

Studies on Lactams. Part IV.¹ Relation between Cotton Effect and Conformation of a Seven-membered Lactam Ring

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The $n \rightarrow \pi^*$ Cotton effects of seven-membered lactams have been investigated; from the results seven-membered lactams have been classified into two types: A having a negative and B a positive Cotton effect. The derived 'lactam rule' has been applied to conformational studies on *N*-methyl-*A*-aza-*A*-homo-tetrahydro- α -santonins and comparisons have been made with *N*-methyl-(-)-menthone lactam. The conformational equilibrium of a fused seven-membered lactam ring is discussed in the light of c.d. data.

RECENTLY we enunciated² a lactam rule, linking the sign of the $n \rightarrow \pi^*$ carbonyl Cotton effect with the conformation of the lactam ring. We based the rule on evidence derived from o.r.d. and c.d. data of four-membered,¹ five-membered,³ six-membered,³ and seven-membered lactam rings,^{2,3} including (-)-menthone lactam and *N*-methyl-(-)-menthone lactam.¹ For example, in the latter cases, lactams of type A showed negative Cotton effects, whereas lactams of type B showed positive Cotton effects (Figure 1). A link between the conformation of the lactam ring and the sign of the $n \rightarrow \pi^*$ Cotton effect had already been observed⁴⁻⁶ and in particular Beecham⁷ and Klyne *et al.*⁸ had suggested that the sign of the $n \rightarrow \pi^*$ Cotton effect of bridged lactam and lactone chromophores depends solely on the enantiomeric nature of the lactam or lactone bridge and not at all on molecular asymmetry elsewhere in the molecule.

In this paper, we report c.d. and o.r.d. data of *A*-aza-*A*-homo-tetrahydro- α -santonins,⁹ their *N*-methyl derivatives, and *A*-aza-*A*-homo-steroids.¹⁰ The peaks studied all showed bathochromic shifts of about 6–15 nm in a less polar solvent, characteristic of an $n \rightarrow \pi^*$ transition.¹¹ The data confirm the relationship between the conformation of the seven-membered lactam ring, as



FIGURE 1

shown in Figure 1, and the sign of the $n \rightarrow \pi^*$ Cotton effect.

The spectra of the santonin derivatives (1)–(6) are complicated, as the molecules possess two chromophores, the lactam and the lactone carbonyl systems. Thus the spectra consist of two overlapping bands. Klyne *et al.*¹²

have measured the o.r.d. spectra of some α -santonin derivatives, and found that they show a positive Cotton

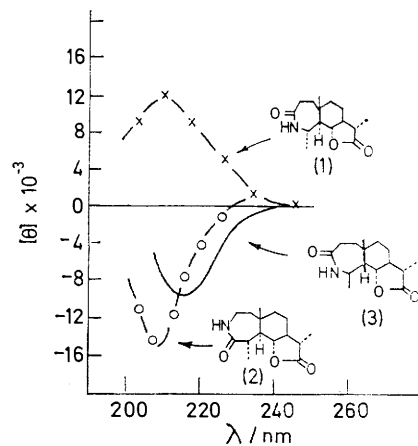


FIGURE 2

effect due to the lactone ring with $[\phi]$ about +2 500 at 225–240 nm. Overberger and Kaye¹³ have noted similar spectra with substituted hexan-6-olides, with similar intensities. It is reasonable to assume therefore that the contribution of the lactone chromophore in structures (1)–(6) is positive with a $[\phi]$ value similar to those found earlier.¹² *trans*-Fused 3-aza-*A*-homo-tetrahydro- α -santonin (2), *cis*-fused 4-aza-*A*-homo-tetrahydro- α -santonin (3) and their *N*-methyl derivatives all show a negative Cotton effect (Figures 2 and 3), and therefore the contribution to the Cotton effect by the lactam ring must be negative. On the other hand, *trans*-fused 4-aza-*A*-homo-tetrahydro- α -santonin derivatives (1) and (4) show a positive Cotton effect with $[\phi]$ +5 200 at 230 nm and $[\theta]$ +2 660 at 216 nm, respectively. These values are larger than those of related compounds containing only a lactone ring (*e.g.* ϕ +1 200 to +3 500),¹²

⁷ A. F. Beecham, *Tetrahedron Letters*, 1969, 4897.

