

*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<sup>14</sup> 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%),  $n_D^{25}$  1.5460. *Anal.* Calcd. for  $C_{13}H_{17}O_4P$ : 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<sup>14</sup> 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.,  $n_D^{25}$  1.5358. *Anal.* Calcd. for  $C_{15}H_{19}O_4P$ : P, 10.1;

(14) J. B. Conant, V. H. Wallingford and S. S. Gandheker, *This Journal*, **45**, 762 (1923).

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,  $n_D^{25}$  1.5348. *Anal.* Found: P, 9.7.

**Condensation Reactions. Diphenyl N,N-Dibutylamino-methylphosphonate.**—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%),  $n_D^{25}$  1.5636. *Anal.* Calcd. for  $C_{23}H_{28}O_3NP$ : 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%),  $n_D^{25}$  1.5225. *Anal.* Calcd. for  $C_{19}H_{25}O_3NP$ : 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.

[CONTRIBUTION FROM THE LABORATORIES OF THE UPJOHN CO.]

## Nitrogen Mustard Derivatives Containing the Phosphonate Group<sup>1</sup>

BY FRED KAGAN, ROBERT D. BIRKENMEYER AND RICHARD E. STRUBE

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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<sup>2</sup> in

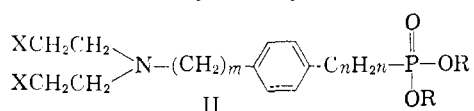
(1) Presented in part before the 134th Meeting of The American Chemical Society, Chicago, Ill., September, 1958.

1946, numerous alkylating agents have been prepared. These compounds are characterized by a high order of selective toxicity toward certain

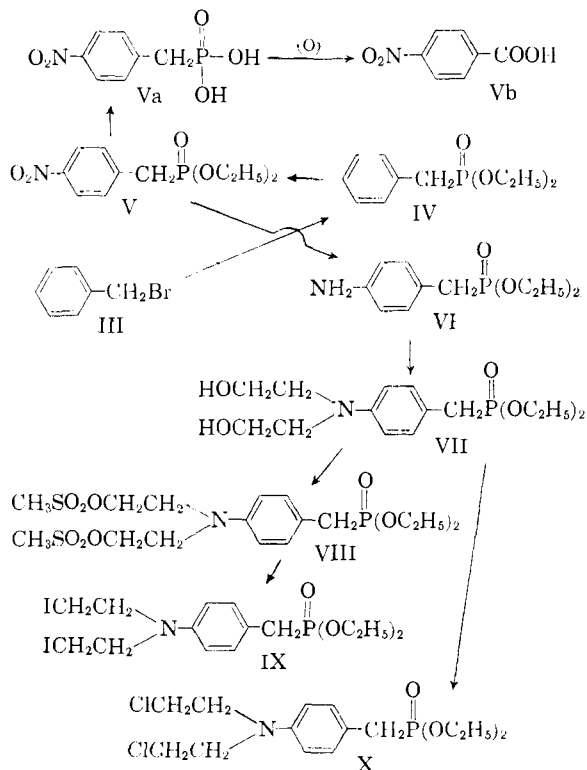
(2) A. Gilman and F. S. Philips, *Science*, **103**, 409 (1946).

types of rapidly growing tissues, e.g., hematopoietic cells in bone marrow and lymphoid organs, the intestinal mucosa, and a few types of neoplastic tissue. Although these compounds have been valuable adjuncts in the treatment of certain neoplastic diseases, particularly those of the hematopoietic system, the limiting factor in their use has been the bone marrow damage they produce. If a nitrogen mustard could be prepared which showed a high degree of cytotoxic specificity toward tumor tissue with little effect on bone marrow and intestinal mucosa, a highly desirable antitumor agent would be at hand. Since phosphorus compounds play such an important role in the economy of living cells, we chose to introduce the phosphonic acid moiety into nitrogen mustard derivatives to determine the effect on antitumor activity and host toxicity.

The compounds reported in this paper can be represented by the generalized formula II, where X is chlorine or iodine,  $m$  is 0 and 1,  $n$  is 0 to 3 inclusive, and R is methyl or ethyl.

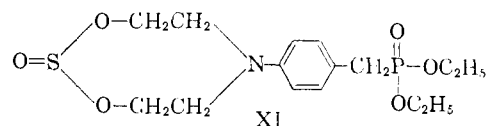


The synthetic scheme used to prepare II in which  $m$  is zero and  $n$  is greater than zero can be illustrated by the synthesis of diethyl *p*-[N,N-bis-(2-iodoethyl)amino]benzylphosphonate (IX) and the corresponding chloro analog X. Benzyl bromide was converted to the phosphonate IV by treatment with triethyl phosphite in a typical Michaelis-Arbusov reaction.<sup>3</sup> The aralkyl phos-

