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# Structure of a 3α-(D-Methylglycoside) of 7,8β-Epoxysinogenin – a Cardioactive Steroid


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**Abstract.** $C_{30}H_{42}O_{10}$, $M_r = 562{\cdot}66$, orthorhombic, $P2_12_12_1$, $a = 10{\cdot}125$ (1), $b = 15{\cdot}632$ (2), $c = 36{\cdot}115$ (4) Å, $V = 5716$ (1) Å$^3$, $Z = 8$, $D_m = 1{\cdot}312$ (2) (flotation), $D_x = 1{\cdot}308$ g cm$^{-3}$, Cu $K\alpha(\lambda = 1{\cdot}5418$ Å), $\mu = 7{\cdot}18$ cm$^{-1}$, $F(000) = 2416$, $T = 295$ K. Final $R(F) = 0{\cdot}07$ for 3348 significant reflections with $I \geq 2{\cdot}5\sigma(I)$. The *A, B, C, D* rings of the aglycone ring are found to be in *cis–trans–cis* fashion forming a buckled structure. The lactone is in C17β conformation. The molecules are stabilized by intermolecular hydrogen bonds. The longest direction of the steroid molecule is nearly parallel to the *a* axis. The conformational features exhibited by the molecule support proposals on activity.


**Introduction.** The title compound (Fig. 1), which is a cardiac glycoside, is extracted from the plant *Cryptolepsis buchanani* (local name Krishna Sariva) and belongs to the class of digitalis. The active components of digitalis are glycosides of digitoxigenins, digoxigenin and gitoxigenin. Digitalis compounds have been categorized as cardiotonic steroids because of their profound effect on the heart. They increase the force of contraction of heart muscle, which makes them a drug of choice in the treatment of congestive heart failure. The activity of a cardiac steroid depends upon the presence of a five- or a six-membered unsaturated lactone ring in the β-configuration at the C(17) position; a hydroxyl group at C(14) and *cis* fusion of rings *C* and *D* are also essential. The C(17) substituent containing a conjugated system, normally a lactone ring, is supposed to enhance the basicity of the carbonyl O and thus act as a proton receptor (Repke & Portius, 1966; Repke & Dittrich, 1982). The sugar residue attached at C(3) does not contribute to the inhibition of the ATPase by these compounds (Bowman & Rand, 1980; Stryer, 1975) but they have been reported to modify the activity of cardiac glycosides. The present study was undertaken to establish the chemical structure of the title compound and to correlate the activity with the observed conformational features.


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**Experimental.** Pale green needles 0·2 × 0·2 × 0·1 mm from methanol, $\theta/2\theta$ scan, $2\theta_{max} = 110°$, Picker four-circle automated diffractometer, graphite-monochromated Cu $K\alpha$ radiation, no absorption correction, data corrected for direct-beam polarization and Lorentz effects, unit-cell parameters from least-squares refinement of measured angle values for 70 reflections with $70 \le 2\theta \le 90°$. 5581 independent measurements, 4051 unique reflections, 3348 observed reflections with $I \ge 2{\cdot}5\sigma(I)$, $0 \le h \le 10$, $0 \le k \le 16$, $0 \le l \le 38$, three standard reflections measured every 100 reflections showed no significant variation. Structure solution, which was non-trivial, was by direct methods using *MULTAN*80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980) incorporated in the *NRCVAX* system with a special subroutine (*SOLVER*) (Gabe, Lee & Le Page, 1985) to accommodate more triplets/reflection, more reflections and to search more sets. Full-matrix least-squares refinement on $I_{obs}$ in *SHELX*76 (Sheldrick, 1976), hydrogen positions, except that bonded to O(37) of molecule (I), were from $\Delta F$ map and were checked against the stereochemically fixed positions, anisotropic refinement for all non-hydrogen atoms while hydrogens were included in the structure-factor calculation only. Last two cycles of refinement in block-diagonal least-squares refinement (Shiono, 1968) with Cruickshank's weighting scheme (Cruickshank, Bujosa, Lovell & Truter, 1961), $w = [A + B(F_{obs}) + C(F_{obs}^2)]^{-1}$ where $A = 10{\cdot}0$, $B = 1{\cdot}0$ and $C = 0{\cdot}02$, $R(F) = 0{\cdot}070$, $wR = 0{\cdot}070$ for 728 parameters with 3348 reflections, $S = 0{\cdot}43$, $(\Delta/\sigma)_{max} = 0{\cdot}21$, $(\Delta/\sigma)_{mean} = 0{\cdot}1$, final $(\Delta\rho)_{max} = 0{\cdot}34$ e Å$^{-3}$. The residual index obtained for the opposite enantiomer was 0·077. Atomic scattering factors for non-hydrogen atoms from *International Tables for X-ray Crystallography* (1968) and for hydrogens from Stewart, Davidson & Simpson (1965).

