51. *Researches in the Menthone Series. Part XI. Diagnosis and Characterisation of the Stereoisomeric Menthols.*

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THE isolation and diagnosis of the stereoisomeric menthols have depended mainly upon the use of their hydrogen phthalates and hydrogen succinates, which were introduced for this purpose by Pickard and Littlebury (J., 1912, **101**, 109). The separative processes may include fractional esterification (Eng. Pat. 297,019) or fractional saponification (Zeitschel and Schmidt, *Ber.*, 1926, **59**, 2303), as well as fractional crystallisation. Among other derivatives, the phenylcarbamates, which are usually crystalline solids melting above 100°, have been used a good deal in the characterisation of menthols.

We have extended (see table) the range of derivatives applicable in the diagnosis and separation of these stereoisomerides. The rotatory powers were determined under similar conditions (*c* 2, in chloroform).

	l-Menthyl.		*l*-*neo*Menthyl.		*d*-*iso*Menthyl.	
	M. p.	$[\alpha]_D$.	M. p.	$[\alpha]_D$.	M. p.	$[\alpha]_D$.
d-Camphor-10-sulphonate	125·5° (decomp. 153°)	− 20·9°	116° (decomp.)	+ 8·9°	30—31° (decomp. 138°)	+35·4°
l-Camphor-10-sulphonate	47 (decomp. 153)	− 77·6	92 (decomp.)	−50·3	33—34 (decomp. 138)	−20·7
d-Menthoxyacetate	91·5	+ 6·7	28·5	+32·0	liquid	+70·8
l-Menthoxyacetate	60	−109·9	64	−81·1	liquid	−48·2
p-Nitrobenzoate	61—62 (*dl* 91)	− 76·1	95 (*dl* 78·5)	−17·9	54 (*dl* 64·5)	+24·9
3 : 5-Dinitrobenzoate	153 (*dl* 121)	− 79·4	153 (*dl* 130)	−23·9	145 (*dl* 130)	+26·5
β-Naphthoate	77 (*dl* 70)	− 69·5	— (*dl* 98)	—	liquid (*dl* liquid)	+22·3

l-Menthyl *d*-camphor-10-sulphonate is one of the most distinctive of all the derivatives of *l*-menthol. With its aid, small amounts of *l*-menthol may be detected in mixtures containing *d*-menthol and *iso*menthols: *d*-menthyl and *d*- or *l*-*iso*menthyl *d*-camphor-10-sulphonate are readily removed by fractional crystallisation, and the relatively insoluble *l*-menthyl ester is then identified by the melting point, decomposing point, rotatory power, and characteristic crystals deposited from cold ethyl acetate (J., 1931, 190). The antimeric ester, *d*-menthyl *l*-camphor-10-sulphonate, may be used similarly in identifying *d*-menthol. As indicated below, this diagnostic method has been applied *inter alia* to establish the presence of (i) *d*-menthol in crude *d-iso*menthol derived from *l*-piperitone, and (ii) *dl*-menthol in a purified specimen of commercial *dl-iso*menthol.

l-Menthyl *d*-camphor-10-sulphonate does not separate so readily from the *neo*menthyl as from the *iso*menthyl camphor-10-sulphonates; the melting- and decomposing-points of the mixtures are much lower than those of pure *d*-menthyl *d*-camphor-10-sulphonate. When the *neo*menthyl camphor-10-sulphonates are heated with light petroleum, decomposition may occur with the production of an insoluble deposit of camphor-10-sulphonic acid. *d*-Menthyl and *l*-menthyl *d*-α-bromocamphor-π-sulphonates have no pronounced diagnostic value.

The menthoxyacetates are particularly useful in resolving *dl*-menthol (*J. Soc. Chem. Ind.*, 1932, **51**, 329T) and *dl-neo*menthol (preceding paper). Menthol may be conveniently separated from a menthol–menthene mixture (cf. J., 1927, 1280; 1931, 193) by conversion into *p*-nitrobenzoate or 3 : 5-dinitrobenzoate; the menthene is then removed by steam distillation, and the menthol recovered from the residual ester by hydrolysis.

