Fig. 1 stellt die Infrarot Spektren von II, III und IV dar. Die dem Pyridazinring zu verdankenden Absorptionsbanden im Infrarot Spektrum des II sind den Spektren von 3-Substituierten-4-amino-6-chlorpyridazinen sehr ähnlich und dagegen unterscheidet sich das Spektrum des III beträchtlich von den letzteren. Daraus kann man mit grosser Wahrscheinlichkeit schliessen, daß II und III die vorerwähnten Strukturen besitzen.

Nächst ließ sich 3-Methoxy-5*H*-benz[*b*]pyridazino[4,3-*e*] [1,4]thiazin (Schmp. >290°, $C_{11}H_9N_3OS$—Ber. : C, 57.14; H, 3.92; N, 18.18. Gef. : C, 57.47; H, 3.61; N, 18.22) dadurch erhalten, daß man Natriummethylat auf II unter Druck einwirken ließ. Auch 3-Dimethylamino-5*H*-benz[*b*]pyridazino[4,3-*e*][1,4]thiazin (Schmp. 275°, $C_{12}H_{12}N_4S$—Ber. : C, 59.01; H, 4.95; N, 22.94. Gef. : C, 59.24; H, 4.92; N, 22.93) wurde aus II und methanolischem Dimethylamin hergestellt. Es war aber nicht gelungen, 5*H*-Benz[*b*]pyridazino[4,3-*e*][1,4]-thiazin zu gewinnen, während wir die Dechlorierung vermittels katalytischer Hydrierung unter verschiedenen Bedingungen versuchten.

Analogerweise wie bei II lieferte III durch Methoxylieren 3-Methoxy-10*H*-benz[*b*]-pyridazino[3,4-*e*][1,4]thiazin (Schmp. 235°, $C_{11}H_9N_3OS$—Ber. : C, 57.14; H, 3.92; N, 18.18. Gef. : C, 57.37; H, 3.58; N, 18.20) und ferner bei der katalytischen Hydrierung mit Palladium-Kohle ergab IV 10*H*-Benz[*b*]pyridazino[3,4-*e*] [1,4]thiazin (Schmp. 263°, $C_{10}H_7N_3S$—Ber. : C, 59.70; H, 3.51; N, 20.89. Gef. : C, 60.03; H, 3.71; N, 21.01).

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Nuclear Magnetic Resonance Spectroscopic Evidence for Distorted Conformations of the C-Rings in 8β,11β- and 11β,13β-Bridged Steroids[*1]

Nuclear magnetic resonance (NMR) studies on conformations of the A-rings in some steroids have been made by several workers, who examined signal peaks of the protons attached to substituent-bearing carbon atoms.[1~3] Recently Nagata, *et al.* have succeeded in synthesizing 8β,11β-[4] and 11β,13β-[5]bridged steroids, the C-rings of which can be expected to be distorted owing to formation of the oxabicyclo[3,2,1]octane ring system. In this communication, NMR spectroscopic evidence for the distorted conformations of the C-rings is described.

Table I lists NMR data for C_{11}-, C_{18}- and C_{19}-protons of the steroids examined, and Fig. 1 shows examples of signal peaks of equatorial protons attached to oxygen-bearing

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[*1] NMR studies on steroids. Part 1.

1) K.L. Williamson, W.S. Johnson : J. Am. Chem. Soc., **83**, 4623 (1961).

2) B.B. Dewhurst, J.S.E. Holker, A. Lablache-Combier, J. Levisalles : Chem. & Ind. (London), **1961**, 1667.

3) R.J. Abraham, J.S.E. Holker : J. Chem. Soc., **1963**, 806.

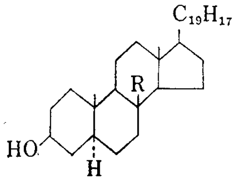
4) W. Nagata, T. Tomita, H. Itazaki : to be published (presented in part at 2nd International Symposium on the Chemistry of Natural Product, Prague, August, 1962).

5) W. Nagata, M. Narisada, T. Sugasawa : Tetrahedron Letters, **1963**, in press.

