Synthetic Plant Hormones. Part III. Aryloxymethylphosphonates.*

By (Miss) M. H. Maguire and G. Shaw.

[Reprint Order No. 5960.]

Several aryloxymethylphosphonates (I; R = Et, R′ = H) have been prepared by the reaction of a number of sodium aryloxides with the iodo-ester (II; R = R′ = Et), which proceeds by way of the half-ester (II; R = Et, R′ = H). The products were readily hydrolysed by concentrated hydrochloric acid to the diacids (I; R = R′ = H). Preliminary biological evaluations of some of these compounds are briefly discussed.

Previous communications in this series have been concerned with the preparation of analogues of the phenoxyacetic acid series of plant hormones, in particular with variation in the aliphatic side chain. The results indicated that only those compounds which by hydrolytic or oxidative processes (but not reductive, *e.g.*, aryl glucosides) could give rise to a phenoxyacetic acid, were active, and that activity was closely associated with that of the corresponding acid. Moreover, with the possible exception of the 2 : 4-dichlorophenoxyacetaldehyde sodium hydrogen sulphite adduct, no enhanced translocation or persistence of the compounds in the plants was observed. The failure of phenoxyacetic acid activity to persist in plant tissue is undoubtedly related to the rapid loss of the carboxyl group (as carbon dioxide), as has been demonstrated by using labelled molecules (Weintraub, Brown, Fields, and Rohan, *Plant Physiol.*, 1952, **27**, 292).

We therefore considered it of interest to attempt the preparation of compounds in which the carboxyl group in chloroaryloxyacetic acids was replaced by some other acidic group which could not be converted simply into a carboxyl group. The synthesis of one such group of compounds, aryloxymethylphosphonic acids (I), is described in this paper (for a note see Maguire, Shaw, and Greenham, *Chem. and Ind.*, 1953, 668); preliminary experiments on the preparation of analogous sulphonates were abandoned after this had been reported by Barber, Cottrell, Fuller, and Green (*J. Appl. Chem.*, 1953, **3**, 253).

$$\underset{\text{(I)}}{\mathrm{ArO{\cdot}CH_2{\cdot}PO(OR)(OR')}} \qquad \underset{\text{(II)}}{\mathrm{I{\cdot}CH_2{\cdot}PO(OR)(OR')}}$$

Aryloxymethylphosphonates (I) have not hitherto been described; the closest reported analogues appear to be 2-phenoxyethylphosphonic acid $PhO{\cdot}CH_2{\cdot}CH_2{\cdot}PO(OH)_2$ (Mikhailova, *Uchenye Zapiski Kazan. Gosudarst Univ. im V.I. Ul'yanova Lenina* 101, No. 3, *Sbornik Studencheskikh Rabot*, No. 2, 58, 1941; *Chem. Abs.*, 1946, **40**, 555) and diethyl benzyloxymethylphosphonate $Ph{\cdot}CH_2{\cdot}O{\cdot}CH_2{\cdot}PO(OEt)_2$ (Abramov, Sergeeva, Chelpanova, *Zhur. obschei Khim.*, 1944, **14**, 1030; *Chem. Abs.*, 1947, **41**, 700); both compounds were prepared by the Arbuzov reaction (Kosolapoff, "Organo-Phosphorus Compounds," Wylie, New York, 1950, p. 121), namely, reaction of an alkyl or aralkyl halide and a trialkyl phosphite: $RX + P(OR')_3 \longrightarrow R{\cdot}PO(OR')_2 + R'X$. The synthesis of aryloxymethylphosphonates by this reaction would require as intermediates the ω-halogenoanisoles $ArO{\cdot}CH_2X$ and until recently (Barber *et al.*, *loc. cit.*) such compounds were unknown and our experiments were then almost complete. Other possible routes to the phosphonic acids included (1) the reaction of a halogenomethylphosphonate (II) and a sodium aryloxide and (2) an extension of a recent reaction (Clayton and Jensen, *J. Amer. Chem. Soc.*, 1948, **70**, 3880; Graf, *Chem. Ber.*, 1952, **85**, 9) whereby oxidative phosphorylation of *cyclo*hexane occurs with phosphorus trichloride in a current of dry oxygen: $3C_6H_{12} + 2PCl_3 + O_2 \longrightarrow C_6H_{11}{\cdot}POCl_2 + (C_6H_{11})_2POCl$. The first of these methods seemed the most promising, although the halogen atom in halogenomethylphosphonates is known to be very unreactive; nevertheless it has been replaced by the amino (Kabachnik and Medved, *Izvest. Akad. Nauk S.S.S.R., Otdel Khim. Nauk*, 1950, 635; *Chem. Abs.*, 1951, **45**, 8444) and the hydroxyl group (Kabachnik and Shepeleva, *ibid.*, 1951, 185; *Chem. Abs.*, 1951, **45**, 10,191) under drastic conditions.

