CHIRAL-OPTICAL PROPERTIES OF SIX- AND SEVEN-MEMBERED BENZOTHIOAMIDES

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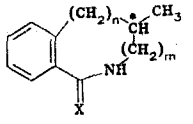
The chiral-optical properties of R-(+)-4-methyl-3,4-di-hydroisoquinoline-1-thione and R-(-)-3-methyl-, R-(+)-4-methyl-, and S-(+)-5-methyl-2,3,4,5-tetrahydrobenz[c]-azepine-1-thiones were studied. A significant increase in the intensities of the Cotton effects (CE), particularly for the CE due to the $n \rightarrow \pi^*$ transition in the benzothioamide chromophore, is observed on passing from six-membered to seven-membered benzothiolactams with the same orientation of the asymmetric center relative to the chromophore. The signs of the CE due to the $n \rightarrow \pi^*$ transition in the benzothioamide chromophore and the $\pi \rightarrow \pi^*$ transition in the aromatic chromophore at 250-280 nm (the ^1L_b band) correlate with the type of conformation of the thiolactam ring.

Our previous investigation of the chiral-optical properties of (+)-3-methyl-3,4-dihydroisoquinoline-1-thione [1] showed that the transition from the benzamide to the benzothioamide makes it possible, with retention of the chromophore of the benzamide type, to "draw apart" the electron transitions and to expand the spectral range of their manifestation. In the present paper we describe a number of new cyclic thioamides containing a chromophore of the benzothioamide type that are similar to the previously investigated oxygen compounds [2, 3]: R-(+)-4-methyl-3,4-dihydroisoquinoline-1-thione (I) and R-(-)-3-methyl- (II), R-(+)-4-methyl- (III), and S-(+)-5-methyl-2,3,4,5-tetrahydrobenz[c]azepine-1-thiones (IV). Thiolactams I-IV were obtained by cyclization of optically active arylalkyl isothiocyanates [4], as described for (+)-3-methyl-3,4-dihydro-isoquinoline-1-thione (V) [1], and their electronic absorption spectra and circular dichroism (CD) were measured.



I-V, Ia-Va

I, Ia n=0, m=1; II, IIa n=2, m=0; III, IIIa n=1, m=1; IV, IVa n=0, m=2; V, Va n=1, m=0; I—V X=S; Ia—Va X=O

Several Cotton effects (CE) are observed in the CD spectra (Fig. 1) of all of the compounds: a long-wave CE at 400-430 nm for the six-membered benzothiolactams (I and the previously investigated (+)-3-methyl-3,4-dihydroisoquinoline-1-thione [1]) and CE at 375-400 nm for the seven-membered benzothiolactams (II-IV). The position of this CE, its dependence on the polarity of the solvent (a hypsochromic shift on passing from isooctane to ethanol), and the intensity of the corresponding absorption band in the electronic band in the electronic absorption spectra (log ε 2.6-2.9) make it possible to assign it to an $n \rightarrow \pi^*$ transition in the benzothioamide chromophore [5] (Fig. 1a). This CE vanishes in the case of measurement of the CE in trifluoroacetic acid; this can be explained by disappearance of the thioamide chromophore as a consequence of the formation of a protonated structure, which additionally confirms the assignment of this CE to an $n \rightarrow \pi^*$ transition [1] (Fig. 1b).

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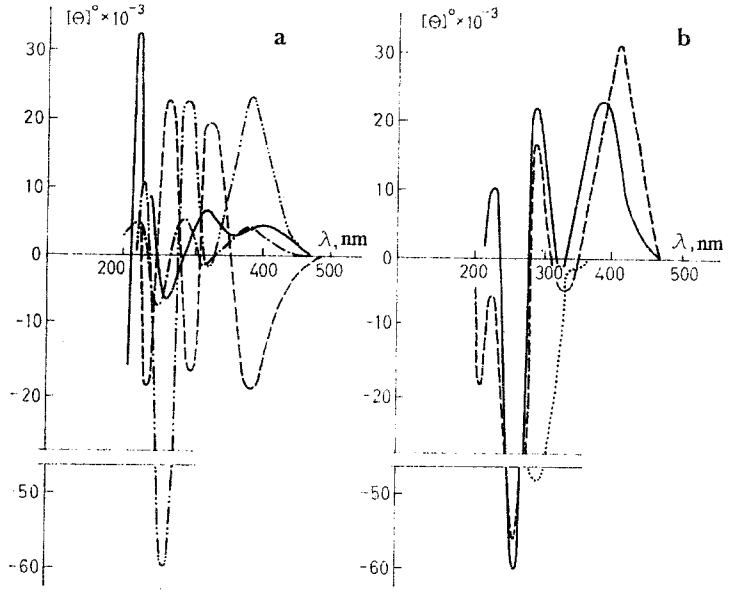
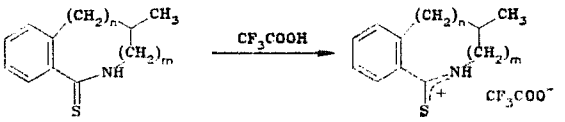


