CCLXXXIX.—*Researches in the Menthone Series. Part V.* d-neoiso*Menthylamine.*

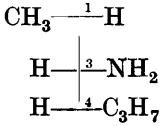
By John Read and George James Robertson.

The constitutional formula of the menthylamines admits of the existence of four optically inactive and eight optically active forms, and of these the only stereoisomerides remaining to be prepared and characterised are the *neoiso*menthylamines (compare J., 1926, 2209, 2223). Wallach (*Annalen*, 1898, **300**, 278) obtained two bases, now called *l*-menthylamine and *d*-*neo*menthylamine, by heating *l*-menthone with ammonium formate. We regard both these bases as derivatives of *l*-menthone (*loc. cit.*); since, however, under the conditions of the experiment *l*-menthone is transformed partly to *d*-*iso*menthone (this vol., p. 1278), we considered that the reaction product should contain a corresponding proportion of formylated *iso*menthylamines. By applying the knowledge already acquired of the derivatives of active forms of the three known bases, we have been able to prepare from this product a new salicylidene (o-*hydroxybenzylidene*) derivative, m. p. 99—100°, $[\alpha]_D$ − 17·9°, which must be regarded as an active form of salicylidene*neoiso*menthylamine (J., 1926, 2225).

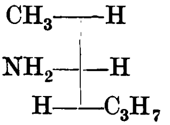
We have already shown that *d*-*iso*menthone, when oximated and reduced, yields *d*-*iso*menthylamine. *l*-Menthone yields *l*-menthylamine in a similar way, and gives a mixture of *l*-menthylamine and *d*-*neo*menthylamine in reaction with ammonium formate. By analogy we anticipated that *d*-*iso*menthone would furnish *d*-*iso*menthylamine and *l*-*neoiso*menthylamine in the last-named reaction. A careful scrutiny of the data suggests that *d*-*iso*menthylamine may exist in the formylated mixture, although it has not yet been isolated therefrom; the new lævorotatory salicylidene derivative, however, yielded upon hydrolysis a feebly dextrorotatory neoiso*menthylamine*, having $[\alpha]_D + 9°$ in chloroform. The *hydrochloride* also was dextrorotatory, having $[\alpha]_D + 20·9°$ in dilute aqueous solution. All the other derivatives, nine in number, as yet prepared from the base display rather small lævo-rotations, thus fulfilling the anticipated tendency. Since, however, the free base is dextrorotatory, we propose to name it *d*-*neoiso*menthylamine. The subjoined summary of melting points and specific rotatory powers indicates some of the more important relationships existing between the four optically active forms under discussion. The values of $[\alpha]_D$ were observed in water for the hydrochlorides and in chloroform for the other derivatives (compare J., 1926, 2225):

		Menthylamines.			
Derivative.		*l*-.	*d*-*neo*-.	*d*-*iso*-.	*d*-*neoiso*-.
Hydrochloride.	m. p.	280°	189°	250°	250°
	$[\alpha]_D$	−36·6°	+21·5°	+23·6°	+20·9°
Formyl.	m. p.	102—103	117—118	45—46	Liquid
	$[\alpha]_D$	−83·8	+53·8	+31·3	−3·9
Acetyl.	m. p.	145	169—170	77—79	99—100
	$[\alpha]_D$	−81·7	+53·0	+30·7	−2·6
Benzoyl.	m. p.	157	121·5	97—98	151
	$[\alpha]_D$	−62·8	+22·7	+18·3	−10·4
β-Naphthalene-sulphonyl.	m. p.	135	208	80—81	120
	$[\alpha]_D$	−53·3	+43·7	−2·8	−10·7
Benzylidene.	m. p.	69—70	45—46	67—68	68—69
	$[\alpha]_D$	−132·5	+61·7	+90·7	−34·2
Salicylidene.	m. p.	57—58	99—100	122	99—100
	$[\alpha]_D$	−119·2	+30·0	+77·6	−17·9

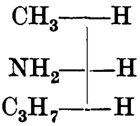
From these data it is evident that no striking general similarity exists between derivatives of the *neo*- and *neoiso*-menthylamines (compare J., 1926, 2224); further, of the four supposed benzomenthylamides described by Tutin and Kipping (J., 1904, **85**, 73) two only can now be regarded as pure substances. The data are of particular interest when considered in conjunction with the configurational scheme advanced some time ago for the menthylamines (J., 1926, 2213) and reproduced below with the amendment that the *trans*-configuration is adopted, in place of the *cis*-, for menthone (compare this vol., p. 1278) :



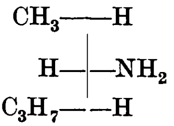
l(or *d*)-
Menthylamine.
(I.)



