# Enantiomers of Benzothiadiazine Diuretics by Direct Chromatographic Resolution of the Racemic Drugs[1]

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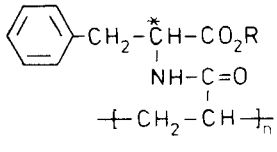
**Abstract** □ A number of racemic benzothiadiazine diuretics and two carbonyl analogue drugs were resolved into their optical isomers by liquid chromatography on chiral polyacrylamides **1**. Enantiomeric resolution, which was, in some cases, almost complete, depended considerably on the substitution of the heterocyclic moiety of the drug molecules. Synthesis of the new adsorbent **Ib** is described. The enantiomers of the benzothiadiazines penflutizide (**2a**) and bendroflumethiazide (**2b**) in high optical purity, as well as enriched (+)-buthiazide (**2j**) were obtained by repeated chromatography on a semipreparative scale. Chiroptical data, optical purity employing the chromatographic method, and first-order racemization kinetics as a function of pH in aqueous solutions were determined.

The optical isomers of chiral drugs often display differences in their pharmacological activities. In the case of diuretic agents, remarkable enantiospecificity in renal effects have been reported for the thiazide-like mefruside,[2] the antihypertensive loop-blocking etozolin[3] and the new high-ceiling diuretic indacrinone.[4] The enantiomers of benzothiadiazines have not previously been determined, although the racemates have been widely used for many years in hypertension therapy. Liquid chromatography on optically active, cross-linked polyacrylamide and methacrylamide stationary phases has proved to be an efficient method for the resolution of a number of racemic drugs.[5] For example, the enantiomers of the diuretic chlorthalidone, which are easily racemized under the influence of acids and bases, have been prepared by chromatography on polyacrylamide **1a**.[6] For chlorthalidone and for the benzothiadiazines, each lacking suitable functional groups, conventional resolving methods via diastereoisomeric salts or derivatives failed.

We now report the optical resolution of a number of benzothiadiazines and two structurally related tetrahydroquinazolinone diuretics, the general structures of which are shown in Tables I and II, respectively, on polyacrylamide **1a** and **1b**. Furthermore, the semipreparative isolation of the optical isomers of penflutizide (**2a**), bendroflumethiazide (**2b**), and buthiazide (**2j**) by chromatography on **1a** is described.



1a : R = $C_2H_5$

b : R = $CH_2$- 

## Results and Discussion

**Chromatographic Resolution**—Analytical chromatography of the racemic thiazides **2a–n** on **1a** revealed at least partial, in some cases an almost complete, optical resolution (Table I). The best results were obtained for penflutizide (**2a**) and bendroflumethiazide (**2b**) both of which possess a trifluoromethyl group at C-6. Figure 1 illustrates the chromatogram of **2a**.

The enantiomeric yields (%) and the retention times depend on the substituents on the heterocyclic ring especially at the chiral center and the cyclic sulfonamide nitrogen atom. Hydrogen bonding between the $SO_2NH$ group adjacent to the chiral center and the stationary phase has a great influence on chiral recognition. Thus, epithizide (**2k**) was well resolved to give $\alpha = 1.12$, whereas *N*-methylated **2l** was eluted faster, exhibiting only one UV peak in the chromatogram. A similar effect of *N*-methylation is observed for **2m** and **2n**. It must, however, be considered that both compounds differ in their substituents at the chiral center, and that this might have an influence, too, on the chromatographic behavior of **2m** and **2n**. Generally, no detailed configuration of the molecular interaction between the optical isomers and the optically active polyacrylamides can be derived from these results in order to explain enantiomeric resolution.

Bemetizide (**2g/h**) exists in four stereoisomeric forms due to the second chiral center in the side chain. A complete separation was obtained for the two diastereoisomers which were, in addition, partially resolved into the enantiomers (Fig. 2). The ratio of diastereoisomers **2g** and **2h** (~5:1) was in good agreement with unpublished data.[7] This may be attributed to asymmetric induction due to the configuration of the 2-phenylpropionaldehyde during ring closure and/or during epimerization of the chiral center of the thiazide moiety. Further details on this subject are under investigation.

