

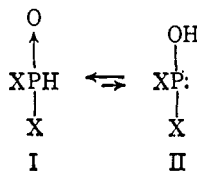
Unsymmetrical Secondary Phosphine Oxides. Synthetic, Isotopic Exchange, and Stereochemical Studies

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Abstract: Two general methods are described for preparing unsymmetrical secondary phosphine oxides. One involves displacement of alkoxide from an ester of a monosubstituted phosphinic acid by a Grignard reagent; the other, reduction of an ester of a disubstituted phosphinic acid by lithium aluminum hydride. Properties of a number of new secondary phosphine oxides prepared by these methods are reported. Of special interest is benzylphenylphosphine oxide, $[\alpha]_D -0.52^\circ$, obtained by reduction of (–)-menthyl benzylphenylphosphinate ($[\alpha]_D -65.4^\circ$). This product is configurationally stable in methanol at room temperature but racemizes in methanol solutions of hydrochloric acid or sodium methoxide. In methanol-*d*, benzylphenylphosphine oxide rapidly exchanges the hydrogen on phosphorus for deuterium, as shown by the change in the intensity of the O–H resonance peak in the pmr spectrum.

Phosphorus compounds of the general type $X_2P(O)H$ undergo a variety of substitution reactions in which H is replaced by another atom or group. Typical examples include replacement of hydrogen by deuterium,^{2–5} halogen,⁶ alkylmercapto,^{7,8} β -substituted alkyl,^{9,10} and α -hydroxyalkyl.^{11,12} Spectral data show that $X_2P(O)H$ compounds exist primarily in the oxide form I.^{13,14} However, a considerable body of evidence derived largely from the kinetics of isotopic exchange and oxidation of dialkyl phosphonates,^{2,3,15,16} phosphorous acid,¹⁷ and hypophosphorous acid¹⁸ is best interpreted in terms of formation of a tautomer (II) of I which serves as a reactive intermediate in the substitution reactions.



(1) Public Health Service Predoctoral Fellow, 1-F1-GM-23,565, 1964–1966.

(2) Z. Luz and B. Silver, *J. Am. Chem. Soc.*, **83**, 4518 (1961); **84**, 1095 (1962).

(3) W. J. Bailey and R. B. Fox, *J. Org. Chem.*, **29**, 1013 (1964); **28**, 531 (1963), and references cited therein.

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(5) D. Samuel, *Pure Appl. Chem.*, **9**, 449 (1964).

(6) R. H. Williams and L. A. Hamilton, *J. Am. Chem. Soc.*, **74**, 5418 (1952).

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(9) A. N. Pudovik and B. A. Arbusov, *Dokl. Akad. Nauk SSSR*, **73**, 327 (1950).

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(13) C. F. Callis, J. R. Van Wazer, J. N. Shoolery, and W. A. Anderson, *ibid.*, **79**, 2719 (1957).

(14) J. R. Van Wazer, "Phosphorus and Its Compounds," Interscience Publishers, Inc., New York, N. Y., 1958, p 368.

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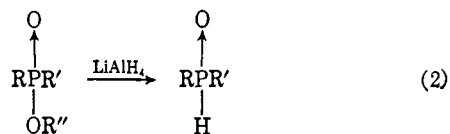
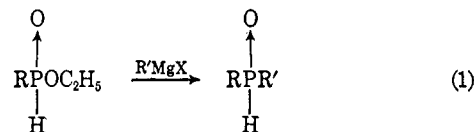
(16) B. Silver and Z. Luz, *J. Am. Chem. Soc.*, **84**, 1091 (1962).

(17) B. Silver and Z. Luz, *J. Phys. Chem.*, **66**, 1356 (1962).

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As in the case of substitution at a carbon center, stereochemical as well as kinetic data should prove helpful in elucidating the mechanisms of reactions involving fission of phosphorus–hydrogen bonds. To date, however, no optically active $XX'P(O)H$ compounds have been described. The objective of the present work was synthesis of such a compound which could be used to investigate the stereochemistry of replacement of hydrogen at phosphorus. To avoid complications stemming from fission of the P–X bonds we selected for study the secondary phosphine oxides (X = alkyl or aryl), in which the X group is firmly joined by a carbon–phosphorus bond.

Unsymmetrical Secondary Phosphine Oxides. Unsymmetrical secondary phosphine oxides have been made by condensation of primary phosphines with ketones¹⁹ and by a series of steps involving reaction of an arenediazonium fluoroborate with phenylphosphonous dichloride, reduction of the product with aluminum, and hydrolysis of the resulting diarylphosphinous chloride.²⁰ Since neither procedure appeared well suited for synthesis of an optically active compound, however, other preparative methods were sought. Two procedures which utilize nucleophilic displacement of OR from P–OR, a reaction type previously exploited in the synthesis of symmetrical secondary phosphine oxides,⁶ proved successful. In one (reaction 1), ethoxide is displaced from an ethyl ester of a monosubstituted phosphinic acid by a Grignard reagent; in the other (reaction 2), the ester of a disubstituted phosphinic acid is reduced with lithium aluminum hydride.



(19) S. A. Buckler and M. Epstein, *ibid.*, **82**, 2076 (1960).

(20) L. D. Quin and R. E. Montgomery, *J. Org. Chem.*, **28**, 3315 (1963).

Table I. Preparation of RR'P(O)H

R	R'	Yield, %	Mp, °C	Mp of analytical sample, °C	Anal, %					
					C		H		P	
					Calcd	Found	Calcd	Found	Calcd	Found
C ₆ H ₅	C ₄ H ₉ ^a	32		136–138 ^c	65.92	65.94	8.30	8.24		
C ₆ H ₅ CH ₂	C ₄ H ₉ ^a	32	58–59	61.5–62	67.32	67.89	8.73	8.40		
<i>p</i> -ClC ₆ H ₄ CH ₂	C ₄ H ₉ ^a	41	82–83	83.5–84.5	57.27	57.28	7.01	6.82	13.43	13.45
C ₆ H ₅ CH ₂	C ₆ H ₅ ^b	75	111–113	121.5–123	72.21	72.20	6.06	6.23	14.32	14.08
<i>p</i> -BrC ₆ H ₄ CH ₂	C ₆ H ₅ ^b	29	155.5–164	160.5–161.5	52.77	52.96	4.36	4.38	10.47	10.27
<i>p</i> -C ₆ H ₅ C ₆ H ₄	C ₆ H ₅ ^b	25	95.5–97	95.5–97	77.69	77.42	5.43	5.68		

^a Prepared from ethyl *n*-butylphosphinate. ^b Prepared from ethyl phenylphosphinate. ^c Boiling point (2.9 mm).

