Anal. Calcd. for $C_{14}H_{19}NOS$: C, 67.44; H, 7.68. Found: C, 67.70; H, 7.74.

N-(Thioncholanyl)morpholine (*XVII*). The usual reaction with 264 mg. of N-(cholanyl)morpholine [m.p. 134.5–136°, white crystals from ethanol–water, $[\alpha]^{26}D$ +24° (*c* 0.891), obtained from cholanic acid[24] by treat-ment of the acid chloride[25] with 50% morpholine in benzene] gave 75 mg. of yellow plates, m.p. 182.5–185°, no infrared absorption between 5 and 6.65 μ, $\lambda_{max}^{dioxane}$ 353 mμ (ϵ 53) and 280 mμ (ϵ 14,700).

Anal. Calcd. for $C_{28}H_{47}NOS$: C, 75.46; H, 10.63. Found: C, 75.04; H, 10.61.

Optical Rotatory Dispersion Studies. XCVIII.[1] The Conformation of the 17-Acetyl Group in Steroids and Its Correlation with Variable-Temperature Circular Dichroism[2]

Keith M. Wellman[3] and Carl Djerassi

Contribution from the Department of Chemistry of Stanford University, Stanford, California. Received August 5, 1964

The conformation of the 17-acetyl side chain in several 20-keto steroids has been examined by conformational analysis and a correlation has been made with the observed temperature-dependent circular dichroism. In general, it has been found that the acetyl group has two preferred orientations: one exhibiting a strong positive Cotton effect, the other a negative one. The presence or absence of β-substituents at C-13 and C-16 alters the conformational preference of the acetyl side chain in a predictable manner for the substances examined.

Although the octant rule[4] has been applied to con-figurational and conformational problems mainly in substituted cyclohexanones where spatial relationships are either well established or can be deduced from the resulting Cotton effect, there is no *a priori* reason why the rule cannot be applied to acyclic carbonyl com-pounds as well. Presumably the hesitancy to use the octant rule in open-chain systems arises from the lack of conformational homogeneity in these substances, as well as the inherent difficulties in making a clear-cut assignment of the preferred conformation in an acyclic system. Nevertheless, a start in this direction has been made by several investigators.[5,6]

17-Acetyl steroids seemed a likely candidate for such a study for two reasons. First, the system is simple in the sense that conformational changes will be localized mainly in rotation about the C-17–C-20 bond and, second, 17-acetyl steroids are of interest both chemically and biologically. In an early piece of work, Djerassi[7] successfully employed optical rotatory dispersion (O.R.D.) measurements to determine the configuration

of 17-acetyl groups. Thus, a strongly positive Cotton effect signified a 17β-acetyl substituent, whereas a negative Cotton effect was associated with a 17α-grouping. This early work was confirmed and further extended by Struck and Hautman[8] to a series of sub-stituted pregnan-20-ones. These authors noted vicinal interactions in certain cases between C-16 substituents and the C-20 keto group. Crabbé has utilized O.R.D.[9] and circular dichroism[9,10] (C.D.) methods in a study of *cis*- and *trans*-16-substituted 17-acetyl steroids and sug-gested that the amplitude changes caused by C-16 substituents were probably due to a combination of effects including steric factors (such as the conforma-tion of the acetyl side chain, ring D, and the C-16 substituent) as well as electronic effects introduced by the C-16 group. Snatzke and his group[11] recently reported upon the contributions of C-15 and C-11 substituents to the rotational strengths of C-20 ketones. Interestingly, Snatzke, as did Crabbé,[10] noted a striking effect on the Cotton effect of 17β-acetyl steroids when a 16β-methyl was introduced into the system, the Cotton effect actually inverting from strongly positive to weakly negative. This transformation was at-tributed to a conformational change of the 20-keto side chain. Dipole moments have been used by Allinger and DaRooge to investigate the conformational preference of a 17-acetyl group.[12] These authors con-cluded that a conformation similar to VIIa (see Figure 1) prevailed at room temperature. A detailed con-formational analysis of the 17-acetyl conformers was not provided by the authors. Rakhit and Engel have also commented upon the conformation of the 20-keto side chain and its relationship to the observed reduction pattern of 20-ketones to give either 20α- or 20β-alcohols.[13] In general, the latter authors

(1) Paper XCVII: J. V. Burakevich and C. Djerassi, *J. Am. Chem. Soc.*, 87, 51 (1965).

(2) Supported in part by Grants No. GP1979 and G-19905 from the National Science Foundation.

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

(4) W. Moffit, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Am. Chem. Soc.*, 83, 4013 (1961).

(5) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill, Book Co., Inc., New York, N. Y., 1960, p. 128.

(6) (a) M. J. T. Robinson, *Chem. Ind.* (London), 932 (1964); (b) J. C. Danilewicz and W. Klyne, *J. Chem. Soc.*, in press.

(7) C. Djerassi, *Bull. soc. chim. France*, 741 (1957).

(8) W. A. Struck and R. L. Hautman, *J. Org. Chem.*, 26, 3883 (1961).

(9) P. Crabbé, *Tetrahedron*, 19, 51 (1963).

