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CHIROPTICAL STUDIES—PART 99[1]
THE CIRCULAR DICHROISM OF SEVEN-MEMBERED LACTAMS AND LACTONES

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Abstract—This empirical analysis of CD data for 7-membered lactams includes examples of all twelve possible structural types in which the lactam is fused to a cyclohexane ring as part of a polycyclic compound. The CD behaviour of several classes of lactams shows 'Ogura's sign rule' to be an over-simplification. The signs and values of $\Delta\epsilon$ for lactams in which the second ring is fused at the 3,4- or 6,7-positions of the lactam ring show considerable deviations from the 'normal' values for 4,5- or 5,6-fused lactams.

No simple pattern of group contributions emerged from this analysis, but a correlation of CD behaviour with the torsion angle in the C–CO–NH–C structural component is suggested, on the basis of a study of Dreiding models, and is supported by the result of an X-ray crystallographic analysis of one of the lactams. This study of CD data is extended to a smaller group of lactones with a seven-membered ring, most of which show Cotton effects opposite in sign and of smaller magnitude than those of the corresponding lactams.

MANY studies have been made of the CD (and ORD) of lactones, lactams and related types of compound which are derived from carboxylic acids.[2-15] The only absorption bands for all such chromophores which are accessible to ordinary CD instruments are of $n\rightarrow\pi^*$ type, normally appearing in the region 210–230 nm; a second band below 200 nm, of uncertain origin, (see p. 552) is found only for lactams, amides and peptides. No satisfactory general rules relating the CD to the absolute configuration are yet available. Several sector rules have been proposed, but each appears to have only a limited range of application. Studies have been complicated by 6-membered lactones and lactams apparently having no single preferred conformation. This is in sharp contrast to the situation for cyclohexanones which are nearly always in chair form, where the $n\rightarrow\pi^*$ Octant Rule[16] in either its original or one of its extended forms[17] is readily applicable.

A 7-membered lactam ring ("ϵ-caprolactam" type), however appears to have a clear preference for a *quasi*-chair conformation, with the C–NH–CO–C system approximately coplanar.[8,9,14,18,19] The geometry of the lactam ring closely resembles that of cycloheptene.[19] The unencumbered ϵ-caprolactam can assume one of two enantiomeric *quasi*-chair conformations (Fig. 1), but substitution, or in particular fusion to one or more alicyclic rings, will normally impose a preference for one of the two enantiomeric forms of the *quasi*-chair lactam ring. Ogura[8,9,14] recently proposed a simple sign rule for the $n\rightarrow\pi^*$ CD of such lactams, showing that the signs of Cotton effects observed for a series of 7-membered lactams of aza-A-homo steroid type, as well as for corresponding structures derived from tetrahydro-α-santonin, correlate with the conformation of the lactam ring in the sense indicated in Fig. 1. Possible effects of other rings were not included in Ogura's analysis, since the conformation of the lactam ring alone appeared to control the *sign* of the CD curve.

Ogura's generalisation seemed a good starting point for study of CD data available to us from a wider range of 7-membered lactams (from Sapporo)[20,21] and lactones (from Westfield),[22] as well as data published from other laboratories. All available CD data for compounds of these types are collected into Tables 1 and 2, respectively. For purposes of classification and comparison, data are presented on the basis of the enantiomer which has its lactam or lactone ring in the conformation depicted in Fig. 1a, for which Ogura's rule would predict a lactam CD band of positive sign in the $n\rightarrow\pi^*$ region (210–230 nm). Values of $\Delta\epsilon$ which are prefixed in the Tables by (E) ("enantiomer") have been reversed in sign for consistency. The actual CD measurements in the cases marked (E) were made on compounds of natural steroid-like configuration where the lactam ring is in the enantiomeric absolute configuration (Fig. 1b), as can readily be seen from study of Dreiding models.

Lactams (and lactones—see later) with adjoining alicyclic rings are classified here according to an extension

(a) c.d. (+) (b) c.d. (−)

Fig. 1. Projections of a seven-membered lactam ring (X=NH), as proposed by Ogura. (X=O represents the corresponding lactones).

†The late Professor 'Bill' Klyne was writing this paper until a few days before his untimely death in November 1977. The analysis of CD data is essentially his. The surviving authors gratefully acknowledge their indebtedness to his inspiration and enthusiasm, and dedicate this paper to his memory.

Table 1. CD data for lactams with a seven-membered ring (in methanol)

Compound	Δε (λ max)	Δε (λ max)	Reference or source of compound
Monocyclic			
[4R,7S]-4-Methyl-7-isopropyl-1-aza-cycloheptan-2-one [(-)Menthone lactam] (1)	(E) +3.4 (209)		a
Class 7t3			
2-Aza-A-homo-5α-cholestan-1-one (2)	-11.1 (230)	+35.3 (200)	b
4-Aza-A-homo-5α-cholestan-4a-one (3)	- 5 (218)		b
Class 7t4			
17β-Acetoxy-3-aza-A-homo-5α-oestran-4-one (4)	(E) {-0.04 (236) +2.2 (206)		d
3-Aza-A-homo-5α-cholestan-4-one (5)	(E) +3.1 (214)		c
17β-Hydroxy-3-aza-A-homo-5α-androstan-4-one (6)	(E) +2.3 (211)		c
4a,4a-Dimethyl-3-aza-A-homo-5α-cholestan-4-one (7)	(E) +2.3 (222)	- 5 (199)	b
2α,4a,4a-Trimethyl-3-aza-A-homo-5α-cholestan-4-one (8)	(E) -3.8 (230)	+14 (202)	b
3-Aza-4-oxo-A-homo derivative (9) from tetrahydro-α-santonin	(E) +4.5 (210)		c
3-Aza-A-homo-5α-cholestan-2-one (10)	(E) +1.5 (211)		e
Class 7t5			
2-Aza-A-homo-5α-cholestan-3-one (11)	+1.5 (213)		e
17β-Acetoxy-4-aza-A-homo-5α-oestran-3-one (12)	+3.2 (213)	-3.31 (195)	d
17β-Hydroxy-4-aza-A-homo-5α-androstan-3-one (13)	+2.1 (211)		c
4-Aza-A-homo-5α-cholestan-3-one (14)	+2.2 (210)		c
4a,4a-Dimethyl-4-aza-A-homo-5α-cholestan-3-one (15)	+0.9 (215)	-1.21 (198)	b
2α,4a,4a-Trimethyl-4-aza-A-homo 5α-cholestan-3-one (16)	+1.5 (220)		h
4-Aza-3-oxo-A-homo derivative (17) from tetrahydro-α-santonin	+3.6 (211)		c
Class 7t6			
1-Aza-A-homo-5α-cholestan-2-one (18)	(E) +4.5 (222)	-6.8 (197)	b
4a-Aza-A-homo-5α-cholestan-4-one (19)	(E) +5.5 (214)		b
Class 7c3ax			
2-Aza-A-homo-5β-cholestan-1-one (20)	(E) -2.9 (230)	+10.1 (204)	b
Class 7c3eq			
4-Aza-A-homo-5β-cholestan-4a-one (21)	(E) +0.5 (217)	+7.3 (198)	b
Class 7c4ax			
3-Aza-A-homo-5α,10α-androstan-4-one (22)	+3 (215)		f

