NEW METHOD OF PREPARATION OF CARDIOGLYCOSIDE HEMISUCCINATES*

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An indirect method for preparation of hemisuccinates (hydrogen butanedioates) is described, consisting in reaction of hydroxy derivatives with 2-(trimethylsilyl)ethyl hemisuccinate (*I*) followed by removal of the 2-(trimethylsilyl)ethyl group from the mixed succinate with tetrabutylammonium fluoride. It has been applied to the synthesis of hemisuccinates derived from cholesterol (*II*), (20*E*)-21-methoxycarbonylpregna-5,20-dien-3β-ol (*V*), digitoxigenin (*XII*), digitoxin (*XV*) and digoxin (*XVIII*). The method, however, is not suitable for the preparation of estrone hemisuccinate *X* which is cleaved with tetrabutylammonium fluoride to give estrone (*VIII*).

Recently, we have described an indirect method for the preparation of digitoxin and digoxin hemisuccinates[1,2] using the 2,2,2-trichloroethyl group for protection of the succinate carboxyl. With digoxin, however, we observed formation of dehydration products during the work-up of the reaction mixture after removal of the protecting group; this could not be completely prevented even when the solvent was removed by lyophilisation. Another complication of this procedure consisted in the formation of salts which also reduced the overall yield. Replacement of the 2,2,2-trichloroethyl group by the 2-(trimethylsilyl)ethyl protecting group allows deblocking in an aprotic medium, avoiding thus the mentioned disadvantages of the original method.

The applicability of the 2-(trimethylsilyl)ethyl protecting group to the indirect preparation of hemisuccinates has been preliminarily checked with simpler hydroxy derivatives[3-5]. The method is analogous to that using the 2,2,2-trichloroethyl group. In the first step, the hydroxy derivative is treated with the 2-(trimethylsilyl)ethyl hemisuccinate (*I*, refs[3,6]) and dicyclohexylcarbodiimide in the presence of 4-dimethylaminopyridine to give the mixed succinate. The reaction can be performed in benzene, benzene–tetrahydrofuran or dichloromethane. The second step comprises removal of the protecting group with tetrabutylammonium fluoride[7,8] in tetrahydrofuran.

This method was successfully applied to the preparation of cholesterol hemisuccinate (*II* → *III* → *IV*) which was obtained in a 81% yield, or of the hemisuccinate

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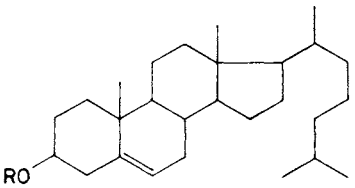
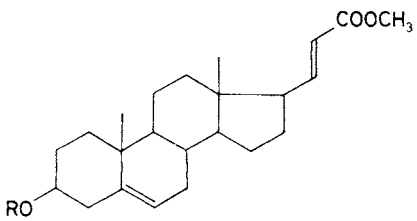
VII from the unsaturated ester *V via* the protected derivative *VI* (70% yield). In the case of estrone (*VIII*), the intermediate ester *IX* was obtained in a 92% yield but its cleavage with tetrabutylammonium fluoride did not afford the desired hemisuccinate *X*. Instead, the starting estrone (*VIII*) was isolated from the reaction mixture in practically quantitative yield (97%). A more detailed study has shown that the hemisuccinate *X* (ref.[9]) was readily cleaved with tetrabutylammonium fluoride to give estrone (*VIII*). Comparison with the reaction of estrone acetate (*XI*) under the same conditions has shown that the cleavage of the hemisuccinate *X* is 2–3 times faster than hydrolysis of the acetate *XI*; this is probably caused by an intramolecular catalysis[10]. Thus, on deprotection of the ester *IX*, the primarily formed hemisuccinate *X* is rapidly cleaved and cannot be obtainted in this way.

