was distilled under vacuum. After 1.1 g. of an unidentified forerun (b.p. 31–84° (5.0 mm.)), 2.5 g. (8%) of VI was collected as a colorless liquid, b.p. 87–88° (5.0 mm.). The identity of this material was established by its infrared spectrum, and by the spectrum of its oxalate, m.p. 207° dec.

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[CONTRIBUTION FROM THE COLLEGE OF PHARMACY OF THE UNIVERSITY OF WASHINGTON]

# Proton Magnetic Resonance Spectra and Stereochemistry of 2-*o*-Tolylcyclohexanol[1]

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The reduction of 2-*o*-tolylcyclohexanone has been investigated by three methods and the reduction mixture analyzed by gas chromatography. Cyclopentylmagnesium bromide gave a mixture of *cis*- and *trans*-2-*o*-tolylcyclohexanol in the ratio of 60% *cis* and 40% *trans*; diphenyltin dihydride yielded 85% *trans* and 15% *cis* and isobutylmagnesium bromide gave an overall yield of about 50% *cis* plus some unidentified material and traces of *trans*. Pure *cis* was obtained through separation of the $\alpha$-naphthylurethans with subsequent reduction with lithium aluminum hydride–aluminum chloride mixture. The NMR spectra of *cis*- and *trans*-2-*o*-tolylcyclohexanol and their acetates are consistent with structures in which the cyclohexane ring is in a chair conformation with the tolyl group in equatorial orientation. The spectra confirm that the spin-spin coupling constant between neighboring hydrogens in axial orientation is much larger than between neighboring hydrogens in other orientations.

The reduction of substituted cyclohexanones affords synthetic routes to the corresponding *cis* and *trans* cyclohexanols, but as was demonstrated by Hardy and Wicker[2] the stereochemistry of many reduction methods is still unpredictable and the assignment of configuration to the resulting substituted cyclohexanols solely on generalyzed rules is still hazardous. In the present work three methods of reduction of 2-*o*-tolylcyclohexanone were investigated for stereospecificity: diphenyltin dihydride,[3] isobutylmagnesium bromide, and cyclopentylmagnesium bromide. The products were analyzed for percentage *trans*-2-*o*-tolylcyclohexanol (I) and *cis*-2-*o*-tolylcyclohexanol (II) by analytical gas chromatography. Pure I was prepared by the stereospecific reaction of *o*-methylphenyllithium and cyclohexene oxide. The proton magnetic resonance spectra of I and II and their acetates were found to provide direct experimental evidence for the configuration and conformation of isomers I and II.

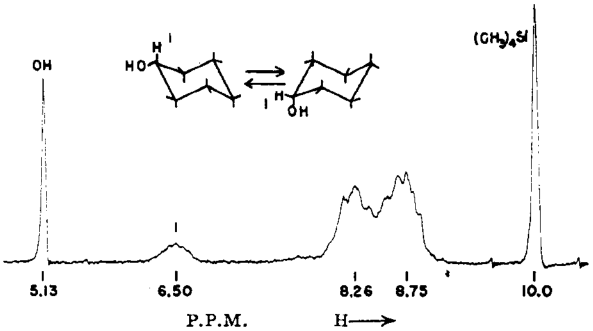

Fig. 1. The proton magnetic resonance of cyclohexanol in carbon tetrachloride at 23° (60 mc.)[8]

Diphenyltin dihydride gave a mixture containing only isomers I and II with approximately 85% I. Isobutylmagnesium bromide yielded a mixture containing slightly less than 50% II, a very small amount of I, some unchanged ketone, and a considerable amount of unidentified substance. Cyclopentylmagnesium bromide gave a mixture of I and II in the ratio of 60% *cis* and 40% *trans*, plus a small amount of unchanged ketone. There was no addition product. The presence of unchanged ketone in the last two reactions is attributed to some enolization of the ketone since unchanged ketone was isolated even upon using a large excess of Grignard reagents. The action of certain organomagnesium halides as reducing agents for aldehydes and ketones is well known,[4] and the stereospecifity of isobutylmagnesium bromide as a reducing agent for certain substituted cyclohexanones has been investigated previously,[5] but there is no evidence of previous investigation of this sterospecificity for cyclopentylmagnesium bromide. Pure II was separated from the mixture of I and II through the separation of the $\alpha$-naphthylurethans with subsequent reduction with lithium aluminum hydride plus aluminum

