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Studies on Digitalis Glycosides. The Structure of Digiprogenin

In the previous papers,[1,2] Satoh and Horie reported that the tertiary hydroxyl group of γ-digiprogenin (I), one of the C_{21}-steroids of *Digitalis purpurea* L. Leaves, appeared to locate at C-17 from the fact that refluxing I with 5% hydrochloric acid in 50% ethanol gave a 16-en derivative (β-digiprogenin, III) through a 17-epimer (α-digiprogenin, II). In this communication we wish to propose a new formula IV for γ-digiprogenin, in which position of the tertiary hydroxyl group is revised to C-14 from the results of oxidative cleavage of the D-ring.

While γ-digiprogenin 3-acetate (IVb) was inert to sodium periodate, it was oxidized with lead tetraacetate to afford an alkali-soluble amorphous product (VI), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3583 (OH), 1784 (γ-lactone), 1726 (Ac), 1717 (six membered ring ketone), NMR ($CDCl_3$) τ : 8.85 (6H, s, 18- and 19-C$\underline{H}_3$), 8.34 (3H, s, $O\text{-}\overset{O}{\overset{|}{\underset{|}{C}}}\text{-}C\underline{H}_3$), 7.98 (3H, s, Ac). Methylation of VI with diazomethane gave a methyl ester (VII), m.p. 125~135°, $C_{24}H_{32}O_7$, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1739, 1728 (Ac and ester), 1712, 1704 (six membered ring and aliphatic ketones), NMR ($CDCl_3$) τ : 8.82 (6H, s, 18- and 19-C$\underline{H}_3$), 7.98 (3H, s, Ac), 7.83 (3H, s, -CO-C$\underline{H}_3$), 6.28 (3H, s, -COOC$\underline{H}_3$). The appearance of a methyl signal at 7.83 τ due to -CO-CH_3 group in the NMR (nuclear magnetic resonance) of VII indicates that the C-17 side chain was not eliminated by lead tetraacetate oxidation of IVb, which observation leads to a consideration that C-14 position for the tertiary hydroxyl group in IVb is more favored than C-17 position. VI is thought to be formed by hemiacetal condensation of lactol of the keto acid (V), a fission product of the 14,15-ketol.[3]

This was further confirmed by the following reaction sequence from IVb to XI. Partial reduction of IVb with sodium borohydride gave three tetrahydro derivatives, A (VIIIa), m.p. 272~275°, $C_{23}H_{34}O_6$, $[\alpha]_D^{23}$ +13.7° (c=1.061, MeOH),*1 IR ν_{max}^{Nujol} cm^{-1}: 1712 (six membered ring ketone), NMR ($CDCl_4$) τ: 8.84 (3H, d, J=6.0 c.p.s., $O\text{-}\overset{|}{C}H\text{-}C\underline{H}_3$), B (VIIIb), m.p. 200~201°, $C_{23}H_{34}O_6$, $[\alpha]_D^{23}-153.9°$ (c=1.075, MeOH),*1 IR ν_{max}^{Nujol} cm^{-1}: 1703 (six membered ring ketone), NMR ($CDCl_3$) τ: 8.82 (3H, d, J=6.0 c.p.s., $O\text{-}\overset{|}{C}H\text{-}C\underline{H}_3$), and C (VIIIc), m.p. 210~213°, $C_{23}H_{34}O_6$, $[\alpha]_D^{23}-83.1°$ (c=1.082, MeOH),*1 IR ν_{max}^{Nujol} cm^{-1}: 1681 (six membered ring ketone), NMR ($CDCl_3$) τ : 8.75 (3H, d, J=6.0 c.p.s., $O\text{-}\overset{|}{C}H\text{-}C\underline{H}_3$). These data from IR and NMR spectra shows that the three tetrahydro derivatives are epimers produced by reduction of the 15- and 20-carbonyl groups.