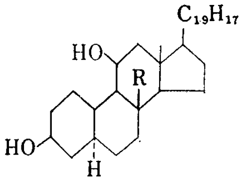
Table I. Nuclear Magnetic Resonance Data

Compound[a]		Chemical shift (τ)[b] C_{19}-H	C_{18}-H	C_{11}-H	Coupling constant (c.p.s.) $J_{11,12}$ or $J_{9,11}$
5α-Ergost-22-en-3β-ol	(I)	9.19	9.33	—	—
8β-Methyl-5α-ergost-22-en-3β-ol	(II)	9.13 (−0.06)	9.23 (−0.10)	—	—
5α-Ergost-22-ene-3β,11β-diol	(III)	8.95 (−0.24)	9.10 (−0.23)	5.73 q	2.5
8β-Methyl-5α-ergost-22-ene-3β,11β-diol	(IV)	8.82 (−0.37)	8.95 (−0.38)	5.54 q	2.5
8β-Aminomethyl-5α-ergost-22-ene-3β,11β-diol	(V)	8.87 (−0.32)	8.97 (−0.36)	5.83 q	2.6
8,11-Methanoepoxy-5α-ergost-22-en-3β-ol	(VI)	8.93 (−0.26)	9.05 (−0.28)	5.69 d	4.6 1.1
11,8-Epoxy(methoxymethano)-5α-ergost-22-en-3β-ol	(VII)	8.95 (−0.24)	9.03 (−0.30)	5.60 d	4.5 1.1
3β,11β-Dihydroxy-5α-ergost-22-ene-8-carboxylic acid 8,11-lactone	(VIII)	9.08 (−0.11)	9.20 (−0.13)	5.36 d	4.5 0.9
3β,11β-Dihydroxy-5α-ergost-22-ene-8-carboimidic acid 8,11-lactone	(IX)	9.07 (−0.12)	9.15 (−0.18)	5.46 d	4.5 1.0
N-Acetyl-3β-acetoxy-11β-hydroxy-5α-ergost-22-ene-8-carboimidic acid 8,11-lactone	(X)	9.02 (−0.17)	9.11 (−0.22)	5.38 d	4.5 1.1
11,8-Epoxy(acetamidomethano)-5α-ergost-22-en-3β-ol	(XI)	8.92 (−0.27)	9.12 (−0.21)	5.78 d	4.3 1.1
18-Dehydroaldosterone 21-acetate	(XII)	8.71	—	5.13 d	6.2 ~0.5
3,3-Ethylenedioxy-11β,17α-dihydroxy-D-homoandrost-5-en-18-oic acid 11,18-lactone	(XIII)	8.88	—	5.20 d	6.3 ~0.5
3,3-Ethylenedioxy-18ξ-acetamido-11β,18-epoxy-D-homoandrost-5-en-17α-ol	(XIV)	8.90	—	5.58 d	6.2 ~0.5

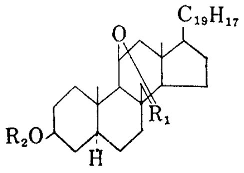
a) The structure of the compound is as follows.



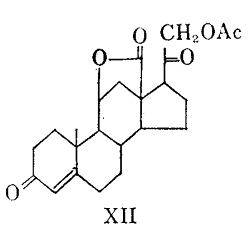
I : R=H
II : R =CH_3



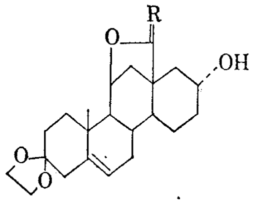
III : R=H
IV : R=CH_3
V : R=CH_2NH_2



VI : $R_1=H_2$, $R_2=H$
VII : $R_1={<}^{H}_{OCH_3}$, $R_2=H$
VIII : $R_1=O$, $R_2=H$
IX : $R_1=NH$, $R_2=H$
X : $R_1=NAc$, $R_2=Ac$
XI : $R_1={<}^{H}_{NHAc}$, $R_2=H$



XII



XIII : R=O
XIV : $R={<}^{H}_{NHAc}$

b) Values in parentheses indicate differences in chemical shifts between I and the corresponding compound (in p.p.m.).
q Quartet
d Slightly tripling doublet