**Discussion.** There are two molecules in the asymmetric unit. Atomic positions and equivalent isotropic temperature factors for non-hydrogens are listed in Table 1.* A stereoview of the molecules is shown in Fig. 2 (Motherwell & Clegg, 1978). Fig. 1 is a schematic diagram with atom numbering. The bond lengths and angles involving non-hydrogen atoms are given in Table 2. The average C($sp^3$)–C($sp^3$) distance is 1·54 (1) Å in both molecules (I) and (II) and is comparable with the 1·54 (3) Å of digitoxigenin (Karle & Karle, 1969). In both molecules, the substituents at C(10), C(13) and C(14) are in $\beta$ conformation while that at C(11) is in $\alpha$ orientation. In molecules (I) and (II) the lactone ring

Table 1. *Fractional positional parameters* ($\times 10^4$) *and* $B_{eq}$ (Å$^2$) *for non-hydrogen atoms with e.s.d.'s in parentheses*

$$B_{eq} = \tfrac{4}{3}\sum_i\sum_j \beta_{ij}\mathbf{a}_i.\mathbf{a}_j.$$

| | $x$ | $y$ | $z$ | $B_{eq}$ |
|---|---|---|---|---|
| Molecule (I) | | | | |
| C(1) | −1389 (9) | 4759 (6) | 5342 (3) | 4·0 (3) |
| C(2) | −978 (10) | 5000 (6) | 5727 (3) | 4·4 (4) |
| C(3) | −617 (10) | 4208 (5) | 5953 (2) | 3·5 (3) |
| C(4) | 435 (8) | 3695 (6) | 5750 (2) | 3·2 (3) |
| C(5) | 2 (8) | 3429 (5) | 5358 (3) | 3·3 (3) |
| C(6) | 1049 (10) | 2852 (6) | 5184 (3) | 4·4 (4) |
| C(7) | 2278 (11) | 3333 (6) | 5047 (3) | 4·6 (4) |
| C(8) | 2163 (9) | 4262 (5) | 4981 (2) | 3·2 (3) |
| C(9) | 909 (8) | 4769 (5) | 5043 (2) | 2·8 (2) |
| C(10) | −354 (9) | 4224 (6) | 5120 (2) | 3·5 (3) |
| C(11) | 810 (8) | 5362 (6) | 4694 (2) | 3·3 (3) |
| C(12) | 1960 (9) | 5959 (6) | 4702 (2) | 3·3 (3) |
| C(13) | 3376 (8) | 5621 (5) | 4747 (2) | 3·2 (3) |
| C(14) | 3465 (8) | 4780 (6) | 4990 (2) | 3·5 (3) |
| C(15) | 3859 (10) | 5096 (6) | 5369 (2) | 4·1 (4) |
| C(16) | 4892 (11) | 5761 (7) | 5289 (3) | 4·9 (4) |
| C(17) | 4206 (9) | 6303 (6) | 4979 (2) | 3·5 (3) |
| C(18) | 3865 (10) | 5469 (6) | 4350 (2) | 3·8 (4) |
| C(19) | −1003 (11) | 3913 (7) | 4752 (3) | 5·2 (5) |
| C(20) | 5115 (10) | 6849 (5) | 4757 (2) | 3·7 (3) |
| C(21) | 4634 (11) | 7720 (6) | 4645 (3) | 4·9 (4) |
| C(22) | 6344 (10) | 6708 (6) | 4632 (3) | 4·7 (4) |
| C(23) | 6719 (11) | 7470 (7) | 4427 (3) | 5·2 (5) |
| O(24) | 5746 (8) | 8073 (5) | 4440 (2) | 5·9 (3) |
| O(25) | 1777 (7) | 6728 (4) | 4650 (2) | 5·2 (2) |
| O(26) | −388 (6) | 5822 (4) | 4678 (2) | 4·5 (2) |
| O(27) | 2129 (7) | 3668 (4) | 4673 (2) | 4·5 (2) |
| O(28) | 4520 (6) | 4263 (4) | 4868 (2) | 4·7 (3) |
| O(29) | −1826 (6) | 3719 (4) | 5990 (2) | 3·8 (2) |