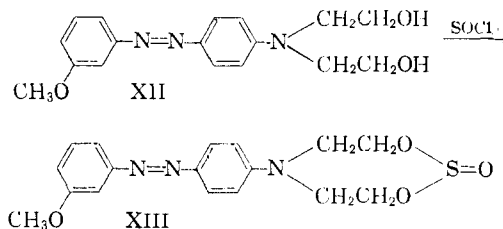


(3) See "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 286.

phonates similar to IV which were prepared in this work were generally liquids which were characterized by acid hydrolysis to the phosphonic acids. Nitration of IV with a nitric acid-sulfuric acid mixture at 0°<sup>4</sup> proceeded smoothly to yield diethyl *p*-nitrobenzylphosphonate (V) in 95% yield, characterized by hydrolysis to the free acid Va and oxidation to *p*-nitrobenzoic acid (Vb). Catalytic hydrogenation of V in the presence of either platinum or 10% palladium-on-charcoal gave diethyl *p*-aminobenzylphosphonate (VI) in good yield. Treatment with ethylene oxide in acetic acid<sup>5</sup> yielded the bis-2-hydroxyethylamine VII as a viscous oil, generally used for further synthesis without purification. Satisfactory yields of X (54%) were obtained by chlorinating with thionyl chloride in chloroform in the presence of pyridine and pyridine hydrochloride. This reaction is complicated by the formation of cyclic compounds involving the chlorinating agent and the bis-2-hydroxyethylamine. In the case of the reaction of VII with thionyl chloride in benzene a compound was isolated which showed no hydroxyl absorption in the 3200-3400 cm.<sup>-1</sup> range in the infrared spectrum, did not contain halogen (Beilstein test), was recovered unchanged (infrared spectrum) after being heated in a solution of pyridine in toluene, and which slowly lost oxides of sulfur on standing. Although this material could not be purified adequately for analysis, it seems likely



from the information at hand that its structure can be represented by XI. Ross and Warwick<sup>6</sup> have reported the formation of a similar type of compound, XIII, from XII.



The iodo analog of X was obtained from VII by conversion to the mesylate VIII with methanesulfonyl chloride in pyridine followed by treatment with sodium iodide in acetone at room temperature for 30 hours.

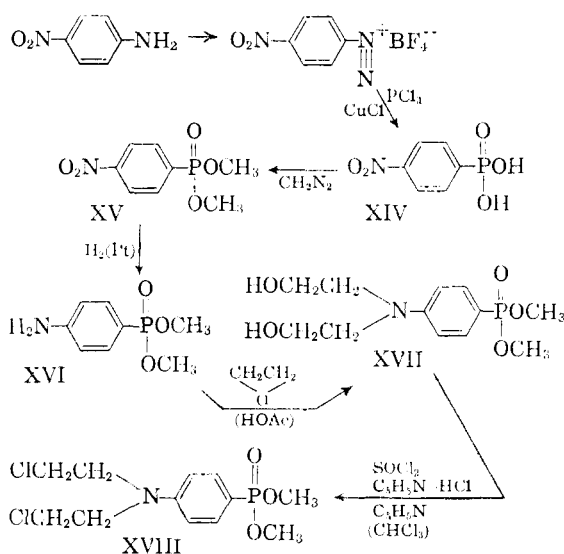
The nitrogen mustard XVIII in which  $n = 0$  (cf. II) was obtained by essentially the same procedure from *p*-nitrophenylphosphonic acid (XIV), which in turn was prepared from *p*-nitroaniline by the method of Doak and Freedman.<sup>7</sup> Esterification of XIV with ethereal diazomethane yielded the methyl ester XV which was carried

(4) G. M. Kosolapoff, *THIS JOURNAL*, **71**, 1876 (1949), method A.

(5) J. I. Everett, J. J. Roberts and W. C. J. Ross, *J. Chem. Soc.*, 2386 (1953).

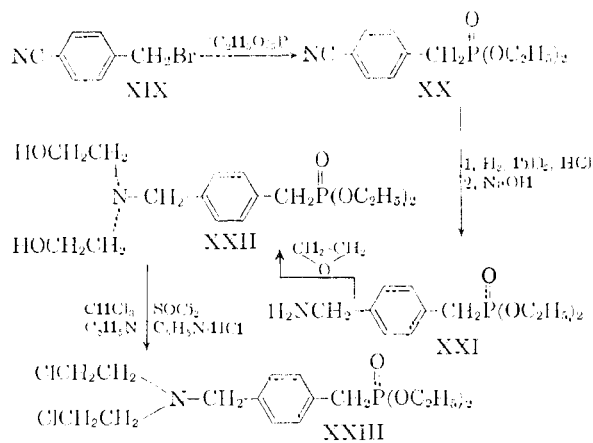
(6) W. C. J. Ross and G. P. Warwick, *ibid.*, 1364 (1956).

(7) C. O. Doak and I. D. Freedman, *THIS JOURNAL*, **73**, 5658 (1951).



through the sequence XVI  $\rightarrow$  XVII  $\rightarrow$  XVIII as described above for the synthesis of X.

