CCXCIII.—*Researches in the Menthone Series. Part II. Optically Active Menthones and Menthylamines.*

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IN the first communication of this series (J., 1925, **127**, 2782), it was shown that *dl*-piperitone could be used as a source of derivatives of either *dl-iso*menthone or *dl*-menthone, since the *dl-iso*menthone which it yields upon reduction may be readily converted into a mixture of these two ketones. A detailed study of the conditions regulating the interconversion of menthone and *iso*menthone then became essential in developing the research. Attention was therefore directed to the optically active forms of the ketones, in which the changes under consideration could be followed polarimetrically; so that the problem of isolating such forms in a state of purity was in turn brought within the ambit of the investigation.

The purest specimen of *l*-menthone prepared by Beckmann (*Annalen*, 1889, **250**, 335) had $[\alpha]_D$ −28·46°, but that this is not an ultimate value is demonstrated by our preparation in the same way of a specimen having $[\alpha]_D^{20°}$ $-29{\cdot}60°$, whilst Pickard and Littlebury (J., 1912, **101**, 124) also recorded the value $[\alpha]_D^{19°}$ $-29{\cdot}10°$. *d*-Menthone having $[\alpha]_D^{18°}$ $+24{\cdot}85°$ was also prepared by these investigators (*loc. cit.*). The availability of piperitone in *d*- and *l*-forms has rendered possible the ready production, by catalytic hydrogenation, of specimens of *l*- and *d*-*iso*menthone, having the respective maximum values $[\alpha]_D^{15°}$ $-71{\cdot}41°$ and $+69{\cdot}10°$.

These specimens, together with *l*-menthone, were used in investigating further the " inversion " of *l*-menthone, first observed by Beckmann (*Annalen*, 1889, **250**, 334) and attributed by Tutin and Kipping (J., 1904, **85**, 66) and Gardner, Perkin, and Watson (J., 1910, **97**, 1756) to a temporary suppression of the asymmetry of carbon atom (4) through enolisation of the adjacent keto-group. The experiments summarised below show that with energetic reagents, such as melting 90% sulphuric acid or alcoholic sodium ethoxide, definite equilibria are rapidly attained between *l*-menthone and *d*-*iso*menthone, the values of $[\alpha]_D^{15°}$ for the equilibrated material being approximately $+26°$ for the former reagent and $+7°$ for the latter, under the conditions adopted. These equilibria were realised experimentally, starting from *d*-*iso*menthone, as well as from *l*-menthone. With certain other reagents the equilibrium is attained much more slowly, so that the expression " inversion " is sometimes not strictly applicable to either of the ketones. Thus the chromic acid mixture used in preparing *l*-menthone from *l*-menthol brings about a comparatively slight fall in the rotatory powers of *l*-menthone and *d*-*iso*menthone. Of special interest also is the marked difference in the equilibrating action of heat at 180° and 200°, since *l*-piperitone, in which the asymmetry is associated solely with carbon atom (4), exhibits parallel behaviour (J., 1923, **123**, 2269), although it is affected only slightly by treatment with cold 90% sulphuric acid (*loc. cit.*, p. 2271). The action of other reagents commonly used in operations dealing with the menthones was also investigated with the aim of imparting precision to the study now in hand of reactions involving the use of the optically active and externally compensated forms of these substances. Similar observations made with *l*-*iso*menthone confirmed the existence of the equilibrium *d*- (or *l*-)*iso*menthone $\rightleftarrows$ *l*- (or *d*-)menthone.

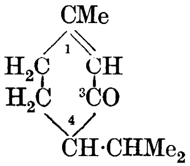
It is at present impracticable to calculate accurately the composition of the various equilibrium mixtures, owing to the uncertainty concerning the maximum optical rotatory powers of *l*- (or *d*-)menthone and *d*- (or *l*-)*iso*menthone. Since *l*-menthone of $[\alpha]_D^{20°}$ $-29{\cdot}60°$ when carefully oximated at the ordinary temperature in the absence of alkali yielded an apparently homogeneous specimen of *l*-menthoneoxime, it would appear to possess a high degree of purity. On the other hand, in spite of the high optical rotation, the purity of the preparations of *l*- and *d*-*iso*menthone now described is questionable, since a specimen of the latter having $[\alpha]_D^{20^\circ}$ $+65{\cdot}14^\circ$ furnished an appreciable quantity of *dl*-*iso*menthone-α-semicarbazone when treated with semicarbazide acetate (J., 1923, **123**, 2924); as the optically active *iso*menthones are incapable of racemising to *dl*-*iso*menthone under such conditions, the presence of *dl*-*iso*menthone in the specimen denotes the presence of *dl*-piperitone in the *l*-piperitone originally used. Whether the implied partial racemisation of the *l*-piperitone was antecedent to the process of hydrogenation is not clear, but the appreciably higher value now noted for *d*-piperitone from the oil of *Andropogon Jwarancusa* suggests the possibility of a slight racemic contamination of the purest *l*-piperitone yet isolated from the oil of *Eucalyptus dives*. A further indication of such contamination may perhaps be discerned in the fact that the oximes prepared from *d*- and *l*-*iso*menthone have as yet been obtained only in the form of viscid oils, the respective values of $[\alpha]_D^{15^\circ}$ being $+46{\cdot}0^\circ$ and $-45{\cdot}2^\circ$ in absolute alcohol. A mixture of equal amounts of these two preparations, however, yielded crystalline *dl*-*iso*menthoneoxime, melting at 99—100°, identical with the substance recently described by Read and Cook (J., 1925, **127**, 2785).

