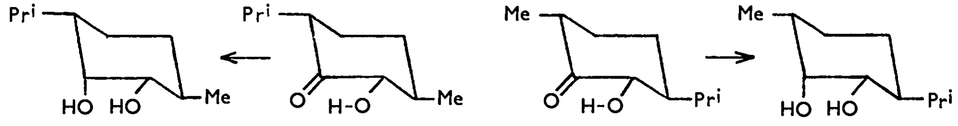
457. *Stereochemistry of* cyclo*Hexane Derivatives. Part III.** *Hydroxylation of* (+)-trans-p-*Menth-2-ene.*

By P. R. Jefferies and B. Milligan.

The configurations of some of the (±)-*p*-menthane-2 : 3-diols have been clarified. Hydroxylation of (±)-*trans-p*-menth-2-ene with a variety of reagents is described and the configurations of the derived glycols have been established. A preliminary examination of the rates of oxidation of a number of glycols by periodate is reported.

Macbeth and Robertson [1] have described seven (±)-*p*-menthane-2 : 3-diols. Six of these isomers were derived by hydroxylation of the *p*-menth-2-enes and a seventh proved to be *cis*-2-hydroxy*neoiso*menthol. A further isomer was considered to arise on reduction of diosphenol by lithium aluminium hydride or the Ponndorf method and was assigned the configuration *cis*-2-hydroxy*neo*menthol (I). Further characterisation of *cis*-2-hydroxymenthol (II) derived from *trans-p*-menth-2-ene with osmium tetroxide has now shown it to be identical with this reduction product from diosphenol. The hitherto unknown (±)-*cis*-2-hydroxy*neo*menthol (I) and the diol (II) have now been obtained by hydroxylation by the iodine–silver acetate–water method.[2] Chromatography of the esterified product afforded the (±)-di-*p*-nitrobenzoate, m. p. 165—166°, of *cis*-2-hydroxymenthol (II) and the ester, m. p. 162°, of the diol (I). This separation is facilitated by use of the *m*-nitrobenzoates. In addition, mixed crystals, m. p. 155°, of the two di-*p*-nitrobenzoates were isolated. These were identical with the unknown di-*p*-nitrobenzoate of the same m. p. derived from the product of hydrogenation of (±)-2-hydroxymenthone with Raney nickel,[3] which thus affords largely (±)-*cis*-2-hydroxy*neo*menthol (I) and (±)-*cis*-2-hydroxymenthol (II).



(I) (III) (IV) (II)

These hydrogenation results can now be explained. It has been pointed out that alkaline hydrolysis of 2-acetoxymenthone would yield a mixture of 2-hydroxymenthones and 3-hydroxycarvomenthones by way of an enediol intermediate, evidence for whose existence was presented.[3] This hydrolysis should yield the ketols in their thermodynamically more favourable conformations. The more stable conformation of the substituent in a polysubstituted *cyclo*hexane derivative depends upon both steric and dipole interaction. It is known that the former effect is minimised when the substituent adopts an equatorial position, although in the case of a *cyclo*hexanone substituted in the 2-position with an equatorial group this stabilisation will be decreased by the eclipsed interaction between the group and the carbonyl-oxygen atom [see (III) and (IV) [4]]. It is apparent that attraction between the carbonyl and the hydroxyl dipoles would be much more significant if the hydroxyl group assumed an equatorial, as opposed to an axial conformation. Thus from both these considerations the mixture of hydroxymenthones and hydroxycarvomenthones must consist predominantly of structures (III) and (IV). The structures related to the *iso*menthone configuration may be disregarded in view of the reduction products.

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* The papers, *J.*, 1955, 2767, and 1956, 805, are regarded as Parts I and II.

[1] Macbeth and Robertson, *J.*, (*a*) 1953, 895; (*b*) 1953, 3512; 1954, 701.

[2] Ginsburg, *J. Amer. Chem. Soc.*, 1953, **75**, 5746.

[3] Jefferies, Macbeth, and Milligan, *J.*, 1954, 705.

[4] Robins and Walker, *J.*, 1955, 1789; *Chem. and Ind.*, 1955, 772.

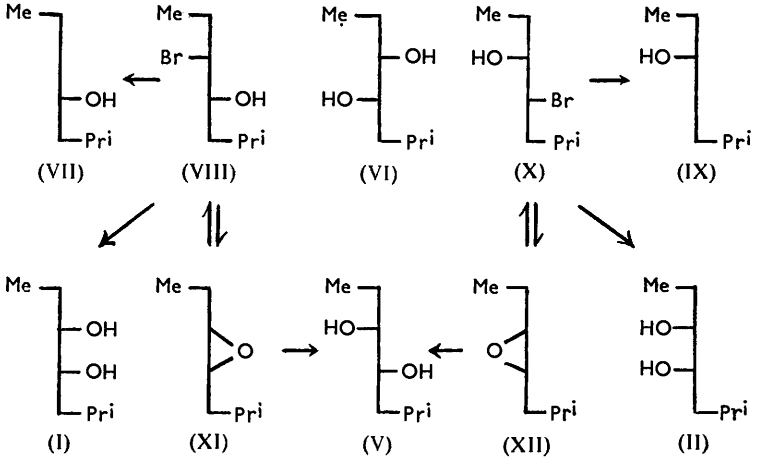
In order to explain the high value for the observed dipole moment (2·9 D) of 2-hydroxy*cyclo*hexanone, Svirbely and Lander [5] assumed the presence of a proportion of the enol in benzene solution. When the accepted link moments,[6] the normal valency angles, the value 3·08 D for *cyclo*hexanone,[7] and coplanarity are assumed, the value 2·7 D is obtained by graphical calculation for 2-hydroxy*cyclo*hexanone in the hydrogen-bonded, equatorial-hydroxyl conformation. This value could be significantly increased by induction, or by bond deformation arising from dipole interaction, and we believe that the proportion of enediol present is small.