| C(30) | −1759 (10) | 3015 (6) | 6231 (3) | 4·3 (3) |
| O(31) | −1574 (6) | 3269 (4) | 6600 (2) | 4·1 (2) |
| C(32) | −2585 (8) | 3807 (6) | 6755 (2) | 3·4 (2) |
| C(33) | −2167(10) | 3994 (7) | 7152 (2) | 4·4 (3) |
| C(34) | −3903 (9) | 3354 (5) | 6729 (2) | 3·1 (3) |
| C(35) | −4202 (9) | 3111 (5) | 6330 (2) | 3·3 (3) |
| C(36) | −3109 (10) | 2553 (6) | 6184 (3) | 4·1 (4) |
| O(37) | −4872 (6) | 3939 (4) | 6871 (2) | 4·3 (2) |
| O(38) | −5442 (6) | 2673 (4) | 6327 (2) | 4·4 (2) |
| C(39) | −6141 (13) | 2762 (8) | 5986 (3) | 6·4 (6) |
| O(40) | 7700 (9) | 7631 (6) | 4258 (3) | 7·7 (5) |
| Molecule (II) | | | | |
| C(1′) | 7010 (10) | 3044 (6) | 2190 (2) | 4·3 (4) |
| C(2′) | 5832 (10) | 2519 (6) | 2058 (3) | 4·6 (4) |
| C(3′) | 5337 (9) | 2790 (6) | 1675 (3) | 4·2 (3) |
| C(4′) | 6452 (9) | 2865 (6) | 1402 (2) | 3·8 (4) |
| C(5′) | 7587 (9) | 3427 (6) | 1546 (2) | 3·3 (3) |
| C(6′) | 8637 (10) | 3546 (6) | 1241 (2) | 4·3 (4) |
| C(7′) | 9503 (9) | 2768 (6) | 1193 (2) | 3·5 (3) |
| C(8′) | 9631 (8) | 2108 (5) | 1493 (2) | 3·0 (2) |
| C(9′) | 8829 (9) | 2184 (5) | 1857 (2) | 3·2 (2) |
| C(10′) | 8192 (9) | 3088 (5) | 1918 (2) | 3·1 (2) |
| C(11′) | 9746 (9) | 1875 (5) | 2163 (2) | 2·9 (2) |
| C(12′) | 10242 (9) | 974 (6) | 2083 (2) | 3·4 (2) |
| C(13′) | 10978 (9) | 819 (5) | 1715 (2) | 3·2 (2) |
| C(14′) | 10116 (9) | 1214 (5) | 1403 (2) | 3·2 (2) |
| C(15′) | 9049 (10) | 547 (6) | 1340 (3) | 4·3 (3) |
| C(16′) | 9811 (12) | −286 (7) | 1343 (4) | 6·0 (4) |
| C(17′) | 10970 (10) | −161 (5) | 1629 (2) | 3·9 (3) |
| C(18′) | 12368 (9) | 1232 (6) | 1761 (2) | 3·7 (2) |
| C(19′) | 9183 (10) | 3735 (6) | 2074 (3) | 4·3 (3) |
| C(20′) | 12255 (11) | −510 (5) | 1502 (3) | 4·4 (4) |
| C(21′) | 13146 (16) | −923 (10) | 1787 (4) | 8·6 (7) |
| C(22′) | 12768 (11) | −580 (6) | 1159 (3) | 4·8 (4) |
| C(23′) | 13994 (14) | −1065 (7) | 1190 (3) | 6·1 (6) |
| O(24′) | 14255 (12) | −1251 (6) | 1550 (3) | 9·6 (6) |
| O(25′) | 10064 (8) | 404 (4) | 2306 (2) | 5·1 (3) |
| O(26′) | 9027 (6) | 1854 (4) | 2506 (1) | 4·2 (2) |
| O(27′) | 10650 (6) | 2736 (4) | 1438 (2) | 3·7 (2) |
| O(28′) | 10894 (6) | 1245 (4) | 1070 (1) | 3·9 (2) |
| O(29′) | 4747 (6) | 3649 (4) | 1689 (2) | 3·9 (2) |
| C(30′) | 3311 (9) | 3622 (6) | 1697 (3) | 3·7 (2) |
| O(31′) | 2906 (6) | 3438 (4) | 2068 (2) | 3·9 (2) |
| C(32′) | 3277 (10) | 4059 (6) | 2344 (3) | 4·5 (3) |
| C(33′) | 2692 (14) | 3721 (8) | 2714 (3) | 6·5 (5) |
| C(34′) | 2653 (11) | 4938 (6) | 2234 (3) | 4·5 (3) |
| C(35′) | 3190 (9) | 5207 (6) | 1855 (3) | 3·7 (3) |
| C(36′) | 2836 (8) | 4499 (6) | 1574 (2) | 3·3 (2) |

