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Crystal and Molecular Structure of 3β-Hydroxy-14,15β-epoxy--5β,14β-card-20,22-enolide (Digirezigenin)*

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The title compound $C_{23}H_{32}O_4$ and its methyl-suberate ester were discovered in Ch'an Su, the dried venom of the Chinese toad. Its crystals are orthorhombic, space group $P2_12_12_1$, and quasi--isostructural with those of the related compound digitoxigenin ($C_{23}H_{34}O_4$). The structure was solved by direct methods and refined by least squares technique to a conventional R index of 0.059 for 2271 unique diffractometer observations. The presence of the rigid 14, 15β-epoxy ring alters considerably the shape of ring D (^{17}E) relative to that in digitoxigenin (^{14}E). However, it has little effect upon the general features of the 14-iso-aethiocholane skeleton and the conformation of the γ-lactone ring. The amount of rotation about the C(17)—C(20) bond is hardly changed while the distance between the position of the carbonyl O relative to digitoxigenin is only 33.2 pm. The conformation of the title compound is also compared with that of a bufa-20, 22-dienolide (cinobufagin) which also possesses a 14, 15β-oxirane ring.

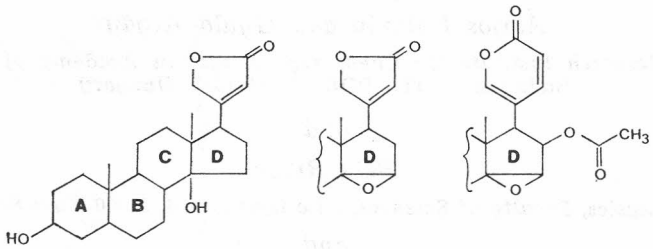
INTRODUCTION

Although the crystal and molecular structures of cardiac glycosides and their genins have been meticulously studied for several years (at least since the X-ray analysis of digitoxigenin[1]) further new information may be expected from the study of the 14-iso-aethicholane skeleton bearing an epoxy group fused to its D ring — as in the case of the title compound. The interest arises from the impact such a rigid D ring substituent can have on the positioning of the lactone corbonyl O, which seems to play an important role in the inotropic or/and toxic effects of Digitalis cardenolides.[2] Prior to this work only a preliminary report[3] on the structure of a bufa-20,22-dienolide (cinobufagin)

* Dedicated to Professor D. Grdenić on occasion of his 65th birthday.

also possessing a 14,15β-epoxy ring has been published. It is worth noting that both of these compounds were isolated from Ch'an Su, the dried venom of the Chinese toad which, as proved by these studies, is a common source of both cardenolides and bufadienolides. The isolation of the title compound was reported first by Höriger et al.[4]. Somewhat later, the methyl ester of the hydrogen suberate of the title compound and that of digitoxigenin were also separated from Ch'an Su.[5]

Since the chemical formula of the title compound (b) differs only sligthly from that (a) of digitoxigenin their structural differences will be discussed in comparison with the relevant parameters of the δ-lactone cinobufagin (c).



a. b. c.

EXPERIMENTAL

The colourless, transparent crystals of the isolated cardenolide melt at 501—507 K.

Crystal Data

From rotation and Weissenberg photographs and from single crystal diffractometry:

$C_{23}H_{32}O_4$, $M = 372.51$, orthorhombic, $a = 728.8(2)$, $b = 1468.6(3)$, $c = 1848.0(3)$ pm, $V = 1.978(1)$ nm^3, $Z = 4$, $D_c = 1.251$, $D_m = 1.25$ Mg · m^{-3} (by flotation) space group $P2_12_12_1$ (No. 19), $F(000) = 808$, μ (MoK$_\alpha$) = 0.78 mm^{-1}, $\lambda = 71.073$ pm, specimen size $0.1 \times 0.15 \times 0.2$ mm^3.

