Stereochemistry of the Alkaline Hydrolysis of Dialkoxyphosphonium Salts[1]

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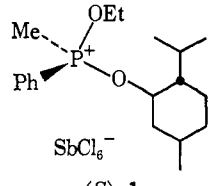
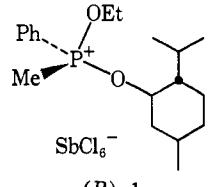
Abstract: The product distribution in the alkaline hydrolysis of the diastereomers of ethoxymenthoxymethylphenylphosphonium hexachloroantimonate provides evidence for pseudorotation in the intermediate phosphoranes. This result contrasts sharply with the complete inversion of configuration previously found for the hydrolysis of acyclic monoalkoxyphosphonium salts. Stereoelectronic demands of the substituents and a steric effect due to the bulk of the menthyl group are discussed in relation to the present observations.

It has been shown[3] that alkaline hydrolysis of acyclic monoalkoxyphosphonium salts to the corresponding phosphine oxides proceeds with complete inversion of configuration at phosphorus. In the phosphorane intermediate resulting from an SN2-type displacement at phosphorus, the electronegative hydroxy and ethoxy groups occupy apical positions, corresponding to the structure of lowest energy.[4] Any loss of stereospecificity in the displacement reaction would require pseudorotation in the intermediate phosphorane. Since the necessary repositioning of electronegative hydroxy and alkoxy groups into equatorial positions, and of a relatively electropositive group into the apical position, renders this a pathway of higher energy, the observed[3] high stereospecificity in the inversion reaction is thus accounted for.



$(S)_P$-1



$(R)_P$-1

The present work, a study of the alkaline hydrolysis of the diastereomers of ethoxymenthoxymethylphenylphosphonium hexachloroantimonate (**1**), an acyclic dialkoxyphosphonium salt, was undertaken in order to put the above interpretation to a test. For reasons elaborated below, the intermediate phosphorane would be expected to contain one apical and one equatorial alkoxy group. A pseudorotation involving either the methyl or the phenyl group as pivot would merely exchange the positions of the two alkoxy groups. Such a step would therefore not represent a high energy pathway. Accordingly, the rate of pseudorotation would increase relative to the rate of loss of alkoxide, and this process might compete to the extent of affecting the stereospecificity of the hydrolysis.

Results

(*S*)-**1**, prepared by O ethylation of menthyl (*S*)-methylphenylphosphinate ((*S*)-**2**),[5] was allowed to react for 1 min at room temperature with 0.5 *M* NaOH in 50 v/v % H_2O–dioxane, containing 3.24 atom % ^{18}O/mole in the H_2O. The reaction was complete under the stated conditions. The nonacidic products, obtained in better than 80% yield, consisted of (*R*)- and (*S*)-**2**, and of (*R*)- and (*S*)-ethyl methylphenylphosphinates (**3**), and contained *ca.* 3.2 atom % ^{18}O/mole (Table I). These results indicate that the hydrolysis of (*S*)-**1** proceeds by exclusive attack of hydroxide on phosphorus, with subsequent P–O bond cleavage. That the ^{18}O incorporation in the ester products had not occurred after hydrolysis was shown by submitting a known sample of each ester to the identical reaction conditions and analyzing the recovered ester for ^{18}O incorporation. In each case, less than 0.05 atom % ^{18}O/mole above natural abundance was detected.[6]

Table I. Products Obtained from the Alkaline Hydrolysis of (*S*)- and (*R*)-**1**

Products	Yield of products (%) from hydrolysis of (*S*)-**1**[a]	(*R*)-**1**[a]	Atom % ^{18}O/mole[b]
(*S*)-**2**	40	27	3.16, 3.25
(*R*)-**2**	20	39	
(*S*)-**3**	38	8	3.15, 3.21
(*R*)-**3**	2	26	

[a] Per cent of total nonacidic products; over-all yield >80%. [b] In the mixture of stereoisomers from the hydrolysis of (*S*)-**1**, standard deviation *ca.* 0.10. Duplicate determinations.

(*R*)-**1** was prepared from (*R*)-**2** as described for the *S* diastereomer. Hydrolysis of (*R*)-**1** yielded the same products as those obtained in the hydrolysis of (*S*)-**1** (Table I), but in different proportions. Evidently

(1) This work was supported by the Air Force Office of Scientific Research under Grant No. AF-AFOSR-1188-B.

(2) U. S. Public Health Service Postdoctoral Fellow, 1967–1969, supported by the National Cancer Institute.

(3) G. Zon, K. E. DeBruin, K. Naumann, and K. Mislow, *J. Am. Chem. Soc.*, **91**, 7023 (1969); R. A. Lewis, K. Naumann, K. E. DeBruin, and K. Mislow, *Chem. Commun.*, 1010 (1969).

