Communications to the Editor

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Studies on Digitalis Glycosides
Structure of Digipronin and Digiprogenin.[1]

Digipronin(I),$C_{28}H_{40}O_9$, m.p. 233~238°(UV : λ_{max}^{EtOH} 300 mμ (log ε 1.92), $[\alpha]_D^{28}$ −64.5°), a non-cardiotonic glycoside isolated from the leaves of *Digitalis purpurea* L., gave isodigipronin (II), $C_{28}H_{40}O_9$, m.p. 296~298°, $[\alpha]_D^{18}$ −72.3°, by treatment with dilute alkali. Digipronin and isodigipronin gave γ-digiprogenin(III), $C_{21}H_{28}O_5$, m.p. 250~253°(UV : λ_{max}^{EtOH} 300 mμ (log ε 1.90), $[\alpha]_D^{31}$ −72.5°), and α-digiprogenin(IV), $C_{21}H_{28}O_5$, m.p. 242~244°(UV : λ_{max}^{EtOH} 296 mμ (log ε 1.90), $[\alpha]_D^{31}$−87.5°), as the aglycone after hydrolysis with acid, respectively. γ-Digiprogenin was converted into α-digiprogenin by treatment with dilute alkali or acid, and both aglycones gave the same anhydrodigiprogenin (β-digiprogenin) (V) on refluxing with acid.

As these digiprogenins show positive Liebermann reaction, and contain 21 carbon atoms and 3 $C-CH_3$ groups in their molecules, they seemed to be steroidal aglycones of digitanol glycoside.[2]

While Oppenauer oxidation of α-digiprogenin produced a Δ^4-3-keto derivative, Rosenheim reaction was negative and consequently α-digiprogenin seems to contain a Δ^5-3-hydroxy group.

Infrared spectra of α-digiprogenin monoacetate, m.p. 258~261° (hydroxyl-band positive), and anhydrodigiprogenin monoacetate, m.p. 168~170° (hydroxyl band negative), indicated the presence of a secondary and tertiary hydroxyl group in the digiprogenin molecule. Wave lengths and intensities of infrared spectrum (5.76<5.86, 7.33 μ) of α-digiprogenin showed the presence of a keto group in the five-membered ring, a six-membered ring, and C-17 side chain ($-CO-CH_3$). This aglycone gave only a dioxime, m.p. 280~283°. According to these results the keto group in the six-membered ring seems to be hindered.

Anhydrodigiprogenin(V) (UV : λ_{max}^{EtOH} 239 mμ (log ε 4.02), IR λ_{max}^{KBr} μ : 5.85, 5.92, 5.96, 6.23) was readily saturated by catalytic hydrogenation over palladium-carbon and produced a dihydro derivative (VI), $C_{21}H_{28}O_4$, m.p. 203~204° (IR λ_{max}^{KBr} μ : 5.74, 5.85) by reduction with zinc and acetic acid. These results indicate the conjugate system of anhydrodigiprogenin to be Δ^{16}-15-keto group.

On the basis of the above experiments, dihydroanhydrodigiprogenin was presumed to be 3-hydroxypregn-5-ene-11,15,20-trione. Oppenauer oxidation of this substance gave a Δ^4-3-keto derivative (VII), $C_{21}H_{26}O_4$, m.p. 218~220° (UV : λ_{max}^{EtOH} 239 mμ (log ε 4.19), IR $\lambda_{max}^{CH_2Cl_2}$ μ: 5.73, 5.83, 5.98, 6.16, $[\alpha]_D^{32}$ +145.9°). These physical data were analogous to those of pregn-4-ene-3,11,15,20-tetrone (X) prepared by Schubert, *et al.*[3] They were found to be not identical on the basis of rotation and mixed fusion,[*1] and so they were presumed to be stereoisomers at C-14 and C-17 positions.

As it is well known that the C/D ring *cis*-inversion readily takes place in the

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[*1] Grateful acknowledgement is expressed to Dr. A. Schubert for kind donation of the samples of 11α,15α-dihydroxyprogesterone and pregn-4-ene-3,11,15,20-tetrone.

