Chiroptical Properties of Optically Active Thiazolidines Derived from Aldoses and Natural Mercapto-amino Acids[1,2]

Zoltán Györgydeák and Albert Lévai

Department of Organic Chemistry, Kossuth Lajos University, H-4010 Debrecen (Hungary)

and

Günther Snatzke

Lehrstuhl für Strukturchemie, Ruhruniversität D-4630 Bochum (F. R. Germany)

Optically active thiazolidines substituted at C(2) or/and C(4) show at least 2 Cotton effects below 260 nm, and different correlations between stereochemistry and CD hold for these compounds and their *N*-acyl derivatives. By such *N*-acylation all CD--bands are enhanced, and the inherently chiral moiety —S—C——N—C(=O)— of absolute conformation shown in Figure 4 always leads to a very strong negative Cotton effect near 205 nm, regardless whether C(4) carries a C(=O)X group or not. Signs, positions, and magnitudes of the other CD bands are strongly influenced by other factors, too. Such a conformation is fixed in the lactones *XXVIII* through *XXXIV*, but is also preferred for 2,4-cis-disubstitution (with a polyhydroxyalkyl group at C(2) and a carboxylic group at C(4)). Exciton interactions between the *N*-acyl and other (C=O)X — groups do not play a decisive role.

INTRODUCTION

Direct investigation of the stereochemistry of sugars by chiroptical methods is impossible due to the lack of characteristic absorption bands in the accessible wavelength range. Therefore, use is often made of »cottonogenic derivatives«, i. e. derivatives containing an appropriate chromophore, whose circular dichroism is then determined by the sterical arrangement in its vicinity.[3] Frequently, C(1) is incorporated into an absorbing heterocyclic ring system, and the configuration at C(2) can be obtained from investigation of individual Cotton effects.[4] Because of the importance of condensation products between sugars and amino acids in biochemistry and physiology[5] we have prepared many model compounds, especially from aldoses with mercapto amino acids.

The structure and stereochemistry of many 2-polyhydroxyalkylthiazolidine-4-carboxylic acid derivatives synthesized by us were determined by chemical transformations and/or by ¹H- and ¹³C-NMR spectroscopy and have already been published.[6-11]

One of the aims of this paper is to test whether such thiazolidine derivatives of aldoses can also be used for determination of the absolute configuration at C(2). Furthermore, since the chiroptical properties of this chromophore have not yet been studied in detail, we present here also systematic studies of relevant simpler model compounds which lack e. g. the carboxylic group or the polyhydroxyalkyl side chain. Furthermore, such studies can assist the interpretation of the CD-data of derivatives with the penam skeleton, the building block of penicillins. Despite the efforts to explain the chiroptical properties of these important antibiotics there are still doubts about the assignment of individual Cotton effects.[12]
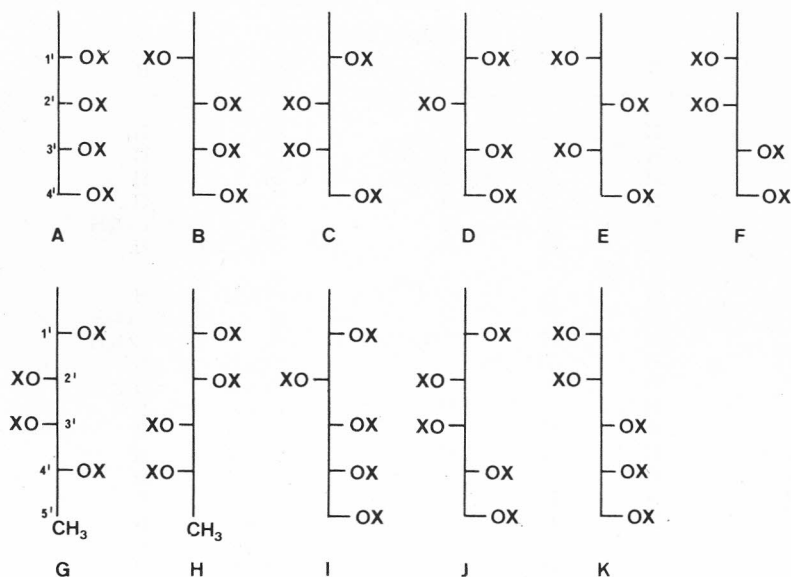
SIMPLE THIAZOLIDINES

A) *Parentage of First UV- and CD-bands*

The HOMOs of both amino and thioether groupings are n-orbitals, and absorption bands at wavelengths longer than appr. 180 nm are usually ascribed to transitions from such an orbital into a σ^*-orbital of appropriate symmetry.[13] In solution, Rydberg-transitions cannot be observed at all, or only in very unpolar solvents.[13] If both heteroatoms are connected to the same carbon atom as in thiazolidines then the two n-orbitals will interact with each other through space and by involving other MOs also through bonds, thus giving rise to two combined MOs. Since the first ionization potentials (and according to KOOPMANS' theorem also the energies of the n-orbitals) of a secondary amine (e. g. dimethyl amine: 8.97 eV) and a thio ether (e. g. dimethyl sulfide: 8.72 eV) are quite close to each other[14], both these n-orbitals will strongly mix and the n_S will slightly more contribute to the energetically higher lying combination than n_N. The through-space interaction will shift the n^--combination to a higher energy than the n^+-orbital, but the through-bond interaction in a thiazolidine obviously inverts these two one-electron configurations, as has been proved by PE-spectra of thiazolidine and some of its methylated derivatives.[15] 3d-orbitals on sulfur do not seem to be of great importance, at least for the first two transitions according to calculations.[15] We may thus expect at least two Cotton effects in the aforementioned wavelength range, which can be assigned (mainly) to transitions from n^+ or n^- into the σ^*-orbital at the lowest energy.

