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Oxazepines and Thiazepines, XXI [1]: CD-Spectra of Optically Active 2-Methyl-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones and Related 3-Phenylthio-butyric Acid Derivatives

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Summary. Chiroptical properties of the title compounds have been studied. The influence of the substitution pattern of the aromatic ring and the configuration of the centre of chirality on the Cotton effects appearing in various wavelengths ranges are discussed.

Keywords. Chiroptical properties; Cotton effects; Optically active thio ethers.

Oxazepine und Thiazepine, 21. Mitt.: CD-Spektren optisch aktiver 2-Methyl-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one und verwandter 3-Phenylthio-buttersäure-Derivate

Zusammenfassung. Die chiroptischen Eigenschaften der im Titel genannten Verbindungen wurden studiert. Der Einfluß des Substitutionsmusters des aromatischen Rings und der Konfiguration des Chiralitätszentrums auf die Cotton-Effekte, die in verschiedenen Wellenlängenbereichen auftreten, werden besprochen.

Introduction

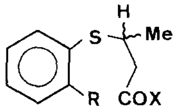
Recently we described the chiroptical properties of 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones substituted at C-2 by phenyl [1]. In the present paper we report on the CD-properties of corresponding 2-methyl analogues and their optically active intermediates. Here too the absolute configuration of one compound (viz. **5**) had been determined by X-ray diffraction [2]. The syntheses of these substances besides that of **26** (see Experimental) have already been published [3], and some of the results have been discussed elsewhere [4].

Results and Discussion

Thioanisol shows UV-bands at 294 (460), 254 (9 900), 214 (9 100), and 204 nm ($\varepsilon = 14\,800$) [5], but for **1** only three distinct bands could be observed, viz. at 254 (6 000), 203 (sh, 17 000), and 190 nm ($\varepsilon = 46\,000$). The CD-spectrum corresponds to this with the usual small shifts for the band positions, and in addition to these a tiny but well recognizable band is found at 292 nm, corresponding to the first fine structure line in the UV-spectrum of thioanisol. All four Cotton effects have the same sign and are e.g. negative for the (*R*)-enantiomer.

The *o*-nitro thioether was available as the brucine salt **2**, the free acid **3**, and its methyl ester **4**. Most characteristic is the Cotton effect around 370 nm of all these compounds, which is neither altered by salt formation (**2**) nor by esterification (**4**). The α-band is shifted to appr. 295 nm, and its CD-sign is the same as for the aforementioned Cotton effects of **3** and **4**, but for the diastereomeric brucine salts **2** it is negative for both. The sign of the 370 nm Cotton effect will be determined by the sense of twist of the nitro group, which cannot be coplanar with the second substituent, and this sense will in turn be governed by the helicity around the centre of chirality. The amide **5** of acid **3** with (*R*)-phenyl ethyl amine was used for the determination of the absolute configuration by X-ray diffraction [2].

If an amino group and thioether are both connected to the benzene ring then the whole system becomes a new complex chromophore and cannot any more be discussed e.g. as a simple substituted aniline. The observed CD-spectra are indeed more complicated, with their first Cotton effect around 310 nm [6, 7]. Empirically we note that the first three CD-bands (310, 245, 225 nm) have the same sign, whereas the fourth (just above 200 nm) is opposite to these others. If the amino group is acylated [8] then there exists no such ideal conjugation, and the first Cotton effect appears below 300 nm, viz. around 290 nm, the sign pattern remains, however, the same.



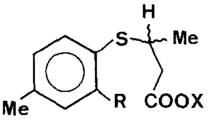
	R	X
1	H	OMe
2	NO_2	OH.Brucin
3	NO_2	OH
4	NO_2	OMe
5	NO_2	$NHC(H,Me)-C_6H_5$
6	NH_2	OH
7	NH_2	OMe
8	NHAc	OMe

From previous work [6, 7] it is known that the introduction of an additional methyl group may change the position of the absorption and CD bands, and even the sign of a given Cotton effect may thereby be inverted [8]. If, however, another very strong perturbation of the benzene chromophore is present, as e.g. the −SR group, then such an additional methyl is of rather negligible influence. This is now also found with **9**, and even more pronounced for **10** to **13**, which contain a second strong perturber. The same holds also for the thioethers **13**–**15**. If the additional methyl group is placed in *m*- instead of *p*-position to the −SR substituent (**16**–**22**) then again no essential difference can be noted between the CD-spectra of substituted and unsubstituted compounds.

