Chiral *OS*-Dialkyl Phosphoramidothioates: their Preparation, Absolute Configuration, and Stereochemistry of their Reactions in Acid and Base

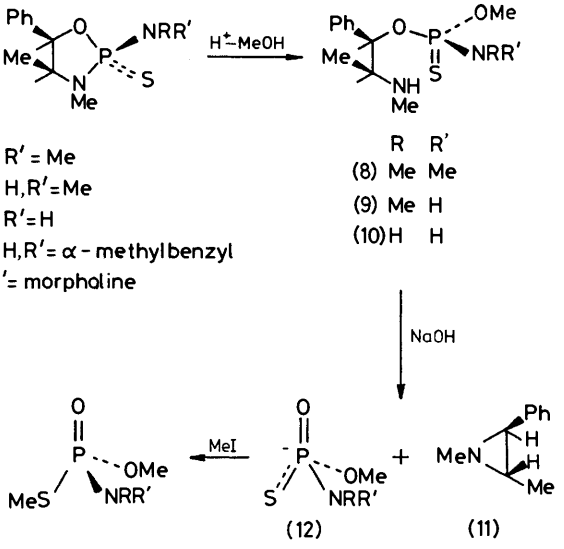
By **C. Richard Hall** and **Thomas D. Inch,*** Chemical Defence Establishment, Porton Down, Salisbury, Wiltshire, SP4 0JQ

With amines, the *cis*- and *trans*-isomers of 2-chloro-1,3,2-oxazaphospholidine-2-thiones, derived from (−)-ephedrine, afford the corresponding 2-amino-derivatives which on sequential treatment with acidic alcohol, sodium hydroxide, and alkyl iodide are converted into *OS*-dialkyl phosphoramidothioates which are usually enantiomerically pure. In methanolic hydrogen chloride the phosphoramidothioates give the corresponding *OS*-dialkyl methylphosphorothioates with preponderant *inversion* of configuration whereas with isopropyl alcohol and hydrogen chloride *OS*-dialkyl isopropylphosphorothioates are formed with preponderant *retention* of configuration. With ethanolic hydrogen chloride, whether the P–N bond in the phosphoramidothioates is cleaved with inversion or retention of configuration is a function of the acid strength and of the substituents on nitrogen. Reactions which proceed with retention of configuration proceed by double displacements, initial formation of chloridates being followed by displacements with alcohol. Reactions of alkoxides with *OS*-dialkyl phosphoramidothioates, irrespective of the degree of substitution on nitrogen, proceed with preponderant inversion of configuration to afford *OO*-dialkyl phosphoramidates.

OS-DIALKYL PHOSPHORAMIDOTHIOATES merit detailed chemical study on two accounts. Firstly they are of interest because the P–S, P–O, and P–N bonds may all be broken under mild conditions. The preponderant reactions depend on the reaction conditions which as yet have been insufficiently investigated to allow confident prediction of the major products. Secondly, some members of the series are potent insecticides but relatively poor anticholinesterases; although their insecticidal activity has been ascribed to metabolic activation the active metabolities are ill-defined and no clear relation between chemical and biological activity has been established. It was pertinent, therefore, to prepare some enantiomeric pairs of *OS*-dialkyl phosphoramidothioates and to carry out some stereochemical studies in an attempt to clarify reaction mechanisms and then to compare selected enantiomeric pairs in biological studies. In this paper details [1] of some synthetic and stereochemical studies are reported.

Previously it has been shown that stereoselective degradation of cyclic phosphoramido-esters of (−)-ephedrine can afford chiral phosphorus derivatives (*e.g.* alkyl alkylphosphonothioic acids, dialkyl phosphorothioic acids) that are usually isolated as single enantiomers and readily transformed to other chiral phosphorus products. It is possible in most cases to assign their absolute configuration on the basis of the synthetic sequences employed. Enantiomerically pure *OS*-dialkyl phosphoramidothioates may be prepared readily by appropriate modification of the general routes described previously.[2-4]

Preparation and Configurational Assignments of OS-*Dialkyl Phosphoramidothioates.*—The key starting materials were the 2-chloro-1,3,2-oxazaphospholidine-2-thiones (1a) and (1b). The preparation of these compounds and evidence that in such compounds nucleophilic displacements of chlorine occur with retention of configuration at phosphorus have been described previously.[3,4] By analogy with these studies (1a) and (1b)



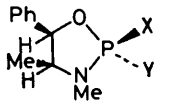
SCHEME 1

were converted with retention of configuration † into (2a) and (2b), (3a) and (3b), (4a) and (4b), and (5a) and (5b) on treatment with dimethylamine, methylamine, ammonia, and (−)-α-methyl-benzylamine respectively (see Table 1 for structures and n.m.r. data of 1,3,2-oxazaphospholidine-2-thiones). The morpholino-derivative (7a) was also obtained by treating (1a) with morpholine.

† One exception to the usual pattern was noted. The reaction of (1a) with imidazole was not stereospecific, the crude product containing a *ca.* 7 : 1 mixture of (6a) and (6b). This product ratio was obtained in three repeat reactions. Since no (6b) could be formed from (6a), by treating (6a) with imidazole or imidazole hydrochloride, and since on treatment with dimethylamine (6a) afforded only (2a), *i.e.* the retention product, special reasons must be sought to account for the non-stereospecific reaction of (1a) with imidazole.

TABLE 1

^{1}H N.m.r. and optical rotation parameters for 2-substituted 1,3,2-oxazaphospholidine-2-ones and -thiones

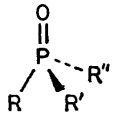


Compound	X	Y	δ H-4	δ H-5	J(Hz) P,H-4	J(Hz) P,H-5	$[\alpha]_D$(°) †
(1a)	Cl	S	3.85	5.81	29.5	1	−121
(1b)	S	Cl	3.73	5.59	13	6.5	−23
(2a)	NMe_2	S	3.52	5.67		<1	−147
(2b)	S	NMe_2	3.76	5.60	22.5	<1	+13.5
(3a)	NHMe	S	3.57	5.65	9	2	−130
(3b)	S	NHMe	3.71	5.56	22.5	<1	+5
(4a)	NH_2	S	3.56	5.54	10	4	−83
(4b)	S	NH_2	3.63	5.52	21.5	1.5	−36
(5a)	NHR *	S	3.51	5.57	9.5	<1	−152
(5b)	S	NHR *		5.66		1	
(6a)	Imidazole	S	3.80	5.87	13.5	<1	−136
(6b)	S	Imidazole		5.70		3.6	
(7a)	Morpholino	S		5.68		<1	−139
(24a)	SEt	O	3.73	5.74	17.5	<1	−66
(24b)	O	SEt	3.59	5.46	15.5	4	

* (−)-α-Methylbenzyl. † Solutions in chloroform.