* Lists of structure factors, anisotropic thermal parameters, H-atom parameters and least-squares-planes data have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 44776 (41 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1 (*cont.*)

| | *x* | *y* | *z* | $B_{eq}$ |
|---|---|---|---|---|
| O(37′) | 3075 (8) | 5539 (5) | 2514 (2) | 5·8 (3) |
| O(38′) | 2557 (7) | 5969 (4) | 1732 (2) | 4·7 (2) |
| C(39′) | 3301 (11) | 6732 (6) | 1790 (3) | 4·9 (3) |
| O(40′) | 14763 (10) | −1294 (5) | 945 (3) | 7·9 (4) |

Table 2. *Bond lengths* (Å) *and angles* (°) *involving non-hydrogen atoms with e.s.d.'s in parentheses*

| | (I) | (II) | | (I) | (II) |
|---|---|---|---|---|---|
| C(1)–C(2) | 1·50 (2) | 1·52 (1) | C(13)–C(18) | 1·54 (1) | 1·56 (1) |
| C(1)–C(10) | 1·56 (1) | 1·55 (1) | C(14)–C(15) | 1·51 (1) | 1·52 (1) |
| C(2)–C(3) | 1·53 (1) | 1·53 (2) | C(14)–O(28) | 1·41 (1) | 1·44 (1) |
| C(3)–C(4) | 1·52 (1) | 1·50 (1) | C(15)–C(16) | 1·50 (1) | 1·51 (1) |
| C(3)–O(29) | 1·45 (1) | 1·47 (1) | C(16)–C(17) | 1·57 (1) | 1·58 (2) |
| C(4)–C(5) | 1·54 (1) | 1·54 (1) | C(17)–C(20) | 1·49 (1) | 1·46 (1) |
| C(5)–C(6) | 1·53 (1) | 1·54 (1) | C(20)–C(21) | 1·50 (1) | 1·47 (2) |
| C(5)–C(10) | 1·55 (1) | 1·57 (1) | C(20)–C(22) | 1·34 (1) | 1·41 (2) |
| C(6)–C(7) | 1·54 (1) | 1·51 (1) | C(21)–O(24) | 1·46 (1) | 1·50 (2) |
| C(7)–C(8) | 1·48 (1) | 1·50 (1) | C(22)–C(23) | 1·45 (1) | 1·50 (2) |
| C(7)–O(27) | 1·46 (1) | 1·46 (1) | C(23)–O(24) | 1·36 (1) | 1·36 (2) |
| C(8)–C(9) | 1·51 (1) | 1·55 (1) | C(23)–O(40) | 1·19 (1) | 1·23 (1) |
| C(8)–C(14) | 1·55 (1) | 1·52 (1) | O(29)–C(30) | 1·40 (1) | 1·45 (1) |
| C(8)–O(27) | 1·45 (1) | 1·44 (1) | C(30)–O(31) | 1·40 (1) | 1·43 (1) |
| C(9)–C(10) | 1·56 (1) | 1·57 (1) | C(30)–C(36) | 1·56 (1) | 1·52 (1) |
| C(9)–C(11) | 1·57 (1) | 1·52 (1) | C(31)–C(32) | 1·44 (1) | 1·44 (1) |
| C(10)–C(19) | 1·56 (1) | 1·53 (1) | C(32)–C(33) | 1·52 (1) | 1·55 (2) |
| C(11)–C(12) | 1·49 (1) | 1·52 (1) | C(32)–C(34) | 1·51 (1) | 1·56 (1) |
| C(11)–O(26) | 1·41 (1) | 1·44 (1) | C(34)–C(35) | 1·52 (1) | 1·53 (1) |
| C(12)–C(13) | 1·54 (1) | 1·54 (1) | C(34)–O(37) | 1·44 (1) | 1·44 (1) |
| C(12)–O(25) | 1·23 (1) | 1·21 (1) | C(35)–C(36) | 1·50 (1) | 1·54 (1) |
| C(13)–C(14) | 1·58 (1) | 1·55 (1) | C(35)–O(38) | 1·43 (1) | 1·42 (1) |
| C(13)–C(17) | 1·60 (1) | 1·56 (1) | O(38)–C(39) | 1·43 (1) | 1·43 (1) |

