[CONTRIBUTION FROM THE PHYSICAL RESEARCH LABORATORY OF THE DOW CHEMICAL COMPANY]

Organic Polyphosphorus Compounds. III. A New Synthesis Principle for Octamethylpyrophosphoramide (OMPA)

BY HENRY TOLKMITH

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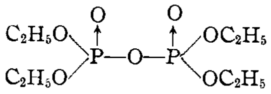
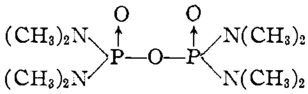
A new synthesis for octamethylpyrophosphoramide, OMPA, is described. It consists in the thermal reaction of three moles of tetramethyldiamidophosphoryl chloride and one mole of ethyl phosphate with at least two moles of hexamethylphosphoramide. The mechanism of this reaction comprises polyphosphorylation, transphosphorylation and transamination.

Introduction

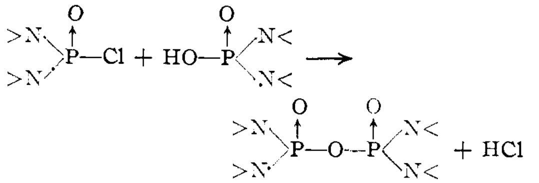
The work on synthetic cholinesterase inhibitors during World War II has shown that a considerable number of organic phosphorus compounds exhibit this type of biological activity, and several of these compounds have found commercial use as insecticides.[1] An especially interesting pair of compounds, with regard to their mode of entomological action,[2,3] are the tetraethyl ester and tetradimethylamide of the pyrophosphoric acid (OMPA).


I

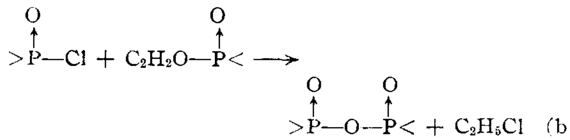

II

Especially in England OMPA has been developed as a selective systemic insecticide which does not kill predatory insects[4] and which has a somewhat greater safety margin than other cholinergic phosphates.[3]

While a variety of synthesis methods for pyrophosphoric esters are known in the literature,[5] only one has been successfully used for the preparation of pyrophosphoric amides. This method exists in two modifications: the reaction of an amido chlorophosphate with an amido phosphoric acid in the presence of an HCl acceptor


(a)

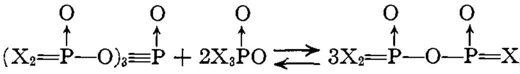
and the thermal reaction of a chlorophosphate with an ethyl phosphate



$$>\overset{\overset{O}{\uparrow}}{P}\text{—Cl} + C_2H_2O\text{—}\overset{\overset{O}{\uparrow}}{P}< \longrightarrow >\overset{\overset{O}{\uparrow}}{P}\text{—O—}\overset{\overset{O}{\uparrow}}{P}< + C_2H_5Cl \quad (b)$$

By method (a) the tetranilide[6] and later OMPA[7] have been prepared. This reaction is known to give yields not exceeding 60%. According to equation (b) OMPA and several pyrophosphoric ester amides[1] have been prepared. This method gives satisfactory yields but requires more preparatory work than method (a).

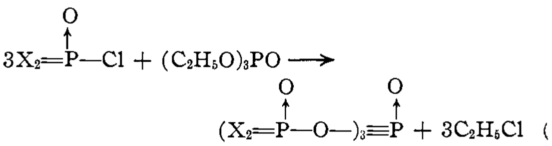
The Synthesis Principle.—A new approach to the problem of synthesizing organic pyrophosphoramides was suggested by some transphosphorylation reactions of organic polyphosphoramides,[8] especially by the reaction



$$(X_2\text{=}\overset{\overset{O}{\uparrow}}{P}\text{—O})_3\equiv\overset{\overset{O}{\uparrow}}{P} + 2X_3\overset{\overset{O}{\uparrow}}{P}O \rightleftarrows 3X_2\text{=}\overset{\overset{O}{\uparrow}}{P}\text{—O—}\overset{\overset{O}{\uparrow}}{P}\text{=}X_2 \quad (c)$$

