

Stereochemistry of organic compounds(3) : On the optical antipodes of oxazolidinone derivatives

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Stereochemistry of Organic Compounds III
On the Optical Antipodes of Oxazolidinone Derivatives

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有機化合物の立体化学 III

オキサゾリデノン誘導体の
対掌体について新潟歯学部 薩摩林 紘子
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概 要

一連の L-アミノ酸トシレートホルムアルデヒドと縮合させて得られた光学活性五員環化合物は、コンホメーションと旋光寄与の間に相関関係があることを前報で述べた。本研究では、新しく D-アミノ酸から五員環オキサゾリデノン誘導体を合成し、前報に報告された L-体を対比させながら、同様な研究を行った。

NMR の結果から、アルキル基の小さい化合物 I が D-, L-体共に AB パターンを示すことが示され、またアルキル基のかさの増した II と III は D-, L-体共に AC パターンを示すことが判った。この五員環の歪みをラクトンセクター則上に投影して拡大解釈するとカルボニル基の $n \rightarrow \pi^*$ に基づく Cotton 効果の sign が正しく求まる。また、D-体化合物、I-D, II-D, III-D のアシメ炭素は S-配置、L-体化合物、I-L, II-L, III-L は R-配置を示すが、カルボニル基の $n \rightarrow \pi^*$ による Cotton 効果が、R-配置で正、S-配置で負を示すことになり、構造と Cotton 効果の単純な相関が示される。

一方、C₄* アシメ炭素からはなれたフェニル基は、C₄* につく $>N-SO_2^-$ を通って光学活性吸収帯となり、benzenoid band による complex Cotton 効果を 250~270 nm に示す。前報でこの Cotton 効果を説明するためアシメ炭素 C₄* を中心にオクタントを設定し、新しく投影法を提案した。I-D, II-D, III-D に観測された 250~270 nm の complex Cotton 効果の CD 極大値は最長波長 276 nm のを除き、よい対称性を示し、Modified

octant projection が有効に活用されることを示す。

更に、大きな側鎖を有するために、完全に rigid でないこれらの誘導体が、I-D と I-L; II-D と II-L; III-D と III-L の RD, CD 曲線にみられる通り、対称性を示すことからアシメ炭素の遷移モーメントが、その旋光寄与を支配することが判る。

Stereochemistry of Organic Compounds III¹⁾

On the Optical Antipodes of Oxazolidinone Derivatives.

In the previous communication¹⁾ the relationship between the rotatory contribution and the conformation of L-oxazolidinone derivatives were determined. As a result, two chromophores of the carbonyl and the phenyl group, were optically active in the measured wavelength region, and CD spectra of L-oxazolidinone derivatives exhibited Cotton effects around 230 and 270 nm. The expansion use of the lacton sector rule by Klyne *et al.*²⁾ was capable of an assignment to the observed positive Cotton effect around 230 nm, but there were no rules to assign the benzenoid band around 270 nm. Therefore, the new modified octant projection was introduced in the previous paper.¹⁾ In confirmation of this projection, this paper will report the newly synthesized compounds which have the different D-configurations but the same groups as the L-compounds already reported on.¹⁾ For that purpose the following six oxazolidinone derivatives have been investigated.

D-4-Methyl-3-*p*-tosyl-1, 3-oxazolidin-5-one (Compound I-D),
L-4-Methyl-3-*p*-tosyl-1, 3-oxazolidin-5-one (Compound I-L),¹⁾
D-4-Isopropyl-3-*p*-tosyl-1, 3-oxazolidin-5-one (Compound II-D),
L-4-Isopropyl-3-*p*-tosyl-1, 3-oxazolidin-5-one (Compound II-L),¹⁾
D-4-Isobutyl-3-*p*-tosyl-1, 3-oxazolidin-5-one (Compound III-D), and
L-4-Isobutyl-3-*p*-tosyl-1, 3-oxazolidin-5-one (Compound III-L).¹⁾

Measurements were made with these compounds on their rotatory dispersion (RD), circular dichroism (CD), ultraviolet absorption (UV), infrared (IR) and NMR spectra.

