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Structures of Two Bufadienolides: Telocinobufagin (3β,5β-Dihydroxy-5β,14β-bufa-20,22-dienolide) Monohydrate and 14α-Artebufogenin (3β-Hydroxy-15-oxo-5β,14α-bufa-20,22-dienolide)

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Abstract. Telocinobufagin monohydrate (1), $C_{24}H_{34}O_5.H_2O$, $M_r = 420.55$, orthorhombic, $P2_12_12_1$, $a = 14.348$ (4), $b = 13.086$ (4), $c = 11.851$ (2) Å, $V = 2225$ (2) Å^3, $Z = 4$, $D_x = 1.255$ g cm^{-3}, λ(Mo $K\alpha$) = 0.71073 Å, $\mu = 0.83$ cm^{-1}, $F(000) = 912$, $T = 296$ (1) K, $R = 0.042$ for 2142 unique observed reflections. 14α-Artebufogenin (2), $C_{24}H_{32}O_4$, $M_r = 384.52$, orthorhombic, $P2_12_12_1$, $a = 7.920$ (1), $b = 11.507$ (1), $c = 22.519$ (2) Å, $V = 2052.3$ (6) Å^3, $Z = 4$, $D_x = 1.244$ g cm^{-3}, λ(Cu $K\alpha$) = 1.54184 Å, $\mu = 6.26$ cm^{-1}, $F(000) = 832$, $T = 296$ (1) K, $R = 0.047$ for 1909 unique observed reflections. The expected isostructuralism of telocinobufagin (5β-hydroxybufalin) with bufalin is hindered by an additional water molecule. Simultaneously, the δ-lactone ring assumes a different rotation about the C(17)—C(20) bond. These together result in a more complicated hydrogen-bond network than that shown by bufalin. In contrast, in 14α-artebufogenin the rotation of the lactone ring about the C(17)—C(20) bond is the same as in bufalin. However, the unusual *cis C/D* junction substantially alters its position relative to the other part of the rigid steroid skeleton. This results in one weak head-to-tail hydrogen bond in which the acceptor is the ether O atom of the lactone ring.

Introduction. In the course of the systematic crystal structure analysis of related bufadienolide pairs (Argay, Kálmán, Ribár, Vladimirov & Živanov-Stakić, 1987; Kálmán, Fülöp, Argay, Ribár, Lazar, Živanov-Stakić & Vladimirov, 1988) performed along with studies on the related cardenolides (Kálmán, Argay, Ribár, Vladimirov & Živanov-Stakić, 1984), a recurrent phenomenon termed as 'main-part' isostructuralism has been discovered and summarized recently by Kálmán, Argay, Scharfenberg-Pfeiffer, Höhne & Ribár (1991). The present work tries to establish why telocinobufagin (1) – in contrast with cinobufagin and cinobufotalin (Kálmán *et al.*, 1988) – cannot be isostructural with bufalin (Rohrer, Fullerton, Kitatsuji, Nambara & Yoshii, 1982). The structure determination of 14α-artebufogenin (2) reveals how the epimerization at

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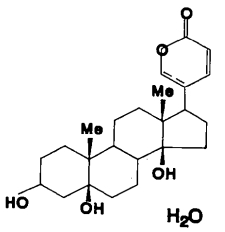
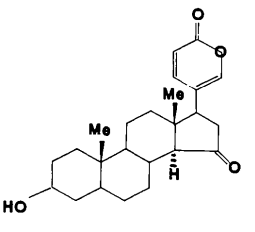
C(14) alters the backbone of the molecule which gives rise to a much weaker 'head-to-tail' hydrogen bond than those found in bufalin and in the related cardenolides (Kálmán *et al.*, 1991).



(1)



(2)

Experimental. Similarly to arenobufagin and gamabufotalin (Argay *et al.*, 1987), telocinobufagin (1) was isolated from the dried venom of the Chinese toad (Ch' an Su) which is a rich source of various bufadienolides and cardenolides (Höriger, Živanov, Linde & Meyer, 1970). The crystals obtained from a mixture of methanol and ethyl acetate melt at 478–481 K. 14α-Artebufogenin (2) was isolated from the same animal skin secretion (Linde & Meyer, 1959). The crystals for X-ray diffraction were obtained from a mixture of acetone and ethanol (m.p. 524–529 K).

