The Synthesis of Tertiary Phosphine Oxides from Elemental Phosphorus[1a]

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Received September 20, 1962

Nucleophilic intermediates produced in the reaction of potassium hydroxide with white phosphorus were trapped by acrylonitrile or acrylamide to give tris(2-cyanoethyl)phosphine oxide and tris(2-carbamoylethyl)phosphine oxide in 53 and 74% yields, respectively. Ethyl acrylate reacted sluggishly to give tris(2-carbethoxyethyl)phosphine oxide in 8% yield. The mechanism is discussed.

White phosphorus reacts with aqueous hydroxide ions to give hydrogen, phosphine, and the hypophosphite and phosphite ions. The reaction can be described by the following equations,[1b] but the processes involved are complex.

$$P_4 + 4OH^- + 4H_2O \longrightarrow 4H_2PO_2^- + 2H_2$$

$$P_4 + 4OH^- + 2H_2O \longrightarrow 2HPO_3^{=} + 2PH_3$$

When the reaction is carried out with sodium hydroxide in aqueous ethanol, hydrogen is evolved and a solution of a dark red intermediate is obtained. The intermediate is unstable, particularly at higher temperatures, evolving hydrogen and phosphine and leaving sodium hypophosphite as the remaining product.[2] Acidification of the dark red solution precipitates a greenish yellow solid having a composition corresponding closely to P_4O.[2,3] Addition of methyl iodide to the dark red solution followed by oxidation with nitric acid has been found to give methylphosphonic acid, dimethylphosphinic acid, and trimethylphosphine oxide, thus demonstrating the nucleophilic character of the intermediate.[4] Isoamyl iodide similarly gave isoamylphosphonic acid along with a small amount of diisoamylphosphinic acid.[4] These results encouraged us to search for other nucleophilic reactions of intermediates produced in the white phosphorus–hydroxide system.

Initial experiments were carried out with acrylonitrile as the trapping agent, since it has been demonstrated that acrylonitrile reacts rapidly with both trivalent[5] and pentavalent phosphorus anions,[6] but is not seriously subject to side reactions under the conditions we wished to employ.

Results

Addition of aqueous potassium hydroxide to a mixture of finely divided phosphorus, acrylonitrile, and acetonitrile at 30–35° resulted in the formation of tris-(2-cyanoethyl)phosphine oxide (Table I). Other products containing the 2-cyanoethyl group were not found, although infrared examination of reaction residues indicated small amounts of amide and carboxylic acid hydrolysis products.

TABLE I

REACTIONS OF ACRYLONITRILE WITH WHITE PHOSPHORUS AND POTASSIUM HYDROXIDE IN ACETONITRILE AT 30–35°[a]

Acrylonitrile, moles	KOH, moles	Acetonitrile, ml.	Yield phosphine oxide,[b] %	Recovered phosphorus, %
0.75	0.25[c]	95	36	5
.82	.25[c]	90	45	Trace
1.00	.28[d]	90	42	Trace
1.00	.38[d]	90	43	Trace
1.12	.36[d]	150	53	Trace
1.5	.30[d]	100	22	Trace

[a] Reactions are based on 0.5 g.-atom of phosphorus. [b] Yields are based on starting phosphorus. [c] Aqueous potassium hydroxide, 5 *N*. [d] Aqueous potassium hydroxide, 10 *N*.

In several experiments potassium phosphite and potassium hypophosphite were identified as inorganic byproducts. Generally, only traces of unchanged phosphorus remained at the end of the reactions.

As indicated in Table I, the yield of tris(2-cyanoethyl)phosphine oxide increased from 36 to 53% as the ratio of moles of acrylonitrile to gram-atoms of phosphorus was varied from 1.5 to 2.25. High acrylonitrile concentrations would be expected to favor the formation of organic products at the expense of inorganic side reactions. Unexpectedly, however, a large excess of acrylonitrile gave a reduced yield.

