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# A Nuclear Magnetic Resonance Spectral Study of Some 5α,14β-Androstanes[1)]

Toshio Nambara, Hiroshi Hosoda, and Shujiro Goya

*Pharmaceutical Institute, Tohoku University School of Medicine*[2)]

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In recent years numerous reports have been published dealing with the nuclear magnetic resonance spectral studies on steroids. The signal shift of angular methyl group has been shown to be characteristic for individual steroid due to the shielding effect of neighboring functional groups.[3)] In consequence the contribution of various substituents to the chemical shift of the angluar methyl group was estimated, and their additivity was discussed with respect to the spatial situation.[4–6)] Detailed investigations, however, have not yet been made on 14β-steroids. In this paper the authors wish to report the chemical shifts of the angular methyl groups of 28 kinds of 3β-hydroxy- and 3β-acetoxy-5α,14β-androstane derivatives having substituents in ring D and also discuss the conformation of the two epimeric 16-bromo-17-ketones.

### Experimental

**Samples**——All the samples were prepared according to the procedures described in the previous papers.[7–11)]

**NMR Spectra**——The NMR spectra were measured by Hitachi H-60 and JNM 3H-60 NMR spectrometers operated at 60 Mcps with *ca.* 5% solution of the sample in $CDCl_3$ using TMS as an internal standard. Accuracy of the measurement is within ±0.02 ppm for chemical shifts.

## Results and Discussion

The samples measured in this study are 3β-hydroxy-5α,14β-androstane (No. 1) and its acetate (No. 2) having substituents at C-16 and/or C-17. In Table I are summarized the chemical shifts of 18- and 19-protons of these compounds. The shift value differences of angular methyl protons from those in the parent compounds, which are the net contribution of monosubstituent in ring D, are listed in Table II.

As can be readily anticipated, the chemical shifts of 19-protons are not significantly affected by the introduction of functional group in ring D with only one exception of 16α, 17α-epoxide (No. 19, 20). This upfield shift may be due to the steric strain of epoxy group

1) This paper constitutes Part XII of the series entitled "Analytical Chemical Studies on Steroids"; Part XI: *Chem. Pharm. Bull.* (Tokyo), **15**, 1232 (1967).
2) Location: *Kita-4-bancho, Sendai.*

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Table I. Chemical Shifts of C-18 and C-19 Protons in 5α,14β-Androstane Derivatives

