chloride, the mercury was separated, and the organic layer was set aside. The aqueous layer was repeatedly extracted, first with tetrahydrofuran, then ether; the combined organic portions were concentrated on a rotary evaporator, and the residue was purified by kugelrohr distillation, with the receiver bulb cooled with Dry Ice. The product, 1.0 g, had infrared and nmr spectra consistent with the structure of methyl 2-hydroxypropyl sulfide. This material was dissolved in 150 ml of methanol and cooled to 0°; a solution of 2.0 g of sodium metaperiodate (1 equiv) in 50 ml of water was added dropwise. The mixture was stirred overnight, precipitated sodium iodate was filtered off, the solution was concentrated (rotary evaporator), and the residue was purified by kugelrohr distillation at 85–90° (0.05 mm). The partly solid distillate was crystallized from ethyl acetate to give white crystals, mp 88–90°, whose nmr spectrum was the same as that of the solid previously isolated from the high-boiling fraction in A. The liquid residue obtained on concentrating the mother liquors had a very similar nmr spectrum and may be the lower melting diastereomer of **17**.

Synthesis and Absolute Configuration of Optically Active Phosphine Oxides and Phosphinates[1,2]

Olaf Korpiun, Robert A. Lewis,[3a] James Chickos,[3b] and Kurt Mislow

Contribution from the Department of Chemistry, Princeton University, Princeton, New Jersey 08540. *Received March 4, 1968*

Abstract: Optically active phosphine oxides are conveniently synthesized by reaction of Grignard reagents with diastereomerically enriched menthyl phosphinates. The displacement reaction proceeds with high stereospecificity and with inversion of configuration at phosphorus. This synthetic approach, besides providing a ready access route to a variety of optically active phosphine oxides, also serves to intercorrelate their absolute configurations and those of the precursor phosphinates.

Optically active phosphine oxides constitute a class of compounds which has occupied a central position in the study of organophosphorus reaction mechanisms and stereochemistry.[4,5] Previous routes[5] to optically active phosphine oxides required resolution[4] of the individual phosphine oxides ($R_1R_2R_3PO$), resolution of quaternary phosphonium salts ($R_1R_2R_3R_4P^+X^-$) followed by cleavage of R_4 with sodium hydroxide or by the Wittig reaction, or oxidation of optically active phosphines ($R_1R_2R_3P$) obtained from resolved quaternary phosphonium salts by cathodic reduction. Thus, whatever the method of preparation, the starting material had to be one in which the three groups, R_1, R_2, and R_3, were present prior to resolution; in addition, preparation from phosphonium salts was feasible only in those cases in which the ease of cleavage of R_4 was substantially greater than that of the other three groups. These conditions not only restricted the scope of the synthetic methods heretofore available, but also severely limited the pathways which were accessible for configurational intercorrelations.

The present paper discusses a synthetic approach which overcomes these difficulties. It had been shown[6] that alkyldiphenylphosphine oxides can be obtained by reaction of alkyl diphenylphosphinates with alkylmagnesium halides, and it had also been demonstrated[7] that nucleophilic attack at phosphorus in alkyl arylphosphinates (transesterification) proceeds with inversion of configuration. Accordingly, it appeared that Andersen's Grignard synthesis of optically active sulfoxides from menthyl sulfinates,[8] a reaction which had been shown[9] to proceed with a high degree of stereospecificity and with inversion of configuration at sulfur, might serve as a model for the generation of optically active phosphine oxides from menthyl phosphinates. This approach proved to be successful and is described below.

The starting materials for this synthesis, the unsymmetrically substituted menthyl phosphinates, were readily obtained by reaction of the corresponding phosphinyl chlorides and (−)-menthol in the presence of pyridine. The synthetic routes to the phosphinyl chlorides followed conventional lines, their choice hinging on the nature of the substituents on phosphorus. For example, methylphenylphosphinyl chloride[10] was prepared by Arbuzov rearrangement of dimethyl phenylphosphonite,[11] followed by reaction with phosphorus

(1) This work was supported by the Air Force Office of Scientific Research under Grant No. AF-AFOSR-1188-67.

(2) For a preliminary account of this work, see O. Korpiun and K. Mislow, *J. Amer. Chem. Soc.*, **89**, 4784 (1967).

(3) (a) Public Health Service Predoctoral Fellow, 1966–1968; (b) Public Health Service Postdoctoral Fellow, 1967.

(4) Resolution of ethylmethylphenylphosphine oxide provided the first example of an optically active phosphorus compound: (a) J. Meisenheimer and L. Lichtenstadt, *Ber.*, **44**, 356 (1911); (b) J. Meisenheimer, J. Casper, M. Höring, W. Lauter, L. Lichtenstadt, and W. Samuel, *Ann.*, **449**, 213 (1926).

