Optical Rotatory Dispersion Studies. C.[1]
Variable-Temperature Circular Dichroism Studies of Ring-Conformational and Rotational Equilibria in Cyclohexanones[2]

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Conformational changes involving interconversion between chair conformers and deformed and/or flexible forms in a variety of cyclohexanones have been investigated by means of variable-temperature circular dichroism (C.D.) measurements. It has been found that distortion of ring A in 1α- and 1β-methyl-5α-dihydrotestosterone acetate is removed when the bulky C-1 methyl group is replaced by a cyano function. Restricted rotation in 2-isopropylcyclohexanones is discussed in terms of the temperature-dependent C.D. curves. Analysis of the C.D. data of 2β-isopropyl-19-nor-5α-androstan-3-one (XI) over the range +25 to −192° indicates that the molecule is conformationally homogeneous. Of the simple 2-alkylcyclohexanones investigated, (+)-2-methylcyclohexanone (XII) and (+)-2-t-butylcyclohexanone (XIV) are unusual in that the rotational strength of the former is temperature independent (+25 to −192°) in contrast to that of the latter which exhibits a temperature dependence. Librations of the t-butyl group about its low energy, staggered conformation may account for the temperature coefficient of the C.D. curves for XIV, although a solvational equilibrium cannot be ruled out. The temperature- and solvent-dependent C.D. curves of 2-oxo-1-p-menthanol (XVI) were measured, and they were found to exhibit a multiple Cotton effect. The temperature studies are interpreted in terms of an equilibrium between the two chair forms XVIa and XVIb over the range of +25 to −192° in EPA and P5M1, although the situation appears more complex at higher temperatures in decalin. Measurements in various solvents indicate that conformer XVIb has an intramolecular hydrogen bond at room temperature.

The composition of an observed circular dichroism curve consists of the Cotton effect contributions of all the species present. In terms of the measure of molecular dissymmetry, the rotational strength $(R_0{}^T)$,[4,5] the C.D. curve is composed of the population-weighted rotational strength contributions of each species (a through n) present as indicated in eq. 1.

$$R_0{}^T = N_aR_a + N_bR_b + \cdots + N_nR_n \qquad (1)$$

The experimental rotational strength of such a system is conveniently measured[5] by the wave-length weighted area under the C.D. band for the spectroscopic transition of interest according to eq. 2, where $[\theta]$ is the molecular ellipticity and λ is

$$R_0{}^T \cong 0.696 \times 10^{-42} \int_{\lambda_1}^{\lambda_2} \frac{[\theta]}{\lambda} \, d\lambda \qquad (2)$$

the corresponding wave length. If the system in question involves an equilibrium between two or more of the species present, the observed rotational strength will be temperature dependent. For the special case where a two-species equilibrium is involved and the entropy change is zero, the relation[6] between the observed rotational strength and the rotational strengths $(R_a$ and $R_b)$ of the a and b forms is given in eq. 3.

$$R_0{}^T = (R_a - R_b)\left(\frac{1}{1 + e^{-\Delta G/NkT}}\right) + R_b \qquad (3)$$

The development of a low-temperature cell[7] and, more recently, a high-temperature cell[8] for measuring temperature-dependent circular dichroism curves has greatly extended the utility of such measurements for studies of equilibria in solution. Thus, variable-temperature measurements have provided quantitative data on conformer populations of (+)-*trans*-2-chloro-5-methylcyclohexanone.[6] On the other hand, many cases are sufficiently complicated so that a quantitative treatment, as was utilized in the simple conformer equilibrium of the α-chloro ketone, cannot be performed. In such cases eq. 3 is often inapplicable because of complicating solvent effects[9] or occurrence of unexpected conformers.

Ring-Conformational Equilibria in 3-Keto Steroids. The conformational homogeneity of 5α-cholestan-3-one (I) in EPA solvent over the temperature range of 25 to −192° has been demonstrated.[7] Furthermore, it has now been found that the rotational strength of I is temperature independent up to 132° $(R_0{}^{25} = +2.48 \times 10^{-40}$ and $R_0{}^{132} = +2.38 \times 10^{-40}$ c.g.s.) in decalin. 5α-Androstan-3β-ol-17-one $(R_0{}^{25} = +9.70 \times 10^{-40}$ and $R_0{}^{164} = +9.45 \times 10^{-40}$ c.g.s.) and (+)-camphor $(R_0{}^{25} = +4.55 \times 10^{-40}$ and $R_0{}^{164} = +4.93 \times 10^{-40}$

(1) Paper XCIX: K. M. Wellman, P. H. A. Laur, W. S. Briggs, A. Moscowitz, and C. Djerassi, *J. Am. Chem. Soc.*, 87, 66 (1965).

(2) Supported in part by Grants No. GP-1979 and G-19905 from the National Science Foundation.

(3) National Institutes of Health Postdoctoral Research Fellow, 1962–1963.

(4) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960.

(5) For a discussion of rotational strength, see A. Moscowitz, ref. 4, Chapter 12.

(6) A. Moscowitz, K. M. Wellman, and C. Djerassi, *J. Am. Chem. Soc.*, 85, 3515 (1963).

(7) K. M. Wellman, E. Bunnenberg, and C. Djerassi, *ibid.*, 85, 1870 (1963).

(8) A description of the high-temperature cell will be reported in a subsequent paper. It suffices now to note that the raw circular dichroism data were corrected for concentration changes but not by a $(n^2 + 2)/3$ Lorentz-type correction in accordance with our previous findings (see footnote 8 in ref. 6).

