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# Oxazepines and Thiazepines, XXVIII [1] Circular Dichroism of Optically Active 2,3-Dihydro-2-methyl-1,5-benzoxazepin-4(5*H*)-ones***

**Albert Lévai**[1,*], **Jürgen Ott**[2], and **Günther Snatzke**[2,**]

[1] Department of Organic Chemistry, Kossuth Lajos University, H-4010 Debrecen, Hungary
[2] Lehrstuhl für Strukturchemie, Ruhr-Universität, D-4630 Bochum, Federal Republic of Germany

**Summary.** Chiroptical properties of the title compounds have been studied. The influence of the substitution pattern of the aromatic moiety and the consequence of the amide → thioamide conversion are discussed as well.

**Keywords.** Chiroptical properties; Circular dichroism; Cotton effects.

**Oxazepine und Thiazepine, 28. Mitt.:**
**Circulardichroismus optisch aktiver 2,3-Dihydro-2-methyl-1,5-benzoxazepin-4(5*H*)-one**

**Zusammenfassung.** Die chiroptischen Eigenschaften der Titelverbindungen wurden untersucht. Der Einfluß des Substitutionsmusters am aromatischen Ring sowie die Folgen der Amid → Thioamid-Umsetzung werden diskutiert.

## Introduction

The first optically active benzoxazepine was prepared by the reaction of a sugar derivative with 2-aminophenol [2]. Later, optically active 1,5-benzoxazepine carboxylic acids possessing angiotensin converting enzyme inhibitor activity were synthesized [3]. Recently Schultz et al. [4, 5] reported the synthesis of optically active 1,4-benzoxazepine derivatives. In the course of our studies on benzoxazepines we prepared a large series of optically active 2,3-dihydro-2-methyl-1,5-benzoxazepin-4(5*H*)-ones [6]. In our present paper the circular dichroism of these benzoxazepines is reported. The circular dichroism of analogous benzodiazepines [7–10] and benzothiazepines [11–13] was investigated in detail but, to our knowledge, no chiroptical data of benzoxazepines have hitherto been described.

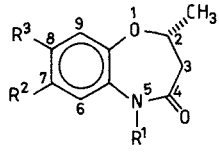
** Deceased on January 14, 1992
*** Dedicated to Prof. Dr. W. Wiegrebe on the occasion of his 60th birthday

## Results and Discussion

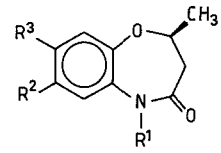
Parent compounds of the compounds under investigation are the enantiomers (*R*)-**1** and (*S*)-**1** of 2,3-dihydro-2-methyl-1,5-benzoxazepin-4(5*H*)-one, the chromophore of which is a benzene ring perturbed by an ether oxygen and a lactam nitrogen. In their UV-spectra three distinct bands with a shoulder (281 nm) are observed (Table 1). In their CD-spectra two maxima can be assigned to each UV-band. In the case of the (*R*)-**1** a weak negative (289 nm) and a weak positive (282 nm) Cotton effect belonging to the α-band can be detected. The rotatory strength of the