I – XXVII   VII
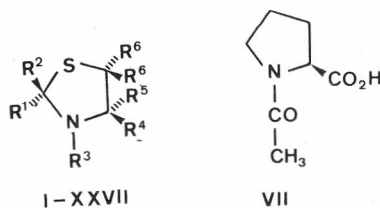
| | | | | Substituents | | | |
Compd. Nr.	R^1	R^2	R^3	R^4	R^5	R^6
I	C_a	H	H	H	H	H
IIa	J_a	H	H	H	H	H
IIb	J_a	H	CH_3CO	H	H	H
IIc	J_f	H	CH_3CO	H	H	H

Compd. Nr.	R^1	R^2	R^3	R^4	R^5	R^6
			Substituents			
IIIa	K_a	H	H	H	H	H
IIIb	K_b	H	CH_3CO	H	H	H
IV	H	J_b	CH_3CO	H	H	H
Va	H	H	H	CO_2H	H	H
E-Va	H	H	H	H	CO_2H	H
Vb	H	H	H	CO_2CH_3	H	H
(HCl-salt)						
Vc	H	H	CH_3CO	CO_2H	H	H
VIa	H	H	H	H	CO_2H	CH_3
VIb	H	H	CH_3CO	H	CO_2H	CH_3
VIII	H	CH_2OH	H	CO_2H	H	H
IX	H	A_a	H	CO_2H	H	H
X	H	D_a	H	CO_2H	H	H
XI	H	E_a	H	CO_2H	H	H
XIIa	H	C_a	H	CO_2H	H	H
XIIb	H	C_b	H	CO_2CH_3	H	H
XIII	H	B_a	H	CO_2H	H	H
XIV	H	F_a	H	CO_2H	H	H
XV	H	G_a	H	CO_2H	H	H
XVI	H	H_a	H	CO_2H	H	H
XVII	H	I_a	H	CO_2H	H	H
XVIII	H	K_a	H	CO_2H	H	H
XIXa	H	J_a	H	CO_2H	H	H
XIXb	H	J_c	H	CO_2H	H	H
XIXc	H	J_b	H	CO_2H	H	H
XIXd	H	J_b	H	CO_2CH_3	H	H
XIXe	H	J_b	H	CO_2CH_2Ph	H	H
XIXf	H	J_b	H	CO_2CHPh_2	H	H
XXa	J_a	H	H	H	CO_2H	H
XXb	J_b	H	H	H	CO_2CH_2Ph	CH_3
XXI	H	J_b	H	H	CO_2CH_3	CH_3
XXIIa	H	C_a	CH_3CO	CO_2CH_3	H	H
XXIIb	H	C_d	CH_3CO	$CON(CH_3)_2$	H	H
XXIIc	H	C_b	CH_3CO	CO_2CH_3	H	H
XXIIIa	H	J_a	CH_3CO	CO_2H	H	H
XXIIIb	H	J_a	CH_3CO	CO_2CH_3	H	H
XXIIIc	H	J_a	CH_3CO	$CONH_2$	H	H
XXIIId	H	J_a	CH_3CO	$CON(CH_3)_2$	H	H
XXIIIe	H	J_a	$CH_3CH_2—CO$	CO_2CH_3	H	H
XXIIIf	H	J_b	CHO	CO_2CH_3	H	H
XXIIIg	H	J_b	CH_3CO	CO_2CH_3	H	H
XXIIIh	H	J_b	CH_3CH_2CO	CO_2H	H	H
XXIIIi	H	J_b	CH_3CH_2CO	CO_2CH_3	H	H
XXIIIj	H	J_e	CH_3CO	$CONH_2$	H	H
XXIIIk	H	J_e	CH_3CO	$CON(CH_3)_2$	H	H
XXIIIl	H	J_b	CH_3CO	$CONH_2$	H	H
XXIIIm	H	J_b	CH_3CO	$CON(CH_3)_2$	H	H
XXIIIn	H	J_b	CH_3CO	CONH-Ad	H	H
XXIVa	J_b	H	CH_3CO	H	CO_2H	H
XXIVb	J_b	H	CH_3CO	H	CO_2CH_3	H
XXV	CH_3	H	CH_3CO	H	CO_2H	CH_3
XXVIa	J_a	H	CH_3CO	CO_2H	H	H
XXVIb	J_a	H	CH_3CO	CO_2CH_3	H	H
XXVIc	J_b	H	CH_3CO	CO_2H	H	H
XXVId	J_b	H	CH_3CO	CO_2CH_3	H	H
XXVII	H	J_b	CH_3CO	H	CO_2H	CH_3

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1'─ OX      XO ─         ─OX      ─OX    XO ─         XO ─
2'─ OX         ─OX    XO ─      XO ─         ─OX    XO ─
3'─ OX         ─OX    XO ─         ─OX    XO ─            ─OX
4'─ OX         ─OX         ─OX         ─OX         ─OX    ─OX

   A           B           C          D           E        F
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   1'─ OX         ─OX         ─OX         ─OX    XO ─
XO ─ 2'            ─OX    XO ─      XO ─         XO ─
XO ─ 3'         XO ─      XO ─      XO ─            ─OX
   4'─ OX    XO ─            ─OX         ─OX         ─OX
   5'                                             ─OX
     CH₃         CH₃            ─OX         ─OX         ─OX

