[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CINCINNATI]

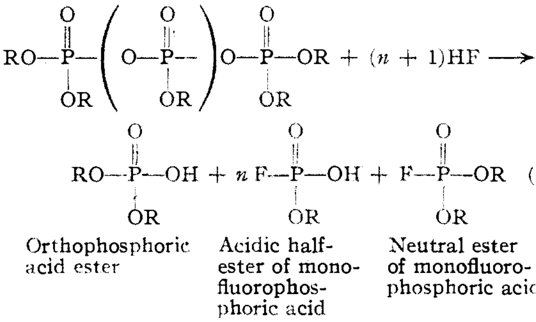
Esters of Monofluorophosphoric Acid[1]

BY ARCHIE HOOD[2] AND WILLY LANGE[3]

The neutral dialkyl esters of monofluorophosphoric acid, $(RO)_2POF$, and in particular the diisopropyl ester, DFP, have become of interest since Adrian, Kilby and Kilby[4] discovered the extreme toxicity of these esters and shortly thereafter found the toxicity to be the result of a pronounced cholinesterase inhibitory power.[4,5] Lange and v. Krueger[6] first synthesized dialkyl monofluorophosphates by means of the reaction of alkyl iodides with silver monofluorophosphate, and they noted the pronounced effects of these neutral esters on the human organism. McCombie, Saunders, and a group of co-workers[7] later developed practical methods for producing the esters, and in particular diisopropyl monofluorophosphate, by methods involving the use of either phosphoryl fluorodichloride, or dialkyl esters of monochlorophosphoric acid as essential intermediates.

Possible medical applications of diisopropyl monofluorophosphate, as discussed recently by Wood,[8] have stimulated an interest in obtaining readily water-soluble derivatives of alkyl esters of monofluorophosphoric acid, containing the grouping $-(RO)POF$, for physiological tests and possible medical application.

The present study was initiated with the aim of producing certain acidic half-esters of monofluorophosphoric acid, $(HO)(RO)POF$, which would be water-soluble as such or in the form of their alkali salts. A method was developed for producing these half-esters, as well as the corresponding neutral esters, by a reaction illustrated by the equation

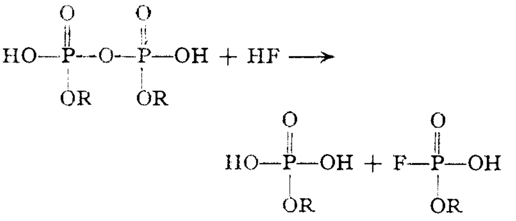


$$\mathrm{RO-\overset{O}{\underset{OR}{P}}-\left(O-\overset{O}{\underset{OR}{P}}-\right)O-\overset{O}{\underset{OR}{P}}-OR} + (n+1)\mathrm{HF} \longrightarrow$$

$$\mathrm{RO-\overset{O}{\underset{OR}{P}}-OH} + n\,\mathrm{F-\overset{O}{\underset{OR}{P}}-OH} + \mathrm{F-\overset{O}{\underset{OR}{P}}-OR} \quad (1)$$

As would be expected from the above equation, the highest yields of neutral esters of monofluorophosphoric acid, $(RO)_2POF$, were obtained from neutral tetra-esters of pyrophosphoric acid, or in other words in the case in which n is zero. As a matter of fact, the synthesis of diethyl monofluorophosphate was found to be nearly quantitative according to the equation in the reaction of a slight excess of anhydrous hydrogen fluoride with tetraethyl pyrophosphate at or below room temperature. Although quantitative experimental results were not obtained with polyphosphates containing three or more phosphorus atoms, since no such esters were available as relatively pure individual compounds, experimental evidence showed that with increasing chain length of the polyphosphoric acid ester there was a corresponding increase in the proportion of monoalkyl monofluorophosphate, $(HO)(RO)POF$, formed and a decrease in yields of dialkyl monofluorophosphate and dialkyl orthophosphate. As expected, therefore, best yields of the half-esters of monofluorophosphoric acid were obtained when the starting material was the metaphosphate, which is believed to be a complex mixture of long-chain polyphosphate esters with an average molecular weight sufficiently great that the over-all effect of the end-groups of the chain is practically negligible.

