Steroidal *versus* Non-steroidal Forms. II.[1] Conformations of 4,6α(*H*),5β(*H*)-Tetrahydro-α-santonin and 4,6α(*H*),5β(*H*)-Tetrahydro-β-santonin

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The conformations of 4,6α(*H*),5β(*H*)-tetrahydro-α-santonin (4) and 4,6α(*H*),5β(*H*)-tetrahydro-β-santonin (5) have been determined by X-ray analysis and examination of the proton nuclear magnetic resonance spectra. The former has a non-steroidal form in the crystalline state, but changes the A-ring conformation in solution, while the latter takes a steroidal conformation both in the crystalline state and in solution. MM2 calculations support the above results.

Keywords 4,6α(*H*),5β(*H*)-tetrahydro-α-santonin; 4,6α(*H*),5β(*H*)-tetrahydro-β-santonin; X-ray analysis; steroidal form; non-steroidal form; crystal structure; *cis*-decalin

Compounds with a *cis*-decalin system can exist either in steroidal or non-steroidal conformations. Methyl *cis*-tetrahydro-α- (**1**) and β-santoninate (**2**) both have non-steroidal (angular methyl group equatorial to B ring) conformations,[1] and 1α,2β,4α,5β-tetrachloro-1,2-dihydro-6β-santonin (**3**) has a steroidal (angular methyl group axial to B ring) conformation[2] in the crystalline state and in solution, as determined by X-ray analysis, circular dichroism (CD) and proton nuclear magnetic resonance (^{1}H-NMR) spectra. Some other compounds with a *cis*-decalin system[3] are believed to adopt non-steroidal conformations, the evidence coming mainly from ^{1}H-NMR spectral analysis. More information is required about the conformations of these similar compounds, and in this paper we describe the conformations of two other *cis*-decalin derivatives, 4,6α(*H*),5β(*H*)-tetrahydro-α-santonin (**4**) and 4,6α(*H*),5β(*H*)-tetrahydro-β-santonin (**5**), as determined in the crystalline state by X-ray analysis and in solution by ^{1}H-NMR spectral analysis.

Experimental

General Methods Unless otherwise stated, the following procedures were adopted. Melting points were taken on a Yanagimoto micro hot-stage apparatus and are uncorrected. ^{1}H-NMR (400 MHz) spectra were measured in $CDCl_3$ solution with tetramethylsilane (TMS) as an internal standard on a JEOL EX-100 spectrometer. CD spectra were measured on a JASCO J-20 spectrometer.

4,6α(*H*),5β(*H*)-Tetrahydro-α-santonin (4) This compound was prepared by the reported procedure,[4] mp 160—162 °C (lit. 134—135 °C). CD (methanol, 20 °C) $[\theta]_{215}$ +9900 and $[\theta]_{285}$ −2670. ^{1}H-NMR (400 MHz) δ: 4.32 (1H, dd, $J_{6,5}$=4.5, $J_{6,7}$=11.5 Hz, 6-H), 2.27 (1H, dd, $J_{11,7}$=12.0, $J_{11,13\ \mathrm{methyl}}$=7.0 Hz, 11-H), 2.35 (1H, ddd, $J_{2\alpha,2\beta}$=15.0, $J_{2\alpha,1\alpha}$=5.0, $J_{2\alpha,1\beta}$=3.0 Hz, 2α-H), 1.85 (1H, m, $J_{7,6}$=11.5, $J_{7,11}$=12.0 Hz, 7-H), 2.53 (1H, m, 2β-H), 2.50 (1H, dd, $J_{4,5}$=11.0, $J_{4,14\ \mathrm{methyl}}$=6.5 Hz, 4-H), 2.10 (1H, dd, $J_{5,4}$=11.0, $J_{5,6}$=4.5 Hz, 5-H), 1.93 (1H, m, 9β-H), 1.79 (2H, m, 1α-, 1β-H), 1.54 (1H, m, 8α-H), 1.97 (1H, m, 8β-H), 1.30 (1H, m, 9α-H), 1.25 (3H, d, J=7.0 Hz, 13-Me), 1.16 (3H, d, J=6.5 Hz, 14-Me), 1.14 (3H, s, 15-Me).

