

adjacent carboxyl group is rotated by 4.5° from the plane of the phenyl ring.

We wish to thank Dr Bernhard Witkop of the National Institutes of Health for bringing this problem to our attention and for valuable discussions concerning the chemical aspects.

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## The Crystal Structure of Digitoxigenin, C<sub>23</sub>H<sub>34</sub>O<sub>4</sub>

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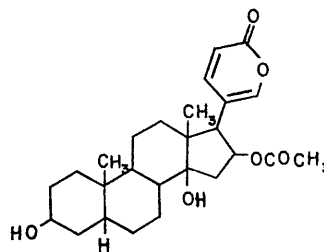
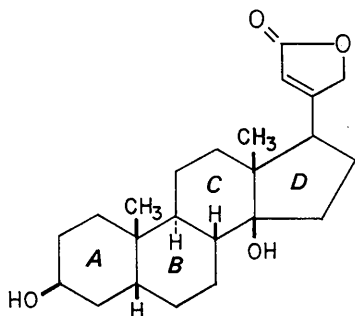
(Received 5 February 1968)

Digitoxigenin is the aglycone of digitoxin, which is one of the active ingredients of digitalis. It crystallizes in space group  $P2_12_12_1$  with  $Z=4$  and  $a=7.250$ ,  $b=15.015$  and  $c=18.464$  Å. A partial structure was determined by obtaining phases directly from the normalized structure factors using the symbolic addition procedure for noncentrosymmetric crystals. The complete structure was derived from the partial structure with the use of the tangent formula. The X-ray analysis confirmed the stereoconfiguration of the molecule as determined by chemical means. The *A/B* and *C/D* ring junctions are both *cis*, giving the molecule a globular shape in contrast to the flat nature of most steroids whose crystal structures have been determined. In the crystal, endless chains of molecules are formed by hydrogen bonding between the terminal -OH and C=O groups. Although cross-linkages between symmetry related molecules involving the terminal and central hydroxyl groups are suggested by the favorable orientation of the hydroxyl groups, the actual O...O distance is 3.4 Å, which is too large for hydrogen bonding.

#### Introduction

Digitalis, a preparation made by extraction of dried seeds and leaves of the purple foxglove, *Digitalis purpurea*, is used extensively in heart therapy. The active components are the glycosides of digitoxigenin, digoxigenin and gitoxigenin. Acid hydrolysis produces the free aglycones which differ from each other only by a hydroxyl group. Digitoxigenin,

although of plant origin, is quite similar to the animal steroid bufotalin,



a toad venom with cardiotoxic properties. Dried and powdered toad skin had been commonly used as a remedy for dropsy until Withering introduced the use of digitalis.

Digitoxigenin differs from other steroids whose structures have been analyzed by X-ray diffraction, e.g. lanostenyl iodoacetate (Fridrichsons & Mathieson, 1953), 7 $\alpha$ -bromocholesteryl bromide (Bürki & Nowacki,

1956), samandarine.HCl, .HBr, .HI (Wölfel, Schöpf, Weitz & Habermehl, 1961), 4-bromoestrone and 4-bromoestradiol (Norton, Kartha & Lu, 1963, 1964), dichloro and dibromo derivatives of cholestane (Geise, Romers & Rutten, 1966; Geise & Romers, 1966), buxine-G (Puckett, Sim, Abushanab & Kupchan, 1966), *p*-bromobenzoate monoacetate of withaferin A (Kupchan, Doskotch, Bollinger, McPhail, Sim & Renauld, 1965), androsterone (High & Kraut, 1966) and diosgenin iodoacetate (O'Donnell & Ladd, 1967) in that the *A/B* ring junction and the *C/D* ring junction are both *cis*. This leads to a molecule with a globular shape rather than one that is fairly flat when the ring junctions are *trans*. Another globular shaped steroid is batrachotoxinin A, a derivative of the Colombian poison arrow frog venom, whose structural formula and stereoconfiguration have been established by X-ray analysis (Tokuyama, Daly, Witkop, Karle & Karle, 1968; Karle & Karle, 1969). The structure of digitoxigenin was derived in the absence of a heavy atom thus avoiding the possible influence of the heavy atom on the packing and the conformation of the molecule. The X-ray analysis confirms the molecular formula and configuration of digitoxigenin as determined by chemical means (see *e.g.* Jacobs & Elderfield, 1935; Fieser & Fieser, 1963).

### Experimental

Commercially available digitoxigenin was recrystallized from ethanol to produce stout prisms. Cell parameters and space group were obtained from precession photographs and diffractometer measurements. The values are listed in Table 1. Intensity data were collected by the multiple-film, equi-inclination Weissenberg technique and read by visual comparison with a calibrated film strip. Layers 0-4 along the *a* axis and layers 0-8 along the *b* axis were recorded. Lorentz, polarization and spot-size corrections were made and normalized structure factors  $|E|$  as well as structure factors  $|F|$  were derived.

Table 1. *Physical constants for digitoxigenin*

Molecular formula	$C_{23}H_{34}O_4$
Molecular weight	374.50
Melting point	253 °C
Habit	Stout prisms
Space group	$P2_12_12_1$
<i>a</i>	$7.250 \pm 0.002 \text{ \AA}$
<i>b</i>	$15.015 \pm 0.004 \text{ \AA}$
<i>c</i>	$18.464 \pm 0.008 \text{ \AA}$
<i>V</i>	$2008.3 \text{ \AA}^3$
$\rho_{\text{calc}}$	$1.238 \text{ g.cm}^{-3}$
$\rho_{\text{obs}}$ (flotation in mixed solvents)	$1.239 \text{ g.cm}^{-3}$
Radiation	Cu $K\alpha$ , $1.5418 \text{ \AA}$
Number of independent reflections	2129

### Structure analysis

A combination of the symbolic addition procedure for noncentrosymmetric space groups (Karle & Karle, 1964, 1966*b*) to obtain a partial structure and a recycling procedure (Karle, 1968), employing the tangent formula (Karle & Hauptman, 1956) to derive the remainder of the structure was used to locate the twenty-three carbon atoms and four oxygen atoms in the asymmetric unit. The details of the structure determination were similar to those described in the papers on a photolysis product,  $C_{12}H_3NO_4$  (Karle, Karle & Estlin, 1967), 6-hydroxycrinamine dimer (Karle, Estlin & Karle, 1967), and reserpine (Karle & Karle, 1968). In the initial *E* map based on phases from the symbolic addition procedure, ring *C* and five atoms attached to it were found. Phases based on the positions of these atoms for those reflections with the largest  $|E|$  values were used in the tangent formula to obtain phases for other reflections. In this manner, all the atoms were located in three cycles. Our experience has shown that the atoms from the more rigid portions of the molecule appear most distinctly in the *E* maps computed with a limited set of data and peaks for those atoms with a considerable amount of thermal motion may be quite weak or absent. In this case, the atoms in the lactone ring with the large thermal parameters were the last

