SECTION C

Organic Chemistry

Some Substitution Reactions at the Phosphorus of 2,2,3,4,4-Pentamethylphosphetans

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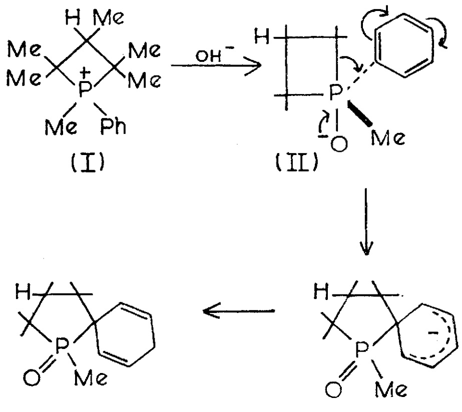
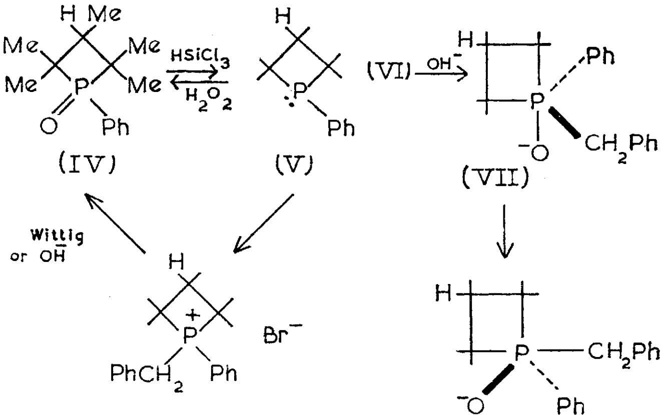
Nucleophilic substitutions at the phosphonium or phosphoryl centres of 2,2,3,4,4-pentamethylphosphetans proceed with retention of configuration at the phosphorus. 1-Aryl-2,2,3,4,4-pentamethylphosphetan oxides when treated with aryl-lithiums give aryl-(3-aryl-1,1,2,3,3-pentamethylpropyl)phosphine oxides. Additional evidence, involving deuterium labelling, is presented for the spirocyclohexa-1,4-diene structure (III) for the oxide from the alkaline hydrolysis of 1,2,2,3,4,4-hexamethylphenylphosphetanium iodide.

WE previously showed[1] that alkaline hydrolysis of the phosphetanium salt (I) gives the phosphine oxide (III) and rationalised this in terms of an intermediate trigonal bipyramid (II) in which the four-membered ring is constrained to occupy an apical-equatorial position. The expected loss of phenyl anion from the apical position opposite to the oxygen cannot therefore occur, and ring expansion results. This paper describes other substitution reactions at the phosphorus of the phosphetan ring; the unexpected results cast light on the course of normal substitutions at tetrahedral phosphorus.[2]



(I) (II) (III)

2,2,3,3,4-Pentamethyl-1-phenylphosphetan oxide (IV) exists as two geometrical isomers, separable by chromatography on alumina. They have similar spectral properties but are not interconverted in refluxing 2N-sodium hydroxide or in concentrated hydrochloric acid.† The major isomer, m.p. 127°, is presumably the one which has been shown by *X*-ray analysis[4] to have the methyl and phenyl on the same side of the ring. This isomer, on reduction with trichlorosilane in the presence of triethylamine, gives a crystalline phosphine (V); configuration at the phosphorus is retained since re-oxidation gives only the oxide, m.p. 127°. The phosphine gives a benzyl salt (VI), which on alkaline hydrolysis or in a Wittig olefin synthesis with benzaldehyde and ethanolic sodium ethoxide gives only the phosphine oxide (IV), m.p. 127°. Quaternisation[5] and the olefin synthesis[6] are known to proceed with retention of configuration; the alkaline hydrolysis must therefore also involve retention of configuration at the phosphorus. This is a consequence of the preference of the four-membered ring for an apical-equatorial position in the intermediate (VII) which either loses benzyl anion from an equatorial position or pseudorotates[7] to the new trigonal bipyramid (VIII) before losing the anion from an apical position. The second possibility is less probable; it involves moving the most electronegative group from an apical to an equatorial position. The difference



(IV) (V) (VII) (VI) (VIII)

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† The failure to interconvert in acid solution is due to the difficulty of placing the ring diequatorially (see ref. 3).

