A Convenient General Procedure for the Conversion of Alcohols into their Monophosphate Esters

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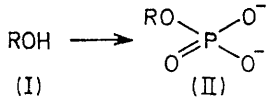
o-Phenylene phosphorochloridate (IV), readily prepared from catechol in good yield, reacts rapidly and quantitatively with stoicheiometric amounts of alcohols (including tertiary alcohols) in the presence of a suitable base (triethylamine or 2,6-lutidine) and in a suitable solvent (dioxan, tetrahydrofuran, or benzene). Alkyl *o*-hydroxyphenyl phosphate salts (IX) were thus obtained in virtually quantitative yields, and sometimes as pure crystalline compounds.

The phosphodiesters (IX) were converted into the corresponding monoalkyl phosphates (II) by treatment with (a) bromine in neutral aqueous buffer solution, (b) periodic acid in aqueous solution, or (c) lead tetra-acetate in dioxan solution, followed by alkaline hydrolysis. The products were easily isolated as pure barium salts. In this way, the barium salts of t-butyl, neopentyl, 2,2,2-trichloroethyl, 2,2,2-tribromoethyl, 2-cyanoethyl, and allyl phosphates have all been prepared in good overall yields. The pure barium salts of 1,1- and 3,3-dimethylallyl phosphates have also been prepared, albeit in lower yields

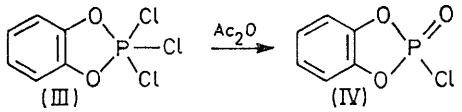
The importance of phosphate esters in biological reactions has led to the development of numerous chemical methods for the conversion of an alcohol (I) into the



(I) (II)

corresponding monophosphate ester (II). However, none of the phosphorylation procedures described in the literature [1,2] stands out as being the most generally useful. A monofunctional reagent is required which is (a) easy to prepare on a large scale, (b) stable for long periods, (c) very reactive, and (d) such that the protected intermediates could be converted into the desired products (II) under very mild conditions. We shall attempt to show here that *o*-phenylene phosphorochloridate (IV) meets all these criteria.†

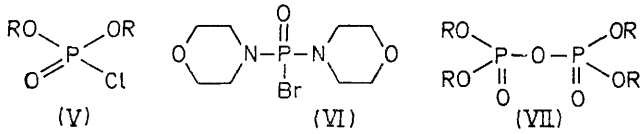
o-Phenylene phosphorochloridate (IV) may be obtained in 87% yield by heating 2,2,2-trichloro-1,3,2-benzodioxaphosph(v)ole [4] (III) with a slight excess of



(III) (IV)

acetic anhydride. The by-product (acetyl chloride [5]) is distilled off, and then the phosphorochloridate (IV) is distilled under reduced pressure. This procedure is superior to that of Anschütz and Broeker.[4] 2,2,2-Trichloro-1,3,2-benzodioxaphosph(v)ole (III) may itself be prepared [4,5] in *ca.* 75% yield by treatment of catechol with a slight excess of phosphorus pentachloride in benzene solution.

o-Phenylene phosphorochloridate (IV) is easy to prepare on a molar scale (see Experimental section) and is a stable crystalline compound (m.p. 59—61°) which, although sensitive to moisture, may be kept indefinitely in a sealed vessel. Thus both criteria (a) and (b) (see before) are satisfied. Of the other widely used monofunctional phosphorylating agents, perhaps only diphenyl phosphorochloridate [6] (V; R = Ph) meets both



(V) (VI) (VII)

these criteria. Dibenzyl phosphorochloridate [7] (V; R = $PhCH_2$) and dimorpholino phosphorobromidate [8] (VI) satisfy criterion (a) but not criterion (b), whereas the opposite is true for bis-*p*-nitrobenzyl phosphorochloridate [9] (V; R = *p*-nitrobenzyl). Tetrakis-*p*-nitrophenyl pyrophosphate [10] (VII; R = *p*-nitrophenyl) is not easy to prepare on a large scale and has not been isolated pure. Bis-2-cyanoethyl phosphorochloridate (V; R = $NC{\cdot}CH_2{\cdot}CH_2$) which has been described only briefly,[11] appears to be a useful phosphorylating agent which merits further investigation.

o-Phenylene phosphorochloridate (IV) certainly fulfils criterion (c); it must be one of the most reactive phos-

† For a preliminary account of some of this work, see ref. 3.

[1] For reviews of this subject see ref. 2 (pp. 13—43) and (*a*) K. Sasse in Houben-Weyl's 'Methoden der Organischen Chemie,' vol. 12/2, Georg Thieme Verlag, Stuttgart, 1964, pp. 143—210; (*b*) D. M. Brown in 'Organic Chemistry: Methods and Results,' vol. 3, Interscience, New York, 1963, p. 75 *et seq.*

[2] H. G. Khorana, 'Some Recent Developments in the Chemistry of Phosphate Esters of Biological Interest,' Wiley, New York, 1961, p. 14.

[3] T. A. Khwaja and C. B. Reese, *J. Amer. Chem. Soc.*, 1966, **88**, 3446.

[4] L. Anschütz and W. Broeker, *Annalen*, 1927, **454**, 109.

[5] H. Gross and J. Gloede, *Chem. Ber.*, 1963, **96**, 1387.

[6] P. Brigl and H. Müller, *Chem. Ber.*, 1939, **72**, 2121; K. Zeile and H. Meyer, *Z. physiol. Chem.*, 1938, **256**, 131.

[7] L. Zervas, *Naturwiss.*, 1939, **27**, 317; F. R. Atherton, H. T. Openshaw, and A. R. Todd, *J. Chem. Soc.*, 1945, 383.

[8] H. A. C. Montgomery and J. H. Turnbull, *J. Chem. Soc.*, 1958, 1963.

[9] L. Zervas and I. Dilaris, *J. Amer. Chem. Soc.*, 1955, **77**, 5354.

[10] J. G. Moffatt and H. G. Khorana, *J. Amer. Chem. Soc.*, 1957, **79**, 3741.

[11] H. Witzel, H. Mirbach, and K. Dimroth, *Angew. Chem.*, 1960, **72**, 751.

phorylating agents known. In the presence of triethylamine, in tetrahydrofuran solution at 20°, it reacts rapidly with a stoicheiometric amount of t-butyl alcohol [3] (Table 1, experiment 1). The reaction is quantitative and is complete within 15 min. It is difficult to make direct comparisons between (IV) and other phosphorylating agents, but the reaction between the related diphenyl phosphorochloridate (V; R = Ph) and tertiary hydroxy-functions has been reported [12] to proceed relatively slowly, even at elevated temperatures. Reaction between (IV) and stoicheiometric amounts of other hindered alcohols such as neopentyl alcohol and 2,2,2-tribromoethanol (experiments 2 and 4, respectively) at 20° is also rapid and quantitative, and the tertiary allylic alcohol, 2-methylbut-3-en-2-ol (experiment 8) undergoes rapid phosphorylation in benzene solution. The yields of products are usually quantitative with respect to both the alcohol and the phosphorylating agent. Thus the method is particularly suited to the phosphorylation of isotopically labelled alcohols.

