

Steroidal versus Non-steroidal Forms. Part 1. Conformation of Methyl *cis*-Tetrahydro- α - and - β -santoninate

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The crystal and molecular structures of methyl *cis*-tetrahydro- α - (I) and - β -santoninate (II) have been determined in order to elucidate their conformations. X-Ray structure analyses reveal that both compounds have non-steroidal conformations in the solid state. Furthermore, positive Cotton effects on the c.d. curves given by both compounds indicate the presence of non-steroidal conformations in solution.

The conformations adopted by *cis*-decalin derivatives are more uncertain than those of the *trans*-derivatives, because the former can exist either in steroidal or non-steroidal forms. The conformation of methyl *cis*-tetrahydro- α -santoninate (I) has been discussed, based upon the sign of the Cotton effect and the absence of intramolecular hydrogen bonding in the i.r. spectrum.¹ Some compounds with a *cis*-decalin system² are believed to adopt non-steroidal conformations, the evidence coming mainly from o.r.d., c.d., and n.m.r. measurements. In this paper we clarify the conformations of methyl *cis*-tetrahydro- α -(I) and - β -santoninate (II) in

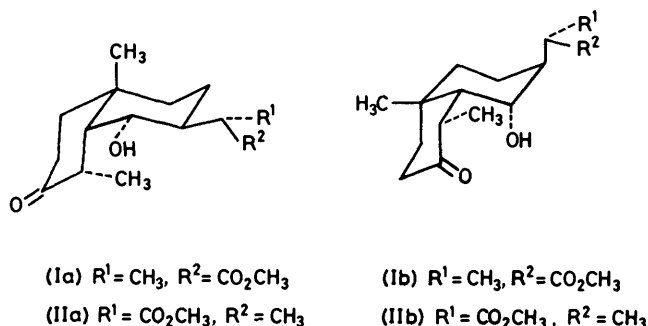


FIGURE 1 Steroidal (a) and non-steroidal (b) forms of compounds (I) and (II)

both solid and solution states by means of X-ray analyses and c.d. and n.m.r. spectra.

EXPERIMENTAL

Methyl cis-Tetrahydro- α -santoninate (I) [*Methyl* (4*S*, 5*R*, 6*S*, 7*S*, 10*S*, 11*S*)-2-(6-Hydroxy-4,10-dimethyl-3-oxo-*euodesman*-7-yl)propionate].—This compound was prepared by the reported procedure,³ m.p. 159–160° (lit.,³ 158–160°); c.d. (methanol) $[\theta]_{276}^{25} + 1950$, $[\theta]_{218} + 1870$; (chloroform) $[\theta]_{285}^{25} + 2136$; (dioxan) $[\theta]_{284}^{19} + 2200$, $[\theta]_{213} + 2590$; $\delta(\text{CDCl}_3)$; 100 MHz) 1.00 (3 H, d, J 7 Hz, 4-Me), 1.14 (3 H, d, 3, J 7 Hz, 11-Me), 1.20 (3 H, s, 10-Me), 1.78 (1 H, dd, $J_{5,4}$ 6.5, $J_{5,6}$ 3 Hz, 5 β -H), 2.49 (1 H, dq, $J_{11,11-\text{Me}}$ 7, $J_{11,7}$ 11.5 Hz, 11-H), 2.70 (1 H, dq, $J_{4,5}$ 6.5, $J_{4,4-\text{Me}}$ 7 Hz, 4 β -H), and 3.64 (3 H, s, OMe).

