

CIRCULAR DICHROISM—LVII¹

CHIROPTICAL PROPERTIES OF SOME α -HALO-PROPIONANILIDES

G. SNATZKE

Organisch-Chemisches Institut der Universität Bonn, 53 Bonn (BRD)

and

M. M. EL-ABADELAH and M. Z. NAZER

Chemistry Department, University of Jordan, Amman, Jordan

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Abstract—The CD of the anilides of α -halo-propionic acids depends on solvent and substitution of the aromatic ring. Changes of the CD with solvent can be explained by taking into account three conformers (G, A⁺ and A⁻ of Fig 1). The CD band around 250 nm is negative for derivatives of the L-acids in all solvents except hydrocarbons in which it is positive. The ¹L_b band Cotton effects are very weak or not observed. The ¹L_a—CD band is much stronger in the *m*- and *o*-substituted anilides than in the *p*- or unsubstituted anilides.

The chiroptical properties of simple α -halo-propionic esters and amides were first investigated by Kuhn, *et al.*,² and recently by Gaffield and Galetto.³ A band at 237 nm in the UV and CD spectra of the bromo ester was originally² attributed to the bromine absorption, but in analogy to the spectra of α -bromo-ketones and α -hydroxy-acids is most probably the $n \rightarrow \pi^*$ band of that rotamer of the ester in which the halogen is anti-clinal to the C(=O) grouping.³ We have recently used a similar reasoning in explaining the CD spectra of some α -amino acid derivatives.⁴ This long-wavelength band shows a negative CD for the acids 1 and 2 with *S*-configuration.³ The CD band at shorter wavelengths is positive and is attributed to the conformation with syn-periplanar arrangement of the halogen with respect to the C(=O) group.^{3,4} We have used now the same center of chirality with the intention to induce optical activity in the absorption bands of acid anilides. The preparation of the compounds⁵ and the use of optically active α -phenylethylamine as NMR solvent to determine optical purity⁶ by Pirkle's method are described separately.⁷ As a result of the method of preparation, the *S*-chloro- and *S*-bromopropionanilides were not completely pure but contained up to about 5% of the *R*-enantiomers. We have not corrected our CD data and the real values may, therefore, be 2–5% larger. This however, does not influence our discussions.

Conformation of α -halo-propionanilides

As expected the amide grouping of acetamide is almost planar in the crystalline state⁸ and the same will be true in solution. The phenyl ring in anilides

is, however, not coplanar with the N–Ac moiety because of steric interaction between the O atom and the H in the *o*-position.⁸ The same should hold for the propionic acid derivatives. In solution the two possible rotamers (positive and negative torsion angle around the phenyl—N bond) will most probably have equal population even in the chiral compounds because of the large distance between the center of chirality and the phenyl ring. In all the following discussions of conformational equilibria we refer to the torsion angle around the single bond C(=O)—C(Hal).

For α -halo-ketones and α -halo-esters the syn-periplanar conformation (torsion angle between C(=O) and C(—Hal) equal to 0°, conformation E of Fig 1) is more stable in the solid and liquid state; the anticlinal conformation (torsion angle $\pm 120^\circ$, conformation A⁺ or A⁻ of Fig 1) is however, more stable in the gas phase.⁹ On the contrary the anti-periplanar conformation (“gauche”, conformation G of Fig 1) is very much preferred in case of α -halo-acid amides in the crystal and in solutions.⁹ In agreement with the examples in the literature⁹ $\nu_{C=O}$ of 4 is nearly independent of the solvent polarity (cyclohexane: 1696 cm⁻¹; acetonitrile: 1697 cm⁻¹; *d*₆-dimethylsulfoxide: 1693 cm⁻¹). The large shift to 1662 cm⁻¹ for KBr disks resembles again that of simpler model compounds⁹ and may e.g. be due to intermolecular hydrogen bridging (NH·····O=C) and not to drastic changes of conformation. Thus whereas for ketones and esters (Fig 1, R = Alk or OAlk) in solution A⁺, A⁻ and E will participate chiefly in the conformational equilibrium, rotamer G will be preponderate in case of halogenated amides (Fig 1, R = NR¹R²).