(9) (a) A. Moscowitz, K. M. Wellman, and C. Djerassi, *Proc. Natl. Acad. Sci. U. S.*, 50, 799 (1963); (b) C. Coulombeau and A. Rassat, *Bull. soc. chim. France*, 2673 (1963).
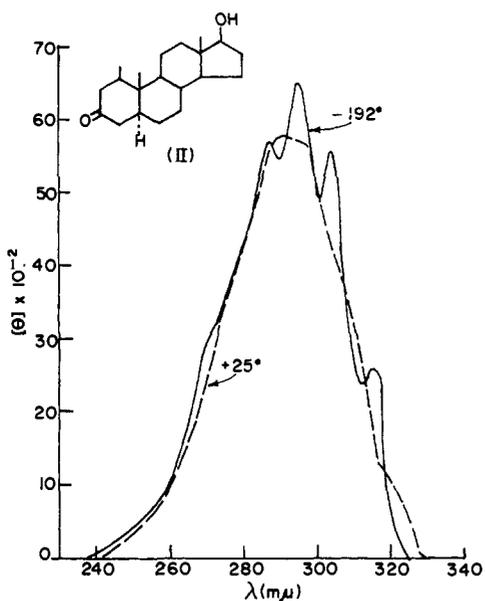
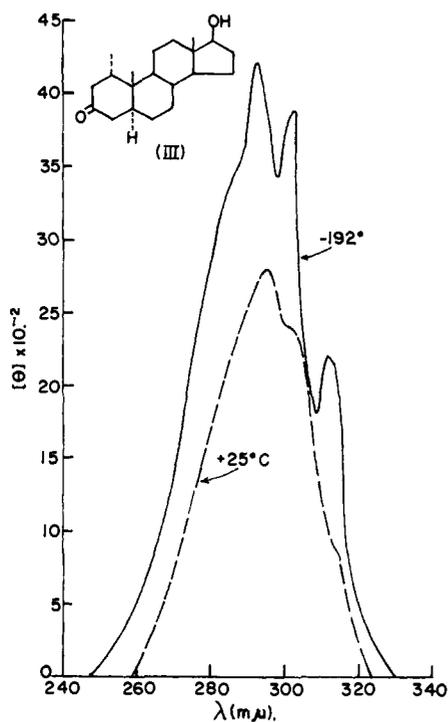Figure 1. Circular dichroism curves of 1β-methyl-5α-dihydro-testosterone (II) in EPA at +25 and −192°

Figure 2. Circular dichroism curves of 1α-methyl-5α-dihydro-testosterone (III) in EPA at +25 and −192°.

The room temperature optical rotatory dispersion (O.R.D.) curve of 1β-methyl-5α-dihydrotestosterone (II) has been commented upon previously,[10] and it seemed appropriate to look at its temperature-dependent C.D. curves as well as that of its 1α-isomer III. In agreement with the earlier O.R.D. work,[10] 1β-methyl-5α-dihydrotestosterone (II, Figure 1) shows a large increase in rotational strength over 5α-cholestan-3-one (I) ($R_0{}^{25}$ = +5.52 × 10^{-40} and +3.31 × 10^{-40} c.g.s. in EPA, respectively) even though the 1β-methyl group -would be expected to make a negative contribution on the basis of the octant rule.[11] Deformation of ring A from a chair toward a positively rotating twist form because of an unfavorable steric interaction between the 1β-methyl and the 11-methylene hydrogen atoms seems most reasonable.[10] It is equally interesting to note that the liquid nitrogen temperature rotational strength ($R_0{}^{-192}$ = +5.75 × 10^{-40} c.g.s.) is virtually unchanged, indicating a fairly static population over this range.
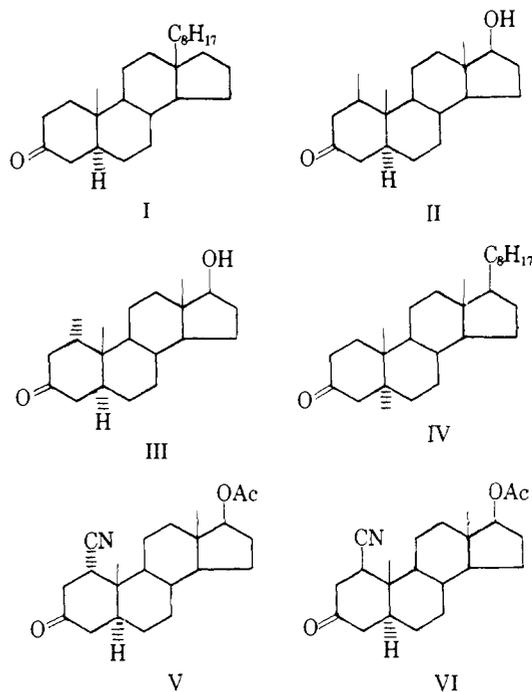
1α-Methyl-5α-dihydrotestosterone (III) and the enantiomerically substituted analog, 5α-methylcholestan-3-one (IV), would be expected to exhibit a decreased and an increased rotational strength, respectively, over the parent ketone according to the tenets of the octant rule[11] since the new methyl group lies in a negative octant in III and a positive one in IV. This expectation is qualitatively met according to the rotational strength of the 1α-methyl-substituted ketone III (Figure 2) for which $R_0{}^{25}$ = +2.78 × 10^{-40} c.g.s. in EPA [compare with 5α-cholestan-3-one (I) above].[12] However, in contrast to I, the rotational strength of III is temperature dependent ($R_0{}^{-74}$ = +3.13 × 10^{-40} and $R_0{}^{-192}$ = +3.62 × 10^{-40} c.g.s.). It should be noted that at liquid nitrogen temperatures the rotational

c.g.s.) behave in a similar manner in decalin. These findings have a twofold meaning. First, this extends the temperature range over which the A-ring of 5α-3-keto steroids acts as a "rigid" group and, second, it demonstrates that solvation effects of decalin over this high-temperature range appear to be minimal. The latter observation in the case of I is in striking contrast to the results with this substance in isopentane-methylcyclohexane solvent in which a large increase in rotational strength was noted accompanied by a blue shift and loss of fine structure upon lowering the temperature to −192°.[9a]

(10) C. Djerassi, E. Lund, and A. A. Akhrem, *J. Am. Chem. Soc.*, **84**, 1249 (1962).

(11) W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *ibid.*, **83**, 4013 (1961).

(12) The use of 5α-cholestan-3-one (I) as a model for III is legitimate since we have found the rotational strength of 5α-dihydrotestosterone and I to be identical within experimental error.
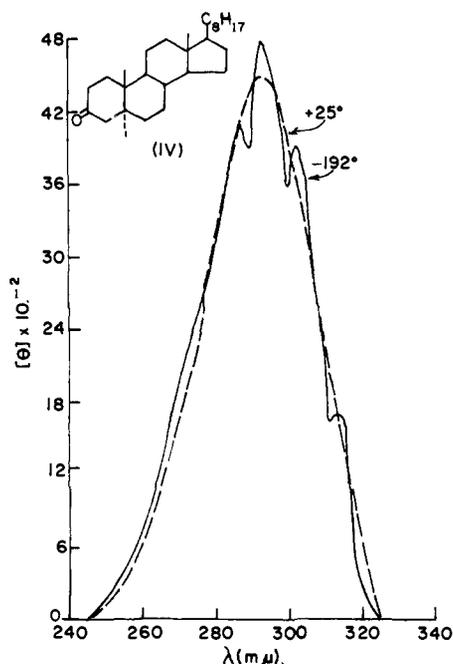
Figure 3. Circular dichroism curves of 5α-methylcholestan-3-one (IV) in EPA at +25 and −192°.

