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I hereby recommend that the thesis prepared under my supervision by Archie Hood

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ESTERS OF MONOFLUOROPHOSPHORIC ACID

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by

Archie Hood

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TABLE OF CONTENTS

INTRODUCTION

It has been known for a number of years that alkyl esters of monofluorophosphoric acid have insecticidal properties. Their use as insecticides, however, has been delayed mainly for the two following reasons: (a) their high volatility, resulting in only temporary usefulness, and (b) the very low solubility in water of the less volatile members of this group of compounds.

The original purpose of this research, therefore, was to make a study of methods of preparing a variety of organic derivatives of monofluorophosphoric acid which were soluble in water and thus satisfactory for subsequent evaluation as insecticides, mothproofing agents, and germicides.

The following two possibilities were considered as a means of attaining this goal:

1. The preparation of neutral esters which could be made soluble in water. The simplest approach in this direction appeared to be the preparation of aromatic esters, which could be sulfonated in the hope of obtaining physiologically active compounds which would act as "colorless dyestuffs" and therefore be useful as permanent mothproofing agents.
2. The synthesis of acid esters, hence monoalkyl monofluorophosphates, which would be soluble in water as such or as an alkali salt. It was hoped that the physiological activity of the FPO grouping in the

neutral esters would be retained in the acid esters and their salts.

During the course of the research, the publication of information concerning the anti-cholinesterase activity of the dialkyl monofluorophosphates and the highly toxic and insecticidal properties of alkyl esters of polyphosphoric acids made it appear desirable to shift the emphasis in the final part of the research toward the second of the above two considerations, or thus toward the acid esters of monofluorophosphoric acid.

The research therefore consisted essentially of a study of the preparation and sulfonation of diphenyl monofluorophosphate and an investigation of the splitting of the P-O-P linkages in alkyl polyphosphates by anhydrous hydrogen fluoride. The latter investigation was considered from the standpoint of the preparation of monoalkyl esters (and neutral dialkyl esters) of monofluorophosphoric acid, and also as a means of furnishing additional experimental data regarding the structures and compositions of the various alkyl polyphosphates which had suddenly become of such great interest as powerful insecticides.

HISTORICAL REVIEW

A. Early Investigations of Dialkyl Monofluorophosphates.

The first esters of any fluorine-phosphorus acid to be reported were dialkyl esters of monofluorophosphoric acid, H_2PO_3F. Although the anhydrous acid was not known at that time, W. Lange and G. v. Krueger[1] succeeded in making the dimethyl and diethyl esters by heating the corresponding alkyl iodide with the silver salt of the acid. The silver salt was produced from a mixture of ammonium mono- and difluorophosphates[2,3] formed by fusing phosphoric anhydride with ammonium fluoride. Although this method was quite laborious and resulted in low yields, it served as a means of isolating the esters for a short study of their physical and physiological properties.

With regard to the physical properties of dialkyl monofluorophosphates, they were found in general to be fairly stable esters, insoluble in water, but soluble in the common organic solvents. The methyl ester, however, was reported to be an exception, as it dissolved in water and underwent hydrolysis easily. The insoluble diethyl ester is stable enough in water that it can be steam-distilled with comparatively little decomposition. The stability of these esters toward dilute aqueous or alcoholic alkaline solutions is quite interesting; although the methyl ester reacts quickly, the higher esters are hydrolyzed with considerable difficulty.

Alkaline hydrolysis results in the splitting of the fluorine-phosphorus bond, with the formation of the very stable salts of dialkyl orthophosphoric acid.

The physiological properties of these esters are particularly interesting. It was expected that dialkyl monofluorophosphates would be somewhat similar to the corresponding dialkyl sulfates, since Lange[3] had earlier noticed the similarity of the reactions of monofluorophosphoric and sulfuric acid, and the isomorphism of their salts. However, the toxicity of dimethyl sulfate when applied to the human skin does not occur with the dialkyl fluorophosphates. The inhalation toxicity of the monofluorophosphates, on the other hand, was much more pronounced than could have been expected from the analogy between the two series of acids. In fact, a very strange physiological effect was noticed. Shortly after breathing the sweet-smelling vapors of the diethyl ester, a shortness of breath occurs, followed by deceptive vision, a feeling of faintness, and a smarting of the eyes when turned toward the light. These effects usually last only a few hours, and apparently no after-effects are produced. Since there are no hydrolytic decomposition products which could cause such effects on the nervous system, Lange came to the conclusion that the odd physiological action must be a specific property of the neutral ester molecule itself.

The esters were tested in the laboratories of the I. G. Farbenindustrie for insecticidal properties[4] and were

found to be quite effective against several pests. However, because of the volatility, the low solubility, and the expensive method of preparation of the esters, they were considered to be of no commercial value at that time, and so work on the esters was discontinued temporarily.

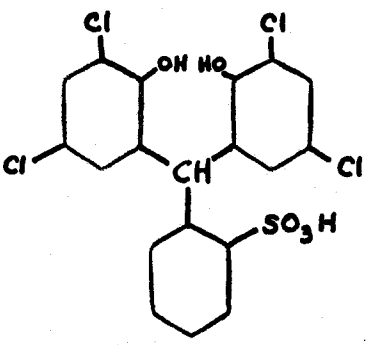
Interest in monofluorophosphoric acid,[3,5,6,7,8,9] H_2PO_3F, and its salts, as well as in difluorophosphoric acid,[2] HPO_2F_2, and its salts, led to methods of production of the anhydrous acids by the reaction of anhydrous hydrogen fluoride with phosphoric anhydride; and the availability of the acids in relatively large quantities[10] led to a renewal of interest in the organic derivatives, with the idea of a possibility of their preparation from the anhydrous acids.

B. Insecticidal Development.

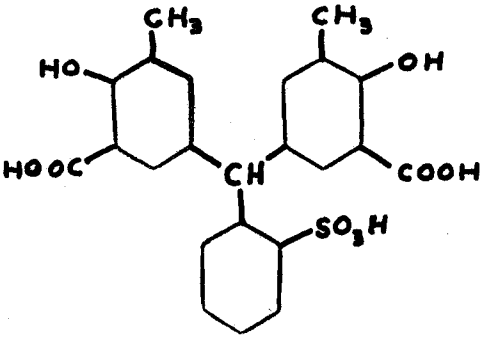
In the meantime, the I. G. Farbenindustrie had developed over a period of about fifteen years the field of colorless mothproofing "dyestuffs" known as Eulans.[11,12,13] Some of these Eulans were chlorinated di- and triphenylmethanes containing solubilizing sulfonic acid groups, by means of which the molecule could be attached to wool fiber to give permanent mothproofing properties. As a matter of fact, the sulfonic acid groups do even more than solubilize the molecule and allow a chemical union with the cloth fiber; the sulfonation of the aromatic compounds actually increases their insecticidal properties considerably. This is an amplification of the established fact that organic

contact poisons in general do not lose their insecticidal properties when they are sulfonated, but instead are converted into effective stomach poisons.

Another important contribution to the field of permanent mothproofing compounds was made by the J. R. Geigy Company[14] of Basel, Switzerland. They developed independently some mothproofing compounds quite similar to the Eulans of I. G. Farbenindustrie, as shown below:[12]



Eulan Neu
(I. G. Farbenindustrie)



Eriochromcyanine R
(J. R. Geigy)

The research in the Geigy laboratories was undertaken principally from the standpoint of dyestuff chemistry. They found that both the position and number of sulfonic acid groups were important in the ability of the molecule to behave as a permanent mothproofing compound; for example, the fewer the sulfonic acid groups, the greater the capacity of such a molecule in general for being drawn up by the fiber. In fact, most of the effective mothproofing compounds developed by Geigy contained only one sulfonic acid group in the molecule. They reported, however, that the fastness of the "colorless dyestuff" could not be explained solely by the linkage of the sulfonic acid to the wool fiber, but that other "secondary

valence forces" within the molecule were also important in causing such an intimate association.

A great amount of research done in the Geigy[15,16] laboratories along closely related lines resulted in the discovery of dichlorodiphenyltrichloromethylmethane, known popularly as DDT, as a powerful insecticide.[17] Their research on the mechanism of contact-poison action brought out the fact that the molecule must contain, in addition to the "toxic component", a lipoid-soluble group which will enable the poison to penetrate through the epicuticula, a lipoid layer, into the nerve cells. Groups conferring lipoid solubility on the molecule are in most cases aliphatic groups derived from inhalation anaesthetics, such as chloroform and cyclopropane, or fat solvents, such as carbon tetrachloride, which have a very high oil/water distribution coefficient. The "toxic component" must be such that the structure of the entire molecule allows a combination with "certain physiologically important components" of the body. Using DDT as an example of a contact poison, the lipoid-soluble group is seen to be the trichloromethyl group. Thus such a molecule can penetrate into the nerve cells, where, because of the toxic nature of the molecule, it injures the nerve cells in some way, producing a state of excitability, which in turn causes misdirected physiological reactions, according to the mechanism proposed by the Geigy Company. The nerve-poison action of DDT does not appear to involve the inhibition of

cholinesterase.[18]

During World War II the I. G. Farbenindustrie developed an interesting insecticide, hexaethyl tetraphosphate, which they called "Bladan". It is usually referred to in the United States as HETP for convenience. G. Schrader[19] first prepared this insecticide at Elberfeld in a study of substitutes for nicotine in the control of plant lice (aphids). Since it is cheap, is extremely effective against plant lice,[20] and is hydrolyzed by water to non-toxic alkyl phosphoric acids, it has a great advantage over nicotine. It serves as a supplement to DDT, which is not effective against mites and aphids.[21,22,23]

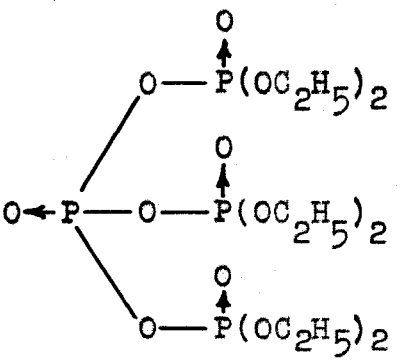
C. Alkyl Polyphosphates.

Hexaethyl tetraphosphate is now being produced on a large scale, and its effectiveness has stimulated a great amount of basic research in the field of alkyl polyphosphates.[24,25]

Schrader[19,26] initially prepared hexaethyl tetraphosphate by means of the following reaction:

$$POCl_3 + 3(C_2H_5)_3PO_4 = 3C_2H_5Cl + (C_2H_5)_6P_4O_{13}.$$

In line with this reaction, he proposed the following structure for the hexaethyl ester:



but analogy with inorganic chemical considerations indicated that such a branched structure would be less likely than a linear structure.[27] A more recent method[28] which has been adopted by the Germans for preparing the insecticide is described by the following equation:

$$4POCl_3 + 9C_2H_5OH = 9HCl + 3C_2H_5Cl + (C_2H_5)_6P_4O_{13}.$$

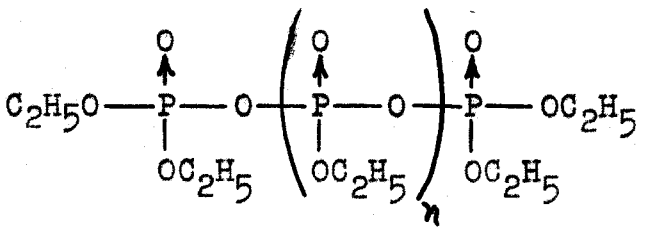
The knowledge of hexaethyl tetraphosphate prior to 1947 has been reviewed by Bronson and Hall[22] and by Roark.[29]

Quite recently, however, Hall and Jacobson[30] have reported that so-called hexaethyl tetraphosphate is not a pure compound, or even a relatively pure one; but instead it is a nondistillable liquid mixture of empirical composition $(C_2H_5)_6P_4O_{13}$ composed of ethyl metaphosphate, tetraethyl pyrophosphate, triethyl orthophosphate, and possible pentaethyl triphosphate. They stated, furthermore, that tetraethyl pyrophosphate is probably the active ingredient of all the toxic, nondistillable, liquid ethyl polyphosphates. In this regard, tetraethyl pyrophosphate was prepared both as distillable and nondistillable liquids, and these products showed a toxicity three to five times as great as that of HETP. This is in reasonable agreement with their report that HETP contains about 20 percent tetraethyl pyrophosphate, as shown by vacuum distillation. Their results are in close agreement with the present knowledge of inorganic polyphosphates; Partridge et al.[31] showed that the highest known member of the system $NaPO_3$-$Na_4P_2O_7$ existing as a crystalline

individual is sodium triphosphate, $Na_5P_3O_{10}$.

At about the same time, Hansen[32] reported the presence of 10 to 20 percent of a "tetraethyl phosphate" as the active ingredient in HETP, but from his analyses he concluded that the active ester was tetraethyl peroxydiphosphate.

Ethyl metaphosphate, which Hall and Jacobson reported to be the primary component of the commercial hexaethyl tetraphosphate, can be prepared conveniently, although in an impure form, by the reaction of phosphoric anhydride with diethyl ether[33] or with triethyl phosphate.[34] According to a recent patent, though, the reaction with diethyl ether produces a substantial proportion of triethyl phosphate.[35] Plimmer and Burch[36] reported that ebullioscopic analysis showed the metaphosphate molecule to be dimeric, while from cryoscopic determinations it was found to be a hexamer. They found that ethyl metaphosphate would react with ethyl alcohol to give both mono- and diethyl phosphoric acids. On the other hand, Audrieth[37] has stated that in determining the molecular weights of such esters, any method which involves a solvolytic reaction will give ambiguous or useless results; instead of a monomeric, dimeric, or even hexameric system, ethyl metaphosphate is probably a complex mixture of very long-chain polymeric molecules of the type



Although several recent publications have appeared with regard to polyphosphoric acids[38] and their salts,[39,40,41,42,43] relatively little has been published with regard to the composition of their alkyl esters, even though a great amount of work is being done in this field. Hence, the "hexaethyl tetraphosphate" problem is not yet completely settled.

As far as their preparation is concerned, however, products with overall compositions of alkyl metaphosphates, pyrophosphates, triphosphates, and tetraphosphates are obtained easily from the reaction of the trialkyl orthophosphates with the proper amount of phosphoric anhydride at low temperatures, as a result of a patent issued recently to the Victor Chemical Works.[34] In addition to this general method, usually referred to as the Woodstock method, and that of Schrader, which involves the reaction of phosphoryl chloride with trialkyl orthophosphates, still another method[30] should be mentioned; it is very satisfactory for preparing tetraethyl pyrophosphate and is described by the following equation:

$$(C_2H_5)_2PO_3Cl + (C_2H_5)_3PO_4 = C_2H_5Cl + (C_2H_5)_4P_2O_7$$

As intimated before, not only HETP but all of these alkyl polyphosphates are effective against mites and aphids. They are also very toxic to humans and can be absorbed readily through the skin, so great care must be used in handling these liquids.[44] That this entire effect is caused by the presence of tetraethyl pyrophosphate, as Hall and Jacobson

stated, has not yet been shown conclusively, but nevertheless the mixtures are all quite toxic. More will be said of the mechanism of this toxic effect below.

D. Synthesis of Dialkyl Monofluorophosphates.

It is desirable at this point to leave the subject of alkyl polyphosphates temporarily and turn to a type of organic esters which do not appear, at first glance, to be closely related to polyphosphates. These are known generally as dialkyl monofluorophosphates.

Until 1941, when McCombie and Saunders began their research on new war gases in the Cambridge University Chemical Laboratory in England, only one paper[1] had been published on dialkyl monofluorophosphates; this paper, by Lange and Krueger, was discussed above. The British workers were interested in the odd physiological properties of these esters, but first a study had to be made for the purpose of finding a more economical and convenient method of synthesis, since that of Lange and Krueger was quite laborious and resulted in overall yields of less than 4 percent of theory. After a considerable amount of research, the British proposed the following methods of synthesis:[45]

(1)
$$\begin{cases} POCl_3 = POCl_2F \\ POCl_2F + 2ROH = (RO)_2POF + 2HCl \end{cases}$$

(2)
$$\begin{cases} 2(RO)_3PO + POCl_3 = 3(RO)_2POCl \\ (RO)_2POCl + NaF = (RO)_2POF + NaCl \end{cases}$$

$$(3)\begin{cases} 3ROH + PCl_3 + 3C_5H_5N = (RO)_3P + 3C_5H_5N\cdot HCl \\ (RO)_3P + Cl_2 = (RO)_2POCl + RCl \\ (RO)_2POCl + NaF = (RO)_2POF + NaCl \end{cases}$$

$$(4)\begin{cases} 3ROH + PCl_3 = (RO)_2POH + RCl + 2HCl & (89\%\ \text{yield}) \\ (RO)_2POH + Cl_2 = (RO)_2POCl + HCl & (80\%\ \text{yield}) \\ (RO)_2POCl + NaF = (RO)_2POF + NaCl & (84\%\ \text{yield}) \end{cases}$$

Method (1) was found to be most useful for exploratory purposes; for example, it was the only method of the four which allowed the synthesis of diaryl esters in good yields. Methods (2), (3), and (4) all involve the intermediate formation of a dialkyl monochlorophosphate, which is then reacted with sodium fluoride to produce the corresponding dialkyl monofluorophosphate. Alkyl and aryl monochlorophosphates have been known for a long time, and earliest methods of preparing them involved the reaction of phosphoryl trichloride with the calculated quantity, or less, of an alcohol[46,47,48] or phenol.[49,50,51,52,53] Catalysts suggested for the reaction include $AlCl_3$, $ZnCl_2$[54] and $MgCl_2$.[55] Although the diaryl monochlorophosphates can be distilled satisfactorily under vacuum, the dialkyl esters are thermally instable and hence cannot be obtained in a pure form by this reaction, since they cannot be separated from the by-products.[47]

Because of the low yields and low purity of dialkyl monochlorophosphates made in this way, the British investigators[56] had to look further for a satisfactory method of preparing them as intermediates for subsequent reaction

with sodium fluoride. The reaction of Gerrard[57], in which $POCl_3$ is reacted with a trialkyl phosphate, makes up the initial step of method (2) listed by McCombie and Saunders.

The chlorination of triethyl phosphite, a reaction which was investigated by Wichelhaus,[58] is the basis for method (3) suggested by the British workers for preparing dialkyl monofluorophosphates. The first step of this method, i.e. the synthesis of a trialkyl phosphite from the action of phosphorus trichloride on an alcohol in the presence of an organic base, had been reported in 1918 by Milobedski and Sachnowski.[59,60] Method (3) was shown to give satisfactory overall yields, but the use of a tertiary base made this method too expensive for a commercial process.

With plant-scale production in mind, an attempt was made by the British researchers to carry out this same series of reactions without the use of an organic base. Instead of obtaining a trialkyl phosphite by means of the reaction of PCl_3 with an alcohol, however, leaving out the organic base resulted in the formation of the dialkyl acid phosphite,[55,61,62] as had been found earlier by Gerrard.[57] This was thought at first to be a useless reaction product, but then it was found that this acid phosphite was converted by chlorination to the corresponding dialkyl monochlorophosphate in a 93% yield. This discovery seems to have strongly furthered the study of dialkyl monofluorophosphates, because it allowed a cheap, easy process for their production on a

commercial scale,[63,64] according to the equations of method (4).

Before leaving the subject of the synthesis of dialkyl monofluorophosphates, some mention should be made of the final step in the synthesis according to methods (2), (3) and (4), namely, the conversion of dialkyl monochlorophosphates to the corresponding monofluorophosphates by heating for a short time with sodium fluoride. This procedure for replacing a chlorine atom with a fluorine atom is identical with that used by Davies and Dick[65,66] in converting sulfonyl chlorides to sulfonyl fluorides, except that McCombie et al. carried out the reactions in carbon tetrachloride rather than in water. This step was not successful in the preparation of aromatic esters, however, so they were required to resort to the reaction of $POCl_2F$ with phenols to obtain derivatives of diphenyl monofluorophosphate.

Fluorinating agents other than sodium fluoride which have been used in similar reactions include AsF_3, SbF_3, ZnF_2, KF, KHF_2, and NH_4F. Davies and Dick showed that sulfonyl fluorides could be prepared conveniently from the corresponding sulfonyl chlorides by boiling for a short time with aqueous solutions of potassium, sodium, or ammonium fluoride, or with a suspension of zinc fluoride in water. Antimony trifluoride was used successfully in the conversion of benzoyl chloride to benzoyl fluoride, in which Voznesenskii[67] reported a 76 per cent yield. In the preparation

of alkyl fluorosilicates from the corresponding chlorosilicates, inorganic fluorides did not give satisfactory yields; but the reaction of SbF_3 with tetraethyl silicate was reported by Peppard, Brown, and Johnson[68] to be a convenient method of synthesis.

E. Physiological Properties and Anti-cholinesterase Activity of Dialkyl Monofluorophosphates.

A thorough study was made by McCombie and Saunders[45,69] of the inhalation toxicity recorded previously by Lange, and these results have been supplemented recently by Kilby and Kilby[70] in a study of the inhalation toxicity in man and animals. It was found that a miotic effect (a constricting effect on the pupil of the eye) and a high toxicity by inhalation usually went together; and these effects were exceedingly pronounced in the cases of esters of secondary alcohols, such as isopropyl, sec.-butyl, and cyclohexyl alcohol.

In 1942, McCombie and Saunders[71] reported that alkyl esters inhibit the action of the enzyme cholinesterase; and the diisopropyl ester, known as DFP, was found to be active in extremely low concentrations (about 10^{-10}M). No other enzyme was found to be inactivated by diisopropyl monofluorophosphate; recent findings,[72] however, indicate that dialkyl monofluorophosphates are not specific inhibitors of cholinesterase.

None of this research was published until 1946,

after secrecy orders had been lifted from such war research. In the meantime, the work had been transferred to the Chemical Warfare Service of the U. S. Army. At the end of the war, the application of diisopropyl monofluorophosphate[73,74] to peace-time uses received much attention in the form of medical research. For example, it was found to have probable beneficial effects in the treatment of the eye condition glaucoma,[75,76,77] and in the treatment of diseases characterized by muscular weakness known as myasthenia gravis.

