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### Phosphorus Derivatives of Fatty Acids. III.<sup>2</sup> Trialkyl $\alpha$ -Phosphonates

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Triethyl  $\alpha$ -phosphonates have been prepared in 60–96% yield from triethyl phosphite and the ethyl ester of the appropriate C<sub>4</sub>–C<sub>18</sub> straight chain  $\alpha$ -bromocarboxylic acid (equation 1: R = C<sub>2</sub>H<sub>5</sub>, C<sub>4</sub>H<sub>9</sub>, C<sub>10</sub>H<sub>21</sub>, C<sub>12</sub>H<sub>25</sub>, C<sub>14</sub>H<sub>29</sub> and C<sub>16</sub>H<sub>33</sub>). Mixed trialkyl  $\alpha$ -phosphonates (formula I) have been similarly prepared in 30–90% yield from the appropriate trialkyl phosphite (trimethyl phosphite, tri-*n*-butyl phosphite or tri-*n*-hexyl phosphite) and alkyl ester of the  $\alpha$ -bromocarboxylic acid (R' = CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, *n*-C<sub>4</sub>H<sub>9</sub>, *n*-C<sub>6</sub>H<sub>13</sub> and 2-ethylhexyl in formula I). The  $\alpha$ -phosphonates are colorless, odorless, thermally stable liquids, insoluble in water and soluble in organic solvents. In contrast to the isomeric diethyl acyloxyethylphosphonates

previously reported, the triethyl  $\alpha$ -phosphonates are resistant to hydrolysis with 0.1 *N* hydrochloric acid, but they are converted to the tribasic  $\alpha$ -phosphonocarboxylic acids (I, R', R'' = H) when refluxed for 18–24 hr. with 20–35% hydrochloric acid. With dilute base in ethanol, the carboxylic ester group is preferentially hydrolyzed yielding  $\alpha$ -diethylphosphonocarboxylic acids (I, R' = H, R'' = C<sub>2</sub>H<sub>5</sub>).

In the first two papers of this series,<sup>5,6</sup> we described the preparation and properties of phosphorus-containing fatty acid derivatives which hydrolyzed in such a way as to separate the parent fatty acid from the phosphorus-containing group.

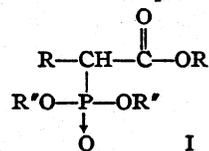
Thus, dialkyl acylphosphonates  $\left[ \begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \uparrow \\ \text{R}-\text{C}-\text{P}-(\text{OR}')_2 \end{array} \right]$  were hydrolyzed readily under neutral conditions

at the  $\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \uparrow \\ \text{C}-\text{P} \end{array}$  bond to regenerate the fatty acid and a fragment believed to be a dialkyl phosphite.<sup>5</sup> Dialkyl acyloxyethylphosphonates

$\left[ \begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \uparrow \\ \text{R}-\text{C}-\text{O}-(\text{CH}_2)_2-\text{P}-(\text{OR}')_2 \end{array} \right]$ , although considerably

more resistant to hydrolysis under neutral conditions than the dialkyl acylphosphonates, hydrolyzed readily under mildly acidic conditions at the carboxylic ester group to give the fatty acid and dialkyl hydroxyethylphosphonate.<sup>6</sup>

An objective of the present investigation was to prepare phosphorus derivatives of fatty acids which on hydrolysis would yield a product having phosphorus attached to the fatty acid chain. The trialkyl  $\alpha$ -phosphonates (I) are such a class of compounds. They were also of considerable interest because it would be possible to study the



effect of variations in R, R' and R'' on numerous physical and chemical properties under investigation. A few low molecular weight trialkyl  $\alpha$ -phosphonates are described in the literature,<sup>7</sup> but aside from them there are no reports on the systematic preparation and study of the physical and chemical properties of trialkyl  $\alpha$ -phosphonates.

(7) G. M. Kosolapoff, "Organophosphorus Compounds," John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 160–161.

(1) A laboratory of the Eastern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture. Article not copyrighted.

(2) Presented at the Fall Meeting of the American Chemical Society, September 8–13, 1957, New York, N. Y. Paper II is reference 6.

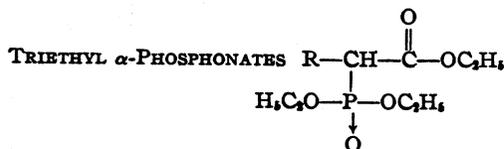
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(5) B. Ackerman, T. A. Jordan, C. R. Eddy and D. Swern, *THIS JOURNAL*, **78**, 4444 (1956).

