Convenient Procedure for the Stereospecific Synthesis of Optically Active Alkyl *S*-Alkyl Methylphosphonothioates, Dialkyl *S*-Alkyl Phosphorothioates, Dialkyl Methylphosphonates, and Trialkyl Phosphates

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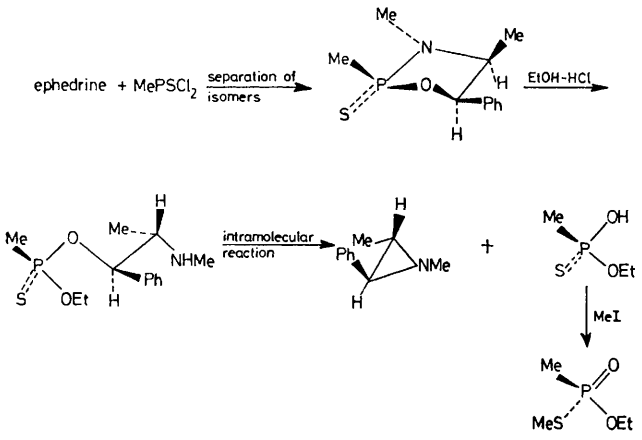
Summary Starting from the optically active cyclic esters prepared from ephedrine and $RPSCl_2$ (R = Cl or Me), optically active alkyl *S*-methyl methylphosphonothioates and dialkyl *S*-methyl phosphorothioates are isolated in yields of 32—60%, by a sequence which permits the assignment of absolute configuration to the products; bromine promoted methanolysis of the S–Me derivatives affords the corresponding *O*-methyl esters with inversion of configuration at phosphorus.

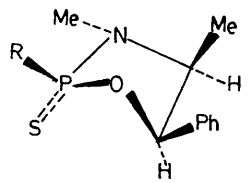
THE methods currently available for the synthesis of optically active phosphorus esters are of limited application. For example, although a range of alkylphosphono-derivatives may be prepared in good yields[1] following classical resolution of alkyl hydrogen alkylphosphonothioates,[2] these procedures have not been extended to include the corresponding phosphorothioates. Further, although carbohydrate intermediates can provide optically active phosphono- and phosphoro-esters of established configuration,[3] it is inconvenient to prepare the large amounts of these

intermediates that would be required for the synthesis of 1—10 g batches of optically active phosphorus esters. In this paper it is suggested that the sequence illustrated in the Scheme, by reference to the synthesis of *O*-ethyl *S*-methyl methylphosphonothioate, may provide a convenient and generally applicable route for the stereospecific synthesis of optically active phosphono- and phosphoro-esters.



SCHEME

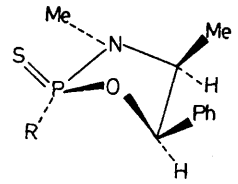
In general terms the synthetic sequence involves the formation and separation of the pairs of isomers formed from (−)-ephedrine [2-(*S*)-methylamino-1-(*R*)-phenylpropan-1-ol] and $RPSCl_2$ (R = Cl and Me). Where R = Me, the esters are treated directly with alcoholic HCl, when P–N bond cleavage with inversion of configuration occurs.[4] Where R = Cl, the isomers are first converted into the corresponding alkoxy-derivatives with retention of con-



(**1**) R = Me; m.p. 73—74°; $[\alpha]_D$ − 128°
(**2**) R = Cl; m.p. 125—128°; $[\alpha]_D$ − 121°
(**3**) R = OMe; syrup; $[\alpha]_D$ − 140°
(**4**) R = OEt; m.p. 74—76°; $[\alpha]_D$ − 122°
(**5**) R = OPr^i; m.p. 73—74°; $[\alpha]_D$ − 123°

figuration at phosphorus[4] by treatment with sodium alkoxides, prior to treatment with alcoholic HCl. The acyclic product, on storage in aqueous alcohol containing NaOH, undergoes spontaneous decomposition following intramolecular attack of the methylamino-function on the benzylic carbon atom thereby forming a chiral phosphorus thioacid and *trans*-1,2-dimethyl-3-phenylaziridine. In practice, the thioacid was not isolated as such but was converted into the more conveniently isolatable S–Me derivative.

Some of the 1,3,2-oxazaphospholan-2-thiones that have been prepared are illustrated in formulae (**1**)—(**10**). The 2-Me derivatives (**1**) and (**6**) (separated following chromatography over silica in 1:4 acetone–light petroleum) were prepared and their structures were assigned as for the corresponding P=O derivatives.[4] The major (**2**) and minor

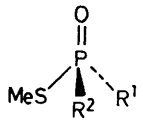


(**6**) R = Me; m.p. 88—90°; $[\alpha]_D$ − 25°
(**7**) R = Cl; m.p. 58°; $[\alpha]_D$ − 23°
(**8**) R = OMe; m.p. 88—89°; $[\alpha]_D$ + 2°
(**9**) R = OEt; m.p. 43—44°; $[\alpha]_D$ − 5·2°
(**10**) R = OPr^i; m.p. 70—71°; $[\alpha]_D$ − 8·4°