The nitrogen mustard XXIII, an aralkylphosphonate derivative of methyl-bis-(2-chloroethyl)-amine, was prepared from *p*-cyanobenzyl bromide (XIX) by conversion to the phosphonate XX in refluxing triethyl phosphite, followed by reduction to the amine XXI which was converted to the nitrogen mustard XXIII by the method described above.



The antitumor evaluation of these compounds in mice was done by Dr. J. S. Evans<sup>8</sup> of these laboratories. His results showed that the phosphonate nitrogen mustard II, in which  $m = 0$ ,  $X = \text{Cl}$ ,  $n = 3$  and  $R = \text{C}_2\text{H}_5$  was much less toxic than Chlorambucil<sup>5,9</sup>; however, it was less active as an antitumor agent. Replacement of the chlorine atoms in the phosphonate nitrogen mustards by iodine enhanced antitumor activity; and diethyl *p*-N,N-bis(2-iodoethyl)-aminobenzylphosphonate (IX) proved to be of the same order of activity as Chlorambucil against Sarcoma 180 and

(8) J. S. Evans, Abstracts 134th Meeting of the American Chemical Society, p. 27-O (1958).

(9) The antitumor activity of Chlorambucil against the Walker tumor was summarized by A. Haddow, Leukemic Research, "Ciba Foundation Symposium," 196 (1954), Little, Brown and Co., Boston, Mass.

TABLE I  
DIALKYL PHOSPHONATES AND THE PHOSPHONIC ACIDS

R	B.p., °C.		Yld., %	$n_D^{20}$	Empirical formula	Analyses, %		Crystall. solvent <sup>a</sup>	M.p., °C.	Empirical formula	Phosphonic acids		Analyses, %					
	Found	Calcd.				Found	Calcd.				Found	Calcd.						
$\text{C}_6\text{H}_5\text{CH}_2-$	160-164	15	95	1.4938	$\text{C}_{11}\text{H}_{19}\text{O}_3\text{P}$	12.09 <sup>d</sup>	12.34 <sup>d</sup>	a	173-175 <sup>b</sup>	$\text{C}_7\text{H}_9\text{O}_3\text{P}$	48.84	5.27	18.00	86	48.81	5.13	17.84	86
$\text{C}_6\text{H}_5\text{C}(\text{CH}_3)\text{H}-$	158-160	15	62	1.4972	$\text{C}_{12}\text{H}_{19}\text{O}_3\text{P}$	12.09 <sup>d</sup>	12.34 <sup>d</sup>	b	153-154.5	$\text{C}_8\text{H}_{11}\text{O}_3\text{P}$	51.61	5.96	16.61	93	51.86	5.89	16.72	95
$\text{C}_6\text{H}_5-\text{CH}_2\text{CH}_2-$	173-177	14	76	1.4910	$\text{C}_{12}\text{H}_{19}\text{O}_3\text{P}$	12.09 <sup>d</sup>	12.34 <sup>d</sup>	a	138.5-140	$\text{C}_8\text{H}_{11}\text{O}_3\text{P}$	51.61	5.96	16.61	93	51.52	5.93	16.76	92
$\text{C}_6\text{H}_5(\text{CH}_2)_2-$	125-128	0.1	87	1.4908	$\text{C}_{12}\text{H}_{19}\text{O}_3\text{P}$	12.09 <sup>d</sup>	12.34 <sup>d</sup>	b	123-125	$\text{C}_9\text{H}_{13}\text{O}_3\text{P}$	51.00	6.54	15.48	100	53.99	6.64	15.55	96
$\text{C}_6\text{H}_5-\text{O}-\text{CH}_2\text{CH}_2-$	135-140	.1	83	1.4947	$\text{C}_{12}\text{H}_{19}\text{O}_3\text{P}$	12.00	11.61											
$\text{C}_6\text{H}_5-\text{O}(\text{CH}_2)_2-$	140-145	.1	84	1.4939	$\text{C}_{13}\text{H}_{21}\text{O}_3\text{P}$	11.38	10.95											

<sup>a</sup> *n*, isopropyl alcohol-methylcyclohexane; <sup>b</sup> ethyl acetate-methylcyclohexane. <sup>c</sup> Kosoloff gave the m.p. as 166° after recrystallization from water; see ref. 10. <sup>d</sup> The equivalent weight was determined by potentiometric titration in aqueous alcohol solution using a Precision Scientific Recordomatic Titrator equipped with a glass-calomel electrode system; standard deviation  $\pm 2\%$ . <sup>e</sup> Calcd.; C, 60.92; H, 8.26. Found: C, 60.92; H, 8.15.

