

frared silica cells of path length 1.00 cm. at *ca.* 25°. The frequencies were calibrated by recording atmospheric water vapor absorption with each spectrum. The accuracy of the frequencies reported is believed to be ± 2 cm.⁻¹ near 3620 and ± 4 cm.⁻¹ near 3500 cm.⁻¹. The absorbance reported is a measure of the peak intensity. Data recorded for 0.0040 *M* solutions of the diols in

dried Spectranalyzed carbon tetrachloride are presented in Table I. A small contribution to absorption at 3490 ± 10 cm.⁻¹, attributable to intermolecular hydrogen bonding, is observed in the 0.0040 *M* solutions. This factor, which appears to cancel out when the absorbance ratio is computed, has been neglected in Table I.

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Conformational Studies. VII.¹ *p*-Menthane-2,5-diols and the Relative "Size" of the Isopropyl Group²

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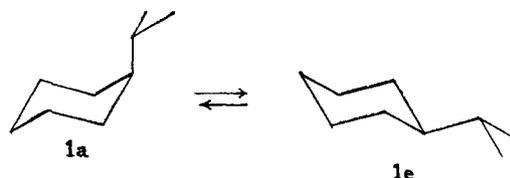
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Unique among the racemic *p*-menthane-*cis*-2,5-diols (4, 8, 9, and 10) is (\pm)-*cis,cis,cis*-*p*-menthane-2,5-diol (4), m.p. 105°, which exhibits significant intramolecular hydrogen bonding. The configurations assigned diols 4, 8, 9, and 10 are discussed, as well as their infrared spectra and their behavior upon gas chromatography. Comparative observations of conformational equilibria of *cis,cis,cis*-2,5-dialkyl-1,4-cyclohexanediols (3-7) suggest that an isopropyl group may have an apparent relative "size" ranging between that of a methyl and a *t*-butyl group, the "size" depending upon the details of the system and the specific observation made upon it.

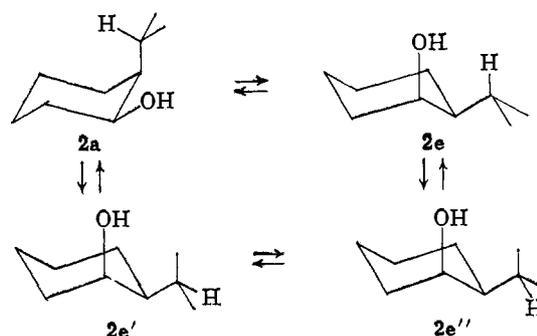
The isopropyl group, when a substituent on a cyclohexane ring, appears almost as "big" as a *t*-butyl group in certain experiments and nearly the same "size" as a methyl group in others.³ A further opportunity to consider the relative "sizes" of the methyl and the isopropyl groups is afforded by the results of a study of the conformational equilibria of (\pm)-*cis,cis,cis*-*p*-menthane-2,5-diol and related compounds.¹ While the actual size of the isopropyl group is obviously constant, its effect upon conformational equilibria depends in part upon its immediate environment, which is far from constant over the range of systems under consideration.^{1,3}

It seems clear that at 25°, the equatorial conformation of isopropylcyclohexane is more stable than the axial conformation by about 2.1 kcal./mole.³⁻⁷ The corresponding value for methylcyclohexane is about 1.7 kcal./mole³⁻⁶; for *t*-butylcyclohexane, >5.5 kcal./mole. The isopropyl group gives nearly the same value as the methyl group.³⁻⁶ In derivatives of isopropylcyclohexane which have the same environment in the immediate vicinity of the isopropyl group as isopropylcyclohexane itself, the isopropyl group would still be expected to appear nearly the same "size" as a methyl group. In derivatives of isopropylcyclohexane which have substituents close enough to produce repulsive interactions with either or both of the isopropyl's methyl groups, these interactions would affect the conformational equilibria. In such an environment the isopropyl group would not necessarily appear nearly the same "size" as a methyl group, as illustrated below.

