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Structure of Ouabagenin Methanol Solvate, $C_{23}H_{34}O_8.CH_3OH$

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Abstract. $M_r = 470{\cdot}6$, monoclinic, $P2_1$, $a = 7{\cdot}816$ (5), $b = 13{\cdot}416$ (1), $c = 10{\cdot}647$ (1) Å, $\beta = 92{\cdot}35$ (2)°, $V = 1115{\cdot}5$ Å^3, $Z = 2$, $D_x = 1{\cdot}401$ Mg m^{-3}, Cu $K\alpha$ ($\lambda = 1{\cdot}5418$ Å, $\mu = 0{\cdot}84$ mm^{-1}), $F(000) = 508$, room temperature, $R = 4{\cdot}8$%, 2465 unique reflections measured. The structure was solved by direct methods and refined by full-matrix least squares. The five-membered ring of this cardiac steroid has a distorted 14β-envelope conformation. The torsion angle C(13)—C(17)—C(20)—C(22) is $-103{\cdot}1$ (3)°. There is a disordered solvent molecule in the asymmetric unit. The hydroxyl groups in the aglycone along with the carbonyl O atom and the solvent O atoms are involved in an extensive hydrogen-bonding network stabilizing the structure.

Introduction. Ouabagenin is the aglycone of ouabain, a cardiac glycoside found useful in cardiac therapy as well as in cancer treatment (Baker, 1979). In their studies on the interactions of ouabain and ouabagenin with Na^+,K^+—adenosine triphosphatase, Wallick, Dowd, Allen & Schwartz (1974) noted that ouabagenin is a reversible inhibitor while ouabain with the sugar intact is pseudo-irreversible. We have obtained crystals of ouabagenin and determined the crystal structure to compare it with our results from ouabain (Go & Kartha, 1981).

Experimental. Colorless needles (from methanol and chloroform), $0{\cdot}1 \times 0{\cdot}15 \times 0{\cdot}7$ mm, Enraf–Nonius CAD-4 automated diffractometer, Ni-filtered Cu $K\alpha$, lattice dimensions by least-squares fit to a set of 25 reflections measured in a θ range 12–28°, ω–2θ scans and integrated counts with $\theta < 77°$, 3004 $\pm hkl$, 2465 independent, 2077 with $I > 2\sigma(I)$, three standard reflections (overall $\sigma = 0{\cdot}04$), Lp correction, empirical (one parameter $-\varphi$) absorption correction; *MULTAN* (Germain, Main & Woolfson, 1971), anisotropic full-matrix least-squares refinement for 31 non-hydrogen atoms; 24 tetrahedral and one trigonal calculated H atoms, three methyl H atoms and the remaining six hydroxyl H atoms (from ΔF synthesis) isotropic, final $R = 0{\cdot}048$, $R_w = 0{\cdot}042$ ($w = 1/\sigma^2$); function minimized was $\sum w(|F_o|-|F_c|)^2$, where $w = 1/\sigma^2(F)$; f curves from *International Tables for X-ray Crystallography* (1962); Enraf–Nonius *SPD* package and local programs.

Discussion. The final parameters are given in Table 1;* standard deviations were calculated using Cruickshank's (1965) expressions.

The overall features of the steroid nucleus of ouabagenin resemble those of other cardiac active steroids. The rings *A*, *B* and *C* have the chair conformation, the *D* ring has a distorted 14β-envelope conformation and the *E* ring (lactone) is planar.* Fig. 1 shows a stereoscopic view of the molecule. Fig. 2 is a drawing superimposing the *B* and *C* fused rings of ouabagenin, ouabain–diethanol and ouabain octahydrate, taking the projection of the aglycone portion onto