Intensity Data, Structure Determination and Refinement

Intensity data were collected on an Enraf-Nonius CAD-4 diffractometer equipped with graphite monochromator using ω-2Θ scan in the range $2\Theta < 60°$. Cell constants were determined by least squares from the setting angles of 25 reflections collected in the upper range of 2Θ scanned by MoK$_\alpha$ radiation. The systematic absences are: $h = 2n + 1$ in h00, $k = 2n + 1$ in 0k0 and $l = 2n + 1$ in 00l reflexions. $h_{max} = 10$, $k_{max} = 20$, $l_{max} = 26$. Standard reflections: (400), (060) and (008) (max variation 1.4%). Number of reflections measured: 3253, number of unique reflections 2271. Number of unobserved reflections with $F < 1.0\,\sigma$ (F) 489. No correction for absorption was applied.

The structure was solved by direct methods using the Multan[6] program. An E-map computed by the use of the phase set for 300 normalized structure factors having $E \geqq 1.70$ revealed the positions of 17 non-hydrogen atoms ($R = 0.40$). The missing 10 non-hydrogen atoms were located in the subsequent Fourier calculation. A block-diagonal least-squares procedure with isotropic thermal parameters reduced R to 0.15 for 1778 observations. After the generation of the H atom positions from assumed geometries the refinement of the non-hydrogen coordinates with anisotropic vibrational parameters led to R 0.061. The coordinates of H (O1) were obtained from a difference electron density map. In the final stage of the least squares procedure H positions were refined in isotropic mode which resulted in a final $R = 0.059$ ($R_w = 0.048$ $R_{tot} = 0.86$). $S = 1.81$, $w = [\sigma^2 (F_o) + 0.25 (pF_o)^2]^{-1}$ where $p = 0.01$. In the final stage the maximum ratio of shift to error was 0.96. The extinction coefficient was not applied. All scattering factors including anomalous dispersion corrections

were taken from ref. 7. All calculations* were carried out on a PDP-11/34 (64K) minicomputer using the Enraf-Nonius SDP program package with local modifications in Budapest.

DESCRIPTION OF THE STRUCTURE AND DISCUSSION

Figure 1/a shows a perspective view of the structure of the title compound computed from the fractional atomic coordinates given with their e.s.d.'s in

