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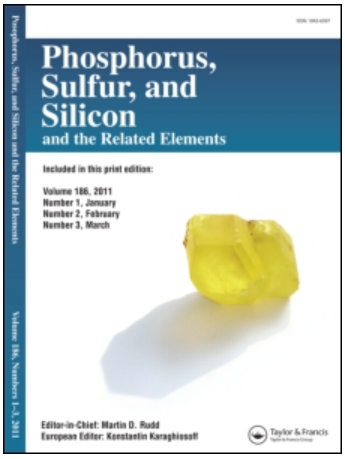

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The Stereochemical Course of Substitution Reactions at Halomethylphosphonates

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THE STEREOCHEMICAL COURSE OF SUBSTITUTION REACTIONS AT HALOMETHYLPHOSPHONATES

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Abstract The stereochemistry of substitution at dihalomethylphosphonothioates is the same as for phosphorothioates whereas that for monohalomethylphosphonothioates is similar to the unsubstituted phosphonothioates.

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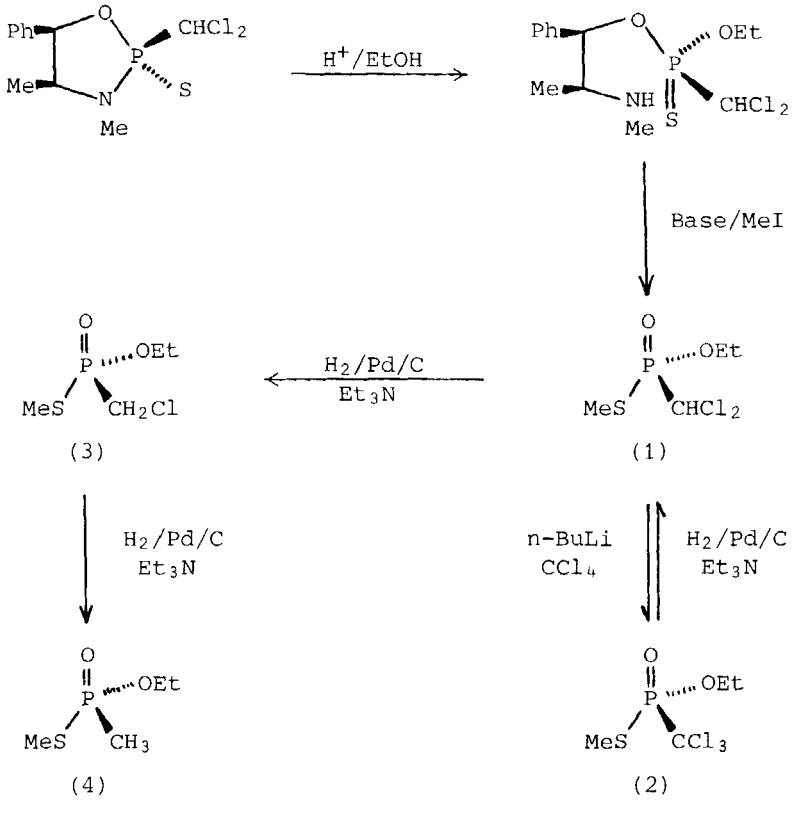
It has been suggested[1] that halomethylphosphonates are electronically better analogues of natural phosphates than the corresponding unsubstituted phosphonates and may therefore be useful in studies of biosynthetic pathways and enzyme mechanisms. Since the stereochemistry of biological processes is also important, it would be useful to establish whether the steric course of the reactions of halomethylphosphonates also parallels that of phosphates. In this context a comparison of the reaction between neutral phosphorus thioesters and alkoxides where P-S bond cleavage occurs with retention of configuration in phosphorothioates but with inversion of configuration in phosphonothioates[2] was likely to be profitable. In this paper results are reported for the reaction of methoxide with chiral mono-, di-, and trichloromethylphosphonothioates, and mono- and di-fluoromethylphosphonothioates.

RESULTS

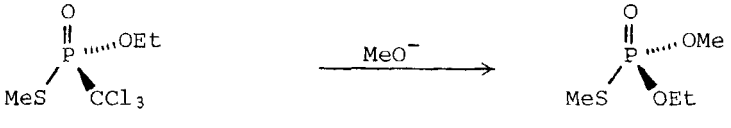
(+)-(R)-O-Ethyl S-methyl dichloromethylphosphonothioate (1), $[\alpha]_D$ +48° (c 1.3, $CHCl_3$), was prepared using (-)-ephedrine as a chiral template by the route outlined in Scheme 1, and previously used for the preparation of other chiral phosphorus esters[2,3].

(1) can be further chlorinated to the trichloromethylphosphonothioate (2), $[\alpha]_D$ +32° (c 1.2), by treatment with n-butyl lithium and quenching of the resulting anion with carbon tetrachloride[4]. Hydrogenolysis of (2) in the presence of triethylamine occurs in a stepwise manner. This both enables the preparation of the



Scheme 1

monochloromethylphosphonothioate (3), $[\alpha]_D$ +62° (c 0.6) and, since it does not involve breaking any bonds to phosphorus, relates the configurations of (1), (2) and (3) to that previously established for the unsubstituted phosphonate (4)[2] (Scheme 1).