(10) P. Crabbé, F. McCapra, F. Comer, and A. I. Scott, *ibid.*, 20, 2455 (1964). For related n.m.r. studies see A. D. Cross and P. Crabbé, *J. Am. Chem. Soc.*, 86, 1221 (1964), and A. D. Cross and C. Beard, *ibid.*, 86, 5317 (1964).

(11) G. Snatzke, H. Pieper, and R. Tschesche, *Tetrahedron*, 20, 107 (1964).

(12) N. L. Allinger and M. A. DaRooge, *J. Am. Chem. Soc.*, 83, 4256 (1961).

(13) S. Rakhit and Ch. R. Engel, *Can. J. Chem.*, 40, 2163 (1964).

agreed with Allinger and DaRooge, although they suggested that a second conformation corresponding to VIa below may also be significant.

In view of the expected dependence of the observed rotational strength of pregnan-20-ones on the conformation of the 17-acetyl group, it seemed worthwhile to apply some of the more recent advances in conformational analysis in an attempt to correlate the preferred conformation with the observed Cotton effects. The availability of an apparatus[14] to make variable-temperature C.D. measurements promised to be very useful. Of immediate interest in this problem is the conformation which the D ring assumes. Brutcher and Bauer have pointed out that there are three most favorable forms—two envelope conformations and a half-chair form.[15] The half-chair is the form which results when Dreiding models are used to construct the steroid nucleus. In general, for the parent compound androstane, as well as several ring D substituted derivatives, the calculations of Brutcher and Bauer indicated that two conformations (one of which was always the half-chair) were at least 1.5 kcal. more stable than the third. These two seldom differed by more than 0.5 kcal. which precluded a large predominance of either one at room temperature. Unfortunately, calculations were not performed on any 17-acetyl derivatives. Because of the *trans* attachment of ring D to the six-membered C ring, the cyclopentane ring is relatively rigid, pseudorotation in the usual sense being removed. Furthermore, Dreiding models indicate that a change in ring D conformation from an envelope form to a half-chair results in only a slight change in the position of the acetyl grouping. Therefore, as a first approximation the half-chair has been assumed to represent adequately ring D throughout the following discussion.

As a result of microwave studies upon molecules of the type $CH_3C(=O)X$, where X is hydrogen,[16] fluorine,[17] chlorine,[18] and the cyano group,[19] several workers have concluded that the carbonyl group in its equilibrium position eclipses a C–H bond. If for the moment we assume that an extension of these findings holds for the 17β-acetyl grouping,[20] three conformations, I–III (see Figure 1), result. In I the carbonyl overlaps the 17α-hydrogen, and in II and III the carbonyl is overlapping a C–C bond. Inspection of Dreiding models immediately shows severe steric problems arising for the model conformations I–III. Thus, in I the interaction between the C-21 and C-18 methyl groups is reminiscent of the steric repulsions present in 1,3- (diaxial) dimethylcyclohexane[21] and would be expected to be highly destabilizing. Conformation
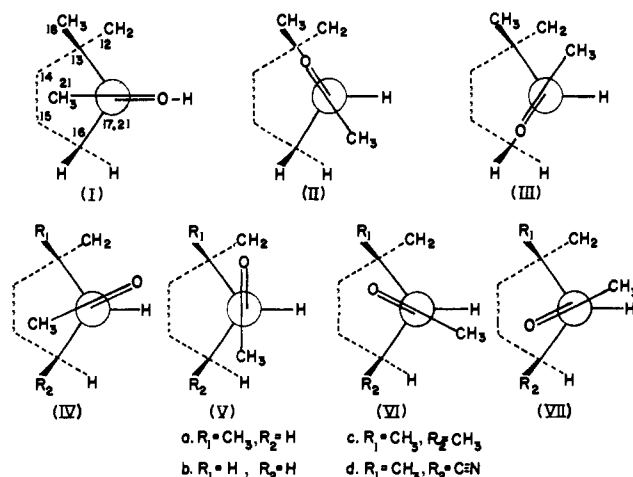

Figure 1. Partial structures showing projections of ring D and the 17β-acetyl group conformations as viewed from C-20 to C-17.

II has an n-*skew*-butanal interaction, *i.e.*, an interaction between the nonbonding electron pair on the oxygen and the hydrogen atoms on the C-18 methyl group, which is destabilizing to the extent of about 1.6 kcal.[22] Finally, in III the interaction between the C-21 methyl group and the hydrogen atoms attached to C-18 and C-12 is similar to, though more severe than, that present in axial methylcyclohexane. The nonbonded interactions in I–III can, however, be greatly relieved by simple rotation about the C-17–C-20 bond. Thus, I leads to IVa, II gives Va and VIa, and III leads to VIIa (see Figure 1). The other possible rotamers which could arise from I and III lead to increased nonbonded interactions as compared to that existing in the original models and therefore may be disregarded.

