A further observation which is in conformity with our conclusions involves the pK_a values of the secondary phosphoryl dissociation of the isomeric nucleotides. It will be noted that the pK_a values in question are higher for the *a* isomers. This decreased acid strength is most probably due to an intramolecular interaction, probably involving hydrogen bonds between the secondary hydroxyl group of the phosphoric acid group and the purine or pyrimidine ring. The group closest to the ring will exhibit a higher degree of hydrogen bonding and thus have a higher pK_a value, or a decreased acid strength. This also leads to a formulation of 2'- and 3'-phosphates for the *a* and *b* isomers, respectively. That the melting point of adenylic acid *b* is higher than that of *a*[4,19,20] is a further confirmation of our conclusion.

Acknowledgment.—The author wishes to express his gratitude to Dr. George Bosworth Brown for helpful discussions and continued interest.

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NEW YORK, N. Y.

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

Organic Polyphosphorus Compounds. I. Synthesis of Aliphatic Amido Polyphosphates

BY HENRY TOLKMITH

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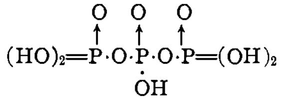
The possibilities of synthesizing aliphatic amido polyphosphates by phosphorylation of pyrophosphates were investigated. The following new polyphosphates were prepared: decamethyltriphosphoramide, linear and pyramidal dodecamethyltetraphosphoramide.

Introduction

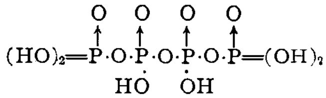
While the chemistry of organic pyrophosphates has become well established during the past three decades, the chemistry of the higher organic polyphosphates is still at its beginning. In recent years the following compounds have been described: adenosine 5'-triphosphate,[1] thiamin triphosphate[2] hydroxythiamin triphosphate,[3] homothiamin and 2'-desmethylthiamin triphosphate,[4] O,N-di-(triphospho)-thiamin,[5] pyridoxamine-5'-triphosphate,[6] uridine triphosphate,[7] inosine triphosphate[8] and decamethyltriphosphoramide.[9] In view of the chemically interesting and biochemically important reactions of adenosine-5'-triphosphate we have attempted to synthesize simple organic derivatives of the polyphosphoric acids

triphosphoric acid



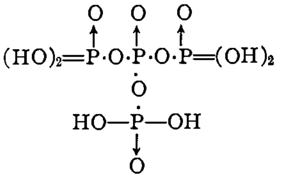
$$(HO)_2{=}\overset{O}{\overset{\uparrow}{P}}\cdot O\cdot\underset{OH}{\overset{O}{\overset{\uparrow}{P}}}\cdot O\cdot\overset{O}{\overset{\uparrow}{P}}{=}(OH)_2$$

linear tetraphosphoric acid



$$(HO)_2{=}\overset{O}{\overset{\uparrow}{P}}\cdot O\cdot\underset{HO}{\overset{O}{\overset{\uparrow}{P}}}\cdot O\cdot\underset{OH}{\overset{O}{\overset{\uparrow}{P}}}\cdot O\cdot\overset{O}{\overset{\uparrow}{P}}{=}(OH)_2$$

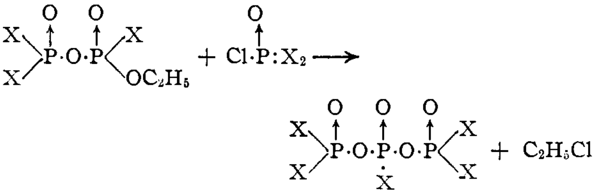
pyramidal tetraphosphoric acid



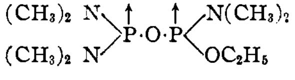
$$(HO)_2{=}\overset{O}{\overset{\uparrow}{P}}\cdot O\cdot\underset{\underset{\underset{\underset{O}{\downarrow}}{HO—P—OH}}{O}}{\overset{O}{\overset{\uparrow}{P}}}\cdot O\cdot\overset{O}{\overset{\uparrow}{P}}{=}(OH)_2$$

It is well-known that attempts to synthesize neutral esters of these parent structures have not been successful.[10] It was therefore decided to investigate the synthesis of their neutral dimethyl amides, *i.e.*, of decamethyltriphosphoramide and the two isomeric dodecamethyltetraphosphoramides.

