392. *New Methods in Stereochemistry. Part II. New Ways of resolving* dl-*Menthol.*

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THE successful use of *l*- and *d*-menthoxyacetic acid as resolving agents for externally compensated menthols (Read and Grubb, *J. Soc. Chem. Ind.*, 1932, **51**, 329T; J., 1933, 167) suggested an examination on similar lines of the related l-*menthylglycine*. As shown below, esters of this acid are readily prepared by the following general series of reactions,

$$CH_2Cl{\cdot}COCl \xrightarrow{R{\cdot}OH\ (heat)} CH_2Cl{\cdot}CO_2R \xrightarrow{C_{10}H_{19}{\cdot}NH_2\ (140^\circ)} C_{10}H_{19}{\cdot}NH{\cdot}CH_2{\cdot}CO_2R$$

hydrogen chloride being produced at each stage. If R·OH is *dl*-menthol, the final product may be represented as $R^-{\cdot}NH{\cdot}CH_2{\cdot}CO_2R^+ + R^-{\cdot}NH{\cdot}CH_2{\cdot}CO_2R^-$. The first of these substances, *d-menthyl l-menthylglycine*, m. p. 82°, $[\alpha]_D$ — 2·0° (chloroform), may be easily separated by fractional crystallisation from the accompanying *l-menthyl l-menthylglycine*, m. p. 63°, $[\alpha]_D$ — 105·3°. Hydrolysis with alcoholic alkali then yields pure *d*-menthol and *l*-menthylglycine.

Furthermore, these esters form crystalline salts with acids, and fractional crystallisation of the mixed sulphates leads rapidly to the isolation of pure *l-menthyl l-menthylglycine sulphate* (m. p. 191°), which yields pure *l*-menthol when hydrolysed. These simple operations furnish a rapid and complete optical resolution of *dl*-menthol. The actual yields obtained in a particular experiment were 55·9% and 65·2% of the calculated amounts of *d*- and *l*-menthol, respectively.

The melting points and specific rotatory powers of the *d*- and *l*-menthyl esters of *l*-menthylglycine, $R{\cdot}NH{\cdot}CH_2{\cdot}CO_2R$, approximate closely to the values for the corresponding esters of *l*-menthoxyacetic acid, $R{\cdot}O{\cdot}CH_2{\cdot}CO_2R$ (*J. Soc. Chem. Ind.*, 1932, **51**, 330T), thus illustrating the structural similarity of the groups ·NH· and ·O·.

Unlike the esters of *l*-menthoxyacetic acid, however, the above esters of *l*-menthylglycine may be acylated. The acyl derivatives resemble the parent esters and their salts in their marked capacity for crystallising. Thus, *dl*-menthyl *N*-acetyl-*l*-menthylglycine, $C_{10}H_{19}{\cdot}N(COMe){\cdot}CH_2{\cdot}CO{\cdot}O{\cdot}C_{10}H_{19}$, furnishes the pure *d*-menthyl ester, m. p. 95°, when fractionally crystallised from methyl alcohol, and this ester when hydrolysed yields pure *d*-menthol; the accompanying *N-acetyl-l-menthylglycine*, m. p. 154°, may be recovered quantitatively and used again.

The following summary shows that the general effect of acylating these esters is to raise the melting point and displace the specific rotatory power in the positive direction :

	l-Menthyl *l*-menthylglycine.		*d*-Menthyl *l*-menthylglycine.	
Acyl group.	M. p.	$[\alpha]_D$.	M. p.	$[\alpha]_D$.
—	63°	−105·3°	82°	− 2·0°
Acetyl	liquid	− 50·9	95	+24·1
Benzoyl	96	− 60·8	106—107	+ 8·6
p-Nitrobenzoyl	146	− 51·0	146	+13·0
3 : 5-Dinitrobenzoyl	170	− 23·7	131	+38·0

A noteworthy point of practical interest in connexion with derivatives of menthoxyacetic acid and menthylglycine is that the stability towards alcoholic alkali increases on passing from the group $\cdot O{\cdot}CH_2\cdot$ through $\cdot NH{\cdot}CH_2\cdot$ to $\cdot N(COR){\cdot}CH_2\cdot$.

It is evident that *l*-menthylglycine is a valuable substance for use in the optical resolution and general characterisation of alcohols. Its esters, even with simple alcohols of low molecular weight, yield crystalline acyl derivatives and salts; for example, the *dl-sec.*-butyl ester forms a crystalline *p*-nitrobenzoyl derivative and sulphate. Moreover, *l*-menthylglycine esters constitute a new series of optically active bases; while *l*-menthylglycine and its acyl derivatives are stable, optically active acids. All these substances have a pronounced capacity for crystallising and giving rise to crystalline derivatives. Together with certain analogous series now under investigation, derived from bases other than *l*-menthylamine, they offer great promise as useful stereochemical agents.

