Stereochemistry of Alkaline Hydrolyses of 1,3,2-Oxazaphospholidine-2-thiones and Related Reactions

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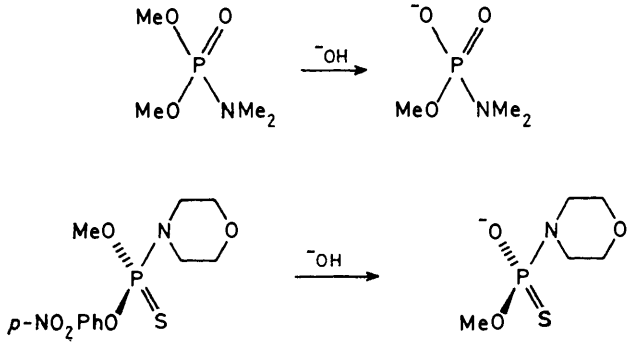
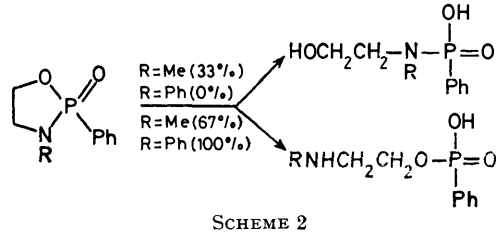
Essentially exclusive cleavage, with retention of configuration, of the endocyclic P–O bond occurs during basic hydrolysis of 2-alkoxy-1,3,2-oxazaphospholidine-2-thiones. In the 2-methyl analogues, P–O bond cleavage occurs with both inversion and retention of configuration and also obtained are products from P–N bond cleavage with inversion. These results are consistent with reaction mechanisms which require nucleophilic attack at phosphorus opposite nitrogen in preference to oxygen. A term, apical potentiality, introduced to refer to apical preference during reactions, is intended to be quite distinct from the term apicophilicity which describes apical preference in stable phosphoranes. *S*-Alkyl groups are displaced from *NN*-dialkyl phosphoramidothioates with retention of configuration, but with inversion in the corresponding phosphono-derivatives.

THE basic hydrolysis of acyclic di-*O*-alkyl *NN*-dialkyl phosphoramidates results in both P–O and C–O bond cleavage but not in any P–N bond cleavage.[1,2] Where phosphorus bears a good leaving group such as *p*-nitrophenate, P–O cleavage is essentially stereospecific and has been assumed to occur with inversion of configuration at phosphorus[3] (Scheme 1). In hydrolyses of 1,3,2-



SCHEME 1

oxazaphospholidines (*i.e.* analogues of the acyclic phosphoramidates in which nitrogen and one oxygen are constrained in a five-membered ring) P–O bond cleavage is not always preponderant and P–N bond cleavage is a much more common feature[1,4] (Scheme 2). One

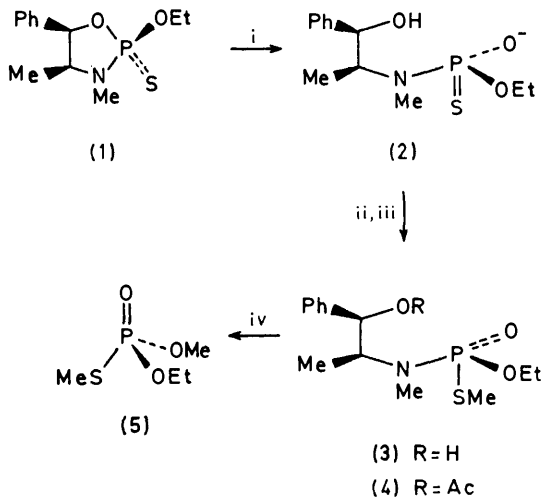


SCHEME 2

mechanism proposed[4] to accommodate both P–O and P–N bond cleavage was nucleophilic attack at hydroxide at phosphorus in-line with endocyclic oxygen, with P–O bond cleavage occurring before, or P–N bond cleavage occurring after, a pseudorotation step.[5] No stereochemical studies were carried out to test this suggestion which requires that P–O bond cleavage occurs with inversion of configuration and P–N bond cleavage with retention of configuration. In this laboratory, 1,3,2-oxazaphospholidines [from (−)-ephedrine] on treatment with alkoxides have given exclusive P–N bond cleavage with inversion of configuration,[6-9] a result not consistent with the above mechanism. We now report the results of studies carried out to examine the stereochemistry of alkaline hydrolysis of 1,3,2-oxazaphospholidine-2-thiones.

