UDC 615.711.5:547.918

8. Daisuke Satoh : Studies on Digitalis Glycosides. XII.[*1] Structures of Digipronin and Digiprogenin.[*2]

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In the preceding paper,[*1] it was reported that hydrolysis of digipronin, $C_{28}H_{40}O_9$, a digitanol glycoside isolated from the leaves of *Digitalis purpurea* L., by the Mannich method, using acetonic 0.4% hydrochloric acid at room temperature gave, together with digitalose, three aglycones which were designated α-, β-, and γ-digiprogenin. Of these aglycones, α- and γ-digiprogenins were isomeric and their analysis agreed with $C_{21}H_{28}O_5$, while β-digiprogenin had a molecular formula, $C_{21}H_{26}O_4$, which must have been produced by elimination of water from either of the former aglycones.

Treatment of digipronin by refluxing with 5% hydrochloric acid in 50% ethanol for 1 hour afforded γ-digiprogenin as a main product, while its heating for 6 hours gave nearly equal amounts of α- and β-digiprogenin, γ-isomer being a minor product.

γ-Digiprogenin was isomerized to α-digiprogenin on treatment with either methanolic 0.1% potassium hydroxide solution in the cold or methanolic 4% hydrochloric acid at 70~75°, although the rate of isomerization was slow in the latter case. Refluxing of α- or γ-digiprogenin with 5% hydrochloric acid in 50% ethanol for 8 hours afforded β-digiprogenin together with a small amount of α-digiprogenin.

These results indicate that γ-digiprogenin is a genuine aglycone of digipronin, and α-digiprogenin its isomerization product, while β-digiprogenin is a dehydrated compound of α-digiprogenin.

Further evidence for this inference was provided by the inversion of digipronin by the action of methanolic 0.1% potassium hydroxide solution to isodigipronin which had the same molecular formula, $C_{28}H_{40}O_9$, as the parent glycoside, but quite different from the starting material in its physical properties.

As was expected, isodigipronin did not give any γ-digiprogenin on hydrolysis for a short time, α-digiprogenin being the main product.

The correlation of isomerizations, hydrolyses, and dehydration of digipronin and digiprogenin is shown in Chart 1.

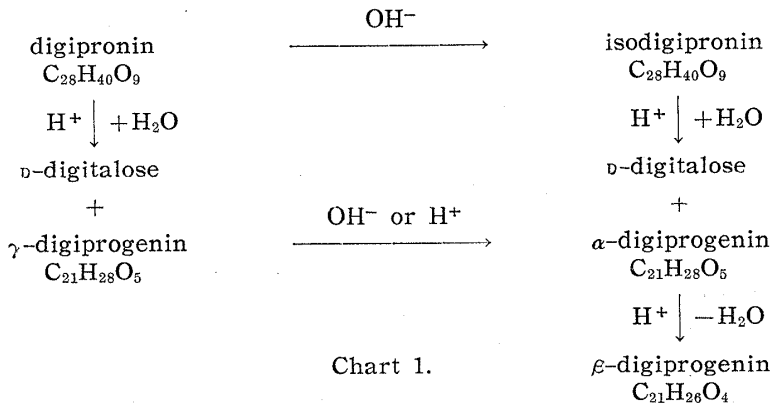

Chart 1.

These digiprogenins were assumed to be C_{21}-steroids on the basis reported in the preceding paper.[*1] Functions of the oxygen atoms were clarified from the following experiments.

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*1 Part XI. D. Satoh, H. Ishii, Y. Oyama, T. Okumura : This Bulletin, **10**, 37 (1962).
*2 For a preliminary report of this investigation see D. Satoh : *Ibid.*, 8, 270 (1960).
*3 Fukushima-ku, Osaka (佐藤大助).

The absorption bands in the infrared spectrum of γ-digiprogenin at 2.86, 3.10, 5.71, 5,84, and 5.92 μ suggested the presence of two hydroxyl and three carbonyl groups in its molecule. Acetylation of γ-digiprogenin with acetic anhydride and pyridine gave a monoacetate, $C_{23}H_{30}O_6$, which still exhibited a hydroxyl band in its infrared spectrum. These results indicated that one of the two hydroxyl groups was acetylable and presumed to be located at C-3 position, analogous to other steroidal aglycones, and the remaining one was tertiary. From the wave lengths of the absorption bands it seemed likely that one of the three carbonyl groups belonged to a five-membered ring ketone, another one to a six-membered ring ketone, and the remaining one to a methyl ketone in the side chain at 17-position, a presumption which was in accord with the band at 7.34 μ.[1]

γ-Digiprogenin gave a dioxime, $C_{21}H_{30}O_5N_2$, which exhibited a band at 5.88 μ of a hindered six-membered ring ketone, probably located at 11-position. A positive tetranitromethane test and ultraviolet absorption at 205 mμ (log ε 3.61) showed the presence of a trisubstituted double bond in γ-digiprogenin.

Oppenauer oxidation of this aglycone gave a Δ^4-3-oxo compound (UV : λ_{max}^{EtOH} 239 mμ; IR $\lambda_{max}^{CHCl_3}$ μ : 6.00, 6.17) but treatment with manganese dioxide did not give any oxidation product. These results indicate the presence of a Δ^5-3-hydroxy function. The above fact that the link between digitalose and γ-digiprogenin in digipronin could readily be split on hydrolysis supports this view.[2]

The infrared absorption of α-digiprogenin at 2.75, 3.00, 5.76, and 5.86 μ, and the fact that the absorption intensity at 5.86 μ was nearly twice as strong as that at 5.76 μ suggest the presence of two hydroxyl and three carbonyl groups in its molecule, analogous to γ-digiprogenin.

