Organic and Biological Chemistry

The Absolute Configuration of Sulfoxides and Sulfinates[1,2]

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Abstract: The absolute configurations of (−)-menthyl (−)-(*S*)-*p*-iodobenzenesulfinate and (−)-(*R*)-3-methylsulfinylpropylamine have been linked by a synthetic sequence involving an odd number of Grignard displacement reactions; consequently, this displacement has been rigorously shown to proceed with inversion of configuration at sulfur. This sequence, joined to present and earlier intercorrelations of sulfinates and sulfoxides, serves to establish absolute configurations in this series of compounds. The absolute configuration of (+)-methyl allyl sulfoxide, a key relay compound in the sequence, has been reassigned. Some apparent discrepancies which appeared in the earlier literature and which bear on the present work have been resolved.

In 1962, Andersen described a new and valuable method for the synthesis of optically active sulfoxides.[4] In the example provided in that germinal paper, reaction of an optically active sulfinate ester, *i.e.*, diastereomerically pure menthyl *p*-toluenesulfinate,[5] (−)-**1**,[6,7] with an organomagnesium halide, *i.e.*, ethylmagnesium iodide, affords an optically active sulfoxide, *i.e.*, (+)-ethyl *p*-tolyl sulfoxide. This reaction proceeds with high stereospecificity.

Considerable evidence has been obtained to indicate that the stereospecificity of the displacement does not vary significantly from reaction to reaction; for example,[8] treatment of diastereomerically pure (−)-**1** with the appropriate Grignard reagents produces *p*-anisyl *p*-tolyl and α-naphthyl *p*-tolyl sulfoxides whose rotations are equal in magnitude to those of the sulfoxides produced by reaction of *p*-tolylmagnesium bromide with the diastereomerically pure menthyl esters of *p*-methoxybenzene- and 1-naphthalenesulfinic acids, respectively. Furthermore, the correlations shown below in Chart I afford numerical values for diastereomeric ratios of sulfinate esters which are mutually consistent even though many different esters and Grignard reagents have been employed.

It can readily be shown that if (and only if) the displacement always proceeds with the same degree of stereospecificity, then the *relative* optical purity of a derived sulfoxide (*i.e.*, the ratio of its specific rotation to that of the same sulfoxide produced from diastereomerically *pure* sulfinate) will be an accurate measure of the diastereomeric ratio in the precursor sulfinate. Since in principle the energies of the relevant diastereomeric transition states for displacement must differ, we would find the *observed* constant stereospecificity of displacement very hard to explain were it to be considerably less than complete. Furthermore, since the absolute rotation of optically active ethyl *p*-tolyl sulfoxide procured by total resolution[9] is in substantial agreement with that for Grignard-derived material,[4] we feel that we can say that the reaction is very nearly completely stereospecific, *i.e.*, that the ratio of enantiomers in the product sulfoxide is very nearly equal to the ratio of diastereomers in the precursor sulfinate.

Because of its high stereospecificity, this general method of synthesis, in contrast to the asymmetric oxidation of unsymmetrical sulfides,[10] furnishes material of high optical purity and has the further advantage, not shared by methods of direct resolution, that unequivocal configurational correlations of sulfoxides and sulfinates are provided by reaction sequences such as those shown in Chart I. This chart gives the correct absolute configurations of the depicted compounds as established in this and preceding papers, and rests on the demonstration, provided in the experiments to be described below, that the Grignard reaction proceeds with inversion of configuration.

Absolute Configuration and Asymmetric Synthesis of Menthyl Sulfinates. When reaction of a menthyl sulfinate, $R_1S(O)OMen$, with an organomagnesium halide, R_2MgX, gives a sulfoxide, $R_1S(O)R_2$, whose sign of rotation is the same as that of $R_1S(O)R_2$ obtained from reaction of $R_2S(O)OMen$ with R_1MgX, it follows that the two menthyl esters must have opposite configurations at sulfur. This conclusion, which is valid regardless of whether the Grignard reaction proceeds with inversion or retention of configuration, provided only

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[2] For a preliminary account of this work, see P. Bickart, M. Axelrod, J. Jacobus, and K. Mislow, *J. Amer. Chem. Soc.*, **89**, 697 (1967).

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[4] K. K. Andersen, *Tetrahedron Lett.*, 93 (1962).

[5] H. F. Herbrandson, R. T. Dickerson, Jr., and J. Weinstein, *J. Amer. Chem. Soc.*, 78, 2576 (1956); H. F. Herbrandson and R. T. Dickerson, Jr., *ibid.*, 81, 4102 (1959).

[6] This, as were all other menthyl sulfinates described in the present paper, was prepared from (−)-menthol and the appropriate sulfinyl chloride. The sign of rotation in the visible region is determined by the chirality of the sulfur atom,[7] and the diastereomers which are epimeric at sulfur have opposite signs of rotation at the D line.[7] The prefix refers to this sign.

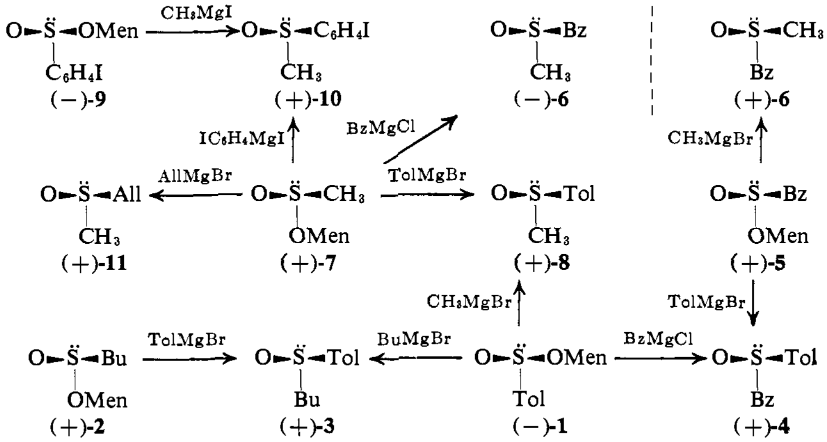
[7] K. Mislow, M. M. Green, P. Laur, J. T. Melillo, T. Simmons, and A. L. Ternay, Jr., *J. Amer. Chem. Soc.*, **87**, 1958 (1965).

[8] K. K. Andersen, W. Gaffield, N. Papanikolaou, J. Foley, and R. Perkins, *ibid.*, **86**, 5637 (1964).

[9] A. C. Cope and E. A. Caress, *ibid.*, **88**, 1711 (1966).

[10] K. Mislow, M. M. Green, and M. Raban, *ibid.*, 87, 2761 (1965), and references cited therein.

