

The Reaction between Sodium Diethylphosphite and Some ω -Chloroalkanols-1

JON SONGSTAD

Chemical Institute, University of Bergen, Bergen, Norway

Sodium diethylphosphite reacts with ω -chloroalkanols, $\text{Cl}-(\text{CH}_2)_n-\text{OH}$ ($n = 3, 4, \text{ and } 5$), to give cyclic phosphonates in rather good yields. From 2-chloroethanol, the main product is 1,2-bis(diethylphosphono)ethane. The yields of diethyl ω -hydroxyalkylphosphonates are low, and these compounds are difficult to obtain pure due to their tendency of cyclization and polymerization.

During an investigation on intramolecular and intermolecular hydrogen bonds in organic phosphoryl compounds, it was of interest to synthesize some diethyl ω -hydroxyalkylphosphonates. While the dialkyl α -hydroxyalkylphosphonates are easily obtained from the base-catalyzed addition of dialkylphosphites to ketones and aldehydes,¹⁻⁴ information is scarce on phosphonates having the hydroxyl group further away from the phosphorus atom. Since dialkyl β -hydroxyalkylphosphonates have been prepared in very low yields from sodium dialkylphosphites and ethylene oxides,^{5,6} the Michaelis-Becker reaction between sodium diethylphosphite and chloroalcohols might lead to improved syntheses.

Dialkylphosphite anions are known to be very powerful nucleophiles towards aliphatic carbon. In methanol the dimethylphosphite anion is as nucleophilic towards methyl iodide as is triphenylphosphine.⁷ The nucleophilic atom is, with very few exceptions, the phosphorus atom.^{8,9} The high nucleophilicity of these anions is due to the basicity as well as the polarizability of the attacking phosphorus atom. The $\text{p}K_{\text{a}}$ of simple dialkylphosphites is approximately 13.5, and this value is a little influenced by different alkyl groups.¹⁰ Small differences are observed in the nucleophilicities of the anions when the alkyl groups are changed.¹¹

Solvation of the phosphite anions through hydrogen bonding makes their rate of substitution on aliphatic carbon fairly slow in hydroxylic solvents. The substitution rates are considerably higher in dipolar aprotic solvents.¹¹ Due to the bulkiness of the anions and the polarizability of the attacking phosphorus atom, the differences in rates are, however, far less pronounced than for the small halide ions.^{12,13}

The properties of the phosphite ions are in fact very similar to those of thiolate ions,¹⁴ *i.e.* they are able to react with both electron-rich and electron-poor electrophilic centers; producing elimination due to their basicity, being excellent nucleophiles in displacement reactions due to high basicity and polarizability, and finally being able to add to double bonds.¹⁵

As the phosphorus atom is the attacking atom, the rate of reaction in nucleophilic substitution reactions is strongly dependent upon the leaving group.^{11,16} Therefore, when alkyl chlorides are used as substrates, as in this work, dipolar aprotic solvents should be used to obtain good yields.

EXPERIMENTAL

Materials. Diethylphosphite, and N,N-dimethylformamide (both Fluka Purum) were redistilled in vacuum before use. 2-Chloroethanol, 3-chloropropanol, and 4-chlorobutanol were commercial products dried by azeotropic distillation with benzene and redistilled, in vacuum if necessary. 5-Chloropentanol was prepared from 1,5-pentanediol according to Kirner and Richter.¹⁷

General procedure. To 69 g of diethylphosphite, 0.5 mole, in 300 ml of sodium-dried ether, was added 0.6 mole of sodium. When the reaction was complete, the excess sodium was removed, 300 ml of dimethylformamide were added and the ether was distilled off. After cooling, 0.5 mole of the chloroalcohol was added through a dropping funnel, and the reaction mixture was finally kept at approximately 80°C for 12 h to complete the reaction. Water was excluded throughout the operations. As the slurry could not be filtered, the solvent was removed in vacuum and 500 ml of ether was added, whereupon the mixture was filtered and the products fractionated in vacuum. In all cases a small, volatile fraction, 5–15 g, b.p.₁ 30–50°C, was obtained, which by VPC was found to consist mainly of unreacted chloroalcohol, dimethylformamide, and some diethylphosphite and ethyl diethylphosphonate. The residues from the filtrations were dried in vacuum and analyzed for ionic chloride. The yield of chloride ions was in all cases found to be higher than 80 %, based on used sodium diethylphosphite. The residues after drying contained hydroxyl and phosphoryl groups, and their aqueous solutions were highly basic, indicating the presence of some unreacted sodium diethylphosphonate.

When ether instead of dimethylformamide was used as solvent throughout the reaction, the yields of ionic chlorine and the other products were much lower, even after reflux for two days.

The fractions containing hydroxylic compounds in small amounts were dissolved in ether, treated with metallic sodium and filtered prior to the final distillation.

Products from 2-chloroethanol. After three fractionations in vacuum, 7 g diethyl 2-hydroxyethylphosphonate was obtained (8 %), b.p._{0.35} 105–109°C, $n_D^{20} = 1.4372$. (Found: C 39.2; H 8.2; P 16.8. Calc. for C₆H₁₅PO₄: C 39.55; H 8.21; P 17.00). $\nu_{PO} = 1247 \text{ cm}^{-1}$, $\nu_{OH} = 3430 \text{ cm}^{-1}$.

