

XXVI.—*Researches in the Menthone Series. Part IX.*
A New Optical Resolution of dl-Menthol and of
dl-Camphor-10-sulphonic Acid.

By JOHN READ and WILLIAM JOHN GRUBB.

ALTHOUGH the naturally occurring form, *l*-menthol, was fairly readily obtained by the optical resolution of *dl*-menthol by Pickard and Littlebury (J., 1912, **101**, 109), the method does not appear to

lend itself to the preparation of *d*-menthol in quantity, the necessary operations being summarised as follows (*loc. cit.*, p. 121): *dl*-menthyl hydrogen phthalate \rightarrow brucine salt (mother-liquors) \rightarrow impure *d*-menthyl hydrogen phthalate \rightarrow impure *d*-menthol \rightarrow impure *d*-menthyl hydrogen succinate \rightarrow cinchonidine salt (six recrystallisations) \rightarrow slightly impure *d*-menthyl hydrogen succinate \rightarrow slightly impure *d*-menthol \rightarrow slightly impure *d*-menthyl benzoate (two recrystallisations) \rightarrow pure *d*-menthyl benzoate. A more recent resolution of *dl*-menthol (Neuberg, Jacobsen, and Wagner, *Fermentforsch.*, 1929, 10, 491) through glucoside formation with α - or β -acetobromoglucose has not led to the isolation of pure *d*-menthol.

Several attempts have been made to render *d*-menthol accessible in useful quantities, but as yet we have had no opportunity of preparing it from *d*-menthylamine (J., 1929, 23).

We now show that a mixture of *l*-menthyl *d*-camphor-10-sulphonate (*l-D*) and *d*-menthyl *d*-camphor-10-sulphonate (*d-D*), which is easily obtained by the interaction of *dl*-menthol and *d*-camphor-10-sulphonyl chloride in quinoline, yields the first of these esters in a state of purity after four recrystallisations. Similarly, pure *d*-menthyl *l*-camphor-10-sulphonate (*d-L*) may be obtained by using *l*-camphor-10-sulphonyl chloride. The process is not hindered by the presence of a little of the antimeric acid chloride, and a yield of more than 40% of the calculated quantity of pure ester is easily secured. Hydrolysing agents furnish mixtures of *l* (or *d*)-menthol and partly racemised *d* (or *l*)- Δ^3 -menthene from these two esters (compare Patterson and McAlpine, J., 1928, 2464), the main reaction proceeding as follows: $C_{10}H_{19}\cdot O\cdot SO_2R \rightarrow C_{10}H_{18} + R\cdot SO_2\cdot OH$. The product obtained by steam-distilling *d*-menthyl *l*-camphor-10-sulphonate in presence of 50% aqueous oxalic acid was shown to contain *d*-menthol corresponding to not less than 25% of the ester, but the yield of pure *d*-menthol actually isolated was only 10%; the substance had m. p. 42°, $[\alpha]_D^{25} + 49.9^\circ$ (alcohol). It is not clear that uncombined *d*-menthol has been previously prepared in a state of stereochemical purity. Its odour, although of the same general character, is fainter than that of *l*-menthol (compare Pickard and Littlebury, *loc. cit.*, p. 112). Pure *dl*-menthol, now prepared for the first time by mixing equal quantities of the *d*- and the *l*-form in light petroleum, melted at 34°, which is the temperature already recorded for specimens prepared directly from optically inactive materials.

The *l*-camphor-10-sulphonyl chloride used in the above process may be recovered; since, also, the operations are simple and easily conducted, the optical resolution of *dl*-menthol in this way provides

a practicable method for the preparation of *d*-menthol, in spite of the unsatisfactory result of the final hydrolysis. The esters *l*-*D* and *d*-*L* should be of use in the diagnosis of *l*- and *d*-menthol, respectively.

