

Structures of Modified Cardenolides. II.* (20*R*)-3β-Hydroxy-22-methylene-5β-card-14-enolide

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Abstract. $C_{24}H_{34}O_3$, orthorhombic, $P2_12_12_1$; $a=11.6191$ (4), $b=15.5087$ (5), $c=11.3141$ (4) Å, $V=2038.8$ Å³; $Z=4$, $M=370.5$, $D_c=1.207$, $D_m=1.215$ g cm⁻³. The configuration of C(20) is *R* and the location of the C(14)–C(15) double bond confirms the NMR interpretation. There are nonbonded contacts between nonhydrogen atoms less than 3.5 Å that involve the O(3) hydroxyl, however, none of these is short enough to be considered a hydrogen bond.

Introduction. Proposed models describing the nature of cardenolide–receptor binding suggest that semisynthetic cardenolides with (1) more reactivity, or (2) more polarizability, or (3) slightly geometrically altered α,β -unsaturated carbonyl systems at C(17) would be good ‘probes’ of cardenolide structure–activity relationships. Two such compounds, 22-methylene card-14-enolides, were synthesized and the Na⁺, K⁺–APTase inhibitory activity measured (Fullerton, Gilman, Ahmed, From, Duax & Rohrer, 1976).

The crystal and molecular structure of $C_{24}H_{34}O_3$ was determined to confirm the location of the C(14)–

C(15) double bond and to assign the stereochemistry of C(20). A crystal with dimensions 0.32 × 0.40 × 0.62 mm was used to measure the lattice parameters and intensities. The systematic absences along the axial rows were consistent with the space group $P2_12_12_1$ (D_2^4 , No. 19) and the cell constants were determined by a least-squares refinement procedure using the θ values for 79 reflections with θ ranging from 25 to 42° [$\lambda(\text{Cu } K\alpha)=1.5418$ Å]. Integrated intensities for 2383 independent reflections were measured on an Enraf–Nonius CAD-4 diffractometer to a maximum θ of 75° with Ni-filtered Cu $K\alpha$ radiation. The intensities were converted to structure factor amplitudes and normalized structure factor amplitudes. The structure was solved by using the multi-solution direct-methods program *MULTAN* (Germain, Main & Woolfson, 1971).

The atomic positional parameters were refined, first isotropically then anisotropically, by a full-matrix least-squares procedure. The hydrogen-atom positions were located from a difference map and included in the final least-squares refinement allowing their positional and isotropic thermal parameters to vary. The quantities $(1/\sigma_F^2)$ were used as weights, where σ_F is defined by Stout & Jensen (1968, equation H14) with an instability factor of 0.07. The 327 data with intensities less than $2.0\sigma_I$ were given weights of 0.0. The R ($=\sum||F_o|-|F_c||/\sum|F_o|$) for the 2056 data with $I > 2.0\sigma_I$ was 0.041 and R for all 2383 data was 0.052. The final positional and thermal parameters are given in Table 1.†

Discussion. The two views of the crystallographically observed conformation of $C_{24}H_{34}O_3$ are shown in Fig. 1. The thermal vibrational ellipsoids for the nonhydrogen atoms in these *ORTEP* (Johnson, 1970) drawings are scaled to a 60% probability level. The hydrogen atoms are included with a B of 1.0 rather than their refined isotropic thermal parameters. The bond distances, bond angles, and endocyclic torsion

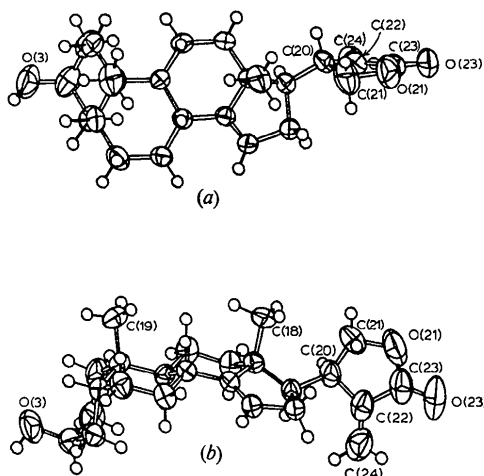


Fig. 1. Two views of the crystallographically observed conformation of (20*R*)-3β-hydroxy-22-methylene-5β-card-14-enolide. The thermal ellipsoids are scaled to a 60% probability level and the hydrogens are shown as circles.

