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Studies on Digitalis Glycosides. XXXII.[1] Condensation of 17β-(3-Furyl)-5β,14β-androstane-3β,14,16β-triol with Carbonyl Compounds[2]

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A novel condensation reaction was found to take place between 17β-(3-furyl)-5β,14β-androstane-3β,14,16β-triol (III) and carbonyl compounds in the presence of anhydrous cuppric sulfate or acid to afford 6′-substituted-6′H-5β,14β-androstano[16,17-2′,3′]furo[3″,2″-4′,5′]pyran-3β,14-diol (IV, IV′, IX, X). The structures of these products were elucidated by their spectral data and chemical transformations.

A favorable method to synthesize furan derivatives from α,β-unsaturated γ-lactones by dialkylaluminum hydride reduction was found by Minato, *et al*[4] and several cardenolides (I) were transformed into the steroids having furan rings as their 17-side chains. The fact that these furanosteroids (II) exhibited cardiotonic activities and cytotoxic as well as antiviral activities analogously to the original cardenolides was revealed by Minesita, *et al*[5] and Katagiri, *et al*[6] respectively. These attractive results prompted us to investigate the acetonide synthesis of these furanosteroids (II) as an extended series of our studies on the lipophylic derivatives of cardenolides. During the work, a novel condensation reaction was found to proceed between 17β-(3-furyl)-5β,14β-androstane-3β,14,16β-triol (III) and acetone as well as some other carbonyl compounds. This paper deals with these findings.

When III was treated with anhydrous cuppric sulfate or *p*-toluenesulfonic acid in acetone at room temperature, an unexpected compound (IV) was readily obtained as a single product. This product (IV), $C_{26}H_{38}O_4$, mp 192—195°, showed positive Ehlrich and also Carr–Price reactions and exhibited a maximum absorption at 213 mμ in the ultraviolet spectrum (UV). This observation indicated the existence of a furan ring in the molecule. The nuclear magnetic resonance spectrum (NMR) of IV exhibited two vinyl proton signals at 2.65 τ and 3.71 τ (doublet, J=2 cps, respectively), while that of the material (III) showed three vinyl proton signals of furan ring[7] at 2.64 τ (broad singlet, 21-H[8]) and 2.63 τ (doublet, J=2 cps, 23-H[8]) and 3.53 τ (triplet, J=1 cps, 22-H[8]). The fact that one of the two protons at α-positions (lower field signals) in the furan ring of III disappeared in IV and the remaining two vinyl proton signals displayed doublets with the same coupling constant (2 cps)[9] showed that

1) Part XXXI: D. Satoh and K. Aoyama, *Chem. Pharm. Bull.* (Tokyo), **18**, 94 (1970).
2) *a*) This work was reported at the Meeting of Kinki-Branch, Pharmaceutical Society of Japan, Osaka, October 26, 1969. *b*) Dedicated to Professor Dr. R. Tschesche on his 65th birthday.
3) Location: *Sagisu, Fukushima-ku, Osaka.*
4) H. Minato and T. Nagasaki, *J. Chem. Soc.* (*C*), **1966**, 377; *idem*, *Ann. Rept. Shionogi Res. Lab.*, **18**, 90 (1968).
5) T. Minesita, R. Hirota, S. Kimoto, M. Uno, and Y. Uemura, *Ann. Rept. Shionogi Res. Lab.*, **18**, 94 (1968).
6) S. Matsuura, M. Maru, A. Nomura, K. Kori, and K. Katagiri, *Ann. Rept. Shionogi Res. Lab.*, **18**, 103 (1968).
7) L.M. Jackman, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, p. 64; R.J. Abraham and H.J. Bernstein, *Can. J. Chem.*, **39**, 905 (1961).
8) Numberings in side chain are tentative.
9) NMR signals of 2,3-vicinal vinyl protons in furan ring fused at 4,5-positions showed analogous patterns in general. L. Canomica, G. Jommi, P. Manitta, and F. Pelizzoni, *Tetrahedron Letters*, **1963**, 2079; G. Lukas, J.C.N. Ma, J.A. McCloskey, and R.E. Wolff, *Tetrahedron*, **20**, 1789 (1964).

