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Crystal and Molecular Structure of Dihydrodigoxigenin Hydrate

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The crystal and molecular structure of the 20,22-dihydro derivative of digoxigenin has been determined by X-ray crystallographic methods using 1501 reflections recorded on a SYNTEX $P\bar{1}$ diffractometer. The crystals are orthorhombic, space group $P2_12_12_1$ with unit cell dimensions $a=8.027(2)$ Å, $b=14.801(5)$ Å, $c=18.376(7)$ Å. The structure was refined to a conventional R-factor of 0.05.

Estimated standard deviations are 7×10^{-3} Å and 0.4° in the interatomic distances and angles when hydrogen atoms are not involved. The asymmetric center created at C20 by the hydrogenation is shown to be S in the 3β,12β,14β trihydrozy derivative.

Structure-activity studies of cardiac glycosides have disclosed the importance of the unsaturated lactone ring and that a hydrogenation of the C20–C22 double bond in this ring abolishes activity.[1] The C20–C22 bond saturation, which seems to be included in the metabolic pathway of such compounds, will change the conformation of the lactone ring as well as introduce a center of asymmetry at C20.[2] Catalytic hydrogenation of dioxygenin has been shown to yield two components which are separable in a "major" and a "minor" fraction,[2] and the present paper presents the crystal and molecular structure of the "minor" component of the hydrogenation process.

EXPERIMENTAL

A sample of about 1.9 mg of dihydrodigoxigenin hydrate was supplied by Dr. Richard H. Reuning, College of Pharmacy, The Ohio State University. The sample was recrystallized from methanol, giving a cluster of prismatic crystals. Only one crystal in the sample was suitable for X-ray crystallographic work and was used throughout the investigation. The experimental conditions are described in Table 1.

Cell parameters were determined by a least squares fit to the diffractometer settings for 15 general reflections. The standard deviations in the

Table 1. Experimental conditions.

Instrument	SYNTEX $P\bar{1}$
Radiation	Graphite crystal monochromated Mo$K\alpha$, $\lambda=0.71069$ Å
Crystal dimensions/mm	$0.2\times0.2\times0.2$
Scanning mode	$\theta/2\theta$
Scan speed/° min^{-1}	3.0 ($2\theta<45.0°$)
	Variable depending on intensity for $2\theta>45.0°$
Scan range	$2\theta\alpha_1-0.7$ to $2\theta\alpha_2+0.9$
Background counts	For 0.35 of scan time at scan limits
Temperature/K	121
2θ range	$2.0<2\theta<60.0$
Number of reflections meas.	2027
Number of reflections $I>2.5\sigma(I)$	1501
Number of standard reflections	3
Number of reflections between standard reflections	57

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measured intensities were calculated as $\delta(I)=|C_T+(0.02\ C_N)^2|^{\frac{1}{2}}$, where C_T is the total number of counts and C_N is the scan count minus the background count. The intensity data were corrected for Lorentz and polarization effects. The variation in the intensities of the test reflections was less than 1 % and no corrections were made on this basis. Scattering factors used were those of Doyle and Turner[3] for O and C and of Stewart, Davidson and Simpson[4] for H.

CRYSTAL DATA

Dihydrodigoxigenin hydrate, $C_{23}O_5H_{36}\cdot H_2O$, orthorhombic, $a=8.027(2)$ Å $b=14.801(5)$ Å, $c=18.376(7)$ Å, $V=2183.2$ Å^3, $M=410.5$, $Z=4$, $F(000)=896$, space group $P2_12_12_1$.

STRUCTURE DETERMINATION

The structure was solved by direct methods using the program assembly MULTAN.[5] Successive Fourier syntheses indicated the positions of all the non-hydrogen atoms. The positions of the hydrogen atoms were introduced from considerations of the molecular geometry and of the hydrogen bond system. All positional parameters, anisotropic temperature factors for the non non-hydrogen atoms and isotropic temperature factors for the hydrogen atoms were refined in successive least squares calculations. The final R-factor was 0.049 and the goodness of fit: $S=[\Sigma w\Delta^2/(m-n)]^{\frac{1}{2}}=1.22$. The corresponding parameters are given in Tables 2 and 3. Tables of observed and calculated structure factors are available from the author.

Table 2. Fractional atomic coordinates and thermal parameters multiplied by 10^4. The anisotropic temperature factor is given by $\exp -2\pi^2(u_{11}a^*h^2+\cdots+2u_{12}a^*b^*hk+\cdots)$. Estimated standard deviations in parentheses.

