

**1095.** (–)-Benzyl *p*-Tolyl [<sup>16</sup>O<sup>18</sup>O]Sulphone: A New Example of Optical Activity due to Isotopic Dissymmetry.

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Oxidation of (+)-benzyl *p*-tolyl sulphoxide with [<sup>16</sup>O·<sup>18</sup>O<sup>18</sup>OH]peracetic acid gives (–)-benzyl *p*-tolyl [<sup>16</sup>O<sup>18</sup>O]sulphone, to which the absolute configuration has been tentatively assigned.

OPTICAL activity in compounds of the type Xabcd in which a and b are isotopes has hitherto been observed<sup>1,2</sup> only when X is carbon and a and b are protium and deuterium, respectively. Synthesis of such compounds requires resolution, asymmetric induction,<sup>1</sup> or stereospecific synthesis with an enantiomer in which one of the isotopes is already in place.<sup>2</sup> The present paper reports the use of the third approach to the synthesis of (–)-benzyl *p*-tolyl [<sup>16</sup>O<sup>18</sup>O]sulphone.

The reaction sequence is shown in the scheme. Treatment of (–)-menthyl (–)-toluene-*p*-sulphinic acid with benzylmagnesium chloride gave (+)-benzyl *p*-tolyl sulphoxide, m. p. 169–170°, [ $\alpha$ ]<sub>D</sub> +252°, which was readily obtained optically pure by repeated recrystallisations (optical rotatory dispersion and circular-dichroism values are given in the Experimental section). This valuable method for the preparation of optically active sulphoxides had previously been used by Andersen<sup>3</sup> for the synthesis of (+)-ethyl *p*-tolyl sulphoxide and it had the advantage in the present work that no other groups, necessary for resolution, were present to interfere with oxidation in the second stage of the synthesis. [<sup>16</sup>O·<sup>18</sup>O<sup>18</sup>OH]Peracetic acid was prepared by treatment of aqueous acetic acid with sodium [<sup>18</sup>O<sup>18</sup>O]peroxide obtained from the reaction of <sup>18</sup>O<sub>2</sub> with a sodium film<sup>4</sup> at 260°. Oxygen-isotope studies have shown<sup>5</sup> that oxygen–oxygen bond fission is not involved in the equilibration of water with per-acids, and the isotopically enriched per-acid

<sup>1</sup> Streitwieser and Wolfe, *J. Amer. Chem. Soc.*, 1959, **81**, 4912, and previous papers.

<sup>2</sup> Eliel, *J. Amer. Chem. Soc.*, 1949, **71**, 3970.

<sup>3</sup> Andersen, *Tetrahedron Letters*, 1962, 93.

<sup>4</sup> Cf. Anbar, *J. Amer. Chem. Soc.*, 1961, **83**, 2031.

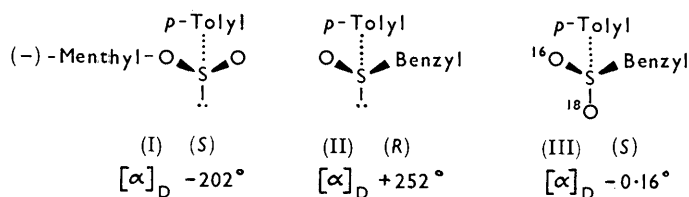
<sup>5</sup> Bunton, Lewis, and Llewellyn, *J.*, 1956, 1226.

was used to oxidise the (+)-sulphoxide. Unchanged sulphoxide present in the resulting sulphone was removed by reduction with buffered titanous chloride. Barnard and Hargrave<sup>6</sup> have shown that this reduction is quantitative and that sulphones are unaffected. This has been confirmed in the present work by reductions of mixtures of benzyl *p*-tolyl sulphone and the optically active sulphoxide. After this purification, the isotopically labelled sulphone had  $[\alpha]_D - 0.16^\circ \pm 0.05^\circ$ . A blank experiment with isotopically normal peracetic acid gave sulphone with  $[\alpha]_D = 0.00^\circ \pm 0.05^\circ$ .

