rapidly equilibrating 1,2-dimethyl-2-benzonorbornenyl cations are best pictured as partially bridged carbenium ions with charge delocaliztion into the fused benzo ring, wherein the related benzonortricyclyl structures are considered only as minor contributors.

Experimental Section

Materials. 2-Methyl-2-*endo*-benzonorborneol (**10**) and 1,2-dimethyl-2-*endo*-benzonorborneol (**22**) were prepared according to the procedures reported by Goering et al.[4,7]

1-Methyl-2-*exo*-chlorobenzonorbornene (**11**) was prepared by chlorination of **10** with concentrated hydrochloric acid at room temperature for two hours. The product was extracted with petroleum ether (30–60 °C), washed, dried ($MgSO_4$), and distilled: bp 54–56 °C (0.02 mm); ^1H NMR ($CDCl_3$, capillary Me_4Si) δ 1.70 (s, 2 H), 2.08 (s, 3 H), 2.60 (m, 2 H), 3.70 (m, 1 H), 4.20 (m, 1 H), and 7.60 (s, 4 H).

2-Ethyl-2-*endo*-benzonorborneol (**14**) was prepared from 2-benzonorbornenone with ethylmagnesium bromide in anhydrous ether: mp 59–60 °C (pentane).

Preparation of Carbocations. In general, benzonorbornenyl cations were prepared by careful addition of a suspension of appropriate benzonorbornenyl precursors in SO_2ClF to either FSO_3H, FSO_3H–SbF_5, or SbF_5 solution in SO_2ClF at dry ice-acetone temperature (ca. −78 °C) with vigorous stirring to give ~10% solutions of the ions. An appropriate portion of the resulting solutions were immediately transferred to precooled NMR tube for NMR measurement. Details are as reported previously.[5]

Proton and Carbon-13 NMR Spectroscopy. Both proton and carbon-13 NMR spectra were obtained as previously reported.[5]

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References and Notes

(1) Stable Carbocations. 187. Part 186: G. A. Olah and D. Forsyth, *J. Am. Chem. Soc.*, **97**, 3137 (1975).
(2) (a) P. D. Bartlett and W. P. Giddings, *J. Am. Chem. Soc.*, **82**, 1240 (1960); (b) W. P. Giddings and J. Dirlam, *ibid.*, **85**, 3900 (1963); (c) H. C. Brown and G. L. Tritle, *ibid.*, 2689 (1968); **88**, 1320 (1966); (d) D. B. Braddon, G. A. Wiley, J. Dirlam, and S. Winstein, *ibid.*, **90**, 1901 (1968); (e) J. P. Dirlam, A. Diaz, S. Winstein, W. P. Giddings, and G. C. Hanson, *Tetrahedron Lett.*, 3133 (1969); (f) L. E. Barstow and G. A. Wiley, *ibid.*, 6309 (1968); (g) D. Lenoir and P.v.R. Schleyer, *Justus Liebigs Ann. Chem.*, **750**, 28 (1971); (h) J. Ipaktschi, M. N. Iqbal, and D. Lenoir, *Chem. Ber.*, **107**, 1126 (1974); (i) H. Tanida, H. Ishitobi, and T. Irie, *J. Am. Chem. Soc.*, **90**, 2688 (1968); (j) H. Tanida and T. Tsushima, *ibid.*, **93**, 3011 (1971); (k) H. Tanida, H. Ishitobi, T. Irie, and T. Tsushima, *ibid.*, **91**, 4512 (1969); (l) H. Tanida, T. Irie, and T. Tsushima, *ibid.*, **92**, 3404 (1970).
(3) (a) P. v. R. Schleyer, C. J. Lancelot, and D. J. Cram in "Carbonium Ions", Vol. 3, G. A. Olah, and P. v. R. Schleyer, Ed., Wiley-Interscience, New York, N.Y., 1972, Chapter 27; (b) H. C. Brown and K. T. Liu, *J. Am. Chem. Soc.*, **91**, 5909 (1969); (c) H. C. Brown, S. Ikegami, and K. T. Liu, *ibid.*, **91**, 5911 (1969); (d) J. P. Dirlam and S. Winstein, *ibid.*, **91**, 5905, 5907 (1969); (e) H. Tanida, *Acc. Chem. Rev.*, **1**, 237 (1968).
(4) H. L. Goering, C. S. Chang, and J. V. Clevenger, *J. Am. Chem. Soc.*, **96**, 7602 (1974).
(5) G. A. Olah, and G. Liang, *J. Am. Chem. Soc.*, **97**, 2236 (1975).
(6) G. A. Olah, and R. D. Porter, *J. Am. Chem. Soc.*, **93**, 6877 (1971); **92**, 7627 (1970).
(7) H. L. Goering, J. V. Clevenger, and K. Humski, *J. Org. Chem.*, **37**, 3019 (1972).
(8) G. A. Olah, A. M. White, J. R. DeMember, A. Commeyras, and C. Y. Lui, *J. Am. Chem. Soc.*, **92**, 4627 (1970); **91**, 3958 (1969); (b) E. Huang, K. Ranganayakulu, and T. S. Sorensen, *ibid.*, **94**, 1780 (1972).
(9) Previously reported ^{13}C NMR assignments for the 2-methyl-2-norbornyl cation (**12**) (see, G. A. Olah and G. Liang, *J. Am. Chem. Soc.*, **96**, 195 (1974)) were partially revised on the basis of obtaining the ^{13}C NMR spectra of 2-methyl-3,3-d_2-2-norbornyl cation (see also, G. A. Olah, *Acc. Chem. Res.*, **9**, 47 (1976). The carbon shifts are shown on structure **12**.
(10) G. A. Olah, G. Liang, J. R. Wiseman, and J. A. Chong, *J. Am. Chem. Soc.*, **94**, 4927 (1972).
(11) (a) G. A. Olah, and G. Liang, *J. Am. Chem. Soc.*, **96**, 189 (1974); (b) G. A. Olah, J. R. DeMember, C. Y. Lui, and R. D. Porter, *ibid.*, **93**, 1442 (1971)

