REVERSIBLE NATURE OF THE OPENING OF THE TETRAHYDROFURAN RING OF DIPHENYL(2-TETRAHYDROFURYLMETHYL)PHOSPHINE OXIDE BY THE DIPHENYLPHOSPHINITE ANION

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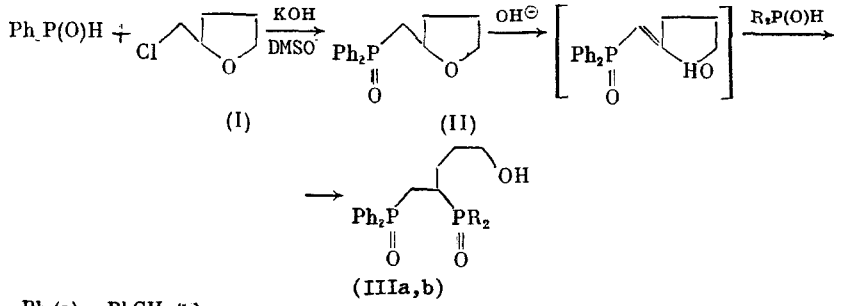
The reaction of diphenyl(2-tetrahydrofurylmethyl)phosphine oxide with diphenylphosphonous acid in DMSO in the presence of KOH proceeds with opening of the tetrahydrofuran ring and leads to 4,5-bis(diphenylphosphinyl)pentanol. This product is converted to the starting oxide upon the reaction with diphenylvinylphosphine oxide. 4,5-Bis(diphenylphosphinyl)pentanol is converted to the corresponding tosylate. The action of alcoholates on this tosylate gives 1-ethoxy-4,5-bis(diphenylphosphinyl)pentane and 1-butoxy-1,5-bis(diphenylphosphinyl)pentane.

In previous work [1], we showed that the reaction of diphenylphosphonous acid with 2-chloromethyltetrahydrofuran (I) in DMSO in the presence of 45% KOH gives 4,5-bis(diphenylphosphinyl)pentanol (IIIa) in high yield, apparently through phosphine oxide (II). In a further study of this reaction, evidence was found for the hypothesis that the reaction proceeds through the formation of diphenyl(2-tetrahydrofurylmethyl)phosphine oxide (II). Oxide (II) may be obtained upon the use of a 5-7-fold excess of chloride (I) relative to $Ph_2P(O)H$. Dioxide (IIIa) is the major product in the case of lower ratios.



R = Ph (a), $PhCH_2$ (b).

The reaction of phosphine oxide (II) with diphenyl- and dibenzylphosphonous acids in DMSO in the presence of 45% KOH with an equimolar reagent ratio leads to the anionic opening of the tetrahydrofuran ring and gives dioxides (IIIa) and (IIIb). We should note that the reaction of 2-chloromethyltetrahydrofuran with two equivalents of $(PhCH_2)_2P(O)H$ leads to a complex product mixture.

The formation of alcohol (IIIa) is reversible in nature, which is found upon its reaction with compounds capable of binding the diphenylphosphinite anion. Thus, the formation of tetraphenylethylenediphosphine dioxide (V) and oxide (II) is observed in the reaction of alcohol (IIIa) with diphenylvinylphosphine oxide in absolute dioxane in the presence of EtONa instead of the expected addition reaction leading to podand (IV).

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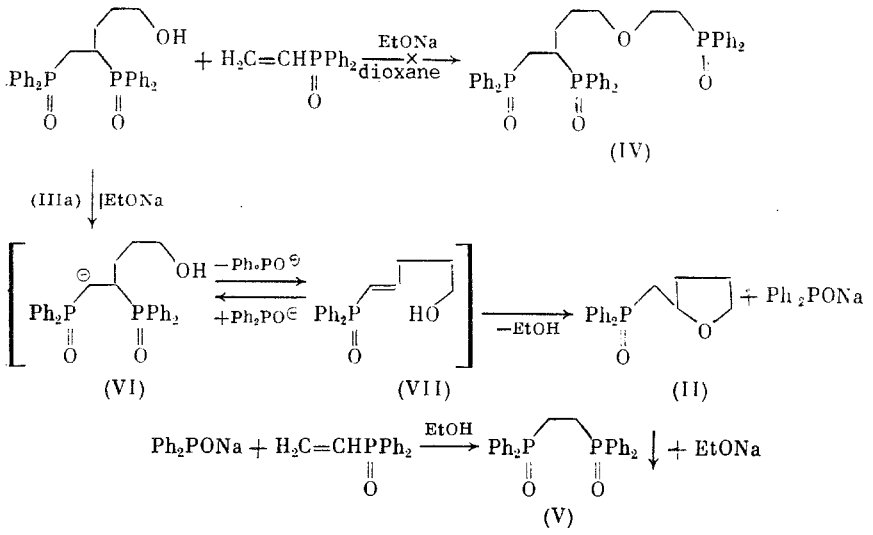
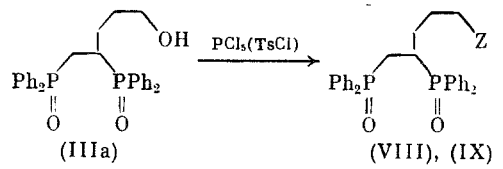
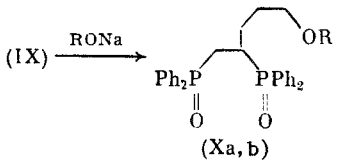