An analysis of the interactions present in IVa–VIIa shows the following. (1) The C-21 methyl–C-18 methyl interaction in I is diminished slightly only at the cost of an energetically unfavorable eclipsing between the C-21 methyl and the C-16 methylene groups in conformer IVa. Therefore, IVa is still a high energy form. (2) In conformer Va, though it has a slightly diminished n-*skew*-butanal interaction, the eclipsing of the 21-methyl and 16-methylene groups will greatly increase its energy. (3) The n-*skew*-butanal destabilizing interaction present in II is essentially the same in VIa; however, the *skew*-butane interaction between the C-21 methyl and the C-16 methylene groups is diminished. Therefore, VIa is of lower energy than II. (4) Lastly, rotation about the C-17–C-20 bond in III to give VIIa has made the van der Waals repulsion between the C-21 methyl group and the hydrogen atoms attached to C-18 and C-12 of secondary importance. At the same time a π-*skew*-butanal interaction (*i.e.*, an interaction between the π-orbital of the carbonyl function and the hydrogen atoms of the C-18 methyl group)[22] also present in III is worsened. However, since this interaction has been shown to be small (*ca.* 0.1 kcal.[22]), it is assumed to be less than 0.5 kcal. in VIIa. In summary, conformations IVa and Va are of high energy relative to VIa and VIIa. The energy difference between the low energy conformers VIa and VIIa is about 1.1 kcal. with VIIa the more stable one.

(14) K. M. Wellman, E. Bunnenberg, and C. Djerassi, *J. Am. Chem. Soc.*, 85, 1870 (1963); K. M. Wellman, R. Records, E. Bunnenberg, and C. Djerassi, *ibid.*, 86, 492 (1964).

(15) F. V. Brutcher and W. Bauer, *ibid.*, 84, 2236 (1962).

(16) R. W. Kilb, C. C. Lin, and E. B. Wilson, *J. Chem. Phys.*, 26, 1695 (1957).

(17) L. Pierce and L. C. Krishner, *ibid.*, 31, 875 (1959).

(18) K. M. Sinnott, *ibid.*, 34, 851 (1961).

(19) L. C. Krishner and E. B. Wilson, *ibid.*, 31, 882 (1959); L. C. Krishner, *ibid.*, 33, 304 (1960).

(20) The extrapolation of the eclipsed carbonyl and carbon–hydrogen bonds found in CH_3COX to 20-keto steroids is of dubious validity. Nevertheless, the resulting model conformations serve as a useful starting point in arriving at the preferred conformations and are used mainly for that reason.

(21) N. L. Allinger and M. A. Miller, *J. Am. Chem. Soc.*, 83, 2145 (1961).

(22) W. D. Cotterill and M. J. T. Robinson, *Tetrahedron*, 20, 777 (1964).

Dreiding models clearly show that conformation VIIa should—in the light of the octant rule[4]—exhibit a strong positive Cotton effect since almost the whole steroid skeleton lies in an upper left, rear octant relative to the 20-keto group. On the other hand, consideration of conformation VIa indicates that most of the steroid skeleton lies near or in one of the nodal planes of the carbonyl and therefore will exert a small effect. The main contributors to the rotational strength of VIa appear to be the C-13 carbon atom and C-16 methylene and C-18 methyl groups. The first two bear a roughly equatorial and axial relationship, respectively, to the carbonyl function in VIa, and therefore the "axial" C-16 methylene substituent with a negative contribution would be expected to dominate the positive contribution of the C-13 atom. The C-18 angular methyl group would definitely contribute in a negative sense. The presence of two such conformers in equilibrium will have predictable effects on the C.D. curves, since the observed curve will be composed of a population-weighted average of the rotational strengths of the species involved.[23] Anticipating the findings below, if the choice between preferred conformers is always that of VI or VII, which show negative and positive Cotton effects, respectively, the trend in the observed rotational strengths on going to lower temperatures will permit a decision on the conformational preference since the less stable rotamer will be frozen out.

As mentioned earlier, 17β-acetyl chromophores generally have strong positive Cotton effects[7–9] at room temperature. For example, 5α-pregnan-3β-ol-20-one acetate has a rotational strength at 27° of $+11.4 \times 10^{-40}$ c.g.s. If the above analysis is correct, the room temperature rotational strength is a population-weighted resultant and would be expected to increase at lower temperatures since the less stable, negatively rotating conformer VIa is diminishing. In agreement with this expectation, the rotational strength at $-192°$ has increased to $+13.6 \times 10^{-40}$ c.g.s. The relationship (eq. 1) between the observed rotational strength

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

$R_0{}^T$ and the rotational strengths (R_a and R_b) of two rapidly interconverting species[23b] (a and b where b is less stable) should be applicable to the equilibrium VIIa $\rightleftarrows$ VIa, where the free energy change is 1.1 kcal. If R_a (rotational strength of VIIa) is taken as 13.5×10^{-40} c.g.s., R_b (rotational strength of VIa) is calculated to be 0.3×10^{-40} c.g.s. Since R_a is a minimum value because it is taken as $R_0{}^T$ at $-192°$, R_b must be considered a maximum value. The calculated value of the rotational strength of conformer VIa then is in good agreement with expectations.