In isopropylcyclohexane (1) the axial isopropyl group exists predominantly in a single rotational conformation, 1a.³ One of its two methyl groups would be sub-



jected to a substantial repulsive interaction by a *cis* (equatorial) substituent on an adjacent carbon atom. For example, consider *cis*-2-isopropylcyclohexanol (2). One would expect the repulsive interaction between the methyl and hydroxyl groups in 2a to be about the same as the direct interaction between an axial methyl group and an axial hydroxyl group in *cis*-3-methylcyclohexanol, since the distance separating the methyl and the hydroxyl groups is about the same in each case.⁸ On the other hand, in 2e, as distinguished from its



rotational conformers 2e' and 2e'', there is an hydrogen-hydroxyl type repulsive interaction, rather than the stronger methyl-hydroxyl type interaction. Since the repulsive interaction between substituents is greater in 2a than in 2e, the interaction tends to shift the conformational equilibrium toward 2e, thus enhancing the apparent "size" of the isopropyl group. By applying to 2 the method of calculation reported for 1 by Allinger and Hu,⁹ one may calculate $-\Delta G^\circ = 2.2$ kcal./mole, for

(1) Paper VI: R. D. Stolor, P. M. McDonagh, and M. M. Bonaventura, *J. Am. Chem. Soc.*, **86**, 2185 (1964).

(2) Presented, in part, at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963. Support of this work by the National Science Foundation is gratefully acknowledged.

(3) N. L. Allinger, L. A. Freiberg, and S.-E. Hu, *J. Am. Chem. Soc.*, **84**, 2836 (1962).

(4) A. H. Lewin and S. Winstein, *ibid.*, **84**, 2464 (1962).

(5) E. L. Eliel and T. J. Brett, Abstracts, 145th National Meeting of the American Chemical Society, New York, N. Y., 1963, p. 19Q.

(6) This value was suggested as an average of the best available experimental values by Prof. E. L. Eliel, during his oral presentation of ref. 5. All values are for 298°K.

(7) It is important to note that the value of 3.3 (or >3.3) referred to in ref. 3 (and ref. 4a and 5 therein) has been retracted in ref. 4.

(8) E. L. Eliel and H. Haubenstock, *J. Org. Chem.*, **26**, 3504 (1961). Some consideration was given this type of interaction by S. Yamana, *Bull. Chem. Soc. Japan*, **34**, 1414 (1961).

(9) N. L. Allinger and S.-E. Hu, *J. Org. Chem.*, **27**, 3417 (1962).

$2a \rightleftharpoons 2e + 2e' + 2e''$.¹⁰ For *cis*-4-isopropylcyclohexanol, the corresponding calculated value is $-\Delta G^\circ = 1.3$ kcal./mole. Therefore, the calculations suggest that the hydroxyl group on the adjacent carbon atom of *cis*-2-isopropylcyclohexanol makes the isopropyl group appear larger than the "normal" 2.1 kcal./mole isopropyl group of 4-isopropylcyclohexanol by the difference of the $-\Delta G^\circ$ values estimated above, $2.2 - 1.3 = 0.9$ kcal./mole. For comparison, the corresponding difference calculated for *cis*-4-methyl- vs. *cis*-2-methylcyclohexanol is zero. Because both chair conformations of *cis*-2-methylcyclohexanol would have approximately the same methyl-hydroxyl skewed interaction, the direct interaction of the two groups cancels out, and the apparent "size" of the methyl group is "normal."

An obvious conclusion at this point is that *cis*-2-isopropylcyclohexanol derivatives (and analogous examples) would not be expected to provide suitable data for a valid direct measurement of the "size" (i.e., $-\Delta G^\circ$) of the isopropyl group in isopropylcyclohexane. Support for this conclusion is found in several of the reported cases of "big" isopropyl groups,¹¹ cases which indeed turn out to be *cis*-2-isopropylcyclohexanol derivatives. Further support for this conclusion is derived from the results reported below of a study of *cis,cis,cis-p*-menthane-2,5-diol (4) and *cis,cis,cis*-2,5-diisopropyl-1,4-cyclohexanediol (6), both of which are also derivatives of *cis*-2-isopropylcyclohexanol (2).

