Preparation of some Chiral Alkyl Alkyl Phosphorothioates and Stereochemical Studies of their Conversion into other Chiral Organophosphates

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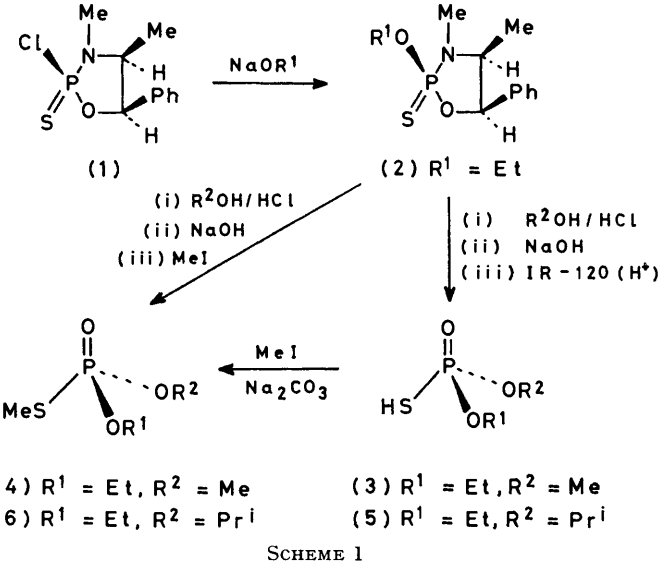
(2*R*,4*S*,5*R*)-2-Chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-thione (1) obtained as a pure isomer following crystallisation of the product from (−)-ephedrine and $PSCl_3$, is readily converted on sequential treatment with sodium ethoxide, methanolic HCl, and sodium hydroxide into optically pure (+)-(*R*)-ethyl methyl hydrogen phosphorothioate. The enantiomeric (−)-(*S*)-ethyl methyl hydrogen phosphorothioate is formed from (1) by reversing the order of alcohol addition. The route to alkyl alkyl hydrogen phosphorothioates is a general one since other alcohols may be used in place of methanol and ethanol. The alkyl alkyl hydrogen phosphorothioates are converted stereoselectively into alkyl alkyl phosphorothiochloridates and alkyl alkyl phosphorochloridates and the chloridates are converted stereoselectively into other products. Whether reactions occur preponderantly with retention or inversion of configuration is established and the degree of stereoselectivity of all reactions is measured by an n.m.r. method using a chiral shift reagent.

In modern organophosphorus chemistry a key concept is that many nucleophilic substitutions at phosphorus proceed through trigonal bipyramidal intermediates that are capable of ligand reorganisation processes (*viz.* pseudorotation) similar to those of stable pentacovalent phosphoranes.[1] Although the various processes involved are a function of all the ligands at phosphorus and are insufficiently understood for confident predictions to be made about the stereochemical outcome of substitutions at phosphorus, the concept of pseudorotation does provide an explanation of why some substitutions occur with inversion of configuration while others occur with retention.[2,3] Further, pseudorotational processes provide an explanation for observed differences in acid- and base-catalysed hydrolyses of 5-membered cyclic phosphates and phosphonates.[4] The results from the latter experiments were interpreted as indicating that the C–P bond in phosphonates provides a constraint to pseudorotation not present in phosphates. (It is usually assumed that bond forming and bond breaking processes only occur at apical positions of the trigonal bipyramid, that reactions which proceed with retention of configuration require pseudorotational involvement, and that those that occur with inversion of configuration usually do not involve pseudorotation). Similarly the result that methoxide displaces the thiomethyl group with retention of configuration from ethyl isopropyl *S*-methyl phosphorothioate, but with inversion of configuration from ethyl *S*-methyl methylphosphonothioate, is consistent with the idea that the C–P bond provides a constraint to pseudorotation.[3,4]

Hitherto, however, the extent of such differences between phosphates and phosphonates and the effects on reaction stereochemistry of changing the four ligands in phosphates have not been explored in any detail because chiral phosphates are rare even as racemates [5] and until recently few optically active phosphates had been reported [6] and no configurational assignments had been made.

In contrast, many stereochemical studies with phosphonates have been described.[7] These phosphonates are usually prepared easily from the readily resolvable alkyl alkyl hydrogen phosphonothioates and there have been many correlative configurational assignments of optically active alkylphosphonates in which the preponderant stereochemical course of a variety of nucleophilic substitutions have been assumed or deduced.

Now, however, it is possible to compare the stereochemical course of many chemical transformations,



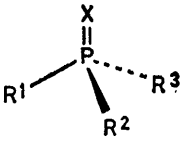
SCHEME 1

previously studied only on phosphonates, by using optically active phosphates prepared as illustrated in Scheme 1 by stereospecific degradation of 1,3,2-oxazaphospholidine-2-thiones derived from (—)-ephedrine.[3,8] Previously only the *S*-alkyl derivatives [*e.g.* (4)] were isolated due to experimental difficulties in isolating the hydrogen phosphorothiates [*e.g.* (3)] in satisfactory yields. These difficulties have now been overcome and in this paper the detailed preparation of chiral hydrogen phosphorothioates is described. Further, the preparations from these thioacids or *S*-alkyl derivatives, either directly or indirectly, of a number of chiral phosphates together with their configurational assign-

ments, are described. The results obtained are compared with corresponding data for phosphonates, as an attempt to summarise available data that must be accommodated within any discussions of pseudorotational processes and how they may or may not be involved in nucleophilic substitutions at phosphorus.

