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'Main-Part' Isostructuralism of Several Cardenolides and Bufadienolides. Structures of Three Cardenolides: (21*S*)-Methyldigitoxigenin, Uzarigenin and Sarmentogenin Methanol Solvate*

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Abstract

'Main-part' isostructuralism is a recurrent phenomenon among cardiotonic steroids. Here (21*S*)-methyldigitoxigenin is found to be isostructural with digitoxigenin [and with 3-*epi*-digitoxigenin, (21*R*)-methyldigitoxigenin and digirezigenin], a fact which allowed the structure amplitudes to be phased using the position of 21 non-H atoms of the 14-isoaethiocholane skeleton. The limits of the phenomenon have been studied by a structure analysis of uzarigenin which differs from digitoxigenin only in its *A*/*B* ring junction but which exhibits a fundamentally different type of packing. Besides the different position of ring *A*, this may also be attributed to the different degree of rotation ($\Delta\varphi \simeq 180°$) of the γ-lactone ring about the C(17)—C(20) bond. The earlier observation that the two energetically favourable conformations of the γ-lactone moiety may occur in the cardenolide structures with almost the same probability is supported by the fact that the crystal of the 1:1 sarmentogenin–methanol adduct contains both conformers, each of which was found either in digitoxigenin or in uzarigenin. These facts help to clarify the conditions and restrictions of isostructuralism not only among digitoxigenin and its derivatives but also between several pairs of analogous bufadienolides. (21*S*)-Methyldigitoxigenin [(21*S*)-3β,14-dihydroxy-21-methyl-5β,14β-card-20(22)-enolide], $C_{24}H_{36}O_4$, $M_r = 388{\cdot}55$, orthorhombic, $P2_12_12_1$, $a = 7{\cdot}193$ (1), $b = 15{\cdot}208$ (3), $c = 19{\cdot}277$ (4) Å, $V = 2108{\cdot}8$ (9) Å^3, $Z = 4$, $D_x = 1{\cdot}224$ g cm^{-3}, λ(Mo $K\alpha$) = 0·71073 Å, $\mu = 0{\cdot}76$ cm^{-1}, $F(000) = 848$, $R = 0{\cdot}049$ for 1754 unique observed reflections. Uzarigenin [3β,14-dihydroxy-5α,14β-card-20(22)-enolide], $C_{23}H_{34}O_4$, $M_r = 374{\cdot}53$, monoclinic, $P2_1$, $a = 6{\cdot}370$ (3), $b = 12{\cdot}072$ (4), $c = 13{\cdot}024$ (3) Å, $\beta = 99{\cdot}87$ (3)°, $V = 986{\cdot}7$ (1·1) Å^3, $Z = 2$, $D_x = 1{\cdot}261$ g cm^{-3}, λ(Mo $K\alpha$) = 0·71073 Å, $\mu = 0{\cdot}79$ cm^{-1}, $F(000) = 408$, $R = 0{\cdot}040$ for 1950 unique observed reflections. Sarmentogenin [3β,11α,14-trihydroxy-5β,14β-card-20(22)-enolide] methanol solvate, $C_{23}H_{34}O_5.CH_3OH$, $M_r = 442{\cdot}57$, orthorhombic, $P2_12_12_1$, $a = 16{\cdot}678$ (5), $b = 13{\cdot}332$ (4), $c = 10{\cdot}063$ (3) Å, $V = 2238$ (2) Å^3, $Z = 4$, $D_x = 1{\cdot}254$ g cm^{-3} λ(Mo $K\alpha$) = 0·71073 Å, $\mu = 0{\cdot}83$ cm^{-1}, $F(000) = 920$, $R = 0{\cdot}051$ for 1840 unique observed reflections.

Introduction

Recognition of isostructuralism between digitoxigenin (I) (Karle & Karle, 1969) and digirezigenin (II) (Kálmán, Argay, Ribár, Vladimirov & Živanov-Stakić, 1984) as well as between the two bufadienolides arenobufagin and gamabufotalin (Argay, Kálmán, Ribár, Vladimirov & Živanov-Stakić, 1987), prompted a systematic survey of all cardenolide and related bufadienolide structures (Kálmán, Argay, Fülöp, Ribár & Lazar, 1987). The survey led to the conclusion that 3-*epi*-digitoxigenin (III) (Messerschmidt, Höhne & Megges, 1981) and (21*R*)-methyldigitoxigenin (IV) (Prasad & Gabe, 1983) are also isostrucutral with (I) and (II). Evidence for this is provided by the similar unit-cell parameters and common space group $P2_12_12_1$ (Table 1). These cardenolides (γ lactones) and bufadienolides (δ lac-

* Dedicated to Professor Dorothy Crowfoot Hodgkin Nobel Laureate on her 80th birthday and also commemorating her early report on the lattice parameters of cinobufagin (Crowfoot, 1935).

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Table 1. *Lattice parameters (space group $P2_12_12_1$) and densities with e.s.d.'s in parentheses*

	a (Å)	b (Å)	c (Å)	D_x (Mg m^{-3})	Ref.
Digitoxigenin (I)	7·250 (2)	15·015 (4)	18·464 (8)	1·238	*a*
Digirezigenin (II)	7·288 (2)	14·686 (3)	18·480 (3)	1·251	*b*
3-*epi*-Digitoxigenin (III)	7·279 (3)	14·685 (9)	18·541 (10)	1·255	*c*
(21*R*)-Methyldigitoxigenin (IV)	7·249 (1)	15·109 (1)	19·268 (3)	1·223	*d*
(21*S*)-Methyldigitoxigenin (V)	7·193 (1)	15·208 (3)	19·277 (4)	1·224	*e*
Scillarenin (IX)	10·387 (2)	12·075 (4)	16·431 (6)	1·239	*f*
Bufalin (X)	10·726 (1)	12·381 (2)	15·717 (1)	1·230	*g*
Gamabufotalin (XI)	7·850 (1)	14·766 (1)	17·836 (1)	1·293	*h*
Arenobufagin (XII)	7·826 (1)	14·864 (2)	17·841 (2)	1·333	*h*
Cinobufagin (XIII)	7·663 (2)	15·900 (5)	19·291 (5)	1·249	*i*/*j*
Cinobufotalin (XIV)	7·631 (1)	15·727 (5)	19·557 (2)	1·297	*j*

(*a*) Karle & Karle (1969); (*b*) Kálmán *et al.* (1984); (*c*) Messerschmidt *et al.* (1981); (*d*) Prasad & Gabe (1983); (*e*) present work; (*f*) reported as 3β,14-dihydroxy-14β-bufa-4,20,22-trienolide by Ribár *et al.* (1983); (*g*) parameters transformed in accordance with those of (IX), Rohrer *et al.* (1982); (*h*) Argay *et al.* (1987); (*i*) Declercq, Germain & King (1977); (*j*) Kálmán *et al.* (1988) and references therein to (XIII).

tones) can be described by the formula $C_{k+r}H_{l+s}O_{m+t}$, where k, l and m denote the number of common atoms in a pair (or group) of the compounds related by the phenomenon of 'isostructuralism', whereas r, s and t (0, ± 1, ± 2) express the difference(s) in their chemical composition (see Fig. 1).

Consequently, the term 'main-part' isostructuralism,* which refers to $C_kH_lO_m$, aims to express the deviation from full isostructuralism defined in general as follows: "Two or more compounds whose atoms are arranged in the same type of crystal structure are said to be isostructural. ... *Isostructuralism* is occasionally called *isotypism* or less desirably *isomorphism*" (Bloss, 1971). In this conventional 'isostructuralism' each related group of compounds can be characterized by a general formula in which the quality of the constituent atoms is changed whilst their relative quantity remains constant.

This work attempts to describe the characteristic features (even the limits) of this phenomenon. Three structure determinations, relevant to the topic, are also reported. The resemblance between the lattice parameters of (21*S*)-methyldigitoxigenin (V) and the other cardenolides (Kálmán *et al.*, 1987) prompted solution of the phase problem (impossible by direct methods) by the use of phases computed from the coordinates of the 21 atoms forming the skeleton of (IV).

A comparison of the crystal structures of (I) and (III), which differ only in the absolute configuration at C(3), suggests that isostructuralism may exist between these steroids even though there is one more hydrogen bond in (III) than in (I). Although there is a possibility that such a hydrogen bond exists in digitoxigenin the O(14)···O(3) separation (3·41 Å) is too large. The fact that (I) and (III) are isostructural in spite of epimerization about C(3) results in a difference of 2·08 Å. This observation prompted further investigations into how this persistent isostructuralism of cardenolides (I)–(V), which possess a flexible *cis*-*A*/*B* ring junction, responds to configurational isomerization about C(5). In order to answer this question the structure of uzarigenin (VI) was determined.