Increasing solvent polarity will shift the equilib-

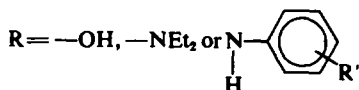
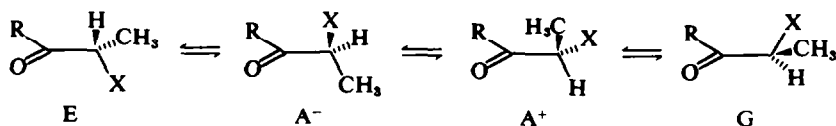


Fig. 1. The four preferred conformations of α -substituted propionic acids and their amides ($X =$ halogen).

rium $E \rightleftharpoons A \rightleftharpoons G$ from right to left and for steric reasons A^- will be preferred over A^+ . Dipole and steric interactions may favour a larger ratio $[G]/[A]$ in the chloro-amides compared to their bromo analogues, though classical treatment could not predict the greater preference of equatorial over axial conformation in α -chloro-cyclohexanones with respect to the α -bromo derivatives.¹⁰ Conformer E has the same relative geometry around the $C(=O)-C_\alpha$ bond as an equatorial α -halocyclohexanone, whilst A^- and A^+ resemble the axial counterpart. From this analogy one can infer, that $[E]/[A]$ is larger for $X = Cl$ than for $X = Br$ (Fig 1).

NMR data lead to the same result. According to the known anisotropy around the keto group,¹¹ which seems also to hold for amides,¹¹ we can expect increasing shielding for the C_α -methine proton in the series $\tau(E) = \tau(A^-) < \tau(G) < \tau(A^+)$, whereas for the C_β -Me protons holds $\tau(E) = \tau(A^+) < \tau(A^-) \approx \tau(G)$. If the differences of the chemical shifts by going from carbon tetrachloride ($\tau(\text{Me}) = 8.27$; $\tau(\text{H}) = 5.53$) to d_6 -DMSO ($\tau(\text{Me}) = 8.36$; $\tau(\text{H}) = 5.34$) are mainly due to a shift of the conformational equilibrium, then increasing of solvent polarity will effect either a change $G \rightarrow A^-$ or $A^+ \rightarrow A^-$. As A^+ and A^- will have very similar polarities, only the first possibility (i.e. $G \rightarrow A^-$) seems reasonable, in full agreement with the above conformational analysis.

UV spectra of α -halo-propionanilides (Table 1)

The UV spectrum of the acid **1** shows a weak band at 220 nm ($\epsilon = 85$, EtOH) to 215 nm (shoulder $\epsilon = 140$, isooctane) which is of $n \rightarrow \pi^*$ origin. In contrast, the corresponding N-diethylamide **3** gives rise to a stronger band at around 215 nm ($\epsilon = 5000$ to 5700), scarcely depending on the solvent, which must have allowed character and is most probably of $\pi \rightarrow \pi^*$ origin. A distinct $n \rightarrow \pi^*$ -band could not be observed in the UV spectrum of **3**.

The anilide **4** shows a strong absorption band at 247 ($\epsilon = 13,000$, EtOH) to 242 nm ($\epsilon = 14,000$, isooctane) which is usually ascribed to the conjugation between the aromatic ring and the N (charge transfer from the N lone pair to the phenyl ring π^* -

orbitals),¹² but may also be due (at least in part) to the red-shifted 1L_a band of the phenyl chromophore. One also observes inflections at about 280 nm in isooctane and to a smaller extent at about 283 nm in ethanol, indicative of the presence of the 1L_b band.¹² The small bathochromic shift observed for this as well as the intense band in ethanol solution compared with isooctane is in accord with their assignments as $\pi \rightarrow \pi^*$ transitions. Substitution of Cl by Br (**14**) leads to a redshift only for ethanol solution. A hypso- and hypochromic shift of the charge transfer band is observed for the N-methyl derivative **E-35**, which may be due to enhanced steric hindrance causing a large torsion angle around the N-phenyl bond and thus reducing $n \rightarrow \pi^*$ conjugation. As expected, an electron donating group in *p*-position (**5,6**) enhances the dipole strength and leads also to a bathochromic shift. *p*-Substitution by the ethoxycarbonyl grouping (**12**) results in augmented conjugation, a charge transfer band appears, therefore, at about 270 nm, and a new band is found around 205 nm. A nitro group at the same position (**13**) leads to an even larger bathochromic shift of the charge transfer band and there is nearly no difference between the spectra of the chloro (**13**) and bromo compound (**23**). Substitution by halogen in the *p*-position (**7-10**) gives a bathochromic and hyperchromic shift for the charge transfer band, and also here the 1L_b band is barely seen on its long-wavelength tail. As expected, *m*-substitution has only a minor influence.