| | (I) | (II) |
|---|---|---|
| C(2)–C(1)–C(10) | 115·2 (7) | 115·5 (7) |
| C(1)–C(2)–C(3) | 111·0 (7) | 112·9 (7) |
| C(2)–C(3)–C(4) | 109·8 (6) | 111·6 (7) |
| C(2)–C(3)–O(29) | 105·9 (6) | 110·8 (7) |
| C(4)–C(30)–O(29) | 111·0 (6) | 104·9 (6) |
| C(3)–C(4)–C(5) | 112·7 (6) | 112·6 (6) |
| C(4)–C(5)–C(6) | 109·9 (7) | 110·0 (6) |
| C(4)–C(5)–C(10) | 111·0 (6) | 112·9 (6) |
| C(6)–C(5)–C(10) | 113·9 (7) | 112·5 (6) |
| C(5)–C(6)–C(7) | 114·0 (7) | 112·7 (6) |
| C(6)–C(7)–C(8) | 117·9 (7) | 121·4 (6) |
| C(6)–C(7)–O(27) | 112·9 (7) | 114·8 (6) |
| C(8)–C(7)–O(27) | 59·2 (5) | 58·1 (4) |
| C(7)–C(8)–C(9) | 124·0 (6) | 120·9 (6) |
| C(7)–C(8)–C(14) | 116·3 (6) | 120·4 (6) |
| C(7)–C(8)–O(27) | 59·7 (5) | 59·5 (4) |
| C(9)–C(8)–C(14) | 115·9 (6) | 115·0 (6) |
| C(9)–C(8)–O(27) | 115·4 (6) | 116·2 (6) |
| C(14)–C(8)–O(27) | 111·8 (6) | 115·5 (5) |
| C(8)–C(9)–C(10) | 115·3 (6) | 113·8 (6) |
| C(8)–C(9)–C(11) | 104·1 (6) | 105·8 (6) |
| C(10)–C(9)–C(11) | 114·4 (6) | 115·8 (6) |
| C(5)–C(10)–C(9) | 110·2 (6) | 110·2 (6) |
| C(1)–C(10)–C(9) | 110·4 (6) | 111·5 (6) |
| C(1)–C(10)–C(19) | 118·8 (7) | 107·6 (6) |
| C(9)–C(10)–C(19) | 111·2 (6) | 112·2 (6) |
| C(1)–C(10)–C(5) | 107·5 (6) | 104·8 (6) |
| C(5)–C(10)–C(19) | 108·6 (7) | 110·3 (6) |
| C(9)–C(11)–C(12) | 107·7 (6) | 110·9 (6) |
| C(9)–C(11)–O(26) | 112·9 (6) | 108·9 (5) |
| C(12)–C(11)–O(26) | 110·6 (6) | 108·0 (5) |
| C(11)–C(12)–C(13) | 121·0 (6) | 117·9 (6) |
| C(11)–C(12)–O(25) | 119·4 (6) | 120·3 (6) |
| C(13)–C(12)–O(25) | 119·5 (6) | 121·8 (6) |
| C(12)–C(13)–C(14) | 113·4 (6) | 106·9 (6) |
| C(14)–C(13)–C(17) | 103·5 (6) | 104·0 (6) |
| C(12)–C(13)–C(17) | 108·5 (6) | 108·8 (5) |
| C(12)–C(13)–C(18) | 104·8 (6) | 106·2 (6) |
| C(17)–C(13)–C(18) | 115·1 (6) | 115·6 (6) |
| C(14)–C(13)–C(18) | 103·5 (6) | 114·9 (6) |
| C(8)–C(14)–C(15) | 114·6 (6) | 115·8 (6) |
| C(8)–C(14)–O(28) | 109·8 (6) | 109·0 (5) |
| C(8)–C(14)–C(13) | 112·0 (6) | 113·1 (6) |
| C(13)–C(14)–C(15) | 104·2 (6) | 103·6 (6) |
| C(13)–C(14)–O(28) | 110·2 (6) | 108·2 (5) |
| C(15)–C(14)–O(28) | 105·7 (6) | 106·7 (6) |
| C(14)–C(15)–C(16) | 103·7 (7) | 103·1 (7) |
| C(15)–C(16)–C(17) | 101·7 (7) | 106·1 (8) |