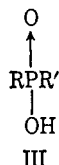
Table II. Unsymmetrical Phosphinic Acids (III) from Phosphine Oxides

R	R'	Oxidizing agent	Yield, %	Mp, ^a °C	Anal, %					
					C		H		P	
					Calcd	Found	Calcd	Found	Calcd	Found
C ₆ H ₅	C ₄ H ₉	PCl ₅	54	Oil ^b						
C ₆ H ₅ CH ₂	C ₄ H ₉	PCl ₅	60	109–110, ^c 95.5–96.5 ^d	62.5	62.23	8.07	7.95		
<i>p</i> -ClC ₆ H ₄ CH ₂	C ₄ H ₉	H ₂ O ₂	47	121.5–122.5	53.96	53.86	6.54	6.55	12.56	12.50
C ₆ H ₅ CH ₂	C ₆ H ₅	O ₂	67	182.5–183.5 ^e	67.20	67.17	5.64	5.84	13.34	13.60
<i>p</i> -BrC ₆ H ₄ CH ₂	C ₆ H ₅	H ₂ O ₂	83	214.5–215.5	50.66	50.32	4.14	4.06	9.93	9.75
<i>p</i> -C ₆ H ₅ C ₆ H ₄	C ₆ H ₅	H ₂ O ₂	81	238–240	73.47	73.22	5.14	5.37	10.52	10.38

^a Melting point of recrystallized sample. ^b Anal. Calcd for C₁₄H₁₅O₂P: neut equiv, 198. Found: neut equiv, 211. The compound was obtained as a crystalline hydrate which became an oil when dried (see also ref 24). ^c Recrystallized from acetone–hexane. ^d Recrystallized from water (lit.²² mp 97–98°). ^e Lit.²³ mp 178–180°.

The general utility of route 1 was demonstrated by preparation of six unsymmetrical secondary phosphine oxides, three from ethyl *n*-butylphosphinate and three from ethyl phenylphosphinate, in yields ranging from 25 to 75% (Table I). Route 2 was demonstrated by the conversion of methyl *p*-biphenylphenylphosphinate to *p*-biphenylphenylphosphine oxide (R = C₆H₅ and R' = *p*-C₆H₅C₆H₄) in 35% yield. This compound was identical with the product from the reaction of *p*-biphenylmagnesium bromide and ethyl phenylphosphinate by route 1.

The oxides were characterized by elemental analyses (Table I), by infrared and proton magnetic resonance spectra, and by oxidation to the corresponding phosphinic acids (III). Each showed a weak band in the 2290–2360-cm⁻¹ region attributable to the P–H stretching vibration and a stronger band in the 1160–1200-cm⁻¹ region attributable to the P–O stretching vibration.²¹ Oxidation to the phosphinic acids was effected by hydrogen peroxide in ethanol, by successive treatment with phosphorus pentachloride and water,⁶ and by oxygen in alkaline methanol. Pertinent data on the phosphinic acids are collected in Table II. Of the compounds listed, benzylbutyl-,²² benzylphenyl-,²³ and butylphenylphosphinic acid²⁴ have been prepared previously in other ways. Benzylbutylphosphinic acid was isolated



(21) N. B. Colthup, L. H. Daley, and S. E. Wiberty, "Introduction to Infrared and Raman Spectroscopy," Academic Press Inc., New York, N. Y., 1964, pp 299–300, 402–405.

(22) M. Sander, *Ber.*, **93**, 1220 (1960).

(23) F. F. Blicke and S. Raines, *J. Org. Chem.*, **29**, 204 (1964).

(24) G. M. Kosolapoff, *J. Am. Chem. Soc.*, **72**, 4292 (1950).

in two crystalline modifications, mp 109–110° and 95.5–96.5°, by recrystallization from acetone–hexane and from water, respectively.

The proton magnetic resonance spectrum of diphenylphosphine oxide consists of bands for the phenyl group and a doublet due to the hydrogen (H_P) bonded to phosphorus (δ 8.00 ppm relative to TMS, *J*_{P–H} = 481 Hz). In the benzyl derivatives the resonance of the H_P proton is split further by coupling with the methylene protons (*J* = 3.0–3.5 Hz). Accordingly the H_P protons give rise to two widely spaced quintets in dibenzylphosphine oxide and to two triplets in benzylphenylphosphine oxide. Since the high-field portion of the H_P resonance falls under that of the methylene protons, however, only the low-field portion of the H_P multiplet is clearly resolved. The methylene protons of the benzyl groups in dibenzyl-, benzyl-*n*-butyl-, and *p*-chlorobenzyl-*n*-butylphosphine oxide give rise to quartets (δ 3.18–3.46 ppm relative to TMS) as a result of spin–spin coupling with both phosphorus (*J* = 15–16 Hz) and H_P. That further splitting is not observed for the diastereotopic methylene protons indicates that Δδ for these protons is quite small. In benzylphenyl- and benzyl-*p*-bromophenylphosphine oxide, however, a three-line pattern consisting of a singlet and a weaker doublet is observed in place of the quartet. This pattern may be ascribed to a coincidence of the high-field triplet portion of H_P resonance and the low-field half of the quadruplet for the methylene protons resonance. The integrated peak areas support this interpretation. In addition, the spectrum of benzylphenylphosphine-*d* oxide, which was prepared by exchanging the proton on phosphorus by deuterium, exhibits the expected simple doublet (δ 3.46 ppm relative to TMS, *J* = 15.3 Hz) in the region for the methylene protons.

Chemical shift and spin–spin coupling values for the H_P proton in the phosphine oxides are given in Table III. For this series the data correlate well with values

calculated by summing empirical parameters for the groups (alkyl, aryl, or benzyl) joined to phosphorus.²⁵ The parameters for the chemical shift (ppm) and coupling constant (Hz), respectively, are taken to be: aryl 4.0, 241; benzyl 3.5, 233; and alkyl 3.3, 221.

