

Figure 7. Circular dichroism curves of 5 $\alpha$ -pregnan-20-one (XI) in EPA at +25 and -192 $^{\circ}$ .

can be expected for XII. The relevant C.D. curves are shown in Figure 7 and, on the basis of the strong negative rotational strength, conformer XI does indeed seem to be the preferred one. The rotational strength of XI ( $R_0^{25} = -6.9 \times 10^{-40}$  c.g.s.,  $R_0^{-192} = -7.4 \times 10^{-40}$  c.g.s.) is only slightly affected by lowering

the temperature. Since the rotational strengths of the two preferred conformations are predicted by the octant rule<sup>4</sup> to be appreciably different, this result implies a large free energy for the interconversion of XI and XII probably approaching 2 kcal. (see Figure 3), if entropy differences in the two conformers are small.

### Experimental

All measurements were performed in Spectrograde solvents. The EPA solvent consisted of ether-isopentane-ethanol in a ratio of 5:5:2 by volume; 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.<sup>39</sup>

**Acknowledgment.** We wish to thank Drs. P. Crabbé and A. D. Cross (Syntex, S. A., Mexico City) and Dr. G. Snatzke (University of Bonn) for furnishing pertinent manuscripts. Also, Dr. J. S. Mills (National Gallery, London) provided a sample of 3 $\beta$ -acetoxyhexanordammar-20-one,<sup>40</sup> and Dr. Crabbé supplied samples of 3 $\beta$ -acetoxy-16 $\beta$ -cyano- $\Delta^5$ -pregnen-20-one<sup>41</sup> and 3 $\beta$ -acetoxy-16 $\beta$ -methyl- $\Delta^5$ -pregnen-20-one. The technical assistance of Ruth Records and W. S. Briggs is gratefully acknowledged.

(39) 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).

(40) J. S. Mills, *J. Chem. Soc.*, 2196 (1956).

(41) J. Romo, L. Rodriguez-Hahn, P. Joseph-Nathan, M. Martinez, and P. Crabbé, *Bull. soc. chim. France*, 1276 (1964).

## Optical Rotatory Dispersion Studies. XCIX.<sup>1</sup> Superposed Multiple Cotton Effects of Saturated Ketones and Their Significance in the Circular Dichroism Measurement of (-)-Menthone<sup>2</sup>

Keith M. Wellman,<sup>3a</sup> P. H. A. Laur,<sup>3b</sup> W. S. Briggs, Albert Moscowitz,<sup>4</sup> and Carl Djerassi

*Contribution from the Departments of Chemistry of Stanford University, Stanford, California, and the University of Minnesota, Minneapolis 14, Minnesota.  
Received August 5, 1964*

The presence of multiple Cotton effects arising from an  $n \rightarrow \pi^*$  transition of a carbonyl chromophore is found to be explicable in terms of: (1) a solvation equilibrium involving differently solvated species and/or (2) a conformational equilibrium. Calculations are presented which show that a complex circular dichroism (C.D.) curve with two oppositely signed extrema separated by ca. 30 m $\mu$  will arise whenever two Cotton effects of similar amplitudes, but opposite sign, are superposed with their individual maxima separated by 1 to 20 m $\mu$ . The difficulties of distinguishing between the two phe-

nomena are discussed. The multiple Cotton effects observed in the C.D. curves of (-)-menthone are most economically attributable to two conformers. The C.D. curves of (+)-isomenthone are also discussed.

### Introduction

It has generally been recognized that variations in solvent are reflected in monochromatic polarimetric rotations as well as in rotatory dispersion work.<sup>5</sup> For example, Pariaud<sup>6</sup> noted variations in the specific rotation of camphor with change in solvent and ascribed this phenomenon to solvational equilibria. A strik-

(1) Paper XCVIII: K. M. Wellman and C. Djerassi, **87**, 60 (1965).

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

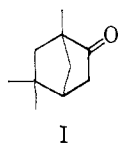
(3) (a) National Institutes of Health Postdoctoral Research Fellow, 1962-1963; (b) NATO Postdoctoral Research Fellow, 1962-1963.

(4) Alfred P. Sloan Fellow.

(5) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p. 29.

(6) J. C. Pariaud, *Bull. soc. chim. France*, 103 (1950).

ing solvent effect has been noted by Gervais and Rassat<sup>7</sup> in the rotatory dispersion of isofenchone (I) and episo-fenchone. They reported an inversion of the Cotton effect when the solvent was varied from methanol to cyclohexane. Circular dichroism measurements, which are generally better able to resolve two overlapping Cotton effects than is possible with optical rotatory dispersion measurements,<sup>8</sup> have shown<sup>9</sup> that isofenchone (I) actually gives rise to two Cotton effects of opposite sign whose amplitudes are solvent dependent. In the case of this rigid molecule, the presence of two Cotton effects in the 300-m $\mu$  region seems best explained in terms of a solvational equilibrium. Although not unequivocal, such an equilibrium is most economically visualized as consisting of two species with different degrees of solvation.



