393. *Researches in the Menthone Series. Part XIII. The Relative Molecular Configurations of the Menthols and Menthylamines.*

By John Read and William J. Grubb.

In seeking evidence bearing upon the relative molecular configurations of the stereoisomeric menthylamines, Read and Storey (J., 1930, 2763) investigated the comparative rates of reaction of these bases with certain symmetric acid anhydrides, acid chlorides, and aldehydes: *neo*menthylamine and *neoiso*menthylamine reacted more rapidly than menthylamine and *iso*menthylamine, respectively. This result appeared to accord with a *cis*-disposition of $NH_2(3)$ and H(4) in the two *neo*-bases (*loc. cit.*, p. 2761).

The above work was qualitative. By means of a refined method we have now determined in certain instances the numerical ratios of the reaction velocities of *l*-menthylamine and *d*-*neo*menthylamine, by allowing equimolecular mixtures of these bases to react competitively in solution at 25° with restricted amounts of various acid chlorides. The influences determining the distribution of the reagent between the two bases are (1) mass action, and (2) the preference of the acid chloride for one of the bases. This preference is expressed in an enhanced rate of reaction. By means of a logarithmic expression (*vide infra*) which allows for the continually changing active masses of the three reactants, it is possible to evaluate the ratio of the two reaction velocities concerned, provided that the yield and composition of the product are known. In each case, *d-neo*menthylamine was found to react faster than *l*-menthylamine; but the values of the ratio were small, falling between **1·16** for β-naphthoyl chloride and **1·45** for *o*-nitrobenzoyl chloride.

A comparison of physical and chemical properties, including notably the optical rotatory powers (this vol., p. 314), provides strong evidence that the nomenclature which has been adopted for the four series of menthylamines and of menthols corresponds in fact to a configurational analogy. Thus, *l*-menthylamine and *d-neo*menthylamine appear to be the respective analogues of *l*-menthol and *d-neo*menthol, and similarly in the *iso*-series.

These amines and alcohols differ, however, in the relationships based upon relative reaction velocity. Vavon and Couderc (*Compt. rend.*, 1924, **179**, 405; *Bull. Soc. chim.*, 1926, **39**, 666) have shown that the rate of esterification of *d-neo*menthol with acetic acid and butyric acid is much slower than that of *l*-menthol, and also that saponification is correspondingly more difficult for the *d-neo*menthyl esters than for the *l*-menthyl esters. Zeitschel and Schmidt (*Ber.*, 1926, **59**, 2303) have applied the differences in the rates of saponification of the hydrogen phthalates in separating *l*-menthol and *d-neo*menthol, the *l*-menthyl ester being the more readily hydrolysed; a similar distinction obtains for the acetates (*loc. cit.*).

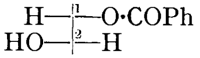
By submitting equimolecular mixtures of various pairs of menthols, dissolved in dry pyridine, to competitive reaction with a series of acid chlorides, we have obtained striking numerical values expressing the relative rates of reaction of two or more of the stereoisomerides with the same reagent. In all the experiments, *l*-menthol reacted much more rapidly than *dl-neo*menthol : with benzoyl chloride the mean ratio of the two reaction velocities was 5·6, and upon introducing a nitro-group into the benzoyl radical the ratio rose to 13·2, 16·5, and 22·5 for *m*-, *p*-, and *o*-nitrobenzoyl chloride, respectively. Thus, by using *p*-nitrobenzoyl chloride as a differential reagent, as described below, it was possible to separate effectively a mixture of *l*-menthol and *dl-neo*menthol (compare *J. Soc. Chem. Ind.*, 1934, **53**, 52T).

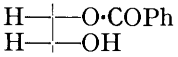
l-Menthol also reacted more rapidly than *dl-iso*menthol; but here the ratio was much smaller, being **1·11** for benzoyl chloride and **1·35** to **1·37** for the three nitrobenzoyl chlorides. Again, *l*-menthol reacted with *p*-nitrobenzoyl chloride 5·4 times as rapidly as *d-neoiso*menthol. The ordinary menthols are thus the most reactive of the four series of menthols, in the reactions under consideration. The mean rates of reaction of the four series with *p*-nitrobenzoyl chloride may be expressed as follows : menthols, 16·5; *iso*menthols, 12·3; *neoiso*menthols, 3·1; *neo*menthols, 1·0. If steric hindrance be accepted as the chief influence determining these differences, OH(3) and H(4) must be assigned a *trans*-disposition in the two series of *neo*menthols. This conclusion is supported by the formation of a predominance of *neo*menthol in the reduction of menthone, whether by catalytic hydrogenation (*Compt. rend.*, 1924, **179**, 407) or by Ponndorf's method (*J. Soc. Chem. Ind.*, 1934, **53**, 52T) : the addition of hydrogen to the keto-group would be expected to take place by preference in the region removed from the large *iso*propyl group.

