Anal. Calcd. for $C_9H_{13}ClNO_4P$: N, 5.27; P, 11.66; neut. equiv., 88.55. Found: N, 5.29; P, 11.48; neut. equiv., 88.9.

Five grams of the above **ethyl *p*-phosphonobenzamidate hydrochloride** was added to 50 ml. of alcoholic ammonia (11.5%) in a pressure bottle. The mixture was heated to 60° for 3 hours and allowed to cool overnight. The crystalline precipitate was removed and recrystallized from hot water. The yield was 81%, m.p. >300°.

Anal. Calcd. for $C_7H_9N_2O_3P$: N, 14.00; P, 15.48. Found: N, 14.05; P, 15.14.

Acknowledgment.—The authors wish to thank Miss Betty Jean Pegram for performing the analyses necessary for this research and Mr. Edward L. Petit for skilled technical assistance.

CHAPEL HILL, N. C.

[CONTRIBUTION FROM THE CENTRAL RESEARCH LABORATORIES, VICTOR CHEMICAL WORKS]

Conversion of Tertiary Phosphites to Secondary Phosphonates. Diphenyl Phosphonate[1]

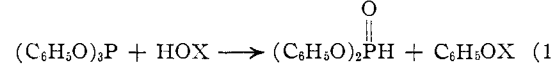
BY E. N. WALSH

RECEIVED SEPEMBER 24, 1958

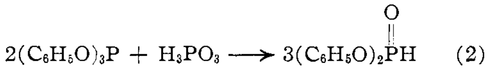
A method of preparing diphenyl phosphonate is described in which triphenyl phosphite is caused to react with phosphorous acid at above 60°. Several of the reactions of diphenyl phosphonate are presented including the reactions with chlorine, alcohols, aldehydes or ketones, and the condensation reaction with secondary amines and aldehydes. The conversion of the tertiary esters of phosphorous acid, obtained from the action of phosphorus trichloride on ethylene oxides, to secondary esters, is also described.

The preparation of diphenyl phosphonate was first described by Milobendzki and Szulgin.[2] These authors used a process in which diphenyl propyl phosphite is treated with anhydrous hydrogen chloride to yield propyl chloride and diphenyl phosphonate. The use of diphenyl phosphonate as an intermediate for diphenyl phosphoramidate has been described by Atherton and Todd[3] and, subsequent to this present work, Kabachnik and Polikarper[4] have reported the preparation of diphenyl phosphonate from the hydrolysis of diphenyl phosphorochloridite.

It was found in this Laboratory that when triphenyl phosphite is heated in the presence of an oxy acid, the acidity of the mixture rapidly decreases. This effect is attributable to the phenylation of the acid by the triphenyl phosphite with the simultaneous formation of diphenyl phosphonate in accord with equation 1.

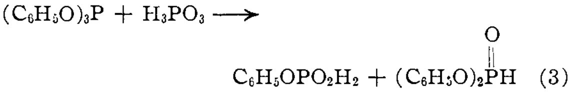

$$(C_6H_5O)_3P + HOX \longrightarrow (C_6H_5O)_2\overset{\overset{\displaystyle O}{\|}}{P}H + C_6H_5OX \quad (1)$$

Since, at this time, our primary interest was in a rather simple preparation of diphenyl phosphonate, a process was devised in which the acidic compound was phosphorous acid, and thus the sole product would be diphenyl phosphonate, as illustrated in equation 2. When this reaction was conducted at temperatures above 60°, good yields of diphenyl

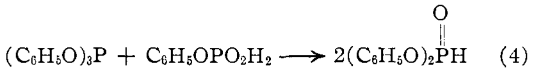

$$2(C_6H_5O)_3P + H_3PO_3 \longrightarrow 3(C_6H_5O)_2\overset{\overset{\displaystyle O}{\|}}{P}H \quad (2)$$

phosphonate were obtained.

The reaction of triphenyl phosphite with phosphorous acid was observed to occur in two stages. The first stage entails the reaction of one mole of phosphorous acid with one mole of triphenyl phosphite to form one mole of diphenyl phosphonate and one mole of phenyl phosphonate; equation 3. This stage of the reaction is rapid at 70°,


$$(C_6H_5O)_3P + H_3PO_3 \longrightarrow C_6H_5OPO_2H_2 + (C_6H_5O)_2\overset{\overset{\displaystyle O}{\|}}{P}H \quad (3)$$

and it occurs simultaneously with the disappearance from the reaction mixture of the phosphorous acid phase. The second stage of the reaction consists of the action of a second mole of triphenyl phosphite with phenyl phosphonate to form two moles of diphenyl phosphonate, as shown in equation 4.


$$(C_6H_5O)_3P + C_6H_5OPO_2H_2 \longrightarrow 2(C_6H_5O)_2\overset{\overset{\displaystyle O}{\|}}{P}H \quad (4)$$

This second stage is a much slower reaction, requiring five hours to approach completion at 70°.

