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# A RELATIONSHIP BETWEEN THE COTTON EFFECT AND THE CONFORMATION OF A SEVEN-MEMBERED LACTAM RING[1)]

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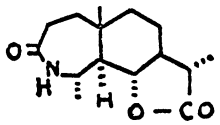
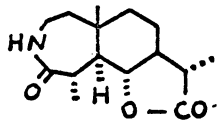
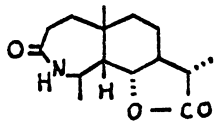
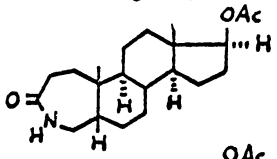
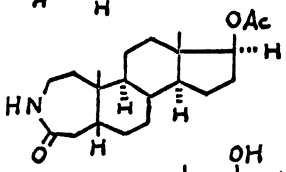
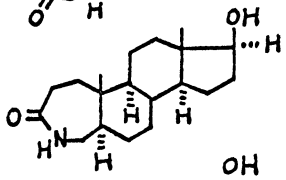
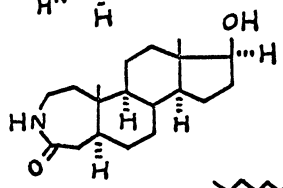
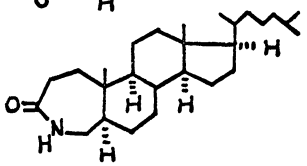
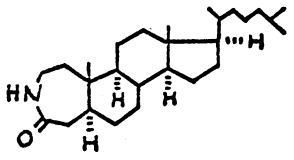
A rule about the n-π* Cotton effect of seven-membered lactam ring was investigated. From this rule, the seven-membered lactam was classified into two types A and B. Type A should have the negative and type B should have the positive Cotton effect.

Conformation of lactam and lactone rings influences the sign of the n-π* Cotton effect.[2,3,4)] Recently, it has been suggested that the sign of the n-π* Cotton effect of lactam and lactone chromophores depends solely on the enantiomeric nature of the bridged lactam and lactone systems and not at all on molecular asymmetry of the peripheral part of the structure.[5,6)]

We herewith wish to report some CD and ORD data[7)] of A-azatetrahydro-α-santonins[8)] and A-azasteroids[9)] derived from their oximes by the Beckmann Rearrangement. These data indicate, as shown later in this paper, that there is a relationship between the conformation of seven-membered lactam ring and the sign of the n-π* Cotton effect.

A-Azatetrahydro-α-santonin derivatives have two chromophores, a lactam and a lactone, in their molecules, and both ORD and CD curves showed overlapped Cotton effect due to these two chromophores. Klyne *et al.*[10)] already reported the ORD data of lactones, and concluded that the lactone in α-santonin derivatives showed the positive Cotton effect with [φ] about +2500 at 225-240 nm. Overberger and Kaye[11)] also reported the relation between the ORD of ε-caprolactones and the ring conformation. They concluded that seven-membered lactone showed the positive n-π* Cotton effect at around 220 nm, and this value was influenced by the configuration of substituents. As shown in the table, compounds 2 and 3 showed a negative Cotton effect. On the other hand, 1 showed a positive Cotton effect with [φ] +5200 at 230 nm which is larger than the values (+1200 to +3500) of the corresponding lactones.[10)] And, lactam Cotton effect of 1 should give a positive. The substituent effect of the lactone is less than that of the lactam. This fact may be explained by the large value of [φ] or [θ]. In our experiment, 5-methyl group in santonin derivatives (1, 2, 3) did not exert much influence on the value as well as steroid derivatives without substituent groups (4-8) didn't. ORD curves of 1, 2, and 3 showed a bathochromic shift of about 6-15 nm in a less polar solution (dioxane).[12)]

TABLE CD and ORD Data of Seven-membered Lactam (in MeOH)

| | Compound | $[\theta] \times 10^{-3}$ | λ(nm) | $[\phi] \times 10^{-3}$ | λ(nm) |
|---|---|---|---|---|---|
| 1 |  | +11.8 | 211 | +5.2 | 230 |
| 2 |  | -14.8<br>(+1.1 | 210<br>234)[d] | -3.9 | 220 |
| 3 |  | -9.7 | 218 | -4.2 | 230 |
| 4 |  | -12.8 | 218 | -6.0 | 230 |
| 5 |  | +16.7<br>(-0.4 | 205<br>225)[e] | +18.0 | 209 |
| 6 |  | +7.0 | 211 | +7.7 | 226 |
| 7 |  | -7.5 | 211 | -4.6 | 228 |
| 8[a] |  | +7.4 | 210 | +4.7 | 223 |
| 9[a] |  | -0.6[b]<br>-10.2[c] | 211<br>214 | -4.3[c] | 227 |

a: Analysis (C,H,N) and mass spectrum showed a satisfactory data.

