Communications to the Editor

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Preparation of Card-17(20)-enolides from Carda-16,20(22)-dienolide[1)]

Reduction of 16-anhydrogitoxigenin 3-acetate (II) with $NaBH_4$-transition metal chloride systems as well as with transition metal hydrides gave geometrically isomeric card—17(20)-enolides, V and VI, new type of cardenolide. Stereochemistry of the products was discussed on the basis of Cotton effect, ^1H- and ^{13}C-nuclear magnetic resonance spectra. The structure and ratio of the products varied depending on the kind of transition elements.

Gitoxigenin (Ia) and digitoxigenin (IIIa) are two main cardiac aglycones isolated from the leaves of *Digitalis purpurea* L., and interconversion of these cardenolides has been one of the subjects of our studies on Digitalis glycosides. Satoh, one of us, and Ishii[2)] previously reported that catalytic hydrogenation of 16-anhydrogitoxigenin 3-acetate (II) on Pd-carbon gave 17α-digitoxigenin 3-acetate (IV) as a main product beside a small amount of digitoxigenin 3-acetate (IIIb). This communication outlines reduction of II with $NaBH_4$ and transition metal chloride as well as with transition metal hydrides.

While reduction of α,β-unsaturated ketones[3)] and esters[4)] with these reagents was reported by several researchers, that of α,β-γ,δ-unsaturated lactone has not been published so far.

Throughout our studies, reduction was performed by the following general method. II (1 mole) was dissolved in methanol containing transition metal chloride (0.3—2 mole), such as $NiCl_2 \cdot 6H_2O$, $CoCl_2 \cdot 6H_2O$, $CuCl_2 \cdot 2H_2O$ and $PdCl_2 \cdot 2H_2O$, and $NaBH_4$ (2—20 mole) was added gradually with stirring at 0—5° until the reaction was completed. The crude product was separated by multiple development TLC (SiO_2, benzene: ether=2: 1). The results of experiments are summarized in Table III.

Reduction of II with $NaBH_4$ and $NiCl_2 \cdot 6H_2O$ gave two isomeric products, A, mp 204 205.5° and B, mp 224—226°, $C_{25}H_{36}O_5$. The spectral and optical data of II and both the products are listed in Table I. Ultraviolet (UV) and infrared (IR) spectra indicated that both products have an isolated double bond together with a γ-lactone ring in place of the butenolide ring of II. Vinyl proton signals due to H-16 and H-22 in the ^1H-nuclear magnetic resonance (NMR) spectra of II disappeared in those of the reduction products. These data suggested that the products have a tetrasubstituted double bond between C-17 and C-20 as shown by formulas V and VI. The natural-abundance ^1H-noise-decoupled ^{13}C FT NMR spectral data on products A and B are listed in Table II. The signal assignments[5)] were performed by single-frequency off-resonance decoupling (SFORD) techniques and comparison of the chemical shift data reported on II and IIIb.[6)] In the SFORD spectra, two singlet olefinic-carbon signals confirmed that the double bond is located between C-17 and C-20.

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1) A part of this work was reported at the Meeting of Chugoku-Shikoku-Branch, Pharmaceutical Society of Japan, Oct., 10, 1975.

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

3) *a*) H.G. Kuivila and O.F. Beumel, *J. Am. Chem. Soc.*, **83**, 1246 (1961); *b*) E. Yoshii and M. Yamasaki, *Chem. Pharm. Bull.* (Tokyo), **16**, 1158 (1968); *c*) T. Nambara, K. Shimada, and S. Goya, *ibid.*, **18**, 453 (1970); *d*) E. Yoshii, H. Ikeshima, and K. Ozaki, *ibid.*, **20**, 1827 (1972); *e*) E. Yoshii and K. Ozaki, *ibid.*, **20**, 1585 (1972).

4) T. Satoh, K. Nanba, and S. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **19**, 817 (1971).

5) We express our sincere gratitude to Dr. K. Tori of Shionogi Research Laboratory for discussion on ^1H- and ^{13}C-NMR.

6) K. Tori, H. Ishii, Z.W. Wolkowski, C. Chachaty, M. Sangaré, F. Piriou, and G. Lukacs, *Tetrahedron Letters*, **1973**, 1077.

