659. *The Influence of Configuration on the Thermal Stability of N-Menthylphthalamic Acids.*

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The results obtained on heating the epimeric menthylamines with phthalic acid or anhydride confirm current views on their configurations. Phthalamic acids derived from *neo*- and *neoiso*-menthylamines resist cyclisation to phthalimides, indicating that these bases have the *cis*-configuration of amino- and *iso*propyl groups.

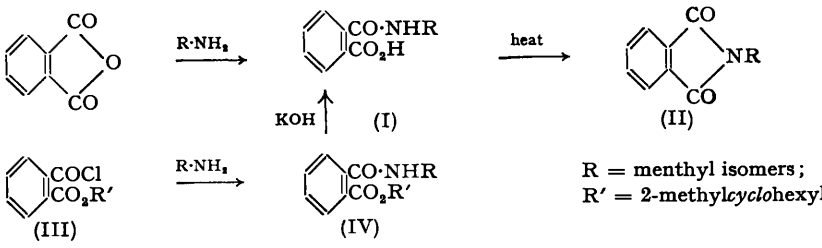
Mixtures of menthylamines may be separated by means of the reaction with phthalic anhydride, and isolation of (±)-*neoiso*menthylamine has been achieved in this way.

Difficulties were encountered when using competitive esterification to determine the relative reactivities of epimeric menthols.

Following the successful use of *N*-(−)-menthylphthalamic acid as a resolving agent for alcohols (Human and Mills, *J.*, 1949, S 77; Macbeth, Mills, and Simmonds, *J.*, 1949, 1011), it was of interest to prepare the phthaloyl derivatives of other epimeric menthylamines as potentially useful resolving agents, and also for characterisation and purification of the bases. Hitherto, only (−)-menthylamine had been converted into the phthalamic acid and phthalimide (Clark and Read, *J.*, 1934, 1775). The investigation had to be suspended before the original aim was achieved, but the preliminary results are presented here because of their practical applications and their important bearing on the stereochemistry of menthylamines.

In agreement with Clark and Read we found that *N*-(−)-menthylphthalamic acid (I; R = menthyl) was very readily dehydrated to the imide (II; R = menthyl), boiling benzene being sufficient to effect the cyclisation. When (−)-menthylamine was heated with phthalic acid or anhydride in boiling toluene water was rapidly evolved, and the base was completely converted into the imide. Under the same conditions (+)-*neo*menthylamine readily afforded *N*-(+)-*neo*menthylphthalamic acid (I; R = *neo*menthyl), but all attempts to convert this acid into the imide (II; R = *neo*menthyl) have failed. Boiling it with chlorobenzene was without effect, and more severe treatment, such as refluxing it with nitrobenzene or with phosphoric oxide in chlorobenzene, caused extensive decomposition, with the production of several

unidentified compounds, none of which appeared to be *N*-(+)-*neo*menthylphthalimide. That the substance in hand actually was *N*-(+)-*neo*menthylphthalamic acid was confirmed by an alternative synthesis : the same acid was obtained by mild alkaline hydrolysis of the diastereo-



isomeric mixture of esters, (±)-*trans*-2-methyl*cyclo*hexyl *N*-(+)-*neo*menthylphthalamate (IV; R = *neo*menthyl), which had been prepared by converting (±)-*trans*-2-methyl*cyclo*hexyl hydrogen phthalate into the acid chloride (III) and treating this with (+)-*neo*menthylamine (Human and Mills, *loc. cit.*).

(−)-Menthylamine and (+)-*neo*menthylamine are epimeric, differing only in the configuration of the amino-group, and the above results indicate that *neo*menthylamine has the *cis*-configuration of the amino-group at $C_{(3)}$ with respect to the *iso*propyl-group at $C_{(4)}$. In *neo*menthylphthalamic acid the orientation of the substituents for any of the possible conformations of the strainless *cyclo*hexane ring provides enough steric hindrance to prevent ring-closure to an imide, whereas in the *trans*-epimer ring-closure is not hindered. However, examination of models of menthylphthalimide suggests that free rotation of the phthalimide group is strongly hindered, and therefore the formation of the *N*-(−)-menthylimide from an unsymmetrically substituted phthalic anhydride may lead to a diastereoisomeric mixture. This possibility is being tested.

