# 76. *Researches in the Menthone Series. Part XII. Isolation and Characterisation of the* neoiso*Menthols.*

By JOHN READ and WILLIAM J. GRUBB.

THE isolation of *neoiso*menthols from mixtures of menthols in which they undoubtedly occur, such as the reduction products of piperitone and *iso*menthone (J., 1925, **127**, 2782; 1927, 1282), has proved to be unusually difficult; and most of the sporadic references in the literature to *neoiso*menthols are not sustained by any convincing evidence that these substances have been obtained free from stereoisomerides. The following data (English Patent 285,394), which are the most definite hitherto available, refer to *dl-neoiso*menthol, obtained by fractional distillation from products of hydrogenation of thymol and *iso*-

menthone below 160° : m. p. 12—14°, b. p. 214·5°/760 mm.; m. p. of hydrogen phthalate, 90—92°; m. p. of *p*-nitrobenzoate, 56°. The exact diagnosis of the *dl*-form is hindered by the lack of a definite criterion of stereochemical purity for the derived ketone, *dl-iso*-menthone; while work on the optically active forms has been handicapped by their extremely low rotatory power, although a predicted value has been available for some time (*Chem. Reviews*, 1930, **7**, 35).

Zeitschel and Schmidt (*Ber.*, 1926, **59**, 2303) have shown that *l*-menthone yields a mixture of *l*-menthol and *d-neo*menthol when reduced with aluminium *iso*propoxide, according to the method of Ponndorf (*Z. angew. Chem.*, 1926, **39**, 138) : a menthol mixture containing about 70% of *d-neo*menthol may thus be obtained (*J. Soc. Chem. Ind.*, **1934**, **53**, 52T). In a similar way, *d-iso*menthone might be expected to yield a mixture of *d-iso*menthol and *d-neoiso*menthol; but owing to the ready inversion of *d-iso*menthone into *l*-menthone (J., 1926, 2215), the product would also contain *l*-menthol and *d-neo*-menthol. *d-iso*Menthone is not yet available in quantity (J., 1927, 1281), and the reduction has not been investigated; Zeitschel and Schmidt (*J. pr. Chem.*, 1932, **133**, 365) have, however, demonstrated the formation of *d*-menthol from *l-iso*menthone in this way.

By applying Ponndorf's method to *dl-iso*menthone, prepared from *dl-iso*menthol, we have now been able to isolate a pure specimen of *dl-neoiso*menthol from the product; but great care is required in the operation, owing to the ease with which the ketone is transformed into *dl*-menthone. *dl-neoiso*Menthol melts at 14°, and is a mobile liquid which forms a characteristic crystalline *p*-nitrobenzoate and 3 : 5-dinitrobenzoate. The separation was achieved by applying the results of an unpublished investigation dealing with the varying rates of reaction of the stereoisomeric menthols with certain acid chlorides and other reagents.

Moreover, it has proved possible to isolate pure *dl*- or *d-neoiso*menthol from hydrogenated *dl*- or *l*-piperitone, by means of progressive purification through the hydrogen phthalate and phosphoric acid compound (see Blagden and Huggett, succeeding paper), followed by conversion into the characteristic and beautifully crystalline **3** : 5-dinitrobenzoate or *p*-nitrobenzoate. *d-neoiso*Menthol—the last of the menthols—has the lowest rotatory power of them all, namely, $[\alpha]_D^{16°} + 0{\cdot}14°$ (homogeneous); it is liquid at the ordinary temperature, the melting point being − 8°. Its stereochemical purity was proved by the fact that upon careful oxidation it yielded *d-iso*menthone with $[\alpha]_D^{16°} + 90{\cdot}60°$ (homogeneous). Although the free alcohol is *d*-rotatory, it gives rise to *l*-rotatory derivatives : in this respect it resembles the allied *d-neoiso*menthylamine (J., 1930, 2766). The striking correspondence in optical rotatory power between the menthylamines (J., 1930, 2764) and menthols (J., 1931, 193; 1933, 169, 173) is shown below :

*Values of $[\alpha]_D$ for Menthylamines and Menthols.*

| | *l*-. | *d-neo*-. | *d-iso*-. | *d-neoiso*-. |
|---|---|---|---|---|
| Menthylamines (homogeneous) ...... | − 44·53° | + 15·12° | + 28·96° | + 2·32° |
| Menthols (in alcohol) ................. | − 49·6 | + 20·7 | + 25·9 | + 2·2 |