$HOOCCH_2CH_2COOCH_2CH_2Si(CH_3)_3$

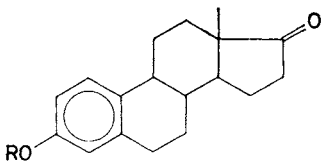
I



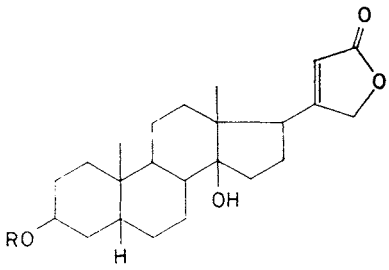
II, R = H
III, R = $OCCH_2CH_2COOCH_2CH_2Si(CH_3)_3$
IV, R = $OCCH_2CH_2COOH$



V, R = H
VI, R = $OCCH_2CH_2COOCH_2CH_2Si(CH_3)_3$
VII, R = $OCCH_2CH_2COOH$



VIII, R = H
IX, R = $OCCH_2CH_2COOCH_2CH_2Si(CH_3)_3$
X, R = $OCCH_2CH_2COOH$
XI, R = $OCCH_3$

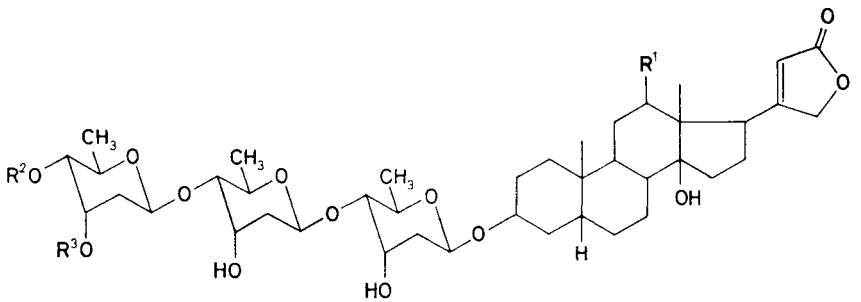


XII, R = H
XIII, R = $OCCH_2CH_2COOCH_2CH_2Si(CH_3)_3$
XIV, R = $OCCH_2CH_2COOH$

Of compounds with an unsaturated five-membered lactone ring, we applied our method first to digitoxigenin (*XII*). Its reaction with hemisuccinate *I*, mediated by

dicyclohexylcarbodiimide–4-dimethylaminopyridine in benzene, afforded in 78% yield the ester *XIII* which was then converted to the hemisuccinate *XIV* in a yield of 69%. This experiment has proved that the used reaction conditions affect neither the hydroxyl in position 14 nor the lactone ring. For the reaction of digitoxin (*XV*) we chose the same conditions, except that dichloromethane was used as the solvent as in the case of the 2,2,2-trichloroethyl protecting group[1,2]. The ester *XVI* was isolated in high yield (96%). Its structure is confirmed by ^{1}H NMR spectra which exhibit signals due to the steroid part of the molecule, two methyl singlets at δ 0·84 and 0·89, and a signal of the proton at the unsaturated lactone double bond (δ 5·84). Signals of the sugar moiety partly overlap and their shifts and multiplicities correspond to those of the analogous derivative[1] with the 2,2,2-trichloroethyl-protected succinate moiety in position 4‴. Substitution at this position is characterized as a doublet of doublets at δ 4·45 with coupling constants 2·7 and 9·9 Hz. The 2-(trimethylsilyl)ethyl group appears in the spectrum as a multiplet of the methylene next to the silicon atom (δ 0·95) and a singlet of the three methyl groups (δ 0·01).

The deprotection was accomplished by treatment with tetrabutylammonium fluoride in tetrahydrofuran, affording after column chromatography on silica gel the hemisuccinate *XVII* in overall yield 69%.



XV, $R^1 = R^2 = R^3 = H$
XVI, $R^1 = R^3 = H$; $R^2 = OCCH_2CH_2COOCH_2CH_2Si(CH_3)_3$
XVII, $R^1 = R^3 = H$; $R^2 = OCCH_2CH_2COOH$
XVIII, $R^1 = OH$; $R^2 = R^3 = H$
XIX, $R^1 = OH$; $R^2 = OCCH_2CH_2COOCH_2CH_2Si(CH_3)_3$; $R^3 = H$
XX, $R^1 = OH$; $R^2 = H$; $R^3 = OCCH_2CH_2COOCH_2CH_2Si(CH_3)_3$
XXI, $R^1 = OH$; $R^2 = OCCH_2CH_2COOH$; $R^3 = H$

The first step of preparation of digoxin 4‴-hemisuccinate (*XXI*) was carried out under conditions suppressing the formation of higher-acylated products[1], *i.e.* using pyridine instead of 4-dimethylaminopyridine. The usual work-up followed by chromatography on silica gel afforded in 41% yield the 4‴-acyl derivative *XIX* as the principal product, together with small amounts of the isomeric 3‴-derivative *XX*. The structure of the main product *XIX* follows from the ^{1}H NMR spectrum in which the steroid

part manifests itself by singlets of two methyl group at δ 0·79 and 0·98, and a signal of the proton at the double bond in the lactone ring (δ 5·93). The position and shape of the signals due to the sugar moiety are practically the same as for the corresponding 2,2,2-trichloroethyl derivative[1]. The presence of a doublet of doublets at δ 4·47 with coupling constants 2·5 and 9·8 Hz confirms that the succinate residue is bonded in position 4‴. The spectrum further contains signals of the protected succinate part: two multiplets at δ 4·18 and 0·98, a singlet at δ 0·04 due to the 2-(trimethylsilyl)ethyl group, and a four-proton multiplet at δ 2·63 due to the succinate moiety.

