SYNTHESIS AND ISOMERIZATION OF OPTICAL ACTIVE 2-[(6,7,8,9-TETRAHYDRO-5H-CYCLOHEPTA[*b*]PYRIDIN-9-YL)SULFINYL]-1H-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 NaOCH₃. 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 ; anti-peptic 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 anti-peptic agent (**2**, TY-11345) with 6,7,8,9-tetrahydro-5H-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 NaHCO₃ 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 NaHCO₃, 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 NaOCH₃ gave (*R*)-(+)-**4** and (*S*)-(–)-**4** in quantitative yield, respectively. Oxidation of the enantiomeric sulfides (*R*)-(+)-**4** and (*S*)-(–)-**4** with *m*-CPBA in CH₂Cl₂ 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 NaHCO₃ 3) recrystallization from EtOH **b** : 1) neutralization with NaHCO₃ 2) D-tartaric acid, MeOH, r.t. 3) neutralization with NaHCO₃ 4) recrystallization from EtOH **c** : CH₃I, 28% NaOCH₃, THF, r.t., 1.5 h **d** : 1) *m*-CPBA, CH₂Cl₂, -18 °C, 1 h 2) chromatographic purification 3) recrystallization from MeOH for (Ss,9R)-(-)-5 and (Rs,9S)-(+)-5, recrystallization from acetone for (Rs,9R)-(+)-5 and (Ss,9S)-(-)-5 **e** : 28% NaOCH₃, CH₂Cl₂, r.t., 5 min **f** : MeOH, r. t., 165 h

Chart 1

The absolute configuration of (Ss,9R)-(-)-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 NaOCH₃ gave predominantly a diastereomerically pure product.³⁾ As expected, optically active (Rs,9R)-(+)-5 and (Ss,9S)-(-)-5 were treated with NaOCH₃ in CH₂Cl₂ to give (Rs,9S)-(+)-5 (88%) and (Ss,9R)-(-)-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,9R)-(+)-5 and (Ss,9S)-(-)-5 were spontaneously inverted to (Ss,9R)-(-)-5 (84%) and (Rs,9S)-(+)-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 H₂O 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. Stereospecific View of the Molecule of (Ss,9R)-(-)-5

Fig.2. Isomerization Mechanism via Sulfurane Intermediate

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

REFERENCES AND NOTES

- 1) a) J. G. Forte, H. C. Lee, *Gastroenterology*, **73**, 921 (1977); b) T. Berglindh, D. A. Dibona, S. Ito, G. Sacks, *Am. J. Physiol.*, **238**, 165 (1980).
- 2) a) W. B. Im, J. C. Sih, D. P. Blakeman, J. P. Mc Grath, *J. Biol. Chem.*, **260**, 4591 (1985); b) A. Brändström, P. Lindberg, U. Junggren, B. Wallmark, *Scand. J. Gastroenterol.*, **21** (Suppl. 118), 54 (1986).
- 3) S. Yamada, T. Goto, E. Shimanuki, S. Narita, *Chem. Pharm. Bull.*, **42**, 718 (1994).
- 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 (Daicel Chemical Industries, Tokyo, Japan); mobile phase, EtOH-hexane (1 : 8, V/V); flow rate 1 ml/min; detection, UV at 300 nm. The optical purities were determined to be 100 % as follows: $(Rs,9R)$ -(+)-**5**, (t_R : 26.88 min); $(Ss,9R)$ -(-)-**5**, (t_R : 14.57 min); $(Ss,9S)$ -(-)-**5** (t_R : 23.49 min); $(Rs,9S)$ -(+)-**5** (t_R : 13.49 min). a) $(Rs,9R)$ -(+)-**5**: a colorless powder, mp 136-138 °C, 46% yield; IR (KBr): 2970, 1581, 1482, 1452, 1287, 1038 cm⁻¹. ¹H-NMR (CDCl₃) 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, CHCl₃). MS (FAB) m/z : 356 (M^+ +1). Anal. Calcd for C₁₉H₂₁N₃O₂S: C, 64.20; H, 5.95; N, 11.82. Found: C, 64.02; H, 5.95; N, 11.77. b) $(Ss,9R)$ -(+)-**5**: a colorless powder, mp 162-163 °C, 28 % yield; IR (KBr): 2928, 1582, 1472, 1458, 1284, 1040 cm⁻¹. ¹H-NMR (CDCl₃) 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, CHCl₃). MS (FAB) m/z : 356 (M^+ +1). Anal. Calcd for C₁₉H₂₁N₃O₂S: C, 64.20; H, 5.95; N, 11.85. Found: C, 64.22; H, 5.96; N, 11.84. c) $(Ss,9S)$ -(-)-**5**: a colorless powder, mp 136-138 °C, 53 % yield; $[\alpha]_D^{25}$ -265° (c =1.0, CHCl₃). MS (FAB) m/z : 356 (M^+ +1). Anal. Calcd for C₁₉H₂₁N₃O₂S: C, 64.20; H, 5.95; N, 11.82. Found: C, 64.05; H, 5.93; N, 11.79. The spectral data (IR, ¹H-NMR) were identical with those of $(Rs,9R)$ -(+)-**5**. d) $(Rs,9S)$ -(+)-**5**: a colorless powder, mp 162-163 °C, 25% yield; $[\alpha]_D^{25}$ +138° (c =1.0, CHCl₃). MS (FAB) m/z : 356 (M^+ +1). Anal. Calcd for C₁₉H₂₁N₃O₂S: C, 64.20; H, 5.95; N, 11.82. Found: C, 64.32; H, 5.96; N, 11.82. The spectral data (IR, ¹H-NMR) were identical with those of $(Ss,9R)$ -(-)-**5**.
- 7) Suitable crystals of $(Ss,9R)$ -(-)-**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 CuK α radiation (λ =1.5418Å). Crystal data for $(Ss,9R)$ -(-)-**5**, C₁₉H₂₁N₃O₂S, are as follows: M_r =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)Å³, Z =4, D_c =1.29 g/cm³. A total of 1731 independent reflections in the range of $2\theta < 124^\circ$ were measured and corrected for Lorentz 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 (R_w =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]-1H-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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