# 1,3,2-Oxazaphospholidines from (−)-Ephedrine. Intermediates for the Stereospecific Synthesis of Optically Active Dialkyl Alkylphosphonothioates and -selenoates, Trialkyl Phosphoro-thioates and -selenoates, Dialkyl Methylphosphonates, and Trialkyl Phosphates

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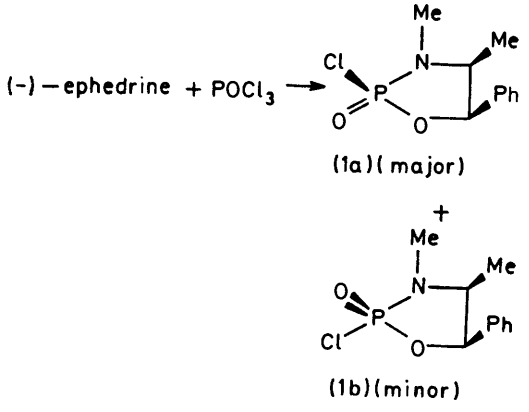
The configurations of the *cis*- and *trans*-isomers of 2-substituted 1,3,2-oxazaphospholidin(e)-2-ones, -2-thiones, and 2-selones derived from (−)-ephedrine have been established by spectroscopic and chemical methods. Displacements of the exocyclic 2-substituents occur with retention of configuration at phosphorus. With sodium alkoxides, the 1,3,2-oxazaphospholidine ring is opened by P–N rather than P–O bond cleavage, and inversion of configuration at phosphorus is observed. Under basic conditions the 2-methylamino-1-phenylpropyl phosphates derived from (−)-ephedrine rearrange to afford aziridines and phosphoric acid derivatives; in the cases of the sulphur- and selenium-containing derivatives optically active phosphorus thioacids and phosphorus selenoacids are formed and can be isolated as SMe and SeMe derivatives. These latter derivatives are converted into *O*-alkyl derivatives on treatment with alcohols in the presence of alkoxides or bromine or silver nitrate, and the stereoselectivities of these reactions have been determined. The optical purities of the title compounds have been measured by an n.m.r. method using chiral shift reagents.

PREVIOUSLY [1] it has been demonstrated that carbohydrates in which the stereochemistry and nature of the functional groups can be modified make excellent frameworks within which the stereochemistry of cyclic phosphorus esters may be studied and from which may be obtained a wide range of optically active non-carbohydrate phosphorus derivatives with absolute configurations that are established by the synthetic route used. By replacing carbohydrates as the optically active precursors with (−)-ephedrine,[2] it has been possible to shorten the synthetic sequences with consequent practical advantages.

In this paper details [3,4] are presented of the preparation, separation, and structural assignments of the *cis*- and *trans*-isomers of 3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin(e)-2-ones and -2-thiones together with details of the stereospecific degradation of the 2-thiones to chiral acyclic phosphorus thioacid derivatives. Particular attention is focused on the stereochemistry of P–N bond breaking reactions under both acidic and basic conditions and on methods for determining the optical purity of the acyclic phosphorus thioacid derivatives and derived products (which do not necessarily contain sulphur). Additionally comparison is made [5] between 1,3,2-oxazaphospholidine-2-thiones and -2-selones as precursors for the synthesis of optically active *OS*-dialkyl phosphorus thioacid esters and *OSe*-dialkyl phosphorus selenoacid esters and between these latter derivatives as intermediates for the synthesis of optically active phosphorus derivatives which contain neither sulphur nor selenium.

*Preparation of 1,3,2-Oxazaphospholidin(e)-2-ones, -2-thiones, and -2-selones.*—All the 1,3,2-oxazaphospholidines prepared from (−)-ephedrine [(1*R*,2*S*)-2-methylamino-1-phenylpropan-1-ol] are listed in Table 1. 1,3,2-Oxazaphospholidin-2-ones were readily prepared by treatment of (−)-ephedrine with appropriate phosphorus halides in the presence of triethylamine. Thus with phosphoryl chloride, (−)-ephedrine afforded a mixture of 2-chloro-1,3,2-oxazaphospholidin-2-ones (1a and b) (Scheme 1).




SCHEME 1

The major isomer (1a), usually purified by crystallisation, has been described previously as the only product from the ephedrine–phosphoryl chloride reaction.[6,7] However, by careful chromatography it was possible to isolate 6% of the minor isomer (1b). The corresponding thiones (7a and b) were prepared similarly by use of thiophosphoryl chloride.

Occasionally during the course of (−)-ephedrine–phosphoryl chloride reactions a third product (1c) was detected by t.l.c. In benzene–acetone (9 : 1) (1c) had $R_F$ 0.3 [*cf.* (1a) 0.4; (1b) 0.6]. The product (1c), *M*

[1] (*a*) D. B. Cooper, T. D. Inch, and G. J. Lewis, *J.C.S. Perkin I*, 1974, 1043; (*b*) D. B. Cooper, J. M. Harrison, T. D. Inch, and G. J. Lewis, *ibid.*, p. 1049; (*c*) J. M. Harrison, T. D. Inch, and G. J. Lewis, *ibid.*, p. 1053; (*d*) D. B. Cooper, J. M. Harrison, T. D. Inch, and G. J. Lewis, *ibid.*, p. 1058; (*e*) J. M. Harrison, T. D. Inch, and G. J. Lewis, *ibid.*, 1975, 1892.

[2] F. Wudl and T. B. K. Lee, *J. Amer. Chem. Soc.*, 1974, **95**, 6349.

[3] D. B. Cooper, J. M. Harrison, and T. D. Inch, *Tetrahedron Letters*, 1974, 2697.

[4] D. B. Cooper, C. R. Hall, and T. D. Inch, *J.C.S. Chem. Comm.*, 1975, 721.

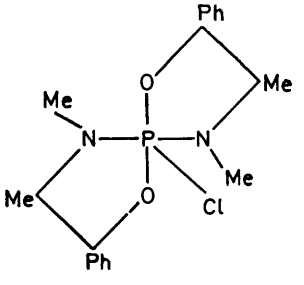
[5] C. R. Hall and T. D. Inch, *Tetrahedron Letters*, 1976, 3645.

[6] J. Devillers, L. T. Tran, and J. Navech, *Bull. Soc. chim. France*, 1970, 182.

[7] J. Devillers and J. Navech, *Bull. Soc. chim. France*, 1970, 4341.

392.86, had spectral characteristics consistent with the bicyclic structure shown. No clear evidence for its source was obtained.

Treatment of (−)-ephedrine with methyl- and phenylphosphonic dichlorides and methyl(thiophosphonic) dichloride afforded the isomeric pairs (2a and b), (3a and b), and (8a and b). The yields of isolated (2a and b) were low because some decomposition occurred during chromatography over silica. No attempts were made to optimise yields or to determine whether ratios of isomers were constant or varied with time and conditions of preparation.



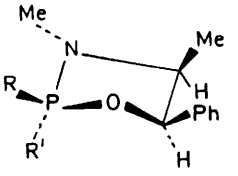
(1c)

The isomers (8a and b) were isolated in approximately equal quantities after chromatography over silica.

An isomeric pair of derivatives (15) and (16) epimeric at phosphorus were obtained by treatment of (+)-ψ-ephedrine [(1S,2S)-2-methylamino-1-phenylpropan-1-ol] with methyl(thiophosphonic) dichloride. The isomers were easily separated by chromatography over silica but no attempts were made to assign stereochemistry at phosphorus.

TABLE 1

1,3,2-Oxazaphospholidines from (−)-ephedrine



| Compound | R | R′ | Yield (%) | $[\alpha]_D$ (°) | Chromatography solvent;* $R_F$ |
|---|---|---|---|---|---|
| (1a) | Cl | O | 65 | −64 | B–A (9 : 1); 0.4 |
| (1b) | O | Cl | 6 | −26 | B–A (9 : 1); 0.6 |
| (2a) | Me | O | 9 | −81 | B–EA–A (2 : 1 : 2); 0.3 |
| (2b) | O | Me | 12 | −65 | B–EA–A (2 : 1 : 2); 0.25 |
| (3a) | Ph | O | 33 | −54 | B–A (7 : 3); 0.3 |
| (3b) | O | Ph | 28 | −40 | B–A (7 : 3); 0.4 |
| (4a) | OMe | O | 91 | −110 | B–A (7 : 3); 0.25 |
| (4b) | O | OMe | 85 | −37 | B–A (7 : 3); 0.4 |
| (5a) | OPh | O | 83 | −102 | B–A (9 : 1); 0.3 |
| (5b) | O | OPh | 91 | −34 | B–A (9 : 1); 0.4 |
| (6a) | 4-$NO_2$·$C_6H_4$ | O | 75 | −135 | B–A (4 : 1); 0.4 |
| (7a) | Cl | S | 61 | −121 | C–CH (1 : 3); 0.4 |
| (7b) | S | Cl | 8 | −23 | C–CH (1 : 3); 0.45 |
| (8a) | Me | S | 21 | −128 | A–LP (1 : 4); 0.5 |
| (8b) | S | Me | 22 | −25 | A–LP (1 : 4); 0.4 |
| (9a) | OMe | S | 80 | −140 | Ether–LP (1 : 2); 0.5 |
| (9b) | S | OMe | 85 | +2 | Ether–LP (1 : 2); 0.5 |
| (10a) | OEt | S | 83 | −122 | C–CH (1 : 3); 0.4 |
| (10b) | S | OEt | 93 | −5 | C–CH (1 : 3); 0.45 |
| (11a) | $OPr^i$ | S | 88 | −123 | C–CH (1 : 3); 0.35 |
| (11b) | S | $OPr^i$ | 86 | −8 | C–CH (1 : 3); 0.4 |
| (12a) | 4-$NO_2$·$C_6H_4$ | S | 83 | −178 | C–CH (1 : 3); 0.1 |
| (13a) | Me | Se | 7 | −97.5 | C–CH (1 : 3); 0.35 |
| (13b) | Se | Me | 20 | −8.6 | C–CH (1 : 3); 0.3 |
| (14b) | Se | OMe | | | C–CH (1 : 1); 0.5 |

* B = benzene, A = acetone, EA = ethyl acetate, C = chloroform, CH = cyclohexane, LP = light petroleum.

