7β-Methylthiodeoxynupharidine. A solution of 35 mg of 7β-methylthiodeoxynupharidin-6α-ol in 2 ml of CH_3OH was treated with 25 mg of $NaBH_4$ at 25° for 24 hr. Tlc (alumina, C_6H_6) indicated about one-third of the hemiaminal (R_f 0.33) had been reduced to the amine (R_f 0.75). The CH_3OH was evaporated and was replaced by 2 ml of C_2H_5OH and 60 mg of $NaBH_4$ was added and additional small amounts of $NaBH_4$ were added periodically during the course of 60 hr. After a total of 70 hr, a tlc of the reaction mixture still showed a trace of starting hemiaminal. The solvent was evaporated and the residue in C_6H_6 was passed through a column of 3 g of neutral alumina. The first 50-ml fraction yielded 20 mg of 7β-methylthiodeoxynupharidine: ir (CCl_4) 3.40, 3.50 (s), 3.62 (s, Bohlmann), 11.45 μ; nmr ($CDCl_3$) δ 0.92 (d, 3 H, C-1 CH_3), 1.32 (s, 3 H, C-7-CH_3), 1.90 (s, 3 H, CH_3S), 1.78 (d, J = 10.5 Hz, 1 H, C-6 H_{ax}), 2.75 (d of d, J = 10.5 and 2.0 Hz, 1 H, C-6 H_{eq}), 2.97 (m, 1 H, C-4 H), 6.36 (m, 1 H, β H of 3-furyl), 7.3 (m, 2 H, α H of 3-furyl); nmr (C_6H_6) δ 0.82 (unresolved d, 3 H, C-1 CH_3), 1.42 (s, 3 H, C-7 CH_3), 1.74 (s, 3 H, CH_3S), 1.93 (d, J = 10.5 Hz, 1 H, C-6 H_{ax}), 2.84 (m, 1 H, C-4 H), 3.04 (d of d, J = 10.5 and 2.0 Hz, 1 H, C-6 H_{eq}); ms *m/e* (rel intensity) 279 (14) (M^+), 264 (6), 250 (5), 233 (100), 178 (38), 164 (24), 144 (25), 136 (36), 107 (38), 96 (49), 94 (52), 88 (37), 81 (28).

A solution of 7β-methylthiodeoxynupharidine in 10 ml of C_2H_5OH was treated with 1.4 ml of 0.2 *M* aqueous $HClO_4$. Evaporation of the solvent left a residue which on two recrystallizations from C_2H_5OH gave 50 mg of the crystalline hydroperchlorate: mp 185–197°; ir (KBr) 3.22 (s), 3.4–3.5 (s), 3.55–4.0 (m), 11.45 μ (s).

Anal. Calcd for $C_{16}H_{26}NO_5SCl$: C, 50.58; H, 6.90; N, 3.69; S, 8.46. Found: C, 50.40; H, 6.88; N, 3.58; N, 3.58; S, 8.60.

7β-Methylthiodeoxynupharidine-6α-d_1. A solution of 35 mg of 7β-methylthiodeoxynupharidin-6α-ol in 2 ml of absolute C_2H_5OH was treated at 12-hr intervals over the course of 80 hr with small portions of $NaBD_4$ (200 mg). The reaction mixture was processed as in the reductions described above to obtain 25 mg of colorless oil: tlc (alumina, C_6H_6) R_f 0.33 (**16**) and 0.75 (**20**). This oil in benzene was passed through a column of 3 g of alumina (neutral, activity II). The first 50-ml fraction gave 18 mg of 7β-methylthiodeoxynupharidine-6α-d_1: ir (CCl_4) 3.4–3.5 (s), 3.61 (s, Bohlmann), 4.93 (w), 11.45 μ (s); nmr ($CDCl_3$) δ 0.92 (br s, 3 H, C-1 CH_3), 1.33 (s, 3 H, C-7 CH_3), 1.89 (s, 3 H, CH_3S), 2.75 (d, J = 10.5 Hz, 0.2 H, C-6 H_{eq}), 2.98 (m, 1 H, C-4 H), 6.39 (m, 1 H, β H of 3-furyl), 7.31 (m, 2 H, α H of 3-furyl); nmr (C_6H_6) δ 0.82 (unresolved d, 3 H, C-1 CH_3), 1.43 (s, 3 H, C-7 CH_3), 1.74 (s, 3 H, CH_3S), 1.93 (d, J = 10.5 Hz, 0.25 H and s, 0.75 H, C-6 H_{ax}), 2.85 (m, 1 H, C-4 H), 3.04 (d of d, J = 10.5 and 2.0 Hz, 0.25 H, C-6 H_{eq}); ms *m/e* (rel intensity) 280 (15) (M^+) (21% d_0, 79% d_1), 265 (6), 250 (2), 234 (100), 179 (33), 164 (28), 145 (31), 136 (26), 107 (41), 97 (37), 94 (52), 88 (30), 81 (27).

Asymmetric Synthesis of Chiral Sulfoxides. II.[1] An Intramolecular O → N Sulfinyl Migration

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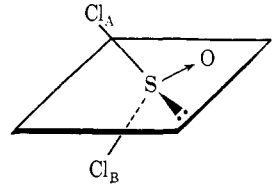
Abstract: The conversion of a 1,2,3-oxathiazolidine 2-oxide (**1**) derived from *l*-ephedrine to methyl aryl sulfoxides *via* sulfinamides (**3**) was studied in detail. The stereochemistry of sulfinyl transfer in an O-sulfinylated ethanolamine (**7**) was investigated. This rearrangement proceeds *via* two competitive paths: intramolecular and intermolecular. The intramolecular path yields a sulfinamide (**3**) with retention of configuration at sulfur.

Chiral menthyl arenesulfinates are converted stereospecifically[2,3] to sulfoxides. This approach to open-chain optically pure sulfoxides, though elegant, is limited. Only *R* aryl alkyl sulfoxides can be prepared in optically pure form because the less soluble diastereomer of the known menthyl arenesulfinates (*l* isomer) is always of the same absolute configuration at sulfur.[3] Furthermore, the diastereomeric mixtures of low molecular weight alkanesulfinates (*e.g.*, menthyl, cedryl, and bornyl methane- to propanesulfinates) are oils at room temperature. These oils proved difficult to separate.[4] While a more recent approach *via* organolithium reactions with deoxyephedrine sulfinamides can lead to either enantiomer of any open-chain sulfoxide, it is restricted to the synthesis of *optically pure* sulfoxides *lacking α hydrogens*.[5,6]

This paper describes the results of one aspect of a possible general approach designed to circumvent the above difficulties. Originally, we envisioned our method to be applicable to the synthesis of molecules containing many different chiral atoms; for example, sulfoxides, selenoxides, phosphine oxides, arsine oxides, silanes, germanes, and the intriguing possibility of a suitable chiral stannane.[7]

Our plan is based on the distinction between the two enantiotopic (prochiral) chlorine atoms (Cl_A and Cl_B) of thionyl chloride by a chiral ethanolamine. Equations 1–4 describe the overall approach.



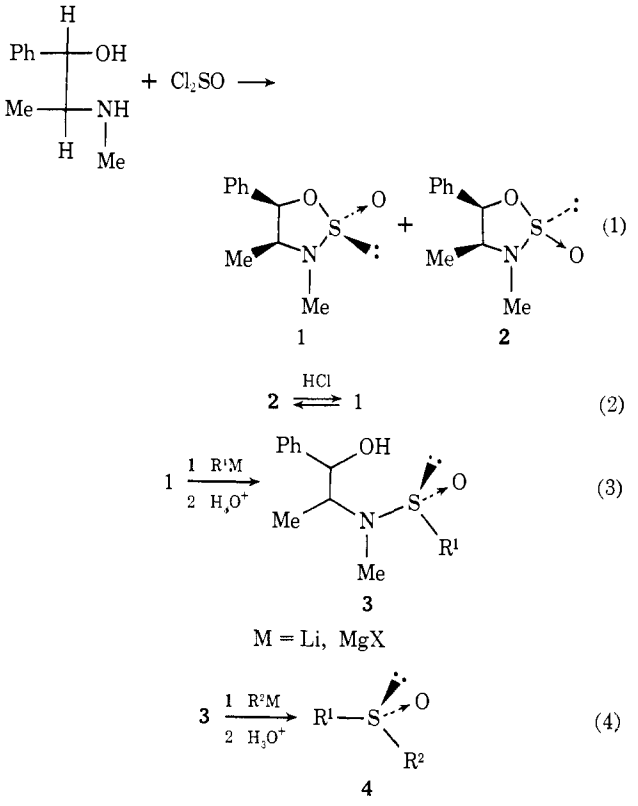
The following features were anticipated to make the above scheme attractive. (1) Any chiral ethanolamine could be a suitable reagent for reaction 1. (2) The epimerization of sulfinyl sulfur (S=O) by hydrogen chloride (reaction 2) was studied by Herbrandson and Dickerson[8] and Mislow.[9a] That is, if reaction 1 would

(1) Paper I: F. Wudl and T. B. K. Lee, *J. Chem. Soc., Chem. Commun.*, 61 (1972).
(2) K. K. Andersen, *Tetrahedron Lett.*, 93 (1962).
(3) K. Mislow, M. M. Green, P. Laur, J. T. Melillo, T. Simmons, and A. L. Ternay, Jr., *J. Amer. Chem. Soc.*, 87, 1958 (1965).
(4) (a) K. K. Andersen, *J. Org. Chem.*, **29**, 1953 (1964); (b) F. Wudl, Ph. D. Dissertation, University of California, Los Angeles, 1967.
(5) J. Jacobus and K. Mislow, *Chem. Commun.*, 253 (1968).
(6) J. Jacobus and K. Mislow, *J. Amer. Chem. Soc.*, **89**, 5228 (1967).
(7) G. J. D. Peddle and G. Redl, *ibid.*, **92**, 365 (1970).
(8) H. E. Herbrandson and R. T. Dickerson, *ibid.*, **81**, 4102 (1959).
(9) (a) K. Mislow, T. Simmons, J. T. Melillo, and A. L. Ternay, Jr., *ibid.*, 86, 1452 (1964). (b) This reasoning by analogy is probably not entirely proper since Mislow's[9a] and Herbandson's[8] investigations were restricted to open-chain sulfoxides and sulfinate esters, respectively, and did not include alkoxysulfinylamines.