Interestingly, the fluorobenzyl isomers, **2e** and **2f**, displayed rather different chromatographic behavior. This was the reason for the detection and subsequent identification of the *ortho* isomer **2f** as an impurity in paraflutizide (**2d**) and its dosage form.[8] Compound **2d** and the *meta* derivative **2e** both were, similar to **2k**, extremely well retained ($k' > 10$ on adsorbent **1a**). However, **2f** was not well retained, indicating that a fluoro atom at a certain distance from the chiral center is involved in supplementary hydrogen bonding. The tetrahydroquinazolinones, **3a** and **3b**, were only weakly resolved (Table II). For **3a**, this result may be explained by the substitution of the lactam nitrogen near the chiral center and would be in good agreement with the resolution data obtained for the benzothiadiazines **2k** and **2l**, and **2m** and **2n**, respectively.

In order to examine the influence of varying the polymer side-chain ester group on resolution behavior, the polyacrylamide **1b** was synthesized in the same way as **1a** by radical polymerization of the amino acid ester monomer with an (*S*)-configuration. Compound **1b** showed chiral recognition to a different extent from that exhibited by **1a** (Table I). A better enantiomeric separation compared with **1a** was achieved for **2k**, which was almost completely resolved, and for **2i** and **2j** both of which have bulky aliphatic side chains. Capacity factors of all racemates were much smaller on **1b** than on **1a**.

**Preparation of the Enantiomers**—The optical isomers of penflutizide (**2a**) and bendroflumethiazide (**2b**) were separated on a semipreparative scale, using adsorbent **1a**, by repeated chromatography of enriched dextro- and levorotatory enantiomer samples. These were obtained by resolution of 200–



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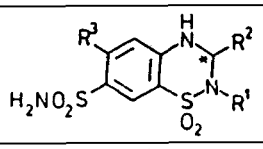
**Table I—Chromatographic Resolution of Racemic Benzothiadiazine Diuretics on Polyacrylamides 1a and 1b[a]**



| Compound | $R^1$ | $R^2$ | $R^3$ | Adsorbent **1a** $k_1'$[b] | Adsorbent **1a** $k_2'$[b] | Adsorbent **1a** Rotation | Adsorbent **1a** Enantiomeric Yield, %[d] | Adsorbent **1b** $k_1'$ | Adsorbent **1b** $k_2'$ | Adsorbent **1b** Rotation | Adsorbent **1b** Enantiomeric Yield, %[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **2a** | H | $CH_2(CH_2)_4CH_3$ | $CF_3$ | 3.41 | 3.98 | (−) | 75 | 1.23 | 1.60 | (−) | 70 |
| | | | | 0.73[e] | | (−) | 18 | | | | |
| **2b** | H | $CH_2C_6H_5$ | $CF_3$ | 5.54 | 6.31 | (−) | 71 | 1.90 | 2.11 | (−) | 39 |
| **2c** | H | $CH_2C_6H_5$ | Cl | 6.60 | 7.07 | (−) | 41 | 2.86 | | (−) | 20 |
| **2d** | H | $CH_2C_6H_4F$ (*para*) | Cl | 12.10 | 12.90 | (−) | 60 | 4.64 | 5.03 | (−) | 30 |
| **2e** | H | $CH_2C_6H_4F$ (*meta*) | Cl | 10.20 | 11.30 | (−) | 52 | | | | |
| **2f** | H | $CH_2C_6H_4F$ (*ortho*) | Cl | 5.89 | 6.23 | (−) | 34 | 2.27 | 2.47 | (−) | 33 |
| | | | | 2.82 | 3.15 | (−) | 55 | 1.30 | 1.54 | (−) | 51 |
| **2g/h**[f] | H | $CHCH_3C_6H_5$ | Cl | | | | | | | | |
| | | | | 5.10 | 5.55 | (−) | 38 | 2.32 | | (−) | 15–25[g] |
| **2i** | H | $CH_2c\text{-}C_5H_9$ | Cl | 5.23 | 5.56 | (−) | 39 | 2.24 | 2.60 | (−) | 62 |
| **2j** | H | $CH_2CH(CH_3)_2$ | Cl | 5.45 | 5.83 | (−) | 38 | 2.22 | 2.56 | (−) | 55 |
| **2k** | H | $CH_2SCH_2CF_3$ | Cl | 9.14 | 10.20 | (−) | 64 | 3.48 | 4.23 | (−) | 84 |
| **2l** | $CH_3$ | $CH_2SCH_2CF_3$ | Cl | 4.70 | | (+) | 26 | 1.85 | | (+) | 9 |
| **2m** | H | $CHCl_2$ | Cl | 6.29 | | (+) | 21 | 2.38 | | (+) | 10 |
| **2n** | $CH_3$ | $CH_2Cl$ | Cl | 5.22 | | (+) | 9 | 2.20 | | (+) | 6 |