(5) For comprehensive reviews giving citations to the original literature, see R. F. Hudson and M. Green, *Angew. Chem. Intern. Ed. Engl.*, 2, 11 (1963); L. Horner, *Pure Appl. Chem.*, **9**, 225 (1964); W. E. McEwen in "Topics in Phosphorus Chemistry," Vol. 2, M. Grayson and E. J. Griffith, Ed., Interscience Publishers, Inc., New York, N. Y., 1965, Chapter 1; G. Kamai and G. M. Usacheva, *Russ. Chem. Rev.*, **35**, 601 (1966); M. J. Gallagher and I. D. Jenkins in "Topics in Stereochemistry," Vol. 3, N. L. Allinger and E. L. Eliel, Ed., John Wiley and Sons, Inc., New York, N. Y., in press.

(6) K. D. Berlin and R. U. Pagilagan, *J. Org. Chem.*, **32**, 129 (1967). For related reactions, see K. D. Berlin in "Topics in Phosphorus Chemistry," Vol. 1, M. Grayson and E. J. Griffith, Ed., Interscience Publishers, Inc., New York, N. Y., 1965, Chapter 2.

(7) M. Green and R. F. Hudson, *J. Chem. Soc.*, 540 (1963).

(8) K. K. Andersen, *Tetrahedron Lett.*, 93 (1962).

(9) M. Axelrod, P. Bickart, J. Jacobus, M. M. Green, and K. Mislow, *J. Amer. Chem. Soc.*, **90**, 4835 (1968), and references cited therein.

(10) C. S. Gibson and J. D. A. Johnson, *J. Chem. Soc.*, 92 (1928).

(11) H. J. Harwood and D. W. Grisley, Jr., *J. Amer. Chem. Soc.*, **82**, 423 (1960).

Table I. Some Characteristics of Menthyl Phosphinates, $R_1R_2P(O)OMenthyl$[a]

No.	R_1	R_2	Chirality at phosphorus	Mp, °C	$[\alpha]D$,[b] deg	Calcd, % C	Calcd, % H	Calcd, % P	Found, % C	Found, % H	Found, % P
1a	n-C_3H_7	C_6H_5	*R*	86	−14	70.77	9.69	9.60	70.98	9.65	9.65
1b	n-C_3H_7	C_6H_5	*S*	40	−81	70.77	9.69	...	70.16	9.86	...
2a	CH_3	C_6H_5	*R*	89	−16	69.36	9.24	10.52	69.54	9.41	10.53
2b	CH_3	C_6H_5	*S*	79–80	−94	69.36	9.24	10.52	69.69	9.35	10.53
3a	CH_3	C_6H_{11}	*c*	110–111	−54	67.97	11.07	10.31	67.97	10.85	10.45
3b	CH_3	C_6H_{11}	*c*	80–81	−59	67.97	11.07	10.31	68.16	11.45	10.52
4a	C_6H_5	β-$C_{10}H_7$	*R*	87–88	−14	76.82	7.68	7.62	76.83	7.75	7.81
4b	C_6H_5	β-$C_{10}H_7$	*S*	103–104	−90	76.82	7.68	7.62	76.62	7.70	7.64

[a] All menthyl phosphinates are derived from (−)-menthol; diastereomers are differentiated by the letter suffix. [b] Rotations in benzene; *c* 1.0–3.0; 23–26°. [c] The chirality at phosphorus is unknown.

Table II. Characteristics of Optically Active Phosphine Oxides Prepared from **2b**

No.	R in $(R)(CH_3)(C_6H_5)PO$	Chirality	Mp, °C	$[\alpha]D$,[a] deg	Calcd, % C	Calcd, % H	Calcd, % P	Found, % C	Found, % H	Found, % P
5	C_2H_5	*R*	50–52	+23[b]						
6	n-C_3H_7	*R*	57–58	+17	65.92	8.34	...	65.86	8.23	...
7	C_6H_{11}	*R*	99–100	+19	70.25	8.62	13.94	70.09	8.69	13.92
8	$C_6H_5CH_2$	*R*	134–135	+51	73.03	6.57	13.45	72.89	6.67	13.14
9	α-$C_{10}H_7CH_2$	*R*	151–152	+40[c]	77.13	6.12	11.05	76.84	6.18	10.95
10	α-$C_{10}H_7(CH_2)_2$	*R*	117–119	−21[d]	77.53	6.51	10.52	77.24	6.53	10.57
11	β-$C_{10}H_7$	*S*	146–147	−12[e]	76.68	5.68	11.63	76.73	5.70	11.58
12[f]	p-$C_6H_5C_6H_4$	*S*	180–181	−12[g]	78.07	5.86	10.60	78.00	6.04	10.65
13	p-$CH_3OC_6H_4$	*S*	120–121	−8	68.28	6.14	12.58	68.07	6.25	12.32