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the hydrogen atoms at 22- and 23- positions retained intact in IV, and further the appearance of a *gem*-dimethyl proton signals at 8.55 τ and 8.60 τ in the NMR of IV suggested that the hydrogen atom at 21-position was replaced by acetone molecule.

Since, on the other hand, 17β-(3-furyl)-5β,14β-androstane-3β,14-diol[4] and its 16,17-dehydro derivative[4] (V) as well as 3,16-diacetate (VI) of III were all unchanged in the analogous reaction with acetone, 16-hydroxyl group should take part in the formation of IV. Moreover, in the NMR of IV, 16-proton signal was observed at 5.39 τ (multiplet) exhibiting a connection of an oxygen linkage at 16-position. The fact that IV gave only a monoacetate (VII)

Table I. Principal NMR Signals of Condensation Products (τ, 60 Mc)

Compd.	16-H	22-H	23-H	24-H[8]	Substituent at C-24
IV (CD_3OD)	5.39 (m)	3.71 (d)	2.65 (d)	—	{8.55 (CH_3,S) 8.60 (CH_3,S)
IX (CD_3OD)	5.59 (m)	3.69 (d)	2.66 (dd)	5.50 (m)	8.58 (CH_3,d)
X ($CDCl_3$)	5.44 (m)	3.70 (d)	2.75 (d)	4.54 (d)	2.61—2.80 (C_6H_5,m)

