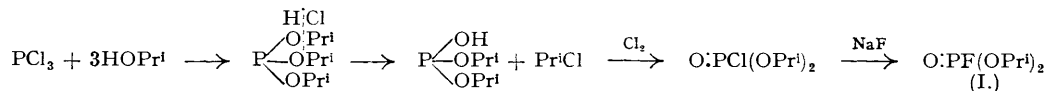


267. Esters Containing Phosphorus. Part X. Radioactive Diisopropyl Fluorophosphonate (D.F.P.).

By B. C. SAUNDERS and T. S. WORTHY.

Radioactive diisopropyl fluorophosphonate has been prepared from phosphorus containing ^{32}P . A description is given of a specially designed apparatus which enables an overall yield of 62% to be obtained.

WE have previously given details of the preparation of diisopropyl fluorophosphonate (I) (McCombie and Saunders, *Nature*, 1946, **157**, 287; Saunders *et al.*, B.P. 601,210; Saunders and Stacey, *J.*, 1948, 695) according to the scheme :



Reference was made in the above papers to the remarkable physiological properties of (I), including its miotic action, clinical applications in connexion with glaucoma and paralytic ileus, and to its powerful anti-cholinesterase activity. Towards cholinesterase it was effective in concentrations as low as 10^{-11} M. In order to throw light on its mode of action with esterases (see Bournsnel and Webb, *Nature*, 1949, **164**, 875) radioactive (I) containing ^{32}P has been prepared (cf. our preliminary announcement, *Nature*, 1949, **163**, 797). The present paper gives a detailed account of its production on what may conveniently be called the "one-gram scale."

Phosphorus containing ^{32}P was obtained from A.E.R.E., Harwell, and small quantities (of the order of 1 g.) were converted into the trichloride. This small-scale conversion presented considerable and unexpected difficulties, the most serious feature being the very ready production of phosphorus pentachloride. [All the reliable descriptions of the preparation of phosphorus trichloride are on a basis of *ca.* 200 g. of phosphorus (cf. *Inorg. Synth.*, **2**, 145).] This tendency to pentachloride formation was checked by the correct geometry of the apparatus and by the method of manipulation.

The active trichloride was converted into diisopropyl hydrogen phosphite and thence through the chlorophosphonate into the fluorophosphonate essentially according to the scheme shown above, although a modified apparatus and techniques were essential (*a*) because of the small scale of the operations, and (*b*) on account of the volatility of the radioactive intermediates and final product.

The reasons for the adoption of the apparatus shown in the diagram are given in the Experimental section where an account is also given of alternative and less satisfactory methods for the small-scale production of phosphorus trichloride.

EXPERIMENTAL.

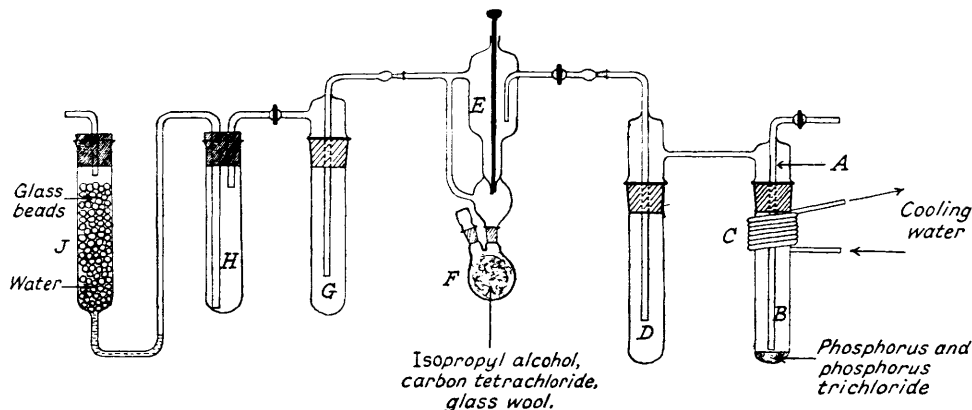
Apparatus.—This is shown in the accompanying diagram. The apparatus was erected in a fume-cupboard equipped with a powerful fan.

- (i) The tube *A* was connected to supplies of dry chlorine and dry nitrogen.
- (ii) The vessel *B* contained phosphorus and phosphorus trichloride.
- (iii) The lower extremity of *A* just touched the top of the P-PCl₃ mixture.
- (iv) The coil-condenser *C* was constructed of lead tubing.
- (v) *E* was a specially designed graduated collecting vessel. By opening the needle-valve, phosphorus trichloride could be dropped into the reaction flask *F*.
- (vi) The trap *G* was cooled in liquid air throughout the experiment. Its purpose was to prevent phosphorus compounds escaping from the apparatus.
- (vii) *H* was used to prevent water from *J* being sucked back into *G*.
- (viii) Escaping gas was washed free from phosphorus compounds by water contained in *J*.
- (ix) All joints were loaded with springs.

Preparation of Phosphorus Trichloride.—The following were placed in the flask *F*: isopropyl alcohol (10 ml.), carbon tetrachloride (5 ml.), and a small quantity of glass wool. The taps between *D* and *E* and between *G* and *H* were opened, and *G* and *D* were cooled in liquid air. Radioactive phosphorus (1 g.) was placed in the vessel *B*, and non-radioactive phosphorus trichloride (1 ml.) then added. *B* was then fixed in position and the bottom of the vessel heated by a free flame so that the phosphorus trichloride refluxed gently. A stream of dry chlorine was then slowly admitted through the inlet-tube *A* until nearly all the phosphorus had reacted. If the rate of ingress of the chlorine was too high, the phosphorus began to glow and phosphorus pentachloride was produced. If, on the other hand, the rate was too slow, the reaction-time was unduly long. [If in spite of all precautions a small quantity of phosphorus pentachloride was produced, this tended to block the lower end of the inlet-tube *A*.

