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ACID AND BASE CATALYSED ALCOHOLYSES OF SOME CHIRAL O,S-DIALKYL PHOSPHORAMIDOTHIOATES

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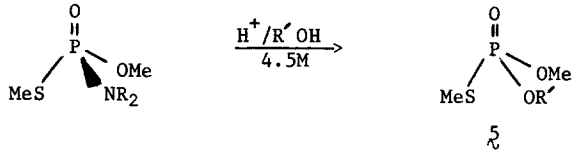
Acidic Alcoholyses Stereochemical studies of the acidic alcoholysis of phosphinamidates have shown that P-N bond cleavage occurs with preponderant inversion of configuration at phosphorus, the stereoselectivity of such reactions depending on the nature of the substituents at phosphorus and on the reaction conditions.[1,2] The results from these studies have been interpreted in terms of an A2 associative mechanism to account for the observed inversion of configuration and in terms of an A1 dissociative mechanism where significant racemisation was evident, although some results were not entirely consistent with this interpretation.[2]

Similar detailed stereochemical studies for other classes of acyclic phosphorus amidates have not been reported, undoubtedly because few chiral phosphorus amidates of known absolute configuration are available. Indeed only for dialkyl N-alkyl phosphoramidothioates and dialkyl N-alkyl phosphoramidates has even indirect evidence (i.e. the consistent stereochemical agreement of a large sequence of inter-related reactions) been obtained to show that P-N bond cleavage occurs with inversion of configuration.[3]

In an attempt to augment the limited available information about the stereochemistry of P-N bond breaking reactions the opportunity has been taken to make use of the chiral O,S -dialkyl phosphoramidothioates described in the preceding paper and to study their conversion into the previously described[4,5] chiral di-O-alkyl S-alkyl phosphorothioates by acidic alcoholysis.

The phosphoramidothioates $\underset{\sim}{1}$, $\underset{\sim}{2}$ and $\underset{\sim}{3}$ were treated with an excess of a solution of anhydrous hydrogen chloride (4.5M) in ethanol or isopropanol at room temperature and stored until no phosphoramidothioate remained. (Although both product and starting material often had very similar R_f values the latter could be selectively visualised by developing t.l.c. plates with ninhydrin). Following basification of the reaction mixture with aqueous sodium carbonate the di-O-alkyl S-alkyl phosphorothioates were isolated in yields of 75 - 90% and their enantiomeric purity and the absolute configuration of the preponderant enantiomers established by the n.m.r. method and by reference to authentic samples.[3,4] The only other significant reaction products were the acids $\underset{\sim}{6}$ which were shown to be formed by dealkylation of the product phosphorothioates $\underset{\sim}{5}$ by amine hydrochloride present in the reaction mixture (Scheme 1). Quenching of the reaction before completion permitted the recovery of starting material of unchanged enantiomeric purity and configuration. The surprising stereochemical outcome of the alcoholyses, summarised in Table 1, was that only for $\underset{\sim}{2}$ and $\underset{\sim}{3}$ in ethanol was

Table 1



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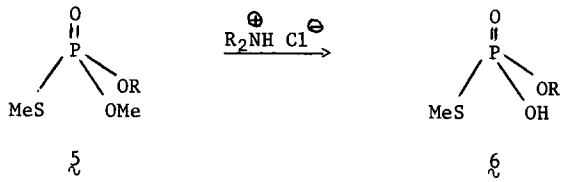
	NR	EtOH	i-PrOH
1	NMe_2 (R)*	86% Retention (R)*	84% Retention (R)*
2	NHMe (R)	60% Inversion (S)	79% Retention (R)
3	NH_2 (R)	84% Inversion (S)	62% Retention (R)

* Refers to the previously established absolute configuration of the starting materials[6] and the major enantiomer of the product.[4,5]

preponderant inversion of configuration observed. Compound 1 with acidic ethanol and compounds 1, 2 and 3 with acidic isopropanol underwent P-N bond cleavage with overall retention of configuration.



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Scheme 1

The effect of acid concentration on product stereochemistry was examined using the N-methyl phosphoramidothioate 2. The results listed in Table 2 show little effect on the reaction taking place with retention of configuration in isopropanol but that in acidic ethanol there was a decrease in the percentage of product formed with inversion of configuration as the acid concentration was increased.[1,2]

Table 2. Effect of Change in Acid Concentration on Reaction Stereochemistry

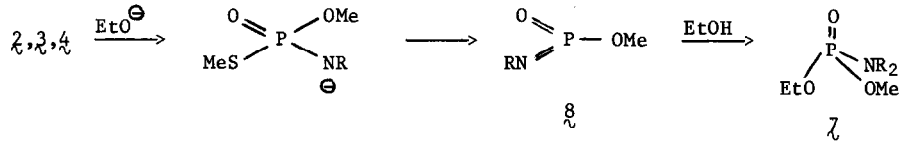
Alcohol	EtOH			i-PrOH		
Acid concentration	0.1M	1M	4.5M	1M	4.5M	7M
2 NHMe	96% I	85% I	60% I	79% Rn	79% Rn	75% Rn

I = Inversion. Rn = Retention.