**Table 1.** UV spectroscopic data

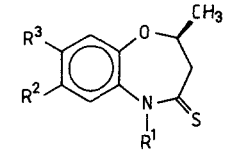
| Compound | $R^1$ | $R^2$ | $R^3$ | λ [nm] (ε) |
|---|---|---|---|---|
| (*R*)-**1**, (*S*)-**1** | H | H | H | 209 (34890), 242 (8540), 275 (1960), 281 (1850) |
| (*R*)-**2** | H | $C_2H_5$ | H | 212 (35290), 242 (9380), 282 (2420), 286 (2430) |
| (*R*)-**3** | H | $CH_3O$ | H | 215 (46700), 240 (9370), 292 (5450) |
| (*R*)-**4** | H | OH | H | 213 (32090), 240 (7200), 292 (4200) |
| (*R*)-**5** | H | $CH_3COO$ | H | 212 (30690), 241 (8850), 283 (2690) |
| (*R*)-**6** | H | COOH | H | 230 (32310), 258 (8220), 298 (2310) |
| (*R*)-**7** | H | $CH_3CO$ | H | 238 (31100), 266 (9410), 304 (2830) |
| (*R*)-**8** | $CH_3CO$ | H | H | 201 (34280), 225 (9940), 268 (1170), 276 (890) |
| (*R*)-**9** | $CH_3$ | $CH_3O$ | H | 217 (27850), 245 (7400), 291 (4190) |
| (*S*)-**10** | H | $CH_3$ | H | 212 (30570), 242 (8000), 281 (2280), 286 (2310) |
| (*S*)-**11** | H | $(CH_3)_3C$ | H | 212 (36810), 243 (8850), 279 (2590), 285 (2590) |
| (*S*)-**12** | H | $NH_2$ | H | 224 (27660), 250 (6770), 310 (3110) |
| (*S*)-**13** | H | Cl | H | 216 (38030), 245 (8470), 285 (2540), 290 2600 |
| (*S*)-**14** | H | $NO_2$ | H | 232 (12350), 252 (15980), 295 (5360), 334 (3920) |
| (*S*)-**15** | H | H | $NH_2$ | 208 (23400), 260 (12710), 302 (2850) |
| (*S*)-**16** | H | H | $(CH_3)_2CHNH$ | 206 (25120), 269 (19020), 308 (3690) |
| (*S*)-**17** | H | H | $CH_3CONH$ | 213 (28230), 264 (20230), 294 (5000) |
| (*S*)-**18** | H | H | Cl | 212 (27790), 249 (11980), 285 (2340) |
| (*S*)-**19** | H | H | Br | 213 (30600), 251 (13410), 283 (2690) |
| (*S*)-**20** | $CH_3$ | H | H | 211 (28410), 244 (8990), 276 (2230) |
| (*S*)-**21** | $C_2H_5$ | H | H | 211 (24630), 244 (9220), 276 (1910) |
| (*S*)-**22** | $C_6H_5CH_2$ | H | H | 194 (38800), 209 (28750), 244 (8450), 276 (1830) |
| (*S*)-**23** | $CH_3$ | H | $NO_2$ | 203 (19950), 233 (7090), 326 (9570) |
| (*S*)-**24** | H | H | H | 204 (17800), 308 (20660) |
| (*S*)-**25** | H | $(CH_3)_3C$ | H | 208 (28570), 310 (24910) |
| (*S*)-**26** | $CH_3$ | H | H | 201 (22310), 298 (23190) |



(R)-1 – (R)-9



(S)-1, (S)-10 – (S)-23



(S)-24 – (S)-26

CD-maxima in the regions of the *p*-band (at 257 and 237 nm) and the *β*-band (at 216 and 200 nm) is much higher. The same type was observed for the enantiomorphous CD-spectrum of the (*S*)-**1** enantiomer (see Fig. 1 and Table 2). The influence of substituents at C-7 and C-8 and N-alkylation, respectively, have been studied as well.

Introduction of a methyl [(*S*)-**10**], ethyl [(*R*)-**2**] or *tert*-butyl [(*S*)-**11**] group into position 7 is almost without influence both on the UV- and the CD-spectra. The presence of a chlorine atom [(*S*)-**13**] or an acetoxy group [(*R*)-**5**] resulted only in a little shift of the CD-maximum to the longer wavelengths. A methoxy [(*R*)-**3**] and a hydroxy [(*R*)-**4**] group in position 7 are stronger perturbers but the basic character of the CD-spectra is unchanged. The rotatory strength in the *β*-region was considerably enhanced by a C-7 carboxylic group [(*R*)-**6**]. The presence of an acetyl group in this position [(*R*)-**7**] resulted in an additional $n \rightarrow \pi^*$ transition giving rise to a new CD-band at 324 nm (Table 2). An amino group at C-7 [(*S*)-**12**] resulted also in considerable changes in all three regions of the CD-spectrum. The influence of a C-7 nitro group [(*S*)-**14**] is reflected in the complete change of the character of the chromophore and chiroptical properties.