Reaction of acrylamide with phosphorus and potassium hydroxide gave tris(2-carbamoylethyl)phosphine oxide. The results of a number of experiments carried out in ethanol are summarized in Table II. As the ratio of moles of acrylamide to gram-atoms of phosphorus was increased from 1.5 to 3.8, the percen-

TABLE II

REACTIONS OF ACRYLAMIDE WITH WHITE PHOSPHORUS AND POTASSIUM HYDROXIDE IN ETHANOL[a]

Acrylamide, moles	KOH, moles	Temp., °C.	Yield phosphine oxide, %[b]
0.30	0.10[c]	30–35	20
.40	.10[d]	0–5	47
.40	.18[c]	0–5	48
.40	.05[d]	30–35	32
.40	.10[d]	30–35	46
.40	.10[d]	65–70	31
.75	.10[c]	30–35	69
1.2	.10[d]	−5 to 0	74
0.75	K_2CO_3 0.05	85	42[e]

[a] Reactions were carried out with 0.2 g.-atom of phosphorus and 100 ml. of 2B (denatured) ethanol. Absolute ethanol gave identical results under several conditions examined. [b] Yields are based on phosphorus. [c] Aqueous potassium hydroxide, 10 *N*. [d] Aqueous potassium hydroxide 10 *N* diluted to 25 ml. with 2B ethanol. [e] Ten per cent of unchanged phosphorus was recovered.

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[1] (a) This is the third paper in a series dealing with the preparation of organophosphorus compounds directly from elemental phosphorus. For the second paper see *J. Org. Chem.*, **28**, 473 (1963); (b) J. R. Van Wazer, "Phosphorus and Its Compounds," Interscience Publishers. Inc., New York, N. Y., 1958, p. 356; (c) pp. 14, 55, 222.

[2] A. Michaelis and M. Pitsch, *Ber.*, **32**, 337 (1899); *Ann.*, **310**, 45 (1899).

[3] D. L. Chapman and F. A. Lidbury, *J. Chem. Soc.*, **75**, 973 (1899); A. Michaelis and K. von Arend, *Ann.*, **314**, 259 (1901); C. H. Burgess and D. L. Chapman, *J. Chem. Soc.*, **79**, 1235 (1901); A. Stock, *Chem. Z.*, **33**, 1354 (1909).

[4] V. Auger, *Compt. rend.*, **139**, 639 (1904).

[5] M. M. Rauhut, I. Hechenbleikner, H. A. Currier, F. C. Schaefer, and V. P. Wystrach, *J. Am. Chem. Soc.*, **81**, 1103 (1959).

[6] R. C. Miller, G. S. Bradley, and L. A. Hamilton, *ibid.*, **78**, 5299 (1956); M. M. Rauhut and H. A. Currier, *J. Org. Chem.*, **26**, 4628 (1961).

tage of starting phosphorus converted to tris(2-carbamoylethyl)phosphine oxide increased from 20 to 69%. A further increase in the acrylamide–phosphorus ratio to 6:1, however, improved the yield only to 74%, suggesting that this yield approached the maximum. The reaction temperature was not critical between 0 and 35°; at higher temperatures, lower yields were obtained, possibly because of amide hydrolysis.

The manner of adding the reactants had little effect on yields, and the ratio of equivalents of potassium hydroxide to gram atoms of phosphorus was not critical above a ratio of about 0.5 to 1. In an experiment where potassium carbonate replaced potassium hydroxide, tris-(2-carbamoylethyl)phosphine oxide was obtained in 42% yield after three hours at reflux, and 10% of the phosphorus was recovered unchanged.