An alternative route to the thiones (7a and b) and (8a and b) involved addition of sulphur to the trivalent phosphorus derivatives prepared from the (−)-ephedrine–trichlorophosphine, and (−)-ephedrine–dichloro(methyl)-phosphine reactions, respectively. The overall yields of (7a and b) or (8a and b) were lower than in the (−)-ephedrine–$RPSCl_2$ (R = Me or Cl) reactions. Although (7b) and (8b) were, respectively, the preponderant isomers, the (7a) : (7b) and (8a) : (8b) ratios depended on exact conditions used, *i.e.* on the extent of purification of the trivalent phosphorus derivatives and on the time after their preparation when sulphur was added.

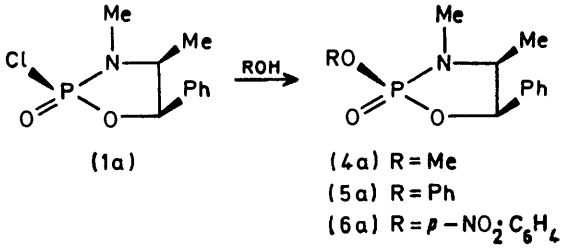
Unlike the 1,3,2-oxazaphospholidine-2-ones and -2-thiones, direct formation of the 2-selones from (−)-ephedrine and $RPSeCl_2$ was not possible owing to the non-availability of $RPSeCl_2$.[8] However, 2-selones were prepared by addition of selenium to appropriate cyclic trivalent phosphorus esters prepared from (−)-ephedrine and $RPCl_2$ (R = Cl or Me). For example, the cyclic

[8] J. Michalski and A. Markowska in 'Organic Selenium Compounds. Their Chemistry and Biology,' ed. D. L. Klayman and W. H. H. Gunther, Interscience, New York, ch. 10.

derivatives (13a and b) were prepared in approximately equal amounts by addition of selenium to the crude product in benzene in the presence of triethylamine from the dichloro(methyl)phosphine–(−)-ephedrine reaction. As for the corresponding sulphur derivatives when prepared in this way, the ratio of (13a) to (13b) varied with reaction conditions.

Attempts to add selenium directly to the trivalent adduct from trichlorophosphine and (−)-ephedrine did not afford 2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-selones. However, when the freshly distilled trivalent 2-chloro-derivative was converted into the corresponding 2-methoxy-derivative, by treatment with methanol in the presence of triethylamine, addition of selenium afforded the essentially pure 2-methoxy-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-selone (14b).

The 2-alkoxy- and 2-aryloxy-derivatives listed in Table 1 were readily prepared from the corresponding chloridates. Thus (1a and b) were readily converted into the corresponding alkoxy-derivatives on treatment with an alcohol in the presence of triethylamine and into aryloxy-derivatives on treatment with the sodium salt of the phenol at room temperature. Replacement of chlorine by an alkoxy- or aryloxy-group occurred with *retention* of configuration, *e.g.* (1a) gave (4a), (5a), and (6a) (Scheme 2). Compound (1b) gave (4b) and (5b), and (7a) gave (9a), (10a), (11a), and (12a); (7b) gave (10b) and (11b).




SCHEME 2

*Assignment of Configuration at Phosphorus in 1,3,2-Oxazaphospholidines.*—Tentative conformational and configurational assignments for the 1,3,2-oxazaphospholidin-2-ones were based on n.m.r. data. Since there is a Karplus-type relation between P–O–C–H vicinal couplings [9] and the corresponding dihedral angles, and provided that the effects of *N*-substituents on nitrogen do not grossly affect similar relations for P–N–C–H couplings, the n.m.r. data in Table 2 for compounds (1a), (2a), (3a), (4a), and (5a) are consistent with a $^1E$ ring conformation in which oxygen is out of the plane of the other four atoms. In this conformation the P–O–C–H dihedral angle approaches 90°, consistent with a small $J_{P,H-5}$ value, and the P–N–C–H dihedral angle is >120°, consistent with a large $J_{P,H-4}$ value. The coupling constant data for compounds (1b), (2b), (3b), (4b), and (5b) are consistent with similar but less puckered conformations. The configurations at phosphorus in compounds (1)—(5) were assigned on the basis that in phosphorus-containing heterocycles those protons in a 1,3-*cis*-relation to a P=O group are deshielded. Thus, since H-4 and H-5 resonate at lower field in compounds (1a)—(5a) than in compounds (1b)—(5b) the P=O group must be *cis* to H-4 and H-5 in the ' a ' series. The deshielding effect is greater for H-5 than for H-4, a result which is to be expected in a $^1E$ conformation in which P=O is closer to H-5 than to H-4. (Recently

TABLE 2

N.m.r. parameters of some 2-substituted 1,3,2-oxazaphospholidines prepared from (−)-ephedrine

| | δ | | | | *J*/Hz | | | |
|---|---|---|---|---|---|---|---|---|
| Compound | NMe | $CH_3$ | H-4 | H-5 | H-4, H-5 | P, H-4 | P, H-5 | P, NMe |
| (1a) | 2.85 | 0.83 | 3.85 | 5.84 | 6.5 | 26 | *ca.* 1 | 13 |
| (1b) | 2.67 | 0.80 | 3.70 | 5.54 | 7 | 14 | 7 | 13 |
| (2a) | 2.78 | 0.68 | 3.69 | 5.74 | 5.8 | 12.2 | 1—2 | 9.5 |
| (2b) | 2.67 | 0.80 | 3.55 | 5.43 | 6 | 14 | 4.5 | 10 |
| (3a) | 2.74 | 0.80 | 3.83 | 5.95 | 6 | 14 | *ca.* 1 | 10 |
| (3b) | 2.58 | 0.88 | 3.76 | 5.62 | 6 | 11 | 5.5 | 11 |
| (4a) | 2.71 | 0.77 | 3.70 | 5.63 | 6.4 | 20 | 1.9 | 10.5 |
| (4b) | 2.68 | 0.79 | 3.64 | 5.52 | 6.5 | 14 | 3.6 | 11 |
| (5a) | 2.78 | 0.58 | 3.61 | 5.65 | 6 | 14 | *ca.* 1 | 10 |
| (5b) | 2.72 | 0.72 | 3.51 | 5.28 | 5.5 | 10 | 4 | 10 |
| (7a) | 2.85 | 0.87 | 3.85 | 5.81 | 6.5 | 29.5 | 1 | 15 |
| (7b) | 2.72 | 0.78 | 3.73 | 5.59 | 7.25 | 13 | 6.5 | 17.5 |
| (8a) | 2.67 | 1.18 | 3.18 | 4.89 | 8.9 | 1.2 | 1 | 11.5 |
| (8b) | 2.58 | 1.14 | 3.11 | 4.87 | 9.0 | <1 | 1.1 | 14 |
| (9a) | 2.72 | 0.80 | 3.65 | 5.60 | 6.25 | 16.25 | 4.4 | 12.5 |
| (9b) | 2.68 | 0.77 | 3.73 | 5.60 | 6.2 | 14.5 | 2.7 | 12.5 |
| (10a) | 2.70 | 0.80 | 3.66 | 4.25 | 6.2 | 16 | 4.2 | 12 |
| (10b) | 2.68 | 0.76 | 3.77 | 4.20 | 6.1 | 14 | 2.8 | 12.5 |
| (11a) | 2.75 | 0.83 | 3.67 | 5.68 | 6.3 | 16.3 | 3.8 | 12 |
| (11b) | 2.70 | 0.78 | | 5.62 | 6.2 | | 2.9 | 12.5 |
| (12a) | 2.94 | 0.78 | 3.82 | 5.81 | 6.3 | 19.4 | 2.8 | 12.5 |
| (13a) | 2.75 | 0.77 | 3.67 | 5.66 | 7.0 | | | 12.8 |
| (13b) | 2.68 | 0.84 | 3.68 | 5.54 | 5.7 | 12.2 | 2.9 | 13.2 |
| (14b) | 2.72 | 1.81 | | 5.66 | 5.8 | | 2.0 | 12.8 |

[9] L. Evelyn, L. D. Hall, P. R. Steiner, and D. H. Stokes, *Org. Magnetic Resonance*, 1974, **5**, 141.

more detailed conformational analyses of oxazaphospholidines and related compounds have been reported.[10])

Previously [6] the only chloridate isolated from the phosphoryl chloride–ephedrine reaction, which had spectral characteristics consistent with the major chloridate (1a), has been assigned the structure (1b). However, a more recent report [11] from the same laboratories accepts the use of the deshielding effect of P=O in structural assignments to oxazaphospholidines.

To confirm the structural assignments to (2a) and (2b) use was made of the fact that the phosphoryl oxygen in 1,3,2-oxazaphospholidin-2-ones is the group most likely to co-ordinate preferentially with lanthanoid shift reagents.[12] Small portions of $Eu(dpm)_3$ were added to 10% solutions of (2a) and (2b) in deuteriochloroform and the $^1H$ n.m.r. spectra were recorded after each addition. Graphs were plotted of the change in chemical shift ($\delta\Delta$/Hz) for each proton or group of protons, against the molar proportion (up to 0.1) of shift reagent. [The molar ratio was measured by integration of convenient signals of (2a), (2b), and $Eu(dpm)_3$.] The slopes of the straight lines for each proton or group of protons [in the order (2a),(2b)] were 3.6,4.0 ($C$-$CH_3$); 7.9,6.2 ($P$-$CH_3$); 5.9,4.8 ($N$-$CH_3$); 5.2,4.1 (H-4); and 6.8,4.6 (H-5). Since it is to be expected that protons in a *cis*-relation to the P=O–shift reagent complex will exhibit a greater slope than those in a *trans*-relation [assuming that any changes in preferred conformation caused by addition of $Eu(dpm)_3$ are insignificant], the slopes are consistent with the designated assignments for (2a) and (2b) with H-4 and H-5 *cis* to P=O in (2a).