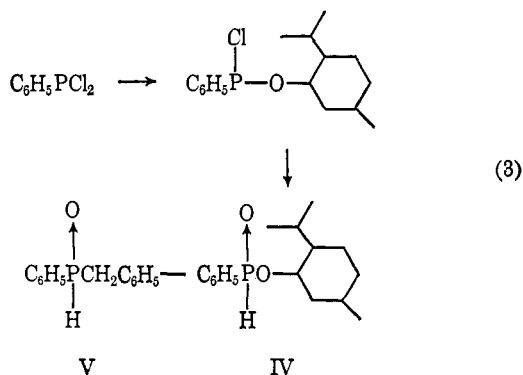
Table III. Proton Magnetic Resonance Data for Hydrogen Joined to Phosphorus^a

R	R'	H _P chemical shift, ppm		P-H _P coupling constant, Hz	
		Obsd	Calcd	Obsd	Calcd
C ₆ H ₅	C ₆ H ₅	8.00	8.0	481	482
C ₆ H ₅	<i>p</i> -C ₆ H ₅ C ₆ H ₄	8.10	8.0	482	482
C ₆ H ₅	C ₆ H ₅ CH ₂	7.50	7.5	474	474
C ₆ H ₅	<i>p</i> -BrC ₆ H ₄ CH ₂	7.52	7.5	476	474
C ₆ H ₅	C ₄ H ₉	7.18	7.3	461	462
C ₆ H ₅ CH ₂	C ₆ H ₅ CH ₂	7.00	7.0	465	466
C ₆ H ₅ CH ₂	C ₄ H ₉	6.80	6.8	455	454
<i>p</i> -ClC ₆ H ₄ CH ₂	C ₄ H ₉	6.83	6.8	460	454

^a The solvent was CDCl₃ and tetramethylsilane was used as an external standard.

(-)-Benzylphenylphosphine Oxide. Attempts to introduce a functional group into a preformed unsymmetrical phosphine oxide to serve as a handle in resolution were unsuccessful. Neither metal-halogen exchange (2 equiv of butyllithium with *p*-bromobenzylphenylphosphine oxide) nor electrophilic substitution in the aromatic ring was realized. Attention was then directed to a stereospecific synthesis from an asymmetric phosphinic ester, a procedure analogous to that used for preparation of optically active sulfoxides.²⁶

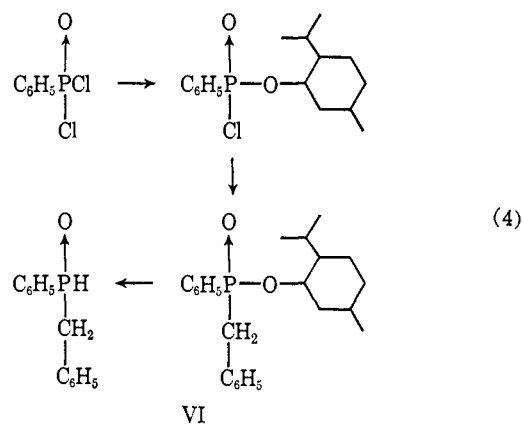
Both pathways (1 and 2) developed for synthesis of unsymmetrical secondary phosphine oxides were explored. For path 1 (-)-menthyl phenylphosphinate (IV) was prepared from phenylphosphonous dichloride and (-)-menthol (reaction scheme 3). On reaction with benzylmagnesium chloride it yielded benzylphenylphosphine oxide (V) satisfactorily; however, the diastereoisomers of (-)-menthyl phenylphosphinate could not be separated for use in the synthesis of an optically active phosphine oxide.



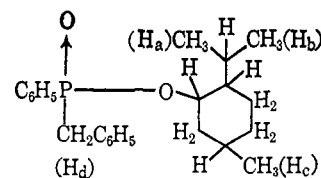
(25) Values of the parameters were selected such that a minimum difference between calculated and observed values would exist for the entire set of compounds. For correlations of ³¹P chemical shift values with change in substitution at phosphorus for other types of compounds see J. R. Van Wazer, C. F. Callis, J. N. Shoolery, and R. C. Jones, *J. Am. Chem. Soc.*, **78**, 5715 (1956); M. L. Nielsen, J. V. Pustinger, Jr., and J. Strobel, *J. Chem. Eng. Data*, **9**, 167 (1964); G. Mavel and G. Martin, *Compt. Rend.*, **257**, 1703 (1963).

(26) K. K. Anderson, *Tetrahedron Letters*, 93 (1962); K. K. Anderson, W. Gaffield, N. E. Papanikolaou, J. W. Foley, and R. I. Perkins, *J. Am. Chem. Soc.*, **86**, 5637 (1964).

For route 2, menthyl phenylphosphonochloridate was prepared from phenylphosphonic dichloride and (-)-menthol and then treated with 1 equiv of benzylmagnesium chloride (reaction scheme 4). The



resulting (-)-menthyl benzylphenylphosphinate (VI), mp 129–130°, [α]_D²⁵ -50.7°, yielded on crystallization from hexane a high-melting form, mp 153–155°, [α]_D²⁵ -65.4°. The infrared spectrum of this isomer was the same as that of the low-melting material. That the high-melting material was a single diastereomer was shown by comparison of its proton magnetic resonance spectrum with that of the mixture which melted at 129–130°. In addition to the phenyl multiplet at 7.5 ppm and the complex pattern of the cyclohexyl ring system, the spectrum of the high-melting product contained four distinct doublets, for which the chemical shifts in parts per million and coupling constants in hertz (given in parentheses) are 0.40 (7.0), 0.84 (7.0), 0.87 (4.6), and 3.28 (18.0). These doublets may be assigned to the H_a, H_b, H_c, and H_d protons, respectively (see formula).²⁷ The mixture (mp 129–130°) exhibited these peaks and, in addition, peaks expected for the epimer. Most distinctive was a new doublet at 3.22 ppm (18.0 Hz, area approximately two-thirds that for the doublet at 3.28) which may be attributed to the benzylic hydrogen atoms of the epimer. The signals for the methyl hydrogens for the mixture were less clearly resolved and overlapped to some extent; they are consistent, however, with values for the H_a, H_b, and H_c hydrogens of the epimer of 0.76 (7.0), 0.87 (7.0), and 0.83 (4.6).



