

Irradiation of the Cyclopropyl Ketone 4. A. In Methanol.—A solution of 30 mg. of ketone 4 and 10 ml. of methanol was irradiated for 120 min. with a 100-watt mercury lamp as described above for lumiprodukt 2a. The reaction mixture was concentrated under reduced pressure on a rotary evaporator, and the residue was chromatographed on 1.5 g. of silica gel. Elution with 200 ml. of benzene gave 17 mg. (57% yield) of a colorless oil which had an infrared spectrum and gas chromatographic retention time identical with the pure specimen of dienone 5 described above.

B. In 50% Acetic Acid.—A solution of 58 mg. of ketone 4 in 10 ml. of 50% acetic acid was irradiated as described above for 2 hr. The reaction mixture was then concentrated under reduced pressure, and the last traces of acetic acid were removed by codistillation with toluene. The resulting amber oil (60 mg.) was chromatographed on 3 g. of silica gel. Elution with 120 ml. of 1:1 hexane-benzene gave 19 mg. (33% yield) of phenol

6, n.m.r. spectrum 3.52 τ , long colorless needles, m.p. 103–105° after recrystallization from hexane, m.p. 103–107° on admixture with an authentic sample of 6.¹⁴

Continued elution with 60 ml. of 1:1 hexane-benzene and 80 ml. of 1:3 hexane-benzene gave 4 mg. which was discarded. Further elution with 260 ml. of benzene gave 27 mg. (47% yield) of dienone 5 as a colorless oil which was identical with an authentic specimen in the infrared spectrum and gas chromatographic retention time.

Hydrogenation of the Cyclopropyl Ketone 4.—A solution of 22 mg. of cyclopropyl ketone 4 in 10 ml. of absolute ethanol was stirred with 10 mg. of 10% palladium-on-charcoal in an atmosphere of hydrogen. Uptake ceased after 10 min. with 1.0 mole equiv. Removal of the catalyst by filtration followed by evaporation of the solvent at reduced pressure gave the dihydro derivative as a colorless oil, λ_{\max} 5.85 μ , λ_{\max} 217 $m\mu$ (ϵ 4300).

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Conformational Analysis. XXXVIII. The Conformations of Cyclohexanone Rings^{1,2}

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A generalized approximate method for the conformational analysis of the flexible form of cyclohexanone is presented, and the method is applied to a few examples, including 2- and 4-methylated-3-keto steroids. The exact conformational arrangements of these compounds and for the D ring in 17,17-dimethyl-17a-keto-D-homosteroids are predicted. Rotatory dispersion measurements and dipole moments are consistent with all of the predictions.

Increasingly detailed studies on the conformations of cyclohexanone rings have brought to light a number of examples of molecules in which such a ring exists primarily in a form other than that of an ordinary chair. It has also become apparent that these nonchair forms are not all alike, and evidence has been accumulated which shows that a number of distinctly different arrangements in fact exist.^{3,4}

Some years ago we began a study of nonchair forms in cyclohexanone rings.⁵ Since the subject has now become of rather general interest, and because recent papers on the subject have always been limited in discussion to special cases, it seemed to us that it would now be appropriate to state in expanded form our earlier comments,⁵ and to carry out the conformational analysis of the general case of the flexible form of cyclohexanone itself, and then to apply these results to some specific examples of more complicated molecules to show the generality of the method.

Sachse⁶ recognized the flexibility of the boat form of cyclohexane as early as 1890, but this flexibility was lost sight of by most chemists until Hazebroek and Oosterhoff called attention to it in 1951.⁷ Because of

the relatively high energy of the flexible form compared to that of the chair (5–6 kcal.), the former is met with only rarely in molecules which are in principle able to adopt the latter.^{3,8} For a cyclohexanone, however, the situation is rather different. Because in certain arrangements of the flexible form of cyclohexanone there is only one eclipsed ethane unit, the energy of this form is thought to be less than 3 kcal./mole above that of the boat.³ This energy difference is sufficiently small that it may be outweighed by the effects of substituents, and the result is that boat forms are, in fact, quite common among cyclohexanone derivatives.³

The flexibility of the boat form is conveniently described in terms of a pseudorotational parameter, θ .⁹ For cyclohexanone we can picture a series of conformations through which the molecule passes as θ goes from 0 to 360° (Fig. 1). Starting with the ketone at the prow of the boat ($\theta = 0^\circ$), pseudorotation leads to six classical boat forms as each carbon becomes the prow in turn. Between these regular boats are the stretched⁷ (also called twist¹⁰) forms. The various forms are illustrated by the cycle shown in Fig. 1. As the rotation proceeds from 180 to 360°, the mirror images of the structures shown result. The approach taken here is that the energy for the cyclohexanone ring as a function of θ can be calculated, and will be approximately the same in any substituted cyclo-

(1) Paper XXXVII: C. Djerassi, R. A. Schneider, H. Vorbrueggen, and N. L. Allinger, *J. Org. Chem.*, **28**, 1632 (1963).

(2) This work was supported by grant A-5836 from the Public Health Service, National Institutes of Health.

(3) The first example of the proof of the existence of a nonchair form in a molecule which was free to adopt either a boat or a chair conformation was reported by D. H. R. Barton, D. A. Lewis, and J. F. McGhie (*J. Chem. Soc.*, 2907 (1957)). Subsequent examples are numerous and are summarized in review articles: (a) J. Levisalles, *Bull. soc. chim. France*, 551 (1960); (b) M. Balasubramanian, *Chem. Rev.*, **62**, 591 (1962). For a discussion of the different types of boats possible and the experimental demonstration of the existence of a form which is in between the chair and the boat, see ref. 4.

(4) N. L. Allinger and M. A. DaRoogé, *J. Am. Chem. Soc.*, **84**, 4561 (1962).

(5) N. L. Allinger, *ibid.*, **81**, 5727 (1959).

(6) H. Sachse, *Ber.*, **23**, 1363 (1890); *Z. physik. Chem.*, **10**, 203 (1892).

(7) P. Hazebroek and L. J. Oosterhoff, *Discussions Faraday Soc.*, **10**, 87 (1951).

(8) M. Svoboda, M. Tichy, J. Fajkos, and J. Sicher, *Tetrahedron Letters*, 717 (1962).