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[1] This investigation was supported by a PHS research grant, No. H-3843 (R1), from the National Heart Institute, Public Health Service. Presented at the 138th Meeting of the American Chemical Society, New York City, N. Y., September 11-16, 1960.

[2] K. D. Hardy and R. J. Wicker, *J. Am. Chem. Soc.,* 80, 640 (1958).

[3] H. G. Kuivila and O. F. Beumel, Jr., *J. Am. Chem. Soc.,* 80, 3798 (1958).

[4] M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances,* Prentice-Hall, New York, 1954, p. 153.

[5] P. Anziani, A. Aubry, G. Barraud, M. M. Claudon, and R. Cornubert, *Bul. soc. chim.,* France, 408 (1955).

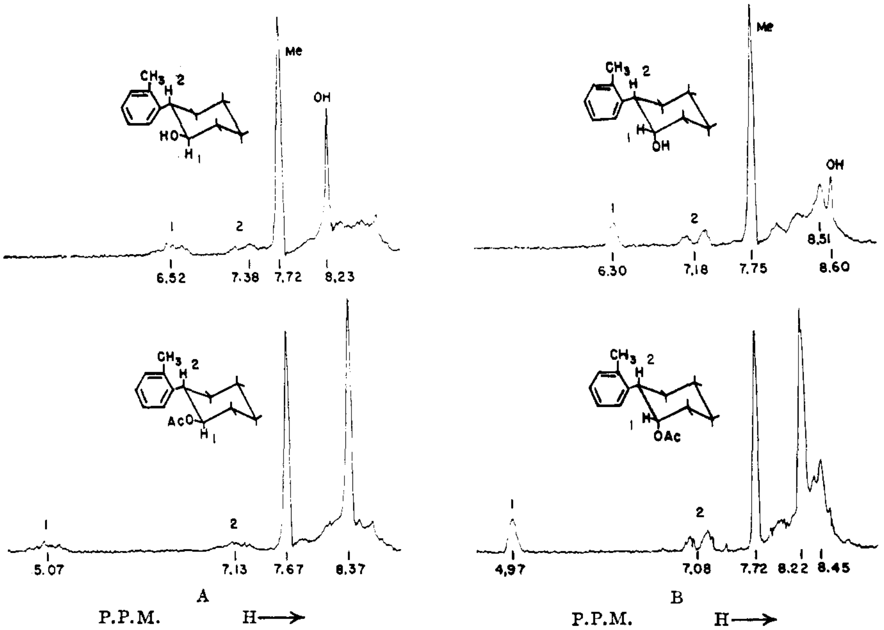

Fig. 2. The proton magnetic resonance spectra of *trans*-and *cis*-2-*o*-tolylcyclohexanol and their acetates (60 Mc; 1*M* in carbon tetrachloride at 23°)

chloride. Mixtures of I and II can also be separated by fractional elution chromatography, the method of Reichstein and Shoppee.[6] Chromatography of one gram of the cyclopentylmagnesium bromide reduction mixture on thirty grams of neutral alumina yielded approximately 40% of I and 60% of II. Evidence is now given from gas chromatography that I, previously obtained from *o*-methylphenyllithium and cyclohexene oxide,[7] is sterochemically homogeneous, and the *trans* configuration of I is now verified by NMR.