RESULTS

Ring-opening Reactions.—On treatment with aqueous sodium hydroxide–dioxan, (2*S*,4*S*,5*R*)-2-ethoxy-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-thione[7] (1) was converted by endocyclic P–O bond cleavage into (2), which was isolated in 90% yield as the *S*-methyl derivative (3), following treatment with methyl iodide. Intramolecular participation of the hydroxy-group in (3) in subsequent reactions was prevented by its acetylation to give (4)

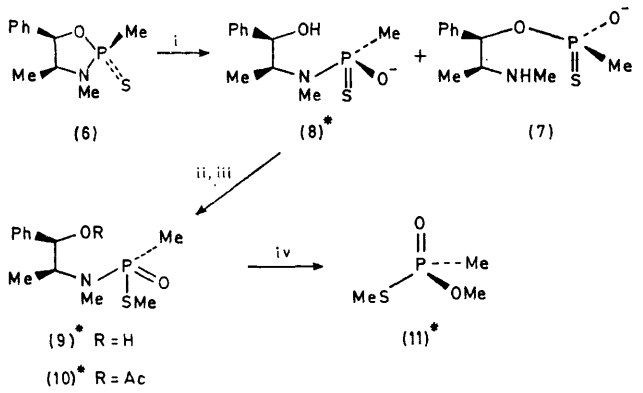


SCHEME 3 *Reagents:* i, HO^-; ii, MeI; iii, Ac_2O–pyridine; iv, MeOH–HCl

which was then converted into *R*-(+)-ethyl *OS*-dimethyl phosphorothioate[7] (5) by treatment with a dilute solution of anhydrous methanolic hydrogen chloride. The above reaction sequence (Scheme 3) occurs with overall inversion of configuration at phosphorus. Since both *S*-alkylation

and *O*-acetylation involve no reaction at phosphorus, and all available evidence is consistent with the fact that under the conditions used P–N bonds in *NN*-dialkyl phosphoramidothioates are cleaved with inversion of configuration,[10] the observed sequence implies that endocyclic P–O bond cleavage occurs with retention of configuration.

The reaction between (6) [7] [the phosphoro-analogue of (1)] and aqueous sodium hydroxide–dioxan yielded two products (Scheme 4). The minor product (7) (≤5%) was



SCHEME 4 *Reagents:* i, HO^-; ii, MeI; iii, Ac_2O–pyridine; iv, MeOH–HCl

* Major isomers only are shown for (8), (9), (10), and (11).

spectroscopically indistinguishable from that obtained on treatment of (6) with hydrochloric acid and subsequent basification. Thus the base-catalysed P–N bond cleavage almost certainly occurs with inversion of configuration. The major product (8) (≥95%) was methylated to give (9), acetylated (10), and treated with methanolic hydrogen chloride in an analogous manner to that described in Scheme 3. In this case however, the *OS*-dimethyl methylphosphonothioate isolated was not stereochemically pure but a 3 : 2 mixture of the *S*- and *R*-enantiomers (11). The excess of the *S*-enantiomer implies that endocyclic P–O bond cleavage in (6) occurs with preponderant inversion of configuration.

The stereoselectivity of P–O bond cleavage and the ratio of P–O to P–N bond cleavage in the basic hydrolysis of (6) are solvent dependent (Table). Similar results but with

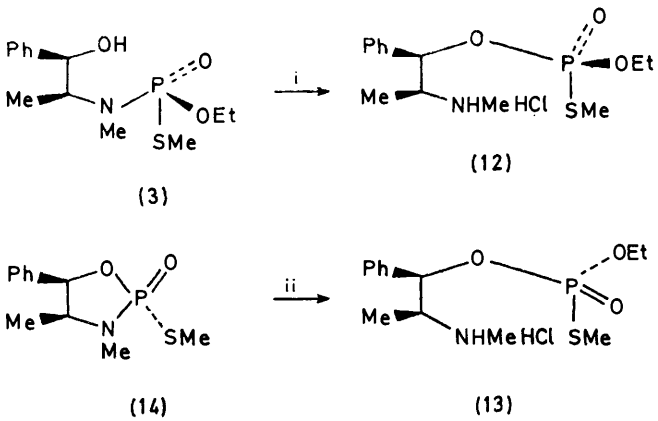
Basic hydrolysis of the 1,3,2-oxazaphospholidine-2-thione (6)

