Preparation of Esters of Phosphoric Acid *via* Quaternary Phosphonium Salts

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The oxidation of triesters of phosphorous acid to triesters of phosphoric acid by means of monobromocyanoacetamide and benzyl alcohol has been extended to the oxidation of diesters of phosphorous acid to diesters of phosphoric acid. When di-*n*-butyl phosphite reacted with monobromocyanoacetamide and benzyl alcohol in refluxing tetrahydrofuran, a 76% yield of di-*n*-butyl hydrogen phosphate was obtained. The reaction may be explained as proceeding through a quaternary phosphonium salt, dibutoxybenzyloxyhydrogenphosphonium bromide (IV, R = *n*-C_4H_9). Further, this was applied to phosphorylation of alcohols and phenol. The reaction of alcohols with dibenzyl phosphite and monobromocyanoacetamide, followed by hydrogenation, resulted in the formation of corresponding alkyl (or phenyl) dihydrogen phosphates in fairly good yields.

The oxidation of triesters of phosphorous acid to triesters of phosphoric acid has been widely studied with various oxidizing reagents; however, diesters of phosphorous acid are known to be more or less resistant to oxidation and only a few instances of their oxidation have been reported.[1-3]

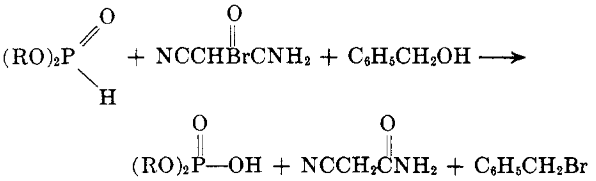
In the preceding paper[4] a successful method of oxidizing various triesters of phosphorous acid or phosphines to triesters of phosphoric acid or phosphine oxides by means of monobromocyanoacetamide with either benzyl or allyl alcohol was reported. The reaction was further extended to the preparation of diethyl hydrogen phosphate in a quantitative yield from diethyl phosphite.

This oxidation method appears to be an efficacious one because the reaction can be considered as proceeding through a quaternary phosphonium salt intermediate and thus trivalent phosphorus compounds would be selectively oxidized to pentavalent phosphorus compounds.

In the present experiment, oxidation of di-*n*-butyl phosphite was attempted at room temperature. It resulted in the formation of a 60% yield of di-*n*-butyl hydrogen phosphate, but 40% of the di-*n*-butyl phosphite was recovered unchanged. However, when the reaction was carried out in refluxing tetrahydrofuran, the yield of dibutyl hydrogen phosphate was increased to 74% (eq. 1, R = *n*-C_4H_9).

When allyl alcohol was used in the place of benzyl alcohol in the above reaction, dibutyl hydrogen phosphate was obtained in a 73% yield even at room temperature.

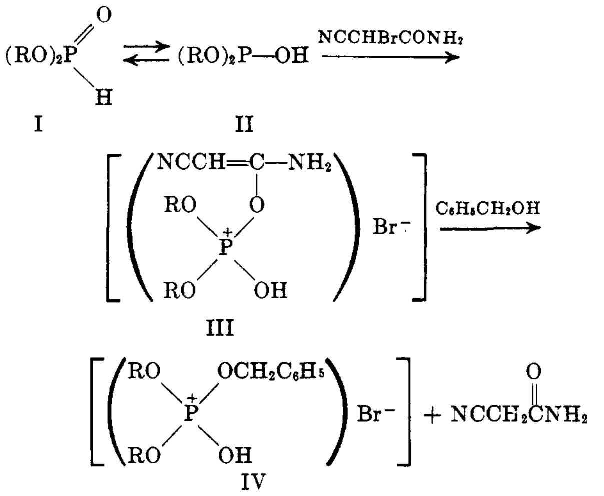
Dibenzyl hydrogen phosphate was obtained in a 20% yield by the reaction of dibenzyl phosphite with monobromocyanoacetamide and benzyl alcohol at room temperature (eq. 1, R = $C_6H_5CH_2$). No noticeable differences were found in the yield of dibenzyl hydrogen phosphate even when the reaction was carried out under more drastic conditions.