Although best yields, on the basis of phosphorus recovered as the half-ester, were obtained with metaphosphates, the use of a symmetrical pyrophosphoric acid diester was found to be more convenient because of the easier separation of the reaction products



$$\mathrm{HO-\overset{O}{\underset{OR}{P}}-O-\overset{O}{\underset{OR}{P}}-OH + HF} \longrightarrow \mathrm{HO-\overset{O}{\underset{OR}{P}}-OH + F-\overset{O}{\underset{OR}{P}}-OH} \quad (2)$$

Reaction Mechanism.—The mechanism of the reaction seems to be essentially one of successive hydrofluorolysis of the P–O–P bridges of the polyphosphate chain, proceeding successively from one end of the chain to the other, with one phosphorus atom being split off at a time as an ester of $(HO)_2POF$. If the chain were broken in a random fashion, rather than in successive steps from one end to the other, the resulting product would contain considerable and equimolar amounts of dialkyl monofluorophosphate and monoalkyl orthophosphate, but this is found not to be the case.

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[1] A portion of a thesis by A. Hood, submitted to the Faculty of the Graduate School of Arts and Sciences, University of Cincinnati, in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1948.

[2] The Shell Oil Company, Houston, Texas.

[3] The Procter and Gamble Company, Cincinnati 17, Ohio.

[4] E. D. Adrian, W. Feldberg and B. A. Kilby, *Brit. J. Pharmacol.*, **2**, 56 (1947).

[5] H. McCombie and B. C. Saunders, *Nature*, **157**, 776 (1946).

[6] W. Lange and G. v. Krueger, *Ber.*, **65**, 1598 (1932).

[7] H. McCombie and B. C. Saunders, *Nature*, **157**, 287 (1946).

[8] J. R. Wood, *Chem. Corps J.*, **2**, No. 3, 6, 51 (1948).

Half-esters of Monofluorophosphoric Acid and Their Salts.—The low-molecular-weight monoalkyl esters of monofluorophosphoric acid are much like the corresponding orthophosphoric acid diesters, $(RO_2)(HO)PO$, in a number of their physical properties and likewise with respect to salt formation. The great solubility of their salts in general and their thermal instability at elevated temperatures make preparation in high purity quite difficult. As yet the most satisfactory means of purification is repeated molecular distillation.

Salts of the half-esters are quite stable to hydrolysis in neutral or slightly alkaline solutions.

Although these salts might be expected to be excellent water-soluble cholinesterase inhibitors, by analogy with the strongly inhibitory, insoluble neutral esters, Fitch[9] has shown recently that the salts exhibit only weakly inhibitory power.

A solution of the alkali salts was effective in preventing the growth of *Aspergillus niger* and *Aspergillus flavus* in the agar cup-plate test using Czapek-Dox agar cultures. A 0.1% solution of the alkali salts gave in this test a zone of complete inhibition 12 to 23 mm. in diameter and a zone of partial inhibition 31 to 47 mm. in diameter. In the zone of partial inhibition no pigment was produced by *A. niger*. Very little effect, however, was obtained in any medium when the salts were added to cultures of yeast or bacteria.

Work is in progress on the reaction of hydrogen fluoride with polyphosphates, such as adenosine triphosphate, which are carriers of energy-rich phosphate bonds of importance in the enzymic transfer of phosphate radicals between molecules.

Experimental

Materials and Apparatus.—The various polyphosphates used in this study were furnished by the Victor Chemical Works, Chicago Heights, Illinois. Anhydrous hydrogen fluoride (HF) was distilled into the reaction vessel from a Harshaw Chemical Company cylinder. Platinum bottles of 100-ml. capacity were used as reaction vessels, but distillations were performed in glass.