Solvent and reactant	Yield (%) (stereochemistry) [a] P–O Cleavage	P–N Cleavage
Dioxan, water, NaOH	95 (60% I)	5 (I)
Ethanol, water, NaOH	83 (80% I)	17 (I)
Ethanol, water, LiOH	90 (90% I)	10 (I)
Benzene, 18-crown-6, NaOH	98 (50% I)	
Acetonitrile, NaOH	95 (85% R)	

[a] I = Inversion of configuration at phosphorus; R = retention of configuration at phosphorus.

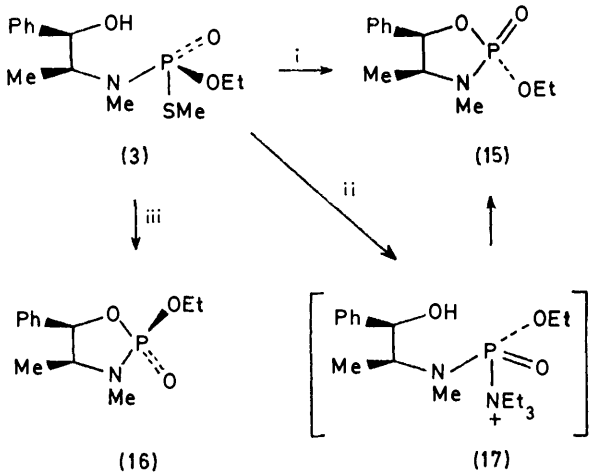
slightly different product ratios were obtained when (6) was replaced with its phosphorus epimer or pseudoephedrine-derived analogues.

Migration and Ring-closing Reactions.–On treatment of (3) with a dilute solution of anhydrous hydrogen chloride in benzene, the phosphorothioate group migrated rapidly from nitrogen to oxygen affording (12). A similar product (13), but epimeric to (12) at phosphorus, was obtained when [11] (14) was dissolved in dilute ethanolic hydrogen chloride (Scheme 5). Since the latter acid-catalysed cleavage of the P–N bond occurred with inversion of configuration the migration (3) to (12) must be with retention of configuration.



SCHEME 5 *Reagents:* i, benzene–HCl; ii, EtOH–HCl

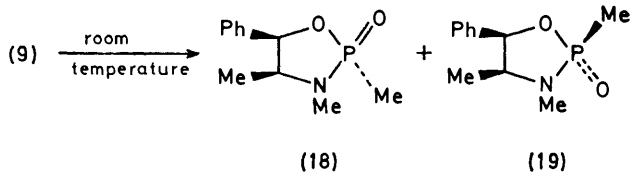
Addition of a trace of alkoxide to a solution of the phosphoro-derivative (3) in methanol caused rapid cyclisation to afford (15) as the only product (Scheme 6). Since the



SCHEME 6 *Reagents:* i, RO^-; ii, $AgNO_3$–Et_3N; iii, $AgNO_3$–Na_2CO_3

structure of (15) was established previously by analogy with other alkoxy-derivatives,[6,7] ring closure occurred with retention of configuration. The epimer of (15), *i.e.* (16), was formed with preponderant (5 : 1) inversion of configuration from (3), when (3) was treated with $AgNO_3$–Na_2CO_3.[7] With $AgNO_3$–triethylamine, (3) gave (15) as the only product, possibly through the intermediacy of (17).

The phosphono-derivative (9), during storage for 24 h at room temperature recyclised spontaneously to afford a 3 : 2 mixture of (18) and (19) (Scheme 7). Since (9) was a 3 : 2



SCHEME 7

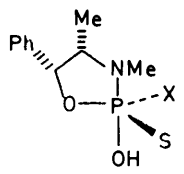
mixture of isomers it is reasonable to assume that ring closure occurred stereospecifically. Further, since the major isomer in (9) is the one depicted in Scheme 4, and (18) is the major isomer in Scheme 7, ring closure occurred with inversion of configuration.