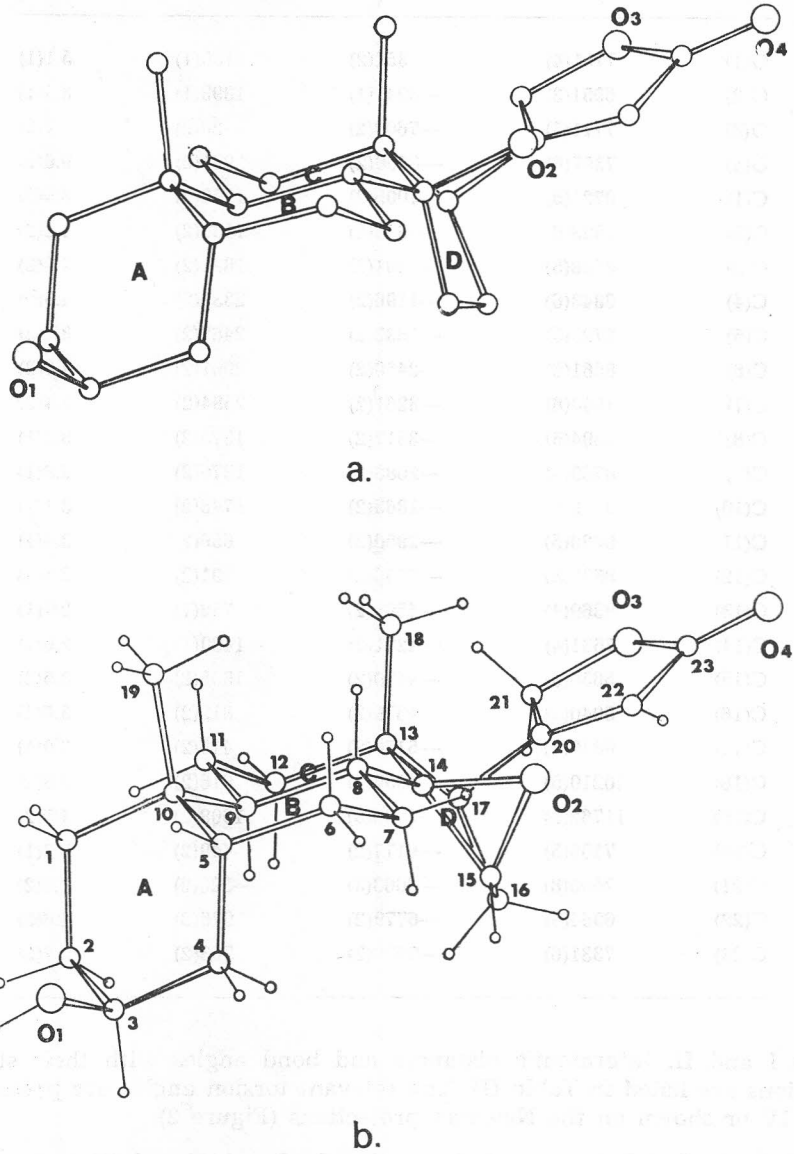


Figure 1. Perspective views of the structures of digitoxigenin without H atoms (a) and the title compound with H atoms (b) showing full ring and atomic numbering for a. The bare numbers are for carbon atoms unless indicated otherwise.

* List of structure factors etc. are available from the authors on request.

TABLE I

Atomic Coordinates (x 10^4) and Equivalent Isotropic Thermal Parameters (x 10^2 pm^2) for Nonhydrogen Atoms. Estimated Standard Deviations are in Parentheses. B_{eq} = 4/3 trace (B*G) where G is the direct metric tensor.*

Atom	x/a	y/b	z/c	B_{eq}
O(1)	7701(4)	352(2)	2180(1)	5.1(1)
O(2)	6951(3)	—5041(1)	1893(1)	3.5(1)
O(3)	7711(5)	—7609(2)	—20(2)	7.7(2)
O(4)	7357(6)	—8400(2)	971(2)	9.6(2)
C(1)	9721(5)	—1009(2)	1272(2)	3.9(2)
C(2)	7823(6)	—639(2)	1130(2)	4.2(2)
C(3)	6838(5)	—401(2)	1821(2)	4.3(2)
C(4)	6843(6)	—1196(2)	2332(2)	4.5(2)
C(5)	8720(5)	—1633(2)	2462(2)	3.5(2)
C(6)	8561(6)	—2458(2)	2961(2)	4.8(2)
C(7)	7648(6)	—3261(2)	2594(2)	4.4(2)
C(8)	8594(5)	—3517(2)	1875(2)	3.1(1)
C(9)	8769(4)	—2680(2)	1376(2)	2.8(1)
C(10)	9719(5)	—1863(2)	1748(2)	3.1(1)
C(11)	9620(5)	—2950(2)	659(2)	3.4(1)
C(12)	8539(5)	—3706(2)	291(2)	3.1(1)
C(13)	8369(4)	—4566(2)	752(1)	2.7(1)
C(14)	7631(4)	—4271(2)	1480(1)	2.6(1)
C(15)	5656(5)	—4470(2)	1505(2)	3.5(2)
C(16)	5040(5)	—4879(2)	812(2)	3.6(1)
C(17)	6819(4)	—5176(2)	415(2)	3.0(1)
C(18)	10210(5)	—5059(2)	816(2)	3.8(2)
C(19)	11762(5)	—2082(3)	1908(2)	4.7(2)
C(20)	7105(5)	—6177(2)	449(2)	3.3(1)
C(21)	7606(8)	—6668(3)	—220(2)	6.6(2)
C(22)	6964(6)	—6779(2)	976(2)	4.6(2)
C(23)	7331(6)	—7676(2)	703(2)	5.7(2)

Tables I and II. Interatomic distances and bond angles with their standard deviations are listed in Table III. The relevant torsion angles are presented in Table IV or shown on the Newman projections (Figure 2).