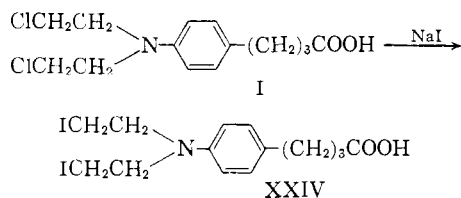
TABLE II  
 DIETHYL *p*-NITROARALKYLPHOSPHONATES

Phosphonate esters											
No.	<i>p</i> -NO <sub>2</sub> R	B.p.		Yield, %	<i>n</i> <sub>D</sub> <sup>25</sup>	Empirical formula	Analyses, %				
		C.	Mm.				Calcd.		Found		
1	O <sub>2</sub> N-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	148-153	0.1	96	1.5220	C <sub>11</sub> H <sub>16</sub> NO <sub>5</sub> P					
2	O <sub>2</sub> N-C <sub>6</sub> H <sub>4</sub> -C(CH <sub>3</sub> )H	153-158	.08	68	1.5172	C <sub>12</sub> H <sub>18</sub> NO <sub>5</sub> P	50.17	6.32	4.88	10.79	
3	O <sub>2</sub> N-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> CH <sub>2</sub>	160-165	.05	88	1.5165						
4	O <sub>2</sub> N-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>	163-168	.1	51	1.5123	C <sub>13</sub> H <sub>20</sub> NO <sub>5</sub> P	51.84	6.60	4.65	10.29	
5		a		44		C <sub>12</sub> H <sub>17</sub> NO <sub>5</sub> P	41.38	4.92	8.05		
6		b		43		C <sub>13</sub> H <sub>19</sub> N <sub>2</sub> O <sub>5</sub> P	43.10	5.29	7.73	8.55	
Phosphonic acids											
No.	M.p. C.	Crystn. solvent	Empirical formula	Analyses, %							
				Calcd.		Found					
1	232-234	c	C <sub>7</sub> H <sub>8</sub> NO <sub>5</sub> P	38.72	3.71	6.45	14.27	38.53	3.92	6.34	14.37
2											
3	174-175	d	C <sub>8</sub> H <sub>10</sub> NO <sub>5</sub> P	41.57	4.36	6.06	13.40 <sup>e</sup>	41.83	4.42	6.20	13.61 <sup>e</sup>
4											
5											
6											

<sup>a</sup> M.p. 88-89°, from methylene chloride-ether. <sup>b</sup> M.p. 73-74°, from isopropylalcohol-ether. <sup>c</sup> Isopropyl alcohol-methylcyclohexane. <sup>d</sup> Ethyl acetate. <sup>e</sup> Equiv. wt. calcd. 116, found 118.

less toxic. It also showed good activity against the Walker 256 tumor in rats and Ehrlich's ascites tumor in mice

The iodine analog XXIV of Chlorambucil was prepared in 37% yield by treatment of the latter



with sodium iodide in acetone solution at 100°. In the phosphonate-containing nitrogen mustard series the iodine compounds were more active antitumor agents than the chloro derivatives. In the carboxylic acid XXIV, however, the iodine derivative was less active than Chlorambucil against the Walker tumor and Sarcoma 180; however it was more effective in prolonging the lives of mice with Ehrlich's ascites tumors.

**Acknowledgments.**—We wish to express our appreciation to Dr. James L. Johnson and his associates for spectral analyses and to Mr. William A. Struck and his associates for microanalyses.

#### Experimental<sup>10</sup>

Diethyl aralkylphosphonates were prepared by heating the appropriate aralkyl halide with an excess of triethyl phosphite at the reflux temperature for 18 hours in a manner similar to that described by Kosolapoff.<sup>11</sup> The products, oils, were purified by distillation through a Claisen head and characterized by acid hydrolysis to the phosphonic acids.

**Diethyl *p*-Nitroaralkylphosphonates.**—Conversion of the diethyl aralkylphosphonates to their *p*-nitro derivatives

was accomplished with a nitric acid-sulfuric acid mixture (1:1 v./v.) at 0°.<sup>3</sup>

**Diethyl *p*-Nitrobenzylphosphonate.**—Treatment of diethyl benzylphosphonate in the above manner yielded an oil (96% yield), b.p. 148-153° (0.1 mm.), *n*<sub>D</sub><sup>25</sup> 1.5220.

*Anal.* Calcd. for C<sub>11</sub>H<sub>16</sub>NO<sub>5</sub>P: N, 5.13; P, 11.34. Found: N, 4.92; P, 11.27.

Acid hydrolysis of this material yielded a phosphonic acid, m.p. 232-234° after recrystallization from isopropyl alcohol-methylcyclohexane. Kosolapoff<sup>3</sup> reported that *p*-nitrobenzylphosphonic acid melted at 226° (from water) and Litthauer<sup>12</sup> reported 217° (from nitric acid). Our material was identical to an authentic sample, prepared by nitration of benzylphosphonic acid, as shown by comparison of their melting points, mixed melting points and infrared spectra.