It is not necessary or desirable to isolate the intermediate phosphotriester (VIII). If the phosphorylation products are treated with at least one molecular equiv. of base * and then with an excess of water, the phosphotriesters (VIII) are quantitatively converted into the corresponding *o*-hydroxyphenyl phosphate esters (IX) (Scheme 1). The latter are stable and may often be obtained crystalline and in high yields (Table 1). In a preliminary study, the readily available methyl *o*-phenylene phosphate [4] (VIII; R = Me) was converted quantitatively into the barium salt of *o*-hydroxyphenyl methyl phosphate (IX; R = Me) when treated with an equivalent amount of aqueous barium hydroxide at 20°. The methyl ester (VIII; R = Me) was also rapidly hydrolysed by aqueous sodium hydrogen carbonate at 20°. However, the product (IX; R = Me) was slowly converted into *o*-hydroxyphenyl phosphate [13] (IX; (R = H) under the latter conditions When methyl *o*-phenylene phosphate was heated with water on a steam-bath, *o*-hydroxyphenyl phosphate was obtained, and could be isolated as the free acid in high yield.

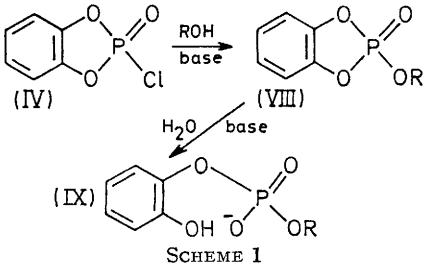
The base used in the phosphorylation is often triethylamine (Table 1). However, if the intermediate phosphotriester (VIII) is especially susceptible to nucleophilic attack (experiments 6 and 7), it is advisable to use the more hindered 2,6-lutidine. For instance methyl *o*-phenylene phosphate (VIII; R = Me) reacted rapidly with pyridine in dioxan solution to give the *N*-methylpyridinium salt of *o*-phenylene phosphate (X).† Triethylamine is also an unsuitable base where the intermediate phosphotriester (VIII) or even phosphodiester (IX) is likely to be particularly base-labile (experiment 5). Pyridine or 2,6-lutidine would then be preferred.

TABLE 1

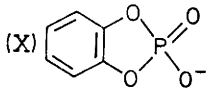
Preparation of *o*-hydroxyphenyl phosphate esters (IX)

Experiment	Alcohol	Base	Solvent	Yield (%)	M.p.
1	$Me_3C{\cdot}OH$	NEt_3	Tetrahydrofuran	83 [a]	116—118°
2	$Me_3C{\cdot}CH_2{\cdot}OH$	NEt_3	Dioxan	83 [a]	78—79
3	$Cl_3C{\cdot}CH_2{\cdot}OH$	NEt_3	Dioxan	72 [a]	99—100
4	$Br_3C{\cdot}CH_2{\cdot}OH$	NEt_3	Dioxan	77 [a]	116—117
5	$NC{\cdot}CH_2{\cdot}CH_2{\cdot}OH$	2,6-Lutidine	Dioxan	(>95) [b]	
6	$CH_2{:}CH{\cdot}CH_2{\cdot}OH$	2,6-Lutidine	Dioxan	(>95) [b]	
7	$Me_2C{:}CH{\cdot}CH_2{\cdot}OH$	2,6-Lutidine	Dioxan	(>95) [b]	
8	$CH_2{:}CH{\cdot}CMe_2{\cdot}OH$	NEt_3	Benzene	(*ca.* 70) [c]	

[a] Phosphorylation was virtually quantitative. This figure represents the yield of crystalline triethylammonium *o*-hydroxyphenyl alkyl phosphate. [b] Phosphorylation was virtually quantitative, but the 2,6-lutidinium *o*-hydroxyphenyl alkyl phosphate could not be induced to crystallize. [c] The triethylammonium salt of 1,1-dimethylallyl *o*-hydroxyphenyl phosphate was not obtained crystalline. The by-product (*ca.* 30%) which was assumed to be triethylammonium *o*-phenylene phosphate (see Experimental section), was most likely formed by the dealkylation of the intermediate phosphotriester (VIII; R = $CH_2{:}CH{\cdot}CMe_2$).



SCHEME 1



In order to fulfil criterion (d), a procedure for converting alkyl *o*-hydroxyphenyl phosphate esters (IX) into the corresponding monoalkyl phosphates (II) under very mild conditions was necessary. Reich,[17] who first suggested the use of (IV) as a phosphorylating agent,

* This is unnecessary if the phosphorylation is carried out in the presence of a two- or three-fold excess of base.

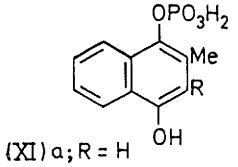
† This compound may be isolated crystalline in high yield. This observation led to a convenient preparation of *o*-phenylene phosphate,[14] which is itself a phosphorylating agent.[15,16]

[12] F. Wold and C. E. Ballou, *J. Amer. Chem. Soc.*, 1959, **81**, 2368.
[13] P. Genvresse, *Compt. rend.*, 1898, **127**, 522.
[14] E. Cherbuliez, M. Schwarz, and J. P. Leber, *Helv. Chim. Acta*, 1951, **34**, 841.
[15] K. Nagasawa, *Chem. and Pharm. Bull. (Japan)*, 1959, **7**, 397.
[16] T. A. Khwaja and C. B. Reese, unpublished observations.
[17] W. S. Reich, *Nature*, 1946, **157**, 133.

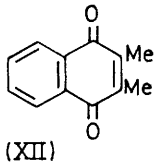
claimed that the intermediate phosphotriesters (VIII) were hydrolysed to give the desired products (II) directly. Lora Tomayo and Calderón subsequently *demonstrated* [18] that this claim was unjustified and that, as expected, hydrolysis of the phosphotriesters (VIII) gave the corresponding *o*-hydroxyphenyl phosphate esters (IX) (Scheme 1). Calderón then showed [19] that the latter diesters could be converted into the desired monoalkyl phosphates (II) by hydrogenolysis over platinum oxide.

Removal of the *o*-hydroxyphenyl group by catalytic hydrogenolysis would only be satisfactory for a simple alkyl derivative. Thus only the first two diesters listed in Table 1 would be expected to give the corresponding monoalkyl phosphates (t-butyl and neopentyl phosphates, respectively). In all other cases the alkyl group would be likely to undergo concomitant hydrogenation or hydrogenolysis. Furthermore this procedure would be relatively inconvenient on a large scale. Nagasawa showed [15] that the *o*-hydroxyphenyl group could be removed from an alkyl *o*-hydroxyphenyl phosphate (IX) enzymatically with snake venom phosphodiesterase. Although this enzyme would be expected to have no effect on alkyl groups, difficulties might be encountered in the isolation of the products (II) and large scale preparations would be relatively inconvenient.

A more convenient method for the removal of the *o*-hydroxyphenyl group was suggested by the oxidative phosphorylation studies of Clark *et al.*,[20] who showed that 4-hydroxy-3-methyl-1-naphthyl phosphate [the mono-



(XI) a; R = H
b; R = Me

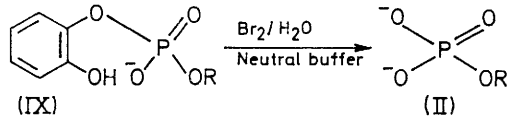


(XII)

or di-anion of (XIa)] underwent slow atmospheric oxidation at pH 6·8 with the release of orthophosphate, and that (XII) was obtained in virtually quantitative yield when a solution of (XIb) in aqueous potassium carbonate was treated with bromine water. They also showed [20] that *o*-hydroxyphenyl phosphate was oxidized by chlorine in dimethylformamide solution to give inorganic pyrophosphate, especially in the presence of tetra-n-butylammonium phosphate.

