Tetraalkyl Oxiranylidenebis(phosphonates). Synthesis and Reactions with Nucleophiles

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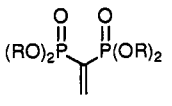
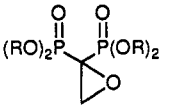
Introduction

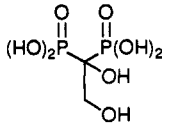
The sodium tungstate-catalyzed reaction of ethenylidenebis(phosphonic acid) (1) and of its tetraethyl ester 2 with hydrogen peroxide was reported in 1974 to give the epoxides, oxiranylidenebis(phosphonic acid) (3) and tetraethyl oxiranylidenebis(phosphonate) (4), respectively.[1] The descriptions of these reactions were not accompanied by yields or analytical data for epoxides 3 and 4. Recently, Gatrone has described his efforts to prepare epoxide 3 by the H_2O_2/Na_2WO_4 method and



1, R = -H
2, R = $-C_2H_5$
6, R = $-CH_3$



3, R = -H
4, R = $-C_2H_5$
7, R = $-CH_3$



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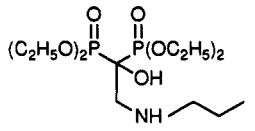
reported that he obtained the trisodium salt of 1,2-dihydroxyethylidene-1,1-bis(phosphonic acid) (5) after adjusting the pH of the reaction to between 6 and 7.[2] He further observed that at low pH, the latter compound was converted to acetylphosphonic acid and phosphoric acid.

For reasons that are unrelated to those of Gatrone, we were interested in obtaining epoxide 4 and examining its reactions with a variety of reagents. We wish to report here a convenient synthesis of epoxides such as 4 and some results from examination of the reactions of 4 with amines and with water.

Results and Discussion

The epoxidation of 2 is achieved very efficiently with the use of alkaline hydrogen peroxide. Reaction of 2[3] in 95% ethanol with 30% aqueous hydrogen peroxide and sodium bicarbonate gives a 93% yield of 4 which is sufficiently pure for use in most further applications. Distillation gives pure 4 having characteristic nuclear magnetic resonance signals at δ 3.28 in the ^1H spectrum for the epoxide protons and at δ 13.85 in the ^{31}P spectrum for the two identical phosphorus nuclei. In the same way, epoxidation of tetramethyl ethenylidene-1,1-diphosphonate (6) gives tetramethyl oxiranylidenebis(phosphonate) (7) in 87% yield.

We examined the reaction of 4 with *n*-propylamine expecting that we might obtain one or more amino alcohols in accord with the results described in the above cited patent[1] and also observed in the reactions of oxiranylidenemonophosphonates.[4] A major product (52% yield) was obtained from the reaction of 4 and *n*-propylamine, but the ^1H NMR spectrum was inconsistent with either of the two possible regioisomeric structures (8 and 9) that can be formulated from a simple epoxide opening reaction with the amine. The key to the structure of the



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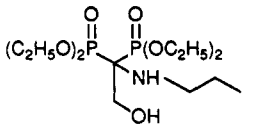

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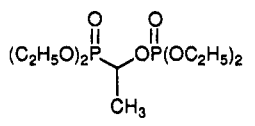
new product was the ^{31}P NMR spectrum in which signals at δ 17.75 and −2.08 (with the spectrometer referenced to trimethyl phosphite at δ 141) clearly showed that there were two different phosphorus atoms in the molecule. Since the two phosphorus atoms in structures 8 or 9 are identical, these compounds would have only one signal in their ^{31}P NMR spectra.

A report in the literature describing an NMR study of the PC(OH)P to PCHOP rearrangement[5] suggests a structure for our reaction product. The phosphinyl phosphate 10 is reported to have signals at δ 21.5 (phosphonate) and −1.7 (phosphate) in its ^{31}P NMR spectrum (referenced to H_3PO_4).[5] The similarity of these chemical shifts to those of our newly isolated product was striking. We also find that the ^1H and ^{13}C NMR data we obtain for our new compound are consistent with such a phosphinyl phosphate structure. Therefore the phosphinyl phosphate structure 11 is assigned to the product isolated for the reaction of epoxide 4 with *n*-propylamine.



