SYNTHESIS AND ISOMERIZATION OF OPTICAL ACTIVE 2-[(6,7,8,9-TETRAHYDRO-5*H*-CYCLOHEPTA[*b*]PYRIDIN-9-YL)SULFINYL]-1*H*-BENZIMIDAZOLE ANALOGS

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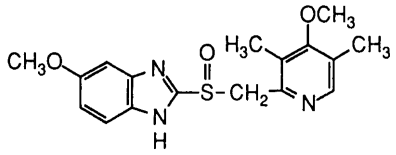
Four stereoisomers, (*Rs*,9*R*)-(+)-**5**, (*Ss*,9*R*)-(−)-**5**, (*Ss*,9*S*)-(−)-**5** and (*Rs*,9*S*)-(+)-**5**, were prepared from optically active (*R*)-(+)-**3** and (*S*)-(−)-**3**, and their absolute structures were unambiguously determined by X-ray crystallographic analysis of (*Ss*,9*R*)-(−)-**5**. Epimerization of the carbon bearing the sulfinyl group of **5** could be carried out with $NaOCH_3$. At the same time, it was found that the stereochemistries of the sulfinyl group of (*Rs*,9*R*)-(+)-**5** and (*Ss*,9*S*)-(−)-**5** were spontaneously inverted in MeOH solution at room temperature.

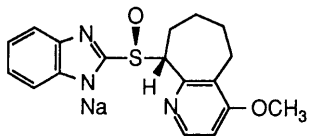
KEYWORDS absolute configuration ; optical resolution ; sulfinyl group isomerization ; chiral sulfoxide ; antipeptic agent

The gastric mucosal (H^++K^+)-ATPase, which is located in the apical membrane of the parietal cell and plays a major role in acid secretion,[1] has become a target for numerous investigations. Among synthetic studies on exploring (H^++K^+)-ATPase inhibitor, omeprazole (**1**)[2] has recently been introduced to the market as a clinically useful agent. We have reported in the preceding paper that a novel antipeptic agent (**2**, TY-11345) with 6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine moiety had a more potent effect than that of omeprazole (**1**).[3] Although compound (**2**) could be synthesized in a diastereomerically pure form,[3] its relative stereochemistry between two chiral centers has not been determined.

In this paper, we report the determination of the stereochemistry of **2**, epimerization of the α-carbon of the sulfinyl group and isomerization of the sulfinyl group.

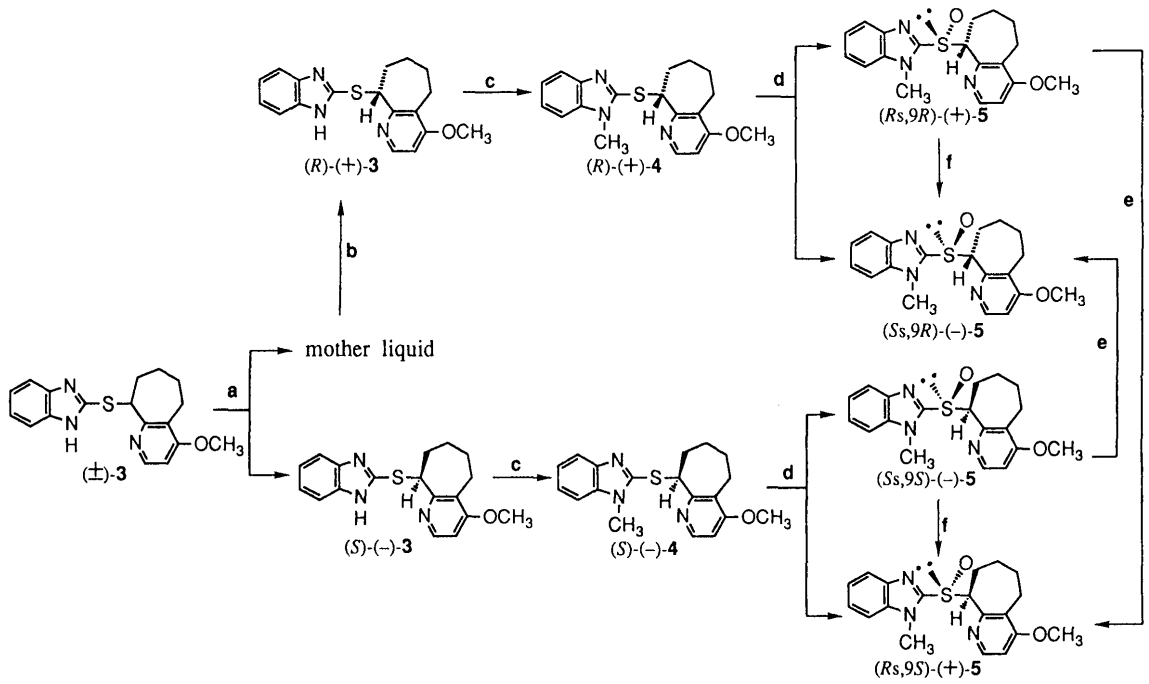


omeprazole (1)



