BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 39 2721—2723 (1966)

A New Method for the Phosphorylation of Alcohols by Means of Bromine and Dibenzylhydrogen Phosphite

By Teruaki MUKAIYAMA, Hajime KOUDA and Kyoko KODERA

Laboratory of Organic Chemistry, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo

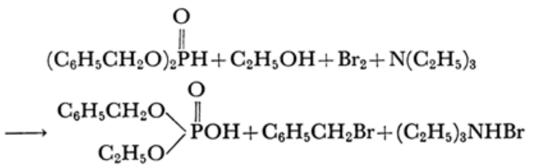
(Received March 12, 1966)

Various alkyldihydrogen phosphates were obtained in good yields by reacting alcohols, dibenzylhydrogen phosphite, and bromine in the presence of triethylamine, followed by catalytic hydrogenation. When benzyl alcohol and diethyl phosphite were used in the above reaction, only the oxidation of the latter took place, giving diethylhydrogen phosphate in an excellent yield. These results suggest that the above phosphorylation of alcohol proceeds through a quaternary phosphonium salt, i. e., dibenzyloxyalkyloxyhydroxy phosphonium bromide, which is then converted into an alkylbenzylhydrogen phosphate. The effect of tertiary amines on this type of phosphorylation was also examined.

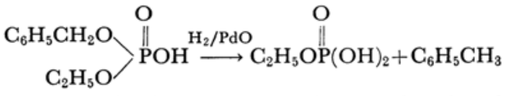
The reactions of various phosphorous compounds with monobromocyanoacetamide and benzylalcohol, and the phosphorylation of alcohols and phenols by means of dibenzyl phosphite (or phosphorous acid) and monobromocyanoacetamide, have been studied in detail.[1–5]

This paper will describe an improved synthesis of monoesters of phosphoric acid, a method in which bromine in the presence of triethylamine is employed as an oxidizing reagent in place of the monobromocyanoacetamide mentioned in the above experiments. In this phosphorylation, it was found that bromine was a more reactive and effective oxidizing reagent than monobromocyanoacetamide, which was prepared from bromine and cyanoacetamide. When bromine was added to a mixture of ethanol, dibenzyl phosphite, and triethylamine in benzene under ice cooling, triethylamine hydrobromide was immediately separated. After the triethylamine hydrobromide (98%) and benzene had been removed and the benzylbromide had been fractionated (97%), the residue, benzylethylhydrogen phosphate, was hydrogenated without further purification.

Thus ethyldihydrogen phosphate was obtained in a 81% yield as its anilinium salt.



$$(C_6H_5CH_2O)_2\overset{O}{\overset{\|}{P}}H + C_2H_5OH + Br_2 + N(C_2H_5)_3 \longrightarrow \begin{matrix}C_6H_5CH_2O\\ C_2H_5O\end{matrix}\!>\overset{O}{\overset{\|}{P}}OH + C_6H_5CH_2Br + (C_2H_5)_3NHBr$$



$$\begin{matrix}C_6H_5CH_2O\\ C_2H_5O\end{matrix}\!>\overset{O}{\overset{\|}{P}}OH \xrightarrow{H_2/PdO} C_2H_5O\overset{O}{\overset{\|}{P}}(OH)_2 + C_6H_5CH_3$$

In a similar fashion, *n*-propyl, isopropyl, *n*-butyl or bornyldihydrogen phosphate was obtained as the anilinium salt in a 98, 78, 82, or 30% yield respectively. Bromine is more reactive than monobromocyanoacetamide, and the phosphorylation of alcohols takes place rapidly at a lower temperature, resulting in the formation of the desired phosphates in good yields without the use of excess alcohols.

It has been reported that the phosphorylation of phenol by the use of dibenzylphosphate and monobromocyanoacetamide gave a 79% yield of phenyldihydrogen phosphate as the anilinium salt. In the present experiment, however, the phosphorylation of phenol failed, and only bromophenols were obtained. Apparently, the isolation of phosphorous acid (as anilinium salt) in a 72% yield, after catalytic hydrogenation, indicates that dibenzyl phosphite did not participate in this reaction and that the preferential bromination of phenol occurred.