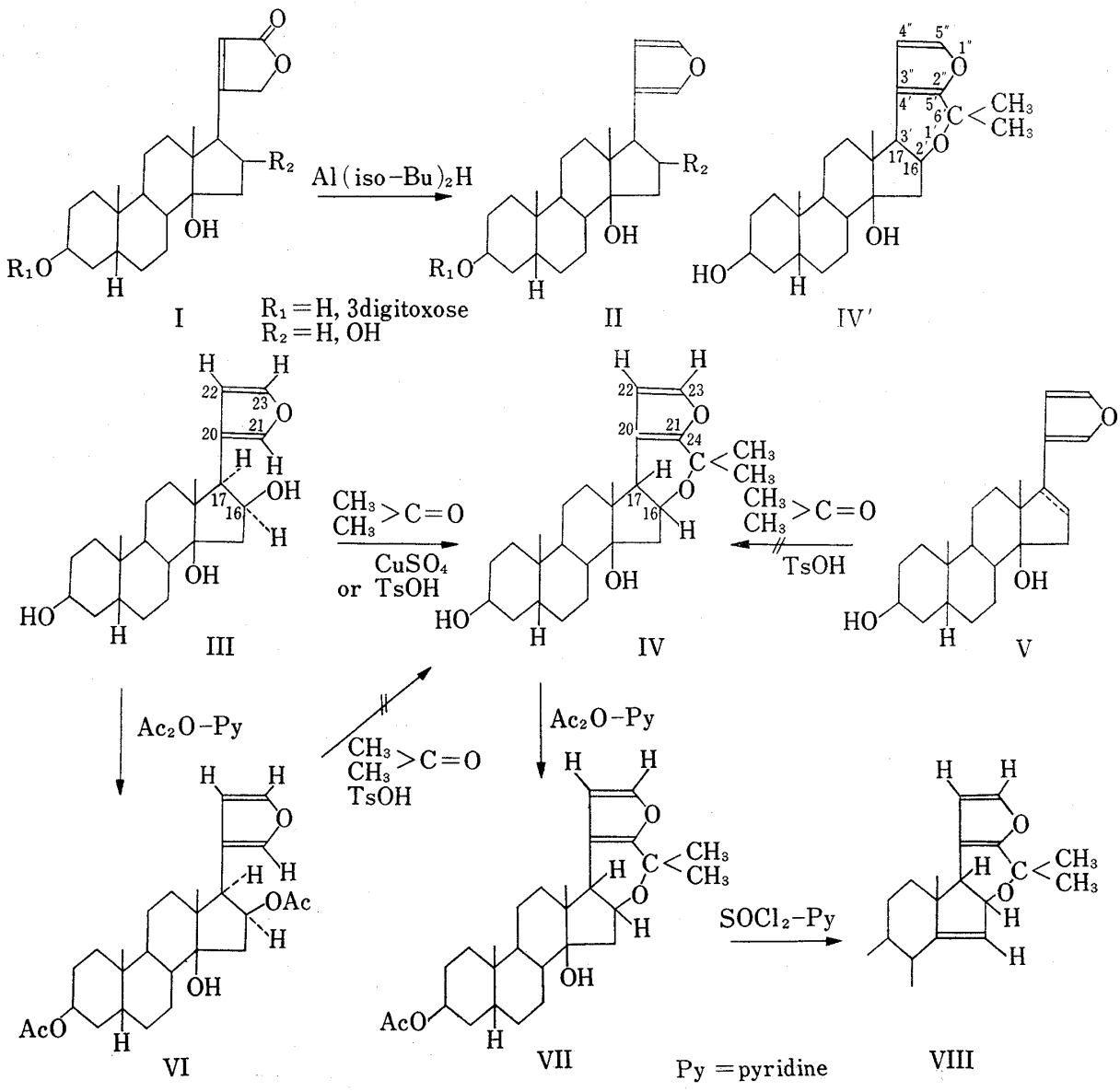

Chart 1

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and VII formed 14-anhydro derivative (VIII) on treatment with thionyl chloride indicated the existence of hydroxyl groups at 3- and 14-positions. From these results, 16-oxygen atom was thought to make a linkage with the acetone substituent at 21-position and formed a dihydro-furopyran ring. Accordingly, it is most reasonable to assign the formula (IV), formally designated as 6′,6′-dimethyl-6′H-5β,14β-androstano[16,17-2′,3′]furo[3″,2″-4′,5′]pyran-3β,14-diol-(IV′), to the condensation product.

Treatment of III with acetaldehyde and benzaldehyde in the presence of acid catalyst (AcOH or TsOH) at room temperature gave condensation product (IX),[10] $C_{25}H_{36}O_4$, mp 197—200°, and (X),[11] $C_{30}H_{38}O_4$, mp 195—196°, respectively. Both products showed positive Ehrlich reaction and exhibited the signals analogous to those of IV as the principal chemical shifts in the NMR as shown in Table I.

These data showed that products IX and X have the analogous partial structure of dihydrofuropyran. From the above mentioned results, it was clarified that 17β-(3-furyl)-5β,14β-androstane-3β,14,16β-triol (III) caused a novel condensation with carbonyl compounds to form dihydrofuropyrano steroids, and its structure was confirmed by the following transformations.

m-Chloroperbenzoic acid oxidation of VII gave a lactol (XI), $C_{28}H_{40}O_7$, mp 216—222°, in good yield, and reduction of XI with sodium borohydride and subsequent acidification afforded a lactone (XII), $C_{28}H_{40}O_6$, mp 229—235°, in fair yield. The lactol and lactone partial structures of the both products were deduced by their physical data analogous to those of gitoxigenin diacetate (XIV) as shown in Table II. Thus, in the NMR of XI and XII, a vinyl proton signal (22-H) of butenolide ring was observed with the comparable chemical shift to that of XIV in the reasonable coupling, respectively, and their UV and infrared (IR) spectra also corresponded to those of XIV. The fact that the lactol (XI) was converted to the lactone (XII) by sodium borohydride reduction was supported in the NMR spectrum by an appearance of one proton signal at 5.31 τ (1H, triplet, 21-H), the chemical shift of which is corresponding to that of XIV (5.07 τ, 2H, triplet, 21-H), instead of a disappearance of the 21-hydroxyl group.[12]

Table II. Characteristic Data in UV, IR and NMR Spectra of Transformation Products

Compds.	UV λ_{max}^{EtOH} mμ (ε)	IR $\nu_{max}^{CHCl_3}$ cm^{-1}		NMR, τ (60 Mc, $CDCl_3$)				
				Vinyl protons			21-H	24 *gem*-$(CH_3)_2$
				15-H	16-H	22-H		
XI	227 (10500)[13]	1762, 1642	1723,	—	5.58 (m)[14]	4.17 (s)	—	8.63 (s) 8.90 (s)
XII	230 (10500)[13]	1752, 1626	1729,	—	5.63 (m)[14]	4.14 (d)	5.31 (1H, t)	8.58 (s) 9.05 (s)
XIV	218 (15000)	1733, 1631	1717,	—	4.50 (m)[14]	4.01 (t)	5.07 (2H, t)	—
XIIIa	230 (10500) 345 (23300)	1736, 1572	1608,	3.95 (dd)	2.94 (d)	4.08 (broad s)	4.89 (1H,d)	8.66 (s) 8.82 (s)
XV	223 (11600) 338 (20700)	1723, 1577	1611,	3.95 (dd)	3.26 (d)	4.17 (t)	4.96 (2H, d)	—