Although absolute rate constants were not measured, qualitatively for reactions with 4.5M hydrogen chloride the rates were 1 (NMe_2) >> 2 (NHMe) > 3 (NH_2); the half life for 1 was ca. 5 min and for 3 was ca. 2 - 3 days. (Further, the rate of acid catalysed alcoholyses and hydrolyses depends critically on the nature of the substituents on nitrogen. For example, with the diastereoisomer O,S-dimethyl-N-(1-(-)-α-methylbenzylamino)phosphoramidothioate 4 hydrolyses in strong alcoholic acid occurred only very slowly probably because of steric hindrance).[7]

The result that some acid catalysed P-N bond reactions occur with retention of configuration with a high degree of stereoselectivity requires a quite different explanation from those previously put forward to account for the variable stereoselectivity observed with phosphinamidates. For the reactions summarised in Tables 1 and 2 there must be at least two competing reactions. One occurring with inversion, is apparently favoured by low acid concentration, a primary alcohol as nucleophile and a low degree of substitution on nitrogen. The other occurring with retention of configuration is favoured by a high degree of substitution on nitrogen, a secondary alcohol as nucleophile and is unaffected by acid strengths. More experimental data from other types of phosphorus amidates are being sought in an attempt to provide a unifying hypothesis for these differences. Clearly, however, tacit assumptions that P-N bonds are cleaved under acidic conditions with inversion of configuration are no longer justified.

Basic Alcoholyses The rates of basic hydrolysis of O,S-dialkyl phosphoramidothioates vary considerably depending on the degree of substitution on nitrogen. Thus amino derivatives are more labile in base than alkylamino derivatives; dialkylamino derivatives are hydrolysed very slowly indeed.[8] To account for these differences in hydrolysis rates, and similar differences found in related compounds, an ElcB mechanism involving a metaphosphorimidate intermediate has been considered to play a key role in the hydrolysis of amino and alkylamino derivatives (Scheme 2).[9] Such a route is not open to dialkylamino derivatives which hydrolyse



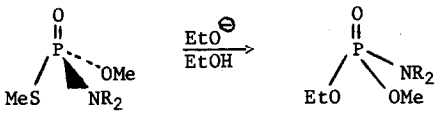
Scheme 2

primarily by hydroxide attack at phosphorus. Despite many attempts, the reaction mechanisms for the hydrolysis of the phosphoramidothioates have not been unequivocally established and indeed recent results have been interpreted as indicating that the ElcB process is relatively unimportant.[10] Stereochemical studies have been inconclusive because of a lack of suitable chiral compounds although in one study[11] the fact that the product from the hydrolysis of an optically active phosphoramidothionate is also optically active was considered contrary to an ElcB mechanism (provided a planar metaphosphorimidate intermediate completely dissociated from the leaving group is involved).

Recent studies in this laboratory (Table 3) in which the chiral compounds 1, 2, 3 and 4 were treated with sodium ethoxide, have done little to clarify the mechanistic situation but do provide more precise stereochemical data than hitherto. The qualitative rates of the reaction are in the order 3 (NH_2) > 2 (NHMe) >>> 1 (NMe_2). In fact the rate for 1 is too slow to be conveniently studied. Reaction of 2 and 4 with ethoxide gives 7 as essentially the only product. However, when 3 is treated with one equivalent of ethoxide in ethanol, 7 was formed in only 30% yield and the major (65%) product is O,O-diethyl phosphoramidate. Control experiments show that this could be formed from the reaction of the primary product 7 with ethoxide. Alternatively a mechanistic pathway involving P-O bond cleavage in the initial phosphoramido-

thioate could be involved.[8] Table 3 shows the enantiomeric composition, again measured using $Eu(hfc)_3$, of the dialkyl phosphoramidates 7 formed by the hydrolysis. However because the absolute stereochemistry has not yet been assigned to 7 no statements on the stereochemical course of the reactions can be made.

Table 3



7

	NR_2			
1	NMe_2		†6 (7 days) →	No reaction
2	NHMe	(l)^{SMe,OMe}	1 (3 hours) →	87% Major enantiomer (h)^{OMe}
3	NH_2	(l)^{SMe}(h)^{OMe}	1 (2 hours) →	82% Major enantiomer (l)^{OMe}
4	NHCHMePh		3 (3 days) →	78% Major enantiomer

h and l refer to the sense of magnetic non equivalence observed in the p.m.r. spectra in the presence of $Eu(hfc)_3$. That enantiomer for which, under standard conditions[3,5] the named signal remains at highest field, is designated h.

† Refers to the number of molar equivalents of ethoxide and the reaction time employed (room temperature).

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