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40. **Takayuki Wada and Daisuke Satoh**: Studies on Digitalis Glycosides. XXI.[*1] 14,15-Epoxy and 15-Oxo Derivatives of 3β-Acetoxy-5β,17α-cardenolide.[*2]

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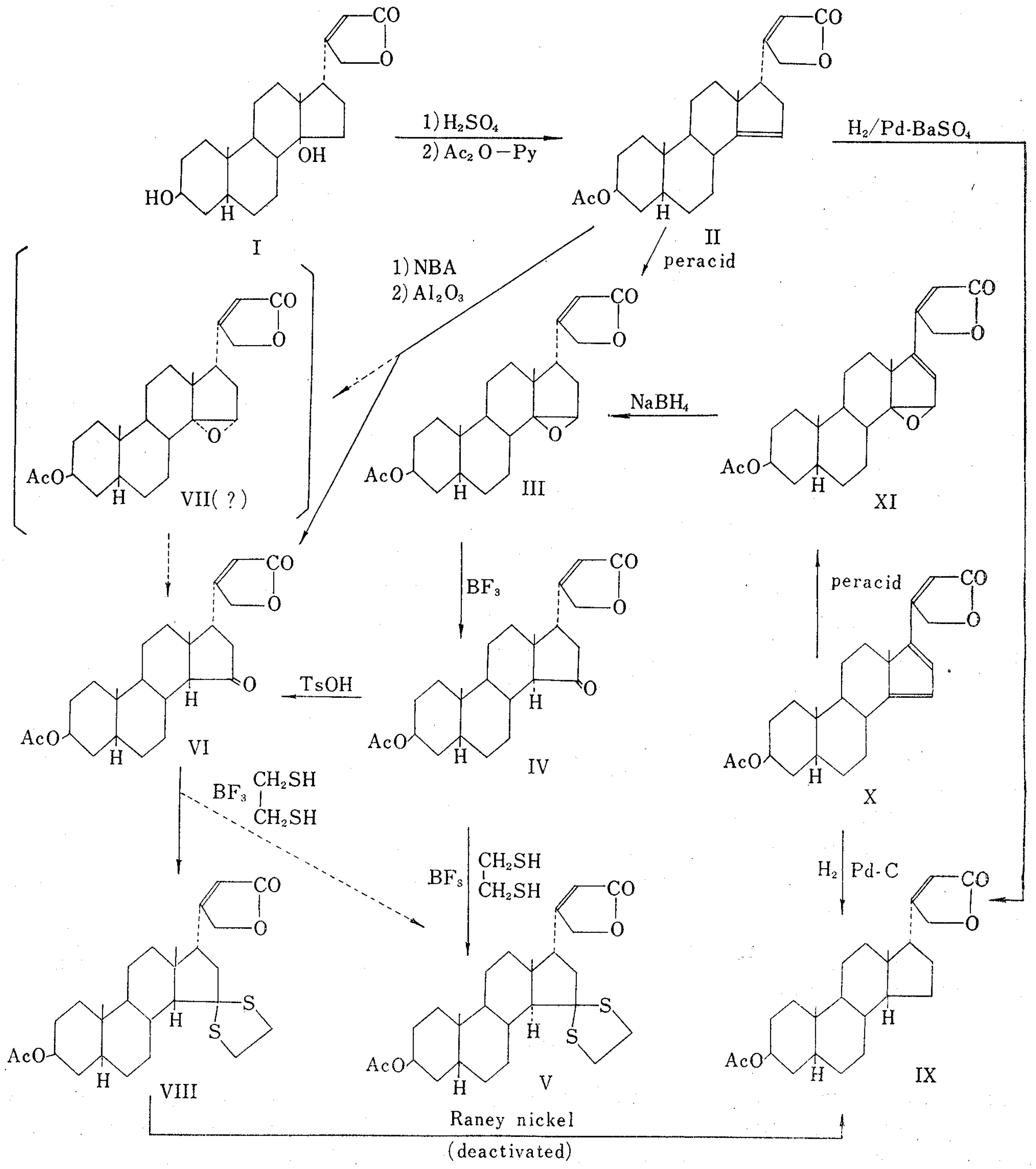
In a previous paper from this laboratory, 14,15-epoxy and 15-oxo derivatives of 5β,17β-cardenolide were reported.[1] The present paper describes the corresponding 17α-isomers derived from 17α-digitoxigenin (I).[2]



[*1] Part XX. D. Satoh, H. Ishii, K. Tori, T. Tozyo, J. Morita: Ann., to be published.

