Table 7. *The shortest intermolecular distances* (Å)

Some distances, equivalent by lattice translations, are not reported [*e.g.* $C(3)_{x,y,z}\cdots C(2)_{x,y,z+1}$ is equivalent to $C(2)_{x,y,z}\cdots C(3)_{x,y,z-1}$].

	294 K	118 K
$C(2)\cdots C^{i}(3)$	3·429 (2)	3·3531 (5)
$C(3)\cdots C^{i}(5)$	3·451 (2)	3·3781 (5)
$C(2')\cdots C^{i}(3')$	3·429 (2)	3·3531 (5)
$C(3')\cdots C^{i}(5')$	3·451 (2)	3·3781 (5)
$C(5)\cdots D^{ii}(1)$	2·774 (3)	2·6988 (7)
$C(5')\cdots D^{ii}(1)$	2·774 (3)	2·6988 (7)
$N(2)\cdots D^{iii}(3')$	2·553 (2)	2·5304 (5)
$N(2')\cdots D^{iv}(2')$	2·553 (2)	2·5304 (5)
$N(2)\cdots D^{v}(2')$	2·753 (2)	2·6994 (6)

Symmetry code

(i)	$x, y, z-1$	(iv)	$1-x, y+\frac{1}{2}, 1-z$
(ii)	$x-1, y, z+1$	(v)	$1-x, y-\frac{1}{2}, -z$
(iii)	$1-x, y-\frac{1}{2}, 1-z$		

The non-planarity of the molecule, presumably related to a residual electronic charge on C(4), is confirmed by an angle of 2·38° between C(4)–C(5) and the best least-squares plane through C(4) and the pyridinium ring (294 K). Table 6 gives the least-squares analysis of the planarity of these last atoms as well as the best plane through C(4), C(5), N(2), C(5′) and N(2′). The two planes make an angle of 5·12° (118 K) whereas a value of 3·94° is found for the room-temperature data.

Short intermolecular atomic distances are reported in Table 7.

X-ray data at the same temperatures have already been collected and their study is at present in progress.

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Structure of Digoxin

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Abstract

The three-dimensional structure of digoxin, a cardiac glycoside, was determined by X-ray diffraction analysis. Digoxin ($C_{41}H_{64}O_{14}$) crystallizes in the triclinic system, space group $P1$, with cell parameters $a = 7{\cdot}404\ (2)$, $b = 12{\cdot}781\ (2)$, $c = 12{\cdot}677\ (2)$ Å, $\alpha = 91{\cdot}15\ (1)$, $\beta = 119{\cdot}89\ (2)$ and $\gamma = 104{\cdot}78\ (2)°$ ($\lambda = 1{\cdot}5418$ Å), $V = 990$ Å^3, $Z = 1$. The structure was solved by vector-search methods using digoxigenin as known fragment followed by tangent-refinement recycling procedures. Refinement was carried out by block-diagonal least-squares calculations to an R factor of 4·2%. The molecule has an extended structure with its aglycone moiety in the 3β,12β,14β-trihydroxy-5β-card-20(22)-enolide conformation and the three digitoxoses joined to the aglycone in a series of $\beta(1\rightarrow 4)$-D-glycosidic linkages. The first and second digitoxoses

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have an intramolecular hydrogen bond between the axial hydroxyl oxygen at the 3 position and the ring oxygen of the second digitoxose and are held in the same plane, but a similar bonding does not exist between the second and the third digitoxoses. The third digitoxose is rotated 63° out of the plane common to the first two digitoxoses. Crystal packing involves intermolecular hydrogen bonds between hydroxyls of the neighboring molecules with both the steroid nucleus and the sugars.

Introduction

Digoxin ($C_{41}H_{64}O_{14}$) was isolated by Smith (1930) from leaves of *Digitalis lanata* Ehrh. It is the most frequently prescribed digitalis steroid for heart-congestion therapy. Two other pharmacologically active cardiac glycosides that are contained in *Digitalis lanata* are digitoxin ($C_{41}H_{64}O_{13}$) which differs from digoxin by one less hydroxyl at the C(12) position of the steroid nucleus and gitoxin ($C_{41}H_{64}O_{14}$) which has the hydroxyl attached to C(16) instead of C(12) as in digoxin. X-ray diffraction studies on digitoxigenin, the aglycone portion of digitoxin, have been reported by Karle & Karle (1969*b*), but this report on digoxin is the first X-ray diffraction analysis of a cardiac glycoside with the sugar still attached (Go, Kartha & Chen, 1979).

Experimental

Commercially available Lanoxin-brand digoxin supplied by Burroughs Wellcome Co., was recrystallized from a mixture of ethyl alcohol and chloroform. The crystals are triclinic with space group $P1$. A crystal of size $0{\cdot}18 \times 0{\cdot}42 \times 0{\cdot}7$ mm was selected for X-ray diffraction studies. Crystal data are summarized in Table 1. Lattice dimensions were refined by a least-squares fit to a set of 25 measured reflections in a θ range 24–47° for Cu radiation. Three-dimensional data were collected first on a General Electric XRD-6 manual diffractometer to a maximum scattering angle 2θ of 160°, using Ni-filtered Cu $K\alpha$ radiation ($\lambda = 1{\cdot}5418$ Å), by the stationary crystal, stationary counter method (Furnas & Harker, 1955), from which the structure was solved. A second set of data were recollected later, on an Enraf–Nonius CAD-4 automated diffractometer using Ni-filtered Cu $K\alpha$ radiation with ω–2θ scans and integrated counts within the Cu sphere up to $2\theta = 154°$. The measured intensities were converted to structure amplitudes in the usual manner, and corrected for Lorentz and polarization effects, as well as empirical absorption corrections. 4324 independent reflections were measured from the first set and 4123 from the second, of which 3656 from the first and 3919 from the second were considered observed [$I > 2\sigma(I)$].