Results and Discussion

The structure of the all compounds studied are indicated in Fig. 1.

The nuclear magnetic resonance spectra showed absorptions at δ 5.60–5.11 ppm, assignable to ring methylene protons, at δ 4.04–3.83 ppm, due to ring methine proton, and at δ 2.47–2.42 ppm and 7.75–7.27 ppm, corresponding to tosyl protons. The

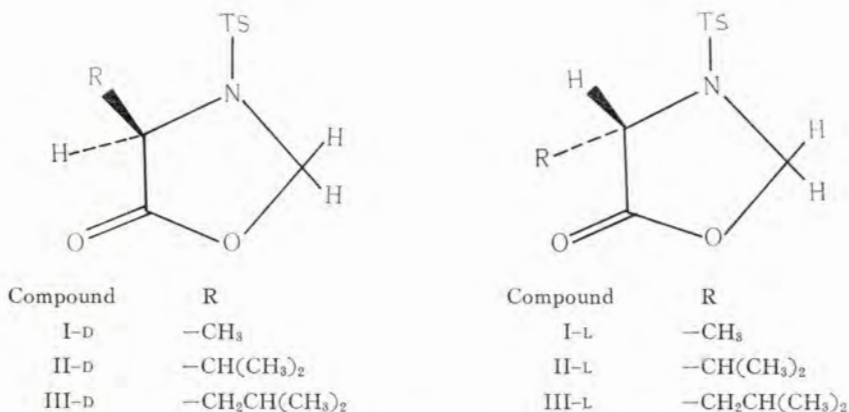
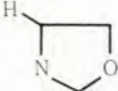
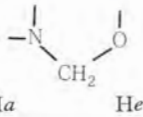
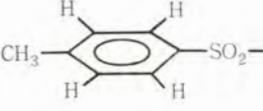


Fig. 1 Structures of all compounds studied.

remaining absorptions are assigned to the alkyl group protons.

Two protons of the ring methylene group are situated in different environments, that is, one is an axial proton (*Ha*) and the other is equatorial (*He*). The δ value of *He* is slightly larger than that of *Ha*, as given in Table 1. In general, two substituents, of the neighboring atoms in a saturated cyclic compound, are placed as alternately as possible to decrease the repulsive force of the bulky substituent, which normally prefers the equatorial position. When the alkyl group is stereochemically large enough, the steric repulsion by the large tosyl group occurs, and the two methylene protons are fixed in the axial and equatorial positions. Hence their

Table 1. ¹H-NMR Data of All Compounds (δ , ppm)

| |  |  |  | R |
|-------|---|---|---|-------------------------------|
| I-D | 3.97(q, 1) | 5.26(d, 1) 5.40(d, 1) | 2.47(s, 3) 7.40(d, 2) 7.75(d, 2) | 1.54(d, 3) |
| I-L | 3.99(q, 1) | 5.24(d, 1) 5.38(d, 1) | 2.46(s, 3) 7.36(d, 2) 7.72(d, 2) | 1.54(d, 3) |
| II-D | 3.83(d, 1) | 5.13(d, 1) 5.59(d, 1) | 2.42(s, 3) 7.33(d, 2) 7.72(d, 2) | 1.10(d, 6) 1.84-2.60(m, 1) |
| II-L | 3.85(d, 1) | 5.11(d, 1) 5.60(d, 1) | 2.42(s, 3) 7.31(d, 2) 7.68(d, 2) | 1.10(d, 6) 1.84-2.59(m, 1) |
| III-D | 4.07(t, 1) | 5.18(d, 1) 5.57(d, 1) | 2.43(s, 3) 7.35(d, 2) 7.70(d, 2) | 1.02(d, 6) 1.50-2.21(m, 3) |
| III-L | 4.04(t, 1) | 5.15(d, 1) 5.54(d, 1) | 2.42(s, 3) 7.27(d, 2) 7.67(d, 2) | 1.00(d, 6) 1.45-2.28(m, 3) |

signals of nuclear magnetic resonance will be observed as typical AC-type splitting. If the alkyl group is small, the two protons are averaged and the signals will be observed as the AB- or A_2 -type pattern. The two protons of the ring methylene group of II-D, II-L, III-D, and III-L are split as in the AC pattern, and those of I-D and I-L are observed as in the AB. All the NMR spectra of D-compounds, I-D, II-D and III-D, are absolutely same as those of L-antipodes, I-L, II-L, and III-L,