(6) B. Ackerman, T. A. Jordan and D. Swern, *ibid.*, **78**, 6025 (1956).

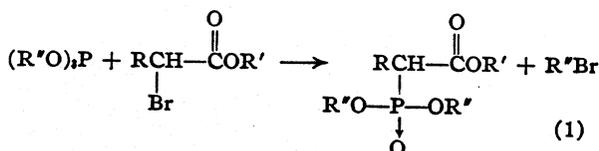
TABLE I



R	Yield, %	B.p. °C.	Mm.	Phosphorus, %		Carbon, %		Hydrogen, %		$n_D^{20}$	$d_4^{20}$	Molecular refraction	
				Calcd.	Found	Calcd.	Found	Calcd.	Found			Calcd.	Found
CH <sub>3</sub> CH <sub>2</sub>	60	65	10	12.3	12.5	47.6	47.4	8.39	9.02	1.4282	1.0642	60.92	61.01
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub>	75	141	4	11.1	11.2	51.4	50.7	8.99	9.15	1.4300	1.0337	70.16	70.05
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub>	88	168	4	9.61	9.81	55.9	54.8	9.65	9.58	1.4359	0.9994	84.02	84.32
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>7</sub>	80	153-156	0.1	8.50	8.34	59.3	58.3	10.2	10.6	1.4398	.9782	97.88	98.16
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>9</sub>	82	173-176	.1	7.89	7.74	61.2	60.6	10.5	10.6	1.4420	.9658	107.1	107.5
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>11</sub>	96	185-187	.2 <sup>a</sup>	7.37	7.07	62.8	62.5	10.8	11.2	1.4432	.9562	116.4	116.7
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>13</sub>	76	185-187	.2 <sup>a</sup>	6.91	6.91	64.3	64.3	11.0	10.6	1.4452	.9497	125.6	125.8

<sup>a</sup> Distilled in an alembic apparatus.

This paper describes the preparation and properties of the triethyl esters of  $\alpha$ -phosphonobutyric, -caproic, -pelargonic, -lauric, -myristic, -palmitic and -stearic acids ( $R' = R'' = \text{C}_2\text{H}_5$  and  $R = \text{C}_2\text{H}_5$  to  $\text{C}_{16}\text{H}_{33}$  in formula I) and various other simple and mixed trialkyl esters of  $\alpha$ -phosphono acids (I,  $R', R'' = \text{CH}_3, \text{C}_2\text{H}_5, n\text{-C}_4\text{H}_9, n\text{-C}_6\text{H}_{13}$  or 2-ethylhexyl).



The trialkyl  $\alpha$ -phosphonates are colorless, odorless, high-boiling liquids insoluble in water and soluble in a wide variety of organic solvents.

Hydrolysis of the  $\alpha$ -phosphonates with dilute and concentrated hydrochloric acid and also with base was studied. It was anticipated that the  $\alpha$ -phosphonates would be hydrolyzed at the carboxylic ester at about the same rate as, or somewhat more slowly than, the acyloxyethylphosphonates.<sup>6</sup> Hydrolysis at 61° in aqueous acetone 0.1 *N* with respect to hydrochloric acid, however, proceeded unexpectedly slowly. Thus, whereas one equivalent of acid was produced per mole of acyloxyethylphosphonate in 30 hr. (the same rate of hydrolysis as that of ethyl laurate), the  $\alpha$ -phosphonates produced less than 0.1 equivalent. At the end of 340 hr. of hydrolysis, only 0.3 equivalent of acid was produced from the  $\alpha$ -phosphonates. With dilute acid, therefore, not only does the phosphonate group remain attached to the fatty acid chain but the phosphonate group in the  $\alpha$ -position makes the carboxylic ester extremely resistant to hydrolysis.

Refluxing the  $\alpha$ -phosphonates with 20-35% aqueous hydrochloric acid for 18 or more hr. gave essentially complete hydrolysis to a tribasic acid as determined by neutralization equivalent of the hydrolyzed material (thymolphthalein indicator). The hydrolysis products from triethyl  $\alpha$ -phosphonolaurate and -stearate were amorphous solids, m.p. ca. 125-130°; that from triethyl  $\alpha$ -phosphonobutyrate was a hygroscopic semi-solid. The phosphonic acids from triethyl  $\alpha$ -phosphonostearate and -laurate were dispersible in hot water and the cooled systems gelled; they are soluble in

ethanol and acetone but insoluble in benzene and hexane.

