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The Molecular Structure of *cis*-4-Aza-A-homo-tetrahydro--α-santonin and *trans*-4-Aza-A-homo-tetrahydro-α-santonin Related to the Lactam Rule[1]

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Stereochemistry of the titled compounds was determined by X-ray structure analysis. The seven-membered lactam rings of both compounds are in a quasi-chair conformation which agrees with the lactam rule. The mean values of the C—NH—CO—C torsion angles are —6° and +5°, respectively, and these values also agree with Klyne's hypothesis.

INTRODUCTION

Recently, we proposed the lactam rule[2] (Ogura's sign rule)[3] that the sign of the n—π* Cotton effect of a seven-membered lactam ring depends solely on classification into two types, A (+ve) and B (—ve), (Figure 1) with regard to the absolute configuration from the CD and ORD data. This rule should be applicable to four-membered,[4,5] five-membered,[4] six-membered,[6,7] and seven-membered lactam rings,[1,4,8,9] owing to the coplanarity of the lactam moiety (C—NH—CO—C).

Figure 1. Standard projection of a seven-membered lactam ring.

On the other hand, Klyne *et al.*[3] proposed the hypothesis that the lactam ring has a positive torsion angle of lactam moiety (C—NH—CO—C) corresponding to the same sign of Cotton effect. This hypothesis most probably used our orbital study on the n—π* Cotton effect of ε-caprolactam.[9] X-ray analysis of D-glucono-1,5-lactam[7] (negative Cotton effect)[10] and (—)-menthone lactam[1] (negative Cotton effect)[4] revealed that their torsion angles are —4.8° and +2°, respectively. Both data are in agreement with Ogura's lactam rule, but the latter is opposite to Klyne's hypothesis.

In this paper, we carried out X-ray analysis of two seven membered lactams to elucidate the stereochemistry based on the lactam rule.

EXPERIMENTAL

The cell dimensions and the diffraction intensities were measured on a Rigaku automated four-circle diffractometer, using graphite monochromated Cu $K\alpha$ radiation at 23 °C. Intensities of 2680 and 2898 independent reflections of compounds *1* and *2* within the range of $2\Theta < 140°$ were collected by the use of the $2\Theta - \omega$ scan mode with a scanning rate of 4° (2Θ) min^{-1}. Totals of 2545 and 2776 independent reflections for *1* and *2* with $|F_0| > 3\sigma|F_0|$ were obtained, and corrected for Lorentz and polarization factors but not for absorption.

The structures of the two compounds were solved by the direct method using MULTAN.[11] Atomic parameters were refined by the block-diagonal-matrix least-squares method with anisotropic temperature factors. Finally, the hydrogen atoms were located in the difference Fourier map, several cycles of the least-squares refinement were carried out including these hydrogen atoms. The atomic scattering factors for C, O, and N were given by Cromer and Mann,[12] and that for H by Stewart *et al.*[13] The final R values for *1* and *2* were 9.5 and 6.2%, respectively, where $R = \Sigma ||F_0| - |Fc|| / \Sigma |F_0|$.

RESULTS AND DISCUSSION

The final atomic parameters of two crystallographically independent molecules, *I* and *II*, of compounds *1* and *2* are listed in Tables II and III, respectively.[14]

TABLE I

Crystal data of cis-*4-aza-A-homo-tetrahydro-α-santonin* (1) *and* trans-*4-aza-A-homo-tetrahydro-α-santonin* (2)

Compound		*1*	*2*
Molecular formula		$C_{15}H_{23}O_3N$	$C_{15}H_{23}O_3N$
Formula weight		265.34	265.34
Crystal dimensions (mm^3)		0.2 × 0.2 × 0.2	0.2 × 0.3 × 0.2
Crystal system		monoclinic	monoclinic
Space group		$P2_1$	$P2_1$
Cell dimensions	a (Å)	15.616(1)	18.823(1)
	b (Å)	8.054(1)	9.665(1)
	c (Å)	11.589(1)	8.270(1)
	β (°)	94.19(1)	109.75(1)
Density ($g \cdot cm^{-1}$)	Dc	1.216	1.230.
Z		4	4

Perspective drawings of the molecular structures of *1* and *2* are shown in Figures 2 and 3 with atomic numbering. The bond angles and bond lengths are listed in Tables IV and V, and torsion angles are listed in Table VI.

