Proton Magnetic Resonance and Stereochemistry of 1-(2-Hydroxyethyl)-2-*o*-tolylcyclohexanols and Related Compounds[1]

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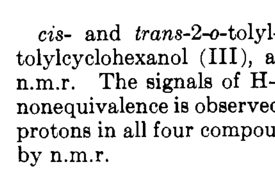
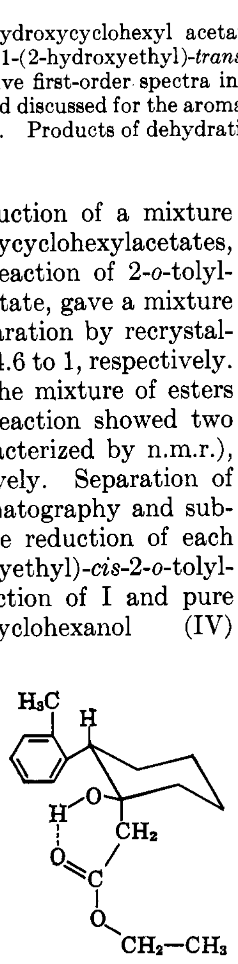
cis- and *trans*-2-*o*-tolyl-1-hydroxycyclohexyl acetate (I and II, respectively), 1-(2-hydroxyethyl)-*cis*-2-*o*-tolylcyclohexanol (III), and 1-(2-hydroxyethyl)-*trans*-2-*o*-tolylcyclohexanol (IV) have been characterized by n.m.r. The signals of H-2 give first-order spectra in compounds I and III but not in II and IV. Magnetic nonequivalence is observed and discussed for the aromatic protons in I and III and for certain geminal methylene protons in all four compounds. Products of dehydration of III and IV by zinc chloride have been characterized by n.m.r.

Lithium aluminum hydride reduction of a mixture of isomeric ethyl 2-*o*-tolyl-1-hydroxycyclohexylacetates, obtained from the Reformatskiĭ reaction of 2-*o*-tolylcyclohexanone and ethyl bromoacetate, gave a mixture of solid materials which upon separation by recrystallization gave III and IV in ratio of 4.6 to 1, respectively. Gas chromatography analysis of the mixture of esters obtained from the Reformatskiĭ reaction showed two main components, I and II (characterized by n.m.r.), in the ratio of 4.8 to 1, respectively. Separation of the two components by gas chromatography and subsequent lithium aluminum hydride reduction of each component gave pure 1-(2-hydroxyethyl)-*cis*-2-*o*-tolylcyclohexanol (III) from the reduction of I and pure 1-(2-hydroxyethyl)-*trans*-2-*o*-tolylcyclohexanol (IV) from the reduction of II.



I



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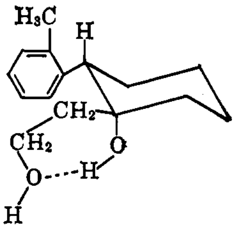
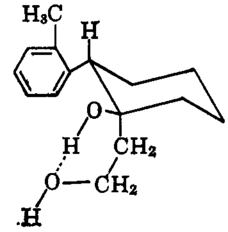
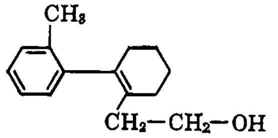


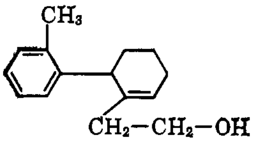
III



IV



V



VI

Dehydration of either III or IV by the method of Ikeda and Takeda,[3] by heating in toluene with zinc chloride, gave V and VI as the main products but in different ratios: III gave V and VI in ratio of 1.22 to 1, respectively, and IV gave V and VI in ratio of 3 to 1, respectively. Further study is in progress on the dehydration of III and IV. Compounds V and VI were separated by gas chromatography and characterized by n.m.r.