Figure 4. Circular dichroism curves of 1α-cyano-5α-dihydrotestosterone acetate (V) in EPA at +25 and −192°.

strength of III is actually larger than that of I (R_0^{-192} = +3.39 × 10^{-40} c.g.s.), indicating that a species with a positive Cotton effect is making an increasingly stronger contribution at lower temperatures. Assuming that solvational equilibria are not operative, a positively rotating, twist conformation of ring A, which minimizes the nonbonded interactions of the 1α-methyl group and its surroundings, seems likely.

Unlike the 1α-methyl-3-keto steroid III which can alter the 1,3-diaxial interactions not only in ring A but also in ring B by deformations of ring A from a chair toward a twist form, 5α-methylcholestan-3-one (IV) can minimize only ring A interactions but *not* ring B interactions because the 5α-methyl group is forced to remain axial with respect to the latter ring. In accord with this reasoning, IV (Figure 3) shows the expected increase (relative to I) in rotational strength (R_0^{25} = +3.96 × 10^{-40} c.g.s.) which is also temperature independent (R_0^{-192} = +4.10 × 10^{-40} c.g.s.). It would appear then that deformation of ring A to a twist or some other conformation is not attractive from an energy standpoint in the presence of a 5α-methyl substituent. It should be noted that the O.R.D. spectrum of IV has been reported[13,14] and exhibits a Cotton effect amplitude a = 73[14] as compared to a = 54[14] or 55[15] for the parent ketone. This agreement between C.D. and O.R.D. indicates that no appreciable background effect[16] is operating in this instance.

Evidence that the deformation of ring A in III is caused by steric effects was strikingly confirmed when the corresponding cyano compound, 1α-cyano-5α-dihydrotestosterone acetate (V), was investigated. The steric requirements of a cyano group are known

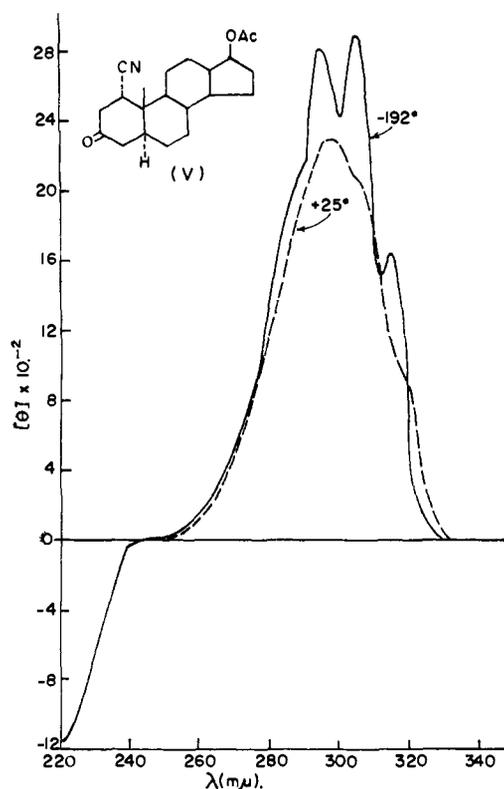to be much smaller than for a methyl group.[17a] Accordingly, it was found that the 1α-cyano group in V makes a negative contribution (R_0^{25} = +2.29 × 10^{-40} c.g.s.) to the rotational strength of the 3-ketone relative to 5α-cholestan-3-one (I), as expected if V exists in a chair conformation. Furthermore, the lack of a temperature-dependent rotational strength (R_0^{-192} = +2.26 × 10^{-40} c.g.s.; see Figure 4) confirms the conformational homogeneity of ring A.

Similarly, 1β-cyano-5α-dihydrotestosterone acetate (VI) showed a reduced rotational strength (R_0^{25} = +3.05 × 10^{-40} c.g.s.) compared with 5α-cholestan-3-one (I), as would be expected with ring A in a chair conformation. Solubility problems with VI prevented low-temperature measurements.

Rotational Isomerism in 2-Isopropyl-3-keto Steroids. Restricted rotation of suitably located alkyl groups lends itself to investigation by variable-temperature C.D. As mentioned in an earlier communication,[7] 2α-methyl-5α-cholestan-3-one (VII) exhibits a constant rotational strength over the low-temperature range. On the other hand, rotational isomerism of the isopropyl group is clearly present in 2α-isopropyl-5α-cholestan-3-one (VIII), as indicated by its rotational strengths: R_0^{25} = +1.53 × 10^{-40}, R_0^{-74} = +1.60 × 10^{-40}, and R_0^{-192} = +2.13 × 10^{-40} c.g.s. A similar result was observed with 2α-isopropyl-19-nor-5α-androstan-3-one (IX) which also displays (Figure 5) temperature-dependent rotational strengths (+1.90, 1.99, and 2.47 × 10^{-40} c.g.s. at +25, −74, and −192°, respectively). The slight increase in rotational strengths

(13) W. Nagata, S. Hirai, H. Itazaki, and K. Takeda, *Ann.*, **641**, 196 (1961).
(14) C. Djerassi and W. Klyne, *J. Chem. Soc.*, 2390 (1963).
(15) C. Djerassi, P. A. Hart, and E. J. Warawa, *J. Am. Chem. Soc.*, **86**, 78 (1964).
(16) C. Djerassi, H. Wolf, and E. Bunnenberg, *ibid.*, **84**, 4552 (1962).

(17) (a) C. Djerassi, R. A. Schneider, H. Vorbrueggen, and N. L. Allinger, *J. Org. Chem.*, **28**, 1632 (1963); N. L. Allinger and W. Szdrybalo, *ibid.*, **27**, 4601 (1962); (b) W. D. Cotterill and M. J. T. Robinson, *Tetrahedron*, **20**, 777 (1964).
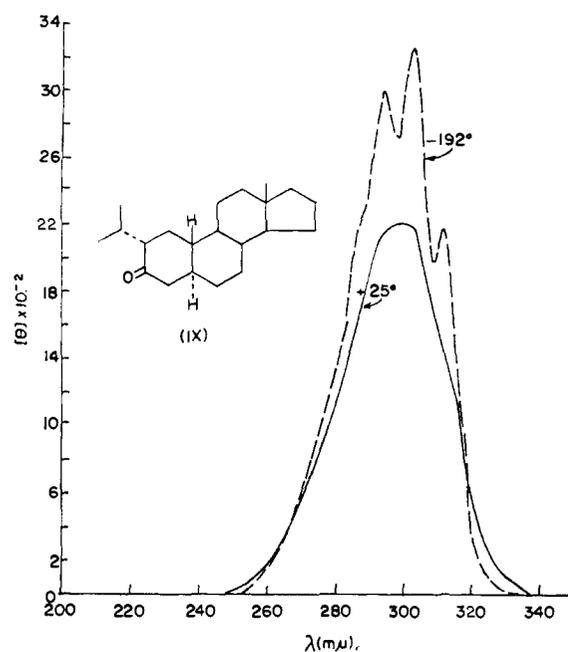
Figure 5. Circular dichroism curves of 2α-isopropyl-19-nor-5α-androstan-3-one (IX) in EPA at +25 and −192°.


of 19-nor-3-keto steroids over the C-10 methylated substances is probably due to distortion of ring A in the latter case owing to the angular methyl substituent. 19-Nor-5α-androstan-3-one ($R_0{}^{25}$ = +3.64 × 10⁻⁴⁰ c.g.s.) also shows a slight rotational strength increase as compared to 5α-cholestan-3-one (see above).

