138.   *Esters containing Phosphorus.   Part IV.   Diisopropyl Fluorophosphonate.*

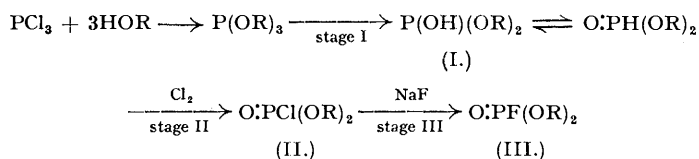By B. C. Saunders and G. J. Stacey.

The preparation of *diisopropyl fluorophosphonate* from the chlorophosphonate is described. An account is given of the preparation of the fluorophosphonate from di*iso*propyl hydrogen phosphite by a " one-stage " process which forms the basis of the large-scale preparation of the compound.   The chemical and physiological properties of this and of certain related compounds are described.

During the late war investigations were carried out at Cambridge on toxic fluorophosphonates and related compounds for the Ministry of Supply, and reports were submitted to the Ministry and were also made available to American workers.   Brief preliminary accounts of some aspects of the work have recently been published (McCombie and Saunders, *Nature*, 1946, **157**, 287, 776). During the years 1941—1945, we prepared a large number of compounds of different types

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containing the $>$POF group. Many of these were highly toxic by inhalation and injection, and possessed powerful miotic action (constriction of the pupils of the eyes) at very low concentrations. The more toxic compounds possessed intense anti-choline-esterase activity.

Until this work began practically nothing was known about the preparation or properties of fluorophosphonic esters. Only two had been reported, *viz.*, the dimethyl and the diethyl ester (Lange and Krüger, *Ber.*, 1932, **65**, 1598). The method of preparation was very tedious and laborious, and yields were so low as to render the method impracticable. In Part I (McCombie, Saunders, and Stacey, *J.*, 1945, 380) was described the preparation of dialkyl hydrogen phosphites (I) in 90% yield from phosphorus trichloride and the appropriate alcohol, the merit of the method being that no tertiary base was necessary to remove the hydrogen chloride produced. It was recorded that chlorine readily converted the dialkyl hydrogen phosphites into the dialkyl chlorophosphonates (II) in high yield.

The present paper describes the conversion of dialkyl chlorophosphonates into the corresponding fluorophosphonates in excellent yield by means of sodium fluoride. (Fluorination could also be effected by means of silver fluoride, zinc fluoride, or antimony trifluoride, but with the last two reagents complexes of the fluorophosphonate and the inorganic salt were formed.)

$$PCl_3 + 3HOR \longrightarrow P(OR)_3 \xrightarrow[\text{stage I}]{} P(OH)(OR)_2 \rightleftharpoons O{:}PH(OR)_2$$
$$(I.)$$

$$\xrightarrow[\text{stage II}]{Cl_2} O{:}PCl(OR)_2 \xrightarrow[\text{stage III}]{NaF} O{:}PF(OR)_2$$
$$(II.) \qquad (III.)$$

The above reactions are of very general application, and the present series of papers will describe the preparation and properties of numerous compounds of type (III) in which R is varied. The present paper is confined mainly to a discussion of di*iso*propyl fluorophosphonate (R = Pr$^\beta$). This compound was first described in 1941 (Saunders, Ministry of Supply Meeting, London, Dec. 11th, 1941; McCombie and Saunders, Report to Ministry of Supply, Dec. 18th, 1941). As shown below, it proved to be of great importance, and because of its remarkable physiological properties a study was made of its preparation on a technical scale. Using carbon tetrachloride as solvent, *iso*propyl alcohol was converted into pure di*iso*propyl hydrogen phosphite (stage I) in 89% yield. Without a solvent the yield was 86·4%. Chlorination of the hydrogen phosphite gave 76% of pure di*iso*propyl chlorophosphonate (stage II). (Yields of 80—90% of slightly less pure chlorophosphonate could, however, be easily obtained.) By heating the chlorophosphonate, dissolved in dry benzene, with dry sodium fluoride (stage III), pure di*iso*propyl fluorophosphonate was obtained in 90% yield. Thus the fluorophosphonate was obtainable in a pure condition by a three-stage process from phosphorus trichloride and *iso*propyl alcohol, and the overall yield was *ca.* 60—70%. The compound so obtained was identical with that obtained by heating an authentic specimen of dry silver fluorophosphonate with *iso*propyl iodide. In the ethyl series the yields of the products at stages I, II, and III were 93%, 87%, and 91% respectively.