When a solution of *o*-hydroxyphenyl phosphate (IX; R = H) in aqueous triethylammonium hydrogen carbonate (pH 7·5) was treated with a sixfold excess of bromine water at 20°, rapid darkening occurred. After 5 min, orthophosphate was shown to be the sole phosphorus-containing component. Under the same conditions, *o*-hydroxyphenyl methyl phosphate (IX; R = Me) was quantitatively converted into methyl phosphate (II; R = Me). This oxidation, which occurs almost instantaneously in neutral aqueous solution at 20°, is the basis of a general method (Scheme 2) for the removal of *o*-hydroxyphenyl groups from intermediate phosphodiesters (IX) to give the monoalkyl phosphates (II).

This oxidation may be conveniently carried out on a 2—3 mmol scale (see Table 2 and Experimental section) by adding an excess (*ca.* sevenfold) of 2% bromine water to a solution of the *o*-hydroxyphenyl phosphate ester (IX) in aqueous 0·2M-barium acetate at 20°. The pure barium salts (II) may then be isolated in good yields



(IX) (II)

SCHEME 2

(Table 2, experiments 3 and 5). For larger scale preparations (experiments 4 and 6), it is more convenient to add a solution of bromine in carbon tetrachloride to a stirred solution of the phosphodiester (IX) in aqueous barium acetate, to give satisfactory yields of pure crystalline barium salts. The oxidation is quantitative, so modifications of the work-up procedure should lead to improved yields of isolated products.

TABLE 2

Oxidation of *o*-hydroxyphenyl phosphate esters (IX) with bromine water in aqueous barium acetate solution

Experiment	Substrate	Scale (mmol)	Yield [a] (%)
1	t-Butyl ester (IX; R = Me_3C)	3·0	67
2	Neopentyl ester (IX; R = $Me_3C{\cdot}CH_2$)	2·8	59
3	2,2,2-Trichloroethyl ester (IX; R = $Cl_3C{\cdot}CH_2$)	3·0	67
4	2,2,2-Trichloroethyl ester (IX; R = $Cl_3C{\cdot}CH_2$)	23·8	53
5	2,2,2-Tribromoethyl ester (IX; R = $Br_3C{\cdot}CH_2$)	2·0	73
6	2-Cyanoethyl ester (IX; R = $NC{\cdot}CH_2{\cdot}CH_2$)	100	46 [b]

[a] This figure represents the isolated yield of crystalline barium alkyl phosphate. The products were isolated as dihydrates, with the exception of barium 2,2,2-tribromoethyl phosphate, which was isolated as a monohydrate. [b] This figure represents the overall yield of barium 2-cyanoethyl phosphate dihydrate, based on 2-cyanoethanol as starting material. The intermediate 2,6-lutidinium *o*-hydroxyphenyl phosphate ester was not isolated pure (see Table 1).

However, this oxidation procedure (Scheme 2) is unsuitable for phosphodiesters (IX) derived from unsaturated alcohols, as olefinic double bonds are not inert under the reaction conditions. This drawback would be serious in the synthesis of biologically important

[18] M. Lora Tomayo and J. Calderón, *Anales real Soc. Españ. Fís. Quím.*, 1950, **46B**, 475 (*Chem. Abs.*, 1951, **45**, 7046e).

[19] J. Calderón, *Anales real Soc. Españ. Fís. Quím.*, 1957, **53B**, 69 (*Chem. Abs.*, 1957, **51**, 11,273f).

[20] V. M. Clark, D. W. Hutchinson, G. W. Kirby, and A. Todd, *J. Chem. Soc.*, 1961, 715.

phosphate esters such as pyrimidine nucleotide and isoprenoid derivatives, which would be susceptible to attack by the oxidizing agent. Thus an alternative oxidation procedure was required.

Bunton and Hellyer recently reported [21] that *p*-hydroxyphenyl phosphate was oxidized by periodate, in aqueous solution at room temperature, to give *p*-benzoquinone and orthophosphate. The reaction was fastest at pH 7, and varied by a factor of *ca.* 15 in the region pH 1—9. Unfortunately, *o*-hydroxyphenyl phosphate esters (IX) were oxidized very slowly by periodate at pH 7 and 20°. Thus thymidine 5′-*o*-hydroxyphenyl phosphate was only *ca.* 2% converted into thymidine 5′-phosphate after 2 h, and the barium salt of 2,2,2-trichloroethyl phosphate (II; R = $Cl_3C{\cdot}CH_2$) could be isolated in only 15% yield after reaction of the corresponding *o*-hydroxyphenyl ester (IX; R = $Cl_3C{\cdot}CH_2$) with an excess of periodate for 40 h. However, at pH 1·2 and 20°, oxidation of the latter compound was complete within 15 min,* and the barium salt of the desired product (II; R = $Cl_3C{\cdot}CH_2$) was isolated in 55% yield (Table 3, experiment 2). In general, the oxidation was carried out by adding an excess (⩾1·75 molecular equiv.) of periodic acid to the phosphodiester intermediate (IX) in aqueous solution at 20°. The product (II) could then be readily isolated as its crystalline barium salt (see Experimental section). This procedure is perhaps more convenient than oxidation with bromine water (Scheme 2), and yields are sometimes better; † it is also suitable for the removal of the *o*-hydroxyphenyl group from esters of unsaturated alcohols.

Crystalline barium allyl phosphate (II; R = $CH_2{:}CH{\cdot}CH_2$) was obtained in 64% overall yield from allyl alcohol (Table 3, experiment 4). The yield of barium 3,3-dimethylallyl phosphate (II; R = $Me_2C{:}CH{\cdot}CH_2$) was lower ‡ (experiment 5) but was nevertheless satisfactory for a two-step process. The results in Tables 2 and 3 clearly show that *o*-phenylene phosphorochloridate (IV) satisfies criterion (d) and hence all the criteria for a monofunctional phosphorylating agent. The methods described for the removal of *o*-hydroxyphenyl groups from the intermediate phosphodiesters (IX) are complementary to each other; the bromine water method is effective at pH 7 and may therefore be used in the preparation of acid-labile phosphate esters (*e.g.* t-butyl phosphate), whereas the periodate method may be used in the preparation of unsaturated phosphate esters (*e.g.* allyl phosphate). In both cases, oxidation occurs rapidly in aqueous solution at 20°.

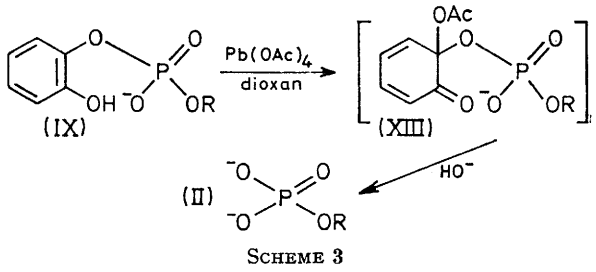
Finally, the preparation of a monoalkyl phosphate, which was both very labile to acid and unsaturated, was undertaken. As such a compound would not be expected to withstand the conditions of either of the foregoing oxidations, a third method, suggested by Wessely's work [22] on the oxidation of phenols with lead tetra-acetate, was examined. It was hoped that an *o*-hydroxyphenyl phosphate ester (IX) would react with lead tetra-acetate (Scheme 3) to give the intermediate (XIII).