The marked difference in reactivity between menthylamine and *neo*menthylamine was utilised in a convenient separation of the two bases. Hydrogenation of (−)-menthoxime in ammoniacal solution furnished a mixture of the two amines in which the *neo*-base predominated (77%), and treatment of the mixture with phthalic anhydride produced a mixture of phthalamic acids, of which only *N*-(−)-menthylphthalamic acid was cyclised in boiling toluene. The imide was separated from the unchanged *N*-(+)-*neo*menthylphthalamic acid, and from each of the products the amines were liberated by treatment with hydrazine. By applying this method of separation it could be shown that the standard preparation of (−)-menthylamine by the reduction of (−)-menthoxime with sodium in ethanol affords a product containing an appreciable amount of (+)-*neo*menthylamine (cf. Tutin and Kipping, *J.*, 1904, **85**, 65). The separation of the two bases does not require polarimetric control, and is equally suitable for active or racemic forms.

The other epimeric menthylamines, *iso*menthylamine and *neoiso*menthylamine, were expected to show the same difference in ease of cyclisation of derived phthalamic acids as was found for menthylamine and *neo*menthylamine. (±)-*iso*Menthoxime was hydrogenated in ammoniacal solution, and the resulting mixture of bases was converted by boiling with phthalic anhydride in toluene into a neutral product and an acid. The acid was evidently crude *N*-(±)-*neoiso*menthylphthalamic acid, as on treatment with hydrazine it afforded an inactive base different from known racemic menthylamines; this appears to be the hitherto unknown (±)-*neoiso*menthylamine, and the method of preparation indicates the expected *cis*-configuration at $C_{(3)}$–$C_{(4)}$. The separation was not as clear-cut in this case, and a study of active bases in the *iso*-series is desirable to clarify the position. There was some evidence of a slow cyclisation of the *neoiso*-phthalamic acid in boiling toluene. This could be the explanation for the much smaller proportion (52%) of crude *neoiso*-phthalamic acid isolated compared with that of *neo*-acid (77%) in the previous experiment (it is assumed that about the same proportion of *cis*-amine will be produced in hydrogenations of menthoxime and *iso*-menthoxime), and why the fraction containing (±)-*iso*menthylphthalimide was a mixture from which a pure compound could not be isolated. Examination of models suggests that the steric hindrance to ring-closure in *neoiso*menthylphthalamic acid may be much less than in the *neo*-acid. This point will be amplified in a later communication.

The usefulness of the phthaloyl derivatives is practically confined to the separation of mixtures. Although they crystallise readily, their complete purification by recrystallisation is apt to be tedious and wasteful, and better results follow if the crude phthaloyl derivatives are

decomposed and the amines purified through suitable salts, Schiff's bases, or formyl derivatives. The phthalimides and phthalamic acids are all cleaved by the action of hydrazine (Ing and Manske, *J.*, 1926, 2348), more readily if 2-ethoxyethanol is used as solvent.

This procedure for separating epimeric primary amines and assigning configurations to them should be applicable to amines other than menthylamines, but its scope has not yet been defined accurately. For *cis*- and *trans*-3-methyl*cyclo*hexylamine the steric effect should be small, and separation of mixtures of these could not be achieved (L. J. Frahn, personal communication). An attempt to separate bornylamine and *neo*bornylamine also was unsuccessful; the chief difficulty here was the extensive decomposition occurring at the high temperatures needed to effect ring-closure of the phthalamic acids. We have at present only utilised differences in thermal stability of the phthalamic acids, and, although quite satisfactory for the menthylamines, this procedure for the preferential cyclisation of one acid probably is the least controllable and least discriminatory of the possible methods. When the steric factors are less pronounced, and the expected difference in thermal stability of the derived phthalamic acids correspondingly less (*e.g.*, the carvomenthylamines), preferential cyclisation of one acid might be achieved in a lower-boiling solvent, such as benzene, but perhaps more readily by the addition of an insufficient amount of a specific dehydrating agent (*e.g.*, thionyl chloride, acetic anhydride, or trifluoroacetic anhydride).