Structures of Modified Cardenolides. 1. Lactam Analogues of Isodigitoxigenin

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Abstract: The crystal structures of two synthetic lactam derivatives of digitoxigenin have been determined by x-ray crystallography. The crystal data for the major product: (20*S*,21*R*)-3β-hydroxy-14,21-epoxy-5β,14β,20-cardanolactam (**4a**) hydrate, orthorhombic system, $P2_12_12_1$, a = 11.953, b = 23.611, c = 7.502 Å, Z = 4. The crystal data for the minor product: (20*R*,21*S*)-3β-hydroxy-14,21-epoxy-5β,14β,20-cardanolactam (**4b**), monoclinic, $P2_1$, a = 11.472, b = 7.7771, c = 11.463 Å, β = 97.71°, Z = 2. These crystal structures establish the stereochemistry of the C(20), C(21) ring junctions as cis-equatorial-axial and cis-axial-equatorial for **4a** and **4b**, respectively. The structure of **4a** also indicates that isodigitoxigenin also has a cis-equatorial-axial configuration. There are no unusually short intramolecular nonbonded contacts involving the lactam rings in either structure, although models had indicated these configurations would require close contacts. The only conformational differences between these two structures and digitoxigenin occur in the region of the lactam ring despite the strain introduced by the formation of a ring to O(14).

Cardiac glycosides and aglycones have an inotropic effect in both the failing heart and isolated cardiac preparations. They also are known to inhibit cardiac microsomal Na^+/K^+-ATPase at the same concentration levels. These observations have led to proposals involving a direct casual relationship between the enzymic inhibition and the positive inotropic response.[2] Other studies, however, suggest a dissociation of the two biological responses.[3-5] Several derivatives of digitoxigenin (**1**) were used in the studies showing the dissociated responses. However, some conflict concerning the stereochemistry of these derivatives (**3, 4a,** and **4b**) has arisen.

Figure 1 shows part of the pathway[3,6] leading to the three digitoxigenin derivatives (**3, 4a,** and **4b**) in question. Ammonolysis of digitoxigenin (**1**) in 75% aqueous methanol afforded two isomeric lactolamides **2a** and **2b**. Heating **2a** to 200 °C or treatment with warm glacial acetic acid caused rapid cyclization to lactam **4a**. Similar treatment of lactol-amide **2b** gave the epimeric lactam **4b**.

The configuration of the E/F rings in isodigitoxigenin (**3**) was first postulated on conformational and steric grounds to have a trans-diequatorial junction,[7] Figure 2c. The alternate trans configuration, Figure 2d, was eliminated on conforma-

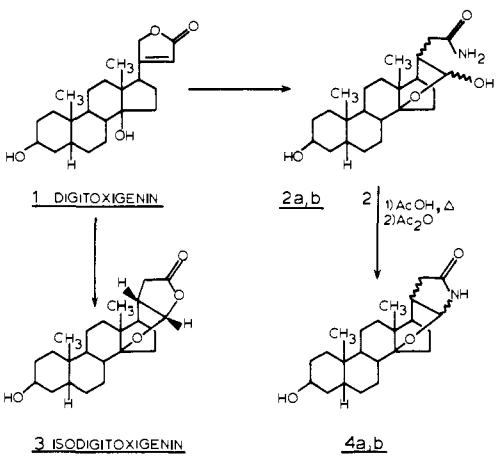


Figure 1. Schematical diagram showing the formation of isodigitoxigenin and the corresponding lactam derivatives from digitoxigenin.

tional grounds requiring a very highly distorted E ring. The cis-axial-equatorial, Figure 2b, configuration was eliminated on steric grounds involving contact between C(18) and C(22). The cis-equatorial-axial, Figure 2a, configuration was not considered possible because of short steric contacts involving O(21) of the lactone ring and C(15) and C(16).

Later NMR spectral data did not support the assignment of a trans-diequatorial configuration.[6,8] The coupling constant J for the C(21) proton was measured to be 4 to 5 Hz. Based on these measurements, the cis-equatorial-axial configuration was chosen as the most likely configuration.[6,8,9] In addition, the lactam derivatives (**4a,b**) of isodigitoxigenin were found to have similar J values for the C(21) proton and were assigned cis-equatorial-axial and cis-axial-equatorial configurations for the major (**4a**) and minor (**4b**) products, respectively.[6] However, the close proximity of two electronegative atoms combined with the same steric arguments made for isodigitoxigenin led to an alternate trans-diequatorial and cis-equatorial-axial configurational assignment for **4a** and **4b**, respectively.[3,4]

The crystal and molecular structures of derivatives **4a** and **4b** have been solved in order to determine their configuration and also conformational features which when combined with the biological data may provide some insight into the shape of the enzyme binding sites.

Experimental Section

(20*S*)- and (20*R*)-3β,21-Dihydroxy-14β,21-oxidonorcholan-23-oic Acid Amides (2a) and (2b). A solution of 6.0 g of digitoxigenin (**1**) in 650 ml of absolute methanol was treated with a stream of dry ammonia gas for 1 h at 0 °C and then stirred for 10 days at 27 °C. The excess ammonia was displaced by bubbling nitrogen through the solution. Evaporation of the solvent under reduced pressure gave a crystalline residue which was washed with water, filtered, and dried. The water washings were acidified with cold 5% HCl and the resulting precipitate was extracted into chloroform. The chloroform extract was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure to afford 0.43 g of colorless needles of isodigitoxigenin (**3**), mp 271–273 °C.

The major crystalline residue separated above was recrystallized from methanol to give 2.1 g of **2a**, which was further recrystallized from methanol to give shiny plates, mp 271–273 °C; $[\alpha]^{20}D$ −5° (*c* 1, pyridine); ν_{max}^{KBr} 3540, 3420, and 1670 cm^{-1}; NMR (pyridine-d_5) 1.00 (C-19 methyl), 1.26 (C-18 methyl), 3.56 (methanol of solvation), 4.36 (3α-H), 4.80 (NH_2), 5.43 (3β-OH), 5.76 (C-21-H), 9.08 (C-21-OH, H-bonded to carbonyl of amide) ppm.