Telocinobufagin (1). A $0.54 \times 0.54 \times 0.95$ mm crystal was mounted on a CAD-4 diffractometer (Ljubljana) and data collected using graphite-monochromated Mo $K\alpha$ radiation. Cell constants were refined by least-squares fit for 25 centred reflections with $7.1 < \theta < 9.9°$. 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 $0.103 \leq (\sin\theta)/\lambda \leq 0.557$ Å^{-1} with h −16 to 0, k −18 to 0, l −20 to 0. Three standard reflections ($\bar{5}\bar{3}0$, $\bar{5}\bar{2}\bar{2}$, $\bar{5}0\bar{3}$) were monitored every 120 min, but no intensity variations were recorded. Of 3604 unique and non-systematically absent reflections, 2142 with $I > 2\sigma(I)$ were taken as observed. The phase problem was solved by the program *SHELX*76 (Sheldrick, 1976). Full-matrix least-squares refinement minimized $\sum w(\Delta F)^2$ for 271 parameters with $w = 4F_o^2/\sigma^2(F_o^2)$. No absorption corrections were applied. Final $R = 0.042$ ($wR = 0.044$, $R_{\text{total}} = 0.079$, $S = 0.82$). Maximum peak height in the final difference map = |0.16| e Å^{-3}. Data were not corrected for extinction. $(\Delta/\sigma)_{\max} = 0.34$. Positions of H atoms bound to C atoms were generated from assumed geometries, whereas those linked to O atoms were located in difference Fourier maps. Their positions were taken into account without refinement in the structure-factor calculations using isotropic temperature factors defined as $B_{iH} = (B_{iX} + 1)$ Å^2 (where X is either a C or O atom).

14α-*Artebufogenin* (2). Data were collected on a crystal of dimensions $0.03 \times 0.25 \times 0.60$ mm, mounted on a CAD-4 diffractometer (Budapest), using graphite-monochromated Cu $K\alpha$ radiation. Cell constants were refined by least-squares fit for 25 centred reflections with $30 < \theta < 37°$. 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 $0.053 \leq (\sin\theta)/\lambda \leq 0.568$ Å^{-1} with h 0 to 9, k 0 to 14, l 0 to 28. Three standard reflections (041, 0,1,12, 340) were checked every 60 min, but no intensity variations were recorded. Of 2429 unique and non-systematically absent reflections, 1909 with $I > 3\sigma(I)$ were

Table 1. *Fractional atomic coordinates for non*-H *atoms and equivalent isotropic temperature factors* (Å^2)

$B_{eq} = \frac{1}{3}$ trace ($B\mathbf{G}$) where $\mathbf{G}$ is the metric tensor.

