**139.** *Esters containing Phosphorus.   Part V.   Esters of Substituted Phosphonic and Phosphonous Acids.*

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A variety of diethyl esters of substituted phosphonic acids (I) has been prepared.   Unless X = F, the compounds described are relatively non-toxic by inhalation and are devoid of miotic action.   If the fluorine atom is separated from the phosphorus atom by the CH_2 group, the toxic properties of the compound are greatly diminished.   *Diethyl 2-fluoroethylphosphonate* has been prepared by the Arbusow rearrangement and by an independent method.

The preparation of a new type of ester, *viz.*, *ethyl difluorophosphonite*, is described.

Bistriethyl-lead fluorophosphonate possesses powerful sternutatory properties.

IN Part IV (preceding paper) it was reported that diethyl fluorophosphonate (I, X = F) was toxic by inhalation and produced powerful miosis. The present communication is concerned mainly with a discussion of phosphonic esters of type (I) in which X is varied. Diethyl hydrogen phosphite and diethyl chlorophosphonate (I; X = Cl), (Part I, McCombie, Saunders, and Stacey, *J.*, 1945, 380) were found to be non-toxic by inhalation and did not produce any miotic effect. Similar remarks apply to diethyl hydrogen phosphate (X = OH), diethyl ethylphosphonate (X = Et), and triethyl phosphate (X = OEt).

$$O=P{\overset{\displaystyle OEt}{\underset{\displaystyle X}{\overline{OEt}}}}$$
(I.)
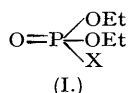
The investigation was then extended to a wide range of new compounds. These compounds were originally described in reports on fluorophosphonates to the Ministry of Supply, Dec. 18th, 1941, onwards.

Potassium thiocyanate reacted readily with diethyl chlorophosphonate giving *diethyl thiocyanatophosphonate* :

$$Et_2PO_3Cl + KSCN = Et_2PO_3SCN + KCl$$
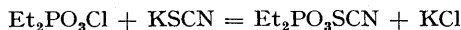
Diethyl cyanophosphonate (II) was not obtained in any appreciable yield by the action of potassium cyanide on the chlorophosphonate, but was prepared by the novel reaction (*A*) :

$$P(OEt)_3 + CNI = O{:}P(CN)(OEt)_2 + EtI \quad . \quad . \quad . \quad . \quad (A)$$
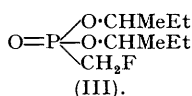(II.)
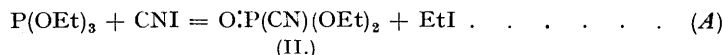
Both the thiocyanatophosphonate and the cyanophosphonate were relatively non-toxic. For example, a concentration of 1 mg./l. of (II) killed 1 out of a batch of 23 small animals. The L.D. 50 for intravenous injection into rabbits was about 4 mg./kg. The symptoms appeared to be purely asphyxial (typical of cyanide rather than of fluorophosphonate). The L.D. 50 for subcutaneous injection into mice was 25 mg./kg.

Gaseous ammonia reacted with the chlorophosphonate at 0° producing solid diethyl amino-phosphonate in accordance with the equation :

$$Et_2PO_3Cl + 2NH_3 = Et_2PO_3NH_2 + NH_4Cl$$
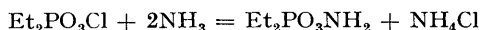
In a similar manner gaseous methylamine gave diethyl methylaminophosphonate, Et_2PO_3NHMe, which was, however, a liquid. The compound could not be acetylated with a mixture of acetic acid and acetic anhydride, and it did not react with either p-toluenesulphonyl chloride or ethylene oxide. Diethyl anilinophosphonate has previously been described (Part I, *loc. cit.*). *Diethyl morpholinophosphonate* has now been prepared by a similar method. The aminophosphonate, the methylaminophosphonate, and the anilinophosphonate were non-toxic and devoid of miotic properties.

