Stereochemistry of Methanolysis of Menthyl *S*-Methyl Phenylphosphonothioate

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Summary Contrary to expectation, displacement of the thiomethyl group in menthyl *S*-methyl phenylphosphonothioate by methoxide ion occurs with inversion of configuration at phosphorus.

DISPLACEMENT of the thiomethyl group in menthyl *S*-methyl $(S)_P$-phenylphosphonothioate (**1a**) by methylmagnesium bromide affords menthyl $(R)_P$-methylphenylphosphinate (**2a**) with retention of configuration (Scheme).[1] It was recently reported[2] that alkaline hydrolysis of the phosphonium hexachloroantimonate (**3a**) also gives phosphinate (**2a**) with retention of configuration, and that this result is consistent with a mechanism involving apical attack of hydroxide ion to give the stereoelectronically favoured phosphorane (**5**), followed either by equatorial loss of the thiomethyl group, or by one pseudorotation and loss of the thiomethyl group from an apical position (Scheme).[3] By analogy, it might thus be predicted that apical attack of methoxide ion on (**1a**) would give (**6**), the similarly favoured diastereomer in the set of phosphoranes derived from (**1a**), and that loss of the thiomethyl group from this intermediate would afford menthyl methyl phenylphosphonate (**4a**), again with overall retention of configuration at phosphorus (Scheme). We now report that, contrary to this expectation, reaction of (**1a**) yields (**4b**) with *inversion* of configuration.[†]

Reaction of diastereomerically pure (>95%) menthyl *S*-methyl $(S)_P$-phenylphosphonothioate (**1a**)[‡] with an equimolar quantity of sodium or lithium methoxide in methanol at room temperature for *ca.* 20 h gave diastereo-

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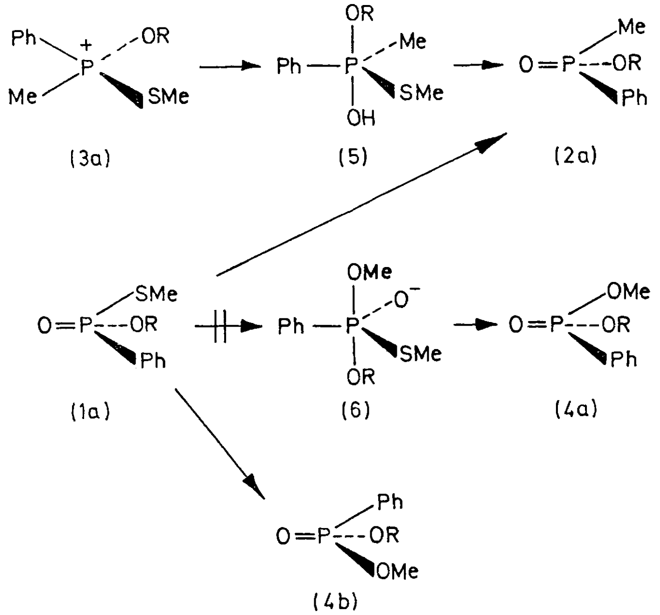
[†] This finding is in accord with the tentative conclusion (H. S. Aaron, R. T. Uyeda, H. F. Frack, and J. I. Miller, *J. Amer. Chem. Soc.*, 1962, **84**, 617) that the displacement of the thiomethyl group by ethoxide ion from isopropyl *S*-methyl methylphosphonothioate proceeds with inversion of configuration.

[‡] The ^1H n.m.r. spectrum ($CDCl_3$) of (**1a**) featured isopropyl methyl doublets at τ 9·04 ($^3J_{HH}$ 7·0 Hz) and 9·10 ($^3J_{HH}$ 6·9 Hz). The ^1H n.m.r. spectrum of (**1b**) featured isopropyl methyl doublets at τ 9·16 ($^3J_{HH}$ 7·0 Hz) and 9·31 ($^3J_{HH}$ 6·9 Hz).

merically pure (>95%) menthyl methyl phenylphosphonate (**4b**).§ Similar treatment of (**1b**)‡ gave (**4a**).§

Because assignment of the configuration at phosphorus in (**4a**) and (**4b**) based upon an extension of the ^{1}H n.m.r. empirical correlation for menthyl alkylarylphosphinates[4] seemed somewhat risky, the structure of phosphonate (**4a**) was established by X-ray analysis. Suitable crystals were obtained by evaporation of a 2,2,4-trimethylpentane solution of (**4a**). Precession photographs showed monoclinic diffraction symmetry with the only observed extinction being 0k0 for k odd. The lattice constants are a = 17·184(14), b = 6·162(5), c = 8·653 (5)Å, β = 102·97(5)°; D_c = 1·153 g cm^{-3}; Z = 2. Since the molecule is chiral, the space group is determined uniquely as $P2_1$-C_2^{2}. A total of 1609 reflections above background was observed with Cu-K_{α} radiation using the moving crystal-moving counter technique. The structure was solved by Patterson and Fourier methods. The final value of R after full-matrix least-squares refinement which allowed for anisotropic thermal motion of all 21 non-hydrogen atoms and which ignored the hydrogen atoms, is 13·7%. A stereographic view of the molecule is shown in the Figure. The configuration of (−)-menthol, used in the preparation of (4a) is 1R, 3R, 4S,[5] and it follows that the configuration at phosphorus is R.