The conclusion thus reached is at variance with the configurations indicated above for the *neo*-amines; but the differences in reaction velocity are so much more pronounced for the menthols than for the menthylamines that the data obtained for the former may reasonably be given the preference. Perhaps also, the neutral menthols, with the simple OH group, are less liable than the strongly basic menthylamines, with the more complex NH_2 group, to respond to disturbing influences in such reactions.

Moreover, some valuable independent evidence bearing upon this matter has been obtained by Mr. N. A. B. Wilson, B.Sc., during a current investigation in these laboratories of the *cis*- and *trans*-forms of **1** : 2-*cyclo*hexanediol, $C_6H_{10}(OH)_2$. Here, the relative dispositions of the hydroxyl groups are known, since one of the compounds has been resolved into optically active components : this is accordingly the *trans*-form. The monobenzoate of the *trans*-diol (I), when mixed in dry pyridine with *m*-nitrobenzoyl, *p*-nitrobenzoyl, or 3 : 5-dinitrobenzoyl chloride, undergoes esterification more rapidly than the monobenzoate of the *cis*-diol (II). In these instances, therefore, the hydroxyl group undoubtedly displays its greater reaction velocity when situated in the *cis*-position to the hydrogen atom, as in configuration (I) :

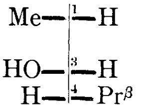
(I.)



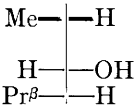


(II.)

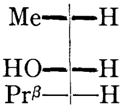
A survey of the whole of the evidence now available thus points to the following relative molecular configurations for the four series of menthols. The effect upon the reaction velocity of rotating the several asymmetric units of the molecule of *l*-, *d*-, or *dl*-menthol (shown by thick lines) through 180° (shown by thin lines after rotation) is also summarised in the diagram by numerals representing the comparative rates of reaction with *p*-nitrobenzoyl chloride :



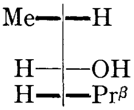
l-Menthol.



d-iso-.



d-neoiso-.



d-neo-.

	l-Menthol.	*d-iso-*.	*d-neoiso-*.	*d-neo-*.
Comparative reaction velocity............	16·5	12·3	3·1	1·0
$[\alpha]_D$ of menthols (in alcohol)...............	−49·6°	+25·9°	+2·2°	+20·7°
$[\alpha]_D$ of menthylamines (homogeneous)...	−44·53°	+28·96°	+2·32°	+15·12°

An examination of the accompanying summary of optical rotatory powers shows that, according to this scheme, the optical rotation is lessened numerically by bringing H(3) and H(4) into the *cis*-position. Also, the least rotatory power is displayed by the *neoiso*-compounds, the configuration of which shows the three hydrogen atoms (**1**, **3**, **4**) on the same side of the plane of the ring. A further interesting feature is the apparent stimulating effect of Me(1) upon the reactivity of OH(3) when these two groups occur in the configurational *cis*-position.

The greater ease of dehydration to Δ^3-menthene, which is characteristic of the two *neo*-series of menthols (see, *e.g.*, *Ber.*, 1926, **59**, 2305), must now be attributed to *trans*-elimination of water between OH(3) and H(4), if, indeed, the initial dehydration can be held to leave H(2) unaffected.

Analogous configurations, in which NH_2 replaces OH in the above formulæ, must be assigned to the menthylamines (this vol., p. 315). Here again, the ready formation of Δ^3-menthene by the action of nitrous acid on the *neo*-bases (J., 1927, 2171) must be attributed to *trans*-elimination of water from the intermediate *neo*menthol, instead of to *cis*-elimination, as originally postulated by Wallach (*Annalen*, 1913, **397**, 218).

The configurations now advanced for the menthols and menthylamines represent a modification of earlier schemes (compare J., 1927, 2170; *Chem. Reviews*, 1930, **7**, 27; J., 1930, 2761). It appears unlikely that chemical evidence of a more decisive nature than that which is now available will be forthcoming; the accumulation of further evidence of a physical nature may, however, follow, now that the substances concerned have all become easily accessible.

EXPERIMENTAL.

Menthylamines.

