[CONTRIBUTION FROM THE LABORATORY OF BIOCHEMISTRY, FACULTY OF AGRICULTURE, NAGOYA UNIVERSITY]

Synthesis of Organic Phosphorus Compounds. I. *p*-Substituted Benzyl Esters

BY MASATERU MIYANO AND SABURÔ FUNAHASHI

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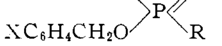
Di-*p*-bromobenzyl, di-*p*-chlorobenzyl and di-*p*-xylyl phosphite were synthesized. The chlorophosphonates derived from them were found to be characteristic phosphorylating agents for amines and alcohols.

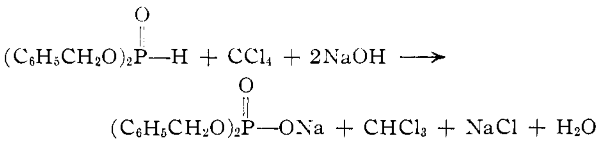
Phosphoric acid esters and amides, compounds of great biochemical significance, have been prepared by the reaction of diphenyl or dibenzyl chlorophosphonate with a tertiary base followed by hydrogenolysis of the protecting groups.

Brigl and Müller[1] synthesized diphenyl chlorophosphonate; dibenzyl chlorophosphonate[2] has been used for the preparation of nucleotides and nucleotide coenzymes by Todd, *et al.*[3]

Since this reagent has some disadvantages,[4] we have studied some di-(*p*-substituted benzyl) chlorophosphonates (II). The substituted benzyl esters, especially the *p*-bromo and *p*-chloro, are crystallized more easily than the corresponding non-substituted esters; it is advantageous to remove the catalyst poison by crystallizing the intermediate before hydrogenation. Since the mechanism of the alkaline hydrolysis of phosphoric acid esters is that of bimolecular substitution, *p*-halobenzyl groups would be expected to be hydrolyzed more easily. Thus, while dibenzyl phosphite was converted to dibenzyl phosphate in 88% yield[5] in the following reaction, the *p*-halobenzyl groups were hydrolyzed completely under these conditions, and even under more moderate conditions considerable hydrolysis occurred. The *p*-xylyl group was not hydrolyzed by alkali.



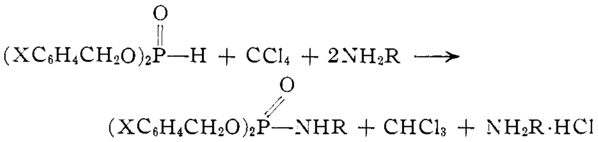
I, R = H; II, R = Cl;
III, R = NH_2; IV, R = NHC_6H_5;
V, R = NHC_6H_{11}



$$(C_6H_5CH_2O)_2\overset{\overset{\textstyle O}{\|}}{P}\text{—}H + CCl_4 + 2NaOH \longrightarrow (C_6H_5CH_2O)_2\overset{\overset{\textstyle O}{\|}}{P}\text{—}ONa + CHCl_3 + NaCl + H_2O$$

Baddiley, *et al.*,[6] reported that the hydrogenolysis of the *p*-bromobenzyl group was very slow, but we found that the *p*-bromobenzyl and *p*-xylyl groups were hydrogenolyzed at a satisfactory rate, and the *p*-chlorobenzyl group at a somewhat slower rate. Unexpectedly, *p*-substituted halogen also was hydrogenolyzed under our conditions to give the halogen acid which, although it accelerates hydrogenolysis of the benzyl group, will decompose some unstable phosphorus compounds.

Monoethyl phosphate was synthesized from di-*p*-bromobenzyl chlorophosphonate. Several amidophosphonates including the anilino(IV) and cyclohexylamino(V) compounds also were synthesized. Amidophosphonates of strong bases such as cyclohexylamine or ammonia could be obtained directly from phosphites in the following reaction, while weak bases such as aniline did not react; thus, anilinophosphonate was prepared by the reaction of chlorophosphonate and aniline. This result was very similar to non-substituted dibenzyl phosphite.[7]



$$(XC_6H_4CH_2O)_2\overset{\overset{\textstyle O}{\|}}{P}\text{—}H + CCl_4 + 2NH_2R \longrightarrow (XC_6H_4CH_2O)_2\overset{\overset{\textstyle O}{/\!/}}{P}\text{—}NHR + CHCl_3 + NH_2R\cdot HCl$$

Experimental

Melting points are not corrected. Analytical values are given in Table I.

