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OPTICAL ROTATORY DISPERSION STUDIES—LXXXI[1] STEREOCHEMICAL STUDIES—XXVII[2]

CONFORMATIONAL DISTORTION IN 2-METHYLCYCLOHEXANONES[3]

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Abstract—Optically active *cis*- and *trans*-2-methyl-4-t-butylcyclohexanone have been synthesized and equilibrated in an alkaline medium. The position of the equilibrium, as determined by optical rotatory dispersion or gas chromatographic measurements, agreed well with earlier published data in the racemic series. The optical rotatory dispersion curve of *cis*-2-methyl-4-t-butylcyclohexanone, a substance which has been used earlier to demonstrate the absence of a "2-alkyl ketone effect," points towards a departure from the ordinary chair conformation, which does not seem to be associated with the bulky t-butyl substituent, but rather with a 2,4-diequatorial substitution pattern, since similar results were encountered with *cis*-2,4-dimethylcyclohexanone. Quantitative comparison of the optical rotatory dispersion molecular amplitude contributions of axially oriented 2-methylcyclohexanones (e.g., *trans*-2,6-dimethylcyclohexanone, *trans*-2-methyl-4-t-butylcyclohexanone, 2β- and 4β-methyl-3-keto-5α-steroids) indicates discrepancies, which are best interpreted in terms of conformational distortion.

IN ORDER to use the octant rule[4] for studies of conformational distortion[5] it is necessary to accumulate standard values for the rotary contribution of substituents, such as alkyl groups, in cyclohexanones. One of the most important figures is the Cotton effect contribution of an axially oriented methyl group adjacent to the carbonyl function in cyclohexanones and the first such value, $a = 56$,[6] was arrived at[4] by substracting the molecular amplitude of (+)-*trans*-2,5-dimethylcyclohexanone (I)[7] from that of

[1] For paper LXXX see K. Mislow, E. Bunnenberg, R. Records, K. Wellman and C. Djerassi, *J. Amer. Chem. Soc.* **85** (1963) in press.

[2] For paper XXVI see J. Zavada, J. Krupička and J. Sicher, *Coll. Czech. Chem. Comm.* **28** (1963) in press.

[3] The work at Stanford University was supported in part by the Rockefeller Foundation and in part by the National Cancer Institute (grant CRTY–5061) of the U.S. Public Health Service.

[4] W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne and C. Djerassi, *J. Amer. Chem. Soc.* **83**, 4013 (1961).

[5] See for instance [a]C. Djerassi, E. J. Warawa, J. M. Berdahl and E. J. Eisenbraun, *J. Amer. Chem. Soc.* **83**, 3334 (1961); [b]C. Djerassi, E. Lund and A. A. Akhrem, *Ibid.* **84**, 1249 (1962); [c]C. Djerassi and W. Klyne, *Proc. Natl. Acad. Sci., U.S.*, **48**, 1093 (1962); [d]C. Djerassi and W. Klyne, *J. Chem. Soc.* 4929 (1962); [e]C. Djerassi and W. Klyne, *Ibid.* 2390 (1963).

[6] For the sake of convenience (see ref. 5*d*), the amplitude a is defined as the difference (molecular rotation) between the peak and trough of a Cotton effect divided by 100.

[7] All structures in this paper represent correct absolute configurations using the conventional steroid notation system.

(+)-2,2,5-trimethylcyclohexanone (II).[8] This derivation assumes that both I and II exist mainly in the chair forms IA and IIA with the largest number of equatorial (and hence smallest number of axial) methyl groups. While this assumption is reasonable, the less favorable conformer IIB of 2,2,5-trimethylcyclohexanone with three, rather than two, 1-3 axial-hydrogen interactions may be present in a high enough proportion to affect considerably the amplitude of the Cotton effect. Thus, in terms of diaxial 1-3 interactions, the energy difference between conformers IIA and IIB corresponds to about 1·4 kcal/mole, due to the one additional methyl-hydrogen interaction[9] present in IIB, which suggests the presence of ca. 9% of the diaxial conformer IIB.

According to the tenets of the octant rule,[4] conformer IIB would exhibit a strongly negative Cotton effect. The identical negative rotatory contribution should also be exhibited by conformer IB of *trans*-2,5-dimethylcyclohexanone, but in this instance, there exist three unfavorable diaxial interactions in IB as compared to IA and therefore well under 5% of conformer IB would be expected to contribute to the conformational equilibrium mixture of (+)-*trans*-2,5-dimethylcyclohexanone. If these premises are granted, then it would appear that the earlier arrived[4] value of $a = 56$ for an axial 2-methyl substituent is too low. It is important, therefore, that independent checks are obtained for the axial 2-methyl contribution and the present paper records experiments along such lines.

A reasonable test case would be *trans*-2,6-dimethylcyclohexanone (III), which has already been described in optically active form,[10] although its rotatory dispersion curve had not yet been measured. If this ketone exists exclusively in the chair form (IIIA), then its rotatory dispersion curve would yield directly the rotatory contribution of an axial 2-methyl substituent, because "flipping" of the ring from one chair form to the other results in exactly the same arrangement (IIIA), while the equatorial methyl group has been presumed not to make any substantial rotatory contribution.[4] Through the kind cooperation of Prof. R. Cornubert (University of Nancy), a sample of completely resolved crystalline (+)-*trans*-2,6-dimethylcyclohexanol was oxidized and the vapor phase chromatographically pure ketone subjected to optical rotatory dispersion measurement. The positive Cotton effect immediately established the absolute configuration of the (+)-antipode as IIIA[7] and its molecular amplitude of +75[6] (unchanged on standing in methanol solution for three months) thus offered for consideration a new value for the rotatory contribution of an axial 2-methyl group—considerably higher than the earlier one of +56 derived[4] from (+)-2,2,5-trimethylcyclohexanone (IIA).