	x	y	z	B_{eq}
Telocinobufagin.H_2O				
O(1)	0.2173 (2)	0.7298 (2)	1.1107 (2)	5.3 (1)
O(2)	0.1757 (1)	0.5897 (2)	0.9561 (2)	3.9 (1)
O(3)	0.3809 (1)	0.6124 (1)	0.4747 (1)	2.9 (1)
O(4)	0.7191 (2)	0.5172 (2)	0.2828 (2)	4.6 (1)
O(5)	0.6889 (2)	0.4489 (2)	0.1162 (2)	5.9 (1)
C(1)	0.3784 (3)	0.6174 (4)	1.0073 (3)	5.0 (2)
C(2)	0.3778 (3)	0.7305 (4)	1.0388 (3)	6.0 (2)
C(3)	0.2813 (3)	0.7743 (3)	1.0304 (3)	5.2 (2)
C(4)	0.2401 (3)	0.7548 (3)	0.9138 (3)	3.8 (1)
C(5)	0.2397 (2)	0.6415 (2)	0.8803 (3)	3.0 (1)
C(6)	0.1994 (2)	0.6281 (3)	0.7626 (3)	3.8 (1)
C(7)	0.2648 (2)	0.6666 (3)	0.6701 (3)	3.5 (1)
C(8)	0.3610 (2)	0.6163 (2)	0.6776 (2)	2.6 (1)
C(9)	0.4036 (2)	0.6366 (2)	0.7949 (2)	2.8 (1)
C(10)	0.3392 (2)	0.5931 (3)	0.8901 (3)	3.3 (1)
C(11)	0.5047 (2)	0.5972 (3)	0.8025 (3)	4.1 (1)
C(12)	0.5645 (2)	0.6331 (3)	0.7035 (3)	3.8 (1)
C(13)	0.5247 (2)	0.6031 (3)	0.5871 (2)	3.0 (1)
C(14)	0.4241 (2)	0.6460 (2)	0.5786 (2)	2.6 (1)
C(15)	0.4399 (2)	0.7611 (3)	0.5590 (3)	3.3 (1)
C(16)	0.5215 (3)	0.7637 (3)	0.4747 (3)	4.1 (1)
C(17)	0.5795 (2)	0.6661 (3)	0.4960 (3)	3.6 (1)
C(18)	0.5302 (2)	0.4873 (3)	0.5720 (3)	3.9 (1)
C(19)	0.3319 (3)	0.4757 (3)	0.8788 (4)	5.2 (2)
C(20)	0.6050 (2)	0.6075 (3)	0.3895 (3)	3.5 (1)
C(21)	0.6909 (2)	0.5708 (3)	0.3763 (3)	3.8 (1)
C(22)	0.5412 (3)	0.5868 (4)	0.3010 (3)	4.7 (2)
C(23)	0.5666 (3)	0.5335 (4)	0.2089 (3)	4.8 (2)
C(24)	0.6584 (3)	0.4963 (3)	0.1956 (3)	4.3 (1)
O(6)	0.2917 (2)	0.7418 (2)	0.3207 (2)	5.9 (1)
14α-Artebufogenin				
O(1)	0.1242 (4)	−0.3102 (2)	0.6870 (1)	7.7 (1)
O(2)	0.5856 (3)	0.1236 (2)	0.4245 (1)	6.4 (1)
O(3)	−0.0165 (4)	0.3096 (2)	0.2530 (1)	7.0 (1)
O(4)	−0.2740 (4)	0.3304 (2)	0.2157 (1)	7.7 (1)
C(1)	−0.0109 (5)	−0.1041 (3)	0.6240 (1)	5.4 (1)
C(2)	−0.0170 (5)	−0.2291 (3)	0.6020 (1)	5.9 (1)
C(3)	0.1359 (6)	−0.2964 (3)	0.6233 (1)	6.1 (1)
C(4)	0.2979 (5)	−0.2345 (3)	0.6077 (1)	5.5 (1)
C(5)	0.3022 (4)	−0.1053 (3)	0.6247 (1)	4.7 (1)
C(6)	0.4659 (5)	−0.0492 (3)	0.6030 (1)	5.6 (1)
C(7)	0.4690 (4)	−0.0307 (3)	0.5357 (1)	5.1 (1)
C(8)	0.3135 (4)	0.0358 (2)	0.5130 (1)	4.1 (1)
C(9)	0.1504 (4)	−0.0239 (2)	0.5349 (1)	4.0 (1)
C(10)	0.1454 (4)	−0.0372 (2)	0.6034 (1)	4.2 (1)
C(11)	−0.0087 (4)	0.0331 (3)	0.5092 (1)	5.2 (1)
C(12)	−0.0064 (4)	0.0380 (3)	0.4409 (1)	4.8 (1)
C(13)	0.1500 (4)	0.0995 (2)	0.4182 (1)	3.7 (1)
C(14)	0.3064 (4)	0.0410 (2)	0.4449 (1)	3.9 (1)
C(15)	0.4460 (4)	0.0944 (3)	0.4084 (1)	4.8 (1)
C(16)	0.3759 (5)	0.1107 (3)	0.3462 (1)	5.4 (1)
C(17)	0.1860 (4)	0.0838 (2)	0.3515 (1)	4.4 (1)
C(18)	0.1440 (5)	0.2291 (2)	0.4341 (1)	4.8 (1)
C(19)	0.1389 (6)	0.0812 (3)	0.6340 (1)	6.3 (2)
C(20)	0.0662 (4)	0.1463 (3)	0.3109 (1)	4.5 (1)
C(21)	0.0979 (5)	0.2498 (3)	0.2869 (1)	5.9 (1)
C(22)	−0.0933 (5)	0.0984 (3)	0.2971 (1)	5.8 (1)
C(23)	−0.2075 (5)	0.1553 (3)	0.2645 (1)	5.9 (1)
C(24)	−0.1772 (5)	0.2672 (3)	0.2428 (1)	5.8 (1)

Table 2. *Bond lengths* (Å)

