Use of Menthyl 2-Methoxynaphthalene-1-sulfinates in the Andersen Synthesis of Optically Active Sulfoxides. Facile Cleavage by Grignard Reagents of Some Aromatic Methyl Ethers

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Abstract

The pure crystalline diastereomers (1*R*,2*S*,5*R*)-menthyl (*R*)- and (*S*)-2-methoxynaphthalene-1-sulfinate (1b) have been prepared and, by reaction with Grignard reagents (the Andersen procedure), converted into optically active alkyl and aryl 2-methoxynaphthyl sulfoxides in 67–77% yields. Use of an excess of Grignard reagent results in facile *O*-alkyl cleavage of the methoxy group to the corresponding naphthol or a competing loss of the alkyl- or aryl-sulfinyl group to form 2-methoxynaphthalene. Pure diastereomers of menthyl 2,7-dimethoxynaphthalene-1-sulfinate (2b) and menthyl 4-methoxynaphthalene-1-sulfinate (3b) have also been prepared and their reactions with Grignard reagents have been studied.

Introduction

Chiral sulfoxides are important intermediates in the synthesis of optically active organic compounds (for reviews see ref. 1). They have been prepared by several methods (for reviews see ref. 2). The most recent employ the reaction of Grignard reagents with chiral *N*-sulfinyloxazolidinones,[3] oxathiazolidine *S*-oxides,[4] or sulfites.[5] All these methods give excellent enantioselectivities. A more established method is the asymmetric oxidation of prochiral sulfides[2] and new reagents for improving enantioselectivity continue to be reported (for some recent examples

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[1] Walker, A. J., *Tetrahedron: Asymmetry*, 1992, **3**, 961; Posner, G. H., in 'The Chemistry of Sulfones and Sulfoxides' (Eds S. Patai, Z. Rappoport and C. Stirling) Ch. 16 (John Wiley: Chichester 1988); Solladie, G., *Synthesis*, 1981, 185.

[2] Andersen, K. K., in 'The Chemistry of Sulfones and Sulfoxides' (Eds S. Patai, Z. Rappoport and C. Stirling) Ch. 3 (John Wiley: Chichester 1988); Drabowicz, J., Kielbasinski, P., and Mikolajczyk, M., in 'The Chemistry of Sulfinic Acids, Esters and their Derivatives' (Ed. S. Patai) Ch. 12 (John Wiley: Chichester 1990); Solladie, G., in 'Comprehensive Organic Synthesis' (Ed. E. Winterfeldt) Vol. 6 (Pergamon: Oxford 1991); Uemura, S., in 'Comprehensive Organic Synthesis' (Ed. S. V. Ley) Vol. 7 (Pergamon: Oxford 1991); Mikolajczyk, M., and Drabowicz, J., *Top. Stereochem.*, 1982, **13**, 333.

[3] Evans, D. A., Faul, M. M., Colombo, L., Bisaha, J. J., Clardy, J., and Cherry, D., *J. Am. Chem. Soc.*, 1992, **114**, 5977.

[4] Benson, S. C., and Snyder, J. K., *Tetrahedron Lett.*, 1991, **42**, 5885.

[5] Rebiere, F., Samuel, O., Ricard, L., and Kagan, H. B., *J. Org. Chem.*, 1991, **56**, 5991; Rebiere, F., and Kagan, H. B., *Tetrahedron Lett.*, 1989, **30**, 3659.

see ref. 6). However, the original method, termed the Andersen procedure,[7,8] in which a chiral menthyl sulfinate is allowed to react with a Grignard reagent, still retains its popularity (for some recent examples of use see ref. 9). Most commonly used is (−)-menthyl (S)-toluene-4-sulfinate and an efficient procedure has been described[10] for the preparation of this pure diastereomer in over 90% yield. The commercial availability (Aldrich Chemical Company) of both diastereomers of menthyl toluene-4-sulfinate testifies to their appeal. Use of alcohols other than menthol has been reported[11] as well as menthyl esters of other sulfinic acids[12] but none has replaced the menthyl toluene-4-sulfinates in general use.

Our recent findings[13,14] on the direct chlorosulfination of aromatic ethers with thionyl chloride to give methoxyarenesulfinyl chlorides prompted us to consider their use to form the corresponding menthyl esters and subsequent application in the Andersen procedure. This report describes our results mostly with menthyl esters derived from 2-methoxynaphthalene-1-sulfinyl chloride (1a).
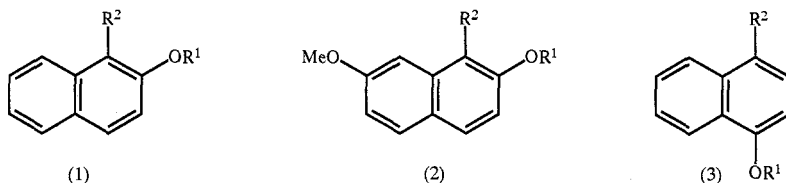
	R^1	R^2		R^1	R^2
(a)	Me	SOCl	(g)	Me	SEt
(b)	Me	S(O)Omenthyl	(h)	Me	S(O$_2$)Et
(c)	Me	SOMe	(i)	H	SOMe
(d)	Me	SOPh	(j)	H	SOPh
(e)	Me	SOEt	(k)	Me	SMe
(f)	Me	SOPr^i			

