

50. *Researches in the Menthone Series. Part X. The Complete Optical Resolution of dl-neoMenthol by means of l-Menthol.*

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ACTIVE modifications of neomenthol have been prepared by Pickard and Littlebury (J., 1912, 101, 112, 121), Vavon and Couderc (*Compt. rend.*, 1924, 179, 405), Zeitschel and Schmidt (*Ber.*, 1926, 59, 2303), and Zeitschel and Eck (*J. pr. Chem.*, 1932, 133, 365).

The production of *l*- and *d*-neomenthol from *dl*-neomenthol is fairly readily achieved by the successive use of *l*- and *d*-menthoxyacetyl chloride (cf. the resolution of *dl*-menthol; Read and Grubb, *J. Soc. Chem. Ind.*, 1932, 51, 329T). *l*-neoMenthyl *l*-menthoxyacetate melts at 64° and *d*-neomenthyl *l*-menthoxyacetate at 28.5°; but in spite of a corresponding difference in solubility the two esters are difficultly separable from each other. After ten or twelve successive fractional crystallisations from methyl alcohol, the formation of mixed crystals prevents further resolution: the regenerated *l*-neomenthol, containing about 1% of its antimeride, is readily purified, however, by fractional crystallisation of the *p*-nitrobenzoate. The observed value,  $\alpha_D^{14} = -8.82^\circ$  (*l* 0.5), for the resulting *l*-neomenthol is in good agreement with  $\alpha_D^{16} = -8.87^\circ$  (*l* 0.5) and  $\alpha_D^{15} = +17.7^\circ$  (*l* 1), observed by Pickard and Littlebury and by Zeitschel and Schmidt, respectively (*loc. cit.*).

Similar relationships hold in the preparation of *d*-neomenthol, with the aid of *d*-menthoxyacetic acid. As in the case of *dl*-menthol, the ultimate optically active reagent used in achieving this complete optical resolution of *dl*-neomenthol is *l*-menthol; and the immediate reagents, *l*- and *d*-menthoxyacetic acid, may be recovered and used again.

The neomenthyl menthoxyacetates are hydrolysed less readily than the corresponding menthyl esters: the proportion of *l*-neomenthyl *l*-menthoxyacetate hydrolysed, under conditions which permit of a quantitative hydrolysis of the menthyl menthoxyacetates, is only about 85%.

*l*-Menthyl *d*-camphor-10-sulphonate was found by Tschugaev (*Ber.*, 1911, 44, 2026) to display anomalous rotatory dispersion. Of the similarly constituted esters, containing an alcohol and an acid radical of opposite rotatory signs, examined in the present research,

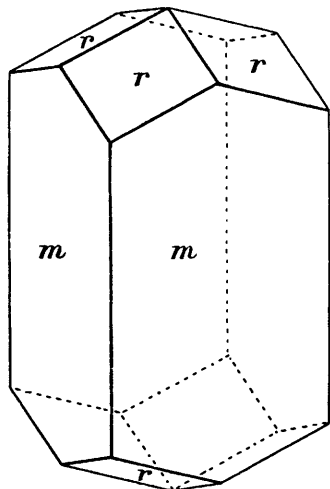
only *l*-neomenthyl *d*-camphor-10-sulphonate shows a slight anomaly; *l*-neomenthyl *l*-camphor-10-sulphonate and all the menthyl and neomenthyl menthoxyacetates have normal dispersion.

The neomenthyl camphor-10-sulphonates decompose even in warm organic solvents, owing to the ready dehydration of the neomenthyl radical, and thus they cannot be applied in the optical resolution of *dl*-neomenthol.

Unlike any of the other known menthols, *dl*-neomenthol readily forms large and well-developed crystals; the crystallographic data now given appear to be the first of the kind to be determined for a menthol. This marked capacity for crystallisation reappears in the neomenthylamine series (J., 1926, 2224).

