CROATICA CHEMICA ACTA CCACAA 62 (2A) 129—134 (1989)

CCA-1847

YU ISSN 0011-1643
UDC 541.653
Original Scientific Paper

Optical Activity of Lactones and Lactams. V.[1] Long-Wavelength Circular Dichroism of β-Thiolactams (2-Azetidinethiones)

Tadeusz Połoński and Maria J. Milewska

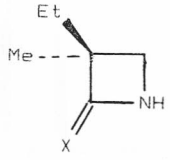
Department of Organic Chemistry, Technical University, 80-952 Gdańsk, Poland

Received November 11, 1988

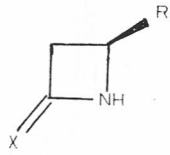
Several optically active azetidinethiones were obtained from the corresponding β-lactams by reaction with Lawesson's reagent. The same Cotton effect sign in the n—π^* region shown by β-lactones and their thioxo analogues points to the similar nature of long-wavelength electronic transitions of both classes of compounds.

Recently, there has been considerable interest in circular dichroism (CD) spectra of thiocarbonyl compounds.[2–4] Owing to their significantly longer wavelength absorption in comparison to the corresponding carbonyl derivatives, their chiroptical spectra may serve both as a sensitive structural probe and a useful tool in studying the nature of electronic transitions.[3] In connection with our studies on CD of lactams[1,5] we turned our attention to thiolactams, which are relatively easily accessible and stable thiocarbonyl derivatives.[6]

The aim of our present work was to prepare some optically active β-thiolactams of known absolute configuration and to compare their CD spectra with those of structurally analogous β-lactams. Despite the amount of research put into the synthesis of β-lactams, little information has been published on the preparation and chemistry of thioxo analogues, most of which were *N*-phenyl substituted compounds.[7]



(*1a*) X = O
(*1b*) X = S



(*2a*) R = Ph, X = O
(*2b*) R = Ph, X = S
(*3a*) R = CO_2Me, X = O
(*3b*) R = CO_2Me, X = S
(*4a*) R = CO_2CH_2Ph, X = O
(*4b*) R = CO_2CH_2Ph, X = S
(*5*) R = CO_2H, X = O

We have converted optically active β-lactams (*1a*)—(*4a*) to 2-azetidinethiones (*1b*)—(*4b*) by reaction with Lawesson's reagent[8] in 1,2-dimethoxy-

ethane solution under very mild conditions. The UV spectra of compounds *(1b)*—*(4b)* are characteristic of thioamides;[6] they show a weak low-energy band at 340 nm corresponding to the n—π^* electronic transition, the intense band at 260 nm can be assigned to the π—π^* excitation, and probably a σ—π^* transition is responsible for the moderately intense band at 220 nm. The most notable feature of the ^{1}H NMR spectra of lactams and thiolactams *(2a,b)*—*(4a,b)* is the non-equivalence of protons at the C-3 atom and a long-range coupling between the NH and C-3 protons (Figure 1). The value of J_{13} is unequal for the C-3 hydrogens oriented *cis* and *trans* to the substituent at C-4. The last feature has been observed and discussed for several 4-substituted 2-azetidinones.[9] The presence of the thiocarbonyl group causes significant deshielding of protons in compounds *(1b)*—*(4b)* in comparison to the corresponding protons in lactams *(1a)*—*(4a)*, whereas the corresponding coupling constants are similar for β-lactams and β-thiolactams. The ^{13}C NMR shows strong deshielding of the thioamide carbon relative to the amide carbon due to the paramagnetic effect of the thiocarbonyl group.[3]