On reduction of the high-melting ester with excess lithium aluminum hydride and hydrolysis of the reaction mixture with aqueous ammonium chloride, benzylphenylphosphine oxide with [α]_D²⁶ -0.52° (in CH₃OH) was obtained. In two other experiments the specific rotation of the oxide isolated was -0.28 and -0.26°. The yield was approximately 45%. No unreacted

(27) These assignments are based on the elegant analysis of related menthyl phosphinates, for which the configurations have been established, by R. A. Lewis, O. Korpiun, and K. Mislow, *ibid.*, **89**, 4786 (1967). A comparison with their data clearly indicates that the isomer of VI melting at 153–155° must have the *S* configuration at phosphorus.

methyl benzylphenylphosphinate was found and 70% of the (–)-menthol was recovered.²⁸

Since the observed rotation is low, the possibility that the optical activity is due to a small amount of an undetected, highly rotating contaminant is particularly troublesome. Indeed, this possibility cannot be rigorously excluded; however, several observations strongly support the view that the activity must stem from the phosphine oxide itself. (a) A levorotatory contaminant would probably be either (–)-menthol or a menthol derivative. As described in the next section, the optically active material racemizes readily in a dilute methanol solution of hydrochloric acid or sodium methoxide. Under these conditions, racemization of menthol or a menthol derivative is highly improbable. (b) When benzylphenylphosphine oxide was prepared from the low-melting sample of menthyl benzylphenylphosphinate ($[\alpha]^{25D} -50.7^\circ$), it was devoid of optical activity. This result is compatible with the view that the low-melting menthyl benzylphenylphosphinate was an unresolved ester of (–)-menthol, which yielded on reduction equal amounts of the *d*- and *l*-phosphine oxide. If the activity in the product obtained on reducing the high-melting form ($[\alpha]_D -65.4^\circ$) had come from a contaminant, some activity in the product from the lower melting ester ($[\alpha]^{25D} -50.7^\circ$) should have been observed as well. (c) In a control experiment it was found that racemic benzylphenylphosphine oxide is cleanly separated from both (–)-menthol and (–)-menthyl benzylphenylphosphinate by the procedure used in isolating the optically active product.

Isotopic Exchange and Racemization Studies. The substitution reaction selected for investigation was hydrogen–deuterium exchange at phosphorus. Extensive studies of isotopic exchange reactions of diethyl phosphonate and related compounds^{2–5} have been reported; however, no work of this type with secondary phosphine oxides has been described.

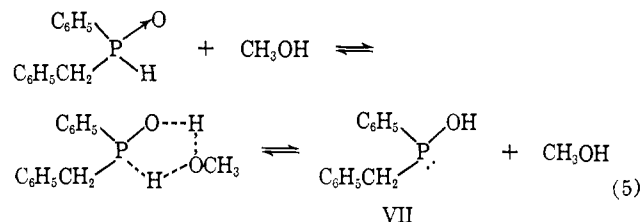
It was found that benzylphenylphosphine oxide in methanol-*d* rapidly exchanges the hydrogen on phosphorus for deuterium. Exchange was complete within 4 min at 25° as judged by the increase in the proton magnetic resonance signal of the methanol-*h* produced in the reaction. Proof of hydrogen–deuterium exchange at phosphorus was obtained by isolating the benzylphenylphosphine-*d* oxide, characterizing it by the proton magnetic resonance and infrared spectra, and reconvertng it to deuterium-free benzylphenylphosphine oxide by treatment with methanol. In the presence of 0.05 *M* HCl or HCl 0.05 *M* in sodium methoxide, the exchange was at least as fast as (probably faster than) in neutral methanol. There was no evidence for exchange at the methylene hydrogens of the benzyl group in any of these reactions.

Diethyl phosphonate reacted much more slowly than benzylphenylphosphine oxide with neutral methanol-*d* (k_{obsd} for the phosphonate = $1.1 \times 10^{-2} \text{ min}^{-1}$ at 26°). The relative reactivity of the secondary phosphine oxide and the phosphonate in the hydrogen–deuterium exchange reaction therefore parallels that for the reaction of secondary phosphine oxides and dialkyl phosphonates with di-*n*-octyl disulfide.²⁹ The exchange

(28) Since completion of this work the preparation of an optically active *t*-phosphine oxide by a similar route, in this case utilizing a Grignard reaction on a menthyl phosphinate, has been reported by O. Korpiun and K. Mislow, *J. Am. Chem. Soc.*, **89**, 4784 (1967).

rate for diethyl phosphonate in methanol-*d* which we observed is somewhat greater than that reported by Luz and Silver² for diethyl phosphonate in deuterium oxide ($k = 2 \times 10^{-3} \text{ min}^{-1}$).

In contrast to the rapid isotopic exchange, no change in optical rotation was observed when a solution of benzylphenylphosphine oxide was allowed to stand in methanol for 4 days at room temperature. This result supports the view that the hydrogen–deuterium (and hydrogen–hydrogen) exchange in methanol occurs exclusively with retention of configuration. Reaction *via* an intermediate benzylphenylhydroxyphosphine (VII) is an attractive possibility. On this basis, benzylphenylhydroxyphosphine, like the alkylarylphosphines,³⁰ must be configurationally stable in methanol at room temperature.



When a solution of the optically active benzylphenylphosphine oxide in methanol was acidified with mineral acid or made basic with sodium methoxide, the rotation of the solution gradually diminished to zero. The pseudo-first-order rate constant, k_{obsd} , for loss of activity for a methanol solution 0.49 *M* in benzylphenylphosphine oxide and 0.05 *M* in sodium methoxide at 25° was $4.5 \times 10^{-3} \text{ min}^{-1}$. Similarly, $k_{\text{obsd}} = 1.4 \times 10^{-2} \text{ min}^{-1}$ for reaction of benzylphenylphosphine oxide in 0.05 *M* hydrochloric acid in methanol at 24°. In 0.05 *N* sulfuric acid under comparable conditions, the reaction was somewhat faster. That the only transformation of benzylphenylphosphine oxide consistent with a loss of optical activity is racemization was demonstrated by isolating the product. Racemic benzylphenylphosphine oxide was recovered in 65–72% yield in each case.