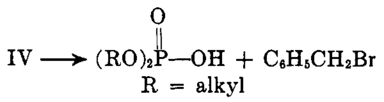
$$(RO)_2P(=O)H + NCCHBrC(=O)NH_2 + C_6H_5CH_2OH \longrightarrow (RO)_2P(=O){-}OH + NCCH_2C(=O)NH_2 + C_6H_5CH_2Br \quad (1)$$

R = C_2H_5, C_4H_9, or $C_6H_5CH_2$

These reactions can be explained in the following manner. A tautomeric pair of pentavalent and trivalent structures (I and II) exists in a dialkyl phosphite.[5,6] A dialkyl phosphite reacts in its trivalent structure with monobromocyanoacetamide to give an enol phosphonium salt III. The intermediate III is in turn changed into IV by the action of benzyl alcohol (eq. 2). From the second intermediate IV, the benzyl group is primarily eliminated as benzyl bromide by the subsequent attack of bromide ion giving dialkyl hydrogen phosphate (eq. 3).



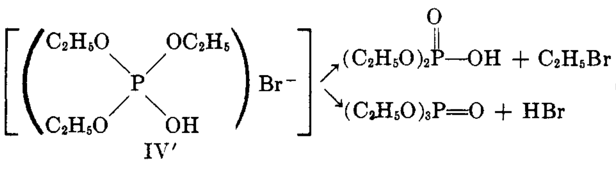
(2)



$$\text{IV} \longrightarrow (RO)_2P(=O){-}OH + C_6H_5CH_2Br \quad (3)$$

R = alkyl

In order to elucidate the proposed mechanism, the reaction was carried out using diethyl phosphite, ethanol, and monobromocyanoacetamide. In this case, since the ethyl group is not so easily eliminated as the benzyl group, it can be expected that both diethyl hydrogen phosphate and triethyl phosphate would be formed by the competing elimination of ethyl bromide and hydrogen bromide from the quaternary phosphonium salt IV′ (eq. 4).



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[1] D. M. Brown and P. R. Hammond, *J. Chem. Soc.*, 4229 (1960).

[2] K. Dimroth and B. Lerch, *Angew. Chem.*, **72**, 751 (1960).

[3] D. Samuel and D. B. Silver, *J. Org. Chem.*, **28**, 2089 (1963).

[4] T. Mukaiyama, O. Mitsunobu, and T. Obata, *ibid.*, **30**, 101 (1965).

[5] G. O. Doak and L. D. Freedman, *Chem. Rev.*, **61**, 31 (1961).

[6] W. J. Bailey and R. B. Fox, *J. Org. Chem.*, **28**, 531 (1963).

TABLE I

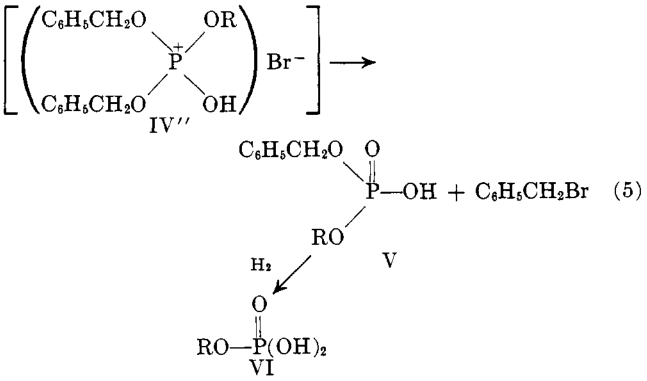
PHOSPHORYLATION OF ALCOHOLS AND PHENOL BY MEANS OF MONOBROMOCYANOACETAMIDE AND DIBENZYL PHOSPHITE

Alcohol or phenol	Product Phosphate (anilinium salt) $RO-\overset{O}{\overset{\|}{P}}<^{OH}_{O^-}$ R	Yield, %	M.p., °C.	N, % Calcd.	Found	R_f[a]
C_2H_5OH	C_2H_5	79	164–165	6.39	6.56	0.37
n-C_3H_7OH	n-C_3H_7	72	136–139	6.01	6.30	0.45
i-C_3H_7OH	i-C_3H_7	85	160–162	6.01	6.29	0.43
n-C_4H_9OH	n-C_4H_9	72	139–141	5.67	5.96	0.52
C_6H_5OH	C_6H_5	79	171–175			0.47

[a] Solvent system: n-propyl alcohol–concentrated ammonium hydroxide–water, 6:3:1.

Indeed, when the reaction was carried out at room temperature, diethyl hydrogen phosphate and triethyl phosphate were obtained in 32 and 46% yields, respectively. Similarly, dibutyl hydrogen phosphate and tributyl phosphate were obtained in 47 and 50% yields, respectively, by the reaction of dibutyl phosphite, butyl alcohol, and monobromocyanoacetamide.

