# **358.** *Organic Phosphorus Insecticides. Part I. Synthesis of Bisdimethylaminophosphonous Anhydride containing* $^{32}$P.

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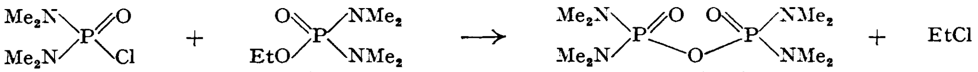
A method is described for the conversion of radioactive phosphoric acid into phosphoryl chloride on a small scale, and thence through chlorobisdimethylaminophosphine oxide (I) into bisdimethylaminophosphonous anhydride (III) (cf. preliminary note, *Research*, 1949, **2**, 590). The labelled product (III) is suitable for tracer work in plants (in which the compound acts as a systemic insecticide) and in animals (where it shows anticholinesterase activity). Preparation of the non-radioactive form of (III) on a larger scale is also described.

The discovery of systemic insecticides by Schrader and Kukenthal (B.I.O.S. Final Report No. 714 H.M.S.O., London, 1947) has opened up new possibilities for the control of insect pests. Certain compounds can be absorbed through the plant cuticle and transported in the sap-stream to render the whole plant poisonous to certain biting and sucking insects. The compounds can also be absorbed through the root system if the plants are watered with aqueous solutions. Among the compounds described by Schrader which displayed this systemic insecticidal action, bisdimethylaminophosphonous anhydride (III) appears to show the greatest promise as its mammalian toxicity is less than those of other systemic insecticides, and in addition, it displays a valuable selective action on insects, being highly toxic to aphides and relatively non-poisonous to beneficial insects (Ripper, Greenslade, and Lickerish, *Nature*, 1949, **163**, 787). If this insecticide is to be used on a significant scale, more information will be desirable on its entry into, transportation in, and disappearance from, plants and on its fate in animals. The radioactive tracer technique should be particularly useful in the biological investigation of these subjects, and we have therefore worked out a suitable method for the synthesis of (III) incorporating $^{32}$P.

A method for the preparation of (III) indicated by Schrader *et al.* (but without experimental details) is to heat an equimolecular mixture of chlorobisdimethylaminophosphine oxide (I) and ethyl bisdimethylaminophosphonite (II) in boiling xylene :



(I.) (II.) (III.)

Alternatively the corresponding sodium salt can be used in place of the ester (II). In the radioactive work, we employed the ester method for convenience of manipulation as the reaction mixture is homogeneous, stirring and filtration being avoided.

Two methods are available for the preparation of (I). In the first (Cook, Ilett, Saunders, Stacey, Watson, Wilding, and Woodcock, *J.*, 1949, 2921) phosphoryl chloride (1 mol.) is treated with anhydrous dimethylamine (4 mol.) in ether :

$$POCl_3 + 4NHMe_2 = (I) + 2NHMe_2,HCl$$

In the second the reaction is carried out in two stages; a single dimethylamino-group can be introduced by refluxing dimethylamine hydrochloride in excess of phosphoryl chloride (Michaelis, *Annalen*, 1903, **326**, 179), giving dichlorodimethylaminophosphine oxide, which is subsequently treated with two equivalents of dimethylamine in ether. The first method is very convenient when working on a small scale, and was used in the preparation of radioactive (II); but when a number of larger batches of non-radioactive (III) were being made, the second method was advantageous as the hydrochloride obtained as a by-product in the second stage was utilized in the first stage of the subsequent run. Compound (II) was prepared by reaction of (I) with sodium ethoxide.

Radio-phosphorus is supplied in the form of phosphoric acid and it is necessary to convert this into phosphoryl chloride. This may be achieved by the passage of carbonyl chloride (or a chlorine–carbon monoxide mixture) over heated metal phosphates (cf. Mellor, "Comprehensive Treatise of Inorganic and Theoretical Chemistry," Vol. VIII, p. 1020). Banks, Boursnell, Dewey, Francis, Tupper, and Wormall (*Biochem. J.*, 1948, **43**, 518) passed carbonyl chloride over heated calcium phosphate–charcoal to prepare radioactive phoshoryl chloride on a small scale. In this method, however, the calcium chloride formed as a by-product coated the unchanged calcium phosphate, necessitating removal of the mixture from the reaction vessel, regrinding, and reheating to complete the reaction. When, however, ferric phosphate (without charcoal) and carbonyl chloride are used (Andreau and du Pont, U.S.P. 1462732, 1923), all the products are volatile at the temperature of reaction and the ferric chloride can easily be condensed out by slight cooling. Yields of up to 93% were obtained in runs in which the theoretical yield was one gram. The sample of (III) obtained as described in the Experimental section had a specific activity of about 18 $\mu$c./g.

