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FURTHER EVIDENCE FOR DISTORTED CONFORMATION OF RING B IN SOME 6β-SUBSTITUTED Δ^4-3-KETOSTEROIDS[*1]

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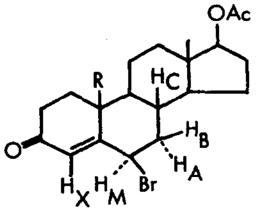
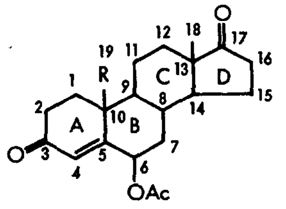
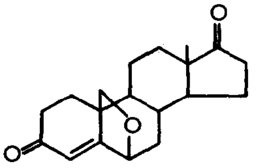
On the basis of a PMR study, we previously reported that the B-ring in several Δ^4-3-ketosteroids having a 6β-substituent bulkier than or equal in size to chlorine is distorted owing to the 1,3-diaxial interaction between the 10-methyl group and the 6β-substituent (1). However, some reservation about this conclusion has been expressed because the $J_{6\alpha,7\alpha}$ and $J_{6\alpha,7\beta}$ values, which led us to the conclusion, were determined by the first-order approximation (2). In order to obtain further evidence for our conclusion, we measured the PMR spectra of 6β-bromotestosterone acetate (I), its 19-nor derivative (II), 6β-acetoxyandrost-4-ene-3,17-dione (III), its 19-nor derivative (IV), and 6β,19-epoxyandrost-4-ene-3,17-dione (V) in both $CDCl_3$ and C_6D_6 at both 60 and 100 Mc.[*2]



(I, $R = CH_3$)
(II, $R = H$)



(III, $R = CH_3$)
(IV, $R = H$)

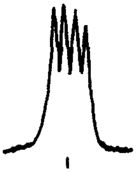


(V)

[*1] NMR Studies on Steroids, Part XII. For Part XI, see K. Tori and E. Kondo, Nippon Kagaku Zasshi **87**, 1117 (1966).

[*2] PMR spectra were taken with a Varian A-60A and an HA-100 spectrometer operating at 100 Mc in the frequency-swept and TMS-locked mode, by using about 5% (w/v) solutions in $CDCl_3$ and C_6D_6 at ordinary probe temperature. The calibration of the spectrometers were carried out by the usual side-band method. Spin-decoupling experiments were carried out by using the HA-100 spectrometer with a Hewlett-Packard HP-200ABR audio-oscillator and an HP-5212A electronic counter.

(I)



$J_{6\alpha,7\alpha}$ = 3.8 cps
$J_{6\alpha,7\beta}$ = 1.8 cps

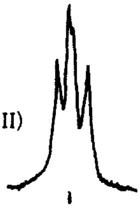
τ 5.01 (in $CDCl_3$)
τ 5.43 (in C_6D_6)

(II)

$J_{6\alpha,7\alpha}$ = 3.2 cps
$J_{6\alpha,7\beta}$ = 2.4 cps

τ 4.98 (in $CDCl_3$)
τ 5.42 (in C_6D_6)

(III)



$J_{6\alpha,7\alpha}$ = 3.0 cps
$J_{6\alpha,7\beta}$ = 2.2 cps

τ 4.57 (in $CDCl_3$)
τ 4.60 (in C_6D_6)

(IV)

$J_{6\alpha,7\alpha}$ = 3.0 cps
$J_{6\alpha,7\beta}$ = 2.2 cps

τ 4.50 (in $CDCl_3$)
τ 4.54 (in C_6D_6)

(V)

$J_{6\alpha,7\beta}$ = 4.8 cps
$J_{6\alpha,7\alpha}$ [*3]

τ 5.27 (in $CDCl_3$)
τ 5.58 (in C_6D_6)

FIG. 1. Signal patterns of $H_{6\alpha}$ in I-V in $CDCl_3$ and C_6D_6 at 100 Mc.

[*3] This value was not determined because of the presence of long-range couplings ($J_{6\alpha,19}$ and $J_{4,6\alpha}$), but may be less than 0.5 cps.