The ketol mixture derived from 2-acetoxymenthone failed to produce a colour with ferric chloride and so must consist predominantly of the forms (III) and (IV).

Reduction with sodium in alcohol would yield both hydroxyl groups in equatorial positions, giving (±)-*trans*-2-hydroxymenthol. Catalytic hydrogenation in neutral media yielded mainly (±)-*cis*-2-hydroxy*neo*menthol (I) and (±)-*cis*-2-hydroxymenthol (II), corresponding to the reduction of the carbonyl group to the axial-hydroxyl group in both (III) and (IV), as expected for a hindered carbonyl group.[8]

In view of the ready availability of (+)-*trans*-*p*-menth-2-ene we have undertaken an examination of its hydroxylation in the hope of making the derived diols available.

By treatment of (+)-*trans*-*p*-menth-2-ene with lead tetra-acetate and subsequent hydrolysis Hückel and Kummerle [9] obtained a glycol characterised as the bisphenylurethane, m. p. 149—150°. Hydroxylation by way of the epoxide [10] yielded a diol which formed a bisphenylurethane, m. p. 83—85°. We have examined hydroxylation with peracetic acid and by the epoxide method.[10] Separation of the product as the *p*-nitrobenzoates gave esters of m. p.s 141° and 174° in the ratio of 1 : 15. Hydrolysis of the latter ester gave (+)-*trans*-2-hydroxy*neo*menthol (V). Hydrolysis of the former ester afforded (—)-*trans*-2-hydroxymenthol (VI).



In contrast approximately equivalent quantities of these diols may be obtained by Prévost's method [11] using the iodine–silver benzoate complex. Although the yield of glycol mixture is inferior to that obtained by using per-acid, the method may prove of some value in preparing diequatorial *trans*-diols. The only product isolated from the reaction with excess of the iodine–silver *p*-nitrobenzoate complex was a small quantity of the *p*-nitrobenzoate of an iodohydrin.

Reaction of (+)-*trans*-*p*-menth-2-ene with osmium tetroxide and esterification gave a

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[5] Svirbely and Lander, *J. Amer. Chem. Soc.*, 1950, **72**, 3756.
[6] Le Fèvre, " Dipole Moments," Methuen and Co., Ltd., London, 1938, p. 64.
[7] Günthard and Gäumann, *Helv. Chim. Acta*, 1951, **34**, 39.
[8] Barton, *J.*, 1953, 1027.
[9] Hückel and Kummerle, *J. prakt. Chem.*, 1942, **160**, 74.
[10] Hückel, Tappe, and Legutke, *Annalen*, 1940, **543**, 191.
[11] Prévost, *Compt. rend.*, 1933, **196**, 1129; **197**, 1661.

p-nitrobenzoate, m. p. 108°, which was assigned the configuration (—)-*cis*-2-hydroxymenthol (II), arising by attack of the olefin *trans* to the *iso*propyl group. Ginsburg's method [2] provided a convenient route to the two *cis*-diols, no *trans*-isomers being detected : esterification of the product and chromatography afforded esters, m. p. 108° and 169°, in the approximate ratio of 2 : 1; as expected, the steric control in this reaction is much less than with osmium tetroxide. The di-*p*-nitrobenzoate of m. p. 108° yielded the parent diol, (—)-*cis*-2-hydroxymenthol (II). The second ester, m. p. 169°, afforded the diol which was assigned the structure (—)-*cis*-2-hydroxy*neo*menthol (I).

None of the above active diols forms a bisphenylurethane similar to that described by Hückel and Kummerle.[9]

Experimental confirmation of the structures assigned to the optically active diols has been obtained by a study of the bromohydrins obtained by reaction with hydrogen bromide of the epoxide mixture derived from (+)-*trans-p*-menth-2-ene. Separation of the bromohydrins as the *p*-nitrobenzoates afforded esters, m. p. 99° and 105°, in the proportion 1 : 5. Reduction of the former with lithium aluminium hydride gave (+)-*neo*menthol (VII). If the normal *trans*-disposition is assumed for the bromine and the hydroxyl group this bromohydrin will have the configuration *trans*-2-bromo*neo*menthol (VIII). Similar treatment of the ester, m. p. 105°, yielded a substance which corresponds closely to the properties expected for the unknown enantiomorph of (—)-*neo*carvomenthol [12] (IX). The bromohydrin is thus *trans*-3-bromo*neo*carvomenthol (X). Preliminary attempts to achieve these relations with chlorohydrins were unsuccessful as the chlorine atoms did not undergo hydrogenolysis. Although the reported reductions may proceed by way of epoxide intermediates the stereochemistry of the products will not be altered.