| No. | Compound | Chemical Shift (τ) C-18-H | Chemical Shift (τ) C-19-H |
|---|---|---|---|
| 1 | 5α,14β-Androstan-3β-ol | 9.01 | 9.21 |
| 2 | 5α,14β-Androstan-3β-ol acetate | 9.01 | 9.20 |
| 3 | 5α,14β-Androst-16-en-3β-ol | 8.91 | 9.20 |
| 4 | 5α,14β-Androst-16-en-3β-ol acetate | 8.92 | 9.18 |
| 5 | 5α,14β-Androstane-3β,17β-diol | 8.97 | 9.20 |
| 6 | 5α,14β-Androstane-3β,17β-diol diacetate | 9.05 | 9.18 |
| 7 | 5α,14β-Androstane-3β,17α-diol | 8.99 | 9.20 |
| 8 | 5α,14β-Androstane-3β,17α-diol diacetate | 9.01 | 9.19 |
| 9 | 5α,14β-Androstane-3β,16β-diol | 8.97 | 9.20 |
| 10 | 5α,14β-Androstane-3β,16β-diol diacetate | 9.05 | 9.20 |
| 11 | 5α,14β-Androstane-3β,16α-diol | 9.02 | 9.22 |
| 12 | 5α,14β-Androstane-3β,16α-diol diacetate | 9.01 | 9.20 |
| 13 | 3β-Hydroxy-5α,14β-androstan-17-one | 8.91 | 9.21 |
| 14 | 3β-Hydroxy-5α,14β-androstan-17-one acetate | 8.92 | 9.18 |
| 15 | 3β-Hydroxy-5α,14β-androstan-16-one | 8.82 | 9.18 |
| 16 | 3β-Hydroxy-5α,14β-androstan-16-one acetate | 8.82 | 9.16 |
| 17 | 5α,14β-Androst-16-ene-3β,17-diol diacetate | 8.94 | 9.19 |
| 18 | 16β,17β-Epoxy-5α,14β-androstan-3β-ol acetate | 8.78 | 9.21 |
| 19 | 16α,17α-Epoxy-5α,14β-androstan-3β-ol | 8.86 | 9.27 |
| 20 | 16α,17α-Epoxy-5α,14β-androstan-3β-ol aceate | 8.87 | 9.24 |
| 21 | 16β-Bromo-3β-hydroxy-5α,14β-androstane-3β,17α-diol | 8.93 | 9.22 |
| 22 | 16β-Bromo-3β-hydroxy-5α,14β-androstan-17-one acetate | 8.75 | 9.18 |
| 23 | 16α-Bromo-3β-hydroxy-5α,14β-androstan-17-one acetate | 8.85 | 9.18 |
| 24 | 3β,16β-Dihydroxy-5α,14β-androstan-17-one diacetate | 8.86 | 9.18 |
| 25 | 3β,16α-Dihydroxy-5α,14β-androstan-17-one diacetate | 8.86 | 9.18 |
| 26 | 3β,17α-Dihydroxy-5α,14β-androstan-16-one diacetate | 8.82 | 9.16 |
| 27 | 17,17-Ethylenedithio-5α,14β-androstan-3β-ol | 8.88 | 9.20 |
| 28 | 17,17-Ethylenedithio-5α,14β-androstan-3β-ol acetate | 8.89 | 9.19 |

Table II. Effects of Substituents on the Chemical Shifts of C-18 and C-19 Protons

| Substituent | Shift Value[a] (ppm) C-18-H 13β,14β | C-18-H 13β,14α | C-19-H 13β,14β | C-19-H 13β,14α |
|---|---|---|---|---|
| $\Delta^{16}$ | −0.10 | −0.04 | −0.02 | −0.01 |
| 16-Oxo | −0.19 | −0.18 | −0.03 | −0.03 |
| 16β-OH | −0.04 | — | −0.01 | — |
| 16α-OH | +0.01 | — | +0.01 | — |
| 16β-OAc | +0.04 | — | 0 | — |
| 16α-OAc | 0 | — | 0 | — |
| 17-Oxo | −0.10 | −0.17[b] | −0.01 | −0.02[b] |
| 17β-OH | −0.04 | −0.03[b] | −0.01 | 0[b] |
| 17α-OH | −0.02 | — | −0.01 | — |
| 17β-OAc | +0.04 | −0.08[b] | −0.02 | 0[b] |
| 17α-OAc | 0 | — | −0.01 | — |
| 16β,17β-Oxido | −0.23 | −0.12 | +0.01 | 0 |
| 16α,17α-Oxido | −0.15 | −0.03 (−0.42[b]) | +0.05 | 0 (−0.01[b]) |
| 17=$(SCH_2-)_2$ | −0.13 | — | 0 | 0 |

a) Plus sign represents an upfield shift b) Zürcher's value[4] and concave nature of C/D–ring fusion. It is of particular interest that in the 14β–series an acetoxyl group at 16β or 17β (No. 10, 6) exhibits a shielding effect on 18–proton rather than a deshielding effect. Part of this property is presumably due to the steric requirement that 18–methyl group is to be located in the region of the shielding anisotropy of C–O bond. In addition it must be noted that both the epimeric 16,17–epoxy groups produce a downfield shift of 18–proton to a greater extent that those in the 14α–series, and shift the 19–proton somewhat upfield.