Preparation of Alkyl Alkyl Hydrogen Phosphorothioates.—The stereospecific synthesis of the optically active hydrogen phosphorothioates follows the sequence used to prepare alkyl alkyl *S*-alkyl phosphorothioates. The usual starting material is (2*R*,4*S*,5*R*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-thione (1) which may be obtained routinely in >60% yields as a thioates. For example (Scheme 1), a dilute solution of (2) with anhydrous hydrogen chloride in methanol was stored at room temperature for 30 min, made basic (to pH 12) with aqueous 10M-sodium hydroxide, stored overnight, and diluted with water. The solution was concentrated *in vacuo* at room temperature to remove the alcohol and then extracted repeatedly with ether until no more materials were being extracted (t.l.c.). The aqueous alkaline solution was passed over Amberlite IR-120 (H^+) resin and the acidic eluate was concentrated. The product was distilled to give (+)-(*R*)-ethyl methyl hydrogen phosphorothioate (3*R*). The (—)-(*S*)-ethyl isopropyl hydrogen phosphorothioate (5*S*) was

Configuration and rotational data for chiral phosphates and their derivatives



Compound	X	R^1	R^2	R^3	Configuration	$[\alpha]_D$ (°) [a]	Sense of non-equivalence [b]
(3)	O	SH	OEt	OMe	*R*	+1.5 (*c* 3)	
	O	SH	OMe	OEt	*S*	—1.4 (*c* 3)	
(4)	O	SMe	OEt	OMe	*R*	+1.0 (*c* 1)	*h* (OMe)
	O	SMe	OMe	OEt	*S*	—0.9 (*c* 1)	*l* (OMe)
(5)	O	SH	OEt	OPr^i	*S*	—5.1 (*c* 3)	
	O	SH	OPr^i	OEt	*R*	+5.0 (*c* 3)	
(6)	O	SMe	OEt	OPr^i	*S*	+3.4 (*c* 2)	*h* (SMe)
	O	SMe	OPr^i	OEt	*R*	—3.5 (*c* 1)	*l* (SMe)
(7)	S	Cl	OEt	OMe	*R*	+6.4 (*c* 5)	
(8)	S	Cl	OEt	OPr^i	*S*	+0.4 (*c* 5)	
(9)	S	OPr^i	OEt	OMe	*S*	—0.7 (*c* 4)	
	S	OPr^i	OMe	OEt	*R*	+0.7 (*c* 1)	
(10)	S	NMe_2	OMe	OEt	*R*	+2.2 (*c* 5)	
(11)	S	NH_2	OMe	OEt	*R*	+2.9 (*c* 5)	
(12)	S	NMe_2	OPr^i	OEt	*S*	+1.0 (*c* 4)	
(13)	S	NH_2	OPr^i	OEt	*S*	—1.5 (*c* 2)	
(14)	O	SMe	OEt	NH_2	*S*	—40 (*c* 1)	*h* (SMe)
	O	SMe	NH_2	OEt	R	+40 (*c* 1)	*l* (SMe)
(15)	O	Cl	OEt	OMe	*R*		*h* (OMe)
	O	Cl	OMe	OEt	*S*		*l* (OMe)
(16)	O	NH_2	OMe	OEt	*R*	+2.5 (c. 0.7)	*h* (OMe)
(17)	O	OMe	OEt	OPr^i	*S*	+0.2 (*c* 7)	*l* (OMe)
	O	OMe	OPr^i	OEt	*R*	—0.2 (*c* 6)	*h* (OMe)
(18)	O	F	OEt	OMe	*R*		*h* (OMe)
	O	F	OMe	OEt	*S*		*l* (OMe)
(19)	O	OPh	OEt	OMe	*R*	+2.8 (*c* 4) [c]	*h* (OMe)

[a] Solutions in chloroform. [b] The sense of non-equivalence is deemed *h* for that enantiomer in which the relevant signal undergoes the least change in chemical shift on addition of $Eu(hfc)_3$ (100 mg) to a solution of mixed enantiomers (30—40 mg) in deuteriochloroform (0.5 ml) at 60 MHz. [c] Value calculated from a 4 : 1 mixture of enantiomers.

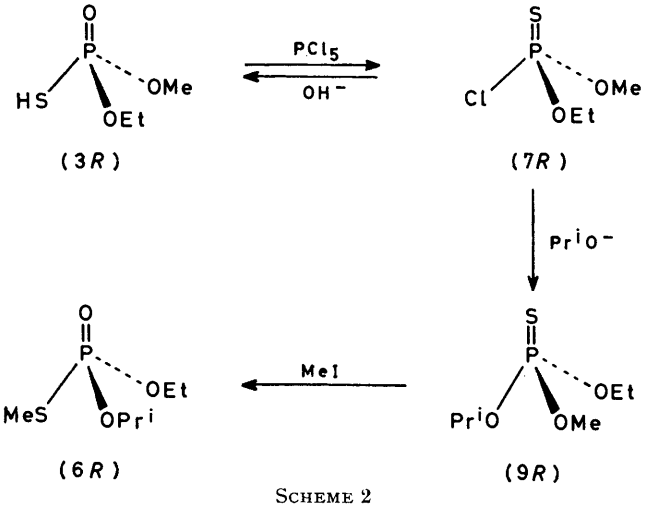
pure isomer by crystallisation of the product from (—)-ephedrine and $PSCl_3$.[3,8] Previously, the (+)-(*R*)-ethyl methyl hydrogen phosphorothioate (3*R*), obtained by sequential treatment of (1) with sodium ethoxide [to give (2)], methanolic hydrogen chloride, and sodium hydroxide, was not isolated directly but only as (4*R*) following alkylation with methyl iodide.[3,8] The enantiomer of (3*R*), *i.e.* (3*S*) isolated as (4*S*), was prepared by reversing the order of addition of alcohols; *i.e.* treatment of (1) with sodium methoxide and ring-opening with ethanolic hydrogen chloride.