It was important to determine whether the fluorine atom must be attached directly to the phosphorus atom in order to produce " fluorophosphonate-like " activity. For this purpose we treated the highly toxic di-*sec.*-butyl fluorophosphonate (to be described later in this series) with diazomethane and obtained a compound which was undoubtedly *di-sec.-butyl fluoromethylphosphonate* (III). Unlike the parent fluorophosphonate, the fluoromethylphosphonate was only slightly toxic and produced negligible miosis. It may be mentioned here that thionyl chloride and carbonyl chloride were converted by means of diazomethane into *bis(chloromethyl) sulphoxide* and *s*-dichloroacetone respectively.

$$O=P{\overset{\displaystyle O{\cdot}CHMeEt}{\underset{\displaystyle CH_2F}{\overline{O{\cdot}CHMeEt}}}}$$
(III).

The next stage was to prepare a compound with a second methylene group between the fluorine and the phosphorus atom. *Diethyl 2-fluoroethylphosphonate* (IV) was prepared by the action of bromofluoroethane on sodium diethyl phosphite. This reaction was first recorded in " Summary of Work carried out for the Ministry of Supply during the period Jan. 1st—March 1st, 1945 " and was the first recorded example of the 2-fluoroethyl group attached to phosphorus. Compound (IV) is of special interest in that it showed neither the toxic properties of the fluorophosphonates nor to any appreciable extent the toxic action associated with the " fluoroacetates ". This may mean that the animal body is probably unable to break the P–C link easily, as shown in equation (*B*), otherwise the compound would have produced the convulsions typical of fluoroethyl alcohol when inhaled by animals (cf. McCombie and Saunders, *Nature*, 1946, **158**, 382).

$$(EtO)_2PO{\cdot}CH_2{\cdot}CH_2F + H_2O = (EtO)_2P{\cdot}OH + HO{\cdot}CH_2{\cdot}CH_2F \quad . \quad . \quad . \quad (B)$$
(IV.)
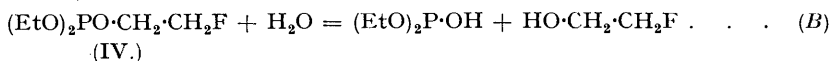
Diethyl benzylphosphonate was prepared in a similar manner using benzyl chloride in place of bromofluoroethane. When p-toluenesulphonyl chloride and naphthalene-2-sulphonyl chloride

were allowed to react with sodium diethyl phosphite, the corresponding disulphones were obtained in small yield.

Arbusow (*Chem. Zent.*, 1906, II, 1640) demonstrated the ready " isomerisation " of trimethyl phosphite to dimethyl methylphosphonate by heating it with methyl iodide.

This method was then extended, and diethyl 2-fluoroethylphosphonate (IV) and diethyl benzylphosphonate were readily prepared by heating triethyl phosphite with bromofluoroethane and benzyl chloride respectively :

$$P(OEt)_3 + Br \cdot CH_2 \cdot CH_2F = O \vdots P(OEt)_2 \cdot CH_2 \cdot CH_2F + C_2H_5Br \quad . \quad . \quad . \quad (C)$$
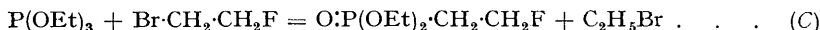
Reaction (C) depended upon the difference in reactivity between the bromine and the fluorine atom in bromofluoroethane. Nevertheless some tetraethyl ethylene- 1 : 2-diphosphonate, $(EtO)_2PO \cdot CH_2 \cdot CH_2 \cdot OP(OEt)_2$, was also produced in this reaction (C) and in reaction (A). The diphosphonate was non-toxic.

The 2-chloroethyl group, which is often an effective toxophore, was then attached to phosphorus through oxygen. No reaction appeared to take place between ethylene chlorohydrin and diethyl chlorophosphonate in the absence of a tertiary base. In the presence of pyridine, however, which removed the hydrogen chloride formed, a smooth reaction took place at 0° with the formation of *diethyl 2-chloroethyl phosphate*, $O \vdots P(OEt)_2 \cdot O \cdot CH_2 \cdot CH_2Cl$ (V.), in good yield. The compound was non-toxic and devoid of miotic action. The fluorine analogue of (V), *diethyl 2-fluoroethyl phosphate*, was prepared in an analogous manner from 2-fluoroethyl alcohol. It proved to be non-toxic by injection.