An equimolecular mixture of the esters *d*-*L* and *l*-*L*, when recovered from an ethereal solution, melted indefinitely over a wide range of temperature and gave no indication of the formation of a partial racemate. Similar behaviour was shown by a mixture of *l*-*D* and *l*-*L*. In both cases, the observed rotatory power in chloroform was practically equal to the mean value for the two components. An equimolecular mixture of *l*-*D* and *d*-*L* appeared to give rise to mixed crystals when allowed to separate slowly from ethyl acetate. Owing to the easy separation of *l*-*D* from *l*-*L*, *dl*-camphor-10-sulphonic acid is readily resolved by conversion into the *l*-menthyl ester, three recrystallisations of the product furnishing pure *l*-*D* in about 65% yield. When heated to 153°, the ester decomposes suddenly and quantitatively into pure *d*-camphor-10-sulphonic acid and partly racemised *d*- Δ^3 -menthene (compare Patterson and McAlpine, J., 1927, 349). It may be added that the velocity of formation of *l*-*D* is appreciably greater than that of *d*-*D*: we are engaged in a further study of this and other problems arising out of the present research.

EXPERIMENTAL.

l-Menthyl *d*-Camphor-10-sulphonate.—To a solution of *l*-menthol (5.2 g.) in freshly distilled anhydrous quinoline (20 c.c.) was added slightly more than 1 mol. (8.5 g.) of *d*-camphor-10-sulphonyl chloride (J., 1930, 2768). The chloride dissolved on gentle warming, the temperature rose spontaneously to 70–80°, and quinoline hydrochloride separated on cooling. The solid ester obtained by treating the product with dilute hydrochloric acid was steam-distilled for 15 minutes in order to remove unchanged menthol; it was then washed with water, dried, and recrystallised from hot ethyl acetate. The yield was about 85% of the calculated amount. The quinoline was recovered and used again. Dry pyridine was also used successfully in the reaction (compare Tschugaeff, *Ber.*, 1911, 44, 2026).

The ester crystallises from light petroleum in slender needles, attaining 5 or 6 cm. in length. From a cold saturated solution in ethyl acetate it is deposited in magnificent doubly-terminated prisms: one such crystal, 6 cm. long, weighed 10 grams. The following report of a crystallographic examination of the substance has been kindly furnished by Miss Mary W. Porter, B.Sc., of the Department of Mineralogy, University of Oxford:

“The system is tetragonal, $c : a = 1.3788 : 1$, the forms being $a(100)$, $m(110)$ and $p(111)$. The habit of the crystals shows $m(110)$

well developed and $a(100)$ narrow (Fig. 1). The angular values obtained from the measurement of five crystals are given in the following table :

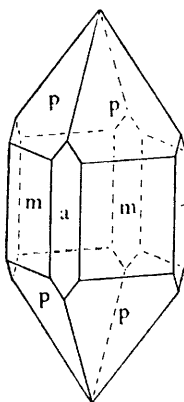
Form.	No. of readings.	Limits.	ϕ		ρ		
			Mean obs.	Calc.	Limits.	Mean obs.	Calc.
$a(100)$	14	359° 51'— 0° 14' 0° 1'	0° 0'	89° 54'	—90° 9'	90° 2'	90° 0'
$m(110)$	19	44 55—45 7 45 1	45 0	89 54	—90 34	90 4	90 0
$p(111)$	20	44 47—45 9 45 0½	45 0	62 34	—63 17	62 51	—

Cleavage : $m(110)$ perfect. Double refraction positive."

l-Menthyl *d*-camphor-10-sulphonate gave α_D^{16} — 0.83°, $[\alpha]_D^{16}$ — 20.9° (*c* 1.9855, chloroform; *l* 2) (compare *Ber.*, 1911, 44, 2026); it melts at 125.5° and decomposes at 153°, forming *d*-camphor-10-sulphonic acid and partly racemised *d*- Δ^3 -menthene (Found : C, 65.2; H, 9.3. Calc. for $C_{20}H_{34}O_4S$: C, 64.8; H, 9.3%). When steam-distilled, the ester does not volatilise, but it undergoes an extremely slow decomposition leading to the formation of *l*-menthol, *d*-camphor-10-sulphonic acid and partly racemised *d*- Δ^3 -menthene; the addition of sodium hydroxide appears to have little or no effect upon this process. The ester is very stable towards hot alcoholic potassium hydroxide; when treated with sodium in hot ethyl alcohol, it breaks down slowly, yielding menthol and menthene, and a similar reaction occurs much more readily when boiling propyl alcohol is substituted for ethyl alcohol. The ester is not affected appreciably when warmed with tin and concentrated hydrochloric acid, or with zinc and glacial acetic acid. Prolonged boiling with 20% hydrochloric or sulphuric acid causes a gradual decomposition of the ester, with the production of menthene, and a similar change occurs rapidly when the substance is heated with a methyl- or ethyl-alcoholic solution of hydrogen chloride. The most satisfactory hydrolysing agent which we have yet applied to the ester is hot 50% aqueous oxalic acid : this yielded a mixture of *l*-menthol, *d*-camphor-10-sulphonic acid and partly racemised *d*- Δ^3 -menthene. *l*-Menthyl benzoate prepared from the volatile product had *m. p.* 54°, $[\alpha]_D^{16}$ — 89.0° (*c* 2.0, alcohol) and $[\alpha]_D^{16}$ — 90.6° (*c* 1.1, benzene) (compare *J.*, 1912, 101, 119).