(4) E. L. Muetterties, W. Mahler, and R. Schmutzler, *Inorg. Chem.*, **2**, 613 (1963); E. L. Muetterties, W. Mahler, K. J. Packer, and R. Schmutzler, *ibid.*, **3**, 1298 (1964); E. L. Muetterties and R. A. Schunn, *Quart. Rev.* (London), **20**, 245 (1966); P. C. Van der Voorn and R. S. Drago, *J. Am. Chem. Soc.*, **88**, 3255 (1966); F. H. Westheimer, *Accounts Chem. Res.*, **1**, 70 (1968); R. Schmutzler in "Halogen Chemistry," Vol. 2, V. Gutmann, Ed., Academic Press, New York, N. Y., 1967, pp 73–113.

(5) (a) O. Korpiun, R. A. Lewis, J. Chickos, and K. Mislow, *J. Am. Chem. Soc.*, **90**, 4842 (1968). (b) In this and subsequent discussion, configurational notation (*R* and *S*) refers to chirality at phosphorus. The menthyl moiety is derived from (−)-menthol.

(6) This result agrees with similar observations of Haake and coworkers.[7]

(7) P. Haake, C. E. Diebert, and R. S. Marmor, *Tetrahedron Lett.*, 5247 (1968); P. Haake, R. D. Cook, W. Schwarz, and D. R. McCoy, *ibid.*, 5251 (1968).

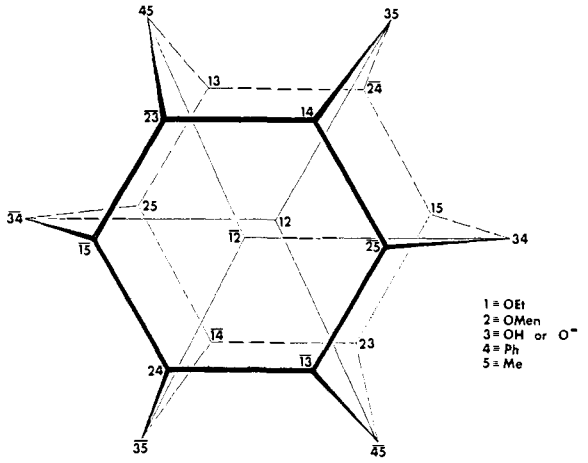


Figure 1.

different concentrations of the same set of intermediates are involved in the hydrolysis of the diastereomers of **1**.

The differential rate of hydrolysis of (*S*)-**2** and **3** changes the molar ratio of residual **2** and **3**. This effect was dealt with by submitting a mixture of (*S*)-**2** and racemic **3** to the same conditions which had been employed in the base-catalyzed hydrolysis of (*S*)-**1**, and observing the change in the composition of the mixture as a function of time. The difference ($k_3 - k_2$) of the pseudo-first-order rate constants for hydrolysis of (*S*)-**2** (k_2) and **3** (k_3) was found to be 1.6×10^{-3} sec^{-1}. The observed ratio of products from the hydrolysis of (*S*)-**1** can therefore be corrected for this preferred decomposition, and the values in Table I are so corrected. As a further control experiment, a mixture of (*S*)-**2** and (*R*)-**2** was submitted to the same conditions which had been employed in the base catalyzed hydrolysis of **1**. After a 5 min exposure, the composition of the mixture was unchanged. It thus appears that, to the extent that any hydrolysis occurs, differences in the rates of hydrolysis of the two esters are negligible.

The exclusive attack of hydroxide at phosphorus in (*S*)-**1** exemplifies the general preference for this mode of attack among the polyalkoxyphosphonium salts, as shown in Table II.

Table II. Hydrolysis of Polyethoxyphosphonium Salts[a]

$R_1R_2P(OEt)_2^+X^-$			Atom % ^{18}O/mole	
R_1	R_2	X	H_2O[b]	Product[b,c]
Ph	Me	NO_3	5.11 (0.10)	5.10 (0.17)
Ph	Me	$SbCl_6$	3.24 (0.05)	3.34 (0.05)
Ph	OEt	$SbCl_6$	4.75 (0.09)	4.53 (0.17)
Ph	OEt	$SbCl_6$	3.24 (0.05)	3.28 (0.12)
OEt	OEt	$SbCl_6$	4.75 (0.09)	4.77 (0.15)
OEt	OEt	$SbCl_6$	3.24 (0.05)	3.41 (0.10)

[a] The hydrolysis was carried out at room temperature by reaction with 0.5 *M* $Na^{18}OH$ in 50 v/v % $H_2{}^{18}O$–dioxane for 1 min. [b] Standard deviation in parentheses. [c] The product is $R_1R_2P(O)OEt$.

