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Circular Dichroism of 3–(Phenoxy)butyric Acid Derivatives

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Chiroptical properties of the title compounds have been studied. Utilization of **(S)–1** for the determination of the absolute configuration of the centre of chirality of these carboxylic acids and related compounds is discussed as well.

INTRODUCTION

We have recently been engaged in the synthesis and spectroscopic studies of optically active 2,3–dihydro–2–methyl–1,5–benzoxazepin–4(5H)–ones.[1–5] In the course of these investigations, an efficient procedure has been developed for the preparation of such optically active benzoxazepines *via* the synthesis and ring closure of optically active 3–(2–aminophenoxy)butyric acids.[3] Furthermore, optically active carboxylic acid intermediates have been utilized not only for synthetic purposes but also for the determination of the optical purity and the absolute configuration of the centre chirality.[2,3] To our knowledge, chiroptical properties of these substances and similar 3–(phenoxy)butyric acids have not been described yet. For this reason, in our present paper, circular dichroism studies of 3–(phenoxy)butyric acid derivatives are reported.

RESULTS AND DISCUSSION

For determination of the absolute configuration of the centre of chirality of carboxylic acid derivatives under investigation, theoretically various procedures are avail-

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able. Since our efforts to produce appropriate crystals necessary for the X-ray analysis were unsuccessful, the determination was carried out by means of a so-called »chiral pool« synthesis. 3(*R*)–Hydroxybutyric acid was allowed to react with 2–nitrofluorobenzene to afford 3(*R*)–(2–nitrophenoxy)butyric acid ((***R***)–**2**) by retention, which could then be used as reference substance for the determination of the absolute configuration of all related compounds.[3]

Synthesis and circular dichroism of the analogous 3(*S*)–(phenylthio)butyric acid methyl ester have been described in our previous papers.[6,7] Its absolute configuration has unambiguously been deduced from X-ray and chiroptical data corroborated by chemical proofs. This compound may be utilized as reference substance for 3–(phenoxy)butyric acid derivatives as well since an ethereal oxygen and a thioether moiety are not considerably different perturbers of the aromatic chromophore. Indeed, both the 3(*S*)–(phenylthio)butyric acid methyl ester[6] and compound **(S)–1** possess positive CD maxima of comparable rotatory strength between 280 and 260 nm (Figure 1) and this similar

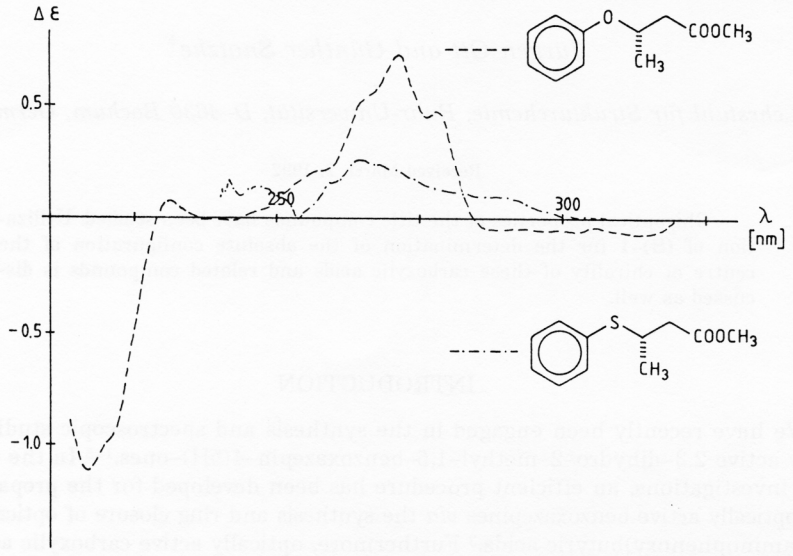

Figure 1. Circular dichroism spectra of **(S)–1** and of the 3–(phenylthio)butyric acid methyl ester.

character of their partial CD spectra can be used as a convenient simple method for the determination of the absolute configuration of such compounds. However, the substituents of the aromatic moiety of these carboxylic acids may considerably influence their chiroptical properties and this should be taken into consideration. Some examples are shown in the following.