An equilibrium involving uncomplexed and complexed forms has been noted in the case of nitriles and benzophenone,<sup>10</sup> ethanol and benzophenone, mesityl oxide and acetophenone,<sup>11</sup> chloroethanols and cyclopentanone,<sup>12</sup> and acetone and dimethyl sulfoxide.<sup>13</sup> Such equilibria might then reasonably account for the appearance of two oppositely signed C.D. absorptions provided the two species have opposite Cotton effects. Furthermore, it has been suggested<sup>9</sup> that the short wave-length C.D. band is that of the solvated species and the long wave-length band that of the unsolvated form. This suggestion is in line with the commonly accepted view that electrostatic effects and/or hydrogen bonding effects arising from solvation of ketones by polar molecules almost invariably result in a blue shift of the carbonyl  $n \rightarrow \pi^*$  transition.<sup>11,14,15</sup> A requirement of the solvation equilibrium hypothesis is an increase of the population of complexed species on going to lower temperature. In terms of the C.D. curves the short wave-length band should increase at the expense of the long wave-length band. This is precisely what is observed in the case of isofenchone<sup>9a</sup> and norcamphor.<sup>16</sup> It is perhaps pertinent to note that similar double-humped C.D. curves have also been noted in cyclohexanones<sup>9a,17</sup> as well as in certain 16 $\beta$ -substituted  $\Delta^5$ -pregnen-20-ones.<sup>1,18</sup> In these latter

- (7) H. P. Gervais and A. Rassat, *Bull. Soc. Chem. France*, 743 (1961).  
 (8) C. Djerassi, H. Wolf, and E. Bunnenberg, *J. Am. Chem. Soc.*, **85**, 4552 (1962); P. Crabbé, *Tetrahedron*, **20**, 1211 (1964).  
 (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).  
 (10) R. S. Becker, *J. Mol. Spectry.*, **3**, 1 (1959).  
 (11) M. Ito, K. Inuzuka, and S. Imanishi, *J. Am. Chem. Soc.*, **82**, 1317 (1960).  
 (12) J. Cantacuzene, *Bull. soc. chim. France*, 747 (1962).  
 (13) C. D. Ritchie and A. L. Pratt, *J. Am. Chem. Soc.*, **86**, 1571 (1964).  
 (14) G. M. Brealey and M. Kosha, *ibid.*, **77**, 4462 (1955).  
 (15) G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman and Co., San Francisco, Calif., 1960, pp. 157-164.  
 (16) Unpublished results from these laboratories.  
 (17) K. M. Wellman, R. Records, E. Bunnenberg, and C. Djerassi, *J. Am. Chem. Soc.*, **86**, 492 (1964); P. Witz, H. Hermann, J.-M. Lehn, and G. Ourisson, *Bull. soc. chim. France*, 1101 (1963); S. Bory, M. Fetizon, and P. Laszlo, *ibid.*, 2310 (1963).  
 (18) P. Crabbé, F. McCapra, F. Comer, and A. I. Scott, *Tetrahedron*, **20**, 2455 (1964).

cases, conformational changes may be superposed upon any solvational equilibria occurring, and the presence of three or more species in solution may be indicated.<sup>9a</sup>

Multiple Cotton effect C.D. curves attributed to conformational equilibria have been observed in halocyclohexanones.<sup>19-23</sup> For example, (+)-*trans*-2-chloro-5-methylcyclohexanone (II) is represented by the conformer equilibrium IIa  $\rightleftharpoons$  IIb. Since the two conformers have opposite Cotton effects and absorb over 20 m $\mu$  apart,<sup>24</sup> negative and positive maxima



separated by *ca.* 30 m $\mu$  are present in the room temperature C.D. curve in EPA solvent.<sup>22,23</sup> The conformer population of II is very sensitive to solvent and, depending upon the polarity of the medium, either the positive Cotton effect of IIa or the strongly negative Cotton effect of IIb was found to dominate the spectrum.<sup>23</sup> Concomitantly, variable-temperature studies in EPA indicated that no significant changes in the degree of solvation need be invoked in order to account for the data for the equilibrium over the temperature range +25 to -192 $^{\circ}$ .

The degree of solvation does not always remain constant over the low-temperature range. Specifically, the C.D. curves of 5 $\alpha$ -cholestan-3-one in isopentane-methylcyclohexane show a large increase in rotational strength accompanied by a blue shift and loss of fine structure upon lowering the temperature to -192 $^{\circ}$ .<sup>9a</sup> Since the conformational homogeneity of the A ring in 5 $\alpha$ -cholestan-3-one (VI) has been demonstrated by low-temperature measurements in EPA solvent<sup>22</sup> and in decalin over the range of +25 to +164 $^{\circ}$ ,<sup>16</sup> the changes observed in the hydrocarbon solvent at low temperatures indicate increased solvation at these temperatures.

Still another type of more subtle solvent effect was noted in a previous communication from these laboratories. It was found<sup>9a</sup> that "increments" of enhanced rotational strength were peculiar to specific solvents, and roughly independent of the rotational strength of the ketone being investigated. Thus, 5 $\alpha$ -cholestan-3-one and 5 $\alpha$ -androstan-16-one show increases of *ca.*  $2 \times 10^{-40}$  c.g.s. units in their rotational strengths upon changing from cyclohexane to chloroform solvent. This solvent effect is not correlated by the usual methods such as dielectric constant or Kosower's Z-values.<sup>25</sup>

## Results and Discussion

With the above factors in mind, it was noted with interest that the room temperature C.D. curve of (-)-menthone (III) in EPA solvent (Figure 1) showed the diagnostic feature of two oppositely signed maxima

- (19) C. Djerassi and L. E. Geller, *ibid.*, **3**, 319 (1958).  
 (20) N. L. Allinger, J. Allinger, L. E. Geller, and C. Djerassi, *J. Org. Chem.*, **26**, 3521 (1961); **25**, 6 (1960).  
 (21) C. Djerassi, L. E. Geller, and E. J. Eisenbraun, *ibid.*, **25**, 1 (1960).  
 (22) K. M. Wellman, E. Bunnenberg, and C. Djerassi, *J. Am. Chem. Soc.*, **85**, 1870 (1963).  
 (23) A. Moscowitz, K. Wellman, and C. Djerassi, *ibid.*, **85**, 3515 (1963).  
 (24) R. C. Cookson, *J. Chem. Soc.*, 28 (1954); R. C. Cookson and S. H. Dandegaonker, *ibid.*, 352 (1955).  
 (25) E. M. Kosower, *J. Am. Chem. Soc.*, **80**, 3253 (1958).