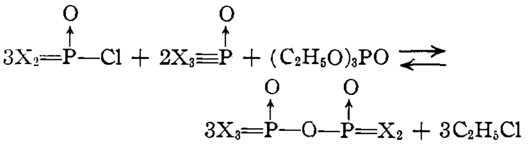
X = dimethylamido group

The tetraphosphate component in (c) can be obtained quantitatively[9] by the reaction



$$3X_2\text{=}\overset{\overset{O}{\uparrow}}{P}\text{—Cl} + (C_2H_5O)_3PO \longrightarrow (X_2\text{=}\overset{\overset{O}{\uparrow}}{P}\text{—O—})_3\equiv\overset{\overset{O}{\uparrow}}{P} + 3C_2H_5Cl \quad (d)$$

For practical purposes it seemed preferable to work on the basis of the combined equations c and d



$$3X_2\text{=}\overset{\overset{O}{\uparrow}}{P}\text{—Cl} + 2X_3\equiv\overset{\overset{O}{\uparrow}}{P} + (C_2H_5O)_3PO \rightleftarrows 3X_3\text{=}\overset{\overset{O}{\uparrow}}{P}\text{—O—}\overset{\overset{O}{\uparrow}}{P}\text{=}X_2 + 3C_2H_5Cl \quad (e)$$

This concept was investigated experimentally by working first with a mixture of the theoretical quantities of the components and then with an excess of X_3PO.

A mixture of three moles of tetramethyldiamidophosphoryl chloride, $[(CH_3)_2N]_2POCl$, two moles of hexamethylphosphoramide, $[(CH_3)_2N]_3PO$, and one mole of triethyl phosphate was heated at 155 to 160°. After 3.5 hours the quantity of ethyl chloride released amounted to 95.4% of theory and the crude reaction product showed a molecular weight of 295 (theory 286.3). This mixture was heated an additional hour at 155° and gave no further release of volatile materials. The product was separated by molecular distillation, which produced the expected OMPA in a yield of 46.7%, besides a considerable amount of polyphosphate residue.

A mixture of the same components was next treated in an analogous manner, but this time three instead of two moles triamidophosphate was used. After four hours the ethyl chloride released

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[1] G. Schrader, "Die Entwicklung neuer Insectizide auf Grundlage organischer Fluor- und Phosphor-verbindungen," Verlag Chemie, Weinheim (1951).

[2] R. L. Metcalf and R. B. March, *J. Ec. Entom.*, **42**, 721 (1949).

[3] K. P. DuBois, J. Doull and J. M. Coon, *J. Pharm. Exp. Ther.*, **99**, 376 (1950).

[4] W. E. Ripper, R. M. Greenslade and G. S. Hartley, *Bull. Ent. Res.*, **40**, 481 (1950).

[5] G. M. Kosolapoff, "Organophosphorus Compounds," John Wiley and Sons, New York, N. Y., 1950.

[6] K. Zeile and W. Kruckenberg, *Ber.*, **75**, 1127 (1942).

[7] D. W. Pound and B. C. Saunders, British Patent 631,549 (1949).

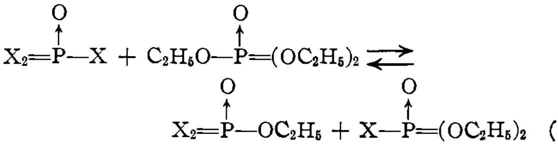
[8] H. Tolkmith, paper II, THIS JOURNAL, **75**, 5273 (1953).

[9] H. Tolkmith, paper I, *ibid.*, **75**, 5270 (1953)

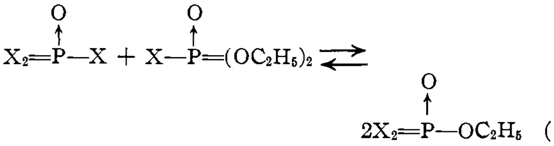
amounted to 87% of theory.[10] From the crude reaction mixture the excess triamidophosphate was removed by the usual vacuum distillation. This crude concentrate showed a noticeably better insecticidal action than a similar product prepared according to equation a. The concentrate was purified by molecular distillation and gave a total OMPA yield of 69%.

