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Structure of Gitoxin

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Abstract

Gitoxin, $C_{41}H_{64}O_{14}$, is monoclinic, $P2_1$, with a = 28·213 (3), b = 7·392 (2), c = 9·615 (2) Å, β = 94·27 (1)°, V = 2000 Å^3, Z = 2, D_x = 1·296, D_m = 1·286 Mg m^{-3}. The structure was solved by direct methods and refined by block-diagonal least squares to an R factor of 4·02% for 3936 reflections. The five-membered ring of this cardiac steroid has a 13α,17β-half-chair conformation. Unlike 5β-hydroxygitoxigenin, there is no intramolecular hydrogen bond between the hydroxyls within the five-membered ring of the steroid. There is also no intramolecular hydrogen bond between the hydroxyl of one sugar to the ring oxygen of the adjacent sugar as in digoxin. Molecules pack in the crystal head to head and tail to tail along the **c** direction and are held together by three intermolecular hydrogen bonds between the neighboring molecules.

Introduction

Gitoxin, first isolated by Windaus & Schwarte (1925) from *Digitalis purpurea*, was later isolated by Smith (1931) from *D. lanata*. It differs from digoxin (Go, Kartha & Chen, 1979, 1980) by having a hydroxyl at C(16) rather than at C(12) (Fig. 1). While both are cardiac-active glycosides and their individual genins resemble each other in many respects, the intact digitalis glycosides do show interesting conformational differences.

Commercially available anhydrous gitoxin from Sigma Chemical Co., was recrystallized from a mixture of equal volumes of chloroform and methyl alcohol. The crystals are monoclinic with space group $P2_1$. The crystal selected for X-ray studies had the dimensions 0·4 × 0·4 × 0·15 mm. Lattice parameters were refined by a least-squares fit to a set of 25 measured reflections in a θ range 12–56° (Cu $K\alpha$). Three-dimensional data were collected on an Enraf–Nonius CAD-4 automated diffractometer using Ni-filtered Cu $K\alpha$ radiation by ω–2θ scans within the Cu sphere of 2θ to 154°. The measured intensities were converted to structure amplitudes in the usual manner, and corrected for Lorentz, polarization, and absorption effects. There were 4514 independent reflections measured, of which 3950 were considered observed [$I > 2\sigma(I)$].

The structure was solved by *MULTAN* (Germain, Main & Woolfson, 1971) using 386 normalized structure factors with $|E| > 1·6$. From the 128 phase sets developed, the E map corresponding to the phase set 85 which had the highest combined figure of merit was computed. The map clearly revealed 50 non-hydrogen atoms of the gitoxin molecule. Initial structure factor calculations gave an R factor of 22%. The remaining five non-hydrogen atoms were obtained by Fourier methods. Six cycles of block-diagonal least squares gave an R of 14%. After assignment of atom types and application of anisotropic temperature parameters, three more refinement cycles reduced R to 8%. All H atoms were located from the difference Fourier maps, and on their inclusion further refinement reduced R to 4·02% for 3936 reflections (isotropic refinement for H atoms). The function minimized was $\sum w(|F_o| - |F_c|)^2$, where $w = 1/\sigma^2(F)$. The final parameters are given in Table 1.* Standard deviations were calculated using Cruickshank's (1949) expressions.

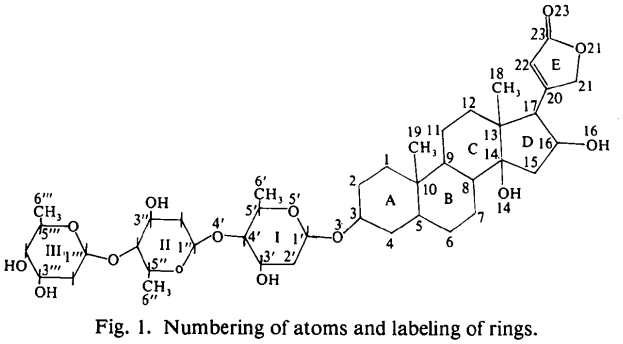

Fig. 1. Numbering of atoms and labeling of rings.

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35571 (23 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Table 1. *Fractional coordinates* ($\times 10^4$, $\times 10^3$ *for* H *atoms*) *with isotropic thermal parameters* (Å^2)

$B_{eq} = 8\pi^2 U_{eq}$ where $U_{eq} = \frac{1}{3}\sum_i \sum_j U_{ij} a_i^* a_j^* (\mathbf{a}_i . \mathbf{a}_j)$. For H atoms $T = \exp[-B(\sin^2\theta)/\lambda^2]$.

