for H_2 and H_3,H_4, respectively; standard deviations were on the order of ±10%. For H_1, the slowest reacting proton, the upper limit given is based on one point only. Decomposition of the sulfonium cation appears not to be a problem in the determination of the exchange rates for H_2 and H_3,H_4. In fact, within the time required (up to 800 min at 75° 1.7 *M* NaOD), the intensity of the H_1 signal (relative to the standard) does not decrease appreciably. On the other hand, for H_1, the decrease of the signal intensity may be due to exchange, or to pyramidal inversion, as well as to decomposition of the substrate. The latter is likely not to be important, however, as no new signal appears in the pmr spectrum.

The thermal stereomutation experiments were performed on a 50-mg sample of II-d_3 (see above) dissolved in 0.8 ml of D_2O directly in the nmr tube, which was sealed and put in a thermostated bath at 90°. The kinetic run comprised eight points between 2 and 50 hr. After each time interval the sample was quenched and the pmr spectrum recorded. Aside from the aforementioned decrease of the 3.58-ppm and increase of the 4.02-ppm signals, no other spectral change was observed in the 2.5–4.5-ppm region. In particular, no significant proton signal appeared in the 2.7–3.3-ppm region (H_3–H_4), while the overall signal intensity in the 3.5–4.1-ppm region (H_1–H_2) remained constant relative to that of the 2.92-ppm signal (S–CH_3).

Pmr spectra were recorded on a Varian H-100 and/or a Jeol PS-100. The nO experiments were carried out on both instruments, following the procedure described by Bell and Saunders.[20] The enhancements reported are the per cent differences in the integrated intensities of a specific signal caused by double irradiation at the S–CH_3 signal and at a blank region of the spectrum, consecutively and using the same irradiating power. The enhancements reported are the average of ten comparisons.

Acknowledgment. The authors are indebted to Dr. P. Chamberlain (University of Cambridge) for suggesting compound II as a conformationally rigid half-chair. A. G. and A. F. thank Du Pont (Europe) and C.N.R., Rome, for financial support.

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Conformation of (−)-Menthone Lactam and *N*-Methylmenthone Lactam[1]

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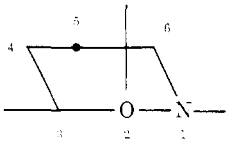
Abstract: A regularity about the n–π* Cotton effect of the seven-membered lactam ring (lactam rule) was applied to (−)-menthone lactam and *N*-methyl-(−)-menthone lactam. Conformational equilibrium of a simple seven-membered lactam ring was discussed on the basis of the lactam rule.

Recently, we suggested[1] 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)) from the CD and ORD data of *A*-azatetrahydro-α-santonins[2] and *A*-azasteroids[3] derived from their oximes by the Beckmann rearrangement.



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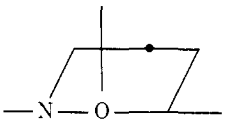

B

Rehling and Jensen[4] reported the relationship between the CD spectra and absolute configuration of β-lactam substituted azetidinones. The azetidinone ring showed coplanarity from its X-ray analysis,[5] and coplanarity of the lactam ring means similarity of the seven-membered lactam ring. Application of the lactam rule to azetidinones should solve problems about the absolute configuration. In this case, the model is so placed that the substituents are above the octant plane. When the substituent R^1 and/or R^3 is above the plane of the octant, corresponding to model B, the compounds should have a positive Cotton effect. On the other hand, when the substituent R^2 and/or R^4 is above the plane of the octant, corresponding to model A, the compounds would be expected to exhibit a negative Cotton effect. The data are summarized in Table I which clearly indicates that the azetidinone derivatives (**1–15**) are present in two types, A and B.

When the substituent is two or more and in mixed positions (R^1 and/or R^3 and R^2 and/or R^4), the decision of the sign of n–π* Cotton effect may be made from the substituent effect. For example, in compounds **8** (R^1 = CH_3, R^2 = $CH{=}CH_2$) and **15** (R^1 = $CH{=}CH_2$, R^2 = CH_3), the $CH{=}CH_2$ group may decide the sign of the Cotton effect.

