Chiroptical Properties – Structure Relationship in Bicyclic Isoxazolidin-5-one Derivatives

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The relationship between chiroptical properties of substituted bicyclic isoxazolidin-5-one derivatives and their molecular structures was investigated. The chromophoric system in isoxazolidinones was found to be nonplanar with a shallow pyramidal configuration at the N-atom. The deviation from planarity can be attributed to the strain imposed by the bicyclic skeleton. Due to the nonplanarity, the isoxazolidinone system becomes inherently dissymmetric, which is supported by the high magnitude of the CD band occurring around 210 nm. In addition, the helicity of lactone moiety in investigated bicyclic isoxazolidinones is controlled by the absolute configuration at C(6). On this basis, a helicity rule correlating a positive (negative) helicity expressed by the O=C(8)–O(9)–N(1) torsional angle with a positive (negative) sign of the CD band around 210 nm was formulated.

Introduction. – Conjugate addition of hydroxylamines to the unsaturated sugar lactones proceeds with opening of the lactone ring and formation of corresponding isoxazolidin-5-ones [1–3]. Although the stereochemical pathway of such a reaction is well-known and allows prediction of the absolute configuration of the product, the direct confirmation of such assignment by the NMR method is somewhat tentative. On the other hand, such assignment can be easily corroborated by circular dichroism (CD) spectroscopy [3].

The present work is a continuation of our studies of the chiroptical properties of isoxazolidin-5-ones [3]. As we have shown [3], the sign of the *Cotton* effect (CE) occurring at *ca.* 220 nm can be correlated with the absolute configuration at the stereogenic center C(3) of isoxazolidin-5-one. Moreover, we have demonstrated that the presence of bulky substituents at C(3) influences the conformation of the heterocyclic ring, which, in turn, is the determining factor for the CE sign. Since isoxazolidin-5-ones represent an important class of compounds owing to their frequent use as substrates for the synthesis of aminodeoxy sugars [4], analogs of β-lactam antibiotics [5], isoxazolidinyl analogs of nucleosides [6], as well as β-lactam derivatives [1], we decided to extend our chiroptical studies to the derivatives of bicyclic isoxazolidin-5-one.

Bicyclic isoxazolidinones can be treated as analogs of β-lactam antibiotics, and their potential biological activity may be of great importance. As bacterial resistance against antibiotics, especially against penicillin and cephalosphorin classes, is more and more frequently observed, the search for new agents with improved bio-activity as well as resistance toward β-lactamases has greatly increased in significance. It should be noted here that some isoxazolidinones such as D-cycloserine exhibit significant biological activity [7]. Moreover, it is well-known that the biological activity of bicyclic β-lactam

antibiotics is closely related to the absolute configuration at the bridge-head C-atom. It could be expected that the configuration at the same C-atom may also be crucial for the biological activity of bicyclic isoxazolidinones. As far as we know, no data on the optical activity of these compounds have been reported hitherto. This prompted us to undertake the systematic study of the relationship between structure and chiroptical properties of these compounds.

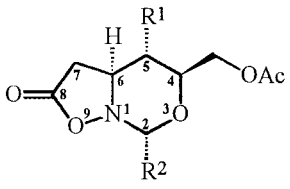
For the present study, a variety of differently substituted bicyclic isoxazolidin-5-one derivatives **1**–**21** (*Fig. 1*) have been selected. To achieve a configurational assignment, circular dichroic and structural studies of model compounds **1**–**21** have been undertaken.

Results and Discussion. – The electronic absorptions and chiroptical data for the compounds **1**–**21** are presented in *Table 1*. The investigated compounds exhibit, in general, one CD band appearing in the 205–212 spectral range, which can be correlated with the electronic absorption maximum occurring at *ca*. 205 nm. In most cases, this UV band is not sufficiently separated and, for isoxazolidinones **1**–**7**, **9** and **17**–**19**, is observed only as a shoulder of the second absorption band with its maximum outside the range of measurement, *i.e.*, below 190 nm. The remaining compounds, *i.e.*, **8**, **10**–**16**, and **20**–**21**, display an additional UV band at *ca*. 195 nm. This band may be connected with the presence of the aromatic substituent(s) in the molecule, which is a characteristic feature of these compounds. In addition, all these compounds exhibit an additional weak absorption band at *ca*. 260 nm associated with the ^1L_b excitation of the aromatic group present in the molecule. For the sake of simplicity, the CD and UV bands in the aromatic spectral range are indicated only in *Table 1*.