[6] Komatsu, N., Hashizume, M., Sugita, T., and Uemura, S., *J. Org. Chem.*, 1993, **58**, 4529; Sakuraba, H., Natori, K., and Tanaka, Y., *J. Org. Chem.*, 1991, **56**, 4124, and references cited therein.
[7] Andersen, K. K., *Tetrahedron Lett.*, 1962, 93.
[8] Andersen, K. K., Gaffield, W., Papanikolaou, N. E., Foley, J. W., and Perkins, R. I., *J. Am. Chem. Soc.*, 1964, **86**, 5637.
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[10] Solladie, G., Hutt, J., and Girardin, A., *Synthesis*, 1987, 173.
[11] Ridley, D. D., and Smal, M. A., *Aust. J. Chem.*, 1982, **35**, 495; Andersen, K. K., Bujnicki, B., Drabowicz, J., Mikolajczyk, M., and O'Brien, J. B., *J. Org. Chem.*, 1984, **49**, 4070; Llera, J. M., Fernandez, I., and Alcudia, F., *Tetrahedron Lett.*, 1991, **32**, 7299.
[12] Mislow, K., Green, M. M., Laur, P., Melillo, J. T., Simmons, T., and Ternay, A. L., Jr, *J. Am. Chem. Soc.*, 1965, **87**, 1958.
[13] Bell, K. H., *Aust. J. Chem.*, 1985, **38**, 1209.
[14] Bell, K. H., and McCaffery, L. F., *Aust. J. Chem.*, 1992, **45**, 1213.

Results and Discussion

Reaction of (1a) with (−)-menthol and pyridine in methylene chloride at 0–5° gave a mixture of approximately equal amounts of the two solid diastereomers (1b). Both were readily detected by their separate (even at 90 MHz) methoxy absorptions in the proton n.m.r. spectrum. This technique provides a convenient means for assessing the effectiveness of subsequent separations of the two diastereomers. One recrystallization from acetone gave the diastereomer with the lower field methoxy absorption [δ (CDCl$_3$) 3·98] in about 95% purity. One further crystallization gave the pure diastereomer ([1]H n.m.r. and constant rotation). The other diastereomer (methoxy absorption at δ 3·95) was obtained by fractional crystallization from light petroleum. Over several runs, and particularly with seeding by pure diastereomers, it was possible to isolate both in a combined yield of 85–87%. The whole procedure from formation of the sulfinyl chloride (1a) to the isolation of the pure low field (of the OMe) diastereomer can be realized in less than 12 h.

The potential usefulness of diastereomeric (1b) in the Andersen procedure was examined by inverse addition of a slight excess of Grignard reagent to a solution of the ester in benzene. Use of this solvent has been reported[15] to give better yields than the use of ether. From the appropriate Grignard reagent and either of the diastereomers (1b), 67–77% yields of the enantiomerically pure sulfoxides (1c–f) were obtained. By comparison of the signs of rotations with closely related compounds of known configuration [e.g. (R)-(+)-methyl, ethyl or isopropyl 4-tolyl sulfoxide,[12] (R)-(+)-1-naphthyl 4-tolyl sulfoxide,[8] (R)-(+)-2-methoxyphenyl phenyl sulfoxide[16]], we assigned the (+)-sulfoxide enantiomers the (R)-configuration. It has been shown[12,8] that the reaction of Grignard reagents with sulfinate esters proceeds with inversion of configuration at sulfur. Thus, we were able to assign the (S)-configuration at sulfur to the diastereomer (1b) with the lower field methoxy group and the (R)-configuration to the other. It should be mentioned that a recent publication[17] has cited examples where use of bulky Grignard reagents and hindered sulfinate esters can yield sulfoxides with retention of configuration. However, in a series of sulfoxides here from methyl, through ethyl and isopropyl to phenyl derived from a single diastereomer, a consistent sign of rotation was obtained and we feel confident in the above configurational assignments. Sulfoxides (1c,d) were crystalline solids but (1e,f) were oils. Attempted vacuum distillation of (1e) gave the volatile sulfide (1g) and sulfone (1h) was detected in the residue. Thermal disproportionation of similar sulfoxides has been noted previously[18].

Both diastereomeric menthyl sulfinates (2b) were also obtained from (2a) and one diastereomer (3b) from (3a). In the latter case the methoxy resonances of the two diastereomers were indistinguishable. Optically active sulfoxides (2c) and (3c) were obtained similarly from (2b) and (3b) respectively by reaction with methylmagnesium iodide.

[15] Drabowicz, J., Bujnicki, B., and Mikolajczyk, M., *J. Org. Chem.*, 1982, **47**, 3325.

[16] Noriyama, M., Yoshimura, T., Furukawa, N., Numata, T., and Oae, S., *Tetrahedron*, 1976, **32**, 3003.

[17] Drabowicz, J., Dudzinski, B., and Mikolajczyk, M., *J. Chem. Soc., Chem. Commun.*, 1992, 1500.

[18] Bell, K. H., *J. Chem. Soc., Perkin Trans 1*, 1988, 1957.

In all the Grignard reactions with (1b) and (2b), but not with (3b), traces of the simple methyl ethers (2-methoxynaphthalene and 2,7-dimethoxynaphthalene) were detected (t.l.c.). When the reactions of (1b) were repeated with an excess (up to 4:1 mole ratio) of Grignard reagent (methylmagnesium iodide and phenylmagnesium bromide), an increased amount of 2-methoxynaphthalene was obtained but the major products were the phenolic sulfoxides (1i) and (1j). Similar treatment of the methoxy sulfoxides (1c) and (1d) gave the same results. This facile demethylation of an aromatic methyl ether by a Grignard reagent contrasts with the harsher conditions (heating the neat components together at 160–200° or very slow reaction in benzene at reflux) normally required.[19a] We suggest for this transformation the 1,6-addition mechanism given in Scheme 1. The shown