Table I. Synthesis of *l*-Ephedrine Alkane(arene)sulfinamides (*cf.* eq 3)

Reagent	Time	Temp, °C	TMEDA	R–S–R (O) yield,[a] %	*l*-Ephedrine alkane(arene)sulfinamides Epimeric ratio % *R*-	% *S*-	Yield, %	Compd
$CH_3C_6H_5MgBr$	1 hr	−16 to −20	−	11[b]	100	0	7	**3a**
	9 hr	−24 to −30	−	35	100	0	18	
	1 hr	−25	+	26	88	12	47	
C_6H_5Li[c]	25 min	−78	−	Trace	70	30	89	**3b**
C_6H_5Li[c]	7 hr	−78	+	Trace	72	28	87	
C_6H_5Li[d]	25 min	−78	+	Trace	76	24	84	
C_6H_5Li[d]	3 hr	−100 to −100	+	Trace	75	25	90	
CH_3MgBr	6 hr	−25	+		72	28	41	**3c**
CH_3Li			+		74	26	61	

[a] Yields calculated based on (*R*)-**1**. [b] Yields are uncorrected for recovered (*R*)-**1** which was found to be 28%. [c] Phenyllithium was obtained from Alfa Chemical Co. [d] Halogen-free phenyllithium prepared from diphenylmercury.



lead to a mixture of **1** and **2**, an equilibrium mixture of these could be "driven" by crystallization (or precipitation) of the less soluble diastereomer.[3,9b] The sulfur–nitrogen bond of acyclic sulfinamides was known to be more difficult to cleave than the sulfur–oxygen bond of sulfinates when Grignard reagents were employed.[5,10,11] Consequently, reactions 3 and 4 had a precedent. Both steps were expected to yield inversion of configuration[2,3,10] (provided cyclic systems such as **1** and **2** behaved as open-chain sulfinamides and sulfinates) so that an overall retention of configuration would have obtained in the correlation between **1** and **4**. (4) If the sequence of organometallic reagents were to be reversed in reactions 3 and 4 (*e.g.*, R^2MgX first, then R^1Li), the enantiomer of the same sulfoxide could be obtained from the same precursor (*i.e.*, **1**).

(10) S. Colonna, R. Giovanni, and F. Montanari, *Chem. Commun.*, 865 (1968).

(11) However, see Jacobus and Mislow.[6] In contrast to other reports,[5,10] in the Experimental Section of ref 6, the reaction of *N*-benzenesulfinylmorpholine and methylmagnesium bromide afforded 91% yield of methyl phenyl sulfoxide at room temperature.

Results

Synthesis. Treatment of *l*-ephedrine with thionyl chloride in the presence of triethylamine at 0° afforded a diastereomeric mixture of **1** and **2** in an overall yield of 80%. The mixture consisted of 72% **1** and 28% **2** as determined *via* nmr[12] (*vide infra*). Diastereomer **1** crystallized preferentially from ether. Treatment of the mother liquors with a trace of hydrogen chloride and pyridine and storage at 5° afforded more **1** (overall yield of isolated, pure **1** = 64%, "theoretical" = 0.8 × 0.72 = 57.6%).

The results of reaction 3 with various organometallic reagents to afford *l*-ephedrine alkane(arene)sulfinamides (**3a–c**) are listed in Table I.

The observations of relatively high yield of symmetric sulfoxide (RSOR, Table I) when Grignard reagents were used (in the absence of tetramethylethylenediamine, TMEDA), and the negligible yield of the same material when organolithium reagents were used, were in complete contrast to our expectations.[10,11] We also determined that an open-chain alkoxysulfinylamine (**5**) displayed "abnormal" behavior (relative to sulfinates and sulfinamides) as can be seen from the results listed in Table II. This table refers to reaction 5.

Table II. Reactions of *N*-Methoxysulfinylpiperidine (**5**) with C_6H_5MgBr and C_6H_5Li[a]

Reagent	TMEDA	C_6H_5–S(O)–NC_5H_{10} Yield, %	C_6H_5–S(O)–C_6H_5 Yield,[b] %
C_6H_5MgBr	+	40	11
C_6H_5MgBr	−	67	15
C_6H_5Li	+		47

[a] Yield for unreacted starting material was not reported since it was lost in the work-up. [b] Yields calculated based on **5**.

Reaction 5 was carried out under the same conditions as the synthesis of **3**. These results indicate that Grignard reagents can displace an amide anion ($-N^{(-)}$) from either an *N*-alkoxysulfinylamine (**5**) or a sulfinamide (**6**). The addition of TMEDA had only a small effect on this reaction. When phenyllithium was employed in reaction 5, sulfinamide **6** could not be

(12) J. A. Deyrup and C. L. Moyer, *J. Org. Chem.*, 34, 175 (1969); F. Wudl, R. Gruber, and A. Padwa, *Tetrahedron Lett.*, 2133 (1969).

Table III. Stereospecific Syntheses of Aryl Methyl Sulfoxides

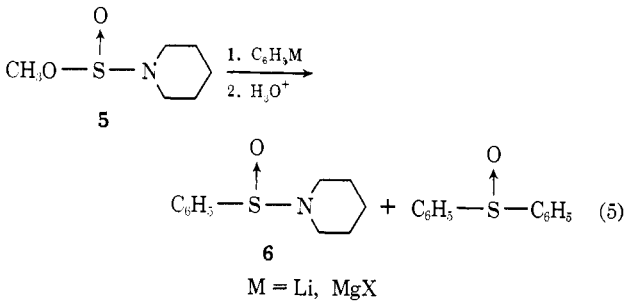
Sulfoxide	R^1	R^2	Reagent	Temp, °C	Yield, %	OP,[a] %
(*R*)-**4a**	$CH_3C_6H_5$	CH_3	CH_3MgBr	0	25	100
(*R*)-**4b**	C_6H_5	CH_3	CH_3Li-TMEDA	−78	70	86
(*S*)-**4c**	CH_3	C_6H_5	C_6H_5Li	−78	75	85

[a] Op = optical purity = $[\alpha]_{obtained}/[\alpha]_{known} \times 100$.

Table IV. Correlation of Absolute Configuration at Sulfur with Chemical Shifts of Diastereomeric Sulfinamides of Structure $C_6H_5CH(X)CH(CH_3)N(CH_3)SOR$

Sulfinamides			Diastereomeric component	Chemical shifts, δ		Abs. config. at sulfur
	X	R		NCH_3	$C_6H_5CH(X)$	
	H	C_6H_5	Major	2.32	2.50–3.00, m	*R*[a]
			Minor	2.54	3.42–4.00, m	*S*[a]
3a	OH	$CH_3C_6H_5$	Major	2.35	4.73, d	*R*
			Minor	2.52	4.84, d	*S*
3b	OH	C_6H_5	Major	2.33	4.74, d	*R*
			Minor	2.52	4.88, d	*S*
3c	OH	CH_3	Major	2.48	4.52, d	*R*
			Minor	2.60	4.63, d	*S*

[a] The absolute configuration at sulfur for this system was assigned by Jacobus and Mislow.[5]



detected (tlc, several solvent pairs) and only diphenyl sulfoxide was isolated. This observation indicates that the phenyllithium reaction with **6** is faster than with **5** since a buildup of some **6** would have been expected if the opposite were true. Finally, a comparison of Tables I and II indicates that the phenyllithium reaction with the alkoxide derived from **3** is much slower than with **6**.

The results listed in Table III refer to the synthesis of chiral sulfoxides from sulfinamides **3a–c** and an excess of organometallic reagent. These sulfoxide syntheses are indicative of the versatility of 1,2,3-oxathiazolidine 2-oxide (**1**) for the preparation of either enantiomer of any open chain sulfoxide. The conditions for the Grignard synthesis (*cf.* Table III) were not optimized and it is probable that the material yield could be improved while maintaining a high degree of stereospecificity. The lack of absolute stereospecificity in the formation of methyl phenyl sulfoxide and methyl *p*-tolyl sulfoxide from epimerically pure **3b** and **3c** with methyllithium or phenyllithium, respectively, or epimerically pure **3a** and methyllithium, was not unexpected.[5,6]

Stereochemical Correlations. The absolute configuration at sulfur in **1** and **2** was determined *via* nmr.[12] These assignments were based on the anisotropy effect of the sulfinyl function; *i.e.*, in a cyclic system, protons syn to the sulfinyl group are deshielded and protons anti to this group are shielded. The nmr spectrum of pure **1** corresponded to the major component of a diastereomeric mixture in which the methyl doublet (CH_3CH), the *N*-methyl singlet, and the aromatic hydrogens were shielded with respect to those of **2** and the methine hydrogens of **1** (OCH, MeNC*H*) were deshielded and appeared at comparable positions to those of known 1,2,3-oxathiazolidine 2-oxides.[12] Since both methine hydrogens must by syn to the sulfinyl group, structure **1** must correspond to the major isomer, and according to the sequence rule[13] the absolute configuration at sulfur is *R*.

If reaction 3 were to occur with inversion of configuration at sulfur, diastereomerically pure **3** should be *R* at sulfur.[13] We determined that this configura- was indeed obtained. The assignment of absolute configuration at sulfur in **3** was derived from the chemical shift values listed in Table IV.