Reaction of the ester, m. p. 99°, of the bromohydrin (VIII) with potassium hydroxide gave the epoxide (XI); and its isomer (XII) was prepared similarly from the ester of m. p. 105°. The epoxides regenerated virtually pure bromohydrins. Hydration of the epoxides gave (+)-*trans*-2-hydroxy*neo*menthol (V) as the major product in both cases, whose structure may now be regarded as established. It is apparent that the proportion of bromohydrins originally separated indicates a predominance of the oxide (XII) in the mixture derived from the menth-2-ene, as expected for the least hindered mode of attack.

The configurations of the *cis*-diols have been confirmed in the following way. Conversion of the bromohydrin (VIII) into its acetate and reaction with silver acetate in moist acetic acid [13] gave *cis*-2-hydroxy*neo*menthol (I). Similar treatment of the bromohydrin (X) yielded *cis*-2-hydroxymenthol (II). In view of the mechanism [13] of these inversions, these structures may be regarded as established. The best overall yields of the *cis*-diol mixture involved conducting this inversion directly on the mixture of bromohydrin acetates, although this required more steps than in the method described by Ginsburg.[2]

It is known that the rupture of epoxides in rigid structures produces axial substituents.[14] For non-rigid systems it is necessary to consider the rupture of the possible conformations of each epoxide.[15] If boat structures are neglected, the epoxide (XI) may be regarded as (XIII) or (XIV), and (XII) as (XV) or (XVI) (R = Me, R′ = H in all cases). The conformations (XIII) and (XV) bearing pseudoequatorial alkyl substituents would exist in greater proportions. Application of the Fürst–Plattner rule to these conformations involves rearside attack at position 2 and 3 respectively, yielding *trans*-2-hydroxy*neo*menthol (XVII or V). Rupture of the less stable conformations (XIV) and XVI) would proceed similarly by attack at position 3 and 2 respectively, giving initially (XVIII) which would undergo conformational inversion yielding the all-equatorial isomer, *trans*-2-hydroxymenthol (VI). The effect of steric factors on the rates of rupture of the different conformations would be slight, although the forms (XIV) and (XVI) might be expected to react somewhat slower than (XIII) and (XV) since greater hindrance will be exerted by the pseudoalkyl groups in the transition state.

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[12] Johnston and Read, *J.*, 1934, 233; 1935, 1138.

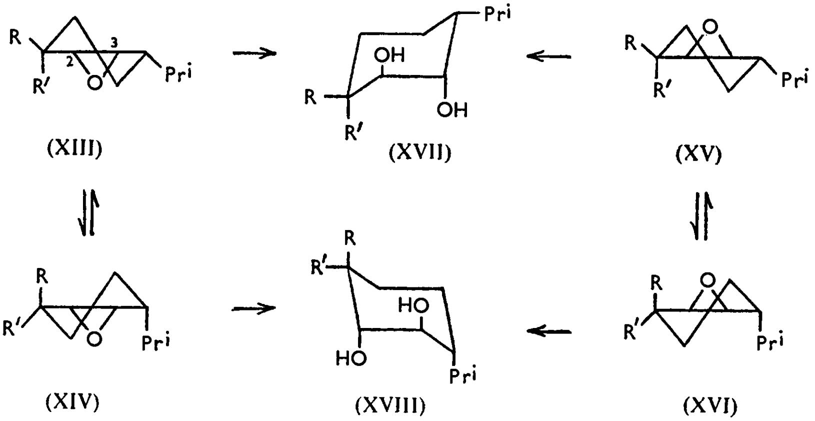
[13] Winstein and Buckles, *J. Amer. Chem. Soc.*, 1942, **64**, 2787.

[14] Fürst and Scotoni, *Helv. Chim. Acta*, 1953, **36**, 1410.

[15] Angyal, *Chem. and Ind.*, 1954, 1230; Bose, Chaudhuri, and Bhattacharyya, *ibid.*, 1953, 1257; Newth, *ibid.*, p. 1257; Cookson, *ibid.*, 1954, 223; Overend and Vaughan, *ibid.*, 1955, 995.

If these considerations are correct, the mixture of diols arising from the rupture of the epoxide mixture would consist almost entirely of the diol (XVII). Measurement of the rotation of the diol mixture indicates 90% of (XVII) and 10% of (XVIII).

Similar reasoning may be applied to the rupture of the epoxides derived from *cis*-menth-2-ene. The epoxide (XIII, XIV; R = H, R′ = Me) will be more stable as (XIII) although the energy difference between the conformations will be considerably less than with *trans-p*-menthane epoxides. The two conformations should have similar rates of rupture. On the other hand, the epoxide represented as conformation (XV, XVI; R = H, R′ = Me) should be more stable as the former and undergo attack somewhat more readily than (XVI) in which this attack is hindered by the larger *iso*propyl group. We should thus expect a mixture of glycols with *trans*-2-hydroxy*neoiso*menthol (XVII; R = H, R′ = Me) in slight excess, corresponding to rupture of (XV) and (XIII). Previous work [1a] indicates this to be the case. Rupture of the epoxides (XI and XII) with hydrogen bromide has so far failed to yield products with equatorial-bromine and -hydroxyl groups, the two observed products (III and IV) corresponding to attack of (XIII and XV; R = Me, R′ = H) by bromide ion. This may be due to the expected greater degree of hindrance to bromide-ion attack on the conformations (XIV, XVI; R = Me, R′ = H).