	x	y	z	B_{eq}/B		x	y	z	B
C(1)	2452 (1)	−5976 (3)	−12230 (2)	2·9	H1-C(4)	140 (1)	−470 (3)	−1143 (3)	4·0
C(2)	2311 (1)	−4042 (3)	−11925 (2)	3·3	H2-C(4)	149 (1)	−527 (4)	−979 (3)	4·7
C(3)	2059 (1)	−3923 (3)	−10594 (2)	3·4	H-C(5)	199 (1)	−752 (3)	−1027 (2)	3·6
C(4)	1640 (1)	−5204 (3)	−10661 (2)	3·3	H1-C(6)	115 (1)	−816 (4)	−1024 (3)	5·3
C(5)	1765 (1)	−7167 (3)	−10992 (2)	2·8	H2-C(6)	141 (1)	−979 (3)	−1116 (2)	3·4
C(6)	1326 (1)	−8381 (3)	−11063 (2)	3·4	H1-C(7)	74 (1)	−864 (3)	−1230 (2)	3·9
C(7)	984 (1)	−7938 (3)	−12334 (2)	3·3	H2-C(7)	84 (1)	−674 (3)	−1231 (3)	3·9
C(8)	1230 (1)	−8060 (3)	−13700 (2)	2·6	H-C(8)	133 (1)	−940 (3)	−1385 (2)	2·2
C(9)	1697 (1)	−6973 (3)	−13655 (2)	2·4	H-C(9)	162 (1)	−571 (2)	−1356 (2)	2·2
C(10)	2037 (1)	−7342 (2)	−12330 (2)	2·5	H1-C(11)	225 (1)	−668 (3)	−1496 (2)	2·9
C(11)	1929 (1)	−7349 (3)	−15015 (2)	3·1	H2-C(11)	199 (1)	−877 (3)	−1516 (2)	2·8
C(12)	1607 (1)	−6650 (3)	−16251 (2)	3·2	H1-C(12)	175 (1)	−685 (4)	−1710 (3)	4·4
C(13)	1109 (1)	−7539 (3)	−16389 (2)	2·7	H2-C(12)	162 (1)	−534 (3)	−1615 (2)	3·0
C(14)	882 (1)	−7500 (3)	−14956 (2)	2·6	H1-C(15)	34 (1)	−566 (3)	−1459 (2)	3·2
C(15)	675 (1)	−5584 (3)	−14852 (2)	3·2	H2-C(15)	84 (1)	−487 (3)	−1412 (3)	3·9
C(16)	679 (1)	−4696 (3)	−16290 (2)	3·1	H-C(16)	93 (1)	−381 (3)	−1627 (3)	3·8
C(17)	788 (1)	−6245 (3)	−17322 (2)	2·8	H-C(17)	97 (1)	−569 (3)	−1805 (2)	2·7
C(18)	1154 (1)	−9436 (3)	−16984 (2)	3·9	H1-C(18)	130 (1)	−942 (4)	−1788 (3)	4·6
C(19)	2255 (1)	−9248 (3)	−12399 (2)	3·5	H2-C(18)	86 (1)	−987 (4)	−1710 (3)	4·5
C(20)	340 (1)	−6945 (3)	−18082 (2)	3·1	H3-C(18)	136 (1)	−1022 (3)	−1639 (3)	3·9
C(21)	−75 (1)	−7807 (4)	−17460 (2)	4·3	H1-C(19)	248 (1)	−924 (4)	−1310 (3)	4·3
C(22)	222 (1)	−6732 (3)	−19436 (2)	3·5	H2-C(19)	240 (1)	−968 (4)	−1145 (3)	5·1
C(23)	−266 (1)	−7329 (3)	−19770 (2)	3·8	H3-C(19)	200 (1)	−1031 (4)	−1272 (3)	4·6
O(3)	2397 (1)	−4467 (2)	−9454 (2)	3·8	H1-C(21)	−20 (1)	−697 (3)	−1668 (3)	3·7
O(14)	509 (1)	−8823 (3)	−15079 (2)	3·7	H2-C(21)	3 (1)	−908 (4)	−1714 (3)	5·8
O(16)	245 (1)	−3757 (3)	−16640 (2)	4·1	H-C(22)	42 (1)	−609 (3)	−2006 (3)	4·0
O(21)	−440 (1)	−7940 (3)	−18599 (2)	4·7	H-O(14)	32 (1)	−837 (4)	−1452 (3)	4·8
O(23)	−504 (1)	−7330 (3)	−20870 (2)	5·0	H-O(16)	31 (1)	−308 (4)	−1735 (3)	4·9
C(1′)	2446 (1)	−3274 (3)	−8340 (2)	3·3	H-C(1′)	213 (1)	−287 (3)	−799 (2)	3·3