Comparison of the nmr spectra of the two diastereomers of deoxyephedrine benzenesulfinamide prepared by Jacobus and Mislow[5] indicated that, due to the sulfinyl function and its chirality, the *N*-methyl singlet as well as the benzyl multiplet corresponding to the major diastereomer (whose absolute configuration was established[5] as *R*) were shielded relative to those corresponding to the minor isomer. Exactly the same behavior was exhibited by the diastereomers of sulfinamides **3a–c**. *Practically identical chemical shifts* of the *N*-methyl singlet of each diastereomer of **3b** and the corresponding diastereomer of deoxyephedrine benzenesulfinamide were observed (*cf.* Table IV). The absolute configurations assigned tentatively to the sulfinamides **3a–c** were internally consistent with conversion of **3a–c** to sulfoxides of known configuration (*cf.* Table III); provided, of course, reaction 4 (*via* Grignard reagents in the absence of TMEDA) occurred with inversion at sulfur.

Discussion

Inspection of Table I indicates that, in reaction 3, the ratio of yields of symmetric sulfoxide to sulfinamide and the stereochemistry vary with the organometallic reagent and the additive TMEDA. Since symmetric sulfoxide production could be due to an intramolecular process (*cf.* Figure 1), which would be accelerated if the Grignard reagent were aggregated or decelerated if the reagent were monomeric and alkyl exchange were

(13) K. R. Hanson, *J. Amer. Chem. Soc.*, **88**, 2731 (1966).

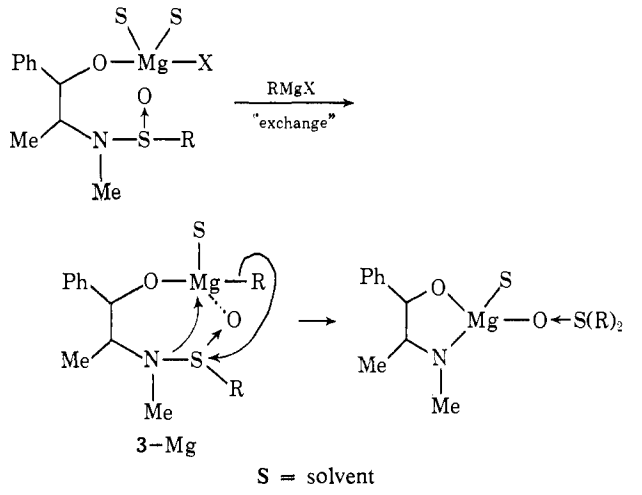


Figure 1.

slowed down, addition of TMEDA was expected to (and did) modify the reactivity of the Grignard reagent as expected.[14-17]

The results obtained when organolithium reagents were employed can also be interpreted in terms of Figure 1. Since the lithium cation is monovalent, species such as **3**-Mg become unimportant.

Concurrent with an increase in material yield of sulfinamide was a *decrease in stereospecificity* of the reaction; *i.e.*, partially epimerized **3** was obtained. This partial epimerization could be due to any of the following reasons: (1) epimerization during work-up, (2) by halide ion, (3) by multiple substitution, and (4) during the displacement reaction proper.

It was possible that product epimerization could occur during mild acid work-up.[8,2,18] Such a possibility was discarded because the same work-up procedure which was employed for the isolation of *epimerically pure* **3a** from the Grignard reaction (without TMEDA) afforded the partially epimerized product from reactions of **1** with organolithium reagents or Grignard reagents modified by TMEDA.

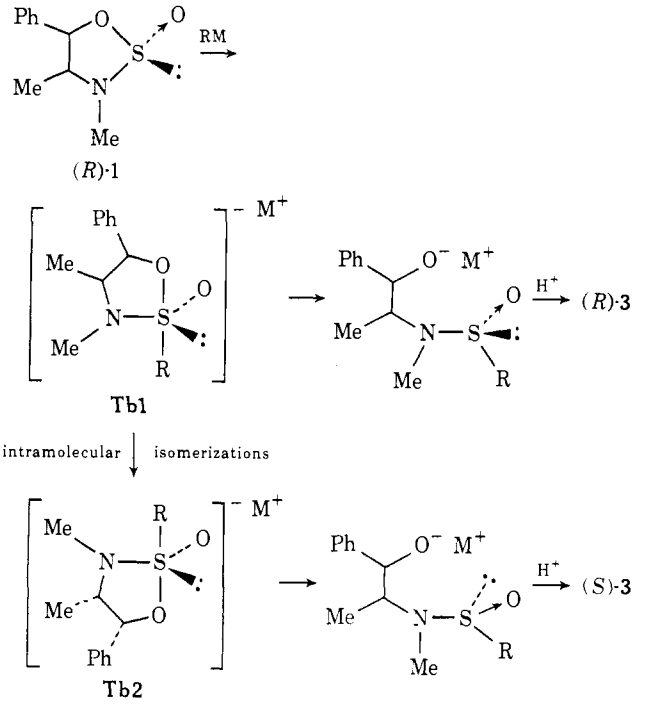
Since a crude reaction mixture containing unepimerized **3a** afforded pure, unepimerized **3a** upon preparative tlc and since nmr spectroscopy of crude reaction mixtures containing epimerized **3** revealed the presence of both isomers *before* and after chromatographic purification, epimerization did not take place during chromatography.

Since commercially available phenyllithium contains lithium halide, it was possible (although improbable) that epimerization by halide could take place. Halide-free phenyllithium afforded the same amount of epimerization of **3b** as did the commercial reagent. Therefore, we also discarded this remotely possible process.

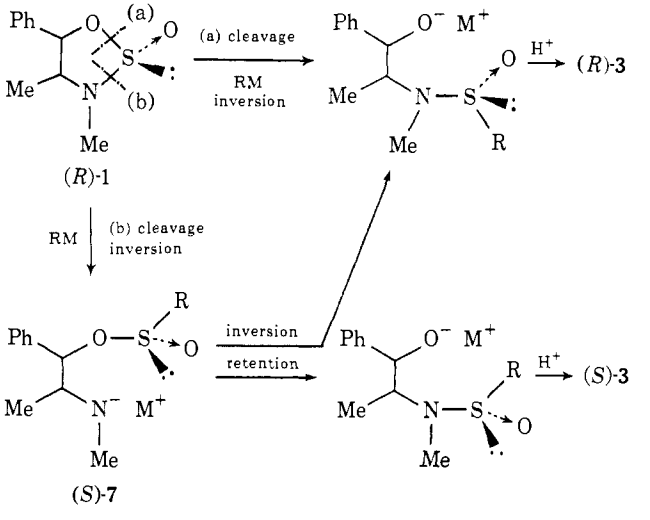
Since some ephedrine dianion was being generated in the reaction mixture, it could conceivably react with either **1** or **3** to afford epimerized material. Since recovered starting material (**1**) was not epimerized and since a symmetric sulfurous acid amide was not isolated, the above epimerization *via* ephedrine dianion was ruled out. When epimerically pure **3a** was allowed to react with an excess of the dianion of ephedrine, pure **3a** (purity determined by nmr and tlc) was recovered. Also, when **3b** was allowed to react with a slight excess of phenyllithium, and then recovered, it was found to be epimerically pure (tlc, nmr).

Since the above controls proved that neither starting material nor product was epimerized during reaction 3, epimerization had to take place during the bond-making and -breaking processes leading from **1** to **3**. Schemes I and II summarize two processes which could lead to epimeric mixtures of **3**.

Scheme I



Scheme II



The trigonal bipyramid **Tb1** is expected to be a metastable, high-energy species, not capable of existing long enough to undergo the five pseudorotations (or five

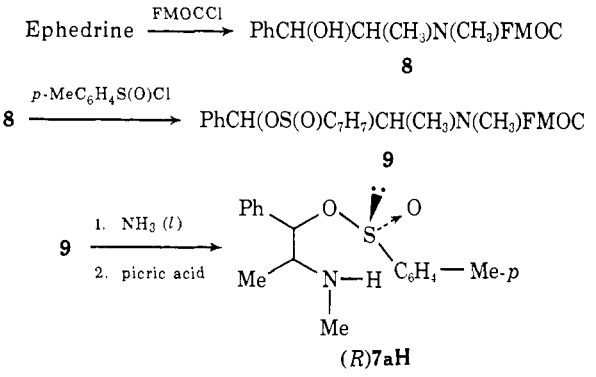
(14) Grignard reagents are monomeric in the presence of TMEDA: G. E. Coates and J. A. Heslop, *J. Chem. Soc. A*, 27 (1966).
(15) TMEDA retards alkyl exchange in Grignard reagents: H. O. House, R. A. Latham, and G. M. Whitesides, *J. Org. Chem.*, 32, 2481 (1967); J. A. Magnuson and J. D. Roberts, *ibid.*, 37, 133 (1972).
(16) TMEDA slows down the rate of Grignard addition to benzophenone: H. O. House and J. E. Oliver, *ibid.*, 33, 92 9(1968); H. O. House, 12th National Organic Chemistry Symposium, June 1967.
(17) E. C. Ashby, *Quart. Rev., Chem. Soc.*, 21, 259 (1967).
(18) H. Kwart and H. Omura, *J. Amer. Chem. Soc.*, 93, 7250 (1971).

turnstile rotations[19]) required[20] to invert it to **Tb2**. Furthermore, one of these five intermediate trigonal bipyramids would require an energetically unfavorable situation of a five-membered ring spanning two equatorial positions.[20] Finally, trigonal-bipyramidal species containing a pair of unshared electrons as a ligand appear to be very short lived.[21] On the basis of these arguments, we discarded Scheme I as a reasonable explanation of our results.

In order to test Scheme II, intermediate **7** was prepared independently and submitted to reaction conditions which would closely parallel reaction 3.

In a synthetic approach to **7**, strong solvolytic procedures (*e.g.*, deprotection of benzyl, trityl, dimethoxybenzyl) had to be avoided since the sulfinate function is a good leaving group.[22] Scheme III depicts our synthetic approach employing FMOC[23] as a protecting group.

