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Phosphoryl Transfer Promoted by Nitriles in the Presence of Highly Reactive Halides

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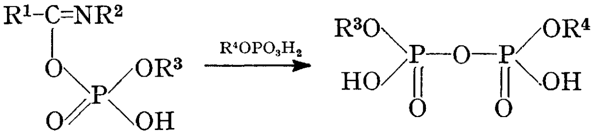
Nitriles, *e.g.* acetonitrile and benzonitrile slowly react at elevated temperatures with mono-substituted phosphoric acids to give *sym*-pyrophosphates. Prior addition of a highly reactive halide, *e.g.* a chloromethyl ether or thioether, gives rise to a much more effective phosphoryl transfer. Both anhydrides and esters can be generated in this way.

THE biochemical importance of esters of phosphoric and polyphosphoric acids has led to the detailed study of phosphoryl transfer; [1] most attention has been given to the activation of phosphoric acid or its monoesters. One method for such activation involves the production of the imidoyl phosphate (I) by addition of a suitable derivative of phosphoric acid to a carbodi-imide (II),[2] a cyanamide (III; $R = R^1_2N$),[3] an isocyanate (IV),[4] a ketenimine (V),[5] or a nitrile activated by an electron-withdrawing group [*e.g.* (III; $R = CCl_3$)].[6]



(I)

$RN{=}C{=}NR$ (II)

$RC{\equiv}N$ (III)

$RN{=}C{=}O$ (IV)

$R_2C{=}C{=}NH$ (V)

RCH_2Cl (VI)

However, phosphoryl transfer can be promoted by nitriles which do not contain electron-withdrawing substituents [*e.g.* (III; R = Me)[7]]; this reaction is greatly enhanced by the addition of certain highly reactive alkyl halides [*e.g.* (VI; R = MeO)].

When heated, a solution of a monoester of phosphoric acid in acetonitrile gives a P^1P^2-diester of pyrophosphoric acid; however, phosphoryl transfer is slow and complete conversion into the pyrophosphate does not occur even after 24 hr. at 80°. This is in contrast to the transfer promoted by (III; $R = CCl_3$), in which case rapid and complete conversion into the pyrophosphate occurs.[6] The yield of pyrophosphate derived from the reaction between a phosphomonoester and acetonitrile is lowered after an initial addition of water. However, the incomplete formation of pyrophosphate (over an extended period) cannot be attributed to adventitious water, as a major change in the concentration of phosphomonoester has no effect on the relative yields of products. On the other hand, addition of methanol to the reaction results in the formation of a phosphodiester at the expense of pyrophosphate. No ester of polyphosphoric acid can be detected by paper electrophoresis.

The rate and efficiency of phosphoryl transfer when acetonitrile (or benzonitrile) is used is increased to a marked extent by the addition of certain reactive halides.

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[3] G. W. Kenner, C. B. Reese, and Sir Alexander Todd, *J. Chem. Soc.*, 1958, 546.

[4] F. Cramer and M. Winter, *Chem. Ber.*, 1959, **92**, 2761.

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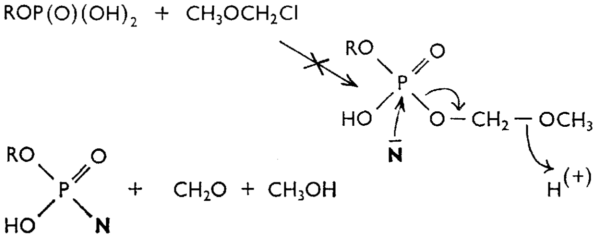
[7] V. M. Clark, D. W. Hutchinson, and P. F. Varey, *Chem. Comm.*, 1966, 309.