The value of $[\alpha]_D$ " for the unknown *d-neoiso*menthol " (in alcohol) was calculated in 1930 as + 2·6° (*Chem. Reviews*, **7**, 35), from ideas based upon an application within defined limits of the so-called principle of optical superposition to the molecular frameworks of menthylamines and menthols. It is interesting to note further that the algebraic sum of the values of $[\alpha]_D$ for the *p*-nitrobenzoates of *l*-, *d-neo*-, *d-iso*-, and *d-neoiso*-menthol is − 38·6°; the sum for the corresponding 3 : 5-dinitrobenzoates is − 38·5° (J., 1933, 170). The table of calculated values for acid and alcohol radicals in the stereoisomeric menthyl menthoxyacetates and camphor-10-sulphonates (J., 1933, 171) may now be completed by adding the respective numbers 57·6, 29·2, 14·0, 11·9, and 2·2, for *neoiso*menthols; the values 14·0 and 11·9 are negative for *d-neoiso*menthol. The table of refractive indices for the four series of menthols given at the end of this paper is also of considerable interest.

To the summary of data given for characteristic *l*-menthyl, *l-neo*menthyl, and *d-iso*-menthyl derivatives (J., 1933, 170), may now be made the following addendum for *neoiso*-menthyl derivatives :

*d-neoiso*Menthyl.

| | M. p. | $[\alpha]_D$ (*c* 2, $CHCl_3$). |
|---|---|---|
| *d*-Camphor-10-sulphonate ................. | 69—70° (decomp. 100°) | + 17·3° |
| *l*-Camphor-10-sulphonate ................. | 84—86° (decomp. 89°) | — 41·0 |
| *d*-Menthoxyacetate ......................... | Liquid | + 43·6 |
| *l*-Menthoxyacetate ......................... | Liquid | — 71·6 |
| *p*-Nitrobenzoate ............................ | 72·5—73° (*dl* 63—64°) | — 5·3 |
| 3 : 5-Dinitrobenzoate ....................... | 100·5—101° (*dl* 73—73·5°) | — 9·5 |
| *β*-Naphthoate ............................... | (*dl* liquid) | — |

Many interesting relationships become evident from an examination of the complete table: for example, the *dl-p*-nitrobenzoates in the two *neo*-series have lower melting points than the corresponding active forms, whereas in the other two series the reverse is the case; or again, the camphor-10-sulphonates decompose, with formation of menthene, much more readily in the *neo*-series than in the others.

All the stereoisomeric menthylamines and menthols have now been isolated and characterised: thereby, a fundamental aim of this series of researches has been achieved. One of the most interesting general results of the work is the establishment of a close correspondence in optical rotatory power between the free menthols and menthylamines (see table on p. 314). This indicates convincingly that the four sets of compounds are stereochemically analogous. The relative molecular configurations (J., 1930, 2761) cannot yet be regarded as definitely settled, and it is hoped before long to publish new work bearing upon this important problem. The appended summary (*J. Soc. Chem. Ind.*, 1932, **39**, 331T, 330T; unpublished observations; J., 1927, 1279; 1933, 173; this paper) shows that externally compensated menthol and *iso*menthol have lower melting points than their optically active components, while in the two *neo*-series the inactive forms have the higher melting points: this relationship was anticipated (*Chem. Reviews*, 1930, **7**, 37).

*Melting Points of the Stereoisomeric Menthols.*

| | Menthols. | *neo*Menthols. | *iso*Menthols. | *neoiso*Menthols. |
|---|---|---|---|---|
| *dl*-Form ..................... | 35—38° | 53° | 53·5° | 14° |
| *d*- or *l*-Form .............. | 42—43 | — 22 | 82·5 | — 8 |

## EXPERIMENTAL.

dl-neoiso*Menthol.*—*dl-iso*Menthol (50 g., m. p. 48—50°) was oxidised with Beckmann's chromic acid mixture (*Annalen*, 1889, **250**, 335). An ethereal solution of the resulting ketone was washed with water until neutral in reaction, the use of alkali being avoided owing to the danger of inversion. The ketone (40 g., b. p. 75—78°/7 mm.) was reduced with aluminium *iso*propoxide (8 g.) in dry *iso*propyl alcohol (120 c.c.), according to the method of Ponndorf (*Z. angew. Chem.*, 1926, **39**, 138). The product was an oil (35 g.), b. p. 82—84°/7 mm., $n_D^{16^\circ}$ 1·4635.