Scheme III



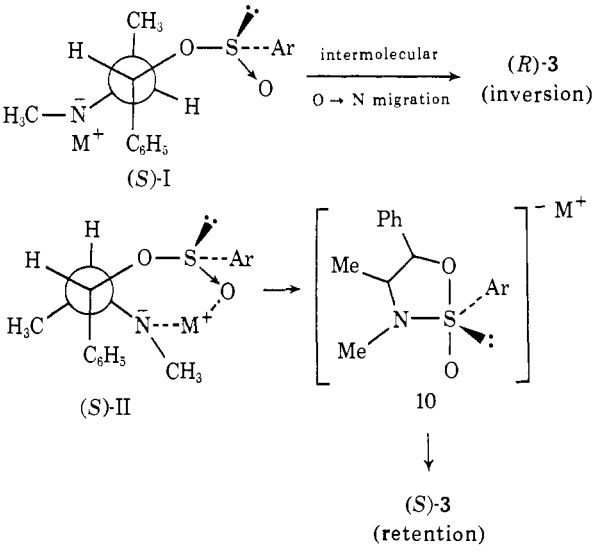
(*R*)**7aH**

An overall yield of 88% of (*R,S*)-**7a-H** (based on *l*-ephedrine) was obtained. According to nmr spectroscopy, unresolved **7a** consisted of a 49:51 mixture of diastereomers. These were separated efficiently (95% of one pure diastereomer could be obtained) *via* their picrate salts and ethanol solvent.

Treatment of a pure epimer (A) of **7a-H** (from the less soluble picrate salt) with excess methylmagnesium bromide (without TMEDA) gave no sulfinamide and only *optically pure* (+)-(*R*)-methyl *p*-tolyl sulfoxide. The absence of **3a** and the optical purity of the sulfoxide indicate that no displacement by amide anion on the sulfinate had occurred. Since (*R*) sulfoxide was obtained and since this reaction can be expected to occur with inversion of configuration,[2,3,24] it follows that the absolute configuration of epimer A of **7a-H** is *R*. Implicit in this result is the unusually slow reaction of amide magnesium halide salts with sulfinate esters. Menthyl *p*-toluenesulfinate does not react with deoxyephedrinylmagnesium bromide at or below 0°.

Intra- and Intermolecular Sulfinyl Transfers. On the basis of Fodor's results[25] on intramolecular acyl transfers in norephedrine and nor-ψ-ephedrine, we expected only a small degree of intramolecular sulfinyl transfer in our system. This is based on the following conformational analysis argument (Scheme IV).

Scheme IV



Conformations I and II correspond to two rotamers of **7a**. Clearly, I will be expected to predominate since it exhibits two gauche interactions. Rotamer II exhibits an additional gauche interaction between the phenyl and methyl groups; furthermore, the latter become eclipsed as **10** is formed. In conformation I, the reactive functional groups are exposed to intermolecular attack. On the other hand, a certain amount of stabilization of (*S*)-II was expected to be derived from coordination of the sulfinyl and amide anion functions to the counterion (Li, Mg). This phenomenon was also expected to activate the sulfinate toward nucleophilic attack.

In Scheme IV, we depicted the intramolecular path to proceed *via* a transition state or intermediate **10**. This trigonal bipyramid would be expected to be involved since its more electropositive ligands occupy equatorial positions and its electronegative ligands axial positions.[26] However, in order to form **10** *directly* from II, an "edge" attack of Me–N$^{(-)}$ on the sulfur pyramid would have to take place (*cf.* reaction 6) since "face" (apical) attack (*cf.* eq 7) would lead to an unfavorable trigonal bipyramid (*e.g.*, **11**) where the two most electronegative elements occupy equatorial positions.[26,27] Furthermore, path 7 would also require one pseudorotation[21,29] or turnstile rotation[19] for conversion into a more stable trigonal bipyramid (**10**). This intramolecular isomerization appears to be a high-

(19) I. Ugi, D. Marquarding, H. Klusacek, P. Gillespie, and F. Ramirez, *Accounts Chem. Res.*, **4**, 288 (1971).

(20) J. D. Dunitz and V. Prelog, *Angew. Chem.*, **80**, 700 (1968); P. C. Lauterbur and F. Ramirez, *J. Amer. Chem. Soc.*, **90**, 6722 (1968).

(21) K. Mislow, *Accounts Chem. Res.*, 3, 321 (1970); R. Tang and K. Mislow, *J. Amer. Chem. Soc.*, **91**, 5644 (1969); D. J. H. Smith and S. Trippett, *Chem. Commun.*, 855 (1969).

(22) D. Darwish and J. Noreyko, *Can. J. Chem.*, **43**, 1366 (1965).

(23) L. A. Carpino and G. Y. Han, *J. Amer. Chem. Soc.*, **92**, 5748 (1970). We thank Professor Carpino for experimental details.

(24) Since the predominant conformation of the Grignard salt of **7** is expected to be I (*cf.* Scheme IV), it is expected to behave as a normal sulfinate ester without interference on the stereochemical course by the amide Grignard salt (*cf.* Scheme IV, structure I, M^+ = MgBr·).

(25) G. Fodor, B. Bruckner, J. Kiss, and G. Ohegyi, *J. Org. Chem.*, **14**, 337 (1949).

(26) E. L. Muetterties and R. A. Schunn, *Quart. Rev., Chem. Soc.*, **20**, 245 (1966).

(27) Even if the exocyclic oxygen were to be assigned a full negative charge, it would still be more electronegative than nitrogen.[28] It is possible, however, that oxygen may back-donate some charge thus stabilizing **11** somewhat.

(28) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1940, pp 65–66.

(29) Since there are several faces and edges open to attack, three possible trigonal bipyramids can be formed by intramolecular attack of –N(–) on each face of the sulfur pyramid of **7a** and all of these can be interconverted (*via* an additional three trigonal bipyramids) according to Mislow's hexasterane scheme.[21]

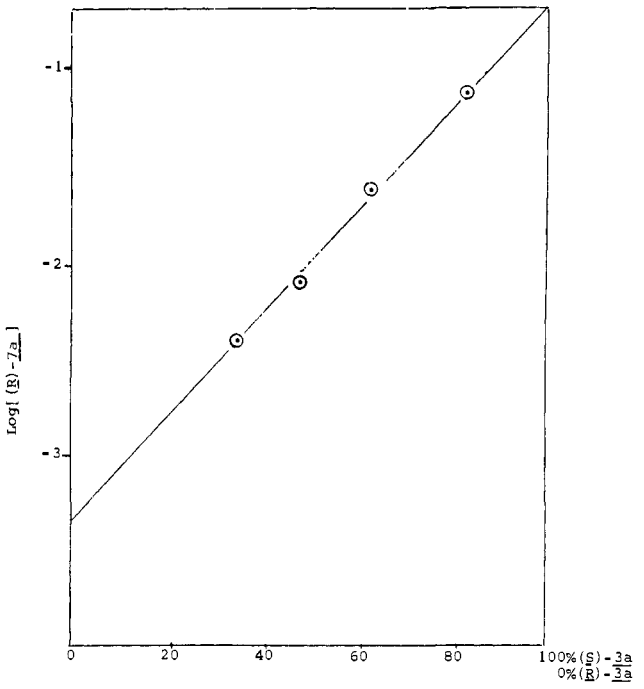
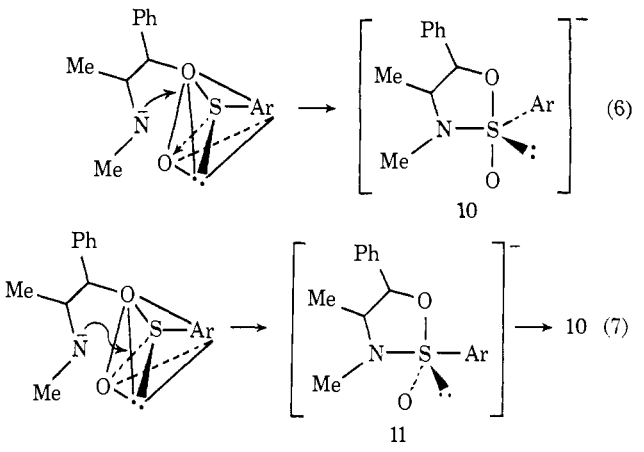


Figure 2. Concentration dependence of the sulfinate → sulfinamide conversion in (*R*)-*l*-ephedrine *p*-toluenesulfinate ((*R*)-**7a**).



energy process for trigonal bipyramids which have a pair of electrons as a ligand and two ligands as part of a ring.[21] Process 6 does not violate the principle of microscopic reversibility.[30]

Therefore, the stereochemical course of anionic sulfinyl transfer in **7a** should be concentration dependent. At high concentrations of (*R*)-**7a**, predominant inversion of configuration should obtain (mostly (*S*)-**3a** should be formed from (*R*)-**7a** or (*R*)-**3a** from (*S*)-**7a**); whereas at very low concentrations, intramolecular sulfinyl transfer will be encouraged and a higher degree of retention of configuration should obtain (*i.e.*, mostly (*R*)-**3a** should form from (*R*)-**7a** or (*S*)-**3a** from (*S*)-**7a**).

The results of a series of experiments designed to test this hypothesis are exhibited in Table V and Figure 2. Deprotonation of (*R*)-**7a** was most efficient with lithium dicyclohexylamide. Under optimum conditions (*e.g.*, experiment 2, Table V), 44% isolated yield

(30) Intuitively, we favor process 8 although the difference between it and process 9 is minor and cannot be substantiated unequivocally. A thorough discussion of applications of the principle of microscopic reversibility to substitutions *via* trigonal bipyramids is given in ref 21.