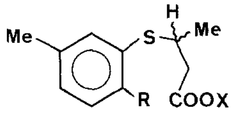
For the ring-closed compounds **23**–**25** the CD-spectra are also quite similar regardless of the additional methyl substituent on the benzene chromophore, but

Table 1. Circular Dichroism of Compounds **1**–**26**

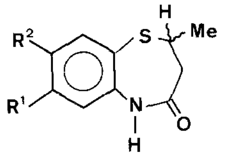
Compound	λ [nm] (Δ ε)
S(+)-**1**	264 (+0.66), 213 (+3.2)
R(−)-**1**	264 (−0.48), 215 (−3.7)
S-**2**	369 (+0.78), 301 (−0.45), 234 (−12.80), 199 (+7.5)
R-**2**	368 (−0.80), 298 (−0.97), 234 (−13.67), 193 (+10.0)
S(+)-**3**	366 (+0.69), 295 (+0.3) sh, 240 (−0.50), 205 (+2.2)
R(−)-**3**	370 (−0.81), 299 (−0.3) sh, 247 (+0.98), 202 (−3.2)
S(+)-**4**	367 (+0.88), 289 (+0.50), 246 (−0.87), 211 (+2.2)
R(−)-**4**	367 (−0.97), 294 (−0.49), 246 (+1.59), 209 (−2.7)
S-**5**	372 (+1.38), 300 (+0.48), 249 (−2.78), 215 (+2.0)
S(+)-**6**	309 (+1.14), 253 (+1.56)
R(−)-**6**	310 (−1.30), 253 (−1.76)
S(+)-**7**	312 (+1.01), 244 (+1.56)
R(−)-**7**	309 (−0.99), 240 (−1.60)
S(+)-**8**	290 (+1.1) sh, 283 (+1.43), 259 (+2.86), 239 (+1.70), 215 (−1.8)
R(−)-**8**	292 (−1.5) sh, 283 (−1.71), 260 (−3.20), 238 (−2.10)
S(+)-**9**	265 (+0.50), 220 (+4.00)
R(−)-**9**	266 (−0.42), 218 (−3.50)
S-**10**	378 (+0.63), 299 (−0.84), 235 (−12.02)
R-**10**	377 (−0.65), 300 (−0.90), 234 (−13.0)
S(+)-**11**	376 (+0.74), 295 (+0.3) sh, 240 (−0.50), 210 (+2.0)
R(−)-**11**	383 (−0.83), 290 (−0.3) sh, 245 (+0.70), 205 (−3.0)
S(+)-**12**	375 (+0.95), 288 (+0.54), 247 (−1.01), 215 (+2.5)
R(−)-**12**	374 (−0.93), 286 (−0.45), 247 (+1.50), 215 (−3.3)
S(+)-**13**	307 (+1.28), 256 (+2.32)
R(−)-**13**	309 (−1.28), 255 (−2.23)
S(+)-**14**	308 (+0.87), 253 (+1.39)
R(−)-**14**	309 (−0.85), 253 (−1.40)
S(+)-**15**	291 (+1.5) sh, 285 (+1.8) sh, 280 (+1.8) sh, 261 (+4.80), 220 (−2.2)
R(−)-**15**	293 (−1.4) sh, 286 (−1.6) sh, 281 (−1.7) sh, 261 (−4.80)
S(+)-**16**	291 (+0.13), 265 (−0.53), 220 (−4.8)
R(−)-**16**	292 (−0.09), 265 (−0.53), 218 (+0.55)
S-**17**	374 (+0.68), 300 (−0.50), 234 (−12.1)
R-**17**	370 (−0.66), 300 (−0.50), 234 (−13.3)
S(+)-**18**	372 (+0.85), 300 (+0.7) sh, 250 (−0.70)
R(−)-**18**	374 (−0.79), 300 (−0.8) sh, 255 (+0.50)
S(+)-**19**	371 (+1.16), 299 (+0.4) sh, 250 (−1.60), 213 (+1.0)
R(−)-**19**	369 (−1.20), 303 (−0.4) sh, 255 (+0.80), 213 (−6.0)
S(+)-**20**	316 (+0.88), 257 (+1.40)
R(−)-**20**	315 (−0.83), 258 (−1.54)
S(+)-**21**	319 (+0.69), 230 (+1.50)
R(−)-**21**	319 (−0.66), 230 (−1.50)
S(+)-**22**	291 (+1.06), 261 (+4.55), 242 (+2.3) sh
R(−)-**22**	292 (−1.23), 263 (−3.53), 241 (−2.1) sh
S(−)-**23**	255 (−3.6) sh, 242 (−11.9)
R(+)-**23**	255 (+3.4) sh, 242 (+11.7)
S(−)-**24**	255 (−4.8) sh, 242 (−12.7)
R(+)-**24**	255 (+4.0) sh, 243 (+12.5)
S(−)-**25**	253 (−5.20), 242 (−14.7)
R(+)-**25**	253 (+4.80), 243 (+13.7)
R(+)-**26**	269 (+4.35), 242 (+3.37)