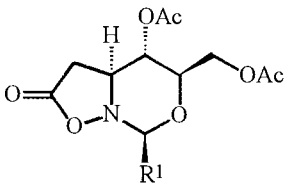
CD Spectra of isoxazolidinones **10**–**16** and **20**–**21**, in addition to the 205–212 nm band, exhibit a further CD band occurring at *ca*. 220 nm. This band is not sufficiently separated, and it is observed as a shoulder of the short wavelength band only. The presence of the 220-nm CD band may be associated with the ^1L_a excitation of the aromatic group(s) present in the molecule. The absence of this band in the CD spectrum of compound **8** may be related to the contributions of the substituents at the C-atoms C(4) and C(6), which bear Si-atoms that may compensate aromatic contributions (*Fig. 2*).

The electronic excitation occurring in the 205–212-nm spectral range cannot unequivocally be assigned to the pure $n \rightarrow \pi^*$ transition because of the absence of the characteristic hypsochromic shift for such a transition caused by polar solvents. Due to the insolubility of most compounds of this series in common nonpolar solvents, it was not possible to study systematically the solvent dependence of the CD spectra. However, the data obtained for compounds **8** and **20** (*Fig. 2*) clearly demonstrate the absence of a solvent effect in series of measurements performed in MeOH through MeCN to methylcyclohexane. The notion that, in the 205–220-nm spectral region, we may be dealing with two or more transitions of similar energy cannot be excluded completely.

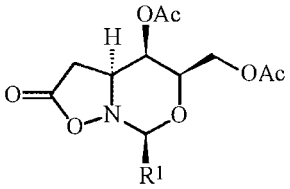
Assuming that CD spectra of thiocarbonyl derivatives of isoxazolidinones may possibly shed more light upon the nature of the electronic transition(s) involved in the absorption and CD bands in the region of 205–220 nm, we decided to convert some representative isoxazolidinones to their corresponding thiono congeners by thionation reaction with *Lawesson*'s reagent [9]. It is well-known that, in contrast to carbonyl



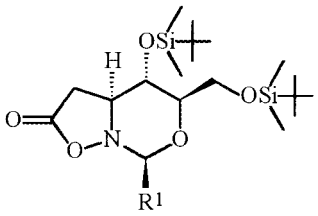
1 $R^1 = R^2 = H$
2 $R^1 = H$; $R^2 = OEt$
3 $R^1 = OAc$; $R^2 = H$



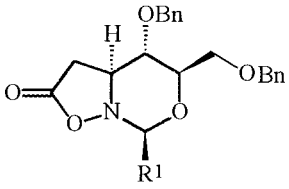
4 $R^1 = Me$
5 $R^1 = CO_2Bu$



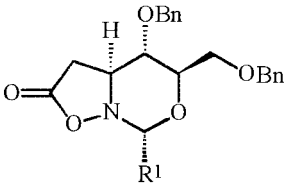
6 $R^1 = H$
7 $R^1 = Me$



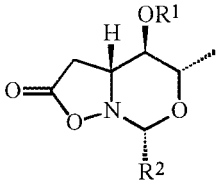
8 $R^1 = CH_2OBn$
9 $R^1 = Me$



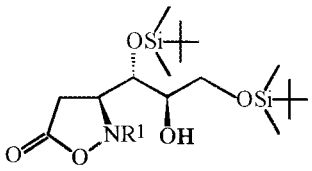
10 $R^1 = Me$
11 $R^1 = OEt$
12 $R^1 = CO_2Bu$
13 $R^1 = CO_2Bn$
14 $R^1 = CH_2OBn$



15 $R^1 = OEt$
16 $R^1 = CO_2Bu$



17 $R^1 = Ac$; $R^2 = H$
18 $R^1 = Ac$; $R^2 = Me$
19 $R^1 = Si(Me)_2(t\text{-}Bu)$; $R^2 = Me$
20 $R^1 = Bn$; $R^2 = Me$
21 $R^1 = Bn$; $R^2 = CH_2OBn$



22 $R^1 = t\text{-}Bu$

Fig. 1. *Investigated bicyclic isoxazolidin-5-one derivatives* **1**–**21** *and model compound* **22**

compounds, the corresponding thiocarbonyl counterparts show their UV and CD bands shifted appreciably to the red, and that the sign of the $n \rightarrow \pi^*$ CE for carbonyls and thiocarbonyls is the same in identical chiral environments [8]. Moreover, the spectra of thiocarbonyl compounds show very well-resolved $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ absorption bands, thus allowing a better understanding of the chromophoric system. However, due to instability of isoxazolidinones to the thionation procedure, even under very mild conditions, our efforts in obtaining respective thiono derivatives failed. Thus, the origin

Table 1. *UV and CD Data of Compounds* **1**–**21** *Recorded in MeCN.* UV and CD values are given as ε [nm] and $\Delta\varepsilon$ [nm], respectively.