(9) From Fig. 1 it is qualitatively clear how the geometry depends on θ . A mathematical definition of θ is complicated. Such a definition is given for the more symmetrical cyclohexane in ref. 7. A similar definition could be formulated for cyclohexanone using any assumed values for bond angles and bond lengths. For present purposes the asymmetry in the carbon system can be neglected, and θ here is then equivalent to $\theta + \pi/2$ in ref. 7. We have chosen to offset the origin because by so doing, a convenient correspondence between θ and the sign of the Cotton effect results.

(10) W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. H. Dreger, and W. N. Hubbard, *J. Am. Chem. Soc.*, **83**, 606 (1961).

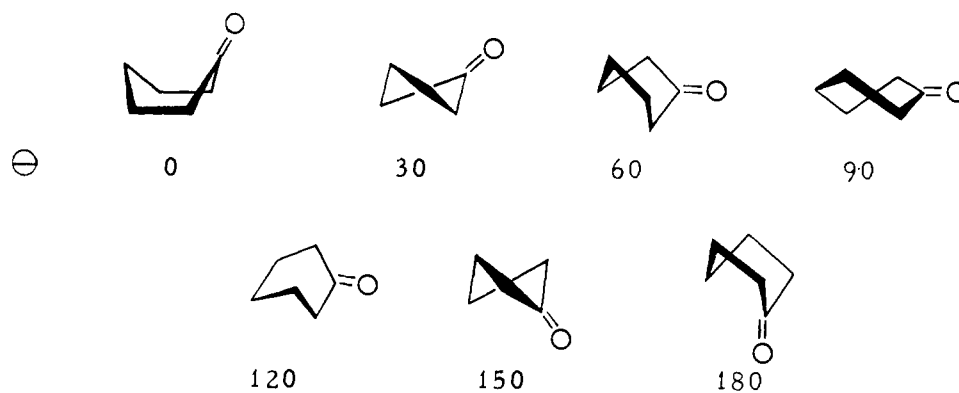


Fig. 1.—The pseudorotational conformations of the flexible form of cyclohexanone.

hexanone. For the latter case, the total conformational energy can be calculated as the sum of the ring energy and the energies of the substituents (from interactions of the substituents with the ring and with one another). These energies can be conveniently divided into torsional, deformational (angular ordinarily, but possibly compressional in some cases), and van der Waals, and it is possible to calculate these individually¹¹ and hence to make rather good estimates of the variation of the total conformational energy (E) with θ .¹² For torsional barriers, that of ethane is 2.8 kcal./mole, and the eclipsing at $\theta = 0^\circ$ is taken to be twice this (curve 1, Fig. 2). (There is an additional small van der Waals repulsion between C₁- and the C₄-methylene, which is considered separately.) The torsional barrier around the bond joining C-1 and C-2 is less well known. It has been shown from microwave studies that the corresponding barrier height is 0.8 kcal./mole in acetone,¹⁴ and various considerations⁵ lead to the conclusion that the stable arrangement has the oxygen staggered rather than eclipsed by the neighboring hydrogen (see below) and an appropriate 3-fold cosine function meeting these requirements will be used here (curve 2, Fig. 2).

(11) F. H. Westheimer in M. S. Newman's "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 523.

(12) It should be recognized that the energy of the system is properly calculated by repeated solution of the Schrödinger equation for all conceivable nuclear arrangements, with explicit inclusion of all electrons and nuclei, until the absolute minimum value for the total energy is determined, together with the corresponding geometry. While such calculations have been carried out for the helium atom (C. f. Pekeris, *Phys. Rev.*, **112**, 1649 (1958)) and the hydrogen molecule (W. Kolos and C. C. J. Roothaan, *Rev. Mod. Phys.*, **32**, 219 (1960)), there is considerable doubt as to whether such problems can ever be solved for systems of the type considered in the present work (C. A. Coulson, *ibid.*, **32**, 170 (1960)); certainly an accurate solution is not possible at the present time. If the problem is to be tackled at all, some brutal approximations are necessarily required. The full-scale Westheimer approximation is about the most complicated that would be feasible for these systems, while the approximation actually employed is about the simplest modification of the Westheimer method that could be expected to yield useful information. In the opinion of the authors, the input data required for a Westheimer approximation are not available with sufficient accuracy to ensure that the results obtained would be any better than can be obtained from a more simple approach; thus, for example, Dreiding models have been used to obtain atomic coordinates, keeping the limitations of the method in mind, and van der Waals energies have been obtained from experimental values on related systems where this is feasible rather than by calculation. While more precise geometric coordinates, better potential functions, etc., may ultimately lead to more accurate predictions, it is thought that the general methods and conclusions developed here will not be changed. The usefulness of such a simplified approach was demonstrated previously by calculations on the conformations of cyclohexane and cycloheptane (ref. 5, 7). While subsequent more refined, much more laborious (and hopefully more accurate) calculations on these systems have now led to numerical values which are more soundly based (ref. 13), the original general conclusions remain unchanged.

(13) J. B. Hendrickson, *J. Am. Chem. Soc.*, **83**, 4537 (1961).

(14) J. D. Swalen and C. C. Costain, *J. Chem. Phys.*, **31**, 1562 (1959).

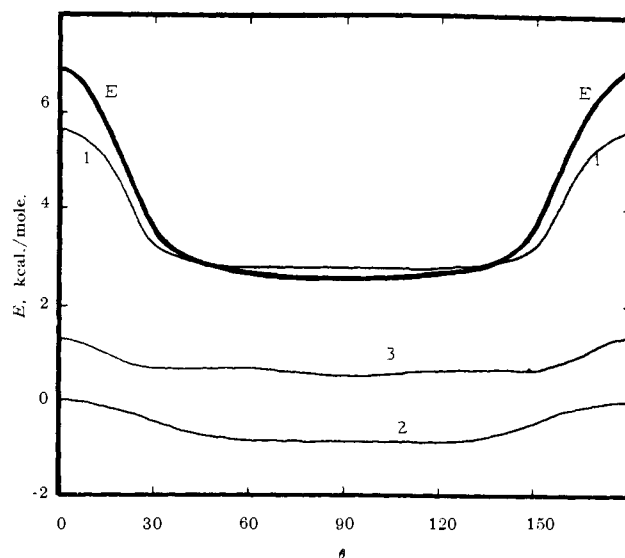


Fig. 2.—The partial and total conformational energies of the flexible form of cyclohexanone (relative to the chair form).