CD spectra of α -halo-propionanilides (Table 1)

The ORD curve of D- α -bromopropionic acid N,N-dimethylamide was published by Kuhn and Braun.² From this they calculated that the absorption band at longer wavelengths ($n \rightarrow \pi^*$) should be positive, and that at shorter wavelengths (assumed as $\pi \rightarrow \pi^*$) weakly negative. We have now directly measured the CD of the corresponding L- α -chloro compound (**3**) as well as that of the anilides **4** to **E-36**. α -Chloropropionic acid (**1**) and its bromo analogue (**2**) give two bands in the CD,³ whose maxima do not coincide with those in the UV spectrum. This was explained³ in terms of the

presence of two conformers in solution, E and A⁻ (Fig 1), which are assumed to have positive and negative Cotton effects, resp. In analogy to the case of some α -amino acid derivatives whose CD we investigated recently,⁴ we believe on the contrary that both A⁺, and A⁻ are all present besides E. This can explain the CD curves even better. As already mentioned, in the anti-clinal conformations A⁺ and A⁻ the relative position of the halogen atom with respect to the C(=O) group is the same as in axial α -halo-ketones. In analogy to the latter we can thus assume that the first sphere is chiral in 13. In such a case the corresponding axial α -halo-ketone rule¹⁴ may be applied. This rule predicts a very strong negative CD for A⁻ and a similar positive one for A⁺. The experimental values of $\Delta\epsilon$ of approximately -0.5 to -1.0 indicate then a slight preponderance of A⁻ over A⁺ in the conformational equilibrium of 1 and 2. The sign of the short-wavelength band corresponding to conformer E cannot be predicted so simply, as this syn-periplanar arrangement is the same as that in equatorial α -halo-ketones, where only third-sphere atoms contribute to the Cotton effect. From experiments it follows that in case of the free acids 1 and 2 conformation E leads to a positive CD (as already assumed by Gaffield and Galetto³).

The situation for the N,N-diethylamide 3 is different. The (positive) CD maximum at shorter wavelengths corresponds exactly with the UV maximum and should, therefore, at least in part, be due to the $\pi \rightarrow \pi^*$ -transition of the amide grouping. The (negative) band at longer wavelengths may again correspond to the anti-clinal conformers A⁺ and A⁻ indicating, as in the case of 1 and 2, the slight preponderance of A⁻ over A⁺ in the conformational equilibrium. Conformer G will give an $n \rightarrow \pi^*$ CD band very similar to that of E.

As discussed earlier, at least for a transoid amide grouping, the torsion angle around the N-phenyl bond should be without great influence upon the CD, because there will be present as many molecules with positive as with negative torsion angles. Thus the contributions to the CD originating from this type of axial chirality should cancel each other. We may, therefore, describe this situation conveniently by using a model in which the phenyl ring is coplanar with the amide grouping.

The CD spectrum of the anilide 4 (Fig 2) shows two bands at around 240 and 210 nm. Inflexions around 270–280 nm indicate the presence of the ¹L_b band, but these are not distinctly separated from the 240 nm band, so that even their sign cannot be determined with certainty. The former two CD bands have the same sign (positive in isoctane, and negative in alcoholic solvents). Therefore, their positions will not be very much influenced by band overlap.¹⁵ Band position and solvent shift for the 240 nm band are the same as in the UV spectrum. This will lead us to ascribe this Cotton

effect as originating, mainly, from the conjugation band. A prediction of its sign cannot be made because of lack of rules. The band at shortest wavelengths (about 210 nm) coincides with a minimum in the UV spectrum and must, therefore, belong to a forbidden transition. The CD values for 2,2,2-trifluoroethanol solution are smaller than those for ethanol solution, a fact which can be seen for nearly all of the CD spectra measured.

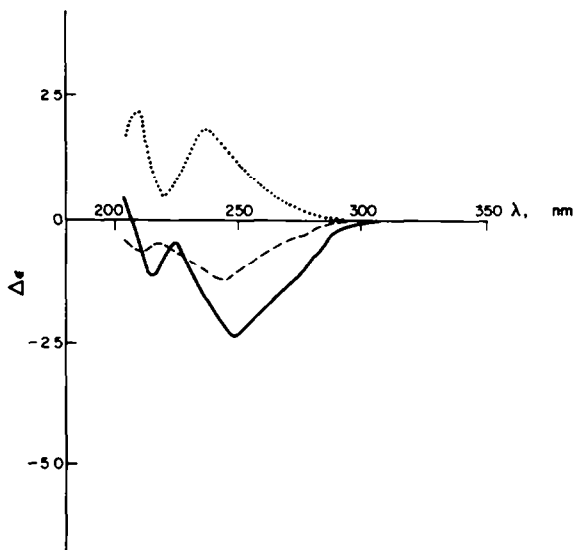


Fig 2. CD of L(-) α -chloropropionanilide (4) in ethanol (—), 2,2,2-trifluoro ethanol (-----), and isoctane (.....).