Discussion

Initial and Ultimate Phosphoranes in the Displacement Reaction. When (*S*)-**1** undergoes nucleophilic attack by hydroxide ion, four phosphoranes may initially be formed from face (a) attack and six from edge (e) attack.[8,9] Allowing for all conceivable pseudorotations, the 20 possible isomers and their interconversions may be conveniently represented by the graph in Figure 1.[8,10] For the purpose of the present discussion, the ligands of phosphorus in the phosphorane resulting from addition of hydroxide to (*S*)-**1** have been labeled as indicated in Figure 1. Of the four possible phosphoranes resulting from a attack (**13**, $\overline{23}$, $\overline{34}$, **35**), two ($\overline{34}$ and **35**) contain the unfavorable placing of both electronegative groups, OEt and OMen, in equatorial positions, and of a relatively electropositive group, Ph or Me, in an apical position.[11] Since all six phosphoranes represented by the points of the star in Figure 1 contain the same unfavorable arrangement of groups, a virtual barrier is developed between the front and the back hexagonal circuits of the graph, and crossover represents a high-energy pathway. Thus, **13** and $\overline{23}$ remain as sole candidates for the initially formed phosphorane. If ethoxide is the leaving group, its departure is expected to occur from an apical position according to arguments based on the principle of microscopic reversibility.[4] It follows that $\overline{13}$, **14**, and $\overline{15}$ are the only ultimate phosphoranes which can arise by pseudorotation from $\overline{23}$; all three result in formation of (*S*)-**2**. Similarly, **13**, $\overline{14}$, and **15** are the ultimate phosphoranes from **13** and yield only (*R*)-**2**. If, on the other hand, menthoxide is the leaving group, $\overline{23}$, **24**, and $\overline{25}$ are the ultimate phosphoranes from $\overline{23}$ and form only (*S*)-**3**, while **23**, $\overline{24}$, and **25** are the ultimate phosphoranes from **13** and yield only (*R*)-**3**. Thus, a predominance of (*S*)-**2** and (*S*)-**3** would indicate preferred initial formation of phosphorane $\overline{23}$, and a predominance of (*R*)-**2** and (*R*)-**3** would point to **13** as the initially formed phosphorane.

A similar analysis can be carried out for e attack. Again invoking the postulate that the points of the star in Figure 1 represent high-energy intermediates, such as **45**, phosphoranes **12**, **14**, $\overline{15}$, $\overline{24}$, and **25** are the only isomers which may be initially formed from (*S*)-**1**. Invoking arguments based on the principle of microscopic reversibility, phosphorane **12** must pseudorotate to allow departure of either the ethoxide or menthoxide group from the equatorial position. However, since *any* pseudorotation converts **12** to one of the high-energy intermediates represented by the points of the star, this phosphorane may be eliminated from further consideration. The fate of the remaining phosphoranes is indicated as part of Scheme I, which summarizes our analysis and which can easily be extended to reactions of (*R*)-**1** by employing the enantiomeric set of phosphoranes in the intermediate stage.

Steric Constraints in Product Control. Since different ratios of the four product esters are obtained in the hydrolyses of (*S*)- and (*R*)-**1** (Table I), it follows that decomposition of the ultimate phosphoranes is not the

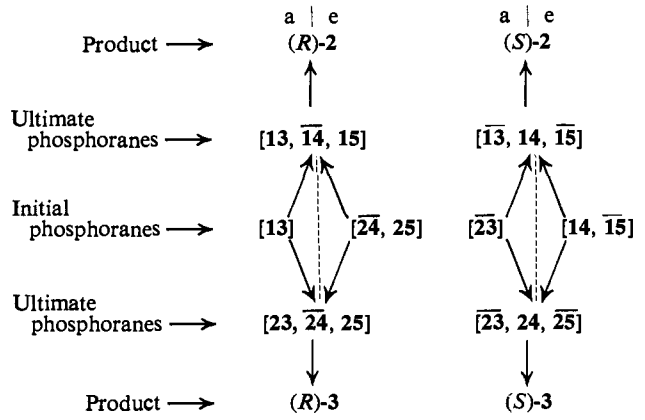
(8) K. E. DeBruin, K. Naumann, G. Zon, and K. Mislow, *J. Am. Chem. Soc.*, **91**, 7031 (1969).

(9) A total of ten isomeric phosphoranes may be initially formed from (*S*)-**1**, and ten others (the set enantiomeric at phosphorus) from (*R*)-**1**.

(10) For an alternative representation, see P. C. Lauterbur and F. Ramirez, *J. Am. Chem. Soc.*, **90**, 6722 (1968); *cf.* also E. L. Muetterties, *ibid.*, **91**, 1636 (1969).

(11) The classification of the OH group as electropositive or electronegative is obscured by the ready conversion of OH to O^- in strongly alkaline media. For the present discussion we will treat this group as satisfying whatever the electronic requirement of its position in the trigonal bipyramidal phosphorane: e for O^- and a for OH.