As shown in Table VI, the conformation of the lactam ring of *1* and *2* is a quasi-chair form, which is similar to that of (—)-menthone lactam[1] and ε-caprolactam.[9,15]

In conclusion, the X-ray analysis data of *1* and *2* have revealed that *1* belongs to B type and *2* to A type in crystalline state, which agrees with the result of NMR and CD spectra in solution.[8] These facts indicate that Ogura's lactam rule could be applied to a seven membered lactam ring.

TABLE II

Atomic coordinates ($\times 10^4$) and equivalent isotropic temperature factors of cis-*4-aza-A-homo-tetrahydro-α-santonin* (1) *(Standard deviations are given in parentheses)*

Atom	X	Y	Z	B_{eq}/Å^2 [a]
Molecule I				
C(1)	6480(5)	—4257(12)	10509(7)	3.3
C(2)	5663(5)	—3212(14)	10535(8)	3.9
C(3)	5426(4)	—2478(11)	9338(8)	3.1
C(4)	6722(4)	—686(10)	9643(7)	2.6
C(5)	7474(4)	—1980(10)	9718(7)	2.4
C(6)	8376(4)	—1281(10)	10048(7)	2.3
C(7)	8477(4)	—438(10)	11220(7)	2.5
C(8)	8373(6)	—1785(13)	12147(8)	3.8
C(9)	7515(6)	—2660(12)	11885(7)	3.6
C(10)	7375(5)	—3402(11)	10626(7)	2.8
C(11)	9327(5)	399(12)	11149(8)	3.7
C(12)	9260(5)	946(12)	9872(9)	3.8
C(13)	9523(6)	1873(14)	11960(10)	5.1
C(14)	6935(5)	943(12)	9053(9)	4.3
C(15)	8009(6)	—4835(11)	10445(10)	4.4
O(1)	4771(3)	—2888(9)	8743(5)	4.1
O(2)	8684(3)	—30(8)	9247(5)	3.2
O(3)	9631(4)	2028(12)	9404(7)	6.5
N(1)	5983(3)	—1368(9)	8961(6)	2.6
Molecule II				
C(1)	5856(5)	6112(12)	5536(8)	3.6
C(2)	5825(5)	6695(12)	3270(8)	3.6
C(3)	5396(5)	5377(12)	3493(7)	3.6
C(4)	6681(5)	3541(11)	3937(7)	2.7
C(5)	6634(5)	3206(10)	5265(7)	2.7
C(6)	7396(5)	2299(10)	5869(7)	2.8
C(7)	8253(5)	3182(12)	5784(8)	3.7
C(8)	8268(7)	4809(15)	6455(9)	5.2
C(9)	7453(6)	5871(13)	6039(9)	4.3
C(10)	6601(5)	4904(12)	5994(7)	3.5
C(11)	8874(5)	1767(15)	6166(8)	4.1
C(12)	8389(6)	294(14)	5643(9)	4.7
C(13)	9804(6)	1930(22)	5766(11)	7.2
C(14)	6963(6)	1975(14)	3261(8)	4.3
C(15)	6378(6)	4496(12)	725(88)	3.8
O(1)	4679(4)	5598(10)	3012(6)	4.7
O(2)	7535(3)	628(8)	5457(5)	3.8
O(3)	8677(4)	—1016(11)	5388(8)	6.6
N(1)	5817(4)	3939(10)	3402(6)	3.4

[a] W. C. Hamilton, *Acta Crystallogr.* **12** (1959) 609.

TABLE III

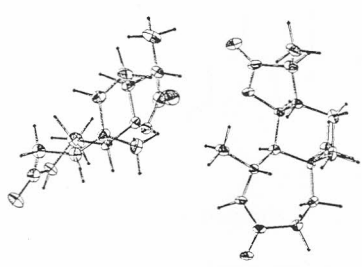
Atomic coordinates ($\times 10^4$) and equivalent isotropic temperature factors of trans-*4-aza-A-homo-tetrahydro-α-santonin* (2) *(Standard deviations are given in parentheses)*