     G           H             I           J           K
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Series   a   X = H

        b   X = CH₃CO

        c   X = 2,3; 4,5 – di – O – isopropylidene –

        d   X = 1' – OH, 2',3',4' – tri – O – acetyl –

        e   X = 1' – OH, 2',3',4',5' – tetra – O – acetyl –

        f   X = 2' – OH, 1',3',4',5' – tetra – O – acetyl –

Ad =
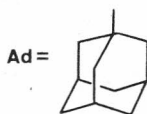
Although in the crystal one conformation must be fixed (cf. e. g. the structure of 4-carboxy thiazolidine hydrochloride (*Va*.HCl), for which the S atom lies outside the approximate plane formed by the other four ring atoms[16]), in solution the thiazolidine ring performs pseudorotation.[17] Thus, for a discussion of chiroptical properties we can assume the average approximate C_{2v}-symmetry for the chromophoric system. The HOMO belongs then to the irreducible representation b_1, the n^--MO to a_2, whereas the σ^*-orbitals transform like a_1 or b_2, and the one shown schematically in Figure 1 is the LUMO (a_1). The first few single electron configurations needn't, even after allowing for configurational interaction and mixing of excited states by the chiral molecular environment, give rise to strong Cotton effects, because we never obtain simultaneously strong components of the electric and the ma-

gnetic transition moments in identical directions. For the same reason, the qualitative MO-theory cannot be used so easily to predict rules for this chromophore.
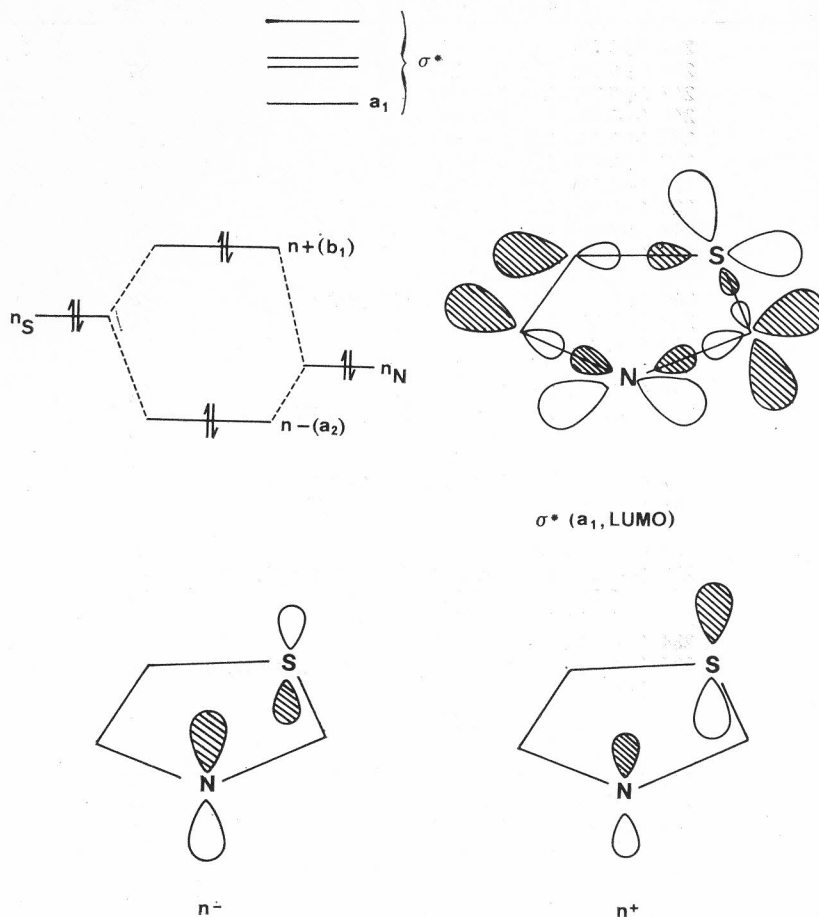

Figure 1: Schematic representation of frontier MOs (n^-, n^+, and the σ^* of lowest energy) of a thiazolidine, and of their energies.

B) Examples

For the three 2-substituted simple thiazolidines *I* (Figure 2), *IIa*, and *IIIa* with (2S)-configuration the first Cotton effect around 240 nm is always positive but of different magnitude, the second one — when measurable — is positive for *IIa*, but negative for *IIIa*. It seems, therefore, that the first Cotton effect is mainly determined by the absolute configuration at the chiral centre C(2) in the ring, and the second at least to a substantial extent by the configuration of the C-atom in the side chain attached to C(2), but there are not enough examples available to establish a definite rule.