Telocinobufagin.H_2O			
O(1)—C(3)	1.445 (6)	C(9)—C(10)	1.564 (5)
O(2)—C(5)	1.453 (5)	C(9)—C(11)	1.542 (5)
O(3)—C(14)	1.447 (4)	C(10)—C(19)	1.545 (6)
O(4)—C(21)	1.374 (5)	C(11)—C(12)	1.527 (6)
O(4)—C(24)	1.378 (5)	C(12)—C(13)	1.544 (5)
O(5)—C(24)	1.209 (6)	C(13)—C(14)	1.552 (5)
C(1)—C(2)	1.525 (8)	C(13)—C(17)	1.570 (5)
C(1)—C(10)	1.533 (6)	C(13)—C(18)	1.527 (6)
C(2)—C(3)	1.501 (8)	C(14)—C(15)	1.540 (5)
C(3)—C(4)	1.525 (6)	C(15)—C(16)	1.540 (6)
C(4)—C(5)	1.535 (6)	C(16)—C(17)	1.545 (6)
C(5)—C(6)	1.520 (6)	C(17)—C(20)	1.521 (6)
C(5)—C(10)	1.567 (5)	C(20)—C(21)	1.332 (6)
C(6)—C(7)	1.530 (6)	C(20)—C(22)	1.419 (6)
C(7)—C(8)	1.531 (5)	C(22)—C(23)	1.346 (7)
C(8)—C(9)	1.542 (5)	C(23)—C(24)	1.413 (7)
C(8)—C(14)	1.531 (5)		
14α-Artebufogenin			
O(1)—C(3)	1.447 (5)	C(9)—C(10)	1.550 (4)
O(2)—C(15)	1.211 (4)	C(9)—C(11)	1.534 (5)
O(3)—C(21)	1.370 (5)	C(10)—C(19)	1.528 (5)
O(3)—C(24)	1.382 (5)	C(11)—C(12)	1.540 (5)
O(4)—C(24)	1.220 (5)	C(12)—C(13)	1.515 (5)
C(1)—C(2)	1.522 (6)	C(13)—C(14)	1.532 (5)
C(1)—C(10)	1.529 (5)	C(13)—C(17)	1.539 (4)
C(2)—C(3)	1.515 (6)	C(13)—C(18)	1.535 (5)
C(3)—C(4)	1.509 (6)	C(14)—C(15)	1.508 (5)
C(4)—C(5)	1.535 (5)	C(15)—C(16)	1.517 (5)
C(5)—C(6)	1.529 (5)	C(16)—C(17)	1.541 (5)
C(5)—C(10)	1.545 (5)	C(17)—C(20)	1.501 (5)
C(6)—C(7)	1.529 (6)	C(20)—C(21)	1.332 (5)
C(7)—C(8)	1.538 (5)	C(20)—C(22)	1.413 (6)
C(8)—C(9)	1.544 (5)	C(22)—C(23)	1.336 (6)
C(8)—C(14)	1.535 (5)	C(23)—C(24)	1.399 (6)

Table 3. *Bond angles* (°)