Results and Discussion

In the preceding paper, the infrared spectra of a series of *cis,cis,cis*-2,5-dialkyl-1,4-cyclohexanediols were interpreted in terms of the nonchair populations of the diols.¹ It was postulated that one would expect a relationship between the nonchair population and the relative "sizes" of the alkyl substituents. The results are listed in Table I.

TABLE I
NONCHAIR POPULATIONS OF *cis,cis,cis*-2-R-5-R'-1,4-CYCLOHEXANEDIOLS^a

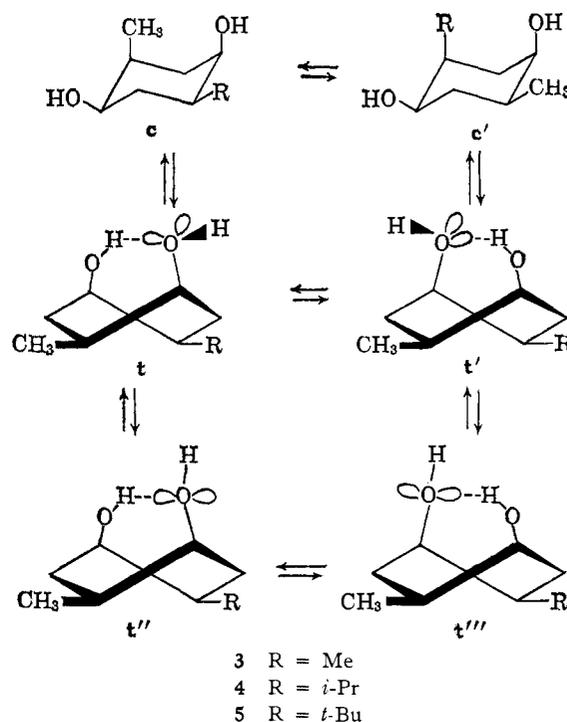
Diol	R	R'	Nonchair, %	Chair \rightleftharpoons Nonchair ΔG	Nonchair $\Delta \Delta G$
3	Me	Me	5	1.8	0.7
4	Me	<i>i</i> -Pr	13	1.1	
5	Me	<i>t</i> -Bu	14	1.1	
6	<i>i</i> -Pr	<i>i</i> -Pr	80	-0.8	1.9
7	<i>t</i> -Bu	<i>t</i> -Bu	>98	...	

^a See ref. 1. The values given are approximate values for dilute solutions of the diols in carbon tetrachloride at 25°.

First, compare the population data for diols 3-5 given in Table I. *cis,cis,cis*-2,5-Dimethyl-1,4-cyclohexanediol (3) is reported as having a nonchair population of ca. 5%, and *cis,cis,cis*-2-*t*-butyl-5-methyl-1,4-cyclohexanediol (5), a nonchair population of ca. 14%. Thus the replacement of a methyl group of diol 3 by the much larger *t*-butyl group (to give diol 5) causes the chair \rightleftharpoons nonchair equilibrium to be shifted significantly toward the right. The nonchair population of ca. 13% reported for *cis,cis,cis-p*-menthane-2,5-diol (4) suggests that the isopropyl group produces nearly the same re-

(10) The calculated value depends upon the parameters chosen.^{8,9} When the values for 1:3 diaxial interactions are (in kcal./mole) CH₃:OH 2.4, CH₃:H 0.95, H:OH 0.4, the calculated values at 298° are: $\Delta S^\circ +0.56$ e.u., $-\Delta H^\circ 2.02$ kcal./mole, $-\Delta G^\circ 2.19$ kcal./mole.

(11) Reference 3, footnotes 6 and 8 therein. Other secondary alkyl groups, such as the cyclohexyl group, would be expected to give analogous results. For example, see E. Galántay, *Tetrahedron*, **19**, 319 (1963).



sponse upon the chair \rightleftharpoons nonchair equilibrium as does the *t*-butyl group ($\Delta \Delta G = 0.7$ kcal./mole, Table I). Therefore, the isopropyl group of diol 4 appears to be almost as "big" as a *t*-butyl group.

