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Studies on Digitalis Glycosides. XXXVII.[1] Diels-Alder Reaction of 16,17-Dehydrodigitoxigenin 3-Acetate (2)[2]

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The product (III) was obtained by Diels–Alder reaction of 16,17-dehydrodigitoxigenin 3-acetate (I) with ethyl acrylate on heating. The structure of III was determined by X-ray analysis, and III was found to be a head to head adduct of ethyl acrylate on the β-side of the 16,20(22)-diene moiety of I. The analogous reaction of I with dimethyl maleate gave two products (VI and VII) in similar yields. The structure of VI was also determined by X-ray analysis, and VII was considered to be the 24-epimer of VI, based on the spectral data and interconversion between VI and VII upon alumina treatment. In VI and VII, the double bond was found to be shifted towards the conjugated position from the original position in the diene synthetic product. Dimethyl fumarate gave a normal product (X) on addition to I on the β-side of the diene system. Upon alumina treatment, X was transformed into VI and VII, confirming the structures of VII and X. By analogy with the β-side addition of the above dienophiles, the configurations of 16-H and 22-H of the dimer (II) were both proposed to be α.

Keywords——16,17-dehydrodigitoxigenin 3-acetate; ethyl acrylate; dimethyl maleate; dimethyl fumarate; Diels-Alder reaction; dimerization; diene synthetic adduct; X-ray analysis; epimerization; spin-spin decoupling

In the previous paper,[1] we reported that the dimerization of 16,17-dehydrodigitoxigenin 3-acetate (I) gave II by a Diels–Alder type reaction. In order to elucidate the stereochemistry of the dimer, we have studied the diene synthetic reaction of I with simple dienophiles, and the present paper reports the results.

I was heated with ethyl acrylate at 110—120°C for 96 h in a closed test tube under a nitrogen atmosphere and the reaction product was crystallized from methanol to give a compound (III),[3,4] mp 175—178°C, $C_{30}H_{42}O_7$, as a main product. Spectral data are listed in Tables I and II. The results of elemental analysis, the blue shift of absorption maximum from 270 nm for I to 211 nm for the product in the ultraviolet (UV) spectrum, and the chemical shifts (δ 1.20 and δ 4.06) due to the ethoxy group in the proton magnetic resonance (^{1}H-NMR) spectrum proved that this product corresponds to a Diels–Alder adduct of ethyl acrylate to the 17,20(22)-diene moiety of I. The mode of addition of ethyl acrylate was found to be head to head type (formula III) since the signal of 22-H (δ 2.88) is a broad doublet; if head to tail type (formula IV) addition had occurred the proton signal of 22-H should be a triplet. In order to determine the type and the orientation of the addition reaction, we carried out X-ray analysis of the product. Crystal data: $C_{30}H_{42}O_7$, $P2_1$ (space group), a=19.457(2), b=6.617(1), c=11.001(1) Å, β=97.07(1)°, Z=2. The structure was solved by use of the program MULTAN 76[5] and refined by the block-diagonal least-squares method to an R value of 0.048 for 2231[6] reflections. Final atomic parameters are listed in Table III. A perspective view of the molecule with the atom numbering scheme[3] is shown in Figure I, from which the formula III was assigned for the product. The structure revealed that the β-side addition of ethyl acrylate is head to head type, affording a *endo* form (III).

I was heated with dimethyl maleate at 110—120°C for 192 h and the reaction mixture was subjected to column chromatography (SiO_2, benzene–ether mixture). The less polar fraction