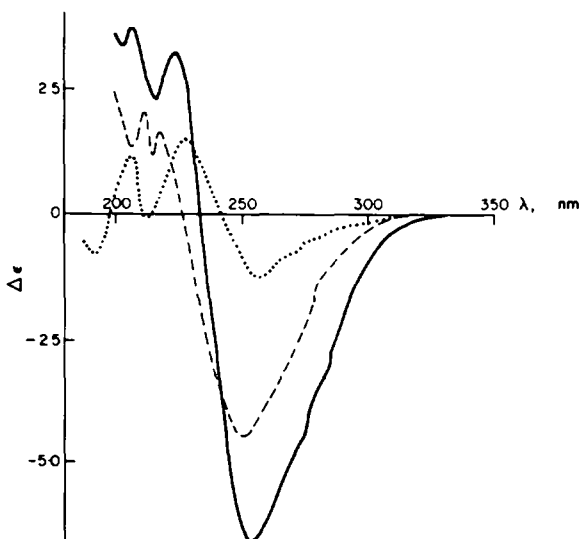


Fig 3. CD of L(-) α -bromopropionanilide (14) in ethanol (—), 2,2,2-trifluoro ethanol (-----), and isoctane (.....).

Table 1. CD and UV spectra of α -halopropionanilides and related compounds

Compound	Solvent ^a	λ_{\max} ($\Delta\epsilon$)	λ_{\max} (ϵ)
1	O	226(-0.56)	215(140), 208 sh(150)
	E	235(-0.44)	220(85), 206 sh(80)
	T	235(-0.36), 207(+0.45)	
	A	234(-0.61)	
2	O	237(-1.15)	257 sh(80), 226(370), 219 sh(355), 206(330)
	E	241(-1.03), 205(+0.24)	258 sh(95), 228(300), 220 sh(285), 208(275)
	T	238(-0.90), 203(+0.27)	
	A	241(-1.29), 203(+0.18)	
3	O	247(-1.06), 215(+2.73)	218 sh(4690), 214(4960)
	E	247(-0.23), 220 sh(+1.70), 215(+2.05)	221 sh(5090), 214(5760)
	T	243(-0.18), 226 sh(+0.89), 213(+2.19)	
	A	248(-0.28), 215(+1.41)	
4	O	237(+1.79), 210(+2.20)	280 sh(730), 270 sh(1650), 242(14000)
	E	282 sh(-0.59), 275 sh(-1.05), 247(-2.32), 215(-1.10)	283 sh(1910), 247(12890)
	T	278 sh(-0.24), 270 sh(-0.38), 243(-1.15), 210(-0.60)	
	O	240(+0.90), 210(+0.83)	285 sh(870), 275 sh(1730), 244(15140)
5	E	288 sh(-0.69), 275 sh(-1.38), 254(-2.48), 216(-0.50)	288 sh(1630), 252(11740), 203(17160)
	T	280 sh(-0.34), 270 sh(-0.61)	
	O	250(+0.77), 215(+0.78)	298 sh(1480), 286 sh(2470), 251(14930)
	E	300 sh(-0.66), 290 sh(-1.12), 258(-2.36), 222(+0.74), 210(-0.21)	298 sh(2090), 286 sh(5230), 257(13010)
6	T	285 sh(-0.33), 275 sh(-0.56), 253(-0.99)	
	A	290 sh(-0.61), 280 sh(-1.07), 258(-2.19), 221(+0.47), 215(-0.15)	
	O	283(+0.04), 240(+0.60), 214(-0.37)	287 sh(1060), 281 sh(1340), 239(12549)
	E	280 sh(-1.05), 246(-2.83), 210(-1.29)	287 sh(1220), 276 sh(2930), 246(11600)
7	T	277 sh(-0.26), 242(-1.10), 209(-0.55)	
	A	280 sh(-0.36), 245(-2.24), 210(-1.07)	
	O	244(+0.74)	290(490), 280 sh(1310), 248(17880)
	E	291 sh(-0.52), 282 sh(-0.96), 253(-2.73), 242 sh(-2.15), 214(-0.37)	291 sh(1250), 282 sh(3750), 253(16590)
8	T	278 sh(-0.46), 250(-1.26), 240 sh(-1.16)	
	A	282 sh(-0.89), 253(-2.61), 215(-0.34)	
	O	249(+0.70), 224(-0.30)	290 sh(680), 280 sh(1650), 251(19300)
	E	290 sh(-0.72), 280 sh(-1.53), 256(-2.95), 242 sh(-2.28), 215(-0.70)	291 sh(1590), 281 sh(4760), 256(17860)
9	T	278 sh(-0.37), 270 sh(-0.63), 253(-1.20), 215(-0.26)	
	A	290 sh(-0.40), 280 sh(-0.69), 255(-2.41), 215(-0.56)	

