1,3,2-Oxazaphospholidine-2-thiones from (+)-Norephedrine: Stereospecific Ring Opening, Possibly by an Elimination–Addition Mechanism

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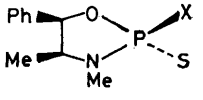
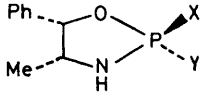
1,3,2-Oxazaphospholidine-2-thiones derived from (+)-norephedrine react with alkoxide to give a product of kinetic control, formed by endocyclic P–O cleavage with inversion of configuration, and one of thermodynamic control, formed by endocyclic P–N cleavage also with inversion of configuration. It is suggested that the product of kinetic control is formed by an elimination–addition process involving a metaphosphorimidate intermediate, and that of thermodynamic control by a mechanism involving nucleophilic attack opposite endocyclic nitrogen.

1,3,2-Oxazaphospholidines, derived in this laboratory from (−)-ephedrine [*e.g.* (1)], undergo endocyclic P–N cleavage with inversion of configuration on treatment with alkoxide.[1] However, when hydroxide is the nucleophile the situation is more complex and although there is usually some P–N cleavage the main reaction is



(1) X = alkyl or alkoxy

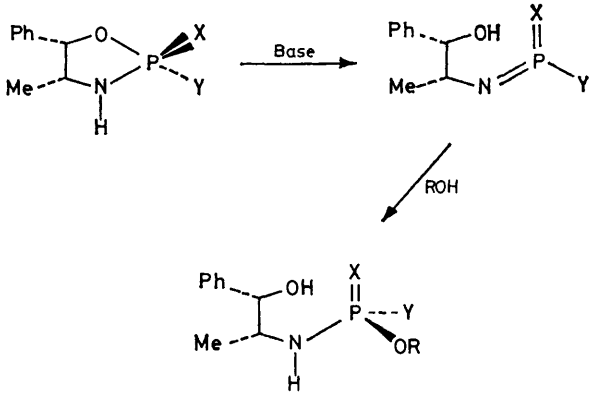
cleavage of the endocyclic P–O bond.[2] In the 2-alkoxy-1,3,2-oxazaphospholidine-2-thiones (1; X = alkoxy), the endocyclic P–O bond was cleaved with retention of configuration, whereas in the 2-alkyl-1,3,2-oxazaphospholidine-2-thiones (1; X = alkyl), P–O cleavage occurred with preponderant inversion of configuration. Such results have been rationalised in terms of mechanisms which require nucleophilic attack at phosphorus opposite nitrogen in preference to oxygen, in association with considerations of the relative ease of reorganisation of the various possible pentaco-ordinate intermediates.[2] Quite different possibilities exist for ring opening of 1,3,2-oxazaphospholidines derived from (+)-norephedrine, where nitrogen is unsubstituted, *e.g.* (2)—(4). For example, ring opening by an elimination–



	X	Y
(2a)	S	Me
(2b)	Me	S
(3a)	O	Me
(3b)	Me	O
(4a)	S	EtO
(4b)	EtO	S

addition mechanism (Scheme 1) may compete with or override mechanisms involving nucleophilic attack at phosphorus. This subject has been studied kinetically and stereochemically in acyclic phosphoramidates, and although the results are not unequivocal there is much to favour an elimination–addition mechanism and the generation of metaphosphorimidate intermediates. In this paper the preparation and ring-opening reactions of some 1,3,2-oxazaphospholidines (2)—(4) are described and mechanisms for ring opening are discussed.

Synthesis.—The 2-methyl-1,3,2-oxazaphospholidine-2-thiones (2a and b) were prepared from $MePSCl_2$ and (+)-norephedrine in the presence of triethylamine. The isomers were separated by rapid, medium-pressure

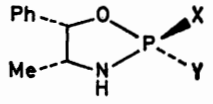
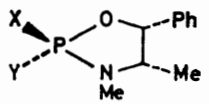