[a] Rotation in methanol except as noted; *c* 1.0–3.0; 22–26°. The rotational prefixes used in the text refer to solvent methanol. [b] $[\alpha]D$ +21° (water). [c] $[\alpha]D$ −41° (chloroform). [d] $[\alpha]D$ −26° (chloroform). [e] $[\alpha]D$ +25° (chloroform). [f] We thank Dr. R. Scartazzini for this preparation. [g] Rotation refers to solvent chloroform.

pentachloride;[12] phenyl-β-naphthylphosphinyl chloride was prepared by reaction of phenyldiethylaminochlorophosphine[13] with β-naphthylmagnesium bromide, oxidation of the resulting N,N-diethylphenyl-β-naphthylphosphonamide to the phosphinamide, hydrolysis, and conversion to the acid chloride with thionyl chloride; cyclohexylmethylphosphinyl chloride[14] was prepared by methanolysis of cyclohexyldiethylaminochlorophosphine,[15] followed by Arbuzov rearrangement of the resulting dimethyl cyclohexylphosphonite and reaction with phosphorus pentachloride.[12] Fractional crystallization of the menthyl esters from pentane or hexane completely separated the isomers,[16] which were diastereomerically pure by pmr.[17] The individual diastereomers thus obtained are listed in Table I, together with some of their properties.[17]

Reaction of the diastereomerically homogeneous menthyl alkylarylphosphinates with alkylmagnesium and arylmagnesium halides gave optically active aryldialkyl- and alkyldiarylphosphine oxides, respectively, in yields ranging from 30 to 70%. Thus, alkylmethylphenylphosphine oxides **5–10** and arylmethylphenylphosphine oxides **11–13**, which are listed in Table II, together with some of their properties, were obtained by reaction of one of the diastereomers of **2** (**2b**, Table I) with the appropriate Grignard reagent.[18]

Evidence bearing on the stereospecificity of the displacement reaction comes from a number of independent sources. First, reaction of diastereomerically pure **2b** with ethylmagnesium bromide afforded (+)-**5**, $[\alpha]^{22}D$ +21° (water); by comparison, the rotation of resolved[4a] **5**, which is also the highest reported, is $[\alpha]D$ +23.1° (water), and the rotation of **5** obtained[19] by basic hydrolysis of resolved (+)-benzylethylmethylphenylphosphonium iodide is $[\alpha]^{25}D$ −22.8 ± 1.0° (water). Second, reaction of diastereomerically pure **2b** with benzylmagnesium chloride gave (+)-**8**, $[\alpha]D$ +51°;[20] by comparison, the highest rotation previously reported[21] for **8** is $[\alpha]D$ +48.8°. Third, reaction of diastereomerically pure **2b** with n-propylmagnesium bromide afforded (+)-**6**, whose rotation, $[\alpha]D$ +17°,[22]

(12) According to the general procedure given by K. Sasse in Houben–Weyl's "Methoden der organischen Chemie," Vol. 12 [11], Georg Thieme Verlag, Stuttgart, 1963, p 243.

(13) H. Hoffmann, R. Grünewald, and L. Horner, *Chem. Ber.*, **93**, 861 (1960).

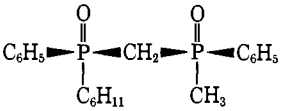
(14) L. Z. Soborovskij and J. M. Zinovjev, *Zh. Obshch. Khim.*, 24, 516 (1954).

(15) K. Issleib and W. Seidel, *Chem. Ber.*, **92**, 2681 (1959).

(16) D. J. Cram, R. D. Trepka, and P.St. Janiak, *J. Amer. Chem. Soc.*, **88**, 2749 (1966), have reported the separation of diastereomeric phosphinates by column chromatography.

(17) A discussion of the pmr properties of the menthyl phoshinates is reserved for the following paper (R. A. Lewis, O. Korpiun, and K. Mislow, *ibid.*, **90**, 4847 (1968)).

(18) In the formation of 7, the bisphosphine dioxide shown below was obtained as a by-product (6%) of the reaction. This product could possibly arise by (a) formation of a new Grignard reagent through abstraction of a proton from the methyl group of 7 by cyclohexylmagnesium bromide, and (b) a second displacement on **2b** by the new Grignard reagent. The abstraction of a proton does not affect the optical purity of the phosphine oxide, as independently shown by the observation that reaction of 7 with n-butyllithium, followed by carbonation, gives carboxymethylcyclohexylphenylphosphine oxide, decarboxylation of which regenerates 7 of unaltered optical purity. The configuration of the product shown below follows from the stereochemical course of the Grignard displacement (inversion), which is discussed in the text.