A series of diaryl phosphonates was prepared in order to determine the scope of the synthesis.

The action of phosphorus trichloride on three moles of alcohol, in the absence of a basic condensation agent, usually leads to the formation of dialkyl phosphonates and alkyl chloride.[5] However, when the alcohol is substituted with strong electronegative groups, as in the case of the 2-nitro alcohols, α-cyano alcohols,[6] and 2,2,2-trichloroethanol,[7] the tertiary phosphite is usually obtained, and little or no dialkyl phosphonate can be isolated. Similarly, the action of phosphorus trichloride on the ethylene oxides leads directly to the formation of the tris-(2-chloroalkyl) phosphite.[8] In preparations where the tertiary phosphite is obtained more readily than the dialkyl phosphonate, the reaction of the tertiary phosphite with phosphorous acid presents a satisfactory method of preparing the corresponding dialkyl phosphonate,

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[1] Presented before the Division of Organic Chemistry, 133rd National A.C.S. Meeting, San Francisco, Calif., April, 1958.

[2] T. Milobendzki and K. Szulgin, *Chem. Polsk.*, **15**, 166 (1917); *C. A.*, **13**, 2867 (1919).

[3] F. R. Atherton and A. R. Todd, *J. Chem. Soc.*, 677 (1947).

[4] M. I. Kabachnik and Yu. M. Polikarper, *Doklady Akad. Nauk S.S.S.R.*, **115**, 512 (1957).

[5] A. Sacks and N. Levitsky, *J. Russ. Phys. Chem. Soc.*, **35**, 211 (1903).

[6] A. Chrzaszczewska and W. Sobieranski, *Roczniki Chem.*, **7**, 470 (1927).

[7] M. Delacre, *Bull. soc. chim.*, **48**, 787 (1887).

[8] M. I. Kabachnik and P. A. Rossiiskaya, *Izvestiya Akad. Nauk S.S.S.R.*, 295 (1946).

especially since the preparation allows a complete conservation of the ester groups.

Several of these tertiary phosphites were prepared and converted to the corresonding dialkyl phosphonate. Those prepared from ethylene oxides and phosphorus trichloride are presented in this report. These secondary esters were converted to the corresponding phosphoramidates using the reaction described by Atherton, Openshaw and Todd.[9]

Diphenyl phosphonate was studied in several of the typical reactions of the P–H group. Diphenyl phosphonate was chlorinated with sulfuryl chloride, and with chlorine, to form the well-known diphenyl phosphorochloridate.[10] However, in the case of diaryl phosphonates which contain alkyl groups on the phenyl group, sulfuryl chloride is the preferred chlorination agent, since chlorine attacks both the P–H and the hydrocarbon group. Diphenyl phosphonate reacts with ammonia in the presence of carbon tetrachloride[8] to yield diphenyl phosphoramidate. The action of alcohol and triethylamine on a solution of diphenyl phosphonate in carbon tetrachloride results in a mixture of neutral ethyl phenyl phosphates. Diphenyl phosphonate readily undergoes alcoholysis to form dialkyl phosphonates, and in the presence of triethylamine reacts with sulfur to form the corresponding salt of diphenyl phosphorothioic acid. Diphenyl phosphonate undergoes addition reactions with aldehydes and ketones, and reacts with secondary amines and aldehydes to form Mannich-type bases.

Experimental

Preparation of Triaryl Phosphites.—The triaryl phosphites used in this work were prepared from the condensation reaction of phosphorus trichloride with the corresponding phenol.[11] A typical preparation is illustrated below.

Triphenyl Phosphite.—A reactor is charged with 310 g. of phenol. The reactor is equipped with a stirrer, dropping funnel, thermometer and an efficient reflux condenser. While stirring the phenol at slightly above its melting point, phosphorus trichloride, 137.5 g., is cautiously added. The reaction temperature rises slightly at the start of the addition of phosphorus trichloride; but, coincident with the saturation of the reaction mixture with the by-product hydrogen chloride, the reaction becomes endothermic and hydrogen chloride is liberated.