10) Full name is 6′-methyl-6′H-5β,14β-androstano[16,17-2′,3′]furo[3″,2″-4′,5′]pyran-3β,14-diol.
11) Full name is 6′-phenyl-6′H-5β,14β-androstano[16,17-2′,3′]furo[3″,2″-4′,5′]pyran-3β,14-diol.
12) Observed at 2.52 τ (s) in NMR (60 Mc, DMSO-*d*6) of XI.
13) Red shift and lower intensity as compared to those of XIV were presumed to due to some strain in butenolide ring caused by fusing hydropyran ring.
14) Proton signal of hydrogen atom attaches to carbon bearing oxygen function and not that of vinyl proton.

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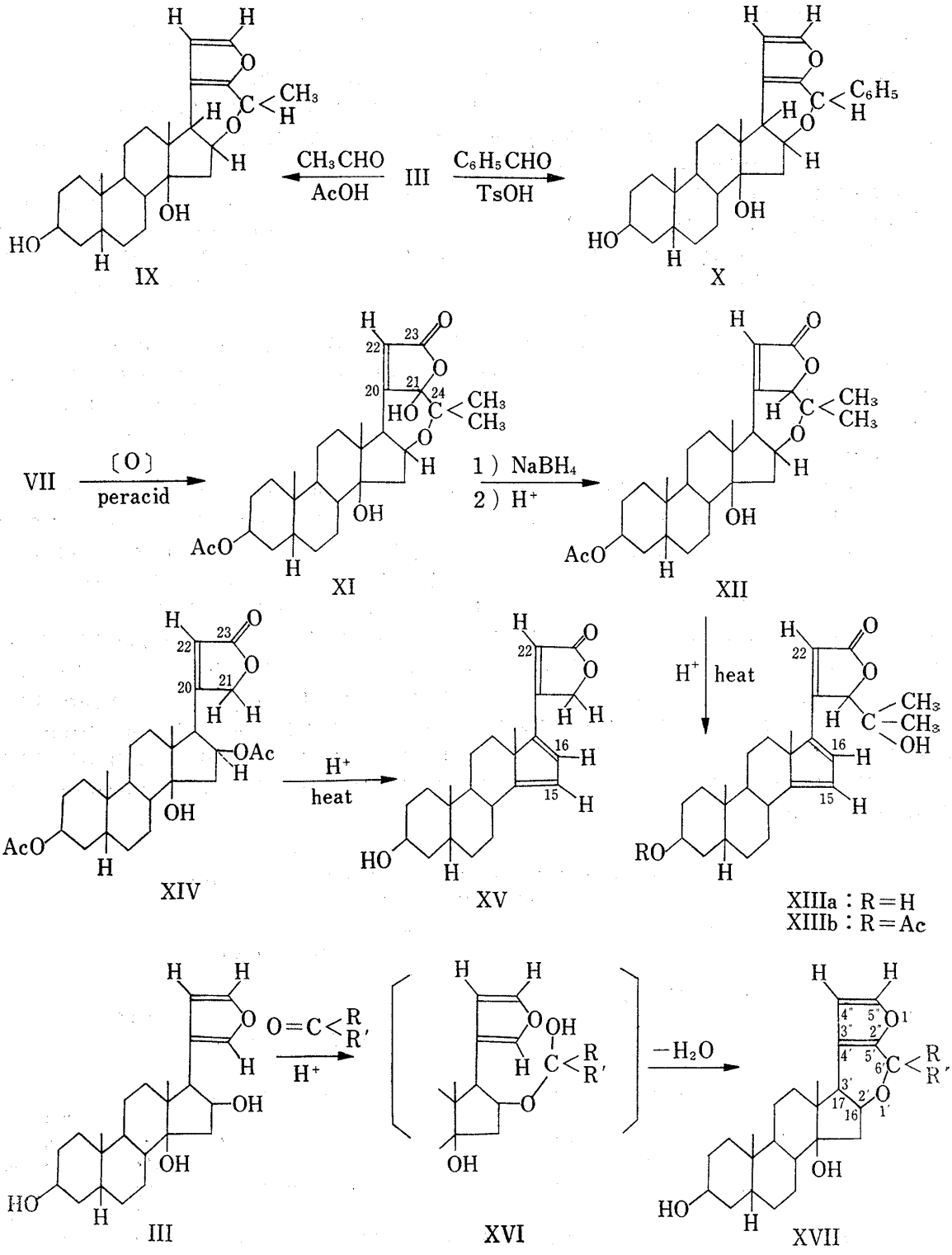