TABLE I

CD-maxima of Thiazolidine Derivatives

	λ_{max}/nm ($\Delta\varepsilon$)	Solvent[a]	Ref.
I	244 (+0.20)	E	23
IIa	245 (+0.09), 211 (+0.27)	W	23
IIb	247 (+0.34), 223 (—1.29)	A	11
IIc	240 (—1.43), 216 (+0.80)	A	11
IIIa	237 (+0.44), 210 (—0.40)	E	23
IIIb	203 (+9.80), 189 (—2.70)	A	11
IV	241 (+1.12), 203 (—17.88)	A	11
Va	238 (—0.52), 204 (—0.91)	W	24
E-Va	241 (+0.41), 203 (+0.72)	W	24
Vb	240 (—0.59), 204 (+1.42)	W	24
Vc	233 (—1.07), 199 (—3.84)	W	24
VIa	246 (+0.76), 221 (—0.44), 198 (+3.51)	W	25
VIb	247 (—0.36), 203 (+6.06)	W	25
VII	225 (—3.71)	A	26
VIII	241 (—0.65), 202 (—1.12)	W	6
IX	238 (—0.77), 200 (—0.82)	W	6
X	239 (—0.55), 217 (+0.04), 201 (—0.83)	W	6
XI	240 (—0.57), 199 (—1.25)	W	6
XIIa	237 (—0.52), 201 (—1.31)	W	6
XIIb	247 (—0.54), 221 (—0.78), 201 (+1.79)	A	6
XIII	241 (—0.56), 218 (+0.05), 200 (—0.77)	W	6
XIV	237 (—0.31), 201 (—1.43)	W	6
XV	237 (—0.48), 200 (—1.35)	W	6
XVI	239 (—0.90), negative at shorter wavelength	W	6
XVII	244 (—0.26), 209 (+1.11)	W	6
XVIII	239 (—0.24), 217 (+0.19), 200 (—1.06)	W	6
XIXa	234 (—1.04), 200 (—2.17)	W	6
XIXb	225 (—0.25), negative at shorter wavelength	A	7
XIXc	235 (—1.02), 203 (+0.82)	A	7
XIXd	244 (—0.51), 203 (+2.74)	A	7
XIXe	246 (—0.62), 218 (—1.03)	A	7
XIXf	246 (—0.62)	A	11
XXa	242 (+0.48), 202 (+0.77)	W	11
XXb	244 (+0.26), 202 (—5.16)	A	9
XXI	247 (+1.90), 203 (—9.03)	A	9
XXIIa	244sh (—0.33), 205 (—15.16)	W	8
XXIIb	242sh (+1.54, 230 (+1.80), 207 (—17.32)	A	8
XXIIc	205 (—14.67)	A	8
XXIIIa	242 (+0.40), 204 (—11.03)	W	7
XXIIIb	245sh (—0.36), 204 (—13.45)	W	7
XXIIIc	245sh (—0.15), 204 (—12.55)	W	7
XXIIId	246 (—0.31), 226 (+2.31), 201 (—13.93)	W	7
XXIIIe	246sh (—0.33), 206 (—13.50)	W	7
XXIIIf	203 (—8.95)	A	7
XXIIIg	203 (—16.20)	A	6
XXIIIh	206 (—14.39)	A	11
XXIIIi	205 (—12.87)	A	7
XXIIIj	243 (+1.45), 206 (—17.85)	A	7
XXIIIk	230 (+3.47), 207 (—15.75)	A	7
XXIIIl	231 (—3.51), 204 (—10.16)	A	7
XXIIIm	237 (—2.01), 205 (—14.44)	A	7
XXIIIn	231 (—4.33), 206 (—9.99)	A	7
XXIVa	231 (+1.08), 202 (—10.07)	A	11
XXIVb	228 (+0.97), 201 (—13.47)	A	11
XXV	256 (—0.13), 211 (+0.95)	A	11
XXVIa	219 (—1.71), 200 (+4.44)	W	7

Table I continued

	λ_{max}/nm ($\Delta \varepsilon$)	Solvent[a]	Ref.
XXVIb	220 (—2.72), 196 (+3.77)	W	7
XXVIc	220 (—2.68)	A	7
XXVId	215 (—3.11)	A	7
XXVII	245 (—1.17), 225 (+0.29), 199 (—24.30)	A	9
XXVIII	258 (+0.88), 222 (—2.30), 204 (—19.80)	E	6
XXIX	254 (+2.49), 207 (—34.67)	A	6
XXX	254 (+2.54), 205 (—35.90)	A	6
XXXI	255 (+2.37), 207 (—34.28)	A	6
XXXII	251 (—2.29), 207 (+38.49)	A	11
XXXIII	254 (—2.81), 205 (+36.20)	E	11
XXXIVa	231 (+3.69), 204 (+15.53)	E	11
XXXIVb	251 (—2.06), 202 (+19.50)	E	11
XXXV	259 (+2.75), 235 (—6.55), 213 (+13.90), 195 (+18.10)	A	10
XXXVI	235 (—7.18), 207 (+17.40)	A	10
XXXVII	247 (—2.18)	A	21

[a] W: water, E: ethanol, A: acetonitril

After N-acetylation (IIb, Figure 2) the first Cotton effect becomes larger and bisignate, indicating the presence of two conformers. Further acetylation of the OH-groups (IIc, IIIb, IV) increases the magnitudes of the Cotton effects even more, and the one around 205 nm becomes very strong for IIIb and IV. Since a similar enhancement of this CD-band is observed with all the other N-acyl derivatives discussed in this paper, it can be associated with the chiral moiety —S—C—N—C(=O)—. The correlation between the absolute stereochemistry and the sign of the CD-band will be described later in the paper (cf. also Figure 4). Exciton interaction between the amide and the O-acetyl chromophores could also be involved, but since the CD-values are nearly independent of the types and configurations of these substituents, such interactions are more responsible for the reduction of the magnitude of this Cotton effect only in the case of IIc than in the general enhancement of the $\Delta\varepsilon$-values for all the other compounds. For IIb this Cotton effect could not be measured because of a very low signal/noise ratio; since the bisignate shape of the first Cotton effect indicated the presence of a conformational equilibrium, obviously a compensation of two CD-bands of opposite signs causes the small magnitude of this 205 nm Cotton effect. The E/Z-equilibrium of the amide group cannot be the reason for this small value since the sense of helicity of the —S—C—N—C(=O)— moiety is the same for both configurations. At room temperature their interconversion should already be fast, because only a weakly broadened singlet could be observed in the ^{1}H-NMR-spectra of all the N-acetyl compounds for the CH_3—C(=O)—N methyl group.

4-CARBOXY-THIAZOLIDINES WITHOUT SUBSTITUENT AT C(2)

Also these compounds give as zwitterions two Cotton effects around 240 and 200 nm of the same sign, but the signal/noise ratio is better than in the case of compounds lacking the COOH-group. With (4R)-configuration both of these Cotton effects are negative (Va), and positive with (4S)-configuration (Figure 2), regardless of whether C(5) is not substituted (Vb) or carries two gem-dimethyls (VIa). In the latter CD-spectrum a new additional Cotton effect

Figure 2: CD-spectra of *IIa* (water, —·—·—·—), *IIb* (acetonitril, —————), and *E-Va* (water, ————).

of opposite sign to the mentioned ones appears around 220 nm, and so most probably the CD-minimum seen in the CD-spectrum of *Va* also represents a Cotton effect.