When all of the phosphorus trichloride is added, the reaction mixture is stirred until it is no longer self-cooling, and it is cautiously heated to reflux. Warm water must be passed through the reflux condenser to prevent clogging with solid phenol. The reaction mixture is stirred at reflux until the rate of liberation of hydrogen chloride becomes less than 0.01 mole per hour, or until the reflux temperature remains constant. The reaction mixture at this point is essentially a solution of phenol in triphenyl phosphite, a mixture which is easily separated by distillation under reduced pressure; yield 291.0 g. (94%), b.p. 183–184° (1 mm.), $n^{25}\text{D}$ 1.5890, d^{25}_{25}, 1.183, m.p. 21–23°.

Anal. Calcd. for $C_{18}H_{15}O_3P$: P, 10.0; Cl, 0.0. Found: P, 10.0; Cl, 0.0.

The following triaryl phosphites were prepared in a similar manner from one mole of phosphorus trichloride and 3.3 moles of the corresponding phenol.

Tris-(2-methylphenyl) phosphite, yield 300.0 g. (85.3%), b.p. 193–194° (1 mm.), $n^{25}\text{D}$ 1.5760, d^{25}_{25} 1.1195. *Anal.* Calcd. for $C_{21}H_{21}O_3P$: P, 8.8; Cl, 0.0. Found: P, 8.8; Cl, 0.0.

Tris-(3-methylphenyl) phosphite, yield 310.5 g. (88.3%), b.p. 188° (1 mm.), $n^{25}\text{D}$ 1.5734, d^{25}_{25} 1.1195. *Anal.* Found: P, 8.9; Cl, 0.0.

Tris-(4-methylphenyl) phosphite, yield 301.0 g. (85.7%), b.p. 194° (1 mm.), $n^{25}\text{D}$ 1.5734, d^{25}_{25} 1.1107. *Anal.* Found: P, 8.8; Cl, 0.0.

Tris-(2-chlorophenyl) phosphite, yield 363.8 g. (88.0%), b.p. 230° (3 mm.), $n^{25}\text{D}$ 1.6041. *Anal.* Calcd. for $C_{18}H_{12}O_3Cl_3P$; P, 7.5; Cl, 25.5. Found: P, 7.5; Cl, 25.8.

Tris-(4-chlorophenyl) phosphite, yield 383.2 g. (92.7%), b.p. 207° (1.5 mm.), m.p. 48–50° (recrystallized from benzene and hexane). *Anal.* Found: P, 7.5; Cl, 25.7.

Tris-(4-*t*-butylphenyl) phosphite, yield 344.2 (72.1%), b.p. 253–254° (1.0 mm.), m.p. 75°. *Anal.* Calcd. for $C_{30}H_{39}O_3P$: P, 6.5; Cl, 0.0. Found: P, 6.4; Cl, 0.0.

Preparation of Tris-(2-chloroalkyl) Phosphites.—Three tris-(2-chloroalkyl) phosphites were prepared from the reaction of one mole of phosphorus trichloride with 3.3 moles of the corresponding cyclic oxide.[8]

Tris-(2-chloroethyl) phosphite was prepared from ethylene oxide and phosphorus trichloride; yield 250.0 g. (93.1%), b.p. 98° (1 mm.), $n^{25}\text{D}$ 1.4825. *Anal.* Calcd. for $C_6H_{12}O_3Cl_3P$: P, 11.5; Cl, 39.5. Found: P, 11.6; Cl, 39.0.

Tris-(2-chloropropyl) phosphite was prepared from propylene oxide and phosphorus trichloride; yield 288.0 g. (92.5%), b.p. 107–108° (1 mm.), $n^{25}\text{D}$ 1.4720, d^{25}_{25} 1.2157. *Anal.* Calcd. for $C_9H_{18}Cl_3O_3P$: P, 10.0; Cl, 34.2. Found: P, 10.1; Cl, 34.0.

Tris-(phenyl-2-chloroethyl) phosphite was prepared from styrene oxide and phosphorus trichloride; yield 486.0 g. (98.0%) (undistilled), $n^{25}\text{D}$ 1.5760. Decomposes during distillation. *Anal.* Calcd. for $C_{24}H_{24}O_3Cl_3P$: P, 6.2; Cl, 21.4. Found: P, 6.3; Cl, 21.6.

