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Migration of Deuterium to C-20 in the Rearrangement Reaction of 17α-Deuterated 5α-Pregnane-3α, 20α-diol Disulfate by Hot Acid Hydrolysis to 17α-Ethyl-17β-methyl-5α-androst-13(14)-en-3α-ol

The mechanism of the hot acid hydrolysis of 5α-pregnane-3α, 20α-diol disulfate was studied with the substrate containing deuterium in the 17α position. About 75% of the isotopic atom was retained in the formation of 17α-ethyl-17β-methyl-5α-androst-13(14)-en-3α-ol. The stereospecific migration of deuterium to ethyl side chain of the product is suggesting that the rearrangement proceeded mainly *via* concerted mechanism.

Keywords——steroid sulfate; hot acid hydrolysis; rearrangement reaction; deuterium labeling; $\Delta^{13(14)}$-steroid; reaction mechanism

Previously we found that pregnanediol 20-sulfate (I), in 4 N hydrochloric acid under heating, gave $\Delta^{13(14)}$ olefin (II) as the main product.[1] Similar result was also obtained in the hot acid hydrolysis of disulfate (IX) to give a corresponding olefin (XIII) accompanied with

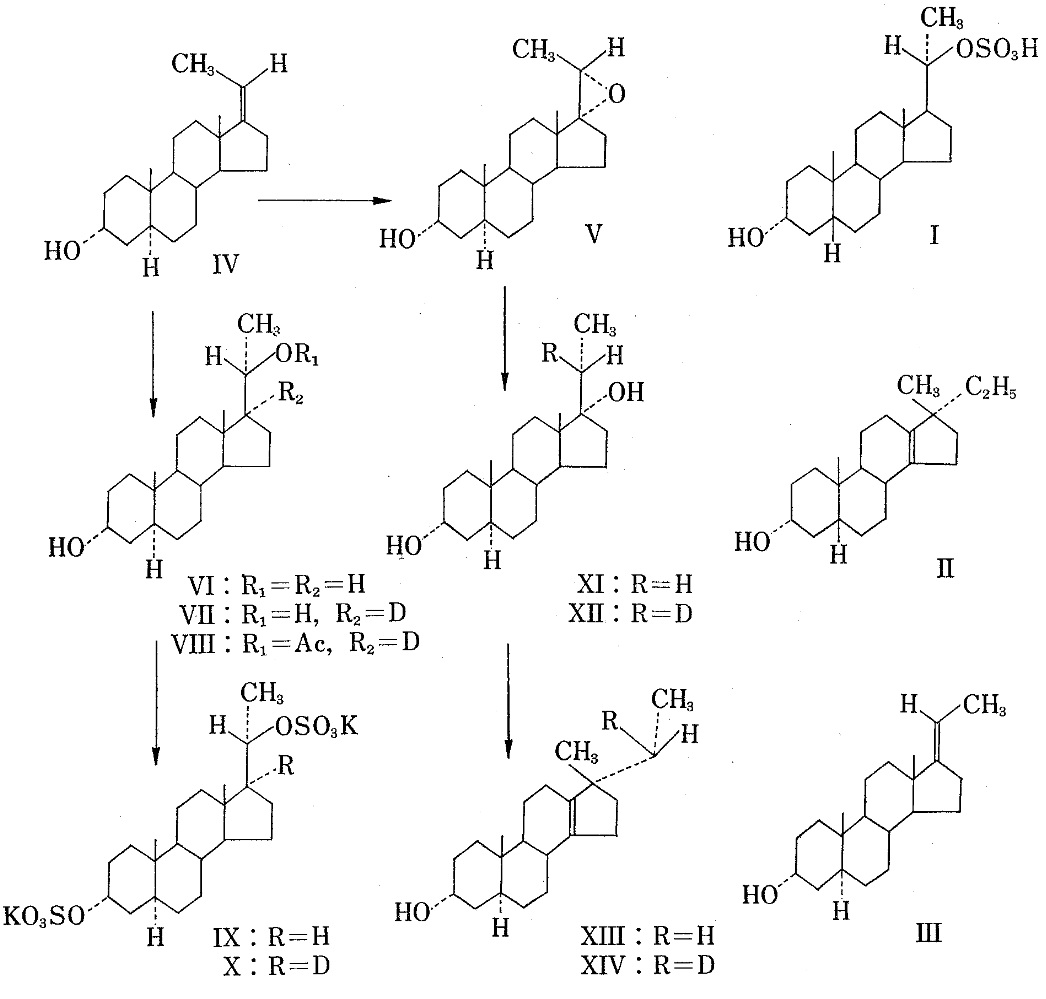

Chart 1

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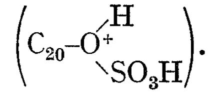
[1] *a*) I. Yoshizawa, T. Miura, M. Kimura, K. Anzai, and S. Matsuda, *Chem. Pharm. Bull.* (Tokyo), **21**, 1622 (1973); *b*) I. Yoshizawa, R. Oh'uchi, A. Nakagawa, T. Miura, M. Kimura, K. Anzai, and S. Matsuda, *Yakugaku Zasshi*, **98**, 215 (1978).

the various minor degradation products.[2] The formation of these olefins from 20α-sulfate contains abnormal bond cleavage between C–O of the sulfate group, which, on normal hydrolysis, is cleaved between S–O bond.

Two reaction mechanisms are possible for the formation of such a rearranged olefin from 20α-sulfate. One is the concerted mechanism as the followings: Protonation occurs initially on the alcoholic oxygen of C-20 to form the protonated sulfate  $\left(C_{20}\text{–}O^{+}\begin{smallmatrix}H\\SO_3H\end{smallmatrix}\right)$. Removal of sulfuric acid from this cation proceeds with simultaneous 1,2-shifts of 17α-hydride to C-20 and 18-methyl group to C-17, and with loss of a proton at C-14, resulting to give $\Delta^{13(14)}$ olefin. The other mechanism is the stepwise: C-20 sulfate group is also removed by the similar bond cleavage, but to give such elimination products as III or IV, and/or corresponding C-20 carbonium ion, which are then converted to the rearranged olefin.