This mixture of menthols was esterified with half the calculated amount of *p*-nitrobenzoyl chloride in presence of dry pyridine. The product was diluted with water, and the ethereal extract was washed with dilute hydrochloric acid, sodium hydroxide solution, and water. The unchanged menthol was then removed from the ester by distillation in steam; when converted into 3 : 5-dinitrobenzoate (22·2 g.) and fractionally crystallised seven times from alcohol, it yielded pure *dl-neo*menthyl 3 : 5-dinitrobenzoate (3·4 g.), m. p. 129—130° (J., 1933, 170).

The crude *p*-nitrobenzoate was a mobile oil, which became partly crystalline when kept. The filtrate (14·7 g.) remained as an oil. The crystalline solid (12·9 g.) had m. p. 48—50°; after three recrystallisations from absolute alcohol, faintly yellow needles of somewhat impure *dl-neoiso*menthyl *p*-nitrobenzoate (3·8 g.) were obtained, with constant m. p. 54—55·5° (Found: C, 67·0; H, 7·7. $C_{17}H_{23}O_4N$ requires C, 66·8; H, 7·6%). The *dl-neoiso*-menthol from this ester melted at 9°. The derived dl-neoiso*menthyl* 3 : 5-*dinitrobenzoate* separated slowly from absolute alcohol in thin, but well-defined rhombic prisms with a faint yellow colour; more rapid crystallisation gave minute and practically colourless, four-sided leaflets, m. p. 73—73·5°. The melting point remained unaltered after recrystallisation (Found: C, 58·4; H, 6·4. $C_{17}H_{22}O_6N_2$ requires C, 58·3; H, 6·3%). Upon hydrolysis with methyl-alcoholic potassium hydroxide, this ester gave dl-neoiso*menthol* (1·5 g.), a colourless mobile liquid with a rather faint odour like that of *neo*menthol: b. p. 81°/6 mm., m. p. 14°,

$n_{D}^{17^\circ}$ 1·4676, $n_{D}^{60^\circ}$ 1·4504 (Found : C, 76·5; H, 12·8. $C_{10}H_{20}O$ requires C, 76·8; H, 12·9%). The β-naphthoate was an oil. The pure p-*nitrobenzoate* formed faintly yellow needles, m. p. 63—64° (Found : C, 67·0; H, 7·6%).

In another preparation, the *p*-nitrobenzoate obtained by partial esterification crystallised only very slowly, and the yield of solid was lower than described above. This solid also had a much higher melting point (84—86° after one recrystallisation), indicating *dl*-menthyl *p*-nitrobenzoate. The residual menthol was again partially esterified : the resulting *p*-nitrobenzoate, after several recrystallisations from alcohol, melted at 49—50°. This was not a homogeneous ester, however, since on hydrolysis and partial re-esterification of the menthol with *p*-nitrobenzoyl chloride the product melted at about 63° after several recrystallisations. This ester was transformed into 3 : 5-dinitrobenzoate; but this was obviously heterogeneous, since upon recrystallisation from alcohol it deposited a mixture of leaflets, characteristic of *dl-neoiso*menthyl 3 : 5-dinitrobenzoate, and needles. Such results are due to an excessive " inversion " of *iso*menthone into menthone before reduction has been completed, thus giving rise to an increased proportion of menthol and *neo*menthol in the product. In the above experiment, for example, the unesterified menthol, forming about 30% of the original reduction product, deposited 14% of its weight of practically pure *dl-neo*menthol when seeded with a minute crystal of that substance.