Chart I[a,b]



[a] Men = (−)-menthyl; Tol = *p*-tolyl; Bz = benzyl; Bu = *n*-butyl; All = allyl. [b] The signs of rotation of **6** refer to solvent ethanol.

that it maintains the same stereochemical direction in both reactions, was illustrated in our previous paper on the subject[7] by the following pair of reactions: (a) a mixture of menthyl 1-butanesulfinates, **2**, prepared by asymmetric synthesis from racemic 1-butanesulfinyl chloride and (−)-menthol at −78°, on reaction with *p*-tolylmagnesium bromide afforded *n*-butyl *p*-tolyl sulfoxide, **3**, with $[\alpha]_D$ +88° (acetone); (b) reaction of diastereomerically pure (−)-**1** with *n*-butylmagnesium bromide gave **3** with $[\alpha]_D$ +187° (acetone). Accordingly, (−)-**1** and the major diastereomer in **2**, (+)-**2**, have opposite configurations at sulfur.[11,12] Similarly, reaction of (−)-**1** with benzylmagnesium chloride affords benzyl *p*-tolyl sulfoxide, **4**,[13] $[\alpha]_D$ +252° (acetone), while reaction of menthyl phenylmethanesulfinate, $[\alpha]_D$ +120° (ethanol), $[\alpha]_D$ +105° (chloroform), **5**, with *p*-tolylmagnesium bromide affords **4** with $[\alpha]_D$ +228° (acetone); (−)-**1** and (+)-**5** thus have opposite chiralities at sulfur. Reaction of (+)-**5** with methylmagnesium bromide gives benzyl methyl sulfoxide, **6**, $[\alpha]_D$ +96° (ethanol), $[\alpha]_D$ −55° (chloroform), while reaction of a mixture of menthyl methanesulfinates,[14] **7**, prepared by asymmetric synthesis from racemic methanesulfinyl chloride and (−)-menthol at −78°, on reaction with benzylmagnesium chloride affords **6** with $[\alpha]_D$ −26° (ethanol);[15] (+)-**5** and (+)-**7** accordingly have the same configuration at sulfur.[16] This conclusion is confirmed by the observation that reaction of (−)-**1** with methylmagnesium bromide gives methyl *p*-tolyl sulfoxide, **8**, $[\alpha]_D$ +156° (ethanol),[17] and that reaction of **7** with *p*-tolylmagnesium bromide gives **8** with $[\alpha]_D$ +47° (ethanol);[14] consequently (−)-**1** and (+)-**7** have opposite configurations at sulfur.

It follows that the dextrorotatory diastereomers[6] of **1**, **2**, **5** and **7**[16] all have the same configuration at sulfur. In the previous paper on the subject,[7] an absolute configuration was assigned to the sulfur center in (+)-**1** (and therefore in (+)-**2**) principally on the ground that both (+)-**1** and the dextrorotatory diastereomer[6] of menthyl *p*-iodobenzenesulfinate, (+)-**9**, are formed in excess in the asymmetric synthesis starting from (−)-menthol and the respective acid chlorides, *p*-toluenesulfinyl and *p*-iodobenzenesulfinyl chloride. On the reasonable assumption that the direction of asymmetric synthesis is not significantly affected by substitution of an iodine atom for a methyl group in the *para* position of the benzenesulfinyl moiety and given that the absolute configuration at sulfur in (−)-**9** had been established as *S* by X-ray analysis,[18] the *R* configuration was assigned to the sulfur center in (+)-**1**. This conclusion has now been rigorously substantiated: reaction of diastereomerically pure (−)-**9**, $[\alpha]_D$ −146° (acetone), with methylmagnesium iodide gives methyl *p*-iodophenyl sulfoxide, **10**, $[\alpha]_D$ +99° (ethanol), and reaction of **7** with *p*-iodophenylmagnesium iodide also gives (+)-**10**, $[\alpha]_D$ +29° (ethanol).[19] Accordingly, (−)-**9** and (+)-**7**[16] have opposite configurations at sulfur and, anchored by (−)-**9**,[18] the absolute configurations of all the related menthyl sulfinates shown in Chart I (**1**, **2**, **5**, **7**) are unambiguously established: the (+) diastereomers[6] have the *R* configuration at sulfur.

When a sample of (+)-**9**, $[\alpha]_D$ +25° (acetone), which was presumed to be optically pure,[20] was reacted with methylmagnesium iodide, the product, **10**, had $[\alpha]_D$ −77° (ethanol). Based on the absolute rotation of **10**, $[\alpha]_D$ + 99°, the optical purity of this product is thus only 77.8% and, given[7] that the ratio of enantiomers in **10** equals the ratio of epimers in the precursor ester **9**,

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[11] It was shown[7] that **2** consists of a mixture of 73.5% of one diastereomer with $[\alpha]_D$ +37° and 26.5% of the other diastereomer with $[\alpha]_D$ −291°. The stereoformula shown for **2** in Chart I thus corresponds to the (+) diastereomer, which is the major component in **2** even though the mixture obtained in the asymmetric synthesis has $[\alpha]_D$ −50° (acetone).[12]

[12] This figure, correctly given in the text of our paper,[7] was accidentally printed as +50° in the experimental section.

[13] C. J. M. Stirling, *J. Chem. Soc.*, 5741 (1963).

[14] J. Jacobus and K. Mislow, *J. Amer. Chem. Soc.*, **89**, 5228 (1967).

[15] In previous work[14] freshly prepared **7** has been shown to contain the two diastereomers in a ratio of (2.0 ± 0.2):1.0. From the optical purity of the product, 27%, and given[7] that the ratio of enantiomers in **6** equals the ratio of epimers in the precursor ester, the ratio of diasteromers in **7** in the present case is 1.74.

[16] In the strictest sense, the conclusion can only be that (+)-**5** and *the major diastereomer* in the mixture (**7**) have the same configuration at sulfur. However, although the sign of rotation of the major diasteromer in **7**, unlike that in **2**, is unknown, it seems reasonable to assume that (+)-**2** and (+)-**7** have corresponding configurations, and we shall therefore employ the notation "(+)-**7**" to stand for "the major diasteromer in **7**."

[17] K. Mislow, M. Axelrod, D. R. Rayner, G. Gotthardt, L. M. Coyne, and G. S. Hammond, *J. Amer. Chem. Soc.*, **87**, 4958 (1965).

[18] E. B. Fleischer, M. Axelrod, M. Green, and K. Mislow, *ibid.*, **86**, 3395 (1964).

[19] From the optical purity of this product, 29.3% based on $[\alpha]_D$ 99° for the absolute rotation of **10**, the ratio of diastereomers in precursor **7** is 1.83, in harmony with expectations.[14,15]

[20] H. F. Herbrandson and C. M. Cusano, *J. Amer. Chem. Soc.*, **83**, 2124 (1961).

the ratio of diastereomers in this sample of **9** must therefore be 88.9% (+)-**9** to 11.1% (−)-**9**. This estimate was independently confirmed from an analysis of the nmr spectrum of the sample with $[\alpha]_D$ +25°, which exhibited a weak signal at τ 9.33. This signal, which is the upfield half of one of the isopropyl methyl proton doublets (centered at τ 9.27, J = 7 Hz) of (−)-**9**, betrays the presence of (−)-**9** in the sample; integration gives an estimate of 11%, in good agreement with the estimate derived from the optical rotation.

