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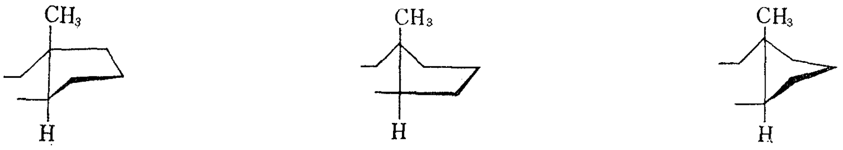
Proton Magnetic Resonance Study of Some 17-Substituted Steroids

Both 17α- and 17β-chlorosteroids have been already prepared and the configuration of the chlorine atom has also been established.[1~3] It may be expected that 17-proton of the steroid, in which halogen, hydroxy group or other substituent is combined at C-17, is analysed as ABX type pattern in proton magnetic resonance, and application of the Karplus equation to the coupling constant is used as an effective mean not only for the elucidation of the configuration at C-17 but also for some informations on the conformation of ring D of the steroid. The consideration concerning the conformation of ring D from the coupling constant of 17-proton in 17-chloro- and 17-hydroxysteroips will be described in this communication.

Recently, Brutcher and Bauer[4] have described that three possible conformations, *viz.* envelope conformations (I) and (II), and half-chair conformation (III) (Chart 1) can be considered to ring D of a steroid, and some discussions have been made from the calculation of bond-bending and torsional energies as well as interaction energies for 1,3-substituents. When the above-mentioned problem is studied by the simple application of the Karplus equation to the coupling constant of a proton at C-17 of 17-substituted steroids, the following two facts must be considered beforehand. 1) It is well-known that the vicinal coupling constant becomes smaller in proportion to the increase of electronegativity of a substituent.[5~8] Even when an electronegative group such as



I II III

Chart 1.

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1) U. Westphal : Ber., **72**, 1233 (1939).
2) W.F. Johns : J. Org. Chem., **26**, 4583 (1961).
3) H. Mori, S. Wada : This Bulletin, **11**, 1409 (1963); H. Mori, K. Tsuneda : *Ibid*., **11**, 1413 (1963).
4) F.V. Brutcher, W. Bauer : J. Am. Chem. Soc., **84**, 2236 (1962).
5) C.N. Bannwell, N. Sheppard, J.J. Turner : Spectrochim. Acta, **16**, 794 (1960).
6) W. Brügel, T. Ankel, F. Krückeberg : Z. Elektrochem., **64**, 1121 (1960).
7) K.L. Williamson : J. Am. Chem. Soc., **85**, 516 (1963).
8) P. Laszlo, P.R. Schleyer : *Ibid*., **85**, 2709 (1963).

halogen atom is introduced at C-17, the coupling constant is a suitable indicator of the conformation or not? 2) Whether Karplus relationship can be apllied to cyclopentane ring or not?

The first problem was solved as follows. It is described that 17α-proton resonance in 17β-hydroxy- and 17β-acetoxysteroids are observed as triplet and the patterns are almost identical.[9] Moreover, the coupling constants of 17-chlorosteroids were found to be almost the same as those of the corresponding 17-hydroxysteroids (See below). Accordingly, the error caused by the difference of electronegativity can be considered not to be serious.[*1]

In general, coupling constant depends upon the strain of a ring: when a ring is strongly strained, the smaller coupling constant is generally observed.[10~12] It has been reported by Chapman[10] that the most close agreement of J_{HH} value of cyclic *cis* olefine calculated from the Karplus equation with the observed value is obtained in cyclopentane series. Recently, Cross and Crabbé[13] have used the Karplus equation to 16-substituted pregnane compounds and determined their configurations. Although an absolute proof cannot be given to the problem, it seems to be possible to use the Karplus equation in our case.

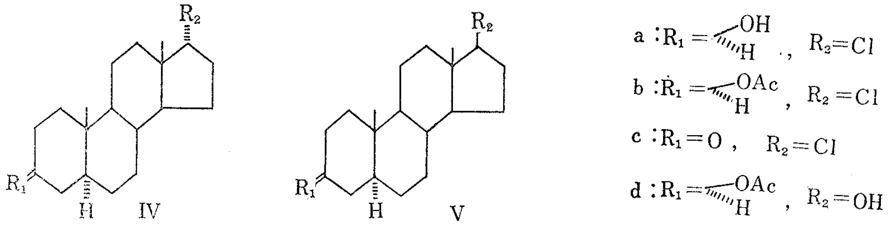

Chart 2.

