Preparation of 3-Methylpentanephosphonic Acid.—Sixteen grams of the acid chloride was hydrolyzed by adding to water and the resulting oil slowly crystallized. After recrystallization from water and drying under vacuum, it was a colorless, semi-solid material and further purification was not attempted.

Anal. Calcd. for $C_6H_{15}PO_3$: P, 18.67; equivalent weight, 83.07. Found: P, 18.60; equivalent weight, 83.09.

The acid was dibasic with a dissociation constant for the first hydrogen of approximately $K_A = 10^{-4}$.

Reaction with Cyclohexane.—Forty-two grams (0.5 mole) of cyclohexane (95% pure) was mixed with 274 g. (2.0 moles) of phosphorus trichloride and bubbled with oxygen until the exothermic reaction was over. The mixture was distilled at 10–15 mm. of mercury pressure and a fraction weighing 49 g. was taken boiling between 115 and 130°. This was redistilled at 15 to 16 mm. of mercury pressure and yielded 36 g. of a colorless liquid boiling between 127.5 and 128.2° which after a short time crystallized to needles with the following properties: d^{20} (supercooled liquid) 1.2955 g./cc., n^{20}_D (supercooled liquid) 1.5059, freezing point (cooling curve) 37.0–37.5°.

Anal. Calcd. for $C_6H_{11}POCl_2$: C, 35.80; H, 5.47; P, 15.43; Cl, 35.28. Found: C, 35.58; H, 5.65; P, 15.35; Cl, 34.95.

Preparation of Cyclohexanephosphonic Acid.—Twenty-six grams of cyclohexanephosphonyl chloride was poured into water, stirred and gently heated. The water was then evaporated until crystallization occurred on cooling. The solid was filtered off, dried in vacuum and the melting point determined (160–163°). It was recrystallized five more times from water using Norite to remove color. The following properties were determined: m. p. 166–167°, K_A(1st H) 4 × 10^{-5}, K_A(2nd H) 2 × 10^{-10}.

Anal. Calcd. for $C_6H_{13}PO_3$: C, 43.87; H, 7.99; P, 18.90. Found: C, 42.27; H, 7.98; P, 18.91. (Low carbon values were obtained on several repetitions of carbon-hydrogen analysis. It was noted that this compound on burning left a black colored glaze on porcelain ware and the low carbon determinations are believed to be due to colloidally dispersed carbon contained in the glaze.)

Reaction with Propane.—A mixture of oxygen and propane was bubbled through phosphorus trichloride until the heat effect had subsided. Distillation yielded phosphorus oxychloride and a small amount of higher boiling material which hydrolyzed to a dibasic acid with an equivalent weight of 64. The calculated equivalent weight of propanephosphonic acid is 62.0.

Summary

A new synthesis for alkane- and cycloalkanephosphonyl chlorides is described. The method involves the reaction of a hydrocarbon with phosphorus trichloride and oxygen, and has been used in the synthesis of several new alkane- and cycloalkanephosphonyl chlorides and phosphonic acids, properties of which are presented.

RICHMOND, CALIFORNIA RECEIVED APRIL 14, 1948

[CONTRIBUTION FROM THE RESEARCH LABORATORY, VICTOR CHEMICAL WORKS]

The Preparation of Tetraethyl Pyrophosphate and Other Tetraalkyl Pyrophosphates

BY A. D. F. TOY

Introduction

The chemistry of the inorganic polyphosphates is quite well established, but very little is known concerning the organic polyphosphates. The discovery by German chemists that the so-called "hexaethyl tetraphosphate"[1,2,3] is of value as an economic poison has shown the necessity for more extended research on the organic polyphosphates. Earlier investigation of the organic polyphosphates in this Laboratory had already led to the development of a superior process[4,5] for the synthesis of hexaethyl tetraphosphate. This process involves the interaction of phosphoric anhydride with triethyl phosphate and yields a product having properties identical with that made by the Schrader[1] process. Subsequent research had shown that hexaethyl tetraphosphate is not a pure compound but consists of a mixture of several ethyl polyphosphates. This conclusion was also verified by Hall and Jacobson.[6]