Fig. 1. Circular dichroism (CD) spectra: a) R-(+)-4-methyl-3,4-dihydroisoquinoline-1-thione (I) (——) and R-(-)-3-methyl- (II) (---), R-(+)-4-methyl- (III) (-·-·-), and S-(+)-5-methyl-2,3,4,5-tetrahydrobenz[c] azepine-1-thione (IV) (-·····-) in ethanol; b) S-(+)-5-methyl-2,3,4,5-tetrahydrobenz[c]azepine-1-thione (IV) in ethanol (——), isooctane (---), and trifluoroacetic acid (.....).



A second CE is observed at 300-320 nm; the reason for this CE is evidently a $\pi \rightarrow \pi^*$ transition in the benzothioamide chromophore (the intensities of the corresponding absorption bands in the electronic absorption spectra log ε = 4.15-4.30) [5]. Another three CE are observed in the shorter-range region at 250-280, ~220, and 200-210 nm, which are evidently due to optically active $\pi \rightarrow \pi^*$ absorption bands of the aromatic chromophore (Fig. 1).

In a comparison of the CD spectra of benzothiolactams I-V and the previously investigated oxygen-containing analogs Ia-Va [2, 3] it was observed that in the case of an identical configuration of the asymmetric center the sign of the CE of the $n \rightarrow \pi^*$ transition in the benzothioamide chromophore of I-V coincides with the sign of the CE of the corresponding benzolactams Ia-Va over the 230-250 nm range.

In the case of seven-membered thiolactams II-IV, as for oxygen analogs IIa-IVa [2, 3], one observes considerably lower intensities of all of the CE for the 4-methyl isomers (III and IIIa) as compared with the 3-methyl (II and IIa) and 5-methyl (IV and IVa) isomers.

A significant increase in the intensities of the Cotton effects (CE) is observed on passing from the six-membered to the seven-membered benzothiolactams with an identical orientation of the asymmetric center relative to the chromophore (V and II and I and IV). This increase is manifested most markedly for the $n \rightarrow \pi^*$ transition in the benzothioamide chromophore (Table 1).

We feel that the reason for this is the formation of strictly a dissymetric chromophore in benzothiolactams with a seven-membered ring, as well as the existence of the preferred conformation of this ring in the 3- and 5-methyl isomers, which determines the sign and magnitude of the observed CE, just as in the case of the analogous cyclic benzamides [2, 3].

TABLE 1. Intensities of the Cotton Effects (CE) and the Absorption Bands Due to the $n \rightarrow \pi^*$ Transition in Six- and Seven-Membered Benzothiolactams

Compound	$[\theta]^{\circ}$ (λ, nm)	log ε (λ, nm), ethanol
V	3500 (405), ethanol [1]	2,58 (400)
II	−20380 (375), ethanol	2,95 (370)
I	5070 (430), isooctane	2,61 (400)
IV	31050 (400), isooctane	2,92 (370)

TABLE 2. Signs of the Cotton Effects (CE) in the Circular Dichroism (CD) Spectra of Benzothiolactams with an R Configuration*

Compound	n	m	$n \rightarrow \pi^*$ transition in the benzothioamide chromophore	$\pi \rightarrow \pi^*$ transition in the aromatic chromophore (^1L_b band)
I	0	1	+	−
II	2	0	−	−
III	1	1	+	+
IV	0	2	−	−
V	1	0	−	+

*Data for compounds with an R configuration of the asymmetric center are presented in the table, although we worked with the (S) enantiomers in the case of IV and V.

Distortion of the planar conjugated system of the benzothioamide chromophore is also confirmed by the hypsochromic shift of the maxima of the CE and the corresponding absorption bands in the electronic spectra on passing from the six-membered compounds to the seven-membered compounds. This shift is manifested most distinctly for the absorption bands of the $n \rightarrow \pi^*$ transition [$\Delta\lambda$ ~ 30 nm (Table 1)] and the $\pi \rightarrow \pi^*$ transition ($\Delta\lambda$ 22-25 nm) in the benzothioamide chromophore.