[*2] A part of this paper was presented at the Kinki Branch Meeting of the Pharmaceutical Society of Japan, Osaka, November 23rd, 1963.

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1) H. Ishii, T. Tozyo, D. Satoh: This Bulletin, 11, 576 (1963).

2) D. Satoh, H. Ishii: Yakugaku Zasshi, 80, 1143 (1960).

Dehydration of I with diluted sulfuric acid in boiling ethyl alcohol, followed by acetylation with pyridine-acetic anhydride afforded anhydro-17α-digitoxigenin acetate (II), m.p. 158~159°, $[\alpha]_D$ +91.6°. When the side chain possesses β-configuration, a molecular rotation difference between 14β-hydroxy and 14-unsaturated derivative is positive for the 8(14)-double bond and negative for the 14(15)-double bond. On the other hand, 14(15)-unsaturated derivatives are feasible to hydrogenation over platinum catalysts, while the 8(14)-isomers are resistant to hydrogenation in a neutral solution.[3] In the case of II, hydrogenation catalysed with palladium-barium sulfate proceeded smoothly, but the molecular rotation difference between I and II was positive. The position of the double bond of II was located at 14(15), on the basis of nuclear magnetic resonance spectrum of II having signal of olefinic proton on C-15 at 4.83 τ, and of conversion of II to the epoxide (III), followed by rearrangement to give a five membered ring ketone (IV). The molecular rotation difference value can rationally be explained by consideration of unsaturated D-ring together with the butenolide ring. Possible rearrangement of the steroid nucleus was excluded by catalytic reduction of II to the authentic IX.[4] From these results, the structure of II was concluded as 3β-acetoxy-5β,17α-carda-14,20(22)-dienolide.

Epoxidation of Δ^{14}-17β-cardenolide[1] with monoperphthalic acid resulted in the formation of 14α,15α-epoxide, while the 17α-isomer (II) gave 3β-acetoxy-14β,15β-epoxy-5β,14β,17α-card-20(22)-enolide (III), m.p. 187~191°. The configuration of III was confirmed by identifying it with the sodium borohydride reduction product of 3β-acetoxy-14β,15β-epoxy-5β,14β-carda-16,20(22)-dienolide (IX), m.p. 186~187°, derived from dianhydrogitoxigenin acetate (X).[5]

Treatment of III with boron trifluoride in ether-benzene afforded a ketone (IV), m.p. 130~135°/150~155°, ν_{max} 1734 cm^{-1}. Assuming *cis*-hydride shift mechanism for this reaction,[6] 14α,15-oxo structure of IV is to be expected. The optical rotatory dispersion curve of IV showed a positive Cotton effect (Fig. 1).

Reaction of IV with ethanedithiol and boron trifluoride was accomplished within 10 minutes to give 3β-acetoxy-15-oxo-5β, 14α, 17α-card-20(22)-enolide cyclic ethylenethioacetal (V), m.p. 227~227.5°/234°, which showed melting point depression on admixture with the 14β-isomer, VIII.

Isomerisation of IV with p-toluenesulfonic acid in refluxing benzene gave an isomeric ketone, 3β-acetoxy-15-oxo-5β, 14β, 17α-card-20(22)-enolide (IV), m.p. 237~239°. The optical rotatory dispersion curve of VI showed a negative Cotton effect (Fig. 1) and the 14β-configuration of VI was confirmed by conversion of VI to VIII and IX.

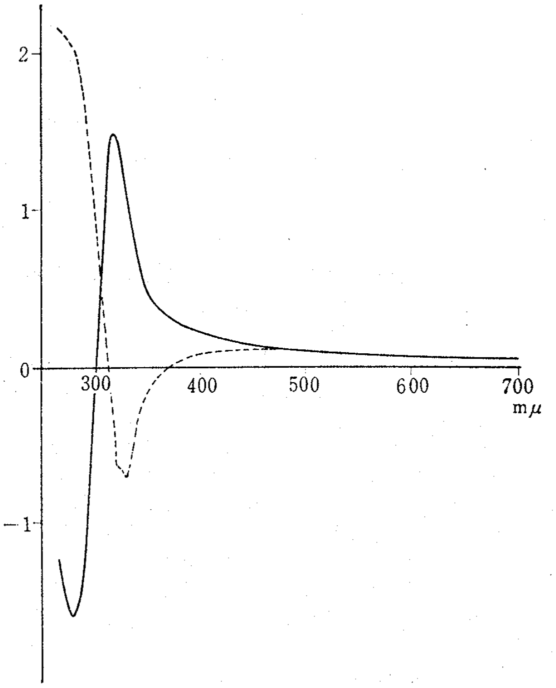

Fig. 1. The Optical Rotatory Dispersion Curves of IV and VI

——— IV VI
(in methanol)

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3) H. M. E. Cardwell, S. Smith : J. Chem. Soc., **1954**, 2012.

