

Subsequent purification procedures as outlined above yielded white platelets of dianilinium phosphate (m.p. 182-183° dec.).

Anal. Calcd. for $C_{12}H_{17}O_4N_2P$: P, 10.9; neut. equiv., 142.12. Found: P, 10.8; neut. equiv., 141.1.
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[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF WESTVACO CHLOR-ALKALI DIVISION OF FOOD MACHINERY AND
CHEMICAL CORPORATION]

The Synthesis of Monovinyl Esters of Phosphorus(V) Acids

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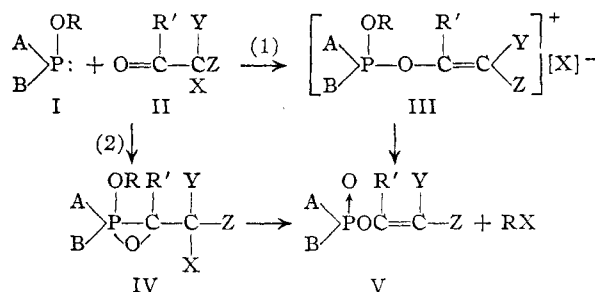
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The reaction of completely esterified acids of trivalent phosphorus containing at least one alkyl ester group with α -halogenated aldehydes, ketones, and some carboxylic acid esters and amides produces a monovinyl ester of the corresponding pentavalent phosphorus acid.

Several investigators have attempted to use α -halo ketones¹ and esters² instead of alkyl halides in the Michaelis-Arbuzov reaction involving esters of phosphorus(III) acids, but in all cases the products have been assumed to be phosphonates of the type expected from a normal Michaelis-Arbuzov reaction. When this work was begun no one had reported the reaction of a polyhalogen compound of the type under consideration with a completely esterified acid of trivalent phosphorus, but recently ethyl trichloroacetate^{2f} and chloral³ have been reported to yield phosphonates, and even more recently chloral,^{4a} bromal^{4a} and methyl 2-chloroacetate^{4b} have been reported to yield vinyl phosphates. It has been shown in this Laboratory also that α -halogenated aldehydes, ketones, and the esters and amides of certain carboxylic acids react with completely esterified acids of trivalent phosphorus to form vinyl esters of the corresponding pentavalent phosphorus acid. The proof of structure of these compounds will be given in detail in another paper, but the structure assignment rests upon the following experimental facts: (a) In the independent synthesis of diethyl vinyl phosphate by the dehydrobromination of diethyl 2-bromoethyl phosphate the product obtained was identical with that obtained by the reaction of triethyl phosphite and chloroacetaldehyde. (b) The products show strong infrared absorption at 6.1μ which is characteristic of the ethylenic double bond. (c) Diethyl vinyl phosphate, obtained from triethyl phosphite and chloroacetaldehyde, was hydrogenated over a nickel catalyst to triethyl phosphate. (d) The products add chlorine and bromine to form dihalides.

(e) Hydrolysis of the product obtained from chloral and triethyl phosphite gave dichloroacetaldehyde.

The reaction may involve a nucleophilic attack by the phosphorus atom on the oxygen of the carbonyl compound (mechanism 1) and the simultaneous expulsion of a chloride ion from the latter. In most cases a stable intermediate is not obtained, but intermediates have been obtained when the



phosphorus compound has phosphorus in a ring system (*e.g.*, I, $A + B = \text{OCH}_2\text{CH}_2\text{O}$). This mechanism is unusual in that it represents the normally nucleophilic oxygen atom of the carbonyl group as being electrophilic. Furthermore, this mechanism would be expected to involve an intermediate having the structure III, but the infrared spectrogram prepared from a mineral oil mull of the intermediate resulting from chloral and ethyl ethylene phosphite did not show the absorption at 6.1μ which is characteristic of the vinyl or substituted vinyl phosphates, and chloride ion was not precipitated by methanolic silver nitrate. A second possible mechanism (2) involves a nucleophilic attack by the phosphorus atom on the carbonyl carbon and a similar attack by the carbonyl oxygen on the phosphorus to form a 3-membered ring (IV) of the type suggested by Conant and MacDonald.⁵

Of the various classes of phosphorus compounds which would be expected to enter into this reaction, only phosphites, amidophosphites, phosphonites and phosphinites have been investigated. The limitations of the reaction with respect to the phosphorus compound appears to be about the same as observed with the Michaelis-Arbuzov reaction. Aromatic esters do not react, at least under normal conditions, but mixed aliphatic and aromatic esters react readily. For example, triphenyl phos-

(5) J. B. Conant and A. D. MacDonald, *THIS JOURNAL*, **42**, 2337 (1920).

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(2) (a) A. E. Arbutov and A. A. Dunin, *J. Russ. Phys.-Chem. Soc.*, **46**, 295 (1914); (b) G. M. Kosolapoff, *THIS JOURNAL*, **68**, 1103 (1946); (c) A. E. Arbutov and G. Kamai, *J. Gen. Chem. (U.S.S.R.)*, **17**, 2149 (1947); (d) Richard H. Wiley, U. S. Patent 2,478,441 (1949); (e) G. Kamai and E. Sh. Bastanov, *Zhur. Obschei Khim. (J. Gen. Chem.)*, **21**, 2188 (1951); (f) Denham Harmon and Roy E. Thorpe, U. S. Patent 2 614,990 (1952).

(3) (a) A. E. Arbuzov and P. I. Alimov, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 530 (1951); (b) Elbert C. Ladd and Merlin P. Harvey, U. S. Patent 2,597,938 (1952); (c) Elbert C. Ladd and Merlin P. Harvey, U. S. Patent 2,631,162 (1953).

(4) (a) Werner Perkow, *Chem. Ber.*, **87**, 755 (1954); (b) Alan R. Stiles, U. S. Patent 2,685,552 (1954).

TABLE I
 TRIVALENT PHOSPHORUS COMPOUNDS

Formula	Yield, %	Phosphorus, %		°C.	B.P., Mm.	n_D^{25}
		Calcd.	Found			
$(C_2H_5O)_2POC_6H_5$	50	14.5	14.3	63-85	1	1.4835
$(p-t-C_4H_9C_6H_4O)_2POCH_3$	69	8.6	8.6	173-179	0.1
$C_2H_5OCH_2CHO \begin{smallmatrix} \text{---CH}_2\text{O---} \\ \text{---} \end{smallmatrix} POCH_3$	59	17.2	17.2	85-95	10	1.4378
$i-C_3H_7OCH_2 \begin{smallmatrix} \text{---CH}_2\text{O---} \\ \text{---} \end{smallmatrix} CHO \text{---} POCH_3$	88	16.0	15.6	90-100	10	1.4378
$n-C_4H_9O_2CCHO \begin{smallmatrix} \text{---CH}_2\text{O---} \\ \text{---} \end{smallmatrix} POCH_3$	80	9.6	9.2
$n-C_4H_9O_2CCHO \begin{smallmatrix} \text{---CH}_2\text{O---} \\ \text{---} \end{smallmatrix} POCH_3$	89	16.1	16.2	74-76	1	1.4580
$C_6H_5OCH_2 \begin{smallmatrix} \text{---CH}_2\text{O---} \\ \text{---} \end{smallmatrix} CHO \text{---} POCH_3$	76	13.6	13.2	118-135	1
$(CH_2)_3O_2POCH_3$	59	22.8	23.3	65-80	20
$(n-C_4H_9S)_3P$	65	10.4	10.5	145-168	2
$i-C_3H_7OCH_2 \begin{smallmatrix} \text{---CH}_2\text{O---} \\ \text{---} \end{smallmatrix} CHO \text{---} PCl^a$	71	15.6	15.6	82-92	5	1.4583

^a Chlorine, calcd. 17.9; found 17.1.

phite and chloral did not react when equimolar quantities of the compounds were refluxed, but ethyl diphenyl phosphite reacted readily with chloral at temperatures above 45° to yield dichlorovinyl diphenyl phosphate and ethyl chloride. Esters of tertiary alcohols do not react normally but form an olefin instead, a behavior analogous to the reaction of alkyl halides and tri-*t*-butyl phosphite.⁶ Trithiophosphites, which do not give a normal Michaelis-Arbuzov reaction, do not react with chloral to form dichlorovinyl thiophosphates, although alkyl chloride is a by-product of the reaction. An infrared trace of the product obtained from chloral and tributyl trithiophosphite did not show absorption at 6.1 μ , but the product obtained from chloral and triethyl dithiophosphite did absorb at 6.1 μ , indicating that at least some vinyl ester was formed.