This reaction probably proceeds through carbanion (VI), which is stabilized due to the loss of a diphenylphosphinite anion to give the corresponding vinyl derivative (VII), which then cyclizes to oxide (II). The exiting diphenylphosphinite anion is irreversibly bound by diphenylvinylphosphine oxide with the formation of insoluble dioxide (V).

Pentanol (IIIa) was used for the synthesis of new potential dioxide complexing agents. The action of PCl_5 or toluenesulfonyl chloride on pentanol (IIIa) leads to chloride (VIII) or tosylate (IX). The reaction of (IX) with alcoholates led to the corresponding esters (Xa) and (Xb).



Z = Cl (VIII), OTs (IX).



R = Et (a), Bu (b)

A characteristic feature of (IIIa), (IIIb), (Xa), and (Xb) is their capacity to form stable solvates with several organic solvents.

EXPERIMENTAL

The reactions with the phosphonous acids were carried out in a dry argon atmosphere. Products (II), (IIIb), (Xa), and (Xb) were separated on a column packed with L100-160μ silica gel using chloroform or 1-5% ethanol/chloroform as the eluent. The thin-layer chromatography was carried out on Silufol UV-254 plates using 20:1 chloroform-ethanol and 1:1 chloroform-acetone as the eluent. The melting points were determined on a Boetius PHMK 05 instrument.

The ^1H and ^{31}P NMR spectra were taken on a Bruker CXP-200 spectrometer in $CDCl_3$ with TMS as the internal standard and 85% H_3PO_4 as the external standard. Downfield shifts were considered positive.

Diphenyl(2-tetrahydrofurylmethyl)phosphine Oxide (II). A sample of 4.0 ml 45% KOH was added to a mixture of 8.1 g $Ph_2P(O)H$ and 24.1 g chloride (I) [2] in 45 ml DMSO, stirred for 2 h at 60°C, cooled to 20°C, diluted with 45 ml water, and extracted with three 40-ml portions of chloroform. The organic layer was dried over $MgSO_4$. The solvent was removed in vacuum and the residue was separated chromatographically to give 6.5 g (56%) oxide (II), mp 140-

141°C (toluene). PMR spectrum (δ, ppm): 1.6-2.1 m (4H), 2.65 m (2H), 3.72 m (2H), 4.2 m (1H), 7.2-7.8 m (1H, OH). ^{31}P NMR spectrum: δ 29.4 ppm. Found: C, 70.9; H, 6.4; P, 11.0%. Calculated for $C_{17}H_{19}O_2P$: C, 71.3; H, 6.6; P, 10.8%.

4,5-Bis(diphenylphosphinyl)pentanol (IIIa). A sample of 2.1 g oxide (II) in 6 ml DMSO was added to a mixture of 1.5 g $Ph_2P(O)H$ and 0.7 ml 45% KOH in 7 ml DMSO and stirred for 1.5 h at 60°C, cooled, diluted with 20 ml water, and extracted with four 8-ml portions of chloroform. The extract was washed with three 10-ml portions of water. The organic layer was separated and dried over $MgSO_4$. The solvent was removed in vacuum to give 3.4 g (94%) dioxide (IIIa) as an oil. The dioxide was identified as the solvate with toluene, mp 120-122°C [1].

