182° (eff.), $[\alpha]_D^{25}$ +33° (*Anal.* Calcd. for $C_{10}H_{15}O_6N_3$: C, 43.96; H, 5.49; N, 15.38. Found : C, 44.17; H, 5.84; N, 15.19). Tetra-acetylation of V, followed by thiation with phosphorus pentasulfide and then ammonolysis yielded the cytosine analog (VI), m.p. 260.5~261° (eff.), $[\alpha]_D^{25}$ +36° (*Anal.* Calcd. for $C_{10}H_{16}O_5N_4$: C, 44.12; H, 5.88; N, 20.59. Found : C, 43.98; H, 6.00; N, 20.46). Tri-O-acetylation of V yielded Va as the hydrochloride salt, m.p. 241~243° (decomp., eff.), in 70% yield, $[\alpha]_D^{25}$ +27° (*Anal.* Calcd. for $C_{16}H_{21}O_9N_3 \cdot HCl$: C, 44.11; H, 5.05; N, 9.65. Found : C, 43.89; H, 5.10; N, 9.38). Nitrous acid deamination of Va gave a new hexosyluracil, probably 1-β-D-allopyranosyluracil (VII), m.p. 241~242° (decomp.), $[\alpha]_D^{25}$ +2° (*Anal.* Calcd. for $C_{10}H_{14}O_7N_2$: C, 43.80; H, 5.11; N, 10.21. Found : C, 43.67; H, 5.22; N, 10.18).

The structural proof of V was as follows : N-Acetylation of V, then catalytic hydrogenation, gave the 5,6-dihydrouracil derivative (VIII), m.p. 152° (eff.), $[\alpha]_D^{25}$ −11° (*Anal.* Calcd. for $C_{12}H_{19}O_7N_3$: C, 45.43; H, 5.99; N, 13.25. Found : C, 45.25; H, 6.18; N, 13.06). Removal of the dihydrouracil moiety of VIII by methanolysis followed by acetylation with acetic anhydride in pyridine yielded the known methyl 3-acetamido-3-deoxy-2,4,6-tri-O-acetyl-α-D-glucopyranoside (IX),[2] m.p. 175~176°, $[\alpha]_D^{25}$ +101°. This conversion (V→IX) establishes the glucosyl configuration in IV, V, Va, VI, and VIII. This conclusion was also supported by nuclear magnetic resonance studies on the N-acetyl and tetra-acetyl derivatives of V.

This reaction should have wide application for the syntheses of 3′-amino-3′-deoxynucleosides. Preliminary studies in this laboratory show that the periodate-nitromethane reaction is also applicable to inosine.

Division of Nucleoprotein Chemistry,
Sloan-Kettering Institute for Cancer Research,
Sloan-Kettering Division of Cornell University Medical College,
New York 21, New York

Kyoichi A. Watanabe (渡辺 恭一)
Jack J. Fox

Received June 30, 1964

2) H. H. Baer : *Ibid.*, **83**, 1882 (1961); M. J. Cron, D. L. Evans, F. M. Palermiti, D. F. Whitehead, I. R. Hooper, P. Chu, R. U. Lemieux : *Ibid.*, **80**, 4741 (1958); S. Peat, L. F. Wiggins : J. Chem. Soc., **1938**, 1810.

[Chem. Pharm. Bull. 12 (8) 976 ~ 978]

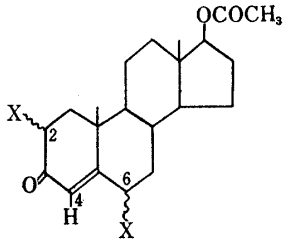
UDC 547.92 : 543.422.25[539.143.43]

Long-range Effect of Halogen in the Nuclear Magnetic Resonance Spectra of Halosteroids

Previous attempts[1,2] to elucidate the magnetic anisotropy of halogen have been made with some simple halo-compounds. Several studies[3~6] have recently been performed to determine the conformation of halosteroids from their chemical shift values in the nuclear magnetic resonance (NMR) spectra.

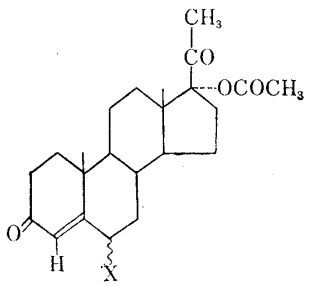
1) H. Spiesecke, W. G. Schneider : J. Chem. Phys., 35, 722 (1961) and references cited therein.
2) G. S. Reddy, J. H. Goldstein : *Ibid.*, 38, 2736 (1963).
3) J. C. Jacquesy, J. M. Lehn, J. Levisalles : Bull. soc. chim. France, **1961**, 2444.
4) J. C. Jacquesy, J. Levisalles : *Ibid.*, **1962**, 1866.
5) D. J. Collins, J. J. Hobbs, S. Sernbell : Tetrahedron Letters, No. 4, 197 (1963).
6) T. A. Wittstruch, S. K. Malhotra, H. J. Ringold : J. Am. Chem. Soc., 85, 1699 (1963).

TABLE I.