The main ^{1}H NMR spectral features of the minor product *XX* agree with those of the corresponding 2,2,2-trichloroethyl derivative[1]. The steroid part is manifested by a signal of proton at the lactone double bond at δ 6·06 and methyl signals at δ 0·93 and 0·78. As concerns the sugar moiety, the presence of a multiplet at δ 5·29 confirms that the succinate residue is bonded in position 3‴. The 2-(trimethylsilyl)ethyl group gives rise to signals at δ 4·18, 1·00, and 0·06.

The ^{13}C NMR spectra of both the protected digoxin derivatives *XIX* and *XX* were measured in deuteriochloroform, with addition of a small amount of methanol in the case of the sparingly soluble *XX*. The signals were assigned to the individual carbon atoms on the basis of comparison with the spectra of the corresponding 2,2,2-trichloroethyl esters[1] and with the spectrum of the 2-(trimethylsilyl)ethyl hemisuccinate *I* (Tables I and II). For the steroid part, the differences between the shifts of the corresponding carbon signals of the 2,2,2-trichloroethyl and 2-(trimethylsilyl)ethyl esters are less than 0·2 ppm (the only exception is the shift of $C_{(23)}$ signal in *XX*, for which the difference amounts to 0·6 ppm; this may be ascribed to the added deuteriomethanol). In the sugar region, the spectra of the corresponding derivatives also compare well, the differences not exceeding 0·3 ppm, even though in some cases the assignment can be done only tentatively (similarly to ref.[1]). The shifts for the protected succinate residues in compounds *XIX* and *XX* are compared with those for the hemisuccinate *I* in Table II.

Removal of the protecting group from the 4‴-acyl derivative *XIX* was carried out again with tetrabutylammonium fluoride in tetrahydrofuran. The usual work-up and column chromatography on silica gel afforded the hemisuccinate *XXI* in 78% yield, the overall yield based on digoxin being 32%. This method thus brings, in addition to simpler processing in the deprotection step, also higher yields than the 2,2,2-trichloro ester method (comp. 25%, ref.[1]) and is therefore the subject of a new patent application[11].

EXPERIMENTAL

Melting points were determined on a micro melting point apparatus Boetius (G.D.R.). Optical rotations were measured at 25°C on a Perkin–Elmer 141 MC polarimeter and IR spectra on a Zeiss UR-20 spectrometer. NMR spectra were taken on Tesla BS-476 (60 MHz for ^{1}H) or on

TABLE I

^{13}C NMR parameters for digoxin derivatives *XIX* and *XX* (digoxin part)

Carbon[a]	*XIX*	*XX*	Carbon[a]	*XIX*	*XX*
1	30·2[b]	29·5[b]	22	117·5	116·8
2	26·5[c]	26·2	23	175·0	175·6
3	72·4	72·4	1′	95·4	95·1
4	29·8[b]	29·5[b]	1″	98·2[d]	98·3[d]
5	36·2	36·1	1‴	98·5[d]	98·4[d]
6	26·6[c]	26·2	2′	37·3[e]	36·8[e]
7	21·6	21·3	2″	37·1[e]	36·5[e]
8	41·3	40·8	2‴	36·7	35·7
9	32·5	32·2	3′	66·4[f]	66·1[f]
10	35·0	34·7	3″	66·4[f]	66·2[f]
11	30·2[b]	29·9[b]	3‴	65·2	70·9
12	75·0	74·3	4′	82·2[g]	82·1[g]
13	55·6	55·6	4″	82·5[g]	82·4[g]
14	85·8	85·4	4‴	75·6	71·1
15	33·1	32·5	5′	68·1[h]	67·8[h]
16	27·4	27·1	5″	68·2[h]	68·0[h]
17	45·6	45·4	5‴	67·2	70·3
18	9·0	8·7	6′	18·2[i]	17·8[i]
19	23·5	23·2	6″	18·2	17·8
20	175·0	176·0	6‴	18·0[i]	17·7[i]
21	73·8	73·8			

[a] Measured in C^2HCl_3 with tetramethylsilane as internal standard; in case of *XX* several drops of $C^2H_3O^2H$ were added; [b–i] values in the columns can be interchanged.