C(2′)	2738 (1)	−4212 (3)	−7168 (2)	3·8	H1-C(2′)	301 (1)	−467 (4)	−758 (3)	4·8
C(3′)	2868 (1)	−2943 (3)	−5965 (2)	4·0	H2-C(2′)	253 (1)	−518 (4)	−682 (3)	5·0
C(4′)	3082 (1)	−1210 (3)	−6498 (2)	2·9	H-C(3′)	307 (1)	−352 (4)	−534 (3)	4·5
C(5′)	2767 (1)	−393 (3)	−7708 (2)	3·0	H-C(4′)	340 (1)	−147 (3)	−682 (2)	2·3
C(6′)	2999 (1)	1205 (3)	−8351 (3)	4·5	H-C(5′)	246 (1)	−3 (3)	−736 (2)	3·6
C(1″)	3528 (1)	−35 (3)	−4480 (2)	2·8	H1-C(6′)	327 (1)	69 (5)	−882 (3)	5·9
C(2″)	3628 (1)	1777 (3)	−3793 (2)	3·6	H2-C(6′)	311 (1)	206 (4)	−769 (3)	5·5
C(3″)	4036 (1)	1606 (3)	−2666 (2)	3·3	H3-C(6′)	280 (1)	167 (5)	−896 (4)	6·4
C(4″)	3948 (1)	43 (3)	−1687 (2)	3·0	H-C(1″)	381 (1)	−41 (3)	−486 (2)	2·8
C(5″)	3816 (1)	−1696 (3)	−2488 (2)	3·2	H1-C(2″)	332 (1)	226 (3)	−330 (3)	3·8
C(6″)	3671 (1)	−3214 (3)	−1552 (3)	5·5	H2-C(2″)	370 (1)	265 (3)	−443 (3)	4·0
C(1‴)	4379 (1)	122 (3)	571 (2)	2·8	H-C(3″)	407 (1)	270 (3)	−214 (2)	3·4
C(2‴)	4861 (1)	−409 (3)	1261 (2)	3·5	H-C(4″)	366 (1)	35 (3)	−111 (2)	3·2
C(3‴)	4902 (1)	198 (3)	2784 (2)	3·3	H-C(5″)	407 (1)	−200 (3)	−299 (2)	3·4
C(4‴)	4788 (1)	2193 (3)	2867 (2)	3·1	H1-C(6″)	380 (1)	−261 (5)	−106 (4)	7·3
C(5‴)	4297 (1)	2590 (3)	2117 (2)	3·2	H2-C(6″)	395 (1)	−369 (5)	−89 (4)	5·9
C(6‴)	4175 (1)	4574 (4)	2089 (3)	5·0	H3-C(6″)	354 (1)	−406 (5)	−220 (4)	6·3
O(5′)	2695 (1)	−1733 (2)	−8779 (2)	3·2	H-C(1‴)	414 (1)	−50 (3)	97 (2)	2·3
O(3′)	2450 (1)	−2569 (3)	−5294 (2)	6·1	H1-C(2‴)	511 (1)	10 (3)	73 (3)	4·2
O(4′)	3131 (1)	150 (2)	−5429 (2)	3·2	H2-C(2‴)	488 (1)	−186 (3)	122 (2)	3·6
O(5″)	3417 (1)	−1323 (2)	−3459 (2)	3·2	H-C(3‴)	521 (1)	12 (3)	319 (2)	3·4
O(3″)	4459 (1)	1281 (3)	−3354 (2)	4·2	H-C(4‴)	498 (1)	292 (3)	241 (2)	3·7
O(4″)	4385 (1)	−294 (2)	−852 (2)	3·4	H-C(5‴)	405 (1)	190 (3)	261 (2)	2·9
O(5‴)	4305 (1)	2005 (2)	694 (2)	3·2	H1-C(6‴)	420 (1)	499 (5)	302 (4)	6·0
O(3‴)	4582 (1)	−806 (2)	3559 (2)	3·9	H2-C(6‴)	441 (1)	510 (5)	169 (4)	6·3
O(4‴)	4806 (1)	2797 (3)	4272 (2)	4·0	H3-C(6‴)	384 (1)	473 (5)	168 (4)	6·2
H1-C(1)	268 (1)	−634 (3)	−1146 (2)	3·8	H-O(3′)	251 (2)	−197 (6)	−458 (4)	7·4
H2-C(1)	262 (1)	−602 (3)	−1306 (2)	3·6	H-O(3″)	464 (1)	109 (4)	−275 (3)	5·2
H1-C(2)	210 (1)	−357 (3)	−1264 (2)	3·2	H-O(3‴)	474 (1)	−116 (4)	433 (3)	4·5
H2-C(2)	258 (1)	−323 (3)	−1189 (3)	4·6	H-O(4‴)	464 (1)	197 (4)	473 (3)	4·7
H-C(3)	197 (1)	−262 (3)	−1039 (2)	2·9					