The fundamental difference between the γ-lactone ring conformation of (VI) and (I), which accompanies the different *A*/*B* ring junctions in the two compounds, made it desirable also to report the structure determination of sarmentogenin (VII). Taken together this group of compounds serves as a basis for a definition of the descriptors of the molecular 'main-part' isostructuralism shown by several pairs of the steroids (Table 1) based on the 14-isoaethiocholane skeleton and possessing a folded globular shape.

Experimental

(21*S*)-Methyldigitoxigenin (V). Data collected on a crystal of dimensions 0·3 × 0·4 × 0·7 mm obtained from methanol and mounted on a CAD-4 diffractometer (Berlin); graphite-monochromated Mo $K\alpha$ radiation. Cell constants were refined by least-squares fit for 25 reflections with $8 \le \theta \le 14°$. Systematic absences $h00$: $h = 2n+1$, $0k0$: $k = 2n+1$, $00l$: $l = 2n+1$. Data were collected by $\omega/2\theta$ scan in the range $0{\cdot}037 \le (\sin\theta)/\lambda \le 0{\cdot}595$ Å^{-1} with h 0 to 8, k 0 to 18, l 0 to 22. Of 2137 unique and non-systematically absent reflections, 1754 with $I \ge \sigma(I)$ were taken as observed. Data were not corrected for absorption. Since the solution of the phase problem by direct methods failed, the observed structure amplitudes were assigned the same phases as computed from the coordinates of the 21 skeletal atoms pertaining to the diastereomeric structure (IV). With 254 variables the structure could be refined (anisotropic non-H atoms) to a final R value of 0·049 ($wR = 0{\cdot}050$, $R_{tot} = 0{\cdot}066$, $S = 0{\cdot}92$); $(\Delta/\sigma)_{max} = 0{\cdot}1$. Maximum and minimum peak heights in final difference map = 0·17 e Å^{-3}. Positions of H atoms bound to C atoms were generated from assumed geometry, while those linked to O atoms were located in a difference Fourier map. Their positions were taken into account without refinement in the structure-factor calculations with a common isotropic temperature factor (5 Å^2). Scattering factors were taken from the *SDP* program system (Enraf–Nonius, 1982) adapted on a PDP 11/34 minicomputer.

Uzarigenin (VI) was isolated from the plant *Uzara*. Data collected on a crystal of dimensions 0·74 × 0·31 × 0·31 mm obtained from methanol (m.p. 421–

* In a previous paper this concept was termed temporarily as quasi-isostructurality (Kálmán, Fülöp, Argay, Ribár, Lazar, Živanov-Stakić & Vladimirov, 1988).

425 K) and mounted on a CAD-4 diffractometer (Ljubljana); graphite-monochromated Mo $K\alpha$ radiation. Cell constants were refined by least-squares fit for 25 reflections with $6 \le \theta \le 11°$. Systematic absences $0k0$: $k = 2n + 1$. Data were collected by $\omega/2\theta$ scan in the range $0{\cdot}025 \le (\sin\theta)/\lambda \le 0{\cdot}704$ Å^{-1} with h −8 to 8, k 0 to 16, l 0 to 18. Standard reflections (201, 1$\bar{3}$2, 200) were monitored every 120 min but no intensity variations were recorded. Of 2974 unique reflections, 1950 with $I > 2\sigma(I)$ were taken as observed. The phase problem was solved using the program *SHELX*76 (Sheldrick, 1976). Full-matrix least-squares refinement minimized $\sum w(\Delta F)^2$ for 244 parameters with $w = 4F_o^2/\sigma^2(F_o^2)$. Neither absorption nor extinction corrections applied. Final $R = 0{\cdot}040$ ($wR = 0{\cdot}043$, $R_{tot} = 0{\cdot}068$, $S = 0{\cdot}51$); $(\Delta/\sigma)_{max} = 0{\cdot}02$. Maximum and minimum peak heights in final difference map = $\pm 0{\cdot}22$ e Å^{-3}. H atoms as for (V) but with B

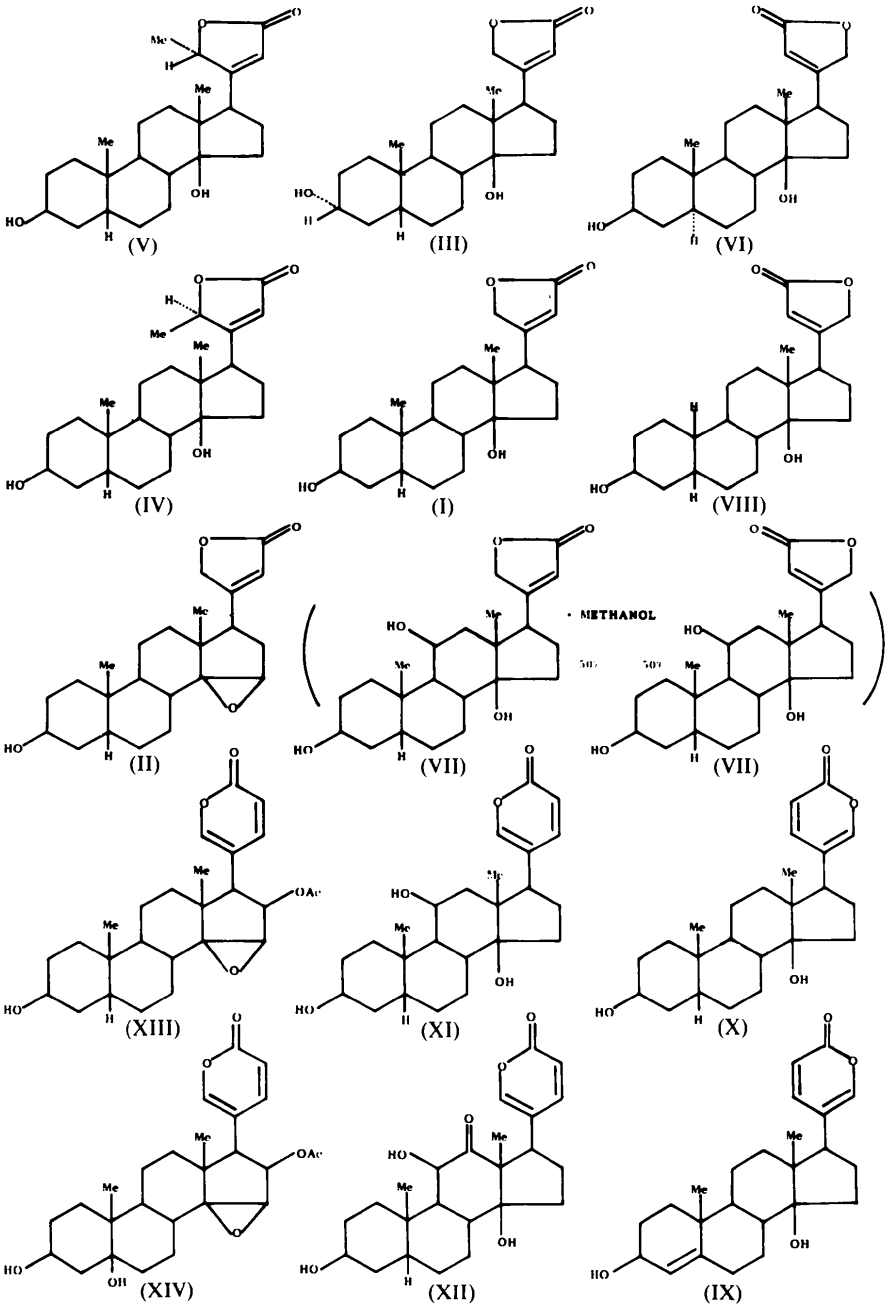

Fig. 1. Structures of some cardenolides and bufadienolides.

values 1Å^2 greater than those of the atoms to which they are bonded. Scattering factors were taken from the program system *SDP-Plus* (Enraf–Nonius, 1982) adapted on a PDP 11/34 minicomputer (Budapest) with local modifications.