Our investigations were therefore extended to the ethyl esters of other phosphoric acids, including pyro- and triphosphoric acids. During the course of these studies we found that tetraethyl pyrophosphate is a much more toxic substance than the so-called "hexaethyl tetraphosphate." This same fact was reported independently by Ludvik and Decker.[7]

The preparation of pure vacuum distillable tetraethyl pyrophosphate has been described by several investigators. Arbuzov and Arbuzov[8] claimed to have obtained it in very small yield when they fractionally distilled a complex mixture resulting from the action of bromine or chlorine on diethyl sodium phosphite. Hall and Jacobson found that the method described by Cavalier[9] and Clermont[10] which involves the action of silver pyrophosphate on ethyl iodide also produces distillable tetraethyl pyrophosphate in low yield. Distillable tetraethyl pyrophosphate may also be obtained in 20–30% yield by extraction with chloroform or benzene of the partially hydrolyzed nondistillable ethyl polyphosphates produced by the modified Schrader or Woodstock processes.[6] The acidic components of these mixtures are removed in the aqueous layer; the tetraethyl pyrophosphate is recovered by the fractional distillation of the organic extract.

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[1] Schrader, German Patent 720,577 (1942); U. S. Patent 2,336,302 (1943).

[2] Hall, P. B. Rept. 252 (1945).

[3] Kilgore, *Soap and Sanit. Chemicals*, [12] **21**, 138 (1945).

[4] Woodstock, U. S. Patent 2,402,703 (1946).

[5] Adler and Woodstock, *Chem. Ind.*, **51**, 516 (1942).

[6] Hall and Jacobson, *Ind. Eng. Chem.*, **40**, 694 (1948).

[7] Ludvik and Decker, *J. Econ. Entomol.*, **40**, 97 (1947).

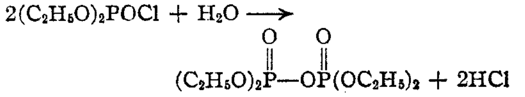
[8] Arbuzov and Arbuzov, *J. prakt. Chem.*, **130**, 103 (1931); *Ber.*, **65**, 195 (1932).

[9] Cavalier, *Compt. rend.*, **142**, 885 (1906).

[10] Clermont, *Ann. chim.*, **44**, 330 (1855).

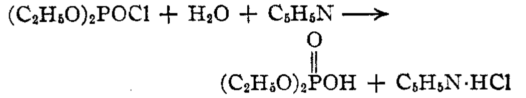
Hall and Jacobson[6] also described a process which involves the action of diethyl chlorophosphate on triethyl phosphate. We have used the same process, but have found it to produce distillable tetraethyl pyrophosphate in unsatisfactory yields. The distilled product is furthermore contaminated not only with some triethyl phosphate but by a small amount of diethyl phosphoric acid.

The present paper describes a simple method for the synthesis of pure tetraethyl pyrophosphate in good yield. This method involves the controlled hydrolysis of diethyl chlorophosphate according to the equation

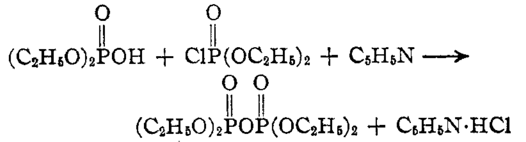


$$2(C_2H_5O)_2POCl + H_2O \longrightarrow (C_2H_5O)_2\overset{\overset{\textstyle O}{\|}}{P}-O\overset{\overset{\textstyle O}{\|}}{P}(OC_2H_5)_2 + 2HCl \qquad (1)$$