The quadrant rule given by Schellman[6] for the amide chromophor shows that the rotation is dominated by the nearest substituent to carbonyl group oxygen. From the quadrant rule a positive Cotton effect for compound **3** (Table I) is anticipated by a positive quadrant substituent (R^4). For the same reason, a negative Cotton effect for compound **11** is anticipated by a negative quadrant substituent (R^3). Thus the same substituent is attached to the same side of the octant plane, and prediction of the sign of the Cotton effect cannot be decided from the quadrant rule. In this case, application of the lactam rule resolves the

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[1] Studies on Lactam, III. For part II see H. Ogura, H. Takayanagi and K. Furuhata, *Chem. Lett.*, 387 (1973).

[2] H. Ogura, H. Takayanagi, and C. Miyahara, *J. Org. Chem.*, 37, 519 (1972).

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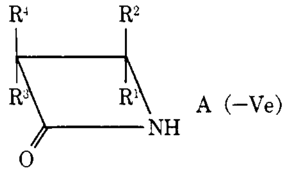
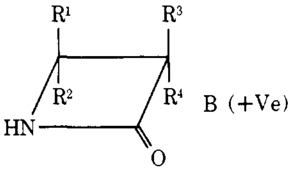
Table I. CD Data of Substituted Azetidinones (in heptane)[4]





	R^1	R^2	R^3	R^4	[θ], deg
1	H	CH_3	H	H	−7,590
2	H	CH_3	CH_3	CH_3	−11,880
3	H	CH_3	H	CH_3	−4,620
4	H	$CH_2{=}CH$	H	H	−21,120
5	H	C_6H_5	H	H	−36,960[a]
6	H	CH_2CH_2	H	CH_2	−726
7	CH_3	C_6H_5	H	H	−26,730
8	CH_3	$CH_2{=}CH$	H	H	−7,590
9	CH_3	H	H	H	+6,930
10	CH_3	H	CH_3	CH_3	+11,880
11	CH_3	H	CH_3	H	+3,960
12	$CH_2{=}CH$	H	H	H	+22,110
13	CH_2CH_2	H	CH_2	H	+2,145
14	C_6H_5	CH_3	H	H	+27,390
15	$CH_2{=}CH$	CH_3	H	H	+6,930

[a] In dioxane.

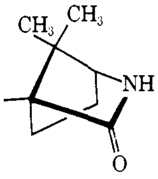
problem. In contrast, when the same substituent is attached to the opposite position as in **16** ($R^1 = R^4 = CH_3$, $R^2 = R^3 = H$) or **17** ($R^1 = R^4 = H$, $R^2 = R^3 = CH_3$), the sign of the Cotton effect cannot be decided from the lactam rule. In this case, the quadrant rule should be applied to resolve the question. To our knowledge, small ring lactams should have a similar problem and not be a special case of amides.

The lactam rule is also applicable to five-membered lactams. From the lactam rule, camphorolactams,[7] 1,7,7-trimethyl-3-azabicyclo[2.2.1]heptan-2-one (**18**), should have a negative Cotton effect and 1,7,7-trimethyl-2-azabicyclo[2.2.1]heptan-3-one (**19**) should have a positive Cotton effect for the n–π* band. In fact, CD spectra of the two lactams, $[\theta]_{225}^{\text{hexane}}$ −32,000° (**18**) and $[\theta]_{225}^{\text{hexane}}$ +30,000° (**19**),[7] exactly fit the lactam rule.