Conversion of Tertiary Phosphites to Secondary Phosphonates. Preparation of Diaryl Phosphonates.—A typical preparation of a diaryl phosphonate is:

Diphenyl phosphonate.—A reactor, equipped with a stirrer, thermometer and reflux condenser is charged with 310 g. (1 mole) of triphenyl phosphite. While stirring at 25° (or above the melting point of the triaryl phosphite) under a stream of dry nitrogen, phosphorous acid (41.0 g., 0.5 mole) is added. The phosphorous acid slowly liquefies forming a lower phase. The reaction is slightly exothermic. The mixture is heated to 70°; at 55° the lower phosphorous acid-rich phase dissolves into the upper phase forming a clear, homogeneous solution. The phosphorous acid content of this solution is less than 1%; the triaryl phosphite content is from 30–40%. The remaining material is a mixture of phenyl phosphonate and diphenyl phosphonate. The reaction mixture is held at 130° for five hours to drive the reaction to completion. This step can be conducted at temperatures as high as 150°. An estimate of the rate of reaction at 70° and at 150° is given in Table I. The yield of the undistilled reaction mixture is 351 g., $n^{25}\text{D}$ 1.5570. Ten grams was distilled under 0.008 mm.; recovery, 9.6 g., b.p. 100°, $n^{25}\text{D}$ 1.5570, d^{25}_{25} 1.2268.

Anal. Calcd. for $C_{12}H_{11}O_3P$: P, 13.3; P (trivalent), 13.3; active hydrogen, 0.428 (based on chloride ion formation during the reaction of the diaryl phosphonate with ammonia in the presence of carbon tetrachloride).[8] Found: P, 13.3; P (trivalent), 13.3; active hydrogen, 0.426.

Table I

Rates of Reaction of Triphenyl Phosphite with Phenyl Phosphonate at 70° and 150°[12]

Time, min.	0	15	30	60	180	300
Mole % $(C_6H_5O)_3P$ in reacn. mixt.						
70°	32	30	27	20	9	2
150°	34	26	20	9	1	

The following diaryl phosphonates were prepared in a similar manner from 0.1 mole of triaryl phosphite and 0.05

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(9) F. R. Atherton, H. T. Openshaw and A. R. Todd, *J. Chem. Soc.*, 660 (1945).

(10) M. Rapp, *Ann.*, **224**, 156 (1884).

(11) A. E. Noack, *ibid.*, **218**, 85 (1883); R. Anschütz and W. O. Emery, *ibid.*, **239**, 301 (1887).

(12) The analytical data for these reaction mixtures were determined by a combination of acid–base titration and alcoholysis followed by selective hydrolysis. The sample is dissolved in alcohol. Hydrolysis with 0.1 *N* hydrochloric acid converts the tertiary phosphite to the secondary phosphonate. Hydrolysis with 0.1 *N* sodiun hydroxide converts the secondary phosphonate to the sodium monoalkyl phosphonate. Direct titration with 0.1 *N* sodium hydroxide is used to determine the phenylphosphonate and phosphorous acid content.

mole of phosphorous acid. Yields are reported for the distilled product.

Bis-(2-methylphenyl) phosphonate, yield 38.5 g. (98.0%), b.p. 100° (0.005 mm.), $n^{25}D$ 1.5495, $d^{25}{}_{25}$ 1.1827. *Anal.* Calcd. for $C_{14}H_{15}O_3P$: P, 11.8; P (trivalent), 11.8. Found: P, 11.7; P (trivalent), 11.7.

Bis-(3-methylphenyl) phosphonate, yield 34.7 g. (88.6%), b.p. 90–100° (0.005 mm.), $n^{25}D$ 1.5468, $d^{25}{}_{25}$ 1.1806. *Anal.* Found: P, 11.9; P (trivalent), 11.7.

Bis-(4-methylphenyl) phosphonate, yield 38.6 g. (98.6%), b.p. 110° (0.005 mm.), $n^{25}D$ 1.5466, $d^{25}{}_{25}$ 1.1569. *Anal.* Found: P, 11.7; P (trivalent), 11.6.

Bis-(2-chlorophenyl) phosphonate, yield 38.0 g. (84.2%), b.p. 125° (0.005 mm.), $n^{25}D$ 1.5750. *Anal.* Calcd. for $C_{12}H_9O_3Cl_2P$: P, 10.2; P (trivalent), 10.2; Cl, 23.4. Found: P, 10.3; P (trivalent), 10.2; Cl, 23.4.

Bis-(4-chlorophenyl) phosphonate, yield 38.6 g. (85.3%), b.p. 125° (0.005 mm.), $n^{25}D$ (supercooled) 1.5708, m.p. 44°. *Anal.* Found: P, 10.4; P (trivalent), 10.3; Cl, 23.4.