10	O	260(-2.77), 220(-0.39), 204(+4.82)	272 sh(8300), 254(22410), 199(25210)
	E	255(-1.15)	282 sh(7870), 259(20760), 204(20110)
	T		
11	O	283 sh(-2.47), 269(-2.84), 230(+0.42), 221(-1.17),	283 sh(3280), 277 sh(11090), 262(27110), 206(25040)
	E	205(+5.90)	282 sh(17190), 278 sh(20190), 269(24230), 208(18960)
	T	272 sh(-1.40), 261(-1.64), 217(-0.71)	
12	O	215(+0.86)	279 sh(15990), 268(24610), 258 sh(21550)
	E	295 sh(-1.60), 275(-2.78), 225(-0.83), 212(+2.53),	210(18080), 206 sh(19120)
	T	205(+4.57)	280 sh(22590), 273(23550), 209(15250)
13	O	290 sh(-0.83), 268 sh(-1.51), 221(-0.49), 208(+1.45)	
	E	270(-0.24), 250(-0.30), 220(+0.63)	317 sh(7580), 294(15980), 225 sh(11310), 219(12930),
	T		203 sh(14690)
	E	310(-1.02), 237(-1.49), 215(+0.08)	312(14970), 224(11060), 206 sh(11220)
	T	305(-0.54), 235(-0.84), 213(-0.40)	
14	O	258(-1.22), 227(+1.53)	280 sh(1630), 243(11780), 228 sh(7620)
	E	283 sh(-3.04), 275 sh(-4.14), 254(-6.56), 223(+3.24)	283 sh(4220), 278 sh(5470), 255(10910), 210 sh(15500)
	T	280 sh(-1.53), 250(-4.45), 217(+1.66)	
	A	285 sh(-2.12), 275 sh(-3.44), 253(-6.38), 223(+2.79)	
	M	283 sh(-2.87), 276 sh(-3.86), 254(-6.31), 222(+2.98)	
	D	286 sh(-2.13), 277 sh(-3.22), 255(-5.59), 223(+2.89)	
	C	257(-1.62), 227(+1.92)	
15	O	260(-1.07), 230(+1.39)	286 sh(1760), 276 sh(3350), 247(12460), 230 sh(7640)
	E	290 sh(-2.49), 282 sh(-3.38), 258(-5.46), 224(+3.38)	285 sh(5530), 258(11490)
	T	285 sh(-1.40), 276 sh(-2.20), 254(-3.64), 220(+1.64)	
16	O	265(-0.94), 232(+1.35)	297(1990), 271 sh(7030), 253(12020)
	E	300 sh(-2.42), 284(-3.43), 260(-4.71), 226(+4.81)	299 sh(4390), 262(11140), 225 sh(5110)
	T	290 sh(-1.52), 275 sh(-2.27), 255(-3.36), 222(+2.32)	
	A	300 sh(-1.87), 285 sh(-2.21), 280 sh(-3.04), 261(-4.91)	
		227(+4.33)	
17	O	257(-0.94), 225(+1.49)	287(1410), 281 sh(2040), 241(10300)
	E	286 sh(-1.50), 252(-4.99), 220(+2.85)	287 sh(2780), 252(10230)
	T	283 sh(-0.77), 247(-3.22), 217(+1.44)	
18	O	260(-1.04), 229(+1.41)	292 sh(3840), 282 sh(7420), 256(15930)
	E	291 sh(-1.82), 280 sh(-3.20), 257(-6.59), 225(+4.31)	290 sh(4720), 259(15250), 202(20690)
	T	199(+9.24)	
		254(-3.92), 221(+3.49)	

Table 1. (Contd).

