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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

### Conformational Analysis. III. Epimerization Equilibria of Alkylcyclohexanols<sup>1</sup>

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The *cis*- and *trans*-4-*t*-butylcyclohexanols have been equilibrated by means of aluminum isopropoxide in isopropyl alcohol. The equilibrium, determined by infrared and gas chromatographic analysis, corresponds to 79% *trans* and 21% *cis* isomer involving a free energy difference of  $-0.96$  kcal./mole, in good agreement with values determined by other methods. Equilibria for the 2-, 3- and 4-methylcyclohexanols and 4-phenylcyclohexanols have been similarly determined and are compared with values in the literature.

In the accompanying paper<sup>1</sup> the equilibrium between the *conformational* isomer of cyclohexanol with an axial hydroxyl group and the isomer with an equatorial hydroxyl group has been determined by a kinetic method. The equilibrium constant was found to be 2.4 corresponding to a free energy difference of  $-0.5$  kcal./mole. A more direct way of approaching this equilibrium is through the *cis*- and *trans*-4-*t*-butylcyclohexanols which, though they are stable *configurational* isomers, may be equilibrated by means of aluminum isopropoxide.<sup>3</sup> Since the *t*-butylcyclohexanols are conformationally homogeneous,<sup>4</sup> the equilibrium between the configurational isomers is as represented in Fig. 1 and thus corresponds to the conformational equilibrium between axial and equatorial hydroxyl. The equilibrium concentration of the two isomers (Fig. 1) was determined both by infrared analysis and

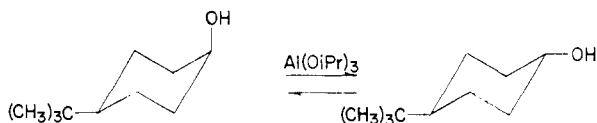


Fig. 1.

by vapor phase chromatography and corresponds to  $79 \pm 2\%$  *trans* and  $21 \pm 2\%$  *cis* isomer, giving an equilibrium constant of 3.76 and a free energy difference of  $-0.96$  kcal./mole. This value, which refers to isopropyl alcohol at  $89^\circ$  as a solvent,<sup>5</sup> is in good agreement with earlier values of  $-0.8$  (at  $40^\circ$  in 75% acetic acid)<sup>4</sup> and  $-0.9$  (in water)<sup>6</sup> and in fair agreement with that of  $-0.5$  (at  $25^\circ$  in pyridine) reported in the accompanying paper.<sup>1</sup>

(1) Paper II, E. L. Eliel and C. A. Lukach, *THIS JOURNAL*, **79**, 5986 (1957).

(2) Texas Co. Fellow, 1954-1956. From the Ph.D. Thesis of Rolland S. Ro.

(3) W. G. Dauben, G. J. Fonken and D. S. Noyce, *THIS JOURNAL*, **78**, 2579 (1956). Professor Dauben kindly made this work available to us in advance of publication, and we wish to acknowledge correspondence with him regarding the equilibria in question both prior and subsequent to publication of his paper.

(4) S. Winstein and N. J. Holness, *ibid.*, **77**, 5562 (1955).

(5) Since a large excess of isopropyl alcohol was present in the equilibration, it may be assumed that most of the *t*-butylcyclohexanol was present as such rather than as an aluminum salt.

(6) S. J. Angyal and D. J. McHugh, *Chemistry & Industry*, 1147 (1956).

It is of some interest to compare the above equilibrium (Fig. 1) with one between alkylcyclohexanols which are not conformationally homogeneous and where both conformational isomers of the two epimers must be considered, such as the 4-methylcyclohexanols (Fig. 2). In this case, the epimeriza-

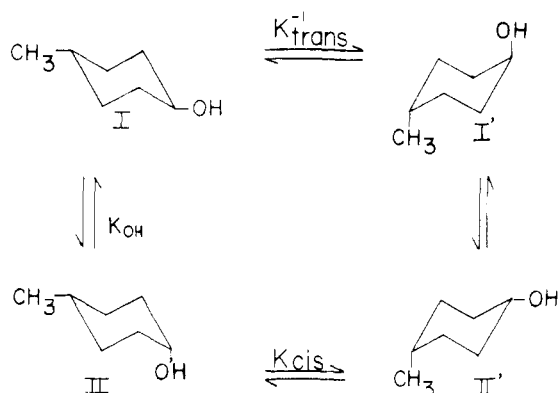


Fig. 2.