The recent stereospecific synthesis[11] of the four isomeric racemic 2-methyl-4-t-butylcyclohexanols provided intermediates suitable for resolution and hence a route to optically active *cis*-(VII) and *trans*-(V) 2-methyl-4-t-butylcyclohexanone. The latter was desired as still another model for determining the rotatory contribution of an axial 2-methyl substituent, while the availability of both optically active isomers would afford the opportunity of studying the *cis-trans* equilibration—so important in examining[12] the "2-alkyl ketone effect"—by means of rotatory dispersion.

[8] C. Djerassi, J. Osiecki and E. J. Eisenbraun, *J. Amer. Chem. Soc.* **83,** 4433 (1961).
[9] N. L. Allinger and L. A. Freiberg, *J. Amer. Chem. Soc.* **84,** 2201 (1962); see also D. S. Noyce and L. J. Dolby, *J. Org. Chem.* **26,** 3619 (1961).
[10] R. Cornubert, P. Anziani, A. Aubry, P. Hartmann and M. Lemoine, *Bull. Soc. Chim.* 636 (1950).
[11] F. Šipoš, J. Krupicka, M. Tichý and J. Sicher, *Coll. Czech. Chem. Comm.* **27,** 2079 (1962).
[12] N. L. Allinger and H. M. Blatter, *J. Amer. Chem. Soc.* **83,** 994 (1961).

The resolution of the *trans*-2-methyl-*cis*-4-t-butylcyclohexanol (IV)[11] was effected through its acid phthalate and (−)-α-phenylethylamine. Only one antipode, (+)-IV, was isolated, thus raising an element of uncertainty concerning the optical purity of this alcohol, but this problem could be settled as shown below. Oxidation of the

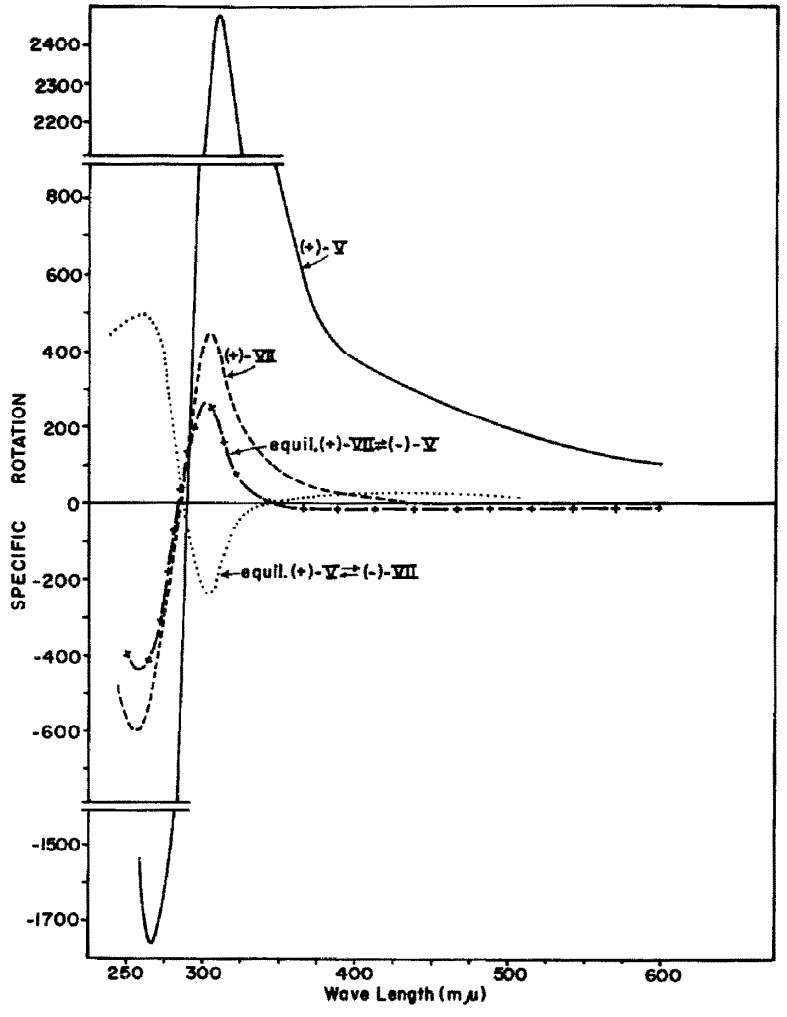


FIG. 1. Optical rotatory dispersion curves (methanol solution) of (+)-*trans*-2-methyl-4-t-butylcyclohexanone ((+)-V) and of (+)-*cis*-2-methyl-4-*t*-butylcyclohexanone ((+)-VII) as well as of their base-catalyzed equilibrium mixtures.