***p*-Substituted Benzyl Alcohols.**—*p*-Bromobenzyl and *p*-chlorobenzyl alcohols were prepared from the corresponding chlorides which were refluxed for 10 hours with a slight excess of potassium acetate in aqueous ethanol and for an additional 8 hours with potassium hydroxide in aqueous ethanol; m.p.'s 77° and 73–74°, respectively. *p*-Xylyl alcohol was obtained by hydrolysis of *p*-xylyl chloride with sodium carbonate followed by recrystallization from petroleum ether; m.p. 59°. These alcohols should be free from *o*-isomer for use in the following reaction.

Di-(*p*-substituted benzyl) Phosphites.—A mixture of 0.764 mole of the *p*-substituted benzyl alcohol and 0.825 mole of dimethylaniline dissolved in 250 ml. of benzene was added to a stirred solution of 34 ml. of phosphorus trichloride in 250 ml. of benzene; the temperature was maintained at 8–10° by cooling in an ice-bath and moisture was excluded. After 20 minutes stirring, water (100 ml.) was added carefully followed by vigorous stirring for an additional 30 minutes. White platelets crystallized; they were filtered, washed with 100 ml. of water, dried over phosphorus pentoxide. The combined filtrates and washings was separated in two layers; the upper layer was washed with 100 ml. of 5% aqueous potassium carbonate solution and 100 ml. of water, dried (calcium chloride) and concentrated to 150 ml. under reduced pressure, a second crop of crystals was obtained when light petroleum ether (b.p. 60–90°) was added. Still more crop was obtained from the mother liquor which was concentrated and set aside in a refrigerator for several days. The crude product can be recrystallized from alcohol, cyclohexane or benzene.

Di-(*p*-substituted benzyl) Chlorophosphonates.—To 0.00955 mole of the di-(*p*-substituted benzyl) phosphite suspended in 25 ml. of carbon tetrachloride was added 0.80 ml. (0.00985 mole) of sulfuryl chloride drop by drop while the mixture was shaken in an ice-bath. The gases evolved, the excess sulfuryl chloride and most of the solvent were removed under reduced pressure at room temperature. The resulting sirup in the proper solvent was used immediately without further purification.

Di-(*p*-substituted benzyl) Amidophosphonates.—The anilinophosphonates were prepared by the addition of 2.0 ml. of aniline to a cold carbon tetrachloride solution of the di-*p*-halobenzyl chlorophosphonate (prepared from 0.01 mole of the corresponding phosphite); the cyclohexylaminophosphonates by the addition of 2.5 ml. (0.0218 mole) of cyclohexylamine to a cold solution of 0.01 mole of the phosphite

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(1) P. Brigl and H. Müller, *Ber.*, **72**, 2123 (1939).

(2) F. R. Atherton, H. T. Openshaw and A. R. Todd, *J. Chem. Soc.*, 382 (1945).

(3) A. R. Todd, *et al.*, *ibid.*, 46 (1954).

(4) F. R. Atherton, H. T. Howard and A. R. Todd, *ibid.*, 1107 (1948).

(5) V. M. Clark and A. R. Todd, *ibid.*, 2030 (1950).

(6) J. Baddiley, V. M. Clark, J. J. Michalski and A. R. Todd, *ibid.* 815 (1949).

(7) F. R. Atherton, H. T. Openshaw and A. R. Todd, *ibid.*, 660 (1945).

