Synthesis and Antiulcer Activity of Optical Isomers of 2-(4-Chlorobenzoylamino)-3-[2(1*H*)-quinolinon-4-yl]propionic Acid (Rebamipide)[1)]

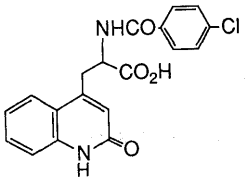
Kenji OTSUBO, Seiji MORITA, Minoru UCHIDA,* Katsuya YAMASAKI, Toshimi KANBE and Takefumi SHIMIZU

Tokushima Research Institute, Otsuka Pharmaceutical Co., Ltd., Kagasuno 463–10, Kawauchi-cho, Tokushima 771–01, Japan. *Received April 1, 1991*

The enantiomers of 2-(4-chlorobenzoylamino)-3-[2(1*H*)-quinolinon-4-yl]propionic acid [(±)-1, rebamipide, OPC-12759], a new antiulcer agent that enhances mucosal resistance, were synthesized from optically active α-amino acid derivatives of 2(1*H*)-quinolinone. The key intermediates, α-amino acid derivatives, were prepared by asymmetric synthesis and optical resolution. The (+)-1 was about 1.7 times as potent as the (−)-isomer in antiulcer activity against ethanol-induced gastric ulcers.

Keywords rebamipide; OPC-12759; asymmetric synthesis; optical resolution; α-amino acid derivative; 2(1*H*)-quinolinone; enantiomer; antiulcer agent; antiulcer activity

The amino acid derivative 2-(4-chlorobenzoylamino)-3-[2(1*H*)-quinolinon-4-yl]propionic acid [(±)-**1**, rebamipide, OPC-12759][2)] (Chart 1) is a new antiulcer agent that enhances mucosal resistance. This compound has an asymmetric carbon at the 2-position of the amino acid moiety and therefore has two enantiomers. The pharmacological and pharmacokinetic properties of these isomers pose an interesting problem. We have already reported the synthesis of optically active rebamipide by optical resolution with (−)-brucine.[3)] In order to investigate the efficient synthesis and the pharmacological properties of both enantiomers, optically active rebamipide was synthesized from α-amino acid derivatives of 2(1*H*)-quinolinone obtained by "Shöllkopf's method."[4)] The key intermediates, optically active α-amino acid derivatives also were prepared by optical resolution using D-(−)-mandelic acid. We describe here the synthesis and antiulcer activity of the optical isomers of rebamipide.



1 (OPC-12759)

Chart 1

Synthesis The intermediates, α-amino acid derivatives of 2(1*H*)-quinolinone [(−)-**8** and (+)-**8**], were prepared as shown in Charts 2 and 3. Reaction of 4-bromomethyl-2(1*H*)-quinolinone[2)] with phosphoryl chloride gave 4-bromomethyl- and 4-chloromethyl-2-chloroquinolines (**3** and **4**). 2,5-Dihydro-3,6-dimethoxy-2(*S*)-isopropylpyrazine [(*S*)-**5**][4)] was treated with *n*-butyllithium in tetrahydrofuran (THF) at −78 °C to give a lithio derivative which was alkylated with halides (**3** and **4**) to afford the alkylation product [(−)-**6**] in good yields and acceptable diastereoselectivity. The high diastereoselectivity presumably arose from the preferential addition of an electrophile (**3** and **4**) at the C′-5 trans to the isopropyl group at the residential chiral center C′-2 of (*S*)-**5**. Hydrolysis of compound [(−)-**6**] (with 0.25 N hydrochloric acid) gave the methyl ester [(−)-**7**], which was hydrolyzed with 6 N hydrochloric

