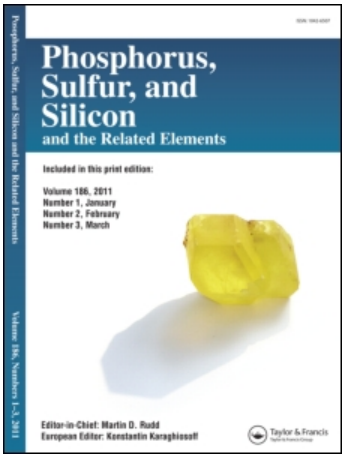

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NEW SYNTHESES OF SUBSTITUTED 1,2-DIHYDROXY-1,2-BISPHOSPHONYLETHANES

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NEW SYNTHESES OF SUBSTITUTED 1,2-DIHYDROXY-1,2-BISPHOSPHONYLETHANES

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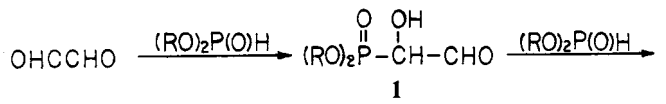
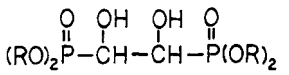
Substituted 1,2-dihydroxy-1,2-bisphosphonylethanes were synthesized by reacting glyoxal with phosphorous acid triesters. The intermediate adduct resulting from a nucleophilic attack of phosphorus on the carbonyl carbon was protonated and dealkylated by a third reagent such as methanol or hydrogen chloride. Evidence for the reaction mechanism was obtained by isolation and identification of dimethylether evolved as a byproduct from the reaction of glyoxal with trimethyl phosphite in the presence of methanol. The yield of substituted 1,2-dihydroxy-1,2-bisphosphonylethanes thus prepared was significantly higher than that of the previously reported reactions of glyoxal with phosphorous acid diesters. In addition, substituted 1,2-dihydroxy-1,2-bisphosphonylethanes were prepared by reacting 2-hydroxy-2-phosphonylethanals with phosphorous acid triesters.

INTRODUCTION

The synthesis of various substituted 1,2-dihydroxy-1,2-bisphosphonylethanes (**2**) by reacting glyoxal with phosphorous acid diesters was recently reported.[1]



1



2

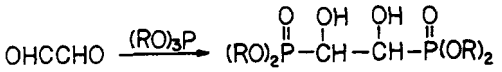
Intermediate 2-hydroxy-2-phosphonylethanals (**1**) were obtained as viscous undistillable liquids which could not be induced to crystallize.[1] The formation of **1** was proven both spectroscopically as well as by the fact that they reacted with urea to yield the corresponding 4-hydroxy-5-phosphonyl-2-imidazolidinones[2] (**3**).

1 **3**

In addition, the reactions of glyoxal with primary[3] as well as with secondary phosphine oxides[4] have been investigated.

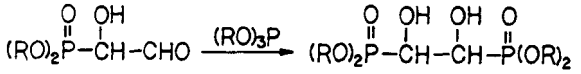
Compounds **2** can be used as starting materials for preparing fire-resistant polymers like polyurethanes[5] and polyesters. Moreover, 1,2-dihydroxy-1,2-bis(dihydroxyphosphonyl)ethane,[1] $(HO)_2P(O)CH(OH)CH(OH)P(O)(OH)_2$, a useful complexing agent,[6] was prepared by acid catalyzed hydrolysis of **2**. Synthesis of compounds **2** is, therefore, of interest not only from the theoretical point of view but also because of their potential applications. It should be noted that the reactions of glyoxal with phosphorous acid diesters gave compounds **2** in relatively low yields (2.3–13.4%).