Since $[\alpha]_D$ of (−)-**9** is −146°,[20] it follows that $[\alpha]_D$ of (+)-**9** is +46°.[21] This result removes an important discrepancy which had been noted in our previous paper.[7] It was then remarked, and surprise was expressed, that the $\Delta\Delta G^{\ddagger}$ values for the asymmetric syntheses of **1** (0.22 kcal/mol) and **9** (0.41 kcal/mol) differed significantly, particularly so since we found it difficult to see why the presence of the methyl and iodo groups, which are far removed from the reaction center, should affect the asymmetric induction to an important degree. However, recalculation of the ratio of diastereomers of **9** produced in the asymmetric synthesis on the basis of the new value for the absolute rotation of (+)-**9** [$-21° = (+46°)(X) + (-146°)(1 - X)$, whence $(X)/(1 - X) = 1.86$] leads to a value of $\Delta\Delta G^{\ddagger}$ for **9** (0.24 kcal/mol) which is in closer agreement with our view that the substituent in the *para* position exerts but a minor effect on the course of the asymmetric synthesis.

When the new value for the absolute rotation of (+)-**9** is used to correct the ORD observed for a sample with $[\alpha]_D$ +23° (Figure 3 of the previous paper[7]), the resulting curve[22] is more nearly enantiomeric to that of (−)-**9** than the one previously reported,[7] strengthening our claim[7] that the chirality of the *p*-iodobenzenesulfinyl chromophore dominates the ORD.[22]

It had earlier been pointed out[7] that the asymmetric synthesis of menthyl sulfinates from sulfinyl chlorides and (−)-menthol is a generally applicable method for the determination of absolute configuration at sulfur, for, as established in the cases of **1**, **2**, and **9**, the predominant diastereomer produced in this asymmetric synthesis has the *R* configuration at sulfur. This conclusion was subsequently confirmed[14] for **7**. In the present work, the additional example of **5** is provided: esterification of phenylmethanesulfinyl chloride with (−)-menthol at −78° yields a product (**5**), which affords (+)-**4**, $[\alpha]_D$ +99° (acetone), upon reaction with *p*-tolylmagnesium bromide. Based on the absolute rotation of **4**,[13] the sulfoxide is 39.3% optically pure, and, since (+)-**5** gives (+)-**4**,[10] **5** is therefore a mixture consisting of 69.7% (+)-**5** and 30.3% (−)-**5**. Again, the predominant diastereomer has the *R* configuration at sulfur. Thus, as seen from the results collected in Table I, the asymmetric synthesis of menthyl sulfinates from (−)-menthol invariably affords a ratio of diastereomers in which the epimer with the *R* configuration at sulfur predominates over the other epimer in a ratio of approximately 2:1, corresponding to a difference in free energy of the diastereomeric transition states ($\Delta\Delta G^{\ddagger}$) of *ca.* 0.3 kcal/mol.

Table I. Asymmetric Syntheses of Menthyl Sulfinates, $RSO_2C_{10}H_{19}$[a]

R	Ratio of epimers produced, (*R*)/(*S*)[b]	$\Delta\Delta G^{\ddagger}$, kcal/mol
p-$CH_3C_6H_4$ (**1**)	1.75[c]	0.22
p-IC_6H_4 (**9**)	1.86[d]	0.24
n-C_4H_9 (**2**)	2.77[c]	0.40
CH_3 (**7**)	1.87[e]	0.24
$C_6H_5CH_2$ (**5**)	2.29[f]	0.32

[a] In ether–pyridine, at −78°. [b] (*R*) and (*S*) refer to the configuration at the sulfur atom. The menthyl moiety derives from (−)-menthol. [c] Reference 7. [d] Reference 7 and present work. [e] Reference 14. [f] Present work.

In the previous paper[7] it was noted that the epimer which is formed in excess in the asymmetric synthesis of **1** and **9** (*i.e.*, (+)-**1** and (+)-**9**) is also the epimer which predominates in the hydrogen chloride catalyzed equilibration of the diastereomers of **1** and **9**.[23] It might be concluded from this observation that the ratio of epimers obtained in the asymmetric synthesis is the result of thermodynamic rather than kinetic control, and the following experiment was performed in order to put this possibility to the test. Normally, the asymmetric synthesis of **1** gives a mixture of *ca.* 64% (+)-**1** and *ca.* 36% (−)-**1**. When the preparation was repeated using 0.017 mol of *p*-toluenesulfinyl chloride and an excess of (−)-menthol in ether–pyridine at −78° *in the presence* of 0.024 mol of (preformed) (−)-**1**, an epimeric ester mixture was obtained which, upon reaction with methylmagnesium iodide, yielded **8** with $[\alpha]_D$ +83° (acetone). Based on an absolute rotation of 161°,[7,17] the ratio of enantiomers in product **8** is 76% (+)-**8** to 24% (−)-**8**, and since the ratio of enantiomers equals the ratio of precursor diastereomers,[7] it follows that the starting ester contains 76% (−)-**1**, in good agreement with the value of *ca.* 73% (−)-**1** predicted for the asymmetric synthesis in the absence of equilibration.[24] It follows from the preceding observations that the product ratio in the asymmetric synthesis of sulfinate esters is kinetically controlled.

One of the most interesting features of the reaction resides in the fact that the ratio of diastereomers produced in the esterification reaction does not appreciably depend on whether menthol or sulfinyl chloride is used in excess. The ratios of diastereomers listed in Table I were obtained in reactions in which the sulfinyl chloride was used in excess;[25] however, when an excess[25]

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(21) It is of interest to note that further recrystallization of (+)-**9**, $[\alpha]_D$ +25° (acetone), fails to alter its properties ($[\alpha]_D$, melting point). This finding illustrates the caution which must be exercised in the commonly made claim for diastereomeric homogeneity on the basis of constancy in rotation and melting point upon successive recrystallizations.

(22) Figure 3 and the appropriate values for "(+)-**1B**" (≡(+)-**9**) in Table II of ref 7 may be corrected to diastereomeric purity by applying at each wavelength the equation $[\alpha]_\lambda = ([\alpha]_\lambda' - 0.11[\alpha]_\lambda'')/0.89$, where $[\alpha]_\lambda$ is the specific rotation of (+)-**9** at λ, $[\alpha]_\lambda'$ the specific rotation of the contaminated sample ($[\alpha]_D$ +23°) at λ, and $[\alpha]_\lambda''$ the specific rotation of (−)-**9** at λ.

(23) Using the value of the absolute rotation of (+)-**9**, $[\alpha]_D$ +46° (acetone), established in the present work, the hydrogen chloride catalyzed equilibrium mixture of **9** contains 57% of the (+) diastereomer, instead of 66% as previously calculated[7] on the basis of the then assumed[20] value for the absolute rotation ($[\alpha]_D$ +23°). By comparison, the hydrogen chloride catalyzed equilibrium mixture[7] of **1** contains 62% of the (+) diastereomer.

(24) Predicted moles of (+)-**1** = 0.017(0.64); predicted moles of (−)-**1** = 0.017(0.36) + 0.024. Note that the predominant diastereomer is the levorotatory epimer, rather than the *dextrorotatory* epimer, which is obtained in excess when the reaction is run in the absence of added ester.

