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# CONFORMATION OF RING A
# IN SOME 2β-HYDROXY- AND 2β-ACETOXY-$\Delta^4$-3-KETOSTEROIDS

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DJERASSI, et al. (1) have pointed out that the optical rotatory dispersion (ORD) curve in substituted-$\Delta^4$-3-ketosteroids reflects conformational distortions in the B-ring rather than in the A-ring. Their conclusion is based on the observation that 17β-acetoxyandrost-4-en-3-one and its 2,2-dimethyl derivative have similar ORD curves, whereas its 6β-methyl derivative shows a completely different curve. On the other hand, Johnson, et al. (2) have found out from their nuclear magnetic resonance (NMR) and ORD studies that the A-ring in 2β-acetoxycholestan-3-one is of a twist conformation, owing to a 1,3-diaxial interaction between the 2β-acetoxyl group and the 19-methyl group. In this paper, we present clear evidence for the distorted conformation of the A-ring in some 2β-hydroxy- and 2β-acetoxy-$\Delta^4$-3-ketosteroids from the ORD and NMR spectroscopies.

The steroids examined are listed in Table I (3). Fig. 1 shows that the ORD curves (4) of 17β-propionyloxyandrost-4-en-3-one (I) and its 2α-acetoxy derivative (IV) are essentially the same, whereas the 2β-acetoxy derivative (V) shows a quite different curve and the same is true for 2β,17β-dihydroxyandrost-4-en-3-one (III), 2β,17α,21-trihydroxypregn-4-ene-3,20-dione (VIII), its acetates (IX, X),

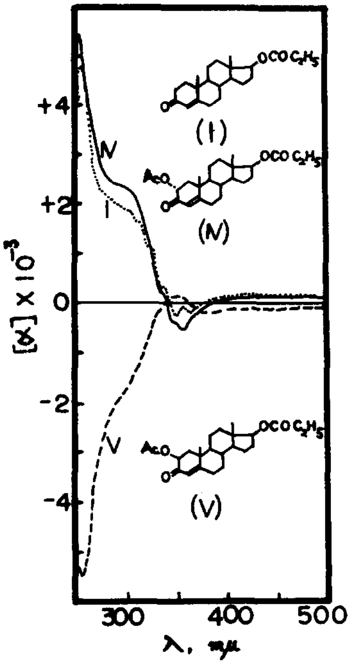

Fig. 1

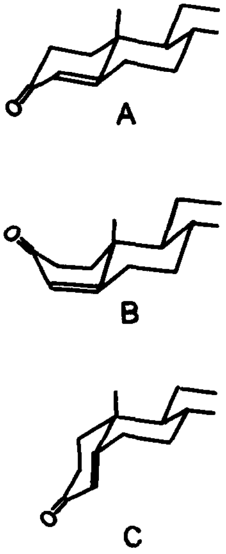

Fig. 2

2β,15β-dihydroxypregn-4-ene-3,20-dione (XI), or its diacetate (XII). In all the ORD curves of the 2β-epimers, the first extremum of the negative K-band Cotton effect is observed at about 260 mμ. Since the parent $\Delta^4$-3-ketones have positive K-band Cotton effects, the $C=C-C=O$ grouping in the 2β-epimers has a chirality opposite to that in the parent ketones and is thought to be twisted in the sense of a left-handed helix (5). This reversal in sign of the K-band Cotton effect implies that the 1,3-diaxial interaction between the 19-methyl group and the 2β-substituent forces the A-ring into the conformation

(B) or (C) shown in Fig. 2.

Further evidence for this consideration is provided by the observation that the ORD curves of the 2β-epimers are practically identical with those of 1β,2β-dihydroxy- and 1β,2β-diacetoxy-25D-spirost-4-en-3-one (XIII, XIV) and the acetonide of XIII because the A-ring in these compounds is believed to be forced into an alternative conformation by mere reason of an interaction between the equatorial 1β-substituent and the 11α-hydrogen atom, as has already been considered for the case of 1β-methyl-19-norpregn-4-ene-3,20-dione (5,6).

In NMR studies of steroids, signal shifts of the angular methyl groups due to a functional group are of great importance (7). In general, this shift value due to a hydroxyl group at a 1,3-diaxial position of the methyl group is -0.16~-0.31 p.p.m., whereas the value due to an acetoxyl group at the corresponding position is -0.04~-0.22 p.p.m. (8,10,11). The values for these groups at other positions fall in the range 0~-0.14 p.p.m. (8,10).