Most of this research on the pharmacological uses of diisopropyl monofluorophosphate, commonly abbreviated to "DFP", has dealt with or has been based on its inhibition of cholinesterase. According to the present chemical theory of transmission of nerve impulses through the nervous system, the rapid splitting of acetylcholine by means of the highly specific enzyme cholinesterase, is necessary for normal functioning. Nachmansohn[78,79,80,81,82,83,84] has presented evidence that the rapid release and removal of acetylcholine is an intracellular process, and that the rate of metabolism of this ester by means of cholinesterase is great enough to parallel the rate of electrical changes produced along the nerve fibers; hence this rate of enzymatic splitting is directly related to the nerve action potential. According to this theory, it can be seen that the inhibition of cholinesterase results in a decreased rate of metabolism of acetylcholine and, therefore, in a corresponding lowering of

the nerve action potential. Physostigmine and neostigmine are known to inhibit reversibly the action of cholinesterase, but studies on the inhibition by DFP[85] indicate that the postulated enzyme-inhibitor complex is not readily reversed, so the cholinergic action of DFP approaches more nearly an irreversible inactivation of cholinesterase.

F. A Proposed Mechanism of Toxicity of Dialkyl Monofluorophosphates and Alkyl Polyphosphates.

The real chemical mechanism of the inactivating effect of DFP and other dialkyl monofluorophosphates toward cholinesterase, however, is not known. According to Lange,[86] this mechanism may involve a phosphorylating action, since these esters are all capable of exhibiting such an action. He came upon this idea while searching for the chemical mechanism of the toxic action of hexaethyl tetraphosphate. He found HETP to be a powerful phosphorylating agent, reacting, for example, with key components of enzyme systems. He showed also that the other liquid alkyl polyphosphates were relatively strong phosphorylating agents;[87] and since dialkyl monofluorophosphates likewise exhibit a phosphorylating effect, Lange suggested the possibility that the reaction mechanism of toxicity of both types of esters involves a phosphorylation of essential compounds in the cholinesterase enzymic system.

His proposed mechanism involves the following steps:

(1) The ester molecule, i.e. dialkyl monofluorophosphate or alkyl polyphosphate, reaches the cholinesterase in the nerves intact.

(2) In the presence of cholinesterase, the ester molecule is split by an enzyme, i.e. a monofluorophosphatase or a pyro(poly) phosphatase, with an immediate phosphorylation of cholinesterase by the split esters.

That step (1) may be true is shown by the fact that fluoride ions, salts of monofluorophosphoric acid, and salts of polyphosphoric acids do not give so great an inactivation effect on cholinesterase as do the dialkyl monofluorophosphates.[88] With regard to step (2), the existence of a pyrophosphatase is well known; and very recently Mazur[89] reported the existence in animal tissue of a monofluorophosphatase capable of splitting the fluorine-phosphorus bond of dialkyl monofluorophosphates. This finding gives additional weight to the possibility of a phosphorylation mechanism. Since Lange proposed this mechanism, further agreement with his ideas has been indicated by means of a study of DuBois and Mangun[90] of the in vivo and in vitro inhibition of cholinesterase by hexaethyl tetraphosphate, in which a strong inhibitory effect was observed. In fact, Burgen[44] et al. have shown that the alkyl polyphosphates are more active than diisopropyl monofluorophosphate in rats, both in vivo and in vitro, and these findings were confirmed by Chadwick and Hill in tests on the American roach.[91]

DISCUSSION OF RESULTS

A. Efforts Directed Toward the Synthesis of a Permanent Mothproofing Agent.

1. Diphenyl Monofluorophosphate.

A method has been developed which allows the synthesis of diphenyl monofluorophosphate, $(C_6H_5)_2PO_3F$, or in general Ar_2PO_3F, in satisfactory yields. This method may be described schematically by means of the following reaction equations:

(1) $2C_6H_5OH + POCl_3 = (C_6H_5)_2PO_3Cl + 2HCl$

(2) $2(C_6H_5)_2PO_3Cl + CaF_2 = 2(C_6H_5)_2PO_3F + CaCl_2$

Step (1) describes a reaction which has been known for nearly seventy-five years and has been discussed extensively in publications. Hence, only the second step of the process is of interest to us from a standpoint of research.

From the results of Davies and Dick,[66] who converted aliphatic and aromatic sulfonylchlorides to the corresponding sulfonylfluorides by heating with aqueous solutions of alkali fluorides or with aqueous suspensions of zinc fluoride, and also from the results of McCombie and Saunders,[45] who obtained dialkyl monofluorophosphates from the monochlorophosphates by heating shortly with sodium fluoride in carbon tetrachloride or benzene, it would appear that alkali fluorides or zinc fluoride should be satisfactory fluorinating agents for the reaction described by equation (2). This was found not be the case, however. The use of sodium fluoride required a

reaction temperature of 140° C. to give approximately 50 per cent conversion to diphenyl monofluorophosphate during a period of 35 hours, while zinc fluoride produced considerable phenolic splitting of the monochlorophosphate with a resulting low yield of not greater than 20 per cent monofluorophosphate.

Precipitated calcium fluoride was found to be the most satisfactory fluorinating agent for this reaction, producing yields of 65 to 70 per cent of theory. In a single reaction with finely-ground, high-grade, native fluorspar (CaF_2), however, a yield of only 15 to 20 per cent of theory was obtained. The difference in yields may be due to a difference in the particle size of the two types of calcium fluoride, but it seems likely that the acidity of the precipitated fluoride may add to its effectiveness.

Diphenyl monofluorophosphate is a stable, colorless liquid at room temperature. It melts at 7 to 10° C. and boils at 140 to 142° C. under a pressure of 3 mm. of mercury, but distillation at pressures above 12 or 15 mm. results in noticeable decomposition.

The ester was reported in 1946 by McCombie and Saunders,[45] who prepared it by the reaction

(3) $POCl_2F + 2C_6H_5OH = (C_6H_5)_2PO_3F + 2HCl$

2. Sulfonation of Diphenyl Monofluorophosphate.

The object of the study of the sulfonation of diphenyl monofluorophosphate was to prepare a mono-sulfonated derivative, which might be expected to have the insecticidal properties of

the unsulfonated ester and at the same time contain a group through which a chemical combination with protein fibers could be effected. Hence it was hoped that a "colorless mothproofing dye" could be obtained in this way. Disulfonation of the molecule, that is, inserting one sulfonic acid group into each of the two phenyl groups of the ester molecule, would be expected to result in a less efficient and less permanent dyestuff, so the emphasis in this study was directed toward the preparation of a monosulfonic acid derivative of diphenyl monofluorophosphate.

Since sodium chlorosulfonate and the addition product of pyridine with sulfur trioxide required high temperatures to bring about any reaction at all, the benzene rings of the ester molecule were shown to be deactivated. This was in agreement with the assumption that the fluorophosphate group attached to the rings would direct any incoming cationoid substituents to the meta positions with deactivation.

The more active sulfonating agents, however, gave mixtures of mono- and disulfonated products. Crystallization of the monosulfonic acid could not be effected, either by cooling or seeding, probably because of the presence of appreciable amounts of the disulfonic acid as an impurity. The extent of contamination with this impurity in the various experiments suggested that the sulfonation state of one benzene ring of the ester molecule had little, if any, effect on the ease of sulfonation of the second ring; in other words, the two benzene rings appeared to be nearly independent of one

another in the sulfonation reaction. A graph (Fig. 1, p. 70) has been drawn to show the relative proportions of the mono- and disulfonic acids as a function of the amount of sulfur trioxide reacted. Since no reasonably pure monosulfonated derivative was able to be isolated, the preparation of a permanent mothproofing compound by this method was considered to be unsatisfactory.

B. Diethyl Monofluorophosphate.

1. General.

The dialkyl monofluorophosphates are important to us because of their strong physiological properties, which were discussed on preceding pages. The diethyl ester was synthesized first by Lange and Krueger,[1] by heating the silver salt of monofluorophosphoric acid with ethyl iodide in a sealed tube, but yields were low and the overall procedure was quite tedious. McCombie and Saunders[45] were able to make the ester in good yields by first preparing the dialkyl acid phosphite, then chlorinating to form the dialkyl monochloro-phosphate, and finally heating shortly with sodium fluoride.

2. Synthesis from Tetraethyl Pyrophosphate.

A new and convenient method has now been found for producing diethyl monofluorophosphate. It was shown that pure tetraethyl pyrophosphate can be split almost quantitatively by anhydrous hydrogen fluoride according to the following equation:

(4) $(C_2H_5)_4P_2O_7 + HF = (C_2H_5)_2PO_3F + (C_2H_5)_2HPO_4$

The boiling points of the two resulting esters are sufficiently far apart to allow easy separation by vacuum distillation, and so the purification of diethyl monofluorophosphate is quite simple.

Even the use of technical or commercial grades of tetraethyl pyrophosphate allows easy separation of diethyl monofluorophosphate, although the yields are necessarily lower than when a pure pyrophosphate is used. For example, tetraethyl pyrophosphate which was prepared at room temperature by the reaction

(5) $P_2O_5 + 4(C_2H_5)_3PO_4 = 3(C_2H_5)_4P_2O_7$

and which certainly contained other ethyl polyphosphates and a considerable amount of unreacted triethyl orthophosphate, reacted with anhydrous hydrogen fluoride to give diethyl monofluorophosphate in a yield of 35 per cent of theory. Consequently, this reaction is of interest from a practical or commercial standpoint.

Furthermore, on the basis of preliminary experiments, this method appears to be applicable to the preparation of other dialkyl monofluorophosphates. It seems that this application is limited mainly by the lack of availability of the various tetra-alkyl pyrophosphates.

3. Miscellaneous Methods of Synthesis.

Although orthophosphoric acid reacts with ethylene at elevated temperatures and pressures to give alkyl

phosphates,[92] the corresponding reaction of monofluorophosphoric acid to form dialkyl monofluorophosphates has not been found to be successful.

Likewise, the investigation of the reaction of triethyl orthophosphate with difluorophosphoric acid, according the the equation

(6) $(C_2H_5)_3PO_4 + HPO_2F_2 = (C_2H_5)_2PO_3F + (C_2H_5)HPO_3F$,

showed that this reaction does not occur under the conditions of temperature and pressure used.

The reaction of antimony trifluoride with triethyl phosphate, proved to be more successful. Upon using the stoichiometric quantities of reactants according to the equation

(7) $SbF_3 + 3(C_2H_5)_3PO_4 = 3(C_2H_5)_2PO_3F + Sb(OC_2H_5)_3$

and using $SbCl_5$ as a catalyst, yields up to 21 per cent of the theoretical amount of diethyl monofluorophosphate were obtained. In this reaction the starting materials were merely heated together in a distilling flask, and the volatile products were distilled as the bath temperature was slowly increased. It would appear that the use of an excess of antimony trifluoride should result in increased yields of the desired ester, but instead it was found to lead to the formation of increasing amounts of a white solid residue during the distillation, and consequently lower yields actually were obtained.

C. Synthesis of Ethyl Monofluorophosphoric Acid from Ethyl Polyphosphates.

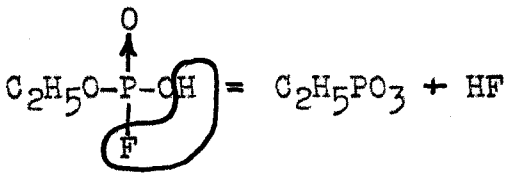
1. General

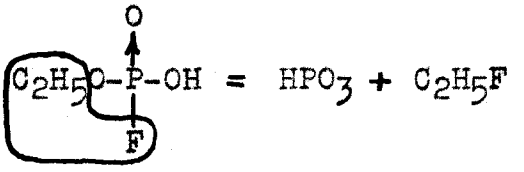
One disadvantage in the use of dialkyl monofluoro-

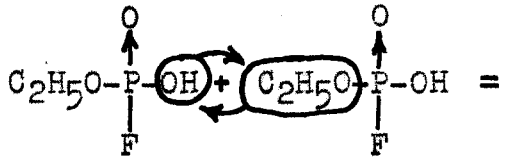
phosphates is the low solubility of these neutral esters in water. In an attempt to overcome this disadvantage and at the same time retain the physiological properties of the esters, a study has been made of the corresponding acid esters of monofluorophosphoric acid, that is, compounds of the type $RHPO_3F$ in which R is an alkyl group. Such compounds would be expected to have soluble alkali salts, and therefore solutions of the salts would be convenient for injection into bodies of test animals, for germicidal tests, etc.

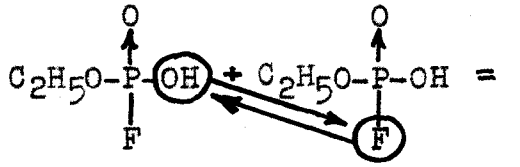
All the methods which have been used successfully, during the course of the present research, in preparing ethyl monofluorophosphoric acid, or hence ethyl acid monofluorophosphate, have involved the splitting of ethyl polyphosphates by means of anhydrous hydrogen fluoride. Four polyphosphates have been investigated in connection with this reaction, and the results are discussed below. Probably the greatest difficulty in all of these studies was the lack of published information regarding the true compositions and structures of the various polyphosphates used.

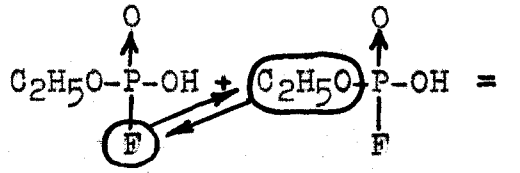
Ethyl monofluorophosphoric acid, $(C_2H_5)HPO_3F$, has not been reported heretofore in any publication. It is a mobile, water-white liquid at room temperature, but it undergoes very slow decomposition even when stored in a closed platinum bottle. This thermal decomposition may take several forms, as shown by equations (8), (9), (10), (11), and (12).

(8)  $= C_2H_5PO_3 + HF$

(9)  $= HPO_3 + C_2H_5F$

(10)  $= (C_2H_5)_2PO_3F + H_2PO_3F$

(11)  $= (C_2H_5)PO_2F_2 + (C_2H_5)H_2PO_4$

(12)  $= (C_2H_5)_2HPO_4 + HPO_2F_2$

Experimental results indicate that all of these types may occur to a very small extent even at room temperature, and the decomposition becomes more pronounced at elevated temperatures. For this reason, purification requires repeated short-path vacuum distillations instead of a conventional vacuum distillation as a means of fractionation. The pure acid ester can be distilled satisfactorily by means of short-path distillation by applying temperatures of 35 to 60° C. at pressures of 0.001 mm. or less. It does not solidify even at -80° C. Experimental values of refractive index (n_D^{20}) and density (d_4^{20}) were 1.3668 and 1.3185 respectively.

Several salts were prepared by neutralizing ethyl monofluorophosphoric acid with aqueous solutions of the desired metal hydroxide and evaporating the resulting neutral salt solutions in a vacuum desiccator. None of the salts made in this way contained water of crystallization.

The sodium and potassium salts were subjected to germicidal and toxicological tests by W. Lange[93] and some interesting results were noted. The salts apparently show no specific toxicity for rats, whereas the corresponding neutral ester, diethyl monofluorophosphate, is highly toxic. Likewise, no bactericidal effect of the salts was observed.

Of the two yeasts tested, a germicidal effect was observed only in the case of the distillers' type yeast Saccharomyces cerevisiae, for which kills of better than 99 per cent were reported.

The salts showed a strong germicidal effect against molds. In extremely small concentrations, however, the salts produced a temporary mutation, characterized by the inability of the organisms to produce their typical pigments. Although this observation has no practical significance at the present, it is of considerable interest as a physiological phenomenon.

Hydrolysis studies on the potassium salts showed the ethyl monofluorophosphate ion, $(C_2H_5PO_3F)^-$, to be surprisingly stable. Boiling a neutral or slightly alkaline aqueous solution of the salt resulted in hydrolysis of the salt at a rate of less than 0.1 per cent per hour, while in aqueous

N/10 HCl at room temperature the average rate of hydrolysis over a period of two days was less than 0.25 per cent per hour.

The potassium salt is soluble in water and 95% ethyl alcohol, moderately soluble in absolute ethyl alcohol, and insoluble in ether. It undergoes a transition at 71 to 73° C., and the resulting modification melts at 166 to 167.5° C. This transition does not involve any decomposition. When the salt is crystallized from alcohol or precipitated with ether, it appears under a polarizing microscope as isotropic crystals exhibiting no well-defined crystal pattern and no display of colors. A heating stage was not available for observing the allotropic transition under the polarizing microscope.

2. Diethyl Diacid Pyrophosphate.

Since anhydrous hydrogen fluoride, HF, was shown to react with tetraethyl pyrophosphate to yield an equimolar mixture of diethyl monofluorophosphate and diethyl orthophosphoric acid, the reaction with diethyl diacid pyrophosphate would be expected to follow the same general mechanism as shown by the equation

(13) $C_2H_5O-\underset{\underset{OH}{|}}{\overset{\overset{O}{\uparrow}}{P}}-O-\overset{H\cdots F}{\underset{\underset{OH}{|}}{\overset{\overset{O}{\uparrow}}{P}}}-OC_2H_5 + HF = (C_2H_5)HPO_3F + (C_2H_5)H_2PO_4$

This mechanism of course assumes a symmetrical molecule. If the molecule is not symmetrical, however, the reaction could follow one or both of the two following schemes:

(14) $(C_2H_5O)_2P(O)(H:F)O-P(O)(OH)_2 + HF = (C_2H_5)_2HPO_4 + H_2PO_3F$

(15) $(C_2H_5O)_2P(O)(F:H)O-P(O)(OH)_2 + HF = (C_2H_5)_2PO_3F + H_3PO_4$

Experimental results show that the ester used in this reaction must have been substantially symmetrical in structure, reacting according to equation (13), but enough of the reaction products of reactions (14) and (15) were found in distillates and residues to account for either a small proportion of unsymmetrical molecules in the original ester or else a decomposition of $(C_2H_5)HPO_3F$.

The diethyl diacid pyrophosphate used in this study was only a technical or commercial grade, but after reaction with anhydrous hydrogen fluoride, ethyl monofluorophosphoric acid could be distilled from the product in yields as high as 86 per cent of theory by means of short-path distillation.

Of all the ethyl polyphosphates used in preparing ethyl monofluorophosphoric acid, diethyl diacid pyrophosphate was found to be the most convenient. Although percentage yields of the acid ester were lower than those afforded by other polyphosphates, there was less contamination of the distillate with $(C_2H_5)_2HPO_4$, $(C_2H_5)_3PO_4$, etc., and so a relatively pure half-ester was able to be obtained with fewer redistillations when diethyl diacid pyrophosphate was used as a starting material.

3. Ethyl Metaphosphate.

By analogy with the reaction of metaphosphoric acid with anhydrous hydrogen fluoride,

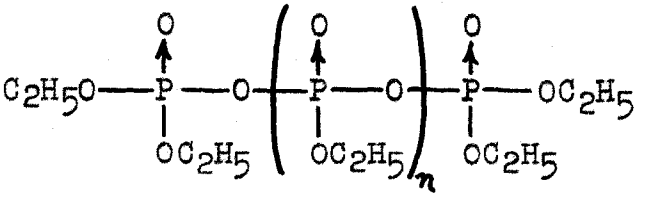
(16) $HF + HPO_3 = H_2PO_3F$,

which R. Livingston[94] reported to be quantitative, it would appear that ethyl metaphosphate should react with hydrogen fluoride in the same manner to give a quantitative yield of ethyl monofluorophosphoric acid, according to the following equation:

(17) $HF + C_2H_5PO_3 = (C_2H_5)HPO_3F$

However, a knowledge of the composition and structure of ethyl metaphosphate and of other ethyl polyphosphates is needed to understand the reason for yields somewhat less than quantitative.

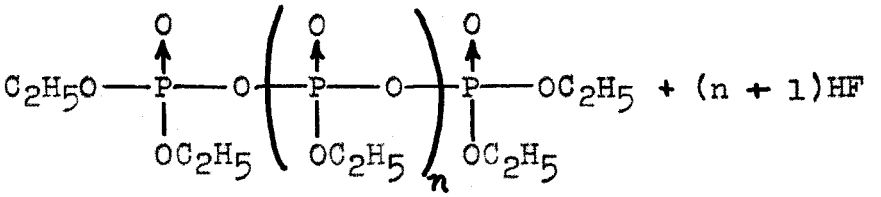
Although earliest analyses[36] indicated that ethyl metaphosphate was a dimer or a hexamer, the determinations were apparently made without consideration of the solvolysis action involved in the ebullioscopic and cryoscopic methods used. The recent trend of thought along the lines of composition and structure suggests that ethyl metaphosphate is a mixture of long-chain polymeric molecules of the type



in which n attains an average value high enough that the end groups have little effect on the empirical formula, which is found to be $C_2H_5PO_3$.

Commercial preparations of ethyl metaphosphate, however, appear to contain appreciable amounts of low-molecular-weight polyphosphate chains, including pyrophosphate and triphosphate. This is quite understandable when we consider the Victor Chemical Works patent[34] for production of alkyl polyphosphates. This patent describes the preparation of ethyl metaphosphate, hexaethyl tetraphosphate, pentaethyl triphosphate, and tetraethyl pyrophosphate by means of the reaction of one mole of phosphoric anhydride with 1, 2, 2.5, and 4 moles of triethyl phosphate respectively. Since there is no analytical method of determining the purity of ethyl metaphosphate, and since only a commercial grade of the ester is available, the purity of the starting material for reaction with hydrogen fluoride is obviously uncertain.