C_{11}-atoms (at 5.2～5.8 τ) together with dihedral angles and coupling constants.[*2] In the spectra of the non-bridged compounds (Ⅲ～Ⅴ), the signal peak always appears as a quartet (J=2.5 c.p.s.) arising from spin-spin coupling between the 11α-proton and the three protons attached to the adjacent carbon atoms (9α-, 12α- and 12β-protons), because the C-ring in these compounds is in the normal chair form in which the dihedral angle between the 11α-proton and each of the three adjacent protons is 60°. This observed coupling constant agrees well with the calculated value corrresponding to the dihedral angle of 60°, when a revised Karplus equation1) was applied.[*3] The signal peak of the 11α-proton in the bridged compounds (Ⅵ～ⅩⅣ), in contrast to the case of the non-bridged ones, appears as a slightly tripling doublet, as shown in Fig. 1 [(B) and (C)]. This fact implies that the dihedral angles between the 11α-proton and each of the three adjacent protons are altered from the normal angle, 60°, because of a distorted chair conformation of the C-ring in the bridged steroids. Recently it has been shown that the coupling constant varies with electronegativities of substituents besides the dihedral angle.9) However, in the present case the difference in the electronegativity between -OH and -O-C$\lessdot$ groups is believed to be small.9) As shown in Fig. 1, the observed coupling constants are in good agreement with the values corresponding to the dihedral angles measured on Dreiding models.[*4] Furthermore, comparison of the coupling constants suggests that the C-ring in 11β,13β-bridged steroids is in a more distorted chair form than that in 8β,11β-bridged steroids. This is supported by examination of Dreiding models. Thus, the distortion of the C-ring in the bridged steroids is confirmed by examination of signal pattern of the C_{11}-proton.

Recent studies on the signal peak of the angular methyl groups in steroids have shown that the signal peak is remarkably shifted to the down-field by introduction of substituents into the 1,3-diaxial positions to the methyl group.10)

[*2] All the spectra were taken with a Varian A-60 analytical NMR spectrometer system on 5～6% (w/v) solutions of the samples in deuterochloroform containing 1% tetramethylsilane as an internal reference. The calibration of the spectrometer was checked by using the signal peaks of pure p-anisaldehyde in 4.0% (w/v) solution in carbon tetrachloride.6) Chemical shifts are expressed in τ-units and coupling constants are in c.p.s. Accuracy limits are about $\pm 0.02\tau$ for the chemical shifts and about ± 0.2 c.p.s. for the coupling constants.

[*3] In the theoretically derived Karplus equation (A),

$$\left.\begin{array}{ll} J=k_1\cos^2\Theta-c; & 0°\leqslant\Theta\leqslant 90° \\ J=k_2\cos^2\Theta-c; & 90°\leqslant\Theta\leqslant 180° \end{array}\right\} \qquad \text{A}$$

J : coupling constant
k_1, k_2, c : constants
Θ : dihedral angle

where $k_1=8.5$, $k_2=9.5$ and $c=0.28$ c.p.s.,7) the values for the coefficients should be replaced by other values which vary with the nature of substituents on the $\rangle$CH-CH$\langle$ fragment.1,3,8,9) For a k_1 value, 10,1) 10.5,8) or 12.43) c.p.s. has been proposed from the experimental results ($c=0$). We have used the equation (B) of Williamson and Johnson,1) because we believe the equation obtained for the -CO·CH(OAc)·CH$_2$·C$\leqslant$ fragment is most suitable for the present cases.

$$J=10\cos^2\Theta;\ 0°\leqslant\Theta\leqslant 90° \qquad \text{B}$$

[*4] In Fig. 1, dihedral angles between the 11α-proton and two C_{12}-protons are shown. The angle between the 11α- and the 12α-proton in each case is almost equal to that between the 11α- and the 9α-proton.

6) G.V.D. Tiers, D.R. Hotchkiss : J. Phys. Chem., **66**, 560 (1962).

7) M. Karplus : J. Chem., Phys. **30**, 11 (1959).

8) R.J. Abraham, K.A. McLauchlan : Mol. Phys., **5**, 513 (1962).

9) For example, see K.L. Williamson : J. Am. Chem. Soc., **85**, 516 (1963).