Table I shows NMR data of the steroids examined (12). If the A-ring in III, IX (13) and XI were of the normal conformation (A) shown in Fig. 2, and hence the 2β-hydroxyl group were axial, the 19-methyl signal of these compounds would appear at about 8.6τ (at a down-field by about 0.20 p.p.m. from the position of the 19-methyl signal of their parent steroids). In reality, the signal of the 19-methyl group in III, IX and XI is little shifted by the hydroxyl group, as seen from Table I. These shift values are close to those due to the 2β-acetoxyl group in V, X and XII. These observations suggest that the hydroxyl group in the 2β-epimers is not in a 1,3-diaxial relation to the 19-methyl group.

Table I

NMR Spectral Data in Deuterochloroform

| Compound | Chemical shift (τ) | | | | Coupling constant, J(c.p.s.) | |
|---|---|---|---|---|---|---|
| | 19-H | 18-H | 4-H | 2-H | $J_{2,1\alpha}$ | $J_{2,1\beta}$ |
| 2α,17β-Dihydroxyandrost-4-en-3-one (II)[b] | 8.70<br>(-0.11) | 9.21<br>(0.00) | 4.22<br>(-0.06) | 5.73 | 13.5<br>13.4[a] | 5.7<br>5.5[a] |
| 2β,17β-Dihydroxyandrost-4-en-3-one (III)[b] | 8.80<br>(-0.01) | 9.19<br>(-0.03) | 4.21<br>(-0.07) | 5.82 | 5.6<br>11.3[a] | 13.7<br>5.3[a] |
| 2α-Acetoxy-17β-propionyloxyandrost-4-en-3-one (IV)[b] | 8.66<br>(-0.13) | 9.16<br>(+0.01) | 4.26<br>(-0.02) | 4.55 | 13.7<br>13.6[a] | 5.7<br>5.6[a] |
| 2β-Acetoxy-17β-propionyloxyandrost-4-en-3-one (V)[b] | 8.78<br>(-0.01) | 9.16<br>(+0.01) | 4.22<br>(-0.02) | 4.69 | 12.0<br>11.7[a] | 5.4<br>5.3[a] |
| 2α,17α,21-Trihydroxypregn-4-ene-3,20-dione (VI)[b] | 8.86[a]<br>(-0.02) | 9.24[a]<br>(+0.01) | 4.17[a]<br>(-0.03) | 5.47[a] | 13.5[a] | 5.5[a] |
| 2α,17α,21-Triacetoxypregn-4-ene-3,20-dione (VII)[b] | 8.66<br>(-0.14) | 9.24<br>(0.00) | 4.24<br>(-0.01) | 4.55 | 13.6<br>13.6[a] | 5.8<br>5.6[a] |
| 2β,17α,21-Trihydroxypregn-4-ene-3,20-dione (VIII)[c] | 8.84[a]<br>(-0.04) | 9.22[a]<br>(0.00) | 4.10[a]<br>(-0.10) | 5.57[a] | 11.3[a] | 5.4[a] |
| 2β,17α-Dihydroxy-21-acetoxypregn-4-ene-3,20-dione (IX)[c,g] | 8.81<br>(0.00) | 9.26<br>(-0.03) | 4.21<br>(-0.04) | 5.83 | 5.6 | 13.8 |
| 2β,21-Diacetoxy-17α-hydroxypregn-4-ene-3,20-dione (X)[c] | 8.79<br>(-0.02) | 9.27<br>(-0.02) | 4.23<br>(-0.02) | 4.68 | 12.0<br>11.7[a] | 5.4<br>5.3[a] |
| 2β,15β-Dihydroxypregn-4-ene-3,20-dione (XI)[d] | 8.77 | 9.05 | 4.18 | 5.81 | 5.6<br>10.9[a] | 13.7<br>5.3[a] |
| 2β,15β-Diacetoxypregn-4-ene-3,20-dione (XII)[e] | 8.75 | 9.12 | 4.21 | 4.70 | 11.8 | 5.4 |
| 1β,2β-Dihydroxy-25D-spirost-4-en-3-one (XIII)[f] | 8.66 | 9.16 | 4.16 | 5.67 | 2.7 | |
| 1β,2β-Diacetoxy-25D-spirost-4-en-3-one (XIV)[f] | 8.82 | 9.17 | 4.17 | 4.31 | 2.5 | |

Values in parentheses are shift values due to a hydroxyl or an acetoxyl group on the $C_2$-atom.

a: Observed in pyridine solutions; b: Cf. F. Sondheimer, St. Kaufmann, J. Romo, H. Martinez and G. Rosenkranz, J. Amer. Chem. Soc. **75**, 4712 (1953); c: Cf. E. Kondo, J. Agr. Chem. Soc. Japan **34**, 762 (1960); d: Kindly supplied by Prof. K. Tsuda; e: Derived from XI; f: Kindly supplied by Dr. T. Kubota and Miss F. Hayashi; g: Cf. Ref. 13.