tion equilibrium constant  $K_{epi} = (I + I')/(II + II')$ , since this constant is based on stoichiometric concentrations. This expression may be transformed as

$$K_{epi} = \frac{I}{II} \times \frac{1 + I'/I}{1 + II'/II} = K_{OH} \frac{1 + K_{trans}^{-1}}{1 + K_{cis}} \quad (i)$$

Since  $K_{trans}^{-1} < K_{cis}$  it follows that  $K_{epi} < K_{OH}$ . The data in Table I, obtained by infrared and gas chromatographic analyses, bear out this prediction.

TABLE I  
EPIMERIZATION EQUILIBRIA AT  $89^\circ$   
Stable isomer,<sup>a</sup> ( $K_{epi}$ ), %

Compound	By infrared	By gas chromatography
4- <i>t</i> -Butylcyclohexanol	77-81 (3.35-4.30)	79 (3.76)
4-Methylcyclohexanol	69-71 (2.23-2.44)	68.5 (2.18)
3-Methylcyclohexanol	77-79 (3.35-3.76)	77 (3.35)
2-Methylcyclohexanol	High	>94 <sup>b</sup>
4-Phenylcyclohexanol	$70 \pm 5$	....

<sup>a</sup> *trans*-4-, *cis*-3- and *trans*-2-isomer. <sup>b</sup> Tentative result; it is possible that equilibrium was not reached.

TABLE II  
COMPOSITION OF ALKYL CYCLOHEXANOL MIXTURES

Compound	Method of preparation	Predominant isomer, %
4-Methylcyclohexanol	Equilibration	69-71% <i>trans</i> <sup>a</sup>
	Lithium aluminum hydride reduction	79-81% <i>trans</i> <sup>b</sup>
	Hydrogenation of <i>p</i> -cresol with ruthenium oxide catalyst	62-64% <i>cis</i>
	Hydrogenation of ketone using platinum oxide in AcOH-HCl	79-81% <i>cis</i>
3-Methylcyclohexanol	Equilibration	77-79% <i>cis</i> <sup>d</sup>
	Lithium aluminum hydride reduction	>85% <i>cis</i> <sup>c</sup>
	Hydrogenation of ketone using platinum oxide in AcOH-HCl	71-73% <i>trans</i>
4- <i>t</i> -Butylcyclohexanol	Equilibration	77-81% <i>trans</i>
	Commercial <sup>11</sup>	75 ± 5% <i>trans</i> <sup>11</sup>
	Lithium aluminum hydride reduction	91-93% <i>trans</i> <sup>e</sup>
	Hydrogenation of <i>p</i> - <i>t</i> -butylphenol with ruthenium oxide	53 ± 3% <i>cis</i>
	Same with platinum oxide	62-64% <i>trans</i>
	Hydrogenation of ketone using platinum oxide in AcOH-HCl	78 ± 3% <i>cis</i>
	Hydrogenation of ketone using platinum oxide in AcOH only	65 ± 3% <i>trans</i> 55 ± 5% <i>trans</i> <sup>12</sup>

<sup>a</sup> Ref. 3 reports 88%. <sup>b</sup> Ref. 10 reports 81%. <sup>c</sup> Ref. 10 reports 92%. <sup>d</sup> Ref. 9a reports 83% for epimerization over Raney nickel at 160°. <sup>e</sup> (Added in proof, 9/18/57) following the publication of O. H. Wheeler and J. L. Mateos, *Chemistry & Industry*, 395 (1957), we have reduced 4-*t*-butylcyclohexanone with LiAlH<sub>4</sub>-AlCl<sub>3</sub>. The reduction product is pure *trans*-4-*t*-butylcyclohexanol, provided a slight excess of ketone is employed. With an excess of hydride, the product is an equilibrium mixture of *cis*- and *trans*-4-*t*-butylcyclohexanol. This surprising result is under further study;