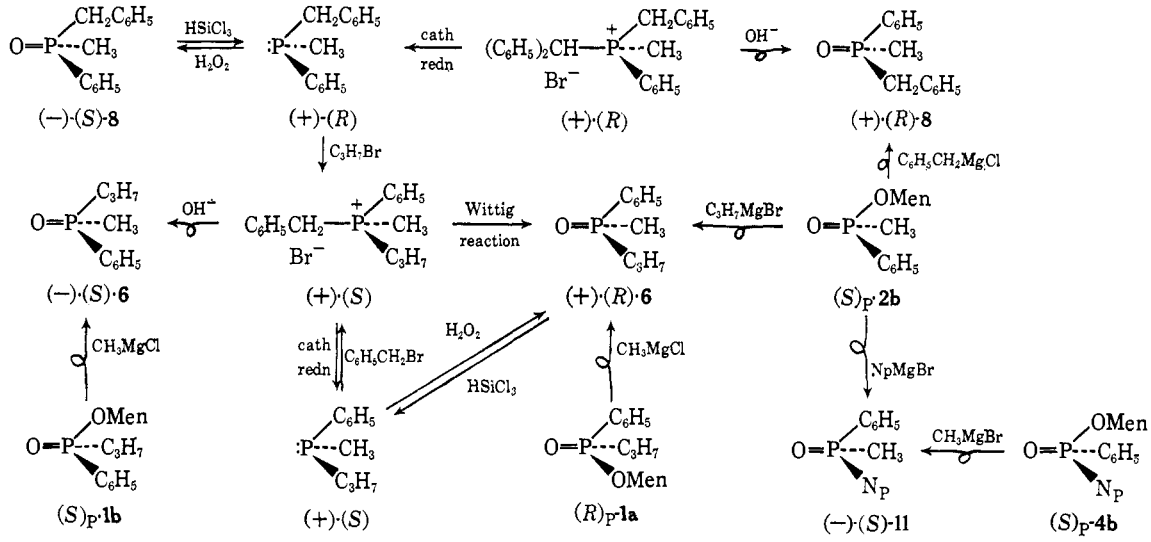
(19) K. F. Kumli, W. E. McEwen, and C. A.Vander Werf, *J. Amer. Chem. Soc.*, **81**, 3805 (1959).

(20) Unless otherwise specified, rotations of phosphine oxides refer to solvent methanol.

(21) L. Horner and H. Winkler, *Tetrahedron Lett.*, 3265 (1964).

(22) The highest reported rotation of **6** is $[\alpha]D$ +19.6° (D. B. Denney and J. W. Hanifin, Jr., *Tetrahedron Lett.*, 2177 (1963)).

Chart I[a,b]



[a] Men = (−)-menthyl; Np = β-naphthyl; C_3H_7 = *n*-propyl. [b] Grignard reactions are described in the text; for other reactions see ref 5.

was equal in magnitude to that of (+)-**6** obtained by reaction of diastereomerically pure **1a** (Table I) with methylmagnesium chloride. Fourth, reaction of a mixture consisting of 88% of **1b** (Table I) and 12% of **1a** (composition determined by pmr[17]) with methylmagnesium chloride afforded (−)-**6**, whose rotation, $[\alpha]_D$ −13°, was consistent with that calculated, $[\alpha]_D$ = (0.76)(−17°) = −13°. Fifth, reaction of diastereomerically pure **2b** with β-naphthylmagnesium bromide gave (−)-**11**, whose rotation, $[\alpha]_D$ −12°, was equal in magnitude to that of (−)-**11** obtained by reaction of diastereomerically pure **4b** with methylmagnesium bromide. Thus, the overwhelming weight of evidence points to the complete or almost complete stereospecificity of the Grignard displacement reaction, and consequently the phosphine oxides listed in Table II may be taken to be optically pure, or very nearly so.

When reaction of a menthyl phosphinate, $R_1R_2P(O)OMen$, with an organomagnesium halide, R_3MgX, gives a phosphine oxide, $R_1R_2R_3PO$, whose sign of rotation is the same as that of $R_1R_2R_3PO$ obtained from reaction of $R_1R_3P(O)OMen$ with R_2MgX or from reaction of $R_2R_3P(O)OMen$ with R_1MgX, it then follows that the stereochemical relationship between the three esters is rigorously defined, provided only that the Grignard reaction maintains the same stereochemical direction, *i.e.*, either retention or inversion, in all three reactions.[23,24] This conclusion is valid regardless of whether the Grignard reaction proceeds with inversion or retention of configuration. Consequently, the configurations of **1a** and **2b** are interlocked through their common product, (+)-**6**, and those of **2b** and **4b** through their common product, (−)-**11**. Since the chirality of the phosphorus atom in **1a** is *R*, as determined by X-ray analysis,[25] it immediately follows that the absolute configurations of **1b**, **2b** and **4b** are all $(S)_P$. These correlations are summarized in Chart I, which also gives the absolute configurations of the relay phosphine oxides, **6** and **11**. That the Grignard reaction proceeds with inversion of configuration at phosphorus, in analogy to the stereochemistry of the sulfoxide synthesis,[9] was established by correlating the reference compound, **1a**, to a second reference compound, (+)-(*S*)-benzylmethylphenyl-*n*-propylphosphonium bromide (whose absolute configuration had also been established by X-ray analysis[26]), by reaction sequences containing an odd number of Grignard displacements (Chart I); given a knowledge of the stereochemistry of the remaining steps,[5] it thus became possible to assign stereochemical direction to the Grignard displacement.

