Tetrahedron, 1967, Vol. 23, pp. 1279 to 1282. Pergamon Press Ltd. Printed in Northern Ireland

CONFORMATIONAL ANALYSIS—LII

THE CONFORMATION OF RING A IN 5β-3-KETOSTEROIDS[1,2]

N. L. ALLINGER and C. L. NEUMANN
Department of Chemistry, Wayne State University, Detroit, Michigan 48202

(*Received in U.S.A.* 20 *July* 1966; *accepted for publication* 26 *September* 1966)

Abstract—5β-Cholane-3,12-dione has been synthesized, and its dipole moment measured in benzene solution. The value of 4·49 D shows that ring A is in the chair form to within the limits of experimental measurement, which indicates that the earlier interpretation of the dipole moment of 5β-androstan-3,17-dione in terms of an equilibrium mixture of boat and chair forms for ring A is improbable, and that the later compound is more likely to have a deformation present in ring D.

IN A pioneering investigation, Nace and Turner measured the dipole moment of 5β-androstan-3,17-dione, for which they found an experimental value of 3·50 D.[3] Utilizing Barton models they calculated that if ring A were in the chair form, the compound should in fact have a dipole moment of 3·04 D. Since the discrepancy seemed well beyond the limits of the errors of the experimental measurements, they suggested that the molecule existed with ring A in the classical boat form (θ — 0°) to the extent of 16%.

The boat form of a cyclohexane ring was a rather speculative subject in 1953, but it has subsequently been studied in considerable detail.[4] While the energy required to force a cyclohexanone ring into a boat form is not very great,[1] the interactions in the chair form in the system in question which would be improved in the boat forms appear to be insufficient to cause any significant fraction of the molecules to adopt the boat conformation. It may be calculated by the usual addition of the interactions involved,[5] that the energies of the various ring A boats of this compound are above that of the corresponding chair by 1·9, 2·9, and 9·9 kcal/mole for values of $\theta = 60°$, 30°, 0°, respectively. Theory therefore indicated that there will be less than 10% boat form in equilibrium with the chair in this type of system, and furthermore, the boat form will be pretty much constrained to the region of $\theta = 30$ to 60°. The dipole moment of the boat form with θ in this range would not differ very much from that of the chair form, and less than 10% of this conformation is not adequate to explain the discrepancy noted by Nace and Turner between the observed and calculated values for the dipole moment of 5β-androstane-3,17-dione. Since the coprostanone-type A/B structure is an important one in nature, the apparent discrepancy between theory and experiment seemed worth clarifying.

---

[1] Paper LI, N. L. Allinger, H. M. Blatter, L. A. Freiberg and F. M. Karkowski, *J. Am. Chem. Soc.* **88**, 2999 (1966).

[2] This investigation was supported by Public Health Service Research Grant A-5836 from the National Institute of Arthritis and Metabolic Diseases.

[3] H. R. Nace and R. B. Turner, *J. Am. Chem. Soc.* **75**, 4063 (1953).

[4] For a recent review, see: E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, *Conformational Analysis* p. 469. Interscience Division, Wiley, New York (1965).

[5] N. L. Allinger, J. Allinger and M. A. DaRooge, *J. Am. Chem. Soc.* **86**, 4061 (1964).

We confirmed the experimental and calculated dipole moments reported by Nace and Turner for the 5β-androstan-3,17-dione molecule. Experimentally, the compound was prepared and its dipole moment was measured in benzene solution at 25° and found to have the value of 3·51 D. The 5α isomer was also prepared, and under the same conditions was found to have a dipole moment of 3·01 D. To calculate what values for these moments are expected, one needs to know the dipole moments of a 5β-3-ketone, a 5α-3-ketone, and of a 17-ketone, and we have previously determined that these have the values 3·10, 3·10 and 3·05 D respectively.[5,6] Utilizing Dreiding models to determine the geometry, together with the above group moments, and proceeding in the ordinary way,[7,8] the dipole moments calculated for the 5β and 5α isomers were 3·17 and 2·85 D.