α-Digiprogenin gave a monoacetate, $C_{23}H_{30}O_6$, with acetic anhydride and pyridine, whose infrared spectrum still exhibited a hydroxyl band. Therefore, it seemed that one of the two hydroxyl groups was acetylable and the other one tertiary. The carbonyl band at 5.76 μ of α-digiprogenin was presumed to belong to a five-membered ring ketone and the one at 5.86 μ seemed likely to belong to methyl ketone in the side chain at 17-position, as confirmed by the presence of a band at 7.33 μ, analogous to γ-digiprogenin.

α-Digiprogenin gave a dioxime, $C_{21}H_{30}O_5N_2$, which exhibited a band at 5.93 μ for a hindered and associated six-membered ring ketone in its infrared spectrum. The ultraviolet absorption of α-digiprogenin at 203 mμ (log ε 3.63) showed the presence of a trisubstituted double bond in its molecule. Oppenauer oxidation of α-digiprogenin gave a Δ^4-3-oxo compound but the Rosenheim test was negative. These facts indicated the presence of a Δ^5-3-hydroxy function in α-digiprogenin molecule.

From these results the functions of the five oxygen atoms in α- and γ-digiprogenin were clarified and it was presumed that any change of hydroxyl and carbonyl group did not take place during the isomerization of γ-digiprogenin to α-digiprogenin, and consequently this isomerization was considered to be steric.

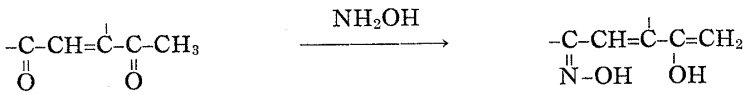
β-Digiprogenin, a monoanhydro compound of α-digiprogenin, gave a monoacetate, $C_{23}H_{28}O_5$, which did not show the band for a hydroxyl group in its infrared spectrum and this indicates that β-digiprogenin is a product formed by elimination of the tertiary hydroxyl group from α-digiprogenin.

The ultraviolet spectrum of β-digiprogenin showed a maximum absorption at 239 mμ (log ε 4.02) and the infrared spectrum exhibited three carbonyl bands at 5.85, 5.92, and 5.96 μ, together with a band for a conjugated double bond at 6.23 μ. Comparison of the absorption spectra of β-digiprogenin with those of α-digiprogenin suggested that the double bond in β-digiprogenin newly introduced by dehydration of α-digiprogenin was

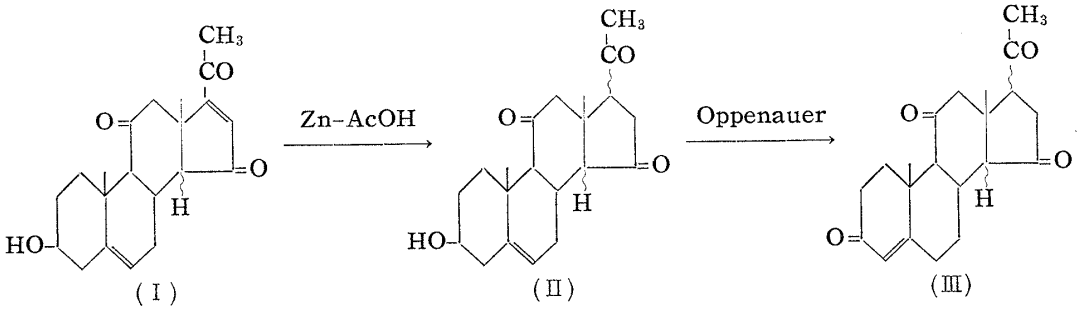
1) R. N. Jones, F. Herling : J. Org. Chem., **19**, 1252 (1954).
2) Ch. Tamm : Fortschr. Chem. org. Naturstoffe, **30**, 150 (1956). Springer-Verlag, Wien.

conjugated to both five-membered ring ketone and C-20 ketone in the side chain forming a monoëne-dione. Consequently it was presumed that the structure of β-digiprogenin is 3-hydroxypregna-5,16-diene-11,15,20-trione (I) and the tertiary hydroxyl group in α- and γ-digiprogenin is located at 17-position.

β-Digiprogenin gave a monoxime, $C_{21}H_{27}O_4N$, and a monosemicarbazone, $C_{22}H_{29}O_4N_3$, whose ultraviolet spectra bands had higher extinctions in a longer wave lengths than those of parent β-digiprogenin, as in the case of oximes and semicarbazones of dienones. This could be explained by assuming that one of the carbonyl groups in the ene-dione was enolized and only the other one formed an oxime as follows :



The absorption bands in the infrared spectrum of this oxime at 6.18 μ and 6.32 μ due to the conjugated double bond and a band at 11.32 μ due to the vinyl group supported this presumption.



β-Digiprogenin was readily reduced by acetic acid and zinc in the manner as applied to other ene-dione compounds and gave a dihydro derivative, $C_{21}H_{28}O_4$, whose absorptions (UV : λ_{max}^{EtOH} 296 mμ (log ε 1.93), IR λ_{max}^{KBr} μ : 5.74, 5.84) indicated saturation of the double bond in the ene-dione grouping of the parent compound. This dihydro-β-digiprogenin gave a dioxime, $C_{21}H_{30}O_4N_2$, which exhibited an absorption in the ultraviolet spectrum at 299 mμ (log ε 1.60), no bathochromic shift being observed by formation of the oxime.