l-Menthyl *l*-Camphor-10-sulphonate.—The crude ester was prepared, in the manner described above, from *l*-menthol and *l*-camphor-10-sulphonyl chloride ($[\alpha]_D^{16}$ — 31.0° in chloroform, *c* 2.0). The

FIG. 1.



resulting colourless oil was steam-distilled for 10 minutes only, in order to remove most of the unchanged menthol. The dried product crystallised slowly in the ice-chest. After two recrystallisations from an ice-cooled solution in rectified spirit, the ester had m. p. 47° , $\alpha_D^{25} - 3.10^{\circ}$, $[\alpha]_D^{25} - 77.6^{\circ}$ (*c* 1.9950, chloroform) (Found : C, 65.0; H, 9.3%). It separates in minute crystals, and is very soluble in all the ordinary organic solvents. When heated to 153° , it decomposes into *l*-camphor-10-sulphonic acid and partly racemised *d*- Δ^3 -menthene. In its behaviour towards hydrolysing agents it resembles *l*-menthyl *d*-camphor-10-sulphonate; it is, however, less resistant than the latter ester, being, for instance, more readily decomposed when steam-distilled. When mixed together in equal quantities, the two esters appear to decompose at about the same rate during steam distillation; so that the above difference may depend upon the fact that the first ester, unlike the second, remains solid in contact with boiling water, when pure.

Resolution of dl-Menthol with d-Camphor-10-sulphonyl Chloride.—*dl*-Menthol (m. p. 28.8 – 31.2°), mixed in quinoline solution with *d*-camphor-10-sulphonyl chloride in the usual way, furnished a crystalline ester having $[\alpha]_D^{25} + 26.0^{\circ}$ (*c* 1.9, chloroform). After two recrystallisations from light petroleum and two from ethyl acetate, this product gave pure *l*-menthyl *d*-camphor-10-sulphonate, identical with the foregoing ester, the yield being about 45% of the calculated amount. When treated with 50% aqueous oxalic acid, in the way described below, the ester yielded (1) partly racemised *d*- Δ^3 -menthene, and (2) crude *l*-menthol, corresponding respectively to 40% and 35% of the amounts theoretically possible. The characteristics were (1) b. p. 45 – $50^{\circ}/7$ mm., n_D^{25} 1.4566, $[\alpha]_D^{25} + 34.0^{\circ}$ (*c* 2.0, alcohol); (2) b. p. 85 – $90^{\circ}/7$ mm., $[\alpha]_D^{25} - 35.6^{\circ}$ (*c* 2.0, alcohol). The second fraction, after purification on porous plate, gave *l*-menthol having m. p. 42° , $[\alpha]_D^{25} - 48.9^{\circ}$, the yield being 10% of the amount theoretically obtainable from the original *l*-menthyl *d*-camphor-10-sulphonate.

Resolution of dl-Menthol with l-Camphor-10-sulphonyl Chloride.—*l*-Camphor-10-sulphonyl chloride, prepared from a stereochemically impure specimen of *l*-camphor ($[\alpha]_D^{25} - 37.0^{\circ}$, *c* 2.5, alcohol), had $[\alpha]_D^{25} - 24.5^{\circ}$ (*c* 2.0, chloroform), and thus contained about 12% of the *d*-antimeride (compare Graham, J., 1912, **101**, 754). In reaction with *dl*-menthol it gave a crystalline ester having $[\alpha]_D^{25} - 19.0^{\circ}$ (*c* 2.0, chloroform). When fractionally recrystallised twice from light petroleum and twice from ethyl acetate, this product yielded 42% of the possible quantity of *d*-menthyl *l*-camphor-10-sulphonate, m. p. 125.5° , $\alpha_D^{25} + 0.86^{\circ}$, $[\alpha]_D^{25} + 20.8^{\circ}$ (*c* 2.0740, chloroform) (Found : C, 64.9; H, 9.2%).