***p*-Nitrobenzylphosphonic Acid.**—Benzylphosphonic acid was treated with fuming nitric acid (sp. gr. 1.5) at -20° for 5 minutes according to the procedure described by Litthauer.<sup>12</sup> The product, *p*-nitrobenzylphosphonic acid, after recrystallization from isopropyl alcohol-methylcyclohexane, melted at 232-234°.

*Anal.* Calcd. for C<sub>7</sub>H<sub>8</sub>NO<sub>5</sub>P: C, 38.72; H, 3.71; N, 6.45; P, 14.27. Found: C, 38.53; H, 3.92; N, 6.34; P, 14.37.

Oxidation of the *p*-nitrobenzylphosphonic acid, m.p. 232-234°, with sodium dichromate-sulfuric acid produced the theoretical yield of *p*-nitrobenzoic acid.

**Diethyl 3-(Dinitrophenoxy)-propylphosphonate.**—Nitration of diethyl 3-(phenoxy)-propylphosphonate yielded a dinitro compound as the only product, m.p. 73-74°, after recrystallization from isopropyl ether.

*Anal.* Calcd. for C<sub>13</sub>H<sub>19</sub>N<sub>2</sub>O<sub>5</sub>P: C, 43.10; H, 5.29; N, 7.73. Found: C, 42.86; H, 5.30; N, 7.31.

**Dimethyl *p*-Nitrophenylphosphonate.**—To a stirred suspension of 25 g. (0.123 mole) of powdered *p*-nitrophenylphosphonic acid<sup>6</sup> in 250 ml. of dry ether was added an excess of ethereal diazomethane<sup>13</sup> at 5-10°. After the addition was completed, stirring was continued for 15 minutes. The excess of diazomethane was destroyed with dilute hydrochloric acid and the colorless ether layer was separated and dried over anhydrous magnesium sulfate. Removal of the

(10) All melting points were taken in capillary tubes with Anschütz total immersion thermometers.

(11) G. N. Kosolapoff, *THIS JOURNAL*, **67**, 2259 (1945).

(12) S. Litthauer, *Ber.*, **22**, 2144 (1889).

(13) A. F. McKay, *THIS JOURNAL*, **70**, 1974 (1948).

TABLE III  
 DIALKYL *p*-AMINOARALKYLPHOSPHONATES

				Aminophosphonates										
<i>m</i>	R	<i>n</i>	R'	Yd., %	M.p., °C.	Empirical formula	Calcd.				Analyses, %			
							C	H	N	P	C	H	N	P
0	H	0	CH <sub>3</sub>	57	105-106.5	C <sub>8</sub> H <sub>12</sub> NO <sub>3</sub> P	47.76	6.01	6.96		48.06	5.85	6.70	
0	H	1	C <sub>2</sub> H <sub>5</sub>	70	91-92	C <sub>11</sub> H <sub>15</sub> NO <sub>3</sub> P	54.31	7.46	5.76	12.74	53.97	7.33	5.47	12.93
0	CH <sub>3</sub>	1	C <sub>2</sub> H <sub>5</sub>	72	116-117	C <sub>12</sub> H <sub>20</sub> NO <sub>3</sub> P	56.02	7.84	5.45		56.06	7.76	5.56	12.05
0	H	2	C <sub>2</sub> H <sub>5</sub>	100	<sup>a</sup>	C <sub>12</sub> H <sub>20</sub> NO <sub>3</sub> P			5.45	12.04			5.47	12.15
0	H	3	C <sub>2</sub> H <sub>5</sub>	100	<sup>a</sup>	C <sub>13</sub> H <sub>22</sub> NO <sub>3</sub> P <sup>d</sup>	57.55	8.18	5.16	11.42	57.86	8.70	4.99	11.00
1	H	1	C <sub>2</sub> H <sub>5</sub>	79		C <sub>12</sub> H <sub>20</sub> NO <sub>3</sub> P			5.45	12.04			5.30	11.79

<sup>a</sup> Small quantities could be distilled in a flash distillation, b.p. 175° (0.07 mm.). Larger quantities could be distilled in a falling film molecular still (Arthur Thomas Co.), b.p. 163-164° (skin temp.) (0.005 mm.), *n*<sub>D</sub><sup>20</sup> 1.5253 (crude yield given). <sup>b</sup> Same as *a*, b.p. in flash distillation, 175° (0.1 mm.), *n*<sub>D</sub><sup>20</sup> 1.5202 (crude yield given). <sup>c</sup> Prepared by catalytic reduction of diethyl *p*-cyanobenzylphosphonate, b.p. 137-139° (0.05 mm.) (flash distillation). <sup>d</sup> Picrate, m.p. 168-169°. Calcd. for C<sub>16</sub>H<sub>22</sub>N<sub>3</sub>O<sub>6</sub>P: C, 45.60; H, 5.04; N, 11.20; P, 6.19. Found: C, 45.65; H, 4.85; N, 10.94; P, 6.09.