Results obtained from reactions of acrylamide with phosphorus and potassium hydroxide carried out in a number of solvents are summarized in Table III. Ethanol provided the best yield; dimethyl sulfoxide, tetrahydrofuran, and methanol gave somewhat poorer results. The reaction failed to take place in water under the conditions studied, possibly because of the extreme insolubility of phosphorus (3×10^{-4} g. per 100 g. of water).[7]

TABLE III

REACTIONS OF PHOSPHORUS, ACRYLAMIDE, AND 10 *N* AQUEOUS POTASSIUM HYDROXIDE IN VARIOUS SOLVENTS[a]

Solvent	Yield, %[b]
Water	0[c]
Methanol[d]	37
Ethanol (absolute)	48
50% aqueous ethanol	14
2-Propanol	14
2-Ethoxyethanol	16
t-Butyl alcohol	[e]
Acetone	[e]
Tetrahydrofuran	40
Dimethyl sulfoxide	42
N,*N*-Dimethylformamide	26
Pyridine	19
Acetonitrile	[e]

[a] Reactions carried out with 6.2 g. (0.2 g.-atom) of phosphorus, 31.9 g. (0.45 mole) of acrylamide, and 10 ml. (0.1 equivalent) of 10 *N* aqueous potassium hydroxide in 100 ml. of solvent at 30–35°. [b] Yields are based on phosphorus. [c] The phosphorus was recovered unchanged. [d] The reaction temperature was −5°. [e] An insoluble gum formed, preventing completion of the reaction.

Reaction of ethyl acrylate with phosphorus and potassium hydroxide proceeded sluggishly, giving tris(2-carbethoxyethyl)phosphine oxide (8% conversion) and tris(2-carbethoxyethyl)phosphine (4%), leaving 51% of the phosphorus unchanged. The tris(2-carbethoxyethyl)phosphine may result from the base-catalyzed addition of phosphine (from the competing normal phosphorus–hydroxide reaction) to the ethyl acrylate.

Since the deeply colored, metastable compound produced in the reaction of aqueous ethanolic hydroxide alone with phosphorus[2] evidently possesses nucleophilic properties,[4] the possibility existed that it was a key intermediate in the tertiary phosphine oxide reaction. If this were the case, addition of the colored compound to the olefinic double bond would have to be rapid, since in none of the experiments with acrylamide or acrylonitrile was even the transient appearance of a red color observed. To test this point, an ethanolic solution of acrylamide was added to a separately prepared solution of the red compound. The color was not discharged, and there was no other evidence of reaction. Even after a prolonged reaction period only a minor amount of tris(2-carbamoylethyl)phosphine oxide was obtained, evidently the consequence of incomplete initial conversion of phosphorus to the metastable compound. Thus it is clear that the red metastable compound is not an intermediate in the phosphorus–hydroxide–acrylamide reaction, and that the acrylamide traps an earlier intermediate in the phosphorus–hydroxide reaction sequence. Similarly, potassium hypophosphite does not appear to be directly involved in the tertiary phosphine oxide reaction since it was found to be substantially unchanged in the presence of potassium hydroxide and acrylonitrile under conditions used for the preparation of tris(2-cyanoethyl)phosphine oxide.

Discussion

Both acrylonitrile and acrylamide efficiently trap nucleophilic intermediates produced in the reaction of potassium hydroxide with white phosphorus, with the result that corresponding tertiary phosphine oxides are obtained in high yields. The results indicate that the tertiary phosphine oxides are formed according to the following balanced equation, which requires that the phosphorus be concurrently oxidized and reduced.

$$\mathrm{P_4 + 2KOH + 4H_2O + 9CH_2{=}CHR \longrightarrow 3(RCH_2CH_2)_3P{=}O + K_2HPO_3}$$

The detailed mechanism is necessarily complex, since each of the six phosphorus–phosphorus bonds in the P_4 tetrahedron must be broken and with each cleavage at least one new organophosphorus intermediate must result. However, the high yields of tertiary phosphine oxides obtained, and the absence of substantial amounts of other organophosphorus products (such as phosphonic or phosphinic acids) suggest that the reaction proceeds by a highly systematic and selective series of steps. The detailed mechanism on p. 480 is tentatively suggested on the basis of the results obtained.

