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The Phosphorylation of Alcohols by the Reaction of Monobromocyanoacetamide with Monobenzyl Phosphite or Inorganic Phosphorous Acid

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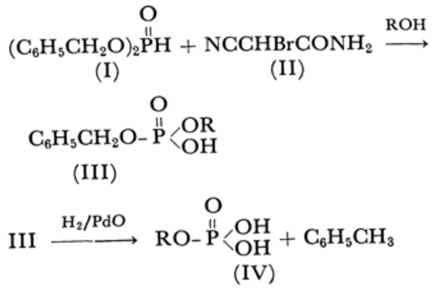
This paper describes a successful method of preparing monoalkyl phosphates by the reaction of monobromocyanoacetamide with monobenzyl phosphite or inorganic phosphorous acid in the presence of alcohols. When equimolar amounts of monobromocyanoacetamide and either of the above-mentioned phosphorus compounds in alcohols were heated at about 100°C, the corresponding monoalkyl dihydrogen phosphates were obtained as anilinium salts in fairly good yields, together with cyanoacetamide and benzyl bromide or hydrogen bromide. The reaction can be interpreted in terms of a mechanism in which the initially-formed enol-phosphonium salts of cyanoacetamide are easily transformed to the second phosphonium salts by the action of the alcohols present from the salts, alkyl dihydrogen phosphates are produced.

A previous paper¹⁾ presented a successful method of oxidizing various triesters of phosphorous acid or phosphines to triesters of phosphoric acid or phosphine oxides by means of monobromocyanoacetamide, along with either benzyl or allyl alcohol. In a similar way, dialkyl phosphates were prepared from the corresponding dialkyl phosphites.²⁾ The reaction was then further extended to the synthesis of monoalkyl dihydrogen phosphates (IV) by the oxidation of dibenzyl phosphite (I) with monobromocyanoacetamide (II) in alcohols and by subsequent catalytic debenzylation.²⁾



$$\underset{\text{(I)}}{(C_6H_5CH_2O)_2\overset{O}{\overset{\|}{P}}H} + \underset{\text{(II)}}{NCCHBrCONH_2} \xrightarrow{ROH}$$

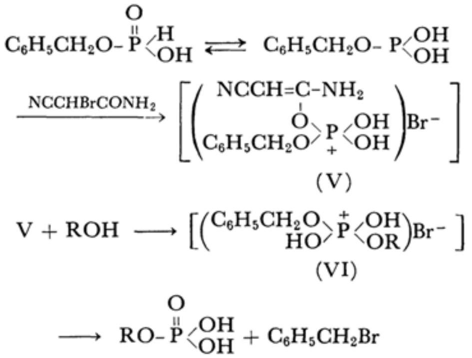
$$\underset{\text{(III)}}{C_6H_5CH_2O\text{-}\overset{O}{\overset{\|}{P}}\begin{smallmatrix}OR\\OH\end{smallmatrix}}$$

$$\text{III} \xrightarrow{H_2/PdO} \underset{\text{(IV)}}{RO\text{-}\overset{O}{\overset{\|}{P}}\begin{smallmatrix}OH\\OH\end{smallmatrix}} + C_6H_5CH_3 \qquad (1)$$

In the present paper, a similar type of the phosphorylation of alcohols was attempted, employing monobenzyl phosphite or inorganic phosphorous acid and monobromocyanoacetamide.

First the reaction of monobenzyl phosphite with monobromocyanoacetamide in the presence of an equimolar amount of benzyl alcohol was attempted; a 27% yield of monobenzyl dihydrogen phosphate was thus obtained.

The result can be explained in terms of the following mechanism involving a quaternary phosphonium salt (VI), which is similar to that shown in the preceding paper²⁾:



$$C_6H_5CH_2O\text{-}\overset{O}{\overset{\|}{P}}\begin{smallmatrix}H\\OH\end{smallmatrix} \rightleftarrows C_6H_5CH_2O\text{-}P\begin{smallmatrix}OH\\OH\end{smallmatrix}$$

$$\xrightarrow{NCCHBrCONH_2} \left[\left(\begin{matrix}NCCH{=}\underset{|}{C}\text{-}NH_2\\ \quad O\\ C_6H_5CH_2O\end{matrix}\begin{matrix}\searrow\\ \nearrow\end{matrix}\overset{}{\underset{+}{P}}\begin{smallmatrix}OH\\OH\end{smallmatrix}\right)Br^-\right]$$

$$\text{(V)}$$

$$V + ROH \longrightarrow \left[\left(\begin{smallmatrix}C_6H_5CH_2O\\HO\end{smallmatrix}\!\!>\overset{+}{P}\begin{smallmatrix}OH\\OR\end{smallmatrix}\right)Br^-\right]$$

$$\text{(VI)}$$

$$\longrightarrow RO\text{-}\overset{O}{\overset{\|}{P}}\begin{smallmatrix}OH\\OH\end{smallmatrix} + C_6H_5CH_2Br \qquad (2)$$