To distinguish these two mechanisms, we prepared 17α-deuterated sulfate (X) and subjected it to hot acid hydrolysis. If the stepwise mechanism is involved, the deuterone is lost into the medium, whereas a shift of deuteride by concerted mechanism would yield labeled $\Delta^{13(14)}$ olefin.

Hydroboration of the olefin (IV)[3] with diborane or deuterated diborane generated by $NaBH_4$ or $NaBD_4$ with BF_3-ether complex by the method as described,[4] gave diols, VI, mp 214°, Mass spectrum (MS), *m/e*: 320 (M^+) and 17α-deuterated diol (VII), mp 214°, MS, *m/e*: 321 (M^+), both of which were recrystallized from ether. The existence of 17α-deuterium of VII was confirmed by nuclear magnetic resonance (NMR) spectrum of 20-monoacetate (VIII), mp 198—198.5°, which was obtained by partial acetylation of VII. Signal at 4.90 ppm attributable to 20β-H is split to quartet ($J=6.0$ Hz) by coupling with only C-21 methyl protons.

Treatment of VI and VII with SO_3-pyridine complex gave quantitatively corresponding disulfates, IX, mp 168—169° (MeOH) and X, mp 169° (MeOH), respectively. Hot acid hydrolysis of these sulfates was carried out by the method as described previously,[1,3] and hydrolyzates obtained were submitted to preparative thin-layer chromatography (Wako gel B5-F impregnated with 10% $AgNO_3$, developed 5 times with cyclohexane–acetone, 20:1). The corresponding $\Delta^{13(14)}$ materials were obtained: the olefin (yield; 48%) from IX, mp 121° (ether) and the other (yield: 53%) from X, mp 120—121° (ether). These products were then compared with the authentic specimens obtained by the following experiment.[3]

Reduction of the epoxide (V) with lithium aluminum hydride and also its deuteride gave corresponding 17α-ols, XI and XII, which on treatment with acid were converted quantitatively to desirable materials, XIII and XIV, respectively. In the NMR spectrum of XIII, C-21 methyl signal is split to doublet-doublet peaks at 0.79 and 0.74 ppm with coupling constant of 7.0 Hz. Deuterated material, on the other hand, has only a couple of peaks at 0.74 ppm ($J=7.0$ Hz). So that, the signal at down field (0.79 ppm) is attributed to the methyl protons coupled with 20β-H and the upper field signal at 0.74 ppm with 20α-H.