resolved alcohol (+)-IV provided (+)-*trans*-2-methyl-4-t-butylcyclohexanone, the positive Cotton effect (Fig. 1) of which immediately established the absolute configuration[7] in terms of stereoformula (+)-V. The t-butyl substituent will obviously remain in an equatorial orientation[13] and, barring conformational distortion (*vide infra*), will freeze the molecule in conformation V. Since the C-4 substituent should not make

[13] S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.* 77, 5562 (1955).

any significant rotatory contribution,[4] the molecular amplitude of V would yield another value for an axial 2-methyl group. The observed figure, $a + 71$, is in fair agreement with the value, $a + 75$, derived from the rotatory dispersion curve of (+)-*trans*-2,6-dimethylcyclohexanone (IIIA), and again appreciably higher than the originally deduced[4] +56 originating from 2,2,5-trimethylcyclohexanone (IIA).

Resolution of racemic *cis*-5-t-butyl-*trans*-2-hydroxycyclohexanecarboxylic acid[14] through its quinine and ephedrine salts, respectively, produced the two antipodes ($[\alpha]_D$ +22·7° and −22·3°). The (+)-acid was smoothly converted to (+)-*trans*-2-methyl-*trans*-4-t-butylcyclohexanol (VI) in good yield by a modification of the earlier described[11] reaction sequence, i.e. by esterification, reaction with dihydropyran, lithium aluminium hydride reduction, mesylation, repeated lithium aluminium hydride reduction and hydrolysis. Oxidation of the alcohol provided (+)-*cis*-2-methyl-4-t-butylcyclohexanone ((+)-VII) with a positive Cotton effect (Fig. 1), the amplitude ($a + 17·5$) of which was greatly reduced (see Fig. 1) after equilibration with sodium methoxide in methanol solution. Similar equilibration of *trans*-2-methyl-4-t-butylcyclohexanone ((+)-V) led to an isomer mixture with a negative Cotton effect (Fig. 1) but possessing an amplitude virtually identical with that of the equilibration mixture of the *cis* ketone (+)-VII.

The composition of the equilibrium mixture was determined in each instance by gas phase chromatography as well as by the use of the Cotton effect molecular amplitudes, the amplitudes of (+)-V and of (+)-VII being taken as reference values, since gas phase chromatography has demonstrated that they were not contaminated with each other. The equilibration of the *trans* ketone V yielded values of 6·2% (chromatographic) and 6·0% (O.R.D.) *trans* ketone remaining, while virtually identical results—6·0% (chromatographic) and 6·4% (O.R.D.)—were observed with the *cis*-isomer VII. These conclusions coincide with the earlier reported[12] 94·13% (*cis*)–5·87% (*trans*) composition of the base-catalyzed equilibration of the racemic ketones, using gas phase chromatography as the analytical tool. Three important conclusions can be reached from the rotatory dispersion results summarized in Fig. 1.

First, the fact that base-catalyzed equilibration of the *trans* ketone (+)-V and of the *cis* ketone (+)-VII gives rotatory dispersion curves of opposite sign, demonstrates that they belong to antipodal series. Since the strongly positive rotatory dispersion curve of (+)-V leads, according to the octant rule,[4] to the clear-cut absolute configurational assignment implicit in stereoformula[7] (+)-V, it follows automatically that the (+)-*cis* ketone and its precursor alcohol can be assigned absolute configurations (+)-VII and (+)-VI.

Second, the optical purity of the (+)-*trans*-2-methyl-*trans*-4-t-butylcyclohexanol (VI) had been assured, as both antipodes of the precursor acid were obtained with identical rotations but of opposite sign. Since the rotatory dispersion amplitude of the equilibrium mixture derived from the *trans* ketone (+)-V was nearly identical (see Fig. 1) with that of the *cis*-ketone equilibration mixture, one can conclude that the *trans*-2-methyl-4-t-butylcyclohexanone ((+)-V) is of practically equal optical purity. This conclusion is important if the molecular amplitude of the trans ketone (+)-V is going to be used for reference purposes as far as the rotatory contribution of an axial 2-methyl group is concerned.

[14] J. Sicher, F. Šipoš and M. Tichý, *Coll. Czech. Chem.* **26**, 847 (1961).

Third, the octant rule[4] would predict[15] a virtually negligible Cotton effect for *cis*-2-methyl-4-t-butylcyclohexanone in the chair conformation (VII). In point of fact, a positive Cotton effect of substantial amplitude (a + 17·5) has been noted (Fig. 1), which we consider to be indicative of conformational deformation from the ideal chair form. The extent and nature of this distortion cannot be deduced at present from the rotatory dispersion curve, but it is pertinent to recall that other authors have already emphasized caution[16] in assuming an undisturbed chair conformation in the presence of a t-butyl substituent. This would suggest that the bulky t-butyl group is responsible for any distortion and consequently we have also examined the 2,4-dimethylcyclohexanones (XI, XII).

For this purpose, the thermal degradation[17] of cycloheximide (actidione) was repeated and the resulting (+)-*trans*-2,4-dimethylcyclohexanone (XI) of established[18] absolute configuration was purified by gas phase chromatography. The observed amplitude (a + 35)[19] of its positive Cotton effect is nearly one-half of that (+67) assigned below to a 2-axial methyl group, thus indicating an approximately equal mixture of the two conformers XIA and XIB, the 1,3-diaxial methyl-hydrogen interactions of which are equal in number. It should be noted that this conclusion is based on the assumption[4,15] that the equatorial methyl group in XIB does not contribute significantly to the amplitude, a point which is explored further below.