---

* Part II, *J.*, 1954, 3669.

Diethyl iodomethylphosphonate (II; R = R′ = Et) failed to react with sodium 2 : 4-dichlorophenoxide in boiling ethanol but some reaction occurred in boiling toluene (see Experimental section). A rapid reaction occurred, however, when dry sodium 2 : 4-dichlorophenoxide (1·5 mols.) and the iodo-ester (1 mol.) were heated together to 160°, there being no apparent decomposition; the products were ethyl hydrogen 2 : 4-dichlorophenoxymethylphosphonate (as I; R = Et, R′ = H) and 2 : 4-dichlorophenetole; an increased yield of the half-ester was obtained when the molar ratios were increased to 2 : 1. It was of interest to determine whether de-esterification or replacement of halogen occurred first, and so reactions were carried out with 1 : 1 and 1 : 2 molar ratios of phenoxide to ester. The 1 : 1 ratio gave a mixture of *o*-chlorophenetole, ethyl hydrogen *o*-chlorophenoxymethylphosphonate, and ethyl hydrogen iodomethylphosphonate (II; R = Et, R′ = H), and the 1 : 2 ratio gave only the phenetole (in increased yield) and the iodo-ester (II; R = Et, R′ = H). These results clearly indicated that de-esterification occurred first, and the reaction scheme may be summarised :

$$(1)\qquad \mathrm{ArONa + I{\cdot}CH_2{\cdot}PO(OEt)_2 \longrightarrow I{\cdot}CH_2{\cdot}PO(OEt)(ONa) + ArOEt}$$

$$(2)\qquad \mathrm{ArONa + I{\cdot}CH_2{\cdot}PO(OEt)(ONa) \longrightarrow ArO{\cdot}CH_2{\cdot}PO(OEt)(ONa) + NaI}$$

The half-esters (I; R = Et, R′ = H) were singularly resistant to alkaline hydrolysis, being almost unaffected by 50% sodium hydroxide solution at 140° or an excess of a sodium aryloxide. The diacids (I; R = R′ = H) were, however, readily and quantitatively prepared by boiling the half-esters for a short time with concentrated hydrochloric acid although the analogous compounds, diethyl 2-phenoxyethylphosphonate and diethyl benzyloxymethylphosphonate are reported to undergo ether fission with 10% hydrochloric acid at 120°, whereas hydrolysis of the former compound with 10% sodium hydroxide solution at 150—160° was quantitative (Mikhailova *et al.*, and Abramov *et al.*, *locc. cit.*).

By the above methods the 2-, 3-, and 4-chloro-, 2 : 4-dichloro-, 2 : 4 : 5- and 2 : 4 : 6-trichloro-phenoxymethylphosphonates, together with the ethyl hydrogen esters and the unsubstituted diacid, were prepared.

Similar attempts to prepare the unsubstituted half-ester (I; R = Et, R′ = H) gave an acidic oil; distillation of this substance *in vacuo* gave a neutral distillate, apparently isomeric with the half-ester, and a residue of the diacid. The latter compound was also obtained by hydrolysis of the crude half-ester and of the neutral liquid.