Methyl cis-Tetrahydro- β -santoninate (II) [*Methyl* (4*S*, 5*R*, 6*S*, 7*S*, 10*S*, 11*R*)-2-(6-Hydroxy-4,10-dimethyl-3-oxo-*euodesman*-7-yl)propionate].—This compound was prepared from tetrahydro- β -santonin⁴ by the same procedure as (I), m.p. 152–153°; c.d. (methanol) $[\theta]_{276}^{25} + 1750$; (chloroform)

$[\theta]_{281}^{25} + 1980$; (dioxan) $[\theta]_{284}^{21} + 1900$; $\delta(\text{CDCl}_3)$; 100 MHz) 1.08 (3 H, d, J 6 Hz, 4-Me), 1.15 (3 H, d, $J_{11-\text{Me},11}$ 6 Hz, 5 β -H), 1.87 (1 H, m, $J_{7,6}$ 3, $J_{7,11}$ 11 Hz, 7 α -H), 2.58 (1 H, dq, $J_{11,11-\text{Me}}$ 6 Hz, 4 β -H), 3.68 (3 H, s, OMe), and 4.06 (1 H, dd, $J_{6,5}$ 3 Hz, 6 β -H) (Found: C, 68.05; H, 9.3. Calc. for $\text{C}_{16}\text{H}_{26}\text{O}_4$: C, 68.05; H, 9.3%).

Structure Solution and Refinement.—The experimental procedures used for the two compounds were closely similar. The crystals of both methyl *cis*-tetrahydro- α -(I) and β -santoninate (II) used for the X-ray analyses were obtained by recrystallization from ethyl acetate. The density of the crystals was measured by the flotation method in carbon tetrachloride–light petroleum.

Space groups and preliminary lattice constants were determined by Weissenberg photographs. Accurate cell dimensions were determined by least-squares refinement using the accurately measured 2θ values of the 20 strong reflections in the range of $4^\circ \leq 2\theta \leq 20^\circ$. The intensities were measured by means of a Rigaku four-circle diffractometer using Mo- K_α radiation (λ 0.710 69 Å). Intensities of reflections with 2θ values up to 45° for compounds (I) and 55° for compound (II) were collected by the θ – 2θ scan method with a 2θ scan rate of 4° min^{-1} . Crystallographic data for the two compounds are presented in Table 1.

TABLE 1
Crystallographic data

Compound	(I)	(II)
Crystal dimensions (mm ³)	0.2 × 0.2 × 0.2	0.2 × 0.2 × 0.2
Space group	Tetragonal, $P4_32_2$	Monoclinic, $P2_1$
Cell dimensions a (Å)	10.437 ± 0.001	14.203 ± 0.007
b (Å)	10.437 ± 0.001	7.550 ± 0.004
c (Å)	29.130 ± 0.008	7.355 ± 0.003
β		96.16 ± 0.06°
Density (g cm ⁻³) Observed	1.18	1.18
Calculated	1.183	1.185
Z	8	2
U (Å ³)	3 172	784
$F(000)$	1 232	308

Three standard reflections, measured at intervals of every 50 reflections, showed no significant decrease in intensity during the course of data collection. The specimens used for intensity measurement were small enough (see Table 1) to neglect absorption corrections. The intensities were corrected for Lorentz and polarization factors.

The total numbers of independently observed reflections of the compounds (I) and (II) above the $3\sigma|F|$ level were 1 324 and 1 465, respectively. The structures of both compounds were solved by the multisolution method (MULTAN).⁵ The E map of the solution with the highest figure of merit showed the skeleton of compounds (I)

and (II) respectively. The rest of the molecule was found by a series of least-square refinements and difference maps.

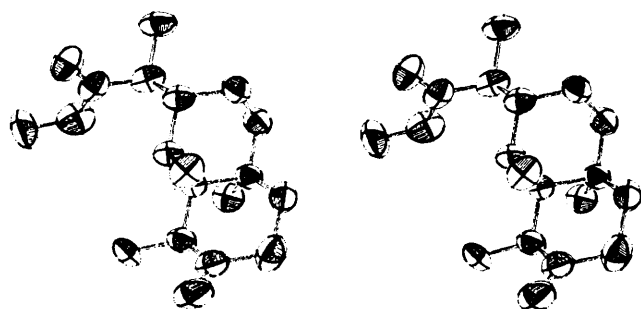


FIGURE 2 ORTEP stereoview of methyl *cis*-tetrahydro- α -santoninate (I)