Steam was passed into a suspension of the powdered ester in hot 50% aqueous oxalic acid, and the distillate was collected. The ester was added in portions of 10 g., at intervals of 30 minutes, an equivalent of sodium hydroxide solution being introduced simultaneously. When dried and fractionally distilled under diminished pressure, the volatile oil produced in this way yielded two main fractions: (1) b. p. 47—48°/7.5 mm., $[\alpha]_D - 31.2^\circ$ (c 2.0, alcohol), $[\alpha]_D - 31.6^\circ$ (c 2.0, ether); (2) b. p. 91—92°/8 mm., $[\alpha]_D + 36.5^\circ$ (c 2.0, alcohol). Fraction 1 was a liquid possessing the characteristics of partly racemised *l*- Δ^3 -menthene; the yield corresponded to 42% of the ester. Fraction 2 was partly crystalline, and consisted of *d*-menthol contaminated with about 16% of menthene; the yield corresponded to 30% of the ester. The *d*-menthol contained in this fraction was thus about 25% of the quantity theoretically obtainable from the original ester. When left on porous plate in a desiccator for 2 days, fraction 2 gave pure *d*-menthol. The oil recovered from the porous plate by extraction with ether was heated with boric acid at 100—120° for 4 hours (*Ber.*, 1929, 62, 2945), and the resulting semi-solid mass was distilled under reduced pressure to remove water and menthene. When steam-distilled with sodium carbonate solution, the residue gave a further quantity of *d*-menthol, which was dried on porous plate as before. The total yield of pure *d*-menthol was 10%, referred to the original *d*-menthyl *l*-camphor-10-sulphonate. The product had m. p. 42°, $\alpha_C^{25} + 1.52^\circ$, $[\alpha]_C^{25} + 38.9^\circ$; $\alpha_D^{25} + 1.95^\circ$, $[\alpha]_D^{25} + 49.9^\circ$; $\alpha_{5461}^{25} + 2.29^\circ$, $[\alpha]_{5461}^{25} + 58.6^\circ$; $\alpha_F^{25} + 2.96^\circ$, $[\alpha]_F^{25} + 75.7^\circ$ (c 1.9550, alcohol). A specimen of natural *l*-menthol, consisting of long prisms, m. p. 42°, had $\alpha_C^{25} - 1.52^\circ$, $[\alpha]_C^{25} - 38.6^\circ$; $\alpha_D^{25} - 1.95^\circ$, $[\alpha]_D^{25} - 49.6^\circ$; $\alpha_{5461}^{25} - 2.29^\circ$, $[\alpha]_{5461}^{25} - 58.2^\circ$; $\alpha_F^{25} - 2.96^\circ$, $[\alpha]_F^{25} - 75.3^\circ$ (c 1.9665, alcohol).

The residue from the hydrolysis was neutralised with milk of lime in order to precipitate the oxalic acid, and the filtrate was evaporated to dryness on the water-bath. The resulting sodium *l*-camphor-10-sulphonate, when treated with thionyl chloride, readily yielded *l*-camphor-10-sulphonyl chloride, $[\alpha]_D^{16} - 31.0^\circ$ (c 2.0, chloroform). Somewhat more than 80% of the sulphonyl chloride corresponding to the pure ester was recovered in this way.

Equimolecular Mixtures of Certain Optically Active Menthyl Camphor-10-sulphonates.—(1) An ethereal solution of equal weights of pure *l*-menthyl *l*-camphor-10-sulphonate (m. p. 47°) and *d*-menthyl *l*-camphor-10-sulphonate (m. p. 125.5°) when evaporated to dryness yielded a product composed of fine crystals. When heated, these softened at about 50°, became completely liquid at about 105°, and decomposed at 153°, yielding *dl*- Δ^3 -menthene and *l*-camphor-10-sulphonic acid. The observed value of $[\alpha]_D^{16}$ in chloroform was

— 28.9° (*c* 2.0), the mean of the values for the two components being — 28.4°.