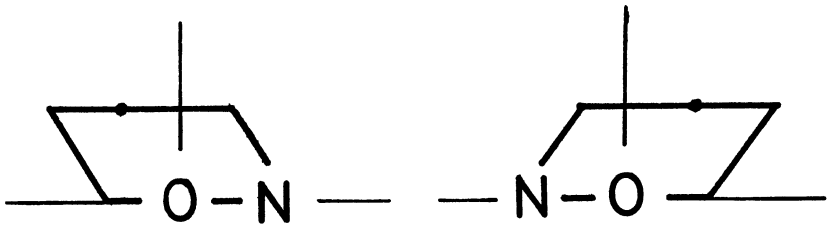
b: Mp 268-271°, prepared by the method of Shoppee and Sly.[15]

c: Mp 278-279°, prepared by the method of Shoppee, Krüger, and Mirrington.[16]

d; e: These Cotton effects are assigned to lactone and acetoxy group, respectively.

The partial double-bond character of the CO-NH bond[13] causes a planar conformation. However, the whole RCH-CO-NH-CHR' group in the seven-membered lactam ring is considered to be in a chair conformation. This was shown by $^{19}F$ nmr spectral studies on γ,γ-difluoro-ε-caprolactam.[14] Our studies on the conformation of A-azatetrahydro-α-santonins also suggested the chair conformation.[8] In A-azasteroids, A ring should also gave a chair conformation. Shoppee and Sly[15] once reported that 5α-cholestan-3-one oxime underwent the Beckmann Rearrangement to give a single compound, 3-aza-A-homo-5α-cholestan-4-one (9), mp 268-271°. However, Shoppee et al.[16] reported in another paper that the same compound produced, through the Beckmann Rearrangement, 4-aza-A-homo-5α-cholestan-3-one (8) and 9, both having mp 295°. In our experiment, 5α-cholestan-3-one oxime underwent the Beckmann Rearrangement after treatment of the oxime with hydrochloric acid to give an isomeric 4-aza compound (8), mp >300°, which showed the positive Cotton effect, [θ] +7400 at 210 nm and [φ] +4700 at 223 nm. Compound 9, mp 278-279°, which prepared by the hydrogenation of 3-aza-A-homo-5α-cholestan-4a-en-4-one produced though the Schmidt Reaction of cholest-4-en-3-one,[16] showed [θ] -10200 at 214 nm and [φ] -4300 at 227 nm. On the other hand, compound 9, mp 268-271°, which obtained by the same method by Shoppee and Sly,[15] showed [θ] -600 at 211 nm and this means that it is about 1:1 mixture of 8 and 9.

Habermehl and Haaf reported that 16β-acetoxy-3-aza-A-homo-5β-androstan-4-one (10) and 16β-acetoxy-4-aza-A-homo-5β-androstan-3-one (11) showed two Cotton effects, the first negative [θ] -2500 at 225 nm, [θ] -7300 at 220 nm and the second positive [θ] +15000 at 203 nm, [θ] +8600 at 200 nm in ethanol, respectively;[17] and 3-aza-A-homo-5α,10α-androstan-4-one (12), 4-aza-A-homo-5α,10α-androstan-3-one (13), and 2-aza-A-homo-5α,10α-androstan-3-one (14) showed positive Cotton effect at around 220 nm ([θ] +8900 at 215 nm, [θ] +2500 at 225 nm, and [θ] +1700 at 220 nm, respectively), and 13 has another negative Cotton effect [θ] -9600 at 202 nm.[18] The sign of the Cotton effect of 10, 11, and 14 is in agreement with our expectation. In the case of 10, the first negative Cotton effect may be owing to the acetoxy group, and in the case of 11, the second positive Cotton effect may be owing to the π-π* Cotton effect. In the case of compounds 12 and 13, the sign of the Cotton effect could not be decided, because the conformation of the seven-membered lactam ring of 12 and 13 was not decided.




A B

In conclusion, a relationship between the sign of the n-π* Cotton effect and the structure can be summarized as follows. The seven-membered lactam rings are classified into two types of A and B as shown by the octant projection. Compounds 2,3,4,7, and 9 belong to the type A, while 1,5,6, and 8 belong to the type B. The table indicates that the type A shows a negative sign of the Cotton effect and the type B shows the positive sign. Therefore, when the CD and ORD signs are negative, the conformation of the seven-membered lactam ring would be the type A and, when positive, the lactam ring is the type B. Application of this regularity to six-membered lactam ring is under investigation in our laboratory.

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