TABLE 2

Absolute configurations and optical rotations of chiral organophosphate derivatives



Compound	R	R′	R″	Configuration	$[\alpha]_D$(°) [a]	Sense of magnetic non-equivalence [b]
(13)	SMe	NMe_2	OMe	*R*	+36 (*c* 1.5)	
(14)	SMe	NHMe	OMe	*R*	+24 (*c* 0.6)	l(SMe), l(OMe)
(15)	SMe	NH_2	OMe	*R*	+24 (*c* 0.5) [e]	l(SMe), h(OMe)
(16)	SMe	NHR [c]	OMe	*R*	−22 (*c* 0.4)	
(17)	SMe	R [d]	OMe	*R*	+46 (*c* 7.6)	
(18)	SMe	R [d]	OEt	*R*	+38 (*c* 3.3)	
(19)	SMe	NMe_2	OEt	*R*	+32 (*c* 4.6)	
(20)	SMe	NH_2	OEt	*R*	+41 (*c* 1.5)	l(SMe)
(29)	Cl	SMe	OMe	*R*		l(SMe), h(OMe)
(34)	Cl	OMe	NMe_2	*S*	−33 (*c* 1.8) [f]	l(OMe), h(NMe_2)
(35)	Cl	OMe	R [d]	*S*	−35 (*c* 2.7)	l(OMe)
(36)	Cl	OEt	R [d]	*S*	−26 (*c* 3.1)	
(37)	OMe	OEt	NMe_2	*R*	−1.5 (*c* 1.5)	
(37)	OEt	OMe	NMe_2	*S*	+0.9 (*c* 2.5) [g]	
(38)	OEt	OMe	NHMe	*S*		h(OMe)
(39)	OMe	OEt	NH_2	*R*	+2.5 (*c* 0.7)	h(OMe)
(39)	OEt	OMe	NH_2	*S*		l(OMe)
(41)	OPr^i	OMe	NHMe	*S*		h(OMe)
(42)	OEt	R [d]	OMe	*R*	+1.6 (*c* 1.2)	
(42)	OEt	OMe	R [d]	*S*	−1.6 (*c* 3.6)	
(44)	NH_2	NMe_2	OMe	*S*	−28 (*c* 0.7) [h]	l(OMe), h(NMe_2)

[a] Solutions in chloroform. [b] The sense of magnetic non-equivalence is deemed 'h' (or l) for that enantiomer in which the relevant signal undergoes the least change (or most change) in chemical shift on addition of $Eu(hfc)_3$ (100 mg) to a solution of racemic phosphorus ester (30—40 mg) in deuteriochloroform (0.5 ml). [c] R = (−)-α-Methylbenzyl. [d] R = morpholino. [e] ^{1}H N.m.r. shows this sample to be *ca.* 97% of the major enantiomer. [f] 93% Major enantiomer. [g] Derived from starting material containing 85% major enantiomer. [h] 98% Major enantiomer.

The cyclic derivatives (2)—(5) and (7) were degraded to the chiral phosphoramidothioates (13)—(17) as shown in Scheme 1 (for examples in the 'a' series) by a reaction sequence which involved treatment of a single isomer with hydrogen chloride in methanol, basification with strong aqueous sodium hydroxide, and alkylation with an excess of methyl iodide. Usually the products from cleavage of the endocyclic P–N bond [*e.g.* (8)—(10)] were not isolated but converted directly by treatment with sodium hydroxide into mixtures of the aziridine (11) and phosphoramidothioic acids [general formula (12)]. The phosphorus derivatives (13)—(17) were isolated as the *O*-alkyl *S*-methyl phosphoramidothioates following alkylation with methyl iodide. By employing a similar reaction sequence but by promoting the endocyclic P–N bond cleavage in ethanolic rather than methanolic hydrogen chloride it was possible to prepare the ethoxy-derivatives (18)—(20) (Table 2). Yields

for the conversion of the 2-amino-1,3,2-oxazaphospholidine-2-thiones into *O*-alkyl *S*-methyl phosphoramidothioates were usually 50—70%.

The products [*e.g.* (8)—(10), Scheme 1] formed by cleaving the endocyclic P–N bond in acidic solution could be isolated as single isomers by extraction with chloroform of the reaction mixture immediately after basification with dilute sodium hydroxide. However if the reaction mixtures were basified with aqueous sodium carbonate, in some cases 3,4(*S*)-dimethyl-5(*R*)-phenyloxazolidin-2-one [5] was isolated in addition to the initial ring-cleaved product. The yields of the oxazolidin-2-one depended on the reaction time and nature of the groups attached to phosphorus.

If, as previously,[3,4] endocyclic P–N bond cleavage in the above 1,3,2-oxazaphospholidines occurs with inversion of configuration at phosphorus, and since subsequent steps in the degradative sequence do not affect the configuration at phosphorus, then the absolute configurations of compounds (13)—(20) are those in Table 2, where specific rotations are also listed. Thus syntheses starting from cyclic phosphoramidothioates in the 'a' series afforded acyclic alkyl *S*-alkyl phosphoramidothioates with the *R* configuration at phosphorus.

The ^{1}H n.m.r. method using the chiral shift reagent Eu(hfc)$_3$ for assessing the enantiomeric purity of phosphorus derivatives [3,6] was not always applicable to the alkyl *S*-alkyl phosphoramidothioates. For the dimethylamino-derivatives (13) and (19) and for the morpholino-derivatives (17) and (18) addition of Eu(hfc)$_3$ caused broadening of signals in both the ^{1}H spectra (at 60 and 100 MHz) and ^{31}P n.m.r. spectra. This behaviour, which was also observed for the *OO*-dialkyl *NN*-dialkyl-phosphoramidates (37) and (42), presumably results because the rate of equilibrium of europium complexed and uncomplexed substrate is such that sharp peaks are not attainable with the n.m.r. conditions employed. Evidence to show that (13) and (19) had a high degree of enantiomeric purity was provided by examination of the enantiomeric purity of some of their reaction products (see later).

The methylamino-derivative (14) was enantiomerically pure as shown by the n.m.r. technique but the enantiomeric purity of the amino-derivative (15) varied with the concentration of sodium hydroxide used during its preparation, ranging from 97% with very dilute base to almost complete racemisation with strong sodium hydroxide. Similar behaviour was observed for the ethoxy-derivative (20). Enantiomerically pure (20) was prepared as previously described.[4]

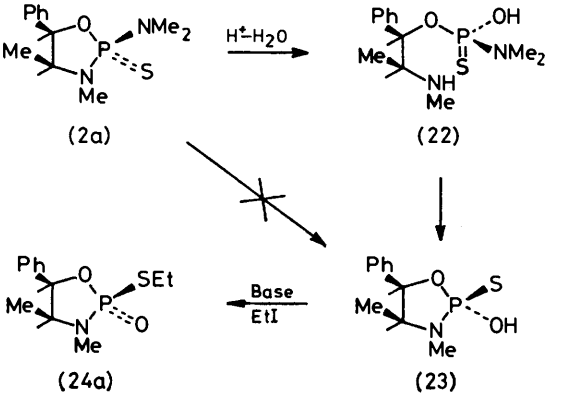
The diastereoisomer (16) was apparently a single isomer by reference to its n.m.r. spectrum. However the spectrum obtained varied with the concentration of (16) in $CDCl_3$. High concentrations (>15% w/v) and low concentrations (<5% w/v) gave distinct but different spectra. Intermediate concentration results in considerable line broadening. This behaviour presumably reflects the formation of hydrogen-bonded dimers.[7]