Bis-(4-*t*-butylphenyl) phosphonate, yield 37.3 g. (72.1%), b.p. 160° (0.005 mm.), $n^{25}D$ 1.5280; slowly crystallizes on standing; m.p. 30–33°. *Anal.* Calcd. for $C_{20}H_{27}O_3P$: P, 9.0; P (trivalent), 9.0. Found: P, 8.9; P (trivalent), 8.9.

Preparation of Bis-(2-chloroalkyl) Phosphonates. Bis-(2-chloroethyl) Phosphonate.—A reactor was charged with 53.9 g. (0.2 mole) of tris-(2-chloroethyl) phosphite. While stirring under a stream of nitrogen at 25°, phosphorous acid (8.2 g., 0.1 mole) was added. No sign of reaction was observed; the phosphorous acid crystals settled to the bottom of the reactor. The reactants were slowly heated to 60° at which temperature the phosphorous acid slowly dissolved. After 10 minutes, all of the phosphorous acid had gone into solution; no significant heat of reaction was observed. The reaction mixture was heated to 80° for two hours and cooled. The product was isolated by distillation[13]; yield 56.9 g. (91.7%), b.p. 110° (0.5 mm.), $n^{25}D$ 1.4701, $d^{25}{}_{25}$ 1.1057. *Anal.* Calcd. for $C_4H_9O_3Cl_2P$: P, 15.0; Cl, 34.4. Found: P, 14.9; Cl, 33.8.

The following two compounds were prepared in a similar manner.

Bis-(2-chloropropyl) phosphonate was prepared from 0.2 mole of tris-(2-chloropropyl) phosphite and 0.1 mole of phosphorous acid; yield 68.3 g. (98.1%), b.p. 120° (1 mm.), $n^{25}D$ 1.4609, $d^{25}{}_{25}$ 1.2640. *Anal.* Calcd. for $C_6H_{13}O_3Cl_2P$: P, 13.2; Cl, 30.2. Found: P, 13.2; Cl, 30.6.

Bis-(phenyl-2-chloroethyl) phosphonate was prepared from 0.2 mole of tris-(phenyl-2-chloroethyl) phosphite; yield 107.7 g. (100% undistilled). The product decomposed during distillation; $n^{25}D$ 1.5625. *Anal.* Calcd. for $C_{16}H_{17}Cl_2O_3P$: P, 8.6; P (trivalent), 8.6; Cl, 19.8. Found: P, 8.4; P (trivalent), 8.4; Cl, 19.4.

Preparation of $(RO)_2PONH_2$.—The dialkylphosphoramidates and diarylphosphoramidates were prepared as follows.[3]

Gaseous ammonia is passed into a solution of 0.1 mole of the secondary phosphonate in 20.0 g. of carbon tetrachloride while stirring at 20–30°. When an exothermic reaction is no longer observed the ammoniation is stopped. The reaction mixture is then treated with water (100 ml.) to dissolve the by-product ammonium chloride. In the case where the product is a chloroform-insoluble solid, the mixture is filtered and the filter cake is dried. When the product is chloroform soluble, the chloroform layer is concentrated and the product is isolated as the undistilled residue. Below are the preparations of four phosphoramidates.

Diphenyl Phosphoramidate.—The product is a white, crystalline solid, insoluble in chloroform; yield 22.0 g. (88.5%), m.p. 148–149°, mixed m.p. with authentic sample 147–149°. *Anal.* Calcd. for $C_{12}H_{12}O_3PN$: P, 12.4; N, 5.6. Found: P, 12.4; N, 5.7.

Triphenyl phosphite failed to react under similar conditions.

Bis-(2-chloroethyl) Phosphoramidate.—The product is a white, crystalline solid, insoluble in chloroform; yield 18.8 g. (84.8%), m.p. 77°. *Anal.* Calcd. for $C_4H_{10}Cl_2O_3NP$: P, 14.0; Cl, 32.0; N, 6.3. Found: P, 13.8; Cl, 32.0; N, 6.2.

Bis-(2-chloropropyl) Phosphoramidate.—The product is a viscous liquid, soluble in chloroform, decomposes during distillation; yield 17.7 g. (70.8%), $n^{25}D$ 1.4725, $d^{25}{}_{25}$ 1.3177. *Anal.* Calcd. for $C_6H_{14}Cl_2O_3NP$: P, 12.4; Cl, 28.4; N, 5.6. Found: P, 12.2; Cl, 30.0; N, 5.5.

Bis-(phenyl-2-chloroethyl) Phosphoramidate.—The product is a viscous liquid, soluble in chloroform. Decomposition occurs during attempts to distil the product; yield 32.0 g. (85.5%). *Anal.* Calcd. for $C_{16}H_{18}Cl_2O_3PN$: P, 8.3; Cl, 19.0; N, 3.7. Found: P, 7.9; Cl, 19.5; N, 3.4.