Scheme I. Mode of Attack and Departure, (*S*)-1



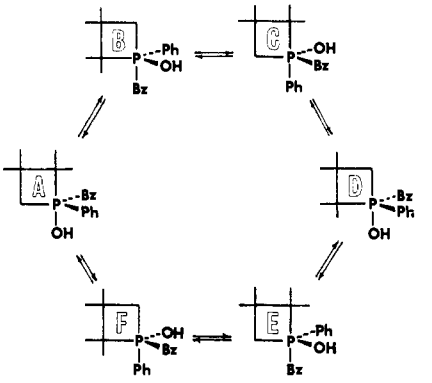


Figure 2.

rate-limiting step in the displacement, for in that case relatively rapid pseudorotation of the intermediate phosphoranes would lead to the same equilibrium mixture of (*S*)- and (*R*)-**1** from either (*S*)- or (*R*)-**1**, by way of a pathway such as (*S*)-**1** ⇄ $\overline{\mathbf{23}}$ ⇄ **14** ⇄ $\overline{\mathbf{25}}$ ⇄ $\overline{\mathbf{13}}$ ⇄ (*R*)-**1**, and hence to the same mixture of esters. In addition, the observation (Table I) that (*S*)-**1** and (*R*)-**1** give rise to markedly different ratios of products (*S*)-**2**/(*S*)-**3** or (*R*)-**2**/(*R*)-**3** indicates that there is no equilibration between $\overline{\mathbf{23}}$, one of the two phosphoranes initially formed by a attack[12] on (*S*)-**1**, and $\overline{\mathbf{13}}$, one of the two phosphoranes initially formed by a attack[12] on (*R*)-**1** (Scheme I). The same observation also rules out equilibration between **23** and **13**. Such an equilibration is not immediately excluded by arguments previously adduced, since no intermediates represented by the points of the star in Figure 1 need be invoked. The barrier to equilibration therefore resides in either **14** or $\overline{\mathbf{25}}$, of which $\overline{\mathbf{25}}$, with an electropositive methyl group in the a position and a bulky menthoxy group also in the a position, is the more likely candidate. For the same reason, **25**, **24**, and $\overline{\mathbf{24}}$ are regarded as high-energy intermediates.

The predominance of *S* products ((*S*)-**2** and (*S*)-**3**) over *R* products ((*R*)-**2** and (*R*)-**3**), 78 and 22%, respectively, in the hydrolysis of (*S*)-**1** is evidence that reaction *via* $\overline{\mathbf{23}}$ (menthoxy group apical) is faster than reaction *via* **13** (menthoxy group equatorial), and supports the view that the bulk of the menthoxy group exerts a significant effect on the product ratio: attack of hydroxide ion on the face of the tetrahedral phosphonium ion opposite the bulky menthoxy group (to form $\overline{\mathbf{23}}$) is *kinetically* preferred over attack opposite the ethoxy group (to form **13**) since, in the latter case, the attacking group is proximate to the bulky (menthoxy) group in the transition state.[13] Once formed, $\overline{\mathbf{23}}$ can either pseudorotate to **14** or $\overline{\mathbf{15}}$, thus relieving steric strain inherent in the a position of the menthoxy group (pseudorotation to $\overline{\mathbf{13}}$ is precluded for reasons stated above), and yield (*S*)-**2** by loss of ethoxide, or it can eliminate menthoxide directly and form (*S*)-**3**. The processes are competitive, as indicated by the 40:38 ratio of (*S*)-**2**:(*S*)-**3**. In contradistinction, **13** can eliminate ethoxide to form (*R*)-**2**, but is effectively prevented from eliminating menthoxide (and forming (*R*)-**3**) by the high energy of the ultimate phosphoranes ($\overline{\mathbf{24}}$ or **25**), or alternatively, by the need to pass through these same intermediates in order to reach the third ultimate phosphorane, **23**. This conclusion is borne out by the observed 10:1 ratio of (*R*)-**2**:(*R*)-**3** (Table I).

Similarly, hydrolysis of (*R*)-**1** results in product ratios which satisfy the constraints outlined above, although the effect is not as marked. The difference between the product ratios from (*R*)-**1** and from (*S*)-**1** can be attributed to the chiral menthoxy group.

The present findings are in harmony with the observation[15] that base-catalyzed hydrolysis of benzyl-*t*-butylmethylphenylphosphonium iodide proceeds with net retention of configuration; evidently, the initially formed (kinetic control) phosphorane, with a *t*-butyl group in the a position, relieves steric strain by pseudorotation to an ultimate phosphorane in which the *t*-butyl group is in the e position.[15] In this connection, we suggest that the apparent discrepancy, heretofore unexplained, between the observation of Cremer, *et al.*,[16] who found that in the base-catalyzed hydrolysis of *cis*- and *trans*-1-benzyl-1-phenyl-2,2,3,4,4-pentamethylphosphetanium bromides (**4**), epimerization of **4** is faster than hydrolysis (resulting in the same mixture of phosphetane 1-oxides from either stereoisomer), and the observation of Trippett *et al.*,[17] who found that base-catalyzed hydrolysis of optically active 1-benzyl-1-phenyl-2,2,3,3-tetramethylphosphetanium iodide (**5**) gives the phosphetane 1-oxide with retention of configuration, is readily resolved by recourse to arguments similar to the ones employed above. The initial phosphoranes A or $\overline{\text{A}}$, which result from a attack of hydroxide on (*R*)- or (*S*)-**5**, respectively, can in principle equilibrate with five diastereomeric phosphoranes,[8] as shown in Figure 2 for the case of (*R*)-**5**. However, A, C, and E are high-energy intermediates since a *t*-butyl-like group is located in the a position. Racemization prior to hydrolysis requires that loss of benzyl is slow compared to pseudorotation and addition–elimination of hydroxide: this requirement is not met in the system studied by Trippett, *et al.*,[17] since access to the requisite ultimate phosphorane (D) is blocked by the *relatively* high energy intermediates, C or E. Hence, pseudorotation to B leads to a relatively stable intermediate, the ultimate phosphorane for loss of benzyl anion with retention of