Blank experiments with the optically active sulphoxide showed that racemisation did not occur under the conditions of oxidation or at the pH of the titanous reduction. It has been assumed, therefore, that the isotopically labelled sulphone is also optically stable under these conditions. Disproportionation of certain sulphoxides to mixtures of sulphide and sulphone has been observed,<sup>7</sup> but both disproportionation and autoxidation during oxidation of the sulphoxide have been excluded in the present work.

Replacement of <sup>16</sup>O by <sup>18</sup>O in diphenyl sulphone has recently been shown<sup>8</sup> to cause shifts in the asymmetrical (1310 cm.<sup>-1</sup>) and symmetrical (1160 cm.<sup>-1</sup>) S=O stretching bands of the infrared spectrum, of 35 and 22 cm.<sup>-1</sup>, respectively. The infrared spectra of the normal and the labelled benzyl *p*-tolyl sulphones show differences only in the region between 1350 and 1050 cm.<sup>-1</sup>, but owing to the multiplicity of bands (Table 2) in this region, the isotopic shift cannot be estimated with certainty. The shifts of the strongest band in the asymmetrical and the symmetrical S=O stretching region are 32 and 8 cm.<sup>-1</sup>, respectively, and a strong band at 1091 cm.<sup>-1</sup> for the normal sulphone is displaced to 1076 cm.<sup>-1</sup> in the labelled sulphone. Accurate measurement of the isotopic content of <sup>18</sup>O-containing sulphones is very difficult,<sup>9</sup> but infrared spectroscopic determinations show that the labelled sulphone contains not less than 80% of Ph·CH<sub>2</sub>·S[<sup>16</sup>O<sup>18</sup>O]·C<sub>6</sub>H<sub>4</sub>Me.

*Absolute Configurations.*—(–)-Menthyl (–)-toluene-*p*-sulphinic acid probably has the *S*-configuration (I).<sup>10</sup> Reaction with the Grignard reagent involves rearside nucleophilic attack leading to inversion of configuration and formation of the (*R*)-sulphoxide<sup>3</sup> in



agreement with other studies.<sup>11</sup> Per-acid oxidation of sulphoxides is bimolecular<sup>12</sup> and probably involves nucleophilic attack by the sulphur atom at the hydroxyl-oxygen of the per-acid.<sup>12,13</sup> The labelled sulphone is therefore tentatively assigned the (*S*)-configuration (III).

#### EXPERIMENTAL

The light petroleum used had b. p. 40–60°. Rotations were determined for the sodium D line and a 1 dm. tube at 18°, unless otherwise stated.

Racemic benzyl *p*-tolyl sulphoxide was prepared both by the peracetic acid oxidation of benzyl *p*-tolyl sulphide and by treatment of ethyl toluene-*p*-sulphinic acid with benzylmagnesium

<sup>6</sup> Barnard and Hargrave, *Analyt. Chim. Acta*, 1951, **5**, 536.

<sup>7</sup> U.S.P. 2,870,215; Kader and Stirling, unpublished work.

<sup>8</sup> Pinchas, Samuel, and Weiss-Brodsky, *J.*, 1962, 3968.

<sup>9</sup> Dr. D. Samuel, personal communication.

<sup>10</sup> Herbrandson and Cusano, *J. Amer. Chem. Soc.*, 1961, **83**, 2124.

<sup>11</sup> Maccioni, Montanari, Secci, and Tramontini, *Tetrahedron Letters*, 1961, 607; Mayr, Montanari, and Tramontini, *Gazzetta*, 1960, **90**, 739; Balenovic, Bregovec, Francetic, Monkovic, and Tornasic, *Chem. and Ind.*, 1961, 469.

<sup>12</sup> Cerniani and Modena, *Gazzetta*, 1959, **89**, 834.