The usefulness of n.m.r. in configurational and conformational analysis of six-membered ring compounds has been well demonstrated.[4] The method has proved especially useful in the assignment of configuration and conformation of 1,2-disubstituted six-membered ring compounds in which the signals of the hydrogens on C-1 and C-2 are isolated from those of other ring hydrogens due to the paramagnetic shifts brought about by the substituents and where at least one of the two possible isomers gives a first-order spectrum.[4e,f,h] The method also has been shown to be applicable to certain 1,1,2-trisubstituted six-membered ring compounds. For example, 1-ethyl-*cis*-2-*o*-tolylcyclohexanol gives a first-order quartet for the signal of the hydrogen on C-2 which establishes the conformation of the cyclohexane ring as the chair form with the tolyl and ethyl groups in equatorial orientation when measured in carbon tetrachloride, while the signal of the hydrogen on C-2 of 1-ethyl-*trans*-2-*o*-tolylcyclohexanol gives a broad unresolved multiplet.[4i] In the *trans* isomer the *o*-tolyl group and the ethyl group are *cis* to each other. The broad multiplet for H-2 could arise from a rapid conformational interconversion of the cyclohexane ring, but this is not the only possible explanation. A first-order spectrum would not be expected for H-2, even if the molecule existed in a preferred conformation with the *o*-tolyl group equatorial, if the difference of chemical shifts between the two hydrogens on C-3 were close to the coupling constant between these two hydrogens.[5] The spectrum of H-2 also can be complicated

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[2] Fellow of the American Foundation for Pharmaceutical Education, 1962–1963. Recipient of the Lunsford Richardson Pharmacy Award for a paper based on the material presented in this publication.

[3] T. Ikeda and S. Takeda, *J. Chem. Soc. Japan*, **57**, 442 (1936).

[4] (a) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc. New York, N. Y., 1959, pp. 387–389; (b) R. M. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Am. Chem. Soc.*, **80**, 6098 (1958); (c) G. E. McCasland, S. Furuta, L. F. Johnson, and J. N. Shoolery, *ibid.*, **83**, 2335 (1961); (d) J. N. Shoolery, L. F. Johnson, S. Furuta, and G. E. McCasland, *ibid.*, **83**, 4243 (1961); (e) A. C. Huitric and J. B. Carr, *J. Org. Chem.*, **26**, 2648 (1961); (f) A. C. Huitric, W. G. Clafke, Jr., K. Leigh, and D. C. Staiff, *ibid.*, **27**, 715 (1962); (g) A. C. Huitric and W. F. Trager *ibid*, **27**, 1926 (1962); (h) W. F. Trager, F. F. Vincenzi, and A. C. Huitric, *ibid.*, **27**, 3006 (1962); (i) A. C. Huitric, W. S. Stavropoulos, and B. J. Nist, *ibid.*, **28**, 1539 (1963).

[5] R. J. Abraham and H. J. Bernstein, *Can. J. Chem.*, **39**, 216 (1961).