Compound	$\varepsilon(\lambda_{max})$ [$dm^3\ mol^{-1}\ cm^{-1}$] ([nm])	$\Delta\varepsilon(\lambda_{max})$ [$dm^3\ mol^{-1}\ cm^{-1}$] ([nm])
1	3100 (204)	+12.82 (207.5)
2	3500 (203) (sh)	+5.56 (207.2)
3	2400 (196) (sh)	+6.70 (207.2)
4	2100 (209) (sh)	+11.51 (207.6)
5	3600 (203) (sh)	+8.81 (206.0)
6	2800 (200) (sh)	+7.64 (204.6)
7	2600 (198) (sh)	+8.60 (204.8)
8	9500 (205)[a]), 21000 (195)	+8.49 (212.0)
9	1600 (208) (sh)	+6.77 (211.5)
10	15100 (206)[a]), 33200 (193)	+5.95 (210.4), +4.14 (223.2) (sh)
11	11700 (205)[a]), 23000 (197)	+3.81 (207.8), +2.20 (221.8) (sh)
12	18000 (206)[a]), 35200 (195)	+9.39 (210.6), +5.47 (222.2) (sh)
13	15400 (205)[a]), 34500 (194)	+7.32 (208.4), +3.79 (222.4) (sh)
14	13200 (206)[a]), 37800 (195)	+8.89 (208.8), +6.56 (220.0)[b]) (sh)
15	18200 (207)[a]), 35500 (194)	+3.51 (212.5), +2.95 (222.5)[b]) (sh)
16	14000 (206)[a]), 22500 (194)	+9.52 (210.5), +8.11 (221.6) (sh)
17	1600 (208) (sh)	−9.54 (206.5)
18	2100 (206) (sh)	−10.49 (208.5)
19	1700 (207) (sh)	−9.75 (211.2)
20	9800 (205)[a]), 23200 (193)	−5.89 (209.0), −4.88 (221.0) (sh)
21	11600 (205)[a]), 25900 (193)	−5.84 (208.0) − 5.19 (220.0)[c]) (sh)

[a]) An additional weak band observed at *ca.* 260 nm. [b]) An additional weak, negative CD band observed at *ca.* 260 nm. [c]) An additional weak, positive CD band observed at *ca.* 260 nm. sh: Shoulder.

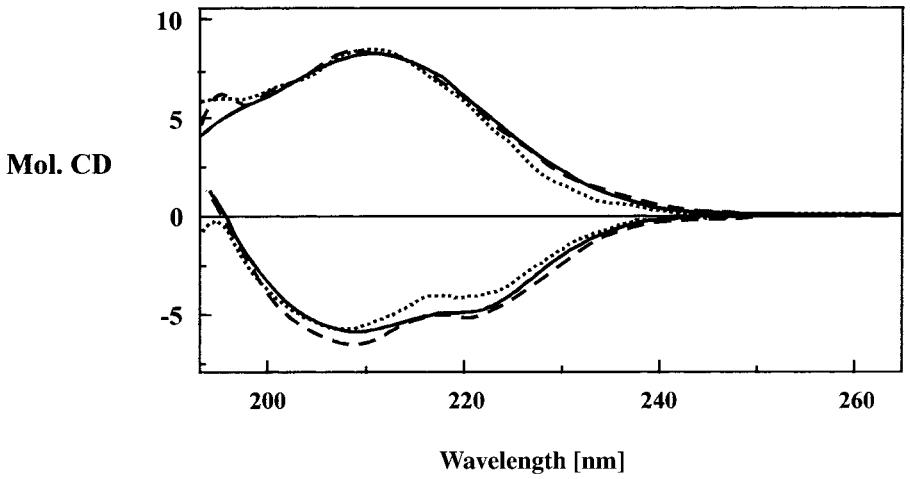


Fig. 2. *CD Spectra of isoxazolidinones* **8** (top) *and* **20** (bottom) *in MeCN* (——), *MeOH* (----), *and methylcyclohexane* (····)

of the electronic excitation involved in a given transition could not be established on the basis of the UV-CD studies of thiocarbonyl counterparts of isoxazolidinones.