Confirmatory evidence that the A-ring in the 2β-epimers takes the conformation (B) or (C) is given by the signal of the proton on the $C_2$-atom (2,14). Thus, if the ring were of the normal form (A), this proton signal should have a triplet-like pattern, as expected from Dreiding models and the Karplus theoretical correlation (15). Actually, the signal of the 2α-proton in all the 2β-epimers appears as a quartet of a first order pattern due to the couplings of the 2α-proton with the two $C_1$-protons. The coupling constants obtained are listed in Table I. This quartet quite resembles the signal pattern of the 2β-proton in all the 2α-epimers. This fact can not be explained without assuming that the A-ring in the 2β-epimers is of the conformation (B) or (C).

Recently, Abraham and Holker (14) have investigated conformations of the A-rings in some 2-bromo-3-ketosteroids, and have revised the Karplus equation (15) using the coupling constants between the $C_2$- and two $C_1$-protons. Having revised the coefficients of the Karplus equation so as to give the mutually consistent dihedral angles for all the compounds examined in this work, we also have reached the same result as that of Abraham and Holker (14);

$$J_1=12.4 \cos^2 \theta \quad 0^\circ \leq \theta \leq 90^\circ \quad ; \quad J_2=14.3 \cos^2 \theta \quad 90^\circ \leq \theta \leq 180^\circ$$

where $J_1$ and $J_2$ are the coupling constants and $\theta$ is the dihedral angle. Thus, the dihedral angles derived (see Table II) clearly show that the A-rings in the 2β-acetoxy and 2β-hydroxy derivatives are of the conformation (B) and (C), respectively. Probably, the intramolecular hydrogen bonding between the 2β-hydroxyl and the carbonyl group contributes to the conformation (C) (16) because the coupling constants obtained from the spectra of the 2β-hydroxy derivatives in pyridine are close to those in the 2β-acetoxy derivatives, whereas the coupling constants obtained from the spectra of the other derivatives in pyridine are not so different from those in deuterochloroform, as shown in Table I.

More detailed spectral data and discussions will be presented in a full paper in near future.

Table II

| Compound | Dihedral angle | | Coupling constant in $CDCl_3$, J (c.p.s.) | |
|---|---|---|---|---|
| | $\theta_{2,1\alpha}$ | $\theta_{2,1\beta}$ | $J_{2,1\alpha}$ | $J_{2,1\beta}$ |
| 2α-Hydroxy-$\Delta^4$-3-ketosteroids | 167° | 47° | 13.5 | 5.7 |
| 2β-Hydroxy-$\Delta^4$-3-ketosteroids | 48° | 168° | 5.6 | 13.7 |
| 2α-Acetoxy-$\Delta^4$-3-ketosteroids | 168° | 48° | 13.7 | 5.7 |
| 2β-Acetoxy-$\Delta^4$-3-ketosteroids | 8° | 128° | 12.0 | 5.4 |

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3. Analysis of all the compounds described corresponded to the calculated values.
4. The ORD curves were recorded on a Rudolf automatic spectropolarimeter (cell path-length, 1~10 mm; 0.2~0.01% solutions in dioxane).
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7. The additivity rule for signal shifts of the angular methyl groups due to shielding by functional groups has been well established (8). However, this additivity rule is no longer valid, if a ring is forced into some other conformation by introduction of some functional group into the ring (9,10). It has frequently been noted that the shift value for a substituent at a 1,3-diaxial position of the methyl group is large as compared with others (8,10,11).

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12. All the spectra were taken with a Varian A-60 spectrometer on 4~6% (w/v) solutions in deuterochloroform or pyridine containing about 1% tetramethylsilane as an internal reference at room temperature. Accuracy limits are about ±0.02 $\tau$ in chemical shifts and about ±0.3 c.p.s. in coupling constants.

13. The assignment of the 19-methyl signal of this compound (IX) presented in a previous paper (11) is mistaken, probably because of the presence of some impurities in the sample or the solvent used. Accordingly, the shift value for the 2β-hydroxyl group in $\Delta^4$-3-ketones cited therein is incorrect.

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