Methods of Analysis.—Phosphorus was determined by precipitation as magnesium ammonium phosphate after removal of fluoride.[10] The Rowley and Churchill[11] modification of the Willard and Winter[12] method was used in determination of fluorine.

General Procedure.—The polyphosphoric acid ester was added in small portions to a small excess of liquid anhydrous hydrogen fluoride in a platinum bottle cooled to about −40°. Additions of the ester were always performed rapidly to ensure minimum exposure of the reactants to atmospheric moisture, and as soon as the platinum stopper was in place again, the contents were agitated by shaking. Continued cooling was necessary to maintain a reaction temperature below 0° because of the great heat of reaction. The final product was allowed to reach room temperature before removing the excess of hydrogen fluoride under vacuum and distilling the desired esters. When both neutral and acidic fluorophosphates were produced, the neutral ester, $(RO)_2POF$, was removed first and purified by conventional vacuum distillation through a column packed with glass helices, and then the residual acidic half-ester, $(RO)(HO)POF$, was purified by repeated short-path distillation.

Hydrogen Fluoride and Tetraethyl Pyrophosphate.—To 3.2 g. (0.16 mole) of HF was added 44.5 g. (0.153 mole) of tetraethyl pyrophosphate, $(C_2H_5O)_4P_2O_3$, with a purity of about 95%. Vacuum fractionation at <0.1 mm. pressure gave a low-boiling fraction of 22.5 g. (0.144 mole) of diethyl monofluorophosphate, $n^{20}D$ 1.3734, d^{20}_4 1.1456, b. p. 170–171°, reported[6] $n^{24.2}D$ 1.3729, $d^{22.2}_4$ 1.144, b. p. 171.5–172° at 757 mm.

Anal. Calcd. for $C_4H_{10}O_3PF$: F, 12.17; P, 19.85. Found: F, 12.0; P, 19.25.

The residue (23.4 g.) was purified by short-path distillation at about 105° at 0.01 mm., distilling almost completely in the form of diethyl orthophosphate.

Anal. Calcd. for $C_4H_{10}O_4P$: neut. equiv., 154. Found: neut. equiv., 149.

Hydrogen Fluoride and Ethyl Metaphosphate.—To 14.5 g. of hydrogen fluoride was added 70 g. of a commercial grade of ethyl metaphosphate. After removal of volatile impurities, there remained 77 g. of crude monoethyl monofluorophosphate, and purification by repeated short-path distillation at 60–100° (0.001 mm.) permitted a recovery of 20 g. (24%) of relatively pure monoethyl monofluorophosphate.

Anal. Calcd. for $C_2H_6O_3PF$: F, 14.84; neut. equiv., 128. Found: F, 14.9; neut. equiv., 134.

Hydrogen Fluoride and "Hexaethyl Tetraphosphate."—To 9.5 g. of hydrogen fluoride was added 76.3 g. of commercial "hexaethyl tetraphosphate," consisting of a mixture of the metaphosphate, pyrophosphate, orthophosphate and possibly triphosphate. After removal of the excess HF, 11.5 g. of diethyl monofluorophosphate was collected in a Dry Ice trap upon heating the residue to 70° at 0.01 mm.

Anal. Calcd. for $C_4H_{10}O_3PF$: F, 12.17. Found: F, 12.9.

Short-path distillation of the residue at 70–125° at 0.001 mm. gave 67 g. of monoethyl monofluorophosphate containing 10.0% F (67% purity). The results show that the original reaction product contained 12% diethyl monofluorophosphate and 45% monoethyl monofluorophosphate.

Hydrogen Fluoride and Pentaethyl Triphosphate.—Pure $Na_5P_3O_{10}\cdot6H_2O$ (56 g., 0.1175 mole) yielded 91 g. (0.115 mole) of $Ag_5P_3O_{10}$. Reaction of 87 g. (0.110 mole) of the silver salt with 82 g. (0.53 mole) of ethyl iodide in ether solution for one day at room temperature yielded 36 g. (0.090 mole, 84%) of crude pentaethyl triphosphate.