It appears that the calculated and measured dipole moments for the 5β compound differ by more than experimental error ($\pm$0·2 D), while the 5α isomer does have the predicted value for the dipole moment.

An interpretation of these data which is an alternative to that given by Nace and Turner is that a portion of the 5β molecule (and perhaps the 5α also) is not accurately represented by Dreiding Models. The angles between the dipoles differ for the two isomers, so it is not unreasonable that a geometric error would lead to different effects in the different isomers. Our suspicions were directed toward the 5-membered ring, since cyclopentanone rings are geometrically not well understood.[9] One may see from models, for example, that if the CO vector from the C-17 CO is tilted in a specific way so as to reduce the angle between it and the C-3 CO by approximately 6° in the 5β isomer, the same tilt could keep the angle unchanged in the 5α isomer, and the calculated dipole moments for the diones would agree with those measured experimentally. It seemed quite likely that an error in the angle of this vector of the order of 6° was possible, since the Dreiding models are certainly limited in their ability to accurately represent a 5-membered ring.

To determine whether or not these suppositions were correct, we considered the molecule 5β-cholane-3,12-dione. In this case the two carbonyls are sufficiently far apart so that they should not interfere with one another, and yet they are both in 6-membered rings, and hence one ought to be able to predict with rather high accuracy the dipole moment of this molecule. It was therefore decided to synthesize the compound, and it was also necessary to determine the group moment for the 12-ketone. The synthesis of these compounds was carried out from 5β-cholane-3α,12a,24-triol by a modification of a published method.[10]

The dipole moments of cholan-12-one and of the corresponding 3,12-dione were measured as previously,[7] and they have the values 2·96, and 4·49 D. Using the values for the 3-, and the 12-ketones, together with measurements on Dreiding models as previously described,[8] the dipole moment of the dione was calculated to have the value 4·44 D, in excellent agreement with the experimentally measured value.

Modern theory indicates that any appreciable amounts of boat forms in systems of the type under discussion are not to be expected. The burden of proof for the

---

[6] N. L. Allinger and M. A. DaRooge, *J. Am. Chem. Soc.* **84**, 4561 (1962).

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

[8] N. L. Allinger, M. A. DaRooge, M. A. Miller and B. Waegell, *J. Org. Chem.* **28**, 780 (1963).

[9] Ref. 4, Page 200.

[10] R. T. Blickenstaff and F. C. Chang, *J. Am. Chem. Soc.* **81**, 2835 (1959).

presence of any such unexpected forms then rests on the side of those who believe otherwise. While we do not feel that the present work is proof of the complete absence of boat forms, we do feel that this work invalidates the conclusion of Nace and Turner that their results are evidence for the presence of boat forms.

TABLE 1. DIPOLE MOMENT DATA

Compound	α	ϵ_1	d_1	β	P_{2_∞}	μ(D)(±0·02D)
5β-Cholane-12-one	12·45	2·2746	0·8733	0·539	284·1	2·96
5β-Cholane-3,12-dione	28·31	2·2737	0·8731	0·727	516·2	4·49
5β-Androstane-3,17-dione	17·57	2·2758	0·8736	0·748	333·5	3·51

EXPERIMENTAL

5β-Cholane-3α,12α,24-*triol* (III). To a 500 ml Erlenmeyer flask, desoxycholic acid (7.84 g) abs EtOH (200 ml) conc H_2SO_4 (30 ml) was added. This mixture was refluxed on the steam bath for 12 hr. To the cooled mixture was then added 200 ml reagent benzene and 150 ml water, and the layers were separated. The aqueous layer was extracted twice with benzene, the benzene washings were combined, washed with $NaHCO_3$aq and dried ($MgSO_4$). Finally, any EtOH or water remaining was removed by careful azeotropic distillation of the benzene soln. Distillation was continued until the soln was reduced to a volume of about 50 ml, and this soln of II was used for the following reduction.