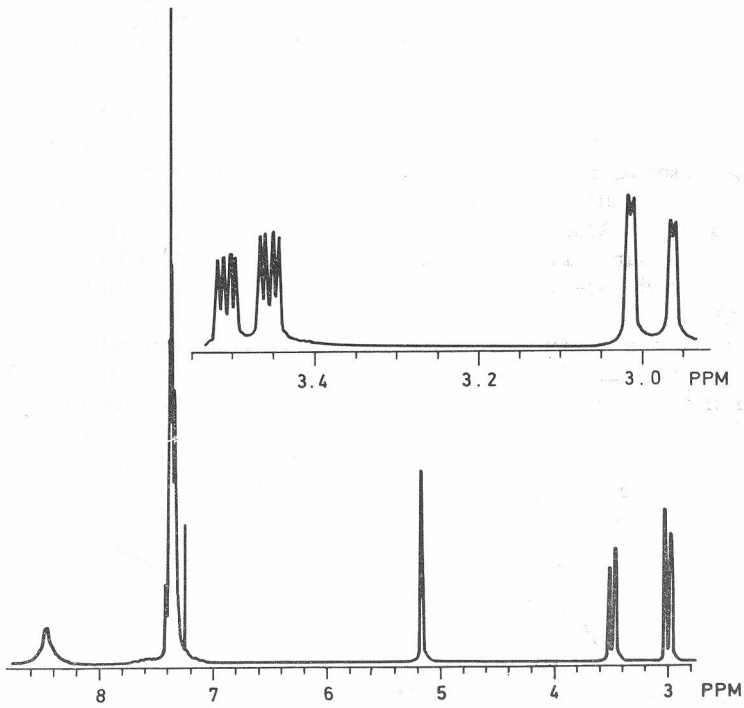


Figure 1. ^{1}H NMR (360 MHz) of thiolactam *(2b)* in $CDCl_3$.

The CD spectra of compounds *(1a,b)*—*(4a,b)* are collected in Table I. In contrast to five- and six-membered ring lactams, where the major part of contribution to the Cotton effect (CE) comes from the chiral ring,[10] the monocyclic four-membered ring lactams and thiolactams, owing to their planarity,[11] are excellent models for studying contributions solely due to

TABLE I

CD data of β-lactams and β-thiolactams ([Θ] in deg cm² dmol⁻¹)

Comp.	Solv.[a]	λ/nm	10^{-3} [Θ]	Comp.	Solv.[a]	λ/nm	10^{-3} [Θ]
(*1a*)[b,c]	C	222	1.05	(*1b*)[b]	C	345	0.83
(*2a*)	CD	218	—32.7	(*2b*)	CL	339	—10.9
		260	—0.74				
(*3a*)	CD	210	—3.09	(*3b*)	CL	342	—2.14
		232	1.99				
(*4a*)	M	214	—4.81	(*4b*)	CL	342	—2.39

[a] C, cyclohexane; CD, cyclohexane-dioxane (4 : 1); CL, dichloromethane; M, methanol.
[b] 83% ee, data corrected to 100% of optical purity.
[c] From ref. 5.

substituents.[5] Inspection of the data in Table I shows that β-thiolactams exhibit the same CE sign in the n—π* region as parent β-lactams, which confirms the close similarity of this electronic transition for both classes of compounds. Rehling and Jensen[12] proposed application of the ketone octant rule[13] for the rationalization of β-lactam CE signs. The modified octant rule has also been applied to some thioamides and thiopeptides.[3] However, the quadrant projection of molecules (*2a,b*)—(*4a,b*) (Figure 2a) reveals that the 4-substituent is lying on or very closely to the nodal surface and then the corresponding CEs should be very weak. Contrary to this prediction, CEs are rather strong and sometimes even very strong [*cf. (2a,b)*]. It seems that a better explanation is given by Weigang's sector rule[14] which requires projection of the amide chromophore along the C(X)—C_α bond (Figure 2b) and then predicts correctly the CE sign for compounds (*1a,b*)—(*4a,b*). The presence of the aromatic and ester chromophores, whose ^1L_a and ester n—π* transitions overlap with the amide n—π* transition, complicates the CD spectra of

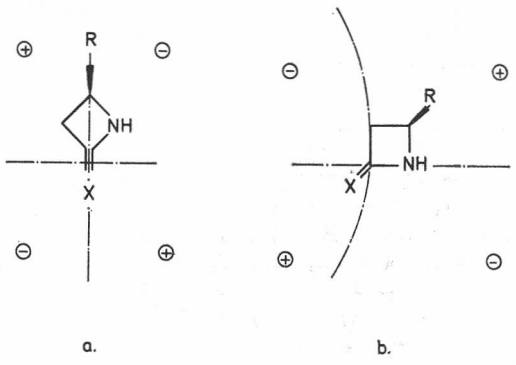


Figure 2. Sector projection of β-lactams and β-thiolactams according to a) octant[13] and b) Weigang's lactam rule[14] (X = O, S).