4) T. Wada, D. Satoh : This Bulletin, **11**, 544 (1963).

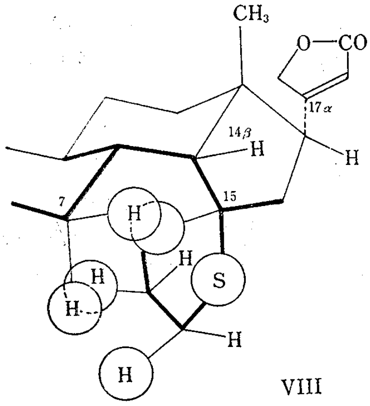
5) M. Okada, A. Yamada, Y. Saito, M. Hasunuma : Reported at the Kanto Branch Meeting of the Pharmaceutical Society of Japan, Tokyo, December 15th, 1962.

6) C. Djerassi : "Steroid Reactions," 161 (1963), Holden-Day, Inc., San Francisco, Calif.

Several runs to prepare the 14α,15α-epoxide (VII) from II using N-bromoacetamide and alumina[7] led to isolation of VI[8] in good yield, the mother liquor of which contained a trace amount of the fraction supposed to be VII.

The 14β-ketone (VI) reacted slowly with ethanedithiol in the presence of boron trifluoride to give 3β-acetoxy-15-oxo-5β,14β,17α-card-20(22)-enolide cyclic ethylenethioacetal (VIII), m.p. 216~219° in yield of 45%, and the 14α-isomer (V) in yield of 4.5%. Desulfurization of VIII with deactivated Raney nickel afforded 3β-acetoxy-5β,14β,17α-card-20(22)-enolide (IX), m.p. 172~174°, which was identical with the authentic sample prepared by hydrogenation of X or II. From this result, 14β-configuration of VI and VIII was confirmed, and the steroid nuclei (having 17α-configuration of the side chain) of all the compounds cited here were proved.

Isomerisation of IV to VI shows that C/D-*cis* junction is more stable than C/D-*trans* junction in 17α-cardenolides.



VIII

Fig. 2.

The reaction rate of cyclic ethylenethioacetal formation of IV and VI under similar condition showed a marked difference. This fact may be explained on the basis of repulsion between 7-methylene group and thioketal group, which are in closer proximity to each other in the 14β-isomer than in the 14α-isomer of 17α-cardenolide as is shown in Fig. 2.

Formation of the different thioketals V and VIII from IV and VI indicates that the reaction does not involve the 14(15)-enol type intermediates in the reaction condition used. However, the isolation of V as a minor component of the reaction mixture from VI suggests that a small part of VI was isomerized to the 14α-isomer, in the course of the reaction by action of boron trifluoride.

VIII is the first instance of thioketal of 14 β, 15-oxo steroid.[9]

Experimental*4

3β-Acetoxy-5β,17α-carda-14,20(22)-dienolide (II)——17α-Digitoxigenin (1.00 g.) was refluxed with 20 ml. of 10% sulfuric acid in 40 ml. of EtOH for 5 hr. The reaction mixture was neutralized, concentrated to a half the original volume and extracted with AcOEt. The organic layer was washed with water, sodium carbonate and hydrochloric acid, dried over sodium sulfate and evaporated to give colorless glass, which was dissolved in 15 ml. of pyridine and 15 ml. of acetic anhydride and left standing for 15 hr. The product was poured into ice water, extracted with AcOEt, washed with water, dried over sodium sulfate and evaporated to give 0.70 g. of prisms (II), m.p. 158~159°, $[\alpha]_D^{27.5}$ +91.6° (c=0.799), UV : λ_{max} mμ (log ε) : 213 (4.21), IR ν_{max}^{Nujol} cm^{-1} : 1784, 1748, 1729, 1630, 1246, 1234. *Anal.* Calcd. for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found : C, 75.14; H, 8.72.