The rotatory dispersion curve of the more relevant (−)-*cis*-2,4-dimethylcyclohexanone (XII) had been measured[18] on material which has recently been shown[17] to contain 10·5% of the *trans* (XI) isomer. Purification by gas phase chromatography and redetermination of the negative Cotton effect has now yielded the remarkably large negative amplitude of a −16·5, which is nearly identical in magnitude, but opposite in sign, with that (a +17·5) of the antipodal *cis*-2-methyl-4-t-butylcyclohexanone ((+)-VII). We must conclude, therefore, that whatever conformational distortion exists in these molecules, it is not necessarily associated with the size of the C-4 substituent (t-butyl *vs.* methyl) and that *the presence of two* 1,3-*diequatorial alkyl groups plays the dominant role.*

The 94% *cis*–6% *trans* composition of the base-catalyzed equilibration of 2-methyl-4-t-butylcyclohexanone led Allinger and Blatter[12] to the conclusion that the "2-alkyl ketone effect" is negligible in 2-methylcyclohexanones.[20] Our present observations indicate that this conclusion is based on a model which departs to an unknown extent from the chair conformation. However, in view of the complementary data of Rickborn[21] in the equilibration of racemic 2,6-dimethylcyclohexanone (91·5% *cis*: 8·5% *trans* (III)) it still appears reasonable that the "2-methyl ketone effect" is insignificant, although the ideal model has not yet been found.

[15] The extremely small contribution of an equatorial 2-methyl group is derived from measurements in the steroid series as summarized in Table 1 of ref. 5*e*.

[16] E. Eliel, *J. Chem. Educat.* **37,** 126 (1960); W. Hückel and M. Hanack, *Liebigs Ann.* **616,** 18 (1958) and subsequent articles.

[17] B. C. Lawes, *J. Amer. Chem. Soc.* **84,** 239 (1962).

[18] E. J. Eisenbraun, J. Osiecki and C. Djerassi, *J. Amer. Chem. Soc.* **80,** 1261 (1958).

[19] The earlier (ref. 17) rotatory dispersion measurement did not cover both extrema of the Cotton effect and was performed on a mixture of *trans* (XI) and *cis* (XII) isomers.

[20] This suggestion was first made by L. F. Fieser and M. Fieser (*Steroids*, p. 213. Reinhold, New York, 1959) by the use of Dreiding models.

[21] B. Rickborn, *J. Amer. Chem. Soc.* **84,** 2414 (1962).

The existence of conformational distortion in *cis*-2-methyl-4-t-butylcyclohexanone (VII) immediately raises a question about the validity to employ its *trans* isomer V or *trans*- 2,6-dimethylcyclohexanone (IIA) as proper models for determining the rotatory contribution of an axial 2-methyl group in the *chair* conformation of a cyclohexanone. In view of the analysis in the introductory section of this article, there seems little doubt that the original value[4] of $a = 56$ is too low. Conversely, the value of $a = 75$ and 71 derived from the rotatory dispersion curves of IIIA and (+)-V may be too high if one assumes the existence of a certain proportion of the twist form (e.g. IIIB) which would make[5c] a strongly positive contribution and thus might lead to an artificially high value. Perhaps the most realistic figure ($a = 67$) is derived from a subtraction of the molecular amplitude of *trans*-1-decalone (VIII)[22] from that[23] of *trans*-9-methyl-1-decalone (IX), which suggests that only a small amount of twist form[5c] enters into the conformational picture of the ketones IIIA and V.

If a value of $a \sim 67$ is used as the contribution of an axial 2-methyl group in the chair form of a cyclohexanone, then serious departures from such a figure can be used as *prima facie* evidence for conformational distortion or presence of other forms in a conformational equilibrium. The recently summarized[5e] amplitude values for numerous steroid ketones and their alkylated analogs lead to a range of $a = 25 - 34$ for the introduction of an adjacent axial methyl group (positions 2β or 4β) in 3-keto-5α-steroids, which on the above outlined premise would point toward deformation of ring A. This seems reasonable, since in each case there exists a serious 1-3 diaxial methyl-methyl interaction involving the angular methyl group and it is noteworthy that NMR studies[24] with the corresponding acetoxy 3-keto steroids also demonstrated the existence of conformational distortion in the axial 2β-acetoxycholestan-3-one.

It is necessary to compare the presently observed amplitude values of 16·5 and 17·5 from *cis*-2,4-dimethylcyclohexanone (XII) and *cis*-2-methyl-4-t-butylcyclohexanone (VII) with that ($a + 12$) recorded recently[25] for (+)-2-methylcyclohexanone (X). The diaxial conformers (e.g. XIIB) of XIIA or VII obviously will not contribute measurably to the conformer equilibrium and therefore only two conclusions can be drawn from the substantial amplitude values ($a \sim 17$) of these two disubstituted cyclohexanones.