The other type of force requiring consideration is van der Waals repulsion.¹⁵ The only significant repulsion at $\theta = 0^\circ$ is between C-1 and C-4, and at $\theta = 60^\circ$ it is between the prow and stern carbons and so on. Repulsions involving hydrogens or oxygen seem in all cases to be negligible. The distance between the closest transannular carbons is 2.9 Å. in the chair, 2.6 Å. at $\theta = 0^\circ$, 2.7 at $\theta = 30^\circ$, 2.7 at $\theta = 60^\circ$, and 2.8 Å. at $\theta = 90^\circ$ (between two pairs). These values correspond to van der Waals repulsions of 0.2, 1.5, 0.9, and 0.8 kcal./mole, respectively,¹⁶ and again the points were connected by cosine curves (curve 3, Fig. 2). In Fig. 2 are given the curves for the torsional and van der Waals energies as functions of θ , and finally their sum which is the conformational energy (E) of the flexible form as a function of θ (curve E, Fig. 2). It can be seen that there exist two energy minima ($\theta = 90^\circ, 270^\circ$), but the over-all ranges from $\theta = 45-135^\circ$ and $\theta = 225-315^\circ$ are less than 3 kcal./mole above the chair, and in various substituted compounds one might expect *a priori* that different conformations in these ranges might be more stable than the corresponding chair.

(15) The approximation is made that the van der Waals attractions are sufficiently similar in the different conformations that they can be neglected¹⁵; Hendrickson's calculations¹³ indicate that this is a reasonable approximation.

(16) (a) T. L. Hill, *J. Chem. Phys.*, **16**, 399 (1948); (b) N. f. Allinger and W. Szkrybalo, *J. Org. Chem.*, **27**, 4601 (1962).

TABLE I
CONFORMATIONAL INTERACTION ENERGIES OF RING A^a

4-Methylated-3-keto steroids						
Interaction	4,4-Dimethyl			4 β -Methyl		
Regular chair forms						
(1) C4 β Me/19Me	3.7			3.7		
(2) C4 β Me/C2 β H	0.8			0.8		
(3) 19Me/C2 β H	.9			.9		
(4) C4 β Me/C6	.9			.9		
(5) C4 α Me/C6	.9			.9		
Totals	7.2			6.3		
Flat chair forms						
(1) C4 β Me/C19	0.9			0.9		
(2) C4/C5 torsion	4.2			3.4		
(3) C1/C2 torsion	1.4			1.4		
(4) Carbonyl torsion	-1.6			-1.6		
(5) Bond angle deformation	1.3			1.3		
Totals	6.2			5.4		
Flexible forms						
	0	30	60	0	30	60
(1) C4 β Me/19Me	0	0.9	3.7	0	0.9	3.7
(2) C10/C1 torsion	0	0.5	1.0	0	0.5	1.0
(3) C4/C5 torsion	3.7	2.8	1.8	3.2	2.0	0.9
(4) C4 α Me/C2 α H	0.8	0	0	0	0	0
(5) 19Me/C3	3.0	0	0	3.0	0	0
(6) Ring	6.9	3.5	2.7	6.9	3.5	2.7
Totals	14.4	7.7	9.2	13.1	6.9	8.3
2-Methylated-3-keto steroids						
Interaction	2,2-Dimethyl			2 β -Methyl		
Regular chair forms						
C2 β Me/19Me	3.7			3.7		
C2 β Me/C4 β H	0.8			0.8		
19Me/C2 β H	0.9			0.9		
Totals	5.4			5.4		
Flat chair forms						
C2 β Me/C19	0.9			0.9		
C4/C5 torsion	1.6			1.6		
C1/C2 torsion	1.9			1.6		
Carbonyl torsion	-1.6			-1.6		
Bond angle deformation	1.3			1.3		
Totals	4.1			3.8		
Flexible forms						
	0	30	60	0	30	60
C1/C10 torsion	0	0.5	1.0	0	0.5	1.0
C4/C5 torsion	0.5	0.2	0	0.5	0.2	0
2 α Me/4 α H	0.8	0	0
2 α Me/5 α H	0	0.3	6.0
C1/C2 torsion	1.0	0.5	0	0.5	0.2	0
19Me/C3	3.0	0	0	3.0	0	0
Ring	6.9	3.5	2.7	6.9	3.5	2.7
Totals	12.2	5.0	9.7	10.9	4.4	3.7

^a The reliability of these calculations is difficult to estimate. Our feeling is that the typical probable error in the conformational energy of a given system is +0.4 kcal./mole. When the calculated energies of two systems differ by less than 1 kcal./mole, the prediction as to which is the more stable can be made but should be viewed with reserve.

To predict the preferred conformation of a given cyclohexanone molecule, one needs in general (to the level of the present development of conformational analysis) to consider the energies of (a) the chair form, (b) deformed chair forms, and (c) the flexible form.

With these ideas in mind, a number of particular examples were chosen for study with the goal of demonstrating a theoretical basis for the existence of various types of nonchair forms. The energies of the regular chair, deformed chair, and flexible form were all cal-

culated, and an effort was made to determine the actual conformation by calculation. The 4,4-dimethyl-3-keto steroids are compounds in which it is apparent from models that serious repulsions exist in the ordinary chair form. The energy of the two methyls and one hydrogen *syn*-axial has been measured in a similar compound¹⁷ (5.5 kcal./mole), and the same value is taken (actually a minimum value since some deformation of the chair has probably occurred) for these interactions in the undeformed chair here (interactions 1-3 in Table I). There are two other interactions to be considered in the regular chair also—the *gauche* interactions between the C₆-methylene and the C₄-methyls (4, 5, Table I). The sum of these interactions gives a total conformational energy of 7.2 kcal./mole, relative to an arbitrary zero.