(25) The excess amount of reagent varied between 20 and 50% in the experiments discussed in this paper.

of menthol was used, it was found that the ratios remained substantially the same. Thus, in asymmetric syntheses of **1**, **2**, **5**, and **7**, use of an excess of menthol yielded epimeric mixtures with (*R*)/(*S*) = 1.7, 3.2, 2.3, and 1.8, respectively, *i.e.*, the same, within experimental error, as the (*R*)/(*S*) ratios obtained when an excess of sulfinyl chloride was used. These observations admit of only two alternative possibilities, either of which involves an effectively achiral sulfinyl chloride. In the first of these, the sulfinyl chloride rapidly inverts pyramidal configuration in the course of the reaction, because of an inherent configurational lability which is certainly not shared by the analogous sulfoxides.[26] A second possibility is that the sulfinyl chloride reacts in the medium to form a discrete achiral intermediate. Possibly sulfines ($RCH{=}S{=}O$), formed by hydrogen halide elimination from $RCH_2S(O)Cl$,[27] might function as such intermediates in **2**, **5**, and **7**, but this possibility is ruled out in reactions of arenesulfinyl chlorides leading to **1** and **9**. Alternatively, the sulfinyl chlorides might form achiral octahedral complexes with bases such as pyridine, as reported for sulfur and selenium oxyhalides.[28]

The converse use of the asymmetric synthesis of sulfinate esters to determine the absolute configuration of secondary alcohols has been discussed elsewhere.[29]

Absolute Configuration of Sulfoxides. With the absolute configurations of the relevant sulfinate esters firmly in hand, the problem of the configurations of the derived sulfoxides could be attacked. In a previous paper[7] these configurations had been assigned on the basis of the reasonable assumption that the Grignard displacement reaction proceeded with inversion at sulfur, as had been established for the cases of alcoholysis of sulfinate esters[30] and hydrolysis of alkoxysulfonium salts;[31] however, a rigorous assignment of configuration was lacking.

The compound which was chosen as the pivot of the proposed configurational correlation was methyl allyl sulfoxide, **11**. This compound could be obtained in optically active form from **7** (the principal diastereomer of which had been shown above to have the *R* configuration), by reaction of **7** with an allylmagnesium halide. Reportedly,[32] (−)-**11** had been prepared from (−)-3-methylsulfinylpropylamine, (−)-**12**, by Hofmann degradation of (−)-**12**, which in turn had been converted[33] into (−)-iberin ((−)-3-methylsulfinylpropyl isothiocyanate), (−)-**13**, a natural product containing the sulfoxide group, by a series of reactions not affecting the configuration at sulfur. Since the *R* configuration had been established for (−)-**13** by X-ray analysis[34] of its thiourea derivative with (*R*)-1-phenylethylamine, the absolute configuration of (−)-**11** appeared to be established as *R*, and it was for this reason that **11** was selected as the appropriate compound with which to interlink sulfoxide and sulfinate configurations.

A preparation[14] of **7** which contained 66.2% of the major, *R*, diastereomer, and which therefore should have produced sulfoxide of 32.4% optical purity, was allowed to react with an excess of allylmagnesium bromide. The product sulfoxide, after work-up in the usual manner (extraction, chromatography, and kugelrohr distillation), had $[\alpha]_D$ +4.9° (ethanol); corrected for optical purity, the $[\alpha]_D$ was +15°.

This result was unanticipated for the following reason. If the Grignard reaction proceeds with inversion of configuration at sulfur, the preparation of **11** from (*R*)-**7** should have led to (*R*)-**11** and therefore[32–34] to (−)-**11**. Consequently, we were forced to conclude that either the literature report[32] of the preparation of (−)-**11** was in error, or that the displacement proceeds with retention of configuration at sulfur, at least in the case where an allylic Grignard reagent is employed. Our result was doubly disturbing because the *magnitude* of the specific rotation (+15°) was less by a factor of 10 than the reported literature value (−158°).

Our material was without question **11**, for the ir and nmr spectra were in perfect accord with the structural assignment (and identical with spectra of (±)-**11** prepared by sodium metaperiodate oxidation[35] of methyl allyl sulfide). In order to make sure that the reaction had not changed its course when the Grignard reagent was changed from alkylmagnesium to allylmagnesium halide, a sample of (+)-**11**, $[\alpha]_D$ +4.9°, was reduced with diimide.[36] The product, (−)-methyl propyl sulfoxide, (−)-**14**, $[\alpha]_D$ −35° (ethanol), was spectrally identical (nmr and ir) with an authentic sample of (−)-**14**, $[\alpha]_D$ −42°, prepared by reaction of *n*-propylmagnesium bromide with an aliquot of **7** from the same batch used in the preparation of (+)-**11**. Thus (+)-**11** and (−)-**14** have the same configuration, and the stereochemical course of the displacement is not reversed when allylmagnesium halide instead of alkylmagnesium halide is used. Furthermore, since (−)-**14** produced by reduction of (+)-**11** is not significantly less optically active than (−)-**14** produced directly from the same lot of **7**, the low rotation of (+)-**11** cannot be attributed to extensive racemization; even if the slightly lower rotation of (−)-**14** prepared by reduction is taken to indicate partial racemization of (+)-**11**, the true $[\alpha]_D$ of (+)-**11**, corrected for an optical purity of $(^{35}/_{42})(32.4)\%$, should be no more than +18°. Since it was established that the Grignard displacement reaction goes with essentially complete stereospecificity, one had to conclude that the literature value[32] of −158° for the specific rotation of **11** was in error.

An indication of the source of the error was apparent in the form of the published[32] ultraviolet absorption spectra of the purported (−)-**11**; these were considerably different from spectra which we and others[37] had obtained for (±)-**11** and in fact were similar to those of dodecyl *vinyl* sulfoxide reported by the same authors.[32] It seemed probable that, under the conditions of Hofmann elimination, the initially produced **11** had isomerized to its α,β-unsaturated isomer, methyl 1-propenyl

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[26] K. Mislow, *Rec. Chem. Progr.*, **28**, 217 (1967).

[27] *Cf.*, *e.g.*, J. Strating, L. Thijs, and B. Zwanenburg, *Rec. Trav. Chim.*, **83**, 631 (1964); W. A. Sheppard and J. Dieckmann, *J. Amer. Chem. Soc.*, **86**, 1891 (1964).

[28] F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," Interscience Publishers, New York, N. Y., 1962, p 434, and references cited therein.

[29] M. M. Green, M. Axelrod, and K. Mislow, *J. Amer. Chem. Soc.*, **88**, 861 (1966).

[30] H. Phillips, *J. Chem. Soc.*, **127**, 2552 (1925).

[31] C. R. Johnson, *J. Amer. Chem. Soc.*, **85**, 1020 (1963).

[32] P. Karrer, N. J. Antia, and R. Schwyzer, *Helv. Chim. Acta*, **34**, 1392 (1951).

[33] P. Karrer, P. E. Scheitlin, and H. Siegrist, *ibid.*, **33**, 1237 (1950).

[34] K. K. Cheung, A. Kjaer, and G. A. Sim, *Chem. Commun.*, 100 (1965).

[35] N. J. Leonard and C. R. Johnson, *J. Org. Chem.*, **27**, 282 (1962).

[36] J. W. Hamersma and E. I. Snyder, *ibid.*, **30**, 3985 (1965).