The removal of hydrogen chloride may be accomplished (1) by carrying out the reaction under reduced pressure, or (2) by employing chemical agents such as pyridine or sodium hydrogen carbonate. The second general method is preferred since high yields are obtained consistently. In carrying out the reaction, a 100% excess of water over that required by the equation may be used but too great an excess of water brings about the formation of increasing quantities of diethyl phosphoric acid. The hydrolysis of diethyl chlorophosphate in the presence of pyridine to give tetraethyl pyrophosphate is apparently a simple stepwise process as illustrated by the equations



$$(C_2H_5O)_2POCl + H_2O + C_5H_5N \longrightarrow (C_2H_5O)_2\overset{\overset{\textstyle O}{\|}}{P}OH + C_5H_5N\cdot HCl \qquad (2)$$



$$(C_2H_5O)_2\overset{\overset{\textstyle O}{\|}}{P}OH + Cl\overset{\overset{\textstyle O}{\|}}{P}(OC_2H_5)_2 + C_5H_5N \longrightarrow (C_2H_5O)_2\overset{\overset{\textstyle O}{\|}}{P}O\overset{\overset{\textstyle O}{\|}}{P}(OC_2H_5)_2 + C_5H_5N\cdot HCl \qquad (3)$$

A good yield of tetraethyl pyrophosphate may also be obtained by adding diethyl chlorophosphate to a pyridine–water mixture containing a 100% excess of water over that required for complete conversion to the pyrophosphate. This would indicate that the reaction represented by equation 3 is faster than the one represented by equation 2. If reaction 2 were faster, then in the presence of the excess water the principal product should have been diethyl phosphoric acid. In order to prove more definitely that the process is stepwise in nature, reaction 3 was carried out separately by bringing together diethylchlorophosphate and diethyl phosphoric acid in the presence of pyridine. Tetraethyl pyrophosphate was produced in good yield.

This process of controlled hydrolysis of dialkyl chlorophosphates may be employed not only for preparing tetraethyl pyrophosphate which is water-soluble and itself sensitive to hydrolysis, but it is also applicable for the preparation of water-insoluble tetraalkyl pyrophosphates. Difficulty was experienced in the preparation of tetramethyl pyrophosphate, but even this ester is obtained, although in low yields, if low temperatures are maintained. In general, however, this process was found to be useful for the preparation of tetraethyl pyrophosphate and its higher homologs in high purity and good yields.

The water-insoluble tetrabenzyl pyrophosphate was prepared by Deutsch and Fernö[11] by hydrolysis of dibenzyl chlorophosphate in a cold dilute potassium hydroxide solution.

Experimental

Tetra-alkyl Pyrophosphates

Tetraethyl Pyrophosphate. (a) Reaction Under Reduced Pressure.—The reaction vessel consisted of a three-necked 500-cc. flask fitted with three rubber stoppers through which were inserted, respectively, (a) a thermometer and a coarse capillary connected to a dropping funnel, (b) a capillary connected to a source of dry air and (c) a connection to a vacuum distillation system. In the flask was placed 151 g. (0.876 mole) of diethyl chlorophosphate. Pressure was reduced to 8–10 mm. and 7.9 g. (0.438 mole) of water introduced slowly below the surface of the liquid through a capillary from the dropping funnel. The temperature was maintained at 31–33° by periodic cooling. Thorough mixing was effected by introducing dry air through the appropriate capillary. After the addition of water had been completed (one and one-half to two hours) the system was maintained at 8 mm. and at 31–33° by periodic cooling, until no further heat of reaction was noted. The product was allowed to stand at room temperature at 5–8 mm. for seventeen hours, heated to 60–70° at 6 mm. for one-half hour, and then carefully fractionated. The lower boiling fraction (52 g., b. p. 50–52° at 0.5 mm., n^{25}_D 1.4152) was shown by analysis to be unreacted diethyl chlorophosphate. The higher boiling fraction (b. p. 135–138° at 1 mm.) consisted of 61 g. of tetraethyl pyrophosphate, corresponding to an over-all yield of 48% (or 73.2% based on the unrecovered diethyl chlorophosphate.) The tetraethyl pyrophosphate has the following physical properties: n^{25}_D 1.4180, sp. gr. 1.1978 at 17°, 1.1901 at 24°.

Anal. Calcd. for $(C_2H_5O)_4P_2O_3$: P, 21.4. Found: P, 21.4.

In other experiments it was shown that the hydrolysis of diethyl chlorophosphate is slow at 0° and very rapid at 35°, but that temperatures above 35° lead to undesirable side reactions. In distilling the crude tetraethyl pyrophosphate, it was necessary to heat the mixture up slowly in order to maintain a pressure of 1–2 mm. to avoid decomposition.

