Biological Activities of Four Stereoisomers of 2-(4-Methoxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-ylsulfinyl)-1*H*-benzimidazole Sodium Salt and Acid-Induced Transformations: Novel Proton Pump Inhibitor

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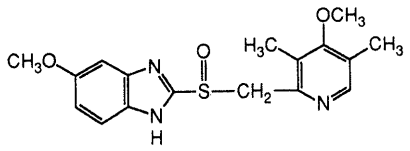
The sodium salts (5) of four stereoisomeric benzimidazolylsulfoxides, (*Ss*,9*R*)-(−)-4, (*Rs*,9*S*)-(+)-4, (*Ss*,9*S*)-(−)-4 and (*Rs*,9*R*)-(+)-4, were prepared from optically pure sulfides, (+)-8 and (−)-8. The sulfoxides (4) were transformed into sulfenamides (6) and symmetric disulfides (9) under acidic conditions, without any change of stererochemical configuration at the α-carbon bearing the sulfinyl group. No significant difference was observed among the four stereoisomers in inhibitory activity towards ($H^+ + K^+$)-ATPase *in vitro*. However, (*Ss*,9*R*)-(−)-5 showed more long-lasting antisecretion activity *in vivo* than that of another enantiomer, (*Rs*,9*S*)-(+)-5.

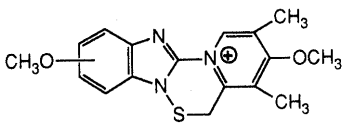
Key words optical resolution; ($H^+ + K^+$)-ATPase inhibitor; acid-transformation; configuration retention

Since ($H^+ + K^+$)-ATPase (the proton pump), which is located in the apical membrane of the parietal cell, plays a major role in the final step in acid secretion,[1] proton pump inhibitors have become candidates for novel antisecretory drugs. Many substituted benzimidazoles have been reported to exert potent antisecretion activity,[2] and some evidence suggested that substituted benzimidazoles, represented by omeprazole (**1**), are transformed into biologically active intermediates such as sulfenamide (**2**) and symmetric disulfide (**3**) in an acidic environment such as that of the apical membrane of the parietal cell.[3,4] These intermediates may react with SH groups of the ($H^+ + K^+$)-ATPase, thereby causing the inhibitory action. Newly synthesized benzimidazole derivatives with a 6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine moiety have marked inhibitory effects on the proton pump both *in vivo* and *in vitro*, as described in our preceding paper.[5,6] The sodium salt (**5**) of a diastereomeric isomer, (*R**s,9*S**)-(±)-**4**, selected as a promising proton pump inhibitor is now under clinical study.

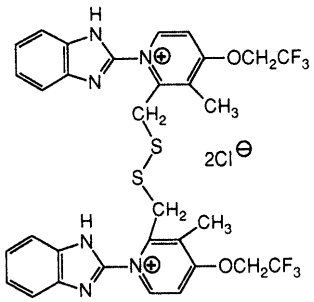
Omeprazole (**1**) is a racemate, having a chiral center at the asymmetric sulfinyl group. However, the chirality is lost in the sulfenamide (**2**) generated through the acid-induced transformation. On the other hand, compound **4** has two chiral centers at the asymmetric sulfinyl group and α-carbon bearing the sulfinyl group. In this paper we report syntheses of the four possible stereoisomers of **4** and the results of comparative examinations of the chemical and biological properties of the stereoisomers.



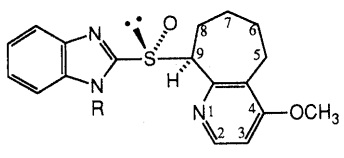
Omeprazole (**1**)



Sulfenamide (**2**)



Disulfide (**3**)



(*R**s, 9*S**)-(±)-**4** R = H
(*R**s, 9*S**)-(±)-**5** R = Na

Chart 1

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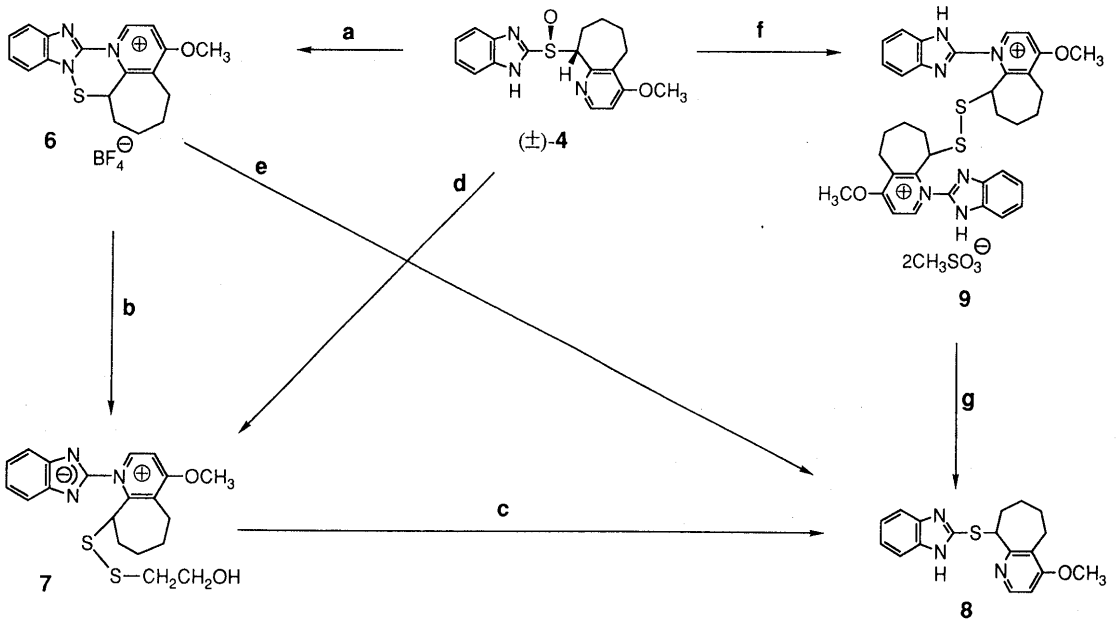


a : HBF_4, MeOH **b** : 1) 2-mercaptoethanol (0.9 equiv.), 1N HCl, CH_3CN 2) $NaHCO_3$ **c** : 2-mercaptoethanol (1 equiv.), 1N HCl, CH_3CN-$CHCl_3$ **d** : 2-mercaptoethanol (1 equiv.), 1N HCl, acetone **e** : 2-mercaptoethanol (2 equiv.), 1N HCl, CH_3CN **f** : CH_3SO_3H, MeOH **g** : 2-mercaptoethanol (large excess), 1N HCl, CH_3CN

Chart 2

The chemical transformations induced by acid treatment of the diastereomer, (*R**s,9*S**)-(±)-**4**, are summarized in Chart 2. Treatment of the sulfoxide [(*R**s,9*S**)-(±)-**4**] with hydrogen tetrafluoroborate in methanol readily gave the pure sulfenamide [(±)-**6**]. Reaction of (±)-**6** with a 0.9 equimolar amount of 2-mercaptoethanol in an acidic medium (1 N HCl) resulted in formation of the disulfide [(±)-**7**]. The sulfenamide [(±)-**6**] was transformed to the sulfide [(±)-**8**] in the presence of excess 2-mercaptoethanol under an acidic condition (1 N HCl). Similarly the disulfide [(±)-**7**] was converted to (±)-**8** *via* S–S bond cleavage by treatment with equimolar 2-mercaptoethanol. On the other hand, an acid-induced transformation of the sulfoxide [(*R**s,9*S**)-(±)-**4**] in the presence of methanesulfonic acid afforded another product, the symmetric disulfide [(±)-**9**]. This disulfide (**9**) was also converted to the sulfide [(±)-**8**] with a large excess of 2-mercaptoethanol in 1 N HCl.

