

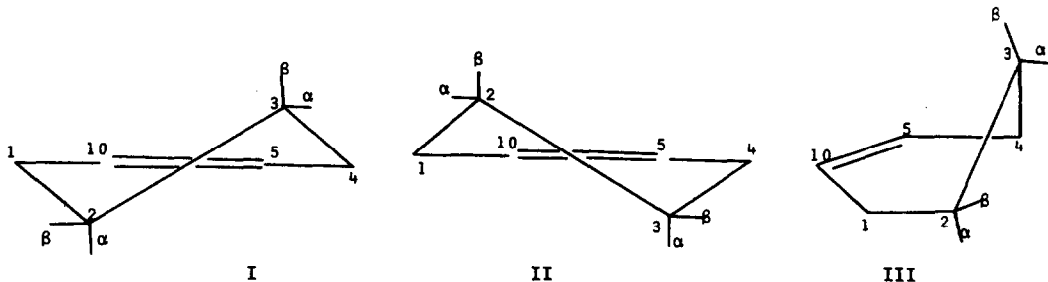
THE PREFERRED HALF-CHAIR  
CONFORMATION OF RING A IN 5(10)-ESTRENES

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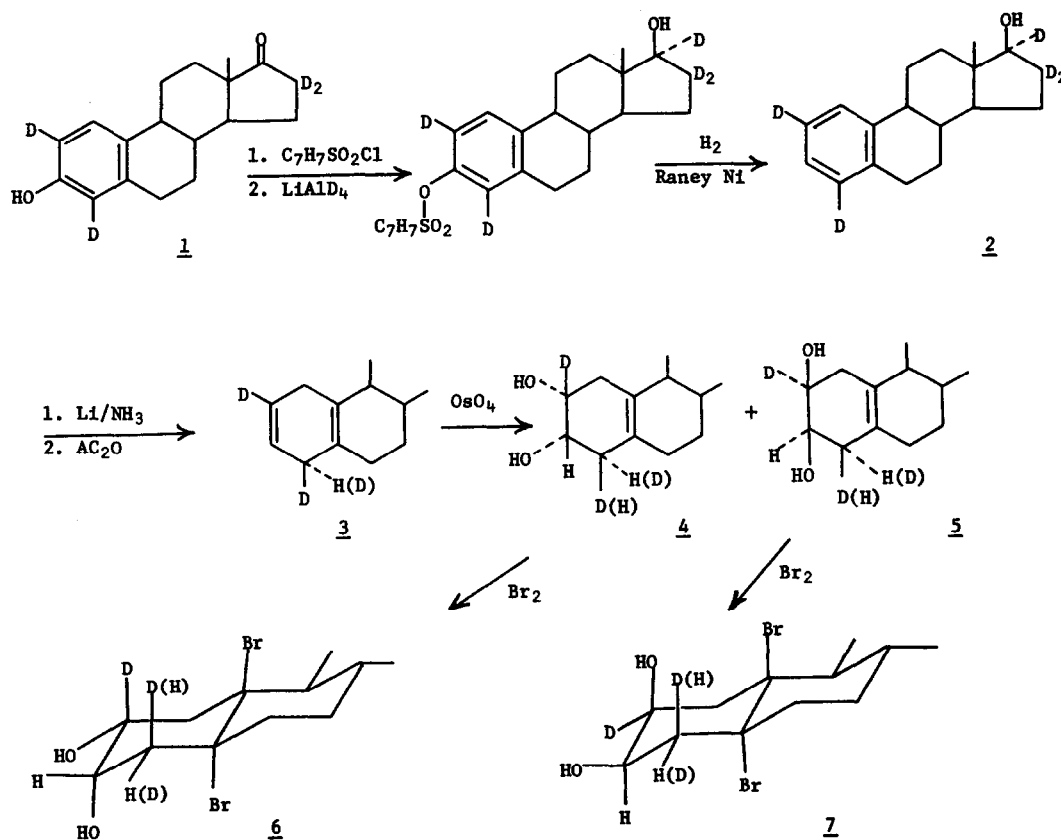
(Received in USA 15 May 1967)

We have previously (2) described an unusual type of conformational preference effect which was found to operate in ring A of some 3-substituted (-OH and -N<sub>3</sub>),  $\Delta^{5(10)}$ -steroids. From the NMR spectra of these epimer pairs in the C-3 proton region, it was evident that the 3 $\alpha$ - and 3 $\beta$ -valence bonds were consistently equatorial and axial, respectively--a conclusion which was in agreement with other physical and chemical evidence. On this basis, it was deduced that, of the two possible half-chair modifications of ring A, I and II, the former is preferred. The possibility of a preferred form other than a half-chair was not considered. In particular, the "1,2-diplanar" (3) conformer III might well be consistent with our previous data; for cyclohexene, this form is estimated to be only 1.2 kcal./mole higher in energy than the half-chair. In view of current interest (4) in the conformations of steroidal cyclohexene rings, we would now like to report on work in the 2,3-*cis* diol series, which has led to additional evidence for the half-chair form I of ring A.