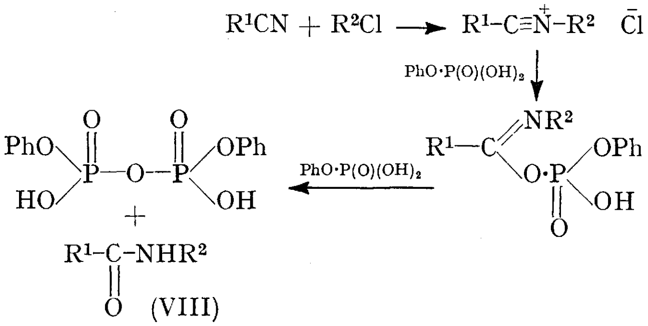
Thus, by use of (VI; $R = 4\text{-MeO}\cdot C_6H_4$) in acetonitrile under reflux, monophenyl dihydrogen phosphate was converted in almost quantitative yield to *sym*-diphenyl pyrophosphate within 1 hr.

The solvolysis of (VI; R = MeO) is 10^{14} times faster[8] than the comparable reaction of methyl chloride, and this ready displacement of halide can be attributed to the stability of the oxygen-substituted carbonium ion produced. Chloromethyl ethers are powerful alkylating agents and might be expected to react with phosphoric acids to give (VII). This is a P–XYZ system,[1] protonation of which might be expected to lead to phosphoryl transfer. However, we have been unable to observe any reaction between a phosphomonoester and an α-halogeno-ether in a variety of solvents (*e.g.* chloroform, nitromethane, and tetrahydrofuran). In contrast, when phenyl or 4-chlorophenyl dihydrogen phosphate is heated under reflux in dry acetonitrile with an excess of (VI; R = MeO), the corresponding *P*¹*P*²-diesters of pyrophosphoric acid are produced in near quantitative yield. The mono- and di-*N*-tetrabutylammonium salts of phenyl dihydrogen phosphate react in an analogous manner. Similar conversions into pyrophosphate are observed when disilver phenyl phosphate is used and when (VI; R = EtO, $4\text{-Cl}\cdot C_6H_4O$, or $2,4\text{-}Cl_2C_6H_3O$) is used as the halogenomethyl ether. No enhancement of phosphoryl transfer is observed when n-butyl iodide, or dibromomethane is used.



The products of the reaction are consistent with the formation of a nitrilium salt analogous to that postulated as an intermediate in the Ritter reaction.[9,10] This could give rise to the *N*-alkylated imidoyl phosphate (I) which in turn would lead to the observed products. Although we have been unable to detect any interaction between (VI; R = MeO) and a nitrile in the absence of phosphate, such nitrilium salts are known to be formed in the presence of strong Lewis acids,[11,12] and could be present in our reaction mixtures at low concentration.

NN'-methylene bisamides (VIII; $R^2 = CH_2\cdot NH\cdot COR^1$), methyl acetate, methyl chloride, and dimethoxymethane are among the non-phosphorus-containing products. The formation of (VIII; $R^2 = CH_2\cdot NH\cdot COR^1$) rather than (VIII; $R^2 = CH_2\cdot OMe$) is unexpected; however, *N*-hydroxymethyl amides are converted into (VIII; $R^2 = CH_2\cdot NH\cdot COR^1$) in the presence of acid.[13] *N*-alkoxymethyl amides resemble acetals and are known[14] to form *NN'*-methylene bisamides under acidic conditions. The formation of dimethoxymethane indicates the liberation of methanol during the reaction and the formation of methyl phenyl phosphate, in competition with pyrophosphate, supports this proposal. In the case of acetonitrile the other products probably arise from the acid-catalysed reaction between the nitrile and methanol; methyl acetate is observed in appreciable quantities only when the reaction is carried out in a sealed tube.


(VIII)

The alkyl halide-promoted phosphorylation reaction is sensitive not only to water (which inhibits the reaction by hydrolysis of both the halogeno-ether and the imidoyl phosphate) but also to alcohols. Addition of small quantities of alcohol gives rise to phosphodiesters in up to 50% yield; large amounts of alcohol lower the yield by reacting with the halogeno-ether.

The best yield of pyrophosphate (>90%) is obtained with a fifteen-fold excess of (VI; R = MeO) over phenyl dihydrogen phosphate in solution in (III; R = Me). This nitrile is the most convenient for the subsequent isolation of products; however, similar, efficient phosphoryl transfer occurs with (III; R = Ph or $Ph\cdot CH_2$). By use of scrupulously dried acetonitrile as solvent, an increased amount of phosphodiester, together with a triester of pyrophosphoric acid, is obtained. When dry potassium cyanide, suspended in tetrahydrofuran under reflux, is used in place of (III), *P*¹*P*²-diphenyl pyrophosphate (50%) is formed.