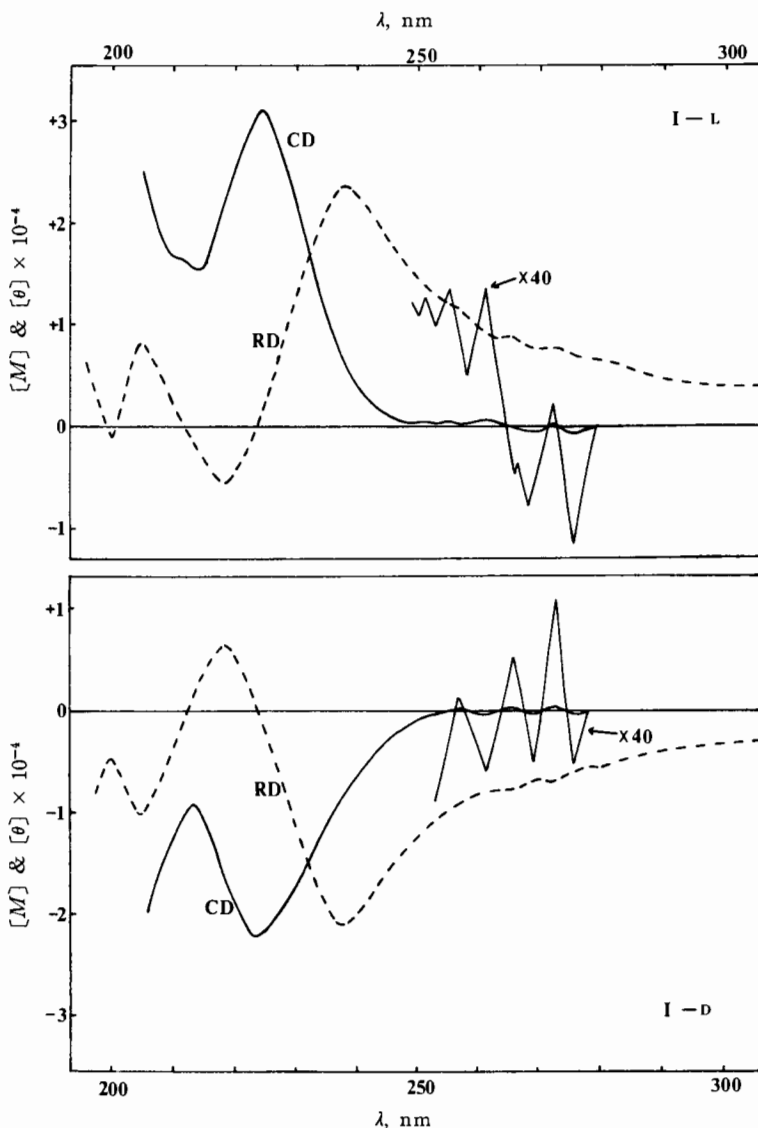


Fig. 2 RD and CD of I-D and I-L

respectively.

