Studies on Digitalis Glycosides. The Structure of Digiprogenin.
Partial Synthesis of Dihydro-\(\alpha\)-digiprogenin Acetate

We have previously reported\(^b\) that the positions of the tertiary hydroxyl groups of \(\gamma\)-digiprogenin (I) and its \(17\)-epimer (\(\alpha\)-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-\(\alpha\)-digiprogenin acetate from 11-oxotigogenin acetate.

Catalytic reduction of II over palladium-charcoal in ethanol gave dihydro-derivative (IIIa), m.p. 215–218\(^\circ\), C\(_{21}\)H\(_{30}\)O\(_8\), IR \(\nu_{\text{max}}^\text{CH} \text{ cm}^{-1}\) : 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\(^\circ\) (decomp.), C\(_{21}\)H\(_{30}\)O\(_{4}\)N\(_2\), 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 \(\tau\) 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-\(\alpha\)-digiprogenin acetate (IIIb), m.p. 200–202\(^\circ\), \([\alpha]_b^D = -40.2^\circ\) (c=0.910, MeOH), C\(_{25}\)H\(_{32}\)O\(_8\), IR \(\nu_{\text{max}}^\text{CH} \text{ cm}^{-1}\) : 3575, 1745, 1720, 1713.

On the other hand, an attempt was successfully made to synthesize compound IIIb starting from 11-oxotigogenin acetate. 3\(\beta\)-Acetoxy-5\(\alpha\)-pregn-16-ene-11,20-dione (IV), m.p. 182–184\(^\circ\), derived from 11-oxotigogenin acetate by the known method,\(^b\) was treated with NBS and subsequently with sodium iodide\(^b\) to give 3\(\beta\)-acetoxy-5\(\alpha\)-pregn-14,16-diene-11,20-dione (V), m.p. 211–212\(^\circ\), \([\alpha]_b^D +306.3^\circ\) (c=1.044, MeOH), C\(_{25}\)H\(_{30}\)O\(_8\), UV \(\lambda_{\text{max}}^\text{UV} \text{ nm} (\epsilon)\) : 303.5 (10480), IR \(\nu_{\text{max}}^\text{CH} \text{ cm}^{-1}\) : 1722 (Ac), 1706 (six membered ring ketone), 1642 and 1532 (conjugated diene system), NMR (CDCl\(_3\)) \(\delta\) : 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=1.5 c.p.s., 16-vinyl proton). These characteristic correspond to the formula V. Oxidation of V with m-chloroperbenzoic acid in chloroform afforded an epoxide (VI), m.p. 170–173\(^\circ\), \([\alpha]_b^n +144.4^\circ\) (c=0.943, MeOH), C\(_{25}\)H\(_{30}\)O\(_8\), UV \(\lambda_{\text{max}}^\text{UV} \text{ nm} (\epsilon)\) : 240 (7395), IR \(\nu_{\text{max}}^\text{CH} \text{ cm}^{-1}\) : 1729 (Ac), 1715 (six membered ring ketone), 1665 and 1595 (\(\alpha\),\(\beta\)-unsaturated aliphatic ketone group), NMR (CDCl\(_3\)) \(\delta\) : 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\(^v\) that epoxidation of pregn-14,16-dien-20-one type compounds give predominantly 14\(\delta\),15\(\beta\)-epoxides, the structure 3\(\beta\)-acetoxy-14\(\beta\),15\(\beta\)-epoxy-5\(\alpha\)-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\(^\circ\), \([\alpha]_b^D -46.0^\circ\) (c=0.522, MeOH), C\(_{23}\)H\(_{28}\)O\(_{4}\), UV \(\lambda_{\text{max}}^\text{UV} \text{ nm} (\epsilon)\) : 241 (11000), IR \(\nu_{\text{max}}^\text{CH} \text{ cm}^{-1}\) : 3540 (OH), 1716 (broad, Ac, \(\alpha\),\(\beta\)-unsaturated five membered ring ketone, and six membered ring ketone), 1693 and 1596 (\(\alpha\),\(\beta\)-unsaturated aliphatic ketone group), NMR (CDCl\(_3\)) \(\delta\) : 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 \(\alpha\),\(\beta\)-unsaturated ketone. The signal of 15 proton observed in NMR spectrum of VII

disappeared in that of \( \Pi \), and the signal of 16-vinyl proton changed from doublet to singlet. These data indicate that the oxidative cleavage of the 14\( \beta \),15\( \beta \)-epoxide of \( \Pi \) afforded a 14-hydroxy-15-ketone grouping, and hence \( \Pi \) 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 14\( \beta \)-hydroxy-15-ketone on chromium trioxide oxidation, compound \( \Pi \) is considered to have the structure 3\( \beta \)-acetoxy-14-hydroxy-5\( \alpha \), 14\( \beta \)-pregn-16-ene-11,15,20-trione. Reduction of \( \Pi \) with zinc powder and acetic acid at room temperature gave a dihydro compound, m.p. 199–201\(^\circ\), \( C_{23}H_{32}O_{9} \), IR \( \nu_{\text{max}} \) cm\(^{-1} \): 3568, 1745, 1721, 1712. The UV and IR spectra of this compound show that 16,17-double bond in \( \Pi \) has been saturated. This dihydro product proved to be identical with \( \Pi b \) by

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\text{Chart 1.}
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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 (Ⅲ) from α-digiprogenin (Ⅱ) with acid may be explained by 1,4-elimination of water in the sequence indicated in Chart 1 from K to Υ. An analogous elimination of water was recently reported with erythrophlegueine by Norin, et al. 9)

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Structure of Serratine

In previous publication,1,3) we have described the isolation and characterization of four new alkaloids, serratine, serratinidine, serratine and serratamine from Lycopodium serratum THUNB. var. Thunbergii MAKINO (ホソバツツゲシバ) and the structures of serratine (I)3) and serratinidine (II)3) which are unique among the lycopodium alkaloids, have been established.

Serratine (Ⅲ), m.p. 253°,1) C_{18}H_{23}O_{2}N,1) [α]_D^25 = -15.0° (c = 1.02 in EtOH), IR,1) ν_{max} cm^{-1}: 3185 (OH), 1730 (C=O), NMR1): 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_{2}O-pyridine at room temperature for six days afforded monoacetylseratine (Ⅳ), m.p. 264–265.5°, C_{19}H_{25}O_{3}N, IR, ν_{max} cm^{-1}: 3550 (OH), 1718 (ester and ketone carbonyl groups), NMR: 8.79 (3H, s, >C-CH_{3}), 8.65 (3H, s, –CO–CH_{3}), 5.21 (1H, m., >CH-OAc). Further treatment of (Ⅳ) with Ac_{2}O-pyridine at

1) All melting points were observed on a microscopic hotstage and are uncorrected.
2) The molecular weight estimation by mass spectrometry made revision of the earlier proposed molecular formula, C_{18}H_{23}O_{2}N,1) of serratine to the present one. All compounds given by molecular formulæ 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.