Sarmentogenin (VII) was isolated primarily from the dried venom of the Chinese toad Ch'an Su by combined chromatographic methods (Argay *et al.*, 1987, and references therein). It can also be isolated from the plant *Strophanthus Semen*. Data collected on a crystal of dimensions 0·4 × 0·2 × 0·2 mm obtained from a 1:1 mixture of methanol and ethyl acetate (m.p. 546–551 K) and mounted on a Philips PW 1100 diffractometer (Zagreb); graphite-monochromated Mo $K\alpha$ radiation. Cell constants were refined by least-squares fit for 18 reflections. Systematic absences $h00$: $h = 2n + 1$, $0k0$: $k = 2n + 1$, $00l$: $l = 2n + 1$. Data were collected by $\omega/2\theta$ scan in the range $0{\cdot}053 \le (\sin\theta)/\lambda \le 0{\cdot}499$ Å^{-1} with h 0 to 23, $k = 0$ to 18, $l = 0$ to 13. Of 2222 unique reflections, 1837 with $I > 3\sigma(I)$ were taken as observed. Final $R = 0{\cdot}051$ ($wR = 0{\cdot}052$, $R_{tot} = 0{\cdot}071$, $S = 1{\cdot}05$). Maximum and minimum peak heights in final difference map = ±0·25 (3) e Å^{-3}. Extinction coefficient 3·76 × 10^{-6} (Zachariasen, 1963). $(\Delta/\sigma)_{max} = 0{\cdot}54$. Difference Fourier syntheses revealed the conformational disorder of the γ-lactone ring. Occupancy factors were refined for atoms C(21), C(22), C(23), O(21) and O(23) assuming two distinct positions marked *A* and *B* in Figs. (2*c*) and (2*d*). For each atom they converged to 0·5 within experimental error. Although C(25) in the methanol molecule exhibited larger anisotropic displacement parameters, no positional disorder could be established. H-atom treatment was as for (VI).

Discussion

Characteristics of the three crystal structures

Atomic coordinates of non-H atoms for (V), (VI) and (VII) are listed in Table 2.* The bond lengths and angles for non-H atoms are given in Tables 3 and 4. A perspective view of each molecule is shown in Fig. 2. Packing diagrams are depicted in Figs. 3, 4 and 5.

The conformation of the 14-isoaethiocholane skeleton in (21*S*)-methyldigitoxigenin (V), including the flexible *D* ring, is basically similar to that observed in (I) and (III) whereas the position of the γ-lactone ring around the C(17)—C(20) bond [measured by the

* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 53456 (36 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Fractional coordinates for non-*H *atoms with e.s.d.'s in parentheses*

$B_{eq} = \frac{4}{3}$ trace (BG), where **G** is the metric tensor.

	x	y	z	B_{eq}(Å^2)
(21*S*)-Methyldigitoxigenin (V)				
O(3)	0·6657 (6)	0·4443 (2)	0·7131 (2)	5·4 (1)
O(14)	0·7201 (5)	0·9741 (2)	0·7045 (1)	3·8 (1)
O(21)	0·6242 (6)	1·2310 (2)	0·5280 (2)	6·8 (1)
O(23)	0·7415 (7)	1·3077 (2)	0·6160 (2)	9·6 (1)
C(1)	0·5015 (8)	0·5840 (3)	0·6248 (3)	4·7 (1)
C(2)	0·6833 (9)	0·5377 (3)	0·6107 (2)	5·4 (1)
C(3)	0·7771 (8)	0·5090 (3)	0·6774 (3)	5·0 (1)
C(4)	0·8021 (7)	0·5874 (3)	0·7260 (2)	4·2 (1)
C(5)	0·6189 (6)	0·6370 (3)	0·7399 (2)	3·3 (1)
C(6)	0·6574 (8)	0·7148 (3)	0·7880 (2)	4·2 (1)
C(7)	0·7548 (7)	0·7903 (3)	0·7511 (2)	4·0 (1)
C(8)	0·6446 (6)	0·8201 (2)	0·6874 (2)	2·8 (1)
C(9)	0·6167 (6)	0·7426 (3)	0·6366 (2)	2·9 (1)
C(10)	0·5163 (6)	0·6642 (3)	0·6728 (2)	3·3 (1)
C(11)	0·5222 (7)	0·7730 (3)	0·5705 (2)	3·8 (1)
C(12)	0·6197 (7)	0·8514 (3)	0·5382 (2)	3·5 (1)
C(13)	0·6349 (5)	0·9319 (2)	0·5869 (2)	2·7 (1)
C(14)	0·7289 (6)	0·9035 (2)	0·6548 (2)	2·7 (1)
C(15)	0·9354 (6)	0·8965 (3)	0·6355 (2)	3·5 (1)
C(16)	0·9690 (6)	0·9705 (3)	0·5831 (3)	4·3 (1)
C(17)	0·7784 (6)	0·9972 (3)	0·5528 (2)	3·0 (1)
C(18)	0·4417 (6)	0·9723 (3)	0·5982 (3)	4·0 (1)
C(19)	0·3124 (7)	0·6890 (3)	0·6931 (3)	5·2 (1)
C(20)	0·7357 (6)	1·0938 (3)	0·5596 (2)	3·3 (1)
C(21)	0·6250 (7)	1·1410 (3)	0·5051 (3)	4·7 (1)
C(22)	0·7892 (8)	1·1508 (3)	0·6068 (2)	4·6 (1)
C(23)	0·7225 (8)	1·2381 (3)	0·5882 (3)	6·0 (1)
C(211)	0·7013 (9)	1·1358 (4)	0·4322 (3)	6·2 (1)
Uzarigenin (VI)				
O(3)	1·0361 (4)	0·0000	−0·3169 (1)	4·2 (1)
O(14)	0·5346 (3)	−0·0053 (2)	0·2868 (1)	3·0 (1)
O(21)	0·4322 (4)	0·0979 (3)	0·5956 (2)	4·6 (1)
O(23)	0·4693 (5)	0·2570 (3)	0·6842 (2)	5·9 (1)
C(1)	1·1115 (5)	0·1240 (3)	−0·0439 (2)	2·8 (1)
C(2)	1·1106 (5)	0·1192 (3)	−0·1624 (2)	3·3 (1)
C(3)	1·0459 (5)	0·0052 (3)	−0·2057 (2)	3·1 (1)
C(4)	0·8301 (5)	−0·0278 (3)	−0·1802 (2)	2·9 (1)
C(5)	0·8355 (5)	−0·0247 (3)	−0·0620 (2)	2·4 (1)
C(6)	0·6332 (5)	−0·0705 (3)	−0·0302 (2)	3·0 (1)
C(7)	0·6538 (5)	−0·0789 (3)	0·0876 (2)	3·1 (1)
C(8)	0·7189 (5)	0·0325 (3)	0·1412 (2)	2·4 (1)
C(9)	0·9218 (4)	0·0801 (2)	0·1065 (2)	2·3 (1)
C(10)	0·8942 (4)	0·0910 (2)	−0·0140 (2)	2·3 (1)
C(11)	0·9873 (5)	0·1886 (3)	0·1639 (2)	3·0 (1)
C(12)	1·0124 (5)	0·1765 (3)	0·2825 (2)	2·9 (1)
C(13)	0·8093 (5)	0·1334 (3)	0·3191 (2)	2·4 (1)
C(14)	0·7422 (4)	0·0238 (2)	0·2612 (2)	2·4 (1)
C(15)	0·9067 (5)	−0·0597 (3)	0·3139 (2)	2·8 (1)
C(16)	0·9384 (5)	−0·0285 (3)	0·4299 (2)	3·3 (1)
C(17)	0·8773 (5)	0·0955 (3)	0·4354 (2)	2·7 (1)
C(18)	0·6354 (6)	0·2230 (3)	0·3024 (2)	3·3 (1)
C(19)	0·7271 (5)	0·1803 (3)	−0·0555 (2)	3·1 (1)
C(20)	0·7171 (5)	0·1190 (3)	0·5056 (2)	2·8 (1)
C(21)	0·5437 (6)	0·0415 (4)	0·5233 (3)	4·3 (1)
C(22)	0·7080 (6)	0·2075 (3)	0·5644 (3)	3·7 (1)
C(23)	0·5288 (6)	0·1962 (3)	0·6215 (3)	4·0 (1)
Sarmentogenin (VII) methanol solvate				
O(3)	0·0840 (2)	0·7290 (3)	0·1144 (3)	3·3 (1)
O(11)	0·3563 (2)	0·4937 (2)	0·2798 (4)	3·1 (1)
O(14)	0·5617 (1)	0·8150 (2)	0·1547 (3)	2·3 (1)
C(1)	0·2242 (2)	0·5868 (3)	0·1429 (5)	2·6 (2)
C(2)	0·1814 (3)	0·6407 (4)	0·2558 (5)	3·1 (2)
C(3)	0·1483 (3)	0·7421 (4)	0·2088 (5)	3·1 (2)
C(4)	0·2139 (2)	0·8038 (4)	0·1437 (5)	2·7 (2)
C(5)	0·2616 (2)	0·7474 (4)	0·0343 (4)	2·3 (1)
C(6)	0·3265 (3)	0·8148 (4)	−0·0231 (5)	2·6 (2)
C(7)	0·3936 (3)	0·8332 (3)	0·0776 (5)	2·5 (2)
C(8)	0·4306 (2)	0·7351 (3)	0·1257 (4)	1·9 (1)
C(9)	0·3663 (2)	0·6618 (3)	0·1831 (5)	1·9 (1)
C(10)	0·2958 (2)	0·6443 (3)	0·0823 (5)	2·0 (1)
C(11)	0·4110 (2)	0·5650 (3)	0·2244 (5)	2·1 (1)
C(12)	0·4740 (2)	0·5890 (3)	0·3280 (5)	2·2 (1)
C(13)	0·5409 (2)	0·6605 (3)	0·2801 (5)	2·1 (1)
C(14)	0·5011 (2)	0·7569 (3)	0·2229 (4)	2·0 (1)
C(15)	0·4790 (3)	0·8170 (3)	0·3459 (5)	2·5 (1)
C(16)	0·5515 (3)	0·8046 (4)	0·4378 (5)	3·2 (2)
C(17)	0·5851 (3)	0·6993 (4)	0·4103 (5)	2·6 (2)
C(18)	0·5951 (3)	0·6078 (3)	0·1798 (5)	2·5 (2)