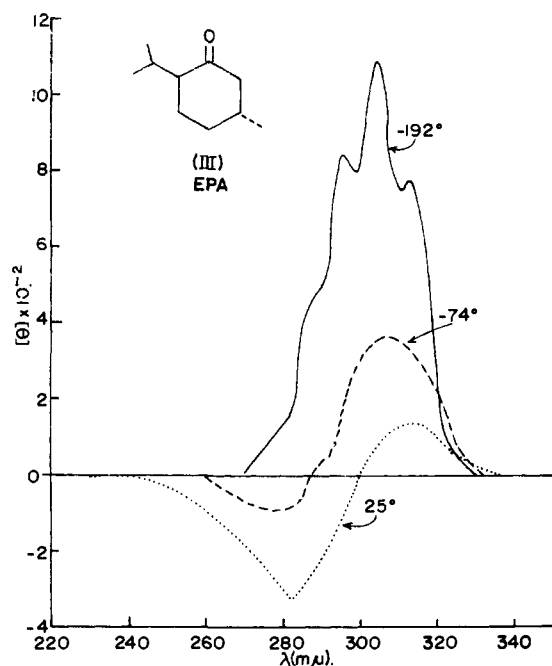
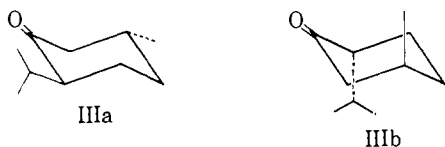
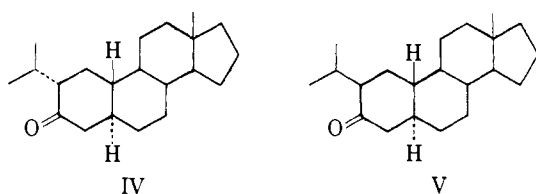


Figure 1. Circular dichroism curves of (-)-menthone (III) in EPA at +25, -74, and -192°.

separated by *ca.* 30  $m\mu$ . The large separation implied<sup>9</sup> that in addition to a possible conformer equilibrium between the diequatorial chair (IIIa) and the diaxial



chair (IIIb) forms, the C.D. curve was complicated by a solvational equilibrium. Such a large wave-length change would hardly be expected for a simple conformational change IIIa  $\rightleftharpoons$  IIIb. In fact, a pair of equatorial-axial steroidal isomers, IV and V,<sup>26</sup> exhibited a maximal difference of 3-5  $m\mu$ <sup>16</sup> in their C.D. However, upon observing the C.D. curves of III at



low temperature (see Figure 1), the long wave-length band was found to increase at the expense of the short wave-length band. *This result is clearly inconsistent with a solvational equilibrium being solely responsible for the two separate peaks*, if, in accord with the above assumptions, the more solvated species is to be identified with the short wave-length peak. An alternate explanation is simply that the positive band at longer wave length is due to IIIa, which would be expected to exhibit a positive Cotton effect on the basis of the octant rule,<sup>27</sup> while the short wave-length

(26) C. Djerassi, P. A. Hart, and C. Beard, *J. Am. Chem. Soc.*, **86**, 85 (1964).

(27) W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *ibid.*, **83**, 4013 (1961); C. Djerassi and W. Klyne, *J. Chem. Soc.*, 4926 (1962); 2390 (1963).

negative band is associated with the strongly negative Cotton effect expected<sup>27</sup> for the diaxial conformer IIIb. However, this latter explanation must also account for the 30- $m\mu$  separation of the C.D. extrema even though the contributing individual curves are separated by no more than 3-5  $m\mu$  (*cf.* IV and V). It is to this point that we now address ourselves. We shall show that under conditions commonly met with in the 300- $m\mu$  transition of saturated ketones, the wave-length separation of the extrema is largely independent of the separation of the contributing bands, and is of the order of 30  $m\mu$ .

Individual circular dichroism bands for the 300- $m\mu$  ketone transition are fairly peaked functions of the wave length that can be roughly approximated by gaussian curves of the form  $A_i \exp[-(\lambda - \lambda_i)^2/\Delta_i^2]$ . Therefore, a good deal of insight into the problem of overlapping c.d. curves of opposite sign can be obtained by considering the superposition  $F(\lambda)$  of two such gaussian curves with positive and negative amplitudes.

$$F(\lambda) = A_1 \exp[-(\lambda - \lambda_1)^2/\Delta_1^2] - A_2 \exp[-(\lambda - \lambda_2)^2/\Delta_2^2] \quad (1)$$

The wave lengths  $\lambda'$  corresponding to the extrema of  $F(\lambda)$  are, for the general case, found most easily with the aid of a digital computer. One simply has the computer generate  $F(\lambda)$  for any desired values of the parameters  $A_i$ ,  $\lambda_i$ , and  $\Delta_i$ , and  $\lambda'$  is then obtained by inspection. This is the general procedure we have followed, and the results are tabulated and discussed below. Before examining them, however, it is quite instructive to examine one special case analytically.