In order to elucidate the proposed mechanism and examine the possibility of its application to the phosphorylation of alcohols, the reaction of ethanol with monobenzyl phosphite and monobromocyanoacetamide was attempted. In this case, it was expected that monoethyl dihydrogen phosphate would primarily be formed, since benzyl bromide, rather than the other alkyl or hydrogen bromide, is preferentially eliminated from the proposed quaternary phosphonium salt (VI, R=C_2H_5); thus, the phosphorylation of alcohols would be successful, and alkyl dihydrogen phosphates could be synthesized by a one-step procedure.

Indeed, when a mixture of monobenzyl phosphite and monobromocyanoacetamide in dry ethanol was refluxed for two hours, monoethyl phosphate and benzyl bromide were obtained in 46% and 63% yields respectively.

Similarly, *n*-propyl, isopropyl and *n*-butyl dihydrogen phosphates were obtained as anilinium salts when the phosphite and monobromocyanoacetamide were treated in the corresponding alcohols.

However, this procedure is not applicable to the phosphorylation of long-chain solid alcohols or those available in only small amounts, because the

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

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

reaction should be carried out in a large excess of alcohol (usually in alcohol solvents); probably, the initially-formed quaternary phosphonium salt (V) is very unstable and the spontaneous decomposition takes place before it reacts with alcohols, giving several kinds of phosphorus compounds, some of which are not well characterized by paper chromatography.

Next, this type of reaction was further extended to a selective phosphorylation of alcohols, starting from inorganic phosphorous acid.

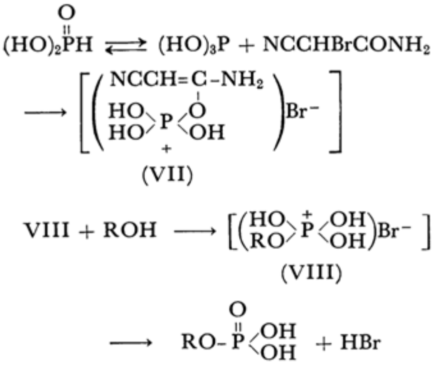
The reaction proceeds through the formation of quaternary phosphonium salt (VII), which is similar in structure to V. Therefore, the subsequent elimination of hydrogen bromide from VIII will result in the formation of alkyl dihydrogen phosphates.

When an equimolar amount of phosphorous acid and monobromocyanoacetamide in ethanol were refluxed for two hours, monoethyl dihydrogen phosphate was obtained in a 78% yield as chromatographically-pure anilinium salt.

Similarly, methyl, *n*-propyl, and *n*-butyl dihydrogen phosphates were obtained from the corresponding alcohols as the anilinium salts in 87, 82 and 64% yields respectively (see Table II).

As is the case with dialkyl or monoalkyl phosphite, inorganic phosphorous acid is expected to react with monobromocyanoacetamide in its tautomeric trivalent structure, giving enol-phos phonium salt of cyanoacetamide (VII), which is in turn transformed to the second quaternary phosphonium salt (VIII) by the action of the alcohols present.

This assumption was confirmed by the following experiments. Phosphoric acid was exclusively produced when water or benzyl alcohol was treated with monobromocyanoacetamide and phosphorous acid; in either case, hydrogen bromide or benzyl bromide was also detected.



$$(HO)_2\overset{O}{\overset{\|}{P}}H \rightleftarrows (HO)_3P + NCCHBrCONH_2$$

$$\longrightarrow \left[\begin{pmatrix} NCCH{=}\underset{|}{C}{-}NH_2 \\ {}^{HO}_{HO}{>}\underset{+}{P}{<}^{O}_{OH} \end{pmatrix} Br^- \right] \quad \text{(VII)}$$

$$\text{VIII} + ROH \longrightarrow \left[\left({}^{HO}_{RO}{>}\overset{+}{P}{<}^{OH}_{OH}\right)Br^-\right] \quad \text{(VIII)}$$

$$\longrightarrow RO{-}\overset{O}{\overset{\|}{P}}{<}^{OH}_{OH} + HBr \qquad (3)$$

(R=H or alkyl)

Monoalkyl phosphates could not be isolated as pure anilinium salts when an equimolar amount of alcohol was to be phosphorylated by this method; at the same time, several uncharacterized phosphorus compounds were also produced, thus making the purification much more difficult.