The molecules of the menthyl menthoxyacetates and camphor-10-sulphonates possess two types of asymmetric radical, derived from the alcohol (*d* and *l*) and the acid (*D* and *L*), respectively. Interesting data, bearing upon the so-called principle of optical superposition (cf. *Trans. Faraday Soc.*, 1930, **26**, 441), are derived by assuming that each type of radical contributes a constant numerical quota to the optical rotatory powers of the diastereoisomeric molecules in which it occurs. On this assumption, the mean (— 49·3 units) of the values of $[\alpha]_D$ (*c* 2, chloroform) for *l*-menthyl *d*-camphor-10-sulphonate (*l* — *D*) and *l*-menthyl *l*-camphor-10-sulphonate (*l* — *L*) may be taken as the quota of the *l*-menthyl radical, and the mean of the values for *d* — *L* and *l* — *L* (— 28·4 units) as the quota of the *l*-camphor-10-sulphonyl radical in these compounds; and similarly for the menthoxyacetates. A summary of data calculated in this way is appended :

	Acid radical.		Alcohol radical.		
	In menthoxyacetates.	In camphor-10-sulphonates.	In menthoxyacetates.	In camphor-10-sulphonates.	Free alcohol (in EtOH).
Menthols	58·3	28·4	51·6	49·3	50·0
*neo*Menthols	56·6	29·6	24·6	20·7	20·7
*iso*Menthols	59·5	28·1	11·3	7·4	25·9

The quota of the menthoxyacetyl radical is sensibly constant in the three series of derivatives, as is also that of the camphor-10-sulphonyl radical. The quota of the menthyl radical is almost the same in the menthoxyacetates and the camphor-10-sulphonates; and a similar relationship holds for the *neo*menthyl radical. These two sets of values appear also to be related to the optical rotatory effects of the free alcohols. The values for the *iso*menthyl radical do not accord so closely. It is evident that the numerical relationships here summarised could be applied to calculate the approximate rotatory power of the second diastereoisomeride from that of the first, *i.e.*, by utilising the value derived for the acid radical from the esters of one of the other menthols.

The optically active *neo*menthols used in this investigation were prepared by resolving *dl-neo*menthol with *d*- and *l*-menthoxyacetyl chloride (preceding paper). No optical resolution of *dl-iso*menthol has yet been recorded, and we now show that neither of the methods which have recently been devised for the resolution of *dl*-menthol (J., 1931, 188; *J. Soc. Chem. Ind.*, 1932, **51**, 329T) is applicable to *dl-iso*menthol. The requisite *d-iso*menthol was therefore prepared from *l*-piperitone by a modification of the method of Read, Robertson, and Cook (J., 1927, 1280). The crude *d-iso*menthol prepared by this method has now been shown to contain some *d*-menthol, derived probably from *d*-menthone produced in the hydrogenation of the original *l*-piperitone : this possibility had been foreseen (compare *Chem. Reviews*, 1930, **7**, 20). Accordingly, the *d-iso*menthylamine concerned in the process was purified by repeated fractional crystallisation of salicylidene-*d-iso*menthylamine, a derivative which is less soluble than any of its stereoisomerides (J., 1926, 2225); the derived *d-iso*menthol was then purified through the 3 : 5-dinitrobenzoate. The optical purity of the resulting *d-iso*menthol is unquestionable, and the physical constants are only slightly different from those recorded by Read, Robertson, and Cook (*loc. cit.*).

EXPERIMENTAL.

Purification of dl-iso*Menthol*.—Somewhat impure *dl-iso*menthol, m. p. 50·5—51·5°, reacted with *d*-camphor-10-sulphonyl chloride to yield an ester (16·0 g.), which crystallised partly after several days. The fraction (0·5 g.) obtained after 4 recrystns. from EtOH had m. p. 100—105°, $[\alpha]_D$ + 3·0° (*c* 2, in $CHCl_3$), and decomposed at 152°. A further slow recrystn. from EtOAc yielded characteristic crystals of *l*-menthyl *d*-camphor-10-sulphonate (J., 1931, 191). The original material thus contained *dl*-menthol.