[a] Toluene:dioxane (1:1) as eluant. [b] Capacity factors $k_1'$ and $k_2'$ were calculated by using the standard term [(retention volume of the less retained ($V_1$), respectively more retained ($V_2$) compound − void volume $V_0$ of column)/void volume $V_0$ of column]. The values of $V_1$ and $V_2$ were derived from the peak maximums of the UV curves. Thus, calculated $k_1'$ and $k_2'$ data differ from the exact $k'$ values of both enantiomers in the cases of strong peak overlapping. Note that enantiomeric resolution may have occurred (see enantiomeric yield, %) even if only one $k'$ value could be determined from a single maximum in the UV curve because of small differences in the retention times of both optical isomers. [c] Rotation of the enantiomer more retained. [d] See *Experimental Section* for enantiomeric yield. [e] Operating conditions: column, 1.0 × 42.0 cm; void volume, $V_0$ = 29.5 mL; toluene:dioxane:methanol (47:47:6) as eluant. [f] Diastereoisomeric ratio of **2g/h**, ~5:1, calculated from the areas under the UV curves. [g] Estimated value.

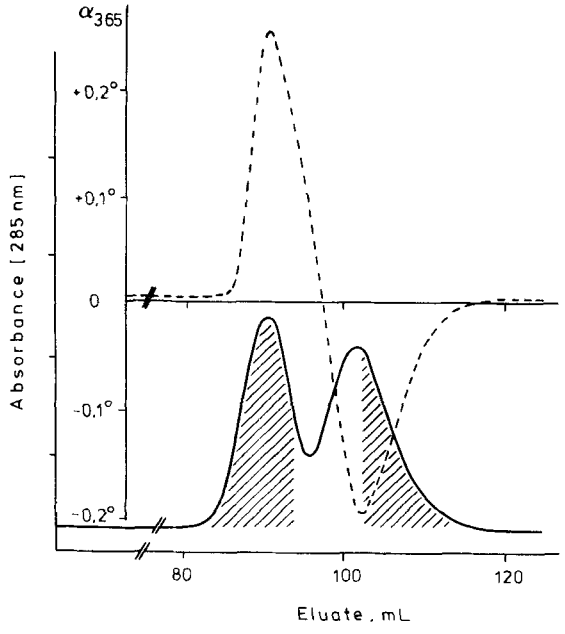



**Figure 1**—*Chromatography of 5.0 mg of (±)-penflutizide (**2a**) on a column (1.0 × 29.5 cm) packed with 5.0 g of adsorbent **1a**; toluene:dioxane (1:1) as eluant. The hatched areas under the UV curve (———) with corresponding rotation values (- - - -) are equivalent to the amounts of the (+)- and (−)-isomer being eluted in the optically pure form.*

250 mg of the racemate at a time in several runs from the first and last eluate fractions. The amorphous enantiomers could not be crystallized. The chiroptical data are listed in Table III.