Experimental.

N-(+)-neo*Menthylphthalamic Acid.*—(*a*) Phthalic acid (1·64 g.) and (+)-*neo*menthylamine (1·55 g.) were added to chlorobenzene (30 ml.), and the mixture was refluxed for 3 hours. The solid quickly dissolved and water was evolved. Next morning the crystals which had separated were collected (2·6 g.), and showed m. p. 225—227°. Recrystallisation from chlorobenzene afforded pure N-(+)-neo*menthylphthalamic acid* as large white needles, m. p. 226—227°, $[\alpha]_D^{18}$ +51° (*c*, 0·8 in acetone) (Found: C, 71·1; H, 8·2; N, 4·9. $C_{18}H_{25}O_3N$ requires C, 71·2; H, 8·2; N, 4·6%). The substance dissolved readily in dilute aqueous sodium hydroxide, from which it was precipitated unchanged by hydrochloric acid. It was moderately soluble in cold alcohol or cold acetone, but only sparingly in benzene, toluene, or chlorobenzene.

(*b*) (±)-*trans*-2-Methyl*cyclo*hexyl *N*-(+)-*neo*menthylphthalamate (Human and Mills, *loc. cit.*) was hydrolysed by refluxing it for an hour with a 10% solution of potassium hydroxide (6 mols.) in methanol. After steam-distillation, acidification of the aqueous alkaline solution precipitated a solid which had m. p. 227°, alone or when mixed with the material prepared as in (*a*) above.

Attempted Cyclisation of the Above Acid.—Prolonged refluxing of the acid with toluene or chlorobenzene did not cause separation of water, and on cooling of the solutions the unchanged acid separated almost quantitatively. Heating the acid a little above its m. p. in an open tube produced a sublimate of the unchanged acid, and a dark liquid which solidified on cooling, and after three crystallisations from light petroleum–ethanol afforded a white *substance* (2·4 g. from 5 g. acid), m. p. 138—139°, $[\alpha]_D^{27}$ +1·5° (*c*, 2 in chloroform). This was not *N*-(+)-*neo*menthylphthalimide (Found: C, 73·6; H, 8·1; N, 3·8. $C_{18}H_{23}O_2N$ requires C, 75·9; H, 8·1; N, 4·9%).

A solution of the acid (5 g.) in pure nitrobenzene (30 ml.) was refluxed for 45 minutes, then the solvent was removed *in vacuo*, and the resulting dark cheesy mass was recrystallised several times from aqueous methanol. White needles were obtained (0·5 g.) of a *substance*, m. p. 153·5—154° $[\alpha]_D^{27}$ +57·6° (*c*, 2 in chloroform) (Found: C, 66·1; H, 10·7; N, 6·0%). When refluxed with phosphoric oxide in chlorobenzene the acid yielded a yellow oil which did not crystallise.

None of the foregoing products could be reconverted into *N*-(+)-*neo*menthylphthalamic acid by boiling alcoholic alkali.

Separation of (−)-*Menthylamine and* (+)-neo*Menthylamine.*—(*a*) (−)-Menthone was converted into the oxime by the action of hydroxylamine acetate at room temperature (Read and Robertson, *J.*, 1926, 2209) and the crude oxime was distilled under reduced pressure. A solution of the freshly distilled oxime (47 g.) in methanol (50 ml.) was saturated with ammonia at 0°, then hydrogenated over Raney nickel during 1·5 hours at 50—70°/80 atm. The reaction mixture was filtered, boiled under reflux to expel ammonia, acidified (hydrochloric acid), and steam-distilled to remove methanol. The acid solution was then made alkaline (sodium hydroxide), and the liberated amines were steam-distilled into dilute hydrochloric acid. Evaporation of the acid under reduced pressure afforded a mixture of the menthylamine hydrochlorides in 90% yield.