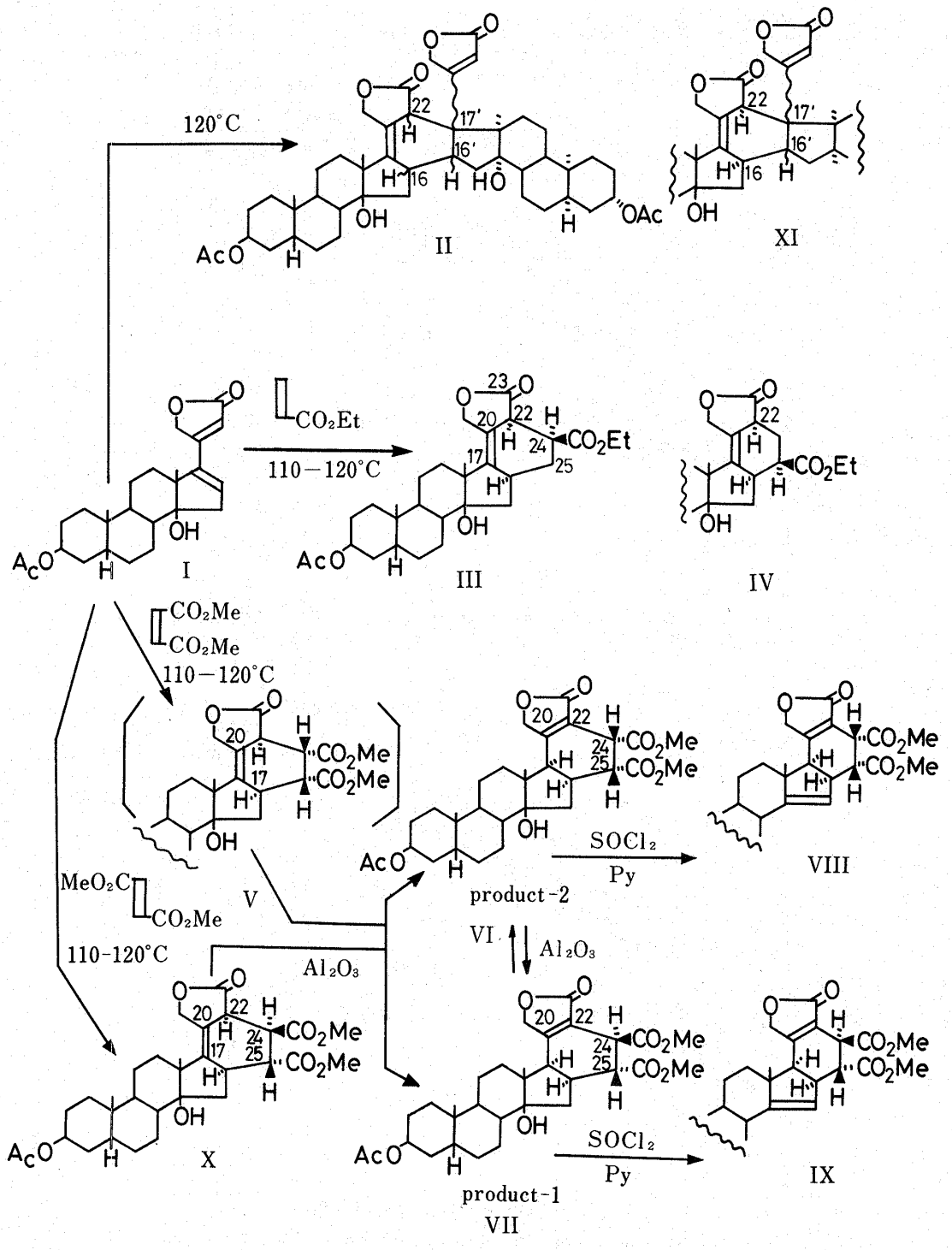


Chart 1

gave product-1 (formula VII),[3,4] mp 175—177°C, $C_{31}H_{42}O_9 \cdot 1/2H_2O$, while the more polar fraction gave product-2 (formula VI),[3,4] mp 207—208°C, $C_{31}H_{42}O_9 \cdot 1/2H_2O$. The yields of both products were similar, and the spectral data are listed in Table I and II.

The results of elemental analysis and the chemical shifts (δ 3.62, 3.69 and δ 3.58, 3.62) in the ^{1}H-NMR spectra due to methoxy groups indicate that the two products are isomers of the Diels–Alder adduct of dimethyl maleate with I. The absorption maximum at 226 nm in the UV spectra of the products suggests that a shift of the double bond from the original position (17(20)-ene) in the diene synthetic adduct (V) to the conjugated position to form a 20(22)-cardenolide ring occurred during the reaction. To confirm this assumption, we carried

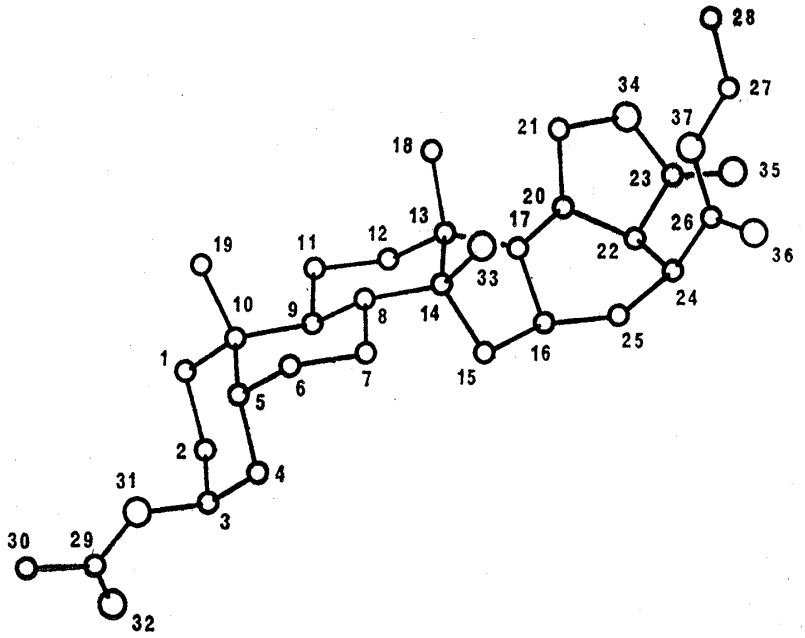


Fig. 1. Perspective View of III

This perspective view is based on the positional parameters in Table III. Circles indicate the positions of oxygen (larger) and carbon (smaller) atoms.