The versatility of this procedure has been extended by recent work which has provided an experimental procedure which, when followed carefully, affords consistent yields (*ca.* 50%) of the hydrogen phosphoro- prepared similarly. Methylation of (3*R*) and (5*S*) under standard conditions gave essentially quantitative yields of (4*R*) and (6*S*), respectively. (4*R*) and (6*S*) were shown by measurement of their ^1H n.m.r. spectra in the presence of the chiral shift reagent $Eu(hfc)_3$ to be single enantiomers.

The rotations of (3*R*), (4*R*), (5*S*), and (6*S*) and of the products derived from them are given in the Table.

The potential general applicability of the above procedure for preparing chiral hydrogen phosphorothiates of known absolute configuration makes favourable comparison with the resolution procedures used previously for such hydrogen phosphorothioates as methyl p-nitrophenyl hydrogen phosphorothioate,[6a,b] ethyl butyl hydrogen phosphorothioate,[6c] and methyl

α-naphthyl hydrogen phosphorothioate [6d] and the route has also been adapted elegantly to enable the preparation of chiral [^{16}O,^{17}O,^{18}O]phosphate monoesters.[9]

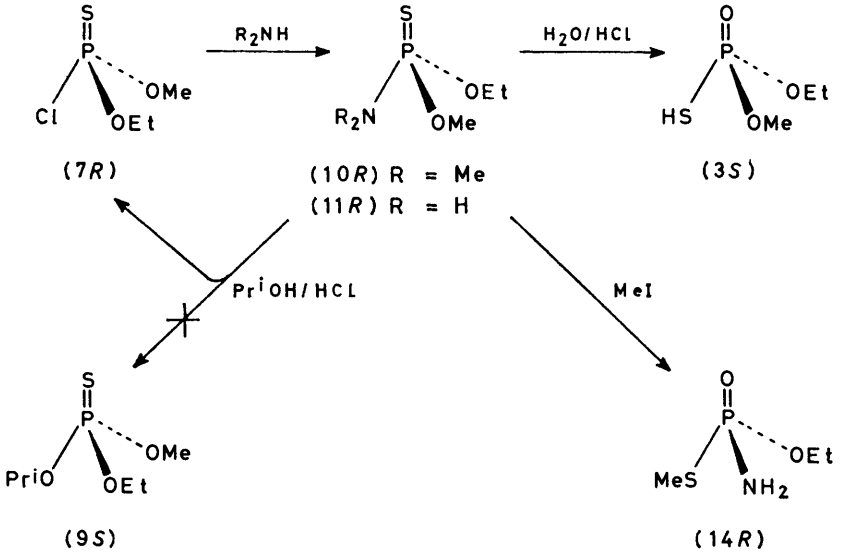


SCHEME 2

Conversion of Hydrogen Phosphorothioates [P(S)OH] *into Phosphorothiochloridates* [P(S)Cl] (*Scheme* 2).—The hydrogen phosphorothioate (3*R*), when added to a cooled suspension of 1 equiv. of phosphorus pentachloride in carbon tetrachloride afforded (+)-(*R*)-ethyl methyl phosphorothiochloridate (7*R*) in 45% yield. The chloridate (7*R*) was optically stable, no change in rotation occurring when it was distilled at 100 °C under reduced pressure or stored at room temperature for several weeks. (The corresponding alkylphosphonothiochloridates are also optically stable [10]). Similarly, (5*S*) afforded the chloridate (8*S*).

The transformations illustrated in Scheme 2 were carried out on (7*R*) and (8*S*). First, (7*R*) was hydrolysed by sodium hydroxide. The sodium salt of the resulting thioacid was treated with an excess of methyl iodide to yield the same enantiomerically pure phosphorothioate (4*R*) as was obtained by similar alkylation of (3*R*), thereby showing that both the chlorination and the hydrolysis were stereospecific processes occurring with the same stereochemistry at phosphorus. The stereospecificity of these reactions is in contrast to that of a similar sequence with (+)-methyl α-naphthyl phosphorothioate where some loss of enantiomeric purity was observed.[11] It is probable that in this case the loss occurred during the chlorination with PCl_5. Unless the PCl_5 is carefully purified a similar loss of enantiomeric purity occurs during chlorination of (3*R*).

Secondly, (7*R*) was converted into (9*R*) by treatment with a solution of sodium isopropoxide. Compound (9*R*) was shown to have the *R* configuration when, on heating with methyl iodide in a sealed tube, (9*R*) was converted into (−)-(*R*)-*S*-methyl ethyl isopropyl phosphorothioate (6*R*) in a reaction known to occur with retention of configuration since no bonds to phosphorus are broken. Use of a chiral shift reagent showed that (6*R*) [and hence (9*R*)] was a single enantiomer. These results demonstrate that the chlorination of (3*R*), the hydrolysis of (7*R*), and the reaction of (7*R*) with sodium isopropoxide must occur with the same stereochemistry;



SCHEME 3

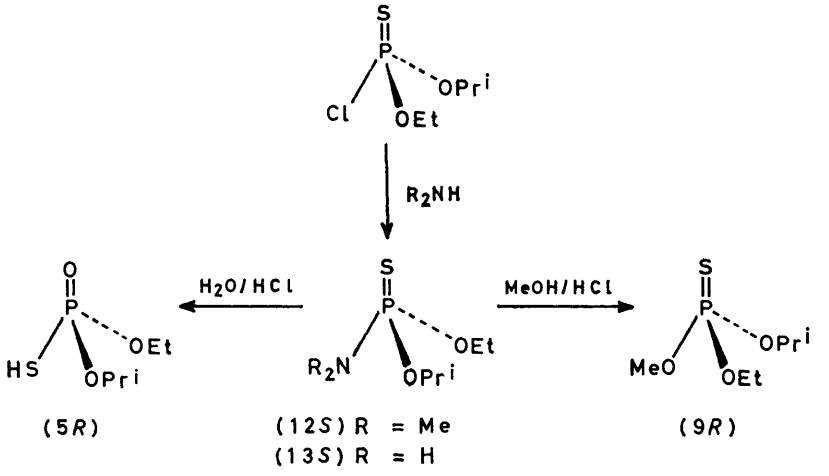
almost certainly all reactions occur with inversion of configuration so that (7) has the *R* configuration.