There are two possible pathways for the formation of monoalkyl phosphate by this procedure: (A) Initially a quaternary phosphonium salt (I) is formod. The intermediate (I) is then converted into another quaternary phosphonium salt (II), which is in turn decomposed to alkylbenzyl phosphate and benzyl bromide. (B) Initially the $(C_6H_5CH_2O)_2(HO)PBr_2$ compound is formed. This compound is then converted to benzylbromophosphonate, $(C_6H_5CH_2O)(HO)\overset{O}{\overset{\|}{P}}Br$, by the elimination of benzyl bromide. The bromophosphonate thus formed reacts with an alcohol in the presence of triethylamine to yield the corresponding alkylbenzyl phosphate.

---

1) T. Hata and T. Mukaiyama, This Bulletin, **35**, 1106 (1962).

2) T. Hata and T. Mukaiyama, ibid., **37**, 103 (1964).

3) T. Mukaiyama, O. Mitsunobu and T. Obata, *J. Org. Chem.*, **30**, 101 (1965).

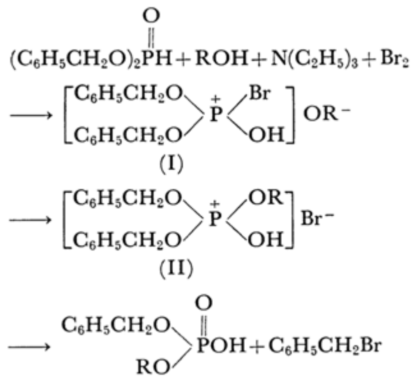
4) O. Mitsunobu, T. Obata and T. Mukaiyama, ibid., **30**, 1071 (1965).

5) T. Obata and T. Mukaiyama, This Bulletin, in press.

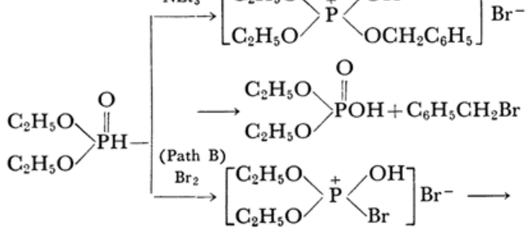
TABLE I. THE PHOSPHORYLATION OF ALCOHOLS BY MEANS OF DIBENZYL PHOSPHITE AND BROMINE IN THE PRESENCE OF TRIETHYLAMINE

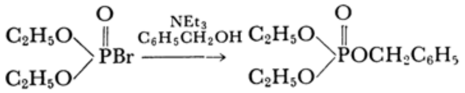
	Product									
	Phosphate (anilinium salt)			Analyses, %						
Alcohol	$RO\overset{O}{\overset{\|}{P}}\langle{}^{OH}_{O^-}$ R	Yield %	M. p. °C	Calcd.			Found			R_f [1]
				C	H	N	C	H	N	
C_2H_5OH	C_2H_5	81	157—158	43.83	6.39	6.56	42.62	7.32	6.48	0.37
n-C_3H_7OH	n-C_3H_7	98	152—153	46.35	6.87	6.01	45.58	7.05	6.01	0.43
i-C_3H_7OH	i-C_3H_7	78	165—166	46.35	6.87	6.01	46.07	6.78	6.05	0.41
n-C_4H_9OH	n-C_4H_9	82	140—142	48.44	7.48	5.69	48.58	7.29	5.67	0.53
$C_{10}H_{17}OH$ (borneol)	$C_{10}H_{17}$	30	195—196	58.89	7.62	4.29	58.91	7.93	4.39	0.63

10 solvent system ; n-propanol - concentrated ammonium hydroxide - water, 6 : 3 : 1.


(I)
(II)

In order to differentiate the two alternatives, A and B, the reaction was tried using diethyl phosphite, benzyl alcohol, and bromine in the presence of triethylamine. In this case, since the ethyl group is not so easily eliminated as the benzyl group or hydrogen, it can be expected that diethyl phosphate will be formed according to the mechanism A, while diethylbenzyl phosphate will be formed according to the mechanism B. When the reaction was carried out at 0°C diethyl phosphate (68%), benzyl bromide (86%), and triethylamine hydrobromide (90%) were obtained. Therefore, it can be concluded that the key intermediate of the above-mentioned phosphorylation is the quaternary phosphonium salt (II), rather than benzylbromophosphonate.