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



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



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

The adoption of configuration (II), rather than (IV), for *d*-*neo*menthylamine (J., 1926, 2213) is now supported by the fact that the sense of the optical rotation undergoes a change throughout the series of substitution derivatives in passing from (I) to (II), but not in passing from (I) to (IV). Further generalisations may also be made which appear to accord with the suggested configurational scheme. Excluding β-naphthalenesulphon-*d*-*iso*menthylamide, which is only feebly active, and also the hydrochlorides, which differ from the other derivatives in being ionisable, it is remarkable that the reversal of the asymmetry of carbon atom (3), carrying the characteristic amino-group, invariably changes the sign of the optical rotation. On the other hand, the reversal of the asymmetry of either of the carbon atoms (1) or (4) does not affect the sign of the optical rotation.

With regard to numerical values, it is seen that the derivatives of *trans*-menthone (I and II) possess greater rotatory powers than the derivatives of *cis*-menthone (III and IV). The most striking numerical relationships yet observed between the optical rotatory powers of corresponding members of the four series are shown by the formyl and acetyl derivatives : the sum of (I) and (IV) is in each instance practically equal in amount, but opposite in sign, to that of (II) and (III); similar results are obtained by comparing the sum of (I) and (III) with that of (II) and (IV), and the sum of (I) and (II) with that of (III) and (IV). These relationships do not hold for the other derivatives described in this communication, but it is hoped to pursue the subject in order to ascertain whether any definite principle of optical superposition can be discerned in this remarkable series of stereoisomerides.

The action of nitrous acid on the four types of stereoisomeric menthylamines is of particular interest. It must be recognised that the configurations which have been assigned to these substances are based largely upon the assumption that the stereoisomeride which passes most readily into a particular menthol when treated with nitrous acid is configurationally similar to that menthol, the accompanying Δ^3-menthene being attributed in such instances to the occurrence of a Walden inversion (compare J., 1926, 2213). Thus, *l*-menthylamine and *d*-*iso*menthylamine yield the largest proportions of *l*-menthol and *d*-*iso*menthol, respectively, when treated with this reagent. Accepting these processes as the normal ones, the simultaneous formation of partly racemised *d*-Δ^3-menthene takes place through a Walden inversion, leading to the intermediate production of *d*-*neo*menthol and an optically active *neoiso*menthol, respectively; these alcohols, since they possess a hydrogen atom (4) in the *cis*-configurative position to the hydroxyl group (3), then undergo dehydration. The formation of partly racemised *d*-Δ^3-menthene as the main product in the remaining instances of *d*-*neo*menthylamine and *d*-*neoiso*menthylamine is accordingly regarded as the normal procedure. *l*-Menthol, which we now show to be present in small amount in the product yielded by *d*-*neo*menthylamine, will in this instance arise by virtue of a Walden inversion, and it appears that *d*-*neoiso*menthylamine yields *d*-*iso*menthol in a similar way.

l-Menthylamine, *d*-*neo*menthylamine, *d*-*iso*menthylamine, and *d*-*neoiso*menthylamine may all be utilised as sources of *d*-Δ^3-menthene, in varying yields, by the action upon them of nitrous acid (compare also Tschugaeff, *Ber.*, 1899, **32**, 3333). In these changes, carbon atom (1) alone retains its asymmetry, and a proof is thus afforded that the spatial disposition of the groups about this atom is similar in the four stereoisomeric bases concerned, as indicated in our configurational scheme. An interesting distinction between the substances is provided by the observation that the salicylidene derivatives of the menthylamines and *iso*menthylamines are phototropic, while those of the *neo*menthylamines and *d*-*neoiso*menthylamine are not.

EXPERIMENTAL.

Isolation and Characterisation of d-neoiso*Menthylamine.*—The crude oily form-*d*-*neo*menthylamide obtained by heating *l*-menthone with ammonium formate (Wallach, *Annalen*, 1898, **300**, 283) was dried in ether solution and distilled under diminished pressure. The first fraction consisted of menthone, but 85% of the material passed over at 160—166°/9 mm. as a clear, pale yellow syrup, which yielded about 30% of its weight of crystalline form-*d*-*neo*menthylamide when kept overnight in contact with dry ether. After separation of the crystals by filtration and removal of the ether, the remaining syrup had $n_D^{15^\circ}$ 1·4840 and $[\alpha]_D^{15^\circ} - 21{\cdot}1^\circ$ in chloroform ($c = 4{\cdot}3$). Examination showed that the aqueous layer formed in the reaction could be discarded.