<sup>13</sup> Davies, "Organic Peroxides," Butterworths, London, 1961.

chloride by a procedure similar to that given below for the (+)-sulphoxide. Both samples had m. p. 140—141° (lit.,<sup>14</sup> 136—137°). Benzyl *p*-tolyl sulphone was obtained both by permanganate oxidation of benzyl *p*-tolyl sulphide and on reaction of benzyl chloride with sodium toluene-*p*-sulphinic acid in ethanol. Both samples had m. p. 146—147° (lit.,<sup>15</sup> 144—145°).

The titanous chloride used was a 15% aqueous solution (B.D.H.).

*Ethyl Toluene-p-sulphinic acid*.—The following procedure is superior to the recorded methods.<sup>16</sup> Toluene-*p*-thiol (49.6 g.) in dry methylene chloride (480 ml.) containing acetic acid (24 g.) was cooled to 0°. Chlorine was bubbled slowly through the solution which gradually became dark orange, and passage of chlorine was continued until the colour faded and chlorine appeared in the effluent gas (starch-iodide). Solvent was removed *in vacuo* (20 mm.) at >40°, and the residue of toluene-*p*-sulphinyl chloride<sup>17</sup> in dry ether (50 ml.) was added to ethanol (27.6 g.) in ether (400 ml.). The solution was kept over anhydrous potassium carbonate (84 g.) until evolution of carbon dioxide had ceased (3 hr.), then water was added and the ethereal layer was separated and dried (K<sub>2</sub>CO<sub>3</sub>). Evaporation and distillation of the residue gave the ester (52.6 g., 72% from the thiol), b. p. 88°/0.15 mm.,  $n_D^{20}$  1.5341 (lit.,<sup>16</sup> b. p. 99—104°/0.1 mm.,  $n_D^{15}$  1.5306).

The ester was converted into (-)-menthyl toluene-*p*-sulphinic acid by Phillips's<sup>16</sup> method. The product had m. p. 105—106°,  $[\alpha]_D^{20}$  -202° (*c* 2 in acetone) {lit.,<sup>3</sup>  $[\alpha]_D^{21}$  -201° (*c* 2 in acetone)}.

(+)-Benzyl *p*-Tolyl Sulphoxide.—Benzyl chloride (6.5 g., 1.35 mol.) and magnesium (1.35 g., 1.45 g.-equiv.) were allowed to react in ether. The mixture was filtered and added to a refluxing solution of (-)-menthyl (-)-toluene-*p*-sulphinic acid (11.07 g., 1 mole) during 20 min. The mixture was refluxed for a further 30 min. and poured into saturated aqueous ammonium chloride at 0°. The mixture was filtered and the residue was taken up in methylene chloride. Evaporation of the combined methylene chloride and ethereal solutions gave a residue which, on extraction with boiling light petroleum (2 × 250 ml.), gave the sulphoxide (7.32 g., 84%), m. p. 169—169.5°, which was recrystallised from ethanol to constant m. p. (169—170°) and rotation  $\{[\alpha]_D = 252^\circ$  (*c* 1 in acetone)} (Found: C, 73.4; H, 6.3. C<sub>14</sub>H<sub>14</sub>OS requires C, 73.0; H, 6.1%). The infrared spectrum (5% solution in chloroform) was identical with that of the racemic sulphoxide. Optical rotatory dispersion and circular dichroism data are given in Table 1.

The removal of traces of menthol and of menthyl toluene-*p*-sulphinic acid from the sulphoxide before recrystallisation was established as follows: equal weights of the racemic sulphoxide and either (-)-menthol or (-)-menthyl toluene-*p*-sulphinic acid were mixed together and extracted with boiling light petroleum as in the preparation of the active sulphoxide. The rotation of each specimen of recovered sulphoxide was then determined. In the experiment with menthol

TABLE 1.