Compounds **(R)–2** – **(R)–4** and **(S)–5** possess an *ortho*–nitrophenoxy moiety and, as known for similar substances,[7] the nitro group is nearly coplanar with the benzene ring. Since both the nitro as well as the phenoxy groups are very strong perturbers of the benzene π-systems,[8] it seems difficult to associate individual CD bands to localized transitions and one can, therefore, discuss the CD spectra in a qualitative way. In the

UV spectra, the band belonging to the longest wavelength is between 320 and 340 nm (Table I). A negative Cotton effect for the *R*-configuration (**(R)–2** – **(R)–4** and a positive one for the *S*-configuration were measured in this region (Table II). Methyl ester formation resulted in a distinct bathochromic shift of this CD band without a change of the sign and without considerable alteration in the magnitude. Another intense

TABLE I

UV spectroscopic data of the compounds studied

Compound	R^1	R^2	R^3	λ[nm] (ε)
(S) –1	CH_3	H	H	195 (37870), 223 (7300), 268 (1010), 273 (1290), 280 (1060)
(S)–2 } **(R)–2**	H	NO_2	H	193 (29290), 194 (28520), 216 (13710), 260 (2930), 327 (2060)
(S)–3 } **(R)–3**	CH_3	NO_2	H	193 (30930), 216 (13760), 261 (2870), 325 (2030)
(S)–4	H	NO_2	CH3	194 (27100), 220 (14240), 240 (4410), 264 (2530), 338 (1930)
(S)–5	CH_3	NO_2	CH_3	219 (15180), 264 (2920), 338 (2130)
(S)–6	C_2H_5	$NHCOCH_3$	H	210 (28680), 246 (13330), 284 (3300), 291 (2650)
(R)–4	H	NO_2	COOH	200 (17820), 241 (18240), 320 (1790)
(R)–5	CH_3	NH_2	H	207 (35670), 242 (8310), 292 (3300)
(R)–6	CH_3	$NHCOCH_3$	H	210 (29690), 245 (13530), 284 (3400), 291 (2720)

TABLE II

Circular dichroism data of the compounds studied

Compound	λ [nm] (Δε)
(S)–1	216 (–1,12), 231 (+0.07), 266 (+0.55), 271 (+0.69), 278 (+0.56)
(S)–2	187 (+3.75), 216 (–1.43), 257 (–0.18), 327 (+0.45)
(S)–3	189 (+4.76), 216 (–2.16), 333 (+0.54)
(S)–4	220 (–2.13), 259 (–0.18), 347 (+0.43)
(S)–5	193 (+1.72), 219 (–2.71), 348 (+0.51)
(S)–6	204 (+1.11), 215 (–1.88), 246 (+1.91), 276 (+0.37)
(R)–2	219 (+1.69). 255 (+0.14), 260 (+0.18), 323 (–0.46), 335 (–0.44)
(R)–3	192 (–5.89), 218 (+2.26), 333 (–0.56)
(R)–4	240 (+2.26), 316 (–0.39)
(R)–5	243 (–2.61), 284 (–0.25), 292 (–0.26)
(R)–6	202 (–2.73), 216 (+2.00), 240 (–1.82), 248 (–1.69), 274 (–0.40)

positive CD band for *R*-compounds is at approx. 220 nm and a negative one for *S*-enantiomers in the same region. The entire spectra of the enantiomers are almost enantiomorphous as expected.

Aminocarboxylic acid methyl ester **(R)–5** gave two relatively weak and an intense negative CD bands (Table II). *N*-Acetylation of **(R)–5** to **(R)–6** resulted in a considerable hypsochromic shift of all bands and the appearance of a new intense positive CD band at 216 nm. CD spectrum of compounds **(S)–6** is almost enantiomorphous in comparison with that of the **(R)–6** with three positive and one negative Cotton effects (Table II). Since both amino and acetamino groups are strong π-system perturbers and the chromophores of substances **(R)–5**, **(R)–6**, and **(S)–6** are complicated, a detailed discussion of the CD spectra awaits further investigations.