In an effort to improve the yield of **2** the following reactions of phosphorous acid triesters with glyoxal or 2-hydroxy-2-phosphonylethanals (**1**) were investigated:



2

2a : R=Me
2b : R=Et
2c : R=Ph



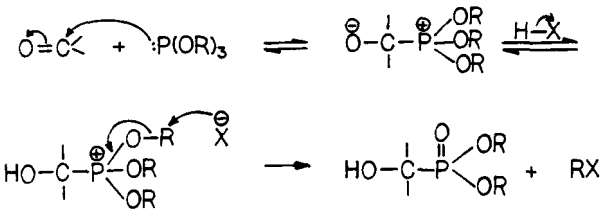
1 **2**

1b , 2b: R=Et
1d , 2d R=n-Bu

Ramirez *et al.*[7] studied the reaction of trimethyl phosphite with glyoxal in an aprotic solvent. 2,2,2-Trimethoxy-2,2-dihydro-1,3,2-dioxaphospholene was formed from a nucleophilic attack of phosphorus on the carbonyl oxygen. This cyclic unsaturated pentaoxyphosphorane was transformed into dimethyl 2-oxoethyl phosphate by anhydrous HCl and into a series α-hydroxy β-keto aldehyde phosphates by carboxilic acid chlorides.

RESULTS AND DISCUSSION

Synthesis of **2** proceeds via a nucleophilic attack of the phosphorus atom of $(RO)_2P(O)H$[1] or $(RO)_3P$ on the carbonyl carbon of glyoxal. Since dialkyl phosphites show little or none of the nucleophilic reactivity of trialkyl phosphites[8a] the latter are more promising for preparing **2**. Trialkyl phosphites, however, do not form stable adducts with simple carbonyl compounds.[8b] In contrast to the low reactivity of trialkyl phosphites with carbonyl compounds under normal conditions, it is possible to obtain compounds **2** by the intervention of a third reagent, HX, such as hydrogen halide and alcohol.



Obtaining compounds **2** would require a nucleophilic addition of $(RO)_3P$ to both carbonyls of glyoxal. The second addition is expected to be slower than the first one because of the presence of the vicinal electron-withdrawing carbonyl group.

The reaction was carried out employing monomeric glyoxal or glyoxal trimer dihydrate, which releases glyoxal *in situ*,[9] or vacuum condensed aqueous glyoxal solution. Water originating from glyoxal trimer dihydrate as well as from the aqueous solution of glyoxal should be azeotropically removed before $(RO)_3P$ addition to avoid hydrolysis of phosphites and phosphonates. The present investigation was extended so as to include the synthesis of **2** by reacting $(RO)_3P$ with 2-hydroxy-2-phosphonylethanals (**1**). The latter were prepared from the reactions of glyoxal with phosphorous acid diesters.[1]

Synthesis of **2** cannot be achieved without involvement of a third reagent H—X. In the reaction of glyoxal–$(MeO)_3P$, methanol was the third reagent most preferred and it was used as solvent. An exothermic reaction was observed when $(MeO)_3P$ was added to a methanolic solution of glyoxal. A number of reaction conditions were tested aiming in promoting the reaction producing **2**. It should be emphasized that the reaction glyoxal–$(MeO)_3P$ in the presence of methanol gave **2a** in a considerably higher yield than the reaction glyoxal–$(MeO)_2P(O)H$. Specifically, the former reaction gave yields of 30.4 and 12.3% utilizing glyoxal trimer dihydrate and aqueous glyoxal solution, respectively, whereas the latter reaction[1] gave a yield of only 4.0%. The incomplete azeotropic removal of water from the mixture should be responsible for the relatively low yield obtained from the reaction of aqueous solution of glyoxal.

Evidence for the reaction mechanism suggested was obtained by isolation of the volatile dimethylether, a byproduct of the reaction glyoxal–$(MeO)_3P$ in the presence of methanol. A stream of argon was bubbled through the reaction mixture and it was subsequently passed through a carbon tetrachloride trap. The IR and ^{1}H-NMR spectra of carbon tetrachloride in the trap, obtained after the reaction, revealed the presence of MeOMe dissolved in CCl_4. Specifically, the IR spectrum showed the following absorption bands associated with dimethylether:[10] 3000, 2900, 2840, 1450, 1170, 1100 and 930 cm^{-1}. In addition, the ^{1}H-NMR spectrum showed a singlet peak at 3.30 δ assigned to the methyl protons.[11]