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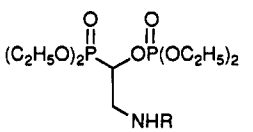

11, R = $-C_3H_7$ (*n*)

12, R = 

13, R = $-CH_2C_6H_5$

14, R =

The phosphinyl phosphates described in the literature generally are obtained from base- and/or heat-promoted rearrangement of 1-hydroxy-1,1-bisphosphonate esters, although such a rearrangement is not observed for the analogous 1-hydroxy-1,1-bisphosphonic acids.[5,6] It seems very likely that the formation of 11 is the result of a similar rearrangement either in concert with (path a) or subsequent to opening of the epoxide with amine and generation of an intermediate alkoxide ion (path b) (see Scheme I).

(1) Kirst, A. F. U.S. Patent 3,808,237, April 30, 1974; *Chem. Abstr.* **1972**, *76*, P56750s (abstract of the equivalent Ger. Offen. 2,117,876, December 2, 1971).
(2) Gatrone, R. C. *J. Org. Chem.* **1989**, *54*, 4272.
(3) Degenhardt, C. R.; Burdsall, D. C. *J. Org. Chem.* **1986**, *51*, 3488.
(4) (a) Griffin, C. E.; Kundu, S. K. *J. Org. Chem.* **1969**, *34*, 1532; (b) Gafurov, E. K.; Uyzbaev, K. M.; Kazantsev, A. V. *Izv. Akad. Nauk. Kaz. SSR, Ser. Khim.* **1979**, 55; *Chem. Abstr.* **1980**, *92*, 198466x; (c) Zygmut, J.; Walkowiak, U.; Mastalerz, P. *Pol. J. Chem.* **1980**, *54*, 233; *Chem. Abstr.* **1980**, *93*, 239526h.
(5) Fitch, S. J.; Moedritzer, K. *J. Am. Chem. Soc.* **1962**, *84*, 1876.
(6) (a) McConnell, R. L.; Coover, H. W., Jr. *J. Am. Chem. Soc.* **1956**, *78*, 4450. (b) Pudovik, A. N.; Konovalora, I. V. *Dokl. Akad. Nauk. SSSR* **1962**, *143*, 875; *Chem. Abstr.* **1962**, *57*, 3480a. (c) Pudovick, A. N.; Konovalora, I. V.; Dedova, L. V. *Dokl. Akad. Nauk SSSR* **1963**, *153*, 616; *Chem. Abstr.* **1964**, *60*, 8060a. (d) Nicholson, D. A.; Vaughn, H. *J. Org. Chem.* **1971**, *36*, 3843. (e) Tromelin, A.; El Manouni, D.; Burgada, R. *Phosphorus Sulfur* **1986**, *27*, 301. (f) Nguyen, L. M.; Niesor, E.; Bentzen, C. L. *J. Med. Chem.* **1987**, *30*, 1426. (g) Kanaan, M.; Burgada, R. *Phosphorus Sulfur* **1988**, *37*, 217.

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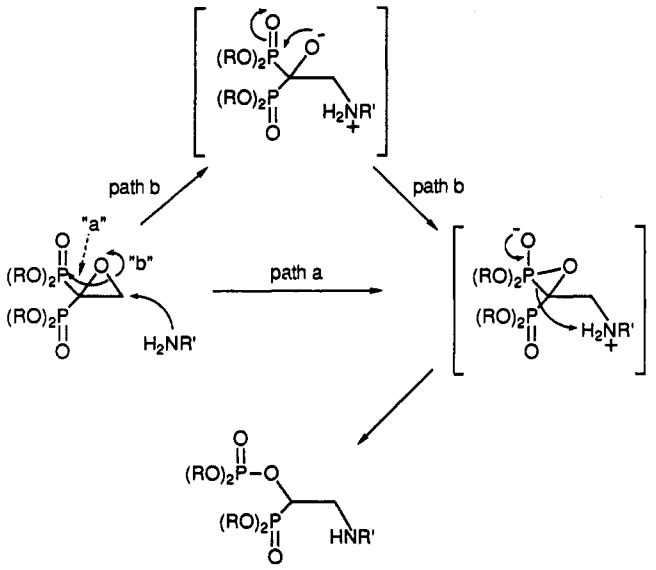
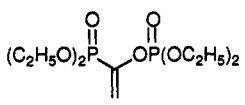
Scheme I