Table 1. (*Contd*)

Compound	Δε (λ max)	Δε (λ max)	Reference or source of compound
Class 7c4eq			
16β-Acetoxy-3-aza-A-homo-5β-androstan-4-one (23)	-0.7 (225)	+4.5 (202)	g
17β-Acetoxy-3-aza-A-homo-5β-androstan-4-one (24)	-1.2 (225)	+5.1 (205)	c
Methyl 12α-acetoxy-4-oxo-3-aza-A-homo-5β-cholan-24-oate (25)	-3.4 (219)	+4.3! (201)	h
Class 7c5ax			
16β-Acetoxy-4-aza-A-homo-5β-androstan-3-one (26)	(E) +3.9 (218) (E) +1.6 (219)	-2.6 (200)	c g
Methyl-12α-acetoxy-3-oxo-4-aza-A-homo-5β-cholan-24-oate (27)	(E) +3.3 (222)	-7.6! (198)	h
4-Aza-3-oxo-A-homo derivative (28) from tetrahydro-α-santonin	(E) +2.9 (218)		c
Class 7c5eq			
4-Aza-A-homo-5α,10α-androstan-3-one (29)	(E) -0.9 (224)	+2.9 (200)	f
Class 7c6ax			
4α-Aza-A-homo-5β-cholestan 4-one (30)	-1.2 (216)	+6.1! (193)	b
Class 7c6eq			
1-Aza-A-homo-5β-cholestan-2-one (31)	+8.0 (225)	-19.1 (200)	b

[a]Ref. 8; [b]ref. 20; [c]ref. 9; [d]H.S., this paper; [e]J.T., Westfield College; [f]G. Habermehl and A. Haaf, Ann. Chem., 723, 181 (1969); [g]G. Habermehl and A. Haaf, Ann. Chem., 722, 155 (1969); [h]Dr. B. Matkovics, Szeged, Hungary.

Table 2. CD data for lactones with a seven-membered ring

			Δε	λ(nm)	Solvent*	Source
7t4	3-Oxa-A-homo-5α-cholestan-4-one (32)	(E)	-1.2	222	H	a
	2,2-Dimethyl-3-oxa-A-homo-5α-cholestan-4-one (33)	(E)	-1.2	214	E	b
	3-Oxa-4-one (34) from friedelin		-4.5	216	M	c
	3-Oxa-A-homo-5α-cholestan-2-one (35)	(E)	-0.6	223	H	a
7t5	4-Oxa-A-homo-5α-cholestan-3-one (36)		-0.4	218-225	M	d
			-1.1	222	H	
	4aα-Methyl-4-oxa-A-homo-5α-cholestan-3-one (37)		-1.0	215	M	b
			-1.0	222	H	
	4aβ-Methyl-4-oxa-A-homo-5α-cholestan-3-one (38)		-0.8	218	E	b
	4a,4a-Dimethyl-4-oxa-A-homo-5α-cholestan-3-one (39)		-0.3	222	A	b
			-0.3	213-220	E	
	4-Oxa-3-one (40) from friedelin	(E)	-0.7 -2.6	213 197	E	e

Table 2. (*Contd*)

			Δε	λ(nm)	Solvent*	Source
7t6	1-Oxa-A-homo-5α-cholestan-2-one (41)	(E)	-0.4	226-236	E	b
	4a-Oxa-A-homo-5α-cholestan-4-one (42)	(E)	+0.4	237	H	a
		(E)	+0.2	230	M	f
			-1.3!	195		
7c5ax	4-Oxa-A-homo-5β-cholestan-3-one (43)	(E)	+0.6	221-224	M	d
			+0.5	228	H	

*H = hexane; E = ethanol; M = methanol; A = acetonitrile.

Sources [a]J.T., Westfield College; [b]Dr. J.S.E. Holker, Liverpool; [c]Dr. W.H. Hui, University of Hong Kong; [d]Dr. R.E. Gall, Sydney, Australia; [e]Dr. J.-C. Bloch, Strasbourg; [f]H.S., Sapporo.

of the method and symbolism introduced by Kirk and Klyne[23] for extended decalones. The lactam (or lactone) ring is numbered from the hetero-atom (X=NH or O) as in Fig. 2. Adjoining cyclohexane rings are indicated as being *trans*- or *cis*-fused to the lactam ring by *t* or *c*, respectively, with a locant (3, 4, 5, or 6) to define the lower-numbered point of ring fusion. In the case of *cis*-fused bicyclic systems, the conformation of that second-ring bond which originates at the *lower-numbered* locant is indicated as *ax* (axial) or *eq* (equatorial) with respect to the lactam ring. The size of the lactam (lactone) ring is indicated by the appropriate integer (in this case, 7) as a prefix. Fig. 3 depicts the four possible *trans*-fused and the eight *cis*-fused bicyclic systems which can be constructed to contain a 7-membered lactam ring in the conformation corresponding to Fig. 1a, with a cyclohexane ring in the chair conformation (an enantiomeric set of another twelve bicyclic systems can also exist, but this complication is excluded from the present analysis by the device of presenting all data for the same absolute configuration of the lactam ring). All twelve bicyclic units are represented among the lactams listed in Table 1.