(b) Reaction in Presence of Pyridine.—In a 500-cc. three-necked flask equipped with a thermometer, a stirrer and a dropping funnel was placed 133.7 g. (0.775 mole) of diethyl chlorophosphate, to which was added slowly with stirring a mixture of 7.14 g. (0.396 mole or 2.2% excess) of water and 62.7 g. (0.794 mole or 2.45% excess) of pyridine. The temperature was maintained at 0 to 2° by means of an ice–salt-bath. Upon completion of the addition (one hour) the reaction mixture was stirred in the ice–salt-bath for twenty minutes and then heated slowly to 35° for twenty minutes. The mixture was then cooled and filtered and the residue was washed with absolute ether. The filtrate and ether washings were combined and subjected to distillation. After the removal of the lower boiling solvents, the product was distilled at 1–2 mm. The main fraction obtained weighed 99 g. (88%), n^{25}_D 1.4182. The above reaction may be carried out in the presence of absolute ether as a solvent with no appreciable changes in the yield even if a 100% excess of water is used. However, when the excess of water was increased to 400% the yield dropped to 71%; the index of refraction was also found to be lower

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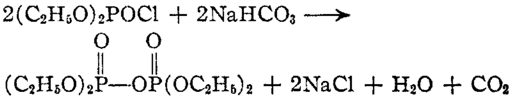
(11) Deutsch and Fernö, *Nature*, **156**, 604 (1945).

($n^{25}\mathrm{D}$ 1.4170), indicating a product of lesser purity. It was found also that when the reaction was carried out using 100% excess of water and by the reverse addition of the reactants, *i. e.*, by addition of diethyl chlorophosphate to pyridine and water mixture in ether solution, the yield decreased slightly (86.2%); the index of refraction, however, was lower ($n^{25}\mathrm{D}$ 1.4172).

(c) **Reaction in Presence of Sodium Hydrogen Carbonate.**—Equation:



$$2(C_2H_5O)_2POCl + 2NaHCO_3 \longrightarrow (C_2H_5O)_2\overset{\overset{\large O}{\|}}{P}—O\overset{\overset{\large O}{\|}}{P}(OC_2H_5)_2 + 2NaCl + H_2O + CO_2 \quad (4)$$

In a 500-cc. three-necked flask equipped with a stirrer, a thermometer and a condenser for carbon dioxide outlet, was placed 86.2 g. (0.5 mole) of diethyl chlorophosphate, 1 cc. of water as catalyst, and finally 43.05 g. (0.512 mole or 2.5% excess) of sodium hydrogen carbonate in one portion. Upon stirring the reaction started gradually. After twenty-eight minutes the temperature had reached 35° but the mixture was then cooled and maintained at 30°. The reaction proceeded with evolution of carbon dioxide. After a total of two hours the temperature dropped to 26° without external cooling. The reaction product was filtered and the residue washed with benzene. The filtrate and washings were combined and distilled under reduced pressure. After the removal of the low boiling solvents 59.5 g. of tetraethyl pyrophosphate was collected at 125–130° at 0.5 mm., $n^{25}\mathrm{D}$ 1.4170.

When the above experiment was carried out using an equivalent quantity of sodium carbonate the reaction was much slower and resulted in a lower yield as well as a product of lower purity.

(d) **Reaction of Diethyl Chlorophosphate and Diethyl Phosphoric Acid in Presence of Pyridine.**—To 16.4 g. (0.1065 mole) of redistilled diethyl phosphoric acid ($n^{25}\mathrm{D}$ 1.4148) and 18.4 g. (0.1065 mole) of diethyl chlorophosphate dissolved in 50 cc. of absolute ether was added with stirring 8.82 g. (0.1115 mole) of pyridine dissolved in 25 cc. of absolute ether. The temperature was maintained at 2–3° by means of an ice–salt-bath. Upon completion of the addition, the stirring was continued in the cold for twenty minutes and then at room temperature for two to three hours. Finally it was heated to 35° for thirty minutes. It was then cooled and filtered and the residue washed with 125 cc. of absolute ether. The combined filtrate and washings were distilled under reduced pressure. After the removal of the low boiling solvents, 27.1 g. (87.8%) of tetraethyl pyrophosphate was collected, $n^{25}\mathrm{D}$ 1.4178.