⁸ J. P. Jennings, W. Klyne, and P. M. Scopes, *J. Chem. Soc.*, 1965, 7229.

⁹ H. Ogura, H. Takayanagi, and C. Miyahara, *J. Org. Chem.*, 1972, **37**, 519.

¹⁰ K. Oka and S. Hara, *Chem. and Ind.*, 1969, 168.

¹¹ B. J. Litman and J. A. Schellman, *J. Phys. Chem.*, 1965, **69**, 978.

¹² J. P. Jennings, W. Klyne, and P. M. Scopes, *J. Chem. Soc.*, 1965, 7211.

¹³ C. G. Overberger and H. Kaye, *J. Amer. Chem. Soc.*, 1967, **89**, 5646, 5649.

¹ Part III, H. Ogura, H. Takayanagi, K. Kubo, and K. Furuhashi, *J. Amer. Chem. Soc.*, 1973, **95**, 8056.

² H. Ogura, H. Takayanagi, and K. Furuhashi, *Chem. Letters*, 1973, 387.

³ H. Ogura, H. Takayanagi, and K. Furuhashi, Abstracts of Papers, 17th Symposium on the Chemistry of Natural Products, 1965, p. 183.

⁴ H. Wolf, *Tetrahedron Letters*, 1965, 1075.

⁵ A. F. Beecham, *Tetrahedron Letters*, 1968, 2355, 3591.

⁶ M. Legrand and R. Bucourt, *Bull. Soc. chim. France*, 1967, 2241.

and therefore the contribution of the lactam chromophore to the Cotton effect is still positive. In all these cases the contribution of the lactone chromophore appears to be less than that of the lactam chromophore.

Comparison of these spectra with those of the steroid derivatives (7)–(12) shows that the 4a-methyl group in

(Figure 4), and 17 β -acetoxy-3-aza-A-homo-5 β -androstan-4-one (8) and 17 β -acetoxy-4-aza-A-homo-5 β -androstan-3-one (9) show positive Cotton effects.

It is well established^{14–16} that the peptide linkage CO·NH is nearly planar, because of the partial double bond character of the carbon–nitrogen bond. A recent