These two reactions demonstrate that equation e is a feasible basis for amidopyrophosphate synthesis and that this equation has an equilibrium character. If the radicals X in equation e represent ethoxy instead of dimethylamido groups, the equation represents a well-known synthesis for tetraethyl pyrophosphate (I).[1] Furthermore, the yield of I (TEPP) should be increased by an excess of triethyl phosphate. This has already proved to be the case.[11]

Synthesis Mechanism.—As the equation e was derived by combination of equation c and d it might be assumed that reactions on the basis of equation e consist in polyphosphorylation followed by transphosphorylation. It is possible, on the other hand, that such reactions proceed exclusively by a stepwise radical exchange

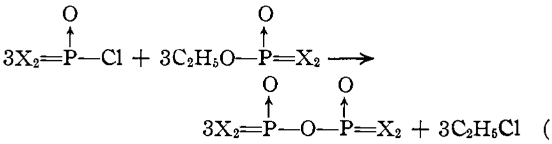


$$X_2{=}\overset{O}{\overset{\uparrow}{P}}{-}X + C_2H_5O{-}\overset{O}{\overset{\uparrow}{P}}{=}(OC_2H_5)_2 \rightleftharpoons X_2{=}\overset{O}{\overset{\uparrow}{P}}{-}OC_2H_5 + X{-}\overset{O}{\overset{\uparrow}{P}}{=}(OC_2H_5)_2 \qquad (f)$$



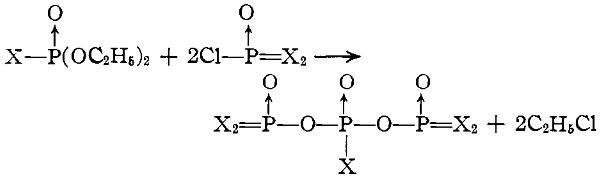
$$X_2{=}\overset{O}{\overset{\uparrow}{P}}{-}X + X{-}\overset{O}{\overset{\uparrow}{P}}{=}(OC_2H_5)_2 \rightleftharpoons 2X_2{=}\overset{O}{\overset{\uparrow}{P}}{-}OC_2H_5 \qquad (g)$$

followed by phosphorylation



$$3X_2{=}\overset{O}{\overset{\uparrow}{P}}{-}Cl + 3C_2H_5O{-}\overset{O}{\overset{\uparrow}{P}}{=}X_2 \longrightarrow 3X_2{=}\overset{O}{\overset{\uparrow}{P}}{-}O{-}\overset{O}{\overset{\uparrow}{P}}{=}X_2 + 3C_2H_5Cl \qquad (h)$$

The equations f and g were therefore checked experimentally. It was found that a mixture of two moles of hexamethylphosphoramide and one mole of triethyl phosphate changes upon heating at 150°. The presence of O,O-diethyl dimethylamidophosphate could be identified clearly by infrared, thus the mixture mentioned shows radical exchange at least to the extent of equation f. This intermediate is known to be phosphorylated by X_2POCl[12] according to the equation



$$X{-}\overset{O}{\overset{\uparrow}{P}}(OC_2H_5)_2 + 2Cl{-}\overset{O}{\overset{\uparrow}{P}}{=}X_2 \longrightarrow X_2{=}\overset{O}{\overset{\uparrow}{P}}{-}O{-}\underset{X}{\underset{|}{\overset{O}{\overset{\uparrow}{P}}}}{-}O{-}\overset{O}{\overset{\uparrow}{P}}{=}X_2 + 2C_2H_5Cl$$

The triphosphate formed is reported to phosphorylate X_3PO with formation of OMPA.[8] Thus, the mechanism of pyrophosphate formation on the basis of equation e actually includes radical exchange. This exchange yields intermediates which can undergo, however, mono- as well as polyphosphorylation. Thus, the concept as characterized by equation f, g and h does not contradict the polyphosphorylation–transphosphorylation theory.

Conclusions

The equation e illustrates a reaction on the basis of which dialkylamides as well as alkyl esters of the pyrophosphoric acid may be prepared.

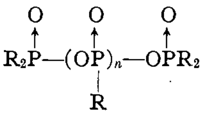
The equilibrium character of this reaction is indicated by the fact that an excess of the phosphorolysis agent X_3PO increases the pyrophosphate yield.

Reactions according to equation e show a mechanism which consists in polyphosphorylation of triethyl phosphate by X_2POCl and phosphorolysis of the polyphosphate intermediate by the component X_3PO with formation of pyrophosphate. At the same time a radical exchange between X_3PO and $(C_2H_5O)_3PO$ occurs, yielding intermediates which can undergo polyphosphorylation and direct pyrophosphate formation, respectively, by reacting with X_2POCl.