All atoms except the methyl hydrogens in compound (I) were eventually located. With anisotropic thermal parameters for non-hydrogen atoms and with isotropic thermal parameters for hydrogen atoms, the final *R* values for (I) and (II) were 9.68 and 6.08%, respectively. Final thermal parameters and anisotropic temperature factors for (I) and (II) are in Supplementary Publication No. SUP 22418 (4 pp.).*

RESULTS AND DISCUSSION

Final co-ordinates and anisotropic thermal parameters for non-hydrogen atoms and isotropic thermal parameters

TABLE 2
Atomic parameters of methyl *cis*-tetrahydro- α -santoninate (I)

Atom	<i>x</i>	<i>y</i>	<i>z</i>
C(1)	0.407 4(9)	0.118 4(10)	0.279 0(3)
C(2)	0.377 6(10)	0.099 4(10)	0.227 7(3)
C(3)	0.233 6(10)	0.104 6(9)	0.217 0(3)
C(4)	0.166 0(9)	0.217 7(9)	0.236 7(2)
C(5)	0.192 5(8)	0.229 4(7)	0.288 8(2)
C(6)	0.119 8(8)	0.127 1(8)	0.315 4(2)
C(7)	0.142 7(9)	0.134 0(8)	0.366 9(3)
C(8)	0.284 6(9)	0.130 0(9)	0.376 8(3)
C(9)	0.356 4(9)	0.237 8(9)	0.352 0(3)
C(10)	0.337 3(8)	0.235 4(9)	0.298 9(3)
C(11)	0.068 1(10)	0.249 0(8)	0.389 3(3)
C(12)	-0.071 4(9)	0.237 2(9)	0.379 8(3)
C(13)	0.299 9(10)	0.361 5(9)	0.279 9(3)
C(14)	0.025 6(9)	0.225 0(11)	0.223 6(3)
C(15)	0.091 9(11)	0.257 7(10)	0.442 3(3)
C(16)	-0.252 4(10)	0.320 3(12)	0.339 4(4)
O(1)	0.183 8(7)	0.030 2(7)	0.190 9(2)
O(2)	0.156 6(6)	0.005 5(5)	0.297 7(2)
O(3)	-0.137 6(7)	0.154 1(7)	0.395 6(2)
O(4)	-0.117 3(8)	0.329 2(7)	0.351 8(2)
H(1ax)	0.385(8)	0.015(8)	0.300(2)
H(1eq)	0.491(8)	0.153(9)	0.282(3)
H(2ax)	0.446(14)	0.216(14)	0.199(4)
H(2eq)	0.397(9)	0.033(9)	0.228(3)
H(4ax)	0.195(7)	0.277(7)	0.223(2)
H(5ax)	0.163(6)	0.320(6)	0.300(2)
H(6eq)	0.006(7)	0.150(7)	0.311(2)
H(7eq)	0.104(7)	0.056(7)	0.382(2)
H(8eq)	0.281(9)	0.132(9)	0.419(3)
H(8ax)	0.336(8)	0.040(8)	0.361(3)
H(9ax)	0.311(7)	0.350(7)	0.365(2)
H(9eq)	0.461(7)	0.231(7)	0.352(2)
H(11)	0.109(7)	0.332(7)	0.382(2)
H[O(2)]	0.104(6)	-0.054(5)	0.305(2)

* For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1978, Index issue.

for hydrogen atoms in compounds (I) and (II) are listed in Tables 2 and 3, respectively. The bond lengths and

TABLE 3

Atomic parameters of methyl *cis*-tetrahydro β -santoninate (II)