Esterification of the COOH-group (to *Vb*) does not change the first Cotton effect in sign or size, but the one around 200 nm is inverted (for the hydro-chloride). *N*-acetylation strongly increases also in these compounds the Cotton effect around 200 nm (*Vc*, *VIb*); in the latter case the CD-band around 240 nm has changed its sign as compared to *VIa*. Most probably this is due to a change of ring conformation because of rehybridization from sp^3 to sp^2 at the *N*-atom in this already sterically overcrowded molecule.

For comparison we have measured the CD-spectrum of *N*-acetyl L-proline (*VII*) in the same solvent, and, of course, the stronger CD-band around 240

nm has disappeared since no n_S is present. The Cotton effect at 225 nm comes from one of the two possible $n \rightarrow \pi^*$-transitions, and down to 200 nm no other strong Cotton effect can be observed, again in full agreement with the above assignment for the 205 nm CD-band. Its CD-spectrum in methanol has already been published[18] and a very small negative Cotton effect around 238 nm has been ascribed to the $n \rightarrow \pi^*$-transition of the E-amide chromophore. Since, however, the corresponding NMR-measurements had been per-
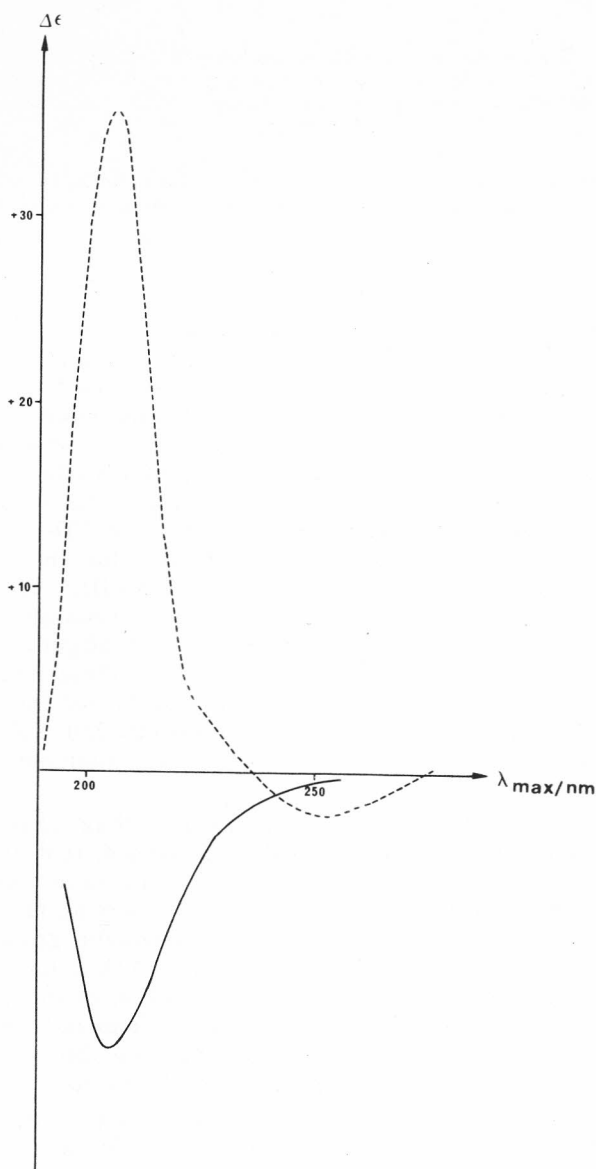
Figure 3: CD-spectra of *XXIIa* (water, ———) and *XXXIII* (ethanol, — — — —).
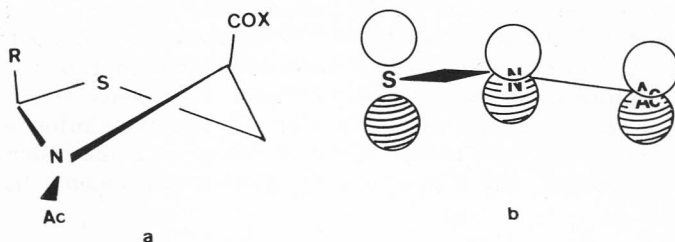
Figure 4: Two different projections of the inherently chiral moiety —S—C—N—C(=O)— that leads to a very strong negative Cotton effect near 205 nm. The ratio of E/Z — configurations of the N-acyl moieties have not been determined.

formed in DMSO-solution[18], we believe that no such detailed conclusion about the stereochemistry of the amide group can be drawn from these CD-measurements.

4-CARBOXY-THIAZOLIDINES WITH SUBSTITUENT AT C(2)

Replacement of H by a HOCH$_2$-group at C(2) in cis-configuration to the carboxylic group (*VIII*) does not change the CD, which leads to the conclusion that neither the ring conformation nor that of the COOH-group is changed by the introduction of this additional moiety. Furthermore, this group must be (quasi-) equatorially arranged because otherwise it should give a recognizable contribution at least to the CD associated with the transitions from the n-orbital combination. Introduction of a longer chain at the C(2)-position (with identical configuration) leads still to the same CD-curve (*IX, X, XI, XIIa, XIII, XIV, XV, XVI*, and *XIXa*), and only for the two compounds derived from D-glucose (*XVII*) and D-mannose (*XVIII*) the usual 220 nm minimum appears as a weak positive maximum between the other two (negative) Cotton effects. No correlation with the configuration of any OH--group in the side chain could thus be observed for these thiazolidines. Even the formation of diacetonide *XIXb* from *XIXa* does not largely alter these Cotton effects. In agreement with this, the cis-compound *XXa* with opposite configurations at C(2) and C(4) gives a CD-curve enantiomorphous to that of all the others.

