thoroughly extracted with 6 N hydrochloric acid, the acidic extract was made strongly alkaline by addition of potassium carbonate, and this basic solution was extracted with ether. After drying with anhydrous magnesium sulfate the ether was carefully distilled off leaving a small quantity (*ca.* 200 mg.) of a white crystalline material with an infrared spectrum identical with that of urethan.

In a similar irradiation of a more concentrated solution of I in cyclohexane (1:10 M ratio) a small amount of diethyl hydrazodiformate (IX) was found.

Attempted Radical-Initiated Decomposition of Ethyl Azidoformate in Cyclohexane. In a water bath of 49 ± 1°, a solution of 1.060 g. (9×10^{-3} mole) of redistilled ethyl azidoformate in 125 ml. of purified cyclohexane was placed in the flask, and the system was flushed with purified nitrogen and then sealed. A total of about 1.8×10^{-2} moles of diethyl peroxydicarbonate[67] was injected in portions over a 4-day period producing a slow evolution of an unidentified gas; the volume evolved at various intervals is recorded in Table IV.

The solvent and other low-boiling material were distilled from the reaction mixture at reduced pressure (minimum 2 mm.) and room temperature. The resulting residue was analyzed by g.l.p.c. on column A (injector 185°, column 145°) and column D (injector 148°, column 132°) and was found to contain not

(67) H. C. McBay and O. Tucker, *J. Org. Chem.*, 19, 869, 1003 (1954).

Table IV

Total reaction time, hr.	Total vol. evolved (uncorr.), ml.
2.7	2
2.5×10^{-3} mole of peroxide added	
3.6	4
5.1×10^{-3} mole of peroxide added	
6.1	39
9.0	100
20.8	202
26.3	216
5.1×10^{-3} mole of peroxide added	
29.6	289
79.0	428
5.1×10^{-3} mole of peroxide added	
100.0	482

more than a 8.7% yield of cyclohexylurethan and a 5.8% yield of urethan; identification was by comparison of g.l.p.c. retention times with those of the authentic materials.

Absolute Configuration and Optical Rotatory Power of Sulfoxides and Sulfinate Esters[1,2]

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Evidence is presented which firmly establishes the absolute configuration of a number of sulfinate esters and sulfoxides. Previous speculations which bear on the problem of the absolute configuration of optically active sulfoxides and sulfinate esters are critically examined. The optical rotatory dispersion of sulfoxides and sulfinate esters has been investigated. The observed Cotton effects are for the most part conveniently categorized according to the previously adopted viewpoint of inherently dissymmetric and asymmetrically perturbed symmetric chromophores.

It has been known for decades that suitably substituted tricoordinate sulfur compounds such as sulfonium salts ($R_1R_2R_3S^+X^-$), sulfoxides (R_1R_2SO), and sulfinate esters (RSOOR) are dissymmetric, configurationally stable under ordinary conditions, and thus, in principle, resolvable into optically active enantiomeric forms.[4] In this paper we shall demonstrate that a correlation exists between the absolute configuration of sulfoxides and sulfinates and their optical activity, expressed in terms of the signs and rotational strengths of appropriate Cotton effects.

(4) R. L. Shriner, R. Adams, and C. S. Marvel, "Organic Chemistry," Vol. 1, H. Gilman, Ed., 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 419 ff.

Absolute Configuration of Sulfinate Esters. Hine and Rogers[5] determined the absolute configuration of (+)-S-methyl-L-cysteine S-oxide by X-ray analysis but there appeared to be no easy way of achieving a reliable configurational correlation between this compound and other sulfoxides of simpler structure, *i.e.*, compounds containing the sulfoxide grouping as the only functionality. For a solution to this problem we turned to the X-ray analysis of (−)-menthyl (−)-*p*-iodobenzenesulfinate (−)-IA.[6,7] The absolute configuration of the menthyl group is known[8] and, as pointed out by Mathieson,[9] the absolute configuration of a dissymmetric grouping can be determined by ordinary X-ray analysis if an internal configurational standard is present in the molecule. In this manner the configuration about the sulfur atom in (−)-IA was rigorously established as (S).[2c,10]

The absolute configuration of (−)-IA anchors our series of configurational correlations. In order to make this substance a useful configurational reference standard, it was further necessary to correlate the configurations of I and of (−)-menthyl (−)-*p*-toluenesulfinate, (−)-IIA,[7,13] since (−)-IIA is a convenient precursor in the Grignard synthesis of optically active sulfoxides[14] (see below). The desired correlation was achieved as follows.

An excess of racemic[15] *p*-iodobenzenesulfinyl chloride was allowed to react with (−)-menthol in ether–pyridine at −78°, yielding a mixture of diastereomeric (−)-menthyl *p*-iodobenzenesulfinates, $[\alpha]_D$ −20.9° (Ia).[16] Given the known[6] rotations of the pure diastereomeric components, $[\alpha]_D$ +22.7 and −145.8°, Ia is found to contain 74.1% of the (+)-diastereomer. Under the nonequilibrating conditions of the experiment, (+)-IB is therefore the kinetically controlled major product. When an excess of racemic[15] *p*-toluenesulfinyl chloride

(5) R. Hine and D. Rogers, *Chem. Ind.* (London), 1428 (1956); R. Hine, *Acta Cryst.*, 15, 635 (1962).
(6) H. F. Herbrandson and C. M. Cusano, *J. Am. Chem. Soc.*, 83, 2124 (1961).
(7) The menthyl sulfinates I, II, and III were all prepared from (−)-menthol. The diastereomers (epimeric at sulfur) happen to have opposite signs of rotation at the D-line. The prefixes refer to these signs. Diastereomers are distinguished by the suffix A or B.
(8) V. Prelog, *Helv. Chim. Acta*, 36, 308 (1953).
(9) A. M. Mathieson, *Acta Cryst.*, 9, 317 (1956).
(10) An ambiguity arises in the configurational designation of sulfinate esters because the prefixes (*R*) and (*S*) are reversed according to whether the S–O bond is regarded as a single or as a double bond. Since this is purely a matter of nomenclature and as such is properly divorced from the actualities of electron distribution, we follow previously established custom[6] and we concur with Andersen[11] that the S–O "double" bond be considered a single bond *for nomenclatural purposes only*. Furthermore, the stereochemical nomenclature rules introduced by R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, 12, 81 (1956), include a subrule to the effect that the role of d-orbitals in octet expansion is not to be considered in the assignment of configurations (V. Prelog, private communication). That S–O bonds in sulfoxides (and, by implication, the S–O "double" bond in sulfinates) behave in some respects as if they were double bonds[12] is therefore irrelevant to our present purpose. The sulfoxide S–O bond might in fact be best described as a partial triple bond, made up of one σ-bond and two partial π-bonds, and having a total bond order of about two: A. B. Burg, "Organic Sulfur Compounds," Vol. 1, N. Kharasch, Ed., Pergamon Press, Inc., New York, N. Y., 1961, pp. 35, 36.
(11) K. K. Andersen, *J. Org. Chem.*, 29, 1953 (1964).
(12) P. Haake, W. B. Miller, and D. A. Tyssee, *J. Am. Chem. Soc.*, 86, 3577 (1964).
(13) H. F. Herbrandson and R. T. Dickerson, Jr., *ibid.*, 81, 4102 (1959).
(14) K. K. Andersen, *Tetrahedron Letters*, No. 3, 93 (1962).
(15) It is assumed that the sulfur atom in this compound is pyramidal. The configurational stability is unknown.
(16) Except for the *p*-toluenesulfinates, whose rotations were measured in nitrobenzene, all rotations reported in this section refer to acetone solutions.

was reacted with (−)-menthol under identical conditions, the resulting mixture of diastereomeric (−)-menthyl *p*-toluenesulfinates (IIa) had $[\alpha]_D$ −38.5°. Since the rotation of only one of the diastereomeric components (*i.e.*, (−)-IIA, $[\alpha]_D$ −206°), was known, the diastereomeric composition of IIa had to be estimated by an indirect method. Reaction of diastereomerically pure (−)-IIA with an excess of *n*-butylmagnesium bromide yielded *n*-butyl *p*-tolyl sulfoxide (3), $[\alpha]_D$ +187°, which was assumed to be optically pure. When IIa was allowed to react with an excess of *n*-butylmagnesium bromide, the produced *n*-butyl *p*-tolyl sulfoxide (3a) had $[\alpha]_D$ −51°. This material therefore contained 63.6% of the (−)-enantiomer. If we assume that of the ratio of enantiomers in 3a accurately reflects the ratio of diastereomers in the starting material IIa,[17] the $[\alpha]_D$ of the unisolated diastereomer of II is +57.4°. Thus (−)-IIA gives (+)-3 and (+)-IIB gives (−)-3. In order to obviate any possibility that the above assumptions are invalid, the following experiment was performed. A mixture ($[\alpha]_D$ −119°) of 3.256 g. of IIa and 3.000 g. of diastereomerically pure (−)-IIA was allowed to react with an excess of *n*-butylmagnesium bromide. The starting mixture now presumably contained 66.9% of the (−)-epimer. The produced *n*-butyl *p*-tolyl sulfoxide (3b) had $[\alpha]_D$ +63.2° and therefore contained 66.9% of the (+)-enantiomer, in perfect accord with the figure predicted from the presumed composition of IIa.

It follows that under the conditions of the asymmetric synthesis of II from (−)-menthol, (+)-IIB is the kinetically controlled major product.

According to the evidence presented in the preceding paragraphs, the (−)-menthyl arenesulfinates I and II of the same sign of rotation[7] have the same configuration at sulfur, for it is difficult to envisage that substitution of a *p*-iodo group by a *p*-methyl group would have the effect of *reversing* the relative barrier heights of the diastereomeric transition states leading from sulfinyl chlorides to corresponding esters or ester-producing intermediates. However, the values for $\Delta\Delta G^*$, 0.407 and 0.216 kcal./mole for I and II, do differ surprisingly in magnitude.

In an ancillary study, reaction of an excess of racemic 1-butanesulfinyl chloride with (−)-menthol at −78° in ether–pyridine afforded a mixture of diastereomeric (−)-menthyl 1-butanesulfinates (IIIa), $[\alpha]_D$ −50°. Reaction of IIIa with an excess of *p*-tolylmagnesium bromide afforded *n*-butyl *p*-tolyl sulfoxide (3c), $[\alpha]_D$ +88° and therefore containing 73.5% of the (+)-enantiomer. Since the ratio of produced enantiomers accurately reflects the ratio of diastereomeric precursor sulfinate esters (see above), the starting material (IIIa) contains 73.5% of one of the diastereomers. To establish the identity of this major diastereomer in III, the esterification was repeated under conditions identical in all respects except for temperature, *viz.*, at 25°. The produced mixture of diastereomeric (−)-menthyl 1-butanesulfinates (IIIb) had $[\alpha]_D$ −72°. On treatment with an excess of *p*-tolylmagnesium bromide this mixture afforded *n*-butyl *p*-tolyl sulfoxide (3d), $[\alpha]_D$ + 63°. The product therefore contained 66.8% of the

(17) The diastereomers must react at different specific rates and incomplete reaction (hopefully prevented by employing an excess of Grignard reagent) would lead to 3a with an enantiomeric composition different from the diastereomeric composition of starting IIa.

(+)-enantiomer, and the starting material (IIIb) accordingly contained 66.8% of the major diastereomer. This result yields several items of information. First, the observation that at higher temperatures the excess of predominant diastereomer decreases from 73.5% at $-78°$ to 66.8% at 25° accords with the expectation that while in a competitive asymmetric synthesis such as this the process which occurs with the lower enthalpy of activation (neglecting ΔS^*) will be favored at all temperatures, an increase in temperature leads asymptotically to the production of the "nonselective" 1:1 ratio of diastereomers. Second, the two experiments together yield the specific rotations of the component diastereomers: $[\alpha]_D +37°$ for the major diastereomer and $-291°$ for the minor diastereomer of III. Third, since (+)-3 is obtained in the Grignard reaction from both $(-)$-IIA and (+)-IIIB, it may be concluded that the two esters have opposite configurations at sulfur and the absolute configuration of (+)-IIIB at sulfur is therefore (R). Fourth, it follows that the predominant and, as it happens, the dextrorotatory diastereomers produced in the asymmetric syntheses of menthyl sulfinates from sulfinyl chlorides and $(-)$-menthol have the (R)-configuration at sulfur in all three cases investigated (I, II, and III). *The present method may therefore by extension be regarded as generally applicable in the assignment of absolute configurations to sulfinate esters.*

The conclusion that $(-)$-IA and $(-)$-IIA have corresponding configurations, (S), at the asymmetric sulfur atom is bolstered by the observation that equilibration[6] of I (starting with either diastereomer) in nitrobenzene 0.179 M in hydrogen chloride gave a mixture having $[\alpha]_D -36°$ and therefore containing 66.4% of the (+)-diastereomer,[18] and that equilibration of II under identical conditions, starting with $(-)$-IIA, gave a mixture having $[\alpha]_D -44.2°$ and therefore containing 62.4% of the (+)-diastereomer.[19] The equilibrium position is assuredly governed to a major extent by steric factors and substitution of a p-iodo group in I by a p-methyl group in II would not be expected to reverse the relative stability of the diastereomeric pairs.[20]

Since the absolute configurations of I and II are now firmly established, it is appropriate to comment briefly on previous configurational assignments in this series. Before doing so, however, we deem it desirable to record some remarks which are intended to place our critique in its proper perspective. These remarks

apply to the discussion in this section as well as to the discussion of previous assignments of absolute configurations in the series of optically active sulfoxides (last section).

A dissymmetric molecule may exist in two and only two enantiomeric forms. Chirality is necessarily dichotomous, and a given enantiomer can only be described by one or another of two mutually exclusive mirror image configurations. These are the "right-handed" and "left-handed" or, in conventional chemical terminology,[21] the (R)- and (S)-configurations. Since absolute configuration is two-valued, any configurational assignment must therefore have *a priori* a 50% chance of being correct. Accordingly, difficult as it is to argue with success, the prudent reader who is faced with a correct assignment of absolute configuration nevertheless avoids jumping to the conclusion that the arguments leading to the assignment are sound, for a toss of a coin could have decided the matter. We are reminded that the Fischer convention, which correctly assigned the (R)- (or D-) configuration to (+)-glyceraldehyde, was the outgrowth of a totally arbitrary decision.[22]

The configuration of I was correctly predicted by Herbrandson and Cusano[6] who equilibrated (+)-IB and $(-)$-IA with hydrogen chloride and found that the (+)-diastereomer was present in excess ($\Delta G° = -215 \pm 45$ cal./mole). Their assignment of the (R)-configuration to sulfur in the (+)-isomer was admittedly "tentative" and rested on a highly speculative conformational analysis patterned after the Cram–Prelog rules[23]; the additional observation that the (+)-epimer undergoes $B_{AC}2$ ethanolysis at about twice the rate of the $(-)$-epimer was rationalized in terms of the above configurational assignment.[6] However, it has since been shown (see last section) that extension of the Cram–Prelog rules to the case of 2-octyl phenyl sulfoxide[24] leads to incorrect assignments, and the premises on which Herbrandson and Cusano[6] rest their conclusions are therefore not necessarily as substantial as the success of their prediction would superficially indicate.