The RD and CD curves of all compounds are shown in Figs. 2-4. As may be seen from the CD curves, the compounds, I-D, II-D and III-D, exhibit the negative Cotton effects around 220 nm, attributed to the $n \rightarrow \pi^*$ transition of carboxylate group. On the other hand, the compounds, I-L, II-L and III-L, show the positive Cotton effects around 220 nm owing to the same transition. The RD, CD and UV

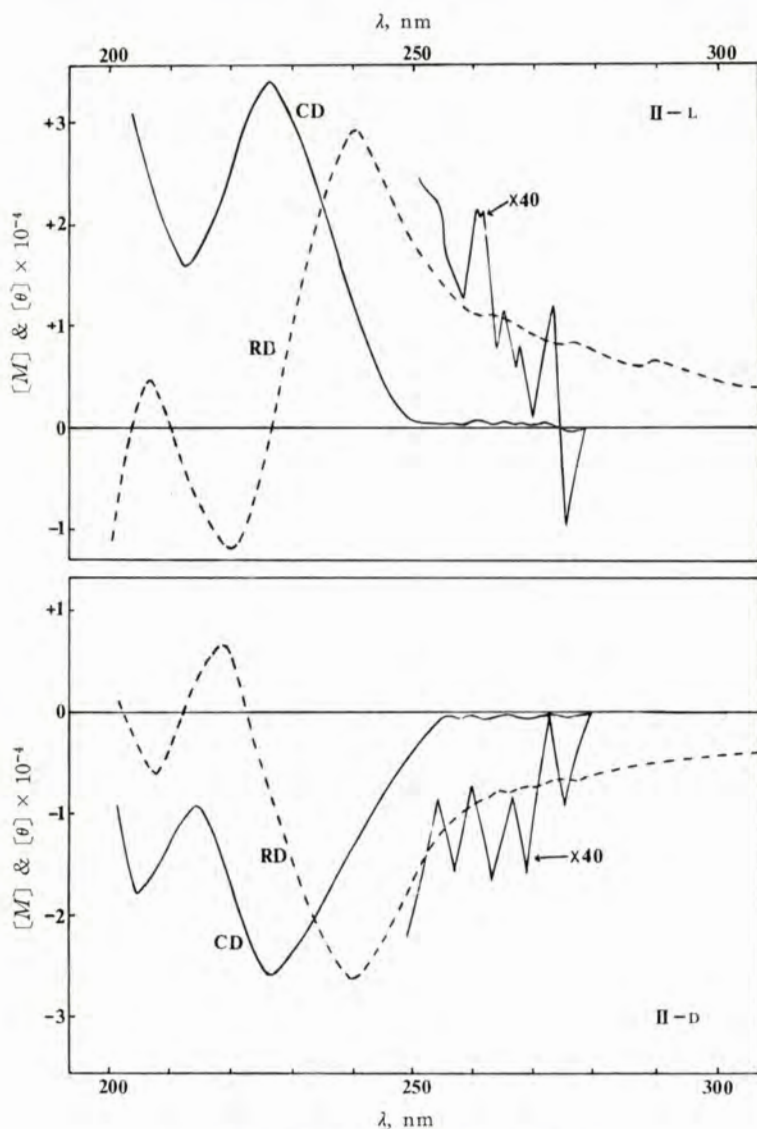


Fig. 3 RD and CD of II-D and II-L

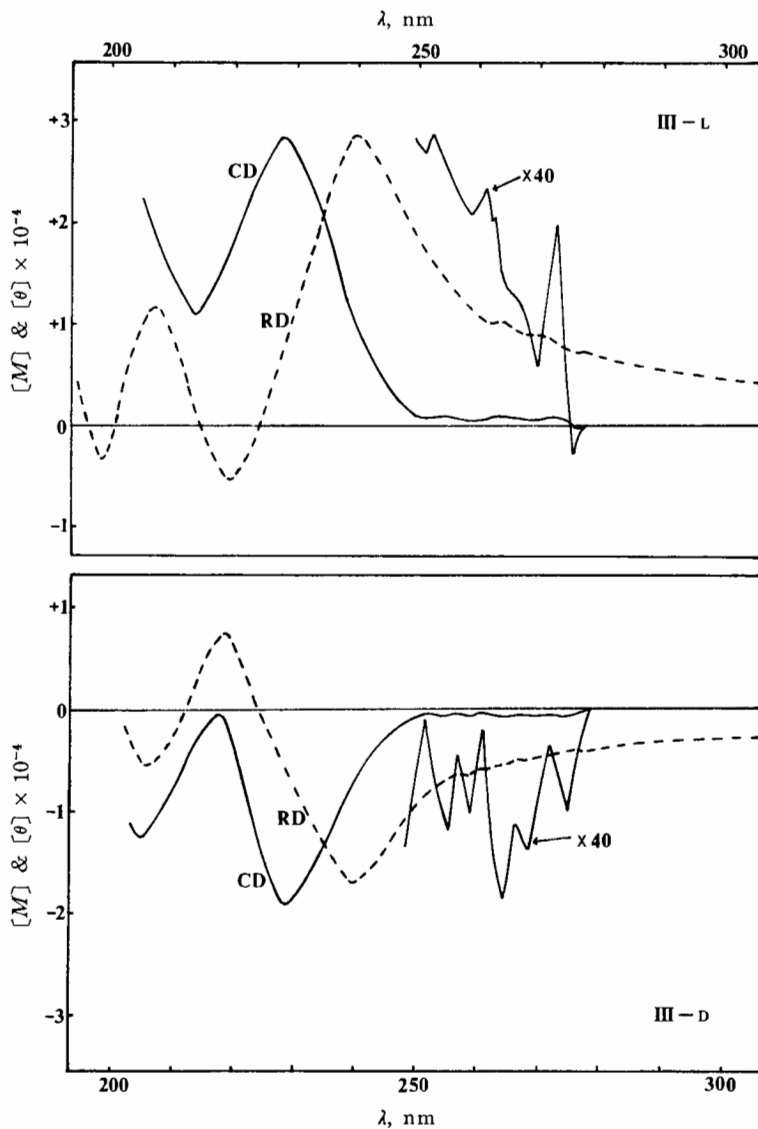