TY-11345 (2)

Four diastereoisomeric sulfoxides (**5**) were prepared as shown in Chart 1. At the outset the racemate (**3**)[3] was treated with equimolar amount of L-tartaric acid in MeOH at room temperature and the crystalline precipitate was treated with $NaHCO_3$ to liberate free amine [(*S*)-(−)-**3**] in 45 % yield. Purification of (*S*)-(−)-**3** was performed by repeated recrystallization from EtOH. The filtrate was neutralized with $NaHCO_3$, and the resultant free amine was treated with 0.65 molar amount of D-tartaric acid in MeOH at room temperature. (*R*)-(+)-**3** was obtained in 45 % yield by a procedure similar to that described for (*S*)-(−)-**3**. The optical purities of (*R*)-(+)-**3** and (*S*)-(−)-**3** were determined to be 100% enantiomer excess (ee), respectively, by high-performance liquid chromatography (HPLC) using a chiral stationary phase column (Chiralcel OD®). Thus (±)-sulfide (**3**) was resolved to (*R*)-(+)-**3** and (*S*)-(−)-**3**. Methylation of (*R*)-(+)-**3** and (*S*)-(−)-**3** with MeI in the presence of $NaOCH_3$ gave (*R*)-(+)-**4** and (*S*)-(−)-**4** in quantitative yield, respectively. Oxidation of the enantiomeric sulfides (*R*)-(+)-**4** and (*S*)-(−)-**4** with *m*-CPBA in CH_2Cl_2 proceeded quantitatively at -18 °C to give a diastereoisomeric mixture of the corresponding sulfoxides (+)-**5** and (−)-**5** in ratios of 1 : 3.8 and 1 : 2.3, respectively.[5,6] The stereoisomers of the sulfoxide (**5**) were easily separated from each other by chromatographic purification of the crude reaction products followed by recrystallization.



a : 1) L-tartaric acid, MeOH, r.t. 2) neutralization with $NaHCO_3$ 3) recrystallization from EtOH **b** : 1) neutralization with $NaHCO_3$ 2) D-tartaric acid, MeOH, r.t. 3) neutralization with $NaHCO_3$ 4) recrystallization from EtOH **c** : CH_3I, 28% $NaOCH_3$, THF, r.t., 1.5 h **d** : 1) *m*-CPBA, CH_2Cl_2, −18 °C, 1 h 2) chromatographic purification 3) recrystallization from MeOH for (*Ss*,9*R*)-(−)-**5** and (*Rs*,9*S*)-(+)-**5**, recrystallization from acetone for (*Rs*,9*R*)-(+)-**5** and (*Ss*,9*S*)-(−)-**5** **e** : 28% $NaOCH_3$, CH_2Cl_2, r.t., 5 min **f** : MeOH, r. t., 165 h

Chart 1

The absolute configuration of (*Ss*,9*R*)-(−)-**5** was confirmed by X-ray crystallographic analysis as shown in Fig.1.[7] Consequently, the absolute configurations at C (9) and sulfinyl group for each isomer of **3** – **5** are assigned as depicted in Chart 1.

We have previously reported that the treatment of a diastereoisomeric mixture with $NaOCH_3$ gave predominantly a diastereomerically pure product.[3] As expected, optically active (*Rs*,9*R*)-(+)-**5** and (*Ss*,9*S*)-(−)-**5** were treated with $NaOCH_3$ in CH_2Cl_2 to give (*Rs*,9*S*)-(+)-**5** (88%) and (*Ss*,9*R*)-(−)-**5** (73%), respectively (Chart 1). The epimerization of the sulfoxides could be interpreted by equilibration *via* the anionic intermediate.[3] Unexpectedly, it was found that (*Rs*,9*R*)-(+)-**5** and (*Ss*,9*S*)-(−)-**5** were spontaneously inverted to (*Ss*,9*R*)-(−)-**5** (84%) and (*Rs*,9*S*)-(+)-**5** (85%) in MeOH at room temperature, respectively (Chart 1). As a possible mechanism of the isomerization, it may be indicated that sulfurane intermediate **A** generated by addition of H_2O in MeOH is involved (Fig.2).[8] In any event, these easy inversions observed in the present study must be attributed to the preference for **B** over **C** for steric and electronic reasons (Fig.3).