Telocinobufagin.H_2O			
C(21)—O(4)—C(24)	121.3 (6)	C(9)—C(11)—C(12)	112.4 (6)
C(2)—C(1)—C(10)	114.9 (7)	C(11)—C(12)—C(13)	113.6 (6)
C(1)—C(2)—C(3)	111.1 (7)	C(12)—C(13)—C(14)	108.0 (5)
O(1)—C(3)—C(2)	112.8 (7)	C(12)—C(13)—C(17)	107.2 (5)
O(1)—C(3)—C(4)	106.5 (6)	C(12)—C(13)—C(18)	109.7 (6)
C(2)—C(3)—C(4)	110.7 (7)	C(14)—C(13)—C(17)	103.4 (5)
C(3)—C(4)—C(5)	113.4 (6)	C(14)—C(13)—C(18)	113.6 (5)
O(2)—C(5)—C(4)	107.1 (5)	C(17)—C(13)—C(18)	114.5 (6)
O(2)—C(5)—C(6)	105.8 (5)	O(3)—C(14)—C(8)	108.8 (5)
O(2)—C(5)—C(10)	110.0 (5)	O(3)—C(14)—C(13)	110.1 (5)
C(4)—C(5)—C(6)	110.5 (6)	O(3)—C(14)—C(15)	103.4 (5)
C(4)—C(5)—C(10)	111.6 (5)	C(8)—C(14)—C(13)	114.1 (5)
C(6)—C(5)—C(10)	111.6 (5)	C(8)—C(14)—C(15)	116.8 (5)
C(5)—C(6)—C(7)	112.7 (6)	C(13)—C(14)—C(15)	103.1 (5)
C(6)—C(7)—C(8)	111.7 (6)	C(14)—C(15)—C(16)	103.4 (5)
C(7)—C(8)—C(9)	109.6 (5)	C(15)—C(16)—C(17)	106.6 (6)
C(7)—C(8)—C(14)	112.3 (5)	C(13)—C(17)—C(16)	106.0 (6)
C(9)—C(8)—C(14)	114.4 (5)	C(13)—C(17)—C(20)	115.2 (6)
C(8)—C(9)—C(10)	110.7 (5)	C(16)—C(17)—C(20)	114.2 (6)
C(8)—C(9)—C(11)	111.6 (5)	C(17)—C(20)—C(21)	120.1 (6)
C(10)—C(9)—C(11)	113.1 (5)	C(17)—C(20)—C(22)	123.7 (6)
C(1)—C(10)—C(5)	108.5 (6)	C(21)—C(20)—C(22)	116.2 (7)
C(1)—C(10)—C(9)	111.2 (6)	O(4)—C(21)—C(20)	123.5 (7)
C(1)—C(10)—C(19)	108.0 (6)	C(20)—C(22)—C(23)	121.6 (7)
C(5)—C(10)—C(9)	109.7 (5)	C(22)—C(23)—C(24)	121.4 (8)
C(5)—C(10)—C(19)	109.5 (6)	O(4)—C(24)—O(5)	117.1 (7)
C(9)—C(10)—C(19)	109.9 (6)	O(4)—C(24)—C(23)	115.9 (7)
		O(5)—C(24)—C(23)	126.9 (8)
14α-Artebufogenin			
C(21)—O(3)—C(24)	121.7 (6)	C(11)—C(12)—C(13)	111.3 (5)
C(2)—C(1)—C(10)	113.7 (6)	C(12)—C(13)—C(14)	108.9 (5)
C(1)—C(2)—C(3)	110.8 (6)	C(12)—C(13)—C(17)	115.2 (5)
O(1)—C(3)—C(2)	108.6 (6)	C(12)—C(13)—C(18)	110.5 (5)
O(1)—C(3)—C(4)	109.7 (6)	C(14)—C(13)—C(17)	100.5 (4)
C(2)—C(3)—C(4)	111.4 (6)	C(14)—C(13)—C(18)	111.1 (5)
C(3)—C(4)—C(5)	114.7 (6)	C(17)—C(13)—C(18)	110.3 (5)
C(4)—C(5)—C(6)	110.4 (5)	C(8)—C(14)—C(13)	116.0 (5)
C(4)—C(5)—C(10)	113.3 (5)	C(8)—C(14)—C(15)	122.2 (5)
C(6)—C(5)—C(10)	111.6 (5)	C(13)—C(14)—C(15)	101.5 (4)
C(5)—C(6)—C(7)	112.8 (5)	O(2)—C(15)—C(14)	128.2 (6)
C(6)—C(7)—C(8)	112.8 (5)	O(2)—C(15)—C(16)	125.2 (6)
C(7)—C(8)—C(9)	110.0 (5)	C(14)—C(15)—C(16)	106.6 (5)
C(7)—C(8)—C(14)	112.4 (5)	C(15)—C(16)—C(17)	105.1 (5)
C(9)—C(8)—C(14)	107.8 (5)	C(13)—C(17)—C(16)	103.5 (5)
C(8)—C(9)—C(10)	112.6 (5)	C(13)—C(17)—C(20)	114.9 (5)
C(8)—C(9)—C(11)	112.1 (5)	C(16)—C(17)—C(20)	118.3 (5)
C(10)—C(9)—C(11)	113.4 (5)	C(17)—C(20)—C(21)	123.8 (6)
C(1)—C(10)—C(5)	107.5 (5)	C(17)—C(20)—C(22)	120.8 (6)
C(1)—C(10)—C(9)	111.9 (5)	C(21)—C(20)—C(22)	115.3 (6)
C(1)—C(10)—C(19)	106.5 (5)	O(3)—C(21)—C(20)	123.4 (6)
C(5)—C(10)—C(9)	109.8 (5)	C(20)—C(22)—C(23)	122.3 (6)
C(5)—C(10)—C(19)	109.9 (5)	C(22)—C(23)—C(24)	121.8 (7)
C(9)—C(10)—C(19)	111.2 (5)	O(3)—C(24)—O(4)	116.9 (6)
C(9)—C(11)—C(12)	112.6 (5)	O(3)—C(24)—C(23)	115.1 (6)
		O(4)—C(24)—C(23)	128.0 (7)