Preparation and Reactions of Phosphoramidothioates (*Schemes* 3 *and* 4).—The phosphoramidothioates (10*R*) and (11*R*) were prepared by treatment of the chloridate (7*R*) with dimethylamine and ammonia, respectively. The isopropyl derivatives (12*S*) and (13*S*) were prepared similarly from the chloridate (8*S*). That the replacement of chlorine by amines occurs stereospecifically with inversion of configuration was confirmed when (11*R*), on treatment with an excess of methyl iodide, was converted, without change in the configuration at

phosphorus, into (+)-(*R*)-ethyl *S*-methyl phosphoramidothioate (14*R*). The phosphoramidothioate (14*R*), whose configurational assignment has been described elsewhere,[12] was shown to be enantiomerically pure by n.m.r. using a chiral shift reagent.

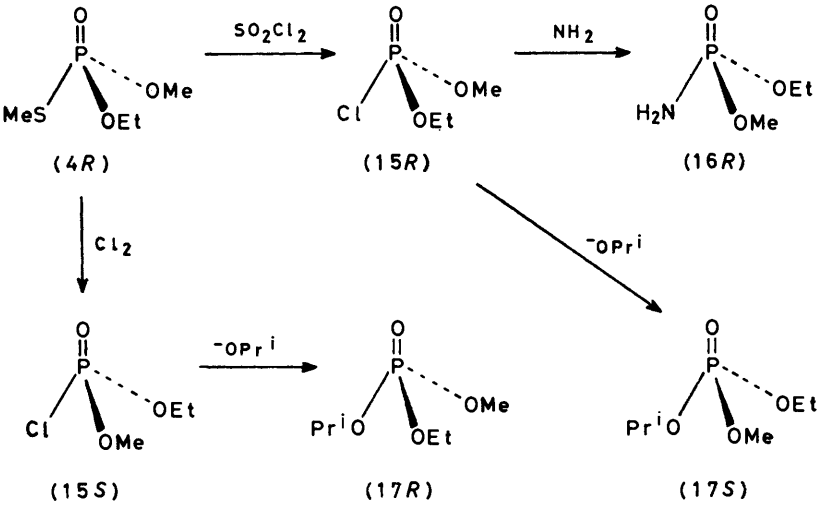
(7*R*) ⟶ (11*R*) ⟶ (3*S*) and (5*S*) ⟶ (8*S*) ⟶ (13*S*) ⟶ (5*R*) require that acid-catalysed hydrolysis of P–N bonds in alkyl alkyl phosphoramidothioates occurs with inversion of configuration.

With anhydrous methanolic hydrogen chloride similar



SCHEME 4

Studies of the behaviour of the phosphoramidothioates (10*R*), (11*R*), (12*S*), and (12*S*) with 2N-hydrochloric acid in aqueous acetone and with anhydrous alcoholic hydrogen chloride produced the following results. Under aqueous conditions (10*R*) and (11*R*) afforded (3*S*); P–N bond cleavage with inversion of configuration was observed with both (12*S*) and (13*S*) being converted into (9*R*). The magnitude of the specific rotation of (9*R*) was the same as that shown previously to be a pure enantiomer. In contrast, when (10*R*) was treated with



SCHEME 5

similarly, (12*S*) and (13*S*) afforded (5*R*). The specific rotations of (3*S*) and (5*R*) were equal in magnitude and opposite in sign to the corresponding acids prepared by degradation of the 1,3,2-oxazaphospholidine-2-thiones (Scheme 1). Confirmation of the optical purity of (3*S*) and (5*R*) was obtained (n.m.r.) following their conversion into the *S*-methyl derivatives (4*S*) and (6*R*). Since chlorination of thioacids with PCl_5 and replacement of chlorine by amines occur with inversion of configuration, the synthetic sequences (3*R*) ⟶ 3N-hydrogen chloride in isopropanol under anhydrous conditions, the major product was the chloridate (7*R*) with no (9*S*) being detected in the crude reaction product which contained several acidic components (Scheme 3).

Formation and some Reactions of P(O)Cl *and* P(O)F *Derivatives* (*Schemes* 5 *and* 6).—Two methods for converting *S*-alkyl phosphorothioates into phosphoryl chlorides have been investigated.