Table 1. *Crystal data*

$C_{41}H_{64}O_{14}$, $M_r = 780{\cdot}92$
Space group: $P1$

$a = 7{\cdot}404$ (2) Å	$V = 990$ Å^3
$b = 12{\cdot}781$ (2)	D_m (flotation) $= 1{\cdot}30$ Mg m^{-3}
$c = 12{\cdot}677$ (2)	$D_c = 1{\cdot}30$
$\alpha = 91{\cdot}15$ (1)°	$Z = 1$
$\beta = 119{\cdot}89$ (2)	$\mu = 0{\cdot}816$ mm^{-1}
$\gamma = 104{\cdot}78$ (2)	
Number of reflections measured	4123
Number of reflections observed	3919

Structure analysis

The structure was solved by vector-search methods (Nordman, 1966), using digoxigenin as the known fragment (Go & Kartha, in preparation). The known Patterson coefficients were calculated using a hypothetical $P1$ unit cell of size $a = 10$, $b = 26$, $c = 11$ Å and $\alpha = \beta = \gamma = 90°$ to cover the size of the aglycone part of the digoxin molecule. This insured clear separation of the Patterson intramolecular and intermolecular vectors. The preliminary search was carried out on a 15° interval over the full rotation range. There were two peaks in the rotation search that were significantly higher than the others and the exact rotation parameters were determined from a 2° grid search. The two peaks from the rotation search are shown in Fig. 1(*a*) and (*b*). Their three angles θ_1, θ_2, θ_3 (abscissa, ordinate, section) obtained from the rotation search are: 107, 175, 184° and 80, 305, 313° respectively. For these orientations, the coordinates of the 28 nonhydrogen atoms of digoxigenin were used to deduce the trial coordinates of the aglycone in the triclinic cell of digoxin. The two coordinate sets were used separately to develop the remaining atomic positions by tangent-refinement recycling procedures (Karle, 1968). Only the first set revealed an additional 19 sensible non-hydrogen atoms in the E maps. The remaining eight non-hydrogen atoms were then obtained by Fourier methods. A few cycles of block-diagonal least-squares calculations gave an R factor of 19%. After assignment of atom types and application of anisotropic temperature factors for the non-hydrogen atoms, a few more cycles of least-squares refinement and inclusion of the contribution of the 43 calculated H atoms, the R factor had dropped to 9% for 3656 reflections. Further refinements were then carried out on the set of data collected from the Enraf–Nonius CAD-4 diffractometer which gave an R factor of 7·8% for non-hydrogen atoms only. At this stage, all H atoms were seen on difference Fourier maps, and three cycles of refinement for 119 atoms (isotropic for H)

Table 2. *Final parameters* ($\times 10^4$, *except for B for* H *atoms*)

For H atoms $T = \exp(-B \sin^2\theta/\lambda^2)$.

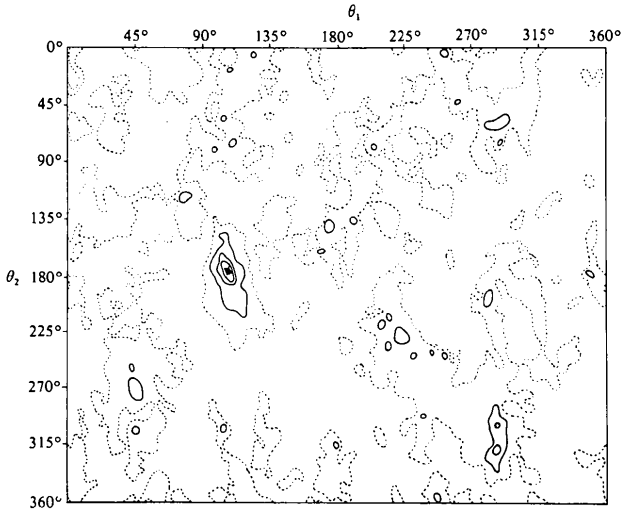
	x	y	z	$U_{eq.}$ or B (Å^2)
C(1)	11594 (1)	1659 (1)	7313 (1)	379
C(2)	10276 (2)	796 (1)	6140 (1)	498
C(3)	8043 (2)	955 (1)	5280 (1)	477
C(4)	6879 (2)	976 (1)	5970 (1)	481
C(5)	8186 (1)	1866 (1)	7125 (1)	437
C(6)	6923 (2)	1927 (1)	7772 (1)	714
C(7)	6708 (1)	943 (1)	8411 (1)	623
C(8)	8939 (1)	825 (1)	9331 (1)	360
C(9)	10191 (1)	724 (1)	8676 (1)	289
C(10)	10461 (1)	1741 (1)	8039 (1)	326
C(11)	12358 (1)	511 (1)	9568 (1)	376
C(12)	11972 (1)	−479 (1)	10158 (1)	337
C(13)	10934 (1)	−336 (1)	10925 (1)	286
C(14)	8743 (1)	−83 (1)	10081 (1)	329
C(15)	7133 (1)	−1210 (1)	9358 (1)	386
C(16)	7671 (2)	−1942 (1)	10349 (1)	409
C(17)	10185 (1)	−1511 (1)	11217 (1)	343
C(18)	12533 (2)	561 (1)	12060 (1)	395
C(19)	11907 (2)	2795 (1)	9013 (1)	465
C(20)	11009 (1)	−1551 (1)	12555 (1)	415
C(21)	10022 (2)	−1250 (1)	13251 (1)	589
C(22)	12721 (2)	−1867 (1)	13330 (1)	497
C(23)	13036 (2)	−1732 (1)	14554 (1)	524
O(3)	8205 (1)	1982 (1)	4835 (1)	456
O(12)	13965 (1)	−742 (1)	10926 (1)	501
O(14)	7952 (1)	228 (1)	10846 (1)	446
O(21)	11539 (2)	−1310 (1)	14525 (1)	638
O(23)	14425 (2)	−1926 (1)	15518 (1)	660
C(1′)	8969 (2)	2149 (1)	4036 (1)	412
C(2′)	7873 (2)	2916 (1)	3210 (1)	501
C(3′)	8845 (2)	3351 (1)	2433 (1)	389
C(4′)	11342 (1)	3779 (1)	3241 (1)	323
C(5′)	12297 (2)	2968 (1)	4067 (1)	416
C(6′)	14715 (2)	3482 (1)	4986 (1)	639
C(1″)	12132 (1)	4862 (1)	1923 (1)	335
C(2″)	13813 (1)	5157 (1)	1542 (1)	370
C(3″)	13423 (1)	6050 (1)	738 (1)	376
C(4″)	11029 (2)	5743 (1)	−292 (1)	376
C(5″)	9492 (2)	5425 (1)	196 (1)	372
C(6″)	7087 (2)	5016 (1)	−805 (1)	518
C(1‴)	9835 (2)	6431 (1)	−2170 (1)	414
C(2‴)	9496 (2)	7455 (1)	−2719 (1)	482
C(3‴)	8639 (2)	7210 (1)	−4096 (1)	523
C(4‴)	10071 (2)	6669 (1)	−4315 (1)	568
C(5‴)	10529 (2)	5723 (1)	−3608 (1)	518
C(6‴)	12250 (3)	5323 (2)	−3652 (1)	857
O(5′)	11282 (1)	2684 (1)	4773 (1)	402
O(3′)	8179 (2)	2501 (1)	1447 (1)	519
O(4′)	12369 (1)	3956 (1)	2525 (1)	378
O(5″)	9993 (1)	4531 (1)	847 (1)	367
O(3″)	14057 (1)	7046 (1)	1532 (1)	400
O(4″)	10697 (1)	6673 (1)	−899 (1)	420
O(5‴)	11394 (1)	6112 (1)	−2332 (1)	454
O(3‴)	6459 (2)	6495 (1)	−4756 (1)	652
O(4‴)	9067 (3)	6286 (2)	−5610 (1)	899
H1-C(1)	13134 (22)	1613 (13)	7906 (12)	2·459
H2-C(1)	11897 (20)	2334 (12)	7113 (11)	2·219
H1-C(2)	11057 (16)	814 (9)	5712 (9)	0·827
H2-C(2)	9974 (33)	66 (20)	6349 (19)	3·605
H-C(3)	7357 (25)	328 (15)	4567 (14)	3·181
H1-C(4)	5330 (24)	1117 (15)	5429 (13)	2·853
H2-C(4)	6562 (24)	272 (15)	6173 (13)	2·685