The present analysis goes beyond that of Ogura in attempting an evaluation of the CD associated with each of the twelve types of *bicyclic* unit. On this basis it has been possible to rationalise the major variations in the magnitude of CD with structure, and to identify certain bicyclic fragments for which Ogura's sign-rule is not obeyed—presumably because of a dominant influence of the second ring. Any third or additional rings have been ignored in the discussion which follows. Their effects seem unlikely to cause more than second-order variations in the magnitude of Δε for the great majority of compounds, as they generally do for ketones.[14,23] Lactam rings are assumed to be essentially in the chair conformation throughout this analysis.

CD results for 7-membered ring lactams

The only available data for a monocyclic lactam of defined conformation were reported by Ogura *et al.*[8] for "(-)menthone lactam" (1), which appears to be held substantially in a conformation of the type in Fig. 1b, with its alkyl substituents equatorial. The value of Δε

Fig. 2. Numbering of 7-membered lactam (X=NH) or lactone (X=O) ring.

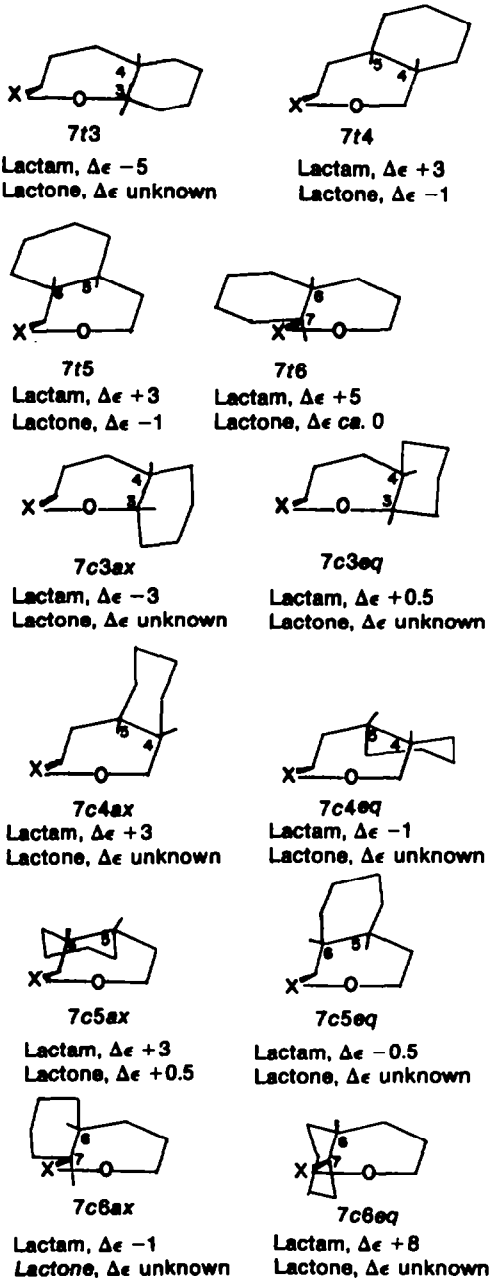
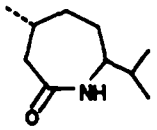


Fig. 3. Projections of the twelve bicyclic lactams (X=NH) or lactones (X=O), based upon Ogura's view of the lactam ring in the conformation of Fig. 1a. (Characteristic values of Δε are indicated to the nearest 0.5 unit, where known.)

varies slightly with solvent and temperature but is *ca* −3 units. The value for the enantiomer, required in the present discussion for comparison with bicyclic structures in the absolute configuration of Fig. 1a and 3, would be *ca* +3.



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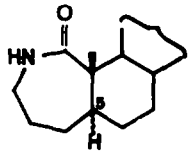
Inspection of the data in Table 1 (n→π* band; *ca* 210–230 nm) suggested a division of the polycyclic lactams into two distinct groups on the basis of values of Δε. One group has values of Δε generally in the range +1.5 to +4.5, which are considered reasonably close to that for the monocyclic lactam. These compounds comprise bicyclic classes *7t4*, *7c4ax*, *7t5* and *7c5ax*, all of which have the second ring attached at positions remote from the amide chromophore. The other group, showing wider variations in Δε or even changes of sign, includes each of the six classes of lactams in which the second ring is adjacent to the chromophoric group, either at the 3,4-positions (*7t3*, *7c3eq*, *7c3ax*) or at the 6,7-positions (*7t6*, *7c6eq*, *7c6ax*). Classes *7c4eq* and *7c5eq* also appear to belong to the "anomalous" second group of compounds. They show negative CD even though the ring fusions are not adjacent to the amide group.

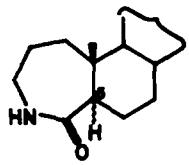
Pursuing this line of thought, and taking note of additional alkyl substituents on the lactam ring in a few of the compounds, the following generalisations emerged from inspection of the values of Δε in Table 1 (see below for discussion of variations in the wavelength of $\Delta\epsilon_{max}$). Approximate additivity of ring contributions is assumed, as for ketones.[23]

Class 7t3: Δε negative. The second ring appears to make a contribution in the order of −8 units, overwhelming the positive contribution of +3 units expected from the lactam ring itself. The "3-axial" Me substitution (10β-Me) in the 2-aza-1-oxo-steroid **2** (Δε −11.1) appears to result in a further large negative contribution. Ring C, however, also lies close to the CO group though in a "front octant" region in compound **2**, and perhaps should not be ignored. Insufficient data are available for evaluation of any possible 'front octant' effects.

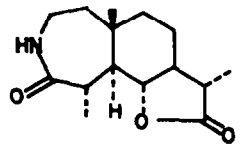
Class 7t4: Δε +3 ±1.5. The second ring seems to make little if any contribution in most of these compounds. The enhanced value (+4.5) for the lactam derivative **9** of tetrahydro-α-santonin probably includes a small positive contribution from the γ-lactone ring (Δε +0.8 at 225–240 nm[24]).