Table 2 (*cont.*)

	x	*y*	*z*	B_{eq}(Å^2)
C(19)	0·3241 (3)	0·5843 (4)	−0·0408 (5)	2·9 (2)
C(20)	0·6753 (2)	0·6963 (3)	0·4053 (4)	2·9 (1)
C(21*A*)*	0·7171 (6)	0·6019 (9)	0·4547 (17)	6·7 (7)
C(22*A*)*	0·7296 (5)	0·7717 (8)	0·3683 (11)	3·9 (4)
C(23*A*)*	0·8107 (6)	0·7222 (15)	0·3809 (14)	8·2 (8)
O(21*A*)*	0·8019 (4)	0·6303 (6)	0·4285 (10)	6·0 (4)
O(23*A*)*	0·8747 (3)	0·7653 (7)	0·3634 (8)	5·1 (3)
C(21*B*)*	0·7282 (5)	0·7693 (7)	0·3670 (10)	3·4 (3)
C(22*B*)*	0·7220 (5)	0·6154 (6)	0·4416 (9)	3·1 (3)
C(23*B*)*	0·8048 (5)	0·6390 (8)	0·4208 (12)	4·3 (4)
O(21*B*)*	0·8085 (3)	0·7327 (4)	0·3760 (6)	3·5 (2)
O(23*B*)*	0·8606 (5)	0·5847 (8)	0·4243 (11)	7·9 (5)
O(24)†	0·4774 (2)	0·9020 (4)	0·7596 (5)	6·7 (2)
C(25)†	0·4752 (7)	1·0034 (8)	0·7594 (15)	11·9 (7)

* Occupation factor 0·5.
† Methanol atoms.

Table 3. *Bond lengths* (Å) *with e.s.d.'s in parentheses*

	(V)	(VI)	(VII) *A*	(VII) *B*
C(1)—C(2)	1·510 (8)	1·543 (5)	1·522 (8)	
C(1)—C(10)	1·535 (7)	1·553 (4)	1·545 (7)	
C(2)—C(3)	1·516 (7)	1·517 (6)	1·535 (9)	
C(3)—C(4)	1·527 (6)	1·522 (4)	1·517 (8)	
C(3)—O(3)	1·444 (6)	1·440 (4)	1·444 (7)	
C(4)—C(5)	1·542 (7)	1·534 (5)	1·553 (7)	
C(5)—C(6)	1·529 (6)	1·524 (4)	1·520 (7)	
C(5)—C(10)	1·546 (6)	1·549 (5)	1·564 (7)	
C(6)—C(7)	1·522 (7)	1·521 (5)	1·530 (8)	
C(7)—C(8)	1·530 (6)	1·538 (5)	1·524 (7)	
C(8)—C(9)	1·545 (5)	1·550 (4)	1·562 (7)	
C(8)—C(14)	1·540 (5)	1·549 (5)	1·558 (7)	
C(9)—C(10)	1·559 (6)	1·555 (5)	1·569 (7)	
C(9)—C(11)	1·516 (6)	1·530 (5)	1·547 (7)	
C(10)—C(19)	1·564 (7)	1·546 (5)	1·549 (8)	
C(11)—C(12)	1·517 (6)	1·533 (5)	1·515 (7)	
C(11)—O(11)			1·430 (6)	
C(12)—C(13)	1·547 (5)	1·544 (4)	1·544 (7)	
C(13)—C(14)	1·535 (5)	1·546 (5)	1·557 (7)	
C(13)—C(17)	1·576 (6)	1·571 (5)	1·590 (7)	
C(13)—C(18)	1·535 (6)	1·537 (5)	1·526 (7)	
C(14)—C(15)	1·535 (6)	1·529 (5)	1·519 (7)	
C(14)—O(14)	1·440 (4)	1·461 (3)	1·447 (6)	
C(15)—C(16)	1·531 (7)	1·536 (5)	1·531 (8)	
C(16)—C(17)	1·545 (6)	1·552 (6)	1·537 (8)	
C(17)—C(20)	1·507 (6)	1·510 (4)	1·506 (7)	
C(20)—C(21)	1·501 (7)	1·494 (6)	1·522 (14)	1·368 (11)
C(20)—C(22)	1·314 (6)	1·322 (6)	1·403 (12)	1·379 (10)
C(21)—O(21)	1·438 (6)	1·444 (5)	1·487 (14)	1·429 (11)
C(21)—C(211)	1·511 (8)			
O(21)—C(23)	1·363 (7)	1·352 (6)	1·324 (21)	1·329 (14)
C(22)—C(23)	1·457 (7)	1·471 (5)	1·511 (17)	1·432 (13)
C(23)—O(23)	1·194 (6)	1·207 (5)	1·224 (15)	1·180 (14)
O(24)—C(25)	–	–	1·352 (13)	