* Lists of structure factors, anisotropic thermal parameters, hydrogen parameters, hydrogen bonds, and torsion angles have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 38231 (15 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Fractional coordinates* ($\times 10^4$) *and equivalent isotropic thermal parameters*

$$B_{eq} = 8\pi^2 U_{eq} \text{ where } U_{eq} = \tfrac{1}{3}\textstyle\sum_i\sum_j a_i^* a_j^* (\mathbf{a}_i.\mathbf{a}_j)\, U_{ij}.$$

	x	y	z	B_{eq}(Å^2)
C(1)	3956 (3)	8430 (2)	5405 (2)	2·7 (4)
C(2)	2394 (4)	8946 (4)	4783 (2)	3·2 (4)
C(3)	707 (4)	8409 (2)	4930 (3)	3·5 (4)
C(4)	864 (3)	7301 (2)	4625 (2)	3·0 (4)
C(5)	2424 (3)	6765 (2)	5250 (2)	2·5 (4)
C(6)	2478 (4)	5680 (2)	4824 (2)	2·9 (5)
C(7)	2824 (4)	5589 (2)	3443 (2)	3·0 (5)
C(8)	4485 (3)	6111 (2)	3114 (2)	2·4 (3)
C(9)	4486 (3)	7227 (2)	3529 (2)	2·2 (3)
C(10)	4145 (3)	7319 (2)	4989 (2)	2·3 (3)
C(11)	6142 (3)	7726 (2)	3121 (2)	2·8 (4)
C(12)	6462 (4)	7546 (2)	1740 (2)	3·1 (4)
C(13)	6511 (3)	6445 (2)	1322 (2)	2·6 (4)
C(14)	4850 (3)	5937 (2)	1717 (2)	2·5 (4)
C(15)	3505 (4)	6315 (2)	754 (2)	3·1 (4)
C(16)	4404 (4)	6294 (3)	−499 (2)	4·3 (5)
C(17)	6360 (4)	6447 (2)	−169 (2)	3·2 (5)
C(18)	8153 (4)	5955 (2)	1870 (2)	3·3 (4)
C(19)	5648 (4)	6844 (2)	5792 (2)	3·3 (5)
C(20)	7494 (4)	5719 (2)	−801 (2)	3·0 (4)
C(21)	7183 (4)	4626 (2)	−950 (3)	4·0 (6)
C(22)	8938 (4)	5937 (2)	−1357 (2)	3·7 (5)
C(23)	9678 (4)	5022 (2)	−1848 (2)	3·4 (5)
O(1)	3893 (3)	8496 (2)	6760 (2)	3·1 (3)
O(3)	158 (3)	8584 (2)	6170 (2)	4·5 (4)
O(5)	2214 (3)	6782 (2)	6593 (2)	3·3 (3)
O(11)	6022 (3)	8785 (2)	3283 (2)	3·7 (3)
O(14)	4956 (3)	4891 (1)	1472 (2)	3·0 (3)
O(19)	6933 (3)	7532 (2)	6200 (2)	4·8 (4)
O(21)	8631 (3)	4257 (2)	−1606 (2)	3·9 (4)
O(23)	10998 (4)	4901 (2)	−2394 (2)	4·5 (4)
C(MeOH)	10875 (6)	3741 (2)	967 (4)	5·0 (8)
O(MeOH1)	12430 (8)	3449 (4)	1546 (4)	5·3 (8)
O(MeOH2)	9270 (9)	3298 (5)	1332 (6)	6·8 (9)

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the best plane through atoms C(5), C(6), C(7), C(8), C(9), C(10), C(11), C(12), C(13) and C(14). Fig. 3 gives the bond lengths (average $\sigma = 0{\cdot}004$ Å) with the numbering of atoms, ring designations and bond angles (average $\sigma = 0{\cdot}4°$).

From Fig. 2, it is seen that although the *D* rings of ouabagenin, ouabain–diethanol (Go & Kartha, 1981) and ouabain octahydrate (Messerschmidt, 1980) are all in the 14β-envelope conformation, the orientations of the lactone ring (*E*) show interesting variations. It appears that regardless of the conformation of the *D* ring, the *E* ring orients itself in one of the two possible conformations *A* and *B*, so as to form an intramolecular C—H···O bond: C(21)···O(14) in conformation *A* and C(22)···O(14) in conformation *B*. The angles C(17)—C(20)—C(21) and C(17)—C(20)—C(22) are almost the same for conformation *A* but differ by about 12° in *B*. Some of the other geometrical parameters describing the orientations of the *E* ring in these two conformations are also shown in Table 2. These two conformations *A* and *B* were reported earlier by