When the main product B (VIIIb) was oxidized with sodium periodate, there was obtained an aldehyde (X), m.p. 206~210°, $C_{23}H_{32}O_6$, $[\alpha]_D^{22}$ -91.5° (c=1.028, MeOH), IR ν_{max}^{Nujol} cm^{-1}: 3453 (OH), 1731, 1720 (CHO and Ac), 1708 (six membered ring ketone), NMR ($CDCl_3$) τ: 8.70 (3H, d, J=6.0 c.p.s., $O\text{-}\overset{|}{C}H\text{-}C\underline{H}_3$), 0.22 (H, t, J=2.0 c.p.s., $\text{-}\overset{|}{C}H_2\text{-}CH\underline{}O$). Further oxidation of X with chromium trioxide gave an acid (XI), m.p. 169~172° (decomp.), $C_{23}H_{32}O_7$, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3593, 3502 (OH), 1748, 1730 (Ac and COOH), 1719 (six membered ring ketone).

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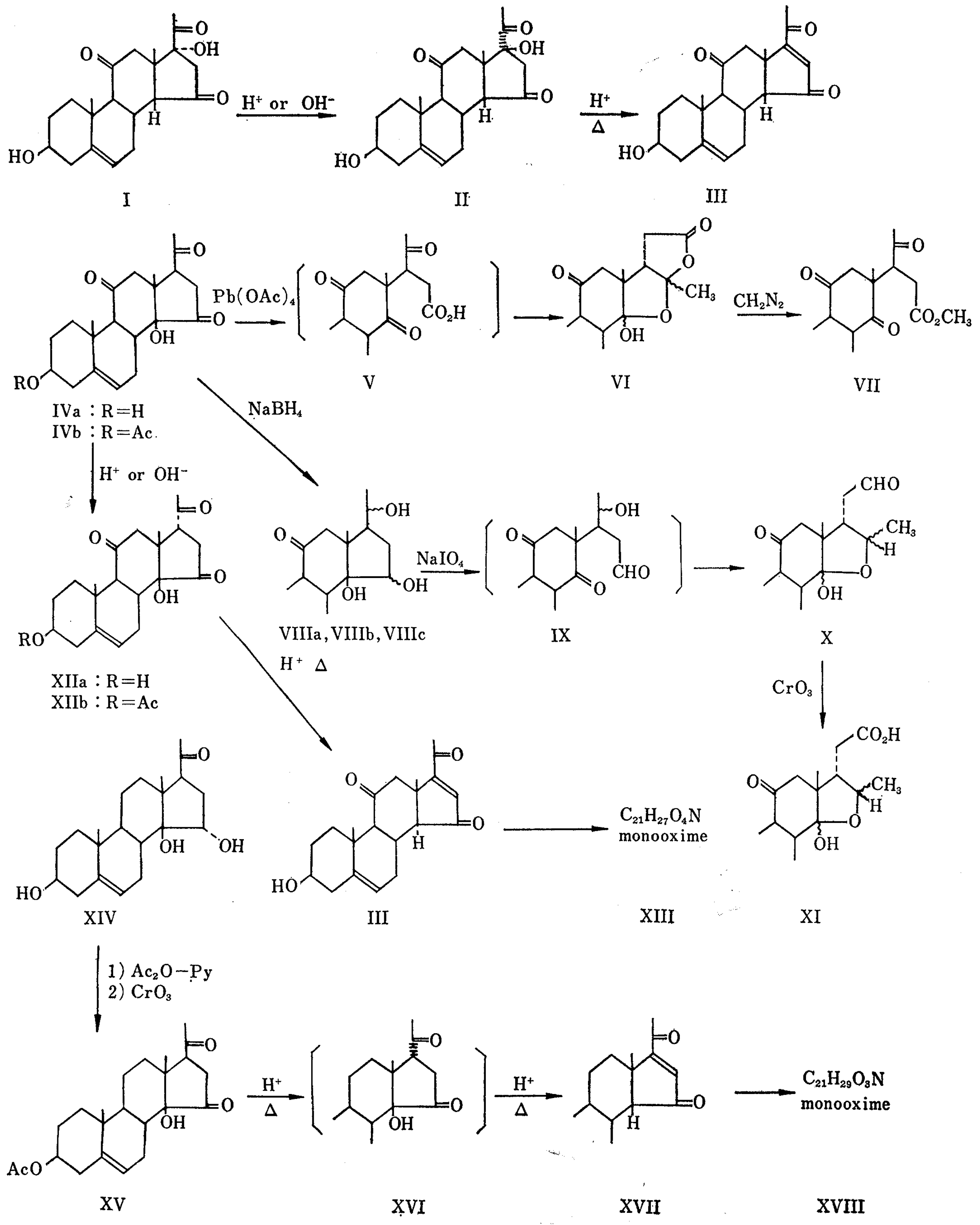
*1 The difference of optical rotations of these products was presumed to due to the dissimilarity of conformations of C-ring.

