

Sulphoxides. Part II.¹ Stereochemistry of the γ -Disulphoxides 2,5-Dithiahexane 2,5-Dioxide and 1,4-Diphenyl-1,4-dithiabutane 1,4-Dioxide

By Hugo Nieuwenhuys and Robert Louw,* Gorlaeus Laboratoria, The University, P.O. Box 75, Leiden, The Netherlands

* Andersen γ -type synthesis of 2,5-dithiahexane 2,5-dioxide (1) and 1,4-diphenyl-1,4-dithiabutane 1,4-dioxide (2), from di-(-)-menthyl ethane-1,2-disulphinate (3) and the appropriate Grignard reagents, yielded higher melting (or α -) *meso*- (1) and *meso*- (2) and optically active lower melting (β -) (1) and (2). The absolute rotation of compound (1) was determined by the isotopic dilution method (and found to be extremely high), the ¹H n.m.r. spectra of optically active (1) in (-)-2,2,2-trifluoro-1-phenylethanol not being decisive for the determination of its optical purity.

Soon after the first publication on optically active sulphoxides,² disulphoxides received a great deal of

¹ Part I, H. Nieuwenhuys and R. Louw, *Tetrahedron Letters*, 1971, 4141.

² P. W. B. Harrison, J. Kenyon, and H. Phillips, *J. Chem. Soc.*, 1926, 2079.

attention in studies by Bell and Bennett.³ These workers isolated the diastereomeric forms of several

³ E. V. Bell and G. M. Bennet, *J. Chem. Soc.*, 1927, 1798; 1928, 3189; 1929, 15; 1930, 1; G. M. Bennett and F. S. Statham, *ibid.*, 1931, 1684; H. Baw, G. M. Bennett, and P. Dearn, *ibid.*, 1934, 680.

disulphoxides; assignment was achieved only if a suitable functional group, *e.g.* an acid function, was present in the molecule. In 1959 Farina *et al.*,⁴ succeeded in assigning the diastereomers of a number of 1,2-bis(arylsulphinyl)ethylenes by chromatography over activated lactose, the (\pm)-pairs being partially resolved. More recently, we assigned the *meso*- and (\pm)-diastereomers of 2,4-dithiapentane 2,4-dioxide (5) on the basis of their ¹H n.m.r. spectra.^{5,*} In addition, preliminary results obtained in the asymmetric oxidation of 2,5-dithiahexane made us conclude that the higher-melting form of 2,5-dithiahexane 2,5-dioxide [α -(1)] is the (\pm)-pair;⁵ the present work proves that this compound is in fact *meso*-(1).



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|-------------------------------------|----------------------------|
| (1) $n = 2$, R = Me | (4) $n = 2$, R = Cl |
| (2) $n = 2$, R = Ph | (5) $n = 1$, R = Me |
| (3) $n = 2$, R = O (-)-
menthyl | (6)–(8) $n = 3$ –5, R = Me |

α = higher-melting, β = lower-melting diastereoisomer

RESULTS AND DISCUSSION

Optically active methyl sulphoxides are conveniently prepared from (–)-menthyl methanesulphinate.⁷ As our attempts to prepare compound (1) from this ester failed,[†] we have used di-(–)-menthyl ethane-1,2-disulphinate (3), obtained as a non-distillable oil from ethane-1,2-disulphinyl chloride⁸ (4) and (–)-menthol. Reaction of compound (3) with methylmagnesium iodide or phenylmagnesium bromide in ether afforded the crude disulphoxides (1) and (2), respectively. After fractional crystallisation, the α -forms of both exhibited negligible optical rotations. However, β -(1) had $[\alpha]_D^{20} +226^\circ$ and β -(2) had $[\alpha]_D^{20} +278^\circ$.[‡]

Consequently, in both cases the α -form is the *meso*-diastereoisomer.[§] For compound (1), this assignment contradicts our earlier conclusion based on the (+)-(1S)-monoperacamporic acid oxidation of 2,5-dithiahexane.⁵ Repetition of this oxidation in diethyl ether at -40° , purification by chromatography over alumina, and fractional crystallisation of the resulting disulphoxide mixture yielded three fractions: (i) optically inactive α -(1) (m.p. 165–166°), (ii) β -(1) (m.p. 128–131°, $[\alpha]_D^{20}$

-4.7°), and (iii) β -(1) (m.p. 118–120°, $[\alpha]_D^{20} -86.7^\circ$). Apparently, β -(1) forms a racemic compound, less soluble (and higher melting) than (+)- or (–)-(1). In our earlier experiment⁵ we isolated only the racemate, m.p. 128–130°.