#### EXPERIMENTAL.

*dl*-neomenthol.—We are indebted to Messrs. Howards and Sons, Ltd., Ilford, for the *dl*-neomenthol used in this work. The specimen contained less than 0.5% of impurities, and had



m. p. 50—51°, b. p. 212.1—212.6°/763 mm. It was purified through the hydrogen phthalate, and the *dl*-neomenthol finally crystallised from light petroleum (b. p. 60—80°). *dl*-neomenthol and *dl*-menthol do not form mixed crystals, and, in the absence of *dl*-isomenthol, pure *dl*-neomenthol separates when mixtures of the two substances containing not less than 35% of *dl*-neomenthol are fractionally crystallised from light petroleum. This observation has an important bearing upon the technical separation of both pure *dl*-menthol and *dl*-neomenthol, either of which may be purified with notable ease under the conditions indicated. Mixtures of *dl*-menthol and *dl*-isomenthol are not separable in this way, owing to the formation of mixed crystals.

Prof. H. L. Bowman, of the Department of Mineralogy, University of Oxford, has kindly supplied the following report of a crystallographic examination of *dl*-neomenthol :

“ The crystals are of stout prismatic habit, up to 1.5 cm. long  $\times$  1 cm., often flattened parallel to a pair of prism-faces, somewhat rough and uneven on the surface, but giving fairly clear signal-images. They resemble tetragonal prisms  $m(110)$ , terminated by  $r(101)$  (see fig.); but their optical

characters show them to be pseudotetragonal mimetic twin-groups, of which the component individuals probably belong to the orthorhombic system, though the crystals are too rough and too liable to evaporation in the air to admit of their exact angles and symmetry being determined by measurement.

“ Referred to tetragonal axes, the crystals have  $c : a = 0.556$ . Forms :  $m(110)$ ,  $r(101)$ .

	Edges.	Limits.	Mean.	Calc.
$mm$ 110 : $\bar{1}\bar{1}0$	8	88° 49'—90° 48'	[90°]	*
$mr$ 110 : 101	10	69° 40'—70° 0'	69° 50½'	69° 53½'
$rr$ 101 : 011	5	40° 11'—40° 15'	40° 13'	*
$rr$ 101 : $\bar{1}01$	3	58° 8'—58° 13'	58° 10'	58° 11'

“ No cleavage was observed.

“ A transverse section, parallel to (001), showed here and there a uniaxial interference-figure with moderately strong negative birefringence, but elsewhere the figure was biaxial, with a narrow angle ( $2E = 7^\circ$  to  $9^\circ$ ), the bisectrix being normal to the plate. The section showed a division into sectors by lines at about  $45^\circ$  to the edges, the plane of the optic axes lying in two directions at right angles in adjacent sectors, and in each sector being perpendicular to the nearest prism-face.

“ These characters, together with straight extinction on the prism-faces, indicate that the apparently tetragonal crystal probably consists of four orthorhombic individuals, bounded outwardly by pinakoid-faces and terminated by a pyramid, which are twinned together about faces of a pseudotetragonal prism.”

*dl*-neomenthyl *p*-nitrobenzoate, prepared and purified similarly to its *l*-form, described below,

separated from warm rectified spirit in fine radiating needles, m. p. 78.5° (Found : C, 66.9; H, 7.6.  $C_{17}H_{23}O_4N$  requires C, 66.8; H, 7.6%).

*dl-neoMenthyl 3 : 5-dinitrobenzoate* crystallised from EtOAc-EtOH in fine, faintly yellow needles, m. p. 130°, moderately sol. in hot EtOH (Found : C, 58.6; H, 6.5.  $C_{17}H_{22}O_6N_2$  requires C, 58.3; H, 6.3%). It is more sol. in EtOAc than *dl-menthyl 3 : 5-dinitrobenzoate*.

*dl-neoMenthyl β-naphthoate*, prepared in the usual way, except that the pyridine solution was warmed gently to start the reaction, crystallised from rectified spirit in minute prisms, m. p. 98° (Found : C, 81.1; H, 8.2.  $C_{21}H_{26}O_2$  requires C, 81.2; H, 8.4%).