lactams (*2a*)—(*4a*), *e. g.* (*3a*) shows two CEs at 230 and 210 nm; however, the last one can be unequivocally assigned to the lactam n—π* transition and the 230 nm band corresponds to the ester n—π* excitation. The exchange of the amide oxygen with the sulphur shifts the n—π* transition in the CD spectra of (*b2*)—(*4b*) to longer wavelengths and then allows its isolation from the contribution of other chromophores.

In comparison to strong CEs corresponding to the magnetic dipole allowed n—π* transition of thiolactams, the CEs corresponding to the electric dipole allowed but magnetic dipole forbiden π—π* excitations are very weak and difficult to measure {*e. g.* $[\Theta]_{260}$ for (*1b*) is almost 0 and for (*2b*) $[\Theta]_{259} = 18800$, which in relation to its strong absorption ($\varepsilon = 17600$ at 255 nm) corresponds to small values of $g = 4R/D$}.

EXPERIMENTAL

CD spectra were recorded on Jasco J-20 and J-600 spectropolarimeters. UV measurements were performed on a Perkin-Elmer Lambda Array 3840 UV/VIS spectrometer. ^{1}H and ^{13}C NMR spectra were taken on a GE-300 (360 MHz) spectrometer in $CDCl_3$ solutions. IR absorptions were measured with a Perkin-Elmer 599 spectrometer. Compounds (*2a*) and (*4a*) were obtained by the literature methods.[15,16] The synthesis of lactam (*1a*) will be described elsewhere.[5]

(S)-3-Ethyl-3-methyl-2-azetidinethione (1b)

(*S*)-3-Ethyl-3-methyl-2-azetidinone (*1a*)[5] (113 mg, 1 mmol) and Lawesson's reagent (300 mg, 0.75 mmol) were refluxed in 1,2-dimethoxyethane (3 ml) for 0.5 h. Then the solvent was evaporated and the residue was chromatographed on silica gel with benzene as eluant. The title product (56 mg) was an oil; $[\alpha]_D^{22} = -25$ (c = 3, $CHCl_3$); UV (cyclohexane) 263 nm ($\varepsilon = 10500$); ^{1}H NMR δ 8.5 (br, 1H, NH), 3.69 (d, $J = 7$ Hz, 1H), 3.53 (d, $J = 7$ Hz, 1H), 1.61 (dq, 2H, CH_2CH_3), 1.27 (s, 3H, CH_3), and 0.93 (t, 3H, CH_2CH_3); ^{13}C NMR δ 213.99 (CS), 57.25 (C-3), 56.45 (C-4), 28.62 (CH_2CH_3), 20.92 (CH_3), and 8.46 (CH_2CH_3); IR (CCl_4) 3430, 3180 (br, NH), 1530, 1480, and 1544 cm^{-1}.

(S)-4-Phenyl-2-azetidinone (2a)

M. p. 118—120 °C; $[\alpha]_D^{20} = -131$ (c = 1, MeOH) (lit.[15] *m. p.* 115—117 °C; $[\alpha]_D^{20} = -131.6$ (c = 1, MeOH)); ^{1}H NMR δ 7.37 (m, 5H, Ph), 6.68 (br, 1H, NH), 4.69 (dd, $J_{cis} = 5.2$ Hz, $J_{trans} = 2.4$ Hz, 1H, CHPh), 3.40 (m, $J_{AB} = 14.8$ Hz, $J_{cis} = 5.2$ Hz, $J_{13} = 2.4$ Hz, 1H) and 2.71 (m, $J_{AB} = 14.8$ Hz, $J_{trans} = 2.4$ Hz, $J_{13} = 2.4$ Hz, 1H); ^{13}C NMR δ 167.90 (CO), 140.36, 128.79, 128.12, and 125.60 (all Ph), 50.32 (C-4), and 47.91 (C-3); IR ($CHCl_3$) 3410, 3260 (br), and 1760 (CO) cm^{-1}.