(a) *Treatment of phosphorothioates with sulphuryl chloride.*[13,14] Addition of one equivalent of sulphuryl

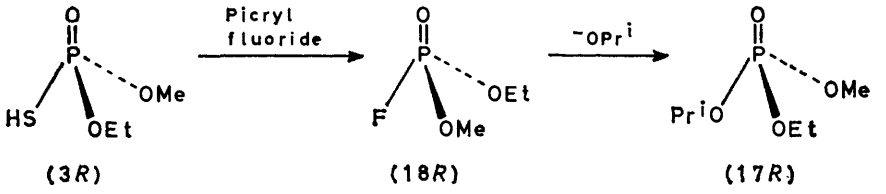
chloride to a solution of the phosphorothioate (4*R*) afforded a phosphoryl chloride, which, following immediate distillation at 50 °C *in vacuo*, was shown to be a 19 : 1 mixture of (*R*)-ethyl methyl phosphoryl chloride (15*R*) and its enantiomer (15*S*). On storage for one week at room temperature, and redistillation, the ratio of the enantiomers had changed to 3 : 2. Although enantiomerically pure phosphoryl chlorides were not obtained from phosphorothioate–sulphuryl chloride interactions it was possible to isolate enantiomerically pure derivatives by appropriate treatment of crude reaction mixtures. For example, the enantiomerically pure amidate (16*R*) was obtained by direct addition of ammonia to the (4*R*)-sulphuryl chloride reaction mixture; similar treatment of the crude mixture with sodium isopropoxide afforded (17*S*) as a single enantiomer. Since the configurations of (4*R*) and (17*S*) are known, and since it is reasonable to assume that displacement of chloride by isopropoxide and ammonia occur with inversion of configuration, then (15*R*) must have *R* configuration, *i.e.* the displacement of *S*-methyl by sulphuryl chloride occurred with *retention* of configuration at phosphorus, and the amidate (16*R*) must have (*R*) configuration.

(b) *Treatment of phosphorothioates with chlorine.*[15] Treatment of (+)-(*R*)-ethyl methyl *S*-methyl phosphorothioate (4*R*) with a solution of chlorine in carbon tetrachloride and distillation of the product afforded a 9 : 1 mixture of (15*S*) and (15*R*), *i.e.* the displacement of *S*-methyl by chlorine occurred at least preponderantly with inversion of configuration. The crude reaction mixture from the (4*R*)–chlorine reaction, on treatment with ammonia and sodium isopropoxide, afforded the single enantiomers (16*S*) and (17*R*), respectively.

Treatment of a 4 : 1 mixture of the chloridates (15*S*) and (15*R*) with sodium phenoxide gave a good yield of the ethyl methyl phenyl phosphates (19*R*) and (19*S*) (4 : 1). Since it can be reasonably assumed that this reaction occurs with inversion of configuration at phosphorus, this result enables the assignment of configuration to the dialkyl phenyl phosphates recently prepared using L-proline derivatives.[16]

Evidence to support the configuration assigned to (16*R*) was provided when the phosphoramidothioate (11*R*) was oxidised stereospecifically by *m*-chloroperbenzoic acid, using conditions which usually favour oxidation of P=S to P=O with retention of configuration,[17] into (16*R*) as a pure enantiomer. [In contrast the oxidation of (9*R*) under similar conditions was not stereospecific although occurring with preponderant (4 : 1) retention of configuration to afford (+)-(*S*)- and (−)-(*R*)-ethyl isopropyl methyl phosphates (17*S*) and (17*R*), respectively].

The stereoselective formation of (*R*)-ethyl methyl



SCHEME 6

phosphoryl fluoride was achieved by treatment of the sodium salt of (3*R*) with two equivalents of picryl fluoride under strictly anhydrous conditions.[18] The isolated ethyl methyl phosphoryl fluoride contained 83% (18*R*) and 17% of the enantiomer (18*S*) (assuming the reaction proceeds with inversion of configuration). Unless water was rigorously excluded from the reaction mixture only racemic product was obtained. Treatment of the enantiomeric mixture with sodium isopropoxide afforded a mixture of the enantiomeric ethyl isopropyl methyl phosphates (18*R*) and (17*S*) in the ratio 4 : 1.

The enantiomeric purity of all of the chiral P=O-containing compounds prepared in the above series of reactions was established using the chiral n.m.r. shift reagent Eu(hfc)$_3$. At least one group of protons was always successfully resolved under standard conditions [organophosphate (30—40 mg) and Eu(hfc)$_3$ (100 mg) in deuteriochloroform (0.5 ml) recorded at 60 MHz] and in each case the relationship between the absolute configuration of the compound and the sense of magnetic non-equivalence of the relevant group of signals (Table) was the same as observed previously for other chiral phosphates and phosphonates.[3]

Comparison of Reactions of Phosphoro- and Phosphono-derivatives.—The observation that methoxide displaces the thiomethyl group with retention of configuration from ethyl isopropyl *S*-methyl phosphorothioate but with inversion of configuration from ethyl *S*-methyl methylphosphonothioate,[3] highlighted the fact that in certain instances reaction of acyclic phosphono- and phosphoro-derivatives can follow quite different stereochemical pathways. In the present work one further example of such a difference was that on treatment with sulphuryl chloride, (+)-(*R*)-ethyl methyl *S*-methyl phosphorothioate (4*R*) was converted into the chloridate (15*R*) with *retention* of configuration (Scheme 2) whereas the SO_2Cl_2–ethyl *S*-ethyl ethylphosphonothioate reaction which affords ethyl ethylphosphonochloridate occurs with *inversion* of configuration. Unfortunately, speculation about the mechanistic significance of this observation is complicated by the finding that the SO_2Cl_2–ethyl *S*-(2-chloroethyl) ethylphosphonothioate reaction is apparently anomalous for the phosphono-series and occurs with *retention* of configuration.

Chlorination of both alkyl alkyl *S*-alkyl phosphorothioates and alkyl *S*-alkyl alkylphosphonothioates

occurs with inversion of configuration. Thus in the phosphoro-series a single isomer, *e.g.* (4*R*), can be converted into an enantiomeric pair; (4*R*) gives the chloridate (15*R*) with sulphuryl chloride and the chloridate (15*S*) with chlorine (Scheme 5). Chloridates such as ethyl methyl phosphorochloridate, although apparently more stable than analogues in the phosphono-series,[14] could not be isolated as pure enantiomers but were sufficiently stable to enable their conversion into derivatives (amidates, esters) which could be isolated pure.