The data collected in *Table 1* demonstrate that the investigated compounds fall under two different classes with respect to the sign of their CE at 205–220 nm. In the first class consisting of compounds **1**–**16**, the sign of the CD band is positive, whereas in the second group, represented by compounds **17**–**21**, this band is negative (*Fig. 3*). With respect to their molecular structure, all compounds of the first group differ from the corresponding compounds of the second group in the configuration of the stereogenic center C(6), which, for both groups, remains in the mirror image relationship. The X-ray data obtained for the representative compounds of both groups, namely compounds **1** [10] and **4** [5] for the first and compound **20** (*Fig. 4*) for the second group, establishes the absolute configuration at the bridgehead C-atom to be (6*R*) and (6*S*), respectively. Based on this result and, assuming that the same molecular species are present in the solid state as well as in the solution, we can conclude that the compounds from the first group, analogously to the compounds **1** and **4**, are (6*R*)-isomers, while isoxazolidinones from the second group, alike compound **20**, are (6*S*)-isomers.

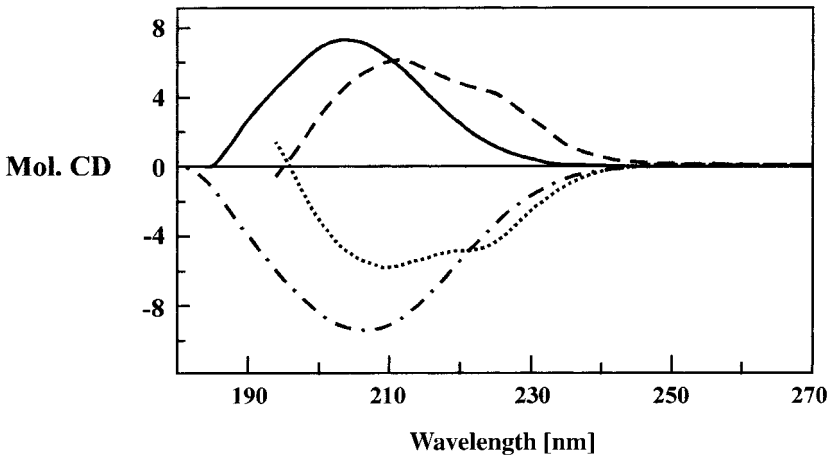


Fig. 3. *CD Spectra of isoxazolidinones* **6** (——), **10** (----), **17** (–·–·–), *and* **20** (····) *recorded in MeCN*

To confirm aforementioned assumption for compounds **4**, **15**, **18**, and **21**, the CD curves in the solid state were also obtained. The results obtained are in good agreement with the respective data recorded in solution, as can be seen from *Fig. 5*, thus providing an additional confirmatiion that the same molecular species are present in the solid state and in solution. It indicates that solute-solvent interactions, which have the potential to considerably affect CD spectra due to both conformational and vicinal effects, are negligible in these cases and points out that the CD observed is largely a molecular property. Thus, in the case of isoxazolidinones **1**–**21**, it seems to be fully justified to correlate directly the solid-state data (X-ray data) with the data obtained for solution (CD data). Therefore, the analysis of the CD data for the purpose of determination of the absolute configuration of isoxazolidinones **1**–**21** can be performed on the basis of chiroptical data obtained for solutions.