With dilute alcoholic potassium hydroxide, the triethyl  $\alpha$ -phosphonates hydrolyzed at the carboxylic ester group with little effect on the  $\alpha$ -phosphonate group. After neutralization of the excess base and conversion of the salt to the free acid with hydrochloric acid, the  $\alpha$ -diethylphosphono fatty acids were isolated by ether extraction. The higher members of the series are solids which can be recrystallized from ethanol.

### Experimental

**Starting Materials.**—The  $\alpha$ -bromo fatty acids were commercial products except for  $\alpha$ -bromopalmitic acid which was prepared from pure palmitic acid and bromine in the conventional way.<sup>8</sup> The ethyl esters of the  $\alpha$ -bromo acids were prepared by refluxing them with a 5-mole excess of absolute ethanol using naphthalene-2-sulfonic acid as catalyst. After several water washes followed by drying, the crude ethyl esters were fractionally distilled in an all-glass apparatus. Methyl  $\alpha$ -bromolaurate was similarly prepared. The other alkyl  $\alpha$ -bromo esters were prepared in the conventional way with azeotropic removal of water<sup>9</sup>; they were also fractionally distilled. Since alkyl esters of  $\alpha$ -bromo acids are not well known, their boiling points and refractive indices are listed.

Ethyl $\alpha$ -bromo-	°C.	B.p.	Mm.	$n_D^{20}$	Bromine, %	
					Calcd.	Found
Butyrate	65	10	1.4429	41.0	41.0	
Caproate	75	4	1.4456	35.8	35.6	
Pelargonate	75	0.5	1.4498	30.1	30.0	
Laurate	101	.1	1.4531	26.0	25.4	
Myristate	128-133	.1	1.4550	23.8	23.6	
Palmitate	163-166	.2	1.4559			
Stearate	172-174	.2	1.4570	20.4	20.1	
Laurate <sup>a</sup>	105-107	.05	1.4551	27.3	27.3	
Caprylate <sup>b</sup>	99-101	.1	1.4489	28.6	28.4	
Laurate <sup>b</sup>	133	.3	1.4535	23.8	23.9	
Stearate <sup>b</sup>	150-160	.3	1.4573			
Caproate <sup>c</sup>	107-108	1.6	1.4505	28.6	28.6	
Stearate <sup>d</sup>	187-191	0.3	1.4596	16.8	15.1	

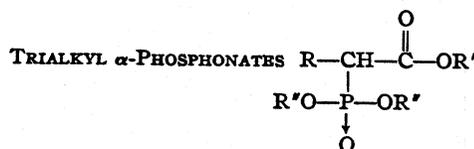
<sup>a</sup> Methyl ester. <sup>b</sup> *n*-Butyl ester. <sup>c</sup> *n*-Hexyl ester. <sup>d</sup> 2-Ethylhexyl ester.

The trialkyl phosphites were commercial materials which were fractionally distilled before use: trimethyl phosphite, b.p. 107-109°; triethyl phosphite, b.p. 151-155°; tri-*n*-butyl phosphite, b.p. 120-124° at 9 mm.; and tri-*n*-hexyl phosphite, b.p. 123-126° at 0.15 mm.

(8) H. T. Clarke and E. R. Taylor in "Organic Syntheses," Coll. Vol. I, 2nd Ed., edited by H. Gilman and A. H. Blatt, John Wiley and Sons, Inc., New York, N. Y., 1944, pp. 115-116.

(9) D. Swern and E. F. Jordan, Jr., *THIS JOURNAL*, **67**, 902 (1945).

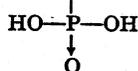
TABLE II



R	Compound R'	R''	Yield, %	B.p.		Phosphorus, %		Carbon, %		Hydrogen, %		$n_D^{20}$	$d_4^{20}$	Molecular refraction	
				°C.	Mm.	Calcd.	Found	Calcd.	Found	Calcd.	Found			Calcd.	Found
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	n-C <sub>4</sub> H <sub>9</sub>	73	210	0.18	7.37	7.18					1.4413	0.9547	116.4	116.5
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	n-C <sub>4</sub> H <sub>9</sub>	53	173	.25	6.50	6.37	65.5	65.1	11.2	11.3	1.4440	.9394	134.8	134.7
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub>	R' = R'' = n-C <sub>4</sub> H <sub>9</sub>		75	182	.6	6.91	7.15	64.3	64.3	11.0	10.7	1.4420	.9462	125.6	125.6
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub>	R' = R'' = n-C <sub>4</sub> H <sub>9</sub>		40	139	.15	6.91	7.45	64.3	63.6	11.0	11.1	1.4405	.9344	125.6	126.6
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub>	R' = R'' = CH <sub>3</sub>		61	156	.7	9.61	9.06	55.9	55.4	9.69	9.71	1.4440	1.0203	84.02	83.9
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub>	n-C <sub>4</sub> H <sub>9</sub>	C <sub>2</sub> H <sub>5</sub>	89	186	.3	7.89	7.79	61.2	60.5	10.5	10.5	1.4416	0.9644	107.1	107.6
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub>	2-Ethylhexyl	C <sub>2</sub> H <sub>5</sub>	73	215	.4	5.82	5.26	67.6	67.3	11.5	11.8	1.4507	.9326	153.3	153.7
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub>	n-C <sub>4</sub> H <sub>9</sub>	C <sub>2</sub> H <sub>5</sub>	79	195	.4	6.50	6.23	65.5	65.0	11.2	11.1	1.4466	.9402	134.8	135.4
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub>	n-C <sub>4</sub> H <sub>9</sub>	n-C <sub>4</sub> H <sub>9</sub>	30	163-171	.3	6.91	6.68	64.3	63.9	11.0	11.2	1.4427	.9438	125.6	125.9