TABLE IV

DIALKYL *N,N*-(2-HYDROXYETHYL)-*p*-AMINOARALKYLPHOSPHONATES<sup>a</sup>

<i>m</i>	R	<i>n</i>	R'	Crude Yd., %	Empirical formula	Calcd.				Analyses, %			
						C	H	N	P	C	H	N	P
0	H	0	CH <sub>3</sub>	95 <sup>c</sup>	C <sub>12</sub> H <sub>20</sub> NO <sub>3</sub> P			4.84	10.79 <sup>e</sup>			4.55	10.37 <sup>e</sup>
0	H	1	C <sub>2</sub> H <sub>5</sub>	97	C <sub>15</sub> H <sub>16</sub> NO <sub>3</sub> P			4.23	9.35			4.27	9.13
0	CH <sub>3</sub>	1	C <sub>2</sub> H <sub>5</sub>	95	C <sub>16</sub> H <sub>26</sub> NO <sub>3</sub> P <sup>b</sup>								
0	H	2	C <sub>2</sub> H <sub>5</sub>	95	C <sub>16</sub> H <sub>28</sub> NO <sub>3</sub> P	55.64	8.17	4.06	8.97	55.06	8.29	4.02	9.12
0	H	3	C <sub>2</sub> H <sub>5</sub>	96	C <sub>17</sub> H <sub>30</sub> NO <sub>3</sub> P			3.90	8.62			3.74	8.06
1	H	1	C <sub>2</sub> H <sub>5</sub>	94	C <sub>16</sub> H <sub>28</sub> NO <sub>3</sub> P			4.06	8.97			3.89	8.40

<sup>a</sup> These compounds were viscous oils which were difficult to purify. They were generally used in the crude form for further synthesis. <sup>b</sup> Not characterized. <sup>c</sup> The infrared spectra of material purified by chromatography over Florisil and the crude product were identical. <sup>d</sup> Bis-(carbamate), m.p. 92-93°. *Anal.* Calcd.: C, 48.92; H, 6.76; N, 10.07; P, 7.42. Found: C, 48.98; H, 7.10; N, 10.27; P, 7.03. <sup>e</sup> Equiv. wt. calcd. 289, found 294.

ether under reduced pressure yielded 21 g. (76%) of dimethyl *p*-nitrophenylphosphonate, m.p. 58-59.5°. Recrystallization from methylcyclohexane yielded the purified product, m.p. 61-62°. This material was catalytically reduced and characterized as the amine.

**Diethyl *p*-Aminoalkylphosphonates.**—Alcohol solutions of the *p*-nitroalkylphosphonates were catalytically hydrogenated in the presence of 10% palladium-on-charcoal or platinum at room temperature at 50-30 p.s.i. in Parr hydrogenation equipment. The products which were solids were easily purified by recrystallization. Those which were oils were purified for analysis by distillation.

**Diethyl *p*-(*N,N*-Bis-(2-hydroxyethyl)-amino)-benzylphosphonate.**—Diethyl *p*-aminoalkylphosphonates were treated with an excess of ethylene oxide in 1 *N* acetic acid according to the method of Everetts, *et al.*<sup>4</sup> The bis-(2-hydroxyethyl)-amino derivatives were viscous oils which were generally used in subsequent steps without purification. In several cases, analytical samples were prepared by chromatography over Florisil<sup>4</sup> with Skellysolve B<sup>15</sup>-acetone as eluting solvent.

**Chloro-nitrogen Mustards.**—Bis-(2-Hydroxyethyl)-amines were converted to the chloro-nitrogen mustards by treatment with thionyl chloride in chloroform solution in the presence of excess pyridine hydrochloride and pyridine. The synthesis of X is a typical example of this type of preparation.

**Diethyl *p*-[*N,N*-Bis-(2-chloroethyl)-amino]-benzylphosphonate.** A solution of VII (0.03 mole) in 200 ml. of chloroform was added dropwise with stirring over a 2-hour period to a mixture of 1 l. of dry chloroform, 25 g. of pyridine hy-

drochloride, 20 ml. of dry pyridine and 75 ml. of thionyl chloride at 25-32°. The chloroform, thionyl chloride and most of the pyridine were removed under reduced pressure, the temperature being kept below 25°. Methylene chloride (500 ml.) was added to the dark residual oil, the solution was cooled to 15° and washed with three 200-ml. portions of ice-water. After being dried over anhydrous sodium sulfate, the solution was concentrated under reduced pressure to a dark oil with a green cast (9.8 g.). Purification was accomplished by chromatography over a 1' × 16" column of Florisil. The crude material was applied in methylene chloride, developed with petroleum ether, and eluted with petroleum ether-acetone (9:1). Six liters of effluent yielded a pale amber oil (6.0 g., 54%) which crystallized after scratching. Recrystallization from petroleum ether yielded an analytical sample, m.p. 58-59°.

