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NEW ASSIGNMENTS FOR CIRCULAR DICHROISM BANDS OF CARBOXYLIC ACID DERIVATIVES

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Abstract—The CD of some carboxylic acid esters has been investigated in various solvents. Two bands were found in the 200–250 nm range for all esters and also for lactone **9**. The band at 230 nm depends on the nucleophilicity of the heteroatom attached to the asymmetric centre, and vanishes in acidic media. On the basis of these observations and of the solvent effect, the 230 nm band has been assigned to the CT transition of an electron from a non-bonding orbital of the heteroatom to the π^* anti-bonding orbital of the carboxyl group, and the 210 nm band to the $n \rightarrow \pi^*$ carboxylate transition.

These results contradict the earlier hypothesis assigning both these bands to the $n \rightarrow \pi^*$ transitions of the carboxyl group belonging to different conformers.

The chiroptical properties of compounds containing the carboxy chromophore have been widely studied in recent years. These compounds were α-substituted alkyl carboxylic acids and esters, especially α-amino-,[1-4] α-hydroxy,[1,4-7] α-halogeno-,[8] α-trimethylammonium-,[9] and α-mercapto- acids.[10] Optically active α-substituted carboxylic acids and some of their derivatives show two bands in the CD spectra near 200–250 nm. Anand and Hargreaves[5] were the first to report the presence of two bands in the CD spectra of lactic acid. The weak longer wavelength band at 245 nm was assigned to the $n \rightarrow \pi^*$ carboxylate transition, and the more intense shorther wavelength band at 210 nm to the $\pi \rightarrow \pi^*$ carboxylate transition. These assignments are in direct conflict with the generally accepted view that the Cotton effect associated with the 210 nm absorption band of carboxylic acids and esters is of $n \rightarrow \pi^*$ origin.[11] Johnson *et al.*[2] recently observed a band at 160 nm of $\pi \rightarrow \pi^*$ origin the CD spectra of alkyl amino acids. Barth *et al.*,[6] basing their arguements on the temperature and solvent-dependence of the CD spectra of several α-hydroxy acids, attributed the presence of the two bands either to specific solvation or to conformational equilibria between conformers with different chiroptical properties. At present many authors[4,7-9,12,13] are attributing these bands to carboxyl transitions arising from the two major conformers.

The α-substituted acyclic acids and esters have free rotation around the C–C bond which connects the asymmetric centre to the chromophore. The three main conformations will be those in which one of the bonds at C_α is synperiplanar position to the carbonyl group of the carboxyl (A, B and C in Fig 1).[14]

Craig and Pereira[4] ascribed the positive effect at 210 nm (for brevity designated as band 1) to the antiperiplanar conformation D, considered by them as more stable, in which the maximum angle is between the dipoles, and the weaker band at 230 nm (band 2) to conformation A, in which coupling of the heteroatom non-bonding orbital with the chromophoric transition of the carbonyl occurs. In contradiction to this, Barth *et al.*[6] explained the temperature and solvent dependence of the CD spectra of α-substituted phenylacetic acids by displacements in the conformation equilibrium between the two low-energy rotamers A and B. Listowsky[7] gave a similar interpretation to the spectra of alkyl-carboxylic acids, and Gaffield and Galetto[8] to the CD spectra of α-halogeno-acids. In accordance with these authors, the two bands are of $n \rightarrow \pi^*$ origin. On the basis of the octant rule, they ascribed the positive CD to conformation A, and the negative CD to conformation B. Conformation C, however, will give only a small CD, because its population is small and there occurs compensation of the contributions from rests R and X. Snatzke recently investigated the chiroptical properties of some amino-,[12] and α-halogeno acid derivatives.[13] He considered the conformer A responsible for band 1, and the conformers B and C for band 2 in the CD spectra of these compounds. This seems strange, as the conformation C with the synperiplanar