TABLE II

Assignment of the ^{13}C signals of the succinate part in digoxin derivatives *XIX* and *XX*

Compound[a]	Carbon[b]						
	1S	2S	3S	4S	1T	2T	M
I	178·4	29·0	29·0	172·3	63·2	17·3	−1·5
XIX	171·4[c]	29·6[d]	29·4[d]	173·3[c]	63·5	17·3	−1·5
XX	172·0[c]	29·1[d]	29·0[d]	172·8[c]	63·0	17·0	−1·9

[a] For conditions see Table I, compound *I* measured in C^2HCl_3; [b] 1S–4S are the succinate carbon atoms, 1T and 2T are carbon atoms of the 2-(trimethylsilyl)ethyl protecting group, M denotes methyl carbon atoms in the trimethylsilyl group; [c,d] values in the lines can be interchanged.

Varian XL-200 instruments at 23°C (200·058 MHz for ^{1}H and 50·309 MHz for ^{13}C). Chemical shifts are given in ppm (δ-scale), coupling constants (J) and bandwidths (W) in Hz. All values were obtained by the first-order analysis. Column chromatography was performed on silica gel (according to Pitra, 60—120 μm) and thin-layer chromatography on silica gel G according to Stahl (Woelm). Solutions in organic solvents were dried over anhydrous sodium sulfate and the solvents were evaporated *in vacuo* (about 2 kPa). Analytical samples were dried over phosphorus pentoxide at 40°C and 26 Pa for 12 h. Identity of samples prepared by different routes was checked by comparison of their IR and ^{1}H NMR spectra, thin-layer chromatography and mixture melting point determination. All reactions were performed in an atmosphere of dry nitrogen. Tetrabutylammonium fluoride in tetrahydrofuran was a commercial product (Aldrich 21,614—3), concentration 1 mol l^{-1}.

5-Cholesten-3β-yl 2-(Trimethylsilyl)ethyl Butanedioate (*III*)

Dicyclohexylcarbodiimide (230 mg; 1·11 mmol) and 4-dimethylaminopyridine (5 mg) were added to a solution of cholesterol (*II*; 387 mg; 1 mmol) and hemisuccinate *I* (refs[3,6]; 424 mg; 1·94 mmol) in benzene (15 ml). After stirring at 27°C for 5 h, the mixture was poured into water and twice extracted with benzene–ether (1 : 1). The extract was twice washed with water and the residue, after solvent evaporation, was chromatographed on a column of silica gel (50 g) in benzene to give 550 mg (85%) ester *III*, m.p. 92—95°C (ether); $[\alpha]_D$ −31° (*c* 0·19; chloroform). IR spectrum (tetrachloromethane), cm^{-1}: 1 739, 1 162 (COOR). ^{1}H NMR spectrum (60 MHz; deuteriochloroform, external lock): 5·36 m (1 H, $C_{(6)}$—H); 4·55 m (1 H, $C_{(3)}$—H, W = 40); 4·19 m (2 H, CH_2O, W = 17); 2·60 s (4 H, $OOCCH_2CH_2COO$); 1·02 s (3 H, $C_{(19)}$—H); 0·69 s (3 H, $C_{(18)}$—H); 0·05 s (9 H, $Si(CH_3)_3$). For $C_{36}H_{62}O_4Si$ (587·0) calculated: 73·67% C, 10·65% H; found: 73·68% C, 10·55% H.

5-Cholesten-3β-yl Hydrogen Butanedioate (*IV*)

A solution of tetrabutylammonium fluoride in tetrahydrofuran (1·5 ml; *c* 1 mol l^{-1}) was added to a solution of ester *III* (460 mg; 0·78 mmol) in tetrahydrofuran (5 ml). After stirring for 2 h at 27°C the mixture was diluted with benzene (150 ml), washed with 10% sulfuric acid (twice) and water (twice). Evaporation of the solvents and crystallization from ether–light petroleum afforded 363 mg (95%) of hemisuccinate *IV*, m.p. 175—178°C, identical with an authentic sample[9].