The (R)-configuration was originally assigned by Andersen[14] to the sulfur atom in (+)-IIB (and, by the same token, the (S)-configuration to the sulfur atom in $(-)$-IIA) by a comparison of the rotation of $(-)$-IA with that of $(-)$-IIA at the D-line. Andersen[14] at that time expressed the opinion that substitution of the p-iodo group in I by a methyl group in II "would not be expected to change the sign of the powerfully rotating sulfinate ester group." His configurational assignment is now known to be correct (see above), and, although it would not have been surprising if the presence of an iodine atom in the molecule had affected the sign of rotation at the D-line (as is the case[25] in 2,2'-diiodo-6,6'-dimethylbiphenyl, whose sign of rotation in the visible region is *opposite* to the sign of

(18) Under similar conditions, Herbrandson and Cusano[6] obtained an equilibrium mixture containing 59 ± 3% of the (+)-diastereomer.

(19) Based on the experimentally observed value of $[\alpha]_D$ of $(-)$-IIA and the calculated value (see above) of (+)-IIB.

(20) Our measured rates of mutarotation of II duplicate those reported by Herbrandson and Dickerson.[13] In harmony with their work, the pseudo-first-order specific rate constant of epimerization of II was found to increase from 1.74×10^{-5} sec.$^{-1}$ in 0.0170 M hydrogen chloride in nitrobenzene to 53.0 × 10^{-5} sec.$^{-1}$ in 0.0170 M hydrogen chloride–0.0119 M tetraethylammonium chloride in nitrobenzene. In marked contrast, the first-order specific rate constant of racemization of (+)-phenyl p-tolyl sulfoxide[3b] decreased from 15.1 × 10^{-5} sec.$^{-1}$ in 0.0170 M hydrogen chloride in nitrobenzene to a value indistinguishable from zero in 0.0170 M hydrogen chloride–0.0119 M tetraethylammonium chloride in nitrobenzene. Thus the hydrogen chloride catalyzed epimerization of sulfinates is not mechanistically analogous to the hydrogen chloride catalyzed racemization of sulfoxides. Specifically, the chloride and/or hydrogen dichloride ions which cocatalyze the epimerization of sulfinates[13] are ineffectual as catalysts in the racemization of sulfoxides; this is consistent with the mechanisms proposed for the epimerization[13] and racemization[3b] reactions.

(21) R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, 12, 81 (1956).

(22) G. W. Wheland, "Advanced Organic Chemistry," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1960, p. 251.

(23) (a) D. J. Cram and F. A. Abd Elhafez, *J. Am. Chem. Soc.*, 74, 5828 (1952); D. J. Cram and D. R. Wilson, *ibid.*, 85, 1245 (1963), and references cited therein; (b) V. Prelog, *Helv. Chim. Acta*, 36, 308 (1953); V. Prelog, *Bull. soc. chim. France*, 987 (1956).

(24) D. J. Cram and S. H. Pine, *J. Am. Chem. Soc.*, 85, 1096 (1963).

(25) K. Mislow, M. A. W. Glass, R. E. O'Brien, P. Rutkin, D. H. Steinberg, J. Weiss, and C. Djerassi, *ibid.*, 84, 1455 (1962).

rotation of the configurationally *related* 2,2'-dibromo- and 2,2'-dichlorobiphenyls), our optical rotatory dispersion work (see below) now reveals that the long wave length sign of I and II does indeed reflect the sign of·the relevant Cotton effect. The dominance of the rotational contribution by the sulfinate ester grouping at the D-line is given by the following figures: the menthyl moiety contributes -61.6 and $-74.5°$ in I and II, respectively,[26] and the sulfinate ester moiety contributes ±84.2 and $\pm132.0°$ in I and II, respectively.[26]

Subsequently, in the light of our preliminary o.r.d. results[2a] which cast doubt on the validity of the earlier conclusions,[14] Andersen[11] re-examined this problem and advanced arguments in support of the opposite view, that $(-)$-IA and $(-)$-IIA have the (R)-configuration at sulfur.[27] It is now known (see above) that these later configurational assignments are incorrect, and a scrutiny of Andersen's more recent arguments[11] is therefore in order.

The key link in Andersen's chain of reasoning[11] is the application of Cram's rule[23a] to the ester interchange step in the kinetic resolution of $(\pm)$-ethyl p-toluenesulfinate by partial crossesterification with (R)-2-octanol. The displacement of ethanol is believed[11] to proceed by an S_N2 mechanism and, according to Andersen,[11] "the CO bonds of entering and leaving alkoxy groups (in the transition state) are considered to lie on a line passing through the sulfur atom and perpendicular to a plane containing the p-toluenesulfinyl group. Arrangement of the p-tolyl group of the ester is considered to be *trans* or *anti* to the n-hexyl group of the 2-octanol." However, even if we grant that the depiction[11] of the geometry of the presumed transition state (see above) has the virtue of accounting for the observed[28] inversion in ester exchange, the straightforward application[11] of Cram's rule[23a] to the conformational analysis of the ester exchange is difficult to justify. The rule in question is an empirical generalization which was formulated for carbonyl addition reactions. The transition states in these reactions differ greatly in topology from those of the ester exchange. For example, the inducing asymmetric carbon atom in the carbonyl addition reactions to which Cram's rule applies is separated from the adjacent reaction center (*i.e.*, the carbonyl carbon atom), to which it is directly attached, by at most 1.53 Å. throughout the course of the reaction; in contrast, the distance between the inducing asymmetric carbon atom (in 2-octanol) and the asymmetric sulfinate sulfur atom, which is the analogous reaction center in the ester exchange transition state, must be greater than the sum of the CO and SO covalent single bond distances, *i.e.*, greater than 3.06 Å.[29] Furthermore,

(26) Figures refer to acetone solutions and are based on the work of Herbrandson and Cusano[6] for I and on the present work for II.

(27) (a) In his paper[11] Andersen emphasized that these arguments were speculative and that further work was needed to test his conclusions. Aware of the discrepancies in the literature which existed at the time,[2a] Andersen considered the absolute configurational assignments uncertain and all configurational relationships in his paper relative; (b) K. K. Andersen, W. Gaffield, N. E. Papanikolaou, J. W. Foley, and R. I. Perkins, *J. Am. Chem. Soc.*, 86, 5637 (1964).

(28) H. Phillips, *J. Chem. Soc.*, 127, 2552 (1925).

(29) Taking C–O as 1.41 Å. (U. Blukis, P. H. Kasai, and R. J. Myers, *J. Chem. Phys.*, 38, 2753 (1963), report this bond length for dimethyl ether) and S–O as 1.65 Å. (W. C. Hamilton and S. J. LaPlaca, *J. Am. Chem. Soc.*, 86, 2289 (1964)).

the role in conformational analysis of the sulfoxide oxygen and of the lone pair on sulfur is by no means clearly understood at present[30]; the factors which enter into an estimate of the conformational requirements of sulfoxide oxygen and of the lone pair of electrons on sulfur in the transition state considered by Andersen[11] therefore remain an unknown quantity.

Absolute Configuration of Sulfoxides Derived from Sulfinate Esters. Optically active sulfoxides are now readily available by the Grignard synthesis.[2] This method, which was first introduced by Andersen,[14] involves as a first step the preparation of epimerically enriched menthyl sulfinate (other activating alcohols could in principle be used). The ester is subjected to the Grignard reaction and an alkyl or aryl group displaces the menthyloxy group in the formation of enantiomerically enriched sulfoxide.

It was shown in the preceding section that the Grignard reaction proceeds with retention of stereochemical integrity, *i.e.*, the ratio of enantiomers in the product sulfoxide equals the ratio of diastereomers in the starting sulfinate esters. However, we have thus far left unanswered the question of whether the reaction proceeds with retention or inversion of configuration.

The Grignard reaction involves nucleophilic attack on sulfur. There is precedent that nucleophilic attack at sulfur proceeds with inversion of configuration: alcoholysis of sulfinate esters[28] and hydrolysis of alkoxysulfonium salts[31] both proceed by inversion mechanisms. Accordingly, it would seem highly probable that the Grignard displacement also occurs with inversion of configuration, and this conclusion is confirmed by the o.r.d. work described in the following sections. Since the absolute configuration of the sulfinate precursors is known (preceding section) the configuration of the derived sulfoxides is thereby established. For example:
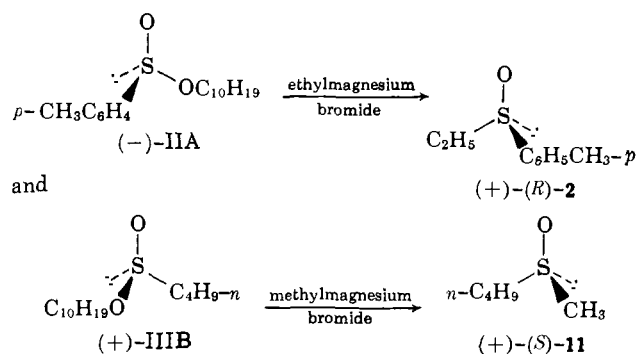
We have prepared a number of optically pure sulfoxides 1–10 of general formula p-$CH_3C_6H_4SOR$, where R is a hydrocarbon grouping, starting with diastereomerically pure $(-)$-IIA. The absolute configuration of all these compounds is therefore known (Table I). The preparation of the diastereomeric 2-octyl p-tolyl sulfoxides requires special comment.

(30) Thus, in thiane 1-oxides, the isomer with oxygen axial is more stable than the isomer with oxygen equatorial: C. R. Johnson and D. McCants, Jr., *ibid.*, 86, 2935 (1964); J. C. Martin and J. J. Uebel,*i bid.*, 86, 2936 (1964). The same is true of 1,4-dithiane *trans*-1,4-dioxides: H. M. M. Shearer, *J. Chem. Soc.*, 1394 (1959); T. Cairns, G. Eglinton, and D. C. Gibson, *Spectrochim. Acta*, 20, 159 (1964).

(31) C. R. Johnson, *J. Am. Chem. Soc.*, 85, 1020 (1963); C. R. Johnson and J. B. Sapp, Abstracts of Papers, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept. 1963, p. 23Q.

Table I. Characteristics of Sulfoxides Prepared from (−)-IIA

No.	R, in p-CH₃-C₆H₄SOR	Absolute config- uration at sulfur	M.p., °C.	[α]D, deg. Acetone	Ethanol (95%)	Calcd. C	H	S	Found C	H	S
1	Methyl	(R)	73.0–74.5	+145.5	+141.0	62.30	6.54	20.79	62.08	6.55	20.64
2	Ethyl	(R)	94 (0.4)ᵃ	+187.5	+176.5	64.25	7.19	19.06	63.93	7.30	19.00
3	n-Butyl	(R)	100 (0.07)ᵃ	+187.0	. . .	67.30	8.22	16.33	67.60	8.26	15.97
4	Isopropyl	(R)	100 (0.4)ᵃ	+176.5	+180.0	65.89	7.74	17.59	65.60	7.66	17.31
5	t-Butyl	(R)	89.5–90.0	+161	+190.0	67.30	8.22	16.33	67.14	7.97	16.25
6A	(R)-2-Octyl	(R)	. . .	+116ᵇ	+104ᵇ	71.37	9.58	12.71	71.07	9.76	12.94
6B	(S)-2-Octyl	(R)	. . .	+144ᵇ	+162ᵇ	71.37	9.58	12.71	71.65	9.37	12.80
7	Phenyl	(R)	91–92.5	+21.1	+27.0	72.18	5.59	14.83	71.91	5.62	15.00
8	m-Tolyl	(S)	63.0–64.0	+15.1	+24.4	73.01	6.13	13.92	72.75	6.10	14.09
9	o-Tolyl	(S)	77.5–78.5	−89.1	−75.6	73.01	6.13	13.92	72.84	6.04	13.63
10	Mesityl	(S)	107.0–107.5	−284	−259	74.37	7.02	12.41	74.21	7.03	12.17

ᵃ Approximate boiling points (Kugelrohr); pressures in mm. are given in parentheses. ᵇ Corrected to diastereomeric purity.

Reaction of (−)-IIA with 2-octylmagnesium bromide gave a mixture of diastereomeric 2-octyl p-tolyl (R)-sulfoxides **6A** and **6B** which were partially separated by chromatography. The two diastereomers differ only in configuration at the asymmetric carbon atom; the configuration at sulfur in both cases is (R). Diastereomer **6A**, [α]D +118.0° (acetone), on oxidation with hydrogen peroxide gave (R)-2-octyl p-tolyl sulfone, [α]D +9.1° (CHCl₃), whose absolute configuration was established by an independent synthesis[32] from optically pure (+)-(S)-2-octanol[33] (SN2 displacement of (S)-2-octyl tosylate by p-thiocresolate, followed by oxidation with hydrogen peroxide). The optically pure (R)-2-octyl p-tolyl sulfone prepared in this manner has [α]D +10.7° (CHCl₃). Hence the sulfone obtained by oxidation of **6A** contains only 92.5% of the (R)-enantiomer and it follows that **6A** is a mixture consisting of 92.5% of (R)-2-octyl p-tolyl (R)-sulfoxide and 7.5% of (S)-2-octyl p-tolyl (R)-sulfoxide. Similarly, diastereomer **6B**, [α]D +137.5° (acetone), on oxidation gave 2-octyl p-tolyl sulfone, [α]D −5.65° (CHCl₃). Since the product sulfone therefore contains 76.4% of the (S)-enantiomer, precursor **6B** is a mixture consisting of 76.4% of (S)-2-octyl p-tolyl (R)-sulfoxide and 23.6% of (R)-2-octyl p-tolyl (R)-sulfoxide. From these figures the specific rotations of the diastereomerically pure compounds are readily calculated: (R)-2-octyl p-tolyl (R)-sulfoxide has [α]D +116° (acetone) for **6A** and (S)-2-octyl p-tolyl (R)-sulfoxide has [α]D +144° (acetone) for **6B**.

The present work also firmly establishes the (R)-configuration for (+)-benzyl p-tolyl sulfoxide, which was prepared from (−)-II by the Grignard reaction,[34] and the (S)-configuration for the derived (−)-benzyl p-tolyl sulfone-¹⁸O,¹⁶O.

The n.m.r. spectra of the alkyl aryl sulfoxides 1–5 are consistent with their structure.

The sulfoxides share an aromatic A₂B₂ quartet with second-order splitting (centers of gravity near τ 2.5 and 2.7, J = 8.5 c.p.s.) and an aromatic C-methyl proton singlet at τ 7.60. Sulfoxide **1** has an S-methyl singlet at τ 7.31 and **5** has an aliphatic C-methyl

singlet at τ 8.84. Sulfoxide **2** has a methyl triplet at τ 8.83 (J = 7.4 c.p.s.) and the expected 16-line methylene proton ABX₃ multiplet centered at τ 7.19. In this compound the methylene protons are diastereomeric,[35] as they are in suitably substituted sulfites,[36] sulfinates, and sulfinamides,[37] and sulfide–borane adducts.[38] Similarly, sulfoxide **4** has a methine proton multiplet centered at τ 7.19, and two methyl proton doublets at τ 8.80 and 8.86 (J = 6.7 c.p.s.) since the methyl groups are diastereomeric.[35]

In addition to the aryl sulfoxides derived from (−)-IIA a dialkyl sulfoxide, (+)-methyl n-butyl sulfoxide (**11**), was prepared by reaction of an excess of methylmagnesium bromide with the previously described mixture of diastereomeric (−)-menthyl 1-butane-sulfinates (IIIa). Since IIIa contains 73.5% of (+)-IIIB which has the (R)-configuration at sulfur, sulfoxide **11** is 47% optically pure and has the (S)-configuration.