Since benzylphenylhydroxyphosphine (VII) was proposed to be a configurationally stable intermediate in the hydrogen–deuterium exchange reaction in methanol, it does not serve as a satisfactory intermediate for rationalizing the racemization reactions effected by mineral acid and sodium methoxide in methanol. Racemization in alkaline solution probably proceeds through anion VIII, the conjugate base of benzylphenylphosphine oxide. The weakly acidic character of the secondary phosphine oxides is well established.⁸ Possibly the inversion frequency of VIII is sufficient to account for the observed racemization; alternatively, a cleavage–recombination mechanism analogous to that proposed for the racemization of sulfoxides³¹ may be operative.³² The acid-catalyzed reaction is formulated as proceeding through a protonated species IX which by reversible addition and elimination of nucleophiles (e.g., halide or methanol) and protons yields a sym-

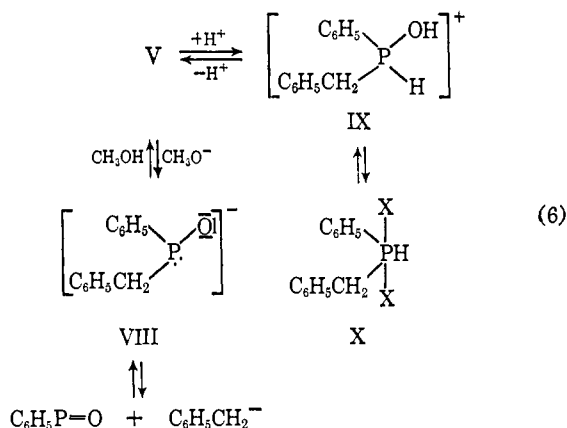
(29) K. A. Petrov, N. K. Bliznyuk, and I. Yu. Mansurov, *Zh. Obshch. Khim.*, **31**, 176 (1961).

(30) L. Horner, H. Winkler, A. Rapp, A. Mentrup, and P. Beck, *Tetrahedron Letters*, 161 (1961); L. Horner, H. Fuchs, H. Winkler, and A. Rapp, *ibid.*, 965 (1963).

(31) J. Jacobus and K. Mislow, *J. Am. Chem. Soc.*, **89**, 5228 (1967).

(32) This mechanism was suggested by a referee.

metrical pentacovalent phosphorous intermediate, X. This pathway is the same as one of the routes proposed to account for racemization of (+)-methylphenyl-*n*-propylphosphine oxide in hydrochloric acid-dioxane solution.³³



Experimental Section

Analyses for carbon, hydrogen, and phosphorus were performed by Micro-Tech Laboratories, Skokie, Ill. Melting points were determined on a Fisher-Johns melting point block and are uncorrected. Infrared spectra were obtained on samples in potassium bromide pellets with a Baird double-beam recording spectrophotometer. Optical rotations were determined with a Rudolph photoelectric polarimeter (Model 80) with an oscillating polarizer; concentrations of solutions are expressed in grams per milliliter. A 1-dm tube was used, and the precision of the polarimetric measurements was $\pm 0.003^\circ$. Proton magnetic resonance spectra were recorded at 60 MHz on a Varian A-60 spectrometer. Chromatographic separations were performed with columns (2 \times 40 cm) packed with Grace grade 950 (60–200 mesh) silica gel.

Ethyl *n*-Butylphosphinate and Ethyl Phenylphosphinate. Ethyl *n*-butylphosphinate was prepared from diethyl phosphorochloridite and *n*-butylmagnesium chloride by the method of Sander;²² bp 69–70° (0.7 mm), n_D^{25} 1.4291 (lit.²² bp 105° (15 mm), n_D^{25} 1.4302).

The alcohol amine procedure used for the preparation of dialkyl arylphosphonites³⁴ was adapted to the preparation of ethyl phenylphosphinate.³⁵ A solution of ethanol (21.6 ml, 0.368 mol) and pyridine (29.6 ml, 0.368 mol) in ether (200 ml) was added dropwise with stirring at room temperature to phenylphosphonous dichloride (50.0 ml, 0.368 mol) in 100 ml of ether maintained under a nitrogen atmosphere. After an additional hour of stirring a solution of water (6.6 ml, 0.37 mol) and pyridine (29.6 ml, 0.368 mol) in ether (200 ml) was added in a similar fashion. Pyridine hydrochloride was removed by filtration. Distillation of the filtrate yielded 37.5 g (59%) of ethyl phenylphosphinate, by 102–103° (0.2 mm), n_D^{24} 1.5196 (lit.²² bp 109° (0.5 mm), n_D^{20} 1.5210). The infrared spectrum showed characteristic bands at 2350 (P–H), 1240 (P–O), and 1045 cm^{-1} (P–O–C).

Preparation of Secondary Phosphine Oxides from Ethyl *n*-Butylphosphinate and Ethyl Phenylphosphinate. Secondary phosphine oxides were prepared from the phosphinates by reaction with the appropriate Grignard reagent. The procedure is represented by the preparation of *n*-butylphenylphosphine oxide.

To 100 ml of an ether solution of phenylmagnesium bromide prepared from 3.89 g (0.160 g-atom) of magnesium and 25.1 g (0.160 mol) of bromobenzene was added dropwise with stirring at 10–15° a solution containing 12.0 g (0.80 mol) of ethyl *n*-butylphosphinate and 48 ml of anhydrous ether. The solution was refluxed for 1 hr, cooled, and mixed with 100 ml of 25% aqueous sulfuric acid; then the layers were separated and the aqueous phase was extracted with 200 ml of benzene. The organic portions were combined and

washed successively with 15% aqueous sodium bicarbonate, water, and saturated aqueous sodium chloride. Drying over magnesium sulfate followed by evaporation of the solvent under reduced pressure gave a light yellow oil, which on distillation yielded 4.6 g (32%) of *n*-butylphenylphosphine oxide, bp 136–138° (2.9 mm).

In other cases the products were obtained as crystalline solids when the organic extracts were concentrated. The data are summarized in Table I. Yields and melting points are reported for materials that had been recrystallized from benzene-hexane. Analytical samples of solids were obtained by recrystallization and chromatography on silica gel with solvents ranging from 1:1 ether-benzene to 50:1 ether-methanol or 1:1 benzene-chloroform to pure chloroform.

Oxidation of Unsymmetrical Secondary Phosphine Oxides. The unsymmetrical secondary phosphine oxides were oxidized to the unsymmetrical phosphinic acids by three procedures. Representative examples of each are provided below.

A. Phosphorus Pentachloride. This is an adaptation of the procedure used by Williams and Hamilton⁶ for oxidizing symmetrical phosphine oxides. A solution containing 1.0 g (5.0 mmol) of benzyl-*n*-butylphosphine oxide, 1.2 g (6 mmol) of phosphorus pentachloride, and 40 ml of dry benzene was refluxed for 2 hr. The mixture was hydrolyzed by stirring with 50 ml of 7% aqueous potassium carbonate and then acidified with 6 ml of 15% aqueous sulfuric acid. The organic phase was separated, washed twice with 40-ml portions of distilled water, dried over magnesium sulfate, and concentrated under reduced pressure. Recrystallization of the residual light yellow solid from acetone-hexane gave 0.58 g (60%) of benzyl-*n*-butylphosphinic acid, mp 108.5–109.5°. The analytical sample prepared by two recrystallizations from acetone-hexane melted at 109–110°.

