136. *Esters containing Phosphorus. Part VIII. Structural Requirements for High Toxicity and Miotic Action of Esters of Fluorophosphonic Acid.*

By H. G. Cook, B. C. Saunders, and F. E. Smith.

An account is given of the synthesis and physiological examination of certain hitherto-undescribed substituted-alkyl esters of fluorophosphonic acid. The results obtained, taken in conjunction with observations made in previous parts of this series, lead to certain general conclusions regarding the structural requirements necessary to produce high toxicity and miotic action.

In Parts IV and VI (*J.*, 1948, 695, 1010) we recorded that the toxicity and miotic activity of di*iso*propyl fluorophosphonate (I) were far greater than that of di-*n*-propyl fluorophosphonate. It was also shown that the toxicity of di*cyclo*hexyl fluorophosphonate was of a very high order. In our Report No. 6 on Fluorophosphonates to the Ministry of Supply (McCombie and Saunders, Sept. 30, 1942) we reported the preparation of *di*-sec.-*butyl fluorophosphonate* (II) by the " hydrogen phosphite method " of Saunders and Stacey (see Part IV, *loc. cit.*). The compound was found to be very toxic and to produce severe miosis in man and animals. The symptoms displayed during and after exposure were identical with those produced by di*iso*propyl fluorophosphonate. The L.C. 50 for di-*sec.*-butyl fluorophosphonate for mice for deaths within 2 hours was 0·6 mg./l., and that for deaths within 48 hours was 0·54 mg./l.

Four human observers were exposed to a concentration of 1 part in 10^6 for 5 minutes. A tightness across the chest was noticed, but three of them were of the opinion that it was perhaps not enough to call for the use of a respirator.* Some five minutes after they had left the chamber, miosis set in, and became intense and caused severe incapacitation which lasted for 5 days. One observer suffered from sickness and diarrhœa in addition to the miotic effect.

We then examined the preparation of the compound from the technical standpoint, and found that it could be prepared by a " one-stage " process from phosphorus trichloride and *sec.*-butyl alcohol in a 72% yield.

$$PCl_3 + 3CHMeEt{\cdot}OH \longrightarrow P(OBu^s)_3 \xrightarrow{HCl} P(OBu^s)_2(OH) + Bu^sCl$$

$$P(OBu^s)_2(OH) \xrightarrow{Cl_2} POCl(OBu^s)_2 \xrightarrow{NaF} POF(OBu^s)_2$$

We had previously stated (Report to Ministry of Supply, Dec. 18, 1941) that *di*-n-*butyl fluorophosphonate* (prepared at that time from silver fluorophosphonate and *n*-butyl bromide) was a compound of low toxicity and produced a negligible miotic effect. It seemed of interest then to determine whether the branching of the chain adjacent to the oxygen atom was a necessary requirement for high toxicity or whether a branching at the end of the chain would do equally well. Accordingly di*iso*amyl fluorophosphonate (III) was prepared by the hydrogen

$POF(O{\cdot}CHMe_2)_2$	$POF(O{\cdot}CHMeEt)_2$	$POF(O{\cdot}\overset{1}{C}H_2{\cdot}CH_2{\cdot}CHMe_2)_2$	$POF(O{\cdot}\overset{1}{C}HMe{\cdot}CH_2{\cdot}CHMe_2)_2$
(I.)	(II.)	(III.)	(IV.)

phosphite method and shown to be almost non-toxic and devoid of miotic properties. A most striking result was obtained on examining the compound derived by branching the chain in (III) by a methyl group on carbon atom 1. This new compound, *di*-(1 : 3-*dimethyl*-n-*butyl*) *fluorophosphonate* (IV), was found to be very toxic and to possess strong miotic action. A 10-minute exposure to a concentration of 1·2 mg./l. killed 3/3 rats, 0/4 guinea-pigs, and 10/10 mice.

Di-(1-*carbethoxyethyl*) *fluorophosphonate* (V) was readily produced by the action of sodium fluoride on the corresponding chlorophosphonate obtained from di-(1-carbethoxyethyl) hydrogen phosphite which in turn was obtained by the action of phosphorus trichloride on ethyl lactate (Part II, *J.*, 1945, 873). Although (V) contained secondary groupings, it was found to be non-toxic and to produce only slight miosis in the pupils of the eyes of rabbits and guinea-pigs.