Estrone-2,4,16,16-d<sub>4</sub> (1) was converted (SCHEME 1) to the 3-deoxy-17 $\beta$ -alcohol 2 following the procedure of Caspi and co-workers (5) for the preparation of the corresponding undeuterated substance. Aromatic proton signals were observable in the NMR (6) spectrum of 2 as slightly broadened singlets, 1H each, at 7.03 and 7.22 $\delta$ . Further reduction with lithium in ammonia and

subsequent acetylation gave the 2,5(10)-diene 17 $\beta$ -acetate 3, m.p. 108–110°, showing a single vinyl proton signal (1H) at 5.16 $\delta$ . Diene 3, when treated with a slight excess of OsO<sub>4</sub>, underwent preponderant attack at the less substituted  $\Delta^2$  double bond leading to the two possible 2,3-*cis*-diols in comparable amounts. These products were efficiently separated by column chromatography on alumina affording diol 4, m.p. 150–153° and diol 5, m.p. 145–147°. Diol 4 reacted instantly with bromine at 0° without evolution of HBr. The homogeneous (by TLC) product was crystallized from ether giving the dibromide 6, m.p. 96–100°, in good yield. Similarly, diol 5 was converted to the dibromide 7, m.p. 119–122°. These products decomposed rapidly on storage at room temperature but freshly prepared samples gave reasonable elemental analysis results. It seems safe to assume that both substances are 5 $\alpha$ , 10 $\beta$ -dibromide adducts (7).



SCHEME 1

The NMR spectrum of dibromide 7 (Fig. 1b) exhibits a one-proton multiplet centered at 4.46 which must be assigned to the C-3 hydrogen. This symmetrical four signal pattern is easily accounted for by recalling that the single C-4 hydrogen was introduced non-stereoselectively *via* metal-ammonia reduction of ring A. The C-3 proton will, then, be split by a 4 $\alpha$ - or a 4 $\beta$ -proton, whichever the case may be in any individual molecule; the resulting pair of doublets, each centered at 4.46, constitutes the multiplet in question. The outer doublet ( $J = 12$  cps) must reflect the strong coupling of 1,2-*trans*, diaxial protons which can only be located at the 3 $\alpha$ - and 4 $\beta$ -positions (8). Dibromide 7 is consequently assigned a 2 $\beta$ , 3 $\beta$ -diol structure. The inner doublet has a separation of 4 cps attributable to 3 $\alpha$  (axial)-4 $\alpha$  (equatorial) coupling.

These structural conclusions are confirmed by the spectrum of dibromide 6 (Fig. 1a), which is, by inference, the 2 $\alpha$ , 3 $\alpha$ -diol. The C-3 hydrogen is in this case equatorial and its coupling to a C-4 proton would be of the equatorial-axial or equatorial-equatorial type depending on the C-4 hydrogen configuration. The resulting C-3 proton doublets should have similar  $J$  values (approximately 4 cps) and are seen superimposed at 4.16. The unsaturated diols 4 and 5 are thereby shown to have 2 $\alpha$ , 3 $\alpha$ - and 2 $\beta$ , 3 $\beta$ -configurations, respectively.