The clear solution obtained by hydrolysing the syrup with hydrochloric acid (*Annalen*, 1893, **276**, 308) was rendered alkaline and steam-distilled; the distillate, when carefully neutralised with hydrochloric acid and evaporated to dryness, yielded a colourless, crystalline mass of a mixture of menthylamine hydrochlorides. A non-volatile part of the alkaline mixture, having b. p. 166—176°/9 mm., $[\alpha]_D^{15^\circ} + 6{\cdot}6^\circ$, proved to consist of unchanged formyl derivative; selective hydrolysis had thus occurred. In subsequent hydrolyses, the boiling with concentrated hydrochloric acid was therefore continued for 4—5 hours after the syrup had dissolved; the mixture of menthylamine hydrochlorides then obtained had $[\alpha]_D^{15^\circ} - 4^\circ$ in water ($c = 5{\cdot}1$).

Attempts to separate the constituents of this mixture by treatment with ether, acetone, methyl alcohol, and other organic solvents yielded unsatisfactory results. Fractional extraction of the liberated base from its solution in ether by agitation with four successive equal quantities of 0·6*N*-hydrochloric acid yielded fractions of hydrochloride having $[\alpha]_D^{15^\circ} - 8{\cdot}4^\circ$, $- 5{\cdot}3^\circ$, $- 4{\cdot}6^\circ$, and $+ 1{\cdot}9^\circ$, respectively, in aqueous solution ($c = 4{\cdot}5$). A certain degree of separation was thus effected, but the best results were obtained by preparing the salicylidene derivative directly from the mixture of hydrochlorides having $[\alpha]_D^{15^\circ} - 4^\circ$, described above. When recrystallised twice from light petroleum and once from alcohol, material made in this way yielded about 8% of pure *salicylidene*-d-*neoisomenthylamine*. This substance forms yellow needles, m. p. 99—100°, $[\alpha]_D^{15^\circ} - 17{\cdot}9^\circ$ in chloroform ($c = 2{\cdot}3$). (Found: C, 78·7. $C_{17}H_{25}ON$ requires C, 78·75%). A mixture of this derivative with about an equal amount of salicylidene-*d*-*neo*menthylamine (m. p. 98—99°) melted at 74—78°.

Hydrolysis was best effected by boiling the substance (12 g.) for 3·5 hours with a mixture of sulphuric acid (8·5 c.c.) and water (72 c.c.). Salicylaldehyde was extracted with ether, and d-*neoisomenthylamine hydrochloride* was then prepared by steam-distilling the basified liquid into the requisite amount of dilute hydrochloric acid. The crystalline powder obtained upon evaporation was very soluble in alcohol or water, and practically insoluble in light petroleum or ether. When dissolved in boiling acetone containing a trace of methyl alcohol, it crystallised with difficulty in fine, silky needles, which did not melt below 250°; $[\alpha]_D^{15^\circ}$ in water ($c = 3{\cdot}1$) was $+ 20{\cdot}9^\circ$ (Found, by titration: Cl, 18·4. $C_{10}H_{21}N,HCl$ requires Cl, 18·5%). Free d-*neoisomenthylamine* is a liquid which resembles the stereoisomeric menthylamines in its odour. The approximate rotatory power was determined by extracting with chloroform the base liberated from a known weight of hydrochloride

(1·669 g.); the dried chloroform solution (50 c.c.) gave $[\alpha]_D^{15^\circ} + 9^\circ$ ($\alpha_D^{15} + 0{\cdot}30^\circ$ in a 1-dcm. tube).