† A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31828 (12 pp., 1 microfiche). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

angles are given in Fig. 2. The range of estimated standard deviations in the bond lengths is from 0.002 to 0.003 Å and the range in the bond angles is from 0.1 to 0.2°. The bond lengths and angles for this structure are all very similar to those observed in the structure of the precursor molecule digitoxigenin (Karle & Karle, 1969).

The *A*, *B* and *C* rings all have a chair conformation. The *C*-ring chair is slightly distorted in the region of the C(13)–C(14) bond, presumably as a result of the C(14)–C(15) double bond. The double bond in the *D* ring results in a C(17) α-envelope conformation rather than a C(14) β-envelope as observed in the 14β-saturated *D* rings of digitoxigenin and strophanthidin (Gilardi & Flippen, 1973). The pseudorotational param-

eters (Altona, Geise & Romers, 1968) for the *D* ring are $\Delta = 100.6^\circ$ and $\varphi_m = 26.6^\circ$. The lactone ring has a C(20), C(21) half-chair conformation. Atoms C(20) and C(21) are displaced -0.193 and 0.142 Å respectively on opposite sides of the plane defined by the remaining three atoms in the ring.

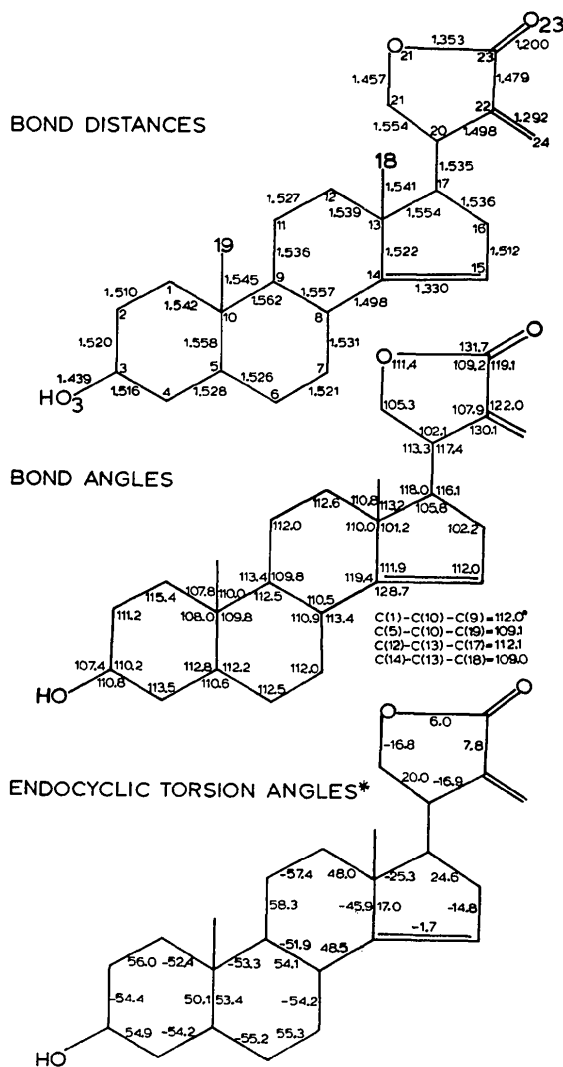
Comparison of the crystal structures of digitoxigenin, Δ -8,14-anhydrodigitoxigenin (Gilardi & Karle, 1969), strophanthidin, and the title compound gives strong indication that there are two preferred orientations for the lactone rings. Three of the structures have the ring oriented such that C(22) is located in the region between C(13) and C(17), see Fig. 3(a)–(c). The other two structures have the lactone ring rotated approximately 180° about the C(17)–C(20) bond, placing

Table 1. Atomic coordinates and thermal parameters, with standard deviations in parentheses

The anisotropic thermal parameter is of the form $\exp [-(B_{11}h^2 + B_{22}k^2 + B_{33}l^2 + B_{12}hk + B_{13}hl + B_{23}kl)]$.