A further similarity between the vinyl ester reaction and the Michaelis-Arbuzov reaction is to be found in the reactions involving phosphites containing phosphorus in a ring system. Arbuzov and co-workers⁷ reported that alkyl ethylene phosphites (I, A + B = ethylenedioxy) reacted with alkyl halides by ring cleavage but that substitution in the ethylene radical stabilized the ring and alkyl halide was obtained. Similar results were reported by Mitchell and Lucas⁸ who found that isopropyl propylene phosphite did not undergo ring cleavage in the reaction with 1-bromopentane. We have found that chloral reacts with ethyl ethylene phosphite by ring cleavage since no ethyl chloride is obtained as by-product but reaction of chloral with ethyl propylene phosphite gave a 22% yield of ethyl chloride. The alkyl radical, however, is important in determining the course of the reaction and methyl is cleaved more readily than ethyl and therefore favors retention of the ring structure. Chloral reacted with methyl ethylene phosphite and with methyl propylene phosphite to give, respectively, 22 and 68% yields of methyl chloride. Isopropyl eth-

ylene phosphite, however, gave propylene and no isopropyl chloride. As would be expected, enlarging the ring increases the stability in both the reaction with alkyl halides⁷ and with chloral, and in reactions with the latter methyl trimethylene phosphite gave 65% methyl chloride and methyl tetramethylene phosphite gave 45% methyl chloride. But substitution even in the larger rings increases the stability and methyl 1-methyltrimethylene phosphite gave 97% methyl chloride.

The formation of stable intermediates in the vinyl ester reaction has been observed only with alkyl ethylene phosphites. When chloral and triethyl phosphite are mixed at 0°, or even lower, a strongly exothermic reaction occurs and ethyl chloride can be obtained immediately by reducing the pressure, but the reaction of ethyl ethylene phosphite and chloral at ordinary temperatures, while exothermic, results in a liquid which soon becomes a waxy solid. Upon heating, the solid melts and at about 130-140° a second strongly exothermic reaction begins.

Of the halogenated carbonyl compounds which have been investigated, chloral and bromal react most readily and the reactivity decreases as the number of halogen atoms on the α -carbon atom decreases. Ketones react less readily than aldehydes and esters are considerably less reactive than ketones. Ethyl trichloroacetate at 50° gave a mildly exothermic reaction with triethyl phosphite to form diethyl 2,2-dichloro-1-ethoxyvinyl phosphate, but ethyl dichloroacetate reacted slowly with triethyl phosphite even at 160° to give a mixture boiling over a wide range and no identifiable product was isolated except ethyl chloride. Diethyl bromomalonate and diethyl dibromomalonate, however, reacted readily with triethyl phosphite at 25° to form the vinyl esters. There was a slight exothermic effect when N,N-diethyltrichloroacetamide and triethyl phosphite were mixed at ordinary temperature, but ethyl chloride was not obtained below 125° when the temperature was raised rapidly. The product was not obtained in pure form but an infrared spectrogram revealed intense absorption at 6.1 μ . An interesting example of vinylogy is in the reac-

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(7) A. E. Arbuzov, V. M. Zoroastrova and N. I. Rizpolozhenskii, *Bull. acad. sci. U.R.S.S., Classe sci. chim.*, 208 (1948).

(8) F. W. Mitchell, Jr., and H. J. Lucas, *THIS JOURNAL*, **72**, 5779 (1950).