Chart 2

Since the synthesis of α,β-unsaturated γ-lactone from furan by peracid oxidation and subsequent reduction is well known,[15] the formation of XI and XII from VII provided a chemical proof of furan ring of VII. Moreover, the fact that the NMR of XII exhibited a

15) K. Takeda, H. Minato, M. Ishikawa, and M. Miyawaki, *Tetrahedron*, **20**, 2655 (1964); F. Catala and M.J. Defaye, *Compt. Rend.*, **258**, 4094 (1964); J.M. Ferland, Y. Lefebvre, and R. Deghenghi, *Tetrahedron Letters*, **1966**, 3617.

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gem-dimethyl signal and a proton signal due to 21-H together with that of 16-H as shown in Table II presented a further evidence for the linkage between C-16 and C-21 with –O–C-$(CH_3)_2$– chain forming a dihydropyran ring.

When lactone (XII) was refluxed with 4% hydrochloric acid in 50% ethanol, a product (XIIIa), $C_{26}H_{36}O_4$, mp 243—246° was obtained. The UV, IR and the NMR spectra of XIIIa were comparable to those of the known 14,16-dianhydrogitoxigenin (XV), formed from gitoxigenin diacetate (XIV) by the similar anhydration reaction, as shown in Table II, except the disappearance of one proton at C-21 owing to a substitution by a group having a *gem*-dimethyl moiety at this position in XIIIa. This dianhydro compound gave monoacetate (XIIIb), $C_{28}H_{38}O_5$, mp 214—216°, whose IR spectrum exhibited hydroxyl bands at 3600 and 3440 cm^{-1}. These results indicated that XIII is a 14,16-dianhydro compound bearing an isopropanol substituent at C-21, formed upon cleavage of dihydropyran ring of XII between C-16 and C-24.[8]

The above mentioned condensation reaction of 17β-(3′-furyl)-5β,14β-androstane-3β,14,16β-triol (III) with carbonyl compounds could be understood to proceed through a hemiacetal (XVI) as a likely intermediate to form 6′-substituted-6′H-5β,14β-androstano[16,17-2′,3′]furo[3″,2″-4′,5′]pyran-3β,14-diol (XVII) as shown in Chart 2.

Experimental[16]

Condensation of 17β-(3-Furyl)-5β,14β-androstane-3β,14,16β-triol (III) with Acetone to IV——i) With $CuSO_4$ Catalyst: To a solution of III (100 mg) in absolute acetone (30 ml) was added anhydrous $CuSO_4$ (1.25 g) and the mixture was stirred at room temperature for 1.5 hr. After removing of $CuSO_4$ by filtration, the filtrate was evaporated to dryness *in vacuo* to give a residue (106 mg) as an almost homogeneous foam, which was recrystallized from acetone to give IV (96 mg) as colorless crystals, mp 192—195°, $[\alpha]_D^{28}$ +28.4° (c=0.162, $CHCl_3$). *Anal.* Calcd. for $C_{26}H_{38}O_4 \cdot \frac{1}{2}H_2O$: C, 73.73; H, 9.28. Found: C, 73.45; H, 8.98. UV λ_{max}^{EtOH} mμ (ε): 213 (6100). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (OH), 1603 (furan ring). NMR datum was described in Table I.

ii) With TsOH Catalyst: A solution of III (100 mg) in acetone (2 ml) containing 1% TsOH was kept at room temperature for 45 min and then neutralized with 5% $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with 5% $NaHCO_3$ to remove TsOH, dried over Na_2SO_4 and evaporated *in vacuo* to give an almost homogeneous product (110 mg), which was recrystallized from acetone–*n*-hexane to afford IV (92 mg) as colorless crystals: mp 192—195°.

