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Studies on Digitalis Glycosides. The Structure of Digiprogenin. Partial Synthesis of Dihydro-α-digiprogenin Acetate

We have previously reported[1] that the positions of the tertiary hydroxyl groups of γ-digiprogenin (I) and its 17-epimer (α-digiprogenin, II) were both considered to be at C-14 from the results of oxidative cleavage of D-ring. We wish now to describe the establishment of the position of the tertiary hydroxyl group by partial synthesis of dihydro-α-digiprogenin acetate from 11-oxotigogenin acetate.

Catalytic reduction of II over palladium-charcoal in ethanol gave dihydro-derivative (IIIa), m.p. 215～218°, $C_{21}H_{30}O_5$, IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3583, 1746, 1710. The absorption at 1710 cm^{-1} appeared with twofold intensity of that at 1746 cm^{-1}, showing that the three carbonyl groups were retained intact. The fact that IR spectrum of the dioxime of IIIa, m.p. 236～240° (decomp.), $C_{21}H_{32}O_5N_2$, exhibited an absorption of a six membered ring ketone at 1705 cm^{-1} supports this consideration. In the NMR spectrum of IIIa, the signal of 6-vinyl proton was not observed and the signal of C-3 proton appeared as a broad multiplet at 6.42 τ ascribable to be axial. These data show that 5,6-double bond of II was hydrogenated from rear side to give IIIa. Acetylation of IIIa with acetic anhydride in pyridine gave dihydro-α-digiprogenin acetate (IIIb), m.p. 200～202°, $[\alpha]_D^{24}$ −40.2° (c=0.910, MeOH), $C_{23}H_{32}O_6$, IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3575, 1745, 1720, 1713.

On the other hand, an attempt was successfully made to synthesize compound IIIb starting from 11-oxotigogenin acetate. 3β-Acetoxy-5α-pregn-16-ene-11,20-dione (IV), m.p. 182～184°, derived from 11-oxotigogenin acetate by the known method,[2] was treated with NBS and subsequently with sodium iodide[3] to give 3β-acetoxy-5α-pregn-14,16-diene-11,20-dione (V), m.p. 211～212°, $[\alpha]_D^{23}$ +306.3° (c=1.044, MeOH), $C_{23}H_{30}O_4$, UV λ_{max}^{EtOH} mμ (ε) : 303.5 (10480), IR ν_{max}^{Nujol} cm^{-1} : 1722 (Ac), 1706 (six membered ring ketone), 1642 and 1532 (conjugated dienone system), NMR ($CDCl_3$) τ : 8.84 (19-CH_3), 8.81 (18-CH_3), 7.67 (21-CH_3), 3.79 (1H, t, J=2.0 c.p.s., 15-vinyl proton), 2.76 (1H, d, J=2.0 c.p.s., 16-vinyl proton). These characteristcs correspond to the formula V. Oxidation of V with *m*-chloroperbenzoic acid in chloroform afforded an epoxide (VI), m.p. 170～173°, $[\alpha]_D^{23}$ +144.4° (c=0.943, MeOH), $C_{23}H_{30}O_5$, UV λ_{max}^{EtOH} mμ (ε) : 240 (7595), IR ν_{max}^{Nujol} cm^{-1} : 1729 (Ac), 1715 (six membered ring ketone), 1665 and 1595 (α,β-unsaturated aliphatic ketone grouping), NMR ($CDCl_3$) τ : 8.89 (19-CH_3), 8.65 (18-CH_3), 7.75 (21-CH_3), 6.03 (1H, d, J=1.5 c.p.s., 15 proton bearing epoxide), 3.04 (1H, d, J=1.5 c.p.s., 16-vinyl proton). These data show that VI is a 14,15-epoxide. As it is known[4,5] that epoxidation of pregn-14,16-dien-20-one type compounds gave predominantly 14β,15β-epoxides, the structure 3β-acetoxy-14β,15β-epoxy-5α-pregn-16-ene-11,20-dione can be assigned to VI.