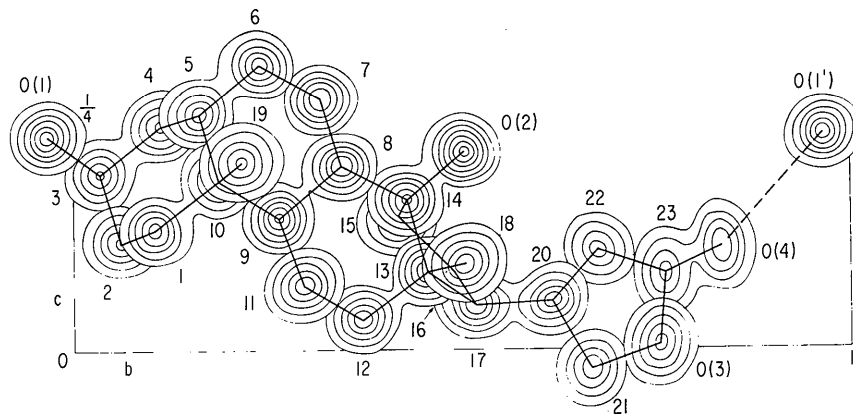


Fig. 1. Sections from a three-dimensional electron density map for digitoxigenin. The contours are evenly spaced and begin with the  $1 \text{ e.}\text{\AA}^{-3}$  contour.

to be found. The molecule is illustrated in the composite electron density map shown in Fig. 1.

Several cycles of least-squares refinement, minimizing the function  $\sum w(|F_o| - |F_c|)^2$  (ORFLS program; Busing, Martin & Levy, 1962) resulted in an  $R$  value of 18.0% using isotropic thermal parameters. The scattering factors used were those listed in *International Tables for X-ray Crystallography*. Several more cycles of refinement with anisotropic thermal factors reduced  $R$  to 13.0%. A difference map computed at this stage (Fig. 2) revealed the approximate location of 28 out of the 34 hydrogen atoms. When the coordinates of these 28 hydrogen atoms (Table 2) were included in the refinement as constant parameters,  $R$  decreased to 11.1%. This portion of the refinement was performed with unit weights. The same operations repeated with  $w=1$  for  $|F_o| < 15$  and  $w=15/|F_o|$  for  $|F_o| > 15$  gave a final  $R$  value of 10.4%. The observed and calculated structure factors for the weighted refinement are listed in Table 3.

### Discussion

The X-ray analysis has confirmed the configuration of digitoxigenin. A three-dimensional view of the molecule may be obtained from the stereodrawings in Fig. 3. Rings  $A$ ,  $B$ , and  $C$  are saturated and in the chair conformation. Ring  $D$  is also saturated and has the  $\alpha$ -envelope conformation. The ring junction  $B/C$  is *trans* while both ring junctions  $A/B$  and  $C/D$  are *cis*. The lactone group is planar.

Fractional coordinates and thermal parameters are listed in Table 4. Values for bond lengths and angles

Table 2. Approximate coordinates for the hydrogen atoms as determined from a difference map\*

Atom	$x$	$y$	$z$
1-1	1.017	0.047	0.138
1-2	1.067	0.125	0.083
2-1	0.700	0.112	0.087
2-2	0.792	0.020	0.088
3	0.583	0.012	0.167
4-1	0.625	0.092	0.290
4-2	0.592	0.170	0.192
5	0.892	0.105	0.278
6-1	0.950	0.268	0.305
6-2			
7-1	0.767	0.388	0.300
7-2	0.600	0.305	0.250
8	0.983	0.357	0.190
9	0.750	0.258	0.125
11-1	1.058	0.308	0.055
11-2	0.967	0.232	0.042
12-1	0.717	0.350	0.010
12-2	0.933	0.417	-0.022
15-1	0.467	0.413	0.172
15-2	0.517	0.358	0.112
16-1	0.433	0.547	0.113
16-2			
17			
18-1	1.083	0.447	0.118
18-2	1.083	0.508	0.027
18-3	1.017	0.560	0.100
19-1	1.242	0.225	0.150
19-2	1.225	0.158	0.217
19-3	1.192	0.272	0.210
21-1	0.633	0.663	-0.047
21-2	0.943	0.638	-0.047
22			

\* Neither of the hydrogen atoms of the two hydroxyl groups was found.

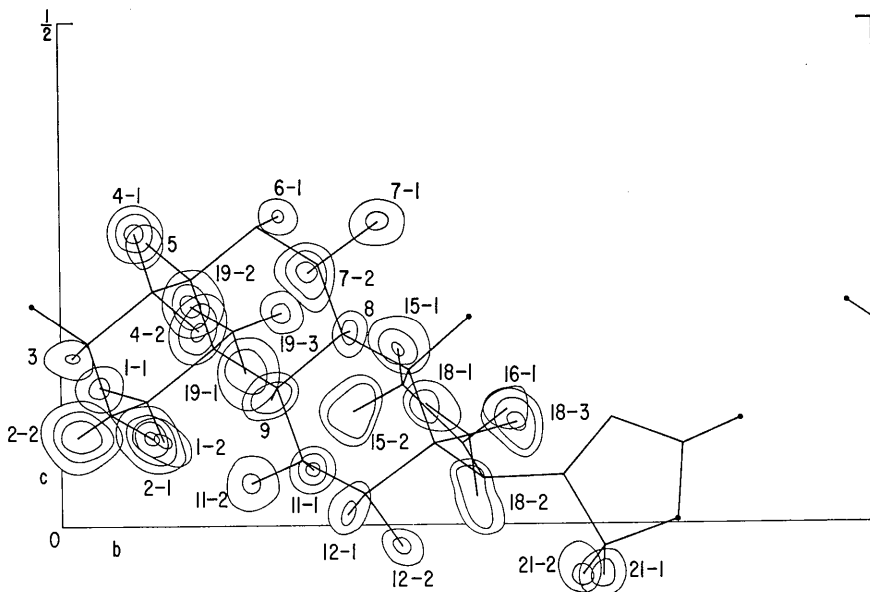


Fig. 2. The difference map for digitoxigenin showing the location of 28 hydrogen atoms. The contours are spaced by  $0.2 \text{ e.}\text{\AA}^{-3}$  beginning with the  $0.2 \text{ e.}\text{\AA}^{-3}$  contour.