TABLE II
 VINYL ESTERS OF PHOSPHORUS(V) ACIDS

Formula	Precursors ¹		Yield, %	Halogen, %		Phosphorus, %		°C.	B.p., Mm.
	P compd.	Car- bonyl compd.		Calcd.	Found	Calcd.	Found		
$(C_2H_5O)_2P(O)OCH=CH_2$	1	2	67	17.2	17.1	79	6
$(C_2H_5O)_2P(O)OC(CH_3)=CH_2^a$	1	3	56	16.0	16.1	72-73	1
$(C_2H_5O)_2P(O)OC(CH_2Cl)=CH_2$	1	4	82	15.5	16.0	13.6	13.7	76-89	1
$(C_2H_5O)_2P(O)OCH=CHCH_2Cl$	1	5	100	15.5	16.6	13.6	13.7
$(C_2H_5O)_2P(O)OCH=CHCHClC_6H_5$	1	6	100	11.6	12.0	10.2	10.6
$CH_3(OC_2H_5)_2OP(O)OCH=CH_2$	7	2	100	10.8	10.9
$(C_2H_5O)_2P(O)OCH=CHCl^b$	1	8	54	16.5	16.5	14.4	14.9	92-105	1-2
$(n-C_3H_7O)_2P(O)OCH=CHCl^c$	9	8	56	14.6	13.4	12.8	12.7	94-100	0.1
$(Iso-C_3H_7O)_2P(O)OCH=CHCl^d$	10	8	37	14.6	14.7	12.8	12.0	74-87	0.1
$(n-C_4H_9CHCH_2O)_2P(O)OCH=CHCl^e$	11	8	82	9.3	8.3	8.1	7.8	156-173	0.1
$\begin{array}{c} C_2H_5O \\ \\ C_2H_5O \end{array} P(O)OCH=CHCl^f$	12	8	79	14.4	14.4	12.6	12.1	118-134	0.1-0.4
$(ClCH_2CH_2O)_2P(O)OCH=CHCl$	13	8	70	37.5	37.5	10.9	11.1	152-157	1
$\begin{array}{c} CH_3-CH_2-CH \\ \quad \quad \\ CH_3-C-C(CH_3)_2-CH \\ \quad \quad \\ (C_2H_5O)_2P(O)OC-CH=CH-Br \end{array}$	1	14	81	21.8	20.6	8.4	8.3
$(C_2H_5O)_2P(O)OC(CH_3)=CClCO_2C_2H_5$	1	15	68	11.8	11.3	10.3	10.5	120-128	1
$(C_2H_5O)_2P(O)OCH=CClCHClCH_3$	1	16	49	25.6	24.9	11.2	11.3	ca. 80	0.01
$(CH_3O)_2P(O)OCH=CCl_2$	18	17	53	32.1	31.2	14.0	14.5	74-87	2
$\begin{array}{c} C_2H_5O \\ \\ CH_3O \end{array} P(O)OCH=CCl_2$	19	17	67	30.2	29.6	13.2	13.2	80-96	1
$(C_2H_5O)_2P(O)OCH=CCl_2$	1	17	38	28.5	28.6	12.4	12.4	114.5-115	5
$(n-C_3H_7O)_2P(O)OCH=CCl_2$	9	17	75	25.6	24.3	11.2	11.0	109-123	3
$(Iso-C_3H_7O)_2P(O)OCH=CCl_2^g$	10	17	62	25.6	25.5	11.2	11.4	96.5	2
$(n-C_4H_9O)_2P(O)OCH=CCl_2$	20	17	80	23.2	21.7	10.2	10.2	107-121	0.5
$(n-C_4H_9CH(C_2H_5)CH_2O)_2P(O)OCH=CCl_2$	11	17	100	17.0	16.7	7.4	7.4
$(ClCH_2CH_2O)_2P(O)OCH=CCl_2^h$	13	17	68	44.6	43.1	9.7	9.7	93-112	0.1
$[CH_2(OC_2H_5)_2O]_2P(O)OCH=CCl_2$	21	17	75	17.9	17.9	7.8	7.8
$\begin{array}{c} C_6H_5O \\ \\ C_2H_5O \end{array} P(O)OCH=CCl_2$	22	17	84	23.9	24.6	10.4	10.3	116-130	0.5
$(p-t-C_6H_4C_6H_4O)_2P(O)OCH=CCl_2$	23	17	89	15.5	14.4	6.8	7.1
$(C_2H_5O)_2P(O)OCH=CCl_2$	1	24	48	47.3	45.1	9.2	9.2	ca 100	0.15
$(C_2H_5O)_2P(O)OC(OC_2H_5)=CCl_2^i$	1	25	53	24.2	23.6	10.6	10.9	120-127	1
$\begin{array}{c} C_6H_5 \\ \\ CH_3O \end{array} P(O)OCH=CCl_2$	26	17	73	26.6	25.6	11.6	11.5	125-137	1
$\begin{array}{c} C_6H_5 \\ \\ C_2H_5O \end{array} P(O)OCH=CCl_2$	12	17	68	25.2	25.2	11.0	11.1	131-144	2-3
$Cl_2C=CHOP(O)C(OCH_2)_2C(CH_2O)_2P(O)OCH=CCl_2^j$	27	17	68	31.5	30.2	13.8	13.6
$(C_2H_5O)_2P(O)OC(C_6H_5)=CH-CH=CCl_2$	1	28	100	20.2	20.2	8.8	8.8
$\begin{array}{c} CH_2O \\ \\ CH_2O \end{array} P(O)OCH=CCl_2$	29	17	24	32.4	32.2	14.1	13.8	110-117	0.5
$\begin{array}{c} CH_2O \\ \\ CH_3CHOP(O)OCH=CCl_2 \end{array}$	30	17	54	30.4	29.5	13.3	13.5	118-123	2
$C_2H_5OCH_2CHO-P(O)OCH=CCl_2$	31	17	99	25.6	26.3	11.2	10.8
$CH_3CHO-P(O)OCH=CCl_2$	32	17	97	28.7	29.1	12.5	12.6	132-140	1
$\begin{array}{c} H_2C-CH_2O \\ \\ C_2H_5CHO \end{array} P(O)OCH=CCl_2$	33	17	81	25.8	24.5	11.3	10.9
$\begin{array}{c} CH_3CH-CH_2O \\ \\ [(CH_3)_2N]_2P(O)OCH=CCl_2^k \end{array}$	34	17	67	28.7	27.8	12.5	12.5	90-95	1
$[(C_2H_5)_2N]_2P(O)OCH=CCl_2$	35	17	74	23.4	22.8	10.2	10.6	115-125	1
$\begin{array}{c} (C_2H_5)_2N \\ \\ ClCH_2CH_2O \end{array} P(O)OCH=CCl_2$	36	17	73	34.3	33.5	10.0	9.9	113-123	0.2

^a n_D^{25} 1.4135, d_4^{25} 1.0579. ^b n_D^{25} 1.4276. ^c n_D^{25} 1.4364. ^d n_D^{25} 1.4307. ^e n_D^{25} 1.4492. ^f n_D^{25} 1.5174. ^g n_D^{25} 1.4372, d_4^{25} 1.1924. ^h n_D^{25} 1.4820. ⁱ n_D^{25} 1.4173. ^j M.p. 130–132° (uncor.; recryst. from 2-propanol). ^k n_D^{25} 1.4708, d_4^{25} 1.2432. ^l Precursors: 1, triethyl phosphite; 2, chloroacetaldehyde; 3, chloroacetone; 4, sym-dichloroacetone; 5, 2,3-dichloropropanal; 6, 2,3-dichloro-3-phenylpropanal; 7, bis-(methoxyethoxyethyl) phenylphosphonite; 8, dichloroacetaldehyde; 9, tripropyl phosphite; 10, triisopropyl phosphite; 11, tris-2-ethylhexyl phosphite; 12, diethyl phenylphosphonite; 13, tris-chloroethyl phosphite; 14, dibromocamphor; 15, ethyl 2,2-dichloroacetoacetate; 16, 2,2,3-trichlorobutanal; 17, chloral; 18, trimethyl phosphite; 19, ethyl dimethyl phosphite; 20, tributyl phosphite; 21, trimethoxyethoxyethyl phosphite; 22, diethyl phenyl phosphite; 23, ethyl bis-*p*-*t*-butylphenyl phosphite; 24, bromal; 25, ethyl trichloroacetate; 26, dimethyl phenylphosphonite; 27, diethyl pentaerythrityl diphosphite; 28, phenyl 3,3,3-trichloropropenyl ketone; 29, ethylene methyl phosphite; 30, methyl propylene phosphite; 31, 3-ethoxypropylene methyl phosphite; 32, methyl 1-methyltrimethylene phosphite; 33, 1-ethyl-2-methyltrimethylene methyl phosphite; 34, ethyl tetramethylphosphorodiamidite; 35, ethyl tetra-ethylphosphorodiamidite; 36, ethylene diethylphosphoramidite.

tions of triethyl phosphite with phenyl trichloromethyl ketone and with its vinylog, phenyl 3,3,3-trichloropropenyl ketone.

Experimental

Preparation of Phosphorus(III) Esters.—The glycol esters were prepared by the two-step method of Lucas, Mitchell and Scully⁹ which involves the use of methylene chloride as solvent in the preparation of the chlorophosphite. In the conversion of the latter to the tertiary ester we preferred triethylamine or diethylaniline as the base. The preparation of tertiary phosphites from phosphorus trichloride and monohydric alcohols made use of hexane as solvent and triethylamine or diethylaniline as base.¹⁰ Phosphites with mixed radicals, (RO)₂POR', were prepared from the appropriate dichlorophosphite, R'OPCl₂, and 2 moles of alcohol or phenol, ROH, in the usual manner. Many of these esters were not isolated in purified form and Table I contains only new compounds having a reasonable degree of purity.

Preparation of Vinyl Esters.—The following examples illustrate the preparation of vinyl phosphates, amidophosphates, phosponates and phosphinates. Other examples are shown in Table II. *Caution: Many substituted vinyl phosphates are powerful cholinesterase inhibitors and therefore highly toxic.*

Diethyl Vinyl Phosphate.—Four moles (665 g.) of triethyl phosphite was added gradually with stirring to 4 moles (314 g.) of chloroacetaldehyde over a period of 40 minutes with sufficient cooling to keep the temperature at 50 to 60°. The mixture then was heated to 110° and 178 g. (70%) of ethyl chloride (b.p. 13°) obtained in a cold trap. Fractionation of the product by means of a 2-foot column packed with glass helices gave a 67% yield of diethyl vinyl phosphate, b.p. 79° (6 mm.), n_D^{25} 1.4100, and d_4^{25} 1.0724.

Anal. Calcd. for C₆H₁₂O₄P: P, 17.2. Found: P, 17.1.