State of Association of Sulfoxides and Sulfinate Esters. In order to provide a meaningful discussion of the optical data which are to follow, it is necessary first to comment on the state of association of sulfoxides in solution.

Mounting evidence indicates that sulfoxides are associated in the liquid state. Dimethyl sulfoxide is said to form association polymers in the neat (undiluted) state and in benzene solution,[39] and it is believed that association in the neat state and in carbon tetrachloride involves primarily, and perhaps exclusively, dimerization.[40] It has also been found that

(32) H. L. Goering, D. L. Towns, and B. Dittmar, *J. Org. Chem.*, 27, 736 (1962).

(33) For a summary of the evidence establishing the absolute configuration of 2-octanol, see P. Newman, P. Rutkin, and K. Mislow, *J. Am. Chem. Soc.*, 80, 465 (1958).

(34) C. J. M. Stirling, *J. Chem. Soc.*, 5741 (1963).

(35) K. Mislow, M. A. W. Glass, H. B. Hopps, E. Simon, and G. H. Wahl, Jr., *J. Am. Chem. Soc.*, 86, 1710 (1964).

(36) H. Finegold, *Proc. Chem. Soc.*, 283 (1960); J. G. Pritchard and P. C. Lauterbur, *J. Am. Chem. Soc.*, 83, 2105 (1961); F. Kaplan and J. D. Roberts, *ibid.*, 83, 4666 (1961).

(37) (a) J. S. Waugh and F. A. Cotton, *J. Phys. Chem.*, 65, 562 (1961); M. Ōki and H. Iwamura, *Bull. Chem. Soc. Japan*, 35, 1428 (1962); J. W. Wilt and W. J. Wagner, *Chem. Ind.* (London), 1389 (1964); (b) R. M. Moriarty, *J. Org. Chem.*, 30, 600 (1965).

(38) T. D. Coyle and F. G. A. Stone, *J. Am. Chem. Soc.*, 83, 4138 (1961). These authors also noted the magnetic nonequivalence of the methylene protons in diethyl and ethyl isopropyl sulfoxides.

(39) H. L. Schläfer and W. Schaffernicht, *Angew. Chem.*, 72, 618 (1960); J. J. Lindberg, J. Kenttämaa, and A. Nissema, *Suomen Kemistilehti*, B34, 98, 156 (1961).

(40) C. D. Ritchie, R. E. Uschold, and A. L. Pratt, Abstracts of Papers, 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965, p. 33P. We are grateful to Professor Ritchie for informing us of these results prior to publication. See also C. D. Ritchie and A. L. Pratt, *J. Am. Chem. Soc.*, 86, 1571 (1964), and references therein.

Table II. Optical Rotatory Dispersion of Menthyl Arene- and Alkanesulfinates

No.[a]	R, in $RSOOC_{10}H_{19}$[b]	Solvent,[c] $c \times 10^3$	$[\phi]_{300}$[d]	Dispersion characteristics[e]
(−)-IIA	p-Tolyl	E, 130-2.59	−5300	276.5 tr (−13800); 274 pk (−12600); 266 pk (−15400); 262 tr (−16100); 251 (0); 235.5 pk (+46100); 219 (0); 207.5 (−32200); 205 (0)
		I′	−7100	277 tr (−19700); 274.5 pk (−19100); 271 tr (−20100); 258 (0); 234 pk (+38600); 219 (0); 205 (−49500)
		I-A, 4.78-2.39	−4200	277.5 sh (−10600); 269 sh (−13800); 255 tr (−21300); 245 (0); 232 pk (+51300); 219 (0); 215 (0)
		2.39		215 (0)
(−)-IA	p-Iodophenyl	E[f], 184-1.48	−8140	283 tr (−17200); 281 pk (−16600); 264 (0); 250 pk (+54500); 231.5 (0); 225 infl (−2200); 215 (0); 205 (−29000)
(+)-IB	p-Iodophenyl	E[g,h], 225-1.80	+3930	283.5 pk (+11000); 280 tr (+10200); 265 (0); 250 tr (−4430); 233.5 (0); 210 (+11300); 205 (0)
IIIa	n-Butyl	E[i], 312-6.24	−770	250 (−1810); 230 (−3600); 221 tr (−4800); 205 (−7900); 199 (0)
		H[j], 378-3.02	−840	250 (−2310); 240 (−3090); 230 (−3620); 230–215 approx. constant; 217 pk (−4650); 206 tr (−7000 approx.)

[a] See text for identification. (+)- and (−)-I are diastereomers which are epimeric at the asymmetric sulfur atom. [b] All sulfinates were prepared from (−)-menthol. [c] E, absolute ethanol; I, isooctane; H, heptane; I-A, isooctane containing about 10 mole equiv. of acid, corresponding to about 1 drop of trifluoroacetic acid in 25 ml. of isooctane; c in g./100 ml. of solution; the range of concentrations is given. [d] At longer wave lengths the curve is plain; rotations decrease and the zero-rotation axis is not crossed. [e] Wave lengths in mμ, molecular rotations in parentheses. The values indicated are peaks (pk), troughs (tr), shoulders (sh), inflection points (infl), and points at which the zero-rotation axis is crossed. The last value listed at the short wave length end is the last rotation for which reliable information could be obtained. [f] Also a shoulder at 240 mμ (+35,800). [g] See also Figure 3. [h] Also a shoulder at 269 mμ (+5690). [i] Plain curve for λ > 221 mμ. [j] Plain curve for λ > 230 mμ; rotations below 230 mμ are uncertain.

2-thiaindan 2-oxide exists as a dimer in cyclohexane.[41] We have found by vapor phase osmometry (v.p.o.)[42] at 37° that sulfoxides are essentially monomeric in ethanol but are associated to varying extents in cyclohexane. In particular, (+)-methyl n-butyl sulfoxide (11) appears to be essentially dimeric, with a dissociation constant which cannot be significantly larger than 10^{-3} M^{-1}. Typical triplicate molecular weight determinations (with molar concentrations given in parentheses) for cyclohexane solutions are 255 (0.055), 267 (0.024), and 238 (0.018); the calculated value for the dimer is 240. In ethanol typically found values are 124 (0.110), 117 (0.058), and 116 (0.016); the calculated value for the monomer is 120. In acetonitrile, found values are 128 (0.093) and 127 (0.034), indicating that in this solvent 11 is essentially monomeric. Our results and those obtained by others in different solvents[39,40] suggest a marked solvent dependence of the dimer dissociation constant. However, we wish to stress that there is no information at present which rigorously excludes the possibility that these dimers are not in fact, fortuitously, mixtures of monomer and various association complexes.

In contrast to dialkyl sulfoxide 11, alkyl aryl sulfoxides 1, 2, 4, and 5, diaryl sulfoxides 7-10, and the precursor menthyl 1-butanesulfinate (IIIa) are not significantly associated either in ethanol or in cyclohexane.[43]

The present findings raise the question of the state of association of sulfoxides at the concentrations of spectroscopic or polarimetric measurements. It is safe to conclude that all the absorption and o.r.d. data of compounds 1-10 and I-III refer to the monomeric species since the rotations and the spectra were measured over the concentration range 10^{-2} to 10^{-4} M, and diaryl and alkyl aryl sulfoxides, as well as sulfinate esters, are essentially monomeric at concentrations as high as ca. 10^{-1} M, which are those employed in v.p.o. Similarly, the absorption and o.r.d. data of 11 in ethanol and acetonitrile may assuredly be attributed to the monomer. In cyclohexane there is some question of whether the data arise from the presence of monomer, dimer, or a mixture thereof; however, the similarity between the spectra and o.r.d. of 11 in cyclohexane and in acetonitrile (see below) suggest that if the data in cyclohexane do in fact refer to the dimer this species has ϵ and $[\phi]$ values which cannot differ greatly from those of the monomer.

Optical Rotatory Power of Sulfoxides and Sulfinate Esters. The important optical data for the sulfinate esters I-III (Tables II-III) and for the sulfoxides 1-11 (Tables IV-X) are displayed in Figures 1-9. In the following, the observed Cotton effects will be discussed in conjunction with the relevant electronic transitions.[44]

(41) R. F. Watson and J. F. Eastham, J. Am. Chem. Soc., 87, 664 (1965).
(42) C. Tomlinson, Microchim. Acta, 457 (1961).
(43) We are currently investigating in further detail the relationship between structure and association of sulfoxides. Preliminary results indicate that the dissociation constant is strongly dependent on steric effects.
(44) For reviews of the ultraviolet behavior of sulfoxides, cf. (a) C. C. Price and S. Oae, "Sulfur Bonding," The Ronald Press Co., New York, N. Y., 1962, Chapter 4 and Appendix; (b) H. H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," John Wiley and Sons, Inc., New York, N. Y., 1962, pp. 491-496.

Table III. Ultraviolet Absorption of Menthyl Arene- and Alkanesulfinates

No.[a]	R, in $RSOOC_{10}H_{19}$[b]	Solvent[c]	Absorption characteristics[d]			
(−)-IIA	p-Tolyl	E	274.5 (500)	263 (1970)	**246.5** (5800)	**225** (10000)
		I[e]			**256** (4350)	**223** (11670)
		I–A	274.5 (420)	263.5 (1130)	**240.5** (7840)	**225.5** (8350)
(+)-IB	p-Iodophenyl	E[f]	273 (6800)	265 (11500)	**246.5** (17600)	215 (12300)
(−)-IA	p-Iodophenyl	E[g]	273.5 (5360)	265.5 (10000)	**247** (15000)	215.5 (9570)
IIIa	n-Butyl	E				**215.5** (2250)
		H				**224** (2380)

[a] See Table II, footnote a. [b] See Table II, footnote b. [c] See Table II, footnote c. [d] Wave lengths in mμ, molecular extinction coefficients (ϵ) in parentheses; maxima are in boldface; all other values refer to shoulders or inflections. [e] Also 196.5 (45,000). [f] Also 258 (14,600). [g] Also 258 (13,200).

Saturated *dialkyl sulfoxides* exhibit shoulders at *ca.* 210–220 mμ (ethanol).[44,45] By extending such work to other solvents, we have found (unpublished work) in addition to these shoulders well defined maxima at shorter wave lengths (near or below 210 mμ), as exemplified by 11 (Table IV). The intensity of the
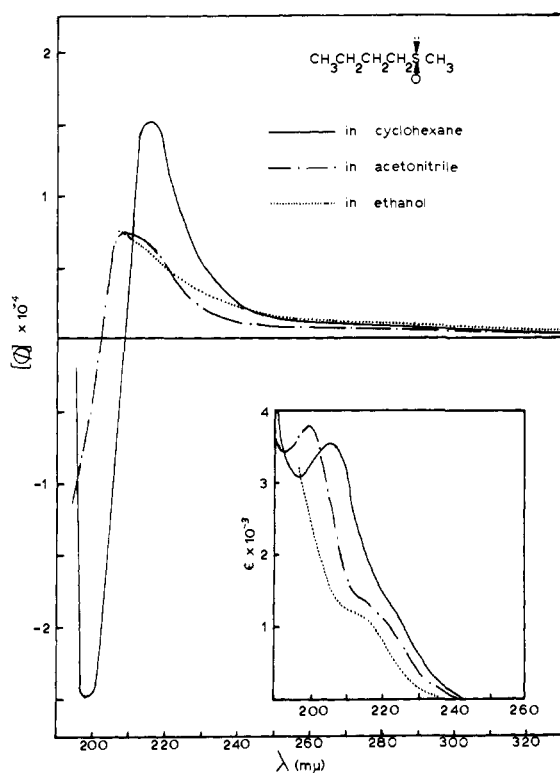

Figure 1. Optical rotatory dispersion curves and ultraviolet spectra of 11 (see Table IV).

absorption (log ϵ *ca.* 3.5–3.6) suggests an allowed singlet–singlet transition, probably the $(3sp^3)^2 \rightarrow (3sp^3)(3d)$ transition.[46] This proposal finds support in the fact that, upon going to polar solvents, blue shifts are observed, suggestive of an n → π^* transition.[47] The ultraviolet spectrum of 11 shows this behavior quite clearly (Figure 1): the short wave length absorp-

tion maximum below 210 mμ is highly solvent dependent. In contrast, the shoulder near 215 mμ is relatively solvent insensitive. The short wave length band is strongly optically active, and the solvent dependence of the o.r.d. curve parallels that of the absorption band (Figure 1). We have been unable to determine whether the shoulder near 215 mμ is also optically active; if a Cotton effect is centered in that region it is hidden by the tail of the short wave length o.r.d. curve.
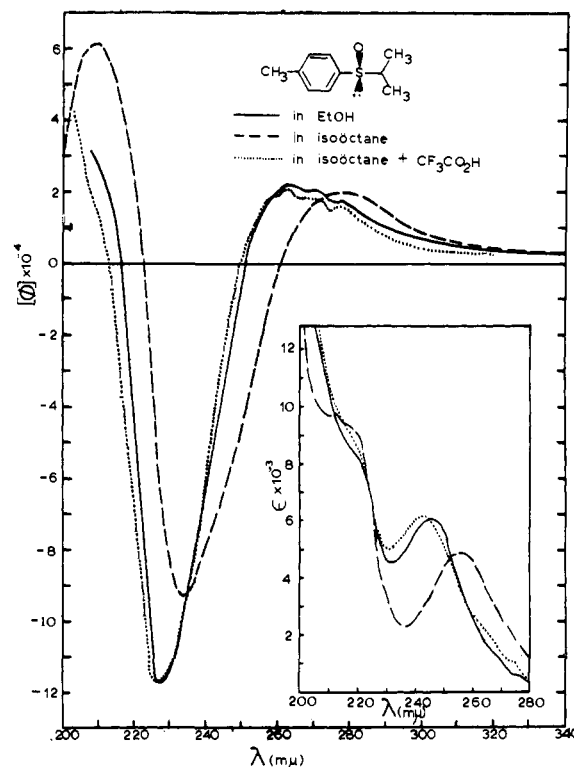

Figure 2. Optical rotatory dispersion curves and ultraviolet spectra of 4 (see Tables V, VI, and X).

The amplitude of the Cotton effect of 11 is surprisingly high. It might have been supposed,[2a] by analogy with the saturated carbonyl compounds,[48] that dialkyl sulfoxides would exhibit behavior characteristic of asymmetrically perturbed symmetric chromophores, since the $\sigma \rightarrow \sigma^*$ transitions of the alkyl groups are not expected to mix significantly with the sulfoxide n → π^* transition. The dependence of the

(45) (a) H. P. Koch, *J. Chem. Soc.*, 2892 (1950); P. Karrer, N. J. Antia, and R. Schwyzer, *Helv. Chim. Acta*, 34, 1392 (1951); (b) A. Mangini, *Gazz. chim. ital.*, 88, 1063 (1958).
(46) G. Leandri, A. Mangini, and R. Passerini, *J. Chem. Soc.*, 1386 (1957).
(47) M. Kasha, *Discussions Faraday Soc.*, No. 9, 14 (1950); H. McConnell, *J. Chem. Phys.*, 20, 700 (1952); G. J. Brealey and M. Kasha, *J. Am. Chem. Soc.*, 77, 4462 (1955).

(48) A. Moscowitz, *Tetrahedron*, 13, 48 (1961).

