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Studies on Digitalis Glycosides. XXXIV.[1] Transformation of Gitoxigenin to Digitoxigenin 3-Acetate[2]

Treatment of 16β,17β-epoxy-17α-digitoxigenin 3-acetate (V), which is readily available from gitoxigenin (Ib), with dilute alkali in absolute ethanol gave 16,17-dehydro-21*R*-ethoxydigitoxigenin 3-acetate (VIII) and 21*S*-epimer (IX). Catalytic hydrogenation of VIII and IX gave stereospecifically 21*R*-ethoxydigitoxigenin 3-acetate (X) and 21*S*-ethoxy-17α-digitoxigenin 3-acetate (XI), respectively. Further reduction of X and XI with $NaBH_4$ effectively eliminated ethoxy group to afford digitoxigenin 3-acetate (IVb) and 17α-epimer (III), respectively. By the sequence of these reactions, chemical transformation of gitoxigenin (Ib) to digitoxigenin 3-acetate (IVb) was achieved in fair yield.

Keywords——gitoxin; digitoxigenin 3-acetate; 17α-digitoxigenin 3-acetate; gitoxigenin; 16-anhydrogitoxigenin 3-acetate; 16β,17β-epoxy-17α-digitoxigenin 3-acetate; 16,17-dehydro-21*R*-ethoxydigitoxigenin 3-acetate; 16,17-dehydro-21*S*-ethoxydigitoxigenin 3-acetate; 21*R*-ethoxydigitoxigenin 3-acetate; 21*S*-ethoxy-17α-digitoxigenin 3-acetate

Gitoxin (Ia) and digitoxin (IVa) are the two main cardiac glycosides of *Digitalis purpurea* L. leaves, and Ia has not been used clinically due to its low solubility, contrary to IVa which exhibits an excellent cardiotonic activity for heart insufficiency. Accordingly, the chemical transformation of Ia to IVa has been one of the subjects in our studies on Digitalis glycosides, but the effective method has not been found to date due to instability and stereochemical limitation of these natural cardenolides. For instance, the partial hydrogenation of 16-anhydrogitoxigenin 3-acetate (II) which is readily available from gitoxigenin 3,16-diacetate (Ic) gave 17α-digitoxigenin 3-acetate (III) as a main product and digitoxigenin 3-acetate (IVb) was only a minor product.[3]

Previously, one of the present authors[4] reported that the treatment of 16β,17β-epoxy-17α-digitoxigenin 3-acetate (V) with K_2CO_3 in dilute ethanol gave 21-ethoxy-16,17-dehydrodigitoxigenin 3-acetate (VI) and a six-membered lactone (VII), but the configuration of 21-ethoxy group of VI remained undecided. Recently, we reinvestigated the reaction of V with alkali under several conditions and isolated two 21-epimers of VI, and determined the configurations by CD (circular dichroism) of the corresponding 16,17-dihydro derivatives, X and XI. Furthermore, we succeeded in the reductive removal of 21-ethoxy groups of the latter compounds leading to digitoxigenin 3-acetate (IVb) and its 17α-epimer (III). Thus, a promising method for the transformation of gitoxigenin to digitoxigenin 3-acetate has been established. This communication outlines these results.

When V was treated with KOH (0.03%) in absolute ethanol at room temperature for one hour, two products possessing the same molecular formula, mp 188—191° (VIII) and mp 213—216° (IX) were obtained in almost same yield (*ca.* 26%) after multiple development thin-layer chromatography (SiO_2, benzene: ether=2: 1). Since VIII was confirmed to be identical with the sample (VI) reported in the previous paper[4] and spectroscopic data of IX[5] showed close similarity with those of VIII, IX was assigned to the 21-epimer of VIII. Partial hydrogenation of VIII and IX on Pd-boride catalyst gave the corresponding dihydro derivatives, X and XI. The physical data are given in Table I.