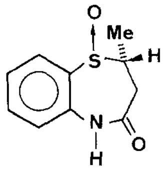
	R	X
9	H	Me
10	NO_2	H.Brucin
11	NO_2	H
12	NO_2	Me
13	NH_2	H
14	NH_2	Me
15	NHAc	Me



	R	X
16	H	Me
17	NO_2	H.Brucin
18	NO_2	H
19	NO_2	Me
20	NH_2	H
21	NH_2	Me
22	NHAc	Me



	R^1	R^2
23	H	H
24	Me	H
25	H	Me



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these Cotton effects differ appreciably from the aforementioned ones, since 1) the conformation of the newly introduced heteroring is fixed, and 2) the $S-C_{al}$ bond is now cisoid to the $C_{ar}-N$ bond and not transoid as in the molecules without this additonal ring.

Three Cotton effects are present between 300 and 180 nm, and the strongest one (around 242 nm) coincides with the strongest UV-band [3]. At longer wavelengths another broad Cotton effect can be found with its maximum $\Delta\varepsilon$-value around 260 nm, the same wavelength where another UV-band is present. Its sign is the same as that of the main band, i.e. positive for the (*R*)-compound. The third Cotton effect of same sign is observed around 200 nm, again coinciding with a UV-band. There is some indication that around 221 nm a small Cotton effect of opposite sign exists, which has no correspondence in the UV-spectrum.

Due to the presence of the aromatic ring and the also planar amide grouping the heterocyclic ring can adopt only two conformations which must both be quite rigid. The methyl group attached to the centre of chirality can be either (quasi-) equatorial or (quasi-) axial; from ^{1}H-NMR-spectra [9] it can safely be deduced that the preferred conformation is the latter. There exists no obvious reason why this equilibrium should depend on the solvent; Fig. 1 shows this conformation in a projection from the aromatic ring towards the second heteroring along the bisectrix of the benzene ring. If one looks only into the geometry of that ring then it seems nearly achiral, but if one takes into account the difference between the two heteroatoms bound directly to the benzene ring, and the carbonyl group of the lactame moiety one might also envisage an inherently chiral chromophore. To differentiate between these two possibilities experimentally, one can make use of the g-number in the maximum, which turned out to be 8×10^{-4}; this indicates that the chromophore under consideration should rather be regarded as an inherently achiral one.

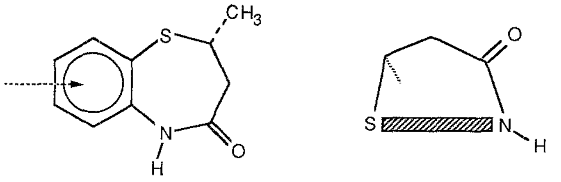

Fig. 1. Projection of (+)-**23** along the direction indicated in the left formula

Although we are not quite certain about the origin of this band we nevertheless can apply the usual sector rule [10], since the carbonyl group of the lactame moiety is definitely the strongest perturber, and it lies in the sector next to the nodal plane bisecting the ring. With the absolute configuration proved, and the projection as shown in Fig. 1, this carbonyl group is lying in a negative sector, in full agreement with the experiment (cf. Table 1).

Aryl alkyl sulphoxides give rise to Cotton effects around 235–255 and 220 nm [10]. The sulphoxide *R*-**26** shows the usual positive Cotton effects like its parent compound *R*-**23**, but the second CD-band is much weaker; between the first and the second effect a distinct positive minimum is recognizable, which is best explained as being actually a negative Cotton effect around 253, exactly at that wavelength where the first sulphoxide band is expected.

Although for the much more flexible intermediates the CD could be discussed only in a descriptive way, we can apply existing rules to the ringclosed ones; they are in full agreement with the results of the X-ray investigations.

Materials and Methods

The syntheses and nonchiroptical properties of all compounds besides **26** have been described in Ref. [3]. CD-spectra were taken with a Jobin-Yvon-ISA dichrograph attached on-line to an AT-computer, concentrations were appr. 0.5 mmol/l.

Preparation of R(+)-**26**

A mixture of 50 mg *R*(+)-**23** and 50 mg *m*-chloroperbenzoic acid in 15 ml methylene chloride was stirred at room temperature for 3 h, then the solution was brought to dryness i. vac., and the residue was crystallized from hexane to afford 30 mg (56%) of colourless prisms of m.p. 178–179°C. UV (acetonitrile): 288 (1 500), 280 (1 700), and 223 nm ($\varepsilon = 15\,000$).

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