*Isolation of l-neoMenthol.*—*l*-Menthoxycetyl chloride (from 43 g. of *l*-menthoxyacetic acid; *J. Soc. Chem. Ind.*, 1932, 51, 329T) was added slowly to a solution of *dl-neomenthol* (31 g.; 1 mol.) in anhyd. pyridine (90 c.c.). Pyridine hydrochloride was pptd., and the mixture became hot; it was kept over-night, and then treated in the usual way (*loc. cit.*). Crude *dl-neomenthyl l*-menthoxyacetate, freed from *neomenthol* by steam distillation, was isolated in 88.4% yield as a yellow oil which slowly crystallised; it had  $[\alpha]_D - 55.0^\circ$  (*c* 2, in  $CHCl_3$ ). The unused *l*-menthoxyacetic acid and *neomenthol* were recovered; the latter contained some *l-Δ<sup>3</sup>-menthene*, and the mixture had  $[\alpha]_D - 3^\circ$  (*c* 12, *l* 2, in EtOH), indicating that *d-neomenthol* reacts more rapidly than *l-neomenthol* with *l*-menthoxyacetyl chloride.

When recryst. 13 times from MeOH, 123.6 g. of the crude ester gave 11.2 g. with  $[\alpha]_D - 79.3^\circ$  (*c* 2, in  $CHCl_3$ ), and further fractionation produced no appreciable change in the rotatory power. This ester (11.2 g.) was heated under reflux for 1 hr. with 1% alc. KOH (270 c.c.; 1.2 mols.). Most of the EtOH was steam-distilled, and the *l-neomenthol* was then collected in a second receiver. From the non-volatile residue, unchanged ester (1.6 g.) was extracted with  $Et_2O$ ; *l*-menthoxyacetic acid (5.4 g.) was then recovered by acidification. The yield of *l-neomenthol* was 65.3% (3.25 g.), b. p. 88°/9.5 mm.,  $n_D^{20} 1.4638$ ,  $\alpha_D^{16} - 8.65^\circ$  (*l* 0.5).

Since this *l-neomenthol* was optically impure, the fractional crystn. was repeated with 293 g. of crude *dl-neomenthyl l*-menthoxyacetate: after 9 recrystns. from MeOH, this gave 42.0 g. of ester with const.  $[\alpha]_D - 78.5^\circ$ . The mother-liquors gave 27.1 g. of equally pure material (total yield, about 47% of the calc.). The *l-neomenthol* obtained by hydrolysing this material had  $\alpha_D^{16} - 17.0^\circ$  (*l* 1). *l-neoMenthyl p-nitrobenzoate* separated from rectified spirit in fine, faintly yellow needles, m. p. 95°,  $[\alpha]_D^{25} - 17.9^\circ$  (*c* 2, in  $CHCl_3$ ), after 3 recrystns. (Found : C, 67.1; H, 7.6.  $C_{17}H_{23}O_4N$  requires C, 66.8; H, 7.6%).

The *p*-nitrobenzoate was boiled for 30 min. with 5% alc. KOH (1.2 mols.). The resulting *l-neomenthol* (10.8 g.) distilled at 97.6°/10 mm., and had  $\alpha_D^{16} - 8.82^\circ$  (*l* 0.5),  $n_D^{20} 1.4638$ . The rotatory dispersion in abs. EtOH at 17° (*c* 2.0465, *l* 2) was normal:  $[\alpha]_C - 16.2^\circ$ ,  $[\alpha]_D - 20.7^\circ$ ,  $[\alpha]_{5461} - 24.2^\circ$ ,  $[\alpha]_F - 30.1^\circ$ . The yield, referred to the original *dl-neomenthol*, was 16.4% of the calc.

*Derivatives of l-neoMenthol.*—The following esters were made by allowing *l-neomenthol* (0.6 g.) to react with the acid chloride (slight excess) in anhyd. pyridine (4 c.c.), adding  $H_2O$  and  $Et_2O$  after 12 hr., washing the extract with dil. HCl, dil. NaOH, and  $H_2O$ , and removing the unchanged *neomenthol* by steam distillation; the ester was dried in  $Et_2O$  solution and recrystallised. The camphor-10-sulphonates were not exposed to steam, as they decompose under this treatment, apparently yielding menthene.

*l-neoMenthyl 3 : 5-dinitrobenzoate*, owing to its moderate solubility in  $Et_2O$ , was extracted with  $C_6H_6$ . It crystallises from EtOAc-rectified spirit in fine, faintly yellow needles, m. p. 153°,  $[\alpha]_D^{18} - 23.9^\circ$  (*c* 2.0220, in  $CHCl_3$ ) (Found : C, 58.5; H, 6.5%).