On the basis of these results, dihydro-β-digiprogenin was presumed to be 3-hydroxy-pregn-5-ene-11,15,20-trione (II).

Oppenauer oxidation of dihydro-β-digiprogenin (II) gave a Δ^4-3-oxo compound (III), $C_{21}H_{26}O_4$, 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, except for rotation, were comparable to those of pregn-4-ene-3,11,15,20-tetrone (VI), $C_{21}H_{26}O_4$, m.p. 217~225°; UV : λ_{max}^{EtOH} 238 mμ (log ε 4,18); IR $\lambda_{max}^{H_2\ l_2}$ μ : 5.71, 5.83, 5.95, 6.15; $[\alpha]_D^{24}$ +325°, which had been prepared from 11α-hydroxyprogesterone (IV) by Schubert, *et al.*[3] Mixed fusion of the two compounds showed a marked depression of the melting point and the infrared spectra were not identical as shown in Fig. 1. Therefore, it was considered that the two compounds might be stereo-isomers.

Past literature[4,5] reported that pregnane-15,20-dione derivatives having C/D-*cis* junc-

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

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); K. Tsuda, T. Asai, E. Ohki, A. Tanaka, M. Hattori : This Bulletin, **6**, 387 (1958); H. Linde, K. Meyer : Helv. Chim. Acta, **42**, 807 (1959); A. Lardon, H.P. Sigg, T. Reichstein : *Ibid.*, **42**, 1457 (1959); S. Bernstein, M. Heller, L.I. Eldman, W.S. Allen, R.H. Blank, C.E. Linden : J. Am. Chem. Soc., **82**, 3685 (1960).

5) J. Fried, *et al.* : Recent Progr. in Hormone Research, **11**, 158 (1955).

ture are more stable than C/D-*trans* isomers and that the latter is readily inverted to the former by treatment with dilute alkali or acid.

Since the Δ^4-3-oxo compound (III) derived from β-digiprogenin was not changed on attempted isomerization with either alkali or acid, it was probable that the C/D-ring juncture in this compound is *cis*. On the other hand, the tetrone (VI) of Schubert has been assigned C/D-*trans* juncture and therefore it was conceivable that this could be inverted by the procedure mentioned above to a compound having C/D-*cis* juncture which might be identical with the Δ^4-3-oxo compound (III). Accordingly the inversion of (VI) was carried out as follows : Pregn-4-ene-3,11,15,20-tetrone (VI) was prepared from 11α-hydroxyprogesterone (IV) through 11α,15α-dihydroxyprogesterone (V) by the Schubert method[3] and isomerized by treatment with methanolic potassium hydroxide or hydrochloric acid. The product, $C_{21}H_{26}O_4$, isolated from the alkaline solution, melted at 218~220°; 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°, and was identical in all respects with the Δ^4-3-oxo compound (III) derived from β-digiprogenin. The infrared spectra of this compound from two sources are reproduced in Fig. 1.

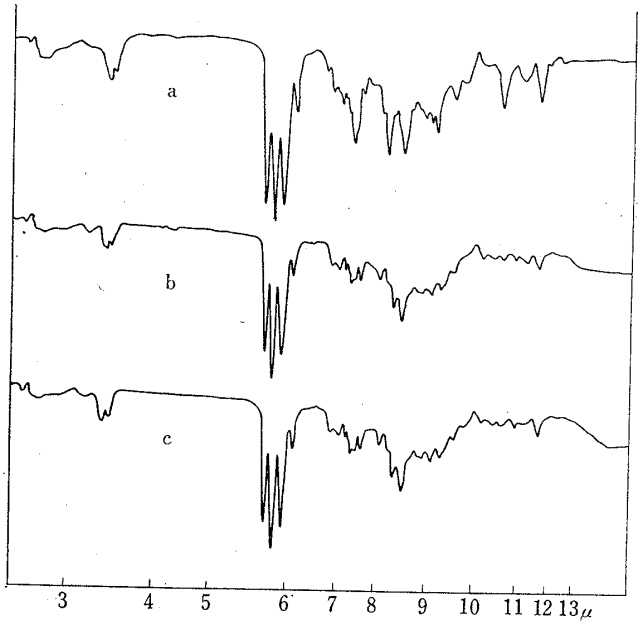
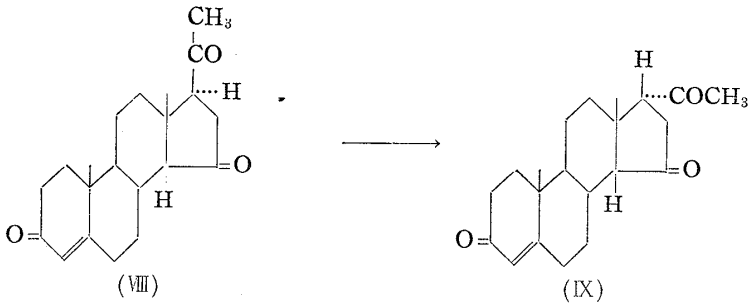


Fig. 1. Infrared Absorption Spectra

a : Pregn-4-ene-3,11,15,20-tetrone (VI)
b : 14β,17α-Pregn-4-ene-3,11,15,20-tetrone (VII) isomerized from (VI)
c : Δ^4-3-Oxo compound (III) derived from β-digiprogenin (XIV)

Previously, Fried, *et al.*[5] assigned to the compound obtained by isomerization of 15-oxoprogesterone (VIII) by alkali, structure (IX), in which, together with inversion of C/D-ring juncture, the side chain at 17-position had been epimerized from β- to α-configuration.