Table 2. *Bond lengths* (Å) *and angles* (°)

(*a*) For gitoxin (I) (with e.s.d.'s 0·003 Å and 0·3° respectively) in comparison with digoxin (II) (e.s.d.'s 0·002 Å and 0·2°) and 5β-hydroxygitoxigenin (III) (e.s.d.'s 0·002 to 0·004 Å and <0·3°)

	(I)	(II)	(III)		(I)	(II)	(III)
C(1)–C(2)	1·518	1·523	1·523	C(10)–C(1)–C(2)	114·9	116·0	114·1
C(2)–C(3)	1·513	1·532	1·513	C(1)–C(2)–C(3)	111·3	110·7	111·1
C(3)–C(4)	1·512	1·507	1·522	C(2)–C(3)–C(4)	110·1	109·8	110·6
C(4)–C(5)	1·533	1·527	1·530	C(3)–C(4)–C(5)	114·2	113·2	113·9
C(5)–C(10)	1·552	1·550	1·562	C(4)–C(5)–C(10)	112·8	112·0	109·3
C(10)–C(1)	1·543	1·541	1·542	C(5)–C(10)–C(1)	108·2	107·8	108·1
C(5)–C(6)	1·527	1·535	1·523	C(10)–C(5)–C(6)	111·3	111·1	111·4
C(6)–C(7)	1·536	1·526	1·528	C(5)–C(6)–C(7)	111·8	112·0	113·6
C(7)–C(8)	1·533	1·525	1·528	C(6)–C(7)–C(8)	111·8	111·5	112·8
C(8)–C(9)	1·541	1·545	1·538	C(7)–C(8)–C(9)	112·7	110·3	109·9
C(9)–C(10)	1·561	1·566	1·565	C(8)–C(9)–C(10)	113·9	110·8	111·3
C(9)–C(11)	1·531	1·534	1·529	C(9)–C(10)–C(5)	110·5	109·9	108·9
C(11)–C(12)	1·530	1·520	1·521	C(8)–C(9)–C(11)	107·7	110·8	111·5
C(12)–C(13)	1·546	1·543	1·547	C(9)–C(11)–C(12)	109·7	110·7	109·6
C(13)–C(14)	1·562	1·560	1·562	C(11)–C(12)–C(13)	114·1	113·3	113·7
C(14)–C(8)	1·554	1·540	1·542	C(12)–C(13)–C(14)	110·2	108·8	109·8
C(14)–C(15)	1·539	1·522	1·527	C(13)–C(14)–C(8)	113·9	113·7	114·8
C(15)–C(16)	1·532	1·533	1·523	C(14)–C(8)–C(9)	111·8	115·4	116·0
C(16)–C(17)	1·560	1·546	1·558	C(13)–C(14)–C(15)	104·9	103·4	103·1
C(17)–C(13)	1·557	1·582	1·581	C(14)–C(15)–C(16)	107·9	103·2	104·2
C(17)–C(20)	1·504	1·496	1·496	C(15)–C(16)–C(17)	105·9	105·2	103·3
C(10)–C(19)	1·541	1·537	1·540	C(16)–C(17)–C(13)	102·6	103·8	106·2
C(13)–C(18)	1·524	1·526	1·526	C(17)–C(13)–C(14)	103·7	103·9	104·4
C(20)–C(21)	1·495	1·493	1·492	C(13)–C(17)–C(20)	120·1	115·0	119·8
C(20)–C(22)	1·329	1·332	1·329	C(16)–C(17)–C(20)	111·3	115·3	113·3
C(22)–C(23)	1·457	1·449	1·441	C(17)–C(20)–C(21)	127·3	125·5	119·4
C(21)–O(21)	1·451	1·456	1·439	C(17)–C(20)–C(22)	125·1	126·4	133·5
C(23)–O(21)	1·341	1·337	1·343	C(21)–C(20)–C(22)	107·3	108·0	107·1
C(23)–O(23)	1·210	1·226	1·214	C(20)–C(21)–O(21)	105·1	104·2	105·3
C(3)–O(3)	1·457	1·439	1·424	C(20)–C(22)–C(23)	110·1	109·1	110·3
C(14)–O(14)	1·436	1·453	1·440	C(22)–C(23)–O(21)	108·5	109·3	108·3
C(16)–O(16)	1·426	1·440*	1·427	C(23)–O(21)–C(21)	109·0	108·8	109·0
				C(22)–C(23)–O(23)	130·3	129·5	132·1
				O(21)–C(23)–O(23)	121·3	121·2	119·6

(*b*) Of the sugar portion with e.s.d.'s of 0·003 Å and 0·3° respectively for gitoxin in comparison with digoxin (e.s.d.'s 0·002 Å and 0·2°)

	Gitoxin	Digoxin		Gitoxin	Digoxin
C(1′)–C(2′)	1·514	1·522	O(5′)–C(1′)–C(2′)	109·5	109·1
C(2′)–C(3′)	1·513	1·524	C(1′)–C(2′)–C(3′)	111·8	113·8
C(3′)–C(4′)	1·522	1·530	C(2′)–C(3′)–C(4′)	110·1	110·1
C(4′)–C(5′)	1·533	1·533	C(3′)–C(4′)–C(5′)	111·4	112·2
C(5′)–C(6′)	1·505	1·511	C(4′)–C(5′)–O(5′)	108·4	110·1
C(1′)–O(5′)	1·420	1·434	C(5′)–O(5′)–C(1′)	112·8	113·9
C(5′)–O(5′)	1·433	1·429	C(4′)–C(3′)–O(3′)	110·8	110·5
C(3′)–O(3′)	1·413	1·430	C(3′)–C(4′)–O(4′)	111·6	112·5
C(4′)–O(4′)	1·438	1·435	C(4′)–C(5′)–C(6′)	112·1	110·9
C(1′)–O(3)	1·387	1·382	C(6′)–C(5′)–O(5′)	106·8	106·6
C(1″)–C(2″)	1·512	1·514	C(4′)–O(4′)–C(1″)	115·4	114·7
C(2″)–C(3″)	1·527	1·531	O(5″)–C(1″)–C(2″)	109·6	109·4
C(3″)–C(4″)	1·522	1·522	C(1″)–C(2″)–C(3″)	110·1	110·4
C(4″)–C(5″)	1·530	1·523	C(2″)–C(3″)–C(4″)	110·7	110·4
C(5″)–C(6″)	1·514	1·517	C(3″)–C(4″)–C(5″)	111·8	112·1
C(1″)–O(5″)	1·420	1·425	C(4″)–C(5″)–O(5″)	108·5	106·8
C(5″)–O(5″)	1·435	1·440	C(5″)–O(5″)–C(1″)	112·0	112·1
C(3″)–O(3″)	1·428	1·425	C(4″)–C(3″)–O(3″)	109·8	111·3
C(4″)–O(4″)	1·441	1·436	C(3″)–C(4″)–O(4″)	107·7	107·9
C(1″)–O(4″)	1·398	1·401	C(4″)–C(5″)–C(6″)	113·0	114·1
			C(6″)–C(5″)–O(5″)	107·2	106·8
			C(4″)–O(4″)–C(1‴)	115·7	113·3

* For digoxin this bond is C(12)–O(12).