Condensation of III with Acetaldehyde to IX——To a solution of III (100 mg) in benzene (30 ml) containing 1% AcOH was added afresh distilled acetaldehyde (1 g), and the mixture was set aside overnight at room temperature. The resulted solution was extracted with 10% $NaHSO_3$ to remove the excess of acetaldehyde and washed with H_2O, dried over Na_2SO_4 and then evaporated to dryness *in vacuo* to give a residue (95 mg). The crude product was submitted to preparative TLC (SiO_2 Merck, $CHCl_3$: acetone=7:1) to separate the main fraction (58 mg) which was recrystallized from AcOEt–*n*-hexane to afford IX (45 mg) as colorless crystals, mp 197—200°, $[\alpha]_D^{22}$ +7.2° (c=0.929, MeOH). *Anal.* Calcd. for $C_{25}H_{36}O_4 \cdot \frac{1}{2}H_2O$: C, 73.31; H, 9.11. Found: C, 73.58; H, 9.00. UV λ_{max}^{EtOH} mμ (ε): 217 (5910). NMR datum was described in Table I.

Condensation of III with Benzaldehyde to X——To a solution of III (100 mg) in benzene (20 ml) saturated with TsOH was added benzaldehyde (1 g), and the mixture was left at room temperature overnight. The solution was extracted with 10% $NaHSO_3$ to remove the excess of benzaldehyde and washed with H_2O, dried over Na_2SO_4 and evaporated to dryness *in vacuo* to afford a crude product (98 mg) which was submitted to preparative TLC (SiO_2 Merck, $CHCl_3$: acetone=8:1). The main fraction (65 mg) was recrystallized from AcOEt–*n*-hexane to give X, mp 195—196°, $[\alpha]_D^{28}$ −40.0° (c=0.430, $CHCl_3$). *Anal.* Calcd. for $C_{30}H_{38}O_4$: C, 77.89; H, 8.28. Found: C, 78.08; H, 7.98. NMR datum was described in Table I.

17β-(3-Furyl)-5β,14β-androstane-3β,14,16β-triol 3,16-Diacetate (VI)——A mixture of III (50 mg), pyridine (0.5 ml) and Ac_2O (0.5 ml) was kept at room temperature for 6 hr and further in a refrigerator overnight. The crude acetate (46 mg) collected in the usual manner was recrystallized from ether–petroleum ether to give VI as colorless crystals, mp 172—174°. *Anal.* Calcd. for $C_{27}H_{38}O_6$: C, 70.71; H, 8.35. Found: C, 70.78; H, 8.25. NMR (CD_3OD, τ): 2.69 (1H, t), 2.76 (1H, m) (21-H and 23-H), 3.37 (1H, d, 22-H), 4.48 (1H, m, 16-H), 4.91(1H, m, 3-H), 7.97 (3H, s, 3-OAc), 8.25[17] (3H, s, 16-OAc), 9.01 (3H, s, 19-CH_3), 9.24[17] (3H, s, 18-CH_3).

16) All melting points are uncorrected and NMR spectra were measured at 60 Mc.

17) Both chemical shifts were shifted to highter field than those (8.04 and 9.06 τ respectively) of gitoxigenin 3,16-diacetate (XIV) owing to anisotropic effect of furan ring.

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Acetylation of IV——A mixture of IV (400 mg), pyridine (4 ml) and Ac_2O (4 ml) was kept at room temperature for 48 hr, and the resulted solution was treated in the usual manner to give a crude acetate (456 mg) which was recrystallized from ether to afford VII (360 mg) as colorless crystals, mp 192—194°. *Anal.* Calcd. for $C_{28}H_{40}O_5$: C, 73.65; H, 8.83. Found: C, 73.73; H, 8.89. NMR (CD_3OD, τ): 2.65 (1H, d, 23-H), 3.72 (1H, d, 22-H), 4.92 (1H, m, 3-H), 5.37 (1H, m, 16-H), 7.97(3H, s, 3-OAc), 8.55 and 8.60 (3-H, S, respectively, *gem*-dimethyl), 9.02 (3-H, s, 19-CH_3), 9.05 (3-H, s, 18-CH_3).