Anal. Calcd for $C_{23}H_{37}NO_4 \cdot 2CH_3OH$: C, 65.90; H. 9.96. Found: C, 66.05; H, 9.77.

The mother liquor from the above recrystallization was evaporated to dryness under reduced pressure, and the resulting residue was dissolved in a mixture of 25 ml of methanol and 5 ml of glacial acetic acid. The mixture was warmed to 80 °C for 3 min, then kept for 8 h at 27 °C. Thin-layer chromatography showed the presence of three products (I, II, III), none of which corresponded to starting materialor **2a.** With the aid of a fraction collector the mixture was separated by column chromatography on 140 g of silica gel (Merck 0.2–0.5 mm) using a mixture of 10% benzene, 20% acetone, and 70% anhydrous ether as eluent. There was obtained 0.20 g of compound **2b,** (fraction III) in crystalline form. Recrystallization from methanol afforded colorless needles with a double mp 200–203 °C and 263–265 °C; $[\alpha]^{20}D$ + 44° (*c* 1, pyridine): ν_{max}^{KBr} 3400, 3250, and 1700 cm^{-1}; NMR (pyridine-d_5) 1.00 (C-19 methyl), 1.18 (C-18 methyl), 3.41 (methanol of solvation), 4.38 (3α-H), 4.83 (C-21-H), 4.86 (NH_2), 5.50 (3β-OH), 9.55 (C-21-OH, H-bonded to carbonyl of amide) ppm.

Anal. Calcd for $C_{23}H_{37}NO_4 \cdot CH_3OH$: C, 68.05; H, 9.76. Found: C, 68.50; H, 10.04.

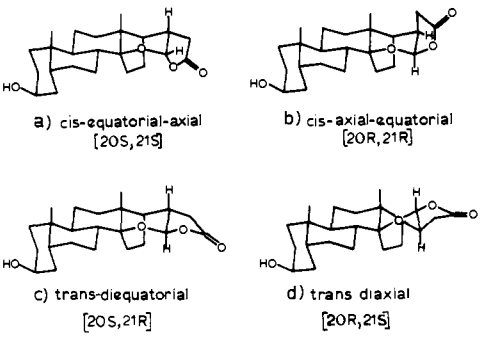


Figure 2. The four possible stereoisomers of isodigitoxigenin.

(20*S*,21*R*)- and (20*R*,21*S*)-3β-Hydroxy-14,21-epoxy-5β,14β,20-cardanolactams (4a,b). When amide **2a** was heated to 200 °C, cyclization to lactam **4a** occurred. The same result was obtained by treatment with warm glacial acetic acid. Recrystallization from aqueous methanol gave shiny plates, mp 275–277 °C; $[\alpha]^{20}D$ −19° (*c* 1, pyridine); ν_{max}^{KBr} 3521, 3448, and 1681 cm^{-1}; NMR 1.00 (C-18 and C-19 methyls), 4.16 (3α-H), 5.45 (d, J = 6 Hz, C-21-H), 5.96 (NH) ppm. The mass spectrum showed M^+ 373 corresponding to the anhydrous material.

Anal. Calcd for $C_{23}H_{35}NO_3 \cdot H_2O$: C, 70.55; H, 9.53; N, 3.58. Found: C, 70.94; H, 9.41; N, 3.57.

Heating amide **2b** to 200 °C in the same way or by treatment with warm glacial acetic acid resulted in cyclization to lactam **4b.** Recrystallization from methanol–ethyl acetate gave colorless crystals: mp 266–268 °C; $[\alpha]^{20}D$ −62° (*c* 1, pyridine); ν_{max}^{KBr} 3472, 3367, 3279, and 1678 cm^{-1}; NMR 0.99 (C-19 methyl), 1.13 (C-18 methyl), 4.15 (3α-H), 5.3 (C-21-H, d, J = 5 Hz), 6.68 (NH) ppm.

Anal. Calcd for $C_{23}H_{35}NO_3$: C, 73.96; H, 9.44; N, 3.75. Found: C, 73.74; H, 9.61; N, 3.81.

The *acetate* of **4a** was obtained on treatment with acetic anhydride in pyridine solution at 27 °C. The analytical sample crystallized from acetone–hexane mp 273–275 °C; $[\alpha]^{20}D$ −39° (*c* 1, $CHCl_3$); ν_{max}KBr 3367, 1724, 1681, 1258, and 1235 cm^{-1}; NMR 1.00 (C-18 and C-19 methyls), 2.03 (3β-acetate), 5.08 (3α-H), 5.41 (d, J = 6.5 Hz, C-21-H), 6.41 (NH) ppm. The mass spectrum showed M^+ 415.

Anal. Calcd for $C_{25}H_{37}NO_4$: C, 72.25; H, 8.97; N, 3.37. Found: C, 72.75; H, 8.89; N, 3.58.

The *acetate* of **4b** was obtained on treatment with acetic anhydride in pyridine solution. Recrystallization from ethanol gave colorless crystals: mp 241–243 °C; $[\alpha]^{20}D$ −25° (*c* 1, $CHCl_3$); NMR 0.99 (C-19 methyl), 1.11 (C-18 methyl), 2.03 (3β-acetate), 2.50 (multiplet C-22 methylene), 5.08 (3α-H), 5.28 (C-21-H, d, J = 5 Hz) 6.80 ppm.

Anal. Calcd for $C_{25}H_{37}NO_4$: C, 72.25; H, 8.97; N, 3.37. Found: C, 72.28; H, 9.04; N, 3.41.