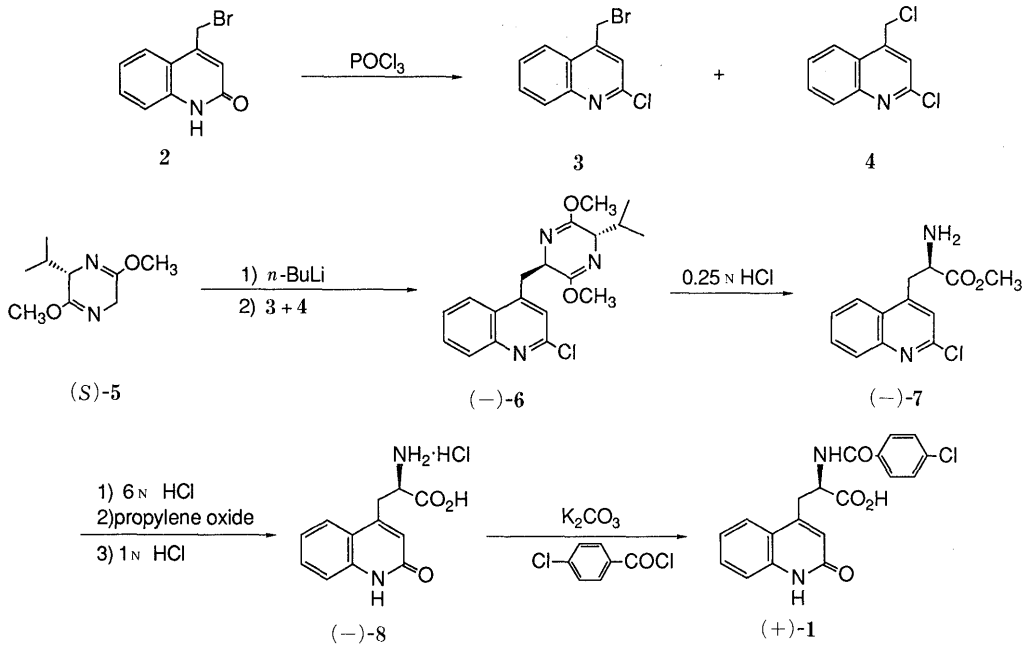


Chart 2

acid to give 2-amino-3-[2(1*H*)-quinolinon-4-yl]propionic acid [(−)-**8**]. The target compound [(+)-**1**] was prepared from (−)-**8** and *p*-chlorobenzoyl chloride using the Shotten–Baumann reaction.

The opposite isomer [(−)-**1**] was obtained similarly from 2,5-dihydro-3,6-dimethoxy-2(*R*)-isopropylpyrazine [(*R*)-**5**], *via* (+)-**6**, which was hydrolyzed with hydrochloric acid. The resulting amino acid [(+)-**8**] was acylated with *p*-chlorobenzoyl chloride to give the desired amide [(−)-**1**]. The optical purities of (+)-**1** and (−)-**1** were determined to be up to 99.5% ee by high-performance liquid chromatography (HPLC) using a chiral stationary phase column.

The key intermediates, (−)-**8** and (+)-**8**, also were synthesized as follows. Esterification of an amino acid derivative (**8**) with methanol–thionyl chloride gave the methyl ester (**9**), which was resoluted with D-(−)-mandelic acid to give **10a** and **10b**. After allowing a mixture of the methyl ester (**9**) and D-(−)-mandelic acid to stir in EtOH, a white crystalline solid was deposited. Recrystallization twice from EtOH gave the salt (**10a**). Another salt (**10b**) was recrystallized from MeOH. Hydrolysis of these isomers with hydrochloric acid gave optically active amino acid derivatives [(−)-**8** and (+)-**8**] (Chart 4). The optical purities of (−)-**8** and (+)-**8** appeared to be 99.5 and 98.4% ee, respectively, as determined by HPLC using a chiral stationary phase column.