The present investigation is on conformational studies of (−)-menthone lactam and its *N*-methyl derivative from the lactam rule. (−)-Menthone lactam (4-methyl-7-isopropyl-1-azacycloheptan-2-one) (**21**) was prepared by the Beckmann rearrangement of (−)-menthone oxime or the Schmidt reaction of (−)-menthone[8] (**20**). In general, configuration of the starting carbonyl compounds is retained in the base-catalyzed Beckmann rearrangement of its oximes.[9] *N*-Methyl-(−)-menthone lactam (1,4-dimethyl-7-isopropyl-1-azacycloheptan-2-one) (**22**) was prepared in 67% yield from **21** with methyl iodide and sodium hydride.[10]

ε-Caprolactam is in boat conformation from the esr studies,[11] although γ,γ-difluoro-ε-caprolactam is in chair conformation from the ^{19}F nmr spectral studies.[12] Our studies on the conformation of *A*-azatetrahydro-α-santonins also suggested the chair conformation from the nmr spectra.[2]

These facts may support the chair conformation for (−)-menthone lactam and *N*-methyl-(−)-menthone lactam. This was further confirmed from the nmr spectra (Figure 1). The *J* values (1.2 and 11.3 Hz) of 3-H_a and 3-H_e with 4-H are adequate for the chair conformation (0.5 and 8.5 Hz) and not for boat conformation (9.3 and 11.0 Hz).



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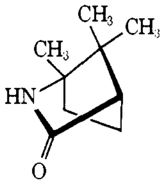

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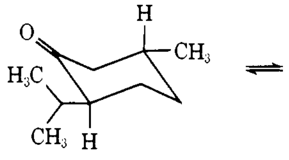

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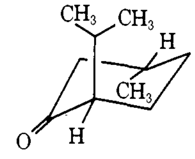

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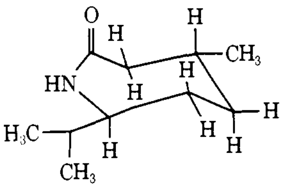

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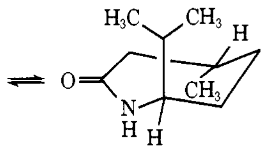

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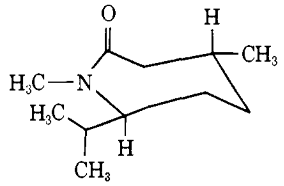

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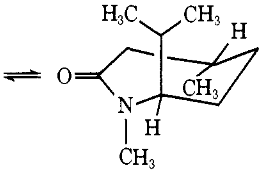

F

From the CD studies of (−)-menthone, Djerassi, *et al.*,[13] stated that the possible conformer equilibrium was between the diequatorial chair (A) and diaxial chair (B) forms. From this fact, (−)-menthone lactam should be shown by the equilibrium between the possible conformers C and D. From the lactam rule, C should have a negative Cotton effect and the other conformer (D) should have a positive Cotton effect. In our experiment, CD curves of **21** in cyclohexane and methanol (Figure 2a) at room temperature (28°)