Consider the case where  $A_1 = A_2$ , and  $\Delta_1 = \Delta_2 = \Delta$ . Setting  $(\delta F/\delta \lambda) = 0$ , one obtains the expression for  $\lambda'$

$$1 - (\lambda_2 - \lambda_1)/(\lambda' - \lambda_1) = \exp\{-2(\lambda_2 - \lambda_1)(\lambda' - \lambda_1)/\Delta^2 + (\lambda_2 - \lambda_1)^2/\Delta^2\} \quad (2)$$

For  $(\lambda_2 - \lambda_1)$  small compared to  $\Delta$ , one may consistently expand the exponential in eq. 2, truncate the series, and obtain

$$\lambda' \approx (\lambda_1 + \lambda_2)/2 \pm \sqrt{(\lambda_2 - \lambda_1)^2 + 8\Delta^2/4} \quad (3)$$

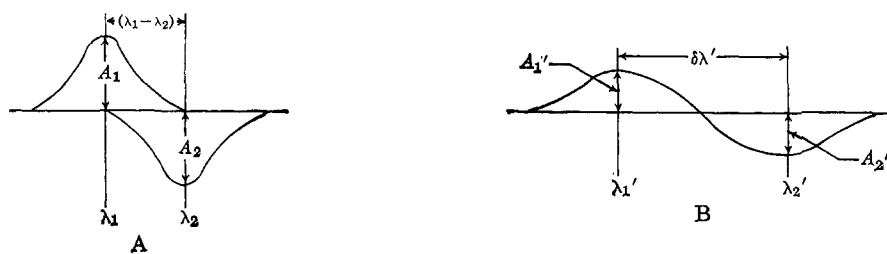
Hence, for  $(\lambda_2 - \lambda_1)$  small compared to  $\Delta$ , the wave-length interval  $\delta\lambda'$  between extrema is given by

$$\delta\lambda' \approx \Delta\sqrt{2} \quad (4)$$

*i.e.*, to a first approximation, for overlapping, oppositely signed C.D. bands of similar amplitude, the wave-length interval  $\delta\lambda'$  between extrema is *independent* of  $(\lambda_2 - \lambda_1)$  for separations small compared to a band half-width. These are precisely the separations of most interest for the present discussion.

Some of the pertinent results obtained from the computer output are presented in Table I for values of the parameters typical of saturated ketones, namely,  $\lambda_1 = 300 m\mu$  and  $\Delta = 20 m\mu$ . As may be anticipated from the above arguments, one of the most important and striking consequences is that the separation between extrema is *always ca.* 30  $m\mu$  for  $(\lambda_2 - \lambda_1)$ , much less than the band half-width. In fact, the statement is seen to hold when  $(\lambda_2 - \lambda_1)$  approaches and even somewhat exceeds the half-width. Table I shows the results of calculations for three separate cases, each

**Table I.** Original Separate C.D. Curves of Species 1 and 2 (A) and Double Cotton Effect Resulting from Superposition of C.D. Curves 1 and 2 (B)<sup>a</sup>



A					B				
$\lambda_1, m\mu^b$	$\lambda_2, m\mu^c$	$\lambda_2 - \lambda_1, m\mu$	$A_1^d$	$A_2^e$	$\lambda_1', m\mu$	$\lambda_2', m\mu$	$A_1', m\mu$	$A_2', m\mu$	$\delta\lambda', m\mu$
Case 1									
300	301	1	+1.000	-1.000	286.4	314.6	0.0429	-0.0429	28
300	302	2	+1.000	-1.000	286.8	315.2	0.0856	-0.0856	28
300	304	4	+1.000	-1.000	287.8	316.2	0.1704	-0.1704	28
300	308	8	+1.000	-1.000	289.6	318.4	0.3341	-0.3341	29
300	310	10	+1.000	-1.000	290.6	319.4	0.4115	-0.4115	29
300	315	15	+1.000	-1.000	292.6	322.4	0.5868	-0.5868	30
300	320	20	+1.000	-1.000	294.6	325.4	0.7304	-0.7304	31
Case 2									
300	301	1	+1.000	-0.500	299.0	...	0.5025	...	..
300	302	2	+1.000	-0.500	298.2	...	0.5097	...	..
300	304	4	+1.000	-0.500	296.8	...	0.5355	...	..
300	308	8	+1.000	-0.500	295.6	329.3	0.6123	-0.0439	34
300	310	10	+1.000	-0.500	295.4	327.8	0.6550	-0.0816	32
300	315	15	+1.000	-0.500	296.0	327.3	0.7580	-0.1874	31
300	320	20	+1.000	-0.500	296.8	328.8	0.8445	-0.2863	32
Case 3									
300	301	1	+1.000	-0.200	299.8	...	0.8006	...	..
300	302	2	+1.000	-0.200	299.6	...	0.8025	...	..
300	304	4	+1.000	-0.200	299.0	...	0.8096	...	..
300	308	8	+1.000	-0.200	298.4	...	0.8348	...	..
300	310	10	+1.000	-0.200	298.4	...	0.8508	...	..
300	315	15	+1.000	-0.200	298.4	336.2	0.8932	-0.0272	38
300	320	20	+1.000	-0.200	298.6	334.6	0.9315	-0.0672	36

<sup>a</sup> Values for  $\lambda_1'$  and  $\lambda_2'$  are calculated to within  $\pm 0.1 m\mu$ . <sup>b</sup> Center of C.D. curve 1. <sup>c</sup> Center of C.D. curve 2. <sup>d</sup> Amplitude of C.D. curve 1. <sup>e</sup> Amplitude of C.D. curve 2.