The optical purity of **2a** and **2b** was determined by using an analytical column packed with **1a** and injecting 5-mg samples of the enantiomers. The resulting chromatograms revealed only one symmetric peak in the UV and rotation value curves, respectively. Addition of 3% racemate to the enantiomers, in each case, could clearly be detected in spite of the expected

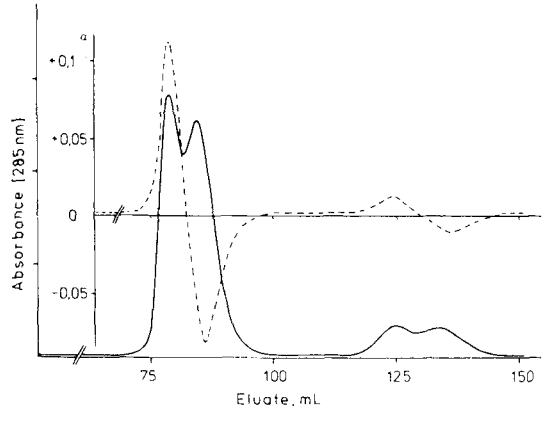
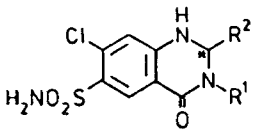



**Figure 2**—*Chromatography of 5.0 mg of bemetizide (ratio of the diastereoisomers **2g** and **2h** is ~5:1) on 5.0 g of **1a**; toluene:dioxane (1:1) as eluant.*

Table II—Resolution of Racemic Tetrahydroquinazolinone Diuretics on 1a[a]



| Compound | $R^1$ | $R^2$ | k'[b] | Rotation[c] | Enantiomeric Yield, %[d] |
|---|---|---|---|---|---|
| **3a** | $CH_3$ | *ortho*-$CH_3C_6H_4$ | 2.87 | (−) | 16 |
| **3b** | H | $CH_2CH_3$ | 8.13 | (+) | 12 |

[a,b,c,d] See Table I.

peak overlapping (see Fig. 1). Determination of the enantiomeric excess of (+)-**2j** was performed by the chromatographic method of Mannschreck et al.[9] using **1b** as adsorbent. Thus, $[\alpha]_D^{20} = +120 \pm 3°$ (ethanol) is calculated for optically pure (+)-**2j**.

**Racemization Kinetics**—For the benzothiadiazine enantiomers, no configurational change at the chiral center was observed in organic solvents at room temperature, but the compounds racemize in aqueous solutions as a function of pH. The decrease of the rotation value of the enantiomers dissolved in ethanol–buffer mixtures followed first-order kinetics. Figure 3 shows, for example, the linear ln $|\alpha_{obs}|$ versus time plot obtained for (+)-bendroflumethiazide (**2b**) at pH 7.4 and 37°C, from which a half-life of $t_{0.5} = 2.3$ h is determined. Compounds **2a**, **2b**, and **2j** showed minimum racemization under acid conditions, the reaction rates tentatively corresponding to the electron-donating effect of the side chain at the chiral center (Fig. 4). The benzyl group of **2b** with an electron-withdrawing effect leads to a markedly slower racemization compared with the aliphatic pentyl group of **2a** and, to a still larger extent, compared with the isobutyl substituent of **2j**. At a lower temperature, 22°C, $t_{0.5} = 35.6$ and 15.4 h were recorded for **2b** at pH 5.0 and 7.4, respectively. In alkaline solutions, $t_{0.5}$ values of each compound ranged between only a few minutes and did not differ significantly. According to the literature,[10] **2b** undergoes hydrolysis, 50% of the compound being decomposed within 1 h at pH 12.0 and 50°C. This indicates that racemization of enantiomeric **2b** occurs more rapidly in alkali compared with hydrolysis of the thiadiazine moiety. The racemization rate profiles of the drugs were also different from those of hydrolytic reactions of benzothiadiazines which have been reported[11] to show reversible kinetic rates depending on pH, and for which a multistep mechanism has been postulated.