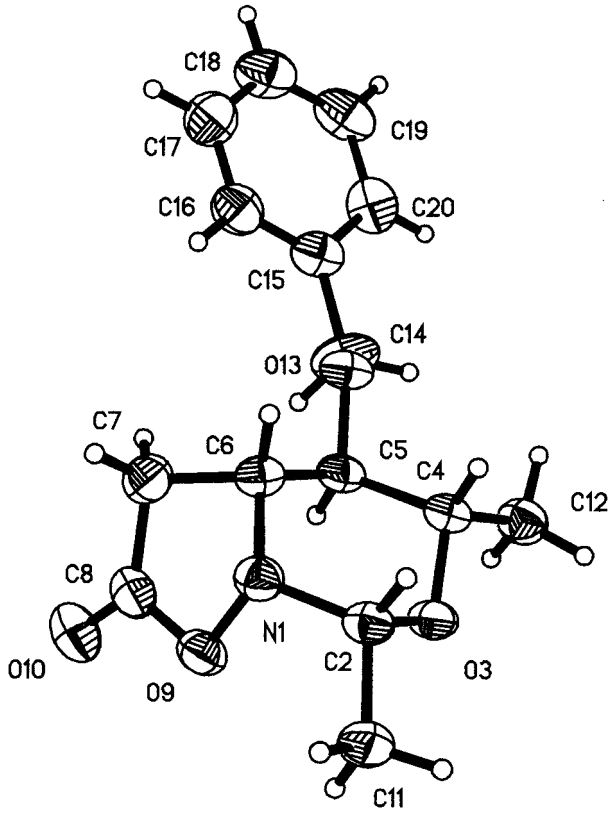


Fig. 4. *Crystal structure of compound* **20** *with the crystallographic numbering scheme.* Thermal ellipsoids are shown at 50% probability level.

Since the optical activity is associated with the electronic transitions of chromophoric groups in a chiral environment, to achieve a correlation between chiroptical data and molecular structure, a chromophoric system present in isoxazolidinones should be precisely defined. Due to the similarity between the five-membered ring of isoxazolidinone and the γ-lactone system, one can assume that, analogously to the monocyclic isoxazolidinones [3], the chromophoric system in compounds **1**–**21** should be mostly limited to the lactone unit. Comparison of the bond lengths of the isoxazolidinone ring in compounds **1**, **4**, and **20** with the corresponding bond lengths of the model system **22** (*Fig. 1*) [3][1]), confirms this assumption. As shown in *Table 2*, the bond lengths in the bicyclic isoxazolidin-5-one system are similar to those of the monocyclic model compound **22**[1]). The N-atom in all compounds discussed is pyramidal (the sum of the valence angles: O(9)–N–C(6), O(9)–N–C(2) and

[1]) The crystallographic data for compound **22** have been deposited with the *Cambridge Crystallographic Data Centre* (*CCDC*) under reference code RIDGAM. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB21EZ, UK, (fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk).

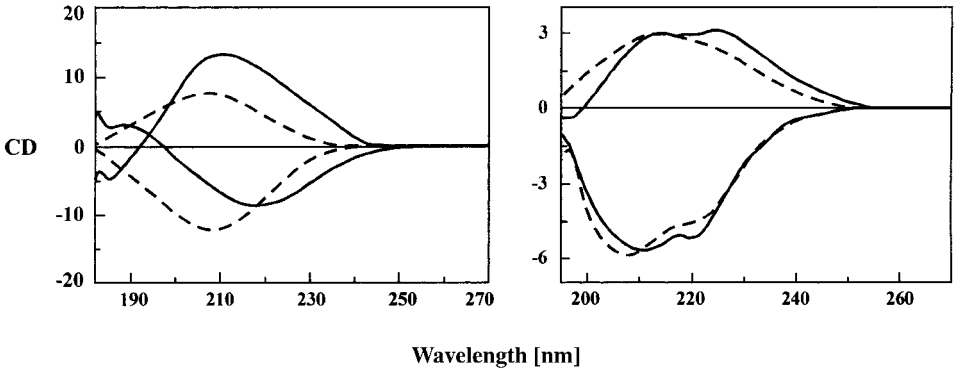


Fig. 5. *Solid-state* (nujol mull) (——) *and MeCN solution* (- - - -) *CD data of compounds* **15** (top) *and* **21** (bottom) (right) *and compounds* **4** (top) *and* **18** (bottom) (left). CD Values for the nujol mull are given in mdeg ([nm]) and for MeCN as $\Delta\varepsilon$ ([nm]), respectively.