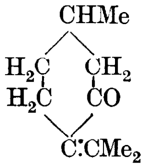
Attempts to prepare specimens of *iso*menthone of higher optical rotation by the catalytic hydrogenation of *d*-pulegone (II) and *l*-Δ^4-*p*-menthen-3-one (III), in the manner originally adopted for *l*- and *d*-piperitone (I), led to the results summarised below:

Unsaturated ketone.	$[\alpha]_D^{15^\circ}$ of unsaturated ketone.	$[\alpha]_D^{15^\circ}$ of derived *iso*menthone.
d-Piperitone	$+62{\cdot}50^\circ$	$-71{\cdot}41^\circ$
l-Piperitone	$-53{\cdot}90$	$+69{\cdot}10$
d-Pulegone	$+23{\cdot}60$	$+33{\cdot}45$
l-Δ^4-*p*-Menthen-3-one	$-78{\cdot}36$	$+43{\cdot}24$

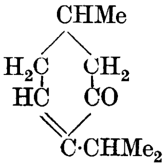
The products formed in the last two instances were proved to consist of mixtures of *l*-menthone and *d*-*iso*menthone; it should be noticed, however, that these results do not necessarily indicate a similar qualitative composition for the products derived from *d*- and *l*-piperitone, since in these instances the spatial additive process is conditioned not by the asymmetry of carbon atom (1), but by that of carbon atom (4):

(I.)





(II.)



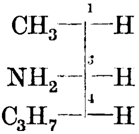
(III.)

As examples of the confusion hitherto existing in the chemistry of the menthones it may be noted that Skita and Ritter (*Ber.*, 1910, **43**, 3394) identified the product obtained by the catalytic reduction of *d*-pulegone as partly racemised *d*-menthone; moreover, Wallach (*Annalen*, 1913, **397**, 214) characterised the ketone prepared similarly from *l*-Δ^4-*p*-menthen-3-one as *l*-menthone.

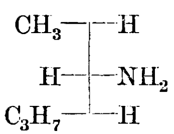
As a result of the " inversion " experiments discussed above, the possibility was next considered of preparing *d*- and *l*-*iso*menthone by oxidising the corresponding optically active *iso*menthols with chromic acid mixture. The results of a simultaneous research (following paper) dealing with optically inactive menthylamines and menthols derived ultimately from *dl*-piperitone, indicated a line of approach through the corresponding *iso*menthylamines. This indication appeared also to be in keeping with a brief mention by Beckmann (*Ber.*, 1909, **42**, 846) of a *d*-*iso*menthone having $[\alpha]_D$ +93·2°, originating from a supposed *d*-*iso*menthylamine hydrochloride. The last-named substance, prepared from the reduction product of the mixture of oximes yielded by " inverted " *l*-menthone, had $[\alpha]_D$ +17·7°. Wallach, however, had stated that the liquid oxime from " inverted " menthone having $[\alpha]_D$ +15·0° gave mainly *l*-menthylamine when reduced (*Annalen*, 1893, **276**, 313); since, moreover, Wallach had described a so-called " R-menthylamine " hydrochloride having $[\alpha]_D$ +17·2° (*loc. cit.*, pp. 306, 324), it became necessary to submit the whole field comprehended by these observations to a careful experimental enquiry.

In the first place, it was found possible to prepare Wallach's " R-menthylamine " by heating either *l*-menthone, *d*-*iso*menthone, or mixtures of these ketones with dry ammonium formate, in accordance with the original method. For the reasons outlined below, this base is considered to be derived from *l*-menthone: following the accepted nomenclature (compare Pickard and Littlebury, J., 1912, **101**, 109), it should thus be termed *d*-*neo*menthylamine. The value $[\alpha]_D^{15^\circ}$ +21·5° was observed for the hydrochloride of the pure base in dilute aqueous solution, but on the whole the data now recorded are in satisfactory agreement with the observations of Wallach. The base is distinguished by the solubility of its hydrochloride in light petroleum, and in general by the beauty of its crystalline derivatives. Pure formyl-*l*-*neo*menthylamine has also been prepared from *l*-*iso*menthone. When treated with nitrous acid, *d*-*neo*menthylamine yields a product consisting mainly of partly racemised *d*-Δ^3-menthene, so that, unlike *l*-menthylamine, it cannot be utilised as a source of the related menthol and menthone.

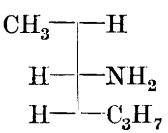
The crude menthylamine hydrochloride, having $[\alpha]_D^{15^\circ}$ −12·5°, obtained by reducing the viscid product formed in oximating "inverted" *l*-menthone, proved to consist of a mixture of which the components could not readily be separated by fractional crystallisation. From the viscid oxime of *d*-*iso*menthone, however, was obtained similarly a crude menthylamine hydrochloride having $[\alpha]_D^{15°}$ +20·63°, and a single recrystallisation furnished a homogeneous hydrochloride with $[\alpha]_D^{15°}$ +23·60°. In spite of the approximately identical rotatory power, this substance differs markedly from *d*-*neo*menthylamine hydrochloride by reason of its high melting point and its insolubility in light petroleum or in ether. Moreover, other corresponding derivatives of the two bases exhibit wide differences in rotatory power as well as in melting point and solubility. In view of its preparation from *iso*menthone, this base is to be regarded as an *iso*menthylamine. Upon treatment with nitrous acid, it yields a crystalline dextrorotatory *iso*menthol; the name *d*-*iso*menthylamine thus appears to be appropriate, since the prefix *neo*- as applied above is associated with the conversion of the base in this way to a menthene and not to a menthol. According to Wallach (*Annalen*, 1898, **300**, 278), the conversion of a menthylamine to a menthene by nitrous acid is conditioned by the *cis*-disposition of -NH_2 and -H, attached respectively to carbon atoms (3) and (4); adopting further the *trans*-configuration for *iso*menthone (compare Meyer u. Jacobson, "Lehrbuch der organischen Chemie," 1923, II, i, 894), *iso*menthylamine may be represented by configuration (VI) and menthylamine by configuration (IV), since both these bases yield a menthol on reaction with nitrous acid:



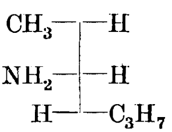
(IV.)
l(or *d*)-
Menthylamine.



(V.)
d(or *l*)-*neo*-
Menthylamine.



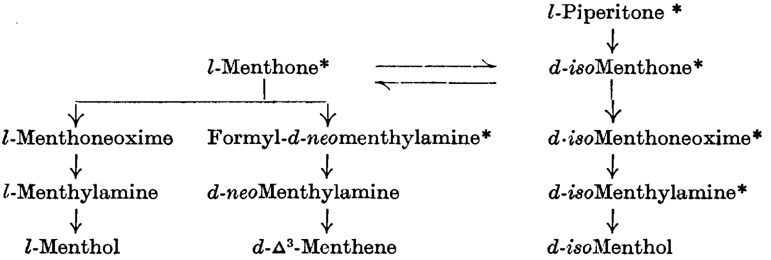
(VI.)
d(or *l*)-*iso*-
Menthylamine.



(VII.)
neoiso-
Menthylamines.

According to the experimental evidence, the base designated above as *neo*menthylamine might be either (V) or (VII). The adoption of configuration (VII), however, would imply that the reversal of the asymmetry of carbon atom (3) of configuration (VI) has practically no influence on the optical rotation, the respective values for the hydrochlorides being +23·60° and +21·50°. Such a result appears extremely less likely than the corresponding change from —36·60° (*l*-menthylamine hydrochloride) to +21·50° (*d*-*neo*menthylamine hydrochloride) indicated by the scheme as given.

Certain optically pure derivatives of *l*-*iso*menthylamine have also been prepared from the viscid oxime of *l*-*iso*menthone, and the preparation and characterisation of *dl-neo*menthylamine and *dl-iso*menthylamine, together with a derived *dl-iso*menthol, are described in the next communication. The only menthylamines remaining to be prepared are thus the *neoiso*menthylamines corresponding to configuration (VII). The operations dealt with in this contribution may be summarised as follows, the changes distinguished by an asterisk having been accomplished also with the enantiomorphous substances :



It is hoped that the somewhat tedious process, now in hand, of accumulating sufficient *d* (and *l*)-*iso*menthol for complete characterisation and oxidation to *d* (and *l*)-*iso*menthone may at last render practicable the realisation of an ideal expressed some years ago, which has influenced the course of this series of investigations, originating in turn from a study of the chemistry of piperitone : " Es wäre eine dankbare Aufgabe, die vier optisch aktiven und die beiden wahren racemischen Modificationen von krystallisirbaren Menthon-Derivaten darzustellen und unter besonderer Berücksichtigung der modernen, von van 't Hoff und Roozeboom vertretenen Anschauungen genau zu untersuchen, da dieser Fall von grundlegender Bedeutung für die Terpenchemie ist " (Meyer u. Jacobson, *op. cit.*).

EXPERIMENTAL.

Conditions affecting the Dynamic Equilibrium between l-*Menthone and* d-iso*Menthone.*

1. The following results were yielded by specimens of *l*-menthone having $[\alpha]_D^{20^\circ}$ $-29{\cdot}60^\circ$ and prepared by oxidising *l*-menthol. When treated with melting 90% sulphuric acid (*Annalen*, 1889, **250**, 334), the resulting ketone exhibited values of $[\alpha]_D^{20^\circ}$ ranging from $+11{\cdot}0^\circ$ to $+25{\cdot}7^\circ$; it would appear that the more quickly the menthone is extracted from the aqueous acid after pouring over ice, the higher is the specific rotation in the dextro sense. When dissolved in 98% formic acid and maintained at 40° for 4 hours, the recovered ketone had $[\alpha]_D^{20^\circ}$ $+13{\cdot}0^\circ$. Upon passing dry hydrogen chloride into ice-cooled *l*-menthone and keeping the deep yellow

solution for a day, the recovered ketone had $[\alpha]_D^{20^\circ}$ +5·2°. Upon adding *l*-menthone to concentrated hydrochloric acid cooled in ice, and then warming the mixture to 30°, the value of $[\alpha]_D^{20^\circ}$ changed to +3·7°. After the ketone had been boiled under reflux for 30 minutes with a 20% solution of oxalic acid, the specific rotation had changed to −21·8°. *l*-Menthone was affected only slightly by the chromic acid mixture used in its preparation from *l*-menthol (*loc. cit.*, p. 325), the specific rotation after a second contact with this reagent being −27·0°. When *l*-menthone was shaken at intervals for a day with 25% aqueous potassium hydroxide the specific rotation changed to −23·6°. Upon adding *l*-menthone (10 g.) to absolute alcohol (40 c.c.) in which sodium (1·5 g.) had been dissolved and keeping the mixture for 20 hours, the recovered ketone had $[\alpha]_D^{20^\circ}$ +6·8°; this specimen, when treated with melting 90% sulphuric acid, reverted to the value $[\alpha]_D^{20^\circ}$ +24·8°. In the above operations, the ketone was recovered from the reaction mixture by dilution with water, or pouring on to ice, followed by extraction with ether or chloroform. When *l*-menthone was kept at 180° in a glass vessel, the specific rotation changed to −10·6° in 3 hours and to −8·2° in 7·5 hours; upon then raising the temperature to 200°, the values of $[\alpha]_D^{20^\circ}$ after 4 and 14 hours were +6·2° and +14·8°, respectively, the last value remaining unaltered after a further period of 16 hours at 200°. Repeated distillation in steam or under diminished pressure had no appreciable effect on the specific rotation of *l*-menthone.