SCHEME 1

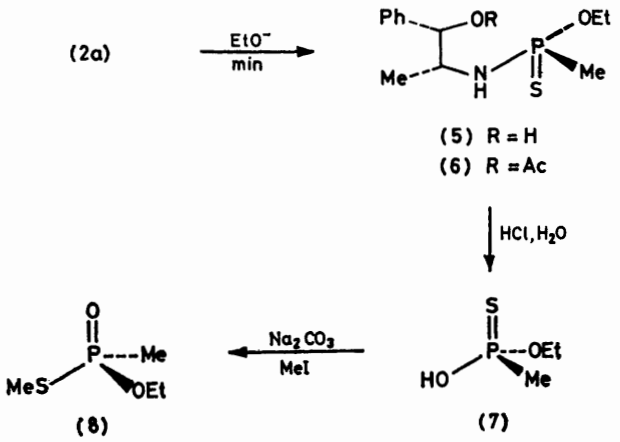
chromatography. Configurations were assigned by consideration of the relative shifts of the H-4, H-5, and P-Me signals in the ^1H n.m.r. spectra of the P=O derivatives (3a and b) formed, presumably with retention of configuration, by treatment of (2a and b) with metachloroperbenzoic acid. The assignments are supported by comparison of the $[\alpha]_D$ values and signs with those of related, well characterised, adducts derived from (−)-ephedrine which are the mirror images (if the nitrogen substituents are neglected). Similarly the phosphoro-adducts (4a and b) were prepared from (+)-norephedrine and $EtOP(S)Cl_2$. Attempts to convert (4a and b) into their P=O analogues were unsuccessful, and so the configurational assignment is made on the basis of comparison of rotations only. The rotations of the corresponding (−)-ephedrine and (+)-norephedrine derivatives are given in the Table.

Ring-opening Reactions.—On treatment with sodium ethoxide, (2a) was rapidly converted by endocyclic P–O cleavage into the thiophosphonamidate (5). Intramolecular participation by the hydroxy-group in (5) in

Comparison of rotations of derivatives from (−)-ephedrine and (+)-norephedrine

(+)-Norephedrine derivatives		(−)-Ephedrine derivatives	
			
$[\alpha]_D°$	X	Y	$[\alpha]_D°$
+176	S	Me	−128 (ref. 1)
+67	Me	S	−25 (ref. 1)
+124	S	EtO	−122 (ref. 1)
+56	EtO	S	−5 (ref. 1)
+157	S	Me_2N	−147 (ref. 3)
	Me_2N	S	+13.5 (ref. 3)

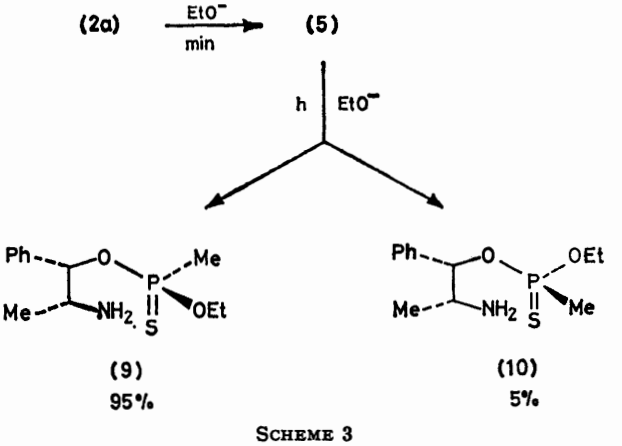
subsequent reactions was prevented by acetylation to give (6). Acid-catalysed (HCl) hydrolysis of (6) yielded the thioacid (7) which, after treatment with sodium carbonate and methyl iodide, was isolated as enantiomerically pure (−)-(*S*)-*O*-ethyl *S*-methyl methylphosphonothioate (8).[1] The reaction sequence (Scheme 2) occurs with overall retention of configuration at phosphorus. Since neither *S*-alkylation nor *O*-acetylation involves reaction at phosphorus, and acid-catalysed cleavage of P–N bonds in compounds such as (6) probably occurs with inversion of configuration,[2,3] then initial



SCHEME 2

P–O cleavage in (2a) must also occur with inversion of configuration at phosphorus.

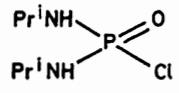
Storage of the basic solution of (2a) for several hours before processing afforded an essentially quantitative yield of the P–N-cleaved product (9), containing approximately 5% of the isomer (10) enantiomeric at phosphorus. The hydrochloride of (9) was identical with that obtained on treatment of (2a) with a solution of anhydrous hydrogen chloride in ethanol. Similar acid-catalysed alcoholyses in (−)-ephedrine-derived adducts occur with inversion of configuration;[1,3] therefore it is reasonable to propose that (9) is formally derived from (2a) also with inversion (Scheme 3). The epimer (2b) undergoes a similar reaction sequence.



