

148. *The Different Reaction Velocities of Enantiomers with a Common Optically Active Reagent. Part II.* Reactions between Stereoisomeric Menthols and Menthyl isoCyanates.*

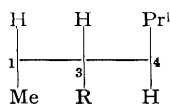
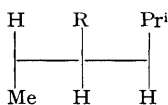
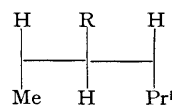
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isoCyanates (carbimides) derived from (–), (±), (+)-*neo*-, and (+)-*iso*-menthylamine have been prepared and brought into reaction with the three corresponding types of menthols. The resulting pure menthyl menthyl-carbamates have been characterised and applied in studying a series of competitive reactions leading to the formation of mixtures of pairs of these compounds. Two new virtual optical resolutions of (±)-menthol and a partial optical resolution of (±)-*isomenthol* are described.

THE present investigation differs in two important respects from that reported in Part I * of this series. First, the stereoisomers now described as reacting with a common optically active reagent were not always enantiomers; secondly, the experiments utilised a series

* Part I, *J.*, 1936, 1219.

of reactants having varied but closely similar molecular configurations. The menthyl isocyanates ($R = \text{NCO}$) and menthols ($R = \text{OH}$) concerned all belonged to the $(-)$ -, $(+)$ -*neo*-, and $(+)$ -*iso*-series, possessing the following relative configurations (Read and Grubb, *J.*, 1934, 1781) :

(I) $(-)$ -(II) $(+)$ -*neo*-(III) $(+)$ -*iso*-

In a series of reactions between an equimolecular mixture of two stereoisomers, present in excess (3 mols.), and an individual optically active reagent (1 mol.), the product was always a pair of stereoisomeric menthyl menthylcarbamates, formed in a bimolecular reaction (Pickard, Littlebury, and Neville, *J.*, 1906, 89, 93), and usually produced in different amounts. The optical rotatory power of each pure constituent being known, it was possible to calculate the quantitative composition of the mixture from its observed optical rotation. Some stereoisomeric preferences of considerable interest were established in the series of nine experiments which are summarised in the following table :

Results of competitive reactions between various menthols and menthyl isocyanates.

Reactants	Predominating ester (%)	Ratio of the two esters
(1) (\pm) -Menthol (3 mols.); $(-)$ -menthyl isocyanate (1 mol.)	$(+)$ -Menthyl (62.3)	1.7 : 1
(2) (\pm) -Menthol (3 mols.); $(+)$ - <i>neomenthyl</i> isocyanate (1 mol.)	$(-)$ -Menthyl (76.9)	3.3 : 1
(3) (\pm) -Menthol (3 mols.); $(+)$ - <i>isomenthyl</i> isocyanate (1 mol.)	$(+)$ -Menthyl (50.8)	1.1 : 1
(4) (\pm) - <i>neo</i> Menthol (3 mols.); $(-)$ -menthyl isocyanate (1 mol.)	$(+)$ - <i>neo</i> Menthyl (50.2)	1.1 : 1
(5) (\pm) - <i>iso</i> Menthol (3 mols.); $(-)$ -menthyl isocyanate (1 mol.)	$(-)$ - <i>iso</i> Menthyl (75.0)	3.0 : 1
(6) $(-)$ -Menthol (1.5 mols.), $(+)$ - <i>neomenthol</i> (1.5 mols.); $(-)$ -menthyl isocyanate (1 mol.)	$(-)$ -Menthyl (69.3)	2.3 : 1
(7) $(-)$ -Menthol (1.5 mols.), $(+)$ - <i>isomenthol</i> (1.5 mols.); $(-)$ -menthyl isocyanate (1 mol.)	$(+)$ - <i>iso</i> Menthyl (50.9)	1.1 : 1
(8) $(-)$ -Menthol (1 mol.); $(-)$ -menthyl isocyanate (1.5 mols.), $(+)$ - <i>neomenthyl</i> isocyanate (1.5 mols.)	$(-)$ -Menthylcarbamate (63.9)	1.8 : 1
(9) $(-)$ -Menthol (1 mol.); $(-)$ -menthyl isocyanate (1.5 mols.), $(+)$ - <i>isomenthyl</i> isocyanate (1.5 mols.)	$(+)$ - <i>iso</i> Menthylcarbamate (65.7)	2.0 : 1

