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Organophosphorus Compounds. X* A New Synthesis of 1,2,3,4-Tetrahydrophosphinolines

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Abstract

A new synthesis of the 1,2,3,4-tetrahydrophosphinoline ring is described. Reaction of 3-phenylpropylphosphonous dichloride with zinc chloride at 170° followed by hydrolysis with hot concentrated hydrochloric acid, then oxidation with bromine, gave 91% of 1-hydroxy-1,2,3,4-tetrahydrophosphinoline 1-oxide (20b). Under conditions where oxidation was incomplete, 1,2,3,4-tetrahydrophosphinoline 1-oxide was isolated. On a small scale the reaction of 3-phenylpropylphosphonous dichloride with a catalytic amount of aluminium chloride at 220° gave 60% of 1-chloro-1,2,3,4-tetrahydrophosphinoline (18).

Treatment of (20b) with thionyl chloride gave 1-chloro-1,2,3,4-tetrahydrophosphinoline 1-oxide which, upon reaction with the appropriate Grignard reagent, afforded 1-ethyl or 1-phenyl-1,2,3,4-tetrahydrophosphinoline 1-oxide. 1-Ethyl-1,2,3,4-tetrahydrophosphinoline 1-oxide was reduced with trichlorosilane to the phosphine, which upon reaction with sulphur yielded the corresponding phosphine sulphide.

The methyl and ethyl esters of (20b) are described.

Introduction

The long and intensive search for synthetic analogues which might possess the pain-deadening properties of the potent analgetic morphine (1) but be free of its deleterious side effects, especially addiction liability, nausea, and respiratory depression, has yielded much information on structure–activity relationships,[1–4] but only limited achievement.[5–7] Synthetic morphine analogues currently in clinical use include ethyl 1-methyl-4-phenylpiperidine-4-carboxylate, 'meperidine' (2), 2-dimethylamino-4,4-diphenylheptan-5-one, 'methadone' (3), and the 1,2,3,4,5,6-hexahydro-2,6-

* Part IX, *Aust. J. Chem.*, 1971, **24**, 777.

[1] Stevens, G. de, (Ed.) 'Analgetics. A Series of Monographs on Medicinal Chemistry' Vol. 5, pp. 123, 179 (Academic Press: New York 1965).

[2] Janssen, P. A. J., and van der Eycken, C. A. M., in 'Drugs Affecting the Central Nervous System. A Series on Monographs on Medicinal Research' (Ed. A. Burger) Vol. 2, p. 25 (Dekker: New York 1968).

[3] Hellerback, J., Schnider, O., Besendorf, H., and Pellmont, B., in 'Synthetic Analgesics' (Int. Series of Monographs on Organic Chemistry) (Eds D. H. R. Barton and W. E. von Doering) Vol. 8, Part IIA (Pergamon: New York 1960).

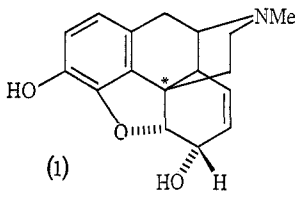
[4] Braenden, O. J., Eddy, N. B., and Halback, H., *Bull. Wld. Hlth. Org.*, 1955, **13**, 937.

[5] Harris, L. S., and Pierson, A. K., *J. Pharmacol. Exp. Ther.*, 1964, **143**, 141.

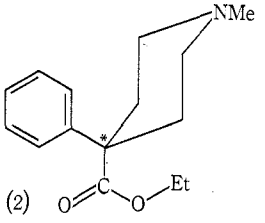
[6] Fraser, H. F., and Rosenberg, D. E., *J. Pharmacol. Exp. Ther.*, 1964, **143**, 149.

[7] Keats, A. S., and Telford, J., *J. Pharmacol. Exp. Ther.*, 1964, **143**, 157.

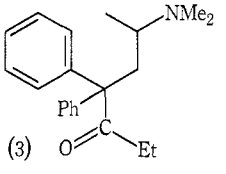
methano-3-benzazocines, 'phenazocine' (4a), 'cyclazocine' (4b), and 'pentazocine (4c). Some 1,5-methano-2,3,4,5-tetrahydro-1*H*-2-benzazepines, including compound (5), were recently reported to show promising analgetic activity.[8,9] A feature common



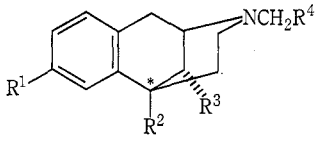
(1) morphine



(2) meperidine

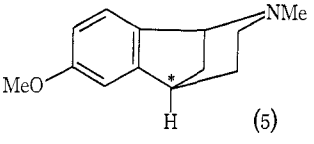


(3) methadone

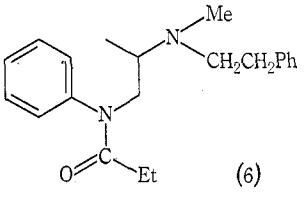


benzazocines

	R^1	R^2	R^3	R^4
(4a)	OH	Me	Me	CH_2Ph
(4b)	OH	Me	Me	cyclopropyl
(4c)	OH	Me	Me	$CH{=}CMe_2$
(4d)	H	Me	H	H
(4e)	H	H	H	H



(5)



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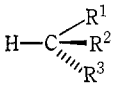
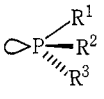
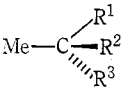


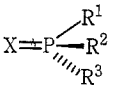
(7)



(8)



(9)



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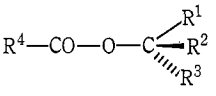

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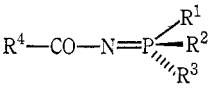


(12)

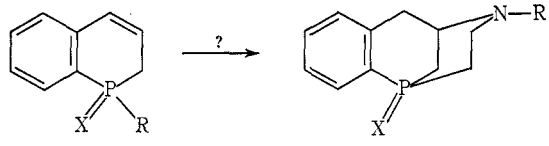
to all of these molecules, and probably essential for analgetic activity[4,10] is the quaternary (or tertiary) benzylic carbon atom 1,4-related to a tertiary nitrogen atom, and marked with an asterisk in formulae (1)–(5).

[8] Jacobson, A. E., and Mokotoff, M. J., *J. Med. Chem.*, 1970, **13**, 7.
[9] Mokotoff, M., and Jacobson, A. E., *J. Heterocycl. Chem.*, 1970, 773.
[10] Beckett, A. H., and Casey, A. F., *J. Pharm. Pharmacol.*, 1954, **6**, 986.

An empirical concept which has proved useful in the design of new biologically active compounds is that of isosteric replacement.[11] It appears that the overall stereochemical similarity of an 'isostere' with its 'parent' is often more important in determining biological activity than the electronic differences of the interchanged atoms or groups. It has been found, for example, that *N*-[2′-{methyl(phenylethyl)-amino}propyl]propionanilide, 'diampromide' (6), an analogue of methadone in which the quaternary benzylic carbon atom is replaced by a tertiary nitrogen atom, possesses analgetic activity comparable with that of meperidine.[12] A proper rationalization of the action of morphine-like analgetics cannot be attempted until the macromolecule of the receptor active site(s) has been identified and characterized, but one might hope that subtle electronic differences between isosteric compounds might produce differences in selectivity, occupation time and subsequent behaviour of the drug–receptor complex. In addition, various isosteres might differ in rates of metabolic inactivation and/or detoxification. Even if such isosteres fail to provide clinically useful drugs, their study should add to our knowledge and understanding of structure–activity relationships.

The geometry and spatial demands of trivalent phosphorus in phosphines resemble those of a tertiary carbon atom; pentavalent phosphorus in phosphine oxides and phosphine sulphides is sterically and geometrically comparable with a quaternary carbon atom. As part of a broad program to test the concept of isosteric replacement of tertiary (7) or quaternary carbon atoms (9) in biologically active molecules with trivalent (8) or pentavalent phosphorus (10), respectively, we set out to synthesize analogues of (2), (3), (4) and (5) in which a trivalent or pentavalent phosphorus atom replaces the asterisked carbon atom. As an extension of this idea, the tertiary ester group (11) might be replaced by the phosphine acylimide moiety (12).