In the majority of reactions studied there is little difference with regard to stereochemistry of reactions of phosphoro- and phosphono-derivatives. For example, phosphonothioic acid derivatives and phosphorothioic acid derivatives on treatment with PCl_5 afford with a high degree of stereoselectivity and with inversion of configuration optically stable phosphonothiochloridates and phosphorothiochloridates, respectively. The mechanism of the PCl_5–hydrogen phosphonothioate reaction has been described [10] and is presumably the same in the phosphoro-series. Although previous results have indicated a higher degree of stereoselectivity in the phosphono-series [10] (*ca.* 98%) than in the phosphoro series [11] the results in this paper suggest that loss of optical purity is probably a function of halide–halide exchange and has no other mechanistic implication.

The results that aqueous alkaline hydrolysis of phosphorothiochloridates occurs with inversion of configuration and that replacement of chlorine by alkoxide in phosphorothiochloridates and phosphorochloridates occurs with inversion of configuration are consistent with the many results of similar experiments in the phosphono-series.[19]

Displacement of chlorine by amines from phosphorothiochloridates occurs with unequivocal inversion of configuration [*i.e.* (7*R*) to (10*R*) and (11*R*)] and there is no reason to suppose that in the phosphorochloridate series the similar conversion of (15*R*) into (16*R*) did not also occur with inversion of configuration. In the phosphono-series there are similar indications that displacement of chlorine by amines occurs with inversion of configuration.[20]

Oxidations of P=S to P=O with *m*-chloroperbenzoic acid under appropriately controlled conditions [19] occur with retention of configuration in both the phosphoro- and phosphono-series. Whether in the phosphoro-series the degree and direction of stereoselectivity of peracid oxidations are so dependent on the peracid and the reaction conditions as in the phosphono-series remains to be established.

With regard to acid-catalysed alcoholysis of phosphonamidates and phosphoramidates it is probably premature to make any generalisation about differences in the two series since all the groups attached to phosphorus affect the overall stereochemistry of reactions at phosphorus. For example, the results from the alkyl alkyl phosphoramidothioates, $RO(RO)P(S)NR_2$, in which substitution of the amine group by OH, OMe, or Cl occurs stereospecifically with inversion of configuration, make an interesting comparison with previous alcoholyses of alkyl *S*-alkyl phosphoramidothioates, $RO(RS)P(O)NR_2$, where stereospecific substitutions were not observed.[21] In some cases the alcoholyses proceeded with preponderant inversion of configuration whereas in others products with retention of configuration were favoured. The stereochemical outcome varied with the alcohol, the acid strength, and the amine group. In view of the formation of the chloridate (7*R*) from (10*R*), it is tempting to speculate that previously the observed retentions of configuration were a consequence of double displacements with inversion of configuration, *i.e.* substitution of amine by chlorine, and substitution of chlorine by alcohol. A similar scheme has been discussed for the hydrogen chloride–catalysed alcoholysis of phosphinamidates.[22]

Preliminary unpublished observations from this laboratory on the aqueous acid-catalysed hydrolysis of phosphonamidothioates $(RO)RP(S)NR_2$ suggest that this reaction also occurs stereospecifically with inversion of configuration, whereas the situation for phosphoramidates $(RO)_2P(O)NR_2$ appears to be more closely related to that of the phosphoramidothioates $RO(RS)P(O)NR_2$ where the inversion/retention pathways are finely balanced. The steric course of these reactions as a function of the steric bulk of both the nucleophile and the substrate are at present being further investigated.

EXPERIMENTAL

Details for the preparation of each compound are not given, but examples of each type of compound and reaction are reported. ^{1}H N.m.r. spectra were measured with a JEOL JNM-MH-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. Enantiomers were pure (n.m.r.) unless otherwise stated. Optical rotations were measured in chloroform (path length 1 dm) and are listed in the Table. 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 (particle size 0.05—0.2 mm). All air- or moisture-sensitive reactions were carried out under dry oxygen-free nitrogen. Solutions 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.

(+)-(R)-*Ethyl Methyl Hydrogen Phosphorothioate* (3R).—A solution of 3N-anhydrous hydrogen chloride in methanol (10 ml) was slowly added to a solution of (2*R*,4*S*,5*R*)-2-ethoxy-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-thione [3] (2) (15.4 g) in methanol (50 ml). After 30 min the solution was made basic (pH 12) by addition of 10N sodium hydroxide, then stored for 24 h, poured into water (100 ml) and concentrated at room temperature to *ca.* 100 ml. The aqueous phase was washed with ether (3×), then passed over Amberlite IR-120 (H^+). The acidic eluate was concentrated and filtered and the residue was distilled at 112°

and 0.5 mmHg to give (3*R*) (5.0 g, 56%) as a clear oil.

(+)-(R)-*Ethyl Methyl* S-*Methyl Phosphorothioate* (4R).—A solution of the thioacid (3*R*) (0.2 g) in ethanol (20 ml) was made basic with 10% aqueous sodium carbonate, then an excess of methyl iodide was added and the mixture stored for 1 h. It was then poured into water and extracted with chloroform. The organic phase was dried, concentrated, and the residue distilled at 115° and 15 mmHg to give (4*R*) (0.2 g, 93%) as a clear oil.[3]

(+)-(R)-*Ethyl Methyl Phosphorothiochloridate* (7R).—A solution of the phosphorothioate (3*R*) (1 g) in carbon tetrachloride (60 ml) was added slowly to a stirred suspension of phosphorus pentachloride (1.34 g) in carbon tetrachloride at 0 °C. The mixture was stored for 1 h, concentrated under reduced pressure, and the residue was dissolved in ether. The ether solution was washed with dilute aqueous sodium hydrogen carbonate, washed twice with water, dried, and concentrated, and the product distilled at 100° and 9 mmHg to give (7*R*), (0.54 g, 48%) as a clear liquid, R_F 0.8 (benzene–light petroleum 1 : 3).