taken as observed. The phase problem was solved by the program *MULTAN*11/82 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1982). Full-matrix least-squares refinement minimized $\sum w(\Delta F)^2$ for 253 parameters with $w = 4F_o^2/\sigma^2(F_o^2)$. At the end of the isotropic refinement of the atomic parameters an empirical absorption correction was performed with the program *DIFABS* (Walker & Stuart, 1983); minimum and maximum absorption corrections were 0.628 and 1.288, respectively. Final $R = 0.047$ ($wR = 0.041$, $R_{\text{total}} = 0.069$, $S = 0.68$) $(\Delta/\sigma)_{\max} = 0.01$. Maximum peak height in the final difference map = |0.18| e Å^{-3}. H-atom treatment was as for (1).

Scattering factors were taken for both structures from the program system *SDP-Plus* (Enraf–Nonius, 1983) adapted on a PDP 11/34 minicomputer (Budapest) with local modifications.

Discussion. Atomic coordinates for non-H atoms for (1) and (2) are listed in Table 1. The bond lengths and angles for non-H atoms are given in Tables 2 and 3.* A perspective view of each molecule is shown in Fig. 1.

The conformation of the 14-isoaethiocholane skeleton in telocinobufagin is similar to that in the parent compound bufalin (Rohrer *et al.*, 1982). There is only a small difference in the pseudorotation of the flexible *D* ring accompanied by a slight increase of the puckering amplitude (Cremer & Pople, 1975). A comparison of the puckering parameters along with the corresponding asymmetry factors (Kálmán, Czugler & Simon, 1982) for a number of related bufalin derivatives (Table 4) shows that the most probable conformation of ring *D* is an E^{14} envelope distorted somewhat towards a ${}_{13}T^{14}$ twist chair. In contrast, in (1) the pseudorotation brings the conformation in the opposite direction gaining a slight ${}_{15}T^{14}$ character.

The rotation of the δ-lactone ring about the C(17)—C(20) bond (Table 4) differs, however, substantially from that of bufalin and its quasi-

* Lists of structure factors, anisotropic thermal parameters, torsion angles and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 55172 (23 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

isostructural pair scillarenin [described originally as dihydrohelleborogenon by Ribár, Argay, Kálmán, Vladimirov & Živanov-Stakić (1983)], which alone may account for the lack of isostructuralism.

It is worth noting that the rotation of the δ-lactone moiety in the bufadienolide structures reported by us hitherto [helleborogenon (Ribár *et al.*, 1983), arenobufagin, gamabufotalin (Argay *et al.*, 1987), bufotalin, cinobufagin and cinobufotalin (Kálmán *et al.*, 1988)] invariably assumes a value close to that observed in telocinobufagin (Table 4).

This is the reason why 14α-artebufogenin drew special attention. Namely, its lactone ring exhibits a similar amount of rotation to those of bufalin and scillarenin, which fall in the second wide potential-energy valley computed by Rohrer *et al.* (1982) and discussed in detail by Kálmán *et al.* (1991). This occurs in a structure where the epimerization at C(14) *via* the altered shape of ring *D* (a distorted $^{13}T_{14}$ twist chair) displaces considerably the lactone ring (in particular the terminal oxo group) from the position assumed in bufalin relative to the rigid part of the steroid skeleton (Fig. 2). This seems to spoil the characteristic 'head-to-tail' hydrogen bond formed by simple translation along the crystal axis which has length 14.5–16.5 Å [*cf.* bufalin/scillarenin and the group of the related cardenolides in Table 1