Replacement of (VI; R = MeO) with (VI; R = MeS) gives rise to *P*¹*P*²-diphenyl pyrophosphate as the only phosphorus-containing product. No diesters can be detected. This is in accordance with a previous observation[15] that sulphides are poor nucleophiles for attack at a phosphoryl centre. Moreover no phosphodiester is detectable when a sulphide is added to the reaction mixture under conditions in which an alcohol gives a substantial amount of phosphodiester.

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[9] J. J. Ritter and P. P. Minteri, *J. Amer. Chem. Soc.*, 1948, **70**, 4045.

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[14] J. W. Weaver, H. A. Schuyten, J. G. Frick, and J. D. Reid, *J. Org. Chem.*, 1951, **16**, 1111.

[15] I. Dostrovsky and M. Halmann, *J. Chem. Soc.*, 1953, 508.

Carboxylic acids and salts of diesters of phosphoric acid do not participate in acyl transfer under the same conditions as phosphomonoesters. This lack of reactivity is due, presumably, to the failure to form an imidoyl ester.

4-Methoxybenzyl chloride is a vinylogue of (VI; R = MeO). It undergoes extremely rapid solvolysis,[16] and might be expected to be an efficient promoter of phosphoryl transfer in the presence of nitriles. This is the case. When equimolar amounts of phenyl dihydrogen phosphate and (VI; R = 4-MeO·C_6H_4) or the corresponding bromide are dissolved in dry acetonitrile and the mixture is heated under reflux for 1 hr., a quantitative yield of P^1P^2-diphenyl pyrophosphate is obtained. The only other detectable product, apart from the hydrogen halide, is (VIII; R^1 = Me, R^2 = 4-MeO·C_6H_4). No reaction was observed between either phenyl dihydrogen phosphate and (VI; R = 4-MeO·C_6H_4), or (III; R = Me) and (VI; R = 4-MeO·C_6H_4) under similar conditions. The reaction apparently proceeds in a manner analogous to that for the aliphatic halogeno-ethers. Although the substituted benzyl halides offer an advantageous method for the preparation of pyrophosphates, their use for the phosphorylation of alcohols is unsatisfactory: the halides react too rapidly with the alcohols.

Paper electrophoretic examination of the reaction mixture from phenyl dihydrogen phosphate, acetonitrile, and (VI; R = 4-MeO·C_6H_4) indicated the presence of a trace of a $P^1P^2P^3$-triester of linear triphosphoric acid, which was identified by comparison with the product formed in the reaction of *NN'*-dicyclohexylcarbodi-imide with phenyl dihydrogen phosphate.[2] This suggests that a triester of trimetaphosphoric acid is an intermediate: such esters undergo rapid hydrolysis to the linear triphosphate.[17]

The rates of solvolysis of substituted benzyl chlorides, under S_N1 conditions,[16] are in the order *para*- > *ortho* ≫ *meta*-methoxybenzyl chloride; the rate for the latter is similar to that for benzyl chloride itself. This order of reactivity is reflected in the phosphorylation reaction, as (VI; R = 2-MeO·C_6H_4) reacts more slowly than the 4-isomer; (VI; R = 3-MeO·C_6H_4) and (VI; R = Ph) do not enhance phosphoryl transfer.

The use of alkylating agents, especially activated benzyl halides, to promote phosphoryl transfer can be extended to include *gem*-dihalides.[18,19]

EXPERIMENTAL

Paper chromatography was carried out with Whatman no. 30 paper [solvent, propan-2-ol–ammonia–water (8 : 1 : 1)]; phosphate was detected by the method of Hanes and Isherwood.[20] The relative amounts of phosphate esters were determined by the method of Usher.[21] Acetonitrile was purified by being heated under reflux over phosphoric oxide and then distilled. It was further purified by treatment with anhydrous potassium carbonate followed by fractional distillation. All reactions were carried out with exclusion of moisture.