Attack by hydroxide ion on the P_4 tetrahedron cleaves the first phosphorus–phosphorus bond giving the phosphide anion I. Addition of the phosphide ion to acrylonitrile in step B gives carbanion II, and reaction with water regenerates hydroxide giving III. Steps B and C are analogous to steps proposed for the base-catalyzed cyanoethylation of phosphine.[5] Repetition of steps A, B, and C breaks the center P—P bond in III giving the cyclotetraphosphine structure IV. (The cyanoethyl group is replaced by R for convenience.) A critical feature in this representation is the absence of tautomerism of trivalent $\mathrm{{>}POH}$ in intermediates I, II, III, and IV to the more generally stable pentavalent form, $\mathrm{{>}P(=O)H}$. The pentavalent phosphine oxide structure would be expected to react rapidly with acrylo-

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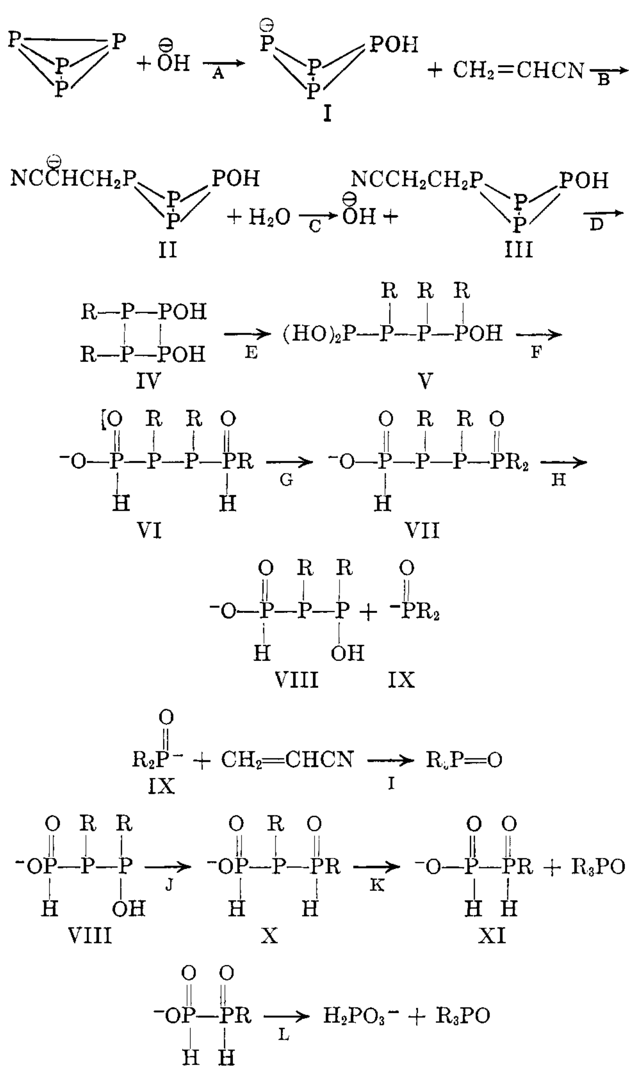
(7) C. Stich, *Pharm. Ztg.*, **48**, 343 (1903), quoted in A. Seidell, "Solubilities of Inorganic and Metal Organic Compounds," 3rd ed., Vol. I, D. Van Nostrand Co., Inc., New York, N. Y., 1940, p. 1362.



nitrile[6] and this would necessarily lead to the formation of phosphonic and phosphonic acids. Moreover, it is reasonable to expect the trivalent form to be stable in cyclic intermediates I, II, III, and IV, because tautomerism to the pentavalent structure would require expansion of the bond angles[1c] and thus seriously increase ring strain.

Repetition of steps A, B, and C cleaves the pinacol-like P—P bond in IV giving linear intermediate V. Tautomerism of V, and neutralization of the acidic hydrogen, give ion VI which incorporates the inactive (toward addition) hypophosphite structure at the left and the active secondary phosphine oxide structure at the right. Base-catalyzed addition of VI to acrylonitrile gives VII in a reaction analogous to the base-catalyzed addition of secondary phosphine oxides to acrylonitrile.[6] Attack by hydroxide on VII might conceivably occur at any of the four phosphorus atoms. But reaction by the path indicated in step H should be favored since it permits elimination of the secondary phosphine oxide ion, IX, rather than a less stable phosphide ion or hypophosphite dianion. Reaction of the secondary phosphine oxide ion with acrylonitrile gives tris(2-cyanoethyl)phosphine oxide. Tautomerism of VIII followed by a repetition of steps G, H, and I gives intermediate XI and a second molecule of tris(2-cyanoethyl)phosphine oxide. Intermediate XI on repetition of steps G, H, and I gives the third molecule of tertiary phosphine oxide and the phosphite anion.