Table 2 (*cont.*)

	Gitoxin	Digoxin		Gitoxin	Digoxin
C(1‴)–C(2‴)	1·520	1·514	O(5‴)–C(1‴)–C(2‴)	110·5	109·5
C(2‴)–C(3‴)	1·528	1·522	C(1‴)–C(2‴)–C(3‴)	110·1	109·2
C(3‴)–C(4‴)	1·513	1·530	C(2‴)–C(3‴)–C(4‴)	109·6	110·4
C(4‴)–C(5‴)	1·541	1·527	C(3‴)–C(4‴)–C(5‴)	110·3	113·0
C(5‴)–C(6‴)	1·506	1·513	C(4‴)–C(5‴)–O(5‴)	108·1	108·4
C(1‴)–O(5‴)	1·413	1·419	C(5‴)–O(5‴)–C(1‴)	112·9	110·9
C(5‴)–O(5‴)	1·437	1·431	C(4‴)–C(3‴)–O(3‴)	109·7	108·3
C(3‴)–O(3‴)	1·421	1·418	C(3‴)–C(4‴)–O(4‴)	111·3	109·9
C(4‴)–O(4‴)	1·420	1·433	C(4‴)–C(5‴)–C(6‴)	112·9	112·5
C(1‴)–O(4‴)	1·404	1·399	C(6‴)–C(5‴)–O(5‴)	107·2	106·1
			C(3)–O(3)–C(1′)	115·3	119·2
			O(4′)–C(1″)–O(5″)	108·0	107·0
			O(4″)–C(1‴)–O(5‴)	108·0	107·3

Discussion

As in digoxin, the gitoxin molecule shows an extended structure. The numbering of the atoms and labeling of the rings are shown in Fig. 1 and a stereoscopic view of the gitoxin molecule is in Fig. 2. An *ORTEP* (Johnson, 1965) drawing of gitoxin in parts showing the aglycone and the sugar moieties (50% probability thermal ellipsoids) is given in Fig. 3(*a*) and (*b*). Bond lengths and angles for gitoxin, digoxin (Go *et al.*, 1980) as well as 5β-hydroxygitoxigenin (Przybylska & Ahmed, 1979) [which is the aglycone of gitoxin with an additional hydroxyl at C(15)] are given in Table 2(*a*). Table 2(*b*) gives the comparison between the corresponding digitoxoses of gitoxin and digoxin.

The C–C bonds of the aglycone of gitoxin range from a minimum of 1·513 Å to a maximum of 1·562 Å with a mean of 1·539 Å. The longer bonds C(5)–C(10), C(9)–C(10), C(13)–C(14), C(14)–C(8) and C(16)–C(17) are associated with fully substituted C atoms as pointed out by Przybylska & Ahmed (1979). Note that in the case of digoxin, which does not have a substituent at C(16) like the other two molecules, C(16)–C(17) is considerably shorter than in the other two compounds. However, the substitutent at C(5) in 5β-hydroxygitoxigenin does not seem to influence the length of C(5)–C(10) appreciably. [In all three cases, there is a methyl-group substitutent at C(10).] As expected for C(sp^3)–C(sp^2) bonds, C(17)–C(20) is shortened in all three molecules. Other bonds do not deviate significantly from standard values (Sutton, 1965).

The bond angles are all in close agreement except for C(17)–C(20)–C(21) and C(17)–C(20)–C(22). These two angles show an interesting correlation with the torsional angle C(13)–C(17)–C(20)–C(22) denoting

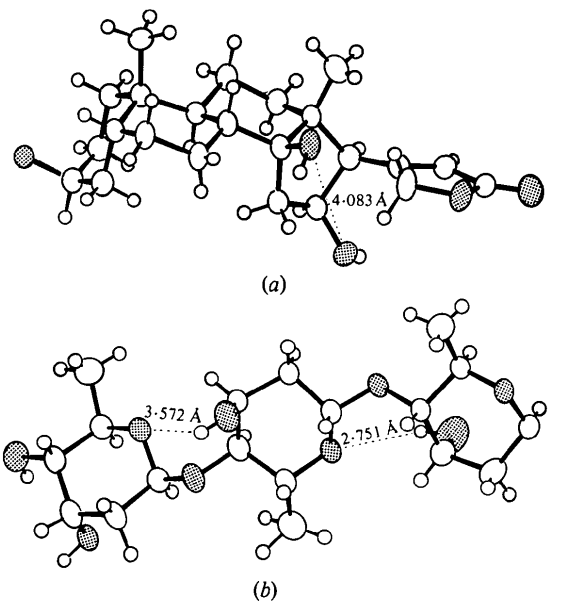

Fig. 3. *ORTEP* drawing of the molecule in parts showing thermal ellipsoids of 50% probability for (*a*) the aglycone portion, (*b*) the sugar portion. Shaded atoms are oxygens.