Reactions of Phosphates with Nitriles in the Presence of α-Halogeno-ethers.—Phosphoryl transfer in acetonitrile. (a) *Pyrophosphate formation.* Phenyl dihydrogen phosphate (0·2 mmole) and various chloromethyl ethers, dissolved in acetonitrile (5 ml.), were heated under reflux for 24 hr. The yields of P^1P^2-diphenyl pyrophosphate and diester, determined chromatographically, are given in Table 1.

TABLE 1

Halogeno-ether (VI) (15 molar excess)	Product yield (%) Diphenyl pyrophosphate	Diester PhO(HO)P(:O)OR
R = MeO	94	5
R = MeO *	75	
R = EtO	65	30
R = 4-Cl·C_6H_4·O	90	10
R = 2,4-Cl_2·C_6H_3·O	70	10

* With a 2 molar excess of (VI) reaction was complete after 3 hr.

(b) *Effect of water on the reaction.* In general, addition of a five-fold excess of water over phenyl dihydrogen phosphate reduced the yield of pyrophosphate, after 24 hr., to *ca.* 50%.

(c) *Isolation of pyrophosphates.* Phenyl dihydrogen phosphate (0·522 g., 3 mmoles) was added to (VI; R = MeO) (3·62 g., 45 mmoles) dissolved in acetonitrile (25 ml.), and the solution was heated under reflux for 12 hr. When cool, the solution was evaporated under reduced pressure and the residual gum was taken up in acetone (50 ml.) to which cyclohexylamine (2 ml.) was then added. The mixture was kept at 0° for 1 hr., then filtered, and the precipitate was crystallised from water (50 ml.) containing cyclohexylamine (a few drops). Colourless platelets of dicyclohexylammonium P^1P^2-diphenyl pyrophosphate (0·715 g., 82%) were obtained; m.p. 260—261° (Found: C, 54·2; H, 6·9; N, 5·0; P, 11·45. Calc. for $C_{24}H_{38}N_2O_7P_2$: C, 54·6; H, 7·2; N, 5·0; P, 11·75%). Dicyclohexylammonium P^1P^2-bis-(4-chlorophenyl) pyrophosphate was obtained (57%) by a similar method; m.p. 270—271° (Found: C, 48·2; H, 6·2; P, 10·4. Calc. for $C_{24}H_{36}Cl_2N_2O_7P_2$: C, 48·2; H, 6·0; P, 10·4%).

(d) *Pyrophosphate from phosphate salts.* Disilver phenyl phosphate (0·776 g., 2 mmoles) was suspended in acetonitrile and a 15-fold excess of (VI; R = MeO) was added. The heterogeneous mixture was heated under reflux for 24 hr. and then cooled. Silver chloride (0·522 g., 91%) was filtered off, and the filtrate was worked up as described earlier to give dicyclohexylammonium P^1P^2-diphenyl pyrophosphate (0·290 g., 55%).

Identification of products not containing phosphorus. (a) *Methylene* NN'*-bisacetamide.* The chloride (VI; R = MeO) (7·26 g., 90 mmoles) was added to phenyl dihydrogen phosphate (1·05 g., 6 mmoles) in acetonitrile (50 ml.) and heated under reflux for 24 hr. The solvent was removed under reduced pressure to leave a gum which was triturated with a little chloroform until crystallisation commenced. The crystals (178 mg.) were filtered off and washed with ethanol. Repeated recrystallisation from ethanol or benzene–ethyl

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[17] F. Cramer and H. Hettler, *Chem. Ber.*, 1958, **91**, 1181.

[18] V. M. Clark, D. W. Hutchinson, and P. F. Varey, *Chem. Comm.*, 1967, 32; *J. Chem. Soc.* (*C*), 1968, 3062.

[19] H. Kaye and Lord Todd, *J. Chem. Soc.* (*C*), 1967, 1420.

[20] C. S. Hanes and F. A. Isherwood, *Nature*, 1949, **164**, 1107.

