dimethylformamide (5 ml). The suspension was then stirred at 40 °C for 12 h under exclusion of moisture. After neutralization with acetic acid and evaporation of the solvent, the product was isolated by chromatography on silica gel (150 ml) in solvent system S4. Under the reaction conditions the N^6-benzoyl group was split off. Yield 288 mg (75%) of product identical with compound *VIII* obtained by procedure *A*.

9-(2-Phosphinomethoxyethyl)adenine (*X*)

Procedure A. Compound *VIII* (0.1 g, 0.26 mmol) was stirred with 50% aqueous trifluoroacetic acid (10 ml) at 80 °C for 8 h. After evaporation and threefold codistillation with dioxane, the mixture was neutralized with triethylamine, applied onto a column of Dowex 1X2 (acetate form, 10 ml) and eluted with a gradient of 0 – 0.5 M acetic acid (à 0.5 liter). The product-containing fractions were combined, concentrated, and the residue was several times codistilled with 2-propanol to remove re-

sidual acetic acid. Crystallization from methanol with addition of ether to turbidity afforded 52 mg (78%) of compound *X*, m.p. 229 – 230 °C. R_F 0.75 (S1). E_{Up} = 0.45. For $C_8H_{12}N_5O_3P$ (257.2) calculated: 37.36% C, 4.70% H, 27.23% N, 12.04% P; found: 37.51% C, 4.84% H, 27.56% N, 12.28% P. Mass spectrum (FAB), *m/z*: 258 (M + H, 100). ^{1}H NMR spectrum (D_2O): 3.56 dd, 2 H, *J*(P,CH) = 7.5, *J*(HP,CH_2) = 2.2 (PCH_2); 3.97 t, 2 H, *J*(CH_2,CH_2) = 5.1 (OCH_2); 4.42 t, 2 H, *J*(CH_2,CH_2) = 5.1 (NCH_2); 6.88 dt, 1 H, *J*(P,H) = 519.3, *J*(HP,CH_2) = 2.2 (PH); 8.17 s, 1 H (H-base); 8.18 s, 1 H (H-base).

Procedure B. Compound *XIV* (1.0 g, 2.33 mmol) was stirred with 50% aqueous trifluoroacetic acid (10 ml) at 80 °C for 8 h until the starting compound disappeared (TLC, S2). After evaporation and codistillation with dioxane, the mixture was neutralized with triethylamine, applied onto a column of Dowex 1X2 (acetate form, 150 ml) and eluted with a gradient of 0 – 0.5 M acetic acid. Yield 550 mg (92%) of compound *X*, identical with the product of procedure *A*.

Ethyl Diethoxymethyl(hydroxymethyl)phosphinate (*XV*)

A mixture of compound *V* (10 g, 51 mmol), paraformaldehyde (1.5 g, 50 mmol) and triethylamine (1 ml) was stirred at 90 – 95 °C for 3 h (until the starting compound disappeared). After 30 min the paraformaldehyde dissolved. Chromatography on silica gel (150 ml) in chloroform afforded 9.7 g (84%) of ester *XV* which was used in the next step. ^{1}H NMR spectrum: 1.145 t, 3 H, *J*(CH_3,CH_2) = 7.1 (CH_3); 1.15 t, 3 H, *J*(CH_3,CH_2) = 7.1 (CH_3); 1.23 t, 3 H, *J*(CH_3,CH_2) = 7.1 (CH_3); 3.605 dd, 1 H, *J*(P,CH) = 3.9, *J*(gem) = 14.4 (PCH_2); 3.73 dd, 1 H, *J*(P,CH) = 4.4, *J*(gem) = 14.4 (PCH_2); 3.78 and 3.78 2 × dq, 2 H, *J*(CH_2,CH_3) = 7.1, *J*(gem) = 9.5 (OCH_2); 3.61 and 3.60 dq, 2 H, *J*(CH_2,CH_3) = 7.1, *J*(gem) = 9.5 (OCH_2); 4.07 p, 2 H, *J*(CH_2,CH_3) = 7.1, *J*(P,OCH) = 7.3 ($POCH_2$); 4.83 d, 1 H, *J*(P,CH) = 7.6 (PCH); 5.65 bs, 1 H (OH).