Since the signal of $H_{6\alpha}$ should appear as the M part of a complex ABC---MX--- spin system (see the structure I, for example), it is highly possible that the signal shows a second-order pattern depending on $\Delta\nu_{ij}/J_{ij}$ values, where $\Delta\nu_{ij}$ is the difference in chemical shifts between H_i and H_j in cps (2, 3). To find the signal of $H_{6\alpha}$ as a first-order pattern, the $\Delta\nu_{ij}/J_{ij}$ values should be sufficiently large to satisfy the first-order condition (3) in this spin system. An alteration in the strength of the applied field from 60 to 100 Mc causes a change in $\Delta\nu_{ij}/J_{ij}$ values. Further, an alteration in the solvent from $CDCl_3$ to C_6D_6 is very effective to change $\Delta\nu_{ij}/J_{ij}$ values because the compounds I-V have the α,β-unsaturated ketones, whose interaction with benzene molecules are known to cause great changes in the chemical shifts of the protons in their neighborhood (4). However, while it must be kept in mind that if one or more $\Delta\nu_{ij}$ values were very small and not changed by the solvent effect of benzene, the signal appearing as a second-order pattern could not be changed significantly by altering the applied field and/or the solvent, such possibility is in fact so meager that we can expect to determine the J values from the signal pattern of $H_{6\alpha}$ with accuracies to within ±0.3 cps or less, if the signal pattern remains essentially unchanged in both $CDCl_3$ and C_6D_6 and at both 60 and 100 Mc. However, in some cases, we should try to determine exact values for J's by using spin-decoupling method.

In FIG. 1 are shown the signal patterns of $H_{6\alpha}$ in I-V and the J values obtained; generally these signal patterns are not changed by altering the solvent and the applied field, except the pattern of I in $CDCl_3$ at 60 Mc that showed a slightly different shape, but they are somewhat sharpened by spin decoupling of H_4 which is very weakly coupled to $H_{6\alpha}$ through long-range allylic couplings (5). It is evident from FIG. 1 and well known Karplus' correlation, even though used in a qulitative sense (2), that the B-ring in I is to some extent distorted owing to the 1,3-diaxial interaction between 10-methyl and 6β-bromine as concluded earlier (1). The signal patterns of $H_{6\alpha}$ in II, III, and IV are essentially the same. The exact values for $J_{6\alpha,7\alpha}$ were, however, determined by spin-decoupling experiments; the $H_{6\alpha}$ signals collapse into doublets on double irradiation at the frequencies of $H_{7\beta}$-signal positions, which were found out by spin decouplings of $H_{6\alpha}$. We infer that the B-rings in III and IV adopt almost the same conformations because we could not find any difference in the $J_{6\alpha,7\alpha}$ and $J_{6\alpha,7\beta}$ values between III and IV within the experimental errors, although the exact $J_{6\alpha,7\beta}$ values were not determined. The difference in the effects of electronegativities of the acetoxyl and the bromine upon $J_{6\alpha,7\alpha}$ and $J_{6\alpha,7\beta}$, if exists (6), is thought to be less than

0.3 cps (compare II with IV in FIG. 1). It should be noted that the H_4 signals in II and IV appear as doublets (J = 1.8 cps) split by $H_{10\beta}$ through long-range allylic couplings (5). Furthermore, the B-ring in V was revealed to be distorted by the bridge-formation between C-19 and C-6β (see FIG. 1), as expected from examination of Dreiding models. Similar facts were previously reported on the A-ring in 2β,19-bridged steroids (7) and the C-ring in 8β,11β- and 11β,18-bridged steroids (8).

Confirmatory evidence for the distortion of B-ring due to the 1,3-diaxial interaction between the 10-methyl and a bulky 6β-substituent or due to the bridge-formation between C-19 and C-6β was thus obtained. This fact is very useful in making it possible to disclose the C-6 substituent effect on CD curves of Δ^4-3-ketosteroids as described in the subsequent paper (9). Full account of this research with detailed data on the spectra including those on other similar compounds will be published later.

This paper is dedicated to Dr. Ken'ichi Takeda, Director of this laboratory and Honorary Editorial Adviser of this Journal, in celebration of the 60th anniversary of his birth.

REFERENCES

1. K. Tori and K. Kuriyama, Chem. and Ind. 1525 (1963).
2. N. S. Bhacca and D. H. Williams, Applications of NMR Spectroscopy in Organic Chemistry, Chapt. 6, Holden Day, San Francisco (1964).
3. For example, see (a) R. H. Bible, Jr., Interpretation of NMR Spectra, Pleum Press, New York, N.Y. (1965); (b) J. I. Musher and E. J. Corey, Tetrahedron **18**, 791 (1962).
4. (a) See Chapt. 7 in Ref. 2; (b) C. J. Timmons, Chem. Commun. 576 (1965); (c) Y. Fujise and S. Itô, Chem. Pharm. Bull. (Tokyo) **14**, 797 (1966).
5. For example, see S. Sternhell, Rev. Pure and Appl. Chem. **14**, 15 (1964).
6. K. L. Williamson, J. Amer. Chem. Soc. **85**, 516 (1963).
7. N. S. Bhacca, M. E. Wolff and R. Kwok, J. Amer. Chem. Soc. **84**, 4976 (1962).
8. K. Tori, T. Tomita, H. Itazaki, M. Narisada and W. Nagata, Chem. Pharm. Bull. (Tokyo) **11**, 956 (1963).
9. K. Kuriyama, M. Moriyama, T. Iwata and K. Tori, the subsequent paper.