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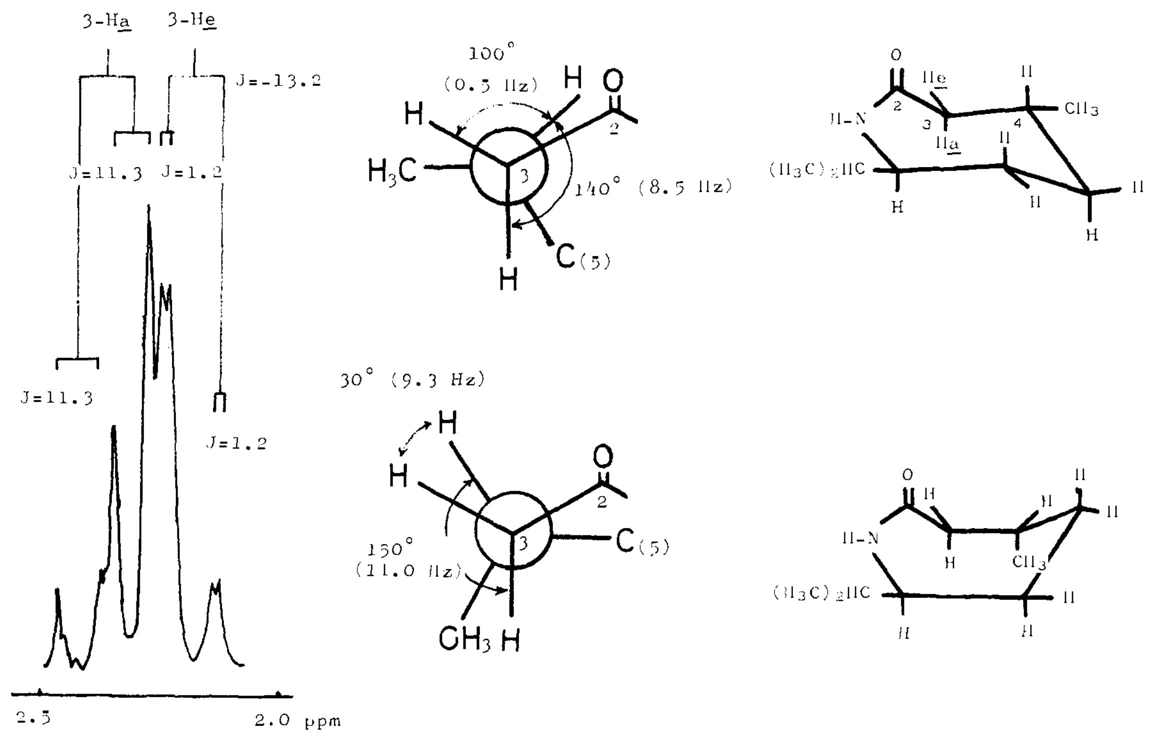

Figure 1.

