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THE PREPARATION AND STEREOCHEMISTRY OF SOME PHOSPHORUS-SELENOATES. THE STEREOCHEMISTRY OF DISPLACEMENTS OF S-ALKYL AND Se-ALKYL GROUPS FROM PHOSPHORUS

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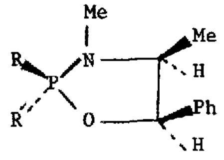
Although many optically active organophosphorus derivatives have been prepared from optically pure organophosphorus thioacids some loss of stereochemical purity is often a consequence of the chemical manipulations employed.[1] Similarly, although optically pure alkyl S-alkyl methylphosphonothioates and dialkyl S-alkyl phosphorothioates may be prepared conveniently[2], the stereoselectivity of the replacement of S-alkyl by O-alkyl depends on the nature of all the phosphorus ligands and only in some cases are stereospecific reactions observed.[3] As part of an investigation to establish whether or not organophosphorus selenoacid derivatives have any advantages (e.g. react more rapidly, or predictably, or stereoselectively or under milder conditions) over the corresponding organophosphorus thioacid derivatives this paper reports the preparation of some optically active alkyl Se-alkyl methylphosphonoselenoates and dialkyl Se-alkyl phosphoroselenoates and compares some of their reactions with the corresponding thio derivatives.

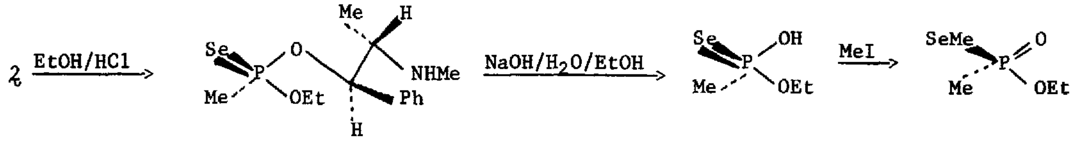
The procedures for preparing the acyclic organophosphorus selenoates were similar to those for the corresponding organophosphorus thioates[2], and involved initial formation of the optically pure cyclic esters (1, 2 and 3) and their subsequent degradation as illustrated in Scheme 1.



1 R = Me, R′ = =Se. $[\alpha]_D$ -97.5° (c. 1.5/$CHCl_3$)

2 R = =Se, R′ = Me. $[\alpha]_D$ -8.6° (c. 1.5/$CHCl_3$)

3 R = =Se, R′ = MeO.

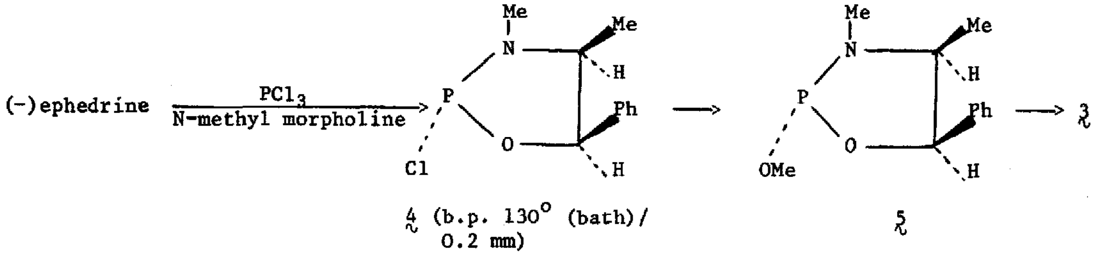


6 7 8

Scheme 1

The cyclic esters 1 and 2 were prepared in the following manner. A cold solution of methylphosphinous dichloride, triethylamine and (-)ephedrine [2-(S)-methylamino-1-(R)-phenylpropan-1-ol] in benzene was stirred under nitrogen for 1 h, an excess of selenium was added and stirring was continued for 24 h. The reaction mixture was processed by standard procedures and 1 (syrup, R_f = 0.35) and 2 (m.p. 100-101° from di-isopropyl ether, R_f = 0.30) were separated by chromatography over silica in chloroform:cyclohexane (1:3).

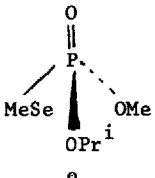
The methoxy derivative 3 was prepared as illustrated in Scheme 2. The chloridate 4, following distillation was a single isomer (although evidence for the presence of the <u>cis</u> isomer in the crude reaction mixture was obtained) which with methanol in the presence of triethylamine afforded 5. The reaction between 5 and selenium to give 3 was rapid compared with the reaction of 4 and selenium.