Reference Derivatives.—Pure specimens of the following reference derivatives of *l*-menthylamine were prepared from the hydrochloride of the base (2 g.) (J., 1930, 2763). This was mixed with 10% sodium hydroxide solution (2 equivs.) and benzene (10—20 c.c.), and then shaken with the appropriate acid chloride (1 mol.). Sufficient chloroform was added to dissolve the product, and the chloroform–benzene solution was washed successively with aqueous alkali and acid, followed by water. The crystalline product obtained upon evaporating the dried solvent was finally purified by recrystallisation. The optical rotatory powers were observed in chloroform solution at 17·5°.

p-*Nitrobenzoyl*-l-*menthylamine* crystallised from aqueous alcohol in pale yellow prisms, m. p. 170°, $[\alpha]_D$ − 53·8° (*c* 5·0) (Found : C, 67·2; H, 7·9. $C_{17}H_{24}O_3N_2$ requires C, 67·1; H, 8·0%).

m-*Nitrobenzoyl*-l-*menthylamine* separated from aqueous alcohol in minute and almost colourless needles, m. p. 135°, $[\alpha]_D$ − 59·4° (*c* 5·0) (Found : C, 66·9; H, 8·0%). o-*Nitrobenzoyl*-l-*menthylamine* was deposited from absolute alcohol in small, pale yellow, rectangular crystals, m. p. 188·5°, $[\alpha]_D$ − 62·9° (*c* 4·0) (Found : C, 67·1; H, 7·9%). 3 : 5-*Dinitrobenzoyl*-l-*menthylamine* crystallised from alcohol–ethyl acetate in yellow microscopic needles, m. p. 193°, $[\alpha]_D$ − 60·0° (*c* 1·0) (Found : C, 58·3; H, 6·6. $C_{17}H_{23}O_5N_3$ requires C, 58·4; H, 6·6%). At 18°, 1 g. of this derivative requires about 80 c.c. of chloroform to dissolve it. β-*Naphthoyl*-l-*menthylamine* formed small glistening needles from alcohol–ethyl acetate, m. p. 180·5°, $[\alpha]_D$ − 51·9° (*c* 2·0) (Found : C, 81·3; H, 8·9. $C_{21}H_{27}ON$ requires C, 81·5; H, 8·8%).

The observed characteristics of the corresponding derivatives of *d*-*neo*menthylamine are summarised below. p-*Nitrobenzoyl*-d-neo*menthylamine* : pale yellow needles from aqueous alcohol, m. p. 151°, $[\alpha]_D$ + 16·1° (*c* 5·0) (Found : C, 67·0; H, 8·1%). m-*Nitrobenzoyl*-d-neo*menthylamine* : flat, pale yellow needles from aqueous alcohol, m. p. 131°, $[\alpha]_D$ + 18·7° (*c* 5·0) (Found : C, 67·2; H, 8·0%). o-*Nitrobenzoyl*-d-neo*menthylamine* : fine, faintly yellow needles from alcohol–ethyl acetate, m. p. 183°, $[\alpha]_D$ + 36·5° (*c* 4·0) (Found : C, 67·0; H, 7·9%). 3 : 5-*Dinitrobenzoyl*-d-neo*menthylamine* : small, deep yellow needles from alcohol–ethyl acetate, m. p. 164°, $[\alpha]_D$ + 22·6° (*c* 1·0) (Found : C, 58·2; H, 6·6%). β-*Naphthoyl*-d-neo*menthylamine* : fine glistening needles from alcohol–ethyl acetate, m. p. 165°, $[\alpha]_D$ + 5·4° (*c* 2·0) (Found : C, 81·2; H, 8·9%).

Comparative Reaction Velocities.—Accurately weighed and exactly equal amounts (*e.g.*, 3·1900 g.) of the hydrochlorides of *l*-menthylamine and *d*-*neo*menthylamine were mixed and stirred mechanically in a suitable reaction vessel, mounted in a thermostat at 25°, with chloroform free from alcohol (25 c.c.) and 10% aqueous sodium hydroxide solution (2 equivs.). A solution of the requisite acid chloride (0·67 mol.) in alcohol-free chloroform (25 c.c.) was then added slowly (20 mins.) with constant stirring. After further stirring (10 mins.), the product was worked up by washing the chloroform with dilute sodium hydroxide solution (twice), dilute hydrochloric acid (twice), and water (until free from chloride); the solvent was evaporated from the dried solution, and the weight and specific rotatory power of the crystalline residue were observed. The hot-water extracts of the products were found to be free from chloride, except in the case of the benzoyl derivatives, for which no satisfactory data were obtained.