It has been suggested[7] on the basis of the temperature-dependent C.D. data of VIII and IX that, of the three low energy rotamers Xa–c, rotamer Xc was the one of preferred conformation at low temperature. However, this suggestion has been criticized by Cotterill and Robinson[17b] on the grounds that conformational analysis indicated conformer Xb to be energetically preferred. In support of this analysis it was suggested[17b] that the trend in $R_0{}^T$ of VIII was consistent with the relative stabilities being in the order Xb → Xc → Xa. Since the rotational strength of VIII increases upon going to lower temperature, the relative stabilities put forth by Cotterill and Robinson imply that conformer Xb makes a greater positive contribution than Xc.[18]

Assuming the isopropyl group to take a fully staggered position with respect to the remaining groups attached to the C-2 carbon,[17b] the only difference[19] between conformation Xb and Xc is the presence of Me_y in Xb and Me_z in Xc, Me_x being the same in both conformers. Inspection of Dreiding models clearly shows that the Me_y group lies in a front, negative octant[11] and, correspondingly, would be expected to make a negative contribution to the Cotton effect in the light of the octant rule.[11] Conversely, Me_z lies

(18) Because of the severe interactions in conformer Xa between the carbonyl and the methyl groups, we shall assume (as did the previous authors)[17b] that it makes a negligible contribution to the rotamer equilibrium of X.

(19) As a first approximation the tertiary hydrogen atom of the isopropyl substituent in conformers Xb and Xc will be ignored. Its contribution to the rotational strength in each conformer will be just opposite to that of the methyl group, but because it is less polarizable and lies closer to the nodal planes of the carbonyl, its effect will be much smaller.
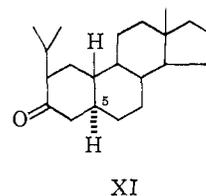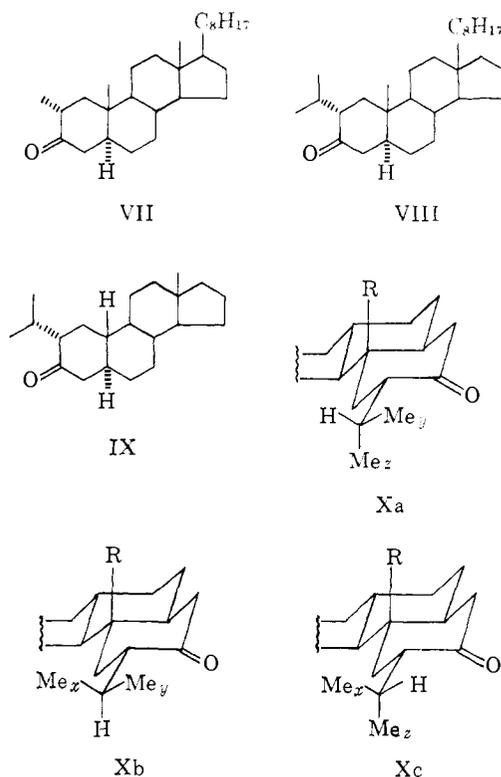
in a front, positive octant or possibly very close to the nodal plane of the carbonyl group. In any event, Me_z in conformation Xc would be expected to make a less negative contribution than the Me_y group in Xb. Thus, the temperature-dependent C.D. curves of 2α-isopropyl-3-keto steroids VIII and X wh ch show (vide supra) an increase in rotational strength upon going to lower temperatures are contradictory to the relative stabilities of Xb and Xc as proposed by Cotterill and Robinson,[20] but are consistent with the order Xc > Xb > Xa.

Sufficient evidence is not yet at hand to determine the discrepancy between the conformational analysis of the previous authors[17b] and the application of the octant rule presented herein. However, two possibilities come to mind. The approximation by Cotterill and Robinson that in the fully staggered conformation Me_y and Me_z in Xb and Xc, respectively, have similar n-skew-butanal interactions (i.e., the interaction between the nonbonding electron pair on the

(20) The suggestion by these authors[17b] that the negative contribution made by the t-butyl group in (−)-2-t-butyl-5-methylcyclohexanone (i) excludes the possibility that Me_y and Me_z are in front octants is incorrect. As mentioned in the present text, Me_y is in a front, negative octant

i
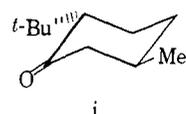
in agreement with the negative contribution of the t-butyl group. The Me_z group is probably in a front octant but its positive contribution is outweighed by the Me_x—C—Me_y atoms, all of which lie in negative octants (for full discussion see ref. 15).
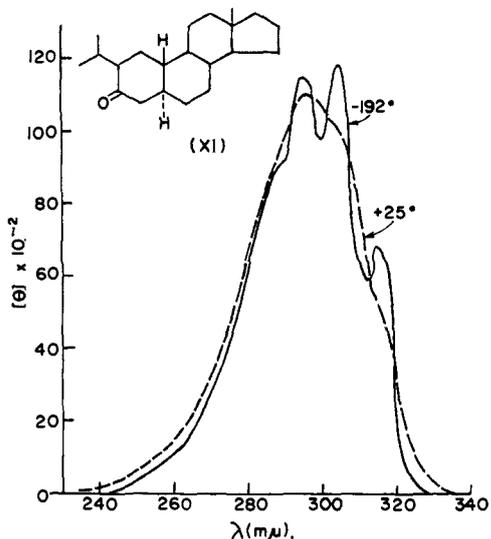
Figure 6. Circular dichroism curves of 2β-isopropyl-19-nor-5α-androstan-3-one (XI) in EPA at $+25$ and $-192°$.

Figure 7. Circular dichroism curves of (+)-2-methylcyclohexanone (XII) in EPA at $+25$ and $-192°$.

carbonyl oxygen and the γ-hydrogens in n-skew-butanal, when the carbonyl group is eclipsing the C-2–C-3 bond) makes the relative energy of conformer Xb too small and that of Xc too large. Dreiding models show that Me$_y$ lies appreciably more in the horizontal nodal plane of the carbonyl than does the Me$_z$ group; hence, the 1-butanal interaction is worse in Xb than in Xc. An estimate of this difference cannot be given, but, in any event, it must be larger than the extra skew-butan interaction present in Xc (but not in Xb) if the conformer energies are to be changed.