Reactions of Diphenyl Phosphonate. Chlorination. (a) **Sulfuryl Chloride. Diphenyl Phosphorochloridate.**—Sulfuryl chloride (42.0 g., 0.312 mole) was added dropwise during 30 minutes to 70.2 g. (0.3 mole) of diphenyl phosphonate at 0–5°. The reaction was exothermic; within 10 minutes hydrogen chloride was liberated. The reaction mixture was stirred at 5° for 20 minutes longer and the temperature was allowed to rise to 25°. The reaction was no longer exothermic. The pressure was reduced as rapidly as possible and the product was distilled; yield 70.1 g. (87.2%), b.p. 141° (1 mm.), $n^{25}D$ 1.5490. *Anal.* Calcd. for $C_{12}H_{10}ClO_3P$: P, 11.5; Cl, 13.2. Found: P, 11.5; Cl, 13.3.

(b) **Chlorine. Diphenyl Phosphorochloridate.**—Chlorine, 28.4 g., was passed into a solution of 93.5 g. (0.4 mole) of diphenyl phosphonate in 400 ml. of carbon tetrachloride at 0–5°. A vigorous exothermic reaction ensued and the by-product hydrogen chloride escaped through the exhaust vent. The end-point was observed as the typical green color of dissolved chlorine appeared in the reaction mixture. The product was isolated by distillation; yield 87.5 g. (81.3%), b.p. 141° (1 mm.), $n^{25}D$ 1.5480. *Anal.* Found: P, 11.4; Cl, 13.3.

Bis-(2-chlorophenyl) Phosphorochloridate.—The preparation was conducted as above on a 0.136-mole scale; yield 47.7 g. (80.2%), b.p. 156° (1 mm.), $n^{25}D$ 1.5670. *Anal.* Calcd. for $C_{12}H_8O_3Cl_3P$: P, 9.2; Cl, 31.6. Found: P, 9.3; Cl, 31.7.

When a similar reaction was conducted with bis-(methylphenyl) phosphonates a considerable amount of the chlorine entered the hydrocarbon group.

Conversion to a Neutral Phosphate. Diphenyl Ethyl Phosphate.—A solution of 33.3 g. of triethylamine and 15.2 g. of ethyl alcohol in 50 ml. of carbon tetrachloride was added dropwise to a solution of 70.2 g. (0.3 mole) of diphenyl phosphonate in 300 ml. of carbon tetrachloride while stirring at 15–20°. An exothermic reaction occurred; triethyl ammonium chloride precipitated. When the addition was complete, the reaction mixture was stirred one hour longer at 15–20°. The reaction mixture was then washed twice with 100 ml. of water to remove the triethylammonium chloride. Titration of the wash waters indicated 0.305 equivalent of chloride ion was formed. The product was separated from the carbon tetrachloride solution by distillation.

A total of 70.0 g. of neutral esters boiling over a temperature range of 150–180° under 2 mm. pressure was collected. Fractional distillation indicated the product was a mixture of ethyl phenyl phosphates; however, no simple rectification was effected. *Anal.* Calcd. for $C_{14}H_{15}O_4P$: P, 11.2; P (trivalent), 0.0. Found: (total distillate) P, 11.0; P (trivalent), 0.0.

Alcoholysis. Bis-(2-ethylhexyl) Phosphonate.—Diphenyl phosphonate (70.2 g., 0.3 mole) was dissolved in 87.0 g. (0.6 mole) of 2-ethylhexanol. The solution was heated to 100° for one hour, cooled and distilled. A forerun of phenol, 52.3 g., was collected, boiling primarily at 55° under 1 mm. pressure. The remaining product was distilled to yield 85.2 g. (93.2%), b.p. 148–151° (1 mm.), $n^{25}D$ 1.4430, $d^{25}{}_{25}$ 0.940; physical constants of an authentic sample: $n^{25}D$ 1.4420, $d^{25}{}_{25}$ 0.930. *Anal.* Calcd. for $C_{16}H_{35}O_3P$: P, 10.1; P (trivalent), 10.1. Found: P, 10.3; P (trivalent), 10.0.

