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THE CONFORMATION OF RING A IN 4,4-DIMETHYL-3-KETO-STEROIDS[1,2]

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THE ground state conformations of the steroid ring systems are in general securely locked in potential wells, can vary but little, and are for the most part well understood. In a 4,4-dimethyl-3-keto-5α-steroid (I) however, there is reason to question whether or not ring A will be in the standard chair form, and the answer to this question is of interest because of the widespread occurrence of this type of structure in nature. Recently, numerical values have been reported for the enthalpies of two quantities related to this question, namely the 1,3-diaxial dimethyl interaction,[4] 3.7 kcal/mole, and the chair→boat transformation of a cyclohexanone,[5] 2.8 kcal/mole. Actually other interactions must be considered, but a first approximation would seem to indicate that ring A in I might be more comfortable in the boat form than in the undeformed (or slightly deformed) chair (II).

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[1] Conformational Analysis XXII. For the preceding paper see N.L. Allinger and S. Hu, J.Amer.Chem.Soc. In press.

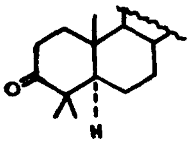
[2] This work was supported in part by Grant No. E-2267 from the Public Health Service, National Institutes of Health.

[3] Predoctoral U.S. Public Health Service Fellow, General Division of Medical Sciences, 1960-62.

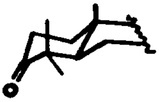
[4] N.L. Allinger and M.A. Miller, J.Amer.Chem.Soc. **83**, 2145 (1961).

[5] N.L. Allinger and H.M. Blatter, J.Amer.Chem.Soc. **83**, 994 (1961).

An examination of models indicates that the boat form under consideration has a certain amount of flexibility, and the most stable arrangement may be either of two extremes, III or IV, or it may be somewhere in between.



I



II

III

IV

V

Another possibility must also be considered, which is V. Here C-3 is moved upward (relative to II) approximately to the plane defined by carbons 1,2,4 and 5. Such a structure is similar to the transition state between boat and chair forms, which for cyclohexanone can be estimated roughly as the sum of two "half-eclipsed" ethanes (3 kcal) plus two acetone barriers (perhaps 2 kcal).[6] The energy of this distorted chair (5 kcal/mole) is therefore comparable in magnitude to the other possibilities and must also be considered.

The non-chair structure for 3-ketones is commonly represented as III.[7,8,9] A general objection to this arrangement is that it contains two eclipsed ethanes (6 kcal), while a boat type IV contains but one (3 kcal).

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[6] J.D. Swalen and C.C. Costain, J.Chem.Phys. 31, 1562 (1959).

[7] D.H.R. Barton, D.A. Lewis and J.F. McGhie, J.Chem.Soc. 2907 (1957).

[8] C. Djerassi, N. Finch, R.C. Cookson and C.W. Bird, J.Amer.Chem.Soc. 82, 5488 (1960).

[9] F. Sondheimer, Y. Klibansky, Y.M.Y. Haddad, G.H.R. Summers and W. Klyne, J.Chem.Soc. 767 (1961).

Offsetting this difference in IV, the latter has a 1,3-diaxial dimethyl interaction which in III is lacking. Something in between III and IV can probably minimize the total energy of a boat form by having each of these unfavourable effects present to a small degree.

In an effort to obtain a decision as to the conformational structure of ring A, a series of dipole moments were measured for the compounds listed in Table 1. Compounds (1) through (4) and (7) were all obtained by standard methods and had properties in good agreement with the literature values. Compounds (5), m.p. 138°, and (6), m.p. 134°, were obtained by oxidation of the known 17 alcohols [10,11] and gave proper analyses.

Table 1

Dipole Moments of Various Ketones
Benzene Solution, 25°C

	Compound	Moment (D)
(1)	Cholestane-3-one	3.01[12]
(2)	Androstane-17-one	2.98
(3)	Androstane-3,17-dione	2.94[13]
(4)	4,4-Dimethylcholestane-3-one[14]	2.78
(5)	4,4-Dimethyl-19-nor-androstane-3,17-dione[10]	2.68
(6)	4,4-Dimethyl-androstane-3,17-dione[11]	2.28
(7)	19-nor-Androstane-3,17-dione	2.90

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[10] A. Bowers and H.J. Ringold, J.Amer.Chem.Soc. 81, 424 (1959).