In a related research, *phthalo-l-menthylamic acid*, $HO_2C{\cdot}C_6H_4{\cdot}CO{\cdot}NH{\cdot}C_{10}H_{19}$, was prepared, with the object of applying it as an optically active acid in the resolution of externally compensated alcohols and bases. It is a readily accessible and well-defined substance; but its use is handicapped by the ease with which it is dehydrated in esterification processes, to form *phthalo-l-menthylimide*.

EXPERIMENTAL.

l-Menthylglycine and Derivatives.—(1) *Ethyl l-menthylglycine.* Ethyl chloroacetate (1·8 g.) was added to a dry solution of *l*-menthylamine (from 5·5 g. of the hydrochloride) in benzene and heated for 7 hours; the benzene was then distilled away. The residual mixture of *l*-menthylamine hydrochloride and ethyl *l*-menthylglycine was separated by treatment with water and ether, the ethereal extract being washed with dilute acid before distillation. The purified ester (2·2 g.) was a colourless liquid, b. p. 139°/10 mm.; it had $[\alpha]_D - 56{\cdot}1^\circ$ (*c* 2·0, chloroform), $n_D^{15^\circ}$ 1·4642.

(2) l-*Menthyl* l-*menthylglycine*. A solution of *l*-menthol (34 g.) and chloroacetyl chloride (25 g.; 1·02 mols.) in dry benzene was boiled under reflux, in an apparatus closed with calcium chloride tubes, until hydrogen chloride ceased to be evolved (5—6 hours). The benzene solution was washed successively with water, sodium hydroxide solution, and again with water; it was then dried over sodium sulphate and fractionally distilled. The resulting *l*-menthyl chloroacetate (47·5 g.; 98% yield) crystallised in the receiver, and had b. p. 136°/13 mm., m. p. 39—40°, $[\alpha]_D - 77{\cdot}5^\circ$ (*c* 2·0, chloroform) (compare Einhorn and Jahn, *Arch. Pharm.*, 1902, **240**, 644; Tschugaev, *J. Russ. Phys. Chem. Soc.*, 1902, **34**, 606; Frankland and Barrow, J., 1914, **105**, 990).

l-Menthyl chloroacetate (47·5 g.) was added to dry benzene containing an excess of *l*-menthylamine (from 140 g. of the hydrochloride), the benzene was distilled off, and the residue was heated for 6 hours at 140° in an apparatus closed by soda-lime tubes. The cold mixture of base, hydrochloride, and ester was then poured into an excess of dilute sulphuric acid and extracted twice with chloroform. Unchanged *l*-menthylamine was recovered from the acid liquor. The chloroform solution was washed six times with water to remove all retained *l*-menthylamine sulphate, once with sodium carbonate solution to ensure that no sulphuric acid remained in combination with the ester, and finally with water. The ester (70 g.; 95·6% yield), which was left upon distilling the chloroform solution, crystallised from methyl alcohol in stout prisms. The purified l-*menthyl* l-*menthylglycine* melted at 63°, and a chloroform solution (*c* 2·0) gave the following polarimetric values at 19·6°: $[\alpha]_C - 82{\cdot}5^\circ$, $[\alpha]_D - 105{\cdot}3^\circ$, $[\alpha]_{5461} - 124{\cdot}3^\circ$, $[\alpha]_F - 160{\cdot}4^\circ$ (Found: C, 75·1; H, 11·7. $C_{22}H_{41}O_2N$ requires C, 75·2; H, 11·6%).

The *N*-acetyl derivative is a colourless syrup, having $[\alpha]_D - 50{\cdot}9^\circ$ (*c* 2·0, chloroform), $n_D^{15^\circ}$ 1·4821. The *N*-benzoyl derivative separates from methyl alcohol in small glistening prisms, m. p. 96°, $[\alpha]_C - 50{\cdot}1^\circ$, $[\alpha]_D - 60{\cdot}8^\circ$, $[\alpha]_{5461} - 70{\cdot}7^\circ$, $[\alpha]_F - 88{\cdot}9^\circ$ (*c* 2·0, chloroform; *t* 18·5°). The N-p-*nitrobenzoyl* derivative crystallises from methyl alcohol in coarse transparent prisms, with a faint green tinge, m. p. 146°, $[\alpha]_D - 51{\cdot}0^\circ$ (*c* 2·0, chloroform) (Found: C, 69·7; H, 8·7. $C_{29}H_{44}O_5N_2$ requires C, 69·6; H, 8·8%). The *N*-3 : 5-dinitrobenzoyl derivative separates from methyl alcohol in felted needles with a faint yellow tinge, m. p. 170°, $[\alpha]_D - 23{\cdot}7^\circ$ (*c* 2·0, chloroform).