Hydrolysis of (+)-(R)-*Ethyl Methyl Phosphorothiochloridate* (7R).—1N-sodium hydroxide (5 ml) was added to a solution of the thiochloridate (7R) (0.11 g) in dioxan (3 ml). After 12 h an excess of methyl iodide was added and the mixture stored for a further 1 h, poured into water, and extracted with chloroform. The organic phase was dried and concentrated and the product distilled at 115° and 15 mmHg to give (4*R*) (0.08 g, 75%) as a clear liquid, R_F 0.6 (benzene–acetone–methanol 8 : 1 : 1).

(−)-(S)-*Ethyl Isopropyl Methyl Phosphorothioate* (9S).—A solution of sodium (0.05 g) in methanol (2 ml) was added slowly to the thiochloridate (8*S*) (0.42 g) in methanol (10 ml). The mixture was stored at room temperature for 2 h, poured into water, extracted with chloroform, dried, and concentrated. The product was distilled at 110° and 3 mmHg to give (9*S*) (0.38 g, 93%) as a clear liquid that fumes in air, R_F 0.2 (benzene–light petroleum 1 : 3). Similarly, (+)-(*R*)-ethyl isopropyl methyl phosphorothioate (9*R*) was obtained in 75% yield on treatment of (7*R*) with sodium isopropoxide.

(−)-(R)-S-*Methyl Ethyl Isopropyl Phosphorothioate* (6R).—A solution of (9*R*) (0.15 g) in methyl iodide (5 ml) was heated in a sealed tube at 100 °C for 4 h. The solution was concentrated and the residue passed over silica in benzene–acetone–methanol (8 : 1 : 1) to give (6*R*) (0.1 g, 66%).

(+)-(S)-*Ethyl Isopropyl* N-*Dimethyl Phosphoramidothioate* (12S).—A solution of the phosphorothiochloridate (8*S*) (0.92 g) in benzene (50 ml) was added slowly to a solution of dimethylamine (0.5 g) in benzene (40 ml), stored at room temperature for 2 h, filtered, washed with water (3×), dried, and concentrated. The product was distilled at 110° and 4 mmHg to give (12*S*) (0.8 g, 84%) as a clear oil, R_F 0.3 (benzene–light petroleum 1 : 3).

(+)-(S)-*Ethyl Isopropyl Phosphoramidothioate* (13S).—Ammonia was bubbled through a solution of the phosphorothiochloridate (8*S*) (0.6 g) in benzene (60 ml) for 3 h. The solution was filtered, washed twice with water, dried, and concentrated, and the product distilled at 110° and 2 mmHg to give (13*S*) (0.4 g, 74%) as a clear oil, R_F 0.1 (benzene–light petroleum 1 : 3).

(+)-(R)-*Ethyl* S-*Methyl Phosphoramidothioate* (14R).—A solution of the phosphoramidothioate (11*R*) (0.3 g) in methyl iodide (10 ml) was boiled inder reflux for 40 h, concentrated, and passed over silica in benzene–acetone–methanol (8 : 1 : 1). The fraction having R_F 0.5 was (14*R*) (0.25 g, 83%) as a white solid, m.p. 87°.

Aqueous Hydrolysis of Alkyl Alkyl Phosphoramidothioates.—For example, a solution of (12*S*) (0.4 g) in 4*N*-hydrochloric acid–acetone (1 : 1; 5 ml) was stored overnight, then poured into water (10 ml) and repeatedly extracted with chloroform. The organic phase was dried and concentrated and the residue distilled at 115° and 0.5 mmHg to give the thioacid (5*R*) (0.3 g, 85%), $[\alpha]_D$ +5.0° (*c* 3) as a clear oil. Alkylation of the product with methyl iodide as previously described gave (6*R*) (0.3 g, 80%).

Treatment of Alkyl Alkyl Phosphoramidothioates with Alcoholic Hydrogen Chloride.—(*a*) A solution of (12*S*) (0.2 g) in anhydrous methanolic hydrogen chloride (2N; 20 ml) was stored at room temperature for 36 h, poured into dilute aqueous sodium carbonate and extracted with chloroform. The chloroform extract was dried and concentrated and the product distilled at 110° and 3 mmHg to give (+)-(*R*)-ethyl isopropyl methyl phosphorothioate (9*R*) (0.14 g, 75%), $[\alpha]_D$ +0.7 (*c* 1). (*b*) A solution of (10*R*) (0.25 g) in anhydrous hydrogen chloride in isopropanol (2N; 20 ml) (prepared by addition of acetyl chloride to dry isopropanol) was stored at room temperature for 48 h, poured into dilute aqueous sodium carbonate, extracted with chloroform, and the chloroform extract dried and concentrated. The product was distilled at 100° and 9 mmHg to give chromatographically homogeneous (7) (0.1 g, 42%) with $[\alpha]_D$ +5.4° (*c* 1), showing (7) was preponderantly the *R* enantiomer.