Table IV. Some Optical Properties of (S)-Methyl n-Butyl Sulfoxide (11)[a]

Solvent,[b] $c \times 10^3$	Absorption characteristics[c]		
E	211 (1100)		
AN	217 (1210)	**200** (3770)	
I and C	225 (1070)	**205**.5 (3540)	
I-A	207 (953)		

	Dispersion characteristics[d]				
E 1233–12.33	300 (+745)				205 (+7200)
AN 19.0–3.80	300 (+510)	210 pk (+7600)	202 (0)		195 (−11000)
I and C 906–2.27	300 (+690)	216 pk (+15250)	208 (0)	200 tr (−25000)	197.5 (−17000)
I-A 13.6	300 (+598)				205 (+4800)

[a] See also Figure 1. The data were calculated on the assumption that 11 is 100% monomeric in solution. [b] See Table II, footnote c; AN, acetonitrile; C, cyclohexane. [c] See Table III, footnote d. [d] See Table II, footnote e. All values of [φ] are corrected to optical purity: $[\phi]_{corr} = [\phi]_{obsd}/0.47$.

rotational strength of this chromophore on the structure of the alkyl groups is presently being studied.

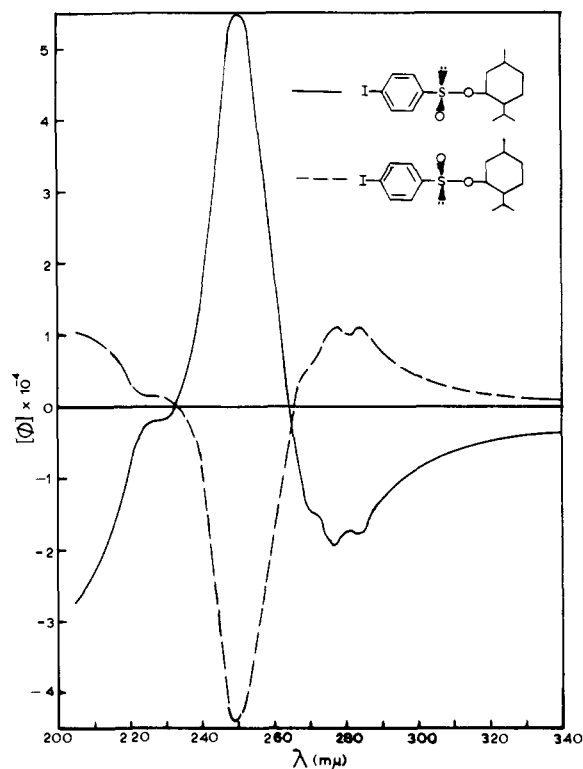Figure 3. Optical rotatory dispersion curves of (−)-IA and (+)-IB (see Table II).

Alkyl aryl sulfoxides show an intense band (log ε ca. 3.5–3.9) at ca. 235–255 mμ which is solvent dependent[34,44–46,49–53] and which will here be referred to as the *primary band*. Although the exact nature of this

(49) H. Bredereck, G. Brod, and G. Höschele, *Chem. Ber.*, 88, 438 (1955).
(50) F. G. Bordwell and P. J. Boutan, *J. Am. Chem. Soc.*, 79, 717 (1957).
(51) A. Cerniani, G. Modena, and P. E. Todesco, *Gazz. chim. ital.*, 90, 3 (1960).
(52) G. M. Gasperini, G. Modena, and P. E. Todesco, *ibid.*, 90, 12 (1960).
(53) I. V. Baliah and R. Varadachari, *J. Indian Chem. Soc.*, 37, 321 (1960).

transition is still subject to debate[44b] it is considered to arise from the interaction of the weak, forbidden phenyl $\pi \rightarrow \pi^*$ (^1L_b) band with the allowed intense sulfoxide $(3sp^3)^2 \rightarrow (3sp^3)(3d)$ transition; the resulting intense band is blue shifted on going to polar sol-
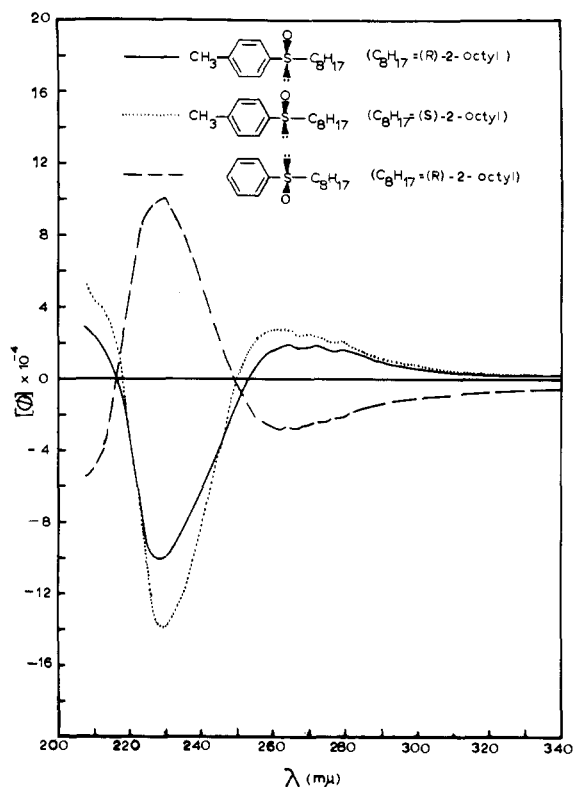
Figure 4. Optical rotatory dispersion curves of 6A, 6B, and 12B (see Tables V and X).

vents.[45b,46,53] The same solvent dependence is observed in the alkyl aryl sulfoxides which are the subject of the present study (Table VI),[54] as illustrated for a

(54) The blue shift in ethanol is essentially duplicated in isooctane containing a few mole equivalents of trifluoroacetic acid. The position of the absorption maximum is thus clearly the effect of hydrogen bonding to the sulfoxide. Not unexpectedly, the addition of trifluoroacetic acid to ethanol produces no significant changes in the spectrum.

Table V. Optical Rotatory Dispersion of Alkyl Aryl Sulfoxides

No.	R, in $p\text{-}CH_3C_6H_4SOR$	Solvent,[a] $c \times 10^3$	$[\phi]_{300}$[b]	Dispersion characteristics[c]								
				pk	tr	pk	tr	pk	z	tr	z	z
1	Methyl	E 50.0-1.00	+4560	276 (+13400)	274 (+12900)		269 sh (+16300)	256 (+21000)	246	226 (-113000)	214	205 (+34000)
		E-A 4.08-2.04	+5000	276 (+14000)	274 (+13600)		269 sh (+17000)	257 (+22100)	246	225.5 (-110000)	214	207 (+37800)
		I[d] 63.6-1.27	+7020	280 sh (+16900)	277 infl (+17300)	272 (+19500)	268 (+18500)	265 (+18600)	255	230 (-103000)	219	200 (+47400)
		I-A 6.36-1.27	+3270	276 (+9680)	274 (+9200)		270 sh (+11800)	251 (+23700)	241	224 (-109000)	204	204 (0)
2	Ethyl	E 70.8-0.708	+5600	276 (+14400)	275 (+13900)		270 infl (+17300)	258 (+21500)	247	226.5 (-115000)	216	205 (+46000)
		I[e] 43.6-0.436	+7630	280 sh (+17600)				274 (+19500)	256.5	232 (-90000)	221	198 (+27000)
3	n-Butyl	E 17.6-1.76	+6250	277 (+17300)	274.5 (+15500)	271 (+20100)	268 (+19900)	260.5 (+23800)	248	227 (-114000)	215	207 (+39000)
4	Isopropyl	E[f] 39.2-0.784	+6530	277 (+17700)	275 (+17100)	270.5 (+20800)	268 (+20400)	262 (+22100)	250.5	227.5 (-118000)	216	205 (+39200)
		E-A 2.24	+6500	277 (+17900)	275.5 (+16900)	270 (+20700)	267.5 (+20200)	262.5 (+22800)	251	227.5 (-122000)	216	205 (+37600)
		I[f,g] 56.8-0.568	+8800	276 (+19800)			268 infl (+14600)		261	233.5 (-92500)	222	199 (+18000)
		I-A[f,h] 1.78	+4140	277 (+15900)	274 (+14900)	271 sh (+18000)		262.5 (+21100)	249	226 (-122000)	212.5	202.5 (+44500)
5	t-Butyl	E 36.0-0.720	+10120	278.5 (+28800)	276 (+27800)	272 (+31900)	265 sh (+28900)		255	227 (-188000)	215	205 (+76000)
		E-A[i] 2.34	+12600	278.5 (+30600)	276 (+30000)	272.5 (+33800)	268 sh (+32600)		254.5	226.5 (-179000)	216	206 (+71000)
		I[j] 72.8-0.364	+13800	282 (+27300)					266	231 (-130000)	220.5	200 (+92000)
		I-A 2.48-1.24	+7540	278.5 (+23100)	275 (+20600)	270.5 (+27500)	268 (+25800)	258 (+34000)	248	224 (-171000)	206.5	204.5 (+9500)
6A	(R)-2-Octyl	E[k,l] 2.48	+5980	279 (+16200)	276 (+15900)	271 (+18500)	268 (+17500)	264 (+18700)	253	228 (-102000)	216	207.5 (+28100)
6B	(S)-2-Octyl	E[k,l] 3.12	+7440	278 (+20900)	276 (+20200)	271 (+23700)	268 (+24200)	262.5 (+27100)	250	229 (-139000)	217.5	207.5 (+53100)
12B	(R)-2-Octyl phenyl (S)-sulfoxide	E[k] 2.40	-10100	274.5 sh (-23400)		268.5 sh (-25000)		263 (tr) (-27600)	248	228.5 (pk) (+98600)	216	207.5 (-54000)

[a] See Table II, footnote c; E-A, ethanol containing about 10 mole equiv. of acid. [b] See Table II, footnote d. [c] See Table II, footnote e; z, zero rotation point. [d] Also pk at 206 (+71,600). Also pk at 213 (+61,100), tr at 210 (+58,900), pk at 208 (+65,000). [f] See also Figure 2. [g] Also pk at 207 (+60,900). [h] Also sh at 260.5 (+19,050). [i] Also infl at 210 (+48,000). [j] Also sh at 241 (-97,200) and at 214 (+86,400) and pk at 205 (+105,000). [k] See also Figure 4. [l] Corrected to diastereomeric purity.

Table VI. Ultraviolet Absorption of Alkyl Aryl Sulfoxides

No.	R, in p-CH₃-C₆H₅SOR	Solvent[a]	Absorption characteristics[b]				
1	Methyl	I	278 (650)	268.5 (1670)	**249** (4830)	217 (9330)	210 (10400)
2	Ethyl	I	279 (750)	270 (1840)	**251** (4980)	218 (9390)	210 (10200)
4	Isopropyl	I[c]	270 (2620)	265 (3500)	**254.6** (4800)	217.6 (9300)	**210.7** (9740)
5	t-Butyl	I			**261** (5030)	**218** (10540)	**211** (10300)
1	Methyl	E	274.5 (440)	264 (1030)	**236** (6350)	218.5 (8110)	
2	Ethyl	E	275 (430)	265 (1120)	**239.5** (6040)	217.5 (7960)	
3	n-Butyl	E	275 (530)	267 (1100)	**240.5** (6020)	217.5 (8190)	
4	Isopropyl	E[c]	275 (650)	267.5 (1470)	**244** (5940)	217.5 (8620)	
6A	(R)-2-Octyl[d]	E	276 (750)	266 (1790)	**245.6** (4980)	**219** (9650)	
6B	(S)-2-Octyl[d]	E	276 (580)	267 (1550)	**244** (7360)	220 (8050)	208 (13300)
12B	(R)-2-Octyl phenyl (S)-sulfoxide	E	273 (750)	265 (1500)	**243** (4820)	217 (6600)	205 (12200)
5	t-Butyl	E	277.5 (1010)		**249.5** (6430)	217 (10250)	
1	Methyl	I-A	275 (430)	265 (1140)	**235** (5670)	218 (7940)	
4	Isopropyl	I-A[c]	276 (500)	267 (1280)	**242** (6100)	219 (8620)	
5	t-Butyl	I-A	276 (590)		**245** (7480)	217 (10050)	
1	Methyl	E-A	275.5 (540)	265.5 (1160)	**236.5** (6540)	218.5 (8750)	
4	Isopropyl	E-A	277 (570)	268 (1500)	**245.5** (5950)	218 (8780)	
5	t-Butyl	E-A	276 (1090)		**249.5** (6510)	216.5 (10720)	

[a] See Table V, footnote a.   [b] See Table III, footnote d.   [c] See Figure 2.   [d] Corrected to diastereomeric purity.

typical compound (4) in Figure 2. The primary band is optically active. In the alkyl p-tolyl sulfoxides (1–6) derived from (−)-IIA the long wave length Cotton effect corresponding to the primary band has a high

wave lengths (around 220 mμ for 4) and this may correspond to one of the shoulders situated at 210–220 mμ in the absorption spectrum. In this connection,
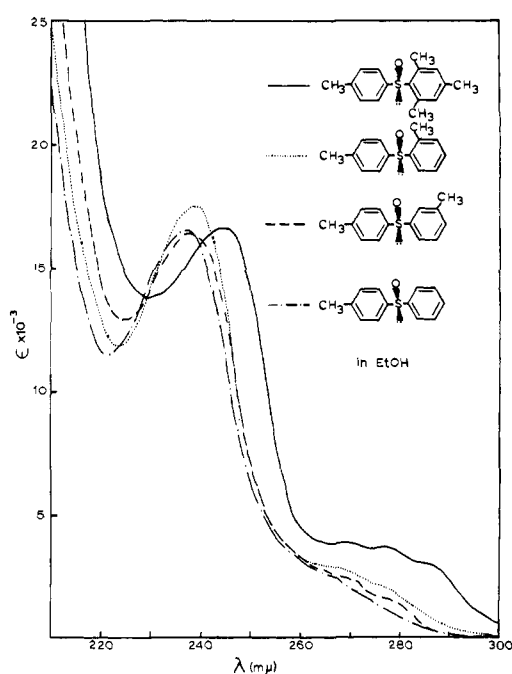

Figure 5. Ultraviolet spectra of diaryl sulfoxides in ethanol (see Table VIII).

Figure 6. Optical rotatory dispersion curves of diaryl sulfoxides in ethanol (see Table VII).

molecular amplitude of the order of 10⁵ (Tables V and X),[55] and *the positive sign characterizes the absolute (R)-configuration (Table I)*.