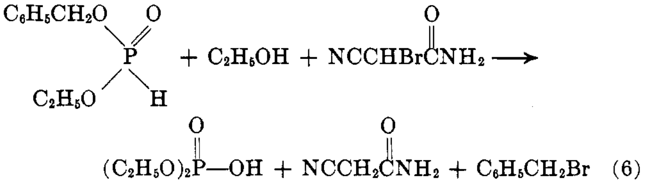
The reaction was further extended to selective phosphorylation of alcohols under the assumption that alkyl benzyl hydrogen phosphate would be formed, if dibenzyl phosphite was used in the above reaction. The reaction would proceed through a quaternary phosphonium salt (IV'') which is similar in structure to IV or IV'. In view of the foregoing results, benzyl bromide, rather than the other alkyl bromide or hydrogen bromide, should be eliminated from IV'' forming alkyl benzyl hydrogen phosphate (V) exclusively; phosphorylation of alcohols has been performed (eq. 5). Further, the resulting alkyl benzyl hydrogen phosphate can be readily converted to alkyl dihydrogen phosphate (VI) by catalytic hydrogenation.



When the mixture resulted from the reaction of ethanol with monobromocyanoacetamide and dibenzyl phosphite was hydrogenated, ethyl dihydrogen phosphate was isolated as the anilinium salt in a 79% yield as expected. Similarly, n-propyl, isopropyl, n-butyl, or phenyl dihydrogen phosphate was obtained as the anilinium salt in a 72, 85, 72, or 79% yield, respectively, by phosphorylation of n-propyl alcohol, isopropyl alcohol, n-butyl alcohol, or phenol. The yields, melting points, and R_f values of them are summarized in Table I.

When ethyl benzyl phosphite was treated with monobromocyanoacetamide and ethanol, an 81% yield of diethyl hydrogen phosphate was obtained along with an 80% yield of benzyl bromide (eq. 6).

As shown above, phosphorylation of alcohols by the use of dibenzyl phosphite and monobromocyanoacetamide selectively gave the corresponding alkyl benzyl hydrogen phosphates. Since the resulting phosphates have one benzyl group and one hydroxy group, they may possibly be employed, without isolation, in another phosphorylation to produce esters of phosphoric acid, pyrophosphates, or phosphoramidates.



$$(C_6H_5CH_2O)(C_2H_5O)\overset{O}{\overset{\|}{P}}H + C_2H_5OH + NCCHBr\overset{O}{\overset{\|}{C}}NH_2 \longrightarrow (C_2H_5O)_2\overset{O}{\overset{\|}{P}}-OH + NCCH_2\overset{O}{\overset{\|}{C}}NH_2 + C_6H_5CH_2Br \quad (6)$$

Experimental

Reagents.—The solvents and alcohols were purified and dried by ordinary procedures. Monobromocyanoacetamide,[7] diethyl phosphite,[8] and dibenzyl phosphite[9] were prepared by literature procedures.

Preparation of Di-n-butyl Phosphite.—Phosphorus trichloride (137 g., 1 mole) was added dropwise over a period of 1.5 hr. to a refluxing solution of n-butyl alcohol (222 g., 3 moles) in 500 ml. of petroleum ether (b.p. 40–50°) with continuous stirring. Stirring was continued for an additional hour and the solution was allowed to stand overnight. The solvent was removed under reduced pressure and the residue was distilled, giving 37 g., 18%, of di-n-butyl phosphite, b.p. 87–89° (0.05 mm.).

Anal. Calcd. for $C_8H_{19}O_3P$: C, 49.48; H, 9.79. Found: C, 49.66; H, 10.08.