TABLE I

Compound	M.p., °C.	Yield, %	Formula	Carbon, % Calcd. Found	Hydrogen, % Calcd. Found	Nitrogen, % Calcd. Found	Halogen, % Calcd. Found
Di-*p*-bromobenzyl phosphite	93–94	72.9	$C_{14}H_{13}PO_3Br_2$	40.0 40.4	3.1 3.1		
Di-*p*-chlorobenzyl phosphite	75	65	$C_{14}H_{13}PO_3Cl_2$	50.8 50.8	4.0 4.0		
Di-*p*-xylyl phosphite	62	62	$C_{16}H_{19}PO_3$	66.2 65.5	6.6 6.5		
Di-*p*-chlorobenzyl anilinophosphonate	103–104	85[a]	$C_{20}H_{18}O_3NPCl_2$	56.8 56.9	4.3 4.5	3.3 3.4	16.8 16.8
Di-*p*-bromobenzyl anilinophosphonate	119–120	83[a]	$C_{20}H_{18}O_3NPBr_2$	47.0 46.5	3.5 3.6	2.8 2.6	31.1 31.3
Di-*p*-chlorobenzyl cyclohexylaminophosphonate	97.5–98.5	81[a]	$C_{20}H_{24}O_3NPCl_2$	56.1 56.1	5.65 5.6	3.3 3.2	
Di-*p*-bromobenzyl cyclohexylaminophosphonate	114–115	90[a]	$C_{20}H_{24}O_3NPBr_2$	46.4 46.4	4.7 5.0	2.7 2.7	
Di-*p*-xylyl cyclohexylaminophosphonate	98.5–99.5	84[a]	$C_{22}H_{30}PO_3N$	68.2 68.0	7.85 7.85	3.6 3.9	
Di-*p*-bromobenzyl aminophosphonate	130–131	48[a]	$C_{14}H_{14}PO_3NBr_2$	38.65 38.4	3.2 3.9	3.2 3.8	
Di-*p*-chlorobenzyl aminophosphonate	136–137	55[a]	$C_{14}H_{14}PO_3NCl_2$	48.6 48.1	4.1 3.9	3.8 3.8	
Sodium di-*p*-xylyl phosphate	....	*ca.* 100[a]	$C_{16}H_{18}O_4PNa$	58.6 58.7	5.5 5.7		
Di-*p*-xylyl phosphate	88	..	$C_{16}H_{19}O_4P$	62.7 63.0	6.3 6.3		
Sodium di-*p*-chlorobenzyl phosphate		Poor	$C_{14}H_{12}O_4PCl_2Na$	45.6 45.4	3.3 3.4		19.2 19.2
Di-*p*-chlorobenzyl phosphate	136.5	..	$C_{14}H_{13}O_4PCl_2$	48.5 48.5	3.8 3.9		20.4 20.8

[a] Yield of crude compound.

in carbon tetrachloride. The reaction mixture was set aside for 30–40 minutes at room temperature and then washed successively with 5% hydrochloric acid, aqueous potassium carbonate solution and water. The material, which crystallized upon removal of the solvent by aeration, was recrystallized from 70% aqueous ethanol.

The di-*p*-halobenzyl aminophosphonates were prepared from a carbon tetrachloride solution of 0.01 mole of the phosphite shaken with 25 ml. of a concentrated aqueous ammonia solution. The mixture was set aside in a refrigerator overnight. The decanted upper layer was washed with water and the solvent removed by aeration. The resulting crystals were recrystallized from chloroform.

Di-*p*-xylyl Phosphate.—Sodium di-*p*-xylyl phosphate, prepared from di-*p*-xylyl phosphite according to the method for preparation of sodium dibenzyl phosphate described by Clark and Todd,[5] was dissolved in warm water. The solution was cooled in an ice-bath and dilute nitric acid added with vigorous shaking. The resulting crystals were recrystallized from cyclohexane.

Di-*p*-bromobenzyl Phosphate.—The following procedure was used as the preceding method resulted in hydrolysis of the *p*-bromobenzyl groups. To a cold solution of di-*p*-bromobenzyl chlorophosphonate (prepared from 8.02 g. of phosphite) in 50 ml. of carbon tetrachloride was added the mixture of 20 ml. of pyridine and 10 ml. of water in one portion and the reaction mixture shaken while immersed in an ice bath. After 30 hours dilute hydrochloric acid was added and separated organic layer extracted with warm aqueous sodium carbonate. The aqueous extract was acidified with hydrochloric acid; the resulting precipitation was filtered and recrystallized from ethanol; m.p. 156.5°, reported[6] 155–156°; the yield was poor.