Oxidative cleavage of the epoxide ring in VI with chromium trioxide in acetic acid gave a hydroxyketone (VII), m.p. 165～168°, $[\alpha]_D^{23}$ −46.0° (c=0.522, MeOH), $C_{23}H_{30}O_6$, UV λ_{max}^{EtOH} mμ (ε) : 241 (11000), IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3540 (OH), 1716 (broad, Ac, α,β-unsaturated five membered ring ketone, and six membered ring ketone), 1693 and 1596 (α,β-unsaturated aliphatic ketone grouping), NMR ($CDCl_3$) τ : 9.15 (19-CH_3), 8.60 (18-CH_3), 7.61 (21-CH_3), 3.40 (1H, s, 16-vinyl proton). The new hydroxyl group in VII is tertiary because it resisted oxidation. The absorption in UV and IR spectra of VII indicated the presence of α,β-unsaturated ketone. The signal of 15 proton observed in NMR spectrum of VI

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2) G. P. Mueller : Nature, **76**, 771 (1958).
3) A. J. Sole, B. Singh : J. Org. Chem., **30**, 1658 (1965).
4) Pl. A. Plattner, L. Ruzicka, H. Heusser, E. Angliker : Helv. Chim. Acta, **30**, 385 (1947).
5) H. Mitsuhashi, T. Nomura : Steroids, **3**, 271 (1964).

disappeared in that of Ⅶ, and the signal of 16-vinyl proton changed from doublet to singlet. These data indicate that the oxidative cleavage of the 14β,15β-epoxide of Ⅵ afforded a 14-hydroxy-15-ketone grouping, and hence Ⅶ has a partial structure of 14-hydroxy-16-ene-15,20-dione. Since, 16-ene-14,15-epoxide[6] as well as 16-saturated 14,15-epoxides[7,8] was reported to give 14β-hydroxy-15-ketone on chromium trioxide oxidation, compound Ⅶ is considered to have the structure 3β-acetoxy-14-hydroxy-5α, 14β-pregn-16-ene-11,15,20-trione. Reduction of Ⅶ with zinc powder and acetic acid at room temperature gave a dihydro compound, m.p. 199~201°, $C_{23}H_{32}O_6$, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3568, 1745, 1721, 1712. The UV and IR spectra of this compound show that 16,17-double bond in Ⅶ has been saturated. This dihydro product proved to be identical with Ⅲb by