Fig. 4. RD and CD of III-D and III-L

data of $n \rightarrow \pi^*$ transition band are shown in Table 2.

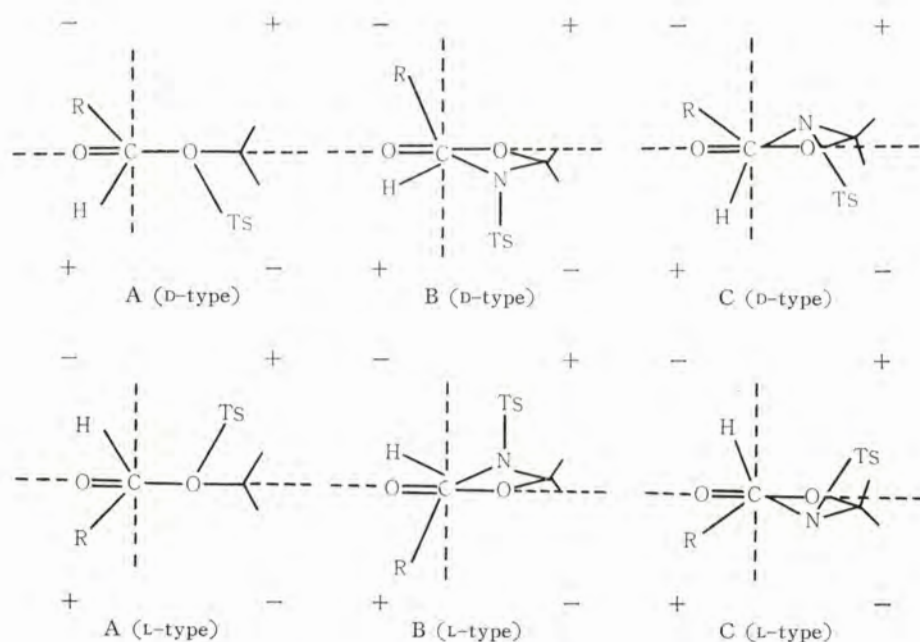
In Fig. 5, the projections A (D-type) and A (L-type) show that the five membered rings of the oxazolidinones establish planar structures, and the projections B and C indicate distorted five membered rings. In the cases of the projections C (D-type) and C (L-type), the alkyl group R is far from the tosyl group, Ts, in comparison with diagrams B (D-type) and B (L-type). All the projections of D-type