(S)-4-Phenyl-2-azetidinethione (2b)

Thiolactam (*2b*) was obtained from (*S*)-4-phenyl-2-azetidinone (*2a*)[15] analogously to compound (*1b*) (reflux 5 minutes); *m. p.* 107 °C (toluene-hexane); $[\alpha]_D^{22} = -197.8$ (c = 1.3, $CHCl_3$); UV (CH_2Cl_2) 338 ($\varepsilon = 60$) and 263 nm ($\varepsilon = 17600$); ^{1}H NMR δ 8.5 (br, 1H, NH), 7.38 (m, 5H, Ph), 5.18 (dd, $J_{cis} = 4.6$ Hz and $J_{trans} = 2.0$ Hz, 1H, CHPh), 3.48 (m, $J_{AB} = 15.5$ Hz, $J_{cis} = 4.6$ Hz, $J_{13} = 2.2$ Hz, 1H), and 2.99 (m, $J_{AB} = 15.5$ Hz, $J_{trans} = 2.0$ Hz, $J_{13} = 0.9$ Hz, 1H); ^{13}C NMR δ 204.40 (CS), 138.21, 129.03, 128.76, and 125.75 (all Ph), 58.85 (C-4), and 51.22 (C-3); IR ($CHCl_3$) 3420, 3180 (br, NH), 1510, 1490, and 1470 cm^{-1}.

Anal. Calcd. for C_9H_9NS (*M* 163.24): C 66.22, H 5.56, N 8.58, S 19.64%; found: C 66.11, H 5.60, N 8.32, S 19.51.

(S)-2-Azetidinone-4-carboxylic Acid (5)

The solution of benzyl ester (*4a*)[16] (5.08 g, 25 mmol) in ethanol (20 ml) and cyclohexane (10 ml) was refluxed with 10% Pd/C (0.3 g) for 10 minutes, then filtered, and evaporated to dryness. The residue was crystallized from acetone-ethyl acetate; yield 2.87 g; *m. p.* 103—104 °C; $[\alpha]_D^{20} = -85.8$ (c = 2.5, H_2O) {lit.[17] *m. p.* 102—104 °C; $[\alpha]_D^{25} = -82.8$ (c = 3, H_2O)}.

(S)-4-Methoxycarbonyl-2-azetidinone (3a)

Methyl ester (*3a*) was obtained from the acid (*5*) by esterification with diazomethane; *m. p.* 51 °C (ethyl acetate-toluene); $[\alpha]_D^{20} = -47.0$ (c = 4, $CHCl_3$); ^{1}H NMR δ 6.76 (br, 1H, NH), 4.13 (dd, $J_{cis} = 5.8$ Hz, $J_{trans} = 2.6$ Hz, 1H, $C_\alpha H$), 3.72 (s, 3H, CO_2Me), 3.27 (m, $J_{AB} = 15.0$ Hz, $J_{cis} = 5.8$ Hz, $J_{13} = 1.4$ Hz, 1H), and 2.99 (m, $J_{AB} = 15.0$ Hz, $J_{trans} = 2.6$ Hz, 1H); ^{13}C NMR δ 171.56 (CO), 166.65 (CO), 52.50 (C-4), 47.15 (C-3), and 43.45 (CH_3); IR ($CHCl_3$) 3450, 3320 (br, NH), 1780 (CO), and 1760 (CO) cm^{-1}.

Anal. Calcd. for $C_5H_7NO_3$ (*M* 129.12): C 46.51, H 5.46, N 10.85%; found: C 46.29, H 5.69, N 10.71%.