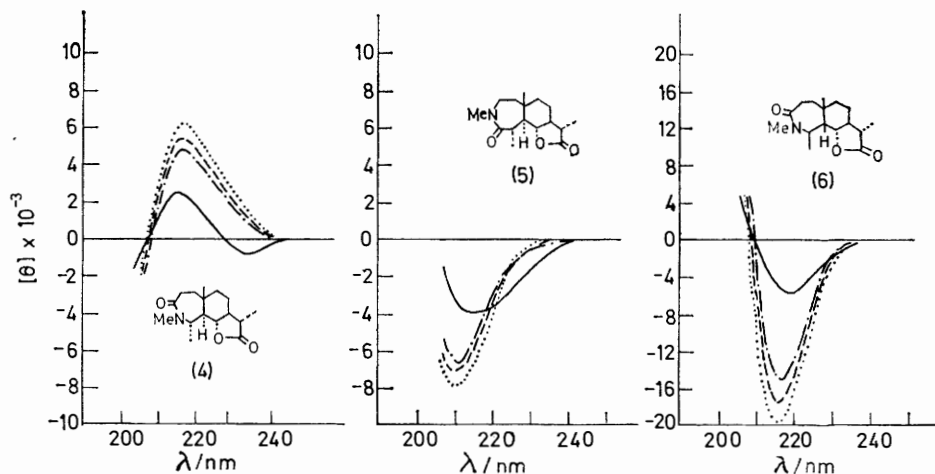


FIGURE 3

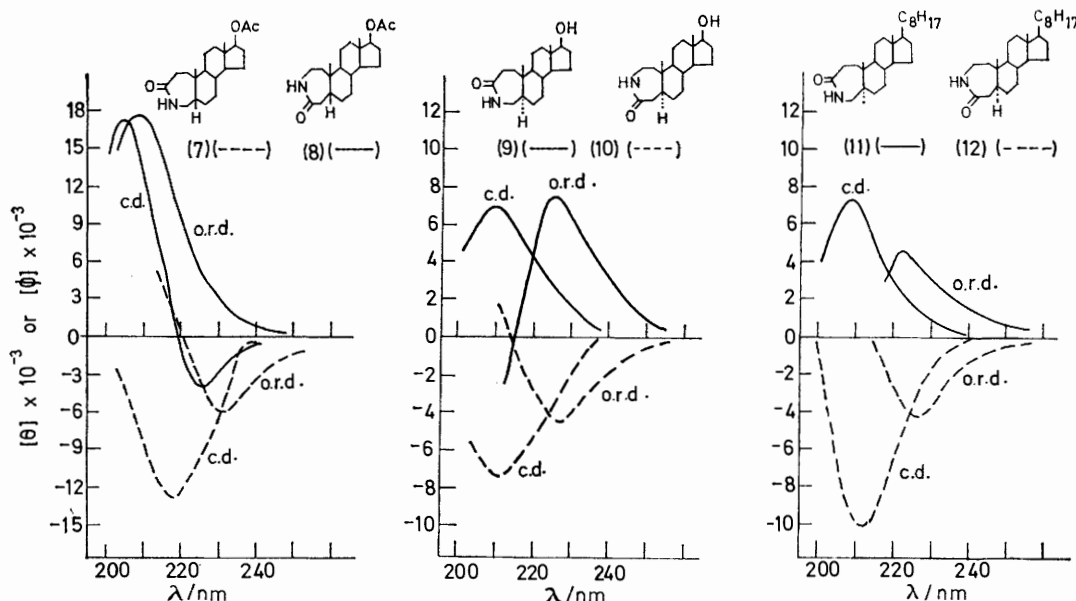


FIGURE 4

the former series has little influence on the shape or intensity of the spectrum. 17 β -Acetoxy-4-aza-A-homo-5 α -androstan-3-one (7) and 17 β -hydroxy-3-aza-A-homo-5 α -androstan-4-one (10) show negative Cotton effects

(X-ray analysis).^{18,19} ¹⁹F N.m.r. studies on 4,4-difluoro-hexane-6-lactam,²⁰ and consistent force field calculations

¹⁴ C. C. Costain and J. M. Dowling, *J. Chem. Phys.*, 1960, **32**, 158.

¹⁵ A. E. Tonelli, *J. Amer. Chem. Soc.*, 1971, **93**, 7153.

¹⁶ M. Tichy, E. Duskova, and K. Blaha, *Tetrahedron Letters*, 1974, 237.

¹⁷ I. Nitta, M. Haisa, N. Yasuoka, K. Kasami, Y. Tomiie, and Y. Okaya, *Ann. Reports Fiber Res. Inst. Osaka Univ.*, 1965, **17**, 1.

¹⁸ F. K. Winkler and I. D. Dunitz, *J. Mol. Biol.*, 1971, **59**, 169.

¹⁹ V. Pattabhi, K. Venkatesan, and S. R. Hall, *Cryst. Struct. Comm.*, 1973, **2**, 223.

²⁰ E. A. Noe and J. D. Roberts, *J. Amer. Chem. Soc.*, 1971, **93**, 7261.

on hexane-6-lactam²¹ also support the planar nature of the CO·NH group in the seven-membered ring.

Our n.m.r. studies on the A-aza-A-homo-tetrahydro- α -santonins (1)—(3)⁹ suggested that ring A existed in a chair conformation. The similarity of the n.m.r. spectra of the corresponding *N*-methyl derivatives (4)—(6) suggests that these also possess a chair ring A (Table 1).