The oxidation of *cis*- and *trans*-*cyclo*hexane-1 : 2-diol by periodate has been examined kinetically by Price and his co-workers.[16] They carried out oxidations at various initial pH values and showed the reaction to be bimolecular and subject to acid-catalysis. In our hands reproducible rate constants could be obtained only by operation in buffered solutions. Taylor [17] has discussed the variation in rate constant with different proportions of ethylene glycol and periodate, and we find a similar increase in the rate constant with increasing periodate concentration for both *cis*- and *trans*-*cyclo*hexane-1 : 2-diol.

Oxidation of diols (0·01M) *with potassium periodate* (0·006M) *in buffer* pH 10·5 *at* 25°.

Diol	k_2 (l. mole^{-1} min.$^{-1}$)	Diol	k_2 (l. mole^{-1} min.$^{-1}$)
cis-*cyclo*Hexane-1 : 2-diol	12	(±)-*cis*-2-Hydroxy*neoiso*menthol	37
trans-*cyclo*Hexane-1 : 2-diol	0·70	(±)- and (−)-*trans*-2-Hydroxymenthol ...	3·8
(−)-*cis*-2-Hydroxy*neo*menthol ...	55	(±)- and (+)-*trans*-2-Hydroxy*neo*menthol	0·083
(−)-*cis*-2-Hydroxymenthol	43	(±)-*trans*-2-Hydroxy*iso*menthol	6·0

We have therefore measured the oxidation rates of the available *p*-menthane-2 : 3-diols at fixed reactant concentrations. The results given in the Table show that the

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[16] Price and Kroll, *J. Amer. Chem. Soc.*, 1938, **60**, 2726; Price and Knell, *ibid.*, 1942, **64**, 552.

[17] Taylor, *ibid.*, 1953, **75**, 3912.

cis-glycols are oxidised much faster than *cis-cyclo*hexane-1 : 2-diol. Similarly *trans*-2-hydroxymenthol and *trans*-2-hydroxy*iso*menthol with conformations stabilised as diequatorial 2 : 3-diols react faster than *trans-cyclo*hexane-1 : 2-diol. The very slow rate of oxidation of *trans*-2-hydroxy*neo*menthol must arise from its diaxial 2 : 3-diol structure. This does not imply that this structure is oxidised since the reaction may proceed by way of the diequatorial diol structure present in the inverted conformation.

In general, the relative rates of oxidation can be reconciled with the strain associated with the formation of a cyclic complex in which the C–O bonds are rotated to some degree of coplanarity.[18]

The similarity of the rotations of the *cis*-diols and their respective derivatives is noteworthy.

EXPERIMENTAL

Light petroleum refers to the fraction of b. p. 60—70°. Rotations were measured in $CHCl_3$ in a 1 dm. tube. Esterifications were normally carried out with a large excess of the acid chloride in pyridine during 48 hr.

cis-*Hydroxylation of* (±)-trans-*Menth*-2-*ene*.—The hydrocarbon (12 g.) in "AnalaR" acetic acid (300 ml.) was stirred mechanically and powdered silver acetate (27·4 g.) was added during 10 min. Iodine (19·5 g.) was added during 30 min., and the mixture heated at 100° for 3 hr. with a solution (4%) of water in acetic acid (33 ml.). Salt (66 g.) was added to the cold solution which was stirred for a further 30 min. The precipitate was separated and washed with hot benzene (100 ml.), and the combined filtrates were evaporated under reduced pressure. Hydrolysis of the residue with potassium hydroxide (6·5 g.) in methanol (50 ml.) overnight and isolation in the usual manner gave a fraction (11 g.), b. p. 104—114°/4 mm., which was esterified with *p*-nitrobenzoyl chloride. The ester (20 g.) in light petroleum–benzene (10 : 1) was absorbed on alumina (250 g.). Elution with light petroleum–benzene (5 : 1) yielded mixed crystals, m. p. 155°, alone or mixed with a sample derived from esterification of the hydrogenation product of (±)-2-hydroxymenthone.[3] Elution with light petroleum–benzene (1 : 1) gave (±)-cis-2-*hydroxy*neo*menthol di*-p-*nitrobenzoate* (0·5 g.) (Found : C, 61·2; H, 5·6; N, 5·9. $C_{24}H_{26}O_8N_2$ requires C, 61·3; H, 5·5; N, 6·0%) as pale yellow prisms, m. p. 162° after repeated crystallisation from methanol–chloroform. Elution with benzene and crystallisation from methanol–chloroform afforded the di-*p*-nitrobenzoate of (±)-*cis*-2-hydroxymenthol (3·0 g.) as pale yellow rhombs, m. p. and mixed m. p. 165—166°. The mixed crystals (6·5 g.), on further chromatography, afforded the esters of (±)-*cis*-2-hydroxymenthol (1·5 g.) and (±)-*cis*-2-hydroxy*neo*menthol (0·7 g.). A similar reaction and esterification of the mixed diols (13 g.) with *m*-nitrobenzoyl chloride yielded after chromatography and fractional crystallisation mixed crystals (8·4 g.), the *di*-m-*nitrobenzoate* of (±)-*cis*-2-hydroxy*neo*menthol (1·8 g.) which formed pale yellow rhombs, m. p. 103° (Found : C, 61·6; H, 5·9; N, 6·2. $C_{24}H_{26}N_2O_8$ requires C, 61·3; H, 5·5; N, 6·0%), and of (±)-*cis*-2-hydroxymenthol (4·6 g.), m. p. 152° (Found : C, 61·6; H, 5·6; N, 6·1%), as prisms from chloroform–methanol. Hydrolysis of either the *m*-nitrobenzoate, m. p. 103° or the *p*-nitrobenzoate, m. p. 162°, in the usual way and distillation at 100° (bath)/0·5 mm. gave (±)-cis-2-*hydroxy*neo*menthol*, m. p. 54° (Found : C, 69·2; H, 11·8. $C_{10}H_{20}O_2$ requires C, 69·7; H, 11·6%). The *monotoluene*-p-*sulphonate*, prepared by means of the acid chloride (1·5 mols.) in pyridine during 24 hr., crystallised from light petroleum as needles, m. p. 99° (Found : S, 10·0. $C_{17}H_{26}O_4S$ requires S, 9·8%). The original sample[1a] of *cis*-2-hydroxymenthol di-*p*-nitrobenzoate had m. p. 165—166° after repeated crystallisation from ethanol. Esterification of a fresh sample of this diol with *m*-nitrobenzoyl chloride gave the ester, m. p. and mixed m. p. 152°. The *monotoluene*-p-*sulphonate*, prepared from each sample, had m. p. and mixed m. p. 124° (Found : C, 63·0; H, 7·9; S, 10·0. $C_{17}H_{26}O_4S$ requires C, 62·6; H, 8·0; S, 9·8%).