Decamethyltriphosphoramide.—The synthesis of this compound was carried out on the basis of the reaction (X = dimethylamido group)



In this reaction only one reaction product was theoretically to be expected. The preparation of the starting products necessary has been described recently.[11] An equimolar mixture of O-ethyl hexamethyltriamidopyrophosphate and tetramethyldiamidophosphoryl chloride $[(CH_3)_2N]_2POCl$ was



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[1] J. Baddiley, A. M. Michelson and A. R. Todd, *J. Chem. Soc.*, 582, 2487 (1949).

[2] L. Velluz, G. Amiard and J. Bartos, *Bull. soc. chim.*, **15**, 871 (1948).

[3] L. Velluz, J. Bartos and G. Amiard, *ibid.*, **17**, 297 (1950).

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[5] H. Roux and A. Callandre, *Experientia*, **6**, 386 (1950).

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[7] A. Kornberg, "Phosphorus Metabolism," Vol 1, The Johns Hopkins Press, Baltimore, Md., 1951.

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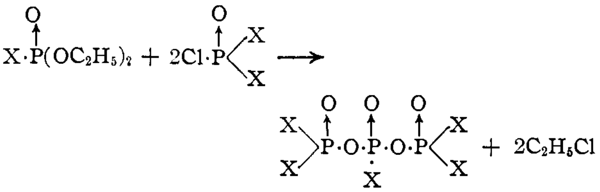
[9] G. S. Hartley, D. F. Heath, J. M. Hulme, D. W. Pound and Mary Whittaker, *J. Sci. Food Agric.*, 303 (1951).

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

[11] G. Schrader, "Die Entwicklung neuer Insektizide auf Grundlage organischer Fluor- und Phosphor-verbindungen," Verlag Chemie, Weinheim, 1951.

found to react at 130° with release of ethyl chloride in an almost quantitative amount, on the basis of the equation stated. Analysis of the product obtained gave values agreeing closely with those for the theoretically expected main product and different from those for the starting product.

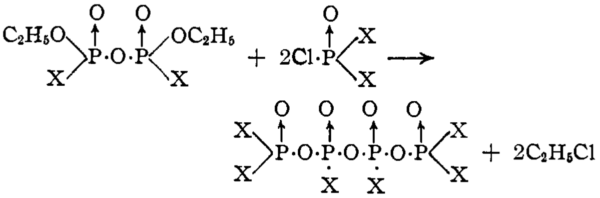
A second synthesis was carried out on the basis of the equation[12]



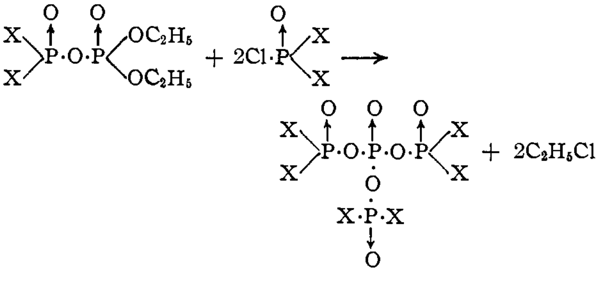
$$X\cdot\overset{\overset{O}{\uparrow}}{P}(OC_2H_5)_2 + 2Cl\cdot\overset{\overset{O}{\uparrow}}{P}\begin{smallmatrix}X\\X\end{smallmatrix} \longrightarrow \begin{smallmatrix}X\\X\end{smallmatrix}\!\!>\!\overset{\overset{O}{\uparrow}}{P}\cdot O\cdot\underset{X}{\overset{\overset{O}{\uparrow}}{P}}\cdot O\cdot\overset{\overset{O}{\uparrow}}{P}\!<\!\begin{smallmatrix}X\\X\end{smallmatrix} + 2C_2H_5Cl$$

The reaction product from this synthesis was found to have a molecular weight of 386. Its analytical data were in good agreement with those required theoretically. The infrared patterns of the reaction products from both syntheses were identical and the products showed the same degree and range of systemic activity toward insects and plants. The triphosphate formed represents therefore in all probability decamethyltriphosphoramide, which is reported to have a boiling range of 180–190° under a pressure of 0.4 mm. and a refractive index of $n^{25}D$ 1.466.[12]