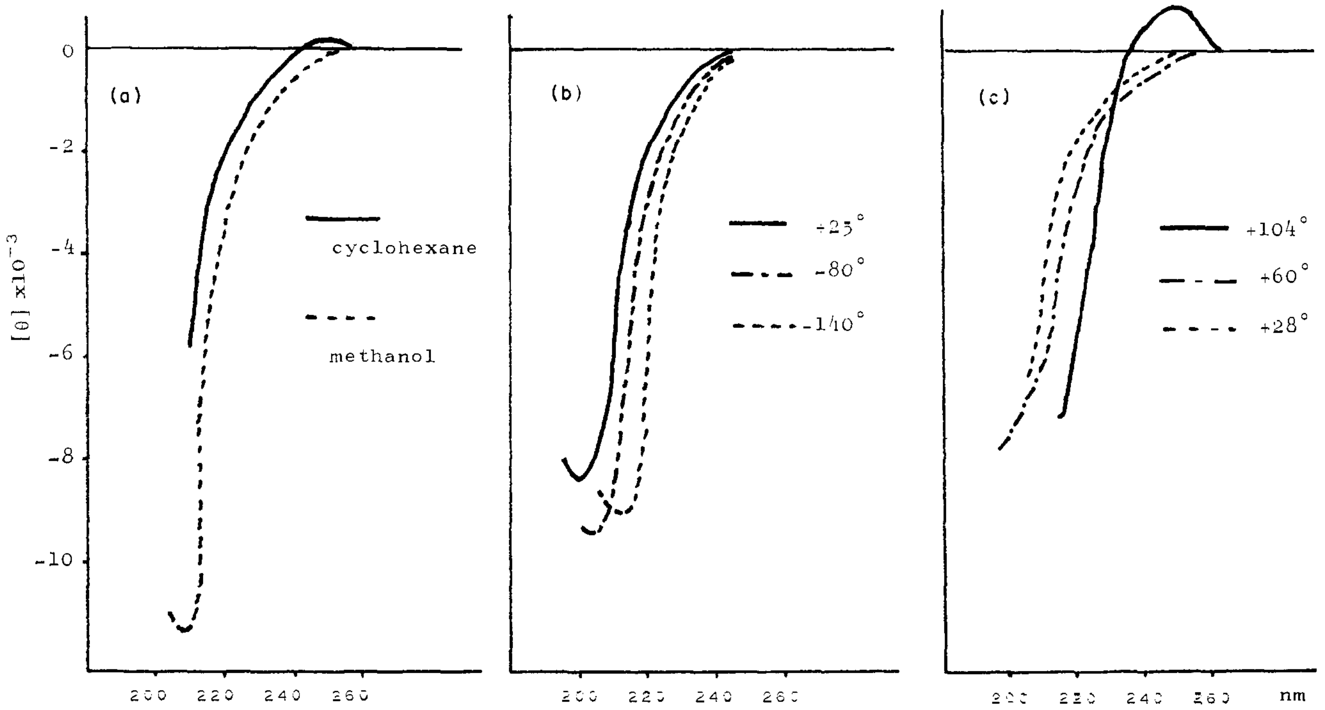

Figure 2. (a) CD curves of (−)-menthone lactam at 28°; (b) CD curves of (−)-menthone lactam at lower temperature in EtOH–MeOH (4:1); (c) CD curves of (−)-menthone lactam at higher temperature in decalin.

showed a negative Cotton effect. At lower temperatures (−80, −140°) CD curves of **21** in methanol–ethanol (Figure 2b) also showed a negative Cotton effect, accompanied by a red shift of about 10 nm. Conformational homogeneity of the C conformer in menthone lactam (**21**) has been demonstrated by the measurement at a lower temperature. On the other hand, it was noted with interest that the higher temperature CD curve of (−)-menthone lactam (**21**) in decalin, shown in Figure 2c, the longer wavelength band, the positive Cotton effect at 240 nm (+800), was found to increase at the expense of the shorter wavelength band. This result is clearly explained by the presence of the other diaxial conformer (D).

On the other hand, the CD curve of *N*-methyl-(−)-menthone lactam (**22**), as shown in Figure 3a, exhibited a markedly positive Cotton effect ($[\theta]_{222}^{\mathrm{MeOH}}$ +8700°, $[\theta]_{230}^{\mathrm{dioxane}}$ +3200°, $[\theta]_{230}^{\mathrm{cyclodexane}}$ +3000°, $[\theta]_{232}^{\mathrm{decalin}}$ +3300°), and the second negative Cotton effect appeared at a shorter wavelength region