Table 2. RD, CD and UV maximum Values of $n \rightarrow \pi^*$ for All Compounds (in Ethanol).

| Comp | RD* ¹ | | | | CD* ¹ | | UV | |
|-------|------------------|-----------------------|----------------|------------------------|------------------|---------------------------|----------------|---------------------------|
| | λ (nm) | $[M] \times 10^{-2}$ | λ (nm) | $[M] \times 10^{-2}$ | λ (nm) | $[\theta] \times 10^{-2}$ | λ (nm) | $\epsilon \times 10^{-2}$ |
| I-D | 238 | -215(T)* ² | 219 | +60.9(P)* ² | 224 | -228 | 228 | 130 |
| I-L | 238 | +238(P) | 219 | -54.3(T) | 224 | +313 | 228 | 130 |
| II-D | 240 | -267(T) | 220 | +64.5(P) | 226 | -263 | 228 | 140 |
| II-L | 240 | +297(P) | 220 | -123(T) | 226 | +343 | 228 | 145 |
| III-D | 240 | -170(T) | 220 | +65.3(P) | 228 | -196 | 227 | 120 |
| III-L | 240 | +287(P) | 220 | -55.5(T) | 228 | +285 | 227 | 115 |

*¹ RD and CD data are not corrected for 100% optical purity of the sample.*² P: Peak, T: Trough.

in Fig. 5 show that the alkyl group, R, attached to the asymmetric carbon falls within the sector of negative contribution, and the observed negative Cotton effects, around 224–228 nm, are in good agreement with the prediction of the sector rule. On the contrary, in case of the upper projections of L-type in Fig. 5, the alkyl group R falls into the positive sector and the signs of Cotton effects around 224–228 nm are positive. This means that the chirality of D-type goes in the opposite

**Fig. 5** Sector projections of D- and L-oxazolidinones.

direction of the L-type, because of being antipodes of each other.

In the next place, discussions will be made about the complex Cotton effects around 270 nm. As elucidated in the previous paper,¹⁾ the UV spectra of I-L, II-L and III-L showed a system of three bands in the range of 260–275 nm, due to the 1L_b bands.^{3,4)} The CD spectra showed at least five maxima in the same spectral range with well-resolved fine structure. In the case of D-type compounds, I-D, II-D and III-D, the UV spectra show the same results. In contrast, the CD spectra of those D-type compounds show different patterns. According to the NMR data in Table 1, the predominant conformers of the compounds I-D and I-L are characterized by the B-type in Fig. 5, and all the other compounds are characterized by the C-type. The modified octant projection we proposed in the previous paper¹⁾ are indicated in Fig. 6. The projections of the upper side in Fig. 6 are for D-type and lower side are for L-type compounds. The projection of B in Fig. 6 corresponds to the distorted structure of B in Fig. 5 and the C in Fig. 6 corresponds to the C in Fig. 5. As mentioned above, the result of NMR spectra of I-D and I-L supported