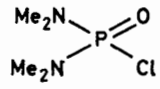
SCHEME 3

DISCUSSION

The above results, showing initial stereospecific P–O cleavage with inversion of configuration on treatment with ethoxide, are distinct from the P–N cleavage found previously in the ephedrine series. In addition, the ring opening occurred more rapidly in the norephedrine than in the ephedrine series. This is a qualitative rather than a quantitative observation, but under essentially the same experimental conditions ring opening of (2a) by P–O cleavage was complete in a few minutes, whereas several hours were required for ring opening by P–N cleavage in the ephedrine series.

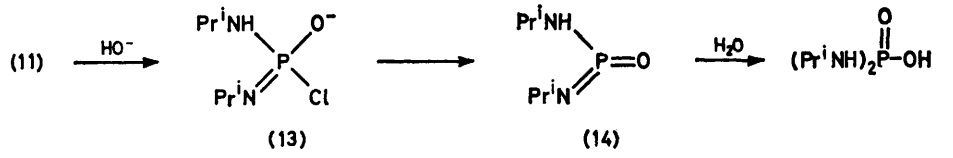


(11)



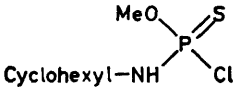
(12)

It was the large ($>4 \times 10^6$) difference in rates of hydrolysis between (11) and (12)[4] that led to the original suggestion[5,6] that the hydrolyses occurred by different mechanisms, *viz.* nucleophilic attack at phosphorus for (12) but through the intermediate anion (13) and the metaphosphorimidate (14) for (11) (Scheme 4). The idea of metaphosphorimidate intermediates has been supported by a three-phase test[7] in which transfer of the phosphorus moiety from one polymer support through a solvent to another seems fully consistent with an unstable reaction intermediate. Also, stereochemical studies which showed complete racemisation[8] during the base hydrolysis of (15) support the concept of planar monomeric metaphosphorimidate intermediates. However, more recent work has provided examples of phosphoramidic compounds which undergo basic reactions at rates consistent with an elimination–addition mechanism, but which proceed with highly stereoselective inversion of configuration.[3,9] Such results necessitate that metaphosphorimidate intermediates, if formed, either are not planar or their reactions are controlled by an intimate directional relationship involving the intermediate, the solvent, and/or the leaving group. Other results also question the general application of an elimination–addition mechanism.[9-11]



SCHEME 4

This paper provides additional evidence consistent with the involvement of an elimination–addition mechanism in basic reactions of 1,3,2-oxazaphospholidines where nitrogen is unsubstituted. In particular, if it is assumed that nitrogen is planar in the substrate, the fixed *trans*-relation between the N–H and the leaving group may be expected to favour elimination with endocyclic P–O cleavage. It should be noted that the mechanism illustrated for the cyclic products in Scheme 1 is rather different from that originally proposed and illustrated in



(15)

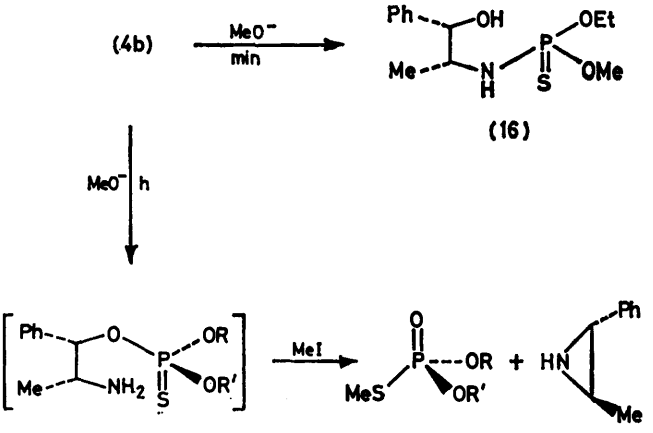
Scheme 4 for the hydrolysis of (11), where the elimination product formed first was assumed to be (13). Subsequent results described later in this paper seem to be most conveniently explained if a *trans*-relation between the N–H and the leaving group is necessary for an elimination mechanism to compete with nucleophilic attack at phosphorus.

There remains the question of the mechanism of rearrangement of (5) to give preponderantly (≥95%) (9). The stereochemistry of (9) is that of a product derived formally from (2a) by P–N bond cleavage with inversion of configuration and in practice there is much to commend such a mechanism involving re-formation of (2a). It is then necessary only for ring opening to occur following direct attack of ethoxide opposite nitrogen in the same way as it occurs in (1; R = Me) in a reaction that competes with but proceeds much more slowly than the P–O cleavage reaction.