Di-*p*-chlorobenzyl Phosphate.—Sodium hydroxide solution (8 g. in 25 ml. of water) was added a cold stirred solution of di-*p*-chlorobenzyl phosphite (6.8 g.) in 25 ml. of carbon tetrachloride and resulting crystals extracted with warm chloroform. When the extract was concentrated on a steam-bath, white needles separated suddenly; they were filtered, recrystallized from hot water and dried over phosphorus pentoxide at 100° *in vacuo* to yield sodium di-*p*-chlorobenzyl phosphate. When a warm aqueous solution of this sodium salt was acidified with nitric acid, crystals of di-*p*-chlorobenzyl phosphate separated which was recrystallized from 70% aqueous ethanol.

When light petroleum was added to the original concentrated mother liquor, fine long needles separated which were recrystallized from cyclohexane; m.p. 100–101°. The analytical data indicate that this product is not the expected pyrophosphate.

Anal. Calcd. for tetra-*p*-chlorobenzyl pyrophosphate, $C_{28}H_{24}O_7P_2Cl_4$: C, 49.7; H, 3.6; Cl, 20.9. Found: C, 53.6; H, 4.0; Cl, 20.1.

Hydrogenolysis.—The di-(*p*-substituted benzyl) phosphates (0.005 mole) were hydrogenated in the presence of 80 ml. of absolute ethanol and 0.5 g. of 10% palladium-charcoal. The results of these preliminary experiments are summarized in Table II.

TABLE II

Phosphate	Total H_2 uptake in ml. (mole)	H_2 uptake in first 3 min., %
Di-*p*-bromobenzyl	51.8 (0.0023)	93
Di-*p*-chlorobenzyl	50.2 (0.0022)	63
Di-*p*-xylyl	28.7 (0.0013)	91

Monoethyl Phosphate.—A mixture of 8 ml. of pyridine and 2.5 ml. of ethanol was gradually added to a cold solution of di-*p*-bromobenzyl chlorophosphonate (from 8.02 g. of the phosphite) in 25 ml. of carbon tetrachloride. After standing for 72 hours at room temperature, the reaction mixture was concentrated under reduced pressure, dilute hydrochloric acid (5%, 50 ml.) added and the mixture extracted 3 times with 30 ml. of ether. The extract was dried over sodium sulfate and freed from solvent by aeration. The resulting partially crystallizing sirup was taken up in 80% alcohol, refluxed with 0.5 g. of activated carbon for 30 minutes, filtered, and washed with a small amount of 80% alcohol. The aqueous alcoholic solution was hydrogenated in the presence of palladium–charcoal. After the uptake of hydrogen had ceased, catalyst was filtered; the filtrate was concentrated under reduced pressure, neutralized with barium hydroxide and concentrated under reduced pressure. The crystals obtained upon the addition of ethanol were filtered with suction, washed with ethanol, and dried over phosphorus pentoxide at 100° *in vacuo*, yield 2.6 g. (52.1%).

Anal. Calcd. for $C_2H_5O_4PBa$: C, 9.2; Ba, 52.5. Found: C, 10.3; Ba, 54.0.

The brucine salt of monoethyl phosphate was prepared in the usual manner; softening temperature *ca.* 135-140°, m.p. *ca.* 174-175° dec.

Anal. Calcd. for $C_{48}H_{59}O_{17}N_4P$: N, 6.5. Found: N, 6.54.