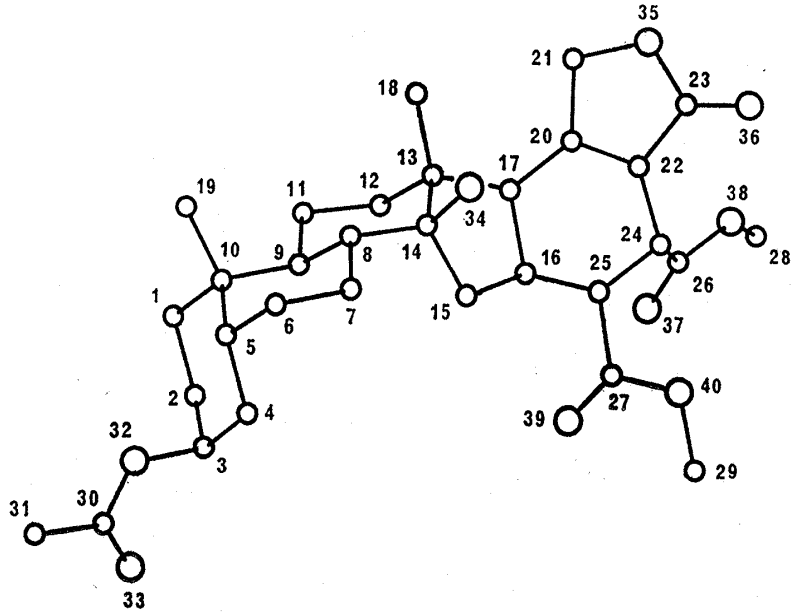
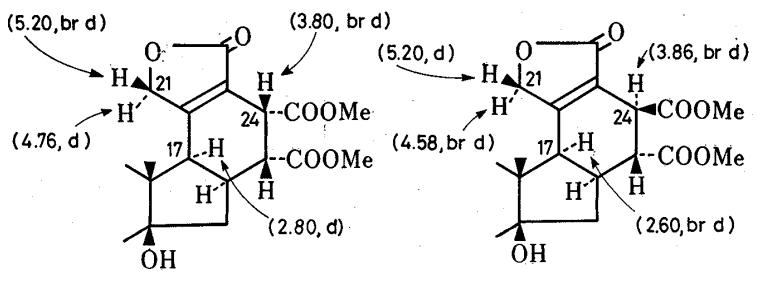


Fig. 2. Perspective View of VI

This perspective view is based on the positional parameters in Table III. Circles indicate the positions of oxygen (larger) and carbon (smaller) atoms.



VI product-2 VII product-1

Chart 2

out X-ray analysis of product-2 crystallized in solvated form from methanol. Crystal data: $C_{31}H_{42}O_9 \cdot CH_3OH$, $P2_1$ (space group), $a=16.758$ (1), $b=10.479(1)$, $c=8.692(1)$ A, $\beta=95.53(1)°$, $Z=2$. The structure was solved and refined as for III. The final R value was 0.057 for 2610[6] reflections. Final atomic parameters are listed in Table III. The methanol molecule is disordered in the crystal.[7] A perspective view of the molecule is given in Fig. 2. The results of X-ray analysis determined the conjugation of the double bond and β-side addition of dimethyl maleate to the 16,20(22)-diene system of I to give the *exo* form as shown in formula VI. Interconversion between product-1 and -2 occurred on alumina treatment in chloroform, and the addition reaction in a slightly basic medium, such as dimethyl formamide, gave product-1 preferentially. The center of epimerization is probably 24-C, because this position is most activated both by the double bond and the methoxycarbonyl group. Thus, the configuration of the methoxycarbonyl group at C-24 of product-1 was considered to be β, as shown in formula VII, and this assignment was supported by the ^{1}H-NMR spectral data. Partial structure and proton signals in the neighborhood of the epimerization center are shown in Chart 2. In the spin-spin decoupling studies, irradiation at the 24β-H signal (δ 3.80) of product-2 changed the broad doublet of 21β-H (δ 5.20) to a doublet, but did not affect the signals of 17α-H and 21α-H, as expected from the structure VI which was determined by