(20*E*)-21-Methoxycarbonylpregna-5,20-dien-3β-yl 2-(Trimethylsilyl)ethyl Butanedioate (*VI*)

Dicyclohexylcarbodiimide (110 mg; 0·53 mmol) and 4-dimethylaminopyridine (5 mg) were added to a solution of hydroxy derivative *V* (ref.[12]; 180 mg; 0·5 mmol) and hemisuccinate *I* (refs[3,6]; 220 mg; 1·01 mmol) in a mixture of benzene (8 ml) and tetrahydrofuran (4 ml). After stirring for 24 h at 27°C the mixture was poured into water, extracted twice with benzene–ether (1 : 1), the extract washed with water and taken down. Chromatography of the residue on a silica gel column (25 g) in benzene gave 232 mg (83%) of the ester *VI*, m.p. 82—85°C; $[\alpha]_D$ −27° (*c* 0·2; chloroform). IR spectrum (tetrachloromethane), cm^{-1}: 1 731, 1 163 (COOR), 1 654 (C=C—COOR). ^{1}H NMR spectrum (60 MHz, deuteriochloroform, external lock): 6·98 dd (1 H, $C_{(20)}$—H, $J_{20,21}$ = 16, $J_{17,20}$ = 7); 5·78 d (1 H, $C_{(21)}$—H, $J_{20,21}$ = 16); 5·38 m (1 H, $C_{(6)}$—H); 4·60 m (1 H, $C_{(3)}$—H, W = 35); 4·17 m (2 H, CH_2O, W = 17); 3·72 s (3 H, $COOCH_3$); 2·59 s (4 H, $OOCCH_2CH_2COO$); 1·04 s (3 H, $C_{(19)}$—H); 0·68 s (3 H, $C_{(18)}$—H); 0·07 s (9 H, $Si(CH_3)_3$). For $C_{32}H_{50}O_6Si$ (558·8) calculated: 68·78% C, 9·02% H; found: 68·60% C, 8·95% H.

(20*E*)-21-Methoxycarbonylpregna-5,20-dien-3β-yl Hydrogen Butanedioate (*VII*)

Tetrabutylammonium fluoride in tetrahydrofuran (0·4 ml; *c* 1 mol l^{-1}) was added to a solution of the ester *VI* (115 mg; 0·21 mmol) in tetrahydrofuran (4 ml). After stirring at 27°C for 2 h, the mixture was diluted with benzene (100 ml), washed with 10% sulfuric acid (twice) and water (twice) and the solvent was evaporated. Crystallization of the residue from light petroleum–dichloromethane afforded 80 mg (84%) of hemisuccinate *VII*, m.p. 173–176°C, identical with an authentic sample[9].

17-Oxo-1,3,5(10)-estratrien-3-yl 2-(Trimethylsilyl)ethyl Butanedioate (*IX*)

Dicyclohexylcarbodiimide (190 mg; 0·92 mmol) and 4-dimethylaminopyridine (10 mg) were added to a solution of estrone (*VIII*; 216 mg; 0·80 mmol) and hemisuccinate *I* (refs[3,6]; 361 mg; 1·65 mmol) in a mixture of benzene (10 ml) and tetrahydrofuran (3 ml). After stirring at 27°C for 6 h the mixture was poured in water and twice extracted with benzene–ether (1 : 1). After double washing with water the extract was taken down and the residue chromatographed on a column of silica gel (40 g). Elution with benzene–ether (97 : 3) afforded 346 mg (92%) of the ester *IX*, m.p. 109–111°C (light petroleum–ether), $[\alpha]_D$ +91° (*c* 0·22; chloroform), IR spectrum (tetrachloromethane), cm^{-1}: 1 742 (COOR and C=O in five-membered ring), 1 762 (COOAr) 1 608, 1 583, 1 494 (C—C arom.). ^1H NMR spectrum (60 MHz, deuteriochloroform, external lock): 7·37 m and 6·85 m (3 H, C—H arom.); 4·18 m (2 H, CH_2—O, W = 17); 2·76 m (4 H, $OOCCH_2CH_2COO$); 0·87 s (3 H, $C_{(18)}$—H); 0·08 s (9 H, $Si(CH_3)_3$). For $C_{27}H_{38}O_5Si$ (470·7) calculated: 68·90% C, 8·14% H; found: 68·64% C, 8·25% H.

