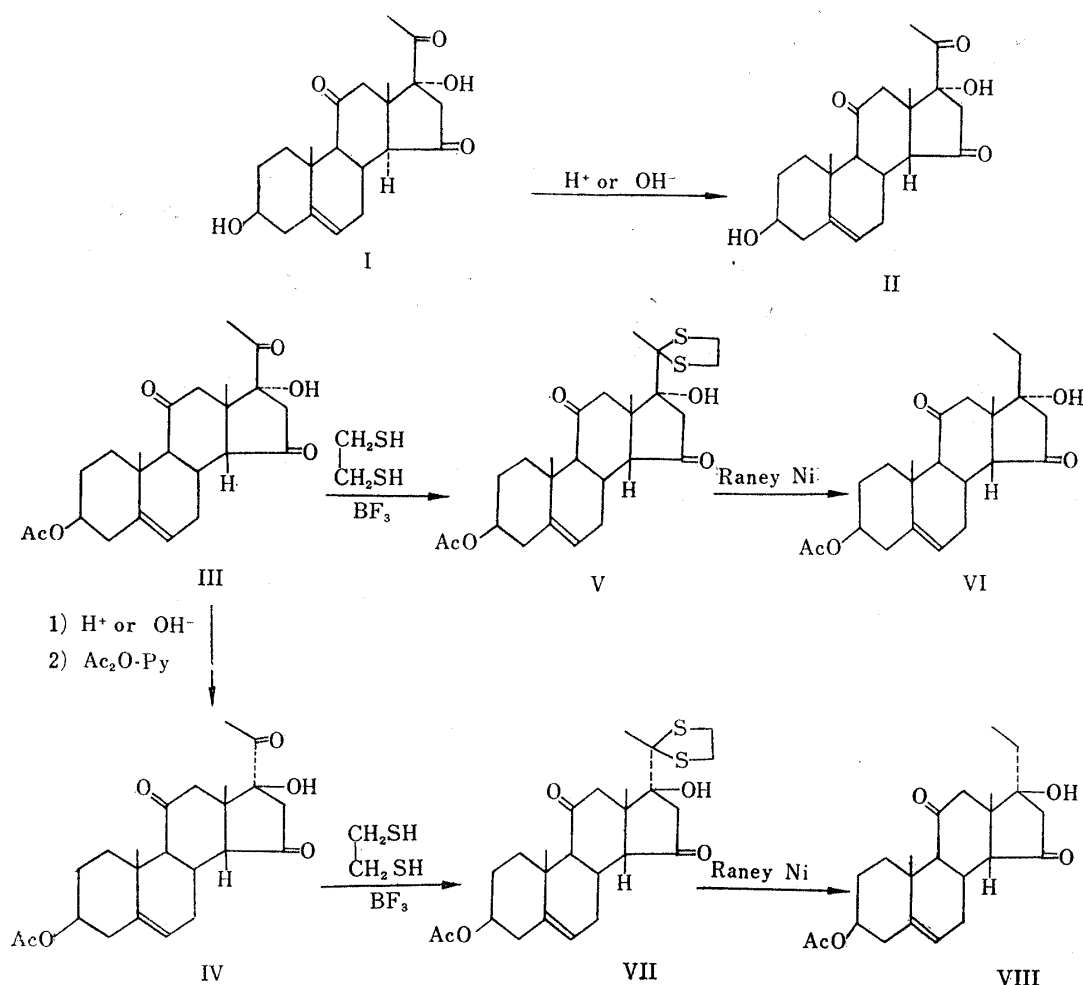


Studies on Digitalis Glycosides. The Configuration of Digiprogenin

In a previous paper,¹⁾ one of the authors proposed tentatively the formula (I) of $14\alpha,17\beta$ -configuration for γ -digiprogenin from analogy to the natural steroids known at that time, and assumed that the epimerization of γ -digiprogenin to α -digiprogenin (II) occurred at C-14 position.

In the later studies, the nuclear magnetic resonance (NMR)*¹ and optical rotatory dispersion (ORD)*¹ spectroscopies of γ - and α -digiprogenin acetates gave the following data :

	γ -Digiprogenin acetate		α -Digiprogenin acetate
NMR signal	18-CH ₃	8.89 τ	8.66 τ
	19-CH ₃	8.89 τ	8.83 τ
ORD [ϕ]		-2950 (335 m μ)	-5640 (337 m μ)
		+4630 (297 m μ)	+6640 (268 m μ)
a		-76	-123



*¹ The NMR spectra and ORD were examined by Dr. K. Tori and Dr. K. Kuriyama of this laboratory, respectively.