[1] S. E. Fishwick, J. Flint, W. Hawes, and S. Trippett, *Chem. Comm.*, 1967, 1113.

[2] Preliminary account of some of this work, W. Hawes and S. Trippett, *Chem. Comm.*, 1968, 295.

[3] L. Horner and H. Winkler, *Tetrahedron Letters*, 1964, 3271.

[4] Mazhar-Ul-Haque and C. N. Caughlan, *Chem. Comm.*, 1968, 1228.

[5] L. Horner, H. Fuchs, H. Winkler, and A. Rapp, *Tetrahedron Letters*, 1963, 965.

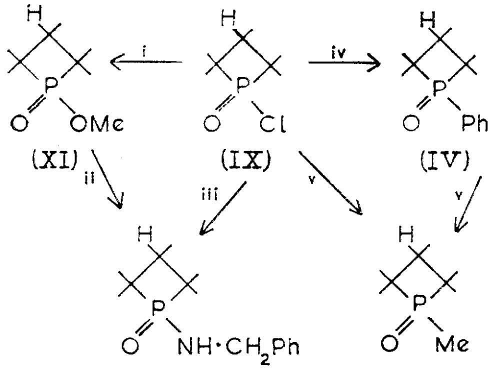
[6] A. Bladé-Font, C. A. VanderWerf, and W. E. McEwen, *J. Amer. Chem. Soc.*, 1960, **82**, 2396.

[7] F. H. Westheimer, *Accounts Chem. Res.*, 1968, **1**, 70.

in behaviour between the methyl (I) and benzyl (VI) salts on hydrolysis is due to the fact that the benzyl anion is more stable than the phenyl anion.

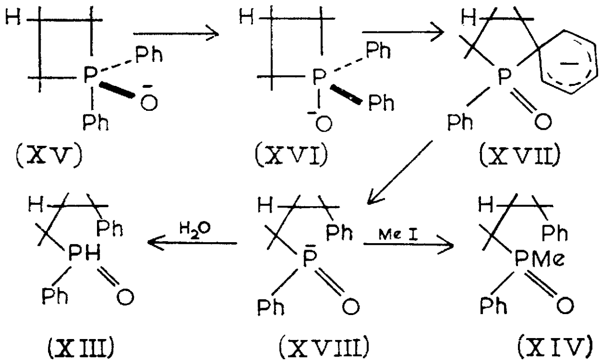
Other substitutions at the phosphorus of this four-membered ring system also probably involve retention of configuration at the phosphorus. Thus the acid chloride[8] (IX), which is highly crystalline and which its p.m.r. spectrum indicates to be one geometrical isomer, gives the same crystalline amide (X) on treatment with benzylamine as is obtained by formation of the ester (XI) followed by treatment with *N*-lithiobenzylamine. Again the acid chloride (IX) with phenyl-lithium gives the phenylphosphine oxide (IV), m.p. 127°, free of its isomer, and with methyl-lithium gives the methylphosphine oxide (XII). The same oxide (XII) is obtained on treatment of the oxide (IV) with methyl-lithium. In this second cycle the actions of phenyl and methyl-lithiums on the acid chloride (IX) presumably involve the same stereochemistry. Whether this is retention or inversion, the action of methyl-lithium on the phenylphosphine oxide must involve retention of configuration at the phosphorus.