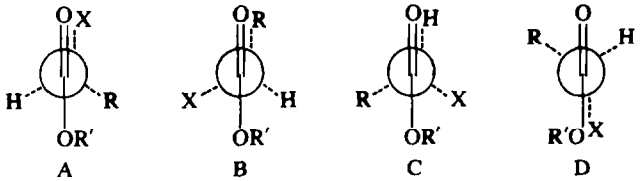


Fig. 1. The four discussed conformations of α-substituted acids and esters (L-series). R = Alkyl, X may be NHR', OH, or Halogen.

hydrogen atom at C_α in relation to the carbonyl group is generally regarded as energetically higher than the other conformations, and less populated.[6-8,14]

In studying the solvent effect on the CD spectra of carboxylic acids, several authors[6-8] observed much greater intensity of band 2 in non-polar solvents than in polar ones. These observations are consistent with the hypothesis according to which with increase of the solvent dielectric constant the population of the rotamer A increases in relation to that of the rotamer B. This is due to the fact that structures, whose carbonyl group is eclipsed by the substituent X, have a higher dipole moment. In the case of acids, this accordance seems only accidental, as those authors did not take into consideration the changing degree of acid dissociation in solvents with various dielectric constant. Such changes are particularly important if one considers that spectropolarimetric methods call for low solute concentrations. It is well known that the CD spectra of acids are strongly dependent on the concentration and the pH of solvents.[15] Increased dissociation in the carboxyl group causes very considerable decrease in the intensity of band 2,[4,7] and may even change the sign of the Cotton effect.[7]

It seems therefore that the problem of assignments for carboxylic chromophore remains unsolved. Is the presence of two CD bands indicative of two different electronic excitations or of two conformational isomers? It was the purpose of this study to reinvestigate that problem using examples of serveral amino acid derivatives. In order to preclude the influence of variation in degree of dissociation on the CD, compounds with an esterified carboxyl group have been examined. The CD spectra of several amino acid esters were measured in acidic and neutral methanolic solutions. In addition, optically active N-hydroxyamino acid esters recently synthesised in our laboratory,[16] some specimens of α-hydroxy, α-chloro acid esters, and several acylated amino acid esters were investigated. The solvent influence on the CD spectra was studied in several cases. The results are summarised in Table 1.

As the optical properties of carboxylic acids are similar to those of esters, some further conclusions can be applied to either of these compound groups. Each of the α-substituted carboxylic esters studied exhibited two CD bands at 200–250 nm in neutral methanolic solution. The spectra of these compounds (all with L-configuration) showed a strong positive effect at 210 nm (band 1) and a weaker negative one near 230 nm (band 2). The intensity of band 2 grows in the series of leucine derivatives in going from the acylated forms **6a** and **6b**, through the free methyl **2a** and t-butyl **2b** esters, to the N - hydroxy - leucine methyl ester **2c** (Fig 2). In the latter case, the intensity of band 2 nearly equals that of band 1. In all these cases band 1 remains almost unchanged. Band 2 disappeared in acidic media in compounds with protonated amino- and hydroxylamino groups, but the effect at 210 nm changed only insignificantly. These observations suggest that the magnitude of the effect at 230 nm is strongly dependent on the nucleophility of the heteroatom attached to the asymmetric centre. The free amino group