Table 3. Observed and calculated structure factors  
The columns indicate the index  $l$ ,  $|F_o|$ ,  $|F_c|$  and  $\phi$  (radians).

Index $l$	$ F_o $	$ F_c $	$\phi$ (radians)		
2 36.8	30.2	-3.14	4 49.2	7.3	0.00
4 6.3	4.6	-3.14	8 49.2	41.7	0.00
6 97.3	92.0	-3.14	12 5.0	57.2	0.00
8 29.8	24.0	-3.14	16 6.6	59.7	-3.14
10 36.4	33.6	0.00	20 6.4	59.8	-3.14
12 12.6	13.8	-3.14	24 6.4	59.8	-3.14
14 0.0	0.1	-3.14	28 22.4	20.0	0.00
16 13.7	13.9	0.00	32 20.0	22.0	0.00
18 28.3	26.6	-3.14	36 13.4	27.3	-3.14
20 0.0	0.4	0.00	40 14.0	35.4	-3.14
22 0.0	0.4	-3.14	44 15.4	24.6	0.00
			48 16.0	1.0	0.00
			52 18.2	0.8	0.00
			56 11.4	10.0	-3.14
			60 7.0	8.1	0.00
			64 6.4	8.2	-1.97
			68 6.0	8.0	0.00
			72 7.4	8.9	1.57
			76 7.2	7.2	1.57
			80 12.3	12.3	-1.57
			84 10.0	3.4	-1.57
			88 10.0	4.0	1.57
			92 13.0	13.0	0.00
			96 14.0	14.0	0.00
			100 11.0	11.0	0.00
			104 15.0	15.0	0.00
			108 16.0	16.0	0.00
			112 15.0	15.0	0.00
			116 16.0	16.0	0.00
			120 16.0	16.0	0.00
			124 16.0	16.0	0.00
			128 16.0	16.0	0.00
			132 16.0	16.0	0.00
			136 16.0	16.0	0.00
			140 16.0	16.0	0.00
			144 16.0	16.0	0.00
			148 16.0	16.0	0.00
			152 16.0	16.0	0.00
			156 16.0	16.0	0.00
			160 16.0	16.0	0.00
			164 16.0	16.0	0.00
			168 16.0	16.0	0.00
			172 16.0	16.0	0.00
			176 16.0	16.0	0.00
			180 16.0	16.0	0.00
			184 16.0	16.0	0.00
			188 16.0	16.0	0.00
			192 16.0	16.0	0.00
			196 16.0	16.0	0.00
			200 16.0	16.0	0.00
			204 16.0	16.0	0.00
			208 16.0	16.0	0.00
			212 16.0	16.0	0.00
			216 16.0	16.0	0.00
			220 16.0	16.0	0.00
			224 16.0	16.0	0.00
			228 16.0	16.0	0.00
			232 16.0	16.0	0.00
			236 16.0	16.0	0.00
			240 16.0	16.0	0.00
			244 16.0	16.0	0.00
			248 16.0	16.0	0.00
			252 16.0	16.0	0.00
			256 16.0	16.0	0.00
			260 16.0	16.0	0.00
			264 16.0	16.0	0.00
			268 16.0	16.0	0.00
			272 16.0	16.0	0.00
			276 16.0	16.0	0.00
			280 16.0	16.0	0.00
			284 16.0	16.0	0.00
			288 16.0	16.0	0.00
			292 16.0	16.0	0.00
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			300 16.0	16.0	0.00
			304 16.0	16.0	0.00
			308 16.0	16.0	0.00
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			388 16.0	16.0	0.00
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			396 16.0	16.0	0.00
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			524 16.0	16.0	0.00
			528 16.0	16.0	0.00
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			624 16.0	16.0	0.00
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			632 16.0	16.0	0.00
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			640 16.0	16.0	0.00
			644 16.0	16.0	0.00
			648 16.0	16.0	0.00
			652 16.0	16.0	0.00
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			692 16.0	16.0	0.00
			696 16.0	16.0	0.00
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			916 16.0	16.0	0.00
			920 16.0	16.0	0.00
			924 16.0	16.0	0.00
			928 16.0	16.0	0.00
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			976 16.0	16.0	0.00
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			984 16.0	16.0	0.00
			988 16.0	16.0	0.00
			992 16.0	16.0	0.00
			996 16.0	16.0	0.00
			100		

Table 3 (cont.)