3β-Hydroxyhexanordammar-20-one acetate (VIII) represents a very interesting case since the C-18 methyl group is lacking. In every conformation (IVb–VIIb) it is found that nonbonded interactions are diminished over those present in ketones with the angular methyl group. Thus, the strong interaction which existed between the C-18 and C-21 methyl groups in IVa is removed in IVb, but a severe van der Waals repulsion

(23) (a) Reference 6a, p. 164; (b) A. Moscowitz, K. Wellman, and C. Djerassi, *J. Am. Chem. Soc.*, **85**, 3515 (1963).

between the $16\beta,13\beta$-hydrogens and the C-21 methyl still remains. In Vb the absence of the 18-methyl has removed the n-*skew*-butanal repulsions present in Va; however, the partial eclipsing of the C-21 methyl

VIII

IX

X

XI
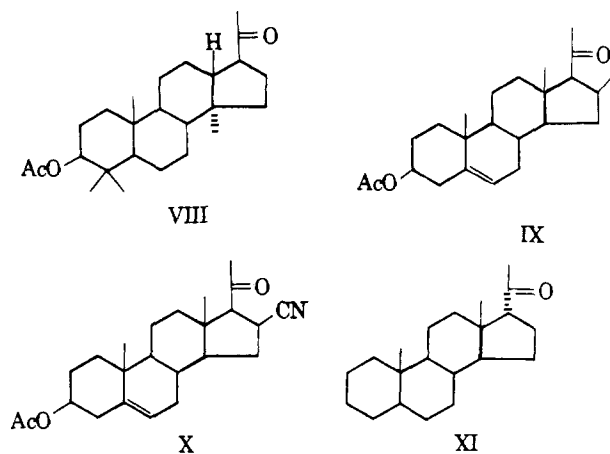
and C-16 methylene groups remains as a strong destabilizing factor. The n-*skew*-butanal interaction present in VIa is removed in VIb, a saving of about 1.6 kcal. of energy. Finally, in VIIa the π-*skew*-butanal interaction which was a small (*ca.* 0.5 kcal.) but destabilizing factor in VIIa is now absent. In the light of these considerations, it appears that VIb and VIIb are again the preferred rotamers and in this instance also of approximately equal energy, while IVb and Vb are energetically much less favored. Unlike the partial eclipsing (approaching an eclipsed butane interaction) of the C-21 methyl and C-16 methylene groups present in IVa and Va, the partial eclipsing of the carbonyl function with the C-16 methylene group in VIIa is of minor importance. This latter interaction is actually analogous to the eclipsing present in 2- (equatorial) methylcyclohexanone which has been shown[24] to be insignificant as a destabilizing factor. However, there remains in VIIb a van der Waals interaction between the C-21 methyl and the C-12 methylene groups not present in VIb, whereas VIb has an interaction between the C-21 methyl and the 16α-proton. All other interactions are assumed to be canceling. A Hill-type calculation[25] using the parameters suggested by Allinger and co-workers[26] indicates that these interactions are both stabilizing in VIb and VIIb, but that conformation VIIb is the more stable one by *ca.* 0.1 kcal. Because of the approximate nature of these calculations,[26,27] no attempt was made to optimize the inter-

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

(25) T. L. Hill, *J. Chem. Phys.*, **16**, 399 (1948).

(26) N. L. Allinger, J. Allinger, L. H. Freiberg, R. F. Czaja, and N. A. LeBell, *J. Am. Chem. Soc.*, **82**, 5877 (1960); N. L. Allinger and W. Szkrybalo, *J. Org. Chem.*, **27**, 722 (1962); N. L. Allinger and L. A. Freiberg, *J. Am. Chem. Soc.*, **84**, 2201 (1962).

(27) Cotterill and Robinson[22] have recently criticized the calculation by Allinger, *et al.*,[28] of the energy difference between 5α- and 5β-cholestan-4-one. The former authors correctly point out that the destabilizing interaction between the 4α- and 7α-hydrogen atoms in 5β-cholestane is not present in 5β-cholestan-4-one as indicated by Allinger, *et al.* There is another discrepancy in the Hill-type calculation made by Allinger, *et al.*,[28] to obtain the van der Waals interaction energy between the carbonyl oxygen and the 7α-hydrogen in 5β-cholestan-4-one. Thus, Dreiding models indicate the distance between the oxygen and the hydrogen to be 2.12 Å. rather than the 2.0 Å. reported.[28] Using this new value to calculate the energy difference between 5α- and 5β-cholestan-4-one, the difference is found to be only 0.34 kcal. rather than 0.88 kcal. when 2.0 Å. is used. Experimentally the energy difference was reported to be >2.1 kcal.[28] This finding illustrates two points. First,
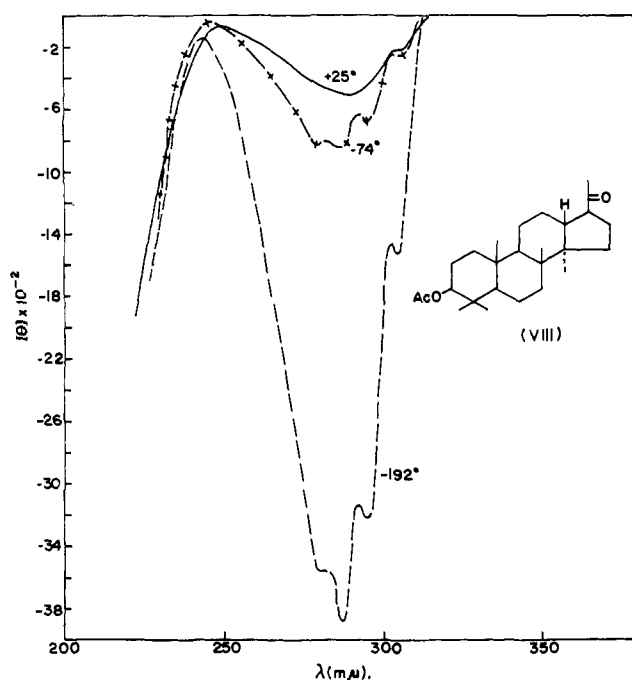
Figure 2. Circular dichroism curves of 3β-acetoxyhexanordam-mar-20-one (VIII) in EPA at +25, −74, and −192°.