In a preliminary study we found[13] that some phosphorus isosteres of methadone (3) showed appreciable analgetic activity. This led us to undertake the synthesis of more complex molecules, including, for example, 1,2,3,4,5,6-hexahydro-1,5-methano-4,1-benzazaphosphocines of the general type (14), in order to assess their biological activities in relation to the potent benzomorphan analgetics (4).



(13) (14)

R = alkyl, arylalkyl etc.
X = lone electron pair, O or S

In planning the synthesis of the compounds (14) consideration was given to the adaptation of routes used for the synthesis of 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocines (4), and to the use of known or new methods for the synthesis of phosphorus heterocycles, particularly 1,2-dihydrophosphinolines (13), and 1,2,3,4-tetra-

[11] Daniels, T. C., and Jorgensen, E. C., in 'Textbook of Organic Medicinal and Pharmaceutical Chemistry' (Eds C. O. Wilson, O. Gisvold, and R. F. Doerge) 6th Edn, p. 43 (Lippincott: Philadelphia 1971).

[12] Jacobson, A. E., May, E. L., and Sargent, L. J., in 'Medicinal Chemistry' (Ed. A. Burger) Part II, 3rd Edn, p. 1340 (Wiley–Interscience: New York 1970).

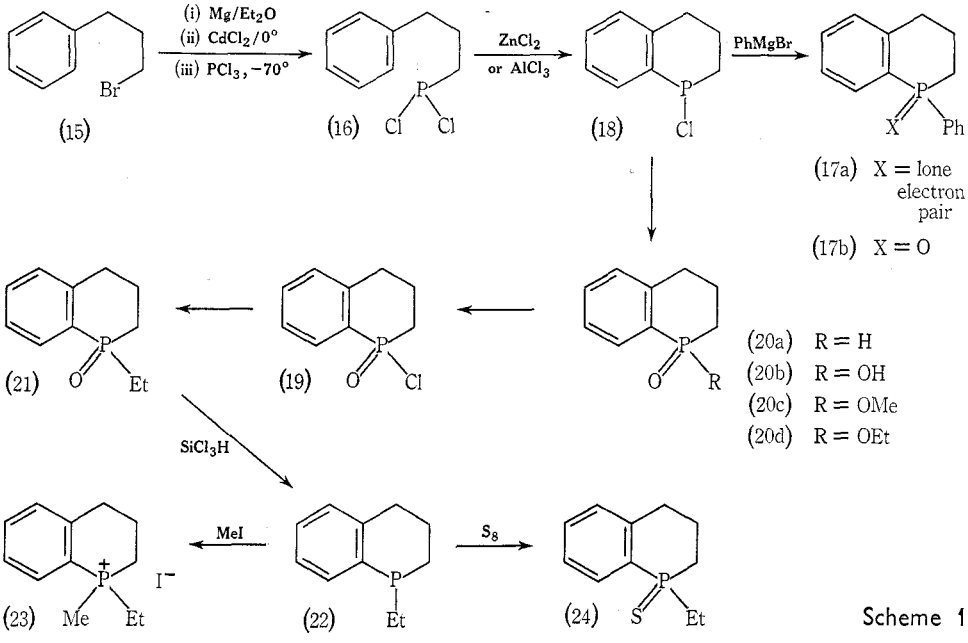
[13] Mollard, S., and Swan, J. M., unpublished data.

hydrophosphinolines such as (18), (19) and (20). The strategy which was eventually decided upon was to construct a 1,2-dihydrophosphinoline with a 2′-aminoethyl group attached to the phosphorus atom (13; R = CH_2CH_2NHR), then effect ring closure to (14) by a nucleophilic addition to the double bond. It was hoped to obtain the required 1,2-dihydrophosphinolines (13) via 1,2,3,4-tetrahydrophosphinolines of type (20). A convenient synthesis of the latter class of compounds is the subject of this paper.

Synthesis of 1,2,3,4-Tetrahydrophosphinolines

The route chosen for the synthesis of 1,2,3,4-tetrahydrophosphinolines involved the preparation and cyclization of 3-phenylpropylphosphonous dichloride (16) (cf. the cyclization of 2-benzylphenylphosphonous dichloride,[14] and analogous preparations of arsinolines[15] and arsindolines[16]).

Bis(3-phenylpropyl)cadmium, prepared from 3-phenylpropyl bromide (15), was added to an excess of phosphorus trichloride in anhydrous ether at −70° (cf. Fox[17]) to give 49% yield of 3-phenylpropylphosphonous dichloride (16) (Scheme 1), which



Scheme 1

showed the expected n.m.r. and mass spectra. Chen and Berlin[18] recently reported the preparation of 3-(2′-naphthyl)propylphosphonous dichloride in 59·5% yield using tetrahydrofuran–ether as solvent. Attempts to convert the phosphonous dichloride (16) into (18) by heating it with one mole equivalent of zinc chloride, or

[14] Doak, G. O., Freedman, L. D., and Levy, J. B., *J. Org. Chem.*, 1964, **29**, 2382.
[15] Burrows, G. J., and Turner, E. E., *J. Chem. Soc.*, 1921, **119**, 426.
[16] Turner, E. E., and Bury, F. W., *J. Chem. Soc.*, 1923, **123**, 2489.
[17] Fox, R. B., *J. Amer. Chem. Soc.*, 1950, **72**, 4147.
[18] Chen, C. H., and Berlin, K. D., *J. Org. Chem.*, 1971, **36**, 2791.

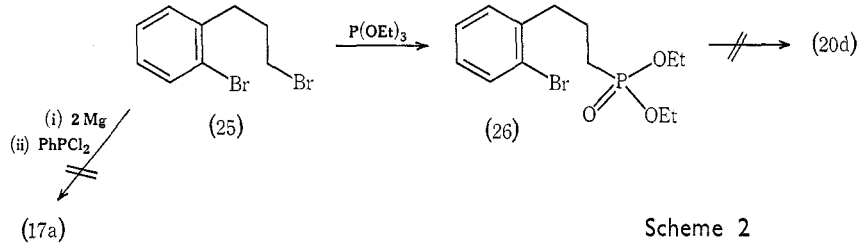
of aluminium chloride (cf.[19]), gave poor yields of the phosphinous chloride (18), due to the formation of non-volatile complexes from which the cyclic phosphinous chloride (18) could not be separated either by treatment with phosphoryl chloride,[20,21] or with one equivalent of water.[21] When the phosphonous dichloride (16) was heated at 220° for 6 h with one-eighth mole equivalent of aluminium chloride (cf. Dewar and Kubba[22]) the crude phosphinous chloride (18) could be obtained in 60% yield by simple distillation from the reaction mixture. Unfortunately, however, this procedure was only satisfactory on a small scale; when less aluminium chloride was used the reaction was sluggish, and a significant amount of polymerization occurred before the reaction was complete. The i.r. spectrum of the phosphinous chloride (18) showed a moderately intense absorption at 1430 cm^{-1} characteristic of an arylphosphorus bond.[23] The p.m.r. spectrum showed H8 as a one-proton doublet of multiplets at δ 7·58, a signal characteristic of an *ortho* proton in the aryl–P group.[24,25] The mass spectrum showed the molecular ion at *m/e* 184 and the base peak at *m/e* 148, which corresponds to M – HCl.