Amido pyrophosphate synthesis according to e comprises, therefore, three major reaction phases: polyphosphorylation, transphosphorylation or phosphorolysis, and transamination.

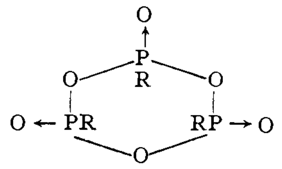
The formation of tetraethyl pyrophosphate from phosphorus oxychloride and triethyl phosphate appears to be controlled by an analogous mechanism, with transethylation in place of transamination.

Pyrophosphate syntheses according to equation e yield, therefore, the following types of polyphosphates as intermediates (R = dialkylamido or alkoxy radicals, n = integer)



$$R_2\overset{O}{\overset{\uparrow}{P}}{-}(O\underset{R}{\underset{|}{\overset{O}{\overset{\uparrow}{P}}}})_n{-}O\overset{O}{\overset{\uparrow}{P}}R_2$$

III



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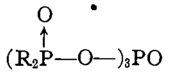

$$(R_2\overset{O}{\overset{\uparrow}{P}}{-}O{-})_3PO$$

V

The experimental results obtained are in agreement with recent evidence that thermal reactions between organic monophosphates frequently yield symmetrical pyrophosphates.[13,14]

Experimental

Starting Materials

	Structure	n^{20}_D	d^{20}_4	B.p. (10 mm.), °C.
Triethyl phosphate	$(C_2H_5O)_3PO$	1.4060	1.0692	89
Tetramethyldiamidophosphoryl chloride	$[(CH_3)_2N]_2POCl$	1.4670	1.1823	110
Hexamethylphosphoramide	$[(CH_3)_2N]_3PO$	1.4582	1.0253	117

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(10) Hexamethylphosphoramide was found to be a good solvent for gaseous organic compounds.

(11) S. A. Hall and M. Jacobson, *Ind. Eng. Chem.*, **40**, 694 (1948).

(12) W. T. Dye, U. S. Patent 2,610,139 (1952).

(13) N. S. Corby, G. W. Kenner and A. R. Todd, *J. Chem. Soc.*, 1234 (1952).

(14) G. M. Kosolapoff, This Journal, **74**, 5520 (1952).

OMPA Synthesis with a Stoichiometric Amount of Triamido Phosphate.—A mixture of 55 g. of tetramethyldiamidophosphoryl chloride, 38.5 g. of hexamethylphosphoramide, and 19.6 g. of triethyl phosphate in the mole ratio of 3:2:1 was heated with agitation at 155°. The released gas was absorbed in ethanol and identified as ethyl chloride. Its amount was determined by weighing the reaction mixture repeatedly as the reaction progressed. According to equation e a total of 20.8 g. of ethyl chloride should be formed. The amount actually released as a function of time was: 1 hr., 86.5%; 2 hr., 91.4%; 3.5 hr., 95.4%; 4.5 hr., 95.4%.

The reaction mixture was then heated to a temperature of 130° under a pressure of 15 mm. in order to remove volatile components still dissolved in the mixture. The clear, dark-brown oil obtained weighed 93.3 g. (theory 92.3 g.).

In a parallel run of equal size the molecular weight of the reaction mixture as a function of time was determined. It was: start, 189; 1 hr., 265; 2 hr., 272; 3.5 hr., 295; 4.5 hr., 296 (through 286.3). From the second run two additional samples were taken after a reaction time of 3.5 and 4.5 hours, respectively, and tested insecticidally. Their activity was found to be the same as that of a material prepared according to equation a.

The reaction mixture from the first run was then separated by molecular distillation (boiling range 75 to 120° under a pressure of 1.0 to 0.5 mm.). It left a residue of 34 g. of an amidopolyphosphate product which could not be identified. The distillate had a weight of 56 g. and was analyzed by infrared. It was found to consist of 77% OMPA and 22% hexamethylphosphoramide. The total amount of OMPA formed was, therefore, 43 g. and represented a yield of 46.7%. The triamidophosphate recovered amounted to 32.0% of the quantity originally used. This was due to the equilibrium character of the synthesis method.

OMPA Synthesis in the Presence of an Excess of Triamidophosphate.—A mixture of 24.5 g. of tetramethyldiamidophosphoryl chloride plus 26.0 g. of hexamethylphosphoramide plus 8.75 g. of triethyl phosphate was heated four hours with agitation at 155°. The reaction mixture contained the components of the mole ratio of 3:3:1. A total of 8.0 g. of ethyl chloride was released, representing only 87% of the theoretical quantity due to the solubility of C_2H_5Cl in the triamidophosphate.