0	3.5	2.5	+3.14	13	31.1	28.3	1.07	11	0.0	3.1	2.74	4	3	L	4	10	L	10	21.7	23.7	6.32	6	1	L	11	0.0	2.0	-2.36			
1	7.0	7.0	+1.13	14	17.4	17.5	1.35	15	0.0	2.8	-0.32	0	29.7	30.7	+3.14	0	28.8	33.8	0.00	12	6.5	6.0	+2.20	12	6.5	6.0	+2.20	11	0.0	2.4	-2.60
2	12.0	8.1	+9.52	15	14.5	15.6	-1.43	16	10.3	11.1	-0.84	1	25.1	26.0	-2.20	1	25.1	26.0	-2.20	13	17.5	17.3	-2.99	1	15.0	16.1	-0.97	13	0.0	2.0	-2.60
3	17.0	13.1	+9.78	16	7.5	7.4	-2.52	17	0.0	2.8	-0.32	2	33.8	34.8	+0.86	2	33.8	34.8	+0.86	14	17.5	17.3	-2.99	2	14.0	15.1	-0.97	14	11.5	2.3	0.81
4	22.0	18.1	+9.78	17	4.5	4.1	-1.53	18	0.0	2.8	-0.32	3	42.5	43.5	+1.00	3	42.5	43.5	+1.00	15	17.5	17.3	-2.99	3	31.0	31.1	+0.20	15	0.0	2.0	-2.60
5	27.0	23.1	+9.78	18	8.5	8.1	-1.09	19	8.0	8.1	-1.09	4	51.2	52.2	+1.00	4	51.2	52.2	+1.00	16	17.5	17.3	-2.99	4	28.0	27.9	-0.16	16	0.0	2.0	-2.60
6	32.0	28.1	+9.78	19	8.5	8.1	-1.09	20	0.0	2.8	-0.32	5	60.0	61.0	+1.00	5	60.0	61.0	+1.00	17	17.5	17.3	-2.99	5	25.0	24.9	-0.16	17	19.0	18.3	1.57
7	37.0	33.1	+9.78	20	13.0	13.0	-2.22	21	0.0	2.8	-0.32	6	68.8	69.8	+1.00	6	68.8	69.8	+1.00	18	17.5	17.3	-2.99	6	20.0	19.9	-0.16	18	0.0	2.0	-2.60
8	42.0	38.1	+9.78	21	18.0	18.0	-2.22	22	0.0	2.8	-0.32	7	77.6	78.6	+1.00	7	77.6	78.6	+1.00	19	17.5	17.3	-2.99	7	15.0	14.9	-0.16	19	18.4	9.0	-9.74
9	47.0	43.1	+9.78	22	23.0	23.0	-2.22	23	0.0	2.8	-0.32	8	86.4	87.4	+1.00	8	86.4	87.4	+1.00	20	17.5	17.3	-2.99	8	10.0	9.9	-0.16	20	0.0	2.0	-2.60
10	52.0	48.1	+9.78	23	28.0	28.0	-2.22	24	0.0	2.8	-0.32	9	95.2	96.2	+1.00	9	95.2	96.2	+1.00	21	17.5	17.3	-2.99	9	5.0	4.9	-0.16	21	0.0	2.0	-2.60
11	57.0	53.1	+9.78	24	33.0	33.0	-2.22	25	0.0	2.8	-0.32	10	104.0	105.0	+1.00	10	104.0	105.0	+1.00	22	17.5	17.3	-2.99	10	0.0	2.0	-2.60	22	0.0	2.0	-2.60
12	62.0	58.1	+9.78	25	38.0	38.0	-2.22	26	0.0	2.8	-0.32	11	112.8	113.8	+1.00	11	112.8	113.8	+1.00	23	17.5	17.3	-2.99	11	0.0	2.0	-2.60	23	0.0	2.0	-2.60
13	67.0	63.1	+9.78	26	43.0	43.0	-2.22	27	0.0	2.8	-0.32	12	121.6	122.6	+1.00	12	121.6	122.6	+1.00	24	17.5	17.3	-2.99	12	0.0	2.0	-2.60	24	0.0	2.0	-2.60
14	72.0	68.1	+9.78	27	48.0	48.0	-2.22	28	0.0	2.8	-0.32	13	130.4	131.4	+1.00	13	130.4	131.4	+1.00	25	17.5	17.3	-2.99	13	0.0	2.0	-2.60	25	0.0	2.0	-2.60
15	77.0	73.1	+9.78	28	53.0	53.0	-2.22	29	0.0	2.8	-0.32	14	139.2	140.2	+1.00	14	139.2	140.2	+1.00	26	17.5	17.3	-2.99	14	0.0	2.0	-2.60	26	0.0	2.0	-2.60
16	82.0	78.1	+9.78	29	58.0	58.0	-2.22	30	0.0	2.8	-0.32	15	148.0	149.0	+1.00	15	148.0	149.0	+1.00	27	17.5	17.3	-2.99	15	0.0	2.0	-2.60	27	0.0	2.0	-2.60
17	87.0	83.1	+9.78	30	63.0	63.0	-2.22	31	0.0	2.8	-0.32	16	156.8	157.8	+1.00	16	156.8	157.8	+1.00	28	17.5	17.3	-2.99	16	0.0	2.0	-2.60	28	0.0	2.0	-2.60
18	92.0	88.1	+9.78	31	68.0	68.0	-2.22	32	0.0	2.8	-0.32	17	165.6	166.6	+1.00	17	165.6	166.6	+1.00	29	17.5	17.3	-2.99	17	0.0	2.0	-2.60	29	0.0	2.0	-2.60
19	97.0	93.1	+9.78	32	73.0	73.0	-2.22	33	0.0	2.8	-0.32	18	174.4	175.4	+1.00	18	174.4	175.4	+1.00	30	17.5	17.3	-2.99	18	0.0	2.0	-2.60	30	0.0	2.0	-2.60
20	102.0	98.1	+9.78	33	78.0	78.0	-2.22	34	0.0	2.8	-0.32	19	183.2	184.2	+1.00	19	183.2	184.2	+1.00	31	17.5	17.3	-2.99	19	0.0	2.0	-2.60	31	0.0	2.0	-2.60
21	107.0	103.1	+9.78	34	83.0	83.0	-2.22	35	0.0	2.8	-0.32	20	192.0	193.0	+1.00	20	192.0	193.0	+1.00	32	17.5	17.3	-2.99	20	0.0	2.0	-2.60	32	0.0	2.0	-2.60
22	112.0	108.1	+9.78	35	88.0	88.0	-2.22	36	0.0	2.8	-0.32	21	200.8	201.8	+1.00	21	200.8	201.8	+1.00	33	17.5	17.3	-2.99	21	0.0	2.0	-2.60	33	0.0	2.0	-2.60