X-Ray Crystallography. Using samples of the two stereoisomers, (20*S*,21*R*) and (20*R*,21), of 3β-hydroxy-14,21-epoxy-5β,14β,20-cardanolactam, intensity data were measured for each using a manually operated GE XRD-5 diffractometer to a maximum 2θ of 145° by the stationary-counter, stationary-crystal technique employing balanced Co–Ni filters. The background contribution was subtracted from the intensities, and they were converted to structure factor amplitudes by correcting for Lorentz and polarization factors. The relatively small size of crystals and the small absorption coefficients made absorption corrections unnecessary. The crystal and intensity data

Table I. Crystal and Intensity Measurement Data

Name	(20*S*,21*R*)-3β-Hydroxy-14,21-epoxy-5β,14β,20-cardanolactam (**4a**) hydrate	(20*R*,21*S*)-3β-Hydroxy-14,21-epoxy-5β,14β,20-cardanolactam
Molecular formula	$C_{23}H_{34}NO_3 \cdot H_2O$	$C_{23}H_{34}NO_3$
Crystallization solvent	Methanol–water	Methanol–water
Crystal size	Rectangular plate 0.15 × 0.40 × 0.58 mm	Rectangular plate 0.08 × 0.38 × 0.67 mm
Space group	$P2_12_12_1$	$P2_1$
Unit cell parameters (esd)	a = 11.953 (1) Å b = 23.611 (4) c = 7.502 (1)	a = 11.472 (1) Å b = 7.7771 (6) c = 11.463 (1) β = 97.71 (1)°
Z	4	2
	2117 Å^3	1014 Å^3
Pycnometry density,		
ρ_{expl}	1.25 g cm^{-3}	1.22 g cm^{-3}
$\rho_{x\text{-}ray}$	1.22	1.22
X-ray radiation	Cu Kα_1	Cu Kα_1
Wavelength	1.5405 Å	1.5405 Å
Max 2θ	140°	140°
Total number of unique data (data 3σ above background)	2421 (2094)	2168 (1972)

Table II. (20*S*,21*R*)-3β-Hydroxy-14,21-epoxy-5β,14β,20-cardanolactam Hydrate

ATOMIC COORDINATES (STANDARD DEVIATIONS ARE GIVEN IN PARENTHESIS)

THE FORM OF THE ANISOTROPIC THERMAL PARAMETER IS EXP[-(B11*H*H + B22*K*K + B33*L*L + B12*H*K + B13*H*L + B23*K*L)].

ATOM	X/A	Y/B	Z/C	B11	B22	B33	B12	B13	B23
C(1)	0.2783(3)	0.3477(2)	0.3461(5)	0.0063(3)	0.00143(6)	0.0139(6)	-0.0006(2)	-0.0046(8)	-0.0002(4)
C(2)	0.3356(3)	0.3488(2)	0.1638(6)	0.0056(2)	0.00194(7)	0.0188(8)	-0.0007(3)	0.0006(9)	0.0012(4)
C(3)	0.2591(4)	0.3728(2)	0.0207(6)	0.0068(3)	0.00198(7)	0.0141(6)	-0.0014(3)	0.0024(8)	0.0012(4)
C(4)	0.1481(4)	0.3482(2)	0.0189(5)	0.0068(3)	0.00182(7)	0.0100(6)	-0.0005(3)	-0.0008(7)	0.0008(4)
C(5)	0.0912(3)	0.3355(1)	0.2017(5)	0.0054(2)	0.00140(6)	0.0096(5)	0.0003(2)	-0.0007(7)	-0.0002(3)
C(6)	-0.0175(3)	0.3008(2)	0.1857(6)	0.0051(2)	0.00146(6)	0.0156(6)	0.0005(2)	-0.0018(8)	0.0005(4)
C(7)	0.0042(3)	0.2374(1)	0.1612(5)	0.0051(2)	0.00142(6)	0.0135(6)	-0.0001(2)	-0.0042(8)	0.0003(3)
C(8)	0.0828(3)	0.2136(1)	0.3043(5)	0.0045(2)	0.00138(5)	0.0102(5)	0.0003(2)	-0.0017(7)	-0.0000(3)
C(9)	0.1932(3)	0.2477(1)	0.3127(5)	0.0047(2)	0.00135(6)	0.0110(5)	-0.0001(2)	-0.0028(7)	-0.0002(3)
C(10)	0.1698(3)	0.3118(1)	0.3484(5)	0.0056(2)	0.00132(6)	0.0096(5)	0.0002(2)	-0.0005(7)	-0.0008(3)
C(11)	0.2785(3)	0.2218(2)	0.4429(6)	0.0062(3)	0.00144(6)	0.0191(8)	0.0005(2)	-0.0076(8)	-0.0005(4)
C(12)	0.2955(3)	0.1589(2)	0.4102(6)	0.0056(2)	0.00146(6)	0.0194(7)	0.0005(2)	-0.0082(8)	-0.0012(4)
C(13)	0.1858(3)	0.1258(2)	0.4189(5)	0.0058(2)	0.00145(6)	0.0186(5)	0.0006(2)	-0.0032(7)	-0.0002(3)
C(14)	0.1028(3)	0.1500(1)	0.2827(4)	0.0045(2)	0.00128(5)	0.0101(5)	0.0000(2)	-0.0010(6)	-0.0002(3)
C(15)	0.1516(3)	0.1316(2)	0.1016(5)	0.0061(2)	0.00155(6)	0.0100(5)	0.0004(2)	0.0004(7)	-0.0005(3)
C(16)	0.2176(4)	0.0762(2)	0.1394(5)	0.0067(3)	0.00156(6)	0.0150(7)	0.0004(2)	0.0012(8)	-0.0014(4)
C(17)	0.1993(3)	0.0652(2)	0.3414(5)	0.0063(3)	0.00134(6)	0.0133(6)	0.0005(2)	-0.0030(8)	0.0003(4)
C(18)	0.1423(4)	0.1264(2)	0.6122(5)	0.0099(4)	0.00184(7)	0.0110(6)	0.0010(3)	-0.0002(9)	0.0003(4)
C(19)	0.1173(4)	0.3211(2)	0.5336(5)	0.0086(3)	0.00153(6)	0.0098(5)	0.0008(3)	0.0015(8)	-0.0009(3)
C(20)	0.2929(4)	0.0313(2)	0.3783(6)	0.0071(3)	0.00137(6)	0.0159(7)	0.0001(2)	-0.0044(8)	0.0006(4)
C(21)	-0.0139(3)	0.0637(2)	0.3195(6)	0.0066(3)	0.00145(6)	0.0159(7)	-0.0003(2)	-0.0025(8)	0.0005(4)
C(22)	0.0857(4)	-0.2244(2)	0.2745(6)	0.0088(3)	0.00120(6)	0.0227(9)	0.0002(3)	-0.0102(10)	0.0005(4)
C(23)	0.0122(4)	-0.0189(2)	0.1164(6)	0.0080(3)	0.00148(6)	0.0219(8)	-0.0005(3)	-0.0095(10)	-0.0010(4)
N(21)	-0.0396(3)	0.0387(1)	0.1454(5)	0.0069(2)	0.00136(5)	0.0200(7)	-0.0001(2)	-0.0070(7)	-0.0013(4)
O(3B)	0.2442(3)	0.4317(1)	0.0543(4)	0.0093(2)	0.00176(5)	0.0170(5)	-0.0018(2)	-0.0028(7)	0.0014(3)
O(14A)	-0.0262(2)	0.1237(1)	0.3104(4)	0.0047(1)	0.00148(4)	0.0151(4)	0.0001(1)	0.0003(5)	-0.0001(2)
O(23)	0.2203(3)	-0.0413(1)	-0.0154(5)	0.0111(3)	0.00194(5)	0.0277(7)	0.0012(2)	-0.0134(8)	-0.0046(3)
O(W)	0.1419(4)	0.4905(2)	0.7902(5)	0.0157(4)	0.00288(7)	0.0205(7)	-0.0025(3)	-0.0114(9)	0.0050(4)