The individual stages having been established, the whole process was then re-examined with a view to preparing di*iso*propyl fluorophosphonate on a technical scale. As a result of many experiments it was found that the process could be run virtually as a " one-stage " process by adding phosphorus trichloride to *iso*propyl alcohol dissolved in carbon tetrachloride, without external cooling. The hydrogen phosphite was not isolated, but the crude product (still in carbon tetrachloride) was chlorinated, and the solution of crude chlorophosphonate thus obtained was heated with sodium fluoride. After filtration and removal of carbon tetrachloride, the residue was distilled giving pure di*iso*propyl fluorophosphonate. The overall yield was *ca.* 75%. The process was patented (B.P., Ministry of Supply, McCombie and Saunders, Sept. 15th, 1943).

An important feature of the above process was that it could be carried out in an all-glass apparatus as no fluorine or hydrogen fluoride was produced. In arriving at this " one-stage " process other useful modifications were worked through. (Details appear in Reports on Fluorophosphonates to the Ministry of Supply Nos. 3 to 8, Feb. 27th, 1942, to March 1st, 1943.)

Di*iso*propyl fluorophosphonate is a practically odourless, mobile liquid, b. p. 183°/760 mm. (by extrapolation), f. p. *ca.* −82°. This wide range of temperature over which the compound is liquid adds to the usefulness. A specimen of the pure liquid has remained unchanged in a glass vessel for several years. Whereas the chlorophosphonate was readily hydrolysed by water, hydrolysis of the fluorophosphonate was slow and took 72 hours for completion

at 15° and then only in the presence of a large excess of water (1% solution; solubility, 1·5%) : $P(OPr^\beta)_2 \cdot OF + H_2O = P(OPr^\beta)_2 \cdot OH + HF$. Dimethyl and diethyl fluorophosphonate were hydrolysed much more quickly, the order being Me > Et > Pr^β; complete hydrolysis of the ethyl ester took about 4 hours. The diisopropyl, but not the diethyl, ester could be steam-distilled. Diisopropyl fluorophosphonate did not, like the chlorophosphonate, give the anilinophosphonate on treatment with aniline.

These dialkyl fluorophosphonates were readily hydrolysed by dilute sodium hydroxide solution according to the equation : $O \vdots PF(OR)_2 + 2NaOH = O \vdots P(ONa)(OR)_2 + NaF + H_2O$.

On Dec. 11th, 1941, one of us (B. C. S.) reported at a Ministry of Supply Meeting in London the highly toxic nature of diisopropyl fluorophosphonate as a lethal inhalant. The quick "knock-out" action of the compound was stated to be comparable with that produced by hydrogen cyanide. Another remarkable effect at much lower, and non-fatal, concentrations was stressed at the time. An intense constriction of the pupils of the eyes took place (miotic effect). Subsequently intensive work was carried out, and the results may be summarised as follows :

(1) *Toxicity by inhalation.** Batches of animals (rabbits, guinea-pigs, rats, and mice) were exposed in a 1·78 m.³ chamber for 10 minutes. A concentration of the ester of 1 in 10,000 killed 18/23 of the animals, all the deaths taking place within 25 minutes of the beginning of the exposure. The dimethyl ester killed 14/23 and the diethyl ester 11/23 at this concentration. More precise experiments showed that the L.C. 50 for diisopropyl fluorophosphonate for 10-minute exposures (deaths within 2 hours) was 0·44 mg./l. for mice and 0·36 mg./l. for rats. This means that the compound is more toxic than carbonyl chloride, cyanogen chloride, or chloropicrin. For exposures of less than about 13 minutes the compound is slightly less toxic, and for exposures longer than 13 minutes more toxic, than hydrogen cyanide. The symptoms were salivation, muscular weakness, gasping, and finally cessation of respiration.

(2) *Miotic effect.* The various dialkyl fluorophosphonates were tested on the persons mentioned at the end of the paper. Members of the team entered a 10 m.³ chamber containing a concentration of 1 in 1,000,000 (*i.e.*, 0·0082 mg./l.) of the isopropyl compound for 5 minutes. Practically nothing was observed until some 5 minutes after leaving the chamber; severe miosis then set in. This often persisted for as long as 7 days, and there was usually no sign of relaxation until after 72 hours. The eye effects may be summarised as follows :

(*a*) Pupil constriction. All subjects affected. The amount of light entering the eye was greatly reduced, and "darkness" set in. The incapacitation was worse in a poor light (*e.g.*, at twilight).

(*b*) Visual acuity affected. Varied from individual to individual.

(*c*) Powers of accommodation affected. The younger subjects usually suffered most.

(*d*) Photophobia and headaches almost always accompanied the miosis. Pain was experienced when changing from a bright to a dull light.