TABLE 3

Oxidation of *o*-hydroxyphenyl phosphate esters (IX) with periodic acid

Experiment	Substrate	Scale (mmol)	Yield (%)
1	Neopentyl ester (IX; R = $Me_3C{\cdot}CH_2$)	5·3	72
2	2,2,2-Trichloroethyl ester (IX; R = $Cl_3C{\cdot}CH_2$)	10	55
3	2-Cyanoethyl ester (IX; R = $NC{\cdot}CH_2{\cdot}CH_2$)	20	55
4	Allyl ester (IX; R = $CH_2{:}CH{\cdot}CH_2$)	20	64 [b]
5	3,3-Dimethylallyl ester (IX; R = $Me_2C{:}CH{\cdot}CH_2$)	20	38 [b]

[a] Yield of crystalline barium alkyl phosphate dihydrate (anhydrous salt in the case of barium allyl phosphate). [b] Overall yield based on alcohol as starting material. The intermediate 2,6-lutidinium *o*-hydroxyphenyl phosphate ester was not obtained crystalline.



SCHEME 3

The latter would then be expected to undergo fragmentation in alkaline solution to give acetate ion, *o*-benzoquinone, and the desired product (II).

In order to test this procedure, the triethylammonium salt of *o*-hydroxyphenyl t-butyl phosphate (IX; R = Me_3C) was treated with a slight excess of lead tetra-acetate in dioxan solution at 20°. The products were worked up after 10 min.; the dioxan-soluble material showed strong i.r. absorption at 1680—1750 cm^{-1}. This material, which therefore could have contained intermediate (XIII; R = Me_3C), was treated with aqueous barium hydroxide (to pH 10) and then neutralized. Crystalline barium t-butyl phosphate was isolated (47%). In the same way, the barium salts of neopentyl and 2,2,2-trichloroethyl phosphates were prepared from the corresponding *o*-hydroxyphenyl derivatives in 64 and

* The oxidation of thymidine *o*-hydroxyphenyl phosphate was not examined under these conditions. However, a good yield of thymidine 5′-phosphate should be obtained, as the thymidine moiety would be expected to withstand such a comparatively mild acidic treatment.

† Compare experiments 1 and 3 in Table 3 with experiments 2 and 6 in Table 2.

‡ 3,3-Dimethylallyl phosphate would be expected to undergo acid-catalysed hydrolysis under the oxidation conditions (pH 1·2; 20°) more readily than allyl phosphate.

[21] C. A. Bunton and J. Hellyer, *Tetrahedron Letters*, **1969**, 187.

[22] F. Wessely and F. Sinwel, *Monatsh.*, 1950, **81**, 1055.

55% yields, respectively (Table 4, experiments 2 and 3). Although neither of the latter products is particularly acid-labile, these experiments point to the general applicability of the lead tetra-acetate method.

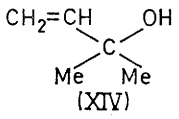
TABLE 4

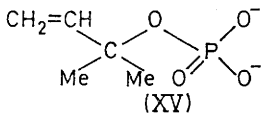
Oxidation of *o*-hydroxyphenyl phosphate esters (IX) with lead tetra-acetate in dioxan solution

Experiment	Substrate	Scale (mmol)	Yield [a] (%)
1	t-Butyl ester (IX; R = Me_3C)	5·0	47
2	Neopentyl ester (IX; R = $Me_3C{\cdot}CH_2$)	5·6	64
3	2,2,2-Trichloroethyl ester (IX; R = $Cl_3C{\cdot}CH_2$)	5·0	55
4	1,1-Dimethylallyl ester (IX; R = $CH_2{:}CH{\cdot}CMe_2$)	20	16 [b]

[a] Yield of crystalline barium alkyl phosphate dihydrate. [b] Overall yield based on 2-methylbut-3-en-2-ol (XIV) as starting material.

When the triethylammonium salt of 1,1-dimethylallyl *o*-hydroxyphenyl phosphate (IX; R = $CH_2{:}CH{\cdot}CMe_2$), which was obtained in *ca.* 70% yield (Table 1, experiment 8) by phosphorylation of 2-methylbut-3-en-2-ol (XIV) in benzene solution, was oxidized by the lead


(XIV)


(XV)

tetra-acetate method, 1,1-dimethylallyl phosphate (XV) was obtained. The latter compound, which is both very labile to acid and unsaturated, was isolated, albeit in low yield (Table 4, experiment 4), as a pure crystalline barium salt; its structure was confirmed by elemental analysis and n.m.r. spectroscopy. It should be possible to improve the yield of (XV) by modifying the isolation procedure.

In the foregoing discussion, the phosphorylation of eight alcohols with *o*-phenylene phosphorochloridate (IV) has been described. Although two were tertiary (Table 1, experiments 1 and 8) and two others also had comparatively hindered hydroxy-functions (experiments 2 and 4), the phosphorylation reactions all proceeded rapidly at room temperature. In four cases, crystalline intermediate phosphodiesters (IX) were isolated and, in all except one case (experiment 8), the yield of crude phosphodiester was virtually quantitative. Of the three procedures which have been devised for the removal of the *o*-hydroxyphenyl group, that involving periodic acid is perhaps the most convenient. However, it is unsuitable for the preparation of acid-labile (*e.g.* tertiary) phosphate esters. The bromine water method may then be used unless the phosphate ester contains an olefinic double bond. In such an instance (*e.g.* experiment 8) the lead tetra-acetate method would be preferred.

Finally, we summarize some of the special merits of the *o*-phenylene phosphorochloridate method for the preparation of monoalkyl phosphates. First, the desired products (II) may generally be prepared from the corresponding alcohols in 2—3 h. This period includes the isolation of the pure crystalline barium salts. Secondly, the products (II) are generally free from inorganic phosphate; indeed, they are often analytically pure *before* recrystallization. Thirdly, the yields of the individual monoalkyl phosphates compare favourably with those obtained by other procedures. Thus, if the isomeric dimethylallyl phosphates are excluded, the average overall yield * (based on alcohol starting material) of pure crystalline barium salt is 57%. The preparation of 3,3-dimethylallyl phosphate is considerably more convenient than the published procedure [23] and 1,1-dimethylallyl phosphate is a new compound. Although the yields of the latter two compounds could be improved, the *o*-phenylene phosphorochloridate method appears to be at least as suitable for the preparation of the phosphate esters involved in terpene biosynthesis as the other published procedures.[23,24] The preparations of t-butyl,[24,25] neopentyl,[26] 2,2,2-trichloroethyl,[27,28] and 2,2,2-tribromoethyl phosphates [28] are superior to those previously published, and the preparations of allyl,[8,11,29] and 2-cyanoethyl phosphates [30] are as convenient as the literature methods.

EXPERIMENTAL

N.m.r. spectra were measured at 100 MHz with a Varian HA 100 spectrometer and at 60 MHz with a Perkin-Elmer spectrometer. U.v. absorption spectra were measured with a Cary recording spectrophotometer, model 14M-50. Ascending paper chromatography was carried out on Whatman no. 1 paper in the following systems: A, butan-1-ol–acetic acid–water (5 : 2 : 3); B, propan-2-ol–aqueous ammonia (*d* 0·88)–water (7 : 1 : 2); C, butan-1-ol–water (86 : 14). Paper electrophoresis on Whatman no. 4 paper was carried out in a carbon tetrachloride-cooled apparatus with 0·1M-sodium phosphate (pH 7·0) and 0·05M-triethylammonium hydrogen carbonate (pH 7·5) buffers. Phosphorus-containing components on paper chromatograms and electrophoretograms were detected by the method of Hanes and Isherwood.[31] Mallinckrodt SilicAR CC7 (100—200 mesh) was used for adsorption chromatography. 2,6-Lutidine and triethylamine were heated with calcium

* This has been calculated by averaging the best yield obtained (see Tables 1—4) for each of the other six monoalkyl phosphates.

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hydride, under reflux, and redistilled before use; dioxan and tetrahydrofuran were purified by distillation from lithium aluminium hydride.