Bis-2-chloroethyl 2-Chlorovinyl Phosphate.—To 56.5 g. (0.5 mole) of technical dichloroacetaldehyde (containing about 15% of chloral) there was gradually added 134.8 g. (0.5 mole) of tris-2-chloroethyl phosphite at about 40°. Mild cooling of the reaction mixture was necessary until about 75% of the phosphite had been added. When addition was complete the temperature was raised gradually to 120° with distillation of ethylene chloride (37.8 g., 77% yield). Distillation of the product gave 100 g. (70% yield), of bis-2-chloroethyl 2-chlorovinyl phosphate, b.p. 152–157° (1 mm.).

Anal. Calcd. for C₈H₁₀O₄Cl₃P: Cl, 37.5; P, 10.9. Found: Cl, 37.2; P, 11.1.

Diethyl 2,2-Dichlorovinyl Phosphate.—Four moles (589.6 g.) of chloral was cooled to 8° and 4 moles (664.8 g.) of technical grade triethyl phosphite added over a two-hour period with cooling by an ice-salt-bath to keep the temperature below 26°. Gradual heating of the product led to the evolution of ethyl chloride (206 g., 80% yield) from 40 to 115°. Rectification of the product through a 20-inch column packed with glass helices gave a 38% yield of diethyl 2,2-dichlorovinyl phosphate, b.p. 114.5–115° (5 mm.), n_D^{25} 1.4428, d_4^{25} 1.2821.

Anal. Calcd. for C₆H₁₀O₄Cl₂P: Cl, 28.5; P, 12.4. Found: Cl, 28.6; P, 12.4.

2,2-Dichlorovinyl Ethyl Phenylphosphonate.—Diethyl phenylphosphonite (0.37 mole) was added gradually with

cooling to chloral (0.37 mole) at 23–28°. Distillation of the product gave 71.0 g. (68% yield) of dichlorovinyl ethyl phenylphosphonate, b.p. 131–144° (2–3 mm.).

Anal. Calcd. for C₁₀H₁₁P₃Cl₂P: Cl, 25.2; P, 11.0. Found: Cl, 25.2; P, 11.1.

Diethyl 1-(Chloromethyl)-vinyl Phosphate.—To 50 g. (0.4 mole) of sym-dichloroacetone cooled to 40 to 50° there was added gradually 66 g. (0.4 mole) of triethyl phosphite. The temperature then was raised to 100° and 21.6 g. of ethyl chloride (85% yield) obtained in a cold trap. Distillation of the product gave an 82% yield of diethyl 1-(chloromethyl)-vinyl phosphate, b.p. 76–89° (1 mm.). The sample analyzed was collected at 84°.

Anal. Calcd. for C₇H₁₄O₄ClP: Cl, 15.5; P, 13.6. Found: Cl, 16.0; P, 13.7.

2,2-Dichlorovinyl Tetraethylphosphorodiamidite.—Ethyl tetraethylphosphorodiamidite (0.35 mole) was added gradually to chloral (0.35 mole) with cooling at 15 to 25°. When the reaction mixture was heated to 45° ethyl chloride began collecting in the cold trap and at 100° the weight of ethyl chloride obtained was 15 g. (66% yield). Distillation of the product gave 78.3 g. of 2,2-dichlorovinyl tetraethylphosphorodiamidite (74% yield) from 115–125° (1 mm.).

Anal. Calcd. for C₁₀H₂₁N₂O₂Cl₂P: Cl, 23.4; P, 10.2. Found: Cl, 22.8; P, 10.6.

Ethylene 2,2-Dichlorovinyl Phosphate.—The gradual addition of 24.4 g. (0.2 mole) of methyl ethylene phosphite to 29.5 g. of chloral (0.2 mole) at 20–45° gave a strongly exothermic reaction, but methyl chloride was not obtained at 125°. Distillation gave 13 g. (24% yield) of 2,2-dichlorovinyl ethylene phosphate, b.p. 110–117° (0.5 mm.).

Anal. Calcd. for C₄H₈O₄Cl₂P: Cl, 32.4; P, 14.1. Found: Cl, 32.2; P, 13.8.

When this reaction was carried out on a larger scale (12 moles), the reaction mixture became solid when about one-third of the phosphite had been added. Upon heating, the solid melted at about 90° and at 140° an exothermic reaction occurred with the formation of methyl chloride (22% yield).

2,2-Dichloro-1-ethoxyvinyl Diethyl Phosphate.—One mole of triethyl phosphite (166 g.) was added rapidly to 1 mole (191.5 g.) of ethyl trichloroacetate at 25°. The temperature rose slowly and mild cooling was necessary to maintain the temperature at 75–80°. When heat was no longer evolved the reaction mixture was heated to 100° for 30 minutes. The yield of ethyl chloride was 87% and distillation of the main product followed by redistillation through a 10-inch Vigreux column gave 155 g. (53% yield) of 2,2-dichloro-1-ethoxyvinyl diethyl phosphate, b.p. 120–127° (1 mm.), n_D^{25} 1.4437, and d_4^{25} 1.2485.

Anal. Calcd. for C₈H₁₆O₅Cl₂P: Cl, 24.2; P, 10.6. Found: Cl, 23.6; P, 10.9.

2-Chlorovinyl Diphenylphosphinite.—To 7.24 g. of dichloroacetaldehyde (0.064 mole) was added over a period of ten minutes 13.8 g. (0.064 mole) of ethyl diphenylphosphinite. The mixture was not cooled during the mixing operation and the temperature rose from 10 to 77°. The product then was heated to 115° and the ethyl chloride (72% yield) removed *in vacuo*. The yield of crude product was 17 g. (100.8%).

Anal. Calcd. for C₁₄H₁₂O₂ClP: Cl, 12.7; P, 11.1. Found: Cl, 13.0; P, 11.0.

Acknowledgment.—The authors wish to thank the Westvaco and Niagara Chemical Divisions of Food Machinery and Chemical Corporation for permission to publish this work. We are indebted

(9) H. J. Lucas, F. W. Mitchell, Jr., and C. N. Scully, *THIS JOURNAL*, **72**, 5491 (1950).

(10) Most of the triethyl phosphite used in this work was technical grade product obtained from the Virginia-Carolina Chemical Corporation.

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CHARLESTON, WEST VIRGINIA

[CONTRIBUTION FROM THE WESTERN UTILIZATION RESEARCH BRANCH, AGRICULTURAL RESEARCH SERVICE, UNITED STATES DEPARTMENT OF AGRICULTURE]

Reaction-Inactivation of Polyphenol Oxidase: Catechol and Oxygen Dependence

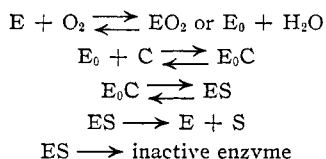
BY LLOYD L. INGRAHAM

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Further studies of the reaction-inactivation of polyphenol oxidase have shown that both the reaction-inactivation and enzymatic oxidation of catechol have the same Michaelis-Menten dependence on catechol concentration and oxygen pressure. This is interpreted as meaning that the reaction-inactivation and oxidation mechanism are identical until the enzyme-semiquinone complex is formed. These results are in agreement with the previously proposed idea that the enzyme-semiquinone complex may decompose by either of two pathways: (1) to active enzyme and semiquinone or (2) to inactive enzyme.