	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> ₁₁ (× 10 ⁵)	<i>B</i> ₂₂ (× 10 ⁵)	<i>B</i> ₃₃ (× 10 ⁴)	<i>B</i> ₁₂ (× 10 ⁴)	<i>B</i> ₁₃ (× 10 ⁴)	<i>B</i> ₂₃ (× 10 ⁴)
C(1)	0.7300 (2)	0.61164 (13)	0.8722 (2)	1004 (16)	425 (7)	85 (1)	9 (2)	-61 (3)	29 (2)
C(2)	0.6655 (2)	0.64116 (15)	0.9808 (2)	823 (15)	581 (9)	130 (2)	44 (2)	-16 (3)	45 (3)
C(3)	0.7387 (2)	0.70112 (14)	1.0558 (2)	1124 (18)	527 (9)	95 (2)	64 (2)	15 (3)	4 (2)
C(4)	0.8524 (2)	0.65843 (11)	1.0856 (2)	936 (15)	410 (7)	67 (1)	28 (2)	-15 (3)	-8 (2)
C(5)	0.9190 (2)	0.62758 (11)	0.9770 (2)	817 (13)	280 (5)	67 (1)	-4 (2)	9 (2)	7 (2)
C(6)	1.0329 (2)	0.58646 (11)	1.0135 (2)	631 (12)	367 (6)	109 (2)	-16 (2)	14 (3)	-7 (2)
C(7)	1.0166 (1)	0.49919 (10)	1.0725 (2)	524 (10)	344 (6)	90 (1)	-1 (1)	-24 (2)	-11 (2)
C(8)	0.9478 (1)	0.43685 (10)	0.9949 (1)	512 (9)	313 (5)	60 (1)	-0 (1)	-2 (2)	-5 (1)
C(9)	0.8310 (1)	0.47749 (10)	0.9569 (1)	573 (10)	323 (6)	54 (1)	2 (1)	-14 (2)	9 (1)
C(10)	0.8464 (2)	0.56717 (10)	0.8960 (1)	873 (14)	348 (6)	50 (1)	-4 (2)	-2 (2)	9 (1)
C(11)	0.7626 (2)	0.41279 (12)	0.8818 (2)	803 (13)	409 (7)	78 (1)	-8 (2)	-68 (2)	8 (2)
C(12)	0.7400 (2)	0.32876 (11)	0.9483 (2)	634 (12)	376 (7)	92 (1)	-16 (1)	-64 (2)	7 (2)
C(13)	0.8516 (1)	0.28496 (10)	0.9903 (1)	596 (10)	321 (5)	56 (1)	-3 (1)	-19 (2)	-8 (1)
C(14)	0.9288 (1)	0.35058 (10)	1.0512 (1)	487 (9)	306 (5)	59 (1)	0 (1)	-7 (2)	-10 (1)
C(15)	0.9739 (2)	0.31952 (10)	1.1505 (1)	609 (11)	313 (5)	65 (1)	-1 (1)	-29 (2)	-4 (1)
C(16)	0.9328 (2)	0.22895 (10)	1.1763 (2)	733 (12)	305 (5)	65 (1)	-1 (2)	-30 (2)	-0 (1)
C(17)	0.8296 (1)	0.22001 (10)	1.0924 (2)	635 (11)	291 (5)	63 (1)	-5 (1)	-13 (2)	-2 (1)
C(18)	0.9172 (2)	0.24512 (12)	0.8853 (2)	1082 (17)	417 (7)	64 (1)	-9 (2)	13 (3)	-30 (2)
C(19)	0.9086 (3)	0.55628 (14)	0.7763 (2)	1512 (25)	505 (9)	57 (1)	-18 (3)	33 (3)	15 (2)
C(20)	0.7947 (2)	0.12756 (12)	1.0598 (2)	949 (15)	324 (6)	85 (1)	-27 (2)	-44 (3)	-4 (2)
C(21)	0.8885 (3)	0.06857 (13)	1.0046 (2)	1695 (32)	409 (8)	120 (2)	-9 (3)	20 (5)	-50 (2)
C(22)	0.7556 (2)	0.07541 (12)	1.1638 (2)	1026 (17)	422 (8)	99 (2)	-44 (2)	-66 (3)	19 (2)
C(23)	0.7949 (2)	-0.01434 (13)	1.1459 (2)	1258 (19)	391 (7)	133 (2)	-33 (2)	-125 (3)	16 (2)
C(24)	0.7010 (3)	0.09894 (17)	1.2579 (3)	1377 (27)	607 (11)	126 (2)	-46 (3)	15 (5)	36 (3)
O(3B)	0.7569 (2)	0.77870 (9)	0.9886 (2)	1693 (19)	417 (6)	138 (2)	62 (2)	-51 (3)	1 (2)
O(21)	0.8650 (2)	-0.01741 (10)	1.0505 (2)	1910 (23)	357 (5)	164 (2)	8 (2)	-70 (4)	-29 (2)
O(23)	0.7740 (2)	-0.07976 (9)	1.1983 (2)	1868 (21)	436 (6)	195 (2)	-53 (2)	-177 (3)	72 (2)