4,6α(*H*),5β(*H*)-Tetrahydro-β-santonin (5) This compound was prepared by the reported procedure.[5] mp 204—206 °C (lit. 203—204 °C). CD (methanol, 20 °C) $[\theta]_{210}$ +2002 and $[\theta]_{284}$ −2703. ^{1}H-NMR (400 MHz) δ: 4.45 (1H, dd, $J_{6,5}$=1.5, $J_{6,7}$=4.0 Hz, 6-H), 2.79 (1H, dd, $J_{11,7}$=12.5, $J_{11,13\ \mathrm{methyl}}$=7.0 Hz, 11-H), 2.51 (1H, ddd, $J_{2\alpha,2\beta}$=14.5, $J_{2\alpha,1\alpha}$=7.0, $J_{2\alpha,1\beta}$=14.0 Hz, 2α-H), 2.42 (1H, dddd, $J_{7,6}$=4.0, $J_{7,11}$=6.5, $J_{7,8\beta}$=12.0, $J_{7,8\alpha}$=6.5 Hz, 7-H), 2.31 (1H, ddd, $J_{2\beta,2\alpha}$=14.5, $J_{2\beta,1\alpha}$=4.5, $J_{2\beta,1\beta}$=4.0 Hz, 2β-H), 2.22 (1H, dd, $J_{4,5}$=12.0, $J_{4,14\ \mathrm{methyl}}$=6.5 Hz, 4-H), 1.97 (1H, dd, $J_{5,4}$=12.0, $J_{5,6}$=1.5 Hz, 5-H), 1.94 (1H, m, 9β-H), 1.75 (2H, ddd and ddd, $J_{1\alpha,1\beta}$=14.0, $J_{1\alpha,2\beta}$=4.5, $J_{1\alpha,2\alpha}$=7.0, $J_{1\beta,1\alpha}$=14.0, $J_{1\beta,2\beta}$=14.0, $J_{1\beta,2\alpha}$=14.0 Hz, 1α-, 1β-H), 1.68 (1H, m, 8α-H), 1.45 (1H, m, 8β-H), 1.30 (1H, m, 9α-H), 1.22 (3H, d, J=7.0 Hz, 13-Me), 1.18 (3H, d, J=6.5 Hz, 14-Me), 1.09 (3H, s, 15-Me).

Structure Determination and Refinement Crystal and intensity data were collected on a Rigaku automated four-circle diffractometer (AF C-4) using Cu K_α radiation (λ=1.5418 Å) monochromated by a graphite plate. Of the unique reflections measured, those observed with $|F_O| > 3\sigma(|F_O|)$ were used. The intensities were corrected for Lorentz and polarization effects, but not for absorption and extinction. The structure was solved by the direct method (MULTAN78),[6] and was refined by the block-diagonal least-squares method. The positions of all hydrogen atoms were calculated and refined only for temperature factors. Crystal data and details of the refinement are summarized in Table I. Scattering factors were taken from "International Tables for X-ray Crystallography".[7] Computations were performed on Hitachi M-680H and M-682H computers in the Computer Centre of the University of Tokyo, using a local version of the UNICS program.[8]

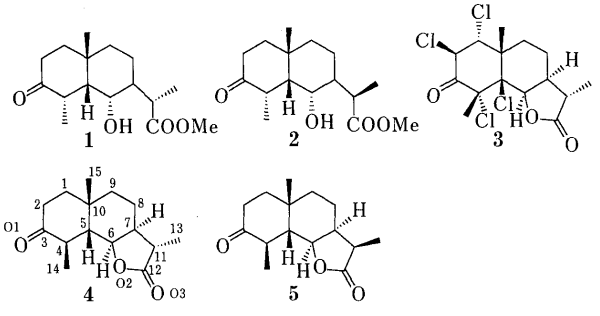


Chart 1

Discussion

Final coordinates and equivalent thermal parameters

TABLE I. Crystal Data and Experimental Details

Compound	4	5
Formula	$C_{15}H_{22}O_3$	$C_{15}H_{22}O_3$
Formula weight	250.34	250.34
Crystal system	Orthorhombic	Orthorhombic
Size (mm)	0.2×0.3×0.2	0.2×0.2×0.2
Lattice parameter		
a (Å)	12.078 (1)	8.338 (1)
b (Å)	14.317 (2)	25.265 (5)
c (Å)	7.860 (1)	6.451 (1)
Space group	$P2_12_12_1$	$P2_12_12_1$
Z	4	4
V (Å^3)	1359.1	1359.0
μ (CuK_α)(/cm^{-1})	0.781	0.781
D_x (g/cm^3)	1.223	1.223
Scan mode	$\omega-2\theta$	$\omega-2\theta$
$2\theta_{max}$	150°	150°
No. of unique reflections	1365	1035
No. of observed reflections	1253	759
Program system	UNICS III	UNICS III
R	0.064	0.064