Two mechanisms for the re-formation of (2a) from (5) are possible. First there is direct intramolecular nucleophilic displacement of the alkoxy-group by the benzylic hydroxy-group. Although, by analogy with intermolecular displacement reactions in *N,N*-disubstituted acyclic phosphoramidates, which proceed exceedingly slowly, this mechanism might appear unlikely, it is supported by the extremely ready displacement of an *S*-alkyl group in a compound formed by initial P–O cleavage in a cyclic ester derived from (—)-ephedrine.[2] Secondly, recyclisation may occur *via* the same metaphosphorimidate intermediate as postulated during ring opening but now formed by elimination of the alkoxy-group. It has not been possible to distinguish between these alternatives, nor indeed to demonstrate the presence of (2a) during conversion of (5) into (9). [^{31}P N.m.r. studies of the ring opening of (2a) showed its complete disappearance.] However, the principle of microscopic reversibility requires that the reaction pathway for the formation of (2a) from (5) should be the reverse of that for the formation of (5) from (2a).

The formation from (5) of (10) (in < 5% yield), *i.e.* the product derived formally from (2a) by P–N cleavage with retention of configuration, could and probably does result from phosphoryl group migration from nitrogen to oxygen *via* a pentaco-ordinate intermediate which pseudorotates and affords (10) from (5) directly without re-formation of (2a). Alternatively, (10) could be formed from (2b) formed first by ring closure of (5) with retention of configuration. This latter possibility is precluded since no epimerisation of (5) to (5b) was detected during the conversion of (5) into (9) [and (10)].

The results of the ring opening of (2a) and (2b), in comparison with similar results from the ephedrine series, were the clearest and most illustrative for discussion of reaction mechanisms. However, other results that were obtained followed the same pattern. For example, the phosphoro-adduct (4b) reacted rapidly with sodium methoxide to give the single P–O-cleaved product (16). On storage of (16) in basic solution at room temperature for several hours, followed by addition

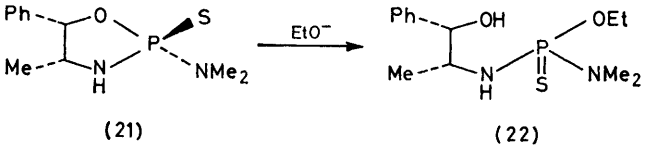


(17) R = Me, R′ = Et (19)
(18) R = R′ = Me (20)

SCHEME 5

of methyl iodide, a mixture of the ethyl methyl phosphorothioate (19) and the dimethyl phosphorothioate (20) in 2 : 3 ratio was formed. The presumed sequence of events is shown in Scheme 5. The fact that the P–N-cleaved products (17) and (18) were not isolated because of their ready rearrangement to phosphorus acids and to aziridine reflects the better leaving group

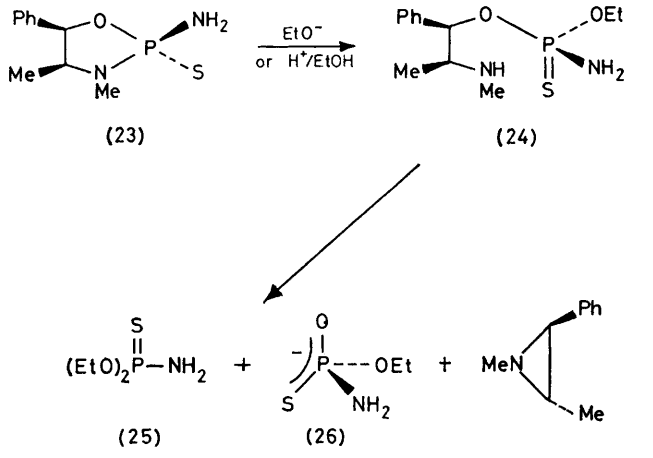
ability of phosphoro- as compared with phosphono-groups. The exchange of alkoxy-groups is fully consistent with a mechanism which requires re-formation of (4b), since during this process there are similar possibilities for displacement of either methoxy- or ethoxy-groups in (16). [Any mechanisms for conversion of (16) into (17) that involved pseudorotation of a pentaco-ordinate intermediate would not lead to alkoxy-group exchange [12].]