In view of this result, it is highly probable that in the isomerization product of Schubert's compound not only C/D-ring juncture but also the side chain underwent epimerization. Thus, the Δ^4-3-oxo compound derived from β-digiprogenin can be assigned the structure, 14β,17α-pregn-4-ene-3,11,15,20-tetrone (VII).

The configuration of dihydro-β-digiprogenin (XV) is also considered to be 14β,17α-type since β-digiprogenin can be derived from α-digiprogenin which has a stable configuration with C/D-*cis* juncture and hydrogenation of the double bond between 16- and 17-position must have taken place from the β-side.[6]

It was reported[4,5] that the inversion of C/D-*trans* juncture to C/D-*cis* juncture gave negative molecular rotation contribution. In the case of inversion of γ-digiprogenin to α-digiprogenin a similar contribution was observed.

γ-digiprogenin M_D	$\longrightarrow$	α-digiprogenin M_D	=	ΔM_D
$-261°$		$-315°$		$-54°$

This result supports the assumption that the juncture of C/D-ring in γ-digiprogenin is *trans* and that of α-digiprogenin *cis*.

The side chain at 17-position in α- and γ-digiprogenin presumably occupies β-orientation analogous to the other natural steroids. Consequently the tertiary hydroxyl group at the same position must be α oriented. The orientation of the hydroxyl group at 3-position is most likely to be β in view of the other natural Δ^5-3-hydroxy steroids.

On the basis of these considerations, it is most appropriate to assign the structures of 3β,17α-dihydroxy-14β-pregn-5-ene-11,15,20-trione (XIII), 3β-hydroxy-14β-pregna-5,16-diene-11,15,20-trione (XIV), and 3β,17α-dihydroxypregn-5-ene-11,15,20-trione (XII) to α-,

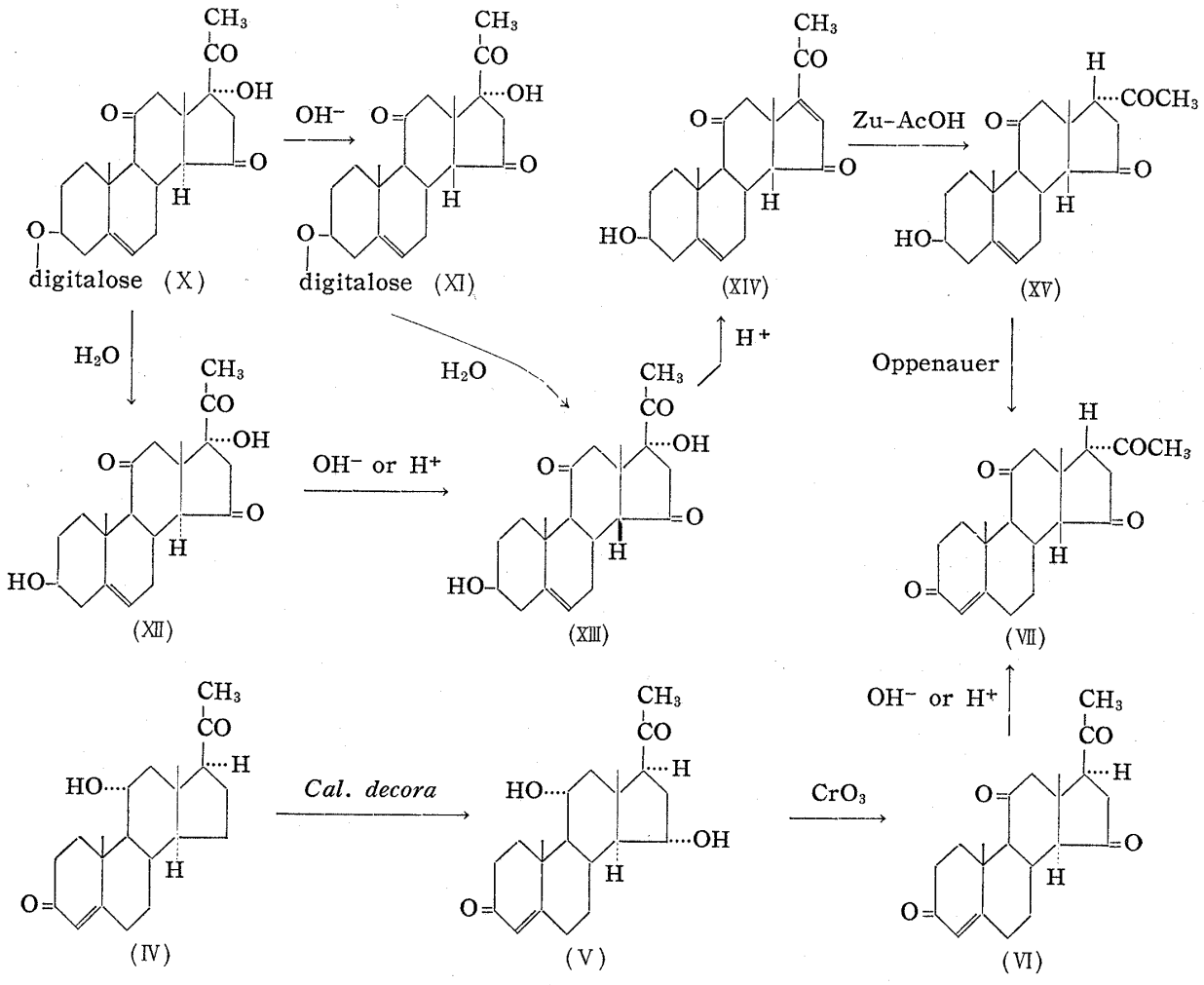


Chart 2.