Ethyl difluorophosphonite (VI) was obtained by the action of sodium fluoride on the corresponding dichlorophosphonite; unlike diethyl fluorophosphonate, it was rapidly attacked by cold water. Alcohol converted (VI) into the fluorophosphonate :

$$O \vdots PF_2 \cdot OEt + EtOH = O \vdots PF(OEt)_2 + HF$$
$$(VI.)$$
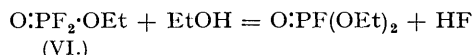
When mice, rats, rabbits, and guinea-pigs were exposed to a concentration of 0·88 mg./l. (*i.e.*, 1 in 5,000) of ethyl difluorophosphonite for 10 minutes there was irritation of the eyes and nose with nasal discharge, lachrymation, and salivation. Four minutes after exposure the mice and some of the rats developed dyspnœa, but all the animals recovered. When animals were exposed to a corresponding concentration of ethyl dichlorophosphonite (1·46 mg./l.; 1 in 5,000) similar symptoms were observed and no deaths resulted.

It has been shown (McCombie and Saunders, *Nature*, 1947, **159**, 491) that triethyl-lead salts are, in general, sternutators. Accordingly *bistriethyl-lead fluorophosphonate*, $O \vdots PF(O \cdot PbEt_3)_2$, was prepared in an attempt to combine sternutatory properties and miotic action. A solid with powerful sternutatory properties, it produced an irrespirable atmosphere at a concentration of 1 part in 10^6. At 1 part in 10^8 the sternutatory properties were still marked. No miotic effect was produced in human beings at a concentration of 1 part in 10^6. Tests at higher concentrations were not carried out on human beings owing to the overwhelming sternutatory effects.

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

Diethyl Thiocyanatophosphonate.—Diethyl chlorophosphonate (34·5 g., 0·2 mol.) was gently warmed under reflux with dry, finely-powdered, potassium thiocyanate (24·3 g., 0·25 mol.). A reaction soon began and a finely-divided white precipitate gradually separated. Heat was applied to maintain very gentle ebullition for 15 minutes. After cooling, the solid was filtered off and thoroughly drained, and the filtrate was distilled under reduced pressure. Two fractions were collected : (i) b. p. 40°/13 mm.; (ii) b. p. 112—116°/13 mm. Fraction (i) was redistilled and gave 5·3 g. of the *thiocyanatophosphonate* (Found : S, 16·9; P, 15·6. $C_5H_{10}O_3NSP$ requires S, 16·4; P, 15·9%).

Diethyl Cyanophosphonate.—Triethyl phosphite (41·5 g., 0·25 mol.) was dissolved in dry ether (500 c.c.) and to this solution iodine cyanide (38·75 g., 0·25 mol.) dissolved in dry ether (100 c.c.) was slowly added. At first there was a vigorous reaction, but no free iodine was produced until the addition was complete; a brown coloration then slowly developed. Ether and other volatile fractions were removed on the water pump at ordinary temperatures during 1½ hours. Almost the entire residue then distilled at 93—98°/14 mm. This was redistilled, and the *cyanophosphonate*, b. p. 95—97°/14 mm., collected. Yield, 18·7 g. (46%). B. p. 90—91°/11 mm. (Found : CN, 15·3. $C_5H_{10}O_3NP$ requires CN, 15·9%).

Diethyl Aminophosphonate.—Diethyl chlorophosphonate (20 g.) was dissolved in dry ether (250 c.c.), cooled in ice, and a stream of dry ammonia passed into the solution until no more solid was precipitated. After removal of ammonium chloride (6·2 g., 100%), the ether was distilled and the residue solidified on standing. Recrystallisation was difficult, and therefore the solid was purified by distillation at 131—138°/0·2 mm.; the white crystalline product (m. p. 54·5°, yield, 14 g.) contained N and P, and was Cl-free (Found : C, 31·6; H, 8·46. Calc. for $C_4H_{12}O_3NP$: C, 31·4; H, 7·9%). This compound was first described in Report to the Ministry of Supply Aug. 8th, 1942. Later Atherton, Openshaw, and

Todd (*J.*, 1945, 662) prepared it by a different method. Their description of the compound agrees with ours, and differs from that given by Pitschimuka (*J. pr. Chem.*, 1911, **84**, 753).