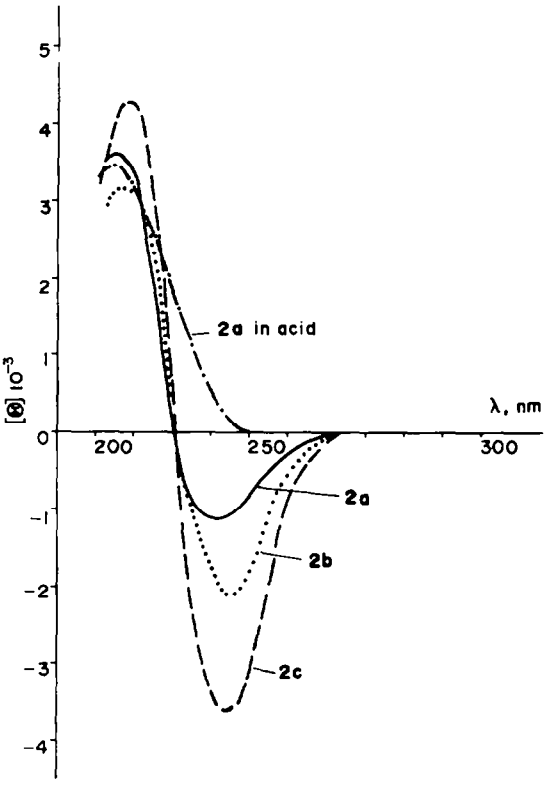


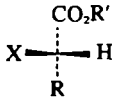
Fig 2. CD of L-leucine derivatives in methanolic solution: methyl ester **2a** (——), t-butyl ester **2b** (· · · · · ·), N - hydroxy - L - leucine methyl ester (– – – –) and **2a** at pH 1 (–·–·–·–).

has a stronger electrodonor character than its acylated form, and the hydroxylamine group is a super-nucleophile[17] as a result of the "alpha" effect. An interesting case is that of the leucine t-butyl ester **2b**, which in regard to the magnitude of band 2 occupies an intermediate position between the corresponding methyl ester **2a** and its N-hydroxy analogue **2c**. This is in agreement with the findings of Błotny,[18] who confirmed that the amino group has a stronger nucleophilic character in t-butyl amino acid esters than it has in the corresponding methyl esters. These findings parallel the observations of Craig and Pereira[4] who also noticed that the magnitude of band 2 depended on the nucleophilicity of the α-substituent, having observed the intensity of band 2 to increase in going from proline to N-methylproline methyl esters, although less evidently than in the examples mentioned above. They also found that this band disappeared for amino acids and esters in acidic solution.

Investigation of the solvent effect on the CD spectra of amino acid ester derivatives gave very interesting results. The magnitude of the CD at 230 nm is strongly dependent on solvent polarity. It reaches its highest value in solvents with a high dielectric constant, to decrease gradually with solvent polarity (Fig 3). A similar solvent dependence was observed in the spectrum of the α-hydroxy acid ester **7**.

The results obtained clearly contradict the former

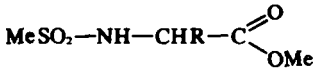
Table 1. CD data of some carboxylic ester (λ_{max} in nm, $[\theta]$ in deg . mole^{-1} . cm^2)



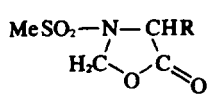
					Band 1		Band 2			
No	X	R	R'	Solvent[a]	λ_{max}	$[\theta]$	λ_{max}	$[\theta]$		
1	NH_2	Me	Me	M	209	+3160	227	−860		
				H	207	+3060		0		
				D	205	+3300	232	−720		
2a	NH_2	Me_2CHCH_2	Me	M	208	+3620	232	−1130		
				H	205	+3450		0		
				C	205	+6000	237	−188		
2b	NH_2	Me_2CHCH_2	C	M	210	+3070	235	−2150		
				C	210	+6150	245	−108		
2c	NHOH	Me_2CHCH_2	Me	M	211	+4290	234	−3650		
				H	209	+5100		0		
				C	209	+6100		0		
3a	NH_2	Me_2CH	Me	M	210	+4300	235	−890		
				H	206	+5090		0		
				C	205	−8600	243	−65		
3b	NHOH	Me_2CH	Me	M	212	+5500	233	−3900		
				H	205	+4600		0		
				C	205	+6200	low negative			
4	NH_2	$MeO_2CCH_2CH_2$	Me	M	210	+2640	232	−900		
				H	212	+3330		0		
				C	209	+5100	235	−340		
5a	NH_2	$C_6H_5CH_2$	Me	M	210	+9000	235	−1300		
				H	212	+10100		0	257	+430
5b	NHOH	$C_6H_5CH_2$	Me	M	212	+8700	235	−1740		
				H	210	+10600		0	255	+71
6a	CH_3SO_2NH	Me_2CHCH_2	Me	M	206	+4600	237	−64		
				D	205	+5900	241	−20		
6b	CH_3CONH	Me_2CHCH_2	Me	M	209	+10700	240	−59		
7	HO	Me_2CHCH_2	Me	M	209	+3800	238	−36		
				C	203	+6100	240	−15		
8	Cl	Me_2CHCH_2	Me	M	203	+2020	232	−530		
				C	204	+1700	230	−1090		
9				M	212	+2420	238	−56		
				D	212	+1300	263	−200		