A Cotton effect approximately equal in amplitude but opposite in sign appears to be centered at shorter

(55) Low-amplitude Cotton effects accompany this primary band Cotton effect and are solvent insensitive; they therefore correspond to separate transitions (probably benzenoid) rather than to vibrational fine structure of the main band.
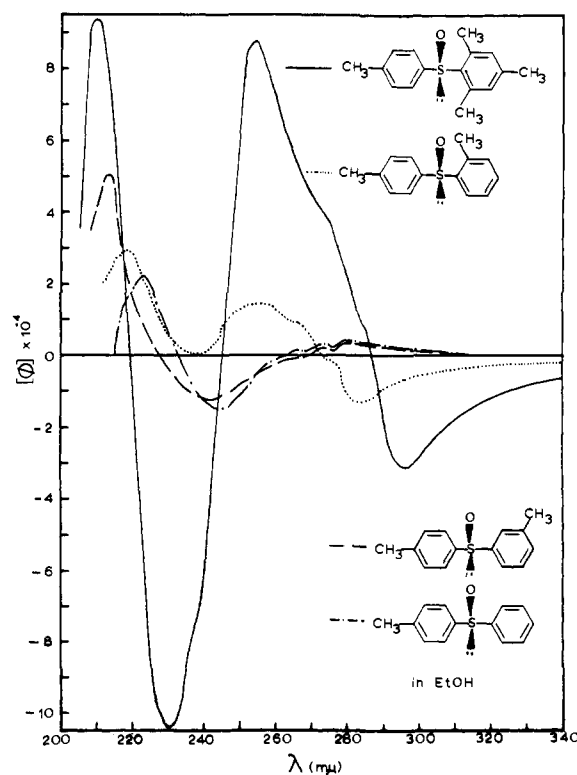
it is noteworthy that Stirling[34] has found in (−)-benzyl p-tolyl sulfoxide a positive c.d. maximum at 250 mμ and a negative c.d. maximum at 220 mμ, with ellipticities of +86,000 and −125,000, respectively.

It has previously been found[51,53] that increased branching of the alkyl group in alkyl phenyl sulfoxides
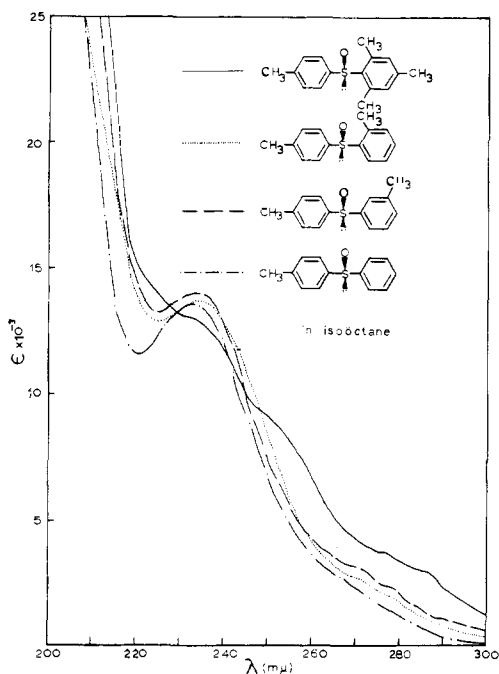
Figure 7. Ultraviolet spectra of diaryl sulfoxides in isooctane (see Table VIII).

causes a red shift in the primary band, presumably the result of steric effects,[56] which is most pronounced in the case of the *t*-butyl compound. The compounds in the present study exhibit the same behavior (Table VI), which is furthermore reflected in the o.r.d. and c.d. patterns (Tables V, IX, and X). The amplitude of the Cotton effect of *t*-butyl *p*-tolyl sulfoxide (5) was found to be significantly larger than that of the other alkyl *p*-tolyl sulfoxides (1–4 and 6), and it was the only compound in this series for which the c.d. curve at −192° could be obtained. A preliminary study of the temperature dependence of the c.d. of the alkyl aryl sulfoxides (Table IX) did not reveal any marked effects.

The above observations are easily accommodated by discussing the optical rotatory power of alkyl aryl sulfoxides from the viewpoint of inherently dissymmetric chromophores.[48] Assuming that the primary band results from strong coupling between the local benzene $\pi \to \pi^*$ and sulfoxide n $\to$ π^* excitations, the arenesulfinyl chromophore may be viewed as an extended dissymmetric array, which is expected to manifest high rotational strength[48,57]; the electronic coupling involves a transfer of intensity from the sulfoxide to the benzene transition.[46] The absolute chirality of inherently dissymmetric chromophores is expressed in the sign of the appropriate Cotton effect.[48,57] For the benzenesulfinyl grouping in compounds such as 1–6, this corresponds to a positive primary band Cotton effect for the (R)-configuration. It is not known to what extent the sign and rotational strength of the primary band Cotton effect depends on conforma-

(56) Steric effects have also been observed in the absorption spectra of methyl aryl sulfoxides[52]; whereas methyl phenyl and methyl *o*-tolyl sulfoxides have λ_{max}^{hexane} near 252 mμ, methyl mesityl sulfoxide absorbs with λ_{max}^{hexane} 267 mμ. The effect of geometry on the absorption spectra of stereoisomeric thianthrene 5,10-dioxides has been discussed by K. Mislow, P. Schneider, and A. L. Ternay, Jr., *J. Am. Chem. Soc.*, **86**, 2957 (1964).

(57) K. Mislow, *Ann. N. Y. Acad. Sci.*, **93**, 457 (1962).

Table VII. Optical Rotatory Dispersion of Aryl *p*-Tolyl Sulfoxides

No.	R, in p-CH3-C6H4SOR	Solvent,[a] c × 10³	[φ]520[b]	Dispersion characteristics[c]										
7	Phenyl	E[d] 48.0–0.96	+640	281 pk (+3400)	276 tr (+1600)	274 pk (+2880)	268.5 tr (+790)	266 pk (+1440)	264 (0)	244 tr (−15900)	232 (0)	222 pk (+20500)	215 (0)	215 (0)
8	*m*-Tolyl	I[e] 65.2–1.63	+550	282 pk (+2700)	277 tr (+2020)	275 pk (+2150)	272 tr (+790)	269 pk (+830)	266 (0)	238 tr (−5100)	230 (0)	220 pk (+11800)	214 (0)	203 (−4900)
		E 44.4–0.56	+570	281 pk (+3400)	275 tr (+1120)	273 pk (+1920)	268 (0)	265 sh (−1100)	264 pk (−900)	242 tr (−11800)	228 (0)	213 pk (+51000)		207.5 (+29000)
		I[f] 45.6–1.14	+605	281 pk (+3000)	276 tr (+1200)	273 pk (+1600)	269 (0)	265.5 tr (−1100)		238 tr (−18000)	227 (0)	215 pk (+50000)	205 (0)	205 (0)
9	*o*-Tolyl	E 18 0.90	−2800	284 tr (−13800)	275 sh (−1200)	272 (0)	265 sh (+9350)	253 pk (+14400)	250.5 (0)	238 tr (0)	229 (0)	218 pk (+30000)		210 (+18600)
		I 39.6 0.79	−3140	293 tr (−7130)	277 (0)		274.5 sh (+2620)	260.5 pk (+12300)	245 (0)	241 tr (−16700)	219 (0)	218 pk (+39000)	203 (0)	203 (0)
10	Mesityl	E 3.68 0.37	−11000	295.5 tr (−30900)	286 (0)	283 sh (+9800)	275 tr (+36400)	254 pk (+88400)	250.5 (0)	230 tr (−106000)	222 (0)	211 pk (+94000)		205 (+35000)
		I and C[g] 29.4 0.47	−17300	305 tr (−27000)	291 (0)	285 sh (+35100)	276 sh (+60400)	265 pk (+72400)		230 tr (−90100)		212 pk (+82300)		200 (+14800)
		E-A 3.68 0.37	−10700	296 tr (−30700)	286 (0)	284 sh (+8060)	275 sh (+37200)	254 pk (+89000)	245 (0)	229 tr (−108000)	219 (0)	211.5 pk (+90500)		205 (+44500)
		I-A[h] 29.4 0.47	−8700	294 tr (−32000)	281.5 (0)		275 sh (+18700)	252 pk (+86500)	242 (0)	228 tr (−79200)	220 (0)	211 pk (+117000)	202 (0)	202 (0)

[a] See Table V, footnote a: see also Figures 6, 8, and 9. [b] See Table II, footnote d. [c] See Table II, footnote e. [d] Also sh at 260 (−1440). [e] Also tr (?) at 210 (−6800). [f] Also tr at 260 (−2900) and pk at 256 (−2400). [g] Also sh at 235 (−87,000); C., cyclohexane. [h] Also sh at 233 (−69,800).

Table VIII. Ultraviolet Absorption of Aryl p-Tolyl Sulfoxides

No.	R, in p-CH₃- C₆H₄SOR	Solvent[a]	Absorption characteristics[b]					C.d.[c]
7	Phenyl	E			273.5 (1680)	266 (2540)	**237** (16400)	(+)[d]
		I			272.5 (2100)	265 (3300)	**232** (17200)	
8	m-Tolyl	E	278 (1570)	271 (2320)	265 (2820)	**238** (16500)		265 (+)
		I	279 (2260)	270.5 (3100)		**233.5** (13900)		
9	o-Tolyl	E		276 (2090)	265 (2900)	**238.5** (17500)		272 (−)
		I	280 (1800)	272.5 (2500)		**234.5** (13700)		
10	Mesityl	E	287 (2940)	**277** (3680)	**269.5** (3820)	**244.5** (16500)		286 (−),
		E–A	287 (2740)	**278** (3470)	**270** (3600)	245 (15900)		245 (+)
		I	285 (2990)	277 (3690)	251 (8850)	238 (12100)	**202** (52600)	
		I–A	288 (2640)	**277.5** (3680)	**269** (4100)	**244** (15500)	**202.5** (47200)	

[a] See Table V, footnote a. [b] See Table III, footnote d; see also Figures 5 and 7; maxima are in boldface. [c] Circular dichroism maxima in solvent EPA (5:5:2 v./v./v. ether–isopentane–ethanol). Figures give position (in mμ) and sign of maximum. [d] Could not be recorded; probably below 260 mμ.

tion since a conformationally rigid system of known absolute configuration has not been available for study and nothing is known at present about overlap control of conformation in alkyl aryl sulfoxides.[58] On

the nonstereosensitivity of 3d-orbital resonance interaction[44,46,58,59] the torsional barriers in $2p\pi$–$3d\pi$ overlap are smaller than in $2p\pi$–$2p\pi$ overlap. Consequently, in the absence of special steric interactions (see below), rotation about the C–S bond axis will
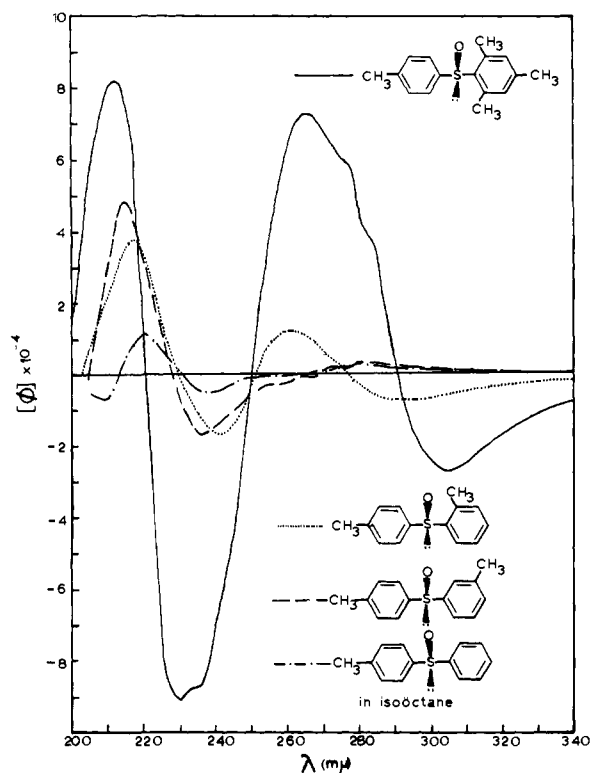

Figure 8. Optical rotatory dispersion curves of diaryl sulfoxides in isooctane (see Table VII).

Figure 9. Optical rotatory dispersion and circular dichroism curves of **10** (see Tables VII and IX).

the assumption that $2p\pi$–$3d\pi$ overlap is important, little overlap is lost by rotation of the phenyl ring about the C–S bond axis for, as a consequence of

(58) In the case of sulfinamides, the consequences of N–S $2p\pi$–$3d\pi$ overlap have been discussed: R. M. Moriarty, *Tetrahedron Letters*, No. 10, 509 (1964), and ref. 37b. In aryl sulfoxides C–S $2p\pi$–$3d\pi$ and $2p\pi$–$3sp^3\pi$ overlap (corresponding to interaction of the lone pair on sulfur with the aromatic ring) are both possible, and correspond to the limiting structures shown (i and ii).
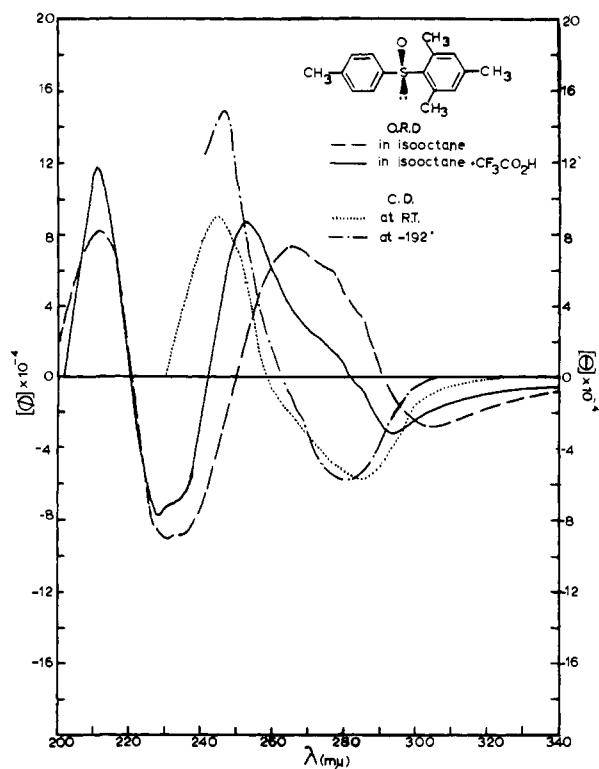
i   ii

be less restricted than would be the case for a partial double bond in C₆H₅–X–, where X is a first row element. The observed Cotton effects are therefore possibly the weighted averages of Cotton effects of numerous accessible and significantly populated conformers, all corresponding to a given absolute configuration. This conclusion is bolstered by the observation that the Cotton effects of t-butyl p-tolyl sulfoxide (**5**) are unusually intense, a consequence, in all probability, of the restriction of conformational freedom.

(59) S. Oae and C. Zalut, *J. Am. Chem. Soc.*, **82**, 5359 (1960).

Table IX. Circular Dichroism of p-Tolyl Alkyl and Aryl Sulfoxides

No.	R, in p-CH₃-C₆H₄-SOR	Temp.,[a] °C.	Concn.,[b] g./l.	C.d. characteristics[c]			
1	Methyl	RT	0.35–0.006	290 (0)	**241** (+ 71700)	236 (+50000)	
		−192	0.006	290 (0)	240 (+149000)		
2	Ethyl	RT	0.184–0.0073	290 (0)	**243** (+70000)	240 (+64000)	
		−192	0.0073	290 (0)	273 (+34000)		
4	Isopropyl	RT	0.133–0.0053	300 (0)	**245** (+86600)	236 (+67000)	
		−192	0.0053	325 (0)	260 (+146000)		
5	t-Butyl	RT	0.02	290 (0)	**252** (+76000)	232 (0)	
		−192	0.004	300 (0)	**247** (+153000)	232 (+76000)	
7	Phenyl	RT	1.03–0.046	300 (0)	260 (+6000)		
		−192	0.046	290 (0)	270 (+5200)		
8	m-Tolyl	RT	0.10–0.052	290 (0)	**265** (+5000)	260 (+4000)	
		−192	0.052	320 (0)	257 (+10000)		
9	o-Tolyl	RT	0.26–0.016	330 (0)	**272** (−18000)	240 (0)	
		−192[d]	0.032–0.016	290 (0)	**276** (−18000)	273 (−12500)	**268** (−22500)	256 (−8000)
10	Mesityl[e]	RT[f]	0.30–0.012	330 (0)	**286** (−58000)	259 (0)	**245** (+90000)	231 (0)
		−192[g]	0.012	310 (0)	**280** (−58000)	263 (0)	**246.5** (+149000)	240 (+120000)

[a] Data at −192° are corrected for density change; RT, room temperature. [b] Solvent EPA (5:5:2 v./v./v. ether–isopentane–ethanol)·
[c] Wave lengths in mμ; molecular ellipticities in parentheses; maxima (positive or negative) are indicated in boldface; the first and last points indicate, respectively, the starting points of the Cotton effect ([θ] = 0) and the last ellipticity for which reliable information could be obtained.
[d] Also a shoulder at 260 mμ ([θ] −12,500). [e] See Figure 9. [f] Also a shoulder at 267 mμ ([θ] −25,000). [g] Also a shoulder at 269 mμ ([θ] −25,000).