Cleavage of Estrone Esters with Tetrabutylammonium Fluoride

a) Tetrabutylammonium fluoride in tetrahydrofuran (1·2 ml; *c* 1 mol l^{-1}) was added to a solution of ester *IX* (270 mg; 0·57 mmol) in tetrahydrofuran (4 ml). After stirring for 24 h at 27°C the mixture was diluted with benzene (120 ml), washed twice with 10% sulfuric acid and water and the solvent was evaporated. Crystallization of the residue from light petroleum–acetone gave 150 mg (97%) of estrone (*VIII*), m.p. 254–257°C, identical with an authetic sample.

b) Tetrabutylammonium fluoride in tetrahydrofuran (0·2 ml; *c* 1 mol l^{-1}) was added to a solution of hemisuccinate *X* (ref. [9]; 27 mg; 0·073 mmol) in tetrahydrofuran (0·4 ml). After stirring at 27°C for 32 h, the mixture was diluted with benzene (5 ml), washed twice with 10% sulfuric acid, water and the solvents were evaporated. The residue was crystallized from light petroleum–acetone to yield 13 mg (66%) of estrone (*VIII*), m.p. 251–254°C, identical with an authentic sample.

c) Tetrabutylammonium fluoride in tetrahydrofuran (0·2 ml; *c* 1 mol l^{-1}) was added to estrone acetate (*XI*; 27 mg; 0·086 mmol) in tetrahydrofuran (0·4 ml). After stirring for 72 h at 27°C, the mixture was diluted with benzene, washed twice with 10% sulfuric acid and water and the solvent was evaporated. Crystallization from light petroleum–acetone furnished 22 mg (94%) of estrone (*VIII*), m.p. 254–257°C, identical with an authentic sample.

14-Hydroxy-5β,14β-card-20(22)-enolid-3β-yl 2-(Trimethylsilyl)ethyl Butanedioate (*XIII*)

Dicyclohexylcarbodiimide (420 mg; 2·04 mmol) and 4-dimethylaminopyridine (8·5 mg) were added to a solution of digitoxigenin (*XII*; 635 mg; 1·70 mmol) and hemisuccinate *I* (refs[3,6];

740 mg; 3·39 mmol) in benzene (50 ml). After stirring at room temperature for 3 h, the separated N,N'-dicyclohexylurea was filtered and the filtrate evaporated *in vacuo*. Column chromatography on silica gel (80 g) in chloroform–ether (98 : 2) gave 758 mg (78%) of amorphous ester *XIII*; $[\alpha]_D$ +10° (*c* 0·4; chloroform). IR spectrum (chloroform), cm^{-1}: 1 778, 1 739 (unsaturated γ-lactone), 3 605 (OH). ^1H NMR spectrum (60 MHz, deuteriochloroform, external lock): 5·83 m (1 H, $C_{(22)}$—H); 5·10 m (1 H, $C_{(3)}$—H); 4·87 m (2 H, $C_{(21)}$—H); 4·15 m (2 H, $COOCH_2CH_2Si(CH_3)_3$, *W* = 17); 2·58 m (4 H, $OOCCH_2CH_2COO$); 0·93 s (3 H, $C_{(19)}$—H); 0·85 s (3 H, $C_{(18)}$—H); 0·02 s (9 H, $Si(CH_3)_3$). For $C_{32}H_{50}O_7Si$ (574·8) calculated: 66·86% C, 8·77% H; found: 66·97% C, 8·98% H.

14-Hydroxy-5β,14β-card-20(22)-enolid-3β-yl Hydrogen Butanedioate (*XIV*)

A solution of tetrabutylammonium fluoride in tetrahydrofuran (2·6 ml; *c* 1 mol l^{-1}) was added to a solution of ester *XIII* (730 mg; 1·27 mmol) in tetrahydrofuran (10 ml). After stirring at room temperature for 3 h, the mixture was poured in water and the product taken up in dichloromethane. The extract was washed with 10% sulfuric acid and water and evaporated. The residue was chromatographed on a column of silica gel (70 g) in chloroform–methanol (98 : 2), affording 413 mg (69%) of hemisuccinate *XIV*, m.p. 232—235°C (ether), identical with an authentic sample[9].