The reaction of ethyl metaphosphate with anhydrous hydrogen fluoride would be expected to follow the equation:

(18) 

$$= (C_2H_5)_2HPO_4 + (C_2H_5)_2PO_3F + \underline{n}(C_2H_5)HPO_3F$$

The greater the average value of n, the larger the proportion of $(C_2H_5)HPO_3F$, and the smaller the proportion of $(C_2H_5)_2PO_3F$ and $(C_2H_5)_2HPO_4$ in the reaction product. Hence the presence of short-chain impurities in the starting material would result in the formation of correspondingly greater amounts of

$(C_2H_5)_2PO_3F$ and $(C_2H_5)_2HPO_4$ as impurities in the reaction product.

Experimental results of the investigation of this reaction show that about 3-8% $(C_2H_5)_2HPO_4$, 6-13% $(C_2H_5)H_2PO_4$, 2-3% H_2PO_3F, and 2-5% $(C_2H_5)_2PO_3F$ are present as impurities in the reaction product, along with at least 70 per cent of the desired $(C_2H_5)HPO_3F$. This indicates the possibility that hydrolysis or alcoholysis of the polyphosphate has occurred, probably before reaction with hydrogen fluoride. In other words, it may be that the appearance of $(C_2H_5)H_2PO_4$ in the reaction product is a result of its presence in the commercial ethyl metaphosphate, or the compound may have been formed by the reaction of HF with acid polyphosphates. Alcoholysis of ethyl metaphosphate is known to produce both $(C_2H_5)_2HPO_4$ and $(C_2H_5)H_2PO_4$, and it is conceivable that such a reaction has occurred to a slight extent in the impure ethyl metaphosphate.

Whatever the composition of the starting material may be, the experimental results show that the predominating reaction which occurs when anhydrous hydrogen fluoride and ethyl metaphosphate are mixed is described satisfactorily by equation (18), in which the average value of n is great enough to give satisfactory yields of ethyl monofluorophosphoric acid.

This reaction makes available the highest proportion of ethyl monofluorophosphoric acid per mole of ethyl polyphosphate used. However, the presence of appreciable amounts

of $(C_2H_5)_2HPO_4$ in the distillate from the reaction product makes purification more difficult than is the case when diethyl diacid pyrophosphate is used as a starting material. If a better method of fractionation can be developed, ethyl metaphosphate should serve as an excellent source of ethyl fluorophosphoric acid.

4. Hexaethyl Tetraphosphate.

The various structures and compositions proposed for hexaethyl tetraphosphate have already been discussed. It is interesting now to study the experimental results of the reaction of the tetraphosphate with anhydrous hydrogen fluoride, in the light of these proposed compositions and structures.

The reactions were carried out by first adding one mole of "100% hexaethyl tetraphosphate" (Monsanto Chemical Company) to three moles of anhydrous hydrogen fluoride at a low temperature with frequent agitation. Subsequent distillations have allowed the following approximations regarding the composition of the reaction product:

49-50% $(C_2H_5)HPO_3F$

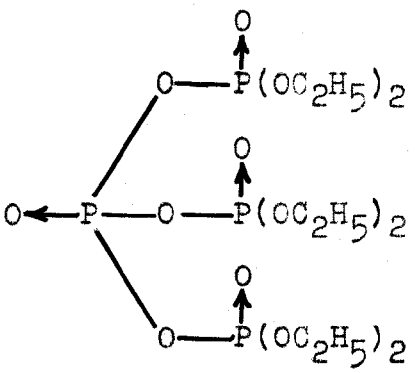
31-33% $(C_2H_5)_2HPO_4$ (including any distillable, unreacted polyphosphates)

12-14% $(C_2H_5)_2PO_3F$ (including possibly HPO_2F_2)

5-6 % Undistilled material ($(C_2H_5)H_2PO_4$, $(C_2H_5)_2HPO_4$, H_2PO_3F, unreacted polyphosphates, etc.)

If we assume first that Schrader's[19] proposed structure is correct, the action of hydrogen fluoride would

be expected to take the following course:



(19) + 3HF

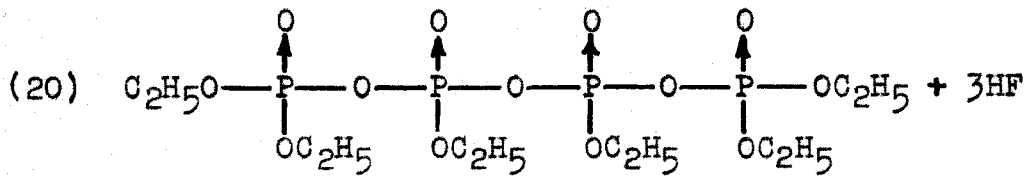
$$= (C_2H_5O)_2\overset{\overset{O}{\uparrow}}{P}\text{-}O\text{-}\overset{\overset{O}{\uparrow}}{\underset{\underset{OH}{|}}{P}}\text{-}O\text{-}\overset{\overset{O}{\uparrow}}{P}(OC_2H_5)_2 + (C_2H_5)_2PO_3F + 2HF$$

$$= (C_2H_5O)_2\overset{\overset{O}{\uparrow}}{P}\text{-}O\text{-}\overset{\overset{O}{\uparrow}}{P}(OH)_2 + 2(C_2H_5)_2PO_3F + HF$$

$$= \begin{cases} 3(C_2H_5)_2PO_3F + H_3PO_4 \\ \text{or} \\ 2(C_2H_5)_2PO_3F + H_2PO_3F + (C_2H_5)_2HPO_4 \end{cases}$$

According to this mechanism, at least half the reaction product would have to be diethyl monofluorophosphate, whereas only 12 to 14 per cent was found experimentally. Also, a distillation residue of 25 per cent should be found, but only 5 to 6 per cent was not distilled. Therefore, Schrader's structure certainly is not satisfactory.

The second structure proposed, a linear polymer, would be expected to react with hydrogen fluoride as follows:



$$= (C_2H_5)_2HPO_4 + 2(C_2H_5)HPO_3F + (C_2H_5)_2PO_3F$$

The expected amount of $(C_2H_5)HPO_3F$ coincides with the experimental value, and the $(C_2H_5)_2HPO_4$ content is not too far out of line; however, the amount of $(C_2H_5)H_2PO_4$ found in the reaction product amounts to only one-half the calculated value. This means no more than half of the original hexaethyl tetraphosphate could possibly have been a linear tetramer as shown above, and therefore this structure does not describe the ester satisfactorily, at least not in terms of a pure compound.

The third composition of hexaethyl tetraphosphate, which was proposed by Hall and Jacobson,[30] is, as was mentioned previously, in close agreement with the knowledge of inorganic polyphosphate systems. These authors suggested that hexaethyl tetraphosphate was a mixture consisting of ethyl metaphosphate containing about 20 per cent tetraethyl pyrophosphate and possibly some pentaethyl triphosphate and triethyl orthophosphate. Keeping in mind the experimental results of the reactions of hydrogen fluoride with the individual components of the mixture, the results of the reaction with "hexaethyl tetraphosphate" (see p. 34) suggest that the tetraphosphate used in the experiments may have had a composition approaching the following mixture:

20% Tetraethyl pyrophosphate

8-10% Pentaethyl triphosphate

50-52% Ethyl metaphosphate

18% Diethyl phosphoric acid

It is difficult to see how such a great proportion of $(C_2H_5)_2HPO_4$ could be accounted for in any way other than by assuming that some of it is present in the starting material. As may be remembered, this is the same conclusion at which we arrived in the study of technical ethyl metaphosphate. Hydrolysis or alcoholysis occurring in the polyphosphate could have caused the formation of this impurity.

Besides affording some additional experimental data regarding the composition of hexaethyl tetraphosphate, the study of the reaction with hydrogen fluoride has shown that ethyl monofluorophosphoric acid can be prepared in reasonable yields by this method. Although lower yields are obtained than by the reaction of hydrogen fluoride with ethyl metaphosphate, the tetraphosphate is very convenient to work with because of its mobility, while the metaphosphate is very viscous and hence difficult to work with, particularly from the standpoint of excluding moisture from systems at low temperatures.

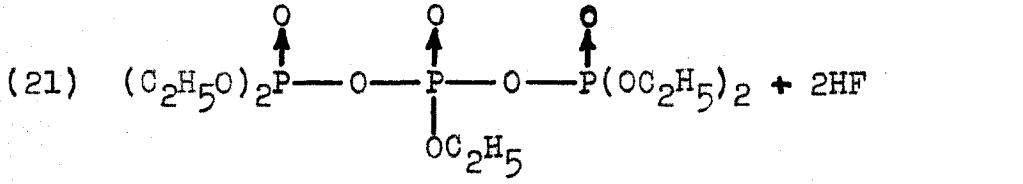
5. Pentaethyl Triphosphate.

This ester, $(C_2H_5)_5P_3O_{10}$, has not been reported as a pure compound in published literature.[30] From the results of the present research, in which it was desired to isolate

the pure ester for subsequent reaction with anhydrous hydrogen fluoride, it appears that the reason no one has reported the triphosphate is that it is not thermally stable enough to withstand even high-vacuum, short-path distillation at temperatures of 90 to 100° C. In fact, it appears that the ester may undergo a disproportionation type of decomposition even at a temperature as low as 50° C.

In an attempt to prepare the pure ester, ethyl iodide was reacted with the corresponding silver salt, which was prepared in turn from a pure sodium salt, $Na_5P_3O_{10}\cdot 6H_2O$, the purity of which had been checked carefully by x-ray analysis. Since the silver salt was precipitated completely within 15 minutes after dissolving the sodium salt in distilled water at room temperature, there is no reason to believe that any silver orthophosphate, pyrophosphate, or metaphosphate was present in the pentasilver triphosphate prepared in this way. In the next step, however, ethyl iodide was reacted with the silver salt below 36° C., and after the resulting silver iodide was removed by filtration, the solvent (diethyl ether) was evaporated at atmospheric pressure, using a bath temperature of less than 50° C. Although the resulting liquid ester, which was expected to be pentaethyl triphosphate, contained nearly the theoretical amount of phosphorus, it is quite possible that it was actually a mixture of ethyl polyphosphates. This was suggested by the results of the reaction of the liquid with hydrogen fluoride,

which would have been expected to proceed according to the equation



(21) $(C_2H_5O)_2P(O)-O-P(O)(OC_2H_5)-O-P(O)(OC_2H_5)_2 + 2HF$

$= (C_2H_5)_2HPO_4 + (C_2H_5)HPO_3F + (C_2H_5)_2PO_3F$

Hence, an equimolar mixture of the three resulting esters would have been obtained if the triphosphate had been pure. Instead, the reaction product was found to have the following approximate composition:

43.4% $(C_2H_5)HPO_3F$

36.5% $(C_2H_5)_2HPO_4$, including probably $(C_2H_5)_3PO_4$

17.8% $(C_2H_5)_2PO_3F$

2.3% nonvolatile matter

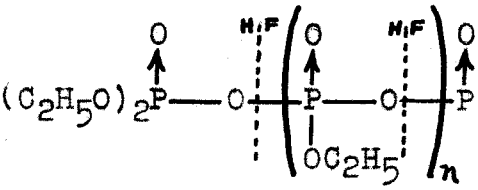
The low value for diethyl monofluorophosphate can account for only about 36% $(C_2H_5)_4P_2O_7$ or 54% $(C_2H_5)_5P_3O_{10}$ in the polyphosphate used for the reaction with HF, indicating that a decomposition of some kind had occurred in the pentaethyl ester. The decomposition seems to have resulted in the formation of a considerable amount of ethyl metaphosphate, as that appears to be the only logical explanation for the fact that ethyl monofluorophosphoric acid was formed, in the reaction with hydrogen fluoride, in a substantially greater amount than was diethyl orthophosphoric acid. Since no temperature greater than 50° C. had been imposed on the

triphosphate salts and ester during the entire series of reactions, it seems, therefore, that pentaethyl triphosphate is not stable at that temperature.

Short-path distillation of the liquid ester at a temperature of 90 to 100° C. and a pressure of less than one micron revealed more clearly the instability of pentaethyl triphosphate. The liquid was separated into a large fraction of the pyrophosphate, a small amount of orthophosphate, and a residue which seemed to be largely the metaphosphate. This type of decomposition seems to fit quite satisfactorily into the general picture of the stability of alkyl polyphosphates. Triethyl orthophosphate is quite stable. Tetraethyl pyrophosphate decomposes, in part, to the metaphosphate and orthophosphate upon high-vacuum distillation.[30] The triphosphate now does not appear to be stable at 50° C., and it is doubtful if hexaethyl tetraphosphate is capable of existence as a pure compound.

Besides yielding experimental data regarding the stability of pentaethyl triphosphate, this study has given additional information regarding the synthesis of the mono- and diethyl esters of monofluorophosphoric acid by splitting the P-O-P linkages of ethyl polyphosphates with anhydrous hydrogen fluoride. Although a pure triphosphate ester was not used in the reaction with HF, no pentaethyl triphosphate of greater purity has been reported, and so this represents the best results possible until more is known about pentaethyl triphosphate.

This is the last of the series of reactions of anhydrous hydrogen fluoride with ethyl polyphosphates. The experimental results have indicated that all of these reactions proceed according to the following general mechanism:

(22) 

$$= (C_2H_5)_2HPO_4 + \underline{n}(C_2H_5)HPO_3F + (C_2H_5)_2PO_3F.$$

EXPERIMENTAL

A. Methods of Analysis.

During the course of the present research, a large number of fluorine and phosphorus analyses were required. The methods used for these analyses are described below.

Fluorine analyses were carried out according to the Rowley and Churchill[95] modification of the Willard and Winter[96] method. Accordingly, a sample containing approximately 0.01 g. of fluorine was weighed into a 250-ml. Claisen flask, 5 ml. of 60% $HClO_4$ was added, and, while the flask was heated with a flame, water was added continuously; distillation was continued until 75 ml. of distillate had been caught. To this distillate was added 8 drops of 0.05% aqueous sodium alizarine sulfonate. The acidity was adjusted back and forth with 2% NaOH and 1:200 HCl until the solution remained very slightly acidic. Then 1 ml. of buffer solution was added; this buffer was prepared by dissolving 9.448 g. of monochloroacetic acid and 2.000 g. of NaOH in 100 ml. of water. The buffer solution was then titrated with N/10 thorium nitrate to the first permanent pink color.

To determine the phosphorus content of materials containing appreciable amounts of fluorine, it is necessary first to remove the fluorine to allow accurate and reproducible results. Therefore, a method quite similar to that described by R. Livingston[97] was used.

According to this method, a sample containing 0.03 to 0.04 g. of phosphorus was weighed into a silver crucible, 3 to 5 ml. of distilled water was added, and 2 or 3 pellets of solid KOH were dropped carefully into the solution. The contents were evaporated cautiously to complete dryness and then fused gently over an open flame for about one-half hour. The fused mass was dissolved and washed into a 400-ml. beaker, where the solution was neutralized with a few drops of concentrated nitric acid, using methyl red as an indicator. After addition of 10 ml. of N/2 $AgNO_3$, a 2% solution of KOH was added dropwise until dark AgOH was just beginning to form. After at least 4 hours of aging, the precipitated silver phosphate was removed by filtration, washing with cold N/10 $AgNO_3$. The silver salt was then dissolved in hot 2.5% HNO_3, and the silver was precipitated by titrating the hot solution with N/1 HCl, adding a slight excess to assure complete precipitation. After four hours or more of aging, with occasional stirring, the silver chloride was removed by filtration, washing with N/100 HNO_3. To the filtrate, which contained the phosphorus as fluorine-free orthophosphate, were added 2 drops of methyl red as indicator and 10 ml. of magnesia solution. After the solution was cooled in an ice bath, concentrated ammonium hydroxide was added dropwise, with good stirring, until the solution was slightly alkaline. Stirring was continued until most of the magnesium ammonium phosphate had precipitated, and then an additional 5 ml. of ammonium

hydroxide was added. Once more a 4-hour period of aging was allowed, and then magnesium ammonium phosphate was separated by filtration, washed with 1:20 ammonium hydroxide, and finally ignited in a platinum crucible to magnesium pyrophosphate.

B. Diphenyl Monofluorophosphate.

1. Synthesis.

An early attempt to prepare diphenyl monofluorophosphate involved the following reaction:

(1) $3(C_6H_5)_3PO_4 + SbF_3 = 3(C_6H_5)_2PO_3F + Sb(OC_6H_5)_3$.

In this experiment 326 g. of triphenyl phosphate was reacted with twice the calculated quantity of sublimed antimony trifluoride, using 0.23 per cent antimony pentachloride as a catalyst. The reactants were heated in a 500-ml. glass flask for 12 hours at a bath temperature of 150° C. and then for 16 to 17 hours at 210 to 225° C. The heating resulted in a partial liquefaction of the original mixture, and a strong phenolic odor was evident. Vacuum distillation of the product yielded a large amount of phenol as the only distillate, and so this method was discarded as being impractical for producing the diphenyl ester.

Preparation of Diphenyl Monochlorophosphate.

Several experiments were performed in a study of the replacement of the chlorine atom with a fluorine atom in diphenyl monochlorophosphate. The chloro-ester used for these experiments was prepared by reacting phenol with a slight

excess of phosphoryl chloride, $POCl_3$. The reactants were heated under reflux until the evolution of HCl ceased, and the product was distilled under vacuum. A considerable proportion of phenyl dichlorophosphate was obtained as a low-boiling fraction, and some triphenyl phosphate remained as a distillation residue. The phenyl dichlorophosphate distilled at 93.5 to 95° C. under a pressure of 2 mm. of mercury, and at 103 to 104° C. at 4 to 5 mm. The boiling point of diphenyl monochlorophosphate was found to be 167 to 168° C. at a pressure of 2 mm., and chlorine analysis showed 13.2% Cl, which is the theoretical value calculated for this ester.

The Reaction of Diphenyl Monochlorophosphate with Sodium Fluoride.

After McCombie and Saunders reported the preparation of dialkyl monofluorophosphates from the corresponding monochlorophosphates by heating shortly with sodium fluoride in carbon tetrachloride, the same reaction conditions were used in an attempt to prepare the diphenyl ester by the reaction

(2) $(C_6H_5)_2PO_3Cl + NaF = (C_6H_5)_2PO_3F + NaCl.$

In this experiment, 50 g. of $(C_2H_5)_2PO_3Cl$ was refluxed for 20 hours in CCl_4 with a 100% excess of NaF. However, after filtration of the reaction product, evaporation of solvent, and vacuum distillation of the evaporation residue, the various distillation fractions were analyzed and were all found to be mixtures of the chloro- and fluoro-esters.

Approximately 20% conversion to diphenyl monofluorophosphate occurred, assuming all the fluorine found in the distillate was present as this ester.

These results suggested the use of a higher-boiling solvent, and so the reaction was repeated using xylene, which boils at about 140° C., as a means of controlling the reaction temperature. 20 g. of diphenyl monochlorophosphate was heated with 7.0 g. of sodium fluoride in 42 g. of dried xylene for 20 hours. Again the product was filtered, the solvent evaporated, and the residue distilled. Analysis of the distillates for fluorine and chlorine content again showed them to be mixtures of the chloro- and fluoro-esters, and the reaction resulted in a 40% conversion to diphenyl monofluorophosphate.

The reaction with sodium fluoride was repeated on a slightly larger scale, and the reaction time was increased to 35 hours. 60.5 g. (0.225 moles) of $(C_6H_5)_2PO_3Cl$ was reacted with 26 g. (0.62 moles) of NaF in 118 g. of xylene. After working up the product in the usual manner, a distillate of 31.5 g. was obtained which contained 0.57% Cl and 7.01 to 7.07% F. The distillation residue amounted to 21 g. and contained 0.37% Cl and 0.163% F. These analyses indicated that only about 3% of the original $(C_6H_5)_2PO_3Cl$ remained unreacted, and at least 53% was converted to $(C_6H_5)_2PO_3F$. Refractionation of the distillate gave 18 to 20 grams of water-white liquid containing 7.36 to 7.39% F, which corresponds to $(C_6H_5)_2PO_3F$ with a purity of about 98 per cent.

The Reaction of Diphenyl Monochlorophosphate with Zinc Fluoride.

As it seemed desirable to study the effect of a stronger fluorinating agent as a means of accomplishing the chlorine-fluorine replacement, zinc fluoride, ZnF_2, was used in such a reaction, with CCl_4 as a reflux medium. After heating 39 g. of $(C_6H_5)_2PO_3Cl$ with excess ZnF_2 in CCl_4 for 5 hours, the product was treated in the usual manner. Almost no diphenyl monochloro- or monofluorophosphate was found in the distillate, but instead a great amount of phenol distilled. Hence, the reaction of zinc fluoride seems to have been too vigorous at the boiling point of carbon tetrachloride.

With this in mind, a similar reaction was carried out in which CCl_4 was replaced by ether as a reflux medium. 30.5 g. of $(C_6H_5)_2PO_3Cl$ was reacted with 12.7 g. of ZnF_2 by heating to reflux in 31.5 g. of diethyl ether for 4 hours. After standing for 3 to 4 days, the solid matter was removed from the product by filtration, and the filtrate was washed with a dilute solution of sodium hydroxide, dried over $CaCl_2$, and evaporated. Distillation yielded first a considerable amount of phenol. Analysis of a higher-boiling fraction of 3 g. and a residue of 3.5 g. showed that a 10-12% conversion to the fluoro-ester had occurred, while only 4 to 5% chloro-ester had remained unreacted and undecomposed. These results indicated that the reaction conditions were still too severe.

In an attempt to decrease the amount of decomposition

of diphenyl monochlorophosphate during the reaction with zinc fluoride, 25 g. of the chloro-ester was stirred with 25 g. of ZnF_2 in 117 g. of CCl_4 at 15 to 22° C. for 8 hours. After standing overnight at 22 to 24° C., it was stirred 2 hours longer, and then it was filtered, evaporated, and distilled. Some decomposition of the monofluorophosphate apparently occurred during the distillation at 11 to 16 mm. of mercury, as fluorine analysis of the 6.5 g. of distillate showed 8.8% F. The results indicated that approximately 17% conversion of the monochlorophosphate to the monofluorophosphate had occurred.