Table V. Concentration Effect on the Sulfinate → Sulfinamide Conversion in (*R*)-*l*-Ephedrine *p*-Toluenesulfinate [(*R*)-**7a**]

Experiment	Concn, *M*	(*R*)-**93a**, %	(*S*)-**93a**, %
1	8.2×10^{-2}	17	83
2	2.9×10^{-2}	37	63
3	8.2×10^{-3}	52	48
4	4.1×10^{-3}	65	35

of sulfinamide **3a** and 14% yield of *N,N*-dicyclohexyl *p*-toluenesulfinamide were obtained. The epimeric composition of **3a** produced from (*R*)-**7a** was determined *via* nmr spectroscopy. At a concentration of 4.1×10^{-3} *M* in **7a** (experiment 4), sulfinyl transfer occurred with predominant retention of configuration. This is the first example of an *intramolecular nucleophilic* substitution at sulfinyl sulfur *via* a five-membered cyclic pentacoordinated sulfur transition state or intermediate.

When the logarithm of the concentration of the reactant (**7a**) was plotted *vs.* the diastereomeric composition of the product, a straight line was obtained (Figure 2). By extrapolation,[31] we predicted that at a concentration of 4.6×10^{-4} *M* in **7a**, the reaction should proceed with absolute retention of configuration, *i.e.*, 100% (*R*)-**3a** should be obtained from (*R*)-**7a**. Whereas at a concentration of 0.24 *M* or greater, the reaction should proceed with absolute inversion. Unfortunately, these two concentration extremes could not be tested in the laboratory. At 4.6×10^{-4} *M*, the reaction was too slow to yield enough **3a** for analytical (nmr) determinations. Also, the amount of *strictly, anhydrous* solvent required was impractically large (*i.e.*, only 1.8×10^{-3} ml of water in *1 l.* of solvent would have quenched the reaction completely). Neither **1** nor **7a** was soluble to the extent of 0.24 *M* in THF at −78°.

Summary

We have shown that Grignard reagents as well as organolithium reagents will convert either open-chain (**5**) or cyclic (**1**) alkoxysulfinylamines to sulfoxides. Discrimination toward preferential displacement of alkoxide by Grignard reagents is greater in the open-chain than in the cyclic system **1** (*cf.* Table II *vs.* I). This difference could be attributed to ring strain and nonbonded interactions. Ring strain probably contributes to lowering the energy of activation toward nucleophilic attack on **1** *vs.* **5** by effectively raising the ground-state energy content of **1**. However, just how much ring strain exists in 3-alkyl-1,2,3-oxathiazolidine 2-oxides is difficult to estimate. Also, the energy of activation toward nucleophilic attack on **1** could be lowered by the same phenomenon invoked by Haake and Westheimer for the hydrolysis of ethylene phosphate esters;[32] *viz.*, energy is released in going from reactant (OSON angle = 108°?) to transition state (OSON angle = 90°). Molecular models indicate serious crowding between the 4-methyl and 5-phenyl in the 1,2,3-oxathiazolidine 2-oxide (**1**). Thus, an

(31) Barring nonlinear behavior at very high or very low concentrations.

(32) P. C. Haake and F. H. Westheimer, *J. Amer. Chem. Soc.*, **83**, 1102 (1961).

overall weakening of the O–SO– and N–SO– bond would be expected for **1** relative to **5**.

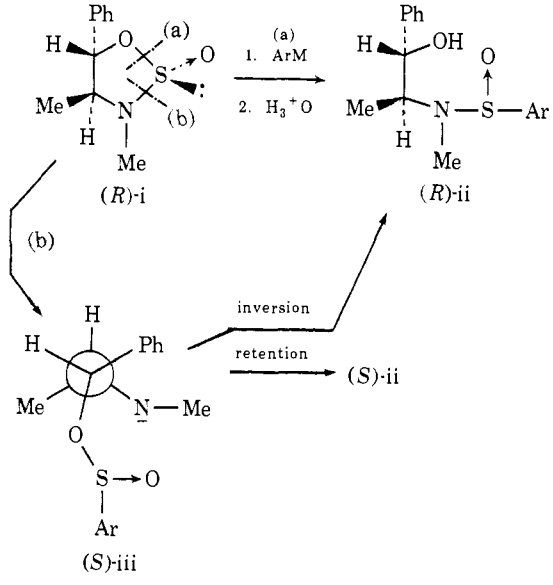
Taking the above arguments and incorporating them in Scheme II (modified by the results of the stereochemical course in anionic sulfinyl transfer), we can summarize our results in the form of Scheme V. The fact that **7** rearranges to **3** is indirect evidence for its intermediacy in the process **1** → **3**. These experiments do not constitute a proof of Scheme V but provide a reasonable support for our rationalization of the stereochemical outcome of reaction **1** → **3** under various conditions.

One oversimplified view could be built upon an assumption of $X \geq 0.5$, and $Y \leq 0.5$, then total (*R*)-**3** $\leq$ 0.75, which is in excellent agreement with the results in Table I. The assumption of $X \geq 0.5$ is quite reasonable on the bases of the above arguments and our results of reaction 5. However, for a given value of X (or $1 - X$), Y is changing continuously.[33] Thus, while X may be a "constant" (*e.g.*, 0.5, or equal probability of (a) and (b) cleavage), Y is an unknown variable dependent on k_3 and k_4. These rate constants will be practically impossible to determine accurately because of the complexity of the reaction procedure (*cf.* Experimental Section). However, it is possible that the "time-averaged"[33] value of Y could be ≤ 0.5.

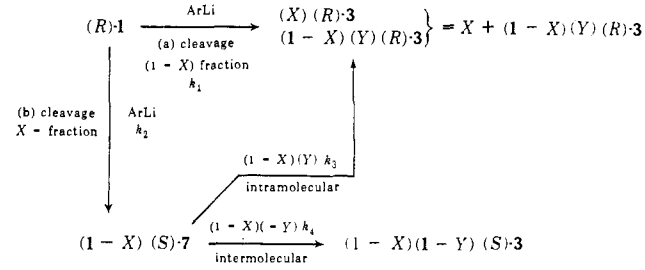
It is also apparent that it will be impossible to produce 100% (*R*)-**3** from (*R*)-**1** as long as (*S*)-**7** is a source of **3**. In the Grignard reaction, (*S*)-**7** is diverted to produce symmetric sulfoxide (*via* a process analogous to Figure 1) before it rearranges to (*S*)-**3**. When ligand exchange on Mg is slowed down, the lifetime of (*S*)-**7** produced in the Grignard reaction is prolonged sufficiently so that some (*S*)-**3** is formed. Hence, the results of Table I are qualitatively interpretable by Scheme V.[34]

(33) During the early stages of the overall conversion of **1** to **3** (*cf.* Scheme V), the concentration of (*S*)-7 is going to be very low (below 10^{-4} *M*) and its anionic rearrangement will produce mainly (*S*)-**3** (*cf.* Figure 2), but as more **1** is consumed, the concentration of (*S*)-**7** will increase (provided $k_4 < k_3 \ll k_1, k_2$, we observed that $k_3, k_4 \ll k_1, k_2$ by qualitatively comparing reaction 3 to the conversion of 7 to 3) and more (*R*)-**3** will now be formed from (*S*)-**7**.

(34) Preliminary results of a parallel study with a pseudoephedrine derivative ((*R*)-i) lend additional support to our interpretations based on Scheme V. The epimeric ratio of isolated ii was found to be 60:40 as contrasted to 76:24 for **3b** when (*R*)-i and (*R*)-**1**, respectively, were subjected to the same reaction conditions. Presumably, in this case, (*S*)-iii (a pseudoephedrine analog of 7) is the predominant conformer



Scheme V



Experimental Section

3,4-Dimethyl-5-phenyl-2-oxo-1,2,3-oxathiazolidine (1). To a solution of 20.66 g (0.125 mol) of *l*-ephedrine (Aldrich Co.) and 35 ml (0.25 mol) of triethylamine in 160 ml of 50:50 *n*-hexane–benzene was added a solution of 10 ml of thionyl chloride in 50 ml of benzene over a period of 40 min at 0°. At the end of the addition, another 35 ml of triethylamine in 50 ml of benzene was added and the reaction was left stirring at 0° overnight. The solvents were evaporated under reduced pressure. The light brown residue was dissolved in 600 ml of methylene chloride and washed with 2 *N* hydrochloric acid and then several portions of water. After drying over anhydrous magnesium sulfate and evaporation, a crude mixture (21 g, 80%) of the two diastereomeric oxathiazolidines **1**, 72%, and **2**, 28%, was obtained. The ratio of these two isomers was determined *via* nmr spectroscopy. Its nmr spectrum ($CDCl_3$) displayed two sets of doublets at δ 0.80 (J = 7.0 Hz) and 0.98 (J = 7.0 Hz) with relative intensities of 7.2:2.8, multiplets at 4.00, two sets of doublets at δ 5.73 and 6.01 with relative intensities of 2.8:7.2, and two singlets at δ 7.43 and 7.52 with relative intensities of 7.2:2.8. Crystallization from ether afforded 6.6 g of pure (*R*)-**1**: mp 126.5–127.5°; $[\alpha]^{25}D$ +2.25° (*c* 1.88, acetone); ir (KBr), 1335 (m) [OS(O)N], 1152 (s) [OS(O)N]; nmr ($CDCl_3$ δ 0.80 (d, 3, J = 7.0 Hz), 2.72 (s, 3), 4.00 (quintet, 1), 6.01 (d, 1, J = 7.5 Hz), 7.43 (s, 5).

Anal. Calcd for $C_{10}H_{13}NO_2S$: C, 56.87; H, 6.16. Found: C, 57.18; H, 6.25.

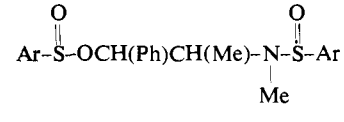
The mother liquor was treated with a drop of pyridine and a trace of hydrogen chloride gas. The cloudy solution was then placed in a refrigerator for 2–7 days. The crystalline residue was separated, dissolved in methylene chloride, extracted with water, dried, and evaporated to yield slightly yellow (*R*)-**1**. One recrystallization from ether afforded pure (*R*)-**1**, 16.3 g. The overall yield of isolated (*R*)-**1** was 65%.