Scheme 1
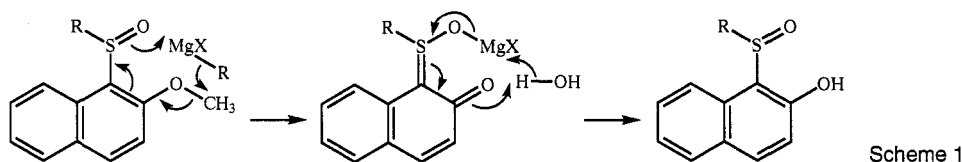
cleavage would be facilitated by presumed complexation of the ether oxygen with the Grignard reagent. Some 1,6-additions to aromatic nitriles and ketones, but not involving ether cleavage, have been reported[19b]. The presence of the *ortho*-sulfinyl group is necessary as shown by the inertness of 2-methoxynaphthalene to methylmagnesium iodide and the formation of (2i) from (2b) or (2c) under the same conditions. That the 2-methoxy group (and not the 7) had been demethylated was shown by the disappearance of the strong *peri*-effect of the sulfinyl group on H8 in the [1]H n.m.r. spectrum of (2i). In (2c) this proton appears as a *meta*-coupled doublet at δ 8·54 ($CD_3 SOCD_3$) (all other aromatic protons are *ortho*-coupled) but in (2i) it occurs normally at δ 7·65, as the sulfinyl group is now hydrogen-bonded to the hydroxy group. Internal hydrogen bonding of the hydroxy group in (2i) was also evident from the infrared spectrum. Formation of the simple ethers, presumably through the sulfoxides, is suggested to take place as shown in Scheme 2. Similar cleavage of aryl sulfoxides by organolithium

Scheme 2
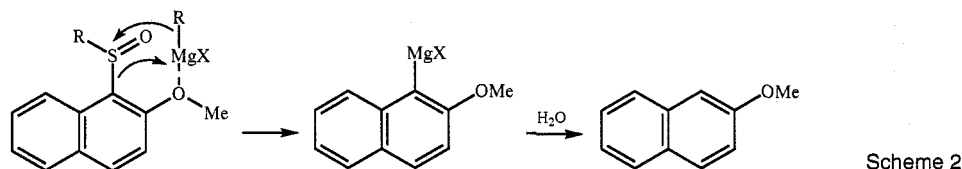
reagents has been reported.[20]* Methyl phenyl sulfoxide and methyl phenyl sulfide, expected by-products in the reaction of (1d) with methylmagnesium iodide, were detected ([1]H n.m.r.) in the crude reaction mixture. Whether this concerted pathway, as shown, is followed or a sulfoxonium salt (R_3SOMgX) is first formed

cannot be decided here. Normally, sulfoxides react slowly at room temperature with Grignard reagents to give unstable sulfoxonium salts[21] but the presence of the methoxy group with the coordinated Grignard reagent may facilitate the reaction. Rate enhancement (15×) by an *ortho*-methoxy group on the reaction of Grignard reagents with benzoate esters has been reported.[22]

The usual products from the reaction of Grignard reagents with sulfoxides are sulfides[23] but a number of other minor products are formed by proposed complex mechanisms[24]. No sulfides were detected in Grignard reactions with the *ortho*-methoxy compounds above but sulfide (3k) was the major product from the reaction of (3b) or (3c) with excess methylmagnesium iodide. The position of the methoxy group thus plays an important role on the course of this reaction and provides some support for the mechanism shown in Scheme 2.

In conclusion, it has been shown that the diastereomeric menthyl esters (1b) could serve as viable alternatives to the usual toluenesulfinates in the Andersen procedure for preparation of optically active sulfoxides, provided due care is taken in the Grignard reactions.

Experimental

[1]H n.m.r. spectra at 89·55 MHz and ^{13}C spectra at 22·49 MHz were measured with a JEOL FX 90Q instrument; tetramethylsilane was used as internal reference. Infrared spectra were recorded with a Bio-Rad FTS-7 instrument. Electron ionization mass spectra were recorded by Mr B. Tattam and Mrs H. Elimelakh at the School of Pharmacy, the University of Sydney, on a Finnigan/MAT TSQ-46 instrument. Optical rotations were measured with a Perkin–Elmer 241 spectropolarimeter in a 1-dm cell kept at 20°. Eastman Chromagram silica gel 13181 sheets were used for thin-layer chromatography. Woelm silica gel was used for medium-pressure column chromatography. Melting points were determined in a Büchi oil-immersion apparatus and are corrected. Microanalyses were by the Australian National University Microanalytical Service, Canberra.

Preparation of Menthyl Sulfinates

(1R,2S,5R)-Menthyl (R)- and (S)-2-Methoxynaphthalene-1-sulfinate (1b)

A suspension of freshly prepared 2-methoxynaphthalene-1-sulfinyl chloride (1a)[13] (20·11 g, 0·084 mol) in dry methylene chloride (200 ml), contained in a three-necked flask fitted with a pressure-equalizing dropping funnel, thermometer and inlet tube connected to a source of dry nitrogen, was stirred magnetically in an ice bath. When the internal temperature had dropped to 2–3°, a solution of (−)-(1R,2S,5R)-menthol (12·95 g, 0·083 mol) in dry methylene chloride (25 ml) and dry pyridine (12·5 ml) was added at such a rate to keep the temperature below 5°. After complete addition, by which time the solid sulfinyl chloride had dissolved and the yellow colour was discharged, the mixture was stirred in the ice bath for an hour. The whole procedure was carried out under a slight positive pressure of dry nitrogen. The mixture was washed successively with ice-cold 5 M HCl (50 ml), water, 1 M Na$_2$CO$_3$ (20 ml) (no precipitate on acidification), sat. NaCl, and dried (MgSO$_4$). Removal of the solvent at less than 20° gave a faintly yellow oil (31·2 g, quantitative) which solidified when stored in the refrigerator. The [1]H n.m.r. spectrum (CDCl$_3$) showed two OMe singlets at δ 3·98 and 3·95 in a percentage ratio of 47:53 respectively. The crude product was dissolved in boiling acetone (50 ml), and cooling slowly to 0°, with seeding by the pure diastereomer from an earlier trial run, gave

[21] Wildi, B. S., Taylor, S. W., and Potratz, H. A., *J. Am. Chem. Soc.*, 1951, **73**, 1965; Hepworth, H., and Clapham, H. W., *J. Chem. Soc.*, 1921, **119**, 1188.