Addition of Sulfur. Triethylammonium Diphenyl Phosphorothioate.—Diphenyl phosphonate (46.8 g., 0.2 mole) was added to a suspension of 6.4 g. (0.2 mole) of sulfur in 100 ml. of ether. No reaction occurred. While stirring the resulting mixture, triethylamine (21.0 g., 0.208 mole), was added dropwise. A vigorous exothermic reaction ensued during which the sulfur was consumed; a dark oil precipitated. The reaction mixture was cooled and the oil phase was separated and extracted with 50 ml. of ether. The residual ether was removed under reduced pressure, and the residue, stabilized at 50° under 1 mm. pressure, was collected as an oil; yield 63.7 g. (86.7%), $n^{25}D$ 1.5535.

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(13) H. G. Cook, B. C. Saunders and F. E. Smith, *J. Chem. Soc.*, 635 (1949).

Anal. Calcd. for $C_{18}H_{26}O_3SNP$: P, 9.3; S, 9.6; N, 4.2. Found; P, 9.3; S, 9.3; N, 4.1.

Addition to Aldehydes and Ketones. Diphenyl 2,2,2-Trichlorohydroxyethylphosphonate.—Diphenyl phosphonate (23.4 g., 0.1 mole) was added dropwise to 14.75 g. of chloral while stirring at 25–45°. An instantaneous exothermic reaction occurred. The reaction mixture was then heated to 80° for 10 minutes and cooled. The product solidified, forming a white mass. Ten grams was recrystallized from benzene; recovery 9.5 g., m.p. 120–127°; after four recrystallizations, m.p. 129–130°. *Anal.* Calcd. for $C_{14}H_{12}O_4Cl_3P$: P, 8.1; Cl, 27.9. Found: P, 8.2; Cl, 28.0.

Diphenyl Phenylhydroxymethylphosphonate.—Diphenyl phosphonate (46.8 g., 0.2 mole) was added to 23.0 g. (0.217 mole) of benzaldehyde. No sign of reaction was observed. Triethylamine (1.6 g.) was added dropwise. A vigorous, exothermic reaction was observed; the temperature rose to 90° (from 23°) within one minute and the reaction mixture solidified. The solid was dissolved in 300 ml. of hot benzene, and the product was isolated by fractional crystallization; yield 53.9 g. (79%); recrystallized from benzene, m.p. 138–140° (m.p. reported[14] 146°). *Anal.* Calcd. for $C_{18}H_{17}O_4P$: P, 9.1; OH, 5.0. Found: P, 9.5; OH, 4.7.

Diphenyl 2-Hydroxy-2-propylphosphonate.—Diphenyl phosphonate (46.8 g., 0.2 mole) was dissolved in 200 ml. of acetone. Sulfuric acid, 0.4 g., was added. A slightly exothermic reaction was observed which subsided within 5 minutes. The mixture was heated at reflux for 16 hours, cooled, and the excess solvent was removed under reduced pressure. The residue at 100° under 2 mm. pressure was collected; yield 55.0 g. (94.6%), $n^{25}D$ 1.5460. *Anal.* Calcd. for $C_{15}H_{17}O_4P$: P, 10.6; OH, 5.8. Found: P, 10.6; OH, 5.6.

An attempt to distil the product led to a decomposition reaction which began at 130°. A solid precipitated on standing; yield 12.0 g., m.p. 113–115° (from benzene and hexane) (m.p. reported[14] 113–114°). *Anal.* Found: P, 10.5; OH, 5.6.

This compound reacts with carbon tetrachloride and ammonia to liberate chloride ion in amount equivalent to the hydroxyl content. This indicates the compound undergoes a reverse reaction under these conditions to liberate acetone and diphenyl phosphonate.

Diphenyl 1-Hydroxybutylphosphonate.—Diphenyl phosphonate (23.4 g., 0.1 mole) was added to 7.4 g. (0.103 mole) of butyraldehyde. A slightly exothermic reaction was observed. Triethylamine was cautiously added; the temperature rose to 65° (from 24°). The triethylamine addition was continued until no further sign of reaction was noted; a total of 2.1 g. of triethylamine was added. The reaction mixture was dissolved in 50 ml. of benzene and 100 ml. of hexane was added. An oil separated which was collected and stabilized to 70° under 2 mm. pressure; yield 14.5 g., $n^{25}D$ 1.5358. *Anal.* Calcd. for $C_{16}H_{19}O_4P$: P, 10.1; OH, 5.6. Found: P, 9.7; OH, 5.7. The product decomposed during an attempted distillation.

The benzene–hexane solution was concentrated under reduced pressure to yield 17.0 g. of viscous oil, $n^{25}D$ 1.5348. *Anal.* Found: P, 9.7.