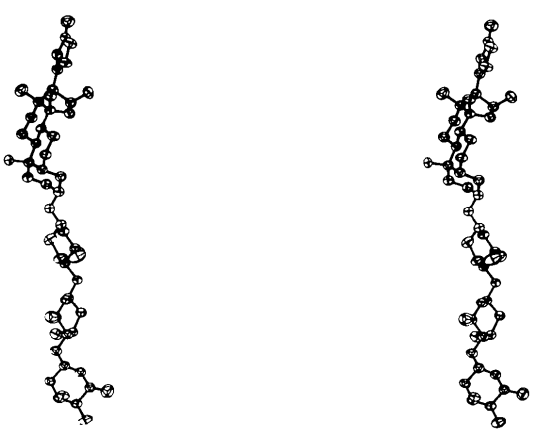

Fig. 2. Stereoscopic view of the molecule.

Table 3. *Torsion angles* (°) (*e.s.d.'s* <0·5°)

(*a*) For the rings of the aglycone and for C(17)–C(20) in gitoxin, digoxin and 5β-hydroxygitoxigenin

	Gitoxin	Digoxin	5β-Hydroxygitoxigenin
Ring *A*			
C(10)–C(1)–C(2)–C(3)	56·6	54·3	57·4
C(1)–C(2)–C(3)–C(4)	−54·5	−53·8	−54·2
C(2)–C(3)–C(4)–C(5)	54·1	57·2	54·0
C(3)–C(4)–C(5)–C(10)	−53·1	−53·7	−57·6
C(4)–C(5)–C(10)–C(1)	49·6	51·7	51·7
C(5)–C(10)–C(1)–C(2)	−52·7	−52·1	−54·7
Ring *B*			
C(5)–C(6)–C(7)–C(8)	56·0	56·3	52·0
C(6)–C(7)–C(8)–C(9)	−50·9	−57·0	−54·1
C(7)–C(8)–C(9)–C(10)	48·9	57·5	58·4
C(8)–C(9)–C(10)–C(5)	−50·1	−56·4	−58·8
C(9)–C(10)–C(5)–C(6)	54·3	54·9	54·9
C(10)–C(5)–C(6)–C(7)	−58·2	−55·2	−52·3
Ring *C*			
C(8)–C(9)–C(11)–C(12)	62·9	53·9	55·7
C(9)–C(11)–C(12)–C(13)	−59·8	−61·0	−62·0
C(11)–C(12)–C(13)–C(14)	49·1	56·8	54·6
C(12)–C(13)–C(14)–C(8)	−44·8	−48·4	−43·0
C(13)–C(14)–C(8)–C(9)	52·1	46·3	41·1
C(14)–C(8)–C(9)–C(11)	−59·8	−48·0	−46·9
Ring *D*			
C(17)–C(13)–C(14)–C(15)	−31·8	−33·0	−28·2
C(13)–C(14)–C(15)–C(16)	12·2	43·6	43·2
C(14)–C(15)–C(16)–C(17)	12·0	−37·1	−40·5
C(15)–C(16)–C(17)–C(13)	−31·5	16·1	22·1
C(16)–C(17)–C(13)–C(14)	38·8	10·2	3·8
About C(17)–C(20) bond			
C(13)–C(17)–C(20)–C(21)	58·8	81·8	−130·7
C(13)–C(17)–C(20)–C(22)	−128·6	−99·0	52·3
C(16)–C(17)–C(20)–C(21)	−61·0	−41·9	102·6
C(16)–C(17)–C(20)–C(22)	111·6	137·4	−74·4

(*b*) For the digitoxose rings

Endocyclic torsion angles

Bonded atoms	Gitoxin	Digoxin
C(1′)–C(2′)	55·8	53·6
C(2′)–C(3′)	−50·4	−48·0
C(3′)–C(4′)	50·7	47·4
C(4′)–C(5′)	−56·0	−53·8
C(5′)–O(5′)	63·3	61·6
O(5′)–C(1′)	−63·5	−60·9
Mean	56·6	54·2
C(1″)–C(2″)	58·1	56·3
C(2″)–C(3″)	−50·6	−49·2
C(3″)–C(4″)	49·7	50·7
C(4″)–C(5″)	−54·6	−57·1
C(5″)–O(5″)	63·5	65·8
O(5″)–C(1″)	−66·2	−66·7
Mean	57·1	57·6
C(1‴)–C(2‴)	56·3	60·8
C(2‴)–C(3‴)	−53·2	−50·3
C(3‴)–C(4‴)	54·8	48·0
C(4‴)–C(5‴)	−58·2	−53·1
C(5‴)–O(5‴)	62·7	63·5
O(5‴)–C(1‴)	−62·6	−68·9
Mean	58·0	57·6

Exocyclic torsion angles (φ) and pseudotorsion angles (ψ)