B. Hydrogen Peroxide.³⁶ To 20 ml of ethanol was added 0.10 g (0.41 mmol) of *n*-butyl-*p*-chlorobenzylphosphine oxide and 5 ml of 30% hydrogen peroxide. The solution was warmed at reflux for 24 hr; then the solvent was evaporated under reduced pressure at room temperature and the residual white crystalline solid was recrystallized twice from aqueous ethanol to give 0.05 g of *p*-chlorobenzylphosphinic acid, mp 121.5–122.5°.

C. Oxygen. To 6 ml of 0.155 *M* sodium methoxide in methanol was added 0.20 g (0.93 mmol) of benzylphenylphosphine oxide. After the mixture had been stirred for 4 days in the presence of oxygen, methanol was removed under reduced pressure and the residual sodium salts were dissolved in distilled water. The solution was acidified and the precipitate was collected and recrystallized twice from aqueous ethanol to give 0.13 g of benzylphenylphosphinic acid melting at 182.5–183.5° (lit.²³ mp 178–180°).

Methyl *p*-Biphenylphenylphosphinate. An ether solution of diazomethane, prepared from 1.0 g (10 mmol) of *N*-methyl-*N*-nitrosourea, was added dropwise at room temperature to a suspension of 1.00 g (3.4 mmol) of *p*-biphenylphenylphosphinic acid in 50 ml of ether. When all of the phosphinic acid had dissolved, excess diazomethane was discharged with a few drops of acetic acid in ether, and the solution was washed with dilute aqueous sodium hydroxide. Further extraction with saturated aqueous sodium chloride solution, drying over magnesium sulfate, evaporation of the ether, and recrystallization of the solid twice from benzene-hexane gave 0.65 g (62%) of methyl *p*-biphenylphenylphosphinate, mp 99.5–100.5°. An analytical sample, mp 100–101°, was obtained by two additional recrystallizations.

Anal. Calcd for $\text{C}_{19}\text{H}_{17}\text{O}_2\text{P}$: C, 74.02; H, 5.56; P, 10.05. Found: C, 74.07; H, 5.68; P, 10.19.

Reduction of Methyl *p*-Biphenylphenylphosphinate. A solution containing 0.50 g (1.62 mmol) of methyl *p*-biphenylphenylphosphinate in 35 ml of ether was added dropwise with stirring at 5° to a slurry of 0.12 g (3.20 mmol) of lithium aluminum hydride in 5 ml of ether under a nitrogen atmosphere. After 18 hr of stirring at 5°, the mixture was treated with 40 ml of distilled water and the ether phase was separated, washed with water, and dried over magnesium sulfate. On evaporation of the ether and recrystallization of the residue 0.15 g (35%) of *p*-biphenylphenylphosphine oxide, mp 92–95°, was obtained. It was characterized by a mixture melting point with the oxide prepared independently by the Grignard reaction and by its infrared spectrum.

Methyl Phenylphosphinate (IV). To a solution containing 25.0 ml (0.185 mol) of phenylphosphonous dichloride and 100 ml of dry benzene was added dropwise with stirring at room temperature a solution containing 28.8 g (0.185 mol) of (–)-menthol, 14.9 ml

(33) D. B. Denney, A. K. Tsois, and K. Mislow, *J. Am. Chem. Soc.* **86**, 4486 (1964).

(34) A. W. Frank, *Chem. Rev.*, **61**, 389 (1961), and references cited therein.

(35) For other procedures for preparing this ester from phenylphosphonous dichloride see ref 25, W. T. Dye, Naval Research Laboratory Report P-3044 (1946), and A. N. Pudovik and D. K. Yarmukhometova, *Izv. Akad. Nauk SSSR*, 902 (1962).

(36) G. M. Kosolapoff and R. H. Watson, *J. Am. Chem. Soc.*, **73**, 4101 (1951).

(0.185 mol) of pyridine, and 100 ml of benzene. Stirring was continued for 2 hr; the pyridine hydrochloride was removed by filtration and 200 ml of water was added slowly with good mixing to the benzene solution. The layers were separated, and the organic phase was washed with aqueous sodium bicarbonate solution, dried with magnesium sulfate, and concentrated under reduced pressure. On distillation of a portion (17.9 g) of the crude product (48.0 g) in a molecular still at 0.1 mm and a bath temperature of 165°, 9.25 g (47%) of menthyl phenylphosphinate was obtained; infrared bands at 2350 (P-H) and 1230 cm^{-1} (P-O); pmr, δ_{HP} 7.42 ppm, $J_{\text{P-H}}$ = 542 Hz.

Anal. Calcd for $\text{C}_{16}\text{H}_{25}\text{O}_2\text{P}$: C, 68.55; H, 8.99; P, 11.05. Found: C, 68.74; H, 9.17; P, 10.79.

Benzylphenylphosphine Oxide from Menthyl Phenylphosphinate. This oxide was prepared from 2.30 g (8.0 mmol) of menthyl phenylphosphinate and benzylmagnesium chloride (prepared from 0.73 g of magnesium and 3.80 g of α -chlorotoluene) in 25 ml of ether. The procedure was the same as employed with ethyl phenylphosphinate. The recrystallized product, 0.63 g (38%), mp 112–114°, was shown to be the same as that obtained from ethyl phenylphosphinate by a mixture melting point and a comparison of the infrared spectra.

Menthyl Phenylphosphonochloridate. This compound was prepared by addition of 39.1 g (0.250 mol) of (–)-menthol and 20.0 ml (0.250 mol) of pyridine in 200 ml of benzene to 48.7 (0.250 mol) of phenylphosphonic dichloride (bp 119.5°) in 300 ml of benzene according to the general procedure of Hersman and Audrieth.³⁷ The reaction mixture was refluxed for 2 hr, pyridine hydrochloride was removed by filtration, and the benzene solution was concentrated under reduced pressure to give 77.5 g of the crude ester, which was used directly without further purification.

Menthyl Hydrogen Phenylphosphonate. To confirm the structure of menthyl phenylphosphonochloridate, 0.5 g of the crude ester was dissolved in 20 ml of ether and the resulting solution was washed several times with 20-ml quantities of water. After drying, the ether was evaporated, leaving a solid which was recrystallized three times to give 0.23 g (50%) of menthyl hydrogen phenylphosphonate; mp 90.5–91.5°.

Anal. Calcd for $\text{C}_{16}\text{H}_{25}\text{O}_3\text{P}$: C, 64.85; H, 8.50; P, 10.45. Found: C, 64.68; H, 8.70; P, 10.40.