DISCUSSION

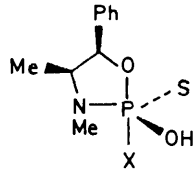
Ring Opening.—In nucleophilic substitution reactions at tetraco-ordinate phosphorus, nucleophilic attack is usually considered to take place opposite the most apicophilic ligand to form a trigonal bipyramidal intermediate (TBP) in which both the nucleophile and ligand occupy apical positions. If the most apicophilic group is also a good leaving group, substitutions occur with inversion of configuration, but where other less apicophilic ligands are good leaving groups displacements with retention of configuration may be observed; such results are usually explained using concepts of pseudorotation.[5] There appears to be no way of rationalising the results described in this paper in terms of these concepts because in all the stable phosphoranes where nitrogen is constrained within a saturated ring and which have been examined by *X*-ray or n.m.r. methods, oxygen is more apicophilic than nitrogen.[12] Results in this paper are rationalised most conveniently if nucleophilic attack occurs opposite nitrogen in preference to oxygen (see below).

The relevance of apicophilicity as applied to reactions at phosphorus must therefore be questioned. Apicophilicity is a term which was coined to facilitate comparisons of the apical preference of ligands in phosphoranes under thermodynamically controlled conditions.[13] Accordingly it does not necessarily have any relevance to reactions at phosphorus where the direction of initial attack is controlled by kinetic factors. Indeed, examples where the kinetic order for the formation of TBPs are widely different from thermodynamic predictions have been reported previously.[14] Consequently, it is suggested that the term ' apicophilicity ' is reserved to describe thermodynamically controlled situations and that the new term ' apical potentiality ' is introduced to facilitate discussion of reactions at phosphorus. Apical potentiality is a concept intended to relate the likelihood, during nucleophilic attack at tetraco-ordinate phosphorus, of a ligand being in-line with the nucleophile and therefore of occupying an apical position in the TBP formed initially. The apical potentiality of any ligand will depend on the other ligands attached to phosphorus, the nature of the nucleophile, the solvent, the presence or absence of metal ions *etc.*, and therefore the term is intended primarily as a descriptive one rather than as a measure of any particular parameter.

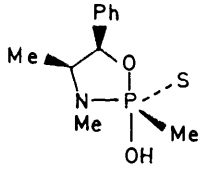
The results of the basic hydrolysis of 1,3,2-oxazaphospholidine-2-thiones are explained conveniently if, in this ring system, nitrogen has a higher apical potentiality than oxygen.* In the phosphoro-series, attack of hydroxide opposite nitrogen gives the TBP (20). Cleavage of the P–N bond (*i.e.* loss of nitrogen anion) in basic solution is unlikely to be rapid and pseudorotation of (20) to (21) will compete. Apical cleavage of the endocyclic P–O bond in (21) will give a product with retention



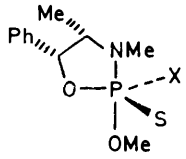
(20) X = OEt
(22) X = Me



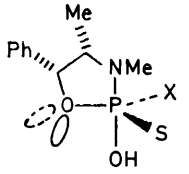
(21) X = OEt
(23) X = Me



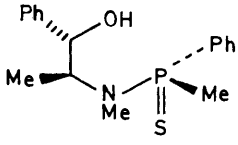
(24)



(25) X = OEt
(26) X = Me



(27)



(28)

of configuration. Thus, the formation of (2) from (1) is unexceptional.

In the phosphono-series, the TBP formed initially is (22). Again, P–N bond cleavage should not be rapid, but in this case pseudorotation of (22) to (23) will be retarded because of the low apicophilicity of the methyl group [compared with the ethoxy-group in (21)]. Thus apical P–N bond cleavage in (22) occurs to a small extent and inversion of configuration is observed [*i.e.* (6) to (7)]. However, the main competitive reaction (except in acetonitrile) is not the unfavoured pseudorotation of (22) to (23) followed by endocyclic P–O bond cleavage with retention of configuration, since the major observed product (9) is formed by P–O bond cleavage with inversion of configuration. This suggests that apical attack of hydroxide opposite endocyclic oxygen to give (24) is competitive with formation of (22) and that the major product is derived from this TBP because of the unfavourable options for breakdown available to (22).