Table I. UV and IR Spectral Data

Compd.	λ_{max}^{EtOH} nm (log ε)	ν_{max}^{KBr} cm^{-1}		
		OH	C=O	C=C
III	211(3.82)	3480	1779, 1729	1650
VI	226(4.05)	3560	1756, 1750	1677
VII	226(4.02)	3500	1752, 1740	1664
VIII	218(4.11)		1766, 1745	1676
IX	219(4.12)		1775, 1744	1677
X	209(3.85)	3540	1781, 1741	1650

Table II. ^{1}H-NMR Spectral Data

Compd.	Chemical Shift[a] (100 MHz, $CDCl_3$, δ)						Others
	17-H	21α-H	21β-H	22-H	24-H	25-H	
III		4.92 (d, $J=14$)	5.20 (d, $J=14$)	2.88 (br d, $J=6$)	3.32 (m)		1.20 (d, $J=7$, $-OCH_2\underline{CH_3}$) 4.06 (m, $-O\underline{CH_2}CH_3$)
VI	2.80 (d, $J=8$)	4.76 (d, $J=16$)	5.20 (br d, $J=16$)		3.80 (br d, $J=4$)	3.06 (d, $J=4$)	3.58, 3.62 (s, $-COOCH_3\times2$)
VII	2.60 (br d, $J=7$)	4.58 (br d, $J=16$)	5.20 (d, $J=16$)		3.86 (br d, $J=4$)	3.46 (dd, $J=4$, 3)	3.62, 3.69 (s, $-COOCH_3\times2$)
VIII	2.86 (d, $J=8$)	4.84 (br s)	4.84 (br s)		3.90 (d, $J=5$)	2.52 (dd, $J=12$, 5)	3.64, 3.70 (s, $-COOCH_3\times2$) 5.41 (br s, 15-H)
IX	2.76 (m)	4.60 (br d, $J=16$)	4.82 (br d, $J=16$)		3.41 (dd, $J=11$, 2)	2.56 (dd, $J=11$, 10)	3.68 (s, $-COOCH_3\times2$) 5.22 (br s, 15-H)
X		4.96 (d, $J=14$)	5.20 (d, $J=14$)	2.52 (d, $J=9$)	2.88 (dd, $J=9$, 4)	3.02 (br d, $J=4$)	3.62, 3.76 (s, $-COOCH_3\times2$)

a) Coupling constants, Hz.
s=singlet, d=doublet, m=multiplet, and br=broad.

X-ray analysis. In contrast, irradiation at the 24-H signal (δ 3.86) of product-1 changed the broad doublets of 17α-H (δ 2.60) and 21α-H (δ 4.58) to doublets, indicating long-range coupling between 24-H and 17α-H as well as 21α-H. These results suggest that the configuration of 24-H of product-1 is α, and this was confirmed by establishing the connection of product-1 with the adduct of dimethyl fumarate, as described below. Treatment of VI and VII with thionyl chloride and pyridine afforded anhydro derivatives VIII, mp 240—243°C, $C_{31}H_{40}O_8$, and IX, mp 175—176°C, $C_{31}H_{40}O_8$, respectively.

I was heated with dimethyl fumarate in toluene at 110—120°C for 96 h by a method analogous to that used for dimethyl maleate, and the reaction mixture was subjected to fractional crystallization to afford a main product X,[3,5] mp 136—137°C, $C_{31}H_{42}O_9 \cdot 1/2H_2O$, whose spectral data are listed in Tables I and II . The results of elemental analysis, the absorption maximum (209 nm) in the UV spectrum and the methoxy signals (δ 3.62 and 3.76) in the ^{1}H-NMR spectrum showed that the product is a normal diene synthetic adduct of dimethyl fumarate to I. Treatment of this product with alumina in chloroform gave VI and VII in similar yields, and the structure of VI was determined by X-ray analysis as described above. Therefore, the structure of the adduct of dimethyl fumarate should be as shown in formula X. Thus, the configuration of the methoxycarbonyl group at 24-C should be β and that at 25-C should be α. It is more reasonable to consider that the double bond (17(20)-ene) shift to the conjugated position (20(22)-ene) gave VII, and further epimerization of the 24-C substituent from β to α afforded VI.

By analogy with β-side addition of the above dienophiles (ethyl acrylate, dimethyl maleate and dimethyl fumarate), the configurations of 16-H and 22-H of the dimer (II) were proposed to be both α, as shown in formula XI, but those of 16′-H and the 17′-substituent remain to be determined.