The crude reaction mixture was then concentrated by heating to a pot temperature of 140° under a pressure of 20 mm. The distillate obtained weighed 13 g. and contained according to infrared analysis 90% triamidophosphate and 10% OMPA.

The clear, dark brown oil residue weighed 37 g.; its analytical data compared in the following way with pure OMPA:

	Reaction product	Pure OMPA
P, %	21.6	21.64
N, %	18.7	19.57
Mol. wt.	288	286.3
d^t_4	1.1632 (20°)	1.1360 (25°)
n^t_D	1.4655 (20°)	1.4620 (25°)

This material was now purified by molecular distillation, which yielded a distillate of 31 g. and 5 g. of a polyphosphate residue. Infrared analysis of the distillate showed the presence of 88% OMPA and 12% triamidophosphate.

The boiling point of the pure OMPA was found to be 119–120° (0.65 mm.).

The total yield of OMPA was, therefore, 1.3 g. in the first distillate (vacuum concentration) plus 27.3 g. in the second distillate (molecular distillation). This quantity represented 69.6% of the theoretical yield.

A mixture of tetramethyldiamidophosphoryl chloride with hexamethylphosphoramide, as necessary for the synthesis described, can be prepared from dimethylamine and phosphorus oxychloride.

Thus, the synthesis of OMPA from $POCl_3$, dimethylamine and ethyl phosphate is possible by a two-step process.

Acknowledgment.—The author is indebted to Drs. A. W. Baker, Ch. W. Young and L. E. Streeter for analyses and to E. E. Kenaga for insecticidal tests reported in this paper.

MIDLAND, MICHIGAN

[CONTRIBUTION FROM THE ROSS CHEMICAL LABORATORY, ALABAMA POLYTECHNIC INSTITUTE]

The Synthesis of Amino-substituted Phosphonic Acids. III[1]

BY MARY E. CHALMERS AND GENNADY M. KOSOLAPOFF

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The interaction of dialkyl phosphites, ammonia and aldehydes was employed for the synthesis of the following dialkyl phosphonates which contain an amino group on the first carbon atom: diethyl and dibutyl α-aminobenzylphosphonates, diethyl α-aminoethylphosphonate, diethyl α-aminopropylphosphonate, diethyl *p*-methoxybenzyl-α-aminophosphonate, diethyl *p*-hydroxybenzyl-α-aminophosphonate, diethyl *o*-hydroxybenzyl-α-aminophosphonate and diethyl β-phenylethyl-α-aminophosphonate. The esters were converted to the free aminophosphonic acids, which were characterized. Additional details concerning the preparation of aminomethylphosphonic acid were obtained.

In continuation of our work on the synthesis and the determination of properties of phosphonic acids that contain an amino group in the molecule we examined the Mannich-type reaction which takes place between dialkyl phosphites, carbonyl compounds and ammonia, a reaction which was reported recently by Kabachnik and Medved in several examples involving ketones as the carbonyl compounds. The reaction can be summarily represented by the equation

$$(RO)_2P(O)H + NH_3 + R'COR'' \longrightarrow (RO)_2P(O)CR'R''NH_2$$[2]

Kabachnik and Medved report rather low yields of the products, but the method has advantages over other possible procedures.[3] Of particular interest to us is the fact that the method produces derivatives that carry the amino group in position adjacent to the phosphono group, thus yielding a number of compounds that are structurally analogous to the common naturally occurring amino acids.

We applied the above reaction to several aliphatic and aromatic aldehydes with satisfactory results. The esters of the amino acids, that were formed in the primary reaction, were characterized either as such or as the hydrochlorides. The esters were then converted to the free amino acids (Kabachnik and Medved dealt primarily with the esters only), which were characterized in the usual way. Thus, seven aminophosphonic acids in the form of race-

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(1) Paper II, THIS JOURNAL, **70**, 1283 (1948).

(2) M. I. Kabachnik and T. Ya. Medved, *Doklady Akad. Nauk S.S.S.R.*, **83**, No. 5, 689 (1952).

(3) G. M. Kosolapoff, THIS JOURNAL, **69**, 2112 (1947).