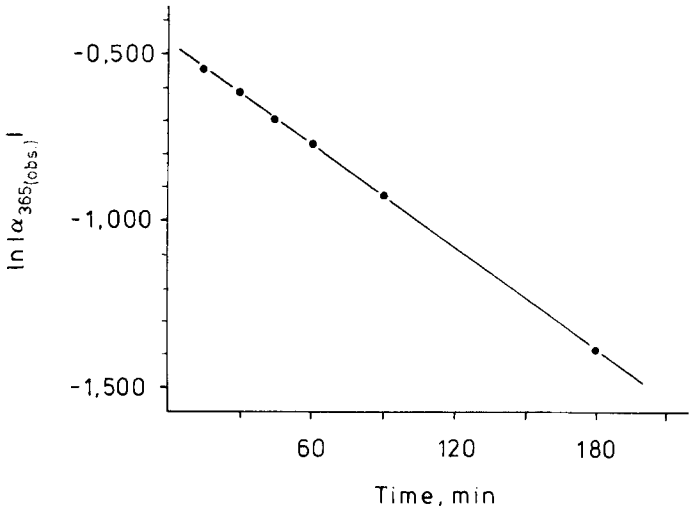



**Figure 3**—*Racemization kinetics of (+)-bendroflumethiazide (**2b**). The decreasing rotation value, α, at 365 nm (path length 10 cm) of the solution of 2.45 mg of (+)-enriched **2b** in 2.0 mL of ethanol:aqueous buffer mixture, pH 7.4, was recorded at 37°C. The correlation coefficient of the regression line was* k = −1.00.

## Experimental Section

**Apparatus**—IR spectra were determined on a Perkin-Elmer 457 spectrometer. Electron-impact MS data (70 eV) were recorded on a Varian MAT 44 S. $^1H$ NMR spectra were recorded on a Bruker Physik WM 300 spectrometer ($Me_4Si$ as internal standard). CD spectra were determined with a Jobin Yvon Dicrographe III (path length 0.1 cm) at the Institute of Organic Chemistry, University of Bonn, F.R.G. TLC was carried out using silica gel 60 $F_{254}$ HPTLC plates (Merck) with the solvent methyl ethyl ketone:*n*-hexane (2:1). Melting points are corrected.

**Materials**—The following drugs were used as supplied: penflutizide (**2a**) (Nordmark GmbH, Uetersen/Holstein, F.R.G.), bendroflumethiazide (**2b**) (Boehringer Ingelheim GmbH, Ingelheim/Rhein, F.R.G.), benzylhydrochlorothiazide (**2c**) (Giulini Pharma GmbH, Hannover, F.R.G.), paraflutizide (**2d**) (Karlspharma GmbH, Kirchheim/München, F.R.G.), bemetizide (**2g/h**) (Sanol Schwarz GmbH, Monheim, F.R.G.), cyclopenthiazide (**2i**) (Ciba Geigy GmbH, Wehr/Baden, F.R.G.), buthiazide (**2j**) (Boehringer Mannheim GmbH, F.R.G.), epithizide (**2k**) (Pfizer Inc., CT), polythiazide (**2l**) (Pfizer GmbH, Karlsruhe, F.R.G.), trichlormethiazide (**2m**) (E. Merck, Darmstadt, F.R.G.), methychlothiazide (**2n**) (Abbott Laboratories Ltd., Queenborough, U.K.), metolazone (**3a**) (G. D. Searle GmbH, München, F.R.G.), and quinethazone (**3b**) (Cyanamid-Lederle GmbH, Wolfratshausen, F.R.G.). The *meta*- and *ortho*-fluoro isomers of paraflutizide, **2e** and **2f**, were synthesized.[8] Solvents for chromatography were purified by distillation, all other chemicals were reagent grade quality.

