198. *Esters Containing Phosphorus. Part VI. Preparation of Esters of Fluorophosphonic Acid by Means of Phosphorus Oxydichlorofluoride.*

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An account is given of the synthesis of esters of fluorophosphonic acid by the action of the appropriate alcohol on phosphorus oxydichlorofluoride, and for this purpose a convenient preparation of the latter compound is given. In particular the preparation and properties of the highly toxic *dicyclohexyl fluorophosphonate* are described.

Phosphorus oxydichlorofluoride also reacts with ethylthiol in the presence of a tertiary base producing *diethyl fluorodithiophosphonate* which, in marked contrast to diethyl fluorophosphonate, is relatively non-toxic and devoid of miotic properties. Among other esters described is *di-2-fluoroethyl fluorophosphonate* which possesses interesting pharmacological properties.

IN a Report to the Ministry of Supply (Feb. 27, 1942) a method was proposed for synthesising esters of fluorophosphonic acid by the reaction between phosphorus oxychloride and the appropriate alcohol:

$$O{:}PCl_2F + 2ROH = O{:}PF(OR)_2 + 2HCl \quad \text{(I.)}$$

The reaction depended upon the marked difference in reactivity between the chlorine atoms and the fluorine atom in phosphorus oxydichlorofluoride. In general the reaction with alcohols was clear cut, and most of the fluorophosphonic esters were obtained in excellent yield and uncontaminated with the phosphoric triester. For example, when ethyl alcohol and phosphorus oxydichlorofluoride were allowed to react in the cold, diethyl fluorophosphonate (I, R = Et) was obtained in 93% yield. No tertiary base was necessary to remove the hydrogen chloride produced in the reaction. The general process was patented during the war (B.P., Ministry of Supply, McCombie, Saunders, Chapman, and Heap, April 17th, 1944).

The method depended upon the availability of phosphorus oxydichlorofluoride, a compound described by Booth and Dutton (*J. Amer. Chem. Soc.*, 1939, **61**, 2937) who devised an elaborate apparatus for the preparation of the compound in a pure condition for physicochemical measurements. We have modified their process to suit the particular needs of this work. The "generator" which we developed for this step-wise fluorination of phosphorus oxytrichloride by antimony trifluoride (and pentachloride as catalyst) is shown in the diagram. Full details of its construction and maintenance are given on p. 1011. On a kilogram scale the yield of pure phosphorus oxydichlorofluoride was *ca.* 20%.

In addition to diethyl fluorophosphonate, *di*-n-*propyl* and di*iso*propyl fluorophosphonate were prepared by the action of phosphorus oxydichlorofluoride on *n*-propyl and *iso*propyl alcohol respectively. The *n*-ester was less toxic and possessed only feeble miotic action compared with the ethyl and the *iso*propyl ester, the order of potency being $Pr^{\beta} > Et > Pr$. The ethyl and *iso*propyl esters were identical with the compounds obtained by the "hydrogen phosphate" method described by Saunders and Stacey (Part IV, this vol., p. 695).

In order to determine whether other secondary alcohols would give fluorophosphonic esters of high potency, *di*cyclo*hexyl fluorophosphonate* (II) was prepared by the action of phosphorus oxydichlorofluoride on *cyclo*hexanol. In this preparation it was essential to remove carefully all the hydrogen chloride before distillation, otherwise decomposition took place. The compound was a colourless, mobile liquid, b. p. 116°/0·3 mm., insoluble in water, and formed a "persistent gas". It was extremely toxic (Report from Prof. Adrian to Ministry of Supply, Jan. 7th, 1943; and Report No. 9 on Fluorophosphonates by McCombie and Saunders, April 10th, 1943); at a nominal concentration of 1 : 12,500, the following died after a 10-minute exposure: 3/3 rabbits, 3/4 guinea-pigs, 6/6 rats, 10/10 mice. The pupils of the animals' eyes contracted to pin-point size and there were the usual "fluorophosphonate-like" convulsions before death. More precise toxicity experiments showed that the approximate L.C. 50 (see Part IV) for a 10-minute exposure for mice, rats, and rabbits was 0·11—0·14 mg./l. (guinea-pigs appeared to be more resistant). This means that di*cyclo*hexyl fluorophosphonate was more toxic than di*iso*propyl fluorophosphonate (Part IV, *loc. cit.*).