Reaction of (18) with phenylmagnesium bromide gave 62% of 1-phenyl-1,2,3,4-tetrahydrophosphinoline (17a), isolated as the perchlorate salt. Atmospheric oxidation of (17a) gave the corresponding phosphine oxide (17b). Since the foregoing preparation of (18) was not adaptable to the large-scale required for the planned multistep synthesis, other procedures were sought. It was found that the Lewis acid complex of (18) which resulted from the reaction of (16) with slightly more than one mole ratio of zinc chloride or aluminium chloride at 170° could be decomposed completely with concentrated hydrochloric acid under reflux to a mixture of 1,2,3,4-tetrahydrophosphinoline 1-oxide (20a) and the corresponding phosphinic acid (20b). Oxidation of this mixture with alkaline hydrogen peroxide or, preferably, with bromine in dilute hydrochloric acid, gave a high yield (91%) of the phosphinic acid (20b). Esterification of (20b) with diazomethane gave the methyl ester (20c), and reaction of (20b) with sodium carbonate and ethyl bromide in ethanol gave a low yield of the ethyl ester (20d). The reaction of the acid (20b) with thionyl chloride yielded 1-chloro-1,2,3,4-tetrahydrophosphinoline oxide (19), treatment of which with phenylmagnesium bromide afforded 1-phenyl-1,2,3,4-tetrahydrophosphinoline 1-oxide (17b), identical with the material described above. Reaction of the acid chloride (19) with ethylmagnesium bromide gave 59% of the 1-ethylphosphine oxide (21). The procedure of Quin and Bryson[26] for the reduction of phosphine oxides to phosphines with trichlorosilane was used to convert (21) into 1-ethyl-1,2,3,4-tetrahydrophosphinoline (22), treatment of which with methyl iodide afforded 1-ethyl-1-methyl-1,2,3,4-tetrahydrophosphinolinium iodide (23), m.p. 183–185°. Beeby and Mann[27] reported m.p. 184–185° for this compound prepared by another

[19] Campbell, I. G. M., and Way, J. K., *J. Chem. Soc.*, 1961, 2133.
[20] Dye, Jr, W. T., *J. Amer. Chem. Soc.*, 1948, **70**, 2595.
[21] Yakubovich, A. Ya., and Motsarev, G. V., *Zh. Obshch. Khim.*, 1953, **23**, 1547 (*Chem. Abstr.*, 1954, **48**, 10642i).
[22] Dewar, M. J. S., and Kubba, V. P., *J. Amer. Chem. Soc.*, 1960, **82**, 5685.
[23] Corbridge, D. E. C., *Top. Phosphorus Chem.*, 1969, **6**, 235.
[24] Keat, R., *Chem. Ind.* (London), 1968, 1362.
[25] Spence, R. A., Ph.D. Thesis, 1969, Monash University.
[26] Quin, L. D., and Bryson, J. G., *J. Amer. Chem. Soc.*, 1967, **89**, 5984.
[27] Beeby, M. H., and Mann, F. G., *J. Chem. Soc.*, 1951, 411.

route. Oxidation of the phosphine (22) with sulphur gave the phosphine sulphide (24) in good yield.

With pure samples of the 1,2,3,4-tetrahydrophosphinolines (17a) and (20d) in hand to facilitate the detection of products, we attempted conversion of the dibromide (25) into 1-phenyl-1,2,3,4-tetrahydrophosphinoline (17a) by modification of a synthesis of 1,1-diphenyl-1,2,3,4-tetrahydro-1-silanaphthalene.[28] We also explored a possible synthesis of the ester (20d) from (25) via the phosphonate (26) (Scheme 2).



Scheme 2

This second sequence was modelled on a synthesis of phosphorinanes by Howard and Braid.[29] 3-(2′-Bromophenyl)propan-1-ol[28] was converted into the dibromide (25) and the derived dimagnesium complex[28] was allowed to react with phenylphosphonous dichloride. G.l.c. analysis of the small amount of colourless oil which was obtained showed that little, if any, of 1-phenyl-1,2,3,4-tetrahydrophosphinoline (17a) was present. An Arbusov reaction of the dibromide (25) with triethyl phosphite gave diethyl 3-(2′-bromophenyl)propylphosphonate (26), the structure of which was confirmed by spectral data and microanalysis. The reaction of (26) with magnesium in refluxing ether followed by acidification gave 3-phenylpropylphosphonate as the only volatile product.

It was apparent that the Grignard reagent had formed smoothly but had failed to effect nucleophilic attack on the phosphonate group. More forcing conditions were then tried. When the Grignard reagent from (26) was heated in anisole at 140° (cf.[29]) none of the ester (20d) was identified in the crude product. In another reaction, the Grignard reagent was heated in anisole containing magnesium bromide to coordinate with the phosphoryl group. The aim of this was to render the phosphorus atom more susceptible to nucleophilic attack,[29–31] but g.l.c. analysis of the neutral product failed to show significant quantities of (20d). The acidic portion of the product was esterified with diazomethane, but g.l.c. analysis of the product showed only an insignificant quantity of the methyl ester (20c). This approach was abandoned and the successful method described above was used to prepare large quantities of 1-chloro-1,2,3,4-tetrahydrophosphinoline 1-oxide (19), which was used for the synthesis of some 1,2,3,4,5,6-hexahydro-1,5-methano-4,1-benzazaphosphocines (14), described in the following paper.

[28] Gilman, H., and Marrs, O. L., *J. Org. Chem.*, 1965, **30**, 325.
[29] Howard, E., Jr, and Braid, M., Abstr. Papers 140th A.C.S. Meeting, 1961, 40Q; *Diss. Abstr.*, 1962, **23**, 434.
[30] Berlin, K. D., Austin, T. H., Peterson, M., and Nagabhushanam, M., *Top. Phosphorus Chem.*, 1964, **1**, 34.
[31] Berlin, K. D., and Butler, G. B., *Chem. Rev.*, 1960, **60**, 243.

Experimental

Melting points and boiling points are uncorrected. Infrared spectra were recorded with a Perkin–Elmer 257 grating spectrometer. Only the wavenumbers of major absorptions are reported. Ultraviolet spectra were determined with a Unicam SP 800A spectrometer. P.m.r. spectra were measured with a Varian A56/60 spectrometer operating at 60 MHz, or with a Varian HA 100 spectrometer. P.m.r. data are reported in the following manner: chemical shifts (δ) are in p.p.m. from internal $SiMe_4$. Multiplicity: s, singlet; d, doublet; t, triplet; q, quartet with intensities approximately 1 : 3 : 3 : 1; dd, doublet of doublets; ddd, double doublet of doublets, etc.; m, multiplet, dm, doublet of multiplets, etc.; b, broad; (exch.) exchanges on shaking with D_2O. Coupling constants (J), in Hz, are actually splittings measured from first-order considerations only. Relative intensities are given in the number of protons, e.g. 3H denotes a relative intensity of three protons.

Mass spectra were recorded at 70 eV with a Hitachi Perkin–Elmer RMU-6E spectrometer. Unless otherwise stated, ions of relative intensity >5% are recorded; observed metastables are reported (calculated value) together with their probable origins, m* ($m^1 \rightarrow m^2$).

Gas–liquid chromatography was carried out with a Perkin–Elmer 881 gas chromatograph using a flame ionization detector and glass columns as follows: A, 6 ft by 1/4 in., 20% (w/w) SE-30 silicone rubber/silanized Chromosorb W (80–100 mesh); B, 6 ft by 1/4 in., 20% (w/w) DC-200 silicone oil/silanized Chromosorb W (80–100 mesh). Silica gel G and silica gel PF 254 were used for analytical and preparative thin-layer chromatography (t.l.c.) respectively.

Microanalyses were carried out by the Australian Microanalytical Service, Melbourne.

(*a*) *3-Phenylpropyl Bromide* (*15*)

A mixture of 3-phenylpropan-1-ol (600 g, 4·4 mol), hydrobromic acid (1000 ml of 48%) and concentrated sulphuric acid (40 g) was heated under reflux for 6 h. Isolation with ether gave 3-phenylpropylbromide (836 g, 95%), b.p. *108–110°/15 mm* (*lit.*[32] 109°/11 mm), the purity of which was confirmed by g.l.c. (column A, 80–250° at 16°/min, 30 ml/min nitrogen, R_t 7·4 min).