Diethyl Methylaminophosphonate.—Diethyl chlorophosphonate (20 g.) was dissolved in dry ether (200 c.c.), and dry methylamine was passed into the solution which was cooled in ice–water. A white precipitate was produced and heat evolved. When no more solid separated, the stream of methylamine was stopped and the mixture filtered. The ether was distilled from the filtrate and the residue fractionated under reduced pressure. The fraction (16·3 g., 84%), b. p. 130°/15 mm., contained P and was Cl-free (Found : N, 8·7. Calc. for $C_5H_{14}O_3NP$: N, 8·4%). We had previously prepared this compound from the unstable iodophosphonate (Part III, *J.*, 1945, 921).

Diethyl Morpholinophosphonate.—To a solution of diethyl chlorophosphonate (4·3 g., 0·025 mol.) in ether (25 c.c.), cooled in ice–water, morpholine (4·4 g., 0·05 mol.) was added drop by drop. When the addition was complete, more ether (15 c.c.) was added and the whole gently warmed under reflux. The solid which had separated was filtered off, ether removed from the filtrate, and the residue distilled. The *morpholinophosphonate* had b. p. 137°/11 mm. Yield, 4·4 g. (79%) (Found : C, 43·55; H, 8·19; N, 6·22. $C_8H_{18}O_4NP$ requires C, 43·04; H, 8·13; N, 6·28%).

Reaction between Diazomethane and Carbonyl Chloride.—Diazomethane was prepared from nitrosomethylurea (20·6 g.), ether (200 c.c.), and sodium hydroxide (60 c.c. of 50% aqueous solution) (*Org. Synth.*, X), and dissolved in ether at 0°. The ethereal solution was dried (KOH) for 10 minutes and poured from the drying-agent. A slow stream of carbonyl chloride was passed into the cooled solution for 1 hour, the temperature being kept below 5°. After removal of the ether, the residue distilled at 173°. The liquid (3·5 g.) solidified to a white crystalline mass, m. p. and mixed m. p. with authentic dichloroacetone, 44° (Found : C, 28·6; H, 3·18. Calc. for $C_3H_4OCl_2$: C, 28·3; H, 3·15%).

Reaction between Diazomethane and Thionyl Chloride.—Diazomethane (from 41·0 g. of nitrosomethylurea) in ether, dried as above, was cooled to 0° and thionyl chloride (10 g.) was added slowly, the temperature being kept below 5°. After removal of the ether, the residue was distilled and two fractions were collected : (i) b. p. 45°/0·7 mm., (3 g.); (ii) b. p. 55°/0·7 mm., (5 g.). Fraction (ii) gave a solid, m. p. 39° (Found : C, 16·4; H, 2·77. $C_2H_4OCl_2S$ requires C, 16·3; H, 2·74%).

Di-sec.-butyl Fluoromethylphosphonate.—Diazomethane (25% excess) in ethereal solution was added slowly to di-*sec*.-butyl fluorophosphonate (10 g.) dissolved in dry ether (50 c.c.) cooled in ice. The colour of the diazomethane was gradually discharged, and the reaction was at no time vigorous. The mixture was left in ice for 3 hours, and then the ether was distilled off. On distillation of the residue, a fraction (5 g.), b. p. 96—100°/3 mm., was obtained (Found : F, 13·46, 13·5. $C_9H_{20}O_3FP$ requires F, 13·7%).

Diethyl 2-Fluoroethylphosphonate.—Sodium diethyl phosphite was prepared from sodium methoxide (32·4 g., 0·6 mol.) and diethyl hydrogen phosphite (82·8 g., 0·6 mol.) in dry ether (700 c.c.). Bromofluoroethane (80·0 g., 0·64 mol.) was then added and the whole heated under reflux for 6 hours, during which time a white solid separated. After 8 hours the solid (mainly sodium bromide) was filtered off. The ether was distilled from the filtrate and the mixture distilled under reduced pressure. A fraction (30 g.), b. p. 70—80°/20—11 mm., was collected; the temperature then rose, and a fraction, b. p. 198—201°/11 mm., came over. The lower fraction was redistilled at 74—75°/11 mm. and proved to be the *fluoroethylphosphonate* identical with the compound obtained by the Arbusow rearrangement (below). The higher fraction deposited a very small amount of solid on standing, and was purified by passing it through ½ in. of animal charcoal on a No. 3 sintered plate, and redistilling at 200—202°/14 mm. The product, a colourless liquid, contained P and was halogen-free. It was undoubtedly *tetraethyl ethylene-1 : 2-diphosphonate* (Found : C, 37·1; H, 7·83. $C_{10}H_{24}O_6P_2$ requires C, 39·7; H, 7·95%).