Atom	<i>x</i>	<i>y</i>	<i>z</i>
C(1)	0.283 4(3)	0.254 8(8)	0.706 4(7)
C(2)	0.209 9(4)	0.120 6(9)	0.756 1(7)
C(3)	0.128 0(4)	0.092 7(9)	0.610 5(7)
C(4)	0.153 6(3)	0.080 0(8)	0.417 2(6)
C(5)	0.221 0(3)	0.230 4(6)	0.371 5(6)
C(6)	0.166 9(3)	0.406 8(7)	0.347 4(6)
C(7)	0.229 8(3)	0.563 4(7)	0.304 5(6)
C(8)	0.317 9(3)	0.571 2(7)	0.443 6(6)
C(9)	0.370 7(3)	0.398 7(7)	0.461 8(7)
C(10)	0.310 5(3)	0.240 4(7)	0.511 9(6)
C(11)	0.249 4(3)	0.558 9(8)	0.101 3(6)
C(12)	0.325 1(4)	0.691 4(8)	0.065 6(7)
C(13)	0.371 0(4)	0.073 6(9)	0.499 6(8)
C(14)	0.067 0(4)	0.058 2(10)	0.275 7(7)
C(15)	0.159 5(4)	0.605 5(11)	-0.026 5(7)
C(16)	0.471 6(5)	0.731 8(14)	-0.054 0(12)
O(1)	0.049 0(3)	0.067 1(8)	0.651 3(5)
O(2)	0.123 8(2)	0.441 6(6)	0.510 9(4)
O(3)	0.319 5(3)	0.847 2(6)	0.085 4(6)
O(4)	0.397 9(3)	0.611 3(7)	-0.000 8(6)
H(1eq)	0.342(3)	0.251(8)	0.799(6)
H(1ax)	0.260(3)	0.365(6)	0.723(5)
H(2eq)	0.184(3)	0.156(7)	0.867(6)
H(2ax)	0.234(3)	-0.026(7)	0.740(6)
H(4ax)	0.188(3)	-0.025(7)	0.401(6)
H(5ax)	0.239(3)	0.214(7)	0.241(6)
H(6eq)	0.114(3)	0.388(6)	0.245(5)
H(7eq)	0.194(3)	0.670(6)	0.328(6)
H(8eq)	0.366(3)	0.669(6)	0.407(6)
H(8ax)	0.297(2)	0.608(6)	0.563(5)
H(9eq)	0.424(3)	0.403(7)	0.569(6)
H(9ax)	0.394(3)	0.370(7)	0.334(6)
H(13a)	0.391(4)	0.064(10)	0.363(8)
H(13b)	0.432(3)	0.088(9)	0.579(6)
H(13c)	0.340(3)	-0.037(7)	0.518(6)
H(14a)	0.087(3)	0.058(8)	0.148(6)
H(14b)	0.038(3)	-0.042(7)	0.294(6)
H(14c)	0.018(3)	0.177(7)	0.286(6)
H[O(2)]	0.063(4)	0.481(11)	0.478(6)
H(11)	0.268(3)	0.428(7)	0.071(6)
H(12a)	0.172(3)	0.603(9)	-0.147(6)
H(12b)	0.106(3)	0.518(8)	-0.019(7)
H(12c)	0.139(4)	0.718(9)	0.016(8)
H(16a)	0.450(5)	0.802(12)	-0.178(10)
H(16b)	0.523(4)	0.660(9)	-0.075(8)
H(16c)	0.477(5)	0.835(11)	0.023(11)

angles calculated from the co-ordinates are shown in Tables 4 and 5 for compounds (I) and (II), respectively. The values are not significantly different from the expected ones.

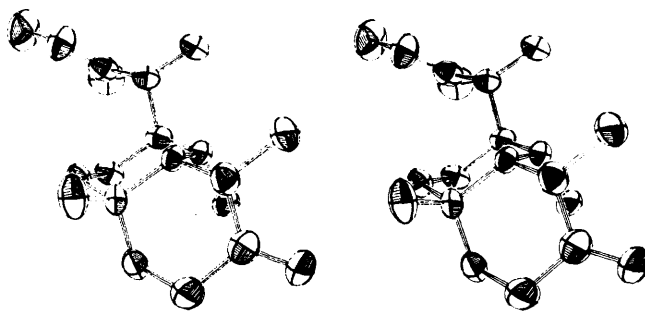


FIGURE 3 ORTEP stereoview of methyl *cis*-tetrahydro- β -santoninate (II)