Oxidation of Di-n-butyl Phosphite by Means of Monobromocyanoacetamide and Benzyl Alcohol.—To a solution of monobromocyanoacetamide (1.63 g., 0.01 mole) and benzyl alcohol (1.1 g., 0.01 mole) in 10 ml. of tetrahydrofuran (THF) was added dropwise a solution of di-n-butyl phosphite (1.95 g., 0.01 mole) in 5 ml. of THF at room temperature. The solution was stirred for an additional 2 hr. and refluxed for 30 min. The solution was allowed to stand overnight, the solvent was removed under reduced pressure, and cyanoacetamide (0.71 g., 84%) was removed by filtration. From the residue, benzyl bromide [1.60 g., b.p. 80–83° (10 mm.), which was contaminated with benzyl alcohol] and di-n-butyl hydrogen phosphate [1.20 g., 57%, b.p. 135–138° (0.03 mm.)] were obtained and 0.90 g. (40%) of di-n-butyl phosphite [b.p. 103–105° (0.03 mm.)] was recovered. The yield of di-n-butyl hydrogen phosphate was increased to 88%, b.p. 140–145° (0.05–0.10 mm.), when a solution of di-n-butyl phosphite, monobromocyanoacetamide, and benzyl alcohol in THF was refluxed for 2 hr. Redistillation gave 6.4 g. (76%), b.p. 135–138° (0.05 mm.) By paper chromatography a single spot was obtained with R_f 0.81 (solvent system,

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(7) T. Hata and T. Mukaiyama, *Bull. Chem. Soc. Japan*, **35**, 1106 (1962).

(8) H. McCombie, B. C. Saunders, and G. J. Stacey, *J. Chem. Soc.*, 380 (1945).

(9) F. R. Atherton, H. T. Openshaw, and A. R. Todd, *ibid.*, 382 (1945). Dibenzyl phosphite used in these experiments was purified in the following manner: the crude ester was dissolved in a mixture of ether and petroleum ether (2:3); after cooling to −40°, pure dibenzyl phosphite precipitated, was separated by decantation, and dried. *Anal.* Calcd. for $C_{14}H_{15}O_3P$: C, 64.12; H, 5.73. Found: C, 63.94; H, 6.06.

n-propyl alcohol–concentrated ammonium hydroxide–water, 6:3:1).

Oxidation of Di-*n*-butyl Phosphite by Means of Monobromocyanoacetamide and Allyl Alcohol.—A solution of di-*n*-butyl phosphite (9.70 g., 0.05 mole) in 30 ml. of THF was added to a solution of monobromocyanoacetamide (8.15 g., 0.05 mole) and allyl alcohol (4.0 g., 0.07 mole) with vigorous stirring at room temperature. Then the solution was refluxed for an additional 1.5 hr. and was allowed to stand overnight. After removal of the solvent under reduced pressure, the residue was filtered to remove cyanoacetamide (3.91 g., 93%). From the filtrate, 9.2 g. (88%) of di-*n*-butyl hydrogen phosphate, b.p. 115–120° (0.01 mm.), was obtained by fractionation. Redistillation gave 8.6 g. (82%), b.p. 122–125° (0.015 mm.). By paper chromatography a single spot was obtained with R_f 0.81.

Oxidation of Dibenzyl Phosphite by Means of Monobromocyanoacetamide and Benzyl Alcohol.—A solution of dibenzyl phosphite (2.70 g., 0.01 mole), monobromocyanoacetamide (1.63 g., 0.01 mole), and benzyl alcohol (1.1 g., 0.01 mole) in 20 ml. of THF was refluxed for 1 hr. and then allowed to stand overnight at room temperature. The solvent was removed under reduced pressure and the residue was filtered to remove cyanoacetamide (0.43 g., 51%). Removal of a mixture of benzyl bromide and benzyl alcohol [1.68 g., b.p. 45–50° (0.4 mm.)] left an oil which was dissolved in 35 ml. of ether. Sodium hydroxide solution (5%, 20 ml.) was added to the ether solution. The aqueous layer was separated and acidified with 5 ml. of concentrated hydrochloric acid giving 0.60 g. (21%) of dibenzyl hydrogen phosphate (m.p. 72–73°). Recrystallization from ether raised the melting point to 78°. A mixture melting point with authentic material was not depressed.

Reaction of Diethyl Phosphite with Ethanol and Monobromocyanoacetamide.—A solution of diethyl phosphite (1.38 g., 0.01 mole) in 10 ml. of ether was added dropwise to a suspension of monobromocyanoacetamide (1.63 g., 0.01 mole) and ethanol (1 ml.) in 10 ml. of ether with vigorous stirring at room temperature. The mixture was allowed to stand overnight and was filtered to remove cyanoacetamide (0.87 g., 103%). From the filtrate, triethyl phosphate [0.83 g., 46%, b.p. 92–94° (12 mm.)] and diethyl hydrogen phosphate [0.49 g., 32%, b.p. 113–116° (0.03 mm.), lit.[10] b.p. 116–118° (0.01 mm.)] were obtained by fractionation.