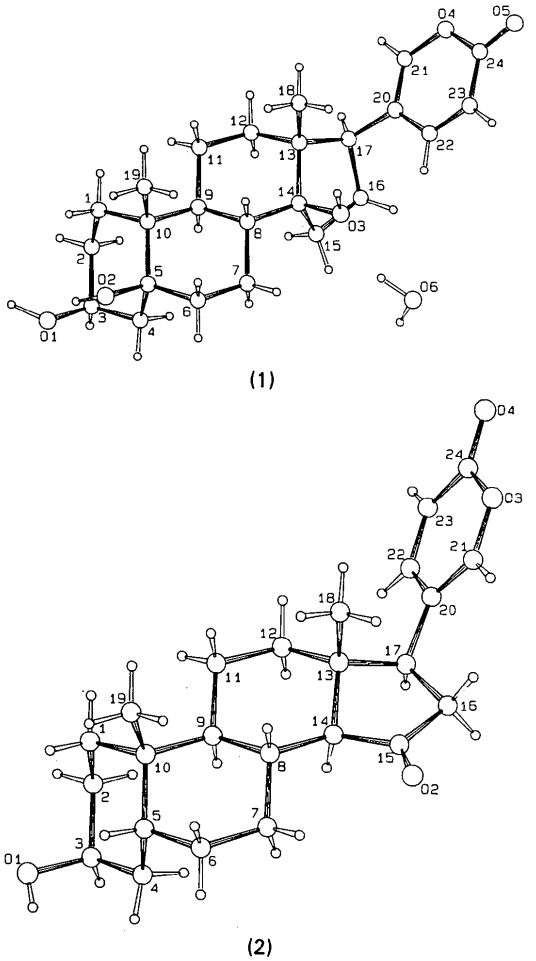


Fig. 1. Perspective views of molecules of (1) telocinobufagin.H_2O and (2) 14α-artebufogenin. The unlabelled numbers are for C atoms.

Table 4. *Descriptors of D-ring puckering and the δ-lactone ring (E) rotation for bufadienolides*

Puckering parameters φ (°) and Q (Å) are those of Cremer & Pople (1975). The asymmetry factors $fC_s[C_x]$ and $fC_2[C_y]$ (pm) (Kálmán *et al.*, 1982) refer to the deviations from the perfect C_s (mirror) and/or C_2 (twofold axis) symmetry bisecting 'approximately' the C atoms of the five-membered ring labelled by *x* or *y*, respectively. The torsion angle τ (°) = C(13)—C(17)—C(20)—C(22).

	φ	Q	$fC_s[C_x]$	$fC_2[C_y]$	τ
(*a*) Gamabufotalin	27 (1)	0.377 (3)	$6.0\ (2)_{14}$	$4.5\ (2)_{16}$	80 (1)
(*b*) Arenobufagin	28 (1)	0.382 (4)	$5.4\ (3)_{14}$	$5.1\ (3)_{16}$	81 (1)
(*c*) Scillarenin	30 (1)	0.372 (6)	$4.0\ (3)_{14}$	$5.9\ (3)_{16}$	−93 (1)
(*d*) Bufalin	34 (1)	0.379 (4)	$1.1\ (3)_{14}$	$8.3\ (3)_{16}$	−87 (1)
(*e*) Bufotalin	34 (1)	0.347 (3)	$1.0\ (2)_{14}$	$7.6\ (2)_{16}$	67 (1)
(*f*) Helleborogenon	39 (1)	0.400 (6)	$2.3\ (4)_{14}$	$7.9\ (4)_{17}$	78 (1)
(*g*) Telocinobufagin	42 (1)	0.413 (5)	$4.3\ (4)_{14}$	$6.7\ (4)_{17}$	78 (1)
(*h*) 14α-Artebufogenin	190 (1)	0.468 (4)	$8.2\ (3)_{13}$	$5.0\ (3)_{16}$	−81 (1)
(*i*) Cinobufagin	317 (1)	0.245 (6)	$3.2\ (5)_{17}$	$3.5\ (5)_{14}$	65 (1)
(*j*) Cinobufotalin	319 (1)	0.244 (5)	$2.1\ (4)_{17}$	$4.3\ (4)_{14}$	65 (1)

References: (*a*), (*b*) Argay *et al.* (1987); (*c*), (*f*) Ribár *et al.* (1983); (*d*) Rohrer *et al.* (1982); (*e*), (*i*) Kálmán *et al.* (1988); (*g*), (*h*) present work; (*j*) Declercq, Germain & King (1977).

