Chem. Pharm. Bull. 13(3) 312~315 (1965)

UDC 547.918.07 : 615.711.5

41. Takayuki Wada : Catalytic Reduction of Dianhydrogitoxigenin.*1

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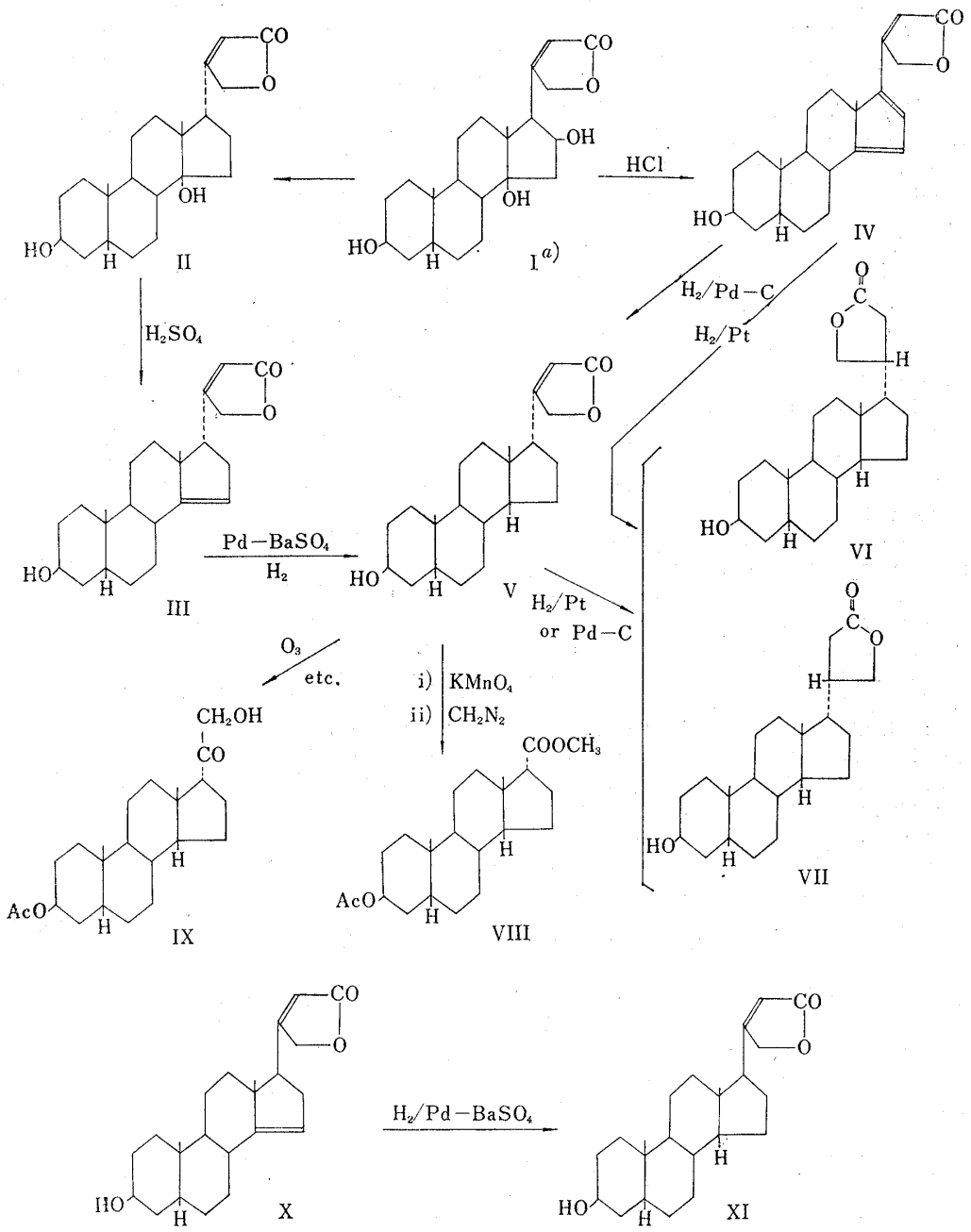
The dehydration of gitoxigenin (I) gives 14-anhydrogitoxigenin, 16-anhydrogitoxigenin and 14,16-dianhydrogitoxigenin (IV).



a) Derivatives a : 3β-hydroxy b : 3β-acetoxy c : 3-oxo

Chart 1.

*1 This paper forms the part XXIII of series entitled "Studies on Digitalis Glycosides" by Daisuke Satoh. (Part XXII. T. Wada : This Bulletin, **13**, 43 (1965)).