The Reaction of Diphenyl Monochlorophosphate with Calcium Fluoride.

Since zinc fluoride seemed to be too strong for the desired chlorine-fluorine replacement, it was decided to study the efficiency of calcium fluoride as a fluorinating agent for this reaction.

In the first experiment in which calcium fluoride was used, 30.4 g. of $(C_6H_5)_2PO_3Cl$ and 13.3 g. of CaF_2 were refluxed in xylene for 25 hours. After filtration, evaporation, and distillation, analysis of the 17.5 grams of distillate showed it to contain 5.89% F and 0.63% Cl. Calculating the fluorine content as the monofluorophosphate, a conversion of at least 48% was attained by this method. The entire experiment seemed to be more convenient and less tedious than the previous experiments with sodium and zinc fluorides.

The experiment was repeated, reacting 84.4 g. of $(C_6H_5)_2PO_3Cl$ with 37 g. of CaF_2 in 71 g. of xylene for 33 hours. A distillate of 51.9 g. (150-152.5° C./4 mm.) was found to contain 8.1 to 8.2% F, and the residue of 14 grams contained 0.61% F. From the results, the conversion to monofluorophosphate was approximately 68% of theory. Redistillation of the monofluorophosphate fraction gave about 45 g. of water-white liquid boiling at 140.7 to 141.0° C. at 3 mm. of mercury; analysis showed 7.4% F, as compared with the calculated value of 7.53% F.

A third reaction of CaF_2 with $(C_6H_5)_2PO_3Cl$ was performed. The chief purpose of this experiment was to obtain a large amount of the monofluorophosphate for subsequent reactions, and so 196 g. of monochlorophosphate was used, refluxing with CaF_2 in xylene for 41 hours. Distillation resulted in a fraction boiling at 140 to 143° C. (3 mm.) which weighed 115 to 120 grams. As the original monochlorophosphate contained an appreciable amount of triphenyl phosphate as an impurity, the yield of diphenyl monofluorophosphate was greater than 65% of theory.

In the fourth reaction with calcium fluoride, 341 g. of diphenyl monochlorophosphate, containing triphenyl phosphate as an impurity, was reacted with 114 g. of CaF_2 in xylene for 36 hours. An attempt was made to use a water aspirator to produce the vacuum for the subsequent distillation, but at a pressure of 27 to 28 mm. of mercury a bath temperature

of 300° C. was not sufficient to allow distillation of the monofluorophosphate. Instead, a phenolic splitting occurred, and the yield of the monofluorophosphate on later distillation at a pressure of 4 to 5 mm. of mercury amounted to only 3 to 4% of theory before the distillation residue suddenly became semi-solid. These results demonstrated that an oil pump was necessary for vacuum distillation of diphenyl monofluorophosphate.

A fifth preparation of the fluoro-ester was carried out with 100 g. of $(C_6H_5)_2PO_3Cl$, 45 g. of CaF_2, and 100 g. of xylene. A reaction time of 38 hours was allowed, and 64 to 67 grams of the monofluorophosphate was recovered.

In the sixth and final reaction carried out with precipitated calcium fluoride, 242 g. of $(C_6H_5)_2PO_3Cl$ was reacted with 100 g. of CaF_2 in xylene for 35 hours, and 160 g. of $(C_6H_5)_2PO_3F$ was obtained on subsequent distillation. This represents a recovered yield of 70.5% of theory, and even this could have been increased by efficient extraction of the monofluorophosphate which was retained in the filtration residue of CaF_2 and $CaCl_2$.

Comparison of Precipitated Calcium Fluoride with Native Fluorspar.

In the experiments described above, precipitated calcium fluoride was used. When a high grade of native fluorspar, CaF_2, ground to -200 mesh, was used in place of the precipitated calcium fluoride, reaction with 29.2 g. of

$(C_6H_5)_2PO_3Cl$ in xylene for 35 hours gave a product containing 5 to 6 g. of monofluorophosphate, which is equivalent to 17 to 20% conversion during this reaction. Most of the unreacted monochlorophosphate was able to be recovered. These results show the finely-ground fluorspar is quite inferior to precipitated calcium fluoride as far as this particular reaction is concerned.

The Reaction of Monophenyl Dichlorophosphate with Metal Fluorides.

While the reaction of diphenyl monochlorophosphate with various fluorinating agents was being studied, a short investigation was made of the following reaction:

(3) $C_6H_5PO_2Cl_2 + 2MF = C_6H_5PO_2F_2 + 2MCl$.

The first fluoride used was sodium fluoride. 36 g. of $C_6H_5PO_2Cl_2$ was heated with 27.8 g. of NaF in xylene at 140° C. for 2 hours, and the reaction product was filtered, evaporated, and distilled. A large amount of phenol was obtained, along with a distillate of 4 to 6 grams containing some phenol, 7.7% F, and no Cl. The conversion to the difluorophosphate could not have been more than 5 or 10% of theory.

Sodium fluoride was used next at a reaction temperature of 76 to 77° C. In this experiment, 41.7 g. of $C_6H_5PO_2Cl_2$, containing 33.4% Cl, was heated with 33.7 g. of NaF in 140 g. of CCl_4 under reflux for 10 hours. The product was worked up as usual. Distillation at a pressure of 40 mm. of mercury

gave a fraction of 7 g. at 90 to 186° C., most of the liquid distilling over at about 122 and 162° C. Analysis of the distillate showed 10.4% F and 10.9% Cl, which is equivalent to 48.9% difluorophosphate and 32.5% dichlorophosphate, although some phenyl chlorofluorophosphate may have been present.

Calcium fluoride was investigated next as a fluorinating agent for reaction (3), since it had been so satisfactory for the corresponding reaction with diphenyl monochlorophosphate.

When phenyl dichlorophosphate was reacted with precipitated calcium fluoride in xylene under reflux, a vigorous reaction occurred with the splitting of phenol.

The reaction with calcium fluoride was attempted next in carbon tetrachloride. 25 g. of $C_6H_5PO_2Cl_2$ was reacted for 22 hours with an equal weight of CaF_2 in 60 to 70 g. of CCl_4. Upon filtration, evaporation, and distillation as usual, all but a very small distillation residue was obtained at 95 to 115° C. at a pressure of 12 mm. of mercury. The distillate was predominantly unreacted phenyl dichlorophosphate containing 0.54% F, which is equivalent to a conversion of only 2% of theory.

As the reaction temperature was apparently too low, toluene (b.p. 110.8° C.) was used to replace carbon tetrachloride (b.p. 76.8° C.). In this experiment 39 g. of $C_6H_5PO_2Cl_2$ was heated with approximately an equal weight of CaF_2 in toluene for 20 hours. Distillation of the filtered

reaction product gave a fraction of 13.5 to 14.0 g. boiling at 71 to 73° C. under a pressure of 26 to 27 mm. of mercury. Analysis gave the following results:

0.1197 g.: 9.82 ml. of 0.128 N $Th(NO_3)_4$ solutiom.

Calculated for $C_6H_5PO_2F_2$: 21.3% F.

Found: 20.0% F.

A fraction of 2 to 4 grams was also obtained, boiling at 98 to 101.5° C. at 25 to 26 mm. of mercury. Analysis of this fraction was as follows:

0.1204 g.: 5.12 ml. of 0.128 N $Th(NO_3)_4$.

0.1327 g.: 6.05 ml. of N/10 $AgNO_3$.

Calculated for $C_6H_5PO_2ClF$: 10.35% F; 19.3% Cl.

Found: 10.3% F; 16.2% Cl.

Therefore, the low-boiling fraction is certainly phenyl difluorophosphate, obtained in a yield of 39 or 40% of theory, while the small high-boiling fraction appears to be phenyl chlorofluorophosphate containing about 15% of a mixture of phenol and phenyl difluorophosphate.

In the next experiment a lower ratio of calcium fluoride to phenyl dichlorophosphate was used in an attempt to obtain a larger proportion of the chlorofluorophosphate. 100 g. of $C_6H_5PO_2Cl_2$ was reacted with 60 g. of dry CaF_2 in 80 g. of toluene for 20 hours. However, the distillate obtained from this experiment amounted to only 11 ml. of impure phenyl difluorophosphate, and no chlorofluorophosphate.

Upon repeating the reaction of $C_6H_5PO_2Cl_2$ with an

equal weight of CaF_2 in toluene, 80 g. of phenyl dichlorophosphate was used. After 20 hours under reflux, and then filtration and evaporation, distillation at 25 mm. gave the following three fractions: 18 g. at about 71° C., 3 to 5 g. at 101 to 105° C., and 15 g. at 126 to 133° C. These represent yields of approximately 27% $C_6H_5PO_2F_2$, 4 to 7% $C_6H_5PO_2ClF$, and 19% unreacted $C_6H_5PO_2Cl_2$, respectively.

2. Sulfonation of Diphenyl Monofluorophosphate.

As explained before, a monosulfonic acid derivative of diphenyl monofluorophosphate was desired as a permanent moth-proofing compound. Attempts to prepare it are described below.

Fuming Sulfuric Acid as a Sulfonating Agent.

In the first attempt to sulfonate the diphenyl ester, a method was used which was previously shown to be satisfactory for monosulfonation of the phenyl ester of fluorosulfonic acid, HSO_3F.[98] 7.5 g. of $(C_6H_5)_2PO_3F$ was added dropwise, with continuous stirring, to 50 g. of 8% fuming sulfuric acid. The temperature of the reaction solution was held at 18 to 19.5° C. by cooling continuously in a water bath kept at about 10° C. Stirring was continued at 18 to 20° C. for about 2 hours after all the monofluorophosphate had been added, and then the solution was poured into a saturated, ice-cold solution of sodium chloride. The only sodium salt to crystallize from the resulting cold solution was sodium chloride. In other words, if sulfonation did

occur according to the equation

(4) $(C_6H_5)_2PO_3F + SO_3 = (C_6H_5)(C_6H_4SO_3H)PO_3F$,

the sodium sulfonate must have been more soluble than the chloride.

The experiment was repeated, and identical results were obtained. There was a noticeable amount of heat liberated upon addition of the ester to the acid, and this suggested that a sulfonation was occurring but that the sodium sulfonate was quite soluble. In a third experiment, the sulfonation product was poured over chipped ice instead of into a cold solution of sodium chloride. The resulting aqueous solution was shaken with ether, but evaporation of the dried ether layer gave no appreciable amount of residue. Since the unsulfonated ester was known to be soluble in ether and insoluble in water, the lack of an evaporation residue at this point indicated that sulfonation had occurred but that recovery and purification were to be the difficult problems.

In the fourth sulfonation experiment, an attempt was made to extract the sodium sulfonate from a solid sulfonate-sulfate mixture. Accordingly, 5.6 g. of diphenyl monofluorophosphate was reacted with 52 g. of 8% oleum in the usual manner; the reaction product was poured into a solution of sodium hydroxide, so that the resulting suspension was very slightly alkaline; some sulfate crystals were removed by

filtration; the filtrate was evaporated; and the bulky evaporation residue was treated with hot, absolute ethyl alcohol and filtered. Only one gram of solid matter was extracted, and it contained 0.7% F, which is equivalent to only 0.13 grams of the monosulfonated ester.

A fifth experiment was designed to extract the sulfonic acid from aqueous solution with amyl alcohol. In this experiment 6.6 g. of monofluorophosphate was used, sulfonating as usual. The reaction product was poured slowly over chipped ice, and the aqueous solution was extracted twice with n-amyl alcohol. The alcohol was filtered, and the filtrate was evaporated. The dark, viscous evaporation residue of 6 to 7 grams was very acidic and had a sweet ester odor, indicating an amyl sulfonate or sulfate. The residue was neutralized with a 10% aqueous solution of potassium hydroxide, and a brown, oily, ether-soluble layer was formed. The aqueous layer was evaporated to recover any soluble potassium salts. Treating the small evaporation residue with hot ethanol showed only a trace of it to be soluble, and so this method was discarded.

Neutralization of the Sulfonation Product with $Ca(OH)_2$.

In a sixth sulfonation, 6 g. of $(C_6H_5)_2PO_3F$ was reacted with 47 g. of 8% fuming sulfuric acid as usual, and the reaction product was allowed to drip slowly into a suspension of 39 g. of $Ca(OH)_2$ containing 1.1 g. of NaOH, at a temperature of 0 to 11° C. The precipitated calcium

sulfate was removed by filtration, and the filtrate was evaporated to dryness. The evaporation residue was treated with hot alcohol, and after filtration, addition of ether to the alcohol solution yielded 1.1 grams of white solid containing 2.29% F. The pure sodium salt of the monosulfonated ester should contain 5.36% F, and that of the disulfonated ester should contain 4.17% F. The evaporation residue was treated again with alcohol, this time containing 3.8% HCl, in an attempt to extract the sulfonate as the free acid. Evaporation of the alcohol gave 6 to 7 grams of white solid containing only 0.5% F. From these results, the fluorine equivalent to only 16 or 17 per cent of the original diphenyl monofluorophosphate could be accounted for.

This experiment was repeated, using 7.3 g. of $(C_6H_5)_2PO_3F$, 41.3 g. of 8% fuming sulfuric acid, and a suspension of 40 g. of $Ca(OH)_2$ in 300 ml. of water containing 1.5 g. of NaOH. The precipitated calcium sulfate was filtered through a Büchner funnel with suction, and the white filtration residue was pressed as dry as possible. The filter cake was then broken up to allow quicker drying at 110° C. Analysis showed that this residue contained 0.35 to 0.40% F, which accounted for about 70% of the monofluorophosphate used in this experiment. Analysis of the filtrate gave a value of 0.114% F, which accounted for 21% of the original fluoro-ester. Because of the solubility of calcium sulfonates, these results indicated that the fuming sulfuric

acid had caused a splitting of the fluorine-phosphorus bond of the diphenyl ester, and hence most of the fluoride appeared as insoluble calcium fluoride in the filtration residue along with calcium sulfate. No insoluble silver or lead sulfonate could be obtained from the filtrate, either because of the great solubility of the salts or because no sulfonated diphenyl monofluorophosphate was present as such in the filtrate.

Pyridine - Sulfur Trioxide as a Sulfonating Agent.

Since a strongly acidic sulfonating agent appeared to have caused considerable decomposition of the ester molecule, it seemed desirable to investigate the effect of a non-acidic sulfonating agent.

In the eighth sulfonation, therefore, sulfur trioxide was used in the form of its addition product with pyridine. This was prepared as a white solid by reacting chlorosulfonic acid with pyridine in dry chloroform, according to the following equation:

(5) $ClSO_3H + 2\ C_5H_5N = C_5H_5N \cdot SO_3 + C_5H_5N \cdot HCl$.[99]

The pyridinium chloride was soluble in chloroform, and so the precipitated pyridine-sulfur trioxide was separated easily by filtration. 2.8 g. of $C_5H_5N \cdot SO_3$ was heated with 4.4 g. of $(C_6H_5)_2PO_3F$ in a 60-ml. glass bottle. The reaction mixture did not become completely liquid until the heating bath had reached a temperature of about 130° C., and two liquid layers

were seen to exist at that point. Upon heating the reaction bottle at 195 to 208° C., the bottom layer gradually increased in size, and after about 4 hours at that temperature only one liquid layer remained. The cooled product was a brown, viscous liquid, and although it contained the theoretical amount of fluorine for the pyridinium mono-sulfonate, it was certainly a mixture containing decomposition products.

This experiment was repeated in an attempt to carry out the reaction at lower temperatures with stirring. After heating the reactants 9 hours at 150° C. and 20 hours at 160° C., the reaction product was still present as two liquid layers. Decomposition set in when the temperature was raised shortly to 170 to 180° C.

In an effort to bring about this reaction in one phase rather than at a liquid-liquid interface, the reactants were heated in pyridine as a solvent, allowing the pyridine to reflux at its boiling point of 115 to 116° C. 7.2 g. of $(C_6H_5)_2PO_3F$ was reacted with 4.2 g. of $C_6H_5N \cdot SO_3$ for 17 hours in this manner. The excess pyridine was removed by distillation, and dry chloroform was added to the residue. About 2 grams of an insoluble solid residue was separated from the chloroform layer by filtration. It contained only 1.2% F, which would represent a maximum yield of about 5 per cent pyridinium sulfonate. An oily layer floating on the chloroform in the filtrate was extracted with water, neutralized

with sodium hydroxide, and evaporated. Attempts to purify the sodium salt showed that its high fluorine content was present as sodium fluoride.

This experiment was repeated with 7.1 g. of monofluorophosphate and 4.4 g. of pyridine-SO_3 in excess dry pyridine. After refluxing for 12 hours, distillation of solvent, and treatment with dry chloroform, only a very small amount of insoluble solid was removed by filtration, and it contained less than 0.5% F. The chloroform layer was shaken with water, the aqueous layer was evaporated, and the residue was dissolved in warm alcohol, cooled, and filtered. The dried filtration residue weighed 1 gram and contained about 37% F. This accounted for nearly all the original monofluorophosphate, showing that extensive decomposition had occurred instead of mere sulfonation.

The Use of Sodium Chlorosulfonate as a Sulfonating Agent.

Sodium chlorosulfonate, $NaSO_3Cl$, was the next sulfonating agent to be investigated in this study. It was prepared by adding small portions of dry sodium chloride to freshly-distilled chlorosulfonic acid according to equation (6).

(6) $HSO_3Cl + NaCl = NaSO_3Cl + HCl$.

The reaction product was heated shortly at 80° C. and then for 5 hours at 45 to 50° C. After cooling to room temperature, the salt was completely solid; it was powdered and used as such for sulfonation experiments.

The reaction with sodium chlorosulfonate was carried

out in dry, distilled carbon tetrachloride, using 10.6 g. of $(C_6H_5)_2PO_3F$, 5.8 g. of $NaSO_3Cl$, and 105 g. of CCl_4. The reactants were heated at 40° C. for 3 to 4 hours with continuous stirring, but no trace of HCl was evolved during that time, and so it was assumed that neither sulfonation nor phenolic splitting had occurred.

A similar reaction was tried in tetrachloroethane (b.p. 142 to 144° C.), using 10.3 g. of monofluorophosphate and 5.7 g. of $NaSO_3Cl$ in 100 g. of $C_2H_2Cl_4$. Following the rate of the reaction by means of the amount of HCl evolved showed that the reaction was less than 5% complete after heating 2 to 3 hours at 80 to 110° C., and about 20 to 25% complete after 30 to 35 hours at 110 to 128° C. 5.8 g. of solid was separated from the product by filtration, and analysis showed it to contain only 0.24% F, which is equivalent to a yield of less than 5 per cent of theory. Fluorine analysis of the filtrate accounted for the remainder of the unreacted monofluorophosphate. These results showed clearly that a stronger sulfonating agent was necessary for the reaction.

Sulfonation with Chlorosulfonic Acid in Carbon Tetrachloride.

Chlorosulfonic acid[100] is known to be a strong sulfonating agent, and it was investigated next. 10 g. of $(C_6H_5)_2PO_3F$ was reacted with 4.8 g. of HSO_3Cl in 50 g. of CCl_4 (b.p. 76.8° C.). The bath temperature was held at 90° C. for 2 hours, but no separation of an insoluble layer

occurred. When the bath temperature was increased to 115 or 120° C., the solution became cloudy, and continued heating at that bath temperature for about 10 hours gave an oily layer weighing 12 grams. The separated oily layer was subjected to vacuum treatment with warming, and 10 to 10.5 g. remained. Analysis of this liquid gave 4.4% F, 0.73% Cl, and an acidity equivalent to 338% RSO_3H, where R is diphenyl monofluorophosphate. The fluorine content was equivalent to 77% RSO_3F, and the chlorine content was equivalent to 2.4% unreacted HSO_3Cl; these two values seemed quite satisfactory, but the high acidity was quite difficult to explain. It was approximately twice the value calculated for a di-sulfonic acid, and a tri- or tetra-sulfonic acid was quite improbable. At any rate, chlorosulfonic acid appears to have been strong enough to bring about sulfonation. Attempts to crystallize the sulfonic acid from the viscous liquid product by cooling, however, were not successful.

The preceding experiment was repeated, but this time using a 2:1 molar ratio of HSO_3Cl to $(C_6H_5)_2PO_3F$ instead of a 1:1 ratio. Accordingly, 10 g. of monofluorophosphate was heated with 9.4 g. of HSO_3Cl in 80 g. of CCl_4 for a total of 16 hours, using a bath temperature of 80 to 95° C. A viscous liquid layer of about 16 grams remained after removal of the solvent layer by decanting. The solvent layer (55 to 60 g.) was found by analysis to contain only 0.45% available Cl, indicating that little HSO_3Cl could have remained in that

layer. The 16 grams of CCl_4-insoluble, viscous liquid was subjected to vacuum treatment for 9 hours, and 14 grams of evaporation residue remained, analysis of which gave the following results:

0.2235 g.: 4.03 ml. of 0.128 N $Th(NO_3)_4$.

0.6265 g.: 4.43 ml. of N/10 $AgNO_3$.

Calculated for 1:1 molar mixture of RSO_2Cl and H_2SO_4:

7.9% Cl, 4.25% F.

Calculated for 1:1 molar mixture of RSO_3H and H_2SO_4:

0% Cl, 4.52% F.

Found: 2.5% Cl, 4.38% F.

The results indicated a mixture of the sulfonic acid and sulfuric acid, containing some chlorosulfonic acid or the sulfonyl chloride of the diphenyl ester. About half the acid mixture was neutralized at 0 to 10° C. with 10% KOH, and the neutral solution was evaporated. The 5.9 g. of powdered evaporation residue contained 2.53% F, suggesting about equal weights of the potassium sulfonate and sulfate were present. Extraction of the dry salt with hot, anhydrous alcohol gave a yield of less than 10% alcohol-soluble salt, and it contained only 1.8% F.

The Use of Chlorosulfonic Acid in the Absence of a Solvent.