Hydroxylation of (±)-trans-p-*Menth*-2-*ene with Peracetic Acid*.—Hydrogen peroxide (30%; 86 ml.) and acetic acid (340 ml.) were kept at 80° for 1 hr.; (+)-*trans*-*p*-menth-2-ene (n_D^{30} 1·4460, d_{30}^{30} 0·8074, $[\alpha]_D^{25}$ +125°; 30 g.) was added; after being kept at 50° for 45 hr., the mixture was poured into water and extracted with benzene (4 × 100 ml.), and the extract washed with 5% aqueous sodium carbonate and water. Removal of the solvent left the crude mixture of monoacetates (25 g.), which was hydrolysed by potassium hydroxide (20 g.) in boiling water

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[18] Angyal and Macdonald, *J.*, 1952, 686.

(70 ml.) for 2 hr. Continuous extraction with ether and evaporation of the dried extract gave the crude diol {18 g.; $[\alpha]_D^{15}$ +28·5° (*c* = 1·0)} which was added to the product (10 g.) from a previous preparation and distilled. Four fractions collected were: (i) 5·2 g., b. p. 68—124°/8 mm.; (ii) 1·4 g., b. p. 124—128°/8 mm.; (iii) 9·3 g., b.p. 128—132°/8 mm., and (iv) 9·8 g., b. p. 132—136°/8 mm.

Fractions (ii) and (iii) were esterified with *p*-nitrobenzoyl chloride in the usual way, and the crude ester (22 g.) in light petroleum–benzene (4 : 1) was chromatographed on alumina (200 g.). Elution with benzene yielded trans-2-*hydroxy*neo*menthol* (–)-*di*-p-*nitrobenzoate* (5·3 g.) as pale yellow prisms, m. p. 174°, $[\alpha]_D^{15}$ –70·5° (*c* 1·0), after crystallisation from methanol–chloroform (Found: C, 61·5; H, 5·7; N, 5·9. $C_{24}H_{26}O_8N_2$ requires C, 61·3; H, 5·5; N, 6·0%). The intractable oil (9·0 g.) obtained by elution with light petroleum–benzene (4 : 1 and 2 : 1) in light petroleum–benzene (10 : 1) was re-chromatographed on alumina (180 g.). Elution with the same solvent yielded the (±)-*di*-p-*nitrobenzoate* of *trans*-2-hydroxymenthol (0·4 g.) as pale yellow needles, m. p. 141°, $[\alpha]_D^{20}$ +235° (*c* 0·5), after five crystallisations from light petroleum–chloroform (Found: C, 61·2; H, 5·4; N, 6·4%). Elution with benzene gave a second crop of the di-*p*-nitrobenzoate, m. p. 174° (1·1 g.). Similar treatment of fraction (iv) yielded the ester, m. p. 141° (0·2 g.), and the ester, m. p. 174° (7·0 g.). The diol mixture prepared by hydration of the epoxides [10] was separated in the same way.

(+)-trans-2-*Hydroxy*neo*menthol*.—The di-*p*-nitrobenzoate, m. p. 174°, was hydrolysed in the usual way, and, after removal of the methanol by fractional distillation, the residue was continuously extracted with ether. Evaporation of the dried extract and distillation of the residue gave *diol* (1·8 g.), b. p. 132°/10 mm., $[\alpha]_D^{20}$ +40·8° (*c* 1·0) (Found: C, 69·6; H, 11·8; $C_{10}H_{20}O_2$ requires C, 69·7; H, 11·6%). The *bis*-3 : 5-*dinitrobenzoate* crystallised from ethanol–chloroform as pale yellow prisms, m. p. 200°, $[\alpha]_D^{20}$ +95·2° (*c* 0·7) (Found: C, 51·5; H, 4·6; N, 10·2. $C_{24}H_{24}O_{12}N_4$ requires C, 51·4; H, 4·4; N, 10·0%). The *bisphenylurethane*, prepared at 150° in the absence of solvent, crystallised from acetone–hexane as needles, m. p. 86—88°, $[\alpha]_D^{15}$ –54·8° (*c* 1·3) (Found: N, 6·7. $C_{24}H_{30}O_4N_2$ requires N, 6·8%).