A limitation of the Grignard synthesis is its extreme sensitivity to variations of the groups on phosphorus and on oxygen, and on the Grignard reagent. Thus, we were foiled in an attempt to correlate the configurations of **3** with that of **2b** through the relay phosphine oxide, **7**, for, although **3a** reacted with phenylmagnesium bromide, no trace of **7** could be detected among the reaction products. On the other hand, methyl cyclohexylmethylphosphinate reacted smoothly with phenylmagnesium bromide to give racemic **7**; evidently the reaction is sensitive to the steric requirement of the alkoxy group, either at the stage of formation of an intermediate ester–Grignard complex or in the transition state of nucleophilic substitution.[6,27] A steric effect[27] may also be invoked to account for failure to isolate methyl-α-naphthylphenylphosphine oxide from the reaction of **2b** with α-naphthylmagnesium bromide,

(23) In contrast to the menthyl sulfinates, where this relationship can be more simply stated[9] in terms of "opposite configurations at sulfur," this simplification is prevented in the case of the phosphinates by the demands of the sequence rule.[24] Thus, $(R)_P$-**1a** and $(S)_P$-**2b** both give (+)-**6**, but $(S)_P$-**2b** and $(S)_P$-**4b** both give (−)-**11**. However, the relationship may be expressed as follows: if in any two of the esters the four ligands on phosphorus are numbered 1 (for menthoxy), 2 (for oxygen), 3 (for the R group which is common to both), and 4 (for the R group which is different in each), and if the numbers are ordered at the corners of two tetrahedra, then these tetrahedra bear a mirror image relationship.

(24) R. S. Cahn, C. Ingold, and V. Prelog, *Angew. Chem. Intern. Ed. Engl.*, **5**, 385 (1966).

(25) E. B. Fleischer and R. Dewar, unpublished results. We thank Professor Fleischer for communicating these results to us prior to publication. For the closely related case of menthyl *p*-iodobenzenesulfinate, see E. B. Fleischer, M. Axelrod, M. Green, and K. Mislow, *J. Amer. Chem. Soc.*, 86, 3395 (1964).

(26) A. F. Peerdeman, J. P. C. Holst, L. Horner, and H. Winkler, *Tetrahedron Lett.*, 811 (1965).

(27) K. D. Berlin and R. U. Pagilagan, *Chem. Commun.*, 687 (1966).

and anisyl- or biphenylylphenyl-β-naphthylphosphine oxides from the reaction of **4b** with anisyl- or biphenylyl magnesium bromides. The lack of success in the instances cited above suggests the need for an occasional modification of the reaction conditions employed, and described in the Experimental Section; exploratory work along these lines is in progress.

Experimental Section[28]

Menthyl methylphenylphosphinates 2a and **2b** were prepared as follows. Pyridine (475 ml, distilled from barium oxide), phenyldichlorophosphine (500 g), and hexane (1500 ml) were combined in a 3-l. flask equipped with a mechanical stirrer, and a solution of methanol (225 ml) and hexane (80 ml) was added dropwise, under nitrogen and at 0°, over a period of 2 hr. After stirring for 1 additional hr, the pyridine hydrochloride was removed by filtration under a stream of dry nitrogen, and the filtrate was concentrated on a rotary evaporator. The residual dimethyl phenylphosphonite was not further purified. A small amount of the crude phosphonite was added to a few drops of methyl iodide which were contained in a three-neck flask, equipped with a dropping funnel, reflux condensor, thermometer, nitrogen inlet, and magnetic stirrer, and the mixture was warmed until a violent exothermic reaction began. The phosphonite was then added at a rate sufficient to maintain the temperature at about 100°. Methyl iodide was added periodically to ensure a continuous reaction. Stirring was continued overnight, and the reaction mixture was distilled at 94° (0.05 mm) to yield 340 g of methyl methylphenylphosphinate (lit.[11] bp 119° (3.5 mm)). The phosphinate (340 g) was dissolved in carbon tetrachloride (1500 ml) and phosphorus pentachloride (418 g) was added under nitrogen at a rate sufficient to maintain the temperature at 40°. The mixture was stirred overnight, solvent was removed, and the residue was distilled, bp 105–110° (0.05 mm), to afford 318 g of methylphenylphosphinyl chloride (lit.[10] bp 155° (11 mm)). The acid chloride (296 g, 1.7 mol) was dissolved in anhydrous ether, and the solution was added slowly to a solution of pyridine (121 g, 1.53 mol) and (−)-menthol (239 g, 1.53 mol, $[\alpha]^{23}D$ −50.4° (ethanol)) in ether (400 ml). Stirring was continued overnight, the mixture was filtered to remove pyridine hydrochloride, the solvent was removed, and the residue, a colorless oil, was dissolved in hexane and stored at 5° for several days. The large needles which deposited were recrystallized several times from hexane[29] to afford 40 g of one of the diastereomeric menthyl methylphenylphosphinates, **2b**. By careful cooling of the original mother liquor, a small amount of diastereomerically pure[29] **2a** was obtained. Properties[17] of the diastereomers are listed in Table I.