Then the signal shift differences were tested on 14β–steroids having two substituents in ring D. As can be seen in Table III, the additivity is not necessarily observed. It has already been reported[12] that the additivity rule of frequency shifts does not hold on the C–18–methyl group of the steroids polysubstituted on ring D owing to the structural and conformational change. The present observation also indicates that the application of this principle to 18–proton resonance of 16,17–disubstituted 14β–steroids should be exercised with the great caution.

Table III. Effects of Substituents on the Chemical Shifts of C–18 and C–19 Protons

| Substituent | Shift Value[a] (ppm) | |
|---|---|---|
| | C–18–H | C–19–H |
| $\Delta^{16}$–17–OAc | −0.07 | −0.01 |
| 16α–Br–17–Oxo | −0.16 | −0.02 |
| 16β–Br–17–Oxo | −0.26 | −0.02 |
| 16β–Br–17α–OH | −0.08 | +0.01 |
| 16α–OAc–17–Oxo | −0.15 | −0.02 |
| 16β–OAc–17–Oxo | −0.15 | −0.02 |
| 16–Oxo–17α–OAc | −0.19 | −0.04 |

a) Plus sign represents an upfield shift.

Examinations were then made on the 16–proton signals for the two epimeric 16–bromo–17–ketones with respect to conformation of cyclopentanone ring. As is seen in Fig. 1, 16–proton signals of a pair of epimers appear as the X portion of an ABX system at 5.58τ ($J$=1.8,

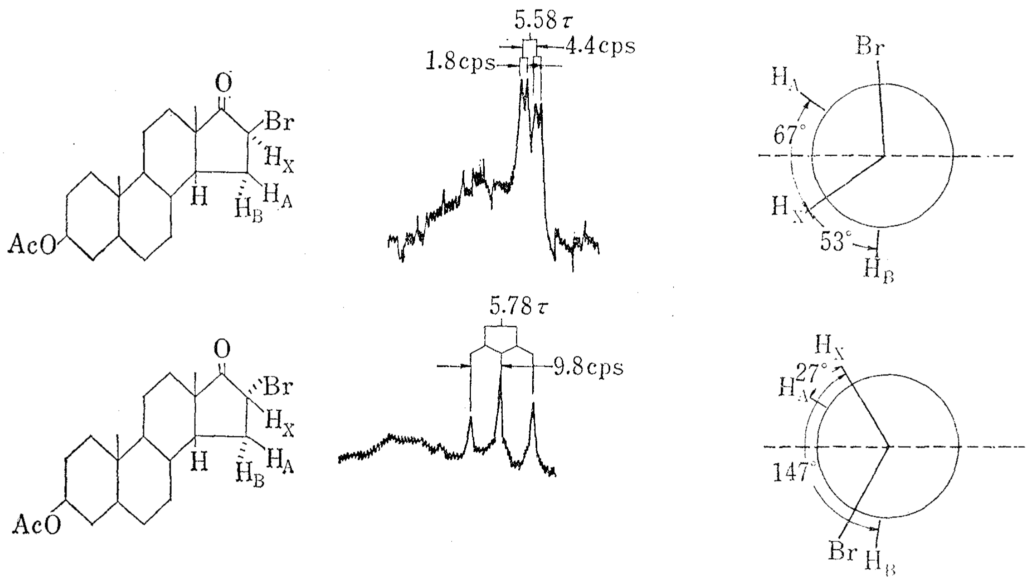


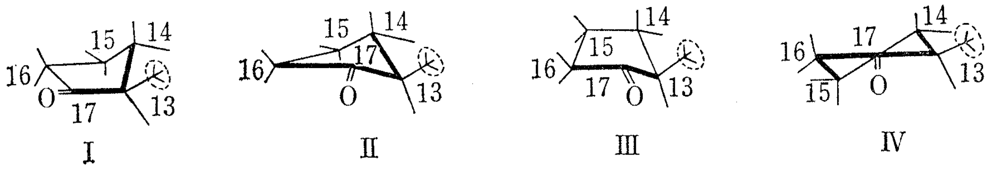

Fig. 1. NMR Spectra and Dihedral Angles of 16–Protons

12) A.D. Cross and C. Beard, *J. Am. Chem. Soc.*, **86**, 5317 (1964).