The difficulty may also arise in regard to the application of the octant rule in the present cases. Since the nodal plane which defines the front and the rear octants does not pass precisely through the center of the carbonyl chromophore, nor is it strictly a plane,[11] the exact contribution of Me$_z$ in Xc is somewhat in doubt.

In contrast to the complex situation apparent in VIII and IX attributed to different rotamer populations, the variable-temperature C.D. data obtained from 2β-isopropyl-19-nor-5α-androstan-3-one (XI) are more easily interpreted. Provided a chair conformation of ring A is maintained, the rotation of the axial isopropyl group will be restricted. Furthermore, of the three low-energy conformations of the axial isopropyl group, the one with the tertiary hydrogen atom pointing toward C-5 will be highly preferred. The other two conformations will have a methyl group directed toward the center of the ring and van der Waals repulsions similar to those in axial t-butylcyclohexane will arise.

These expectations appear to be justified by the C.D. measurements (Figure 6). Thus, the rotational strength of XI is temperature independent over the low-temperature range ($R_0{}^{25} = +10.3 \times 10^{-40}$ and $R_0{}^{-192} = +9.95 \times 10^{-40}$ c.g.s.) which demonstrates the conformational homogeneity of both ring A and the isopropyl group. Also, the large increase in rotational strength over the parent substance, 19-nor-5α-androstan-3-one, is consistent with a chair conformation of ring A and an axial isopropyl group.

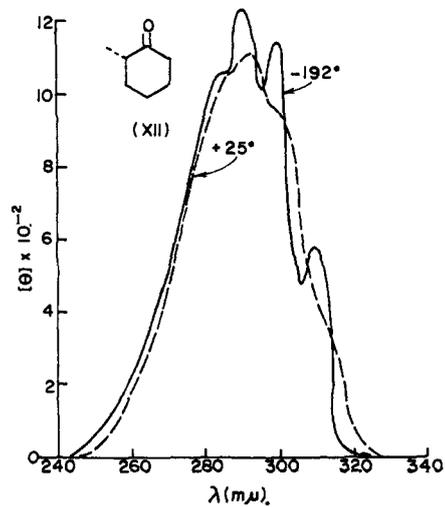*Conformational Equilibria in Simple Cyclohexanones.* Unlike 3-keto-5α-steroids in which ring A can take up

only one chair form and a few specific flexible forms, simple cyclohexanones have a much wider range of conformations available.

One of the simplest such molecules is 2-methylcyclohexanone (XII).[21] The variable-temperature rotational strengths of XII are particularly pertinent because of the discrepancy between Cotton effect amplitudes (a) obtained[21] for the contribution of an equatorial methyl group as in XIIa. These values lie in the range of $a = +9$ to $+17$.

If we accept the most recent determination[22] of the free energy change ($\Delta G = 2.2$ kcal.) in the cis $\rightarrow$ trans epimerization of both 2,5-dimethylcyclohexanone and 2-methyl-5-t-butylcyclohexanone as suitably describing the energy change in the chair–chair transformation XIIa $\rightleftarrows$ XIIb, then it is possible to estimate the per cent change expected in the apparent rotational strength of XII upon lowering the temperature. The accepted Cotton effect amplitude for 2- (axial) methylcyclohexanone (XIIb) is $a = +67$,[21] and the apparent amplitude contribution, when the mole fraction of this conformer is 0.03 (derived from $\Delta G = 2.2$ kcal.), will be 2. Since the mole fraction of XIIa is ca. 0.97, its apparent contribution to the Cotton effect amplitude of XII at room temperature will be about $+9$ or $+17$ depending upon which value is more correct. Accordingly, the apparent amplitude of XII at room temperature will be $+11$ or $+19$, and, since the contribution of the axial conformer XIIb should be negligible at $-192°$, a decrease of about $18\%(2/11)$ or $10\%(2/19)$ in the rotational strength over the range of $+25$ to $-192°$ can be anticipated[23] if only XIIa and XIIb contribute to the conformational equilibrium.

The C.D. curves of XII in EPA at $+25$ and $-192°$ are shown in Figure 7. Measurements were also made at -5, -29, -41, and $-74°$ and in all cases remained

(21) C. Beard, C. Djerassi, J. Sicher, F. Šipoš, and M. Tichy, *Tetrahedron*, **19**, 919 (1963).

(22) W. D. Cotterill and M. J. T. Robinson, *ibid.*, **20**, 765 (1964).

(23) Here, the reasonable assumption[5] is made that the C.D. curves of XIIa and XIIb are gaussian in shape and have similar half-widths. It then follows that the ratio of the amplitude contribution of XIIb (which becomes negligible at $-192°$) to the total amplitude at room temperature is a measure of the decrease in rotational strength expected since the Cotton effect amplitude is proportional[5] to the rotational strength.
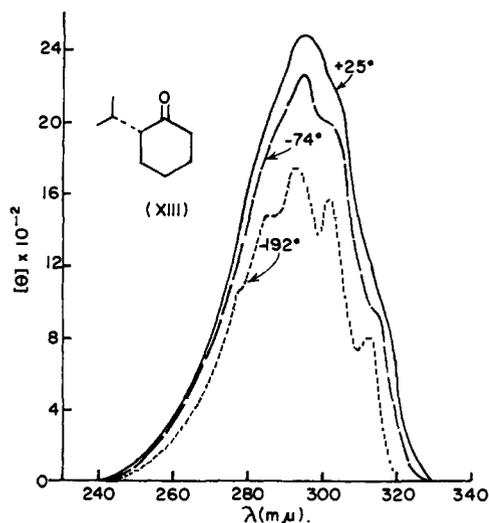
Figure 8. Circular dichroism curves of (+)-2-isopropylcyclo-hexanone (XIII) in EPA at +25, −74, and −192°.
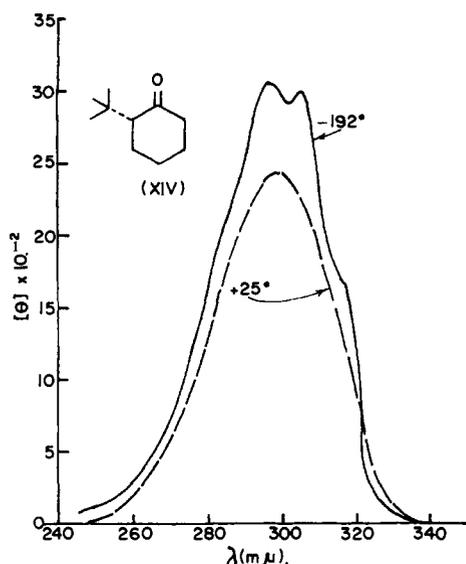

Figure 9. Circular dichroism curves of (+)-2-*t*-butylcyclohexanone (XIV) in EPA at +25 and −192°.

essentially constant at 1.01×10^{-40} c.g.s., with a deviation of less than 3%, which is inconsistent with any amplitude value currently accepted[21] for an equatorial methyl group. The only possible explanation that we can offer at this time is the existence of one or more conformers in addition to XIIa and XIIb.