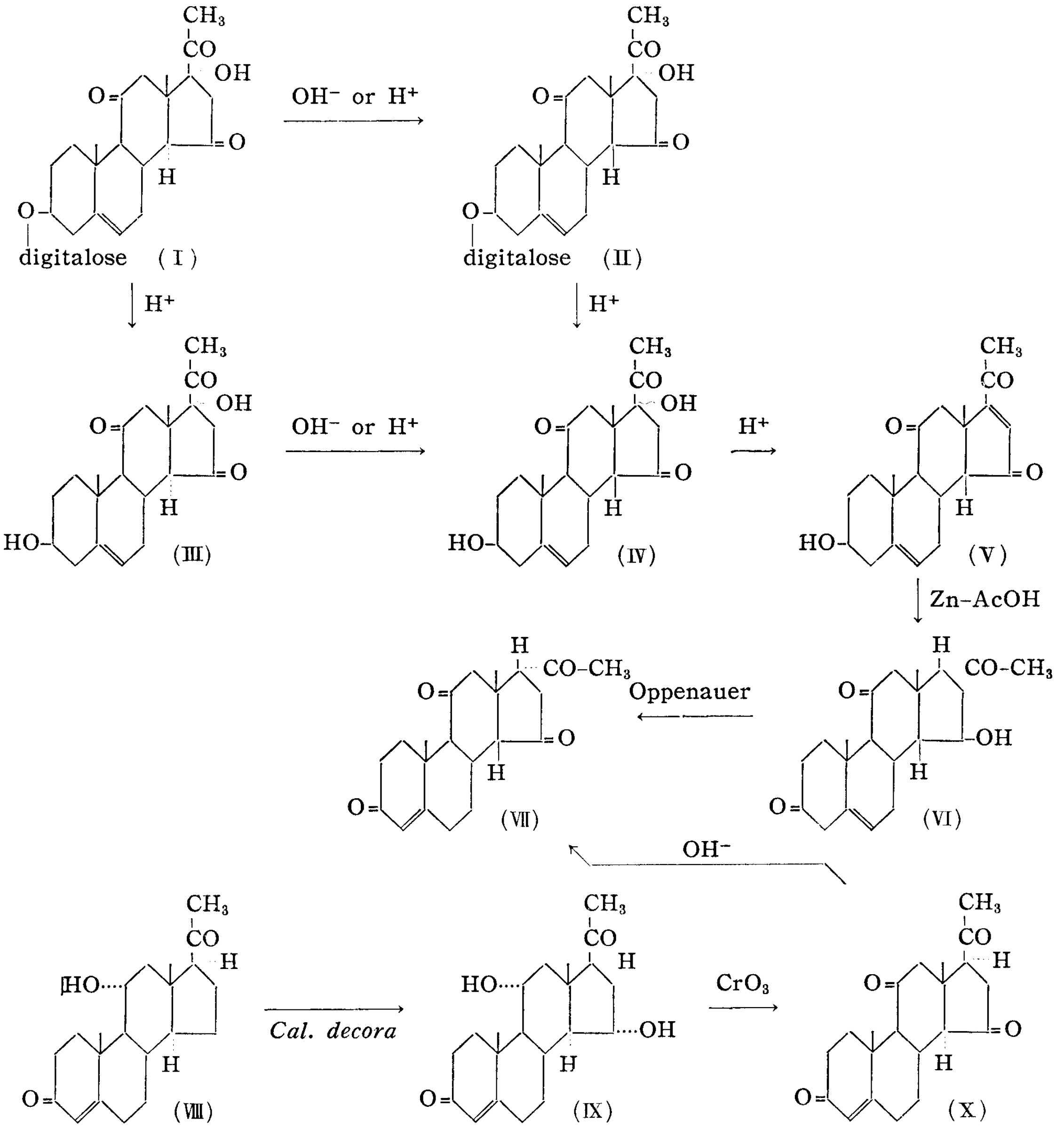
[1] D. Satoh, H. Ishii, Y. Oyama, T. Okumura : Yakugaku Zasshi, **75**, 1025, 1573 (1955); D. Satoh: *Ibid.*, **79**, 1474(1959). R. Tschesche and his collaborators also isolated digipronin and published some results of studies on digiprogenin. cf. R. Tschesche, G. Lipp, G. Grimmer : Ann., **606**, 160(1957); R. Tschesche, G. Lipp : *Ibid.*, **615**, 210(1958).

[2] R. Tschesche, G. Buschauer : Ann., **603**, 59(1957).

[3] A. Schubert, G. Langbein, R. Siebert : Chem. Ber., **90**, 2576(1957); A. Schubert, R. Siebert: *Ibid.*, **91**, 1856(1958).

treatment of 15,20-dioxopregnane analogs with acid or alkali,4) the Δ^4-tetrone derivative (X) was subjected to the same reaction.