(*e*) Congestive iritis was caused by rather higher concentrations than the above, *e.g.*, at 0·05 mg./l. for 5 minutes.

Apart from controlled experiments such as the above, we repeatedly found when working with the compound that amounts undetectable chemically caused miosis, even when protective measures were taken. Minute traces of the vapour adhering to clothing could produce significant miosis. We observed, as early as 1941, that the dimethyl and the diethyl ester produced far less intense miosis than that caused by the diisopropyl ester. The effect of the dimethyl compound usually wore off in a matter of hours, whereas that of the ethyl compound usually lasted about 2 days.

(3) *Toxicity by injection.†* For intravenous injection into rabbits the L.D. 50 of diisopropyl fluorophosphonate in normal saline was *ca.* 0·5 mg./kg. Pupil-constriction began 2 minutes after injection, followed by loss of muscular co-ordination and then by respiratory collapse. For subcutaneous injection into mice the figure was higher at approximately 4·0 mg./kg.

(4) *Anti-choline-esterase activity.* The dialkyl fluorophosphonates have been shown to be powerful inhibitors of the enzyme choline-esterase. Here again the order was Pr^β > Et > Me. M. Dixon (Report to Ministry of Supply, 1942) showed that our specimens of the diisopropyl ester were effective in concentrations as low as $10^{-10}M$, and were therefore much more powerful than eserine. On the other hand, sodium fluoride and ammonium fluorophosphonate required

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* Toxicity by inhalation (L.C. 50) is expressed as the concentration in mg. per l. required to kill 50% of the animals exposed.
† Toxicity by injection is expressed as the dose in mg. per kg. body weight required to kill 50% of the animals treated.

concentrations of 10^{-2}M to produce 50% inhibition in the standard test. W. Feldberg (Report to Ministry of Supply, Nov., 1942), using a different technique with these same samples, also showed that the di*iso*propyl ester was much more potent than eserine towards choline-esterase.
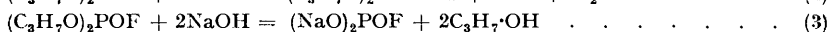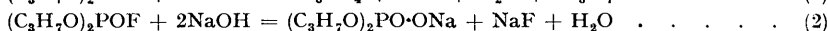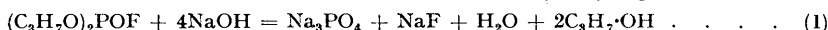
Mixtures.—The freezing points of mixtures of 2 : 2'-dichlorodiethyl sulphide (H) and di*iso*propyl fluorophosphonate were determined, measured volumes of the liquids of known densities being used, and great accuracy is not claimed. A mixture of 60% of H and 40% of the ester melted at *ca.* 0°, and a mixture containing 90% of the ester melted as low as $-38°$.

Other Uses.—In two British Patents (above, and also April 17th, 1944) it has been claimed that some of these toxic compounds might be useful as insecticides, fungicides, bactericides, and disinfectants, and that they might be capable of general clinical application. Such claims are now being realised, particularly in connexion with myasthenia gravis, glaucoma, and paralytic ileus.*

<div align="center">Experimental.</div>

*Di*iso*propyl Fluorophosphonate.*—Di*iso*propyl chlorophosphonate (298 g.) was dissolved in dry benzene (150 c.c.) and gently heated with dry finely powdered sodium fluoride (140 g.) in a flask fitted with a reflux condenser and mechanical stirrer. The temperature was adjusted so that the benzene solution was kept gently boiling, vigorous stirring being maintained. After $3\frac{1}{2}$ hours a small quantity of kieselguhr was added, and the mixture shaken and filtered. The benzene was distilled off (and used for subsequent runs) and the *ester* distilled at 73°/16 mm. Yield, 246 g. (90%) (Found : F, 10·32. $C_6H_{14}O_3FP$ requires F, 10·32%). The determination of fluorine in this and related compounds was carried out by a special technique to ensure non-interference by phosphorus. The procedure employed throughout this work was due to Chapman, Heap, and Saunders, and full details will appear elsewhere.