Table X. Alkyl Aryl Sulfoxides. Summary of Spectroscopic Data

No.	R, in p-CH₃C₆H₄SOR	Solvent[a]	Optical rotatory dispersion[b] Midpoint of Cotton curve, mμ	Amplitude × 10⁻³	Circular dichroism[c] Max., mμ	[θ] × 10⁻³	Absorption[d] max., mμ
1	Methyl	E	241	134	241	+72	236
		E–A	241	132			236.5
		I	248	122			249
		I–A	238	133			235
2	Ethyl	E	241	137	243	+70	239.5
		I	253	110			251
3	n-Butyl	E	244	138			240.5
4	Isopropyl	E	245	140	245	+87	244
		E–A	245	145			245.5
		I	255	112			254.6
		I–A	244	143			242
6A	(R)-2-Octyl[e]	E	246	121			245.6
6B	(S)-2-Octyl[e]	E	246	166			244
5	t-Butyl	E	250	220	252 (247 at −192°)	+76	249.5
		E–A	250	213			249.5
		I	257	157			261
		I–A	241	205			245
12B	(R)-2-Octyl phenyl (S)-sulfoxide	E	246	126			243

[a] See Table V, footnote a. [b] From data in Table V. [c] Room temperature data from Table IX. [d] From data in Table VI. [e] Corrected to diastereomeric purity.

In the case of the absorption spectra of methyl p-toluenesulfinate[49] and menthyl p-toluenesulfinate (II, Table III), it has been demonstrated that the esters exhibit behavior closely paralleling that of the alkyl p-tolyl sulfoxides, including solvent dependence. It is therefore likely that the electronic transition which is responsible for the primary band in p-toluenesulfinates is closely similar and comparable to the corresponding transition in alkyl p-tolyl sulfoxides so that our conclusions concerning the latter may be extended to the former. The high-amplitude, negative Cotton effect for the primary band in (−)-IIA (Table II) is thus directly comparable with the high-amplitude, positive Cotton effect for the primary band in (+)-(R)-alkyl

p-tolyl sulfoxides 1–6 (Table V). The inversion of configuration in the Grignard reaction accompanying the conversion of (−)-II to (+)-1 and related sulfoxides is thus reflected by the change in sign of the primary band Cotton effect, and, in our interpretation, by the change in chirality of the inherently dissymmetric p-toluenesulfinyl chromophore which is common to both.

It has been pointed out[48] that if a molecule contains an inherently dissymmetric chromophore, sign and magnitude of the Cotton effect associated with such a chromophore may for all intents and purposes be ascribed entirely to the sense and extent of twist of the chromophore proper. The contributions to the optical

activity attributable to inherent dissymmetry greatly outweigh those that can be attributed to perturbation by asymmetrically disposed substituents, and, accordingly, the sign of the Cotton effect will be determined solely by the chirality of the inherently dissymmetric chromophore.[60] We earlier referred to the dominance of the contribution by the sulfinate ester grouping at the D-line, also remarked upon by others,[14,24] and we now illustrate our view that the above description nicely fits the case of the arenesulfinyl chromophore by two examples. Figure 3 displays the o.r.d. curves of the diastereomeric menthyl p-iodobenzenesulfinates (+)-IB and (−)-IA (Table II). Although the menthyl moiety is the same (i.e., derived from (−)-menthol) in the two diastereomers, the p-iodobenzenesulfinyl chromophore, which is of opposite chirality in the two epimers, so dominates the o.r.d. spectrum that the two curves are essentially enantiomeric. Similarly, the two diastereomeric 2-octyl p-tolyl (R)-sulfoxides 6A and 6B have essentially superimposable o.r.d. curves (Figure 4), even though the 2-octyl moieties in the two compounds have opposite configurations. Here again, the chirality of the p-toluenesulfinyl chromophore, which is the same in the two compounds, exerts the dominating effect on the optical rotatory power and the primary band Cotton effect is essentially indistinguishable from that of the simple analog 4 (Figure 2, Tables V and X).

The remaining discussion in this section concerns the optical rotatory power of simple diaryl sulfoxides.[61] The ultraviolet spectra at 233–250 mμ (ethanol) of such sulfoxides have been studied[44–46,53,59]; the simple derivatives of diphenyl sulfoxide are characterized by a very intense (log ε ca. 4.1–4.3) primary band at 233–250 mμ (ethanol), accompanied by a somewhat less intense (log ε ca. 3.3–3.5) secondary band at ca. 265–275 mμ (ethanol). The ultraviolet spectra of diaryl sulfoxides 7–10 (Table VIII) in ethanol exhibit this characteristic behavior (Figure 5); the only noteworthy feature is the red shift of the primary band and the intensification of the secondary band which differentiates p-tolyl mesityl sulfoxide (10) from the other members of this series; the effect of double ortho substitution on the spectral characteristics of diaryl sulfoxides has been previously discussed.[44,46,59]

The o.r.d. behavior of the four diaryl sulfoxides 7–10 (Table VII) in ethanol may be profitably discussed from the viewpoint that the diphenyl sulfoxide chromophore is inherently dissymmetric in all conformations except for those in which the relative disposition of the two phenyl rings introduces a plane of symmetry into the molecule. The extent of the molecular dissymmetry is related to the angle of twist of one phenyl ring relative to the other. A macroscopic sample of diphenyl sulfoxide in solution contains as many dissymmetrically skewed conformers of one chirality as of the other, and it follows that the macroscopic sample consists for the most part of racemic

mixtures of inherently dissymmetric chromophores. It is therefore correct to describe diphenyl sulfoxide as an essentially symmetric chromophore[2a,61] provided it be understood that reference is made to an effective average conformation possessing a plane of symmetry. This view is borne out by an inspection of the o.r.d. curves of phenyl and m-tolyl p-tolyl sulfoxides, 7 and 8 (Figure 6). The methyl groups in these compounds asymmetrically perturb the essentially symmetric diphenyl sulfoxide chromophore, and the Cotton effects of the two compounds are manifested as virtually superimposable o.r.d. curves of low amplitude. The introduction of one o-methyl substituent (9) dramatically changes the character of these o.r.d. curves, including the sign at long wave lengths (Figure 6); this ortho effect is even more strikingly demonstrated in the curve for p-tolyl mesityl sulfoxide (10), whose optical rotatory properties are enormously changed from those of the parent compound 7 (Figure 6). Very similar behavior is exhibited in isooctane (Tables VII and VIII, Figures 7 and 8); in terms of the change in sign and amplitude of the Cotton effects within the series 7–10, and aside from shifts in the band positions, the ortho effect is therefore not markedly solvent sensitive. Inspection of the high-amplitude o.r.d. curve of 10 (Figures 6 and 8) suggests the presence of two intense Cotton effects of opposite signs, negative at longer wave lengths and positive at shorter wave lengths, in the region above 240 mμ. This inference is borne out by an examination of the c.d. curve (Table IX) of 10 in EPA (a polar solvent) which clearly reveals two Cotton effects of opposite sign (Figure 9) with apparent maxima at 286 mμ (negative) and at 245 mμ (positive). The c.d. curves are not significantly changed in position or intensity by a change from room temperature to −192°.

The ortho effect and its accompanying o.r.d. and c.d. manifestations clearly originates in a breakdown of the average symmetry of the diphenyl sulfoxide chromophore (above). The nonbonded interaction of the ortho methyls in the mesityl group of 10 with the other substituents on the sulfur atom is not balanced by a similar nonbonded interaction of the ortho hydrogens in the p-tolyl group of 10. As a result, the conformation in which one of the phenyl rings is twisted in one direction by a given amount differs in free energy from a conformation in which the other phenyl ring has been twisted to the same extent but in the opposite direction. Accordingly, whereas the ratio of enantiomeric conformations of the diphenyl sulfoxide chromophore in 7 and 8 is essentially unity, that ratio is significantly displaced from unity in 9 and even more so in 10. The relative temperature insensitivity of the c.d. curves of 9 and 10 (Table IX) strongly suggests that conformational freedom in these compounds is seriously restricted even at room temperature.[62]

Although the preceding discussion is intended to serve merely as an empirical and qualitative guide to the understanding of the optical rotatory power of sulfoxides, extensions to other systems are possible even at this stage of development of the subject. The remainder of this paper will be devoted to some of these extensions.

(60) K. Mislow, "Introduction to Stereochemistry," W. A. Benjamin, Inc., New York, N. Y., 1965, pp. 64, 157.

(61) After this work was completed (see ref. 2b, and J. T. Melillo, Ph.D. Dissertation, New York University, 1964), a publication appeared by Andersen, et al.,[27b] in which some of the subject material of this subsection is also discussed, although in part from a different point of view. This paper in addition discusses the stereospecificity of the Grignard reaction used[14] in the preparation of optically active sulfoxides from (−)-IIB.

(62) See also K. M. Wellman, E. Bunnenberg, and C. Djerassi, J. Am. Chem. Soc., 85, 1870 (1963).

Absolute Configuration of Dialkyl Sulfoxides. The absolute configuration at asymmetric sulfur in (+)-S-methyl-L-cysteine S-oxide ($CH_3SOCH_2CHNH_2COOH$) is (S), as unambiguously determined by X-ray analysis.[5] The observation[63] that the diastereomeric sulfoxides derived from S-methyl-L-cysteine have essentially equal and opposite rotations, $[\alpha]$D +124 and −127°, shows that the sulfoxide chromophore exerts a dominating influence in these compounds. On the questionable[11,64] assumption that the vicinal action of the α-amino acid group is negligible, one may extend[64] this observation to cover the general case of other aliphatic compounds with structure CH_3SOCH_2R; according to this criterion (+)-**11** should have the (S)-configuration, which is indeed the case (above). A more convincing correlation is afforded by the work of Klyne, Day, and Kjær[65] who examined the long wave length o.r.d. of naturally derived asymmetric sulfoxides of type $CH_3SO(CH_2)_n NH–CX–NHR$, where $n = 3–5$ and 8–10, X = S or O, and R = H, phenyl, or benzyl. All compounds were levorotatory in the visible region and showed plain negative curves; these are tails of negative sulfoxide Cotton effects similar to that of **11**, centered near 203 mμ (acetonitrile).[66]

Similarly, (−)-sulphoraphane,[45a,67,68] (−)-4-methyl-sulfinylbutyl isothiocyanate, has a negative Cotton effect.[69] The absolute configuration at asymmetric sulfur in the closely related (−)-3-methylsulfinylpropyl isothiocyanate is (R)[70] and the tentative generalization (above) is therefore firmly anchored. In summary, (−)-*methyl alkyl sulfoxides which do not contain other strongly perturbing groups have negative Cotton effects centered at the strong absorption band near 200 mμ (acetonitrile), and have the (R)-configuration.* Since the absolute configuration of (+)-(S)-**11** is therefore established beyond any shadow of a doubt, and since (+)-(S)-**11** was formed from (+)-IIIB which has the (R)-configuration at asymmetric sulfur, it follows that the inversion stereochemistry of the Grignard displacement[14] is firmly established, in consonance with the independent conclusions of Andersen.[11]

Asymmetric Synthesis of Sulfoxides. Oxidation of (R)-2-octyl phenyl sulfide with *t*-butyl hydroperoxide gives two epimeric (R)-2-octyl phenyl sulfoxides, **12A** and **12B**, which differ in configuration at the asymmetric sulfur atom and which have $[\alpha]$D +140 and −155° (ethanol), respectively.[24] The o.r.d. curve of (−)-**12B** is essentially enantiomeric with the o.r.d. curves of (R)-2-octyl and (S)-2-octyl *p*-tolyl (R)-sul-

foxides (+)-**6A** and (+)-**6B** (Figure 4).[71] Since the o.r.d. is almost completely determined by the chirality of the benzenesulfinyl chromophore, it follows that the higher melting epimer (−)-**12B** is identified as (R)-2-octyl phenyl (S)-sulfoxide, and the lower melting epimer (+)-**12A** as (R)-2-octyl phenyl (R)-sulfoxide. This finding is at variance with the earlier conclusion of Cram and Pine, who assigned the (R)- and (S)-configurations to the asymmetric sulfur atom in (−)-**12B** and (+)-**12A**, respectively.[24] The invalidation of the earlier assignment calls into question the basis on which this assignment was made.

Cram and Pine had arrived at their conclusions by two independent lines of argument. In the first of these, application of the "principles of steric control of asymmetric induction" to the oxidation of (R)-2-octyl phenyl sulfide led[24] to structure **12A** for the higher melting isomer (actually **12B**), which was produced in excess over the congener by a factor of 1.6. Their conclusion was based on "the reasonable assumption that the peroxide attacks the electron pair on sulfur which is distributed between hydrogen and *n*-hexyl when the molecule is in its most stable conformation."[24] Three distinct objections may be raised against the preceding argument, two of which are essentially identical with the objections earlier raised (see above) against Andersen's arguments[11] (which also led to erroneous conclusions). First, the empirical rules which have been formulated to summarize directions of asymmetric carbonyl additions according to a large–medium–small (L–M–S) scheme[23] cannot be extended directly to the very different system in which oxidative attack takes place on a sulfur atom which is attached to an asymmetric carbon atom (C–S = 1.81 Å.). The extrapolation[24] is therefore of dubious significance. Second, the role of the lone pairs of electrons on sulfur in conformational analysis is not at present understood (see above).[72] Finally, the nature of the oxidant may crucially determine the stereochemistry of the product.[73]

The second line of argument used by Cram and Pine to assign configurations to **12A** and **12B** originated with the observation[24] that epimerization (at carbon) of (+)-**12B** or (+)-**12A** with potassium *t*-butoxide in dimethyl sulfoxide yields an equilibrium mixture containing 38% of (+)-**12A** and 62% of (+)-**12B**.[74a] Using an extension of earlier tenets of conformational analysis,[74b] Cram and Pine erroneously assigned[24] configuration **12A** to the more stable isomer (actually **12B**) and configuration **12B** to the less stable isomer (actually **12A**). The failure of this second line of

(63) C. J. Morris and J. F. Thompson, *J. Am. Chem. Soc.*, **78**, 1605 (1956).

(64) W. Klyne, "Steric Aspects of the Chemistry and Biochemistry of Natural Products," J. K. Grant and W. Klyne, Ed., Cambridge University Press, Cambridge, England, 1960, pp. 15–18.

(65) W. Klyne, J. Day, and A. Kjær, *Acta Chem. Scand.*, **14**, 215 (1960).

