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Methyldigitoxigenin, $C_{24}H_{36}O_4$*†

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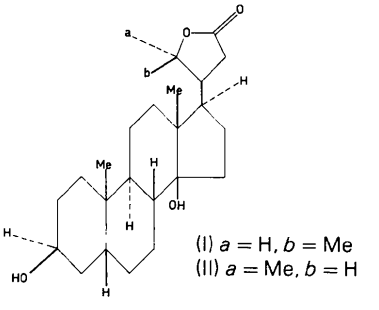
Abstract. $M_r = 388{\cdot}54$, orthorhombic, $P2_12_12_1$, $a = 7{\cdot}249$ (1), $b = 15{\cdot}109$ (1), $c = 19{\cdot}268$ (3) Å, $V = 2110{\cdot}33$ Å^3, $Z = 4$, $D_c = 1{\cdot}223$ Mg m^{-3}, λ(Cu $K\alpha_1$) = 1·5406 Å, $\mu = 0{\cdot}61$ mm^{-1}, $T = 296$ K. Final $R = 0{\cdot}075$ for 1210 observed reflections. The structure is similar to that of digitoxigenin. The ring junctions *A*/*B* and *C*/*D* are *cis*. The molecules are linked together by hydrogen bonds between terminal OH and C=O groups, forming infinite chains parallel to the *b* axis.

Introduction. The naturally occurring *Digitalis* glycosides are the most effective drugs used in the treatment of heart disease, but at the same time they are highly toxic. Until recently it was believed that the inotropic and the toxic effects of *Digitalis* cardenolides could not be separated. However, in an effort to prepare cardenolide analogues with low toxicity, the two epimeric methyldigitoxigenins (I and II) have been synthesized by Professor K. Wiesner and his colleagues at the University of New Brunswick, Canada. In one of the epimers, one face of the active lactone group is blocked by a methyl group. If the inotropic and toxicity receptors used opposite faces of the lactone group, then one of the derivatives will be inotropic while the other will be toxic. Investigations are in progress to study the toxic and inotropic effects of methyldigitoxigenin. We report here the crystal-structure analysis of the major epimer of methyldigitoxigenin, which has been undertaken to determine the conformation of the lactone group and the configuration at C(21).



(I) a = H, b = Me
(II) a = Me, b = H

Experimental. Colourless, irregular plate-like crystals of the major epimer of methyl-digitoxigenin supplied by Professor K. Wiesner, 0·15 × 0·3 × 0·35 mm crystal, graphite-monochromatized Cu $K\alpha$, Picker four-circle automatic diffractometer, 3111 reflections up to 110° in 2θ measured by $\theta/2\theta$ scan method, line-profile analysis (Grant & Gabe, 1978), 1554 unique, 1210 had $I_{net} \geq 2{\cdot}5\sigma(I_{net})$, corrected for measured direct-beam polarization (Le Page, Gabe & Calvert, 1979) but not for absorption; cell parameters from least-squares refinement of the setting angles of 56 reflections with $2\theta > 60°$; structure solved using *MULTAN* (Germain, Main & Woolfson, 1971) and 241 largest E values; H atoms located in a difference map but parameters not refined; least-squares refinement with anisotropic parameters for C and O, $w = 1/\sigma^2(F)$ where $\sigma(F)$ is based on counting statistics, final $R = 0{\cdot}075$, $R_w = 0{\cdot}047$ for observed reflections and $R = 0{\cdot}096$, $R_w = 0{\cdot}048$ for all reflections, extinction correction included (Larson, 1970); $F(000) = 848$, scattering curves for neutral atoms from *International Tables for X-ray*

* 3β,14β-Dihydroxy-21-methyl-5β-card-20(22)-enolide.

† NRCC publication No. 20720.

Crystallography (1974); NRC PDP8-e system of programs (Larson & Gabe, 1978) used for all calculations.

Discussion. Atomic positional and equivalent isotropic temperature factors are listed in Table 1.*

A stereoview of the molecule is shown in Fig. 1 and the atom names, bond distances and angles are shown in Fig. 2.

The bond lengths and angles are similar to those of other cardenolides: digitoxigenin (Karle & Karle, 1969), anhydrodigitoxigenin (Gilardi & Karle, 1970), strophanthidin (Gilardi & Flippen, 1973), 5β-hydroxygitoxigenin (Przybylska & Ahmed, 1979), digoxigenin dihydrate (Rohrer & Fullerton, 1980) and the aglycone portion of the cardiac glycosides, digoxin (Go, Kartha & Chen, 1980) and gitoxin (Go & Kartha, 1980).