(12) In this and in subsequent discussion, analysis is restricted to apical attack and departure, the preferred mode of reaction.[4,8]

(13) This argument is similar to the one commonly employed in rationalizing the relatively high barrier to SN2 displacements on neopentyl carbon, and is applicable to substitution at phosphorus.[14]

(14) W. Hawes and S. Trippett, *Chem. Commun.*, 577 (1968).

(15) N. J. De'Ath and S. Trippett, *Chem. Commun.*, 172 (1969).

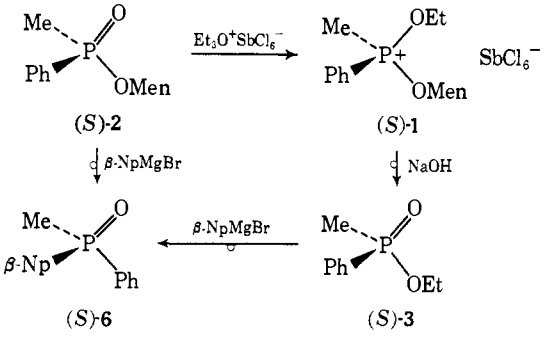
(16) S. E. Cremer, R. J. Chorvat, and B. C. Trivedi, *ibid.*, 769 (1969).

(17) J. R. Corfield, J. R. Shutt, and S. Trippett, *ibid.*, 789 (1969).

configuration, and rate of loss of benzyl is greater than rate of pseudorotation. By contrast, in the system studied by Cremer, *et al.*,[16] the corresponding phosphoranes derived from **4** *all* have *t*-butyl-like groups in the a position and *all* intermediates are therefore of comparably high energy. It follows that pseudorotation and loss of hydroxide can successfully compete with loss of benzyl anion.[18]

An Optically Active Phosphinate with Phosphorus the Sole Chiral Center. The synthesis and hydrolysis of (*S*)-**1** yielded (*S*)-**3** of 88% optical purity in *ca.* 30% over-all yield. This is a useful synthetic entry to optically active phosphinates in which phosphorus is the sole chiral center.[19] It is interesting to note that (*S*)-**3** is obtained from (*S*)-**2**, *i.e.*, with over-all retention of configuration at phosphorus, even though only one step in this interconversion proceeds with inversion at phosphorus. Similarly, the cycle portrayed in Scheme II, which was used to assign configurations at phosphorus in **2** and **3**, involves an odd (three) number of inversions, and thus represents something of a stereochemical curiosity.

Scheme II[a]



[a] Np = β-naphthyl; Men = (−)-menthyl.[5b]

Experimental Section[20]

Synthesis of (*S*)$_P$- and (*R*)$_P$-Ethoxymenthoxymethylphenylphosphonium Hexachloroantimonates, (*S*)$_P$- and (*R*)$_P$-1. A solution of diastereomerically pure menthyl (*S*)$_P$-methylphenylphosphinate, (*S*)$_P$-**2** (500 mg, 1.7 mmol), $[\alpha]_D$ −95° (lit.[5a] $[\alpha]_D$ −94°), in dichloromethane (10 ml) was added to a solution of triethyloxonium hexachloroantimonate in dichloromethane (10 ml).[21] The mixture was stirred at room temperature for 10 hr and was then concentrated under vacuum to 5 ml. Addition of this residue to anhydrous ether (100 ml) produced a white crystalline material which was identified as (*S*)$_P$-ethoxymenthoxymethylphenylphosphonium hexachloroantimonate, (*S*)$_P$-**1** (840 mg, 75%), mp 92–93° dec. The pmr spectrum of this material was consistent with that expected for diastereomerically pure (*S*)$_P$-**1** and featured PCH_3, d, τ 7.54, J_{PCH} = 14 Hz; $POCH_2CH_3$, broad triplet, τ 8.53, J_{HCCH} = 7 Hz; $POCH_2CH_3$, apparent quintet, τ 5.73, J_{HCCH} = 7 Hz, J_{POCH} = 7 Hz. The upfield doublet in the pmr spectrum of (*S*)$_P$-**2**[22] was shifted to τ 9.0 upon ethylation to (*S*)$_P$-**1**.