The amines were liberated from an aqueous solution of these hydrochlorides by addition of alkali, and extracted into toluene (400 ml.). The toluene solution was dried (NaOH) and then mixed with a solution of phthalic anhydride (42 g.) in warm toluene (200 ml.). An exothermic reaction occurred, with separation of white solid, which dissolved when the mixture was boiled. The solution was refluxed with a water-separator attached until water was no longer evolved (1·5 hours). On the solution's being set aside overnight *N*-(+)-*neo*menthylphthalamic acid (50 g.) crystallised, and a further quantity (15·5 g.) was obtained by extraction of the mother-liquor with sodium carbonate solution; the total yield was 77·5%. Evaporation of the toluene yielded crude *N*-(−)-menthylphthalimide (16·5 g., 21%). Five recrystallisations from aqueous ethanol afforded the pure imide (6 g.), m. p. 107—108° (cf. Clark and Read, *loc. cit.*).

Four recrystallisations of the crude *N*-(+)-*neo*menthylphthalamic acid from large volumes of chlorobenzene caused considerable losses without much improvement in m. p. (218—220°). A portion of the impure acid (19 g.) was added to a solution of 12M-hydrazine hydrate (7·2 ml.) in 2-ethoxyethanol (70 ml.), and the mixture was refluxed for 4 hours. Addition of 5N-hydrochloric acid (150 ml.) and warming for 2 hours liberated the amine from the complex, then the solution was filtered, steam-distilled to remove 2-ethoxyethanol, and made alkaline, and the amine steam-distilled into dilute hydrochloric acid. Concentration of the solution yielded several crops of slightly impure (+)-*neo*menthylamine hydrochloride (total 9·7 g., 81%), $[\alpha]_D^{18}$ +18° (*c*, 2 in water), compared with $[\alpha]_D$ +21·5° recorded by Read and Robertson (*loc. cit.*).

(*b*) Several batches of (−)-menthylamine had been prepared by reducing (−)-menthoxime with sodium in ethanol (Wallach, *Annalen*, 1893, **276**, 296) and purifying the crude amine through its formyl derivative. The combined light petroleum mother-liquors from the recrystallisation of the formyl compound were evaporated and the residue was hydrolysed with boiling 15% hydrochloric acid, affording a mixture of menthylamines with α_D^{20} −15° (homogeneous). This mixture was treated with phthalic anhydride in boiling toluene, and 22% of it was recovered as crude *N*-(+)-*neo*menthylphthalamic acid, m. p. 212—217°, which afforded the pure acid after repeated recrystallisation from chlorobenzene.

(±)-neoiso*Menthylamine*.—(±)-Piperitone (50 g.), dissolved in alcohol (100 ml.), was hydrogenated at room temperature and 50 atmospheres' pressure over palladium–charcoal (3·5 g. of 10%), and the solution of crude (±)-*iso*menthone was converted into the oxime under the condition used for (−)-menthone. The resulting crude oily oxime solidified on chilling, and the combined material from three preparations was recrystallised from 60% ethanol until the m. p. was constant; the yield of (±)-*iso*menthoxime, m. p. 98—100°, was 25%.

The purified oxime was hydrogenated under the conditions used for (−)-menthoxime, but the mixture of menthylamines (92%) was isolated in the free state, and not as hydrochlorides. The mixture was refluxed for 1 hour with the calculated quantity of phthalic anhydride in toluene, with separation of water. On cooling, the solution deposited some solid, and the solid and the mother-liquor were worked up for acidic and neutral components by extraction with sodium carbonate solution. The yields of acidic and neutral products were 52% and 48% respectively (*i.e.*, quantitative recovery) on the assumption that they were menthylphthalamic acid and menthylphthalimide.