The superposed effects of a chair–chair equilibrium and restricted rotation of the isopropyl group would be anticipated in the C.D. curves (Figure 8) of (+)-2-isopropylcyclohexanone (XIII).[24] Since the "2-alkyl ketone" effect is operative in α-isopropylcyclohexanones,[17,25] the conformer population of XIII will contain the positively rotating conformer XIIIa and the even more positively rotating form XIIIb. Since the more stable equatorial conformer XIIIa will make increasing contributions to the apparent rotational

(24) C. Djerassi, P. A. Hart, and C. Beard, *J. Am. Chem. Soc.*, **86**, 85 (1964).
(25) Reference 5, pp. 105–106; N. L. Allinger and H. M. Blatter, *J. Am. Chem. Soc.*, **83**, 994 (1961); B. Rickborn, *ibid.*, **84**, 2414 (1962).
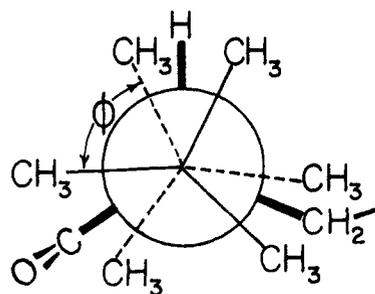

Figure 10. Librations of the *t*-butyl group (viewed from the quaternary carbon to C-2) in equatorial *t*-butylcyclohexanone (XIV).

strength as the temperature is lowered, the net effect will be a decrease in $R_0{}^T$ at low temperatures. From the previous discussion with the (enantiomeric) 2α-isopropyl-3-keto steroids VIII and IX, a less positive rotation for the equatorial conformer XIIIa would be anticipated on lowering the temperature. The C.D. results contained in Figure 8 bear out these two assumptions.

XII, R = Me   XIIa   XIIb
XIII, R = *i*-Pr   XIIIa
XIV, R = *t*-Bu   XIVa   XIIIb

XIVc

XV
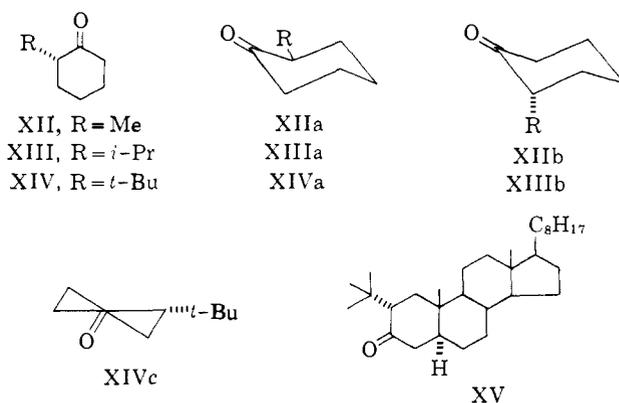
The C.D. curves (Figure 9) of (+)-2-*t*-butylcyclohexanone (XIV) are interesting in that they show an increase in rotational strength with lowering of temperature ($R_0{}^{25}$, $R_0{}^{-74}$, and $R_0{}^{-192}$ are $+2.34 \times 10^{-40}$, $+2.38 \times 10^{-40}$, and $+3.15 \times 10^{-40}$ c.g.s. in EPA). In the usual chair form with the *t*-butyl group equatorial, the nonbonded interactions present between the methyl groups and the carbonyl and C-3 methylene groups are approximately two n-*skew*-butanal interactions (*ca.* 2×1.6 kcal.[17]) and two *skew*-butane interactions (2×0.9 kcal.). This severe interaction cannot be appreciably relieved by passing *into* the most favorable flexible form such as XIVc, and it seems appropriate to assume that the temperature-dependent rotational strength of XIV is not due to a chair-flexible form equilibrium.

If we accept a single chair conformation for XIVa, two alternate explanations of its temperature-dependent $R_0{}^T$ come to mind. The first, a solvational equilibrium,[1,9] cannot be unequivocably ruled out; however, the lack of a wave-length shift of the C.D. band over the temperature range does not favor this explanation. A second hypothesis involves restricted rotation of the *t*-butyl group. Although the three low-energy, staggered conformers of the *t*-butyl group are identical, the *t*-butyl will not be constrained to a *specific* confor-
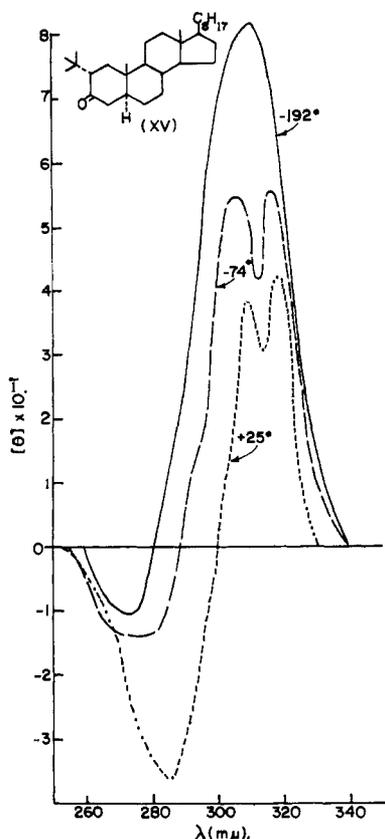
Figure 11. Circular dichroism curves of 2α-t-butyl-5α-cholestan-3-one (XV) in EPA at +25, −74, and −192°.

Figure 12. Circular dichroism curves of 2α-t-butyl-5α-cholestan-3-one (XV) in P6M1 and methanol at +25°.

mation but will oscillate through some angle φ about an equilibrium position. This situation is shown schematically in Figure 10 and represents a conformer equilibrium in the usual sense. Because the various positions of the t-butyl group will be expected to make dissimilar contributions to the rotational strength of XIV, a temperature-dependent C.D. will be observed.

