

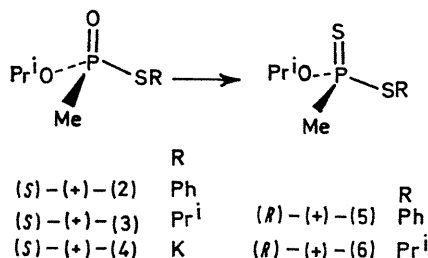
Stereoselective Synthesis of Phosphonothionates from Phosphonate Analogues: Basic Hydrolysis of Chiral Phosphonothionates to a Racemic Product

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Summary Chiral phosphonates reacted with P_4S_{10} to give their thiono-analogues with predominant (if not complete) retention of configuration; basic hydrolysis of the phosphonothionates gave completely racemic products.

THE conversion of quadricovalent $P=O$ compounds into their thiono-analogues ($P=S$) by treatment with P_4S_{10} is a well-known synthetic procedure.¹ With (*R*)-(-)-isopropyl methylphosphinate [$Me(H)P(O)OPr^i$, (**1**)], this reaction proceeds with predominant retention of configuration at the phosphorus atom.² Since (**1**) contains a potentially enolizable hydrogen, it is uncertain whether it reacts as the quadrivalent species, or as its (postulated) trivalent tautomer [$MeP(OH)OPr^i$]. Therefore, it was of interest to determine whether a stereoselective reaction would also be obtained for quadricovalent compounds which do not contain a P-H bond. We have now determined that such compounds also react with predominant (if not complete)



retention of configuration, apparently *via* a four-membered ring intermediate.³ Thus, (*S*)-(+)-*O*-isopropyl *S*-phenyl methylphosphonothioate (**2**), 9.4 mmol, $[\alpha]_D + 1.00^\circ$ (benzene), presumably 1.1% optically pure,⁴ was heated under reflux in 5 ml of benzene for 12 h with a total of 1.9 mmol

of P_4S_{10} (half taken initially, and half added after 6 h), to give (*R*)-(+)-*O*-isopropyl *S*-phenyl methylphosphonodithioate² (**5**), b.p. 71–73° (10 μ m), 33% yield (94% pure by g.l.p.c.), $[\alpha]_D + 1.06^\circ$ (benzene).

If optically pure starting material had been used, the calculated $[\alpha]_D$ is $+103^\circ$ for the (+)-(**5**) product, corrected for its chemical purity. The reaction is believed to have been stereospecific, based upon the coincidence of the specific rotation to that of (*S*)-(-)-(**5**), $[\alpha]_D - 103^\circ$, previously obtained from the reaction of (*R*)-(+)-*O*-isopropyl methylphosphonochloridodithioate (**7**) with sodium thiophenylate.² The stereochemistry of the reaction follows from the known configurations of (*S*)-(+)-(**2**) and (*R*)-(+)-(**5**).^{2,4}

Also, (*S*)-(+)-*OS*-di-isopropyl methylphosphonothioate (**3**), 97% optically pure, was similarly converted (44% yield) into (*R*)-(+)-*OS*-di-isopropyl methylphosphonodithioate (**6**). Here, however, some racemization occurred, since the product had only 80% of the optical purity of that of (*S*)-(-)-(**6**), $[\alpha]_D - 28.4^\circ$ (benzene), obtained from the reaction of (*R*)-(+)-(**7**) with sodium isopropylthiolate.

With the intent to establish, independently, optical purities by comparison to their hydrolysis products, (+)-(**5**) and (+)-(**6**) were treated with a large excess of potassium hydroxide in aqueous methanol or aqueous dioxan, and the reactions followed polarimetrically. Unexpectedly, completely *racemic* products, (\pm)-(**4**), were obtained, isolated as their dicyclohexylammonium salts. It was determined that (+)-(**4**) is not racemized by hydroxide, nor (-)-(**5**) by thiophenylate ion, under the reaction conditions. Apparently, pseudorotation⁵ of the reaction intermediates occurred during hydrolysis.

These results appear to be relevant to recent hydrolysis studies of phosphoramidothionates, in which a planar metaphosphorimidothioate [$RO(S)P=NR$] intermediate

was suggested to explain the extensive racemization often observed.⁶ Our results, together with other experimental data,⁶ suggest pseudorotation is more likely responsible for the racemization observed in these systems.^{6,7}

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