23	117.0	113.1	+9.78	36	93.0	93.0	-2.22	37	0.0	2.8	-0.32	22	209.6	210.6	+1.00	22	209.6	210.6	+1.00	34	17.5	17.3	-2.99	22	0.0	2.0	-2.60	34	0.0	2.0	-2.60
24	122.0	118.1	+9.78	37	98.0	98.0	-2.22	38	0.0	2.8	-0.32	23	218.4	219.4	+1.00	23	218.4	219.4	+1.00	35	17.5	17.3	-2.99	23	0.0	2.0	-2.60	35	0.0	2.0	-2.60
25	127.0	123.1	+9.78	38	103.0	103.0	-2.22	39	0.0	2.8	-0.32	24	227.2	228.2	+1.00	24	227.2	228.2	+1.00	36	17.5	17.3	-2.99	24	0.0	2.0	-2.60	36	0.0	2.0	-2.60
26	132.0	128.1	+9.78	39	108.0	108.0	-2.22	40	0.0	2.8	-0.32	25	236.0	237.0	+1.00	25	236.0	237.0	+1.00	37	17.5	17.3	-2.99	25	0.0	2.0	-2.60	37	0.0	2.0	-2.60
27	137.0	133.1	+9.78	40	113.0	113.0	-2.22	41	0.0	2.8	-0.32	26	244.8	245.8	+1.00	26	244.8	245.8	+1.00	38	17.5	17.3	-2.99	26	0.0	2.0	-2.60	38	0.0	2.0	-2.60
28	142.0	138.1	+9.78	41	118.0	118.0	-2.22	42	0.0	2.8	-0.32	27	253.6	254.6	+1.00	27	253.6	254.6	+1.00	39	17.5	17.3	-2.99	27	0.0	2.0	-2.60	39	0.0	2.0	-2.60
29	147.0	143.1	+9.78	42	123.0	123.0	-2.22	43	0.0	2.8	-0.32	28	262.4	263.4	+1.00	28	262.4	263.4	+1.00	40	17.5	17.3	-2.99	28	0.0	2.0	-2.60	40	0.0	2.0	-2.60
30	152.0	148.1	+9.78	43	128.0	128.0	-2.22	44	0.0	2.8	-0.32	29	271.2	272.2	+1.00	29	271.2	272.2	+1.00	41	17.5	17.3	-2.99	29	0.0	2.0	-2.60	41	0.0	2.0	-2.60
31	157.0	153.1	+9.78	44	133.0	133.0	-2.22	45	0.0	2.8	-0.32	30	280.0	281.0	+1.00	30	280.0	281.0	+1.00	42	17.5	17.3	-2.99	30	0.0	2.0	-2.60	42	0.0	2.0	-2.60
32	162.0	158.1	+9.78	45	138.0	138.0	-2.22	46	0.0	2.8	-0.32	31	288.8	289.8	+1.00	31	288.8	289.8	+1.00	43	17.5	17.3	-2.99	31	0.0	2.0	-2.60	43	0.0	2.0	-2.60
33	167.0	163.1	+9.78	46	143.0	143.0	-2.22	47	0.0	2.8	-0.32	32	297.6	298.6	+1.00	32	297.6	298.6	+1.00	44	17.5	17.3	-2.99	32	0.0	2.0	-2.60	44	0.0	2.0	-2.60
34	172.0	168.1	+9.78	47	148.0	148.0	-2.22	48	0.0	2.8	-0.32	33	306.4	307.4	+1.00	33	306.4	307.4	+1.00	45	17.5	17.3	-2.99	33	0.0	2.0	-2.60	45	0.0	2.0	-2.60
35	177.0	173.1	+9.78	48	153.0	153.0	-2.22	49	0.0	2.8	-0.32	34	315.2	316.2	+1.00	34	315.2	316.2	+1.00	46	17.5	17.3	-2.99	34	0.0	2.0	-2.60	46	0.0	2.0	-2.60
36	182.0	178.1	+9.78	49	158.0	158.0	-2.22	50	0.0	2.8	-0.32	35	324.0	325.0	+1.00	35	324.0	325.0	+1.00	47	17.5	17.3	-2.99	35	0.0	2.0	-2.60	47	0.0	2.0	-2.60
37	187.0	183.1	+9.78	50	163.0	163.0	-2.22	51	0.0	2.8	-0.32	36	332.8	333.8	+1.00	36	332.8	333.8	+1.00	48	17.5	17.3	-2.99	36	0.0	2.0	-2.60	48	0.0	2.0	-2.60
38	192.0	188.1	+9.78	51	168.0	168.0	-2.22	52	0.0	2.8	-0.32	37	341.6	342.6	+1.00	37	341.6	342.6	+1.00	49	17.5	17.3	-2.99	37	0.0	2.0	-2.60	49	0.0	2.0	-2.60
39	197.0	193.1	+9.78	52	173.0	173.0	-2.22	53	0.0	2.8	-0.32	38	350.4	351.4	+1.00	38	350.4	351.4	+1.00	50	17.5	17.3	-2.99	38	0.0	2.0	-2.60	50	0.0	2.0	-2.60
40	202.0	198.1	+9.78	53	178.0	178.0	-2.22	54	0.0	2.8	-0.32	39	359.2	360.2	+1.00	39	359.2	360.2	+1.00	51	17.5	17.3	-2.99	39	0.0	2.0	-2.60	51	0.0	2.0	-2.60
41	207.0	203.1	+9.78	54	183.0	183.0	-2.22	55	0.0	2.8	-0.32	40	368.0	369.0	+1.00	40	368.0	369.0	+1.00	52	17.5	17.3	-2.99	40	0.0	2.0	-2.60	52	0.0	2.0	-2.60
42	212.0	208.1	+9.78	55	188.0	188.0	-2.22	56	0.0	2.8	-0.32	41	376.8	377.8	+1.00	41	376.8	377.8	+1.00	53	17.5	17.3	-2.99	41	0.0	2.0	-2.60	53	0.0	2.0	-2.60
43	217.0	213.1	+9.78	56	193.0	193.0	-2.22	57	0.0	2.8	-0.32	42	385.6	386.6	+1.00	42	385.6	386.6	+1.00	54	17.5	17.3	-2.99	42	0.0	2.0	-2.60	54	0.0	2.0	-2.60
44	222.0																														