Next, compare diol 4 (methyl, isopropyl) with diol 6 (diisopropyl). Upon replacement of the methyl group of diol 4 by an isopropyl group to give *cis,cis,cis*-2,5-diisopropyl-1,4-cyclohexanediol (6), the nonchair population is greatly increased, from ca. 13% for 4 to ca. 80% for 6, ($\Delta \Delta G = 1.9$ kcal./mole). Yet note that upon similar replacement of the methyl group of diol 5 (methyl, *t*-butyl) by a *t*-butyl group to give diol 7 (di-*t*-butyl), the increase in the nonchair population is much greater, from ca. 14% for 5 to >98% for 7. Therefore, the isopropyl groups of diol 6 appear to be much "larger" than methyl groups, but not as "big" as *t*-butyl groups. The same conclusion may be reached by direct comparison of the population data (Table I) for diols 3 (dimethyl) and 6 (diisopropyl), $\Delta \Delta G = 2.6$ kcal./mole. Furthermore, one of the isopropyl groups of diol 6 appears to be much "bigger" than the other ($\Delta \Delta G = 0.7$ vs. 1.9 kcal./mole). Thus, while the actual size of the isopropyl group is obviously constant, its apparent "size," that is, its effect upon conformational equilibria, can range from methyl-like to *t*-butyl-like, depending upon its immediate environment.

There is more to consider in the interpretation of the results presented above than was involved in the introductory analysis of *cis*-2-isopropylcyclohexanol. For diol 3 (or 6), the two chair conformations are equivalent. For diol 5, conformation 5c', which has an axial *t*-butyl group, would be expected to be much less stable than conformation 5c, in which the *t*-butyl group is equatorial. Therefore, for different reasons, both diols 3 and 5 may be considered to exist in a single chair conformation. As for the nonchair conformations, each pair that is equivalent for 3 would correspond to a pair of distinctly different conformations for 5 (5t and 5t', 5t'' and 5t''', etc.), the members of which, in those expected to be most populous, would be expected to have

were isolated from the hydrogenation product of (–)-*p*-menth-1-ene-3,6-diol, m.p. 167° (11).¹⁴ Blumann, *et al.*, reported the same reaction and products, along with a proof of the configuration of (+)-8.¹⁵ The configuration assigned to (+)-9, although not proved, is most reasonable for a coproduct of (+)-8 formed in the hydrogenation of (–)-11. By use of this reaction, preparation of (+)-8 and (+)-9 from (–)-11 was repeated successfully.¹⁶

Two additional samples, reported by Schenck,¹⁴ were assigned configurations (+)-10 and (+)-4: (A), m.p. 148°, $\alpha_D^{20} + 20^\circ$; and (B) m.p. 103°, $\alpha_D^{20} + 24^\circ$, although which was which remained in question. With the kind cooperation of Prof. Schenck, his former student, Dr. S. Schroeter, and Dr. Blumann, it has been possible to examine both of these samples in direct comparison with (±)-4, m.p. 105°. By gas chromatography, it was found that neither A nor B contained much of diol 4. Sample A, m.p. 148°, appeared to contain ca. 98% of a single component, clearly different from 4 and 8 upon gas chromatography. In addition, ca. 2% of diol 8 appeared to be present as an impurity in A. Sample B, m.p. 103°, is definitely not a pure compound; it should be withdrawn from further consideration as such. The gas chromatogram of B showed three significant peaks with relative heights 5:1:8, and relative areas 8:1:12. By use of synthetic mixtures, it was shown that the gas chromatogram was consistent with interpretation in terms of a mixture of (+)-8 and A (major peaks amounting to >90%) with <10% of 4 (minor peak). Detailed infrared analysis, as well as the optical rotation, was reasonably consistent with the above interpretation of the composition of B, m.p. 103°. Although the data in Table II for A would be reasonable for structure 10, the optical rotation of A, $\alpha_D + 20^\circ$, stands far outside the expected limit of error of the predicted rotation for 10, α_D ca. -40° (absolute configuration as illustrated above).¹⁷ Therefore, tentative assignment of configuration 10 to sample A was questioned.