***l*-Ephedrine Alkane(arene)sulfinamides. A. Grignard Reactions. *l*-Ephedrine *p*-Toluenesulfinamide (3a).** An atmosphere of argon was maintained throughout the procedure of all the Grignard reactions studied.

A Grignard reagent prepared from 0.73 g of magnesium and 5.13 g of *p*-bromotoluene in 20 ml of THF was added with stirring to a solution of 3.16 g (14.9 mmol) of (*R*)-**1** in 30 ml of THF over a period of 15 min at −30°. The reaction mixture was stirred for 9 hr at −26 to −30° and was quenched at that temperature with 6 ml of saturated aqueous ammonium chloride solution. After filtration, the THF was evaporated. The residue was dissolved in methylene chloride and washed with 15% H_2SO_4 solution and water, dried, and evaporated to give 3.56 g of a yellow solid. This material was chromatographed on 80 g of silica gel starting with petroleum ether. The polarity of the solvent was increased with ether up to 100% ether. The third band consisted of 1.22 g (35%) of di-*p*-tolyl sulfoxide: mp 94–95° (lit.[35] mp 92°); ir (KBr)

which (in contrast to (*S*)-7)[25] rearranges predominantly *via* an intramolecular process to (*S*)-ii.

In addition, some runs of experiment 1, Table V, afforded a small amount of iv, thus strengthening the argument that *inversion* of con-



iv

figuration is due to an *intermolecular* path in the reaction 7 → **3**.

(35) "Handbook of Chemistry and Physics," 48th ed, The Chemical Rubber Company, Cleveland, Ohio, 1967.

1088 (s), 1040 (s), 1011 (s) cm^{-1} [identical with Sadtler spectrum no. 20593] and the fifth band was identified as the sulfinamide (*R*)-**3a** (0.83 g, 18.3%), mp 136–138°; $[\alpha]^{25}D$ +1.9° (*c* 2, acetone); ir (KBr) 3320 (s), 2900 (w), 1700 (w), 1450 (m), 1380 (w), 1300 (w), 1210 (w), 1160 (w), 1082 (s), 1040 (s), 997 (s), 940 (w), 870 (s), 813 (s), 757 (s), 727 (m), 687 (s); nmr ($CDCl_3$) δ 1.38 (d, 3, J = 7.0 Hz), 2.35 (s, 3), 2.38 (s, 3), 3.75 (m, 1), 4.2 (broad s, 1, disappeared upon addition of D_2O), 4.8 (d, 1, J = 5.5 Hz) 7.1–7.6 (m, 9).

Anal. Calcd for $C_{17}H_{21}NO_2S$: C, 67.33; H, 6.93. Found: C, 67.22; H, 7.14.

The results of this reaction under other conditions are shown in Table I.

When the reaction was carried out with 2 equiv of the Grignard reagent and in the presence of 4 equiv of tetramethylethylenediamine (TMEDA), the yield of the sulfinamide increased, but the nmr spectrum ($CDCl_3$) of the mixture displayed two sets of closely spaced doublets whose chemical shift difference was so small that they collapsed into a broad doublet at δ 1.35 (J = 7.0 Hz), singlet at δ 2.32, two sets of singlets at δ 2.35 and 2.52 with relative intensities (RI) of 88:12, two closely spaced quartets at δ 3.72, a broad multiplet at 3.96, two sets of doublets at δ 4.73 and 4.84 (J = 5.5 Hz) (RI, 88:12), and multiplets at δ 7.1–7.6.

The recovered starting material (*R*)-**1** in all cases was not epimerized since its nmr spectrum was identical with that of pure (*R*)-**1** and none of the absorptions corresponding to (*S*)-**1** could be detected.

***l*-Ephedrine Methanesulfinamide (3c).** Similarly, this sulfinamide was prepared using 2 equiv of methylmagnesium bromide and 4 equiv of TMEDA. A 26% yield of di-*p*-tolyl sulfoxide and a 41% yield of a mixture of diastereomeric sulfinamides (**3c**) were obtained. Its ir spectrum (KBr) is characteristic of that of an *l*-ephedrine alkanesulfinamide; 3380 (s), 1082 (m), 1052 (s), 1008 (s), 947 (m), 935 (m), 879 (m). The nmr spectrum ($CDCl_3$) of this mixture of isomers showed a slightly broadened doublet at δ 1.18 (J = 7.0 Hz), two sets of singlets at δ 2.04 and 2.13 (RI 2.57:1), two sets of singlets at δ 2.48 and 2.60 (RI, 2.57:1), a multiplet (which became a quintet upon the addition of D_2O), two sets of doublets at δ 4.52 and 4.63 (J = 5.5 Hz) (RI, 2.57:1), and a singlet at δ 7.22. The major isomer (*R*)-**3c** was obtained by recrystallization from ether and petroleum ether over a period of 2 days. It is a white crystalline solid: mp 113–114°; $[\alpha]^{25}D$ +0.273° (*c* 1.0, acetone); nmr ($CDCl_3$) δ 1.22 (d, 3, J = 7.0 Hz), 2.20 (s, 3), 2.78 (s, 3), 3.52 (quintet, 1, J = 7.5 Hz), 4.02 (broad s, 1), 4.63 (d, 1, J = 5.5 Hz), 7.22 (s, 5). The slight difference in some of the chemical shifts in the spectrum of pure (*R*)-**3c** from that in the mixture seemed to be an effect of difference in concentration. The doublet at δ 4.63, however, was unaffected. The ir of (*R*)-**3c** was superimposable on that of the diastereomeric mixture.

Anal. Calcd for $C_{14}H_{23}NO_2S$: C, 58.11; H, 7.55. Found: C, 57.91; H, 7.50.

B. Organolithium Reaction. *l*-Ephedrine Benzenesulfinamide (3b). An atmosphere of argon was maintained throughout the procedure of all the alkyllithium reactions studied.

A solution containing 10.5 ml of 0.95 *M* (10 mmol) phenyllithium (in benzene–ether, prepared from diphenyl mercury and lithium) and 1.162 g (10 mmol) of purified (distilled from phenyl isocyanate) TMEDA in 40 ml of THF was placed in a dropping funnel equipped with a cooling jacket containing an ice–methanol mixture. This cold solution (−12°) was then added to a solution of 2.11 g (0.01 mol) of (*R*)-**1** in 300 ml of THF at a temperature of −78° over a period of 20 min. The reaction was stirred for 25 min and then quenched with 10 ml of saturated ammonium chloride solution at that temperature. The white precipitate was then filtered and the THF was evaporated.

The residue was dissolved in 50 ml of methylene chloride and washed with 15% sulfuric acid and then water. After drying over anhydrous magnesium sulfate and evaporation of the solvent, 3.34 g of white, crystalline **3b** was isolated. The presence of two diastereoisomers in a ratio of 76:24 was determined by the relative intensities of the two sets of doublets at δ 4.62 and 4.78 for C_6H_5-CH(OH) in the nmr spectrum of this crude material. Thick-layer chromatography of 246 mg of this material gave 200 mg of the pure **3b**, mp 120–130°, which contained the same ratio of diastereoisomers (with overall yield 84%). Its nmr spectrum ($CDCl_3$) displayed an unsymmetrical triplet (the overlapping of two unequal doublets) at δ 1.16, two singlets at δ 2.19 and 2.46 (RI 76:24), a multiplet at δ 3.27–3.84, a broad singlet at δ 4.23 (disappeared on the addition of D_2O), two sets of doublets at δ 4.62 and 4.78 (RI 76:24), and a multiplet at δ 6.98–7.72. Its ir spectrum (KBr) was typical of that for *N*-sulfinylephedrine: 3295 (s), 1450 (m), 1083 (s), 1033 (s), 1020 (s), 992 (s), 940 (m).

The two diastereoisomers of **3b** were separated by fractional crystallization. The properties of these two components are as follows. Diastereomer (*R*)-**3b**: the major component, mp 127–128°; $[\alpha]^{25}D$ +0.113° (*c* 0.86, acetone); nmr ($CDCl_3$) δ 1.36 (d, 3, J = 7 Hz), 2.33 (s, 3), 3.71 (m, 2; became a quintet upon the addition of D_2O), 4.74 (d, 1, J = 5.5 Hz), 7.33 (aromatic s, 10); ir spectrum identical with that of the mixture.

Anal. Calcd for $C_{16}H_{19}NO_2S$: C, 66.45; H, 6.57. Found: C, 66.24; H, 6.57.

Diastereomer (*S*)-**3b**: mp 140–141° $[\alpha]^{25}D$ +0.697° (*c* 0.31, acetone); nmr ($CDCl_3$) δ 1.32 (d, 3, J = 7.0 Hz), 2.52 (s, 3), 2.09–3.08 (s, broad, 1, disappeared upon addition of D_2O), 3.67 (m, 1), 4.88 (s, broad, 1, which became a doublet upon the addition of D_2O, J = 5.5 Hz), 7.32, 7.38 (aromatic s, 10); ir spectrum also identical with that of the mixture. The recovered starting material (*R*)-**1** was not epimerized as determined *via* nmr.

Variation in time, temperature, and phenyllithium reagent, as well as presence or absence of TMEDA, seemed to have no effect on the material yield of the sulfinamide **3b** nor its diastereomeric ratio. Also, as a control experiment, epimerically pure (*R*)-**3b** was treated with 1 equiv of phenyllithium and 1 equiv of dilithium salt of *l*-ephedrine under the same experimental conditions. The recovered (*R*)-**3b** was *not* epimerized by nmr determination.

***l*-Ephedrine Methanesulfinamide (3c).** Similarly, **3c** was prepared from methyllithium (Alfa Chemical Co.) in *ca.* 61% yield as a 74:26 mixture of diastereomers.