Anal. Calcd for $C_{19}H_{32}PO_2SbCl_6$: C, 34.69; H, 4.90; P, 4.71. Found: C, 34.74; H, 5.07; P, 4.76.

The synthesis of (*R*)$_P$-**1** from diastereomerically pure (*R*)$_P$-**2**, $[\alpha]_D$ −17° (lit.[5a] $[\alpha]_D$ −16.3°) was similar to that of (*S*)$_P$-**1**; however, all attempts to induce crystallization of (*R*)$_P$-**1** failed. The crude product was purified by decanting three times with ether (100 ml) to afford (*R*)$_P$-**1** in 85% yield. The pmr spectrum of this material featured $POCH_2CH_3$, broad triplet, τ 8.48, $J_{HCCH} \approx$ 7 Hz; $POCH_2CH_3$, apparent quintet, τ 5.58, J_{HCCH} = 7 Hz, J_{POCH} = 7 Hz; PCH_3, d, τ 7.53, J_{PCH} = 14 Hz. The pmr spectrum is conspicuously void of a signal in the region of the upfield doublet of (*S*)$_P$-**1**.

Hydrolysis of (*S*)$_P$- and (*R*)$_P$-Ethoxymenthoxymethylphenylphosphonium Hexachloroantimonates, (*S*)$_P$- and (*R*)$_P$-1. The hydrolyses of (*S*)$_P$-**1** and (*R*)$_P$-**1** were carried out by identical procedures. A solution (50 ml) of 0.5 *M* NaOH in 50 v/v % aqueous dioxane was added to a solution of either (*S*)$_P$- or (*R*)$_P$-**1** (500 mg, 0.76 mmol) in dioxane (0.5 ml), and the heterogeneous mixture was stirred for 1 min. The reaction mixture was extracted with dichloromethane and the combined organic layers were dried (magnesium sulfate). Removal of solvent under reduced pressure gave a mixture of both diastereomers of **2**, (*S*)$_P$- and (*R*)$_P$-**2**, ethyl methylphenylphosphinate (**3**), and *l*-menthol. The total products (*ca.* 200 mg) from the hydrolysis of (*S*)$_P$-**1** or (*R*)$_P$-**1** were analyzed as follows.

The P-CH_3 group in each of the three products from the hydrolysis of **1** ((*S*)$_P$-**2**, (*R*)$_P$-**2**, and **3**[23]) has a characteristic signal in the pmr spectrum: (*S*)$_P$-**2**, τ 8.34, J_{PCH} = 14.5 Hz; (*R*)$_P$-**2**, τ 8.38, J_{PCH} = 14.5 Hz; and **3**, τ 8.37, J_{PCH} = 14.5 Hz. With the aid of a Du Pont Model 310 curve resolver, the proportions of the three compounds were estimated by integration of the upfield half of each doublet.

The relative amounts of **2** and **3** were estimated by glpc analysis (6 ft, SE-30, 200°) of the crude mixture of products from the hydrolysis of (*S*)$_P$- and (*R*)$_P$-**1**.

Rapid distillation (Kugelrohr) at 80° (0.1 mm) separated the volatile menthol and **3** from the relatively nonvolatile mixture of (*S*)$_P$- and (*R*)$_P$-**2**. A pmr analysis of the nonvolatile material afforded a measure of the relative amounts of the two components by direct comparison of the intensities of the corresponding signals due to the P-CH_3 group.[22] The ratio of (*S*)$_P$- and (*R*)$_P$-**2** thus obtained agreed well (within 1%) with that determined on the crude mixture.

Menthol was separated from **3** by chromatography on silica gel. Benzene eluted menthol, leaving **3** which was readily eluted with chloroform. The sample of **3** was further purified by collection from a gas chromatograph (SE-30, 150°).

The optical purity and absolute configuration of **3** were established by its conversion to methyl-β-naphthylphenylphosphine oxide (**6**) with β-naphthylmagnesium bromide.[5a] The sample of **3**, $[\alpha]_D$ −41°, obtained from hydrolysis of (*S*)$_P$-**1**, yielded (*S*)-**6**, $[\alpha]_D$ +24° (chloroform). Assuming the Grignard reaction proceeded stereospecifically with inversion,[5a] this sample of **3** was 88% optically pure, based on the highest reported rotation of **6**,[5a] with a predominance of the *S* isomer. It follows that the absolute rotation of **3** is 41°/0.88 = 45°. Consequently, **3**, $[\alpha]_D$ +24°, obtained from hydrolysis of (*R*)$_P$-**1**, was 64% optically pure, with a predominance of the *R* isomer.

The results of the various analyses are collected in Table III.