(66) As determined in these laboratories on $CH_3SO(CH_2)_5NHCSNH_2$. We are indebted to Professor W. Klyne for a sample of this material.

(67) H. Schmid and P. Karrer, *Helv. Chim. Acta*, **31**, 1497 (1948); *cf.* also Ž. Procházka, *Collection Czech. Chem. Commun.*, **24**, 2429 (1959); A. Kjær and B. Christensen, *Acta Chem. Scand.*, **12**, 833 (1958).

(68) We are indebted to Dr. Ž. Procházka for a sample of this material.

(69) As judged by the o.r.d. above 225 mμ, using a Rudolph automatic recording spectropolarimeter Model 260/655/850/810-614 (J. T. Melillo, Ph.D. Dissertation, New York University, 1964).

(70) As unambiguously determined by X-ray analysis of the thiourea formed in the reaction between the isothiocyanate and (R)-1-phenylethylamine: A. Kjær, private communication. We are grateful to Professor Kjær for informing us of these results prior to publication.

(71) The following symbolism has been adopted for the present discussion: the prefix (+) or (−) refers to the sign of rotation at the D-line and thus identifies the enantiomer, the boldface figure identifies the sulfoxide (**6** ≡ 2-octyl *p*-tolyl sulfoxide, and **12** ≡ 2-octyl phenyl sulfoxide, and the suffix letter identifies the diastereomer (**A** ≡ (R)-2-octyl (R)-sulfoxide or (S)-2-octyl (S)-sulfoxide, and **B** ≡ (R)-2-octyl (S)-sulfoxide or (S)-2-octyl (R)-sulfoxide).

(72) T. A. Claxton, *Chem. Ind.* (London), 1713 (1964), has recently pointed to the need for caution in conformational arguments involving lone pairs.

(73) Thus Johnson[31] has shown that periodate oxidation of 4-(*p*-chlorophenyl)thiane gives *cis*- and *trans*-4-(*p*-chlorophenyl)thiane 1-oxide in the ratio 7:3, whereas oxidation with hydrogen peroxide in acetone yields the *cis* and *trans* products in the reverse ratio of 3:7.

(74) (a) In an extension of this work, we have found that epimerization at the sulfur atom of (−)-**12B**, using dioxane–aqueous hydrochloric acid,[2b] gives an equilibrium mixture containing 54% of (−)-**12B** and 46% of (+)-**12A** (Experimental). Thus **12B** is the predominant diastereomer in both epimerizations. (b) F. A. Abd Elhafez and D. J. Cram, *J. Am. Chem. Soc.*, **75**, 339 (1953).

argument underscores our thesis that *conformational rules empirically derived from one type of system may not be legitimately extrapolated and transferred to another*. We wish to stress that *this procedure is equally objectionable when the resulting configurational assignment proves to be correct* for, as we have been at pains to emphasize, the toss of a coin could in principle decide the matter.

Thus, in the assignment of configurations, a heavy burden of proof rests on the credibility of the transition state proposed in asymmetric syntheses, or on the critical analysis which underlies the weighting of conformational populations in mobile equilibria, whichever applies. In the case of asymmetric syntheses, it is granted that the direction is generally governed by secondary forces which may be expressed in terms of the Cram–Prelog[23] order of eclipsing effects (L–M–S), and which give rise to the difference in energy between diastereomeric transition states. *However, in order to predict absolute configurations by this method in the absence of established analogy, it is essential to postulate a plausible topology for these diasteromeric transitions states;* a qualitative estimate of strain energies may then be made, thus providing the basis for deciding which one of the diastereomeric transition states has the lower ΔG^*, *i.e.*, which one will give rise to the predominant stereoisomer. The remainder of this paper will be devoted to a brief critique of some earlier configurational assignments to optically active sulfoxides which have been conspicuously lacking in the application of this principle.

It has been shown[75] that perbenzoic acid oxidation of *o*-(methylthio)benzoic acid esters of optically active alcohols, followed by saponification, yields optically active methyl *o*-carboxyphenyl sulfoxide of optical purity as high as 20%. Maccioni, *et al.*,[75] have proposed a transition state for the oxidation step, the topology of which has led these authors to assign the (*R*)-configuration to (+)-methyl *o*-carboxyphenyl sulfoxide, given the absolute configuration of the inducing alcohols. The authors believe that the "most probable conformation of the sulphide is that where the carbonylic oxygen is placed in the less hindered region, *i.e.*, between S and M," apparently by analogy with the Cram–Prelog model[23]; however, quite aside from the objections already cited in connection with the arguments advanced by Cram and Pine, there are in the present case no fewer than *five* bonds separating the center of attack (sulfur) from the asymmetric carbon atom.

In the preceding examples,[24,63,75] asymmetric sulfoxide syntheses were achieved by employing dissymmetric sulfides and nondissymmetric oxidizing agents.[76] Asymmetric sulfoxide syntheses have also been achieved[75,77–81] by employing nondissymmetric sulfides and dissymmetric oxidizing agents,[82] such as peracids,[75,77–80] or microbial systems.[81] The stereospecificity in these asymmetric oxidations[75,77–81] is extremely low, to judge by the apparent optical yields.[83] Since the diastereomeric transition states differ only minutely in free energy,[83] the structural distinction between them must therefore be a subtle one. In this light, none of the proposed[75,77,79] transition states come close to satisfying the requirement of credibility stated above.

The Italian workers[75,77] oxidized alkyl phenyl, *m*-carboxyphenyl, and *o*-carboxyphenyl sulfides with (+)-*cis*-monopercamphoric acid[84] and (*S*)-perhydratropic acid. Electrophilic attack of the peracid was envisaged[77] in a direction which was "to a first approximation" supposedly perpendicular to the C–S–C plane of the sulfide. On the assumption that the most probable conformation in the "transition state" was "staggered," the Italian workers[75,77] proposed the structures for diastereomeric "transition states" of oxidation which are depicted below.
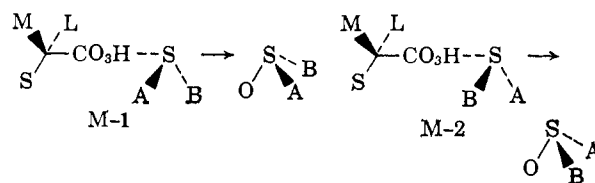
"Transition state" M-1 was said[75,77] to be lower in energy than "transition state" M-2 since in the former "the larger group A is placed in the less hindered position."[75]

The oxidation of *n*-alkyl phenyl sulfides with (+)-*cis*-monopercamphoric acid yields (+)-*n*-alkyl phenyl sulfoxides,[77] and since these compounds unquestionably have the (*R*)-configuration, in analogy with the (+)-*n*-alkyl *p*-tolyl sulfoxides (see above), M-1 leads to (*R*)-*n*-alkyl phenyl sulfoxides, exactly as predicted by the arguments advanced by the Italian workers.[75,77] However, we are now forced to assert that these arguments, which are summarized by the above drawings and which are detailed in print,[75,77] are as fanciful as they are successful in predicting the correct absolute configuration of alkyl phenyl sulfoxides.[85] Indeed, the proposed[75,77] picture of the "transition state" yields no information whatever regarding the structure and geometry of the transition state of oxidation.

(75) A. Maccioni, F. Montanari, M. Secci, and M. Tramontini, *Tetrahedron Letters*, **No. 17**, 607 (1961).

(76) Other examples are the oxidations of L-methionine (T. F. Lavine, *J. Biol. Chem.*, **169**, 477 (1947); B. Iselin, *Helv. Chim. Acta*, **44**, 61(1961)) and of α-phenethylthioglycolic acid (B. Holmberg, *Arkiv Kemi Mineral. Geol.*, **13A**, No. 15 (1939)) with hydrogen peroxide.

(77) A. Mayr, F. Montanari, and M. Tramontini, *Gazz. chim. ital.*, **90**, 739 (1960).

(78) K. Balenović, N. Bregant, and D. Francetić, *Tetrahedron Letters*, **No. 6**, 20 (1960).

(79) K. Balenović, I. Bregovec, D. Francetić, I. Monković, and V. Tomašić, *Chem. Ind.* (London), 469 (1961).

(80) M. Janczewski and T. Bartnik, *Bull. Acad. Polon. Sci. Ser. Sci. Chim.*, **10**, 271 (1962).

(81) R. M. Dodson, N. Newman, and H. M. Tsuchiya, *J. Org. Chem.*, **27**, 2707 (1962), and references cited therein.

(82) The two approaches to asymmetric sulfoxide syntheses have their counterparts in carbon chemistry; compare, for example, the lithium aluminum hydride reduction of menthyl phenylglyoxylate (dissymmetric carbonyl compound, nondissymmetric reducing agent), which produces optically active phenylethylene glycol (V. Prelog, M. Wilhelm, and D. B. Bright, *Helv. Chim. Acta*, **37**, 221 (1954)), and the reduction of RCOCH₃ (R = Et, *i*-Pr, *t*-Bu, and Ph) with diisopinocamphenylborane (dissymmetric reducing agent, nondissymmetric carbonyl compound), which gives optically active RCHOHCH₃ (H. C. Brown and D. B. Bigley, *J. Am. Chem. Soc.*, **83**, 3166 (1961)).

(83) The products of the asymmetric oxidations[75,77–81] were all alkyl aryl sulfoxides. Rotations of such compounds in the optically pure state are generally high (see text, *e.g.*, Table I). The [α]D values of the sulfoxides obtained in the asymmetric oxidations using peracids[75,77–80] were uniformly low and generally ranged from 1 to 5°. Taking 5% as a conservative *upper* limit for the optical purity of the sulfoxides produced in these asymmetric oxidations, $\Delta\Delta G^*$ of the diastereomeric transition states is *ca.* 0.05 kcal./mole at the temperature of oxidation.

(84) N. A. Milas and A. McAlevy, *J. Am. Chem. Soc.*, **55**, 349 (1933).

(85) This includes the correct prediction[77] that (−)-*t*-butyl phenyl sulfoxide, which is produced by the same asymmetric oxidation, has the (*S*)-configuration.

There are no fewer than three bonds separating the center of attack (oxygen) from the asymmetric carbon; this puts the present model on a par with Prelog's[23b] model.
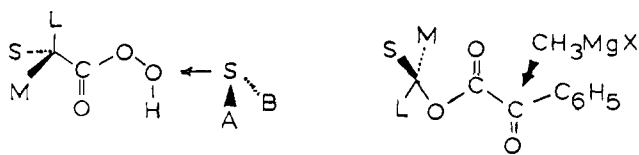
Here the analogy ends for several reasons. First, there is no way of knowing which is the preferred arrangement of L–M–S in the peracid, although, by analogy with Cram's model[23a] and keeping in mind that the peroxide bond is skewed[86] one might hypothesize some conformation such as seen below. However,

locus of attack by A-S̤-B
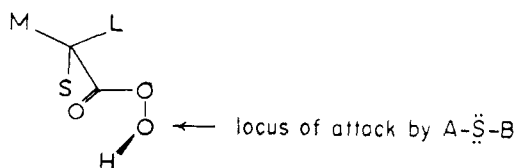
second, there is no way of ascertaining the preferred direction of attack by the sulfide A–S–B. The posture of the attacking molecule determined the stereochemical outcome, yet any rotameric conformation indicated on the cone of attack below gives a sulfoxide of the *same* absolute configuration.
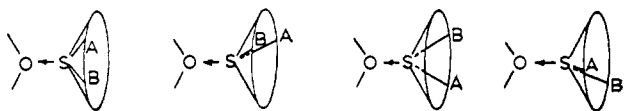
Similarly, any rotameric conformation indicated on the cone of attack below gives the *enantiomeric* sulfoxide.
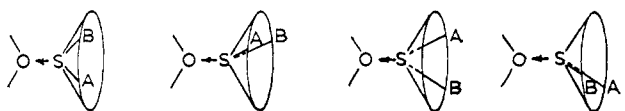
Not only is the geometric disposition of the groups unknown, but there exists absolutely no basis in fact for deciding between the postures leading to the (R)- and to the (S)-isomer, respectively. In short, the interpretation[75,77] of a 50-cal./mole difference in free energy between the diastereomeric transition states in terms of the proposed[75,77] model is unacceptable. Indeed, as will be shown in a subsequent communication, the relationship[75,77] between the absolute configuration of the produced alkyl phenyl sulfoxides and the relative size of the groups on the sulfur atom cannot be generally extended to other systems.

We may easily dispose of the arguments advanced[79] by Balenović, *et al.*, in conjunction with the asymmetric oxidation[75,79] of m-(methylthio)- and m-(ethylthio)benzoic acid methyl esters and methyl phthalimidomethyl sulfide with monopercamphoric and monoperglutaric acids; the claim[79] that peracids of type HOOC–C(R)–C–C–CO₃H are needed for the asymmetric oxidations (and that a pseudo-six-membered ring is therefore required in the postulated transition

state) is invalidated by the finding[75] that perhydratropic acid may be used in such asymmetric oxidations.

In summary, there exists no justification for the extravagant conjectures which have been advanced[75,77,79] to account for the stereochemistry of the asymmetric oxidation of sulfides, and the geometry of the relevant transition states of oxidation remains unknown.

Experimental[87]

Optically Active Alkyl p-Tolyl Sulfoxides. Compounds 1–5 were prepared from *l*-menthyl p-toluenesulfinate[13,88] ((−)-IIA), m.p. 105–106°, $[\alpha]^{26}D$ −198° (c 1.0, acetone) (lit.[88] m.p. 106–107°, $[\alpha]^{25}D$ −199.19°), and the appropriate Grignard reagents by the method of Andersen[14] and were shown to be free of menthol by g.l.c. on a 122-cm. column packed with 10% Dow Corning Silastic LS-422 on Chromosorb at 125–175° (under these conditions all sulfoxides other than 1 and diaryl sulfoxides were observed to pyrolyze).[89] Sulfoxides 1 and 5 were obtained as crystalline solids, the other alkyl p-tolyl sulfoxides being obtained as liquids which were purified by distillation. A typical procedure, the preparation of 4, is described below.

A solution of 16.0 g. of (−)-IIA in 300 ml. of ether was treated dropwise with the Grignard reagent (ca. 50% excess) prepared by the reaction of 10.0 g. of isopropyl bromide and 1.91 g. of magnesium in 120 ml. of ether. After the addition was complete (ca. 0.75 hr.) the reaction mixture was washed with 10% hydrochloric acid, 10% sodium carbonate solution, and water. The ethereal layer was concentrated to an oil and the residue was steam distilled in the presence of a 20% solution of potassium hydroxide. Ether extraction of the aqueous phase afforded an oil which was distilled to yield 2.2 g. (22%) of the desired product, b.p. 100° (0.4 mm.), $[\alpha]D$ +176.5° (c 2.5, acetone).

Elemental analyses and specific rotations of 1–5 are given in Table I. The n.m.r. characteristics have been described in the text. Absorption spectral, o.r.d., and c.d. characteristics are collected in Tables V, VI, IX, and X.

Optically Active Aryl p-Tolyl Sulfoxides. Compounds 7–10 were prepared from (−)-IIA and the appropriate Grignard reagents as described above for compounds 1–5. All compounds were obtained as crystalline solids which were purified by crystallization (e.g., from ligroin), or by chromatography (e.g., elution with chloroform from Florisil). Melting points, elemental analyses, and specific rotations are given in Table I. Absorption spectral, o.r.d,, and c.d.c haracteristics are collected in Tables VII–IX.