2 5α-cholestane
20 5β-cholestane



3 5α-cholestane
21 5β-cholestane



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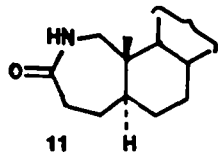
The 19-nor steroidal lactam **4** is somewhat anomalous in giving what appears to be a bisignate curve, with a weakly negative component (−0.04) at 236 nm and a strongly positive Cotton effect (+2.2) with its maximum at the unusually short wavelength of 206 nm (these signs of Δε refer to the enantiomer). The 17β-acetoxy group would contribute only +0.2 (210 nm).[12] Since bisignate curves have apparent maxima displaced from their true values and cannot reliably be resolved,[25] we tentatively accept the value Δε = +2.2 as being sufficiently close to the norm to indicate no major contribution from the 10β-Me group, which occupies the '5-axial' position on the lactam ring. The 2α,4a,4a-trimethylated lactam **8** is so heavily substituted that its deviation from normal CD behaviour is not surprising, although the corresponding 4a,4a-dimethyl compound **7** shows no such deviation. The CD of the trimethyl compound **8** may be another instance of a bisignate curve (note the second band at 202 nm), the reason for which is not clear.

Class 7t5: Δε +3 ±1. The second ring again has no significant effect, but the presence of a 10β-Me substituent in steroidal derivatives is associated with a reduction in Δε by *ca* 1-1.5 unit (contrast **12** with **11**, **13**, and **14**. The exceptionally small value (+0.9) for the 4a,4a-dimethyl-4-aza-3-oxo compound **16** probably indicates some further influence of the dimethyl substitution adjacent to the amide group.



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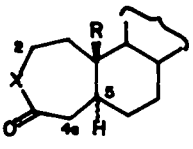
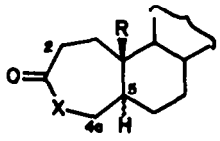
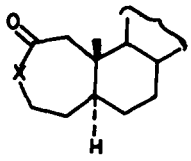
Class 7t6: Δε +5 ±0.5. The second ring appears to make a small positive contribution (*ca* +2) additional to



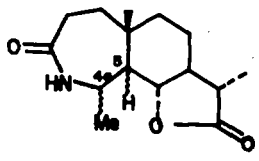
4 X = NH, R = H, 17β-OAc-5α-oestrane
5 X = NH, R = Me, 5α-cholestane
6 X = NH, R = Me, 17β-OH-5α-androstane
7 as **5**, 4a,4a-Me$_2$
8 as **5**, 2α,4a,4a-Me$_3$
23 X = NH, R = Me, 16β-OAc-5β-androstane
24 X = NH, R = Me, 17β-OAc-5β-androstane
25 X = NH, R = Me, 12α-OAc-5β-cholan-24-oic acid, Me ester
32 X = O, R = Me, 5α-cholestane
33 as **32**, 2,2-Me$_2$



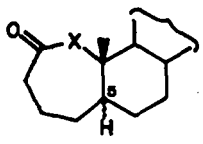
12 X = NH, R = H, 17β-OAc-5α-oestrane
13 X = NH, R = Me, 17β-OH-5α-androstane
14 X = NH, R = Me, 5α-cholestane
15 as **14**, 4a,4a-Me$_2$
16 as **14**, 2α,4a,4a-Me$_3$
26 X = NH, R = Me, 16β-OAc-5β-androstane
27 X = NH, R = Me, 17β-OAc-5β-androstane
36 X = O, R = Me, 5α-cholestane
37 as **36**, 4aα-Me
38 as **36**, 4aβ-Me
39 as **36**, 4a,4a-Me$_2$
43 X = O, R = Me, 5β-cholestane



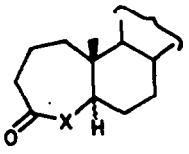
10 X = NH
35 X = O



17 4aα-Me, 5α-H
28 4aβ-Me, 5β-H



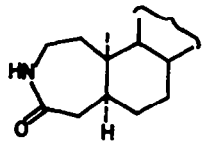
18 X = NH, 5α-H
31 X = NH, 5β-H
41 X = O, 5α-H



19 X = NH, 5α-H
30 X = NH, 5β-H
42 X = O, 5α-H

the +3 units for the lactam ring. Any possible effect of the 10β-Me group ("7-axial") in the 1-aza-2-oxo compound (**18**) is too small to assess.

Class 7*c*3*ax*: Only one compound, Δε *ca* −3. As in



22

class 7*t*3, the second ring appears to make a large negative contribution (*ca* −6 units).

Class 7*c*3*eq*: Only one compound, Δε +0.5. This appears to be yet another instance of a negative effect (*ca* −2.5) of a second ring fused at the 3,4-position.

Class 7*c*4*ax*: Only one compound, Δε +3. No contribution from the second ring.

Class 7*c*4*eq*: Δε negative. The second ring seemingly makes a substantial negative contribution (*ca* −4) [note that 12α-OAc in compound **25** would itself contribute *ca* −1[12]].

Class 7*c*5*ax*: Δε *ca* +3. There is no appreciable contribution from the second ring.

Class 7*c*5*eq*: Only one compound, Δε −0.5. This anomaly is similar to that noted above for class 7*c*4*eq*, representing a second ring contribution of *ca* −3.5 units.

Class 7*c*6*ax*: Only one compound, Δε −1.2. The second ring appears to make a significant negative contribution (*ca* −4).

Class 7*c*6*eq*: Only one compound, Δε +8. The second ring (and perhaps the '7-equatorial' 10β-Me group) enhance the positive contribution of the lactam ring by *ca* +5.

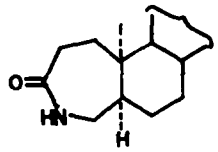
Clearly Ogura's simple rule has a limited range of applicability, having been based largely upon data for compounds in which the second ring is fused to the lactam ring at its 4,5- or 5,6-positions and makes little or no contribution. The "rule" also correctly predicts *signs* for compounds of class 7*t*6 and 7*c*6*eq*, where the second rings merely enhance the CD, without affecting its sign. The rule fails to predict even the sign of Δε in most of those cases where the second ring appears to make a

Table 3. Effect of varying temperature on lactam CD

(All compounds are A-homo-cholestanes.)