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TOKYO, JAPAN

[CONTRIBUTION FROM THE LABORATORY OF BIOCHEMISTRY, FACULTY OF AGRICULTURE, NAGOYA UNIVERSITY]

Synthesis of Organic Phosphorus Compounds. II. Exhaustive Debenzylation Reactions

BY MASATERU MIYANO[1]

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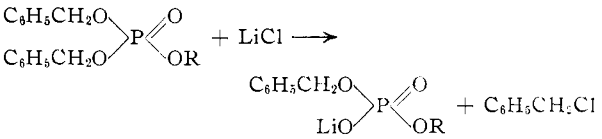
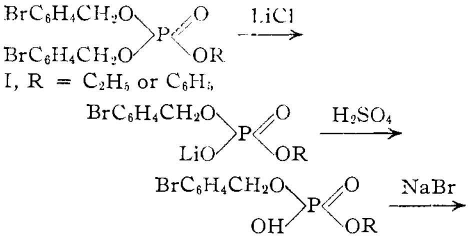
Ethyl phosphate and phenyl phosphate were prepared from di-*p*-bromobenzyl ethyl phosphate (I, R = C_2H_5) and di-*p*-bromobenzyl phenyl phosphate (I, R = C_6H_5), respectively, by the stepwise removal of two *p*-bromobenzyl groups on heating with an inorganic salt in an anhydrous solvent. This reaction "exhaustive debenzylation," a development of the "specific debenzylation" studied by other investigators,[2,3] seems to be a new generally applicable method for the preparation of monoalkyl and monoaryl esters of phosphoric acid. *p*-Chlorobenzyl phosphate and *p*-bromobenzyl phosphate also were prepared by a similar method.

Neutral esters of phosphoric or phosphorous acid, such as tribenzyl phosphate, dibenzyl alkyl phosphate, dibenzyl alkylamidophosphonate and dibenzyl phosphite lose one benzyl group when heated with a strong tertiary amine, amine hydrochloride or better with an inorganic salt in an anhydrous solvent.[2,3]

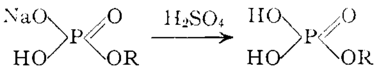
Lithium chloride in ethoxyethanol is in general the best reagent for this purpose.



It was suggested that this reaction is applicable only to neutral and not to ionizable esters. However, in this paper is described the removal of *p*-halobenzyl groups from acidic esters (II) as well as neutral esters (I) by heating with lithium chloride or sodium bromide in ethoxyethanol or diethylene glycol. The stepwise splitting off of two *p*-halobenzyl groups, as shown below, is termed exhaustive debenzylation.

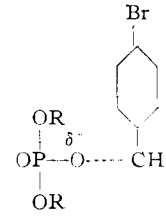

I, R = C_2H_5 or C_6H_5

II, R = C_2H_5 or C_6H_5



These reactions constitute a third method for the preparation of monoalkyl or monoaryl phosphates by the removal of protecting groups; the other methods are hydrolysis and hydrogenolysis. Although the yield obtained by exhaustive debenzylation is somewhat lower than that obtained by hydrogenolysis, this method is useful for cases in which hydrogenolysis is not feasible.

Since $-S_2$ substitution reactions are generally accelerated by a $+I$ substituent or a $-E$ substituent,[4] *para*-substituted bromine which has both a $+I$ and a $-E$ effect should accelerate $-S_2$ reaction.



This was borne out by our finding[5] that the alkaline hydrolysis (which is believed to follow as $-S_2$ mechanism (X = OH)) of *p*-halobenzyl groups proceeded more easily than that of benzyl groups. If debenzylation reactions also proceed by a $-S_2$ mechanism (X = Cl or Br), the *p*-bromobenzyl group would be expected to be removed more easily than the unsubstituted benzyl group, although the latter still may undergo exhaustive debenzylation.

Di-*p*-bromobenzyl phosphate (IVa) and di-*p*-chlorobenzyl phosphate (IVb) were prepared in

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(1) Department of Agricultural Chemistry, Tokyo University.

(2) J. Baddiley, V. M. Clark, J. J. Michalski and A. R. Todd, *J. Chem. Soc.*, 815 (1949).

(3) V. M. Clark and A. R. Todd, *ibid.*, 2023 (1950); (b) 2030 (1950).

(4) M. J. S. Dewar, "The Electronic Theory of Organic Chemistry," Oxford University Press, London, 1949, pp. 71-72.

(5) M. Miyano and S. Funahashi, THIS JOURNAL, **77**, 3522 (1955).