with  $(\lambda_2 - \lambda_1)$  varying from 1 to 20  $m\mu$ . In the first case, the amplitudes of the two contributing C.D. curves are the same in magnitude (normalized to 1.00) but opposite in sign. In this instance, the amplitudes  $A_1'$  and  $A_2'$  of the resulting double Cotton effect extrema are identical in magnitude and vary from a value of |0.043| when the curves are offset by only 1  $m\mu$ , and are largely canceling, to |0.729| when  $(\lambda_2 - \lambda_1)$  equals 20  $m\mu$ . *The important point to note here is that when two oppositely signed C.D. curves of similar amplitude are overlapping strongly, the resulting apparent rotational strengths are only about  $1/25$  (for  $\lambda_2 - \lambda_1$  of the order of 1  $m\mu$ ) of those of the contributing curves.* Coulombeau and Rassat<sup>9b</sup> have commented on the weak amplitudes observed in the double-humped C.D. curves. These weak amplitudes are understandable in the light of the present calculations.

The second and third cases in Table I have  $A = +1.000$ ,  $B = -0.500$  and  $A = +1.000$ ,  $B = -0.200$ , respectively. The resultant C.D. curves are no longer symmetrical; however, the separation between the two extrema, when both are present, is *ca.* 32  $m\mu$  in the second case and 37  $m\mu$  in the third case. The amplitudes of the resulting extrema vary according to the separation, but in the range of interest for  $\lambda_2 - \lambda_1$ ,  $A_2'$  suffers a much larger diminution in magnitude relative to  $A_2$  than  $A_1'$  relative to  $A_1$ .

It is evident from these calculations that whenever one observes a double-humped C.D. curve, with maxima separated by *ca.* 30  $m\mu$ , resulting from a substance containing only a single carbonyl chromophore, *either solvational<sup>9a</sup> and/or conformational equilibria are implied.* The distinction between the possibilities will be difficult unless conformational homogeneity is required as in the case of the bridged bicyclics<sup>9</sup> or unless temperature-dependent C.D. measurements clearly are inconsistent with the solvational equilibrium hypothesis. When viewed in the light of these new findings, our previous remarks<sup>9a</sup> regarding 2 $\alpha$ -*t*-butylcholestan-3-one and lupan-3-one can no longer be considered unequivocal.

To return now to the (-)-menthone (III) example, the temperature-dependent C.D. curves in EPA (Figure 1) exclude the possibility of a solvation equilibrium being the sole cause of the two bands. The C.D. curves of III in P5M1 (isopentane-methylcyclohexane 5:1 v./v.), shown in Figure 2, are also inconsistent with a dominant solvational equilibrium since at low temperature the band shifted to long wave lengths increases in strength. In changing from the more polar solvent (EPA) to the nonpolar hydrocarbon (P5M1), *both* bands are red shifted to similar extents (*ca.* 5-8  $m\mu$ ); however, the wave-length separation between the two extrema remains at 30  $m\mu$ , as expected

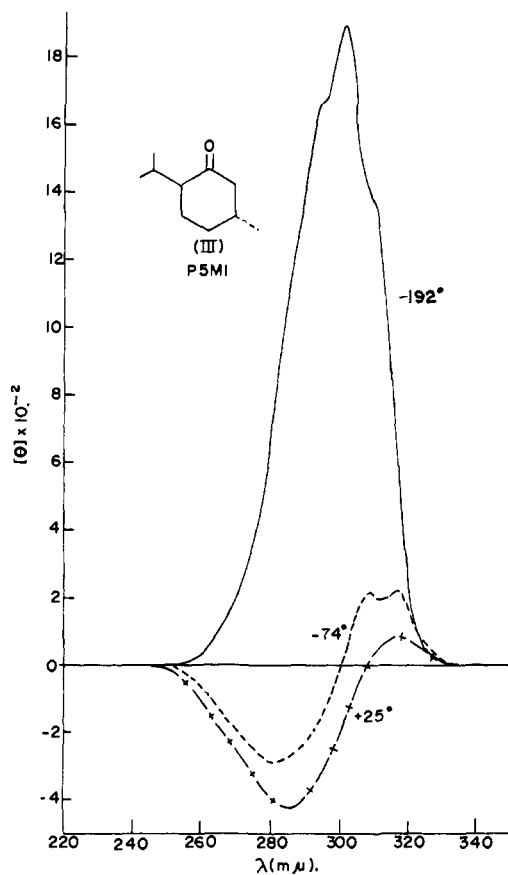


Figure 2. Circular dichroism curves of (-)-menthone (III) in 5:1 isopentane-methylcyclohexane at +25, -74, and -192°.