Table 2 (*cont.*)

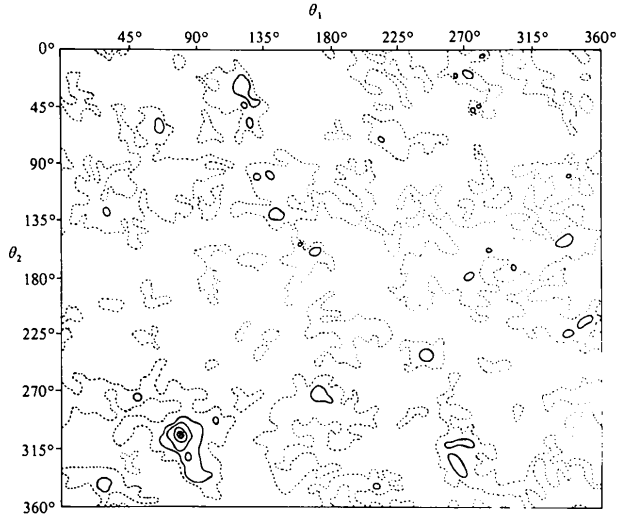
	x	y	z	B (Å^2)
H-C(5)	8491 (19)	2523 (11)	6815 (10)	1·777
H1-C(6)	7416 (51)	2573 (31)	8304 (28)	5·764
H2-C(6)	5376 (30)	1956 (18)	7112 (17)	4·048
H1-C(7)	5897 (22)	941 (13)	8828 (12)	2·458
H2-C(7)	5876 (20)	310 (12)	7862 (11)	1·961
H-C(8)	9828 (21)	1548 (13)	9908 (12)	2·356
H-C(9)	9300 (14)	108 (8)	8076 (8)	0·528
H1-C(11)	13079 (14)	355 (9)	9117 (8)	0·483
H2-C(11)	13332 (20)	1145 (12)	10221 (11)	1·900
H-C(12)	10905 (13)	−1104 (8)	9445 (7)	0·000
H1-C(15)	5683 (26)	−1092 (16)	9027 (15)	3·540
H2-C(15)	7517 (17)	−1328 (10)	8782 (10)	1·311
H1-C(16)	6935 (17)	−1880 (10)	10848 (9)	1·111
H2-C(16)	7123 (28)	−2740 (17)	10014 (16)	3·726
H-C(17)	10918 (17)	−1940 (10)	10951 (9)	1·332
H1-C(18)	11922 (23)	565 (14)	12598 (13)	2·448
H2-C(18)	13091 (32)	1255 (19)	11890 (18)	4·328
H3-C(18)	13916 (21)	393 (13)	12522 (12)	1·442
H1-C(19)	11306 (21)	2910 (13)	9527 (12)	2·144
H2-C(19)	11931 (25)	3422 (15)	8514 (14)	3·211
H3-C(19)	13248 (37)	2730 (22)	9445 (20)	5·382
H1-C(21)	9722 (27)	−460 (16)	13092 (15)	3·579
H2-C(21)	8590 (38)	−1790 (23)	13044 (21)	5·729
H-C(22)	13648 (33)	−2184 (20)	13157 (19)	4·719
H-O(12)	14886 (27)	−478 (16)	10717 (15)	3·488
H-O(14)	8283 (34)	962 (20)	10979 (19)	4·815
H-C(1′)	8836 (23)	1468 (14)	3621 (13)	2·590
H1-C(2′)	6402 (27)	2528 (16)	2647 (15)	3·637
H2-C(2′)	8181 (24)	3635 (15)	3878 (13)	3·131
H-C(3′)	8197 (23)	3954 (14)	2065 (13)	2·698
H-C(4′)	11804 (16)	4494 (10)	3795 (9)	1·190
H-C(5′)	11948 (19)	2334 (11)	3558 (10)	1·868
H1-C(6′)	15088 (47)	2870 (28)	5298 (26)	6·928
H2-C(6′)	15549 (34)	3626 (20)	4492 (19)	4·672
H3-C(6′)	14687 (59)	4158 (36)	5399 (33)	8·521
H-C(1″)	12240 (18)	5476 (11)	2515 (10)	1·565
H1-C(2″)	15222 (18)	5469 (11)	2240 (10)	1·586
H2-C(2″)	13765 (20)	4543 (12)	1098 (11)	2·013
H-C(3″)	14317 (13)	6118 (8)	350 (7)	0·008
H-C(4″)	10730 (20)	5137 (12)	−833 (11)	1·886
H-C(5″)	9817 (17)	6054 (10)	788 (9)	0·964
H1-C(6″)	6858 (45)	4289 (27)	−1469 (25)	6·579
H2-C(6″)	6699 (37)	5727 (22)	−1312 (21)	5·285
H3-C(6″)	5979 (33)	4768 (20)	−447 (18)	4·752
H-C(1‴)	8250 (24)	5795 (15)	−2605 (14)	3·015
H1-C(2‴)	8265 (27)	7612 (16)	−2527 (15)	3·575
H2-C(2‴)	11042 (20)	8001 (12)	−2269 (11)	2·055
H-C(3‴)	8782 (28)	8039 (17)	−4432 (16)	3·974
H-C(4‴)	11743 (30)	7317 (18)	−3920 (17)	4·265
H-C(5‴)	8942 (25)	5090 (15)	−4031 (14)	3·366
H1-C(6‴)	11546 (65)	5213 (39)	−4602 (36)	9·369
H2-C(6‴)	12291 (64)	4652 (39)	−3040 (36)	9·179
H3-C(6‴)	13824 (57)	5972 (35)	−3302 (32)	8·331
H-O(3′)	9032 (55)	2858 (34)	1040 (31)	7·968
H-O(3″)	13711 (42)	7667 (26)	978 (24)	6·022
H-O(3‴)	5192 (77)	6765 (47)	−4888 (43)	10·635
H-O(4‴)	7409 (68)	6232 (41)	−5834 (38)	9·768

gave a final R factor of 4·2% for 3919 reflections. Final parameters are given in Table 2.*

* Lists of observed and calculated structure factors and anisotropic thermal parameters for non-hydrogen atoms have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35230 (23 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.