(S)-**1**-(S)-**6** (R)-**2**-(R)-**6**

Scheme

EXPERIMENTAL

Synthesis of all the compounds studied, except for **(S)–1**, **(R)–5**, and **(R)–6**, has been described earlier by us.[1-3] UV spectra were measured with a Philips PU 8740 apparatus in CH_3CN solution at room temperature. Circular dichroism (CD) spectra were taken with a Jasco 600 instrument in CH_3CN solutions (concentrations were approx. 0.5 ml/liter for both UV and CD measurements) at room temperature. ^{1}H-NMR spectra were recorded on Bruker WP-80 and AM-400 instruments in $CDCl_3$ solution (internal standard TMS, σ 0.0 ppm) at room temperature. Infrared spectra were measured on a Perkin-Elmer 1310 spectrometer for KBr discs. Mass spectra were obtained on a Varian MAT CH-5 instrument at 70 eV. Optical rotation was measured on a Perkin-Elmer 141 apparatus.

3(S)–(Phenoxy)butyric Acid Methyl Ester ((S)–1)

To a mixture of 3(*S*)–(2–aminophenoxy)butyric acid (1.0 mmol), 4M HCl (7.0 ml), and 50% H_3PO_2 (10.0 ml) $NaNO_2$ 1.0 mmol dissolved in water (1.0 ml was added at 0 °C. The reaction mixture was stirred at room temperature for further 2.5 hours and then extracted with CH_2Cl_2. The organic phase was washed with water, dried with $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was dissolved in anhydrous methanol (12.0 ml), some drops of concentrated H_2SO_4 were added and the mixture refluxed for 2 hours. The solvent was then evaporated and the residue triturated with CH_2Cl_2. The solution was dried with $MgSO_4$ and the solvent evaporated to afford 0.025 g (13%) of colorless oil. $[\alpha]_D^{20} = +26$ (c = 0.65, $CHCl_3$). IR : 3020, 1735, 1600, 1490, 1230 cm^{-1}. ^{1}H-NMR: 1.35 (d, 3H), 2.53 (dd, 1H), 2.80 (dd, 1H) 3.67 (s, 3H), 4.81 (m, 1H), 6.90–7.25 (m, 5 aromat.). MS (*m/z*, % relat. int.): 194 (16, M^+), 163(3), 121(14), 101(12), 94(100), 77(10), 51(6), 50(29).

3(R)–(2–Aminophenoxy)butyric Acid Methyl Ester ((R)–5)

Compound **(R)–3** (1.0 mmol) dissolved in methanol (20 ml) was allowed to react with hydrogen in the presence of 10% Pd/C (0.05 g) until the end of hydrogen consumption. The catalyst was then filtered off and the solvent was evaporated under reduced pressure to obtain

0.17 g (90%) of colorless oil. $[\alpha]_D^{20}$ = –47 (c = 1.4, $CHCl_3$): IR: 3460, 3380, 1610, 1500, 1230 cm^{-1}. ^1H–NMR: 1.35 (d, 3H), 2.56 (dd, 1H), 2.81 (dd, 1H), 3.68 (s, 3H), 3.80 (brs, NH_2), 4.75 (m, 1H), 6.67–6.82 (m, 4 aromat.). MS (*m/z*, % relat. int.): 209 (17, $M^{+\cdot}$), 178(2), 109(100), 69(12), 41(8).

*3(R)–(2–Acetaminophenoxy)butyric Acid Methyl Ester ((**R**)–**6**)*

A mixture of compound **(R)–5** (0.11 g), acetic anhydride (1.0 ml), and anhydrous CH_2Cl_2 (10 ml) was left to stand overnight at room temperature. The solution was washed with $NaHCO_3$ solution, then with water, dried with $MgSO_4$, and the solvent was evaporated to yield 0.11 g (83%), *mp.* 67 - 68 °C, solid material. $[\alpha]_D^{20}$ = –36 (c = 0.72, $CHCl_3$). IR: 3290, 1745, 1655, 1595, 1535 cm^{-1}. ^1H-NMR: 1.34 (d, 3H), 2.21 (s, 3H), 2.69 (m, 2H), 3.69 (s, 3H), 4.66 (m, 1H), 6.90 – 8.38 (m, 4 aromat.). MS (*m/z*, % relt. int.): 251 (20, $M^{+\cdot}$), 209(2), 178(2), 151(6), 109(100), 69(9), 59(18), 43(12).

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SAŽETAK

Cirkularni dikroizam derivata 3–(fenoksi)butan–kiseline

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Istraživana su kiroptička svojstva naslovnih spojeva i upotrebljivost spoja **S–1** za određivanje apsolutne konfiguracije kiralnog centra tih karboksilnih kiselina i srodnih spojeva.