C(6)–N–C(2) for **1**, **4**, and **20** amounts to 323.9, 324.3, and 324.4, resp.) Moreover, the N–C(6) distance in isoxazolidinones **1**, **4**, and **20** is 147.8, 147.1, and 148.2 pm, respectively, and approximates the standard length of the N(sp^3)–C(sp^3) in amines (147 pm) [11a] and in hydroxylamine derivatives (146.9–148.4 pm) [11b,c]. This data indicates that no inclusion of the N-atom in the lactone chromophoric system takes place. Thus, analogously to the monocyclic isoxazolidinones [3], their bicyclic derivatives can be treated as being structurally related to γ-lactones, and the lactone unit alone can be considered a chromophore. The CD band present in the CD spectra of **1**–**21**, therefore, may belong to the $n \rightarrow \pi^*$ transition or, more probably, constitutes a mixture of the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ electronic transitions of the lactone chromophore. On the other hand, the N-atom is directly connected to the lactone chromophore and, therefore, its n-electron pair of sp^3-like character interacts electronically with the cyclic ester structure. This interaction is demonstrated by a hyperchromic effect on both the absorption and CD bands compared with those of bicyclic γ-butyrolactones [12].

Table 2. *Some Bond Lengths of Compounds* **1**, **4**, **20**, *and* **22**, *and Differences in Bond Lengths* |**22**–**1**|, |**22**–**4**|, *and* |**22**–**20**| *in pm*[a])

Bond	**1**	|**22**–**1**|	**4**	|**22**–**4**|	**20**	|**22**–**20**|	**22**
C(8)–O(9)	134.4(4)	0.8	135.3(3)	0.1	134.7(5)	0.5	135.2(10)
C(8)–O(8)	119.7(4)	0.4	119.8(3)	0.5	120.7(5)	1.4	119.3(11)
N(1)–O(9)	147.6(3)	0.1	149.1(3)	2.4	149.2(4)	1.7	147.5(7)
C(7)–C(8)	149.5(4)	4.6	150.3(4)	5.4	149.7(5)	4.8	144.9(12)
N(1)–C(6)	147.8(3)	0.5	147.1(3)	1.2	148.2(4)	0.1	148.3(8)
C(6)–C(7)	151.1(5)	2.2	152.4(4)	0.9	151.6(6)	1.7	153.3(9)

[a]) X-Ray data taken from: for **1** [10], **4** [5], **20** [this work], **22** [11].

There are several rules correlating the sign of the $n \rightarrow \pi^*$ *Cotton* effect with the absolute configuration of lactones [13]. Among these rules, a more general one, known as the 'ring-chirality rule' and stating that the chirality of the lactone ring is the sign-determining factor of the $n \rightarrow \pi^*$ transition, was established by *Legrand* and *Bucourt*

[14]. The rule is validated for five-, six-, and seven-membered lactones and relates the CD band of the $n \rightarrow \pi^*$ lactone transition to the sign of the O–C(=O)–C(α)–C(β) torsional angle. According to the rule, a negative (positive) $n \rightarrow \pi^*$ band correlates with a positive (negative) O–C(=O)–C(α)–C(β) torsional angle of the lactone unit. Recently, the ring-chirality rule was successfully applied to the configurational and conformational assignments of various classes of lactones [15].

However, the *Legrand-Bucourt* rule is valid only for the coplanar carboxylic chromophore that is, therefore, inherently achiral. X-Ray studies have shown that this is approximately the case for most lactones investigated [16], although, in some special cases, deviations from the planarity of the lactone unit are known in the literature [17]. For compounds **1**, **4**, and **20**, regarded as a representative for isoxazolidinones **1**–**21**, the values of torsional angles of the isoxazolidinone ring indicate a significant degree of deviation from planarity of the lactone chromophore, as evident from values of the torsional angle O=C(8)–O(9)–N(1) amounting to 171° [10], 173° [5], and −175°, respectively.

The loss of planarity causes an intrinsic dissymmetry of the system analyzed. Since the torsional angle of O=C(8)–O(9)–N(1) structural unit is different from 180° and 360° (or 0°), this unit represents a skewed system that can be treated as an inherently dissymmetric chromophore. The inherently dissymmetric chromophores, in general, give strong contributions to the CEs. This is in accordance with the experimental data presented in *Table 1*, which shows relatively strong magnitudes for CD bands. Contributions from other rings and substituents (chiral second and third spheres, according to *Snatzke* [18]) should also be considered but the sign-determining factor for the CD band(s) is the helicity of the chromophore (chiral first sphere [18]). In the case of isoxazolidinones **1**–**16**, the positive CD band at *ca.* 210 nm reflects the positive lactone helicity given by the positive torsional angle of the O=C(8)–O(9)–N(1) structural unit, whereas the negative CD band in compounds **17**–**21** reflects the negative helicity of the same unit.