Thus, the essential features of the reaction can be accounted for in a consistent and reasonable manner; yet, it is clear that additional evidence will be required to establish the mechanism decisively.

Experimental[8,9]

Tris(2-cyanoethyl)phosphine Oxide.—A mixture of 7.7 g. (0.25 g.-atom) of white phosphorus, 29.7 g. (0.56 mole) of acrylonitrile, and 75 ml. of acetonitrile was warmed to 50° under nitrogen in a creased flask. The mixture was stirred vigorously and cooled to 30° so that the phosphorus solidified in a finely divided state. To this mixture was added dropwise with vigorous stirring 18.0 ml. (0.18 equivalent) of 10 *N* aqueous potassium hydroxide during 20 min. The temperature was maintained at 30–35° by cooling and the mixture was stirred at this temperature one additional hour. By the end of the reaction period, a dense white solid had separated. The reaction mixture was diluted with a solution of 10 ml. of concentrated hydrochloric acid in 300 ml. of water. The solid dissolved giving a neutral solution containing only traces of unchanged white phosphorus. The mixture was warmed to 50° to melt the phosphorus, cooled to room temperature and the solution was decanted under nitrogen. The solution was filtered through diatomaceous earth and evaporated to dryness under reduced pressure. The residue was extracted with 200 ml. of hot methanol. The extract when cool deposited 23.5 g. (45%) of tris-(2-cyanoethyl)phosphine oxide, m.p. 165–169°. Concentration of the filtrate gave an additional 4.5 g. (9%), m.p. 165–169°. Recrystallization from aqueous isopropyl alcohol gave material melting at 172–173° (lit.,[6] m.p. 172–173°) which did not depress the melting point of an authentic sample. The insoluble residue remaining from the methanol extraction was dissolved in water. Tests for phosphate ion on an aliquot of the solution were negative, but a positive ammonium molybdate-sulfurous acid test[10] for hypophosphite was obtained. Treatment of the solution with barium chloride precipitated barium phosphite (19% conversion of phosphorus) identified by its infrared spectrum and by phosphorus analysis. An aqueous solution of the methanol-insoluble residue from a similar experiment was treated with lead acetate to precipitate lead phosphite in 17% conversion.

Results of similar experiments are summarized in Table I.

Tris(2-carbamoylethyl)phosphine Oxide.—A solution of 20 ml. (0.2 equivalent) of 10 *N* aqueous potassium hydroxide in 80 ml. of 2B ethanol was added dropwise during 30 min. to a well stirred mixture of 12.4 g. (0.4 g.-atom) of finely divided white phosphorus, 63.9 g. (0.9 mole) of acrylamide, and 200 ml. of 2B ethanol under nitrogen. The temperature was maintained at 30–35° by gentle cooling. The mixture, from which the product had begun to separate, was stirred an additional 45 min. at 35°, cooled to 5°, and filtered to obtain 50.1 g. (48%) of white solid, m.p. 195–200°. The solid was dissolved in 125 ml. of hot glacial acetic acid, and the solution was cooled to room temperature. (While unchanged phosphorus was not generally found, if present it can be separated conveniently at this point by decantation under nitrogen.) The solution was filtered through diatomaceous earth, diluted with 600 ml. of 2B ethanol, and cooled at 5° for 30 min. The white solid was collected and washed with 2B ethanol to obtain 41 g. (44%) of tris(2-carbamoylethyl)phosphine oxide, m.p. 206–209°. Recrystallization from dimethylformamide gave an analytical sample, m.p. 208–210°.

Anal. Calcd. for $C_9H_{18}N_3O_4P$: N, 15.96; P, 11.76. Found: N, 16.37; P, 11.68.