Synthesis of Dodecamethyltetraphosphoramides.—It appeared possible to prepare the two isomeric dodecamethyltetraphosphoramides in a manner analogous to the first synthesis described for decamethyltriphosphoramide, *i.e.*, to operate on the basis of the equations



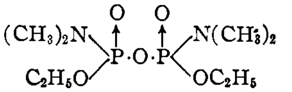
$$\begin{smallmatrix}C_2H_5O\\X\end{smallmatrix}\!\!>\!\overset{\overset{O}{\uparrow}}{P}\cdot O\cdot\overset{\overset{O}{\uparrow}}{P}\!<\!\begin{smallmatrix}OC_2H_5\\X\end{smallmatrix} + 2Cl\cdot\overset{\overset{O}{\uparrow}}{P}\!<\!\begin{smallmatrix}X\\X\end{smallmatrix} \longrightarrow \begin{smallmatrix}X\\X\end{smallmatrix}\!\!>\!\overset{\overset{O}{\uparrow}}{P}\cdot O\cdot\underset{X}{\overset{\overset{O}{\uparrow}}{P}}\cdot O\cdot\underset{X}{\overset{\overset{O}{\uparrow}}{P}}\cdot O\cdot\overset{\overset{O}{\uparrow}}{P}\!<\!\begin{smallmatrix}X\\X\end{smallmatrix} + 2C_2H_5Cl$$



$$\begin{smallmatrix}X\\X\end{smallmatrix}\!\!>\!\overset{\overset{O}{\uparrow}}{P}\cdot O\cdot\overset{\overset{O}{\uparrow}}{P}\!<\!\begin{smallmatrix}OC_2H_5\\OC_2H_5\end{smallmatrix} + 2Cl\cdot\overset{\overset{O}{\uparrow}}{P}\!<\!\begin{smallmatrix}X\\X\end{smallmatrix} \longrightarrow \begin{smallmatrix}X\\X\end{smallmatrix}\!\!>\!\overset{\overset{O}{\uparrow}}{P}\cdot O\cdot\underset{\underset{\underset{\underset{O}{\downarrow}}{X\cdot P\cdot X}}{O}}{\overset{\overset{O}{\uparrow}}{P}}\cdot O\cdot\overset{\overset{O}{\uparrow}}{P}\!<\!\begin{smallmatrix}X\\X\end{smallmatrix} + 2C_2H_5Cl$$

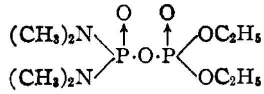
The amidopyrophosphates necessary for this procedure were prepared as described in the literature.[11] It is known that unsymmetrical pyrophosphoric esters frequently symmetrize at higher temperature.[13,14] The amidopyrophosphates synthesized, however, did not show thermal rearrangement when individually heated at 130°. Their boiling points under a pressure of 1 to 2 mm. are eleven degrees apart. The isomerism of the two pyrophosphate starting materials could thus reappear in the final tetraphosphate products and, theoretically, yield two isomeric tetraphosphates representing the two different structural forms mentioned for tetraphosphoric acid derivatives.

The actual reaction of one mole of either starting product, I and II, with two moles of tetramethyldiamidophosphoryl chloride at 130° yielded ethyl chloride in an almost quantitative amount, and the product was found to have the expected composition and molecular weight.



$$\begin{smallmatrix}(CH_3)_2N\\C_2H_5O\end{smallmatrix}\!\!>\!\overset{\overset{O}{\uparrow}}{P}\cdot O\cdot\overset{\overset{O}{\uparrow}}{P}\!<\!\begin{smallmatrix}N(CH_3)_2\\OC_2H_5\end{smallmatrix}$$

I

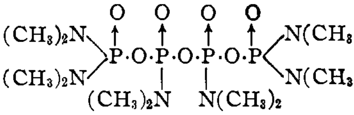


$$\begin{smallmatrix}(CH_3)_2N\\(CH_3)_2N\end{smallmatrix}\!\!>\!\overset{\overset{O}{\uparrow}}{P}\cdot O\cdot\overset{\overset{O}{\uparrow}}{P}\!<\!\begin{smallmatrix}OC_2H_5\\OC_2H_5\end{smallmatrix}$$

II

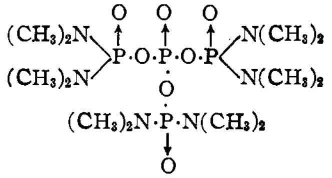
Furthermore, the compounds prepared were found[15] to undergo transphosphorylation reactions which are characteristic of organic polyphosphates. Thus, the formation of tetraphosphoramides evidently occurred in either reaction described.