*l-neoMenthyl d-camphor-10-sulphonate* separates from light petroleum (b. p. 60—80°) in glistening, cm.-long needles, m. p. 116° (decomp.); the optical rotatory dispersion in  $CHCl_3$  at 18° (*c* 2.0125) appears to be slightly anomalous:  $[\alpha]_C + 5.3^\circ$ ,  $[\alpha]_D + 8.9^\circ$ ,  $[\alpha]_{5461} + 12.3^\circ$ ,  $[\alpha]_F + 22.1^\circ$  (Found : C, 64.7; H, 9.2.  $C_{20}H_{34}O_4S$  requires C, 64.8; H, 9.3%). *l-neoMenthyl l-camphor-10-sulphonate* separates from light petroleum in irregular cryst. aggregates, m. p. 92° (decomp.). The optical rotatory dispersion at 18° (*c* 2.0190, in  $CHCl_3$ ) is normal:  $[\alpha]_C - 38.5^\circ$ ,  $[\alpha]_D - 50.3^\circ$ ,  $[\alpha]_{5461} - 61.3^\circ$ ,  $[\alpha]_F - 84.4^\circ$  (Found : C, 64.6; H, 9.2%).

*l-neoMenthyl l-menthoxyacetate* separates from MeOH in flat needles, m. p. 64° with normal rotatory dispersion (*c* 2.0140, *t* 19°, in  $CHCl_3$ ):  $[\alpha]_C - 64.2^\circ$ ,  $[\alpha]_D - 81.1^\circ$ ,  $[\alpha]_{5461} - 95.3^\circ$ ,  $[\alpha]_F - 123.0^\circ$  (Found : C, 75.0; H, 11.3.  $C_{22}H_{40}O_3$  requires C, 74.9; H, 11.6%). *l-neoMenthyl d-menthoxyacetate* was obtained as a syrup, which slowly crystallised to colourless needles, m. p. 28.5°. The rotatory dispersion (*c* 2.0275, *t* 19°, in  $CHCl_3$ ) was normal:  $[\alpha]_C + 25.1^\circ$ ,  $[\alpha]_D + 32.0^\circ$ ,  $[\alpha]_{5461} + 37.1^\circ$ ,  $[\alpha]_F + 49.3^\circ$  (Found : C, 74.9; H, 11.3%).

*Isolation of d-neoMenthol.*—Crude *d-neomenthol* (27.8 g. with  $[\alpha]_D + 5.0^\circ$ ), regenerated from the first 4 mother-liquors of the first optical resolution described above, was converted into

*d*-menthoxyacetate in the usual way, with the acid chloride prepared from 1 mol. (38.2 g.) of *d*-menthoxyacetic acid. The yield of crude ester, after treatment with steam, was 91.4%, and 0.9 g. of *d*-menthoxyacetic acid was recovered.

When recryst. 10 times from MeOH, 58.2 g. of the crude ester gave 7.2 g. with  $[\alpha]_D + 80.9^\circ$ , and the material recovered from the last mother-liquor had  $[\alpha]_D + 78.0^\circ$ .

When heated under reflux for 1 hr. with 1% alc. KOH (1.2 mols.), the ester having  $[\alpha]_D + 80.9^\circ$  yielded *d*-neomenthol (1.8 g.), together with unchanged material (1.2 g.). The *d*-neomenthol was a colourless liquid, b. p.  $87^\circ/8$  mm.,  $n_D^{20}$  1.4638,  $\alpha_D^{20} + 8.65^\circ$  (*l* 0.5), and was thus not quite optically pure.

In recovering crude *d*-neomenthol and *l*-menthoxyacetic acid from a large quantity (200 g.) of impure *d*-neomenthyl *l*-menthoxyacetate, the ester was boiled for 20 min. with 1% alc. KOH (800 c.c.; 0.2 mol.). Six further additions of KOH (5.1 g. each time), dissolved in a little H<sub>2</sub>O, were made to the boiling alc. solution at intervals of 20 min., and the solution was then boiled for 1 hr. The recovered *d*-neomenthol had  $[\alpha]_D + 5.0^\circ$  (*c* 2, in EtOH), and the amount of unchanged ester was small (6.9 g.).

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