To obtain larger quantities of the readily crystallized isomer, **2b**, which served as the precursor to most of the phosphine oxides described in this work, the mother liquors from the crystallization were reconverted to racemic methylphenylphosphinyl chloride by the following technique. Menthyl methylphenylphosphinate (78 g) remaining from the crystallization of the **2b** isomer was dissolved in carbon tetrachloride (100 ml) and the solution was heated to 50°. Thionyl chloride (119 g) was added over a period of about 2 hr, and the solution was heated under reflux for a period of 24 hr. The solvent was removed under reduced pressure and the residue was distilled at 125° (1 mm). Racemic methylphenylphosphinyl chloride (37 g, 80%) was thus obtained, $[\alpha]D$ 0.00 ± 0.04° (chloroform). Reaction of an aliquot with cyclohexylmagnesium bromide at 0° afforded racemic cyclohexylmethylphenylphosphine oxide, $[\alpha]D$ 0.00 ± 0.04° (methanol). The acid chloride was treated with (−)-menthol as described above and a further quantity of **2b** was obtained from the resulting mixture of diastereomeric esters.

Menthyl phenyl-*n*-propylphosphinates 1a and **1b** were prepared in a similar manner. The crude mixture of menthyl esters was chromatographed on silica gel and eluted with benzene, and the eluate dissolved in hexane. The crystals which formed upon cooling were recrystallized twice[29] from hexane to yield one of the diastereomers, **1a**. The original mother liquor upon careful cooling yielded crystals[29] of the other diastereomer, **1b**. Properties[17] of the diastereomers are listed in Table I.

Menthyl cyclohexylmethylphosphinates 3a and **3b** were prepared as follows. Cyclohexyldiethylaminochlorophosphine was prepared from 139 g of diethylaminodichlorophosphine, following the procedure of Issleib and Seidel.[15] The reaction mixture was filtered and the ethereal filtrate was diluted with absolute methanol (350 ml), under nitrogen, and heated under reflux overnight. The mixture was cooled, solvent was removed under reduced pressure, and ether was added to the residue. The mixture was filtered to remove diethylamine hydrochloride, the ether was evaporated from the filtrate, and the residue[30,31] was treated with a few drops of methyl iodide. After the exothermic reaction had subsided, the material was distilled at 90° (1.2 mm) to yield 73 g of **methyl cyclohexylmethylphosphinate,** whose pmr spectrum featured a PCH_3 doublet at τ 8.64 (J = 13 Hz) and an OCH_3 doublet at τ 6.93 (J = 10 Hz). The phosphinate (52.6 g) was treated with phosphorus pentachloride, as in the preparation of **2**, to yield 41.3 g of cyclohexylmethylphosphinyl chloride, bp 100° (1.2 mm) (lit.[14] bp 102° (3 mm)), which solidified upon standing. A mixture of the phosphinyl chloride (18.1 g), (−)-menthol (15.6 g), and pyridine (8.7 g) was heated under reflux in benzene (300 ml) for 15 hr. The mixture was filtered, the solvent was removed under reduced pressure, and the residual oil was chromatographed on silica gel, using benzene as eluent. The mixture of diastereomers was distilled (kugelrohr) at 150° (0.07 mm), and the distillate was dissolved in pentane. The solution was cooled to 0°, and the crystals which formed were recrystallized from pentane[29] to yield 5 g of one diastereomer of menthyl cyclohexylmethylphosphinate, **3a**. The more soluble diastereomer was obtained in low yield from the original mother liquor by careful cooling. The solid was recrystallized from 2-methylbutane[29] to yield 0.5 g of **3b**. Properties[17] of the diastereomers are listed in Table I.