Table III. Analysis of Products from Hydrolyses of (*R*)$_P$- and (*S*)$_P$-**1**

	—Products from (*S*)$_P$-**1**, %—				—Products from (*R*)$_P$-**1**, %—			
Method	(*S*)$_P$-**2**	(*R*)$_P$-**2**	(*S*)-**3**	(*R*)-**3**	(*S*)$_P$-**2**	(*R*)$_P$-**2**	(*S*)-**3**	(*R*)-**3**
Pmr	40	20	←40→		28	40	←32→	
Glpc	←60→		←40→		←69→		←31→	
$[\alpha]_D$[a]			38	2			8	24

[a] Based on $[\alpha]_D$ −45° for optically pure (*S*)-**3** (see text). The absolute percentages are based on the totals (for **3**) found by pmr and glpc.

(18) If the displaced group has better leaving ability, the displacement may again successfully compete with epimerization (K. E. DeBruin, G. Zon, K. Naumann, and K. Mislow, *J. Am. Chem. Soc.*, **91**, 7027 (1969)); S. E. Cremer, R. J. Chorvat, and B. C. Trivedi, paper presented at the 3rd Great Lakes Regional Meeting of the American Chemical Society, Northern Illinois University, DeKalb, Ill., June 5, 1969).

(19) For other approaches, see D. M. Coyne, W. E. McEwen, and C. A. VanderWerf, *J. Am. Chem. Soc.*, **78**, 3061 (1956); H. P. Benschop, G. R. van den Berg, and H. L. Boter, *Rec. Trav. Chim.*, **87**, 387 (1968).

(20) Elemental analyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y. Pmr spectra were recorded on a Varian A-60A spectrometer and refer to *ca.* 10% solution in deuteriochloroform, with tetramethylsilane as internal standard. Optical rotations were measured on a Schmidt and Haensch visual polarimeter and refer to solvent benzene (*c* 1–3 g/100 ml), except as noted. Determinations of ^{18}O content were made from mass spectra obtained with an AEI MS-9 high-resolution mass spectrometer. We thank the National Science Foundation for providing the funds for the purchase of the mass spectrometer under Grant No. GP-5200.

(21) H. Meerwein, *Org. Syn.*, **46**, 113 (1966); H. Meerwein, E. Battenberg, H. Gold, E. Pfeil, and G. Willfang, *J. Prakt. Chem.*, **154**, 83 (1939).

(22) R. A. Lewis, O. Korpiun, and K. Mislow, *J. Am. Chem. Soc.*, **90**, 4847 (1968).

(23) In an achiral medium, the enantiomers of **3** are indistinguishable by pmr.

Control Experiments. That a preferential hydrolysis of $(S)_P$-**2** or $(R)_P$-**2** did not occur under the reaction conditions for hydrolysis of **1** was shown by submitting a mixture of 68 mol % $(S)_P$-**2** and 32 mol % $(R)_P$-**2** to these exact conditions. Recovery of the unreacted **2** after 5 min yielded a mixture of unchanged composition, as estimated by pmr.

The differential rate of hydrolysis of **2** and **3** was determined by submitting a mixture consisting of 70 mol % of **3** and 30 mol % of $(S)_P$-**2** to the conditions of the hydrolysis of **1**. Aliquots were taken and quenched by extracting with dichloromethane, and the recovered mixture of **3** and $(S)_P$-**2** was analyzed by pmr. A plot of ln [(**3**)/(**2**)] against time yielded a slope ($k_3 - k_2$, assuming pseudo-first-order kinetics) of 1.6×10^{-3} sec^{-1}. From the value of $k_3 - k_2$, the yields of the products of the hydrolysis of **1** (Table III) were corrected for the differential rate of hydrolysis and are given in Table I.

Hydrolysis of $(S)_P$-1 with Na^{18}OH. A solution (5 ml) of 0.5 *M* NaOH in 50 v/v % H_2O–dioxane, containing 3.24 atom % ^{18}O/mol in the H_2O, was added to a solution of $(S)_P$-**1** (200 mg, 0.30 mmol) in dioxane (0.1 ml), and the mixture was stirred for 1 min. Work-up, as above, yielded a mixture of $(S)_P$-**2**, $(R)_P$-**2**, and **3** in the same ratio as that obtained in the experiments using ordinary water. Separation of **2** from **3** was accomplished by glpc and each mixture of stereoisomers was analyzed for ^{18}O incorporation by mass spectrometry as described below. The fraction of **2** contained 3.16 ± 0.16 atom % ^{18}O/mol (assuming that only one oxygen atom was involved in the hydrolysis); similarly, **3** was found to contain 3.15 ± 0.10 atom % ^{18}O/mol. A duplicate hydrolysis resulted in the incorporation of 3.25 ± 0.13 atom % ^{18}O/mol into **2** and 3.21 ± 0.12 atom % ^{18}O/mol into **3**.

To determine the extent of ^{18}O incorporation into **2** or **3** after hydrolysis of **1**, samples (50 mg) of **2** and **3** were submitted to hydrolysis under the same conditions as those employed in the hydrolysis of **1**. The recovered esters were found to contain the natural abundance of ^{18}O/mol.