Dehydration of VII to VIII——To a solution of VII (200 mg) in pyridine (2 ml) was added $SOCl_2$ (0.3 ml) under stirring at −20° and stirring was continued for 30 min at the same temperature. The excess of $SOCl_2$ was decomposed with ice and the mixture was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with 5% HCl, 5% $NaHCO_3$, and H_2O successively, dried over Na_2SO_4 and evaporated to dryness *in vacuo* to afford a crude product (207 mg), which was submitted to preparative TLC (SiO_2 Merck, $CHCl_3$) to seperate a main product. Recrystallization of the main fraction (128 mg) from petroleum ether to give VIII (63 mg) as colorless crystals, mp 154—155°. *Anal.* Calcd. for $C_{28}H_{38}O_4$: C, 76.67; H, 8.73. Found: C, 76.24; H, 9.01. NMR (CD_3OD, τ): 2.65 (1H, d, 23-H), 3.77 (1H, d, 22-H), 4.58 (1H, m, 15-H), 4.96 (1H, m, 3-H), 5.35 (1H, m, 16-H), 8.56 (6H, s, *gem*-2CH_3), 8.97 (3H, s, 19-CH_3), 9.16 (3H, s, 18-CH_3).

Oxidation of VII to Lactol (XI)——To a solution of VII (175 mg), AcOH (0.18 ml) and AcONa (175 mg) in $CHCl_3$ (9 ml) was added *m*-chloroperbenzoic acid (250 mg, 80% content, 3 moles) in portionwise at 0° under stirring. After the mixture was further stirred for 2 hr at room temperature, an aqueous solution of $NaHSO_3$ (100 mg) was added to destroy the excess of the peracid, and the mixture was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with 5% $NaHCO_3$ and H_2O to remove *m*-chlorobenzoic acid, dried over Na_2SO_4 and evaporated to dryness *in vacuo* to afford a crude product (210 mg), which was recrystallized from CH_2Cl_2 to give XI (147 mg), mp 216—222°. $[\alpha]_D^{25}$ −95.2° (c=0.545, $CHCl_3$). *Anal.* Calcd. for $C_{28}H_{40}O_7$: C, 68.83; H, 8.25. Found: C, 68.61; H, 8.03. UV, IR and NMR data were described in Table II.

Reduction of XI to Lactone (XII)——To a solution of XI (200 mg) in 95% dioxane (15 ml) was added $NaBH_4$ (75 mg) in portionwise under stirring at room temperature, and the mixture was further stirred for 1 hr at the same temperature to complete the reduction. After acidification with 5% HCl to pH 2.2, the resulted solution was kept at room temperature for 5 hr. The acidic solution was neutralized with 5% Na_2CO_3, concentrated *in vacuo* and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried over Na_2SO_4 and evaporated to dryness *in vacuo* to afford a crude product (180 mg) which was submitted to preparative TLC (SiO_2 Merck, benzene: AcOEt=1:1) to seperate the main product. Recrystallization of the main fraction (88 mg) from CH_2Cl_2–ether gave XII (75 mg) as colorless crystals, mp 229—235°. *Anal.* Calcd. for $C_{28}H_{40}O_6$: C, 71.16; H, 8.53. Found: C, 71.13; H, 8.78. UV, IR and NMR data were described in Table II.

Cleavage of XII to XIIIa——A mixture of XII (115 mg) and 4% HCl in 50% EtOH (20 ml) was refluxed for 5 hr and the resulted solution was neutralized with 5% Na_2CO_3. The precipitate (59 mg) was collected by filtration and recrystallized from MeOH to give XIIIa (42 mg) as pale yellow crystals, mp 243—246°. *Anal.* Calcd. for $C_{26}H_{36}O_4$: C, 75.69; H, 8.80. Found: C, 75.64; H, 9.08. UV, IR and NMR data of XIIIa were described in Table II.

Acetylation of XIIIa——A mixture of XIIIa (25 mg), pyridine (1 ml) and Ac_2O (1 ml) was left at room temperature overnight. The resulted solution was treated in the usual manner to afford a crude acetate, which was recrystallized from AcOEt–*n*-hexane to give XIIIb (15 mg) as colorless crystals, mp 214—216°. *Anal.* Calcd. for $C_{28}H_{38}O_5$: C, 73.98; H, 8.43. Found: C, 74.10; H, 8.53. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3440 (OH), 1735, 1608 (Ac, butenolide ring), 1573 (conjugated double bond).

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