The variability in the enantiomeric purity of (15) as a function of the base concentration used in its preparation is undoubtedly the result of competing mechanisms. That predominant at low base concentration is probably as previously discussed,[3] *i.e.* base-catalysed attack of the amino-group in (10) at the benzylic carbon with concomitant formation of the *trans*-aziridine (11) and the thioacid salt (12*R*). As the base concentration increases direct nucleophilic attack of the hydroxide at phosphorus and displacement of ephedrine also occurs, producing the enantiomeric thioacid salt (12*S*). That this competition is only observed in the unsubstituted amino-compound reflects the known greater P–O bond lability in these systems compared with their *N*-substituted analogues.[7]

The cyclic thioamidates (2)—(5), like other similar compounds,[3] undergo endocyclic P–N bond cleavage on addition of sodium alkoxides with the same stereochemistry as the corresponding acid-catalysed reaction. Thus (3a) was converted into enantiomerically pure (14) by treatment with sodium methoxide followed by methyl iodide. In contrast (4a) afforded a mixture of *OO*-dimethyl phosphoramidothioate, $(MeO)_2PS{\cdot}NMe_2$, (21) (29%) and *OS*-dimethyl phosphoramidothioate (15) (24%). The latter product was a 3 : 2 mixture of (15*R*) and its enantiomer (15*S*). These results are also indicative of competition between C–O and P–O bond cleavage with attack of methoxide at phosphorus in (10) either resulting in (21) by displacement of ephedrine or in reducing the enantiomeric purity of (15) by methoxide exchange prior to C–O bond cleavage. In this case enantiomerically pure (15) also affords similar products, *i.e.* (15*R*), (15*S*), and (21) in the presence of sufficient methoxide.

The good yields of (13)—(20) obtained on treatment of (2)—(5) and (7) with acidic alcohol demonstrate that, as expected, endocyclic P–N bond cleavage is much preferred to the corresponding exocyclic cleavage. However, treatment of (2a) with aqueous hydrochloric acid followed by basification and alkylation with ethyl iodide gave the cyclic phosphoramidothioate (24a) (20%). The configuration of (24a) was confirmed by comparison of its ^{1}H n.m.r. with that of its epimer (24b), prepared, almost certainly with retention of configuration, by displacement of chloride from (1a) with hydroxide in the presence of the crown ether dicyclohexyl-18-crown-6. Direct cleavage of the exocyclic P–N bond in (2a) with inversion of configuration seems unlikely on energy considerations [8] and is supported by the fact that all other displacements of exocyclic substituents in similar systems occur with retention of configuration. Alternatively hydrolysis of (2a) to (22) (Scheme 2) which then re-cyclised by displacement of dimethylamine at phosphorus with inversion of configuration could afford (24a). If this were the case one might expect the yield of (24a) to increase as the acidic solution was stored for longer periods. In fact the yield steadily decreases, possibly due to slow acid-catalysed endocyclic P–N bond cleavage in (23).

Acidic Alcoholyses of OS-Dialkyl Phosphoramidothioates.—Most reported work on the mechanism of acid catalysed P–N bond cleavage has been with phosphinamidates, where the stereoselectivity has been shown to depend on the nature of the substituents at phosphorus and on the reaction conditions.[9–12] The results of these studies have been interpreted in terms of an *A*2 associative mechanism [11] to account for the observed inversion of configuration and in terms of an *A*1 dissociative mechanism [9,10] where significant racemisation was evident. Not all results are entirely consistent with this interpretation, the *A*1 dissociative route having been particularly questioned.[11,12] Recently Harger [12] has discussed, amongst other likely mechanisms, the possible importance of nucleophilic catalysis by the acid anion. Thus, uncatalysed reactions occur with inversion of configuration, whilst catalysed reactions occur with double inversion, *i.e.* overall retention of configuration. With phosphonoamidates and phosphoramidates there have been no



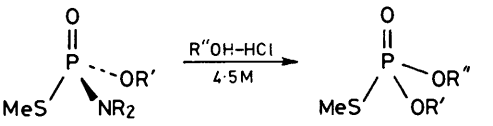
SCHEME 2

detailed studies and usually assumptions (probably correct in the cases reported) have been made that P–N bond cleavage occurs with inversion of configuration. However, doubts about the validity of this assumption were raised by preliminary results [13] on the stereochemistry of acid-catalysed P–N bond cleavage in *OS*-dialkyl phosphoramidothioates, which are more fully reported here. It now seems probable that the double-inversion mechanism may be of general importance for most types of P–N bond-breaking reactions.

The *OS*-dialkyl phosphoramidothioates (13), (14), (15), (19), and (20) were treated with an excess of a solution of anhydrous hydrogen chloride in ethanol, isopropyl alcohol, or methanol at room temperature and stored until no starting material remained. Following basification of the reaction mixtures with aqueous sodium carbonate the *OO*-dialkyl *S*-alkyl phosphorothioates (25)—(27) were isolated in high yields and their enantiomeric purity and the absolute configuration of the preponderant enantiomers was established by the ^{1}H n.m.r. method and by reference to authentic samples.[3] The stereochemical results are recorded in Table 3.

TABLE 3

Stereochemical outcome of the hydrogen chloride catalysed alcoholysis of phosphoramidothioates [a]

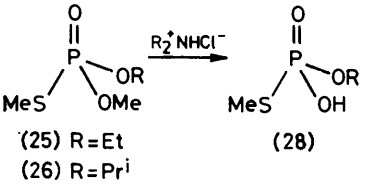


(25) R' = Me, R" = Et
(26) R' = Me, R" = Pr^i
(27) R' = Et, R" = Pr^i

	NR_2	R'	R"OH = MeOH	EtOH	Pr^{i}OH
(13)	NMe_2	Me		85% Rn	84% Rn
(14)	NHMe	Me		60% I	79% Rn
(15)	NH_2	Me		84% I	62% Rn
(19)	NMe_2	Et	70% I [b]		
(20)	NH_2	Et	97% I [c]		95% Rn [c]

[a] Results are calculated on the assumption that the starting materials are enantiomerically pure. Rn = Retention of configuration, I = Inversion of configuration. [b] Similar reactions in 1M and 0.1M acid gave 95% and 100% inversion respectively. [c] 2.5M-Acid.

Although absolute rate constants were not measured, qualitatively for reactions with 4.5M hydrogen chloride in ethanol the rates were (13; NMe_2) ≫ (14; NHMe) > (15; NH_2); the half life for (13) was *ca.* 5 min and for (15) was *ca.* 2—3 days. The rate for (16) was very slow indeed. The only other significant reaction products were the acids (28) which were shown to be formed by dealkylation of the product phosphorothioates (25) and (26) by amine hydrochloride present in the reaction mixture (Scheme 3). Quenching of the



SCHEME 3

reaction before completion permitted the recovery of starting material of unchanged enantiomeric purity and configuration. The effect of changes in acid concentration on product stereochemistry were examined using the phosphoramidothioates (13) and (14). The results are reported in Table 4.