Although first-order analyses of the $^1H$ n.m.r. spectra of 1,3,2-oxazaphospholidine-2-thiones and 1,3,2-oxazaphospholidine-2-selones (see Table 2) were possible, it was not easy to assign configurations and conformations to these compounds on the basis of the observed chemical shifts and coupling constants. No consistent deshielding of H-4 and H-5 when *cis* to P=S or P=Se was observed. In addition the variation in coupling constants necessitates the use of chemical methods for the determination of stereochemistry.

Configurational assignments to the thiones and selones listed in Table 1 were made on the basis that P=S and P=Se are oxidised to P=O by *m*-chloroperbenzoic acid with retention of configuration.[13] The oxidations took place stereospecifically and in high yield. For example (8a) was converted into (2a) in 95% yield. Additionally, a mixture of the selenium derivatives (13a and b) in the ratio 1 : 3 was converted by hydrogen peroxide into a mixture of (2a) and (2b) in the ratio 1 : 3. Oxidations of similar selenium derivatives by hydrogen peroxide have been shown to take place with retention of configuration.[14]

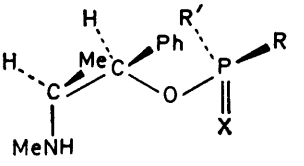
Additional comparative evidence for the structures of the thiones and of the isomeric pair of selones (13a and b) comes from optical rotations. For the P=O derivatives all the compounds in the ' b ' series have higher rotations (*i.e.* less negative) than those in the ' a ' series. It is reasonable to assume that the P=S and P–Se compounds follow the same trend.

The n.m.r. data and the correlation of specific rotations show that chlorine is displaced from both P=O and P=S compounds with retention of configuration. Supporting chemical evidence for this conclusion was obtained when (1a) was converted into (6a) by treatment with sodium 4-nitrophenoxide in benzene, and (6a) was then converted into (4a) by treatment with sodium methoxide. Similarly (7a) was converted directly into (11a) on treatment with sodium isopropoxide and also converted into (11a) by the sequence (7a) ⟶ (12a) ⟶ (11a).

P–N *Bond Cleavage in 2-Substituted 1,3,2-Oxazaphospholidines.*—The compounds prepared by treatment of the 1,3,2-oxazaphospholidine-2-ones and -2-thiones with alcohols in the presence of acid are listed in Table 3.

TABLE 3

Products obtained by treating compounds in Table 1 with acidified alcohol




| Compound | Starting material | Alcohol used | R | R′ | X |
|---|---|---|---|---|---|
| (17) | (8b) | MeOH | OMe | Me | O |
| (18) | (8a) | MeOH | Me | OMe | O |
| (19) | (8b) | EtOH | OEt | OMe | O |
| (20) | (8a) | EtOH | OMe | OEt | O |
| (21) | (8b) | EtOH | OEt | Me | S |
| (22) | (8a) | EtOH | Me | OEt | S |
| (23) | (8a) | Cyclopentanol | Cyclopentyloxy | Me | S |
| (24) | (9a) | EtOH | OMe | OEt | S |
| (25) | (10a) | MeOH | OEt | OMe | S |
| (26) | (11b), (9a) | MeOH, $Pr^iOH$ | OMe | $OPr^i$ | S |
| (27) | (9b), (11a) | $Pr^iOH$, MeOH | $OPr^i$ | OMe | S |
| (28) | (10a) | $Pr^iOH$ | OEt | $OPr^i$ | S |
| (29) | (11a) | EtOH | $OPr^i$ | OEt | S |

Essentially pure compounds were extracted from the reaction mixtures after basification with aqueous sodium carbonate, but extensive decomposition of the products occurred on storage or on attempted chromatography over silica. The $^1H$ n.m.r. parameters listed in Table 4 show that pairs enantiomeric at phosphorus are easily distinguished by their n.m.r. spectra. On this basis it was easily seen that pure isomers were obtained by acid-catalysed treatment which caused cleavage of the P–N bond.

The same products were obtained when the 1,3,2-oxazaphospholidines were treated with sodium alkoxides. The absence of any P,NMe-coupling in the n.m.r. spectra

[10] J. Devillers, M. Cornus, and J. Navech, *Org. Magnetic Resonance*, 1974, **6**, 211.
[11] M. Evel, J. Roussel, J. Navech, and F. Mathis, *Org. Magnetic Resonance*, 1976, **8**, 399.
[12] A. F. Cockerill, G. L. O. Davies, R. C. Harden, and D. M. Rackham, *Chem. Rev.*, 1973, **73**, 553.
[13] A. W. Herriott, *J. Amer. Chem. Soc.*, 1971, **93**, 3304.
[14] W. J. Stec, A. O. Kurszck, and J. Michalski, *J. Org. Chem.*, 1976, **41**, 233.

of the crude products showed exclusive P–N bond and no P–O bond cleavage. As with the products from the acid-promoted alcoholysis, some decomposition occurred on storage. Initially, however, the products were stereochemically pure, both acid- and base-promoted P–N bond cleavage giving products with the same stereochemistry at phosphorus.

TABLE 4

N.m.r. parameters (δ) of compounds in Table 3

| Compound | C*Me* | N*Me* | C*H*Ph | P*Me* | PO*Me* | OC*H*$_2$Me |
|---|---|---|---|---|---|---|
| (17) | 1.03 | 2.42 | 5.38 | 1.48 | 3.38 | |
| (18) | 1.08 | 2.43 | 5.33 | 1.43 | 3.70 | |
| (19) | 1.08 | 2.44 | 5.34 | | 3.68 | 1.17 |
| (20) | 1.08 | 2.43 | 5.33 | | 3.56 | 2.32 |
| (21) | 1.07 | 2.44 | 5.51 | 1.58 | | 4.17 |
| (22) | | 2.42 | 5.62 | 1.87 | | 3.34 and 3.73 |
| (23) | | 2.95 | 6.12 | 2.14 | | |
| (24) | 1.03 | 2.40 | 5.38 | | 3.62 | 3.60 |
| (25) | 1.08 | 2.45 | 5.49 | | 3.49 | 4.10 |
| (26) | 1.01 | 2.49 | 5.52 | | 3.72 | |
| (27) | 1.07 | 2.45 | 5.51 | | 3.46 | |
| (28) | 0.86 | 2.30 | 5.70 | | | 4.02 |
| (29) | 0.83 | 2.31 | 5.70 | | | 4.75 |

That P–N bond cleavage under acidic or basic conditions occurred to give identical products was most easily shown when the derivatives from (+)-ψ-ephedrine, (15) and (16), were compared. With acidic ethanol or with sodium ethoxide (15) afforded (30) and (16) afforded (31). Both (30) and (31) were stable under basic conditions and thus more easily compared than similar derivatives from (−)-ephedrine.

It has been demonstrated that acid-catalysed cleavage of P–N bonds in acyclic phosphinates [15] and in acyclic alkyl methylphosphonamidothioates [16] occurs with inversion of configuration at phosphorus. It has also been shown that acid-catalysed cleavage of P–N bonds in tetrahydro-1,3,2-oxazaphosphorines occurs with inversion of configuration.[1c] It is therefore reasonable to assume that acid-catalysed P–N bond cleavage in 1,3,2-oxazaphospholidines results in inversion of configuration at phosphorus.

That ready P–N bond cleavage in 1,3,2-oxazaphospholidines under basic conditions also occurred with inversion of configuration has mechanistic implications that will be discussed subsequently in this paper.

*Formation of* 1,2-*Dimethyl*-3-*phenylaziridines and Phosphorus Acid Derivatives from* 2-*Methylamino*-1-*phenylpropyl Phosphates*.—By analogy with sulphate esters of ephedrine and ψ-ephedrine,[17] which under basic conditions readily cyclise to aziridines, it was expected that the phosphate esters of (−)-ephedrine [(17)—(29)] and ψ-ephedrine [(30) and (31)] would cyclise similarly. Further, in the case of the sulphur-containing derivatives (21)—(29) [and (30) and (31)] it was expected that the phosphorus thioacids would be optically active.

In the event, although the derivatives (21)—(29) from (−)-ephedrine were unstable in base and afforded (−)-*trans*-1,2-dimethyl-3-phenylaziridine, it was not possible to isolate the expected phosphorus acids from the reaction mixtures. A possible explanation for the experimental difficulties encountered may be related to the fact, reported elsewhere [18] and confirmed in this work, that *trans*-1,2-dimethyl-3-phenylaziridine is difficult to purify. When aqueous alcoholic alkaline reaction mixtures were extracted with ether some *trans*-1,2-dimethyl-3-phenylaziridine was isolated as a reasonably pure liquid (on the basis of the n.m.r. spectrum). Attempts to purify the aziridine were unsuccessful with rapid decomposition affording a white solid insoluble in water and chloroform. Attempts to isolate phosphorus acids by extraction of the acidified residual aqueous solution with organic solvents were unsuccessful, with only badly defined products being isolated. Presumably in these residues some polymerisation of the aziridine had occurred which effectively trapped the phosphorus acids.