There is good agreement between the infrared and gas chromatography analyses in Table I, implying that the data are probably quite accurate. It is, however, somewhat surprising that  $K_{epi}$  for 3-methylcyclohexanol is so much larger than  $K_{epi}$  for 4-methylcyclohexanol. If one writes equation (i) in the more general form  $K_{epi} = K_{OH}(1 + K_{e,e}^{-1}) / (1 + K_{e,a})$  (where  $K_{e,e}$  refers to the diequatorial *cis*-3- or *trans*-4-isomer and  $K_{e,a}$  to the equatorial-axial *trans*-3- or *cis*-4-isomer), it is evident that  $K_{epi}$  should actually be slightly smaller for the 3-isomer (since  $K_{e,e}^{-1}$  for this isomer is practically zero, whereas for the 4-isomer it is finite, and on the other hand  $K_{e,a}$  should be about the same for the two isomers). A similar apparent anomaly has been observed in equilibrium studies on the dimethylcyclohexanes.<sup>7,8</sup>

In the course of this work, the composition of alkylcyclohexanols obtained by a variety of methods was determined by infrared analysis. The results—of interest mainly from the preparative point of view—are summarized in Table II. Because of interest in this matter in other quarters<sup>9</sup> a systematic investigation of isomer ratios in products of catalytic reduction was not undertaken.

The figures reported here for the 4-methylcyclohexanol equilibrium differ appreciably from those (88% *trans*,  $K = 7.33$ ) reported by earlier investigators.<sup>3</sup> The earlier investigation was concerned primarily with the stereochemistry of lithium aluminum hydride reduction, and it was stated<sup>3</sup> that the lithium aluminum hydride reduction product of 4-methylcyclohexanone contains more *cis*-alcohol (e,

a-product) than the equilibrium mixture of the 4-methylcyclohexanols. The present figures (Table II) show the opposite to be the case: in the 4-methyl- and the 3-methylcyclohexanol as well as the 4-*t*-butylcyclohexanol series, the lithium aluminum hydride reduction product contains less of the unstable (e, a) alcohol than does the equilibrium mixture.<sup>13</sup> This point is also borne out by visual comparison of the infrared spectra of the LAH reduction products with those of the equilibrium mixtures.

In the course of this investigation, improved methods were developed for the convenient preparation of *cis*-4-*t*-butylcyclohexanol<sup>4</sup> and the phenylcyclohexanols.<sup>14</sup>

### Experimental<sup>15</sup>

***cis*-4-*t*-Butylcyclohexanol.**—In a typical run, 30.9 g. (0.20 mole) of 4-*t*-butylcyclohexanone<sup>4</sup> in 100 ml. of glacial acetic acid containing 7.6 g. of hydrogen chloride gas was reduced catalytically in the presence of 1.0 g. of platinum oxide at room temperature and 57 p.s.i. initial pressure. The theoretical amount of hydrogen was absorbed in 10 minutes in an exothermic reaction. Products from three hydrogenation runs were combined, filtered, poured into 500 ml. of water and 500 g. of ice and extracted with four 300-ml. portions of petroleum ether (b.p. 40-60°). The extracts were washed with three 500-ml. portions of saturated aqueous sodium bicarbonate, dried over sodium and magnesium sulfates and concentrated. Since some of the resulting product was in the form of an acetate, the residue (102 g.) was saponified by boiling for 7 hr. with a solution of 35.5 g. of potassium hydroxide in 50 ml. of water and 240 ml. of methanol. The solution was poured into 1 l. water and 500 g. of ice and the precipitated solid filtered, redissolved in 900 ml. of ether, dried and concentrated to give 86.5 g. (93%) of *cis*-rich 4-*t*-butylcyclohexanol, m.p. 69-71°.

Other methods of obtaining *cis*-rich 4-*t*-butylcyclohexanol were investigated with a view to (a) avoiding the time-consuming saponification step and (b) using the readily available 4-*t*-butylphenol as a starting material. Thus the ketone was reduced as described above but in the absence of hydrogen chloride,<sup>4</sup> and the same reduction was then repeated using fresh ketone but the same batch of catalyst.<sup>12</sup> The re-

(13) This would not necessarily affect the argument on product development control in ref. 3, since the equilibrium that matters in the LAH reduction is that of the aluminum-complex of the cyclohexanols, not that of the free cyclohexanols.

(14) H. E. Ungnade, *J. Org. Chem.*, **13**, 361 (1948).

(15) All melting and boiling points are uncorrected.

(7) A. K. Roebuck and B. L. Evering, *THIS JOURNAL*, **75**, 1631 (1953).