Following the Schubert method,3) 11α,15α-dihydroxyprogesterone (IX), obtained by microbiological oxidation of 11α-hydroxyprogesterone (VIII) with *Calonectoria decora*,*2 was oxidized with chromium trioxide and produced Δ^4-3,11,15,20-tetrone (X), $C_{21}H_{26}O_4$, m.p. 218~220° (UV : λ_{max}^{EtOH} 238 mμ (log ε 4.18), IR $\lambda_{max}^{CH_2Cl_2}$ μ : 5.72, 5.84, 5.98, 6.17, $[\alpha]_D^{24}$ +356.4°), was treated with 0.02*N* methanolic KOH for 18 hours at room temperature, and a crystalline product (VII), $C_{21}H_{26}O_4$, m.p. 217~220° (UV : λ_{max}^{EtOH} 239 mμ (log ε 4.19), IR $\lambda_{max}^{CH_2Cl_2}$ μ: 5.74, 5.84, 5.96, 6.17, $[\alpha]_D^{22}$ +146.2°), was obtained. This substance was assumed to be a Δ^4-tetrone derivative containing the C/D-*cis* fusion and 17α side-chain. Comparison of this compound with Δ^4-tetrone obtained from digiprogenin in the present series of experi-



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*2 Furnished by Centraalbureau Voor Schimmelcultures, Baarn, Hollande.

4) C. Djerassi, L. B. High, J. Fried, E. F. Sabo : J. Am. Chem. Soc., **77**, 3673(1955); C. Djerassi, J. J. Grossnickle, L. B. High : *Ibid.*, **78**, 3166(1956); A. Gubler, Ch. Tamm : Helv. Chim. Acta, **41**, 301(1958); H, Linde, K. Meyer : *Ibid.*, **42**, 807(1959); A. Lardon, H. P. Sigg, T. Reichstein: *Ibid.*, **42**, 1457(1959). Inversion of C/D-*trans* into C/D-*cis* indicates levorotatory contribution.

ments showed the identity of these substances on the bases of the melting point, spectral data, and optical rotation. According to this result, the sites of the secondary hydroxyl group and three keto groups of digiprogenin were confirmed to agree with the presumed positions. The tertiary hydroxyl group was assumed to occupy the C-17 position in view of the conjugate system of anhydrodigiprogenin.

With respect to the conformation, the juncture of C/D rings is most likely to be *trans* in digipronin and γ-digiprogenin, and *cis* in isodigipronin and α-digiprogenin, on the basis of molecular rotations as follows :

$$\begin{array}{llll} \text{digipronin } M_D & \longrightarrow & \text{isodigipronin } M_D & = \Delta M_D \\ -335.4^\circ & \longrightarrow & -376.0^\circ & = -40.6^\circ \end{array}$$

$$\begin{array}{llll} \gamma\text{-digiprogenin } M_D & \longrightarrow & \alpha\text{-digiprogenin } M_D & = \Delta M_D \\ -261.0^\circ & \longrightarrow & -315.0^\circ & = -54.0^\circ \end{array}$$

Verification by chemical method is still to be made. Orientation of the 3-hydroxyl group was considered to be β, analogous to other natural steroids.

From these facts, it seems to be appropriate to assign (I), (II), (III), (IV) and (V) as the respective formulae for digipronin, isodigipronin, γ-digiprogenin, α-digiprogenin, and anhydrodigiprogenin.

Research Laboratory,
Shionogi & Co., Ltd.,
Imafuku, Amagasaki, Hyogo-ken.

Daisuke Satoh (佐藤大助)

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NMR Study of the Liquid Structure of Fatty Acids

The dilution shifts of the proton magnetic resonance in fatty acid-benzene and fatty acid-pyridine mixtures were measured. The fatty acids used in this experiment were acetic, dichloroacetic, propionic, butyric, isobutyric, and isovaleric acids.

Resonance of the Methyl Group

The observed shifts of the fatty acid-benzene mixture are shown in Fig. 1, where dichloroacetic acid (Curve A) and acetic acid (curve B) show larger shift than those of the others, for example, of isobutyric acid (curve C). Consistent with the result on chloroform-benzene mixture reported by Reeves and Schneider,[1] these high field shifts may be interpreted in terms of the π-complex formation between benzene and fatty acid molecule as illustrated in Fig. 2. By considering the values of these shifts, it is known that the strength of the bond between π-electron system and the methyl-hydrogen depends on chemical activity of the methyl group rather than on the molecular size and other steric effects.

In Fig. 3, the observed shifts of the fatty acid-pyridine mixtures are shown, where the active methyl, for example, that of acetic acid (curve A), shows shift to a low field more clearly than that of the less active methyl of butyric acid (curve B). This low field shift will suggest that the methyl-hydrogen locates in the plane of the pyridine ring, near the lone-pair electrons of the nitrogen as $-CH_3\cdots N$. Thus, it is clear from

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1) L. W. Reeves, W. G. Scheider : Can. J. Chem., 35, 251(1957).