Compound	Temp.(°C)	C.D. Δε	C.D. λ(nm)
Trans-			
4a-aza-4-one, 5α[a] (19)	+29	-6.02	218-220
" [b]	-25	-7.3	220
" [b]	-51	-7.3	219
4-aza-4a-one, 5α[b] (3)	+25	-5.0	218
"	-40	-5.2	218
"	-71	-5.2	218
Cis-			
1-aza-2-one, 5β[c] (31)	+29	+9.7	226
"	-35	+12.5	226
"	-56	+13.7	225

a 0.08% solution; b 0.04% solution; c 0.05% solution.



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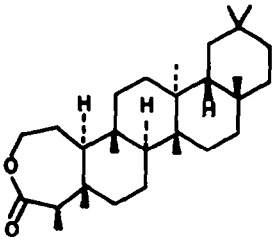

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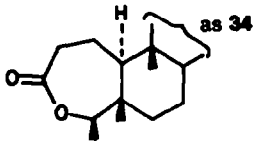

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substantial contribution of sign opposite to that due to the lactam ring itself. Possible explanations of these "anomalous" cases are discussed later.

Lactams

Wavelengths of CD maxima. The lowest-energy CD maximum for many of the lactams in Table 1 occurs at about 215 ±5 nm in methanolic solution, a range similar to that covered by acetamido-steroids.[12] The data contain notable exceptions, however, with maxima red-shifted in some cases to as far as 230 nm. It may well be significant that all the largest red-shifts ($\lambda > 224$ nm) occur among those compounds which have the second ring attached to the lactam at either the 3,4- or the 6,7-bond; these are the very compounds which either fail to obey Ogura's sign rule, or give $\Delta\epsilon$ values markedly different from the "norm" of ±3 units (see discussion, p. 551). Classes 7*c*4*eq* and 7*c*5*eq*, the others which exhibit anomalous CD (negative sign), also show a significant red-shift in their CD maxima.

Lactones with 7-membered rings (Table 2)

The number of compounds for which data are available is very limited. Only four of the twelve possible bicyclic classes are represented.

Earlier workers[2,15] have noted the curious fact that lactones and lactams of similar structure generally give $n \rightarrow \pi^*$ CD bands of opposite signs in the 210–220 nm region. Weigang[15] has recently offered a theoretical explanation (see discussion, p. 551). The present data for lactones show the expected signs for classes 7*t*4 and 7*t*5, reversing those of the corresponding lactams. Moreover the magnitudes for $\Delta\epsilon$ for these lactones generally cluster around −1 unit, which we take to be the contribution of the lactone ring itself, in the chair conformation (Fig. 1a: sign reversed for the conformation of Fig. 1b). The numerical values of $\Delta\epsilon$ for lactone and lactam rings in conformation 1(a) (*ca* −1 and +3 units, respectively), are in approximately the same ratio as those noted recently[12] for corresponding pairs of acetoxy- and acetamido-steroids. Unfortunately no lactones of classes 7*t*3, 7*c*3*ax* or 7*c*3*eq* were available, so it has not yet been possible to confirm the expectation of "abnormal" $\Delta\epsilon$ values among these compounds to match the anomalous behaviour of the corresponding lactams. The two lactones of class 7*t*6 are anomalous in regard to both the magnitude of $\Delta\epsilon$ and wavelength of the CD maximum, and include one instance of a reversal of the expected sign. The effect of the second ring seems significant in this class, as it is among lactams. The only available *cis* fused lactone (class 7*c*5*ax*) is anomalous in giving a sign matching that of $\Delta\epsilon$ for the corresponding lactam.

Temperature and solvent effects

The influence of temperature on CD was studied for three lactams in the present series (Table 3). Only the 1-aza-2-oxo-5β-compound (31) showed a modest increase in $\Delta\epsilon$ as the temperature was reduced, suggesting that the *trans*-fused lactams in particular have little conformational flexibility.

A few compounds examined in solvents of differing polarity (Table 4) showed the blue-shift with increased polarity which is a feature of $n \rightarrow \pi^*$ transitions,[26] as a consequence mainly of the stabilization of the ground-state n-orbital by solute-solvent association. Values of $\Delta\epsilon$ showed no systematic variation with solvent polarity, apart from an appreciable increase in trifluoroethanol as compared with methanol as solvent. Lactams were generally insoluble in hydrocarbon solvents.

DISCUSSION

The observation that significant second-ring contributions arise when that ring is fused as positions 3,4-or 6,7- of the lactam suggested two possible mechanisms for chiral perturbation of the lactam chromophore. The first mechanism, analogous to that believed to operate in cyclohexanones,[23,27,28] would be a direct through-bond coupling between orbitals associated with the chromophore and those of suitably placed substituent bonds attached at adjacent sites on the lactam ring. By analogy with the $n \rightarrow \pi^*$ CD of ketones, dominant contributions would be expected from those bonds which are of 'α-axial' type with respect to the CO group, and from bonds defined[23] as comprising a periplanar "primary zig-zag"; in the lactam system such a zig-zag would include the 4-equatorial ("β-equatorial") bond (Fig. 4), which forms part of the second ring in classes 7*t*3 and 7*t*4. However, the absence of any appreciable contribution from the second ring of bicyclic class 7*t*4 seems to imply that the 'β-equatorial' bond has no effect on a lactam (contrast the large effect of the second ring in *trans*-2-decalone[24]). The present data, in fact, give no indication of any 'primary zig-zag' contribution, either from substituent bonds at the β-C atom in relation to the CO group, or from those similarly placed with respect to the N atom (i.e. the 6-equatorial bond). Furthermore, one of the largest contributions (*ca* −5 units) comes from the

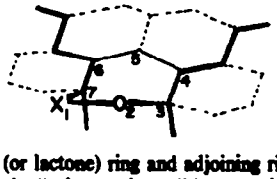

Fig. 4. Lactam (or lactone) ring and adjoining rings, with bonds relevant to the "primary zig-zag" hypothesis thickened.

Table 4. Effect on CD of changing polarity of solvent

All A-homo-5α-cholestanes; TFE = 2,2,2-trifluoro-ethanol.