Atom	X	Y	Z	B_{eq}/Å^2
Molecule I				
C(1)	4693(4)	1829(10)	2502(8)	4.1
C(2)	5332(4)	815(11)	3364(9)	4.9
C(3)	5708(4)	1193(11)	5201(8)	4.4
C(4)	4514(3)	673(8)	5864(7)	3.1
C(5)	3967(3)	1722(7)	4662(7)	2.6
C(6)	3159(3)	1687(7)	4701(7)	2.7
C(7)	2671(3)	2824(7)	3625(7)	3.0
C(8)	2598(4)	2632(9)	1740(8)	4.0
C(9)	3401(4)	2664(10)	1640(8)	4.2
C(10)	3923(3)	1544(8)	2733(7)	3.1
C(11)	1986(3)	2717(7)	4258(8)	3.2
C(12)	2375(4)	2511(7)	6144(8)	3.2
C(13)	1440(4)	3914(8)	3880(10)	4.3
C(14)	4375(4)	406(9)	7575(8)	4.1
C(15)	3650(4)	71(9)	2050(9)	3.9
O(1)	6372(3)	1516(9)	5728(6)	5.9
O(2)	3074(2)	1566(5)	6396(5)	3.1
O(3)	2157(3)	2780(6)	7308(6)	4.0
N(1)	5288(3)	1170(8)	6265(6)	4.0
Molecule II				
C(1)	2388(3)	—2554(7)	6830(7)	2.8
C(2)	2724(3)	—3913(8)	7769(7)	3.1
C(3)	3169(3)	—3640(8)	9607(8)	3.1
C(4)	1978(3)	—2897(7)	10154(7)	2.7
C(5)	1758(3)	—1618(6)	8955(6)	1.9
C(6)	1048(3)	—854(6)	8959(7)	2.2
C(7)	943(3)	444(6)	7892(7)	2.3
C(8)	781(4)	90(7)	6020(7)	3.0
C(9)	1453(3)	—730(7)	5882(7)	2.7
C(10)	1644(3)	—2019(6)	7028(7)	2.2
C(11)	381(3)	1258(7)	8507(7)	2.8
C(12)	622(3)	831(7)	10378(8)	3.0
C(13)	392(4)	2850(8)	8277(10)	3.9
C(14)	1810(4)	—2748(9)	11869(8)	4.0
C(15)	1026(3)	—3103(8)	6372(8)	3.2
O(1)	3848(2)	—3795(7)	10133(5)	4.7
O(2)	1065(2)	—299(5)	10650(5)	2.6
O(3)	469(3)	1399(6)	11535(6)	4.2
N(1)	2792(3)	—3149(6)	10635(6)	3.0

TABLE IV

Bond lengths (Å) and angles (°) of cis-*4-aza-A-homo-tetrahydro-α-santonin* (1)
(Standard deviations are given in parentheses)

Molecule	*I*	*II*		*I*	*II*
C(1) —C(2)	1.529(12)	1.538(13)	C(2) —C(1) —C(10)	120.0(8)	118.7(7)
C(1) —C(10)	1.555(11)	1.538(13)	C(1) —C(2) —C(3)	110.0(7)	109.5(8)
C(2) —C(3)	1.529(13)	1.516(13)	C(2) —C(3) —N(1)	115.6(6)	117.0(7)
C(4) —C(5)	1.568(10)	1.569(11)	C(2) —C(3) —O(1)	122.6(8)	121.2(9)
C(4) —C(14)	1.528(13)	1.564(14)	O(1) —C(3) —N(1)	121.8(8)	121.8(9)
C(5) —C(6)	1.539(10)	1.522(11)	N(1) —C(4) —C(5)	109.9(6)	110.0(6)
C(5) —C(10)	1.571(12)	1.610(13)	N(1) —C(4) —C(14)	105.7(7)	104.3(6)
C(6) —C(7)	1.516(11)	1.525(11)	C(4) —C(5) —C(10)	114.3(6)	112.0(7)
C(7) —C(8)	1.544(13)	1.523(15)	C(4) —C(5) —C(6)	116.1(6)	116.3(7)
C(7) —C(11)	1.495(11)	1.541(14)	C(5) —C(6) —C(7)	114.8(6)	114.0(7)
C(8) —C(9)	1.524(13)	1.579(14)	C(5) —C(6) —O(2)	115.3(6)	115.1(6)
C(9) —C(10)	1.578(12)	1.540(13)	C(6) —C(7) —C(8)	107.4(7)	110.4(8)
C(10)—C(15)	1.545(12)	1.565(14)	C(6) —C(7) —C(11)	100.8(6)	100.0(7)
C(11)—C(12)	1.540(14)	1.511(15)	C(7) —C(8) —C(9)	108.8(7)	109.1(8)
C(11)—C(13)	1.531(15)	1.562(14)	C(8) —C(9) —C(10)	114.8(7)	114.3(8)
N(1) —C(3)	1.343(10)	1.339(12)	C(1) —C(10)—C(9)	108.1(7)	108.3(8)
N(1) —C(4)	1.457(9)	1.479(10)	C(5) —C(10)—C(9)	109.3(7)	112.8(7)
O(1) —C(3)	1.235(9)	1.227(10)	C(9) —C(10)—C(15)	111.2(7)	109.0(7)
O(2) —C(6)	1.475(10)	1.450(11)	C(7) —C(11)—C(12)	100.6(7)	100.3(7)
O(2) —C(12)	1.362(10)	1.361(11)	C(7) —C(11)—C(13)	117.0(8)	115.6(9)
O(3) —C(12)	1.199(13)	1.193(14)	C(11)—C(12)—O(2)	110.0(7)	111.4(8)
			C(11)—C(12)—O(3)	130.0(9)	127.4(9)
			C(6) —O(2) —C(12)	107.0(6)	107.5(7)
			C(3) —N(1) —C(4)	125.6(7)	126.4(7)
			C(5) —C(4) —C(14)	114.1(6)	112.8(7)
			C(6) —C(5) —C(10)	103.5(6)	102.7(6)
			O(2) —C(6) —C(7)	103.9(6)	104.9(6)
			C(8) —C(7) —C(11)	119.6(7)	120.2(8)
			C(12)—C(11)—C(13)	111.4(8)	113.4(9)
			C(1) —C(10)—C(5)	113.4(6)	113.5(7)
			C(1) —C(10)—C(15)	103.8(7)	103.7(7)
			C(5) —C(10)—C(15)	111.0(7)	109.3(7)
			O(2) —C(12)—O(3)	120.1(9)	121.2(9)