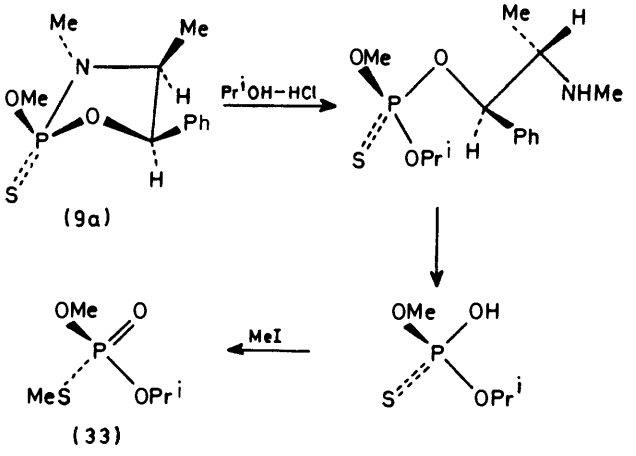
An alternative approach to the isolation of phosphorus thioacids by base-promoted cyclisation of (30) and (31) was also unsuccessful. It was hoped that since *cis*-1,2-dimethyl-3-phenylaziridine is more easily purified than the *trans*-isomer [18] there would be no complications resulting from further reactions of the *cis*-aziridine. In practice, it was not possible to promote cyclisation of (30) and (31), which were unchanged when stored in 6N-sodium hydroxide for several weeks. Presumably, in the derivatives from (−)-ephedrine [(21)—(29)] the intermediate for aziridine formation (*i.e.* with the methylamino- antiperiplanar to the phosphate group) has no unfavourable steric interactions, whereas the corresponding conformation of the ψ-ephedrine derivatives has the methyl and phenyl groups in an unfavourable *cis*-relation.

The problems of isolating optically active phosphorus thioacid derivatives following aziridine formation from (21)—(29) were overcome by treating the basic reaction mixture directly with methyl iodide. The phosphorus thioacids were converted into chloroform-soluble *S*-alkyl derivatives and the aziridine was converted into water-soluble derivatives. [The *S*-alkyl derivatives gave distinctive yellow spots on t.l.c. plates sprayed with palladium chloride in hydrochloric acid (0.7%).] The *S*-alkyl phosphorothioates listed in Table 5 were optically pure. For example, from the 2-OMe derivative (9a) a sequence involving treatment with (i) Pr$^i$OH–H$^+$, (ii) base, and (iii) MeI afforded (+)-(*S*)-*OS*-dimethyl isopropyl phosphorothioate (33) (*e.g.* Scheme 3) and from the 2-OPr$^i$ derivative (11a) a sequence involving treatment with (i) MeOH–H$^+$, (ii) base, and (iii) MeI afforded (−)-(*R*)-*OS*-dimethyl isopropyl phosphorothioate (32). The *S*-methyl and *Se*-methyl derivatives (34)—(45) were prepared by similar sequences.

As neither the C–O bond breaking process nor the

[15] M. J. P. Harger, *J.C.S. Chem. Comm.*, 1976, 520.
[16] C. R. Hall and T. D. Inch, unpublished observations.
[17] S. J. Brois and G. P. Beardsley, *Tetrahedron Letters*, 1966, 5113.
[18] I. Okada, K. Ichimura, and R. Sudo, *Bull. Chem. Soc. Japan*, 1970, **43**, 1185.

*S*-alkylation affect the configuration at phosphorus, and since P–N bond cleavage occurs with inversion of configuration, the absolute configurations * of the products are those shown in Table 5. Additionally since the




SCHEME 3

absolute configuration of (+)-(*R*)-ethyl methylphosphonothioic acid has been established elsewhere by other procedures,[19] the formation of the (+)-(*R*)-ethyl methylphosphonothioic acid derivatives from the ephedrine derivative (8a) by the sequence employed further confirms that cleavage of the endocyclic P–N bond occurs with inversion of configuration at phosphorus.

2-Methyl-(or 2-alkoxy-) 1,3,2-oxazaphospholidine-2-selones were converted into *OSe*-dialkyl methylphosphonoselenoates (or trialkyl phosphoroselenoates) by essentially the same procedure as for the corresponding sulphur derivatives except that no attempts were made to isolate the products from acid-catalysed ring opening.

*Conversion of* P-*Alkylthio- and* P-*Alkylseleno- into* P-*Alkoxy-groups.*—Three procedures that have been described for converting *P*-alkylthio- into *P*-alkoxy-groups are (*a*) treatment with sodium alkoxide,[20,21] (*b*) treatment with halogen in alcohol,[22] and (*c*) treatment with silver nitrate in alcohol.[23] These procedures were compared with *S*-alkyl phosphonothioates and phosphorothioates and *Se*-alkyl phosphonoselenoates and phosphoroselenoates to establish the degree and nature of the stereoselectivity of the various procedures and to rank their reaction rates and their preparative convenience.

(a) *Treatment with sodium alkoxides.* Reactions of *S*-alkyl methylphosphonothioates with sodium alkoxides have been investigated in detail previously: it was shown that replacement of *S*-alkyl by *O*-alkyl occurs with preponderant but not necessarily exclusive *inversion* of configuration at phosphorus.[20,21] In agreement with these results, when (+)-(*R*)-ethyl *S*-methyl methylphosphonothioate (38) was treated with sodium methoxide, the preponderant reaction occurred with inversion of configuration; † the ethyl methyl methylphosphonate isolated (79%) was a 4 : 1 mixture of the isomers (47) and (46). (Similar results were obtained when *S*-propyl rather than *S*-methyl was the leaving group.) The enantiomeric composition of the ethyl methyl methylphosphonate was established by $^1$H n.m.r. experiments with the optically active shift reagent Eu(hfc)$_3$ (see below).

In contrast to the preponderant *inversion* of configuration at phosphorus observed for alkoxide–*S*-alkyl methylphosphonothioate reactions, the corresponding alkoxide–*S*-alkyl phosphorothioate reactions took place with exclusive *retention* of configuration. For example, treatment of (+)-(*S*)-ethyl isopropyl *S*-methyl phosphorothioate (37) with sodium methoxide afforded (+)-(*S*)-ethyl methyl isopropyl phosphate (49). Compound (49) was also formed by treatment of (32) with sodium ethoxide or (39) with sodium isopropoxide.

The selenium phosphono-derivatives (42) and (43) and phosphoro-derivatives (44) and (45) all underwent reactions with alkoxides with *inversion* of configuration at phosphorus. For example, with sodium methoxide (−)-(*S*)-ethyl *Se*-methyl methylphosphonoselenoate (43) afforded (47) in 80% yield and with sodium ethoxide (−)-(*R*)-*OS*-dimethyl isopropyl phosphoroselenoate afforded (48) in 75% yield. In these reactions the products were enantiomerically pure within the limits of the $^1$H n.m.r. procedure used for assessment.

(b) *Treatment with bromine in alcohol.* The formation of compounds (46)—(49) from (32)—(45) as appropriate (Table 5) was accomplished by dropwise addition of bromine to a solution of the phosphorus thioate or phosphorus selenoate in the relevant alcohol. The reactions were almost instantaneous. Yields of the isolated phosphates and phosphonates usually exceeded 80% and the products were enantiomerically pure. All reactions proceeded with inversion of configuration.

For the simple alkyl derivatives listed in Table 5 the bromine-promoted alcoholysis was clearly the method of choice for converting *P*-alkylthio and *P*-alkylseleno into *P*-alkoxy. However, it must not be assumed that all such substitutions proceed with exclusive inversion of configuration, for evidence exists which suggests that in certain sterically crowded situations bromine-

* In previous papers from these laboratories errors have occurred in the *R* and *S* assignments to some classes of chiral phosphorus esters. These arose because P=O was considered as a double rather than as a single bond when the Sequence Rule was used. However it is believed that the structural formulae given in previous papers correctly depict the absolute configurations of the compounds in question.

† The absolute stereochemistry of the phosphonates and phosphates has been established previously.[24]

[19] M. Mikolajczyk, J. Omelanczuk, and M. Para, *Tetrahedron*, 1972, **28**, 3855; M. Mikolajczyk, M. Para, J. Omelanczuk, M. Kaytar, and G. Snatzke, *Tetrahedron*, 1972, **28**, 4357.

[20] K. E. DeBruin and D. M. Johnson, *J. Amer. Chem. Soc.*, 1973, **95**, 7921.

[21] W. B. Farnham, K. Mislow, N. Mandil, and J. Donohue, *J.C.S. Chem. Comm.*, 1972, 120.

[22] C. J. M. Stirling, *J. Chem. Soc.*, 1957, 3597; A. F. Cook, M. J. Holman and A. L. Nussbaum, *J. Amer. Chem. Soc.*, 1969, **91**, 1522; T. Wieland and R. Lambert, *Chem. Ber.*, 1956, **89**, 2476.

[23] W. J. Stec, *Bull. Acad. polon. Sci. Sér. Sci. chim.*, 1973, **21**, 709.

[24] C. R. Hall, T. D. Inch, G. J. Lewis, and R. A. Chittenden, *J.C.S. Chem. Comm.*, 1975, 720.

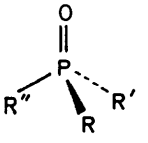
promoted alcoholyses take place with preponderant retention of configuration.[25]

(c) *Treatment with silver nitrate in alcohol.* The procedure involved mixing a solution of the thioate or selenoate in acetonitrile, triethylamine, and alcohol with a solution of silver nitrate in acetonitrile. For the (+)-(*R*)-ethyl *S*-methyl methylphosphonothioate (**38**)–methanol reaction, the mixture was processed after 12 h to afford a 40% recovery of (**38**) (which remained enantiomerically pure), and ethyl methyl methylphosphonate (45%) as a 4 : 1 mixture of (**47**) and (**46**). That is, the preponderant product was formed from (**38**) with inversion of configuration at phosphorus.

problems where the specific rotations are small and where practical convenience requires the use of small quantities of materials in synthetic sequences. In the work reported in this paper these difficulties have been circumvented by a $^1$H n.m.r. procedure which utilises the optically active shift reagent tris-{3-[heptafluoro-(hydroxy)butylidene]-(+)-camphorato}europium(III) [Eu(hfc)$_3$]. This method appears more generally applicable than n.m.r. methods that require formation of diastereoisomeric salts [26] and gives bigger shift differences than methods which use chiral solvents.[27]

For compounds containing the P=O group, satisfactory enantiomeric shift differences (3—13 Hz) were