(*b*) *3-Phenylpropylphosphonous Dichloride* (*16*)

A solution of 3-phenylpropylmagnesium bromide was prepared from 3-phenylpropyl bromide (240 g, 1·2 mol) in anhydrous ether (1200 ml) and magnesium turnings (40 g, 1·66 mol). The excess of magnesium was removed by filtration through glass wool with a positive pressure of nitrogen. The filtrate was cooled in an ice bath and stirred vigorously under nitrogen whilst powdered anhydrous cadmium chloride (120 g, 0·66 mol, re-dried at 150°/1 mm for 24 h over phosphorus pentoxide) was added rapidly. The suspension was stirred at 0° for 2 h, then added in 200 ml portions to a rapidly stirred solution of freshly distilled phosphorus trichloride (274 g, 2·4 mol) in anhydrous ether (200 ml). During the addition the temperature of the reaction mixture was kept below −20°. The last traces of the cadmium reagent were flushed into the phosphorus trichloride mixture with additional anhydrous ether. The cooling bath was removed and the mixture allowed to warm to room temperature (30 min), then heated under reflux for 2·5 h. When the reaction mixture was cooled to room temperature a thick white precipitate separated out. Most of the ethereal supernatant was decanted, and the remainder was filtered in vacuum through a sintered glass Buchner funnel. Ether washings of the precipitate were combined with the main ether solution and evaporated. G.l.c. (column A, 80–259° at 16°/min, 30 ml/min nitrogen) indicated that the residue contained four major volatile components (R_t 3·1, 6·3, 8·9, 11·8 min). The lowest-boiling component (R_t 3·1), presumably the excess of phosphorus trichloride, was removed by distillation under water pump pressure and the remaining liquid was distilled carefully under high vacuum through a 9-in. Vigreux column (packed or spiral columns were unsuitable because of the high viscosity of the product). The product was obtained as a pungent colourless liquid (130 g, 49%), b.p. 76–79°/0·2 mm. G.l.c. revealed that this material (R_t 8·9 min) was contaminated with about 5% of an impurity (R_t 6·3 min). A pure sample of *3-phenylpropylphosphonous dichloride* was obtained as a middle fraction after redistillation, b.p. 78°/0·2 mm (Found: C, 48·6; H, 5·0; P, 14·2. $C_9H_{11}Cl_2P$ requires C, 48·9; H, 5·0; P, 14·0%). ν_{max} (film): 3070, 3050, 3020, 2920, 2850, 1600, 1495, 1450, 1075, 1030, 750, 705 cm^{-1}. P.m.r. (100 MHz, $CDCl_3$): 7·0–7·3, m, 5H (aromatic); 2·68, t, $J_{2,3}$

[32] Rupe, H., and Burgin, J., *Ber. Deut. Chem. Ges.*, 1910, **43**, 172.

7, 2H (H 3,3); 1·8–2·5, m, 4H (H 1,1,2,2). The mass spectrum showed the molecular ion at *m/e* 220 (1·4) and the expected isotope peaks at *m/e* 222 (1·0) and 224 (0·19), respectively, together with 119 (6), 118 (8), 116 (7), 103 (7), 101 (6), 92 (10), 91 (100), 89 (7), 78 (8), 77 (11), 66 (6), 65 (38), 63 (12), 52 (6), 51 (21), 50 (7), 41 (26%).

(*c*) *1-Chloro-1,2,3,4-tetrahydrophosphinoline* (*18*)

A mixture of anhydrous aluminium chloride (0·30 g, 2·26 mmol) and 3-phenylpropylphosphonous dichloride (4·0 g, 18·2 mmol) was heated in an air bath at 220° under nitrogen. As the temperature of the mixture was raised a rapid evolution of hydrogen chloride ensued, and the mixture became homogeneous. The evolution of hydrogen chloride then slowed, and apparently ceased after 6 h. The mixture was cooled and the volatile components distilled (bulb-to-bulb) at 130°/0·01 mm. Fractional distillation of this material through a semimicro Vigreux column gave 1-chloro-1,2,3,4-tetrahydrophosphinoline as a colourless fuming liquid (2·0 g, 60%), b.p. 55–56°/0·001 mm, the purity of which was confirmed by g.l.c. (column A, 80–250° at 24°/min, 30 ml/min nitrogen, R_t 5·8 min) (Found: C, 59·1; H, 5·3; P, 17·2. $C_9H_{10}ClP$ requires C, 58·6; H, 5·5; P, 16·8%). ν_{max} (film): 3070, 3050, 3020, 2940, 2880, 1600, 1560, 1490, 1470, 1430 (Ar–P), 1400, 1300, 1270, 1220, 1170, 1150, 1080, 1030, 1000, 970, 920, 880, 870, 820, 800, 770, 750, 720, 700, 680, 660 cm^{-1}. P.m.r. (100 MHz, $CDCl_3$): 7·58, dm, $J_{8,P}$ 11·0, 1H (H 8); 7·0–7·4, m, 3H (H 5,6,7); 2·82, m, 2H (H 4,4); 1·8–2·5, m, 4H (H 2,2,3,3). Mass spectrum (*m/e* >10%): 184 (18), 169 (17), 156 (11), 149 (30), 148 (100), 147 (33), 145 (13), 134 (14), 133 (71), 121 (50), 120 (52), 118 (22), 117 (23), 116 (27), 115 (82), 107 (28), 105 (10), 104 (15), 103 (17), 102 (15), 95 (18), 93 (12), 92 (13), 91 (66), 89 (27), 81 (21), 80 (15), 78 (28), 77 (62), 76 (14), 75 (14), 74 (13), 69 (33), 68 (18), 65 (36), 64 (11), 63 (50), 62 (16), 57 (22), 56 (13), 53 (16), 52 (16), 51 (56), 50 (28), 46 (14), 41 (20%).

On a somewhat larger scale with 3-phenylpropylphosphonous dichloride (12·0 g, 54·5 mmol) and aluminium chloride (1·0 g, 7·5 mmol), the reaction yielded a 2 : 1 mixture of 3-phenylpropylphosphonous dichloride and 1-chloro-1,2,3,4-tetrahydrophosphinoline, estimated by characteristic signals in the p.m.r. spectra of these compounds.

(*d*) *1-Phenyl-1,2,3,4-tetrahydrophosphinoline* (*17a*)

A solution of 1-chloro-1,2,3,4-tetrahydrophosphinoline (4·0 g, 21·7 mmol) in anhydrous ether (20 ml) was added slowly, under nitrogen, to a vigorously stirred solution of phenylmagnesium bromide, prepared from bromobenzene (4·1 g, 26·0 mmol) and magnesium (0·61 g, 26 mmol) in anhydrous ether (40 ml). The reaction mixture was heated under reflux for 2 h, then the excess of Grignard reagent was hydrolysed by the addition of a saturated solution of ammonium chloride. The ether layer, together with benzene extracts of the aqueous layer, was washed with water, dried (Na_2SO_4), and evaporated. The residual colourless oil was dissolved in ether and perchloric acid (70%) was added. The colourless solid which formed was filtered off, washed with ether and recrystallized from ethanol to yield pure *1-phenyl-1,2,3,4-tetrahydrophosphinoline perchlorate* as colourless crystals (4·4 g, 62%), m.p. 167–168° (Found: C, 54·9; H, 5·3; P, 9·9. $C_{15}H_{16}ClO_4P$ requires C, 55·1; H, 5·0; P, 9·5%). The free phosphine was obtained by stirring a portion of the perchlorate with 50% sodium hydroxide followed by extraction with benzene. The combined extracts were washed with a saturated solution of ammonium chloride, then with water, dried (Na_2SO_4) and evaporated. Bulb-to-bulb distillation of the residue at 120°/0·001 mm gave *1-phenyl-1,2,3,4-tetrahydrophosphinoline* as colourless, air-sensitive crystals, m.p. 80–81°, the purity of which was confirmed by g.l.c. (column B, 80–250° at 24°/min, 30 ml/min nitrogen, R_t 8·6 min) (Found: C, 79·0; H, 6·5. $C_{15}H_{15}P$ requires C, 79·6; H, 6·7%). ν_{max} (film): 3050, 3000, 2920, 2850, 1585, 1475, 1435 (Ar–P), 1270, 1165, 1040, 900, 830, 800, 770, 750, 725 cm^{-1}. P.m.r. (60 MHz, CCl_4): 7·0–7·5, m, 9H (aromatic); 2·82, m, 2H (H 4,4); 1·6–2·2, m, 4H (H 2,2,3,3). Mass spectrum (*m/e* >10%): 226 (11), 165 (16), 148 (12), 147 (15), 133 (36), 115 (33), 110 (12), 109 (13), 107 (19), 105 (65), 103 (10), 102 (10), 91 (33), 89 (11), 85 (40), 83 (62), 82 (31), 81 (15), 79 (11), 78(32), 77(100), 76 (12), 75 (12), 74 (35), 73 (27), 69 (21), 68 (20), 65 (17), 63 (18), 59 (36), 57 (19), 56 (13), 55 (70), 54 (33), 53 (26), 52 (22), 51 (76), 50 (32), 49 (17), 48 (20), 47 (39), 45 (22), 44 (20), 43 (72), 42 (46), 41 (100), 40 (22%).