Abbreviations used: [a]M = methanol, C = cyclohexane, D = cyclohexane : dioxane (9 : 1), H = methanol pH 1.

views on the chiroptical properties of carboxylic acids. Although conformation A is the most preferred in polar solvents, and in these solvents band 2 reaches its maximum intensity for all non-cyclic esters examined (with the exception of α-chloro ester **8**), it seems that both bands ought to be ascribed to the form A with a planar carboxyl group and the substituent X. This was confirmed by synthesising the methanesulfonyl - L - leucine* methyl ester **6a** and its cyclic analogue **9** which corresponds to conformation D, but, like conformation A, has a planar arrangement of the carbonyl and X groups. In the last-mentioned case the conformation equilibrium described above is of course impossible. Despite this, the two bands are still present in the CD spectrum of **9**, as in the acyclic ester **6a**, although band 2 is considerably weaker in the latter.



6a



9

R = Me_2CHCH_2

The intensity of band 2 in the CD spectra of **9** increases in going from methanol to cyclohexane. This is in contrast to what occurs in acyclic derivatives, a fact easy to explain if one remembers that the conformer D has the lowest dipole moment. Increase in solvent polarity causes

*The alkylsulfonyl groups do not exhibit any absorption band in the 200–250 nm region (see: E. A. Fehnel and M. Carmack, *J. Am. Chem. Soc.* **71**, 231 (1949); F. Nerdel, H. Goetz and E. Fabienke, *Liebigs Ann.* **643**, 6 (1961).

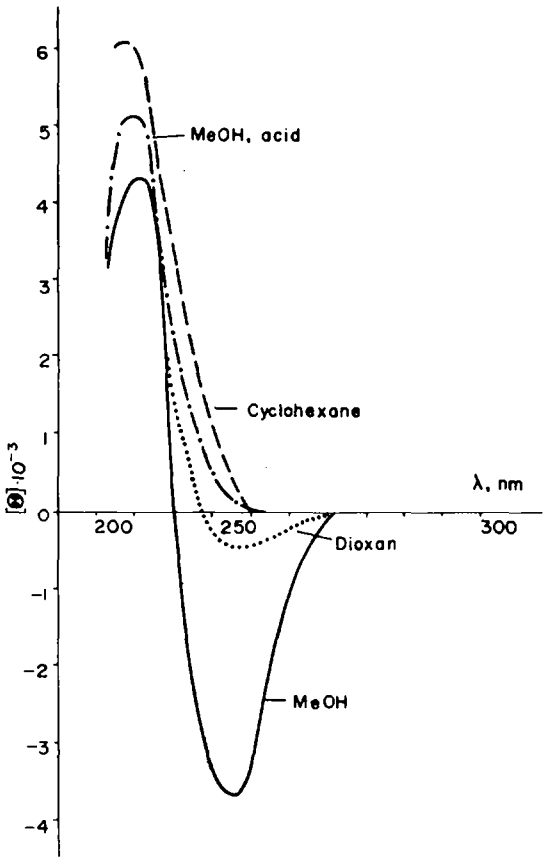


Fig 3. CD of N - hydroxy - L - leucine methyl ester **2c** in methanol (——), dioxane (· · · · · ·), cyclohexane (– – – – – –) and methanol at pH 1 (— · — · —).

deviations of the carboxyl and the heteroatom at the asymmetric centre from planarity.