Ethyl Diethoxymethyl(*p*-toluenesulfonyloxymethyl)phosphinate (*XVI*)

p-Toluenesulfonyl chloride (4.9 g, 25.7 mmol) was gradually added with cooling (0 °C) to a mixture of compound *XV* (5.81 g, 25.7 mmol), triethylamine (3 ml) and dichloromethane (20 ml). After 12 h, the separated triethylammonium chloride was filtered off and the residue was concentrated and chromatographed on silica gel in chloroform. Yield 7.0 g (72%) of *XVI*. ^{1}H NMR spectrum: 1.07 and 1.09 2 × t, 6 H, *J*(CH_2,CH_3) = 7.1 (CH_3); 1.20 t, 3 H, *J*(CH_2, CH_3) = 7.1 (CH_3); 2.43 s, 3 H (CH_3(Ts)); 3.53 and 3.55 2 × dq, 2 H, *J*(CH_2,CH_3) = 7.1, *J*(gem) = 9.5 (OCH_2); 3.72 and 3.74 2 × dq, 2 H, *J*(CH_2,CH_3) = 7.1, *J*(gem) = 9.7 (OCH_2); 4.07 br pent., 2 H, *J*(CH_2,CH_3) = 7.1, *J*(P,OCH) = 7.3 ($POCH_2$); 4.24 dd, 1 H, *J*(P,CH) = 6.3, *J*(gem) = 13.2 (PCH_2); 4.29 dd, 1 H, *J*(P,CH) = 7.1, *J*(gem) = 9.5 (PCH_2); 4.84 d, 1 H, *J*(P,CH) = 8.8 (PCH); 7.51 and 7.82 2 × d, 4 H, J = 8.3 (arom.(Ts)).

Ethyl Diethoxymethyl(methanesulfonyloxymethyl)phosphinate (*XVII*)

Methanesulfonyl chloride (2.53 g, 22.1 mmol) was added dropwise with cooling (0 °C) to a mixture of compound *XV* (5.0 g, 22.1 mmol), triethylamine (3 ml) and dichloromethane (20 ml). After 12 h, the separated triethylammonium chloride was filtered off and the residue was concentrated and chromatographed on silica gel in chloroform. Yield 5.24 g (78%) of ester *XVII* which was used in the next step. ^{1}H NMR spectrum: 1.14 and 1.16 2 × t, 6 H, *J*(CH_2,CH_3) = 7.1 (CH_3); 1.27 t, 3 H, *J*(CH_2,CH_3) = 7.1 (CH_3); 3.27 s, 3 H (SO_2CH_3); 3.80 and 3.81 2 × dq, 2 H, *J*(CH_2,CH_3) = 7.1, *J*(gem) = 9.5 (OCH_2); 3.64 and 3.65 2 × dq, 2 H, *J*(CH_2,CH_3) = 7.1, *J*(gem) = 9.5 (OCH_2); 4.16 dq, 2 H, *J*(CH_2,CH_3) = 7.1, *J*(P,CH) = 7.8 ($POCH_2$); 4.49 dd, 1 H, *J*(P,CH) = 6.1, *J*(gem) = 13.4 (PCH_2); 4.54 dd, 1 H, *J*(P,CH) = 6.8, *J*(gem) = 13.4 (PCH_2); 4.92 d, 1 H, *J*(P,CH) = 8.3 (PCH).