Hydrolysis by N/2-*sodium hydroxide.* Di*iso*propyl fluorophosphonate (2·224 g.) was heated gently under reflux with 100 ml. of 0·49N-sodium hydroxide for 30 minutes; back titration of an aliquot by 0·5N-sulphuric acid (phenolphthalein as indicator) showed that 1 mol. of the fluorophosphonate required 1·94 mols. of sodium hydroxide. Now 4 mols. are required to effect complete hydrolysis to sodium orthophosphate according to equation (1), but only 2 mols. are required either for the removal of fluorine alone and conversion into sodium di*iso*propyl phosphate (2) or for conversion into disodium fluorophosphonate (3). To decide between these reactions, half of the above hydrolysis product was rendered

$$(C_3H_7O)_2POF + 4NaOH = Na_3PO_4 + NaF + H_2O + 2C_3H_7\cdot OH \quad . \quad . \quad . \quad . \quad (1)$$

$$(C_3H_7O)_2POF + 2NaOH = (C_3H_7O)_2PO\cdot ONa + NaF + H_2O \quad . \quad . \quad . \quad . \quad (2)$$

$$(C_3H_7O)_2POF + 2NaOH = (NaO)_2POF + 2C_3H_7\cdot OH \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

acid to bromophenol-blue with dilute nitric acid, and the sodium fluoride determined as PbClF : it corresponded to 41·1 g. (0·98 mol.) per mol. of di*iso*propyl fluorophosphonate. The hydrolysis is therefore in accordance with equation (2).

A small portion of the hydrolysis solution was strongly acidified with concentrated nitric acid, and warm ammonium molybdate solution added. No visible change took place, and it was only after some minutes' boiling that a yellow coloration was produced. This is good evidence against equation (1). Presumably sodium di*iso*propyl phosphate requires to be broken down with boiling nitric acid before phosphoric acid is produced.

Hydrolysis by N/2-*sodium hydroxide at room temperature.* (a) Di*iso*propyl fluorophosphonate (2·0532 g.) was shaken with 100 ml. of 0·49N-sodium hydroxide at 17°. The oily drops disappeared only after about 5 minutes. The shaking was continued for a total of 30 minutes, and then 25 ml. were withdrawn and required 13·35 ml. of 0·5N-sulphuric acid for neutralisation (phenolphthalein). Therefore 1 mol. of the fluorophosphonate had reacted with 1·994 mols. of alkali.

(b) Di*iso*propyl fluorophosphonate (2·3355 g.) was allowed to *stand* in contact with 100 ml. of 0·49N-sodium hydroxide without shaking. After 30 minutes a considerable amount of unchanged oil still remained, and titration showed that hydrolysis had proceeded to an extent of about 16%. This result is important in indicating that decontamination by cold dilute alkali is effective only when accompanied by vigorous agitation. This point should be borne in mind when dealing with apparatus contaminated by di*iso*propyl fluorophosphonate.

Pure Diammonium Fluorophosphonate.—When prepared according to the method of Lange and Krüger (*loc. cit.*), diammonium fluorophosphonate contains ammonium phosphate and ammonium difluorophosphonite, $(NH_4O)POF_2$. Diammonium fluorophosphonate (50 g.) was dissolved in a mixture of methyl alcohol (600 c.c.) and water (200 c.c.). The mixture was filtered, and the clear solution left overnight. The crystals (20 g.) which had separated were filtered off, washed with methyl alcohol, and dried in a vacuum desiccator. The pure compound is colourless and sublimes at *ca.* 230° [Found : NH_4, 24·0; F, 12·3. Calc. for $(NH_4)_2PO_3F,H_2O$: NH_4, 23·68; F, 12·5%].

Disilver Fluorophosphonate.—Good samples were prepared by adding the calculated quantity of silver nitrate in concentrated aqueous solution to the calculated quantity of diammonium fluorophosphonate also in concentrated aqueous solution, and leaving the mixture in an ice-chest for 2 hours. The solid which separated was washed with a small quantity of cold water, alcohol, and then ether, and dried in a desiccator screened from light.

With impure samples of diammonium fluorophosphonate containing ammonium phosphate, a yellow precipitate of silver phosphate was produced on the addition of silver nitrate solution. The silver phosphate was filtered off and the calculated quantity of powdered silver nitrate was then stirred into

* *Recent References added in Proof*—Whitby (*Practitioner*, 1947, 243); J. P. Quilliam and T. A. Quilliam (*Medical Press*, 1947, Oct. 22nd).

the solution until dissolved. The solution was then treated as above. It was sometimes necessary to add alcohol to the cold solution to promote separation of the silver fluorophosphonate.

Diisopropyl Fluorophosphonate from Silver Fluorophosphonate.—Dry silver fluorophosphonate (62·8 g., 0·2 mol.) was added to a solution of *iso*propyl iodide (76·5 g., 0·4 mol.) in dry toluene (120 c.c.). Heat was evolved and the gentle ebullition which occurred was maintained for 30 minutes. After cooling, the silver iodide was filtered off, and the filtrate distilled, the fraction, b. p. 75—89°/23 mm. (17·0 g.), being collected. This was distilled several times until a fraction, b. p. 74—75°/17 mm., was collected (Found : F, 10·1. Calc. for $C_6H_{14}O_3PF$: F, 10·32%).