[37] A. Mangini, *Gazz. Chim. Ital.*, **88**, 1063 (1958).

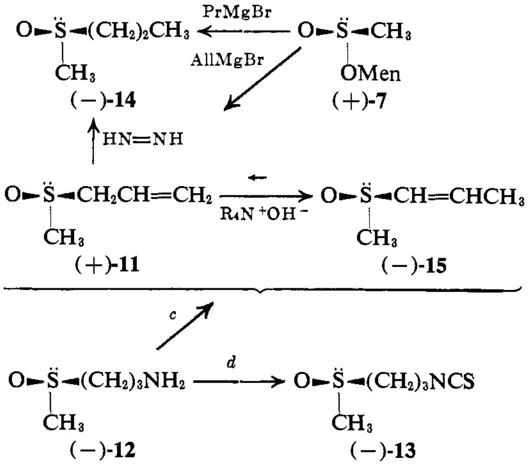
sulfoxide, **15**. It had been reported[38] that **11** undergoes base-catalyzed isomerization to a mixture of sulfoxides containing 20% of **11** and 80% of **15**. Since a strong base (the tetraalkylammonium hydroxide) is always present until elimination is complete, isomerization is in principle possible during the course of the elimination; it remained to be determined whether or not such isomerization was actually responsible for the discrepancy between our results and those in the literature.[32] To resolve this discrepancy, (−)-**12**[33] was quaternized[32] with methyl iodide to yield (−)-3-methylsulfinylpropyltrimethylammonium iodide, (−)-**16**. The physical properties of all intermediates were in reasonably good agreement with those reported[32,33] (melting points and absolute rotations were slightly lower than the literature values, indicating incomplete resolution), and the spectral properties (ir, nmr) were consonant with the assigned structures. When (−)-**16** was treated with 1 equiv of freshly prepared thallous hydroxide solution and decomposed in accordance with the literature procedure,[32] a levorotatory product, [α]D −142° (ethanol) (lit.[32] −158°, ethanol), was obtained. That the product contained the sulfoxide group was shown by the characteristic strong ir band (S–O stretch) at 1050 cm^{-1}. The 60-MHz nmr spectra of this product appeared as a superposition of two nicely separated sets of signals, A and B. Set A, identical with the nmr of (±)-**11** prepared by sodium metaperiodate oxidation[35] of methyl allyl sulfide, consisted of a singlet at τ 7.42 (S-methyl), two broadened singlets at τ 6.57 and 6.45 (S-methylene), and a multiplet centered at τ 4.45 (vinyl); the relative integrated intensities of the S-methylene and vinyl signals were 2 and 3. Set B, corresponding to constitution **15** of unspecified *cis*/*trans* geometry, consisted of a multiplet centered at τ 8.07 (C-methyl), a singlet at τ 7.44 (S-methyl), and a multiplet centered at τ 3.61 (vinyl); the relative integrated intensities of the C-methyl and vinyl signals were 3 and 2. The product of the Hofmann degradation of (−)-**16** was thus revealed to be a mixture of **11** and **15**. Both compounds necessarily have the *R* configuration.[33,34] The composition of the mixture (20 ± 1% **11** and 80 ± 1% **15**) was determined by weighted comparison of the relative integrated intensities of the two vinyl multiplets at τ 4.45 and 3.61 and independently confirmed by weighted comparison of the C-methyl and S-methylene signals with the combined S-methyl signals.

In simulation of the conditions encountered in the Hofmann elimination, a sample of (+)-**11**, [α]D +4.9° (ethanol), was allowed to come into brief contact with tetramethylammonium hydroxide, then distilled away from the base. A product was obtained, [α]D −45° (ethanol), whose nmr spectrum showed the same product ratio as that of the product (mixture of **11** and **15**) of Hofmann degradation. Corrected for an optical purity of 32.4%, the specific rotation of this material is −139°, in good agreement with the rotation of the product obtained by Hofmann degradation of (−)-**16**.

Corrected to optical purity, the [α]D of **15** is calculated to be [(−139°) − (0.20)(15°)]/0.80 = −177°. A correction factor of 1.2 to account for possible partial racemization of (+)-**11** in the course of preparation (see above) would give an alternate value of −212°. The actual value is presumably between these extremes, since, if one assumes the literature value of the rotation,[32] −158°, and uses values of +15 to +18° for the [α]D of (+)-**11**, the [α]D calculated for (−)-**15** is −202°. At any rate, it is readily seen that the negative rotational contribution of the strongly levorotatory (−)-**15**, present in the mixture to the extent of 80%, completely masks the weak positive contribution of the minor constituent, (+)-**11**.

Since the *R* configuration has been established for (−)-**12**[33,34] and thus for the levorotatory mixture of sulfoxides (**11** and **15**) derived therefrom by Hofmann degradation, and since the identical mixture is obtained on base-catalyzed isomerization of (+)-**11** (Chart II), it follows that (+)-**11** must also have the *R* configuration. Consequently, since (+)-(*R*)-**7** yields (+)-(*R*)-**11**, *it is rigorously proven that the Grignard displacement reaction proceeds with inversion of configuration at sulfur.*

Chart II[a,b]



[a] Men = (−)-menthyl; Pr = *n*-propyl; All = allyl. [b] The signs of rotation of **11**, **14**, and **15** refer to solvent ethanol. [c] Reference 32. [d] Reference 33.

The earlier[32] attribution of structure **11** to the product of Hofmann degradation of (−)-**16**, and therefore[34] of the *R* configuration to (−)-**11**, can be traced to the misassignment of constitution to a by-product, **17**, mp 87–88°, formed when **16** is degraded in the presence of silver oxide. In the earlier work[32] this substance was thought to be a sulfone, produced (presumably) by silver oxide oxidation of the sulfoxide; since **17** yielded formaldehyde but no acetaldehyde upon ozonolysis, it was considered to be methyl allyl sulfone, and therefore the parent sulfoxide was assumed to be **11**. In the course of the present work it was shown, by spectra, analysis, and independent synthesis, that **17** is actually methyl 2-hydroxypropyl sulfoxide, formally the product of Michael addition of water across the carbon–carbon double bond of **15**; there is precedent[39] for nucleophilic additions to α,β-unsaturated sulfoxides.

The apparently anomalous[7] positive [α]D (ethanol) of (*R*)-**11** is in fact only superficially so, since in the light of spectral measurements on **11**, the allyl group

(38) D. E. O'Connor and W. I. Lyness, *J. Amer. Chem. Soc.*, **86**, 3840 (1964).