Digitoxin-4‴-yl 2-(Trimethylsilyl)ethyl Butanedioate (*XVI*)

Dicyclohexylcarbodiimide (729 mg; 3·53 mmol) and 4-dimethylaminopyridine (39 mg) were added to a solution of digitoxin (*XV*; 2·3 g; 3 mmol) and hemisuccinate *I* (refs[3,6]; 930 mg; 4·26 mmol) in dichloromethane (210 ml). After stirring at room temperature for 4 h, the mixture was diluted with light petroleum (50 ml) and the precipitated N,N'-dicyclohexylurea was removed by filtration. The filtrate was evaporated *in vacuo* and the oily residue was chromatographed on a column of silica gel (200 g) in dichloromethane–methanol (98 : 2) to afford 2·8 g (96%) of the amorphous ester *XVI*; $[\alpha]_D$ +11° (*c* 0·2, pyridine). IR spectrum (chloroform), cm^{-1}: 3 540 (OH), 1 780 shoulder, 1 743 (unsaturated γ-lactone), 1 743 (COOR), 1 619 (C=C). ^1H NMR spectrum (200 MHz, deuteriochloroform, tetramethylsilane): 5·84 bs (1 H, $C_{(22)}$—H); 4·45 dd (1 H, $C_{(4''')}$—H, $J_{3''',4'''}$ = 2·7, $J_{4''',5'''}$ = 9·9); 4·02 m (1 H, $C_{(5''')}$—H), 3·77 m (2 H, $C_{(5')}$—H and $C_{(5'')}$—H); 3·20 m (2 H, $C_{(4')}$—H and $C_{(4'')}$—H); 2·61 m (4 H, $OOCCH_2CH_2COO$); 1·20 d (6 H, $C_{(6')}$—H and $C_{(6'')}$—H, *J* = 6·5); 1·17 d (3 H, $C_{(6''')}$—H, $J_{5''',6'''}$ = 6·5); 0·95 m (2 H, CH_2Si), 0·89 s (3 H, $C_{(19)}$—H); 0·84 s (3 H, $C_{(18)}$—H); 0·01 s (9 H, $Si(CH_3)_3$). For $C_{50}H_{80}O_{16}Si$ (965·3) calculated: 62·22% C, 8·35% H; found: 62·51% C, 8·57% H.

Digitoxin-4‴-yl Hydrogen Butanedioate (*XVII*)

A solution of tetrabutylammonium fluoride in tetrahydrofuran (5·5 ml; *c* 1 mol l^{-1}) was added to a solution of ester *XVI* (2·6 g; 2·69 mmol) in tetrahydrofuran (35 ml). After stirring at room temperature for 4 h, another portion of the tetrabutylammonium fluoride solution (2·2 ml; *c* 1 mol l^{-1}) was added and the stirring was continued for 2 h. The mixture was poured in water and extracted with chloroform. The extract was washed with 10% sulfuric acid and water and the solvent was evaporated. Chromatography of the residue on a column of silica gel (200 g) in dichloromethane–methanol (95 : 5) afforded 1·68 g (72%) of hemisuccinate *XVII*, m.p. 194—198°C (dichloromethane–light petroleum), identical with an authentic sample[1].

Digoxin-4‴-yl 2-(Trimethylsilyl)ethyl Butanedioate (*XIX*)