These results unequivocally contradict the view that the two bands in the CD spectra of carboxylic acids and esters have their origin in the $n \rightarrow \pi^*$ transition arising from two rotamers with different chiroptical properties.

The shifting of band 2 up to 270 nm in mercaptopropionic acid derivatives, as observed by Scopes *et al.*,[10] seems not to lend support to the hypothesis that both bands correspond to transitions of the same nature.

What is then the genesis of these bands? This question is answered in part by the fact that band 2 in CD spectra of amino and N-hydroxyamino acid esters disappears in acidic media, i.e. on blocking of the lone pair on the nitrogen, and that its intensity depends on the nucleophilicity of the heteroatom attached to the asymmetric centre. It is also significant that band 2 is absent in α-alkyl[7] and α-trimethylammonium[9] acids, which have no substituent with an electron pair at C_α. One cannot accept Craig's[4] hypothesis according to which the origin of one band is the $n - \pi^*$ transition in the conformer D, and that of the other excitation in the carboxyl chromophore coupled with the non-bonding orbital of the heteroatom, because it is consistent with the presence of two bands in one and the same conformer, as pointed above.

It seems that band 2 can be assigned as an intramolecular charge transfer (CT) transition of an electron from a non-bonding orbital of the heteroatom attached to the asymmetric centre, to the anti-bonding π^* orbital of the carboxyl group. The planarity of these groups in the A or D conformers provides maximum overlapping of these orbitals.

However, band 1 is a $n - \pi^*$ carboxylate transition. This hypothesis is supported by the UV spectra of some amino acid derivatives, which in methanolic solution show two overlapping absorption bands at 208 nm and 220 nm (Fig 4).

The intensity of the longer wavelength absroption band increases from compound **2a** to **2c**, as the nucleophilicity of the group at the asymmetric centre increases, and vanishes in acidic medium. For this reason the 208 nm band must be attributed to the $n \rightarrow \pi^*$ carboxylate transition, and 220 nm band probably to a CT transition. This hypothesis is supported by the CT interaction in cyclic amino ketones observed by Leonard *et al.*[19] In the absorption spectra of these compounds, they observed a new strong absorption band at 230 nm, which they assigned as a CT excitation.[20] Recently several authors[21,22] observed a CT band in systems with carbonyl and amino groups which were even separated by two saturated C atoms.

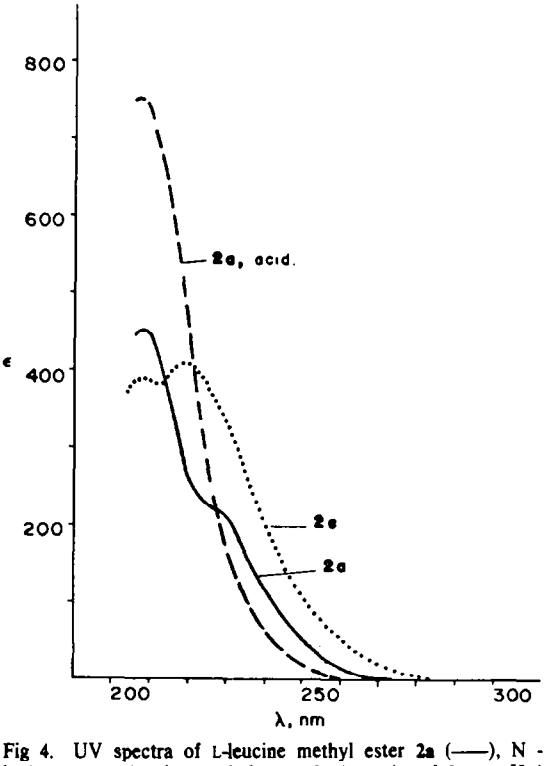


Fig 4. UV spectra of L-leucine methyl ester **2a** (——), N - hydroxy - L - leucine methyl ester **2c** (· · · · ·) and **2a** at pH 1 (– – – – –).