Whereas diethyl fluorophosphonate was hydrolysed in aqueous solution in about 4 hours, the di*iso*propyl ester required some 72 hours for complete hydrolysis, and could be steam-distilled. Di*cyclo*hexyl fluorophosphonate was very stable, and vigorous shaking with water did not produce any appreciable hydrolysis. It was hydrolysed by boiling water only after several hours. When stirred vigorously with 2% sodium hydroxide solution at 28·5°, the time taken to bring about hydrolysis according to the equation $(C_6H_{10}O)_2POF + 2NaOH = (C_6H_{10}O)_2PO{\cdot}ONa + NaF + H_2O$ was of the order of 90 minutes. On prolonged shaking, hydrolysis proceeded beyond the stage represented above. With occasional shaking (*i.e.*, under conditions comparable with those employed in decontamination) in the presence of 2% sodium hydroxide hydroxide solution at 20°, hydrolysis proceeded to an extent of only 64% after 220 minutes.

In view of the greater toxicity often observed with derivatives of *o*-cresol compared with derivatives of phenol itself, it seemed worth while to prepare *di-*(o-*methyl*cyclo*hexyl*) *fluorophosphonate.* At a concentration of 0·65 mg./l., only 3 out of a batch of 23 animals (rabbits, guinea-pigs, rats, and mice) were killed. The animals which died (the rabbits) exhibited muscular twitchings, but miosis was not very marked. The compound was therefore much less toxic than the corresponding unsubstituted di*cyclo*hexyl fluorophosphonate.

Di-2-chloroethyl fluorophosphonate was obtained from phosphorus oxydichlorofluoride and chlorohydrin, and in a chamber at a concentration of 1 : 10,000 (1·0 mg./l.) caused some irritation of the eyes and nose of the animals. After exposure, the irritant effects rapidly subsided and no other effects were observed. A small number of animals died as follows: 0/3 rabbits, 1/4 guinea-pigs (12 hours), 1/6 rats (4½ days), 3/10 mice (12 hours, 5½ days, 7½ days). The compound was therefore relatively non-toxic. Elsewhere it is recorded that 2-fluoroethyl alcohol is highly toxic (McCombie and Saunders, *Nature*, 1946, **158**, 382), and that 2-fluoroethyl fluoroacetate is markedly more toxic than either fluoroethyl alcohol or fluoroacetic acid (weight for weight). In view of this enhanced toxicity it seemed desirable to investigate the effect of introducing the 2-fluoroethyl group into the fluorophosphonate molecule. Accordingly, *di-*(2-*fluoroethyl*) *fluorophosphonate* (III) was prepared from phosphorus oxydichlorofluoride and fluoroethyl alcohol. The compound, a mobile liquid, exhibited lower toxicity than either fluoroethyl alcohol or diethyl fluorophosphonate. At a concentration of 0·5 mg./l. (10 mins.' exposure) it did, however, produce a remarkable effect on rats. An hour or so after exposure two out of six rats became extremely violent, rushed about the cage, and exhibited a type of hyperactivity which caused them to bite the legs of their companions. The two rats died of convulsions of an unusual type. The phenomenon was repeatable. The compound also caused miosis.

$$\underset{\text{(II.)}}{O{:}PF(O{\cdot}C_6H_{11})_2} \qquad \underset{\text{(III.)}}{O{:}PF(O{\cdot}CH_2{\cdot}CH_2F)_2} \qquad \underset{\text{(IV.)}}{O{:}PF(SEt)_2}$$

Diphenyl fluorophosphonate was prepared in 60% yield by the action of phosphorus oxydichlorofluoride on phenol in the presence of dimethylaniline to take up the hydrogen chloride formed. Gottlieb (*J. Amer. Chem. Soc.*, 1936, **58**, 532) claimed to have prepared this compound in 7% yield by the action of potassium fluoride on the corresponding chlorophosphonate. His compound was rapidly decomposed by water, whereas ours was stable (in accordance with expectation); furthermore, he gave no fluorine analysis. It is doubtful therefore whether Gottlieb obtained an authentic specimen of diphenyl fluorophosponate. We showed that diphenyl fluorophosphonate was non-toxic and possessed negligible miotic action.