As was already apparent from the fairly similar lattice parameters (a = 725.0, b = 1501.5, c = 1846.4 pm) and space group symmetry ($P2_12_12_1$) of digitoxigenin[1] (the difference in the volumes of the unit cells is only 0.032 nm^3) the general conformation of the steroid skeleton (including the γ-lactone ring)

TABLE II

Atomic Coordinates (x 10^3) and Isotropic Thermal Parameters (x 10 pm^2) for Hydrogen Atoms. Estimated Standard Deviations are in Parentheses

Atom	x/a	y/b	z/c	B_i
H(1a)	1049(5)	—55(2)	156(2)	5.7(9)
H(1b)	1033(5)	—118(2)	76(1)	4.5(8)
H(2a)	791(4)	—12(2)	79(1)	4.3(7)
H(2b)	698(5)	—111(2)	79(1)	4.9(8)
H(3)	546(5)	—21(2)	172(2)	5.3(8)
H(4a)	599(5)	—165(2)	219(1)	3.6(8)
H(4b)	635(5)	—98(2)	279(2)	4.2(8)
H(5)	948(4)	—118(2)	267(1)	2.6(7)
H(6a)	789(4)	—234(2)	335(1)	4.1(7)
H(6b)	970(5)	—264(2)	310(2)	5.5(9)
H(7a)	638(5)	—313(2)	249(2)	5.0(9)
H(7b)	756(5)	—379(2)	284(2)	5.8(8)
H(8)	987(4)	—375(2)	204(1)	4.1(8)
H(9)	763(4)	—248(2)	128(1)	3.8(6)
H(11a)	1088(4)	—319(2)	69(1)	3.9(7)
H(11b)	963(4)	—243(2)	30(1)	3.1(7)
H(12a)	904(4)	—383(2)	—19(1)	2.2(7)
H(12b)	727(5)	—345(2)	16(2)	3.8(9)
H(15)	475(5)	—413(2)	176(2)	5.8(8)
H(16a)	444(4)	—444(2)	48(1)	3.5(7)
H(16b)	422(4)	—539(2)	85(1)	4.6(7)
H(17)	683(4)	—501(2)	—10(1)	3.1(7)
H(18a)	1067(5)	—527(2)	27(2)	6.1(9)
H(18b)	1110(4)	—464(2)	104(1)	4.8(8)
H(18c)	1002(4)	—563(2)	111(1)	5.5(8)
H(19a)	1244(5)	—221(2)	149(2)	7.9(10)
H(19b)	1232(5)	—159(2)	224(2)	5.2(9)
H(19c)	1185(5)	—262(2)	227(2)	7.1(9)
H(21a)	876(6)	—646(3)	—33(2)	5.8(11)
H(21b)	668(6)	—658(3)	—52(2)	9.3(11)
H(22)	663(5)	—669(2)	148(1)	5.5(7)
H(O1)	762(5)	80(2)	192(2)	6.3(9)

TABLE III

Interatomic Distances (pm) and Angles (°) with Estimated Standard Deviations in Parentheses

