The low-temperature measurements were accomplished by passing precooled nitrogen through a dewar-jacketed probe with monitoring of the temperature by a copper–constantan thermocouple. For the spectra taken with the A-56/60A spectrometer, the Varian V-6057 variable temperature accessory was used. The temperatures were calibrated by replacing the sample tube with a similar one containing another thermocouple, and also by the temperature dependence of the chemical shift of the methanol hydroxyl group. The temperatures are believed to be accurate to ±2°.

The theoretical spectra and the Arrhenius plots were computed by an IBM 7094 II computer coupled to a Moseley X–Y plotter.

All of the *gem*-fluorocyclohexanes used in this study (except 1,1-difluorocyclohexane) and 1,1,2,2-tetrafluorocyclohexane were synthesized by the reaction of sulfur tetrafluoride with the corresponding ketones.[29] The ketones were synthesized as below or obtained commercially.

1,1-Difluorocyclohexane was obtained from K & K Laboratories, Plainview, N. Y.; bp 97–98° (745 mm), n^{22}D 1.3914 (lit.[30] bp 100.5°, n^{22}D 1.3906).

4,4-Dimethylcyclohexanone was prepared starting from isobutyraldehyde and methyl vinyl ketone, according to the procedure described by Bordwell and Wellman;[31] mp 38–39° (lit.[31] 39–40°).

4-Methyl-4-ethylcyclohexanone. 4-Acetyl-4-methylpimelonitrile was prepared from methyl ethyl ketone and acrylonitrile,[32] and converted *via* several intermediates into 4-methyl-4-ethylcyclohexane;[33] bp 92–95° (13 mm); carbonyl absorption, 1710 cm⁻¹ (lit.[33] bp 95–98° (15 mm)).

4-Chlorocyclohexanone was prepared starting from 1,4-cyclohexanediol, by way of 4-chlorocyclohexanol obtained from the mono-*p*-toluenesulfonate ester.[34] Oxidation[35] with sodium dichromate–sulfuric acid in ether at 0° gave the expected ketone (carbonyl absorption, 1715 cm⁻¹) which was used without purification.

The difluorocyclohexanes[29] were purified by distillation, except for the 4-*t*-butyl and 4-chloro compounds, which required preparative vpc at 90–100°. The purity of the products was checked by analytical vpc, infrared spectra (absence of carbonyl absorption), and elemental analyses. The proton nmr spectra were in agreement with the assigned structures, but not very characteristic, there being sharp signals for the alkyl substituents and broad peaks for the ring protons in the aliphatic region. The best evidence for the structure of the compounds was usually the fluorine resonance spectra.

The conditions used for synthesis[29] and physical properties of the hitherto unknown six *gem*-fluorocyclohexanes and 1,1,2,2-tetrafluorocyclohexane are summarized in Table IV.

In attempting to synthesize 2-methyl-1,1-difluorocyclohexane in a similar way from the corresponding ketone, a liquid with bp 111–112° (744 mm) was isolated, which seems to be **2-methyl-1,1,2-trifluorocyclohexane** (10% yield). This substance had in its proton resonance spectrum a doublet centered at 1.5 ppm for the methyl group (J_{HF} = 22 cps) and broad multiplet (1.4–2.5 ppm) for the ring protons. The fluorine spectrum showed a closely packed multiplet at about 2030 cps upfield from trifluoroacetic acid. Practically no change in the spectrum was observed at low temperature. Significant infrared absorptions were observed at 900, 980, 1045, 1120, 1175, 1350, and 1440 cm⁻¹.

Anal. Calcd for C₇H₁₁F₃: C, 55.25; H, 7.28. Found: C, 54.68; H, 7.09.

Several attempts to prepare 1,1,4,4-tetrafluorocyclohexane through the reaction of 1,4-cyclohexanedione with sulfur tetrafluoride at various conditions were unsuccessful, only starting material being isolated from the reaction mixture.

(29) W. R. Hasek, W. C. Smith, and V. A. Engelhardt, *J. Am. Chem. Soc.*, 82, 543 (1960).

(30) F. Cuthbertson and W. K. R. Musgrave, *J. Appl. Chem.*, 7, 99 (1957).

(31) F. G. Bordwell and K. M. Wellman, *J. Org. Chem.*, 28, 1347 (1963).

(32) H. A. Bruson and T. W. Riener, *J. Am. Chem. Soc.*, 64, 2850 (1942).

(33) R. N. Burnell and W. I. Taylor, *J. Chem. Soc.*, 3307 (1957).

(34) L. N. Owen and P. A. Robins, *ibid.*, 320 (1949).

(35) S. Sabetay and L. Palgray, *Bull. Soc. Chim. France*, 43, 906 (1928).

Preferred Conformations of the Cycloheptane Rings of A-Homosteroids[1]

J. Bryan Jones, J. Malcolm Zander, and Philip Price

Contribution from the Lash Miller Laboratories, Department of Chemistry, University of Toronto, Toronto 5, Ontario, Canada. Received August 30, 1966

Abstract: The conformational analytical procedure developed by Hendrickson for cycloheptanes has been applied to ring A of the A-homosteroids I–IV. Dipole moment, nuclear magnetic resonance, and optical rotatory dispersion data were used to assist in the selection of the preferred conformations, and, of these physical methods, the latter proved the most informative. The data in each case were consistent with a room-temperature equilibrium mixture of three "twist-chair" conformations. The reported conformations of the seven-membered rings of several other A-homosteroids, and of (+)-3- and (−)-4-methylcycloheptanones, for which ORD or CD data were available, have been reexamined and the previous assignments shown to be incorrect. Twist-chair conformations appear to be favored exclusively for the examples studied and, in the absence of overriding control of the conformations by bulky substituents, the carbonyl group prefers to be situated at the axis or adjacent carbon of the twist chair.

Duing the course of our studies on the specificities of certain steroidases and on the factors controlling the activity of steroid hormones, a series of steroids possessing a seven-membered ring A was synthesized. The structural and configurational range of A-homosteroids prepared to date[2,3] is summarized by structures I–IV. Since the steroidases of interest to us exhibit marked stereospecificity[4] in their combination with substrates and inhibitors, it was necessary to establish the preferred conformations of the cycloheptane rings of the above steroids in order that meaningful specificity studies could be carried out.