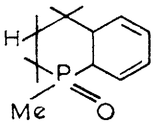
In some of the above substitutions, *e.g.* (IX) ⟶ (XI) the incoming and leaving groups are very similar in character. In view of this, the principle of microscopic reversibility suggests that the intermediate trigonal bipyramids must pseudorotate to allow the leaving groups to depart from an apical position. Unlike the situation in phosphonium salt hydrolysis these pseudorotations are not inhibited by the movement of electronegative groups from apical to equatorial positions: the intermediates have several electronegative groups, one of which is always apical.



Reagents: i, NaOMe–MeOH; ii, $PhCH_2{\cdot}NHLi$; iii, $PhCH_2{\cdot}NH_2$; iv, PhLi; v, MeLi.

The yields of the oxides (IV) and (XII) obtained from the actions, respectively, of phenyl-lithium on the acid chloride and of methyl-lithium on the oxide (IV) are low because of a competing reaction of phenyl-lithium with the oxide (IV). When this oxide is treated separately with phenyl-lithium protonation of the product gives the secondary phosphine oxide (XIII), while the addition of methyl iodide to the mixture leads to the oxide (XIV). Deuterium labelling of the two phenyl nuclei shows that they become equivalent during the reaction. Presumably the first intermediate is the trigonal bipyramid (XV), which pseudorotates to (XVI). The latter is analogous to the intermediate (II) postulated in alkaline hydrolysis of the salt (I). Ring expansion of (XVI) therefore gives the cyclohexadienyl anion (XVII) which, since it cannot be protonated, in this mixture, rearomatises to form the anion (XVIII). Cremer and Chorvat[9] have recently described similar rearrangements.





(XIX)

Shortly after our communication[1] on the structure of the hydrolysis product (III), Cremer and Chorvat[9] described the same reaction and assigned structure (XIX) to the product. Cremer has very recently[10] agreed with our structure (III) on the basis of deuterium labelling experiments. We have also carried out similar experiments starting from dichloro-*p*-deuteriophenylphosphine. This with 2,4,4-trimethylpent-2-ene and aluminium chloride gives the *p*-deuteriophenyl analogue of the oxide (IV), which on reduction and quaternisation leads to the salt (XX). This salt on hydrolysis in aqueous sodium hydroxide gives an oxide (XXI), in which, as shown by the p.m.r. spectrum, the deuterium occupies an allylic and not a vinylic position. However, hydrolysis of the salt in deuterium oxide containing sodium deuteroxide gives an oxide (XXII) in which both deuteriums are allylic. These data are in agreement with structure (III) for the hydrolysis product but not with structure (XIX).

A rearrangement similar to that leading to the oxide (III) occurs during the reaction of the phosphine (V) with ethyl propiolate in wet ether and gives the ring-expanded oxide (XXIII). Rearrangements during the reactions of phosphines with methyl propiolate were first

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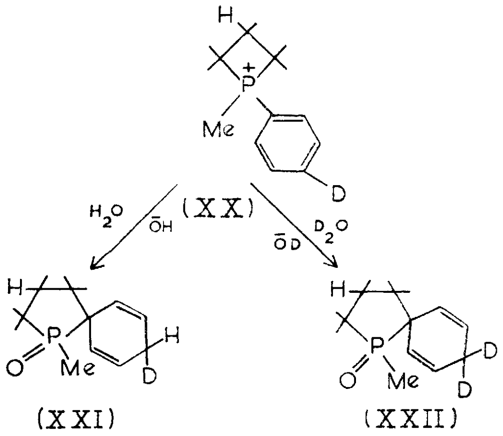
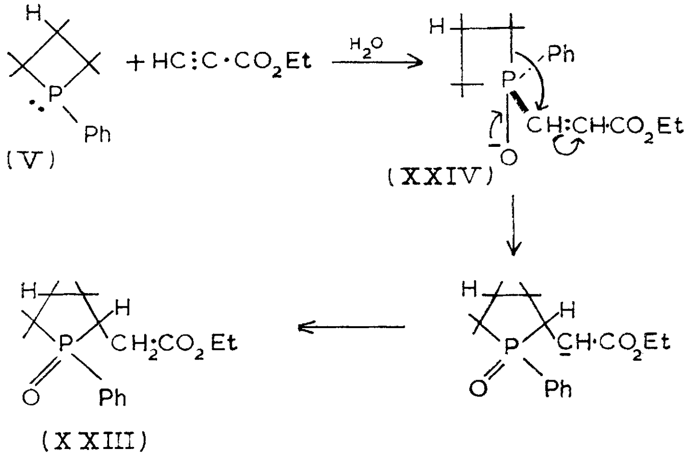
[8] J. J. McBride, E. Jungermann, J. V. Killheffer, and R. J. Clutter, *J. Org. Chem.*, 1962, **27**, 1833.

