261. *Esters Containing Phosphorus. Part VII. Substituted Diaminofluorophosphine Oxides.*

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Substituted diaminofluorophosphine oxides are readily prepared by the action of phosphorus oxydichlorofluoride on the appropriate primary or secondary amine. They are stable compounds and possess toxic properties in varying degrees. In particular bisdimethylaminofluorophosphine oxide (II) is a highly toxic compound, but without miotic action. The sulphur analogue (*dimethylaminosulphonyl fluoride*, VI) of (II) has been synthesised and examined.

In Part VI (this vol., p. 1010) was described the reaction between phosphorus oxydichlorofluoride and alcohols, phenols, and thiols, which afforded dialkyl, di*cyclo*alkyl, and diaryl fluorophosphonates and dialkyl fluorodithiophosphonates. In a Report to the Ministry of Supply on Fluorophosphonates (Sept. 30th, 1942) was described a new type of " nitrogen fluorophosphonate " formed by the action of 4 mols. of aniline on 1 mol. of phosphorus oxydichlorofluoride, the fluorine atom being unaffected :

$$O{:}PFCl_2 + 4NH_2Ph = O{:}PF(NHPh)_2 + 2NH_2Ph,HCl$$
(I.)

The compound (I) was a highly crystalline, stable substance and is best named *dianilinofluorophosphine oxide*. A solution in propylene glycol was injected subcutaneously into mice, and the L.D. 50 found to be about 90 mg./kg.

Later, American workers (Burg, communications of 19/2/43 and 15/3/43) described the preparation of this type of compound by an uneconomical method which necessitated the loss of two-thirds of the fluorine concerned in the reaction. They prepared bisdimethylaminofluorophosphine oxide (II) by the action of phosphorus oxyfluoride on the calculated quantity of dimethylamine In addition, it should be emphasised that phosphorus oxyfluoride is a gas and is more difficult than the liquid phosphorus oxydichlorofluoride to manipulate. In Report No. 14 on fluorophosphonates to the Ministry of Supply (Sept. 30th, 1943) it was shown that our reaction could also be applied to the preparation of bisdimethylaminofluorophosphine oxide, and was of very general application (see B.P. 602,446, Ministry of Supply, McCombie, Saunders, Chapman, and Heap, April 17th, 1944).

It was found that bisdimethylaminofluorophosphine oxide was very toxic and had an L.D. 50 of the order of 1·0 mg./kg. for subcutaneous injection into mice; the concentration for rabbits was higher at 3·0 mg./kg. (intravenously). The Cambridge figure for toxicity by inhalation agreed with that found by American workers, the L.C. 50 for mice being 0·095 mg./l. for a 10-minute exposure. We also carried out experiments with four human observers exposed to a concentration of one part in a million for 5 minutes. No effects of any kind were noted, and in particular, miotic action was completely absent. In this respect, therefore, the highly toxic

$O{:}PF(NMe_2)_2$	$O{:}PF(NEt_2)_2$	$O{:}PF(O{\cdot}CHMe_2)_2$	$O{:}PF(O{\cdot}CHEt_2)_2$	$NMe_2{\cdot}SO_2F$
(II.)	(III.)	(IV.)	(V.)	(VI.)

compound (II) differed markedly from the highly toxic di*iso*propyl fluorophosphonate (IV), in that the latter showed powerful miotic action. It is to be noted also that, whereas (IV) caused 50% inhibition of choline-esterase activity at a concentration of the order of 10^{-10}M, a concentration of *ca.* 8×10^{-5}M of (II) was necessary to produce the same percentage inhibition (Dixon and Mackworth, Report to Ministry of Supply, April 23rd, 1942; also Dixon and Webb, May 18th, 1944).