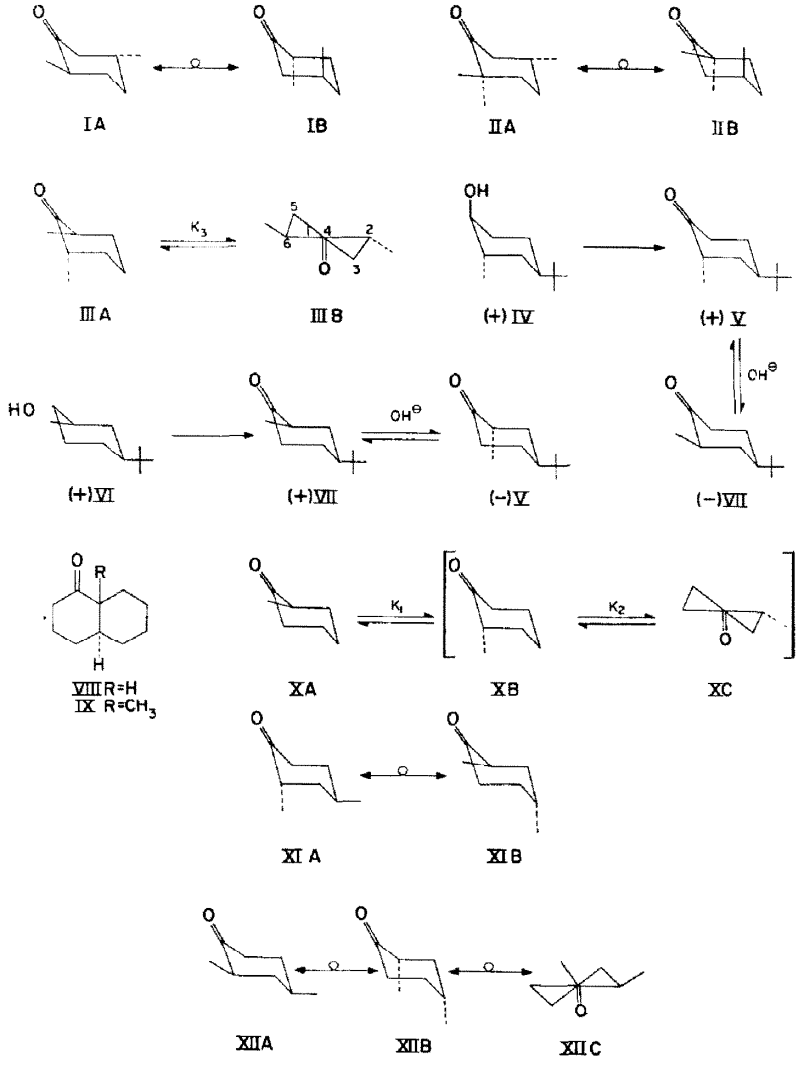
First, the equatorial 2-methyl substituent actually makes a rotatory amplitude contribution of considerable magnitude ($a \sim 17$) in contrast to the earlier assumptions of the octant rule.[4,15] If this were true, then the $a + 17$ value would have to be the minimum amplitude value for (+)-2-methylcyclohexanone (XA), since its axial conformer (XB) has a much larger amplitude. In point of fact, the observed amplitude amounts to only +12,[25] thus leading to the inevitable second conclusion that at least part of the Cotton effect amplitudes of the two *cis*-2,4-dialkyl cyclohexanones VII, XIIA) must be associated with a conformational departure from the chair form. The factors responsible for such deformation must be rather subtle in origin, but it should be noted that contributions by the appropriate twist[5] form (e.g. XIIC) to the conformer equilibrium would lead to rotational values of the right sign.

However, if (+)-2-methylcyclohexanone (X) exists to a considerable extent in the

[22] C. Djerassi and J. Staunton, *J. Amer. Chem. Soc.* **83,** 736 (1961).
[23] C. Djerassi, E. Lund and A. A. Akhrem, *J. Amer. Chem. Soc.* **84,** 1249, footnote 23 (1962).
[24] K. L. Williamson and W. S. Johnson, *J. Amer. Chem. Soc.* **83,** 4623 (1961).
[25] C. Beard, C. Djerassi, T. Elliott and R. C. C. Tao, *J. Amer. Chem. Soc.* **84,** 874 (1962).

twist form XC,[25] then one would expect (+)-*trans*-2,6-dimethylcyclohexanone (III) to exist in the corresponding form (IIIB) to approximately the same extent (i.e., $k_2 \cong k_3$) as does XC in the conformational equilibrium XB and XC, because the additional equatorial methyl group in IIIA should not exert much influence. If this supposition is granted, then an inconsistency arises when the Cotton effect contribution of XA is assumed to be zero:

Putting $k_1 \cong 19$ (i.e. $\Delta F - 1{\cdot}8$ kcal./mole),[21] there is only 5% of the non-equatorial form present. If XA makes no contribution to the observed[25] amplitude (+12), then this 5%, consisting of XB and XC together, has an effective molecular amplitude of *a* +240. Since the twist form IIIB of *trans*-2,6-dimethylcyclohexanone possesses an additional substituent (C-6 methyl group) in a positive octant, its amplitude should be greater than +240, while the observed value is +75.



