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Synthesis of the Alkaloid from *Thermoactinomyces* Species

Masayuki Onda and Yaeko Konda

School of Pharmaceutical Sciences, Kitasato University[1]

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The (*S*)-(+)-acid (**3**) obtained from (*S*)-(+)-alanine is protected the amino group with the benzyloxycarbonyl group and is combined with tryptamine to give the (*S*)-amide-urethane (**5**). Hydrogenolysis of **5** affords the (*S*)-(−)-amide (**6**) which is identified as the alkaloid (**1**) obtained from *Thermoactinomyces* strain TM-64.

Keywords——protection of the amino group; hydrogenolysis; indole derivative; thiazole derivative; circular dichroism curve; nuclear magnetic resonance

Previously, we reported the structure of the alkaloid obtained from *Thermoactinomyces* strain TM-64 to be N-3′-β′-indolylethyl-2-α-aminoethylthiazole-4-carboxamide (**1**) on the basis of its chemical reactions and physico-chemical properties.[2] Also, the *S*-configuration of the α-carbon to the thiazole ring of **1** was assigned by the circular dichroism (CD) curve of the

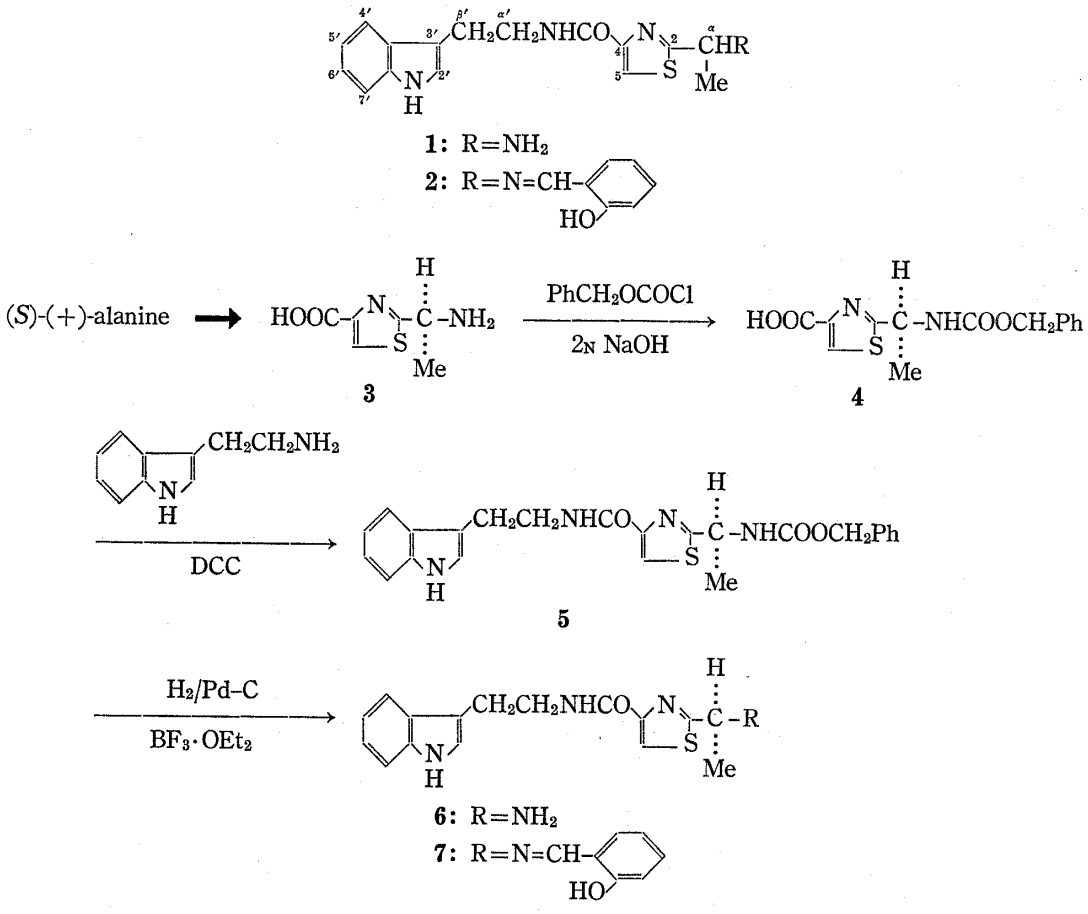

Chart 1

1) Location: *Minato-ku, Tokyo 108, Japan.*
2) Y. Konda, Y. Suzuki, S. Ōmura, and M. Onda, *Chem. Pharm. Bull.* (Tokyo), **24**, 92 (1976).

N-salicylidene derivative (**2**). We now report the synthesis of **1** which unequivocally confirmed the above conclusion.

The points of this synthesis are to gain (αS)-2-α-aminoethylthiazole-4-carboxylic acid (**3**) and to combine **3** with tryptamine without loss of the optical purity.