3β-Acetoxy-14β,15β-epoxy-5β,14β,17α-card-20(22)-enolide (III)——a) from II : A mixture of 0.8 g. of II, 186 mg. of monoperphthalic acid, 3 ml. of $CHCl_3$ and 6 ml. of ether was allowed to stand at room temperature for 13 hr. in the dark. The reaction mixture was diluted with $CHCl_3$, washed with sodium carbonate, hydrochloric acid and water, dried over sodium sulfate and evaporated to leave 0.9 g. of residue. Recrystallization from acetone-ether gave 0.8 g. of plates (III), m.p. 187~191°, $[\alpha]_D^{27.5}$ +66.8° (c=1.003), UV : λ_{max} mμ (log ε) : 216 (4.16), IR ν_{max}^{Nujol} cm^{-1} : 1787, 1756, 1730, 1632, 1257, 1244. *Anal.* Calcd. for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found : C, 72.65; H, 8.45.

b) from XI : A solution of 170 mg. of XI in 7 ml. of MeOH was added to a solution of 62.4 mg. of sodium borohydride in 3 ml. of MeOH. After 1 hr., solvent was removed, the residue was diluted with water

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*4 All the melting points were measured on Monoskop and uncorrected. UV spectra were taken in 95% EtOH and specific rotations were determined in $CHCl_3$. The reactions and products were checked by thin-layer chromatography.

[7] P. Hofer, H. Linde, Kuno Meyer : Helv. Chim. Acta, **45**, 1041 (1962).

[8] A. Lardon, T. Reichstein : *Ibid.*, **45**, 943 (1962).

[9] H. J. E. Loewenthal : Tetrahedron, **6**, 292 (1959).

and extracted with AcOEt. The extract was washed with water, dried over anhydrous sodium sulfate and evaporated to dryness. The reside was chromatographed on silica gel to give 20 mg. of Ⅲ, m.p. 187～189°, when mixed with Ⅲ from Ⅱ, m.p. 186～191°. The IR spectra of both samples were indistinguishable.

3β-Acetoxy-15-oxo-5β,14α,17α-card-20(22)-enolide (IV)——A mixture of 0.75 g. of Ⅱ, 5 ml. of benzene and 0.05 ml. of boron trifluoride in ether was allowed to stand for 15 min. The product was taken up in ether-AcOEt, washed with sodium carbonate and water, dried over anhydrous sodium sulfate and evaporated to give 0.60 g. of residue. Recrystallization from benzene gave plates (Ⅳ), m.p. 130～135°/150～155°, $[\alpha]_D^{27.5}$ +29.4°(c=1.064), UV : λ_{max} mμ (log ε) : 214 (4.18), IR ν_{max}^{Nujol} cm^{-1} : 1793, 1734, 1628, 1255. *Anal.* Calcd. for $C_{25}H_{34}O_5 \cdot C_6H_6$: C, 75.58; H, 8.18. Found : C, 75.31; H, 8.27.

3β-Acetoxy-15-oxo-5β,14α,17α-card-20(22)-enolide Cyclic Ethylenethioacetal (V)——To a solution of 85 mg. of Ⅳ in 0.2 ml. of ethanedithiol, 0.2 ml. of boron trifluoride etherate was added. After 10 min., almost of ether was evaporated *in vacuo*, sodium carbonate (solid) was added to the reaction mixture, which was diluted with AcOEt. The solution was washed with sodium hydroxide and water, dried over sodium sulfate and evaporated to give 80 mg. of residue. Chromatographic purification gave 35 mg. of prisms (V), m.p. 227～227.5°/234°, $[\alpha]_D^{24.5}$ +24.8°(c=1.032), UV : λ_{max} mμ (log ε) : 215 (4.14), IR ν_{max}^{Nujol} cm^{-1} : 1781, 1753, 1731, 1632, 1260, 1250. *Anal.* Calcd. for $C_{27}H_{38}O_4S_2$: C, 66.10; H, 7.81. Found : C, 65.84; H, 7.77.