Table 4. *Bond angles* (°) *with e.s.d.'s in parentheses*

	(V)	(VI)	(VII) *A*	(VII) *B*
C(2)—C(1)—C(10)	114·8 (7)	113·0 (5)	115·0 (8)	
C(1)—C(2)—C(3)	111·5 (7)	111·1 (5)	110·8 (8)	
C(2)—C(3)—O(3)	110·7 (7)	112·0 (5)	111·3 (8)	
C(4)—C(3)—O(3)	107·8 (7)	108·8 (5)	108·5 (8)	
C(2)—C(3)—C(4)	110·4 (7)	110·7 (5)	110·5 (8)	
C(3)—C(4)—C(5)	112·8 (7)	110·3 (5)	114·4 (8)	
C(4)—C(5)—C(6)	109·2 (6)	112·9 (5)	110·4 (7)	
C(4)—C(5)—C(10)	113·2 (6)	112·9 (5)	113·1 (7)	
C(6)—C(5)—C(10)	112·8 (6)	112·0 (5)	112·2 (7)	
C(5)—C(6)—C(7)	112·6 (7)	111·6 (5)	111·4 (8)	
C(6)—C(7)—C(8)	111·1 (6)	111·7 (5)	111·7 (7)	
C(7)—C(8)—C(9)	110·5 (6)	111·4 (5)	112·2 (7)	
C(7)—C(8)—C(14)	111·6 (6)	111·8 (5)	110·2 (7)	
C(9)—C(8)—C(14)	114·9 (5)	112·2 (4)	113·8 (7)	
C(8)—C(9)—C(10)	111·1 (6)	111·6 (4)	111·6 (7)	
C(8)—C(9)—C(11)	111·0 (6)	110·3 (5)	106·9 (7)	
C(10)—C(9)—C(11)	113·7 (6)	113·2 (5)	114·3 (7)	
C(1)—C(10)—C(5)	109·0 (6)	107·1 (4)	106·1 (7)	
C(1)—C(10)—C(9)	111·7 (6)	108·9 (4)	113·4 (7)	
C(1)—C(10)—C(19)	106·1 (6)	108·9 (5)	107·1 (7)	
C(5)—C(10)—C(9)	111·0 (6)	108·0 (4)	110·1 (7)	
C(5)—C(10)—C(19)	107·6 (6)	112·6 (5)	108·5 (7)	
C(9)—C(10)—C(19)	111·2 (6)	111·3 (5)	111·4 (7)	
C(9)—C(11)—C(12)	112·2 (6)	112·5 (5)	110·0 (7)	
C(11)—C(12)—C(13)	113·9 (6)	113·3 (5)	114·7 (7)	
C(12)—C(13)—C(14)	109·0 (5)	108·3 (5)	108·5 (7)	
C(12)—C(13)—C(17)	107·0 (5)	106·8 (5)	106·2 (7)	
C(12)—C(13)—C(18)	109·8 (6)	110·0 (5)	110·5 (7)	
C(14)—C(13)—C(17)	104·1 (5)	103·2 (4)	103·5 (7)	
C(14)—C(13)—C(18)	113·0 (6)	113·6 (5)	112·8 (7)	
C(17)—C(13)—C(18)	113·6 (6)	114·5 (5)	114·8 (7)	
C(8)—C(14)—O(14)	109·0 (5)	108·2 (4)	109·2 (6)	
C(13)—C(14)—O(14)	109·8 (5)	106·3 (4)	108·7 (6)	
C(15)—C(14)—O(14)	104·8 (5)	108·5 (4)	105·9 (7)	
C(8)—C(14)—C(13)	114·0 (5)	113·9 (4)	113·6 (7)	
C(8)—C(14)—C(15)	115·0 (6)	115·9 (5)	115·2 (7)	
C(13)—C(14)—C(15)	103·8 (5)	103·5 (4)	103·8 (7)	
C(14)—C(15)—C(16)	105·2 (6)	104·2 (5)	104·1 (7)	
C(15)—C(16)—C(17)	107·6 (6)	106·8 (5)	106·1 (8)	
C(13)—C(17)—C(16)	104·9 (6)	105·5 (5)	106·1 (7)	
C(13)—C(17)—C(20)	116·4 (6)	115·2 (5)	115·3 (7)	
C(16)—C(17)—C(20)	113·9 (6)	114·2 (5)	113·2 (8)	
C(17)—C(20)—C(21)	120·9 (7)	124·8 (6)	117·9 (11)	129·3 (10)
C(17)—C(20)—C(22)	130·1 (7)	127·2 (6)	129·4 (10)	125·1 (9)
C(21)—C(20)—C(22)	108·9 (7)	108·0 (6)	112·6 (13)	105·5 (11)
C(20)—C(21)—O(21)	104·0 (7)	105·4 (6)	99·6 (16)	110·0 (13)
C(21)—O(21)—C(23)	109·5 (7)	108·8 (6)	113·9 (18)	107·4 (13)
C(20)—C(22)—C(23)	109·5 (7)	109·4 (6)	104·0 (16)	109·5 (14)
O(21)—C(23)—O(23)	120·8 (9)	121·3 (7)	125·6 (24)	123·3 (19)
C(22)—C(23)—O(21)	108·0 (7)	108·4 (6)	109·6 (20)	107·5 (15)
C(22)—C(23)—O(23)	131·3 (9)	130·3 (7)	124·3 (22)	128·5 (19)
C(9)—C(11)—O(11)		–	110·7 (7)	
C(12)—C(11)—O(11)			108·4 (7)	
C(20)—C(21)—C(211)	115·7 (8)	–	–	
O(21)—C(21)—C(211)	109·7 (7)	–		

torsion angle φ = C(13)—C(17)—C(20)—C(22)] changes from 66 (1) (III) through 76 (2) (I) to 93 (1)° (V). Despite these small differences, the fractional atomic coordinates of the molecules in the similar orthorhombic cells are close to each other (Fig. 3). The molecules in each of the four crystal lattices [(I), (II), (IV) and (V)] are bound together by only one head-to-tail hydrogen-bond chain along the *b* axis (Table 5, bond No. 1). The O(14)···O(3)($1-x,\frac{1}{2}+y,\frac{1}{2}-z$) close contact mentioned above is somewhat shorter for (V) (3·23 Å) than for (IV) (3·31 Å) and (I) (3·41 Å), but still too long to be acceptable as a hydrogen bond. The bulky methyl group attached to digitoxigenin, giving rise either to the (21*S*) (V) or the (21*R*) (IV) configuration, does not change the crystal packing either. The packing coefficient† is the same for (IV) and (V) within experimental error, but somewhat (by 1·6%) less than that for digitoxigenin (I) (Table 6) which means that in both cases the crystal lattice can readily accommodate the bulky methyl group without altering the existing molecular packing.

Uzarigenin (VI), which displays the *A* and *E* ring positions shown in Fig. (2*b*), is not isostructural

† The packing coefficient (Dunitz, 1979) is defined as pc = V_M/V^*, where V^* is the volume for the asymmetric unit while V_M is the volume of the molecule calculated from the atomic coordinates with constant *X*—H distances (where *X* = C, N and O) and using the atomic radii recommended by Kitaigorodsky (1961) (r_C = 1·80, r_N = 1·58, r_O = 1·52 and r_H = 1·17 Å) by a program written by Mr Cs. Kertész (Budapest). This program computes atomic volume increments, taking into account the differences in their hybridizations and environments.

with digitoxigenin (I) (space groups: $P2_1$ *versus* $P2_12_12_1$). By rotation around C(17)—C(20) the γ-lactone ring assumes an orientation almost opposite to that found in (I). The corresponding torsion angles are $\varphi = -93\,(1)$ (VI) and $76\,(2)^\circ$ (I). These alterations, which result from substantial changes in the donor/acceptor positions, account for the differences in hydrogen bonding. Instead of the O(3)···O(23) hydrogen bond which is found in (I) (Fig. 3), in uzarigenin (Fig. 4) there is a weak

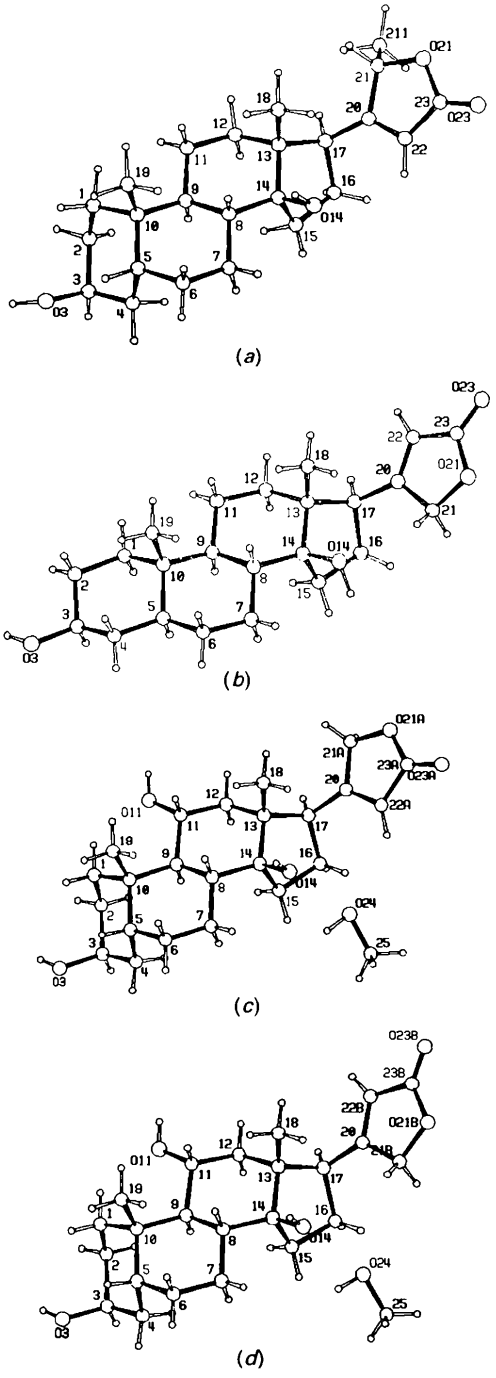

Fig. 2. Perspective views of molecules: (*a*) (21*S*)-methyldigitoxigenin (V); (*b*) uzarigenin (VI); (*c*) sarmentogenin, conformer (VII*A*); (*d*) conformer (VII*B*).

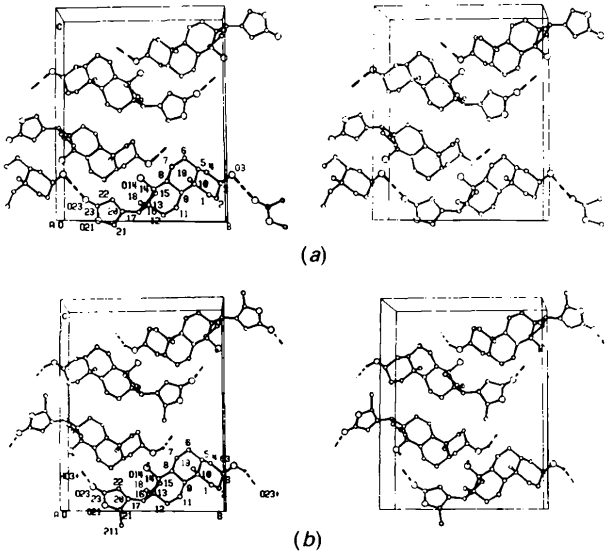

Fig. 3. Stereoscopic views of the molecular packing of (*a*) digitoxigenin (I) (Karle & Karle, 1969) and (*b*) (21*S*)-methyldigitoxigenin (V) showing their isostructuralism. H atoms are omitted. The head-to-tail hydrogen bond O(3)—H···O(23) is formed by translation along *b*.