The position of the Cotton effect observed need not exactly correspond to the maximum absorption in the UV, as in the case of overlapping CD bands with opposite signs a CD curve is formed with more widely separated extrema.[23]

The chloro acid ester **8** differs from the remaining derivatives with the same side chain by a small intensity of band 1 and an opposite solvent effect. All this makes it similar to ester **9**. An explanation can here be offered by the latest findings from investigations of fluoroacetic acid by microwave spectra[24] suggesting the presence of a conformation equilibrium between the A and D forms of that acid. The population of the D conformation can increase owing to the high dipole moment of the carbon–halogen bond.

Band 1 in the CD spectra of carboxylic acids and their derivatives serves for assigning the configuration of these compounds. However, it seems a too far-reaching simplification to apply the octant rule to the $n \rightarrow \pi^*$ carboxyl chromophore transition corresponding to band 1[6,8] as in the case of ester **9** this would lead to predicting an opposite CD sign. Better results can be attained by using the Klyne sector rule[25] or the revised Snatzke sector rule.[26]

An important feature of the CD spectra is increase of band 1 in going from polar to non-polar solvents. This is particularly conspicuous in amino acid esters. In the latter case a certain influence is exerted by overlapping of the adjacent $n \rightarrow \sigma^*$ band. Nonetheless, band 1 increases also for the acyl derivative **6a** and for the α-hydroxy ester **5**, although less conspicuously. In contrast to acyclic esters, lactone **9** exhibits a lower intensity of band 1 in cyclohexane than it does in methanol. It appears that even small conformational changes may strongly influence the CD spectra of esters. This occurs when the substituents are situated near the nodal planes. (Fig 5). Changes in band intensity in the CD spectra of conformationally mobile systems in consequence of polarity changes of the solvent need not necessarily be caused by shifts in the conformation equilibrium shown in Fig 1. As a result of complex intramolecular interactions, the conformation of the most populated rotamer may undergo changes. In non-polar solvents, the unfavourable action of dipoles in the A structure may diminish owing to the increase of the angle between the $C_\alpha COO$ and CCX planes, giving the modified conformation A'. Application of the sector rule[25] to these two conformers allows us to suggest that the reason for the increase of band 1 is shifting of the heteroatom from the nodal plane to the lower left sector with positive contribution to the CD (Fig 5). In the case of compound **9**, the heteroatom shifts in polar solvents to the upper right sector, this causing increase of band 1.

In conclusion, the results of this study indicate that the two bands in the 200–250 nm range in the CD spectra of carboxylic acid derivatives are very probably associated with two different electronic transitions. These observations contradict the earlier hypothesis assigning both these bands to the $n \rightarrow \pi^*$ transitions of the carboxyl group in various conformers. It is apparent from the complex patterns shown above that great caution is necessary in applying chiroptical methods to the conformational analysis of carboxylic acids and their derivatives.

EXPERIMENTAL

CD measurements were performed at room temp on a Jasco model J-20 spectropolarimeter, the cell length was 10 mm, concentration was varied from 0·1 mg/ml to 4 mg/ml. UV spectra were recorded on a Specord UV–VIS spectrophotometer. Esters of amino acids have been freshly prepared from corresponding hydrochlorides. Esters of N-hydroxyamino acids have been obtained by method described elsewhere.[16]

*Methanesulfonyl-*L*-leucine* was obtained from L-leucine and methanesulfonyl chloride by standard Schotten–Baumann procedure with 76% yield, oil; NMR (δ, $CDCl_3$): 8·37 (1H, s, CO_2H), 5·73 (d, 1H, SO_2NH), 4·0 (m, 1H, $C_\alpha H$), 2·89 (s, 3H, CH_3SO_2), 2·0–1·2 (complex, 3H, $CHCH_2$), 0·87 (d, 6H, $(CH_3)_2CH$); dicyclohexylammonium salt: m.p. 193°, $[\alpha]_D^{20}$ −17·0° (*c*, 3, $CHCl_3$); (Found: C, 58·10; H, 9·68; N, 6·95; $C_{19}H_{38}N_2O_4S$ requires: C, 58·44; H, 9·81; N, 7·17%).