The *sulphate* was prepared by shaking a chloroform solution of the ester with an excess of dilute sulphuric acid. The residue obtained upon distilling the dried chloroform crystallised from rectified spirit in long slender needles, m. p. 191°, $[\alpha]_D - 93{\cdot}0^\circ$ (*c* 2·0, chloroform) [Found: C, 66·3; H, 10·7. $(C_{22}H_{41}O_2N)_2,H_2SO_4$ requires C, 66·0; H, 10·5%]. The sulphate is practically insoluble in water, acetone, ether or light petroleum, slightly soluble in cold methyl or ethyl alcohol, and moderately soluble in chloroform or benzene. The hydrochloride was prepared similarly; it forms fine needles, m. p. 69°, $[\alpha]_D - 77{\cdot}7^\circ$. The *oxalate*, formed by dissolving oxalic acid (0·9 g.) in a warm chloroform solution of the ester (3·5 g.), crystallises from rectified spirit in long colourless needles, m. p. 168·5°, $[\alpha]_D - 76{\cdot}4^\circ$ (Found: C, 65·1; H, 9·7. $C_{22}H_{41}O_2N,C_2H_2O_4$ requires C, 65·3; H, 9·8%).

(3) d-*Menthyl* l-*menthylglycine*. *dl*-Menthylglycine chloroacetate, prepared from *dl*-menthol by the method described above for the *l*-menthyl ester, was obtained as a liquid, b. p. 130°/9·5 mm., $n_D^{15^\circ}$ 1·4671. This ester (100 g.), when heated with *l*-menthylamine (250 g.; 3·4 mols.) at 120—130° for 6 hours (*vide supra*), yielded crude *dl*-menthyl *l*-menthylglycine (150 g.) as a hard waxy solid, with an indefinite melting point, and having $[\alpha]_D - 43{\cdot}0^\circ$ (*c* 2·0, chloroform). The product crystallised readily from methyl alcohol, and after six fractional recrystallisations furnished pure d-*menthyl* l-*menthylglycine* (32·7 g.; 43·6% yield) in large prisms, m. p. 82°, $[\alpha]_D - 2{\cdot}0^\circ$ (*c* 2·0, chloroform) (Found: C, 75·2; H, 11·5. $C_{22}H_{41}O_2N$ requires C, 75·2; H, 11·6%). The observed values of $[\alpha]$ were sensibly constant between the C and F lines.

The N-*acetyl* derivative crystallises from methyl alcohol in small felted needles, m. p. 95°, $[\alpha]_D + 24{\cdot}1^\circ$ (*c* 2·0, chloroform) (Found: C, 73·1; H, 10·7. $C_{24}H_{43}O_3N$ requires C, 73·3; H, 10·9%). The *N*-benzoyl derivative separates from aqueous methyl alcohol in small needles, m. p. 106—107°, $[\alpha]_D + 8{\cdot}6^\circ$. The N-p-*nitrobenzoyl* derivative crystallises from methyl alcohol in handsome prismatic needles with a greenish-yellow tinge, m. p. 146°, $[\alpha]_D + 13{\cdot}0^\circ$ (Found: C, 69·4; H, 8·8. $C_{29}H_{44}O_5N_2$ requires C, 69·6; H, 8·8%). The *N*-3 : 5-dinitrobenzoyl derivative forms soft, faintly yellow needles, m. p. 131°, $[\alpha]_D + 38{\cdot}0^\circ$.

The sulphate crystallises from ethyl acetate in fine needles, m. p. 176°, $[\alpha]_D + 3{\cdot}7°$ (*c* 2·0, chloroform).

(4) N-*Acetyl*-l-*menthylglycine*. *l*-Menthyl *l*-menthylglycine (24 g.) was warmed on the water-bath for 4 hours with a mixture of pyridine (10 c.c.) and acetic anhydride (20 c.c.). After treatment with water and sodium carbonate solution the crude *l*-menthyl *N*-acetyl-*l*-menthylglycine was hydrolysed by boiling it for 2 hours with a solution of potassium hydroxide (4·5 g.; 1·2 mols.) in absolute alcohol (450 c.c.). After steam distillation the aqueous residue was extracted with ether, to remove any unhydrolysed material, and then acidified. The resulting N-*acetyl*-l-*menthylglycine* (14·7 g.) crystallised from rectified spirit in slender needles, m. p. 154°, $[\alpha]_D - 43{\cdot}6°$ (*c* 2·0, chloroform) (Found: C, 65·8; H, 9·8. $C_{14}H_{25}O_3N$ requires C, 65·9; H, 9·8%). The substance is very stable towards acid or alkali, being attacked only very slowly by hot 50% sulphuric acid or 10% sodium hydroxide solution; it is almost insoluble in cold water, but dissolves appreciably in hot water.