[22] Vavon, G., Barbier, M., and Thiebaut, G., *Bull. Soc. Chim. Fr.*, 1934, **1**, 806.

[23] Harpp, D. N., Vines, S. M., Montillier, J. P., and Chan, T. H., *J. Org. Chem.*, 1976, **41**, 3987.

[24] Manya, P., Sekera, A., and Rumpf, P., *Tetrahedron*, 1970, **26**, 467.

chunky, colourless cubes (12·34 g) which showed two OMe singlets at δ 3·98 (95%) and 3·95 (5%) in the ^{1}H n.m.r. spectrum. One further crystallization from acetone (again with seeding) gave 11·84 g of pure *(−)-(1R,2S,5R)-menthyl* (S)-*2-methoxynaphthalene-1-sulfinate* (1b), m.p. 118–120° (dec.) (Found: C, 69·7; H, 8·1; S, 8·8. $C_{21}H_{28}O_3S$ requires C, 70·0; H, 7·8; S, 8·9%). [α] −179·3 (589 nm), −187·7 (578), −216·4 (546), −415·4 (436) (*c*, 0·0110 in CHCl$_3$). ^{1}H n.m.r. δ (CDCl$_3$) 9·08, dd, J_{ortho} 8·5, J_{meta} 1·5 Hz, H 8; 7·96–7·14, m, ArH; 4·33–4·05, m, CHOS; 3·98, s, OMe; 2·4–0·85, broad envelope with Me at 0·96–0·85. ^{13}C n.m.r. δ (CDCl$_3$) 156·3 (Ar C 2), 134·6, 130·0, 129·7, 128·5, 127·7, 126·3, 124·5, 124·1, 112·7 (Ar C 3), 79·8 (CHOS), 56·9 (OMe), 47·9, 42·0, 34·1, 31·7, 25·4, 23·2, 22·0 (Me), 20·9 (Me), 15·6 (Me). ν_{max} (CHCl$_3$) 3009, 2957, 2924, 2869, 2848, 1621, 1594, 1506, 1465, 1430, 1339, 1272, 1250, 1108, 1067, 1024, 950, 911, 847 cm^{-1}. The acetone filtrates from above were combined and reduced in volume to 20 ml. Cooling to 0° and seeding gave an additional 2·20 g (80% pure) of (S)-(1b). Two more recrystallizations from acetone gave the pure diastereomer (1·64 g). The total yield of (S)-(1b) was 13·48 g.

The acetone filtrates from the above recrystallizations were combined and evaporated to dryness. The crude product was dissolved in boiling light petroleum (90 ml), a little charcoal was added, and the mixture was filtered. Cooling and seeding with a pure sample of the second diastereomer gave 14·52 g of colourless crystals of about 90% purity (^{1}H n.m.r.). Two further recrystallizations from light petroleum, or, alternatively, a last crystallization from a small volume of acetone, gave 12·86 g of pure *(+)-(1R,2S,5R)-menthyl* (R)-*2-methoxynaphthalene-1-sulfinate* (1b), m.p. 99–101° (dec.) (Found: C, 70·0; H, 7·6; S, 8·7. $C_{21}H_{28}O_3S$ requires C, 70·0; H, 7·8; S, 8·9%). [α] +80·5 (589 nm), +85·1 (578), +98·9 (546), +208·3 (436) (*c*, 0·0121 in CHCl$_3$). ^{1}H n.m.r. δ (CDCl$_3$) 9·10, dd, J_{ortho} 8·5, J_{meta} 1·5 Hz, H 8; 7·95–7·13, m, ArH; 4·33–4·05, m, CHOS; 3·95, s, OMe; 2·40–0·73, broad envelope with Me at 1·00–0·73. ^{13}C n.m.r. δ (CDCl$_3$) 156·3 (Ar C 2), 134·6, 129·8, 129·7, 128·5, 127·7, 126·6, 124·4, 124·2, 112·6 (Ar C 3), 82·9 (CHOS), 56·7 (OMe), 48·2, 43·7, 34·0, 31·9, 25·4, 23·3, 22·0 (Me), 20·7 (Me), 15·7 (Me). ν_{max} (CHCl$_3$) 3009, 2955, 2926, 2869, 2849, 1621, 1594, 1507, 1466, 1430, 1272, 1250, 1105, 1067, 951, 912, 869, 811 cm^{-1}.

The combined yield of both diastereomers was 26·34 g (87%). Further runs under similar conditions gave yields of 85–88%. Other runs carried out in different solvents (CHCl$_3$, ether) gave the low field diastereomer in slight excess (51–53%). The sulfinate esters are stable indefinitely at −15° but slowly darken at room temperature with a considerable change in rotation after 1 week.

(1R,2S,5R)-Menthyl (R)- *and* (S)-*2,7-Dimethoxynaphthalene-1-sulfinate* (2b)