Next the energy of the flexible form can be considered, and the minimum value and corresponding geometry determined. The fusion of the B ring is such that the A ring can assume only conformations having θ between 0 and 60° (Fig. 3). It can be seen that the 60° form is made unfavorable by the interaction of the *syn*-axial β -methyls at C-4 and C-10 (3.7 kcal./mole,¹⁸ interaction 1, Table I, and Fig. 4); while this interaction amounts to 0.9 kcal. at $\theta = 30^\circ$, it is negligible at 0°. With $\theta = 60^\circ$, there is a torsional energy of the isobutane type (3.8 kcal./mole¹⁹) between C-10 and C-2, which adds to the values for the unsubstituted ring an amount which varies from 1.0 kcal./mole at $\theta = 60^\circ$, to zero at $\theta = 0^\circ$. A similar analysis for $\theta = 0^\circ$ shows C-5 and C-4 are eclipsed. The C4 β Me/C6 interaction is an eclipsed *n*-butane (6.0 kcal.^{18,20}), plus 0.5 kcal. for the C4 α Me/5 α H. Since 2.8 kcal. of this amount will be considered as part of the ring (below), this amount must be subtracted here, giving 3.7 kcal. (interaction 3). The interaction of the C4 α Me with the C-2 α hydrogen adds an additional 0.8 kcal./mole.²¹ The former is reduced to two *gauche* interactions at $\theta = 60^\circ$; the latter goes to zero at $\theta = 30^\circ$. The C-19 methyl interaction with C-3 is taken as 3.0 kcal./mole,¹⁸ and this goes to zero at $\theta = 30^\circ$. Finally the energy of the ring must be added. These energies are all indicated in Fig. 4. The flexible form is seen to be energetically very unfavorable, even at its energy minimum near $\theta = 40^\circ$.

Since both the chair and the flexible forms have quite high energies, at least one other possibility needs to be considered as an alternative. This is a deformed or flattened chair (Fig. 3) where C-1, C-2, C-3, and C-4 are all approximately in one plane. (The exact deformation may differ somewhat from this planar form,⁴ but the latter should be a fair approximation and is assumed in order to facilitate the calculations.) The C-4/C-5 torsional energy is half-way between that of the 0° boat (6.5 kcal.) and the chair (1.8 kcal.) or 4.2 kcal./mole. The C-1/C-2 eclipsing similarly is 1.4

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

(18) Such large energies are difficult to estimate, but since they are large the molecule is unlikely to exist in such a conformation and the error is therefore unimportant.

(19) J. G. Aston, in E. A. Braude and F. C. Nachod's "Determination of Organic Structures by Physical Methods," Academic Press, Inc., New York, N. Y., 1955, p. 525.

(20) (a) K. S. Pitzer, *Chem. Rev.*, **27**, 39 (1940); (b) K. Ito, *J. Am. Chem. Soc.*, **75**, 2430 (1953).

(21) N. L. Allinger and H. M. Blatter, *ibid.*, **83**, 994 (1961); B. Rickborn, *ibid.*, **84**, 2414 (1962). The torsional barrier about the C₁-C₂ bond is taken to be unaffected by the presence of the methyl group.

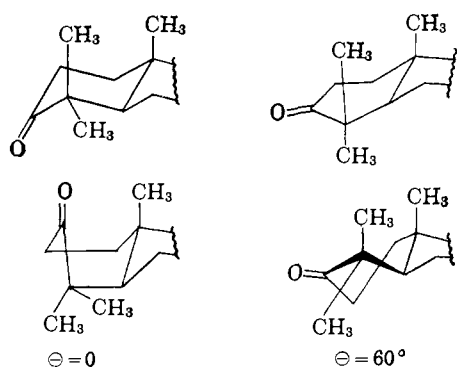


Fig. 3.—Possible conformations of ring A in a 4,4-dimethyl-3-keto steroid.

kcal./mole. The C-19/C-4 β -methyl repulsion here is estimated from models to be 0.9 kcal./mole, and the carbonyl torsion has been improved relative to the ordinary chair by 1.6 kcal./mole. Bond angle distortion must also be considered here. From the data of Hendrickson,¹³ such a flat form has C-C-C bond angles of 117° at C-2 and C-4, and 120° at C-3. This means about 6° of strain at C-2 and C-4 and 2° at C-3. If we take the "composite" bending constant¹¹ for distortion of such angles as 17.5 cal./mole deg.² the deformation energy is 1.3 kcal./mole. Addition of these various quantities gives the conformational energy of the flat form as 6.2 kcal./mole. It is seen that the flat chair is energetically favored over the other possibilities, and this calculation is consistent with experiment.⁴

A flattened chair has been shown to be the actual structure of the 4,4-dimethyl compound, and the available data on the others are also consistent with the general arrangement.⁴ No pertinent data for 2,2,4,4-tetramethylcholestanone have yet been reported, but calculations by present methods indicate that the flat form (8.4 kcal./mole) is favored over the flexible form (9.4 kcal./mole at $\theta = 30^\circ$) or regular chair (12.2 kcal./mole). The rotatory dispersion curve of the compound is consistent with the flattened chair.²²

Another type of compound which seemed deserving to study was the 17 α -keto-D-homosteroid system, for which there was already chemical evidence for the existence of a boat form during chemical reactions.²³ The fact that a boat form can be demonstrated as a reaction intermediate is suggestive, but proves nothing about the geometry of the ground state. It is the latter which determines many physical properties of interest, such as n.m.r. spectra, dipole moments, rotatory dispersion, and the like, and with which the present work is concerned.

The utility of dipole moments and rotatory dispersion for the quantitative solution of conformational problems has been very thoroughly demonstrated previously,¹ and these methods were used here. The compound chosen for the principal study was 17,17-dimethylandrostan-3,17 α -dione (IVd). The analogs with fewer or no methyls at C-17 (IVa-c) (and the corresponding 3-alcohols V) were also considered, and the