The unexpected variations in the stereochemical outcome with apparently minor changes in nucleophile,

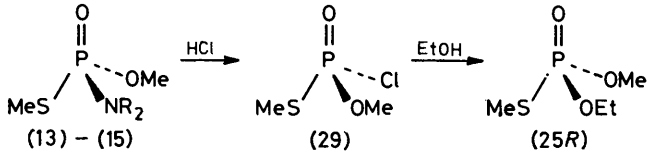
TABLE 4

Effect of changes in hydrogen chloride concentration on the stereochemical outcome of P–N bond cleavage

Alcohol	EtOH			Pr^{i}OH		
Acid concentration	0.1M	1M	4.5M	1M	4.5M	7M
(13) NMe_2	90% I	70% I	85% Rn		84% Rn	
(14) NHMe	96% I	85% I	60% I	79% Rn	79% Rn	75% Rn

Rn = Retention, I = Inversion.

e.g. P–N cleavage in (14) and (15) changes from predominant inversion of configuration for an ethanol nucleophile to predominant retention for isopropyl alcohol nucleophile, and with the nature of the leaving group, *e.g.* for an ethanol nucleophile (14) and (15) react

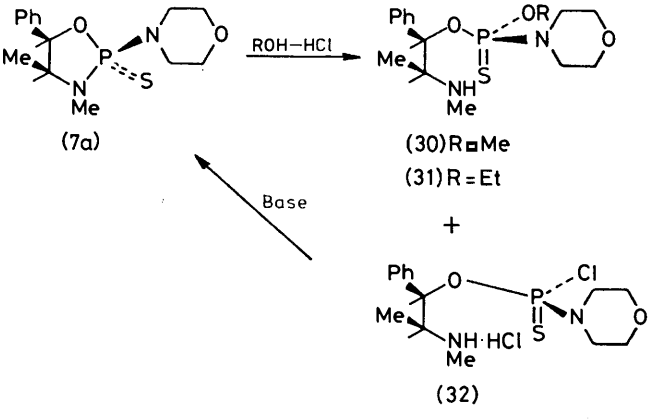


SCHEME 4

with predominant inversion but (13) reacts with predominant retention, are most conveniently explained in terms of two competing mechanisms. (i) An inversion process, probably occurring by direct displacement of the protonated leaving group (*A*2 type) by the alcohol. (ii) A retention process, probably involving direct displacement of the protonated leaving group by chloride ion (with inversion) followed by a similar displacement of the chloride by alcohol (Scheme 4). The two major factors which affect the competition between chloride and alcohol as a nucleophile in these systems appear to be as follows. (a) A steric factor. Chloride apparently always competes favourably with isopropyl alcohol but for equal acid strengths chloride only competes favourably with ethanol in displacement of the relatively bulky dimethylamino-leaving group. As the leaving group size decreases so inversion becomes the preponderant reaction. In neither of the examples examined does chloride compete favourably with methanol (Table 3). (b) A concentration factor. As the acid concentration (and thus the relative concentration of chloride to alcohol) is reduced so reactions with an ethanol nucleophile at least become increasingly stereoselective with inversion (Table 4). This trend is most pronounced for (13) where the overall stereochemistry changes from 85% retention for a 4.5M-acid solution to 90% inversion for a 0.1M-solution. Apparently the steric factor is dominant since relatively large changes in acid concentration have very little effect on the outcome of reaction in isopropyl alcohol. The overriding importance of the steric size and/or 'nucleophilicity' of the alcohol compared with the steric bulk of the substrate is illustrated by the preponderant inversion observed for displacement of dimethylamino from (19) by methanol, but preponderant retention observed for the similar displacement from (13) by ethanol. Also noteworthy is the high stereoselectivity and the almost complete reversal in the stereochemical outcome of the reaction of (20) in methanol and isopropyl alcohol (Table 3). Previous results obtained for similar reactions such as: the formation of *OO*-dialkyl phosphorochlorothioates from *OO*-dialkyl phosphoramidothioates and hydrogen chloride in isopropyl alcohol, in contrast to the observed thiophosphate formation with less bulky alcohols,[4] the stability of certain phosphinamidate hydrochlorides,[11] the observed rate increases in the acid-catalysed hydrolysis of phosphinamidates as the size of the groups at phosphorus is reduced[14] and the lack of P–N bond cleavage when cholesteryl phosphorodimorpholides are treated with aqueous acid,[15] are consistent with the proposed high steric requirement of this type of reaction. Presumably the lack of reaction of (16) can also be attributed to this fact, although the changes in relative rates for (13)—(15) are more likely a consequence of the relative basicity of the amine groups.

Further evidence for the involvement of chloride ion in this type of reaction was obtained when (13) and (15) were treated with a dilute solution of anhydrous hydrogen chloride in benzene. In both cases the chloridate (29) in a *ca.* 7 : 3 ratio of enantiomers (29*R*) to (29*S*) was isolated. If the acidic solution was stored for six days before processing only racemic (29) resulted. When (13) was first treated with anhydrous hydrogen chloride in benzene until no starting material remained then ethanol was added to the acidic solution, the result was formation of the phosphorothioate (25) with *ca.* 81% retention of configuration. Likewise (15) gave the phosphorothioate (25) with *ca.* 70% retention, almost the reverse of the *ca.* 84% inversion of configuration observed when the same reaction was carried out in hydrogen chloride and ethanol alone. The loss in stereospecificity in these reactions can most likely be attributed to halide exchange with inversion in the acidic benzene solutions, although mechanisms involving permutational isomerisation of trigonal bipyramidal intermediates cannot be excluded.

That chloride also competes with alcohol as a nucleophile in the acid-catalysed endocyclic P–N bond cleavage of the 1,3,2-oxazaphospholidine-2-thiones was particularly evident for the morpholino-derivative (7a). Treatment of (7a) with a 4.5M-solution of hydrogen chloride in methanol afforded only the expected acyclic system (30) (Scheme 5). Similar treatment with



SCHEME 5

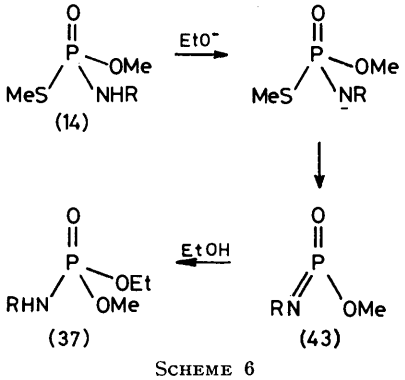
hydrogen chloride in ethanol led to *ca.* 90% of the acyclic system (31) and *ca.* 10% of recovered starting material of unchanged configuration. Treatment of (7a) with hydrogen chloride in isopropyl alcohol or benzene solution resulted only in the recovery of un-

changed starting material, even though t.l.c. of the acidic solutions showed no (7a) present. Purging of such an acidic solution with nitrogen followed by addition of light petroleum led to the precipitation of P–N bond-cleaved product (32). Treatment of a solution of (32) with either sodium hydroxide or methoxide resulted in a high yield of recovered (7a). [There was no evidence for the epimeric (7b)]. Compound (32) was recovered unchanged after being allowed to stand in acidic methanol for one day. These results suggest that although intramolecular displacement of chloride, with inversion of configuration, from (32) by the free amine group is fast and stereospecific, neither halide exchange nor displacement of halide by alkoxide is competitive for the free base, or significant in its hydrochloride salt.