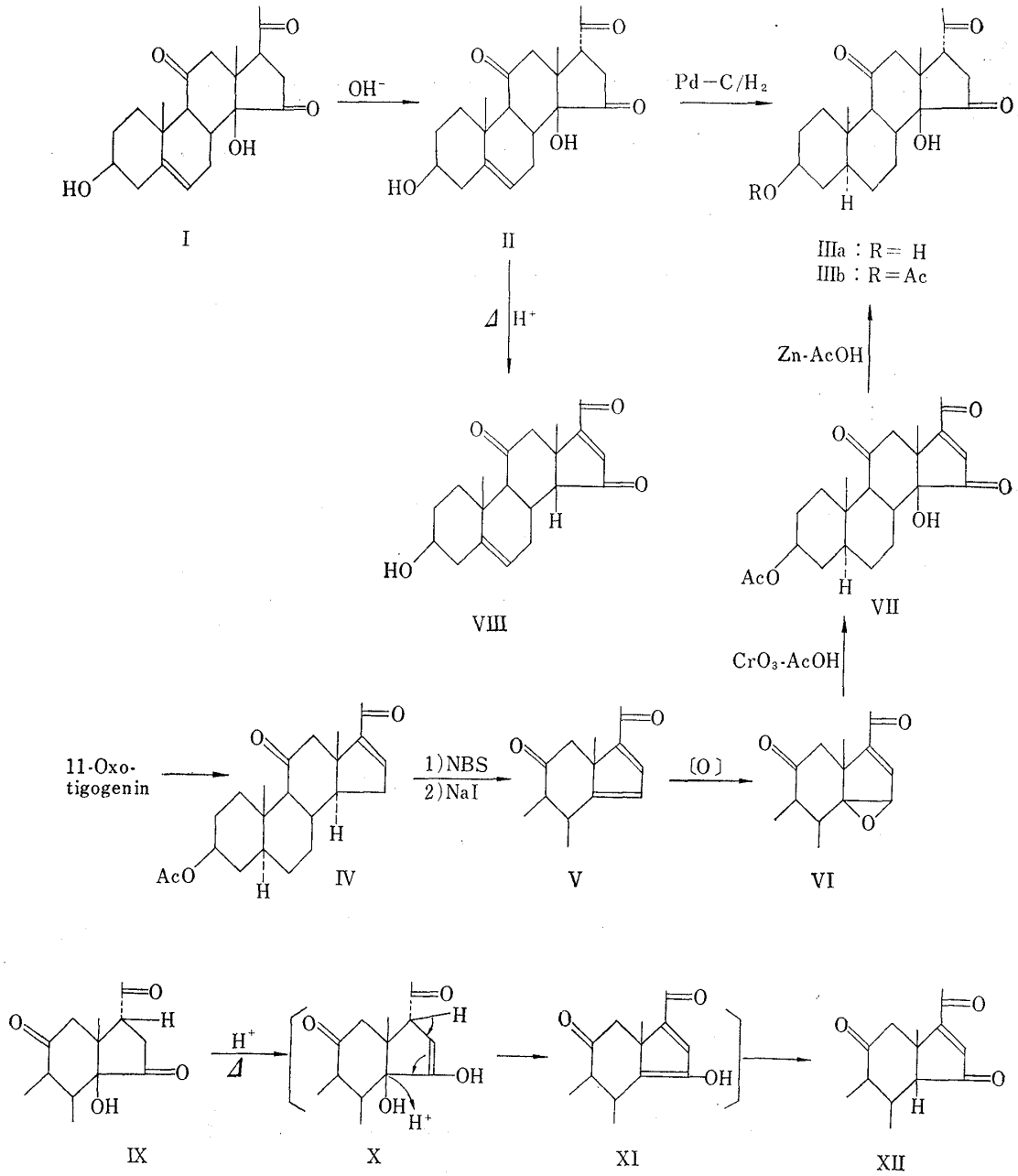

Chart 1.

6) H. Mitsuhashi, M. Fukuoka : This Bulletin, **14**, 809 (1966).
7) A. Lardon, T. Reichstein : Helv. Chim. Acta, **45**, 943 (1962).
8) M. Okada, M. Hasunuma : Yakugaku Zasshi, **85**, 822 (1965).

mixed melting point and comparisons of thin-layer chromatography and IR spectra. This result established the 14-position of the tertiary hydroxyl group in digiprogenin.

The formation of β-digiprogenin (Ⅷ) from α-digiprogenin (Ⅱ) with acid may be explained*1 by 1,4-elimination of water in the sequence indicated in Chart 1 from Ⅸ to Ⅻ. An analogous elimination of water was recently reported with erythrophleguine by Norin, *et al.*[9]

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*1 Prof. C. W. Shoppee informed us in private communication that he developed independently the same explanation of this dehydration.

9) O. Lindwall, F. Sandberg, R. Thorsén, T. Norin : Tetrahedron Letters, No. 47, 4203 (1965).

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Structure of Serratine

In previous publication,[1,3] we have described the isolation and characterization of four new alkaloids, serratinine, serratinidine, serratine and serratanine from *Lycopodium serratum* Thunb. var. *Thunbergii* Makino (ホソバトウゲシバ) and the structures of serratinine (Ⅰ)[2] and serratinidine (Ⅱ)[3] which are unique among the lycopodium alkaloids, have been established.

Serratine (Ⅲ), m.p. 253°,*1 $C_{16}H_{25}O_3N$,*2 $[\alpha]_D^{22}$ −15.0° (c=1.02 in EtOH), IR,*3 ν_{max} cm^{-1} : 3185 (OH), 1730 (C=O), NMR*3 : in pyridine, 8.69 τ (3H, s., ≥C-CH_3).

At the beginning of this study, it was anticipated that serratine would possess the serratinine skeleton because the mass spectrum of this alkaloid showed the prominent peaks at M^+-28 (in this case, m/e 251), m/e 152 and m/e 150 which seem to be diagnostically important fragments for the mass spectra of serratinine type alkaloids.*4

Acetylation of serratine (Ⅲ) with Ac_2O-pyridine at room temperature for six days afforded monoacetylserratine (Ⅳ), m.p. 264～265.5°, $C_{18}H_{27}O_4N$, IR, ν_{max} cm^{-1} : 3550 (OH), 1718 (ester and ketone carbonyl groups), NMR : 8.79 (3H, s., ≥C-CH_3), 8.05 (3H, s., -CO-CH_3), 5.21 (1H, m., >CH-OAc). Further treatment of (Ⅳ) with Ac_2O-pyridine at

*1 All melting points were observed on a microscopic hotstage and are uncorrected.

*2 The molecular weight establishment by mass spectrometry made revision of the earlier proposed molecular formula, $C_{17}H_{27}O_3N$,[1] of serratine to the present one. All compounds given by molecular formulae gave satisfactory elementary analyses.

*3 IR spectra were measured on Nujol mulls and unless otherwise noted, NMR spectra were taken in $CDCl_3$ on a Varian A-60 at 60 Mc. Chemical shifts are reported in τ values, using tetramethylsilane as an internal reference.

*4 The mass spectrometric analyses of this series of alkaloids will be presented in elsewhere.

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