2. Specimens of *d-iso*menthone, prepared by hydrogenating *l*-piperitone and having values of $[\alpha]_D^{20^\circ}$ ranging from about +57° to +65°, gave equilibrium values corresponding closely to those recorded above when submitted to similar processes. Upon treating a specimen having $[\alpha]_D^{20^\circ}$ +59·26° successively with melting 90% sulphuric acid, alcoholic sodium ethoxide, and again with sulphuric acid, the corresponding values of $[\alpha]_D^{20^\circ}$ were +26·8°, +7·2°, and +23·4°. When *d-iso*menthone with the maximum value of $[\alpha]_D^{15^\circ}$ +69·10°, prepared in the same way from *l*-piperitone having $[\alpha]_D^{15^\circ}$ −53·90°, was added to chromic acid mixture at 30° and treated in the manner adopted by Beckmann (*loc. cit.*, p. 325) in the preparation of *l*-menthone, the value declined only to $[\alpha]_D^{15^\circ}$ +59·3°.

The Dynamic Equilibrium between d-*Menthone and* l-iso*Menthone.*

The *d*-piperitone used as the starting point in this section of the work was isolated from the essential oil of *Andropogon Jwarancusa* by fractional distillation under diminished pressure (J., 1923, **123**, 2269). The necessary material was kindly collected and distilled in the autumn of 1923 by Colonel C. R. Johnson, Abbottabad, to whom, as also to Professor J. L. Simonsen, we express our cordial thanks. The crude oil afforded a 68% (vol.) yield of *d*-piperitone, b. p. 95—97°/7·5 mm., $n_D^{16\cdot5°}$ 1·4860, $\alpha_D^{15°}$ +58·42°, $[\alpha]_D^{15°}$ +62·50°. The hydrogenation to *l*-*iso*menthone was conducted essentially as described by Hughesdon, Smith, and Read (J., 1923, **123**, 2920), but it was found advantageous to initiate the operation at 30° and to accelerate the stirring. The yield of *l*-*iso*menthone was 76% of the theoretical amount, and the following physical constants were observed for the refractionated material: b. p. 79—80°/7 mm., $n_D^{13°}$ 1·4580, $\alpha_D^{15°}$ −64·24°, $[\alpha]_D^{15°}$ −71·41°.

When treated with melting 90% sulphuric acid, as described above for *l*-menthone, this specimen of *l*-*iso*menthone gave a product having $[\alpha]_D^{15°}$ −14·3°. Further, a second portion of the same specimen had $[\alpha]_D^{15°}$ −5·7° when recovered from a solution in absolute-alcoholic sodium ethoxide. The corresponding values of $[\alpha]_D^{15°}$ for the *l*-menthone–*d*-*iso*menthone equilibrium, recorded above, are +11·0° to +25·7° and +6·8°, respectively.

The Catalytic Hydrogenation of d-*Pulegone.*

Upon submitting oil of pennyroyal (400 c.c.) of French origin (stated to be from *Mentha Pulegium*) to three successive fractional distillations under diminished pressure, a specimen of pulegone (170 c.c.) was obtained with the following characteristics: b. p. 96·6—97·6°/12·5 mm., $n_D^{15°}$ 1·4852, $[\alpha]_D^{15°}$ +23·60°. When hydrogenated at 20° in presence of colloidal palladium, in accordance with the method adopted for *l*-piperitone (J., 1923, **123**, 2921), *d*-pulegone (35 g.) absorbed the theoretical quantity of hydrogen in 2·5 hours. The product was extracted with ether and purified by distillation under diminished pressure: the menthone fraction amounted to about 80% of the calculated yield, and the higher fraction had an odour of menthol. The refractionated menthone distilled at 81—82°/11 mm., and had $n_D^{15°}$ 1·4561, $[\alpha]_D^{15°}$ +26·17°, and $d_{4°}^{16°}$ 0·900. In two similar experiments, owing to some unknown adverse condition, hydrogenation was incomplete; the first fractions (b. p. 89—94°/13 mm.) were accordingly mixed and rehydrogenated at a temperature which gradually declined from 30° to 15°. The refractionated menthone distilled at 86—88°/13 mm. and had $n_D^{15°}$ 1·4555 and $[\alpha]_D^{15°}$ +30·80°. The highest value of $[\alpha]_D^{15°}$ observed for a specimen of menthone prepared in this way was +33·45°.

When the specimen of menthone having $[\alpha]_D^{15°}$ +30·80° was treated with melting 90% sulphuric acid, the specific rotation fell to $[\alpha]_D^{15°}$ +27·07°, whilst renewed treatment with alcoholic sodium ethoxide brought about a further decline to $[\alpha]_D^{15°}$ +7·93°. These inversion experiments show definitely that the product obtained by hydrogenating *d*-pulegone consisted of a mixture of *d*-*iso*menthone and *l*-menthone; this view is also supported by the fact that the oxime furnished by this product was an oil which could not be induced to crystallise.