The reaction of glyoxal with $(EtO)_3P$ is examined next. Kabachnik[12] has suggested the following reactivity series for some alkoxy substituted trivalent phosphorus compounds which act as nucleophiles:

$$MeO > EtO > n\text{-}PrO > n\text{-}BuO$$

This series is apparently the reverse of that expected from the inductive effects of the substituents. It seems probable that the relative rates observed are actually determined by variations in the entropy of activation, which reverse the effects of

smaller changes in nucleophilicity.[8a] Triethyl phosphite is, therefore, expected to show a lower reactivity towards glyoxal than trimethyl phosphite. It was impossible to obtain **2b** from the reaction glyoxal–$(EtO)_3P$ in the presence of ethanol. Compound **2b**, on the contrary, was obtained in a yield of 3.1% by reacting glyoxal with $(EtO)_3P$ under the same experimental conditions with methanol as reaction solvent. Since the pK_a of ethanol is about 2.6 units higher than that of methanol and the dealkylation of ethoxy intermediate is slower than the corresponding methoxy-compound, the reaction in the presence of ethanol follows a path not leading to **2b**. An analogous behavior has been observed in the reaction of chloroacetone with trialkyl phosphites.[13] It should be noted that **2b** was obtained in a significantly higher yield (13.6%) when dry hydrogen chloride was bubbled through the mixture of glyoxal and $(EtO)_3P$. Apparently, protonation as well as dealkylation of the intermediate adduct proceed more easily in the presence of hydrogen chloride. Note that the reaction glyoxal–$(EtO)_3P$–HCl gave **2b** in a yield of 13.6% whereas the reaction glyoxol–$(EtO)_2P(O)H$ gave it in a yield of only 6.3%. Birum *et al.*[14] prepared some diphosphorus ester hydrocarbon diols by reacting trialkyl phosphites with a dialdehyde in the presence of HCl. The dialdehyde reactant had a formula OHC–R–CHO wherein R is phenylene or an alkylene having from 2 to about 10 carbon atoms.

Similarly, anhydrous HCl was passed through the mixture of glyoxal and $(PhO)_3P$ to obtain **2c**. Diphosphonate **2c** thus prepared was obtained in a yield of 5.5% whereas the reaction glyoxal–$(PhO)_2P(O)H$ gave it in a yield of 2.8%.

The reactions of substituted 2-hydroxy-2-phosphonylethanals (**1**) with trialkyl phosphites seem to be more complex. Compounds **1** were prepared by reacting glyoxal with $(RO)_2P(O)H$ and were obtained as viscous liquids after removal of volatile components. Partial hydrolysis of phosphites and phosphonates during this reaction resulted in strong acidity of the crude products containing **1**. They were a mixture of various phosphorus-containing compounds.[1] ^{31}P-NMR spectra of the viscous liquid containing **1b**, for example, showed the presence of $P(OH)_3$, $(EtO)P(O)(H)OH$, $(EtO)_2P(O)H$, $(EtO)_2P(O)CH(OH)CHO$ and in small concentration of **2b**. In addition, it contained $(EtO)_2P(O)OCH_2CHO$ resulting from isomerization of **1b**. In the reaction of **1** with $(RO)_3P$ the protonation as well as the dealkylation of the intermediate adduct occurred by other reagents of the mixture which were not identified.

A strong exothermic reaction was observed when trialkyl phosphites were added portionwise to crude **1** dissolved in an inert solvent such as toluene. A moderate heating of the mixture, after subsidence of the exothermic reaction, favored the formation of **2**. Excessive heating should be avoided due to a possible thermal isomerization of **1** to the corresponding formyl methylphosphates $(RO)_2P(O)$-OCH_2CHO. Moreover, the reaction products **2** can be altered when they are strongly heated in the presence of excess of phosphites. The reaction of **1b** with $(EtO)_3P$ gave **2b** in the highest yield obtained for this product (15.3%).