Figure 3. Rotational strength $(R_0{}^T)$ vs. temperature (T) for a two-species equilibrium with ΔG of 0.1, 0.3, 1.0, and 2.0 kcal.

actions in VIb and VIIb by small rotations about the C-17–C-20 bond. Therefore, this calculation can only be taken to imply that the energy difference between the conformations VIb and VIIb of VIII is very small.

Removal of the angular 18-methyl group will not be expected to influence greatly the Cotton effects of the two low energy conformers VI and VII. Consequently, if the acetyl group of VIII exists in conformation VIb, a negative Cotton effect can be expected, while a positive one would be predicted for VIIb. In this case the observed temperature-dependent C.D. curves can provide the answer to the relative stabilities of conformers VIb and VIIb. Since the observed rotational strength will be weighted according to the composition of the conformers and their rotational strengths, which have a canceling effect in this case, it is not surprising that a *weak* negative Cotton effect $(R_0{}^{25} = -0.47 \times 10^{-40}$ c.g.s.) is noted at room temperature (see Figure 2). On the other hand, there is a striking increase in the negative rotational strength upon lowering the temperature to −192° $(R_0{}^{-192} = -3.4 \times 10^{-40}$ c.g.s.; see Figure 2). Thus, the C.D. curves indicate a conformational preference in VIII for VIb which is opposite to the result obtained in pregnan-20-ones which possess an angular methyl group. It is interesting to note that there is only a slight increase in $R_0{}^T$ of

the Hill calculation accounts rather poorly for the energy difference in the cholestan-4-ones and, therefore, for an n-*skew*-butanal interaction.[22] Secondly, because van der Waals repulsive interactions increase exponentially upon close approach, the Hill calculation is very sensitive to distances when two atoms interact strongly. This is indicated by the energy change in the above example when the distance changes from 2.0 to 2.12 Å. However, it is precisely when steric interactions are most unfavorable that deformation of bond angles occur,[29] making an accurate estimate of the critical distances difficult. These problems which are inherent in the Hill calculation further serve to emphasize its approximate nature.

(28) N. L. Allinger, M. A. DaRooge, and R. B. Hermann, J. Org. Chem., **26**, 3626 (1961).

(29) E. L. Eliel and J.-C. Richer, Abstracts, 130th National Meeting of the American Chemical Society, St. Louis, Mo., March 1961, p. 41-O; D. S. Noyce and L. J. Dolby, J. Org. Chem., **26**, 3619 (1961).
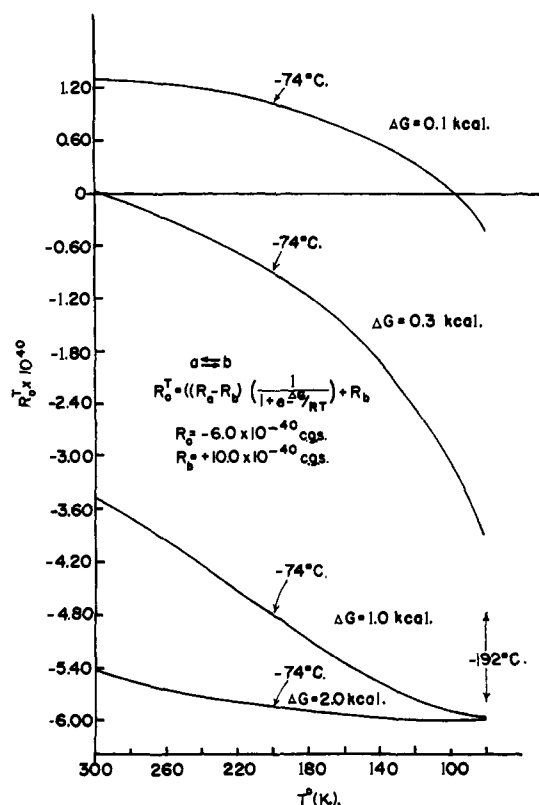
VIII down to −74°. This is expected when the free energy difference between conformers is small as is the case for VIb and VIIb. For example, Figure 3 shows a plot of $R_0{}^T$ vs. the temperature T for the case of two conformers (a and b) with various ΔG; the arbitrarily assumed rotational strengths for a and b are −6.0 × 10^{-40} and 10 × 10^{-40} c.g.s., respectively. As can be seen from the plot for the case where ΔG = 0.1 kcal., $R_0{}^T$ varies only slightly (ca. 13%) from 25 to −74°, the main change occurring from −74 to −192°. As ΔG increases, the change noted over the +25 to −74° range increases until, at ΔG = 2.0 kcal, the major change in the observed rotational strength occurs in that temperature region.