The effect of carrying out the reaction of diphenyl monofluorophosphate with chlorosulfonic acid in the absence of a solvent was studied next. In this regard, 9.3 g. (0.08 moles) of HSO_3Cl was added dropwise to 10 g. (0.04 moles) of

$(C_6H_5)_2PO_3F$. Heat and some HCl vapors were liberated during the addition. After subsequent heating and vacuum treatments, 17.4 g. of a viscous liquid remained. Analysis of this residual liquid gave 4.36% F, which is nearly identical with the value found for the corresponding reaction product obtained when a solvent was used (see page 63). However, 6.1% Cl was shown to be present, and a considerable portion of the reaction product was found to be unreacted diphenyl monofluorophosphate by means of its insolubility in dilute alkali. All these results indicated that the reaction with chlorosulfonic acid gave a mixture of the sulfonic acid, the sulfonyl chloride, unreacted chlorosulfonic acid, unreacted diphenyl monofluorophosphate, and sulfuric acid.

Sulfonation with Dry Sulfur Trioxide Vapor.

Since the purification of the desired sulfonic acid had appeared to be quite difficult, it was felt that a sulfonation reaction yielding a less complex mixture of products would be more satisfactory. With this in mind, a study of SO_3 alone as a sulfonating agent was undertaken.

A sulfonation apparatus was set up so that dry air could be passed through fuming sulfuric acid and then through a reaction bulb containing the ester to be sulfonated. The apparatus consisted of the following parts: (1) a mercury safety trap; (2) a drying tower containing KOH pellets; (3) a 2-foot vertical column filled with an intimate mixture of

P_2O_5 and glass beads; (4) a gas washing bottle, containing 20% fuming sulfuric acid, submerged in a heating bath; (5) a by-pass around the fuming sulfuric acid bottle; (6) a glass-wool trap to remove any droplets of sulfuric acid; (7) a reaction bulb; and (8) a wash bottle containing concentrated H_2SO_4 to prevent any back-diffusion of moisture. All connections were made with standard-taper, ground-glass joints.

In the first experiment in which dry air containing vapors of SO_3 was passed through diphenyl monofluorophosphate, 10 g. of the ester was used. After a few hours, the ester was no longer completely soluble in an excess of dry carbon tetrachloride. After 30 hours the reaction product was washed with CCl_4 and separated. It was partially soluble in water, and it became nearly glassy on cooling, but no crystals formed. After heating for several hours at 70 to 80° C. under a pressure of 10 to 15 mm. of Hg, the viscous, amber liquid contained 3.56% F.

Calculated for RSO_3H: 5.72% F.

Calculated for $R(SO_3H)_2$: 4.6% F.

Again an attempt to obtain a crystalline sulfonic acid by cooling this liquid was of no avail. All of these results seemed to indicate that an appreciable amount of a disulfonic acid was being formed, as that could account for the low fluorine content and probably for the lack of crystallization of a monosulfonic acid.

When the reaction was repeated, a liquid product was

obtained which contained 3.82% F, and again, no crystallization occurred upon cooling.

Absorption of a Known Weight of Sulfur Trioxide Vapor.

The next experiment was carried out on a quantitative basis, using an accurately weighed amount of diphenyl monofluorophosphate (9.444 g.) and passing SO_3 vapors through it until the increase in weight was equivalent to the formation of a monosulfonic acid. However, the vapor pressure of the unreacted ester was great enough that some was lost on passing so much dry air through it, and so an increase in weight of only 2.961 g. was allowed instead of the calculated value of 3.000 grams. Analysis of the reaction product, after it had remained in a vacuum desiccator for several days, gave 5.1% F, as compared with the theoretical value of 5.7% F for the monosulfonic acid. The sulfonated ester was allowed to stand in a vacuum desiccator for several days, and then an attempt was made to determine its freezing point for comparison with that of the unsulfonated ester (m.p. 7 to 10° C.). However, the reaction product could not be solidified on prolonged cooling, and, as a matter of fact, no crystals were obtained upon seeding the viscous liquid with crystals of p-toluenesulfonic acid monohydrate. These facts again suggested that some disulfonation had occurred.

This experiment was repeated with 6 g. of $(C_6H_5)_2PO_3F$, but sulfonation was continued only until the fluorine content of the product had decreased to the value calculated

for monosulfonation. After 11 hours, dry air was passed through the reaction product to remove free SO_3, and analysis gave 5.91% F. After another hour of reaction, dry air was passed through the product for about 80 hours, and analysis gave 5.75% F, as compared with the calculated value of 5.72% F for the monosulfonated ester. Again, all attempts to obtain a crystalline product by cooling and by seeding with p-toluenesulfonic acid were unsuccessful. This was explained when the reaction product was found to be only partially soluble in water; hence it was probably a mixture of the monosulfonic acid with about equal weights of the disulfonic acid and unsulfonated ester.

The Probability of Simultaneous Mono- and Disulfonation.

When the experiment was repeated, identical results were obtained. This indicated that an appreciable amount of disulfonation was occurring before monosulfonation was complete. In fact, the amount of unsulfonated ester, and thus the disulfonic acid, was large enough to suggest that the sulfonation of one benzene ring of the ester molecule seemed to be independent of whether the other benzene ring of the molecule already contained a sulfonic acid group. Assuming this was true, a differential equation was set up for the following reactions to allow the construction of a graph showing the composition of the reaction product as a function of the amount of SO_3 reacted:

(7) $R + SO_3 = RSO_3H$

(8) $RSO_3H + SO_3 = R(SO_3H)_2$

in which R represents the unsulfonated ester, $(C_6H_5)_2PO_3F$.

The equation (9) fitting the above assumptions was derived as follows:

Let:

x = moles of monosulfonic acid present
y = moles of disulfonic acid present
E = moles of unsulfonated ester present
S = moles of sulfur trioxide reacted

where

$S = x + 2y$
$E = 1-x-y$

The differential equation for the series of reactions is

$dy = k \frac{x}{x+E} ds$, where k is assumed to be 1, in accordance with the above considerations.

$$dy = \frac{S-2y}{1-y} ds$$

$$\frac{dy}{dS} = \frac{S-2y}{1-y}$$

To convert this equation to a homogenous one, let:

$y' = y-1$
$S' = S-2$

Thus

$$\frac{dy'}{dS'} = \frac{dy}{dS} = \frac{(S' + 2) - 2(y' + 1)}{1 - (y' + 1)} = \frac{2y' - S'}{y'} = f(S',y')$$

Since this is homogenous, let:

$$y' = vS'$$

Then

$$f(1,v) = \frac{2v-1}{v} = v + S' \frac{dv}{dS'}$$

$$\frac{dS'}{S'} = \frac{vdv}{2v-1-v^2} = -\frac{vdv}{(v-1)^2}$$

$$-\ln S = -\frac{1}{v-1} + \ln(v-1) - C$$

$$-\ln S' = \frac{-S'}{y'-S'} + \ln \frac{y'-S'}{S'} - C$$

$$-\ln(S-2) = -\frac{S-2}{(y-1)-(S-2)} + \ln \frac{y-S+1}{S-2} - C$$

$$\ln(y-S+1) = \frac{S-2}{y-S+1} + C$$

When $S = 0$, $y = 0$

Therefore $C = 2$

and

(9) $$\ln(y-S+1) = \frac{S-2}{y-S+1} + 2$$

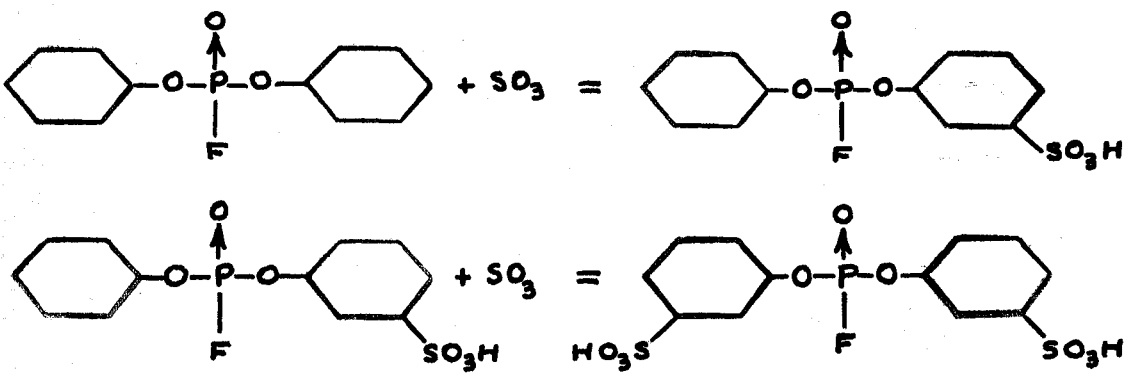
The graph of this equation is shown in Fig. 1, page 70.

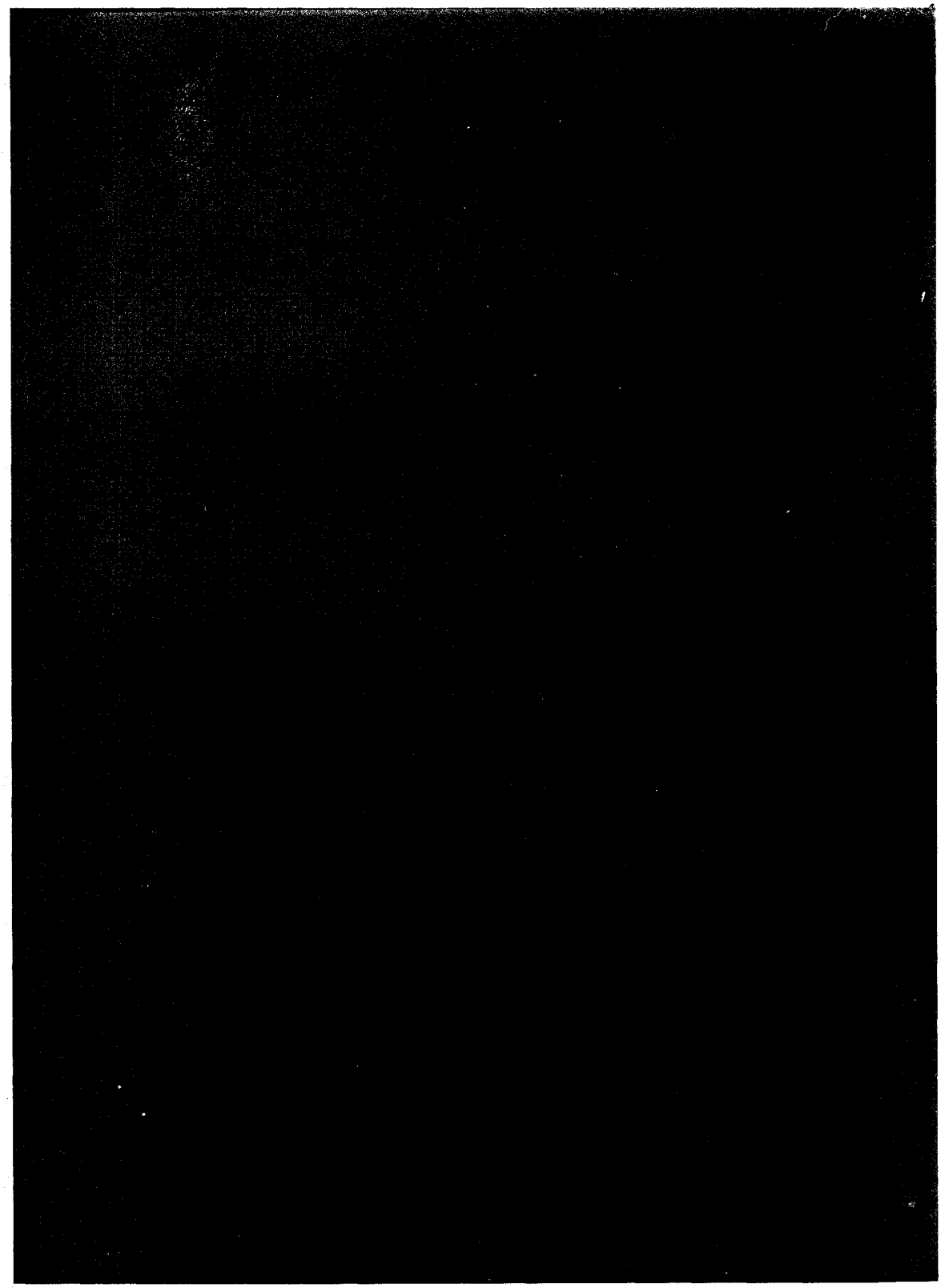
Although the sulfonation of one benzene ring may not be absolutely independent of the sulfonation state of the other, this at least gives a good idea of the resulting compositions, and it shows that a low degree of sulfonation will be required to give a reasonably great ratio of the mono- to the disulfonated ester.

With this in mind, the next experiment was allowed to proceed only until 0.4 to 0.6 moles of SO_3 had reacted per mole of diphenyl monofluorophosphate used. In this experiment 13.193 g. of monofluorophosphate was placed in the reaction bulb, and dry air containing SO_3 vapors was passed through the ester until the increase in weight of the

Figure 1

A graph showing the composition as a function of the amount of sulfur trioxide reacted for the following simultaneously-occurring reactions:





bulb amounted to 1.671 g., which is equivalent to 0.4 moles of SO_3 per mole of ester. Analysis gave 6.4 to 6.5% F, which is equivalent to a value of 0.55 to 0.6 moles of SO_3 per mole of ester used. The reaction product was shaken twice with an excess of dry CCl_4 in a separatory funnel to extract any unreacted ester, and the separated CCl_4-insoluble layer was subjected to high vacuum for several hours to remove any remaining solvent and free SO_3. Analysis of the sulfonated ester was found then to be 5.6% F, as compared with the value of 5.72% F calculated for the monosulfonic acid of diphenyl monofluorophosphate. On freezing for several hours with dry ice, a glass was formed which exhibited no crystalline properties whatsoever under the polarizing microscope. The same result was obtained on prolonged cooling at -18° C. On treating the sulfonated ester with water, an appreciable proportion was observed to be insoluble, which means that the unsulfonated ester was not removed completely by the previous treatment with CCl_4. The water-soluble portion was neutralized with a slurry of $Ba(OH)_2$, the Ba^{++} was precipitated as $BaCO_3$ by addition of the required amount of Na_2CO_3, and, after filtration, the slightly alkaline solution of sodium salts was evaporated in a platinum dish placed over concentrated sulfuric acid in a vacuum desiccator. The resulting white solid was easily powdered, and on analysis it was found to contain 3.25% F, as compared with the value of 5.36% F calculated for the sodium salt of the

monosulfonated ester. It contained the sodium salts of both the mono- and disulfonic acids, as well as a trace of sodium carbonate.

Another partial sulfonation was carried out with 13.082 g. of $(C_6H_5)_2PO_3F$. Analysis of the sulfonated ester gave 7.08% F, which is equivalent to 0.25 moles of SO_3 per mole of ester used in the reaction. The reaction was completely soluble in CCl_4, and so the CCl_4 solution of the product was shaken with water to extract the sulfonated ester. The aqueous extract was neutralized with sodium hydroxide, using methyl red as an indicator, and the neutral solution was evaporated over H_2SO_4 in a vacuum desiccator. The resulting pink solid was slightly hygroscopic.

0.1505 g.: 2.75 ml. of 0.1285 N $Th(NO_3)_4$.

Calculated for $C_6H_5(C_6H_5SO_3)PO_3F$: 5.36% F.

Calculated for $(C_6H_5SO_3)_2PO_3F$: 4.16% F.

Found: 4.46% F.

Again a mixture of mono- and disulfonic acid salts seems to have been present.

The final experiment in which dry air containing sulfur trioxide vapors was passed through diphenyl monofluorophosphate as a means of sulfonating the ester, was allowed to proceed for a long time in hopes of preparing a fairly pure disulfonic acid. In this sulfonation 11.551 g. of $(C_6H_5)_2PO_3F$ was used. After several days of reaction, the very viscous liquid contained 5.35% F. According to

Fig. 1, page 70, the fluorine value corresponds to a composition of about 19% unsulfonated ester, 31% monosulfonic acid, and 49% disulfonic acid, on a molar basis. Therefore, after sulfonation until the product was too viscous to allow further reaction conveniently, the disulfonic acid was present in a yield of only 49 molar per cent. At any rate the viscous liquid was washed with dry carbon tetrachloride to remove the unsulfonated ester, and the separated sulfonic acid mixture was neutralized with a cold suspension of barium hydroxide. After the required amount of sodium carbonate was added and the precipitated barium carbonate was removed by filtration, the salt solution was evaporated in a vacuum desiccator as usual. Analysis of the dry sodium salt showed only 1.80% F, whereas the sodium disulfonate should contain 4.17% F and the monosulfonate 5.4% F. Since tri- and tetra-sulfonation are quite improbable, the salt must have been contaminated with a considerable amount of Na_2CO_3 and Na_2SO_4.

The Use of Stabilized Liquid Sulfur Trioxide as a Sulfonating Agent.

The next series of investigations regarding the sulfonation of diphenyl monofluorophosphate involved the use of a stabilized sulfur trioxide, which is sold in liquid form by General Chemical Company under the name of "Sulfan B".[101] Solutions of the desired strength were made up by transferring a known weight of liquid SO_3 to the desired amount of dry CCl_4 or $C_2H_2Cl_4$ in a glass-stoppered bottle. A large glass bulb with a long tip was found to be quite satisfactory for

sampling, weighing, and transferring the sulfur trioxide.

In the first experiment involving the use of "Sulfan B", 22 g. of a 7.8% solution of SO_3 in CCl_4 was added dropwise to a cold (10° C.) solution of 5.4 g. of $(C_6H_5)_2PO_3F$ in 20 to 30 ml. of CCl_4 with continuous stirring. The resulting solution was allowed to stand overnight at room temperature, and the next day there were droplets of a very viscous liquid floating on the CCl_4 solution. Only 1 or 2 grams of the viscous liquid remained after two washings with dry CCl_4, and it contained only 2.5% F; hence, the extent of the reaction appeared to be very low.

This experiment was repeated on a larger scale. Accordingly, 140 g. of solution of 7.83% SO_3 in CCl_4 was added slowly to 24.3 g. of $(C_6H_5)_2PO_3F$ in 58 g. of CCl_4 at 10° C. with mechanical stirring. After standing at room temperature for two weeks, however, no oily layer had formed, and so it was felt that possibly too much solvent had been used to allow a reasonable rate of reaction.

A solution of 11.5% of SO_3 in CCl_4 was prepared, and 21 g. of the solution was added at room temperature to 7.5 g. of diphenyl monofluorophosphate. No apparent change occurred upon standing several days at room temperature. The reaction product was allowed to reflux slowly for 7 hours, but only a very few oily droplets were formed.

These results indicated that a still greater concentration or else a higher reaction temperature might be

necessary, and the effect of the latter was investigated next.

A solution of 9.97% SO_3 in $C_2H_2Cl_4$ (b.p. 142-144° C.) was made up, and 33 g. of the solution was added to 10.0 g. of the ester at room temperature. The reactants were heated at the boiling point of $C_2H_2Cl_4$ for several hours without any observed formation of an insoluble liquid layer.

"Sulfan B" was used without dilution in the next sulfonation. After cooling 9.0 g. of the ester to -10° C., 2.5 g. of liquid SO_3 was added dropwise by means of a dropping funnel. A considerable amount of heat was liberated during the reaction. Stirring was discontinued after the addition of SO_3 was complete, and the temperature of the reaction product was allowed to rise slowly to 25° C., during which time the liquid gradually became dark and viscous. After standing at room temperature for about 4 hours, the liquid was shaken with dry CCl_4, and a small dark layer separated from the solvent. However it would not crystallize on prolonged cooling, and it appeared to contain a considerable amount of decomposition products.

One more sulfonation was undertaken, this time using 3.8 g. of CCl_4 was added to 6 g. of $(C_6H_5)_2PO_3F$ at a) g.. of SO_3 in 3.8 g. of CCl_4 was added to 6 g. of $(C_6H_5)_2PO_3F$ at a temperature of 4 to 8° C. with stirring. No great heat of reaction was noticed, and the product was still a single liquid layer after standing several hours. Addition of excess CCl_4 failed to cause the formation of a second liquid layer, and so the

reaction which had occurred on using pure SO_3 did not occur on using a 33% solution of SO_3 in CCl_4.

C. The Reaction of Ethyl Polyphosphates with Anhydrous Hydrogen Fluoride.

1. Ethyl Metaphosphate

A commercial, or technical, grade of ethyl metaphosphate was used in the investigation of this reaction, which was expected to proceed according to the following equation:

(10) $C_2H_5PO_3 + HF = (C_2H_5)HPO_3F$.

A sample obtained from Monsanto Chemical Company was used in the early experiments, but most of the investigations were carried out with a product obtained from Victor Chemical Works. The Victor metaphosphate was produced by the reaction of triethyl orthophosphate with an equimolar quantity of phosphoric anhydride.[34]

The source of anhydrous hydrogen fluoride for these experiments was a cylinder obtained from Harshaw Chemical Company. The cylinder was fitted with a stainless-steel adapter so that the HF could be distilled conveniently into any desired receiver or reactor.

The first reaction of ethyl metaphosphate with HF was carried out in a stainless-steel vessel. Approximately 21 g. of anhydrous hydrogen fluoride was condensed rather tediously in a paraffin-lined glass flask and then poured quickly into 114 g. of ethyl metaphosphate in the steel

reaction vessel. A considerable amount of heat was evolved on mixing. The reaction vessel was sealed and then heated for 20 hours at about 65° C. Using a water aspirator, vacuum was applied for about 3 hours to remove excess hydrogen fluoride. 65 g. of the liquid was used for distillation at 30 mm. of mercury. 29 g. of distillate was caught at a temperature of 95 to 117° C.; analysis showed 16.9% F. The residue of 26 grams contained 4.03% F, and about 10 g. was lost through the aspirator, apparently as a result of decomposition. The distillate was redistilled at 3 mm. of mercury yielding 7.5 g. of liquid boiling at 43 to 85° C. and 9 g. at 85 to 113° C., along with a non-distillable residue of 6 g. of viscous liquid. Hence decomposition certainly had occurred during the first distillation.