Experimental

Materials.—Monobromocyanoacetamide[3] and mono benzyl phosphite[4] were prepared by the method given in the literature. Inorganic phosphorous acid was obtained from a commercial source and dried over phosphorus pentoxide under a high vacuum. The alcohols and solvents used were purified by ordinary procedures. Phosphorus compounds were identified by paper chromatography; solvent system: *n*-propyl alcohol : conc. NH_4OH : H_2O=6 : 3 : 1.

The Oxidation of Monobenzyl Phosphite by Means of Monobromocyanoacetamide and Benzyl Alcohol.—A solution of equimolar amounts of monobenzyl phosphite (1.54 g., 0.01 mol.), monobromocyanoacetamide (1.63 g., 0.01 mol.) and benzyl alcohol (1.08 g., 0.01 mol.) in 20 ml. of dry peroxide-free tetrahydrofuran was refluxed for 2 hr. under a nitrogen atmosphere. After the solvent had then been removed under reduced pressure, 10 ml. of dry ether was added to separate the cyanoacetamide (0.57 g., 68%). The filtrate was concentrated and distilled to give benzyl bromide (b. p. 32—36°C/0.15 mmHg; 0.93 g., 54%). The oily residue was dissolved in 99% ethanol (10 ml.), and aniline (4 g., 0.04 mol.) was added. Precipitated anilinium salt of monobenzyl phosphate was filtered, washed twice with 99% ethanol (2 ml.) and dried over phosphorus pentoxide in a desiccator (0.89 g., 24%). Paper chromatography showed one spot (R_f: 0.57); this was identical with that of an authentic specimen. One recrystallization from 95% ethanol gave an analytical sample, m. p. 149—152°C.

Found: N, 7.56, Calcd. for $C_{19}H_{18}N_2O_4P$: N, 7.48%.

The Phosphorylation of Ethanol by the Reaction of Monobenzyl Phosphite and Monobromocyanoacetamide.—A solution of equimolar amounts of monobenzyl phosphite (1.54 g., 0.01 mol.) and monobromocyanoacetamide (1.63 g., 0.01 mol.) in absolute ethanol (10 ml.) was refluxed for an hour under a nitrogen atmosphere. The reaction mixture was concentrated and 10 ml. of chloroform was added to separate the cyanoacetamide (0.78 g., 92%). From the filtrate, benzyl bromide (b. p. 46—47°C/2 mmHg, 1.08 g., 63%) was obtained by fractionation. The residue was dissolved in 99% ethanol (10 ml.), and aniline (1.7 g.) was added. After the mixture had been cooled to −20°C, anilinium salt of monoethyl phosphate (m. p. 132—149°C, 1.02 g., 46%) was filtered. One recrystallization from acetonitrile-water gave an analytically-pure sample (m. p. 160—164°C; lit.[2] 164—165°C).

Found: N, 6.30, Calcd. for $C_8H_{14}NO_4P$: N, 6.39%.

The R_f-value shown by paper chromatography was identical with that of an authentic specimen.[2]

Similarly, the other alkyl phosphates were prepared and characterized by comparison with authentic samples[2] (see Table I).

The Phosphorylation of Ethanol by the Reaction of Phosphorous Acid and Monobromocyanoacetamide.—Equimolar amounts of phosphorous acid (0.82 g., 0.01 mol.) and monobromocyanoacetamide (1.63 g., 0.01 mol.) were dissolved in absolute ethanol

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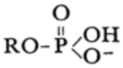
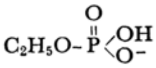
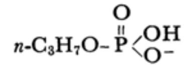
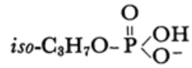
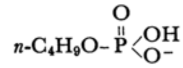
[3] T. Hata and T. Mukaiyama, This Bulletin, **35**, 1106(1962).