1) D. Satoh : This Bulletin, **10**, 43 (1962).
2) D. Satoh, M. Horie : *Ibid.*, **12**, 979 (1964).
3) H. Hasegawa, Y. Sato, K. Tsuda : *Ibid.*, **9**, 409 (1961).

From the NMR spectra it was found that X retains the methyl group which originates in C-21 methyl group in γ-digiprogenin and that X contains an aldehyde group. These facts could not be explained if γ-digiprogenin possesses the structure I. X and XI have the hydroxyl group according to IR spectra which did not undergo any oxidation with chromium trioxide, and XI failed to oxime formation, These results indicate that the fission of D-ring took place between C-14 and C-15 to produce the keto-aldehyde (IX) which formed a hemiacetal (X).



Since the 14β,17β- and 14β,17α-configurations were given to γ- and α-digiprogenin respectively,[2] it is most reasonable to assign the structure 3β-acetoxy-14-hydroxy-14β,17β-pregn-5-ene-11,15,20-trione (IVb) to γ-digiprogenin 3-acetate and the structure 3β-acetoxy-14-hydroxy-14β,17α-pregn-5-ene-11,15,20-trione (XIIb) to α-digiprogenin 3-acetate. These assignment can easily explain the conversion of γ-digiprogenin to α-digiprogenin with acid or alkali[1,2] as a usual epimerization of the C-17 side chain. A strong hydrogen bonding observed in IR spectrum of γ-digiprogenin is also understandable by the formula IV.

β-Digiprogenin has a formula (III) as reported previously.[1] NMR spectrum, ($CDCl_3$) τ: 8.96 (3H, s, 19-$C\underline{H}_3$), 8.43 (3H, s, 18-$C\underline{H}_3$), 3.48 (H, s, >C=C$\underline{H}$-CO), supports this formula (III). Accordingly formation of β-digiprogenin (III) by refluxing γ-digiprogenin (IV) with acid should occur through an unusual dehydration process.

In order to examine this reaction process, 3β-acetoxy-14-hydroxy-14β,17β-pregn-5-ene-15,20-dione (XV), m.p. 207~209°, $C_{23}H_{32}O_5$, derived from purpnigenin (XIV) of the known structure,[4] was refluxed with 5% hydrochloric acid in 50% ethanol to yield an anhydro compound (XVII, amorphous), which gave a monooxime (XVIII), m.p. 275~276° (decomp.), $C_{21}H_{29}O_3N$. The following table lists the data from UV, IR and NMR spectra of XVII and XVIII together with III and its monooxime (XIII). The data from XVII and XVIII are shown to be comparable with those from III and XIII, respectively. These facts indicate the possibility of formation of 16-ene-15,20-dione from 14β-hydroxy-15,20-dione by dehydration with acid.

	UV λ_{max}^{EtOH} mμ (ε)	IR $\nu_{max}^{CHCl_3}$ cm^{-1}	NMR ($CDCl_3$) τ
III	240 (11,350)	3608, 1710, 1705, 1690, 1604	7.58 (s, 21-CH_3), 3.48 (s, 16-H)
XVII	242 (8,880)	3595, 1705, 1688, 1600	7.59 (s, 21-CH_3), 3.44 (s, 16-H)

	UV λ_{max}^{EtOH} mμ (ε)	IR ν_{max}^{Nujol} cm^{-1}
XIII	273 (16,600)	3509, 3247, 1701, 1684, 1583
XVIII	273 (18,070)	3470, 3240, 1684, 1583

The further studies to confirm C-14 position of the tertiary hydroxyl group by interconversion of digiprogenin with purpnigenin, and investigations on the mechanism of the unusual dehydration are now in progress.

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4) H. Ishii: This Bulletin, **9**, 411 (1961); **10**, 351, 354 (1962).