Atom	9793(4)	4540(2)	3637(2)	255(22)	329(22)	259(20)	27(20)	18(19)	145(17)
O12	7634(4)	1299(2)	6927(2)	284(22)	145(18)	246(19)	12(18)	10(19)	11(14)
O14	7266(4)	4358(2)	7920(2)	257(22)	250(19)	160(17)	46(19)	30(18)	−93(16)
Ow	0408(5)	4762(2)	8357(2)	319(22)	351(23)	327(21)	−104(21)	97(21)	55(19)
O21	4038(5)	2023(3)	9709(2)	383(26)	527(27)	252(22)	−98(24)	77(22)	71(20)
O23	5836(5)	1092(3)	10262(2)	461(28)	711(31)	326(25)	−140(28)	41(23)	228(24)
C1	10345(6)	3306(3)	4865(2)	151(27)	269(29)	148(25)	15(26)	32(25)	135(24)
C2	8820(6)	3313(3)	4359(3)	198(3)	231(28)	157(26)	16(28)	19(24)	−14(22)
C3	8429(6)	4250(3)	4102(3)	186(31)	244(31)	241(31)	−14(26)	6(27)	49(26)
C4	8221(6)	4888(3)	4741(3)	169(28)	187(28)	299(31)	−26(25)	5(27)	40(26)
C5	9658(7)	4886(3)	5284(3)	184(27)	139(26)	224(28)	0(24)	61(27)	46(24)
C6	9322(7)	5503(3)	5935(3)	257(33)	139(26)	276(30)	9(26)	0(29)	−22(24)
C7	8024(6)	5124(3)	6454(3)	248(32)	211(28)	236(28)	48(27)	62(26)	−100(24)
C8	8461(6)	4170(3)	6715(3)	178(29)	197(29)	129(26)	−15(24)	22(24)	25(23)
C9	8716(6)	3543(3)	6054(3)	185(3)	196(28)	165(26)	21(25)	58(24)	−21(23)
C10	10098(6)	3914(3)	5544(2)	168(29)	185(27)	173(25)	−21(25)	14(23)	−27(23)
C11	8951(6)	2554(3)	6296(3)	195(28)	195(27)	140(25)	55(26)	14(24)	44(23)
C12	7520(7)	2249(3)	6766(3)	218(3)	121(25)	213(27)	89(25)	5(28)	−14(22)
C13	7369(7)	2801(3)	7486(3)	160(27)	202(27)	133(24)	24(25)	0(25)	25(22)
C14	7172(6)	3815(3)	7272(3)	217(32)	204(28)	150(26)	56(27)	8(23)	−35(22)
C15	5341(6)	3886(3)	7025(2)	148(25)	212(28)	187(26)	32(24)	73(25)	−57(24)
C16	4412(6)	3285(3)	7571(3)	155(28)	282(29)	270(28)	−13(28)	25(27)	−12(26)
C17	5670(6)	2558(4)	7862(3)	192(3)	258(29)	180(26)	−54(27)	33(26)	−25(25)
C18	8935(7)	2647(3)	7952(3)	235(3)	274(32)	180(28)	7(28)	2(26)	28(25)
C19	11807(6)	3947(3)	5938(3)	165(29)	264(30)	242(29)	33(26)	16(25)	37(26)
C20	5659(6)	2538(3)	8697(3)	207(3)	197(27)	219(27)	−17(26)	24(26)	−50(24)
C21	3894(7)	2468(4)	9005(3)	335(35)	337(32)	241(30)	9(33)	66(29)	34(28)
C22	6480(7)	1695(4)	9051(3)	263(32)	329(32)	235(28)	−17(30)	11(28)	62(27)
C23	5481(8)	1546(4)	9739(3)	345(38)	506(43)	247(33)	−159(37)	109(34)	23(31)

Table 3. Fractional atomic coordinates and isotropic temperature factors for the hydrogen atoms.

Atom	*X*	*Y*	*Z*	*B*
HO3	0.941	0.484	0.334	1.8
HO12	0.682	0.101	0.678	6.2
HO14	0.821	0.446	0.801	11.2
H104	0.083	0.466	0.875	2.0
H204	0.087	0.531	0.823	9.0
H1C1	1.131	0.355	0.460	2.6
H2C1	1.064	0.270	0.507	2.3
H1C2	0.901	0.289	0.394	0.8
H2C2	0.784	0.307	0.466	0.9
HC3	0.734	0.424	0.381	0.2
H1C4	0.806	0.552	0.457	0.5
H2C4	0.710	0.473	0.498	1.3
HC5	1.052	0.511	0.503	0.3
H1C6	1.037	0.560	0.623	1.0
H2C6	0.902	0.614	0.577	0.7
H1C7	0.790	0.552	0.691	0.4
H2C7	0.691	0.510	0.620	1.5
HC8	0.951	0.415	0.698	3.4
HC9	0.766	0.363	0.578	−0.1
H111	0.905	0.218	0.587	2.0
H211	1.011	0.246	0.657	3.2
HC12	0.646	0.237	0.650	−0.3
H115	0.494	0.455	0.706	−0.0
H215	0.523	0.367	0.650	1.8
H116	0.401	0.370	0.800	2.4
H216	0.343	0.299	0.738	1.3
HC17	0.533	0.196	0.768	1.1
H118	0.881	0.289	0.838	2.8
H218	0.918	0.197	0.802	1.0
H318	0.992	0.286	0.770	0.3
H119	1.176	0.429	0.641	4.7
H219	1.223	0.333	0.610	0.3
H319	1.270	0.417	0.562	2.7
HC20	0.620	0.308	0.889	−0.4
H121	0.333	0.307	0.908	1.5
H221	0.313	0.209	0.868	5.1
H122	0.766	0.181	0.922	2.1
H222	0.628	0.116	0.872	3.4