(39) J. F. Carson and L. E. Boggs, *J. Org. Chem.*, **31**, 2862 (1966); D. J. Abbott and C. J. M. Stirling, *Chem. Commun.*, 165 (1968).

must be considered a strongly perturbing chromophore; this point has been discussed elsewhere.[40]

Experimental Section[41]

Preparation of Menthyl Phenylmethanesulfinate ((+)-5). Benzylmagnesium chloride was prepared from 100 g (0.8 mol) of benzyl chloride and 24 g (1 g-atom) of magnesium in 1.5 l. of dry ether in a predried 3-l., three-necked, round-bottomed flask fitted with an overhead stirrer, pressure-equalizing addition funnel, and nitrogen purge. The temperature of the resulting black solution was lowered to −50°, at which point sulfur dioxide (diluted with nitrogen) was added. A white precipitate immediately formed and the temperature rose. Addition was continued until no further temperature increase occurred. The resulting slurry was warmed to *ca.* −10° and 600 g (5 mol) of thionyl chloride was added in one portion, causing an immediate clearing of the solution followed by the formation of a slightly pink gelatinous precipitate. This semisolid mass was stirred for 1.5 hr, slurried with benzene, and filtered. The resulting clear yellow filtrate was flash evaporated, yielding 29 g (21%) of a dark oil. The crude phenylmethanesulfinyl chloride was treated in its entirety with 15.6 g of (−)-menthol and 20 g of pyridine at −78° as previously described[7] for the preparation of the mixture of menthyl 1-butanesulfinates (**2**). In this manner 31 g of a light yellow oil was obtained which rapidly crystallized upon standing. A portion of this material was repeatedly recrystallized from boiling ligroin to yield a white crystalline solid, (+)-**5**, 75.7–76.5°, $[\alpha]_D$ +120° (*c* 0.25, ethanol), the properties of which did not change on further recrystallization. The ir spectrum (Nujol mull) displayed a strong band at 1135 cm^{-1}; the nmr spectrum showed a singlet at τ 2.7 (5 H, aromatic), a singlet at τ 6.15 (2 H, benzylic methylene), and a complex multiplet at τ 8–9.5 (menthyl residue).

Anal. Calcd for $C_{17}H_{26}O_2S$: C, 69.3; H, 8.9; S, 10.9. Found: C, 69.0; H, 8.9; S, 11.4.

The recrystallized (+)-**5** so prepared was converted to benzyl *p*-tolyl sulfoxide (**4**) by reaction with *p*-tolylmagnesium bromide in the usual manner.[7] The reaction mixture was worked up by quenching with saturated aqueous ammonium chloride solution and washing with water. The ether layer was dried over magnesium sulfate, treated with activated charcoal, and filtered; the filtrate was flash evaporated, leaving a residual wet solid which was washed with low-boiling ligroin to yield **4** in 55% yield as a white crystalline solid: mp 164–165°, $[\alpha]_D$ +228° (*c* 0.44, acetone) (lit.[13] mp 169–170°, $[\alpha]_D$ +252° (*c* 0.9, acetone)).

In precisely the same manner, the *unrecrystallized* (+)-**5** obtained above was converted to **4**, $[\alpha]_D$ +75° (*c* 1.78, acetone), mp 138–153°. Both samples of **4** were identical by ir (Nujol mull) with an authentic sample.[13]

Preparation of Benzyl Methyl Sulfoxide (6). A.[42] **From 7 and Benzylmagnesium Chloride.** Benzylmagnesium chloride was prepared in the usual fashion from 13.9 g (0.11 mol) of benzyl chloride and 4.8 g (0.2 g-atom) of magnesium in 250 ml of dry ether. The Grignard reagent was filtered through a plug of glass wool into a stirred ethereal solution of 21.8 g (0.1 mol) of a mixture of diastereomeric menthyl methanesulfinates,[14] **7**. When reaction was complete 100 ml of saturated aqueous ammonium chloride solution was added. The mixture was extracted with two 500-ml portions of water; the combined aqueous extracts were then saturated with sodium chloride and extracted with two 100-ml portions of chloroform. The organic extracts were combined, dried over magnesium sulfate, filtered, and concentrated on a rotary evaporator, leaving an oily residue which crystallized upon cooling. The product was treated with pentane and filtered to yield 7.4 g of material, mp 46–57°. This substance was chromatographed on 75 g of silica gel using 600 ml of benzene, then 500 ml of 4:1 ethyl acetate–benzene; the product was eluted with the latter solvent mixture. Removal of solvent, followed by repeated kugelrohr distillation at 100° (0.2 mm) and rechromatography as above (until the material was pure by vpc), gave product, **6**, $[\alpha]^{24}_D$ −26° (*c* 3.2, ethanol), which was spectrally identical with racemic material.

B. From (+)-5 and Methylmagnesium Bromide. By a procedure akin to A, an ether solution of 2 g (0.007 mol) of (+)-**5**, $[\alpha]_D$ +120° (ethanol), was treated with 0.015 mol of methylmagnesium bromide. Work-up as in A yielded 0.80 g (74%) of material, **6**, mp 56–59°, spectrally identical with authentic material; $[\alpha]^{25}_D$ +96° (*c* 0.95, ethanol).

Preparation of Methyl *p*-Iodophenyl Sulfoxide (10). A. From (−)-Menthyl *p*-Iodobenzenesulfinate ((−)-9). A 6-ml portion of a 3 *M* solution of methylmagnesium iodide in ether was *very* rapidly injected into a solution of 1.1 g of (−)-**9**, $[\alpha]^{22}_D$ −142° (acetone) (lit.[20] $[\alpha]^{32}_D$ −145.8° (acetone)), in 1:1 anhydrous ether–tetrahydrofuran. The solution yellowed immediately and a brown gum deposited, leaving a fine white suspension in the ether phase. Excess Grignard reagent was carefully decomposed with saturated aqueous ammonium chloride solution. Extraction into a total of 1.5 l. of water, followed by work-up as described for **6**, yielded a yellow solid which was purified by chromatography on silica gel (benzene, then ethyl acetate) and kugelrohr distillation (95°, 0.02 mm). A white solid, 150 mg, mp 99–103.5°, $[\alpha]^{25}_D$ +98° (*c* 1.66, ethanol), was obtained, which was homogeneous by vpc (2-ft silicone gum rubber column). The structural assignment was strengthened by the observation of a strong ir absorption at 1050 cm^{-1} (Nujol) and by the nmr spectrum which exhibited resonances at τ 2.4 (AA′BB′ quartet, 4 H, aromatic) and 7.35 (singlet, 3 H, methyl). Recrystallization from *n*-hexane yielded (+)-**10** as colorless needles: mp 104–104.5°, $[\alpha]^{25}_D$ +99° (*c* 1.56, ethanol).

Anal. Calcd for C_7H_7IOS: C, 31.59; H, 2.65; I, 47.69; S, 12.05. Found: C, 31.83; H, 2.75; I, 47.78; S, 11.96.

B. From (+)-9. A sample of (+)-**9**, $[\alpha]^{21}_D$ +25° (acetone) (lit.[20] $[\alpha]^{25}_D$ +22.7°, acetone), was treated with methylmagnesium iodide as in the preparation of (+)-**10** above. Purification as before (but omitting the final recrystallization) gave (−)-**10**: mp 93–100°, $[\alpha]^{25}_D$ −77° (*c* 1.135, ethanol), identical by nmr, ir and vpc with (+)-**10**.

Anal. Calcd for C_7H_7IOS: C, 31.59; H, 2.65; I, 47.69; S, 12.05. Found: C, 31.86; H, 2.88; I, 47.59; S, 12.33.