To the best of our knowledge, (+)-(1) constitutes the first reported aliphatic disulphoxide showing high optical activity. We were therefore interested in the absolute rotation of this compound. Optically active 2,2,2-trifluoro-1-phenylethanol is well suited for use in the determination of the optical purity and the absolute configuration of sulphoxides.¹¹ The ¹H n.m.r. spectrum of *meso*-(1) together with (–)-2,2,2-trifluoro-1-phenylethanol in deuteriochloroform revealed the non-equivalence of the methyl protons (δ 2.02 and 2.06 p.p.m.). Unfortunately, the methyl proton absorptions in racemic and optically active (1) remain sharp singlets under these conditions. Neither the methine proton absorption nor the ¹⁹F n.m.r. spectra of the chiral solvent gave any information about the optical purity of (1); neither did variation of the co-solvent (carbon tetrachloride, hexadeuteriobenzene, or nitrobenzene). This behaviour, however, is not general for disulphoxides. We measured the ¹H n.m.r. spectra of compounds (5)–(8) together with (–)-2,2,2-trifluoro-1-phenylethanol in deuteriochloroform or carbon tetrachloride. In all cases, the methyl protons are non-equivalent ($\Delta\delta$ 0.01–0.04 p.p.m.). The central methylene protons of (\pm)-(5) exhibit a singlet in deuteriochloroform;⁵ as expected, two absorptions ($\Delta\delta$ 0.02 p.p.m.) are observed in the chiral solvent. The corresponding AB quartet of *meso*-(5) remains essentially unchanged.

Therefore, we decided to apply the isotopic dilution method.^{12,13} Thus, [3-¹⁴C]-(1) was prepared from 1,2-dibromo[¹⁴C]ethane. After fractional crystallisation (\pm)-[¹⁴C]-(1) with specific activity 1.981×10^6 disint. min⁻¹ mmol⁻¹ was obtained. This material was added to optically active (1) and the mixture was recrystallised twice. The specific activity and rotation were determined and the absolute rotation of (1) was found to be $225 \pm 8^\circ$. The highest observed specific rotation was 226° ; consequently, this material had an optical purity $\geq 97\%$. In general, aliphatic monosulphoxides exhibit much smaller absolute rotations.⁹

* Green and Shevlin⁶ applied tris(dipivaloylmethanato)-europium for the comparable diastereomeric assignment of the bis(phenylsulphinyl)methanes. The same result (splitting of the signal due to the central methylene group) can simply be obtained by using trifluoroacetic acid as solvent.

† The Grignard reagent MeS·CH₂·CH₂MgX should react with (–)-menthyl methanesulphinate to produce optically active 2,5-dithiahexane 2-oxide, which could be oxidised to (1). However, neither 2-bromoethyl methyl sulphide nor 2-chloroethyl methyl sulphide reacted with magnesium under a wide variety of reaction conditions. Attempted preparations of the corresponding lithium compounds were not successful either.

‡ The predominant diastereomers produced in the asymmetric synthesis of menthyl sulphinates have the *R*-configuration at sulphur.⁹ Consequently, (+)-(1) is expected to be the *S,S*- and (+)-(2) the *R,R*-enantiomer.

§ For compound (2), Cinquini *et al.*¹⁰ arrived at the same assignment by partial resolution of the lower-melting diastereomer.

⁴ G. Farina, F. Montanari, and A. Negrini, *Gazzetta*, 1959, **89**, 1548.

⁵ R. Louw and H. Nieuwenhuysse, *Chem. Comm.*, 1968, 1561.