The results suggest that the sulfoxide [(±)-**4**] undergoes the acid-induced transformation similar to those of omeprazole (**1**)[3a,b] and its analogs.[3b,4]

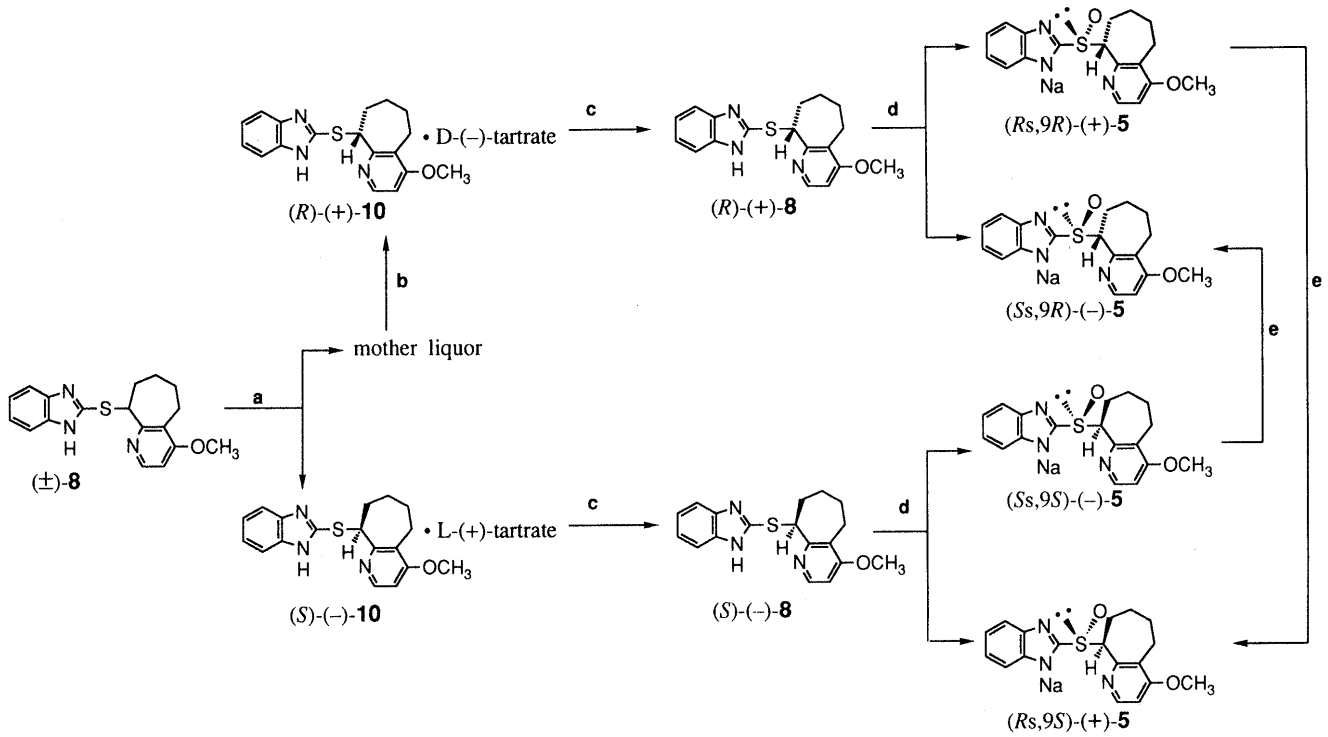
Four possible stereoisomers of the sulfoxide (**4**) were prepared as shown in Chart 3. According to the method described in our preceding paper, in which we reported a determination of the absolute configuration of **4** by X-ray analysis,[7] the racemic sulfide [(±)-**8**] was resolved by recrystallization of the diastereomeric tartrate (**10**). Each enantiomer, (+)-**8** and (−)-**8**, was determined to be 100% ee by high-performance liquid chromatography (HPLC) using a chiral stationary phase column. Oxidation of the enantiomeric sulfides [(+)-**8** and (−)-**8**] with *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane gave an 8 : 2 diastereomeric mixture of the corresponding sulfoxides (**4**) separately. In methanol as a solvent, the ratio of the diastereomeric sulfoxides (**4**) was altered to *ca.* 1 : 1.

After transformation of the 8 : 2 diastereomeric mixture of (*R*s,9*R*)-(+)-**4** and (*S*s,9*R*)-(−)-**4** into sodium salts (**5**) with equimolar $NaOCH_3$ in dichloromethane, the sodium salt of the sulfoxide [(*R*s,9*R*)-(+)-**4**] could be selectively isolated in good yield by recrystallization from acetone, because the sodium salt [(*R*s,9*R*)-(+)-**5**] formed fine crystals solvated with acetone, while the counterpart diastereomer [(*S*s,9*R*)-(−)-**5**] did not under the conditions used. The constitution of the solvated crystals was supported by the IR spectra (1698 cm^{-1}) and ^{1}H-NMR spectra (δ: 2.16 ppm, 6H, singlet).

The mixture of the diastereomeric sulfoxides (**4**) readily underwent epimeric equilibration at the α-carbon bearing the sulfinyl group in the presence of excess $NaOCH_3$ (more than an equimolar amount) in dichloromethane,[6] and the sodium salt of another diastereomer [(*S*s,9*R*)-(−)-**5**] was selectively precipitated by gradual addition of diethyl ether. This sodium salt (**5**) was reprecipitated in the same manner. However, these sodium salts (**5**) could not be obtained in a stereochemically pure form. Another pair of diastereomeric sulfoxides was also treated by the same procedure, and the sodium salts of the sulfoxides, [(*S*s,9*S*)-(−)-**5**] and [(*R*s,9*S*)-(+)-**5**] were obtained separately.