10) G. Slomp, Jr., B.G. McGarvey : J. Am. Chem. Soc., **81**, 2200 (1959); R.F. Zürcher : Helv. Chim. Acta, **44**, 1380 (1961); J.C. Jacquesy, J.M. Lehn, J. Levisalles : Bull. soc. chim. France, **1961**, 2444; Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T. Okamoto, K. Tsuda : This Bulletin, **10**, 338 (1962).

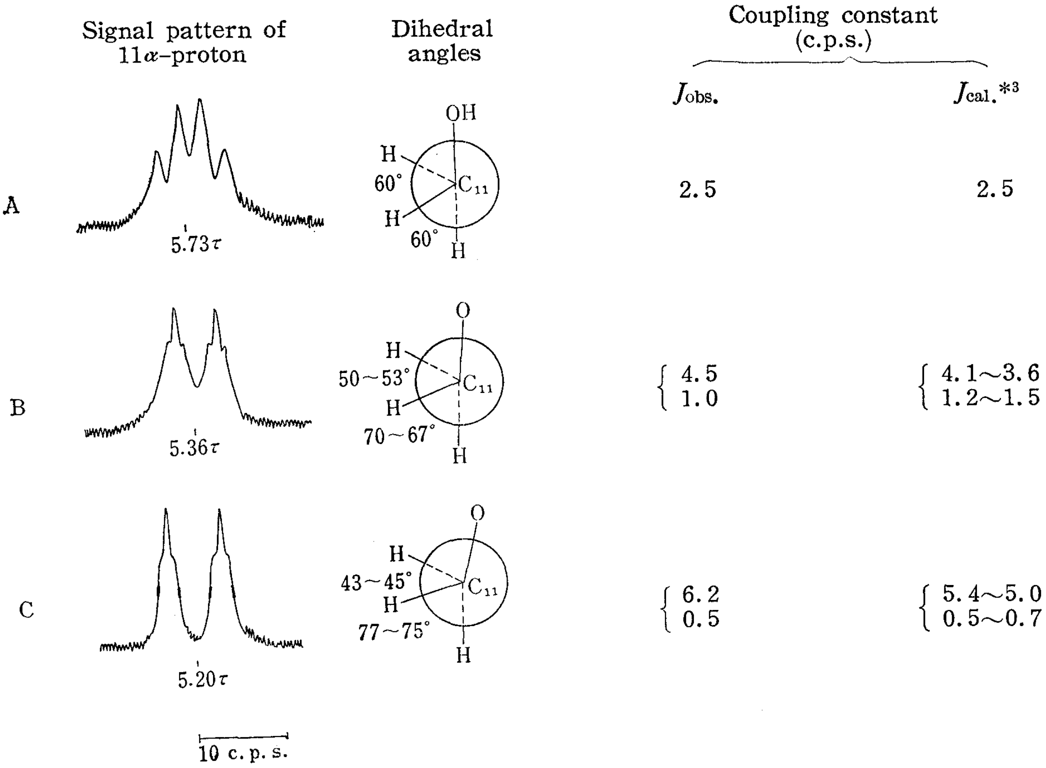


Fig. 1. Signal patterns of 11α-protons of III, VIII, and XIII [(A), (B) and (C), respectively]

As shown in Table I (IV and V), introduction of 8β-methyl and 11β-hydroxyl groups to I markedly shifts the angular methyl signal to the down-field. However, formation of the bridge, in general, leads to a rather small shift (VI~XI); the shift values in VI, VII and XI are relatively small in comparison with that in IV and are close to that in III; the shift values in VIII, IX and X are still smaller. In the latter case, the angular methyl signals may be shifted to the high-field by the effect of magnetic anisotropy of the keto and the imino group[11] in the bridge and this effect results in the smaller shift of the methyl signals.

These rather small shifts of the angular methyl signals and the appearance of the slightly tripling doublet pattern as a 11α-proton signal are characteristic of the bridged structure. Therefore, the bridge formation can be easily checked by examination of the signal patterns in the nuclear magnetic resonance spectra.

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April 30, 1963

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[11] L. M. Jackman: "Applications of Nuclear Magnetic Resonance Spectroscopy in organic Chemistry.", p. 124, Pergamon Press, New York (1959).