Isomerism of Dodecamethyltetraphosphoramides.—The phosphorylation products prepared from I and II should have the structure



$$\begin{smallmatrix}(CH_3)_2N\\(CH_3)_2N\end{smallmatrix}\!\!>\!\overset{\overset{O}{\uparrow}}{P}\cdot O\cdot\underset{(CH_3)_2N}{\overset{\overset{O}{\uparrow}}{P}}\cdot O\cdot\underset{N(CH_3)_2}{\overset{\overset{O}{\uparrow}}{P}}\cdot O\cdot\overset{\overset{O}{\uparrow}}{P}\!<\!\begin{smallmatrix}N(CH_3)_2\\N(CH_3)_2\end{smallmatrix}$$

III (from I)



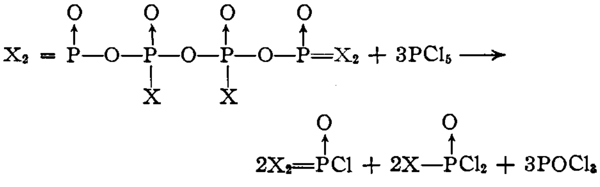
$$\begin{smallmatrix}(CH_3)_2N\\(CH_3)_2N\end{smallmatrix}\!\!>\!\overset{\overset{O}{\uparrow}}{P}\cdot O\cdot\underset{\underset{\underset{\underset{O}{\downarrow}}{(CH_3)_2N\cdot P\cdot N(CH_3)_2}}{O}}{\overset{\overset{O}{\uparrow}}{P}}\cdot O\cdot\overset{\overset{O}{\uparrow}}{P}\!<\!\begin{smallmatrix}N(CH_3)_2\\N(CH_3)_2\end{smallmatrix}$$

IV (from II)

Infrared analysis showed that the compounds synthesized, III and IV, are not identical. They have different absorption bands between 14 and 15 μ. Compound III has a band at 14.9 μ and no band at 14.23 μ. Compound IV has a unique band at 14.23 μ and no band at 14.9 μ.

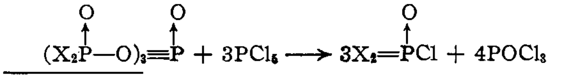
Entomological tests showed that compound III, in a concentration of one-thirtieth of a pound per 100 gallons of spray, gives 90% control of *tetranychus bimaculatus*. Compound IV requires a concentration of one-half of a pound per 100 gallons of spray to achieve 85% control of this insect. Compound III is almost twice as active as compound IV in the control of *aphis fabae*.

The compounds III and IV yielded different degradation products when treated with phosphorus pentachloride. Compound III reacted according to (X = dimethylamino group)



$$X_2=\overset{\overset{O}{\uparrow}}{P}-O-\underset{X}{\overset{\overset{O}{\uparrow}}{P}}-O-\underset{X}{\overset{\overset{O}{\uparrow}}{P}}-O-\overset{\overset{O}{\uparrow}}{P}=X_2 + 3PCl_5 \longrightarrow 2X_2=\overset{\overset{O}{\uparrow}}{P}Cl + 2X-\overset{\overset{O}{\uparrow}}{P}Cl_2 + 3POCl_3$$

Compound IV reacted according to the equation



$$(X_2\overset{\overset{O}{\uparrow}}{P}-O)_3\equiv\overset{\overset{O}{\uparrow}}{P} + 3PCl_5 \longrightarrow 3X_2=\overset{\overset{O}{\uparrow}}{P}Cl + 4POCl_3$$

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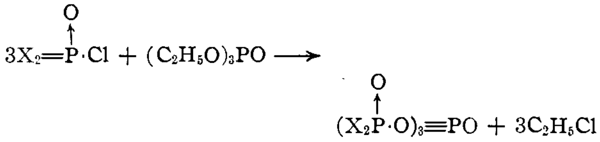
[12] W. T. Dye, U. S. Patent 2,610,139 (1952).