**Chromatographic Methods**—Resolutions were performed on a low-pressure liquid chromatographic system.[6] The eluate was passed through the flow cell of a UV detector (Knauer model 8700 UV-VIS spectrometer) operating at 285 nm and

Table III—Chiroptical Data of the Diuretics Penflutizide (2a), Bendroflumethiazide (2b), and Buthiazide (2j)

| Compound | $[\alpha]_D^{20}$, deg·cm²·g⁻¹ | c[a] | Optical Purity, %[b] | $\Delta\varepsilon(\lambda_{max})$, 1·cm⁻¹·mol⁻¹[c] | c, mmol·10⁻³ |
|---|---|---|---|---|---|
| **2a** | −133.5 | 0.19 | >97 | −5.07(266), −3.81(277) −2.87(328) | 1.34 |
| | +134.0 | 0.19 | | +4.80(268), +3.34(280) +2.91(328) | 1.51 |
| **2b** | −105.3 | 0.19 | >97 | −3.32(266), −3.04(272) −2.07(328) | 0.72 |
| | +106.2 | 0.31 | | +3.24(267), +2.83(275) +2.16(329) | 1.20 |
| **2j** | +100.0 | 0.17 | 66 ± 2 | | |

[a] Concentration (g/100 mL) in absolute ethanol. [b] See text for determination. [c] CD spectra in methanol at 22°C.

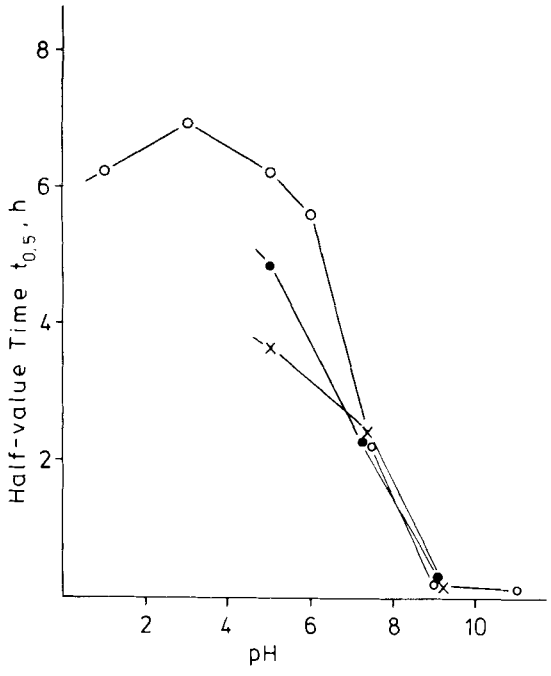



**Figure 4**—*Racemization rates ($t_{0.5}$) versus pH profiles of penflutizide (**2a**) (●), bendroflumethiazide (**2b**) (○), and buthiazide (**2j**) (×) in ethanol:aqueous buffer mixtures at 37°C.*

the 80-μL micro flow cell of a polarimeter (Perkin-Elmer model 241), and collected in volume fractions (Multi Rac 2111, LKB). For analytical chromatography, 5.0 g of **1a**[12] prepared by a slightly modified method[13] (volume of the stationary phase: 1.0 × 29.5 cm; void volume: $V_0$ = 20.5 mL) and 5.1 g of **1b** (1.0 × 31.0 cm; $V_0$ = 21.0 mL), each suspended in the eluant, were packed into glass columns (Pharmacia GmbH, F.R.G.). The racemates (5.0 mg) dissolved in 0.5–2.0 mL of the eluant were injected and eluted at room temperature. The flow rate was 10–15 mL/h with a pressure of 2.5–3.0 bar.

For chromatography on a semipreparative scale, a glass column with Teflon adapters packed with 235 g of **1a** (3.8 × 78.5 cm) was used [toluene:dioxane (1:1) as eluant; flow rate 50 mL/h; 3.0 bar].

**Enantiomeric Yield**—The percentage value is equivalent to the total amount of the dextro- and levorotatory enantiomers which can be isolated theoretically in optically pure form by a single chromatographic run (see Fig. 1), i.e., a 100% value corresponds to a complete separation. The values were calculated by cutting out and weighing the corresponding areas under the UV curves of the chromatograms. These areas can be derived from the rotation value ($\alpha$) versus concentration ($C$) diagrams[9] in which the volume range of eluate containing the pure enantiomers is indicated by a linear relationship between $\alpha$ and the concentration.