This impure *dl-iso*menthol was converted into the *p*-nitrobenzoate. The pure ester, m. p. 64·5° after 4 recrystns. from abs. EtOH, was boiled with 5% alc. KOH : it yielded *dl-iso*menthol, b. p. 97·4°/10·5 mm., m. p. 53—54° in a thin capillary tube when the temp. was raised 2° per min. No *dl*-menthol could be detected in the purified material, which appeared to be identical with a specimen of carefully purified *dl-iso*menthol kindly supplied by Messrs. Howards and Sons. The latter specimen consisted of short opaque needles, for which the following constants were stated : b. p. 218·5—218·6°/760 mm.; m. p. 53·5—54·5°; hydrogen phthalate, m. p. 117°. When observed under the conditions stated above, the m. p. of this specimen was identical with that of the material purified through the *p*-nitrobenzoate. Both specimens were optically inactive (*c* 2, *l* 2, in EtOH).

Various esters were prepared and purified (preceding paper) from *dl-iso*menthol which had been purified through the *p*-nitrobenzoate. dl-iso*Menthyl* p-*nitrobenzoate* separates from abs. EtOH as a yellowish cryst. powder, m. p. 64·5° (Found : C, 66·9; H, 7·5. $C_{17}H_{23}O_4N$ requires C, 66·8; H, 7·6%), and the 3 : 5-*dinitrobenzoate* in minute yellowish needles, m. p. 130° (Found : C, 58·3; H, 6·3. $C_{17}H_{22}O_6N_2$ requires C, 58·3; H, 6·3%). A mixture of the latter with the stereoisomeric *dl-neo*-derivative melted at 108—112°.

The β-naphthoate is a syrup. The *l*-menthoxyacetate, when distilled in vac., formed a yellow oil, more mobile than *d-iso*menthyl *d*- and *l*-menthoxyacetate, b. p. 206—207°/9 mm., $[\alpha]_D^{17°}$ − 57·3° (*c* 2, in $CHCl_3$). Equiv. amounts of *dl-iso*menthol and *l*-menthoxyacetyl chloride were used in this prepn.; since the unchanged *iso*menthol (removed by steam distillation) had $[\alpha]_D$ − 3·4° (*c* 2, in EtOH), *d-iso*menthol reacts more rapidly than *l-iso*menthol with *l*-menthoxyacetyl chloride. The ester obtained by the interaction of *dl-iso*menthol and *d*-camphor-10-sulphonyl chloride in pyridine was a viscid mass, having $[\alpha]_D$ + 27·5° (*c* 2, in $CHCl_3$). Owing to the ready solubility of this product in org. solvents, a separation of the constituent diastereoisomeric esters was impracticable. The unused and recovered *iso*menthol had $[\alpha]_D$ + 7·2° (*c* 2, in EtOH), and thus *l-iso*menthol reacts more rapidly than *d-iso*menthol with *d*-camphor-10-sulphonyl chloride.

d-iso*Menthol and Derivatives*.—*d-iso*Menthol was prepared from *d-iso*menthylamine hydrochloride (J., 1927, 1279) having $[\alpha]_D$ + 23·0° (*c* 2, in H_2O). The fraction of b. p. 94—95°/11 mm. crystallised on cooling, and was used without further purification in preparing *d-iso*menthyl *l*-camphor-10-sulphonate. The resulting yellow oil (5·2 g.) crystallised slowly and had $[\alpha]_D$ − 18·3° (*c* 2, in $CHCl_3$). After seven crystns. from EtOH it yielded 0·2 g. of *d*-menthyl *l*-camphor-10-sulphonate, m. p. 124—125°, $[\alpha]_D$ + 20·9° (*c* 2, in $CHCl_3$). Hence the *d-iso*menthol contained a little *d*-menthol.