Other Tetraalkyl Pyrophosphates

Tetramethyl Pyrophosphate.—To 28.9 g. (0.2 mole) of dimethyl chlorophosphate dissolved in 50 cc. of absolute ether was added a mixture of 1.89 g. (0.105 mole) of water and 16.6 g. (0.21 mole) of pyridine dissolved in 30 cc. of absolute ether. The temperature of the addition was maintained at 0 to 2°. Upon completion of the addition (one and one-half hours) the mixture was stirred in the cold-bath for thirty minutes and then filtered while cold. The residue was washed with absolute ether. The combined filtrate and ether washings were heated under reduced pressure to remove the solvent and then distilled. The principal fraction collected at 114–116° at 0.5 mm. weighed 9 g. (38.6%). Redistillation gave a product with the following properties: $n^{25}\mathrm{D}$ 1.4121, sp.gr. 1.3608 at 25°.

Anal. Calcd. for $(CH_3)_4P_2O_7$: P, 26.6. Found: P, 26.3.

It is important to note that in the above reaction, the product must be separated from the reaction mixture while it is still cold. When the mixture was allowed to stand for several days at room temperature or when heated to 35° in the presence or absence of ether as solvent, the solid pyridine hydrochloride became a sirupy mass and gas was evolved. Some decomposition had apparently occurred and no tetramethyl pyrophosphate was isolated.

Tetra-*n*-propyl Pyrophosphate.—To 63.9 g. (0.319 mole) of di-*n*-propyl chlorophosphate ($n^{25}\mathrm{D}$ 1.4229, sp. gr. 1.1163 at 25°) was added, with stirring, a mixture of 3 g. (0.167 mole) of water and 26.5 g. (0.336 mole) of pyridine at 28–30°. Five minutes were required for the addition. The thick mixture was stirred at room temperature until no more heat of reaction was observed. It was then heated to 35° for thirty minutes in order to insure completion of the reaction; fifty cc. of absolute ether was added and the slurry filtered. The residue was washed with a total of 150 cc. of absolute ether. The ether filtrate and washings were evaporated under reduced pressure to remove the solvents. The residue was found to be acidic to methyl orange and was therefore washed with 50 cc. of cold 5% sodium hydrogen carbonate solution. The resultant neutral oil was then heated under reduced pressure to remove the water and distilled. The distillate, weighing 40 g. (72.5%), boiled at 112–116° at 0.01 mm., $n^{25}\mathrm{D}$ 1.4248 and sp. gr. 1.1037 at 25°. Arbuzov and Razumov[12] reported the isolation of this compound from the complex mixture resulting from the reaction of dipropyl sodium phosphite with bromine in ligroin.

Anal. Calcd. for $(C_3H_7)_4P_2O_7$: P, 17.9. Found: P, 17.4.

Tetraisopropyl Pyrophosphate.—To 63.9 g. (0.319 mole) of diisopropyl chlorophosphate was added 26.5 g. (0.336 mole) of pyridine and 3 g. (0.167 mole) of water. Upon completion of the reaction 50-cc. of ice-water was added to the slurry to dissolve the pyridine hydrochloride. The oily layer was washed twice with 50-cc. portions of ice-water. All washings were neutral to methyl orange. The oil was then heated under reduced pressure to remove residual moisture and finally distilled. The main fraction, boiling at 92–95° at 0.01–0.02 mm., weighed 52 g. (94%). The ester is a water-white liquid, freezing at 14–15°, $n^{25}\mathrm{D}$ 1.4170, sp. gr. 1.0854 at 25°.

Anal. Calcd. for $(i\text{-}C_3H_7)_4P_2O_7$: P, 17.9. Found: P, 17.9.

When the above reaction was carried out in ether as solvent, it proceeded very slowly. Several hours of refluxing were required for the completion of the reaction.