Experiment (1) illustrates the pronounced tendency of an asymmetric reacting molecule or radical to show a preference for its enantiomeric rather than its coincident form; a comparative neglect of the coincident form is shown also in (9). $(-)$ -Menthyl $(-)$ -menthylcarbamate is formed with the greater alacrity only in two experiments (6 and 8) in which the production of the second (*neomenthyl*) ester is retarded by the presence of a *cis-isopropyl* radical (see II, above).

In the first four experiments the diastereoisomer of higher melting point is invariably formed in greater amount, denoting a higher reaction velocity; this is most likely the case in (5) also, but in this instance the melting point of $(+)$ -*isomenthyl* $(-)$ -menthylcarbamate is at present unknown. As a similar example in another series, Read and Grubb (*J. Soc. Chem. Ind.*, 1932, 51, 329r) found that $(+)$ -menthol reacted more rapidly than $(-)$ -menthol with $(-)$ -menthoxyacetyl chloride, and that the $(+)$ -menthyl ester had the higher melting point. Again, $(+)$ -menthyl $(-)$ -menthylglycine, with its two enantiomeric menthyl radicals, has a higher melting point than $(-)$ -menthyl $(-)$ -menthylglycine (Clark and Read, *J.*, 1934, 1776), and would probably be the predominating product of a reaction between $(-)$ -menthylamine and an excess of (\pm) -menthyl chloroacetate.

These observations afford at any rate a partial answer to two queries raised by Galloway and Read (*loc. cit.*, p. 1220) : (1) it has proved possible "to adduce a sustained and connected series of reactions throughout which a common molecule or radical" shows a preference in each instance for its enantiomeric form; and (2) "the relative rates of formation of the two diastereoisomeric products" of a considerable variety of reactions have been correlated to some extent "with the comparative physical properties of the two substances." In the last four of the nine experiments listed above the two products are not truly diastereoisomeric, and the relationships in question do not hold.

In view of the strong preference shown by (–)-[as against (+)-] menthol for (+)-*neomenthyl isocyanate* in (2), the formation of a correspondingly large excess of (+)-*neomenthyl* (–)-menthylcarbamate might have been expected in (4); in this case, however, the two esters are produced in practically equal amounts. A similar example is provided in (5) and (3). The order of allocation of the two reactive groups (–OH and –NCO) to the two stereoisomeric radicals concerned is therefore an important factor in determining the relative velocities of reaction.

A comparison of experiments (1) and (5) shows that (–)-menthyl *isocyanate* prefers to react with (+)- [rather than (–)-] menthol, and with (–)-*iso*- [rather than (+)-*iso*-] menthol. A supplementary experiment (7) shows further that this reagent has a practically equal tendency to react with (–)-menthol and (+)-*isomenthol*.

It is clear from such considerations that experiments of this kind could be extended with profit in many directions. One related matter that has been explored in the present investigation is the bearing of such reactions upon the resolution of externally compensated menthols into their optically active components. That such an optical resolution is possible by a static method, depending upon fractional crystallisation of an equimolecular mixture of diastereoisomeric carbamates, is shown by the work of Pickard and his collaborators, who resolved (\pm)-1-*p*-hydroxyphenyl-2-phenylethane and (\pm)-*ac*-tetrahydro-2-naphthol (*J.*, 1906, **89**, 467, 1254) by fractionally crystallising the (–)-menthylcarbamates. As shown below, the mixture of esters obtained in experiments (1) and (2) above readily yielded pure (+)-menthyl (–)-menthylcarbamate and (–)-menthyl (+)-*neomenthylcarbamate* respectively when fractionally crystallised; so far, however, it has not proved possible to detach the pure (+)- and (–)-menthol by hydrolysis, owing to the great stability of these esters.