A sample exposed to the atmosphere slowly liquified over a 12 h period. Preparative t.l.c. (chloroform/methanol 15/1) of a sample which had been exposed to the atmosphere for 1 week gave one major band (R_F 0·53) of a new compound. Elution of this with methanol, and bulb-to-bulb

distillation of the residue at 170°/0·005 mm, gave a colourless hygroscopic liquid which slowly crystallized and gave i.r., p.m.r. and mass spectra identical with those of an authentic sample of 1-phenyl-1,2,3,4-tetrahydrophosphinoline 1-oxide (17b) (see later).

(*e*) *1-Hydroxy-1,2,3,4-tetrahydrophosphinoline 1-Oxide* (*20b*)

A mixture of 3-phenylpropylphosphonous dichloride (120 g, 0·54 mol) and freshly fused, powdered zinc chloride (90 g, 0·66 mol) was stirred rapidly and heated under a nitrogen atmosphere in an oil bath kept at 170°. A rapid evolution of hydrogen chloride ensued and the mixture became homogeneous; it was sometimes necessary to heat the mixture above 170° for a short period to initiate the reaction. After approximately 4 h, the evolution of hydrogen chloride appeared to have ceased. The mixture was heated for a further 30 min, then concentrated hydrochloric acid (300 ml) was added cautiously to the hot mixture. The mixture was heated under reflux for 15 min, then the hydrochloric acid was removed under vacuum (water pump). The thick cream-coloured oil was dissolved in dilute hydrochloric acid (500 ml) and stirred at 0° whilst bromine was added cautiously until the bromine colour persisted. The solution was stirred for a further 1 h, extracted with chloroform, the extract was washed several times with dilute hydrochloric acid, then the acidic product was extracted into sodium hydroxide solution (2M). The alkaline extract was washed with chloroform, acidified with concentrated hydrochloric acid and the product isolated with chloroform. The colourless viscous oil crystallized exothermically (90 g, 91%), m.p. 142–144°. Recrystallization from ethanol followed by sublimation at 135°/0·001 mm gave a pure sample of *1-hydroxy-1,2,3,4-tetrahydrophosphinoline 1-oxide*, m.p. 146–147° (Found: C, 59·3; H, 5·8; P, 17·2. $C_9H_{11}O_2P$ requires C, 59·3; H, 6·1; P, 17·0%). ν_{max} (Nujol): 2550, 2280, 1630 (all due to P(O)OH), 1600, 1450 (Ar–P), 1315, 1230, 1180, 1165, 1150, 1100, 1030, 980, 970, 800, 785 cm^{-1}. P.m.r. (100 MHz, $CDCl_3$): 12·76, s, 1H(>P(=O)OH); 7·91, dm, $J_{8,P}$ 13·0, 1H (H 8), this signal collapsed to a d with a splitting of 13·0 Hz upon irradiation of the multiplet at δ 7·0–7·4; 7·0–7·4, m, 3H (H 5,6,7); 2·79, m, 2H (H 4,4); 1·9–2·4, m, 4H (H 2,2,3,3). Mass spectrum: *m/e* 182 (30), 183 (6), 181 (31), 167 (28), 163 (15), 149 (17), 141 (7), 133 (8), 118 (7), 117 (37), 116 (34), 115 (72), 107 (8), 105 (8), 103 (12), 102 (9), 92 (14), 91 (73), 90 (64), 89 (100), 88 (6), 87 (7), 86 (6), 79 (19), 78 (33), 77 (60), 76 (18), 75 (22), 74 (18), 66 (5), 65 (80), 64 (42), 63 (97), 62 (35), 61 (6), 53 (10), 52 (24), 51 (96), 50 (52), 49 (5), 48 (13), 47 (83), 43 (5), 41 (28), 40 (30%); m*: 180 (182 → 181), 153·2 (182 → 167), 146·8 (181 → 163), 132·9 (167 → 149), 113·1 (117 → 115).

A reaction carried out as above but with aluminium chloride instead of zinc chloride gave a 75% yield of the crude product.

(*f*) *1,2,3,4-Tetrahydrophosphinoline 1-Oxide* (*20a*)

3-Phenylpropylphosphonous dichloride was allowed to react with zinc chloride as in (*e*), but the product was oxidized with alkaline hydrogen peroxide. The oil obtained from evaporation of the concentrated hydrochloric acid solution was dissolved in sodium hydroxide (500 ml of 2M) and hydrogen peroxide (110 ml of 30%) was added. The mixture was stirred for 12 h, then acidified and extracted with chloroform. The acidic and neutral fractions were isolated as above. The acid fraction (40 g, 41%), m.p. 142–144°, crystallized upon standing and gave i.r. and p.m.r. spectra identical with those of 1-hydroxy-1,2,3,4-tetrahydrophosphinoline 1-oxide described in (*e*). The neutral fraction yielded colourless deliquescent crystals, m.p. 98–102°, after drying at 0·001 mm over phosphorus pentoxide for 10 days. The purity of this material was confirmed by t.l.c. and g.l.c. (column A, 80–250° at 24°/min, 30 ml/min nitrogen, R_t 5·5 min) (Found: C, 65·1; H, 6·8; P, 18·1. $C_9H_{11}OP$ requires C, 65·1; H, 6·7; P, 18·6%). ν_{max} (Nujol): 2315 (P–H), 1590, 1440 (Ar–P), 1300, 1190 (P=O), 1150, 1140, 1130, 1085, 990, 940, 760, 735, 720 cm^{-1}. λ_{max} (ε): 264 (663), 271 (1056), 278sh nm (945), P.m.r. (100 MHz, $CDCl_3$): 7·83, dm, $J_{8,P}$ 13·6, 1H (H 8); 7·57, distorted ddd, $J_{1,P}$ 476, the other splittings which could not be assigned were 4·3 and 3·2 Hz, 1H (H 1), this signal collapsed to a sharp d with splitting 476 Hz upon irradiation of the multiplet at δ 1·7–2·4; 7·0–7·5, m, 3H (H 5,6,7); 2·82, m, 2H (H 4,4); 1·7–2·4, m, 4H (H 2,2,3,3). Mass spectrum (*m/e*): 166 (100), 167 (12), 165 (78), 151 (41), 149 (6), 148 (11), 147 (16), 133 (18), 119 (5), 117 (17), 116 (6), 115 (37), 109 (5), 105 (9), 91 (46), 89 (13), 78 (6), 77 (11), 65 (17), 63 (14), 51 (13), 50 (5), 47 (5), 41 (7%). m*: 164 (166 → 165), 137·4 (166 → 151), 130·9 (165 → 147), 113·1 (117 → 115). A sample of the product which had been exposed to the atmosphere for a short time showed additional broad absorption bands at 3400 and 1630 cm^{-1}, which may be attributed to the presence of water.

Re-treatment of the crude 1,2,3,4-tetrahydrophosphinoline 1-oxide with alkaline hydrogen peroxide as above yielded a further crop of 1-hydroxy-1,2,3,4-tetrahydrophosphinoline 1-oxide (50 g, 50%) from the acidic fraction.