**Poly-[(*S*)-*N*-(benzyloxycarbonyl-2-phenylethyl)acrylamide] (1b)**—To a suspension of 9.0 g (31 mmol) of (*S*)-phenylalanine benzyl ester·HCl[14] in 120 mL of chloroform (cooled to 0°C), 4.9 g (54 mmol) of acryloyl chloride (stabilized with 1% pyrocatechol) was added in a dropwise manner with stirring. The mixture was kept at pH 8–9 by the addition of a saturated solution of sodium carbonate and was then stirred for 1 h at 0–5°C. Purification of the product was achieved as described[12] with benzene as eluant. Recrystallization from benzene:petroleum ether gave the *N*-acryloyl-(*S*)-phenylalanine benzyl ether (74% yield) as colorless needles, mp 93°C; $[\alpha]_D^{20}$ +50.6° (*c* 0.5, benzene); IR (KBr): 3300 (NH), 1725 (ester), 1650, 1615, 1525, 1495, and 1215 $cm^{-1}$ (ester); $^1H$ NMR ($CDCl_3$): δ 3.14 (dd, 1, $J$ = 5.3, 14.4 Hz, $CH_aH_bCH$), 3.19 (dd, 1, $J$ = 5.8, 14.4 Hz, $CH_aH_bCH$), 5.01 (m, 1, CH), 5.13 (d, 1, $J$ = 12.1 Hz, $COCH_aH_b$), 5.17 (d, 1, $J$ = 12.1 Hz, $COCH_aH_b$), 5.66 (dd, 1, $J$ = 1.5, 10.2 Hz, $CH_c{=}CH_aH_b$), 6.06 (br s, 1, NH), 6.07 (dd, 1, $J$ = 10.2, 17.0 Hz, $CH_c{=}CH_aH_b$), 6.29 (dd, 1, $J$ = 1.5, 17.0 Hz, $CH_c{=}CH_aH_b$), and 7.0–7.4 ppm (m, 10, ArH). MS: $m/z$ 238 (4%), 120 (27%), 91 (100%), 77 (18%), and 55 (97%). MS (chemical ionization with isobutane as reactant gas): $m/z$ 310 (100%, $[M + 1]^+$).

**Anal.—Calc.** for $C_{19}H_{19}NO_3$: C, 73.76; H, 6.19; N, 4.53. Found: C, 73.84; H, 6.17; N, 4.42.

This monomer (5.57 g, 18.0 mmol), dissolved in 9.2 g of benzene and 0.31 g (1.8 mmol) of 1,2-ethane diacrylate, was polymerized[12] to give 5.48 g (93% yield) of **1b**. IR (KBr): 1730 (C=O, ester) and 1670 $cm^{-1}$ (C=O, amide).

**Anal.—Calc.** for $(C_{19}H_{19}NO_3 + 0.1\ C_8H_{10}O_4)_n$: N, 4.29. Found: N, 4.26.

**(+)- and (−)-Penflutizide (2a)**—Chromatography of 210 mg of **2a** (mp 197–199°C) resulted in a partial resolution [retention volume of (+)- and (−)-**2a**: 3800 and 4300 mL, respectively; separation factor $\alpha$ = 1.15]. Then, 79 mg of (+)- and 73 mg of (−)-**2a** (optical purity ~85%) were obtained from the first and the last fractions of the eluate, respectively. Resolution of totally 753 mg of the racemate was repeated three times. Enriched (+)-**2a** (246 mg) from the overall first fractions and enriched (−)-**2a** (223 mg) from the last fractions were chromatographed again to give the enantiomers as colorless oils. The oils were precipitated from a concentrated solution in absolute ether by addition of an excess of absolute diisopropyl ether, separated, and washed with petroleum ether (30–40°C) to give amorphous (+)-**2a** (127 mg), mp 194–197°C, and amorphous (−)-**2a** (104 mg), mp 168–170°C. Chemical purity of the isomers was proved by TLC ($R_f$ 0.71). The $^1H$ NMR and MS spectra each were identical with that of the racemate; $^1H$ NMR (acetone-$d_6$): δ 0.91 (t, 3, $J$ = 6.8 Hz, $CH_3$), 1.2–1.7 [m, 6, $CH_3(CH_2)_3$], 1.97 (m, 2, $CH_2CH$), 5.03 (m, 1, CH), 6.67–6.71 (s, d, 3, NH), 7.38 (s, 1, NH), 7.39 (s, 1, H-5), and 8.32 ppm (s, 1, H-8); MS: $m/z$ 401 (4%, $[M]^+$), 330 (100%), 255 (23%), 239 (29%), and 200 (20%).