[21] D. A. Usher, *J. Chromatog.*, 1963, **12**, 262.

acetate (3 : 1) failed to remove the last traces of phosphate. The product had i.r. and n.m.r. spectra identical with those of an authentic sample of methylene *NN'*-bisacetamide (Found: C, 46·4; H, 7·9; N, 21·6. Calc. for $C_5H_{10}N_2O_2$: C, 46·2; H, 7·7; N, 21·5%).

(b) *Methyl acetate, dimethoxymethane, methyl chloride, and methyl formate.* 4-Chlorophenyl dihydrogen phosphate (1·68 g., 8 mmoles), the chloride (VI; R = MeO) (9·68 g., 120 mmoles) and acetonitrile (9·84 g., 240 mmoles) were sealed in a tube under an atmosphere of nitrogen and heated at 60° for 20 hr. The tube was cooled in acetone–solid carbon dioxide, opened, and connected to a gas cell. The tube was warmed gently. The i.r. spectrum of the volatile material showed all the bands characteristic of methyl chloride.[22] The upper layer of the residual two-phase mixture was separated and examined by g.l.c. (Wilkens Autoprep, 20 ft. × 3/8 in., 30% S.E. 30 column, 80°); the four compounds observed were identified as methyl formate, dimethoxymethane, methyl acetate, and acetonitrile by comparison of retention times and n.m.r. spectra, with those of authentic samples.

Phosphoryl transfer in very dry acetonitrile. Acetonitrile was dried by applying the usual procedure three times; each stage was completed by distillation through a Fenske column (45 cm.). The nitrile (b.p. 81·5°) thus obtained (5 ml.) was used immediately to dissolve phenyl dihydrogen phosphate (0·035 g., 0·2 mmole) and (VI; R = MeO) (0·242 g., 3 mmoles). This solution was heated under reflux for 24 hr. and then examined by electrophoresis and paper chromatography. The latter technique revealed the presence of a compound (33%) R_F 0·74 which, on electrophoresis at pH 8·3, had a mobility of 0·42 relative to phenyl phosphate (1·00). It was isolated by preparative paper chromatography on Whatman 3 MM paper. After development of the chromatogram the compound was eluted with water, and the aqueous solution was concentrated (<35°/1 mm.) and divided into four portions. Sample (i) was rechromatographed and found to be unchanged. Sample (ii) was freeze-dried and the residue was dissolved in pyridine–water (1 : 1, v/v; 9·4 ml.). After 24 hr., paper chromatography revealed the presence of phenyl phosphate, methyl phenyl phosphate, and a trace of diphenyl pyrophosphate. Sample (iii) was also freeze-dried and the residue was dissolved in pyridine–methanol (1 : 1, v/v; 0·4 ml.). After 24 hr., paper chromatography indicated that methyl phenyl phosphate was the major product. Paper chromatographic examination of the aqueous sample (iv) showed a slow non-specific breakdown to phenyl phosphate, methyl phenyl phosphate, and P^1P^2-diphenyl pyrophosphate. This behaviour was consistent with the compound being P^1-methyl P^1P^2-diphenyl pyrophosphate.

Phosphoryl transfer in benzonitrile. Phenyl dihydrogen phosphate (0·2 mmole) together with an α-chloroether (3 ml.) were dissolved in benzonitrile and heated at 100° for 24 hr.; the mixture was then analysed by paper chromatography (see Table 2).

TABLE 2

Ether (VI)	Product yield (%) Diphenyl pyrophosphate	Diester $PhO(HO)P(:O)OR$
R = MeO	75	15
R = EtO	55	45