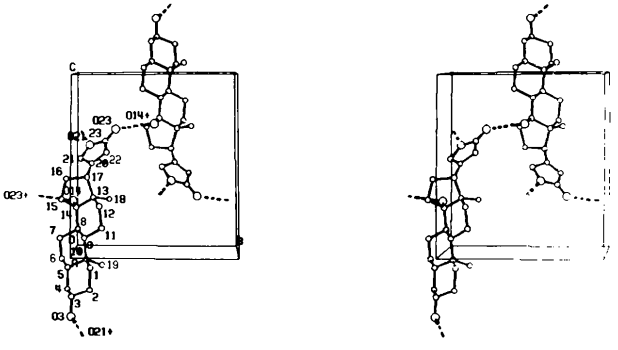

Fig. 4. Stereoscopic view of the molecular packing of uzarigenin (VI) showing hydrogen bonds.

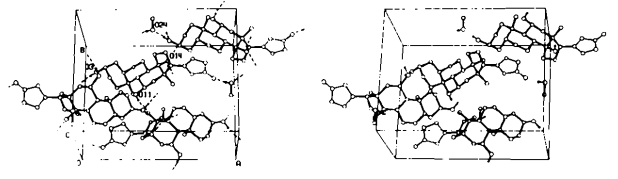

Fig. 5. Stereoscopic view of the molecular packing of sarmentogenin (VII) methanol solvate. Only conformer *B* is shown.

Table 5. *Intermolecular hydrogen bonds for* (V), (VI) *and* (VII)

No.	Compound	Donor	Acceptor	Symmetry relation	H···O (Å)	O···O (Å)	OH···O (°)
1	(V)	O(3)—H	O(23)	$(x, y+1, z)$	1·84 (2)	2·849 (5)	150·5 (8)
2	(VI)	O(3)—H	O(21)	$(x+1, y, z-1)$	2·23 (1)	3·169 (4)	168·8 (7)
3	(VI)	O(14)—H	O(23)	$(1-x, y-\frac{1}{2}, 1-z)$	1·95 (1)	2·895 (4)	172·7 (9)
4	(VII)	O(3)—H	O(24)	$(x-\frac{1}{2}, \frac{1}{2}-y, 1-z)$	1·87 (1)	2·796 (6)	178·7 (5)
5	(VII)	O(11)—H	O(14)	$(1-x, y-\frac{1}{2}, \frac{1}{2}-z)$	1·99 (1)	2·824 (4)	168·8 (4)
6	(VII)	O(14)—H	O(3)	$(x+\frac{1}{2}, \frac{1}{2}-y, -z)$	2·04 (1)	2·795 (4)	161·5 (4)
7	(VII*B*)	O(24)—H	O(23*B*)	$(x-\frac{1}{2}, \frac{1}{2}-y, 1-z)$	1·77 (1)	2·69 (1)	172·2 (6)

O(3)···O(21) hydrogen bond (Table 5, bond No 2). Atom O(23) acts as acceptor in a second, stronger hydrogen bond donated by O(14)—H and formed around the screw axis (Table 5, bond No 3). This results in a smaller asymmetric unit volume [493·4 (5) Å^3] relative to (I) [502·5 (5) Å^3].

According to the energy calculations of Höhne & Pfeiffer (1983) the two possible lactone-ring orientations represented by digitoxigenin (I) and uzarigenin (VI) have the same probability. Indeed, using data from a review of γ-lactone ring rotations around C(17)—C(20) (Scharfenberg-Pfeiffer, Höhne & Wunderwald, 1987; Table 2), and adding the corresponding rotational parameters of (II)–(VI), the ratio of the two conformers is 9:9 (*i.e.* 50%–50%). The statistics are supported by the disordered crystal structure of sarmentogenin (VII) in which both conformers appear in equal proportions. The conformers *A* and *B* are depicted in Figs. 2(*c*) and 2(*d*), the torsion angle φ_{VIII} for *A* being 94 (1) and for *B* −88 (1)°.

The observed conformational disorder and the presence of a methanol molecule creates a complicated hydrogen-bond network in (VII). The molecules are bound together by three hydrogen bonds formed by the hydroxy groups bonded to carbon atoms C(3), C(11), C(14) (Table 5, Nos. 4–6). There is an additional hydrogen bond (Table 5, No. 7) occurring with 50% probability which involves methanol as donor to the carbonyl group of conformer *B*. Conformer *A* can only maintain a weak O(24)—H···O(21*A*) contact with an O···O distance of 3·51 (1) Å.

Conditions and limits of 'main-part' isostructuralism

Table 1 shows that the five cardenolides (I)–(V) are isostructural, whereas the closely related uzarigenin (VI) is not. Of course, because of the presence of the solvent molecule, (VII) cannot be isostructural either. The common feature of the isostructural cardenolides [(II)–(V)], arranged around (I) in Fig. 1, is the similar conformation of the γ-lactone ring (with the ring oxygen on the left-hand side). The non-isostructural (VI) and 19-nordigitoxigenin (Scharfenberg-Pfeiffer *et al.*, 1987) (VIII) exhibit the opposite lactone-ring conformation equally (with the ring oxygen on the right-hand side). Sarmentogenin (VII) exhibits both conformers. Of the three bufadienolide pairs [(IX)/(X), (XI)/(XII) and (XIII)/(XIV)] the first bears the δ-lactone ring in the opposite position to that assumed in the other two, but the lactone-ring orientation is similar to that found in (VI), (VIII) and (VII*B*). Consequently, they are listed together in the third column of Fig. 1. Gamabufotalin (XI), or 11-hydroxybufalin, is shown on the left side of bufalin (X) in the second column. The lower part of the first column shows a cardenolide (II) and two bufadienolides [(XIII), (XIV)] related by the presence of a 14,15β-epoxy ring.

A review of the 14 steroid structures shown in Fig. 1 suggests that rotation of the lactone ring about C(17)—C(20), in either of the two energetically preferred ranges (Höhne & Pfeiffer, 1983), is one of the principal factors which controls the isostructuralism between two (or more) closely related steriod structures. For example, in contrast to (IV) and (V) ($r = 1, s = 2, t = 0$), (VIII) ($r = -1, s = -2, t = 0$) is not isostructural with (I). A comparison of the φ torsion angles shows that in (VIII) the γ-lactone ring is rotated by *ca* 180° from the preferred [by (I) and the other cardeonolides (II)–(V)] range of 65–93°, preferring a second energy minimum around −100° [$\varphi_{VIII} = -97$ (1)°] which is also revealed by the potential-energy calculations of Höhne & Pfeiffer (1983). This conformational change apparently alters 'the head-to-tail' molecular packing found in (I) and hinders the isostructuralism. On the other hand, scillarenin (IX) (3β,14-dihydroxy-14β-bufa-4,20,22-trienolide), which is formed from helleborogenone (14-hydroxy-3-oxo-14β-bufa-1,4,20,22-tetraenolide) *via* partial *A*-ring saturation (Ribár, Argay, Kálmán, Vladimirov & Živanov-Stakić, 1983), becomes isostructural with bufalin (X) (Rohrer, Fullerton, Kitatsuji, Nambara & Yoshii, 1982) in such a way that its δ-lactone ring, at least in the crystalline state, undergoes a rotation of 171° from the first to the second potential-energy valley. In spite of the difference between the conformation of ring *A* (half chair *versus* chair), the similar δ-lactone ring position [$\varphi_{IX} = 93$ (1) and $\varphi_X = 87$ (1)°] seems to stabilize their isostructuralism.