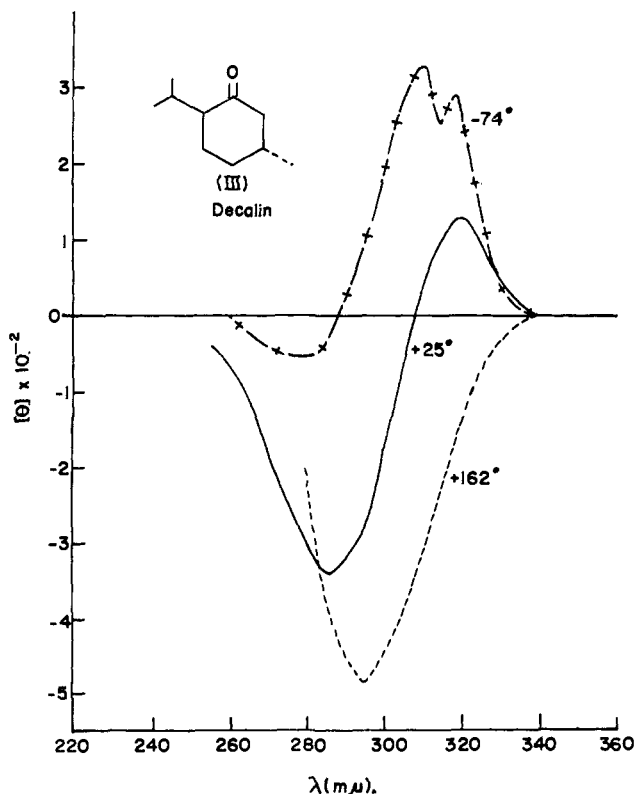


Figure 3. Circular dichroism curves of (-)-menthone (III) in decalin at -74, +25, and +162°.

from the calculations. The high-temperature C.D. curves<sup>28</sup> in decalin (Figure 3) are also consistent with

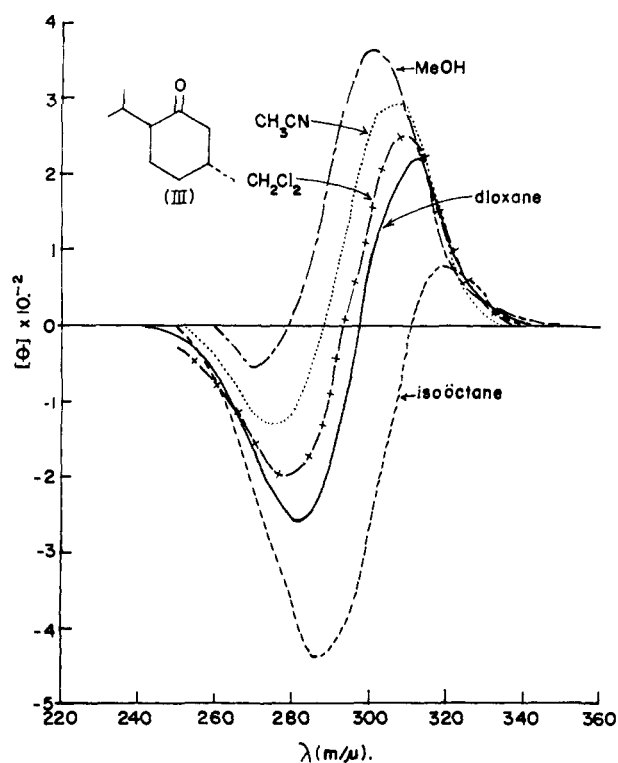


Figure 4. Circular dichroism curves of (-)-menthone (III) in various solvents at +25°.

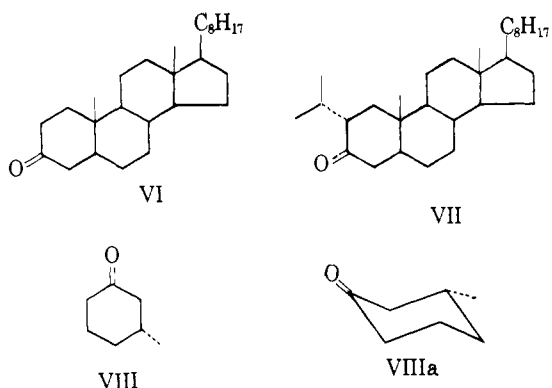
conclusions of the low-temperature results in that the apparent rotational strength of the short wave-length band increases with increasing temperature as expected if this band is attributed to the less stable conformer IIIb.

Our earlier suggestion<sup>29</sup> that (-)-menthone (III) exists almost completely to the diequatorial chair conformation IIIa is justified; however, the presence of the negative Cotton effect (Figures 1-3) clearly implies the existence of the strongly negative rotating conformer IIIb. If we assume that the equilibrium IIIa  $\rightleftharpoons$  IIIb operates, an estimate of the conformer population is possible from available O.R.D. data. The Cotton effect amplitude  $a$  of the diequatorial chair conformer IIIa is a result of the contribution of the 2- (equatorial) isopropyl group and the 5- (equatorial) methyl group. The amplitude of the 2- (equatorial) isopropyl group has been experimentally determined<sup>29</sup> to be -17, -15, and -21. The first value was estimated from O.R.D. measurements on (-)-menthone itself in methanol; but, since this is a resultant of two oppositely rotating Cotton effects (see Figure 4 below), it is a low estimate. The second value arises from the difference in the amplitudes of 5 $\alpha$ -cholestan-3-one (VI) and 2 $\alpha$ -isopropyl-5 $\alpha$ -cholestan-3-one (VII). The third was obtained in a similar manner from IV and the parent 19-nor-5 $\alpha$ -androstan-3-one.

Since the angular 19-methyl group of VI and VII introduces a slight distortion into ring A, the last value ( $a = 21$ ) derived from the 19-nor series (IV) would seem most valid for the amplitude of a 2- (equatorial)

(28) 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. 23).