The above argument hinges on the apparently reasonable supposition that $k_2 \cong k_3$ and, if accepted, can furnish an approximate value for the contribution of an equatorial α-methyl substituent, hitherto assumed[15] to be negligible.[26] Putting the contribution of an axial α-methyl substituent at $a \cong 67$ and assuming no twist form (XC) participation, then $k_1 = 19$ will yield $a = 9$ as the amplitude contribution of such an equatorial methyl substituent. The difficulty with this calculation is that it ignores the very real possibility of a twist form (XC), for which no quantitative values are available, but which should have a much greater rotatory dispersion amplitude[5c] than the corresponding chair form (XB) with an axial methyl group. To the extent that the twist form XC participates, the amplitude value of an equatorial methyl group becomes smaller than $a = 9$ (to be considered a probable maximum value) and a firm decision on this subtle point can be reached only by the synthesis of an optically pure and conformationally rigid model compound.

In conclusion, the present studies define within relatively narrow limits the rotatory amplitude contribution of an axial 2-methyl substituent in a cyclohexanone and they also demonstrate the hitherto unrecognized existence of some conformational distortion in *cis*-2,4-dialkylcyclohexanones. While an equatorial methyl group makes, in any event, a rather small contribution, which can be ignored in the usual[4,5d] qualitative applications of the octant rule, its precise value is of some significance in employing rotatory dispersion as an indicator of small conformational deviations.

EXPERIMENTAL[27]

(+)-2-*Methylcyclohexanone* (X). (+)-*Trans*-2-methylcyclohexanol methyl tri-O-acetyl-β-D-glucosiduronate (200 mg)[25,28] was heated under reflux for 3 hr with 10 cc 1N HCl. The resulting clear yellow solution was cooled and neutralized by the addition of solid sodium bicarbonate, then extracted with four 3 cc portions ether. The combined extracts were dried and evaporated at 25°/150 mm to leave a residue of 59 mg (+)-*trans*-2-methylcyclohexanol,[25,29] which was dissolved in acetone (1·5 cc) and oxidized at 0° in the presence of anhydrous magnesium sulfate with 8N chromic acid solution.[30,31] Dropwise addition of a slight excess of the oxidizing solution required 10 min and the mixture was stirred at 0° for a further 3 min before being neutralized with solid sodium bicarbonate. The mixture was diluted with ether, dried and the ether evaporated at 25°/150 mm. The residual crude ketone (30 mg) was redistilled at 25° under red. press. to yield 24 mg pure (+)-2-methylcyclohexanone (X), $\lambda_{max}^{CHCl_3}$ 5·85 μ, which exhibited only one peak (retention time 4·5 min on a Craig succinate column operated at 100°) in a gas phase chromatogram. R. D. in methanol (*c*, 0·23): $[\alpha]_{589}$ +14°, $[\alpha]_{305}$ +515°, $[\alpha]_{265}$ −565°, $[\alpha]_{240}$ −274°, remained unchanged upon storage in methanol solution for at least 5 days.

[26] A recent estimate (ref. 4) of the angle between the carbonyl plane and the bond connecting the equatorial α-methyl substituent in cyclohexanone amounts to 4°3′. While the equatorial substituent thus lies nearly in the nodal plane, it does not do so entirely and a finite contribution on the part of methyl group may, therefore, be expected.

[27] M.P.s were determined on a Kofler block. The optical rotatory dispersion curves were determined by Mrs. Ruth Records on a Nippon Bunko (Japan Spectroscopic Co.) automatically recording spectropolarimeter model ORD-2. Gas phase chromatography was performed with a Wilkens Hy–Fi or a CHROM 1 gas chromatography apparatus.

[28] Kindly supplied by Prof. T. Elliott and Dr. R. C. C. Tao of the Department of Pharmaceutics, University of Singapore.

[29] G. A. L. Gough, H. Hunter and J. Kenyon, *J. Chem. Soc.* 2052 (1926).

[30] K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.* 39 (1946).

[31] In our experience (see G. Ohloff, J. Osiecki and C. Djerassi, *Chem. Ber.* **95**, 1400 (1962)) this method of oxidation does not cause any perceptible epimerization.

(+)-Trans-2,6-*dimethylcyclohexanone* (III). (+)-*Trans*-2,6-dimethylcyclohexanol (50 mg, $[\alpha]_D$ +43·2°, kindly supplied by Prof. Cornubert[10]) was dissolved in 3 cc acetone and oxidized exactly as described above to furnish 35 mg crude ketone, which, upon redistillation at 25°/0·1 mm, led to 22 mg pure ketone, $\lambda_{max}^{CCl_4}$ 5·82 μ. Gas phase chromatography on a Craig succinate column at 113° showed that the ketone (retention time 11 min) was free of alcohol (retention time 17 min). R.D. in methanol (*c*, 0·11): $[\alpha]_{589}$ +130°, $[\alpha]_{310}$ +3160°, $[\alpha]_{272}$ −2800°, $[\alpha]_{255}$ −2080°, unchanged upon standing in methanol solution for 3 months. A second oxidation experiment provided ketone with exactly the same molecular amplitude, thus indicating the unlikelihood of racemization occurring during the oxidation.