		Gitoxin	Digoxin
φ_1	O(5″)–C(1″)–O(4′)–C(4′)	−81·9	−79·0
$\varphi_{1'}$	C(2″)–C(1″)–O(4′)–C(4′)	159·5	163·0
φ_2	C(1″)–O(4′)–C(4′)–C(3′)	80·4	71·9
$\varphi_{2'}$	C(1″)–O(4′)–C(4′)–C(5′)	−157·8	−165·5
ψ_1	O(5″)–C(1″)···C(4′)–C(3′)	−3·0	−8·6
$\psi_{1'}$	O(5″)–C(1″)···C(4′)–C(5′)	137·6	128·8
ψ_2	C(2″)–C(1″)···C(4′)–C(5′)	1·1	−5·0
$\psi_{2'}$	C(2″)–C(1″)···C(4′)–C(3′)	−140·0	−142·5
$\psi_{av} = \frac{1}{2}(\psi_1 + \psi_2)$		−1·0	−6·8
φ_1	O(5‴)–C(1‴)–O(4″)–C(4″)	−63·4	−63·1
$\varphi_{1'}$	C(2‴)–C(1‴)–O(4″)–C4″)	177·5	178·5
φ_2	C(1‴)–O(4″)–C(4″)–C(3″)	111·8	123·8
$\varphi_{2'}$	C(1‴)–O(4″)–C(4″)–C(5″)	−127·5	−113·8
ψ_1	O(5‴)–C(1‴)···C(4″)–C(3″)	40·8	51·1
$\psi_{1'}$	O(5‴)–C(1‴)···C(4″)–C(5″)	−172·2	−157·2
ψ_2	C(2‴)–C(1‴)···C(4″)–C(5″)	62·4	78·8
$\psi_{2'}$	C(2‴)–C(1‴)···C(4″)–C(3″)	−84·6	−72·9
$\psi_{av} = \frac{1}{2}(\psi_1 + \psi_2)$		51·6	65·0

the orientation of the lactone ring. When this orientation is negative, as in gitoxin and digoxin, the above two angles are similar. However, when the orientation is positive, as in digitoxigenin and 5β-hydroxygitoxigenin, these two angles differ by as much as 14°.

Among the internal angles in the digitoxoses, those angles involving the ring O atoms are largest, and those at the 5 position C atoms the smallest as also observed in α-lactose (Fries, Rao & Sundaralingam, 1971). Similarly, the C(4′)–C(5′)–C(6′) type angles are consistently larger than the C(6′)–C(5′)–O(5′) type in all of the digitoxoses. In general, all bond lengths and angles fall in the range reported (Arnott & Scott, 1972) for β(1 → 4)-D-saccharides.

Torsion angles are given in Table 3(*a*) and (*b*), where (*a*) gives the comparison between gitoxin, digoxin and 5β-hydroxygitoxigenin and (*b*) the comparison between gitoxin and digoxin including the pseudotorsion angles. As in all cardiac-active steroids studied so far (Tokuyama, Daly, Witkop, Karle & Karle, 1968; Karle & Karle, 1969*a*,*b*; Gilardi & Flippen, 1973; Przybylska & Ahmed, 1979; Go *et al.*, 1979, 1980),

Table 4. *Hydrogen bonds in gitoxin*

$D\cdots A$	O···O	O–H	H···O	∠O–H···O	Cell unit	M*
O(14)···O(16)	2·790 (2) Å	0·856 Å	2·030 (3) Å	147·7°	0 0 $\bar{1}$	2
O(3‴)···O(4‴)	2·804 (2)	0·874	1·949 (3)	165·6	1 $\bar{1}$ 1	2
O(4‴)···O(3″)	2·785 (2)	0·901	2·018 (3)	142·4	0 0 $\bar{1}$	1

* Second atom of the intermolecular contact is with a symmetry-equivalent molecule (M) in the unit cell translated ($t_1t_2t_3$) from the parent molecule. Here $M = 1$ corresponds to the parent molecule and $M = 2$ the molecule related by the symmetry transformation $-x, \frac{1}{2}+y, -z$.

the *A* and *D* rings are *cis* with respect to the fused *B* and *C* rings. The overall conformation is almost identical to that of digoxin with the *D* ring in gitoxin having a 13α,17β-half-chair conformation while in digoxin, it is a 14β,15α half chair. Unlike the intact cardiac glycosides, all the genins observed so far have the envelope conformation for the *D* ring.

Of particular interest are the glycosidic exocyclic torsion angles φ (Sundaralingam, 1968) and the pseudotorsion angles ψ (Rohrer, 1972). There is striking agreement between these angles for gitoxin and digoxin, yet, unlike digoxin, there is no intramolecular hydrogen bond between the hydroxyl at C(3′) of the first digitoxose and the ring O atom of the second digitoxose. Mo & Jensen (1978), from their examination of the crystal structures of a number of $\beta(1\rightarrow 4)$-linked disaccharides, suggest that if the ψ_{av} of the bridge falls within the range $-12{\cdot}5$ to 39°, then there results the possibility of an intramolecular hydrogen bond between the OH at the 3 position of the sugar and the ring O atom of the adjacent sugar. However, in spite of the fact that ψ_{av} is $-1°$ for digitoxoses I and II of gitoxin, well within the range of Mo & Jensen's findings, this does not result in an intramolecular hydrogen bond. As seen from Fig. 3(*b*), O(5″)···H(O3′) is 2·751 Å and O(3′)–H···O(5″) is 3·269 Å, and they are clearly beyond the range of formation of a hydrogen bond. Unlike the case of 5β-hydroxygitoxigenin, no intramolecular hydrogen bond between O(14) and O(16) is found in gitoxin. The O(14)···O(16) distance in gitoxin is 4·083 Å.