(—)-menthone lactam and *N*-methyl(—)-menthone lactam.¹

Preparation of Compounds.—The A-aza-A-homo-compounds (1)—(3) were prepared *via* Beckmann rearrangement of the corresponding oximes, and the *N*-methyl compounds (4)—(6) by methylation of (1)—(3) with methyl iodide.

TABLE 1

N.m.r. data of A-aza-A-homo-tetrahydro- α -santonins (100 MHz; CDCl ₃ ; δ values; <i>J</i> in Hz)								
Compd.	H-4a	H-5	H-6	4a-CH ₃	10-CH ₃	11-CH ₃	N-CH ₃	NH
(1)	3.75 (m) <i>J</i> _{4,4a} 4.0 <i>J</i> _{4a,4a-Me} 6.9 <i>J</i> _{4a,5} 6.5	2.18 (dd) <i>J</i> _{4a,5} 6.5 <i>J</i> _{5,6} 7.0	3.75 (dd) <i>J</i> _{5,6} 7.0 <i>J</i> _{6,7} 11.0	1.35 (d) <i>J</i> 6.9	1.09 (s)	1.20 (d) <i>J</i> 6.75		5.97 (d) <i>J</i> 4.0
(2)	2.83 (m) <i>J</i> _{4a,4a-Me} 7.4 <i>J</i> _{4a,5} 8.0	2.25 (dd) <i>J</i> _{4a,5} 8.0 <i>J</i> _{5,6} 8.6	3.86 (dd) <i>J</i> _{5,6} 8.6 <i>J</i> _{6,7} 11.0	1.27 (d) <i>J</i> 7.4	1.14 (s)	1.17 (d) <i>J</i> 7.0		6.74 (t) <i>J</i> 5.3
(3)	3.76 (m) <i>J</i> _{4,4a} 4.5 <i>J</i> _{4a,4a-Me} 6.7 <i>J</i> _{4a,5} 9.0	2.05 (dd) <i>J</i> _{4a,5} 9.0 <i>J</i> _{5,6} 4.3	4.36 (dd) <i>J</i> _{5,6} 4.3 <i>J</i> _{6,7} 11.0	1.24 (d) <i>J</i> 6.7	1.16 (s)	1.23 (d) <i>J</i> 6.75		5.99 (d) <i>J</i> 4.5
(4)	3.80 (m) <i>J</i> _{4a,4a-Me} 7.1 <i>J</i> _{4a,5} 6.3 (6.5) ^a		3.80	1.40 (d) <i>J</i> 7.1	1.04 (s)	1.20 (d) <i>J</i> 6.9	2.85 (s)	
(5)	2.86 (m) <i>J</i> _{4a,4a-Me} 7.4 <i>J</i> _{4a,5} 7.5	2.25	3.83	1.33 (d) <i>J</i> 7.4	1.06 (s)	1.18 (d) <i>J</i> 6.9	2.96 (s)	
(6)	3.96 (m) <i>J</i> _{4a,4a-Me} 7.0 <i>J</i> _{4a,5} 6.9	2.0	4.37 (dd) <i>J</i> _{5,6} 4.4 <i>J</i> _{6,7} 11.3	1.34 (d) <i>J</i> 7.0	1.12 (s)	1.21 (d) <i>J</i> 6.6	2.85 (s)	

^a *J* Value at -30 °C.

In the A-aza-steroids, ring A should also possess a chair conformation.

Of the established relationships between the sign of the Cotton effect and the configuration around a carbonyl group, the well-known octant rule for ketones²² does not explain our results. This is not unexpected, but, more surprisingly, neither Klyne's sector rule for lactones,^{8,12,23} nor the quadrant rule for amides²⁴⁻²⁶ is satisfactory (Table 2). On the other hand, our lactam rule fits the experimental facts, for both the santonin derivatives (Table 2; Figures 2 and 3) and the steroid derivatives (Figure 4). An unusual feature appears in the c.d.