Acetylation of the hydroxy groups in the side chain (*XIIb, XIXc*) leaves the Cotton effect around 240 nm practically unchanged, that at approximately 200 nm becomes, however, positive. From the small value one cannot differentiate whether this positive CD comes from the new acetate chromophores, or whether also exciton interaction with the carboxylic group at C(4) takes place. Further esterification of the COOH-group (*XIXd*) increases somewhat the positive 200 nm Cotton effect. Even the formation of the strongly absorbing benzyl (*XIXe*) or diphenylmethyl ester (*XIXf*) does not render impossible the determination of absolute configuration from the 240 nm Cotton effect, which in both CD-spectra could be detected with the usual magnitude.

For the corresponding 5,5-dimethyl derivative *XXb* with the same configuration as *XXa*, the 240 nm Cotton effect is of the usual magnitude and correct sign, a second Cotton effect around 220 nm is barely detectable as a shoulder, and that around 200 nm is negative, again in full agreement with

the fact that the OH-groups in the side chain are acetylated. Inversion of the configuration at C(2) to *XXI* increases distinctively the $\Delta\varepsilon_{max}$ values but does not change the signs. The CD gives, thus, unequivocally the absolute configuration of the carboxylic group at C(4); whether this difference in magnitudes is characteristic of the configuration at C(2) or not cannot, however, be deduced from one example.

N-ACYL-4-CARBOXY-THIAZOLIDINES WITH SUBSTITUENTS AT C(2)

*N*-acetylation of 4-carboxy thiazolidines without a substituent at C(2) increased already significantly the Cotton effect around 200 nm, but in the presence of a 2-cis-substituent this CD-band becomes so strong that the 240 nm Cotton effect cannot be detected any more or only as a tail on its long wavelength side (cf. Figure 3).

Molecular models show that a conformation with an undistorted amide group and a (quasi) equatorial arrangement of the two cis-substituents at C(2) and C(4) is not possible for steric reasons, in contrast to the parent molecules with an NH-group. Either the amide group must be strongly twisted or the ring adopts the conformation which keeps both substituents (quasi) axial (*XXIIa-c, XXIIIa-n*). In this ring system such a diaxial conformation of the 2- and 4-substituents does not seem so unfavourable on the basis of molecular models, and in the crystal structure of both *IIc*[19] (sugar chain at C(2)) and the hydrochloride of *Va*[16] (COOH at C(4)) these substituents are indeed axially disposed. Figure 4 shows a stereoprojection of a (*2R,4R*)-stereoisomer like *XXIIa*, together with the chiral —S—C—N—C(=O)— chromophore; the absolute conformation of this latter should then lead to the recorded strong negative CD. This type of interaction resembles that of β,γ-unsaturated oxo compounds[20] of appropriate geometry, where also the two interacting chromophores are separated by an sp³-carbon. The first Cotton effect shows up clearly only for *XXIIIa*, because it is of the opposite sign to the strong one at 205 nm, and in the CD-spectra of most 4-carboxamide derivatives, regardless of whether it has the same (*XXIIId* (bisignate), *XXIIIl, XXIIIm, XXIIIn*) or opposite sign (*XXIIb, XXIIIlj, XXIIIk*).

Starting from D-cysteine the opposite configurations at C(2) and C(4) in the thiazolidine ring can be obtained (*XXIVa,b*), but since these compounds are diastereomeric to those of the general formula *XXIII* no enantiomorphous CD-curves should be expected. It is nevertheless, surprising that also for these compounds a strong negative Cotton effect around 205 nm appears, together with a smaller positive one at appr. 230 nm. It must be the different relative configuration at C(2) in the side chain that does not allow the diaxial arrangement of the two substituents at C(2) and C(4), so the opposite ring chirality is adopted. The CD of these two compounds strongly supports our assignment of the 205 nm Cotton effect, since a quite different magnitude of this CD-band should be expected if it came from any interaction between the amide and the COOR-grouping(s).

Introduction of two additional geminal methyl groups at C(5) (*XXV*) gives rise to strong steric interactions on both sides of the ring. The molecule must, therefore, adopt a very distorted geometry, or an equilibrium between several conformers might be present. In accord with this, its CD is small and not characteristic.

Furthermore, if the above assumption about the preferred conformation is correct, then one can predict that also with two trans-substituents (*XXVI-a-d*, (2S,4R)) a conformational equilibrium should exist. CD again supports this: with *XXVIa* and *XXVIb* bisignate smaller Cotton effects are obtained around 200 nm, whereas *XXVIc* and *XXVId* give rather small negative CD-bands. Two additional gem-methyls at C(5) stabilize, however, the one of the two ring conformations which keeps the substituent at C(2) in the (quasi) axial position, as can be deduced from the usual very strong negative Cotton effect around 200 nm (*XXVII*).
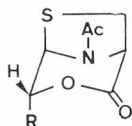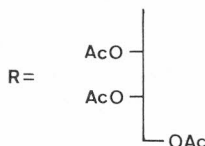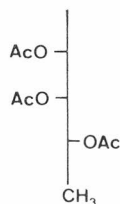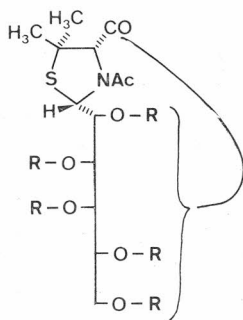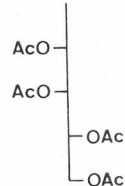