Tetra-*n*-butyl Pyrophosphate.—To 45.5 g. (0.2 mole) of di-*n*-butyl chlorophosphate was added a mixture of 1.89 g. (0.105 mole) of water and 16.6 g. (0.21 mole) of pyridine. Upon completion of the reaction fifty cc. of ice-water was added to the pasty slurry. The oily layer was separated and washed twice with 3–5% sodium chloride solution, since there was a tendency for the product to form an emulsion. The oil was heated under reduced pressure to remove moisture and then distilled. A water-white liquid insoluble in water, weighing 34 g. (84.5%) was obtained, b. p. 143–146° at 0.01 mm., $n^{25}\mathrm{D}$ 1.4296, sp. gr. 1.0533 at 25°.

Anal. Calcd. for $(C_4H_9)_4P_2O_7$: P, 15.4. Found: P, 15.2.

Hydrolysis

The rates of hydrolysis of the various tetraalkyl pyrophosphates vary with the nature of the alkyl groups. Results of a comparative study are presented in Figs. 1 and 2. The hydrolysis reaction of tetraethyl pyrophosphate is of the first order as has been shown by Hall and Jacobson.[6] Hydrolysis of the methyl ester likewise depends only on the concentration of the solute, but the rate is much faster. In the case of the *n*-propyl and isopropyl ester it became apparent from reference to the Curve III, Fig. 1, and Curve I, Fig. 2, that deviations appear after hydrolysis has proceeded to the extent of approximately 85 and 50%, respectively. It is of interest to note that the iso-

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[12] Arbuzov and Razumov, *J. Gen. Chem.* (*U. S. S. R.*), **7**, 1762 (1937).

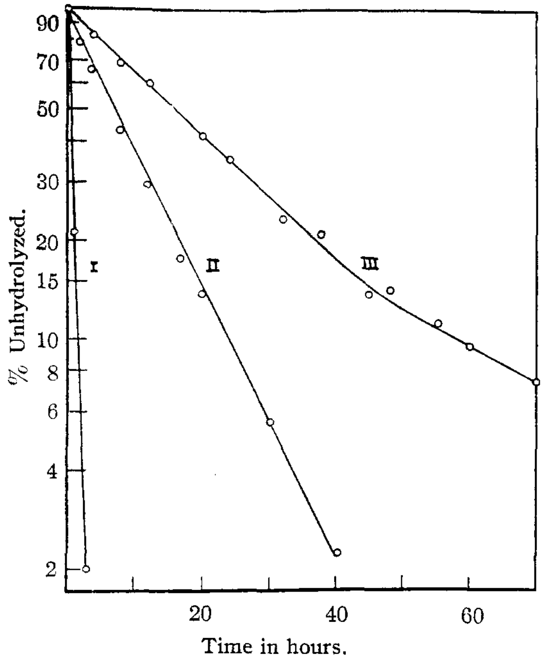

Fig. 1.—Rate of hydrolysis of tetraalkyl pyrophosphates ($R_4P_2O_7$), 0.02 *M* solution in water at 25°: I, R = methyl; II, R = ethyl; III, R = *n*-propyl.

propyl ester has a much slower rate of hydrolysis compared with that for the *n*-propyl ester. For the tetrabutyl pyrophosphate which is only slightly soluble in water, hydrolysis was carried out by stirring the ester continuously with water in the presence of an emulsifier (Triton X-100). Obviously the extent of hydrolysis depends in this case on many factors such as degree of agitation and degree of emulsification (droplet size). Data for the butyl ester are therefore not directly comparable with those obtained for the lower water soluble homologs. The zero hour point on all the curves was determined by titrating the compound dissolved in acetone with a standard ethylene glycol solution of sodium hydroxide. In such a solution, only the free acid present as an impurity is determined. The product of hydrolysis under the prescribed conditions is the dialkyl phosphoric acid as indicated by the form of the *p*H titration curve characteristic for a strong monobasic acid. No evidence for the formation of a dibasic acid was detected.

When the hydrolysis of tetraethyl pyrophosphate was carried out using the theoretical quantity of water [$(C_2H_5)_4P_2O_7$:H_2O = 1:1], the rate of hydrolysis at room temperature was very slow at the beginning, as shown in Curve III, Fig. 2. It is therefore possible to prepare the tetraethyl derivative from the diethylchlorophosphate even in the presence of 100% excess of water when sodium hydrogen carbonate is used as the condensation agent.