On treatment with sodium methoxide the phosphoro-derivative (1) and the phosphono-derivative (6) both undergo exclusive P–N bond cleavage with inversion of

* In discussions of the formation and rearrangements of TBPs in this paper the conclusions of a recent [15] review are assumed, *i.e.* nucleophilic substitutions at phosphorus are inherently stereospecific in the sense that TBPs break down either directly or following a single Berry Pseudorotation or Turnstile rotation process; multiple turnstile rotations which could lead to racemisation do not occur in reaction intermediates.

configuration [7-9] [although some analogues of (6) appear to give small amounts of P–O bond cleavage under similar conditions [16]]. These results are consistent with initial nucleophilic attack opposite nitrogen to form the TBPs (25) and (26), although subsequent events are different from those observed with hydroxide. In the phosphoro-series, essentially no pseudorotation occurs with methoxide, although with hydroxide this is the key feature of the reaction. It may be argued that pseudorotation of (20) will be more favourable than for (25) because the apical OH in (20) may be wholly or partially deprotonated by the base or the adjacent P–S and the apicophilicity of P–O is low. A similar explanation was used to account for the favoured exocyclic P–O bond cleavage in the basic hydrolysis of 2-alkoxy-1,3,2-dioxaphospholan-2-ones.[17] However, even if such an argument is acceptable it provides no explanation why in the reaction of methoxide with (1) and (6) initial attack opposite endocyclic oxygen does not compete with P–N bond cleavage as it apparently does in the reaction between hydroxide and (6).

The results in the Table illustrate that whether reactions occur following attack opposite nitrogen with P–N bond cleavage, or pseudorotation followed by P–O bond cleavage, or whether P–O cleavage resulting from direct attack opposite oxygen is a competitive process is balanced to such an extent that changes in reaction conditions can have a marked effect on reaction products. Similar results have been reported for reactions of Grignard reagents and alkyl-lithiums with 1,3,2-oxazaphospholidines where, although nitrogen is usually of higher apical potentiality than oxygen, whether the P–N bond is cleaved or whether the P–O is cleaved with retention or inversion of configuration varies with the Grignard reagent or alkyl-lithium and the particular 1,3,2-oxazaphospholidine.[15,18]

Some clarification of the reasons for the experimental results might be possible if it were known why nitrogen has a higher apical potentiality than oxygen during some nucleophilic substitution reactions in 1,3,2-oxazaphospholidines. Perhaps stereoelectronic considerations [19] may provide an answer, at least in part. Correctly orientated (*trans*-antiperiplanar, *app*) lone pairs of electrons on ligands that are, or are about to become, equatorial in a TBP can overlap with antibonding orbitals in an adjacent apical bond thereby weakening and lengthening it. Since this is what is required of the bond to one ligand as it makes the transition from tetrahedral to TBP geometry (apical bonds are longer and weaker than equatorial ones) nucleophilic attack might be expected to be directed opposite the ligand that is potentially *app* to the greatest number of lone pairs. In the TBP (27) the endocyclic oxygen has two lone pairs constrained partially *app* to the apical P–N bond and this, according to Gorenstein,[19b] results in a greater net overlap than from one completely *app* lone pair. The equatorial nitrogen in (24) has only one lone pair to encourage lengthening of an apical endocyclic P–O bond. The effects of the lone pairs on the exocyclic oxygens are neglected since they are free to rotate and are unlikely to adopt conformations more favourable for overlap in (24) than in (27). Similarly in acyclic phosphoramidate derivatives there is no reason to suppose any greater overlap of the lone pairs on the equatorial oxygens when nitrogen is apical than when oxygen is apical, so that oxygen retains a higher apical potentiality than nitrogen.

Although there have been some very interesting suggestions about the role of stereoelectronic effects in determining the course of reactions in organic chemistry in general,[20] the relevance of such considerations in phosphorus chemistry remains to be demonstrated. Attempts to demonstrate their importance in six-membered rings containing phosphorus were unsuccessful [21] because the fact that the rings may not be in chair conformations during bond-forming and -breaking processes [15,22] provides too many variables.

Another possible explanation for the higher apical potentiality of nitrogen over oxygen in 1,3,2-oxazaphospholidines is a steric one. Nucleophilic attack opposite oxygen to form a TBP such as (24) may be hindered by the fixed bulk of the methyl substituent on nitrogen; hence attack opposite nitrogen preponderates. This possibility is currently under investigation.