During the polyphenol oxidase catalyzed aerobic oxidation of catechol the enzyme activity gradually decreases and finally disappears after about 20 minutes. This effect, called reaction-inactivation,¹ has been shown in previous research to depend upon the first power of the enzyme concentration.²

It has been proposed that the reaction-inactivation is due to the possibility that the enzyme-semiquinone complex may decompose by either of two pathways: (1) to active enzyme and semiquinone or (2) to inactive enzyme by an internal oxidation-reduction reaction. The over-all mechanism would be described by the reactions³



where E is reduced enzyme, E_0 is oxidized enzyme, C is catechol, S is semiquinone and O_2 is oxygen. If this mechanism holds, the formation of product must have a Michaelis-Menten dependence on not only the catechol concentration but also the oxygen concentration. In addition, however, the reaction-inactivation must also have a Michaelis-Menten dependence on both catechol concentration and oxygen pressure. The integrated rate equation which includes the dependence on catechol concentration and oxygen pressure may be derived in the same manner as equation 1 which is only valid for the experimental conditions where the oxidation is zero order in catechol concentration and oxygen pressure.

$$Q = \frac{k_0' E_0}{k_1} [1 - e^{-k_1' t}] \quad (1)$$

This equation shows how the amount of oxidation, Q , varies in time, t , at given initial concentration of enzyme, E_0 . The "constants" k_0' and k_1' are the rate constants for oxidation and inactivation, respectively, which also include the catechol and

oxygen dependence of each reaction. If we substitute $k_0' = k_0 f(C, O)$ and $k_1' = k_1 g(C, O)$ where $f(C, O)$ is the Michaelis-Menten dependence the oxidation reaction has on catechol and oxygen and $g(C, O)$ is the Michaelis-Menten dependence the inactivation has on catechol and oxygen in the rate equations used to derive equation 1, the integration of the rate equation is not affected. This is because the catechol concentration and oxygen pressure are kept constant during the reaction in our experiments. The catechol concentration is kept constant by adding enough ascorbic acid to the reaction mixture to continually reduce any semiquinones or *o*-quinones formed back to catechol and the oxygen pressure is kept constant by passing a slow stream of an oxygen-nitrogen gas mixture through the reaction mixture. Since the integration is not affected by the substitution one may in effect substitute the values for k_0' and k_1' in equation 1 to obtain equation 2

$$Q = \frac{k_0 f(C, O) E_0}{k_1 g(C, O)} [1 - e^{-k_1 g(C, O) t}] \quad (2)$$

which holds at all concentrations of catechol and all oxygen pressures. Equation 2 predicts, as one would expect, that the initial rate of reaction

$$\left(\frac{dQ}{dt} \right)_{t=0} = k_0 E_0 f(C, O) \quad (3)$$

has a Michaelis-Menten relationship on both catechol concentration and oxygen pressure. However, equation 2 also predicts that if our proposed mechanism is valid, then the ultimate amount of oxidation

$$\lim_{t \rightarrow \infty} Q = \frac{k_0 f(C, O) E_0}{k_1 g(C, O)} = \frac{k_0 E_0}{k_1} \quad (4)$$

is independent of both the catechol concentration and oxygen pressure, since $f(C, O)$ is identical with $g(C, O)$ in the proposed mechanism.

Experimental values of the initial rates of oxidation catalyzed by mushroom enzyme at various percentages of oxygen-nitrogen mixtures are shown in Fig. 1. A locus of the experimental values is found to approximate the theoretical Michaelis-Menten curve corresponding to a maximum activity of 20 and a Michaelis constant of 9% oxygen.

(1) See I. Asimov and C. R. Dawson, *THIS JOURNAL*, **72**, 820 (1950) and preceding papers.

(2) L. L. Ingraham, J. Corse and B. Makower, *ibid.*, **74**, 2623 (1952).

(3) L. L. Ingraham, *ibid.*, **76**, 3777 (1954).



The tertiary phosphine in any solvent can be titrated directly with a solution of iodine in 95% ethanol. The end-point is very sharp and is observed by the appearance of a bright yellow color. The alcohol and water in the titration solutions accelerate the sulfur-phosphine reaction in the aliquots during the direct titration with iodine. This caused an error which was most noticeable in the early part of a run. Such errors were eventually eliminated by quenching each aliquot in an excess of standard iodine solution and then back-titrating with standard triphenylphosphine; however, the rate constants so obtained were identical with those from the latter part of each direct-titration run, and such runs are included in Table III. The solutions of

iodine and phosphine for titration were made in benzene containing 20–25% ethanol (95%). The concentration of the phosphine solution must be checked from time to time in order to avoid errors due to the oxidation of the phosphine. When tri-*p*-chlorophenylphosphine is used, oxidation does not occur at room temperatures; on the other hand, tri-alkyl phosphines cannot be used since they oxidize extremely rapidly in the presence of air. To minimize errors due to oxidation of the liberated HI, about 5 g. of pyridine was added to one liter of iodine solution. Using this method a sample of triphenylphosphine crystallized three times from 95% ethanol analyzed as 99.4% Ph_3P .

The presence of sulfur, phosphine sulfides, phosphine oxides or tertiary amines (in not very large amounts) does not introduce any error nor affect the end-point.

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[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF WESTVACO CHLOR-ALKALI DIVISION OF FOOD MACHINERY AND CHEMICAL CORPORATION]

Structure of the Reaction Products of Fully Esterified Phosphorus(III) Acids and α -Halo Carbonyl Compounds¹

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The products obtained by the reaction of α -halo carbonyl compounds and completely esterified acids of trivalent phosphorus were shown to be vinyl esters of pentavalent phosphorus acids by the independent synthesis of diethyl vinyl phosphate by the action of sodium hydride on diethyl 2-bromoethyl phosphate, by the addition of hydrogen, chlorine and bromine and by infrared absorption characteristic of the ethylenic double bond.

In a recent paper² the reaction products of α -halogenated carbonyl compounds and completely esterified acids of trivalent phosphorus were represented as vinyl esters of the corresponding pentavalent phosphorus acids, and the reasons for the structure assignment were stated briefly. We now wish to present in detail some of the experimental evidence for the vinyl ester structure. In the meantime other investigators³ have published data supporting the vinyl ester structure and eliminating certain other structures originally thought possible, making a detailed description of some of our work unnecessary.

The vinyl ester structure is supported by a considerable body of evidence, the most important being (a) the independent synthesis of diethyl vinyl phosphate by the dehydrobromination of diethyl 2-bromoethyl phosphate and by the debromination by zinc of the bromine adduct of the product obtained from chloral and triethyl phosphite; (b) the addition of hydrogen, chlorine and bromine to certain members of the series to form saturated products; (c) the hydrolysis of the reaction product of chloral and triethyl phosphite to dichloroacetaldehyde; and (d) infrared absorption at 6.1μ .

Upson⁴ has described the preparation of diethyl vinyl phosphate and divinyl phenylphosphonate by

the dehydrochlorination of the corresponding 2-chloroethyl esters. Upson^{4b} reported the formation of a viscous polymeric diethyl vinyl phosphate when diethyl chloroethyl phosphate and triethylamine were refluxed for 84 hours, and although we obtained a similar product by the same procedure, neither of the two liquid phases obtained gave a positive test for chloride ion, indicating that triethylammonium chloride was not obtained. Furthermore, when triethylamine was refluxed for 84 hours with the product obtained from triethyl phosphite and chloroacetaldehyde a crystalline solid was obtained which appears to be an addition product of the two reactants. These results suggest that the Upson reaction does not give diethyl vinyl phosphate as an intermediate but that both reactions may involve alkylation (or vinylation in the case of the vinyl phosphate) of the amine. A 5% excess of triethylamine reacted with diethyl 2-bromoethyl phosphate in refluxing isopropyl ether to give a 46% yield of bromide ion and a small liquid fraction distilling at $81-110^\circ$ (3 mm.) which decolorized bromine and presumably contained diethyl vinyl phosphate. Our efforts to repeat Upson's dehydrochlorination with ethanolic potassium hydroxide and other basic reagents resulted primarily in ethanolysis and degradation and only traces of unsaturated products were obtained.