Nevertheless there is some similarity of structure between compounds (II) and (IV). It will be shown (Part VIII of this series) that with *gem*-diethyl groups in the fluorophosphonate molecule [*e.g.*, di-(1-ethyl-*n*-propyl) fluorophosphonate, V], the toxicity is less than with *gem*-dimethyl groups (di*iso*propyl fluorophosphonate, IV). We found that similarly *di(ethylamino)fluorophosphine oxide* (III) was very much less toxic than (II). This applied to subcutaneous as well as to inhalation experiments. By subcutaneous injection the L.D. 50 of (III) for mice was *ca.* 160 mg./kg. This close analogy between the two types of compound cannot, however, be pressed too far. The toxicities by subcutaneous injection into mice of other hitherto undescribed substituted *diaminofluorophosphine oxides* were found to be as follows:

Fluorophosphine oxide.	L.D. 50, mg./kg.	Fluorophosphine oxide.	L.D. 50, mg./kg.
Di-(*n*-butylamino)	16	Dimorpholino	400
Di(benzylamino)	10	Dipiperidino	320
Di(*cyclo*hexylamino).....	9	Di-(*N*-methylanilino)	160

In the British Patent (*ibid.*), we claimed the use of compounds of the above type as insecticides, bactericides, and fungicides, and indicated their general clinical application.

The compounds are, in general, stable and fairly resistant to hydrolysis in spite of the > POF grouping. We showed, for example, that dianilinofluorophosphine oxide could be recrystallised from aqueous alcohol. Bisdimethylaminofluorophosphine oxide was not affected to any extent by contact with water at 18° for 6 hours. The reaction between N/2-aqueous sodium hydroxide solution and the compound was studied. The extent of hydrolysis (removal of fluorine) after 30 minutes was about 8·9%, and even after 500 hours it was only 29·9%. The compound is affected by acid, but the reaction is somewhat complex.

In view of the high toxicity of (II), it seemed that the sulphur analogue, dimethylaminosulphonyl fluoride (VI), might be of some interest. We therefore studied the fluorination of dimethylaminosulphonyl chloride. The reaction with potassium fluoride was incomplete, and that with zinc fluoride unsatisfactory, but that with antimony trifluoride using benzene as a solvent proved to be very satisfactory, and an 80% yield of (VI) was obtained. Physiological examination showed that (VI) caused no irritation when small animals were exposed to a concentration of 1 mg./l. for 10 minutes, and no deaths took place. With the sulphonyl chloride

at the same concentration, lachrymation and nasal irritation were caused: no deaths were recorded, and all the animals recovered almost immediately on being removed from the chamber.

Experimental.

For the preparations described below, phosphorus oxydichlorofluoride was prepared according to the method given in Part VI (*loc. cit.*).

Dianilinofluorophosphine Oxide.—Aniline (75 g., 1% excess) was dissolved in dry benzene (100 c.c.) and cooled in ice. Phosphorus oxydichlorofluoride (27·4 g.), dissolved in dry benzene (100 c.c.), was slowly run in, the mixture kept for 30 mins., and then heated to boiling. The aniline hydrochloride (m. p. 198°) was filtered off from the boiling solution, and the filtrate, on cooling, deposited white granular crystals. A further yield of *oxide* was obtained by extracting the aniline hydrochloride with benzene (Soxhlet); total yield, 40 g. Recrystallisation from aqueous alcohol (animal charcoal) and slow cooling afforded long, colourless needles, m. p. 145°, soluble in hot water. The compound contained phosphorus but not chlorine (Found: N, 11·38; F, 7·81. $C_{12}H_{12}ON_2FP$ requires N, 11·2; F, 7·6%).

Bisdimethylaminofluorophosphine Oxide.—Phosphorus oxydichlorofluoride (27·4 g., 0·2 mol.), dissolved in dry ether (150 c.c.), was added slowly to a solution of anhydrous dimethylamine (36 g., 0·8 mol.) also in dry ether (180 c.c.). A vigorous reaction took place and dimethylamine hydrochloride was precipitated. This was filtered off, and the ethereal solution dried (Na_2SO_4), filtered, the ether distilled off, and the residue fractionated. Practically the whole of it distilled at 86°/15 mm.; yield, 20·6 g. (67%). The oxide, a mobile liquid, contained phosphorus but not chlorine; $d_4^{25°}$ 1·1. It was soluble in cold water (Found: N, 17·5; F, 12·3. Calc. for $C_4H_{12}ON_2FP$: N, 18·1; F, 12·34%).