$\Delta^{13(14)}$ Olefin obtained from sulfate (IX) was completely identical with XIII in all respects. On the other hand, the olefin derived from X was not identical with XIII nor XIV in MS and NMR spectra as described below. This product in MS has two molecular ions at 303 and 302, the ratio of which is 75:25. The material has the following signals in NMR spectrum: 4.02 (1H, broad singlet, 3β-H), 0.95 (3H, singlet, 17β-CH_3), 0.77 (3H, singlet,

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[2] I. Yoshizawa, R. Oh'uchi, and A. Nakagawa, *Jap. J. Clin. Chem.*, **7**, 1 (1978).

[3] The preparation methods of the compounds; IV, V, XI, XII, XIII, and XIV are described in the previous paper: R. Oh'uchi, N. Kawahara, and I. Yoshizawa, *Chem. Pharm. Bull.* (Tokyo), **26**, 2262 (1978).

[4] E.P. Oliveto, "Organic Reactions in Steroid Chemistry," ed. by J. Fried and J.A. Edwards, Van Nostrand Reinhold Co., New York, 1972, Vol. 2, pp. 131—132.

19-CH_3), 0.79 (doublet, $J=7.0$ Hz, 20β-H), 0.73 (doublet, $J=7.0$ Hz, 20α-H). The rough ratio of 20α-H to 20β-H is about 3—4 (Fig. 1). The result is almost agreeable to that obtained by MS spectrum.

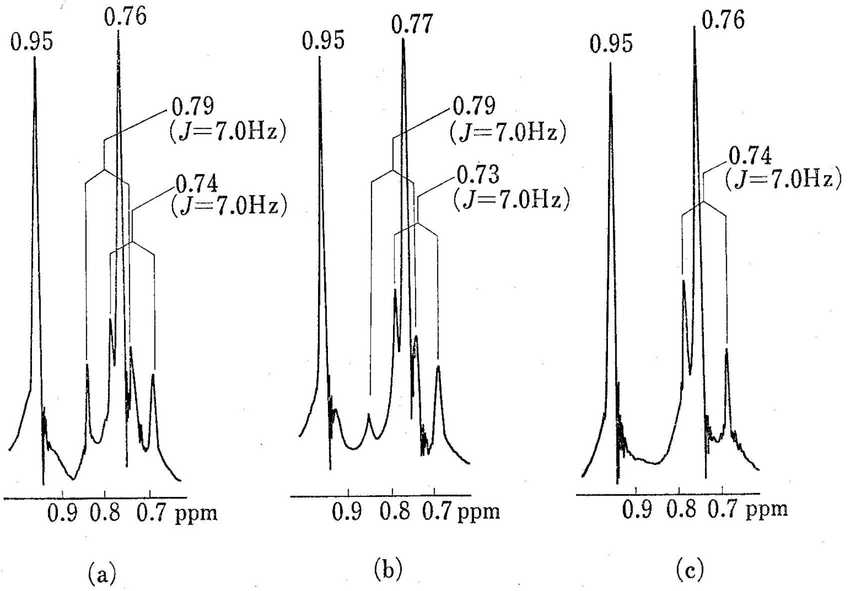

Fig. 1. Partial Nuclear Magnetic Resonance Spectra of XIII (a), Hydrolysis Product of X (b), and XIV (c), in $CDCl_3$ recorded on a JEOL–JNM–PS–100

The scales are expanded × 4.

As the starting material (VII) was over 98% deuterated and as deuterium of XIV was not lost even when it was heated in acidic methanol for a long period,[1b] the loss of deuterium during the hydrolysis is calculated as about 23%.

Migration of deuterium from 17α to C-20 may represent that $\Delta^{13(14)}$ olefin was formed mainly *via* concerted mechanism and partial loss of deuterium is suggesting that other minor pathways for this rearrangement are participated. The extent of each reaction mechanism involved may be elucidated by the structure assignment of other minor degradation products, which will be published in the near future.

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