Menthyl Benzylphenylphosphinate (VI). Benzylmagnesium chloride (prepared from 12.2 g of magnesium and 63.3 g of α -chlorotoluene in 300 ml of ether) was added to a vigorously stirred, refluxing solution of crude menthyl phenylphosphonochloridate, 72.4 g (~0.23 mol) in 200 ml of benzene, until the reaction mixture retained a pale green color.³⁸ Reflux was continued for 1.7 hr; then the mixture was cooled to 10° and 300 ml of water was slowly added. The benzene layer, together with benzene washings of the aqueous layer, was evaporated and the resulting solid was recrystallized from aqueous ethanol to give 43.4 g (50%) of menthyl benzylphenylphosphinate, mp 129–130°, $[\alpha]^{25\text{D}}$ –51.9° (c 0.0303, CHCl_3). For separation of the diastereoisomers 42 g of the phosphinate was divided into six portions, each of which was dissolved in 700 ml of warm hexane. On standing 4 days at room temperature a crystalline solid separated from these solutions. It was collected (7.0 g, mp 149–151.5°) and recrystallized from aqueous ethanol to give 6.7 g of menthyl benzylphenylphosphinate melting at 153–155°, $[\alpha]^{25\text{D}}$ –65.4° (c 0.0314, CHCl_3).

In a similar experiment, 6.8 g of menthyl benzylphenylphosphinate (mp 150–152°, $[\alpha]^{25\text{D}}$ –63.6° in CHCl_3) was crystallized from 30 g of ester (mp 132–133°). The infrared spectra of the 132–133° and 150–152° melting samples were the same, and the elemental analyses of the two samples agreed within the accuracy of the measurement.

Anal. Calcd for $\text{C}_{23}\text{H}_{31}\text{O}_2\text{P}$: C, 74.57; H, 8.44; P, 8.37. Found (sample mp 132–133°): C, 74.72; H, 8.44; P, 8.80; (sample mp 150–152°): C, 74.48; H, 8.59.

The mother liquors from the hexane recrystallizations yielded on concentration 7.3 g of menthyl benzylphenylphosphinate, mp 139–149°. On evaporation of the residual liquors and recrystallization of the residue from ethanol, menthyl benzylphenylphosphinate, mp 129–130°, $[\alpha]^{25\text{D}}$ –50.7°, was obtained.

Benzylphenylphosphine Oxide from Menthyl Benzylphenylphosphinate (Experiment A). A solution of 3.0 g (8.1 mmol) of menthyl

benzylphosphinate, mp 129–130°, in 300 ml of ether was added dropwise with stirring to 0.60 g (16.2 mmol) of lithium aluminum hydride suspended in 50 ml of ether and maintained at 0° under an atmosphere of nitrogen. The reaction mixture was held at 0° for 18 hr, whereupon saturated aqueous ammonium chloride was added dropwise with vigorous stirring until the lithium salts had precipitated and were granular. After removal of the inorganic salts by filtration, the solvent was evaporated at reduced pressure. The residual solid was dissolved in 10 ml of benzene and chromatographed on silica gel. Twenty-four 250-ml fractions were collected as the eluent was changed from 5% (v/v) chloroform–benzene to pure chloroform. Menthol was eluted in fractions 5–12 and benzylphenylphosphine oxide (0.80 g) was eluted in fractions 16–22. No evidence for unreacted menthyl benzylphenylphosphinate was found. Recrystallization of the crude oxide from benzene–hexane yielded 0.64 g (37%) of optically inactive benzylphenylphosphine oxide, mp 119.5–120.5°, which was characterized by a mixture melting point and by comparison of the infrared and proton magnetic resonance spectra with the spectra of the sample prepared independently from ethyl phenylphosphinate and benzylmagnesium chloride.

Experiment B. A repetition of the reduction with the high-melting diastereomer of menthyl benzylphenylphosphinate, mp 150–152°, $[\alpha]^{25\text{D}}$ –63.6° (CHCl_3), yielded 0.84 g of crude benzylphenylphosphine oxide. On recrystallization from benzene–hexane 0.26 g (15%) of optically active benzylphenylphosphine oxide was obtained; mp 121.5–123°, $[\alpha]^{25\text{D}}$ –0.52° (c 0.0735, CH_3OH), $[\alpha]^{26\text{D}}$ –0.74° (c 0.0190, C_6H_6).

Experiment C. In this experiment a sample of menthyl benzylphosphinate, mp 153–155°, $[\alpha]^{25\text{D}}$ –65.4° (CHCl_3), was used and the reaction time with lithium aluminum hydride was reduced to 5 hr. Benzylphenylphosphine oxide, mp 118–120°, $[\alpha]^{24\text{D}}$ –0.26° (c 0.1048, CH_3OH), $[\alpha]^{24\text{D}}$ –0.44° (c 0.0204, C_6H_6), was isolated in 36% yield (0.63 g). In addition 0.89 g (70%) of menthol, $[\alpha]^{25\text{D}}$ –43.9° (c 0.0361, CHCl_3), was obtained. The rotation of the menthol was the same as that of the menthol used in preparing the phosphinate. Essentially the same results were obtained when the reduction time was 21 hr at 0°.

Experiment D. The procedure used for experiment B was followed except that excess hydride was destroyed by adding successively 1.2 ml of water and 0.8 ml of 10% aqueous sodium hydroxide. The benzylphenylphosphine oxide, 0.70 g (40%), mp 118.5–120°, isolated in this case was optically inactive. This experiment points up the necessity of avoiding exposure of the oxide to alkaline conditions in the work-up procedure.

In the chromatography of the products from these reactions approximately 3.5 l. of solvent was collected between the fractions containing (–)-menthol and the phosphine oxide. As a control to eliminate the possibility that the rotation of the phosphine oxide came from contamination by (–)-menthol or (–)-menthyl benzylphenylphosphinate, a synthetic mixture containing racemic benzylphenylphosphine oxide, (–)-menthol, and (–)-menthyl benzylphenylphosphinate was chromatographed in the same manner as the product mixture obtained from the reduction with lithium aluminum hydride. The menthyl benzylphenylphosphinate was eluted between menthol and benzylphenylphosphine oxide and was separated cleanly from benzylphenylphosphine oxide; 1 l. of the eluting solvent was collected between these two fractions. That the separation was effective was shown by the fact that the optical rotation of the benzylphenylphosphine oxide thus obtained was zero.