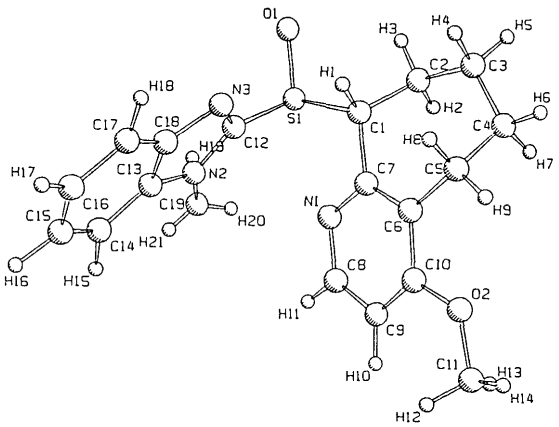


Fig.1. Stereoscopic View of the Molecule of (*Ss*,9*R*)-(−)-**5**

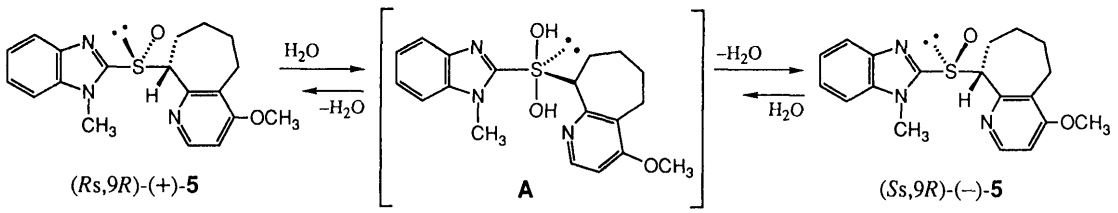


Fig. 2. Isomerization Mechanism *via* Sulfurane Intermediate

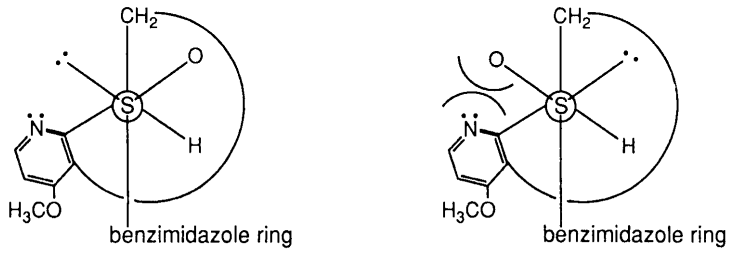


Fig. 3. Newman Projections of (*Ss*,9*R*)-(–)-**5** and (*Rs*,9*R*)-(+)-**5**

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4) The optical purities of (*S*)-(–)-**3** and (*R*)-(+)-**3** were measured by HPLC under the following conditions : Chiralcel OD® of 4.6 mm i.d. x 25 cm (Daicel Chemical Industries, Tokyo, Japan) ; mobile phase, EtOH - hexane (1 : 5, V/V) ; flow rate, 0.4 ml / min ; detection, ultraviolet (UV) at 300 nm : (*S*)-(–)-**3**, 100 % ee (t_R : 16.93 min), $[\alpha]_D^{25}$ –272 ° (*c*=1.0, MeOH) ; (*R*)-(+)-**3**, 100% ee (t_R : 15.38 min), $[\alpha]_D^{25}$ +272 ° (*c*=1.0, MeOH).

5) The oxidation of enantiomeric sulfide [(*R*)-(+)-**3**] with *m*-CPBA also afforded a diastereoisomeric mixture of the corresponding sulfoxides. However, it was difficult to isolate each isomer in a pure form by repeated recrystallization.