In view of the high toxicity and very pronounced miotic effect of di*iso*propyl fluorophosphonate, *di*-(1 : 3-*dichloroisopropyl*) *fluorophosphonate* (VI) was of special interest. It was prepared from 1 : 3-dichlorohydrin and phosphorus trichloride. It did not have any appreciable miotic effect and the toxicity was of a low order. *Di*-(1-*ethylpropyl*) *fluorophosphonate* (VII),

$POF(O{\cdot}CHMe{\cdot}CO_2Et)_2$	$POF[O{\cdot}CH(CH_2Cl)_2]_2$	$POF(O{\cdot}CHEt_2)_2$	$P(OH)(O{\cdot}CH_2{\cdot}CH_2Cl)_2$
(V.)	(VI.)	(VII.)	(VIII.)

prepared from phosphorus trichloride and the corresponding alcohol, caused constriction of the pupils of the eyes of rabbits and guinea-pigs at a concentration of 1 : 10,000 (1·07 mg./l). The material (b. p. 98°/2 mm.) formed a fine fog on atomisation. In spite of the secondary groupings the toxicity was not of a high order and only 13/23 of a batch of small animals died when exposed to the above concentration. Thus it becomes apparent that there is a falling off of toxicity

* Negligible sensory irritation was caused by di*iso*propyl fluorophosphonate at a concentration of 1 part in 10^6. This, coupled with the fact that the odour was practically undetectable, means that sufficient warning is not usually given at this concentration to suggest the use of respirators. Exposures at this concentration caused severe miosis which persisted for several days and caused considerable incapacitation (Report No. 12 by McCombie and Saunders to Ministry of Supply, Aug. 4, 1943).

as methyl groups are replaced by ethyl groups, the potencies of compounds of this class being in the order (I) >(II) >(VII).

In Part VI (*loc. cit.*) we described the preparation of di-(2-chloroethyl) fluorophosphonate by the action of phosphorus oxydichlorofluoride on ethylene chlorohydrin. The compound can also be prepared by the fluorination of *di-(2-chloroethyl) chlorophosphonate*, prepared from *di-(2-chloroethyl) hydrogen phosphite* (VIII), obtained by the action of phosphorus trichloride on ethylene chlorohydrin. This partial fluorination was effected by means of sodium fluoride, although the yield was not high. The chlorine atoms of the 2-chloroethyl groups were not affected by this procedure, a fact which falls into line with the observation of Saunders and Stacey (to be published) that ethylene chlorohydrin is not fluorinated by sodium fluoride, but only by potassium fluoride under pressure in a rotating autoclave (cf. McCombie and Saunders, *Nature*, **1946**, **158**, 382).

Discussion.—From the investigations of the compounds described in this and in previous papers of this series, it is evident that the miotic effect and toxicity of the phosphonate molecule $POX(O{\cdot}CHR_1R_2)_2$ depend upon the nature of X, R_1, and R_2. It seems to be essential in this type of molecule that X should be fluorine, for miotic effect is absent and toxicity is of a low order if X = H, Et, OEt, $O{\cdot}CH_2{\cdot}CH_2Cl$, $O{\cdot}CH_2{\cdot}CH_2F$, Cl, NH_2, NHMe, NHPh, CH_2F, $CH_2{\cdot}CH_2F$, CN, SCN, or morpholino.

In the fluorophosphonate molecule (X = F), the pupil-constricting action and toxicity are increased by a secondary grouping (*e.g.*, $R_1 = R_2 = Me$; $R_1 = Me$, $R_2 = Et$; R_1R_2 = *cyclo*-hexyl; $R_1 = Me$, $R_2 = CH_2{\cdot}CHMe_2$). Furthermore, it appears that for non-cyclic compounds both R_1 and R_2 must, for the best results, be unsubstituted hydrocarbon radicals (*e.g.*, if $R_1 = Me$ and $R_2 = CO_2Et$ the compound is scarcely toxic). Similarly, if $R = R_2 = CH_2Cl$, both the miotic effect and toxicity are of a low order. Among unsubstituted (non-cyclic) secondary radicals, the best results seem to be obtained when one group, at least, is Me, for, *e.g.*, if $R_1 = R_2 = Et$, the toxicity is considerably reduced.

Turning again to primary phosphonates ($R_2 = H$), if R is substituted [*e.g.*, di-(2-chloroethyl) fluorophosphonate], the toxicity and miotic effect are greatly inferior to those shown by the unsubstituted diethyl fluorophosphonate. Toxicity is also very low in the aromatic series; for example, diphenyl fluorophosphonate is non-toxic and devoid of miotic properties. Similar remarks apply to sulphur analogues, *e.g.*, diethyl fluorodithiophosphonate, $POF(SEt)_2$.

Experimental.*

Di-sec.-*butyl Hydrogen Phosphite.*—Phosphorus trichloride (137·5 g.), dissolved in dry ether (150 c.c.), was slowly run into *sec.*-butyl alcohol (222 g.) also dissolved in dry ether (150 c.c.). Dry air was passed through during the addition to remove as much hydrogen chloride as possible. Dry ammonia was then passed into the mixture to remove excess of hydrogen chloride as ammonium chloride, which was filtered off, this treatment being repeated if necessary. The ether was distilled off from the filtrate, and the *ester* distilled at 111°/15 mm.; yield 156 g. (70%) (Found: C, 49·1; H, 9·8. $C_8H_{19}O_3P$ requires C, 49·5; H, 9·8%).