Scheme 2

Careful treatment of the trichloro derivative (2) with methoxide results in the already configurationally established phosphorothioate (5)[2]. The reaction therefore involves P-C bond cleavage with inversion of configuration (Scheme 2).

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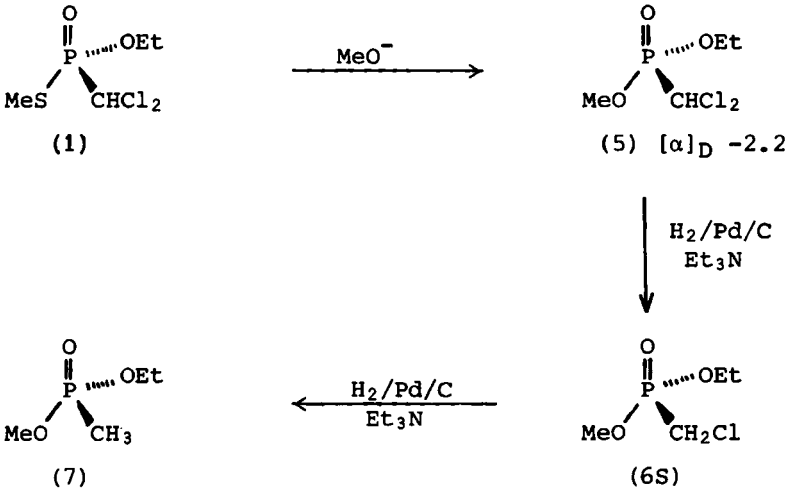
Treatment of the dichloro derivative (1) with methoxide results in stereospecific P-S bond cleavage. The configuration of the product (5), and of its monochloro analogue (6) were determined

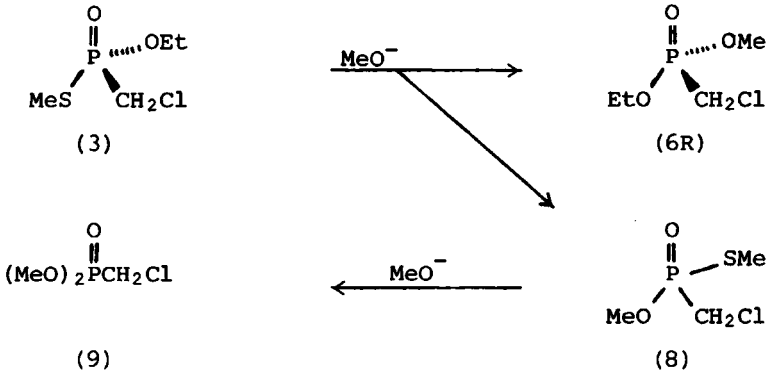


(1) (5) $[\alpha]_D$ -2.2° (7) (6S)

Scheme 3

by hydrogenolysis to the already established unsubstituted phosphonate (7)[2]. P-S bond cleavage in (1) therefore occurs with retention of configuration (Scheme 3).

The monochloro derivative (3) reacts with methoxide with both P-S (85%) and P-O (15%) bond cleavage. The major product is a 7:3 ratio of 6R:6S. P-S bond cleavage therefore occurs with



(3) (6R) (9) (8)

Scheme 4

∿70% inversion of configuration. The stereochemistry of P-O bond cleavage has not been established because the primary product (8)

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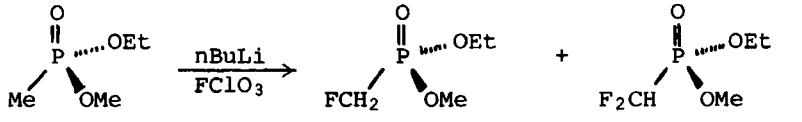
(Scheme 4) rapidly reacts with more methoxide to give the achiral (9).

(+)-(R)-O-Ethyl S-methyl difluoromethylphosphonothioate, $[\alpha]_D$ +56° (c 1.5), and its monofluoro analogue, $[\alpha]_D$ +74° (c 1.6), were also prepared using (-)-ephedrine as chiral template. Both reacted with methoxide in the same way as their chlorine containing analogues (Table). In this case, however, since the product fluoromethylphosphonates (8) and (9) could not be easily hydrogenolysed, their configuration was established by fluorination of the unsubstituted phosphonate (7) (Scheme 5).



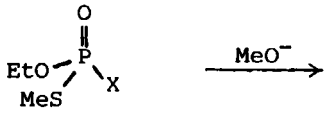
(7) (8) $[\alpha]_D$ +2.3° (9) $[\alpha]_D$ +1.2°

Scheme 5

CONCLUSION

The chemical and stereochemical course of the reaction of dichloro- and difluoro-methylphosphonothioates with methoxide parallels that of phosphorothioates whereas the monochloro- and monofluoro- analogues are closer to the corresponding unsubstituted phosphonothioates. The trichloro- derivative undergoes atypical P-C bond cleavage.

TABLE



X =	Cleavage P-S	Cleavage P-O
Me	INVN	
CH_2Cl	70% INVN	∿15%
CH_2F	80% INVN	∿15%
$CHCl_2$	RETN	
CHF_2	RETN	
OPr	RETN	
CCl_3	P-C cleavage with INVN	

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