Torsion angles in the rings are shown in Table 6. The A and B rings take slightly deformed chair conformations. The distortion of ring A seems to be caused mainly by the interactions between the bulky axial

methyl group and the axial 2- and 4-hydrogen atoms, and that of ring B by the interactions between the bulky axial isopropyl residue and the axial hydrogen atoms at C(5) and C(9). Considering the magnitude of the

TABLE 4

Bond lengths (Å) and angles (°) of (I) (standard deviations are referred to the last digits)

C(1)–C(2)	1.54(1)	C(2)–C(1)–C(10)	111.8(0.8)
C(1)–C(10)	1.54(1)	C(3)–C(2)–C(1)	113.0(0.8)
C(2)–C(3)	1.54(1)	C(4)–C(3)–C(2)	114.4(0.8)
C(3)–C(4)	1.49(1)	C(4)–C(3)–O(1)	123.4(0.8)
C(3)–O(1)	1.20(1)	C(2)–C(3)–O(1)	121.8(0.8)
C(4)–C(5)	1.55(1)	C(5)–C(4)–C(3)	110.9(0.7)
C(4)–C(14)	1.52(1)	C(5)–C(4)–C(14)	114.6(0.7)
C(5)–C(6)	1.53(1)	C(3)–C(4)–C(14)	113.5(0.7)
C(5)–C(10)	1.54(1)	C(6)–C(5)–C(4)	110.7(0.6)
C(6)–C(7)	1.52(1)	C(6)–C(5)–C(10)	115.1(0.6)
C(6)–O(2)	1.43(1)	C(4)–C(5)–C(10)	111.5(0.6)
C(7)–C(8)	1.51(1)	C(7)–C(6)–C(5)	112.7(0.7)
C(7)–C(11)	1.57(1)	C(7)–C(6)–O(2)	110.7(0.6)
C(8)–C(9)	1.53(1)	C(5)–C(6)–O(2)	107.4(0.6)
C(9)–C(10)	1.56(1)	C(8)–C(7)–C(6)	110.3(0.7)
C(10)–C(13)	1.57(1)	C(8)–C(7)–C(11)	115.3(0.7)
C(11)–C(12)	1.49(1)	C(6)–C(7)–C(11)	111.3(0.7)
C(11)–C(15)	1.57(1)	C(9)–C(8)–C(7)	111.7(0.7)
C(12)–O(3)	1.20(1)	C(10)–C(9)–C(8)	113.1(0.7)
C(12)–O(4)	1.35(1)	C(13)–C(10)–C(1)	109.5(0.7)
C(16)–O(4)	1.46(1)	C(13)–C(10)–C(5)	112.0(0.7)
		C(13)–C(10)–C(9)	106.5(0.7)
		C(1)–C(10)–C(5)	111.2(0.7)
		C(1)–C(10)–C(9)	109.0(0.7)
		C(5)–C(10)–C(9)	108.4(0.7)
		C(12)–C(11)–C(7)	110.2(0.7)
		C(12)–C(11)–C(15)	110.1(0.7)
		C(7)–C(11)–C(15)	112.0(0.7)
		O(3)–C(12)–C(11)	123.5(0.8)
		O(3)–C(12)–O(4)	122.9(0.8)
		C(11)–C(12)–O(4)	113.7(0.8)
		C(12)–O(4)–C(16)	116.6(0.8)

TABLE 5

Bond lengths (Å) and angles (°) of (II) (standard deviations are referred to the last digits)