⁶ J. L. Greene, jun., and P. B. Shevlin, *Chem. Comm.*, 1971, 1092.

⁷ K. K. Andersen, W. Gaffield, N. E. Papanikolaou, J. W. Foley, and R. I. Perkins, *J. Amer. Chem. Soc.*, 1964, **86**, 5637; K. K. Andersen, *J. Org. Chem.*, 1964, **29**, 1953.

⁸ I. B. Douglass, B. S. Farah, and E. G. Thomas, *J. Org. Chem.*, 1961, **26**, 1996.

⁹ K. Mislow, M. M. Green, P. Laur, J. T. Melillo, T. Simmons, and A. L. Ternay, jun., *J. Amer. Chem. Soc.*, 1965, **87**, 1958.

¹⁰ M. Cinquini, S. Colonna, and F. Taddei, *Boll. sci. Fac. Chim. ind. Bologna*, 1969, **27**, 231.

¹¹ W. H. Pirkle and S. D. Beare, *J. Amer. Chem. Soc.*, 1968, **90**, 6250.

¹² M. Raban and K. Mislow, *Topics Stereochem.*, 1967, **2**, 199.

¹³ J. A. Berson and D. A. Ben Efraim, *J. Amer. Chem. Soc.*, 1959, **81**, 4083.

EXPERIMENTAL

N.m.r. spectra were recorded with a Varian HA100 spectrometer (tetramethylsilane as internal standard). Optical rotations were measured with a Bendix NPL Automatic Polarimeter model 143 D. Radioactive 1,2-dibromomethane was purchased from the Radiochemical Centre, Amersham. Radioactivity measurements were performed with a Packard Tri-carb 3310 Liquid Scintillation Spectrometer.

Di-(-)-menthyl Ethane-1,2-disulphinate (3).—This was prepared from ethane-1,2-disulphinyl chloride⁸ (4) (25 g) and (-)-menthol (40 g) in ether (500 ml) and pyridine (53 ml) at -60° as described for (-)-menthyl methane-sulphinate,⁷ and obtained (49.3 g, 87%) as an oil, $[\alpha]_D^{20} -75.0^\circ$ (*c* 1.2 in EtOH), ν_{\max} (neat) 1128 cm⁻¹ (S=O str.); δ 3.01 ([CH₂]₂); equiv. wt. found 220, 223; calc. 217.

(+)-2,5-Dithiahexane 2,5-Dioxide (1).—To the Grignard reagent prepared from methyl iodide (6.0 g) and magnesium (0.97 g) in ether (40 ml) was added dropwise a solution of compound (3) (6.5 g) in ether (20 ml). The precipitate was filtered off, washed with ether, and dissolved in water (25 ml). The aqueous solution was filtered, neutralised with dil. hydrochloric acid, and evaporated. The residue was extracted with 1:1 ethanol-chloroform; the extract was dried and evaporated and the residue was chromatographed over alumina (eluant chloroform-methanol, 9:1). Fractional crystallisation from ethanol and ethyl acetate gave *meso*-(1) (0.3 g), m.p. 158–162° (lit.,³ 163–164°), $[\alpha]_D^{20} < 2^\circ$, several mixed fractions, and (\pm)-(1) (0.2 g), m.p. 117–119° [lit.,³ for β -(1), 128–130°], $[\alpha]_D^{20} 226^\circ$ (*c* 0.34 in EtOH).

(+)-1,4-Diphenyl-1,4-dithiabutane 1,4-Dioxide (2).—Compound (3) (15 g) in ether (50 ml) was added to the Grignard reagent prepared from bromobenzene (18.8 g) and magnesium (2.9 g) in ether (150 ml). The mixture was then stirred for another 5 min and poured into an excess of aqueous ammonium chloride. The ethereal layer was separated and extracted three times with water (50 ml). The combined water layers were extracted with chloroform (5 × 100 ml). The chloroform solution was dried and evaporated. The residue was crystallised from toluene. Two kinds of crystals formed, which were filtered off and separated mechanically to give *meso*-(2) (45 mg), m.p. 157–163° (lit.,³ 166°), $[\alpha]_D^{20} < 0.1^\circ$ and (+)-(2) (23 mg), m.p. 123–124° [lit.,³ for β -(2) 123°], $[\alpha]_D^{20} 278^\circ$ (*c* 0.4 in EtOH).