In the prepn. of *d-iso*menthol of undoubted purity for this work, *d-iso*menthylamine was purified by fractional crystn. of the salicylidene derivative instead of the hydrochloride : 350 g. of crude *d-iso*menthylamine hydrochloride yielded 433 g. of the salicylidene derivative, which after seven crystns. from rectified spirit gave 151 g. of pure salicylidene-*d-iso*menthylamine, m. p. 122°, $[\alpha]_D$ + 78·2° (*c* 2, in $CHCl_3$); the sixth separation had $[\alpha]_D$ + 78·2°, and the solid from the last mother-liquor had $[\alpha]_D$ + 78·1°. Upon hydrolysis (J., 1927, 2172), 147 g. of this salicylidene derivative gave 103·2 g. of *d-iso*menthylamine hydrochloride, $[\alpha]_D^{17°}$ + 24·6° and + 24·0°, mean value + 24·3° (*c* 1·6395 and 2·4085, *l* 2, $\alpha_D^{17°}$ + 0·807° and + 1·155°, in H_2O). The yield of the pure hydrochloride was 27% of the crude salt, which had $[\alpha]_D$ + 15·0°; by direct crystn. of the hydrochloride, Read and Robertson (J., 1926, 2222) obtained a 33% yield from a crude hydrochloride with $[\alpha]_D$ + 20·6°, the purified substance having $[\alpha]_D$ + 23·6°.

Upon treatment with HNO_2 (J., 1927, 1280), 102·7 g. of *d-iso*menthylamine hydrochloride gave 53·0 g. of the usual menthol–menthene mixture; the *d-iso*menthol fraction (32·1 g.) was collected at 67—83°/10 mm. This product was shown, by treating a portion of it with *l*-camphor-10-sulphonyl chloride in pyridine (J., 1930, 2769), to contain traces of *d-iso*menthylamine; thus, the steam distillate from the HNO_2 reaction should be carefully washed with dil.

acid in such cases. Another portion of the crude *d-iso*menthol was washed with dil. acid and converted into the 3 : 5-dinitrobenzoate; * after three recrystns. from abs. EtOH–EtOAc (1 : 1), pure d-iso*menthyl* 3 : 5-*dinitrobenzoate* was obtained in fine, faintly yellow needles, m. p. 145°, $[\alpha]_{\mathrm{D}}^{16^\circ}$ + 26·5° (Found : C, 58·2; H, 6·3. $C_{17}H_{22}O_6N_2$ requires C, 58·3; H, 6·3%).

The ester was boiled for an hr. with 5% alc. KOH (1·2 mols.); the *d-iso*menthol isolated distilled completely at 96·2—96·8°/10 mm. and formed a hard, white, cryst. solid, m. p. 82·5°. The rotatory dispersion was normal (*c* 2·0305, *t* 17°, *l* 2, in EtOH) : α_{C} + 0·82°, $[\alpha]_{\mathrm{C}}$ + 20·1°; α_{D} + 1·053°, $[\alpha]_{\mathrm{D}}$ + 25·9°; α_{5461} + 1·248°, $[\alpha]_{5461}$ + 30·7°; α_{F} + 1·636°, $[\alpha]_{\mathrm{F}}$ + 40·2°. The values recorded by Read, Robertson, and Cook (J., 1927, 1280) were m. p. 81·5°, $[\alpha]_{\mathrm{D}}$ + 27·0° (*c* 1·8, in EtOH).

d-iso*Menthyl* p-*nitrobenzoate* crystallises from rectified spirit in small, pale yellow needles, m. p. 54°, $[\alpha]_{\mathrm{D}}^{15^\circ}$ + 24·9° (*c* 2, in $CHCl_3$) (Found : C, 67·0; H, 7·5. $C_{17}H_{23}O_4N$ requires C, 66·8; H, 7·6%). *d-iso*Menthyl *l*-menthoxyacetate forms a yellowish syrup, $[\alpha]_{\mathrm{D}}^{15^\circ}$ − 48·2° (*c* 2, in $CHCl_3$); *d-iso*menthyl *d*-menthoxyacetate is similar in appearance, $[\alpha]_{\mathrm{D}}^{15^\circ}$ + 70·8°.