6) The enantiomeric purities and the diastereoisomeric purities of four stereoisomeric sulfoxides (**5**) were measured by HPLC under the following conditions : Chiralcel OD® of 4.6 mm i.d. x 25 cm (Diacel Chemical Industries, Tokyo, Japan) ; mobile phase, EtOH-hexane (1 : 8, V / V) ; flow rat 1 ml / min ; detection, UV at 300 nm. The optical purities were determined to be 100 % as follows : (*Rs*,9*R*)-(+)-**5**, (t_R : 26.88 min) ; (*Ss*,9*R*)-(–)-**5**, (t_R : 14.57 min) ; (*Ss*,9*S*)-(–)-**5** (t_R : 23.49 min) ; (*Rs*,9*S*)-(+)-**5** (t_R : 13.49min). a) (*Rs*,9*R*)-(+)-**5** : a colorless powder, mp 136-138 °C, 46% yield ; IR (KBr) : 2970, 1581, 1482, 1452, 1287, 1038 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 1.15-3.45 (8H, m), 3.83 (3H, s), 4.10 (3H, s), 4.93-5.18 (1H, m), 6.67 (1H, d, *J*= 5.0Hz), 7.08-7.46 (3H, m), 7.67-7.92 (1H, m), 8.16 (1H, d, *J*=5.0Hz). $[\alpha]_D^{25}$ +265 ° (*c*=1.0, $CHCl_3$). MS (FAB) *m/z* : 356 (M^++1). *Anal.* Calcd for $C_{19}H_{21}N_3O_2S$: C, 64.20 ; H, 5.95 ; N, 11.82. Found : C, 64.02 ; H, 5.95 ; N, 11.77. b) (*Ss*,9*R*)-(+)-**5** : a colorless powder, mp 162-163 °C, 28 % yield ; IR (KBr) : 2928, 1582, 1472, 1458, 1284, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 1.16-3.42 (8H, m), 3.73 (3H, s), 4.12 (3H, s), 5.42 (1H, d, *J*=9.0Hz), 6.47 (1H, d, *J*=5.0Hz), 7.10-7.46 (3H, m), 7.53-8.02 (1H, m), 7.89 (1H, d, *J*=5.0Hz). $[\alpha]_D^{25}$ –137 ° (*c*=1.0, $CHCl_3$). MS (FAB) *m/z* : 356 (M^++1). *Anal.* Calcd for $C_{19}H_{21}N_3O_2S$: C, 64.20 ; H, 5.95 ; N, 11.85. Found : C, 64.22 ; H, 5.96 ; N, 11.84. c) (*Ss*,9*S*)-(–)-**5** : a colorless powder, mp 136-138 °C, 53 % yield ; $[\alpha]_D^{25}$ –265 ° (*c*=1.0, $CHCl_3$). MS (FAB) *m/z* : 356 (M^++1). *Anal.* Calcd for $C_{19}H_{21}N_3O_2S$: C, 64.20 ; H, 5.95 ; N, 11.82. Found : C, 64.05 ; H, 5.93 ; N, 11.79. The spectral data (IR, ^{1}H-NMR) were identical with those of (*Rs*,9*R*)-(+)-**5**. d) (*Rs*,9*S*)-(+)-**5** : a colorless powder, mp 162-163 °C, 25% yield ; $[\alpha]_D^{25}$ +138 ° (*c*=1.0, $CHCl_3$). MS (FAB) *m/z* : 356 (M^++1). *Anal.* Calcd for $C_{19}H_{21}N_3O_2S$: C, 64.20 ; H, 5.95 ; N, 11.82. Found : C, 64.32 ; H, 5.96 ; N, 11.82. The spectral data (IR,^{1}H-NMR) were identical with those of (*Ss*,9*R*)-(–)-**5**.

7) Suitable crystals of (*Ss*,9*R*)-(–)-**5** for X-ray crystallographic analysis were grown from a MeOH solution. A crystal with dimensions of 0.2 x 0.25 x 0.25 mm was used for data collection. Diffraction measurements were carried out on a Rigaku AFC-5R diffractometer using graphite-monochromated Cu*Kα* radiation (λ=1.5418Å). Crystal data for (*Ss*,9*R*)-(–)-**5**, $C_{19}H_{21}N_3O_2S$, are as follows : *Mr*=355.45, monoclinic, space group $P2_1$, *a*=9.262(4)Å, *b*=30.381(5)Å, *c*=6.495(4)Å, *V*= 1828(2)Å^3, *Z*=4, *Dc*=1.29 g / cm^3. A total of 1731 independent reflections in the range of $2\theta < 124°$ were measured and corrected for Lorenz and polarization factors. The structure was solved by a direct method, and atomic parameters were refined by a full-matrix least-squares method. The final *R* value was 0.042 (*Rw*=0.048) for the 2711 observed reflections.

8) A detailed mechanism of this isomerization is not manifest, but the sulfinyl group included in 2-[(2-pyridylmethyl)sulfinyl]-1*H*-benzimidazole system such as omeprazole (**1**) would be inverted gradually. See P. Erlandsson, R. Isaksson, P. Lorentzon, P. Lindberg, *J. Chromatogr., Biomed. Appl.*, 532, 305 (1990).

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