The conformational hindrance to isostructuralism between (VI) and (I) arises from the differences in orientation of the γ-lactone ring and from the configurational isomerization about C(5), which results in a rigid *trans-A/B* junction. This is supported by the fact that (VI) and (VIII) are not isostructural either in spite of the similarity in the orientation of the lactone ring [$\varphi_{VI} = -93$ (1) *versus* $\varphi_{VIII} = -97$ (1)°]. As shown by the superposition of the steroid skeletons (VI), (IX) and (X) (Fig. 6), the flexible Δ^4-half-chair shape of ring *A* (IX) displaces O(3) from the position observed in (X) by 1·33 Å, but retains, at least partly, the half-moon shape of the 14-isoaethiocholane skeleton. This is presumably

Table 6. *Quantitative descriptors of isostructuralism for eight crystal pairs*

The definition of the I_D^n values is as follows: n = 19 (19 skeletal C atoms), n = 20 [19 + O(3)], n = 21 [20 + O(14)], n = 27 (21 + γ-lactone ring), n = 28 (21 + δ-lactone ring) except for j = 5 [27 + C(211)], n = 29 [28 + O(11)], n = 32 (28 + β-acetoxy group). φ is the C(13)—C(17)—C(20)—C(22) torsion angle. The e.s.d.'s for $I_D^n(j)$ also indicate the marked changes in the degree of isostructurality.

j	A/B	I_D^{19}	I_D^{20}	I_D^{21}	I_D^{27}	I_D^{28}	I_D^{29}	I_D^{32}	π	Δ(pc)	φ_A (°)	φ_B (°)
1	(I/II)	85 (8)	85 (8)	79 (14)	79 (13)				0·007	0·1	76 (2)	76 (1)
2	(I/III)	78 (10)	49 (42)	49 (41)	44 (41)				0·006	1·6	76 (2)	66 (1)
3	(I/IV)	90 (4)	89 (5)	89 (5)	84 (9)				0·022	−1·6	76 (2)	68 (2)
4	(I/V)	90 (4)	90 (4)	90 (4)	80 (14)				0·023	−1·6	76 (2)	93 (1)
5	(IV/V)	90 (4)	89 (4)	90 (5)	74 (20)	71 (22)			0·001	0·1	68 (2)	93 (1)
6	(IX/X)	51 (27)	51 (27)	50 (27)	–	48 (25)			0·002	−0·5	−93 (1)	−87 (1)
7	(XI/XII)	95 (2)	94 (3)	95 (3)	–	95 (2)	95 (2)		0·002	−0·2	80 (1)	81 (1)
8	(XIII/XIV)	94 (2)	94 (3)	94 (3)	–	89 (6)	–	90 (6)	0·001	1·4	65 (1)	65 (1)

the reason why (IX) remains isostructural with (X). However, the rigid *trans-A/B* ring junction in (VI) changes this shape completely, displacing O(3) still further (by 1·75 Å). This new O(3) position does not allow the formation of the head-to-tail hydrogen bond developed in (I) and (X).

A further condition of isostructuralism is that the changes in chemical composition expressed by the indices r, s, t should not alter the existing hydrogen-bond network. For example, in spite of the 14,15β-epoxy ring closure in bufotalin which gives rise to cinobufagin (Kálmán *et al.*, 1988) (II) remains isostructural with (I). This can be attributed to the long intermolecular O(14)···O(1) distance observed in (I) [and (II), (IV) and (V)]. In other words, the formation of a 14,15β-epoxy ring in (II) does not hamper the formation of hydrogen bonds; this is not the case, however, when cinobufagin is formed from bufotalin.

Numerical descriptions of isostructuralism

The similarities and differences in the conformations and hydrogen bonding of the 14 steroid structures summarized in Table 1 and shown in Fig. 1 allow the definition of a few descriptors of isostructuralism. These descriptors should reflect the crystallographic consequences caused either by tolerable conformational differences [*e.g.* (IV) *versus* (V)] or by changes in the chemical composition of the isostructural pairs expressed by the indices r, s and t in the general formula given above. The structural differences influence the volume of the asymmetric unit (V^*), the cell parameters and the fractional coordinates of the common atoms of the $C_kH_lO_m$ fragment. The first effect can be estimated from the packing coefficient increment Δ(pc):

$$\Delta(\text{pc}) = \frac{\Delta(rst) - \Delta V^*}{V^*} \qquad (1)$$

where ΔV^* is the change in volume of the asymmetric unit, while $\Delta(rst)$ is the net difference between the volume of the newly added and/or deleted atoms, by including the volume alteration resulting from the adjoining C atoms. A low $\Delta(rst)$ (Table 6) suggests a high degree of isostructurality. Of course, to avoid any marked change in the packing, Δ(pc) must be kept as low as possible (*ca* ± 2·0%) in such a way that the lattice parameters change slightly, the increment of some cell edges being balanced by a decrease in others. This can be expressed as follows:

$$\pi = \left| \frac{a + b + c}{a' + b' + c'} - 1 \right| \simeq 0. \qquad (2)$$

For example, even the bulky CH_3 group added to (I) resulting in either (IV) or (V) only gives rise to π = 0·022–0·023 (Table 6), whereas the corresponding Δ(pc) = −1·6%. In contrast, for cinobufagin (XIII) and cinobufotalin (XIV) (Kálmán *et al.*, 1988) π is even smaller (0·001) but Δ(pc) is 1·4% indicating an increase in the packing coefficient. In other words, the hydroxy group formed at the *cis-A/B* junction can be accommodated by the lattice of (XIV) without any noticeable perturbation. An almost similar phenomenon is shown by gamabufotalin (XI) and arenobufagin (XII) (Argay *et al.*, 1987) where two H atoms are replaced by an oxygen (>CH_2→ >C=O). Since the oxo group participates only in an intramolecular hydrogen bond it leaves the packing almost unaffected [π = 0·002, Δ(pc) = −0·2%].

Two pairs of cardenolides (I)/(III) and (IV)/(V) represent special cases of 'main-part' isostructuralism. Namely, in these pairs there are only common

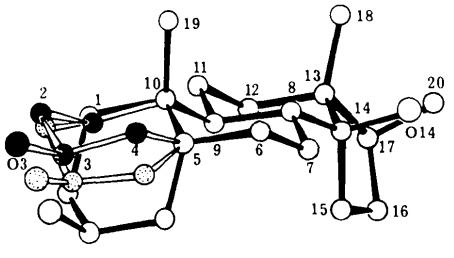

Fig. 6. A superposition of the steroid skeletons of (VI) (full circles), (IX) (dotted), and (X) (open circles), showing the differences in the conformations of ring *A*. The good fit among the other skeletal atoms (r.m.s. positional difference is 0·05 Å) justifies considering the 14-isoaethiocholane skeleton as common to all three.

(k, l and m) atoms and, consequently, both their π and Δ(pc) values should be zero. Indeed, (IV) and (V) differ only in the chirality of C(21) and have π = 0·001 and Δ(pc) = 0·1%, while the other diastereomeric pair (I)/(III) exhibits π = 0·006 with Δ(pc) = 1·6%. The latter can be attributed to the additional hydrogen bond, readily formed as the 3-OH group moves from β-axial to α-equatorial position, decreasing the O(3)···O(14) distance from 3·41 (I) to 2·93 Å (III). This additional hydrogen bond decreases the volume of the asymmetric unit by 8·0 Å^3.

Since both π and Δ(pc) refer only to alterations in the cell dimensions, the internal degree of isostructurality should be quantified in some other way. We calculate the distances, ΔR_i, between the common non-H atoms ($n = k + m$) within the same section of the asymmetric units of the related structures. Since the H-atom positions (l varies in the range 32–36) are generally less precisely determined than the heavy atoms they have been excluded from the calculations. For a reliable descriptor of isostructuralism, we suggest:

$$I_D^n = \left[1 - \left(\frac{\sum \Delta R_i^2}{n}\right)^{1/2}\right] \times 100 \qquad (3)$$

normalized to unit length (Å). Since n varies between 27 and 32, the isostructuralism of the eight pairs can only be compared if $I_D^n(j)$ values are calculated for the same atomic pairs: n denotes the number of the atomic pairs for which the calculation is performed, whereas j refers to the serial number of the isostructural pairs (see Table 6). Subtracting stepwise the contribution of each substituent on the steroid skeleton (such as the lactone ring, *etc.*) we compute $I_D^n(j)$ values for the remaining groups down to the 19 skeletal C atoms including C(18) and C(19). The increments between these steps are also greater than 3–4%, although only on a scale relative to the conformational and/or packing differences.

From the above definitions, we observe the following:

(*a*) The highest degree of isostructurality (95%), in accordance with the previous discussion of π and Δ(pc) values, is shown by pair 7. This is also confirmed by the excellent agreement between I_D^{19} (7) and I_D^{29} (7). The second best agreement is shown by pair 8. Even the 16β-acetoxy group occupies a similar position as is shown by the value I_D^{28} (8) − I_D^{32} (8) = −1%.