(+)-Trans-(XI) and (−)-Cis-(XII) 2,4-*Dimethylcyclohexanone*.[17] Cycloheximide (kindly supplied by the Upjohn Company, Kalamazoo, Michigan) was pyrolyzed according to the directions of Lawes[17] and the resulting (+)-*trans*-2,4-dimethylcyclohexanone (XI) was purified by preparative gas phase chromatography at 95° on a 6 ft. Carbowax 20M-firebrick column and distilled at 25°/0·1 mm. The material used for optical rotatory dispersion measurements contained less than 1% of the *cis* isomer. R. D. in methanol (*c*, 0·21): $[\alpha]_{589}$ +48°, $[\alpha]_{308}$ +1446°, $[\alpha]_{263}$ −1304°, $[\alpha]_{240}$ −780°.

Base-catalyzed equilibration of the *trans* isomer XI, by heating under reflux for 15 min in 1N methanolic potassium hydroxide solution, followed by gas phase chromatographic purification and distillation afforded (−)-*cis*-2,4-dimethylcyclohexanone (XII), which contained less than 1% of the *trans* isomer. R. D. in methanol (*c*, 0·45): $[\alpha]_{589}$ 0°, $[\alpha]_{304}$ −623°, $[\alpha]_{256}$ +690°, $[\alpha]_{240}$ +490°.

Resolution of trans-2-*methyl*-cis-4-t-*butylcyclohexanol* (IV)

Acid phthalate of trans 2-*methyl*-cis-4-t-*butylcyclohexanol*. A solution of *trans*-2-methyl-*cis*-4-t-butylcyclohexanol[11] (3·0 g) and phthalic anhydride (2·6 g) in dry pyridine (3 cc) was heated for 6 hr to 105°. The usual isolation procedure, followed by crystallization from benzene, afforded 4·4 g (78%) of the acid phthalate, m.p. 134–135·5°. (Found: C, 71·59; H, 8·09, $C_{19}H_{26}O_4$ requires: C, 71·67; H, 8·23%).

Resolution with (−)-α-*phenylethylamine*. A hot solution of the acid phthalate (4·2 g) in 30 cc acetone was treated with a hot solution of (−)-α-phenylethylamine (1·6 g) in acetone (5 cc). The precipitated salt after 4 crystallizations from ethanol had $[\alpha]_D^{23}$ +23·3° (*c*, 3·00, ethanol), yield 0·9 g (Found: C, 73·82; H, 8·60; N, 3·04. $C_{27}H_{37}NO_4$ requires: C, 73·77; H, 8·48; N, 3·19%). Acidification of the salt afforded 0·55 g of the (+)-acid phthalate, m.p. 139–139·5° (benzene), $[\alpha]_D^{22}$ +38·0° (*c*, 6·0, ethanol). (Found: C, 71·77; H, 8·03. $C_{19}H_{26}O_4$ requires: C, 71·67; H, 8·23%).

The (+)-acid phthalate (0·55 g) was taken up in 20% aqueous sodium hydroxide (5 cc) and the solution steam distilled. (+)-*Trans*-2-methyl-*cis*-4-t-butylcyclohexanol (IV), isolated from the distillate in the usual manner was purified by sublimation at 12 mm to yield 0·25 g fine needles, m.p. 81·5–82·5°, $[\alpha]_D$ +36° (*c*, 1·9 chloroform), homogeneous by gas phase chromatography. (Found: C, 77·57; H, 12·85. $C_{11}H_{22}O$ requires: C, 77·59; H, 13·02%).

(+)-Trans-2-*methyl*-4-t-*butylcyclohexanone* (V). The above resolved alcohol IV (34 mg, $[\alpha]_D$ +36°) in 1·5 cc acetone (freshly distilled from permanganate) was treated at 0° with 0·2 cc 6N chromic acid solution (0·2 mole chromium trioxide and 0·3 mole sulfuric acid diluted with water to 100 cc) and vigorous stirring continued at that temp. for 6 min. The solution was diluted with ether, poured into ice cold dil. sodium bicarbonate solution and the ether layer washed with water, dried and evaporated at 25°/20 mm. Distillation of the residual oil at 45°/0·1 mm gave 31 mg ketone V, $\lambda_{max}^{CHCl_3}$ 5·86 μ. Gas phase chromatography on a diethyleneglycol succinate column at 116° indicated the presence of less than 1% of unchanged alcohol (retention time 14 min) or *cis*-ketone (retention time 9·5 min as compared to 10·5 min for the *trans*-isomer). The trace of *cis*-ketone (−)-VII may well have been produced by isomerization on the column. R. D. (Fig. 1) in methanol (*c*, 0·14): $[\alpha]_{589}$ +117°, $[\alpha]_{310}$ +2482°, $[\alpha]_{266}$ −1752°, $[\alpha]_{250}$ −1197°.

A sample (23 mg) of the *trans* isomer (+)-V was heated under reflux for 3 hr with 2 cc methanol and 34 mg sodium. The solvent was removed at 25°/20 mm, water was added and the product was extracted with ether. Evaporation of the washed and dried ether solution followed by distillation of the residual oil at 0·1 mm provided 12 mg of the equilibrated ketone, gas phase chromatography (diethyleneglycol succinate column) of which indicated the presence of 6·2% of *trans* isomer V, the remainder corresponding to the *cis* ketone VII. R. D. (Fig. 1) in methanol (*c*, 0·15): $[\alpha]_{589}$ +6°, $[\alpha]_{303}$ −238°, $[\alpha]_{260}$ +491°, $[\alpha]_{240}$ +446°.