ATOM	X/A	Y/B	Z/C	BISO	ATOM	X/A	Y/B	Z/C	BISO
H(1A)	0.2573	0.3908	0.3808	3.5000	H(12B)	0.3313	0.1530	0.2727	3.5000
H(1B)	0.3378	0.3312	0.4415	3.5000	H(15A)	0.2060	0.1646	0.2498	3.5000
H(2A)	0.3618	0.3263	0.1326	3.5000	H(15B)	0.0856	0.1239	0.0074	3.5000
H(2B)	0.4094	0.3754	0.1731	3.5000	H(16A)	0.3073	0.0832	0.1089	3.5000
H(3A)	0.3011	0.3663	-0.1090	3.5000	H(16B)	0.1886	0.0423	0.0567	3.5000
H(4A)	0.1644	0.2974	-0.0333	3.5000	H(17A)	0.2735	0.0440	0.3975	3.5000
H(4B)	0.0932	0.3612	-0.0758	3.5000	H(18A)	0.1276	0.1698	0.6550	3.5000
H(5B)	0.2673	0.3774	0.2436	3.5000	H(18B)	0.0652	0.1025	0.6243	3.5000
H(6A)	-0.0646	0.3168	0.0725	3.5000	H(18C)	0.2044	0.1276	0.7038	3.5000
H(6B)	-0.2669	0.3058	0.3046	3.5000	H(19A)	0.0995	0.3644	0.5536	3.5000
H(7A)	0.0424	0.2305	0.0286	3.5000	H(19B)	0.0425	0.2953	0.5452	3.5000
H(7B)	-0.0736	0.2142	0.1633	3.5000	H(19C)	0.1774	0.3063	0.6358	3.5000
H(8B)	0.0428	0.2194	0.4305	3.5000	H(20)	0.0895	0.0222	0.5204	3.5000
H(9A)	0.2292	0.2456	0.1786	3.5000	H(21)	-0.0784	0.0523	0.4121	3.5000
H(11A)	0.2534	0.2291	0.5747	3.5000	H(22A)	0.0508	-0.0573	0.3606	3.5000
H(11B)	0.3548	0.2442	0.4199	3.5000	H(22B)	0.1698	-0.0383	0.2345	3.5000
H(12A)	0.3549	0.1421	0.5016	3.5000					

are given in Table I. The crystal structure of each was solved by application of the automatic structure solutions program MULTAN.[10] The structure solution for **4a** was routine. However, the structure solution of **4b** was facilitated by the application of the negative quartets figure of merit to the multiple solutions. Details of the application of this technique to this structure are given elsewhere.[11]

The atomic coordinates and thermal parameters of the nonhydrogen atoms in each structure were refined using a full-matrix least-squares procedure first with isotropic temperature factors, then anisotropic temperature factors. Fixed theoretical positions for hydrogens in each structure were calculated and used in the final least-squares cycles. A modified Hughes weighting scheme was used during the least-squares procedures:[12] $w = a/|F_o|$ for $|F_o| \geq a$; $w = |F_o|/a$ for $|F_o| < a$; the value of a was 12.0 for **4a** and 18.0 for **4b**. The final $R = (\Sigma||F_o| - |F_c||)/\Sigma|F_o|$ factors for all data are 0.077 and 0.079 for **4a** and **4b**, respectively. The final coordinates and anisotropic tem-

Table III. (20*R*,21*S*)-3β-Hydroxy-14,21-epoxy-3β,14β,20-cardanolactam

ATOMIC COORDINATES (STANDARD DEVIATIONS ARE GIVEN IN PARENTHESIS)

THE FORM OF THE ANISOTROPIC THERMAL PARAMETER IS EXP[-(B11*H*H + B22*K*K + B33*L*L + B12*H*K + B13*H*L + B23*K*L)].