2-Propyl 2-Chlorethoxymethyl[bis(2-propoxy)methyl]phosphinate (*XIII*)

Trifluoroacetic acid (7 g) was added dropwise during 20 min at room temperature to a mixture of phosphorous acid (33 g, 0,5 mol) and tris(2-propyl) orthoformate[20] (285 g, 1.5 mol). A mildly exothermic reaction took place. The mixture was set aside at room temperature for 70 h under nitrogen and then concentrated in vacuo (water pump, bath temperature below 30 °C). The residue was dissolved in dichloromethane (500 ml), the solution was washed with aqueous sodium hydrogen phosphate solution (to neutral reaction) and then with a small amount of water. The organic phase was separated, dried over magnesium sulfate and the solvent was evaporated. The residue was distilled in vacuo (oil pump), fraction boiling at 105 – 110 °C /12 Pa being taken; yield 99.5 g (52%) of compound *XI*.

A mixture of compound *XI* (23.8 g, 0.1 mol) and hexamethyldisilazane (16.2 g, 0.1 mol) was heated at 120 – 130 °C for 3 h under nitrogen. After cooling, the mixture was distilled in vacuo to give 28.5 g of silylated intermediate *XII*, b.p. 85 – 95 °C/12 Pa. This product was heated with 2-chloroethyl chloromethyl ether (12.9 g, 0.1 mol) at 120 – 130 °C for 3 h. Chromatography on silica gel (200 g) in chloroform afforded 27.4 g (83%) of isopropyl ester *XIII* which was characterized by its ^{1}H NMR spectrum. ^{1}H NMR spectrum: 1.13 d, 3 H, $J(CH_3,CH)$ = 6.1 (CH_3); 1.14 d, 3 H, $J(CH_3,CH)$ = 6.1 (CH_3); 1.16 d, 6 H, $J(CH_3,CH)$ = 6.1 (2 × CH_3); 3.72 – 4.00 m, 8 H ($ClCH_2$, OCH_2, 2 × OCH, PCH_2); 4.71 dsept, 1 H, J(P,OCH) = 7.8, $J(CH,CH_3)$ = 6.1 (POCH); 4.89 d, 1 H, J(P,CH) = 8.1 (PCH). ^{13}C NMR spectrum: 22.22 s (CH_3); 22.44 s (CH_3); 22.97 s (CH_3); 23.12 s (CH_3); 24.06 s (CH_3); 24.26 s (CH_3); 46.38 s ($ClCH_2$); 64.71 d, J(C,P) = 103.8 (PCH_2); 69.81 d, J(C,P) = 6.1 (POCH); 70.88 d, J(C,P) = 9.2 (PCOCH); 71.09 d, J(C,P) = 9.2 (PCOCH); 72.73 d, J(C,P) = 10.7 (OCH_2); 96.08 d, J(C,P) = 148.0 (PCH).

2-Propyl [2-(Adenin-9-yl)ethoxy]methyl[bis(2-propoxy)methyl]phosphinate (*XIV*)

A mixture of adenine (540 mg, 4 mmol), sodium hydride (160 mg, 4 mmol) and dimethylformamide (30 ml) was heated at 90 °C for 30 min. Ester *XIII* (1.0 g, 3 mmol) was added at 60 °C and the mixture was stirred at this temperature for 72 h under exclusion of moisture. After neutralization with a drop of acetic acid, the solvent was evaporated and the product was chromatographed on silica gel (200 g) in the system S4 to yield 1.07 g (83%) of ester *XIV*. For $C_{18}H_{32}N_5O_5P$ (429.5) calculated: 50.34% C, 7.51% H, 16.31% N, 7.21% P; found: 50.14% C, 7.70% H, 16.50% N, 7.40% P. ^{1}H NMR spectrum ($CDCl_3$): 1.04 d, 3 H, $J(CH_3,CH)$ = 6.1 (CH_3); 1.09 d, 3 H, $J(CH_3,CH)$ = 6.1 (CH_3); 1.13 d, 6 H, $J(CH_3,CH)$ = 6.1 (2 × CH_3); 1.20 d, 3 H, $J(CH_3,CH)$ = 6.1 (CH_3); 1.25 d, 3 H, $J(CH_3,CH)$ = 6.1 (CH_3); 3.76 dd, 1 H, J(gem) = 13.5, J(P,CH) = 6.3 (PCH_2); 3.82 dd, 1 H, J(gem) = 13.5, J(P,CH) = 4.9 (PCH_2); 3.86 sept, 2 H, $J(CH,CH_3)$ = 6.1 (2 × OCH); 3.89 m, 2 H, (OCH_2); 4.35 m, 2 H (NCH_2); 4.70 d, 1 H, J(P,CH) = 7.6 (PCH); 4.74 m, 1 H, J(P,OCH) = 7.3, $J(CH,CH_3)$ = 6.1 (POCH); 6.35 s, 2 H (NH_2); 7.95 s, 1 H (H-base); 8.27 s, 1 H (H-base).