Several other primary amines, including cyclohexylamine, benzylamine, and allylamine, all react with 4 to give phosphinyl phosphates (see Experimental Section for products 12–14, respectively) analogous to 11. When, however, the secondary amine, di-*n*-propylamine was used



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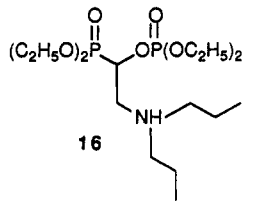

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in the reaction with 4, a second product (15, 32%) was formed in addition to the phosphinyl phosphate (16, 20%). The spectral properties of this second reaction product identify it as 15, a compound which has been previously described in the literature.[7] The formation of this compound may result from the loss, by elimination, of $(Pr)_2NH$ from the phosphinyl phosphate 16.

We have exposed epoxide 4 to hydrolytic conditions and find that the compound reacts only very slowly. The fate of 4 in aqueous solutions at different pHs was followed by ^{31}P NMR (δ 16.6 in D_2O for 4). Using conditions of pH similar to those described by Gatrone, *i.e.*, pH 2, 6, and 10, we observed at room temperature the very slow development of a new signal at δ 19.9 in all three solutions. After 19 days at room temperature the conversions to the new signal amounted to approximately 18, 12, and 7% at pH 2, 6, and 10, respectively. An additional, very small signal at δ 18.2 is seen in the pH 2 solution. We conclude that epoxide 4 reacts with water only very slowly under these conditions.

In summary, we report that 1,1-bis(phosphonate) epoxides such as 4 and 7 are conveniently prepared by base-catalyzed hydrogen peroxide epoxidation of the olefins 2 and 6. These 1,1-bis(phosphonate) epoxides react readily with amines, giving phosphonate phosphates as a consequence of a rearrangement following the epoxide opening reaction. The epoxides react very slowly with water, even under moderately acidic or alkaline conditions.

(7) Brittelli, D. R. *J. Org. Chem.* **1985**, *50*, 1845.

Experimental Section

Tetraethyl Oxiranylidenebis(phosphonate) (4). A solution of tetraethyl ethenylidene-1,1-bis(phosphonate) (2, 1.510 g, 0.0050 mol), 30% aqueous H_2O_2 (1 mL), and $NaHCO_3$ (0.424 g) in 95% EtOH (5 mL) was stirred at rt for 2 h, diluted with brine, and extracted twice with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give 4 as a clear, colorless oil (1.472 g, 0.00465 mol, 93%): IR (neat) 1260, 1026, 1023, 978 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.28–4.19 (m, 8H, OCH_2), 3.28 (t, 2H, J = 6.0 Hz, CH_2O), 1.37 (t, 12H, J = 7.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 63.4 (OCH_2), 49.3 (epoxide CH_2), 47.2 (t, J_{P-C} = 182 Hz, P–C–P), 16.1 (CH_3); ^{31}P NMR ($CDCl_3$) δ 13.85; mass spectrum, found 316.0840 m/z, $C_{10}H_{22}O_7P_2$ requires 316.0841. A sample of the oil was distilled, bp 121–123 °C (0.07 mmHg). Anal. Calcd for $C_{10}H_{22}O_7P_2$: C, 37.98; H, 7.01; P, 19.59. Found: C, 37.60; H, 7.14; P, 19.44.

Tetramethyl Oxiranylidenebis(phosphonate) (7). A solution of tetramethyl ethenylidene-1,1-bis(phosphonate) (6, 7.702 g, 0.0315 mol), 30% aqueous H_2O_2 (6.6 mL), and $NaHCO_3$ (2.8 g) in 95% EtOH (32 mL) was stirred overnight at rt. The solution was diluted with water and extracted three times with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give 7 as a colorless oil (7.153 g, 0.027 mol, 87%): ^1H NMR ($CDCl_3$) δ 3.91–3.86 (m, 12H, CH_3), 3.29 (5-line signal, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ 53.9–53.8 (m, CH_3), 49.2, 47.1 (t, J = 182.2 Hz, P–O–P); ^{31}P NMR ($CDCl_3$) δ 15.86. A sample of the oil was distilled, bp 123–124 °C (0.07 mmHg). Anal. Calcd for $C_6H_{14}O_7P_2$: C, 27.70; H, 5.43; P, 23.81. Found: C, 27.40; H, 5.69; P, 23.63.