Table III. Fractional Coordinates ($\times 10^4$) and Equivalent Isotropic Temperature Factors (Å$^2 \times 10^2$) for III and VI[a]

Compd.	Atom	x	y	z	B_{eq}
III	C (1)	761(2)	−45(9)	−4578(3)	403(9)
	C (2)	983(2)	1578(9)	−5442(3)	466(11)
	C (3)	1424(2)	714(9)	−6351(3)	449(10)
	C (4)	2038(2)	−481(9)	−5709(3)	423(10)
	C (5)	1821(2)	−2108(8)	−4832(3)	376(9)
	C (6)	2457(2)	−3205(8)	−4189(3)	413(9)
	C (7)	2903(2)	−1840(8)	−3290(3)	382(9)
	C (8)	2479(2)	−965(8)	−2323(3)	325(8)
	C (9)	1821(2)	133(8)	−2940(3)	320(8)
	C)10)	1369(2)	−1223(8)	−3879(3)	359(8)
	C)11)	1414(2)	1023(9)	−1957(3)	430(10)
	C (12)	1864(2)	2443(9)	−1114(3)	404(9)
	C (13)	2519(1)	1429(8)	−441(3)	306(8)
	C (14)	2932(1)	388(0)	−1403(2)	284(7)
	C (15)	3314(2)	2140(8)	−1938(3)	319(8)
	C (16)	3487(2)	3653(8)	−871(3)	340(8)
	C (17)	3006(2)	3047(7)	61(3)	310(8)
	C (18)	2324(2)	−56(8)	540(3)	403(9)
	C (19)	1043(2)	−2985(9)	−3215(9)	469(10)
	C (20)	3102(2)	4008(8)	1132(3)	328(8)
	C (21)	2756(2)	3861(9)	2279(3)	482(11)
	C (22)	3664(2)	5560(8)	1337(3)	378(9)
	C (23)	3664(2)	6129(8)	2665(3)	453(10)
	C (24)	4359(2)	4795(8)	974(3)	346(8)
	C (25)	4245(2)	3552(8)	−247(3)	402(9)

Compd.	Atom	x	y	z	B_{eq}
	C (26)	4773(2)	3491(8)	1935(3)	382(9)
	C (27)	4775(2)	1655(9)	3814(4)	538(12)
	C (28)	4295(3)	1639(11)	4782(4)	684(15)
	C (29)	653(2)	124(13)	−8190(3)	697(17)
	C (30)	297(3)	−1582(17)	−8940(4)	1040(27)
	O (31)	1021(1)	−717(8)	−7164(2)	563(8)
	O (32)	652(2)	1869(11)	−8417(3)	949(15)
	O (33)	3436(1)	−874(7)	−692(2)	316(5)
	O (34)	3124(1)	5258(7)	3123(2)	522(8)
	O (35)	4063(2)	7218(8)	3280(3)	672(10)
	O (36)	5379(1)	3114(8)	1922(3)	637(10)
	O (37)	4412(1)	2803(7)	2767(2)	434(7)
IV	C (1)	4040(2)	4415(6)	4942(5)	493(12)
	C (2)	3529(3)	3679(6)	3674(6)	608(15)
	C (3)	3514(3)	4322(7)	2116(6)	601(14)
	C (6)	3617(3)	7851(6)	3529(6)	606(14)
	C (7)	2774(3)	8026(6)	4054(5)	532(12)
	C (8)	2701(2)	7405(5)	5629(4)	377(9)
	C (9)	2962(2)	5999(5)	5630(4)	355(9)
	C (10)	3814(2)	5815(5)	5097(4)	386(9)
	C (11)	2858(3)	5392(6)	7222(5)	520(13)
	C (12)	1989(3)	5554(5)	7632(5)	491(12)
	C (13)	1712(2)	6950(5)	7654(4)	328(8)
	C (14)	1849(2)	7575(0)	6104(4)	326(8)
	C (15)	1190(2)	7019(6)	4973(4)	415(10)
	C (16)	463(2)	6745(5)	5897(4)	340(8)
	C (17)	775(2)	6941(5)	7644(4)	322(8)
	C (18)	2153(2)	7649(7)	9047(5)	524(13)
	C (19)	4464(3)	6421(7)	6270(6)	619(15)
	C (20)	341(2)	7997(5)	8376(4)	382(9)
	C (21)	575(3)	8754(7)	9815(6)	683(16)
	C (22)	−406(2)	8353(5)	7848(4)	365(9)
	C (23)	−686(3)	9350(6)	8862(5)	515(12)
	C (24)	−867(2)	7852(5)	6443(4)	361(9)
	C (25)	−253(2)	7581(5)	5271(4)	363(9)
	C (26)	−1349(2)	6675(5)	6810(4)	356(8)
	C (27)	−624(3)	7027(6)	3747(5)	445(10)
	C (28)	−2411(3)	5956(6)	8196(5)	492(12)
	C (29)	−1694(4)	7133(8)	1808(7)	817(20)
	C (30)	4407(4)	3365(8)	525(6)	756(19)
	C (31)	5232(4)	3417(9)	−40(8)	958(26)
	O (32)	4309(2)	4227(6)	1558(4)	762(12)
	O (33)	3887(4)	2649(9)	67(8)	1639(31)
	O (34)	1690(2)	8914(4)	6315(3)	448(7)
	O (35)	−127(2)	9535(6)	10040(5)	726(12)
	O (36)	−1300(2)	9952(5)	8727(4)	632(10)
	O (37)	−1280(2)	5645(5)	6280(4)	558(9)
	O (38)	−1871(2)	6968(5)	7799(3)	459(7)
	O (39)	−330(2)	6255(6)	2990(4)	738(12)
	O (40)	−1331(2)	7551(5)	3320(3)	619(10)
	C (41)	3607(7)	10773(12)	6858(15)	1441(44)
	O (42)	3279(15)	10258(19)	8036(21)	1802(86)
	O (42′)	3894(30)	11696(32)	7057(42)	2034(190)
	O (42″)	3038(14)	10862(29)	6004(33)	1658(101)