Di-sec.-*butyl Chlorophosphonate.*—The hydrogen phosphite (60 g.) was chlorinated at 0°, and the excess of hydrogen chloride removed by a stream of dry air. Powdered lead carbonate was added, and the mixture kept agitated by the bubbles of air. It was usually possible to ascertain when sufficient carbonate had been added by the fact that the lead salts tended to settle easily and leave a clear supernatant liquid. The lead chloride and carbonate were then filtered off, and the *chlorophosphonate* distilled at 92—94°/0·8 mm.; yield 42 g. (66%) (Found: Cl, 15·78, 15·72. $C_8H_{18}O_3ClP$ requires Cl, 15·53%).

Di-sec.-*butyl Fluorophosphonate.*—Fluorination without a solvent was not very successful. The best of a variety of conditions examined were as follows: The chlorophosphonate (57 g.) was dissolved in dry benzene (30 c.c.), sodium fluoride (16 g.) added, and the mixture very gently heated under reflux for 2 hours. The product was filtered and treated with lead carbonate to remove any acid (which would cause decomposition during the subsequent distillation), refiltered, and the residue distilled. Practically the whole of the *fluorophosphonate* came over at 62—64°/0·8 mm.; yield 39·5 g. (68%) (Found: F, 8·7. $C_8H_{18}O_3FP$ requires F, 8·9%).

Preparation of sec.-*Butyl Fluorophosphonate by the " One-stage " Process.*—*sec.*-Butyl alcohol (222 g.) was dissolved in approximately half its volume of carbon tetrachloride, and phosphorus trichloride (137·5 g.), dissolved in carbon tetrachloride (an equal volume), was slowly run in, the temperature of the mixture being kept down to about 10—12°. Air was drawn through the mixture during the reaction and for about 5 hours subsequently, in order to remove as much hydrogen chloride as possible (it was found, however, not absolutely essential to remove the last traces of hydrogen chloride at this stage). More carbon tetrachloride was added to the hydrogen phosphite solution thus produced, and chlorine passed in until a faint yellow coloration persisted. Air was then drawn through the product for 4 hours to remove hydrogen chloride. The solution of the chlorophosphonate was then transferred to a 750-c.c. round-bottomed flask fitted with a stirrer and reflux condenser. A small quantity of carbon tetrachloride (to make up loss in bulk) and sodium fluoride (50 g., 1·2 mols.) were added, and the mixture

* Several of the preparations here described are covered by B.P. 601,210, Sept. 15th, 1943.

gently heated to initiate the reaction, which then proceeded for a short time without application of heat. After the reaction had subsided, the mixture was heated so that the total time of the reaction did not exceed 45 minutes. The product was then cooled, shaken with dry lead carbonate, left for some time, and then filtered (after adding kieselguhr, if necessary to hasten filtration). The carbon tetrachloride was then distilled off from the filtrate, and the residue boiled at 64·5°/0·15 mm.; yield 132 g. (72%) (Found : F, 8·9. Calc. for $C_8H_{18}O_3FP$: F, 8·9%).

Di-n-*butyl Fluorophosphonate.*—Disilver fluorophosphonate (21·0 g.) and *n*-butyl iodide (24·4 g.) in toluene (50 c.c.) were heated under reflux for about 2 hours. After cooling, the silver salts were filtered off and washed with toluene. Toluene was distilled from the filtrate, and the residue fractionated. The *di*-n-*butyl fluorophosphonate*, b. p. 128°/30 mm., was collected; yield 4 g. (Found : C, 45·1; H, 8·1. $C_8H_{18}O_3FP$ requires C, 45·2; H, 8·5%).

Di-n-*amyl Fluorophosphonate.*—Prepared in the usual way from the disilver salt and *n*-amyl iodide, this *ester* had b. p. 143—144°/30 mm. (Found : C, 49·5; H, 9·1. $C_{10}H_{22}O_3FP$ requires C, 50·0; H, 9·16%).

*Di*isoamyl *Fluorophosphonate.*—The chlorophosphonate (77·0 g., 0·3 mol.) was added to sodium fluoride (37·8 g., 0·9 mol.) suspended in dry toluene, and the mixture gently heated under reflux with stirring for 2 hours. No fuming occurred with careful heating. After filtering and distilling off the toluene, the residue distilled at 137—147°/27 mm. On careful refractionation *di*isoamyl *fluorophosphonate* boiled at 135—138°/23 mm.; yield 43·0 g. (Found : F, 8·03, 7·97. $C_{10}H_{22}O_3FP$ requires F, 7·92%). The identity of the compound was further established by its preparation from disilver fluorophosphonate (cf. Part IV, *loc. cit.*). This salt (21·0 g.), *iso*amyl iodide, and dry ether (50 c.c.) were heated together under reflux for 1—2 hours. After filtration (and washing of the precipitate with ether), the ether was distilled off and the fraction of b. p. 142°/28 mm. was collected; yield 3 g. (Found : C, 49·2; H, 9·0%).