(g) 1-Methoxy-1,2,3,4-tetrahydrophosphinoline 1-Oxide (20c)

A sample of crude 1-hydroxy-1,2,3,4-tetrahydrophosphinoline 1-oxide (10 g, 55 mmol) was dissolved in methanol and an ethereal solution of diazomethane was added until the yellow diazomethane colour persisted. Evaporation of the solvent and bulb-to-bulb distillation of the residue at 130°/0·005 mm gave *1-methoxy-1,2,3,4-tetrahydrophosphinoline 1-oxide* as a colourless hygroscopic oil (1·0 g, 93%), b.p. 110°/0·005 mm, the purity of which was confirmed by g.l.c. (column B, 80–250° at 24°/min, 30 ml/min nitrogen, R_t 7·1 min), t.l.c. (R_F 0·50, chloroform/methanol 30/1), and the p.m.r. spectrum, which showed only one set of doublets, δ 3·64, attributable to a >P(=)OCH$_3$ group. The analytical sample was obtained by preparative t.l.c. followed by bulb-to-bulb distillation at 130°/0·005 mm. A sample of this was redistilled twice and sealed for analysis without exposure to the atmosphere. However, the result indicated that the sample had taken up water during handling for analysis (Found: C, 60·0; H, 7·0; P, 15·6. $C_{10}H_{13}O_2P$ requires C, 61·2; H, 6·7; P, 15·8. $C_{10}H_{13}O_2P,0·2H_2O$ requires C, 60·1; H, 6·8; P, 15·5%). Analysis of a sample which had been exposed to the atmosphere for several days indicated that it had taken up more than one mole equivalent of water (Found: C, 55·5; H, 7·1; P, 14·0. $C_{10}H_{13}O_2P,1·1H_2O$ requires C, 55·6; H, 7·1; P, 14·3%). ν_{max} (film): 2930, 1600, 1440 (Ar–P), 1310, 1220 (P=O), 1150, 1090, 1040 (P–O–CH$_3$), 1010, 930, 800, 780, 770 cm^{-1}. P.m.r. (100 MHz, $CDCl_3$): 7·82, dm, $J_{8,P}$ 12·2, 1H (H 8); 7·05–7·5, m, 3H (H 5,6,7); 3·64, d, $J_{P,OMe}$ 10·6; 3H (>P(=)OCH$_3$); 2·81, m, 2H (H 4,4); 1·9–2·4, m, 4H (H 2,2,3,3). Mass spectrum (*m/e* >10%): 196 (23), 195 (17), 181 (30), 166 (26), 165 (16), 163 (21), 153 (27), 151 (13), 149 (16), 147 (14), 133 (16), 117 (50), 116 (50), 115 (100), 109 (16), 107 (13), 105 (15), 103 (12), 102 (11), 91 (81), 90 (50), 89 (97), 87 (10), 83 (11), 79 (25), 78 (30), 77 (53), 76 (13), 75 (17), 74 (14), 69 (12), 65 (60), 64 (32), 63 (88), 62 (27), 55 (13), 52 (18), 51 (72), 50 (32), 47 (68), 45 (12), 44 (13), 43 (26), 42 (13), 41 (36), 40 (17%); m*: 113·1 (117 → 115). The appearance of broad bands at 3400 and 1630 cm^{-1} in the i.r. spectrum of a sample which had been exposed to the atmosphere is consistent with the hydroscopic nature of the product.

(h) 1-Ethoxy-1,2,3,4-tetrahydrophosphinoline 1-Oxide (20d)

A mixture of 1-hydroxy-1,2,3,4-tetrahydrophosphinoline 1-oxide (1·5 g, 8·2 mmol), sodium carbonate (1·0 g, 9·5 mmol) and ethyl bromide (2·0 g, 18·2 mmol) in ethanol (20 ml) was heated under reflux for 4 h. The ethanol was evaporated in vacuum, the residue treated with sodium hydroxide solution (2M), and the neutral material extracted into chloroform. The extract was washed with saturated ammonium chloride, then with water, dried (Na_2SO_4) and evaporated. Preparative t.l.c. (chloroform/methanol 15/1) of the residue gave one major band and subsequent bulb-to-bulb distillation at 140°/0·003 mm gave *1-ethoxy-1,2,3,4-tetrahydrophosphinoline 1-oxide* as a colourless hygroscopic oil (200 mg, 12%). The purity of this material was confirmed by g.l.c. (column A, 80–250° at 24°/min, 30 ml/min nitrogen, R_t 8·1 min) (Found: C, 59·9; H, 7·2; P, 14·5. $C_{11}H_{15}O_2P$ requires C, 62·8; H, 7·2; P, 14·7. $C_{11}H_{15}O_2P,0·5H_2O$ requires C, 60·2; H, 7·3; P, 14·1%). ν_{max} (film): 2995, 2950, 1605, 1485, 1445 (Ar–P), 1395, 1305, 1295, 1270, 1220 (P=O), 1160, 1150, 1090, 1030 (P–O–CH$_2$), 1005, 955, 930, 875, 830, 795, 760, 740 cm^{-1}. P.m.r. (100 MHz, $CDCl_3$): 7·82, dm, $J_{8,P}$ 12·5, 1H (H 8); 7·05–7·5, m, 3H (H 5,6,7); 4·03, AB part of an ABMX$_3$-type pattern for which $|J_{A,M}| \approx |J_{B,M}| \approx 10$, $|J_{A,B}| \approx 14$, $|J_{A,X}| \approx |J_{B,X}| \approx 7$, $|\nu_A - \nu_B| \approx 28·4$ Hz, 2H (>P(=)OCH$_2$–); 2·81, m, 2H (H 4,4); 1·9–2·4, m, 4H (H 2,2,3,3); 1·24, t, J(CH$_2$,CH$_3$) 7, 3H (=POCH$_2$CH$_3$). Mass spectrum (*m/e*): 210 (69), 211 (14), 209 (7), 183 (12), 182 (83), 181 (100), 168 (6), 167 (46), 166 (52), 165 (31), 164 (10), 163 (28), 154 (7), 153 (8), 151 (13), 149 (16), 148 (7), 147 (25), 146 (5), 145 (7), 137 (5), 136 (8), 134 (5), 133 (14), 121 (5), 118 (9), 117 (41), 116 (42), 115 (80), 109 (11), 107 (10), 103 (10), 102 (8), 92 (7), 91 (53), 90 (34), 89 (53), 83 (6), 79 (8), 78 (17), 77 (26), 76 (7), 75 (7), 65 (30), 64 (11), 63 (29), 62 (7), 52 (6), 51 (21), 50 (8), 47 (26), 45 (9), 43 (10), 41 (9%); m*: 180 (182 → 181), 157·8 (210 → 182), 153·2 (182 → 167), 146·8 (181 → 163), 130·9 (165 → 147), 113·1 (117 → 115). The appearance of broad bands at 3400 and 1630 cm^{-1} in the i.r. spectrum of a sample which had been exposed to the atmosphere is consistent with the hygroscopic nature of the product.