A solution of dicyclohexylcarbodiimide (960 mg; 4·65 mmol) in dichloromethane (20 ml), followed by a solution of hemisuccinate *I* (refs[3,6]; 1·11 g; 5·08 mmol) in benzene (4 ml), was added to an ice-cooled stirred solution of digoxin (*XVIII*; 2·9 g; 3·71 mmol) in a mixture of pyridine (10 ml) and dichloromethane (40 ml). After stirring for 1 h in an ice bath and for 48 h at room temperature, water (0·5 ml) was added and the solvents were evaporated. The residual solvents were removed by coevaporation with toluene, the semi-solid mixture was suspended in a small amount of dichloromethane and the solids were removed by passing through a short column of silica gel which was then washed with dichloromethane–methanol (10 : 1). After removal of solvents, the product was chromatographed on a silica gel column (25 mm × 37 cm; 20 μm). Elution with dichloromethane–2-propanol (20 : 1) afforded, beside an unidentified mixture of less polar products (220 mg), 1·5 g (41%) of amorphous succinate *XIX*; $[\alpha]_D$ +27° (*c* 0·18; chloroform). IR spectrum (chloroform), cm^{-1}: 3 605 (OH), 1 780, 1 743 (unsaturated γ-lactone, COOR). ^1H NMR spectrum (200 MHz, deuteriochloroform, tetramethylsilane): 5·93 bs (1 H, $C_{(22)}$—H); 4·90 m (5 H, $C_{(21)}$—H_2, $C_{(1')}$—H, $C_{(1'')}$—H, $C_{(1''')}$—H); 4·47 dd (1 H, $C_{(4''')}$—H, $J_{3''',4'''}$ = 2·5, $J_{4''',5'''}$ = 9·8); 4·29 m (1 H, $C_{(3''')}$—H); 4·25 m (2 H, $C_{(3')}$—H, $C_{(3'')}$—H); 4·18 m (2 H, $OCH_2CH_2Si(CH_3)_3$); 4·05 dq (1 H, $C_{(5''')}$—H, $J_{4''',5'''}$ ~ 10, $J_{5''',6'''}$ ~ 6); 3·80 bm (2 H, $C_{(5')}$—H, $C_{(5'')}$—H); 3·23 m (2 H, $C_{(4')}$—H, $C_{(4'')}$—H); 2·63 p (4 H, $COCH_2CH_2CO$); 1·23 d, (6 H, $C_{(6')}$—H_3, $C_{(6'')}$—H_3, $J_{5',6'} = J_{5'',6''}$ ~ 6); 1·20 d (3 H, $C_{(6''')}$—H_3, $J_{5''',6'''}$ ~ 6); 0·98 m (2 H, $OCH_2CH_2Si(CH_3)_3$); 0·98 s (3 H, $C_{(19)}$—H_3); 0·79 s (3 H, $C_{(18)}$—H_3); 0·04 s (9 H, $Si(CH_3)_3$). For $C_{50}H_{80}O_{17}Si$ (981·3) calculated: 61·20% C, 8·22% H; found 61·07% C, 8·15% H. The more polar fractions on HPLC (Separon 10 μm, dichloromethane–2-propanol (10 : 1)) afforded the minor succinate *XX* (100 mg) as an amorphous foam, $[\alpha]_D$ +23° (*c* 0·3; chloroform). IR spectrum (chloroform), cm^{-1}: 3 605 (OH), 1 780, 1 743 (unsaturated γ-lactone, COOR). ^1H NMR spectrum (200 MHz, deuteriochloroform–tetradeuteriomethanol, tetramethylsilane): 6·06 bs (1 H, $C_{(22)}$—H); 5·29 m (1 H, $C_{(3''')}$—H); 4·86 m (5 H, $C_{(21)}$—H_2, $C_{(1')}$—H, $C_{(1'')}$—H, $C_{(1''')}$—H); 4·24 m (2 H, $C_{(3')}$—H, $C_{(3'')}$—H); 4·18 m (2 H, $OCH_2CH_2Si(CH_3)_3$); 3·85 dq (1 H, $C_{(5''')}$—H, $J_{4''',5'''}$ ~ 9·5, $J_{5''',6'''}$ ~ 6); 3·75 dq (2 H, $C_{(5')}$—H, $C_{(5'')}$—H, $J_{4',5'} = J_{4'',5''}$ ~ ~ 9·5, $J_{5',6'} = J_{5'',6''}$ ~ 6); 3·46 m (1 H, $C_{(12)}$—H); 3·32 dd (1 H, $C_{(4''')}$—H, $J_{3''',4'''}$ ~ 3, $J_{4''',5'''}$ ~ 9·5); 3·22 bd (2 H, $C_{(4')}$—H, $C_{(4'')}$—H, $J_{4',5'} = J_{4'',5''}$ ~ 9·5); 2·67 p (4 H, $COCH_2CH_2CO$); 1·30 d (3 H, $C_{(6''')}$—H, $J_{5''',6'''}$ = 6·2); 1·23 d (6 H, $C_{(6')}$—H, $C_{(6'')}$—H, $J_{5',6'} = J_{5'',6''}$ = 6·1); 1·00 m (2 H, $CH_2Si(CH_3)_3$); 0·93 s (3 H, $C_{(19)}$—H); 0·78 s (3 H, $C_{(18)}$—H); 0·06 s (9 H, $Si(CH_3)_3$). For $C_{50}H_{80}O_{17}Si$ (981·3) calculated: 61·20% C, 8·22% H; found: 61·33% C, 8·05% H. The most polar fraction consisted of digoxin (*XVIII*; 700 mg; 24%).

Digoxin-4‴-yl Hydrogen Butanedioate (*XXI*)

A solution of tetrabutylammonium fluoride in tetrahydrofuran (3·2 ml; *c* 1 mol l^{-1}) was added to a solution of ester *XIX* (1·5 g; 1·53 mmol) in tetrahydrofuran (20 ml). After stirring for 5 h at room temperature, the mixture was diluted with chloroform (100 ml), washed with 10% sulfuric acid and water and the solvent was evaporated. The residue was chromatographed on silica gel column (130 g) in chloroform–methanol (96 : 4), affording 1·05 g (78%) of the amorphous hemisuccinate *XXI*, identical with an authentic sample[1].

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