Under similar conditions to the previous preparations, from 2,7-dimethoxynaphthalene-1-sulfinyl chloride[13] (2a) was obtained a crude mixture of diastereomers which showed three OMe absorptions (δ 3·96, 3·94, 3·92) in the ^{1}H n.m.r. spectrum. Fractional crystallization from acetone gave colourless crystals (41% yield) of *(−)-(1R,2S,5R)-menthyl* (S)-*2,7-dimethoxynaphthalene-1-sulfinate* (2b), m.p. 116–117° (Found: C, 67·7; H, 7·9. $C_{22}H_{30}O_4S$ requires C, 67·7; H, 7·7%). [α]$_D$ −117·0 (*c*, 0·0114 in CHCl$_3$). ^{1}H n.m.r. δ (CDCl$_3$) 8·52, d, J_{meta} 2·6 Hz, Ar H 8; 7·80, d, J_{ortho} 9 Hz, ArH; 7·64, d, J_{ortho} 9 Hz, ArH; 7·03, dd, J_{meta} 2·6, J_{ortho} 9 Hz, Ar H 6; 7·01, d, J_{ortho} 9 Hz, ArH; 4·32–4·05, m, CHOS; 3·96, 3·92, both s, 2×OMe; 2·4–0·85, broad envelope with Me at 0·96–0·85. The *other diastereomer* (R)-(2b) was obtained as fine needles from light petroleum (37% yield), m.p. 88–90° (dec.) (Found: C, 67·4; H, 7·9. $C_{22}H_{30}O_4S$ requires C, 67·7; H, 7·7%). [α]$_D$ −19·8 (*c*, 0·0103 in CHCl$_3$). ^{1}H n.m.r. δ (CDCl$_3$) 8·53, d, J_{meta} 2·6 Hz, Ar H 8; 7·82, d, J_{ortho} 9 Hz, ArH; 7·66, d, J_{ortho} 9 Hz, ArH; 7·04, dd, J_{meta} 2·6, J_{ortho} 9 Hz, Ar H 6; 7·01, d, J_{ortho} 9 Hz, ArH; 4·33–4·05, m, CHOS; 3·94, br s, 2×OMe; 2·41–0·85, broad envelope with Me absorptions from 0·96 to 0·85.

(1R,2S,5R)-Menthyl (S)-*4-Methoxynaphthalene-1-sulfinate* (S)-*(3b)*

The crude mixture of diastereomers in this case showed a single OMe absorption at δ (CDCl$_3$) 4·03 in the ^{1}H n.m.r. spectrum and at δ 55·7 in the ^{13}C n.m.r. spectrum but two peaks due to CHOS at 81·0 and 78·8 in the latter spectrum. Two recrystallizations from acetone gave the (S)-*diastereomer* (3b) in 35% yield as colourless crystals, m.p. 105–107° (dec.) (Found: C, 69·8; H, 8·1. $C_{21}H_{18}O_3S$ requires C, 70·0; H, 7·8%). [α] −334·7 (589

nm), $-351 \cdot 2$ (578), $-407 \cdot 2$ (546), $-781 \cdot 2$ (436) (c, $0 \cdot 0139$ in CHCl$_3$). ^{1}H n.m.r. δ (CDCl$_3$) $8 \cdot 37$–$8 \cdot 23$, m, ArH; $8 \cdot 12$, d, J_{ortho} $8 \cdot 3$ Hz, Ar H 2; $7 \cdot 68$–$7 \cdot 50$, m, ArH; $6 \cdot 90$, d, J_{ortho} $8 \cdot 3$ Hz, Ar H 3; $4 \cdot 32$–$4 \cdot 04$, m, CHOS; $4 \cdot 03$, s, OMe; $2 \cdot 40$–$1 \cdot 05$, broad aliphatic H envelope with Me at $0 \cdot 96$, $0 \cdot 76$, $0 \cdot 46$, all d, J 7 Hz. ^{13}C n.m.r. δ (CDCl$_3$) $158 \cdot 8$ (Ar C 4), $132 \cdot 0$, $130 \cdot 2$, $127 \cdot 5$, $125 \cdot 8$, $125 \cdot 6$, $125 \cdot 0$, $122 \cdot 8$, $122 \cdot 1$, $102 \cdot 6$ (Ar C 3), $78 \cdot 8$ (CHOS), $55 \cdot 7$ (OMe), $47 \cdot 7$, $42 \cdot 8$, $33 \cdot 9$, $31 \cdot 6$, $24 \cdot 9$, $23 \cdot 0$, $22 \cdot 0$ (Me), $20 \cdot 7$ (Me), $15 \cdot 1$ (Me).

The other diastereomer was not isolated.

Reaction of the Sulfinates with Grignard Reagents

General Conditions

The Grignard reagent was prepared in a three-necked 100-ml round-bottom flask fitted with a magnetic follower, a pressure-equalizing dropping funnel, a serum cap and a coil condenser connected to a source of high-purity nitrogen. All glassware was dried overnight at 140° and assembled hot under nitrogen. Grignard grade magnesium (BDH) was used. The halides were redistilled before use and kept over freshly regenerated 4A molecular sieves. The solvents, ether and benzene, were anhydrous A.R. grade (BDH) and were maintained in that state by storage over 4A molecular sieves. Reactions were initiated by rapid stirring and the rate of addition of the halide in ether was controlled to maintain gentle reflux. After complete addition the mixture was heated under reflux for 10 min, cooled, and then transferred with a syringe fitted with a coarse filter through a serum cap into a stirred solution at 0–5° of the sulfinate in dry benzene (50 ml of solvent per $0 \cdot 005$ mol of sulfinate). The original flask was rinsed with a little additional ether and this too was transferred to the sulfinate solution with the syringe. In all cases, on addition of the Grignard solution a colourless precipitate formed. The mixture was stirred under nitrogen overnight and then decomposed carefully with 20% aqueous ammonium chloride. On stirring the precipitate dissolved. The organic layer was separated, washed with sat. NaCl, dried (MgSO$_4$), and the solvent removed on a rotary evaporator. The crude product was examined by t.l.c. and ^{1}H n.m.r. and then chromatographed over silica gel under medium pressure.

Use of Approximately Equimolar Amounts of Grignard Reagent and Sulfinate

In practice a 10% excess of the Grignard reagent was used to offset slight losses due to coupling or decomposition.