TABLE 5




| Compound | R | R′ | R″ | Precursor | $[\alpha]_D$ (°) [a] | Configuration | Sense of non-equivalence [b] | δΔ/Hz [b] |
|---|---|---|---|---|---|---|---|---|
| (32) | Pr$^i$O | MeO | MeS | (11a) | −3.0 (*c* 0.6) | *R* | h [c] l [d] | 5.5,[c] 2 [d] |
| (33) | MeO | Pr$^i$O | MeS | (9a) | +3.1 (*c* 0.4) | *S* | l [c] h [c] | |
| (34) | EtO | MeO | MeS | (10a) | +1.0 (*c* 1.4) | *R* | h [c] | 6 |
| (35) | MeO | EtO | MeS | (9a) | −0.9 (*c* 1.0) | *S* | l [c] | |
| (36) | Pr$^i$O | EtO | MeS | (11a) | −3.5 (*c* 0.5) | *R* | l [c] | 2 |
| (37) | EtO | Pr$^i$O | MeS | (10a) | +3.4 (*c* 1.9) | *S* | h [d] | |
| (38) | Me | EtO | MeS | (8a) | +85.5 (*c* 1.7) | *R* | l [d,e] h | 6,[d] 3.5[f] |
| (39) | EtO | Me | MeS | (8b) | −87.5 (*c* 2.2) | *S* | h [d,e] l [f] | |
| (40) | Me | Cyclopentyloxy | MeS | (8a) | +70 (*c* 0.6) | *R* | l [d,e] | 13,[d] 5.5 [e] |
| (41) | Cyclopentyloxy | Me | MeS | (8b) | −69 (*c* 0.5) | *S* | h [d,e] | |
| (42) | Me | EtO | MeSe | (13a) | +81 (*c* 0.4) | *R* | l [e,g] h [f] | |
| (43) | EtO | Me | MeSe | (13b) | −80 (*c* 0.4) | *S* | h [e,g] l [f] | |
| (44) | Pr$^i$O | MeO | MeSe | (14b) | −5.3 (*c* 0.3) | *R* | h [c] l [g] | |
| (45) | MeO | Pr$^i$O | MeSe | | | *S* | l [c] h [g] | |
| (46) | EtO | Me | MeO | | +1.9 (*c* 1.2) | *R* | h [c] | 7 |
| (47) | Me | EtO | MeO | | −1.9 (*c* 1.2) | *S* | l [c] | |
| (48) | Pr$^i$O | EtO | MeO | | −0.2 (*c* 5.9) | *R* | h [c] | 3 |
| (49) | EtO | Pr$^i$O | MeO | | +0.2 (*c* 6.8) | *S* | l [c] | |
| (50) | Me | EtO | Pr$^i$O | | | *R* | h [h] | |
| (51) | Ph | Me | MeO | | +57 | *R* | h [e,i] | |
| (52) | Me | Ph | MeO | | −57 | *S* | l [e,i] | |

[a] Solutions in chloroform. [b] Shift differences are quoted for solutions of racemic phosphorus ester (30—40 mg) in deuteriochloroform (0.5 ml) containing Eu(hfc)$_3$ (100 mg) at 60 MHz. The sense of non-equivalence is deemed 'h' for that enantiomer in which the relevant signal undergoes the least change in chemical shift under such conditions. [c] Refers to the OMe resonance. [d] PS*Me*. [e] P*Me*. [f] POCH$_2$*Me*. [g] PSe*Me*. [h] POC*H*$_2$Me. [i] Sample supplied by Dr. M. J. P. Harger, University of Leicester.

Under similar conditions (−)-(*R*)-ethyl *S*-methyl isopropyl phosphorothioate (**36**) when stored with silver nitrate and methanol at room temperature for 1 week afforded (**48**) (77%) as a single enantiomer; again the conversion took place with inversion of configuration.

*Optical Purity of Phosphorus Esters.*—Hitherto, many studies designed to follow the stereochemical integrity of reactions at phosphorus have produced equivocal results because of difficulties in assessing the optical purity of starting materials and products. Although conventional polarimetric methods are satisfactory where optically pure standards are available and where specific rotations are large, there have been major

usually obtained for at least one group of protons by adding the shift reagent (*ca.* 100 mg) to a solution of the phosphorus ester (30—40 mg) in deuteriochloroform (0.5 ml). The spectra were measured at 60 MHz since in several instances spectra obtained at 100 MHz showed considerable broadening. (This presumably reflects the rate of equilibration between complexed and non-complexed material.) Control experiments indicated that in most cases <5% of the minor isomer can be detected readily and in some cases the percentage of minor isomer detectable may be very small. The signal which splits in the presence of shift reagent varies with the racemate. For example, for ethyl *OS*-dimethyl phosphorothioate only significant splitting of the OMe signal was observed. For ethyl isopropyl *S*-methyl

[25] T. D. Inch and G.J. Lewis, *Carbohydrate Res.*, 1975, **45**, 65.

[26] M. Mikolajczyk, M. Para, A. Ejchart, and J. Jurczak, *Chem. Comm.*, 1970, 654; M. Mikolajczyk, A. Ejchart, and J. Jurczak, *Bull. Acad. polon Sci. Sér. Sci. Chim.*, 1971, **19**, 721.

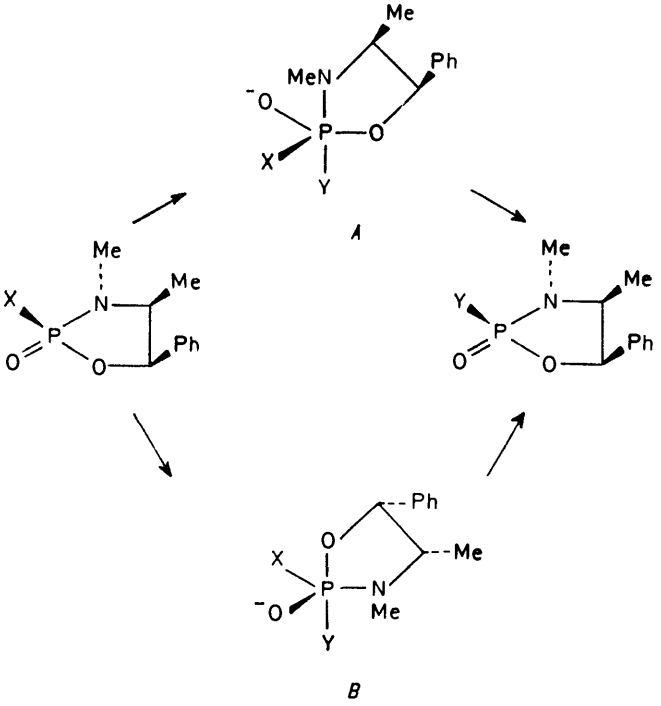
[27] W. H. Pirkle and S. D. Beare, *J. Amer. Chem. Soc.*, 1968, **90**, 6250.

phosphorothioate the SMe signal was split and for ethyl *S*-methyl methylphosphonothioate splitting of the SMe, PMe, and $OCH_2Me$ signals was observed.

In an attempt to establish whether the source of the shift differences could be related to either absolute configuration or sign of rotation the results listed in Table 5 were inspected. Compounds (50)—(52) were included although not directly connected with the preparative work described in this paper. In Table 5 'h' denotes that for a given isomer the proton signal recorded was at high field relative to the corresponding signal, denoted 'l,' in the enantiomer. [The shift relation was determined by adding *ca.* 20% of the racemate to either enantiomer in the presence of $Eu(hfc)_3$.] The results show that the sense of non-equivalence bears no simple relation to the sign of rotation but has some sort of relation to the absolute configuration. For example, for all compounds in which splitting of the OMe signal was observed, the *R*-isomers had high-field shifts; for all compounds for which splitting of the SMe signal was observed, the *R*-isomers had low-field shifts. Without far more detail about the nature of the complexes formed between $Eu(hfc)_3$ and the phosphorus compounds it is not possible to propose any model to explain these observations. From the limited results available it is possible, however, to put forward a simple generalisation consistent with the data in Table 5 and which allows the assignment of absolute configuration provided at least that the signals for one set of protons can be resolved. The generalisation is that when viewing the molecule along the O=P bond from oxygen to phosphorus (i) where splitting of the largest of the remaining three groups (Sequence Rule) is observed, the enantiomer with the lower field signal has the *R* configuration, (ii) the group in a clockwise relation to the largest group always has a high-field shift, and (iii) the group in an anticlockwise relation to the largest group always has a low-field shift. We stress that this is an empirical generalisation with no mechanistic significance.[28]

*Mechanism of Endocyclic and Exocyclic Bond-breaking Reactions in* 1,3,2-*Oxazaphospholidines.*—In the studies of the displacement of labile exocyclic 2-substituents described in this paper, the clear evidence is that substitution occurs with retention of configuration at phosphorus. This result is consistent with previous findings for exocyclic displacements from phosphorus ($P^V$) constrained within a small ring [29] and is consistent with the notion of the formation of trigonal bipyramidal intermediates followed by pseudorotation prior to apical departure of the exocyclic leaving group [30] (Scheme 4).

For displacement to occur with retention of configuration it is immaterial whether the initial attack at phosphorus leads to *A* or *B*. However, at present the usually accepted view is that attack opposite the most apicophilic group, *i.e.* oxygen, as in *B*, is preferred.