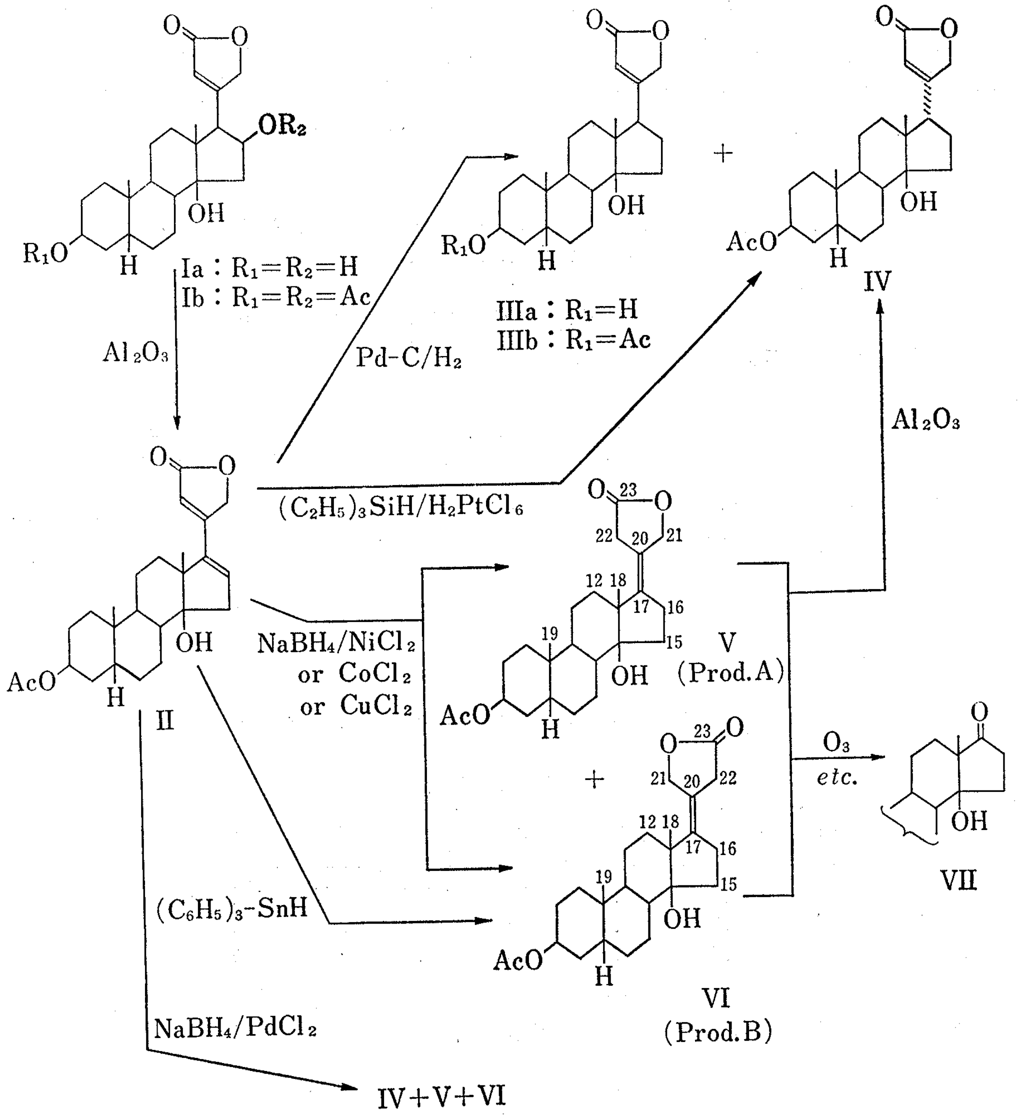

Chart 1

Positive Raymond[7] test, isomerization to IV by treating with Al_2O_3 in a benzene-$CHCl_3$ solution, and formation of 17-oxo compound (VII), mp 238—239°, by ozonolysis of both products chemically proved the card-17(20)-enolide structure of the products. From these results, both products were revealed to be geometrical isomers. The structures V and VI were assigned[8,9] to A and B, respectively, on the basis of the positive Cotton effect for A and the negative one for B in their circular dichroism (CD) spectra as shown in Table I. Furthermore, the ^1H-NMR signals due to 21-CH_2 in VI and 22-CH_2 in V appear at field lower than those due to 21-CH_2 in V and 22-CH_2 in VI, respectively (Table I). This observation also supports that 21-CH_2 in VI and 22-CH_2 in V interact with 12-CH_2 as suggested by Dreiding model examinations; it is well known that an interaction by a steric compression causes a downfield shift for the signal of a proton interacted.[10] It should be noted that the positions

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[7] W.D. Raymond, *Analyst*, **63**, 478 (1938).

[8] W. Klyne and P.M. Scopes, "Fundamental Aspects and Recent Developments in optical Rotatory Dispersion and Circular Dichroism," ed by., F. Ciardelli and P. Salvadori, Heyden and Son Ltd., London, 1973, p. 126.

[9] We express our sincere gratitude to Dr. K. Kuriyama of Shionogi Research Laboratory for his advice on the assignment of Cotton effects.