Methyl *p*-Tolyl Sulfoxide. A solution of methylmagnesium bromide (based on 0.17 g (7 mmol) of magnesium) in 15 ml of THF was added dropwise with stirring over a period of 15 min to a solution of 300 mg (0.99 mmol) of *l*-ephedrine *p*-toluenesulfinamide (**3a**) in 10 ml of THF at 0°. The reaction mixture was stirred for 15 min at 0° and 15 min at room temperature and then quenched with 1.4 ml of saturated ammonium chloride solution. The precipitate formed was filtered and the THF was evaporated. The residue was dissolved in 50 ml of methylene chloride and washed with 15% aqueous sulfuric acid and then water. After drying over anhydrous magnesium sulfate and evaporation of the solvent, 300 mg of crude material was obtained. Thick-layer chromatography using acetonitrile afforded a 25% yield of methyl *p*-tolyl sulfoxide, mp 73–74°, $[\alpha]^{25}_{546}$ +183.0° (*c* 2.1, acetone) (lit.[36] $[\alpha]^{25}_{546}$ +180.5° (*c* 2.5, acetone)).

(*S*)-(−)-Methyl Phenyl Sulfoxide. A solution of 2.86 ml of 0.95 *M* (2.72 mmol) phenyllithium in 10 ml of ether was added dropwise to a solution of 310 mg (1.36 mmol) of (*S*)-(+)-**3c** (mp 113–114°) in 20 ml of THF cooled to −78°. The reaction mixture was stirred for 15 hr and then hydrolyzed with 3 ml of saturated ammonium chloride solution at that temperature.

The white precipitate was filtered and the THF was evaporated. The residue was dissolved in 40 ml of methylene chloride solution, washed with dilute 15% sulfuric acid and water, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to give 212 mg of crude product. Thick-layer chromatography using 1:1 ether–methylene chloride solvent mixture afforded 143 mg (75%) of (*S*)-(−)methyl phenyl sulfoxide; $[\alpha]^{25}D$ −127.5° (*c* 2.2, ethanol) (lit.[6] $[\alpha]^{24}D$ +149°); nmr ($CDCl_3$) δ 2.68 (s, 3), 7.40–7.7 (m, 5).

(*R*)-(+)-Methyl phenyl sulfoxide was prepared similarly from (*S*)-(−)-*N*-phenylsulfinylephedrine and methyllithium in the presence of TMEDA in 70% yield; $[\alpha]^{25}D$ +128.5° (*c* 152, ethanol).

Reaction of *N*-Methoxysulfinylpiperidine (5) with C_6H_5MgX. *N*-Methoxysulfinylpiperidine was prepared according to the procedure of Zinner:[37] bp 93° (5.3 mm) (lit.[37] bp 100° (10 mm)); ir (CH_2Cl_2), 1424 (m), 1203 (m), 1137 (s), 1042 (m), 990 (s), 908 (s) cm^{-1}.

A solution of phenylmagnesium bromide (based on 83.5 mg (3.43 mmol) of magnesium in 10 ml of THF) was added to a well-stirred solution of 500 mg of **5** in 25 ml of THF over a period of 15 min at −20 to −30°. The reaction mixture was stirred for 5 hr and then hydrolyzed with 2 ml of saturated ammonium chloride solution. The white solid was filtered and the THF was evaporated. The residue was dissolved in 40 ml of methylene chloride, washed with 155 ml of aqueous sulfuric acid and water, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to give 710 mg of crude **6**. Thick-layer chromatography of 100 mg of this material using a 20% ether–methylene chloride solvent mixture

(36) K. K. Andersen, W. Gaffield, N. Papanikolaou, J. W. Foley, and R. I. Perkins, *J. Amer. Chem. Soc.*, 86, 5637 (1964).

(37) G. Zinner, *Ber.*, 91, 966 (1958).

afforded 60 mg which corresponds to 66.5% overall yield of benzenesulfinylpiperidine (**6**): mp 83–84° (lit.[38] mp 83°); ir (KBr), 2950 (m), 2870 (m), 1435 (m), 1086 (s), 1050 (s), 905 (s), 952 (s), 8685 (s) cm^{-1}; nmr ($CDCl_3$) 1.33–1.78 (m, 6), 2.75–3.20 (m, 4), 7.34–7.72 (m, 5); and 14 mg (15% based on **5** of diphenyl sulfoxide, mp 68–69.5°); ir (CH_2Cl), 1092 (s), 1047 (s), 1020 (s) cm^{-1}; superimposable on that of diphenyl sulfoxide (Sadtler spectrum no. 16313 or 418)].

This reaction, when carried out in the presence of TMEDA, afforded 40% of **6** and 11% (based on **5**) of diphenyl sulfoxide.

Reaction of *N*-Methoxysulfinylpiperidine with Phenyllithium–TMEDA. This reaction was carried out in essentially the same way as the reaction of phenyllithium–TMEDA with *l*-ephedrine methanesulfinamide (**3c**). The crude material obtained after work-up was used for thick-layer chromatography with 20% ether–methylene chloride as the solvent. Diphenyl sulfoxide was obtained in 47% yield (based on **5**) and no *N*-benzenesulfinylpiperidine could be isolated.

***N*-(9-Fluorenyl)methoxycarbonyl-*l*-Ephedrine (FMOC–Ephedrine).** The procedure of Carpino[23] for protection of amino groups was used for this synthesis. A solution of 16.3 g (63 mmol) of 9-fluorenylmethyl chloroformate (Aldrich Chemical Co.) in 120 ml of ether was added slowly into a well-stirred solution of 10.2 g (62 mmol) of *l*-ephedrine and 15.4 g (146 mmol) of sodium carbonate in 156 ml of water and 150 ml of ether at 0° (ice–water bath). After the addition, the reaction was allowed to continue for 3 hr at that temperature. The ether layer was then separated, washed with 15% aqueous sulfuric acid and water, and dried over anhydrous magnesium sulfate. The solvent was concentrated to a volume of about 60 ml. Approximately 20 ml of petroleum ether was added to this solution. After storing in the refrigerator overnight, 23.1 g (96%) of the *N*-FMOC–ephedrine was collected by suction filtration. A small amount of 40% ether–petroleum ether was used to wash the white FMOC–ephedrine crystals: mp 126–126.5°; ir (KBr) 3400 (s), 2960 (m), 1770 (s), 1472 (m), 1420 (s), 1398 (m), 1320 (s), 1235 (m), 1150 (s), 1030 (s), 1083 (m), 1020 (s), 810 (w), 757 (s), 738 (s), 699 (s) cm^{-1}; nmr ($CDCl_3$) 0.92–2.36 (m, 3), 2.60 (s, 3), 3.38 (quintet, 1, J = 7.0 Hz), 3.84–4.24 (m, 2), 4.24–4.90 (m, 3), 7.03–7.85 (m, 13).

Anal. Calcd for $C_{24}H_{23}NO_3$: C, 77.52; H, 6.46. Found: C, 77.42; H, 6.50.

***N*-FMOC-*l*-Ephedrine *p*-Toluenesulfinate.** A solution of 7 ml (54 mmol) of *p*-toluenesulfinyl chloride, bp 92–95° (0.5 mm) (lit.[39] 99–102° (0.5 mm)), in 25 ml of methylene chloride was added dropwise into a solution of 15.7 g (41.5 mmol) of *N*-FMOC–ephedrine in 65 ml of methylene chloride at 0° with stirring. When the addition of the *p*-toluenesulfinyl chloride was complete, a solution of 3.4 ml (41.5 mmol) of pyridine in 15 ml of methylene chloride was added dropwise into the reaction mixture at 0°. The reaction was allowed to continue overnight at that temperature. The reaction mixture was treated with water, the methylene chloride layer was separated, and the aqueous layer was extracted once with 50 ml of methylene chloride. The combined methylene chloride solution was washed with dilute $NaHCO_3$ and then 15% sulfuric acid and water. After drying over anhydrous magnesium chloride and evaporation under reduced pressure, 25.5 g (quantitative) of the *N*-FMOC–ephedrine *p*-toluenesulfinate (**9**), mp 46–50°, was obtained: ir spectrum (neat, as a melt) 1785 (s), 1425 (s), 1400 (m), 1315 (s), 1172 (m), 1139 (s), 955 (s), 910 (s), 809 (m), 775 (s), 756 (s), 741 (s), 726 (s), 703 (m) cm^{-1}; nmr ($CDCl_3$) spectrum appeared to consist of a mixture of two diastereomers δ 1.00 (d, 1, J = 8.0 Hz), 1.22 (d, 1, J = 3.5 Hz), 1.32 (d, 1, J = 3.5 Hz), 2.34 (s, 2), 2.61 (s, 1), 2.78 (d, 2, J = 4 Hz), 3.46 (quintet, 0.5, J = 7.0 Hz), 3.80–4.60 (m, 3.5), 4.74–4.96 (m, 0.5), 5.38 (d, 0.5, J = 7.0 Hz), 6.72–7.84 (m, 17).

This material was used directly in the following reaction without further purification.

Cleavage of FMOC-*l*-Ephedrine *p*-Toluenesulfinate by Liquid Ammonia. The FMOC-*l*-ephedrine *p*-toluenesulfinate prepared *via* the above reaction was dissolved in 60 ml of ether. With the use of a cold finger condenser, ammonia was distilled into the reaction vessel. When *ca.* 700 ml of liquid ammonia was collected, the cold finger condenser was removed and the ammonia was allowed to evaporate while vigorous stirring was maintained throughout the procedure. The residue was treated with 30 ml of ether and 130 ml of ice-cold 15% sulfuric acid. The acidic aqueous fraction was separated and washed once with 30 ml of ether. With cooling in an ice–water bath and in presence of 100 ml of ether, it was *carefully* neutralized with 15% sodium hydroxide. The ether layer was separated and the aqueous solution was extracted twice with 50-ml portions of ether. The combined ethereal extract was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure to give 11.5 g (91.5% yield based on *N*-FMOC-*l*-ephedrine) of the *l*-ephedrine *p*-toluenesulfinate (**7a**): ir 3320 (m), 3000 (s), 2800 (m), 1498 (w), 1446 (s), 1136 (s), 1115 (m), 1084 (m), 1030 (w), 810 (m), 791 (m), 740 (m), 700 (s); nmr spectrum ($CDCl_3$) indicatedt hat it consisted of a 51 : 49 mixture of diastereomers, δ 0.92 (two overlapping doublets, J = 7.0 Hz), 2.22 (broad, s), two singlets at δ 2.22 and 2.32 (RI 1.03:1), 2.57–2.86 (m), two sets of doublets at δ 5.11 and 5.29 (RI 1.04:1), 6.88–7.62 (m).