Bisdiethylaminofluorophosphine Oxide.—Phosphorus oxydichlorofluoride (25 g.) was dissolved in dry toluene (50 c.c.) and cooled in ice–hydrochloric acid. Anhydrous diethylamine (50 g., 4 mols.), dissolved in dry toluene (100 c.c.), was added slowly. After the addition was complete, the precipitated diethylamine hydrochloride was filtered off and toluene was distilled from the filtrate (at 20 mm.). The residue was fractionated at 0·1 mm. in an atmosphere of nitrogen. Three fractions were obtained: (1) b. p. 82°, containing chlorine (4 g.), (2) b. p. 92°, chlorine-free (18 g.), (3) a high-boiling fraction (3 g.). The main fraction (2) was redistilled (without passing nitrogen through the flask), and the *oxide* had b. p. 124·5—125·5°/20 mm., 127—128°/22 mm. (Found: N, 13·5; F, 9·2. $C_8H_{20}ON_2FP$ requires N, 13·33; F, 9·05%).

Di-(n-butylamino)fluorophosphine Oxide.—A solution of phosphorus oxydichlorofluoride (4·69 g.) in dry ether (20 c.c.) was added slowly to a solution of *n*-butylamine (10 g., 4 mols.) in dry ether (20 c.c.), the mixture being kept cool in ice–water (much heat was evolved). After several hours' standing the hydrochloride was filtered off and washed with dry ether. The ethereal solution was evaporated under reduced pressure at 20° and a viscous oil remained. On distillation at 177°/2·5 mm. some decomposition took place. The distillate, however, partly solidified and was recrystallised from dry light petroleum (b. p. 100—110°). (The recrystallisation had to be carried out in dilute solution with cooling from 30° to room temperature, otherwise the product separated as an oil.) The *oxide* (yield, 3 g.) formed long, fine, colourless needes, m. p. 59·5°, soluble in benzene, and contained fluorine but not chlorine (Found: N, 13·9. $C_8H_{20}ON_2FP$ requires N, 13·33%).

Di(benzylamino)fluorophosphine Oxide.—This was prepared from phosphorus oxydichlorofluoride (3·8 g.) and benzylamine (12 g.) each in dry ether (50 c.c.), the usual precautions being observed. After all the oxydichlorofluoride had been added, the mixture was filtered, and the solid washed with dry ether. (The filtrate and washings were evaporated leaving no residue, showing that the fluorophosphine oxide was insoluble in ether.) The solid was extracted with warm water (40°) and filtered off. The aqueous filtrate contained benzylamine hydrochloride. The insoluble residue was recrystallised twice from 90% aqueous alcohol. The pure *oxide* (yield, 5·1 g., 66%) had m. p. 96° and contained fluorine but not chlorine (Found: N, 10·4. $C_{14}H_{16}ON_2FP$ requires N, 10·08%).

Di(cyclohexylamino)fluorophosphine Oxide.—Phosphorus oxydichlorofluoride (4 g.), dissolved in dry benzene (25 c.c.), was added slowly (cooling in ice) to *cyclo*hexylamine (12 g.; *i.e.*, 4 mols. + 4% excess) also dissolved in dry benzene (25 c.c.). After standing for some time the precipitation of hydrochloride (mixed with fluorophosphine oxide) was complete. The mixture was then heated to boiling and filtered hot. On cooling the benzene filtrate, colourless crystals of the *oxide* separated; yield, 7·5 g. (95%). It could be obtained in a highly crystalline condition by recrystallisation from aqueous alcohol at about 50°; m. p. 127° (Found: C, 55·20; H, 9·37; N, 10·9; F, 7·76. $C_{12}H_{24}ON_2FP$ requires C, 54·96; H, 9·16; N, 10·68; F, 7·25%).

Dimorpholinofluorophosphine Oxide.—This was prepared in the usual manner from morpholine (34·8 g., 0·4 mol.) in dry ether (60 c.c.) and phosphorus oxydichlorofluoride (13·7 g., 0·1 mol.) also in dry ether, with cooling in ice–hydrochloric acid. The morpholine hydrochloride was filtered off, and the ethereal filtrate dried (Na_2SO_4). After distillation of the ether, the residual oil crystallised on standing overnight. Recrystallised from anhydrous ether, the *oxide* formed colourless, slightly hygroscopic crystals (3·4 g.), m. p. *ca.* 40°, and contained phosphorus but no chlorine (Found: N, 11·5; F, 7·4. $C_8H_{16}O_3N_2FP$ requires N, 11·7; F, 8·0%). The compound was readily soluble in all ordinary organic solvents in the cold, but only slightly soluble in water.