The variable-temperature C.D. of the analogous substance, 2α-t-butyl-5α-cholestan-3-one (XV), in P6M1 (6:1 isopentane–methylcyclohexane) solvent has already been discussed in a preliminary communication.[1,9a] The steric interactions in this substance are complicated by the presence of the 19-methyl group and the buttressing effect of the skew-butane interaction involving the t-butyl methyl groups and the C-1 methylene hydrogen atoms, and a like interaction between the C-1 and C-11 hydrogen atoms. Since $R_0{}^T$ of XV in P6M1 was found to pass through a minimum, it was suggested[9a] that three or more forms of XV existed in solution. Interestingly, $R_0{}^T$ of XV in EPA (Figure 11), rather than the hydrocarbon mixture, does not pass through a minimum over the +25 to −192° range, and an equilibrium between only two species is consistent with the data. The room temperature C.D. curves of XV in methanol and P6M1 are also shown in Figure 12, and a strong solvent dependence is apparent. Since it is not immediately evident what conformers, other than the usual chair, may be present in XV and since the temperature-dependence of the C.D. of XV is not inconsistent with a solvational equilibrium,[1] no decision can be made at this time regarding the specific forms of 2α-t-butyl-5α-cholestan-3-one (XV) in P6M1 or EPA.

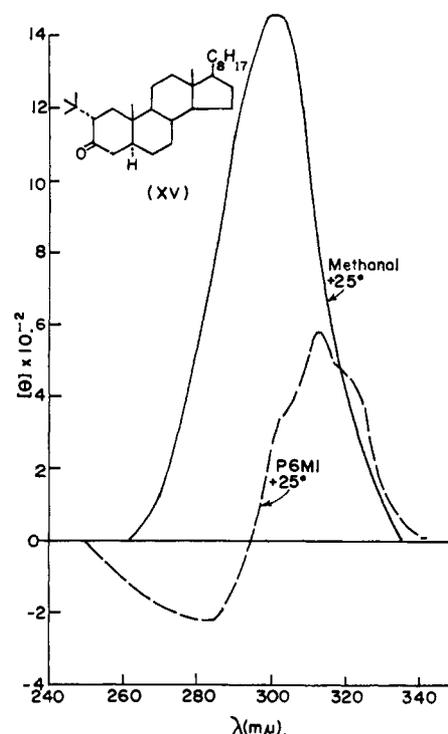2-Oxo-1-p-menthanol[26] (XVI) represents a very interesting example because, in addition to a possible chair–chair conformer equilibrium, intramolecular hydrogen bonding can be expected. The room temperature O.R.D. curves of XVI in several solvents have been interpreted in terms of these effects[27]; however, the variable-temperature C.D. spectra were expected to furnish further insight into the interplay of conformational, solvational, and hydrogen-bonding effects present in XVI. Not unexpectedly, XVI exhibits a multiple Cotton effect C.D. curve in either EPA or P5M1 (5:1 isopentane–methylcyclohexane) at room temperature (Figures 13 and 14). The separation between the two extrema, when visible, remains at ca. 30 mμ for the various curves in Figures 13 and 14 as predicted[1] for two overlapping, oppositely signed C.D. curves.

As discussed in the previous communication in this series,[1] complex Cotton effects arising from n → π* transitions in a saturated ketone can be explained in terms of solvational equilibria and/or conformational equilibria. Furthermore, in substances in which this phenomenon appears, a distinction between the various alternatives will be possible only in certain instances. Fortunately, in the present case it is possible to make just such a distinction as follows.

If a solvational equilibrium were solely responsible for the double-humped Cotton effect observed in XVI, the short wave-length C.D. band can be attributed to the solvated species and the long wave-length band to the unsolvated form.[1,9] If this be the case, the apparent rotational strength of the blue-shifted band would increase at lower temperatures. In actual fact,

(26) W. F. Newhall, J. Org. Chem., 24, 1673 (1959).
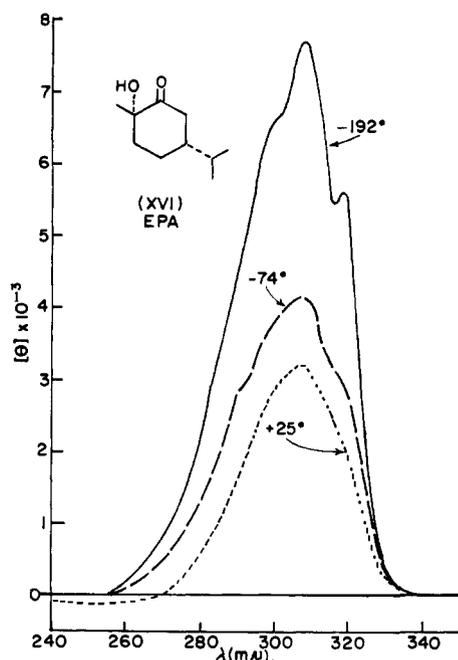(27) C. Djerassi, R. Records, and B. Bach, Chem. Ind. (London), 258 (1958).

Figure 13. Circular dichroism curves of 2-oxo-1-p-menthanol (XVI) in EPA at +25, −74, and −192°.

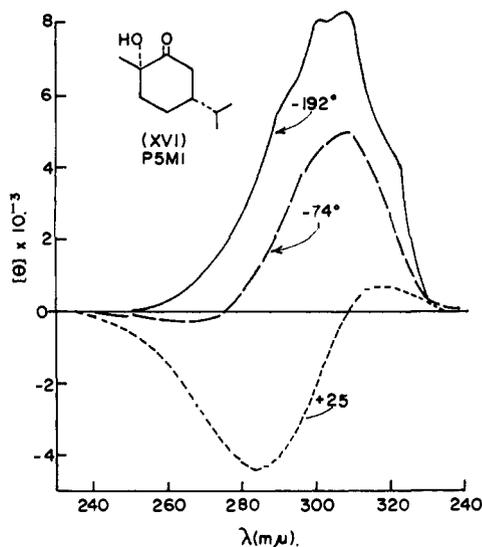Figure 14. Circular dichroism curves of 2-oxo-1-p-menthanol (XVI) in P5M1 at +25, −74, and −192°.

the opposite result obtains in both EPA (Figure 13) and P5M1 (Figure 14). This result is inconsistent with a solvational equilibrium being solely responsible for the double-humped C.D. curves of XVI.