Table 4. Bond lengths and angles. Estimated standard deviations are 7×10^{-3} Å in the bond lengths and 0.4° in the angles.

Bond lengths (Å)		Bond angles (°)	
C1–C2	1.537	C1–C2–C3	111.3
C2–C3	1.498	C2–C3–C4	110.8
C3–O3	1.454	C3–C4–C5	114.7
C3–C4	1.516	C4–C5–C6	112.2
C4–C5	1.525	C4–C5–C10	112.0
C5–C6	1.529	C5–C10–C1	108.5
C6–C7	1.521	C10–C1–C2	112.4
C7–C8	1.532	C2–C3–O3	107.5
C8–C9	1.543	O3–C3–C4	110.8
C9–C10	1.552	C5–C10–C19	108.4
C10–C1	1.552	C5–C10–C9	110.5
C10–C5	1.557	C1–C10–C19	106.3
C10–C19	1.551	C9–C10–C19	111.2
C9–C11	1.542	C1–C10–C9	111.8
C11–C12	1.507	C5–C6–C7	113.1
C12–O12	1.440	C6–C7–C8	112.3
C12–C13	1.560	C7–C8–C9	109.8
C13–C14	1.560	C8–C9–C10	110.9
C14–O14	1.438	C8–C9–C11	111.1
C14–C8	1.548	C7–C8–C14	111.5
C14–C15	1.542	C9–C11–C12	110.9
C15–C16	1.535	C11–C12–O12	111.2
C16–C17	1.569	C11–C12–C13	112.8
C17–C13	1.570	O12–C12–C13	110.1
C13–C18	1.539	C12–C13–C14	107.4
C17–C20	1.535	C12–C13–C18	109.3
C20–C21	1.529	C12–C13–C17	108.7
C20–C22	1.554	C8–C14–O14	108.9
C22–C23	1.513	C8–C14–C13	115.2
C21–O21	1.457	C14–C13–C18	111.5
C21–C23	1.358	C18–C13–C17	115.5
C23–O23	1.207	C13–C14–C15	103.7
		C13–C14–O14	108.9
		C14–C15–C16	103.4
		C15–C16–C17	107.9
$\overline{C-H}$	1.03	C16–C17–C13	104.6
		C16–C17–C20	110.5
$\overline{O-H}$	0.80	C13–C17–C20	116.7
		C17–C20–C21	112.1
		C17–C20–C22	115.5
		C21–C20–C22	100.6
		C20–C22–C23	104.0
		C20–C21–O21	106.6
		C21–O21–C23	109.8
		O21–C23–C22	110.0
		O21–C23–O23	121.5
		C22–C23–O23	128.4

DESCRIPTION AND DISCUSSION

The labelling of the atoms is indicated in Fig. 1 which also illustrates the molecular packing as well as the hydrogen bond system. Bond lengths and angles are given in Table 4 and the values are found to be in agreement with those reported for similar structures.[6-11] The atomic coordinates in Table 2 describe the steroid nucleus in the well-known configuration of a 3β,12β,14β-trihydroxy derivative, the six-membered rings being in chair conformation and the five-membered D-ring existing in a 14β envelope form. An analysis of the ring conformations is given in Table 5. A least squares plane through the six atoms: C5, C6, C8, C9, C12, C13 shows