As shown above, in experiment (5), (–)-*isomenthol* reacts much more rapidly than (+)-*isomenthol* with (–)-menthyl *isocyanate*: a dynamic method of optical resolution should therefore be possible in which the chemical reaction becomes the effective resolving agent. In a first operation of this kind, the residual specimen of *isomenthol* contained 67% of the (+)-form, from which it is clear that pure (+)-*isomenthol* could be obtained by repeating the operation a number of times. In working practice it should be possible to prepare pure (+)-*isomenthol* by fractionally crystallising a mixture obtained from (\pm)-*isomenthol* by this method and containing a relatively small amount of (–)-*isomenthol*, since (+)-*isomenthol* (m. p. 82.5°) is less soluble than (\pm)-*isomenthol* (m. p. 53.5°). Up to the present the optical resolution of (\pm)-*isomenthol* has not been accomplished and therefore the possibility now indicated has a particular interest.

EXPERIMENTAL

Preparation and Characterisation of Menthyl isoCyanates.—(–)-*Menthyl isocyanate*. Ethyl (–)-menthylcarbamate, prepared from (–)-menthylamine, ethyl chloroformate, and sodium hydrogen carbonate, by Neville and Pickard's method (*J.*, 1904, **85**, 688), had b. p. 112–115°/0.4 mm., m. p. 54.5–55.5°, $[\alpha]_D^{25} = -83.6^\circ$ (*c.* 0.9 in ethanol); when distilled with phosphoric oxide at 15–30 mm. it yielded (–)-menthyl *isocyanate*, b. p. 98–100°/15 mm., $[\alpha]_D^{17} = -55.01^\circ$ (1 dm., homogeneous).

(\pm)-*Menthyl isocyanate*. Ethyl (\pm)-menthylcarbamate, prepared from (\pm)-menthylamine [obtained from (\pm)-menthol, *via* (\pm)-menthone and (\pm)-menthone oxime], formed stout prisms, m. p. 93–94°, from aqueous alcohol (Found: N, 6.3. $C_{13}H_{25}O_2N$ requires N, 6.2%). (\pm)-*Menthyl isocyanate*, prepared similarly to the (–)-compound, was a mobile oil, b. p. 120–123°/16 mm. (Found: N, 7.9. $C_{11}H_{19}ON$ requires N, 7.7%).

(+)-*neoMenthyl isocyanate*. Ethyl (+)-*neomenthylcarbamate*, prepared in the usual way from (+)-*neomenthylamine*, crystallised from aqueous alcohol in large transparent prisms, m. p. 49.5–50°, $[\alpha]_D^{25} +46.5^\circ$ (*c.* 1.8 in ethanol) (Found: N, 6.2%). (+)-*neoMenthyl isocyanate* formed a mobile oil, b. p. 108–110°/16–17 mm., $[\alpha]_D^{14} = -29.86^\circ$ (1 dm., homogeneous) (Found: N, 7.8%).

(+)-*isoMenthyl isocyanate*. Ethyl (+)-*isomenthylcarbamate*, prepared from (+)-*isomenthylamine*, formed a viscid oil; this crystallised readily in a mixture of snow and salt, but reverted to a thick fluid at room temperature, $[\alpha]_D^{17} +38.4^\circ$ (*c.* 1.5 in ethanol) (Found: N, 6.4%).

(+)-*isoMenthyl isocyanate* had b. p. 116—117°/35 mm., $\alpha_D^{16} +26.20^\circ$ (1 dm., homogeneous) (Found: N, 7.9%).