The above discussion has described results which show that in certain reactions of 1,3,2-oxazaphospholidines nitrogen has a higher apical potentiality than oxygen, unlike the situation in acyclic phosphoramidates where oxygen has a higher apical potentiality than nitrogen. No attempt has been made to discuss six-membered tetrahydro-1,3,2-oxazaphosphorines [23] where oxygen and nitrogen have similar apical potentialities but where presently available results do not show any pseudoration processes. There are many other problems relating to apical potentiality where P–N bonds are not involved. For example in acyclic phosphorothioates oxygen has a higher apical potentiality than sulphur (SR groups are displaced with retention of configuration [24]) whereas in the corresponding phosphonothioates sulphur has the higher apical potentiality. It has been established by kinetic measurements [25] that the products result because of a true preference for attack opposite sulphur and not because TBPs generated by attack opposite oxygen do not pseudorotate. Similar factors appear to operate in the ring closures caused by displacement of SMe groups described below.

Ring Closure.—The spontaneous ring closure of (9) and the alkoxide-catalysed ring closure of (3) to generate only cyclic derivatives of (—)-ephedrine (Schemes 7 and 6) confirms that the ring-opening reactions to form (8) and (2) (Schemes 3 and 4) must have occurred by attack of hydroxide at phosphorus and not by attack at benzylic carbon. In the latter situation ring closure would give pseudoephedrine and not ephedrine derivatives.

The alkoxide-catalysed ring closure of (3) occurred with retention of configuration, by a mechanism presumably involving initial apical attack opposite OEt, followed by pseudorotation and apical loss of SMe. This result parallels the displacement of SR from phosphoro-

thioates by alkoxides.[24] Previous attempts to monitor a similar but intermolecular displacement in acyclic phosphoramidates were unsuccessful because the reaction rate was too slow for convenient study.[10] The reactions catalysed by silver nitrate are of some interest. In the presence of sodium carbonate (used as an acid acceptor to prevent further reaction of the first-formed product), silver presumably co-ordinates with sulphur, making SMe a better leaving group and encouraging the observed displacement with preponderant inversion of configuration. The overall retention of configuration observed when triethylamine is the acid acceptor suggests that the amine is involved in nucleophilic catalysis, *i.e.* the reaction involves displacement of SMe by amine with inversion followed by displacment of the amine by OH again with inversion (Scheme 6). Consistent with such a proposal is the short reaction half-life for $AgNO_3$–triethylamine (3 min) compared with the long half-life for $AgNO_3$–Na_2CO_3 (5 h). In the absence of $AgNO_3$, (12) is stable in the presence of triethylamine.

Ring closure of (9) occurs by apical attack opposite SMe, with displacement occurring with inversion of configuration as it does in acyclic phosphonothioates.

Migration Reactions.—The migration of the phosphorothioate group in (3) to form (12) with retention of configuration is consistent with a mechanism which involves intramolecular attack of the hydroxy-group opposite OEt, followed by pseudorotation and loss of the protonated nitrogen group from an apical position. This may be contrasted with the previously described reaction [18] of (28) with anhydrous hydrogen chloride in benzene when only MePhP(S)Cl was obtained. Presumably because of the low apical potentiality of both the methyl and phenyl groups in (28) relative to OEt in (3), only the intermolecular displacment of $\overset{+}{N}RMe$ by Cl^- is possible rather than any intramolecular reaction. The fact that Cl^- can compete very effectively with RO^- as a nucleophile for displacing $\overset{+}{N}R$ from phosphorus has been demonstrated previously.[10]

EXPERIMENTAL

Details of the preparation of each compound are not given but examples of each type are reported. ^1H N.m.r. spectra were measured at 100 or 60 MHz in deuteriochloroform as solvent and with tetramethylsilane as internal standard. The enantiomeric purity of chiral phosphorus compounds was determined by the previously described [8,9] n.m.r. method using the chiral shift reagent $Eu(hfc)_3$. Alkaline hydrolysis reactions were first monitored by ^{31}P n.m.r. spectroscopy in the appropriate solvent, then the major product(s) was isolated from a preparative reaction as examples describe. Optical rotations were measured in chloroform (path length 10 cm). All organic solutions of reaction products were dried over $MgSO_4$. Light petroleum refers to the fraction of b.p. 60—80 °C.