d-iso*Menthyl* d-*camphor*-10-*sulphonate,* prepared as usual and freed from *d-iso*menthol by steam distillation, was obtained as a syrup which soon crystallised. It melts at 30—31° and decomposes at 138°, forming menthene; $[\alpha]_{\mathrm{D}}^{15^\circ}$ + 35·4° (*c* 2, in $CHCl_3$). It is too sol. to permit of recrystn. (Found : C, 65·0; H, 9·2. $C_{20}H_{34}O_4S$ requires C, 64·8; H, 9·3%). d-iso*Menthyl* l-*camphor*-10-*sulphonate* resembles its diastereoisomeride, m. p. 33—34°, decomp. 138°, $[\alpha]_{\mathrm{D}}^{15^\circ}$ − 20·7° (Found : C, 65·2; H, 9·3%). The β-naphthoate is a stiff syrup, $[\alpha]_{\mathrm{D}}^{17^\circ}$ + 22·3° (*c* 2, in $CHCl_3$).

Derivatives of l-*Menthol.*—*l*-Menthyl *p*-nitrobenzoate is readily sol. in Et_2O and only moderately in EtOH. It crystallises from rectified spirit, containing a little EtOAc, in small yellowish needles, m. p. 61—62°, $[\alpha]_{\mathrm{D}}^{16^\circ}$ − 76·1° (*c* 2, in $CHCl_3$) (cf. *J. Russ. Phys. Chem. Soc.*, 1902, **34**, 615; J., 1905, **87**, 1191). *l*-Menthyl 3 : 5-dinitrobenzoate is moderately sol. in warm light petroleum, acetone, or EtOH. It crystallises from warm EtOAc in faintly yellow needles, m. p. 153°, $[\alpha]_{\mathrm{D}}^{16^\circ}$ − 79·4°, $[\alpha]_{5461}^{16^\circ}$ − 94·5° (*c* 2, in $CHCl_3$) (cf. J., 1906, **89**, 1481; 1915, **107**, 57). *l*-Menthyl β-naphthoate dissolves readily in most of the common org. solvents; it is not very sol. in rectified spirit, but crystallises from abs. EtOH in colourless plates, m. p. 77°, $[\alpha]_{\mathrm{D}}^{17^\circ}$ − 69·5° (cf. Tschugaev, *J. Russ. Phys. Chem. Soc.*, 1902, **34**, 606). *l*-Menthyl *d*-α-bromocamphor-π-sulphonate, prepared by warming *l*-menthol with *d*-α-bromocamphor-π-sulphonyl chloride (J., 1895, **67**, 357) in pyridine, forms a glass, $[\alpha]_{\mathrm{D}}^{17^\circ}$ + 27·9°. l-*Menthyl* l-α-*bromocamphor*-π-*sulphonate* separates from light petroleum in irregular cryst. masses, m. p. 96—97°, $[\alpha]_{\mathrm{D}}^{17^\circ}$ − 109·2° (Found : C, 53·4; H, 7·5. $C_{20}H_{33}O_4BrS$ requires C, 53·4; H, 7·4%).

Derivatives of dl-*Menthol.*—*dl*-Menthyl *d*-α-bromocamphor-π-sulphonate, m. p. 34—36°, forms a glass, $[\alpha]_{\mathrm{D}}^{17^\circ}$ + 68·1° (*c* 2, in $CHCl_3$). dl-*Menthyl* p-*nitrobenzoate* is only moderately sol. in EtOH; it crystallises slowly from EtOAc in large, yellowish, doubly-terminated prisms, m. p. 91°, but if the solution is stirred it is pptd. rapidly as a microcryst. powder (Found : C, 67·0; H, 7·6%). dl-*Menthyl* 3 : 5-*dinitrobenzoate* is more sol. than the corresponding *l*-menthyl ester; it is deposited from hot EtOAc as a faintly yellow, cryst. powder, m. p. 121° (Found : C, 58·3; H, 6·3%). Mixtures with the stereoisomeric *dl-neo-* and *dl-iso*-derivative melted, respectively, at 106—110° and 120—123°. dl-*Menthyl* β-*naphthoate* was isolated as an oil, which slowly crystallised when treated with dry Et_2O. It separates from abs. EtOH as a cryst. powder, m. p. 70° (Found : C, 81·0; H, 8·1%).

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