2-Propyl Bis(2-propoxy)methyl(hydroxymethyl)phosphinate (*XIX*)

A mixture of compound *XI* (10 g, 42 mmol), paraformaldehyde (1.5 g, 50 mmol) and triethylamine (1 ml) was stirred at 90 – 95 °C for 3 h (until the starting compound disappeared). After 30 min the paraformaldehyde dissolved. Chromatography on silica gel (150 g) in chloroform afforded 10.0 g (89%) of compound *XIX*. ^{1}H NMR spectrum: 1.12 d, 3 H, $J(CH_3,CH)$ = 6.1 (CH_3); 1.135 d, 3 H, $J(CH_3,CH)$ = 6.1 (CH_3); 1.15 d, 6 H, $J(CH_3,CH)$ = 6.1 (2 × CH_3); 1.25 d, 6 H, $J(CH_3,CH)$ = 6.1 (2 × CH_3); 3.68 2 × ddd, 2 H, J(gem) = 14.4, J(CH,OH) = 5.6, J(P,CH) = 4.5 (PCH_2); 3.96 sept, 2 H, $J(CH,CH_3)$ = 6.1 (2 × OCH); 4.68 dsept, 1 H, J(P,OCH) = 7.8, $J(CH,CH_3)$ = 6.1 (POCH); 4.89 d, 1 H, J(P,CH) = 7.6 (PCH); 5.24 dt, 1 H, J(P,OH) = 9.5, $J(CH_2,OH)$ = 5.6 (OH).

2-Propyl Bis(2-propoxy)methyl(methanesulfonyloxymethyl)phosphinate (*XVIII*)

Methanesulfonyl chloride (2.13 g, 18.6 mmol) was added dropwise with cooling (0 °C) to a mixture of compound *XIX* (5.0 g, 18.6 mmol), triethylamine (3 ml) and dichloromethane (20 ml). After 12 h, the separated triethylammonium chloride was filtered off and the residue was concentrated and chromatographed on silica gel in chloroform. Yield 5.03 g (78%) of ester *XVIII*. ^{1}H NMR spectrum: 1.14 d, 3 H, $J(CH_3,CH)$ = 6.1 (CH_3); 1.15 d, 3 H, $J(CH_3,CH)$ = 6.1 (CH_3); 1.17 d, 6 H, $J(CH_3,CH)$ = 6.1 (2 × CH_3); 1.28 d, 3 H, $J(CH_3,CH)$ = 6.1 (CH_3); 1.29 d, 3 H, $J(CH_3,CH)$ = 6.1 (CH_3); 3.26 s, 3 H (CH_3); 3.97 sept, 2 H, $J(CH,CH_3)$ = 6.1 (2 × OCH); 4.41 dd, 1 H, J(gem) = 13.2, J(P,CH) = 7.3 (PCH_2); 4.51 dd, 1 H, J(gem) = 13.2, J(P,CH) = 6.3 (PCH_2); 4.76 dsept, 1 H, J(P,OCH) = 7.8, $J(CH,CH_3)$ = 6.1 (POCH); 4.99 d, 1 H, J(P,CH) = 8.3 (PCH).

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