4.4 cps) and 5.78 $\tau$ ($J$=9.8 cps), respectively. Recently, Brutcher and Bauer[13] discussed the conformation of the substituted cyclopentane in fused ring system through the vector analytical techniques. The torsional angles thereby employed being applied to the 14$\beta$-steroids, the H16, 15 dihedral angles ($\phi_{AX}$ and $\phi_{BX}$) can be estimated for each of the four possible conformations, I, II, III and IV.[14] In Table IV the coupling constants calculated by Abraham's equation[15] are listed and are compared with the experimental results mentioned above. It is evident that in the case of 16$\beta$-bromo compound (No. 22) the observed values are in good accordance with those for I and IV. On the other hand in the case of its epimer (No. 23) the data available exclude conformation III, but do not permit the definite choice among the remaining I, II and IV. The conformation of these $\alpha$-haloketones has already been investigated by means of infrared, ultraviolet and optical rotatory dispersion spectroscopic methods, and in consequence it was concluded that the 16$\beta$-bond would be quasi-axial, while the 16$\alpha$-epimer quasi-equatorial.[7] This finding is obviously inconsistent with conformation II for 16$\alpha$-bromo compound. Conformation I and IV appear to fulfill the requirement for nuclear magnetic resonance spectra as well as optical properties.

TABLE IV. Coupling Constants derived from the Abraham's Equation

| | | $\phi_{AX}$[a] | $\phi_{BX}$[a] | $J_{AX}$[b] | $J_{BX}$[b] | $J_{AX}+J_{BX}$[b] |
|---|---|---|---|---|---|---|
| 16$\beta$-Bromo-17-ketone | | | | | | |
| Conformation | I | 83.5 | 36.5 | 0.2 | 8.0 | 8.2 |
| | II | 101 | 19 | 0.5 | 11.1 | 11.6 |
| | III | 120 | 0 | 3.6 | 12.4 | 16.0 |
| | IV | 70 | 50 | 1.5 | 5.1 | 6.6 |
| Observed | | 67 | 53 | 1.8 | 4.4 | 6.2 |
| 16$\alpha$-Bromo-17-ketone | | | | | | |
| Conformation | I | 36.5 | 156.5 | 8.0 | 12.0 | 20.0 |
| | II | 19 | 139 | 11.1 | 8.2 | 19.3 |
| | III | 0 | 120 | 12.4 | 3.6 | 16.0 |
| | IV | 50 | 170 | 5.1 | 13.9 | 19.0 |
| Observed | | 27 | 147 | 9.8 | 9.8 | 19.6 |




a) In degrees. b) In cycles per second.
Abraham, *et al.* (1963)[15]
$J=12.4\cos^2\phi$ $(0° \leq \phi \leq 90°)$ $J=14.3\cos^2\phi$ $(90° \leq \phi \leq 180°)$

It must, however, be emphasized that the present data apply with certainty only to ring D of 16-bromo-17-ketone, and the conformation of ring D is very likely quite different when C-17 is tetrahedral. It is hoped that further work will provide the data necessary for a definition of the conformation of ring D of 14$\beta$-steroid.

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13) F.V. Brutcher, Jr. and W. Bauer, Jr., *J. Am. Chem. Soc.*, **84**, 2233, 2236 (1962).
14) Conformation I, II and III are common to the five-membered D-ring and are designated as $\beta$-envelope, half-chair and $\alpha$-envelope, respectively. Inspection of Dreiding model shows that another half-chair conformation, that is IV where 17-C=O bond is an axis of rotation, would be possible.
15) R.J. Abraham and J.S. E. Holker, *J. Chem. Soc.*, **1963**, 806.