An unexpected development occurred in an attempt to dehydrobrominate diethyl 2-bromoethyl phosphate with sodium *t*-butoxide in *t*-butyl alcohol. The product closely resembled the product obtained from triethyl phosphite and chloroacetaldehyde in physical properties, including infrared absorption, but the specific gravity and phosphorus content were significantly low, suggesting that the vinyl compound was contaminated with

(1) Presented at the 128th Meeting of the American Chemical Society, Minneapolis, Minnesota, September 11–16, 1955.

(2) J. F. Allen and O. H. Johnson, *THIS JOURNAL*, **77**, 2871 (1955).

(3) (a) W. F. Barthel, B. H. Alexander, P. A. Giang and S. A. Hall, *ibid.*, **77**, 2424 (1955); (b) A. M. Mattson, J. T. Spillane and G. W. Pearce, *J. Agr. Food Chem.*, **3**, 319 (1955); (c) W. Perkow, *Chem. Ber.*, **87**, 755 (1954); (d) W. Perkow, W. Krockow and K. Knoevenagel, *ibid.*, **88**, 662 (1955); (e) W. Lorenz, A. Henglein and G. Schraeder, *THIS JOURNAL*, **77**, 2554 (1955); (f) M. S. Kharasch and I. S. Bengelsdorf, *J. Org. Chem.*, **20**, 1356 (1955).

(4) (a) R. W. Upson, *THIS JOURNAL*, **75**, 1763 (1953); (b) R. W. Upson, U. S. Patent 2,557,805 (1951).

TABLE I
 HALOGEN ADDITION PRODUCTS OF VINYL PHOSPHATES

Compound	Yield, ^a %	Halogen, % or meq./g. ^b Calcd. Found	Phosphorus, % Calcd. Found	°C. B.p.	Mm.	n _D ²⁰
(EtO) ₂ P(O)OCHClCHCl ₂	43	37.3 36.8	10.9 10.7	111-142	1	1.4512
(EtO) ₂ P(O)OCHClCCl ₃	74	44.3 44.4	9.7 9.0	125-145	1.5	1.4600
(EtO) ₂ P(O)OCHBrCBrMe ₂	100	43.4 43.5	8.4 8.6
(EtO) ₂ P(O)OCBrCHBrCH ₂ CH ₂ CH ₂ CH ₂	100	40.6 40.9	7.9 7.9
(EtO) ₂ P(O)OCHClCH ₂ Br ^c	48	6.8 6.7	10.4 10.0	106-112	1	1.4579
(EtO) ₂ P(O)OC(CH ₂ Cl)BrCH ₂ Br	98	7.7 7.9	8.0 8.4
(EtO) ₂ P(O)OCHBrCHBrCl	38	8.0 7.4	8.3 8.5	120-122	1	1.4660
(ClCH ₂ CH ₂ O) ₂ P(O)OCHBrCHBrCl	98	11.0 10.9	6.8 7.1
(EtO) ₂ P(O)OCHBrCBrCl ₂	71	9.8 9.6	7.6 8.0	114-121	0.2	1.4867
(<i>n</i> -PrO) ₂ P(O)OCHBrCBrCl ₂	47	9.2 8.9	7.1 7.3	152-160	1	1.4828
(CH ₃) ₂ O ₂ P(O)OCHBrCBrCl ₂	100	10.2 10.1	7.9 8.6
OCHEtCHMeCH ₂ OP(O)OCHBrCBrCl ₂	100	9.2 8.6	7.1 7.3
(CCl ₃ CH ₂ O) ₂ P(O)OCHBrCBrCl ₂	100	16.2 17.2	5.0 5.3

^a The yields given are for individual experiments but in several cases the same reactants gave little or no adduct. ^b When two halogens are present the halogen content is expressed as milliequivalents per gram. ^c The positions of the halogen atoms are not known but are assumed on theoretical grounds to be as shown.

diethyl *t*-butyl phosphate, a compound not previously described. This compound was synthesized from diethyl phosphorochloridate and sodium *t*-butoxide and was found to react vigorously with bromine. The reaction with bromine gave isobutene dibromide and other unidentified products. Diethyl *t*-butyl phosphate, as would be expected, did not show infrared absorption at 6.1 μ .

Our only preparation of pure diethyl vinyl phosphate by the dehydrohalogenation reaction was by the action of sodium hydride on diethyl 2-bromoethyl phosphate in ether solution and the yield was only 10%. A careful comparison of physical properties, including infrared absorption, of this product and the product obtained from triethyl phosphite and chloroacetaldehyde indicated them to be identical. When refluxed with triethylamine both products gave similar crystalline derivatives.

The hydrogenation of the product obtained from triethyl phosphite and chloroacetaldehyde to triethyl phosphate was best accomplished in cyclohexane with palladium chloride on carbon as catalyst. The infrared absorption and other physical properties were essentially identical with those determined on a purified sample of commercial triethyl phosphate. Incomplete hydrogenation of the unsaturated phosphate was accomplished by Raney nickel in ether and by palladium chloride on carbon in dioxane, but a modification of reaction conditions would probably have given satisfactory results.

The addition of halogen by vinyl phosphates has been noted by others^{3a,b,c,d} but no one has described an anomalous reaction which frequently occurs with either chlorine or bromine. Perkow^{3c} described certain tetrabromoethyl esters which he found to be undistillable and which were destroyed by warming with excess bromine, and Mattson and co-workers^{3b} noted that although dimethyl dichlorovinyl phosphate readily absorbed bromine the derivative could not be isolated. We have observed that good yields of distillable addition products can frequently be obtained (Table I) from

either chlorine or bromine. In other experiments, however, for no apparent reason, the same reactants give rise to very little of the addition product but produce (a) alkyl halide, (b) a product which upon heating decomposes to a carbonyl compound containing one more halogen atom than the original phosphate, and (c) a viscous, non-volatile liquid of an unknown nature.

This anomalous reaction is well illustrated by the addition of bromine at 60° and in the presence of ultraviolet light to an equimolar quantity of diethyl 2-chlorovinyl phosphate dissolved in carbon tetrachloride. The yield of diethyl 1,2-dibromo-2-chloroethyl phosphate was only 5% but considerable quantities of ethyl bromide and bromochloroacetaldehyde, not previously described, were produced.

The normal halogen addition and the anomalous reaction appear to be entirely independent of each other and the relative amounts of the two reactions seem to be independent of temperature, solvent, order of mixing, molar ratios and the presence or absence of ultraviolet light. We have found that 1,2-dibromo-2,2-dichloroethyl diethyl phosphate is stable to excess bromine at 30° but the anomalous reaction has been observed below 0°.

An interesting difference between the halogen adducts and the products of the anomalous reaction is that the former are powerful cholinesterase inhibitors and are highly toxic to certain insects while the latter possess little or no biological activity.

Several unsuccessful attempts were made to perform other reactions with diethyl vinyl phosphate and other products which normally add to an ethylenic double bond. These included epoxidation in acetic acid, hydrogen chloride with anhydrous aluminum chloride, 2,4-dinitrobenzenesulfonyl chloride in acetic acid, and carbon tetrachloride with benzoyl peroxide. The last of these may have been partly successful since a product was isolated in 31% yield which contained 71% of the theoretical chlorine content of the expected adduct.

The hydrolysis of the product obtained from the reaction of chloral with triethyl phosphite to dichlo-

roacetaldehyde is consistent with the vinyl structure.