Fig. 4 shows the packing of molecules in gitoxin, viewed down the *b* axis. The molecules are packed in a head-to-head and tail-to-tail manner and held together by three intermolecular hydrogen bonds. In forming the hydrogen bonds, the hydroxyl O(4‴) at the end serves as donor to the hydroxyl O(3″) of digitoxose II of its next neighbor and as acceptor from the hydroxyl O(3‴) of digitoxose III of the next neighbor related by a twofold screw. The third bond is formed between O(14) as a donor and O(16) as an acceptor in the two molecules also related by a twofold screw. These distances are given in Table 4.

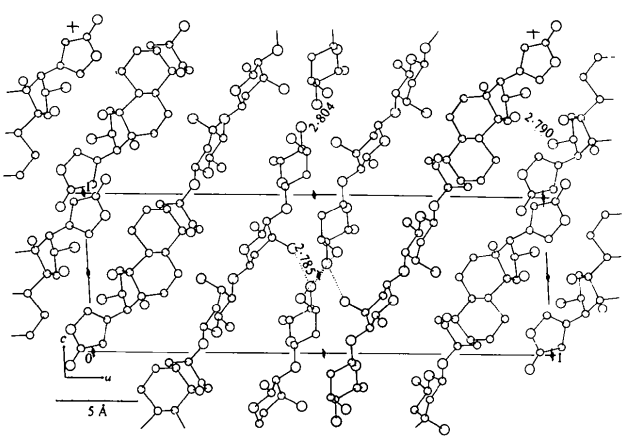

Fig. 4. Packing of molecules in the unit cell viewed down the *b* axis.

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Staphisine

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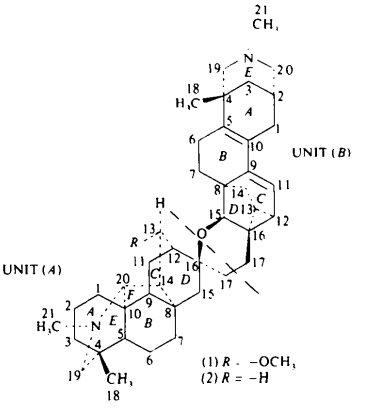
Abstract

The crystal structure of staphisine, $C_{43}H_{60}N_2O_2$, has been determined by direct methods and refined by block-diagonal least squares to $R = 0{\cdot}049$ and $R_w = 0{\cdot}068$ for 2529 observed reflections. The crystals are orthorhombic, space group $P2_12_12_1$, $a = 16{\cdot}122\ (9)$, $b = 25{\cdot}490\ (15)$, $c = 8{\cdot}822\ (4)$ Å, $D_m = 1{\cdot}150$ and $D_x = 1{\cdot}165$ Mg m^{-3} ($Z = 4$). The 3858 unique reflections with $2\theta \leq 140°$ were measured using Cu $K\alpha$ radiation on an automated four-circle diffractometer. The compound is composed of two diterpene alkaloid-like units. One of the units may have undergone prior rearrangement which modified its ring system and produced a nonplanar diene functionality. Steric interaction of the methoxy group with an *N*-methyl appears to be responsible for the shift in ^{1}H NMR resonance for the *N*-methyl relative to its resonance in the non-methoxy companion alkaloid, staphidine.

Introduction

Staphisine was first isolated in 1941 from the seeds of *Delphinium staphisagria* and at that time was tentatively assigned the molecular formula $C_{44}H_{60}N_2O$ (Jacobs & Craig, 1941). Its molecular formula was later corrected to $C_{43}H_{60}N_2O_2$ on the basis of an X-ray diffraction study of its monomethiodide (Pelletier, Kapadi, Wright, Page & Newton, 1972). The study showed staphisine to be a combination of two atisine-type diterpene alkaloid molecules. Puzzling at the time were the unusually low microanalyses for methoxy and the unclearness of the methoxy group in electron density maps. Subsequently it was discovered that the staphisine sample had actually been a mixture of staphisine (1) and the non-methoxy alkaloid staphidine (2) (Pelletier, Mody, Djarmati, Mićović & Thakkar, 1976). The crystal used for the X-ray study, while primarily staphisine methiodide, had also contained some of the staphidine derivative. A method of cleanly separating the two alkaloids was devised and crystals of pure staphisine were obtained. A more accurate X-ray crystallographic study of staphisine was then accomplished using these crystals and the details of the analysis are presented here.



Experimental

A crystal of approximate dimensions 0·6 × 0·3 × 0·1 mm was chosen for the X-ray experiment. Crystal data are listed in Table 1. Cell constants were determined by a least-squares fit to precisely measured θ values of 15 reflections. The space group was unambiguously determined from the systematic absence of $h00$, $0k0$,

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