(**7**) chloridates were prepared by an ephedrine–$PSCl_3$ reaction. The major isomer was purified by fractional crystallisation from Pr^i_2O but the minor isomer was only purified following chromatography over silica in 1:3 $CHCl_3$–cyclohexane [R_f 0·40 for (**2**), 0·45 for (**7**)]. The alkoxy-derivatives (**3**), (**4**), and (**5**) were prepared by treatment of (**2**) with NaOMe, NaOEt, and $NaOPr^i$ respectively; similarly (**7**) afforded (**8**), (**9**), and (**10**). Structures were assigned by analogy with the corresponding P=O derivatives.[4] Specific rotations were measured in $CHCl_3$ (*c* 0·5—2). Most of the compounds were crystallised from Pr^iOH or Pr^i_2O.

TABLE
Yields, specific rotations and absolute configurations of phosohono- and phosphoro-thioates

Precursor	Product	Yield (%)	$[\alpha]_D$ ($CHCl_3$)	Configuration
(**1**)	(**11**)	28	+85° (*c* 1·7)	*S*
(**3**)	(**12**)	36	−87·5° (*c* 2·2)	*R*
(**9**)	(**13**)	32	−0·9° (*c* 1·0)	*S*
(**4**)	(**14**)	46	+1·0° (*c* 1·4)	*R*
(**9**)	(**15**)	42	+3·1° (*c* 0·4)	*S*
(**8**)	(**16**)	60	−3·0° (*c* 0·6)	*R*
(**4**)	(**17**)	34	+3·5° (*c* 0·5)	*S*
(**8**)	(**18**)	38	−3·4° (*c* 1·9)	*R*



(**11**) R^1=OEt, R^2=Me
(**12**) R^1=Me, R^2=OEt
(**13**) R^1=OEt, R^2=OMe
(**14**) R^1=OMe R^1=OEt
(**15**) R^1=OPr^i, R^2=OMe
(**16**) R^1=OMe, R^2=OPr^i
(**17**) R^1=OPr^i, R^2=OEt
(**18**) R^1=OEt, R^2=OPr^i

The ethyl *S*-methyl methylphosphonothioates (**11**) and (**12**) and the dialkyl *S*-methyl phosphorothioates (**13**)—(**18**) listed in the Table were prepared without isolation of intermediates in the following manner. The selected cyclic intermediate, in a solution of the appropriate alcohol containing HCl was stored at room temperature for 1 h. The solution was made alkaline (pH 12) with conc. aq. NaOH and the mixture was stored overnight at room temperature. MeI was added, the solution was stored at room temperature for 1 h, the solution was diluted with chloroform, washed with water, dried, concentrated, and passed over silica in benzene–acetone–methanol (8:1:1). In this solvent the S–Me derivatives had R_f = 0·5—0·6 and when sprayed with $PdCl_2$ (0·5%) in aqueous HCl (0·7%) were visible on t.l.c. plates as a characteristic yellow spot.

All products were finally purified by bulb to bulb distillation at *ca.* 75 °C at 0·2 mmHg. Rotations, yields, and configurations of the S–Me derivatives are given in the Table. The configurations, assigned on the basis of the synthetic sequence, are consistent with those established by degradation of carbohydrate intermediates[3] [for compounds (**11**), (**12**), and (**17**)] and other literature data[1c] [for compounds (**11**) and (**12**)].

The dialkyl *S*-methyl phosphorothioates and the ethyl *S*-methyl methylphosphonothioates were smoothly and stereospecifically converted with inversion of configuration into the corresponding dialkyl methyl phosphates and ethyl methyl methylphosphonates on treatment with Br_2 in MeOH at room temperature. For example (**11**) was converted into (+)-(*R*)-ethyl methyl methylphosphonate (**19**), $[\alpha]_D$ + 1·9° (*c* 1·2), (**17**) was converted into (−)-(*S*)-ethyl methyl isopropyl phosphate (**20**), $[\alpha]_D$ −0·2° (*c* 5·9), and (**18**) was converted into (+)-(*R*)-ethyl methyl isopropyl phosphate (**21**), $[\alpha]_D$ + 0·2° (*c* 6·8). The essential enantiomeric purity of the above phosphates, phosphonates, and phosphorothioates was established by n.m.r.[3] using the optically active shift reagent $Eu(hfc)_3$. That the bromine-promoted methanolyses occurred with inversion of configuration followed from comparisons of (**19**), (**20**), and (**21**) with the corresponding products obtained from carbohydrate intermediates.[3] The phosphonothioate (**11**) was also converted with inversion of configuration into (**19**) on treatment with NaOMe although in this case the reaction was not stereospecific, *ca.* 20% of the (−)-(*S*)-isomer also being formed.[5] In sharp contrast and in agreement with recently reported results,[6] the reactions of the phosphorothioates with sodium alkoxide took place with retention of configuration, *i.e.* (**17**) afforded (**21**), and (**18**) afforded (**20**).

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