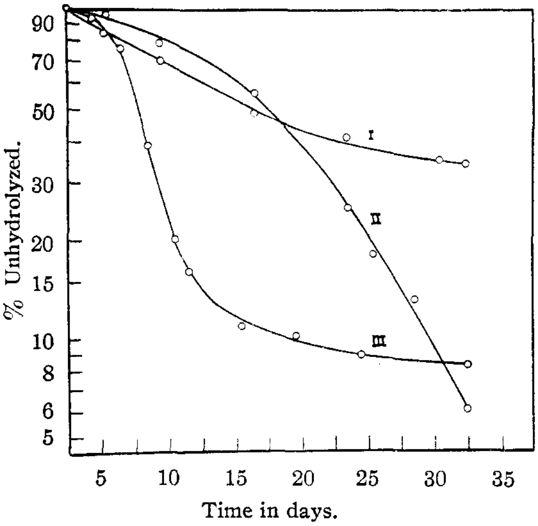

Fig. 2.—Rate of hydrolysis of tetraalkyl pyrophosphates under varying conditions at 25°: I, tetra-*i*-propyl pyrophosphate, 0.02 *M* solution; II, tetra-*n*-butyl pyrophosphate, 0.02 *M* in contact with water; III, tetraethyl pyrophosphate, [$(C_2H_5O)_4P_2O_3 \cdot H_2O$ = 1:1].

The hydrolysis of tetraethyl pyrophosphate does, however, serve as a simple method for the preparation of diethyl phosphoric acid in high purity. When tetraethyl pyrophosphate was heated for sixteen hours at 60° in the presence of 2.5 times the required amount of water and the excess water removed by heating to 50–55° at 1 to 2 mm., the residue contained 97.7% of diethyl phosphoric acid contaminated with approximately 1% of monoethyl phosphoric acid. Such a mixture was further purified by distillation under reduced pressure. The distilled product had a boiling point of 116 to 118° at 0.01 mm., n^{25}D 1.4146 to 1.4152, and was found to contain 98.6 to 99.5% diethyl phosphoric acid by titration.

The above method for isolating pure diethyl phosphoric acid is obviously simpler than the known process for isolation by the acidification of the barium salt derived from the complex reaction product of phosphoric anhydride and ethyl alcohol. It was found that unless the diethyl phosphoric acid is at least 94–95% pure, it cannot be distilled without extensive decomposition. Even distillation of the fairly pure product is accompanied by some decomposition. The contaminant in the distillate is triethyl phosphate.

TABLE I

	MLD_{50}, mg./kg.
Tetramethyl[a]	1.9
Tetraethyl[a]	0.82
Tetra-*n*-propyl	9.5
Tetra-*i*-propyl	13.3
Tetra-*n*-butyl	14.2

[a] These compounds were also submitted to G. H. Mangun who presented a report of their toxicity in a paper before the Pharmacology Section of the American Society for Pharmacology and Experimental Therapeutics, May, 1947, Chicago, Illinois.

Toxicity

The toxicity of the tetraalkyl pyrophosphates was determined by intraperitoneal injection on male white mice. The toxicity data are summarized in Table I.

Acknowledgment.—The author expresses thanks to Mr. A. R. Wreath for the analyses and the data on hydrolysis, to Mr. W. B. Coleman for the data on toxicity and to Dr. Howard Adler for his helpful advice.

Summary

1. Tetraethyl pyrophosphate has been prepared by the controlled hydrolysis of diethyl chlorophosphate. Removal of hydrogen chloride was effected either under reduced pressure or by chemical treatment with bases such as pyridine or sodium hydrogen carbonate.

2. The method of controlled hydrolysis of dialkyl chlorophosphates in the presence of pyridine has been employed for the preparation of the methyl, *n*-propyl, isopropyl and *n*-butyl pyrophosphates.

3. Diethyl phosphoric acid has been prepared in high purity from the initial hydrolysis product of tetraethyl pyrophosphate.