TABLE II. Fractional Coordinates ($\times 10^4$) and Equivalent Isotropic Thermal Parameters (B_{eq}/Å^2) for Non-hydrogen Atoms of 4,6α(*H*),5β(*H*)-Tetrahydro-α-santonin (**4**) with Estimated Standard Deviations in Parentheses

Atom	*x*	*y*	*z*	B_{eq}
O1	12530 (3)	5668 (3)	4882 (6)	6.4
O2	9331 (3)	5219 (2)	2006 (5)	4.7
O3	7664 (4)	5480 (3)	971 (6)	7.5
C1	11764 (5)	3265 (4)	4400 (8)	4.6
C2	12412 (5)	4042 (4)	5336 (8)	4.8
C3	11920 (4)	4997 (4)	5066 (7)	4.2
C4	10684 (4)	5110 (3)	5104 (7)	4.2
C5	10054 (4)	4273 (3)	4344 (6)	3.0
C6	10039 (4)	4405 (4)	2390 (7)	3.7
C7	9524 (4)	3623 (4)	1348 (7)	4.4
C8	9873 (6)	2650 (4)	1947 (10)	6.8
C9	9862 (5)	2542 (4)	3866 (9)	5.7
C10	10526 (4)	3302 (3)	4826 (7)	3.6
C11	8270 (4)	3887 (4)	1483 (7)	4.6
C12	8342 (5)	4924 (4)	1448 (8)	5.1
C13	7534 (6)	3466 (5)	97 (9)	7.1
C14	10340 (5)	5376 (5)	6941 (10)	7.4
C15	10343 (6)	3076 (5)	6731 (8)	6.2

$B_{eq} = (4/3)\Sigma_i\Sigma_j\beta_{ij}(\boldsymbol{a}_i \cdot \boldsymbol{a}_j)$.

TABLE III. Fractional Coordinates ($\times 10^4$) and Equivalent Isotropic Thermal Parameters (B_{eq}/Å^2) for Non-hydrogen Atoms of 4,6α(*H*),5β(*H*)-Tetrahydro-β-santonin (**5**) with Estimated Standard Deviations in Parentheses

Atom	*x*	*y*	*z*	B_{eq}
O1	2773 (8)	5173 (2)	11973 (11)	5.3
O2	794 (6)	3033 (2)	9469 (10)	4.0
O3	−3 (7)	2205 (2)	8954 (12)	5.9
C1	−1045 (10)	4676 (3)	10963 (20)	5.5
C2	−8 (12)	4998 (3)	12463 (20)	6.2
C3	1719 (10)	4846 (3)	12225 (17)	4.8
C4	2079 (9)	4267 (3)	12355 (16)	4.0
C5	989 (9)	3939 (3)	10862 (15)	3.4
C6	1315 (8)	3354 (3)	11260 (16)	3.7
C7	493 (9)	3087 (3)	13125 (15)	3.9
C8	−1271 (9)	3262 (4)	13354 (16)	4.6
C9	−1470 (9)	3853 (3)	13146 (17)	4.5
C10	−837 (9)	4072 (3)	11068 (16)	4.2
C11	669 (10)	2509 (3)	12491 (16)	4.2
C12	444 (9)	2534 (3)	10184 (18)	4.4
C13	−402 (13)	2089 (4)	13545 (18)	6.3
C14	3871 (9)	4142 (3)	12074 (20)	5.7
C15	−1802 (10)	3850 (4)	9245 (17)	5.5

for non-hydrogen atoms in compounds **4** and **5** are listed in Tables II and III, respectively. Bond lengths and angles of **4** and **5** are shown in Tables IV and V, respectively. The values are not significantly different from standard ones. Selected dihedral angles are shown in Table VI. The A ring of **5** takes a slightly deformed chair conformation, but in **4**, a rather more deformed chair conformation. The steric interaction between the axial angular methyl group and the axial 4-methyl group resulted in the deformation of the A ring in **4**, causing it to be rather flattend around C4 and C5. On the other hand, the B rings of **4** and **5** are deformed in the same mode, caused by the *cis* juncture of the lactone to the B ring, but in **5**, the interaction between the axial angular methyl group and the lactone ring makes the C5 and C10 region more flattened than in **4**. The results