The conformations and NMR spectra of *trans*- and *cis*-2-*o*-tolylcyclohexanol and their acetates are presented in Fig. 2. Fig. 1 gives the same data for cyclohexanol. The spectra were measured in carbon tetrachloride and the chemical shifts, expressed as $\tau$ values, are related to tetramethylsilane as an internal reference. The NMR spectra of deuterated I and II were also determined. The signals were assigned to the various hydrogens as follows: The hydroxyl hydrogens were assigned by the disappearance of the signal upon deuterium exchange and from the disappearance of the signal upon acetylation. The sharp intense signal which for the various compounds appears within the narrow range of 7.67 to 7.75 p.p.m., and is absent in cyclohexanol, is obviously due to the hydrogen of the methyl group on the aromatic ring. The signal for each tolyl substituted compound appearing immediately downfield from that of the aromatic methyl hydrogens, and which is split into a doublet for the *cis* compounds but gives a poorly resolved broad multiplet for all *trans* compounds, is attributed to the hydrogen on the 2-carbon. The signal which occurs still further downfield (6.30 p.p.m. for the *cis* alcohol and 6.52 p.p.m. for the *trans*) is assigned to the hydrogen on the 1-carbon from the large downfield chemical shift occurring upon acetylation. The signals for the aromatic hydrogens are not shown.

The application of NMR spectroscopy in conformation analysis of polysubstituted six-membered ring compounds is well established.[9–12] Of special interest for the assignment of configuration and conformation in such structures is the fact that in compounds having the fixed chair conformation there is stronger spin-spin coupling between axial hydrogens on neighboring carbons than between neighboring hydrogens in other orientations.[9] The NMR spectra of *cis* and *trans*-2-*o*-tolylcyclohexanol and their acetates (Fig. 2) are consistent with structures in which the cyclohexane ring is in a chair conformation with the tolyl group in equatorial orientation. This is obviously the most stable conformation for the *trans* compounds but this conformation could not be assigned apriori to the *cis* compounds, especially to the *cis* acetoxy derivative.

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(6) T. Reichstein and C. W. Shoppee, *Far. Soc. Disc.*, **7**, 305 (1949).

(7) A. C. Huitric, T. C. West, R. A. Durbin, and G. H. Bryan, *J. Am. Pharm. Assoc., Sci. Ed.*, **48**, 131 (1959).

(8) The NMR spectra were determined by B. J. Nist, Dept. of Chemistry, University of Washington.

(9) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Am. Chem. Soc.*, **80**, 6098 (1958).

(10) E. L. Eliel, *Chem. & Ind.* (*London*), 568 (1959).

(11) S. Brownstein and R. Miller, *J. Org. Chem.*, **24**, 1886 (1959).

(12) J. A. Pople, W. G. Schneider, H. J. Bernstein, *High-resolution Nuclear Magnetic Resonance*, McGraw-Hill, New York, 1959, pp. 387–399.

The broad unresolved multiplet with half-width of about 18 c.p.s for the 1-hydrogen of the *trans* alcohol, and its acetate, indicates strong spin-spin coupling between the axial hydrogen and the two nonidentical adjacent axial hydrogens. In contrast to this the signal of the 1-hydrogen for the corresponding *cis* alcohol and acetate exhibits a singlet with half-width of 6 c.p.s. This indicates that a high population of the *cis* compounds exists in the chair conformation with the 1-hydrogen in equatorial orientation, and rules out a rapid equilibrium between the two possible chair conformations at room temperature. This argument is strongly substantiated by the signal of the 2-hydrogen which exhibits a broad unresolved multiplet in the *trans* alcohol and *trans* acetate but gives a doublet in each of the corresponding *cis* isomers. The NMR spectrum of the *cis* acetate determined at −25° exhibits a singlet and a doublet for the 1- and 2-hydrogens, respectively, which are identical to those obtained at room temperature. In the conformation assigned to the *cis* compounds the axial 2-hydrogen is adjacent to only one other axial hydrogen. If the coupling between the 2-hydrogen and the equatorial 1- and 3-hydrogens is very small the 2-hydrogen and the axial 3-hydrogen in the *cis* compounds approximate an AB system.[13] In such a system the inner component of each doublet will have a greater intensity than the outer component if the ratio $J_{AB}/\delta_B\text{-}\delta_A$) is greater than 0.1.[14] This ratio cannot be calculated in the present case since the signal for the axial 3-hydrogen is overlapped by signals of the other ring hydrogens and the chemical shift between the two hydrogens is not known. But the ratio is certainly greater than 0.1 and probaby closer to 0.2. The greater intensity of the inner component of the doublet of the 2-hydrogen is as expected. The coupling constant $J_{AB}$ between the 2-hydrogen and the axial 3-hydrogen is about 11.8 c.p.s.