Ultraviolet absorption, circular dichroism, and optical rotatory dispersion of (+)-benzyl <i>p</i> -tolyl sulphoxide.							
$\lambda$ (m $\mu$ )	$\epsilon$	$\Delta\epsilon$	$10^{-2}\phi$	$\lambda$ (m $\mu$ )	$\epsilon$	$\Delta\epsilon$	$10^{-2}\phi$
210	—	-16	—	300	10	0	+100
220	—	-38 (min.)	—	400	—	—	+15
233	—	0	—	500	—	—	+9
250	4000 (max.)	+26 (max.)	—	600	—	—	+3
270	1400	+10	—				

the sulphoxide had  $\alpha = 0^\circ \pm 0.02^\circ$  (*c* 10.31 in CHCl<sub>3</sub>) and with menthyl toluene-*p*-sulphinic acid had  $\alpha = 0^\circ \pm 0.02^\circ$  (*c* 5.85 in CHCl<sub>3</sub>). (-)-Menthol has  $[\alpha]_D = -45^\circ$  (*c* 5.66 in CHCl<sub>3</sub>), and menthyl toluene-*p*-sulphinic acid has  $[\alpha]_D = -194^\circ$  (*c* 1.25 in CHCl<sub>3</sub>).

*Racemisation Tests*.—(a) *Under oxidation conditions*. A mixture of the sulphoxide (50.9 mg.), acetic acid (3.3 ml.), water (1.7 ml.), and sodium acetate (0.25 g.) had  $\alpha = 0.78^\circ$ . The rotation of the solution was unchanged after it had been kept for 16 hr. at 20° or in a sealed tube at 100° for 16 hr. The solution from the sealed-tube experiment was diluted with water, and the precipitated sulphoxide, before recrystallisation, had m. p. 169—170°,  $[\alpha]_D = +252^\circ$  (*c* 1 in acetone).

<sup>14</sup> Frömm, *Annalen*, 1913, **396**, 75.

<sup>15</sup> Otto, *Ber.*, 1880, **13**, 1272.

<sup>16</sup> Phillips, *J.*, 1925, 2552.

<sup>17</sup> Cf. Barnard and Percy, *J.*, 1962, 1667.

(b) *Under reduction conditions.* The titanous chloride–acetic acid–sodium acetate mixture used for reduction of the sulphoxide (below) had pH 2.3. The active sulphoxide (70 mg.) was kept at 100° for 1 hr. in a mixture of acetic acid (5 ml.), water (4 ml.), and 0.1N-hydrochloric acid (1 ml.) (*i.e.*, pH of the mixture ~2). Dilution of the mixture with water precipitated the sulphoxide (55 mg.), m. p. 169–170°,  $[\alpha] = 251^\circ$  (*c* 1 in acetone).

*Test of Autoxidation and Disproportionation of the Sulphoxide.*—The sulphoxide (150 mg.) was kept for 17 hr. at 100° in a mixture of acetic acid (7 ml.), water (3 ml.), and sodium acetate (0.6 g.). Titanous chloride (2 ml.) and sodium acetate (1 g.) were added and heating was continued for 1 hr. with passage of carbon dioxide. Extraction was with chloroform and the extracts were washed with saturated aqueous sodium hydrogen carbonate. Evaporation gave a residue completely soluble in light petroleum (the sulphone and sulphoxide are insoluble) and evaporation of the solution gave benzyl *p*-tolyl sulphide (130 mg., 93%), m. p. and mixed m. p. 43–44° (from methanol).

*Sodium [<sup>18</sup>O<sub>2</sub>]Peroxide.*—As the directions stated by Anbar<sup>4</sup> are brief, details are given here. A Pyrex bulb (8 cm. in diameter) was outgassed at 260°/1 × 10<sup>-4</sup> mm. A film of sodium was thrown on to the internal surface of the bulb by heating electrically a piece of sodium supported in a tungsten spiral at the centre of the bulb, the pressure being kept at 1 × 10<sup>-4</sup> mm. The bulb was then disconnected from the pump and checked for vacuum-tightness (Tesla coil), and enriched oxygen (Yeda Ltd.) (100 ml., 20% excess) was admitted from a break-seal container. The bulb was kept at 260° for 50 min. and then cooled to –20°. It was rinsed with a partially frozen (~–20°) mixture of acetic acid (7 ml.) and water (3 ml.). These conditions are necessary to prevent inflammation after contact between aqueous acetic acid and sodium peroxide. An aliquot part (0.5 ml.) was treated with an excess of aqueous potassium iodide and a trace of ammonium molybdate. The liberated iodine was titrated with 0.05N-thio-sulphate (starch–iodide); the yield of hydrogen peroxide was 40%; in nine preliminary runs with <sup>18</sup>O<sub>2</sub>, the average yield was 47% with a range of 30–70%.