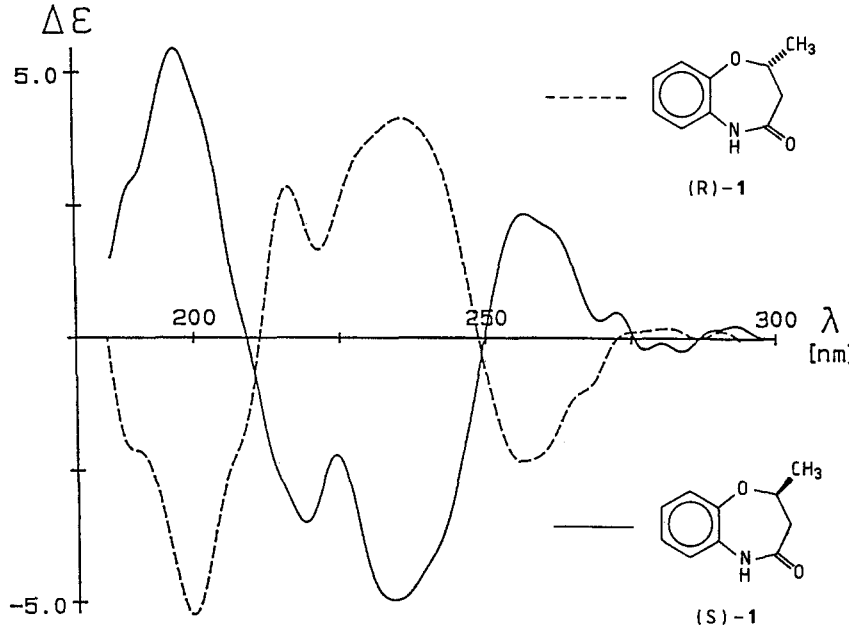



**Fig. 1.** Circular dichroism spectra of compounds (*R*)-**1** and (*S*)-**1**

**Table 2.** Circular dichroism data

| Compound | $\lambda$[nm]($\Delta\varepsilon$) |
|---|---|
| (*R*)-**1** | 200 (−5.22), 216 (+2.84), 237 (+4.45), 257 (−2.43), 282 (+0.07), 289 (−0.06) |
| (*R*)-**2** | 204 (−4.02), 220 (+2.93), 234 (+3.40), 239 (+3.50), 258 (−1.70), 286 (+0.21), 295 (−0.05) |
| (*R*)-**3** | 238 (+5.10), 257 (−1.95), 290 (+0.35), 297 (+0.37) 307 (−0.09) |
| (*R*)-**4** | 239 (+3.79), 258 (−1.37), 297 (+0.35) |
| (*R*)-**5** | 199 (−3.18), 215 (+3.16), 223 (+2.62), 236 (+3.35), 257 (−2.08), 287 (−0.17), 295 (−0.06) |
| (*R*)-**6** | 237 (+7.43), 269 (−2.62), 294 (+0.05) |
| (*R*)-**7** | 240 (+4.91), 270 (−1.89), 324 (+0.24) |
| (*R*)-**8** | 197 (−7.43), 230 (+2.32), 259 (−0.34), 278 (+0.15) |
| (*R*)-**9** | 241 (+3.19), 298 (+0.79) |
| (*S*)-**1** | 197 (+5.44), 219 (−3.47), 235 (−4.24), 257 (+2.15), 282 (−0.11), 291 (+0.08) |
| (*S*)-**10** | 199 (+3.38), 203 (+3.25), 217 (−2.53), 235 (−3.63), 258 (+1.66), 280 (−0.18), 287 (+0.25) |
| (*S*)-**11** | 211 (−8.05), 235 (−4.78), 257 (+2.58), 280 (−0.08), 285 (−0.18), 292 (+0.06) |
| (*S*)-**12** | 229 (−4.68), 265 (+0.48), 314 (−0.47) |
| (*S*)-**13** | 204 (+3.55), 221 (−3.87), 240 (−3.30), 259 (+2.47), 284 (−0.18), 290 (−0.23) |
| (*S*)-**14** | 216 (+1.99), 232 (−1.52), 277 (+0.22), 318 (−0.42) |
| (*S*)-**15** | 204 (+6.92), 254 (−2.98), 307 (−0.17) |
| (*S*)-**16** | 209 (+6.33), 234 (−0.93), 265 (−2.61), 308 (−0.15) |
| (*S*)-**17** | 247 (−2.18), 276 (+0.93) |
| (*S*)-**18** | 218 (−2.11), 240 (−3.49), 263 (+1.73), 289 (−0.07) |
| (*S*)-**19** | 223 (−2.55), 240 (−3.54), 264 (+1.80), 291 (−0.07), 301 (+0.04) |
| (*S*)-**20** | 196 (+3.79), 202 (+4.53), 242 (−4.27), 276 (−0.59) |
| (*S*)-**21** | 202 (+3.61), 239 (−3.45), 277 (−0.53) |
| (*S*)-**22** | 201 (+2.77), 215 (−2.55), 238 (−2.89), 276 (−0.42), 281 (−0.39) |
| (*S*)-**23** | 207 (+2.83), 301 (−0.73) |
| (*S*)-**24** | 188 (+7.75), 208 (−4.74), 233 (+7.82), 306 (−8.03), 383 (+1.08) |
| (*S*)-**25** | 205 (−11.74), 233 (+7.51), 260 (−1.15), 308 (−9.26), 342 (−1.07), 382 (+1.54) |
| (*S*)-**26** | 189 (+10.80), 218 (−3.65), 234 (+6.91), 296 (−7.07), 367 (−1.94) |