The Catalytic Hydrogenation of l-Δ^4-p-*Menthen*-3-*one.*

In order to ensure the highest possible optical purity of the product, the intermediate stages in the preparation of the ketone were carefully controlled. The methyl ester of *l*-menthylxanthic acid, prepared by the method of Tschugaev (*Ber.*, 1899, **32**, 3333) from *l*-menthol, was obtained in 66% yield: m. p. 39°, $[\alpha]_D^{15^\circ}$ $-80{\cdot}5^\circ$ in benzene ($c = 2{\cdot}30$). Upon dry distillation at about 200°, the ester gave 80% of the calculated yield of *d*-Δ^3-menthene: b. p. 59—60°/9 mm., $n_D^{15^\circ}$ 1·4570, $[\alpha]_D^{15^\circ}$ $+106{\cdot}6^\circ$ in ether ($c = 2{\cdot}63$) and $+118{\cdot}6^\circ$ in alcohol ($c = 1{\cdot}65$). The nitrosochloride was then prepared by the method of Richtmann (*Amer. Chem. J.*, 1896, **18**, 762), the yield being increased to 42% through careful cooling: $[\alpha]_D^{15^\circ}$ $+221{\cdot}0^\circ$ in benzene ($c = 4{\cdot}57$). When treated with 10% alcoholic potassium hydroxide (*loc. cit.*), this substance furnished 80% of the calculated yield of the oxime of *l*-Δ^4-*p*-menthen-3-one, which was purified by distillation in steam: m. p. 63—64°, $[\alpha]_D^{15^\circ}$ $-57{\cdot}8^\circ$ in alcohol ($c = 2{\cdot}51$). *l*-Δ^4-Menthen-3-one, prepared in 66% yield by hydrolysing the oxime with hydrochloric acid, was a straw-coloured liquid, b. p. 85—88°/11 mm., $n_D^{14^\circ}$ 1·4765, $\alpha_D^{15^\circ}$ $-72{\cdot}02^\circ$, $[\alpha]_D^{15^\circ}$ $-78{\cdot}36^\circ$.

Upon hydrogenating the ketone (30 g.) in the usual way at 15°, absorption of hydrogen was well maintained for 4 hours. The product recovered after 7 hours' treatment was, however, still slightly lævorotatory and contained a certain amount of thymol. The fraction distilling at 83—99°/11 mm. was rehydrogenated for 1·5 hours, at a temperature which declined gradually from 30° to 20°. Upon refractionation, the product furnished, in a yield of 43%, a specimen of menthone having b. p. 85·5—87·5°/12 mm., $n_D^{15^\circ}$ 1·4550, $[\alpha]_D^{15^\circ}$ $+43{\cdot}24^\circ$.

When the above specimen of menthone was treated successively with melting 90% sulphuric acid and alcoholic sodium ethoxide, the values of $[\alpha]_D^{15^\circ}$ shown by the respective products were $+27{\cdot}22^\circ$ and $+7{\cdot}95^\circ$. The menthone obtained by the hydrogenation of *l*-Δ^4-*p*-menthen-3-one was therefore a mixture of *d*-*iso*menthone and *l*-menthone, in which the former substance predominated.

The Optically Active neo*Menthylamines.*

Experiments on the Formation of d-neo*Menthylamine.*—1. *l*-Menthone, $[\alpha]_D^{15^\circ}$ $-27{\cdot}50^\circ$, when heated with dry ammonium formate in accordance with Wallach's method (*Annalen*, 1898, **300**, 283), yielded a viscid liquid (b. p. 160—163°/9 mm.), which could only be induced to crystallise with difficulty unless inoculated with crystalline material prepared as in method (2) below. When mixed with concentrated hydrochloric acid, the product gave *formyl-*d-neo*menthylamine hydrochloride*, which crystallised from light petroleum in fine opaque needles, m. p. 75—80°; this derivative was stable in dry air, but underwent rapid decomposition in contact with water. When hydrolysed with hot concentrated hydrochloric acid, the viscid product of the original reaction gave a specimen of crude menthylamine hydrochloride having $[\alpha]_D^{15°}$ +5·5° in water; neglecting the possible presence of other isomerides, the product thus appeared to consist of about 28% of *l*-menthylamine hydrochloride in admixture with 72% of *d*-*neo*menthylamine hydrochloride. When fractionally recrystallised from ethyl acetate, the first fraction had $[\alpha]_D^{15°}$ +8·8° in dilute aqueous solution, but the preparation of pure *d*-*neo*menthylamine hydrochloride from such a mixture was difficult.

2. Crystalline formyl-*d*-*neo*menthylamine was obtained more easily by using "inverted *l*-menthone," having $[\alpha]_D^{15°}$ +25·5°, in place of *l*-menthone. After the ketone had been heated for 48 hours with dry ammonium formate, the oily product was separated while hot from the aqueous layer which had formed. After steam-distilling away the unchanged menthone, the residue was separated and then dried by heating with a little alcohol on the water-bath under diminished pressure. The addition of dry ether to the cold dry residue resulted in the immediate separation of crystals (30%), the remainder of the product being an uncrystallisable syrup; 15 g. of ketone yielded on an average 4·4 g. of crystalline product. After one recrystallisation from ether the formyl-*d*-*neo*menthylamine was pure. When hydrolysed (*Annalen*, 1893, **276**, 308), it yielded its own weight of *d*-*neo*menthylamine hydrochloride, having $[\alpha]_D^{15°}$ +20·1° in water (c = 1·44); this value rose to +21·5° after fractional recrystallisation from water.