A reaction conducted at 60° for 20 hr. in a sealed tube with phenyl dihydrogen phosphate (0·70 g., 4 mmoles), (III; R = Ph) (6·3 g., 60 mmoles), and (VI; R = MeO) (4·84 g., 60 mmoles) gave methyl phenyl phosphate (50%), isolated by extraction of the contents of the tube with water and concentration of the aqueous phase to a small volume. This was adjusted to pH 8 with 0·01M-triethylammonium hydrogen carbonate solution and chromatographed on a DEAE cellulose column (34 × 2 cm.). The first u.v.-absorbing material to be eluted was evaporated to dryness under reduced pressure. The residue was dissolved in acetone (200 ml.) and the solution was filtered. After addition of cyclohexylamine (1 ml.), the solution was concentrated to a small volume and set aside at 0°. Cyclohexylammonium methyl phenyl phosphate separated as colourless crystals (0·444 g., 40%), m.p. 151—152° (Found: C, 54·8; H, 7·9; N, 5·2; P, 10·5. Calc. for $C_{13}H_{22}NO_4P$: C, 54·7; H, 7·7; N, 4·9; P, 10·8%). From a reaction in a sealed tube, under similar conditions, crystalline methylene *NN'*-bisbenzamide (60%; m.p. 224—225°) was obtained (Found: C, 70·4; H, 5·9; N, 10·7. Calc. for $C_{15}H_{14}N_2O_2$: C, 70·9; H, 5·5; N, 10·0%). G.l.c. of the mother liquors (Wilkens Autoprep. 20 ft. × 3/8 in., 30% S.E. 30 column, 80°) showed the presence of methyl chloride, dimethoxymethane, and methyl benzoate as well as (III; R = Ph) and (VI; R = MeO). All volatile compounds were identified by comparison of retention times and n.m.r. spectra with those of authentic samples. Cyclohexylammonium ethyl phenyl phosphate (0·110 g., 10%; m.p. 110—112°) (Found: C, 56·0; H, 8·1; P, 10·2. Calc. for $C_{14}H_{24}NO_4P$: C, 55·8; H, 8·0; P, 10·3%) was isolated by a procedure similar to that outlined above when (VI; R = EtO) was used.

Phosphoryl transfer with the nitrile (III; R = $PhCH_2$). Phenyl dihydrogen phosphate (0·2 mmole) was added to (VI; R = MeO) (3 mmoles) in (III; R = $PhCH_2$) (5 ml.) and the mixture was heated at 100° for 24 hr. Chromatographic analysis revealed the presence of P^1P^2-diphenyl pyrophosphate (70%) and a phosphodiester (10%). From a similar reaction conducted on a larger scale, methylene *NN'*-bis-(phenylacetamide) was isolated; m.p. 218—219° (Found: C, 72·3; H, 6·7; N, 10·1. Calc. for $C_{15}H_{18}N_2O_2$: C, 72·3; H, 6·3; N, 9·9%). The presence of methyl chloride, dimethoxymethane, and methyl phenylacetate was confirmed by g.l.c.

Phosphoryl transfer promoted by the chloride (VI; R = MeS). The chloride (VI; R = MeS)[23] (0·193 g., 2 mmoles) was added dropwise with stirring to a solution of phenyl dihydrogen phosphate (0·07 g., 0·4 mmole) in acetonitrile (5 ml.). The mixture was heated under reflux for 5 hr., cooled, filtered to remove a trace of sulphur, and worked up in the usual manner to yield dicyclohexylammonium P^1P^2-diphenyl pyrophosphate (0·088 g., 83%). When this reaction was repeated on a larger scale [30 mmoles of (VI)] and the mixture distilled under reduced pressure bismethylthiomethane, b.p. 60°/25 mm. was obtained. Analysis of the n.m.r. spectrum of the mixture before distillation indicated that the bismethylthiomethane was present in *ca.* 60% yield.

Phosphorylation with potassium cyanide. A suspension of dry potassium cyanide (3 mmoles) in tetrahydrofuran (5 ml.) containing phenyl dihydrogen phosphate (0·2

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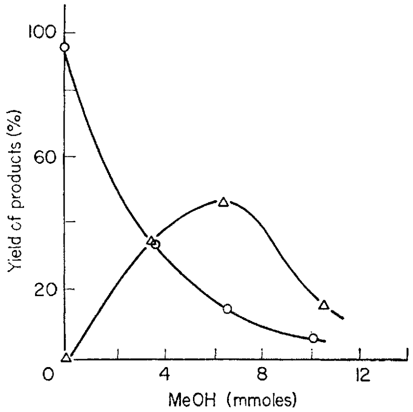
[22] R. H. Pierson, A. N. Fletcher, and E. St. C. Gantz, *Analyt. Chem.*, 1956, **28**, 1218.