(29) C. Djerassi, P. A. Hart, and C. Beard, *J. Am. Chem. Soc.*, **86**, 85 (1964).



isopropyl group. The generally accepted contribution for an equatorial  $\beta$ -methyl group as in IIIa is +25 on the basis of the Cotton effect amplitude of (+)-3-methylcyclohexanone (VIII).<sup>30</sup> It is recognized that this value is low because of the lack of conformational homogeneity in VIII at room temperature. This suspicion has been borne out by low-temperature C.D. studies<sup>22</sup> in which it was found that the rotational strength ( $R_0^T$ ) of (+)-3-methylcyclohexanone (VIII) changed from  $+1.65 \times 10^{-40}$  c.g.s. at  $25^\circ$  to  $+2.18 \times 10^{-40}$  c.g.s. at  $-192^\circ$ . The latter value may be used to approximate the rotational strength of the equatorial (+)-3-methylcyclohexanone (VIIIa). These rotational strengths can be used to estimate a Cotton effect amplitude for the pure equatorial chair conformer VIIIa. First, it is necessary to make the reasonable assumption<sup>31</sup> that gaussian-shaped curves with identical half-widths will adequately represent the observed C.D. curves of (+)-3-methylcyclohexanone. It then follows, since the rotational strength is proportional to the molecular ellipticity maximum, which in turn is proportional to the Cotton effect amplitude,<sup>31</sup> that the ratio of the rotational strengths,  $R_0^{-192}/R_0^{25} = 1.32$ , will correct the population-weighted amplitude of VIII to the amplitude of the equatorial chair conformer VIIIa. The value so obtained is +33 (as compared to +25<sup>30</sup>), and this value represents a more correct contribution of the methyl group in VIIIa. The contribution of the axial isopropyl group in IIIb is -98.<sup>29</sup> On the other hand, the contribution of an axial methyl group as in IIIb is not known, but as a first approximation it will be assumed to be  $\geq -33$ , the contribution of an equatorial methyl substituent in that octant. Using these values, the Cotton effect amplitudes of conformers IIIa and IIIb are +12 ( $a_1$ ) and -131 ( $a_2$ ), respectively. Then, from the observed amplitude ( $a = +8$ )<sup>32</sup> for (-)-menthone and the relationship,  $a = (1 - N_2)a_1 + N_2a_2$ , the mole fraction,  $N_2$ , of conformer IIIb can be found. The mole fraction of IIIb is calculated to be 0.028 and the free energy difference between the two conformers, IIIa and IIIb, is *ca.* 2 kcal. A free energy difference for this equilibrium was estimated by Rickborn<sup>33</sup> to be 2.4 kcal. based on the menthone-isomenthone isomerization. The two values are in good agreement and indicate that at best only  $\sim 3\%$  of the diaxial chair conformer IIIb can be present.<sup>34</sup>

(30) C. Djerassi and G. W. Krakower, *J. Am. Chem. Soc.*, **81**, 237 (1959); C. Djerassi and W. Klyne, *J. Chem. Soc.*, 2390 (1963).

(31) A. Moscowitz, ref. 5, Chapter 12.

(32) G. Ohloff, J. Osiecki, and C. Djerassi, *Ber.*, **95**, 1400 (1962).

(33) B. Rickborn, *J. Am. Chem. Soc.*, **84**, 2414 (1962); however, see W. D. Cotterill and M. J. T. Robinson, *Tetrahedron*, **20**, 777 (1964).

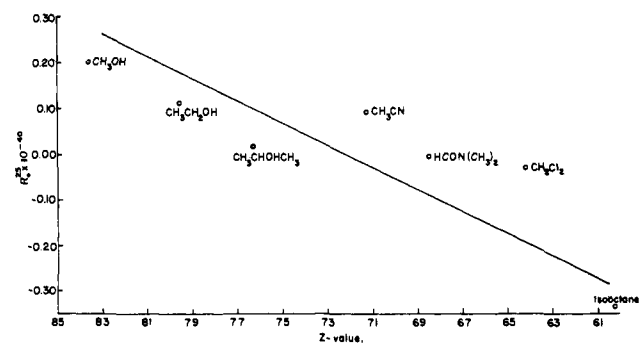


Figure 5. Plot of rotational strengths ( $R_0^{25}$ ) of (-)-menthone (III) in various solvents vs.  $Z$ -values.

This result requires that the absolute rotational strength of IIIb be much larger than that of IIIa in order not to be swamped out by the larger population level of IIIa. The large calculated amplitude for IIIb of -131 as compared to +12 for conformer IIIa is consistent with this requirement. A similar situation is found in the equilibrium  $\text{IIa} \rightleftharpoons \text{IIb}$ .<sup>23</sup>

The circular dichroism of (-)-menthone exhibits a strong solvent dependence. Some of the curves are shown in Figure 4 and the rotational strengths in various solvents are given in Table II. A rough correlation of the rotational strength,  $R_0^{25}$ , and Kosower's  $Z$ -values<sup>25</sup> (an empirical index of solvent polarity) is shown in Figure 5. The scatter in the  $Z$ -value plot is not wholly unexpected (see above) since solvent effects such as those occurring with  $5\alpha$ -cholestan-3-one,<sup>9a</sup> which are not correlated with  $Z$ -values, are probably also operative. Nevertheless, it appears that the diequatorial chair conformer is favored to an increasing extent in polar solvents.

Table II. Rotational Strengths of (-)-Menthone and (+)-Isomenthone in Selected Solvents

Solvent	$R_0^{25} \times 10^{40}$	
	(-)-Menthone	(+)-Isomenthone
Chloroform		+6.50
Methyl alcohol	+0.20	+6.63
Methyl formate	+0.12	+5.57
Ethyl alcohol	+0.11	
Acetonitrile	+0.09	+5.27
Ethyl ether	+0.05	
Isopropyl alcohol	+0.02	
Dimethylformamide	+0.00	
Methylene chloride	-0.02	+6.66
Dioxane	-0.07	+5.12
EPA (5:5:2)	-0.14	
Carbon tetrachloride	-0.22	+5.94
P5M1 <sup>a</sup>	-0.31	
Isopentane	-0.33	
Isooctane	-0.33	+4.75

<sup>a</sup> Isopentane-methylcyclohexane (5:1).