3. *d*-*iso*Menthone (7·2 g.), having $[\alpha]_D^{15°}$ +63·4°, was heated with dry ammonium formate (9 g.) for 45 hours. Unchanged menthone was removed by steam distillation, and after extraction with chloroform the formyl derivative was distilled under diminished pressure (6·1 g.; b. p. 170°/15 mm.). The crystalline material obtained by the addition of ether (1 g.) was identical with formyl-*d*-*neo*menthylamine produced as indicated above.

Characterisation of d-neo*Menthylamine.*—The following observations were made, and for purposes of comparison the corresponding constants noted by Wallach (*Annalen*, 1893, **276**, 306) for "R-menthylamine" are appended in square brackets. Free *d-neo*menthylamine, $[\alpha]_{\rm D}^{20^\circ}$ +15·73° [+14·71°]; acetyl-*d-neo*menthylamine, m. p. 169—170°, $[\alpha]_{\rm D}^{15^\circ}$ +53·0° in chloroform ($c = 1{\cdot}20$) [168—169°, +50·57°]; benzoyl-*d-neo*menthylamine, m. p. 121·5°, $[\alpha]_{\rm D}^{15^\circ}$ +22·7° in chloroform ($c = 2{\cdot}02$) (compare J., 1904, **85**, 68); benzylidene-*d-neo*menthylamine, m. p. 45—46°, $[\alpha]_{\rm D}^{15^\circ}$ +61·7° in chloroform ($c = 1{\cdot}56$) [42—43°]; salicylidene-*d-neo*menthylamine m. p. 99—100°, $[\alpha]_{\rm D}^{15^\circ}$ +30·0° in chloroform ($c = 1{\cdot}50$) [96—97°]. β-*Naphthalenesulphonyl*-d-neo*menthylamine*, $C_{10}H_{19}{\cdot}NH{\cdot}SO_2{\cdot}C_{10}H_7$, is deposited from alcohol containing a little chloroform in colourless leaflets, m. p. 208°, $[\alpha]_{\rm D}^{15^\circ}$ +43·7° in chloroform ($c = 2{\cdot}02$).

The formyl derivative and the hydrochloride of this base, which are particularly distinctive, have been characterised in greater detail. *Formyl*-d-neo*menthylamine*, $C_{10}H_{19}{\cdot}NH{\cdot}COH$, melts at 117—118° and has $[\alpha]_{\rm D}^{15^\circ}$ +53·8° in chloroform ($c = 1{\cdot}76$) and +62·4° in alcohol ($c = 1{\cdot}53$) [117·5°, +54·11°]. It is moderately easily soluble in warm ether or light petroleum, but it is most conveniently crystallised from methyl alcohol. Crystals prepared in this way have been examined by Dr. T. V. Barker, of the Department of Mineralogy, University of Oxford, to whose courtesy we owe the following description :

"The crystals belong to the orthorhombic system. Although optically active in solution, they exhibit no hemihedral facets, the holohedral forms being *o*(111), *m*(110) and *q*(011) in the proportions shown in Fig. 1. The axial ratios, $a : b : c = 0{\cdot}8566 : 1 : 0{\cdot}7246$, were computed from the following mean results of measurement of two crystals :

	m.	*o.*	*q.*
φ	*49° 25′	49° 27′ (−21)	0° 0′
ρ	90 0	*48 5	36 2 (−6)."

d-neo*Menthylamine hydrochloride*, $C_{10}H_{19}{\cdot}NH_2,HCl$, melts at 189°, and has $[\alpha]_{\rm D}^{15^\circ}$ +21·50° in water ($c = 1{\cdot}44$) [189°, +17·2°]. It dissolves readily in warm light petroleum (b. p. 60—80°), from which it separates slowly in large, transparent prisms. Crystals of the substance were kindly measured by Dr. T. V. Barker, who reports as follows :

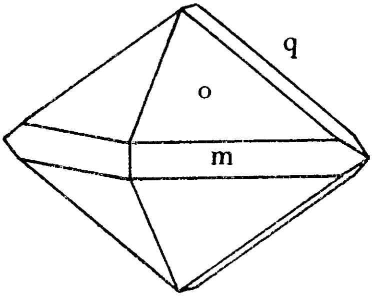
"The crystals belong to the monoclinic system, but exhibit no certain hemihedral character, the forms expressed holohedrally being *b*(010), *m*(110), *a*(100), *s*(021), *q*(011), and, rarely, *o*($\bar{1}$11), as shown in Fig. 2. The elements, $a : b : c = 0{\cdot}3512 : 1 : 0{\cdot}3430$, $\beta = 100°49'$, were computed from the following mean results of measurements of three crystals :

	b.	*m.*	*a.*	*s.*	*q.*	*o.*
φ	Polar	0° 0′	0° 0′	*79° 11′	*79° 11′	129° 7′ (−10)
ρ	face.	*70 58	90 0	*56 2	*71 23	75 3 (1)

"There is a poor *b*-cleavage. Optically, the negative acute bisectrix is normal to *b* with a wide axial angle. The third mean line makes an angle $-15°$ with the vertical."