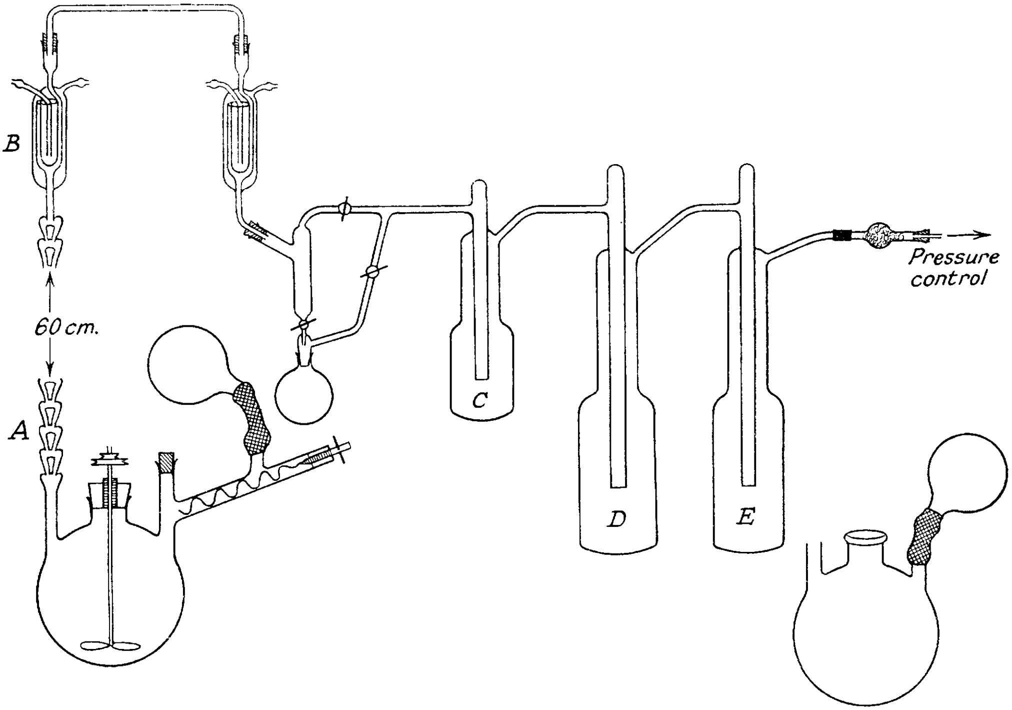
There appeared to be no appreciable reaction between ethylthiol and phosphorus oxydichlorofluoride, whereas the sodium thioethoxide reacted with all three halogen atoms producing triethyl trithiophosphate, $O{:}P(SEt)_3$. It was found, however, that if dimethylaniline were used as the condensing agent then the two chlorine atoms were removed while the fluorine atom remained unaffected. *Diethyl fluorodithiophosphonate* (IV) thus obtained was a liquid, and unlike the corresponding oxygen analogue (I, R = Et) was non-toxic and devoid of miotic properties.

EXPERIMENTAL.

Phosphorus Oxydichlorofluoride.—Apparatus. The generator employed is shown in the diagram. Important points are: (1) The column *A* was efficient and designed so that throttling was avoided; it was at least 2 feet long and surmounted by a reflux double-surface water-condenser *B*. (2) A Perkin triangle (air-cooled), inserted between the down-condenser and the traps, enabled any phosphorus oxychloride which distilled to be removed (usually only a small quantity condensed in the triangle during a normal run). (3) It was convenient to have three traps, *viz.*, *C*, ice–salt; *D*, acetone–carbon dioxide; *E*, liquid air. (4) The intermittent addition of the solid antimony trifluoride presented a problem. The mechanical "solid" feed shown in the diagram proved fairly satisfactory over short periods of working. There was a tendency, however, for the wire screw-feed to become jammed as the antimony fluoride became damp during the experiment. A less elegant, but more reliable device for long periods of working is shown in the small diagram. It consists of a round-bottomed flask attached directly to the reaction vessel by means of a flexible, special quality, corrosion-resisting, rubber hose. (5) The stirrer was made of stainless steel with strengthened paddles; the stirrer gland was packed freshly before each run, and was filled as full as possible. (6) Silicone grease was used on all joints. Ground-glass joints were used where possible, but some rubber connexions (strong pressure tubing) were employed at certain points to provide flexibility. Considerable vibration was caused by vigorous stirring. The necessary reduced pressure (200 mm.) was maintained by a steel water-pump and moving-bell type manostat.

Procedure. Finely powdered antimony trifluoride (800 g.) was placed in the reservoir of the feed. Phosphorus oxychloride (2000 g.) and then antimony pentachloride (500 g.) were placed in the reaction vessel. The temperature of the bath was maintained, thermostatically, at 75° and the pressure kept at 190—200 mm., and the antimony trifluoride was then added slowly from the feed. The duration of addition varied from 2 to 6 hours, the slowest rate being the best. The distillates in the traps were united and fractionated. The distillate, up to b. p. 90°/760 mm., was collected and carefully refractionated, giving 360 g.(20%) of pure phosphorus oxydichlorofluoride, b. p. 54°.