Conclusions. – The chiroptical properties – molecular structure relationship of isoxazolidinones **1**–**21** was investigated by means of X-ray diffraction and CD spectroscopy. The most important feature of the molecular structure of isoxazolidinones studied is the nonplanarity of the lactone unit and the pyramidal configuration of the N-atom. The deviation from planarity can be attributed to the strain imposed by the bicyclic skeleton, since, in previously described monocyclic isoxazolidinones, the lactone unit was planar [3]. In bicyclic isoxazolidinones, however, the rigidity of the bicyclo[4.3.0]system forces the N-atom in a defined and fixed pyramidalization that corresponds to the energetically much more favorable *cis*-linkage of carba analogs. This structural effect imposes an intrinsic dissymmetry of the isoxazolidinone ring, which is expressed in a right or left helicity. The sence of chirality of the chromophore is controlled by the (6*R*) or (6*S*) absolute configuration and is also the sign-determining factor for the CD band. Moreover, the helicity of the lactone unit appears to be independent of the nature and the position of other substituents present in the isoxazolidinone molecules.

On this basis, a rule for the prediction of the CD band sign for bicyclic isoxazolidinones can be formulated as follows: a positive (negative) helicity expressed

by O=C(8)–O(9)–N(1) torsional angle correlates with a positive (negative) sign of the CD band at *ca.* 210 nm.

Experimental Part

General. Merck silica gel *60* (230–400 mesh) was used for flash chromatography (FC), and anal. TLC was performed on *Merck* percoated silica gel *60-F_{254}* plates. M.p.: *Boetius* hot-stage apparatus, uncorrected. Optical rotations: *JASCO P-2010* polarimeter at ambient temp. UV Spectra: *Cary 100* spectrophotometer in MeCN. CD Spectra: between 180–400 nm at r.t. with a *JASCO J-715* spectropolarimeter, MeCN solns. Solns. with concentrations in the range 0.8×10^{-4} to 1.2×10^{-3} M were examined in cells with pathlength 0.1 or 1 cm. In some cases, CD and UV spectra were taken in methylcyclohexane and MeOH solns. For solid-state CD measurements, a crystalline compound (1–3 mg) was ground with nujol to form a nujol mull, which was put into a special cell (*Hellma*) and rotated around the optical axis during the entire measurement with original *JASCO* equipment for this purpose. IR Spectra: *Perkin-Elmer FT-IR Spectrum 2000* spectrophotometer. ^{1}H- and ^{13}C-NMR spectra: *Varian Gemini-AC-200* and *Bruker Avance-500* spectrometers at ambient temp.; chemical shifts (δ) in ppm, with residual solvents as internal standard. MS: *AMD 604 Inectra GmbH* spectrometer.

Source of Compounds. Compounds **1**–**19** were obtained according to literature procedures [5]. Compounds **20** and **21** were obtained according to the procedure described below.

General Procedure. Additions of hydroxylamine to lactones was carried out according to the procedure described in [5]. Isoxazolidin-5-ones were purified on a silica-gel column and, after evaporation, were used directly in the reaction with aldehydes.

*(2*R*,4*S*,5*R*,6*R*)-5-(Benzyloxy)-2,4-dimethyl-3,9-dioxa-1-azabicyclo[4.3.0]nonan-8-one* (**20**). Crude (3*R*)-3-[(1*R*,2*S*)-1-(benzyloxy)-2-hydroxypropyl]isoxazolidin-5-one (0.5 mmol, 0.126 g) was dissolved in MeCHO (1.0 ml) and stirred for 3 h. After evaporation of excess MeCHO, crude product resulted, which was purified by FC (hexane/AcOEt 8:2) to afford **20** (0.132 g, 95%). M.p. 92–94°. $[\alpha_D] = -59.6$ ($c = 1.1$, CH_2Cl_2). IR ($CHCl_3$): 1795, 1778. ^{1}H-NMR ($CDCl_3$): 7.40–7.27 (*m*, 5 arom. H); 4.75, 4.54 (2*d*, *J* = 11.2, PhC*H*$_2$); 4.50 (*q*, *J* = 6.0, H–C(2)); 3.59 (*dd*, *J* = 7.0, 9.3, H–C(2)); 3.52 (*dq*, *J* = 6.1, 9.3, H–C(4)); 3.16 (*t*, *J* = 9.3, H–C(5)); 2.98 (*dd*, *J* = 7.0, 16.8, H–C(7)); 2.42 (*d*, *J* = 16.8, H–C(7)); 1.49 (*d*, *J* = 6.0, Me–C(2)); 1.42 (*d*, *J* = 6.1, Me–C(4)). HR-MS: 278.13923 ($[M+M]^+$; $C_{15}H_{20}NO_4$; calc. 278.14087).