ATOM	X/A	Y/B	Z/C	B11	B22	B33	B12	B13	B23
C(1)	0.7986(3)	0.2988(7)	0.2378(4)	0.0049(3)	0.0172(9)	0.0078(3)	-0.0021(9)	0.0049(5)	-0.0035(11)
C(2)	0.8074(4)	0.4987(7)	0.2191(4)	0.0058(3)	0.0196(10)	0.0067(3)	-0.0030(10)	0.0023(5)	0.0032(10)
C(3)	0.8163(4)	0.5901(6)	0.3339(4)	0.0055(3)	0.0114(7)	0.0076(3)	-0.0027(9)	0.0012(5)	0.0043(9)
C(4)	0.7163(3)	0.5388(6)	0.4017(4)	0.0043(3)	0.0138(8)	0.0069(3)	-0.0001(9)	0.0016(5)	-0.0026(10)
C(5)	0.7121(3)	0.3436(6)	0.4220(3)	0.0040(2)	0.0117(7)	0.0056(3)	-0.0018(8)	0.0009(5)	0.0022(8)
C(6)	0.6136(4)	0.2996(7)	0.4967(4)	0.0056(3)	0.0221(10)	0.0052(3)	-0.0069(10)	0.0021(5)	0.0007(11)
C(7)	0.4927(3)	0.3389(7)	0.4298(3)	0.0049(3)	0.0192(9)	0.0058(3)	-0.0036(10)	0.0034(5)	-0.0037(10)
C(8)	0.4739(3)	0.2335(6)	0.3127(3)	0.0044(3)	0.0110(7)	0.0045(3)	-0.0018(7)	0.0030(4)	-0.0009(8)
C(9)	0.5727(3)	0.2779(6)	0.2366(3)	0.0046(3)	0.0110(7)	0.0055(3)	-0.0016(8)	0.0038(4)	-0.0017(8)
C(10)	0.6969(3)	0.2421(6)	0.3048(4)	0.0042(3)	0.0106(7)	0.0068(3)	0.0008(8)	0.0023(5)	0.0001(9)
C(11)	0.5583(4)	0.1074(7)	0.1161(3)	0.0065(3)	0.0199(10)	0.0056(3)	-0.0067(10)	0.0050(5)	-0.0072(11)
C(12)	0.4267(4)	0.2259(8)	0.0523(4)	0.0067(3)	0.0233(11)	0.0058(3)	-0.0079(11)	0.0042(5)	-0.0042(11)
C(13)	0.3288(4)	0.1737(7)	0.1255(3)	0.0059(3)	0.0159(8)	0.0042(3)	-0.0051(9)	0.0017(5)	-0.0016(9)
C(14)	0.3514(3)	0.2653	0.2454(3)	0.0044(2)	0.0106(7)	0.0045(3)	-0.0018(8)	0.0037(4)	0.0004(8)
C(15)	0.3187(4)	0.4544(7)	0.2168(4)	0.0058(3)	0.0137(8)	0.0073(4)	0.0006(9)	0.0011(6)	0.0010(10)
C(16)	0.2321(4)	0.4511(8)	0.1033(4)	0.0078(4)	0.0200(10)	0.0072(4)	0.0010(12)	-0.0001(6)	0.0063(12)
C(17)	0.2068(4)	0.2586(7)	0.0777(3)	0.0068(3)	0.0198(10)	0.0048(3)	-0.0026(10)	0.0007(5)	0.0028(10)
C(18)	0.3284(4)	-0.0233(7)	0.1357(4)	0.0068(3)	0.0163(9)	0.0080(4)	-0.0076(10)	0.0016(6)	-0.0065(11)
C(19)	0.7161(4)	0.0463(7)	0.3301(5)	0.0079(4)	0.0098(8)	0.0139(5)	0.0002(11)	0.0033(8)	-0.0016(13)
C(20)	0.1096(3)	0.1493(6)	0.1476(4)	0.0042(3)	0.0233(10)	0.0059(3)	-0.0031(10)	0.0004(5)	0.0022(11)
C(21)	0.1473(3)	0.2117(7)	0.2629(4)	0.0038(3)	0.0190(10)	0.0066(3)	-0.0018(9)	0.0019(5)	0.0019(11)
C(22)	0.0579(4)	0.0166(8)	0.1265(4)	0.0051(3)	0.0284(13)	0.0079(4)	-0.0093(11)	0.0016(6)	-0.0036(13)
C(23)	0.2542(4)	-0.0548(9)	0.2485(4)	0.0045(3)	0.0291(13)	0.0094(4)	-0.0100(11)	0.0020(6)	0.0022(14)
N(21)	0.0986(3)	0.0643(6)	0.3286(3)	0.0039(2)	0.0229(9)	0.0072(3)	-0.0060(8)	0.0020(4)	0.0017(10)
O(3B)	0.9261(2)	0.5563(5)	0.4073(3)	0.0049(2)	0.0192(6)	0.0080(2)	-0.0048(7)	0.0011(4)	0.0006(8)
O(14A)	0.2716(2)	0.1985(4)	0.3288(2)	0.0040(2)	0.0165(6)	0.0049(2)	-0.0028(6)	0.0029(3)	0.0022(7)
O(23)	0.2284(4)	-0.2001(6)	0.2688(4)	0.0144(4)	0.0288(9)	0.0151(4)	-0.0264(9)	0.0086(7)	0.0015(12)