The reaction between methylmagnesium iodide and (S)-(1b) gave a crude product which, by t.l.c. (benzene), showed the presence of 2-methoxynaphthalene (R_F $0 \cdot 9$), a trace of starting material (R_F $0 \cdot 8$), menthol (R_F $0 \cdot 7$) and the desired sulfoxide (R_F $0 \cdot 15$). Chromatography, with benzene as eluent, allowed the recovery of 96% of the menthol and (+)-(R)-*2-methoxy-1-naphthyl methyl sulfoxide* (1c) (67% yield), which crystallized from light petroleum in colourless needles, m.p. 106–107° (Found: C, $65 \cdot 3$; H, $5 \cdot 6$. C$_{12}$H$_{12}$O$_2$S requires C, $65 \cdot 4$; H, $5 \cdot 5$%). [α] $+181 \cdot 4$ (589 nm), $+192 \cdot 2$ (578), $+230 \cdot 2$ (546), $+559 \cdot 0$ (436) (c, $0 \cdot 0315$ in CHCl$_3$). ^{1}H n.m.r. δ (CDCl$_3$) $9 \cdot 03$, dd, J_{ortho} $8 \cdot 5$, J_{meta} $1 \cdot 5$ Hz, H 8; $7 \cdot 90$–$7 \cdot 16$, m, ArH; $3 \cdot 97$, s, OMe; $3 \cdot 06$, s, SOMe. ^{13}C n.m.r. δ (CDCl$_3$) $155 \cdot 9$ (Ar C 2), $134 \cdot 0$, $132 \cdot 0$, $129 \cdot 6$, $128 \cdot 8$, $127 \cdot 7$, $124 \cdot 4$, $122 \cdot 5$, $113 \cdot 0$ (Ar C 3), $56 \cdot 9$ (OMe), $39 \cdot 2$ (SOMe). ν_{max} (CHCl$_3$) 2957, 2924, 2842, 1621, 1585, 1504, 1465, 1269, 1248, 1149, 1135, 1041, 1022, 950 cm^{-1}. Mass spectrum m/z 220 (50%, M), 205 (100), 188 (21), 175 (13), 159 (18), 147 (30), 131 (45), 114 (20), 102 (15), 62 (16), 44 (29).

Similarly, from (R)-(1b), (−)-(S)-*2-methoxy-1-naphthyl methyl sulfoxide* (1c) was obtained in 69% yield as colourless needles from light petroleum, m.p. 106–107° (Found: C, $65 \cdot 1$; H, $5 \cdot 7$. C$_{12}$H$_{12}$O$_2$S requires C, $65 \cdot 4$; H, $5 \cdot 5$%). [α] $-178 \cdot 1$ (589 nm), $188 \cdot 4$ (578), $226 \cdot 4$ (546), $551 \cdot 2$ (436). Spectra of this compound were identical with those of the (+)-enantiomer above.

Use of ethyl 2-methoxynaphthalene-1-sulfinate[13] and methylmagnesium iodide gave *racemic 2-methoxy-1-naphthyl methyl sulfoxide* (1c) in 74% yield as colourless needles from light petroleum, m.p. 95–95·5° (Found: C, $65 \cdot 1$; H, $5 \cdot 6$. C$_{12}$H$_{12}$O$_2$S requires C, $65 \cdot 4$; H, $5 \cdot 5$%). Spectra were identical with those of the enantiomers.

Phenylmagnesium bromide and (S)-(1b) gave (+)-(R)-*2-methoxy-1-naphthyl phenyl sulfoxide* (1d) in 68% yield as colourless, feathery crystals from light petroleum, m.p. 100–100·5° (Found: C, $72 \cdot 2$; H, $5 \cdot 1$. C$_{17}$H$_{14}$O$_2$S requires C, $72 \cdot 3$; H, $5 \cdot 0$%). [α] $+241 \cdot 1$ (589 nm),

+253·1 (578), +294·7 (546), +610·1 (436) (c, 0·0109 in CHCl$_3$). ^{1}H n.m.r. δ (CDCl$_3$) 8·71, dd, J_{ortho} 9, J_{meta} 1·5 Hz, H 8; 7·99–7·20, m, ArH; 3·94, s, SOMe. ν_{max} (CHCl$_3$) 3010, 2957, 2924, 2843, 1620, 1593, 1505, 1468, 1271, 1249, 1150, 1034, 1024, 783 cm^{-1}. Mass spectrum m/z 282 (44%, M), 265 (57), 234 (100), 205 (15), 187 (21), 173 (26), 145 (21), 127 (37), 114 (31), 77 (26), 51 (38).

Racemic 2-methoxy-1-naphthyl phenyl sulfoxide (1d) was obtained from the ethyl ester as above in 76% yield as colourless needles from light petroleum, m.p. 120–120·5° (Found: C, 72·3; H, 5·0. C$_{17}$H$_{14}$O$_2$S requires C, 72·3; H, 5·0%). Spectra were identical with those of the (+)-isomer.

Reaction of (S)-(1b) with ethylmagnesium bromide gave (+)-(R)-*ethyl 2-methoxy-1-naphthyl sulfoxide* (1e), in 73% yield after chromatography, as a faintly yellow oil which could not be induced to crystallize. Satisfactory analytical data could not be obtained but t.l.c. (R_F 0·05 benzene, 0·25 CHCl$_3$) and spectra (following) showed the compound to be pure. [α] +191·2 (589 nm), +203·0 (578), +242·7 (546), 586·9 (436) (c, 0·0084 in CHCl$_3$). ^{1}H n.m.r. δ (CDCl$_3$) 9·10, dd, J_{ortho} 8·5, J_{meta} 1·5 Hz, H 8; 7·93–7·11, m, ArH; 3·94, s, OMe; 3·35, dq, J 7·5 Hz, CH$_2$CH$_3$; 1·27, t, J 7·5 Hz, CH$_2$CH$_3$. ^{13}C n.m.r. δ (CDCl$_3$) 156·2 (Ar C 2), 133·9, 132·7, 129·6, 128·7, 128·3, 127·6, 124·3, 122·8, 112·9 (Ar C 3), 56·9 (OMe), 46·5 (SOCH$_2$), 8·0 (CH$_2$CH$_3$). Mass spectrum m/z 234 (46%, M), 205 (100), 188 (15), 175 (17), 159 (18), 147 (32), 131 (31), 43 (28).