Pure Menthyl Esters of Menthylcarbamic Acids.—(-)-*Menthyl (-)-menthylcarbamate*. An equimolecular mixture of (-)-menthol and (-)-menthyl isocyanate was heated for 10 hours on a boiling-water bath. The product was steam-distilled, and the residue extracted with ether. Upon removal of ether from the dried extract, (-)-menthyl (-)-menthylcarbamate remained as a viscous oil which soon crystallised. Recrystallisation from light petroleum yielded small needles, m. p. 110—110.5°, $[\alpha]_D^{17} -94.2^\circ$ (*c.* 1.1 in ethanol) (Found: C, 74.5; H, 11.7. $C_{21}H_{39}O_2N$ requires C, 74.8; H, 11.6%). (+)-*Menthyl (-)-menthylcarbamate*, prepared similarly from (+)-menthol, separated from light petroleum in transparent needles up to 2.5 cm. long, m. p. 120—121°, $[\alpha]_D^{18} -5.0^\circ$ (*c.* 0.75 in ethanol) (Found: C, 74.4; H, 11.7%). (\pm)-*Menthyl (-)-menthylcarbamate*, prepared from (\pm)-menthol, formed small needles, m. p. 73—75°, $[\alpha]_D^{17} -50.8^\circ$ (*c.* 1.2 in ethanol). The mean value of $[\alpha]_D$ for the pure (+)- and (-)-components of this ester is -49.6° . (-)-*Menthyl (\pm)-menthylcarbamate* was obtained from (-)-menthol and (\pm)-menthyl isocyanate as a crystalline mass, m. p. 97—98°, $[\alpha]_D^{15} -43.3^\circ$ (*c.* 2.1 in ethanol). The mean value of $[\alpha]_D$ for the esters of (+)- and (-)-menthylcarbamic acid with (-)-menthol (above) is -44.6° . (+)-*neoMenthyl (-)-menthylcarbamate*, prepared in the usual way, formed small needles, m. p. 121—122°, $[\alpha]_D^{17} -35.8^\circ$ (*c.* 1.1 in ethanol) (Found: C, 73.8; H, 11.5%). (-)-*neoMenthyl (-)-menthylcarbamate* formed minute needles, m. p. 107—108°, $[\alpha]_D -62.9^\circ$ (*c.* 1.6 in ethanol) (Found: C, 74.7; H, 11.6%). (+)-*isoMenthyl (-)-menthylcarbamate* separated from ethanol in small prisms, m. p. 84—85°, $[\alpha]_D^{19} -27.0^\circ$ (*c.* 0.9 in ethanol) (Found: C, 74.9; H, 11.6%). (\pm)-*isoMenthyl (-)-menthylcarbamate* formed an amorphous solid mass, m. p. 73—74°, $[\alpha]_D^{16} -37.8^\circ$ (*c.* 0.7 in ethanol). From these observations the calculated value $[\alpha]_D -48.6^\circ$ is obtained for (-)-*isomenthyl (-)-menthylcarbamate*.

(-)-*Menthyl (+)-neomenthylcarbamate* was prepared from (-)-menthol and (+)-*neo*-menthyl isocyanate in the usual way, except that the heating was continued for 40 hours. The compound crystallised from ethanol in fine needles up to 2.5 cm. long, m. p. 114—115°, $[\alpha]_D^{15} -9.1^\circ$ (*c.* 1.1 in ethanol) (Found: C, 74.7; H, 11.6%). (+)-*Menthyl (+)-neomenthylcarbamate*, prepared similarly, separated from ethanol in small transparent plates containing combined ethanol (2 mols.), m. p. 74.5—75.5°, $[\alpha]_D^{14} +85.0^\circ$ (*c.* 1.4 in ethanol) (Found: C, 71.3; H, 11.3. $C_{21}H_{39}O_2N, 2C_2H_6O$ requires C, 70.6; H, 11.1%).