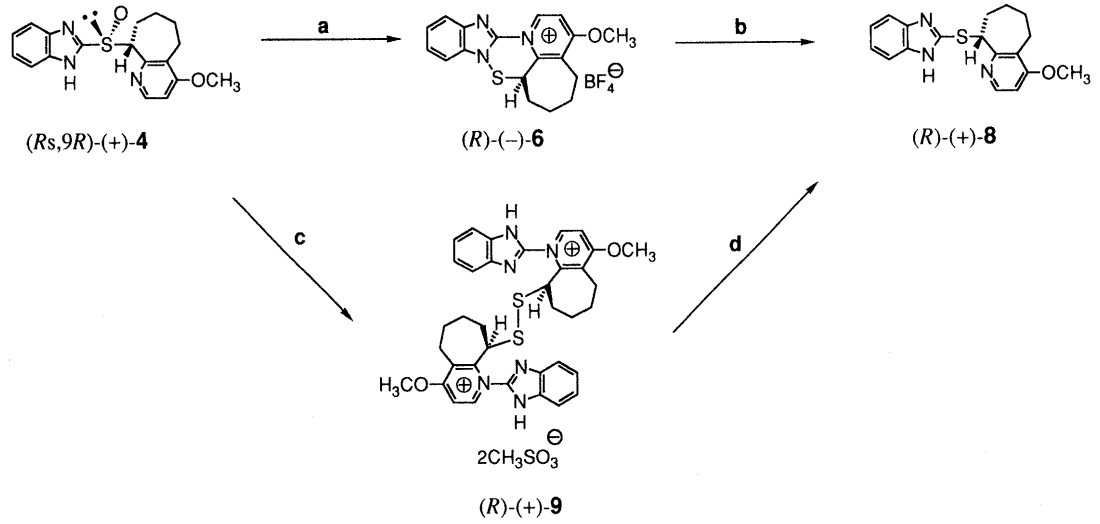
Based on HPLC with a chiral stationary phase column, the stereoisomeric purities of (*R*s,9*R*)-(+)-**5**, (*S*s,9*S*)-(−)-**5**, (*S*s,9*R*)-(−)-**5** and (*R*s,9*S*)-(+)-**5** were 100, 100, 88.9 and 95.0%, respectively.

As shown in Chart 4, the chemical transformation of the optically pure sulfoxide [(*R*s,9*R*)-(+)-**4**] obtained from the corresponding sodium salt (**5**) in an acidic medium (NH_4Cl) was investigated by the same procedure as used for the racemic compound. In the acid treatments,



a : L-tartaric acid, MeOH **b** : 1) neutralization with $NaHCO_3$ 2) D-tartaric acid, MeOH **c** : 1) neutralization with 10% NaOH 2) recrystallization from EtOH **d** : 1) *m*-CPBA, CH_2Cl_2 or MeOH 2) 28% $NaOCH_3$ 3) recrystallization from acetone or CH_2Cl_2-Et_2O **e** : 1) 28% $NaOCH_3$ 2) recrystallization from CH_2Cl_2-Et_2O

Chart 3



a) HBF_4, MeOH **b**) 2-mercaptoethanol (3 equiv.), 1N HCl, CH_3CN **c**) CH_3SO_3H, MeOH **d**) 2-mercaptoethanol (large excess), 1N HCl, CH_3CN

Chart 4

optically pure sulfenamide [(−)-**6**] and symmetric disulfide [(+)-**9**] were prepared, as expected. Furthermore, the sulfide [(+)-**8**] was obtained from the sulfenamide [(−)-**6**] and the symmetric disulfide [(+)-**9**] was formed by treatment with excess 2-mercaptoethanol in the presence of 1 N HCl without any contamination by other stereoisomers. The specific optical rotation of (+)-**8** recovered from acid-induced transformation of (*Rs*,9*R*)-(+)-**4** was identical with that of the original (+)-**8** resolved from the racemate (**8**). Furthermore, HPLC analysis showed that the counterpart sulfide [(−)-**8**] was undetectable in the reaction mixture. The configuration at the α-carbon of the sulfinyl group, the asymmetric carbon in the cyclohepta[*b*]pyridine ring, was completely retained during the acid-induced transformations.

We next examined the biological properties of the stereoisomers synthesized in the present study.

In order to compare their potencies *in vitro*, inhibition

Table 1. Inhibitory Effects of Four Stereoisomeric Sulfoxide Sodium Salts (**5**) on $(H^+ + K^+)$-ATPase of Rabbit Gastric Mucosa

Compd.[a]	$(H^+ + K^+)$-ATPase IC_{50} (μM)[b]
(*Ss*,9*R*)-(−)-**5**	7.5 (6.1— 9.3)
(*Rs*,9*S*)-(+)-**5**	9.4 (8.3—10.6)
(*Ss*,9*S*)-(−)-**5**	9.3 (8.4—10.3)
(*Rs*,9*R*)-(+)-**5**	7.8 (6.8— 8.9)
(*R**s,9*S**)-(±)-**5**	5.8 (4.8— 7.0)
(*R**s,9*R**)-(±)-**5**	8.0 (6.5— 9.7)
Omeprazole (**1**)	16.1 (13.6—19.2)

a) Steroisomeric purities of (*Ss*,9*R*)-(−)-**5**, (*Rs*,9*S*)-(+)-**5**, (*Ss*,9*S*)-(−)-**5** and (*Rs*,9*R*)-(+)-**5** were 88.9, 95.0 100 and 100%, respectively. *b*) The IC_{50} values were calculated from the dose–inhibition relationships for 3 to 5 rabbits by the probit method. Numbers in parentheses represent the 95% confidence limits of the IC_{50} values.

Table 2. Inhibitory Effect of Four Stereoisomeric Sulfoxide Sodium Salts (**5**) on Tetragastrin-Stimulated Gastric Acid Secretion in Rats (n=3—5)

Compd.[a]	Dose, (mg/kg, i.v.)	Inhibition (%)	
		1 h after dosing	3 h after dosing
(*Ss*,9*R*)-(−)-**5**	0.5	82.2	82.4
(*Rs*,9*S*)-(+)-**5**	0.5	77.1	55.4
(*Ss*,9*S*)-(−)-**5**	0.5	65.4	25.8
(*Rs*,9*R*)-(+)-**5**	0.5	75.9	41.5
(*R**s,9*S**)-(±)-**5**	0.5	76.8	76.3
(*R**s,9*R**)-(±)-**5**	0.5	79.7	68.9
Omeprazole (**1**)	0.5	61.3	49.7

a) Stereoisomeric purities of (*Ss*,9*R*)-(−)-**5**, (*Rs*,9*S*)-(+)-**5**, (*Ss*,9*S*)-(−)-**5** and (*Rs*,9*R*)-(+)-**5** were 88.9, 95.0, 100 and 100%, respectively.

of gastric proton pump was tested by using $(H^+ + K^+)$-ATPase prepared from gastric mucosa of rabbits according to the method reported by Saccomani *et al.*[8] As shown in Table 1, sodium salts (**5**) of the four stereoisomers (**4**) all inhibited $(H^+ + K^+)$-ATPase at pH 6 in a concentration-dependent manner with IC_{50} values lying within the range of 5.8—9.4 μM. These potencies are considered to be essentially the same. The chirality of the sulfinyl group is lost in the process of acid-transformation into the sulfenamide (**6**). In fact, comparative examinations between two enantiomers of benzimidazole derivatives such as lansoprazole[9] and Ro 18-5364[10] did not reveal any significant difference in the inhibition of $(H^+ + K^+)$-ATPase activity *in vitro* (they have a single chiral center at the sulfinyl group).