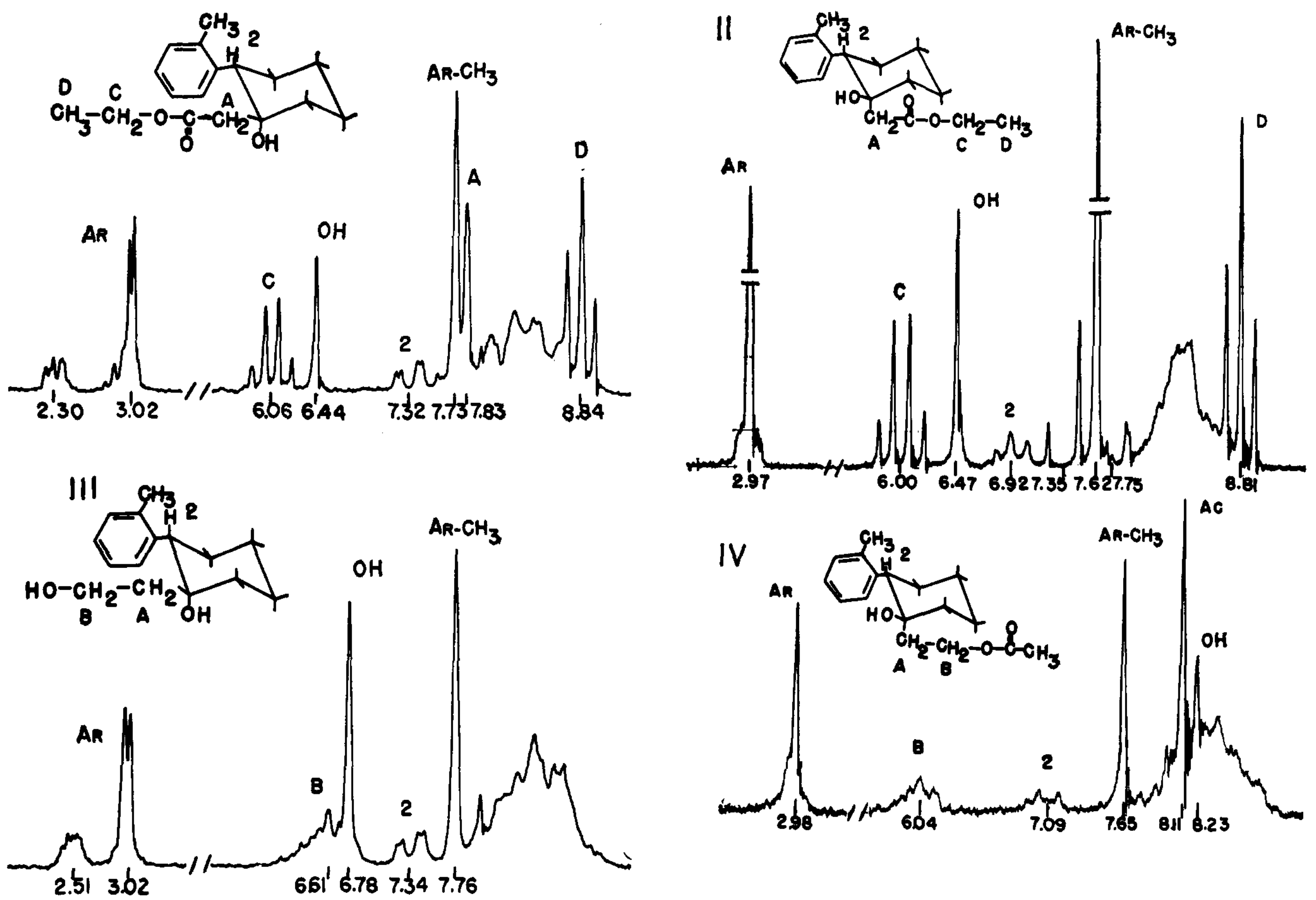

Fig. 1.—N.m.r. spectra of ethyl *cis*-2-*o*-tolyl-1-hydroxycyclohexylacetate (I), ethyl *trans*-2-*o*-tolyl-1-hydroxycyclohexylacetate (II), 1-(2-hydroxyethyl)-*cis*-2-*o*-tolylcyclohexanol (III), and 1-(2-acetoxyethyl)-*trans*-2-*o*-tolylcyclohexanol (IV); 60 Mc.; about 1 *M* in carbon tetrachloride at 23°.

by virtual long-range coupling[6] from the axial hydrogen on C-4 if the difference between the chemical shift of this hydrogen and that of the axial hydrogen on C-3 approaches the coupling constant between them. In the *cis* isomer the axial hydroxyl group causes a deshielding of the axial hydrogen on C-3 and this probably contributes to the observed first-order spectrum of the hydrogen on C-2. The actual cause of the complicated spectrum of H-2 of the *trans* isomer is being investigated in this laboratory through selectively deuterated compounds. The important thing for the present investigation is the establishment that in 1-alkyl-2-*o*-tolylcyclohexanols the isomer with the tolyl group and the hydroxyl group *cis* to each other gives a first-order spectrum for the hydrogen on C-2 while the other isomer does not.[4i]