Similarly, di-*n*-butyl phosphite (1.95 g., 0.01 mole) was treated with *n*-butyl alcohol (1.5 g.) and monobromocyanoacetamide (1.63 g., 0.01 mole) in 15 ml. of THF at room temperature and tri-*n*-butyl phosphate [1.07 g., 50%, b.p. 103–105° (0.3 mm.)] and di-*n*-butyl hydrogen phosphate [0.99 g., 47%, b.p. 130–138° (0.02 mm.)] were obtained by fractionation.

Phosphorylation of Alcohols by Means of Monobromocyanoacetamide and Dibenzyl Phosphite.—Monobromocyanoacetamide (1.63 g., 0.01 mole) was added to a solution of dibenzyl phosphite (2.70 g., 0.01 mole) and ethanol (2 ml.) in 20 ml. of THF with vigorous stirring at room temperature. Stirring was continued for 1 hr. and the solution was refluxed for an additional 30 min. The solution was allowed to stand overnight, the solvent was removed under reduced pressure, and cyanoacetamide (0.77 g., 92%) was removed by filtration. From the filtrate, benzyl bromide, 1.30 g., 76%, b.p. 40–46° (0.5 mm.), was removed and the residue was dissolved in 50 ml. of aqueous ethanol (1:1). The solution was hydrogenated over palladium oxide (100 mg.) at room temperature and atmospheric pressure. After absorption of the quantitative amount of hydrogen, the catalyst was removed by filtration and the solvent was removed under reduced pressure. The residue was dissolved in 10 ml. of 99% ethanol and aniline (1.90 g.) was added giving anilinium ethyl hydrogen phosphate (1.73 g., 79%, m.p. 155–158°). The product was rinsed with 50 ml. of dry acetone and was recrystallized from acetonitrile–water, m.p. 164–165°.

Anal. Calcd. for $C_8H_{14}NO_4P$: N, 6.39. Found: N, 6.56.

Similarly, *n*-propyl, isopropyl, and *n*-butyl dihydrogen phosphates were obtained as anilinium salts by phosphorylation of *n*-propyl, isopropyl, and *n*-butyl alcohols (Table I).

Phosphorylation of Phenol by Means of Monobromocyanoacetamide and Dibenzyl Phosphite.—A solution of dibenzyl phosphite (2.70 g., 0.01 mole), monobromocyanoacetamide (1.63 g., 0.01 mole), and phenol (0.95 g., 0.01 mole) in 20 ml. of THF was refluxed for 1.5 hr. The solution was allowed to stand for 2 days and the solvent was removed under reduced pressure. After removal of cyanoacetamide (0.75 g., 89%) and benzyl bromide [1.3 g., 76%, b.p. 34–36° (3 mm.)], the residue was dissolved in 20 ml. of THF and hydrogenated over palladium oxide (100 mg.) at room temperature and atmospheric pressure. After absorption of hydrogen had ceased, the catalyst was removed by filtration and the solvent was removed under reduced pressure. The residue was dissolved in 10 ml. of 95% ethanol and aniline (1.9 g.) was added, giving anilinium phenyl hydrogen phosphate (2.12 g., 79%, m.p. 158–172°). Recrystallization from acetonitrile–water raised the melting point to 171–174°. A mixture melting point with an authentic sample was not depressed.

Phosphorylation of Ethanol by Means of Monobromocyanoacetamide and Benzyl Ethyl Phosphite.—A solution of benzyl ethyl phosphite (1.00 g., 0.005 mole) and monobromocyanoacetamide (0.82 g., 0.005 mole) in 5 ml. of ethanol was refluxed for 2 hr. The solution was cooled and cyanoacetamide (0.08 g., 19%) was removed by filtration. After removal of the solvent under reduced pressure, 5 ml. of chloroform was added to the residue and the resulting mixture was filtered to remove cyanoacetamide (0.31 g., 74%, m.p. 110–115°). From the filtrate, benzyl bromide [0.68 g., 80%, b.p. 48–56° (2 mm.)] and diethyl hydrogen phosphate [0.63 g., 81%, b.p. 116° (0.01 mm.)] were obtained by fractionation. Diethyl hydrogen phosphate was identified by paper chromatography, R_f 0.71 (solvent system, *n*-propyl alcohol–concentrated ammonium hydroxide–water, 6:3:1).

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[10] A. D. F. Toy, *J. Am. Chem. Soc.*, **70**, 3882 (1948).