Although the synthesis of **3** was already reported by Dean *et al.*,[3] its optical rotation was not described therein. We carefully followed their procedure and obtained the (*S*)-(+)-acid (**3**) as colorless crystals of $[\alpha]_D^{20}$ +12° from (*S*)-(+)-alanine. The Schotten-Baumann reaction of **3** with benzyl chloroformate gave the (*S*)-urethane (**4**). Its infrared (IR) band at 1720 cm^{-1} (NHCOO) and proton magnetic resonance (PMR) signal at δ 5.03 (2H, s, CH_2Ph) support the structure of **4**. Reaction of **4** with tryptamine in the presence of dicyclohexylcarbodiimide (DCC) afforded the (*S*)-amide-urethane (**5**). Its IR spectrum shows the band due to the newly introduced amide group at 1660 cm^{-1} instead of the carbonyl band of carboxyl group at 1690 cm^{-1} in **4**. Hydrogenolysis of **5** over palladium-carbon in the presence of boron trifluoride etherate provided the (*S*)-(−)-amide (**6**), mp 134—136°, $[\alpha]_D^{20}$ −2.6°. Although its physical constants are smaller than those (mp 145—147°, $[\alpha]_D^{20}$ −8.3°) of **1**, their IR and PMR spectra resemble closely. The N-salicylidene derivative (**7**) derived from **6** shows $[\alpha]_D^{20}$ +16.2° which is smaller than $[\alpha]_D^{20}$ +81° of **2**. The CD curve of **7** shows a similar pattern with weaker molecular ellipticity to that of **2**. The optical properties of **6** and **7** observed exhibit the presence of racemate in both compounds. Nevertheless, since **6** and **7** show the optical behaviors similar to those of **1** and **2**, respectively, the configuration of the alkaloid (**1**) can be surely determined to be *S*.

Experimental

Melting points were determined on a micro hot-stage and are uncorrected. IR spectra were taken on a JASCO IR-G. PMR spectra were measured with a JEOL JNM PS-100 at 100 MHz. CD curves were taken on a JASCO J-20. Mass spectra (MS) were recorded on a JEOL JMS-OIS.

(αS)-(+)-2-α-Aminoethylthiazole-4-carboxylic Acid (3)[3]——Colorless pillars of mp *ca.* 280° (dec) (from EtOH–H_2O). $[\alpha]_D^{20}$ +12° (*c*=0.83, H_2O). IR ν_{max}^{KBr} cm^{-1}: 1575 (COO⁻). PMR (D_2O) δ: 8.18 (1H, br s, 5-H), 4.98 (1H, q, *J* 7 Hz, α-H), 1.85 (3H, d, *J* 7 Hz, α-Me). MS *m/e*: M^+, 172.031. Calcd. for $C_6H_8N_2O_2S$: M, 172.030. The HCl salt: Colorless needles of mp 260—262° (dec.) (from ethyl acetate–MeOH).

(αS)-2-α-Benzyloxycarbonylaminoethylthiazole-4-carboxylic Acid (4)——To a stirred solution of the HCl salt (48 mg) of **3** in 2 N NaOH (0.2 ml) were alternately added 30% benzyl chloroformate–toluene solution (91 mg) and 4 N NaOH (0.05 ml) in one-fourth portion over 30 min at 5°. After 40 min of stirring at room temperature, the reaction mixture was extracted with ether. The aqueous layer was acidified with conc. HCl and then extracted with chloroform. The residue (45 mg) obtained from the chloroform layer was recrystallized from chloroform to give **4** as colorless needles of mp 180—181°. IR ν_{max}^{KBr} cm^{-1}: 1720 (NHCOO), 1690 (COOH). PMR (acetone-d_6) δ: 8.17 (1H, s, 5-H), 7.25 (5H, s, aromatic H's), 7.08 (2H, br, COOH and NH), 5.19—4.85 (1H, m, α-H), 5.03 (2H, s, CH_2Ph), 1.57 (3H, d, *J* 7 Hz, α-Me). MS *m/e*: M^+, 306.067. Calcd. for $C_{14}H_{14}N_2O_4S$: M, 306.067.