C. From 7. Magnesium ribbon, 2.4 g (0.1 g-atom), was introduced into a jacketed reaction vessel under nitrogen, at the base of which was a coarse sintered-glass filter and take-off drain. The metal surface was activated by adding ethylene iodide in ether. When the magnesium was well pitted, *p*-diiodobenzene, 6.0 g in 35 ml of anhydrous ether, was added and the mixture was stirred vigorously. As the initially colorless solution yellowed, ice–water was circulated through the cooling jacket. A dense brown oil shortly began to collect at the bottom of the vessel; this was periodically drawn by gentle suction into a lower chamber containing a stirred solution of 2.0 g of a mixture of diastereomeric menthyl methanesulfinates, **7**,[14] in 65 ml of ether and 25 ml of tetrahydrofuran. After the entire contents of the upper chamber were drained through the filter into the lower solution, the reaction was quenched and worked up as in A. Purification as in B (no recrystallization) gave (+)-**10**, 0.070 g (3%), $[\alpha]^{23}_D$ +29° (*c* 0.180, ethanol), spectrally identical with (−)-**10** prepared in B.

Anal. Calcd for C_7H_7IOS: C, 31.59; H, 2.65; I, 47.69; S, 12.05. Found: C, 31.73; H, 2.78; I, 47.75; S, 12.33.

Asymmetric Synthesis of a Mixture of Menthyl *p*-Toluenesulfinates (1). A. In the Presence of Preformed (−)-1. A solution of 3.0 g (0.017 mol) of *p*-toluenesulfinyl chloride in 150 ml of anhydrous ether was placed in a 300-ml, predried, three-necked, round-bottomed flask fitted with nitrogen purge, overhead stirrer, and pressure-equalizing addition funnel. A solution of 3.2 g (0.02 mol) of (−)-menthol, 5.0 g (0.063 mol) of pyridine, and 7.0 g (0.024 mol) of diastereomerically pure (−)-**1**[5] in 100 ml of anhydrous ether was added to the cooled (−78°) sulfinyl chloride, solution causing the immediate formation of a white precipitate. The mixture was stirred for 4 hr and then warmed to *ca.* 0°; ether was added and the suspension was extracted repeatedly with 5% aqueous sodium bicarbonate solution and water, once with 1% hydrochloric acid, and then several more times with water. The ether layer was dried over magnesium sulfate, treated with activated charcoal, and flash evaporated, yielding 13.0 g of an oily crystalline solid. A 4.0-g (0.013-mol) sample of this material was dissolved in ether and added rapidly to a solution of methylmagnesium iodide prepared under nitrogen in a 100-ml, three-necked flask from 0.96 g (0.04 g-atom) of magnesium and 5.6 g (0.04 mol) of methyl iodide. The solution immediately refluxed vigorously; it was then poured into saturated aqueous ammonium chloride solution (vigorous evolution of gas!). The ether layer was extracted with water; the aqueous extracts were saturated with sodium chloride and extracted four times with chloroform. The organic extracts were dried over

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[40] M. Axelrod, P. Bickart, M. L. Goldstein, M. M. Green, A. Kjaer, and K. Mislow, *Tetrahedron Lett.*, 3249 (1968).

[41] Elemental analyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y. Nmr spectra were recorded using a Varian A-60A spectrometer and refer to *ca.* 10% v/v solutions in deuteriochloroform with tetramethylsilane as internal standard. Optical rotations were taken at the sodium D line with a Schmidt and Haensch visual polarimeter; optical rotatory dispersion spectra were taken on a Cary 60 recording spectropolarimeter.

[42] D. R. Rayner, Ph.D. Dissertation, Princeton University, 1967.

magnesium sulfate and concentrated under reduced pressure to yield 1.2 g of a yellow oil which was purified by kugelrohr distillation at 140° (0.07 mm) to give 0.53 g of methyl *p*-tolyl sulfoxide (**8**), [α]D +83° (*c* 1.9, acetone).

B. In the Presence of Excess Menthol. As described above in part A, 7.7 g (0.044 mol) of *p*-toluenesulfinyl chloride was allowed to react with a mixture of 7.2 g (0.046 mol) of (−)-menthol and 10 g (0.126 mol) of pyridine. The resulting oily solid product was isolated as in A and an 8.0-g portion (0.03 mol) was treated with methylmagnesium iodide prepared from 1.92 g (0.08 g-atom) of magnesium and 11.4 g (0.08 mol) of methyl iodide to yield (after work-up as in A) 2 g (43%) of crystalline material, [α]D −37° (*c* 1.85, acetone), identical by ir with authentic **8**.

Preparation of (+)-Methyl Allyl Sulfoxide ((+)-11). A mixture of diastereomeric menthyl methanesulfinates, **7**, was prepared and calibrated as previously described;[14] the ratio of diastereomers was such as to produce (+)-methyl *p*-tolyl sulfoxide of 32.4% optical purity. A solution of 21.7 g (0.1 mol) of **7** in 25 ml of ether was added at room temperature to the Grignard reagent prepared from 14.5 g (0.12 mol) of allyl bromide and 2.92 g (0.12 g-atom) of magnesium metal in 100 ml of ether. The reaction mixture was immediately hydrolyzed with a saturated aqueous solution of ammonium chloride and poured into 100 ml of water, and the aqueous layer was separated. The aqueous layer was washed with two 50-ml portions of 30–60° petroleum ether, then saturated with sodium chloride and extracted with three 50-ml portions of chloroform. The combined chloroform extracts were dried over anhydrous magnesium sulfate and concentrated on a rotary evaporator to a colorless oil. This oil was chromatographed on silica gel with benzene, then ethyl acetate, then 90% ethyl acetate–10% methanol; the sulfoxide was eluted at the solvent front of the last solvent mixture. The material was concentrated under reduced pressure and distilled (kugelrohr) at 50° (0.1 mm) to give 0.723 g of **11**, [α]^{24}D +4.9° (*c* 2.14, ethanol). The nmr spectrum (described in the text) is identical with that of racemic **11** prepared by sodium metaperiodate oxidation[35] of methyl allyl sulfide.

Anal. Calcd for C_4H_8OS: C, 46.12; H, 7.74; S, 30.79. Found: C, 46.26; H, 7.74; S, 30.49.

Preparation of (−)-Methyl Propyl Sulfoxide ((−)-14). A From 7 and *n*-Propylmagnesium Bromide. In a procedure analogous to that given for the preparation of (+)-**11** above, 5.43 g (0.025 mol) of a mixture of menthyl methanesulfinates, **7**,[14] from the same preparation of **7** which was used for the preparation of (+)-**11**, was dissolved in 25 ml of ether and treated with a solution of *n*-propylmagnesium bromide prepared from 3.7 g (0.03 mol) of *n*-propyl bromide and 0.73 g (0.03 g-atom) of magnesium in 50 ml of ether. Work-up as before gave an oil which, after kugelrohr distillation at 50° (0.15 mm), afforded pure sulfoxide, [α]^{23}D −42° (*c* 1.27, ethanol). The infrared spectrum matched that reported[43] for racemic **14**. The nmr spectrum consisted of a multiplet centered at τ 7.26 (S-methylene), partly obscured by a singlet at τ 7.42 (S-methyl), totaling 5 H, a multiplet centered at τ 8.1 (central methylene of propyl group), 2 H, and an asymmetric triplet at τ 8.91 (C-methyl), 3 H.