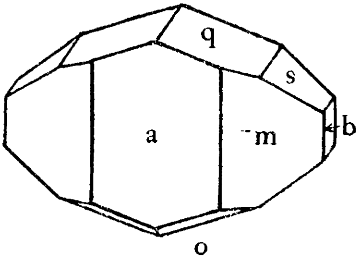
d-*neo*Menthylamine hydrochloride was treated in aqueous solution with the calculated quantity of sodium nitrite solution at **70°** (*Annalen*, 1898, **300**, 285); the resulting oil distilled completely at 61°/12 mm., had $n_{\rm D}^{15^\circ}$ 1·4555, $[\alpha]_{\rm D}^{15^\circ}$ +58·6° in ether (c = 1·79), and appeared to consist of partly racemised *d*-Δ^3-menthene.

FIG. 1.



Formyl-d-neo*menthylamine.*

FIG. 2.



d-neo*Menthylamine hydrochloride.*

l-neo*Menthylamine.*—A specimen of *l*-*iso*menthone (13·5 g.), having $[\alpha]_{\rm D}^{15^\circ}$ $-37·0°$, and prepared from *d*-piperitone by catalytic hydrogenation followed by partial equilibration, when heated in the usual way with ammonium formate yielded a viscid syrup consisting mainly of a mixture of the formyl derivatives of *l*-*neo*menthylamine and *d*-menthylamine. Crystallisation of the dry crude material was induced by nucleating it with formyl-*d*-*neo*menthylamine in presence of dry ether. The resulting crystals of *formyl*-l-neo*menthylamine* (2·5 g.), after recrystallisation from absolute alcohol, melted at 116—117° and had $[\alpha]_{\rm D}^{15^\circ}$ $-53·6°$ in chloroform (c = 1·79). The substance is thus enantiomorphous with formyl-*d*-*neo*menthylamine described above, and is of particular interest as the first derivative of *l*-*neo*menthylamine to be prepared.

Formyl-dl-neo*menthylamine*, prepared by mixing ether solutions of the two enantiomers, melted at 86°. Similar mixtures containing 89, 76, 66, 55, and 24% of formyl-*d*-*neo*menthylamine melted at 110—114°, 102—104°, 95·5—97·5°, 87—89°, and 103—105°, respectively. The character of the corresponding melting-point curve suggests that an equimolecular mixture of the two enantiomers forms a conglomerate (Roozeboom, *Z. physikal. Chem.*, 1899, **28**, 507).

The Optically Active iso*Menthylamines.*

Experiments on the Formation of d-iso*Menthylamine.*—1. The oxime prepared in good yield from *l*-menthone by treatment for several days with hydroxylamine acetate in aqueous alcohol at the ordinary temperature appeared to be homogeneous; the resulting needles, some of which exceeded 5 cm. in length, melted at 58° and had $[\alpha]_D^{15^\circ}$ −39·7° in absolute alcohol ($c = 1·89$). When reduced with sodium and alcohol (*Annalen*, 1893, **276**, 360), the oxime furnished its own weight of crude *l*-menthylamine hydrochloride, having $[\alpha]_D^{15^\circ}$ −32·6° in water ($c = 1·97$); this value rose to −35·8° after one recrystallisation from water. From this result, the crude product would appear to contain not more than 6·7% of *d-iso*menthylamine hydrochloride, assuming other isomerides to be absent. When treated with nitrous acid, the purified product yielded *l*-menthol, together with some *d*-Δ^3-menthene.

2. When a specimen of "inverted *l*-menthone," having $[\alpha]_D^{15^\circ}$ +19·0°, was treated with hydroxylamine acetate for 6 hours on the water-bath (compare J., 1922, **121**, 586), it gave a 73% yield of a viscid oily oxime, having $[\alpha]_D^{15^\circ}$ −14·3° in alcohol ($c = 1·93$). The derived menthylamine hydrochloride had $[\alpha]_D^{15^\circ}$ −12·5° in aqueous solution, corresponding, in the absence of other isomerides, to a mixture of about 60% of *l*-menthylamine hydrochloride with 40% of *d-iso*menthylamine hydrochloride. After recrystallisation from water, a first fraction showed $[\alpha]_D^{15^\circ}$ −19·2°, indicative of an increased content of *l*-menthylamine hydrochloride, and a similar result attended the use of ethyl acetate as a solvent. The fractional crystallisation of this mixture of hydrochlorides is therefore unsuitable for the ready preparation of pure *d-iso*menthylamine.

3. d-iso*Menthoneoxime*, $C_{10}H_{18}:NOH$, was prepared from *d-iso*menthone, having $[\alpha]_D^{15^\circ}$ +65·7° and obtained by hydrogenating *l*-piperitone. The ketone was mixed in aqueous alcoholic solution with hydroxylamine acetate and kept at the ordinary temperature for 3 days. Most of the alcohol was distilled off, and the product worked up in the usual way (*loc. cit.*). The oxime was isolated in 86% yield, as a viscid oil which could not be induced to crystallise from any of the ordinary organic solvents. Cooling in a freezing mixture and prolonged keeping in a vacuum over concentrated sulphuric acid were also without effect in this respect. The oxime had $[\alpha]_D^{15^\circ}$ +46·0° in absolute alcohol ($c = 1·67$), and $n_D^{15^\circ}$ 1·4845.

d-iso*Menthylamine Hydrochloride*, $C_{10}H_{19}\cdot NH_2,HCl$.—When reduced with sodium in alcoholic solution, the above oxime (82 g.) yielded a crude menthylamine hydrochloride having $[\alpha]_D^{15^\circ}$ +20·63° in aqueous solution ($c = 1{\cdot}53$). After one recrystallisation from boiling acetone containing a little methyl alcohol, a fraction (33 %) was obtained having $[\alpha]_D^{15^\circ}$ +23·60°, and this value was unaffected by further recrystallisation. The pure substance formed clusters of long, silky needles, which did not melt below 250° (Found: Cl, 18·3. $C_{10}H_{21}N,HCl$ requires Cl, 18·5%). The mother-liquors yielded fractions of lower dextrorotation, which have been reserved for further examination.