Trialkyl  $\alpha$ -phosphonates were prepared by heating the alkyl  $\alpha$ -bromo ester with a 100% molar excess of trialkyl phosphite at 160-190° in an atmosphere of nitrogen. The alkyl bromide formed was swept out and collected in a Dry Ice trap. The reaction was stopped when the weight of alkyl bromide became constant (usually 4-5 hr.). Generally, 90% of the calculated amount of alkyl bromide was obtained. The entire reaction mixture was then fractionally distilled to obtain the pure  $\alpha$ -phosphonates (Tables I and II).

**Hydrolysis Studies.** (a) Dilute Acid.—The procedure described previously for the hydrolysis of acyloxyethylphosphonates was employed.<sup>8</sup> The trialkyl  $\alpha$ -phosphonates were extremely resistant to hydrolysis under conditions which gave complete hydrolysis of the acyloxyethylphosphonates (or ethyl laurate) at the carboxylic ester. (b) Concentrated Acid.—Three triethyl  $\alpha$ -phosphonates were refluxed for 18-24 hr. with a large excess of 20-35% hydrochloric acid. The reaction mixture was transferred to an evaporating dish and evaporated to dryness. The crude residues from the hydrolysis of triethyl  $\alpha$ -phosphonostearate and -laurate were hard, brittle solids, m.p. 125-130°; the residue from triethyl  $\alpha$ -phosphonobutyrate was a hygroscopic semi-solid. The neutralization equivalents found (thymolphthalein indicator) were, respectively, 129, 101 and 58 (calculated for the tribasic acids, R-CH-CO<sub>2</sub>H,



122, 94 and 56). Thus, essentially complete hydrolysis occurred. (c) Dilute Alkali.—In a kinetic study it was shown that one equivalent of base was consumed in about 1 hr. The following hydrolysis-isolation procedure was, therefore, employed to obtain the  $\alpha$ -diethylphosphonocarboxylic acid: approximately 0.5-1 g. of triethyl  $\alpha$ -phosphon-

ate (accurately weighed) was refluxed for 1 hr. with exactly 25 ml. of 0.2 N KOH in aldehyde-free 95% ethanol. The excess alkali was back titrated with 0.1 N HCl (phenolphthalein indicator) which permitted calculation of the saponification equivalent of the  $\alpha$ -phosphonate, if desired. A few ml. of concentrated HCl was then added and the reaction mixture was evaporated to dryness. The residue was washed several times with ethyl ether and the combined ether solutions were filtered. Evaporation of the ether from the filtrate yielded the  $\alpha$ -diethylphosphonocarboxylic acid, on which the neutralization equivalent was then determined. The saponification equivalents of the triethyl  $\alpha$ -phosphonates and the neutralization equivalents of the  $\alpha$ -diethylphosphonocarboxylic acids prepared from them are given in Table III.

TABLE III

SAPONIFICATION EQUIVALENT OF TRIETHYL  $\alpha$ -PHOSPHONATES AND NEUTRALIZATION EQUIVALENT OF  $\alpha$ -DIETHYLPHOSPHONOMONOCARBOXYLIC ACIDS ISOLATED

$\alpha$ -Phosphonate	Sapon. equiv.		Neut. equiv. of isolated acid	
	Calcd.	Found	Calcd.	Found
Butyrate			228	247
Caproate	280	290 <sup>a</sup>	252	230-240
Pelargonate			294	297
Laurate	364	356-362	336	344
Myristate			364	366
Palmitate	421	413-426	392	396
Stearate	449	428-437	420	417

<sup>a</sup> 0.1 N KOH in 80% aldehyde-free ethanol was used.