*Methanesulfonyl-*L*-leucine methyl ester* (**6a**). Methanesulfonyl-L-leucine was esterified by diazomethane. Compound **6a** was obtained in quantitative yield as an oil; $[\alpha]_D^{27}$ −31·9° (*c*, 4·9, $CHCl_3$); NMR (δ, $CDCl_3$): 5·2 (br, 1H, NH), 4·02 (t, 1H, $C_\alpha H$), 3·71 (s, 1H, CO_2CH_3), 2·88 (s, 3H, CH_3SO_2), 2·0–1·2 (complex, 3H, $CHCH_2$), 2·90 (d, 6H, $(CH_3)_2CH$); IR (in cyclohexane): 3230 br(NH), 1750(CO), 1210 and 1170(SO_2); (Found: N, 6·31; $C_8H_{17}NO_4S$ requires: N, 6·27%).

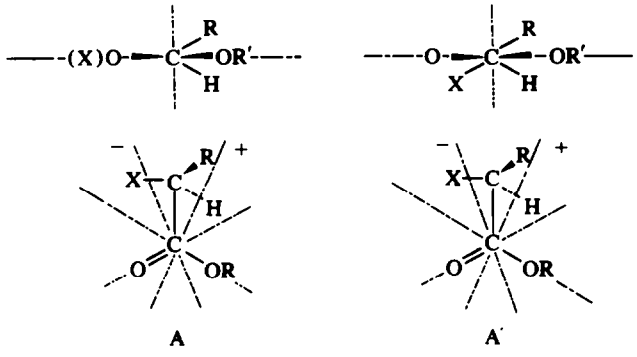


Fig 5. Application of the sector rule[25] to A and modified A' conformations of carboxylic acid derivatives. (a) View in the $XC_\alpha COO$ plane. (b) View from above the $XC_\alpha COO$ plane showing sectors contributing to the CD.

N - *methanesulfonyl* - 4 - *isobutyl* - 5 - *oxazolidinone* (L) (**9**) have been prepared according to the Ben-Ishai method.[27] A mixture of methanesulfonyl - L - leucine, (4·1 g; 0·02 mole) paraformaldehyde (3·0 g) and *p*-toluenesulfonic acid (0·2 g) in 200 ml benzene were refluxed for 2 h, the liberated water being trapped in Dean–Stark distilling receiver. The benzene soln was washed with $NaHCO_3$ aq and dried over Na_2SO_4. The benzene was evaporated and the residue crystallized from ether–light petroleum; yield, 3·0 g (71%); m.p. 49–50°; $[\alpha]_D^{27}$ +102·5° (*c*, 2, $CHCl_3$); NMR (δ, $CDCl_3$): 5·50 (d, J = 8 Hz, 1H) and 5·12 (d, J = 8 Hz, 1H, CO_2CH_2N), 4·13 (t, J = 7 Hz, 1H, $C_\alpha H$), 2·83 (s, 3H, CH_3), 2·1–1·2 (complex, 3H, $CHCH_2$), 0·92 (d, 6H, $(CH_3)_2CH$); IR (KBr): 1800 and 1780(CO), 1355, 1200, 1170; (Found: C, 43·13; H, 6·61; N, 6·38; $C_8H_{15}NO_4S$ requires: C, 43·44; H, 6·86; N, 6·33%).

Methyl L - α - *chloroisocapronate* (**8**). L - α - chloroisocaproic acid ($[\alpha]_D^{27}$ −24·4° (*c*, 5, MeOH), ref[4] $[\alpha]_D^{27}$ −18·3° (MeOH)) was esterified by diazomethane; b.p. 96–100°;[15] $[\alpha]_D^{27}$ −15·3° (neat, l = 0·5 dm); (Found: C, 50·81; H, 8·15; $C_7H_{13}O_2Cl$ requires: C, 51·00; H, 7·99%).

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