(5) N-*Benzoyl*-l-*menthylglycine*. *l*-Menthyl benzoyl-*l*-menthylglycine (6 g.) was hydrolysed with hot 2% alcoholic potassium hydroxide (60 c.c.). N-*Benzoyl*-l-*menthylglycine* (4 g.), isolated as in (4) above, formed a thick syrup, which crystallised from ether–light petroleum in coarse prisms, m. p. 118°, $[\alpha]_D - 73{\cdot}5°$ (Found: C, 71·7; H, 8·5. $C_{19}H_{27}O_3N$ requires C, 71·9; H, 8·5%). The acid is insoluble in water.

(6) l-*Menthylglycine*. The alkaline solutions obtained in the hydrolysis of *l*- or *d*-menthyl *l*-menthylglycine (*vide infra*) gave no precipitate when acidified. Upon concentrating such a solution to half bulk, saturating it with carbon dioxide, and keeping it over-night, a crystalline separation of l-*menthylglycine* was obtained. This crystallised from warm water, in which it was moderately soluble, in small glistening prisms, m. p. 191°, $[\alpha]_D - 61{\cdot}5°$ (*c* 2·0, chloroform) (Found: C, 67·5; H, 10·8. $C_{12}H_{23}O_2N$ requires C, 67·6; H, 10·8%). The substance decomposes upon melting, with the formation of *N*-methyl-*l*-menthylamine and carbon dioxide.

Optical Resolutions of dl-*Menthol by Means of* l-*Menthylglycine*.—(1) *Isolation of* d-*menthol through* dl-*menthyl* l-*menthylglycine*. Six fractional crystallisations of crude *dl*-menthyl *l*-menthylglycine from methyl alcohol furnished pure *d*-menthyl *l*-menthylglycine in a yield of 43·6% of the calculated amount (see under 3, above). This ester (10 g.) was heated under reflux for 2 hours with 1% alcoholic potassium hydroxide (250 c.c.; 1·25 mols.). The excess of alkali was almost neutralised, and the *d*-menthol was isolated by steam-distillation, followed by extraction with ether in the usual way. The *d*-menthol (3·8 g.) had b. p. 98°/12 mm., m. p. 42—43°, $[\alpha]_D + 50{\cdot}6°$ (*c* 2·0, alcohol). The yield was 36·6% of the possible amount, based upon the *dl*-menthol used: this was a commercial specimen (Bush), m. p. 28·8—31·2° (1° per minute).

(2) *Isolation of* d- *and* l-*menthol through* dl-*menthyl* l-*menthylglycine and its sulphate*. Crude *dl*-menthyl *l*-menthylglycine was prepared by the method described above under the heading of *l*-menthyl *l*-menthylglycine, except that the final washing with sodium carbonate solution was omitted. Upon distilling away the chloroform, crystalline *dl*-menthyl *l*-menthylglycine normal sulphate was obtained in a yield of 95·6%, based upon the original *dl*-menthol used; it had $[\alpha]_D - 38{\cdot}0°$ (*c* 2·0, chloroform).

The sulphate (76 g.) was warmed for an hour under reflux with acetone (200 c.c.); the crystalline deposit from the cold solution (29·8 g., $[\alpha]_D - 66{\cdot}0°$), upon recrystallisation from a mixture of rectified spirit (100 c.c.) and acetone (70 c.c.), yielded almost pure *l*-menthyl *l*-menthylglycine sulphate (16 g.), with $[\alpha]_D - 91{\cdot}8°$. The solid residues from the combined mother-liquors were dissolved in chloroform and shaken with dilute sodium hydroxide solution. The recovered impure *d*-menthyl *l*-menthylglycine (51·3 g.) had $[\alpha]_D - 34{\cdot}2°$; after two recrystallisations from methyl alcohol this material yielded almost pure *d*-menthyl ester (17·7 g.), with $[\alpha]_D - 2{\cdot}7°$. By means of a systematic alternating treatment of this kind it was found readily possible to isolate pure *l*-menthyl *l*-menthylglycine sulphate in 74% yield (28·2 g.) and *d*-menthyl *l*-menthylglycine in 60% yield (20·1 g.). The latter ester, when heated on the water-bath for 2 hours with 5% alcoholic potassium hydroxide (100 c.c.), gave a 95·6% yield of *d*-menthol, having b. p. 99°/12·5 mm., m. p. 42°, $[\alpha]_D^{17°} + 49{\cdot}8°$ (*c* 2·0, alcohol).