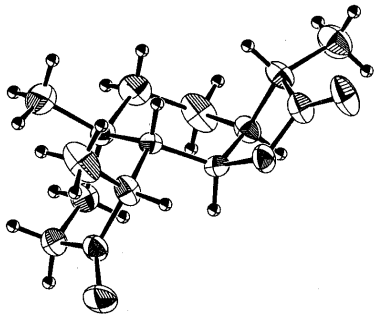
TABLE IV. Bond Lengths (Å) of 4,6α(*H*),5β(*H*)-Tetrahydro-α-santonin (**4**) and 4,6α(*H*),5β(*H*)-Tetrahydro-β-santonin (**5**) with Estimated Standard Deviations in Parentheses

	4	**5**
O1–C3	1.219 (7)	1.216 (10)
O2–C6	1.478 (7)	1.417 (10)
O2–C12	1.340 (7)	1.373 (10)
O3–C12	1.202 (8)	1.208 (11)
C1–C2	1.546 (8)	1.532 (15)
C1–C10	1.533 (8)	1.537 (11)
C2–C3	1.506 (8)	1.498 (13)
C3–C4	1.501 (8)	1.496 (11)
C4–C5	1.541 (7)	1.562 (11)
C4–C14	1.550 (10)	1.538 (10)
C5–C6	1.547 (7)	1.526 (10)
C5–C10	1.549 (7)	1.565 (10)
C6–C7	1.520 (8)	1.540 (12)
C7–C8	1.529 (9)	1.542 (11)
C7–C11	1.565 (8)	1.524 (11)
C8–C9	1.516 (10)	1.508 (12)
C9–C10	1.548 (9)	1.544 (14)
C10–C15	1.548 (9)	1.532 (13)
C11–C12	1.488 (8)	1.501 (15)
C11–C13	1.530 (9)	1.545 (13)

TABLE V. Bond Angles (°) of 4,6α(*H*),5β(*H*)-Tetrahydro-α-santonin (**4**) and 4,6α(*H*),5β(*H*)-Tetrahydro-β-santonin (**5**) with Estimated Standard Deviations in Parentheses

	4	**5**
C6–O2–C12	109.5 (4)	107.7 (8)
C2–C1–C10	111.4 (5)	115.8 (8)
C1–C2–C3	112.7 (5)	110.0 (8)
O1–C3–C2	119.6 (5)	122.3 (7)
O1–C3–C4	121.3 (5)	121.7 (7)
C2–C3–C4	119.1 (5)	116.0 (7)
C3–C4–C5	113.6 (5)	111.6 (7)
C3–C4–C14	108.2 (4)	113.0 (6)
C5–C4–C14	114.8 (5)	112.5 (7)
C4–C5–C6	107.2 (4)	107.9 (7)
C4–C5–C10	114.9 (4)	113.5 (6)
C6–C5–C10	110.9 (4)	111.5 (6)
O2–C6–C5	107.8 (4)	110.4 (7)
O2–C6–C7	103.5 (4)	103.9 (5)
C5–C6–C7	116.7 (4)	118.4 (6)
C6–C7–C8	113.1 (5)	112.0 (6)
C6–C7–C11	100.5 (4)	99.6 (6)
C8–C7–C11	117.8 (5)	113.1 (6)
C7–C8–C9	113.4 (6)	112.3 (6)
C8–C9–C10	114.1 (6)	113.3 (7)
C1–C10–C5	109.7 (4)	108.6 (6)
C1–C10–C9	112.0 (5)	110.9 (7)
C5–C10–C9	108.7 (4)	109.3 (7)
C5–C10–C15	111.8 (4)	111.6 (7)
C7–C11–C12	100.6 (5)	102.4 (7)
C7–C11–C13	114.8 (5)	119.0 (7)
C12–C11–C13	114.5 (5)	113.1 (7)
O2–C12–O3	120.1 (6)	118.4 (9)
O3–C12–C11	128.8 (6)	131.4 (8)
C1–C10–C15	110.1 (5)	105.7 (7)
C9–C10–C15	104.5 (5)	110.8 (6)
O2–C12–C11	111.1 (5)	110.2 (7)

of X-ray analysis revealed that compound **4** has a non-steroidal form and **5** has a steroidal form in the crystalline state, as shown in Fig. 1. The conformations of **4** and **5** in solution were confirmed by analysis of the ^{1}H-NMR ($CDCl_3$) spectra. The Karplus equation[9] predicts that