The C.D. curves of (+)-isomenthone (IX) in EPA (Figure 6) and in other solvents (Figure 7) are distinct

(34) (a) Since the energy necessary to cause ring deformation to a twist form in cyclohexanones is about 2.7 kcal.,<sup>34b</sup> appreciable amounts of such conformations relative to IIIb may be present in the conformer equilibrium of III. However, the nonbonded interactions (which are destabilizing compared to twist-cyclohexanone itself) due to the methyl and isopropyl groups indicate the possible importance of these forms will be small. (b) N. L. Allinger, *J. Am. Chem. Soc.*, **81**, 5727 (1959).

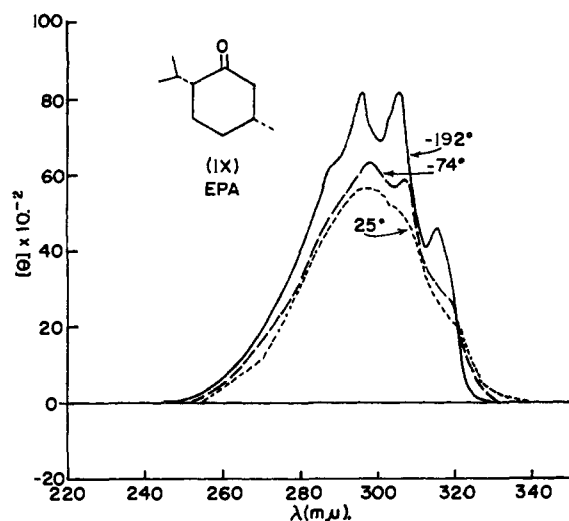
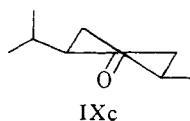


Figure 6. Circular dichroism curves of (+)-isomenthone (IX) in EPA at +25, -74, and -192°.

from those of (-)-menthone (III) in that they show only a single maximum in the 300-m $\mu$  region. The increase in rotational strength upon going to lower temperature (in EPA:  $R_0^{25} = +5.21 \times 10^{-40}$  c.g.s.,  $R_0^{-192} = +6.66 \times 10^{-40}$  c.g.s.) confirms that the positive rotating conformer IXa<sup>35</sup> is the more stable one in agreement with previous findings.<sup>29, 33, 35</sup> The



other conformer IXb would be expected to exhibit a weak negative Cotton effect in light of the octant rule.<sup>27</sup> The rotational strengths of (+)-isomenthone in various solvents are given in Table II. These rotational strengths are not correlated with  $Z$ -values<sup>25</sup> as was the case with (-)-menthone (III) and appear more similar

(35) The possibility that the highly positive-rotating twist form IXc,<sup>29</sup> makes a major contribution to the circular dichroism of IX is doubtful on the following grounds. Since IXc is energetically less favorable than IXa, its population will decrease on lowering the temperature. Accordingly, the strongly positive contribution of IXc will be replaced by the weaker positive contribution of IXa and a net decrease in rotational strength of IX at lower temperatures would be expected. The observed increase in rotational strength of IX at low temperatures speaks against this possibility.

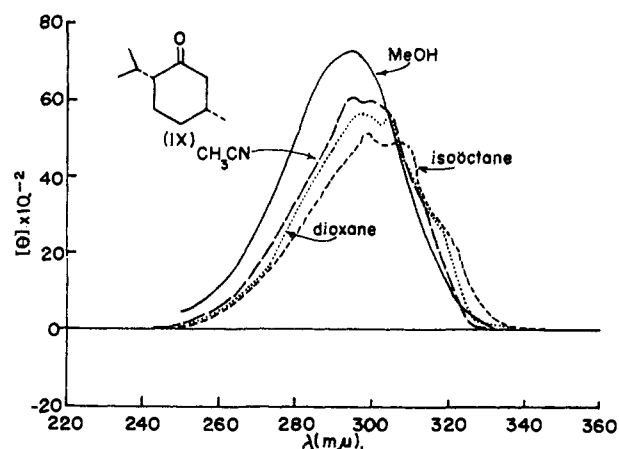


Figure 7. Circular dichroism curves of (+)-isomenthone (IX) in various solvents at +25°.

to the "increment" type<sup>9a</sup> of solvent effect. For example, IX shows a rotational strength increment change in going from isooctane to chloroform of  $+1.75 \times 10^{-40}$  c.g.s. units as compared with a change of  $+1.83 \times 10^{-40}$  c.g.s. units<sup>9a</sup> for a similar solvent change in 5 $\alpha$ -cholestan-3-one (VI). It would appear then that solvents do not greatly affect the conformational equilibrium IXa  $\rightleftharpoons$  IXb, in contrast to the striking effect noted with the epimer III.

#### Experimental

All measurements were performed in Spectrograde or purified solvents. The EPA solvent consisted of ether-isopentane-ethanol in a ratio of 5:5:2 by volume. The circular dichroism measurements were made using a Baird-Atomic/Jouan dichrograph operating with a photo-multiplier voltage of 1.2 kv. and following the procedures and molecular ellipticity calculations outlined earlier.<sup>36</sup>

*Acknowledgment.* We are greatly indebted to Mrs. Ruth Records for her able technical assistance in the circular dichroism measurements and to Mr. T. Bouman (University of Minnesota) for his contributions to the computer calculations.

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