In spite of the presence of two chiral centers in the sodium salt (**5**) of the sulfoxide (**4**), all the stereoisomers of **5** showed essentially identical activity for inhibition of $(H^+ + K^+)$-ATPase *in vitro*. The results observed in this study may suggest that the activated sulfoxide (**4**) in an acidic environment can smoothly form a disulfide bond to react with an SH group of $(H^+ + K^+)$-ATPase, without any significant stereochemical influence of the asymmetric carbon in the cyclohepta[*b*]pyridine ring. The sulfenamide (**6**) and symmetric disulfide (**9**) prepared in the present study showed inferior activity to the parent sulfoxide (**4**) in the *in vitro* bioassay system because these compounds decomposed under the experimental conditions (data not shown), while the sulfenamide (**2**) and disulfide (**3**) derived from other benzimidazole congeners, such as omeprazole (**1**)[3a] and lansoprazole,[3c] were reported to have superior activities to the respective parent compounds.

For the evaluation of pharmacological effect *in vivo*, antisecretory activity against tetragastrin-stimulated gastric acid secretion in rats was tested by utilizing the method presented in our previous paper.[5,6a] The results are summarized in Table 2. All the stereoisomers of the sulfoxide (**5**) showed superior activities to that of omeprazole (**1**). In addition, the durations of action of the enantiomers, (*Ss*,9*R*)-(−)-**5** and (*Rs*,9*S*)-(+)-**5**, were longer than those of the diastereomeric counterparts, (*Ss*,9*S*)-(−)-**5** and (*Rs*,9*R*)-(+)-**5**. These results are substantially identical with previously reported data on diastereomeric racemates of the sulfoxide (**5**)[6a] (Table 2). Intravenous administration of (*Ss*,9*R*)-(−)-**5** resulted in a longer suppression of gastric acid secretion than that of (*Rs*,9*S*)-(+)-**5**. A similar result was obtained in comparing (*Rs*,9*R*)-(+)-**5** and (*Ss*,9*S*)-(−)-**5**. Thus, the apparent differences in biological activities *in vivo* seem likely to be mainly attributable to the configuration of the chiral carbon at the 9-position in the cyclohepta[*b*]pyridine ring.

We next examined the pharmacokinetic properties of the enantiomeric sulfoxides (**5**). After intravenous administration of enantiomeric and racemic sulfoxides, (*Ss*,9*R*)-(−)-**5**, (*Rs*,9*S*)-(+)-**5** and (*R**s,9*S**)-(±)-**5**, to male rats, plasma concentrations of each enantiomer were traced by using HPLC with a chiral stationary phase column. The level of free form sulfoxide, (*Ss*,9*R*)-(−)-**4**, in plasma was consistently higher than that of (*Rs*,9*S*)-(+)-**4**, and the area under the plasma concentrations–time curve (*AUC*) value of the former was larger than that of the latter. Similar results were obtained from pharmacokinetic studies, analyzing the stereoisomers after administration of the racemic sulfoxide [(*R**s,9*S**)-(±)-**5**], in other experimental animals[11] and also in healthy male volunteers.[12] No interconversion of enantiomers occurred under the experimental conditions used or in the whole body. Therefore, the results were considered to be due to differences in tissue distribution and in metabolism *in vivo* between the two enantiomers.[11] Such differences may lead to the different potency of antisecretion activity and duration of action in rats.

Experimental

Melting points were determined on a Yanagimoto apparatus without correction. IR spectra were recorded on a Hitachi 270-30 spectrometer. ^{1}H-NMR spectra were recorded on a Hitachi R-90H NMR spectrometer or a JEOL JNM-GX 270 NMR. Chemical shifts are given in δ values (ppm) with tetramethylsilane as an internal standard, and coupling constants (J) are given in Hz. Low-resolution mass (MS) was obtained with a JEOL JMS-D 300 mass spectrometer. The fast atom bombardment mass spectra (FAB-MS) were obtained by using *m*-nitrobenzyl alcohol as the matrix. Optical rotations were measured on a JASCO DIP-360 digital polarimeter. Elemental analysis (C, H, N) was performed on a Perkin-Elmer 240 or 2400 C, H, N instrument. Reactions were followed by thin-layer chromatography (TLC) on TLC plates, Silica gel $60F_{254}$ precoated (E. Merck), and chromatographic separation was carried out on silica gel (Wakogel C-300) or alumina (about 300 mesh) manufactured by Wako Pure Chemical Industries, Ltd.

Optical Resolution of 2-(4-Methoxy-6,7,8,9-tetrahydro-5*H*-cyclohepta-[*b*]pyridin-9-ylthio)-1*H*-benzimidazole (8) The racemate **8** (13.0 g, 40 mmol) and L-tartaric acid (6.0 g, 40 mmol) were dissolved in MeOH (90 ml) at about 70 °C and the mixture was stirred at room temperature

for 20 h. The resulting crystalline precipitate was collected and washed with cold MeOH–Et_2O (1 : 2), giving the L-tartrate (*S*)-(−)-**10** (6.75 g). The mother liquor and washing were combined, concentrated *in vacuo*, and dissolved in water. After neutralization with saturated aqueous $NaHCO_3$ solution, the resultant free amine was extracted with $CHCl_3$, and the $CHCl_3$ layer was concentrated *in vacuo*. The resultant amine residue (8.39 g) was added to a solution of D-tartaric acid (3.90 g, 26 mmol) in MeOH (58 ml) and the mixture was dissolved at about 70 °C. It was stirred for 20 h at room temperature, and the resultant crystalline precipitate was collected by filtration and washed with cold MeOH–Et_2O (1 : 2), giving the D-tartrate (*R*)-(+)-**10** (7.53 g). The mother liquor was treated again in the same manner as described above to give additional L- and D-tartrate, (*S*)-(−)-**10** (1.78 g) and (*R*)-(+)-**10** (0.98 g), respectively. L-Tartrate (*S*)-(−)-**10**: 45% yield, mp 173—174 °C, $[\alpha]_D^{26}$ −215° (*c* = 1.0, MeOH). *Anal.* Calcd for $C_{18}H_{19}N_3OS \cdot C_4H_6O_6$: C, 55.57; H, 5.30; N, 8.84. Found: C, 55.49; H, 5.25; N, 8.89. D-tartrate (*R*)-(+)-**10**: 44% yield, mp 174—175 °C, $[\alpha]_D^{27}$ +213° (*c* = 1.0, MeOH). *Anal.* Calcd for $C_{18}H_{19}N_3OS \cdot C_4H_6O_6$: C, 55.57; H, 5.30; N, 8.84. Found: C, 55.55; H, 5.30; N, 8.90.