Preparation of Alkyl Alkyl Phosphorochloridates.—(*a*) A solution of sulphuryl chloride (0.32 g) in benzene (5 ml) was added slowly to a solution of (4*R*) (0.4 g) in benzene (30 ml) at 8—10 °C. The solution was stored for 2 h, concentrated at room temperature and 12 mmHg and the product distilled at 70° and 1 mmHg to give preponderantly ethyl methyl phosphoryl chloride (15*R*) (0.19 g, 51%), R_F 0.5 (ether–light petroleum 1 : 1). N.m.r. spectroscopy in the presence of $Eu(hfc)_3$ showed (15*R*) was in admixture with *ca.* 5% of the enantiomer (15*S*). (*b*) A solution of chlorine (0.13 g) in carbon tetrachloride (5 ml) was added slowly to a solution of (4*R*) (0.3 g) in carbon tetrachloride (5 ml). The solution was stored at room temperature for 15 min, concentrated, and distilled at 70° and 1 mmHg to give (15*S*) (0.2 g, 72%). The n.m.r. spectrum in the presence of $Eu(hfc)_3$ showed the presence of *ca.* 10% (15*R*).

(+)-(R)-*Ethyl Methyl Phosphoramidate* (16R).—A solution of sulphuryl chloride (0.32 g) in benzene (5 ml) was added slowly to a solution of (4*R*) (0.4 g) in benzene (30 ml) at 8—10 °C. The mixture was stored for 2 h, then anhydrous ammonia gas was bubbled through. After 1 h the solution was filtered, concentrated and the residue passed over silica (15 g) in benzene–acetone–methanol (8 : 2 : 2) to give (16*R*) (0.11 g, 63%), R_F 0.5 as a clear oil.

(−)-(R)-*Ethyl Methyl Isopropyl Phosphate* (17R).—A solution of chlorine in carbon tetrachloride (5 ml) was added slowly to a solution of (4*R*) (0.3 g) in carbon tetrachloride (5 ml). The mixture was stored for 15 min, then concentrated at room temperature and 12 mmHg and the residue dissolved in isopropanol (5 ml). A solution of 1N-sodium isopropoxide in isopropanol (2 ml) was slowly added and the mixture was stored for 10 h, then poured into water and extracted with chloroform. The organic phase was dried and concentrated and passed over silica (20 g) in benzene–acetone–methanol (8 : 1 : 1) to give (17*R*) (0.06 g,

25%). The n.m.r. spectrum in the presence of $Eu(hfc)_3$ showed $<5\%$ of the enantiomer (17*S*).

Oxidation of (+)-(R)-*Ethyl Methyl Phosphoramidothioate* (11R).—A solution of *m*-chloroperbenzoic acid (0.28 g) in methylene chloride (5 ml) was added slowly to a solution of (11*R*) (0.25 g) in methylene chloride (10 ml) at 0 °C. After 1 h the mixture was poured into water and extracted twice with ether. The aqueous phase was concentrated and the residue passed over silica (20 g) in benzene–acetone–methanol (8 : 2 : 2) to give (16*R*) (0.1 g, 45%) as a clear oil.

Oxidation of (+)-(R)-*Ethyl Methyl Isopropyl Phosphorothioate* (9R).—A solution of *m*-chloroperbenzoic acid (0.2 g) in methylene chloride (5 ml) was added slowly to a solution of (9*R*) (0.2 g) in methylene chloride (5 ml) at 0 °C. A yellow solid was immediately precipitated from solution. After 30 min the solution was filtered, washed with dilute sodium carbonate and water, dried, and concentrated and the residue distilled at 65° and 0.2 mmHg to give preponderantly (17*S*) as a clear oil. The n.m.r. spectrum in the presence of $Eu(hfc)_3$ showed *ca.* 20% of the enantiomer (17R).

(S)-*Ethyl Methyl Phosphorofluoridate* (18S).—A solution of the sodium salt of the thioate (3*R*) (0.32 g) in methyl acetate (5 ml) was added slowly to a solution of picryl fluoride (0.9 g) in methyl acetate (10 ml). The mixture was stirred for 30 min, then filtered, concentrated, and the residue distilled at 70° and 3 mmHg to give (18*S*) (0.12 g, 47%) as a clear oil, R_F 0.8 (ether). The n.m.r. spectrum in the presence of $Eu(hfc)_3$ showed *ca.* 17% of the enantiomer (18*R*).

P–F Bond Cleavage with Isopropoxide.—A solution of 1N-sodium isopropoxide (0.7 ml) was added slowly to a solution of (18*S*) [containing *ca.* 17% (18*R*)] (0.1 g). The mixture was stirred for 3 h, then poured into water and extracted with chloroform. The organic phase was dried, concentrated, and the residue distilled at 65° and 0.2 mmHg to give preponderantly (17*R*) (0.07 g, 55%) as a clear oil. The n.m.r. spectrum in the presence of $Eu(hfc)_3$ showed *ca.* 20% of the enantiomer (17*S*).

(+)-(R)-*Ethyl Methyl Phenyl Phosphate* (19R).—A solution of sodium phenoxide (0.28 g) in acetonitrile (5 ml) was added slowly to a solution of the chloridate (15*S*) [containing *ca.* 20% (15*R*)] (0.38 g) in acetonitrile (15 ml). The mixture was stored for 2 h, then poured into water and extracted with ether. The organic phase was dried and concentrated and the residue passed over silica (25 g) in ether (R_F 0.5) to give (19*R*) (0.4 g, 78%), b.p. 80° at 0.05 mmHg, $[\alpha]_D$ +1.7° (*c* 3.8). The n.m.r. spectrum in the presence of $Eu(hfc)_3$ showed *ca.* 20% of the enantiomer (19*S*).

[8/736 *Received*, 20*th April*, 1978]

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