(S)-4-Methoxycarbonyl-2-azetidinethione (3b)

Thiolactam (*3b*) was obtained from lactam (*3a*) analogously to compound (*2b*); *m. p.* 31 °C (toluene); $[\alpha]_D^{22} = -3.8$ (c = 1, $CHCl_3$); UV (CH_2Cl_2) 263 nm ($\varepsilon = 12600$); ^{1}H NMR δ 8.62 (br, 1H, NH), 4.65 (dd, $J_{cis} = 5.3$ Hz, $J_{trans} = 2.1$ Hz, 1H, $C_\alpha H$), 3.77 (s, 3H, CO_2Me), 3.37 (m, $J_{AB} = 15.0$ Hz, 1H), and 3.09 (m, $J_{AB} = 15.0$ Hz, 1H);* ^{13}C NMR δ 203.31 (CS), 169.87 (CO), 54.56 (C-3), and 45.90 (CH_3); IR ($CHCl_3$) 3420, 3280 (br, NH), 1760 (CO), 1485 and 1455 cm^{-1}.

Anal. Calcd. for $C_5H_7NO_2S$ (*M* 145.18): C 41.37, H 4.86, N 9.69, S 22.08%; found: C 41.11, H 4.99, N 9.50, S 22.19%.

(S)-4-Benzyloxycarbonyl-2-azetidinone (4a)

Lactam (*4a*) was obtained according to the literature method[16] and had *m. p.* 138 °C; $[\alpha]_D^{25} = -47$ (c = 5, $CHCl_3$); ^{1}H NMR δ 7.33 (s, 1H, Ph), 6.24 (br. 1H, NH), 5.19 (dd, $J_{cis} = 5.3$ Hz, $J_{trans} = 2.3$ Hz, 1H, $C_\alpha H$), 3.31 (m, $J_{AB} = 15.5$ Hz, $J_{cis} = 5.3$ Hz, $J_{13} = 1.4$ Hz, 1H), and 3.10 (m, $J_{AB} = 15.5$ Hz, $J_{trans} = 2.3$ Hz, $J_{13} = 1.4$ Hz, 1H); ^{13}C NMR δ 170.77 (CO), 166.15 (CO), 135.00, 128.71, and 128.42 (all Ph), 67.45 (CH_2Ph), 47.32 (C-4), and 43.59 (C-3); IR ($CHCl_3$) 3410, 3270 (br), 1780 (CO), and 1740 (CO) cm^{-1}.

(S)-4-Benzyloxycarbonyl-2-azetidinethione (4b)

Thiolactam (*4b*) was obtained from lactam (*4a*)[16] analogously to compound (*2b*); *m. p.* 124 °C (etyl acetate-hexane); $[\alpha]_D^{20} = -61.6$ (c = 2, $CHCl_3$); UV (CH_2Cl_2) 337 ($\varepsilon = 45$) and 265 nm ($\varepsilon = 13500$); ^{1}H NMR δ 8.42 (br, NH, 1H), 7.37 (s, 5H, Ph), 5.19 (s, 2H, CH_2Ph), 4.64 (dd, $J_{cis} = 5.3$ Hz, $J_{trans} = 2.3$ Hz, 1H, $C_\alpha H$), and 3.32 (m, $J_{AB} = 15.5$ Hz, $J_{cis} = 5.2$ Hz, $J_{13} = 1.4$ Hz, 1H), and 3.09 (m, $J_{AB} = 15.5$ Hz, $J_{trans} = 2.2$ Hz, $J_{13} = 1.5$ Hz, 1H); ^{13} C NMR δ 203.22 (CS), 169.28 (CO), 134.73, 128.81, and 128.77 (all Ph), 67.75 (CH_2Ph), 54.70 (C-4), 45.93 (C-3); IR ($CHCl_3$) 3430, 3270 (br, NH), 1765 (CO), 1485 cm^{-1}.

Anal. Calcd. for $C_{11}H_{11}NO_2S$ (*M* 238.28): C 55.45, H 5.08, N 5.90, S 13.45%; found: C 55.65, H 5.06, N 6.30, S 13.48%.

Acknowledgements. — We thank Dr. J. K. Gawroński for reading the manuscript and for helpful discussion. We thank the Polish Academy of Sciences for partial support (CPBP 01.13).

* The resolution was too low for measurements of long-range coupling constants.