Phosphoric Acid, 1-(Diethoxyphosphinyl)-2-(*n*-propylamino)ethyl Diethyl Ester (11). A solution of 4 (10.016 g. 0.0316 mol) in *n*-propylamine (18.70 g, 26 mL, 0.31 mol) was prepared. Evolution of heat was observed upon preparation of the solution, and the reaction flask was cooled in a cold water bath. The solution was stirred for 20 h, brine was added, and the mixture was extracted with ether (4x). The combined extracts were dried ($MgSO_4$) and concentrated to give a clear yellow oil (8.041 g). Part (1.572 g) of the oil was chromatographed (silica gel, low pressure column, 5% methanol in acetone) to give 11 (1.236 g, 78% recovery, 52% yield) as a clear colorless oil: ^1H NMR ($CDCl_3$, TMS) δ 4.83–4.73 (m, 1H, PC*H*OP), 4.26–4.13 (m, 8H, CH_2), 3.09 (dd, 2H, J = 6.0, 9.0 Hz, NHCH_2CH(P)OP), 2.71–2.49 (m, 2H, EtCH_2NH), 1.50 (sextet, 2H, J = 7.2 Hz, CH_3CH_2-CH_2NH), 1.36 (two t, 12H, J = 7.0 Hz, OCH_2CH_3), 0.92 (t, 3H, J = 7.3 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 72.0 (dd, J_{C-P} = 167 Hz, J_{C-O-P} = 7 Hz, PCHOP), 64.0 (t, J_{C-O-P} = 6.4 Hz, $CH_2OP(O)$), 62.7 (t, J_{C-O-P} = 7.4 Hz, $CH_2OP(O)$), 50.8 ($NHCH_2Et$), 49.6 ($OCHCH_2NH$), 22.9 ($NHCH_2CH_2CH_3$), 16.2 ($P(O)OCH_2CH_3$), 15.8 ($P(O)OCH_2CH_3$), 11.5 (CH_3); ^{31}P NMR ($CDCl_3$) δ 17.75 (d, J_{POP} = 25 Hz, [$(EtO)_2P(O)CH$]), −2.08 (d, J_{POP} = 23 Hz, [$(EtO)_2P(O)O$]); mass spectrum, found 346.1184, $C_{11}H_{26}NO_7P_2$ requires 346.1188, 330, 317.

Phosphoric Acid, 2-(Cyclohexylamino)-1-(diethoxyphosphinyl)ethyl Diethyl Ester (12). Using the procedure described for preparation of 11, cyclohexylamine (3.6 mL, 3.14 g, 0.0316 mol) and 4 (2.066 g, 0.00632 mol) in ether (3 mL) were stirred at rt for 24 h after which more cyclohexylamine (2.601 g, 0.026 mol) was added. Following workup, 3.233 g of crude product was obtained. Flash chromatography (400 g silica gel, 40-mL fractions) of the crude product with increasing proportions (from 0 to 10%) of 10% NH_4OH/methanol in acetonitrile gave the desired product (12, 1.046 g, 0.00251 mol, 40%) in fractions 102–147 as a colorless oil: ^1H NMR ($CDCl_3$, TMS) δ 4.80–4.70 (m 1H, PC*H*OP), 4.26–4.13 (m, 8H, OCH_2CH_3), 3.21–3.00 (m, 2H, CH_2-NH-cyclohexyl), 2.52–2.45 (m, 1H, NHC*H*-c-C_5H_{10}), 1.89–1.59 (m, 5H, equatorial ring protons), 1.38–1.02 (m, 17H, OCH_2CH_3, axial ring protons); ^{13}C NMR ($CDCl_3$) δ 72.4 (dd, J_{C-P} = 167.0 Hz, J_{COP} = 7.6 Hz, PCHOP), 64.1 (m, $P(O)OCH_2CH_3$), 62.8 (m, $P(O)OCH_2CH_3$), 55.6 (ring C*H*NH), 46.5 (CH_2NH), 33.1, 32.7, 25.8, 24.6, 24.5, 16.3–15.8 (m, OCH_2CH_3); ^{31}P NMR ($CDCl_3$) δ 17.61 (d, J = 22.5 Hz, P(O)CH), −1.89 (d, J = 24 Hz, P(O)O); mass spectrum, found 416.1968, $C_{16}H_{35}NO_7P_2$ requires 416.1967. Anal. Calcd for $C_{16}H_{35}NO_7P_2$: C, 46.26; H, 8.49; N, 3.37. Found: C, 45.96; H, 8.58; N, 3.59.