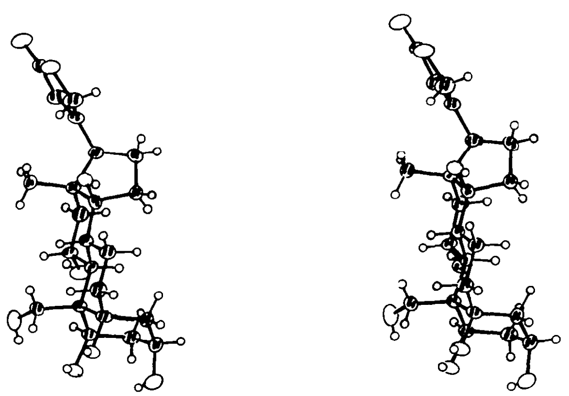

Fig. 1. Stereoscopic view of ouabagenin. Thermal ellipsoids are scaled to the 50% probability level. (C atoms are shaded, larger open ellipsoids are O.)

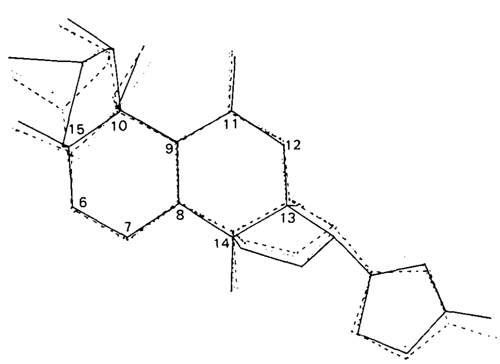

Fig. 2. Superimposition of the fused *B* and *C* rings [best plane through atoms C(5), C(6), C(7), C(8), C(9), C(10), C(11), C(12), C(13) and C(14)] of ouabagenin (————), ouabain–diethanol (– – – –), ouabain octahydrate (. . . . .).

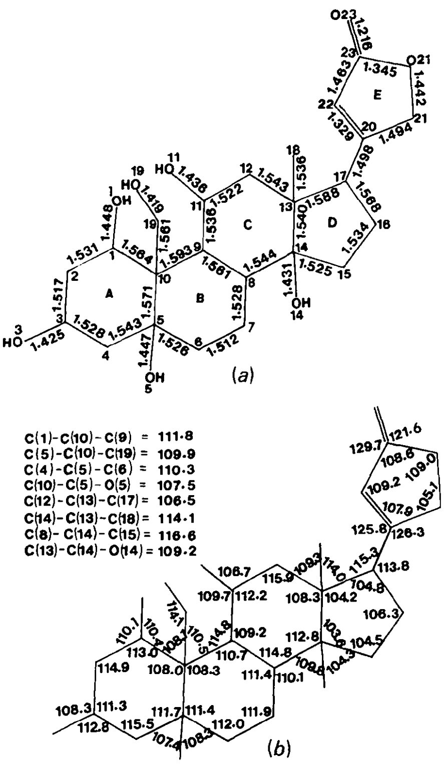

Fig. 3. (*a*) Bond lengths (Å) with numbering of atoms and ring designations (average e.s.d. 0·004 Å). (*b*) Bond angles (°) (average e.s.d. 0·4°).

Table 2. *Some geometric data about the lactone ring in cardiac steroids*

	Ouabagenin	Ouabain		Oleandrin (Kartha & Go, 1981)
		Diethanol	Octahydrate	
Bond lengths (Å)				
C(17)—C(20)	1·498 (4)	1·535	1·518	1·505
C(20)—C(21)	1·494 (4)	1·487	1·489	1·504
C(20)—C(22)	1·329 (4)	1·314	1·329	1·319
C(23)—O(21)	1·345 (4)	1·335	1·395	1·348
C(23)—O(23)	1·216 (4)	1·241	1·196	1·213
C(22)—C(23)	1·463 (4)	1·454	1·546	1·478
Bond angles (°)				
C(17)—C(20)—C(21)	126·3 (4)	125·8	117·1	118·8
C(17)—C(20)—C(22)	125·8 (4)	125·0	130·9	132·8
C(21)—C(20)—C(22)	107·9 (4)	108·8	111·8	108·3
C(22)—C(23)—O(23)	129·7 (5)	128·9	134·1	130·9
C(22)—C(23)—O(21)	108·6 (4)	110·8	110·9	108·3
O(21)—C(23)—O(23)	121·6 (5)	120·2	115·4	120·5
Torsion angles (°)				
C(13)—C(17)—C(20)—C(22)	−103·1 (3)	−122·8	80·9	65·6
Angle formed by the extension of bonds C(17)—C(20) and C(23)—O(23) (°)	146·1 (3)	146·1	159·5	154·8
Interatomic distances (Å)				
C(21)—O(14)	3·189 (4)	2·953	4·527	4·722
C(22)—O(14)	4·637 (4)	4·664	3·095	3·048