6) L. Ruzicka, Pl. A. Plattner, H. Heusser, K. Meier : Helv. Chim. Acta, **30**, 1342 (1947); D. Satoh, H. Ishii : Yakugaku Zasshi, **80**, 1143 (1960).

β-, and γ-digiprogenin respectively. Digipronin and isodigipronin are accordingly represented by the formulae (X) and (XI), respectively.

This is the first instance that the pregnenolone skeleton has been established in some of the digitanol glycosides.

Experimental

Hydrolysis of Digiprogenin (X)——a) Under drastic condition : A mixture of 1 g. of digipronin (X) and 100 cc. of 5% HCl (50% EtOH) was refluxed for 6 hr. on a water bath and the pale yellowish brown solution was concentrated in a reduced pressure to remove EtOH. The crude aglycone (620 mg.) that precipitated was collected and triturated with hot AcOEt. The insoluble residue was recrystallized from MeOH to α-digiprogenin (XIII) as colorless prisms, m.p. 242~244°. Yield, 230 mg. $[\alpha]_D^{31}$ −87.5°(c=1.010, $CHCl_3$-MeOH (1:1)). UV : λ_{max}^{EtOH} 296 mμ (log ε 1.90). *Anal.* Calcd. for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found : C, 70.04; H, 7.86.

Concentration of the filtrate of AcOEt from α-digiprogenin gave crude β-digiprogenin (XIV) which was crystallized from a mixture of AcOEt and benzene as pale yellowish brown needles, m.p. 192~194°. Yield, 190 mg. $[\alpha]_D^{31}$ +2.7°(c=0.802, $CHCl_3$-MeOH (1:1)). UV : λ_{max}^{EtOH} 239 mμ (log ε 4.02). *Anal.* Calcd. for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66; mol. wt., 342.42. Found : C, 73.72; H, 7.71; mol. wt. (Rast), 354.97.

The residue from the $CHCl_3$ extraction of the aqueous filtrate from the crude aglycone was recrystallized from MeOH to γ-digiprogenin (XII) as colorless needles, m.p. 250~253°. Yield, 20 mg. $[\alpha]_D^{31}$ −72.5°(c=0.967, $CHCl_3$-MeOH (1:1)). UV : λ_{max}^{EtOH} 300 mμ (log ε 1.90). *Anal.* Calcd. for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found : C, 70.26; H, 7.95.

b) Under mild condition : Refluxing of 300 mg. of digipronin (X) with 300 cc. of 5% HCl (50% EtOH) for 1 hr. completed hydrolysis and gave 120 mg. of γ-digiprogenin (XII) of m.p. 249~253° as the main product after treatment as above.

β-Digiprogenin (XIV) from α-Digiprogenin (XIII)——A mixture of 50 mg. of α-digiprogenin (XIII) and 5 cc. of 5% HCl (50% EtOH) was refluxed for 8 hr., the resulting solution was concentrated, and the transformed product thereby obtained was recrystallized from AcOEt to pale yellowish brown needles, m.p. 191~193°. Yield, 32 mg. Mixed fusion with β-digiprogenin (XIV) did not show any depression of the melting point.

β-Digiprogenin (XIV) from γ-Digiprogenin (XII)——A mixture of 50 mg. of γ-digiprogenin (XII) and 5 cc. of 5% HCl (50% EtOH) was treated as in the case of α-digiprogenin to afford 30 mg. of β-digiprogenin (XIV), m.p. 190~193°.

Isodigipronin (XI) from Digipronin (X)——A solution of 100 mg. of digipronin (X) dissolved in 10 cc. of a mixture of MeOH and $CHCl_3$(1:1) containing 0.2 cc. of 5% KOH in MeOH was allowed to stand at room temperature (20~23°) for 18 hr. in N_2 atmosphere, 1 cc. of H_2O was added, and the mixture was concentrated in a reduced pressure after neutralization. The white precipitate that deposited was collected on a filter and recrystallized from a mixture of MeOH and $CHCl_3$(1:1) to isodigipronin (XI) as colorless fine needles, m.p. 296~298°. Yield, 70 mg. $[\alpha]_D^{18}$ −72.3°(c=0.855, pyridine). UV : λ_{max}^{EtOH} 298 mμ (log ε 1,91). *Anal.* Calcd. for $C_{28}H_{40}O_9$: C, 64.59; H, 7.74. Found: C, 64.80; H, 7.63.

Hydrolysis of Isodigipronin (XI)——A mixture of 50 mg. of isodigipronin (XI) and 5 cc. of 5% HCl (50% EtOH) was refluxed for 1 hr. on a water bath and the resulting solution was treated analogously to the hydrolysis of digipronin to give α-digiprogenin (XIII), m.p. 239~242°, as the main product. Yield, 21 mg.