[23] W. E. Truce, B. H. Birum, and E. T. McBee, *J. Amer. Chem. Soc.*, 1952, **74**, 3594.

mmole) and (VI; R = MeO) (3 mmoles) was heated under reflux for 20 hr. and then analysed chromatographically; P^1P^2-diphenyl pyrophosphate (55%) had been formed but no diester was present.

Phosphorylation of alcohols. Methanol was added to solutions of phenyl dihydrogen phosphate (0·2 mmole) and (VI; R = MeO) (3 mmoles) in (III; R = Me) (5 ml.) and each solution was heated under reflux for 24 hr., then analysed by paper chromatography. The yield varied as shown in the Figure.



Variation in yield of methyl phenyl phosphate (—△—) and P^1P^2-diphenyl pyrophosphate (—○—) with amount of methanol added

When methanol was added *after* 24 hr. and the heating under reflux was continued for a further 24 hr., the pyrophosphate was destroyed, and methyl phenyl phosphate was formed in *ca.* 50% yield.

Attempted reaction with a salt of a phosphodiester. Silver diphenyl phosphate and (VI; R = MeO) were heated together in acetonitrile as described for silver monophenyl phosphate. After 24 hr., t.l.c. on silicic acid did not show the presence of any tetraesters of pyrophosphoric acid. N.m.r. analysis of the mixture gave no evidence for the formation of dimethoxymethane.

Attempted reaction with a carboxylic acid. When benzoic acid (1·2 g., 10 mmoles) and (VI; R = MeO) (12·0 g., 150 mmoles) were heated in acetonitrile under reflux for 24 hr., no change in the i.r. spectrum of the solution was observed.

Phenyl dihydrogen phosphate and various nitriles. (a) *Acetonitrile.* Phenyl dihydrogen phosphate (0·035 g., 0·2 mmole) was dissolved in (III; R = Me) (5 ml.); there was no reaction in the cold, but P^1P^2-diphenyl pyrophosphate was slowly formed when the mixture was heated under reflux. After several days, the yield of pyrophosphate was *ca.* 60%. Further heating did not lead to any increase in yield. A similar conversion into pyrophosphate was observed when a molar solution of phenyl dihydrogen phosphate in acetonitrile was used. In this case, electrophoresis at pH 8·3 after 41 hr. revealed that phenyl phosphate and diphenyl pyrophosphate were the only phosphorus-containing materials. When a two-fold excess of water was added, the yield of pyrophosphate fell to 20%.

(b) *Benzo- or phenylaceto-nitrile.* Solutions of phenyl dihydrogen phosphate in (III; R = Ph or PhCH_2) were heated under reflux for several days; again the conversion to P^1P^2-diphenyl pyrophosphate never exceeded 60%.

Reaction with methanol. A solution of phenyl dihydrogen phosphate (1·05 g., 6 mmoles) in acetonitrile was heated under reflux for 40 hr.; methanol (0·096 g., 3 mmoles) was then added and heating was continued for a further 24 hr. Methyl phenyl phosphate (35%) was formed at the expense of pyrophosphate.

Interaction between α-chloro-ethers and nitriles. A mixture of acetonitrile and (VI; R = MeO) (1 : 1, v/v) was heated in a sealed tube at 60°; there was no change in the i.r. and n.m.r. spectra after 24 hr., nor was there any spectroscopic change when a similar mixture of (III; R = Ph) and (VI; R = MeO) was heated at 100° in a sealed tube.

Attempted reaction between a phosphomonoester and an α-chloro-ether. When (VI; R = MeO) (12 mmoles) and phenyl dihydrogen phosphate (0·8 mmole) were heated together in a sealed tube at 60° for 24 hr., the phosphate was recovered unchanged. A similar result was obtained when dimethoxymethane was used instead of (VI; R = MeO). When mixtures of phosphate and (VI; R = MeO) were heated under reflux in chloroform, nitromethane, carbon tetrachloride, tetrahydrofuran, or *NN*-dimethylformamide, no pyrophosphate could be detected by paper chromatography after 24 hr.