(–)-trans-2-*Hydroxymenthol*.—The di-*p*-nitrobenzoate, m. p. 141° (1·2 g.), was hydrolysed with methanolic potassium hydroxide as before. Continuous extraction of the aqueous filtrate with ether yielded the diol (0·5 g.). Wasteful crystallisation of the original material from water containing a little methanol gave the pure *diol* as needles, m. p. 85°, $[\alpha]_D^{15}$ –9·3° (*c* 0·5) (Found: C, 70·2; H, 11·65. $C_{10}H_{20}O_2$ requires C, 69·7; H, 11·6%). The *bis*-3 : 5-*dinitrobenzoate* crystallised from methanol–benzene as needles, m. p. 192·5°, $[\alpha]_D^{15}$ +96° (*c* 0·5), retaining benzene of crystallisation (Found: C, 53·3; H, 4·8; N, 9·7. $C_{24}H_{24}O_{12}N_4,0{\cdot}33C_6H_6$ requires C, 53·2; H, 4·4; N, 9·6%). A *bisphenylurethane*, prepared as above, crystallised as needles, m. p. 186°, $[\alpha]_D^{15}$ –19·1° (*c* 0·7) (Found: N, 7·3%).

Hydroxylation of (+)-trans-p-*Menth*-2-*ene by the Prévost Reaction*.—(i) A solution of iodine (12·7 g.) in anhydrous benzene (120 ml.) was added dropwise to a stirred suspension of silver benzoate (32·3 g.) in benzene (160 ml.). (+)-*trans*-*p*-Menth-2-ene (7·8 g.) in benzene (30 ml.) was added slowly, and the mixture refluxed for 3 hr. and then filtered. The residue was washed with chloroform (150 ml.), and the combined filtrates were washed with 5% aqueous sodium hydroxide (2 × 100 ml.), then water, and dried. Evaporation gave the crude benzoates (14·0 g.) which were chromatographed on alumina. Elution with hexane–benzene and benzene failed to yield any crystalline fraction, and the combined material was hydrolysed with methanolic potassium hydroxide in the usual way. The diol (1·5 g.; b. p. 90—102°/0·2 mm.) gave a crude *p*-nitrobenzoate (4·0 g.) which was chromatographed in benzene–hexane (1 : 10) on alumina (80 g.). Elution with this solvent afforded the (+)-*p*-nitrobenzoate of *trans*-2-hydroxymenthol (1·05 g.), and benzene eluted the (–)-*p*-nitrobenzoate of *trans*-2-hydroxy*neo*menthol (0·8 g.).

(ii) Iodine (12·7 g.), silver *p*-nitrobenzoate (38·8 g.), and (+)-*trans*-*p*-menth-2-ene (7·8 g.) were caused to react. and worked up as above, the alkaline washing being omitted. The product (18·5 g.) in benzene–hexane (1 : 10) was chromatographed on alumina (200 g.). Elution with this solvent gave an *iodohydrin* p-*nitrobenzoate* (0·35 g.) which crystallised from methanol as needles, m. p. 137° (Found: C, 47·3; H, 5·2; N, 3·1. $C_{17}H_{22}O_4NI$ requires C, 47·3; H, 5·1; N, 3·2%). Other eluants gave fractions which failed to crystallise.

cis-*Hydroxylations*.—(*a*) (+)-*trans*-*p*-Menth-2-ene (1·0 g.) was treated with osmium tetroxide (1 g.) by the usual method.[1a] The partly crystalline product (0·7 g.) in light petroleum was chromatographed on alumina (15 g.). Elution with ether–benzene (1 : 1) gave prisms, m. p. 58° (0·45 g.). Recrystallisation could not be achieved. Esterification gave (–)-cis-2-*hydroxymenthol di*-p-*nitrobenzoate*, m. p. 108°, $[\alpha]_D^{15}$ –165° (*c* 0·6), as pale yellow needles, after three crystallisations from methanol (Found : C, 61·7; H, 5·5; N, 6·1. $C_{24}H_{26}O_8N_2$ requires C, 61·3; H, 5·5; N, 6·0%).

(*b*) (+)-*trans-p*-Menth-2-ene (16 g.) was treated with silver acetate, iodine, and aqueous acetic acid as for the inactive hydrocarbon and after hydrolysis, isolation, and distillation gave a fraction (12 g.), b. p. 110—118°/4 mm., $[\alpha]_D^{15}$ −10·6° (*c* 4·0). Esterification with *p*-nitrobenzoyl chloride gave the crude ester (20 g.) which was dissolved in light petroleum–benzene (10 : 1) and absorbed on alumina (250 g.). Elution with light petroleum–benzene (1 : 5 and 1 : 1) gave a mixture (6·0 g.) which on fractional crystallisation from methanol–chloroform gave the (−)-*di*-p-*nitrobenzoate* of *cis*-2-hydroxy*neo*menthol (2·1 g.) as pale yellow prisms, m. p. 160°, $[\alpha]_D^{15}$ −170° (*c* 1·0) (Found : C, 61·5; H, 5·5; N, 6·2%). Elution with benzene afforded the (−)-di-*p*-nitrobenzoate of *cis*-2-hydroxymenthol (3·6 g.) as needles, m. p. 108°, alone or mixed with a sample obtained by use of osmium tetroxide. A similar chromatogram of crystals (6·0 g.) isolated from mother-liquors gave di-*p*-nitrobenzoates, m. p. 108° (2·3 g.) and 169° (1·0 g.).