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Catalytic reduction of 16-anhydrogitoxigenin with Adams catalyst furnishes 20-isomers of 3β,14β-dihydroxy-5β,17α-cardanolide[1] and hydrogenation of IV gives the isomers of 3β-hydroxy-5β-cardanolide.[2,3] The hydrogenation of 16-anhydrogitoxigenin over palladium-charcoal furnishes 17α-digitoxigenin (II) and the 17β-isomer, digitoxigenin.[4] The α,β-butenolide ring of these compounds are not reduced with this catalyst. The hydrogenation of dianhydrogitoxigenin (IV) over palladium-charcoal proceeds stepwise to give a tetrahydrodianhydrogitoxigenin (V)[5] and hexahydrodianhydrogitoxigenins (VI, VII). At the first stage of hydrogenation of IV, the reaction proceeds rapidly, until two moles of hydrogen are absorbed. Then a marked retardation of the reaction rate takes place, and a slow absorption of hydrogen follows. At the end of the first stage, the main product was isolated and purified to give a tetrahydrodianhydrogitoxigenin (V) and the steroid character of V was confirmed by oxidation of Vb to the authentic VIII and identity of V with the reduction product of III.

Presence of an α,β-butenolide ring in V is confirmed by the following data : Positive Raymond test; ultraviolet absorption maximum at 218 mμ; infrared peaks at 1793, 1730, and 1623 cm^{-1}; nuclear magnetic resonance spectrum having a signal at 4.17 τ; oxidation of Vb to an etianate (VIII); and ozonisation of Vb to 3β,21-dihydroxy-5β,14β,17α-pregnan-20-one 3-acetate (IX).

17α-Configuration of the α,β-butenolide side chain of V is shown by identity of Va with the reduction product of 3β-hydroxy-5β,17α-carda-14,20(22)-dienolide (IIIa) derived from 17α-digitoxigenin (II). The selective hydrogenation of the 14(15)-double bond prior to that of butenolide ring of 3β-hydroxy-5β,17β-carda-14,20(22)-dienolide (X) affords 14-deoxy-digitoxigenin (XI), 14α-configuration of which has been confirmed by synthesis from 3β,21-dihydroxy-5β-pregnan-20-one. For these selective hydrogenations, palladium-barium sulfate is employed successfully, besides palladium on carbon gives the same product by slower reaction.[6] It is known that hydrogenation of the 14(15)-double bond leads to the 14α-configuration if the substituent at C-17 has the β-orientation and to the 14β-configuration, if the substituent at C-17 has the α-orientation.[7]

14β-Configuration of V was established by oxidation of Vb to the methyl etianate (VIII), identical with the authentic sample of methyl 3β-acetoxy-5β,14β,17α-etianate.*3

Va furnished a monoacetate (Vb) by acetylation with acetic anhydride-pyridine and a 3-oxo derivative (Vc) by oxidation with chromic trioxide.

From these results, the structure of Va is elucidated as 3β-hydroxy-5β,14β,17α-card-20(22)-enolide.

This evidence shows that by analogy with the case of 16-anhydrogitoxigenin, the double bond of butenolide is not easily reduced with palladium-charcoal. Formation of 14β,17α-cardenolide is the result of preferential front side attack of hydrogen atom. The analogous observations were reported that among the products of hydrogenation of 3β-acetoxypregna-5,14,16-trien-20-one over palladium-calcium carbonate[8] or of methyl 3β-acetoxy-5β-etia-14,16-dienate over platinum catalyst,[1] corresponding 14β,17α-derivatives were the main product.

When the hydrogenation of IV over palladium-charcoal was continued until three moles of hydrogen were consumed, the products were the hexahydrodianhydrogitoxi-

*3 The authentic sample of the etianate was kindly supplied by Prof. Kuno Meyer.

1) Kuno Meyer : Helv. Chim. Acta, **29**, 718, 1908 (1946).
2) H. M. E. Cardwell, S. Smith : J. Chem. Soc., **1954**, 2012.
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5) T. Wada, D. Satoh : This Bulletin, **11**, 544 (1963); A. Windaus, G. Bandte : Ber., **56**, 2001 (1923).
6) B. T. Brown, S. E. Wright : J. Pharm. Pharmacol., **13**, 262 (1961).
7) L. Ruzicka, Pl. A. Plattner, H. Heuser, Kd. Meier : Helv. Chim. Acta, **30**, 1342 (1947).
8) Pl. A. Plattner, H. Heuser, A. Segre : *Ibid.*, **31**, 249 (1948).