The results of preliminary biological tests on a few of these compounds have been published (Greenham, *Austral. J. Sci.*, **1953**, **16**, 66); in both the split-pea, and pea-epicotyl tests, ethyl hydrogen 2 : 4-dichlorophenoxymethylphosphonate had slight but significant auxin properties. In addition the latter compound and also ethyl hydrogen 2-chloro- (but not 4-chloro-)phenoxymethylphosphonate significantly increased the dry weights of wheat-seedling tops, although they were without effect on germination. On the other hand the corresponding 2 : 4 : 5-trichloro-half-ester reduced the dry weight of rape-seedling tops. The weight effects appear to be a function of the phosphonate group since methylphosphonic acid had a similar effect at low concentrations.

EXPERIMENTAL

Triethyl phosphite was prepared by Ford-Moore and Williams's method (*J.*, **1947**, **1465**) and diethyl iodomethylphosphonate by the Arbuzov reaction (Arbuzov and Kushkova, *J. Gen. Chem., U.S.S.R.*, **1936**, **6**, **283**; Ford-Moore and Williams, *loc. cit.*) from triethyl phosphite and methylene iodide. The sodium aryloxides were prepared by the addition of sodium to a solution of the phenol in boiling toluene; the salts were filtered off, washed with benzene, and dried *in vacuo*.

Reaction of Sodium 2 : 4-Dichlorophenoxide and Diethyl Iodomethylphosphonate.—(a) *In ethanol.* A solution of sodium 2 : 4-dichlorophenoxide (3·3 g.) and diethyl iodomethylphosphonate (5 g.) in ethanol (150 ml.) was boiled for 24 hr. The solution was evaporated to dryness and the residual paste extracted with ether, leaving unchanged phenoxide (3·1 g.); evaporation of the ether and distillation of the residue *in vacuo* gave the iodo-ester (4 g.), b. p. 130—134°/5 mm.

(b) *In toluene.* Diethyl iodomethylphosphonate (20 g.) was added to a suspension of sodium 2 : 4-dichlorophenoxide (13·3 g.) in boiling toluene (300 ml.); a clear solution was obtained immediately and this was boiled under reflux for 24 hr. The cooled toluene solution was filtered from a trace of solid and extracted with water (3 × 30 ml.); the aqueous solution was acidified with hydrochloric acid and extracted with ether (3 × 30 ml.); evaporation of the dried extract gave an oil (4·2 g.) with a strong phenolic odour which could not be satisfactorily purified. The toluene solution was distilled *in vacuo*, to give a fraction (6·2 g.), b. p. 90—100°/5 mm., with a phenetole-like odour, and diethyl iodomethylphosphonate (6·5 g.), b. p. 130—134°/5 mm. The first fraction was redistilled several times at atmospheric pressure and finally had b. p. 236—238° corresponding to 2 : 4-dichlorophenetole, b. p. 236—238° (Fischer, *Annalen Suppl.*, 1870, **7**, 183, gives b. p. 236—238°) (Found: C, 49·8; H, 3·95. Calc. for $C_8H_8OCl_2$: C, 50·3; H, 4·2%).

(c) A mixture of sodium 2 : 4-dichlorophenoxide (5 g.) and diethyl iodomethylphosphonate (5 g.) was heated at 160° (bath), whereupon a reaction commenced, then the temperature was kept at 160—170° for 1 hr. The viscous pale brown product was stirred with water (50 ml.), giving an emulsion which was extracted with benzene (3 × 20 ml.); evaporation of the benzene and distillation of the residue gave 2 : 4-dichlorophenetole (1·7 g.), b. p. 238°. The aqueous solution was acidified with hydrochloric acid and extracted with ether (5 × 30 ml.); evaporation of the ether left an oil which soon crystallised; *ethyl hydrogen* 2 : *4-dichlorophenoxymethylphosphonate* (2·5 g.) separated from benzene–light petroleum as needles, m. p. 79—81° (Found : C, 37·95; H, 3·8%; equiv., 283·5. $C_9H_{11}O_4Cl_2P$ requires C, 37·9; H, 3·9%; equiv., 285). The half-ester (1 g.) and concentrated hydrochloric acid (8 ml.) were boiled together for 4 hr. The solution was evaporated to dryness to give a crystalline residue; 2 : *4-dichlorophenoxymethylphosphonic acid* (0·9 g.) separated from ethyl acetate–light petroleum as plates, m. p. 141—143° (Found : C, 32·55; H, 2·8. $C_7H_7O_4Cl_2P$ requires C, 32·7; H, 2·75%); a solution of the acid in ether with *n*-pentylamine gave the *di*-n-*pentylammonium salt* which crystallised from ethanol–ether as needles, m. p. 221—223° (Found : C, 47·35; H, 7·55; N, 6·5. $C_7H_7O_4Cl_2P,2C_5H_{13}N$ requires C, 47·35; H, 7·7; N, 6·5%).