(*c*) The epoxide mixture (14·5 g.) derived from (+)-*trans-p*-menth-2-ene [10] (15 g.) in absolute ether (100 ml.) was saturated with dry hydrogen bromide at 0°. Ice was added and the ethereal layer washed with aqueous sodium hydrogen carbonate and dried. The product (15·8 g.) had b. p. 80—82°/0·4 mm. A portion (10 g.) was esterified with *p*-nitrobenzoyl chloride. Crystallisation of the product from methanol–chloroform afforded (−)-trans-3-*bromo*neo*carvomenthol* p-*nitrobenzoate* (7·5 g.) as large pale yellow prisms, m. p. 105°, $[\alpha]_D^{15}$ −35·2° (*c* 1·2) (Found: C, 52·9; H, 6·2; N, 3·6. $C_{17}H_{22}O_4NBr$ requires C, 53·1; H, 5·7; N, 3·6%). Fractionation of the residue from methanol afforded a further quantity of the above ester (1·0 g.) and the *ester* (1·6 g.), m. p. 99°, $[\alpha]_D^{15}$ −52·7° (*c* 1·4), of (−)-*trans*-2-bromo*neo*menthol (Found : C, 53·0; H, 5·6%). The remainder of the bromohydrin mixture (5·8 g.) was acetylated with acetic anhydride and sulphuric acid, and the acid removed with calcium carbonate. Distillation of the filtrate yielded the acetate mixture (5·8 g.), b. p. 134—137°/18 mm., which was added to freshly prepared silver acetate (4·5 g.) in " AnalaR " acetic acid (100 ml.) containing water (0·5 ml.) and heated at 100—115° with stirring for 11 hr. The precipitate was separated and washed with benzene. The combined filtrates were evaporated under reduced pressure and the residue was hydrolysed in the usual way. Isolation with ether yielded the mixture of *cis*-diols (2·75 g.), b. p. 87—88°/0·3 mm., m. p. 60—62°, a part (1·8 g.) of which was esterified and separated as in (*b*), to give the ester of (−)-*cis*-2-hydroxymenthol (2·5 g.) and of (−)-*cis*-2-hydroxy*neo*menthol (0·6 g.).

(−)-cis-2-*Hydroxymenthol*.—Hydrolysis of the di-*p*-nitrobenzoate, m. p. 108°, gave the *diol* which, after vacuum-sublimation, had m. p. 67°, $[\alpha]_D^{15}$ −32·9° (*c* 1·0) (Found : C, 69·8; H, 11·7. $C_{10}H_{20}O_2$ requires C, 69·7; H, 11·6%). The *bisphenylurethane* crystallised from acetone–hexane as needles, m. p. 168°, $[\alpha]_D^{15}$ −113° (*c* 1·4) (Found : N, 6·8. $C_{24}H_{30}O_4N_2$ requires N, 6·8%). The *monotoluene*-p-*sulphonate* was prepared with an excess of the acid chloride in pyridine, yielding prisms, m. p. 80°, $[\alpha]_D^{15}$ −60° (*c* 0·8), from hexane (Found : C, 62·5; H, 8·0; S, 9·9. $C_{17}H_{26}O_4S$ requires C, 62·6; H, 8·0; S, 9·8%).

(−)-cis-2-*Hydroxy*neo*menthol*.—A similar hydrolysis of the di-*p*-nitrobenzoate, m. p. 169° (1·2 g.), gave the *diol* (350 mg.) which after vacuum-sublimation had m. p. 81°, $[\alpha]_D^{15}$ −29·4° (*c* 1·2) (Found : C, 70·1; H, 12·1%). A *mono*-3 : 5-*dinitrobenzoate* crystallised from methanol as needles, m. p. 209°, $[\alpha]_D^{15}$ −46·9° (*c* 0·6) (Found : C, 55·7; H, 6·1; N, 7·8. $C_{17}H_{22}O_7N_2$ requires C, 55·7; H, 6·0; N, 7·7%). The *bisphenylurethane* crystallised from acetone–hexane as needles, m. p. 182·5°, $[\alpha]_D^{15}$ −113° (*c* 1·0) (Found : N, 6·8%). The *monotoluene*-p-*sulphonate* crystallised from hexane as prisms, m. p. 115°, $[\alpha]_D^{15}$ −60·3° (*c* 1·0) (Found : C, 62·8; H, 8·0; S, 9·9%).

Reaction of the Mixed Epoxides with Hydrochloric Acid.—The epoxide mixture (15 g.) was shaken overnight with 10% hydrochloric acid (200 ml.), and the solution continuously extracted with ether. Fractionation gave unchanged epoxide (9·5 g.) and a viscid fraction (5·4 g.), b. p. 82—90°/0·4 mm. Esterification and crystallisation from chloroform–methanol gave the *chlorohydrin* p-*nitrobenzoate* as prisms, m. p. 127°, $[\alpha]_D^{23}$ −21·1° (*c* 2·5) (Found : C, 59·8; H, 7·0; N, 4·1; Cl, 10·4. $C_{17}H_{22}O_4NCl$ requires C, 60·1; H, 6·5; N, 4·1; Cl, 10·5%). The mother-liquors afforded the *p*-nitrobenzoate (1·0 g.) of (+)-*trans*-2-hydroxy*neo*menthol. Attempted hydrogenolysis of the chlorohydrin ester (platinum at 80°/400 lb. per sq. in.) afforded the p-*aminobenzoyloxy-compound* as needles, m. p. 93·5°, $[\alpha]_D^{15}$ −34° (*c* 1·3) (Found : C, 65·7; H, 7·9; N, 4·5; Cl, 12·0. $C_{17}H_{24}O_2NCl$ requires C, 65·7; H, 7·8; N, 4·5; Cl, 11·4%), from hexane. This ester produced the chlorohydrin, isolated as the *p*-nitrobenzoate, on treatment with excess of lithium aluminium hydride in boiling ether during 8 hr.