**Anal.**—Calc. for $C_{13}H_{18}F_3N_3O_4S_2$: C, 38.90; H, 4.52; N, 10.31. Found for (+)-**2a**: C, 38.62; H, 4.62; N, 10.28. Found for (−)-**2a**: C, 38.48; H, 4.48; N, 10.31.

**(+)- and (−)-Bendroflumethiazide (2b)**—As described above, repeated chromatography [retention volume of (+)- and (−)-**2b**: 5200 and 5700 mL, respectively; $\alpha$ = 1.12] of a total amount of 1270 g of racemate (mp 210°C), and precipitation of the enantiomers from ethanol by addition of petroleum ether yielded amorphous (+)-**2b** (141 mg), mp 174–178°C, and amorphous (−)-**2b** (104 mg), mp 175–178°C. The chemical purity of the isomers was shown by TLC ($R_f$ 0.67). $^1H$ NMR (acetone-$d_6$): δ 3.3 (m, 2, $CH_2$), 4.30 (m, 1, CH), 6.74 (s, 2, NH), 6.87 (d, 1, $J$ = 11.9 Hz, NH), 7.3–7.5 (m, 6, ArH, NH), 7.42 (s, 1, H-5), and 8.31 ppm (s, 1, H-8); MS: $m/z$ 421 (5% $[M]^+$), 333 (100%), 319 (17%), 302 (27%), 255 (20%), 239 (18%), and 220 (62%).

**Anal.**—Calc. for $C_{15}H_{14}F_3N_3O_4S_2$: C, 42.75; H, 3.55; N, 9.97. Found for (+)-**2b**: C, 42.41; H, 3.54; N, 9.23. Found for (−)-**2b**: C, 42.52; H, 3.52; N, 9.25.

**(+)-Buthiazide (2j)**—Resolution of 253 mg of **2j** gave 53 mg of optically enriched (+)-**2j** (mp 185–190°C) from the first fractions of the eluate. The chemical purity was proved by TLC ($R_f$ 0.56). $^1H$ NMR (acetone-$d_6$): δ 0.99 (d, 3, $J$ = 6.5 Hz, $CH_3$), 1.00 (d, 3, $J$ = 6.5 Hz, $CH_3$), 1.7–2.0 [m, 3, $(CH_3)_2CHCH_2$], 5.03 (m, 1, CH), 6.62 (d, 1, $J$ = 12.2 Hz, NH), 6.70 (s, 2, NH), 7.04 (s, 1, H-5), 7.10 (s, 1, NH), and 8.16 ppm (s, 1, H-8). MS: $m/z$ 353 (5%, $[M]^+$), 296 (100%), 221 (23%), and 205 (28%).

**Anal.**—Calc. for $C_{11}H_{16}ClN_3O_4S_2$: C, 37.34; H, 4.56; N, 11.89. Found: C, 37.93; H, 4.73; N, 11.77.

**Kinetics Methods**—To determine the racemization rates of the enantiomers, the aqueous buffer solutions hydrochloric acid (pH 1.0), citrate (pH 3.0 and 5.0), phosphate (pH 6.0 and 7.4), borate (pH 9.0), and carbonate (pH 11.0) were used. Reaction solutions were prepared by adding a solution of 2.0–

3.0 mg of the enantiomer in 1.0 mL of ethanol to 2.0 mL of buffer. The rotation value $\alpha$ of the solution at a constant temperature was measured at intervals. The first-order rate constants and half-life, $t_{0.5}$, of racemization were calculated from the regression lines of ln $|\alpha_{obs.}|$ versus time plots.

## References and Notes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