Reaction of Sodium o-*Chlorophenoxide and Diethyl Iodomethylphosphonate*.—(*a*) A mixture of sodium *o*-chlorophenoxide (7 g., 1 mol.) and diethyl iodomethylphosphonate (13 g., 1 mol.) was kept at 160—170° (bath) for 1 hr. (reaction commenced at 160°). The cooled mixture was stirred with water (50 ml.), and the resultant emulsion was extracted with benzene (3 × 20 ml.); evaporation of the dried benzene solution and distillation of the residue gave *o*-chlorophenetole (3 g.), b. p. 208° (Kurbatow, *Annalen*, 1875, **176**, 39, gives b. p. 208—208·5°) (Found : C, 61·55; H, 5·85. Calc. for C_8H_9OCl : C, 61·35; H, 5·8%), diethyl iodomethylphosphonate (1·3 g.), b. p. 130°/5 mm., and a tarry residue (1·4 g.). The aqueous solution was acidified with concentrated hydrochloric acid and saturated with sodium chloride, then extracted with ether (3 × 25 ml.). The ethereal solution was extracted with 5% sodium hydrogen carbonate solution (25 ml.), and the extract acidified and saturated with sodium chloride, then extracted with ether (3 × 20 ml.); evaporation of the dried extracts gave an acidic gum (4·8 g.) which when stirred with benzene–*cyclo*hexane gave *ethyl hydrogen* o-*chlorophenoxymethylphosphonate* (0·2 g.) which crystallised from carbon tetrachloride–light petroleum as laths, m. p. 86—88° (Found : C, 43·05; H, 4·75. $C_9H_{12}O_4ClP$ requires C, 43·15; H, 4·8%). The aqueous solutions were combined and again extracted with ether (5 × 25 ml.); evaporation of the ether gave an acidic oil which crystallised when set aside; *ethyl hydrogen iodomethylphosphonate* (1·5 g.) crystallised from carbon tetrachloride–light petroleum as plates m. p. 46—49° (Found: C, 14·65; H, 3·1. $C_3H_8O_3IP$ requires C, 14·4; H, 3·2%). A solution of the ester (1·5 g.) in concentrated hydrochloric acid (10 ml.) was boiled under reflux for 2½ hr., then evaporated to dryness on a water-bath, to leave a deliquescent crystalline solid (1·3 g.). An ethereal solution of the solid with *n*-pentylamine precipitated *di*-n-*pentylammonium iodomethylphosphonate* which crystallised from propan-2-ol as plates, m. p. 162° (softening from 148°) (Found : C, 33·4; H, 7·5; N, 6·85. $CH_4O_3IP,2C_5H_{13}N$ requires C, 33·35; H, 7·65; N, 7·05%).

(*b*) Sodium *o*-chlorophenoxide (14 g., 2 mol.) and diethyl iodomethylphosphonate (13 g., 1 mol.) were heated together as above, to give *o*-chlorophenetole (5·5 g.) and ethyl hydrogen *o*-chlorophenoxymethylphosphonate (7·7 g.), m. p. 87°. A solution of the ester (1 g.) in concentrated hydrochloric acid (8 ml.) was boiled under reflux for 3 hr. When the solution was cooled a crystalline precipitate separated; o-*chlorophenoxymethylphosphonic acid* (0·7 g.) crystallised from acetone–benzene–carbon tetrachloride as plates, m. p. 133—134° (Found : C, 37·5; H, 3·7. $C_7H_8O_4ClP$ requires C, 37·75; H, 3·6%). A further quantity of the acid (0·2 g.) was obtained by evaporation of the aqueous hydrolysis solution.