Characterisation of d-iso*Menthylamine.*—*Formyl*-d-iso*menthylamine*, $C_{10}H_{19}{\cdot}NH{\cdot}COH$, prepared by heating the free base with anhydrous formic acid in a sealed tube at 200° for several hours, is extremely soluble in the ordinary organic solvents. From light petroleum it separates in soft, feathery needles, m. p. 45—46°, $[\alpha]_D^{15^\circ}$ +31·3° in chloroform ($c = 1{\cdot}69$). *Acetyl*-d-iso*menthylamine*, $C_{10}H_{19}{\cdot}NH{\cdot}CO{\cdot}CH_3$, forms very soluble, colourless needles, m. p. 77—79°, $[\alpha]_D^{15^\circ}$ +30·7° in chloroform ($c = 1{\cdot}96$). *Benzoyl*-d-iso*menthylamine*, $C_{10}H_{19}{\cdot}NH{\cdot}COPh$, crystallises from acetone, in which it is readily soluble, in coarse needles, m. p. 97—98°, $[\alpha]_D^{15^\circ}$ + 18·3° in chloroform ($c = 3{\cdot}1$). β-*Naphthalenesulphonyl*-d-iso*menthylamine*, $C_{10}H_{19}{\cdot}NH{\cdot}SO_2{\cdot}C_{10}H_7$, prepared by the Schotten–Baumann method, crystallises from alcohol in large plates, m. p. 80—81°, $[\alpha]_D^{15^\circ}$ —2·8° in chloroform ($c = 1{\cdot}80$). *Benzylidene*-d-iso*menthylamine*, $C_{10}H_{19}{\cdot}N{:}CHPh$, separates from methyl alcohol in colourless plates, m. p. 67—68°, $[\alpha]_D^{15^\circ}$ +90·7° in chloroform ($c = 1{\cdot}68$). *Salicylidene*-d-iso*menthylamine*, $C_{10}H_{19}{\cdot}N{:}CH{\cdot}C_6H_4{\cdot}OH$, is deposited from alcohol in coarse, yellow needles, m. p. 122°, $[\alpha]_D^{15^\circ}$ +77·6° in chloroform ($c = 1{\cdot}80$). d-iso-*Menthylcarbamide*, $C_{10}H_{19}{\cdot}NH{\cdot}CO{\cdot}NH_2$, crystallises from ether–light petroleum in minute, colourless needles, m. p. 141·5—142·5°, $[\alpha]_D^{15^\circ}$ +29·0° in chloroform ($c = 1{\cdot}34$). d-iso-*Menthylphenylcarbamide*, $C_{10}H_{19}{\cdot}NH{\cdot}CO{\cdot}NHPh$, separates from methyl alcohol in long, colourless needles, m. p. 142°, $[\alpha]_D^{15}$ +21·8° in chloroform ($c = 1{\cdot}38$). d-iso*Menthylphenylthiocarbamide*, $C_{10}H_{19}{\cdot}NH{\cdot}CS{\cdot}NHPh$, crystallises from light petroleum containing a little alcohol in colourless needles, m. p. 114·5—115·5°, $[\alpha]_D^{15^\circ}$ +46·7° in chloroform ($c = 1{\cdot}33$). All these derivatives were readily obtained pure, thus indicating the homogeneity of the original base.

Upon treatment with nitrous acid, *d-iso*menthylamine yielded a crystalline dextrorotatory *iso*menthol, the characteristics of which will be described in a later communication.

l-iso*Menthylamine.*—Upon oximation in the manner described above for *d-iso*menthone, a specimen of *l-iso*menthone having $[\alpha]_D^{15^\circ}$ —71·41° yielded *l*-iso*menthoneoxime* as a viscid oil, with $n_D^{15^\circ}$ 1·4870 and $[\alpha]_D^{15^\circ}$ —45·2° in absolute alcohol ($c = 1{\cdot}93$). Upon reduction with sodium and alcohol, this gave crystalline l-iso*menthyl*-

amine hydrochloride, having $[\alpha]_D^{15^\circ}$ −19·1° in water (c = 2·77). When recrystallised from boiling acetone containing a little methyl alcohol, the crude hydrochloride yielded a first fraction (20%) having $[\alpha]_D^{15^\circ}$ −21·88° in water. *Salicylidene*-l-iso*menthylamine* crystallises from alcohol in coarse, yellow needles, m. p. 122°, $[\alpha]_D^{15^\circ}$ −76·8° in chloroform (c = 1·72). The base is therefore proved to be enantiomorphous with the preceding *d-iso*menthylamine.

Salicylidene-dl-iso*menthylamine*, prepared by mixing equal weights of the *d*- and *l*-components in alcohol, melted at 95°.

The authors are indebted to the Carnegie Trust for a Teaching Fellowship which enabled one of them (Dr. Robertson) to take part in the work. The investigations are being continued; a cognate research is also in hand, dealing with the corresponding relationships of the carvomenthones.

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