α-Digiprogenin (XIII) from γ-Digiprogenin (XII)——a) Alkali method : A solution of 50 mg. of γ-digiprogenin (XII) dissolved in 10 cc. of MeOH, containing 0.2 cc. of 5% KOH in MeOH was allowed to stand for 18 hr. at room temperature (20~23°) in N_2 atmosphere, 2 cc. of H_2O was added, and the solution was concentrated in a reduced pressure after neutralization. The deposited precipitate was recrystallized from MeOH to colorless prisms, m.p. 240~243°. Yield, 35 mg. Mixed fusion with α-digiprogenin (XIII), m.p. 240~244°, melted at 240~243°.

b) Acid method : A solution of 50 mg. of γ-digiprogenin (XII) in 20 cc. of MeOH containing 2 cc. of conc. HCl was heated at 70~75° in a water bath for 2 hr., 10 cc. of H_2O was added, the solution was neutralized with dilute alkali, and MeOH was evaporated *in vacuo*. The precipitate that deposited was collected by filtration and recrystallized from MeOH to colorless prisms, m.p. 234~239°. Yield, 30 mg. Mixed fusion with α-digiprogenin (XIII) melted at 236~241°, but that with the starting material melted at 213~225°.

Alkali Treatment of α-Digiprogenin (XIII)——A solution of 50 mg. of α-digiprogenin (XIII) dissolved in 10 cc. of MeOH, containing 0.2 cc. of 5% KOH in MeOH, was allowed to stand for 18 hr. at room temperature and the solution was treated as above, from which 37 mg. of the starting compounds (XIII) was recovered as colorless prisms, m.p. 241~244°.

α-Digiprogenin Monoacetate——A solution of 200 mg. of α-digiprogenin in a mixture of 2 cc. of pyridine and 1 cc. of Ac_2O was allowed to stand overnight at room temperature. The solution was concentrated in a reduced pressure and diluted with H_2O to give a crude acetate which was recrystallized from a mixture of MeOH and $CHCl_3$(1:1) to α-digiprogenin monoacetate as colorless needles, m.p. 258~261°. *Anal.* Calcd. for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51; $COCH_3$, 10.69. Found : C, 68.95; H, 7.68; $COCH_3$, 10.64.

β-Digiprogenin Monoacetate——A solution of 50 mg. of β-digiprogenin in a mixture of 2 cc. of pyridine and 1 cc. of Ac_2O was allowed to stand overnight at room temperature. The reaction mixture was treated in a usual way to give a crude acetate which was recrystallized from MeOH to β-digiprogenin monoacetate as pale yellow needles, m.p. 168~170°. *Anal.* Calcd. for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34; $COCH_3$, 11.20. Found : C, 72.19; H, 7.39; $COCH_3$, 11.51.

γ-Digiprogenin Monoacetate——Crude acetate obtained from 100 mg. of γ-digiprogenin, 2 cc. of pyridine, and 1 cc. of Ac_2O was recrystallized from a mixture of MeOH and $CHCl_3$(1:1) to γ-digiprogenin monoacetate as colorless needles, m.p. 247~250°. *Anal.* Calcd. for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51; $COCH_3$, 10.69. Found : C, 68.73; H, 7.53; $COCH_3$, 11.04.

α-Digiprogenin Dioxime——To a solution of 40 mg. of α-digiprogenin in 25 cc. of MeOH, a solution of 100 mg. of $NH_2OH \cdot HCl$ and 200 mg. of AcONa in 0.2 cc. of H_2O was added and the mixture was refluxed for 3 hr. The crude product that deposited after dilution with H_2O was collected on a filter and recrystallized from MeOH to α-digiprogenin dioxime as colorless needles, m.p. 280~283° (decomp.). *Anal.* Calcd. for $C_{21}H_{30}O_5N_2$: C, 64.59; H, 7.74; N, 7.17. Found : C, 64.29; H, 8.02; N, 7.25.

β-Digiprogenin Monoxime——To a solution of 50 mg. of β-digiprogenin in 25 cc. of MeOH, a solution of 120 mg. of $NH_2OH \cdot HCl$ and 230 mg. of AcONa in 0.2 cc. of H_2O was added and the mixture was refluxed for 3 hr. The crude product was recrystallized from MeOH to ε-digiprogenin monoxime as colorless needles, m.p. 278~280°(decomp.). UV : λ_{max}^{EtOH} 273 mμ (log ε 4.22). *Anal.* Calcd. for $C_{21}H_{27}O_4N$: C, 70.56; H, 7.61; N, 3.92. Found : C, 70.35; H, 7.86; N, 4.25.

γ-Digiprogenin Dioxime——The crude oxime, obtained from 50 mg. of γ-digiprogenin by a method similar to the formation of ε-digiprogenin oxime was recrystallized from MeOH to γ-digiprogenin dioxime as colorless needles, m.p. 237~240°(decomp.). *Anal.* Calcd. for $C_{21}H_{30}O_5N_2$: C, 64.59; H, 7.74; N, 7.17. Found : C, 64.38; H, 7.96; N, 7.16.

β-Digiprogenin Monosemicarbazone——A solution of 50 mg. of β-digiprogenin in 2.5 cc. of MeOH was refluxed for 3.5 hr. with 180 mg. of semicarbazide hydrochloride and 230 mg. of AcONa in 0.4 cc. of H_2O. The crude product obtained after concentration and dilution with H_2O was recrystallized from MeOH to ε-digiprogenin monosemicarbazone as colorless needles, m.p. 288~290°(decomp.). UV : λ_{max}^{EtOH} 309 mμ (log ε 4.39). *Anal.* Calcd. for $C_{22}H_{29}O_4N_3$: C, 66.14; H, 7.32; N, 10.52. Found: C, 65.83; H, 7.49; N, 10.46.