1) Part XXXIII: D. Satoh and T. Hashimoto, *Chem. Pharm. Bull.* (Tokyo), **24**, 1950 (1976).
2) This work was reported at the 97th Annunal Meeting of the Pharmaceutical Society of Japan, April 6, 1977.
3) D. Satoh and H. Ishii, *Yakugaku Zasshi*, **80**, 1143 (1960).
4) D. Satoh, H. Ishii, K. Tori, T. Tozyo, and J. Morita, *Ann.*, **685**, 246 (1965).
5) Spectroscopic data of IX: UV λ_{max}^{EtOH} nm (ε): 283 (18420); IR ν_{max}^{KBr} cm^{-1}: 3580 (OH), 1725, 1745 (C=O), 1620 (C=C); NMR ($CDCl_3$, δ). 6.50 (br. s., 16-H), 6.20 (br. s., 21-H), 1.28 (t, J=7 cps, 21-$OCH_2\underline{CH_3}$), 6.02 (br. s., 22-H).

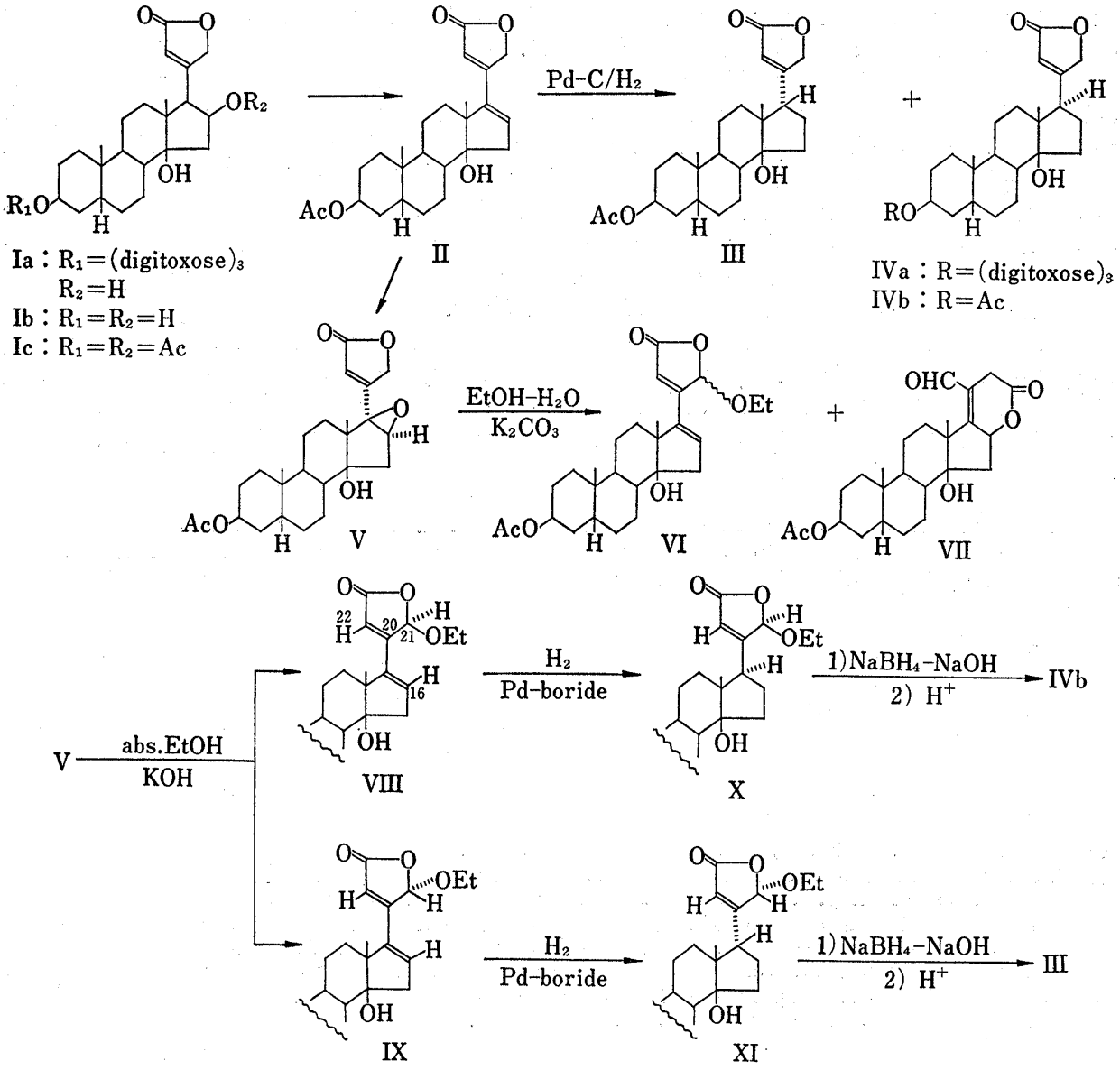

Chart 1

TABLE I. Physical Data of X and XI

		X ($C_{27}H_{40}O_6$)	XI ($C_{27}H_{40}O_6$)
mp		189—190°	178—180°
UV λ_{max}^{EtOH} nm (ε)		221.5(11150)	221(12530)
IR ν_{max}^{KBr} cm^{-1}	OH	3520	3500
	C=O	1760, 1720	1765, 1735
	C=C	1650	1640
NMR ($CDCl_3$) δ (ppm)	17-H	2.64(m)	3.24(m)
	21-H	5.67(br. s)	5.74(br. s)
	21-$OCH_2\underline{CH_3}$	1.28(t, J=7 cps)	1.28(t, J=7 cps)
	22-H	6.08(br. s)	5.91(br. s)
CD λ_{max}^{MeOH} nm ($\Delta\varepsilon$)	π-π^*	227.5 (+5.03)	225 (−9.30)
	n-π	250 (−5.39)	248.5 (+9.39)

The ultraviolet (UV) and nuclear magnetic resonance (NMR) data supported that VIII as well as IX underwent hydrogenation at 16,17-double bond,[4] and CD data disclosed the configuration at C-21: 21*R* for X and 21*S* for XI.[6,7]

The reduction of X and XI with $NaBH_4$ in the presence of NaOH and the subsequent acidification afforded digitoxigenin 3-acetate (IVb) and 17α-digitoxigenin 3-acetate (III), respectively in good yield. The result offered us a new method for the conversion of gitoxigenin (Ib) to digitoxigenin 3-acetate (IVb) and also allowed the assigment of the full stereochemistry of X and XI.[8] From these results, the structures of 16,17-dehydro-21*R*-ethoxydigitoxigenin 3-acetate and 21*R*-ethoxydigitoxigenin 3-acetate were assigned to VIII and X, and the structures of 16,17-dehydro-21*S*-ethoxydigitoxigenin 3-acetate and 21*S*-ethoxy-17α-digitoxigenin 3-acetate were also assigned to IX and XI, respectively.