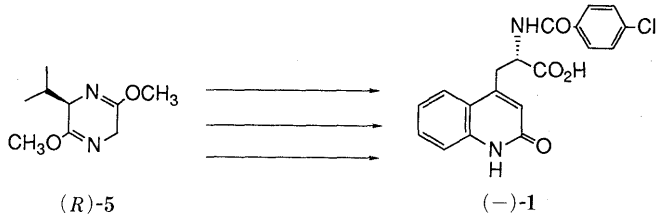
Consequently, we have been able to obtain optically active rebamipide by using three efficient methods. The first method was optical resolution of rebamipide with (−)-brucine. This method required recrystallization many times to obtain a pure enantiomer (98% ee). Next, asymmetric synthesis of the amino acids *via* metalated bis-lactim ethers of 2,5-diketopiperazines provided yields in an essentially optically pure form. However, this method, which uses expensive starting material, is not considered practical for accessing a relatively large amount of product. Finally, optical resolution of the amino acid derivatives was the most convenient method of obtaining the optical isomers of rebamipide.

Antiulcer Activity The antiulcer activities of (+)-, (−)- and (±)-**1** against acetic acid-induced gastric ulcers were reported in the previous paper.[3] Both enantiomers were again evaluated for antiulcer activity using the sensitive method. It was suggested that the mucosal protective effect[5] of rebamipide presumably results from enhancement of the generation of endogenous prostaglandins. Therefore, EtOH-induced gastric ulcers, which have reference to endogenous prostaglandins,[6] were investigated. (+)-, (−)- and (±)-**1** (10—100 mg/kg i.p.) dose-dependently inhibited the formation of gastric lesions induced by absolute EtOH. The ED_{50} values were 17.2, 32.7 and 26.4 mg/kg, respectively (Table I). From these results, it was speculated

Table I. Effect of (−)-, (+)- and (±)-OPC-12759 against Absolute Ethanol-Induced Gastric Necrosis

Drug	Dose mg/kg i.p.	*n*	% inhibition
(−)-OPC-12759	10	10	14.0
	30	10	41.9[a]
	100	10	88.6[a]
(+)-OPC-12759	10	10	19.5
	30	10	80.7[a]
	100	10	100.0[a]
(±)-OPC-12759	10	10	−2.8
	30	10	70.1[a]
	100	10	94.7[a]

a) $p<0.05$ *vs.* control.