## EXPERIMENTAL

*Reduction of 2-o-tolylcyclohexanone by cyclopentylmagnesium bromide.* To a solution of cyclopentylmagnesium bromide, prepared from 44.0 g. (0.3 mole) of bromocyclopentane and 6.65 g. of magnesium turnings in 160 ml. of anhydrous ether, was added with stirring and gentle heating a solution of 22.4 g. (0.12 mole) of 2-*o*-tolylcyclohexanone[15] in 175 ml. of anhydrous ether (addition time was 1.5 hr.). The mixture was refluxed for an additional 2 hr., hydrolyzed by pouring into 250 ml. of ice water mixture and acidified with hydrochloric acid. The ether layer was separated and the aqueous layer extracted with ether. The combined ether solution was neutralized with sodium bicarbonate solution and dried over anhydrous calcium sulfate. After removing the ether the crude product was treated with Girard's "T" reagent and 1.3 g. of unchanged 2-*o*-tolylcyclohexanone was recovered. Distillation of the Girard's "T" treated product yielded 19.1 g. of colorless viscous liquid, b.p. 80–82° at 0.15–0.20 mm.

Gas chromatography at 203°, using a five-foot Carbowax 20,000 column and helium at 12 pounds pressure as the carrier gas, gave two well defined symmetrical peaks with curve area ratios of exactly 2 to 3. The smallest peak, emergence time of 24 minutes, was characterized as *trans*-2-*o*-tolylcyclohexanol by comparison with the gas chromatography curves obtained from a sample of the pure *trans*, (compound I), and from a sample of the mixture to which pure I had been added. The emergence time of the *cis* isomer was 28 min. A 5-foot Ucon polar column at 200° also gave good separation of the *cis* and *trans* isomers. The *cis* and *trans* isomers were separated by fractional recrystallization of the α-naphthylurethans from hexane and ethanol.

| α-Naphthylurethan of: | M.P. | | | Calcd. | Found |
|---|---|---|---|---|---|
| *trans*-2-*o*-Tolylcyclohexanol | 122–123 | $C_{24}H_{25}NO_2$ | C | 80.19 | 80.32 |
| | | | H | 7.01 | 7.20 |
| *cis*-2-*o*-Tolylcyclohexanol | 174–175 | $C_{24}H_{25}NO_2$ | C | 80.19 | 80.16 |
| | | | H | 7.01 | 7.13 |
| Phenylurethan of: | | | | | |
| *trans*-2-*o*-Tolylcyclohexanol | 137.5–138 | $C_{20}H_{23}NO_2$ | C | 77.64 | 77.88 |
| | | | H | 7.49 | 7.28 |
| | | | N | 4.53 | 4.22 |
| *cis*-2-*o*-Tolylcyclohexanol | 107.5–108.5 | $C_{20}H_{23}NO_2$ | C | 77.64 | 77.66 |
| | | | H | 7.49 | 7.37 |
| | | | N | 4.53 | 4.62 |

*α-Naphthyl- and phenylurethans.* The α-naphthyl- and phenylurethans were prepared by refluxing the 2-*o*-tolycyclohexanol with the appropriate isocyanate in anhydrous toluene for 3 hr. Of the two α-naphthylurethans obtained from the cyclopentylmagnesium bromide reduction mixture the one with the lowest melting point proved to be identical to the α-naphthylurethan of pure I, while in the case of the phenylurethans the one with the highest melting point was identical to the phenylurethan of pure I.