(8) See, however, G. Chiurdoglu, J. Versluys-Evrard and J. Decot, *Bull. soc. chim. Belg.*, **66**, 192 (1957).

(9) (a) R. J. Wicker, *J. Chem. Soc.*, 2165 (1956); (b) S. Siegel, private communication.

(10) D. S. Noyce and D. B. Denney, *THIS JOURNAL*, **72**, 5743 (1950).

(11) Dow Chemical Co. According to their analysis, this product is 72-77% *trans* (private communication from Dr. Walter B. Trapp).

(12) The second figure refers to catalyst which was re-used after having been used once in the same reduction. This experiment was suggested and carried out by Dr. Ralph G. Haber.

TABLE III  
 GAS CHROMATOGRAPHY DATA OF ALKYL CYCLOHEXANOLS

Band	Per cent. (retention time, min.)			
	2-Methyl	3-Methyl	4-Methyl	4- <i>t</i> -Butyl
Material of low retention	6.1(2.8-11.3) <sup>a</sup>	2.9(3.7-6.8) <sup>b</sup>	2.5(3.8-14.4) <sup>c</sup>	None
<i>cis</i> -Isomer	?	75 (19.1)	31 (16.5)	21(39)
<i>trans</i> -Isomer	94 (13.5)	22 (16.5)	67 (20.5)	79(48)

<sup>a</sup> Five components. <sup>b</sup> Three components. <sup>c</sup> Four components.

used catalyst gave somewhat faster reduction and higher stereospecificity, but whereas these reductions as well as the reduction of *p*-*t*-butylphenol in 95% ethanol with ruthenium oxide catalyst at 60° and 1800-1500 p.s.i. or with platinum oxide in acetic acid at room temperature and 50 p.s.i. gave *t*-butylcyclohexanol free of esters, in no case was the product sufficiently rich in *cis* isomer to allow ready purification through a derivative (cf. Table II).

The 4-*t*-butylcyclohexanol, m.p. 69-71°, was converted to the *p*-nitrobenzoate by treatment with a 20% excess of *p*-nitrobenzoyl chloride in a six-molar excess of pyridine. After two recrystallizations from petroleum ether (b.p. 60-80°), the ester melted at 133-134° (lit.<sup>16</sup> 130.2-131.0°), yield 39%. The ester (64.5 g.) was saponified by means of 15 g. of sodium hydroxide in 90 ml. of water and 250 ml. of methanol. After 6 hr. of reflux the solution was poured into 1500 ml. of water and 500 g. of ice, and the precipitated *cis*-4-*t*-butylcyclohexanol was crystallized from petroleum ether (b.p. 40-60°), yield 32 g. (94%), m.p. 82.5-83.5° after sublimation (lit.<sup>4</sup> m.p. 82-83°, lit.<sup>16</sup> m.p. 82-82.5°).

*trans*-4-*t*-Butylcyclohexanol was prepared from the commercial alcohol<sup>11</sup> by purification *via* the acid phthalate,<sup>4</sup> m.p. 146-147° (lit.<sup>4</sup> 146.2-146.7°) and melted at 81-82° (lit.<sup>4</sup> 81-82°) after sublimation.

*trans*-4-Phenylcyclohexanol.—Three hundred grams of *p*-phenylphenol in 300 ml. of methanol in which 0.9 g. of sodium had been dissolved was reduced at 140-170° and *ca.* 2700 p.s.i. in the presence of 18 g. of Raney nickel catalyst.<sup>14</sup> Hydrogen uptake became very slow when about three equivalents had been taken up. The reduction was stopped, the reaction mixture filtered, concentrated to half-volume, poured into dilute aqueous potassium hydroxide and extracted with ether. The ether extract was washed with aqueous potassium hydroxide and water, dried over potassium carbonate and concentrated to yield 197 g. of crude material melting at 50-68°. Recrystallization from petroleum ether (b.p. 60-90°) gave a first crop (69 g.) of crystals melting at 80-101° and a second crop (118 g.), m.p. 59-67°.