[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).

[15] H. Tolkmith, paper II, *ibid.*, **75**, 5273 (1953).

Finally, the reaction of 3 moles of tetramethyldiamidophosphoryl chloride with one mole of triethyl phosphate according to



$$3X_2{=}\overset{\overset{O}{\uparrow}}{P}{\cdot}Cl + (C_2H_5O)_3PO \longrightarrow (X_2\overset{\overset{O}{\uparrow}}{P}{\cdot}O)_3{\equiv}PO + 3C_2H_5Cl$$

gave a tetraphosphoramide the analytical and entomological data of which were nearly identical with the data of compound IV.

The experimental evidence obtained supports the assumption that the phosphorylation of the pyrophosphates I and II resulted in the synthesis of two new and isomeric tetraphosphoramides, III and IV. Linear and pyramidal dodecamethyltetraphosphoramide are suggested as tentative names for these compounds.

Experimental

Starting Products.—Triethyl phosphate, $(C_2H_5O)_3PO$: $n^{20}D$ 1.4060, $d^{20}{}_4$ 1.0692, b.p. 89° (10 mm.); O,O-diethyl dimethylamidophosphate, $(CH_3)_2NPO(OC_2H_5)_2$: $n^{20}D$ 1.4231, $d^{20}{}_4$ 1.0473, b.p. 93° (10 mm.); tetramethyldiamidophosphoryl chloride, $[(CH_3)_2N]_2POCl$[16]: $n^{20}D$ 1.4670, $d^{20}{}_4$ 1.1823, b.p. 110° (10 mm.); *sym*-O,O-diethyl tetramethyldiamidopyrophosphate,[16] $[(CH_3)_2N](C_2H_5O)P(O)OP(O)(OC_2H_5)[N(CH_3)_2]$, $C_8H_{22}N_2O_5P_2$: $n^{25}D$ 1.4413, $d^{25}{}_4$ 1.1602, b.p. 129° (1.5 mm.); *asym*-O,O-diethyl tetramethyldiamidopyrophosphate,[16] $[(CH_3)_2N]_2P(O)OP(O)(OC_2H_5)_2$, $C_8H_{22}N_2O_5P_2$: $n^{25}D$ 1.4379, $d^{25}{}_4$ 1.1623, b.p. 140° (1.5 mm.); O-ethyl hexamethyltriamidopyrophosphate,[16] $[(CH_3)_2N]_2P(O)OP(O)(OC_2H_5)[N(CH_3)_2]$, $C_8H_{23}N_3O_4P_2$: $n^{25}D$ 1.4505, $d^{25}{}_4$ 1.1417, b.p. 138° (2 mm.).

Syntheses of Decamethyltriphosphoramide.—A mixture of 21 g. (0.073 mole) of the triamidopyrophosphate $C_8H_{23}N_3O_4P_2$ with 12.5 g. (0.073 mole) of tetramethyldiamidophosphoryl chloride was heated two hours with agitation at 130°. The gas released was absorbed in ethanol and identified by infrared as ethyl chloride. Its quantity amounted to 4.25 g. (90.5% of theory). The residue was heated to 130° under a pressure of 15 mm. in order to remove any unreacted monophosphate. The remaining yellow-brown oil was analyzed as to its identity with the triphosphate desired.

Anal. Calcd. for $C_{10}H_{30}N_5O_5P_3$: N, 17.81; P, 23.6; mol. wt., 393.4. Found: N, 17.2; P, 23.2; mol wt., 405 (in benzene, lowering of freezing point); $n^{20}D$ 1.4644; $d^{20}{}_4$ 1.1931; yield, 29.2 g. (theor. 28.8 g.).

A mixture of 13.3 g. (0.073 mole) of O,O-diethyl dimethylamidophosphate with 25.0 g. (0.146 mole) of tetramethyldiamidophosphoryl chloride reacted as described; recovered ethyl chloride, 8.3 g. (87.9%).