A 25-gram portion of the above reaction product was neutralized with carbonate-free NaOH solution at a temperature of about 10° C., and the neutral solution was shaken with ether to extract any water-insoluble impurity, such as diethyl monofluorophosphate. Evaporation of the separated and dried ether layer gave only 1 to 2 g. of viscous liquid containing 5.45% F. From these results it was calculated that no more than 5 or 10% of the reaction product could have been diethyl monofluorophosphate.

The above reaction was repeated on a smaller scale. In this experiment, however, the hydrogen fluoride was distilled directly from the HF cylinder into a well-cooled 100-ml.

platinum bottle, and the ethyl metaphosphate was added in small portions. In this manner, 34 g. of ethyl metaphosphate was reacted with 8.3 g. of anhydrous hydrogen fluoride in the platinum bottle. After heating shortly at 50° C., the contents of the flask were analyzed and found to contain 15.1% F, as compared with the desired value of 14.84% F, which is the calculated fluorine content of ethyl monofluorophosphoric acid. A small amount of the reaction product was neutralized with a suspension of barium hydroxide, but a nonfilterable, milky solution containing a rather slimy precipitate was formed. A second larger portion (15 g.) of the reaction product was distilled, using a short, packed column for fractionation at a pressure of 1 to 2 mm. of mercury. Only 3 g. was distilled at 41 to 48.5° C. as the bath temperature climbed from 130 to 210° C. Roughly one-fourth of this fraction was insoluble in water, and it was assumed to be diethyl monofluorophosphate. Another 3 g. of liquid was caught in the dry ice trap (20.5% F), and a residue of 7 g. remained. The distillation shows that decomposition occurs to a considerable extent when such high temperatures are used.

In the third reaction of ethyl metaphosphate with hydrogen fluoride, 30.5 g. of the ester was added in small portions to 6.0 g. of HF in a platinum bottle with cooling, and after standing 2 hours at room temperature with occasional agitation, the reaction product was found to contain 14.9% F. The product was allowed to stand at room temperature for

3 days, and then dry air was bubbled through the liquid for 6 hours, after which the fluorine content was found to be 14.65% F. This is only slightly below the value of 14.84% F calculated for $(C_2H_5)HPO_3F$. Standing overnight in a sealed platinum bottle seemed to cause a slight decomposition, as indicated by the characteristic odor of HF.

About 2.5 g. of the reaction product was neutralized with a suspension of $Ba(OH)_2$, and most of the precipitated solid matter was removed from the milky solution with difficulty by filtration. Addition of the required amount of Na_2CO_3 as an aqueous solution and subsequent removal of the precipitated $BaCO_3$ by filtration gave a clear filtrate, which was then evaporated in a platinum dish over concentrated sulfuric acid in a vacuum desiccator. The evaporation residue was a slightly sticky, hygroscopic powder containing 8.65% F, which is about two-thirds of the value of 12.7% F calculated for the desired $C_2H_5NaPO_3F$.

A destructive distillation was performed on 12.5 g. of the above reaction product at atmospheric pressure. The first fuming occurred at a bath temperature of 180° C., and a distillate of 2.1 g. was caught at a bath temperature of 208 to 330° C. Analyses of the fractions of this distillate ranged from 17.5 to 23.4% F. The residue of 10 g. contained 10.4% F. These results showed little except that the acid-ester does not decompose simply to form the neutral monofluorophosphate and the dibasic acid as originally expected.

The Great Solubility of Salts of Ethyl Monofluorophosphoric Acid, and the Preparation of Insoluble Salts of Some of the Impurities.

An attempt was made to prepare some insoluble salts of the acid ester, using the above reaction product. An equimolar mixture of pyridine with the reaction product, calculated as $(C_2H_5)HPO_3F$, was a homogeneous liquid which afforded no crystals of a pyridinium salt at all. When dry, gaseous ammonia was bubbled through a pyridine solution of the reaction product, a crystal sludge separated out. Analysis of the crystals gave the following results:

0.0786 g. : 4.47 ml. of 0.1285 N $Th(NO_3)_4$.

0.1414 g. : 4.05 ml. of 0.484 N HCl.

Calculated for $(C_2H_5)NH_4PO_3F$: 13.1% F; 9.65% N.

Calculated for $(NH_4)_2PO_3F$: 14.2% F; 20.9% N.

Found: 13.9% F; 19.4% N.

Hence the only crystallized ammonium salt was diammonium monofluorophosphate. When the experiment was repeated as a means of determining the amount of H_2PO_3F present, 7.27 g. of the reaction product gave 1.8 g. of the ammonium salt, which is equivalent to about 18 or 19% H_2PO_3F present as an impurity. Identical results were obtained when the diammonium salt was precipitated by neutralizing the reaction product directly with concentrated ammonium hydroxide.

Attempts to prepare brucine and strychnine salts gave only fluorine-free salts assumed to be those of monoethyl

orthophosphoric acid.

Attempts to prepare the silver and lead salts gave only small amount of mixtures of salts of H_2PO_3F, H_3PO_4, and $(C_2H_5)H_2PO_4$.

When 0.95 g. of the crude acid ester was neutralized with KOH and an excess of concentrated nitron acetate solution was added, 0.6 g. of pink salt was obtained. It contained 7.9% F, whereas the nitron salt of HPO_2F_2 contains 9.2% F and that of $(C_2H_5)HPO_3F$ should contain 4.3% F. Probably the precipitated nitron salt was a mixture of these two.

Attempts to Purify the Ethyl Monofluorophosphoric Acid by Distillation.

In the next reaction of hydrogen fluoride with the metaphosphate, 7.85 g. of HF was reacted with 40.9 g. of the ester, and the product was found to contain only 12.33% F, which is equivalent to an 83% splitting of the metaphosphate with HF. When 40 g. of the resulting liquid was taken for distillation (Fig. 2, page 82), 2.5 g. of volatile material was trapped, by means of dry ice, at a bath temperature of up to 53° C. and a pressure of 0.03 mm. of mercury as dry air was allowed to bubble through a capillary into the distilling flask. The trapped liquid contained 23.5% F. Distillation of the remaining 37.5 g. in a short-path still (Fig. 3, page 83) gave 20 g. of distillate containing 15.8% F and 13 to 14 g. of residue containing 3.5% F. Redistillation of 19 g. of the distillate gave about 15.5 g. of liquid below

Figure 2

A small still

used for conventional type vacuum distillation

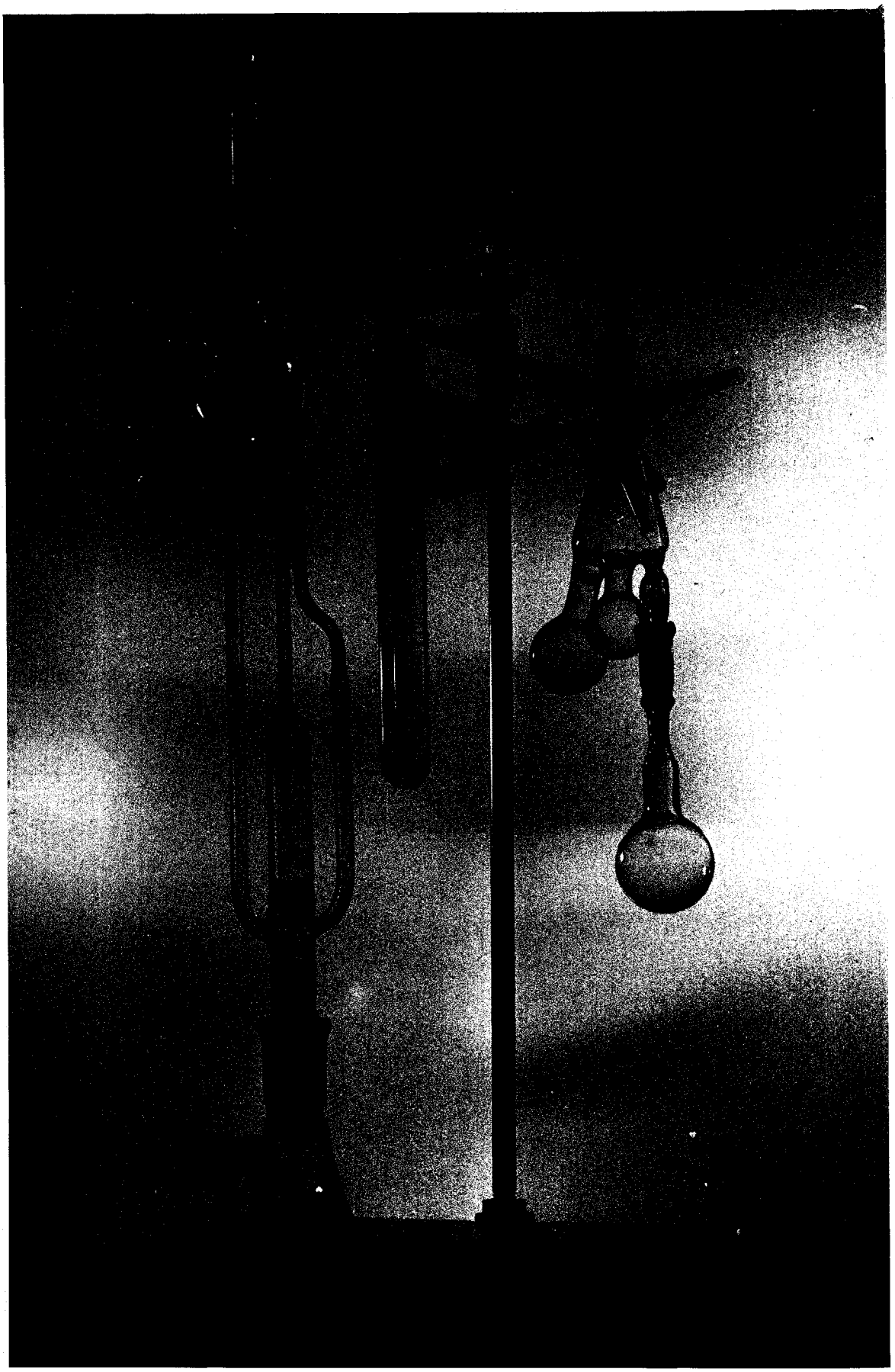
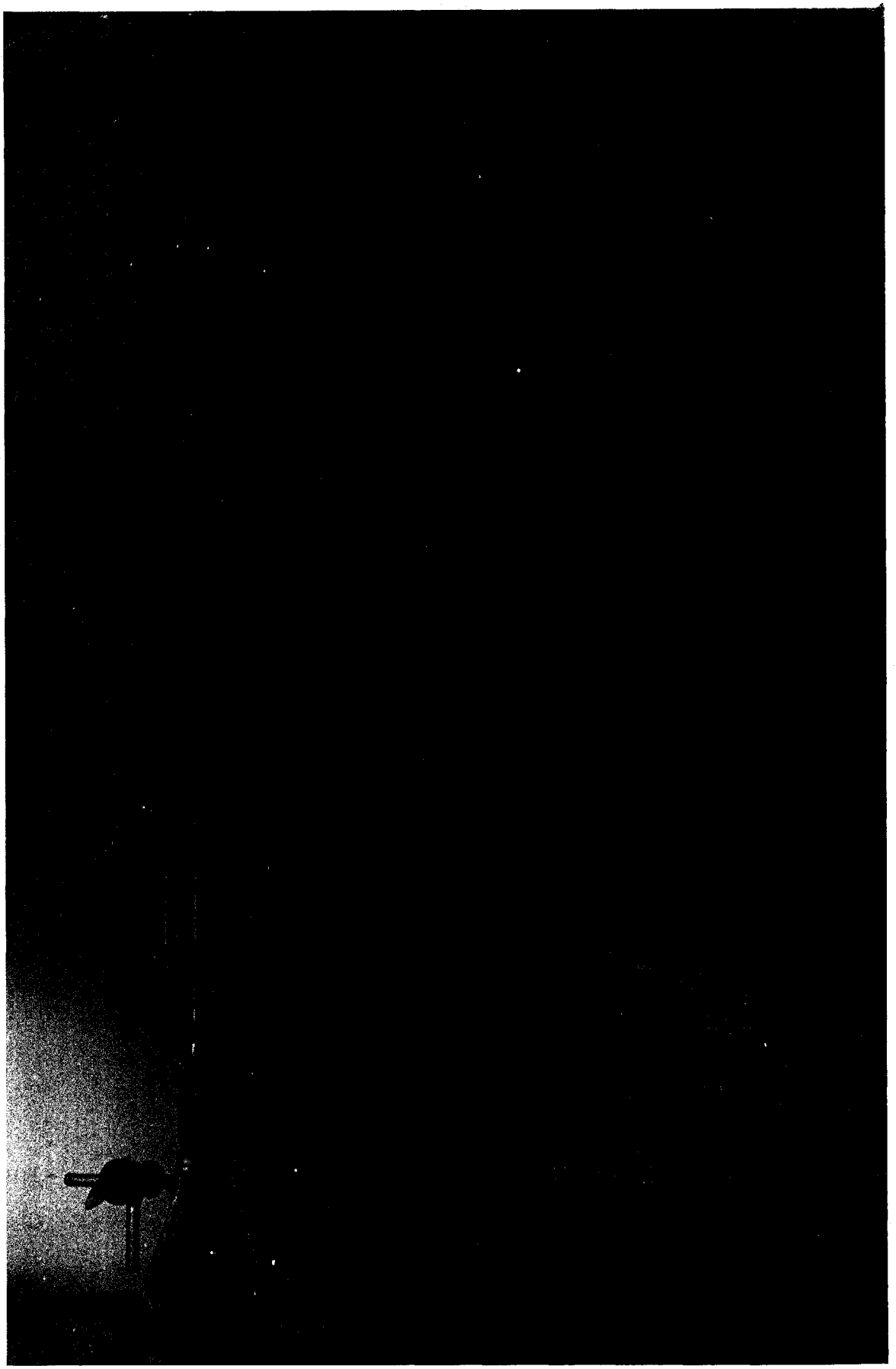


Figure 3

Short-path Still



a jacket temperature of 88° C. at a pressure of 0.1 mm. of mercury. Analysis of this distillate gave the following results:

0.0657 g. : 3.95 to 4.00 ml. of 0.128 N $Th(NO_3)_4$.

0.2053 g. : 14.77 ml. of 0.102 N NaOH.

Calculated for $(C_2H_5)HPO_3F$: 14.84% F; M.W. 128.05.

Found: 14.7 to 14.9% F; M.W. 135-6.

The barium salt of this acid was prepared by neutralizing it with an aqueous suspension of $Ba(OH)_2 \cdot 8H_2O$, filtering, and evaporating the filtrate over concentrated H_2SO_4 in a vacuum desiccator. After drying finally over phosphoric anhydride, analysis of the barium salt gave 8.25% F, whereas $Ba(C_2H_5PO_3F)_2$ should contain 9.7% F.

Another reaction of HF with ethyl metaphosphate was undertaken in which care was taken to have a slight excess of HF in the reaction product. When 75 g. of the resulting liquid was subjected to conventional vacuum distillation treatment, there was found to be less than 2 g. of volatile material below 60° C. A distillate of 22 g. (16.5% F) was caught, along with 15 g. of trapped vapors, at a bath temperature of 80 to 105° C. and a pressure of 0.07 mm. of Hg over a period of 3 hours. Redistillation gave 16.5 g. of liquid containing 15.7 to 16.1% F and a molecular weight of 138. Indications were that the high temperatures required in the conventional type of distillation (Fig. 2) caused some decomposition. However, this distillate was used in preparing

ammonium, sodium, and potassium salts of the acid ester by neutralization with aqueous solutions of the corresponding bases and evaporating over H_2SO_4 in a vacuum desiccator. The experimental results of the fluorine analyses, along with the calculated values in parentheses, are as follows: $NH_4C_2H_5PO_3F$, 13.8% F (13.1); $NaC_2H_5PO_3F$, 13.3% F (12.7); and $KC_2H_5PO_3F$, 11.6% F (11.4).

The next reaction of ethyl metaphosphate with hydrogen fluoride was undertaken with the idea of distilling the reaction product in a short-path still at a pressure low enough to avoid appreciable decomposition during the distillation. Accordingly, 76 g. of a crude ethyl monofluorophosphoric acid containing 15.6% F was subjected to a pressure of 0.05 mm. in the short-path still. Practically no liquid appeared in the dry-ice trap until the jacket temperature of the distilling flask had climbed to about 90° C., hence showing that no appreciable amount of HPO_2F_2, $(C_2H_5)_2PO_3F$, $C_2H_5PO_2F_2$, or C_2H_5OH was present in the original product from the reaction of HF with the metaphosphate. As the jacket temperature was increased from 90 to 120° C., however, 10 to 15 g. of liquid appeared in the dry-ice trap as 1 to 2 g. of liquid was distilling.

The Use of a Mercury Diffusion Pump in an Attempt to Obtain Minimum Decomposition during Short-path Distillation.

Only an oil pump had been used to produce the vacuum in previous experiments, but from the above results, a mercury

diffusion pump appeared to be necessary in order to avoid decomposition. In the next experiment, short-path distillation was undertaken with such a pump in the system, and 49 g. of a reaction product gave 17.2 g. of liquid (16.8% F) at 60 to 90° C. and a pressure of less than one micron. Heating at 90 to 120° C. gave an additional distillate of 9.5 g. (12.4% F). The residue of 12. g. of viscous liquid contained 5.2% F and had a molecular weight (neutralization equivalent) of about 100 with about an equimolar distribution of mono- and dibasic acids. More of the original reaction product was distilled in the same manner, and the combined fractions were redistilled, giving 32 g. of liquid (15.9 to 16.0% F) at a jacket temperature of 53 to 74° C. in the short-path still at a pressure of less than one micron. A second redistillation gave 3.5 g. (19.7% F) at 35 to 48° C., 12 g. (16.1% F) at 48 to 50° C., and 9 g. (14.4% F, M.W. 137) also at 48 to 50° C. The middle fraction was redistilled, and 8 g. of distillate containing 14.9% F was obtained at a jacket temperature below 37° C. in the short-path still. This fraction was neutralized with aqueous KOH, and after evaporation over H_2SO_4 and drying over P_2O_5, analysis of the resulting potassium salt gave the following results:

0.1110 g. : 5.22 ml. of 0.1290 N $Th(NO_3)_4$.

Calculated for $KC_2H_5PO_3F$: 11.42% F.

Found: 11.5% F.

This indicates that there is no water of crystallization in the potassium salt.

2. Diethyl Diacid Pyrophosphate.

The diethyl diacid pyrophosphate used in the investigation of this reaction was a commercial product obtained from Victor Chemical Works. They had produced it according to the following reaction:

(11) $P_2O_5 + 2C_2H_5OH = (C_2H_5)_2H_2P_2O_7$.[24]

The determination of the neutralization equivalent, or hence the equivalent weight as an acid, of this viscous, amber liquid gave the following results:

0.2804 g. : 4.40 ml. of 0.484 N NaOH.

Calculated for $(C_2H_5)_2H_2P_2O_7$: E.W. 117.

Found: E.W. 120.

In the first reaction of this pyrophosphate with anhydrous hydrogen fluoride, 113.3 g. of the ester was added in small portions to 11.3 g. of HF in a platinum bottle. Analysis showed the resulting liquid to contain 8.25% F, while a stoichiometric value of 7.48% F was calculated for the following reaction equation:

(12) $(C_2H_5)_2H_2P_2O_7 + HF = (C_2H_5)H_2PO_4 + (C_2H_5)HPO_3F$

Dry air was bubbled through the liquid for 8 or 10 hours, but, as a result, the fluorine content dropped only to 8.20% F. When 1.87 g. of this reaction product was neutralized and then treated with excess nitron acetate solution, 0.2 g. of salt precipitated. This is equivalent to 2.6% HPO_2F_2 as an impurity. When 1.2 g. of the same reaction product was neutralized and solid silver nitrate was added, some yellow

silver orthophosphate precipitated along with a considerable amount of the expected $Ag_2(C_2H_5)PO_3F$.

Approximately 60 g. of the above product from the reaction of HF with the pyrophosphate was used in an attempted distillation at a pressure of 2 mm. of mercury in a conventional type still. A bath temperature of less than 160° C. did not cause the appearance of any liquid in the dry-ice trap, thus showing that no impurities as volatile as diethyl monofluorophosphate or difluorophosphoric acid were present in appreciable amounts. The distillation of ethyl monofluorophosphoric acid, however, was accomplished only with great difficulty and with noticeable decomposition.

Short-path distillation was more satisfactory, however, 11.8 g. of the same reaction product gave 4 g. of water-white distillate (12.34% F, M.W. 132) at a jacket temperature of 105 to 112° C. and a pressure of 0.01 to 0.10 mm. of mercury. An additional 1.5 g. of liquid (10.6% F, M.W. 120-124.5) distilled at 110 to 137° C., and 5 g. of viscous, amber liquid (1.5% F) remained as a residue.

A second reaction of diethyl diacid pyrophosphate with hydrogen fluoride was carried out so that the short-path distillation could be repeated. In this experiment 113 g. of the pyrophosphate was reacted in the usual manner with 11.0 g. of anhydrous hydrogen fluoride, and analysis then showed the liquid product to contain 8.2% F, which represents about 10% excess fluoride. Less than 2 g. of volatile matter could be

removed from 120 g. of the reaction product, indicating little contamination with $(C_2H_5)_2PO_3F$, HPO_2F_2, or unreacted HF. A mercury diffusion pump was used to produce a pressure of less than 0.001 mm. of mercury in the short-path still used in distillation of 63 g. of the above liquid. At a jacket temperature of 80 to 100° C., 10 g. of liquid (15.0% F) was distilled. 10.5 g. (13.1% F) distilled at 100 to 120° C., and another 10.5 g. (10.83% F) was obtained at 120 to 135° C. The residue of 28.5 g. contained only 0.94% F, and the 3.5 g. of liquid which appeared in the trap during distillation was not analyzed. The decreasing fluorine contents were the result of increasing amounts of monoethyl phosphoric acid in the distillates. From the results of this distillation, about 43 to 46% of the reaction product was accounted for as ethyl monofluorophosphoric acid, and this is equivalent to a yield of 85 to 91% of theory, which is quite satisfactory for a reaction involving a commercial grade of the pyrophosphate. Redistillation of the first two fractions gave a fraction of 2.5 g. at 25 to 40° C. with a refractive index ($n_4^{20.5}$) of 1.3632, and another fraction at 40 to 52° C. giving the following analytical results:

0.0761 g. : 4.64 ml. of 0.129 N $Th(NO_3)_4$.