B. By Diimide Reduction of (+)-11. A solution of 150 mg (0.00144 mol) of (+)-**11**, [α]D +4.9° (ethanol), in 10 ml of ether was added to a slurry of 6.6 g (0.034 mol) of potassium azodicarboxylate in 50 ml of ether. The magnetically stirred slurry was chilled to 0° while 6.6 ml (*ca.* 0.090 mol) of propionic acid was added dropwise over a period of 1.5 hr. The ice bath was then removed and the mixture was allowed to warm slowly to room temperature. Stirring was continued an additional 2.5 hr; the mixture was then filtered and the solid was washed with ether. The filtrate was washed with two 50-ml portions of saturated aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate and filtered. The solvent was removed on a rotary evaporator. Kugelrohr distillation at 50° (0.15 mm) gave a material which showed no vinyl absorption in the nmr. The nmr and ir spectra were identical with those of (−)-**14** produced by method A. The material had [α]^{25}D −35° (*c* 2.15, ethanol).

Preparation of 3-Methylsulfinylpropyltrimethylammonium Iodide (16). A. (±)-16. A solution of 7.0 g of racemic 3-methylsulfinylpropylamine,[33] **12**, in 40 ml of methanol was placed in a 300-ml, round-bottomed flask equipped with magnetic stirrer, dropping funnel, and drying tube. A solution of 30 g of methyl iodide and 20 ml of methanol was then run in, and a solution of 7.0 g of sodium methoxide in 150 ml of methanol was added dropwise over a period of 2 hr. The mixture was allowed to stand at room temperature for 4 hr, and then was stripped on a rotary evaporator. The residue was taken up in ethanol, filtered, and crystallized. Recrystallization from ethanol gave 9 g of **16** as colorless flakes, mp 187–188° (lit.[32] mp 188–189°).

B. (−)-16. A sample of **12** was resolved in accordance with the literature procedure;[33] this was quaternized as in A with methyl iodide and sodium methoxide. Treatment as above yielded (−)-**16** as colorless crystals: mp 191–192°, [α]D −60.3° (*c* 1.16, water) (lit.[32] mp 197–198°, [α]D −72.7° (*c* 1.004, water)).

Hofmann Degradation of (−)-16. A solution of thallous sulfate, 2.169 g (0.0043 mol) in 40 ml of warm water, was added to a warm solution of 98% barium hydroxide octahydrate, 1.384 g (0.0043 mol) in 50 ml of water. The resulting precipitate was removed by vacuum filtration through sintered glass, and the filtrate was then concentrated under reduced pressure to a volume of *ca.* 10 ml. A solution of 2.50 g (0.0085 mol) of (−)-**16** in 10 ml of water was added; the yellow precipitate of thallous iodide was removed by vacuum filtration through sintered glass, and the solution was concentrated on a rotary evaporator. The glassy residue was decomposed by kugelrohr distillation at 50–70° (0.05 mm) to yield a pale yellow oil, [α]D −142° (*c* 1.12, ethanol) (lit.[3] [α]D −158° (ethanol)). The nmr spectrum of this product, a mixture containing 20 ± 1% of **11** and 80 ± 1% of methyl 1-propenyl sulfoxide, **15**, is described in the text.

Isomerization of 11 by Base. A solution of 58 mg (0.00144 mol) of sodium hydroxide in 5 ml of water was added to a solution of 245 mg (0.00144 mol) of silver nitrate in 10 ml of water. The precipitated silver oxide was washed by decantation and added to a solution of tetramethylammonium chloride, 158 mg (0.00144 mol) in 10 ml of water. The silver chloride was removed by vacuum filtration and the filtrate was taken to dryness under reduced pressure. (+)-Methyl allyl sulfoxide, [α]D +4.9° (ethanol), 150 mg (0.00144 mol), was then added to the prewarmed solid tetramethylammonium hydroxide and the mixture was immediately distilled at 60° (0.2 mm). The total distillation time was *ca.* 30 sec. The nmr spectrum of the product, [α]^{24}D −45° (*c* 1.85, ethanol), was identical with that of the mixture of **11** and **15** prepared by Hofmann degradation of (−)-**16** (see above).

Preparation of Methyl 2-Hydroxypropyl Sulfoxide (17). A. By Hofmann Degradation of Racemic 16 with Silver Oxide. A solution of (±)-**16**, 6.8 g in 10 ml of water, was treated with 5 g of freshly precipitated silver oxide in 0.2-g portions. The mixture was stirred for 6 hr and filtered free of silver salts, and excess water was removed on a rotary evaporator. The residue was decomposed by kugelrohr distillation. Two fractions were collected. One, distilling at 50–70° (0.2 mm), was the 80:20 mixture of **15** and **11** described above; the second, distilling at 80–125°, partly crystallized on cooling. This latter fraction was taken up in ethyl acetate and crystallized. A crop of white crystals was collected and recrystallized from ethyl acetate, mp 87–90°; sublimed, mp 89–90° (lit.[32] mp 87–88°). The nmr spectrum displayed no vinylic resonances, anticipated for methyl allyl sulfone; the spectrum consisted of a broad two-proton signal at τ 5.2–6.0, half of which was exchangeable with deuterium oxide, a two-proton multiplet centered at τ 7.20, a sharp three-proton singlet at τ 7.35, and a three-proton doublet at τ 8.65, $J = 7$ Hz. The ir spectrum (in chloroform) showed a large hydroxyl band (*ca.* 3300 cm^{-1}) and a band at 1050 cm^{-1} but was missing the characteristic sulfone bands at *ca.* 1150 and 1300 cm^{-1}. These results, taken with the elemental analysis below, allow only one reasonable structure for this product, that of methyl 2-hydroxypropyl sulfoxide.

Anal. Calcd for $C_4H_8O_2S$: C, 39.98; H, 6.71; S, 26.68. Calcd for $C_4H_{10}O_2S$: C, 39.32; H, 8.25; S, 26.25. Found: C, 39.12; H, 8.24; S, 26.47.

The analysis reported[32] for this compound (C, 39.56; H, 6.79) would seem to be in error. Other workers[38] have prepared methyl allyl sulfone and found it to be a liquid, bp 60° (0.1 mm).

B. By Oxymercuration–Hydration[44] and Oxidation of Methyl Allyl Sulfide. To a solution of 15.9 g (0.05 mol) of mercuric acetate in 50 ml of water was added 50 ml of tetrahydrofuran. The orange suspension was stirred at room temperature while 4.4 g (0.05 mol) of methyl allyl sulfide was cautiously added. After 20 min, 50 ml of 3 *M* sodium hydroxide solution was added, followed by 50 ml of a solution containing 0.95 g (0.025 mol) of sodium borohydride in 3 *M* sodium hydroxide. The mixture was saturated with sodium

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(43) C. C. Price and R. G. Gillis, *J. Amer. Chem. Soc.*, **75**, 4750 (1953).

(44) H. C. Brown and P. Geoghegan, Jr., *ibid.*, **89**, 1522 (1967).

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]

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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

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(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.

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