O(1) — C(3)	143.5(4)	C(8) — C(14)	150.1(4)
O(2) — C(14)	145.2(3)	C(9) — C(10)	154.6(4)
O(2) — C(15)	145.2(4)	C(9) — C(11)	151.6(5)
O(3) — C(21)	143.3(5)	C(10) — C(19)	155.2(5)
O(3) — C(23)	136.8(5)	C(11) — C(12)	152.2(5)
O(4) — C(23)	117.3(4)	C(12) — C(13)	152.8(4)
C(1) — C(2)	150.9(6)	C(13) — C(14)	151.2(3)
C(1) — C(10)	153.2(5)	C(13) — C(17)	157.1(4)
C(2) — C(3)	150.6(5)	C(13) — C(18)	152.9(5)
C(3) — C(4)	150.2(5)	C(14) — C(15)	146.9(5)
C(4) — C(5)	153.0(5)	C(15) — C(16)	148.4(5)
C(5) — C(6)	152.7(5)	C(16) — C(17)	155.2(5)
C(5) — C(10)	154.4(5)	C(17) — C(20)	148.6(4)
C(6) — C(7)	151.4(5)	C(20) — C(21)	147.7(5)
C(7) — C(8)	154.3(5)	C(20) — C(22)	131.9(5)
C(8) — C(9)	154.2(5)	C(22) — C(23)	143.6(4)
C(14) — O(2) — C(15)	60.8(3)	C(12) — C(13) — C(14)	106.7(4)
C(21) — O(3) — C(23)	108.1(6)	C(12) — C(13) — C(17)	108.0(4)
C(2) — C(1) — C(10)	113.2(5)	C(12) — C(13) — C(18)	111.3(4)
C(1) — C(2) — C(3)	111.9(5)	C(14) — C(13) — C(17)	105.1(4)
O(1) — C(3) — C(2)	111.2(5)	C(14) — C(13) — C(18)	112.3(4)
O(1) — C(3) — C(4)	107.9(5)	C(17) — C(13) — C(18)	113.1(4)
C(2) — C(3) — C(4)	110.6(5)	O(2) — C(14) — C(8)	118.6(4)
C(3) — C(4) — C(5)	115.3(5)	O(2) — C(14) — C(13)	111.5(4)
C(4) — C(5) — C(6)	111.1(5)	O(2) — C(14) — C(15)	59.6(3)
C(4) — C(5) — C(10)	112.3(5)	C(8) — C(14) — C(13)	118.5(4)
C(6) — C(5) — C(10)	112.2(5)	C(8) — C(14) — C(15)	126.1(5)
C(5) — C(6) — C(7)	112.4(5)	C(13) — C(14) — C(15)	108.6(4)
C(6) — C(7) — C(8)	112.3(5)	O(2) — C(15) — C(14)	59.6(3)
C(7) — C(8) — C(9)	111.0(5)	O(2) — C(15) — C(16)	112.9(5)
C(7) — C(8) — C(14)	112.9(5)	C(14) — C(15) — C(16)	110.5(5)
C(9) — C(8) — C(14)	109.6(5)	C(15) — C(16) — C(17)	105.6(5)
C(8) — C(9) — C(10)	112.9(5)	C(13) — C(17) — C(16)	104.7(4)
C(8) — C(9) — C(11)	110.4(5)	C(13) — C(17) — C(20)	116.5(5)
C(10) — C(9) — C(11)	114.1(5)	C(16) — C(17) — C(20)	112.0(5)
C(1) — C(10) — C(5)	108.2(5)	C(17) — C(20) — C(21)	118.8(6)
C(1) — C(10) — C(9)	112.4(5)	C(17) — C(20) — C(22)	133.1(6)
C(1) — C(10) — C(19)	106.2(5)	C(21) — C(20) — C(22)	108.1(6)
C(5) — C(10) — C(9)	109.8(5)	O(3) — C(21) — C(20)	105.6(6)
C(5) — C(10) — C(19)	109.6(5)	O(3) — C(23) — O(4)	118.3(6)
C(9) — C(10) — C(19)	110.7(5)	O(3) — C(23) — C(22)	108.4(6)
C(9) — C(11) — C(12)	111.7(5)	O(4) — C(23) — C(22)	133.3(7)
C(11) — C(12) — C(13)	113.3(5)	C(20) — C(22) — C(23)	109.9(6)

TABLE IV

Endocyclic and Relevant Exocyclic Torsion Angles (°). Estimated Standard Deviations are in Parentheses