The n.m.r. spectra I and II, Fig. 1, are those of the two isomeric ethyl 2-*o*-tolyl-1-hydroxycyclohexylacetates. Spectrum III is that of the diol obtained from lithium aluminum hydride reduction of the ester which gives spectrum I, and spectrum IV is that of the monoacetate of the diol obtained from the reduction of the ester giving spectrum II. There is a striking difference in the signal of H-2 in spectra I and III compared with spectra II and IV. The typical first-order quartets[4i] of H-2 at 7.32 in spectrum I and 7.34 τ in spectrum III arise from spin–spin coupling of H-2 with the two hydrogens on C-3, axial–axial splitting of 12 c.p.s., and axial–equatorial splitting of 2.5 to 2.8 c.p.s. Structures I and III are consistent with the observed quartets for H-2, and these quartets are consistent with the spectrum of H-2 in 1-ethyl-*cis*-2-*o*-tolylcyclohexanol, the structure of which was established unequivocally.[4i] In contrast to spectra I and III, the signal of H-2 at 6.92 in spectrum II and 7.09 τ in spectrum IV do not give first-order spectra. Spectrum IV gives a broad unresolved multiplet for the signal of H-2. This could arise either from virtual long-range coupling with hydrogens on C-4 or from conformational changes. Spectrum II gives a fairly symmetrical triplet with a spacing of 16.2 c.p.s. between the two outer components. This suggests an ABX system where X and A are strongly coupled but the coupling between X and B is very small, and A and B are strongly coupled but the chemical shift between A and B is less than 2 J_{AB}.[5] Structure II would satisfy these conditions. The fact that spectra II and IV do not give a first-order spectra for H-2 is consistent with what was observed in the n.m.r. spectrum of 1-ethyl-*trans*-2-*o*-tolylcyclohexanol, the structure of which was established unequivocally.[4i] Structure I for the ester giving spectrum I and structure III for the diol giving spectrum III are further substantiated from the downfield shift of the signal of one of the aromatic hydrogens. The same phenomenon was observed in the spectrum of 1-ethyl-*cis*-2-o-tolylcyclohexanol, where the hydroxyl group is axial, but it was absent in the spectrum of the *trans* isomer.[4i] The equatorial substituent on C-1 restricts rotation of the *o*-tolyl group. The magnetic nonequivalence of the

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(6) J. I. Musher and E. J. Corey, *Tetrahedron*, **18**, 791 (1962).

aromatic hydrogens results from a preferred conformation of the aromatic ring causing the ortho-hydrogen to be in close proximity to the axial hydroxyl group.

Another interesting example of magnetic nonequivalence resulting from conformational preference is observed for the methylene hydrogens A of structure I and II (spectra I and II), and the methylene hydrogens B of structures III and IV (spectra III and IV). In each of the four structures a preferred conformation can result from intramolecular hydrogen bonding. The magnetic anisotropy of the asymmetric center, of the aromatic ring, and of the carbonyl group of the ester function can all contribute to the magnetic nonequivalence. In the ester series this nonequivalence is especially pronounced in structure II, where the signal of one of the methylene hydrogens adjacent to the carbonyl carbon gives a doublet at 7.35 τ. One component of the doublet of the other hydrogen, 7.75 τ, is overlapped by the signal of the aromatic methyl group. Integration is consistent with this interpretation. The difference in chemical shift between the two methylene hydrogens A of structure II is 24 c.p.s. and the coupling constant between them is 15.2 c.p.s. The nonequivalence is not nearly so pronounced for structure I, but with high resolution signal A gives a doublet. In spectrum II the shoulder to the right of the hydroxyl group signal has been shown to be due to impurities. The nonequivalence of methylene hydrogens B in structures III and IV is shown by the unresolved multiplet of each signal which results from coupling with the adjacent methylene hydrogens A. If the two hydrogens of methylene group B were magnetically equivalent and freedom of rotation existed, the resulting signal should be a triplet from coupling with the two hydrogens on methylene group A.

Spectrum V, Fig. 2, is the n.m.r. spectrum of the component obtained in largest amount from the dehydration of either III or IV. The spectrum establishes structure V by the absence of olefinic hydrogens and the absence of a hydrogen on C-2. The conjugated double bond also is indicated from the ultraviolet spectrum which shows absorption in the 240-mμ region analogous to that of 1-*o*-tolylcyclohexene. Spectrum VI, Fig. 2, is the n.m.r. spectrum of the other main component of the dehydration of either III or IV. The signal of 4.24 τ establishes the presence of one olefinic hydrogen. The triplet given by the methylene hydrogens B results from spin–spin splitting by the methylene hydrogens A, and establishes that the double bond is endocyclic. If the double bond were exocyclic, signal B would be a doublet. Integration shows that signal B represents three hydrogens. The signal of the hydrogen on C-3, the carbon to which the tolyl group is bonded, is overlapped by signal B. The ultraviolet spectrum shows the absence of strong absorption in the region of 240 mμ.