The relative reaction velocities, $k_{d\text{-}neo}/k_l$, were calculated from the following equation, in which *d*-*neo*- and *l*-menthylamine are indicated by their prefixes : $k_{d\text{-}neo}/k_l$ = [log (weight of *d*-*neo* used) − log (weight of *d*-*neo* left)]/[log (weight of *l* used) − log (weight of *l* left)]. The values thus obtained are summarised below. The composition of the mixed product was calculated from its observed specific rotatory power, the value of $[\alpha]_D$ being known for each of the two constituents : the weight of each base entering into reaction was thus deducible.

Reagent.	$k_{d\text{-}neo}/k_l$.	Reagent.	$k_{d\text{-}neo}/k_l$.
p-Nitrobenzoyl chloride	1·19 and 1·27	3 : 5-Dinitrobenzoyl chloride	1·18
m-Nitrobenzoyl chloride	1·36 and 1·29	β-Naphthoyl chloride	1·16
o-Nitrobenzoyl chloride	1·33 and 1·56		

Menthols.

Reference Derivatives.—The specific rotatory powers of the following derivatives of *l*-menthol (J., 1905, **87**, 1191; 1933, 170; etc.) were observed in chloroform solution (*c* 5·0) at 15° : benzoate, $[\alpha]_D$ − 87·1°; *p*-nitrobenzoate, − 75·9°; *m*-nitrobenzoate, − 83·6°; *o*-nitrobenzoate, − 153·8°; 3 : 5-dinitrobenzoate, − 79·9°; β-naphthoate, − 69·9°; hydrogen phthalate, − 90·0°; hydrogen succinate, − 66·1°. Further, *d*-*neo*menthyl *p*-nitrobenzoate had $[\alpha]_D$ + 17·8° under similar conditions, and *d*-*neoiso*menthyl *p*-nitrobenzoate had $[\alpha]_D$ − 5·3° (*c* 2·0) (this vol., p. 315). The exceptionally high rotatory power of *l*-menthyl *o*-nitrobenzoate is noteworthy.

Comparative Reaction Velocities.—Accurately weighed and exactly equal amounts (*e.g.*, 2·600 g.) of the two menthols concerned were mixed and dissolved in dry pyridine (25 c.c.) in a vessel immersed in a thermostat at 25°. The powdered acid chloride (0·67 mol.) was then introduced slowly (20 mins.), with mechanical stirring. After further stirring (10 mins.), the solution was diluted with water and extracted with ether. The ethereal extract was washed well with dilute acid, alkali, and water; ether was removed by distillation and unchanged menthols by steam distillation; the purified ester mixture was then isolated by extraction with ether. Its weight and rotatory power were observed. The relative reaction velocities were calculated from the equation given above.

Mixtures of *l*-menthol with each of *dl-neo-*, *dl-iso-*, and *d-neoiso*-menthol were examined in this way, with the following results :

Reagent.	$k_l/k_{dl\text{-}neo}$.	$k_l/k_{dl\text{-}iso}$.	$k_l/k_{d\text{-}neoiso}$.
Benzoyl chloride	5·4 and 5·8	1·11	
p-Nitrobenzoyl chloride	16·3 and 16·7	1·34 and 1·35	5·4
m-Nitrobenzoyl chloride	13·2, 14·2, and 12·1	1·38 and 1·33	
o-Nitrobenzoyl chloride	22·2 and 22·8	1·39 and 1·35	
3 : 5-Dinitrobenzoyl chloride	6·9, 7·2, and 6·9	1·22	
β-Naphthoyl chloride	17·5	1·14	

Similarly, a mixture of *d*-menthol and *l-neo*menthol gave the value 17·2 when treated with *p*-nitrobenzoyl chloride.

The comparative rates of formation of various menthyl hydrogen phthalates and hydrogen succinates were investigated similarly, equimolecular mixtures of two menthols being heated for 9 hours with phthalic anhydride or succinic anhydride (0·67 mol.) in an oil-bath at 120°. The results in these instances were liable to disturbance, through the formation of menthene and other factors. On the whole, menthols appeared to react with these anhydrides about three times as fast as *neo*menthols and only about half as fast as *iso*menthols.

Separation of l-*Menthol and* dl-neo*Menthol.*—A mixture of equal weights of *l*-menthol and *dl-neo*menthol (10·40 g. of each) was esterified in dry pyridine with 70% of the quantity of *p*-nitrobenzoyl chloride theoretically required. The product was worked up in the usual way (compare *J. Soc. Chem. Ind.*, 1934, **53**, 53T), unchanged menthols being removed by steam distillation. This recovered menthol (3·46 g.) crystallised, and one recrystallisation from light petroleum yielded pure *dl-neo*menthol (2·54 g.), in large clear crystals which melted at 53° and were optically inactive (*c* 2·0, alcohol).

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