1) D. Satoh : This Bulletin, 10, 43 (1962).

According to Zürcher,²⁾ the expected chemical shifts of the 18-CH₃ and 19-CH₃ groups in the NMR spectrum of a compound having the formula (I) can be calculated to be 9.27 and 8.97 τ , respectively. The 18-CH₃ signals of the authentic samples of several pregnan-20-ones having 14 α ,17 β -configurations appear at ca. 9.3 τ when measured in this laboratory. Therefore, the formula (I) should be excluded for the structure of γ -digiprogenin.

In order to study the configurations of γ - and α -digiprogenin by ORD, we proceeded the partial elimination of the carbonyl groups of these aglycones. Treatment of γ -digiprogenin acetate with ethanedithiol and boron fluoride-ether in acetic acid solution afforded a monothioketal of γ -digiprogenin acetate (V), m.p. 252~255°, C₂₅H₃₄O₅S₂, IR $\lambda_{\text{max}}^{\text{Nujol}}$ μ : 5.74, 5.85, 5.88. Because the NMR spectrum of V lacks the signal of the 17-COCH₃, V was clarified to be a 20-thioketal. The ORD curve of V showed a negative Cotton effect, $[\phi]$ -9480 (331 m μ), -8820 (327 m μ), -9950 (321 m μ), +6710 (278 m μ), a -167. Desulfurization of V with Raney nickel gave 20-deoxo- γ -digiprogenin acetate (VI), m.p. 191~194°, C₂₃H₃₂O₅, IR $\lambda_{\text{max}}^{\text{Nujol}}$ μ : 5.73, 5.84, 5.87 indicating the existence of 11- and 15-keto groups besides the acetoxyl group. The ORD curve of VI showed a negative Cotton effect, $[\phi]$ -4320 (334 m μ), -3670 (327 m μ), -3850 (325 m μ), +5980 (285 m μ), a -103.

Generally it is well known that the Cotton effect of 11- and 15-ketones are positive in C/D-*trans* juncture and negative in C/D-*cis* juncture.³⁾ Therefore, the C/D-juncture of V and VI were deduced to be *cis* in both cases. Because the γ -digiprogenin acetate was not isomerized on treatment with boron fluoride-ether in acetic acid solution in blank test, the C/D-juncture of γ -digiprogenin acetate (III) was thought to be *cis* originally.

20-Monothioketal (VII) of α -digiprogenin acetate, m.p. 263~267°, C₂₅H₃₄O₅S₂, IR $\lambda_{\text{max}}^{\text{Nujol}}$ μ : 5.73, 5.78, 5.83, obtained from α -digiprogenin acetate by the method similar to that used for γ -digiprogenin acetate, gives no signal corresponding to the 17-COCH₃ in its NMR spectrum, and was shown to be not identical with V in mixed fusion and infrared spectra. The ORD curve of VII showed a negative Cotton effect, $[\phi]$ -2620 (338 m μ), +2930 (298 m μ), a -56. 20-Deoxo- α -digiprogenin acetate (VIII), m.p. 229~231°, C₂₃H₃₂O₅, IR $\lambda_{\text{max}}^{\text{Nujol}}$ μ : 5.72, 5.84, 5.87, showed a negative Cotton effect, $[\phi]$ -3980 (340 m μ), +5300 (295 m μ), a -93 in its ORD curve. These facts indicated that the C/D-juncture of VII and VIII and furthermore of the parent substance, α -digiprogenin acetate (IV), are all *cis*.

As the C/D-juncture of γ - and α -digiprogenin acetates have been clarified to be both *cis*, the center of epimerization seems to be C-17 position.

In the course of NMR studies of steroids in this laboratory, it was found that a 17 α -COCH₃ markedly shifts the 18-CH₃ signal downfield in comparison with a 17 β -COCH₃ as follows:

14,15-Configuration	Shift value due to a 17-COCH ₃ (p.p.m.)* ²	
	18-CH ₃	19-CH ₃
14 α -H, 17 β -COCH ₃	+0.08	+0.01
14 β -H, 17 β -COCH ₃	+0.03	-0.01
14 α -H, 17 α -COCH ₃	ca. -0.2	ca. +0.02
14 β -H, 17 α -COCH ₃	ca. -0.25	ca. 0.00

As described above, the 18-CH₃ signals of γ - and α -digiprogenin acetates appear at 8.89 and 8.66 τ , respectively. Accordingly, the configurations of these aglycones can be considered as a 14 β ,17 β -type for γ -digiprogenin acetate and a 14 β ,17 α -type for α -digiprogenin acetate as shown in formulae (III) and (IV), respectively.