Ring A	C(1) — C(2) — C(3) — C(4)	—53.0(5)
	C(2) — C(3) — C(4) — C(5)	50.3(5)
	C(3) — C(4) — C(5) — C(10)	—50.9(5)
	C(4) — C(5) — C(10) — C(1)	51.2(5)
	C(5) — C(10) — C(1) — C(2)	—56.3(5)
	C(10) — C(1) — C(2) — C(3)	58.6(5)
Ring B	C(5) — C(6) — C(7) — C(8)	53.8(5)
	C(6) — C(7) — C(8) — C(9)	—52.6(5)
	C(7) — C(8) — C(9) — C(10)	53.5(5)
	C(8) — C(9) — C(10) — C(5)	—54.2(5)
	C(9) — C(10) — C(5) — C(6)	54.2(5)
	C(10) — C(5) — C(6) — C(7)	—55.1(5)
Ring C	C(8) — C(9) — C(11) — C(12)	56.1(5)
	C(9) — C(11) — C(12) — C(13)	—58.1(5)
	C(11) — C(12) — C(13) — C(14)	52.4(4)
	C(12) — C(13) — C(14) — C(8)	—52.3(4)
	C(13) — C(14) — C(8) — C(9)	53.4(5)
	C(14) — C(8) — C(9) — C(11)	—52.0(4)
Ring D	C(13) — C(14) — C(15) — C(16)	—0.7(4)
	C(14) — C(15) — C(16) — C(17)	15.1(4)
	C(15) — C(16) — C(17) — C(13)	—22.8(4)
	C(16) — C(17) — C(13) — C(14)	22.3(4)
	C(17) — C(13) — C(14) — C(15)	—13.8(4)
	O(1) — C(3) — C(2) — C(1)	66.9(5)
	O(1) — C(3) — C(4) — C(5)	—71.5(5)
	O(2) — C(14) — C(13) — C(17)	50.1(3)
	O(2) — C(15) — C(16) — C(17)	—49.5(4)
	C(15) — C(16) — C(17) — C(20)	104.3(5)
	C(13) — C(17) — C(20) — C(21)	—106.1(6)
	C(13) — C(17) — C(20) — C(22)	75.9(7)
	C(21) — O(3) — C(23) — O(4)	—179.7(7)

resembles that of digitoxigenin depicted in Figure 1/b. (It was computed from the inverted coordinates given in ref. 1.) As expected, the strained oxirane ring formed between C(14) and C(15) atoms alters the conformation of ring D. It moves from the most frequently observed ^{14}E form to an unusual ^{17}E envelope, while the puckering amplitude[8] (Q) decreases significantly (Table V).

The oxirane ring has the same effect on ring D in cinobufagin.* Naturally, due to the presence of an additional 16-acetyl moiety its envelope form, as shown clearly by the lowest assymmetry factors[9] (Table V), is less perfect than in the title compound.

TABLE V

The Puckering Parameters[8] and the Lowest Asymmetry Factors[9] for the Title Compound, Digitoxigenin[1] and Cinobufagin.[3]

	Q/pm	φ/°	f C_S/pm
digitoxigenin	34.4	32.8	1.9 at C(14)
digirezigenin	23.5	322.9	0.5 at C(17)
cinobufagin	23.9	319.6	1.8 at C(17)

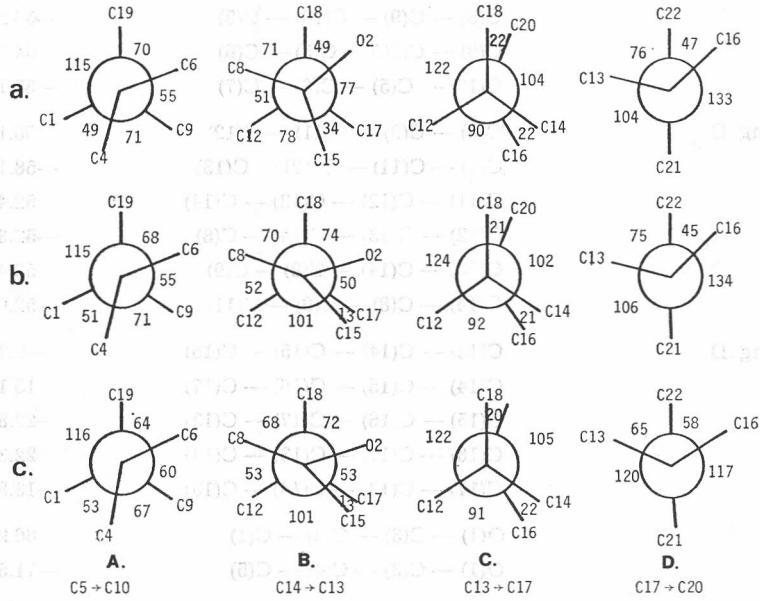


Figure 2. Newman projections showing the characteristic moieties for digitoxigenin (a), digirezigenin (b) and cinobufagin (c)