(*b*) The lowest degree of isostructurality is exhibited by pair 6 which can be attributed to the relevant difference (see above) between the conformation of ring *A* and its surroundings (half chair *versus* chair). This can be estimated from the difference between I_D^{19} (6) and the average of I_D^{19} for pairs 7 and 8 (ΔI_D = 43·5%). In contrast, the almost identical position (conformation) of the δ-lactone rings is illustrated by the small value of I_D^{21} (6) − I_D^{28} (6) (2%).

(*c*) The similar $I_D^{19}(j)$ values (90%) obtained for the pairs j = 3, 4 and 5 suggest that neither the presence of the 21-methyl group nor a change in the chirality at C(21) alter considerably the position of the 19 skeletal atoms. Similarly, they do not influence the positions of the skeletal oxygens O(3) and O(14) either. The average of the $I_D^{20}(j)$ and $I_D^{21}(j)$ values is still 89·5 (5)%.

(*d*) However, the 21-methyl group and its position account for the degree of rotation about C(17)—C(20) within the first potential-energy valley at φ = 67–97°. This is shown by the $\Delta\varphi$ values (−8, 17 and 25°) for the pairs j = 3, 4 and 5: the $\Delta I_D(j - j')$ values are almost directly proportional to $\Delta\varphi$ (ΔI_D^{27} of 4% corresponds to *ca* 10° of internal rotation of ring *E*). As suggested by the low I_D^{27} (5) − I_D^{28} (5) value (3%), the internal rotation of ring *E* brings the 21-methyl group into a common, favourable position in the void of the isostructural lattices.

(*e*) The I_D^{19} (average) − I_D^{19} (1) = 5% difference can be attributed to the change in the conformation of ring *D* pertaining to (II) [the envelope shape ^{14}E found in (I) is shifted to ^{17}E]. This is in accordance with the formation of the 14,15β-epoxy ring which is indicated directly by I_D^{20} (1) − I_D^{21} (1) = 6%. Despite these alterations the position of the γ-lactone ring is undisturbed [I_D^{21} (1) − I_D^{27} (1) = 0% *versus* $\Delta\varphi$ = 0°].

(*f*) Finally, for the diastereomeric pair (I)/(III), in addition to the effect of epimerization around C(3), indicated by I_D^{19} (2) − I_D^{20} (2) = 29%, and the rotation ($\Delta\varphi$ = 10°) about C(17)—C(20) [I_D^{21} (2) − I_D^{27} (2) = 5%], the second hydrogen bond accounts directly for a significant decrease in isostructuralism as estimated by I_D^{19} (1) − I_D^{19} (average) = 12%. This points to the significant contribution of even one hydrogen bond to the lattice packing.

Concluding remarks

The introduction of the descriptors π, Δ(pc) and $I_D^n(j)$ help to describe the phenomenon termed as 'main-part' isostructuralism for several pairs of cardenolides and bufadienolides. All of these compounds crystallize in the space group $P2_12_12_1$. In spite of the differences in their chemical composition, the hydrogen-bonding patterns are constant: the hydroxy groups act both as donors and acceptors and the oxo group of the γ- or δ-lactone rings acts as an acceptor. The isostructuralism of cardenolides is so recurrent that even the biosides of digitoxigenin and gitoxigenin were found to be isostructural (Go & Bhandary, 1989).

To understand this phenomenon further structure determinations of crystalline adducts of related pairs (*e.g.* digitoxigenin and digirezigenin 1:1) are now in progress.

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References

ARGAY, GY., KÁLMÁN, A., RIBÁR, B., VLADIMIROV, S. & ŽIVANOV-STAKIĆ, D. (1987). *Acta Cryst.* C**43**, 922–926.
BLOSS, F. D. (1971). *Crystallography and Crystal Chemistry*, pp. 249–250. New York: Holt, Rinehart & Winston.
CROWFOOT, D. (1935). *Chem. Ind.* pp. 568–569.
DECLERCQ, J.-P., GERMAIN, G. & KING, G. S. D. (1977). *Abstr. 4th Eur. Crystallogr. Meet.*, Oxford, pp. 279–280.
DUNITZ, J. D. (1979). *X-ray Analysis and the Structure of Organic Molecules*, pp. 106–111. Ithaca: Cornell Univ. Press.
Enraf–Nonius (1982). *Structure Determination Package*. Enraf–Nonius, Delft, The Netherlands.
GO, K. & BHANDARY, K. K. (1989). *Acta Cryst.* B**45**, 306–312.
HÖHNE, E. & PFEIFFER, D. (1983). *Stud. Biophys.* **97**, 81–86.
KÁLMÁN, A., ARGAY, GY., FÜLÖP, V., RIBÁR, B. & LAZAR, D. (1987). *Acta Cryst.* A**43**, S66–S67.
KÁLMÁN, A., ARGAY, GY., RIBÁR, B., VLADIMIROV, S. & ŽIVANOV-STAKIĆ, D. (1984). *Croat. Chem. Acta*, **57**, 519–528.
KÁLMÁN, A., FÜLÖP, V., ARGAY, GY., RIBÁR, B., LAZAR, D., ŽIVANOV-STAKIĆ, D. & VLADIMIROV, S. (1988). *Acta Cryst.* C**44**, 1634–1638.
KARLE, I. L. & KARLE, J. (1969). *Acta Cryst.* B**25**, 434–442.
KITAIGORODSKY, A. I. (1961). *Organic Chemical Crystallography*, pp. 5–17. New York: Consultants Bureau.
MESSERSCHMIDT, A., HÖHNE, E. & MEGGES, R. (1981). *Cryst. Struct. Commun.* **10**, 149–156.
PRASAD, L. & GABE, E. J. (1983). *Acta Cryst.* C**39**, 273–275.
RIBÁR, B., ARGAY, GY., KÁLMÁN, A., VLADIMIROV, S. & ŽIVANOV-STAKIĆ, D. (1983). *J. Chem. Res.* (*M*), pp. 1001–1042.
ROHRER, D. C., FULLERTON, D. S., KITATSUJI, E., NAMBARA, T. & YOSHII, E. (1982). *Acta Cryst.* B**38**, 1865–1868.
SCHARFENBERG-PFEIFFER, D., HÖHNE, E. & WUNDERWALD, M. (1987). *Cryst. Res. Technol.* **22**, 1403–1408.
SHELDRICK, G. M. (1976). *SHELX76*. Program for crystal structure determination. Univ. of Cambridge, England.
ZACHARIASEN, W. H. (1963). *Acta Cryst.* **16**, 1139–1144.

Acta Cryst. (1991). B**47**, 77–86

Pseudoinversion Centers in Space Group $P\bar{1}$ and a Redetermination of the Crystal Structure of 3,4-Dimethoxycinnamic Acid. A Study of Non-Crystallographic Symmetry

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Abstract

A survey of the 11691 $P\bar{1}$ crystal structures in the Cambridge Structural Database shows that 1166 have $Z = 4$. Of these, a mere 20 have local pseudocenters of symmetry relating the atoms in the two halves of the asymmetric unit. The coordinates of these local pseudocenters often include the special values of 0, $\frac{1}{4}$ and $\frac{1}{2}$, but can also be perfectly general. As an example of the latter, the crystal structure of 3,4-dimethoxycinnamic acid ($C_{11}H_{12}O_4$, $M_r = 208{\cdot}21$) was re-examined at both room temperature and at 173 K. The poor refinement reported in the original study of this compound was ascribed to the low data/parameter ratio and the presence of the pseudocenter. The present study, however, clearly demonstrates that the refinement is unaffected by the presence of the pseudocenter when the data/parameter ratio is reasonable (>5). This could be true in this specific case because the center is located at a general position: 0·217, 0·433, 0·319. At room temperature, $a = 8{\cdot}449\ (1)$, $b = 15{\cdot}034\ (2)$, $c = 8{\cdot}449\ (1)$ Å, $\alpha = 99{\cdot}47\ (1)$, $\beta = 94{\cdot}57\ (1)$, $\gamma = 101{\cdot}53\ (1)°$, $V = 1029$ Å^3, 1893 reflections, 367 variables, $R = 0{\cdot}041$, $wR = 0{\cdot}038$. At 173 K, $a = 8{\cdot}412\ (2)$, $b = 14{\cdot}959\ (2)$, $c = 8{\cdot}341\ (2)$ Å, $\alpha = 100{\cdot}28\ (2)$, $\beta = 94{\cdot}80\ (2)$, $\gamma = 101{\cdot}83\ (2)°$, $V = 1003$ Å^3, 2543 reflections, $R = 0{\cdot}041$, $wR = 0{\cdot}040$.

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