2-[(9*S*)-4-Methoxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-ylthio]-1*H*-benzimidazole ((−)-8) A solution of the L-tartrate (*S*)-(−)-**10** (8.51 g, 17.9 mmol) in H_2O (100 ml) was neutralized with 10% aqueous NaOH solution and extracted with $CHCl_3$. The extract was washed with brine and dried ($MgSO_4$). After removal of the solvent *in vacuo*, the residue was purified by recrystallization from EtOH to give (*S*)-(−)-**8** (4.68 g, 80%) as a colorless powder, mp 188—190 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.06—2.39 (6H, m), 2.53—3.46 (2H, m), 3.83 (3H, s), 5.15 (1H, t, *J* = 4 Hz), 6.76 (1H, d, *J* = 6 Hz), 7.03—7.72 (4H, m), 8.32 (1H, d, *J* = 6 Hz). IR (KBr) : 2928, 1582, 1452, 1436, 1290, 1234 cm^{-1}. $[\alpha]_D^{25}$ −272° (*c* = 1.0, MeOH). MS (FAB) *m/z*: 326 ($M^+ + 1$). *Anal.* Calcd for $C_{18}H_{19}N_3OS$: C, 66.43; H, 5.88; N, 12.91. Found: C, 66.35; H, 5.85; N, 13.02.

2-[(9*R*)-4-Methoxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-ylthio]-1*H*-benzimidazole ((+)-8) The D-tartrate (*R*)-(+)-**10** (8.53 g, 18 mmol) was converted to (*R*)-(+)-**8** as described above: (4.71 g, 82%) a colorless powder, mp 188—189 °C, $[\alpha]_D^{25}$ +272° (*c* = 1.0, MeOH). MS (FAB) *m/z*: 326 ($M^+ + 1$). *Anal.* Calcd for $C_{18}H_{19}N_3OS$: C, 66.43; H, 5.88; N, 12.91. Found: C, 66.48; H, 5.89; N, 12.98. The spectral data (^{1}H-NMR, IR) were identical with those of (*S*)-(−)-**8**.

Determination of the Optical Purities of (*S*)-(−)-8 and (*R*)-(+)-8 The optical purities of (*S*)-(−)-**8** and (*R*)-(+)-**8** were measured by HPLC: Chiralcel OD® of 4.6 mm × i.d. × 25 cm (Daicel Chemical Industries, Tokyo); mobile phase, EtOH–hexane (1 : 5, v/v); flow rate, 0.4 ml/min; detection, ultraviolet (UV) at 300 nm. The optical purities were determined to be as follows: (*S*)-(−)-**8**, 100% ee (t_R: 16.93 min); (*R*)-(+)-**8**, 100% ee (t_R: 15.38 min).

2-[(*Rs*,9*R*)-4-Methoxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-ylsulfinyl]-1*H*-benzimidazole Sodium Salt ((+)-5) *m*-CPBA (945 mg, 4.38 mmol) was added to a solution of (*R*)-(+)-**8** (1.50 g, 4.62 mmol) in CH_2Cl_2 (72 ml) in portions at −18 °C. The mixture was stirred at the same temperature for 5 min, washed with a saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$) and concentrated *in vacuo*. To the obtained residue [the corresponding sulfoxides (*Rs*,9*R*)-(+)-**4**: (*Ss*,9*R*)-(−)-**4** in a ratio of *ca.* 8 : 2] was added a solution of 28% $NaOCH_3$ (750 mg, 3.92 mmol) in CH_2Cl_2 (15 ml) at 0 °C. The mixture was stirred at the same temperature for 2 min, then concentrated *in vacuo*. The residue was crystallized from acetone, and repeated recrystallizations from acetone gave (*Rs*,9*R*)-(+)-**5** (3.0 g, 75%) as a colorless powder, mp 182—183 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 1.00—1.80 (6H, m), 2.16 (6H, s), 2.46—2.78 (2H, m), 3.66 (3H, s), 4.50—4.75 (1H, m), 6.52 (1H, d, *J* = 6.0 Hz), 6.90—7.15 (2H, m), 7.39—7.56 (2H, m), 7.83 (1H, d, *J* = 6.0 Hz). IR (KBr): 3376, 2932, 1698, 1578, 1473, 1372, 1290, 1272, 1053 cm^{-1}. $[\alpha]_D^{28}$ +224° (*c* = 1.0, MeOH). MS (FAB) *m/z*: 342 ($M^+ - Na + 1$). *Anal.* Calcd for $C_{18}H_{18}N_3O_2SNa \cdot C_3H_6O \cdot H_2O$: C, 57.39; H, 5.50; N, 9.56. Found: C, 57.09; H, 5.83; N, 9.44.

2-[(*Ss*,9*S*)-4-Methoxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-ylsulfinyl]-1*H*-benzimidazole Sodium Salt ((−)-5) (*Ss*,9*S*)-(−)-**5** was prepared from (*S*)-(−)-**8** in 78% yield in a similar manner to that described above, as a colorless powder, mp 183—184 °C (dec.). $[\alpha]_D^{28}$ −224° (*c* = 1.0, MeOH). MS (FAB) *m/z*: 342 ($M^+ - Na + 1$). *Anal.* Calcd for $C_{18}H_{18}N_3O_2SNa \cdot C_3H_6O \cdot 2H_2O$: C, 55.13; H, 5.29; N, 9.18. Found: C, 55.36; H, 5.50; N, 9.48. The spectral data (^{1}H-NMR, IR) were identical with those of (*Rs*,9*R*)-(+)-**5**.

2-[(*Ss*,9*R*)-4-Methoxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-ylsulfinyl]-1*H*-benzimidazole Sodium Salt ((−)-5) Procedure A: A 28% $NaOCH_3$ solution (28 μl, 0.146 mmol) was added to a solution of (*Ss*,9*S*)-(−)-**5** (106 mg, 0.305 mmol) in MeOH (1 ml) at 0 °C. The mixture was stirred at room temperature for 1 h, then concentrated *in vacuo*. Acetone was added to the residue [the corresponding sulfoxides (*Ss*,9*S*)-(−)-**5**: (*Ss*,9*R*)-(−)-**5** in a ratio of *ca.* 1 : 1] at 0 °C and the precipitated crystals were removed by filtration. After concentration of the filtrate *in vacuo*, the residue was crystallized from CH_2Cl_2–Et_2O and repeated recrystallizations from CH_2Cl_2–Et_2O gave (*Ss*,9*R*)-(−)-**5** (57 mg, 54%) as a colorless powder.