The *dl*-menthol used in this work (Howards) had a purity of 99·5%, and was identical with the specimen used by Read and Grubb (*J. Soc. Chem. Ind.*, 1932, **51**, 329T). The yields of pure *d*- and *l*-menthol obtained were 55·9% and 65·2% of the calculated amounts, respectively; the corresponding yields obtained by the successive application of *l*- and *d*-menthoxyacetyl chloride were 53·4% and 47·4%, respectively (*loc. cit.*).

(3) *Isolation of* d-*menthol through* dl-*menthyl* N-*acetyl*-l-*menthylglycine*. Thionyl chloride (6·0 c.c.), dissolved in dry benzene (40 c.c.), was added slowly (1 hour) to a warm solution of

N-acetyl-*l*-menthylglycine (*vide supra*) (20 g.) and *dl*-menthol (12·6 g.) in benzene (100 c.c.), contained in a refluxing apparatus closed with calcium chloride tubes. The mixture was afterwards heated for 2 hours on the water-bath. The cold liquid was washed successively with water, dilute aqueous sodium hydroxide, and again with water; benzene and *dl*-menthol were removed by steam distillation; and the residual ester, consisting of crude *dl*-menthyl *N*-acetyl-*l*-menthylglycine, after being dried in ether, was obtained as a thick oil (26 g.) which crystallised from methyl alcohol when seeded with pure *d*-menthyl *N*-acetyl-*l*-menthylglycine.

After six recrystallisations the pure *d*-menthyl ester (2·5 g.) was obtained, with m. p. 95°, $[\alpha]_D + 23{\cdot}8°$ (*c* 2·0, chloroform). When hydrolysed with hot 5% alcoholic potassium hydroxide, it furnished pure *d*-menthol, the yield of which (from the *dl*-menthol used) was 7·5% of the calculated amount.

Direct treatment of *N*-acetyl-*l*-menthylglycine or its salts with thionyl chloride in the absence of a solvent led to decomposition. *dl*-Menthyl *N*-acetyl-*l*-menthylglycine may also be readily prepared by acetylating *dl*-menthyl *l*-menthylglycine, by the method described above under *N*-acetyl-*l*-menthylglycine.

dl-Menthyl *l*-menthylglycine reacted in pyridine with *p*-nitrobenzoyl chloride to yield crude *dl*-menthyl *N*-*p*-nitrobenzoyl-*l*-menthylglycine, $[\alpha]_D - 16{\cdot}3°$ (*c* 2·0, chloroform). After three recrystallisations from methyl alcohol a fraction was obtained with $[\alpha]_D - 5{\cdot}2°$. This contained 71·8% of the *d*-menthyl ester, and it was considered unnecessary to carry the purification to completion.

dl-Menthyl *N*-benzoyl-*l*-menthylglycine was obtained as a thick syrupy liquid which could not be induced to crystallise.

Phthalo-l-*menthylamic Acid.*—*l*-Menthylamine hydrogen phthalate, prepared by mixing equivalent weights of the acid and base in chloroform solution, readily yielded *phthalo*-l-*menthylimide* when heated for 2 hours at 150°/360 mm. This crystallised from alcohol in beautiful lustrous prisms of a symmetrical habit, m. p. 109°, $[\alpha]_D - 18{\cdot}9°$ (*c* 5·0, chloroform) (Found: C, 75·6; H, 8·1. $C_{18}H_{23}O_2N$ requires C, 75·8; H, 8·1%). The same substance resulted when *l*-menthylamine was heated with *l*-menthyl hydrogen phthalate or with phthalic anhydride.

Phthalo-*l*-menthylimide (7 g.) was heated under reflux for 2 hours with 5% alcoholic potassium hydroxide (40 c.c.). *Phthalo*-l-*menthylamic acid* (6·5 g.) was obtained upon removing the alcohol and acidifying; it crystallised from alcohol in fine needles, m. p. 171°, $[\alpha]_D - 71{\cdot}8°$ (*c* 1·2, chloroform) (Found: C, 71·1; H, 8·3. $C_{18}H_{25}O_3N$ requires C, 71·3; H, 8·3%). Upon treating this substance or its sodium salt with thionyl chloride phthalo-*l*-menthylimide was produced; a similar result was attained when a solution of the acid amide in molten *l*-menthol was saturated with dry hydrogen chloride at 80°.

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