In the reactions of $(RO)_3P$ with glyoxal or with **1** it seems unlikely that an initial hydrolysis of $(RO)_3P$ occurs to the corresponding anions $(RO)_2P(O)^{\ominus}$ followed by a subsequent reaction of the latter with the carbonyl group. Trialkyl and triphenyl phosphites are not hydrolyzed rapidly under the reaction conditions utilized.[15]

The structure of **2** was confirmed by elemental analysis, IR, ^1H-NMR and ^{31}P-NMR spectroscopy. The data are in good agreement with those of **2** prepared by reacting glyoxal with phosphorous acid diesters.[1]

EXPERIMENTAL

Materials. Phosphorous acid triesters were purified by refluxing and fractional distillation under reduced pressure from sodium. Commercially available glyoxal trimer dihydrate and aqueous 30% solution of glyoxal (Ega Chemie) were utilized. Monomeric anhydrous glyoxal was prepared by heating a mixture of glyoxal trimer dihydrate and phosphorus pentoxide (mol ratio 1.0 : 1.2) at 120–135°C according to the procedure described by Ramirez *et al.*[7] All other reagents were of analytical grade.

Instrumentation. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Varian T-60A spectrometer at 60.0 MHz and at 30°C, normal probe temperature. Chemical shifts (δ) are given in parts per million with tetramethylsilane as an internal standard. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 137 Infracord spectrophotometer. Melting points were determined on a Büchi apparatus and are uncorrected. Elemental analyses were carried out by Dr. Mantzos of the Microanalytical Laboratory of the National Hellenic Research Foundation in Athens, Greece.

Synthesis of 1,2-dihydroxy-1,2-bis(dimethoxphosphonyl)ethane (**2a**)

(A) Trimeric glyoxal dihydrate (3.5 g, 16.7 mmol) was dissolved in 80 ml of anhydrous methanol in which a few drops of sulfuric acid had been added. From the mixture 30 ml of methanol was distilled to remove water azeotropically. Next, 30 ml of anhydrous methanol was added and the azeotropic distillation was repeated. Trimethyl phosphite (12.41 g, 100.0 mmol) was added dropwise while the mixture was stirred and refluxed. Methanol was subsequently allowed to reflux for about 2 hours. Acetone was added to the concentrate obtained after removal of the volatile components by a rotary evaporator and the mixture was cooled at 2°C overnight. Compound **2a** precipitated as a white solid and was removed by filtration (4.23 g, yield 30.4%). Recrystallizations from methanol gave an analytical sample: mp 190–192°C (decomp.). Anal. Calcd for $C_6H_{16}O_8P_2$: C, 25.91%; H, 5.80%. Found: C, 26.05%; H, 5.82%.

(B) Aqueous glyoxal (30% solution) (145 g, 0.75 mol) was concentrated by using a rotary evaporator. The viscous liquid obtained was diluted with 300 ml of methanol and the water was removed by azeotropic distillation of about 100 ml methanol. Anhydrous methanol (100 ml) was added and the azeotropic distillation was repeated. Trimethyl phosphite (372 g, 1.50 mol) was added dropwise to the vigorously stirred solution at such a rate that the temperature of the mixture remained at the boiling point of methanol. Refluxing of methanol was continued for 1 hour. Acetone was added to the concentrate obtained after removal of the volatile components by a rotary evaporator and the mixture was cooled at 2°C overnight. Compound **2a** precipitated and was isolated by filtration (25.65 g, yield 12.3%).

(C) Gaseous glyoxal was prepared by heating a mixture of glyoxal trimer dihydrate and phosphorus pentoxide (mol ratio 1.0 : 1.2) at 120–135°C. The gaseous glyoxal together with a stream of argon was passed through a trap containing 50 ml of anhydrous methanol until 4.10 g (70.7 mmol) of glyoxal were absorbed. Trimethyl phosphite (17.54 g, 141.4 mmol) was added dropwise to the methanolic solution of glyoxal and the mixture was subsequently heated to the boiling point of methanol for 1 hour. The concentrate obtained after removal of solvent by a rotary evaporator was diluted with acetone and cooled at 2°C. Diphosphonate **2a** was obtained in a yield of 9.5% (1.87 g).