[9] S. E. Cremer and R. J. Chorvat, *Tetrahedron Letters*, 1968, 413.

[10] S. E. Cremer, *Chem. Comm.*, 1968, 1132.



described by Richards and Tebby.[11] The mechanism is not established but may involve in our case the intermediate (XXIV).



The above data can be rationalised in terms of apical attack by the nucleophile leading to an intermediate trigonal bipyramid which prefers the leaving group to depart from an apical position. It remains to be established whether the intermediate can, in certain cases, lose a group from an equatorial position.

EXPERIMENTAL

Experiments involving trivalent phosphorus compounds were carried out under oxygen-free nitrogen. ^{1}H N.m.r. spectra were recorded for solutions in deuteriochloroform with a Varian A-60 spectrometer. Mass spectra were determined with an A.E.I. MS9 instrument; in each case the molecular ion is given first followed by peaks of structural significance. Light petroleum had b.p. 40—60°.

2,2,3,4,4-*Pentamethyl*-1-*phenylphosphetan Oxide*.—2,4,4-Trimethylpent-2-ene (29 g.) was added slowly to a solution of aluminium chloride (33·3 g.) and dichlorophenylphosphine (44·8 g.) in methylene chloride (150 ml.), with the temperature maintained below 10°. The solution was kept at room temperature for 1 hr., then water (150 ml.) was added dropwise, with cooling to keep the temperature of the stirred mixture below 25°. The organic layer was washed with water, aqueous sodium hydroxide, and water, dried, and evaporated. The residue was chromatographed on basic alumina (500 g.). Elution with ether–light petroleum (b.p. 40—60°) (1 : 1) gave the *phosphine oxide* (35 g.), m.p. 126—127°, $\nu_{max.}$ 1190, 1165, 750, 715, and 703 cm.$^{-1}$, *m/e* 236, 235, 220, 168, 166, 125, 119, and 108, τ 8·6 (6H, d, J_{PH} 17 c./sec.), 8·9 (6H, d, J_{PH} 18 c./sec.), and 8·93 (3H, d, *J* 15 c./sec.) (Found: C, 71·05; H, 8·8; P, 13·2 $C_{14}H_{21}OP$ requires C, 71·2; H, 9·0; P, 13·1%). Elution with ether containing methanol (2%) gave the *phosphine oxide* (1·8 g.), m.p. 117—118°, $\nu_{max.}$ 1180, 1155, 757, 743, 715, and 693 cm.$^{-1}$, *m/e* as for the oxide m.p. 126—127°, τ 8·58 (6H, d, J_{PH} 15 c./sec.), 8·66 (6H, d, J_{PH} 19 c./sec.), and 9·04 (3H, d, *J* 15 c./sec.) (Found: C, 71·05; H, 8·8; P, 13·3. $C_{14}H_{21}OP$ requires C, 71·2; H, 9·0; P, 13·1%).

2,2,3,4,4-*Pentamethyl*-1-*phenylphosphetan*.— The oxide m.p. 127—128° (20 g.) in benzene (100 ml.) was added slowly to a stirred solution of trichlorosilane (10 ml.) and triethylamine (10 g.) in benzene (200 ml.) and the mixture was heated under reflux for 15 hr., and then cooled during the cautious addition of 2N-sodium hydroxide (50 ml.). The organic layer was washed with saturated aqueous sodium chloride, dried, and evaporated. Distillation gave the *phosphetan* (14 g.), b.p. 111°/1·5 mm., m.p. *ca.* 50°, τ (*o*-dichlorobenzene) 7·18 (1H, q, *J* 7 c./sec.), 8·71 (6H, d, J_{PH} 24 c./sec.), 8·94 (6H, d, J_{PH} 13 c./sec.), and 9·2 (3H, d, *J* 7 c./sec.).