(*R*)-5 (−)-1

Chart 3

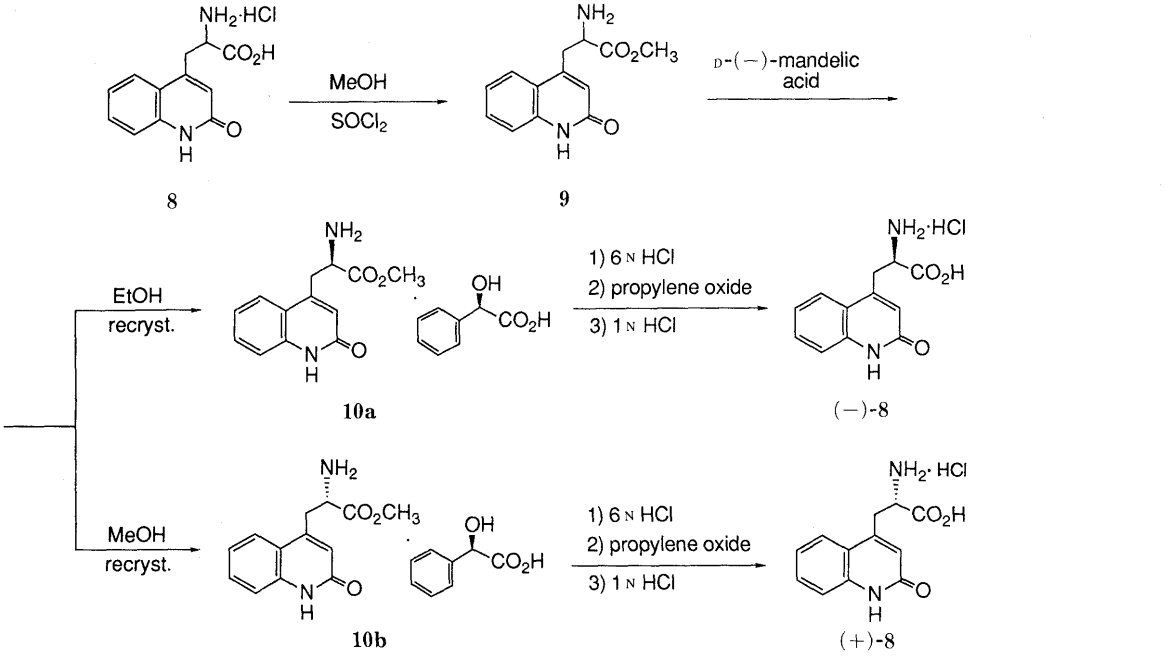


Chart 4

that (+)-**1** was about 1.7-fold were potent than (−)-**1** and about 1.4-fold more potent than (±)-**1**. Both enantiomers showed antiulcer activity against acetic acid-induced gastric ulcers and EtOH-induced gastric ulcers. The pair of enantiomers showed a small difference in activity. Therefore, rebamipide of the racemic mixture was developed.

Experimental

Melting points were determined with a Yamato MP-21 apparatus and are uncorrected. Infrared (IR) spectra were recorded on a JASCO IRA-2 spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded in deuteriodimethyl sulfoxide-d_6 (DMSO-d_6) on a Bruker AC-200 spectrometer. Mass spectra (MS) were obtained on a Varian MAT-312 instrument. Optical rotations were measured on a DIP-360 digital polarimeter (Japan Spectroscopic Co., Ltd.).

Reaction of 4-Bromomethyl-2(1*H*)-quinolinone with Phosphoryl Chloride 4-Bromomethyl-2(1*H*)-quinolinone (**2**) (20.0 g, 84 mmol) was added to a stirred and ice-cooled phosphoryl chloride (40 ml). The reaction mixture was heated at 80—90 °C for 40 min with stirring, then allowed to cool. The mixture was poured into ice-H_2O. The precipitates were collected by filtration and dissolved in CH_2Cl_2. The extract was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was recrystallized from AcOEt–hexane to give 4-bromomethyl- and 4-chloromethyl-2-chloroquinolines [**3** and **4**, **3**:**4** = 1:4 (from NMR), 8.85 g, 48%] as pale yellow needles. mp 83—85 °C. NMR ($CDCl_3$) δ: 4.79 (0.4H, s, bromomethyl), 4.95 (1.6H, s, chloromethyl), 7.46 (1H, d, J=10 Hz), 7.61—7.70 (1H, m), 7.77 (1H, dt, J=1.4, 6.1 Hz), 8.05 (2H, dt, J=1.6, 8.8 Hz). IR (KBr): 3070, 1590, 1510, 1420, 1300, 1150, 1100, 910, 760 cm^{-1}. MS *m/z* (%): 257 (23), 255 [M$^+$ (bromomethyl), 18], 229 (13), 227 (35), 213 (22), 212 (23), 211 [M$^+$ (chloromethyl), 32], 178 (21), 176 (100).

(−)-2-Chloro-4-[2′,5′-dimethoxy-6′-isopropyl-3′,6′-dihydropyrazin-3′-yl)methyl]quinoline [(−)-6] To a stirred solution of 2,5-dihydro-3,6-dimethoxy-2(*S*)-isopropylpyrazine [(*S*)-**5**] (1.3 g, 7.07 mmol) in THF (15 ml) at −78 °C, a 1.6 N solution (4.42 ml, 7.07 mmol) of *n*-butyllithium in hexane was added by syringe and the reaction mixture was stirred for 10 min at the same temperature. Then, a solution of **3** and **4** (1.5 g, 7.07 mmol) in THF (15 ml) was added and the mixture was stirred for 7 h at −78 °C. After removal of the solvent, the residue was poured into H_2O and extracted with Et_2O. The extract was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, eluent; CH_2Cl_2:AcOEt = 100:1) to give (−)-**6** (2.06 g, 81%) as colorless oil. $[\alpha]_D^{20}$ = −31.2° (c=0.2, 99.7% MeOH). NMR ($CDCl_3$) δ: 0.62 (3H, d, J=6.8 Hz), 0.97 (3H, d, J=6.8 Hz), 2.09—2.24 (1H, m), 3.21 (1H, dd, J=7.6, 13.4 Hz), 3.53 (3H, s), 3.66—3.78 (1H, m), 3.74 (3H, s), 4.35—4.42 (1H, m), 7.28 (1H, s), 7.50—7.58 (1H, m), 7.65—7.73 (1H, m), 7.99 (1H, d, J=8.5 Hz), 8.15 (1H, d, J=8.5 Hz). IR (neat): 2950, 1700, 1590, 1440, 1300, 1240, 760 cm^{-1}. *Anal.* Calcd for $C_{19}H_{22}ClN_3O_2 \cdot 1/2H_2O$: C, 61.87; H, 6.28; N, 11.39. Found: C, 61.68; H, 6.12; N, 11.16. MS *m/z* (%): 360 (2), 359 (M$^+$, 1), 316 (2), 183 (27), 177 (28), 141 (100).