Systematic analysis[3] does not reveal a simple rationale (*e.g.*, nucleophilic attack at phosphorus on the face opposite the ligand 'OMen', followed either by equatorial departure of the thiomethyl group or by pseudorotation and apical departure of the leaving group) which satisfactorily accounts for the stereochemical course of *both* (**1**)→(**4**) *and* (**3**)→(**2**). Although *ad hoc* hypotheses may be formulated to account for the present and related[1,2] results, such schemes in our view lack the generality of a unifying hypothesis and therefore cannot be relied upon to predict the stereochemistry of many other displacement reactions at phosphorus in which restraints[3] are lacking.



SCHEME. R = (−)-menthyl.

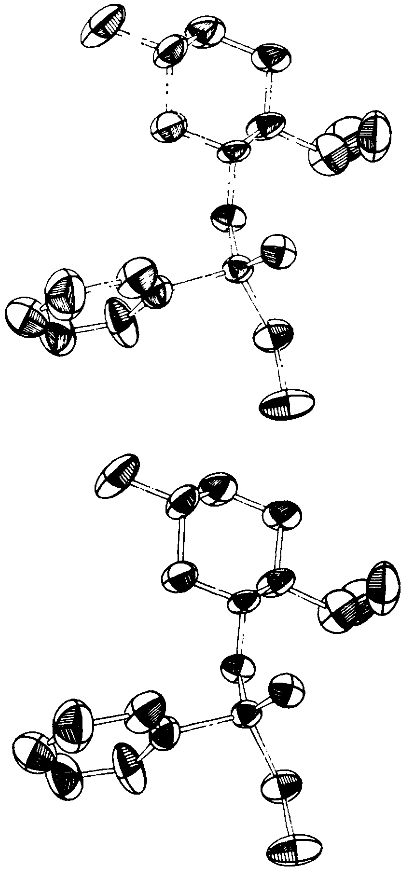


FIGURE. *Stereoview of menthyl methyl* (R)$_P$-*phenylphosphonate* (**4a**). *The hydrogen atoms are not shown.*

We thank the National Science Foundation for the support of this research, and the U.S. Public Health Service for a predoctoral (W.B.F.) fellowship.

(*Received, November* 15*th*, 1971; *Com.* 1973.)

§ Satisfactory elemental analyses were obtained. The ^{1}H n.m.r. spectrum (CDCl$_3$) of (**4b**), m.p. 59—61°, [α]$_D$ −41° (benzene), displayed isopropyl methyl doublets at τ 9·20 ($^{3}J_{HH}$ 7·0 Hz) and 9·46 ($^{3}J_{HH}$ 6·9 Hz). The ^{1}H n.m.r. spectrum of (4a), m.p. 78°, [α]$_D$ − 58° (benzene), displayed isopropyl methyl doublets at τ 9·06 ($^{3}J_{HH}$ 7·0 Hz) and 9·14 ($^{3}J_{HH}$ 6·9 Hz).

[1] J. Donohue, N. Mandel, W. B. Farnham, R. K. Murray, jun., K. Mislow, and H. P. Benschop, *J. Amer. Chem. Soc.*, 1971, **93**, 3792.

[2] N. J. De'ath, K. Ellis, D. J. H. Smith, and S. Trippett, *Chem. Comm.*, 1971, 714.

[3] For a discussion of the role of pentaco-ordinate intermediates in nucleophilic displacement reactions, see K. Mislow, *Accounts Chem. Res.*, 1970, **3**, 321.

[4] R. A. Lewis, O. Korpiun, and K. Mislow, *J. Amer. Chem. Soc.*, 1967, **89**, 4786; 1968, **90**, 4847. Application of this correlation method has provided supporting evidence for configurational assignments to several diastereomeric menthyl phosphinates (T. L. Emmick and R. L. Letsinger, *J. Amer. Chem. Soc.*, 1968, **90**, 3459; W. B. Farnham, R. K. Murray, jun., and K. Mislow, *ibid.*, 1970, **92**, 5809; W. B. Farnham, R. K. Murray, jun., and K. Mislow, *Chem. Comm.*, 1971, 146) and to the diastereomeric *O*-menthyl methylphenylphosphinothioates (A. W. Herriott, *J. Amer. Chem. Soc.*, 1971, **93**, 3304; Trippett and his co-workers, ref. 2).

[5] V. Prelog, *Helv. Chim. Acta*, 1953, **36**, 308; numbering of carbon atoms as in *p*-menthan-3-ol. See also R. Parthasarathy, J. Ohrt, A. Horeau, J. P. Vigneron, and H. B. Kagan, *Tetrahedron*, 1970, **26**, 4705.