Aqueous hydrogen peroxide (30%; 5 ml.) was added slowly to a stirred, cooled solution of the phosphetan (1 g.) in methylene chloride (15 ml.) and the mixture was stirred overnight at room temperature. The organic layer was washed with water, dried, and evaporated. The residue gave an almost quantitative yield of the phosphetan oxide, m.p. and mixed m.p. 126—127° (from ether–light petroleum), n.m.r. spectrum identical with that of an authentic sample.

Quaternisation of the phosphetan with benzyl bromide gave the *benzylphosphetanium bromide*, m.p. 220—221° (decomp.) (from chloroform–ethyl acetate), $\nu_{max.}$ 1115 and 865 cm.$^{-1}$, τ 5·01 (2H, d, J_{PH} 14 c./sec.), 8·07 (6H, d, J_{PH} 20 c./sec.), 8·39 (6H, d, J_{PH} 19 c./sec.), and 8·88 (3H, d, *J* 8 c./sec.) (Found: C, 65·0; H, 6·9; P, 8·0. $C_{21}H_{28}BrP$ requires C, 64·5; H, 7·2; P, 7·9%). Hydrolysis for 15 hr. in ethanol–2N-potassium hydroxide (1 : 1) under reflux gave only the phosphetan oxide, m.p. 126—127°, free of its isomer.

Wittig Olefin Synthesis with 1-*Benzyl*-2,2,3,4,4-*pentamethyl*-1-*phenylphosphetanium Bromide*.—The salt (1 g.) and benzaldehyde (0·3 g.) were dissolved in ethanol (14 ml.) containing sodium (0·06 g.), and the solution was set aside at room temperature for 3 days. G.l.c. (2 m. Apiezon L at 200°) showed the presence of *cis*- and *trans*-stilbenes (80%; 1 : 5). The ethanol was removed and the residue was shaken with ether and water. The organic layer was dried and evaporated and the residue was chromatographed on basic alumina. After stilbenes had been eluted with light petroleum, elution with ether gave 2,2,3,4,4-pentamethyl-1-phenylphosphetan oxide (0·2 g.), m.p. and mixed m.p. 126—127°, n.m.r. spectrum identical with that of an authentic sample.

1-*Benzylamino*-2,2,3,4,4-*pentamethylphosphetan Oxide*.—(*a*) 1-Chloro-2,2,3,4,4-pentamethylphosphetan oxide (4 g.) and benzylamine (4·4 g.) were heated under reflux overnight in benzene (40 ml.). The solution was then washed with dilute hydrochloric acid and with water, and dried. Evaporation and chromatography of the residue on basic alumina

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[11] E. M. Richards and J. C. Tebby, *Chem. Comm.*, 1967, 957.

gave the required *oxide*, m.p. 159—160° (from ether–light petroleum), $\nu_{max.}$ 3180, 1160, 860, 730, and 695 cm.$^{-1}$, *m/e* 265, τ 2·62 (5H, s), 5·75 (2H, t, *J* 7 c./sec.), 8·74 (6H, d, J_{PH} 17 c./sec.), 8·84 (6H, d, J_{PH} 19 c./sec.), and 9·1 (3H, m) (Found C, 67·6; H, 9·3; N, 5·3. $C_{15}H_{24}NOP$ requires C, 67·9; H, 9·1; N, 5·3%). The triplet at τ 5·75 collapsed to a doublet (*J* 7 c./sec.) on addition of small amounts of acidic compounds.