## EXPERIMENTAL.

*Dichlorodimethylaminophosphine Oxide.*—Dimethylamine hydrochloride (638 g., recrystallised from ethanol and dried over phosphoric oxide *in vacuo*) and phosphoryl chloride (4·2 kg.; redistilled) were heated under reflux for 20 hours until evolution of hydrochloric acid had ceased and the hydrochloride was completely in solution. Fractionation through a Fenske column gave the product, b. p. 85—88°/15—18 mm. (1272 g., 94%) (Found : C, 15·3; H, 3·8; N, 8·6; Cl, 44·3. Calc. for $C_2H_6ONCl_2P$ : C, 14·8; H, 3·7; N, 8·6; Cl, 43·8%). About 2·8 kg. of phosphoryl chloride were recovered.

*Chlorobisdimethylaminophosphine Oxide.*—(*a*) Dichlorodimethylaminophosphine oxide (340 g.) in dry ether (1·5 l.) was cooled in ice, and a solution of dimethylamine (190 g.) in ether (500 ml.) added during 90 minutes with stirring, which was continued overnight as the mixture warmed to room temperature. The precipitate of dimethylamine hydrochloride was removed and washed with ether (1 l.). Fractionation of the combined ethereal solution and washings yielded the product, b. p. 97—98°/4 mm. (299 g., 84%) (Found : C, 28·1; H, 6·9; N, 16·1; Cl, 21·4. Calc. for $C_4H_{12}ON_2ClP$ : C, 28·2; H, 7·0; N, 14·3; Cl, 20·8%).

(*b*) Phosphoryl chloride (155 g.) in ether (1 l.) was cooled in ice, and dimethylamine (187·5 g.) in ether (500 ml.) added with stirring during 1 hour, and the whole left overnight. The solid hydrochloride was filtered off and washed with ether, and the filtrate fractionated. The product (112 g., 64%) had b. p. 97°/6 mm. (cf. Cook *et al.*, *loc. cit.*).

*Ethyl Bisdimethylaminophosphonite.*—Chlorobisdimethylaminophosphine oxide (341 g.) in ethanol (500 ml.) was added with stirring to a solution of sodium (46 g.) in ethanol (1500 ml.) during 20 minutes, and the mixture heated under reflux for a further 20 minutes. The precipitate of sodium chloride was removed, alcohol distilled off, and the residue fractionated *in vacuo*. The product (318 g., 88·5%) was collected from 93·5°/7 mm. to 95·5°/10 mm.

*Bisdimethylaminophosphonous Anhydride.*—Chlorobisdimethylaminophosphine oxide (68·2 g.) and ethyl bisdimethylaminophosphonite (72 g.) in xylene (300 ml.) were heated for 20 hours under reflux. Ethyl chloride was evolved. On distillation of the residue, the product was obtained as a colourless and almost odourless liquid, b. p. 110—112°/0·003 mm. (92·6 g., 81%), completely miscible with water (Found : C, 33·9; H, 8·5; N, 19·8. $C_8H_{24}O_3N_4P_2$ requires C, 33·6; H, 8·4; N, 19·6%). The b. p. varied slightly for different preparations, being rather dependent on the bath-temperature.

*Radioactive Ferric Phosphate.*—Active phosphoric acid solution (1140 $\mu$c. in 0·54 ml.) was washed out from its ampoule with phosphoric acid solution (20 ml. containing 31·92 g./l.) and water into a 100-ml. graduated flask. A sample (1 ml.) was withdrawn as a standard for radioactive assay, and the remainder was added slowly with vigorous stirring to a solution (50 ml.) of ferric acetate in acetic acid (8·25 g. of Fe and 120 ml. of acetic acid per litre). Solid ammonium acetate (5 g.) was then added and the mixture boiled for 5 minutes. The precipitate of ferric phosphate was removed by centrifuging, washed once with ethanol and twice with ether, dried at 120°, powdered with a glass rod, and transferred to a silica tube. After being heated to red heat for 90 minutes, the voluminous precipitate had shrunk to a third of its original volume. When cool, the granular powder was packed into a silica tube as shown in Fig. 1, for use in the following preparation. Losses of radioactive material during precipitation and drying were less than 2%.