The presence of a substituent at C-8 resulted in a considerable intensity increase of the *p*-band of the UV-spectra of each compound (Table 1). A chlorine [(*S*)-**18**] or a bromine [(*S*)-**19**] atom at position 8 is almost without influence on the chiroptical properties. However, the introduction of an amino [(*S*)-**15**] or substituted amino [(*S*)-**16**] and [(*S*)-**17**] group into this position resulted in considerable changes of the whole spectrum.

N-Alkylation causes little change in the UV-spectra since the chromophore remains unaltered, whereas in the CD-spectra of compounds (*S*)-**20**, (*S*)-**21**, and (*S*)-**22** the rotatory strength of the *p*-band is considerably enhanced. This may be a consequence of the alteration in the conformational equilibrium as a consequence of the N-alkylation [14].

As a result of the amide → thioamide conversion, the 'three-band character' of the UV-spectra disappeared and entirely new spectra were obtained with two intense

bands: One between 300 and 310 nm may belong to the $\pi \rightarrow \pi^*$ transition of the C=S group and the other (at approx. 200 nm) to the electron transitions of the aromatic $\pi$ orbitals. In their CD-spectra at least five Cotton effects were found. In the case of compounds (*S*)-**24** and (*S*)-**25** an intense positive CD-band appears at approx. 380 nm which may belong to the $n \rightarrow \pi^*$ transition of thioamide moiety. The second intense negative CD-band around 300 nm corresponds to the UV-maximum of substances (*S*)-**24**, (*S*)-**25**, and (*S*)-**26** and may be a consequence of an electronically allowed $\pi \rightarrow \pi^*$ transition of the thioamide chromophore. Three other Cotton-effects are found in the shorter wavelength region (Table 2) but their unambiguous assignment is impossible at present. The presence of a *tert*-butyl group at C-7 [(*S*)-**25**] and N-methylation [(*S*)-**26**] are almost without influence on the CD-spectra.

## Experimental Part

The compounds investigated were synthesized as described earlier [6]. UV-spectra were measured with a Philips PU 8740 apparatus in $CH_3CN$ solution at room temperature. Circular dichroism (CD) spectra were recorded with a Jasco 600 instrument in $CH_3CN$ solution (concentrations were approx. 0.5 mmol/l both for UV- and CD-measurements) at room temperature.

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