Compound	Solvent ^a	λ_{\max} ($\Delta\epsilon$)	λ_{\max} (ϵ)
19	O	266(-0.78), 228(+1.16)	290 sh(1380), 280 sh(3320), 253(16820)
	E	293 sh(-1.90), 283 sh(-3.79), 260(-6.63), 224(+5.13) 202(+10.52)	261(15900)
	T	286 sh(-1.27), 275 sh(-2.44), 256(-4.02), 221(+2.34)	
	A	292 sh(-1.71), 282 sh(-3.19), 259(-6.50), 224(+4.22)	
20	O	266(-0.99), 232(+1.52), 198(-5.67)	293 sh(2200), 282 sh(5510), 257(20040)
	E	277 sh(-6.51), 264(-7.93), 229(+6.25), 208(+6.91)	276 sh(14990), 264(17940), 239 sh(6630)
	T	259(-5.09), 227(+3.11), 202(+4.56)	
21	O	282 sh(-0.94), 262(-1.57), 232(+1.18)	283 sh(6460), 278 sh(13320), 263(25330), 207(23800)
	E	286 sh(-6.27), 273(-8.27), 233(+4.80), 210(+8.42)	285 sh(19030), 280 sh(22200), 273(23730), 211(17500)
	T	265(-6.17), 229(+3.46), 202(+7.43)	
22	O	270(-1.21), 238(+1.09), 214(+1.40)	280 sh(17070), 268(23930), 216 sh(11690), 210(16560)
	E	276(-6.93), 235(+4.64), 213(+7.15)	282(22940), 213(13180)
	T	270(-4.88), 23(+2.58), 210(+4.44)	
23	O	295(-0.39), 273(-0.46), 215(-0.45)	230 sh(7010), 296(17230), 226 sh(11590), 220(12650), 205 sh(14030)
	E	335 sh(-1.41), 310(-2.23), 278(-1.52), 245(-1.35), 222(-2.40)	315(15600), 225(9930), 205 sh(12730)
	T	340 sh(-0.71), 305 sh(-1.60), 272 sh(-1.10), 240(-1.35), 220(+1.88)	
24	O	250(-2.13), 218(-3.40), positive at shorter wavelengths	282(790), 276 sh(1140), 243(13120), 204(27910)
	E	246(-0.70), 218(-0.70)	284 sh(2050), 276 sh(3720), 249(12240), 206(23020)
	T		
25	O		288(3500), 280(3430), 256 sh(7460), 244(11460), 213(26620)
	E	286 sh(-0.53), 253(-1.90), 219(-3.40)	289(4170), 282(4510), 250(11020), 215(22730)
	T	285 sh(-0.16), 248(-0.87), 215(-2.00)	
26	O	286(-0.62), 277(-0.96), 250(-2.40), 219(-5.30), positive at shorter wavelengths	286(970), 277(1220), 243(1430), 208(30750)
	E	246(-1.82), 218(-2.40)	287(1500), 279 sh(2600), 249(13810), 210(25900)
	T		
27	O	287(-0.56), 279(-0.93), 248(-2.35), 221(-5.35)	286(1010), 278(1260), 244(13720), 211(31680)
	E	250(-0.80), about 219(-1.00)	287(1430), 280 sh(2530), 249(13600), 212(27430)
	T		