TABLE 5

Relative paper electrophoretic mobilities [a] of *o*-hydroxyphenyl phosphate esters (IX) in 0·1M-sodium phosphate buffer (pH 7·0)

R	Relative mobility
Me_3C	0·50
$Me_3C{\cdot}CH_2$	0·51
$Cl_3C{\cdot}CH_2$	0·55
$Br_3C{\cdot}CH_2$	0·47
$NC{\cdot}CH_2{\cdot}CH_2$	0·52
$CH_2{:}CH{\cdot}CH_2$	0·62
$Me_2C{:}CH{\cdot}CH_2$	0·50
$CH_2{:}CH{\cdot}CMe_2$	0·42

The mobilities are relative to *o*-hydroxyphenyl phosphate, which is taken as 1·00. The relative mobility of *o*-phenylene phosphate (X) in this system is 0·72.

TABLE 6

R_F Values [a] of monoalkyl phosphates (II)

Neopentyl phosphate (II; R = $Me_3C{\cdot}CH_2$)	0·78
2,2,2-Trichloroethyl phosphate (II; R = $Cl_3C{\cdot}CH_2$)	0·65
2,2,2-Tribromoethyl phosphate (II; R = $Br_3C{\cdot}CH_2$)	0·69
2-Cyanoethyl phosphate (II; R = $NC{\cdot}CH_2{\cdot}CH_2$)	0·46
Allyl phosphate (II; R = $CH_2{:}CH{\cdot}CH_2$)	0·55
3,3-Dimethylallyl phosphate (II; R = $Me_2C{:}CH{\cdot}CH_2$)	0·70

[a] For ascending paper chromatography on Whatman no. 1 paper in system A.

2,2,2-*Trichloro*-1,3,2-*benzodioxaphosph*(v)*ole* (III).—Catechol (121 g, 1·1 mol) was added in small portions during 2 h to a stirred suspension of phosphorus pentachloride (287 g, 1·25 mol) in anhydrous benzene (1250 ml). The reactants were then heated under reflux on a water-bath for 2 h, the benzene was evaporated off, and the residue was distilled under reduced pressure. After the unchanged phosphorus pentachloride had sublimed over, the benzodioxaphosphole, b.p. 104° at 1·3 mmHg (lit.,[4] 132° at 11 mmHg) was distilled off, and was collected as a pale yellow solid; yield (after redistillation), 200 g (74%).

o-*Phenylene Phosphorochloridate* (IV).—A mixture of the benzodioxaphosphole (III) (200 g, 0·81 mol) and acetic anhydride (80 ml, 0·85 mol), was heated on a water-bath for 20 min and acetyl chloride was distilled off. The products were then distilled under reduced pressure to give *o*-phenylene phosphorochloridate as a colourless solid, b.p. 80—81° at 1·2 mmHg, m.p. 59—61° (lit.,[4] b.p. 122° at 12 mmHg, m.p. 58—59°) (135 g, 87%).

N-*Methylpyridinium Salt of* o-*Phenylene Phosphate* (X).—Pyridine (4·4 g, 55 mmol) was added to a solution of methyl *o*-phenylene phosphate (5·2 g, 28 mmol) in anhydrous dioxan (10 ml) at 20°. A precipitate appeared after *ca.* 15 min. The reactants were left for 16 h and then filtered. The crystalline residue (6·78 g, 91%) was washed with dioxan (10 ml) and gave N-*methylpyridinium* o-*phenylene phosphate* (from ethanol–ethyl acetate) as a hygroscopic, colourless solid, m.p. 83—85° [Found (in material dried *in vacuo* over P_2O_5): C, 54·1; H, 4·7; N, 5·5. $C_{12}H_{12}NO_4P$ requires C, 54·35; H, 4·5; N, 5·3%]; R_F 0·38 (system B); electrophoretic mobility of anion (hydrogen carbonate buffer; pH 7·5) 0·80 times that of *o*-hydroxyphenyl phosphate.

o-*Hydroxyphenyl Phosphate*.—Methyl *o*-phenylene phosphate (5 g) was heated with water (50 ml) on a steam-bath for 25 min. The products were concentrated to dryness under reduced pressure and dissolved in ethyl acetate (2 ml). The solution was treated with benzene (25 ml), concentrated to *ca.* 15 ml, and set aside at 20°, to give crystals of *o*-hydroxyphenyl phosphate [Found (material dried at 50° *in vacuo* over P_2O_5): C, 36·8; H, 4·0. Calc. for $C_6H_7O_5P$, $0{\cdot}5H_2O$: C, 36·2; H, 4·0%], m.p. 145° (lit.,[13] 139°), (4·6 g, 88%); R_F 0·51 (system A) and 0·36 (system B).

Hydrolysis of Methyl o-*Phenylene Phosphate with Aqueous Sodium Hydrogen Carbonate*.—A solution of methyl *o*-phenylene phosphate (0·08 g, 0·43 mmol) in aqueous 0·34M-sodium hydrogen carbonate (1·5 ml) was set aside at 20°. Paper chromatography (system B) of the products after 25 min revealed only one component (R_F 0·63). Later, a second component (R_F 0·36), corresponding to *o*-hydroxyphenyl phosphate, was detected.

Barium o-*Hydroxyphenyl Methyl Phosphate*.—Methyl *o*-phenylene phosphate (1·0 g, 5·4 mmol) was dissolved in aqueous 0·091N-barium hydroxide (60 ml) at 20°. After 25 min, the products were concentrated under reduced pressure and extracted with hot methanol; the extract was filtered. *Barium* o-*hydroxyphenyl methyl phosphate* crystallized from the concentrated filtrate; it was recrystallized from methanol [Found (material dried *in vacuo* over P_2O_5 for 5 hr): C, 30·55; H, 3·35; P, 11·05. $C_7H_8Ba_{\frac{1}{2}}O_5P$ requires C, 30·6; H, 2·9; P, 11·3%]; $\lambda_{max.}$ (H_2O) 270 nm (ε 2040); $\lambda_{min.}$ 238 nm (ε 510); R_F 0·63 (system B).

Small-scale Oxidations with Bromine Water.—Solutions of (a) *o*-hydroxyphenyl phosphate (0·01 mmol) and (b) *o*-hydroxyphenyl methyl phosphate (0·01 mmol) in 0·2M-triethylammonium hydrogen carbonate buffer (pH 7·5; 0·5 ml) were treated with 0·12M-bromine water (0·5 ml) at 20°. Both solutions darkened rapidly. After 5 min, paper electrophoresis (hydrogen carbonate buffer; pH 7·5) and paper chromatography (system A) showed that the sole phosphorus-containing components in solutions (a) and (b) corresponded to inorganic orthophosphate and methyl phosphate, respectively.

Triethylammonium o-*Hydroxyphenyl t-Butyl Phosphate*.—A solution of *o*-phenylene phosphorochloridate (9·53 g, 50 mmol) in anhydrous tetrahydrofuran (30 ml) was added dropwise to a stirred solution of t-butyl alcohol (3·7 g, 50 mmol) and triethylamine (6·82 ml, 50 mmol) in tetrahydrofuran (20 ml), maintained at 20°. After 30 min, the precipitated triethylammonium chloride was filtered off and washed with tetrahydrofuran (20 ml). The combined filtrate and washings were treated with triethylamine (10 ml, 73 mmol) and then with water (3 ml). The products were set aside overnight at 20°, and were then concentrated under reduced pressure to give a yellow glass, which was dissolved in ethyl acetate (20 ml); the solution was filtered, and set aside at 0° overnight. *Triethylammonium* o-*hydroxyphenyl t-butyl phosphate* [Found (recrystallized material dried *in vacuo* over P_2O_5 at 50° for 6 h): C, 55·1; H, 8·5; N, 3·8; P, 9·2. $C_{16}H_{30}NO_5P$ requires C, 55·35; H, 8·65; N, 4·0; P, 8·9%] formed colourless needles (14·4 g, 83%), m.p. 116—118°; $\lambda_{max.}$ (H_2O) 270 nm (ε 2000); $\lambda_{min.}$ 239 nm (ε 160); R_F 0·80 (system B); electrophoretic mobility of anion (hydrogen carbonate buffer; pH 7·5) 0·53 times that of *o*-hydroxyphenyl phosphate.