C(1)–C(2)	1.521(7)	C(2)–C(1)–C(10)	115.1(5)
C(1)–C(10)	1.531(6)	C(3)–C(2)–C(1)	114.7(5)
C(2)–C(3)	1.512(7)	C(4)–C(3)–C(2)	115.6(5)
C(3)–C(4)	1.514(7)	C(4)–C(3)–O(1)	123.3(5)
C(3)–O(1)	1.210(6)	C(2)–C(3)–O(1)	120.8(5)
C(4)–C(5)	1.551(7)	C(5)–C(4)–C(3)	112.1(4)
C(4)–C(14)	1.534(6)	C(5)–C(4)–C(14)	113.7(4)
C(5)–C(6)	1.544(7)	C(3)–C(4)–C(14)	113.0(4)
C(5)–C(10)	1.556(5)	C(6)–C(5)–C(4)	110.3(4)
C(6)–C(7)	1.537(7)	C(6)–C(5)–C(10)	113.4(4)
C(6)–O(2)	1.437(5)	C(4)–C(5)–C(10)	111.9(4)
C(7)–C(8)	1.535(6)	C(7)–C(6)–C(5)	113.4(4)
C(7)–C(11)	1.554(6)	C(7)–C(6)–O(2)	110.0(4)
C(8)–C(9)	1.506(7)	C(5)–C(6)–O(2)	108.4(4)
C(9)–C(10)	1.540(7)	C(8)–C(7)–C(6)	110.1(4)
C(10)–C(13)	1.540(7)	C(8)–C(7)–C(11)	115.3(4)
C(12)–C(11)	1.548(7)	C(6)–C(7)–C(11)	110.5(4)
C(11)–C(15)	1.515(7)	C(9)–C(8)–C(7)	113.0(4)
C(15)–O(3)	1.193(7)	C(10)–C(9)–C(8)	114.3(4)
C(15)–O(4)	1.340(7)	C(13)–C(10)–C(1)	108.3(4)
C(16)–O(4)	1.471(9)	C(13)–C(10)–C(5)	110.2(4)
		C(13)–C(10)–C(9)	107.2(4)
		C(1)–C(10)–C(5)	110.9(4)
		C(1)–C(10)–C(9)	111.9(4)
		C(5)–C(10)–C(9)	108.4(4)
		C(15)–C(11)–C(7)	111.0(4)
		C(15)–C(11)–C(12)	107.5(4)
		C(7)–C(11)–C(12)	111.1(4)
		O(3)–C(15)–C(11)	125.1(5)
		O(3)–C(15)–O(4)	123.9(4)
		C(11)–C(15)–O(4)	110.9(4)
		C(15)–O(4)–C(16)	114.7(5)

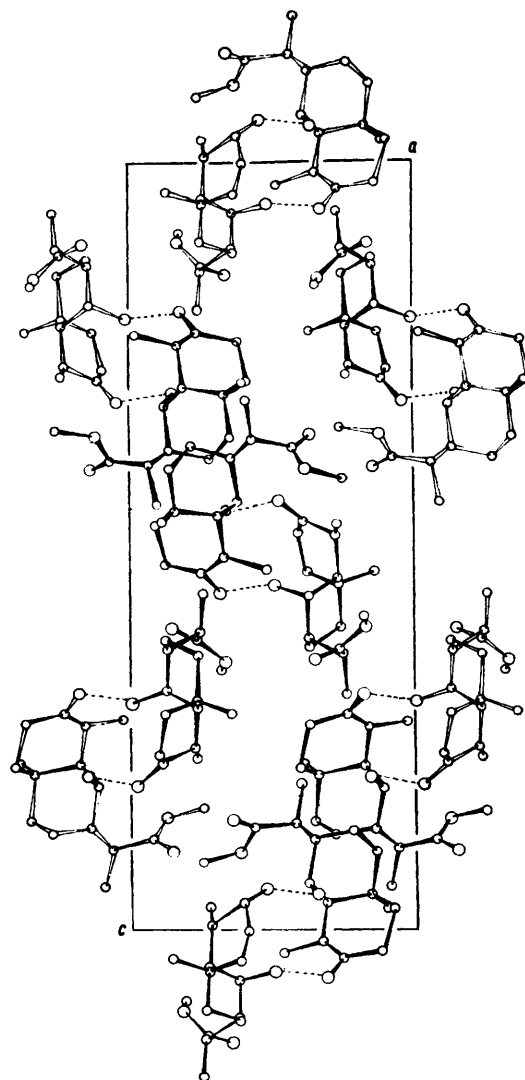


FIGURE 4 Crystal structure of (I) projected along the *b* axis (hydrogen bonds are shown as broken lines)