The procedures reported in the literature for the

(1) Part IV of the series: Steroids and Steroidases; part III, J. B. Jones and D. C. Wigfield, *Can. J. Chem.*, 44, 2517 (1966). Presented in part at the 49th Canadian Chemical Conference, Saskatoon, June 1966.
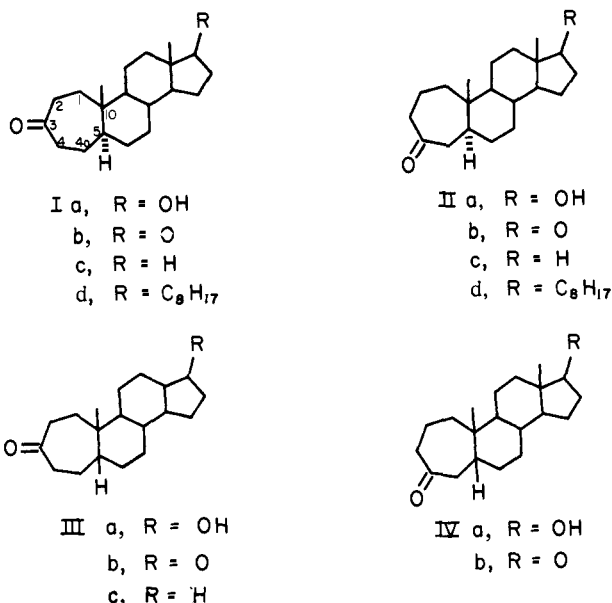
(2) J. B. Jones and P. Price, *Can. J. Chem.*, 44, 999 (1966).

(3) J. B. Jones, J. M. Zander, and P. Price, to be published.

(4) P. Talalay, *Ann. Rev. Biochem.*, 34, 347 (1965).

I a, R = OH
  b, R = O
  c, R = H
  d, R = C₈H₁₇

II a, R = OH
   b, R = O
   c, R = H
   d, R = C₈H₁₇

III a, R = OH
    b, R = O
    c, R = H
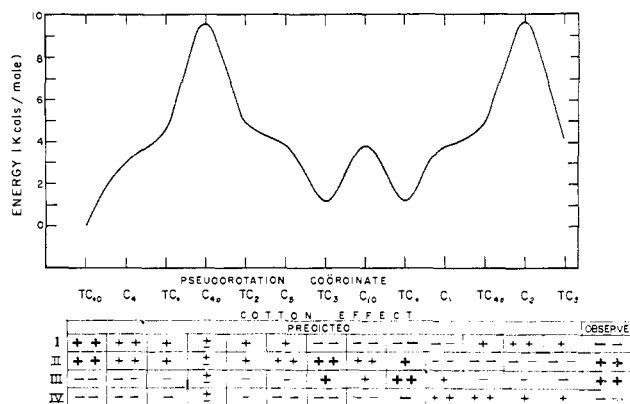
IV a, R = OH
   b, R = O

Figure 1. Energy functions calculated for the pseudo-rotation sequences of the cycloheptanone rings of I-IV. The signs and relative magnitudes of the Cotton effects predicted for each conformation were estimated from models[17] as illustrated in Figure 2. The predicted Cotton effects accentuated by heavy lines are those of the preferred conformations. Numerical values for the observed amplitudes of each compound studied are given in Table II.

conformational analysis of compounds containing a saturated seven-membered ring have been derived from studies on cycloheptane and its closely related monocyclic derivatives.[5] The most detailed calculations were carried out by Hendrickson[6] who showed that the preferred conformation, the twist chair (TC), was 2.2 kcal/mole lower in strain energy than the full chair (C), and 2.5 kcal/mole lower than the twist boat (TB). Other conformations, for example, full boat, were considered to be energetically prohibitive.[7] The general applicability of this analysis to more complex cycloheptane systems was illustrated by its

twist chair   chair

success in deriving the stereochemistry of some perhydroazulene sesquiterpenes.[6] A further application of this scheme to A-homo-5α-androstan-17β-ol-4-one (IIa) by Snatzke, Zeeh, and Müller[8] led to the conclusion that for this compound ring A existed as the twist chair with C₁₀ as the axis carbon (TC₁₀). Analysis of this conformation by the octant-rule[9],[10] method correctly predicted[8] the positive Cotton effect observed in the CD spectrum.

A similar analysis of the other 17β-hydroxy-A-homosteroids available to us, Ia–IVa, also pointed to TC₁₀ as the preferred conformation of ring A in each case. However, it was discovered that, whereas for the TC₁₀ conformations of the A-homo-4-ones IIa and IVa, the signs of the predicted (octant rule) and

observed Cotton effects were in agreement, those for the 3-ketones Ia and IIIa were not (see Figures 1 and 2). These conflicting results showed that the Hendrickson cycloheptane analysis could not alone be relied upon for the more complex derivatives, and led us to consider its application to A-homosteroids in greater detail using physical methods sensitive to differences in conformation such as ORD, nmr, and dipole moment determinations, as additional guides for the selection of the preferred conformations.[11]

A complete study[14] of the pseudo-rotation sequences for the A-homo ketones I–IV led to identical energy functions in each case (Figure 1). If this function represented accurately the relative energies of the conformations, then TC₁₀ would undoubtedly be preferred, being favored over TC₃ and TC₄ by 1.4 kcal/mole. This difference in strain energy would give a room temperature equilibrium mixture containing >90%[16] of TC₁₀ and ~4.5% each of TC₃ and TC₄. The proportion of C₄, with a predicted strain energy 3 kcal/mole greater than that of TC₁₀, should be <1% and the contributions of all the other, still higher energy, conformations insignificant.

Models[17] of each conformation were examined and estimates made of the signs and relative magnitudes of the Cotton effects to be expected.[18] The results,

(5) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, pp 206–210.
(6) J. B. Hendrickson, J. Am. Chem. Soc., 83, 4537 (1961); Tetrahedron, 19, 1387 (1963).
(7) These calculations[6] give quantitative significance to the similar, qualitative conclusions drawn by earlier workers.[5]
(8) G. Snatzke, B. Zeeh, and E. Müller, Tetrahedron, 20, 2937 (1964).
(9) W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, J. Am. Chem. Soc., 83, 4013 (1961).
(10) P. Crabbé, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1965, Chapter 6.