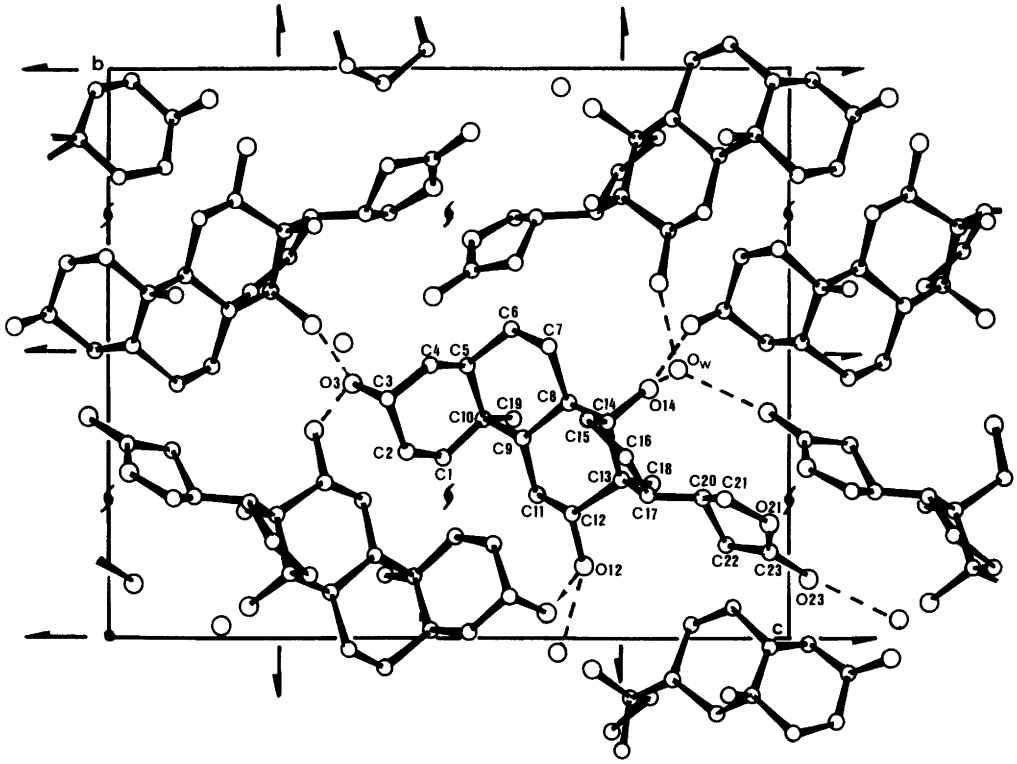

Fig. 1. Packing of dihydrodigoxigenin molecules in the crystal as seen along the *a*-axis.

Table 5. Distances from least squares planes in the ring system. The atoms defining the respective planes are all less than 0.016 Å from these planes; the largest deviations found in the C- and D-rings.

A-ring	B-ring	C-ring	D-ring	Lactone ring
Least squares planes defined by				
C2,C3,C5,C10	C5,C10,C7,C8	C9,C11,C13,C14	C13,C15,C16,C17	O23,O21,C23,C22
Distance (Å)				
C1: 0.68	C6: 0.63	C12: −0.69	C14:0.61	C21: −0.08
C4: −0.60	C9: −0.69	C8: 0.56		C20: 0.41

Table 6. Distances and angles concerning the hydrogen bond system.

D	A	Ekv. pos	D−A	D−H	H···A	∠D−H···A
O3	O14	$1.5-x, 1-y, z-\frac{1}{2}$	2.670	0.77	1.95	155.6
O12	O3	$x-\frac{1}{2}, \frac{1}{2}-y, 1-z$	2.795	0.83	1.97	172.0
O14	O4	$1+x, y, z$	2.714	0.79	1.93	172.4
O4	O12	$1-x, \frac{1}{2}+y, 1.5-z$	2.813	0.92	1.93	164.5
O4	O23	$x-\frac{1}{2}, \frac{1}{2}-y, -z$	2.854	0.82	2.12	149.4

deviations of ±0.08 Å indicating a twist between the B and C ring. The angle between the planes through C5, C6, C9 and C8, C12, C13 is found to be 7.7°.

The lactone ring in the present structure is saturated and hence not planar and the conformation of the ring may be described as a C20-envelope form. The conformation about the C17–C20 bond is staggered with HC17 and HC20 in *trans* position. The torsion angle C13–C17–C20–C22 is −76° and C13–C17–C20–C21 is 169°. Thus in the present structure neither C21 nor C22 but HC20 is in a synclinal position relative to C13 and C16 and in this respect the conformation about the C17–C20 is different from those earlier reported for similar structures.[8] The absolute configuration at C20 is *S* in the "minor" component of the 3β,12β,14β derivative and this is actually equivalent with the *R* configuration in (20*R*)-3β-hydroxy-22-methylene-5β-card-14-enolide.[8]

An extensive hydrogen bond system binds the molecules together in the crystal. Each of the three hydroxy groups is involved in two hydrogen bonds, both as donor and acceptor, whereas the carbonyl oxygen is engaged as acceptor in one hydrogen bond. The O3–O12 bond connects molecules in a helix about one of the screw axes and the O3–O14 bond connects molecules in a chain along the *c*-axis. The rest of the hydrogen bonds involve water molecules each of which is engaged in three such bonds, two as a donor and one as an acceptor. The geometry of the hydrogen bond system is described in Table 6.

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