*Reduction of 2-o-tolylcyclohexanone by isobutylmagnesium bromide.* This was carried out by the same procedure as that described for the cyclopentylmagnesium bromide reduction using the same excess of Grignard reagent. The mixture was distilled without treating with Girard "T" reagent, giving an overall recovery of 85%, boiling range of 81–95° at 0.175 mm. Gas chromatography of this distilled mixture indicated a trace of I, approximately 50% of II, some unreacted ketone and a considerable amount of unidentified material.

*Reduction of 2-o-tolylcyclohexanone by diphenyltin dihydride.* The experimental procedure is essentially that de-

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(13) H. J. Bernstein, J. P. Pople, and W. G. Schneider, *Can. J. Chem.*, **35**, 65 (1957).

(14) L. M. Jackman, *Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, Pergamon, New York, N. Y., 1959, pp. 89–90.

(15) A. C. Huitric and W. D. Kumler, *J. Am. Chem. Soc.*, **78**, 614 (1956).

scribed by H. S. Kuivila.[16] Diphenyltin dihydride was prepared from diphenyltin dichloride just before using. A solution of 18.6 g. (0.054 mole) of diphenyltin dichloride in 40 ml. of anhydrous ether was added with stirring over a period of 15 min. to a mixture of 1.5 g. (0.039 mole) of lithium aluminium hydride in 25 ml. of anhydrous ether under nitrogen. The mixture was stirred for 30 min. and hydrolyzed by dropwise addition of 10 ml. of water. The ether layer was filtered through anhydrous sodium sulfate, cooled in ice, and used directly for the reduction of the ketone.

The cold ether solution of diphenyltin dihydride was added all at once to an ice cold solution of 5.0 g. (0.026 mole) of 2-*o*-tolylcyclohexanone in 40 ml. of anhydrous ether and the mixture was allowed to stand at room temperature for 3 days. The resulting yellow diphenyltin was filtered off by means of Celite filter-aid. Ten milliliters of acetaldehyde was added to destroy the unreacted diphenyltin dihydride and the mixture was allowed to stand at room temperature for 1 week. The resulting diphenyltin was again filtered by means of Celite filter aid. Distillation after removal of solvent yielded 4.28 g., 85% of theory, of colorless liquid, b.p. 79° at 0.16 mm. The product analyzed by gas chromatography was found to contain only I and II with about 85% I.

It is essential to destroy the excess diphenyltin dihydride before distillation because it distills over with the product. Distillation of the reaction mixture without the aldehyde treatment resulted in a colorless liquid in which a precipitate of yellow diphenyltin would gradually form upon standing. The time of the aldehyde treatment could undoubtedly be shorter than that used in this work.

*Reduction of phenylurethan of cis-2-o-tolylcyclohexanol.* To 0.47 g. (0.012 mole) of lithium aluminum hydride in 4 ml. of anhydrous tetrahydrofuran was added a solution of 0.95 g. (0.0031 mole) of phenylurethan of *cis*-2-*o*-tolylcyclohexanol in 6 ml. of anhydrous tetrahydrofuran and the mixture refluxed for 18 hr. The excess lithium aluminum hydride was destroyed by dropwise addition of ethyl acetate. The mixture was hydrolyzed by pouring into 25 ml. of ice water, acidified with 10% hydrochloric acid, extracted with ether, and the ether solution washed with 10% hydrochloric acid, 5% sodium bicarbonate, water, and dried over anhydrous calcium sulfate. Removal of the solvent and distillation yielded 0.37 g. of colorless liquid, b.p. 76–78° at 0.15–0.17 mm. Analysis by gas chromatography showed the product to be pure II.