(+)-2-Chloro-4-[(2′,5′-dimethoxy-6′-isopropyl-3′,6′-dihydropyrazin-3′-yl)methyl]quinoline [(+)-6] Compound [(+)-**6**] (2.17 g, 85%) was prepared by a procedure similar to that used for (−)-**6** with 2,5-dihydro-3,6-dimethoxy-2(*R*)-isopropylpyrazine [(*R*)-**5**] (1.3 g, 7.07 mmol), *n*-butyllithium in hexane (4.42 ml, 7.07 mmol) and **3** and **4** (1.5 g, 7.07 mmol). $[\alpha]_D^{20}$ = +30.4° (c=0.8, 99.7% MeOH). *Anal.* Calcd for $C_{19}H_{22}ClN_3O_2$: C, 63.42; H, 6.16; N, 11.68. Found: C, 63.08; H, 6.11; N, 11.49.

Methyl (−)-2-Amino-3-(2-chloroquinolin-4-yl)propionate [(−)-7] A mixture of (−)-**6** (2.2 g, 6.1 mmol) and 0.25 N HCl (48.4 ml) was stirred at room temperature for 18 h. The reaction mixture was evaporated *in vacuo*. The residue was dissolved in H_2O, adjusted to pH 9 with a 25% ammonia solution and extracted with Et_2O. The extract was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, eluent; CH_2Cl_2:MeOH = 100:1) and recrystallized from Et_2O to give (−)-**7** (1.3 g, 81%) as pale yellow needles, mp 57—59 °C. $[\alpha]_D^{20}$ = −31.3°(c=0.2, 99.7% MeOH). NMR ($CDCl_3$) δ: 2.11 (2H, br s), 3.20 (1H, dd, J=8.6, 14.1 Hz), 3.61 (1H, dd, J=5.2, 13.8 Hz), 3.70 (3H, s), 3.94 (1H, m), 7.33 (1H, s), 7.56—7.64 (1H, m), 7.70—7.77 (1H, m), 8.05 (2H, d, J=8.0 Hz). IR (KBr): 3360, 2950, 1730, 1590, 1280, 1150, 760 cm^{-1}. *Anal.* Calcd for $C_{13}H_{13}ClN_2O_2$: C, 58.99; H, 4.95; N, 10.58. Found: C, 58.64; H, 4.97; N, 10.49.

Methyl (+)-2-Amino-3-(2-chloroquinolin-4-yl)propionate [(+)-7] Compound [(+)-**7**] (0.2 g, 20%) was prepared by a procedure similar to that used for (−)-**7** with (+)-**6** (1.99 g, 5.5 mmol) and 0.25 N HCl (43.8 ml) as white prisms from Et_2O–hexane), mp 52—54 °C. $[\alpha]_D^{20}$ = +31.3° (c=0.2, 99.7% MeOH). *Anal.* Calcd for $C_{13}H_{13}ClN_2O_2$: C, 58.99; H, 4.95; N, 10.58. Found: C, 58.55; H, 4.89; N, 10.48.