(-)-*Menthyl (+)-isomenthylcarbamate* was obtained by heating an equimolecular mixture of (-)-menthol and (+)-*isomenthyl isocyanate* at 100° for 12 hours, in the usual way. It formed transparent needles from ethanol, having m. p. 79—80°, $[\alpha]_D^{18} -24.6^\circ$ (*c.* 0.7 in ethanol) (Found: C, 74.8; H, 11.3%). (+)-*Menthyl (+)-isomenthylcarbamate* had m. p. 82—83°, $[\alpha]_D^{17} +64.7^\circ$ (*c.* 0.7 in ethanol) (Found: C, 74.5; H, 11.3%).

Competitive Reactions.—In all the following experiments an equimolecular mixture of two stereoisomerides (3 mols.) was brought into reaction with an individual optically active reagent (1 mol.), under the conditions specified for the first experiment. All the optical rotatory powers quoted were measured in absolute ethyl alcoholic solution (*c.* 1—3).

(1) (\pm)-*Menthol (3 mols.) and (-)-menthyl isocyanate (1 mol.)*. (\pm)-Menthol (23 g.) was heated on a boiling-water bath in a small flask fitted with reflux condenser and dropping funnel, each of which was closed with a calcium chloride tube. (-)-Menthyl isocyanate (8.75 g.) was admitted gradually through the dropping funnel (2 hours), local concentration being avoided by vigorous shaking. After 12 hours' further heating the excess of menthol was removed by steam-distillation, the residual mixture of diastereoisomeric esters being then extracted with ether, the extract dried, and the solvent removed. The mixed esters weighed 13.92 g. and had $[\alpha]_D^{19.5} -38.6^\circ$, corresponding to 62.3% of (+)-menthyl ester and 37.7% of (-)-menthyl ester. The recovered menthol had $[\alpha]_D^{19.5} -2.0^\circ$, showing that partial optical resolution of the (\pm)-menthol had occurred as a result of the more rapid reaction of (+)-menthol.

(2) (\pm)-*Menthol (3 mols.) and (+)-neomenthyl isocyanate (1 mol.)*. In this experiment the heating was prolonged to 70 hours. The value, $[\alpha]_D^{14} +26.6^\circ$ (0.8801 g. made up to 50 c.c. gave $\alpha_D^{14} +1.87^\circ$ in a 4-dm. tube), indicated the presence of 76.9% of (-)- and 23.1% of (+)-menthyl ester. The unchanged menthol had $[\alpha]_D^{14} +0.2^\circ$.

(3) (\pm)-*Menthol (3 mols.) and (+)-isomenthyl isocyanate (1 mol.)*. The ester mixture obtained after 12 hours' heating had $[\alpha]_D^{15} +20.8^\circ$, and the unchanged menthol showed no measurable optical activity under the usual conditions. The calculated proportion of the (+)-ester is 50.8%, and of the (-)-menthyl ester 49.2%.

(4) (\pm)-*neoMenthol (3 mols.) and (-)-menthyl isocyanate (1 mol.)*. After 15 hours' heating

under the usual conditions the mixture of esters had $[\alpha]_D -49.3^\circ$, and the unchanged *neo*-menthol showed no measurable optical activity. The calculated proportions are 50.2% of the (+)- and 49.8% of the (-)-*neomenthyl* ester.

(5) (\pm)-*isoMenthol* (3 mols.) and (-)-*menthyl isocyanate* (1 mol.). The mixed esters resulting after 10 hours' heating crystallised when kept *in vacuo* for a short time, and had $[\alpha]_D -43.2^\circ$, corresponding to 75.0% of the (-)- and 25.0% of the (+)-*isomenthyl* ester. The unchanged *isomenthol* was dextrorotatory.

(6) (-)-*Menthol* (1.5 mols.), (+)-*neomenthol* (1.5 mols.), and (-)-*menthyl isocyanate* (1 mol.). (-)-*Menthyl isocyanate* was added gradually to a mixture of (-)-*menthol* and (+)-*neomenthol*, and after 12 hours' heating the mixture of esters was isolated in the usual way. This product was an oil which readily solidified to an amorphous mass, having $[\alpha]_D^{17} -76.3^\circ$, corresponding to 69.3% of (-)-*menthyl* ester and 30.7% of (+)-*neomenthyl* ester.