(-)-2,2,2-Trifluoro-1-phenylethanol.—This was prepared by the method of Pirkle *et al.*,¹⁴ and had $[\alpha]_D^{20} -31.2^\circ$ (*c* 1.8 in CHCl₃) [lit.,¹¹ $[\alpha]_D^{20} -40.8$ (neat)].

¹⁴ W. H. Pirkle, S. D. Beare, and T. G. Burlingame, *J. Org. Chem.*, 1969, **34**, 470.

¹⁵ J. H. Parmentier and F. E. L. ten Haaf, *Internat. J. Appl. Radiation Isotopes*, 1969, **20**, 305.

¹⁶ E. T. Bush, *Analyt. Chem.*, 1963, **35**, 1024.

The Disulphoxides (6)–(8) and [3-¹⁴C]-(1).—These were prepared from the corresponding $\alpha\omega$ -dibromoalkanes by treatment with alcoholic sodium methanethiolate and oxidation of the resulting dithioethers with hydrogen peroxide.

Determination of the Absolute Rotation of the Disulphoxide (1).—In a typical experiment (\pm)-[¹⁴C]-(1) (0.11378 g; spec. activity 1.981×10^6 disint. min⁻¹ mmol⁻¹) was mixed with (+)-(1) (0.05759 g; $[\alpha]_D^{20} +204.3^\circ$). After two recrystallisations, material was obtained with $[\alpha]_D^{20} 15.5^\circ$, spec. activity 1.420×10^6 disint. min⁻¹ mmol⁻¹. Hence,¹⁴ $[\alpha]_{\max} =$

$$\left[\frac{1.420 \times (0.05759)^2 \times (204.3)^2 - 1.981 \times 0.11378 \times 0.05759 \times 204.3 \times 15.5}{1.420 \times (0.05759 + 0.11378)^2 - 1.981 \times 0.11378 \times (0.11378 + 0.05759)} \right]^{1/2} = 225 \pm 8^\circ$$

The radioactivity measurements were carried out by liquid scintillation counting.¹⁵ The weighed samples were dissolved in methanol (0.5 ml) and scintillation liquid (15 ml) [2,5-diphenyloxazole (5 g) and 1,4-bis-(4-methyl-5-phenyloxazol-2-yl)benzene (0.3 g) per litre of toluene]. The efficiency of the measurements was computed by the channel ratio method.¹⁶ Specific activities quoted are mean values of five measurements; the reproducibility was $\pm 0.8\%$. The error in the absolute rotation was computed by standard methods.

Asymmetric Oxidation of 2,5-Dithiahexane.¹⁷—(+)-(1S)-Monoperacamporic acid¹⁸ (100 mmol) in ether (250 ml) was added dropwise to 2,5-dithiahexane (47 mmol) in ether (250 ml) at -40°. The precipitated crude disulphoxide was filtered off and chromatographed over alumina (chloroform-methanol, 9:1). The collected fractions containing (1) were evaporated and the residue was crystallised from ethanol. After five recrystallisations, *meso*-(1), $[\alpha]_D^{20} < 0.1^\circ$, m.p. 165–166°, was obtained. Crystallisation of the evaporated mother liquors from ethyl acetate and toluene yielded two fractions of optically active β -(1) with i.r. spectra identical with that of authentic β -(1) from the hydrogen peroxide oxidation of 2,5-dithiahexane. The highest-rotation fraction had $[\alpha]_D^{20} -86.7^\circ$ (*c* 0.4 in MeOH) and m.p. 118–120°.

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¹⁷ U. Folli, D. Iarossi, F. Montanari, and G. Torre, *J. Chem. Soc. (C)*, 1968, 1317.

¹⁸ N. A. Milas and A. McAlevy, *J. Amer. Chem. Soc.*, 1933, **55**, 349.