FIG. 1.

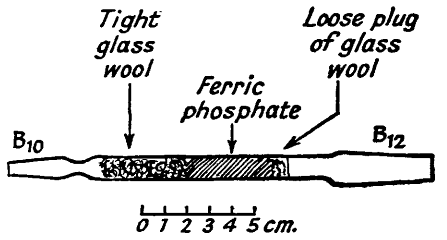
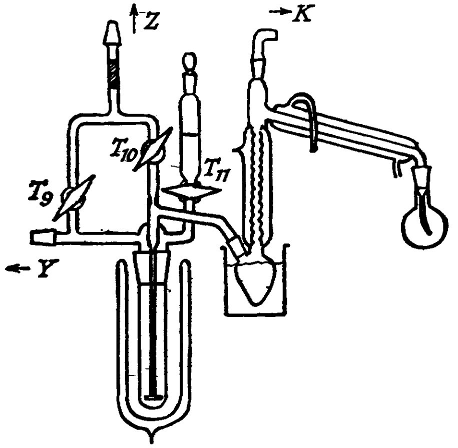
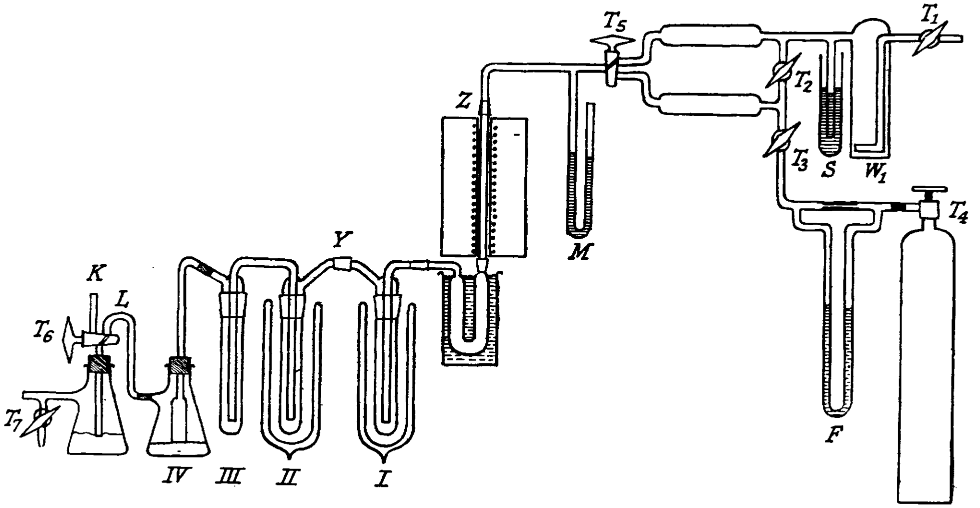


FIG. 3.



*Radioactive Phosphoryl Chloride.*—The apparatus used is shown diagramatically in Fig. 2. Dry nitrogen (or air), carbonyl chloride, or a mixture was admitted to the reaction vessel by adjustment of the stopcocks $T_1$ to $T_5$ ($S$, safety valve; $W_1$, wash-bottle containing concentrated sulphuric acid; $M$, mercury manometer; $F$, flowmeter). Carbonyl chloride was obtained from a cylinder connected with polyvinyl chloride tubing. From $T_5$ to trap III, the apparatus was constructed in short sections joined by standard ground-glass joints to give flexibility and to facilitate cleaning. The reaction vessel $Z$ was a silica tube (10 cm. long, 1 cm. internal diameter) heated in a small electric tube furnace to 400—450°, and was followed by a U-tube packed with glass wool and maintained at 120—130° in a metal bath (to condense out ferric chloride). Traps I and II were jacketed and fitted with close-fitting brass shields to prevent spilling of radioactive material in the event of accidental breakage. These traps were surrounded by solid carbon dioxide–alcohol. The product and excess of carbonyl chloride were collected in trap I, while II served as a safety trap against sucking back and also to remove any traces of product not condensed by I. Any carbonyl chloride remaining in the gas stream was removed by trap III containing water, and by trap IV containing soda-lime. Waste gas was passed through $T_6$ into a bubbler, past an air leak (controlled by $T_7$) into a water-pump. During operation, the apparatus was at all times run with a slight negative pressure to avoid any escape of volatile radioactive material.