Table 3 (cont.)

0 5.9	3.1	0.10	0 2.8	4.4	-3.14	0 0.0	1.0	0.00	0 5.4	3.0	0.00	0 0.0	2.0	-1.97
1 5.8	3.0	-1.97	1 6.2	3.8	0.00	1 0.0	0.0	0.00	1 5.9	3.0	0.00	1 0.0	2.0	-1.97
2 0.0	1.0	-3.14	2 2.9	1.8	1.92	2 0.0	0.0	0.00	2 6.8	4.0	-0.02	2 4.3	2.0	2.86
3 3.1	2.0	-1.97	3 4.7	1.8	-1.92	3 0.0	0.0	0.00	3 6.5	0.1	-0.00	3 7.1	7.4	-4.13
4 0.0	4.0	-3.14	4 0.0	1.8	-2.38	4 0.0	0.0	-0.00	4 7.9	0.0	0.77	4 7.0	0.0	-0.49
5 4.0	4.0	-3.14	5 4.0	3.0	0.00	5 0.0	0.0	0.00	5 8.0	0.0	0.00	5 4.0	0.0	-1.00
6 0.0	3.0	-3.14	6 4.0	4.0	-1.00	6 0.0	0.0	0.00	6 8.8	7.4	-2.05	6 4.2	2.0	-0.74
7 0.0	0.0	0.00	7 4.0	3.0	0.00	7 0.0	0.0	0.00	7 8.0	0.0	0.00	7 0.0	0.0	0.00
8 4.0	3.0	0.00	8 4.0	3.0	0.00	8 0.0	0.0	0.00	8 8.8	0.0	0.00	8 7.7	1.0	1.00
9 13.2	11.0	-1.97	9 0.0	3.0	0.00	9 0.0	0.0	0.00	9 7.4	0.0	1.48	9 8.0	0.4	-1.92
10 5.8	0.0	1.97	10 6.7	7.4	1.77	10 0.0	0.0	0.00	10 6.1	5.7	0.92	10 0.0	0.0	-0.47
11 0.0	0.0	1.97	11 0.0	0.0	0.00	11 0.0	0.0	0.00	11 0.0	0.0	0.00	11 0.0	0.0	-1.97
12 6.8	0.0	0.00	12 0.0	0.0	0.00	12 0.0	0.0	0.00	12 0.0	0.0	0.00	12 0.0	0.0	-1.97
0 9.4	9.0	0.00	0 0.0	2.0	-3.14	0 0.0	1.4	-3.14	0 0.7	0.0	0.00	0 2.0	3.1	-1.97
1 6.1	2.0	0.00	1 0.0	3.0	0.17	1 0.0	0.0	0.00	1 0.0	2.1	1.09	1 2.0	0.0	0.00
2 5.2	4.0	-3.94	2 0.0	1.0	-1.99	2 0.0	0.0	0.00	2 0.0	0.0	2.00	2 0.0	0.0	0.00
3 4.2	3.0	-3.94	3 0.0	3.0	0.99	3 0.0	0.0	0.00	3 3.7	3.0	0.04	3 0.0	0.0	-1.97
4 6.2	4.0	1.78	4 0.0	2.0	0.42	4 0.0	0.0	0.00	4 5.2	0.0	0.10	4 7.0	0.0	-1.97
5 11.0	9.0	-3.94	5 0.0	0.0	0.00	5 0.0	0.0	0.00	5 0.0	0.0	0.00	5 12.0	0.0	-1.97
6 5.8	4.0	1.78	6 0.0	4.0	2.75	6 0.0	0.0	0.00	6 0.0	0.0	0.00	6 0.0	0.0	0.00
7 12.0	8.0	0.00	7 0.0	7.0	1.69	7 0.0	0.0	0.00	7 0.0	0.0	0.00	7 0.0	0.0	0.00
8 7.9	0.0	0.00	8 0.0	4.0	-2.40	8 0.0	0.0	0.00	8 9.9	0.0	2.37	8 0.0	0.0	0.00
9 6.0	1.0	-2.13	9 0.0	1.0	0.00	9 0.0	0.0	0.00	9 0.0	0.0	0.00	9 0.0	0.0	0.00
10 5.2	3.0	1.93	10 0.0	0.0	0.00	10 0.0	0.0	0.00	10 0.0	0.0	0.00	10 0.0	0.0	0.00
11 3.2	3.0	-1.92	11 0.0	0.0	0.00	11 0.0	0.0	0.00	11 0.0	0.0	0.00	11 0.0	0.0	0.00

Table 4. Fractional coordinates and thermal parameters for digitoxigenin

The thermal parameters are of the form  $T = \exp [-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)]$ .  
Each thermal parameter is multiplied by  $10^4$ .

	<i>x</i>	<i>y</i>	<i>z</i>	$\beta_{11}$	$\beta_{22}$	$\beta_{33}$	$\beta_{12}$	$\beta_{13}$	$\beta_{23}$
C(1)	0.9751	0.1042	0.1250	252	30	19	13	11	2
C(2)	0.7920	0.0615	0.1109	320	34	17	-7	-1	-2
C(3)	0.7020	0.0341	0.1818	274	33	26	3	0	2
C(4)	0.6879	0.1142	0.2315	216	42	24	-5	20	3
C(5)	0.8715	0.1625	0.2436	200	30	15	8	1	1
C(6)	0.8428	0.2412	0.2951	342	29	15	11	-1	-4
C(7)	0.7420	0.3187	0.2570	291	30	13	10	10	2
C(8)	0.8470	0.3463	0.1883	161	28	12	4	2	-1
C(9)	0.8685	0.2652	0.1358	114	27	12	17	0	0
C(10)	0.9707	0.1879	0.1743	120	32	17	19	0	2
C(11)	0.9609	0.2959	0.0645	200	40	16	26	25	4
C(12)	0.8536	0.3723	0.0305	177	30	12	8	13	1
C(13)	0.8412	0.4572	0.0786	96	30	14	1	-4	2
C(14)	0.7533	0.4273	0.1527	127	20	15	-3	11	-5
C(15)	0.5502	0.4195	0.1362	109	35	22	-9	14	5
C(16)	0.5048	0.4910	0.0801	101	42	25	9	13	3
C(17)	0.6941	0.5166	0.0444	87	32	15	0	-1	-1
C(18)	1.0311	0.4996	0.0857	119	43	26	-5	-4	7
C(19)	1.1761	0.2111	0.1905	118	56	42	10	-29	9
C(20)	0.7248	0.6155	0.0469	159	32	22	9	-7	3
C(21)	0.7876	0.6634	-0.0190	539	28	35	-12	29	4
C(22)	0.7056	0.6744	0.1021	339	30	38	8	-47	-10
C(23)	0.7534	0.7631	0.0732	351	33	54	9	-69	-3
O(1)	0.8125	-0.0341	0.2176	396	29	26	19	2	9
O(2)	0.7693	0.5021	0.2030	265	26	16	-6	7	-7
O(3)	0.8020	0.7560	0.0026	610	28	63	-38	-17	15
O(4)	0.7542	0.8342	0.1023	647	23	87	15	-110	-13
Standard deviations									
C(1-20)	0.0013	0.0005	0.0004	17	3	2	9	6	2
C(21-23)	0.0020	0.0006	0.0006	37	4	4	11	11	3
O(1-2)	0.0011	0.0003	0.0003	20	2	2	7	4	2
O(3-4)	0.0017	0.0005	0.0006	38	3	4	11	12	3

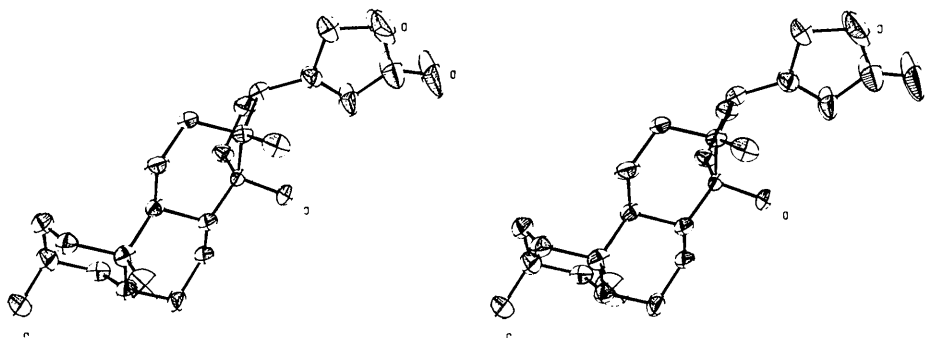


Fig. 3. A stereodiamgram of the digitoxigenin molecule (Johnson, 1965).

are shown in Table 5 and Fig. 4. The standard deviations as derived from the least-squares refinement are 0.012 Å for the bonds and 0.7° for the angles except in the lactone group where the standard deviations have been computed to be 0.016 Å for the bond lengths and 0.9° for the angles. If experimental errors other than those revealed in the least-squares fit are con-

sidered, the standard deviations would be larger, perhaps by a factor of two.