SCHEME 6

Since the difference in ring opening reactions of cyclic phosphorus esters from ephedrine and norephedrine may be attributed to the fact that the endocyclic N–H in the norephedrine series allows displacements to occur *via* an elimination–addition mechanism, it was pertinent to determine whether or not exocyclic 2-amino-groups in 1,3,2-oxazaphospholidines also facilitate such a mechanism. Thus the 2-amido-derivative (23) and the 2-dimethylamino-derivative (21) were prepared: the latter from (+)-norephedrine and $Me_2NP(S)Cl_2$. Its configuration was assigned only by comparison with that of the analogue in the ephedrine series.

The 2-dimethylamino-derivative (21) reacted rapidly with ethoxide to give the P–O-cleaved product (22) (Scheme 6). The reaction was stereospecific but the



SCHEME 7

stereochemistry of (22) was not determined. The 2-amino-derivative (23) [prepared from (−)-ephedrine] gave the same P–N-bond cleaved product (24) with ethoxide as produced on treatment with ethanolic hydrogen chloride (Scheme 7).[3] Direct monitoring by ^{31}P n.m.r. showed (24) was the primary product, there being no trace of P–O-cleaved products. Storage of the basic solution resulted eventually in a mixture of (25) and (26) (Scheme 7). These results suggest that endocyclic but not exocyclic N–H groups facilitate an elimination–addition mechanism for endocyclic P–O cleavage, and raise the question of the importance of directional effects in this mechanism, for although exocyclic N–H bonds can be orientated *trans* to endocyclic P–O, they are not constrained in this position.

In studies of the aqueous basic hydrolysis of 1,3,2-oxazaphospholidines (1) the dependence of products on reaction conditions was a complicating factor in interpreting possible reaction mechanisms.[2] It is not surprising therefore that aqueous basic hydrolysis of the 1,3,2-oxazaphospholidines (2)—(4) showed no distinct differences in products from the corresponding reactions in the ephedrine series, although there may have been differences in mechanisms. Thus treatment of a dioxan solution of (2a) with aqueous sodium hydroxide resulted in P–O cleavage, presumably with inversion of configuration, although this was not determined.

EXPERIMENTAL

^1H N.m.r. spectra were recorded at 100 MHz with deuteriochloroform as solvent and tetramethylsilane as internal standard, and optical rotations were measured for solutions in chloroform (path length 1 dm) unless otherwise stated. Column chromatography was performed over Merck Kieselgel 60, particle size 0.040—0.063 mm, under a slight positive pressure.[13] All organic solutions of reaction products were dried over magnesium sulphate. Light petroleum refers to the fraction of b.p. 60—80 °C.

(2S,4R,5S)- *and* (2R,4R,5S)-2,4-*Dimethyl*-5-*phenyl*-1,3,2-*oxazaphospholidine*-2-*thiones* (2a and b).—A solution of methyl thiophosphorodichloridate (4 g) in benzene (30 ml) was slowly added to a suspension of (+)-norephedrine hydrochloride [(1*S*,2*R*)-2-amino-1-phenylpropan-1-ol hydrochloride] (5 g) in triethylamine (12 ml) and benzene (100 ml). The mixture was stored overnight, poured into water and extracted with benzene. The extract was concentrated; chromatography of the residue (eluting with 4 : 1 light petroleum–ethyl acetate) gave the *oxazaphospholidines* (2a) (3.4 g, 56%), $[\alpha]_D$ +176° (*c* 1.1); δ 0.75 (3 H, d, *J* 7 Hz), 2.15 (3 H, d, *J* 15 Hz), 4.02 (1 H, m), and 5.67 (1 H, br, d, *J* 5.3 Hz); and (2b) (2.1 g, 35%), m.p. 66—67 °C (from light petroleum, $[\alpha]_D$ +67° (*c* 1.3); δ 0.85 (3 H, d, *J* 6.5 Hz), 1.98 (3 H, d, *J* 14.6 Hz), 3.89 (1 H, m) and 5.43 (1 H, dd, *J* 9.2 and 6.4 Hz) (Found: C, 53.0; H, 6.4; N, 6.1. $C_{10}H_{14}NOPS$ requires C, 52.9; H, 6.2; N, 6.2%).