(i) 1-Ethyl-1,2,3,4-tetrahydrophosphinoline 1-Oxide (21)

A solution of 1-hydroxy-1,2,3,4-tetrahydrophosphinoline 1-oxide (7·0 g, 38·4 mmol) in thionyl chloride (30 ml) was heated under reflux for 30 min. The excess of thionyl chloride was evaporated in vacuum, then toluene was added and evaporated to remove the last traces of thionyl chloride. The residual light yellow crystalline solid gave a p.m.r. spectrum consistent with 1-chloro-1,2,3,4-tetrahydrophosphinoline 1-oxide (31). P.m.r. (60 MHz, $CDCl_3$): 7·95, dm, $J_{8,P}$ 15·0, 1H (H 8); 7·0–7·6, m, 3H (H 5,6,7); 1·8–3·1, m, 6H (H 2,2,3,3,4,4). To a vigorously stirred solution of this material in anhydrous ether was added during 30 min a filtered solution of ethylmagnesium bromide prepared from ethyl bromide (6·0 g, 54·6 mmol), magnesium (1·5 g, 61·7 mmol) and anhydrous ether (50 ml). A tacky orange material separated out. The mixture was stirred and heated under reflux for 30 min, then cooled, and a solution of ammonium chloride (2M) was added to decompose the excess of Grignard reagent. The ether layer, together with chloroform extracts of the aqueous phase, were washed with a solution of sodium hydroxide (2M), then with water, dried (Na_2SO_4) and evaporated. Bulb-to-bulb distillation of the residue at 110°/0·01 mm afforded a colourless hygroscopic liquid (4·4 g, 59%), g.l.c. of which (column A, 80–250° at 24°/min, 30 ml/min nitrogen) showed a major component (R_t 8·0 min), and a minor component (R_t 10·8, approximately 5% by peak areas). Preparative t.l.c. of a portion (chloroform/methanol 8/1), elution of the major band (R_F 0·50) with methanol, and distillation of the residue yielded *1-ethyl-1,2,3,4-tetrahydrophosphinoline 1-oxide* as a colourless hygroscopic oil, the purity of which was confirmed by g.l.c. A portion of this material was distilled and sealed for microanalysis without exposure to the atmosphere (Found: C, 67·6; H, 7·9; P, 15·8. $C_{11}H_{15}OP$ requires C, 68·0; H, 7·8; P, 16·0%). ν_{max} (film): 2970, 2930, 2780, 1595, 1480, 1460, 1440 (Ar–P), 1410, 1305, 1270, 1240, 1175 (P=O), 1150, 1135, 1085, 1035, 820, 790, 760, 735 cm^{-1}. λ_{max} (ε): 264 (952), 269 (1190), 277 nm (1165). P.m.r. (100 MHz, $CDCl_3$): 7·77, dm, $J_{8,P}$ 11·6, 1H (H 8), this signal collapsed to a d with a splitting of 11·0 Hz upon irradiation of the multiplet at δ 7·0–7·4; 7·0–7·4, m, 3H (H 5,6,7); 2·82, m, 2H (H 4,4); 1·6–2·4, m, 6H (H 2,2,3,3, $=PCH_2CH_3$); 1·10, dt, $J(P,CH_2CH_3)$ 17·2, $J(CH_2,CH_3)$ 7, 3H ($>P(=)CH_2CH_3$). Mass spectrum (*m/e*): 194 (82), 195 (10), 193 (36), 179 (22), 167 (10), 166 (100), 165 (57), 151 (14), 149 (8), 148 (8), 147 (52), 145 (7), 137 (7), 133 (8), 117 (22), 116 (17), 115 (40), 109 (10), 107 (5), 103 (5), 91 (20), 90 (5), 89 (14), 77 (9), 65 (12), 63 (8), 51 (6), 47 (8%); m*: 142 (194 → 166), 137·4 (166 → 151), 130·9 (165 → 147), 113·1 (117 → 115).

A sample briefly exposed to the atmosphere showed additional broad absorption bands at 3400 and 1630 cm^{-1} in the i.r. spectrum, and additional sharp singlets at δ 3·06 and 4·62 in the p.m.r. spectrum, due to the uptake of water.

(j) 1-Ethyl-1-methyl-1,2,3,4-tetrahydrophosphinolinium Iodide (23)

A solution of crude 1-ethyl-1,2,3,4-tetrahydrophosphinoline 1-oxide (0·50 g, 2·58 mmol) in benzene (20 ml) was dried by azeotropic distillation, then cooled to room temperature and placed under a nitrogen atmosphere. Whilst the solution was stirred, trichlorosilane (1 ml, 10 mmol) was added and the mixture heated under reflux for 2 h. G.l.c. analysis of a small sample of the organic phase (alkali washed) showed it to contain one major component (column A, 80–250° at 24°/min, 30 ml/min, nitrogen R_t 5·66), presumably the desired 1-ethyl phosphine (cf. R_t 8·0 min for the phosphine oxide). The benzene solution was washed with sodium hydroxide (2M), then the basic material was extracted into dilute hydrochloric acid (2M). The acid extract was washed with benzene, basified with sodium hydroxide (5M), and the product isolated with benzene. Bulb-to-bulb distillation at 100°/0·01 mm afforded a colourless liquid which upon treatment with methyl iodide rapidly formed a white solid. Crystallization from ethanol afforded 1-ethyl-1-methyl-1,2,3,4-tetrahydrophosphinolinium iodide as colourless crystals (150 mg, 18%), m.p. 183–185° (lit.[33] 184–185°). The methiodide salt rapidly turned bright yellow upon exposure to the light.

(k) 1-Ethyl-1,2,3,4-tetrahydrophosphinoline 1-Sulphide (24)

A solution of 1-ethyl-1,2,3,4-tetrahydrophosphinoline 1-oxide (0·60 g, 3·1 mmol) in benzene (30 ml) was treated with trichlorosilane (1 ml, 10 mmol) and the mixture heated under reflux for 2 h. The excess of trichlorosilane was removed by evaporation of the solution to half of its original

[33] Fry, E. M., and May, E. L., *J. Org. Chem.*, 1961, **26**, 2592.

volume. Sulphur (1 g) was added and the mixture was stirred at room temperature for 12 h. The benzene solution was washed alternatively with sodium hydroxide solution (2M) and a saturated solution of ammonium chloride, dried (Na_2SO_4) and evaporated. Most of the excess of sulphur was removed by extraction of the product into a small volume of chloroform. The residual oil from this extract was subjected to preparative t.l.c. (successive developments with benzene and chloroform). Bulb-to-bulb distillation of the material from the major band (R_F 0·65) at 150°/0·01 mm afforded *1-ethyl-1,2,3,4-tetrahydrophosphinoline 1-sulphide* as a colourless hygroscopic liquid (0·48 g, 77%). G.l.c. (column A, 80–250° at 24°/min, 30 ml/min) showed only one peak, R_t 8·3 min (cf. the phosphine oxide R_t 8·0 min). A portion of this material was redistilled twice and sealed without exposure to the atmosphere. However, microanalysis of this sample, and a sample obtained by further preparative t.l.c., gave consistently low carbon values, presumably due to the rapid uptake of water when they were opened for analysis (Found: C, 61·5; H, 7·2; P, 14·8; S, 15·0. $C_{11}H_{15}PS$ requires C, 62·8; H, 7·2; P, 14·7; S, 15·1%). ν_{max} (film): 3050, 2965, 2935, 2875, 1590, 1475, 1450, 1440 (Ar–P), 1410, 1160, 1135, 1080, 1040, 1020, 1000, 820, 785, 755, 735, 695 cm^{-1}. λ_{max} (ε): 250 nm (2590). P.m.r. (100 MHz, $CDCl_3$): 7·85, dm, $J_{8,P}$ 13·8, 1H (H 8); 7·0–7·4, m, 3H (H 5,6,7); 2·92, m, 2H (H 4,4); 1·7–2·5, m, 6H (H 2,2,3,3, >P(=)CH_2CH_3); 1·16, dt, J(P,CH_2CH_3) 19·0, J(CH_2,CH_3) 7·0, 3H (>P(=)CH_2CH_3). Mass spectrum (*m/e*): 210 (100), 212 (5), 211 (25), 209 (5), 195 (5), 183 (12), 182 (82), 181 (19), 178 (6), 153 (14), 152 (12), 149 (53), 148 (90), 147 (35), 146 (5), 145 (10), 135 (5), 133 (21), 121 (8), 117 (12), 116 (12), 115 (26), 109 (5), 197 (5), 91 (17), 89 (6), 77 (11), 65 (7), 63 (13), 51 (5%); m*: 157·8 (210 → 182), 120·3 (182 → 148), 113·1 (117 → 115). The appearance of broad absorption bands at 3400 and 1630 cm^{-1} in the i.r. spectrum of a sample which had been exposed to the atmosphere is consistent with the hygroscopic nature of the compound.