(*c*) A mixture of sodium *o*-chlorophenoxide (6 g., 1 mol.) and diethyl iodomethylphosphonate

(22 g., 2 mol.) was kept at 160—170° (bath) for 1½ hr. The product was treated with water (50 ml.), and the resulting emulsion extracted with benzene (4 × 30 ml.); evaporation of the benzene and distillation of the residue *in vacuo* gave *o*-chlorophenetole (4 g.), b. p. 103—104°/26 mm., and diethyl iodomethylphosphonate (7·6 g.), b. p. 110—112°/3 mm. The aqueous solution was acidified with hydrochloric acid, saturated with sodium chloride, and thoroughly extracted with ether; evaporation of the ether gave an oil (8·1 g.) which soon crystallised; ethyl hydrogen iodomethylphosphonate separated from carbon tetrachloride–light petroleum as plates (5·5 g.), m. p. 46—49°.

Reaction of Sodium 2 : 4 : 5-*Trichlorophenoxide and Diethyl Iodomethylphosphonate.*—A mixture of sodium 2 : 4 : 5-trichlorophenoxide (20·5 g., 1 mol.) and diethyl iodomethylphosphonate (13 g., 1 mol.) was kept at 190—200° (bath) for 1 hr. The cold semi-solid product was treated with water (50 ml.). A crystalline solid separated which was washed with water and benzene; hydrated *sodium ethyl* 2 : 4 : 5-*trichlorophenoxymethylphosphonate* (10·1 g.) crystallised from propan-2-ol as needles, m. p. 191—193° (Found : C, 28·05; H, 3·6. $C_9H_9O_4Cl_3NaP,2\frac{1}{2}H_2O$ requires C, 27·95; H, 3·65%). The sodium salt (10 g.) was dissolved in warm water (300 ml.), and the solution acidified with hydrochloric acid, saturated with sodium chloride, and extracted with ether (4 × 100 ml.); evaporation of the solvent gave *ethyl hydrogen* 2 : 4 : 5-*trichlorophenoxymethylphosphonate* (9·1 g.) which crystallised from carbon tetrachloride as needles, m. p. 97° (Found : C, 33·85; H, 3·15%; equiv., 317. $C_9H_{10}O_4ClP$ requires C, 33·85; H, 3·15%; equiv., 319·5). The aqueous filtrate from the first-mentioned reaction was extracted with a further quantity of benzene (3 × 50 m.); evaporation of the solvent and distillation of the residue gave 2 : 4 : 5-trichlorophenetole (9·2 g.), b. p. 256—264°, m. p. 42—43° (Agfa, D.-R.P. 411,052/1924, gives m. p. 95°) (Found : C, 42·7; H, 3·05. Calc. for $C_8H_7OCl_3$: C, 42·6; H, 3·15%). The aqueous solution was acidified with hydrochloric acid and extracted with ether, to give a further quantity of the half-ester (2 g.), m. p. 96—97°; a solution of this (1 g.) in concentrated hydrochloric acid (8 ml.) was boiled under reflux for 4 hr.; the solution was cooled, to give a crystalline precipitate; 2 : 4 : 5-*trichlorophenoxymethylphosphonic acid hemihydrate* (0·9 g.) separated from acetone–benzene as needles, m. p. 179—180° (Found : C, 27·65; H, 2·35. $C_7H_6O_4Cl_3P,\frac{1}{2}H_2O$ requires C, 28·0; H, 2·35%).