Dihydro-β-digiprogenin (XV)——To a solution of 200 mg. of β-digiprogenin (XIV) in 20 cc. of AcOH, 1 g. of fine Zn granules was added and the mixture was stirred at 110~120° for 40 min. in an oil bath. Excess of Zn was filtered off and washed with AcOH. The solid resulting from evaporation of AcOH in a reduced pressure was extracted with $CHCl_3$, washed with H_2O, and dried over anhyd. Na_2SO_4. The residue from the $CHCl_3$ extract was recrystallized from AcOEt to dihydro-β-digiprogenin (XV) as colorless prisms, m.p. 203~204°. Yield, 120 mg. *Anal.* Calcd. for $C_{21}H_{28}O_4$: 73.22; H, 8.19. Found : C, 73.48; H, 8.39.

Dihydro-β-digiprogenin Monoacetate——The crude acetate obtained from 50 mg. of dihydro-β-digiprogenin (XV) by acetylation with Ac_2O and pyridine was recrystallized from a mixture of AcOEt and hexane to dihydro-β-digiprogenin monoacetate as colorless plates, m.p. 187~190°. *Anal.* Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82; $COCH_3$, 11.14. Found : C, 71.72; H, 8.04; N, 11.53.

Dihydro-β-digiprogenin Dioxime——The crude oxime obtained from 50 mg. of dihydro-β-digiprogenin (XV) in a manner analogous to β-digiprogenin was recrystallized from MeOH to dihydro-β-digiprogenin dioxime as colorless needles, m.p. 255~257°(decomp.). *Anal.* Calcd. for $C_{21}H_{30}O_4N_2$: C, 67.35; H, 8.08; N, 7.28. Found : C, 67.56; H, 8.22; N, 6.93.

MnO_2 Oxidation of γ-Digiprogenin (XII)——To a solution of 30 mg. of γ-digiprogenin in 6 cc. of $CHCl_3$, 300 mg. of MnO_2 prepared by the Rosenkranz method[7] was added and the mixture was stirred for 4 hr. at room temperature. The excess of MnO_2 was filtered off and washed with $CHCl_3$. Evaporation of $CHCl_3$ gave 25 mg. of the starting material as colorless needles, m.p. 248~252°.

Oppenauer Oxidation of α-Digiprogenin (XIII) (Preliminary test)——After heating a mixture of 10 mg. of α-digiprogenin, 0.5 cc. of cyclohexanone, and 2.4 cc. of toluene (both redistilled before use) at 140~150° in an oil bath in order to dry the system by azeotropic distillation, 50 mg. of (iso-PrO)$_3$Al was added and stirred for 1.5 hr. at the same temperature. The reaction mixture was treated in a usual manner to give a crude oxidation product as a slightly colored gum. UV : λ_{max}^{EtOH} 239 mμ. IR $\lambda_{max}^{CHCl_3}$ μ : 5.73, 5.85, 6.00, 6.17.

7) O. Mancera, G. Rosenkranz, F. Sondheimer : J. Chem. Soc., **1953**, 2189.

Oppenauer Oxidation of Dihydro-β-Digiprogenin (XV)——A mixture of 80 mg. of dihydro-β-digiprogenin (XV), 0.8 cc. of cyclohexanone, and 4 cc. of toluene (both redistilled before use) was stirred at 145~150° in an oil bath in order to dry the system by azeotropic distillation, 80 mg. of $(iso\text{-}PrO)_3Al$ was added, and the mixture was stirred for 1 hr. at the same temperature with protection from moisture. A saturated aqueous solution of potassium sodium tartarate was added to the reaction mixture to dissolve the precipitate of aluminium salt and extracted with $CHCl_3$. A residue from the $CHCl_3$ extract was submitted to steam distillation to remove cyclohexanone, extracted with $CHCl_3$ again, and purified by chromatography over alumina. The residue was recrystallized from MeOH to Δ^4-3-oxo compound as colorless prisms, m.p. 218~220°. $[\alpha]_D^{32}$ +145.9°(c=0.470, $CHCl_3$). The absorption bands of this product are described in the main text. Yield, 42 mg. Admixture with pregn-4-ene-3,11,15,20-tetrone (VI), m.p. 218~220°, kindly supplied by Dr. Schubert, showed a depression of m.p. to 172~185°. *Anal.* Calcd. for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66. Found: C, 73.96; H, 7.50.

Treatment of Δ^4-3-Oxo Compound with Alkali——A solution of 30 mg. of Δ^4-3-oxo compound derived from dihydro-β-digiprogenin in 6 cc. of 0.1% KOH in MeOH was allowed to stand overnight at room temperature in N_2 atmosphere. The alkaline solution was neutralized, concentrated in a reduced pressure, and extracted with $CHCl_3$. The extract was washed with H_2O and dried over anhyd. Na_2SO_4. The residue from $CHCl_3$ was recrystallized from MeOH to 25 mg. of the starting material as colorless prisms, m.p. 218~220°.

Pregn-4-ene-3,11,15,20-tetrone (VI) from 11α,15α-Dihydroxyprogesterone (V)——To a solution of 100 mg. of 11α,15α-dihydroxyprogesterone (V), prepared from 11α-hydroxyprogesterone (IV) by microbiological oxidation with *Calonectoria decora* following the Schubert method,[3] in 1 cc. of 80% AcOH, a CrO_3 solution (77 mg. of CrO_3 in 0.5 cc. of AcOH) was added at 15~20° and the mixture was stirred for 4.5 hr. at the same temperature. Excess of CrO_3 was reduced with MeOH, the mixture was neutralized with 10% Na_2CO_3 solution to weak acidity (pH 4.6), and extracted with $CHCl_3$. The extract was washed with H_2O and dried over anhyd. Na_2SO_4. The residue from $CHCl_3$ extract was recrystallized from MeOH to pregn-4-ene-3,11,15,20-tetrone (VI) as colorless prisms, m.p. 218~220°. Yield, 52 mg. $[\alpha]_D^{24}$ +356.4°(c=1.028, $CHCl_3$). 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. Admixture with the sample kindly supplied by Dr. Schubert did not show any depression of the melting point.