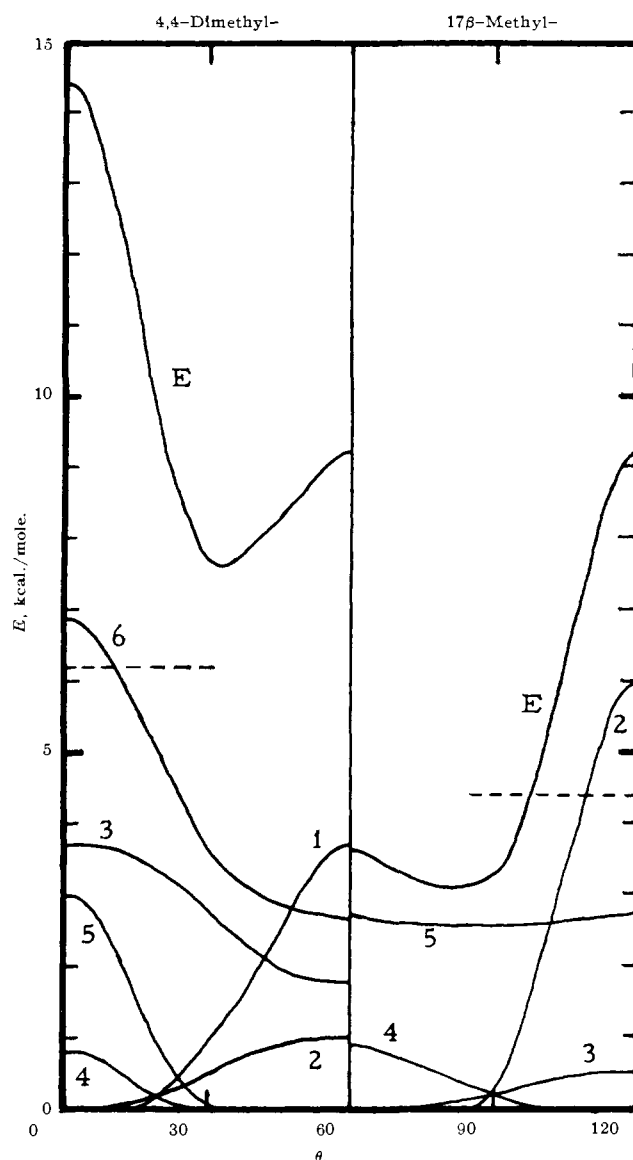
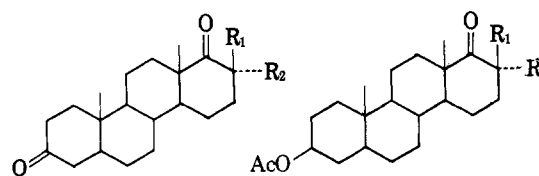


Fig. 4.—Conformational energies: solid lines, partial and total conformational energies of the flexible forms (Tables I and II); dotted lines, the corresponding flattened chairs.

synthesis of some of these compounds was in fact reported while this work was in progress.²³



- IVa, R₁ = H, R₂ = H
 b, R₁ = Me, R₂ = H
 c, R₁ = H, R₂ = Me
 d, R₁ = Me, R₂ = Me

An examination of models indicates that for an undistorted chair a 17 β -methyl is considerably more distant from the C₁₈-methyl when there is a ketone at C-17 α than in the corresponding hydrocarbon, and the repulsion between the methyls should therefore be less. There is some question²⁴ as to the accuracy of the Dreiding model, however, since the bonds from the carbonyl to the α -carbons are somewhat shorter than the ordi-

(24) W. Moffitt, R. B. Woodward, A. Moscovitz, W. Klyne, and C. Djerassi, *J. Am. Chem. Soc.*, **83**, 4013 (1961).

(22) M. A. DaRooge and C. K. Riew, unpublished.

(23) (a) M. Heller, S. M. Stolar, and S. Bernstein, *J. Org. Chem.*, **26**, 5036 (1961); (b) N. E. Wendler, *Tetrahedron*, **11**, 213 (1960) (also *Chem. Ind. (London)*, 1662 (1958), and 20 (1959)); (c) R. S. Rosenfeld, *J. Am. Chem. Soc.*, **79**, 5540 (1957); (d) D. K. Fukushima, S. Dobriner, and R. S. Rosenfeld, *J. Org. Chem.*, **26**, 5025 (1961).

nary value, and the bond angle is probably less than 120° . In any event, the experimental energy of an axial methyl adjacent to a carbonyl is 1.6 kcal./mole, only slightly less than in the hydrocarbon.²¹ Hence the repulsion between the 17β -methyl and the C_{15} -methyl is probably similar to that found in a hydrocarbon (3.7 kcal./mole¹⁷), and it has been assigned the value 3.0 kcal./mole somewhat arbitrarily.¹⁹ If the interaction energy is this high for the chair, the system will not exist this way; alternative forms are the flat chair, or a series of boats which range from a favorable boat ($\theta = 60^\circ$) through a stretched form ($\theta = 90^\circ$) to another favorable boat ($\theta = 120^\circ$) (Fig. 5). The rest of the pseudorotational cycle is prohibited by the fused C ring. It may be noted that this type of system is constrained to a range of θ from 60 to 120° , which is more favorable than the corresponding range available to the 3-ketones (0 – 60°).

The energetics of the flexible conformations of IVd can now be considered. It turns out that at $\theta = 60^\circ$ the distance between the 14α -hydrogen and the carbon of the 17α -methyl is 1.9 Å., which is energetically impossible, and this interaction is assigned a value of 6 kcal./mole.¹⁹ Similarly at 120° the 16β -hydrogen and carbon 18 are 1.9 Å. apart. Hence the only flexible conformations that are favorable have θ near 90° , and the only other possibility appears to be a flattened chair. The numerical calculations were carried out as for the 3-ketones, and the data are presented in Table II. The flexible form with $\theta = 90^\circ$ is seen to be only slightly better than the flat chair.

TABLE II
CONFORMATIONAL ENERGIES OF RING D IN D-HOMOSTEROIDS

Interaction	17,17-Dimethyl			17 β -Methyl			No methyl		
	Regular chair form								
β -syn-Axial interactions	4.8			4.8			1.6		
Total	4.8			4.8			1.6		
Flat chair forms (C-16, C-17, C-17a, and O all coplanar)									
18Me/15 β H	0.9			0.9			0.9		
17 β Me/15 β H		
Carbonyl torsion	-1.2			-1.2			-1.2		
C16/C17 torsion	2.8			2.5			2.1		
17 β Me/18Me	0.4			0.4			...		
Bond angle deformation	1.8			1.8			1.8		
Total	4.7			4.4			3.6		
Flexible forms									
	60	90	120	60	90	120	60	90	120
(1) 17 α Me/14 α H	6.0	0.3	0	0	0	0
(2) 18Me/16 β H	0	.3	6.0	0	0.3	6.0	0	0.3	6.0
(3) C14/C15 torsion	0	.2	0.5	0	.2	0.5	0	.2	0.5
(4) 18Me/15 β H	0.9	.2	0.0	0.9	.2	0.0	0.9	.2	0
(5) Ring	2.7	2.6	2.7	2.7	2.6	2.7	2.7	2.6	2.7
Total	9.6	3.6	9.2	3.6	3.3	9.2	3.6	3.3	9.2

These arguments also apply to the 17β -monomethyl compound (Fig. 4, Table II), except in this case the interaction on the underside of the ring is between α hydrogens at C-14 and C-17 and is negligible; hence an average θ of near 80° is predicted.