(*a*)



(*b*)

Fig. 1. The rotation function in terms of Cartesian angles θ_1, θ_2, θ_3. Two peaks significantly higher than the others as shown in the figures: (*a*) at $\theta_1 = 107°$, $\theta_2 = 175°$, $\theta_3 = 184°$; (*b*) at $\theta_1 = 80°$, $\theta_2 = 305°$, $\theta_3 = 313°$.

Results and discussion

General features

The digoxin molecule shows an extended structure. A stereoscopic view of the molecules in the unit cell is shown in Fig. 2. The numbering of the atoms and labeling of the rings are shown in Fig. 3. The conformation of the digoxigenin portion is typical of cardiac glycosides, in that the *A* and *D* rings of the aglycone are *cis* with respect to the fused *B* and *C* rings, giving rise to a folded steroid nucleus (Tamm, 1961). This characteristic has also been seen in other cardiac-active steroids, *e.g.* batrachotoxinin A (Tokuyama, Daly, Witkop, Karle & Karle, 1968; Karle & Karle, 1969*a*), digitoxigenin (Karle & Karle, 1969*b*), strophanthidin (Gilardi & Flippen, 1973) and 5β-hydroxygitoxigenin (Przybylska & Ahmed, 1979). The aglycone has the conformation 3β,12β,14β-trihydroxy-5β-card-20(22)-enolide, and the digitoxoses are joined to C(3) of the aglycone in a series of $\beta(1 \rightarrow 4)$-D-glycosidic linkages and are of the $^4C_1$ chair conformation. The methyl group at the 5 position of each digitoxose is equatorial while the three hydroxyls at the 3 positions of the digitoxoses are axial. There is evidence of weak intramolecular hydrogen bonding (O···O is 2·905 Å) between the hydroxyl at the 3 position of the first digitoxose and the ring oxygen of the second digitoxose (this bond is shown in Fig. 2), but a similar hydrogen bonding does not exist between the second and the third digitoxose. This may be due to the hydrogen-bonding scheme between the neighboring molecules (Fig. 2) as all hydroxyls except one are involved in the hydrogen-bonding network. (For further discussion on hydrogen bonding, see below.)

Bond lengths and angles

Table 3(*a*) and (*b*) gives the bond lengths and angles in comparison with other structurally related cardiac steroids and Table 3(*c*) and (*d*) gives the bond lengths and angles in comparison with other structurally related $\beta(1 \rightarrow 4)$-linked saccharides. There is generally

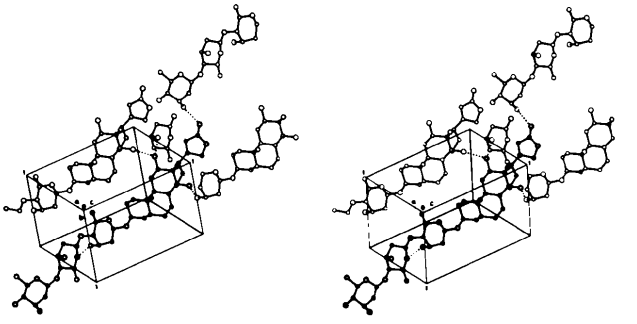


Fig. 2. Stereoscopic view of the unit cell showing hydrogen-bonding scheme (one intramolecular and four intermolecular bonding to neighboring molecules in three directions).

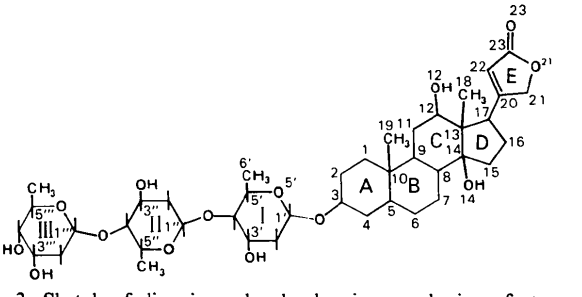


Fig. 3. Sketch of digoxin molecule showing numbering of atoms and labeling of rings.

Table 3. *(a) Bond distances and (b) angles in the aglycone portion in comparison with other structurally related genins and (c) bond distances and (d) angles for the sugar portion in comparison with other structurally related saccharides*

An asterisk in (*a*) and (*b*) indicates incomparable data due to disorder or different types of bonds or angles. The dagger in (*a*) refers to C(16)–O(16) for 5β-hydroxygitoxigenin.