Di-(1 : 3-*dimethyl*-n-*butyl*) *Fluorophosphonate.*—The chlorophosphonate (20 g.) was heated in toluene with sodium fluoride (5 g.) for 2 hours. After separation of the sodium salts, and distillation of the toluene, the residue was fractionated, and the fraction of b. p. 94—97°/0·9 mm. collected. This on refractionation gave *di*-(1 : 3-*dimethyl*-n-*butyl*) *fluorophosphonate*, b. p. 102—103°/2·7 mm.; yield 15 g. (Found : F, 7·11. $C_{12}H_{26}O_3FP$ requires F, 7·09%). This ester contained phosphorus but no chlorine.

Di-(1-*carbethoxyethyl*) *Fluorophosphonate.*—The chlorophosphonate (72·0 g.) was heated in benzene for 30 minutes with silver fluoride (43 g.). The silver salts were then filtered off, the benzene distilled, and the residue fractionated. The fluoro-compound had b. p. 127—130°/0·9 mm.; yield 36·8 g. (54%). The remainder consisted of unchanged chlorophosphonate. The *fluorophosphonate* was redistilled at 126—128°/0·6 mm. (Found : F, 6·2. $C_{10}H_{18}O_7FP$ requires F, 6·33%); it contained phosphorus and was free from chlorine.

Di-(1 : 3-*dichloro*iso*propyl*) *Fluorophosphonate.*—The chlorophosphonate (20 g.) was fluorinated by heating in benzene with sodium fluoride (5 g.) for 2 hours. After distillation of the benzene, the residue boiled at 165—168°/1 mm. On redistillation, the *fluorophosphonate*, b. p. 163—165°/0·7 mm., was collected (Found : C, 21·8; H, 2·9; F, 5·74. $C_6H_{10}O_3Cl_4FP$ requires C, 22·35; H, 3·1; F, 5·90%); it may not have been quite pure as it decomposed slowly on standing and etched the tube slightly.

Di-(1-*ethyl*-n-*propyl*) *Fluorophosphonate.*—The crude chlorophosphonate (49 g.) was heated in benzene solution with sodium fluoride (10 g.) for 2 hours. After separation of the sodium salts, the benzene was distilled off (water-pump) and the residue distilled at 99—101°/2·1 mm.; yield 16 g. The liquid was redistilled and the *fluorophosphonate*, b. p. 97—98°/2·0 mm., collected; it contained phosphorus but was chlorine-free (Found : F, 7·81, 7·78. $C_{10}H_{22}O_3FP$ requires F, 7·92%).

Di-2-*chloroethyl Hydrogen Phosphite.*—The hydrogen phosphite–ammonia method (see Part I, *J.*, 1945, 380) was used, with phosphorus trichloride (9·06 g.) and ethylene chlorohydrin (160 g.). After distillation of the ether, the *hydrogen phosphite* had b. p. 129°/0·6 mm.; yield 100 g. (72%) (Found : Cl, 34·5. $C_4H_9O_3Cl_2P$ requires Cl, 34·3%).

Di-2-*chloroethyl Chlorophosphonate.*—The hydrogen phosphite was saturated with chlorine in the usual way; the excess of chlorine was then removed by a current of air, and the hydrogen chloride by treatment with lead carbonate. After filtration, the *product* boiled at 139°/2·3 mm. and contained phosphorus; yield *ca.* 50% [Found : Cl (Stepanow), 45·46. $C_4H_8O_3Cl_3P$ requires Cl, 44·21%].

Di-2-*chloroethyl Fluorophosphonate.*—The chlorophosphonate (24 g.) and sodium fluoride (12·6 g.) were heated together under reflux for 20 minutes. The product was extracted with dry ether, and the ethereal solution dried (Na_2SO_4). After distillation of the ether, the product distilled at 180—200°/30 mm. On careful refractionation a liquid of b. p. 142°/15 mm. was obtained; it contained both phosphorus and fluorine (Found : Cl, 31·99. Calc. for $C_4H_8O_3Cl_2FP$: Cl, 31·56%). The b. p. of the liquid obtained by the action of phosphorus oxydichlorofluoride on ethylene chlorohydrin was 142—144°/15 mm.

We thank the Chief Scientist of the Ministry of Supply for permission to publish this work.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, June 16th,* 1948.]