Diethyl Fluorophosphonate.—Diethyl chlorophosphonate (103·6 g., 0·6 mol.), dry sodium fluoride (54·6 g., 1·3 mol.), and dry benzene were heated under reflux with vigorous stirring for 2 hours. The product was then cooled, filtered (kieselguhr), and the benzene distilled off under reduced pressure. The residue (84·5 g.; 90·3%) distilled almost entirely at 76—77°/25 mm., and had b. p. 63°/12 mm., 70—72°/18 mm., 74—76°/23 mm., 171°/760 mm. (Found : F, 12·2; Cl, nil. Calc. for $C_4H_{10}O_3PF$: F, 12·17%).

From silver fluorophosphonate. To silver fluorophosphonate (62·8 g.) suspended in benzene (800 c.c.) was added dry ethyl iodide (68·8 g., 10% excess), and the mixture heated under reflux, with stirring, for 30 minutes. After removal of silver iodide, the filtrate was distilled under reduced pressure and the fraction, b. p. 88—90°/45 mm., was collected and shown to be pure diethyl fluorophosphonate. Lange and Krüger carried out their reaction in a sealed tube and used no solvent; their yield from the silver salt was only 24%. Ether could also be used as solvent, but the reaction was slower than with benzene.

Diisopropyl Fluorophosphonate : *"One-stage" Process.*—*iso*Propyl alcohol (180 g., 3 mols.) was dissolved in carbon tetrachloride (100 c.c.), and phosphorus trichloride (137·5 g., 1 mol.) added slowly without external cooling. It was necessary for the mixture to warm to *ca.* 50—60° in order to allow the reaction to proceed at a reasonable speed. When the addition was complete, the mixture was kept under reduced pressure with a stream of dry air passing through it for 1 hour. The product was chlorinated at 0° by a moderate stream of chlorine, until a permanent green coloration was obtained (about 2 hours). The liquid was then treated with a stream of dry air under reduced pressure to remove excess of chlorine and hydrogen chloride. This usually took about 3 hours, although the period could often be substantially reduced. (It did seem essential, however, to remove as much hydrogen chloride as possible before fluorination.) The fluorination was carried out by adding another quantity of carbon tetrachloride (about 40 c.c.) to replace that lost by evaporation, and then adding dry sodium fluoride (94·5 g., 2·25 mols.). The mixture was mechanically stirred and then warmed. After the initial fairly vigorous reaction had subsided, the mixture was gently refluxed for 3 hours, during which time no fuming occurred. The product was cooled, filtered, and the carbon tetrachloride distilled off under reduced pressure, and the residual liquid distilled. A very small fraction was collected at 70—75°/21 mm., followed by the main fraction (138 g.; 75%, based on phosphorus trichloride) at 78—84·5°/21 mm. of very nearly pure di*iso*propyl fluorophosphonate. This main fraction distilled almost entirely at 82—83°/21 mm. giving the pure compound (Found : F, 10·25%).

Mixtures of 2 : 2′-Dichlorodiethyl Sulphide and Diisopropyl Fluorophosphonate.—The freezing points of mixtures of 2 : 2′-dichlorodiethyl sulphide (H) and di*iso*propyl fluorophosphonate (FP) were determined. Cooling agents used were ice, ice–salt, acetone–solid carbon dioxide, and liquid air. The H used had *d* 1·275 g./c.c., and the FP had *d* 1·067 g./c.c., at 19°

H (%).	FP (%).	M. p.	H (%).	FP (%).	M. p.	H (%).	FP (%).	M. p.
100	0	11·5°	61·44	38·56	0·4°	37·42	62·58	−11°
90·54	9·46	8·9	54·46	45·54	− 3·3	42·76	57·24	− 7·5
82·73	17·27	6·3	0	100	*ca.* −82	47·27	52·73	− 5·4
76·11	23·89	4·8	13·00	87·00	−36	51·11	48·89	− 4·2
68·21	31·79	2·8	22·99	77·01	−22	54·46	45·54	− 3·3
65·66	34·34	2·1	31·94	69·06	−15			

The following were exposed to various concentrations of the different fluorophosphonates (mentioned in this and subsequent papers) dispersed in a 10 m.³ chamber : F. J. Buckle, N. B. Chapman, H. G. Cook, R. Heap, J. D. Ilett, B. A. Kilby, H. McCombie, F. L. M. Pattison, B. C. Saunders, F. E. Smith, G. J. Stacey, F. Wild, I. G. E. Wilding, S. J. Woodcock.

Toxicity experiments on animals were carried out by B. A. Kilby *et al.*

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