Phosphorothioates. Substitution at Phosphorus with Inversion of Configuration

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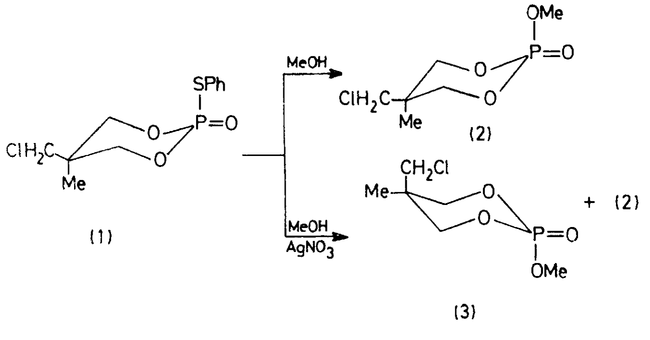
Summary Although methanolysis of 5-chloromethyl-5-methyl-2-oxo-2-phenylthio-1,3,2-dioxaphosphorinan under normal conditions proceeds with retention of configuration at phosphorus, in the presence of cations capable of co-ordinating with sulphur, both inversion and retention pathways are observed.

RECENT reports have indicated that *S*-alkyl or *S*-phenyl phosphorothioates, in which the substituents are incorporated into a 1,3,2-dioxaphosphorinan system, undergo substitution of the thio-group with retention of configuration at phosphorus.[1] The results are in contrast to similar substrates where a better leaving group than RS^-, *e.g.* Cl^-, is employed. In this case inversion of configuration at phosphorus predominates.



Scheme

As a consequence of our interest in the effect of added cations on the mechanisms of substitution at phosphorus,[2] we have observed that although retention of configuration is the sole pathway for substitution of an *S*-phenyl substituent in the absence of an added cation, inversion can be made to predominate. A change in product composition is accomplished by the inclusion of a cation capable of coordinating with the leaving group as shown in the Scheme. Thus pure *trans*-(**1**), when dissolved in CD_3OD and the solution monitored by observing the appearance and disappearance of groups at the 5-position by n.m.r. spectroscopy, requires over 6 months for complete methanolysis. The product was isolated and its spectral and physical properties were identical with those of an authentic sample of the *trans*-2-methoxy phosphorinan (**2**).[3] When the reaction was repeated in the presence of 1 equiv. of $AgNO_3$, a mixture of the geometrical isomers (**2**) and (**3**) in a 1·3 : 1 ratio was obtained with the ratio decreasing to 1 : 2·5 in the presence of a four-fold excess of $AgNO_3$. The catalysed reactions were complete in less than 3 days. Hg^{2+}, but not Na^+, K^+, or Mg_2^+, has a similar effect.

Substitution at phosphorus, in which the phosphorus atom is incorporated into a cyclic phosphorinan system, proceeds either through a common trigonal bipyramid intermediate regardless of the stereochemical pathway or *via* two separate intermediates.[4] In the latter case inversion or retention of configuration is accounted for by assuming attack by the nucleophile at different faces of the tetrahedral phosphate with the ring spanning either basal–basal or basal–apical positions. In the light of our observation that i.r. and n.m.r. spectra of MeCN solutions of (**1**) are essentially identical regardless of the presence or absence of the added salt or the nature of the salt, it appears that the initial position of attack by the nucleophile is identical for both pathways. The nucleophile, methanol, attacks from an apical position with the departure of the leaving group, catalysed by the added cation, also from an apical position. In the absence of catalyst, pseudorotational permutations are favoured with retention of configuration being the ultimate result. It is not unlikely that the catalysed inversion process entails partial bond cleavage prior to complete bond formation, and that a formal trigonal bipyramid intermediate may not be formed.

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[2] W. S. Wadsworth and Yuh-Geng Tsay, *J. Org. Chem.*, 1974, **39**, 984.

[3] The preparation and spectral properties of a series of geometrical isomers has been published: W. S. Wadsworth, S. Larsen, and H. L. Horten, *J. Org. Chem.*, 1973, **38**, 256.

[4] See ref. 1, and M. Mikolzjczyk, J. Krzywanski, and B. Ziemnicka, *Tetrahedron Letters*, 1975, 1607.