Pure *dl-neoiso*menthol was obtained also from *dl*-piperitone by the method described immediately below, except that the final purification was accomplished through the 3 : 5-dinitrobenzoate.

d-neoiso*Menthol*.—*l*-Piperitone was hydrogenated below 100° under an over-pressure of 3 atm. in presence of an active hydrogenation catalyst with very weak isomerising power, until about 95% of the calculated amount of hydrogen had been absorbed. The product (containing *ca.* 200 g. of menthols) was heated with phthalic anhydride (270 g.) for 2 hours at 120°, after which unesterified material was removed by steam distillation from water (1500 c.c.) containing ammonia (100 c.c., *d* 0·880). The residual ester was hydrolysed by steam distillation with sodium hydroxide (120 g.). The low yield of menthols (140 g.) showed that some dehydration had occurred during the esterification. The distilled menthols (120 g., b. p. 214—218·5°/760 mm.) formed a sticky paste when treated with 100% phosphoric acid (30 g.) in presence of light petroleum (30 c.c.). The expressed dry solid, after crystallisation from light petroleum (30 c.c.), melted at 58° (55 g.). A further recrystallisation (50 c.c. of solvent) raised the melting point to 60° (constant) (43 g.). The resulting d-neoiso*menthol phosphoric acid* formed soft colourless needles, with a faint odour of the menthol; it gave no appreciable optical rotation ($\alpha_D$) when examined in chloroform solution (*c* 2·0) in a 2-dcm. tube. When decomposed with boiling water, this compound (38 g.) yielded *d-neoiso*menthol (30 g.; calc. for $3C_{10}H_{20}O,H_3PO_4$, 31·4 g.), b. p. 214·6—214·7°/760 mm., m. p. – 8°, $\alpha_{D}^{15^\circ}$ + 0·82° (1-dcm. tube).

Some of this product (18·4 g.) was treated with *p*-nitrobenzoyl chloride (24·1 g.; 1·1 mols.) in dry pyridine (40 c.c.); the resulting ester, after purification by washing and steam distillation (see under *dl-neoiso*menthol), had m. p. 69—73°, $[\alpha]_{D}^{16^\circ}$ – 5·8° (*c* 2·0, chloroform) (32·9 g., 91·5% yield). When recrystallised from hot absolute alcohol (50 c.c.), it yielded pure d-neoiso*menthyl* p-*nitrobenzoate* in fine, pale yellow prisms, up to 1 cm. long; these (30·3 g.) had m. p. 72·5—73°, $[\alpha]_{D}^{15^\circ}$ – 5·3° (*c* 2·0, chloroform), and the values remained constant after further recrystallisation (Found : C, 66·9; H, 7·7. $C_{17}H_{23}O_4N$ requires C, 66·8; H, 7·6%).

The ester was completely hydrolysed when boiled for 30 minutes with 5% methyl-alcoholic potassium hydroxide (155 c.c.; 1·1 mols.). Pure d-neoiso*menthol* (13·7 g.) was isolated by steam distillation, followed by distillation under diminished pressure, as a colourless oil, somewhat more mobile than *dl-neoiso*menthol, with a rather faint odour reminiscent of *neo*menthols. It had b. p. 84·2°/7·5 mm.; m. p. – 8°; $n_{D}^{18^\circ}$ 1·4674, $n_{D}^{60^\circ}$ 1·4503; $d_{4^\circ}^{18^\circ}$ 0·9131; $[R_L]_D$ 47·50 (calc., 47·70); $\alpha_{C}^{16^\circ}$ + 0·06°, $[\alpha]_{C}^{16^\circ}$ +0·07°, $\alpha_{D}^{16^\circ}$ + 0·13°, $[\alpha]_{D}^{16^\circ}$ + 0·14°, $\alpha_{5461}^{16^\circ}$ + 0·14°, $[\alpha]_{5461}^{16^\circ}$ + 0·15° (homogeneous, in 1-dcm. tube); $[\alpha]_{C}^{16^\circ}$ + 1·7°, $[\alpha]_{D}^{16^\circ}$ + 2·2°, $[\alpha]_{5461}^{16^\circ}$ + 2·3° (*c* 2·0, absolute alcohol) (Found : C, 76·8; H, 12·7. $C_{10}H_{20}O$ requires C, 76·8; H, 12·9%). Upon oxidising *d-neoiso*menthol with Beckmann's chromic acid mixture, the temperature rose rapidly. When the black addition compound decomposed (*ca.* 50°), the mixture was quickly cooled, and the ethereal extract of the ketone was washed several times with water, to neutral reaction. The resulting *d-iso*menthone had $\alpha_{D}^{16^\circ}$ + 81·40°, $[\alpha]_{D}^{16^\circ}$ + 90·60°, before distilling (cf. J., 1927, 1281); and after distillation under diminished pressure it had $\alpha_{D}^{16^\circ}$ + 79·70°, $[\alpha]_{D}^{16^\circ}$ + 88·70°, $n_{D}^{17^\circ}$ 1·4548.