Scheme 2

The configurations assigned to 1 to 5 were made on the basis that oxidation of trivalent phosphorus by m-chloroperbenzoic acid and additions of sulphur and selenium to trivalent phosphorus occur with retention of configuration[4] and also that oxidations of P=Se (like P=S) with m-chloroperbenzoic acid occur with retention of configuration.[5] Compounds 1 to 5 were converted as appropriate, into the corresponding P=O and P=S compounds with previously established configurations.[2,6]

On treatment with ethanolic hydrogen chloride, 2 was converted into 6 (Scheme 1) with inversion of configuration at phosphorus (by analogy with similar reactions of P=O and P=S compounds). The conversion of 6 into 7 by intramolecular attack by the methylamino group at the benzylic carbon resulting in C-O bond cleavage and the subsequent methylation at selenium to give 8 do not affect the configuration at phosphorus. Compound 8, $[\alpha]_D$ -80° (c. 0.4/$CHCl_3$) has the S configuration at phosphorus.[7] Compound 9 with the R configuration at phosphorus and $[\alpha]_D$ -5.3° (c. 0.3/$CHCl_3$) was prepared from 3 by a similar sequence which involved treatment of 3 with hydrogen chloride in propan-2-ol. The configurational assignments to these organophosphorus selenoates are among the first reported and indicate that the absolute configuration - optical rotation relation is the same in organophosphorus thioates and organophosphorus selenoates.



9

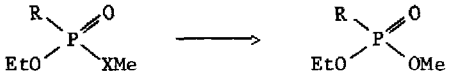
The enantiomeric purity of **8** and **9** was established by p.m.r. using the chiral shift reagent tris-[3-(heptafluoro-n-propylhydroxymethylene)-(+)-camphorato]europium (III) [$Eu(hfc)_3$].[8] The compounds in deuteriochloroform (0.5 ml, 8 - 10% w/v) containing $Eu(hfc)_3$ (0.1 g) were examined at 60 MHz. Doublets for the PSeMe and PMe signals in **8** and for the POMe and PSeMe signals in **9** were observed as compared to pairs of doublets in the corresponding racemates. In **8** the signals for PMe and PSeMe were the low field corresponding signals in the racemate whereas in **9** the PSeMe signal corresponded to the low field doublet and the POMe signal corresponded to the high field doublet in the racemate.

All the compounds containing selenium were much less stable than their sulphur analogues. In particular **1**, **2** and **3** readily deposited selenium when neat and were preferably stored below 0° as dilute deoxygenated solutions.

Comparison of the replacement in phosphoro- and phosphono- derivatives of S-alkyl and Se-alkyl by O-alkyl was made using sodium alkoxide, bromine in alcohol and silver nitrate in alcohol.[9] The results of replacement by OMe are shown in the Table. Notably in the phosphoro series displacement of S-alkyl by alkoxide occurs with complete retention of configuration, whereas Se-alkyl is displaced with complete inversion of configuration. In the phosphono series the displacement of Se-alkyl is stereospecific with complete inversion of configuration, whereas with the S-alkyl some retention of configuration is also observed. Qualitative observations were that the relative rates of displacement of SeR and SR by alkoxide and bromine in alcohol are similar. Replacement of silver nitrate by other heavy metal salts (Hg^{2+}, Zn^{2+}, Cu^{2+}, Cd^{2+}, Ni^{2+}) gave at best only low yields of the desired products. In cases where non-stereospecific reactions occurred quenching at 50% completion led to recovery of the starting material without racemisation.

If popular concepts[10] of the involvement of trigonal bipyramidal intermediates in phosphorus chemistry are accepted, the results that in the phosphoro series Se-alkyl is displaced from phosphorus with inversion of configuration whereas S-alkyl is displaced with retention of configuration and that in the phosphono series the Se-alkyl displacement is stereospecific whereas the S-alkyl displacement is not, lead to the conclusion that the relative apicophilicities of SeR, SR and OR differ in the phosphoro and phosphono series. In the phosphono series the relative apicophilicities are SeR > SR > OR whereas in the phosphoro series the order is SeR > OR > SR. Trippett et al.[11] have also shown that the relative apicophilicity of SR and OR groups is affected by the nature of the other substituents at phosphorus.

Table. Comparison of Displacement of SeR and SR by OMe



R	X	Reagent	Stereochemistry[†]
i-PrO	S	$MeO^{\ominus}$	100% Retention
		Br_2/MeOH	100% Inversion
		$AgNO_3$/MeOH	100% Inversion
i-PrO	Se	$MeO^{\ominus}$	100% Inversion
Me	S	$MeO^{\ominus}$	80% Inversion
		Br_2/MeOH	100% Inversion
		$AgNO_3$/MeOH	80% Inversion
Me	Se	$MeO^{\ominus}$	100% Inversion
		Br_2/MeOH	100% Inversion
		$AgNO_3$/MeOH	Complex Formation

[†] The absolute configuration and enantiomeric purity of all starting materials and products were determined by observation and comparison of their p.m.r. spectra in the presence of the chiral shift reagent Eu(hfc)$_3$.[2,8]

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