a) $B_{eq}=4/3\sum_i\sum_j\beta_{ij}\mathbf{a}_i\mathbf{a}_j$. Anisotropic thermal parameters, β_{ij}, obtained at the last cycle of the least-squares refinement were used. They are available on request from one of the authors (M.S.), but are not shown here for the sake of brevity. The estimated standard deviations are given in parentheses.

Experimental[8]

Adduct (III) from 16,17-Dehydrodigitoxigenin 3-Acetate (I) and Ethyl Acrylate——A mixture of I (500 mg) and ethyl acrylate (2 ml, excess) was heated at 110—120°C for 96 h in a closed test tube under nitrogen in an oil bath. Thin layer chromatography (TLC) (SiO_2, benzene: Et_2O=1: 4) of the reaction mixture showed the formation of a main product besides the unchanged materials. The sirupy reaction mixture was diluted with MeOH (1 ml) and left to stand overnight in a refrigerator. The crude product (277 mg) that resulted was collected by filtration and recrystallized from MeOH to give III (234 mg, 37.9%) as colorless prisms, mp 175—178°C, $[\alpha]_D^{23}$ +33.8° (c=0.5, $CHCl_3$), *Anal.* Calcd for $C_{30}H_{42}O_7$: C, 70.01; H, 8.23. Found: C, 69.78; H, 8.26.

Adduct (VI and VII) from I and Dimethyl Maleate——A mixture of I (1000 mg) and dimethyl maleate (4 ml, excess) was heated at 110—120°C for 192 h in a closed test tube under nitrogen in an oil bath. TLC (SiO_2, benzene: Et_2O: $CHCl_3$=2: 2: 1) of the reaction mixture showed the formation of two main products besides small amounts of a by-product and unchanged material (I), and the products were separated by column chromatography. Thus, the reaction mixture was diluted with benzene (3 ml) and adsorbed on SiO_2 (160 g), then eluted with benzene and benzene–Et_2O mixtures (9: 1)=(480 ml), (8: 2)=(480 ml), (7: 3)=(2520 ml), and (6: 4)=(4000 ml) successively; 40 ml fractions were collected. The residue (461 mg) from fraction Nos. 40—60, eluted with benzene–Et_2O (7: 3) mixture, was recrystallized from Et_2O to give VII (385 mg, 28.4%) as a colorless crystalline powder, mp 175—177°C, $[\alpha]_D^{23}$ −50.7° (c=0.5, $CHCl_3$), *Anal.* Calcd for $C_{31}H_{42}O_9 \cdot 1/2H_2O$: C, 65.59; H, 7.65. Found: C, 65.71; H, 7.91. The residue (472 mg) from fraction Nos. 65—88, eluted with the same solvent was recrystallized from MeOH to give VI (370 mg, 27.5%) as colorless plates, mp 207—208°C, $[\alpha]_D^{23}$ −59.7° (c=0.5, $CHCl_3$), *Anal.* Calcd for $C_{31}H_{42}O_9 \cdot 1/2H_2O$: C, 65.59; H, 7.65. Found: C, 65.41; H, 8.05. From fraction Nos. 29—39, eluted with the same solvent, and fraction Nos. 91—100, eluted with benzene–Et_2O (6: 4) mixture, an unknown by-product (68 mg) and the unchanged material (I, 45 mg) were recovered, respectively.