Attempted replacement of an α-chloro-ether with other halides. Solutions of phenyl dihydrogen phosphate (0·2 mmole) in acetonitrile (5 ml.) were heated under reflux for 24 hr. in the presence of the following halides: n-butyl iodide, t-butyl chloride, and dibromomethane. In no case was there any enhancement of the reaction between phenyl dihydrogen phosphate and the nitrile.

Phosphoryl transfer with 4-methoxybenzyl halides. The benzyl halide (VI; R = $4\text{-MeO·C}_6\text{H}_4$) (1·88 g., 6 mmoles) was added to a solution of phenyl dihydrogen phosphate (1·05 g., 6 mmoles) in (III; R = Me) (5 ml.) and the mixture was heated under reflux for 1 hr. Hydrogen chloride was evolved. The mixture was cooled and dicyclohexylammonium P^1P^2-diphenyl pyrophosphate (1·24 g., 81%; m.p. 260—261°) was isolated in the usual manner. When 4-methoxybenzyl bromide was used under the same conditions, paper chromatographic examination indicated near quantitative formation of pyrophosphate. *N*-4-Methoxybenzylacetamide (40%; m.p. 95—96°) was isolated by t.l.c. on alumina from the reaction with the chloride, and was shown to be present in the reaction with the bromide. When the reaction with (VI; R = $4\text{-MeO·C}_6\text{H}_4$) was repeated and the mixture cooled after 10 min., electrophoresis at pH 8·3 revealed a new compound (*ca.* 1%, relative mobility 0·65) in addition to phenyl phosphate (relative mobility 1·00), and P^1P^2-diphenyl pyrophosphate (relative mobility 0·84). Treatment of phenyl dihydrogen phosphate (0·2 mmole) in pyridine (1 ml.) with a solution of *NN'*-dicyclohexylcarbodi-imide (1 mmole) in pyridine (1 ml.) gave a compound with the same electrophoretic mobility at pH 8·3. This is taken to be $P^1P^2P^3$-triphenyl triphosphate.[2] From the reaction between 4-chlorophenyl dihydrogen phosphate, and (VI; R = $4\text{-MeO·C}_6\text{H}_4$) in solution in (III; R = Ph), a high yield of pyrophosphate (80%) could be detected (by paper chromatography) after 6 hr. No phosphoryl transfer was observed when phenyl dihydrogen phosphate was heated in benzene under reflux with an equivalent amount of (VI; R = $4\text{-MeO·C}_6\text{H}_4$) for 2 hr. Moreover, there was no detectable change in the n.m.r. spectrum of a mixture of (III; R = Me) and (VI; R = $4\text{-MeO·C}_6\text{H}_4$) heated under reflux for 4 hr.

Phosphorylation of alcohols. The reaction between (VI; R = $4\text{-MeO·C}_6\text{H}_4$) and phenyl dihydrogen phosphate could be redirected by the addition of an excess of methanol after 1 hr. In the latter case, after a further 2 hr. under reflux, methyl phenyl phosphate (50%) was detected by paper chromatography.

Phosphoryl transfer with tetra-n-butylammonium salts of phenyl phosphoric acid. The mono- and the bis-tetra-n-butylammonium salts of phenyl phosphoric acid (0·4 mmole) were separately added to solutions of (VI; R = 4-MeO·C_6H_4)(0·8 mmole) in acetonitrile (5 ml.) and the mixtures were heated under reflux for 1 hr. Paper chromatographic examination of the two mixtures revealed the formation of pyrophosphate both from the mono- (40%) and from the bis-salt (95%).

Phosphoryl transfer with substituted benzyl halides. The benzyl halide (6 mmoles) and phenyl dihydrogen phosphate (6 mmoles) were dissolved in (III; R = Me) (5 ml.) and heated under reflux for 6 hr. Paper chromatographic analysis gave the results shown in Table 3.

TABLE 3

Halide	Yield (%) of P^1P^2-diphenyl pyrophosphate
None	35
(VI; R = Ph)	35
(VI; R = 3-MeO·C_6H_4)	35
(VI; R = 2-MeO·C_6H_4)	60
(VI; R = 4-MeO·C_6H_4)	95
4-Methoxybenzyl cyanide	50

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