The sign of the Cotton effect to be predicted for these compounds in the various possible conformations can now be considered. Since the energy differences are small in many cases, mixtures are anticipated. Ordinarily only the form which dominates the rotatory dispersion will be detected by this method. The unsubstituted D-homo-17a-ketone Va does not show a Cotton effect,^{24,25} and this fact has been interpreted

(25) C. Djerassi and W. Klyne, *Proc. Natl. Acad. Sci. U. S.*, **48**, 1093 (1962).

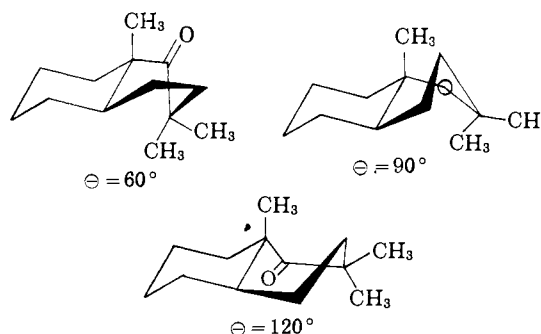


Fig. 5.—Conformations of the flexible form of a 17,17-dimethyl-17a-keto steroid.

as caused by a cancelling of the effect of the 18-methyl (negative) by that of the A and B rings (positive), which is consistent with the expected chair form for ring D (Table II). The 17α -methyl derivative Vc shows a similar curve, as expected for the D-chair. The 17β -methyl derivative Vb, on the other hand, shows a Cotton effect curve with $[A] +159$, while the 17,17-dimethyl derivative has a curve with $[A] -46$.²³ For the regular chair, since the unmethylated compound shows a negligible Cotton effect, both the β -methyl and the dimethyl compounds should look simply like an axial methyl²⁴ ($+56^\circ$). If a deformation similar to that found in the 4,4-dimethyl-3-ketones occurs in the 17,17-dimethyl compound, this value would be reduced, perhaps to zero, but it does not seem possible for it to be negative as is the experimental curve.

For $\theta = 120^\circ$, the two methyls at C-17 have equal and opposite effects, as should C-18 and C-14; C-11, C-12, C-13, C-15, and C-16 are on symmetry planes and do not contribute. The only contribution therefore will come from the A and B rings. Since this contribution is similar to that in the chair form of the unmethylated compound, which is exactly balanced by an axial methyl (C-18), and the contribution of an axial methyl²⁴ is $\pm 56^\circ$, this form would have an amplitude of about $+56^\circ$. As noted earlier, the observed Cotton effect ($[A] -46^\circ$) is not at all consistent with this conformation.²⁶ In conformation $\theta = 60^\circ$, the 17α -methyl should cancel C-16; C-18 should cancel C-12; and C-13, C-14, C-15, and the 17β -methyl are on symmetry planes. The only contribution again comes from distant atoms, C-11 and the A and B rings, and should be large and positive, with which the observed curve is again inconsistent. The amplitude is more difficult to predict for $\theta = 90^\circ$. Here the 17α -methyl and C-18 should exert large negative effects, C-14 and C-16 small positive effects, and the other parts of the molecule small positive effects. The resultant curve should probably have a negative sign, but its magnitude cannot now be predicted. The rotatory dispersion evidence therefore offers the least inconsistency for the flexible form with $\theta = 90^\circ$ as the conformation of the dimethyl compound.

The rotatory dispersion arguments for the 17β -monomethyl derivative are lengthy, and do not lead to a definite conclusion, but appear to favor the flexible form with θ unspecified.

The dipole moment of IVd was also measured.

(26) M. Uskokovic, M. Gut, E. N. Trachtenberg, W. Klyne, and R. I. Dorfman, *J. Am. Chem. Soc.*, **82**, 4965 (1960).

Rather different moments are calculated for certain conformations and, while the dipole moment was not expected to establish unequivocally the conformation, it would allow certain possibilities to be eliminated. The group moments for the two ends of the molecule were also needed, and they were determined from the moments of the molecules as listed in Table III.

TABLE III
DIPOLE MOMENTS OF VARIOUS COMPOUNDS IN BENZENE
SOLUTION AT 25°

Compound	Moment, D.
(1) Cholestan-3-one ^a	3.10 ^a ± 0.03
(2) D-Homoandrostan-3,17a-dione	3.48 ± .01
(3) 17,17-Dimethyl-D-homoandrostan-17a-one	3.04 ± .02
(4) 17,17-Dimethyl-D-homoandrostan-3,17a-dione	3.49 ± .05
(5) D-Homoandrostan-17a-one	3.06 ± .02
(6) Cholestane	0.16 ± .09 ^b

^a A moment of 3.01 D. was previously reported for this compound (ref. 27) which was calculated taking atomic polarization as $P_e + P_a = 1.10\text{MR}$. Subsequently, determination of the moment of cholestane (Table III) showed that the results were more accurate if atomic polarization was neglected and the values herein are calculated with such neglect. ^b This probable error does not allow for error in atomic polarization.

Dreiding models of 17,17-dimethyl-D-homoandrostan-3,17a-dione, with ring D in the regular chair conformation, and in the flexible form with $\theta = 60, 90, \text{ and } 120^\circ$ were then constructed, and the coordinates of the pertinent atoms were determined as previously described.²⁵ Using the moments of (1) and (3) for the group moments of IVd, the resultant moment of the latter was calculated for each conformation with the aid of an electronic computer and a previously described program,²³ and the calculated values for the various conformations are given in Table IV. A similar calculation for IVd gave (within the limits of error) the same numerical values as for IVa. The theory, supported by the rotatory dispersion evidence, indicated that IVa should be predominantly in the chair form, while IVd should be predominantly in the flexible form with $\theta = 90^\circ$. The observed moments are expected to agree with the calculated ones within $\pm 0.2\text{ D.}$, which they do.