(11) Nmr and CD measurements have already proven valuable in conformational studies on benzocycloheptenes[12] and unsaturated A-homosteroids.[13]
(12) See S. Kabuss, et al., Tetrahedron Letters, 719 (1966); 469 (1965); H. Hart and J. L. Corbin, J. Am. Chem. Soc., 87, 3135 (1965); E. Grunwald and E. Price, 87, ibid., 3139 (1965), for leading references.
(13) G. Snatzke, B. Zeeh, and E. Müller, Tetrahedron Letters, 1425 (1963).
(14) One possible weakness in the use of the Hendrickson analysis, computed for systems with sp³-hybridized carbons only, for cycloheptanone derivatives is the difficulty of making an allowance for the influence of the carbonyl group. However, Hendrickson considers that the presence of one sp²-hybridized carbon does not affect the validity of the method. In addition, Allinger has concluded[15] that for cyclohexanone the analysis derived for the parent hydrocarbon can be applied.
(15) N. L. Allinger, J. Am. Chem. Soc., 81, 5727 (1959).
(16) Reference 5, p 11.
(17) Framework Molecular Models, obtainable from Prentice Hall Inc., Englewood Cliffs, N. J., were found to be the most convenient for studying the many A-homosteroid conformations surveyed.
(18) At present, it is not possible to calculate the quantitative contributions made to the amplitude of the Cotton effect by the same or different groups in various positions in an octant.[10] (From the recent
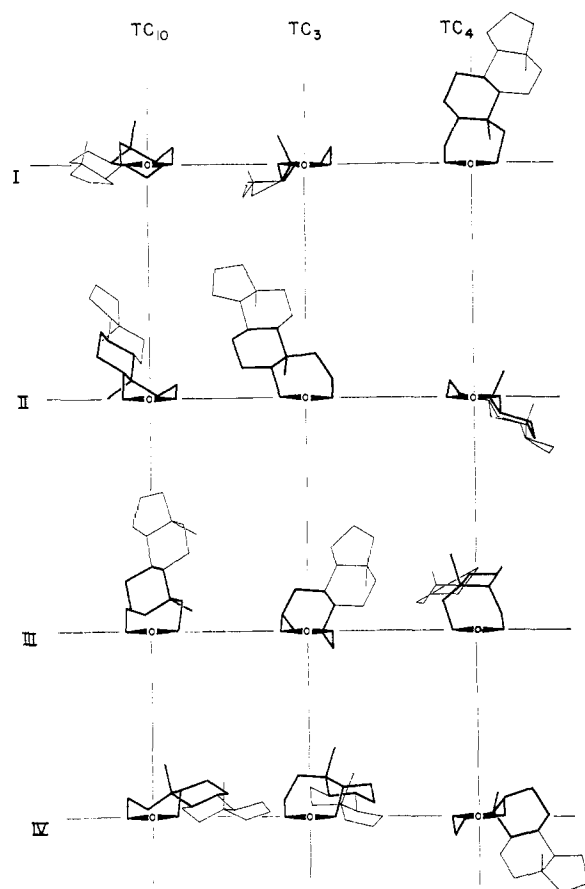
TC₁₀   TC₃   TC₄

I

II

III

IV

Figure 2. Illustrations of the octant-rule projections used to predict[18] the sign and magnitude of the Cotton effects of the various ring A conformations of the A-homoketones I–IV. Only the conformations eventually considered to be preferred are shown. Rings A and B are in heavy lines; C_{17} substituents have been omitted.

which are summarized in Figure 1, showed that for the ketones I and III, the supposedly preferred TC_{10} conformation predicts a Cotton effect *opposite* in sign to that observed, whereas application of the octant rule to TC_3 and TC_4 leads to the correct prediction in all cases. It seems unlikely that the presence in the room-temperature equilibrium mixture of only 9% of TC_3 and TC_4, as indicated by the unmodified Hendrickson analysis, could account satisfactorily for the large amplitudes recorded in the ORD curves[19] especially since for I and III the opposite contribution of TC_{10} to the amplitude should be substantial (see Figure 2).

These data indicate that for the A-homoketones I–IV, TC_3, TC_4, and TC_{10} are of comparable strain energy and that at room temperature an equilibrium

report by J. C. Tai and N. L. Allinger, *J. Am. Chem. Soc.*, **88**, 2179 (1966), it appears that this difficulty may well be overcome in the not too distant future.) The factors considered in arriving at the relative magnitudes indicated in Figure 1 were, in order of importance, the positions in the octants and dissymmetry in relation to the carbonyl chromophore of (a) the cycloheptane ring, (b) C_{10}-methyl and ring B, (c) rings C and D, (d) C_{17}-substituent. In several cases it was difficult even to predict the sign of the Cotton effect to be expected. This was particularly true for some conformations of the 5β series where both front and back octants had to be considered. Fortunately, for all cases where ambiguity existed, the relatively high energy of the conformation in question precluded its consideration as a preferred structure.

(19) The domination of the sign of Cotton effects of equilibrium mixtures by small proportions of one conformation has temporarily resulted in incorrect conformational assignments in the past. However, in such cases, the amplitudes of the ORD curves have been small, *e.g.*, C. Djerassi, *et al.*, *Experientia*, **21**, 565 (1965); *J. Am. Chem. Soc.*, **86**, 465 (1964).

mixture exists which contains significant proportions of all three with the ORD dominated by the contributions of the Cotton effect of TC_3 and TC_4. Support for the modification of the Hendrickson, hydrocarbon-derived, analysis in this way can be drawn from the data of Allinger[15] who has calculated the strain energy of cycloheptanone to be 1.1 kcal/mole lower than that of cycloheptane itself. Also, for the A-homoketones I–IV, TC_3 and TC_4 represent the twist chairs with the carbonyl groups at the axis or adjacent carbon, and it has been suggested[5] that the steric strain should be least with the carbonyl group in these positions.