A situation somewhat similar to that present in the nordammarone VIII is present in 3β-acetoxy-16β-methyl-Δ5-pregnen-20-one (IX). The steric effects of the 18-methyl and 16β-methyl groups in the preferred conformations VIc and VIIc roughly tend to cancel; however, there are small energy differences which make a choice between the two conformations difficult. The C.D. curves, which will indicate the conformational preference of IX, are unusual in the sense that they exhibit a double maximum in the 300-mμ region (Figure 4). This unique feature has been noted previously,[30] and in the case of highly asymmetric molecules such as the bridged bicyclics this phenomenon appears to be associated with solvation effects.[31] However, in other cases the presence of two oppositely signed

(30) For full discussion, see K. M. Wellman, P. H. A. Laur, W. S. Briggs, A. Moscowitz, and C. Djerassi, J. Am. Chem. Soc., **87**, 66 (1965).

(31) A. Moscowitz, K. M. Wellman, and C. Djerassi, Proc. Natl. Acad. Sci. U. S., **50**, 799 (1963); C. Coulombeau and A. Rassat, Bull. soc. chim. France, 1673 (1963).

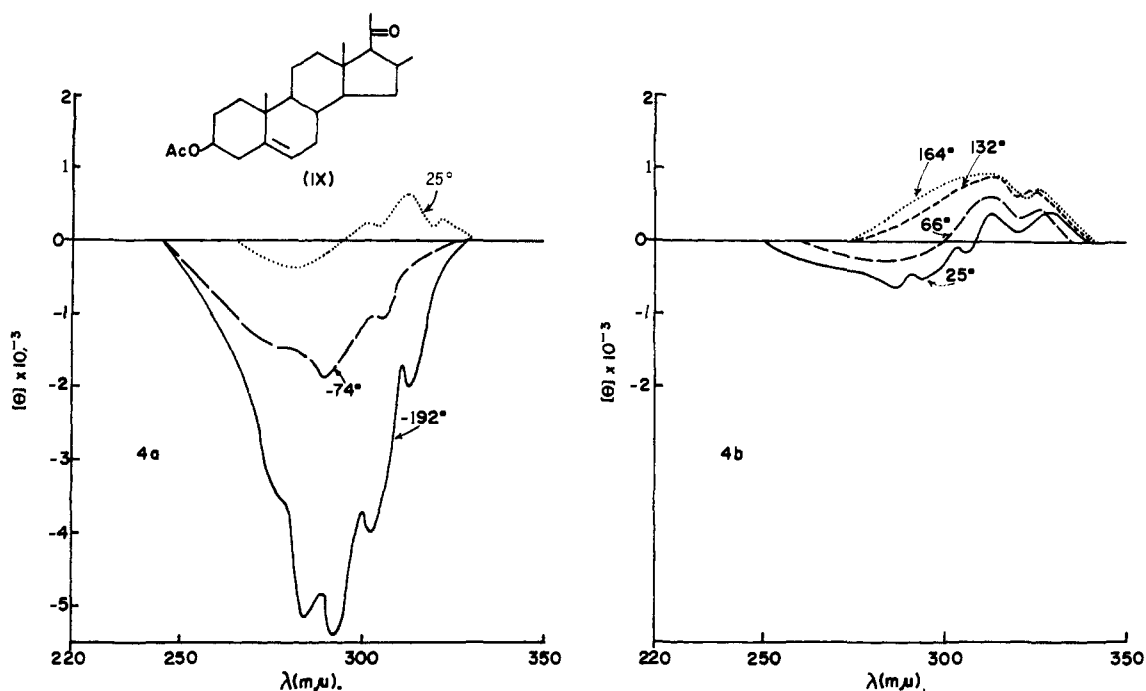Figure 4. Circular dichroism curves of 3β-acetoxy-16β-methyl-Δ⁵-pregnen-20-one (IX) in EPA (a) at +25, −74, and −192°, and in decalin (b) at +25, +66, +132, and +164°.
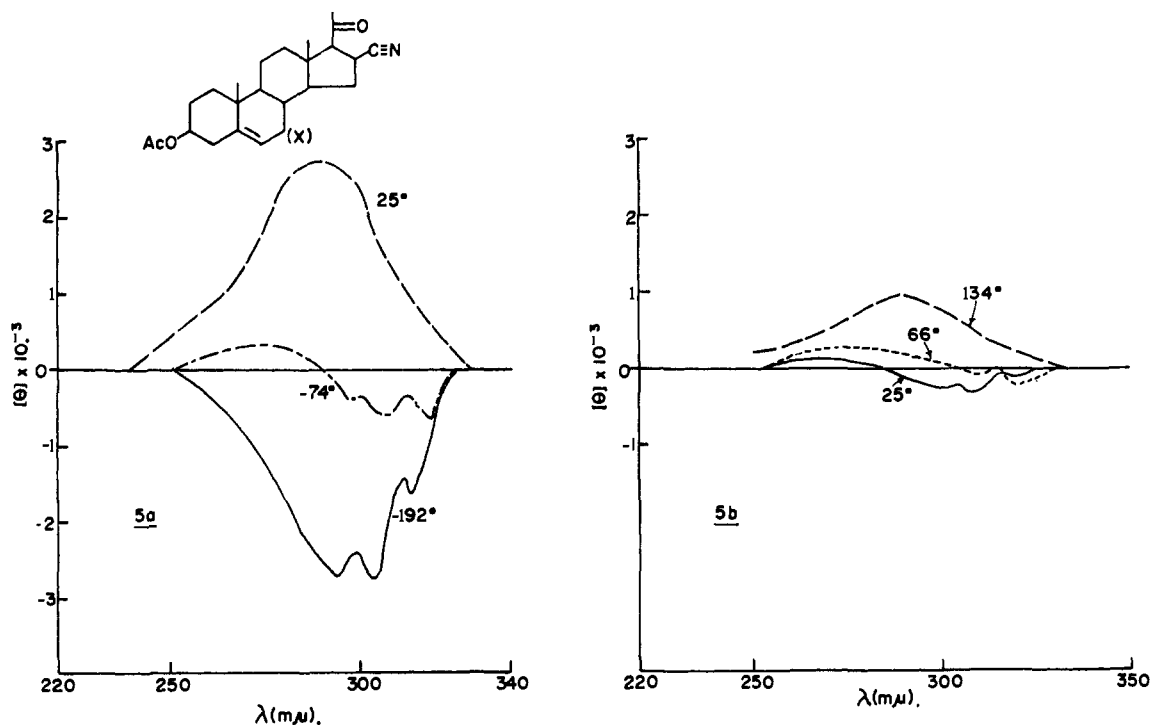