In order to examine the effect of tertiary amines on this type of phosphorylation, the reaction of diethyl phosphite, bromine, and benzyl alcohol in the presence of triethylenediamine, N-methylmorpholine, pyridine, or hexamethylenetetramine was attempted under identical conditions (see Table II). The results show that the yield of diethyl phosphate is influenced by the basicity of amine, increasing with an increase in the basicity.

Concerning the phosphorylation of alcohol with phosphorous compounds and halogen, it has been reported by Kirby[6] that 4-hydroxy but-2-enyl phosphate was obtained in a 86.5% yield by treating butene-1, 4-diol with iodine, and phosphorous acid in the presence of triethylamine. In the present experiment, however, it was found that the reaction of iodine, dibenzyl phosphite,

TABLE II. THE REACTION OF DIETHYL PHOSPHITE WITH BROMINE AND BENZYL ALCOHOL IN THE PRESENCE OF VARIOUS TERTIARY AMINES

Tertiary amines	Diethyl phosphite yield, %	Benzyl bromide yield, %	Tertiary amines hydrobromide yield, %
Triethylamine	68	86	90
Triethylenediamine	60	74	98[1]
N-Methylmorpholine	36	74	66
Pyridine	50	65	34
Hexamethylene-tetramine	68	49	—[2]

1) The yield of the salt is shown as triethylenediamine dihydrobromide.
2) Pure hexamethylenetetramine monohydrobromide could not be isolated because of the contamination of N-benzylhexamethylenetetraminium bromide.

---

[6] A. J. Kirby, *Chem. & Ind. (London)*, **1963**, 1877.

and alcohols in the presence of triethylamine resulted in the formation of a large quantity of unidentified red tarry products.

Experimental

Reagents.—The solvents, alcohols, and amines were purified and dried by ordinary procedures. Diethyl phosphite[7] and dibenzyl phosphite[8] were prepared according to the procedures described in the literature.

The Phosphorylation of Alcohols by Means of Bromine and Dibenzyl Phosphite in the Presence of Triethylamine.—A solution of bromine (1.60 g.; 0.01 mole) in 10 ml. of benzene was vigorously stirred, drop by drop, into a solution of dibenzyl phosphite (2.70 g.; 0.01 mole), ethanol (0.50 g.; 0.01 mole), and triethylamine (1.01 g.; 0.01 mole) in 10 ml. of benzene under ice cooling. After stirring had been continued for 1 hr., the solution was heated at 40—50°C for an additional hour. The solution was then allowed to stand overnight and filtered to remove triethylamine hydrobromide (1.77 g.; 98%; m. p. 246—247°C). From the filtrate, benzene and benzyl bromide (1.68 g.; 97%; b. p. 75—82°C/23 mmHg) were fractionated, and the residue was dissolved in 50 ml. of 99% ethanol. The solution was then hydrogenated over palladium oxide (100 mg.) at room temperature under atomospheric pressure. After the absorption of quantitative amount of hydrogen, the catalyst was removed by filtration and the solution was concentrated to about 10 ml. under reduced pressure. Aniline (1.9 g.) was then added, giving anilinium ethyldihydrogen phosphate (1.76 g.; 81%; m. p. 155—157°C). The anilinium salt was purified by chromatography (cellose-*n*-butanol - water) and recrystallized from acetonitrile-water, m. p. 157—158°C. A mixed-melting-point determination with an authentic sample was not depressed.

Found: C, 42.23; H, 7.83; N, 6.48. Calcd. for $C_8H_{14}NO_4P$: C, 43.84; H, 6.39; N, 6.56%.

Ethyl phosphate itself was also identified with an authentic specimen by paper chromatography (R_f 0.37) *n*-propyl, isopropyl, *n*-butyl, and bornyldihydrogen phosphates were obtained as their anilinium salts by the phosphorylation of *n*-propanol, isopropanol, *n*-butanol and borneol respectively (see Table I).