Consideration of these facts lead us to attempt repetition of the work reported by Schenck¹⁴ on the prep-

aration of diols 4 and 10. We have isolated (+)-*cis,cis,cis-p*-menthane-2,5-diol ((+)-4), m.p. 132°, $\alpha_D^{20} + 23^\circ$ (ethanol), which gives an infrared spectrum and a retention time in gas chromatography identical with that of (±)-4, m.p. 105° (Table II).¹⁸ Along with (+)-4, a second diol was isolated, m.p. 157°, $[\alpha]_D^{27} - 42^\circ$ (ethanol), to which we have assigned structure (–)-10 (Table II).¹⁸ Further studies are in progress.¹⁹

Experimental

(+)-*trans,trans,trans-p*-Menthane-2,5-diol ((+)-8).—(–)-*p*-Menth-1-ene-3,6-diol (11), m.p. 168–169°, was hydrogenated by the procedure of Blumann, *et al.*^{15,16} To 1.93 g. (0.0114 mole) of 11 in 100 ml. of 95% ethanol was added 1.9 g. of neutral Raney nickel catalyst (moist with ethanol). At 30° and ca. 3 atm. hydrogen pressure, completion of the reaction required 12 hr. with a Parr apparatus (Model 3911). Isolation of the product and recrystallization from acetone gave diol (+)-8, m.p. 136–138°.

(+)-*p*-Menthane-2,5-diol, "M.p. 176°" ((+)-9).—Fractional recrystallization of the above acetone filtrates gave diol (+)-9, m.p. 175–176°, in poor yield.¹⁶

Comparison of *p*-Menthane-2,5-diols 4, 8, 9, and A, by Gas Chromatography (with Arthur E. Clements).—The diols were analyzed by use of a flame ionization detector and column S, a 240 cm., 0.188 in. o.d. copper column packed with 4.0% sucrose diacetate hexaisobutyrate (Eastman) plus 0.10% polyethylene glycol 1500 (Matheson Coleman and Bell, 9135) on 100–120 mesh Gas Chrom P (Applied Science Laboratories). When the column was operated at 150° with a nitrogen carrier gas flow rate of 27 ml./min., the diols gave the retention times recorded in Table II. Under the same conditions, *p*-menth-1-ene-3,6-diol (11) gave retention time 33 min. Better resolution of diol 11 was achieved by use of a 90 cm., 0.188 in. o.d. copper column packed with 4% Versamid 900 (General Mills) on 100–120 mesh Gas Chrom P at 119°. While the Versamid column gave retention time 46 min. for diol 11, and 39 min. for diol 8, it failed to resolve diols 4, 9, and A from one another under these conditions (retention time 30 min.). Both columns were used in the analyses of two samples obtained from Prof. G. O. Schenck. The results obtained with column S are discussed above in the section titled: "*p*-Menthane-2,5-diols." Sample B, m.p. 103°, which itself gave three peaks, was analyzed by adding each individual diol, in turn, to the sample, and observing enhancement of one of the original peaks. Finally, the individual diols were used to prepare a 6:3:1 mixture of diols (+)-8, A, and (±)-4, respectively. The gas chromatogram of the synthetic mixture, similar to that of B, showed conclusively by direct comparison that B contained <10% of diol 4.

Infrared Spectra of *p*-Menthane-2,5-diols 4, 8, 9, and 10.—Infrared spectra were recorded as previously reported,¹ by use of 0.0040 *M* solutions of the diols in dried Spectranalyzed carbon tetrachloride in 1.00-cm. cells at ca. 25°. The data are presented in Table II.

(18) R. D. Stolow, K. Sachdev, and A. Clements, unpublished work.

(19) NOTE ADDED IN PROOF.—It is now clear that, like B, sample A is also a mixture of at least three components, as shown by thin layer chromatography on alumina by K. Sachdev.

(15) A. Blumann, E. W. Della, C. A. Henrick, J. Hodgkin, and P. R. Jefferies, *Australian J. Chem.*, **15**, 290 (1962).

(16) The author is indebted to Dr. A. Blumann for his kind gift of a sample of (–)-11, isolated from *Eucalyptus dives* oil.¹⁵

(17) The calculated optical rotation of structure 10 follows from the work of J. H. Brewster, *J. Am. Chem. Soc.*, **81**, 5483 (1959), and references cited. The molecular rotation of 10 was calculated as the sum of the observed molecular rotations of (–)-neomenthol and (–)-carvomenthol.