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THE PREPARATION AND ABSOLUTE CONFIGURATION OF SOME CHIRAL O,S-DIALKYL PHOSPHORAMIDOTHIOATES

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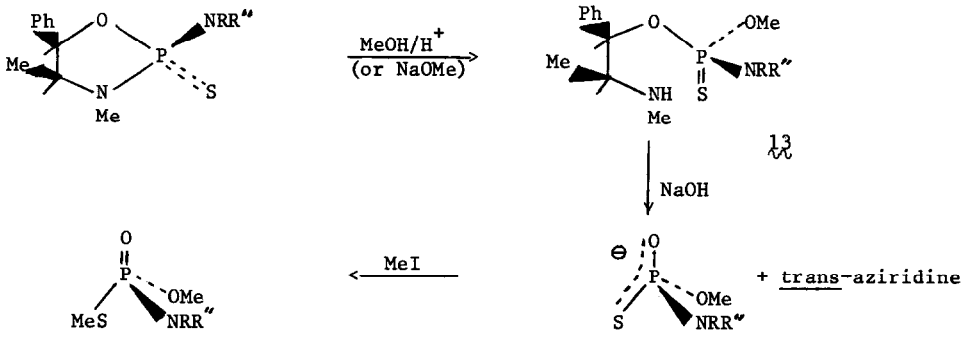
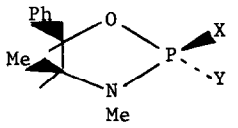
Phosphoramidothioates are of biological interest because of their insecticidal properties.[1] Chemically, such compounds merit detailed study because the P-O, P-S and P-N bonds may all be broken under mild conditions, the preponderant reaction depending critically on the reaction conditions employed.[2] To facilitate studies attempting to relate chemical and biological properties of phosphoramidothioates a series of chiral O,S-dialkyl phosphoramidothioates was required.[3] In this paper are described the preparations of such compounds by a stereospecific route which allows assignment of their absolute configurations.

The key synthetic intermediates, the 2-chloro-1,3,2-oxazaphospholidine-2-ones (1a and 1b in Table 1) from (-)-ephedrine,[4] afforded the amidates 2a and 2b respectively, on treatment with dimethylamine in benzene. The p.m.r. spectra of 2a and 2b were consistent with the assigned structures (e.g. H-4 and H-5 in 2a were at lower field than in 2b because of deshielding caused by their cis-relationship to phosphoryl oxygen) showing that dimethylamine like non-nitrogen nucleophiles[5] displaces chlorine with retention of configuration from 1,3,2-oxazaphospholidine-2-ones. By analogy the thiochloridates 3a and 3b afforded the pairs of isomers 4a and 4b, 5a and 5b, 6a and 6b and 7a and 7b on treatment with the appropriate amine. The 2-(alkyl)amino-1,3,2-oxazaphospholidine-2-thiones 4a, 5a, 6a and 7a were converted as illustrated in Scheme 1 into the chiral methyl S-methyl phosphoramidothioates 8, 9, 10 and 11 (Table 2).



Scheme 1

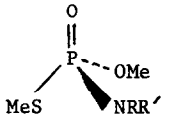
Table 1. P.m.r. and Optical Rotation Parameters for 2-substituted 1,3,2-oxazaphospholidine-2-ones and thiones.



	X	Y	δ H-4	δ H-5	J(Hz) P,H-4	J(Hz) P,H-5	$[\alpha]_D$
1a	Cl	O	3.85	5.84	26	∿ 1	- 64°
1b	O	Cl	3.70	5.54	14	7	- 26°
2a	NMe_2	O	3.60	5.68	9.5	< 1	-104°
2b	O	NMe_2	3.62	5.46	-	3.5	-
3a	Cl	S	3.85	5.81	29.5	1	-121°
3b	S	Cl	3.73	5.59	13	6.5	- 23°
4a	NMe_2	S	3.52	5.67	-	< 1	-147°
4b	S	NMe_2	3.76	5.60	22.5	< 1	+ 13.5°
5a	NHMe	S	3.57	5.65	9	2	-130°
5b	S	NHMe	3.71	5.56	22.5	< 1	+ 5°
6a	NH_2	S	3.56	5.54	10	4	- 83°
6b	S	NH_2	3.63	5.52	21.5	1.5	- 36°
7a	NHR*	S	3.51	5.57	9.5	< 1	-152°
7b	S	NHR*	-	5.66	-	1	-
12a	SEt	O	3.73	5.74	17.5	< 1	- 66°
12b	O	SEt	3.59	5.46	15.5	4	-

P.m.r. spectra were measured at 60 MHz in deuteriochloroform. R* = 1-(-)-α-methylbenzylamine.

Table 2. Acyclic Phosphoramidothioates.



	R	R′	Precursor	Yield %	M.p.°	$[\alpha]_D$
8	Me	Me	4a	60	Syrup	+ 36° (c. 1.5)
9	H	Me	5a	32	Syrup	+ 24° (c. 0.6)
10	H	H	7a	30	64 - 65[a]	+ 24° (c. 0.5)[b]
11	H	R*	6a	26	82 - 83[a]	- 22 (c. 0.4)

Rotations were measured in chloroform. [a] From chloroform - light petroleum. [b] P.m.r. shows the sample to be 97% one enantiomer.