The following principle is observed when one compares the signs of the CE of the $n \rightarrow \pi^*$ transition in the benzothioamide chromophore (Table 2): compounds with an R configuration of the asymmetric center adjacent to the thioamide fragment of the chromophore (II and V) have CE with a negative sign. When the asymmetric center is separated from the amide fragment by one CH_2 group (I and III), the CE takes on the opposite sign, and when the asymmetric center is separated by two CH_2 groups (IV), the sign of the CE of the $n \rightarrow \pi^*$ transition again becomes negative.

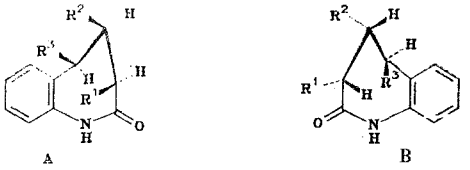
A similar principle is also observed for the CE due to the $\pi \rightarrow \pi^*$ transition at 250-280 nm (the ^1L_b band) in the aromatic chromophore (Table 2): compounds with an R configuration of the asymmetric center adjacent to the aromatic fragment of the chromophore (I and IV) have CE with a negative sign. When the asymmetric center is separated from the aromatic chromophore by one CH_2 group (V and III), the CE take on the opposite sign, and the sign of the aromatic CE again becomes negative when it is separated by two CH_2 groups (II).

A change in the CE over the 230-250 nm range is also observed in the series of oxygen-containing analogs Ia-Va [3] when the asymmetric center is separated from the amide fragment of the chromophore: for compounds with an R configuration of the asymmetric center the sign of the CE is negative when n = 0 (IIa, Va), positive when n = 1 (Ia, IIIa), and negative when n = 2 (IVa). This dependence is not observed for the sign of the aromatic CE of the benzolactams (the ^1L_b band).

The reversal of the sign of the CE when the asymmetric center is separated from the chromophore by a methylene group (the so-called "proximity rule" or "β effect") was first observed by Djerassi and Geller [6] for carbonyl compounds of the aliphatic series and was later observed for amines [7], carboxylic acids and their derivatives [8], and other compounds [9]. According to the Djerassi assumption [6], the development of the "β effect" is associated with preponderance of that conformer which makes the principal contribution to the sign of the optical activity. However, the real relationship of all of the possible conformations of a molecule cannot always be taken into account in a series of conformationally labile compounds. A cyclic structure simplifies this problem.

An examination of molecular models of benzothiolactams I-V confirmed the existence for them of the same conformational relationships as for the oxygen analogs [3], i.e., the

chiral character of the ring differs in the two possible stable conformations of the seven-membered thiolactam ring (A and B):



A B

As in the case of seven-membered benzamides [3], a conclusion regarding the preponderance of one or the other conformation can be drawn starting from the configuration of the asymmetric center and the preferableness of a quasi-equatorial orientation of the methyl group. In the case of (R)-3-methyl isomer II a quasi-equatorial orientation of the methyl group is achieved in the B conformation, whereas it is achieved in the A conformation in the case of (S)-5-methyl isomer IV. From a comparison with the experimental data it may be concluded that a positive CE corresponds to the A conformer and that a negative CE corresponds to the B conformer. In the case of the (R)-4-methyl isomer there are evidently two conformations of the thiolactam ring with close energies, the contributions of which to the optical activity mutually cancel one another, which explains the small magnitudes of the CE. A positive CE evidently constitutes evidence for a certain degree of preponderance of the A conformer.

If the asymmetric center (and the methyl group) is separated from the thioamide fragment of the conjugated chromophore by one CH_2 group (III), the preferred conformation of the molecule differs from that of the other thioamides (II and IV), i.e., the A(+) conformer predominates in the mixture of conformers when n = 1, and the B(-) conformer predominates when n = 0.2, and this determines the reversal of the sign of the CE. A similar change in the signs of the CE is also observed when the asymmetric center is separated from the aromatic fragment.

Thus replacement of the amide oxygen atom by sulfur does not change the general principles of the spectropolarimetric behavior of benzolactams. The transition to the thio analogs makes it possible, with retention of the chromophore of the benzamide type and the stereochemistry of the cyclic structure of benzolactams, to expand the spectral range of absorption and to isolate in the spectra the Cotton effects due to the individual electron transitions in the conjugated chromophore system. The optically active $n \rightarrow \pi^*$ transition in the benzothioamide chromophore reacts most sensitively to structural and conformational changes in the benzothiolactam molecule.