Isomerization of Pregn-4-ene-3,11,15,20-tetrone (VI) to 14β,17α-Pregn-4-ene-3,11,15,20-tetrone (VII)——a) Alkali method (a): A solution of 40 mg. of pregn-4-ene-3,11,15,20-tetrone (VI) in 8 cc. of 0.1% KOH in MeOH was allowed to stand for 18 hr. at room temperature in N_2 atmosphere. The alkaline solution was neutralized, concentrated in a reduced pressure, and extracted with $CHCl_3$. The extract was washed with H_2O, dried over anhyd. Na_2SO_4, and the residue from $CHCl_3$ extract was recrystallized from MeOH to 14β,17α-pregn-4-ene-3,11,15,20-tetrone (VII) as colorless prisms, m.p. 218~220°. Yield, 14 mg. $[\alpha]_D^{22}$ +146.2°(c=0.585, $CHCl_3$). Absorption bands of this product are described in the main text. *Anal.* Calcd. for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66. Found: C, 74.05; H, 7.68.

b) Alkali method (b): A solution of 20 mg. of pregn-4-ene-3,11,15,20-tetrone (VI) in 3 cc. of 3% KOH in MeOH was heated in a water bath at 75~80° for 1 hr. in N_2 atmosphere. The alkaline solution was treated in the manner described above to give 14β,17α-pregn-4-ene-3,11,15,20-tetrone (VII) as colorless prisms, m.p. 217~220°. Yield, 5 mg.

c) Acid method: A solution of 40 mg. of (VI) in 10 cc. of MeOH containing 1 cc. of conc. HCl was heated at 70~75° for 2.5 hr. in a water bath and then treated in the manner analogous to the alkali method to give (VII) as colorless prisms, m.p. 218~220°. Yield, 16 mg.

Identification of Δ^4-3-Oxo Compound derived from β-Digiprogenin with 14β,17α-Pregn-4-ene-3,11,15,20-tetrone (VII)——Comparison of absorption spectra and optical rotations are described in the main text.

	Δ^4-3-Oxo compd. derived from β-Digiprogenin	14β,17α-Pregn-4-ene-3,11,15,20-tetrone	Mixture
m.p. (°C)	218~220	218~220	218~220
Rf*	0.76	0.76	0.76

* MeCOEt-xylene (1:1) saturated with $HCONH_2$, descending method, at 23~25°.

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Summary

Digipronin, a digitanol glycoside, and its aglycone, γ-digiprogenin, were respectively converted to isodigipronin and its aglycone, α-digiprogenin, by treatment with dilute alkali or acid. On refluxing with acid, α-digiprogenin lost an element of water and formed β-digiprogenin. The structure of the Δ^4-3-oxo compound, obtained from β-digiprogenin by reduction with acetic acid and zinc dust followed by Oppenauer oxidation, was established as 14β,17α-pregn-4-ene-3,11,15,20-tetrone by comparison with the product of isomerization of pregn-4-ene-3,11,15,20-tetrone with alkali or acid. Consequently, the structure of β-digiprogenin was presumed as 3β-hydroxy-14β-pregna-5,16-diene-11,15,20-trione and the tertiary hydroxyl group in α- and γ-digiprogenin would be located at 17-position. In view of the stability of α-digiprogenin to dilute alkali or acid and its negative contribution to optical rotation compared to γ-digiprogenin, it would be appropriate to give the structure of 3β,17α-dihydroxy-14β-pregn-5-ene-11,15,20-trione and 3β,17α-dihydroxypregn-5-ene-11,15,20-trione to α- and γ-digiprogenin, respectively. Digipronin is a monodigitaloside of γ-digiprogenin.

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9. Masatomo Hamana and Motoyoshi Yamazaki: Studies on Tertiary Amine Oxides. X.*1 Alkaline Ferricyanide Oxidation of Some Aromatic N-Oxides.

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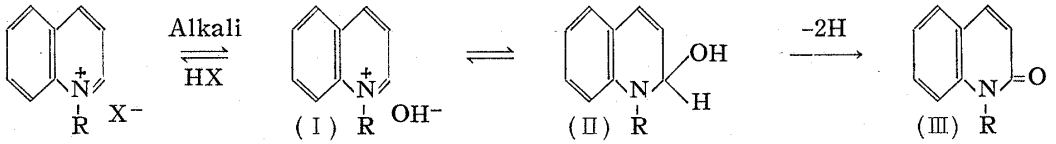
It is well known that quaternary salts of aromatic nitrogen heterocycles, such as N-substituted pyridinium and quinolinium salts, are oxidized by alkaline ferricyanide to N-substituted α-oxo compounds.[1,2] This reaction is generally assumed,[1,2] for example in a quinoline series, to proceed through isomerization of the corresponding quaternary hydroxide (I) to a pseudobase (II), which is subsequently dehydrogenated by ferricyanide to an 2(1*H*)-quinolone (III).



R=alkyl or aryl X=acid anion

In a previous paper of this series,[3] it was shown that 1-benzoyloxy-2-hydroxy-1,2-dihydroquinoline (IV) was isolated as an unstable intermediate in the reaction of quinoline 1-oxide with benzoyl chloride and sodium carbonate solution, which was derived to

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*2 Katakasu, Fukuoka (浜名政和, 山崎企善).
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