In a smaller-scale experiment, the following quantities were used : Phosphorus oxychloride (500 g.), antimony trifluoride (200 g., added during 3—4 hours), antimony pentachloride (60 c.c.). After the conclusion of the experiment 137 g. of phosphorus oxychloride were recovered from the residue in the reaction-vessel by distillation up to 200° (at which antimony compounds began to come over), and 57 g. from the Perkin triangle and traps. The yield of oxydichlorofluoride was 90 g., *i.e.*, 20%, or 34% after allowance for the oxychloride recovered. When double the quantity of antimony trifluoride was used, there was no excess of phosphorus oxychloride left in the reaction vessel, but there was no increase in the yield of oxydichlorofluoride : it appeared that the extra antimony trifluoride had converted the " excess " of phosphorus oxychloride into oxychlorodifluoride and oxytrifluoride.



Diethyl Fluorophosphonate.—Phosphorus oxydichlorofluoride (5·5 g.) was placed in a Claisen flask (possessing a fractionating column) and fitted with a calcium chloride tube. Ethyl alcohol (4 g., 10% excess) was slowly run in, the temperature not being allowed to rise above 5°. The hydrogen chloride was removed by suction at room temperature, and the residue carefully heated to remove excess of alcohol and hydrogen chloride. When the residue was distilled under reduced pressure, almost the entire liquid came over at 70—72°/18 mm.; yield, 5·8 g. (93%). The product contained fluorine and only traces of chloride. A second distillation at 70—72°/18 mm. gave a product completely free from chloride (Found : F, 12·2. Calc. for $C_4H_{10}O_3FP$: F, 12·17%) which was further characterised by its b. p., 171°/760 mm., and powerful miotic action. 1 Mol. of the compound required 2 mols. of sodium hydroxide (N/2 solution) for hydrolysis in the cold or on being gently heated under reflux for 30 minutes; this is in accordance with the equation $PO(OEt)_2F + 2NaOH = PO(OEt)_2ONa + NaF + H_2O$ (see Part IV).

*Di-*n*-propyl Fluorophosphonate.*—*n*-Propyl alcohol (20 g., 15% excess) was slowly run into phosphorus oxydichlorofluoride (20 g.). Heat was evolved during the reaction and the temperature was kept down to 5°. The mixture was set aside for several hours, and the excess of hydrogen chloride removed by drawing air through the liquid, which was then distilled. The fraction of b. p. 96—102°/20 mm. (25 g., 93%) was almost pure *di-*n*-propyl fluorophosphonate.* It was redistilled at 98—100°/20 mm. (Found : F, 10·28, 10·39. $C_6H_{14}O_3FP$ requires F, 10·32%).

*Di*iso*propyl Fluorophosphonate.*—Phosphorus oxydichlorofluoride (50 g.) was dissolved in dry ether

(100 c.c.), *iso*propyl alcohol (dried over calcium oxide; 50 g., 15% excess) in dry ether (100 c.c.) was added slowly with cooling, and the mixture kept for one hour. Dry ammonia was then passed through the liquid, with cooling. The liquid was then filtered, if necessary, and the excess of ammonia and ether taken off at room temperature. The residue was distilled, and the fraction, b. p. 37—47°/0·5 mm., collected. This redistilled at 84—85°/25 mm.; yield, 60 g. (45%) (Found : F, 10·1%).

*Di*cyclo*hexyl Fluorophosphonate.*—Phosphorus oxydichlorofluoride (68·5 g., 0·5 mol.) was dissolved in dry ether (150 c.c.) and well cooled in ice–salt. *cyclo*Hexanol (100 g., 1·0 mol.) in dry ether (150 c.c.) was slowly dropped in and the mixture kept over-night. In order to remove hydrogen chloride, air (dried with H_2SO_4, NaOH, and P_2O_5) was drawn through the resultant liquid for about 5 hours. More dry ether was then added, and dry ammonia passed through the liquid until no more ammonium chloride was precipitated. The ammonium chloride was filtered off, and the filtrate kept over lead carbonate for some time, filtered, and the filtrate dried (Na_2SO_4). After distillation of the ether, the residue was distilled in a " semi-molecular " still, without air-leak, glass-wool being used to prevent splashing. The fraction of b. p. 90—96°/0·02 mm. was collected. The liquid could also be distilled at slightly higher pressures in an atmosphere of nitrogen. After the " initial " distillation the above precautions were usually not necessary for further distillations; yield, 126 g. (70%). *Di*cyclo*hexyl fluorophosphonate* was a colourless, mobile liquid, insoluble in water (Found : F, 7·3, 6·9. $C_{12}H_{22}O_3FP$ requires F, 7·12%).