0.2106 g. : 14.17 ml. of 0.1158 N NaOH

Calculated for $(C_2H_5)HPO_3F$: 14.84% F; M.W. 128.05.

Found: 14.9% F; M.W. 128-129; $n_D^{20.2}$ 1.3650.

Potassium Ethyl Monofluorophosphate.

The latter fraction (40 to 52° C.) was neutralized with concentrated, aqueous KOH, and the salt solution was evaporated to dryness over H_2SO_4 in a vacuum desiccator. The dry salt was dissolved in the minimum amount of absolute ethyl alcohol, the solution was filtered to remove any undissolved KF, dry ether was added to the filtrate, and the precipitated potassium salt was dried over P_2O_5. Analysis of the salt gave the following results:

0.1043 g. : 5.04 ml. of 0.129 N $Th(NO_3)_4$.

0.2002 g. : 0.1338 g. of $Mg_2P_2O_7$.

0.2008 g. : 0.1338 g. of $Mg_2P_2O_7$.

Calculated for $KC_2H_5PO_3F$: 11.44% F; 18.65% P.

Found: 11.8% F; 18.60, 18.55% P.

The salt was found to sinter at 71 to 73° C., hence apparently undergoing a transition below its melting point. The resulting modification melted at 166 to 167.5° C. When 0.9166 g. of the salt was heated at 170 to 200° C. in a closed platinum crucible, no loss of weight whatsoever was detected after cooling. A concentrated aqueous solution of a portion of the resulting melt gave no precipitate on adding a large crystal of $AgNO_3$, showing that decomposition to salts of H_2PO_3F, $(C_2H_5)H_2PO_4$, etc. did not occur. No polarizing microscope fitted with a heating stage was available for viewing the transition, and so an attempt was made

to observe a difference in crystal structure after chilling a melt of the salt. However the original potassium salt and the chilled melt both appeared under the polarizing microscope as isotropic crystals with no well-defined crystal pattern and no display of colors. Hence the allotropic transition, if that is what actually occurred, was not able to be observed satisfactorily.

A hydrolysis study of potassium ethyl monofluorophosphate was carried out with 0.3564 g. of the precipitated salt. An aqueous solution of the salt was allowed to reflux while standard N/10 sodium hydroxide was added from time to time to keep the solution slightly alkaline to phenolphthalein. After 10 hours at 100° C., hydrolysis of the P-F bond was calculated to be approximately 7% complete; during the following 8 hours the average hydrolysis rate was 0.08% per hour.

This hydrolysis study was repeated, using a potassium salt (11.5% F) prepared in experiments in which ethyl metaphosphate had been used as a starting material. Hydrolysis was only 2.6% complete after 38 hours at 100° C. in this case, and the rate was approximately 0.02% per hour after the first 16 hours.

A sample of the potassium salt mentioned in the preceding paragraph was dissolved in N/10 HCl and allowed to stand for two days at room temperature. Titration of the resulting solution with standard sodium hydroxide solution showed that the increase in acidity on standing was equivalent

to 11.6% hydrolysis. The rate of hydrolysis of $KC_2H_5PO_3F$ in the acid solution was therefore less than 0.25% per hour.

Analytical Data for Pure Ethyl Monofluorophosphoric Acid.

In order to obtain a larger supply of ethyl monofluorophosphoric acid for accurate density determinations and to increase the supply of the potassium salt, a third reaction with diethyl diacid pyrophosphate was performed. On the second short-path redistillation, a fraction of about 28 g. of water-white liquid distilled at 55 to 58° C.

0.0829 g. : 5.00 ml. of 0.129 N $Th(NO_3)_4$.

0.2095 g. : 0.1842 g. of $Mg_2P_2O_7$.

7.1231 g. (20.0° C.) : 73.1177 g. of Hg(24.9° C.)

Calculated for $(C_2H_5)HPO_3F$: 14.84% F; 24.19% P.

Found: 14.8% F; 24.47% P;

n_D^{20} 1.3668; d_4^{20} 1.3185.

The density determination was made with a pycnometer calibrated with distilled mercury, and all weighings were corrected for buoyancy of air.

3. Hexaethyl Tetraphosphate.

In the investigation of the solvolytic splitting of hexaethyl tetraphosphate by hydrogen fluoride, a 3:1 molar ratio of acid to ester was used in all experiments. The ester was a commercial grade produced by Monsanto Chemical Company under the name "100% Hexaethyl Tetraphosphate".

The first reaction was carried out in a stainless-steel container. 100 g. of hexaethyl tetraphosphate was

weighed into the reactor, and 11.9 g. of anhydrous HF, which had been condensed in a paraffin-lined glass flask, was poured in quickly, resulting in a noticeable liberation of heat. The steel container was sealed and then heated 20 hours at 60 to 65° C. over a period of three days. After a 3-hour vacuum treatment, the liquid product was found to contain only 7.83% F, as compared with the desired value of 10.07% F. Although splitting had therefore not been complete, because of loss of HF by volatilization before reaction, 60 g. of the liquid was transferred to a conventional type still and subjected to distillation at 3 mm. of mercury. 8 g. of water-white liquid (11.3% F) distilled at 36 to 56° C. as the bath temperature was increased to 136° C., and 26 g. (8.9% F) distilled with some decomposition at 57 to 119° C. as the bath temperature climbed to 213° C. The first fraction was predominantly diethyl monofluorophosphate (12.17% F).

When the experiment was repeated, a platinum bottle was used, and an effort was made to see that a slight excess of hydrogen fluoride was present to allow complete splitting of the polyphosphate. Consequently, 7.3 g. of anhydrous HF was condensed in a 100-ml. platinum bottle, and 53 g. of hexaethyl tetraphosphate was added in small portions with agitation and cooling. After dry air was passed through the liquid for about one hour, analysis showed the reaction product to contain 10.5% F, whereas the value calculated for a 3:1 ratio of acid to ester is 10.07% F. When 2 g. was

neutralized with concentrated NaOH and a large crystal of silver nitrate was added, 0.23 g. of silver salt was precipitated. Another 0.12 g. was obtained on adding alcohol. The total weight of silver salt was therefore equivalent to about 6.5% $(C_2H_5)_2HPO_4$ in the original reaction product. Likewise, 0.332 g. of a nitron salt was obtained on adding an excess of nitron acetate solution to a neutralized solution of 1.9 g. of the reaction product, indicating that as much as 4.2% HPO_2F_2 may have been present as another impurity.

Vacuum distillation of 30 g., using a short, packed column, gave no distinct fractions but, instead, slow distillation with some decomposition. It appeared that the use of a fractionating column required bath temperatures high enough to cause decomposition to occur, and, because of the presence of decomposition vapors, it was quite difficult to maintain the required low pressures in the system.

When 22 g. of the same reaction product was distilled by means of a short-path still, about 3.2 g. of vapor was trapped as a liquid in the dry-ice trap before actual distillation began. A jacket temperature of 70 to 126° C. yielded 8.5 g. of water-white liquid (16.3% F, M.W. 132.4) and an equal weight of residue (6.9% F).

In order to obtain enough material to repeat the short-path distillation, a third reaction of HF with hexaethyl tetraphosphate was necessary. In this experiment 9.5 g. of HF was reacted with 76.3 g. of the ester, and the resulting

liquid contained 10.3% F, which indicated that a very slight excess of HF had been used. 84 g. of this liquid was subjected to vacuum distillation, and about 6 g. of liquid (12.9% F) appeared in the dry-ice trap as the bath temperature was raised to 45° C. at a pressure of 0.01 to 0.1 mm. of mercury. Then 45 g. of the residue was transferred to a short-path still, and distillation was carried out at about 0.001 mm. of mercury. A jacket temperature of 50 to 70° C. gave 2 g. of distillate, 70 to 86° C. gave 16 g. water-white liquid (13.2% F), 86 to 125° C. gave 22 g. (7.6% F), and a residue of 2 to 3 g. remained. Also, 3.5 g. was caught in the dry-ice trap during the distillation; it was insoluble in water, and apparently was mostly diethyl monofluorophosphate. After two redistillations of the 16-gram fraction, a fraction boiling at 38 to 40° C. was obtained which had a density (d_4^{20}) of 1.313 and a refractive index (n_D^{20}) of 1.367.

From the results of the above distillations, it was calculated that the reaction of hydrogen fluoride with hexaethyl tetraphosphate gave a product of the following approximate composition:

49-50% $(C_2H_5)HPO_3F$.

31-33% $(C_2H_5)_2HPO_4$ (including any distillable, unreacted ethyl polyphosphates).

12-14% $(C_2H_5)_2PO_3F$ (including possibly some HPO_2F_2).

5-6% nondistillable liquid.

4. Pentaethyl Triphosphate.

The greatest problem involved in this study was the preparation of a relatively pure pentaethyl triphosphate. Its preparation was necessary because the pure ester has not been reported in literature, and not even experimental samples of the crude ester were available from the most likely sources.

Attempts to Prepare Pentaethyl Triphosphate.

In the first attempt to make the pentaethyl ester, pure $Na_5P_3O_{10}\cdot 6H_2O$ was used as a starting material; its purity had been ascertained by means of x-ray analysis. 30.4 g. of the sodium salt was dissolved in one liter of distilled water at room temperature, and about 150 ml. of 28% $AgNO_3$ solution was added slowly from a buret. The precipitated silver salt was separated by filtration, washing thoroughly with cold water. The salt was dried for several days in a vacuum desiccator, and the weight of the dry silver salt amounted to 50.5 g., whereas the weight equivalent to 30.4 g. of the sodium salt is 50.6 g. It was found by analysis to contain 66.5% Ag as compared to the theoretical value of 68.08% Ag calculated for $Ag_5P_3O_{10}$.

To 49.5 g. of the silver salt in 70 g. of diethyl ether was added 46.5 g. of ethyl iodide,[102] and the reactants were stirred for 5 hours at 20 to 50° C. and 1 hour at 50 to 64° C. The solid matter was removed by suction filtration, washing the residue several times with dry ether. The solvent was evaporated at reduced pressure, and an evaporation residue

of 11 g. of slightly yellow liquid remained. This weight was equivalent to a 43.5% yield of the ethyl ester. When the residue was subjected to high-vacuum short-path distillation, (see Figure 4), however, the following results were obtained on heating to a jacket temperature of 110° C.:

Fraction	Weight	$n_D^{t^\circ}$ C.
in dry-ice trap	1.0 g.	1.4043 (24.8)
distillate	6.2 g.	1.4150 (24.6)
residue	3.8 g.	1.4268 (24.8)

Comparison of these results with Table I would indicate that the orthophosphate, pyrophosphate, and a mixture of triphosphate and metaphosphate made up the respective fractions obtained on distillation.

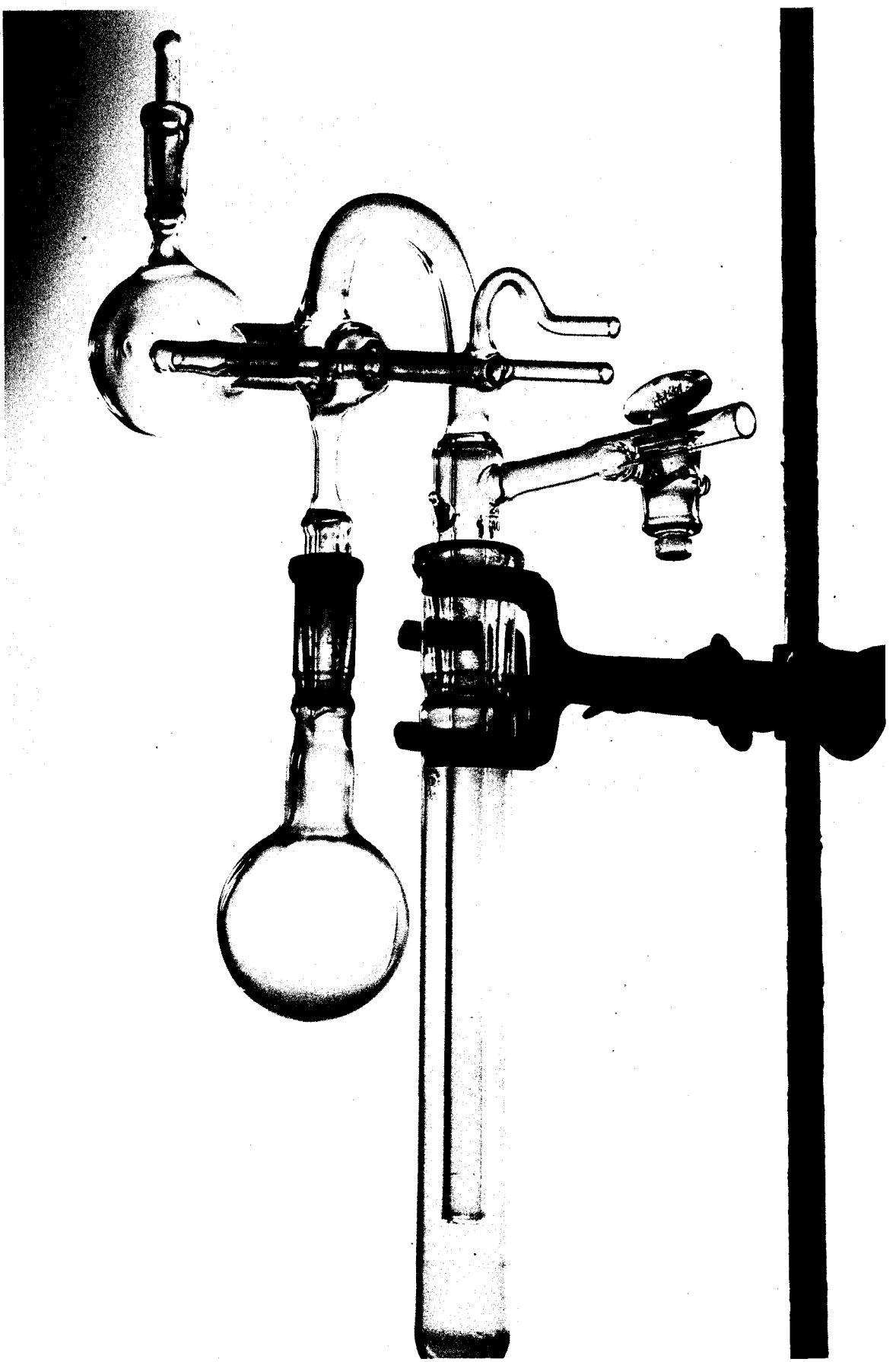
Table I

Polyphosphate	Refractive index (n_D^{25})	%P
$(C_2H_5)_3PO_4$	1.4039	17.0
$(C_2H_5)_4P_2O_7$	1.418	21.35
$(C_2H_5)_5P_3O_{10}$	1.424*	23.4
$(C_2H_5)_6P_4O_{13}$	1.425*	24.5
$(C_2H_5PO_3)_n$	1.438*	28.7

* values for commercial grades prepared from P_2O_5 and $(C_2H_5)_3PO_4$.[24]

Figure 4

Small Short-path Still



That the distillate was predominantly tetraethyl pyrophosphate was confirmed by a phosphorus analysis; the experimental value was 20.8% P.

The experiment was repeated, starting with 56 g. of pure $Na_5P_3O_{10}\cdot 6H_2O$. The dry silver salt derived from it weighed 91 g., which again was nearly the stoichiometric value. The following analytical results were obtained:

0.2997 g. : 0.2672 g. of AgCl.

0.3017 g. : 0.1313 g. of $Mg_2P_2O_7$.

0.3004 g. : 0.1290 g. of $Mg_2P_2O_7$.

Calculated for $Ag_5P_3O_{10}$: 68.08% Ag; 11.73% P.

Found : 67.1% Ag; 11.95, 12.1% P.

When 87 g. of the silver salt was reacted with 82 g. of ethyl iodide, the temperature of the mixture was kept at room temperature for one day after a spontaneous rise to nearly 40° C. for 2 or 3 hours. The reaction product was filtered, washing well with dry ether. Removal of the solvent by evaporation gave a nonvolatile liquid residue of 36 g., which could be calculated in terms of pentaethyl triphosphate as a yield of 80% of theory. It contained 22.9% P, as compared with the calculated value of 23.4% P (see Table I). When a small amount of the liquid was subjected to short-path distillation, however, approximately one-half of it distilled in the form of tetraethyl pyrophosphate, which was identified by its refractive index ($n_D^{25.0}$ 1.4178).

Reaction with Anhydrous Hydrogen Fluoride.

As the triphosphate was not able to be purified by distillation, it was used as such in a reaction with anhydrous hydrogen fluoride, which would be expected to proceed in accordance with the following equation:

(12) $(C_2H_5)_5P_3O_{10} + 2HF = (C_2H_5)_2HPO_4 + (C_2H_5)HPO_3F + (C_2H_5)_2PO_3F$.

In this reaction, 29.3 g. of the ester was added to 3.7 g. of HF. Distillation of the reaction product and fluorine analysis of the various fractions allowed the following approximations regarding the composition of the reaction product:

43.4% $(C_2H_5)HPO_3F$

36.5% $(C_2H_5)_2HPO_4$, including probably some triethyl orthophosphate.

17.8% $(C_2H_5)_2PO_3F$

2.3% nonvolatile material.

An equimolar mixture of the three esters would have been expected from pure pentaethyl triphosphate.

5. Tetraethyl Pyrophosphate.

Two experiments were carried out in the investigation of this reaction, which was expected to proceed according to the following equation:

(13) $(C_2H_5)_4P_2O_7 + HF = (C_2H_5)_2HPO_4 + (C_2H_5)_2PO_3F$.

The tetraethyl pyrophosphate used in the first experiment was a water-white liquid of approximately 95% purity. It was obtained from the research laboratories of the Victor Chemical Works, where it was prepared by a method

which has not yet been published. 44.5 g. of this ester was added in small portions to 3.2 g. of anhydrous hydrogen fluoride, and the resulting liquid contained 5.8% F by analysis, which is approximately 95 per cent of the stoichiometric value. When 22.2 g. of this liquid was transferred to a small conventional type still, 10.3 g. of liquid was trapped with dry ice as the distillation flask was heated to 85° C. at a pressure of 0.003 mm. of mercury. Analysis of the liquid gave the following results:

0.0757 g. : 3.70 ml. of 0.129 N $Th(NO_3)_4$.

0.3270 g. : 0.70 ml. of 0.1011 N NaOH.

Calculated for $(C_2H_5)_2PO_3F$: 12.17% F.

Found: 12.0 % F; acidity equivalent to 0.43% HF.

The residue (11.9 g.) was subjected to short-path distillation at a pressure of 0.01 mm. of mercury. Distillation began at about 50° C., but most of the liquid distilled at a jacket temperature of 105° C. Only a trace of residue remained, and 2-3 drops of liquid, most of which was diethyl monofluorophosphate, was found in the dry-ice trap. Analysis of the second fraction (10.7 g.) gave the following results:

0.1730 g. : 1.0 ml. of 0.129 N $Th(NO_3)_4$.

0.1220 g. : 8.10 ml. of 0.1011 N NaOH (Methyl Red);
8.15 ml. of 0.1007 N NaOH (Phenolphthalein).

Calculated for $(C_2H_5)_2HPO_4$: 0% F, M.W. 151.

Found: 1.4% F, M.W. 149.

Consequently, it appears that the reaction of hydrogen fluoride

with tetraethyl pyrophosphate was as nearly quantitative as the purity of the original ester and the relative weights of reactants could allow.

The second experiment was carried out with an impure grade of tetraethyl pyrophosphate produced at room temperature according to the reaction

(14) $4(C_2H_5)_3PO_4 + P_2O_5 = 3(C_2H_5)_4P_2O_7$,

which is included in a patent of the Victor Chemical Works.[34] To produce the crude tetraethyl pyrophosphate, 20.7 g. of P_2O_5 was added to a solution of 106.0 g. of pure triethyl orthophosphate in 127 g. of dry chloroform at room temperature. After a few hours, most of the solvent was distilled off at atmospheric pressure, and the residue, calculated to contain 13.6% undistilled chloroform, was used as such for reaction with hydrogen fluoride. Accordingly, 105.5 g. of the crude ester was added to 6.5 g. of HF, and 79 g. of the reaction product was used for distillation. Nearly 20 g. of distillate was caught at a pressure of 15 to 20 mm. of mercury and a bath temperature of 60 to 90° C., while several grams of chloroform appeared in the dry-ice trap. The pressure was decreased to about 3 mm., and 10 or 15 g. of triethyl orthophosphate distilled before the distillation was discontinued. Redistillation of the low-boiling fraction at atmospheric pressure gave about 2 g. of distillate below 170° C., 7.8 g. at 170 to 171° C., and a residue of 4.5 g., which represented the hold-up of the fractionation column. Analysis of the

middle fraction gave the following results:

0.1234 g. : 5.32 ml. of 0.129 N $Th(NO_3)_4$.

0.2062 g. : 0.1425 g. of $Mg_2P_2O_7$.

Calculated for $(C_2H_5)_2PO_3F$; 12.17% F, 19.85% P.

Reported by Lange and Krueger:[1] 12.30% F, 19.62% P, $n_D^{24.2}$ 1.3729, $d_4^{22.2}$ 1.144.

Found: 11.6% F, 19.25% P, n_D^{20} 1.3734, d_4^{20} 1.1456.