Determination of the Optical Purities of (−)- and (+)-7 Compounds [(−)- and (+)-**7**] were subjected to HPLC (column, Chiralcel OJ, 4.6 mm i.d. × 25 cm; solvent, *n*-hexane : iso-PrOH : diethylamine = 900 : 100 : 1; detection, UV 240 nm). The optical purities were determined to be as follows: (−)-**7**, 75.6% ee; (+)-**7**, 91.6% ee.[7]

(−)-2-Amino-3-[2(1*H*)-quinolinon-4-yl]propionic Acid Hydrochloride [(−)-8] A suspension of (−)-**7** (0.85 g, 3.21 mmol) in 6 N HCl (32 ml) was refluxed for 6 h. After removal of the solvent, the residue was refluxed in propylene oxide (4 ml) and EtOH (10 ml) for 15 min. The precipitated product was isolated by suction and dissolved in 1 N HCl (5 ml). After removal of H_2O, the residue was recrystallized from EtOH–H_2O–Et_2O to give (−)-**8** (0.25 g, 29%) as white granules, mp 242—244 °C. $[\alpha]_D^{20}$ = −20.2° (c=0.1, DMSO). NMR δ: 3.00—3.70 (2H, m), 4.13 (1H, t, J=3.2 Hz), 6.47 (1H, s), 7.22 (1H, t, J=5.0 Hz), 7.34 (1H, d, J=6.4 Hz), 7.52 (1H, t, J=6.0 Hz), 7.76 (1H, d, J=6.0 Hz, 8.00—8.80 (2H, br s), 11.70 (1H, s). IR (KBr): 3450, 1665, 1520, 1410, 1270, 760 cm^{-1}. *Anal.* Calcd for $C_{12}H_{12}N_2O_3 \cdot HCl$: C, 53.64; H, 4.88; N, 10.43. Found: C, 53.48; H, 4.79; N, 10.28.

(+)-2-Amino-3-[2(1*H*)-quinolinon-4-yl]propionic Acid Hydrochloride [(+)-8] Compound [(+)-**8**] (0.17 g, 55%) was prepared by a procedure similar to that used for (−)-**8** with (+)-**7** (0.3 g, 1.1 mmol) and 6 N HCl (12 ml) as white granules, mp 244—246 °C. $[\alpha]_D^{20}$ = +21.5° (c=0.1, DMSO). *Anal.* Calcd for $C_{12}H_{12}N_2O_3 \cdot HCl$: C, 53.64; H, 4.88; N, 10.43. Found: C, 53.53; H, 4.81; N, 10.40.

Determination of the Optical Purities of (−)- and (+)-8 Compounds [(−)- and (+)-**8**] were subjected to HPLC (column, YMC-A3120DS, 4.6 mm i.d. × 25 cm; solvent, 20% MeOH containing [$Cu(CH_3CO_2)_2$: L-phenylalanine = 1 : 2]; detection, UV 295 nm). The optical purities were determined to be as follows: (−)-**8**, 98.2% ee; (+)-**8**, 98.4% ee.

(+)-2-(4-Chlorobenzoylamino)-3-[2(1*H*)-quinolinon-4-yl]propionic Acid [(+)-1] A solution of *p*-chlorobenzoyl chloride (82.2 mg, 0.47 mmol) in acetone (25 ml), was added dropwise to a stirred and ice-cooled solution of (−)-**8** (122 mg, 0.45 mmol) and K_2CO_3 (124 mg, 0.9 mmol) in H_2O (2.5 ml) and the reaction mixture was stirred for 2 h. The mixture was acidified with dil. HCl. The resulting precipitates were collected by filtration. Recrystallization from dimethylformamide (DMF)–H_2O gave (+)-**1** (48.1 mg, 29%) as white granules, mp 300—302 °C (dec.). $[\alpha]_D^{20}$ = +106.2° (c=1.0, DMF). NMR δ: 3.15—3.50 (2H, m), 4.60—4.80 (1H, m), 6.43 (1H, s), 7.22 (1H, t, J=7.0 Hz), 7.29 (1H, d, J=3.8 Hz), 7.46—7.55 (1H, m), 7.55 (2H, d, J=8.5 Hz), 7.82 (2H, d, J=8.5 Hz), 8.89 (1H, d, J=8.0 Hz), 11.63 (1H, s), 13.02 (1H, br s). IR (KBr): 3540, 3310, 1670, 1640 cm^{-1}. *Anal.* Calcd for $C_{19}H_{15}ClN_2O_4 \cdot H_2O$: C, 58.69; H, 4.41; N, 7.20. Found: C, 58.58; H, 4.37; N, 7.22.