*² Plus sign represents an upfield shift.

2) R. F. Zürcher: *Helv. Chim. Acta*, **46**, 2054 (1963).

3) C. Djerassi, W. Klyne: *J. Chem. Soc.*, **1962**, 4929; *Ibid.*, **1963**, 2390.

Moreover, by subtracting the ORD curve of VI from that of III, the contribution of the two carbonyl groups at C-11 and C-15 were eliminated and the resultant curve showed a positive Cotton effect whose amplitude ($a = ca. +92$) was comparable to that of 14 β ,17 β -acetyl. On the contrary, the subtraction of the ORD curve of VIII from that of IV gave a negative Cotton effect whose sign and amplitude ($a = ca. -74$) were characteristic for a 14 β ,17 α -acetyl in steroids.

The position of a hydroxyl group in the D ring of γ -digiprogenin acetate was presumed to be C-17 from the fact that it did not undergo acetylation in the previous paper,¹⁾ and this position was supported by the datum of NMR and resistibility of this acetate to the oxidation with chromium trioxide in the later studies.

Since the epimerization of 17-hydroxypregnan-20-one at the C-17 position have never been reported in the literature, the further detailed examination on the mechanism for the epimerization is now in progress.

Shionogi Research Laboratory,
Shionogi & Co., Ltd.,
Fukushima-ku, Osaka

Daisuke Satoh (佐藤大助)
Mieko Horie (堀江美恵子)

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On the Structure of Tomentogenin

The isolation of sarcostin and tomentogenin from the stem of *Marsdenia tomentosa* DECNE. (Asclepiadaceae) has been reported previously¹⁾ and a tentative structure was proposed.²⁾

In this communication, experiments leading to the structural determination of tomentogenin (I) and the correlation of utendin*¹ are described. In the previous paper,¹⁾ the molecular formula of "tomentogenin" was given as $C_{21}H_{34}O_5$, but careful examination by paper chromatography (formamide- $CHCl_3$)³⁾ showed very close two spots, in about 3:1 intensity ratio, which were hardly separable. Crude tomentogenin absorbed about 1/3 mole of hydrogen by catalytic hydrogenation to give a compound which showed a single spot on the paper chromatogram, as the spot was identical with the major spot of crude tomentogenin, it seems probable that the crude tomentogenin is a mixture of tomentogenin (I) and dehydrotomentogenin (I').

Tomentogenin (I), m. p. 265~268°, $C_{21}H_{36}O_5$ (Anal. Calcd. : C, 68.44; H, 9.85. Found: C, 68.15; H, 9.99); IR ν_{\max}^{Nujol} cm^{-1} : 3400, 3150, $[\alpha]_D^{16} +36^\circ$ ($c=0.95$, MeOH) seems to have

*¹ Professor T. Reichstein suggested the possible identity of tomentogenin with utendin (Helv. Chim. Acta, 42, 1014, 1959, IUPAC Symposium, 1964, Kyoto) and sent a sample (march 9, 1964). The two compounds were compared by thin-layer chromatography and paper chromatography. Utendin and dehydrotomentogenin are very similar. $[\alpha]_D$ of these compounds in MeOH are; utendin $+9.6^\circ$, tomentogenin dehydrotomentogenin mixture (about 3:1) $+23^\circ$, and tomentogenin $+36^\circ$. Professor Reichstein sent us again tri-O-acetyl-5 α -dihydrotomentogenin (may 19, 1964), the identity of this compound and tomentogenin triacetate (II) was established by mixed melting point and paper chromatography.

1) H. Mitsuhashi, I. Takemori, Y. Shimizu, T. Nomura, E. Yamada : This Bulletin, 10, 804 (1962).
2) A part of this work was reported at the 83rd Annual Meeting of the Pharmaceutical Society of Japan, Nov. 2, 1963, Tokyo.

3) H. Mitsuhashi, Y. Shimizu, E. Yamada, I. Takemori, T. Nomura : This Bulletin, 10, 808 (1962).