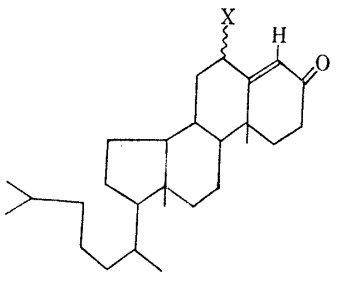
Compd.	Chemical shifts (p.p.m.)[a]	
	19-Methyl	C_4-Proton
Testosterone acetate (I)	1.19_2	5.66_7
2α-Chlorotestosterone acetate (II)	1.29_5	5.77_6
2α-Bromotestosterone acetate (III)	1.28_5	5.80_3
6α-Chlorotestosterone acetate (IV)	1.22_9	6.30_3 (J=1.6 c.p.s.)
6β-Chlorotestosterone acetate (V)	1.46_9	5.83_1
2α,6α-Dichlorotestosterone acetate (VI)	1.30_5	6.39_9 (J=1.6 c.p.s.)
2α,6β-Dichlorotestosterone acetate (VII)	1.54_5	5.93_4
2α,2β,6β-Trichlorotestosterone acetate (VIII)	1.69_1	5.99_9
Dihydrotestosterone acetate (IX)[7]	1.03	—

TABLE II.



Compd.	Chemical shifts (p.p.m.)[a]	
	19-Methyl	C_4-Proton
17α-Acetoxyprogesterone (X)	1.19_9	5.67_0
6α-Chloro-17α-acetoxyprogesterone (XI)	1.21_1	6.29_6 (J=1.5 c.p.s.)
6β-Chloro-17α-acetoxyprogesterone (XII)	1.46_9	5.83_9

TABLE III.



Compd.	Chemical shifts (p.p.m.)[a]	
	19-Methyl	C_4-Proton
Cholest-4-en-3-one (XIII)	1.18_3	5.68_2
6α-Bromocholest-4-en-3-one (XIV)	1.21_7	6.37_9 (J=1.7 c.p.s.)
6β-Bromocholest-4-en-3-one (XV)	1.52_3	5.85_3

a) All spectra were measured using a Varian V-4311 NMR Spectrometer (60 Mc.). Samples were dissolved in deuterochloroform at 0.5*M* and degased in a high vacuum apparatus ($10^{-5.8}$~$10^{-4.7}$ mm.Hg). The p.p.m. values were calculated using tetramethylsilane as an internal standard (0 p.p.m.).

7) NMR Spectra Catalog (Varian Associates), 1962.

The authors, as a part of the NMR research of steroids, have measured NMR spectra of compounds in which halogens (chlorine and bromine) were substituted at C_2 and C_6 of testosterone acetate (I), 17α-acetoxyprogesterone (X) and cholest-4-en-3-one (XIII). Chemical shifts of both 19-methyl group and olefinic proton at C_4 were observed and the results are summarized in Tables I, II and III.

Based on these results it is clearly defined that the 2α-halogen causes the chemical shift of the 19-methyl group to be displaced to lower field by approximately 0.1 p.p.m., while an additional halogen at 2β causes a further displacement, namely by another 0.15 p.p.m. In the case of C_6-halogen a 6α-halogen has little effect on the chemical shift of the 19-methyl group, but a 6β-halogen causes low field shift of approximately 0.25 p.p.m. The difference between the effects of 2β- and 6β-halogen on 19-methyl group might be rationalized by the fact that while B-ring retains a chair form, A-ring may assume a half boat form. This reveals that the low field shift of 19-methyl signal can be observed when the halogen and the methyl group are in a 1,3-diaxial position.

On the other hand, the C_4-olefinic proton of 6α-chlorosteroids has shifted to low field by approximately 0.5 p.p.m. more than that of 6β-derivatives and appeared as a doublet[5,6] (J=1.5~1.7 c.p.s.). Conformations of the C_4 proton and C_6 halogen are shown in Chart I, and such an effect would be expected since the 6α-halogen and olefinic proton are eclipsed. These result obtained above could be utilized as a valuable means in determining the conformation of halosteroids.

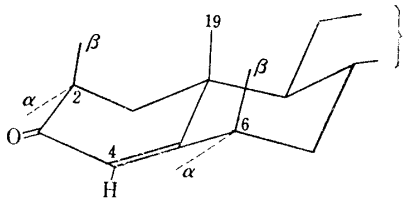


Chart 1.

The contributions of halogen which affect chemical shifts may be summed up as follows: 1. inductive effect, 2. repulsive unshielding (non-bonded repulsive interaction),[8] 3. diamagnetic anisotropy of the C-X bond[9] and 4. partial double-bond character of the C-X bond.[9,10] The results appearing in Tables I, II and III, are not sufficient to estimate correctly the sole contribution of the inductive effect on chemical shifts. However, the fact that the influence 2α, 2β, or 6β halogen on the C_4-olefinic proton is about one fifth that of the 6α halogen and also 6α halogen does not show any significant effect on the chemical shift of 19-methyl group reveal the small contribution of an inductive effect of halogen.

Although in rigid ring systems, groups in a 1,3-diaxial relationship exhibit a low field shift, the authors assume that the main cause responsible for the low field shift is the characteristic diamagnetic anisotropy of the C-X bond.

A detailed discussion of this work will be presented in this Bulletin.

The authors are greatly indebted to Assist. Prof. T. Ikenoue, Chemical Research Institute of Non-Aqueous Solutions, Tohoku University, for numerous profitable discussions and valuable technical assistance.

Pharmaceutical Institute,
Tohoku University School of Medicine,
Kitayomban-cho, Sendai

Yoshikazu Kondo (近藤嘉和)
Tsunematsu Takemoto (竹本常松)

Research Laboratory,
Teikoku Hormone Mfg. Co., Ltd.,
1604, Shimosakunobe,
Kawasaki

Kikuo Yasuda (安田喜久男)

Received March 16, 1964

8) G.V.D. Tiers: J. Am. Chem. Soc., 78, 2914 (1956).
9) A.A. Bothner-By, C. Naar-Colin: Ann. N.Y. Acad. Sci.. 70, 833 (1958).
10) L.H. Meyer, H.S. Gutowsky: J. Phys.Chem,. 57, 481 (1953).