Procedure B: *m*-CPBA (202 mg, 0.938 mmol) was added to a solution of (*R*)-(+)-**8** (321 mg, 0.987 mmol) in MeOH (15 ml) in portions at −18 °C. The mixture was stirred at the same temperature for 5 min, then Et_3N (1 ml) was added. After removal of the solvent *in vacuo*, the residue was extracted with CH_2Cl_2 and the extract was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue [the corresponding sulfoxides (*Ss*,9*R*)-(−)-**4**: (*Rs*,9*R*)-(+)-**4** in a ratio of *ca.* 1 : 1] was dissolved in CH_2Cl_2 (3 ml) and 28% $NaOCH_3$ (171 μl, 0.889 mmol) was added at 0 °C. The mixture was stirred at the same temperature for 2 min, then concentrated *in vacuo*. Acetone was added to the residue at 0 °C and the precipitated crystals were removed by filtration. After concentration of the filtrate *in vacuo*, the residue was crystallized from CH_2Cl_2–Et_2O, and repeated recrystallizations from CH_2Cl_2–Et_2O gave (*Ss*,9*R*)-(−)-**5** (146 mg, 41%).

2-[(*Rs*,9*S*)-4-Methoxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-ylsulfinyl]-1*H*-benzimidazole Sodium Salt ((+)-5) (*Rs*,9*S*)-(+)-**5** was prepared from (*Rs*,9*R*)-(+)-**5** in 31% yield and from (*S*)-(−)-**8** in 47% yield in the same manner as described above for procedures A and B, respectively.

(*Ss*,9*R*)-(−)-**5**: A colorless powder, mp 178—184 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 1.01—2.63 (7H, m), 2.95—3.43 (1H, m), 3.82 (3H, s), 4.75 (1H, d, *J* = 6 Hz), 6.65 (1H, d, *J* = 5 Hz), 6.85—7.10 (2H, m), 7.40—7.65 (2H, m), 8.23 (1H, d, *J* = 5 Hz). IR (KBr): 2926, 1581, 1476, 1473, 1383, 1287, 1269, 1080, 1056 cm^{-1}. $[\alpha]_D^{26}$ −21.0° (*c* = 0.17, MeOH). MS (FAB) *m/z*: 342 ($M^+ - Na + 1$).

(*Rs*,9*S*)-(+)-**5**: A colorless powder, mp 176—183 °C (dec.). $[\alpha]_D^{26}$ +13.2° (*c* = 0.4, MeOH). MS (FAB) *m/z*: 342 ($M^+ - Na + 1$). The spectral data (^{1}H-NMR, IR) were identical with those of (*Ss*,9*R*)-(−)-**5**.

Determination of the Optical Purities of the Four Stereoisomeric Sulfoxides (5) The stereoisomeric purities of (*Rs*,9*R*)-(+)-**5**, (*Ss*,9*R*)-(−)-**5**, (*Ss*,9*S*)-(−)-**5** and (*Rs*,9*S*)-(+)-**5** were measured by HPLC: Chiralcel OD® of 4.6 mm × i.d. × 25 cm (Daicel Chemical Industries, Tokyo); mobile phase, EtOH–hexane (1 : 8, v/v); flow rate, 1.0 ml/min; detection, UV at 300 nm.

The optical purities were determined to be as follows: (*Rs*,9*R*)-(+)-**5**, 100% (t_R: 26.64 min); (*Ss*,9*S*)-(−)-**5** 100%, (t_R: 27.44 min); (*Ss*,9*R*)-(−)-**5** 88.9%, (t_R: 15.07) (*Rs*,9*S*)-(+)-**5** 95.0%, (t_R: 13.06). Further purification of (*Ss*,9*R*)-(−)-**5** and (*Rs*,9*S*)-(+)-**5** by chromatographic purification was unsuccessful owing to their inherent instability.

2-(4-Methoxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-ylsulfinyl)-1*H*-benzimidazole (4) A 10% NH_4Cl solution (45 ml) was added to a solution of **5** (726 mg, 2 mmol) in CH_2Cl_2 (30 ml) and the mixture was extracted with CH_2Cl_2. The extract was washed with brine, and dried ($MgSO_4$). After removal of the solvent *in vacuo*, the residue was recrystallized from EtOH to give **4** (552.4 mg, 81%) as a colorless powder, mp 118—120 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 1.02—2.75 (7H, m), 3.13—3.55 (1H, m), 3.88 (3H, s), 4.88 (1H, d, *J* = 9 Hz), 6.75 (1H, d, *J* = 6 Hz), 7.08—7.43 (2H, m), 7.43—7.90 (2H, m), 8.34 (1H, d, *J* = 6 Hz). IR (KBr) : 3176, 3064, 2936, 1578, 1472, 1432, 1404, 1282, 1268, 1052 cm^{-1}. *Anal.* Calcd for $C_{18}H_{19}N_3O_2S$: C, 63.32; H, 5.61; N, 12.31. Found: C, 63.19; H, 5.50; N, 12.39. MS (FAB) *m/z*: 342 ($M^+ + 1$).

2-[(*Rs*,9*R*)-4-Methoxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-ylsulfinyl]-1*H*-benzimidazole ((+)-4) According to the above procedure, (+)-**4** was obtained quantitatively from (*Rs*,9*R*)-(+)-**5** as a yellow amorphous solid, which was used for the following reactions without further purification. ^{1}H-NMR ($CDCl_3$) δ: 1.03—2.53 (7H, m), 2.90—3.33 (1H, m), 3.89 (3H, s), 4.75—5.10 (1H, m), 6.79 (1H, d, *J* = 6.0 Hz). 7.13—7.82 (4H, m), 8.36 (1H, d, *J* = 6.0 Hz). IR (KBr): 3064, 2926, 1578, 1476, 1431, 1284, 1269, 1050 cm^{-1}. $[\alpha]_D^{25}$ +109° (*c* = 1.0, MeOH). MS (FAB) *m/z*: 342 ($M^+ + 1$).

General Procedure for the Preparation of 6 as BF_4 Salts The sulfoxides (**4**) were dissolved in a stirred mixture of MeOH and equimolar 85% $HBF_4 \cdot Et_2O$ at 30—40 °C for several minutes and then allowed to stand at room temperature. The precipitates formed were collected by filtration,

washed with a small quantity of cold MeOH and MeOH–Et_2O (4 : 1), and dried under reduced pressure to yield the analytically pure sulfenamides (**6**).