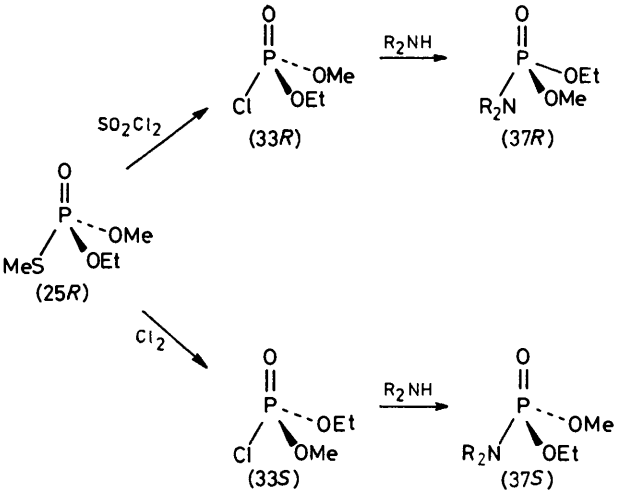
The results from the acid-catalysed alcoholyses in Tables 3 and 4 provide evidence of the high enantiomeric purity of the dimethylamino-derivatives (13) and (19) that was not directly available by examination of these compounds by the n.m.r. technique. Thus in 0.1M-methanolic HCl, (19) afforded (25*S*), which was enantiomerically pure by the n.m.r. method. Similarly the result of treating (13) with 0.1M-ethanolic HCl gave (25) which was 90% of the *R* isomer. There is no reason to suppose other than that (13) was enantiomerically pure and that loss of purity occurred during the alcoholyses.

All the reported acid-catalysed alcoholyses were extremely moisture sensitive, small amounts of water resulting in major percentages of aqueous hydrolysis. Thus attempted alcoholyses which involved the addition of concentrated sulphuric acid to ethanolic solutions of phosphoramidothioates led to predominant hydrolysis. Attempts to use trifluoroacetic or toluene-*p*-sulphonic acids as catalysts were generally unsuccessful.

Basic Alcoholyses of OS-*Dialkyl Phosphoramidothioates.* The rates of basic hydrolysis of *OS*-dialkyl phosphoramidothioates vary considerably depending on the degree of substitution at nitrogen. Thus amino-derivatives are more labile in base than alkylamino-derivatives; dialkylamino-derivatives are hydrolysed very slowly indeed.[16] To account for these differences in hydrolysis rates, and similar differences in related compounds, an *E*1cB mechanism involving a metaphosphorimidate intermediate has been considered to play a key role in the hydrolysis of amino- and alkyl-



SCHEME 6



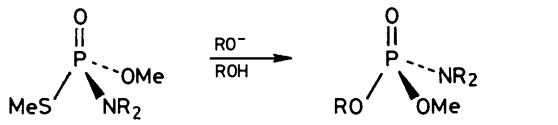
SCHEME 7

amino-derivatives (Scheme 6).[17] Such a route is not open to dialkylamino-derivatives which hydrolyse primarily by attack of hydroxide at phosphorus. Despite many attempts, the reaction mechanisms for the hydrolysis of phosphoramidothioates have not been unequivocally established and indeed recent results have been interpreted as indicating that the *E*1cB process is relatively unimportant.[18] Stereochemical studies have been inconclusive because of the lack of suitable chiral compounds although in one study [19] the fact that the product from the hydrolysis of an optically active phosphoramidothionate is also optically active was considered contrary to the *E*1cB mechanism.

Recent studies in this laboratory in which the chiral phosphoramidothioates (13) to (16) were treated with sodium ethoxide showed that non-racemic *OO*-dialkyl phosphoramidates were formed. It was not possible, however, to assign the stereochemistry of the reaction because the absolute configuration of the products was not known. This has now been established by a series of reactions reported previously.[4] Briefly (Scheme 7), treatment of the phosphorothioate (25*R*) with sulphuryl chloride afforded the phosphorochloridate (33*R*) formed with retention of configuration, whereas similar treatment with chlorine gave the enantiomeric phosphorochloridate (33*S*) formed with inversion. Displacement of chloride from (33*R*) and (33*S*) almost certainly occurs with inversion of configuration to form the phosphoramidates (37*R*) and (37*S*) respectively.

The qualitative rates for the reaction of phosphoramidothioates with ethoxide are in the order (15; NH_2) > (14; NHMe)⋙ (13; NMe_2). In fact the rate for (13) is too slow to be studied conveniently. In each case displacement of SR by alkoxide occurs with 78—90% inversion of configuration (Table 5). This is similar to the *ca.* 80% observed inversion of configuration for the displacement of SR from phosphonothioates by alkoxide,[3] but contrary to the almost stereospecific retention of configuration observed for similar displacements from phosphorothioates.[3] The

TABLE 5



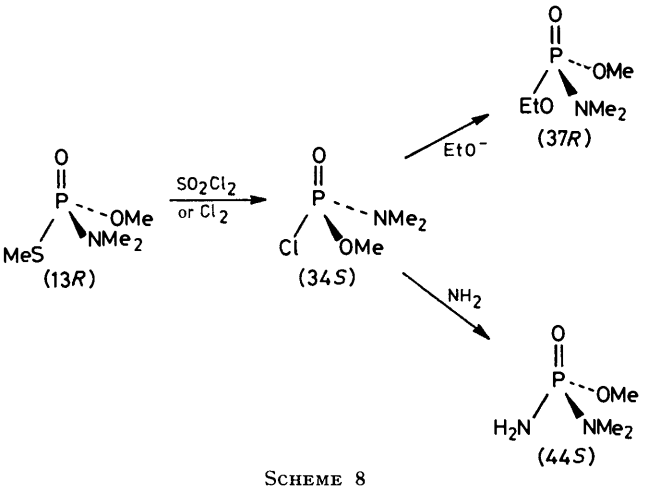
Starting material	NR_2	R	Product	Reaction stereochemistry percentage inversion
(13)	NMe	Et	No reaction	
(14)	NHMe	Et	(38)	87
(15)	NH_2	Et	(39)	82
(16)	NHR *	Et	(40)	78
(14)	NHMe	Pr^i	(41)	90

yield of phosphoramidate from (14) and (16) was essentially quantitative but when (15) was treated with one equivalent of ethoxide, (39) was formed in only 30% yield, the major product being *OO*-diethyl phosphoramidate. Control experiments showed that this could be formed from the reaction of the primary product (39) with ethoxide. Alternatively a mechanistic pathway involving P–O bond cleavage in the initial phosphoramido-thioate could be involved.[16]

The preponderant inversion of configuration observed for these base-catalysed P–N bond cleavage reactions is not consistent with a mechanism involving discrete planar metaphosphorimidate intermediates (43), since these would be expected to yield racemic products. It is possible however that intermediates such as (43) (Scheme 6) are not planar, or that there is an intimate directional reaction between (43) and the solvent and/or leaving group which specifically directs the nucleophile. Alternatively the rate enhancement observed for the basic hydrolysis of systems containing at least one proton on nitrogen may result from some preferential proton transfer from nitrogen to the leaving group. This, if the reaction occurs by way of a trigonal bipyramidal intermediate it may be facilitated by the known preferential orientation of the PNR_2 group in stable phosphoranes, *i.e.* with the nitrogen substituents in the same plane as the apical groups [20] (which includes the leaving group).