Attempted purification of (1e) by Kugelrohr distillation gave a volatile fraction (b.p. 220°/0·2 mm) which consisted of a little 2-methoxynaphthalene and the sulfide. Chromatography over silica gel and elution with light petroleum, followed by distillation, gave pure *ethyl 2-methoxy-1-naphthyl sulfide* (1g) as a colourless oil (Found: C, 71·9; H, 6·3; S, 14·5. C$_{13}$H$_{14}$OS requires C, 71·5; H, 6·5; S, 14·7%). ^{1}H n.m.r. δ (CDCl$_3$) 8·65, dd, J_{ortho} 8·5, J_{meta} 1·5 Hz, H 8; 7·83–7·08, m, ArH; 3·95, s, OMe; 2·86, q, J 7·5 Hz, SCH$_2$CH$_3$; 1·14, t, J 7·5 Hz, CH$_2$CH$_3$. Mass spectrum m/z 218 (100%, M), 203 (11), 189 (13), 161 (15), 143 (18), 128 (15), 115 (33). The non-volatile residue from the distillation consisted of a little sulfoxide (1e), the sulfide (1g) but mostly the sulfone (1h), identified by comparison (t.l.c., n.m.r.) with an authentic sample.[18] Small amounts of other unidentified components were present.

From (S)-(1b) and isopropylmagnesium bromide was obtained in 77% yield (R)-*isopropyl 2-methoxy-1-naphthyl sulfoxide* (1f) as a faintly yellow oil which did not crystallize. Satisfactory microanalyses were not obtained but t.l.c. (R_F 0·05 benzene, 0·2 CHCl$_3$) and spectra (following) showed the compound to be pure. [α] +176·0 (589 nm), +186·5 (578), +221·9 (546), +510·9 (436) (c, 0·0133 in CHCl$_3$). ^{1}H n.m.r. δ (CDCl$_3$) 8·93, dd, J_{ortho} 8·5, J_{meta} 1·5 Hz, H 8; 7·96–7·17, m, ArH; 4·01–3·74, m, SOCHMe$_2$; 3·96, s, OMe; 1·52, 1·02, both d, J 7 Hz, CH(CH$_3$)$_2$. Mass spectrum m/z 248 (14%, M), 206 (100), 191 (32), 158 (20), 85 (63), 83 (98).

(+)-(R)-*2,7-Dimethoxy-1-naphthyl methyl sulfoxide* (2c) was obtained in 73% yield from (2b) as a colourless oil (Found: C, 62·3; H, 6·1. C$_{13}$H$_{14}$O$_3$S requires C, 62·4; H, 5·6%). [α] +100·4 (589 nm), +106·8 (578), +127·2 (546), +303·0 (436). ^{1}H n.m.r. δ (CD$_3$SOCD$_3$) 8·54, dd, J_{meta} 2 Hz, H 8; 8·02, d, J_{ortho} 9 Hz, ArH; 7·88, d, J_{ortho} 9 Hz, ArH; 7·32, d, J_{ortho} 9 Hz, ArH; 7·10, dd, J_{meta} 2, J_{ortho} 9 Hz, H 6; 3·96, 3·85, both s, 2×OMe; 3·00, s, SOMe. Mass spectrum m/z 250 (60%, M), 235 (100), 218 (11), 204 (29), 203 (33), 189 (10), 177 (12), 161 (20), 156 (11), 145 (8).

Reaction of (3b) with methylmagnesium iodide gave (+)-(R)-*4-methoxy-1-naphthyl methyl sulfoxide* (3c) in 81% yield as a colourless oil after chromatography (Found: C, 65·8; H, 5·8. C$_{12}$H$_{12}$O$_2$S requires C, 65·4; H, 5·5%). [α] +326·5 (589 nm), +343·6 (578), +402·6 (546), +832·2 (436) (c, 0·0110 in CHCl$_3$). ^{1}H n.m.r. δ (CDCl$_3$) 8·45–8·26, m, ArH; 8·05, d, J_{ortho} 8 Hz, Ar H 2; 7·94–7·84, m, ArH; 7·57–7·47, m, ArH; 6·93, d, J_{ortho} 8 Hz, Ar H 3; 3·98, s, OMe; 2·77, s, SOMe. ^{13}C n.m.r. δ (CDCl$_3$) 157·9 (Ar C 4), 132·2, 129·6, 127·7, 125·9, 125·6, 123·5, 123·3, 121·2, 103·7 (Ar C 3), 55·8 (OMe), 43·0 (SOMe). Mass spectrum m/z 220 (31%, M), 205 (100), 189 (12), 174 (27), 152 (12), 83 (32), 47 (48), 43 (32).

Use of an Excess of Grignard Reagent

Reaction of (R)-(1b) with 4 mol. equiv. of methylmagnesium iodide gave a crude product showing (t.l.c., benzene) the absence of starting material (R_F 0·65) and (1c) (R_F 0·05),

and the presence of 2-methoxynaphthalene (R_F 0·75) and the phenolic component (R_F 0·2). The latter could be isolated directly by base extraction followed by acidification but it was accompanied by a difficult-to-remove coloured impurity and it was preferable to chromatograph the crude product before base extraction. In this way (−)-(S)-*1-methylsulfinyl-2-naphthol* (1i) was obtained in 59% yield as colourless, long (some more than 3 cm), needles from light petroleum, m.p. 112–113° (Found: C, 64·5; H, 4·9. $C_{11}H_{10}O_2S$ requires C, 64·1; H, 4·9%). [α] −403·6 (589 nm), −422·8 (578), −489·3 (546), −904·8 (436) (c, 0·0102 in $CHCl_3$). ^{1}H n.m.r. δ (CD_3SOCD_3) 8·03–7·12, m, ArH; 3·07, s, SOMe. ν_{max} ($CHCl_3$) 3100–2700, 3015, 2957, 1623, 1597, 1464, 1269, 1239, 1132, 1010, 990, 957 cm^{-1}. Mass spectrum m/z 206 (62%, M), 191 (100), 163 (22), 147 (15), 115 (29), 102 (10). Early fractions from the column gave 2-methoxynaphthalene (28% yield) and menthol (93% recovery).