(*l*) *1-Phenyl-1,2,3,4-tetrahydrophosphinoline 1-Oxide* (*17b*)

1-Hydroxy-1,2,3,4-tetrahydrophosphinoline 1-oxide (5·0 g, 27·5 mmol) was treated with thionyl chloride (30 ml) as described in (*i*), and the acid chloride was dissolved in anhydrous tetrahydrofuran (20 ml). To the stirred solution at room temperature under nitrogen was added, during 30 min, a solution of phenylmagnesium bromide, prepared from bromobenzene (6·0 g, 38·0 mmol), magnesium (1·0 g, 41·7 mmol) in anhydrous tetrahydrofuran (80 ml). The mixture was stirred for 2 h, then treated with hydrochloric acid (2M) to hydrolyse the excess of Grignard reagent. A chloroform extract of the product was concentrated to remove the tetrahydrofuran, more chloroform was added and the solution was washed successively with sodium hydroxide (2M), and ammonium chloride (2M), dried (Na_2SO_4), and evaporated. Bulb-to-bulb distillation of the residue at 180°/0·005 mm and crystallization of the distillate from cyclohexane–benzene (5/1) gave *1-phenyl-1,2,3,4-tetrahydrophosphinoline 1-oxide* as colourless, slightly hygroscopic needles (5·1 g, 77%), m.p. 107–198°. G.l.c. (column A, 80–250° at 24°/min, 30 ml/min nitrogen) showed only one peak, R_t 11·0 min (cf. the corresponding phosphine, R_t 8·6 min) (Found: C, 74·5; H, 6·4; P, 13·0. $C_{15}H_{15}OP$ requires C, 74·4; H, 6·3; P, 12·8%). ν_{max} (Nujol): 1450 (Ar–P), 1380, 1180 (P=O), 1165, 1135, 1115, 1080, 1000, 925, 820, 770, 745, 730, 710, 675 cm^{-1}. λ_{max} (ε): 264 (1345), 271 (1580), 278 nm (1150). P.m.r. (100 MHz, $CDCl_3$): 7·1–7·8, m, 9H (aromatic); 2·95, m, 2H (H 4,4); 1·8–2·5, m, 4H (H 2,2,3,3). Mass spectrum (*m/e*): 242 (100), 243 (16), 241 (81), 228 (10), 227 (32), 166 (5), 165 (16), 163 (7), 151 (6), 149 (14), 147 (7), 133 (7), 121 (5), 117 (10), 116 (11), 115 (17), 109 (5), 91 (12), 89 (6), 77 (10), 65 (6), 63 (5), 51 (18), 47 (10%); m*: 212·9 (242 → 227).

(*m*) *3-(2′-Bromophenyl)propyl Bromide* (*25*)

3-(2′-Bromophenyl)propan-1-ol was prepared from 2′-bromobenzyl bromide (71 g, 0·26 mol) by the method of Beeby and Mann.[27] Fractional distillation of the product gave a major fraction which distilled over a large temperature range. The crude alcohol was heated under reflux for 6 h with a mixture of hydrobromic acid (100 ml, 48%) and concentrated sulphuric acid (2 ml). Isolation with ether and distillation of the residue through a short Vigreux column gave 3-(2′-bromophenyl)-propyl bromide (32 g, 41%), b.p. 86–90°/0·1 mm (lit.[27] 84–85°/0·3 mm), which showed only one peak on g.l.c. (column A, 80–250° at 16°/min, 30 ml/min nitrogen, R_t 8·9 min). ν_{max} (film): 3050, 3000, 2950, 2930, 1570, 1470, 1440, 1270, 1230, 1050, 1025, 755, 670 cm^{-1}. P.m.r. (60 MHz, $CDCl_3$): 7·54, m, 1H (H 3′); 6·8–7·4, m, 3H (H 4′,5′,6′); 3·48, t, J(CH_2,CH_2Br) 7, 2H (CH_2Br); 2·92, t, $J_{3,2}$ 7, 2H (benzylic); 2·16, quintet, 2H (CH_2CH_2Br).

(*n*) *Diethyl 3-(2′-Bromophenyl)propylphosphonate* (*26*)

A mixture of 3-(2′-bromophenyl)propyl bromide (25 g, 84 mmol) and triethyl phosphite (150 ml) was heated under reflux for 6 h with rapid stirring, and with hot water passing through the condenser to facilitate expulsion of the ethyl bromide formed. The excess of triethyl phosphite together with the triethyl phosphate formed were removed in vacuum and the residue distilled in vacuum. More triethyl phosphite was added and the mixture heated under reflux for an additional 6 h. Removal of the volatile materials, and distillation through a short Vigreux column afforded *diethyl 3-(2′-bromophenyl)phosphonate* as a colourless liquid (21·5 g, 76%), b.p. 138–140°/0·005 mm, the purity of which was confirmed by g.l.c. (column A, 80–250° at 24°/min, 30 ml/min nitrogen, R_t 9·8 min) (Found: C, 46·5; H, 6·1; P, 9·4. $C_{13}H_{20}BrO_3P$ requires C, 46·6; H, 6·0; P, 9·2%). ν_{max} (film): 2960, 2910, 2880, 2850, 1465, 1435, 1390, 1235 (P=O), 1160, 1095, 1040, (P–O–CH_2), 960, 845, 800, 760, 670 cm^{-1}. P.m.r. (60 MHz, $CDCl_3$): 7·68, m, 1H (H 3′); 7·0–7·5, m, 3H (H 4′,5′,6′); 4·07, dq, $J(CH_2,CH_3)$ 7, $J(P,OCH_2)$ 9, 4H (2× >P(=)OCH_2); 2·93, m, 2H (benzylic); 1·5–2·3, m, 4H (>P(=)CH_2CH_2–); 1·34, t, 6H (2× CH_3).

(*o*) *Attempts to Effect Cyclization of Diethyl 3-(2′-Bromophenyl)propyl Phosphonate* (*26*)

(i) *Magnesium in ether.*—A solution of the bromophosphonate (1·5 g) in dry ether (25 ml) was allowed to react with magnesium (0·13 g) during 18 h under reflux. The mixture was treated with dilute hydrochloric acid and the ether solution washed, dried and evaporated. Bulb-to-bulb distillation gave an almost quantitative yield of diethyl 3-phenylpropylphosphonate, b.p. < 170°/0·1 mm, identified by comparison of the i.r. and p.m.r. spectra with those of an authentic sample prepared by the method of Kagan *et al.*[34]

(ii) *Magnesium in anisole.*—The Grignard reagent, prepared as in (i), was heated in anisole at 140° for 16 h. G.l.c. showed none of the ethyl ester (20d) in the neutral fraction nor any of the methyl ester (20c) in the acidic fraction after treatment with diazomethane.

(iii) *Magnesium/magnesium bromide in anisole.*—Magnesium bromide, prepared from dibromoethane (3·2 g, 17·0 mmol) in ether (20 ml) and magnesium (0·60 g, 25·0 mmol), was filtered through glass wool, and to the two-phase ether/ether + $MgBr_2$ mixture the bromophosphonate (2·0 g, 6·0 mmol) was added rapidly with shaking. The two-phase mixture was shaken for 1 h, then anisole (10 ml) was added and the homogeneous solution was added with stirring to iodine-activated magnesium turnings (0·3 g, 12·5 mmol) in anisole (20 ml) heated in an oil bath at 135–138°. The addition was made during 2 h whilst the ether was removed by distillation. The mixture was stirred and heated for a further 2 h, cooled and treated with 2M HCl. The organic layer, together with an ether extract of the aqueous phase, was washed, dried and evaporated. A chloroform solution of the residue was separated into neutral and acidic factions by extraction with 2N sodium hydroxide. G.l.c. of the neutral material (120 mg) from the original chloroform extract showed very little, if any, of the ethyl ester (22d). Esterification of the acid fraction with diazomethane gave a neutral product (0·45 g). G.l.c. of this showed very little, if any, of the methyl ester (22d), but several unidentified components.

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