Anal. Calcd. for $C_{10}H_{25}O_{10}P_3$: P, 23.4. Found: P, 22.9.

Short-path distillation of about 11 g. at 90–110° at 0.001 mm. gave 1 g. of trapped triethyl phosphate ($n^{24.8}D$ 1.4043), 6.2 g. of distilled tetraethyl pyrophosphate ($n^{24.6}D$ 1.4150), and a residue of 4 g. of ethyl metaphosphate ($n^{24.8}D$ 1.4268). Reaction of another portion, 29.3 g., with 3.7 g. of hydrogen fluoride, followed by distillation and analysis, allowed the following approximations regarding the composition of the reaction product: 43.4% $(C_2H_5O)(HO)POF$; 36.5% $(C_2H_5O)_2(HO)PO$, including some $(C_2H_5O)_3PO$; 17.8% $(C_2H_5O)_2POF$; 2.3% nonvolatile material.

Hydrogen Fluoride and Diethyl Diacid Pyrophosphate.—To 11.0 g. (0.55 mole) of HF was added 113 g. (0.482 mole) of commercial diethyl diacid pyrophosphate $(C_2H_5O)_2(HO)_2P_2O_3$. The reaction product contained 45.6% monoethyl monofluorophosphate and 48.7% monoethyl orthophosphate, the latter value possibly including some triethyl orthophosphate and diethyl orthophosphate. Purification by means of repeated shortpath distillation at 55–58° at less than 0.001 mm. gave 19–20 g. (0.15 mole) of

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[9] H. M. Fitch, Department of Therapeutics, N. Y. University-Bellevue Medical Center, private communication.

[10] W. Lange, *Ber.*, **62**, 786 (1929).

[11] R. J. Rowley and H. V. Churchill, *Ind. Eng. Chem., Anal. Ed.*, **9**, 551 (1937).

[12] H. H. Willard and O. B. Winter, *ibid.*, **5**, 7 (1933).

monoethyl monofluorophosphate of high purity, n^{20}_D 1.3668, d^{20}_4 1.3185.

Anal. Calcd. for $C_2H_6O_3PF$: F, 14.84; P, 24.2; neut. equiv., 128.05. Found: F, 14.8; P, 24.8; neut. equiv., 128–129.

Hydrogen Fluoride and Phenyl Polyphosphate.—The phenyl polyphosphate was prepared by treating 15.6 g. (0.055 mole) of phosphoric anhydride with 90 g. (0.276 mole) of triphenyl orthophosphate, according to the equation[13]

$$5(C_6H_5O)_3PO + P_4O_{10} \longrightarrow 3(C_6H_5O)_5P_3O_5 \quad (3)$$

Then 91 g. of this crude phenyl polyphosphate was mixed with 7.5 g. of anhydrous hydrogen fluoride; 21.2 g. of crude diphenyl monofluorophosphate was recovered by distillation at 1–2 mm., and redistillation of an intermediate fraction gave 3.8 g. of the relatively pure ester, b.p. 117–120° at 0.1–0.5 mm., reported[14] 115–118° at 0.4 mm.

Anal. Calcd. for $C_{12}H_{10}O_3PF$: F, 7.53. Found: F, 7.59.

Half-esters of Monofluorophosphoric Acid, and Their Salts.—One-tenth molar aqueous solutions of potassium monoethyl monofluorophosphate hydrolyzed to the fluoride and monoethyl orthophosphate at a rate of less than 0.1% per hour at 100° at *p*H 7–9, and less than 0.25% per hour at room temperature at *p*H 1 (HCl).

This great hydrolytic stability was reflected in toxicity tests with rats. LD_{50} values greater than 250 mg./kg. were found for sodium salts of both monoethyl and monoisopropyl monofluorophosphates by intraperitoneal injection.