Shoppee *et al.*²⁷ have reported that 5 α -cholestan-3-one oxime undergoes the Beckmann rearrangement to give 3-aza-A-homo-5 α -cholestan-4-one (12) and 4-aza-A-homo-5 α -cholestan-3-one (11), both with m.p. 295°. In an

TABLE 2

C.d. and o.r.d. data of seven-membered lactams (in MeOH)

Compd.	Observed		Predicted sign of Cotton effect		
	$[\theta] \times 10^{-3}$ nm	$[\phi] \times 10^{-3}$ nm	Octant rule	Amide rule	Lactam rule
(1)	+11.9	+1.3	+	+	+
(2)	+11.9	+1.3	+	+	+
(3)	+11.9	+1.3	+	+	+
(4)	+11.9	+1.3	+	+	+
(5)	+11.9	+1.3	+	+	+
(6)	+11.9	+1.3	+	+	+

In our hands, the oxime obtained by isomerisation of 5 α -cholestan-3-one oxime with hydrochloric acid rearranged to give the 3-ketone (11), m.p. >300°. The isomeric 4-ketone (12) was prepared by hydrogenation of

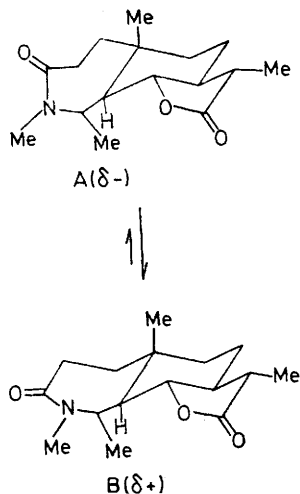


FIGURE 5

3-aza-A-homo-5 α -cholest-4a-en-3-one,²⁷ and had m.p. 278—279°. Comparison of Cotton effects (see Table 2) shows that the mixture prepared by the method of Shoppee and Sly²⁸ was a *ca.* 1 : 1 mixture of (11) and (12).

EXPERIMENTAL

N.m.r. spectra were measured for solutions in CDCl₃ at 100 MHz with a JMS-PS-100 spectrometer (tetramethylsilane as internal standard). C.d. curves were measured with a Japan Spectroscopic model J-20 recording polarimeter.

N-Methyl-4-aza-A-homo-trans-tetrahydro- α -santonin (4).—Sodium hydride (360 mg) was added to a stirred solution of 4-aza-A-homo-trans-tetrahydro- α -santonin (1) (1.3 g) in dry benzene (30 ml) under nitrogen. The mixture was heated to reflux, methyl iodide (1.07 g) in dry benzene (20 ml) was added dropwise, and the mixture was refluxed for a further 7 h and set aside overnight. Ethanol was added to destroy the excess of hydride, followed by water. The benzene layer was separated, dried (CaCl₂), and evaporated, and the residue was crystallised from methanol-ether to give the *N*-methyl-lactam (4) as prisms (300 mg), m.p. 223—224°, $[\theta]_{218}^{20} + 2\ 660$, $[\theta]_{234}^{20} - 720$, $[\theta]_{216}^{-80} + 5\ 010$, $[\theta]_{215.5}^{-110} + 5\ 520$, $[\theta]_{218}^{-150} + 6\ 130$ (EtOH-MeOH, 4 : 1), ν_{\max} (KBr) 1 774 (lactone) and 1 631 (lactam) cm⁻¹ (Found: C, 68.75; H, 9.05; N, 4.75%; M^+ , 279. C₁₆H₂₅NO₃ requires C, 68.8; H, 9.0; N, 5.0%; M , 279).