The Reaction of Diethyl Phosphite with Benzyl-Alcohol and Bromine in the Presence of Triethylamine.—A solution of bromine (1.60 g.; 0.01 mole) in 10 ml. of benzene was vigorously stirred, drop by drop, into a solution of diethyl phosphite (1.38 g.; 0.01 mole), benzyl alcohol (1.10 g.; 0.01 mole), and triethylamine (1.01 g.; 0.01 mole) in 10 ml. of benzene under ice cooling. The mixture was then allowed to stand overnight and filtered to remove triethylamine hydrobromide (1.63 g.; 90%). From the filtrate, benzyl bromide (1.48 g.; 86%; b. p. 75—85°C/23 mmHg) and diethyl phosphate (1.05 g.; 68%; b. p. 114—117°C/0.02 mmHg) were obtained by fractionation. Diethyl phosphate was identified with an authentic sample by paper chromatography (R_f 0.70; solvent system, *n*-propanol - concentrated ammonium hydroxide - water 6 : 3 : 1).

The Reaction of Diethyl Phosphite with Bromine and Benzyl Alcohol in the Presence of Various Tertiary Amines.—A solution of bromine (1.60 g., 0.01 mole) in 10 ml. of benzene was vigorously stirred, drop by drop, into a solution of diethyl phosphite (1.38 g.; 0.01 mole), benzyl alcohol (1.10 g.; 0.01 mole) and triethylenediamine (0.60 g.; 0.005 mole) under ice cooling. The mixture was then allowed to stand overnight and filtered to remove triethylenediamine dihydrobromide (1.24 g.; 98% d. p. 347—348°C). From the filtrate, benzyl bromide (1.29 g.; 74% b. p. 70—84°C/6 mmHg) and diethyl phosphate (0.92 g.; 60%; b. p. 118—121°C/0.03 mmHg) were obtained by fractionation.

Similarly, diethyl phosphate was obtained in yields ranging from 68% to 36% by treating alcohol with diethyl phosphite and benzyl alcohol and bromine in the presence of various amines, such as pyridine, *N*-methylmorpholine and hexamethylenetetramine. The results are listed in Table II.

The Reaction of Phenols and Dibenzyl Phosphite with Bromine in the Presence of Triethylamine.—A solution of bromine (1.60 g.; 0.01 mole) in 10ml. of benzene was vigorously stirred, drop by drop, into a solution of dibenzyl phosphite (2.70 g.; 0.01 mole), phenol (0.95 g.; 0.01 mole) and triethylamine (1.01 g.; 0.01 mole) in 10 ml. of benzene under ice cooling. The mixture was allowed to stand overnight and then filtered to remove triethylamine hydrobromide (1.73 g.; 95%). From the filtrate, *o*-bromophenol (34%; it was identified by gas chromatography) was removed by distillation under reduced pressure. The residue was dissolved in 30 ml. of 99% alcohol and hydrogenated over palladium oxide (100 mg.) at room temperature under atmospheric pressure. After the 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% alcohol, and aniline (1.9 g.) was added to the solution. The anilinium salt of phosphorous acid (1.25 g.; 71.5%; m. p. 170—173°C) was obtained; recrystallization from acetonitrile-water raised the melting point to 173—175°C. It was identified by paper chromatography (R_f 0.31; an authentic sample, R_f 0.30; solvent system, *n*-propanol - concentrated ammonium hydroxide - water, 6 : 3 : 1).

Found: C, 41.21; H, 6.26; N, 8.32. Calcd. for $C_6H_{10}NO_3P$: C, 41.14; H, 5.71; N, 8.32%.

Similarly, phosphorous acid (m. p. 172—173°C) resulted as anilinium salt in the case of the reaction of *p*-nitrophenol, and no depression was observed in a mixed-melting-point determination with an authentic sample.

The authors wish to express their hearty thanks to Dr. Oyo Mitsunobu and Mr. Teisuke Obata for their kind help during the course of this experiment, and to Miss Keiko Nakamura for her microanalysis.

---

[7] H. McCombie, B. C. Saunders and G. J. Stacey, *J. Chem. Soc.*, **1945**, 380.

[8] F. R. Atherton, H. T. Openshaw and A. R. Todd, ibid., **1945**, 382.