Adduct (VII) from I and Dimethyl Maleate in the Presence of *N*,*N*-Dimethylformamide——A mixture of I (100 mg), dimethyl maleate (0.4 ml) and dimethylformamide (DMF, 0.2 ml) was heated at 110—120°C for 144 h in a closed test tube under nitrogen in an oil bath. The reaction mixture was treated with MeOH (5 ml) and the crystals that resulted (dimer of DMF, 159 mg) were separated by filtration. The filtrate was evaporated to dryness *in vacuo*, and the residue (230 mg) was subjected to double development preparative TLC (SiO_2, benzene: Et_2O: $CHCl_3$=2: 2: 1). The least polar fraction was unchanged material (dimethyl-maleate), and a less polar fraction (112 mg, main product) was recrystallized from Et_2O to afford VII (98 mg, 72.8%), as a colorless crystalline powder, mp 174—176°C.

Adduct (X) from I and Dimethyl Fumarate——A mixture of I (500 mg), Dimethyl fumarate (999 mg, excess) and toluene (1.3 ml) was heated at 110—120°C for 96 h in a closed test tube under nitrogen in an oil bath. TLC (SiO_2, benzene: Et_2O: $CHCl_3$=2: 2: 1) indicated the formation of a main product besides small amounts of two by-products. The reaction mixture was separated by fractional crystallization with MeOH into the unchanged material (dimethyl fumarate, 585 mg) and the crude product (440 mg). The crude product was recrystallized from MeOH to give X (397 mg, 58.8%) as colorless needles, mp 136—137°C, $[\alpha]_D^{23}$ −4.2° (c=0.5, $CHCl_3$). *Anal.* Calcd for $C_{31}H_{42}O_9 \cdot 1/2H_2O$: C, 65.59; H, 7.65. Found: C, 65.19; H, 7.81.

Anhydro Derivative (VIII) from Adduct (VI)——A solution of VI (102 mg) in dry pyridine (2 ml) was chilled at −10°C with ice–NaCl mixture in a desiccator and a solution of $SOCl_2$ (0.6 ml) in dry pyridine (0.5 ml) was added dropwise with stirring. Stirring was continued for 1 h at the same temperature, then excess $SOCl_2$ was decomposed with ice and the precipitate thus formed was collected by filtration and dried *in vacuo*. The crude product (86 mg) was recrystallized from MeOH to afford VIII (58 mg) as a colorless crystalline powder, mp 175—176°C, *Anal.* Calcd for $C_{31}H_{40}O_8$: C, 69.00; H, 7.28. Found: C, 68.89; H, 7.69.

Anhydro Derivative (IX) from Adduct (VII)——VII (105 mg) was treated with $SOCl_2$ by a method analogous to that used for VI to give the crude anhydro derivative (87 mg), which was recrystallized from MeOH to afford IX (59 mg) as a colorless crystalline powder, mp 240—243°C, *Anal.* Calcd for $C_{31}H_{40}O_8$: C, 69.00; H, 7.28. Found: C, 68.77; H, 7.58.

Formation of VI by Alumina Treatment of VII——Activated Al_2O_3 (15 g) was added to a solution of VII (257 mg) in $CHCl_3$ (13.5 ml), and the mixture was left to stand at room temperature for 96 h, then extracted with $CHCl_3$–MeOH (1: 1) mixture (40 ml) to give the crude product (145 mg), which was separated by double development preparative TLC (SiO_2, $CHCl_3$: Et_2O=2: 1). The less polar fraction (59 mg) was identical with the material (VII) and the more polar fraction (49 mg) was recrystallized from MeOH to afford VI (36 mg) as colorless plates, mp 206—208°C. The latter was identical with the authentic sample (mixed melting point test and infrared (IR) spectral comparison).

Formation of VII by Alumina Treatment of VI——Activated Al_2O_3 (1 g) was added to a solution of VI (20 mg) in $CHCl_3$ (0.9 ml) and the mixture was left to stand at room temperature for 96 h, then extracted with $CHCl_3$–MeOH (1: 1) mixture to give the crude product (11 mg). TLC (SiO_2, benzene: Et_2O=3: 2) of the crude product showed the formation of VII in a similar amount to that of unchanged material (VI).

Formation of VI and VII by Alumina Treatment of X——Activated neutral Al_2O_3(3 g) was added to a solution of X (61 mg) in $CHCl_3$ (2.7 ml) and the mixture was left to stand at room temperature overnight.

The residue (60 mg) obtained from the extract of the reaction mixture with $CHCl_3$–MeOH (1: 1) mixture was separated by double development preparative TLC (SiO_2, $CHCl_3$: Et_2O=2: 1). The less polar fraction (21 mg) was recrystallized from Et_2O to give VII (15 mg) as a colorless crystalline powder, mp 174—176°C, and the more polar fraction (6 mg) was recrystallized from MeOH to give VI (4 mg) as colorless plates, mp 206—208°C. These products were identified by comparison with authentic samples (mixed melting point test, *Rf* value and IR spectra).