ATOM	X/A	Y/B	Z/C	BISO	ATOM	X/A	Y/B	Z/C	BISO
H(1A)	0.7856	0.2366	0.1517	3.5000	H(12B)	0.4140	0.1561	-0.0292	3.5000
H(1B)	0.8805	0.2529	0.2851	3.5000	H(15A)	0.3963	0.5276	0.2834	3.5000
H(2A)	0.7309	0.5343	0.1626	3.5000	H(15B)	0.2789	0.5122	0.2871	3.5000
H(2B)	0.8842	0.5185	0.1788	3.5000	H(16A)	0.2692	0.5120	0.0324	3.5000
H(3A)	0.8287	0.7257	0.3143	3.5000	H(16B)	0.1515	0.5167	0.1160	3.5000
H(4A)	0.6337	0.5801	0.3527	3.5000	H(17A)	0.1865	0.2361	-0.0153	3.5000
H(4B)	0.7279	0.6040	0.4859	3.5000	H(18A)	0.4127	-0.0650	0.1793	3.5000
H(5B)	0.7946	0.3057	0.4720	3.5000	H(18B)	0.2598	-0.0605	0.1871	3.5000
H(6A)	0.6242	0.3702	0.5755	3.5000	H(18C)	0.3114	-0.0777	0.0490	3.5000
H(6B)	0.6208	0.1658	0.5226	3.5000	H(19A)	0.8011	0.0276	0.3817	3.5000
H(7A)	0.4828	0.4672	0.4118	3.5000	H(19B)	0.6477	-0.0810	0.3779	3.5000
H(7B)	0.4271	0.2911	0.4832	3.5000	H(19C)	0.7128	-0.0209	0.2472	3.5000
H(8B)	0.4806	0.0978	0.3333	3.5000	H(20)	0.0382	0.2865	0.1261	3.5000
H(9A)	0.5673	0.4143	0.2210	3.5000	H(21)	0.1157	0.3306	0.3144	3.5000
H(11A)	0.6146	0.2313	0.0629	3.5000	H(22A)	0.1117	-0.0610	0.0773	3.5000
H(11B)	0.5666	0.0502	0.1296	3.5000	H(22B)	-0.0303	0.0242	0.0777	3.5000
H(12A)	0.4190	0.3616	0.0352	3.5000					

perature factors are given in Tables II and III. A list of observed and calculated structure factor amplitudes are given in Tables IV and V (see Supplementary Material).

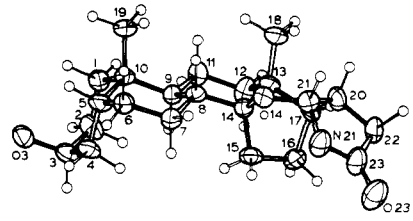
Results and Discussion

The crystallographically observed molecular structures of the two lactam derivatives **4a** and **4b** are shown in Figure 3 ORTEP[13] drawings. The bond lengths and valence angles shown on Figure 4a and 4b are all within the range of values found in other steroid molecules of this type (see Supplementary Material). The average estimated standard deviations are 0.005 and 0.006 Å in the bond lengths and 0.2 and 0.3° in the bond angles for derivatives **4a** and **4b**, respectively. Figure 4c shows the intra-ring torsion angles.

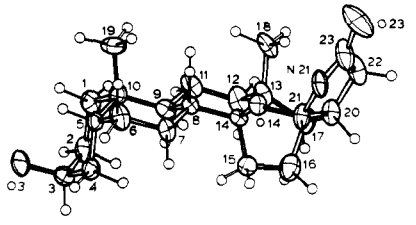
Figure 5 shows the configuration of C(20) and C(21) to be (20*S*,21*R*) for the major lactam derivative (**4a**) and (20*R*,21*S*) for the minor lactam derivative (**4b**). These configurations correspond to the cis-equatorial-axial and cis-axial-equatorial configuration for **4a** and **4b**, respectively, described earlier for the possible structures of isodigitoxigenin (**3**).[14] Since spectral studies indicate that the major lactam derivative and isodigitoxigenin are configurationally equivalent, isodigitoxigenin must also have the cis-equatorial-axial configuration at C(20) and C(21).

The A, B, and C rings in both derivatives all have chair conformations, and the corresponding rings in each structure are nearly the same despite dissimilar packing environments. The D rings in each structure also have very similar C(13) α-envelope conformations. The pseudo-rotational parameters[15] Δ and ϕ_m are 39.8 and −48.7° for **4a** and 49.0 and −47.8° for **4b**.

The E rings in each structure have highly distorted chair conformations. Both structures have very large intra-ring



a) The (20S,21R) Structure, **4a**



b) The (20R,21S) Structure, **4b**

Figure 3. The ORTEP[13] drawings of the major (**4a**) and minor (**4b**) lactam derivatives.

torsion angles involving C(13) and relatively small torsion angles involving C(20) and C(21). Distortions of this type are partially caused by the steric interactions between C(20) and C(21) of the E ring and C(15) and C(16) of the D ring. The distance between C(20) and C(16) are 2.561 and 2.424 Å for **4a** and **4b**. The corresponding distances between C(21) and C(15) are 3.026 and 2.758 Å.

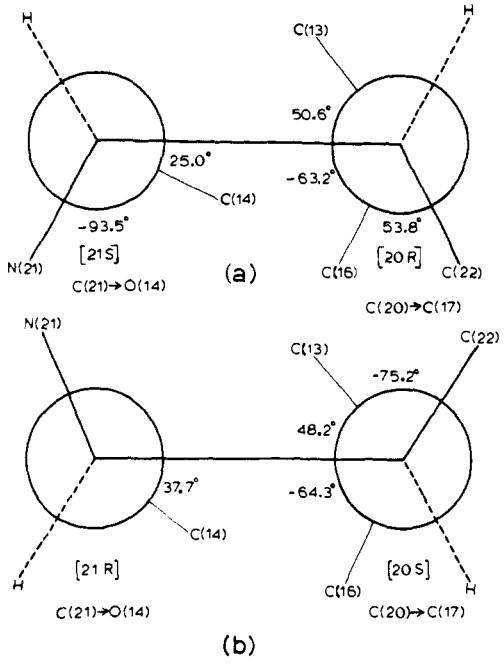


Figure 5. The stereochemistry of **4a** and **4b**.