4-Dibenzylphosphinyl-5-diphenylphosphinylpentanol (IIIb). A sample of 1.3 ml 45% KOH was added dropwise to a mixture of 3.4 g (II) and 3.2 g $(PhCH_2)_2P(O)H$ in 13 ml DMSO and stirred for 5 h at 60°C, cooled to about 20°C, diluted with 15 ml water, and extracted with four 10-ml portions of chloroform. Chromatography of the extract gave 0.5 g (18%) starting oxide (II) and 1.38 g (22%) dioxide (IIIb) as a colorless glassy mass. PMR spectrum (δ, ppm): 1.4-2.3 m (7H), 2.5-3.3 m (6H), 3.4 m (2H, CH_2OH), 4.6 s (1H, OH), 7.1-7.8 m (20H). ^{31}P NMR spectrum: δP^1 = 33.5, δP^2 = 48.4 ppm, $J_{P^1P^2}$ = 39 Hz. Found: C, 72.2; H, 7.0; P, 12.2%. Calculated for $C_{31}H_{34}O_3P_2$: C, 72.1; H, 6.6; P, 12.0%. Treating (IIIb) with toluene gave a solvate 2(IIIb)·$C_6H_5CH_3$, mp 147-148°C. Found: C, 73.6; H, 6.6; P, 11.1%. Calculated for $C_{69}H_{75}O_6P_4$: C, 73.8; H, 6.7; P, 11.0%.

Reaction of Diphosphine Dioxide (IIIa) with Diphenylvinylphosphine Oxide.* A mixture of 7.0 g (IIIa), 3.2 g diphenylvinylphosphine oxide, and 0.1 g EtONA in 70 ml abs. dioxane was heated at reflux for 5 h and left overnight. The precipitate formed was filtered off and recrystallized from ethanol to give 2.7 g (44%) tetraphenylethylenediphosphine dioxide, mp 266-267°C [4], identified by ^1H and ^{31}P NMR spectroscopy. Dioxane was removed in vacuum and the residue was chromatographed to give 1.38 g (38%) phosphine oxide (II), mp 140-141°C, identified by ^1H and ^{19}F NMR spectroscopy.

1-Chloro-4,5-bis(diphenylphosphinyl)pentane (VIII). A sample of 5.8 g dioxide (IIIa) in 30 ml abs. chloroform was added to 2.5 g ground PCl_5 in 20 ml abs. chloroform at 20°C, stirred for 20 min at 20°C, washed with three 20-ml portions of water, 15 ml saturated aq. sodium carbonate, and three 10-ml portions of water, and dried over $MgSO_4$. The solvent was removed in vacuum and the residue was recrystallized from benzene to give 4.5 g (60%) dioxide (VIII), mp 168-170°C. PMR spectrum (δ, ppm): 1.7 m (2H), 1.9 m (2H), 2.7 m (2H), 3.1 m (3H, CH_2C + CHP), 7.2-7.8 m (20H). ^{31}P NMR spectrum: δP^1 = 37.3, δP^2 = 31.1 ppm, $J_{P^1P^2}$ = 48.8 Hz. Found: C, 69.0; H, 5.7; Cl, 6.8; P, 12.5%. Calculated for $C_{29}H_{29}ClO_2P_2$: C, 68.9; H, 5.7; Cl, 6.8; P, 12.3%.

4,5-Bis(diphenylphosphinyl)pentanol Tosylate (IX). A sample of 18.9 g *p*-toluenesulfonyl chloride was added to a mixture of 32.0 g dioxide (IIIa) and 26 ml pyridine in 120 ml chloroform at 0°C and stirred for 2 h at 0-5°C and then for 5 h at 20°C. The solvent was removed in vacuum and the residue was treated with 120 ml hot 1:1 water-ethanol. The oily layer was removed, dried in vacuum, and crystallized from ethanol to give 27.6 g (72%) (IX), mp 183-184°C. PMR spectrum (δ, ppm): 1.5 m (2H), 1.9 m (2H), 2.4 s (3H), 2.6 m (1H), 2.9 m (1H), 3.6 m (2H), 7.2-7.8 m (24H). ^{31}P NMR spectrum: δP^1 = 36.6, δP^2 = 30.0 ppm, $J_{P^1P^2}$ = 46.6 Hz. Found: C, 66.9; H, 5.7; P, 9.9; S, 5.2%. Calculated for $C_{36}H_{36}O_5P_2$: C, 67.3; H, 5.6; P, 9.6; S, 5.0%.