REFERENCES

1. For Part IV see T. Połoński, *Tetrahedron* **41** (1985) 611.
2. M. Legrand and M. J. Rougier, *Stereochemistry; Fundamentals and Methods*, H. B. Kagan (Ed.), Vol. 2, Thieme, Stuttgart, 1977, p. 33; H. Numan, F. Meuwese, and H. Wynberg, *Tetrahedron Lett.* (1978) 4857; P. H. Schippers and H. P. J. M. Dekkers, *Chem. Phys.* **69** (1982) 19; T. Połoński, *J. Chem. Soc., Chem. Commun.* (1988) 853.
3. M. Kajtár, M. Hollosi, J. Kajtár, and Z. Majer, *Tetrahedron*, **42** (1986) 3931; M. Kajtar, M. Hollosi, J. Kajtar, Z. Majer, and A. Vass-Lakatos in *Proceedings of the FECS International Conference on Circular Dichroism*, Sofia, 1985, p. 126.
4. D. A. Lightner, T. D. Bouman, W. M. D. Wijekoon, and A. E. Hansen, *J. Amer. Chem. Soc.* **106** (1984) 934.
5. M. J. Milewska and T. Połoński, in preparation.
6. W. Walter and J. Voss in *The Chemistry of Amides*, J. Zabicky, (Ed.), Interscience, London, 1970, chap. 8.
7. K. R. Henery-Logan, H. P. Knoepfel, and J. V. Rodricks, *J. Hetero. Chem.* **5** (1968) 433; E. Schaumann, *Chem. Ber.* **109** (1976) 906; S. L. Spassov, B. D. Panajotova, M. W. Poneva, and A. W. Spassov, *Z. Chem.* **19** (1979) 109; J. Marchand-Brynaert, M. Moya-Portuguez, J. Huber, and L. Ghosez, *J. Chem. Soc., Chem. Commun.* (1983) 818.
8. B. Yde, N. M. Yousif, V. Pedersen, J. Thomsen, and S.-O. Lawesson, *Tetrahedron* **40** (1984) 2047.
9. K. D. Barrow and T. M. Spotswood, *Tetrahedron Lett.* (1965) 3325; E. J. Moriconi and W. C. Meyer, *J. Org. Chem.* **36** (1971) 2841.
10. W. Klyne and P. M. Scopes in *Fundamental Aspects and Recent Developments in Optical Rotatory Dispersion and Circular Dichroism*, F. Ciardelli and P. Salvadori (Eds.), Heyden, London, 1973, chap. 3.3 and refs. therein.
11. Q. C. Yang, P. Seiler, and J. D. Dunitz, *Acta Cryst.* **C43** (1987) 565; M. Van Meersche, J. P. Declerq, B. de Clef, and H. G. Viehe, *Bull. Soc. Chim. Belq.* **92** (1983) 309.
12. H. Rehling and H. Jensen, *Tetrahedron Lett.* (1972) 2793.
13. W. Moffit, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Amer. Chem. Soc.* **83** (1961) 4013.
14. E. C. Ong, L. C. Cusachs, and O. E. Weigang, *J. Chem. Phys.* **67** (1977) 3289.
15. H. H. Wasserman, G. D. Berger, and K. R. Cho, *Tetrahedron Lett.* **23** (1982) 465.
16. T. N. Salzmann, R. W. Ratcliffe, B. G. Christensen, and F. A. Bouffard, *J. Amer. Chem. Soc.* **102** (1980) 6161.
17. H. Pietsch, *Tetrahedron Lett.* (1976) 4053.

SAŽETAK

Optička aktivnost laktona i laktama. V. Cirkularni dikroizam β-tiolaktama (2-azetidintiona) kod većih valnih duljina

Tadeusz Połoński i Maria J. Milewska

Reakcijom sa Lawessonovim reagensom pripravljeno je nekoliko optički aktivnih azetidinetiona polazeći od odgovarajućih β-laktama. Isti predznak Cottonova efekta u području $n \rightarrow \pi^*$ prelaza β-laktama i njihovih tiokso-analoga upućuje na sličnu prirodu elektronskog prijelaza kod većih valnih duljina za obje skupine spojeva.