Compound	Solvent	C.D.	
		Δε	λ(nm)
4-oxa-3-one (36)	Hexane	-1.15	222
"	Acetonitrile	-1.09	214
"	Methanol	-1.10	213
"	TFE	-1.39	210
4a,4a-dimethyl-4-oxa-3-one* (39)	Hexane	-0.34	237
"	Acetonitrile	-0.33	222
"	Methanol	-0.31	214
"	TFE	(no max. above 200 nm)	
4a-oxa-4-one (42)	Hexane	-0.35	237
"	Acetonitrile	-0.31	233
"	Methanol	-0.38	227
"	TFE	-0.57	220
4a-aza-4-one** (19)	Methanol	-5.45	214
"	TFE	-9.4	212

* From Dr. J.S.E. Holker, Liverpool

** Insoluble in hexane or acetonitrile.

presence of a second ring of 7*t*3 type, which includes two bonds *equatorial* to the lactam ring, whereas the second ring of class 7*c*3*ax*, with a bond "α-axial" instead of 'α-equatorial' to the lactam, makes a smaller contribution (−3 units). The 'α-axial' bond clearly exerts no dominant effect. We note, moreover, that *any* second ring attached at the 3,4-bond of the lactam, in the absolute configuration illustrated, makes a substantial negative contribution irrespective of whether the ring extends mainly above or below the approximate plane defined by the atoms C(7)–NH–CO–C(3).

Me substitution at C-3 and/or C-7 (i.e. adjacent to the chromophore) appears in several compounds to make a significant contribution to Δε. At C-3 the sign of this contribution seems generally to be negative for the absolute configuration illustrated, regardless of whether the Me group is quasi-axial or quasi-equatorial, but from the limited data available the magnitude of the Me contribution seems widely variable, and cannot generally be wholly separated from contributions allotted to rings. No regular pattern has emerged with respect to substituent effects at C-7. For these various reasons we reject the concept of any close parallel between the CD behaviour of ε-caprolactam and cyclohexanone derivatives, while recognising that substituents immediately adjacent to the chromophore probably make some contribution to Cotton effects.

The second hypothesis, which ignores direct effects of substituents, is based upon X-ray crystallographic data for ε-caprolactam itself, which has been shown[18] to be an imperfect quasi-chair with a mean C(7)–NH–CO–C(3) torsion angle of ±4.2°. The sense of twist (Fig 3) is such that the sign of this torsion angle is positive for the structure represented by Fig. 1a, which corresponds to the absolute configuration used in the present analysis, or negative for the enantiomeric structure of Fig. 1b.

Other significant C–C–C–C torsion angles within the ring represented by Fig. 1a are:[18] C(3)–C(4) bond, −81.9°, C(4)–C(5), +63.5°; C(5)–C(6), −60.7°; C(6)–C(7), +77.0°. We note that the torsion angles about the C(4)–C(5) and C(5)–C(6) bonds are close to ideal (*ca* 60°) for fusion to a cyclohexane ring. The torsion angles about the C(3)–C(4) and C(6)–C(7) bonds, however, are both much larger than 60° and would have to contract considerably in order to allow fusion of ε-caprolactam to a cyclohexane ring in the chair form without distorting it excessively. X-ray crystallographic data have recently been obtained[29] for 2-aza-A-homo-5α-cholestan-1-one (2) showing that the torsion angle about the C(5)–C(10) bond [which corresponds to C(3)–C(4) of the ε-caprolactam ring] is reduced by ring fusion from −81.9° to −73° (Fig. 6). The resulting distortion of the lactam ring changes the torsion angle about the NH–CO bond from +4.2° to −20°. We therefore propose that the abnormal Cotton effect for the steroidal lactam 2 (Δε = −11.1) results from the strongly negative torsion angle of the 'amide' chromophore itself.

Extending this hypothesis, is seems reasonable to infer that those lactams which belong to the six classes which

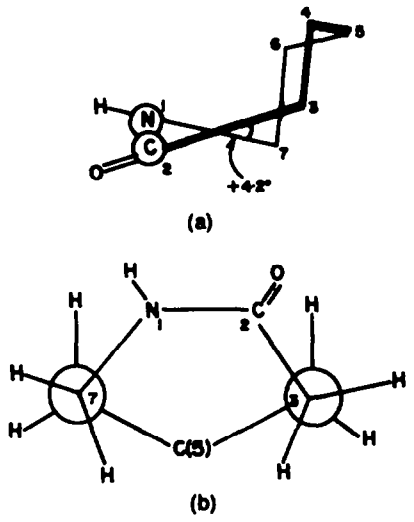

Fig. 5. Conformation of ϵ-caprolactam. (a) illustrates the preferred C(7)–NH–CO–C(3) torsion; (b) Newman projections about the C(3)–C(4) and C(7)–C(6) bonds, illustrating their non-ideal torsion angles.

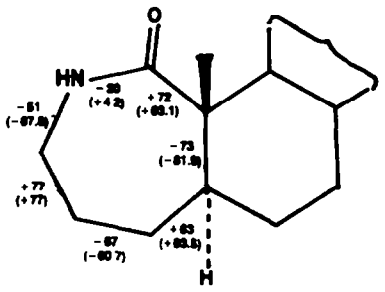

Fig. 6. Torsion angles (X-ray) in ring A of 2- aza - A - homo - 5α - cholestan - 1 - one (values in parentheses refer to the monocyclic ϵ-caprolactam—see Ref. 18).

have second rings attached at either the 3,4- or the 6,7-bonds of the lactam ring, and which also have abnormal CD, have their lactam rings appreciably distorted from the conformation preferred in ϵ-caprolactam itself. Moreover it appears from study of Dreiding models that the effects of such distortions on the the C(7)–NH–CO–C(3) torsion angle will be opposite in sign: fusion at C(3)–C(4) to a cyclohexane ring tends to reduce the positive torsion angle of C(7)–NH–CO–C(3), or may perhaps even reverse its sign as in lactam 2, whereas a cyclohexane fused at C(6)–C(7) tends to increase the positive torsion angle of the amide chromophore. These signs correspond precisely to expectation on the hypothesis that the chiral lactam ring of Fig. 1a contains an inherently dissymmetric amide chromophore, and that its positive torsion corresponds to a Cotton effect of the same sign. The contributions of additional rings would then stem mainly from their effect either in enhancing the amide twist (6,7-fusion), or in reducing or reversing it (3,4-fusion).