The average of twenty-two C–C single bonds in rings *A*, *B*, *C*, *D* and adjacent methyl groups is 1.538 Å and the two C–OH bond lengths are 1.458 and 1.462 Å, all expected values. In the lactone group it is obvious that the two C–C bonds adjacent to the C=C are significantly shorter than the single-bond value of 1.54 Å. Furthermore, the two C–O bonds in the ring are unequal with the shorter C–O bond occurring adjacent

to the carbonyl group. Similar observations for a lactone group have been made previously (see *e.g.* Fridrichsons & Mathieson, 1962; Kartha & Haas, 1964; Karle & Karle, 1966a).

Least-squares planes (Schomaker, Waser, Marsh & Bergman, 1959) were computed for various portions of the molecule. They are:

Atoms	Plane
20, 21, 22, 23, O(3), O(4):	$6.8990x - 2.1841y + 4.9171z = 3.8924$ (1)
5, 6, 8, 9, 12, 13:	$7.2048x + 1.2690y + 0.9331z = 6.6951$ (2)
6, 7, 8, 13, 14:	$4.1749x + 9.4708y + 9.5911z = 8.6178$ (3)
5, 9, 10, 11, 12:	$4.0150x + 9.8893y + 9.3937z = 7.3918$ (4)
1, 2, 4, 5:	$-2.5029x + 12.4924y - 8.0088z = -2.1258$ (5)
13, 15, 16, 17:	$1.1233x + 10.5333y + 12.8496z = 6.7794$ (6)

The values on the right are the origin-to-plane distances in Å. Coordinates listed in Table 4 may be substituted directly into these equations. The lactone group (1) is planar, the largest deviation from the plane being 0.009 Å. In addition, the adjacent C(17) deviates by only 0.014 Å from the lactone plane. For rings *B* and *C*, three planes (2–4) were computed. In plane (4), the largest deviation was 0.006 Å, while the largest deviations from planes (2) and (3) were 0.04 Å. These deviations reflect the distortion of ring *C* from an ideal

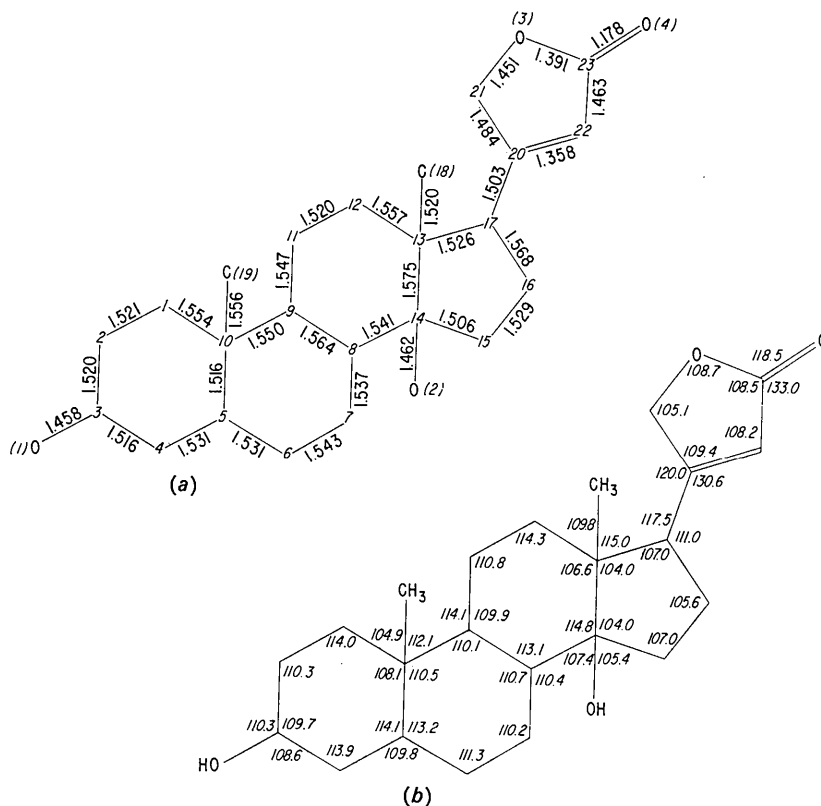


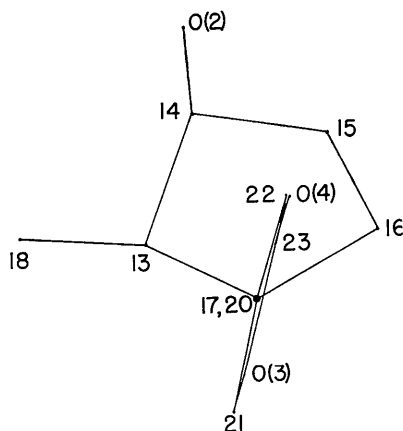
Fig. 4. Bond lengths and angles in digitoxigenin.

Table 5. Bond lengths and angles in digitoxigenin

O(1)–C(3)	1.458 Å	O(1)C(3)C(2)	110.3°
		O(1)C(3)C(4)	108.6
O(2)–C(14)	1.462	O(2)C(14)C(13)	107.6
		O(2)C(14)C(15)	105.4
O(3)–C(21)	1.451	O(2)C(14)C(8)	107.4
O(3)–C(23)	1.391	C(21)O(3)C(23)	108.7
O(4)–C(23)	1.178		
		O(4)C(23)O(3)	118.5
C(1)–C(2)	1.521	O(4)C(23)C(22)	133.0
C(2)–C(3)	1.520	C(10)C(1)C(2)	114.0
C(3)–C(4)	1.516	C(1)C(2)C(3)	110.3
C(4)–C(5)	1.531	C(2)C(3)C(4)	109.7
C(5)–C(6)	1.531	C(3)C(4)C(5)	113.9
C(5)–C(10)	1.516	C(4)C(5)C(6)	109.8
		C(4)C(5)C(10)	114.1
C(6)–C(7)	1.543	C(6)C(5)C(10)	113.2
C(7)–C(8)	1.537	C(5)C(6)C(7)	111.3
C(8)–C(9)	1.564	C(6)C(7)C(8)	110.2
C(8)–C(14)	1.541	C(7)C(8)C(9)	110.7
		C(7)C(8)C(14)	110.4
C(9)–C(10)	1.550	C(9)C(8)C(14)	113.1
C(9)–C(11)	1.547	C(8)C(9)C(10)	110.1
		C(8)C(9)C(11)	109.9
C(10)–C(1)	1.554	C(10)C(9)C(11)	114.1
		C(9)C(10)C(1)	110.7
C(10)–C(19)	1.556	C(5)C(10)C(1)	108.1
		C(5)C(10)C(9)	110.5
C(11)–C(12)	1.520	C(1)C(10)C(19)	104.9
C(12)–C(13)	1.557	C(5)C(10)C(19)	110.3
C(13)–C(14)	1.575	C(9)C(10)C(19)	112.1
C(13)–C(17)	1.526	C(9)C(11)C(12)	110.8
		C(11)C(12)C(13)	114.3

Table 5 (cont.)