Table I. Derivatives of Hexahydrodianhydrogitoxigenin

Configuration at C-20	Substituent at C-3	m.p.	$[\alpha]_D$	Reference
20β (VI)	a) β-OH	218°	+72.9°[b]	2)
	b) β-OAc	157°/162°	+36.6°[a]	5)
	c) oxo	209°	+83.5°	3)
20α (VII)	a) β-OH	203°	+16.3°	2)
	b) β-OAc	146°	+17.1°	*a*)
	c) oxo	158~160°/170~171°[a]	+40.2°[a]	cf. 2)

a) Data of the present author.
b) m.p. 214~216°, $[\alpha]_D^{24}$ +44.8°(c=1.023).[a]

genins (VI, VII), which were identical with the authentic samples obtained by hydrogenation of IV or V with platinum catalyst.[2,3] It has been reported that some of the α,β-butenolide rings are susceptible to hydrogenation over palladium-strontium carbonate or palladium-barium sulfate to give the cardanolides.[9] As the reduction products of IVa are identical with those of Va, it is apparent that they have 14β,17α-configuration.

These isomers (VI, VII) were resolved by fractional crystallization from appropriate solvents, differentiating their crystal form. Both of them have positive specific rotation and a critical point of the difference between the two crops of crystal is their plain rotatory dispersion (RD) curves of positive (VIb) and negative (VIIb) sign. This evidence is attributable to C-20 isomerism and distinction of C-20 configuration can be made by molecular rotation difference of the two isomers by the usual method without ambiguity.[6,10]

From these results, 3β-hydroxy-5β,14β,17α,20β-cardanolide is assigned for structure of VIa and the 20α-isomer for VIIa.

Experimental*4

3β-Hydroxy-5β,17α-carda-14,20(22)-dienolide (IIIa)——A solution of 100 mg. of IIa in 10 ml. of EtOH and 10 ml. of 2*N* H_2SO_4 was refluxed for 3 hr. to afford 70 mg. of needles (IIIa), m.p. 172~174°, $[\alpha]_D^{28}$ +100.6°(c=0.711), UV: λ_{max} 214 mμ (log ε 4.19), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3590, 1785, 1744, 1633. *Anal.* Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.24; H, 8.95.

Acetylation of IIIa gave the monoacetate (IIIb).

3β-Hydroxy-5β,14β,17α-card-20(22)-enolide (Va)——Dianhydrogitoxigenin (IVa, 100 mg.) in 20 ml. of MeOH was hydrogenated over 30 mg. of 2% palladium-charcoal for 1 hr. with 2 moles of hydrogen at 1 atm. to give 60 mg. of plates (Va), m.p. 198~200°, $[\alpha]_D^{24}$ +76.2° (c=1.022), UV: λ_{max} mμ (log ε): 218 (4.17), IR ν_{max}^{Nujol} cm^{-1}: 3525, 1793, 1730, 1623. *Anal.* Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.98; H, 9.64.

Hydrogenation of IIIa (50 mg.) over 100 mg. of palladium-barium sulfate in 10 ml. of glacial acetic acid gave 30 mg. of Va, m.p. 198~200°.

3β-Acetoxy-5β,14β,17α-card-20(22)-enolide (Vb)——Dianhydrogitoxigenin acetate (IVb, 100 mg.) in 20 ml of EtOH was hydrogenated over 30 mg. of 5% palladium-charcoal for 1 hr. with 2 moles of hydrogen to give 56 mg. of needles (Vb), m.p. 173~174°, $[\alpha]_D^{24}$ +75.3° (c=1.018), UV: λ_{max} mμ (log ε): 218 (4.20), IR ν_{max}^{Nujol} cm^{-1}: 1783, 1748, 1729, 1720, 1630, 1264, 1237. *Anal.* Calcd. for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 74.91; H, 8.92.

Hydrogenation of IIIb (30 mg.) over 50 mg. of palladium-barium sulfate in 5 ml. of glacial acetic acid gave 17 mg. of Vb, m.p. 172~174°.

Acetylation of Va gave Vb.

*4 All the melting points were determined on Monoskop and uncorrected. UV spectra were taken in 95% EtOH and specific rotations were measured in $CHCl_3$.

9) Pl. A. Plattner, A. Segre, O. Ernst: Helv. Chim. Acta, **30**, 1432 (1947).
10) L. Ruzicka, Pl. A. Plattner, J. Pataki: *Ibid.*, 28, 389 (1943).

3-Oxo-5β,14β,17α-card-20(22)-enolide (Vc)——Dianhydrogitoxigenon (Ⅳc, 100 mg.) in 20 ml. of acetone was hydrogenated over 30 mg. of palladium-charcoal for 1 hr. with 2 moles of hydrogen to give prisms (Vc), m.p. 211~213°, $[\alpha]_D^{25}$ +102.5°(c=1.010), UV : λ_{max} mμ (log ε) : 218(4.17), IR ν_{max}^{Nujol} cm^{-1} : 1792, 1755, 1709, 1628. *Anal.* Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found : C, 77.62; H, 9.11.