(86) S. C. Abrahams, R. L. Collin, and W. N. Lipscomb, *Acta Cryst.*, 4, 15 (1951).

(87) Elemental analyses by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Molecular weights were determined at 37° using a Mechrolab vapor pressure osmometer, Model 301A. Ultraviolet absorption spectra were measured on a Cary 14 recording spectrophotometer using 1.0- and 0.1-cm. cells. Unless otherwise indicated,[69] optical rotatory dispersion curves were measured on a Cary 60 recording spectropolarimeter using 1-cm. cells maintained at 27° and a spectral slit width of 1.0 mμ for the whole wave length range. N.m.r. spectra were measured on a Varian A-60 spectrometer and refer to 8–10% solutions in deuteriochloroform with tetramethylsilane serving as internal standard. Circular dichroism data were obtained at Stanford University by using a Roussel-Jouan dichrograph Model JO-1; we are grateful to Professor C. Djerassi for permitting us the use of this facility.

(88) H. F. Herbrandson, R. T. Dickerson, Jr., and J. Weinstein, *J. Am. Chem. Soc.*, 78, 2576 (1956).

(89) Under carefully controlled conditions, sulfoxides may be gas chromatographed without undue pyrolysis: V. E. Cates and C. E. Meloan, *Anal. Chem.*, 35, 658 (1963); T. J. Wallace and J. J. Mahon, *Nature*, 201, 817 (1964).

Optically Active 2-Octyl Phenyl Sulfoxide.[90] A diastereomeric mixture of (R)-2-octyl phenyl (R)- and (S)-sulfoxides was prepared from (S)-2-octanol,[33] $[\alpha]^{25}D$ +9.76° (neat), according to the procedure described by Cram and Pine.[24] Chromatography on 100–200 mesh silica gel, using 1:5 ether–hexane as eluent, afforded material having m.p. 20.5–23.0° and $[\alpha]^{29}_{546}$ −184.1° (c 1.5, 95% ethanol). The high-melting diastereomer is reported[24] to have m.p. 20.5–21.5° and $[\alpha]^{25}_{546}$ −192 ± 3°. The low-melting diastereomer which accompanies this preparation[24] has $[\alpha]^{27}_{546}$ +173 ± 3°. Our preparation of (R)-2-octyl phenyl (S)-sulfoxide, (−)-**12B**, is therefore 98% diastereomerically pure.

Sulfoxide (−)-**12B** (0.8325 g.) was dissolved in 25 ml. of a 2:1 v./v. mixture of dioxane and 12.17 *M* aqueous hydrochloric acid. The system was flushed with nitrogen and maintained at 25.0° and the mutarotation was followed polarimetrically. The k_1^{25} of mutarotation was found to be 2.08 × 10⁻⁴ sec.⁻¹ ($t_{1/2}^{25}$ 56 min.) After 24 hr., when the system had been at apparent equilibrium for several hours, the solution was made basic with sodium hydroxide (at 0°), the alkaline solution was extracted with ether, and the ether extracts were evaporated to give a residual oil (0.8173 g., 98.2% recovery) having $[\alpha]^{25}D$ −19.1° (c 2.9, 95% ethanol). Based on the reported[24] rotations of (−)-**12B** ($[\alpha]D$ −155°) and (+)-**12A** ($[\alpha]D$ +140°), the mixture consists of 53.9% (−)-**12B** and 46.1% (+)-**12A**.

Optically Active 2-Octyl p-Tolyl Sulfoxides. A diastereomeric mixture of (R)- and (S)-2-octyl p-tolyl (R)-sulfoxides **6A** and **6B** was prepared from (−)-IIA and 2-octylmagnesium bromide, following the procedure described above for compounds **1–5**. Chromatography on 100–200 mesh silica gel, using 3:7 ether–hexane as eluent, afforded two major fractions: **6A**, an oil, $[\alpha]^{22}D$ +118° (c 1.2, acetone), and **6B**, an oily solid (clarification point *ca.* 45°), $[\alpha]^{22}D$ +137.5° (c 1.0, acetone). Analyses are given in Table I. Absorption spectral and o.r.d. characteristics are collected in Tables V, VI, and X.

Mutarotation in a 2:1 v./v. mixture of dioxane and 12.17 *M* aqueous hydrochloric acid gave values for k_1^{25} (mutarotation) of 2.37 × 10⁻⁴ sec.⁻¹ and 2.23 × 10⁻⁴ sec.⁻¹ for **6A** and **6B**, respectively. These values are in excellent accord with the value of 2.07 × 10⁻⁴ sec.⁻¹ observed for the structurally similar sulfoxide (−)-**12B**.

Optically Active 2-Octyl p-Tolyl Sulfones. **A.** To a solution of **6A** (1.1 g.) in glacial acetic acid (15 ml.) at 96° was added 30% hydrogen peroxide (30 ml.) over a period of 5 hr.[91] The mixture was boiled for 1 additional hr., and allowed to stand overnight. The mixture was diluted with water (100 ml.) and extracted with hexane (100 ml.) and benzene (50 ml.). The organic layers were combined, washed with 10% sodium carbonate and water, dried, and evaporated. Distillation (Kugelrohr) at *ca.* 130° (0.001 mm.) gave a viscous oil, $[\alpha]^{20}D$ +9.1° (c 4.6, chloroform).

Anal. Calcd. for $C_{15}H_{24}O_2S$: C, 67.12; H, 9.01;

S, 11.95. Found: C, 67.41; H, 9.24; S, 11.67.

B. A similar preparation starting from **6B** gave the enantiomeric sulfone as a waxy solid liquefying at 48°, $[\alpha]^{20}D$ −5.65° (c 3.1, chloroform).

Anal. Calcd. for $C_{15}H_{24}O_2S$: C, 67.12; H, 9.01; S, 11.95. Found: C, 66.62; H, 9.00; S, 12.31.

C. p-Toluenesulfonyl chloride (40 g.) in 100 ml. of pyridine was added dropwise over a period of 2 hr. to an ice-cold solution of (+)-2-octanol, 20.0 g., $[\alpha]^{23}D$ +9.76° (neat), in pyridine (40 ml.). The usual work-up yielded 40.1 g. of 2-octyl tosylate, an oil which was not further characterized. This oil was added over a period of 0.5 hr. to a solution of sodium p-thiocresolate prepared by adding a saturated solution of p-toluenethiol (17.4 g.) in ethanol to a solution of sodium (3.2 g.) in ethanol (100 ml.). The usual work-up[32] yielded 31.7 g. of product (96% yield) which gave one spot on t.l.c. and which was purified by two fractional distillations, followed by a molecular distillation. The colorless liquid, (−)-(R)-2-octyl p-tolyl sulfide, had b.p. 118° (0.2–0.3 mm.), $[\alpha]^{22}D$ −10.55° (l = 1, neat).

Anal. Calcd. for $C_{15}H_{24}S$: C, 76.20; H, 10.23; S, 13.56. Found: C, 76.19; H, 10.17; S, 13.76.

Oxidation of the sulfide by the procedure described in part A gave a sulfone with $[\alpha]^{26}D$ +10.7° (c 4.9, chloroform), m.p. 59.5–60.5° (lit.[32] m.p. 58.3–60.3°), infrared identical with that of the sulfones obtained in procedures A and B.

Menthyl Sulfinates. The menthyl esters of p-iodobenzene- and p-toluenesulfinates were prepared as described in the following for menthyl 1-butanesulfinate. A solution of (−)-menthol (7.0 g.) in pyridine (10 g.) containing a small amount of ether (to effect homogeneity) was added over a period of about 0.5 hr. to a solution of 1-butanesulfinyl chloride[92] (10.0 g.) in anhydrous ether (200 ml.) at −78°. The reaction mixture was blanketed under nitrogen throughout the addition. After completion of the addition, the mixture was stirred for 2 hr. at −78° and warmed to 0°. Ether was added and the suspension was extracted at 0° with 5% sodium carbonate, water, 1% hydrochloric acid, and water. The ether layer was dried and evaporated to give a pale yellow oil (11.7 g.) which was purified by chromatography on silica gel, using benzene as eluent, followed by Kugelrohr distillation. The product (IIIa) had b.p. *ca.* 110° (0.08 mm.), $[\alpha]D$ +50° (c 2.6, acetone). Absorption spectral and o.r.d. characteristics are collected in Table III.

Anal. Calcd. for $C_{14}H_{28}O_2S$: C, 64.56; H, 10.84; S, 12.31. Found: C, 65.02; H, 11.03; S, 12.16.

Optically Active Methyl n-Butyl Sulfoxide. A solution of 5.0 g. of menthyl 1-butanesulfinate (IIIa, above) in 70 ml. of anhydrous ether was added rapidly to 20 ml. of ethereal 3 *M* methylmagnesium bromide (Arapahoe Chemical Co.) under the exclusion of moisture and air. After the addition, the reaction mixture was stirred for 0.5 hr. The reaction mixture was decomposed with aqueous ammonium chloride and the ether layer was extracted with water. The combined aqueous layers were saturated with sodium chloride and extracted with chloroform. Evaporation of the chloroform yielded 4.3 g. of a yellow oil which

(90) Dr. D. W. Slocum and Mr. R. Gans kindly carried out this preparation.
(91) The procedure of H. Gilman and N. J. Beaber, *J. Am. Chem. Soc.*, 47, 1449 (1925).
(92) I. B. Douglass and D. R. Poole, *J. Org. Chem.*, 22, 536 (1957).

was purified by chromatography on silica gel, using a 19:1 mixture of ethyl acetate–methanol as eluent. Kugelrohr distillation yielded the product, 11, as a colorless oil, n^{20}D 1.4691 (lit.[93] for racemic material

(93) L. Bateman, J. I. Cunneen, and J. Ford, J. Chem. Soc., 3056 (1956).

n^{20}D 1.4695), [α]^{27}D +42° (c 0.91, isooctane)). Absorption spectral and o.r.d. characteristics are collected in Table IV.

Anal. Calcd. for $C_5H_{12}OS$: C, 49.95; H, 10.06; S, 26.67. Found: C, 49.80; H, 10.27; S, 26.05.

A Synthesis of Pyrimido[4,5-e]-as-triazines (6-Azapteridines)[1a,b]

Edward C. Taylor and Robert W. Morrison, Jr.[2]

Contribution from the Frick Chemical Laboratory, Princeton University, Princeton, New Jersey. Received October 7, 1964

Condensation of dibromomalononitrile (as its potassium bromide complex) with aminoguanidine bicarbonate has been shown to give 3,5-diamino-6-aminocarbonyl-as-triazine (14), which has been cyclized to derivatives of pyrimido[4,5-e]-as-triazine (2) by the use of appropriate one-carbon reagents. The structure of the cyclization product with diethyl carbonate, 3-amino-6,8-dioxo-5,6,7,8-tetrahydropyrimido[4,5-e]-as-triazine (15), was confirmed by an independent synthesis from alloxan and aminoguanidine to give alloxan β-guanyl hydrazone (16), followed by careful cyclization with dilute ammonium hydroxide. Attempts to prepare a derivative of the pyrimido[4,5-e]-as-triazine system by hydrogen sulfide reduction of 2-phenyl-4,6-diamino-5-phenylazopyrimidine (3) to the hydrazo stage, followed by cyclization with triethyl orthoformate, or by hydrogen sulfide reduction of the formyl derivative of 3, led only to 2-phenyladenine (7).

The antibiotics Toxoflavin and Fervenulin, derivatives of the pyrimido[5,4-e]-as-triazine system (1), have aroused considerable recent interest[3] because of their close structural similarity to the physiologically active pteridines and purines and because of the extreme toxicity of the former compound, apparently due to its participation in the formation of hydrogen peroxide.[4] The structural simplicity of these antibiotics raised the possibility that the high degree of physiological activity observed might be structurally nonspecific. The present paper describes the preparation and properties of derivatives of the isomeric pyrimido[4,5-e]-as-triazine system (2), which at the time this work was begun was unknown.[5]

pyrimido[5,4-e]-as-triazine
1

pyrimido[4,5-e]-as-triazine
2

H. M. Taylor, in an unpublished Ph.D. thesis,[6] described a number of unsuccessful attempts to prepare derivatives of this system by condensation of alloxan and 1,3-dimethylalloxan with semicarbazide, thiosemicarbazide, and aminoguanidine. He encountered considerable difficulty in the final cyclization reactions designed to lead to the bicyclic system because of extreme base lability of the pyrimidine ring. An alternative approach commencing with an as-triazine precursor likewise failed. Recently, and concurrently with the present work, Heinisch, Ozegowski, and Mühlstadt[7] reported the successful condensation of alloxan and 1-methylalloxan with S-alkylisothiosemicarbazides to give intermediates which subsequently cyclized on heating in pyridine to 3-S-alkyl derivatives of the desired pyrimido[4,5-e]-as-triazine system.

We first examined the possibility that derivatives of pyrimido[4,5-e]-as-triazine might be accessible from 4-amino-5-phenylazopyrimidine precursors (i.e., 3). Reduction of the phenylazo grouping under appropriately mild conditions might allow the hydrazo intermediate reduction stage (4) to be trapped by a suitable one-carbon reagent, thus leading either to a triazinopyrimidine (5) or to a 7-anilinopurine (6). The reduction of phenylazo groupings proceeds through the hydrazo stage, but cleavage of the N–N bond inevitably takes place in the presence of strong reducing agents. Isolation of the intermediate hydrazo compounds is possible, however, when hydrogen sulfide is used as the reducing agent.[8] Accordingly, 2-phenyl-4,6-diamino-5-phenylazopyrimidine (3) was reduced with hydrogen sulfide in dimethylformamide solution in the presence of triethyl orthoformate. Surprisingly, the product was

(1) (a) This work was supported in part by a research grant (CA-02551) to Princeton University from the National Cancer Institute, National Institutes of Health, Public Health Service. (b) A preliminary report of this work has appeared: E. C. Taylor and R. W. Morrison, Jr., *Angew. Chem.*, 76, 342 (1964); *Angew. Chem. Intern. Ed. Engl.*, 3, 312 (1964).

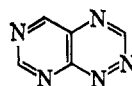(2) N.S.F. Summer Fellow, 1961; National Institutes of Health Fellow, 1961–1964.

(3) G. D. Daves, R. K. Robins, and C. C. Cheng, *J. Am. Chem. Soc.*, 84, 1724 (1962), and references cited therein.

(4) H. E. Latuasan and W. Berends, *Biochim. Biophys. Acta*, 52, 502 (1961).
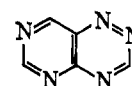
(5) E. Jeney and T. Zsolnai, *Zentr. Bakteriol. Parasitenk. Abt. I Orig.*, 177, 220 (1960), have stated that 3-amino-6,8-dioxo-5,6,7,8-tetrahydropyrimido[4,5-e]-as-triazine hydrochloride was tested for anti-

tubercular activity, but no reference was made to the source or properties of the compound nor was its synthesis reported.

(6) H. M. Taylor, Ph.D. Thesis, University of North Carolina (1959); University Microfilms, Inc., Ann Arbor, Mich., library card no. MIC 59–5587.

(7) L. Heinisch, W. Ozegowski, and M. Mühlstadt, *Ber.*, 97, 5 (1964).

(8) H. Zollinger, "Azo and Diazo Chemistry," Interscience Publishers Inc., New York, N. Y., 1961, p. 300.