Additional experiments are summarized in Tables II and III.

Reaction of White Phosphorus, Potassium Hydroxide, and Ethyl Acrylate.—To a well stirred mixture of 30.9 g. (1 g.-atom) of finely divided white phosphorus, 170.2 g. (1.7 moles) of ethyl acrylate, and 300 ml. of acetonitrile was added 50 ml. (0.5 equivalent) of 10 *N* aqueous potassium hydroxide during 15 min. The temperature of the mildly exothermic reaction was maintained at 30–35°. After stirring for two additional hours at this

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[8] Caution: White phosphorus is highly toxic and burns spontaneously when warmed in air. In an emergency, white phosphorus can be treated with aqueous copper sulfate solution which coats it with a relatively inert layer of copper phosphide. Solid sodium bicarbonate is recommended for fires.

[9] Melting and boiling points are uncorrected.

[10] F. P. Treadwell and W. T. Hall, "Analytical Chemistry," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 362.

temperature, the organic phase was carefully siphoned from the mixture of aqueous phase and unchanged phosphorus. The organic phase was neutralized with 2 drops of concentrated hydrochloric acid, dried over anhydrous sodium sulfate, and distilled under reduced pressure to obtain 12.7 g. (4%) of tris(2-carbethoxyethyl)phosphine, b.p. 160–180° (0.3 mm.) (lit.,[5] b.p. 193–194/1 mm.), identified by comparison of its infrared spectrum with that of an authentic sample, and 28.1 g. (8%) of tris(2-carbethoxyethyl)phosphine oxide, b.p. 205–220° (0.5 mm.). The latter was redistilled to obtain an analytical sample, b.p. 199–203° (0.2 mm.), n^{25}_D 1.4682.

Anal. Calcd. for $C_{15}H_{27}O_7P$: C, 51.42; H, 7.77; P, 8.84. Found: C, 51.85; H, 7.58; P, 8.84.

From the aqueous phase was recovered 15.9 g. (51.2%) of white phosphorus.

Reaction of Aqueous Ethanolic Potassium Hydroxide with Phosphorus Followed by Addition of Acrylamide.—To a well stirred mixture of 9.0 g. (0.29 g.-atom) of finely divided white phosphorus and 100 ml. of 2B ethanol was added dropwise during 15 min. 15 ml. (0.15 equivalent) of 10 *N* aqueous potassium hydroxide solution. The temperature was maintained at 5–10° during the addition and for an additional 45 min. Most, but not all, of the phosphorus dissolved leaving a deep red solution. The n.m.r. spectrum of the solution showed only a triplet centered at −2 p.p.m. (relative to 85% phosphoric acid) corresponding to hypophosphite ion.

To the deep red solution, stirred at 5–10°, was added dropwise during 15 min. a solution of 32.0 g. (0.45 mole) of acrylamide in 75 ml. of 2B ethanol. Neither a color change nor an exotherm was observed. The mixture was stirred at 5–10° for an additional 30 min. and allowed to warm to room temperature. The color lightened on standing, and the mixture became colorless after standing overnight. A small amount of oil separated from the reaction mixture and was collected. Treatment with methanol and acetone gave 4.6 g. (6%) of tris(2-carbamoylethyl)phosphine oxide, m.p. 200–204°. Attempts to obtain other products from the main body of the reaction mixture were unsuccessful.

Acknowledgment.—The authors are indebted to Dr. Martin Grayson for his interest and encouragement. The authors also wish to express their appreciation to Dr. J. A. Kuck and associates for microanalyses, to Mr. N. Colthup for infrared spectra, and to Dr. J. E. Lancaster for n.m.r. spectra.