Anal. Found: N, 17.25; P, 22.9; mol. wt., 386; yield, 30.0 g. (theor. 28.85 g.); $n^{20}D$ 1.4639; $d^{20}{}_4$ 1.1938.

The rate of formation of decamethyltriphosphoramide from one mole of $(CH_3)_2NPO(OC_2H_5)_2$ and two moles of $[(CH_3)_2N]_2POCl$ was studied at 100 and 130° by measuring the amount of C_2H_5Cl released.

Reacn. temp., °C.	Ethyl chloride formed, %	
	After one hour	After 2 hours
100	10	19
130	72	88

Synthesis of Linear Dodecamethyltetraphosphoramide (III).—A mixture of 14.4 g. (0.05 mole) of *sym*-O,O-diethyl tetramethyldiamidopyrophosphate with 17.1 g. (0.1 mole) of tetramethyldiamidophosphoryl chloride was heated for two hours at 130° with agitation; amount of gas released, 5.8 g. (90%). The reaction product was heated to 130° under a pressure of 15 mm., to give a brownish oil, which was analyzed.

Anal. Calcd. for $C_{12}H_{36}N_6O_7P_4$: N, 16.76; P, 24.76; mol. wt., 500.4. Found: N, 16.2; P, 24.0; mol. wt., 510 (in benzene, lowering of freezing point); yield, 25.6 g. (theor. 25.02); $n^{20}D$ 1.4719; $d^{20}{}_4$ 1.2561.

Syntheses of Pyramidal Dodecamethyltetraphosphoramide (IV). A.—A mixture of 14.4 g. (0.05 mole) of *asym*-O,O-diethyl tetramethyldiamidopyrophosphate with 17.1 g. (0.1 mole) of tetramethyldiamidophosphoryl chloride was heated for two hours at 130° with agitation; ethyl chloride released, 5.9 g. (91.6%). The reaction product was heated to 130° under a pressure of 15 mm. to produce a brownish oil which was isolated and analyzed.

Anal. Found: N, 16.0; P, 24.3; mol. wt., 487, yield 25.5 g., $n^{20}D$ 1.4681, $d^{20}{}_4$ 1.2471.

B.—A mixture of 87.0 g. (0.51 mole) of tetramethyldiamidophosphoryl chloride with 31.0 g. (0.17 mole) of triethyl phosphate was heated with agitation for three hours at 130°. A mixture of the same composition was heated under analogous conditions at 150°. These should yield, theoretically, 33 g. of ethyl chloride and 85 g. of a tetraphosphate with a molecular weight of 500.4. Actually, the following results were found:

Reacn. time, hr.	C_2H_5Cl released, g.		Mol. wt. of reacn. prod.	
	130°	150°	130°	150°
1	19.8	28.4	397	504
$1^2/_3$	25.4	29.0	421	550
3	29.0	29.0	514	450

The run at 130° was repeated without taking out samples. After three hours the product was put under a reduced pressure of 15 mm. A total of 30.5 g. (92.3%) of ethyl chloride was released. The amber, oily polyphosphate residue was analyzed.

Anal. N, 16.5; P, 24.2; Cl, 0.4; mol. wt., 457, $n^{20}D$ 1.4690, $d^{20}{}_4$ 1.2485; yield 87 g.

Reaction of III and IV with PCl_5.—Five grams (0.01 mole) of the compounds III and IV, respectively, were dissolved in 15 cc. of carbon tetrachloride. The solutions were separately added to two portions of 6.5 g. of phosphorus pentachloride (0.031 mole) under CCl_4 and then refluxed. Infrared analysis of the clear solutions revealed the following: The linear tetraphosphate III gave a product containing $[(CH_3)_2N]_2POCl$ and $(CH_3)_2NPOCl_2$ in the mole ratio of about 1:1. The pyramidal tetraphosphate IV yielded a product which contained $[(CH_3)_2N]_2POCl$ only.

Acknowledgment.—The author wishes to express his appreciation to Drs. A. W. Baker, Ch. W. Young and L. E. Streeter for analyses and to E. E. Kenaga for entomological tests reported in this paper.

MIDLAND, MICHIGAN

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[16] Prepared according to G. Schrader, ref. 11.