(*a*) Bond lengths (Å) (with an e.s.d. of 0·002 Å) for the aglycone portion

	(I)	(II)	(III)	(IV)	(V)	(VI)	(VII)
C(1)–C(2)	1·523	1·511	1·523	1·497	1·527	1·535	1·589
C(2)–C(3)	1·532	1·519	1·513	1·520	1·530	1·580	1·463
C(3)–C(4)	1·507	1·510	1·522	1·516	1·501	1·503	1·487
C(4)–C(5)	1·527	1·531	1·530	1·538	1·532	1·571	1·477
C(5)–C(10)	1·550	1·562	1·562	1·517	1·550	1·545	1·532
C(10)–C(1)	1·541	1·539	1·542	1·552	1·536	1·555	1·567
C(5)–C(6)	1·535	1·533	1·523	1·531	1·520	1·517	1·584
C(6)–C(7)	1·526	1·532	1·528	1·544	1·543	1·553	1·539
C(7)–C(8)	1·525	1·531	1·528	1·536	1·509*	1·584	1·527
C(8)–C(9)	1·545	1·537	1·538	1·564	1·521	1·576	1·542
C(9)–C(10)	1·566	1·566	1·565	1·550	1·572	1·595	1·592
C(9)–C(11)	1·534	1·537	1·529	1·547	1·531	1·567	1·537
C(11)–C(12)	1·520	1·511	1·521	1·522	1·531	1·530	1·540
C(12)–C(13)	1·543	1·548	1·547	1·556	1·525	1·573	1·510
C(13)–C(14)	1·560	1·556	1·562	1·575	1·525*	1·582	1·545
C(14)–C(8)	1·540	1·545	1·542	1·540	*	1·498	1·541
C(14)–C(15)	1·522	1·532	1·527	1·508	1·525	1·538	1·543
C(15)–C(16)	1·533	1·524	1·523	1·523	1·547	1·593	1·540
C(16)–C(17)	1·546	1·548	1·558	1·570	1·536	1·590	1·557
C(17)–C(13)	1·582	1·586	1·581	1·527	1·573	1·594	1·578
C(17)–C(20)	1·496	1·501	1·496	1·485	1·499	1·493	*
C(10)–C(19)	1·537	1·535	1·540	1·558	1·546	1·534	1·500
C(13)–C(18)	1·526	1·522	1·526	1·523	1·533	1·538	1·546
C(20)–C(21)	1·493	1·385*	1·482	1·485	1·499	1·493	*
C(20)–C(22)	1·332	1·385*	1·329	1·357	1·317	1·313	*
C(22)–C(23)	1·449	1·401*	1·441	1·476	1·457	1·512	*
C(21)–O(21)	1·456	1·381*	1·439	1·450	1·438	1·428	*
C(23)–O(21)	1·337	1·512*	1·343	1·355	1·365	1·370	*
C(23)–O(23)	1·226	1·124*	1·214	1·195	1·202	1·222	*
C(3)–O(3)	1·439	1·436	1·424	1·459	1·453	1·459	1·442
C(12)–O(12)	1·440	1·434	1·427†				
C(14)–O(14)	1·453	1·440	1·448	1·462		1·413	

(*b*) Bond angles (°) (with an e.s.d. of 0·2°) for the aglycone portion

	(I)	(II)	(III)	(IV)	(V)	(VI)	(VII)
C(10)–C(1)–C(2)	116·0	114·6	114·1	115·5	114·5	112·5	110·1
C(1)–C(2)–C(3)	110·7	111·6	111·1	110·3	111·4	110·6	109·2
C(2)–C(3)–C(4)	109·8	109·9	110·6	109·6	110·5	108·8	114·6
C(3)–C(4)–C(5)	113·2	114·3	113·9	113·9	113·9	115·8	112·7
C(4)–C(5)–C(10)	112·0	113·7	109·3	114·1	112·5	111·0	115·3
C(5)–C(10)–C(1)	107·8	108·1	108·1	107·5	108·4	110·2	115·3
C(10)–C(5)–C(6)	111·1	111·5	111·4	113·2	111·9	113·2	111·5
C(5)–C(6)–C(7)	112·0	112·1	113·6	111·3	112·2	112·0	110·5
C(6)–C(7)–C(8)	111·5	111·1	112·8	110·2	112·1	110·3	111·5
C(7)–C(8)–C(9)	110·3	110·3	109·9	110·7	114·0*	108·8	111·3
C(8)–C(9)–C(10)	110·8	112·1	111·3	110·3	110·6	113·0	110·5
C(9)–C(10)–C(5)	109·9	110·0	108·9	110·4	109·8	108·4	109·1
C(8)–C(9)–C(11)	110·8	110·1	111·5	109·8	113·7	108·1	109·4
C(9)–C(11)–C(12)	110·7	111·3	109·6	110·7	112·9	108·4	110·1
C(11)–C(12)–C(13)	113·3	112·9	113·7	114·3	110·8	111·0	112·8
C(12)–C(13)–C(14)	108·8	109·1	109·8	106·6	109·8	109·2	109·8
C(13)–C(14)–C(8)	113·7	114·2	114·8	114·7	*	112·5	114·7
C(14)–C(8)–C(9)	115·4	113·5	116·0	113·2	*	113·1	113·9
C(13)–C(14)–C(15)	103·4	103·5	103·1	104·0	*	104·2	104·1
C(14)–C(15)–C(16)	103·2	105·6	104·2	107·0	104·7	104·7	104·5
C(15)–C(16)–C(17)	105·2	107·1	103·3	105·6	103·7	105·2	108·1
C(16)–C(17)–C(13)	105·9	105·6	106·2	107·1	103·4	106·5	104·6
C(17)–C(13)–C(14)	103·8	103·7	104·4	104·1	100·4*	103·9	104·5
C(13)–C(17)–C(20)	115·0	115·8	119·8	117·5	115·2	117·2	115·6

Table 3 (*cont.*)

	(I)	(II)	(III)	(IV)	(V)	(VI)	(VII)
C(16)–C(17)–C(20)	115·3	113·6	113·3	111·0	114·6	111·1	108·7
C(17)–C(20)–C(21)	125·5	128·4	119·4	119·9	120·8	124·7	102·9*
C(17)–C(20)–C(22)	126·4	123·2	133·5	130·7	131·1	124·3	130·9
C(21)–C(20)–C(22)	108·0	108·3	107·1	109·4	108·0	111·1	*
C(20)–C(21)–O(21)	104·2	110·5*	105·3	105·1	105·3	105·5	*
C(20)–C(22)–C(23)	109·1	110·6*	110·3	107·0	109·8	105·9	*
C(22)–C(23)–O(21)	109·3	104·4*	108·3	109·8	108·5	109·2	*
C(23)–O(21)–C(21)	108·8	106·0*	109·0	108·7	108·5	108·1	*
C(22)–C(23)–O(23)	129·5	*	132·1	130·1	131·3	129·5	*
O(21)–C(23)–O(23)	121·2	*	119·6	120·1	120·2	121·1	*

References for (*a*) and (*b*): (I) Digoxin (this work). (II) Digoxigenin (in preparation). (III) 5β-Hydroxygitoxigenin (Przybylska & Ahmed, 1979). (IV) Digitoxigenin (Karle & Karle, 1969*b*). (V) Anhydrodigitoxigenin (Gilardi & Karle, 1970). (VI) and (VII) Strophanthidin (*A*) and (*B*) respectively (Gilardi & Flippen, 1973).