Phosphoric Acid, 2-(Benzylamino)-1-(diethyoxyphosphinyl)ethyl Diethyl Ester (13). A mixture of 4 (2.085 g, 0.00632 mol) and benzylamine (3.40 g, 0.0316 mol) in ether (4 mL) was stirred at rt for 18 h after which TLC (50% EtOAc in methanol, 50% acetone in hexane) indicated that some epoxide remained unreacted. Additional benzylamine (2.94 g, 0.0274 mol) was added and stirring continued another 24 h. Volatiles were removed *in vacuo* and the residue was chromatographed (flash, 400 g silica gel, 45 mL fractions) using 2.5–5% of 10% NH_4OH/CH_3OH in methylene chloride to elute the column. The desired product eluted in fractions 94–104 which were pooled to give 13 (1.069 g, 0.00253 mol, 40%) as a colorless oil: ^{1}H NMR ($CDCl_3$, TMS) δ 7.34–7.23 (m, 5H, ArH), 4.87–4.77 (m, 1H, P(O)-C*H*OP(O)), 4.24–4.07 (m, 8H, O*CH*$_2$CH$_3$), 3.88 (d, 1H, J = 13.2 Hz, C*H*$_2$Ar), 3.78 (d, 1H, J = 13.2 Hz, C*H*$_2$Ar), 3.14–3.09 (m, 2H, C*H*$_2$NHCH$_2$Ar), 1.36–1.24 (m, 12H, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 139.8, 128.3, 128.1, 126.9, 72.2 (d, J_{C-P} = 160.4 Hz, P(O)*C*HO-P(O)), 64.2 (m, O*CH*$_2$CH$_3$), 62.9 (m, O*CH*$_2$CH$_3$), 53.1 (*C*H$_2$Ar), 49.2 (CH*C*H$_2$NH), 16.5–16.0 (m, OCH$_2$*C*H$_3$); ^{31}P NMR ($CDCl_3$) δ 17.55 (d, J_{C-P} = 24.5 Hz, *P*(O)CHOP), –1.90 (d, J = 24.4 Hz, P(O)CHO*P*(O)); mass spectrum, found 424.1655, $C_{17}H_{31}NO_7P_2$ requires 424.1654.

Phosphoric Acid, 1-(Diethoxyphosphinyl)-2-(2-propen-1-ylamino)ethyl Diethyl Ester (14). A solution of allylamine (2.855 g, 0.05 mol) and 4 (3.00 g, 0.0095 mol) in methanol (20 mL) was cooled to 0–5 °C by means of an ice–water bath. The mixture was stirred while the low temperature bath came to rt and then stirring was continued overnight at rt. TLC (10% of a 10% NH_3/CH_3OH solution in CH_2Cl_2) indicated that starting material was consumed. The solvent and excess of allylamine were removed *in vacuo* to give 3.621 g of crude material from which 1.025 g was chromatographed (flash, 160 g, 0.0403–0.063 mm silica gel, 4 cm wide, 20–30% acetone in CH_2Cl_2) to give 14 (0.635 g, 63% overall yield) as a clear oil: ^{1}H NMR ($CDCl_3$) δ 5.87 (ddt, 1H, J = 5.9, 10.3, 17.2 Hz, C*H*=CH$_2$), 5.19 (dd, 1H, J = 1.7, 17.2 Hz, CH=C*H*$_2$(trans)), 5.09 (dd, J = 1.5, 10.2 Hz, CH=C*H*$_2$(cis)), 4.83–4.72 (m, 1H, P(O)CHOP(O)), 4.26–4.12 (m, 8H, CH$_2$OP-(O)), 3.34 (ddt, 1H, J = 1.4, 5.8, 14.0 Hz, CH$_2$=CHC*H*$_2$), 3.24 (ddt, J = 1.4, 5.9, 14.1 Hz, CH$_2$=CHC*H*$_2$), 3.12–3.07 (m, 2H, CHC*H*$_2$N), 1.38–1.32 (m, 12H, C*H*$_3$CH$_2$OP(O)); ^{13}C NMR ($CDCl_3$) δ 136.2 (CH$_2$=*C*H), 116.0 (*C*H$_2$=CH), 72.2 (dd, J_{PC} = 167.3 Hz, J_{POC} = 7.5 Hz, P(O)CHOP(O)), 64.2–64.0 (m, CH$_2$OP(O)), 62.9–62.5(m, CH$_2$OP(O)), 51.4 (CH$_2$=CH*C*H$_2$), 49.0 (CH*C*H$_2$N), 16.4–15.9 (*C*H$_3$CH$_2$OP(O)); ^{31}P NMR ($CDCl_3$) δ 17.30 (d, J_{PCOP} = 24.1 Hz, *P*(O)CHOP(O)), –2.04 (d, J_{PCOP} = 24.1 Hz, P(O)CHO*P*(O)). Anal. Calcd for $C_{13}H_{29}NO_7P_2$: C, 41.82; H, 7.83; N, 3.75. Found: C, 42.14; H, 7.84; N, 3.58.