	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> _{iso}	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> _{iso}	
H(1A)	0.685 (2)	0.5732 (12)	0.820 (2)	5.7 (6)	H(12A)	0.690 (2)	0.3454 (12)	1.017 (2)	5.0 (5)
H(1B)	0.750 (3)	0.6660 (12)	0.823 (3)	6.8 (7)	H(12B)	0.696 (2)	0.2924 (12)	0.901 (2)	4.5 (5)
H(2A)	0.642 (2)	0.5925 (14)	1.026 (2)	5.6 (5)	H(15)	1.021 (2)	0.3509 (10)	1.203 (2)	3.2 (4)
H(2B)	0.590 (2)	0.6644 (12)	0.968 (2)	5.4 (5)	H(16A)	0.910 (2)	0.2161 (11)	1.261 (2)	3.8 (4)
H(3O)	0.778 (3)	0.8208 (17)	1.046 (3)	10.2 (9)	H(16B)	0.994 (2)	0.1926 (12)	1.159 (2)	5.0 (5)
H(3A)	0.693 (2)	0.7029 (16)	1.124 (2)	8.1 (8)	H(17A)	0.762 (1)	0.2415 (9)	1.140 (2)	2.1 (3)
H(4A)	0.839 (2)	0.6073 (12)	1.138 (2)	3.9 (4)	H(18A)	0.936 (2)	0.3004 (13)	0.831 (2)	6.2 (6)
H(4B)	0.900 (2)	0.7072 (13)	1.134 (2)	4.5 (5)	H(18B)	0.991 (2)	0.2156 (13)	0.913 (2)	5.3 (5)
H(5B)	0.932 (2)	0.6881 (13)	0.935 (2)	5.4 (5)	H(18C)	0.872 (2)	0.2087 (13)	0.850 (2)	4.5 (5)
H(6A)	1.078 (2)	0.6297 (16)	1.059 (2)	5.4 (5)	H(19A)	0.913 (3)	0.6129 (18)	0.746 (2)	7.3 (7)
H(6B)	1.078 (2)	0.5775 (11)	0.947 (2)	3.7 (4)	H(19B)	0.987 (3)	0.5228 (13)	0.787 (2)	6.8 (6)
H(7A)	0.977 (2)	0.5128 (10)	1.150 (1)	3.1 (4)	H(19C)	0.857 (2)	0.5314 (12)	0.721 (2)	4.6 (5)
H(7B)	1.091 (2)	0.4700 (14)	1.098 (2)	6.8 (6)	H(20)	0.727 (2)	0.1335 (13)	1.006 (2)	3.7 (4)
H(8B)	0.994 (1)	0.4269 (10)	0.923 (2)	3.0 (4)	H(21A)	0.967 (2)	0.0687 (13)	1.048 (2)	7.0 (7)
H(9A)	0.787 (2)	0.4902 (13)	1.027 (2)	3.7 (4)	H(21B)	0.883 (2)	0.0571 (13)	0.924 (2)	6.5 (6)
H(11A)	0.690 (2)	0.4436 (11)	0.858 (2)	4.5 (5)	H(24A)	0.669 (3)	0.1567 (13)	1.274 (2)	7.0 (7)
H(11B)	0.811 (2)	0.4015 (13)	0.802 (2)	5.0 (5)	H(24B)	0.688 (3)	0.0591 (14)	1.309 (3)	9.4 (9)