*Anal.* Calcd. for C<sub>15</sub>H<sub>21</sub>Cl<sub>2</sub>NO<sub>3</sub>P: C, 48.92; H, 6.57; Cl, 19.26; N, 3.80; P, 8.41. Found: C, 48.62; H, 6.44; Cl, 18.43; N, 3.79; P, 8.49.

**Diethyl *p*-Cyanobenzylphosphonate.**—A mixture of 370 g. (1.88 moles) of *p*-cyanobenzyl bromide<sup>16</sup> and 400 g. (2.41 moles) of triethyl phosphite were slowly heated over a 3-hour period to 150° and this temperature maintained for an additional two hours. The excess of triethyl phosphite was then removed under reduced pressure and the residual oil distilled under high vacuum. A 96% yield of product was obtained (456 g.) b.p. 146-150° (0.03 mm.), which was used in the next step without further purification.

**Diethyl *p*-Aminomethylbenzylphosphonate.**—To a solution of 63.3 g. (0.25 mole) of diethyl *p*-cyanobenzylphosphonate in 400 ml. of absolute ethanol was added 30 g. (0.83 mole) of hydrogen chloride gas. This solution was hydrogenated in a glass-lined autoclave at 25° and 50 p.s.i.

(11) A synthetic silica-gel manufactured by The Floridin Co., Warren, Penna.

(15) A saturated hydrocarbon fraction, b.p. 60-71°, Skelly Oil Co., Kansas City, Mo.

(16) F. H. Case, THIS JOURNAL, **47**, 1143 (1925).

TABLE V  
 CHLORO-NITROGEN MUSTARDS CONTAINING THE PHOSPHONATE GROUP

m	R	n	R'	Yd., %	M.p., °C.	Recrystn. solvent	Empirical formula	Analyses, %											
								Calcd.				Found							
								C	H	N	P	C	H	N	P				
11	H	0	CH <sub>3</sub>	27	Oil	Chromatog. <sup>a</sup>	C <sub>12</sub> H <sub>22</sub> Cl <sub>2</sub> NO <sub>3</sub> P				4.29	9.50							
0	H	1	C <sub>2</sub> H <sub>5</sub>	54	58-59	Petr. ether	C <sub>15</sub> H <sub>21</sub> Cl <sub>2</sub> NO <sub>3</sub> P	48.92	6.57	3.80	8.41	48.62	6.44	3.79	8.49				
0	CH <sub>3</sub>	1	C <sub>2</sub> H <sub>5</sub>	30	61.5-72.5	Petr. ether	C <sub>16</sub> H <sub>26</sub> Cl <sub>2</sub> NO <sub>3</sub> P	50.27	6.86 <sup>d</sup>	3.66	8.10	50.35	7.16 <sup>d</sup>	3.60	7.46				
0	H	3	C <sub>2</sub> H <sub>5</sub>	31	Oil <sup>b</sup>	Chromatog. <sup>a</sup>	C <sub>17</sub> H <sub>25</sub> Cl <sub>2</sub> NO <sub>3</sub> P	51.52	7.12	3.51	7.83	51.76	7.77	3.21	7.90				
1	H	1	C <sub>2</sub> H <sub>5</sub>	64	Oil <sup>c</sup>	Chromatog. <sup>a</sup>	C <sub>16</sub> H <sub>26</sub> Cl <sub>2</sub> NO <sub>3</sub> P			3.66	8.10			3.76	7.84				

<sup>a</sup> Chromatograms run on a Florisil column; eluting solvent system was acetone-petroleum ether, approximately 1:9 by volume. <sup>b</sup> *n*<sub>D</sub><sup>25</sup> 1.5092. <sup>c</sup> *n*<sub>D</sub><sup>25</sup> 1.5143. <sup>d</sup> Calcd.: Cl, 18.55. Found: Cl, 18.40. <sup>e</sup> Calcd.: Cl, 18.55. Found: Cl, 18.58.

 TABLE VI  
 IODO-NITROGEN MUSTARDS CONTAINING THE PHOSPHONATE GROUP

n	R	R'	Yd. <sup>a</sup> %	M.p. (°C.)	Recrystn. solvent	Empirical formula	Analyses, %											
							Calcd.			Found								
							I	N	P	I	N	P						
1	H	C <sub>2</sub> H <sub>5</sub>	46	62-64	Petr. ether	C <sub>15</sub> H <sub>24</sub> I <sub>2</sub> NO <sub>3</sub> P	46.05 <sup>c</sup>	2.54	5.62	46.02 <sup>c</sup>	2.56	5.38						
1	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	18	80-82	Petr. ether	C <sub>16</sub> H <sub>25</sub> I <sub>2</sub> NO <sub>3</sub> P	44.91	2.48	5.48	44.69	2.57	5.77						
2	H	C <sub>2</sub> H <sub>5</sub>	35	Oil	Chromatog. <sup>b</sup>	C <sub>16</sub> H <sub>26</sub> I <sub>2</sub> NO <sub>3</sub> P		2.48	5.48		2.67	5.67						
3	H	C <sub>2</sub> H <sub>5</sub>	30	Oil	Chromatog. <sup>b</sup>	C <sub>17</sub> H <sub>28</sub> I <sub>2</sub> NO <sub>3</sub> P		2.42	5.35		2.82	5.79						