Phosphoric Acid, 1-(Diethoxyphosphinyl)ethenyl Diethyl Ester (15) and Phosphoric Acid, 1-(Diethoxyphosphinyl)-2-(di-*n*-propylamino)ethyl Diethyl Ester (16). A mixture of 4 (1.014 g, 0.0033 mol) and di-*n*-propylamine (2.952 g, 0.029 mol) was stirred at rt for 18 h. Ether, saturated aqueous $NaHCO_3$ (0.5 mL), and brine were added to the reaction mixture. The layers were separated, and the aqueous phase was extracted further with ether (3x). The combined extracts were dried ($MgSO_4$) and concentrated to give 0.739 g of crude product. This material was chromatographed (flash, silica gel, 25–50% acetone in hexane) with compound 16 (0.278 g, 0.000666 mol, 20%) eluting first followed by compound 15 (0.336 g, 0.00106 mol, 32%). Analytical data for 16: ^{1}H NMR ($CDCl_3$, TMS) δ 4.82–4.71 (m, 1H, P(O)C*H*OP(O)), 4.25–4.12 (m, 8H, O*CH*$_2$CH$_3$), 2.89 (m, 2H, CHC*H*$_2$N), 2.55–2.37 (m, 4H, N(C*H*$_2$Et)$_2$), 1.46 (sextet, 4H, J = 7.2 Hz, CH$_2$C*H*$_2$CH$_3$), 1.37–1.29 (m, 12H, OCH$_2$C*H*$_3$), 0.86 (t, 3H, J = 7.3 Hz, –CH$_3$); ^{13}C NMR ($CDCl_3$) δ 71.9 (d, J_{C-P} = 117 Hz, P(O)*C*HOP(O)), 63.8 (d, J_{COP} = 5.5 Hz, O*CH*$_2$CH$_3$), 62.7 (d, J_{COP} = 6.2 Hz, O*CH*$_2$CH$_3$), 56.1 (N(*C*H$_2$Et)$_2$), 55.2 (CH$_2$N), 19.6 (CH$_2$*C*H$_2$CH$_3$), 16.4–16.0 (m, OCH$_2$*C*H$_3$), 11.8 (CH$_3$); ^{31}P NMR ($CDCl_3$) δ 18.83 (d, J = 18.3, *P*(O)CHOP(O)), –2.39 (P(O)-CHO*P*(O)); mass spectrum, 417.2022 m/z, $C_{16}H_{37}NO_7P_2$ requires 417.2045. Analytical data for 15: ^{1}H NMR ($CDCl_3$, TMS) δ 5.94–5.78 (m, 2H, =CH$_2$), 4.26–4.11 (m, 8H, O*CH*$_2$CH$_3$), 1.40–1.31 (m, 12H, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 145.6 (d, J = 286.8 Hz, P(O)*C*OP(O)), 114.5 (d, J = 20.6 Hz, =CH$_2$), 64.6 (d, J = 6.2 Hz, O*CH*$_2$CH$_3$), 62.9 (d, J = 5.1 Hz, O*CH*$_2$CH$_3$), 16.1–15.7 (m, OCH$_2$*C*H$_3$); ^{31}P NMR ($CDCl_3$) δ 5.81 (d, J = 27.5 Hz, *P*(O)COP-(O)), –7.85 (d, J = 27.5 Hz, P(O)CO*P*(O)); mass spectrum, found 316.0841 m/z, $C_{10}H_{22}O_7P_2$ requires 316.0844.