This diastereomeric mixture was converted to its picrate salt by treating an ethanolic solution (115 ml) of this material with a solution of 8.7 g of picric acid in 230 ml of 95% ethanol. Crystallization in a refrigerator overnight afforded 10 g (95% based on the major epimer) of the picrate of the (*R*)-*l*-ephedrine *p*-toluenesulfinate [(*R*)-**7a**]: mp 165–166° (mp 167–167.5° after one recrystallization); $[\alpha]^{25}D$ −0.79° (*c* 0.85, acetone); ir 3410 (w), 3170 (m), 2800 (w, broad), 1760 (s), 1720 (s), 1600 (s), 1480 (m), 1455 (m), 1430 (m), 1370 (s), 1310 (s), 1265 (s), 1160 (s), 1135 (s), 1075 (s), 960 (s), 935 (m), 922 (m), 910 (m), 865 (w), 845 (w), 812 (m), 778 (s), 750 (s), 708 (s).

Anal. Calcd for $C_{23}H_{25}N_4O_9S$: C, 51.78; H, 4.69. Found: C, 52.05; H, 4.64.

This picrate was *carefully* neutralized with cold 15% NaOH solution in the presence of ether to give the (*R*)-*l*-ephedrine *p*-toluenesulfinate (*R*)-**7a**: $[\alpha]^{25}D$ −0.818° (*c* 1.63 acetone); ir spectrum was identical with that of the diastereomeric mixture; nmr ($CDCl_3$) δ 0.95 (d, 3, J = 7.0 Hz), 1.41 (s, 1), 2.40 (s, 6), 2.82 (quintet, 1, J = 5.5 Hz), 5.30 (d, 1, J = 5.5 Hz), 7.33 (s, 5), 7.42 (A_2B_2 aromatic quartet, 4). Evaporation of the mother liquor of the picrate solution afforded picric acid and a diastereomeric mixture of the picrates of *l*-ephedrine *p*-toluenesulfinate enriched in the *S* isomer: nmr ($CDCl_3$) δ 1.02 (d, J = 7.0 Hz), 1.27 (broad, s), two singlets at 2.28 and 2.40, 2.64–2.96 (m), two sets of doublets at δ 5.20 and 5.37 (RI 8:1), 6.98–7.80 (m). No further attempt was made to resolve this mixture.

Base Induced Sulfinate–Sulfinamide Conversion of (*R*)-*l*-Ephedrine *p*-Toluenesulfinate ((*R*)-7a). Lithium Dicyclohexylamide. An aliquot of 0.31 ml of 2.67 *M* (0.82 mmol) *n*-butyl lithium in hexane was added to a solution of 0.24 ml (1.23 mmol) of dicyclohexylamine in 4.5 ml of THF at room temperature. The resulting lithium dicyclohexylamide solution was then added dropwise with stirring to a solution of 250 mg (0.82 mmol) of (*R*)-**7a** in 5 ml of THF at −78° over a period of 5 min. The reaction was continued for 0.5 hr and then hydrolyzed with 1 ml of saturated ammonium chloride solution at that temperature. The white precipitate was filtered and the THF was evaporated under reduced pressure. The residue was treated with 60 ml of ether and washed with 15% sulfuric acid, then aqueous sodium carbonate solution, and water. After the residue was dried over anhydrous magnesium sulfate and evaporation of the solvent under reduced pressure, 195 mg of crude material was obtained. Thick-layer chromatography of this material using 2:1 methylene chloride–ether solvent mixture as the eluent afforded 110 mg (44%) of *l*-ephedrine *p*-toluenesulfinamide (**3a**) identified by comparative thin-layer chromatography (tlc) and ir spectroscopy with a pure sample of **3a**. Its nmr spectrum indicated that it consisted of a mixture of diastereomers, 83% of the *S* isomer and 17% of the *R* isomer, as determined by the relative intensities of the two singlets at δ 2.38 (NCH_3,$CH_2C_6H_5$) and 2.54 (NCH_3) in a ratio of 1.39:1 and the two sets of doublets at δ 4.78 and 4.90 ($C_6H_5CH(OH)$) in a ratio of 1:4.9. Also isolated was 40 mg (14%) of *N*-dicyclohexyl *p*-toluenesulfinamide as a white solid: mp 136–137°; ir spectrum (KBr), 2945 (s), 2840 (m), 1420 (w), 1158 (w), 1107 (m), 1060 (m), 1055 (s), 1038 (m), 963 (m), 868 (w), 835 (w), 811 (m), 735 (w) cm^{-1}; nmr ($CDCl_3$) δ 0.91–2.22 (m, 20), 2.41 (s, 3), 2.88–3.30 (m, 4), 7.42 (A_2B_2 aromatic quartet, 4).

Anal. Calcd for $C_{19}H_{29}NOS$: C, 71.47; H, 9.09. Found: C, 71.39; H, 9.13.

This reaction was similarly repeated at three other concentrations. The diastereomeric ratio of the sulfinamide **3a** formed as determined by nmr spectroscopy as above was found to differ drastically.

These results are shown in Table V. In these two latter runs, the starting material (**7a**) was recovered and its nmr spectrum was identical with that of pure **7a**; thus, the starting material did not epimerize under the reaction conditions. Another minor product

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was also isolated which had the following spectroscopic properties: ir spectrum (CH_2Cl_2) showed absorptions characteristic of sulfinates, 1128 (s) and 952 (s), and of sulfinamides, 1085 (s), 1057 (s), 1016 (m), 868 (m); nmr ($CDCl_3$) δ 1,39 (d, 3, J = 7.0 Hz), 2.38 (s, 3), 2.41 (s, 3), 3.70 (quintet, 1, J = 7.0 Hz), 5.24 (d, 1, J = 7.0 Hz), 7.2–7.61 (m, 13). This material was presumably *l*-ephedrine *O*-(*p*-toluenesulfinyl)-*p*-toluenesulfinamide.

Methylmagnesium Bromide. A solution of methylmagnesium bromide (based on 40 mg (1.64 mmol) of magnesium) and 190 mg of (1.64 mmol) TMEDA in 15 ml THF was added dropwise with stirring to a soluton of 250 mg (0.82 mmol) of (*R*)-*l*-ephedrine *p*-toluenesulfinate [(*R*)-**7a**] in 20 ml of THF at −25°. The reaction was allowed to continue for 1.5 hr. The usual work-up followed by thick-layer chromatography using 20% methylene chloride and acetonitrile solvent mixture as the eluent afforded 63 mg (51%) of pure methyl *p*-tolyl sulfoxide: mp 75–76° (lit.[3,36] mp 74–75.5°); $[\alpha]^{25}_{546}$ +182.5° (*c* 2.13, acetone) (lit.[36] $[\alpha]^{25}_{546}$ +180.5° (*c* 1.61, acetone)). No *l*-ephedrine *p*-toluenesulfinamide (**3a**) could be detected or isolated.

A similar result was obtained when this reaction was carried out in the absence of TMEDA.

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Electric Field Effects in the ^{13}C Nuclear Magnetic Resonance Spectra of Unsaturated Fatty Acids. A Potential Tool for Conformational Analysis[1a]

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Abstract: The source of nonequivalence in the ^{13}C chemical shifts of unsaturated carbons in fatty acids is shown to arise from a linear electric field effect. The behavior of the nonequivalence is in accord with predictions of direction, magnitude, distance, and solvent dependence. The effect is larger than previously reported for protons and fluorine and is discernible at least eight C–C bonds away from the head group dipole. We predict that this linear electric field effect, which is dependent both on distance and orientation factors, will play an important part in future cmr conformational studies.

Conformational data on molecules which are large or members of complex structures are essential to our understanding of many problems of chemical and biological interest. Proton magnetic resonance spectroscopy has in the past been a principle source of this type of data, and for most molecules it will continue to be so. However, as the molecules of interest become larger and more complex, line broadening and spectral overlap tend to detract from the ease with which information can be obtained by this technique. In these cases, carbon-13 magnetic resonance (cmr) offers potential advantages in the form of great dispersion of ^{13}C chemical shifts, smaller line broadening, and the consequent improved resolution.[2] Before cmr can be applied to conformational studies a number of conformationally dependent parameters must be identified. One such parameter, the γ-carbon contribution to chemical shift, has been identified[3] and applied to the analysis of hydrocarbon chain conformation in a model membrane system.[4] However, progress in such cmr studies has in general been restricted by the small number of parameters, such as the γ effect, known to be conformationally dependent, and the accuracy of any conformational interpretations, particularly those of cmr shift data, has been limited by uncertainties in the contributions from other, unknown, effects.

The present study provides evidence for the existence of a significant electric field dependent contribution to ^{13}C chemical shift, which should be useful in conformational analysis and describes in detail the dependence of this contribution on molecular geometry and functionality. The existence of such an effect has been suggested by Horsley and Sternlicht[5a] and by McFarlane[5b] but their papers have received surprisingly little attention and, to our knowledge, no application to conformational problems has been suggested. This linear field dependent contribution can be interpreted on the basis of polarization of the bonds between carbon and adjacent atoms by an electric field originating at a molecular dipole, point charge, or other intra- or intermolecular source and, as for analogous effects in fluorine and proton magnetic resonance,[6,7] the contribution to chemical shift can be represented as a sum of terms with linear and second-order de-

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