(*c*) Bond distances (Å) (with an e.s.d. of 0·002 Å) for the sugar portion

	(I)	(II)	(III)	(IV)	(V)	(VI)	(VII)	(VIII)	(IX)
C(1′)–C(2′)	1·522	1·514	1·514	1·525	1·515	1·515	1·526	1·515	1·521
C(2′)–C(3′)	1·524	1·531	1·522	1·521	1·543	1·518	1·527	1·526	1·538
C(3′)–C(4′)	1·530	1·522	1·530	1·527	1·518	1·517	1·519	1·524	1·536
C(4′)–C(5′)	1·533	1·523	1·527	1·527	1·519	1·537	1·519	1·531	1·523
C(5′)–C(6′)	1·511	1·517	1·513			1·517	1·511	1·508	1·510
C(1′)–O(5′)	1·434	1·425	1·419	1·442	1·409	1·414	1·419	1·413	1·431
C(5′)–O(5′)	1·429	1·440	1·431	1·440	1·431	1·427	1·438	1·440	1·436
C(3′)–O(3′)	1·430	1·425	1·418	1·434	1·436	1·431	1·421	1·426	1·408
C(4′)–O(4′)	1·435	1·436	1·433	1·425	1·448	1·422	1·449	1·424	1·451
C(1′)–O(3)	1·382	1·401	1·399	1·393	1·397	1·395	1·361	1·402	1·388

(*d*) Bond angles (°) (with an e.s.d. of 0·2°) for the sugar portion

	(I)	(II)	(III)	(IV)	(V)	(VI)	(VII)	(VIII)	(IX)
O(5′)–C(1′)–C(2′)	109·1	109·4	109·5	109·1	110·7	110·0	109·6	110·4	110·6
C(1′)–C(2′)–C(3′)	113·8	110·4	109·2	109·0	112·0	109·3	110·0	109·7	109·3
C(2′)–C(3′)–C(4′)	110·1	110·4	110·4	111·8	112·4	109·0	109·8	108·3	112·1
C(3′)–C(4′)–C(5′)	112·2	112·1	113·0	110·8	109·9	110·3	110·7	110·4	112·0
C(4′)–C(5′)–O(5′)	110·1	106·8	108·4	110·1	108·0	110·4	109·2	109·2	108·7
C(5′)–O(5′)–C(1′)	113·9	112·1	110·9	110·4	110·0	112·9	114·5	113·2	113·3
C(4′)–O(4′)–C(1″)	114·7	113·3		113·8		116·3		116·5	

References for (*c*) and (*d*): (I), (II), (III) The three digitoxoses (this work). For digitoxose II, replace ′ by ″ and for digitoxose III, replace ′ by ‴. For the C(1′)–O(3) bond, replace by C(1″)–O(4′) for digitoxose II, and C(1‴)–O(4″) for digitoxose III. (IV), (V) Xylose portion of aldotriuronic acid (Moran & Richards, 1973). (VI), (VII) Diacetylchitobiose (Mo & Jensen, 1978). (VIII), (IX) β-Lactose (Hirotsu & Shimada, 1974). For (IV)–(IX) replace ″ by ′ and ′ by no primes for the corresponding notations. Replace C(1′)–O(3) by C(1)–O(1) or C(1′)–O(1′) accordingly.

good agreement between corresponding bond lengths and angles, especially for those corresponding to data of better accuracy. In the steroid portion, C–C bonds

thidin(*A*) in which the conformation at C(20) is related to that of the other cardiac steroids by a rotation of 180° about the C(17)–C(20) bond.

Table 4. *Torsion angles* (°) (*e.s.d.* 0·2°)

(*a*) Torsion angles for the rings of the aglycone and for C(17)–C(20). [For digoxigenin, C(21) and C(22) are a combination of both atomic positions of C(21) and C(22) that are related by a flip over of about 180°.]

	Digoxin	Digoxigenin	Digitoxigenin	Strophanthidin (*A*)	(*B*)
Ring *A*					
C(10)–C(1)–C(2)–C(3)	54·3	57·8	58·3	58·9	55·6
C(1)–C(2)–C(3)–C(4)	−53·8	−55·3	−55·4	−55·7	−57·0
C(2)–C(3)–C(4)–C(5)	57·2	53·0	53·6	53·6	53·9
C(3)–C(4)–C(5)–C(10)	−57·6	−51·2	−52·5	−52·5	−49·3
C(4)–C(5)–C(10)–C(1)	51·7	48·0	48·8	50·6	49·5
C(5)–C(10)–C(1)–C(2)	−52·1	−52·3	−53·6	−56·5	−51·7
Ring *B*					
C(5)–C(6)–C(7)–C(8)	56·3	57·0	55·3	57·5	55·0
C(6)–C(7)–C(8)–C(9)	−57·0	−57·2	−57·5	−55·8	−56·1
C(7)–C(8)–C(9)–C(10)	57·5	56·7	58·0	55·9	57·4
C(8)–C(9)–C(10)–C(5)	−56·4	−54·4	−55·7	−54·6	−57·9
C(9)–C(10)–C(5)–C(6)	54·9	52·8	54·9	54·7	57·3
C(10)–C(5)–C(6)–C(7)	−55·2	−55·0	−54·9	−58·1	−56·8
Ring *C*					
C(8)–C(9)–C(11)–C(12)	53·9	56·6	55·2	61·6	57·2
C(9)–C(11)–C(12)–C(13)	−61·0	−60·1	−61·1	−63·5	−62·1
C(11)–C(12)–C(13)–C(14)	56·8	54·6	56·3	56·9	55·4
C(12)–C(13)–C(14)–C(8)	−48·4	−48·7	−51·0	−51·4	−47·7
C(13)–C(14)–C(8)–C(9)	46·3	49·1	51·4	53·3	47·1
C(14)–C(8)–C(9)–C(11)	−48·0	−51·2	−51·3	−57·7	−50·9
Ring *D*					
C(17)–C(13)–C(14)–C(15)	−33·0	−35·8	−34·2	−36·4	−36·9
C(13)–C(14)–C(15)–C(16)	43·6	37·4	33·8	39·3	35·5
C(14)–C(15)–C(16)–C(17)	−37·1	−24·1	−19·0	−26·8	−20·6
C(15)–C(16)–C(17)–C(13)	16·1	1·4	−2·1	4·0	−2·0
C(16)–C(17)–C(13)–C(14)	10·2	21·2	22·0	19·3	23·8
About C(17)–C(20) bond					
C(13)–C(17)–C(20)–C(21)	81·8	88·8	−103·3	69·6	−103·7
C(13)–C(17)–C(20)–C(22)	−99·0	−94·3	76·3	−110·9	84·9
C(16)–C(17)–C(20)–C(21)	−41·9	−33·7	133·0	−53·2	139·0
C(16)–C(17)–C(20)–C(22)	137·4	143·2	−47·4	126·3	−32·3