Reactions of (−)-trans-2-*Bromo*neo*menthol and* (−)-trans-3-*Bromo*neo*carvomenthol*.—(*a*) The *p*-nitrobenzoate, m. p. 99° (1·7 g.), in ether (50 ml.) was added to a stirred suspension of lithium aluminium hydride (0·8 g.) in ether (150 ml.), and the mixture was boiled for 4 hr. After decomposition with dilute sulphuric acid the ether layer was separated and dried. Evaporation gave a residue which was washed with light petroleum (b. p. <40°) and the insoluble azobenzyl alcohol separated. The petroleum residue on esterification gave (−)-*neo*menthyl 3 : 5-dinitrobenzoate, m. p. 153°. Similar reduction of the bromohydrin *p*-nitrobenzoate, m. p. 105°, and esterification of portion of the product gave (+)-neo*carvomenthyl* 3 : 5-*dinitrobenzoate*, m. p. 128·5°, $[\alpha]_D^{15}$ +23° (*c* 1·6) (Found : C, 58·0; H, 6·4; N, 8·0. $C_{17}H_{22}O_6N_2$ requires C, 58·3; H, 6·4; N, 8·0%), as needles from methanol. The remainder of the product after crystallisation from light petroleum afforded the p-*nitrobenzoate* as prisms, m. p. 95°, $[\alpha]_D^{15}$ +24° (*c* 1·3) (Found : C, 67·0; H, 7·7; N, 4·6. $C_{17}H_{23}O_4N$ requires C, 66·9; H, 7·5; N, 4·6%).

(*b*) The *p*-nitrobenzoate (2·5 g.), m. p. 99°, of (−)-*trans*-2-bromo*neo*menthol with potassium hydroxide (10 g.) in methanol (30 ml.) was distilled in steam. After isolation with ether the epoxide was shaken with 5% aqueous perchloric acid (15 ml.) for 3 hr. Extraction with ether and esterification gave (+)-*trans*-2-hydroxy*neo*menthol di-*p*-nitrobenzoate, m. p. and mixed m. p. 173° after crystallisation from ethanol.

(−)-*trans*-3-Bromo*neo*carvomenthyl *p*-nitrobenzoate (17·5 g.), m. p. 105°, was converted into the *epoxide* in the same way. The pure product (2·5 g.) had b. p. 82°/17 mm., n_D^{15} 1·4538, $[\alpha]_D^{15}$ +49·3° (*c* 0·8) (Found : C, 77·9; H, 11·8. $C_{10}H_{18}O$ requires C, 77·9; H, 11·7%). Hydration with aqueous perchloric acid as above and esterification afforded the same ester, m. p. 173°.

(*c*) The epoxide (0·35 g.), derived from the bromohydrin *p*-nitrobenzoate of m. p. 99°, in ether was saturated with hydrogen bromide at 0°. Isolation in the usual way gave the bromohydrin which was acetylated with acetic anhydride and sulphuric acid. The bromide acetate was treated with silver acetate in moist acetic acid as described for the reaction with the mixture of bromohydrins. Hydrolysis of the acetate gave (−)-*cis*-2-hydroxy*neo*menthol, m. p. 79·5° alone or mixed with a sample derived previously. Preparation of the monotoluene-*p*-sulphonate confirmed the identity.

This reaction sequence was also applied to the epoxide derived from the bromohydrin *p*-nitrobenzoate, m. p. 105°. The *bromohydrin* on distillation had m. p. 30°, $[\alpha]_D^{15}$ +34·8° (*c* 1·5) (Found : C, 51·5; H, 8·1; Br, 33·8. $C_{10}H_{19}OBr$ requires C, 51·1; H, 8·1; Br, 34·0%). The derived acetate (2·9 g.) was a liquid, b. p. 72°/0·1 mm. It was treated similarly with silver acetate in moist acetic acid and after hydrolysis, isolation, and sublimation at 50°/0·5 mm. yielded (−)-*cis*-2-hydroxymenthol (1·4 g.), m. p. 65—66° alone or mixed with material obtained previously.

Periodate Oxidations.—Solutions of glycol (0·01M) and potassium periodate (0·006M) were made up in buffer, pH 10·5, prepared by addition of 0·1N-hydrochloric acid (100 ml.) to sodium carbonate (5·301 g.) in water (500 ml.) and dilution to 1 l. Equal volumes of diol and periodate were mixed and kept at 25° and the reaction followed by quenching aliquot parts (5 ml.) in borate buffer, pH 7·8 (15 ml.). The iodine was estimated with 0·005N-sodium arsenite. Rate constants were calculated by the usual method and were reproducible within 5%.

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