Proton magnetic resonances of eight compounds shown in Chart 2 were measured and the results are shown in Table I. From Table I. it is readily apparent that, 17-proton signal of 17α-substituted steroids is always doublet, while that of 17β-substituted steroids is triplet. The coupling constants between 16-proton and 17-protons, which

TABLE I.

Compounds	17-Proton[a]		Compounds	17-Proton[a]	
	δ (p.p.m.)	J (c.p.s.)		δ (p.p.m.)	J (c.p.s.)
IVa	4.0	doublet, 6.1	IVc	4.01	doublet, 5.7
Va	3.65	triplet, 9.0	Vc	3.62	triplet, 8.1
IVb	3.98	doublet, 5.3	IVd	3.65	doublet, 5.8
Vb	3.65	triplet, 9.0	Vd	3.57	triplet, 7.6

[a] Hitachi H-60 NMR spectrometer (60 Mc.) was used and TMS was used as an internal standard. Chemical shifts are quoted as p.p.m. downfield from the TMS reference (0.0 p.p.m.). Samples were dissolved in deuteriochloroform at 0.5 mole.

[*1] Laszlo, *et al.* (see reference 8) showed that the relationship between the coupling constants and the electronegativities of the vicinal substituent is linear. Accordingly, the factor of electronegativity must be considered in the strict sense, when dihedral angle (Φ) is calculated from the Karplus equation. The error caused by this factor, however, can be considered to be within an experimental error.

9) N.S. Bhacca, D.H. Williams: "Applications of NMR Spectroscopy in Organic Chemistry, Illustration from the Steroid" p. 77 (1964), Holden-Day, Inc. (San Francisco).

10) O.L. Chapman: J. Am. Chem. Soc., **85**, 2014 (1963).

11) G.V. Smith, H. Kriloff: *Ibid.*, **85**, 2016 (1963).

12) P. Laszlo, P.R. Schleyer: *Ibid.*, **85**, 2017 (1963).

13) A.D. Cross, P. Crabbé: *Ibid.*, **86**, 1221 (1964).

were calculated from the Karplus equation[14] by use of dihedral angles (Φ) between two adjacent protons (16 and 17) of three possible conformations described above,[*2] are shown in Table II and III.

TABLE II. 17α-Substituted Steroids

envelope I		envelope II		half-chair III	
$J_{17\beta,16\beta}$	$J_{17\beta,16\alpha}$	$J_{17\beta,16\beta}$	$J_{17\beta,16\alpha}$	$J_{17\beta,16\beta}$	$J_{17\beta,16\alpha}$
8.1	3.2	6.2	ca. 0.1	7.7	0.7

TABLE III. 17β-Substituted Steroids

envelope I		envelope II		half-chair III	
$J_{17\alpha,16\beta}$	$J_{17\alpha,16\alpha}$	$J_{17\alpha,16\beta}$	$J_{17\alpha,16\alpha}$	$J_{17\alpha,16\beta}$	$J_{17\alpha,16\alpha}$
1.1	8.0	6.6	6.6	4.5	7.9

The conformations of 17α-substituted steroids, which can be expected to show a doublet signal for 17-proton, are envelope II and half-chair III. Although the calculated value for envelope II agrees well with the observed one, 1,3-interaction between 17α-substituent and 14α-hydrogen should be considered as an unstablizing factor for the envelope conformation (II). Therefore, half-chair conformation (III) is probably the most suitable conformation for 17α-substituted steroids. Concerning 17β-substituted steroids, the triplet signal cannot be explained without assuming the ring D is of the envelope conformaition (II).

These observations suggest that the configuration of other substituent than chlorine or hydroxy group, such as -OMe, -COR and -SH, will be determined by proton magnetic resonance technic.

Signal of 17β-proton is always in down field than that of 17α-proton. The same relationship is observed in 16-substituted pregnane series, and Cross and Crabbé stated that this shift is caused by anisotropy effect due to the largely undisturbed orientation. In the case of 17-substituted steroids, however, it is more reasonable that the shift depends upon σ-bond anisotropy as considered in cyclohexane derivatives.

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

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[*2] Dihedral angles were measured by Dreiding model (A. S. Dreiding : Helv. Chim. Acta, **42**, 1339 (1959)), and the errors were within 5°. The mean value of angles was used for the Karplus calculation. Coupling constants, J, were expressed in c.p.s. units.

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