Synthesis of Polyalkoxyphosphonium Hexachloroantimonates. The polyalkoxyphosphonium hexachloroantimonates were prepared by a procedure similar to that employed for the synthesis of **1**. After the reaction mixture had been stirred for 10 hr, the solutions were added directly to anhydrous ether, inducing the respective salts to precipitate. In this manner, ethyl methylphenylphosphinate was converted to **diethoxymethylphenylphosphonium hexachloroantimonate**: mp 67–68°; pmr PCH_3, d, τ 7.53, J_{PCH} = 14 Hz; $POCH_2CH_3$ t, τ 8.41, J_{HCCH} = 7 Hz; $POCH_2CH_3$, apparent quintet, τ 5.43,, J_{HCCH} = 7 Hz, J_{POCH} = 7 Hz; PC_6H_5, m, τ 2.0–2.2.

Anal. Calcd for $C_{11}H_{18}PO_2SbCl_6$: C, 24.12; H, 3.31; P, 5.66. Found: C, 23.63; H, 3.14; P, 5.60.

Similarly, **triethoxyphenylphosphonium hexachloroantimonate**, mp 81.5–82.5°, was prepared from diethyl phenylphosphonate. The pmr spectrum showed $POCH_2CH_3$, t, τ 8.41, J_{HCCH} = 7 Hz; $POCH_2CH_3$, apparent quintet, τ 5.21, J_{HCCH} = 7 Hz, J_{POCH} = 7 Hz; PC_6H_5, m, τ 2.0–2.2.

Anal. Calcd for $C_{12}H_{20}PO_3SbCl_6$: C, 24.95; H, 3.49; P, 5.36. Found: C, 25.04; H, 3.45; P, 5.26.

Triethylphosphate was converted into **tetraethoxyphosphonium hexachloroantimonate**: mp 116–117°; pmr $POCH_2CH_3$, doubled triplet, τ 8.45, J_{HCCH} = 7 Hz, J_{POCCH} = 1 Hz; $POCH_2CH_3$, apparent quintet, τ 5.39, J_{HCCH} = 7 Hz, J_{POCH} = 7 Hz.

Anal. Calcd for $C_8H_{20}PO_4SbCl_6$: C, 17.61; H, 3.70; P, 5.68. Found: C, 17.81; H, 3.53; P, 5.23.

Hydrolysis of Polyalkoxyphosphonium Hexachloroantimonates with Na^{18}OH. The hydrolysis of the three polyalkoxyphosphonium hexachloroantimonates was carried out by the procedure outlined for the hydrolysis of $(S)_P$-**1** with Na^{18}OH. The ^{18}O incorporation into the product ester from hydrolysis of each phosphonium salt was obtained from a mass spectral analysis, as described below. The ^{18}O enrichment in the H_2O used for the respective hydrolysis and the results of the ^{18}O study are given in Table II.

By submitting each of the product esters to the conditions used for the hydrolysis of the phosphonium salts, it was shown that there was no incorporation of excess ^{18}O during the hydrolysis.

Synthesis and Hydrolysis of Diethoxymethylphenylphosphonium Nitrate. Diethoxymethylphenylphosphonium hexachloroantimonate (270 mg, 0.5 mmol) was added to a solution of silver nitrate (500 mg, 3.0 mmol) in anhydrous methanol (50 ml) and the heterogeneous mixture was stirred for 5 min. Filtration, concentration under reduced pressure, and decantation with ether (100 ml) afforded diethoxymethylphenylphosphonium nitrate as an oil. The pmr spectrum was unchanged from that of the hexachloroantimonate salt. The hydrolysis was carried out as described above.

Mass Spectral Analysis of ^{18}O Content. The samples analyzed by mass spectrometry contained P + 1 and P + 2 peaks of greater intensity, relative to the intensity of P, than predicted, assuming natural abundance of all isotopes. This phenomenon is believed to result from protonated substrate and the following procedure was therefore adopted. An authentic sample ("blank") of each ester was analyzed on the same day as the sample ("unknown") of unknown ^{18}O content. The values (x and y) of (P + 2)/[P + (P + 2)] for the blank and unknown, respectively, were calculated. The contribution due to the natural abundance of ^{18}O in one oxygen (0.0020) was subtracted from x, yielding the remaining sum (x − 0.0020) of all other contributions to x. Subtraction of (x − 0.0020) from y yielded the contribution of ^{18}O of the one oxygen to y (eq 1).

$$\text{atom \% } ^{18}\text{O/mol} = [y - (x - 0.0020)] \times 100 \qquad (1)$$

A resulting value of 0.20 atom % ^{18}O/mol would indicate natural abundance ($x = y$).

For the analysis of **2**, a parent peak could not be obtained due to cleavage of the menthyl group. Therefore, the analysis was carried out on the *m/e* 184 region (methylphenylphosphinic acid). All other analyses utilized the parent peaks.