(*b*) The 1-chlorophosphetan oxide (10 g.) in methanol (30 ml.) was added slowly to a stirred solution of sodium (1·3 g.) in methanol (50 ml.) and the mixture was set aside at room temperature overnight, then filtered. The methanol was evaporated off and the residue was partitioned between methylene chloride and water. The organic layer was dried and evaporated and the residue was distilled to give the methyl ester (7·6 g.), b.p. 75—77°/5 mm., $\nu_{max.}$ 1250, 1200, and 1035 cm.$^{-1}$, τ 6·28 (3H, d, J_{PH} 10 c./sec.), 8·85 (12H, d, *J* 18 c./sec.), and 9·13 (3H, d, *J* 17 c./sec.).

Butyl-lithium (2·5N; 11·5 ml.) was added to benzylamine (3 g.) in ether (50 ml.), followed by the above methyl ester (1·4 g.) in ether (25 ml.), and the solution was set aside at room temperature for 1 hr. Dilute hydrochloric acid was then added, and the organic layer was washed with water, dried, and evaporated. The residue gave the 1-benzylaminophosphetan oxide, m.p. and mixed m.p. 159—160° (from ether–light petroleum), n.m.r. spectrum identical with that of the authentic compound.

1,2,2,3,4,4-*Hexamethylphosphetan Oxide*.—(*a*) Ethereal methyl-lithium (1·45N; 7·1 ml.) was added slowly to a stirred solution of the 1-chlorophosphetan oxide (2 g.) in ether (20 ml.). Water (30 ml.) was then added and the organic layer was dried and evaporated. The residue gave 1,2,2,3,4,4-*hexamethylphosphetan oxide*, m.p. 160—162° (from ether–light petroleum), $\nu_{max.}$ 1160 and 895 cm.$^{-1}$, *m/e* 174 and 104, τ 8·46 (3H, d, J_{PH} 14 c./sec.), 8·72 (6H, d, J_{PH} 16 c./sec.), 8·72 (6H, d, J_{PH} 16 c./sec.), and 9·08 (3H, d, *J* 8 c./sec.) (Found: C, 62·0; H, 10·7; P, 18·0. $C_9H_{19}OP$ requires C, 62·1; H, 10·9; P, 17·8%).

(*b*) Freshly prepared ethereal methyl-lithium (0·97N; 9·4 ml.) was added slowly to a stirred solution of the 1-phenylphosphetan oxide (2 g.), m.p. 126—127°, in ether (25 ml.) and the mixture was heated under reflux for 1 hr. Dilute hydrochloric acid was then added and the organic layer was dried and evaporated. Sublimation of the residue at 0·1 mm. gave the hexamethylphosphetan oxide, m.p. 159—160°, n.m.r. spectrum identical with that of an authentic sample.

Reaction of Phenyl-lithium with 2,2,3,4,4-*Pentamethyl*-1-*phenylphosphetan Oxide*.—Ethereal phenyl-lithium (1·5N; 6 ml.) was added to a stirred solution of the oxide (2 g.) m.p. 126—127°, in ether (25 ml.), and the mixture was heated under reflux for 0·5 hr. Dilute hydrochloric acid was then added and the organic layer was dried and evaporated. The residue gave (1,1,2,3,3-*pentamethyl*-3-*phenylpropyl*)-*phenylphosphine oxide*, m.p. 83—84° (from ether–light petroleum), $\nu_{max.}$ 2310, 1430, 1140, and 935 cm.$^{-1}$, *m/e* 314, 244, 195, and 119, τ 2·2—2·6 (5H, m), 2·83 (5H, s), −0·97 and 6·97 (1H, d, J_{PH} 476 c./sec.), 8·68 (6H, d, *J* 12 c./sec.), 8·76 (6H, d, *J* 11 c./sec.), 8·98 (1H, m), and 9·35 (3H, d, *J* 19 c./sec.). The oxide was hygroscopic and a satisfactory analysis was not obtained.