In an attempt to gain further insight into the nature of the equilibrium mixture, dipole moment studies were carried out on the diketones Ib–IVb.

The most convenient method for determining the relative orientations of the carbonyl groups of the diketones was found to be from photographs of a model[17] of each conformation taken in three mutually perpendicular planes. The vector sums were then calculated by simple trigonometry. The errors in the calculated moments obtained in this way are estimated to be 0.1–0.2 D. The dipole moment of cycloheptanone (3.07 D.[20]) was taken as representative of the ring A carbonyl, and the influence of the steroid skeleton was neglected in all calculations. (This latter omission was not considered serious as experimentally the moments of the hydrocarbons 5α- and 5β-androstanes were too low to be determined accurately by the usual method.[21]) The virtual identity of the observed moments of cyclohexanone (3.08 D.[20]) and 5α-androstan-3-one (3.10 D.[25a]) provides additional justification for this assumption.

Choosing a value for the moment of the C_{17} carbonyl was less clear-cut as the reported values for cyclopentanone and 5α-androstan-17-one differ significantly (2.93[20] and 3.05 D.,[25b] respectively). A survey of the literature[26,27] indicated cyclopentanone itself to be the better model. In practice, its selection over 5α-androstan-17-one was not of great significance as the substitution of one moment for the other in the calculations gave resultants differing by not more than 0.07 D.

The influence of the conformation of ring D on the orientation of the C_{17} carbonyl was also considered. The somewhat conflicting data available[26–28] did not permit a valid choice between the three possibilities (two envelopes and a half-chair). Again, however,

(20) A. L. McClellan, "Tables of Experimental Dipole Moments," W. H. Freeman and Co., San Francisco, Calif., 1963.

(21) Owing to the low α values (see Table III) obtained for 5α-and 5β-androstane and the inaccuracies inherent in the tables used for calculating molar refractivities[22,23] it was not possible to calculate the dipole moments of the two hydrocarbons by the usual method.[24] It was not considered worthwhile to measure the solid dielectric constant of each, without which the moments cannot be calculated, since it was obvious that the values were negligibly small.

(22) F. Eisenlohr, *Z. Physik. Chem.*, **79**, 129 (1912).

(23) A. I. Vogel, W. T. Cresswell, G. J. Jeffery, and J. Leicester, *Chem. Ind.* (London), **358** (1950).

(24) I. F. Halverstadt and W. D. Kumler, *J. Am. Chem. Soc.*, **64**, 2988 (1942).

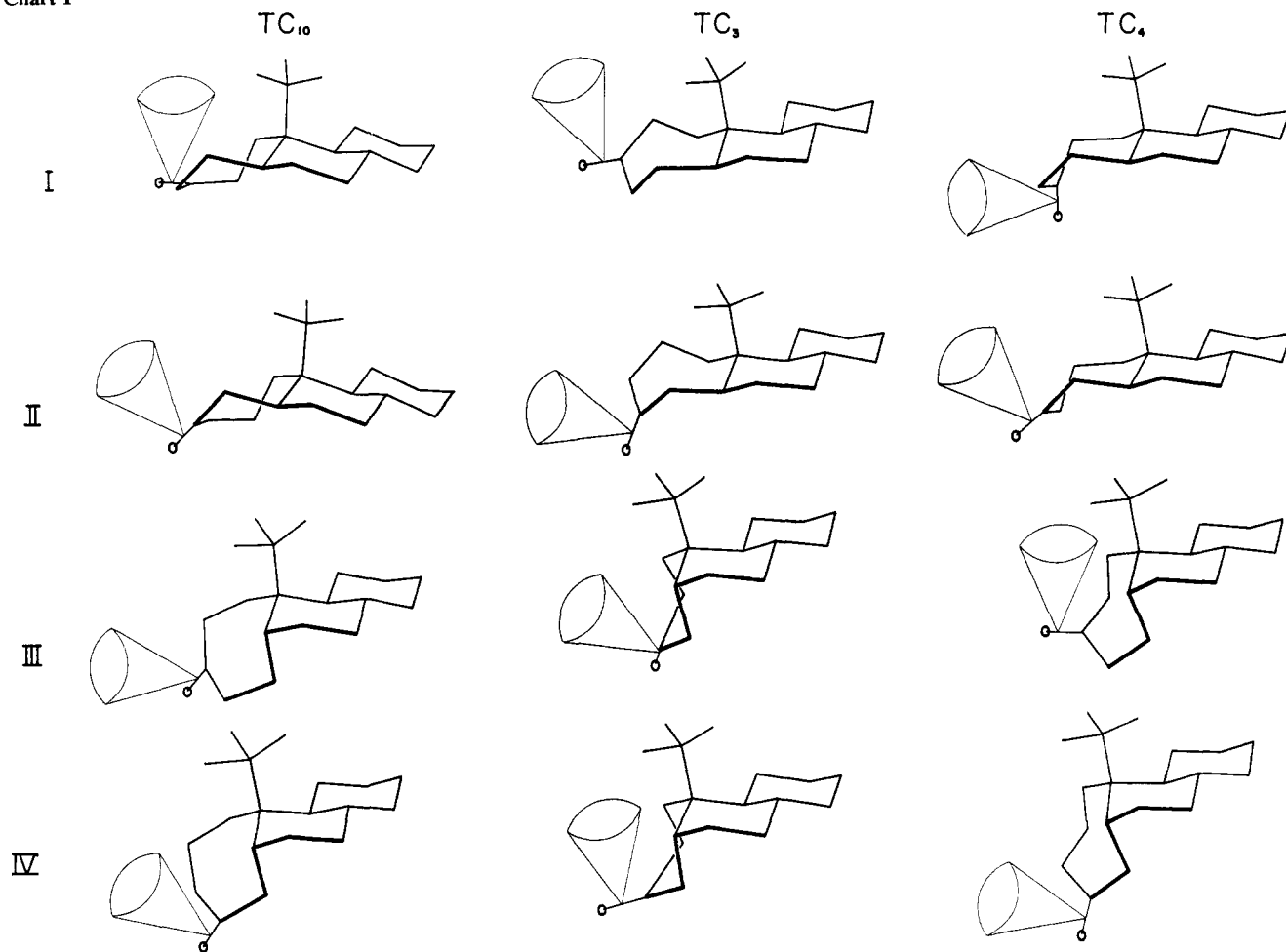(25) (a) N. L. Allinger, J. Allinger, and M. A. DaRooge, *ibid.*, **86**, 4061 (1964); (b) N. L. Allinger and M. A. DaRooge, *ibid.*, **84**, 4561 (1962).