Other Displacement Reactions.—Unlike the reversal in observed stereochemistry when the phosphorochloridate (33) is formed from the phosphorothioate (25) by treatment with sulphuryl chloride and with chlorine (Scheme 7), the corresponding reactions of phosphoramidothioates to generate the phosphoramidochloridate (34) both occur with the same stereochemistry (Scheme 8). Since the displacement of chloride from (34*S*) by ethoxide is likely to occur with inversion of configuration and since the absolute configuration of the resulting phosphoramidate (37*R*) is already known [4] (Scheme 7), then both the chlorination reactions must occur with inversion of configuration. This fact is supported by the ^{1}H n.m.r. spectrum of (34*S*) in the presence of $Eu(hfc)_3$.[3] ^{1}H N.m.r. results also support the assumption that displacement of halide from (34*S*) by ammonia to form (44*S*) occurs with inversion of configuration.

As has been demonstrated for both phosphono- and phosphoro-thioates,[3] silver-nitrate-catalysed P–S bond cleavage in phosphoramidothioates by alcohols proceeds with predominant inversion of configuration. Thus, treatment of (14) with silver nitrate and ethanol led to a product containing a *ca.* 3 : 1 ratio of the phosphoramidates (37*S*) : (37*R*).



SCHEME 8

EXPERIMENTAL

Details of the preparation of each compound are not given, but examples of each type of compound are reported. ^{1}H N.m.r. spectra were measured with a JEOL JNM-MH-100 spectrometer at 100 MHz or a Perkin-Elmer R-24A at 60 MHz, with deuteriochloroform as solvent and tetramethylsilane as internal standard. The enantiomeric purity of chiral phosphorus compounds was determined by the previously described n.m.r. method at 60 MHz, using the chiral shift reagent $Eu(hfc)_3$.[3] Unless otherwise stated chiral compounds were enantiomerically pure. Optical rotations were measured in chloroform (path length 1 dm). Small-scale distillations were carried out under reduced pressure with a Kugelrohr oven; temperatures quoted are the bath temperatures at which distillation commenced. Column chromatography was performed with Merck silica gel of particle size 0.05—0.2 mm. All air- or moisture-sensitive reactions were carried out under an atmosphere of dry, oxygen-free, nitrogen. Solutions were dried over $MgSO_4$; light petroleum refers to the fraction of b.p. 60—80 °C.

(2R,4S,5R)- *and* (2S,4S,5R)-2-*Amino*-3,4-*dimethyl*-5-*phenyl*-1,3,2-*oxazaphospholidine*-2-*thiones*.—In each case a solution in benzene of the relevant chloridate, (1a) or (1b),[3] was treated with an excess of the required amine. On completion of the reaction (1—5 h) the solution was filtered, washed with water, dried, and concentrated. A ^{1}H n.m.r. spectrum of the crude material showed in each case only a single isomer. The products were purified by column chromatography and/or crystallisation. The following were obtained: (2R,4S,5R)-2-*dimethylamino*-3,4-*dimethyl*-5-*phenyl*-1,3,2-*oxazaphospholidine*-2-*thione* (2a) (93%) as a clear oil, R_F 0.3 (benzene), b.p. 130 °C (bath) at 0.1 mmHg, (2S,4S,5R)-2-*dimethylamino*-3,4-*dimethyl*-5-*phenyl*-1,3,2-*oxazaphospholidine*-2-*thione* (2b) (66%) as a low-melting-point white solid, R_F 0.3 (benzene) (Found: C, 53.3; H,

7.2; N, 10.2. $C_{12}H_{19}N_2OPS$ requires C, 53.3; H, 7.0; N, 10.4%); (2R,4S,5R)-2-*methylamino*-3,4-*dimethyl*-5-*phenyl*-1,3,2-*oxazaphospholidine*-2-*thione* (3a) (98%), m.p. 156—157 °C (from di-isopropyl ether–chloroform) (Found: C, 51.5; H, 6.7; N, 10.9. $C_{11}H_{17}N_2OPS$ requires C, 51.6; H, 6.6; N, 10.9%); (2S,4S,5R)-2-*methylamino*-3,4-*dimethyl*-5-*phenyl*-1,3,2-*oxazaphospholidine*-2-*thione* (3b) (68%), m.p. 119—120 °C; (2R,4S,5R)-2-*amino*-3,4-*dimethyl*-5-*phenyl*-1,3,2-*oxazaphospholidine*-2-*thione* (4a) (90%), m.p. 107—108 °C (from di-isopropyl ether), R_F 0.4 (acetone–benzene, 1 : 19) (Found: C, 49.7; H, 6.3; N, 11.8. $C_{10}H_{15}N_2OPS$ requires C, 49.6; H, 6.2; N, 11.6%); (2S,4S,5R)-2-*amino*-3,4-*dimethyl*-5-*phenyl*-1,3,2-*oxazaphospholidine*-2-*thione* (4b) (70%), m.p. 125—127 °C, R_F 0.35 (acetone–benzene, 1 : 19) (Found: C, 49.6; H, 6.3; N, 11.8%); (2R,4S,5R)-2-(−)-α-*methylbenzylamino*-3,4-*dimethyl*-5-*phenyl*-1,3,2-*oxazaphospholidine*-2-*thione* (5a) (34%), m.p. 141 °C (from di-isopropyl ether–chloroform) (Found: C, 62.6; H, 6.4; N, 8.3. $C_{18}H_{23}N_2OPS$ requires C, 62.4; H, 6.6; N, 8.1%); (2R,4S,5R)-2-*morpholino*-3,4-*dimethyl*-5-*phenyl*-1,3,2-*oxazaphospholidine*-2-*thione* (7a) (80%), m.p. 143—144 °C (from di-isopropyl ether), R_F 0.3 (acetone–light petroleum, 1 : 9) (Found: C, 53.8; H, 6.7; N, 8.9. $C_{14}H_{21}N_2O_2PS$ requires C, 53.9; H, 6.7; N, 9.0%). Treatment of (1a) with an excess of imidazole led to a 7 : 1 mixture of isomers. Chromatography gave the major, more mobile product; (2S,4S,5R)-2-*imidazolyl*-3,4-*dimethyl*-5-*phenyl*-1,3,2-*oxazaphospholidine*-2-*thione* (6a) (30%) as a clear oil, R_F 0.6 (benzene–acetone–methanol, 8 : 1 : 1).