TABLE 6
Torsional angles (°)

Ring A	(I)	(II)
C(10)–C(1)–C(2)–C(3)	–48	–42
C(1)–C(2)–C(3)–C(4)	50	42
C(2)–C(3)–C(4)–C(5)	–53	–47
C(3)–C(4)–C(5)–C(10)	56	54
C(4)–C(5)–C(10)–C(1)	–56	–53
C(5)–C(10)–C(1)–C(2)	51	48
Ring B		
C(10)–C(5)–C(6)–C(7)	52	53
C(5)–C(6)–C(7)–C(8)	–5	–51
C(6)–C(7)–C(8)–C(9)	57	53
C(7)–C(8)–C(9)–C(10)	–57	–56
C(8)–C(9)–C(10)–C(5)	52	54
C(9)–C(10)–C(5)–C(6)	–50	–51

deformed torsion angles in rings A and B, the steric hindrance associated with the methyl and isopropyl groups is almost identical.

Crystal structures of (I) and (II) projected along the *b* and *c* axes, respectively, are shown in Figures 4 and 5. Hydrogen bonds are shown by broken lines. In the case of methyl *cis*-tetrahydro- β -santoninate (II), there are hydrogen bonds between the carbonyl group of one and the hydroxy group of a neighbouring molecule, forming a spiral along the *b* axis. In the case of methyl *cis*-tetrahydro- α -santoninate (I), there are intermolecular hydrogen bonds between the carbonyl group and the hydroxy group forming a dimeric structure. We had expected intramolecular hydrogen bonding between the carbonyl group and the hydroxy group forming a six-membered ring which would stabilize the non-steroid form. However, no such intramolecular hydrogen bonds were observed in the solid state.

The conformations of (I) and (II) in solution were

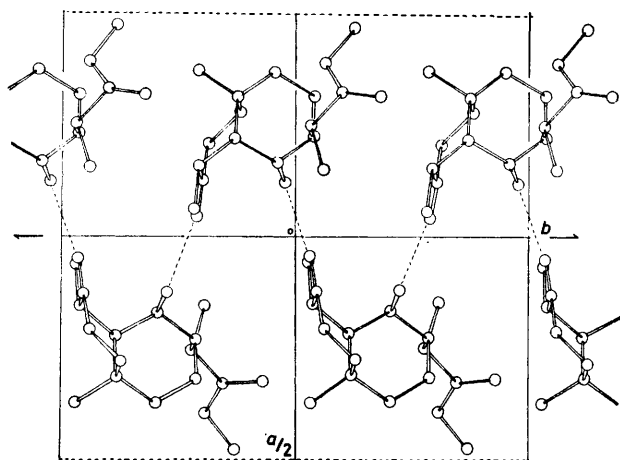


FIGURE 5 Crystal structure of (II) projected along the *b* axis (hydrogen bonds are shown as broken lines)

confirmed by c.d. and n.m.r. data. The Karplus equation⁶ predicts that the vicinal coupling constant between the hydrogen atoms attached to C(6) and C(7) should be *ca.* 1.8 for the non-steroidal form and 9 Hz for the steroidal form, because the dihedral angles between these hydrogen atoms are 60° and 180°, respectively. The observed coupling constant $J_{6,7}$ of compound (II) is 3 Hz, which indicates that the compound has a non-steroidal conformation. In the case of compound (I), the 6- and 7- signals overlap with other peaks and so cannot be detected. The $J_{7,11}$ value is 11 Hz in both compounds (I) and (II). The ester group appears therefore to be sterically hindered. Its rigid conformation may be almost the same as in the solid state, if the relationship⁶ between the *J* value and dihedral angles holds.