The effect of the oxirane ring on the *cis*-C/D junction is shown by the Newman projections in column B of Figure 2. The C(13) — C(17) and C(14) — C(15) bonds are almost eclipsed both in the title compound and in cinobufagin. No significant difference can be seen, of course, about the other flexible *cis*-A/B junctions depicted in column A. Similarly the Newman projections perpendicular to C(13) — C(17) and the exocyclic C(17) — C(20) bonds (columns C and D) do not exhibit noticeable differences, from which it follows that the γ-lactone rings in the title compound and digitoxigenin do not assume different confor-

* The still unpublished atomic coordinates of cinobufagin were kindly provided by Professor G. S. D. King (Catholic University of Leuwen, Belgium) in 1982.

mations about the exocyclic C(17) — C(20) bond. The δ-lactone ring in the cinobufagin rotates somewhat (by ca. 12—15°) out of this position. Consequently, only the alteration in the conformation of ring D can account for the small difference (33.2 pm) in the positioning of the lactone carbonyl O, computed from the best superpositions of atoms C(1) — C(14) [rings A, B and C], C(18) and C(19) of the title compound with those of digitoxigenin by the use of the ABCLS program[10]. The average deviation of the fitted 16 atoms is 7.2 pm. Since in the title compound C(17) is on the flap of the envelope assumed by D ring the lactone ring is bent out by an average 28.1 pm from the plane occupied in digitoxigenin. Due to the formation of the epoxy ring, O(2) departs by 68.8 pm from the position occupied in digitoxigenin. The epoxy ring shortens the C(14) — C(15) from 150.8(12) to 146.9(5) pm and with the two C—O bonds (both 145.2(4) pm large) forms three bond angles of 60° (within the 3σ limit). The plane of this triangle makes a dihedral angle of 81.7(2)° with the least squares plane of ring D. Similar geometry was found in cinobufagin and in 3,5-dimethyl-2',3':0^6,5'-dianhydrouridine[11].

As observed by Karle and Karle[1] in digitoxigenin there is only one hydrogen bond chain formed by O(1) — H ... O(4) linkages parallel to the *b* axis while O(2) — H does not participate in any hydrogen bonding.* Accordingly, the altered function of O(2) (hydroxyl to opoxy) does not affect the formation of the hydrogen bonds in digirezigenin. It possesses the same infinite O(1) — H ... O(4) chain parallel to the *b* axis with the following parameters:

	O ... O	H ... O	∢ OH ... O
O(1) — H(x, y, z) ... O(4) (x, 1 + y, z)	290.2(4)	212(3) pm	160(3)°

This packing of the molecules may, along with the similar features of the molecules account for the phenomenon that crystals of digirezigenin and digitoxigenin are quasi-isostructural.

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* It should be noted, however, that O(2) hydroxyl groups in general take part in forming hydrogen bonds e. g. in the crystals of the related bufalin[12] (δ-lactone analogue of digitoxigenin) and its precursors.[13]

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SAŽETAK

Kristalna i molekulska struktura 3β-hidroksi-14,15β-epoksi-5β,14β-kard-20,22-enolida (Digirezigenin)

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Istraživani spoj $C_{23}H_{32}O_4$ i njegov metil-suberatni ester otkriveni su u Ch'an Su, osušenom otrovu kineske žabe. Kristali su rompski, prostorna grupa $P2_12_12_1$, i kvazi-izostrukturni sličnom spoju digitoksigeninu ($C_{23}H_{34}O_4$). Struktura je riješena direktnim metodama i utočnjena metodom najmanjih kvadrata do indeksa $R = 0{,}059$ za 2271 neovisan difraktometrijski podatak. Prisutnost krutog 14,15β-epoksi-prstena znatno mijenja oblik D-prstena (^{17}E) u usporedbi s onim u digitoksigeninu (^{14}D). To pak malo utječe na osnovni skelet 14-izo-etiokolana i konformaciju γ-laktonskog prstena. Kut rotacije oko veze C(17) — C(20) neznatno se promijenio, a udaljenost karbonilnog O relativno prema digitoksigeninu iznosi samo 33,2 pm. Dana je usporedba bufa-20,22-dienolida (cinobufagina) koji također sadržava 14,15β-oksiranski prsten.