Barium t-Butyl Phosphate.—(*a*) To a solution of triethylammonium *o*-hydroxyphenyl t-butyl phosphate (1·04 g, 3 mmol) in aqueous 0·2M-barium acetate (150 ml) at 20° was added 2% bromine water (180 ml, 22·5 mmol). After 10 min, the products were filtered and the filtrate was extracted with ether (2 × 150 ml). The aqueous layer was concentrated (under reduced pressure below 40°) to *ca.* 80 ml, warmed with charcoal, filtered, and then further concentrated (to *ca.* 40 ml). Ethanol (10 ml) was added, to give colourless crystals of *barium t-butyl phosphate dihydrate*. A further crop (0·14 g) was obtained from the mother liquors; total yield 0·65 g (67%). The product recrystallized from water to give a colourless dihydrate [Found (material dried *in vacuo* over P_2O_5 at 80° for 4 h): C, 14·25; H, 3·7; P, 9·9. $C_4H_9BaO_4P,2H_2O$ requires C, 14·75; H, 4·0; P, 9·75%]; R_F 0·14 (system B).

(*b*) To a solution of triethylammonium *o*-hydroxyphenyl t-butyl phosphate (1·75 g, 5 mmol) in dioxan (100 ml) at 20° was added a solution of lead(IV) acetate (3·0 g, 6·8 mol) in dioxan (50 ml). The mixture darkened immediately. After 10 min, the products were centrifuged and the supernatant liquid was concentrated under reduced pressure to an oil. This material, which showed a strong broad absorption in the region 1680—1750 cm^{-1}, was treated with aqueous barium hydroxide at 20° until the pH rose to 10. The products were set aside for 10 min, neutralized (from pH 10) with acetic acid, and then centrifuged. The supernatant liquid was concentrated to *ca.* 50 ml and ethanol (*ca.* 10 ml) was added to give crystalline barium t-butyl phosphate dihydrate (0·75 g, 47%).

Triethylammonium o-Hydroxyphenyl Neopentyl Phosphate.—A solution of *o*-phenylene phosphorochloridate (4·97 g, 26 mmol) in dioxan (10 ml) was added to a cooled, stirred solution of neopentyl alcohol (2·21 g, 25 mmol) and triethylamine (2·55 g, 25 mmol) in dioxan (60 ml). After 20 min, triethylammonium chloride was filtered off and washed with dioxan. The combined filtrate and washings were treated with triethylamine (2·63 g, 26 mmol) and water (0·90 ml, 50 mmol). After 30 min, the products were concentrated under reduced pressure to give a gum which was treated with ethyl acetate to give colourless crystals (6·22 g) of *triethylammonium o-hydroxyphenyl neopentyl phosphate* (Found: C, 56·8; H, 8·9; N, 3·6; P, 9·1. $C_{17}H_{31}NO_5P$ requires C, 56·6; H, 8·7; N, 3·9; P, 8·9%), m.p. 78—79°. Another crop (1·26 g) was obtained from the chromatographed (on SilicAR CC7) mother liquors; total yield, 7·48 g (83%); R_F 0·74 (system C); electrophoretic mobility of anion (phosphate buffer; pH 7) 0·51 times that of *o*-hydroxyphenyl phosphate.

Barium Neopentyl Phosphate.—(*a*) To a stirred solution of triethylammonium *o*-hydroxyphenyl neopentyl phosphate (1·01 g, 2·8 mmol) in aqueous 0·2M-barium acetate (120 ml) at 20° was added 2% bromine water (150 ml, 18·8 mmol). After 30 min., the orange-yellow precipitate was filtered off, and the filtrate was extracted with ether (2 × 100 ml.). The aqueous layer was concentrated to *ca.* 100 ml, decolourized with charcoal, concentrated further under reduced pressure, and treated with ethanol until a faint turbidity persisted. *Barium neopentyl phosphate dihydrate* (Found: C, 17·4; H, 4·2; P, 9·2. $C_5H_{11}BaO_4P,2H_2O$ requires C, 17·65; H, 4·4; P, 9·4%) readily crystallized from this solution, in colourless shining plates (0·56 g, 59%); τ ($CF_3{\cdot}CO_2H$) 6·18 (2H, d, *J ca.* 4 Hz) and 9·01 (9H, s); R_F 0·78 (system A).

(*b*) A solution of periodic acid (8·0 g, 35 mmol) in water (30 ml) was added to a stirred solution of triethylammonium *o*-hydroxyphenyl neopentyl phosphate (1·90 g, 5·3 mmol) in water (250 ml) at 20°. After 15 min aqueous M-barium acetate was added to the dark products until the pH rose to *ca.* 4. The products were then neutralized with aqueous barium hydroxide, and the heavy precipitate was collected by centrifugation. The supernatant liquid was decolourized with charcoal, and then concentrated to *ca.* 250 ml to give silvery-white crystals of barium neopentyl phosphate dihydrate (1·28 g, 72%).

(*c*) A solution of lead(IV) acetate (3·5 g, 7·9 mmol) in dioxan (50 ml) was added to a solution of triethylammonium *o*-hydroxyphenyl neopentyl phosphate (2·0 g, 5·6 mmol) in dioxan (100 ml) at 20°. The products were worked up and treated with aqueous barium hydroxide (to pH 10) as already described in the preparation of t-butyl phosphate. Colourless crystals (1·21 g, 64%) of barium neopentyl phosphate dihydrate (Found: C, 17·7; H, 4·1%) were obtained.

Triethylammonium o-Hydroxyphenyl 2,2,2-Trichloroethyl Phosphate.—A solution of *o*-phenylene phosphorochloridate (9·55 g, 50 mmol) in dioxan (15 ml) was added to a cooled, stirred solution of 2,2,2-trichloroethanol (7·45 g, 50 mmol) and triethylamine (5·05 g, 50 mmol) in dioxan (80 ml). After 30 min, the triethylammonium chloride, which had begun to precipitate immediately, was filtered off and washed with dioxan. The combined filtrate and washings were treated with triethylamine (5·08 g, 50 mmol) and water (1·16 g, 65 mmol). After 5 min, the products were concentrated under reduced pressure to a gum, which was dissolved in ethyl acetate to give colourless crystals (14·91 g) of *triethylammonium o-hydroxyphenyl 2,2,2-trichloroethyl phosphate* (Found: C, 40·0; H, 5·6; N, 3·0; P, 7·6. $C_{14}H_{22}Cl_3NO_5P$ requires C, 39·8; H, 5·3; N, 3·3; P, 7·6%), m.p. 99—100°. Another crop (1·58 g) was obtained from the chromatographed (on SilicAR CC7) mother liquors; total yield 16·49 g (72%); R_F 0·76 (system C); electrophoretic mobility of anion (phosphate buffer; pH 7) 0·55 times that of *o*-hydroxyphenyl phosphate.