Rohrer, Duax & Fullerton (1976) as the two energetically favored orientations for the E ring.

The hydrogen bonds* form an extensive network stabilizing the structure, as shown in Fig. 4. The solvent molecule, presumably a disordered methanol, has its O in two positions, (1) and (2). In position (1), this O is at hydrogen-bonding distance to hydroxyl O(14) and also to O(19) of the adjacent molecule, while in position (2) this O is capable of hydrogen bonding with O(3).

* See deposition footnote.

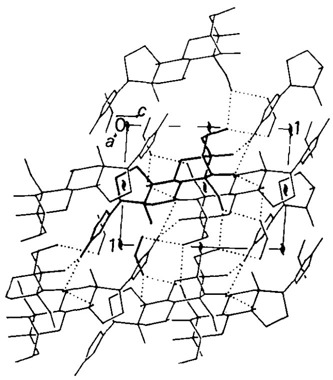

Fig. 4. Packing of molecules in the unit cell (viewed down **b**) with H bonding indicated by dotted lines.

It appears that in spite of the additional sugar unit, the aglycone portion of ouabain shows little conformational change from that of ouabagenin; hence the irreversible inhibition of ouabain may be associated with the binding of the sugar moiety, as postulated earlier (Yoda, 1973; Wallick *et al.*, 1974).

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Tricyclo[4.4.1.0^{1,6}]undeca-2,4,7,9-tetraene-11,11-dicarbonitrile, $C_{13}H_8N_2$, at 150 K

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Abstract. $M_r = 192\cdot2$, orthorhombic, space group $P2_12_12_1$, $a = 5\cdot969$ (2), $b = 10\cdot370$ (3), $c = 15\cdot546$ (5) Å, $V = 962\cdot3$ (5) Å^3, $Z = 4$, $D_m = 1\cdot280$ (5), $D_x = 1\cdot327$ Mg m^{-3}, λ(Mo $K\alpha$) = 0·71069 Å, $\mu = 0\cdot075$ mm^{-1}, $F(000) = 400$. Final $R = 0\cdot048$ based on 2307 observed independent reflections. The X-ray study of the title compound has shown the presence of the cyclopropane ring with normal bond lengths. The alternation of single and double bonds along the annulene perimeter confirms the bis-8,9,10-trinorcaradienic character of the molecule.

Introduction. The equilibrium [10]annulene ⇄ bis-8,9,10-trinorcaradiene has attracted the interest of organic chemists for many years (Vogel, 1967, 1969) and has been extensively studied by X-ray diffraction in our laboratory. On going from (1) to (2) a large variation in the C(1)—C(6) distance is involved. Reported values for this distance are 2·269 (5) Å ($R = R' = $ F, 1*a*) (Pilati & Simonetta, 1976), 2·235 (3) Å ($R = R' = $ H, 1*b*) (Bianchi, Pilati & Simonetta, 1980), 1·771 (8), 1·827 (8) Å ($R = R' = CH_3$, 2*b*) (Bianchi, Morosi, Mugnoli & Simonetta, 1973), and 1·640–1·851 Å ($R = CH_3$, $R' = $ CN, 2*c*) Bianchi, Pilati & Simonetta, 1978, 1981). The title compound ($R = R' =$CN, 2*a*) has been recently synthesized (Vogel, Scholl, Lex & Hohlneicher, 1982) and NMR results suggested the form (2) with a strong C(1)—C(6) bond (Günther & Schmickler, 1974). So, the crystal structure has been determined to check its polyenic character. To

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