Hydrogen–Deuterium Exchange Experiments. Methanol-*d*, bp 64.7–65°, was prepared as described by Streitwieser, *et al.*,³⁹ from 400 g of dimethyl carbonate, 16 g of dimethyl sulfate, and 100 g of deuterium oxide. As judged by comparison of the signals arising from the OH impurity and the ^{13}C side band in the proton magnetic resonance spectrum, the methanol-*d* was 99.4% pure. The exchange experiments were carried out in pmr sample tubes, exchange being followed by the increase in height of the OH peak (I_{OH}) relative to the low-field C^{13} side band ($I_{\text{C}^{13}}$) for the methyl absorption. This procedure was selected in preference to that which utilizes the resonance peak of the P–H hydrogen² since measurements of the intensity of the P–H multiplet in benzylphenylphosphine were less accurate than measurements of the single peak for O–H.

In a typical experiment, the proton magnetic resonance spectrum of a 0.44 *M* solution of benzylphenylphosphine oxide in CH_3OD was recorded between 4.0 and 4.8 ppm at 25° within 65 sec after

(37) M. F. Hersman and L. F. Audrieth, *J. Org. Chem.*, **23**, 1889 (1958).

(38) This procedure is patterned after that used by K. A. Petrov, N. K. Bliznjuk, and V. P. Koratkova, *Zh. Obshch. Khim.*, **30**, 2955 (1960), for similar compounds.

(39) A. Streitwieser, L. Verbit, and P. Stang, *J. Org. Chem.*, **29**, 3706 (1964).

preparation of the solution and at approximately 1-min intervals thereafter. The data in Table IV show that the reaction was complete in less than 4 min. The structure of the product was confirmed by evaporating the solvent at reduced pressure and determining the pmr spectrum in deuteriochloroform. Integration of the spectrum indicated that greater than 90% of the product was in the P-D form. In addition, an infrared spectrum (KBr pellet) was the same as that of benzylphenylphosphine oxide except that one P-H band was replaced by a P-D band at 1680 cm^{-1} . When the benzylphenylphosphine-*d* oxide was dissolved in methanol and reisolated, the product was the hydrogen form ($\sim 90\%$ pure as indicated by the pmr spectrum).

Table IV. H-D Exchange of Benzylphenylphosphine Oxide

Time, sec	$I_{\text{OH}}/I_{13\text{C}}$
0 ^a	0.3
65	0.9
130	1.1
190	1.2
250	1.3
315	1.3
370	1.3

^a Solvent only.

Exchange data for the reaction of 0.500 *M* diethyl phosphonate in 10.0 ml of methanol-*d* at 26° are listed in Table V. The slope of a plot of $\log [(I_{\text{OH}}/I_{13\text{C}})_{360 \text{ sec}} - (I_{\text{OH}}/I_{13\text{C}})_0]$ vs. time corresponds to a first-order rate constant of $1.1 \times 10^{-2} \text{ min}^{-1}$.

Table V. H-D Exchange for Diethyl Phosphonate

Time, min	$I_{\text{OH}}/I_{13\text{C}}$
2	0.53
12	0.65
30	0.75
55	0.98
80	1.18
110	1.24
140	1.43
170	1.48
360	1.68

Racemization of Benzylphenylphosphine Oxide. A. Neutral Solution. The observed rotation, $\alpha^{24\text{D}}$, of a solution of 0.1506 g of benzylphenylphosphine oxide in 2.00 ml of methanol (0.35 *M* solu-

Table VI. Racemization in 0.05 *M* Sodium Methoxide in Methanol at 24°

Time, min	$\alpha^{24\text{D}}$, deg
30	-0.022
60	-0.019
90	-0.017
150	-0.012
210	-0.010
260	-0.008
390	-0.004
1200	-0.000

tion) was found to be -0.021, -0.022, -0.020, and -0.020° after the solution had stood for 1, 24, 38, and 96 hr, respectively. Accordingly, no racemization was observed over this time span.

B. Basic Solution. Optical rotations for a deoxygenated methanol solution 0.47 *M* in benzylphenylphosphine oxide (0.2096 g of oxide from preparation C in 2.00 ml of solution) and 0.05 *M* in sodium methoxide are recorded in Table VI. For verification that benzylphenylphosphine oxide was present at the end of the reaction, the solution was neutralized with Dowex 50 (H^+ form) and the solvent removed under reduced pressure. Precipitation of the residue from benzene by addition of hexane afforded racemic benzylphenylphosphine oxide (70% recovery); mp 114-117°. The infrared spectrum of this material was the same as that of the optically active oxide and of the racemic oxide prepared independently.

Acidic Solution. To a solution of 0.2099 g of benzylphenylphosphine oxide (from preparation C) in 1.8 ml of deoxygenated methanol was added 100 μl of deoxygenated 1.0 *M* methanolic hydrochloric acid (prepared by diluting 0.83 ml of concentrated hydrochloric acid to 10.00 ml with methanol). The solution was immediately diluted to 2.00 ml with methanol and transferred to a polarimeter tube. Optical rotations are given in Table VII. For product verification the solvent was removed under a stream of nitrogen and the residue precipitated from benzene by addition of hexane. Racemic benzylphenylphosphine oxide (72% recovery), mp 115-117°, was obtained. The infrared spectrum was the same as that of the optically active material.

Table VII. Racemization in 0.05 *M* Hydrochloric Acid in Methanol at 24°

Time, min	$\alpha^{24\text{D}}$, deg
30	-0.067
55	-0.041
85	-0.028
105	-0.023
120	-0.019
155	-0.012
180	-0.008
480	-0.000

A similar experiment was carried out with sulfuric acid. In this case 0.2042 g of benzylphenylphosphine oxide (from preparation C) was dissolved in 1.8 ml of deoxygenated methanol. (The sulfuric acid solution was prepared by diluting 3.33 ml of concentrated sulfuric acid to 10.0 ml with distilled water and diluting the resulting solution to 100 ml with methanol.) The polarimeter readings are recorded in Table VIII.

Table VIII. Racemization of Benzylphenylphosphine Oxide in 0.025 *M* Sulfuric Acid in Methanol at 24°

Time, min	$\alpha^{24\text{D}}$, deg
30	-0.021
45	-0.005
60	-0.003
240	-0.000

The racemization was too rapid to follow accurately by the technique used; however, the half-life appeared to be of the order of 15 min. Racemic benzylphenylphosphine oxide (65% recovery), mp 115-118°, was isolated from the mixture at the end of the reaction.