The combined first crop from two runs (95 g.) was equilibrated by boiling for 103 hr. with 60 g. of freshly purified aluminum isopropoxide and 10 ml. of acetone in 900 ml. of anhydrous isopropyl alcohol.<sup>3</sup> The solution was concentrated (about 500 ml. of solvent being removed), poured into 2 l. of dilute hydrochloric acid and extracted with ether. The ether was washed with sodium bicarbonate solution and dried over, potassium carbonate and concentrated to give *ca.* 90 g. of solid which upon recrystallization from ethyl acetate and petroleum ether (b.p. 60-90°) gave 45 g. of pure *trans*-4-phenylcyclohexanol, m.p. 120-121° (lit.<sup>14</sup> 117.2-118.5°).

*cis*-4-Phenylcyclohexanol.—Material from the second crop described above melting at 59-67° (52 g.) was converted to the *p*-nitrobenzoate which, after two recrystallizations from methanol-ethyl acetate, melted at 132-134°, weight 22 g. Saponification gave 11 g. (21% over-all recovery) of pure *cis*-4-phenylcyclohexanol, m.p. 73-76°, raised to 75-77° by recrystallization from petroleum ether (lit.<sup>14</sup> 76-77°).

Methylcyclohexanols were prepared as reported before.<sup>1</sup>

**Equilibrium Procedure.**—The desired alcohol (3-10 g.) was heated under reflux with an equal amount of freshly distilled aluminum isopropoxide<sup>17</sup> in 100 ml. of anhydrous<sup>17</sup> isopropyl alcohol containing 1 ml. of acetone for 96 hr. The internal temperature was 88-89°. The solution was

poured into 500 ml. of water containing 30 ml. of concentrated hydrochloric acid and extracted with ether. The ether extract was washed with water and saturated aqueous sodium bicarbonate, dried over potassium carbonate and concentrated. The equilibrated product was recovered in 95% yield after removal of the last traces of solvent *in vacuo*. Solid products were analyzed as obtained, whereas liquid products were subjected to straight distillation prior to analysis to ensure absence of solvent.

In all cases except for the 2- and 3-methylcyclohexanols, equilibrium was reached from both sides, using either the pure isomers or a highly enriched mixture as starting material. The starting material for the 3-methylcyclohexanol equilibration was rich in *trans* isomer, that for 2-methylcyclohexanol was pure *trans* isomer. In the case of the 4-methylcyclohexanol, our equilibrium mixture was compared by infrared spectroscopy with one obtained by Dauben, Fonken and Noyce<sup>3</sup> and kindly supplied by Professor W. G. Dauben. Except for a few per cent. of ketonic material which had developed in the sample supplied to us due to prolonged storage, the sample was identical in composition (or very nearly so) with the ones obtained in the present investigation.

**Analytical Procedures.**—Unknowns (0.100 g.) were dissolved in chloroform (0.50 ml.) and the spectra recorded in a 0.05-mm. cell (except where noted otherwise) on a Baird double-beam instrument. Calibration samples were obtained by mixing appropriate volumes of stock solutions containing 1.000 g. of the pure alcohols in 5 ml. of chloroform. Calibration spectra were obtained at 5-10% intervals of composition for compositions in the vicinity of those of the unknowns. Within these intervals, composition was estimated inside a 2-4% range.<sup>18</sup> In the case of the phenylcyclohexanol, only an approximative analysis could be obtained, as the depth of the salient bands did not vary very much with composition.

Gas chromatographic analyses of the mixtures were performed at the Dow Chemical Co. at 190° using 60-mesh Tide in an 18 ft. × 1/4" copper tube) as the stationary phase and helium (6 p.s.i.) as the carrier gas. The analyses are summarized in Table III. Since the liquid samples all seemed to contain impurities of low retention time,<sup>19</sup> compositions as indicated in Table I are normalized for the two major components. This procedure failed in the case of *cis*-2-methylcyclohexanol, since no major peak other than that for the *trans* isomer was recorded.

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NOTRE DAME, INDIANA

(18) The complete spectral data may be found in the doctoral thesis of Rolland S. Ro, University of Notre Dame, 1957, available on inter-library loan.

(19) These impurities may account for the discrepancy of the analysis of the 4-methylcyclohexanol equilibrium mixture as determined by density (ref. 3) with the present values (Table II).

(16) G. Stork and W. N. White, *THIS JOURNAL*, **78**, 4617 (1950).

(17) Aluminum isopropoxide was dissolved in dry benzene and filtered prior to vacuum distillation. Isopropyl alcohol was boiled over calcium oxide for 6 hr. and then distilled.