Table 2 (*cont.*)

| | (I) | (II) |
|---|---|---|
| C(13)–C(17)–C(16) | 104·3 (6) | 104·8 (7) |
| C(13)–C(17)–C(20) | 115·2 (6) | 114·4 (6) |
| C(16)–C(17)–C(20) | 114·9 (7) | 116·1 (7) |
| C(17)–C(20)–C(22) | 131·3 (7) | 127·3 (7) |
| C(17)–C(20)–C(21) | 117·7 (7) | 122·2 (8) |
| C(21)–C(20)–C(22) | 111·0 (7) | 110·3 (8) |
| C(20)–C(21)–O(24) | 103·3 (7) | 103·6 (9) |
| C(20)–C(22)–C(23) | 106·2 (7) | 106·5 (7) |
| C(22)–C(23)–O(24) | 111·1 (7) | 110·5 (8) |
| C(22)–C(23)–O(40) | 130·6 (8) | 129·3 (8) |
| O(24)–C(23)–O(40) | 118·2 (7) | 120·2 (8) |
| C(21)–O(24)–C(23) | 108·3 (6) | 109·1 (8) |
| C(7)–O(27)–C(8) | 61·1 (5) | 62·4 (4) |
| C(3)–O(29)–C(30) | 115·4 (6) | 112·3 (6) |
| O(29)–C(30)–O(31) | 111·9 (6) | 108·1 (6) |
| O(29)–C(30)–C(36) | 104·7 (7) | 106·5 (6) |
| O(31)–C(30)–C(36) | 110·6 (7) | 111·4 (6) |
| C(30)–O(31)–C(32) | 116·1 (6) | 116·0 (6) |
| O(31)–C(32)–C(33) | 106·3 (6) | 105·4 (7) |
| O(31)–C(32)–C(34) | 109·3 (6) | 108·1 (7) |
| C(33)–C(32)–C(34) | 113·1 (6) | 111·3 (7) |
| C(32)–C(34)–C(35) | 110·6 (6) | 109·0 (7) |
| C(32)–C(34)–O(37) | 106·4 (6) | 105·9 (7) |
| C(35)–C(34)–O(37) | 111·2 (6) | 110·0 (7) |
| C(34)–C(35)–C(36) | 109·3 (6) | 107·9 (7) |
| C(34)–C(35)–O(38) | 107·6 (6) | 110·4 (7) |
| C(36)–C(35)–O(38) | 111·4 (6) | 106·9 (6) |
| C(30)–C(36)–C(35) | 109·8 (7) | 112·4 (6) |
| C(35)–O(38)–C(39) | 113·3 (6) | 114·6 (6) |

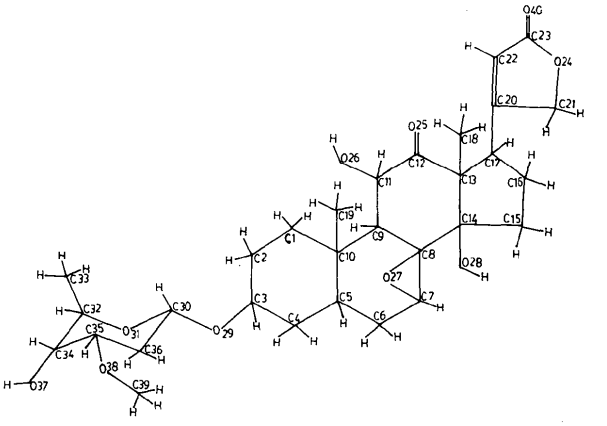


Fig. 1. Schematic diagram with atom numbering.