EXPERIMENTAL

The CD measurements were made with a JASCO J-20 spectropolarimeter in cuvettes with thicknesses of 1 and 0.1 mm. The UV spectra were recorded with a Cary-219 spectrophotometer. The PMR spectra of solutions in CCl_4 were recorded with a Varian XL-100 spectrometer with hexamethyldisiloxane (HMDS) as the internal standard. The mass spectra were obtained with an MKh-1303 spectrometer with direct introduction of the samples into the ion source at an ionizing-electron energy of 50 eV.

The synthesis of the optically active arylalkyl isothiocyanates was described in [4].

Optically Active Benzothiolactams. The optically active isothiocyanate was heated with stirring in polyphosphoric acid (PPA) in a mass ratio of 1:40. The cyclization temperature was held constant for 8-10 h, after which the reaction mixture was cooled and decomposed with ice water. The aqueous mixture was extracted with benzene, the extract was washed with sodium bicarbonate solution and water and dried with magnesium sulfate, and the solution was evaporated *in vacuo*. The substances obtained (yellow crystalline powders or oils) were purified by recrystallization from benzene with isooctane or, if this was insufficient, by preparative thin-layer chromatography (TLC) on aluminum oxide in a benzene–acetone system (5:1).

The compounds listed below were obtained via this general method.

R-(+)-4-Methyl-3,4-dihydroisoquinoline-1-thione (I). This compound, with mp 65°C and R_f 0.68, was obtained in 95% yield from R-(-)-2-phenylpropyl isothiocyanate at a reaction temperature of 135-140°C. Found: C 67.9; H 6.1%. $C_{10}H_{11}NS$. Calculated: C 67.8; H 6.2%. PMR spectrum: 1.3 (3H, d, CH_3), 3.4 (3H, m, CH_2—CH), 7.3 (3H, m, C_6H_3), and 8.5 ppm (1H, m, 8-H). Electronic absorption spectra (in ethanol), λ_{max} (log ε): 400 (inflection, 2.61), 3.25 (4.17), 302 (4.11), 260 (4.28), and 220 nm (4.17). CD spectra: in ethanol (c 0.07), [θ]° (λ, nm): 0 (450), 4670 (400), 2420 (360), 7950 (320), 0 (285), —7950 (265), 10 620 (240), 6890 (235), 34,000 (220), 0 (213); in isooctane (c 0.003), [θ]° (λ, nm): 0 (475), 5070 (430), 0 (370), 5310 (325), 590 (277), 17,100 (255), 3420 (230), 15,330 (218), 4710 (210). 18,300 (206); in trifluoroacetic acid (c 0.03), [θ]° (λ, nm): 750 (350), 19,100 (323), 8350 (280), 6230 (270).

R-(—)-3-Methyl-2,3,4,5-tetrahydrobenz[c]azepine-1-thione (II). This compound, with mp 110°C and R_f 0.68, was obtained in 20% yield from R-(—)-1-methyl-3-phenylpropyl isothiocyanate at a reaction temperature of 150-155°C. Found: M^+ 191. $C_{11}H_{13}NS$. Calculated: M 191. PMR spectrum: 1.35 (3H, d, CH_3), 2.0 (2H, m, 4-CH_2), 2.6-3.3 (3H, m, 5-CH_2, CH), 7.1 (3H, m, C_6H_3), and 7.7 ppm (1H, m, 9-H). UV spectrum (in ethanol), λ_{max} (log ε): 370 (inflection, 2.95), 303 (4.27), 244 (4.21), and 220 nm (4.24). CD spectra: in ethanol (c 0.004), [θ]° (λ, nm): 0 (470), —12,900 (400) —20,380 (375), 0 (342), 19,100 (304), 0 (291), —18,000 (280), 0 (268), 23,900 (250), 0 (229), —20,500 (218), 0 (208); in isooctane (c 0.004), [θ]° (λ, nm): 0 (500), —5690 (450), —2920 (409), 0 (346), —19,800 (385), 12,750 (310), 0 (293), —12,750 (280), 0 (267), 55,800 (250), 0 (225), —12,250 (215), 0 (210); in trifluoroacetic acid (c 0.006), [θ]° (λ, nm): 0 (350), 25,960 (300), 70,900 (278), 22,800 (260).