Barium 2,2,2-Trichloroethyl Phosphate.—(*a*) To a stirred solution of triethylammonium *o*-hydroxyphenyl 2,2,2-trichloroethyl phosphate (1·24 g, 3·0 mmol) in aqueous 0·2M-barium acetate (120 ml) at 20° was added 2% bromine water (180 ml, 22·5 mmol). After 30 min, the orange-yellow precipitate, which had begun to form immediately, was filtered off, and the filtrate was extracted with ether (2 × 150 ml). The aqueous layer was decolourized with charcoal, concentrated to *ca.* 50 ml, and treated with ethanol until a faint turbidity persisted. The solution then deposited shining colourless crystals (0·78 g, 67%) of *barium 2,2,2-trichloroethyl phosphate dihydrate* (Found: C, 6·3; H, 2·1; P, 7·85. $C_2H_2BaCl_3O_4P,2H_2O$ requires C, 6·0; H, 1·5; P, 8·0%); R_F 0·65 (system A).

(*b*) A solution of bromine (25 g, 156 mmol) in carbon tetrachloride (50 ml) was added dropwise during 30 min to a vigorously stirred solution of triethylammonium *o*-hydroxyphenyl 2,2,2-trichloroethyl phosphate (10 g, 23·8 mmol) and barium acetate (25 g, 98 mmol) in water (300 ml) at 20°. During this period, a heavy precipitate formed and the pH dropped from 7 to 2—3.

The aqueous suspension was extracted with ether (3 × 150 ml), neutralized with barium hydroxide, and filtered. The filtrate was treated with ethanol until a faint turbidity persisted. Barium 2,2,2-trichloroethyl

phosphate dihydrate then crystallized readily (4·81 g, 53%).

(*c*) Triethylammonium *o*-hydroxyphenyl 2,2,2-trichloroethyl phosphate (4·22 g, 10 mmol) was oxidized with periodic acid (8·0 g, 35 mmol) under the conditions and with the work-up procedure described for the corresponding neopentyl derivative. When ethanol was added to the concentrated supernantant liquid, shining colourless crystals of barium 2,2,2-trichloroethyl phosphate dihydrate (2·10 g, 55%) were obtained.

(*d*) A solution of triethylammonium periodate [35 mmol; prepared by neutralizing periodic acid (8 g) with triethylamine] in water (25 ml) was added to a solution of triethylammonium *o*-hydroxyphenyl 2,2,2-trichloroethyl phosphate (4·22 g, 10 mmol) in water (50 ml) at 20° (resultant pH 7). After 40 h, water (150 ml) and then aqueous 0·5M-barium acetate (50 ml) were added. The products were centrifuged and the supernatant liquid was decanted and concentrated to *ca.* 50 ml. Ethanol (*ca.* 10 ml) was then added and crystals (0·55 g, 15%) of barium 2,2,2-trichloroethyl phosphate dihydrate were obtained.

(*e*) A solution of lead(IV) acetate (3·0 g, 6·8 mmol) in dioxan (50 ml) was added to a solution of triethylammonium *o*-hydroxyphenyl 2,2,2-trichloroethyl phosphate (2·1 g, 5 mmol) in dioxan (100 ml) at 20°. The products were worked up and treated with aqueous barium hydroxide (to pH 10) as described in the preparation of t-butyl phosphate. Colourless crystals (1·10 g, 55%) of barium 2,2,2-trichloroethyl phosphate dihydrate (Found: C, 6·6; H, 1·85%) were obtained.

Triethylammonium o-*Hydroxyphenyl* 2,2,2-*Tribromoethyl Phosphate*.—A solution of *o*-phenylene phosphorochloridate (0·953 g, 5 mmol) in dioxan (5 ml) was added to a cooled solution of 2,2,2-tribromoethanol (1·41 g, 5 mmol) and triethylamine (1·0 ml, 7·2 mmol) in dioxan (20 ml). After 30 min, the products were filtered and the residue was washed with dioxan. The combined filtrate and washings were treated with triethylamine (1·0 ml, 7·2 mmol) and water (0·25 g, 14 mmol). After 5 min, the products were concentrated under reduced pressure to a gum, which was treated with ethyl acetate to give colourless crystals (1·96 g) of *triethylammonium* o-*hydroxyphenyl* 2,2,2-*tribromoethyl phosphate* (Found: C, 29·9; H, 4·1; N, 2·2; P, 5·6. $C_{14}H_{22}Br_3NO_5P$ requires: C, 30·2; H, 4·0; N, 2·5; P, 5·75%), m.p. 116—117°. Another crop (0·09 g) was obtained from the chromatographed (on SilicAR CC7) mother liquors; total yield 2·05 g (77%); R_F 0·81 (system C); electrophoretic mobility of anion (phosphate buffer; pH 7) 0·47 times that of *o*-hydroxyphenyl phosphate.

Barium 2,2,2-*Tribromoethyl Phosphate*.—To a stirred solution of triethylammonium *o*-hydroxyphenyl 2,2,2-tribromoethyl phosphate (1·14 g, 2·0 mmol) in aqueous 0·2M-barium acetate (100 ml) was added 2% bromine water (120 ml, 15 mmol). After 20 min., the products were filtered, and the filtrate was extracted with ether (2 × 100 ml), decolourized with charcoal, and then concentrated to *ca.* 60 ml. Colourless crystals of *barium* 2,2,2-*tribromoethyl phosphate, monohydrate* (Found: C, 4·6; H, 1·2; P, 5·95. $C_2H_2BaBr_3O_4P,H_2O$ requires: C, 4·5; H, 1·3; P, 5·95%) were filtered from the cooled solution. A second crop was obtained by adding ethanol to the filtrate; total yield 0·76 g (73%); R_F 0·69 (system A).

2,6-*Lutidinium* 2-*Cyanoethyl* o-*Hydroxyphenyl Phosphate*.—A solution of *o*-phenylene phosphorochloridate (1·91 g, 10 mmol) in dioxan (4 ml) was added to a cooled solution of 2-cyanoethanol (0·71 g, 10 mmol) and 2,6-lutidine (1·07 g, 10 mmol) in dioxan (20 ml). After 5 min, 2,6-lutidinium chloride was filtered off and washed with dioxan. The combined filtrate and washings were treated with 2,6-lutidine (1·10 g, 10·3 mmol) and water (0·214 g, 11·9 mmol). After 5 min, the products were concentrated under reduced pressure to a gum. Paper electrophoresis of this material (phosphate buffer; pH 7) revealed a principal component with a mobility 0·52 times that of *o*-hydroxyphenyl phosphate, and a trace component with a mobility corresponding to that of *o*-hydroxyphenyl phosphate.

The products were chromatographed on a column (14 cm × 7 cm²) of SilicAR CC7. 2,6-Lutidinium *o*-hydroxyphenyl 2-cyanoethyl phosphate [R_F 0·59 (system C)] was eluted by chloroform–methanol (96 : 4); it could not be induced to crystallize.

Barium 2-*Cyanoethyl Phosphate*.—(*a*) A solution of bromine (100 g, 625 mmol) in carbon tetrachloride (100 ml) was added dropwise during 30 min to a vigorously stirred solution of unchromatographed (see before) 2,6-lutidinium *o*-hydroxyphenyl 2-cyanoethyl phosphate [prepared as before from 2-cyanoethanol (7·1 g, 100 mmol)] and barium acetate (75 g, 294 mmol) in water (700 ml) at 20°.