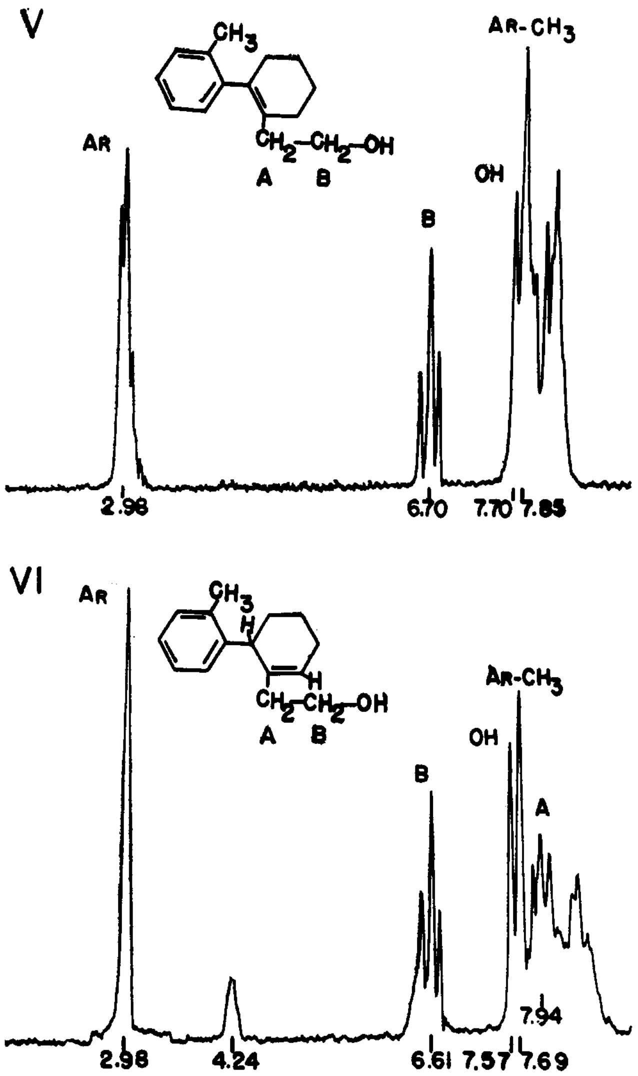

Fig. 2.—N.m.r. spectra of 1-(2-hydroxyethyl)-2-*o*-tolylcyclohexene (V) and 2-(2-hydroxyethyl)-3-*o*-tolylcyclohexene (VI); 60 Mc.; About 1 *M* in carbon tetrachloride at 23°.

Experimental

Ethyl 2-*o*-Tolyl-1-hydroxycyclohexylacetate.—The method used for the preparation of this compound is essentially that described in "Organic Reactions" for preparation of ethyl 1-hydroxycyclohexylacetate.[7] A mixture of 2-*o*-tolylcyclohexanone (30.0 g., 0.17 mole), ethyl bromoacetate (26.1 g., 0.17 mole), 70 ml. of anhydrous benzene, and 60 ml. of anhydrous toluene was prepared. To one-third of this mixture was added 10.4 g. (0.17 g.-atom) of zinc foil which was scarred with sandpaper and cut in strips, and the mixture heated to reflux. After the initial vigorous reaction had subsided, the remaining mixture was added dropwise with heating to maintain gentle reflux. After completion of addition the mixture was refluxed an additional 2 hr. After cooling the mixture was hydrolyzed by pouring into 600 ml. of ice-cold 10% ammonium chloride solution. The mixture was then extracted with ether and the solid zinc hydroxide filtered and washed with ether. The ether extracts were washed with water and dried over anhydrous calcium sulfate. The solvents were then removed with a rotary film evaporator. The product was distilled under reduced pressure and three fractions were collected. Fraction 1, 5 g., b.p. 114–124° (0.7 mm.), was mostly unchanged ketone. Fraction 2, 3.5 g., b.p. 124–130°, also was collected. The third and main fraction, 25 g., b.p. 130–140°, was a colorless, viscous liquid.