Table 5. *Inter- and intramolecular hydrogen-bond geometry* (Å, °)

D—H···*A*	Symmetry relation	H···*A*	*D*···*A*	*D*—H···*A*
14α-Artebufogenin				
O(1)—H···O(3)	$\frac{1}{2}-x, -y, \frac{1}{2}+z$	2.81 (1)	3.444 (3)	147.8 (4)
Telocinobufagin.H_2O				
O(2)—H···O(1)	x, y, z	1.74 (1)	2.660 (3)	154.7 (3)
O(3)—H···O(2)	$\frac{1}{2}-x, 1-y, z-\frac{1}{2}$	1.87 (1)	2.774 (3)	162.0 (2)
O(1)—H···O(6)	$x, y, z+1$	1.61 (1)	2.711 (3)	172.3 (3)
O(6)—H(1)···O(5)	$1-x, y+\frac{1}{2}, \frac{1}{2}-z$	1.83 (1)	2.825 (3)	160.4 (3)
O(6)—H(2)···O(3)	x, y, z	1.88 (1)	2.801 (3)	156.6 (3)

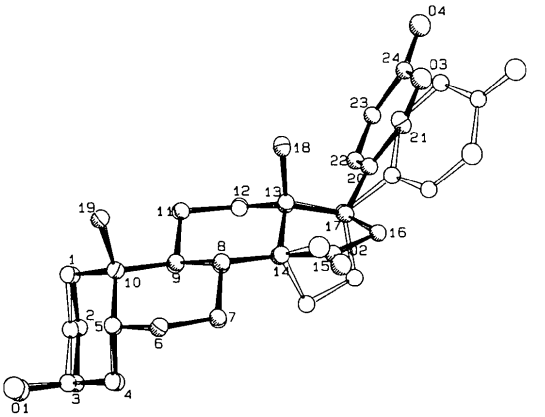


Fig. 2. A superposition of rings *B* and *C* of the steroid skeleton for (2) (shaded circles with label and full lines) and bufalin (open circles) showing the marked difference in the positions of the δ-lactone ring. The H atoms are deliberately omitted.

of Kálmán *et al.* (1991)]. Instead, a much weaker hydrogen bond is formed alone, along the longest (*c*) axis *via* the screw axis at $\frac{1}{4}$, 0, *z* in which the acceptor is the ether O atom of the lactone ring (Table 5). A similar type of hydrogen bond is formed in uzarigenin (Kálmán *et al.*, 1991) with somewhat better geometry.

The hydrogen-bond network of telocinobufagin (Table 5) is considerably influenced by the presence of a water molecule which, independently from the position of the lactone ring, spoils the isostructuralism with bufalin. The characteristic 'head-to-tail' hydrogen bond is terminated in such a way that O(1) donates to the water molecule which in turn donates to the oxo group of the lactone ring. In addition, the water molecule builds a third hydrogen bond to the 14β-hydroxy moiety. The latter donates its own intermolecular hydrogen bond to the 5β-hydroxy moiety. In contrast to this, in cinobufotalin (Kálmán *et al.*, 1988) the 5β-hydroxy group acts exclusively as a donor in an intramolecular hydrogen bond to the 3β-hydroxy group. This is common with telocinobufagin. To shed light directly on the lactone-ring effect, crystallization of water-free telocinobufagin has been attempted in various ways, but in vain. Even the co-crystallization of telocinobufagin with bufalin was fruitless.

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Structure of the Antipsychotic Drug 3-{2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl}-2,9-dimethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (Ocaperidone)*

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Abstract. $C_{24}H_{25}FN_4O_2$, $M_r = 420.5$, monoclinic, $P2_1/n$, $a = 19.95$ (1), $b = 9.782$ (5), $c = 22.07$ (1) Å, $\beta = 102.82$ (3)°, $V = 4201$ (3) Å^3, $Z = 8$, $D_m = 1.32$, $D_x = 1.329$ Mg m^{-3}, graphite-monochromated Mo $K\alpha$ radiation, $\lambda = 0.71069$ Å, $\mu = 0.087$ mm^{-1}, $F(000) = 1776$, $T = 293$ K, final $R = 0.071$ for 7404 unique observed reflections with $|F_o| \geq 4\sigma(|F_o|)$. The asymmetric unit contains two independent molecules *A* and *B*. In both molecules the piperidine ring adopts a chair conformation. For molecule *A*, this ring exhibits site-occupation disorder with the two distinct positions of the piperidine ring almost perpendicular to each other. Molecules *A* and *B* are

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