(2S,4R,5S)- *and* (2R,4R,5S)-2-*Ethoxy*-4-*methyl*-5-*phenyl*-1,3,2-*oxazaphospholidine*-2-*thiones* (4b and a).—A similar procedure to the above, using $EtOP(S)Cl_2$ (4.5 g), gave the *oxazaphospholidines* (4b) (2.5 g, 36%), m.p. 79 °C (from light petroleum), $[\alpha]_D$ +57° (*c* 1.0); δ 0.85 (3 H, d, *J* 6.4 Hz), 1.34 (3 H, t, *J* 7.2 Hz), 4.19 (2 H, dq, *J* 7.2 and 10.7 Hz), and 5.64 (1 H, dd, *J* 5.8 and 4.7 Hz) (Found: C, 51.0; H, 6.4; N, 5.2. $C_{11}H_{16}NO_2PS$ requires C, 51.3; H, 6.2; N, 5.4%); and (4a) (1.5 g, 22%), $[\alpha]_D$ +124° (*c* 1.6); δ 0.82 (3 H, d, *J* 6.4 Hz), 1.37 (3 H, t, *J* 7.0 Hz), 4.25 (2 H, dq), and 5.68 (1 H, br, dd, *J* 5.9 and 2.2 Hz).

(2R,4R,5S)-2-*Dimethylamino*-4-*methyl*-5-*phenyl*-1,3,2-*oxazaphospholidine*-2-*thione* (21).—A suspension of (+)-norephedrine hydrochloride (3.58 g) in triethylamine (8.0 ml), $Me_2NP(S)Cl_2$ (3.4 g), and benzene (100 ml) was boiled under reflux for 3 days. Conventional processing and

chromatography (17 : 3 light petroleum–ethyl acetate) gave the *product* (21) (0.8 g, 16%), m.p. 102—103 °C (from light petroleum), $[\alpha]_D$ +157° (*c* 1.0); δ 0.79 (3 H, d, *J* 6.8 Hz), 2.99 (6 H, d, *J* 12.0 Hz), 4.06 (1 H, m), and 5.78 (1 H, d, *J* 6.6 Hz) (Found: C, 51.7; H, 6.7; N, 10.9. $C_{11}H_{17}N_2OPS$ requires C, 51.6; H, 6.7; N, 10.9%).

(2R,4R,5S)- *and* (2S,4R,5S)-2,4-*Dimethyl*-5-*phenyl*-1,3,2-*oxazaphospholidin*-2-*ones* (3a and b).—A solution of methyl phosphonodichloridate (2.1 g) in benzene (20 ml) was slowly added to a suspension of (+)-norephedrine hydrochloride (3 g) in triethylamine (10 ml) and benzene (30 ml). After 1 h the solution was filtered and concentrated. ^{1}H N.m.r. showed the residue to consist of a 1 : 1 mixture of (3a), δ 0.70 (3 H, d), 1.75 (3 H, d, *J* 17.1 Hz), and 5.66 (1 H, d, *J* 5.7 Hz); and (3b), δ 0.83 (3 H, d), 1.66 (3 H, d), and 5.32 (1 H, dd).

^{1}H N.m.r. demonstrated that careful addition of solid *m*-chloroperbenzoic acid to a solution of (2a) in deuteriochloroform generated (3a). Likewise (2b) generated (3b).

Reaction of 1,3,2-*Oxazaphospholidine*-2-*thiones with Sodium Ethoxide*.—A few drops of a dilute solution of sodium ethoxide in ethanol was added to a solution of (2a) (0.5 g) in ethanol (20 ml). After 5 min the mixture was poured into water and extracted with chloroform, and the combined extracts were concentrated to give *O*-ethyl *N*-(β-hydroxy-α-methylphenethyl)-*P*-methylphosphonamidothioate (5) (0.55 g, 92%) as a clear oil, $[\alpha]_D$ −26.5° (*c* 0.9), δ 0.98 (3 H, d, *J* 6.7 Hz), 1.26 (3 H, t), 1.78 (3 H, d, *J* 15 Hz), 3.73 (1 H, m), and 4.75 (1 H, d, *J* 3.4 Hz). Likewise (2b) gave the *stereoisomer* of (5), $[\alpha]_D$ +62° (*c* 1.6), δ 1.03 (3 H, d), 1.29 (3 H, t), 1.71 (3 H, d), 3.61 (1 H, m) and 4.71 (1 H, d, *J* 3.8 Hz); (4b) with sodium methoxide gave *O*-ethyl *O*-methyl *N*-(β-hydroxy-α-methylphenethyl)-phosphoramidothioate (16), δ 0.94 (3 H, d, *J* 6.7 Hz), 1.29 (3 H, t, *J* 7.2 Hz), 3.66 (3 H, d, *J* 13.9 Hz), 4.04 (2 H, dq, *J* 6.7 and 6.7 Hz), and 4.78 (1 H, d, *J* 3.1 Hz); and (21) gave the phosphorodiamidothioate (22), δ 0.96 (3 H, d, *J* 6.8 Hz), 1.30 (3 H, t, *J* 7.0 Hz), 2.65 (6 H, d, *J* 12.4 Hz), 3.62 (1 H, m), 4.06 (2 H, dq, *J* 9.4 and 7.0 Hz), and 4.83 (1 H, d, *J* 3.2 Hz).