Analysis of the main boiling fraction by gas chromatography showed two main components, 1 and 2, in ratio of 4.9 to 1, respectively, plus a small amount of unchanged ketone. The analysis by gas chromatography was accomplished by using a 5 ft. × 0.25 in. column packed with 18% Dow Silicone QF-1 on acid-washed Chromosorb W at 185°. At 200° or above some dehydration was observed. The infrared spectra of both components showed an OH stretching band at 3500 and a carbonyl stretching band at 1710 cm.$^{-1}$. The infrared spectrum of component 1 gave a band at 990 cm.$^{-1}$ which did not appear in the infrared spectrum of component 2. The infrared spectrum of component 2 gave two bands, one at 910 and the other at 1065

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[7] R. L. Shriner, "Organic Reactions," Coll. Vol. I; John Wiley and Sons, Inc., New York, N. Y., 1944, p. 17.

cm.$^{-1}$, which did not appear in the infrared spectrum of component 1. The n.m.r. spectra of the components showed that component 1 is the isomer in which the *o*-tolyl group and the hydroxyl group are *cis* to each other and component 2 is the isomer in which the *o*-tolyl group and the hydroxyl group are *trans* to each other.

Anal. Calcd. for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: *cis* isomer, C, 73.56; H, 8.81; *trans* isomer, C, 73.84; H, 9.06.

1-(2-Hydroxyethyl)-*cis*-2-*o*-tolylcyclohexanol.—A solution of 1.9 g. (0.007 mole) of ethyl *cis*-2-*o*-tolyl-1-hydroxycyclohexylacetate in 10 ml. of anhydrous ether was added dropwise with stirring to a mixture of 0.28 g. (0.0074 mole) of lithium aluminum hydride in 5 ml. of anhydrous ether at such a rate to cause gentle reflux. Stirring was continued for 30 min. after the addition of the ester. The remaining lithium aluminum hydride was decomposed by very slow addition of ethyl acetate, and 15 ml. of 10% ammonium chloride solution was then added. The ether phase was decanted and the aqueous phase was repeatedly extracted with ether. The ether extractions were combined, washed with water, and dried over anhydrous sodium sulfate. Removal of the solvent with a rotary film evaporator gave 1.1 g. of solid material and a small amount of oily substance. Recrystallization from boiling hexane with enough methanol to clarify the solution gave 1.0 g. (62%) of a white crystalline material, m.p. 83.5–85°. The infrared spectrum using a potassium bromide disk showed a broad, intense OH stretching band at 3250 cm.$^{-1}$. The infrared spectrum in carbon tetrachloride, 0.3 M (0.1-mm. cell path), showed a broad OH stretching band at 3450 with a shoulder at 3660 cm.$^{-1}$. When measured in a 3-mm. pathway cell at 0.01 M, a concentration where intermolecular hydrogen bonding is insignificant, two sharp bands result: one band occurring at 3575, is due to the intramolecular hydrogen bonded OH, and the other band, at 3660 cm.$^{-1}$, is due to the free OH group. The nuclear magnetic resonance spectrum shows that the conformation of the cyclohexane ring is in the chair form with the *o*-tolyl group and the hydroxyethyl group both equatorial.

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.57; H, 9.30.

1-(2-Hydroxyethyl)-*trans*-2-*o*-tolylcyclohexanol.—Lithium aluminum hydride reduction of 0.24 g. (0.009 mole) of ethyl *trans*-2-*o*-tolyl-1-hydroxycyclohexylacetate by the method described for the *cis* isomer yielded 0.16 g. of colorless crystalline product, m.p. 202–203.5°, after recrystallization from benzene.

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.83; H, 9.24.

The compound was found to form polymorphic crystal structures. When the compound was allowed to crystallize very slowly from ethanol, a first crop of crystals was obtained which melted at 222–224°. This substance could be converted to the 202–203.5° melting material by refluxing the solid material in hexane for several hours. The low (m.p. 202–203.5°) and high (m.p. 222–224°) melting substances gave identical infrared spectra from potassium bromide disks. The two samples were shown to be different crystalline structures of the same substance by zone-fusion analysis.[8]

Lithium aluminum hydride reduction of 8.6 g. of the original mixture of ethyl 2-*o*-tolyl-1-hydroxycyclohexylacetate yielded 6 g. of solid material and a small amount of oily material. Fractional recrystallization gave 4.5 g. of a white crystalline solid with m.p. 83.5–85° and 1 g. of a white crystalline solid with m.p. 202–203.5°.