R = 4 × Ac , 1× lactone

XXXIV a,b

No doubt about, the conformation can exist when a lactone ring is closed between the two substitutents at C(2) and C(4), as in the compounds *XXVIII* through *XXXIV*. *XXVIII* was prepared from *VIII* and its geometry is that given in Figure 4. The Cotton effect around 205 nm is strongly negative, and this was used to »calibrate« the aforementioned rule. Application of the exciton theory to the interaction between the amide and the lactone chromophores predicts for both configurations of the *N*-acetyl group positive CD for the band at longer wavelengths, and thus the strong 205 nm Cotton

XXXII   XXXIII

R =   ⌐ OAc   R =   ⌐ OAc
      ⊢ OAc   ⊢ OAc
      ⌊ OAc   ⌊ OAc

R' = H   R' = CH₃

effect has to come from the inherently chiral —S—C—N—C(=O)—moiety. In addition, a positive Cotton effect of medium magnitude is observed at 257 nm and a similar negative one (seen only as a shoulder) at 232 nm. The lactones *XXIX* through *XXXI* give practically identical CD-spectra as *XXVIII*; the nature of the side chain connected to C(2') is, as expected, without any influence.

XXXII, the enantiomer of *XXIX*, gives, of course, a CD-curve which is practically enantiomorphous to those of *XXVIII* through *XXXI*. Introduction of two geminal methyls at C(5) cannot change the skeleton conformation in these lactones, and, therefore, the CD-spect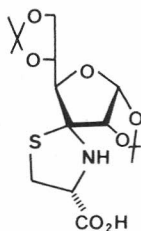rum of *XXXIII* resembles closely that of *XXXII*. The size of the lactone ring in *XXXIVa* and *XXXIVb* has not yet been proved, but it cannot be the usual ring closure towards C(2') since the 205 nm Cotton effect in both spectra is only appr. half as large as in all other lactones. Whether this is due to a release of ring strain or to contributions from an exciton couplet is not clear; the overall conformation of *XXXIVb* should resemble more that of the usual lactones that that of *XXXIVa,* since the two additional Cotton effects at longer wavelengtsh have the usual signs and magnitudes for the first isomer, but not anymore for the second one.

Both dioxopiperazines *XXXV* and *XXXVI* have in common the relatively strong negative Cotton effect around 235 nm and an even stronger one (positive) around 200 nm, which belongs to a band with such strong absorption that the magnitude of the CD-band could not be determined anymore with the usual certainty. *XXXVI* lacks, however, the CD-band around 259 nm, which is usually present in the CD-spectra of the lactones.

Recently, Tronchet and Gentile[21] described a thiazolidine derivative (*XXXVII*) in the sugar series, which is prepared from L-cysteine. As expected by comparison with the CD of the methyl ester *XIIb*, a negative Cotton effect around 250 nm shows up. Its magnitude is, however, nearly three times as large, and also the band positions of the CD-maxima are somewhat different, which must be caused by conformational changes due to the spiro--ring connected to C(2).

Z. GYÖRGYDEÁK ET AL.

XXXV

R¹=R²=CH₃

XXXVI

R¹ =

R² = H

XXXVII

In summarizing our results we found that, in general, optically active thiazolidines with various substituents at C(2) and/or C(4) show two or more Cotton effects below 260 nm. Their signs and magnitudes are determined by the chirality of the heterocyclic chromophore, but not by the substituent at C(1') of a 2-polyhydroxy-alkyl side chain, which corresponds to C(2) of the original sugar. If the nitrogen is acylated, the —S—C—N—C (=O) moiety forms a combined chromophore, whose sense of helicity determines unequivocally the sign of the very strong and characteristic Cotton effect around 205 nm when it is inherently chiral. This same type of chromophore is also present in the penicillins. Since the C(5)-substituent(s) do not change drastically the CD of our optically active thiazolidines, these simple compounds can indeed be used as good models for the study of the chiroptical properties of penicillins and the related antibiotics.[22]

EXPERIMENTAL

The syntheses and all other physical properties of these thiazolidines have already been published.[1,6-11] CD has been measured in water, ethanol or acetonitril solution at concentrations of app. 1 mg/ml at room temperature with the ISA-Jobin-Yvon dichrographe models 185 or Mark III.