In the light of these results, further purification of the diethyl monofluorophosphate was felt to be unnecessary for identification. Analysis of a mixture of the low- and high-boiling fractions gave a value of 8.3% F, and hence it was calculated that the total yield of the overall reaction, starting with phosphoric anhydride and triethyl phosphate and then adding hydrogen fluoride, amounted to approximately 35% of theory. The low overall yield apparently came as a result of the poor reaction of $(C_2H_5)_3PO_4$ with P_2O_5, since the splitting of tetraethyl pyrophosphate with HF was shown in the previous experiment to be nearly quantitative.

D. Other Methods Investigated for the Preparation of Diethyl Monofluorophosphate.

1. The Reaction of Triethyl Orthophosphate with Antimony Trifluoride.

This reaction was investigated as a possible method for the preparation of the neutral and acid esters of H_2PO_3F according to the equation

(15) $(C_2H_5)_3PO_4 + HPO_2F_2 = (C_2H_5)_2PO_3F + (C_2H_5)HPO_3F.$

Two experiments were carried out in the investigation, one at atmospheric pressure and the other at a pressure of 200 pounds per square inch.

In the first experiment 195 g. (1.07 moles) of triethyl orthophosphate was reacted with 109 g. (1.07 moles) of difluorophosphoric acid by merely mixing at atmospheric pressure in a stainless-steel vessel. The mixing resulted in the evolution of a considerable amount of heat, but neutralization of the resulting homogeneous liquid with aqueous KOH yielded no observed insoluble diethyl monofluorophosphate and likewise no typical odor of that ester.

The second experiment was carried out by weighing 189.5 g. of the orthophosphate and 107.7 g. of the acid into a steel autoclave, and then building up the pressure of the autoclave by means of compressed nitrogen. The reactants were heated 12 hours at a temperature of 80° C. and a pressure of 90 to 120 p.s.i. The reaction product, however, gave no evidence of the presence of diethyl monofluorophosphate upon neutralization with aqueous KOH. Extraction of the neutral solution with ether and subsequent evaporation confirmed the absence of the neutral diethyl monofluorophosphate, and so the investigation was discontinued.

2. <u>The Reaction of Triethyl Orthophosphate with Antimony Trifluoride</u>.

In the hope that this reaction would proceed

according to the equation

(16) $3(C_2H_5)_3PO_4 + SbF_3 = 3(C_2H_5)_2PO_3F + Sb(OC_2H_5)_3$,

it was investigated as another method of producing diethyl monofluorophosphate .

In the first experiments, equimolar mixtures of the reactants were heated at about 200° C. for 1 or 2 hours, using $SbCl_5$ as a catalyst for the reaction. In each case the cooled reaction product was a gray, solid mass from which very little of the desired monofluorophosphate could be recovered by treatments with water, alcohol, or ether.

To avoid the inconvenience of the solid matter, it was decided to attempt to distill the ester directly from the reaction product, as this type of procedure had been used successfully by Peppard et al.[68] in the preparation of ethyl fluorosilicate from ethyl silicate and antimony fluoride. Consequently, 93.6 g. (0.514 moles) of $(C_2H_5)_3PO_4$, 62.9 g. (0.351 moles) of SbF_3, and 1.1 g. of $SbCl_5$ were heated together in a 500-ml. distilling flask. At a bath temperature of 210 to 267° C. approximately 23 g. of liquid distilled, even though the reaction mixture had become completely solid at a bath temperature of 230° C. The distillate contained 8.2 to 8.4% F, whereas the value calculated for $(C_2H_5)_2PO_3F$ is 12.17% F. This represents a 19% recovery of the desired diethyl monofluorophosphate. Redistillation through a short fractionation column yielded 11 g. of liquid at 168 to 178° C. containing 11.9% F. The amount of diethyl monofluorophosphate

recovered in a reasonable degree of purity was therefore about 14 per cent of theory.

The experiment was repeated, using a smaller excess of antimony trifluoride. Accordingly, 97 g. (0.532 moles) of $(C_2H_5)_3PO_4$, 32.7 g. (0.183 moles) of SbF_3, and 3 g. of $SbCl_5$ were heated together, and the distillate which was caught at a bath temperature of 225 to 254° C. was refractionated through a short column at atmospheric pressure. About 22 g. of liquid (9.7% F) distilled at 169 to 201° C., and 30 g. of distillate, mostly unreacted triethyl orthophosphate, was caught at 201 to 216° C. The 22-gram fraction represented a 21% recovery of diethyl monofluorophosphate.

These results show that only small yields of the diethyl ester can be prepared in this manner, but the procedure is so simple that the method may be considered useful.

3. The Reaction of Ethylene with Monofluorophosphoric Acid.

This reaction, which was expected to proceed according to the equation

(17) $H_2PO_3F + 2C_2H_4 = (C_2H_5)_2PO_3F$,

was investigated first at atmospheric pressure and later at superatmospheric pressures, but no diethyl monofluorophosphate was isolated, regardless of the reaction conditions imposed.

In the first experiment, 3 g. of $HgSO_4$ in 15 ml. of concentrated sulfuric acid was added to 100 ml. of anhydrous monofluorophosphoric acid in a gas washing bottle, and the

mixture was allowed to stand at room temperature as dry ethylene was bubbled through it at atmospheric pressure for 17 hours. Ethylene was then passed through the reaction mixture for 40 hours at 80° C. before the product was neutralized by pouring slowly into KOH solution with good stirring and cooling. No insoluble diethyl monofluorophosphate was observed, however, and only a very faint ester-like odor could be detected.

The experiment was repeated, using 3 g. Ag_2SO_4 in place of $HgSO_4$. Identical results were obtained.

A third experiment was carried out at 140 to 145° C., but the acid mixture was decomposed quickly at that temperature.

Two experiments were undertaken to study the effect of adding dioxane to the reaction mixture as a means of increasing the solubility of ethylene in the monofluorophosphoric acid. In one of the experiments, 0.3 g. of Hg_2SO_4, 5 ml. of concentrated sulfuric acid, and 5 g. of dioxane were added to 40 g. of monofluorophosphoric acid, while in the second experiment $HgSO_4$ was used in place of Hg_2SO_4. In both cases, ethylene was passed through the acid mixture for over 100 hours at room temperature. Neutralization with aqueous KOH required nearly the amount of alkali calculated to neutralize the acid mixture before treatment with ethylene, indicating little, if any, reaction. No insoluble diethyl monofluorophosphate could be isolated from the neutral solution, but the odor of the

ester could be detected.

Acetic acid anhydride was used in the next experiment as a catalyst for the esterification reaction. Approximately 19 to 20 moles of dry ethylene was passed through a solution of 204 g. of H_2PO_3F and 19 ml. (20 to 21 g.) of acetic anhydride over a period of 73 hours, including 53 hours at a temperature of 95 to 120° C. The reaction product was neutralized with aqueous KOH, but extraction of the resulting solution with ether and subsequent evaporation of the solvent yielded no diethyl monofluorophosphate.

Since the reaction was not successful at atmospheric pressure, the next experiment was carried out in a stainless-steel autoclave under a pressure of about 200 pounds per square inch. 223 g. of H_2PO_3F and 18 g. of 100% H_2SO_4 were weighed into the autoclave, and ethylene was forced in from a pressure cylinder. The autoclave was shaken for 10 hours at room temperature and 8 hours at 95° C., but little, if any, ethylene appeared to be reacting, as there was no great drop in the pressure in the reactor.

A similar investigation was carried out at a pressure of 350 to 400 p.s.i., using 95.5 g. of H_2PO_3F, 19.3 g. of 100% H_2SO_4, and 5 to 6 g. of $HgSO_4$. Ethylene was forced in to build up the pressure of the system to about 350 pounds. The autoclave was heated for 35 hours at 80 to 120° C. with agitation, and the reaction product was neutralized at 3 to 10° C. with aqueous KOH. Extraction with ether and subsequent

evaporation of the solvent gave no diethyl monofluorophosphate. The neutral aqueous solution was evaporated to dryness, and the solid salt was crushed and heated with absolute alcohol, but practically no alcohol-soluble salt was recovered. Since the sodium salt of monoethyl monofluorophosphoric acid would be expected to be soluble in alcohol, the investigation showed that neither mono- nor di-esterification occurred under the reaction conditions used.

E. The Germicidal and Toxicological Evaluation of Sodium and Potassium Ethyl Monofluorophosphate.[93]

1. Toxicology.

An acute toxicity test was carried out with a 2.5% solution of $NaC_2H_5PO_3F$ by administering it to rats intraperitoneally at a level of 250 mg. per kilogram of body weight. A slight irritation, as manifest by the way the animals scratched their noses, was noticeable about 2.5 hours after injection; however, this irritation disappeared a short time later. The animals were sacrificed after one week, but no particular abnormalities were observed.

Skin sensitivity tests gave negative results when 1% solutions of the sodium and potassium salts were painted onto the shaved backs of rats, and likewise when the applications were repeated three days later.

2. Germicidal Activity.

Tables II and III show the results of germicidal tests on bacteria and yeasts. The tests were carried out in

nutrient media at pH 6.8 in the absence of additional organic matter, and therefore the results represent the activity of the sodium and potassium salts under idealized conditions. 5 ml. of aqueous salt solution was transferred aseptically into sterile test tubes, which were then placed in a constant-temperature water bath at 37° C. After the tubes and contents had been allowed to reach the temperature of the bath, they were seeded with 0.5 ml. of an 18- to 20-hour broth culture of the test organism. After 15 minutes contact of the organism with the salt solution, one standard inoculating loopful (0.01 ml.) of the mixture was removed from the contact tube and subcultured into broth. One ml. of the same mixture was plated on solid medium for the estimation of the number of surviving organisms.

Table II includes Staphylococcus aureus, Pseudomonas aeruginosa, and a spore-forming organism isolated from powdered glue as organisms representative of pathogenic, intestinal, and air- and dust-borne bacteria, respectively. Identical results were obtained with the sodium and potassium salts. No germicidal activity against the three test organisms was observed.

In Table III, it should be mentioned that the low count reported for S. faecalis was a result of the difficulty experienced in getting the organism to grow on poured plates.

Table II

15-Minute Contact of Organism with (1) 0.095% and (2) 0.95% of $KC_2H_5PO_3F$ or $NaC_2H_5PO_3F$.

	S. aureus	P. aeruginosa	Spore-forming aerobe
(1) Total original inoculum	$>5 \times 10^9$	1.57×10^9	4.25×10^6
Total organisms after contact	$>10^6$	$>10^6$	$>10^6$
Total organisms after contact and 1:1000 dilution (subculture)	growth	growth	growth
(2) Total original inoculum	3.105×10^9	4.95×10^8	2.5×10^6
	5.2×10^9	1.63×10^9	---
Total organisms after contact	$>10^9$	$>10^9$	$>10^9$
	$>10^9$	$>10^9$	$>10^9$
Total organisms after contact and 1:1000 dilution (subculture)	growth	growth	growth

Table III

15-Minute Contact of Organism with 0.95% $KC_2H_5PO_3F$ or $NaC_2H_5PO_3F$.

Organism	Total Initial Inoculum	Total Organisms after Contact		Total Organisms After Contact and then 1:1000 Dilution (subculture)
		K	Na	
Lactobacillus casei	29,250,000	$> 10^6$	$> 10^6$	growth
Streptococcus faecalis	8,750,000	$< 10^3$	2×10^3	growth
Proteus vulgaris	78,500,000	$> 10^6$	$> 10^6$	growth
Torula utilis	144,000	$> 10^3$	$> 10^3$	growth
Saccharomyces cerevisiae	119,000	200	200	growth

Lactobacillus acidophilus, an organism found in the mouth, is associated with dental caries by the production of acid. Since fluorine compounds in general are of considerable interest in oral hygiene, it was desired to test the effect of the sodium and potassium salts of ethyl monofluorophosphoric acid on the acid production of the organism. The experimental results, which are shown in Table IV, indicated that neither salt was effective in concentrations of 0.1% even after a contact period of 96 hours.

Table IV

Inhibition of acid production of Lactobacillus acidophilus as indicated by pH values.

Contact time in hours	pH		
	Culture medium (blank)	0.1% K salt in medium	0.1% Na salt in medium
24	5.39	5.70*	5.28
48	4.83, 4.72, 5.31	4.82, 4.8, 5.35*	4.98, 4.5, 4.9
72	6.1*, 5.2	6.59*, 4.7	5.53, 4.82
96	4.58, 5.09	4.88, 4.53	4.99, 4.65

* contaminated

The effect of the sodium and potassium salts on mold growth on a solid medium and in liquid media is shown in Tables V and VI respectively. It is seen that there was no effect on the organisms in liquid media, while on agar the Aspergillus molds were found to be quite sensitive. At very low concentrations the salts produced a temporary mutation in A. niger, with a resulting loss in its ability to produce aspergillin, the typical black pigment in the spores of the organism (see Fig. 5, page 115). Color development returned after the second transfer to fluoride-free media.

Table V

0.2 cc. of 0.1% solution of the F compound added to a cup cut into the agar layer in a Petri plate.

Mold	Diameter of zone of inhibition (mm.) on Czapek-Dox Agar	
	K salt	Na salt
Penicillium notatum	no zone	no zone
Aspergillus niger	15 (43 P)*, 14 (40 P)	12 (49 P), 16 (47 P)
Aspergillus flavus	34 P, 35 P, 35 P, 31 P	31 P, 35 P, 33 P, 23 (42 P)

* (Values followed by P indicate zones of partial inhibition, resulting in the prevention of the formation of pigment. See Fig. 5.)

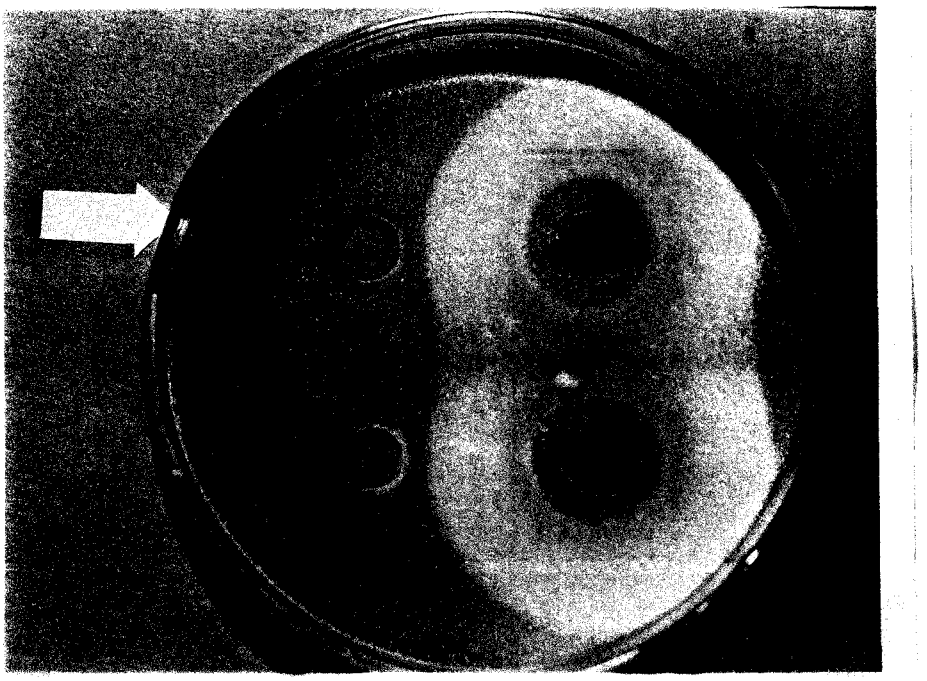


Figure 5

The effect of traces of sodium and potassium salts of $(C_2H_5)HPO_3F$ on the pigment-producing ability of A. niger (see Table V), showing a small dark zone of dead organisms, a wide white zone of organisms producing colorless spores, and, beyond that, a dark zone consisting of unaffected mold organisms.

Table VI

0.099% of the F compound in Czapek-Dox broth.

Mold	Medium without F compound	K salt	Na salt
Penicillium notatum	++++*	++++	++++
Aspergillus niger	++++	++++	++++
Aspergillus flavus	+	+	+

* degree of growth.

F. Isopropyl Monofluorophosphoric Acid.

Preliminary experiments on the preparation of isopropyl monofluorophosphoric acid and its potassium salt were completed after the typist had begun work on the first part of this thesis; therefore, only a limited description can be given at this time.

No isopropyl polyphosphates were available for reaction with hydrogen fluoride, and hence it was necessary to prepare them by the reaction of triisopropyl orthophosphate with phosphoric anhydride, in accordance with the method described for alkyl polyphosphates in the previously-discussed patent of the Victor Chemical Works.[34] As the orthophosphate was not available either, it was made by the following method:[103]

(18) $3C_3H_7OH + POCl_3 + 3C_5H_5N = (C_3H_7)_3PO_4 + 3C_5H_5N \cdot HCl$

When triisopropyl orthophosphate was reacted with phosphoric anhydride at room temperature in the stoichiometric ratio according to the equation

(19) $4(C_3H_7)_3PO_4 + P_2O_5 = 3(C_3H_7)_4P_2O_7$,

the reaction seems to have gone only as far as the metaphosphate stage, as shown in the following equation:

(20) $(C_3H_7)_3PO_4 + P_2O_5 = 3C_3H_7PO_3$.

This was seen from the results of the splitting of the polyphosphate with anhydrous hydrogen fluoride. The reaction product was shown by distillation methods to contain almost no diisopropyl monofluorophosphate, which should have been formed on splitting tetraisopropyl pyrophosphate. Instead, high-vacuum short-path distillation at 60 to 100° C. yielded fractions of unreacted orthophosphate containing as much as 72 per cent isopropyl monofluorophosphoric acid, according to solubility experiments and fluorine analyses.

In another experiment triisopropyl orthophosphate was reacted with phosphoric anhydride at room temperature and then allowed to stand several days, during which time the cloudy solution became clear. Subsequent reaction with hydrogen fluoride gave a liquid containing a mixture of $(C_3H_7)_2PO_3F$, $(C_3H_7)_3PO_4$, $(C_3H_7)_2HPO_4$, and $(C_3H_7)HPO_3F$, and after partial purification of the desired isopropyl monofluorophosphoric acid by means of two short-path distillations, it was neutralized with potassium hydroxide solution. The

neutral solution was evaporated, and the residue was treated with dry ether to remove any triisopropyl orthophosphate. After drying over P_2O_5, a hygroscopic, white powder remained. Analysis gave 8.50% F, as compared with the theoretical value of 10.55% F, thus indicating a purity of 80% $(i\text{-}C_3H_7)KPO_3F$.

The potassium salt will be evaluated for its germicidal and toxicological properties.

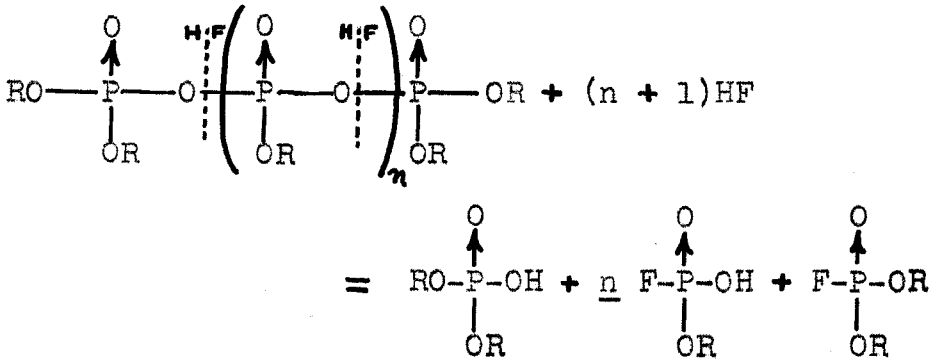
SUMMARY

A method has been developed for the preparation of diphenyl monofluorophosphate in yields approximating seventy per cent of theory according to the following equation:

$$2(C_6H_5)_2PO_3Cl + CaF_2 = 2(C_6H_5)_2PO_3F + CaCl_2.$$

All attempts to prepare a monosulfonic acid of diphenyl monofluorophosphate, however, resulted in mixtures of mono- and disulfonated esters. The monosulfonic acid, which was desired for subsequent evaluation as a permanent mothproofing agent for wool, could not be isolated from these mixtures either as the acid or as a salt.

The study of the reaction of hydrogen fluoride with ethyl polyphosphates has indicated that the general reaction occurs according to the following mechanism:



Accordingly, it was shown that tetraethyl pyrophosphate (n = 0) of 95% purity was split by hydrogen fluoride to form an equimolar mixture of diethyl phosphoric acid and diethyl monofluorophosphate in nearly quantitative yields. This reaction represents a new and convenient method of preparing

dialkyl monofluorophosphates.

Commercial grades of the ethyl polyphosphates were shown to be mixtures, in agreement with recent literature, and they were found to react with hydrogen fluoride to give considerable amounts of mono- and diethyl monofluorophosphates, depending upon the relative amounts of the various polyphosphates making up the mixtures. Ethyl metaphosphate, hexaethyl tetraphosphate, diethyl diacid pyrophosphate, and pentaethyl triphosphate were all found to be satisfactory for producing ethyl monofluorophosphoric acid, while tetraethyl pyrophosphate was the most satisfactory for obtaining diethyl monofluorophosphate.

Sodium and potassium salts of ethyl monofluorophosphoric acid, a new compound, exhibited an unexpected great stability toward neutral, slightly alkaline, and even acidic solutions. They showed no specific toxicity to mammals and no germicidal action toward bacteria and yeasts, with the exception of Saccharomyces cerevisiae. The new compounds were found to be quite effective germicides for molds. In minute traces, i.e. in concentrations lower than the germicidal dose, the salts were found to produce a temporary mutation in molds, whereby the pigment-producing ability of the molds was inhibited temporarily. The possibility of pharmacological uses of these salts is indicated.

Isopropyl monofluorophosphoric acid and its potassium salt have been prepared in impure form.

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