1-(2-Acetoxyethyl)-*trans*-2-*o*-tolylcyclohexanol.—A mixture of 0.25 g. (0.001 mole) of 1-(2-hydroxyethyl)-*trans*-2-*o*-tolylcyclohexanol and 0.45 g. (0.004 mole) of acetic anhydride in 5 ml. of anhydrous pyridine was prepared and allowed to stand at room temperature for 24 hr. with occasional shaking. This solution was then poured into 20 ml. of ice–water and extracted repeatedly with ether. The combined ether extracts were washed successively with cold dilute hydrochloric acid, 10% sodium carbonate solution, and water. The ether solution was dried over anhydrous sodium sulfate and the solvent was removed with a rotary film evaporator. The product was distilled under reduced pressure, b.p. 126–128° (0.23 mm.) to yield a clear, viscous liquid. The infrared spectrum showed an OH stretching band at 3500 and a carbonyl stretching band at 1735 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 74.01; H, 8.66.

The n.m.r. spectrum of 1-(2-acetoxyethyl)-*trans*-2-*o*-tolylcyclohexanol showed that the configuration of this compound was the same as the configuration of ethyl *trans*-2-*o*-tolyl-1-hydroxycyclohexylacetate and hence the same as the configuration of 1-(2-hydroxyethyl)-*trans*-2-*o*-tolylcyclohexanol. The n.m.r. spectrum of 1-(2-hydroxyethyl)-*trans*-2-*o*-tolylcyclohexanol was not determined because of its low solubility in solvents commonly used for n.m.r.

Dehydration of 1-(2-Hydroxyethyl)-*cis*-2-*o*-tolylcyclohexanol.—The method used is essentially that described by Ikeda and Takeda.[3] A mixture of 2.0 g. (0.008 mole) of 1-(2-hydroxyethyl)-*cis*-2-*o*-tolylcyclohexanol (III), 0.4 g. of zinc chloride, and 10 ml. of freshly distilled xylene, in a micro flask equipped with a Dean and Stark water separator tube, was heated in an oil bath at 185–195° for 90 min. Cloudiness occurred in the water separator tube toward the beginning of the refluxing. Twenty milliliters of benzene was added to the cooled mixture and the mixture was washed with distilled water until the washings were free of chloride ions. The mixture was dried over anhydrous calcium sulfate; the solvent removed with a rotary evaporator, and the product distilled under reduced pressure, b.p. 100–104° (0.3 mm.).

Analysis by gas chromatography at 160°, using a 5 ft. × 0.25 in. column packed with 18% Dow Silicone QF-1 on acid-washed Chromosorb W, showed two main components, 1 and 2, in ratio of 1.22 to 1, respectively. Several other components were also present in much smaller amounts but no attempt was made to characterize these. Compounds 1 and 2 were separated by gas chromatography at 160° using a 10 ft. × $^5/_8$ in. column packed with the same packing as for the analysis. The infrared spectra of both components, determined on a film of the pure liquid, have an OH stretching band at 3275 cm.$^{-1}$.

Component 1 was identified as 1-(2-hydroxyethyl)-2-*o*-tolylcyclohexene (V) from the ultraviolet and n.m.r. spectra. The ultraviolet spectrum shows absorption analogous to that of 1-*o*-tolylcyclohexene in the region of 240 mμ, and thus establishes the conjugated double bond. Then n.m.r. spectrum establishes the absence of olefinic hydrogens and the absence of a hydrogen on C-2.

Component 2 was identified as 2-(2-hydroxyethyl)-3-*o*-tolylcyclohexene (VI) from the absence of strong absorption in the region of 240 mμ and from the n.m.r. spectrum. The n.m.r. spectrum establishes the presence of one olefinic hydrogen and establishes that the double bond is endocyclic from the signal of the two hydrogens next to the hydroxyl group, 6.61 τ, which is split into a triplet by the two adjacent methylene hydrogens.

The dehydration of 1-(2-hydroxyethyl)-*trans*-2-*o*-tolylcyclohexanol (IV) by the method described for the *cis* isomer (III) also gave compounds V and VI as the main products but in the ratio of 3 to 1, respectively. Analysis by gas chromatography showed the presence of small amounts of other components, but these were not characterized. The main components were shown to be identical with V and VI, obtained from the dehydration of III, from their infrared, ultraviolet, and n.m.r. spectra.

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[8] We are indebted to Dr. N. Barker of Findlay College, Findlay, Ohio, for the zone-fusion analysis.