Alkaline Hydrolysis of (2S,4S,5R)-2-*Ethoxy*-3,4-*dimethyl*-5-*phenyl*-1,3,2-*oxazaphospholidine*-2-*thione* (1) (*Scheme* 3).—A solution of (1) [12] (2.5 g) in 1 : 1 (v/v) dioxan–1M-aqueous sodium hydroxide (80 ml) was stored overnight then poured into water. The solution was washed three times with ether then its basicity was reduced by addition of acetic acid. An excess of methyl iodide and sufficient methanol to ensure solution was added. After 0.5 h the mixture was poured into water and extracted with chloroform. The extract was concentrated to give (3) (2.5 g, 90%) as a white solid, m.p. 74—76 °C (from chloroform–light petroleum), $[\alpha]_D$ −7.5° (*c*, 1.3), δ 1.16 (3 H, t), 1.26 (3 H, d, *J* 6.8 Hz), 2.14 (3 H, d, *J* 14.4 Hz), 2.52 (3 H, d, *J* 11.3 Hz), 4.08 (1 H, m), and 4.68 (1 H, d, *J* 5.8 (Hz), δ_P −37.2.

The alcohol (3) (2.4 g) was dissolved in pyridine–acetic anhydride (2 : 1 v/v; 45 ml) and stored overnight. Conventional processing gave the acetate (4) (2.5 g, 92%) as a light yellow oil, $[\alpha]_D$ −26.3° (*c*, 2.0), δ 1.08 (3 H, t), 1.27 (3 H, d), 2.07 (3 H, s), 2.14 (3 H, d), 2.56 (3 H, d), and 5.82 (1 H, d, *J* 4.0 Hz), δ_P −35.6.

Acidic Alcoholysis of (4).—A solution of anhydrous hydrogen chloride in methanol (4 ml) (2.9M) was added to a solution of (4) (1.1 g) in methanol (20 ml). The mixture was stored overnight, poured into water, and extracted with ether. The extract was concentrated and the residue distilled [75 °C (bath) at 0.2 mmHg] to give (5) (0.25 g, 46%) as a clear oil.[7] The n.m.r. spectrum in the presence of $Eu(hfc)_3$ showed (5) to be ⩾98% the (*R*)-enantiomer.

Acid Catalysed Rearrangement of (3).—A solution of (3) (0.45 g) in anhydrous hydrogen chloride–benzene (50 ml) (0.1M) was stored for 0.5 h then purged with nitrogen and concentrated to give (12) (0.4 g, 80%) as a clear oil, $[\alpha]_D$ −2° (*c*, 0.5), δ 1.24 (3 H, t), 1.37 (3 H, d), 2.27 (3 H, d), and 6.24 (1 H, dd, *J* 6.0 and <1 Hz), δ_P −30.3.

(2S,4S,5R)-2-*Methylthio*-3,4-*dimethyl*-5-*phenyl*-1,3,2-*oxazaphospholidine*-2-*one* (14).—A mixture of dicyclohexyl-18-crown-6 (0.3 g), finely ground sodium hydroxide (1 g), and (2*S*,4*S*,5*R*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-thione [7] (3 g) in benzene (100 ml) was boiled under reflux for 2 h, cooled, and filtered. An excess of methyl iodide was added, and the mixture was stirred for 0.5 h, poured into water, and extracted with benzene. The extract was concentrated and the residue crystallised to give (14) (1.9 g, 65%) as a white solid.[11]

Acidic Alcoholysis of (14).—A solution of (14) (0.5 g) in anhydrous hydrogen chloride–ethanol (50 ml) (0.1M) was stored overnight, purged with nitrogen and concentrated to give (13) (0.5 g, 76%) as a white solid, m.p. 119 °C (from chloroform–light petroleum), $[\alpha]_D$ −0.6° (*c*, 1.1), δ 1.43 (3 H, t), 1.45 (3 H, d), 2.17 (3 H, d), and 6.25 (1 H, dd, *J* 6.0 and <1 Hz), δ_P −31.8.

(2R,4S,5R)-2-*Ethoxy*-3,4-*dimethyl*-5-*phenyl*-1,3,2-*oxazaphospholidine*-2-*one* (15). *Ring Closure of* (3).—A catalytic amount of sodium methoxide was added to a solution of (3) (0.3 g) in methanol (10 ml). After 15 min the solution was poured into water and extracted with chloroform. The extract was concentrated to give (15) (0.23 g, 92%) as a syrup, δ 0.90 (3 H, d, *J* 6.3 Hz), 1.37 (3 H, t), 2.70 (3 H, d, *J* 10.3 Hz), 3.68 (1 H, dq, *J* 6.3 and 6.3 Hz), and 5.54 (1 H, dd, *J* 6.3 and 3.6 Hz), δ_P −20.0.