(–)-Benzyl *p*-Tolyl [<sup>18</sup>O<sup>18</sup>O]Sulphone.—The (+)-sulphoxide (330 mg., 1 mol.) was added to the residual solution which was kept at 95° for 16 hr. The solution was faintly oxidising (starch–iodide), and titanous chloride (5.3 ml.) and sodium acetate (2.7 g.) were added. Heating was continued for 1 hr. at 95° with passage of carbon dioxide. The mixture was extracted with chloroform (4 × 100 ml.) and the extracts were washed with saturated aqueous sodium hydrogen carbonate. Evaporation gave a residue which, on treatment with warm light petroleum (50 ml.), gave the sulphone (231.2 mg.), m. p. 143.5–145°,  $\alpha = -0.02^\circ \pm 0.02^\circ$  (*c* 8 in CHCl<sub>3</sub>). A part (218.2 mg.) was re-reduced with titanous chloride (5 ml.) and water (3 ml.) at 95° for 1 hr. in an atmosphere of carbon dioxide. Re-extraction as before gave the sulphone (207.2 mg.) which was recrystallised to constant m. p. (146–147°, alone or mixed with isotopically normal sulphone) first from benzene–pentane and subsequently from ethanol. The pure sulphone had  $[\alpha] = -0.16^\circ \pm 0.05^\circ$  (*c* 7.8195 in CHCl<sub>3</sub>, *l* 0.1998) (Ericsson photoelectric polarimeter). Recrystallisation did not affect the rotation within the experimental error.

*Infrared Spectra and Isotopic Content of the Labelled Sulphone.*—Infrared spectra of the labelled and the normal sulphone in the region 4000–650 cm.<sup>-1</sup> were identical both in band position and intensity except at the frequencies given in Table 2.

TABLE 2.

Infrared absorption frequencies (cm.<sup>-1</sup>) of normal (N) and benzyl *p*-tolyl [<sup>18</sup>O<sup>18</sup>O]sulphone (L).

(a) 0.3% in KBr.

N: 1325sh, 1307s, 1299s, 1282s, 1255w, 1182w, 1149s, 1131s, 1114s, 1083s

L: 1325sh, 1307sh, 1292s, 1279s, 1256m, 1181w, 1156s, 1149m, 1138s, 1130s, 1114sh, 1075s

(b) 5% in CHCl<sub>3</sub>.

N: 1316s, 1305m, 1292m, 1155s, 1126m, 1091m

L: 1316sh,\* 1304sh, 1299s, 1284s, 1160sh,\* 1147s, 1135sh, 1119s, 1087sh,\* 1076s

\* Shoulder used in analysis.

As overlapping of bands in the spectra of the normal and the labelled sulphones is considerable, accurate analysis of the labelled sulphone could not be attempted. Comparison of the spectrum of a 5% chloroform solution of the labelled sulphone with that of a 1% chloroform

solution of the normal sulphone showed that the bands at 1316, 1155, and 1091  $\text{cm}^{-1}$  in the latter were considerably more intense than the corresponding shoulders at 1316, 1160, and 1087  $\text{cm}^{-1}$  in the former. It is therefore concluded that the labelled sulphone contains not less than 80% of  $\text{Ph}\cdot\text{CH}_2\cdot\text{S}^{16}\text{O}^{18}\text{O}\cdot\text{C}_6\text{H}_4\text{Me-}p$ .

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