(26) J. Fishman, *ibid.*, **87**, 3455 (1965); *J. Org. Chem.*, **31**, 520 (1966).

(27) F. V. Brutcher and W. Bauer, *J. Am. Chem. Soc.*, **84**, 2236 (1962).

(28) T. Takemoto, Y. Kondo, and H. Mori, *Chem. Pharm. Bull.*, **13**, 897 (1965).

Chart I

this turned out to be relatively unimportant as the moments calculated using each of the three possible ring D conformations differed by up to 0.15 D. only. Arbitrarily, the half-chair[27,28] conformation was used in calculating the values reported in this communication.[29]

The dipole moments of Ib–IVb were determined in benzene solution. Figure 3 shows the comparison of the experimental values with those predicted for the preferred conformations, TC_3, TC_4, and TC_{10}, of each diketone. For the sake of clarity, the calculated moments for the other higher conformations of the pseudo-rotation sequences have been omitted.

Unfortunately the experimental data do not allow any unambiguous estimate to be made of the relative proportions of each conformation present at room temperature, but from the ORD and dipole moment results it would appear that the energy differences are small.

In order to magnify the small energy differences, the nmr spectra of the diketones Ib–IVb were measured at low temperature in carbon disulfide solution. It was felt that the increase in population of the lower energy conformations on cooling should reflect itself in changes in the composite shielding of the C_{19} methyl group by the variously oriented carbonyl groups of the different conformations of ring A. That such a situa-

(29) During the preparation of our manuscript, F. V. Brutcher and J. Leopold, *J. Am. Chem. Soc.*, **88**, 3156 (1966), reported the results of their calculations based on X-ray data which showed ring D of estrone to be in the α-envelope conformation in the crystalline state.

tion occurred was demonstrated by the shifts observed in the positions of the C_{19}-methyl peaks in the nmr spectra of each compound on cooling the solutions to $-55°$. Owing to the relative inflexibility of ring D,
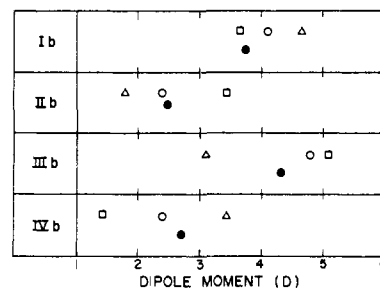
Figure 3. Comparison of the dipole moments observed, ●, for the diketones Ib–IVb with the values calculated for the preferred conformations of ring A: TC_3, □; TC_4, △; and TC_{10}, O.

little change was expected in the shielding effect exerted by the C_{17} carbonyls on the C_{18}-methyl groups on lowering the temperature, and experimentally no significant shifts in the positions of these peaks were detected. The chemical shifts observed are recorded in Table I. The possibility that the variations in the positions of the C_{19}-proton peaks might have arisen from differences in the solvation of the ring A carbonyl group at the lower temperature is considered unlikely since the positions of the C_{18}-proton peaks remained essentially

Table I. Influence of Temperature on the Chemical Shifts of the C_{19} Protons of Ib–IVb

Compound	Temp, °C	ν, cps		C_{19} $ν_{30°}$ $- ν_{-55°}$	Predicted influence of Ring A carbonyl on C_{19}	
		C_{19}	C_{18}		Shielding	Deshielding
A-Homo-5α-androstane-3,17-dione (Ib)	30	49.4	47.5	+1.9	TC_3, TC_{10}	
	−55	47.5	47.5			
A-Homo-5α-androstane-4,17-dione (IIb)	30	53.2	46.5	−2.1		TC_4, TC_{10}
	−55	55.2	46.4			
A-Homo-5β-androstane-3,17-dione (IIIb)	30	62.5	47.2	−1.4		TC_3, TC_{10}
	−55	63.0	47.3			
A-Homo-5β-androstane-4,17-dione (IVb)	30	59.1	46.8	−0.4		TC_4, TC_{10}
	−55	59.5	46.8			

unaltered. Estimates of the degree of relative shielding or deshielding of the C_{19}-methyl protons by the carbonyl groups to be expected for the various conformations were obtained from models as depicted in Chart I. The results in each case, that is, for compounds I–IV, were consistent with the twist chair having the carbonyl at the axis carbon being of lower strain energy than that with the carbonyl adjacent to the axis position.[30] No decision could be taken regarding the energy of TC_{10} relative to the latter conformations. It is hoped that low-temperature circular dichroism will resolve this problem, and the preparations of suitable compounds for this study are in hand.

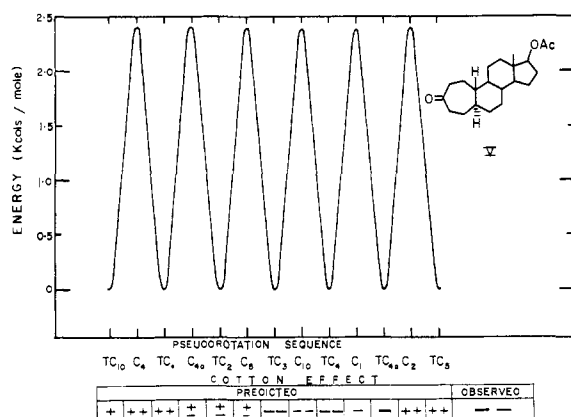Figure 4. Energy function for the A-homosteroid V, together with the Cotton effects predicted for each conformation of the pseudo-rotation sequences. The signs shown in heavy lines are those of the preferred conformations.

The above evidence for the existence at room temperature of an equilibrium mixture of several preferred conformations, each of comparable strain energy, prompted us to reexamine other A-homosteroids containing saturated cycloheptanone rings for which the conformation of the A-homo ring had been discussed previously. Consideration was given only to the compounds for which ORD and CD data were available to assist in selecting the preferred conformation(s).