*A torsion angle α - β - γ - δ is positive if, when viewed down the β - γ bond, the α - β bond will eclipse the γ - δ bond when rotated less than 180° in a clockwise direction.

Fig. 2. Intramolecular geometry: bond lengths; bond angles; endocyclic torsion angles.

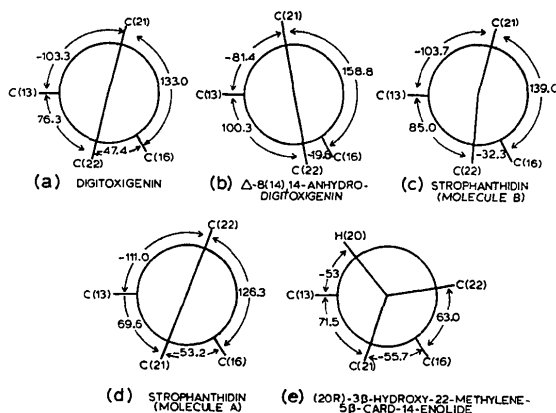


Fig. 3. Newman projections as viewed from C(20) to C(17) showing the two preferred orientations of the cardenolide lactone ring.

C(22) in that region, see Fig. 3(d) and (e). These two preferred orientations for the lactone ring place the ring oxygen and the carbonyl oxygen in quite different locations relative to the rest of the steroid backbone. Since models for the nature of the cardenolide-receptor binding (Kupchan, Ognyanov & Moniot, 1971; Thomas, Boutagy & Gelbart, 1974) involve the lactone ring, an understanding of the nature of the relative conformational preferences for the lactone ring and the steroid backbone may be necessary to provide better models of this binding.

Table 2. Nonbonded intermolecular contacts less than 3.5 Å

	Distance (Å)	Symmetry operator on second atom
O(3)···C(6)	3.337	$\frac{1}{2}+x \quad \frac{3}{2}-y \quad 2-z$
O(3)···C(24)	3.261	$\frac{3}{2}-x \quad 1-y \quad -\frac{1}{2}+z$
O(3)···O(21)	3.472	$x \quad 1+y \quad z$
O(3)···O(23)	3.237	$x \quad 1+y \quad z$

There does not appear to be any hydrogen bonding in this crystal structure, despite the presence of a 3β -hydroxyl group. However, all of the nonbonded contacts between nonhydrogens less than 3.5 Å involve O(3), see Table 2. There are two O(3) to oxygen contacts among this group, however, the shortest contact distance is 3.237 Å involving O(23). The corresponding H(O3) to O(23) distance is 2.31 Å and the O(3)-H(O3)···O(23) angle is 163° . At best, this could only be a weak attractive interaction.

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