(−)-2-(4-Chlorobenzoylamino)-[2(1*H*)-quinolinon-4-yl]propionic Acid [(−)-1] Compound [(−)-**1**] (112.5 mg, 55%) was prepared by a procedure similar to that used for (+)-**1** with (+)-**8** (148 mg, 0.55 mmol), *p*-chlorobenzoyl chloride (106 mg, 0.61 mmol) and K_2CO_3 (228 mg, 1.65 mmol) as white granules, mp 301—303 °C. $[\alpha]_D^{20}$ = −108.0° (c=1.0, DMF). *Anal.* Calcd for $C_{19}H_{15}ClN_2O_4 \cdot 1/3H_2O$: C, 60.66; H, 4.18; N, 7.45. Found: C, 60.49; H, 4.39; N, 7.39.

Determination of the Optical Purities (+)- and (−)-1 Compounds (+)- and (−)-**1** were subjected to HPLC [column, Sumipax OA-4000 4.6 mm i.d. × 25 cm (Sumitomo Chemical Co., Ltd.); solvent, acetonitrile : phosphate buffer (pH 5) = 3 : 2; detection, UV 254 nm]. The optical purities were determined to be as follows: (+)-**1**, 99.8% ee; (−)-**1**, 99.6% ee.

Methyl 2-Amino-3-[(1*H*)-quinolinon-4-yl]propionate (9) Thionyl chloride (8.8 g, 74 mmol) was added dropwise to a stirred and ice-cooled suspension of **8** (10 g, 37 mmol)[2] in MeOH (100 ml) and the reaction mixture was refluxed for 3 h. The mixture was evaporated to dryness *in vacuo*. The residue was poured into a $NaHCO_3$ aqueous solution and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was recrystallized from MeOH–AcOEt to give **9** (8.5 g, 93%) as white powder, mp 185—186 °C. NMR ($CDCl_3$) δ: 1.59 (2H, br s), 2.97 (1H, dd, J=8.5, 14 Hz), 3.45 (1H, dd, J=5, 14 Hz), 3.89 (1H, dd, J=5, 8.5 Hz), 6.66 (1H, s), 7.20—7.80 (4H, m), 12.75 (1H, br s). IR (KBr): 2950, 2850, 1740, 1670, 1620, 1560, 1440, 1290, 1200, 1180, 760 cm^{-1}. *Anal.* Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.23; H,5.69; N, 11.36.