Sodium Diethyl Phosphite.—The sodium diethyl phosphite required in subsequent preparations was prepared as follows. Sodium dust (46 g., 2·0 at.) in dry ether (600 c.c.) was placed in a flask fitted with a reflux condenser, and diethyl hydrogen phosphite (276 g., 2·0 mol.) was added from a dropping-funnel. It was necessary to exercise care during the early stages of the addition because the reaction (an exothermic one) was usually delayed. (If a large quantity of the hydrogen phosphite was added before the reaction started, the mixture would subsequently boil violently with frothing, and the finely-powdered sodium would ignite on exposure to the air.)

During the reaction between sodium diethyl phosphite and an organic halide, the sodium halide often separated in a colloidal condition. It could be coagulated by the addition of about 6 times the original volume of ether, but as this procedure was rather wasteful, the solid was usually filtered off as completely as possible, washed with a small quantity of ether, and the filtrate distilled; it still contained traces of colloidal sodium halide.

Diethyl Benzylphosphonate.—To sodium diethyl phosphite, prepared from diethyl hydrogen phosphite (27·6 g., 0·2 mol.) and sodium (4·6 g., 0·2 at.) in dry ether (200 c.c.), benzyl chloride (25·2 g., 0·2 mol.) was added, and the whole heated under reflux for 4 hours and then worked up as above. After removal of the ether, the residue was fractionated and the *benzylphosphonate*, b. p. 155°/14 mm., collected. Yield, 21 g. (45%) (Found : C, 55·7; H, 7·36; P, 13·55. $C_{11}H_{17}O_3P$ requires C, 57·8; H, 7·46; P, 13·6%).

Reaction between Sodium Diethyl Phosphite and p-Toluenesulphonyl Chloride.—To sodium diethyl phosphite (0·5 mol.) in dry ether (800 c.c.), *p*-toluenesulphonyl chloride (100 g., 1·02 mol.) was added slowly. The reaction, which was vigorous at first, moderated later. After heating under reflux for one hour, the solid (S) formed was filtered off.

After removal of the ether from the filtrate, *p*-toluenesulphonyl chloride (70 g.) separated and was recrystallised from light petroleum; m. p. and mixed m. p. 66—68°.

The solid (S) was washed with hot water (100 c.c.) to remove inorganic salts, and the residue was recrystallised from 90% acetic acid giving colourless needles, m. p. 204°. Yield, 1·8 g. (Found : C, 54·06; H, 4·55; S, 20·8. Calc. for $C_{14}H_{14}O_4S_2$: C, 54·2; H, 4·52; S, 20·64%).

Naphthalene-2-sulphonyl chloride behaved in a similar manner. The disulphone was recrystallised from aqueous acetic acid and then twice from benzene; m. p. 188° (Found : C, 62·5; H, 3·91; S, 16·4. Calc. for $C_{20}H_{14}O_4S_2$: C, 62·8; H, 3·67; S, 16·75%).

Diethyl Ethylphosphonate.—A mixture of triethyl phosphite (33·2 g., 0·2 mol.) and ethyl iodide

(31·2 g., 0·2 mol.) was heated under reflux for 12 hours. After removal of ethyl iodide, the entire product distilled at 90—92°/16 mm. Yield, 31·2 g. (94%).

Diethyl 2-Fluoroethylphosphonate.—Triethyl phosphite (24·9 g.) and bromofluoroethane (18·9 g.) were gently heated under reflux for 1 hour. The product was distilled, and fractions, b. p. 86·5—88°/18 mm. and 203—206°/15 mm., were collected. The first fraction was redistilled at 74—75°/11 mm. The liquid (7·4 g., 17%) contained P (Found : F, 10·8. $C_6H_{14}O_3FP$ requires F, 10·3%). The higher fraction was the diphosphonate.