28	O E T	247(-3.91), positive at shorter wavelengths 247(-2.20)	315(1500), 258 sh(9980), 236(25370) 322(1560), 244(21380), 201(9930)
29	O E T	258(-1.12), 230(+0.30) 287 sh(-2.43), 280 sh(-3.54), 255(-7.12), 226(-6.00) 201(+6.50) 275 sh(-1.86), 251(-4.80), around 220(-ve), 200(+8.30)	286(1470), 277 sh(2210), 246(12450), 211(30580) 288 sh(3170), 280 sh(5020), 254(12330), 212(22980)
30	O E T	252(-9.30), about 212(+7.60) 248(-7.35), 203(+6.00)	317(1540), 275 sh(3770), 260 sh(10930), 238(22450) 325(1480), 249(19160), 203(11960)
31	O E T A	242(+0.84), 217(-0.65) 283 sh(-0.12), 233(-2.35), 210(-3.50) 230(-1.02) 238(-1.47)	280(720), 270 sh(2050), 243(11530) 283 sh(470), 241 sh(5780), 233(6300)
32	O E T A	285 sh(-0.02), 275 sh(+0.10), 240(+1.15) 285 sh(-0.11), 275 sh(-0.15), 240(-2.05), 216(-3.90) 242(-1.05) 245(-1.20), 217(-2.30)	285(840), 278 sh(1120), 246(14520) 284 sh(660), 277 sh(1330), 244(9280)
33	O E T A	257(-0.30), 230(+0.86) 275 sh(-0.60), 265 sh(-1.15), 244(-2.75), 220(+0.23) 200(+3.36) 240(-1.93) 270(-1.05), 245(-2.40), 220(+0.25)	281 sh(1570), 273 sh(2870), 245(9980) 243 sh(5620), 238(5790)
34	O E T	256(-0.90), 231(+1.16) 248(-3.46), 220(-2.11), 201(+10.87) 247(-2.05), 219(-0.54)	283(1620), 276 sh(2670), 247(12490), 205(27320) 286 sh(1430), 278 sh(2550), 247(8130), 202(23350)
35	O E T	270 sh(-1.10), 240(-4.39) 263 sh(-0.68), 235(-3.95), 205(-2.67) 260 sh(-0.48), 230(-4.26)	230(6320), 205 sh(15300) 227(7930)
36	O E T	275(+4.18), 250(-7.72), 215(-8.95) 275(+2.46), 242(+4.32), 215(-5.10) 275(+1.24), 260 sh(+0.43), 235(-0.56) 215(-2.28), 205(-4.42)	284 sh(2010), 264 sh(6020), 245(11040), 233 sh(8030) 270 sh(3370), 260 sh(4790), 235(10660) 264(3310), 225(11830)

^aAbbreviations used: A: acetonitrile, E: ethanol, C: cyclohexane, D: dioxane, M: methanol, O: isooctane, T: 2,2,2-trifluoroethanol.

If this assignment is correct, then *p*-substitution in the aniline ring would be expected to produce in both the UV and CD spectra similar shifts for the 240 nm band. This is indeed the case and supports thus our assumption.

The bromo analogue **14** shows similar band positions in the UV and CD spectra (Fig 3) to those for the chloro compound **4**. There is, however, a characteristic difference between these two cases. The two CD bands for **14** have opposite signs, which show no inversion in going from isoctane or cyclohexane to ethanol or other polar solvents, though the long wavelength band acquires very large rotational strength in the latter solvents. The small hypsochromic shift observed for **14** by this mentioned change of solvents leads us to conclude that the strong negative CD band around 250 nm comes mainly from the $n \rightarrow \pi^*$ transition of conformer A^- , and that the contribution of the conjugation band to the CD is relatively small. To the 225 nm CD band contribute most probably both the 1L_a band of the benzene ring and the $n \rightarrow \pi^*$ -band of the amide chromophore of conformer G .

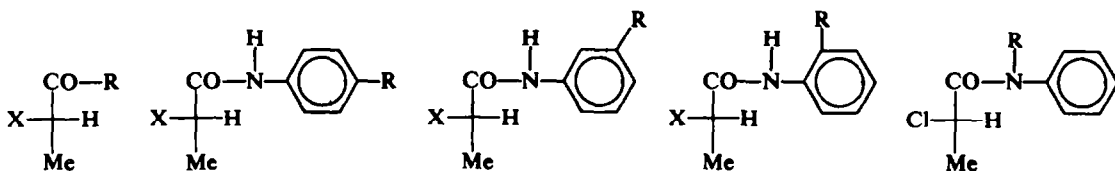
The changes of the CD with the change of solvents are in full agreement with the conformational analysis given above. Increasing the solvent polarity strongly increases the magnitude of the negative Cotton effect as expected from a shift of the equilibrium $G \rightarrow A^-$. The magnitude of this change of rotational strength is very similar for the chloro analogue **4**, though the CD is positive in non-polar

solvents and negative only in polar ones. This difference in absolute values of $\Delta\epsilon_{\max}$ can be explained either by a larger ratio $[G]/[A^-]$ for **4** than for **14**, or by a stronger contribution of the conjugation band Cotton effect in case of **4**. Signs, magnitudes and changes of $\Delta\epsilon_{\max}$ with solvents are thus reasonably explained by the assumption of such an equilibrium between G , A^- and A^+ .

This general behaviour of **4** and **14** is found also for all the *p*-substituted derivatives; by such a substitution the conformational equilibrium should not be effected. Only for the ethoxycarbonyl (**12**, **22**) and nitro (**13**, **23**) derivatives additional bands appear in the CD spectra because of strong conjugation with the acylamino grouping. Substitution by Me at the N atom changes considerably the conformational equilibrium as already seen from the UV spectrum and we no longer observe the sign inversion in case of the α -chloro compound **E-35** by going from isoctane to ethanol as solvent.