(−)-2-Amino-3-[2(1*H*)-quinolinon-4-yl]propionic Acid Hydrochloride [(−)-8] D-(−)-Mandelic acid (3.0 g, 20 mmol) was added to a suspension of **9** (4.9 g, 20 mmol) in EtOH (50 ml) and the reaction mixture was stirred for 1 h at room temperature. The precipitated crystals (7.6 g, 96%) were separated by filtration. Two recrystallizations from EtOH gave the pure salt [**10a**, 1.8 g (23%)], mp 181—181.5 °C. $[\alpha]_D^{20} = -118°$ ($c = 0.2$, DMF). NMR δ: 3.00 (1H, dd, $J = 8.0$, 13.9 Hz), 3.19 (1H, dd, $J = 6.2$, 13.8 Hz), 3.59 (3H, s), 3.79 (1H, dd, $J = 6.2$, 7.9 Hz), 4.90 (1H, s), 5.63 (1H, br s), 6.39 (1H, s), 7.16—7.54 (8H, m), 7.74 (1H, d, $J = 7.2$ Hz), 11.70 (1H, br s). IR (KBr): 3400, 2920, 2880, 1740, 1670, 1640, 1610, 1570, 1510, 1440, 1430, 1270, 1080, 760, 700 cm^{-1}. *Anal.* Calcd for $C_{21}H_{22}N_2O_6$: C, 63.31; H, 5.57; N, 7.03. Found: C, 63.24; H, 5.49; N, 7.03. Then a solution of the salt (1.8 g) in 6 N HCl (20 ml) was refluxed for 5 h. The reaction mixture was concentrated *in vacuo*. The residue was refluxed in propylene oxide (20 ml) and EtOH (50 ml) for 30 min. The precipitated product was isolated by suction and dissolved in 1 N HCl. After removal of H_2O, the residue was recrystallized from H_2O–EtOH–Et_2O to give (−)-**8** (0.6 g, 11%). *Anal.* Calcd for $C_{12}H_{12}N_2O_3 \cdot HCl$: C, 53.64; H, 4.88; N, 10.43. Found: C, 53.37; H, 4.86; N, 10.34. The product was identical with a previous synthetic sample on the basis of NMR, IR, specific rotation and HPLC comparisons.

(+)-2-Amino-3-[2(1*H*)-quinolinon-4-yl]propionic Acid Hydrochloride [(+)-8] D-(−)-Mandelic acid (3.0 g, 20 mmol) was added to a suspension of **9** (4.9 g, 20 mmol) in EtOH (50 ml) and the reaction mixture was stirred for 1 h at room temperature. The precipitated crystals (7.5 g, 95%) were separated by filtration. Two recrystallizations from MeOH gave the pure salt [**10b**, 1.8 g (23%)], mp 158.5—159.5 °C. $[\alpha]_D^{20} = -88.4°$ ($c = 0.2$, DMF). NMR δ: 2.98 (1H, dd, $J = 7.9$, 13.9 Hz), 3.18 (1H, dd, $J = 6.2$, 13.9 Hz), 3.59 (3H, s), 3.76 (1H, dd, $J = 6.2$, 7.9 Hz), 4.92 (1H, s), 4.50—5.70 (1H, br s), 6.39 (1H, s), 7.17—7.54 (8H, m), 7.74 (1H, d, $J = 7.1$ Hz), 11.67 (1H, br s). IR (KBr): 3400, 3150, 3050, 1760, 1670, 1650, 1610, 1550, 1440, 1400, 1280, 1060, 760, 700 cm^{-1}. *Anal.* Calcd for $C_{21}H_{22}N_2O_6$: C, 63.31; H, 5.57; N, 7.03. Found: C, 63.12; H, 5.57; N, 7.02. Then compound [(+)-**8**] (0.8 g, 15%) was prepared by a procedure similar to that used for (−)-**8**. *Anal.* Calcd for $C_{12}H_{12}N_2O_3 \cdot HCl$: C, 53.63; H, 4.88; N, 10.43. Found: C, 53.73; H, 4.86; N, 10.40. The product was identical with a sample prepared by the previous method.

Antiulcer Activity Method: Male Wistar rats weighing between 200 and 250 g were fasted for 24 h, but were allowed water *ad libitum* prior to the study. Test compounds and the vehicle were given intraperitoneally 30 min before the oral administration of 1 ml of absolute EtOH. The animals were killed 1 h after the irritant was given, and the stomachs were removed. After light fixation with formalin, the surface of the gastric mucosa was graded planimetrically. The total surface area damage in each animal was calculated and used as the lesion index. Percentage inhibition was calculated as follows: [(lesion index of control − lesion index test compound)/lesion index of control] × 100. The doses inhibiting absolute EtOH-induced lesions by 50% (ED_{50}) were calculated by linear regression analysis.

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