Diethyl Benzylphosphonate.—Triethyl phosphite (24·9 g.) and benzyl chloride (17·1 g.) were heated under reflux in an oil-bath at 150—160° for 10 hours. The gas evolved was condensed in an ice–hydrochloric acid trap, and identified as ethyl chloride by conversion into tetraethylammonium chloride. The benzylphosphonate (14·8 g., 74%) was collected at 169—171°/25 mm.

Diethyl 2-Chloroethyl Phosphate.—Diethyl chlorophosphonate (86·3 g., 0·5 mol.) was added slowly to a mixture of ethylene chlorohydrin (40·3 g., 0·5 mol.) and pyridine (39·6 g., 0·5 mol.) cooled in ice–water. After the addition, the mixture was left for 1 hour and then the solid which had separated was filtered off and washed with ether. After removal of the ether, the fraction, b. p. 139—148°/17 mm., was collected. On redistillation, the *chloroethyl phosphate* had b. p. 144—145°/18 mm. Yield, 76·7 g. (Found : Cl, 16·20; 16·44. $C_6H_{14}O_4ClP$ requires Cl, 16·3%). (In the determination by the Carius method it was necessary to use at least 3 c.c. of fuming nitric acid per 0·4 g. of ester to prevent the formation of viscous material.)

Diethyl 2-Fluoroethyl Phosphate.—Diethyl chlorophosphonate (43 g.) dissolved in dry ether (25 c.c.) was added slowly to a mixture of fluoroethyl alcohol (16 g.) and dry pyridine (20 c.c.) in dry ether (25 c.c.) cooled in ice–water. After the addition, the mixture was left for 30 minutes and then the pyridine hydrochloride was filtered off. The filtrate was dried (Na_2SO_4), the ether removed, and the residue fractionated and collected at b. p. 123—124°/13 mm. Yield, 30 g. (Found : C, 36·3; H, 6·6; F, 9·5. $C_6H_{14}O_4FP$ requires C, 36·0; H, 7·0; F, 9·5%).

Ethyl Dichlorophosphonite.—Ethyl alcohol (54 g.) was added slowly to phosphorus oxychloride (180 g.) in dry ether (210 c.c.) cooled to 5°. After 2 hours, the product was distilled under reduced pressure; ether, hydrogen chloride, and unchanged alcohol were first removed, and the fraction of b. p. 63°/19 mm. was collected. Yield, 157 g. (83%) (Found : Cl, 44·1. Calc. for $C_2H_5O_2Cl_2P$: Cl, 43·5%).

Ethyl Difluorophosphonite.—Ethyl dichlorophosphonite (53·5 g.) and sodium fluoride (29·3 g.; 10% excess) were mixed in a flask cooled in ice–water. The flask was fitted with a water condenser to the end of which were attached (*a*) a conical flask to act as a trap, (*b*) a liquid-air trap, arranged in series. After about 1 minute a vigorous reaction set in and the gaseous products condensed in the traps. The reaction was completed by warming the mixture for 10 minutes. The crude material (20 g.) in the traps was fractionated, and 12·2 g. of the *difluorophosphonite*, b. p. 85—86°, were collected. The product contained P, was Cl-free, and reacted readily with cold water (Found : F, 29·47. $C_2H_5O_2F_2P$ requires F, 29·23%).

Reaction between Ethyl Alcohol and Ethyl Difluorophosphonite.—Ethyl alcohol (4·6 g.) was added to freshly prepared ethyl difluorophosphonite (6·5 g.), and the mixture left for 2 hours. The reaction was completed by heating on a water-bath for 30 minutes. The product was then distilled under reduced pressure; the distillate on refractionation gave diethyl fluorophosphonate (1·6 g.), b. p. 168—171°.

Bistriethyl-lead Fluorophosphonate.—Silver fluorophosphonate (9·5 g.) suspended in dry benzene (50 c.c.) was added to triethyl-lead chloride (20 g.) also in dry benzene (50 c.c.), and the mixture refluxed for 3 hours, cooled, and filtered. The solid was extracted with boiling ethyl acetate from which a colourless solid (m. p. indef. >260°) separated. Yield, 11 g. The *compound* contained F and P and was soluble in acetone (Found : Pb, 60·59. $C_{12}H_{30}O_3FPPb_2$ requires Pb, 60·36%).