[10] S. Winstein, P. Carter, F.A.L. Anet, and A.J.R. Bowrn, *J. Am. Chem. Soc.*, **87**, 5247 (1965).

of the ^{13}C-NMR signals due to C-21 in V and VI as well as those due to C-22 in V and VI are different, respectively (Table II). It is interesting to know that 1,4-addition of hydrogen took place in the 16,20(22)-diene lactone system of II to give card-17(20)-enolides, V and VI, in this reaction. These compounds are a new type of cardenolide.

TABLE I. UV, IR, and ^{1}H-NMR Spectral Data and Cotton Effects of the Reduction Products

Compd No.	UV λ_{max}^{EtOH} nm (ε)	IR ν_{max}^{KBr} cm^{-1}	^{1}H-NMR ($CDCl_3$), δ (ppm) from TMS					CD λ_{max}^{MeOH} nm ([θ])
			16-H	18-H	19-H	21-H	22-H	
II	270 (18700)	1790 1750 1720	6.14 (H, t)	1.28 (3H, s)	1.00 (3H, s)	4.97 (2H, d)	5.94 (H, t)	
Prod. A (V)	212 (6094)	1780 1740		1.21 (3H, s)	0.97 (3H, s)	4.75 (2H, m)	3.24 (2H, m)	220(+10700)
Prod. B (VI)	210.5(4815)	1770 1715		1.17 (3H, s)	0.97 (3H, s)	5.00 (2H, m)	3.05 (2H, m)	224(−10700)

TABLE II. ^{13}C-NMR Spectral Data of Cardenolides[a]

Compds No.	^{13}C-Chemical shifts (in $CDCl_3$), δ									
	C-12	C-13	C-16	C-17	C-18	C-19	C-20	C-21	C-22	C-23
II[b]	40.6	52.6	133.8	161.2	16.6	24.1	172.8	72.6	111.7	176.3
III[b]	40.3	50.3	27.3	51.5	16.0	23.9	177.1	74.7	117.4	176.3
V	30.5	49.7	26.4	118.3 or 145.2	17.5	23.7	145.2 or 118.3	72.3	31.1	176.7
VI	30.6	49.7	28.6	119.0 or 145.9	17.6	23.8	145.9 or 119.0	70.3	33.7	175.9

[a] The spectra were recorded on a Varian NV-14 FT NMR spectrometer at 15.087 MHz; δ (ppm downfield from internal TMS) ±0.1. We thank NEVA Ltd. for the measurements.

[b] Data taken from ref. (6).

TABLE III. The Results of Reduction of II with various Reagents

II	Reduction Reagents (mole)	Reduction products (%)[a]		
		Prod. A (V)	Prod. B (VI)	IV
900 mg	$NaBH_4$-$NiCl_2\cdot6H_2O$ (2.0) (0.3)	14.2	15.9	
300 mg	$NaBH_4$-$CoCl_2\cdot6H_2O$ (4.0) (0.5)	55.7	8.3	
300 mg	$NaBH_4$-$CuCl_2\cdot2H_2O$ (20.0) (2.0)	10.3	44.1	
300 mg	$NaBH_4$-$PdCl_2\cdot2H_2O$ (3.0) (0.5)	23.2	16.6	20.9
500 mg	$(C_6H_5)_3SnH$ (7.0)		51.9	
200 mg	$(C_2H_5)_3SiH$-$H_2PtCl_6\cdot6H_2O$ (3.0) (0.1)			30.9

[a] theoretical yield

As II was inert to $NaBH_4$ alone, $NiCl_2 \cdot 6H_2O$ was inferred to participate with this reaction. In order to investigate the effect of transition element other than nickel, reduction of II with $NaBH_4$ and transition metal chloride such as $CoCl_2 \cdot 6H_2O$, $CuCl_2 \cdot 2H_2O$ and $PdCl_2 \cdot 2H_2O$ was examined, and the results are summarized in Table III. While the reduction with $NaBH_4$ and $NiCl_2 \cdot 6H_2O$ gave almost equal amounts of V and VI, that with $CoCl_2 \cdot 6H_2O$ yielded V as a main product in contrast to that with $CuCl_2 \cdot 2H_2O$ where VI was a main product. On the other hand, nearly equal amounts of IV, V, and VI were isolated from the reduction mixture using $NaBH_4$ and $PdCl_2 \cdot 2H_2O$. These results pointed out that the product ratio is markedly affected depending on the kind of the transition elements. Reduction of II with $(C_6H_5)_3SnH$ and that with $(C_2H_5)_3SiH$–$H_2PtCl_6 \cdot 6H_2O$ afforded VI and IV, respectively, as a exclusive product.

It is concluded that the stereochemistry and the ratio of the reduction products, V andVI, depend on the kind of transition elements. The mechanisms of the participation of transition elements are now under study.

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