X-Ray Crystal Structure Analyses of III and VI——Crystals with dimensions of $0.2\times0.2\times0.1$ mm were used. The space groups were determined by the systematic absence of $0k0$ when k is odd. Intensity data were collected on a Rigaku diffractometer with graphite-monochromated Cu $K\alpha$ radiation. Integrated intensities were measured in the range of $\theta\leqq70°$ with an ω-2θ scan, a constant scan speed of 0.05° s^{-1} and an ω scan range of $(1.0+0.2\cdot\tan\theta)°$. The background was counted for 5 s at each end of the scan. 2473 and 2799 independent reflections were recorded for III and VI, respectively. Lorentz and polarization corrections were applied, but not absorption correction.

All the hydrogen atoms, except for those of methanol in VI, were located in difference electron density maps calculated after block-diagonal least-squares refinement of the positional and anisotropic thermal parameters of the non-hydrogen atoms. The temperature factor of each hydrogen atom was assumed to be isotropic and equal to that of the atom to which it was bound. The positional and thermal parameters of the hydrogen atoms were fixed in the subsequent refinements.

The weighting scheme was $w=1/\sigma^2(F_o)$ for $|F_c|\geqq\sigma(F_o)$ and $w=0$ for $|F_c|\geqq\sigma(F_o)$ or $|\Delta F|\geqq3\sigma(F_o)$. $\sigma(F_o)$ was estimated as $\sigma(F_o)=[\sigma_1{}^2(F_o)+c^2|F_o|^2]^{1/2}$, where $\sigma_1(F_o)$ is the standard deviation due to counting errors and the values of c^2 are 0.00132 and 0.00171 for III and VI, respectively. The least-squares refinement was carried out to minimize the function $\sum(w|\Delta F|^2)$. The atomic scattering factors were calculated using the analytical expression $f=\sum[a_i\exp(-b_i\lambda^{-2}\sin^2\theta]+c$ $(i=1\sim4)$.[9]

Bond lengths and angles are all as expected. The absolute configurations of the molecules were determined on the basis of the β-configuration of the methyl group at the 18-position in steroids.

Lists of structure factors, anisotropic thermal parameters of the non-hydrogen atoms, positional parameters of the hydrogen atoms, and bond lengths and angles are available on request from one of the authors (M.S.).

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References and Notes

1) Part XXXVI: T. Hashimoto, Y. Kato, Y. Nagaoka, T. Ohta, and D. Satoh, *Chem. Pharm. Bull.*, **28**, 2799 (1980).
2) This work was reported at the 101st Annual Meeting of the Pharmaceutical Society of Japan, Kumamoto, April 1981.
3) Numbering of carbon atoms over C-23 is given tentatively as shown in the formulae.
4) Full names of the products are as follows: III=3β-acetoxy-5′β-ethoxycarbonyl-14-hydroxy-1′α,4′α,5′,6′-tetrahydro-5β,14β-benzo[16,17,20,22]carda-16,20(22)-dienolide, VI=3β-acetoxy-5′α,6′α-bis(methoxycarbonyl)-14-hydroxy-1′α,2′α,5′,6′-tetrahydro-5β,14β-benzo[16,17,20,22]carda-16,20(22)-dienoline, VII=3β-acetoxy-5′β,6′α-bis(methoxycarbonyl)-14-hydroxy-1′α,2′α,5′,6′-tetrahydro-5β,14β-benzo[16,17,20,22]-carda-16,20(22)-dienolide, X=3β-acetoxy-5′β,6′α-bis(methoxycarbonyl)-14-hydroxy-1′α,4′α,5′,6′-tetrahydro-5β,14β-benzo[16,17,20,22]carda-16,20(22)-dienolide.
5) P. Main, L. Lessinger, M.M. Woolfson, G. Germain, and J.P. Declercq, MULTAN 76, A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data. University of York, England, and Louvain, Belgium (1976).
6) Number of reflections having non-zero weight. The weight for each reflection was calculated in the manner described in Experimental.
7) The oxygen atom is disordered at the 42 (degree of occupancy=0.45), 42′ (0.22) and 42″ (0.33) positions as shown in Table III.
8) All melting points are uncorrected. Specific rotations were measured with a Jasco DIP-180 digital polarimeter. UV spectra were obtained on a Shimadzu UV-300 spectrophotometer, IR spectra on a Shimadzu IR-27G spectrometer, and ^{1}H-NMR spectra on a JEOL JNMPS-100 spectrometer.
9) "International Tables for X-ray Crystallography," Vol. IV, Kynoch Press, Birmingham, 1974, p. 71.