(7) (-)-*Menthol* (1.5 mols.), (+)-*isomenthol* (1.5 mols.), and (-)-*menthyl isocyanate* (1 mol.). The heating was continued for 10 hours, and the mixture of esters, which crystallised readily, had $[\alpha]_D^{15} -60.0^\circ$, corresponding to 50.9% of (+)-*isomenthyl* ester and 49.1% of (-)-*menthyl* ester.

(8) (-)-*Menthyl isocyanate* (1.5 mols.), (+)-*neomenthyl isocyanate* (1.5 mols.), and (-)-*menthol* (1 mol.). In this experiment the (-)-*menthol* was added progressively to the mixture of *isocyanates*, and the heating was maintained for 25 hours. After steam-distillation the residual mixture of esters was obtained as a viscid syrup, $[\alpha]_D^{16} -63.5^\circ$, corresponding to 63.9% of (-)-*menthyl* (-)-*menthylcarbamate* and 36.1% of (-)-*menthyl* (+)-*neomenthylcarbamate*.

(9) (-)-*Menthyl isocyanate* (1.5 mols.), (+)-*isomenthyl isocyanate* (1.5 mols.), and (-)-*menthol* (1 mol.). A similar procedure with these three compounds yielded a mixture of esters having $[\alpha]_D^{18} -48.5^\circ$, which therefore consisted of 65.7% of (-)-*menthyl* (+)-*isomenthylcarbamate* and 34.3% of (-)-*menthyl* (-)-*menthylcarbamate*.

Experiments on the Optical Resolution of Externally Compensated Menthols.—Virtual resolution of (\pm)-menthol with (-)-menthyl isocyanate. The mixture of esters from experiment (1) in the preceding section, containing 62.3% of (+)-*menthyl* (-)-*menthylcarbamate*, was crystallised from aqueous alcohol. The product (m. p. 90—91°) after three recrystallisations from absolute ethanol gave pure (+)-*menthyl* (-)-*menthylcarbamate*, m. p. 120—121°, $[\alpha]_D -5.0^\circ$ (c, 0.75 in ethanol).

Virtual resolution of (\pm)-menthol with (+)-neomenthyl isocyanate. The mixture of esters from experiment (2) above, containing 76.9% of (-)-*menthyl* (+)-*neomenthylcarbamate*, was subjected to fractional crystallisation from aqueous alcohol. After three crystallisations pure (-)-*menthyl* (+)-*neomenthylcarbamate* was obtained, m. p. 114.5—115.5°, $[\alpha]_D^{16} -9.2^\circ$ (c, 1.5 in ethanol).

In neither of these two instances was it possible to liberate the free optically active menthol, since the carbamates resisted hydrolysis with alcoholic potassium hydroxide, 20% sulphuric acid, and other reagents; concentrated sulphuric acid broke down the esters, giving rise to menthene. It is of interest that (-)-*menthyl phenylcarbamate* (m. p. 104—105°, $[\alpha]_D^{19} -91.7^\circ$) yielded to hydrolysis with 2% alcoholic potassium hydroxide, giving (-)-*menthol* and aniline.

Partial Resolution of (\pm)-isoMenthol with (-)-Menthyl isoCyanate.—(-)-*Menthyl isocyanate* (2.23 g., 1 mol.) was brought into reaction with (\pm)-*isomenthol* (3.84 g., 2 mols.) in the usual way. After 10 hours' heating on a boiling-water bath, the excess of *isomenthol* was removed by steam-distillation followed by extraction with ether. The product (1.9 g.) had $[\alpha]_D^{18} +8.9^\circ$ (0.6776 g. made up to 50 c.c. in ethanol gave $\alpha_D^{18} +0.48^\circ$ in a 4-dm. tube), and thus contained about 67% of (+)-*isomenthol* and 33% of (-)-*isomenthol*.

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