Notes on the preparation. (a) The *cyclo*hexanol was heated under reflux over quicklime and redistilled before use. (b) It was essential to remove all the hydrogen chloride produced in the reaction, otherwise decomposition was likely to take place during the final distillation. (c) Occasionally, specimens of di*cyclo*hexyl fluorophosphonate contain traces of ammonium chloride. This is readily removed by washing with water, drying (Na_2SO_4), and redistilling.

*Hydrolysis of Di*cyclo*hexyl Fluorophosphonate.*—(a) *By water at* 20°. The ester (7·9 g.) was suspended in water, and the mixture made up to 250 ml. with distilled water and *vigorously stirred* in a thermostat at 20°, 25 ml. being withdrawn at intervals and titrated with standard alkali (about N/2), phenolphthalein being used as indicator. After 227 mins.' stirring the hydrolysis was only 0·025%, and this remained unchanged after a further 990 mins.' standing (this value is less than the experimental error of the determination). At the end of the experiment, the ester was separated, dried, and distilled, 5·8 g. being recovered; after allowance for losses, this confirms that the ester was practically unhydrolysed.

(b) *By approx.* N/2-*sodium hydroxide with vigorous stirring at* 28·5°. 8·85 G. of ester (0·0311 mol.) were stirred vigorously with 250 ml. of 0·642N-sodium hydroxide and 20-ml. samples withdrawn at intervals, and titrated against sulphuric acid (phenolphthalein as indicator) :

Time, mins.	9	20	30	62·5	92	121·5	140
Hydrolysis, %	8·6	26·5	38·8	82·9	109·7	138·0	149·0

After a further 18 hours' standing, the hydrolysis was 153·1%.

(c) *By approx.* N/2-*sodium hydroxide with occasional shaking at* 20°. A similar experiment with 0·02934 mol. of ester and 250 ml. of 0·6415N-alkali gave the following results :

Time, mins.	27	59	100	151	230
Hydrolysis, %.	56·8	58·3	58·9	60·7	64·0

After a further 985 mins.' standing, the hydrolysis was 73·9% and the residue was undistillable at 0·3 mm. in nitrogen.

(d) *By approx.* N/2-50% *aqueous ethanolic sodium hydroxide at* 20°. 0·03481 Mol. of ester and 250 ml. of 0·5958N-alkali gave the following results :

Time, mins.	32·5	87	105	147	184	225	1215
Hydrolysis, %	18·7	114·0	111·2	109·7	111·6	114·0	111·6

The variations after 87 mins. are within the limits of experimental error.

Di-(o-*methyl*cyclo*hexyl*) *Fluorophosphonate.*—Phosphorus oxydichlorofluoride (34·25 g., 1 mol.) was dissolved in dry ether (100 c.c.) and cooled in ice and salt. *o*-Methyl*cyclo*hexanol (dried by refluxing over quicklime and distilling, 57 g., 2 mols.), dissolved in dry ether (100 c.c.), was added slowly to the oxydichlorofluoride solution, and the mixture kept overnight. Dry air was then passed through for 6—8 hours to remove hydrogen chloride, and then dry ammonia was passed in with ice-cooling to ensure complete removal of the residual hydrogen chloride. The ammonium chloride thus formed was filtered off, and the filtrate kept over lead carbonate, refiltered, and dried (Na_2SO_4 and kieselguhr). The ether was distilled off from the filtered solution, and the residue fractionated in a stream of nitrogen; b. p. 120°/0·1 mm., 137°/0·15 mm.; yield, 42 g. (60%). The b. p. was to some extent dependent upon the bath temperature, which was 190° for the second value. The *product* may have been a mixture of *cis*- and *trans*-isomers (Found : F, 6·53, 6·58. $C_{14}H_{26}O_3FP$ requires F, 6·51%).