The main product was 24 g 1,2-bis(diethylphosphono)ethane, (34 %), b.p._{0.3} 133–134°C, $n_D^{20} = 1.4420$ (lit.¹⁸ b.p.₂ 164–165°C, $n_D^{20} = 1.4410$). (Found: C 39.8; H 7.6; P 20.2. Calc. for C₁₀H₂₄P₂O₆: C 39.73; H 8.00; P 20.49). The structure of this compound was established through its NMR spectrum which showed three peaks at 80, 108, and 247 cps, relative to TMS (integrated ratio 3:1:2). The IR spectrum of the compound was superimposable on that of a sample of the ester made from ethylene dibromide and triethylphosphite. The corresponding tetra-acid, obtained by acidic hydrolysis of the ester, had m.p. 223–224°C (from water-acetone mixture), undepressed by acid made from ester synthesized according to the alternative procedure (lit.¹⁹ m.p. 220–223°C).

The residue consisted of 20 g undistillable substance which showed phosphoryl adsorption and very strong absorption in the 3400–3600 cm⁻¹ region.

When 2-bromoethanol was used as substrate, the rate of reaction was, as anticipated, highly increased, but the yields and product ratio were not altered.

Products from 3-chloropropanol. After the low-boiling fraction had been removed, the temperature was raised to 100°C, whereupon a decomposition occurred, indicated by a decrease in the temperature. A low-boiling liquid, later shown to be ethanol, con-

densed in the CO₂-acetone trap. After fractionations in vacuum, 34 g (45 %) pure ethyl trimethylenephosphonate was obtained, b.p._{0.4-0.7} 80–81°C, $n_D^{20} = 1.4508$ (lit.²⁰ b.p.₁₀ 128°C, $n_D^{20} = 1.4498$, b.p._{0.55} 74°C²¹). The IR spectrum of the compound was identical with that of a pure sample prepared from triethylphosphite and 1,3-dibromopropane²⁰ ($\nu_{PO} = 1238$ and 1273 cm⁻¹).

10 g of a compound b.p._{0.7} 120–125°C, was further obtained having strong IR absorption at 3420 cm⁻¹. It was partly unstable toward distillation and storage (changing index of refraction), whereby more ethanol and cyclic phosphonate was formed. Presumably this compound was unpure diethyl-3-hydroxypropylphosphonate. The amount of undistillable material was negligible.

Products from 4-chlorobutanol. Similarly, 32 g (39 %) pure ethyl tetramethylenephosphonate was obtained, b.p._{0.8} 89–90°C, $n_D^{20} = 1.4581$ (lit.²⁰ b.p.₁₀ 130–130.5°C, $n_D^{20} = 1.4585$). The IR spectrum ($\nu_{PO} = 1250$ and 1270 cm⁻¹) was identical with that of a pure sample prepared from 1,4-dibromobutane and triethylphosphite.²⁰ A fraction (5 g), b.p.₁ 150–160°C, showed strong hydroxyl absorption at 3430 cm⁻¹, but due to decomposition the compound could not be obtained pure. Approximately 10 g of undistillable material remained in the distillation flask.

Products from 5-chlorobutanol. 18 g (20 %) of ethyl pentamethylenephosphonate b.p._{0.7} 93–95°C, $n_D^{20} = 1.4596$ was obtained. (Found: C 46.8; H 8.30; P 16.9. Calc. for C₇H₁₅PO₃: C 47.18; H 8.48; P 16.38).

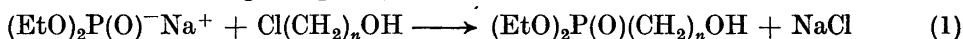
The IR spectrum of this compound was identical with one of a sample prepared from triethylphosphite and 1,5-dibromopentane (see below) ($\nu_{PO} = 1246$ and 1264 cm⁻¹). Further, approximately 5 g of a compound, b.p._{0.7} 140–150°C, containing hydroxyl ($\nu_{OH} = 3430$ cm⁻¹), and unstable towards further purification, was obtained. A considerable amount of undistillable material remained in the flask.

Ethyl pentamethylenephosphonate from triethylphosphite and 1,5-dibromopentane. 115 g 1,5-dibromopentane and 83 g triethylphosphite (0.5 mole) were heated very carefully until approximately 0.75 mole of ethylbromide had distilled off. After cooling, 300 ml petroleum ether (b.p. 40–50°C) were added and the reaction mixture stirred for 30 min. The petroleum ether phase was then decanted from the flask and distilled. After several distillations, 4 g (4.5 %) of the desired product was obtained, b.p._{0.7} 95–96°C, $n_D^{20} = 1.4603$. The final product contained traces of bromide (2 % by analysis) due to contamination with unreacted dibromide; this may explain the slightly higher index of refraction. From several unsuccessful attempts to prepare this cyclic phosphonate from triethylphosphite and dibromopentane, it was found that the following conditions must be carefully maintained in order to get detectable yields: (1) A very careful temperature control during the reaction, (2) avoidance of a complete second step in the Michaelis-Arbuzov reaction, (3) a solvent must be used to remove the products from the polymeric materials prior to distillation. Even diethyl ether dissolved too much of the polymers to give detectable yields on distillation.