Dipiperidinofluorophosphine Oxide.—This was prepared as above from piperidine (17 g., 0·2 mol.) and phosphorus oxydichlorofluoride (6·85 g., 0·05 mol.) each dissolved in dry ether (75 c.c.). The piperidine hydrochloride was filtered off, and the filtrate dried (Na_2SO_4). After distillation of the ether, the residual oil was fractionated at 0·3 mm. in a current of nitrogen. After unchanged piperidine had distilled, the main fraction came over at 145°/0·3 mm.; yield 5 g. (43%). On standing, a small quantity of piperidine hydrochloride separated. After this had been removed, the residual oil was redistilled. The *oxide* was chlorine-free and contained phosphorus and fluorine (Found: N, 12·2. $C_{10}H_{20}ON_2FP$ requires N, 12·0%).

Di-(N-methylanilino)fluorophosphine Oxide.—This was obtained from phosphorus oxydichlorofluoride

(16 g.) and methylaniline (50 g., 4 mols.) both in dry benzene (50 c.c.), with ice-cooling. After standing overnight, the methylaniline hydrochloride was filtered off, and the benzene filtrate evaporated under reduced pressure. The residual viscous oil was distilled: a small amount of unchanged methylaniline was recovered, and then the fraction boiling at 165—175°/0·1 mm. was collected (19 g., 60%). The *oxide*, which contained traces of ionic chloride, was further purified by washing it with cold water, separating it, drying it (Na_2SO_4), and redistillation; b. p. 163—165°/0·08 mm. (Found: N, 10·4. $C_{14}H_{16}ON_2FP$ requires N, 10·08%).

Stability of Bisdimethylaminofluorophosphine Oxide.—(a) *Water.* The compound dissolved readily in water, giving an almost neutral solution which did not undergo any detectable change in 6 hours. Even after longer periods but little change took place.

(b) *Hydrolysis by hot* N-*sodium hydroxide.* The compound (1 g.) was gently boiled under reflux with 50 ml. of N-alkali for 30 minutes. After cooling, the product and washings were titrated with N-sulphuric acid (phenolphthalein) and required 37·1 ml. Thus 1 g. of compound = 12·9 c.c. of N-alkali. The reaction $POF(NMe_2)_2 + 2NaOH = PO(NMe_2)_2{\cdot}ONa + H_2O + NaF$ requires 13·0 c.c.

(c) *Hydrolysis by* 0·518N-*sodium hydroxide at* 15°. The compound (8·08 g.) was dissolved in 210 ml. of the alkali, and 25 ml. of the mixture were titrated by standard acid at intervals. The degree of hydrolysis thus found was as follows:

Time, mins.	7	14·5	29	65	131	259	380	500
Hydrolysis, %	8·9	9·6	9·7	12·2	15·7	22·6	25·4	29·9

Dimethylaminosulphonyl Chloride (cf. Behrend, *Annalen*, 1884, **222**, 119).—A mixture of dimethylamine hydrochloride (61·2 g., 0·75 mol.) and sulphuryl chloride (67·5 g., 0·5 mol.) was heated under reflux on a water-bath. During the first 2 hours' heating a further quantity of sulphuryl chloride (84·4 g., 0·625 mol.) was slowly added. The mixture was then heated under reflux for a further hour. After cooling, the mixture was poured into water (75 c.c.), extracted with ether, washed with aqueous sodium carbonate solution, and dried (Na_2SO_4). After distillation of the ether, the residue distilled at 72—73°/13 mm.; yield, 60·7 g. (56·4%) (Found: N, 9·40. Calc. for $C_2H_6O_2NClS$: N, 9·76%).

Dimethylaminosulphonyl Fluoride.—A mixture of dimethylaminosulphonyl chloride (43·1 g., 0·3 mol.), dry antimony trifluoride (35·8 g., 0·2 mol.), and antimony pentachloride (2 c.c.) was refluxed in dry benzene (40 c.c.) for 1½ hours, with frequent shaking. After cooling and filtering, the benzene was distilled off, and the residual liquid distilled under reduced pressure. The fraction of b. p. 48—50°/17 mm. was collected (29·8 g., 78·2%), and a black residue was left. On redistillation, most of the liquid came over at 148—150°/760 mm. without decomposition. The *fluoride* was free from chlorine (Found: N, 10·6; S, 25·7. $C_2H_6O_2NFS$ requires N, 11·0; S, 25·2%).

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