*Reduction of α-naphthylurethans.* Lithium aluminum hydride reduction of the α-naphthylurethan of the *cis* isomer proved more difficult than that of the *trans*. Refluxing of 4 g. of α-naphthylurethan of I in anhydrous tetrahydrofuran for 30 min. with excess lithium aluminum hydride yielded 1.2 g. of unchanged material and 1.0 g. of pure I. Three hours of refluxing of the α-naphthylurethan of II under identical conditions yielded only unchanged starting material. The reduction was effected by using a mixture of lithium aluminum hydride and aluminum chloride with prolonged refluxing.

To a suspension of 1.26 g. (0.033 mole) of lithium aluminum hydride in 25 ml. of anhydrous tetrahydrofuran was added slowly with cooling 4.43 g. (0.033 mole) of anhydrous aluminum chloride. Caution should be observed during this addition as a vigorous reaction occurs upon addition of aluminum chloride to tetrahydrofuran. The mixture was stirred for 20 min. and a solution of 4.0 g. (0.011 mole) of α-naphthylurethan of *cis*-2-*o*-tolycyclohexanol in 25 ml. anhydrous tetrahydrofuran was added with stirring over a period of 7 min. The mixture was stirred for 2.5 hr. at room temperature and refluxed for 21 hr., and allowed to stand at room temperature for 16 hr. The excess lithium aluminum hydride was destroyed by dropwise addition of ethyl acetate and the reaction mixture was worked up as for the phenylurethan reduction. Distillation of the product yielded 1.45 g. of colorless liquid, b.p. 80° at 0.175 mm.

*Anal.* Calcd. for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 81.84; H, 9.39. The product, analyzed by gas chromatography, was found to be pure II. A very small amount of unchanged α-naphthylurethan was also recovered.

*2-o-Tolylcyclohexyl acetates.* The 2-*o*-tolylcyclohexanol (0.40 g.) was refluxed with 2.16 g. of acetic anhydride in 5 ml. of anhydrous pyridine for 1 hr. The cooled mixture was poured into 25 ml. of ice water, the mixture was extracted with ether, the ether solution washed successively with 2% hydrochloric acid, 5% sodium bicarbonate, and water, and then dried with anhydrous calcium sulfate. Distillation after removal of the solvent gave a colorless liquid, b.p. 77° at 0.150 mm.

*Anal.* Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: *trans*, C, 77.76; H, 8.85; *cis*, C, 77.21; H, 8.75.

The infrared spectrum of each 2-*o*-tolylcyclohexanol, measured on the pure liquid, has an intense OH stretching band which has a maximum at 3370 cm.$^{-1}$ and a less intense peak at 3510 cm.$^{-1}$ for the *trans* isomer as compared to 3410 cm.$^{-1}$ and 3510 cm.$^{-1}$ for the *cis* isomer. These peaks are attributed to hydrogen-bonded and unassociated hydroxyl groups respectively. The slight discrepancy between the present values for the *trans* isomer and those previously reported[7] is attributed to differences in the instrument since the two spectra show a discrepancy of similar magnitude in the region of the C—H stretching band. There are no discrepancies at higher wave lengths. The spectra of the isomeric alcohols and their acetates all have a band in the region of 959–970 cm.$^{-1}$, a region which falls within the range of characteristic absorption for cyclohexane derivatives[7,17]: 964 and 967 cm.$^{-1}$ for the *trans* alcohol and acetate respectively; 969 and 959 cm.$^{-1}$ for the *cis* alcohol and acetate respectively. The *trans* alcohol and acetate give a band at 847 cm.$^{-1}$ which is absent in the spectra of the corresponding *cis* isomers. The *cis* alcohol and acetate each give sharp bands at 747 and 766 cm.$^{-1}$ while the *trans* alcohol and acetate each give a single intense broad band with a maximum at 753 cm.$^{-1}$

The melting points were determined with a Kofler micro hot stage.

SEATTLE, WASH.

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[16] Personal communication from H. S. Kuivila and H. J. Dauben, October 21, 1959.

[17] L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Wiley, New York, 1958, p. 31.