Experimental

Dehydrobromination of Diethyl 2-Bromoethyl Phosphate.—This reaction was carried out with a 100% excess of phosphate in order to minimize side reactions. To a solution of 636.5 g. (2.44 moles) of diethyl 2-bromoethyl phosphate in 300 ml. of dry ether was gradually added 29.3 g. of sodium hydride over a period of 4 hours. The solution was refluxed (43°) for 85 hours, filtered by gravity and the ether removed *in vacuo*. Distillation of the product through a 10-inch Vigreux column gave 42.5 g. distilling at 52–78° and fractionation of the distillate through a 1-foot column packed with glass helices gave 21.5 g. (10% yield) of diethyl vinyl phosphate, b.p. 60–64° (1 mm.), n_D^{25} 1.4070, and d_4^{25} 1.0687 (literature² values for the product obtained from chloroacetaldehyde and triethyl phosphite are b.p. 79° (6 mm.), n_D^{25} 1.4100, and d_4^{25} 1.0724). Infrared spectrograms prepared from this product and the one obtained from chloroacetaldehyde and triethyl phosphite were essentially identical.

Anal. Calcd. for $C_6H_{13}O_4P$: P, 17.2. Found: P, 17.5.

The diethyl 2-bromoethyl phosphate used in this preparation was made by mixing equimolar quantities of pyridine, bromoethanol and diethyl phosphorochloridate in the order given at 0–10°, stirring the mixture at room temperature for 2 hours, and removing of pyridinium chloride by filtration. Distillation of the product gave a 61% yield, b.p. 100–102° (1 mm.), n_D^{25} 1.4388, and d_4^{25} 1.3898.

Anal. Calcd. for $C_6H_{14}BrO_4P$: Br, 30.6; P, 11.9. Found: Br, 29.6; P, 12.3.

Hydrogenation of Diethyl Vinyl Phosphate.—The catalyst for this reaction was prepared by hydrogenating palladium chloride on carbon in cyclohexane at 50 pounds pressure for 2 hours in a Parr low-pressure apparatus. To 50 g. of highly purified product obtained from chloroacetaldehyde and triethyl phosphite was added 8.1 g. of wet catalyst (equivalent to 4 g. of dry catalyst) and 150 g. of pure cyclohexane. After 1 hour at 60 pounds pressure a sample of product was isolated for an infrared spectrogram and found to contain an estimated 10% of diethyl vinyl phosphate. Six grams of wet catalyst was then added to the reaction mixture and hydrogenation contained at 50 pounds pressure over the week end. Distillation gave a 73% yield of triethyl phosphate, b.p. 75° (5 mm.), n_D^{25} 1.3975, d_4^{25} 1.0549, and no absorption at 6.1 μ . In order to obtain a direct comparison under the same conditions with an authentic sample of triethyl phosphate, a sample of commercial product was fractionated at 10% take off through a 6-foot column packed with glass helices. The fraction chosen for comparison had b.p. 79° (5 mm.), n_D^{25} 1.3990, and d_4^{25} 1.0544. Infrared spectrograms of the two samples were essentially identical.

Anal. Calcd. for $C_6H_{13}O_4P$: P, 17.0. Found: for hydrogenation product, 16.4 and 16.6; for the purified commercial product, 16.5 and 16.7.

Diethyl 1,2,2,2-Tetrachloroethyl Phosphate.—One-half mole (124.5 g.) of diethyl 2,2-dichlorovinyl phosphate and 185 ml. of carbon tetrachloride were placed in a 500-ml. 3-neck flask equipped with a stirrer, an adapter bearing a thermometer and a Dry Ice condenser, and a 100-ml. graduated addition funnel surmounted by a Dry Ice condenser. About 0.75 mole of chlorine, liquefied in the condenser and collected in the addition funnel, was added dropwise to the reactor at about 60°. The reaction proceeded readily under the influence of a mercury vapor lamp. When the reaction was complete the solvent and excess chlorine were removed *in vacuo* and the product distilled. The yield of diethyl 1,2,2,2-tetrachloroethyl phosphate was 118 g. (74%), b.p. 125–145° (1.5 mm.), and n_D^{25} 1.4600.

Anal. Calcd. for $C_6H_{11}Cl_4O_4P$: Cl, 44.3; P, 9.7. Found: Cl, 44.4; P, 9.0.

Diethyl 1,2-Dibromo-2,2-dichloroethyl Phosphate.—One-half mole (80 g.) of bromine was added to 0.5 mole (124.5 g.) of diethyl 2,2-dichlorovinyl phosphate dissolved in 300 ml. of carbon tetrachloride. The temperature rose spontaneously to about 60° and the reaction was allowed to continue in a dark cabinet for 3 days. The solvent and a small amount of bromine were removed *in vacuo* and the product distilled. The yield of diethyl 1,2-dibromo-2,2-dichloro-

ethyl phosphate was 145 g. (71%); b.p. 114–121° (0.2 mm.), n_D^{25} 1.4867 and d_4^{25} 1.741.

Anal. Calcd. for $C_6H_{11}Br_2Cl_2O_4P$: halogen, 9.8 meq./g.; P, 7.6. Found: halogen, 9.6; P, 8.0.

Diethyl Bromochloroethyl Phosphate.—One-tenth mole each of bromine and chlorine were dissolved in 75 ml. of carbon tetrachloride at 0° and 0.2 mole of diethyl vinyl phosphate added gradually with cooling to about 20°. Removal of the solvent *in vacuo* and distillation gave 28 g. (48%) of diethyl bromochloroethyl phosphate, b.p. 106–112° (1 mm.), n_D^{25} 1.4518 and d_4^{25} 1.4579.

Anal. Calcd. for $C_6H_{13}BrClO_4P$: halogen, 6.8 meq./g.; P, 10.4. Found: halogen, 6.7; P, 10.0.

Anomalous Reaction of Bromine with Diethyl 2-Chlorovinyl Phosphate.—Two moles (429 g.) of diethyl 2-chlorovinyl phosphate was dissolved in 1 liter of carbon tetrachloride and 2 moles of bromine added gradually with cooling at about 60°. A mercury vapor lamp was used to activate the halogen. The carbon tetrachloride, which was removed first at atmospheric pressure and then *in vacuo*, contained a considerable quantity of lower boiling liquid, presumably ethyl bromide, but this was not isolated and identified. An attempt to distill the product at reduced pressure resulted largely in decomposition and only 40 g. (5%) of diethyl 1,2-dibromo-2-chloroethyl phosphate was obtained, b.p. 148–150° (1.5 mm.).

Anal. Calcd. for $C_6H_{12}Br_2ClO_4P$: halogen, 8.0 meq./g.; P, 8.3. Found: halogen, 7.8; P, 8.6.

A smaller (28 g.) and more volatile fraction of product collected at 70–95° (1 mm.) had n_D^{25} 1.4025 and was probably triethyl phosphate.

About 40 g. of liquid collected in a cold trap placed between the vacuum source and the condenser and an additional quantity was probably lost. Redistillation of this material at atmospheric pressure gave 27 g., b.p. 111.5–112°, n_D^{25} 1.4864 and d_4^{25} 1.8576.

Anal. Calcd. for C_2H_2BrClO : halogen, 12.1 meq./g. Found: halogen, 12.7.

This product was further identified as bromochloroacetaldehyde by reaction with an equimolar quantity of triethyl phosphite to form ethyl bromide (80%, b.p. 33–40°) and diethyl chlorovinyl phosphate (63%, b.p. 88–94° (1 mm.)), and n_D^{25} 1.4269 (literature² values are b.p. 92–105° at 1–2 mm., and n_D^{25} 1.4276).