1-Ethoxy-4,5-bis(diphenylphosphinyl)pentane (Xa). A mixture of 6.7 g tosylate (IX) and a solution of EtONa, obtained from 0.45 g sodium and 50 ml abs. ethanol, was stirred for 4 h at reflux, and left overnight. Ethanol was removed in vacuum. The residue was dissolved in 12 ml chloroform and washed with three 4-ml portions of water. Chromatography gave 2.8 g (52%) (Xa) as a glassy mass. PMR spectrum (δ, ppm): 1.05 t (3H), 1.3-1.8 m (5H), 2.6 m (2H), 2.9-3.4 m (4H), 7.2-7.8 m (20H). ^{31}P NMR spectrum: δP^1 = 37.8, δP^2 = 31.0 ppm, $J_{P^1P^2}$ = 46.6 Hz. Found: C, 72.6; H, 6.7; P, 12.0%. Crystallization from heptane gave a solvate 2(Xa)·C_7H_{16}, mp 146-147°C. Found: C, 72.9; H, 7.2; P, 10.9%. Calculated for $C_{69}H_{84}O_6P_4$: C, 73.1; H, 7.4; P, 11.0%.

1-Butoxy-4,5-bis(diphenylphosphinyl)pentane (Xb). A solution of BuONa obtained from 0.22 g sodium in 5 ml absolute butanol was evaporated in vacuum and a solution of 6.0 g tosy-

*Diphenylvinylphosphine oxide was prepared from diphenyl-2-hydroxyethylphosphine oxide [3]. The authors express their gratitude to N. A. Bondarenko for supplying these compounds.

late (IX) in 18 ml abs. DMF was added to the residue and stirred for 4 h at 100°C, cooled to about 20°C, diluted with 20 ml water, and extracted with three 20-ml portions of chloroform. The extract was washed with three 15-ml portions of water, dried over $MgSO_4$, and purified by chromatography to give 2.1 g (41%) (Xb) as a colorless glassy mass. PMR spectrum (δ, ppm): 1.0 t (3H), 1.3-1.8 m (7H), 2.6 m (2H), 2.9-3.2 m (6H), 7.2-7.8 m (20H). ^{31}P NMR spectrum: $\delta P^1 = 37.2$, $\delta P^2 = 30.6$ ppm, $J_{P^1P^2} = 46.6$ Hz. Found: C, 72.4; H, 6.7; P, 11.7%. Calculated for $C_{33}H_{38}O_3P_2$: C, 72.8; H, 7.0; P, 11.4%. Crystallization from heptane gave a solvate $2(Xb)\cdot C_7H_{16}$, mp 123-125°C. Found: C, 73.4; H, 7.7; P, 10.2%. Calculated for $C_{73}H_{92}O_6P_4$: C, 73.7; H, 7.7; P, 10.4%.

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CHOLINE ESTERS OF ALKYLENEBISPHOSPHONIC ACIDS

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The reaction of the acid chlorides of alkylenebisphosphonic acids with ethylene glycol and ethylene chlorohydrin gave ethylene glycol and β-chloroethyl esters of alkylenebisphosphonic acids. The quaternization of these products leads to choline esters of alkylenebisphosphonic acids.

There has been considerable attention in the synthesis and properties of various biologically active phosphonic acid derivatives since the 1960's [1]. The presence of a hydrolytically stable P–C bond not subject to enzymatic cleavage [2] permits the preparation of long-action drugs based on these phosphonates.

In the present work, we synthesized choline esters of alkylenebisphosphonic acids, which may serve as models for products of the metabolism of biological membranes and as new drugs.

The key compounds for the synthesis of the desired products were acid chloride derivatives of alkylenebisphosphonic acids (ABPA AC) obtained according to the following scheme

$$PCl_3 + ROH \longrightarrow HP(O)(OR)_2 \xrightarrow{Na} NaP(O)(OR)_2 \xrightarrow[n=4,6,10]{Br_2(CH_2)_n} (RO)_2P(O)(CH_2)_nP(O)(OR)_2 \xrightarrow{HCl}$$
$$\longrightarrow (HO)_2P(O)(CH_2)_nP(O)(OH)_2 \xrightarrow{PCl_5} Cl_2P(O)(CH_2)_nP(O)Cl_2$$

The optimum method for the synthesis of ABPA AC is treatment of equivalent amounts of the corresponding ABPA and their tetraalkyl esters with PCl_5. The yield of ABPA AC is 70-80% [3].

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