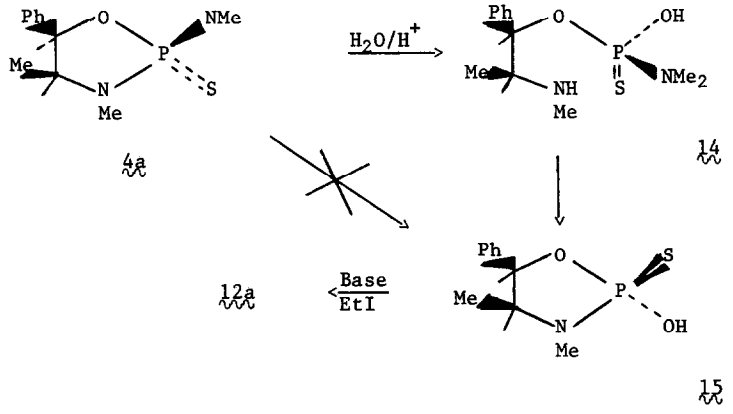
The procedure used consisted of acid catalysed endocyclic P-N bond cleavage followed by intramolecular cleavage of the benzylic C-O bond to form an aziridine plus thioacid salt and isolation of the thioacid as its S-methyl derivative. If as in previous cases[5] P-N bond cleavage in these systems occurs with inversion of configuration, then since subsequent steps do not alter the configuration at phosphorus then the absolute stereochemistry of the products can be assigned.

The methylamino derivative 9 (from 5a) was shown to be enantiomerically pure by p.m.r., making use of the chiral shift reagent $Eu(hfc)_3$. In the presence of this reagent[6] the p.m.r. spectrum of 9 showed doublets for POMe and PSMe whereas for racemic 9, pairs of doublets (POMe, $\delta\Delta$ = 11Hz; PSMe, $\delta\Delta$ = 4Hz) were observed.[7] The enantiomeric purity of 10, varied with the strength of NaOH used during its preparation. With very dilute NaOH the product was 97% enantiomerically pure but this purity dropped rapidly as base concentration was increased. The diastereoisomer 11 was apparently only one isomer. However at high concentrations (> 10%) in deuteriochloroform, the p.m.r. spectrum of 11 was different from that observed at low concentrations (< 5%). This variation is consistent with the observation[8] that phosphinic amides form hydrogen bonded dimers in non-polar solvents. No direct estimation of the enantiomeric purity of 8 was possible since with $Eu(hfc)_3$ in deuteriochloroform poorly resolved spectra were obtained. However subsequent work[3] showed 8 must have an enantiomeric purity of at least 84% and since N-dimethyl phosphoramidothioates are relatively stable to base 8 was probably enantiomerically pure.

The loss of enantiomeric purity of the amino derivative 10 in contrast to the stereospecific preparations of the methylamino derivatives (9 and 11) almost certainly reflects the greater lability to base of P-O bonds in amino compared to alkylamino compounds - in particular the greater lability of P-O bonds in 13 (R = R″ = H) (Scheme 1) than in 13 (R = Me, R″ = H). This is exemplified by the following experiments. The 1,3,2-oxazaphospholidines 4 to 7 in Table 1, like other similar compounds,[5] undergo endocyclic P-N bond cleavage on addition of sodium alkoxides with the same stereochemistry as the corresponding acid catalysed reaction (although in this case the reaction takes hours rather than minutes). Thus as an alternative to the acid catalysed P-N bond cleavage in Scheme 1, 5a was converted into enantiomerically pure 9 in 50% yield on treatment with sodium methoxide followed by methyl iodide. In contrast 6a, under similar conditions afforded a mixture of dimethyl phosphoramidothionate 16 (50%) and O,S-dimethyl phosphoramidothioate (80%). The latter product was a 3:2 mixture of 10 and its enantiomer. The difference in the degradations of 5a and 6a may be attributed to the fact that 13 (R = Me, R″ = H) from 5a only undergoes intramolecular benzylic C-O bond cleavage, whereas 13 (R = R″ = H) from 6a undergoes P-O bond cleavage with replacement of the ephedrine moiety by methoxide to form 16, and of some methoxy by methoxide prior to cleavage of the benzylic C-O bond. This latter step reduces the enantiomeric purity of 10.

In all the experiments with 2-(alkyl)amino-1,3,2-oxazaphospholidines it was assumed that endocyclic P-N bond cleavage would be much preferred to exocyclic P-N bond cleavage. Indeed, this assumption appeared justified by the satisfactory product yields obtained (Table 2). It was therefore at first surprising to find that when 4a was treated with 3N HCl in aqueous acetone for 20 min, followed by basification and alkylation with ethyl iodide, the product isolated in 20% yield was the oxazaphospholidine 12a. Comparison of the p.m.r. spectrum of

12a with that of its epimer 12b[9] confirmed that 12a was formed from 4a with inversion of configuration at phosphorus. Direct cleavage of the exocyclic P-N bond with inversion appears unlikely on energy considerations and this is supported by the fact that all other displacements of exocyclic substituents from phosphorus in these 1,3,2-oxazaphospholidines occur with retention of configuration.[5] Alternatively hydrolysis of 4a to 14 (Scheme 2) which then undergoes intramolecular trans-amination[10] could afford 15, both reactions occurring with inversion of configuration at phosphorus. Attempts to confirm this sequence have been unsuccessful.



Scheme 2

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