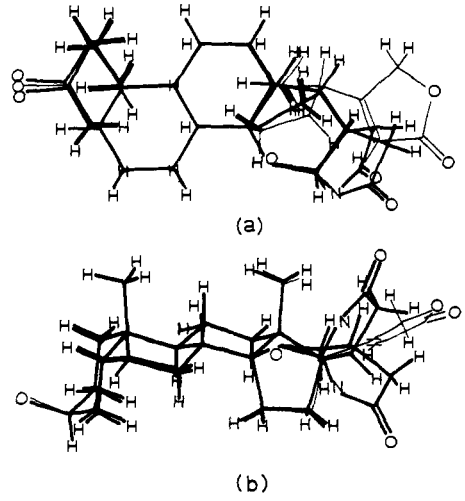


Figure 6. Superposition of **4a**, **4b**, and digitoxigenin (light lines).

Table VI. Hydrogen Bonds

Hydrogen bonded atoms	Distance, Å	Symmetry operator
4a crystal structure		
O(3B)···N(21)	3.068	$\frac{1}{2}+x, \frac{1}{2}-y, -z$
O(3B)···O(W)	2.711	$x, y, -1+z$
O(3B)···O(W)	2.891	$\frac{1}{2}+x, \frac{3}{2}-y, -1-z$
O(23)···O(W)	2.775	$-x, -\frac{1}{2}+y, \frac{1}{2}-z$
4b crystal structure		
O(3B)···O(23)	2.782	$1+x, 1+y, z$
O(3B)···N(21)	3.060	$1-x, \frac{1}{2}+y, 1-z$

The conformations of the lactam rings are quite different. The different intramolecular steric environments acting on these rings result in a C(20) envelope conformation in the structure of **4a** and a C(21), N(21) half-chair conformation in **4b**. These conformational differences minimize the steric interactions in **4a** and **4b** that were thought to make these configurations unlikely. The contact distances between N(21) of the lactam ring and C(15) and C(16) are 3.185 and 3.200 Å in **4a**. The contact in **4b** between C(22) and C(18) is 3.145 Å and the C(22) to H(18B) contact distance is 2.58 Å.

Comparison of the two lactam structures to the structure of digitoxigenin (**1**)[16] by superimposing structural drawings, Figure 6, of the three molecules shows that the entire steroid backbone structures are nearly identical. In addition, the O(3) and O(14) positions in each structure are also identical. The major structural differences occur in the area of the lactam and lactone rings. The lactone ring in the structure of digitoxigen nearly bisects the angle formed by the two lactam rings; see Figure 6b. The positions of the functional oxygen or nitrogen in each structure are also quite different.

The hydrogen bonding in the crystal structure of the major derivative **4a** is a three-dimensional network involving O(3), N(21), O(23), and the water. Table VI gives the hydrogen bond distances. The hydrogen bonding in the crystal structure of **4b** is much simpler. Table VI also gives the hydrogen bond distances in this structure.

Summary

(1) The conformation of the steroid backbone and the O(3) and O(14) positions are not significantly different from digitoxigenin despite the strain introduced by the formation of the E ring. Furthermore, there are no unusually close intmolecular nonbonded contacts involving the lactam rings as molecular models had suggested. (2) The configurations of C(20) and C(21) are *S* and *R* or cis-equatorial-axial in the major product **4a** while they are *R* and *S* or cis-axial-equatorial in the minor product **4b**. The combination of spectral evidence with this structure determination indicates that isodigitoxigenin (**3**) has a (20*S*,21*S*) or cis-equatorial-axial configuration.

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Supplementary Material Available: A listing of observed and calculated structure factor amplitudes for (20*S*,21*R*)-3β-hydroxy-14,21-epoxy-5β,14β,20-cardanolactam (**4a**) hydrate and (20*R*,21*S*)-3β-hydroxy-14,21-epoxy-5β,14β,20-cardanolactam (**4b**) (Tables IV and V) and Figure 4 showing (a) the bond lengths, (b) the bond angles, and (c) the intra-ring torsion angles of **4a** (top number) and **4b** (bottom values) (23 pages). Ordering information is given on any current masthead page.

References and Notes

(1) (a) Medical Foundation of Buffalo; (b) University of California.
(2) (a) H. R. Besch, J. C. Allen, G. Glick, and A. Schwartz, *J. Pharmacol. Exp. Ther.*, **171**, 1 (1970). (b) K. Repke, *Klin. Wochenschr.*, **42**, 157 (1964).
(3) B. G. Katzung, J. A. Muñoz, D. Y. S. Shirachi, A. J. Trevor, H. H. Chang, and M. E. Wolff, *Experientia*, **26**, 1189 (1970).
(4) J. N. Davisson, J. A. Muñoz, B. G. Katzung, M. E. Wolff, and A. J. Trevor, *Proc. West. Pharmacol. Soc.*, **15**, 31 (1972).
(5) K. S. Lee and W. Klaus, *Pharmacol. Rev.*, **23**, 193 (1971).
(6) J. M. Ferland, Y. Lefebvre, R. Dinoi, and R. Deghenghi, *Can. J. Chem.*, **49**, 2676 (1971).
(7) O. Schindler and T. Reichstein, *Helv. Chim. Acta*, **39**, 1876 (1956).
(8) G. R. Pettit, T. R. Kasturi, J. C. Knight, and J. Occolowitz, *J. Org. Chem.*, **35**, 1404 (1970).
(9) A. F. Krasso, M. Binder, and Ch. Tamm, *Helv. Chim. Acta*, **55**, 1352 (1972).
(10) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. A*, **27**, 368 (1971).
(11) G. T. DeTitta, J. W. Edmonds, D. A. Langs, and H. Hauptman, *Acta Crystallogr., Sect. A*, **31**, 472 (1975).
(12) E. W. Hughes, *J. Am. Chem. Soc.*, **63**, 1737 (1941).
(13) C. K. Johnson, ORTEP, Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1970.
(14) The change to N(21) in the lactam derivatives from O(21) in isodigitoxigenin reverses the configurational notation for C(21).
(15) C. Altona, J. J. Geise, and C. Romers, *Tetrahedron*, **24**, 13 (1968).
(16) I. L. Karle and J. Karle, *Acta Crystallogr., Sect. B*, **25**, 434 (1969).