Figure 5. Circular dichroism curves of 3β-acetoxy-16β-cyano-Δ⁵-pregnen-20-one (X) in EPA (a) at +25, −74, and −192°, and in decalin (b) at +25, +66, and +134°.

maxima separated by *ca.* 30 mμ in C.D. spectra are indicative of simple conformational changes.[30] In the case of the 16β-cyanopregnen-20-one (X) discussed below, the double maxima (Figure 5) are clearly attributable to conformational changes rather than direct solvation changes. By analogy we will assume the positive and negative maxima observed for IX to be attributable to two oppositely signed Cotton effects separated by 1–5 mμ and associated with conformations

VIc and VIIc, respectively. The fact that the molecular ellipticities of the positive and negative maxima in Figure 4 are very weak rather than strong, as predicted for the Cotton effects associated with conformers VIIc and VIc, further indicates that the maxima are displaced only slightly, which is compatible with conformational changes.[30] The absence of two peaks in the analogous substance VIII simply means that the two conformers have their C.D. curves centered at

the same wave length. The increase in the negative Cotton effect band at low temperature (see Figure 4a) indicates that conformer VIb of IX is the more stable one in agreement with the nordammarone VIII, to which it bears a strong resemblance. The high temperature curves[32] of IX (Figure 4b) show an augmentation of the Cotton effect in the expected manner owing to the unstable rotamer until 134°, where the positive Cotton effect completely dominates the spectrum. The vibrational fine structure present at 66° in decalin disappears at the higher temperatures because of the increase of low frequency vibrations. If it is assumed that the entropy difference between VIb and VIIb is small, the positive rotational strength observed at high temperatures requires that the absolute value of the rotational strength of VIIb be greater than that of VIb; a similar conclusion is reached from an application of the octant rule through inspection of Dreiding models.

3β-Acetoxy-16β-cyano-Δ^5-pregnen-20-one (X) offers another interesting example. Conformer VIIa was estimated to be 1.1 kcal. more stable than VIa (see above). Introduction of a 16β-cyano group into VIIa should raise the van der Waals repulsion energy only slightly because the steric requirements of a cyano group are small.[33] However, the presence of the cyano group does introduce strong electrostatic repulsions into VIId because the carbonyl and cyano group dipoles are oriented almost parallel, whereas in VId the dipoles are farther apart and oriented at cross angles to one another. A calculation of the energy difference between VId and VIId arising from electrostatic repulsions was made according to the general procedure employed by Corey[34] and Allinger and Allinger.[35] The relationship derived by Jeans[36] for two dipoles interacting in a medium of a dielectric constant of 2[35] was used. Dreiding models were employed to estimate distances and angles between the dipoles which were assumed to be localized at seven-eighths the C=O or C=N bond distance and near the oxygen or nitrogen. The electrostatic interaction was found to be 0.98 kcal. in VId and 2.73 kcal. in VIId. Since VIIa is ca. 1.1 kcal. more stable than VIa, the introduction of the cyano group results in a net preference for VId by 0.6 kcal. The steric repulsions in VIId, as discussed above, will tend to make this energy difference even larger. Therefore, at low temperatures the negative Cotton effect of conformer VId would be expected to dominate the C.D., and this is exactly what is observed (Figure 5a). Thus, the rotational strength at −192° is −2.4 × 10⁻⁴⁰ c.g.s. At room temperature it is +2.7 × 10⁻⁴⁰ c.g.s. in EPA as would be expected for an increase in the population of the strongly positive-rotating conformer VIId. Interestingly, maxima of the C.D. bands of the two conformers are apparently