C(13)–C(18)	1.520	C(12)C(13)C(14)	106.6
		C(12)C(13)C(17)	106.4
C(14)–C(15)	1.506	C(14)C(13)C(17)	104.1
		C(12)C(13)C(18)	109.8
C(15)–C(16)	1.529	C(14)C(13)C(18)	114.2
C(16)–C(17)	1.568	C(17)C(13)C(18)	115.0
C(17)–C(20)	1.503	C(13)C(14)C(15)	104.0
		C(8)C(14)C(15)	117.0
C(20)–C(21)	1.484	C(8)C(14)C(13)	114.8
C(20)–C(22)	1.358	C(14)C(15)C(16)	107.0
		C(15)C(16)C(17)	105.6
C(22)–C(23)	1.463	C(13)C(17)C(20)	117.5
		C(16)C(17)C(20)	111.0
		C(13)C(17)C(16)	107.1
		C(17)C(20)C(21)	120.0
		C(17)C(20)C(22)	130.6
		C(21)C(20)C(22)	109.4
		C(20)C(21)O(3)	105.1
		C(20)C(22)C(23)	108.2
		C(22)C(23)O(3)	108.5

Fig. 5. Projection along the (17)–(20) bond showing the orientation of the lactone ring with respect to ring *D*.

chair conformation at the junction of the five-membered ring *D*. In ring *B*, atoms (10) and (7) are 0.70 Å above and below plane (2), whereas in ring *C*, atoms (11) and (14) are 0.66 and 0.58 Å above and below plane (2), which indicates a slight flattening of ring *C* near atom (14). In ring *A*, atoms (3) and (6) are 0.66 and 0.65 Å below and above plane (5) formed by atoms (1), (2), (4) and (5).

The five-membered ring *D* in digitoxigenin is different than in all the other steroids whose crystal structures have been studied by X-ray diffraction, except for batrachotoxinin A (Karle & Karle, 1969), in that it has a *cis* junction with ring *C*. Ring *D* assumes the  $\alpha$ -envelope conformation with atom (14) 0.53 Å out of the plane formed by atoms (13), (15), (16) and (17), plane (6). The envelope is somewhat flatter than that found in steroids with a *trans* *C/D* junction such as e.g. 4-bromoestradiol (Norton, Kartha & Lu, 1964) and buxene-G dihydroiodide (Puckett, Sim, Abushanab & Kupchan, 1966) where the out-of-plane atoms are displaced by more than 0.7 Å. The torsion angle about the (13)–(14) bond is 32° in digitoxigenin as compared to ~45° for various steroids with the *trans* *C/D* junction (Brutcher & Leopold, 1966). In batrachotoxinin A, where the *C/D* junction is *cis*, ring *D* also assumes the  $\alpha$ -envelope conformation, except that it is even flatter than in digitoxigenin, possibly because of the double bond at (16)–(17).

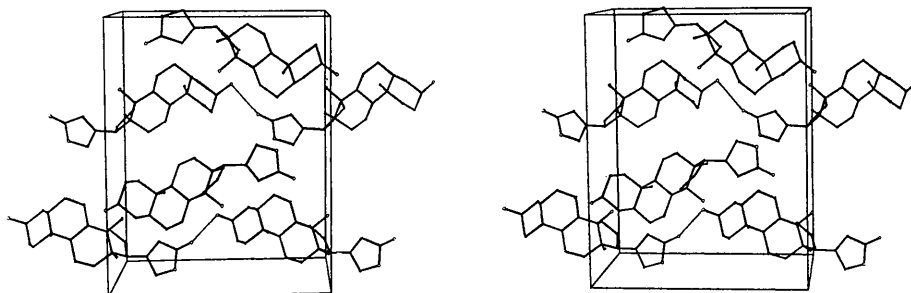
Fig. 6. A stereodiagram of the molecular packing in digitoxigenin. The *b* axis is horizontal and the *c* axis is vertical.



Fig. 5, a projection along the (17)–(20) bond, shows the orientation of the lactone ring with respect to ring *D*. The plane of the lactone ring is nearly parallel to the (13)–(14) bond. The orientation of the lactone group about the (17)–(20) bond is probably governed by the presence of O(2) and the methyl group at (18) on ring *D*.

The packing of the molecules is illustrated in Fig. 6. A hydrogen bond of length 2.94 Å between the terminal hydroxyl group and the carbonyl of the lactone group links the molecules in infinite chains parallel to the *b* axis. Although cross-linkages between symmetry related molecules ( $x, y, z$ ;  $\bar{x}, \frac{1}{2} - y, \frac{1}{2} + z$ ) involving the terminal and central hydroxyl groups are suggested by the favorable orientation of the hydroxyl groups, the actual O(1)···O(2) distance is 3.41 Å, which is too large for hydrogen bonding. The intermolecular distances between non-hydrogen atoms are all quite large, for the most part considerably larger than 3.8 Å. The nearest approaches, in addition to those already mentioned, are 3.63 Å between O(3) and O(3') related by a screw axis and 3.42 Å between C(16) and C(18') related by a unit translation along the *a* axis.

Twenty-eight of the thirty-four hydrogen atoms were located in the difference map, Fig. 2. The six hydrogen atoms of the two methyl groups, C(18) and C(19) are oriented in the staggered configurations with respect to adjacent bonds. In fact, these methyl groups are quite rigid since their positions are constrained by other hydrogen atoms attached to the rings. The hydrogen atoms in the two hydroxyl groups were not found in the difference map. Presumably the hydrogen atom on O(1) is directed toward O(4) to form a hydrogen bond. The orientation of the hydrogen atom on O(2) is unknown. A model of the molecule built with the hydrogen atoms included shows that the molecule, except for the lactone group, occupies an ellipsoidal volume.

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