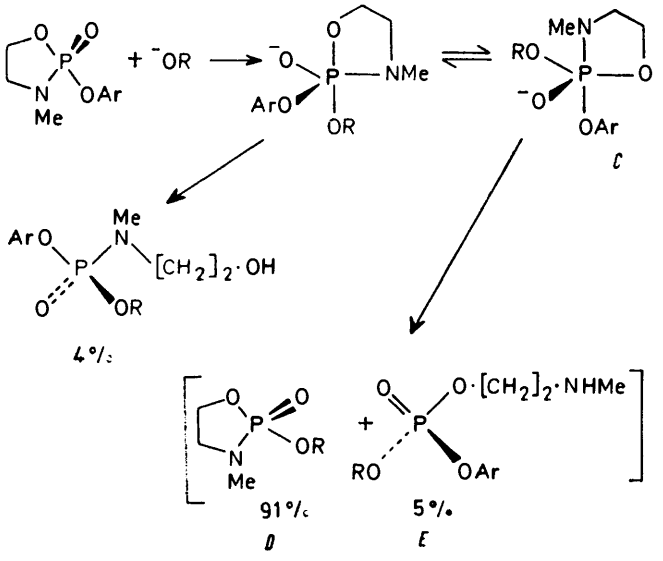

SCHEME 4

Consequently, in cases where treatment of 1,3,2-oxazaphospholidines with base causes cleavage of the P–N bond, initial attack opposite the ring oxygen has been considered the first step with P–N cleavage occurring only after pseudorotation.*,[31] Thus Scheme 5 (R = H) was postulated to account for the products of the aqueous alkaline hydrolysis of 2-phenoxy-1,3,2-oxazaphospholidin-2-one. The evidence in this paper and elsewhere that P–N cleavage under both acidic and basic conditions occurs with inversion of configuration at phosphorus does not fit this attractive hypothesis. In the case described in Scheme 5 (R = H) the aqueous basic hydrolysis destroys the chirality at phosphorus but where R = alkyl the chiral intermediate *C* would afford chiral products *D* and *E*, both with retention of configuration. The finding that that the P–N bond is broken with inversion of configuration at phosphorus provides little support for the suggestion that a square pyramidal intermediate is involved.[32] We conclude that whereas for exocyclic displacements from phosphorus in 1,3,2-oxazaphospholidines a trigonal bipyramidal intermediate and a pseudorotation step are

* Unlike the examples quoted in this paper where P–N cleavage preponderates, other examples of alkaline hydrolyses of 1,3,2-oxazphospholidines show significant and sometimes exclusive P–O bond cleavage depending on the nature of the substituents on phosphorus and nitrogen.[31,32]

[28] W. H. Pirkle, *Chem. Comm.*, 1970, 1525.
[29] J. R. Corfield, N. J. De'ath, and S. Trippett, *Chem. Comm.*, 1970, 1502.
[30] R. Luckenbach, 'Dynamic Stereochemistry of Pentacoordinated Phosphorus and Related Elements,' Thieme, Stuttgart, 1973.
[31] C. Brown, J. A. Boudreau, B. Hewitson, and R. F. Hudson, *J.C.S. Chem. Comm.*, 1975, 504; *J.C.S. Perkin I*, 1976, 888.
[32] J. A. Boudreau, C. Brown, and R. F. Hudson, *J.C.S. Chem. Comm.*, 1975, 679.

probably involved, it is not necessary to invoke any pseudorotation as a prelude to P–N bond cleavage. It is only necessary to accept that within a 1,3,2-oxazaphospholidine ring the P–N bond is sufficiently weak to undergo direct $S_N2$ displacement or that the apicophilicity of nitrogen relative to oxygen encourages direct formation of a trigonal bipyramid in which nitrogen is apical. This latter possibility seems less likely than direct $S_N2$ displacement.




SCHEME 5

It is interesting to speculate on reasons for the considerable differences in P–N bond strengths in acyclic as compared with cyclic phosphorus amidates. In acyclic phosphorus amidates presumably the nitrogen group adopts a conformation relative to phosphorus in which maximum orbital overlap occurs between the lone electron pair on nitrogen and suitable *d* orbitals on phosphorus. The consequences are (*a*) a strong bond, (*b*) reduced electropositive character at phosphorus, making nucleophilic attack less favourable, and (*c*) reduced basicity at nitrogen. This latter point may be of some importance since during P–N bond breaking an early abstraction of a proton from the solvent is required, as $\bar{N}R_2$ is an unacceptable leaving group. If, by incorporation of the P–N bond into a ring, orbital overlap is reduced as compared with the acyclic case, the P–N bond will be weakened, phosphorus becomes relatively more electropositive, and nitrogen becomes more basic. All these factors will contribute to the lability to base of P–N bonds in cyclic systems and lead to the observations that P–N bonds incorporated into six-membered rings [1e] are intermediate in lability between those in acyclic phosphorus amidates and those in 1,3,2-oxazaphospholidines.

*Mechanisms of* P–S *and* P–Se *Bond Cleavage.*—The finding that trialkyl phosphorothioates are hydrolysed in aqueous sodium hydroxide more rapidly than dialkyl methylphosphonothioates is anomalous since the expected higher electron density at phosphorus in the phosphoro-derivatives relative to the phosphono-derivatives should encourage faster hydrolysis of the latter.[33] This result prompted a previous study to establish whether the stereochemical courses of the hydrolyses of the phosphonothioates and phosphorothioates were also different. The observation that nucleophilic substitution at phosphorus in *S*-alkyl phosphorothioates occurs with retention of configuration, whereas similar substitutions in *S*-alkyl methylphosphonothioates occur with preponderant inversion of configuration, provided a possible explanation for the anomalous kinetic data.[33] The inference was that in the phosphonothioates substitution occurs *via* an $S_N2$ mechanism or *via* a trigonal bipyramid involving direct formation of an apical P–S bond, whereas in the phosphorothioates initial attack is opposite an alkoxy-group with P–S bond cleavage occurring only after pseudorotation.

The phosphoroselenoates and alkylphosphonoselenoates appear to present a different situation. Anomalous rate data (*i.e.* phosphoro faster than phosphono) were again observed in the hydrolysis of diethyl *Se*-propyl phosphoroselenoate and ethyl *Se*-propyl methylphosphonoselenoate,[34] [the observed rate constants were 0.76 (phosphono) and 2.2 (phosphoro) l mole$^{-1}$ s$^{-1}$] but for both compounds substitution with methoxide ion occurred with exclusive inversion of configuration at P. These data are readily accommodated in terms of a substitution mechanism with some degree of $S_N1$ character, *i.e.* cleavage of P–SeR is more advanced than formation of P–OR. This would result first in inversion of configuration (as observed) and secondly in enhanced rates for phosphoro- over phosphono-derivatives where for the former additional π-bonding ligands are available to assist in the stabilisation of a positive charge generated on phosphorus in the early stages of the reaction prior to attack by the incoming nucleophile.

The postulated differences in mechanisms of substitution between *S*-alkyl and *Se*-alkyl phosphorus derivatives may simply reflect an inherent thermodynamic weakness of the P–Se bond.

The consistent exclusive inversion of configuration at phosphorus observed when P–SR and P–SeR bonds are broken by alcohols in the presence of bromine is consistent with formation of P–$\overset{+}{S}$R–Br and P–$\overset{+}{S}$eR–Br groups which make the P–S and P–Se bonds more labile and increase the susceptibility of phosphorus to nucleophilic attack. If this is the explanation, the silver-nitrate-promoted methanolyses would be expected to occur by a similar mechanism. It is therefore surprising that the methanolysis of ethyl *S*-methyl methylphosphonothioate in the presence of silver nitrate was no more stereoselective than the corresponding reaction with sodium methoxide. Of the possible

[33] T. D. Inch, G. J. Lewis, P. Watts, and R. G. Wilkinson, *J.C.S. Chem. Comm.*, 1975, 500.

[34] C. R. Hall, T. D. Inch, and R. G. Wilkinson, unpublished results.

mechanisms for the silver-nitrate-promoted alcoholysis of P–S and P–Se bonds that have been considered,[23] none appears fully consistent with available experimental data.

## EXPERIMENTAL

Details for the preparation of each compound are not given, but examples of each type of compound are reported. In some cases physical data to complement those in Tables 1 and 2 are also provided.

$^1$H N.m.r. spectra were measured with a JEOL JNM-4-H-100 spectrometer at 100 MHz, with deuteriochloroform as solvent and tetramethylsilane as internal standard except when the chiral shift reagent $Eu(hfc)_3$ was employed (when a Perkin-Elmer R-24A operating at 60 MHz was used). Optical rotations were measured in chloroform (path length 1 dm) and are listed in Tables 1 and 5. Small-scale distillations were carried out under reduced pressure with a Kugelrohr oven; temperatures quoted are the bath temperatures at which distillation commenced. Column chromatography was performed with Merck silica gel of particle size 0.05—0.2 mm. Solvents for column and thin-layer chromatography are given in Table 1 for many of the compounds. All air-sensitive reactions were carried out under dry nitrogen. Solvents were dried over $MgSO_4$; light petroleum refers to the fraction of b.p. 60—80 °C. $Eu(hfc)_3$ was purchased from the Ryvan Chemical Company, Southampton.

(2R,4S,5R)- *and* (2S,4S,5R)-2-*Chloro*-3,4-*dimethyl*-5-*phenyl*-1,3,2-*oxazaphospholidin*-2-*ones* (1a *and* b).—Phosphoryl chloride (3.2 g, 0.2 mol) was added to a stirred solution of (−)-ephedrine hydrochloride (4.1 g, 0.2 mol) and triethylamine (10.0 g, 0.1 mol) in dry benzene (100 ml). After a mildly exothermic reaction, the mixture was stirred for a further 2 h, stored overnight at room temperature, filtered, and concentrated. The residue was chromatographed to give the *products* (1b) (0.3 g, 6%), m.p. 111—113° (from di-isopropyl ether) (Found: C, 48.7; H, 5.2; N, 5.7. $C_{10}H_{13}ClNO_2P$ requires C, 48.9; H, 5.3; N, 5.7%), and (1a) (3.2 g, 65%), m.p. 88—89° (from di-isopropyl ether) (Found: C, 48.6; H, 5.2; N, 5.7%).

In some experiments a third product, 5-*chloro*-3,4,8,9-*tetramethyl*-2,7-*diphenyl*-1,6-*dioxa*-4,9-*diaza*-5-*phosphaspiro*-[4.4]*nonane* (1c), was isolated; $R_F$ 0.3 in benzene–acetone (9 : 1), δ 0.71 (3 H, d, *J* 6.5 Hz), 1.49 (3 H, d, *J* 7 Hz), 2.24 (3 H, d, *J* 10 Hz), 2.56 (3 H, d, *J* 10 Hz), 3.51 (1 H, ddq, *J* 6.5 and 19 Hz), 4.18 (1 H, ddq, *J* 7, 8, and 15 Hz), 5.14 (1 H, d, *J* 9 Hz), 5.31 (1 H, dd, *J* 6.5 and 3 Hz), and 7.38 (10 H, m) (Found: C, 61.7; H, 6.6; Cl, 9.3; N, 7.0. $C_{20}H_{26}ClN_2O_2P$ requires C, 61.2; H, 6.7; Cl, 9.0; N, 7.1%).