Di-(2-*chloroethyl*) *Fluorophosphonate.*—Phosphorus oxydichlorofluoride (34·25 g.) was dissolved in dry ether (50 c.c.) and well cooled in ice–salt, and ethylene chlorohydrin (40·25 g.) in dry ether (50 c.c.) was slowly added. Hydrogen chloride was copiously evolved, the resultant liquid was set aside overnight, and dry air was then pulled through for at least 5 hours. The brown liquid so obtained was diluted with dry ether, and dry ammonia passed in until no more ammonium chloride was precipitated. The solid was filtered off, and the cloudy filtrate dried (Na_2SO_4), refiltered, and clarified with kieselguhr. The ether was distilled off, and the residue distilled at 0·4 mm. in an atmosphere of nitrogen. The crude distillate was redistilled at 15 mm. and had b. p. 142—144°. The *ester* contained phosphorus and chlorine (Found : F, 8·9. $C_4H_8O_3Cl_2FP$ requires F, 8·45%). (The slightly high fluorine content may be explained in that a modification of our usual technique was employed : it was necessary to use sufficient sodium to break the C–Cl as well as the P–F bonds, and this resulted in a final alcohol content of 15%, and a concentration of sodium chloride higher than is suitable in this analysis. These factors would cause coprecipitation of lead chloride with the chlorofluoride.)

Di-(2-fluoroethyl) Fluorophosphonate.—Phosphorus oxydichlorofluoride (24·0 g.) was placed in a Claisen flask fitted with a dropping-tube and calcium chloride outlet tube, and 2-fluoroethyl alcohol (22·5 g.) was added slowly, the temperature of the mixture (thermometer in the liquid) being kept at 0—5°. The hydrogen chloride evolved escaped through the calcium chloride tube. The mixture was set aside overnight and freed from hydrogen chloride by aeration as usual. The dark residue was distilled at 13 mm. and had b. p. 125—127°; yield, 15 g. (50%). The *ester* contained phosphorus (Found : F, 30·35. $C_4H_8O_3F_3P$ requires F, 29·6%).

Diphenyl Fluorophosphonate.—Dimethylaniline (60·5 g.) and phenol (47 g.) were mixed, and dry ether (50 c.c.) 'added. The mixture was cooled in ice-water, and phosphorus oxydichlorofluoride (34·3 g.) slowly run in. After standing overnight, the mixture crystallised spontaneously; more dry ether was added, and the dimethylaniline hydrochloride (*ca.* 70 g.) was filtered off. The ethereal filtrate was dried (Na_2SO_4), the ether distilled off, and the residue fractionated. The fraction of b. p. 115—118°/0·4 mm. was collected and redistilled at 106—108°/0·07 mm.; yield, 37·6 g. (60%) (Found : F, 7·93, 8·03. $C_{12}H_{10}O_3FP$ requires F, 7·54%).

Reaction between Ethylthiol and Phosphorus Oxydichlorofluoride.—(*a*) Ethylthiol was run into phosphorus oxydichlorofluoride, but no reaction occurred.

(*b*) Ethylthiol (10 g.) was dissolved in dry ether (50 c.c.) and sodium (3·7 g.) added. This mixture was added to a solution of phosphorus oxydichlorofluoride (12 g., 10% excess) in dry ether (50 c.c.). The ether was distilled off, and the residue fractionated. The fraction, b. p. 168—200°/20 mm., was refractionated and collected at 175°/18 mm.; a third distillation gave a fraction, b. p. 172—174°/16 mm. [Found : S, 40·46. $C_4H_{10}OFPS_2$ requires S, 34·04. $C_6H_{15}OPS_3$ requires S, 41·75%]. As the compound also contained phosphorus but no chlorine, it was considered to be *triethyl trithiophosphate*, and as it contained traces of fluorine it was probably contaminated with a small quantity of the ester described below.

(*c*) Dimethylaniline (60·5 g.) and ethylthiol (31 g.) were mixed, and phosphorus oxydichlorofluoride (34·25 g.) added in portions of *ca.* 5 g. The reaction was carried out at room temperature, and any rise in temperature checked by cooling in cold water. The mixture was kept for 2 days and then solidified on addition of a crystal of dimethylaniline hydrochloride. Dry ether was then added, and this hydrochloride (*ca.* 72 g.) filtered off. The filtrate was dried (Na_2SO_4), the ether distilled off, and the residue fractionated at 15 mm. The fraction of b. p. 104—107°/15 mm. was collected and found to be *diethyl fluorodithiophosphonate* (Found : F, 10·03, 9·7. $C_4H_{10}OFPS_3$ requires F, 10·1%). (Dimethylaniline has b. p. 90°/25 mm., and the trithio-ester, b. p. 174—175°/20 mm.).

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