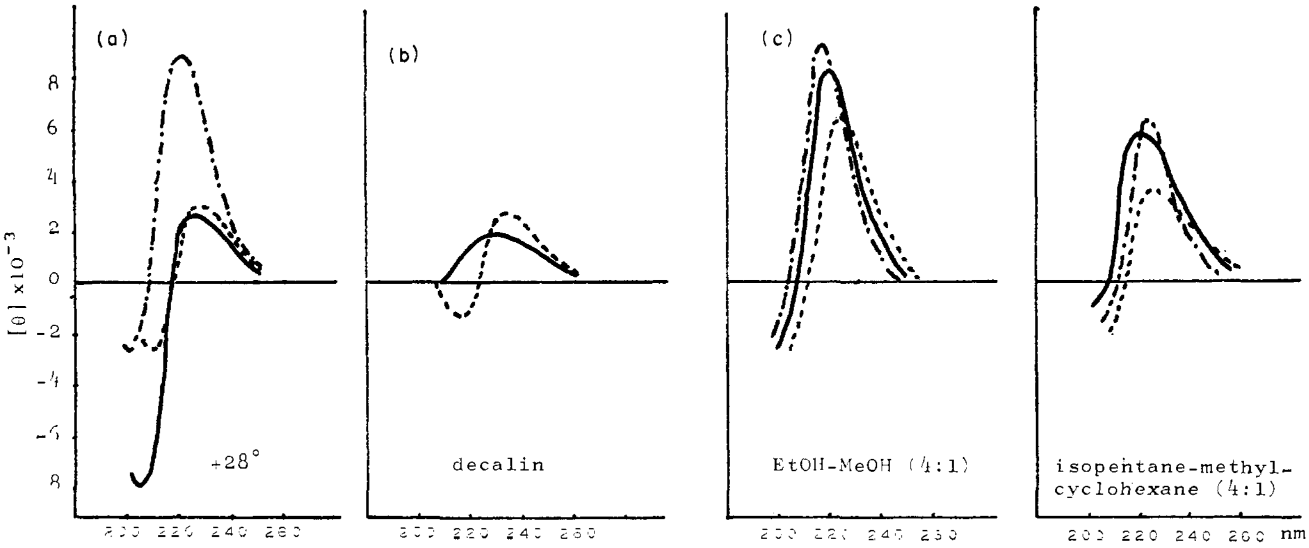

Figure 3. (a) CD curves of *N*-methylmenthone lactam (**22**) at 28°: (—) cyclohexane, (- - -) dioxane, (—·—) methanol. (b) CD curves of *N*-methylmenthone lactam (**22**) at higher temperature in decalin: (- - - -) +28°, (—) +104°. (c) CD curves of *N*-methylmenthone lactam (**22**) at lower temperature: (- - -) +25°, (—) −80°, (—·—) −130°.

($[\theta]_{204}^{\mathrm{MeOH}}$ −3300°, $[\theta]_{212}^{\mathrm{dioxane}}$ −2900°, $[\theta]_{207}^{\mathrm{cyclohexane}}$ −8400°, $[\theta]_{216}^{\mathrm{decalin}}$ −2000°). This result may be an indication that the solvational equilibrium is due to E and F and the contribution of the conformer F is predominant. In changing from a more polar solvent (MeOH) to nonpolar solvents (dioxane, cyclohexane, decalin), both bands gave a red shift of a similar extent (5–10 nm) but the wavelength separation between the two extremes remained about 20 nm. This result is similar in extent to the case of (−)-menthone, (+)-isomenthone, and 5α-cholestan-3-one.[13]

The high-temperature CD curve of **22** in decalin (Figure 3b) is similar to the results of menthone lactam. Accordingly the short wavelength band apparently disappeared as expected if this band is attributed to the equatorial conformer (E). Although the measurement at a lower temperature of **22** is shown in Figure 3c, there can not be found so much change until −130°.

Experimental Section

Temperatures are uncorrected. Nmr spectra were measured in $CDCl_3$ at 100 MHz with a JMS-PS 100 spectrometer, and Me_4Si was used as an internal reference. CD curves were measured with a Japan Spectroscopic Model J-20 recording polarimeter.

4-Methyl-7-isopropyl-1-azacycloheptan-2-one (21). To a solution of 15.0 g (0.1 mol) of (−)-menthone in 50 ml of concentrated HCl, 10 g (0.15 mol) of NaN_3 was added carefully at room temperature. After mixture was allowed to stand for 2 days, the reaction mixture was neutralized with 10% NaOH. Precipitated NaCl was filtered off, and the filtrate was repeatedly extracted with ethyl acetate. The combined extracts were washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. The residual crystals were collected and recrystallized from hexane to yield 11.3 g (69%) of **21** as white needles: mp 118–118.5°, reported mp 118–119°;[8] ir (KBr) 3240, 3090 (NH), 1666 (br, CO) cm^{-1}.

1,4-Dimethyl-7-isopropyl-1-azacycloheptan-2-one (22). To a solution of 9.3 g (0.06 mol) of **21** dissolved in 13 ml of dry benzene, 4 g (0.17 mol) of NaH was added with stirring under nitrogen atmosphere. The solution was brought to reflux and 11.8 g (0.08 mol) of MeI in 10 ml of dry benzene was added dropwise. After the mixture was stirred for an additional 7-hr period the excess NaH was decomposed with EtOH and then with water. The organic layer was separated, washed with NaCl solution and water, dried, and evaporated. Distillation of the resulted liquid gave the purified **22** (7.1 g, 67%): bp 120–122° (5 mm); ir 1635 (CO) cm^{-1}; mass *m/e* 183 (M^+). *Anal.* Calcd for $C_{11}H_{21}ON$: C, 72.08; H, 11.55; N, 7.64. Found: C, 71.75; H, 11.32; N, 7.76.