Condensation Reactions. Diphenyl N,N-Dibutylaminomethylphosphonate.—Dibutylamine (45 g., 0.35 mole) was caused to react with 11.0 g. (0.367 mole) of formaldehyde by heating the mixture to 100–120°. The resulting product was cooled to 20–25° and 78.8 g. (0.337 mole) of diphenyl phosphonate was added dropwise while cooling to maintain the temperature. When the addition was complete, the reaction mixture was allowed to warm to 40° and this temperature was maintained until the reaction was no longer exothermic (20 minutes). The reaction mixture was then heated to 80° for 30 minutes and cooled. After standing for one day at room temperature, the mixture solidified. Fractional crystallization from benzene yielded 59.0 g. (47%) of crystals, m.p. 86–88°. The mother liquor, when concentrated, yielded 67.0 g. (52%) of solid product, m.p. 75–82°, as a residue. *Anal.* of recrystallized product: Calcd. for $C_{21}H_{30}O_3PN$: P, 8.3; N, 3.7. Found: P, 8.0; N, 3.7.

Diphenyl Phenyl N,N-Diethylaminomethylphosphonate.—Diethylamine (14.6 g., 0.2 mole) was added to a solution of 10.6 g. (0.1 mole) of benzaldehyde in 100 ml. of benzene. To the resulting solution was added 23.4 g. (0.1 mole) of diphenyl phosphonate at below 30° while stirring in a cooling bath. The reaction mixture was stirred for 30 minutes longer at 30° and then heated at reflux for one hour. The reaction mixture was concentrated under reduced pressure, and the residue at 70° under 1 mm. pressure, a viscous oil, was collected. Attempts to crystallize this residue from various organic solvents were unsuccessful; yield 39.5 g. (100%), $n^{25}D$ 1.5636. *Anal.* Calcd. for $C_{23}H_{26}O_3NP$: P, 7.8; N, 3.5. Found: P, 7.7; N, 3.3. The product decomposed during an attempted distillation.

Diphenyl 1,1-N,N-Diethylaminobutylphosphonate.—Diphenyl phosphonate (23.4 g., 0.1 mole) was added dropwise while cooling, to the reaction product of 7.5 g. (0.103 mole) of diethylamine and 7.4 g. (0.103 mole) of butyraldehyde in 100 ml. of benzene. The reaction was exothermic; the temperature was held at below 35°. When the addition was complete, the reaction mixture was heated at reflux for 30 minutes. The solvents were then removed by distillation. The residue at 70° under 1 mm. pressure, a viscous, undistillable oil, was collected; yield 35.8 g. (99%), $n^{25}D$ 1.5225. *Anal.* Calcd. for $C_{13}H_{28}O_3NP$: P, 8.6; N, 3.9. Found: P, 8.6; N, 3.6.

Acknowledgment.—The author is indebted to Messrs. D. Bernhart and W. Chess for the analytical data presented in this paper. He also wishes to acknowledge the valuable assistance and advice of Drs. L. F. Audrieth, T. M. Beck and A. D. F. Toy, during the course of this investigation.

CHICAGO HTS., ILL.

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[14] J. B. Conant, V. H. Wallingford and S. S. Gandheker, THIS JOURNAL, **45**, 762 (1923).

[CONTRIBUTION FROM THE LABORATORIES OF THE UPJOHN CO.]

Nitrogen Mustard Derivatives Containing the Phosphonate Group[1]

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RECEIVED OCTOBER 15, 1958

A group of nitrogen mustard derivatives containing a dialkyl phosphonate group was prepared. The synthesis of the appropriate aralkylphosphonate esters followed by nitration, reduction and alkylation with ethylene oxide yielded dialkyl *p*-[N,N-*bis*-(2-hydroxyethyl)-amino]-aralkylphosphonates (*e.g.*, VII). Treatment with thionyl chloride in the presence of pyridine and excess pyridine hydrochloride yielded the chloro nitrogen mustards (*e.g.*, X) and treatment with methanesulfonyl chloride followed by sodium iodide yielded the iodo nitrogen mustards (*e.g.*, IX). The most potent antitumor agent in this series, IX, prolonged the life of ascitic mice longer than Chlorambucil, was of the same order of activity as Chlorambucil against Sarcoma 180, and was somewhat less active against Walker 256 in rats. Compound IX appeared to be less toxic than Chlorambucil.

Since the discovery of the cytotoxic properties of nitrogen mustard by Gilman and Philips[2] in 1946, numerous alkylating agents have been prepared. These compounds are characterized by a high order of selective toxicity toward certain

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[1] Presented in part before the 134th Meeting of The American Chemical Society, Chicago, Ill., September, 1958.

[2] A. Gilman and F. S. Philips, *Science*, **103**, 409 (1946).