(αS)-N-3′-β′-Indolylethyl-2-α-benzyloxycarbonylaminoethyl-thiazole-4-carboxamide (5)——To a stirred solution of **4** (125 mg) in acetonitrile (2 ml) were added a solution of tryptamine (32.5 mg) in methylene chloride (1 ml) and then a solution of DCC (21.2 mg) in methylene chloride (1 ml) at 0—5°. After stirring for 1 hr at 0—5°, again, a solution of tryptamine (32.5 mg) in methylene chloride (1 ml) and a solution of DCC (21.2 mg) in methylene chloride (1 ml) were added and stirring was continued for 8 hr at 0—5°. The reaction mixture was filtered to remove off N,N′-dicyclohexylurea and the filtrate was evaporated *in vacuo*, giving an oil. Its pre TLC[4] (silicagel plates, 0.4 mm; $CHCl_3$/MeOH=20/1, v/v) gave **5** (71 mg) as colorless needles of mp 147—149° (from hexane). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (NHCOO), 1660 (NHCO). PMR ($CDCl_3$) δ: 8.24 (1H, br, $N_{(1')}$ H), 7.96 (1H, s, 5-H), 7.64 (1H, q, *J* 8 and 3 Hz, 7′-H), 7.42 (1H, m, NHCO), 7.37 (5H, s, aromatic H's), 7.20—7.00 (4H, m, aromatic H's), 5.55 (1H, d, *J* 8 Hz, NHCOO), 5.13 (2H, s, CH_2Ph), 5.09 (1H, quin, *J* 8 Hz, α-H), 3.72 (2H, q, *J* 7 Hz, α′-H_2), 3.04 (2H, t, *J* 7 Hz, β′-H_2), 1.53 (3H, d, *J* 8 Hz, α-Me). MS *m/e*: M^+, 448.158. Calcd. for $C_{24}H_{24}N_4O_3S$: M, 448.156.

(αS)-(−)-N-3′-β′-Indolylethyl-2-α-aminoethylthiazole-4-carboxamide (6)——A mixture of **6** (40 mg), $BF_3 \cdot OEt_2$ (55 mg) and 10% Pd-C (40 mg) in dry methanol (4 ml) was shaken with H_2 for 4 hr at 40°. The

3) B.M. Dean, M.P.V. Mijovic, and J. Walker, *J. Chem. Soc.*, **1961**, 3394.
4) Preparative thin-layer chromatography.

reaction mixture was filtered and the filtrate was evaporated *in vacuo*. The remaining residue was purified by pre TLC (silica gel plates, 0.4 mm; $CHCl_3$/MeOH=10/1, v/v) to afford **6** (11 mg) as light yellow needles of mp 133—134° (from benzene). $[\alpha]_D^{20}$ −2.6° (c=1, EtOH). IR ν_{max}^{KBr} cm^{-1}: 1645 (NHCO). PMR ($CDCl_3$) δ: 8.15 (1H, br, $N_{(1')}$ H), 7.99 (1H, br s, 5-H), 7.64 (1H, q, J 8 and 3 Hz, 7'-H), 7.47 (1H, m, NHCO), 7.43—7.04 (4H, m, aromatic H's), 4.29 (1H, q, J 7 Hz, α-H), 3.78 (2H, q, J 7 Hz, α'-H_2), 3.08 (2H, t, J 7 Hz, β'-H_2), 1.70 (2H, s, NH_2), 1.49 (3H, d, J 7 Hz, α-Me). MS m/e: M^+, 314.121. Calcd. for $C_{16}H_{18}N_4OS$: M, 314.119.

The Alkaloid (1)[2,5]——Light yellow needles of mp 145—147°. $[\alpha]_D^{20}$ −8.3° (c=1, EtOH). IR ν_{max}^{KBr} cm^{-1}: 1645 (NH). PMR ($CDCl_3$) δ: 8.64 (1H, br, $N_{(1')}$ H), 7.97 (1H, br s, 5-H), 7.65 (1H, q, J 8 and 3 Hz, 7'-H), 7.52 (1H, m, NHCO), 7.41—7.03 (4H, m, aromatic H's), 4.27 (1H, q, J 7 Hz, α-H), 3.75 (2H, q, J 7 Hz, α'-H_2), 3.06 (2H, t, J 7 Hz, β'-H_2), 1.85 (2H, s, NH_2), 1.47 (3H, d, J 7 Hz, α-Me).

The Salicylidene Derivative (7)——A solution of **6** (8 mg) and salicylaldehyde (3.7 mg) in dry ethanol (3 ml) was refluxed for 2.5 hr. After removal of the solvent *in vacuo*, the resulting residue was purified by pre TLC (silica gel plates, 0.4 mm; $CHCl_3$/MeOH=50/1, v/v) to give **7** (7 mg) as colorless plates of mp 158—160° (from benzene–hexane). $[\alpha]_D^{20}$ +16.2° (c=0.59, EtOH). CD (c=0.0015, EtOH) $[\theta]^{20}$ (nm): +920 (316) (positive maximum), −1393 (273) (negative maximum), +2784 (247) (positive maximum), +2090 (237) (negative maximum), +3622 (229) (positive maximum). MS m/e: M^+, 418.143. Calcd. for $C_{23}H_{22}N_4O_2S$: M, 418.146.

The Salicylidene Derivative (2)[2]——Light yellow needles of 155—156° (from benzene–hexane). $[\alpha]_D^{20}$ +81° (c=0.38, EtOH). CD (c=0.001, EtOH) $[\theta]^{23}$ (nm): +19228 (316) (positive maximum), −1881 (276) (negative maximum), +94050 (252) (positive maximum), +31350 (237) (negative maximum), +52250 (230) (positive maximum).

5) The data were taken after repeated recrystallizations and those reported in lit.[2] are revised herein.