(*b*) Endocyclic torsion angles for the digitoxose rings

C(1′)–C(2′)	53·6	C(1″)–C(2″)	56·3	C(1‴)–C(2‴)	60·8
C(2′)–C(3′)	−48·0	C(2″)–C(3″)	−49·2	C(2‴)–C(3‴)	−50·3
C(3′)–C(4′)	47·4	C(3″)–C(4″)	50·7	C(3‴)–C(4‴)	48·0
C(4′)–C(5′)	−53·8	C(4″)–C(5″)	−57·1	C(4‴)–C(5‴)	−53·1
C(5′)–O(5′)	61·6	C(5″)–O(5″)	65·8	C(5‴)–O(5‴)	63·5
O(5′)–C(1′)	−60·9	O(5″)–C(1″)	−66·7	O(5‴)–C(1‴)	−68·9
Mean	54·2		57·6		57·6

(*c*) Exocyclic torsion angles of digitoxoses in $\beta(1 \rightarrow 4)$-linked bridges. Torsion angles φ_1, $\varphi_{1'}$, φ_2, $\varphi_{2'}$ are according to Sundaralingam (1968). Pseudo-torsion angles ψ_1, $\psi_{1'}$, ψ_2, $\psi_{2'}$ define rotations about the vectors C(1″)–C(4′) and C(1‴)–C(4″) according to Rohrer (1972). For digitoxose II and III bridge torsion angles, replace ′ by ″ and ″ by ‴.

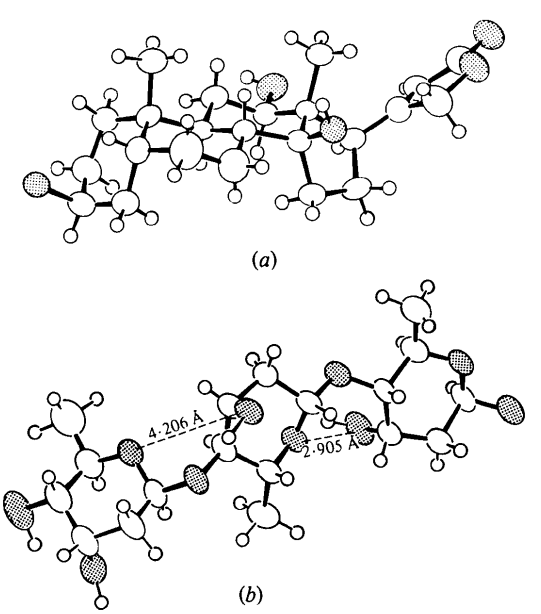
		Digitoxoses I & II	Digitoxoses II & III
φ_1	O(5″)–C(1″)–O(4′)–C(4′)	−79·0	−63·1
$\varphi_{1'}$	C(2″)–C(1″)–O(4′)–C(4′)	163·0	178·5
φ_2	C(1″)–O(4′)–C(4′)–C(3′)	71·9	123·8
$\varphi_{2'}$	C(1″)–O(4′)–C(4′)–C(5′)	−165·5	−113·8
ψ_1	O(5″)–C(1″)···C(4′)–C(3′)	−8·6	51·1
$\psi_{1'}$	O(5″)–C(1″)···C(4′)–C(5′)	128·8	−157·2
ψ_2	C(2″)–C(1″)···C(4′)–C(5′)	−50·0	78·8
$\psi_{2'}$	C(2″)–C(1″)···C(4′)–C(3′)	−142·5	−72·9
$\psi_{a'} =$	$\frac{1}{2}(\psi_1 + \psi_2)$	−6·8	65·0

Torsion angles

Table 4(*a*) gives the torsion angles for the aglycone in comparison with structurally related cardiac-active steroids. They all have a slightly flattened chair conformation for rings *A*, *B* and *C*. However, the *D* ring of digoxin has a 14β,15α-distorted half-chair conformation whereas the other genins have the 14β-envelope conformation except for 5β-hydroxygitoxigenin which has a 15α-envelope possibly due to the hydroxyl substituent at the C(16) position. Interestingly, the intact cardiac glycoside appears to differ from the individual genins in the conformation of the *D* ring.

Viewed down C(17)–C(20), the torsion angle C(13)–C(17)–C(20)–C(22) is −99° in digoxin, 76° in digitoxigenin and −111° in strophanthidin(*A*). Hence, the lactone-ring conformation of digoxin and strophanthidin(*A*) are very nearly the same but are related to digitoxogenin by a rotation of nearly 180°. It appears that both orientations (mentioned above) of the lactone ring are energetically favorable and may coexist in solution (Rohrer & Fullerton, 1978).

The torsion angles for the digitoxose rings are given in Table 4(*b*) and (*c*). They are all flattened chair conformations having a mean value of 54° for the one closest to its aglycone, and 57° for both the second and the third. The exocyclic torsion angles differ from the fully extended conformation of −110 and +110° for φ_1 and φ_2 respectively (Ramachandran, Ramakrishnan & Sasisekharan, 1963). The same differences were observed in other similarly linked saccharides (Chu & Jeffrey, 1968; Ham & William, 1970; Fries, Rao & Sundaralingam, 1971; Moran & Richards, 1973; Mo & Jensen, 1978). As pointed out by Fries *et al.* (1971), the lactose molecule exhibits a symmetrical twist about the bridge bonds, having $\varphi_1 = -92{\cdot}6°$ and $\varphi_2 = +94{\cdot}6°$, while an asymmetrical twist is exhibited by cellobiose,



(*a*)

(*b*)

Fig. 4. *ORTEP* (Johnson, 1965) drawings of digoxin in parts showing different geometries (ellipsoidal shape of 50% probability). Shaded atoms indicate oxygens. (*a*) Aglycone portion of digoxin, viewed sideways to the *B* and *C* fused rings. (*b*) Digitoxoses I, II and III.

having $\varphi_1 = -77{\cdot}8°$ and $\varphi_2 = +106°$, a difference of about 30°. Apparently, there is a limit to the asymmetrical twist about the bridge bonds when the intramolecular hydrogen bond cannot be formed. In digoxin, the bridge bonds between the first and the second digitoxose have $\varphi_1 = -79°$ and $\varphi_2 = +72°$, where the hydrogen bond exists: the difference is 7° and is within the range of 30°, while the bridge bonds between the second and the third digitoxose have $\varphi_1 = -63°$ and $\varphi_2 = +124°$; here the difference is 61° and the hydrogen bond cannot be formed. Xylobiose and diacetylchitobiose, which do not form the hydrogen bond, have differences in the two angles φ_1 and φ_2 of 80° and 54° respectively (Moran & Richards, 1973; Mo & Jensen, 1978).