The reasons for the departure from the normal CD behaviour in classes 7*c*4*eq* and 7*c*5*eq* is not clear. In both systems the 'second-ring' contribution appears to be strongly negative, although in neither case is there any obvious need for the lactam ring to adjust its geometry to permit fusion to the cyclohexane ring;† moreover the second rings project respectively below and above the lactam ring in the conformation and orientation illustrated. The effects of these rings remain unexplained at present, but may perhaps be clarified by an X-ray study of the conformations of these compounds.

†We note, however, that structure 7*c*4*eq* includes a C–C bond which is '5 -axial' to the lactam ring, and that the particular compound 29 of class 7*c*5*eq* has a similarly-placed Me substituent (10α–CH_3): these axial substituents must interact with the '3-axial' and '7-axial' groups on the lactam ring, and may introduce a distortion which cannot at present be assessed. It would be most interesting to examine the CD behaviour of the 19-nor analogue of compound 29, where such axial-axial interactions would be much reduced.

Changes in torsion angles resulting from the presence of substituents on the lactam ring may lie at the root of the variable effects of methyl groups at C-3 and/or C-7, mentioned above.

A further feature of present data, which may provide some support for the torsion hypothesis, is the CD red-shift observed for those lactams which exhibit abnormal Cotton effects. If the conformation found for ϵ-caprolactam itself corresponds to the minimum energy of the ring and of the ground state n-orbital of the chromophore, any distortion would be expected to elevate the energy of the ground state, and probably also lower the energy of the excited state (π^*) orbital, resulting in a red-shift of the transition.

Unfortunately, UV spectra determined for a selection of these lactams were of little use in confirming this red-shift, for the $n \rightarrow \pi^*$ absorption band could be seen at best only as a broad shallow hump on a strong background absorption.

The concept of an inherently chiral n-orbital, twisted by its dissymmetric environment, is similar in some respects to the postulated twisting of the n-orbital of a chiral ketone, which according to recent MO calculations[28,30] is the principal source of the $n \rightarrow \pi^*$ Cotton effect of ketones. The main difference between lactams and ketones appears to lie in the highly delocalised character of the ketone n-orbital,[27,28] which explains the dominant effect of extended primary zig-zags. The absence of primary zig-zag effects in lactams would suggest an n-orbital more nearly localised in the N–C=O system, but chiral by virtue of its torsion or immediate environment.

Clearly, the additivity of ring contributions assumed above is not valid if the CD of polycyclic lactams is determined largely by changes in the conformation of the lactam ring to accommodate fusion to additional rings, as we suggest. Additivity is, nevertheless, a convenient assumption for the purpose of assessing empirically the effects of structural features adjoining the lactam ring, until accurate conformations become known. Unpublished data for a limited number of lactams (and lactones) of "middle ring" type (rings B or C of steroids) cannot at present be correlated with the set of ring contributions presented in Fig. 3, and must await the accumulation of results for a wider range of such compounds.

Weigang's sector rule,[15] derived by considering both static and dynamic coupling mechanisms between the chromophore and its surroundings for lactams and related chromophores, does not succeed in predicting the pattern of second-ring contributions deduced during the present work. It does, however, offer an inter-

pretation of the reversal in sign of the second CD band for lactams (below 200 nm), which may have mixed $n \rightarrow \pi^*$ and $\sigma \rightarrow \pi^*$ character. According to Weigang, the CD band observed near 214 nm for lactones is also of this latter type, the ordering of transitions being reversed between lactams and lactones.

Our limited data for lactones would appear to be mainly consistent with Weigang's assignment, and to suggest a chromophore-torsion correlation between CD and structure which is the opposite of that found for the "214 nm" transition of lactams, as well as giving Cotton effects of approximately ⅓ of the magnitude.

The conclusions of the present analysis are regarded as empirical estimates of $\Delta\epsilon$ for bicyclic lactams and lactones which should be of value towards confirmation of structures and configurations of related compounds. The validity or otherwise of the torsion hypothesis can only be judged when X-ray crystallographic data are available for an extensive range of compounds of the types discussed here.

EXPERIMENTAL

Routine CD measurements were made in MeOH in a 1 cm cell on a Cary 61 instrument in Westfield College. CD measurements at varying temps were made in MeOH in a 1 cm cell on a Jasco J-15 instrument in the Institute of Low Temperature Science, Hokkaido University. M.ps were determined with a Yanagimoto micro-m.p. apparatus. IR spectra were determined for Nujol mulls. 100 MHz NMR spectra were determined with a JEOL PS 100 high-resolution spectrometer (solvent $CDCl_3$; Me_4Si as internal reference). Tlc was carried out on Wakogel B-5. Low resolution mass spectra were taken by the staff of the Faculty of Pharmaceutical Sciences of Hokkaido University with a Hitachi RMU-6E spectrometer (direct inlet system; source temp *ca* 200°; ionizing voltage 79 eV). High resolution mass spectra were recorded with a Hitachi-RMU-7MF double focussing mass spectrometer (direct inlet system; ionizing voltage 70 eV). Elemental analyses were performed by the staff of the Faculty of Pharmaceutical Sciences, Hokkaido University.

19-*Nor-lactams* (4) *and* (12) *by Beckmann rearrangement of* 17β *- acetoxy - 5α- estran - 3 - one oxime* (by N. Maeda). The oxime was prepared in the usual way from 17β-acetoxy-5α-estran-3-one.[31] It was obtained as a mixture of *syn* and *anti* isomers m.p. 172–175° (from ether–hexane), ν_{max} 3256 (OH), 1734 (OAc), 1245, 1039 and 1021 cm^{-1}; τ 9.25 (s, 18-H_3), and 5.46 (t, J 7.5 Hz, 17α–H). (Found: C, 71.9, H, 9.3; N, 4.1; $C_{20}H_{31}NO_3$ requires: C, 72.0; H, 9.4: N; 4.2%). Thionyl chloride (0.6 ml) was added to the oxime (66 mg) in dry dioxan (10 ml), and the mixture was stirred for 10 min at room temp.