A similar procedure, but with the basic solution stored for 2 h prior to work-up, gave a 19 : 1 mixture (0.53 g, 88%) of phosphonothioate diesters (9) and (10). The hydrochloride salt of (9) showed $[\alpha]_D$ +76° (*c* 2.6 in ethanol); δ(CD_3OD) 0.88 (3 H, t, *J* 7 Hz), 1.14 (3 H, d, *J* 6.8 Hz), 1.95 (3 H, d, *J* 16 Hz), and 5.86 (1 H, dd, *J* 12.6 and 3.7 Hz); that of (10) showed $[\alpha]_D$ +47° (*c* 0.6 in ethanol), δ(CD_3OD) 1.29 (3 H, t), 1.27 (3 H, d), 1.66 (3 H, d, *J* 15.4 Hz), 3.70 (1 H, m), and 5.69 (1 H, dd, *J* 12.6 and 4.5 Hz). Likewise (23) gave (24),[3] δ 1.02 (3 H, d, *J* 6.6 Hz), 1.15 (3 H, dt), 1.50 (3 H, s), and 5.60 (1 H, dd, *J* 12.9 Hz), and after treatment with methyl iodide (4b) gave a 3 : 2 mixture of (20) and (19).[1]

Acetylation of the Phosphonamidothioate (5).—A solution of (5) (0.8 g) in 2 : 1 pyridine–acetic anhydride was stored for 3 h, then poured carefully into cold dilute aqueous sodium carbonate. The mixture was extracted with ether, and the extract was washed with water and concentrated to give the acetyl derivative (6) (0.8 g, 87%), $[\alpha]_D$ −23° (*c* 1.1); δ 1.09 (3 H, d, *J* 6.8 Hz), 1.25 (3 H, t), 1.71 (3 H, d, *J* 15 Hz), 2.13 (3 H, s), and 5.73 (1 H, d, *J* 4.2 Hz). Likewise the *P*-enantiomer of (5) gave the *N*-acetyl derivative, $[\alpha]_D$ +65° (*c* 2.0); δ 1.12 (3 H, d), 1.27 (3 H, t), 1.68 (3 H, d, *J* 15.2 Hz), 2.13 (3 H, s), and 5.67 (1 H, d, *J* 4.4 Hz).

Acid Hydrolysis of the N-*Acetyl Derivative* (6).—A solution of (6) (0.5 g) in 4 : 1 acetone–4N-hydrochloric acid was stored overnight then poured into water. The mixture was extracted with ether and the combined extracts were washed with dilute aqueous sodium carbonate. The aqueous layer was treated with an excess of methyl iodide and sufficient methanol to ensure a single phase. After 30 min the mixture was poured into water and extracted with chloroform. Concentration and distillation of the residue gave *O*-ethyl *S*-methyl methylphosphonothioate (8), $[\alpha]_D$ −85.3° (*c* 1.3).[1]

Acid Hydrolysis of 1,3,2-*Oxazaphospholidine*-2-*thiones*.—For example, a solution of (4b) (0.12 g) in a dilute methanolic anhydrous hydrogen chloride was stored for 15 min, then purged with nitrogen and evaporated to dryness to give the hydrochloride of the phosphorothioate (17) (0.15 g, 100%), $[\alpha]_D$ +47.5° (*c* 1.0 in methanol); δ(CD_3OD), 1.08 (3 H, t, *J* 7.0 Hz), 1.29 (3 H, d, *J* 7.1 Hz), 3.74 (3 H, d, *J* 14.0 Hz), and 5.73 (1 H, dd, *J* 11.3 and 4.1 Hz).

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