Oxidation of Va gave Vc.

Methyl 3β-Acetoxy-5β,14β,17α-etianate (VIII)——A solution of 224 mg. of 3β-acetoxy-5β,14β,17α-card-20(22)-enolide (Vb) in 15 ml. of acetone was oxidized with 230 mg. of powdered potassium permanganate for 2 hr. The acid fraction was methylated with diazomethane to give needles (Ⅷ), m.p. 156~159°, IR ν_{max}^{Nujol} cm^{-1} : 1729, 1262, 1237. *Anal.* Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64; Found : C, 73.28; H, 9.73.

Ⅷ was identified with the authentic specimen of methyl 3β-acetoxy-5β,14β,17α-etianate by mixed melting point determination and by comparison of IR spectra.

3β,21-Dihydroxy-5β,14β,17α-pregnan-20-one 3-Acetate (IX)——A solution of 100 mg. of 3β-acetoxy-5β,14β,17α-card-20(22)-enolide (Vb) in 20 ml. of EtOAc was treated with 1 mole of ozone at −80°. The solution was brought to room temperature, the solvent was removed and the residue was stirred with 200 mg. of zinc dust in 1 ml. of acetic acid. The product was hydrolysed with potassium bicarbonate in aqueous MeOH to give 61 mg. of plates (Ⅸ), m.p. 124~126°, IR ν_{max}^{Nujol} cm^{-1} : 3410, 1728, 1700, 1261, 1235. *Anal.* Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found : C, 73.34; H, 9.46.

3β-Hydroxy-5β,14β,17α,20α-cardanolide (VIIa) and 3β-Hydroxy-5β,14β,17α,20β-cardanolide (VIa)——Dianhydrogitoxigenin (Ⅳa, 100 mg.) was hydrogenated over 100 mg. of palladium-charcoal in 20 ml. of MeOH for 28 hr. to give 92 mg. of product which was purified by chromatography to give 20 mg. of Va and 48 mg. of mixture of Ⅵa and Ⅶa. Fractional crystallization of the mixture gave 24 mg. of Ⅵa, m.p. 212°, and 10 mg. of Ⅶa, m.p. 200°, which were identical with the authentic sample prepared from Ⅳa with platinum catalyst.

3β-Acetoxy-5β,14β,17α,20α-cardanolide (VIIb) and 3β-Acetoxy-5β,14β,17α,20β-cardanolide (VIb)——Acetylation of Ⅶa gave Ⅶb, m.p. 144~146°, $[\alpha]_D^{23}$ +17.1°(c=1.092), IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1771, 1723, 1260. *Anal.* Calcd. for $C_{25}H_{38}O_4$: C, 74.59; H, 9.52. Found : C, 74.69; H, 9.65.

Acetylation of Ⅵa gave Ⅵb, m.p. 157°/162°, $[\alpha]_D^{23}$ +36.6°(c=1.041), IR ν_{max}^{Nujol} cm^{-1} : 1783, 1724, 1266, 1238. *Anal.* Calcd. for $C_{25}H_{38}O_4$: C, 74.59; H, 9.52. Found : C, 74.61; H, 9.64.

14-Deoxydigitoxigenin (XI)——β-Anhydrodigitoxigenin (Ⅹ, 100 mg.) in 10 ml. of acetic acid was hydrogenated over 100 mg. of palladium-barium sulfate for 1 hr. with 1 mole of hydrogen to give 64 mg. of needles (Ⅺ), m.p. 224~225°, $[\alpha]_D^{22.5}$ +15.2°(c=1.030), UV : λ_{max} mμ (log ε) : 217 (4.23), IR ν_{max}^{Nujol} cm^{-1} : 3610, 3465, 1787, 1732, 1630, 1622. *Anal.* Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found : C, 76.77; H, 9.62.

The author wishes to express his gratitude to Prof. Kuno Meyer, for his gift of the sample of the etianate. He is grateful to Prof. E. Ochiai and Dr. Ken'ichi Takeda, director of this Laboratory, for their interest and encouragement throughout this work.

Summary

On hydrogenation of dianhydrogitoxigenin with palladium catalysts, 3β-hydroxy-5β,14β,17α-card-20(22)-enolide and the 20-isomers of 3β-hydroxy-5β,14β,17α-cardanolides were obtained. The stereochemistry of the products are also described.

(Received October 28, 1964)