An excess of a saturated solution of silver nitrate in acetonitrile was added to a solution of (3) (0.25 g) and triethylamine (0.5 ml) in acetonitrile (20 ml). After 15 min the mixture was poured into ether and filtered. The solution was washed with water then concentrated to give (15) (0.2 g, 95%).

Similarly an excess of a saturated solution of silver nitrate in acetonitrile was added to a suspension of anhydrous sodium carbonate in a solution of (3) (0.1 g) in acetonitrile (15 ml). After 24 h, work-up gave an 85 : 15 ratio

of (16) to (15) (0.07 g, 83%). Chromatography gave (16) δ 0.78 (3 H, d, *J* 6.3 Hz), 1.40 (3 H, t), 2.73 (3 H, d, *J* 10.5 Hz), 3.70 (1 H, m), and 5.65 (1 H, dd, *J* 6.3 and 2.1 Hz).

Alkaline Hydrolysis of (2R,4S,5R)-2,3,4-*Trimethyl*-5-*phenyl*-1,3,2-*oxazaphospholidine*-2-*thione* (6) (*Scheme* 4).—A solution of (6) [7] (2.5 g) in 1 : 1 (v/v) dioxan–1M-aqueous sodium hydroxide (100 ml) was stored for 4 days then poured into water. The solution was washed three times with ether then its basicity was reduced by the addition of acetic acid. An excess of methyl iodide and sufficient methanol to ensure solution were added. After 15 min, rapid work-up gave an unstable oil (2.6 g, 92%) which ^{1}H n.m.r. showed a mixture of isomers (*ca.* 3 : 2) of (9); δ 1.29 (3 H, d, *J* 6.9 Hz), 1.47 (3 H, d, *J* 14.1 Hz), 2.10 (3 H, d, *J* 12 Hz), 2.65 (3 H, d, *J* 11.6 Hz), and 4.81 (1 H, d, *J* 5.5 Hz), and δ 1.22 (3 H, d, *J* 14.5 Hz), 1.28 (3 H, d, *J* 6.2 Hz), 2.14 (3 H, d, *J* 12 Hz), 2.42 (3 H, d, *J* 12.2 Hz), and 4.67 (1 H, d, *J* 6 Hz). After storage at room temperature for several days the above mixture of isomers was converted into a 3 : 2 mixture of (18) and (19) [7] (Scheme 7).

Immediate treatment of a crude sample of (9) with pyridine–acetic anhydride (2 : 1 v/v), followed by conventional processing gave the acetates (10) (90%) as a 3 : 2 ratio of isomers, δ 1.27 (3 H, d, *J* 6.8 Hz), 1.34 (3 H, d, *J* 14 Hz), 1.87 (3 H, d, *J* 6.8 Hz), 2.63 (3 H, d, *J* 12 Hz), 2.05 (3 H, s), 4.06 (1 H, m), and 5.83 (1 H, d, *J* 7.6 Hz), and δ 0.90 (3 H, d), 1.23 (3 H, d), 1.85 (3 H, d), 2.42 (3 H, d), 2.08 (3 H, s), and 5.71 (1 H, d) (*J* values as above).

Acid Catalysed Hydrolysis of (6).—Hydrochloric acid (10M) was added dropwise to a solution of (6) (0.8 g) in acetone (20 ml) until the solution just became cloudy. After 10 min the solution was reduced to dryness to give the white solid (7), as its hydrochloride (0.9 g), $[\alpha]_D$ −67° (*c*, 1.8 in MeOH), δ 1.24 (3 H, d, *J* 6.2 Hz), 1.90 (3 H, d, *J* 15.6 Hz), 2.89br (3 H, s), and 6.20br (1 H, d, *J* 12.2 Hz), δ_P −91.7.

Acidic Alcoholysis of (10).—The same procedure as for the phosphoro-analogue (4) gave *OS*-dimethyl methylphosphorothioate (11) (60%). The n.m.r. spectrum in the presence of Eu(hfc)$_3$ showed (11) to be a 3 : 2 ratio of the *S*- and *R*-enantiomers.[12]

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