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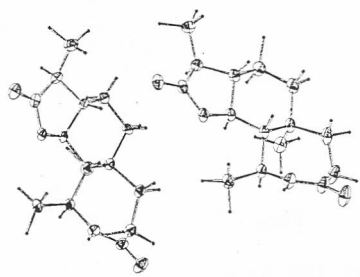

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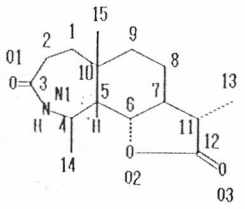
Figure 2. Perspective views of compounds *1* and *2*.

TABLE V

Bond lengths (Å) and angles (°) of trans-*4-aza-A-homo-tetrahydro-α-santonin* (2)
(Standard deviations are given in parentheses)

Molecule	*I*	*II*		*I*	*II*
C(1) —C(2)	1.547(14)	1.558(10)	C(2) —C(1) —C(10)	117.2(7)	118.2(6)
C(1) —C(10)	1.544(12)	1.547(9)	C(1) —C(2) —C(3)	111.7(8)	111.6(6)
C(2) —C(3)	1.513(15)	1.518(11)	C(2) —C(3) —N(1)	117.5(6)	117.2(5)
C(4) —C(5)	1.566(10)	1.559(9)	C(2) —C(3) —O(1)	122.1(7)	122.0(6)
C(4) —C(14)	1.538(12)	1.552(11)	O(1) —C(3) —N(1)	120.4(6)	120.7(5)
C(5) —C(6)	1.531(10)	1.528(9)	C(3) —N(1) —C(4)	126.5(5)	126.0(5)
C(5) —C(10)	1.782(10)	1.590(9)	N(1) —C(4) —C(5)	110.3(6)	110.8(5)
C(6) —C(7)	1.531(10)	1.511(9)	N(1) —C(4) —C(14)	106.4(5)	104.6(4)
C(7) —C(8)	1.534(12)	1.523(9)	C(5) —C(4) —C(14)	115.4(6)	114.7(6)
C(7) —C(11)	1.535(10)	1.524(10)	C(4) —C(5) —C(10)	113.1(5)	111.9(5)
C(8) —C(9)	1.544(12)	1.526(10)	C(4) —C(5) —C(6)	116.0(5)	116.5(5)
C(9) —C(10)	1.553(12)	1.540(9)	C(6) —C(5) —C(10)	105.8(4)	105.7(4)
C(10)—C(15)	1.560(11)	1.536(10)	C(5) —C(6) —C(7)	113.3(6)	111.0(5)
C(11)—C(12)	1.520(10)	1.530(10)	C(5) —C(6) —O(2)	114.2(4)	114.1(4)
C(11)—C(13)	1.515(11)	1.551(11)	C(7) —C(6) —O(2)	101.6(5)	102.2(5)
N(1) —C(3)	1.351(13)	1.349(10)	C(6) —C(7) —C(8)	110.9(6)	110.9(5)
N(1) —C(4)	1.472(11)	1.480(9)	C(6) —C(7) —C(11)	99.8(5)	102.3(5)
O(1) —C(3)	1.231(13)	1.228(10)	C(8) —C(7) —C(11)	121.0(5)	120.7(5)
O(2) —C(6)	1.483(9)	1.489(8)	C(7) —C(8) —C(9)	105.5(5)	106.2(4)
O(2) —C(12)	1.371(9)	1.350(8)	C(8) —C(9) —C(10)	114.3(7)	114.7(6)
O(3) —C(12)	1.186(9)	1.212(9)	C(1) —C(10)—C(5)	110.1(4)	109.8(4)
			C(1) —C(10)—C(9)	104.7(6)	104.8(5)
			C(5) —C(10)—C(9)	109.9(6)	110.8(5)
			C(1) —C(10)—C(15)	109.7(6)	110.3(5)
			C(5) —C(10)—C(15)	112.0(6)	112.1(5)
			C(9) —C(10)—C(15)	110.2(5)	108.9(4)
			C(7) —C(11)—C(12)	99.6(5)	100.2(5)
			C(7) —C(11)—C(13)	117.7(6)	115.7(6)
			C(12)—C(11)—C(13)	113.4(6)	112.4(6)
			C(11)—C(12)—O(2)	110.3(6)	111.4(6)
			C(11)—C(12)—O(3)	128.8(6)	127.4(6)
			O(2) —C(12)—O(3)	120.9(5)	121.2(6)
			C(6) —O(2) —C(12)	107.4(4)	107.4(4)