Acid-catalysed Endocyclic P–N *Bond-cleavage in* 2-*Substituted* 1,3,2-*Oxazaphospholidine*-2-*thiones*.—A solution of anhydrous hydrogen chloride in methanol (1N; 15 ml) was added slowly to a solution of (2a) (0.35 g) in methanol (5 ml). After 1 h excess of dilute aqueous sodium hydroxide solution was added and the mixture extracted with chloroform. The organic phase was dried and concentrated. ^{1}H N.m.r. of the crude product (0.32 g) showed a single isomer of the P–N bond-cleaved product (8), δ 1.00 (3 H, d), 2.40 (3 H, s), 2.73 (6 H, d), 3.33 (3 H, d) and 5.44 (1 H, dd). Likewise (3a) gave (9), δ 1.01 (3 H, d), 2.46 (3 H, s), 2.62 (3 H, d), 3.48 (3 H, d) and 5.50 (1 H, dd), (4a) gave (10), δ 1.01 (3 H, d), 2.50 (3 H, s), 3.55 (3 H, d) and 5.56 (1 H, dd), and (7a) gave (30), δ 1.02 (3 H, d), 2.23 (3 H, s), 3.40 (3 H, d), and 5.46 (1 H, dd), and (31), δ 2.42 (3 H, s) and 5.44 (1 H, dd), and after a non-basic work-up (see text) (7a) gave (32) which gave very broad n.m.r. signals at both 60 and 100 MHz δ 1.47 (3 H), 6.07 (1 H), 7.44 (5 H). In some preparative runs when sodium carbonate was used to neutralise the excess of acid, varying amounts of a second major product, 3,4(*S*)-dimethyl-5(*R*)-phenyloxazolidin-2-one were isolated by column chromatography, R_F 0.8 (benzene–acetone–methanol, 8 : 1 : 1), δ 1.38 (3 H, d, J = 6.1 Hz), 2.88 (3 H, s), 3.56 (1 H, dq), and 4.93 (1 H, d, J = 7.8 Hz).[5]

Base-catalysed Endocyclic P–N *Bond Cleavage in* 2-*Substituted* 1,3,2-*Oxazaphospholidine*-2-*thiones*.—A solution of sodium (0.05 g) in methanol (5 ml) was slowly added to a solution of (3a) (0.25 g) in methanol (5 ml) and the mixture was stored for three days. Excess of methyl iodide was added and the solution was stirred for 1 h, then poured into water, and extracted with chloroform. The organic phase was dried, concentrated, and chromatographed to give (14) (0.08 g, 53%).

A similar treatment of (4a) with methoxide yielded *OO*-dimethyl phosphoramidothioate (0.3 g, 29%) and *OS*-dimethyl phosphoramidothioate (15) (0.25 g, 24%). ^{1}H N.m.r. spectroscopy in the presence of the chiral shift reagent Eu(hfc)$_3$ showed this to be a 3 : 2 mixture of (15*R*) and (15*S*).

Isolation of OS-*Dialkyl Phosphoramidothioates*.—All the acyclic chiral phosphoramidothioates were prepared from the precursors listed in Table 1 by the following general procedure illustrated for the formation of (+)-(*R*)-*OS*-dimethyl *NN*-dimethylphosphoramidothioate (13) from (2a).

A solution of anhydrous hydrogen chloride in methanol (3M; 5 ml) was added to a solution of (2a) (1 g) in methanol (5 ml) and the mixture was stirred for 1 h. The solution was then made basic (to *ca.* pH 12) by the careful addition of concentrated aqueous sodium hydroxide, and stored overnight. The solution was poured into water and extracted three times with ether. The ether was discarded. An excess of methyl iodide (4 ml) was added to the aqueous phase; the solution was stirred for 1 h and then extracted three times with chloroform. The combined organic extracts were dried and concentrated and the residue chromatographed to give (13) (0.4 g, 64%), R_F 0.6 (benzene–acetone–methanol, 8 : 1 : 1).

During the preparation of (15) and (20) a more dilute solution of sodium hydroxide was used to basify the reaction. Extraction of the crude alkylated product from aqueous solution was in this case continuous.

The ^{1}H n.m.r. spectrum of (16) varied with the concentration. At high (>15% w/v) concentration (associated form) δ 1.46 (3 H, d), 0.95 (3 H, d), 3.63 (3 H, d), and 4.40 (1 H, m). At low (<5% w/v) concentrations (unassociated form) δ 1.52 (3 H, d), 2.10 (3 H, d), 3.72 (3 H, d), and 4.47 (1 H, m).

(2S,4S,5R)-2-*Ethylthio*-3,4-*dimethyl*-5-*phenyl*-1,3,2-*oxazaphospholidin*-2-*one* (24b).—A mixture of dicyclohexyl-18-crown-6 (0.2 g), finely ground sodium hydroxide (0.2 g), and (1a) (0.3 g) in benzene (10 ml) was boiled under reflux for 1 h and then allowed to cool. An excess of ethyl iodide was added and the mixture was stirred for ½ h and then poured into water and extracted with benzene. The organic phase was dried, concentrated, and the residue chromatographed to give (24b) (0.13 g, 42%) as a clear oil, R_F 0.75 (benzene–acetone–methanol, 8 : 1 : 1), δ 0.93 (3 H, d, J = 6.2 Hz), 2.72 (3 H, d, J = 11 Hz), 3.59 (1 H, ddq, J = 6.2, 6.2, and 15.6 Hz), and 5.46 (1 H, dd, J = 6.1 and 3.7 Hz).

Exocyclic P–N *Bond Cleavage in* 2-*Substituted*-1,3,2-*oxazaphospholidine*-2-*thiones* (*Scheme* 2).—A solution of (2a) (0.4 g) in a mixture of acetone (20 ml), water (5 ml), and concentrated hydrochloric acid (7 ml) was stored for ½ h. The mixture was made basic with sodium hydroxide and then an excess of ethyl iodide was added. After ½ h it was poured into water and extracted with chlofororm. The organic phase was dried, concentrated, and the residue chromatographed to give (2a) (0.1 g, 32%), R_F 0.7, δ 0.70 (3 H, d, J = 6.5 Hz), 2.75 (3 H, d, J = 11.5 Hz), 3.73 (1 H, ddq, J = 6, 6.5 and 17.5 Hz), and 5.74 (1 H, d, J = 6 Hz). As the original acidic solution was stored for progressively longer periods before being basified, so the yield of (24a) gradually dropped.

Displacement of Imidazole from (6a).—Methylamine gas was bubbled through a solution of (6a) (0.11 g) in tetrahydrofuran (5 ml) for 3 h. The solution was then poured into water and extracted with benzene. The organic phase was dried, concentrated, and chromatographed to give (3a) (0.09 g, 94%).