TABLE IV
CALCULATED AND OBSERVED MOMENTS FOR COMPOUNDS
IVa AND IVd

Conformation	Calcd. IVa and IVd, D.
Chair	3.6
Flat chair	3.3
Flexible, $\theta = 60^\circ$	2.4
90	3.3
120	3.6
Observed (for both IVa and IVd)	3.5

One further point can be made in contrasting these cases with the 4,4-dimethyl-3-ketones, assuming the 1,3-dimethyl interactions are similar in the two cases. The 17a-ketones are able to take up conformations with θ in the $60\text{--}90^\circ$ range, while the ring A ketone was really limited to a flexible form with θ near 30° , or to

a flat chair. The 1,3-dimethyl interaction amounts to 3.7 kcal./mole, and is eliminated in the 90° form of the 17a-ketone at the cost of 2.8 kcal./mole for the ring torsion, and hence ring D does assume a boat form. In the ring A case, the available boat in which there is no *syn*-diaxial dimethyl interaction has a much larger torsional energy, and hence the molecule in this case prefers basically a chair form.

Conformational analysis predicts quantitatively what the behavior of these systems should be, and experiment supports the conclusions drawn from the calculations (but does not always prove that they are correct). This analysis can now with some confidence be applied to a number of methylated and brominated keto steroids, some of which have previously appeared to be anomalous, and such discussion will form the basis of a later paper.²⁹

Subsequent to completion of the above work, the paper by Djerassi and Klyne appeared²⁵ in which they concluded (from the rotatory dispersion curves alone) that: (a) 17 β -methyl- and 17,17-dimethyl-17a-oxo-D-homosteroids have different conformations; (b) the 17 β -methyl derivative exists in conformation with $\theta = 90^\circ$ (15,17a-RT in their nomenclature); and (c) the dimethyl compound exists with $\theta = 120^\circ$ (14,17-LT in their nomenclature). As far as point (a), we do not feel this has been proved, but the present analysis suggests that it is correct. Our conclusions are different from those of Djerassi and Klyne with regard to (b) and (c). They prefer conformation $\theta = 120^\circ$ for the dimethyl compound because it allows the 17a-

(29) The following discussion is added at the suggestion of a referee. The problem of the rotational barrier in acetone, and the bearing it has on cyclohexanone, is a vexing one (see also J. D. Cox, *Tetrahedron*, **19**, 1175 (1963), and K. S. Pitzer and W. E. Donath, *J. Am. Chem. Soc.*, **81**, 3213 (1959), and ref. 5). The height of the barrier in acetone is known to be 0.8 kcal./mole (ref. 14), but the conformation of minimum energy is unknown. The heat of hydrogenation of cyclohexanone is 2.0 kcal./mole less than that of acetone, which appears to indicate an unfavorable steric effect of this magnitude in the cyclohexanone molecule (H. C. Brown, J. H. Brewster, and H. Shechter, *ibid.*, **76**, 467 (1954)). The simplest interpretation of these two pieces of data would appear to be that the eclipsing of the carbonyl group in cyclohexanone is unfavorable by approximately 1 kcal./mole on each side, and in acetone where the molecule may adopt a staggered configuration it does so. The geometry of minimum energy for acetone therefore appears to be that in which the carbonyl is staggered with respect to a pair of hydrogens on each methyl group. No other interpretation of the above-cited experimental facts is apparent to the authors, and the calculations in this paper are based upon this assumed conformation of minimum energy in acetone. From the microwave spectra of a number of compounds such as acetaldehyde (R. W. Kilb, C. C. Lin, and E. B. Wilson, Jr., *J. Chem. Phys.*, **26**, 1695 (1957)), it has been concluded that the barrier to rotation of the methyl group is in each case of the order of 1 kcal./mole, and that the geometry of minimum energy is one in which a hydrogen eclipses the carbonyl oxygen. The acetone molecule is somewhat different from these others, however, but one is left with an uneasy feeling with regard to the assignment of the minimum energy conformation for acetone. The calculations reported herein have therefore been carried through for the alternative case where the eclipsed carbonyl corresponds to the energy minimum in order to see what effect on the results would be observed. These calculations indicate that in each case the regular chair would be more stable than the flat chair. Since the truth must be in reality somewhere between the extremes (from the rotatory dispersion data in ref. 4), this does not really change significantly the comparison between calculation and experiment. The 4-substituted 3-ketones and the 2,2-dimethyl-3-ketone now have the (regular) chair form more stable, while for the 2 β -methyl the (regular) chair and boat are similar in energy, as previously. The parent D-homo ketone is again predicted to have a more stable chair form, while the methylated compounds have their boat forms of comparable energy with the chair forms, so that boat-chair mixtures would probably be obtained. This situation might be experimentally detectable under appropriate conditions, but not from the data available to us. Thus the conclusions drawn in the present work are rather insensitive to the form of the barrier in acetone, and in fact even if the maxima and minima were to be reversed from those assumed originally in this work, there is still no definite conflict between theory and experiment. Conversely, the apparent good agreement between theory and experiment is not strong evidence that the barrier has been correctly assigned.

(27) N. L. Allinger, H. M. Blatter, M. A. DaRooge, and L. A. Freiberg, *J. Org. Chem.*, **26**, 2550 (1961).

(28) N. L. Allinger, M. A. DaRooge, M. A. Miller, and B. Waegell, *ibid.*, **28**, 780 (1963).

methyl to get away from the 14α -hydrogen. These authors overlook the fact that in this conformation there is generated a very bad interaction between the C_{18} -methyl and $C_{18\beta}$ -hydrogen. In the conformation $\theta = 90^\circ$, neither of these interactions is very serious. Similarly, the present analysis indicates that the 17β -methyl conformation should be somewhat different from that suggested by Djerassi and Klyne.

Experimental³⁰

D-Homo-5 α -androstan-3 β -ol-17a-one was prepared essentially as described by Goldberg and Wydler³¹ and crystallized from acetone to give plates, m.p. 168–169° (reported³¹ m.p. 170–172°).