[11] H.J. Ringold and G. Rosenkranz, J.Org.Chem. 22, 602 (1957).

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

[13] H.R. Nace and R.B. Turner, J.Amer.Chem.Soc. 75, 4063 (1953) report a dipole moment of 3.1 D for this compound. Since they did not account for atomic polarization in calculating the moment their value is slightly higher than ours.

[14] C. Djerassi, O. Halpern, V. Halpern and B. Riniker, J.Amer.Chem.Soc. 80, 4001 (1958).

The moments of (1) and (2) give the group moments of (3). A calculated value for the resultant moment of the latter was arrived at by projecting a Dreiding model of the molecule into a co-ordinate system, and determining the angle between the carbonyl groups and the resultant moment by standard trigonometric methods. It is estimated that the angle between the dipoles could be determined on the models to within 2 or 3° which gave errors of 0.1-0.2 D in the calculated moments. The moment calculated for (3) was 2.80 D, and the experimental value is 2.94 D, hence the model seems to portray the system to within the accuracy of measurement. As a check, the moment of (7) was determined and found to be 2.90 D, within experimental error of the value found for (3).

The presence of a 4,4-dimethyl grouping lowers the moment of the 3-ketone somewhat (from 3.01 in (1) to 2.78 in (4)). Using the group moments from (2) and (4), the moment of (5) was calculated, assuming a chair form. This assumption seems justified since there is no 1,3-diaxial dimethyl interaction. Here the calculated (2.75 D) and the experimental (2.68 D) values are in good agreement.

Table 2

Dipole Angles and Moments (D)
for Possible Structures of (6)

Structure	Angle°	$\mu_{calc.}$(D)
II	124	2.75
III	110	3.29
IV	121	2.88
V	131	2.46

Compound (6) was then examined. The angle between the dipoles of the ordinary chair was as for (3) and (5), 124° (Table 2). For boat IV this angle was measured as slightly smaller (121°), while III has an angle of only 110°. These are the extremes of the flexible form, any angle between these limits is possible. The calculated moment of any boat form then is higher than that of II. The experimentally determined moment of (6) was, however, only 2.28 D, much smaller than calculated for the chair, and well outside of the range defined by the flexible form. A structure similar to the form V appears to be the only arrangement which will lower the calculated resultant moment. The value calculated for planar structure is 2.46 D, within experimental error of the measured value.

The rotatory dispersion curves[14] of 19-nordihydrotestosterone and its 4,4-dimethyl derivative show that the introduction of the latter grouping causes the predicted[1,15] large negative shift in the Cotton effect. The corresponding shift with the cholestan-3-one derivatives is similar though smaller, and is consistent with II. If III were the structure of these systems, a large positive shift would be predicted,[15] and its absence serves to eliminate this structure, but further conclusions do not appear warranted.

The planar form V should have the angle between C-2 and C-4 expanded slightly above its normal value. Such bond angle expansion has been detected[16] by the shift in carbonyl frequency using the relationship suggested by Halford[17]. The carbonyl frequencies of (1), (4) and of 4,4-dimethyl-19-norandrostan-17β-ol-3-one were therefore measured in chloroform solution. The latter showed absorption at 1706 cm^{-1}, as did (1). Compound (4) showed the predicted decrease to 1699 cm^{-1}.

The infra-red spectrum of (6) was determined, both in carbon tetrachloride

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[15] C. Djerassi, Optical Rotatory Dispersion p.178. McGraw-Hill, New York (1960).

[16] N.L. Allinger and S. Greenberg, J.Amer.Chem.Soc. 81, 5733 (1959).

[17] J.O. Halford, J.Chem.Phys. 24, 830 (1956).

solution, and as a mull. No bands could be detected in solution which were not present in the solid, although there was some change in the relative intensities of a few bands. With such a complicated molecule such a result may not be definitive, but it suggests the molecule is in a single conformation.

The structure of ring A in (6) which best fits the data is neither a chair nor a boat, but rather a flattened form in between the two.

Lehn, Levisalles and Ourisson[18] have preferred to interpret their data on a similar (but different) system as indicating an equilibrium between boat and chair forms. It may well be that their system behaves differently from the one studied by us. With our system we have found no evidence requiring a boat form, although the possibility of the presence of a small amount cannot be eliminated with certainty.

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[18] J. Lehn, J. Levisalles and G. Ourisson, following communication. We are indebted to Professor Ourisson for a copy of the manuscript prior to publication.