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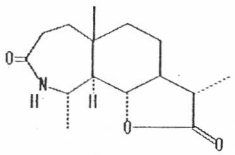

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Figure 3. Structure with atomic numbering of compounds *1* and *2*.

Also, the mean values of the lactam moiety torsion angles (C—NH—CO—C) of *1* and *2* are —6° and +5°, respectively, and these values agree with Klyne's hypothesis.[3]

TABLE VI

Selected torsion angles of cis-*4-aza-A-homo-tetrahydro-α-santonin* (1) *and* trans-*4-A-homo-tetrahydro-α-santonin* (2) *(Standard deviations are given in parentheses)*

Compound	*1*		Molecule	*2*	
Molecule	*I*	*II*		*I*	*II*
C(1)—C(2)—C(3)—N(1)	—65.6(9)	—67.4(10)	C(1)—C(2)—C(3)—N(1)	61.9(9)	63.9(7)
C(2)—C(3)—N(1)—C(4)	— 7.6(11)	— 3.4(12)	C(2)—C(3)—N(1)—C(4)	6.8(11)	2.3(9)
C(3)—N(1)—C(4)—C(5)	78.2(9)	75.7(10)	C(3)—N(1)—C(4)—C(5)	—72.5(9)	—71.4(8)
N(1)—C(4)—C(5)—C(10)	—78.9(8)	—79.7(8)	N(1)—C(4)—C(5)—C(10)	81.4(6)	84.0(6)
C(4)—C(5)—C(10)—C(1)	49.9(9)	54.1(9)	C(4)—C(5)—C(10)—C(1)	—62.3(7)	—62.9(6)
C(5)—C(10)—C(1)—C(2)	—54.4(10)	—57.5(10)	C(5)—C(10)—C(1)—C(2)	65.5(8)	64.0(7)
C(10)—C(1)—C(2)—C(3)	82.5(9)	82.4(10)	C(10)—C(1)—C(2)—C(3)	—84.4(8)	—83.1(7)

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SAŽETAK

Molekulska struktura *cis*-4-aza-A-homo-tetrahidro-α-santonina i *trans*-4-aza-A-homo-tetrahidro-α-santonina u odnosu na laktamsko pravilo

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Stereokemija naslovnih spojeva određena je rentgenskom analizom kristala. Sedmočlani laktamski prsten zauzima u oba spoja konformaciju poput (kvazi) stolca, što je u skladu s laktamskim pravilom. Srednje vrijednosti torzijskih kuteva iznose -6° i $+5^\circ$, i u skladu su s Klyneovim pravilom.