The overall yield of IVb starting from Ib could have been raised to 22.6% by improving the yield of VIII by using 0.03% K_2CO_3 in dilute ethanol, where VIII was obtained in 61.6% along with 12.6% VII and trace of IX. In terms of the transformation of Ib to IVb, the present method is apparently superior than the previous method (3.4%), though three more steps are required.

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6) I. Uchida and K. Kuriyama, *Tetrahedron Lett.*, **1974**, 3761.
7) G. Snatzke, H. Schwang, and P. Welzel, "Some Newer Physical Methods in Structural Chemistry," ed. by R. Bonnet and J.D. Davis, United Trade Press, London, 1967, p. 159.
8) The stereospecific hydrogenation of 16,17-double bonds in VIII and IX could be explained by the participation of 21-ethoxy groups. Since 16,20(22)-dienolactone system is believed to take a transoid form,[9] as shown in structures, attack of hydrogen was strongly favored on the opposite side of the 21-substituent.
9) The transoid form of II was proved by CD Cotton effect of the mixture of II and some transition metal salt, and the results will be published in the near future.

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Ammonia Adducts of Chloramphenicol and Chloramphenicol Palmitate

Chloramphenicol and chloramphenicol palmitate were found to form adducts with ammonia. Both ammonia adducts are so unstable at room temperature that ammonia free antibiotics are easily recovered by rapid elimination of ammonia. Particle size was reduced for chloramphenicol palmitate by repeating sorption and subsequent desorption of ammonia.

Keywords——chloramphenicol; chloramphenicol palmitate; ammonia compound; ammonia adduct; particle size reduction

We have studied the particle size reduction of barbiturates, sulfonamides, antidiabetics, and others by desorption of ammonia from their ammonia compounds, or their ammonia adducts. Recently, chloramphenicol (CP) and chloramphenicol palmitate (CP-palmitate) were found to form adducts with ammonia.