Similar experiments led to : *sodium ethyl* p-*chlorophenoxymethylphosphonate* (4·7 g. from 14 g. of the phenoxide and 13 g. of diethyl iodomethylphosphonate), needles (from propan-2-ol), m. p. 286—287° (Found : C, 39·75; H, 4·1. $C_9H_{11}O_4ClNaP$ requires C, 39·65; H, 4·05%) (the acid failed to crystallise); *p*-chlorophenetole (4·2 g.), b. p. 205—208° (Kurbatow, *loc. cit.*, gives b. p. 210—212°), and p-*chlorophenoxymethylphosphonic acid* (0·8 g. from 1·5 g. of the sodium salt of the half ester), plates (from acetone–carbon tetrachloride), m. p. 155—156° (Found : C, 37·6; H, 3·5%); S-*benzylthiuronium ethyl* m-*chlorophenoxymethylphosphonate* (8·7 g. of crude acid from 11·4 g. of the phenoxide and 10·5 g. of diethyl iodomethylphosphonate), needles (from ethyl acetate–light petroleum), m. p. 137—138° (Found : C, 48·8; H, 5·25; N, 6·6. $C_9H_{12}O_4ClP,C_8H_{10}N_2S$ requires C, 49·0; H, 5·3; N, 6·7%) (the acid and its sodium salt failed to crystallise); *m*-chlorophenetole (4 g.), b. p. 200° (Reverdin and Eckhard, *Ber.*, 1899, **32**, 2626, give b. p. 191—192°/728 mm.), and *di*-n-*pentylammonium* m-*chlorophenoxymethylphosphonate hydrate* (the acid failed to crystallise) as needles (from propan-2-ol), m. p. 160—180° (decomp.) (Found : C, 48·95; H, 8·45; N, 6·4. $C_7H_8O_4ClP,2C_5H_{13}N,H_2O$ requires C, 49·2; H, 8·75; N, 6·75%); *ethyl hydrogen* 2 : 4 : 6-*trichlorophenoxymethylphosphonate* (7·9 g. from 20·5 g. of the phenoxide and 13 g. of diethyl iodomethylphosphonate at 185—201°), needles (from carbon tetrachloride–light petroleum), m. p. 167° (Found : C, 33·6; H, 3·15%; equiv., 319); 2 : 4 : 6-trichlorophenetole (10·3 g.), b. p. 246—250° (Faust, *Annalen*, 1869, **149**, 152, gives b. p. 246°) (Found : C, 42·4; H, 3·0%), and 2 : 4 : 6-*trichlorophenoxymethylphosphonic acid* [1·8 g. from 2 g. of the half-ester; considerable frothing occurred in this reaction, and an excess of hydrochloric acid (50 ml.) was required because of the insolubility of the half ester], needles (from acetone–carbon tetrachloride), m. p. 217—218° (Found : C, 28·75; H, 2·1. $C_7H_6O_4Cl_3P$ requires C, 28·85; H, 2·1%). Reaction of sodium phenoxide (9·2 g.) and diethyl iodomethylphosphonate (9·2 g.) in a similar manner gave phenetole (3·7 g.), b. p. 170° (Pinette, *Annalen*, 1888, **243**, 35, gives b. p. 170·3°), and an acidic oil (9 g.); this was distilled *in vacuo* to give a neutral fraction (1·5 g.), b. p. 138°/2 mm. (Found : C, 50·2; H, 6·5. Calc. for $C_9H_{13}O_4P$: C, 50·0; H, 6·05%), and a residue (5·6 g.) which crystallised; this, *phenoxymethylphosphonic acid*, separated from acetone–carbon tetrachloride as plates, m. p. 139—141°, which retained a small amount of water of crystallisation after being dried *in vacuo* (Found : C, 43·75; H, 4·8. $C_7H_9O_4P,\frac{1}{4}H_2O$ requires C, 43·65; H, 4·95%); the same acid was also obtained by hydrolysis of either the acidic oil or the neutral compound with concentrated hydrochloric acid; an ethereal solution of the acid with *n*-pentylamine gave the n-***pentylammonium salt hemihydrate*** which separated from propan-2-ol as laths, m. p. 170° (decomp.) (Found: C, 55·05; H, 9·6; N, 7·75. $C_7H_9O_4P,2C_5H_{13}N,\frac{1}{2}H_2O$ requires C, 54·95; H, 9·75; N, 7·55%).

We thank Dr. E. Challen for the microanalyses and the Commonwealth Scientific and Industrial Research Organisation for a maintenance grant (to M. H. M.).

THE UNIVERSITY OF TECHNOLOGY,
SYDNEY, N.S.W., AUSTRALIA.

[*Received, December* 14*th*, 1954.]