The conformation of the molecule is seen to be (I). The ring junctions *A*/*B* and *C*/*D* are *cis* and *B*/*C* is *trans*. Rings *A*, *B* and *C* have the chair conformation,

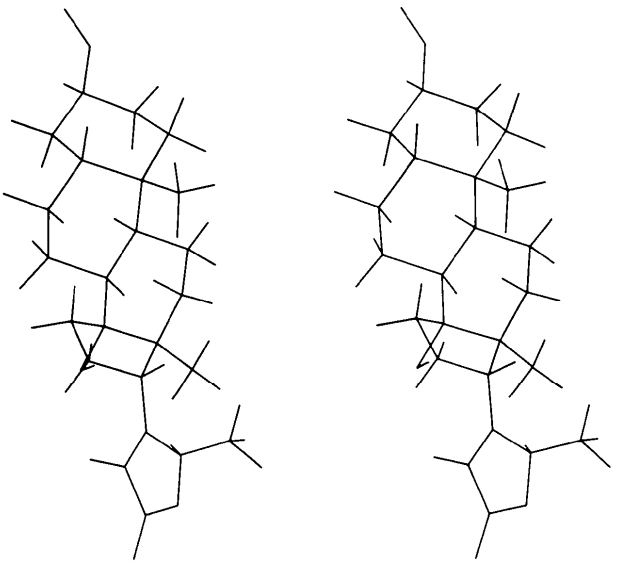


Fig. 1. Stereoscopic pair of the molecule.

* Lists of anisotropic thermal parameters, H-atom parameters and structure factors have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 38169 (14 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Atomic coordinates and equivalent isotropic thermal parameters*

E.s.d.'s refer to the last digit printed.

	x	*y*	*z*	B_{eq}*(Å^2)
O(1)	0·6597 (8)	0·4482 (3)	0·71139 (24)	6·4 (3)
O(2)	0·7370 (8)	0·9784 (3)	0·70648 (20)	4·2 (3)
O(3)	0·7356 (10)	1·2384 (3)	0·5161 (3)	9·2 (4)
O(4)	0·7159 (10)	1·3092 (3)	0·6167 (3)	10·9 (5)
C(1)	0·5147 (11)	0·5875 (4)	0·6227 (4)	4·9 (5)
C(2)	0·6965 (12)	0·5399 (5)	0·6115 (4)	5·7 (5)
C(3)	0·7799 (14)	0·5113 (4)	0·6783 (3)	5·6 (5)
C(4)	0·8008 (11)	0·5883 (4)	0·7268 (4)	5·3 (5)
C(5)	0·6255 (11)	0·6387 (5)	0·7390 (4)	4·3 (4)
C(6)	0·6565 (11)	0·7189 (4)	0·7879 (3)	4·9 (5)
C(7)	0·7591 (13)	0·7931 (4)	0·7534 (3)	4·6 (4)
C(8)	0·6550 (11)	0·8251 (4)	0·6877 (3)	3·4 (4)
C(9)	0·6323 (10)	0·7473 (4)	0·6374 (3)	3·0 (4)
C(10)	0·5265 (11)	0·6676 (4)	0·6710 (3)	4·0 (4)
C(11)	0·5471 (10)	0·7777 (4)	0·5698 (3)	4·1 (4)
C(12)	0·6505 (11)	0·8556 (4)	0·5381 (3)	3·9 (4)
C(13)	0·6671 (10)	0·9372 (4)	0·5858 (3)	3·4 (4)
C(14)	0·7483 (11)	0·9064 (4)	0·6562 (3)	3·5 (4)
C(15)	0·9558 (10)	0·8993 (4)	0·6415 (4)	4·1 (4)
C(16)	0·9978 (10)	0·9750 (5)	0·5893 (4)	4·8 (4)
C(17)	0·8162 (9)	1·0004 (4)	0·5552 (3)	3·0 (4)
C(18)	0·4749 (10)	0·9776 (5)	0·5958 (4)	4·5 (4)
C(19)	0·3257 (12)	0·6959 (5)	0·6872 (4)	5·5 (5)
C(20)	0·7821 (10)	1·0975 (4)	0·5602 (3)	4·0 (4)
C(21)	0·7659 (13)	1·1489 (4)	0·4930 (4)	6·6 (5)
C(22)	0·7727 (12)	1·1537 (4)	0·6105 (4)	5·7 (5)
C(23)	0·7354 (13)	1·2400 (5)	0·5848 (4)	7·8 (6)
C(24)	0·6325 (17)	1·1245 (6)	0·4429 (4)	10·4 (7)

* B_{eq} is the arithmetic mean of the principal axes of the thermal ellipsoid.