A similar reaction in which methyl iodide (2 g.) was added before the dilute acid gave methyl-(1,1,2,3,3-pentamethyl-3-phenylpropyl)phenylphosphine oxide, m.p. 106—111°, having the spectral properties recorded by Cremer and Chorvat.[9] When *p*-deuteriophenyl-lithium was used in this experiment the n.m.r. [τ 2·2—2·6 (4·5H, m, PPh) 2·85 (4·5H, s, CPh)] and mass (equal intensity peaks at *m/e* 119 and 120, and 209 and 210) spectra of the product showed that the deuterium was equally distributed among the two phenyl groups.

Reaction of Phenyl-lithium with 1-*Chloro*-2,2,3,4,4-*pentamethylphosphetan Oxide*.—Ethereal phenyl-lithium (1·9N; 12·5 ml.) was added to a stirred solution of the oxide (4·8 g.) in ether (35 ml.). Water (30 ml.) was then added and the organic layer was dried and evaporated. Chromatography of the residue on silica gave, on elution with ether, 2,2,3,4,4-pentamethyl-1-phenylphosphetan oxide, m.p. and mixed m.p. 126—127°, and the secondary phosphine oxide, m.p. 83—84°, described before.

1-p-*Deuteriophenyl*-1,2,2,3,4,4-*Hexamethylphosphetanium Iodide*.—Ethereal *p*-deuteriophenyl-lithium (0·225 mole; prepared from *p*-deuteriobromobenzene) was added dropwise to a stirred solution of chlorobis(diethylamino)phosphine[12] (47 g.) in ether (200 ml.) at −10°, and the mixture was allowed to warm to room temperature and then heated under reflux for 1·5 hr. Distillation then gave *p*-deuteriophenylbis(diethylamino)phosphine (46 g.), b.p. 132—134°/2 mm. This was dissolved in ether (50 ml.) and stirred at −10° during the addition of anhydrous hydrogen chloride (40 g.) in ether (200 ml.). The mixture was set aside at room temperature overnight and filtered, and the filtrate was distilled to give dichloro-*p*-deuteriophenylphosphine (23·4 g.), b.p. 59—60°/1 mm. This was converted into the phosphetanium iodide as described by Cremer and Chorvat.[9] The methiodide, m.p. 279—281° (from chloroform–ethyl acetate) had the same n.m.r. spectrum as the phenyl analogue, except that the aromatic region was more complex and integrated for only four protons.

The methiodide (1 g.) was stirred at room temperature with N-sodium hydroxide (20 ml.) for 15 hr. Ether extraction then gave the phosphine oxide (XXI), m.p. 133—134°, the n.m.r. spectrum of which was the same as that of the oxide (III), except that the allylic region at τ 7·26 integrated for only one proton. A similar experiment with N-sodium deuteroxide in deuterium oxide gave the phosphine oxide (XXII), m.p. 133—134°, the n.m.r. spectrum of which was the same as that of the oxide (III) except for the absence of resonance in the allylic region around τ 7·3.

Reaction of 2,2,3,4,4-*Pentamethyl*-1-*phenylphosphetan with Ethyl Propiolate*.—The ester (0·5 g.) was added to a solution of the phosphetan (1 g.) in wet ether (15 ml.). A vigorous exothermic reaction occurred and a white solid was precipitated, which gave 2-*ethoxycarbonylmethyl*-3,3,4,5,5-*pentamethyl*-1-*phenylphospholen oxide*, m.p. 131—132° (from ether–light petroleum), $\nu_{max.}$ 1715, 1430, 1260, and 1160 cm.$^{-1}$, *m/e* 336, 291, 224, 195, and 125, τ 4·12 (2H, q, *J* 7 c./sec.) (Found: C, 67·85; H, 8·55; P, 9·1. $C_{19}H_{29}O_3P$ requires C, 67·9; H, 8·6; P, 9·2%).

We thank Roche Products Ltd. for a research studentship.

[9/183 *Received, February 3rd*, 1969]

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[12] H. Nöth and H.-J. Vetter, *Chem. Ber.*, 1961, **94**, 1505.