The CD of the *N,N*-diphenyl derivative **E-36** cannot be directly compared with the others, because of strong steric hindrance and presence of two like chromophores which even may interact with each other.

m-Substitution (**24-30**) causes no steric effect and thus should not influence the conformational equilibrium. Indeed, the 250 nm CD band is very similar to that in the *p*-substituted analogues (Fig 4). The CD band at around 220 nm is, however, much more negative than in the *p*-isomers. Also in this



X	R	X	R	X	R	X	R	R
1	Cl OH	4	Cl H	24	Cl Me	31	Cl Me	E-35 Me
2	Br OH	5	Cl Me	25	Cl OMe	32	Cl Cl	E-36 Ph
3	Cl NEt ₂	6	Cl OMe	26	Cl Cl	33	Br Me	
		7	Cl F	27	Cl Br	34	Br Cl	
		8	Cl Cl	28	Cl NO ₂			
		9	Cl Br	29	Br Br			
		10	Cl I	30	Br NO ₂			
		11	Cl CN					
		12	Cl CO ₂ Et					
		13	Cl NO ₂					
		14	Br H					
		15	Br Me					
		16	Br OMe					
		17	Br F					
		18	Br Cl					
		19	Br Br					
		20	Br I					
		21	Br CN					
		22	Br CO ₂ Et					
		23	Br NO ₂					

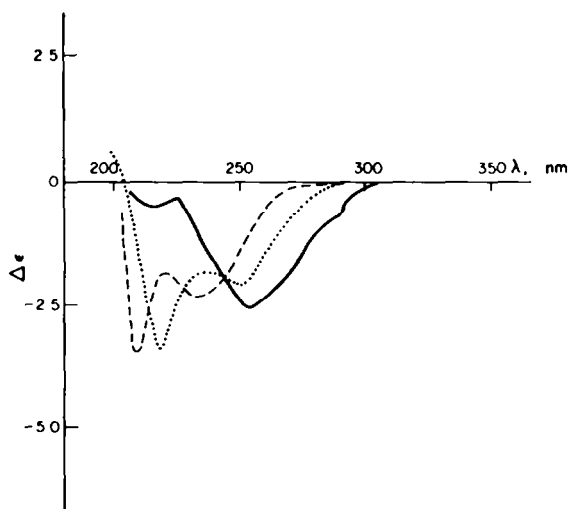


Fig 4. CD of L(-)-*p*-methyl- α -chloropropionanilide (5) (—), L(-)-*m*-methyl- α -chloropropionanilide (24) (.....), and L(-)-*o*-methyl- α -chloropropionanilide (31) (-----) in ethanol.

series the Cotton effects are smaller in trifluoroethanol solution (at least those at longer wavelengths) than in ethanol solution.

o-Substitution (31–34), on the other hand, introduces some steric hindrance. This is seen e.g. from the blue-shift of the CD bands around 240–250 nm as compared to the bands in the *p*-substituted analogues (Fig 4). In addition, the second CD band at shorter wavelengths (around 217 nm in EtOH solution) is more negative (less positive for 33). The sign inversion of the 240–250 nm CD band is also observed in this series by going from cyclohexane to ethanol as solvent, and $\Delta\epsilon_{\max}$ -values are smaller in trifluoroethanol than in ethanol solution. Apparently, trifluoroethanol behaves as if it were less polar than ethanol.

Our original hope to get more information on the applicability of our modified rules¹⁶ for the benzene chromophore could thus not be realized in this study because the CD within the 1L_b band is too small to be seen with certainty. Nevertheless, the other CD bands vary characteristically with solvent and substitution. In all solvents but hydrocarbons the CD band around 250 nm is negative for the anilides of the L- α -halo-propionic acids studied so far. This is even true for the nitro compounds, though the origin of the band must not necessarily be the same.

EXPERIMENTAL

All CD spectra were taken with a Roussel-Jouan dichrograph model 185 in cells of 0.01 to 2.00 cm path lengths at +20°. Concentrations were about 0.1–1.0 mg/ml. UV spectra were recorded with a Cary-14 spectrometer in cells of 0.1 cm path length.

Spectral data other than those mentioned in Table 1, and elemental analysis for all new compounds used in this study are consistent with the assigned structures, and are presented in a separate paper.⁵

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