*Derivatives of* d-neoiso*Menthol*.—The *p*-nitrobenzoate is described above. The 3 : 5-*dinitrobenzoate* crystallised from absolute alcohol, containing a little ethyl acetate, in long, fine, and almost colourless needles, m. p. 100·5—101°, $[\alpha]_{D}^{15°}$ − 9·5° (*c* 2·0, chloroform) (Found: C, 58·4; H, 6·4. $C_{17}H_{22}O_6N_2$ requires C, 58·3; H, 6·3%). The d-*camphor*-10-*sulphonate* separated from light petroleum (b. p. 60—80°) in rosettes of small colourless prisms, m. p. 69—70°, $[\alpha]_{C}^{16°}$ + 12·3°, $[\alpha]_{D}^{16°}$ + 17·3°, $[\alpha]_{5461}^{16°}$ + 22·3°, $[\alpha]_{F}^{16°}$ + 35·2° (*c* 2·0, chloroform). The ester decomposed at 100°, yielding *d*-camphor-10-sulphonic acid and menthene (cf. J., 1931, 190). From a cold saturated solution in light petroleum it was deposited in well-developed, doubly-terminated prisms (Found: C, 64·6; H, 9·2. $C_{20}H_{34}O_4S$ requires C, 64·8; H, 9·3%). The l-*camphor*-10-*sulphonate* crystallised from light petroleum in small colourless needles, m. p. 84—86°, decomp. 89°. In chloroform solution (*c* 2·0) it had $[\alpha]_{C}^{16°}$ − 31·2°, $[\alpha]_{D}^{16°}$ − 41·0°, $[\alpha]_{5461}^{16°}$ − 50·5°, $[\alpha]_{F}^{16°}$ − 70·8° (Found: C, 64·7; H, 9·3%). The d-*menthoxyacetate* was a yellow syrup, $[\alpha]_{C}^{14°}$ + 34·5°, $[\alpha]_{D}^{14°}$ + 43·6°, $[\alpha]_{5461}^{14°}$ + 51·4°, $[\alpha]_{F}^{14°}$ +67·7° (Found: C, 74·6; H, 11·4. $C_{22}H_{40}O_3$ requires C, 74·9; H, 11·6%). The l-*menthoxyacetate* also was a yellow syrup, $[\alpha]_{C}^{14°}$ − 56·6°, $[\alpha]_{D}^{14°}$ − 71·6°, $[\alpha]_{5461}^{14°}$ − 84·4°, $[\alpha]_{F}^{14°}$ − 107·5° (*c* 2·0, chloroform) (Found: C, 74·7; H, 11·4%). None of the last four esters displayed any marked anomaly of optical rotatory dispersion (cf. Tschugaeff, *Ber.*, 1911, **44**, 2026).

*Refractive Indices of Menthols at* 60°.—At 60° all the menthols except *d*- and *l*-*iso*menthol (m. p. 82·5°) are liquid. The following values of $n_{D}^{60°}$ are of particular interest in relation to the Auwers–Skita rule, according to which *cis*-compounds display higher numerical values than the corresponding *trans*-compounds for refractive index, density, etc. (*Annalen*, 1915, **410**, 287; 1920, **420**, 91):

| | | | |
|---|---|---|---|
| *d*-*neo*menthol (*ex* pure *p*-nitrobenzoate) | 1·4448 | *d*-*neoiso*menthol | 1·4503 |
| *dl*-*neo*menthol (Howards) | 1·4450 | *dl*-*neoiso*menthol | 1·4504 |
| *l*-menthol (Howards) | 1·4461 | *dl*-*iso*menthol (Howards) | 1·4510 |
| ,, (Bush) | 1·4462 | ,, (*ex* pure *p*-nitrobenzoate) | 1·4510 |
| *dl*-menthol (Howards) | 1·4461 | | |
| ,, (*ex* pure *p*-nitrobenzoate) | 1·4465 | | |

We thank the Carnegie Trust for the Universities of Scotland for the award of a Fellowship to one of us (W. J. G.).

THE UNIVERSITY, ST. ANDREWS.

[*Received, January* 8*th*, 1934.]