The phthalimide fraction was evidently a mixture, and after four recrystallisations from 75% ethanol, with considerable losses, the material still melted over the range 81—86°. It was not further examined at this stage.

The phthalamic acid as isolated had an indefinite m. p., 176—182° (decomp.) in a sealed tube, and this was not altered by recrystallisation from toluene, which was attended by large losses. It was concluded that the product was fairly pure *N*-(±)-neoiso*menthylphthalamic acid*, which was undergoing slow cyclisation during the heating with toluene (Found: C, 71·6; H, 8·2. $C_{18}H_{25}O_3N$ requires C, 71·2; H, 8·2%).

The crystalline acid and the material recovered from the mother-liquors of its crystallisation were combined and decomposed by hydrazine hydrate in boiling 2-ethoxyethanol, and the menthylamine was isolated as the hydrochloride. The salt (15·2 g.) was dissolved in warm water (60 ml.), and the solution was mixed with a solution of sodium picrate, made by dissolving sodium hydroxide (3·2 g.) and picric acid (18·2 g.) in the minimum quantity of hot water. A yellow solid separated at once, and after cooling overnight it was collected and washed with a little water; it had m. p. 165—172°; the yield was 30·7 g. Recrystallisation from ethanol containing a little water afforded pure (±)-neoiso*menthylamine picrate* (21·6 g.), m. p. 175·5—177° (sealed tube) (Found: C, 50·2; H, 6·4; N, 14·9. $C_{16}H_{24}O_7N_4$ requires C, 50·4; H, 6·4; N, 14·9%).

The picrate was dissolved in warm water, and the amine was liberated by the addition of sodium hydroxide solution, extracted with ether, dried (NaOH), and distilled through a short column of glass helices. The (±)-*neoiso*menthylamine had b. p. 101—102°/30 mm. and n_D^{27} 1·4622, and was obtained in a yield of 92% from the picrate, and of 20% from (±)-*iso*menthoxime. Standard methods afforded the *benzoyl*, m. p. 188° (Found: C, 78·5; H, 9·4; N, 5·4. $C_{17}H_{23}ON$ requires C, 78·8; H, 9·7; N, 5·4%), and the *phenylcarbamyl* derivative, m. p. 132—133° (Found: C, 74·5; H, 9·2; N, 10·8. $C_{17}H_{26}ON_2$ requires C, 74·5; H, 9·5; N, 10·9%).

Appendix: *The relative reactivities of epimeric menthols and menthylamines.*

In addition to the above new method for assigning configurations to cyclic primary amines, we briefly examined some of the published kinetic methods for determining configurations of menthols and menthylamines, and experienced difficulties in applying the competitive acylation technique of Read and Grubb (*J.*, 1934, 1779). These authors allowed menthols to react in pairs with an insufficient amount of an acid chloride in pyridine, and from the products calculated the relative reaction velocities of the menthols; with *p*-nitrobenzoyl chloride in pyridine at 25° these were 16·5, 12·3, 3·1, and 1·0 for menthol, *iso*menthol, *neoiso*menthol, and *neo*menthol, respectively.

The order of reactivities appears to be correct, but the numerical values are open to question. Experiments with menthol–*neo*menthol mixtures and *p*-nitrobenzoyl chloride carried out under Read and Grubb's conditions, but with various ratios of menthol to *neo*menthol instead of the fixed, exactly equal amounts used by Read and Grubb, showed that, when the composition of the menthol mixture was varied, the apparent ratio of reaction velocities, $R = k_{menthol}/k_{neo}$,

also varied over a considerable range (*ca.* 15—25). The calculations of R could only be approximate, as the yield of esters was less than the theoretical, *e.g.*, 88%, and some free *p*-nitrobenzoic acid was always present; with mixtures rich in *neo*menthol an insoluble by-product was often noted as well. The latter afforded some pyridine and *p*-nitrobenzoic acid when boiled with alkali, and may have been derived from an acylpyridinium complex, which probably is an intermediate in the esterification. To suppress the possible adverse influence of pyridine as solvent (cf. Mills, *J.*, 1951, 2332), some reactions were carried out in benzene with only a small excess of pyridine, but R still varied somewhat as the composition of the menthol mixture was varied.