Also similar trends are exhibited by the pseudo-torsion angles (Rohrer, 1972), as shown in Table 4(*b*). Mo & Jensen (1978) pointed out that for xylobiose and diacetylchitobiose, the helical twist, ψ_{av} (defined as $\psi_{av} = \frac{1}{2}\{\psi_1 + \psi_2\}$) is 81 and 54° respectively. For the corresponding ψ_{av} between the second and the third digitoxose, it is 65°. In all these cases, the hydrogen bond cannot be formed. These O···O distances between the hydroxyl at the 3 position and the ring oxygen of the adjacent ring are found to be 3·31 and 3·36 Å for xylobiose and diacetylchitobiose. In the case of digoxin, the corresponding distance between the second and the third digitoxose is 4·21 Å. Mo & Jensen (1978) concluded that the intramolecular hydrogen bond exists in $\beta(1 \rightarrow 4)$-linked disaccharides in the ψ_{av} range −12 to 39°, and this bond constrains only mildly the conformational freedom about the glycosidic bridge. The results of this study again corroborate the above conclusion.

Table 5. *Least-squares planes and deviations of atoms*

Planes of the form $lX + mY + nZ = p$, where X, Y, Z and p are in Å relative to the crystal axes

Plane	Through atoms	*l*	*m*	*n*	*p*	E.s.d. (Å)
A	C(1), C(2), C(4), C(5)	0·1345	0·8211	−0·5547	−3·3883	0·01
B	C(6), C(7), C(9), C(10)	−0·0471	0·4591	0·8872	7·8954	0·01
C	C(8), C(11), C(12), C(14)	0·0309	0·4811	0·8761	8·5369	0·05
D	C(13), C(16), C(17)	−0·6522	0·2999	0·6962	6·6293	0·01
E	C(20), C(21), C(22), C(23), O(21)	0·3415	0·9210	0·1877	−1·2145	0·03
I	C(1′), C(2′), C(3′), C(4′), C(5′), O(5′)	−0·3426	0·7144	0·6101	3·0788	0·22
II	C(1″), C(2″), C(3″), C(4″), C(5″), O(5″)	−0·3745	0·7093	0·5972	2·6746	0·24
III	C(1‴), C(2‴), C(3‴), C(4‴), C(5‴), O(5‴)	0·6432	0·6535	0·3990	9·0259	0·24

Deviations (Å) of atoms from the least-squares planes*

	A	*B*	*C*	*D*	*E*		I	II	III
C(1)	−0·01					O(3)	0·39*	0·64*	
C(2)	0·01					C(1′)	−0·23	0·00*	
C(3)	0·67*					C(2′)	0·20	0·45*	
C(4)	−0·01					C(3′)	−0·19	0·04*	
C(5)	0·01	−0·67*				C(4′)	0·29	0·37*	
C(6)		0·00				C(5′)	−0·24	−0·08*	
C(7)		0·00				C(6′)	0·34*	0·44*	
C(8)		0·69*	−0·05			O(5′)	0·26	0·44*	
C(9)		0·00	−0·62*			O(3′)	−1·60*	−1·36*	
C(10)	−0·65*	0·00				O(4′)	−0·41*	−0·27*	
C(11)			0·05			C(1″)		0·25	
C(12)			−0·05			C(2″)		−0·20	
C(13)			0·65*	0·00		C(3″)		0·02	
C(14)			0·05	0·27*		C(4″)		−0·22	
C(15)				−0·41*	0·01*	C(5″)		0·26	
C(16)				0·00	−0·80*	C(6″)		−0·23*	
C(17)				0·00	0·12*	O(5″)		−0·29	
C(18)			2·15	1·01*		O(3″)		1·61*	
C(19)	−0·31*	1·45*				O(4″)		0·35*	0·15*
C(20)				1·06	0·03	C(1‴)		−0·60*	−0·28
C(21)					−0·04	C(2‴)		0·11*	0·23
C(22)					−0·01	C(3‴)		−0·93*	−0·19
C(23)					−0·02	C(4‴)		−2·03*	0·19
O(3)	2·06*					C(5‴)		−2·57*	−0·23
O(12)			0·49*			C(6‴)		−3·48*	0·36*
O(14)				1·67*		O(5‴)		−1·47*	0·29
O(21)					0·04	O(3‴)		−1·53*	−1·59*
O(23)					−0·05*	O(4‴)		−3·10*	−0·39

Table 6. *Hydrogen bonds in digoxin*

Donor Acceptor	O–H	Distances (Å) O–H···O	H···O	Angle O–H···O (°)	Cell unit *a b c*
O(3′)···O(5″)	1·030	2·905 (1)	2·135	130·0	0 0 0
O(3″)···O(12)	1·065	2·953 (1)	2·000	147·4	0 1 $\bar{1}$
O(12)···O(14)	0·846	2·949 (1)	2·139	160·4	1 0 0
O(3‴)···O(23)	1·019	2·916 (1)	2·031	143·7	$\bar{1}$ 1 $\bar{2}$
O(14)···O(3′)	0·899	2·931 (1)	2·073	159·1	0 0 1

It is evident that these bridge torsion angles and the pseudotorsion angles are very important in determining the formation of intramolecular hydrogen bonding between the hydroxyl at the 3 position of the sugar ring to the ring oxygen of the adjacent ring.

Fig. 4(*a*) and (*b*) are *ORTEP* drawings of the molecule in parts, showing the geometry of the aglycone portion, and the relationship between the digitoxoses. The lactone ring *E* of the aglycone is planar and makes an angle of about 95° with the least-squares plane of ring *D*, similar to the other cardiac steriods except that they are related in some cases by a rotation of 180° as mentioned above. Digitoxoses I and II are almost in a plane while digitoxoses II and III form an angle of 63° with each other. Equations of various least-squares planes and distances of the atoms from the planes are given in Table 5.

Table 6 gives a list of hydrogen bonds in digoxin. They are indicated in Fig. 2 by dotted lines. The first in the list is the intramolecular hydrogen bond which may be responsible for holding the first two digitoxoses in the same plane while the third digitoxose has twisted about 63° out of the plane common to the first two. This could be the result of the intermolecular hydrogen bonding between the neighboring molecules which hold the molecules together. Fig. 2 shows the bonding in the unit cell. All hydroxyl hydrogens at the 3 positions of the digitoxoses as well as the hydroxyl hydrogens in the aglycone are fully utilized in the hydrogen-bonding network. One of the intermolecular hydrogen bonds involves the bonding between the hydroxyl hydrogen at the 3 axial position of the third digitoxose and the carbonyl oxygen of the aglycone with a distance of 2·916 Å, while the closest distance between the carbonyl oxygen and the hydroxyl at C(4‴) is 3·550 Å, which is too far to form a hydrogen bond. The two other hydrogen bonds formed are between the hydroxyls of the neighboring molecules, crossing between the genin and the digitoxoses.

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