<sup>a</sup> From the bis-methanesulfonates; crude yield of the mesylates ranged from 85 to 95%. <sup>b</sup> Chromatogram run on a Florisil column; eluting solvent system was acetone-petroleum ether, approximately 1:9 by volume. <sup>c</sup> Calcd.: C, 32.69; H, 4.39. Found: C, 32.48; H, 4.75.

pressure using platinum oxide catalyst. After filtration and removal of the solvent under reduced pressure, the residual oil was made basic with cold sodium hydroxide solution and extracted with benzene. Distillation of the benzene extract under reduced pressure yielded 51 g. (79%) of crude product. Attempted purification of this material by conventional distillation was unsuccessful as the crude product solidified in the distillation pot. Flash distillation of small quantities was successful, b.p. 137-139° (0.05 mm.).

*Anal.* Calcd. for C<sub>12</sub>H<sub>20</sub>NO<sub>3</sub>P: N, 5.45; P, 11.65. Found: N, 5.30; P, 11.79.

**Iodo-nitrogen Mustards.**—Bis-(2-Hydroxyethyl)-amines were first converted to the bis-mesylates with methanesulfonyl chloride in pyridine, then to the iodo-nitrogen mustards by treatment with sodium iodide in acetone. The syntheses of VIII and IX are typical examples of this type of conversion.

**Diethyl *p*-[N,N-Bis-(2-hydroxyethyl)-amino]-benzylphosphonate Bis-methanesulfonate.**—To a solution of 5.0 g. (0.015 mole) of VII, 5.5 g. (0.07 mole) of dry pyridine and 50 ml. of dry benzene at 5° was added with stirring 5.0 g. (0.044 mole) of methanesulfonyl chloride over a 10-minute period. Stirring was continued at 5 to 10° for 16 hours at which time the benzene was removed under reduced pressure and the residue was poured onto cracked ice. After extraction with methylene chloride and removal of solvent, 6.0 g. (95%) of a dark amber oil was obtained. An aliquot of this material was purified for analysis by chromatography over Florisil. Elution was carried out with Skellysolve B-acetone (3:2). The purified material showed essentially the same infrared spectrum as the crude product.

*Anal.* Calcd. for C<sub>17</sub>H<sub>30</sub>NO<sub>3</sub>PS<sub>2</sub>: C, 41.88; H, 6.20; N, 2.87; P, 6.35; S, 13.15. Found: C, 42.00; H, 6.46; N, 3.05; P, 6.08; S, 13.69.

In general, the mesylates of the bis-(2-hydroxyethyl)-amines were used in the crude form for further synthesis.

**Diethyl *p*-[N,N-Bis-(2-iodoethyl)-amino]-benzylphosphonate.**—Five grams (0.012 mole) of the bis-methanesulfonate VIII and 3.5 g. (0.024 mole) of sodium iodide were dissolved in 65 ml. of acetone. The reaction mixture was shaken for 30 hours at room temperature in the dark. Precipitated sodium methanesulfonate was removed by filtration and the filtrate was concentrated under reduced pressure to a dark amber semi-solid material. Purification by chromatography over Florisil [elution with Skellysolve B-acetone (7:3)] yielded 3.0 g. (46%) of a crystalline solid. Recrystallization from petroleum ether yielded an analytical sample, m.p. 62-64°.

*Anal.* Calcd. for C<sub>15</sub>H<sub>24</sub>I<sub>2</sub>NO<sub>3</sub>P: C, 32.69; H, 4.39; N, 2.54; P, 5.62. Found: C, 32.48; H, 4.75; N, 2.56; P, 5.38.

For large scale preparation the chromatography was eliminated. The crude reaction product was extracted with boiling petroleum ether. On cooling, pure crystalline material separated and was removed by filtration.

**4-*p*-[Bis-(2-iodoethyl)-amino]-phenyl]-butyric Acid.**—A solution made up of 5.0 g. (0.0164 mole) of Chlorambucil<sup>4</sup> (I), and 7.0 g. (0.0466 mole) of sodium iodide dissolved in 100 ml. of acetone was placed in a glass-lined, stainless steel autoclave and heated at 100° for 12 hours. Filtration of the reaction mixture followed by evaporation of the solvent and recrystallization of the residue from benzene-petroleum ether yielded 3.0 g. (37%) of product, m.p. 111-112°.

*Anal.* Calcd. for C<sub>14</sub>H<sub>19</sub>I<sub>2</sub>NO<sub>2</sub>: N, 2.88; I, 52.11. Found: N, 2.84; I, 52.09.

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