(2) The product obtained in a similar way from *l*-menthyl *l*-camphor-10-sulphonate and *l*-menthyl *d*-camphor-10-sulphonate was indistinguishable in appearance from the foregoing material. When heated, it softened at about 48°, melted completely at about 105°, and decomposed at 153°, yielding partly racemised *d*- Δ^3 -menthene and *dl*-camphor-10-sulphonic acid. The observed and the calculated value of $[\alpha]_D^{25}$ (*c* 2.0, chloroform) were — 49.6° and — 49.3°, respectively.

(3) The optically inactive product obtained by evaporating to dryness an ethereal solution containing equal weights of *l*-menthyl *d*-camphor-10-sulphonate and *d*-menthyl *l*-camphor-10-sulphonate melted sharply at 102°. A large crystal obtained by slow deposition from ethyl acetate had $[\alpha]_D^{25} + 5.9^\circ$ (chloroform), corresponding to a mixture of about 64% of *d*-*L* and 36% of *l*-*D*.

Resolution of dl-Camphor-10-sulphonic Acid with l-Menthol.—*dl*-Camphor-10-sulphonyl chloride (57.6 g.; 1 mol.) was stirred into a solution of *l*-menthol (53.8 g.; 1.5 mols.) in anhydrous pyridine (100 c.c.). At the end of the reaction the mixture was poured into water, and an ethereal extract of the resulting oily product was washed with dilute sulphuric acid and water. Excess of menthol was removed by steam distillation, and the crude ester was then isolated by extraction with ether; it was obtained in 90% yield, and had $[\alpha]_D^{25} - 47.4^\circ$ (*c* 2.1, chloroform). Three successive recrystallisations from hot ethyl acetate furnished pure *l*-menthyl *d*-camphor-10-sulphonate ($[\alpha]_D^{25} - 20.9^\circ$, *c* 2.0, chloroform) in about 65% yield.

When heated to about 155° in an oil-bath, the ester decomposed, yielding partly racemised *d*- Δ^3 -menthene and *d*-camphor-10-sulphonic acid; the latter substance formed a crystalline mass in the flask. The two products of the reaction were readily separated by treatment with water and ether, or with light petroleum alone, the perfectly anhydrous acid being obtained in the latter case. When evaporated on the water-bath, the aqueous layer from the first process yielded the crystalline acid: after being dried in a vacuum desiccator, this was found by titration to contain 7.5% of water, and it gave $[\alpha]_D^{25} + 19.8^\circ$, $[\alpha]_{5461}^{25} + 26.1^\circ$ (*c* 5.1, water); the corrected values were thus $[\alpha]_D^{18} + 21.4^\circ$ and $[\alpha]_{5461}^{18} + 28.2^\circ$. The acid was therefore optically pure (compare Pope and Gibson, *J.*, 1910, **97**, 2214; Burgess and Gibson, *J. Soc. Chem. Ind.*, 1925, **44**, 496r). The yield from the ester was almost theoretical. The *d*- Δ^3 -menthene formed in the reaction had $[\alpha]_D^{25} + 19.8^\circ$ (*c* 2.1, alcohol).

The acid obtained by washing the decomposition product of the ester directly with dry ether, followed by light petroleum, consisted

of a crystalline powder, the particles of which differed from those of the foregoing specimen of the acid by showing no tendency to cohere: $\alpha_D^{16^\circ} + 2.17^\circ$, $[\alpha]_D^{16^\circ} + 21.4^\circ$; $\alpha_{5461}^{16^\circ} + 2.84^\circ$, $[\alpha]_{5461}^{16^\circ} + 28.0^\circ$ (*c* 5.0735, water) (Found: C, 51.5; H, 7.0. $C_{10}H_{16}O_4S$ requires C, 51.7; H, 6.9%).

We express our thanks to the Carnegie Trust for a scholarship awarded to one of us (W. J. G.).

UNITED COLLEGE OF ST. SALVATOR AND ST. LEONARD,

UNIVERSITY OF ST. ANDREWS. [Received, November 28th, 1930.]