By increasing the rate of heating, the more vigorous refluxing would, in general, partly dislodge the solid phosphorus pentachloride and enable the gas to pass through *A*.]

The water passing through the condenser *C* was then cut off, and a stream of nitrogen substituted for the chlorine. This swept the phosphorus trichloride into *D*, where it was trapped. The phosphorus trichloride collected in *D* sometimes contained small quantities of phosphorus and phosphorus pentachloride. These impurities were not, however, carried over in the next stage of the operation, which was to sweep the phosphorus trichloride from *D* into the graduated vessel *E*, the latter being cooled in liquid air while *D* was gently warmed. When the transference was complete, the temperature of *E* was allowed to rise to room temperature and the volume of phosphorus trichloride produced measured on the scale. Yield, ca. 90%.



Diisopropyl Fluorophosphonate.—The rod in *E* was raised and the phosphorus trichloride allowed to drop slowly into the flask *F*, which was then detached from the apparatus. The central neck of *F* was fitted to a gas-inlet tube, and a reflux water-condenser attached to the side arm. The top of the condenser was then connected to a gas-washing system similar in construction to *H* and *J*. Nitrogen was passed through the liquid for 2 hours, followed by a stream of chlorine for 25 minutes, *F* being cooled in ice-water while the chlorine was passed. At this stage the liquid was yellowish-green. Nitrogen was again passed through the liquid for 2 hours in order to remove hydrogen chloride and excess of chlorine. The gas-inlet tube was replaced by a mercury-sealed stirrer, and dry sodium fluoride (4.5 g.) was placed in the flask *F*. The mixture was then gently heated under reflux for 5 hours, with vigorous stirring. After cooling, the carbon tetrachloride was removed under reduced pressure and the residual diisopropyl fluorophosphonate distilled: it had b. p. 63–66°/14 mm.

Results.—Phosphorus (1 g.) + phosphorus trichloride (1 ml.) were used. The weight of diisopropyl fluorophosphonate obtained was 5.5 g. (62%). The purity, determined by fluorine analysis on 50 mg. of the active product, was 98.5%.

N.B. In an earlier experiment in which the stirring was omitted, the product contained only 10% of diisopropyl fluorophosphonate.

The radioactive phosphorus used had an activity of 28,000 counts/min./mg. (counter efficiency ca. 1%, i.e., specific activity ca. 1 mc./g.), whilst the radioactive diisopropyl fluorophosphonate had an activity of 2,200 counts/min./mg. (corrected to zero time). Details of the determination of the purity and of the assessment of the radioactivity will be given in a separate paper.

Precaution against Radiation.—(i) All materials were handled in a fume-cupboard which was provided with stainless-steel trays covered by filter paper. In the event of active material being spilled, the paper could be disposed of and the trays washed.

(ii) Surgical gloves were worn, both to prevent direct contact with active material and to reduce the radiation absorbed by the hands.

(iii) To reduce the radiation a screen of plate glass, lead glass, or "Perspex" was placed in front of the apparatus.

Investigations in Connexion with the Small-scale Preparation of Phosphorus Trichloride.—The standard large-scale preparation of phosphorus trichloride (*Inorg. Synth.*, 2, 145) utilises a mixture of red phosphorus (200 g.) and phosphorus trichloride (250 ml.) into which chlorine is passed. Even on this scale it is important to keep the trichloride refluxing, otherwise phosphorus pentachloride is produced. In working out "the one-gram scale" method described above, preliminary experiments were conducted using non-radioactive phosphorus. Some of the more significant observations are recorded below.

(1) In the first experiments, the condenser *C* was not used, as it was expected that the height of the vessel *B* would suffice to prevent the phosphorus trichloride from being swept over into *D*. However, in the absence of a condenser phosphorus trichloride was swept over very rapidly. Even when a condenser was subsequently employed care had to be taken to moderate the gas stream, otherwise some phosphorus trichloride passed into *D*. For this reason, attempts made to prevent the formation of phosphorus pentachloride by diluting the chlorine with nitrogen were abandoned.

(2) If the lower extremity of the tube *A* was placed too high above the surface of the phosphorus-phosphorus trichloride mixture in *B*, excess of chlorine escaped into *D* where it converted the phosphorus trichloride (which had collected) into phosphorus pentachloride. If, on the other hand, the lower extremity of *A* was too low, the orifice almost invariably became blocked with phosphorus penta-

chloride. The best results were obtained when the end of *A* just touched the surface of the reaction mixture.

(3) The effect of variations in the diameter of the lower end of *A* was examined. If this diameter was less than 1 cm., blocking by phosphorus pentachloride was likely. The optimum diameter was 1 cm.

(4) It was supposed that the formation of phosphorus pentachloride would be facilitated by the large size of the bubbles of chlorine. The lower end of *A* was therefore packed with glass wool in an attempt to reduce the bubble size. Although this was in some degree successful, any advantage was outweighed by the fact that the glass wool tended to collect any phosphorus pentachloride formed, and a hard compact mass was formed at the end of *A*. In subsequent experiments the glass wool was not used.

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