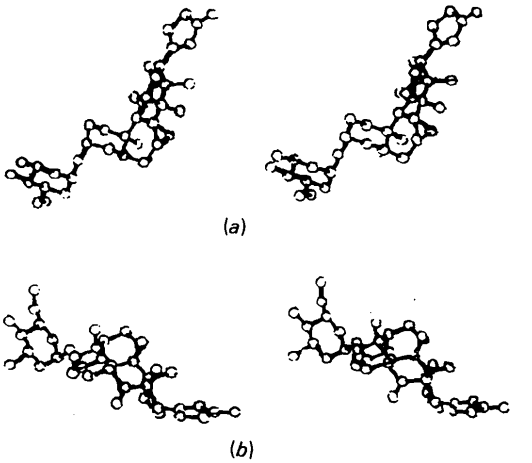


Fig. 2. Stereoview of the molecules in the asymmetric unit. (*a*) Molecule I; (*b*) molecule II.

angles C(22)–C(23)–O(40) [130·6 (8) and 129·3 (8)° respectively] are widened and compare well with 131·0 (3)° in oleandrin (Kartha & Go, 1981) and 129·5 (2)° in digoxin (Go, Kartha & Chen, 1980). Further, the two C–O bonds in the lactone ring are unequal with the shorter C–O bond occurring adjacent to the carboxyl group. In both the molecules the *A* rings are in typical chair conformation and the *B* and *D* rings are in half-chair conformation. In molecule (I) the *C* ring is in a sofa conformation while it is in a chair conformation in molecule (II). The endocyclic torsion angles are given in Fig. 3. The *A, B, C, D* rings are fused in *cis–trans–cis* fashion exhibiting a buckled structure which is common in cardioactive steroids. The lactone rings in both the molecules are in C17$\beta$ conformations. C(13)–C(17)–C(20)–C(22) = −83 (1) and −91 (1)° for molecules (I) and (II) respectively. The sugar rings are in typical chair conformations [average torsion angles are 57·4 (8) and 55·6 (8)°]. The longest direction of the steroid molecule is nearly parallel to the *a* axis. In the unit cell the molecules are stabilized by O–H···O type hydrogen bonds. Out of six hydroxyl protons available for hydrogen bonding four are involved in hydrogen-bond formation.

*Structure and activity.* The pharmacological activity of cardiac glycosides resides in the genins (aglycone). It has been reported (Bowman & Rand, 1980) that the sugar residue modifies the activity and the effects of the genins are short-lasting compared to those of the glycosides and hence the genins are not suitable for therapeutic use. The affinity of cardiac glycosides for cardiac muscle is conferred by the glycoside linkage with one or more sugars. Thus the present compound is likely to be more effective than that of cardionilide sinogenin. Several models have been proposed to describe the structure and activity of these molecules (Repke & Portius, 1966; Repke & Dittrich, 1982; Thomas, Boutagy & Gelbart, 1974; Thomas, Brown, Boutagy & Gelbart, 1980). It has been reported that the presence of a hydroxyl group at C(14) and methyl groups at C(13) and C(10) plays an additional role in activity, and introduction of hydroxyl groups at C(1), C(6), C(11) and C(16) and keto groups at C(11) and C(12) reduces the activity. It has also been suggested that the presence of a lactone ring at C(17) plays a major role in the activity since either removal of this group or the inversion of its orientation from $\beta$ to $\alpha$ results in complete loss of activity (Bowman & Rand, 1980). A double bond in the lactone ring has been considered important for its activity and binding at the receptor. However, Rohrer, Fullerton, Yoshioka, Kitatsuji, Ahmed & From (1983) have disproved this claim and suggest that the double bond plays rather a geometric role in positioning the lactone carbonyl oxygen relative to the steroid backbone. In this context it is interesting to note that a spatial relation of about 13 Å between the two oxygens O(29) and O(40) is maintained in cardiotonic steroids with unsaturated lactones (Table 3). The present compound possesses the basic requirements, *viz.* a hydroxyl group at C(14) and a methyl group at C(13) and also a lactone ring in $\beta$

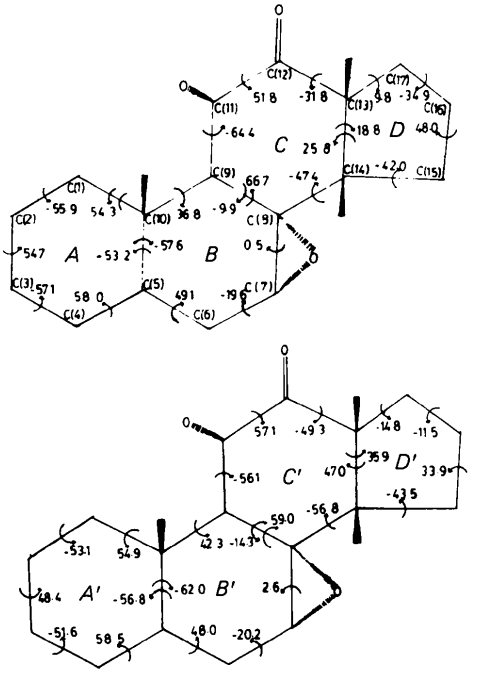


Fig. 3. Endocyclic torsion angles (°) observed in the aglycone ring.