3β-Acetoxy-15-oxo-5β,14β,17α-card-20(22)-enolide (VI)——a) from Ⅱ : To a solution of 50 mg. of Ⅱ in 4 ml. of acetone, a solution of 35 mg. of N-bromoacetamide in 1 ml. of water was added and left standing for 30 min. Then the solution was diluted with water until the solution was turbid. The mixture was cooled to 0°, the separated flickering crystals were collected and recrystallized twice from acetoneether to give 25 mg. of plates (Ⅵ), m.p. 237～239°, $[\alpha]_D^{24.5}$ +36.1°(c=1.000), UV : λ_{max} mμ (log ε) : 215 (4.14), IR ν_{max}^{Nujol} cm^{-1} : 1798, 1730, 1720, 1626, 1264, 1246. *Anal.* Calcd. for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found : C, 72.57; H, 8.28. This crystal gave negative Beilstein test. The aqueous filtrate was extracted with AcOEt, and the extract was chromatographed on alumina to give 10 mg. of crystals identical with Ⅵ. The fraction, which was supposed to be Ⅶ, was obtained by preparative thin-layer chromatography and did not crystallize. The solution of this fraction in $CHCl_3$ gave only one spot identical with that of Ⅵ after 1 hr. b) from Ⅳ : A mixture of 10 mg. of Ⅳ, 2 mg. of *p*-toluenesulfonic acid and 1 ml. of benzene was refluxed for 12 hr. under nitrogen atmosphere. The reaction mixture was diluted with benzene, washed with water, dried over sodium sulfate, evaporated and crystallized from acetone-ether to give Ⅵ, m.p. 230～235°, identical with Ⅵ from Ⅱ.

3β-Acetoxy-15-oxo-5β,14β,17α-card-20(22)-enolide Cyclic Ethylenethioacetal (VIII)——A solution of 0.3 ml. of boron trifluoride in ether was added to a solution of 150 mg. of Ⅵ in 0.3 ml. of ethanedithiol. After 50 hr., almost of ether was evaporated *in vacuo*, sodium carbonate (solid) was added to the reaction mixture, which was diluted with AcOEt. The solution was washed with sodium hydroxide and water, dried over sodium sulfate, and evaporated to give 170 mg. of residue. Chromatographic purification on silica gel gave 81 mg. of prisms (Ⅷ), m.p. 216～219°, $[\alpha]_D^{24.5}$ +40.6° (c=1.009), UV : λ_{max} mμ (log ε) : 213 (4.24), IR ν_{max}^{Nujol} cm^{-1} : 1787, 1740, 1720, 1623, 1260, 1240. *Anal.* Calcd. for $C_{27}H_{38}O_4S_2$: C, 66.10; H, 7.81. Found : C, 66.14; H, 7.87. Ⅷ was instable to aqueous acid.[9]

The slowly eluted fraction gave 8 mg. of plates, m.p. 227～229°, which was identical with V.

3β-Acetoxy-5β,14β,17α-card-20(22)-enolide (IX)——A solution of 50 mg of Ⅷ in 20 ml. of EtOH was refluxed for 2 hr. with Raney nickel prepared from 3 g. of alloy (deactivated with boiling acetone for 2 hr.). The catalyst was filtered off, and the filtrate was evaporated to dryness, and the residue was chromatographed on silica gel to give 20 mg. of crystals (Ⅸ), m.p. 172～174°, when mixed with the authentic material, m.p. 172～174°. The IR spectra of both specimen were identical.

3β-Acetoxy-14β,15β-epoxy-5β,14β-carda-16,20(22)-dienolide (XI)——A mixture of 100 mg. of dianhydrogitoxigenin acetate (X), 160 mg. of monoperphthalic acid, 4 ml. of ether and 1 ml. of $CHCl_3$ was kept standing in the dark for 17 hr. The mixture was diluted with ether-AcOEt, washed with water and sodium carbonate, dried over sodium sulfate and evaporated to give 101 mg. of residue, which gave 50 mg. of prisms (Ⅺ), m.p. 186～187°, $[\alpha]_D^{24}$ +160.5°(c=1.020), UV : λ_{max} mμ (log ε) : 276 (4.17), IR ν_{max}^{Nujol} cm^{-1} : 1789, 1747, 1723, 1620, 1570, 1263, 1240. *Anal.* Calcd. for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82. Found : C, 72.66; H, 7.86. A compound, m.p. 205～213°, was isolated as a by-product (15 mg.). *Anal.* Calcd. for $C_{25}H_{32}O_6$: C, 70.07; H, 7.53. Found : C, 70.10; H, 7.57. This compound was not studied further.

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Summary

14,15-Epoxy and 15-oxo derivatives of 3β-acetoxy-5β,17α-cardenolides were described. Epoxidation of 14-double bond of the 17α-cardenolide with monoperphthalic acid resulted in the formation of 14β,15β-epoxide, contrary to the 17β-isomer.

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