Other A-Homosteroids

17β-Acetoxy-A-homo-5α-estran-3-one (V). The energy function calculated for V by the Hendrickson procedure shows all the twist-chair conformations, TC_{10},

(30) The nmr spectrum of the cycloheptyl ketyl radical is also compatible with this conclusion: J. W. Lown, *Can. J. Chem.*, 43, 3294 (1965).

TC_1, TC_2, TC_3, TC_4, TC_{4a}, and TC_5, to be equally preferred (see Figure 4). However, if all these conformers were of equivalent energy the over-all ORD curve should show a weakly positive Cotton effect, whereas in fact a strongly negative effect ($a = -73.9$) is reported.[31] This indicates that TC_3 and TC_4, for which the carbonyl group again occupies the axis and adjacent positions, respectively, dominate the ORD and are the largest contributors to the room-temperature conformational mixture.[32] TC_2, for which the carbonyl group is also adjacent to the axis carbon, should also be preferred but would contribute only marginally to the over-all Cotton effect.

2α-Methoxy-17β-hydroxy-A-homo-5α-androstan-4-one (VI). For VI it has been suggested on the basis of the CD spectrum[8] that C_{10} represents the preferred conformation of ring A. However, the energy function obtained by Hendrickson analysis (Figure 5) again
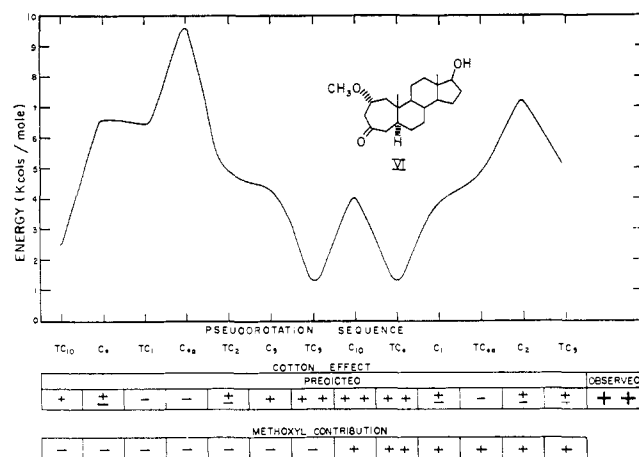
Figure 5. Energy function for the A-homosteroid VI; see also caption to Figure 4.

shows the twist-chair conformations with the carbonyl at the axis and adjacent carbons, TC_4 and TC_3, respectively, are each preferred by 1.1 kcal/mole over the next most favored form TC_{10}, and by 2.6 kcal/mole over C_{10}. On the basis of the conclusions drawn from the low-temperature nmr experiments described above, it is predicted that of the two preferred conformations, TC_4 (axis carbonyl) would be of somewhat lower energy. This is borne out by the CD curve of VI for which the amplitude ($+10.2^8$) is somewhat more

(31) Reference 10, p 117.
(32) In ref 31, a "twist conformation" for V is postulated. However, it is not possible to assign a specific conformation from the description given.

Figure 6. Energy function for the A-homosteroid VIIa; see also caption to Figure 4.
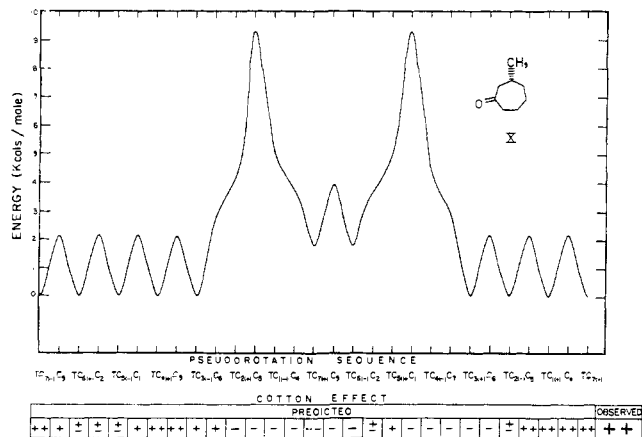

Figure 7. Energy function for the A-homosteroid VIIb; see also caption to Figure 4.

positive than that ($+9.37^8$) of the parent ketone IIb. This experimental observation is in better accord with $\mathbf{TC_4}$, in which the methoxyl group falls into a positive octant, than for $\mathbf{TC_3}$, when it would make a negative contribution to the over-all Cotton effect (see Figure 5).

3β-Acetoxy-5β-methyl-A-homo-B-nor-25D-spirostan-4a-one (VIIa) and -4a-α-ol (VIIb). The A-homo-B-norsteroids VIIa and b have been presumed to exist in one of the two possible $\mathbf{C_3}$ conformations.[33,34] In fact, the Hendrickson energy function for the ketone VIIa (Figure 6) predicts $\mathbf{TC_{3(+)}}$[35] and $\mathbf{TC_{3(-)}}$ to be the preferred conformations, each being at least 1 kcal/mole lower in energy than the least strained of the two possible $\mathbf{C_3}$ conformations.[36] The contributions of $\mathbf{TC_{3(+)}}$ and $\mathbf{TC_{3(-)}}$ to the Cotton effect should be small negative and large positive, respectively. The

(33) D. N. Kirk and V. Petrow, *J. Chem. Soc.*, 4657 (1960).
(34) M. T. Davies, B. Ellis, D. N. Kirk, and V. Petrow, *Tetrahedron*, 21, 3188 (1965).
(35) For many cycloheptane derivatives, *e.g.*, VIIa, it becomes necessary to distinguish between the two twist-chair conformations that are possible for the same axis carbon. These can be readily distinguished by means of an "octant-rule" type projection. The twist chair with the

cycloheptane ring symmetrically disposed in "positive octants" is designated $\mathbf{TC}_{n(+)}$ where n = axis carbon. Similarly

is designated $\mathbf{TC}_{n(-)}$. It should be noted that since the chromophore is not always at the axis carbon, the sign in brackets does not necessarily indicate the direction of the predicted Cotton effect for the conformation in question.