3-Methoxy-5,6,7,7a-tetrahydro-4*H*-cyclohepta[*b*]pyrido[1′,9′a,9′:4,5,6][1,2,4]thiadiazino[2,3-*a*]benzimidazol-15-ium Tetrafluoroborate (6) According to the general procedure, **4** (1.18 g, 3.46 mmol) was treated with 85% $HBF_4 \cdot Et_2O$ (0.66 ml, 3.46 mmol) in MeOH (16 ml) to give **6** (1.03 g, 72%) as a yellow powder, mp 184—187 °C (dec.). ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) δ: 1.23—3.72 (8H, m), 4.34 (3H, s), 5.37—5.66 (1H, m), 7.20—8.03 (5H, m), 9.66 (1H, d, J = 6.0 Hz). IR (KBr): 2956, 1622, 1562, 1478, 1420, 1326, 1054 cm^{-1}. MS (FAB) *m/z*: 324 ($M^+ - BF_4$). *Anal.* Calcd for $C_{18}H_{18}N_3OS \cdot BF_4$: C, 52.54; H, 4.41; N, 10.22. Found: C, 52.54; H, 4.26; N, 10.22.

(7a*R*)-3-Methoxy-5,6,7,7a-tetrahydro-4*H*-cyclohepta[*b*]pyrido[1′,9′a,9′:4,5,6][1,2,4]thiadiazino[2,3-*a*]benzimidazol-15-ium Tetrafluoroborate ((−)-6) According to the general procedure, (*Rs*,9*R*)-(+)-**4** (990 mg, 2.89 mmol) was treated with 85% $HBF_4 \cdot Et_2O$ (0.55 ml, 2.89 mmol) in MeOH (10 ml) to give (−)-**6** (783 mg, 66%) as a yellow powder, mp 176—180 °C (dec.). ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) δ: 1.26—3.76 (8H, m), 4.30 (3H, s), 5.25—5.51 (1H, m), 7.42 (3H, br s), 7.60—8.06 (2H, m), 9.57 (1H, d, J = 7.0 Hz). IR (KBr): 1623, 1560, 1476, 1419, 1320, 1053 cm^{-1}. $[\alpha]_D^{25}$ −154° (c = 1.0, DMSO). MS (FAB) *m/z*: 324 ($M^+ - BF_4$). *Anal.* Calcd for $C_{18}H_{18}N_3OS \cdot BF_4$: C, 52.57; H, 4.41; N, 10.22. Found: C, 52.38; H, 4.43; N, 10.20.

Reaction of 6 with 2-Mercaptoethanol: (A) 2-{9-[2-Hydroxyethyl)-dithio]-4-methoxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridinium-1-yl}benzimidazolide (7) A 1 N HCl solution (0.19 ml, 0.19 mmol) and 2-mercaptoethanol (52 μl, 0.71 mmol) were added to a suspension of **6** (300 mg, 0.79 mmol) in CH_3CN (3 ml) and the mixture was stirred for 5 min. After removal of the CH_3CN *in vacuo*, ice-water was added and the pH of the solution was adjusted to 8—9 by addition of saturated aqueous $NaHCO_3$ solution. The reaction mixture was extracted with $CHCl_3$. The extract was washed with brine and dried ($MgSO_4$). After removal of the solvent *in vacuo*, the residue was purified by recrystallization from CH_3CN to give **7** (183 mg, 62%) as a pale yellow powder, mp 127—128 °C (dec.). ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) δ: 1.10—3.96 (13H, m), 4.20 (3H, s), 4.73—4.97 (1H, m), 6.94—7.23 (2H, m), 7.39 (1H, d, J = 7.0 Hz), 7.46—7.76 (2H, m), 8.72 (1H, d, J = 7.0 Hz). IR (KBr); 3220, 2926, 1620, 1479, 1431, 1398, 1350, 1305, 1263, 1044 cm^{-1}. MS (FAB) *m/z*: 402 ($M^+ + 1$). *Anal.* Calcd for $C_{20}H_{23}N_3O_2S_2$: C, 59.82; H, 5.77; N, 10.47. Found: C, 59.81; H, 5.77; N, 10.39.

(B) 2-(4-Methoxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-ylthio)-1*H*-benzimidazole (8) 2-Mercaptoethanol (0.1 ml, 1.43 mmol) and 1 N HCl (0.1 ml, 0.1 mmol) were added to a suspension of **6** (300 mg, 0.73 mmol) in CH_3CN (3 ml) at room temperature, and the reaction mixture formed a clear solution. After 5 min, the mixture was evaporated *in vacuo*, and ice-water was added to the residue. The pH of the mixture was adjusted to 8—9 by addition of saturated aqueous $NaHCO_3$ solution and extracted with $CHCl_3$. The extract was washed with brine and dried ($MgSO_4$). After removal of the solvent *in vacuo*, the residue was purified by recrystallization from $CHCl_3$–Et_2O to give **8** (149 mg, 63%) as a colorless powder, mp 176—179 °C. MS (FAB) *m/z*: 326 ($M^+ + 1$). The spectral data (^{1}H-NMR, IR) were identical with those of an authentic sample.[6a]

Reaction of 7 with 2-Mercaptoethanol: (C) 2-(4-Methoxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-ylthio)-1*H*-benzimidazole (8) 2-Mercaptoethanol (35 μl, 0.50 mmol) and 1 N HCl (66 μl, 0.66 mmol) were added to a solution of **7** (200 mg, 0.50 mmol) in CH_3CN (2 ml) and $CHCl_3$ (2 ml) at room temperature and the mixture was stirred at the same temperature for 0.5 h. After removal of CH_3CN and $CHCl_3$ *in vacuo*, ice-water was added and the pH of the solution was adjusted to 8—9 by addition of saturated aqueous $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2 and the extract was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by recrystallization from $CHCl_3$–Et_2O to give **8** (98 mg, 61%) as a colorless powder, mp 176—179 °C.

Reaction of 4 with 2-Mercaptoethanol: (D) 2-{9-[(2-Hydroxyethyl)-dithio]-4-methoxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridinium-1-yl}-benzimidazolide (7) 2-Mercaptoethanol (0.14 ml, 1.93 mmol) and 1 N HCl (4.2 ml) were added to a solution of **4** (700 mg, 1.93 mmol) in acetone (14 ml) at room temperature and then the mixture was stirred at room temperature for 30 min. After removal of the acetone, ice-water was added to the residue and the pH of the solution was adjusted to 8—9 by addition of saturated aqueous $NaHCO_3$ solution. The mixture was extracted with $CHCl_3$ and the extract was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by recrystallization from CH_3CN to give **7** (560 mg, 72%) as a colorless powder, mp 127—128 °C (dec.). MS (FAB) *m/z*: 402 ($M^+ + 1$). *Anal.* Calcd for $C_{20}H_{23}N_3O_2S_2$: C, 59.82; H, 5.77; N, 10.47. Found: C, 59.79; H, 5.78; N, 10.36. The spectral data (^{1}H-NMR, IR) were identical with those of **7** prepared from **6**.