(2R,4S,5R)- *and* (2S,4S,5R)-3,4-*Dimethyl*-2,5-*diphenyl*-1,3,2-*oxazaphospholidin*-2-*ones* (3a *and* b).—Phenylphosphonic dichloride (1.8 g, 0.01 mol) was added to a stirred solution of (−)-ephedrine hydrochloride (2.05 g, 0.01 mol) and triethylamine (5.0 g, 0.05 mol) in benzene (50 ml). Stirring was continued for 5 h, and the mixture was filtered and concentrated. Chromatography of the residue gave the *products* (3b) (0.8 g, 28%), m.p. 159—161° (from di-isopropyl ether–acetone) (Found: C, 66.6; H, 6.3; N, 4.8. $C_{16}H_{18}NO_2P$ requires C, 66.9; H, 6.3; N, 4.9%), and (3a) (0.95 g, 33%), m.p. 134—136° (from di-isopropyl ether–acetone) (Found: C, 66.4; H, 6.3; N, 4.8%).

(2R,4S,5R)- *and* (2S,4S,5R)-2-*Methoxy*-3,4-*dimethyl*-5-*phenyl*-1,3,2-*oxazaphospholidin*-2-*ones* (4a *and* b).—(*a*) Triethylamine (1.5 g) was added to the chloridate (1a) (1.5 g) in methanol (10 ml) and the mixture was stored for 1 h at room temperature. No starting material and only one product were then detected by t.l.c. (benzene–methanol–acetone, 8 : 1 : 1). Conventional processing and chromatography gave (4a) (1.35 g, 91%) as a clear syrup.

(*b*) By a similar procedure (1b) (0.06 g) afforded (4b) (0.051 g, 85%).

(2R,4S,5R)- *and* (2S,4S,5R)-2-*Chloro*-3,4-*dimethyl*-5-*phenyl*-1,3,2-*oxazaphospholidine*-2-*thiones* (7a *and* b).—A solution of thiophosphoryl chloride (6.9 g) in benzene (25 ml) was slowly added to a suspension of (−)-ephedrine hydrochloride (8.2 g) in triethylamine (25 g) and benzene (150 ml). The mixture was stirred overnight at room temperature and then poured into an excess of water. The aqueous layer was extracted with benzene. The combined extracts were concentrated and the resulting oil was crystallised from di-isopropyl ether to give the *product* (7a) (6.5 g, 61%), m.p. 125—128° (from di-isopropyl ether) (Found: C, 45.8; H, 4.8; N, 5.6. $C_{10}H_{13}ClNOPS$ requires C, 45.9; H, 5.0; N, 5.4%). The mother liquor was concentrated and the resulting clear oil was chromatographed to give, in addition to residual (7a), the *product* (7b) (0.87 g, 8%), m.p. 58° (from chloroform–light petroleum) (Found: C, 46.0; H, 5.1; N, 5.3%).

Alternatively a solution of phosphorus trichloride (1.7 g) in benzene (10 ml) was slowly added to a cooled solution of (−)-ephedrine (2 g) and triethylamine (6 ml) in benzene (50 ml) under nitrogen. The solution was allowed to warm to room temperature and stirred for 1 h, then sulphur (0.4 g) was added and the mixture was stored overnight. Work-up as above gave (7a) (0.16 g, 5%) and (7b) (0.24 g, 7.6%).

(2R,4S,5R)- *and* (2S,4S,5R)-2,3,4-*Trimethyl*-5-*phenyl*-1,3,2-*oxazaphospholidine*-2-*thione* (8a *and* b).—A solution of methyl(thiophosphonic) dichloride (8 g) in benzene (25 ml) was slowly added to a suspension of (−)-ephedrine hydrochloride (10 g) in triethylamine (40 ml) and benzene (200 ml), and the mixture was stored overnight. Conventional processing and chromatography yielded the *products* (8a) (2.9 g, 21%), m.p. 73—74° (from light petroleum) (Found: C, 54.7; H, 6.9; N, 5.6. $C_{11}H_{16}NOPS$ requires C, 54.7; H, 6.7; N, 5.8%), and (8b) (3.1 g, 22%), m.p. 88—90° (from light petroleum) (Found: C, 54.8; H, 6.8; N, 5.7%).

Alternatively a solution of dichloro(methyl)phosphine (1.4 g) in benzene (10 ml) was slowly added to a cooled solution of (−)-ephedrine (2 g) and triethylamine (5 ml) in benzene (50 ml) under nitrogen. The solution was allowed to warm to room temperature and stirred for 1 h, then sulphur (0.5 g) was added and the mixture was stored overnight. Work-up as above gave (8a) (0.4 g, 16%) and (8b) (0.7 g, 28%).

(2R,4S,5R)- *and* (2S,4S,5R)-2-*Alkoxy*- *and* -*Aryloxy*-3,4-*dimethyl*-5-*phenyl*-1,3,2-*oxazaphospholidine*-2-*thiones*.—A solution (*ca.* 2M) of 1 mol. equiv. of alkoxide in the relevant alcohol was slowly added to a solution of the chloridate (7a or b) in the alcohol. The mixture was stirred for *ca.* 20 h, poured into water, and extracted with methylene chloride. The extract was concentrated and the product was chromatographed over silica or distilled. The following were obtained: (2S,4S,5R)-2-*methoxy*-3,4-*dimethyl*-5-*phenyl*-1,3,2-*oxazaphospholidine*-2-*thione* (9a) (80%) as a clear oil, b.p. 140° (bath) at 0.1 mmHg (Found: C, 51.4; H, 6.3; N, 5.4. $C_{11}H_{16}NO_2PS$ requires C, 51.3; H, 6.3; N, 5.4%); (2R,4S,5R)-2-*methoxy*-3,4-*dimethyl*-5-*phenyl*-

1,3,2-*oxazaphospholidine*-2-*thione* (9b) (85%), m.p. 88—90° (from di-isopropyl ether) (Found: C, 51.4; H, 6.3; N, 5.4%); (2S,4S,5R)-2-*ethoxy*-3,4-*dimethyl*-5-*phenyl*-1,3,2-*oxazaphospholidine*-2-*thione* (10a) (83%), m.p. 74—76° (from propan-2-ol) (Found: C, 52.8; H, 6.8; N, 5.0. $C_{12}H_{18}NO_2PS$ requires C, 53.1; H, 6.7; N, 5.2%); (2R,4S,5R)-2-*ethoxy*-3,4-*dimethyl*-5-*phenyl*-1,3,2-*oxazaphospholidine*-2-*thione* (10b) (93%), m.p. 43—44° (from propan-2-ol) (Found: C, 53.3; H, 6.8; N, 5.1%); (2S,4S,5R)-2-*isopropoxy*-3,4-*dimethyl*-5-*phenyl*-1,3,2-*oxazaphospholidine*-2-*thione* (11a) (88%), m.p. 73—74° (from propan-2-ol) (Found: C, 54.6; H, 7.1; N, 5.2. $C_{13}H_{20}NO_2PS$ requires C, 54.7; H, 7.1; N, 4.9%); (2R,4S,5R)-2-*isopropoxy*-3,4-*dimethyl*-5-*phenyl*-1,3,2-*oxazaphospholidine*-2-*thione* (11b) (86%), m.p. 70—71° (from propan-2-ol) (Found: C, 54.7; H, 7.2; N, 4.8%); (2S,4S,5R)-3,4-*dimethyl*-2-p-*nitrophenoxy*-5-*phenyl*-1,3,2-*oxazaphospholidine*-2-*thione* (12a) (83%) as a clear oil, b.p. 170° (bath) at 0.1 mmHg (Found: C, 52.3; H, 4.8. $C_{16}H_{17}N_2O_4PS$ requires C, 52.7; H, 4.7%).

*Treatment of the Thione* (12a) *with Isopropoxide*.—A solution of sodium isopropoxide [from sodium (0.036 g)] in propan-2-ol (9 ml) was slowly added to a solution of (12a) (0.54 g) in propan-2-ol (15 ml). The mixture was stirred for 5 h. Conventional processing gave a black oil which on chromatography gave (11a) (0.3 g, 70%).

(2R,4S,5S)- *and* (2S,4S,5S)-2,3,4-*Trimethyl*-5-*phenyl*-1,3,2-*oxazaphospholidine*-2-*thione*, (15) *and* (16).—A solution of methyl(thiophosphonic) dichoride (8 g) in benzene (25 ml) was slowly added to a suspension of (+)-$\psi$-ephedrine (10 g) in triethylamine (30 ml) and benzene (100 ml). The mixture was stirred for 5 h; work-up and chromatography yielded the *products* (15) (3.8 g, 32%), m.p. 120° (from cyclohexane), $[\alpha]_D$ +30.3° (*c* 0.7), $R_F$ 0.4 (acetone–light petroleum, 1 : 4), δ 1.17 (3 H, d, *J* 6.0 Hz), 2.67 (3 H, d, *J* 12.0 Hz), 3.14 (1 H, ddq, *J* 6.0, 8.9, and 1.3 Hz), and 4.89 (1 H, dd, *J* 8.9 and 1.0 Hz) (Found: C, 55.0; H, 6.8; N, 5.8. $C_{11}H_{16}NOPS$ requires C, 54.7; H, 6.7; N, 5.8%), and (16) (3.0 g, 25%), a syrup, $[\alpha]_D$ +62° (*c* 0.4), $R_F$ 0.3, δ 1.14 (3 H, d, *J* 6.1 Hz), 2.58 (3 H, d, *J* 15.0 Hz), 3.11 (1 H, ddq, *J* 6.1, 9.0, and <1 Hz), and 4.77 (1 H, dd, *J* 9.0 and 1.1 Hz).