(32) The high temperature cell was developed by Dr. P. H. A. Laur in this laboratory and full details 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. 23b).
(33) C. Djerassi, R. A. Schneider, H. Vorbrueggen, and N. L. Allinger, *J. Org. Chem.*, 28, 1632 (1963); N. L. Allinger and W. Szkrybalo, *ibid.*, 27, 4601 (1962); B. Rickborn and F. R. Jensen, *ibid.*, 27, 4606 (1962).
(34) E. J. Corey, *J. Am. Chem. Soc.*, 75, 2301 (1953).
(35) J. Allinger and N. L. Allinger, *Tetrahedron*, 2, 64 (1958).
(36) J. H. Jeans, "Mathematical Theory of Electricity and Magnetism," 5th Ed., The University Press, Cambridge, Mass., 1933, p. 377.
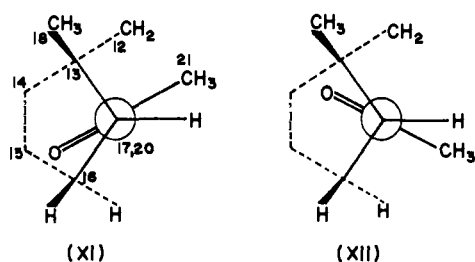

Figure 6. Partial structures showing ring D and the 17α-acetyl group conformations as viewed from C-17 to D-20.

separated slightly and, being of opposite sign, give rise to a C.D. curve with double maxima. At −74° in EPA (Figure 5a) or room temperature in decalin (Figure 5b) a double-humped C.D. curve is observed with the positive C.D. maximum of conformer VIId appearing at shorter wave length than VId, in contrast to the situation existing in the 16β-methyl analog IX (Figure 4). The observation that the short wavelength band increases at the expense of the long wavelength band with *increasing* temperature (Figure 5) is not consistent with the short wave-length band being a solvated species and the long wave-length band a nonsolvated species.[30] Of equal interest is the fact that at room temperature in decalin (Figure 5b) the population of the species VId has increased such that its negative Cotton effect is apparent, whereas in EPA at room temperature (Figure 5a) the population of VId has diminished to such an extent that the positive Cotton effect of the less stable conformer VIId dominates the spectrum. This result is expected since the polar character of EPA solvent would increase the stability, and hence the population, of VIId by decreasing its unfavorable electrostatic interaction.

The possible conformers of 17-isopregnan-20-one (XI) were analyzed in a manner similar to that outlined above. Interactions between the C-21 methyl group and hydrogen atoms attached to C-12, C-14, or C-16 are highly destabilizing in all conformations except XI and XII (Figure 6). The main energy difference between these two conformers is associated with a minor interaction between the hydrogen atoms on C-21 and C-12 in XI, and the interaction between the oxygen and the C-12 and C-14 β-hydrogens in XII (Figure 6). It should be noted that this latter interaction is similar to that between the oxygen and *t*-butyl methyl groups in 2- (equatorial) *t*-butylcyclohexanone. An experimental determination of this oxygen–*t*-butyl interaction has not been made although it must be strong. For example, *cis*-4,6-di-*t*-butylcyclohexane-1,3-dione is converted almost quantitatively into the *trans* isomer by aqueous alkali.[37] Even more pertinent is the report that the interaction between the oxygen of an 11-keto steroid with the C-1 proton, an interaction which is formally analogous to that found in 2- (equatorial) *t*-butylcyclohexanone, causes conformational changes in ring A[14] and/or ring C.[38] In view of these facts conformer XI would be expected to dominate strongly an equilibrium between species XI and XII. Inspection of models indicates that the conformation XI should exhibit a negative Cotton effect, whereas a positive one

(37) N. J. W. Pumphrey and M. J. T. Robison, *Tetrahedron Letters*, 741 (1963).
(38) G. Snatzke and D. Becher, *Tetrahedron*, 20, 1921 (1964).

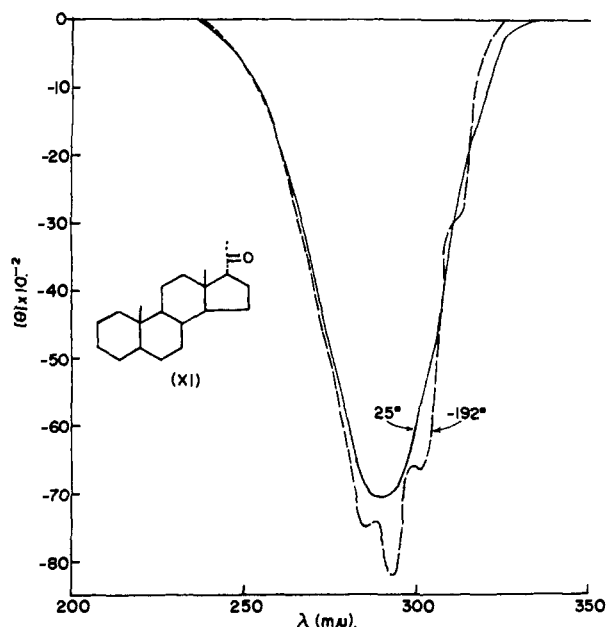Figure 7. Circular dichroism curves of 5α-pregnan-20-one (XI) in EPA at +25 and −192°.

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[4] 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.[39]

(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.[1]
Superposed Multiple Cotton Effects of Saturated Ketones and Their Significance in the Circular Dichroism Measurement of (−)-Menthone[2]

Keith M. Wellman,[3a] P. H. A. Laur,[3b] W. S. Briggs, Albert Moscowitz,[4] 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 → π* 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 mμ will arise whenever two Cotton effects of similar amplitudes, but opposite sign, are superposed with their individual maxima separated by 1 to 20 mμ. The difficulties of distinguishing between the two phenomena 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.[5] For example, Pariaud[6] 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).