Cleavage of P–S *Bonds with Alkoxides*.—As an example, a solution of sodium (0.02 g) in ethanol (5 ml) was slowly added to a solution of *O*-methyl *S*-methyl *N*-methylphosphoramidothioate (14) (0.1 g) in ethanol (5 ml). After 3 h an excess of solid carbon dioxide was added. The solution was filtered, concentrated, and the residue chromatographed to give the phosphoramidate (38S) (0.08 g, 80%), R_F 0.4 (benzene–acetone–methanol, 8 : 1 : 1). ^{1}H N.m.r. spectroscopy in the presence of Eu(hfc)$_3$ showed the product to contain *ca.* 13% of its enantiomer (38*R*).

Similar treatment of a solution of (15) with one equivalent of sodium ethoxide gave *OO*-diethyl phosphoramidate (60%) and *O*-ethyl *O*-methyl phosphoramidate (39S) (30%). ^{1}H N.m.r. spectroscopy in the presence of Eu(hfc)$_3$ showed this to contain *ca.* 18% of its enantiomer (39*R*).

Similar treatment of a solution of *OO*-diethyl phosphoramidate with one equivalent of sodium methoxide in methanol led to recovered starting material (67%) and (39) (33%).

Cleavage of P–S *Bonds with Silver Nitrate and Alcohol*.—A solution of silver nitrate (1 g) in ethanol–acetonitrile (3 : 1) (20 ml) was added to a solution of (14) (0.4 g) in ethanol (5 ml) and triethylamine (1.5 ml). The mixture was stored in the dark for 60 h and then an excess of ether was added. The solution was filtered, concentrated, and the residue chromatographed to give (37*S*) (0.25 g, 64%). ^{1}H N.m.r. spectroscopy in the presence of Eu(hfc)$_3$ showed the product to contain *ca.* 25% of its enantiomer (37*R*).

Acid-catalysed P–N *Bond Alcoholyses in* OS-*Dialkyl Phosphoramidothioates*.—As an example a solution of (14) (0.45 g) in 4.5M-hydrogen chloride–ethanol (15 ml) was stored overnight and then poured into dilute sodium carbonate solution and extracted with chloroform. The organic phase was dried, concentrated, and the residue chromatographed to give (25*S*) (0.37 g, 75%). ^{1}H N.m.r. spectroscopy in the presence of Eu(hfc)$_3$ showed the product to contain *ca.* 40% of its enantiomer (25*R*). The aqueous phase was made acidic with hydrochloric acid and extracted repeatedly with chloroform. The combined extracts were dried and concentrated to give *O*-ethyl *S*-methyl phosphorothioate (28) (0.07 g, 15%).

Quenching of the reaction before completion led to the recovery of starting material of unchanged configuration and optical purity.

A solution of the phosphorothioate (26) (0.1 g) in isopropyl alcohol (5 ml) and methylamine (0.5 g) was made acidic by the addition of a solution of hydrogen chloride in isopropyl alcohol and stored for 3 days. The mixture was poured into dilute sodium carbonate solution and washed with chloroform. The aqueous phase was acidified and repeatedly extracted with chloroform. The combined extracts were dried and concentrated to give *O*-isopropyl *S*-methyl phosphorothioate (0.05 g, 56%).

OS-*Dimethyl Phosphorothiochloridate* (29).—Anhydrous hydrogen chloride was bubbled through a solution of the phosphoramidothioate (13) (0.4 g) in benzene (40 ml) for 1 h. The solution was purged with nitrogen for a further 1 h, filtered and concentrated to give (29*R*) (0.35 g, 92%). ^{1}H N.m.r. in the presence of Eu(hfc)$_3$ showed the product to contain *ca.* 32% of its enantiomer (29*S*).

A similar ratio of enantiomers, (29*R*) : (29*S*) *ca.* 7 : 3, was obtained when (15) was the starting material.

If the acidic solution of (13) was stored for 6 days before being worked-up completely racemic (29) resulted; δ 2.47 (3 H, d, J = 19 Hz), 3.92 (3 H, d, J = 15 Hz).

Treatment of (29) *with Acidic Alcohol*.—As an example; anhydrous hydrogen chloride was bubbled through a solution of the phosphoramidothioate (13) (0.15 g) in benzene (25 ml) for 1 h. An excess of ethanol was added and the mixture was stored for ½ h, and then poured into dilute sodium carbonate solution and extracted with chloroform. The organic phase was dried, concentrated, and the residue distilled to give (25*R*) (0.1 g, 66%). ^{1}H N.m.r. spectroscopy in the presence of Eu(hfc)$_3$ showed the product to contain *ca.* 19% of its enantiomer (25*S*).

Likewise treatment of the phosphoramidothioate (15) with hydrogen chloride–benzene and ethanol gave (25*R*) (42%) which ^{1}H n.m.r. spectroscopy in the presence of Eu(hfc)$_3$ showed to contain *ca.* 30% of its enantiomer (25*S*).

O-*Methyl* NN-*Dimethylphosphoramidochloridate* (34).—A solution of freshly distilled sulphuryl chloride (0.22 ml) in benzene (15 ml) was slowly added to an ice-cooled solution of the phosphoramidothioate (13) (0.45 g) in benzene (25 ml) and the mixture was stored for 1 h; it was then concencentrated and distilled at 85 °C/9 mmHg to give (34*S*) (0.3 g, 71%). ^{1}H N.m.r. spectroscopy in the presence of Eu(hfc)$_3$ showed the product to contain *ca.* 7% of its enantiomer (34*R*).

A solution of chlorine in carbon tetrachloride (1.5 ml; 0.088 g ml^{-1}) was slowly added to a solution of the phosphoramidothioate (13) (0.3 g) in carbon tetrachloride (10 ml). The mixture was stored for ½ h and then concentrated and distilled to give (34*S*) (0.22 g, 79%), R_F 0.8 (benzene–acetone–methanol, 8 : 1 : 1).

O-*Ethyl* O-*Methyl* NN-*Dimethylphosphoramidate* (37).—A solution of sodium (0.025 g) in ethanol (1 ml) was slowly added to a solution of (34*S*) (0.18 g) in ethanol (5 ml). The mixture was stirred for ½ h, and then poured into water and extracted with chloroform. The organic phase was dried, concentrated, and the residue distilled at 85 °C/9 mmHg to give (37*R*) (0.17 g, 89%) as a clear oil, R_F 0.4 (benzene–acetone–methanol, 8 : 1 : 1).

The sample (37*S*) quoted in Table 2 was prepared according to Scheme 7.[4] ^{1}H N.m.r. spectroscopy showed the starting material to be a mixture of (33*S*) and (33*R*) in a ratio of *ca.* 85 : 15.

O-*Methyl* NN-*Dimethylphosphorodiamidate* (44).—Ammonia gas was bubbled through a solution of (34*S*) (0.18 g) in benzene (20 ml) for 5 h. The solution was purged with nitrogen, filtered, concentrated, and the residue chromatographed to give (44*S*) (0.12 g, 76%) as a clear oil, R_F 0.2 (benzene–acetone–methanol, 8 : 1 : 1), δ 2.68 (6 H, d, J = 11 Hz) and 3.62 (3 H, d, J = 10 Hz).

[8/1287 *Received*, 10*th July*, 1978]

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