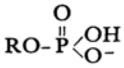
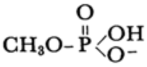
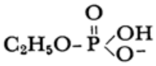
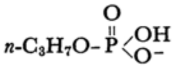
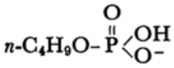
[4] J. Baddiley, V. M. Clark, J. J. Michalshi and A. R. Todd, *J. Chem. Soc.*, **1949**, 815.

TABLE I. PHOSPHORYLATION OF ALCOHOLS BY MEANS OF MONOBENZYL PHOSPHITE AND MONOBROMOCYANOACETAMIDE

Alcohol	Product					R_f*
	Phosphate (anilinium salt)	Yield %	M. p. °C	Anal. (N, %)		
				Found	Calcd.	
ROH	 $RO-\overset{O}{\overset{\|}{P}}<^{OH}_{O^-}$					
C_2H_5OH	 $C_2H_5O-\overset{O}{\overset{\|}{P}}<^{OH}_{O^-}$	46	160—165	6.30	6.39	0.37
n-C_3H_7OH	 $n\text{-}C_3H_7O-\overset{O}{\overset{\|}{P}}<^{OH}_{O^-}$	49	142—145	6.13	6.01	0.44
iso-C_3H_7OH	 $iso\text{-}C_3H_7O-\overset{O}{\overset{\|}{P}}<^{OH}_{O^-}$	68	158—162	6.18	6.01	0.42
n-C_4H_9OH	 $n\text{-}C_4H_9O-\overset{O}{\overset{\|}{P}}<^{OH}_{O^-}$	50	144—147	5.74	5.67	0.50

* Solvent system : n-propyl alcohol : conc. NH_4OH : $H_2O=6:3:1$.

TABLE II. PHOSPHORYLATION OF ALCOHOLS BY MEANS OF INORGANIC PHOSPHOROUS ACID AND MONOBROMOCYANOACETAMIDE

Alcohol	Product				
	Phosphate (anilinium salt)	Yield %	M. p. °C	Anal. (N, %)	
				Found	Calcd.
ROH	 $RO-\overset{O}{\overset{\|}{P}}<^{OH}_{O^-}$				
CH_3OH	 $CH_3O-\overset{O}{\overset{\|}{P}}<^{OH}_{O^-}$	87	163—165	6.69	6.80
C_2H_5OH	 $C_2H_5O-\overset{O}{\overset{\|}{P}}<^{OH}_{O^-}$	82	162—164	6.37	6.39
n-C_3H_7OH	 $n\text{-}C_3H_7O-\overset{O}{\overset{\|}{P}}<^{OH}_{O^-}$	76	148—150	6.23	6.02
n-C_4H_9OH	 $n\text{-}C_4H_9O-\overset{O}{\overset{\|}{P}}<^{OH}_{O^-}$	64*	145—152	6.03	5.67

* A trace of phosphorous acid is contaminated in the product.

ml.), and then the mixture was refluxed for 2 hr. under a nitrogen atmosphere. After the excess ethanol had been evaporated, cyanoacetamide (0.79 g., 92%) was filtered out. The filtrate was dissolved in 99% ethanol (5 ml.) and then aniline (2 ml.) was added. After the mixture had stood for 30 min., monoethyl dihydrogen phosphate (1.67 g., 82%) was filtered out. Recrystallization from 15 ml. of 95% ethanol gave an analytical sample (m. p. 162—164°C; 1.15 g.; lit.[2]) 164—165°C).

Found: N, 6.37. Calcd. for $C_8H_{14}NO_4P$: N, 6.39%. Paper chromatography showed one spot, R_f: 0.37 (lit.[2]) 0.36—0.37).

The other alkyl dihydrogen phosphates were prepared by a similar method. The yields and the physical constants are summarized in Table II.

The Reaction of Phosphorous Acid with Monobromocyanoacetamide in the Presence of Water or Benzyl Alcohol.—A solution of equimolar amounts of phosphorous acid (0.41 g.) and monobromocyanoacetamide (0.82 g.) in acetonitrile (15 ml.) and water (2 ml.) was refluxed for an hour. The paper chromatography of the reaction mixture showed only one yellow spot of inorganic phosphoric acid (R_f: 0.17—0.18); the strong blue spot of inorganic phosphorous acid (R_f: 0.28) had completely disappeared. This shows that the phosphorylation of water or the oxidation of phosphorous acid has taken place. The same result was also observed when benzyl alcohol was employed in place of water in the above reaction. In this case, a good deal of benzyl bromide was formed; it was characterized by distillation and by its lachrymatory odor.

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