N-Methyl-3-aza-A-homo-trans-tetrahydro- α -santonin (5).—3-Aza-A-homo-trans-tetrahydro- α -santonin (2) (420 mg)

under the same conditions afforded the corresponding *N*-methyl-lactam (5) which was purified by chromatography over silica gel (elution with chloroform). Crystallisation from ether-methanol gave needles (100 mg), m.p. 207—209°, $[\theta]_{215}^{20} - 4\ 110$, $[\theta]_{212}^{-80} - 6\ 840$, $[\theta]_{212}^{-110} - 7\ 300$, $[\theta]_{211}^{-150} - 8\ 320$ (EtOH-MeOH, 4 : 1), ν_{\max} (KBr) 1 758 (lactone) and 1 633 (lactam) cm⁻¹ (Found: C, 68.8; H, 8.9; N, 4.8%; M^+ , 279).

N-Methyl-4-aza-A-homo-cis-tetrahydro- α -santonin (6).—4-Aza-A-homo-cis-tetrahydro- α -santonin (3) under the same conditions afforded the corresponding *N*-methyl-lactam (6) as prisms (30%) (from ether), m.p. 113—114°, $[\theta]_{218}^{20} - 5\ 840$, $[\theta]_{217}^{-80} - 15\ 560$, $[\theta]_{216}^{-110} - 18\ 570$, $[\theta]_{215.5}^{-150} - 21\ 750$ (EtOH-MeOH, 4 : 1), ν_{\max} (KBr) 1 765 (lactone) and 1 640 (lactam) cm⁻¹ (Found: C, 68.85; H, 9.1; N, 5.1%).

Beckmann Rearrangement of 5 α -Cholestan-3-one Oxime.—(a) *Shoppee's method.*²⁷ 5 α -Cholestan-3-one oxime (2.4 g) [m.p. 196—197° (lit.,²⁹ 199°; lit.,³⁰ 197—201°)] in dry dioxan (70 ml) was warmed to 40 °C, and thionyl chloride (3.0 ml) was added with stirring over 5 min. The mixture was kept at 40 °C for 10 min, and then neutralised with sodium hydrogen carbonate solution. Water was added, and the aqueous solution was extracted with a large volume of ether. The ether layer afforded a solid (2.2 g) which was chromatographed on alumina (elution with benzene-ether). The product (1.6 g) was a mixture of α -aza-compounds, m.p. 268—271° (lit.,²⁷ 268—271°), ν_{\max} (KBr) 3 200, 3 070 (NH), 1 675, 1 667, and 1 630 (CO) cm⁻¹ (Found: C, 80.65; H, 11.9; N, 3.4%; M^+ , 401. Calc. for C₂₇H₄₇NO: C, 80.75; H, 11.8; N, 3.5%; M , 401).

(b) Dry hydrogen chloride was bubbled through a solution of 5 α -cholestan-3-one oxime (4.8 g) (m.p. 196—197°) in dry ether (100 ml). The oxime hydrochloride was precipitated. The precipitate was neutralised with sodium hydrogen carbonate solution to afford the isomerised oxime (4.5 g), m.p. 195—196°. Beckmann rearrangement of this oxime in the same manner as in (a) afforded 4-aza-A-homo-5 α -cholestan-3-one (11), m.p. >300°, ν_{\max} (KBr) 3 200, 3 075 (NH), 1 680, and 1 630 (CO) cm⁻¹ (Found: C, 80.6; H, 11.8; N, 3.55%; M^+ , 401. C₂₇H₄₇NO requires C, 80.75; H, 11.8; N, 3.5%; M , 401).

3-Aza-A-homo-5 α -cholestan-4-one (12b).—3-Aza-A-homo-5 α -cholest-4a-en-4-one (400 mg) (prepared by a Schmidt reaction of cholest-4-en-3-one) was hydrogenated to give 3-aza-A-homo-5 α -cholestan-4-one (12) (250 mg), m.p. 278—279° (lit.,²⁸ 294—296°), ν_{\max} (CHCl₃) 3 420, 3 300, 3 220 (NH), and 1 652 cm⁻¹ (CO) (Found: C, 80.85; H, 11.85; N, 3.6%; M^+ , 401).

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