To a 3 neck 300 ml flask equipped with dropping funnel, magnetic stirrer, thermometer and condenser was added 100 ml dry ether and LAH (1 mole, 3·7 g). This mixture was stirred for 10 min, and then the previously prepared soln of II was added. The temp was maintained at about +8° during the addition by means of an ice bath. After the addition, the soln was tested for excess reducing agent with a drop of water. None was present, so more LAH was added until a drop of water produced an immediate reaction. This mixture was stirred at 8° for ½ hr, and then cautiously hydrolyzed with 6 N HCl until the soln was acid (pH $<$ 3). The mixture was extracted with 3 × 150 ml portions of Chf (or better, AcOEt), the Chf extracts were combined, washed with $NaHCO_3$aq and dried with $MgSO_4$. Evaporation of the Chf yielded two crops of crystals, m.p. 113-117° with gas evolution, (m.p. here may be variable) and resolidification to a glass which melted approximately 148° (lit.[10], m.p. variable over the range 107-185°). The total yield of cholane-3α, 12α, 24-triol (which contains solvent of crystallization), was 8·84 g.

Reduction of cholane-3α,12α,24-*triol* (III) *via the tosylate*. A soln of 6·77 g (17·9 5mmoles) cholanetriol was prepared in 40 ml anhyd pyridine. To this soln was added 8·00 g *p*-toluenesulfonyl chloride in 13·4 ml pyridine over a 2 hr period, with the temp maintained at 2-5°. The soln was stirred an additional ½ hr and then ice was added to the mixture. The mixture was acidified with HCl, extracted with ether 3 times, and the ether washings were combined, washed with $NaHCO_3$aq, dried over $MgSO_4$, and reduced in volume to about 50 ml. The resulting soln was treated with LAH (3·00 g in 150 ml ether) as described above. The ether soln of the product was chromatographed.

A large chromatography column was packed with 1000 g Fisher neutral alumina to a height of about 15 inches in ether. Chromatography of the above soln, eluting with ether in 500 ml fractions, yielded 2 fractions containing solid material, followed by 8 empty fractions. Further elution with 5% EtOH in ether gave 2 empty fractions followed by 3 containing material, then 5 more empty ones.

Fractions 1 and 2 were concentrated and recrystallized from acetone-water to give crystals of VI m.p. 100–101·5° Lit.[10] 100-101·3°. Fractions through 15 were concentrated and recrystallized from acetone–heptane to yield crystals of VII, m.p. 170-171°, Lit.[10] 171·2–172·2°.

5β-Cholan-12-*one* (VIII). Compound VI (2·2 g) was oxidized in acetone at 25° with Jones Reagent in the usual manner.[11] The crude reaction mass was filtered through a 1 inch high alumina column to remove the Cr salts, and the residue from the eluate was crystallized from acetone to yield needles, 1·95 g, m.p. 116–117°. (Found: C, 83·71; H, 11·70. Calc. for $C_{24}H_{40}O$: C, 83·65; H, 11·70.)

5β-Cholane-3,12-*dione* (IX). Compound VII (2·0 g) was oxidized as described for the prep of VIII, and after crystallization from acetone, 1·54 g of product was obtained as white needles, m.p. 138°. (Found: C, 80·15; H, 10·76. Calc. for $C_{24}H_{38}O_2$: C, 80·38, H, 10·69.)

---

[11] R. G. Curtis, I. M. Heilbron, E. R. H. Jones and G. F. Woods, *J. Chem. Soc.* 457 (1953).

5β-Androstane-3,17-*dione*. The dione was prepared according to the lit.,[11] and had m.p. 132·5–133°; lit. (12), 131–132°.

Dipole moments. The experimental dipole moments were determined at 25° in benzene soln using previously described apparatus,[7] and methods.[8]

The dipole moment of each conformation was calculated from measurement of atomic coordinates with Dreiding models, using previously described methods.[8]

Acknowledgement—The authors are indebted to Dr. M. A. DaRooge and to Mrs. L. W. Chow for measuring the experimental dipole moments reported herein.

---

[11] N. L. Allinger and S. Greenberg, *J. Org. Chem.* **25**, 1399 (1960).