D-Homo-5 α -androstan-3,17a-dione.—D-Homo-5 α -androstan-3 β -ol-17a-one, 1.0 g., was dissolved in 25 ml. of acetone (previously distilled from potassium permanganate) and treated with an excess of 8 *N* chromic acid (Jones reagent)³² for 5 min. The mixture was poured into water and the solid was collected. Crystallization from acetone afforded plates, m.p. 180–182° (reported³¹ m.p. 183–185°).

3 β -Hydroxy-17,17-dimethyl-D-homoandrostan-17a-one was prepared essentially as described.²⁶ The product was crystallized from acetone and gave needles, m.p. 149–151° (reported³² m.p. 152–155°).

17,17-Dimethyl-D-homoandrostan-3,17a-dione.—One gram of 3 β -hydroxy-17,17-dimethyl-D-homoandrostan-17a-one was oxidized with an excess of Jones reagent as described for the preparation of D-homo-5 α -androstan-3,17a-dione. The product was crystallized from methanol to yield 0.82 g. of flakes, m.p. 130–131° (reported²⁶ m.p. 129–131.5°).

D-Homo-5 α -androstan-17a-one.—D-Homo-5 α -androstan-3 β -ol-17a-one, 3.5 g., was dissolved in 35 ml. of dry pyridine and 1.7 g. of *p*-toluenesulfonyl chloride was added. The mixture was allowed to stand overnight. The mixture was poured into cold water, acidified with 10% sulfuric acid, and filtered. The solid was crystallized from methanol–ether to give 3.1 g. of needles, m.p. 164–166° dec.

The tosylate (2.5 g.) was dissolved in 75 ml. of benzene and added dropwise to a slurry of 1.2 g. of lithium aluminum hydride in 50 ml. of ether and 100 ml. of benzene. The mixture was refluxed 48 hr. The excess hydride was decomposed with 1:1 acetic acid–water. The organic phase was separated and the aqueous layer extracted twice with benzene. The combined extracts were washed well with water, saturated bicarbonate solution, and water. After removal of the solvent the residue was taken up in 30 ml. of acetone and treated with an excess of Jones reagent as described for D-homo-5 α -androstan-3,17a-dione. The semisolid residue was chromatographed on basic alumina to give 1.2 g. of material, m.p. 119–121°.

Anal. Calcd. for $C_{25}H_{32}O$: C, 83.27; H, 11.18. Found: C, 82.97; H, 11.31.

17,17-Dimethyl-D-homo-5 α -androstan-17a-one.—Two grams of 17,17-dimethyl-D-homo-5 α -androstan-3,17a-dione was treated with 0.3 g. of hydrazine (85%) and 2 g. of potassium hydroxide in 40 ml. of diethylene glycol. After refluxing 20 min. the condenser was removed and the temperature allowed to rise to 175°. After refluxing 3 hr. the mixture was poured into water and extracted with ether. The ether was washed several times with water, dried, and removed. The residue was chromatographed on basic alumina. Crystallization from methanol of the material obtained from elution with hexane–1% benzene afforded 0.9 g. of ketone, m.p. 99–101.5°.

Anal. Calcd. for $C_{22}H_{30}O$: C, 83.48; H, 11.46. Found: C, 83.40; H, 11.24.

When a larger excess of hydrazine was used, 17,17-dimethyl-D-homo-5 α -androstan-17a-one was also obtained, m.p. 60–62°.

Anal. Calcd. for $C_{22}H_{30}$: C, 87.34; H, 12.66. Found: C, 87.59; H, 12.80.

Dipole Moments.—The dipole moments of the various ketones were run at 25° in benzene solution, and the data are given in Table V. The dipole moment apparatus has been described previously.²⁷ The moments were calculated by essentially the method of Halverstadt and Kumler,³³ utilizing an IBM 650 computer programmed as described earlier.³⁴ Atomic polarization is neglected. Molar refractivities were obtained from tables.³⁵

TABLE V

DIPOLE MOMENT DATA IN BENZENE SOLVENT AT 25°

N_2	d_{12}	ϵ_{12}
D-Homoandrostan-3,17a-dione, MR 86.18 cc.		
0.00000000	0.873105	2.2719
.00039516	.873394	2.2786
.00086345	.873762	2.2851
.00132243	.874134	2.2946
.00167409	.874369	2.3007
α 17.230	ϵ_1 2.2719	d_1 0.87312
β 0.766	$P_{2\infty}$ 333.2	μ 3.48 \pm 0.02 D.
17,17-Dimethyl-D-homoandrostan-3,17a-dione, MR 95.48 cc.		
0.00000000	0.873282	2.2737
.000436441	.873599	2.2808
.000739378	.873915	2.2861
.000897643	.874053	2.2894
.00109992	.874153	2.2928
α 17.452	ϵ_1 2.2735	d_1 0.87327
β 0.832	$P_{2\infty}$ 343.8	μ 3.49 \pm 0.05 D.
17,17-Dimethyl-D-homoandrostan-17a-one, MR 95.51 cc.		
0.00000000	0.873575	2.2723
.000182846	.873688	2.2744
.000423436	.873807	2.2776
.000576651	.873874	...
.000883799	.873982	2.2837
α 13.041	ϵ_1 2.2721	d_1 0.87359
β 0.477	$P_{2\infty}$ 285.0	μ 3.05 \pm 0.03 D.
D-Homoandrostan-17a-one, MR 86.21 cc.		
0.00000000	0.873140	2.2723
.00050739	.873334	2.2795
.00077706	.973517	2.2827
.00131794	.873823	2.2900
.00159141	.873980	2.2934
α 13.275	ϵ_1 2.2724	d_1 0.87311
β 0.541	$P_{2\infty}$ 277.1	μ 3.06 \pm 0.02 D.
Cholestane, MR 118.75 cc.		
0.00000000	0.873605	2.2758
.00137565	.873922	2.2754
.00190109	.874025	2.2766
.00395643	.874505	2.2756
.00519319	.874835	2.2753
α 0.0568	ϵ_1 2.2757	d_1 0.87359
β 0.236	$P_{2\infty}$ 119.2	μ 0.16 \pm 0.09 D.

Acknowledgment.—The authors are indebted to Dr. C. Djerassi, Stanford University, for making available rotatory dispersion information in advance of publication, and to C. L. Neumann for some of the dipole moment determinations.

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