Stereochemistry of Acid-catalysed Solvolysis at the Sterically Hindered Thiophosphoryl Centre

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Summary t-Butylphenylphosphinothioic methanesulphonic anhydride undergoes acid-catalysed hydrolysis and methanolysis with inversion of configuration at the sterically hindered thiophosphoryl centre.

IN connection with the general interest in the stereochemistry at sterically hindered phosphorus P^{IV} centres[1,2] we prepared t-butylphenylphosphinothioic methanesulphonic anhydride as a model for studies of nucleophilic displacement at the thiophosphoryl group. The anhydrides (**2**) were prepared by condensation of the corresponding enantiomeric t-butylphenylphosphinothioic acids† (**1**) with methanesulphonyl chloride in the presence of triethylamine.‡

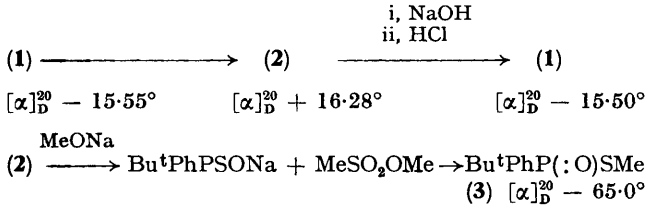
$$\underset{(1)}{Bu^tPhP(:S)OH} \xrightarrow{MeSO_2Cl} \underset{(2)}{Bu^tPhP(:S)OSO_2Me}$$

$[\alpha]_D^{20} + 15{\cdot}1°$ $[\alpha]_D^{20} - 16{\cdot}25°$

The reaction of (**2**) with NaOH in dioxan–water as well as with methanolic NaOH resulted in attack of the nucleophile on the sulphonyl centre and removal of the anion derived from (**1**) as a leaving group with full retention of configuration at the thiophosphoryl centre. The formation

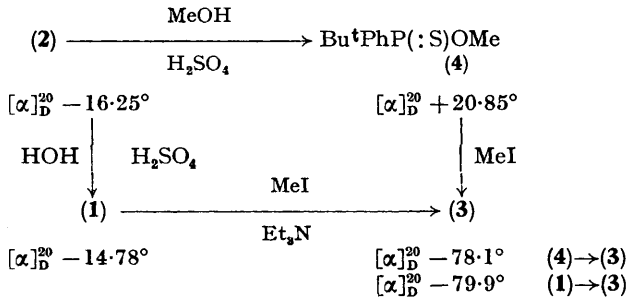
† The resolution of (**1**) was described by Trippett *et al.*,[1] and can be carried out *via* its diastereoisomeric salts with α-phenylethylamine.

‡ This is to our knowledge the first authentic preparation of thiophosphorus acid sulphonic anhydride. Reactions leading to anhydrides of type (**2**) described in the patent literature are in our experience erroneous [G. Schrader, D.B.P. 818,046(1949); see Houben-Weyl, 'Methoden der Organischen Chemie,' 12/2, p. 842, 1964; G. Schrader, D.B.P. 896,643 (1944) (*Chem. Zentr.*, 1954, 8203); Belg. P. 606,292 (1961) see Houben-Weyl, 'Methoden der Organischen Chemie,' 12/1, p. 833, 1964.]



of the *S*-methyl thio-ester (**3**) as final product of the reaction of (**2**) with NaOMe is an obvious consequence of the *S*-methylation of the thioacid (**1**) anion by methyl methanesulphonate.

During a search for stereochemical evidence for the formation of the $>P(S)^+$ ion we found that acidic hydrolysis and methanolysis of (**2**) takes an entirely different course and is accompanied by almost full inversion at the thiophosphoryl centre. The anhydride (**2**) was heated under reflux



in acetone–water (3:1) in the presence of H_2SO_4 (0·02%). The hydrolysis was complete in 48 h. The acid (**1**) obtained was of opposite configuration to that from which anhydride (**2**) was prepared.§ Since in the step (**1**) → (**2**) there is no bond-breaking around the chiral phosphorus atom this is a definitive proof of Walden inversion at the thiophosphoryl centre. Similarly the anhydride (**2**) was heated for 80 h in MeOH in the presence of H_2SO_4 (0·02%) at 60 °C. The *O*-methyl thio-ester (**4**) formed was converted by the Pishtchimuka reaction into the isomeric *S*-methyl thio-ester (**3**), which was shown to be of opposite configuration to that prepared by direct methylation of the triethylammonium salt of the starting acid (**1**). Since in steps (**1**)→(**2**) and (**4**)→(**3**) and also in methylation of an anion of (**1**), step (**1**)→(**3**), there is no bond-breaking around the phosphorus it is evident that the acid hydrolysis step (**2**)→(**4**) takes place with inversion of configuration at the thiophosphoryl centre.

The possibility that (**4**) could be formed in a reaction between MeOH and (**1**) arising from solvolytic attack on the sulphonyl centre was excluded in the following way. The acid (**1**) was allowed to react with MeOH in the presence of H_2SO_4. The *O*-methyl thio-ester was formed quantitatively.

(**1**) + MeOH → (**3**)

This is a very rare case of direct esterification of the phosphorus acid.[3] Because of the almost full inversion of configuration in the present solvolytic reactions there is no stereochemical indication for the intermediacy of $>P(S)^+$ cationic species. Our conclusion is somewhat similar to that of Haake derived from solvolysis of phosphinoamidates.[2] These solvolytic reactions seem to be facilitated by protonation at the sulphur atom attached to phosphorus, and proceed through the formation of the quinque covalent trigonal bipyramidal transition state (intermediate) in which apicophilicity of substituents are in favour of apical attack of the nucleophile and apical departure of the leaving group. The striking difference in the site of nucleophilic attack on the anhydride (**2**) in basic and acidic medium can be attributed to steric factors.

The relatively large size of strongly solvated hydroxide and methoxide anions prevents attack on the sterically hindered phosphorus atom whereas, under acidic conditions, water or methanol can preferentially attack the thiophosphoryl centre assisted by the presence of a good leaving group.

All compounds mentioned gave satisfactory i.r., n.m.r., and analytical results.

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§ In a control experiment the acid (**1**) was shown to be only slightly racemized under conditions of acidic hydrolysis of (**2**).

[1] N. J. De'ath, K. Ellis, D. J. H. Smith, and S. Trippett, *Chem. Comm.*, 1971, 714; and references cited therein.
[2] D. A. Tyssee, L. P. Bausher, P. Haake, *J. Amer. Chem. Soc.*, 1973, **24**, 8066; and references cited therein.
[3] T. R. Hopkins and P. W. Vogel, *J. Amer. Chem. Soc.*, 1956, **78**, 4447; A. F. Millikan and G. W. Crosby, U.S.P., **3,005,006** (1957) *Chem. Abs.*, 1962, **56**, 5026); W. A. Higgins, T. R. Hopkins, U.S.P., 2,858,327 (1958) (*Chem. Abs.*, 1960, **54**, 1424).