Resolution of trans-2-*hydroxy*-cis-5-t-*butylcyclohexane-carboxylic acid*[11]

A hot solution of the acid (48 g, 0·24 mole) in acetone (250 cc) was treated with a hot solution of quinine (78 g, 0.24 mole) in acetone (900 cc), the solution allowed to cool, the crystals filtered off and recrystallized 6 times from methyl ethyl ketone to yield 27·0 g quinine salt as filtered needles, m.p. 173·5–174°, $[\alpha]_D^{25}$ −112° (*c*, 4·96, ethanol). (Found: N, 5·27, $C_{31}H_{44}N_2O_5$ requires: N, 5·34%). Treatment of the quinine salt with 1:1 aqueous hydrochloric acid afforded the (+)-antipode of the acid, m.p. 171–172° (ethyl acetate); $[\alpha]_D^{24}$ +22·7° (*c*, 6·00, ethanol); yield 8·05 g (Found: C, 65·89; H, 9·90. $C_{11}H_{20}O_3$ requires: C, 65·97; H, 10·07%).

The combined mother liquors from the crystallization of the quinine salt were taken to dryness, the liberated acid (20·6 g) taken up in acetone (140 cc) and treated with a solution of ephedrine (17·0 g) in acetone (20 cc). The ephedrine salt, after crystallization, alternately from acetonitrile and methyl ethyl ketone, afforded 8·0 g of material, m.p. 159–162°, $[\alpha]_D^{22}$ −32·4° (*c*, 4·01, ethanol). (Found: C, 69·97: H, 9·64. $C_{21}H_{35}O_4$ requires: C, 69·0; H, 9·65%). Decomposition of the salt afforded the (−) antipode of the acid, m.p. 171–172° (ethyl acetate), $[\alpha]_D^{23}$ −22·3° (*c*, 6·00, ethanol).

(+)-Trans-2-*methyl*-trans-4-t-*butylcyclohexanol* (VI). The (+)-antipode of the above acid (5 g) was converted to the methyl ester by treatment with ethereal diazomethane. According to gas phase chromatography the crude product contained about 3% of the O-methyl ether. Low temperature crystallization from pentane afforded 4·7 g (88%) of the pure ester, m.p. 85–86° which was taken up in dihydropyran (10 cc) containing a catalytic amount of ethereal hydrogen chloride and the solution allowed to stand overnight. The tetrahydropyranyl derivative which was isolated in the usual manner was found to contain a considerable amount of the starting hydroxy-ester. The procedure was therefore repeated and the product distilled, the fraction, b.p. 135°/0·2 mm, 5·4 g (82%) being collected. The I.R. spectrum contains no hydroxyl band. (Found: C, 68·53; H, 10·04. $C_{17}H_{30}O_4$ requires: C, 68·42; H, 10·13%).

The tetrahydropyranyl derivative (5·4 g) was refluxed for 1 hr with 25 cc of an ethereal solution containing 1·2 g lithium aluminum hydride. The reaction mixture was decomposed with aqueous sodium hydroxide, the crude product obtained by the usual isolation procedure was taken up in pyridine (20 cc), treated with methanesulfonyl chloride (3·0 g) and the mixture allowed to stand for 1 hr at room temp. The usual isolation procedure afforded 6·1 g mesylate in the form of an oil containing traces of pyridine.

This crude product was taken up in a solution of tetrahydrofuran (50 cc), containing 1·6 g lithium aluminum hydride, and kept under reflux for 2 hr. The greater part of the solvent was then distilled off, the residue decomposed with dil. hydrochloric acid and the product taken up in ether. The crude reaction product was heated under reflux with 1:1 aqueous hydrochloric acid (20 cc) and ethanol (10 cc) for 30 min, the solution diluted with water and extracted with pentane. The residue obtained from the pentane extracts was chromatographed on alumina (grade II–III). The benzene and benzene-ether eluates contained the pure alcohol IV, as shown by gas phase chromatography. The combined pure fractions were sublimed at 0·3 mm to yield 1·75 g fine needles, m.p. 46–48°, $[\alpha]_D$ +18° (*c*, 2·3, chloroform). (Found: C, 77·67; H, 12·97. $C_{11}H_{22}O$ requires: C, 77·59; H, 13·02%). The overall yield of the sequence acid to alcohol is 41%.

(+)-Cis-2-*Methyl*-4-t-*butylcyclohexanone* (VII). The oxidation of 34 mg alcohol VI ($[\alpha]_D$ +18°) was performed exactly as described above for the isomer IV (except that the reaction time was doubled) and provided 29 mg required ketone (+)-VII, $\lambda_{max}^{CHCl_3}$ 5·86 μ, which contained ca. 2% of unreacted alcohol as determined by gas phase chromatography. R. D. (Fig. 1) in methanol (*c*, 0·13): $[\alpha]_{589}$ 0°, $[\alpha]_{304}$ +448°, $[\alpha]_{258}$ −598°, $[\alpha]_{245}$ −500°. The base equilibration was conducted precisely as reported for the *trans* ketone (+)-V and led to a ketone mixture, which according to gas phase chromatography consisted of 6% *trans* and 94% *cis* ketones. R. D. (Fig. 1) in methanol (*c*, 0·18): $[\alpha]_{589}$ −11°, $[\alpha]_{303}$ +269°, $[\alpha]_{256}$ −437°, $[\alpha]_{250}$ −412°.