4. Comparative data are presented for the hydrolysis rates and the toxicities to white mice of a series of tetraalkyl pyrophosphates.

CHICAGO HEIGHTS, ILLINOIS RECEIVED JUNE 28, 1948

[CONTRIBUTION FROM THE CHEMICAL CORPS TECHNICAL COMMAND, ARMY CHEMICAL CENTER, MD.]

Radioactive Diisopropyl Fluorophosphate

BY BENJAMIN WITTEN AND JACOB I. MILLER

Diisopropyl fluorophosphate has been shown to have a specific action on the enzyme cholinesterase.[1,2,3] As part of a program to investigate the mode of action in the body more completely by means of radioactive tracer techniques, we have synthesized, on a millimole scale, diisopropyl fluorophosphate containing the radioisotope P32 as part of the molecule.

The synthesis of diisopropyl fluorophosphate has been previously described.[2,3,4] Radioactive phosphorus trichloride, a necessary intermediate, was synthesized from radioactive potassium dihydrogen phosphate or radioactive phosphoric acid, in which case potassium monohydrogen phosphate was added as a carrier.

Experimental

1. **Preparation of Calcium Phosphate—Pyrophosphate Mixture.**—A mixture of 1 g. of radioactive potassium dihydrogen phosphate and 0.412 g. of potassium hydroxide was dissolved in 3.5 ml. of water. The solution was added, with stirring, to a 15-ml. centrifuge tube containing 2.2 g. of calcium chloride dissolved in 7 ml. of water. Dicalcium phosphate and some calcium phosphate precipitated.[5] The mixture was centrifuged, and washed three times with 3 ml. of water per washing to remove the excess calcium chloride. The tube containing the moist dicalcium and calcium phosphates was heated at 500° for three hours in an electric furnace to convert the dicalcium phosphate to calcium pyrophosphate.[6]

2. **Conversion to Phosphorus Pentachloride and Oxychloride Mixture.**—A quartz tube, 15 mm. i.d. × 60 cm., was ground to fit a 25-ml. collecting flask with a side-arm to which was attached a drying tube containing Drierite.

The calcium phosphate–pyrophosphate mixture (0.93 g.) was intimately mixed with 2.5 g. of 30 to 60 mesh charcoal. The mixture was introduced into the quartz tube. The tube, which was held in a horizontal position during the run, was heated by an electric furnace at 700°. While the mixture was heated, a stream of chlorine at a flow rate of 20–25 ml. per minute was passed through the tube. The collecting flask was cooled with a Dry Ice-bath during the run. After six hours, the exposed part of the tube was heated with free flame of a Meker burner to volatilize and collect any product which remained in the tube. The yield of product, which consisted of a mixture of phosphorus pentachloride and oxychloride, was 1.5 g.[7,8]

3. **Phosphorus Trichloride.**—The collecting flask was connected to a quartz tube, 4 mm. i.d. × 19 cm., into which was introduced 0.35 g. of 30- to 60-mesh charcoal. The quartz tube, which was held in a horizontal position, was attached to a 5-ml. two-necked receiver. A stirrer, consisting of a piece of soft iron completely sealed in glass was placed into the receiver. Stirring was accomplished by rotating a magnet beneath the flask. The receiver was connected to a water condenser, which terminated in a drying tube containing Drierite. The quartz tube was heated at 650° in an electric furnace.

The collecting flask was cooled with Dry Ice and 0.9 g. of powdered antimony (20-mesh and finer) was rapidly sprayed into it from an eye dropper in such a manner as to cover completely the surface of the phosphorus pentachloride–oxychloride mixture. The Dry Ice-bath was removed, and the flask was cautiously heated with a free flame until the exothermic reaction between antimony and the pentachloride set in. The antimony reduced the pentachloride to the trichloride.[9] In some runs it was even necessary to moderate the reaction with an ice-bath. When the vigorous reaction had subsided, the mixture was heated by an oil-bath. The bath temperature was gradually raised over a period of ninety minutes to 150°. Phosphorus oxychloride was reduced to the trichloride as the vapors passed over the carbon in the hot tube.[8,10]

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