The analysis of the C.D. data is consistent with a conformer equilibrium on the following basis. The two chair conformers expected[27] are XVIa and XVIb. Conformer XVIa would be expected to make a net positive contribution to the Cotton effect of XVI since the relatively negative effect anticipated[21] for the equatorial methyl group would be outweighed by the combined positive contributions of the hydroxyl and isopropyl groups. By the same token, XVIb[28] will

(28) The boat form XVIc or the corresponding twist (with C-2 and C-5 the points of the twist) are equally compatible with the experimental results.
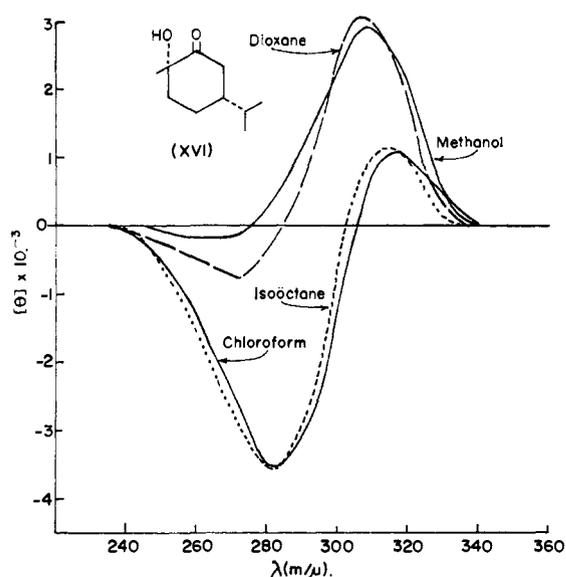

Figure 15. Circular dichroism curves of 2-oxo-1-p-menthanol (XVI) in selected solvents at +25°.

exhibit a strong negative Cotton effect according to the tenets of the octant rule.[11] On this basis, the short wave-length band is that attributed to conformer XVIb[28] and the red-shifted band that of XVIa. These assignments are in agreement with findings of previous workers[29] who reported axial hydroxyl groups to cause a red shift of the O.R.D. curve peak by about 13 mμ, whereas an equatorial hydroxyl group resulted in a blue shift of about 2 to 10 mμ.

XVI

XVIa

XVIb

XVIc

XVId
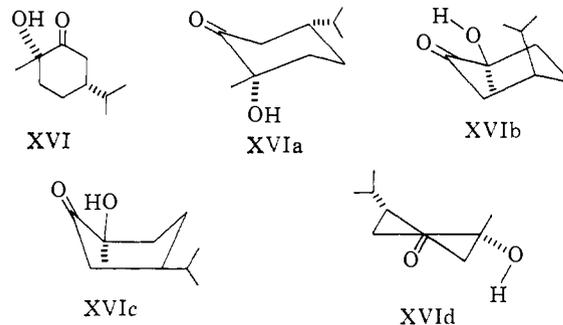
Of particular interest are the low-temperature C.D. curves. If the C.D. band assignments are accepted, the augmentation of the long wave-length band at lower temperature indicates that conformer XVIa is energetically favored. Such a result might have been predicted on the basis of steric requirements only; however, since conformer XVIb[28] can be stabilized by hydrogen bonding between the carbonyl and the hydroxyl group (a saving of ca. 2–5 kcal. energywise), a clear-cut distinction between relative energies of XVIa and XVIb would be difficult.

The solvent-dependent C.D. curves (Figure 15) of XVI offer further evidence on the point of hydrogen bonding in conformer XVIb.[28] As the solvent is changed from the polar solvent methanol to a hydrocarbon solvent such as cyclohexane, the population of conformer XVIb[28] increases assuming it is measured by the apparent rotational strength of the short wave-length

(29) C. Djerassi, O. Halpern, V. Halpern, O. Schindler, and C. Tamm, Helv. Chim. Acta, 41, 250 (1958).

band. This result is contrary to expectations based on an electrostatic interaction between the C=O and C—OH dipoles, since the more polar form XVIb would be favored in solvents such as methanol which minimize electrostatic interactions.[30] Conversely, methanol is an excellent hydrogen-bonding solvent and will tend to form intermolecular hydrogen bonds to both the carbonyl and the hydroxyl group with a concomitant decrease in the population of XVIb because the stabilizing intramolecular hydrogen bond will be broken. As can be seen from Figure 15, the positively rotating conformer XVIa completely dominates the C.D. curve in methanol in agreement with the latter hypothesis.

In hydrocarbon solvents the population of the species XVIb[28] will increase because the destablizing electrostatic interaction between the C=O and the axial C—OH bond in XVIa is replaced by a favorable interaction in XVIb, i.e., by formation of a hydrogen bond. The C.D. curves of the α-hydroxy ketone XVI in other solvents (Figure 15) are in qualitative agreement with a competition of electrostatic effects and intramolecular or intermolecular hydrogen bonding.

The C.D. curves of XVI (Figure 16) in decalin over the range from −74 to +156° are interesting in that R_0^T passes through a minimum. In terms of the C.D. curves, it is observed that the short wave-length band amplitude first increases in changing from −74 → +25° and then diminishes over the range +25 → 156°. In contrast, the apparent rotational strength of the long wave-length band remains almost constant. These observations are not consistent with the simple equilibrium XVIa ⇌ XVIb being the sole factor in decalin at the higher temperatures since R_0^T would be expected to vary in the same direction throughout the temperature range. A simple explanation for this result is not obvious. Indeed, since at higher temperatures the hydrogen-bonded form of XVIb would diminish with increasing amounts of the nonbonded form of XVIb[28] and/or the positively rotating twist form XVId present, a complex situation would be anticipated.

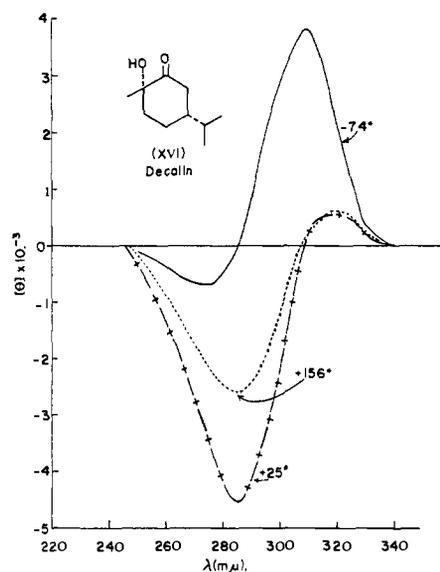(30) E. J. Corey, J. Am. Chem. Soc., 75, 2301 (1953); J. Allinger and N. L. Allinger, Tetrahedron, 2, 64 (1958).

Figure 16. Circular dichroism curves of 2-oxo-1-p-menthano (XVI) in decalin at −74, +25, and +156°.

Experimental

All measurements were performed using Spectrograde or purified solvents. C.D. curves were obtained using a Baird-Atomic/Jouan dichrograph operating with a photomultiplier voltage of 1.2 kv. and following the procedures and molecular ellipticity calculations outlined earlier.[31]

(31) C. Djerassi, H. Wolf, and E. Bunnenberg, J. Am. Chem. Soc., 84, 4552 (1962); K. Mislow, E. Bunnenberg, R. Records, K. Wellman, and C. Djerassi, ibid., 85, 1342 (1963); C. Djerassi and E. Bunnenberg, Proc. Chem. Soc., 299 (1963).