R-(+)-4-Methyl-2,3,4,5-tetrahydrobenz[c]azepine-1-thione (III). This compound, with mp 115°C and R_f 0.68, was obtained in 20% yield from R-(—)-2-methyl-3-phenylpropyl isothiocyanate at a reaction temperature of 160°C. Found: C 69.4; H 7.4%. $C_{11}H_{13}NS$. Calculated: C 69.1, H 6.9%. PMR spectrum: 1.0 (3H, d, CH_3), 2.4-3.1 (5H, m, CH_2CHCH_2), 7.2 (3H, m, C_6H_3), and 7.8 ppm (1H, m, 9-H). UV spectrum (in ethanol), λ_{max} (log ε): 370 (inflection, 2.95), 303 (4.27), 244 (4.20), and 220 nm (4.24). CD spectra: in ethanol (c 0.01), [θ]° (λ, nm): 0 (450), 2340 (400), 4000 (375), —1365 (310), 0 (300), 5080 (284), —8780 (250), 0 (232), 5850 (223), 0 (208); in isooctane (c 0.006), [θ]° (λ, nm): 0 (475), 3160 (430), 5380 (407), 0 (347), —510 (335), 10,600 (300), 4430 (290), —8550 (245), —950 (230), —6250 (217), 0 (208); in trifluoroacetic acid (c 0.033), [θ]° (λ, nm): 0 (340), —2040 (320), —8850 (285), —3400 (270).

S-(+)-5-Methyl-2,3,4,5-tetrahydrobenz[c]azepine-1-thione (IV). This compound, with mp 115°C and R_f 0.68, was obtained in 15% yield from S-(+)-3-methyl-3-phenylpropyl isothiocyanate at a reaction temperature of 150°C. Found: C 69.0; H 6.6%. $C_{11}H_{13}NS$. Calculated: C 69.1, H 6.9%. PMR spectrum: 1.3 (5H, m, 4-CH_2, CH_3), 3.0 (3H, m, 1-CH_2, CH), 7.2 (3H, m, C_6H_3), and 7.7 ppm (1H, m, 9-H). UV spectrum (in ethanol), λ_{max} (log ε): 370 (inflection, 2.92), 300 (4.24), 243 (4.14), and 220 nm (4.21). CD spectra: in ethanol (c 0.011), [θ]° (λ, nm): 0 (475), 12,700 (400), 23,400 (375), 0 (325), —3780 (310), 0 (296), 23,500 (280), 0 (268), —60,600 (250), 0 (230), 11,400 (220), 0 (211); in isooctane (c 0.008), [θ]° (λ, nm): 0 (475), 16,650 (430), 31,500 (400), 0 (341), —6130 (320), 0 (297), 17,350 (280), 0 (266), —57,300 (250), —4200 (219), —3820 (200); in trifluoroacetic acid (c 0.04), [θ]° (λ, nm): 0 (350), —2240 (330), —2640 (300), —7000 (287), —31,800 (280).

LITERATURE CITED

1. V. M. Potapov, V. M. Dem'yanovich, L. D. Solov'eva, and O. E. Vendrova, Khim. Geterotsikl. Soedin., No. 1, 94 (1976).
2. V. M. Potapov, V. M. Dem'yanovich, L. D. Solov'eva, and O. E. Vendrova, Khim. Geterotsikl. Soedin., No. 5, 675 (1981).
3. V. M. Potapov, V. M. Dem'yanovich, O. E. Vendrova, and L. D. Solov'eva, Khim. Geterotsikl. Soedin., No. 1, 97 (1984).
4. V. M. Potapov, V. M. Dem'yanovich, L. D. Solov'eva, and O. E. Vendrova, Dokl. Akad. Nauk SSSR, 241, 592 (1979).
5. J. Sandström and B. Uppström, Acta Chem. Scand., 19, 2432 (1965).
6. C. Djerassi and L. E. Geller, J. Am. Chem. Soc., 81, 2789 (1959).
7. J. C. Craig, R. P. K. Chan, and S. K. Roy, Tetrahedron, 23, 3573 (1967).
8. V. M. Potapov, V. M. Dem'yanovich, G. F. Lelyak, and T. N. Maksimova, Zh. Org. Khim., 8, 2319 (1972).
9. L. Verbit, A. S. Rao, and J. W. Clark-Lewis, Tetrahedron, 24, 5839 (1968).