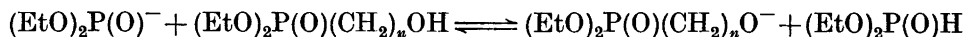
All IR measurements were performed on liquid films.

DISCUSSION

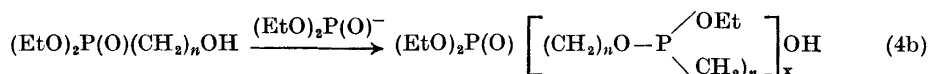
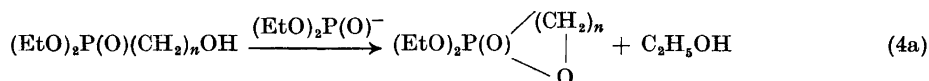
The rate determining step in these reactions is the nucleophilic attack on carbon according to eqn. (1):



As mentioned in the introduction, the aliphatic phosphites have pK_a values around 13.5.¹⁰ When $n = 3, 4,$ and $5,$ the electron-attracting effect of the chloro atom or the diethylphosphoryl group will therefore be insufficient (provided a transmission coefficient of 0.3–0.5) to force the following equilibria significantly to the right:



It is well known that the phosphoryl centre is very susceptible to attack by hard nucleophiles.^{22,23} The final step in these reactions (when $n > 2$) will therefore be a base-catalyzed attack of the oxygen atom on the phosphoryl group, either intramolecularly to cyclic phosphonates (4a) or intermolecularly to undistillable polymers (4b):

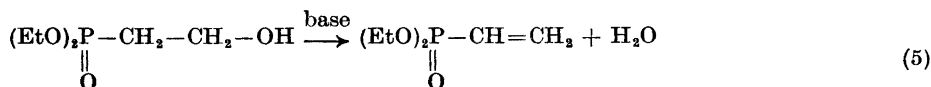


The decreasing yield of cyclic phosphonates and increasing yield of polymers with increasing number of methylene groups is similar to what is encountered in the preparation of cyclic phosphonates from trialkylphosphites and ω -dibromoalkanes,²⁰ cyclization of ω -aminoalkyl bromides,²⁴ and in lactonization of anions of bromo acids.²⁵

Where $n = 2$, *i.e.*, when the substrate is 2-chloroethanol, the mechanism is more complex as shown by the product, 1,2-bis(diethylphosphono)ethane. A possible explanation may be that equilibria (2) and (3) are no longer completely in favour of the phosphite anion. 2-Chloroethanol has a $\text{p}K_{\text{HA}}$ value of 14.3.²⁶ If there is any intramolecular hydrogen bonding in the presumed intermediate, diethyl 2-hydroxyethylphosphonate, this will greatly affect the acidity by hindering the ionization of the hydrogen atom involved. As the absorption due to the hydroxyl group is found at 3430 cm^{-1} , which is far higher than that for dialkyl hydroxymethylphosphonates,³ approx. 3200 cm^{-1} , it is conceivable that the extent of intramolecular hydrogen bonding in diethyl 2-hydroxyethylphosphonate is of minor importance.

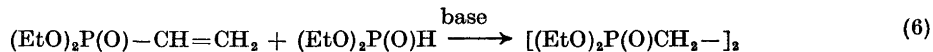
Recently,²⁷ the $\text{p}K_{\text{a}}$ value of the amine, $(\text{C}_2\text{H}_5)_2\text{NCH}_2\text{CH}_2\text{P}-(\text{O})(\text{OC}_2\text{H}_5)_2$, has been found to be 8.2. Thus, a diethylphosphoryl group in 2-position with respect to the basic center is causing a base weakening effect of 2.4 $\text{p}K_{\text{a}}$ units, as compared with 1.9 $\text{p}K_{\text{a}}$ units when a chloro atom is in the same position.²⁸ The diethylphosphoryl group is therefore more electron-attracting than a chloro atom. Using the values for ρ^x given by Clark *et al.*,^{28,29} one calculates the $\text{p}K_{\text{HA}}$ value of 2-diethylphosphorylethanol to be approximately 13.9 (provided the effect of intramolecular hydrogen bonding can be neglected).

This strong electron-attracting effect of the phosphoryl group makes it likely that diethyl 2-hydroxyethylphosphonate will be subject to base-catalyzed elimination:



It is well known that dehydration of alcohols by bases can only be achieved when the alcohol is activated by very strong electron-attracting groups.³⁰⁻³² The phosphoryl group being more electron-attracting than a phenyl group, reaction (5) is conceivable. A special case is 4-(2-hydroxyethyl)pyridine which undergoes base-catalyzed elimination with remarkable ease.³³

The final step in the reaction will then be a base-catalyzed addition of diethylphosphite to diethyl vinylphosphonate:



Base-catalyzed addition of dialkyl phosphites to double bonds is well established.¹⁸

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