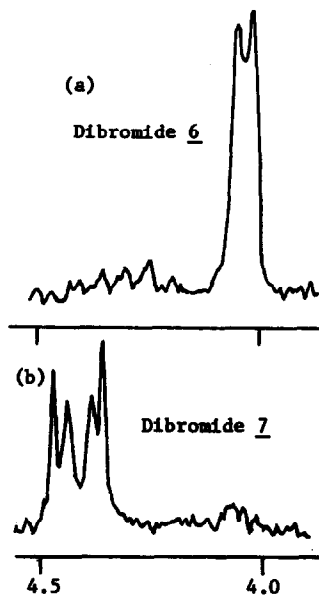


FIG. 1

Partial NMR spectra of dibromides 6 and 7 in  $\text{CDCl}_3$

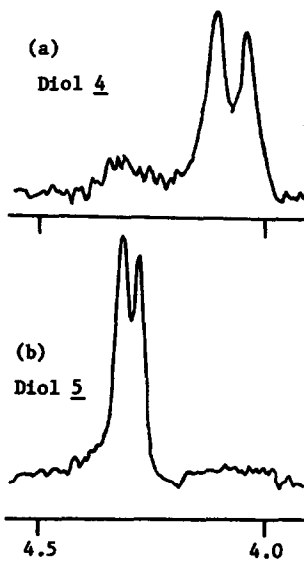


FIG. 2

Partial NMR spectra of diols 4, 5, 4', and 5' in pyridine

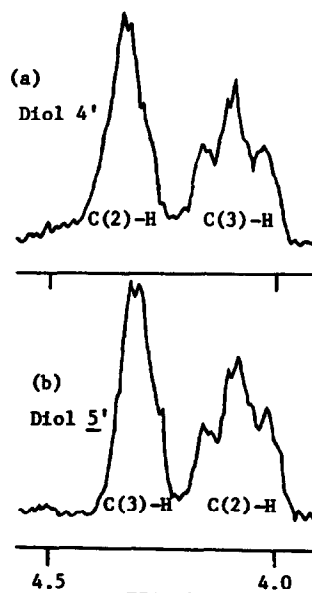


FIG. 3

Partial NMR spectra of diols 4 and 5 appear in Figures 2a and 2b, respectively. The corresponding ring A undeuterated substance 4' and 5' were also prepared and their spectra are shown in Figures 3a and 3b. (Employing pyridine as solvent resulted in maximum separation of absorption bands). Comparison of these sets allows proton assignments to be made for the undeuterated diols as given in Figure 3.

A direct comparison of the spectra of diols 4' and 5' is now pertinent. The overall similarity of the two curves is striking, while the high and low field proton assignments are opposite. It is apparent that the broad, high field (axial) proton at 2 $\alpha$  in diol 5'--and the similarly describable 3 $\beta$ -proton in diol 4'--are nearly identical in their immediate environments. The same can be said, based on these spectra, for the equatorial protons which lie 3 $\alpha$  in diol 5' and 2 $\beta$  in diol 4'. Such a situation follows from the half-chair conformation I and is incompatible with any of the other (3) cyclohexene forms for ring A (9). We consider these spectral observations sufficient only for identification of the predominant form of ring A; the presence of relatively smaller amounts of other ring A forms in conformational equilibrium cannot be excluded (10).

It is significant that similar evidence for the half-chair form I was seen in the NMR spectra of diols 4' and 5' when measured in CCl<sub>3</sub> solution. In this case, intramolecular H-bonding (11) of the vicinal cis-diols might have been expected to favor one or another of the non-half-chair conformers, any of which would have a smaller HO-C-C-OH dihedral angle. Since no such distortion of ring A was in fact detectable, it appears that this H-bonding effect is small energetically in comparison with those factors which favor the half-chair form.

Diols 4' and 5' both form acetonide derivatives under mild (CuSO<sub>4</sub>-acetone) conditions. The product, in each case, exhibits C-2 and C-3 proton resonance in a single composite band (complex, at  $\delta$  - 4.36) reflecting similar environments for the two protons as would be expected for conversion to a boat-like form of ring A. It should be anticipated that ring A conformational equilibrium in  $\Delta^5(10)$ -steroids will also be influenced by other structural modifications of a less forcing sort. Studies along these lines are in progress.

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REFERENCES AND FOOTNOTES

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8. The chemical shift of the 3 $\alpha$ -proton reflects a deshielding effect of approximately 0.6 ppm as expected for its location 1,3-diaxial with respect to a halogen substituent. E.g., see N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry", Holden-Day, Inc., San Francisco, California, 1964, Chapter 8.
9. We concur with the Referee who has pointed out that our data can not exclude conformation III for diol 4' providing that diol 5' also assumes a 1,2-diplanar conformation but one in which C-1, C-3, and C-4 are in the plane of the double bond and C-2 is below that plane. Although we consider such a situation unlikely, we hope that experimental clarification of this point will result from our later work.
10. Attempts to observe shifts in relative conformer populations by obtaining the NMR spectra of diols 4' and 5' at high and low temperature have led only to inconclusive results.
11. The IR spectra of diols 4' and 5' at 0.006M in CCl<sub>4</sub>, both show internal H-bonding:  
 $\nu_{\text{OH, free}}$  3622 cm<sup>-1</sup> (weak);  $\nu_{\text{OH, bonded}}$  3588 cm<sup>-1</sup> (strong).