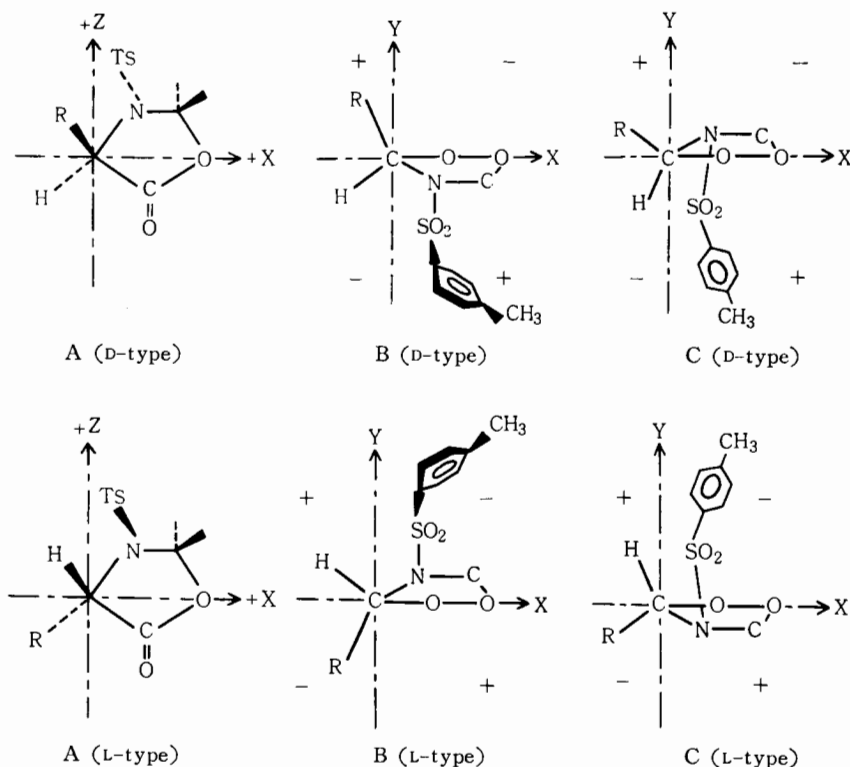



Fig. 6 Modified octant projections oxazolidinones.

the conformation projected in Fig. 6-B. In Fig. 6-B (L-type), the $>N-SO_2$ part attached to the asymmetric carbon is placed in negative octant and the  group is situated in the front side of the upper right part. This indicates that Cotton effects vary from the negative sign to the positive sign. In the case of D-type, the signs are reversed as indicated in the upper projections of Fig. 6. Therefore, the complex Cotton effects of I-D and I-L in Fig. 2 are an explanation of the projections B (D-type), and B (L-type) in Fig. 6.

Furthermore, the projections of C (D-type) and C (L-type) in Fig. 6 are given to the AC type compounds, II and III. In Fig. 6-C (D-type), the nitrogen atom attached to the asymmetric carbon enters into the negative octant, whereas in the case of the L-type projection, the nitrogen atom is placed in the positive octant. Therefore, major Cotton effects of D-type and L-type are negative and positive respectively. This supports the results of CD measurements in Figs. 3 and 4.

Experimental

The preparation of all the compounds was carried out in a similar manner as previously stated in earlier research.¹⁾ D-Alanine, D-Valine and D-Leucine by Aldrich Co. Ltd were used as raw materials for the synthesis.

The infrared spectra were measured in a potassium bromide disc using a Hitachi 285 Grating Infrared spectrometer. The nuclear magnetic resonance spectra were recorded with a JNR-PMX spectrometer at room temperature. Chloroform-d was used as solvents, and tetramethylsilane was used as an internal reference. The chemical shifts were recorded in values and were followed by a splitting pattern: s, single; d, doublet; t, triplet; q, quarted; m, multiplet. The rotatory dispersion and circular dichroism were measured in ethanol at 23-25 °C in the wavelength region from 190 to 400 nm with a JASCO ORD/UV-5 type optical rotatory dispersion recorder. The ultraviolet absorption was measured with a Hitachi 320 type spectrophotometer.

D-4-Methyl-3-*p*-tosyl-1, 3-oxazolidin-5-one (Compound I-D). White needles; mp 135-136 °C. The RD and CD were measured at 25 °C (c 0.1120): $[\alpha]_{400} - 455^\circ$, $[\alpha]_{280} - 2080^\circ$, $[\alpha]_{278} - 2030^\circ$, $[\alpha]_{271} - 2550^\circ$, $[\alpha]_{269} - 2530^\circ$, $[\alpha]_{265} - 3060^\circ$, $[\alpha]_{261} - 2990^\circ$, $[\alpha]_{238} - 8430^\circ$, $[\alpha]_{219} + 2390^\circ$, $[\alpha]_{205} - 3960^\circ$, $[\alpha]_{200} - 1930^\circ$, $[\alpha]_{198} - 3180^\circ$, $[\theta]_{278} 0^\circ$, $[\theta]_{276} - 122^\circ$, $[\theta]_{272} + 291^\circ$, $[\theta]_{269} - 125^\circ$, $[\theta]_{266} + 148^\circ$, $[\theta]_{262} - 122^\circ$, $[\theta]_{257} + 35.7^\circ$, $[\theta]_{224} - 22800^\circ$, $[\theta]_{214} - 9480^\circ$, $[\theta]_{206} - 20200^\circ$. The UV was measured at 25 °C in ethanol: ϵ_{272} 499, ϵ_{268} 672, ϵ_{263} 810.