Menthyl β-naphthylphenylphosphinates 4a and **4b** were prepared as follows. A solution of β-naphthylmagnesium bromide (from β-naphthyl bromide (300 g) and magnesium (34 g)) in ether was slowly added to a solution of phenyldiethylaminochlorophosphine[13] (305 g) in ether (400 ml) at −10°. The mixture was allowed to warm to room temperature, and filtered. The ether was removed from the filtrate, the residue was dissolved in acetone (400 ml), and hydrogen peroxide (15%, 300 ml) was added at a rate sufficient to maintain strong reflux. After 4 hr of additional heating, the reaction mixture was hydrolyzed with concentrated hydrochloric acid (350 ml). Upon cooling to room temperature, crystals precipitated; they were removed by filtration, washed with acetone, and recrystallized from ethanol to yield 68 g of **β-naphthylphenylphosphinic acid,** mp 165–166°.

Anal. Calcd for $C_{16}H_{13}O_2P$: C, 71.64; H, 4.88. Found: C, 71.62; H, 4.79.

A mixture of the acid (68 g) and of thionyl chloride (150 ml) was heated under reflux for 1 hr; the excess thionyl chloride was removed by distillation, and the residue was distilled (kugelrohr) at *ca.* 195° (0.05 mm). The distillate solidified upon standing to yield 70 g of **β-naphthylphenylphosphinyl chloride.** A solution of the acid chloride (70 g), (−)-menthol (38 g), and pyridine (21 g) in benzene (50 ml) was heated under reflux for 45 hr. The mixture was filtered, and the solvent was removed from the filtrate to yield the crude ester as an oil. The residue was dissolved in hexane (1 l.), and the precipitate which formed upon cooling (unreacted phosphinyl chloride) was removed by filtration. The solution was concentrated to 200 ml, and the crystals which formed upon cooling were recrystallized from hexane,[29] affording 19 g of one of the diastereomeric menthyl β-naphthylphenylphosphinates, **4b**. A small amount of the other diastereomer, **4a**, was isolated from the mother liquor and was purified by repeated crystallizations from hexane.[29]

(28) Elemental analyses (*cf.* Tables I and II) by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y. Pmr spectra were recorded on a Varian A-60A spectrometer and refer to *ca.* 10% solutions in deuteriochloroform, with tetramethylsilane as internal standard. Rotations were measured on a Schmidt and Haensch visual polarimeter, and mass spectra on 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.

(29) The diastereomers were recrystallized until constant melting point and rotation was obtained, *and until the pmr spectra showed the presence of only one isomer.*[17]

(30) Distillation of a portion of the residue yielded two fractions: dimethyl cyclohexylphosphonite, bp 76° (1.6 mm), and methyl cyclohexylmethylphosphinate, bp 94° (1.6 mm); the former reacted violently with methyl iodide to give the latter. The phosphonite had thus rearranged to some extent in the reaction mixture, a not uncommon occurrence in the preparation of alkyl phosphonites.[31]

(31) F. W. Hoffmann, D. H. Wadsworth, and D. H. Weiss, *J. Amer. Chem. Soc.*, **80**, 3945 (1958); M. I. Kabachnik, E. N. Cvetkov, and C. Chang, *Dokl. Akad. Nauk SSSR.*, **131**, 1334 (1960); *Chem. Abstr.*, **54**, 20845 (1960); B. A. Arbusov and N. I. Rispoloshenskij, *Isv. Akad. Nauk SSSR*, 854 (1952); *Chem. Abstr.*, 47, 9903 (1953).

Optically Active Phosphine Oxides. Alkylmethylphenylphosphine oxides **5–10** and arylmethylphenylphosphine oxides **11–13** were prepared from the appropriate menthyl phosphinate and a four- to fivefold excess of the appropriate Grignard reagent. Some typical preparations are described below. Properties[17] are listed in Table II.

Methylphenyl-*n*-propylphosphine Oxide (6). A. From 2b. A solution of menthyl methylphenylphosphinate, **2b** (7 g, 0.024 mol), in benzene (90 ml) was added to *n*-propylmagnesium bromide (0.098 mol) in ether (50 ml). The ether was removed by distillation until the pot temperature reached 70°, and the solution was heated under reflux for 18 hr. The mixture was cooled to 0° and hydrolyzed by addition of saturated ammonium chloride solution (100 ml). The aqueous layer was extracted six times with 100-ml portions of chloroform and the combined extracts were dried over sodium sulfate. Evaporation of the solvent afforded 8.7 g of an oily residue, from which the menthol was removed by distillation (kugerlohr) at 110° (0.1 mm). Crystallization of the residue from hexane yielded 2.30 g of the desired phosphine oxide, 6.

B. From 1a. A solution of menthyl phenyl-*n*-propylphosphinate, **1a** (8 g), was treated with methylmagnesium chloride, as described above for the reaction of **2b** with *n*-propylmagnesium bromide. The product (1.5 g) was identical in every respect with that obtained above.