(2R,4S,5R)- *and* (2S,4S,5R)-2,3,4-*Trimethyl*-5-*phenyl*-1,3,2-*oxazaphospholidine*-2-*selone* (13a *and* b).—A solution of dichloro(methyl)phosphine (6 g) in benzene (20 ml) was slowly added to a solution of (−)-ephedrine (8.5 g) in triethylamine (40 ml) and benzene (150 ml). The mixture was stirred under nitrogen for 5 h, then selenium (4 g) was added and stirring was continued for a further 3 days. The mixture was filtered, poured into an excess of water, and extracted with benzene, and the extract was concentrated to a brown oil which on chromatography yielded the *products* (13a) (1.0 g, 7%) as a syrup, and (13b) (2.8 g, 20%), m.p. 100—101° (from di-isopropyl ether) (Found: 45.9; H, 5.6; N, 5.0. $C_{11}H_{16}NOPSe$ requires C, 45.8; H, 5.6; N, 4.9%).

(2R,4S,5R)-2-*Methoxy*-3,4-*dimethyl*-5-*phenyl*-1,3,2-*oxazaphospholidine*-2-*selone* (14b).—A solution of phosphorus trichloride (3.2 g) in benzene (50 ml) was slowly added to a solution of (−)-ephedrine (10 g) and *N*-methylmorpholine (10 g) in benzene (100 ml). After 3 h the solution was filtered and evaporated to dryness, and the resulting oil was distilled [b.p. 130° (bath) at 0.1 mmHg]. $^1$H N.m.r. data suggested that the product was (2*R*,4*S*,5*R*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine, δ 0.73 (3 H, d, *J* 6 Hz), 2.72 (3 H, d, *J* 16 Hz), 3.66 (1 H, m), 5.84 (1 H, dd, *J* 8 and 1.6 Hz), and 7.45 (5 H, m). The oil was dissolved in benzene (50 ml) and triethylamine (10 g) and an excess of methanol was slowly added. After stirring for 1 h, red selenium (6 g) was added, and the mixture was stored for 24 h, filtered, concentrated and chromatographed to give (14b) (0.8 g, 7%) as a syrup.

*Oxidation of* 2-*Substituted* 1,3,2-*Oxazaphospholidine*-2-*thiones and* -*selenones*.—In all cases oxidation with peroxy-acid was carried out as in the following example. A solution of *m*-chloroperbenzoic acid (0.13 g) in methylene chloride (5 ml) was slowly added to a solution of (8a) (0.2 g) in methylene chloride (10 ml). The solution was stirred for 1 h then poured into aqueous 10% sodium carbonate and extracted with methylene chloride. Removal of the solvent at reduced pressure and chromatography of the resulting oil gave (4a) (0.16 g, 95%).

*Oxidation with Hydrogen Peroxide*.—Hydrogen peroxide (30%; 100 vol.; 1 ml) was slowly added to a solution of (13a and b) (1 : 3; 0.2 g) in methanol (5 ml). The mixture was set aside for ½ h and was then concentrated to give a white solid (0.15 g, 95%), which $^1$H n.m.r. showed to be a 1 : 3 mixture of (2a) and (2b).

P–N *Bond Cleavage in* 2-*Substituted* 1,3,2-*Oxazaphospholidine*-2-*thiones*.—Acid-catalysed P–N bond cleavage is typified by the reaction of (10a) with methanol and hydrogen chloride to give (25). A solution (3M) of hydrogen chloride in methanol (2 ml) was slowly added to a solution of (10a) in methanol (10 ml). The mixture was stirred for 45 min, poured into an excess of aqueous sodium carbonate solution, and extracted with methylene chloride, and the extract was concentrated to give (25) (0.16 g, 72%) as an unstable clear oil.

Base-catalysed P–N bond cleavage gave an indistinguishable product. A solution of (10a) (0.1 g) with an excess of sodium methoxide in methanol was stored for 1 h, poured into water, and extracted with chloroform; the organic extract was concentrated to a clear oil. N.m.r. showed the presence of (25) (*ca.* 75%) and no trace of (24).

Treatment of the $\psi$-ephedrine adducts (15) and (16) with either ethanolic hydrogen chloride or sodium ethoxide gave the P–N-cleaved products, (30), δ 0.88 (3 H, d), 1.51 (3H, d), 2.48 (3 H, s), 4.13 (2 H, m) and 5.30 (1 H, dd), and (31), δ 0.85 (3 H, d), 1.82 (3 H, d), 2.42 (3 H, s), 3.2 (1 H, m), 3.75 (1 H, m), and 5.37 (1 H, dd), respectively.

*Isolation of Phosphorus Thioesters and Selenoesters*.—All phosphorus thioesters and selenoesters were prepared from the precursors listed in Table 5 by the following general procedure illustrated for the formation of (+)-(*S*)-*OS*-dimethyl isopropyl phosphorothioate (33) from the (−)-ephedrine adduct (9a).

A 3.5M-solution of hydrogen chloride in propan-2-ol (20 ml) was slowly added to a solution of (9a) (5 g) in propan-2-ol (20 ml) and the mixture was stirred for 1 h. The solution was then made basic (to *ca.* pH 12) by addition of concentrated aqueous potassium hydroxide, and stored overnight. An excess of methyl iodide (20 ml) was added; the solution was stirred for 1 h and poured into water and the aqueous layer was extracted four times with methylene chloride. The combined organic extracts were dried and concentrated to a light yellow oil which, when chromatographed in benzene–acetone–methanol (8 : 1 : 1) gave (33) (0.9 g, 42%), $R_F$ 0.6.

The $\psi$-ephedrine adducts (30) and (31) were unchanged when kept at room temperature in aqueous sodium hydroxide (6M) for 20 days.

(2S,3S)-1,2-*Dimethyl*-3-*phenylaziridine*.—For example, a 3M-solution of hydrogen chloride in ethanol (2 ml) was slowly added to a solution of (11a) in ethanol (3 ml), and the mixture was stirred for 30 min, basified with a concentrated aqueous sodium hydroxide, and stored for 3 days at room temperature. Work-up in the usual way gave an oil which was chromatographed in dry ether to afford the aziridine (0.1 g, 39%), $R_F$ 0.7.

*Cleavage of* P–S *and* P–Se *Bonds with Alkoxide*.—A piece of sodium (*ca.* 0.05 g) was dissolved in a solution of (+)-(*R*)-ethyl *S*-methyl methylphosphonothioate (38) (0.25 g) in methanol (10 ml) at 0 °C and the solution was stored overnight. Conventional processing gave a light yellow oil which on chromatography in 4% methanol in ether gave ethyl methyl methylphosphonate (0.15 g, 79%), $R_F$ 0.5, $[\alpha]_D$ +1.1° (*c* 0.8). $^1$H N.m.r. data obtained in the presence of the chiral shift reagent Eu(hfc)$_3$ confirmed that the product contained *ca.* 80% (46) and 20% (47).

Likewise treatment of (+)-(*S*)-ethyl isopropyl *S*-methyl phosphorothioate (37) with sodium methoxide, treatment of (−)-(*R*)-*OS*-dimethyl isopropyl phosphorothioate (32) with sodium ethoxide, and treatment of (−)-(*S*)-ethyl *OS*-dimethyl phosphorothioate (35) with sodium isopropoxide gave the single enantiomer (+)-(*S*)-ethyl methyl isopropyl phosphate (49) in 50—95% yields.

Treatment of (−)-(*S*)-ethyl *OSe*-dimethyl phosphonoselenoate (43) with sodium methoxide gave the single enantiomer (47) (80%), and treatment of (−)-(*R*)-*OSe*-dimethyl isopropyl phosphoroselenoate (44) with sodium ethoxide gave the single enantiomer (48) (75%).

*Cleavage of* P–S *and* P–Se *Bonds by Bromine and Alcohol*.—All the chiral phosphorus thio- and seleno-esters listed in Table 5, when treated with bromine and the relevant alcohol by the general procedure outlined below for (−)-(*R*)-ethyl isopropyl *S*-methyl phosphorothioate (36), gave a single enantiomer of either ethyl methyl methylphosphonate or ethyl methyl isopropyl phosphate.

Neat bromine was added dropwise to a stirred solution of (36) (0.4 g) in methanol (20 ml) until the solution just retained a red colour. After stirring for 1 h the mixture was poured into an excess of dilute aqueous sodium bicarbonate and extracted with methylene chloride. The organic layer dried was concentrated to a light yellow oil which on chromatography in benzene–acetone–methanol (8 : 1 : 1) gave (+)-(*S*)-ethyl isopropyl methyl phosphate (49) (0.3 g, 84%), $R_F$ 0.6.

*Cleavage of* P–S *and* P–Se *Bonds with Silver Nitrate and Alcohol*.—For example, a solution of silver nitrate (0.75 g) in acetonitrile (25 ml) was slowly added to a solution of (+)-(*R*)-ethyl *S*-methyl methylphosphonothioate (38) (0.5 g) in acetonitrile (5 ml), methanol (2 ml), and triethylamine (2 ml) and the mixture was stored in the dark for 12 h. It was then poured into an excess of ether and the inorganic material was filtered off. The filtrate was concentrated and chromatographed in 4% methanol in ether, to give (38) (0.2 g, 40%) of unchanged configuration and ethyl methyl methylphosphonate (0.2 g, 45%). $^1$H N.m.r. data obtained in the presence of the chiral shift reagent Eu(hfc)$_3$ showed this product to contain *ca.* 80% (46) and 20% (47).

A product of identical configuration was obtained when the reaction was carried out in the absence of triethylamine or in the presence of an excess of sodium carbonate.

Likewise, treatment of (−)-(*R*)-ethyl isopropyl *Se*-methyl phosphorothioate (36) with silver nitrate and methanol for 1 week gave the single enantiomer (49) (77%), and treatment of (−)-(*S*)-ethyl *Se*-methyl methylphosphonoselenoate (43) with silver nitrate and methanol for 5 h gave the single enantiomer (47) (30%).

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