D-4-Isopropyl-3-*p*-tosyl-1, 3-oxazolidin-5-one (Compound II-D). White needles; mp 74-75 °C. The RD and CD were measured at 23 °C (c , 0.1160): $[\alpha]_{400} - 483^\circ$,

$[\alpha]_{276} - 2260^\circ$, $[\alpha]_{275} - 2170^\circ$, $[\alpha]_{269} - 2590^\circ$, $[\alpha]_{268} - 2490^\circ$, $[\alpha]_{266} - 2850^\circ$, $[\alpha]_{264} - 2690^\circ$,
 $[\alpha]_{263} - 3090^\circ$, $[\alpha]_{261} - 3020^\circ$, $[\alpha]_{240} - 9450^\circ$, $[\alpha]_{220} + 2280^\circ$, $[\alpha]_{208} - 1170^\circ$, $[\alpha]_{202} + 34.5^\circ$,
 $[\theta]_{278} 0^\circ$, $[\theta]_{276} - 229^\circ$, $[\theta]_{272} - 19.5^\circ$, $[\theta]_{269} - 371^\circ$, $[\theta]_{267} - 205^\circ$, $[\theta]_{264} - 415^\circ$, $[\theta]_{259}$
 $- 183^\circ$, $[\theta]_{258} - 396^\circ$, $[\theta]_{254} - 205^\circ$, $[\theta]_{226} - 26300^\circ$, $[\theta]_{216} - 8980^\circ$, $[\theta]_{204} - 18200^\circ$. The
UV was measured at 25°C in ethanol: ϵ_{274} 685, ϵ_{269} 898, ϵ_{264} 1160, ϵ_{228} 14000.

D-4-Isobutyl-3-*p*-tosyl-1, 3-oxazolidin-5-one (Compound III-D). White needles;
mp 113-114°C. The RD and CD were measured at 23°C (c , 0.1075): $[\alpha]_{400} - 266^\circ$,
 $[\alpha]_{276} - 1420^\circ$, $[\alpha]_{275} - 1290^\circ$, $[\alpha]_{268} - 1680^\circ$, $[\alpha]_{266} - 1590^\circ$, $[\alpha]_{265} - 1880^\circ$, $[\alpha]_{263} - 1730^\circ$,
 $[\alpha]_{262} - 2050^\circ$, $[\alpha]_{260} - 1860^\circ$, $[\alpha]_{240} - 5730^\circ$, $[\alpha]_{220} + 2200^\circ$, $[\alpha]_{206} - 1920^\circ$, $[\alpha]_{200} - 149^\circ$,
 $[\theta]_{278} 0^\circ$, $[\theta]_{275} - 245^\circ$, $[\theta]_{272} - 77.8^\circ$, $[\theta]_{269} - 333^\circ$, $[\theta]_{266} - 281^\circ$, $[\theta]_{264} - 467^\circ$, $[\theta]_{261}$
 $- 50.0^\circ$, $[\theta]_{259} - 267^\circ$, $[\theta]_{257} - 106^\circ$, $[\theta]_{256} - 300^\circ$, $[\theta]_{252} - 22.2^\circ$, $[\theta]_{228} - 19600^\circ$, $[\theta]_{218}$
 $- 111^\circ$, $[\theta]_{204} - 12700^\circ$. The UV was measured at 25°C in ethanol: ϵ_{273} 574, ϵ_{269}
658, ϵ_{264} 918, ϵ_{227} 12000.

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