*(2*R*,4*S*,5*R*,6*R*)-5-(Benzyloxy)-2-[(benzyloxy)methyl]-6-methyl-3,9-dioxa-1-azabicyclo[4.3.0]nonan-8-one* (**21**). Crude (3*R*)-3-[(1*R*,2*S*)-1-(benzyloxy)-2-hydroxypropyl]isoxazolidin-5-one (0.5 mmol, 0.126 g), (benzyloxy)acetaldehyde (1.5 mmol, 0.275 g) and 5 mg of TsOH were refluxed in toluene (10 ml) for 0.5 h. The solvent was distilled off, and crude product was purified by FC (silica gel; hexane/AcOEt 8:2) to afford **21** (0.157 g, 82%). M.p. 87–90°. $[\alpha]_D = -47.2$ ($c = 1.1$, CH_2Cl_2). IR ($CHCl_3$): 1795, 1780. ^{1}H-NMR ($CDCl_3$): 7.40–7.26 (*m*, 5 arom. H); 4.75, 4.53 (2*d*, *J* = 11.2, PhC*H*$_2$O–C(5)); 4.61, 4.59 (2*d*, *J* = 12.0, PhC*H*$_2$OCH$_2$); 4.57 (*dd*, *J* = 5.0, 6.0, H–C(2)); 3.77 (*dd*, *J* = 5.0, 10.5, 1 H, PhCH$_2$OC*H*$_2$); 3.68 (*dd*, *J* = 6.0, 10.5, 1 H, PhCH$_2$OC*H*$_2$); 3.62 (*dd*, *J* = 6.9, 9.3, H–C(6)); 3.55 (*dq*, *J* = 6.2, 9.3, H–C(4)); 3.17 (*t*, *J* = 9.3, H–C(5)); 3.00 (*dd*, *J* = 6.9, 16.8, 1 H–C(7)); 2.40 (*d*, *J* = 16.8, 1 H–C(7)); 1.43 (*d*, *J* = 6.2, Me). HR-MS: 384.18110 ($[M+M]^+$; $C_{22}H_{26}NO_5$; calc. 384.18256).

Crystallographic Data (*Table 3*). A colorless plate of approximate dimensions $0.385 \times 0.21 \times 0.14$ mm was covered by epoxy glue and used for data collection on a *Nonius MACH3* diffractometer under graphite monochromated CuK_α radiation ($\lambda = 1.54178$ Å). Cell parameters were calculated by the least-squares fit of the setting angles for 25 reflections measured in the θ range 22.45–42.72°.

The structure was solved by standard direct and *Fourier* methods and refined by full-matrix least-squares procedures. The H-atoms attached to C-atoms were placed in calculated positions and allowed to ride on the adjacent C-atoms. The H-atoms attached to O-atoms were found from $\Delta\rho$ maps and refined with no restrictions. The calculations were performed with the SHELX97 [20] programs contained in the WINGX suite [21].

The crystallographic data have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC 181119. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk).

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Table 3. *Crystal Data and Structure Refinement for Compound* **20**

Empirical formula	$C_{15}H_{19}NO_4$
Formula weight	277.31
Crystal system, space group	Monoclinic, $P2_1$
Unit-cell dimensions	
a [Å]	10.0661(7)
b [Å]	12.3623(8)
c [Å]	12.0728(8)
β [°]	101.165(6)
V [Å^3]	1474.3(9)
Z, Calculated density [Mg m^{-3}]	4, 1.249
Absorption coefficient [mm^{-1}]	0.746 mm^{-1}
$F(000)$	592
θ Range for data collection [°]	3.73 to 74.18
Reflections collected/unique	3289/3141 (R(int) = 0.0398)
Completeness to $2\theta = 74.18$	99.7%
Data/restraints/parameters	3141/1/366
Goodness-of-fit on F^2	1.046
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0453$, $wR_2 = 0.1310$
R indices (all data)	$R_1 = 0.0607$, $wR_2 = 0.1496$
Absolute structure parameter	−0.1(3)
Extinction coefficient	0.0024(6)
Largest diff. peak and hole [e · Å^{-3}]	0.198 and −0.196

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