Methyl-β-naphthylphenylphosphine Oxide (11). A. From 2b. A solution of menthyl methylphenylphosphinate, **2b** (4.4 g, 0.015 mol), in benzene (60 ml) was added to β-naphthylmagnesium bromide (0.076 mol) in ether (50 ml). Reaction conditions and work-up were as described above. After the menthol and naphthalene had been removed by kugelrohr distillation, the residual crude oxide (4.4 g) was chromatographed on silica gel, using benzene–chloroform as eluent. The eluate was recrystallized from methylene chloride–hexane to give **11**.

B. From 4b. Menthyl β-naphthylphenylphosphinate, **4b** (3 g), was treated with a fourfold excess of methylmagnesium bromide in tetrahydrofuran–benzene (1:1). The solvent was removed, and the residue was heated at 95° (bath temperature) under nitrogen for 24 hr. The mixture was cooled, 50 ml of benzene was added, and the mixture was hydrolyzed with saturated ammonium chloride solution. The aqueous layer was extracted with chloroform, and the combined organic layers were dried and evaporated. The residue was chromatographed on silica gel, eluting with benzene to remove menthol, then with chloroform. The product from the chloroform eluate was recrystallized from ethyl acetate–hexane to yield **11** which was identical in every respect with that obtained above.

Cyclohexylmethylphenylphosphine Oxide (7). A solution of menthyl methylphenylphosphinate, **2b** (5.0 g, 0.017 mol), in benzene (50 ml) was added to cyclohexylmagnesium bromide (0.068 mol) in ether. The ether was removed by distillation, and the solution was heated under reflux for 44 hr. The mixture was cooled and hydrolyzed with saturated ammonium chloride solution (100 ml), the aqueous layer was extracted three times with 100-ml portions of benzene, and the combined organic layers were dried and concentrated. Chromatography on silica gel yielded menthol (eluent, benzene) and **7** (eluent, benzene–chloroform, 1:1) which was purified by recrystallization from hexane. Continued elution with chloroform provided 0.19 g of a white, crystalline material which was further purified by recrystallization from hexane–methylene chloride. The last product had mp 205–207°, $[\alpha]^{23}D$ +21° (*c* 0.8, methanol). The pmr spectrum shows a doublet at τ 8.27 (J = 14 Hz) and a multiplet at *ca.* τ 7.3.

Anal. Calcd for $C_{20}H_{26}P_2O_2$: C, 66.66; H, 7.27; P, 17.19; mol wt, 360. Found: C, 66.96; H, 7.51; P, 16.96; M^+, *m/e* 360.

The cited properties of the high melting, polar compound are consistent with the structure shown in ref 18.

Carboxylation of Cyclohexylmethylphenylphosphine Oxide. A solution of *n*-butyllithium in hexane (0.005 mol) was added dropwise to **7** (0.94 g, 0.004 mol) dissolved in ether. The yellow solution was stirred for 0.5 hr and poured into a Dry Ice–ether slurry. The mixture was hydrolyzed with a minimum amount of water and extracted with chloroform. The organic extracts were discarded. The aqueous phase was saturated with ammonium chloride, acidified, and extracted with chloroform. The chloroform layers were combined, dried, and concentrated; the residue crystallized upon trituration with ether. Recrystallization from benzene afforded 0.74 g of the product, **carboxymethylcyclohexylphenylphosphine oxide,** mp 170° dec, $[\alpha]^{20}D$ −5° (methanol).

Anal. Calcd for $C_{14}H_{19}PO_3$: C, 63.15; H, 7.19; P, 11.63. Found: C, 63.35; H, 7.18; P, 11.72.

When this material was heated for 5 min at 170°, it eliminated carbon dioxide to regenerate **7**, mp 99–102°, $[\alpha]D$ +19° (methanol).

Racemic Cyclohexylmethylphenylphosphine Oxide. Methyl cyclohexylmethylphosphinate (3.6 g, 0.02 mol) was dissolved in benzene (50 ml) and added to phenylmagnesium bromide (0.06 mol) in ether (50 ml). The solvents were distilled from the mixture, and the bath was kept at 100° for 3 hr. The residue was cooled, slurried in benzene, and hydrolyzed with saturated ammonium chloride solution. The mixture was filtered; the filtrate was washed several times with benzene, and the organic layer of the filtrate was removed. The aqueous phase was washed twice with 50-ml portions of benzene, the combined organic layers were dried, and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel, eluting with benzene, followed by chloroform. The chloroform fraction yielded a pale yellow oil which crystallized upon standing; it was recrystallized from hexane to afford 1.5 g of long needles, mp 89–92°, whose pmr spectrum was superimposable on that of **7**.