C.d. data also support the n.m.r. results. If the two compounds were to take the steroid-like forms [(Ia) and IIa)], the octant rule predicts a strongly negative Cotton effect for the $n-\pi^*$ transition of the 3-carbonyl

group. However, these compounds actually exhibit a positive Cotton effect both in protic and aprotic solvents,

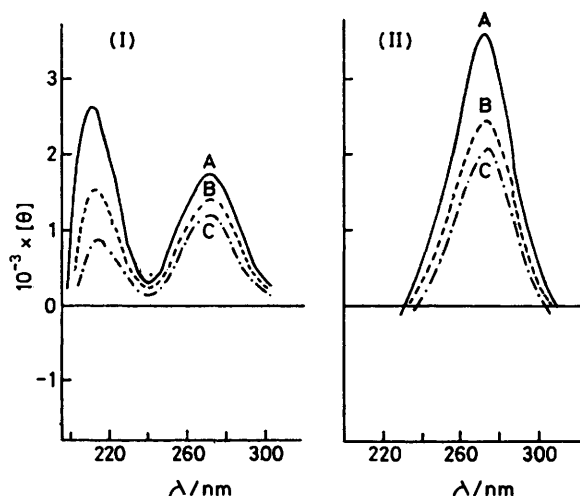


FIGURE 6 C.d. curves of (I) and (II) in EtOH-MeOH (4:1): A, -150° ; B, -50° ; C, $+20^\circ$

which indicates the non-steroidal conformation [(Ib) and (IIb)]. Moreover, the c.d. curves for both compounds are not markedly influenced by decreasing the temperature from 20 to -150° as shown in Figure 6.

In the case of (I), the second positive Cotton effect which appears at *ca.* 220 nm is due to the ester group. From the octant and sector projections for the ester carbonyl group of (I) and (II), the weight of the molecule of (I) falls in the back upper right sector and a positive Cotton effect is predicted, in agreement with the experimental facts. The weight of the molecule of (II) falls in the back upper neutral sector and almost no Cotton

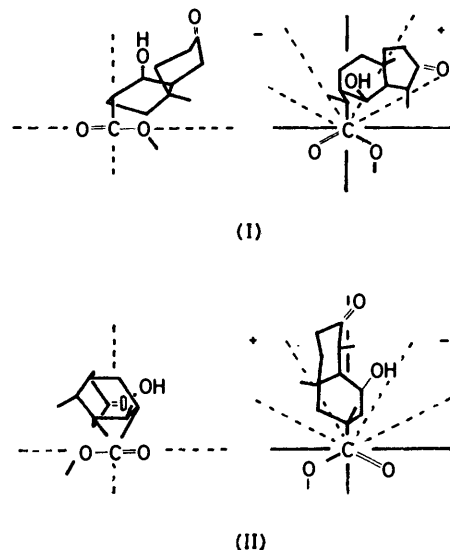


FIGURE 7 Octant and sector projections of compounds (I) and (II)

effect is predicted, also in agreement with the experimental facts.

There are two possible reasons why the non-steroid form is more stable in both compounds (I) and (II) than the steroid form. One of them is steric hindrance. In the case of the non-steroid form (Ib) and (IIb), there is steric hindrance between the bulky axial methyl group and axial 2- and 4-hydrogen atoms in ring A, and the axial isopropyl residue and the axial 5- and 9-hydrogen atoms in ring B. On the α -face of the molecule there are other repulsions between the axial 6-hydroxy group and the 1- and 8-hydrogen atoms. In the case of the steroid forms (Ia) and (IIa), there is the same methyl-hydrogen steric hindrance as in the non-steroid form in ring B and hydrogen-hydrogen repulsions between the 2 α - and 7 α -hydrogen atoms, but in this case there is another strong repulsion between the 4 α -methyl group and axial 7- and 9-hydrogen atoms. Dreiding models suggest that the distance between them is *ca.* 1.7 Å, so that the overall steric strain is greater in the steroid than in the non-steroid conformations.

The other possible reason is that the non-steroid form is stabilized by intramolecular hydrogen bonding. But

this should probably be excluded for the following reason. C.d. data indicate that the non-steroid form is probably the only conformation even in polar methanol solution which destroys inter- and intra-hydrogen bonds. Further studies on the stabilization of non-steroid form are in progress.

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