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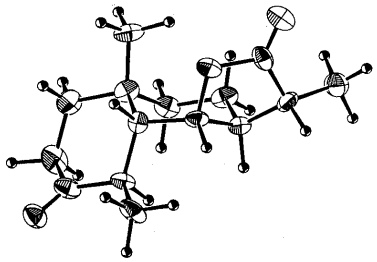

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Fig. 1. Perspective Drawings of 4,6α(*H*),5β(*H*)-Tetrahydro-α-santonin (**4**) and 4,6α(*H*),5β(*H*)-Tetrahydro-β-santonin (**5**)

TABLE VI. Selected Dihedral Angles (°) of 4,6α(*H*),5β(*H*)-Tetrahydro-α-santonin (**4**) and 4,6α(*H*),5β(*H*)-Tetrahydro-β-santonin (**5**) with Estimated Standard Deviations in Parentheses

	4	5
Ring A		
C10–C1–C2–C3	52 (1)	53 (1)
C1–C2–C3–C4	40 (1)	52 (1)
C2–C3–C4–C5	33 (1)	51 (1)
C3–C4–C5–C10	39 (1)	50 (1)
C4–C5–C10–C1	53 (1)	50 (1)
C5–C10–C1–C2	58 (1)	52 (1)
Ring B		
C10–C5–C6–C7	50 (1)	45 (1)
C5–C6–C7–C8	43 (1)	42 (1)
C6–C7–C8–C9	44 (1)	46 (1)
C7–C8–C9–C10	52 (1)	58 (1)
C8–C9–C10–C5	58 (1)	59 (1)
C9–C10–C5–C6	54 (1)	51 (1)

the vicinal coupling constant between the hydrogen atoms attached to C4 and C5 should be *ca.* 1 Hz for the non-steroidal form and 12 Hz for the steroidal form, and that between C5 and C6 should be *ca.* 11 Hz for the non-steroidal form and 1 Hz for the steroidal form, because the dihedral angles of H4–C4–C5–H5 are 82° and 178° for **4** and **5**, and the dihedral angles of H5–C5–C6–H6 are 167° and 78° for **4** and **5**, respectively. The observed coupling constants $J_{4,5}$ and $J_{5,6}$ of compound **5** are 12 and 1.5 Hz, which indicate that the compound **5** has a steroidal conformation in solution. On the other hand, the values of the observed coupling constants $J_{4,5}$ and $J_{5,6}$ of compound **4** are 11 and 4.5 Hz, respectively, which indicate that in solution, compound **4** does not have the same conformation as that in the crystalline state. It can be assumed that in solution, the A ring of **4** changes its conformation to decrease the steric repulsion between the 1,3-diaxial methyl groups attached to the A-ring, and as a result, the value of the dihedral angle of H4–C4–C5–H5 increases and that of H5–C5–C6–H6 decreases. This is supported by the fact that the value of the dihedral angle of H4–C4–C5–H5 changes from 82° (X-ray) to *ca.* 150° ($J_{4,5}=11.0$ Hz) and that of H5–C5–C6–H6 from 167° (X-ray) to 125° ($J_{5,6}=4.5$ Hz).

To confirm the results of X-ray analysis, steric energies of the two compounds were calculated by the force field method (MM2).[10] The MM2 calculations clarified that in compound **4**, the non-steroidal form is more stable than the steroidal form by 3.7 kcal/mol and in **5**, the steroidal form is more stable than the non-steroidal form by 4.3 kcal/mol. These results agree well with those from X-ray analysis. From the ^{1}H-NMR spectral patterns of compounds **1**, **2**, **3**, **4** and **5**, each of them seems to take only one conformation in solution, though no clear explanation can be found as to why compounds **1**, **2** and **4** have non-steroidal form and **3** and **5** take steroidal form.

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