FIG. 2.



After the packed reaction tube had been fitted, the heating units were switched on and the apparatus was dried out by a stream of dry nitrogen or air, the stopcocks being adjusted so that the manometer $M$ showed a negative pressure of about 8 cm. Hg. When dry, the cooling baths were fitted and a slow stream of carbonyl chloride mixed with air was admitted. As reaction proceeded, the air supply was stopped and the carbonyl chloride stream increased. About 50 ml. of liquid carbonyl chloride were collected during 6 hours (coarseness of control of $T_4$ prevented a slower rate of flow). The carbonyl chloride stream was then stopped and the apparatus swept out with air. The tube of trap I was removed and connected to a simple stillhead. Most of the carbonyl chloride was then allowed to boil off slowly at room temperature (air-jacket around the tube), and the final traces were removed by heating the tube to about 75° in a water-bath. The receiver-tube was then cooled in liquid air, the distillation of the phosphoryl chloride being completed by evacuation for a short time. The apparatus was then allowed to warm to room temperature, dry air admitted, and the receiver rapidly removed, stoppered, and weighed. The yield was 0·93 g. (93%).

*Radioactive Chlorobisdimethylaminophosphine Oxide.*—The apparatus shown diagrammatically in Fig. 3 was fitted in place of the reaction tube, traps, etc., between the points *K*, *Y*, and *Z* in Fig. 2. The reaction vessel for this stage was the receiver into which phosphoryl chloride had previously been distilled. With $T_{10}$ open, $T_9$ and $T_{11}$ closed, and $T_6$ set to *L*, a stream of nitrogen could be passed down the narrow centre tube and through the sintered-glass disc (10-mm. diameter) to stir the reactants and then escape through the trap system. With $T_{10}$ closed, $T_9$ open, and $T_6$ set to *K*, the liquid contents of the reaction tube could be filtered into the flask of a micro-fractionating apparatus which was being heated in a water-bath to about 50°.

To the tube containing the known amount of phosphoryl chloride (0·93 g.), sodium-dried ether (10 ml.) was added and the tube quickly fitted to the apparatus described above. The solution was stirred vigorously by a stream of nitrogen, and the reaction vessel then cooled in solid carbon dioxide–alcohol. The calculated quantity of dimethylamine solution in ether (10% w/v; 10·5 ml., 4 mols.) was then added slowly *via* $T_{11}$, care being taken to keep the reactants always well stirred. The tap-funnel was then washed out with 10 ml. of ether, and the apparatus allowed to warm to room temperature and left overnight with gas stirring. The reaction vessel was then again cooled (to reduce the solubility of the dimethylamine hydrochloride), the taps were adjusted as described above, and the mixture was filtered into the micro-distillation flask where the ether distilled off. The solid hydrochloride, well cooled, was washed 3 times with cold dry ether. When the crude product had been transferred in this manner to the distillation flask, this was set for fractionation, glass wool being added to prevent bumping. Inert chlorobisdimethylaminophosphine oxide (*ca.* 7 g. in 2 portions) was added at this stage as a diluent, and distillations carried out at a low pressure, the flask being heated in a stirred oil-bath. The fractions, b. p. 62—64°/1—1·1 mm. (bath-temp. 82—84°), were collected and weighed (7·2 g.). A small sample was taken for radioactive assay and showed a yield of 42·7% calculated on $^{32}$P content of the original 99 ml. of phosphoric acid solution.

*Radioactive Bisdimethylaminophosphonous Anhydride.*—Active chlorobisdimethylaminophosphine oxide (7·2 g.) from the previous experiment was washed with dry benzene (15 ml.) into a 50-ml. flask, ethyl bisdimethylaminophosphonite (10 g., slight excess) added, and the mixture heated overnight under reflux in a stirred oil-bath at 130—145°, moisture being excluded by a calcium chloride tube. The mixture was then distilled through a short Vigreux column. A small first fraction distilling up to 128°/1·5 mm. consisted mainly of unchanged ester, while the main fraction, b. p. 139—140°/1·5 mm. (bath temperature 160°), consisted of the anhydride. The yield was 9·44 g. (78%) and specific activity 18·4 $\mu$c./g.

The overall yield, calculated from the activities of the original phosphoric acid and the final product, was 19·9%. (The glass wool added to prevent bumping on the above fractionations retained appreciable amounts of radioactive material.)

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