The non-volatile material from this reaction (424 g.) was a viscous liquid, soluble in ether and methanol but insoluble in water, and was found to contain 12.9% phosphorus and 6.7 milliequivalents of halogen per gram.

Debromination of Diethyl 1,2-Dibromo-2,2-dichloroethyl Phosphate.—Fifty grams (0.122 mole) of diethyl 1,2-dibromo-2,2-dichloroethyl phosphate dissolved in 100 ml. of ether was treated gradually with an equivalent quantity of zinc dust (8 g.). The initial reaction was very vigorous and some of the product was lost by foaming. After refluxing for 3 hours the solution was extracted with water, the organic layer dried and the ether removed *in vacuo*. Rectification of the product gave a fraction with b.p. 60° (0.1 mm.) and n_D^{25} 1.4423 (literature² value for diethyl 2,2-dichlorovinyl phosphate, n_D^{25} 1.4428). Spectral traces from 1.8 to 15 μ prepared from this sample and a sample of diethyl 2,2-dichlorovinyl phosphate were essentially identical.

Hydrolysis of Diethyl 2,2-Dichlorovinyl Phosphate.—Sixty-five grams (0.262 mole) of diethyl 2,2-dichlorovinyl phosphate, 126 ml. of 37% hydrochloric acid and 100 ml. of water were mixed and refluxed for 5 hours. The vent gases were dried and passed into a cold trap which condensed 34 g. (79%) of ethyl chloride, b.p. 12.5°. The reaction mixture was extracted 5 times with ether, the combined ether extracts dried over sodium sulfate, and the ether removed *in vacuo*. Fractionation of the residue gave 15.6 g. (53%) of dichloroacetaldehyde, b.p. 95.5–96.4°. This product and an authentic sample of dichloroacetaldehyde were converted to 1:1 condensation products with urea by dissolving 5 g. of the aldehyde and 5 g. of urea in 6 ml. of water and separating the resulting white solid by filtration. The melting point and mixed melting point were 125–126°.

Reaction of Diethyl Vinyl Phosphate with Triethylamine.—One-tenth mole (18 g.) of diethyl vinyl phosphate and 0.11 mole (11 g.) of triethylamine were refluxed for 84 hours. Upon cooling a crystalline solid separated and this was washed with ether and dried.

Anal. Calcd. for $C_{12}H_{25}NO_4P$: P, 11.0. Found: P, 11.1.

Diethyl *t*-Butyl Phosphate.—Sodium *t*-butoxide was prepared by refluxing 125 ml. (1.32 moles) of *t*-butyl alcohol containing 3.45 g. (0.15 mole) of finely cut sodium until reaction was complete. To this mixture was added gradually with stirring and cooling 25.9 g. (0.15 mole) of diethyl phosphorochloridate at 25–30°. After stirring for 2 hours at room temperature the excess *t*-butyl alcohol was removed *in vacuo*, 25 ml. of water added to dissolve the sodium chloride, and the resulting solution extracted with ether. Removal of the ether and distillation gave 9.8 g. (31%) of diethyl *t*-butyl phosphate, b.p. 63–66° (1 mm.), n_D^{25} 1.4042 and d_4^{25} 1.0105.

Anal. Calcd. for $C_8H_{19}O_4P$: P, 14.8. Found: P, 15.2.

To 21 g. (0.1 mole) of diethyl *t*-butyl phosphate was gradually added 16 g. (0.1 mole) of bromine at 10–15°. Distillation gave a high boiling product and 18 g. (83%) of 1,2-dibromo-2-methylpropane, b.p. 140–154°, and n_D^{25} 1.4992 (literature⁵ b.p. 145–148°, n_D^{25} 1.5050).

(5) N. A. Milas and C. N. Winnick, *THIS JOURNAL*, **71**, 748 (1949).

Anal. Calcd. for $C_4H_9Br_2$: Br, 74.1. Found: Br, 74.3.

The high-boiling product, 10.2 g., b.p. 136–148° (1 mm.), may be a mixture of diethyl hydrogen phosphate and diethyl phosphorobromidate. Analysis indicated 17.9% phosphorus, 10.8% bromine and 4.9 milliequivalents of acid per gram.

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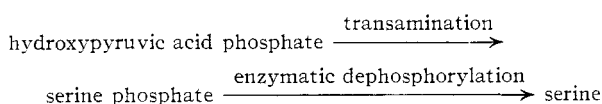
The Synthesis and Properties of Hydroxypyruvic Acid Phosphate

BY CLINTON E. BALLOU AND ROBERT HESSE

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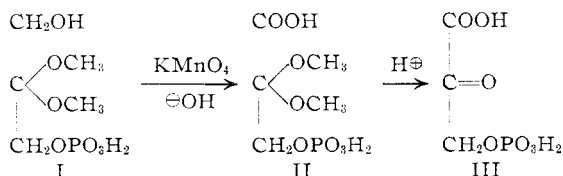
Hydroxypyruvic acid phosphate, a possible intermediate in the biosynthesis of serine phosphate, has now been obtained by synthesis and some of its properties have been determined. This synthetic material has been shown by other workers to be a good precursor of serine in a partially purified enzyme system prepared from rat liver.

Hydroxypyruvic acid phosphate has been postulated as a possible precursor of serine phosphate and of serine *via* the pathway¹



However, since the hydroxypyruvic acid phosphate has not been available either by isolation or synthesis, it has been impossible to test its biological activity in such a role.

We wish to report the synthesis of hydroxypyruvic acid phosphate by a definitive method, using as starting material the cyclohexylammonium salt of dihydroxyacetone phosphate dimethyl or diethyl ketal.² The reaction scheme is outlined below.



The cyclohexylammonium salt of dihydroxyacetone phosphate dimethyl ketal (I) was converted to the potassium salt, which was oxidized to II with potassium permanganate. The salt of II was converted to the free acid by passage through a column

of Dowex 50 (H^+). The acid eluate was neutralized with cyclohexylamine to give the salt, which was isolated in crystalline form from water by the addition of acetone.

The titration curves for I and II show the presence of a carboxyl group in the oxidation product, II (one mole per mole of primary or secondary phosphate), and are confirmation of the assigned structure.

The ketal structure of II is more stable at the pH of its own free acid than is that of I, being only slowly hydrolyzed to the ketone III, at 40°. However, incubation of the acidic solution at 40° for 4 days does hydrolyze the ketal, with the liberation of very little inorganic phosphate. The ultraviolet absorption spectra of the ketal and of the hydrolyzed compound show a shift in absorption toward the longer wave lengths following the hydrolysis of the ketal structure, which may serve as the basis of a useful spectrophotometric assay. The preparation of III by way of the diethyl ketal is in some respects preferable, since hydrolysis of the diethyl ketal proceeds about three times more readily than the dimethyl ketal.

III has the following properties. The phosphate group was liberated by acid hydrolysis at a rate comparable to that of dihydroxyacetone phosphate (half-time of hydrolysis about 20 minutes in 1 *N* hydrochloric acid at 90°).² In contrast, liberation of the phosphate group in alkali was more difficult, requiring 15 hours at room temperature in 1 *N* alkali for the elimination of 50% of the phosphate. Conditions for the quantitative elimination of phosphate in alkali were not found. Dephosphorylation

(1) H. J. Sallach, in H. B. McElroy and B. Glass, "A Symposium on Amino Acid Metabolism," Johns Hopkins Press, Baltimore, Md., 1955, p. 782.

(2) C. E. Ballou and H. O. L. Fischer, *THIS JOURNAL*, **78**, 1659 (1956).