The *formyl* derivative is a viscid oil, having $[\alpha]_D^{15^\circ} - 3{\cdot}9^\circ$ in chloroform ($c = 4{\cdot}4$). The *acetyl* derivative is very soluble in organic solvents; it crystallised from light petroleum in needles which softened at 87°, melted at 99—100°, and showed $[\alpha]_D^{15^\circ} - 2{\cdot}6^\circ$ in chloroform ($c = 2{\cdot}7$). The *benzoyl* derivative crystallises from alcohol in fine, silky needles, m. p. 151°, $[\alpha]_D^{15^\circ} - 10{\cdot}4^\circ$ in chloroform ($c = 2{\cdot}3$). The *β-naphthalenesulphonyl* derivative, after three recrystallisations from alcohol, formed hard aggregates, m. p. 120°, $[\alpha]_D^{15^\circ} - 10{\cdot}7^\circ$ in chloroform ($c = 2{\cdot}9$). *Benzylidene*-d-neoiso*menthylamine* separates from hot methyl alcohol in coarse, colourless needles, m. p. 68—69°, $[\alpha]_D^{15^\circ} - 34{\cdot}2^\circ$ in chloroform ($c = 2{\cdot}0$). A mixture with benzylidene-*l*-menthylamine (m. p. 69—70°) melted at 45—51°. d-neoiso*Menthylcarbamide* crystallised from ether–light petroleum in fine needles, m. p. 115—116°, $[\alpha]_D^{15^\circ} - 3{\cdot}1^\circ$ in chloroform ($c = 1{\cdot}9$). d-neoiso*Menthylphenylcarbamide* forms small needles, m. p. 149—150°, $[\alpha]_D^{15^\circ} - 12{\cdot}1^\circ$ in chloroform ($c = 2{\cdot}5$); the pure derivative was readily obtained in 75% yield. d-neoiso*Menthylphenylthiocarbamide* crystallises from ether–light petroleum in well-developed prisms, m. p. 99°, $[\alpha]_D^{15^\circ} - 6{\cdot}7^\circ$ in chloroform ($c = 3{\cdot}0$).

Action of Nitrous Acid on d-neo*Menthylamine and* d-neoiso-*Menthylamine*.—1. *d-neo*Menthylamine hydrochloride (50 g.), obtained by hydrolysing form-*d-neo*menthylamide (m. p. 114—116°), was treated with nitrous acid in the usual manner (this vol., p. 1280). The product contained tarry matter. When distilled it yielded a first fraction (16 g.) having b. p. 57—83°/11 mm., $[\alpha]_D^{15^\circ} + 58{\cdot}6^\circ$ (in ether; $c = 1{\cdot}8$), $n_D^{15^\circ}$ 1·4555, and a second fraction (4·2 g.) having b. p. 83—102°/11 mm., $\alpha_D^{15^\circ} - 18{\cdot}12^\circ$, $[\alpha]_D^{15^\circ} - 20{\cdot}1^\circ$, $n_D^{15^\circ}$ 1·4630. The latter fraction had an odour of menthol; when heated with phthalic anhydride, it yielded a product which, after two recrystallisations from light petroleum containing a little alcohol, had m. p. 111°, $[\alpha]_D^{15^\circ} - 81{\cdot}5^\circ$ (in chloroform; $c = 2{\cdot}1$). A mixture of this substance with *l*-menthyl hydrogen phthalate (m. p. 112—113°) melted at 111—113°; it was therefore diagnosed as slightly impure *l*-menthyl hydrogen phthalate (compare Pickard and Littlebury, J., 1912, **101**, 109).

2. *d-neoiso*Menthylamine hydrochloride (6 g.) was treated similarly, a little dilute hydrochloric acid being added during the progress of the reaction. The crude product (3 g.) when distilled yielded a first fraction (2·1 g.) having b. p. 76—109°/21 mm., $\alpha_D^{15^\circ} + 17{\cdot}64^\circ$, $n_D^{15^\circ}$ 1·4591, and a second fraction (0·6 g.) having b. p. 90—100°/9 mm., $[\alpha]_D^{15^\circ} + 5{\cdot}5^\circ$ (in alcohol; $c = 3{\cdot}7$), $n_D^{15^\circ}$

1·4675. The second fraction, which showed no tendency to crystallise, possessed an odour of *iso*menthol (this vol., p. 1280).

Phototropy of Salicylidenementhylamines.

Of the twelve possible stereoisomeric salicylidenementhylamines, nine have now been described, the remaining three being the derivatives of *d*-menthylamine, *l*-*neoiso*menthylamine, and *dl*-*neoiso*menthylamine. The nine stereoisomerides are all normally pale yellow in colour, but it is remarkable that certain of them display phototropy, while the others do not. When exposed for a few minutes to sunlight or to bright daylight, salicylidene-*l*-menthylamine assumes a deep orange colour, but reverts to pale yellow when kept for a while in subdued daylight or in the dark. A less pronounced change of a similar kind is exhibited by the three salicylidene*iso*menthylamines, and to a slight extent by salicylidene-*dl*-menthylamine, but the three salicylidene*neo*menthylamines and salicylidene-*d*-*neoiso*menthylamine are unaffected by the treatment indicated. Salicylidene-*dl*-menthylamine was originally obtained as a liquid (J., 1926, 2227), but when kept for several months it changed to a pale yellow, crystalline mass, which softened at 60° and melted indefinitely at about 80°. It is hoped in due course to undertake a more detailed study of the phototropy of these derivatives.

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