Table 3. *Spatial distance* (Å) *between* O(29) *and* O(40) (*cardiotonic steroids with unsaturated lactone*)

| Compound | O(29)···O(40) | Reference |
|---|---|---|
| 3$\beta$,14-Dihydroxy-12$\beta$-acetoxy-5$\beta$,-14$\beta$-card-20(22)-enolide | 13·34 | 1 |
| Ouabain diethanol | 13·44 | 2 |
| Ouabain | 12·36 | 3 |
| Digoxin | 12·25 | 4 |
| Anhydroxy digitoxigenin | 13·41 | 5 |
| Oleandrin | 13·10 | 6 |
| Digitoxigenin | 13·22 | 7 |
| Digoxigenin dihydrate | 13·57 | 8 |
| (20*S*)-20(22)-Dihydroxydigitoxigenin | 11·14 | 9 |
| Molecule (I) | 13·02 | 10 |
| Molecule (II) | 13·03 | 10 |
| (with saturated lactone) | | |
| (20*R*)-3-Hydroxy-22-methylene-5-card-14-enolide | 11·098 | 11 |
| (20*S*)-22-Methylene-20(22)-dihydroxy-digitoxigenin Mol. (I) | 9·54 | 9 |
| Mol. (II) | 11·97 | 9 |

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2. Go & Kartha (1981).
3. Messerschmidt (1980).
4. Go, Kartha & Chen (1980).
5. Gilardi & Karle (1970).
6. Kartha & Go (1981).
7. Karle & Karle (1969).
8. Rohrer & Fullerton (1980).
9. Rohrer, Fullerton, Yoshioka, Kitatsuji, Ahmed & From (1983).
10. Present work.
11. Rohrer, Duax & Fullerton (1976).

Table 4. *Conformations of the aglycone ring observed in various steroids*

| Ring A | B | C | D | Lactone | | Reference* |
|---|---|---|---|---|---|---|
| chair | chair | chair | envelope | C17β | | 1 |
| chair | chair | chair | envelope | C17β | | 2 |
| flattened | puckered | puckered | envelope | C17β | | 3 |
| flattened | flattened | flattened | half chair | C17β | | 4 |
| flattened | flattened | chair | envelope | C17β | | 5 |
| chair | chair | chair | envelope | C17β | | 6 |
| chair | chair | chair | chair | C17β | | 7 |
| chair | half chair | sofa | half chair | C17β | I | 10 |
| chair | half chair | chair | half chair | C17β | II | 10 |

* For references see Table 3.

orientation at C(17), for its activity. Further, except for the hydroxyl substituent at C(11), all the others are in the β orientation which further ensures the activity. One may further add that minor variations observed in the conformation of the steroid nucleus induced by the substituents do not affect the activity of the molecule (Table 4).

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# Détermination Structurale du Poly{bis[(butoxycarbonylméthylcarbamoyloxy)-4 butyl]-1,2 butène-1 yne-3 ylène} [poly(4BCMU)] par Minimisation des Energies d'Interactions Moléculaires

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(*Reçu le* 16 *novembre* 1987, *accepté le* 3 *février* 1988)

**Abstract.** $(C_{26}H_{40}N_2O_8)_n$, $M_r = (508)_n$, orthorhombic, *Pmab*, $a = 53{\cdot}75$ (2), $b = 10{\cdot}997$ (3), $c = 4{\cdot}880$ (5) Å, $V = 2885$ (7) Å$^3$, $Z = 4$, $D_x = 1{\cdot}17$ Mg m$^{-3}$, $\lambda$(Cu $K\alpha$) $= 1{\cdot}54178$ Å, $\mu = 0{\cdot}72$ mm$^{-1}$, $F(000) = 1096$, $T = 293$ K, $R = 0{\cdot}17$. The refinement is not carried out in a trivial way. First, refinement of a structural model for

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