After neutralization with 2M KOH the product (71 mg) was extracted with ether, and subjected to preparative tlc with a 1:3 mixture of acetone–dichloromethane, to afford three fractions. The most mobile fraction (6 mg) crystallized from MeOH to afford unidentified crystals (3 mg), m.p. 153–155°. The next fraction (36 mg) crystallized from hexane to afford a mixture of 4 and 12, m.p. 222–223°. A slightly less mobile third fraction (20 mg) crystallized from acetone also to yield a mixture (7 mg) of the lactams, m.p. 220.5–222.5°. The lactam mixtures were combined and subjected to hplc (Waters, Model M-6000A: Column, Bondapak CN, 6 mm × 30 cm; solvent: diethyl ether saturated with water; flow rate, *ca* 90 ml/h; detector, JASCO Unidec-100, *ca* 220 nm). The lactam (5 mg) having the shorter retention time was the 3-*aza*-4-*oxo isomer* (4), which crystallized from MeOH (2 mg), m.p. 252–255°. (Found: M^+ 333.2252. $C_{20}H_{31}NO_3$ requires: M^+ 333.2302); ν_{max} 3177 and 3061 (NH), 1743 (OAc), 1678, 1630 sh (lactam CO), 1238 and 1037 cm^{-1}; τ 6.78 (br.t., 2α- and 2β-H), 3.95 (br.s., $W_{1/2}$ 21.0 Hz, NH), 7.47 (dd, J 9.9 and 13.5 Hz, 4aβ–*H*), 7.87 (br.d., J 13.5 and 3 Hz, 4aα–H), 9.22 (s, 18-H_3) and 5.44 (dd, J 7.5 and 9.0 Hz; 17α–H); *m/e* 333 (M^+, 64.1), 305 (33.3), 273 (25.6), 248 (25.6), 149 (53.8), 91 (64.1), 69 (35.9), 55 (53.8), 43 (100). The lactam (10 mg) having the longer retention time was the 4-*aza*-3-*oxo isomer* (12). After recrystallization from MeOH (2 mg) it showed m.p. 274–276°. (Found: M^+ 333.2293. $C_{20}H_{31}NO_3$ requires: M^+ 333.2302); ν_{max} 3280, 3180, and 3060 (NH), 1739 (OAc), 1693 and 1643 (lactam CO), 1253 and 1041 cm^{-1}. τ 7.49–7.60 (m, 2α- and 2β-H), 3.79 (br.s., $W_{1/2}$ 18.0 Hz, NH), 7.18 (dd, 7.5 and 14.3 Hz, 4aα-H), 6.83 (dd, 7.5 and 14.3 Hz, 4aβ-H), 9.22 (s, 18-H_3), and 5.46 (dd, 7.5 and 9.0 Hz, 17α-H); *m/e* 333 (M^+, 35.3), 305 (100), 290 (23.1), 273 (25.5), 149 (33.3), 81 (45.1), 69 (56.9), 55 (76.5) and 43 (86.3). The ratio of 12 to 4 as determined by hplc was 67:33.

The respective structural assignments of 4 and 12 were confirmed by NMR spin-decoupling and D_2O exchange experiments. In isomer 12, with NH adjacent to C-4a, the 4aα- and 4aβ-protons appeared as double doublets, centered at τ 7.18 and 6.83. After D_2O exchange of the NH proton, the double doublet at τ 7.18 (J 7.5 and 14.3 Hz) collapsed to a doublet (J 14.3 Hz), showing the magnitude of coupling between NH and one of the C-4a protons to be 7.5 Hz. On irradiation at τ 8.72, corresponding to 5α-H, the double doublet at τ 6.83 (J 7.5 and 14.3 Hz) collapsed to a broad doublet with J 14.3 Hz. Assuming the quasi-chair conformation of ring A with 4aβ-H quasi-axial and 4aα-H quasi-equatorial, the relevant coupling constants are: $J_{4a\alpha,4a\beta}$, 14.3 Hz; $J_{4a\alpha,5\alpha} < 1$ Hz; $J_{4a\beta,5\alpha}$, 7.5 Hz; $J_{4a\alpha,NH}$ 7.5 Hz.

In lactam 4, with CO adjacent to C-4a, the 4aα- and 4aβ-protons appeared as a broad doublet centred at τ 7.87 (J 13.5 and 3 Hz) and a double doublet centred at τ 7.47 (J 9.9 and 13.5 Hz). On irradiation at τ 8.58, corresponding to 5α-H, the double doublet at τ 7.47 collapsed to a broad doublet with J 13.5 Hz and the broad doublet at τ 7.87 sharpened. Assuming the quasi-chair conformation of ring A with 4aβ-H quasi-axial and 4aα-H quasi-equatorial, the relevant coupling constants are : $J_{4a\alpha,4a\beta}$, 13.5 Hz; $J_{4a\alpha,5\alpha} < 3$ Hz; $J_{4a\alpha,5\beta}$, 9.9 Hz.

4a - *Oxa - A - homo - 5α - cholestan - 4 - one* (42) (by A. Osada). 5α - Cholestan - 4 - one[32] (30 mg) in dichloromethane (3 ml) containing *m*-chloroperbenzoic acid (60 mg) and toluene-*p*-sulfonic acid (30 mg) was set aside for 62 hr at room temp in the dark, then treated with 5% $Na_2S_2O_3$ aq and the product was extracted with dichloromethane. The organic layer was washed with $NaHCO_3$ aq and water and dried (Na_2SO_4). The crystalline residue (31 mg) was purified by preparative tlc with a 4:1 mixture of benzene and diethyl ether and recrystallized from MeOH to yield the *lactone* (16 mg), m.p. 117–119° (lit.[33] oil). (Found: C, 80.7; H, 11.35; $C_{27}H_{46}O_2$ requires: C, 80.5; H, 11.5%) ν_{max} 1736 cm^{-1} (lactonic C=O), (lit.[33] 1715 cm^{-1}); τ 9.34 (s, 18-H_3), 9.10 (s, 19-H_3), 7.40 (m, 3-H_2), and 5.88 (dd, J 5.7 and 11.4 Hz, 5α-H); *m/e* 402 (100%, M^+), 248 (87.4%), and 247 (82.1%).

Treatment of 5β-cholestan-4-one with *m*-chloroperbenzoic acid in a similar manner also gave 4a-oxa-A-homo-5α-chlolestan-4-one.

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