(36) Hendrickson[6] has cautioned against the indiscriminate application of his analysis to all fused ring systems and to cycloheptanes containing multiple substituents. Accordingly, the analyses of VIIa and b should not be given too much quantitative significance. In particular, the extremely unfavorable interactions between the two angular methyl groups in the two $\mathbf{C_3}$ conformations should add several kcal/mole[6] to the strain energies indicated in Figure 6. For the twist chairs $\mathbf{TC_{3(+)}}$ and $\mathbf{TC_{3(-)}}$, these interactions are much less severe.

experimentally observed small positive addition to the amplitude of the parent spirostane curve[33] suggests that the equilibrium mixture contains equal proportions of both conformations, thereby giving rise to an over-all weakly positive contribution to the ORD. In contrast, the energy function[37] for the alcohol VIIb (Figure 7) indicates $\mathbf{TC_{3(-)}}$ alone to be the preferred conformation, being favored by $\sim$2.5 kcal/mole over its nearest neighbor $\mathbf{TC_{3(+)}}$. The $\mathbf{TC_{3(-)}}$ conformation, VIII, in which the C_6–C_{10} and C_5–OH bonds are *trans* and coplanar, accounts more satisfactorily than does the originally proposed[34] $\mathbf{C_3}$ for the stereospecific rearrangement to IX observed during dehydration of VIIb with thionyl chloride. It is also equally compatible with the nmr data quoted[34] in support of the particular $\mathbf{C_3}$ conformation chosen. (It should be noted that for VIIa the preferred conformations $\mathbf{TC_{3(+)}}$ and $\mathbf{TC_{3(-)}}$ are those in which the total steric interactions of the two angular methyl groups are minimized, and that the preference of the carbonyl group for the axis or adjacent carbon is relatively unimportant in this case.)

(+)-3- and (−)-4-Methylcycloheptanones

It was considered worthwhile to apply the method to 3- and 4-methylcycloheptanones, X and XI, respectively, since the ORD measurements upon which the earlier conclusions[38] regarding the conformations of these compounds were based have recently been shown to be incorrect.[39] Of the 28 possible conformations of (+)-3-methylcycloheptanone (X), eight twist chairs

are of equivalent minimum energy (Figure 8). How-

(37) In the analysis of VIIb, the contribution to the strain energy of the hydroxyl group was taken as one-half that of a methyl substituent.[6] Since this is an approximation (see ref 5, p 44), the energy values must be regarded as semiquantitative only.
(38) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p 188.
(39) C. Djerassi, B. F. Burrows, C. G. Overberger, T. Takekoshi, C. D. Gutsche, and C. T. Chang, *J. Am. Chem. Soc.*, 85, 949 (1963).

Figure 8. Energy function for the methylcycloheptanone X; see also caption to Figure 4.

Figure 9. Energy function for the methylcycloheptanone XI; see also caption to Figure 4.

ever, only three, $TC_{1(+)}$, $TC_{4(+)}$, and $TC_{7(-)}$, would be expected to give rise to positive Cotton effects sufficiently large to dominate the ORD and account for the observed amplitude of $+16.2$.[39] Since the remaining five, $TC_{2(-)}$, $TC_{3(+)}$, $TC_{3(-)}$, $TC_{5(-)}$, and $TC_{6(+)}$, should have a marginal influence only on the Cotton effect, their contribution to the equilibrium mixture cannot be estimated in this way. Analogy with the A-homosteroid ketones suggests the selection of $TC_{1(+)}$ (axis carbonyl) and $TC_{2(-)}$ and $TC_{7(-)}$ (carbonyls adjacent to axis) as the preferred conformations of X.

For ($-$)-4-methylcycloheptanone (XI), the energy function again indicated eight twist chairs to be of identical minimum strain energy (Figure 9). However, only two of these, $TC_{1(-)}$ and $TC_{7(+)}$, with the carbonyl group at the axis and adjacent carbons, respectively, and possibly $TC_{4(-)}$, could account for the large negative Cotton effect ($a = -21.5$[39]) observed. $TC_{2(+)}$, for which the carbonyl is also adjacent to the axis, should also be energetically favored but would have little effect on the ORD spectrum.

Summary

The procedure developed by Hendrickson for determining the preferred conformations of cycloheptanes is generally applicable to relatively complex cycloheptanone derivatives. For all the examples considered the twist-chair conformations[40] predominated, and in

(40) The recent X-ray structure determination of i by T. Sato, H. Minato, M. Shiro, and H. Koyama, *Chem. Commun.*, 73 (1966), is of interest since the seven-membered ring in the crystal has the full-chair
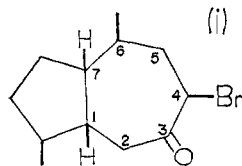
conformation C_4, with the Br atom in the equatorial position. From the energy function of the pseudo-rotation sequence $TC_{1(-)}$ and $TC_{7(+)}$ are predicted to be the preferred conformations in solution. However, neither of these is unequivocally compatible with the ORD and CD data[41] whereas the C_4 conformation accords well with the negative Cotton effects observed and it seems probable that Hendrickson analysis is not directly applicable to this compound[36,41a]

(41) We are grateful to Dr. K. Takeda for making these available to us prior to publication.

(41a) NOTE ADDED IN PROOF. Dr. Takeda has recently informed us that the C_4 chair cycloheptane conformation for i shown by Sato, *et al.*, in their published figure was a misrepresentation of that actually found, *viz.* $TC_{1(-)}$. Also, detailed ORD and CD studies have shown $TC_{4(+)}$ to be almost equally preferred.[41]
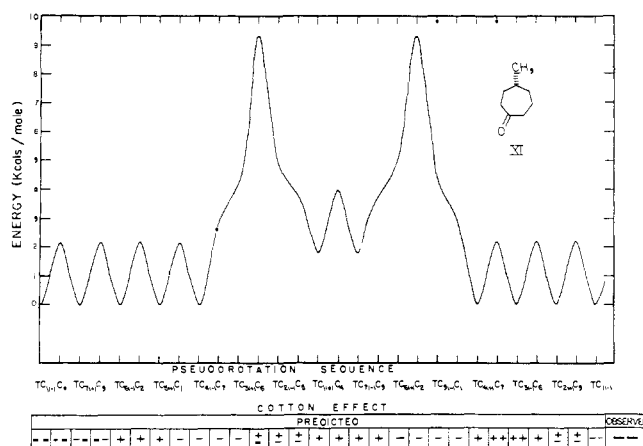
the absence of overriding influences by bulky substituents, those twist chairs with the carbonyl at the axis carbon, or adjacent to it, were preferred. Of these two favored conformers, the former appeared to be marginally the lower in strain energy. For most of the cycloheptanones studied, the existence at room temperature of a complex equilibrium of several twist chairs of comparable energy was indicated. This was not an unexpected result in view of the ease with which cycloheptane rings undergo pseudo-rotation. It is of interest to note that the most recent nmr studies on the even more flexible cyclooctane[42] also indicate a complex equilibrium at room temperature of the conformations predicted[43] to be of lowest energy.