A Selective Phosphorylation by Means of Dibromomalonamide and Trialkyl Phosphites

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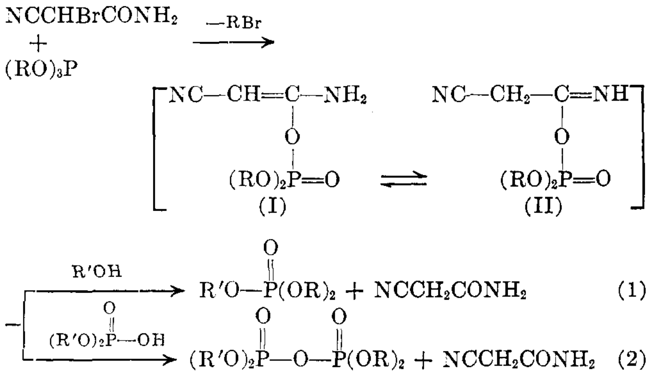
Received September 17, 1962

A selective phosphorylation of alcohols and phosphates forming mixed esters of phosphoric acid and unsymmetrical pyrophosphates by the use of one mole of dibromomalonamide and two moles of trialkyl phosphite has been investigated. By this method, various phosphates and pyrophosphates were obtained in high yields under mild conditions.

It has been demonstrated in a previous paper that trialkyl phosphites react with α-bromocyanoacetoamide to give a reactive intermediate, enol- (I) or imidoylphosphate (II), from which either mixed esters of phosphoric acid or unsymmetrical pyrophosphates can be obtained by further reaction with an alcohol or with diethyl hydrogen phosphate.[1]



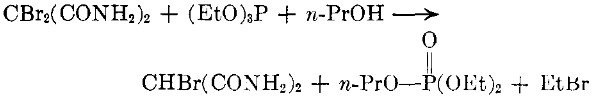
$$R'O-\overset{O}{\overset{\|}{P}}(OR)_2 + NCCH_2CONH_2 \quad (1)$$

$$(R'O)_2\overset{O}{\overset{\|}{P}}-O-\overset{O}{\overset{\|}{P}}(OR)_2 + NCCH_2CONH_2 \quad (2)$$

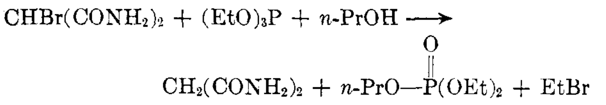
A selective phosphorylation can be effected successfully by this method without isolating the intermediate, I or II, since it reacts exclusively with nucleophilic reagents such as alcohols, amines, and dialkyl hydrogen phosphates, under mild conditions, but it does not react with trialkyl phosphite.

In the present experiment, a selective phosphorylation of alcohols and phosphates was tried further by the use of dibromomalonamide and trialkyl phosphites.

When dibromomalonamide was treated with two molecular equivalents of trialkyl phosphite in a large excess of anhydrous *n*-propyl alcohol at room temperature, an instantaneous reaction took place and *n*-propyl diethyl phosphate was obtained in high yield. A similar result was obtained when two equivalents of *n*-propyl alcohol were used in the above reaction.



$$CBr_2(CONH_2)_2 + (EtO)_3P + n\text{-}PrOH \longrightarrow CHBr(CONH_2)_2 + n\text{-}PrO-\overset{O}{\overset{\|}{P}}(OEt)_2 + EtBr \quad (3)$$



$$CHBr(CONH_2)_2 + (EtO)_3P + n\text{-}PrOH \longrightarrow CH_2(CONH_2)_2 + n\text{-}PrO-\overset{O}{\overset{\|}{P}}(OEt)_2 + EtBr \quad (4)$$

The reaction is considered to involve two steps of phosphorylation (equations 3 and 4). First, one mole of dibromomalonamide and one mole of triethyl phosphite were used for the phosphorylation of one mole of *n*-propyl alcohol, and *n*-propyl diethyl phosphate and monobromomalonamide were obtained in good yields. In a second reaction, one mole of monobromomalonamide and one mole of triethyl phosphite were treated with one mole of *n*-propyl alcohol; *n*-propyl diethyl phosphate was also obtained in good yield along with malonamide. The mechanism of these reactions is believed to be similar to that already discussed for α-bromocyanoacetoamide.

The generality of the technique was established by the preparation of a number of simple alkyl diethyl phosphates (see Table I).

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