REFERENCES

1. This paper forms Part XII in the series »Heterocyclic Compounds from Sugars« of the Debrecen authors. Part XI: R. B o g n á r, Z. G y ö r g y d e á k, L. S z i l á g y i, P. S á n d o r, and L. R a d i c s, *Liebigs Ann. Chem.* (1979) 101.
2. This paper forms Part LXXXV in the series on Circular Dichroism of the Bochum author. Part LXXXIV: B. G r e e n, F. S n a t z k e, G. S n a t z k e, G. R. P e t t i t, Y. K a m a n o, and M. L. N i v e n, *Croat. Chem. Acta* **58** (1985) 371.
3. W. S. C h i l t o n and R. C. K r a h n, *J. Amer. Chem. Soc.* **89** (1967) 4129.
4. G. S n a t z k e, F. W e r n e r - Z a m o j s k a, L. S z i l á g y i, R. B o g n á r, and I. F a r k a s, *Tetrahedron* **28** (1972) 4197.
5. a. G. P. E l l i s, *Advan. Carbohydr. Chem.* **14** (1959) 63.
   b. J. A d r i a n, *World Rev. Nutr. Diet.* **19** (1974) 71.
   c. G. O h l o f f and I. F l a m e n t, *Heterocycles* **11** (1978) 663.
   d. G. O h l o f f and I. F l a m e n t, *Fortschr. Chem. Org. Naturst.* **36** (1979) 231.
   e. G. O h l o f f and I. F l a m e n t, *Koryo* **126** (1979) 97; *CA* **92** (1980) 179124t.
   f. J. M a u r o n, *Progr. Food Nutr. Sci.* **5** (1981) 5.
   g. W. B a l t e s, *Food Chem.* **9** (1982) 59.
   h. W. D. A n n a n and W. M a n s o n, *Food Chem.* **6** (1981) 255.
   i. G. V e r n i n, J. M e t z g e r, and T. O b r e t n o v, *Actual. Chim.* (1983) 7; *CA* **98** (1983) 215938w.
6. R. B o g n á r, L. S o m o g y i, and Z. G y ö r g y d e á k, *Liebigs Ann. Chem.* **738** (1970) 68.
7. R. B o g n á r, Z. G y ö r g y d e á k, L. S z i l á g y i, and L. S o m o g y i, *Liebigs Ann. Chem.* (1975) 1637.
8. R. B o g n á r, Z. G y ö r g y d e á k, L. S z i l á g y i, G. H o r v á t h, G. C z i r a, and L. R a d i c s, *Liebigs Ann. Chem.* (1976) 450.
9. R. B o g n á r, Z. G y ö r g y d e á k, L. S z i l á g y i, G. C z i r a, and L. R a d i c s, *Liebigs Ann. Chem.* (1977) 1536.
10. Z. G y ö r g y d e á k, Z. D i n y a, and R. B o g n á r, *Khim. geterotsikl. soed.* (1979) 1211.
11. Z. G y ö r g y d e á k, *Thesis,* Debrecen (1984).
12. a. D. B. B o y d, C.-H. Y e h, and F. S. R i c h a r d s o n, *J. Amer. Chem. Soc.* **98** (1976) 6100.
    b. F. S. R i c h a r d s o n, C.-Y. Y e h, T. C. T r o x e l l, and D. B. B o y d, *Tetrahedron* **33** (1977) 711.
    c. D. B. B o y d, J. P. R i e h l, and F. S. R i c h a r d s o n, *Tetrahedron* **35** (1979) 1499.
    d. R. B u s s o n, E. R o e t s, and H. V a n d e r h a e g h e, in *Recent Advances in the Chemistry of β-Lactam Antibiotics, Chem. Soc. Spec. Publ.* **28** (1977) 304, and references cited therein.
13. M. B. R o b i n: *Higher Excited States of Polyatomic Molecules,* Vol. 1 Academic Press, New York—London (1974).
14. K. K i m u r a, S. K a t s u m a t a, Y. A c h i b a, T. Y a m a z a k i, and S. I w a t a: *Handbook of He I Photoelectron Spectra of Fundamental Organic Molecules,* Japan Scientific Press, Tokyo (1981).
15. J. S. R o s e n f i e l d and A. M o s c o w i t z, *J. Amer. Chem. Soc.* **94** (1972) 4797.
16. K. K. C h a c k o, M. C h e n g i a h, and S. S w a m i n a t h a n, *Cryst. Struct. Comm.* **10** (1981) 473, and references cited therein.

17. G. E. W i l s o n, Jr. and T. J. B a z z o n e, *J. Amer. Chem. Soc.* **96** (1974) 1465; F. A. M. B o r r e m a n s, W. H. N a c h t e r g a e l e, B. B u d ě š í n s k ý, M. J. O. A n t e u n i s, A. K o l o d z i e j c z y k, and B. L i b e r e k, *Bull. Soc. Chim. Belges* **89** (1980) 101.
18. H. N i s h i h a r a, K. N i s h i h a r a, T. U e f u j i, and N. S a k o t a, *Bull. Chem. Soc. Jap.* **48** (1975) 553.
19. Private communication by Prof. C a r l K r ü g e r, MPI für Kohlenforschung, Mülheim. We again thank Prof. K r ü g e r for determining the structure by X-ray diffraction.
20. K. M i s l o w, M. A. W. G l a s s, R. E. O' B r i a n, P. R u t k i n, D. H. S t e i n b e r g, J. W e i s s, and C. D j e r a s s i, *J. Amer. Chem. Soc.* **84** (1962) 1455.
21. J. M. J. T r o n c h e t and B. G e n t i l e, *Helv. Chim. Acta* **63** (1980) 1779. We again thank Prof. T r o n c h e t, Geneva University, for providing us with a sample.
22. Work in progress, to be published later.
23. W. A. B o n n e r and W. M e y e r zu R e c k e n d o r f, *Chem. Ber.* **94** (1961) 22.
24. S. R a t n e r and H. T. C l a r k e, *J. Amer. Chem. Soc.* **59** (1937) 200.
25. H. T. C l a r k e, J. R. J o h n s o n, and R. R o b i n s o n, *The Chemistry of Penicillin*, Princeton University Press, Princeton (1949) 464.
26. D. H a m e r and J. P. G r e e n s t e i n, *J. Biol. Chem.* **193** (1951) 81.

SAŽETAK

Kiroptička svojstva optički aktivnih tiazolidina izvedenih od aldoza i prirodnih merkapto-aminokiselina

Zoltan Györgydeák, Albert Lévai i Günther Snatzke

Optički aktivni tiazolidini supstituirani na C(2) i/ili C(4) pokazuju barem dva Cottonova efekta ispod 260 nm. Utvrđeno je više korelacija između stereokemijskih svojstava i CD spektara kako osnovnih spojeva tako i njihovih N-acil-derivata. N-Acetilacija vodi redovito do pojačanih CD vrpci, a inherentno kiralna jedinica —S—C—N—(C=O), s apsolutnom konformacijom prikazanom u slici 4, pokazuje redovito vrlo snažan negativni Cottonov efekt oko 205 nm, neovisno o tomu da li C(4) nosi (C=O)x skupinu ili ne. Ista konformacija ukrućena je u laktonima *XXVIII—XXXIV,* a također je ukrućena za 2,4-cis-disupstituirane derivate s poli-hydroxialkilnom skupinom na C(2) i karboksilnom skupinom na C(4). Ekscitonska interakcija između N-acilnih i drugih C(=O)x skupina ne igra značajnu ulogu.