Similarly, (S)-(1b) gave (+)-(R)-*1-methylsulfinyl-2-naphthol* (1i) in 60% yield as long, colourless needles from light petroleum, m.p. 113–113·5° (Found: C, 64·3; H, 5·1. $C_{11}H_{10}O_2S$ requires C, 64·1; H, 4·9%). [α] +402·0 (589 nm), +421·3 (578), +487·1 (546), +901·2 (436) (c, 0·0143 in $CHCl_3$). Spectra were identical with those of the (−)-isomer. Use of 2 mol. equiv. of the Grignard reagent gave a mixture of (1c) 56%, (1i) 25%, and 2-methoxynaphthalene 6%.

When sulfoxide (R)-(1c) was treated with 2 mol. equiv. of methylmagnesium iodide, (R)-(1i) was obtained (66% yield) together with some 2-methoxynaphthalene (19%).

When 2-methoxynaphthalene was treated with 4 mol. equiv. of methylmagnesium iodide it was recovered unchanged in 98% yield.

The dimethoxy sulfinate (S)-(2b) on treating with 2 mol. equiv. of methylmagnesium iodide gave (R)-(2c) (42% yield), a little 2,7-dimethoxynaphthalene, and (+)-(R)-*7-methoxy-1-methylsulfinyl-2-naphthol* (2i) in 35% yield as colourless, flat needles from light petroleum, m.p. 76° (Found: C, 60·8; H, 5·1. $C_{12}H_{12}O_3S$ requires C, 61·0; H, 5·1%). [α] +438·0 (589 nm), +460·4 (578), +536·9 (546), +1070 (436) (c, 0·0117 in $CHCl_3$). ^{1}H n.m.r. δ (CD_3SOCD_3) 7·90, d, J_{ortho} 6 Hz, ArH; 7·80, d, J_{ortho} 6 Hz, ArH; 7·65, d, J_{meta} 2·5 Hz, H 8; 7·07, dd, J_{ortho} 9, J_{meta} 2·5 Hz, H 6; 6·98, d, J_{ortho} 9 Hz, ArH; 3·87, s, OMe; 3·07, s, SOMe. ν_{max} ($CHCl_3$) 3100–2705, 3015, 2957, 2842, 1618, 1597, 1270, 1238, 1130, 1010 cm^{-1}. Mass spectrum m/z 236 (52%, M), 221 (100), 193 (20), 190 (21), 177 (12), 161 (16), 145 (41), 133 (18), 115 (17), 102 (32), 89 (36), 75 (30). Use of 4 mol. equiv. of the same Grignard reagent gave (2i) in 61% yield together with 2,7-dimethoxynaphthalene (19%).

From ethyl 2-methoxynaphthalene-1-sulfinate and 4 equiv. of phenylmagnesium bromide *racemic 1-phenylsulfinyl-2-naphthol* (1j) was obtained in 65% yield as colourless needles from light petroleum, m.p. 67·5–68° (Found: C, 71·6; H, 5·0. $C_{16}H_{12}O_2S$ requires C, 71·6; H, 4·5%). ^{1}H n.m.r. δ (CD_3SOCD_3) 7·85–7·42, m, ArH. ν_{max} ($CHCl_3$) 3400–3100, 3010, 2957, 1618, 1476, 1444, 1238, 1089, 1039, 1021 cm^{-1}. Early fractions from the column gave a 21% yield of 2-methoxynaphthalene.

Reaction of racemic (1d) with 4 equiv. of methylmagnesium iodide gave racemic (1j) in 72% yield accompanied by 2-methoxynaphthalene (19% yield). The ^{1}H n.m.r. spectrum of the crude product showed small peaks at δ 2·76 and 2·42 which were augmented on addition of samples of methyl phenyl sulfoxide and methyl phenyl sulfide respectively.

Sulfoxide (R)-(3c) on treating with 4 equiv. of methylmagnesium iodide gave a partly crystalline crude product. T.l.c. (benzene) showed no starting material and only one major spot (R_F 0·8). T.l.c. with light petroleum showed this spot to consist of a major component (R_F 0·38) and two trace components (R_F 0·1 and 0·05). Isolation of the major component by column chromatography gave 4-methoxy-1-naphthyl methyl sulfide (3k) as colourless crystals from light petroleum (79% yield), m.p. 66–67° (lit.^{25} 65–66°, EtOH). ^{1}H n.m.r. δ ($CDCl_3$) 8·40–8·21, m, ArH; 7·63–7·41, m, ArH; 6·67, d, J_{ortho} 8 Hz, Ar H2; 3·90, s, OMe; 2·42, s, SMe. ^{13}C n.m.r. δ ($CDCl_3$) 155·1 (Ar C1), 132·5, 128·8, 126·9, 126·2, 125·7, 125·4, 124·9, 122·6, 103·9 (Ar C2), 55·4 (OMe), 18·5 (SMe). Mass spectrum m/z 204 (93%, M), 189 (100), 161 (18), 146 (20), 145 (19), 102 (24).

^{25} Srinivasan, C., Perumal, S., and Arunugam, N., *J. Chem. Soc., Perkin Trans. 2*, 1984, 2065.