We had already applied the procedure of Read and Grubb to a pair of relatively labile, but unhindered, epimeric alcohols, (−)-*trans*- and (+)-*cis*-4-*iso*propyl*cyclo*hex-2-en-1-ol (Gillespie, Macbeth, and Mills, *J.*, 1948, 996), and in this instance it gave satisfactory results : in pyridine at 25°, with *p*-nitrobenzoyl chloride sufficient to esterify one-half of the mixed alcohols, the observed ratio, k_{cis}/k_{trans}, was reasonably constant (range, 1·00—1·09) for mixtures containing from 30—60% of the *cis*-alcohol. Only traces of free *p*-nitrobenzoic acid were detected, and no insoluble pyridine complex.

It seems that the method of competitive esterification is less satisfactory for sterically hindered alcohols. One or more of the following factors may account for the inconsistent results with the menthol mixtures : (*a*) partial dehydration of the menthols; (*b*) a side-reaction, leading to the insoluble product and rapid enough to compete with the esterification; (*c*) a departure from the strictly bimolecular mechanism of reaction assumed in the calculation of R. Working with a constant ratio of menthol to *neo*menthol, as in Read and Grubb's experiments, can obscure the effect of these adverse factors, and lead to consistent, but not necessarily correct, values for R. There is no doubt that menthol is much more reactive than *neo*menthol (cf. Vavon and Couderc, *Compt. rend.*, 1924, **179**, 405; Zeitschel and Schmidt, *Ber.*, 1926, **59**, 2298), but the numerical value of the difference is in doubt, except in the few cases where rate constants have been determined separately for the epimers. The rather easy separation of *neoiso*- and *neo*-menthol achieved by Hückel and Niggemeyer (*Ber.*, 1939, **72**, 1354) suggests that the reactivities of this pair differ more widely than is indicated by Read and Grubb's figure.

The original results of competitive acylation studies on menthylamines were unsatisfactory, and at variance with other evidence (Read and Grubb, *loc. cit.*), and our experiments have not clarified the position. Read and Grubb found that *neo*menthylamine was rather more reactive than menthylamine when competing for aromatic acid chlorides in a two-phase system containing aqueous alkali, although the difference between the epimers was surprisingly small. We obtained a similar result from the homogeneous competitive reaction with benzoyl chloride in pyridine ($k_{neo}/k_{menthylamine} = 1{\cdot}44$), but when competing for phenyl *iso*cyanate in benzene (Davis and Ebersole, *J. Amer. Chem. Soc.*, 1934, **56**, 885) menthylamine reacted somewhat more readily than *neo*menthylamine (ratio, 1·32 : 1). A bimolecular mechanism was assumed for these reactions.

At present the method of competitive acylation should be discounted as a means of determining the configuration of these and similar amines. There is considerable evidence from the general properties of menthols and menthylamines (Read and Grubb, *loc. cit.*; Barton, *Experientia*, 1950, **6**, 316), and from non-competitive kinetic studies by Vavon and Chilouet (*Compt. rend.*, 1936, **203**, 1526), that menthylamine has the *trans*-configuration at $C_{(3)}$–$C_{(4)}$, and this is supported by the results in the first part of this paper, and the similar but less decisive observations by Read and Hendry (*Ber.*, 1938, **71**, 2544) on the course of thermal degradations of *N*-menthyl- and *N*-*neo*menthyl-glycine to *NN'*-dimenthyldiketopiperazines.

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