Synthesis of 1,2-dihydroxy-1,2-bis(diethoxyphosphonyl)ethane (**2b**)

(A) Trimeric glyoxal dihydrate (3.5 g, 16.7 mmol) was dissolved in 80 ml of dioxane containing a few drops of sulfuric acid and the water was azeotropically removed by distillation. Triethyl phosphite (16.62 g, 100.0 mmol) was added portionwise. A stream of dry hydrogen chloride (3.65 g, 100.0 mmol) was bubbled through the mixture while the temperature of the mixture was maintained at 35–40°C by external cooling. The mixture was subsequently stirred at ambient temperature for 1 hour and then it was concentrated by a rotary evaporator. The concentrate was diluted with ether and cooled at 2°C. Compound **2b** was precipitated as a white solid and it was removed by filtration (2.27 g, yield 13.6%). An analytical sample was obtained by recrystallizations from dioxane: mp 175–177°C. Anal. Calcd for $C_{10}H_{24}O_8P_2$: C, 35.93%; H, 7.24%. Found: C, 36.05%; H, 7.16%.

(B) 2-Hydroxy-2-(diethoxyphosphonyl)ethanal (**1b**) was prepared by reacting trimeric glyoxal dihydrate (14.00 g, 66.7 mmol) with diethyl phosphite (27.62 g, 200.0 mmol) in 50 ml of dioxane. The reaction was carried out by heating to the boiling point of dioxane for 35 min with simultaneous azeotropic distillation of water. The mixture was subsequently concentrated under reduced pressure. The viscous liquid containing **1b** was diluted with 40 ml of toluene. To the vigorously stirred solution triethyl phosphite (33.24 g, 200.0 mmol) was added rapidly. After subsidence of the exothermic reaction the mixture was heated at 50°C for 1 hour. Upon cooling, **2b** was precipitated (10.22 g, yield 15.3%).

Synthesis of 1,2-dihydroxy-1,2-bis[di(n-botoxy)phosphonyl]ethane (**2d**). 2-Hydroxy-2-[di(*n*-butoxy)phosphonyl]ethanal (**1d**) was prepared by reacting trimeric glyoxal dihydrate (14.00 g, 66.7 mmol) with di(*n*-butyl) phosphite (38.84 g, 200.0 mmol) in 50 ml of dioxane. The mixture was boiled for 60 min while the water was removed by azeotropic distillation. A viscous liquid containing **2d** was obtained after

concentration by a rotary evaporator. To the vigorously stirred solution of the concentrate in 40 ml of toluene tri(*n*-butyl) phosphite (50.06 g, 200.0 mmol) was added dropwise. After subsidence of the exothermic reaction the mixture was heated at 50°C for 1 hour. Compound **2d** was precipitated as a white solid by cooling the mixture at 2°C (9.63 g, yield 10.8%). Recrystallizations from acetonitrile gave an analytical sample: mp 170–172°C. Anal. Calcd for $C_{18}H_{40}O_8P_2$: C, 48.42%; H, 9.03%. Found: C, 48.29%; H, 8.95%.

Synthesis of 1,2-dihydroxy-1,2-bis(diphenoxyphosphonyl)ethane (**2c**). Trimeric glyoxal dihydrate (7.0 g, 33.4 mmol) was dissolved in 150 ml of dioxane containing a few drops of sulfuric acid and the water was azeotropically removed by distillation. Triphenyl phosphite (62.06 g, 200.0 mmol) was added portionwise to the stirred solution. Dry hydrogen chloride (7.30 g, 200.0 mmol) was bubbled through the mixture while the temperature of the mixture was maintained at 35–40°C by external cooling. After stirring of the mixture at ambient temperature for 1 hour it was cooled at 2°C and **2c** precipitated. It was removed by filtration (2.87 g, yield 5.5%). Recrystallizations from dioxane gave an analytical sample: mp 208–209°C. Anal. Calcd for $C_{26}H_{24}O_8P_2$: C, 59.32%; H, 4.60%. Found: C, 59.20%; H, 4.55%.

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