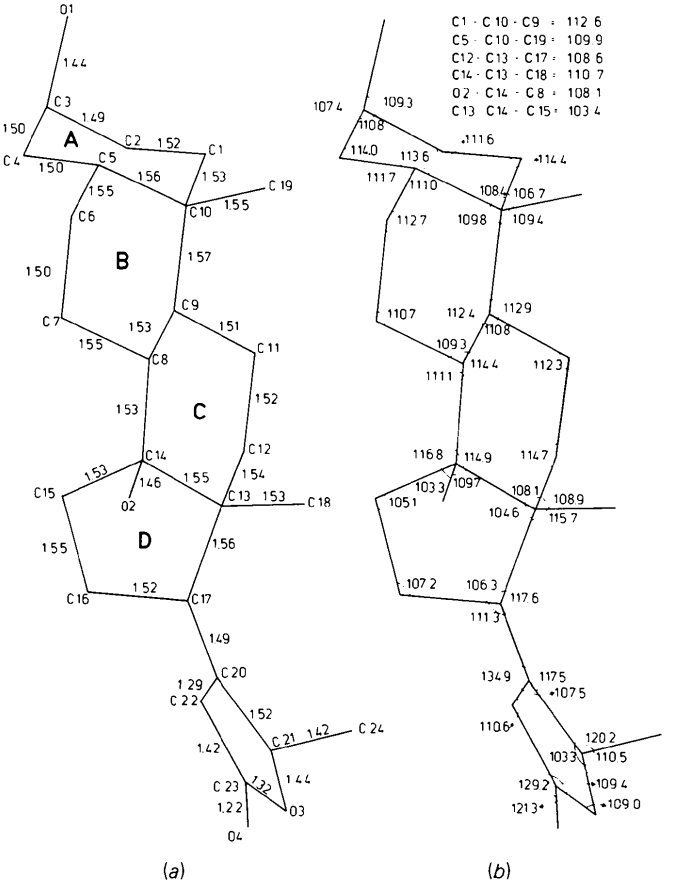


Fig. 2. (*a*) Atom numbering and bond distances (Å) (uncorrected for thermal motion). The e.s.d.'s on bond distances are 0·01 Å. (*b*) Angles (°). The e.s.d.'s range from 0·5 to 0·7°.

Table 2. *Torsion angles* (°) (*e.s.d.'s* ≃0·6°)

Ring *A*:	C(1)		C(2)		C(3)		C(4)		C(5)		C(10)	C(1)
		56·1		−54·9		54·2		−52·0		48·5		−50·9
Ring *B*:	C(6)		C(7)		C(8)		C(9)		C(10)		C(5)	C(6)
		57·8		−58·4		57·9		−55·3		52·0		−55·1
Ring *C*:	C(9)		C(11)		C(12)		C(13)		C(14)		C(8)	C(9)
		52·5		−56·9		52·5		−48·4		49·3		−49·6
Ring *D*:	C(13)		C(14)		C(15)		C(16)		C(17)		C(13)	
		−35·6		34·6		−20·6		−1·7		23·1		

About C(17)–C(20)

C(13)–C(17)–C(20)–C(21)	−118·1	C(16)–C(17)–C(20)–C(21)	118·9
C(13)–C(17)–C(20)–C(22)	67·0	C(16)–C(17)–C(20)–C(22)	−55·9

ring *D* has the α-envelope conformation and the lactone ring is planar.

Comparison of torsion angles in this structure (Table 2) to those in related structures (Go, Kartha & Chen, 1980; Go & Kartha, 1980) shows that the main differences between these structures are in the conformations of ring *D* and the lactone group. The conformation of methyldigitoxigenin is similar to those of digitoxigenin (Karle & Karle, 1969) and strophanthidin B (Gilardi & Flippen, 1973).

The correlation observed by Go & Kartha (1980) between the bond angles C(17)–C(20)–C(21) and C(17)–C(20)–C(22), and the torsion angle C(13)–C(17)–C(20)–C(22) is observed in methyldigitoxigenin. When this torsion angle is negative as in gitoxin (Go & Kartha, 1980) and digoxin (Go, Kartha & Chen, 1980), the above two bond angles are similar; whereas the difference between the two angles is about 14° when the torsion angle is positive as in digitoxigenin (Karle & Karle, 1969), anhydrodigitoxigenin (Gilardi & Karle, 1970) and 5β-hydroxygitoxigenin (Przybylska & Ahmed, 1979). In the present study also, the torsion angle is positive (with the steroid backbone having the same configuration as in the other structures) and the difference between the bond angles is 17·4°.

The packing of the molecules is similar to that of digitoxigenin (Karle & Karle, 1969). A hydrogen bond of length 2·81 (0·1) Å, between the terminal hydroxyl group O(1) and the carbonyl oxygen O(4) of the lactone group, forms infinite chains along the *b* axis.

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Structures of Polycyclic Polyamines: 1,5,9,13-Tetraazatricyclo[11.3.1.1^{5,9}]octadecane, $C_{14}H_{28}N_4$*

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Abstract. $M_r = 252·8$, monoclinic, $P2_1/c$, $a = 10·624$ (4), $b = 9·010$ (2), $c = 31·433$ (4) Å, $\beta = 96·61$ (2)°, $V = 2988·8$ Å^3, $D_x = 1·122$ Mg m^{-3}, $Z = 8$, $\lambda(\text{Cu } K\alpha_1) = 1·5406$ Å, $\mu = 0·491$ mm^{-1}, $T = 296$ K. Final $R = 0·056$ for 2713 observed reflections. The central 12-membered ring adopts the 'square' [3333] conformation.

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