2-[(9*R*)-4-Methoxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-ylthio]-1*H*-benzimidazole ((+)-8) 2-Mercaptoethanol (78 μl, 1.08 mmol) and 1 N HCl (0.1 ml, 0.1 mmol) were added to a suspension of (−)-**6** (150 mg, 0.36 mmol) in CH_3CN (2 ml) at room temperature and the reaction mixture was stirred at the same temperature for 40 min. After removal of the CH_3CN *in vacuo*, ice-water was added to the residue and the pH of the solution was adjusted to 8—9 by addition of saturated aqueous $NaHCO_3$ solution. The mixture was extracted with $CHCl_3$ and the extract was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by recrystallization from $CHCl_3$–Et_2O to give (+)-**8** (59 mg, 50%) as a colorless powder, $[\alpha]_D^{25}$ +272° (c = 0.8, MeOH). mp 188—189 °C. MS (FAB) *m/z*: 326 ($M^+ + 1$). The spectral data (^{1}H-NMR, IR) were identical with those of (+)-**8** resolved from the racemate (**8**).

General Procedure for the Preparation of 9 as CH_3SO_3H Salts The sulfoxides (**4**) were dissolved in a stirred mixture of MeOH and equimolar CH_3SO_3H at 40 °C for 2 min. After removal of the solvent *in vacuo*, the residue was recrystallized from CH_3CN to yield the analytically pure disulfides (**9**).

9,9′-Dithiobis[1-(2-benzimidazolyl)-4-methoxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridinium] Bis(methanesulfonate) (9) According to the general procedure, **4** (1.33 g, 3.90 mmol) was treated with CH_3SO_3H (0.25 ml, 3.90 mmol) in MeOH (10 ml) to give **9** (736 mg, 45%) as a colorless powder. mp 159—163 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 1.30—3.72 (16H, m), 2.70 (6H, s), 4.17 (6H, s), 4.50—4.81 (2H, m), 7.02—7.55 (8H, m), 7.53 (2H, d, J = 5.0 Hz), 8.54 (2H, d, J = 5.0 Hz). IR (KBr): 3450, 2930, 1621, 1490, 1350, 1212, 1053 cm^{-1}. MS (FAB) *m/z*: 745 ($M^+ - CH_3SO_3$), 649, 324. *Anal.* Calcd for $C_{38}H_{44}N_6O_8S_4 \cdot H_2O$: C, 53.26; H, 5.17; N, 9.81. Found: C, 52.91; H, 5.10; N, 9.71.

9,9′-Dithiobis[(9*R*)-1-(2-benzimidazolyl)-4-methoxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridinium] Bis(methanesulfonate) ((+)-9) According to the general procedure, (*Rs*,9*R*)-(+)-**4** (770 mg, 2.26 mmol) was treated with CH_3SO_3H (0.15 ml, 2.26 mmol) to give (+)-**9** (388 mg, 41%) as a colorless powder, mp 186—188 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 1.50—3.72 (16H, m), 2.70 (6H, s), 4.18 (6H, s), 4.50—4.80 (2H, m), 7.05—7.40 (8H, m), 7.46 (2H, d, J = 5.0 Hz), 8.55 (2H, d, J = 5.0 Hz). IR (KBr): 3466, 2932, 1620, 1485, 1350, 1212, 1053 cm^{-1}. $[\alpha]_D^{26}$ +497° (c = 1.0, $CHCl_3$). MS (FAB) *m/z*: 745 ($M^+ - CH_3SO_3$), 649, 324. *Anal.* Calcd for $C_{38}H_{44}N_6O_8S_4 \cdot 3/2H_2O$: C, 52.58; H, 5.46; N, 9.68. Found: C, 52.72; H, 5.42; N, 9.72.

Reaction of 9 with 2-Mercaptoethanol: (A) 2-(4-Methoxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-ylthio)-1*H*-benzimidazole (8) 2-Mercaptoethanol (74 μl, 2.26 mmol) and 1 N HCl (0.1 ml, 0.1 mmol) were added to a solution of **9** (200 mg, 0.24 mmol) in CH_3CN (3 ml) at room temperature and the mixture was stirred at the same temperature for 30 min. After removal of the CH_3CN, ice-water was added and the pH of the solution was adjusted to 8—9 by addition of saturated aqueous $NaHCO_3$ solution. The reaction mixture was extracted with $CHCl_3$ and the extract was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on alumina with AcOEt–hexane (1 : 3). Recrystallization of the product from $CHCl_3$–Et_2O gave **8** (58 mg, 74%) as a colorless powder, mp 177—179 °C. MS (FAB) *m/z*: 326 ($M^+ + 1$). The spectral data (^{1}H-NMR, IR) were identical with those of an authentic sample.[6a]

(B) 2-[(9*R*)-4-Methoxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-ylthio]-1*H*-benzimidazole ((+)-8) By the same procedure as described for **8**, (+)-**9** (200 mg, 0.24 mmol) was allowed to react with 2-mercaptoethanol (74 μl, 2.26 mmol) in the presence of 1 N HCl (0.1 ml, 0.1 mmol) in CH_3CN (3 ml) to give (+)-**8** (68 mg, 89%) as a colorless powder, $[\alpha]_D^{25}$ +272° (c = 1.0, MeOH). mp 188—189 °C. MS (FAB) *m/z*: 326 ($M^+ + 1$). The spectral data (^{1}H-NMR, IR) were identical with those of (+)-**8** resolved from the racemate (**8**).

Inhibition of ($H^+ + K^+$)-ATPase Activities The assay procedure was described in detail in our preceding paper.[5,6a] Japanese white rabbits (1.5—3.5 kg) were used and gastric ($H^+ + K^+$)-ATPase was obtained from the parietal cell-rich fraction of the rabbit stomach in accordance with the method of Saccomani *et al.*[8] Briefly, membrane protein (80 μg

protein) was preincubated for 30 min at 37°C in an assay medium consisting of 10 mM imidazole buffer (pH 6.0) and various concentrations of compounds (final volume of 0.5 ml). The enzyme reaction was started by adding 0.5 ml of a solution containing 4 mM $MgCl_2$, 4 mM ATP, 2×10^{-5} M valinomycin and 80 mM imidazole buffer (pH 7.4), with or without 20 mM KCl. The reaction was stopped after a 15 min incubation at 37 °C by placing the tubes in ice-slush and adding 1 mM ice-cold 12% trichloroacetic acid. Inorganic phosphate produced from ATP hydrolysis was measured by using a commercially available assay reagent for inorganic phosphate (Iatron-Ma 701 Pi, Iatron, Tokyo) and an automatic analyzer (COBAS FARA, Roche, Switzerland).

Inhibition of Gastric Acid Secretion Measurement of gastric acid secretion was performed according to the method described in our preceding paper.[5,6a)] Male Sprague-Dawley (213—364 g) rats received a double-lumen cannula into the forestomach and the pylorus was ligated. The gastric secretion was stimulated by a constant infusion of tetragastrin and the gastric effluent was collected at 10 min intervals. The acid output was determined by titration of the perfusate with 0.01 N NaOH. Test compounds were administered intravenously after gastric acid secretion reached a plateau.

References and Notes

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