It should perhaps be emphasized that the preferred conformations of the seven-membered rings of substituted and polycyclic cycloheptane derivatives are not always immediately apparent and that the strain energy of each conformation of the pseudo-rotation sequence should be estimated, and use made of the physical data available, before any conformational assignments are made.

Experimental Section

Compounds. The A-homosteroids used in this investigation were prepared and purified as described previously[2] until no impurity could be detected by thin-layer or gas-liquid partition chromatography, and until a constant ORD curve was obtained. References to all the other compounds discussed are given in Table II. 5α-Androstane, plates from methanol, mp 48–49°, and 5β-androstane, needles from methanol, mp 80–81°, were obtained by Wolff–Kishner reduction of 5α- and 5β-androstan-3-ones, respectively.[44]

Optical rotatory dispersion measurements were performed on a Jasco–Durrum ORD 5 spectropolarimeter. The solvents used and the amplitudes observed for each compound, together with the literature values for those not available to us, are recorded in Table II.

Dipole moments of the diketones Ib–IVb, and of 5α- and 5β-androstanes, were measured at 25° in benzene solution with the dipole moment apparatus described by Meredith and Wright.[45] The moments were calculated using the equations of Halverstadt and Kumler.[24] Molar refractivities were taken as the mean of the Eisenlohr[22] and Vogel[23] values, and atomic polarization was neglected. The data are summarized in Table III.

(42) F. A. L. Anet, and M. St. Jacques, *J. Am. Chem. Soc.*, **88**, 2585, 2586 (1966).

(43) J. B. Hendrickson, *ibid.*, **86**, 4854 (1964); K. B. Wiberg, *ibid.*, **87**, 1070 (1965).

(44) L. Mamlok and J. Jacques, *Bull. Soc. Chim. France*, 484 (1960).

(45) C. C. Meredith and G. F. Wright, *Can. J. Technol.*, **83**, 182 (1955).

Table II. ORD and CD Data for the A-Homosteroids I–VI and the Methylcycloheptanones X and XI[a]

Compound		⌐— CD —⌐ [Θ] × 10⁻³	⌐— ORD —⌐ [Φ] × 10⁻²
A-Homo-5α-androstan-3-one-17β-ol	Ia		−87 (D, H), −101 (M)
A-Homo-5α-androstan-3-one	Ic		−70 (I)³, −98 (M)³
A-Homo-5α-cholestan-3-one	Id		−60 (M)ᶜ
A-Homo-5α-androstan-4-one-17β-ol	IIa	+9.37 (X)⁸	+131 (M)
A-Homo-5α-androstane-4,17-dione	IIb	+17.69 (X)⁸	
A-Homo-5α-androstan-4-one[b]	IIc	+2.82 (I)³	+20 (H)³, +22 (M)³
A-Homo-5α-cholestan-4-one[b]	IId	+1.4 (I)	+14 (H), +15 (M)
17β-Acetoxy-A-homo-5α-androstan-4-one		+8.81 (X)⁸	
A-Homo-5β-androstan-3-one-17β-ol	IIIa	+3.93 (D)¹³, +4.17 (M)¹³	+63 (M)
A-Homo-5β-androstane-3,17-dione	IIIb	+3.6 (D)¹³	
A-Homo-5β-androstan-3-one	IIIc		+69 (M)³, +55 (I)³
A-Homo-5β-androstan-4-one-17β-ol	IVa		−59 (M)
17β-Acetoxy-A-homo-5α-estran-3-one	V		−73.9 (X)¹⁰
2α-Methoxy-A-homo-5α-androstan-4-one-17β-ol	VI	+10.20 (X)⁸	
(+)-3-Methylcycloheptanone	X		+16.2 (M)³⁹
(−)-4-Methylcycloheptanone	XI		−21.5 (M)³⁹

[a] Solvents: (D), dioxane; (H), heptane; (I) isooctane; (M), methanol; (X), not reported. [b] Preferred values (cf. ref 2). ᶜ N. A. Nelson, personal communication.

Table III. Dipole Moment Data for the Diketones Ib–IVb

Compound	α	ε	d	β	M_R	P_t	μ, D.
A-Homo-5α-androstane-3,17-dione (Ib)	5.08	2.27415	0.87377	0.243	85.96	375.74	3.74 ± 0.03
A-Homo-5α-androstane-4,17-dione (IIb)	2.44	2.2733	0.87363	0.270	85.96	219.45	2.48 ± 0.03
A-Homo-5β-androstane-3,17-dione (IIIb)	6.87	2.27415	0.87377	0.255	85.96	470.62	4.31 ± 0.005
A-Homo-5β-androstane-4,17-dione (IVb)	2.885	2.27415	0.87377	0.250	85.96	244.64	2.77 ± 0.005
5β-Androstane	−0.05ᵃ	2.27415	0.87379	0.104	83.0	81.1	Very small
5α-Androstane	∼0	2.27415	0.87379	0.111	83.0	. . .	Very small

ᵃ It is unusual for α to be negative.

Variable-temperature nuclear magnetic resonance measurements were carried out on a Varian A-60 instrument, fitted with a Varian low-temperature probe, on the diketones Ib–IVb as 3–4% solutions in carbon disulfide and using tetramethylsilane as internal standard. The results are given in Table I.