Fitch[9] found the relative molar activity of sodium salts of monoethyl and monoisopropyl monofluorophosphates against cholinesterase to be 2.5×10^{-6} and 7.5×10^{-6}, respectively, compared with DFP as unity.

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Summary

1. The reaction of anhydrous hydrogen fluoride with polyphosphoric acid esters has been studied as a means of preparing esters of monofluorophosphoric acid, $(HO)_2POF$. In this reaction the P–O–P bridges of the polyphosphate chain are split in rapid succession, from one end of the chain to the other, by molecules of hydrogen fluoride, with a fluorine atom becoming attached, in each step, to the phosphorus atom which is split from the end of the chain.

2. Two types of esters of monofluorophosphoric acid have been prepared: (a) the known neutral esters, $(RO)_2POF$, and (b) the hitherto unreported acidic half-esters, $(RO)(HO)POF$, and their alkali salts.

3. In contrast to the neutral esters, salts of the acidic half-esters, *i. e.*, of monoalkyl monofluorophosphates, showed very little toxicity and practically no anti-cholinesterase activity. The alkali salts were effective in preventing the growth of certain molds on solid agar media.

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[13] W. H. Woodstock (to Victor Chemical Works), U. S. Patent 2,402,703, June 25, 1946.

[14] N. B. Chapman and B. C. Saunders, *J. Chem. Soc.*, 1010 (1948).

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, AND THE INSTITUTE OF POLYMER RESEARCH, POLYTECHNIC INSTITUTE OF BROOKLYN]

Cyclic Sulfones. II. The Polymerization of Styrene in the Presence of 3,4-Diphenylthiophene-1-dioxide and 3,4-Di-(*p*-chlorophenyl)-thiophene-1-dioxide[1]

BY C. G. OVERBERGER,[2] HARRY J. MALLON AND RALPH FINE

This paper describes the polymerization of styrene catalyzed by benzoyl peroxide in the presence of 3,4-diphenylthiophene-1-dioxide (III, R = C_6H_5-) and 3,4-di-(*p*-chlorophenyl)-thiophene-1-dioxide (III, R = *p*-ClC_6H_4-) and a study of the retarding properties of these dioxides when present in small concentrations.

We have found that when styrene is polymerized to low conversions with benzoyl peroxide as the catalyst in the presence of small quantities of these thiophene dioxides, the molecular weight of the polystyrene is markedly reduced below that of control experiments, some retardation of the polymerization rate occurs, and the polymer chain contains sulfur in the case of III, R = C_6H_5-, and sulfur and chlorine (in approximately the correct ratio) in the case of III, R = *p*-ClC_6H_4-. When styrene is polymerized in the presence of small quantities of the 3,4-disubstituted thiophenes, the molecular weight of the polystyrene is not appreciably reduced, no retardation is noted, and the polymers contain no sulfur and chlorine.

For the experiments using 3,4-diphenylthiophene-1-dioxide, the rate at low conversions was measured using the dilatometer[3] technique. Although some error is involved due to variations in polymer density for very low molecular weight polymers, we feel that this method is much more satisfactory than precipitation procedures all of

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[1] For the first paper in this series, see THIS JOURNAL, **72**, 2856 (1950). Part of the work described in this manuscript was done under the sponsorship of the Office of Rubber Reserve, Reconstruction Finance Corporation, in connection with the Government Synthetic Rubber Program. Presented in part before the Division of Organic Chemistry of the American Chemical Society at Chicago, September, 1946. A portion of this paper comprises parts of theses presented by Harry J. Mallon and Ralph Fine in partial fulfillment of the requirements for the Master of Science degree in the graduate School of the Polytechnic Institute of Brooklyn.

[2] Department of Chemistry, Polytechnic Institute of Brooklyn.

[3] Goldfinger and Lauterbach, *J. Polymer Sci.*, **3**, 145 (1948).