The aqueous suspension was extracted with ether (3 × 200 ml), neutralized with barium hydroxide, and filtered. Both the filtrate and residue were retained. When ethanol was added to the filtrate, colourless crystals (12·3 g) of *barium* 2-*cyanoethyl phosphate dihydrate* (Found: C, 10·6; H, 2·7; N, 4·15; P, 10·6. Calc. for $C_3H_4BaNO_4P,2H_2O$: C, 11·2; H, 2·5; N, 4·3; P, 9·9%) were obtained. A further crop (1·62 g) was obtained from the residue; total yield, 13·92 g (46% overall yield, based on 2-cyanoethanol); τ ($CF_3{\cdot}CO_2H$) 5·64 (2H, dt, *J ca.* 5·5 and 6·5 Hz) and 7·12 (2H, t, *J ca.* 5·5 Hz); R_F 0·46 (system A).

(*b*) Unchromatographed (see before) 2,6-lutidinium *o*-hydroxyphenyl 2-cyanoethyl phosphate [prepared as before from 2-cyanoethanol (1·42 g, 20 mmol)] was oxidized with periodic acid (8·0 g, 35 mmol) under the conditions described in preparation (*b*) of barium neopentyl phosphate; concentration of the neutralized, decolourized solution to *ca.* 200 ml, gave colourless shining plates of barium 2-cyanoethyl phosphate dihydrate. When ethanol was added to the mother liquors of the first crystallization, a second crop was obtained; total yield 3·50 g (55% overall, based on 2-cyanoethanol).

Barium Allyl Phosphate.—A solution of *o*-phenylene phosphorochloridate (3·83 g, 20 mmol) in dioxan (20 ml) was added to a cooled solution of allyl alcohol (1·16 g, 20 mmol) and 2,6-lutidine (2·14 g, 20 mmol) in dioxan (60 ml). After 10 min, 2,6-lutidinium chloride was filtered off and washed with dioxan. The combined filtrate and washings were treated with 2,6-lutidine (2·14 g, 20 mmol) and water (2·0 g, 111 mmol). After 5 min, the products were concentrated under reduced pressure to a gum. Paper electrophoresis of this material (phosphate buffer; pH 7) revealed a principal component with a mobility 0·62 times that of *o*-hydroxyphenyl phosphate, and a trace component with a mobility corresponding to that of *o*-hydroxyphenyl phosphate; the principal component had R_F 0·73 (system C).

This material was oxidized with periodic acid (8·0 g, 35 mmol) under the foregoing conditions with the same work-up procedure. When the neutralized, decolourized solution was concentrated to *ca.* 100 ml and treated with ethanol,

colourless crystals of *barium allyl phosphate* (Found: C, 13·1; H, 1·8; P, 11·3. $C_3H_5BaO_4P$ requires: C, 13·1; H, 1·85; P, 11·6%) were obtained (3·50 g, 64% overall based on allyl alcohol); τ ($CD_3{\cdot}CO_2D$) 3·80—4·24 (1H, m), 4·52—4·96 (2H, m), and 5·59 (2H, m); R_F 0·55 (system A).

Barium 3,3-Dimethylallyl Phosphate.—A solution of *o*-phenylene phosphorochloridate (3·83 g, 20 mmol) in dioxan (20 ml) was added to a cooled solution of 3,3-dimethylallyl alcohol [23] (1·72 g, 20 mmol) and 2,6-lutidine (2·14 g, 20 mmol) in dioxan (60 ml). The products were worked up as described in the preparation of barium allyl phosphate, to give the intermediate 2,6-lutidinium *o*-hydroxyphenyl 3,3-dimethylallyl phosphate as a gum [paper electrophoretic (phosphate buffer; pH 7) mobility 0·50 times that of *o*-hydroxyphenyl phosphate; R_F 0·81 (system C)].

This material was oxidized with periodic acid (8·0 g, 35 mmol) for 2 min [see preparation (*b*) of barium neopentyl phosphate] and the products were worked up in the same way. The neutralized, decolourized solution was concentrated to *ca.* 100 ml and treated with ethanol to give colourless crystals (2·56 g, 38% overall based on 3,3-dimethylallyl alcohol) of *barium 3,3-dimethylallyl phosphate dihydrate* [Found: C, 17·8; H, 3·7; P, 9·65. $C_5H_9BaO_4P,2H_2O$ requires C, 17·8; H, 3·4; P, 9·5%); τ ($CD_3{\cdot}CO_2D$) 4·61 (1H, m), 5·57 (2H, distorted t, *J ca.* 7·5 Hz), 8·04 (3H, s), and 8·10 (3H, s); R_F 0·70 (system A).

Barium 1,1-Dimethylallyl Phosphate.—A solution of *o*-phenylene phosphorochloridate (3·85 g, 20 mmol) in benzene (50 ml) was added to a stirred solution of 1,1-dimethylallyl alcohol (1·72 g, 20 mmol) and triethylamine (6·05 g, 60 mmol) in benzene (150 ml) at 20°. After 10 min, triethylammonium chloride was filtered off, and the filtrate was treated with water (1 ml, 56 mmol). Paper electrophoresis of the products (phosphate buffer; pH 7) revealed a major (*ca.* 75%) and a minor (*ca.* 25%) component with respective mobilities 0·42 and 0·72 times that of *o*-hydroxyphenyl phosphate. The mobility of the minor component corresponded to that of *o*-phenylene phosphate.

When the products were concentrated under reduced pressure and the gum was redissolved in ethyl acetate, a hygroscopic crystalline precipitate * (1·60 g) was obtained, which was filtered off; the filtrate was found by paper electrophoresis to contain a single anionic species with a mobility corresponding to that of the foregoing major component. Concentration of the filtrate gave a gum: τ ($CDCl_3$) 3·02 (4H, m), 3·73 (1H, dd, *J ca.* 10 and 17 Hz), 4·57—5·07 (2H, m), 7·00 (6H, m), 8·40 (6H, s), and 8·78 (9H, t, *J ca.* 6 Hz).

To a solution of the gum in dioxan (100 ml) was added a solution of lead(IV) acetate (8·0 g, 18 mmol) in dioxan (100 ml.) at 20°. The products were worked up and treated with aqueous barium hydroxide (to pH 10) as described for the preparation of t-butyl phosphate. The concentrated supernatant liquid (*ca.* 50 ml) was decolourized with charcoal at 20°, and then ethanol (10 ml.) was added, to give colourless crystals (1·10 g, 16% based on 1,1-dimethylallyl alcohol) of *barium 1,1-dimethylallyl phosphate dihydrate* (Found: C, 18·1; H, 3·6; P, 9·4. $C_5H_9BaPO_4,2H_2O$ requires C, 17·8; H, 3·4; P, 9·5%). The n.m.r. spectrum (D_2O) of the magnesium salt included the following signals: τ 3·84 (dd, *J ca.* 10 and 17 Hz), 4·67—5·17 (m), and 8·57 (s).

Action of Neutral Periodate on Ammonium Thymidine 5′-o-Hydroxyphenyl Phosphate.—A solution of triethylammonium periodate (0·2 mmol; prepared by neutralizing 0·045 g of periodic acid with triethylamine) in water (0·5 ml.) was added to a solution of ammonium thymidine 5′-*o*-hydroxyphenyl phosphate [3] (0·022 g, 0·05 mmol) in water (0·5 ml.) at 20°. The pH of the resulting solution was 7. After 2 h, paper electrophoresis (phosphate buffer; pH 7) revealed starting material contaminated with a trace (*ca.* 2%) of thymidine 5′-phosphate.

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* This material, m.p. 112—114°, was assumed to be triethylammonium *o*-phenylene phosphate on the basis of its paper electrophoretic mobility.