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Synthetic Studies on β -Lactam Antibiotics. XIV.¹⁾ Synthesis of 7H-Azeto[1,2-*a*]thieno[2,3-*c*]pyridine Derivatives²⁾

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Cycloaddition of the 4,5-dihydrothieno[2,3-*c*]pyridine (6) and phthalimidoacetyl chloride gave a novel tricyclic β -lactam; methyl 4,5,8,8a-tetrahydro-7-oxo-8-phthalimido-7H-azeto[1,2-*a*]thieno[2,3-*c*]pyridine-5-carboxylate (7). On deprotection followed by acylation, this gave the 8-acylamino derivatives 9 and 10.

Keywords—tricyclic β -lactam; azeto[1,2-*a*]thieno[2,3-*c*]pyridine derivative; 4,5-dihydrothieno[2,3-*c*]pyridine; imine-ketene cycloaddition; β -lactam antibiotics

It has recently been found that non-classical β -lactam antibiotics, having structures differing from penam and cephem, possess interesting biological activities.⁴⁾ These findings have brought to light a new problem concerning the structure-activity relationship of β -lactam antibiotics. Syntheses of new types of β -lactam have been achieved by several workers^{5,6)} leading to the discovery of some therapeutically useful compounds possessing antibiotic activities as potent as those of the natural penicillins and cephalosporins.⁶⁾ We previously reported the synthesis of 1,9b-dihydro-2H,4H-2-oxoazeto[1,2-*c*][1,3]benzoxazine derivatives (1) in a search for new antibiotics.⁷⁾ In a continuation of this study, the synthesis of novel tricyclic β -lactams containing the 7H-azeto[1,2-*a*]thieno[2,3-*c*]pyridines skeleton (2) has been investigated and our results are described here.



Chart 1

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- 3) Location: a) Aobayama, Sendai 980, Japan; b) Sakurashinmachi, Setagaya-ku, Tokyo 154, Japan.
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The important intermediate, 4,5-dihydrothieno[2,3-*c*]pyridine (6), was prepared by means of the Bischler-Napieralski reaction⁸⁾ as follows. Condensation of 3-thienyl bromide (3)⁹⁾ with diethyl formamidomalonate¹⁰⁾ in the presence of sodium methoxide, followed by demethoxycarbonylation of the resulting dimethyl ester (4)¹¹⁾ by heating with sodium chloride in wet dimethyl sulfoxide,¹²⁾ gave the amido ester (5). Bischler-Napieralski reaction of 5 was carried out by stirring with phosphorus pentachloride in chloroform at room temperature to afford the 4,5-dihydrothieno[2,3-*c*]pyridine (6) in 71% yield. The nuclear magnetic resonance (NMR) spectrum of 6 showed two aromatic protons at 6.97 and 7.45 ppm, each as a doublet with a coupling constant $J=4.8$ Hz, indicating that cyclization has occurred at the α -position of the thiophene ring.^{13,14)}

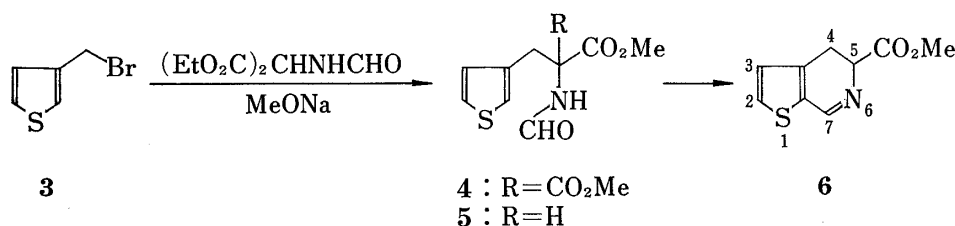


Chart 2

Since Bose and co-workers reported that imine group in a dihydropyridine ring reacted with a ketene to yield the β -lactam compound,^{5b)} cycloaddition of the above cyclic imine (6) with a ketene was examined. On treatment of 6 with phthalimidoacetyl chloride¹⁵⁾ in the presence of triethylamine, the β -lactam (7) was obtained in 24% yield. The coupling constant, $J=2.5$ Hz, between the protons at the C₈ and C_{8a} positions, observed at 5.21 and 5.29 ppm in the NMR spectrum, indicated *trans* substitution at these positions.¹⁶⁾ However, the stereochemistry of the methoxycarbonyl group at the C₅-position could not be determined.

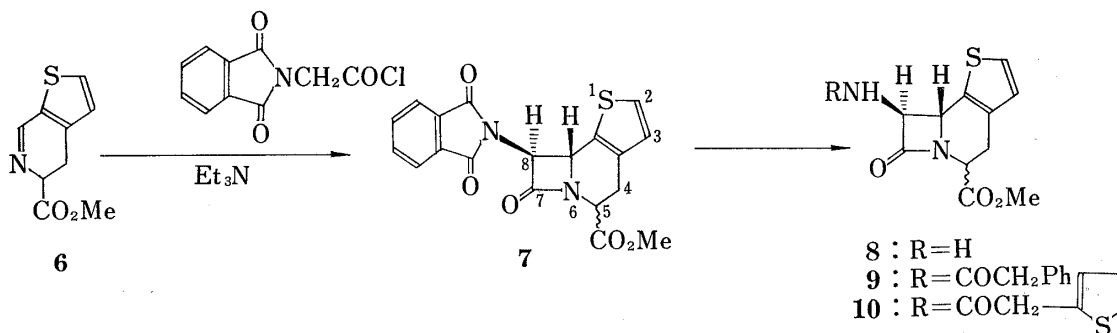


Chart 3

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Treatment of the β -lactam (7) with dimethylaminopropylamine¹⁷⁾ furnished, in 87% yield, the 8-amino β -lactam (8) which was converted to the 8-phenylacetamide (9) and to the 8-(2-thienyl)acetamide (10).

Thus we have achieved the synthesis of a new tricyclic β -lactam and are now investigating antibacterial activities of the new compounds prepared in this study.

Experimental

All melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were measured on a Hitachi 215 recording spectrometer and NMR spectra on a JNM PMX-60 spectrometer using tetramethylsilane as an internal standard.

Dimethyl 3-Thienylformamidomalonate (4)—A mixture of 3-thienyl bromide (3)⁹⁾ (8.8 g), diethyl formamidomalonate¹⁰⁾ (10 g), methanol (100 ml) and sodium methoxide (28% in methanol) (10 g) was heated under reflux for 3.5 hr. The mixture was concentrated and the residue was poured into ice-water and extracted with chloroform. The organic layer was washed with water, dried (Na_2SO_4), and concentrated to leave a solid, recrystallization of which from benzene afforded 4 (8.5 g, 64%) as needles, mp 165–166°, IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3280 (NH), 1735 (C=O), 1665 (C=O) and 1645 (N-CHO). NMR (CDCl_3) δ : 3.70 (3H, s, CH_2), 3.80 (6H, s, $2 \times \text{OMe}$), 6.75–7.10 (3H, m, ArH, NH), 7.25–7.40 (1H, m, ArH) and 8.22 (1H, d, $J=1.5$ Hz, CHO). Anal. Calcd for $\text{C}_{11}\text{H}_{13}\text{NO}_5$: C, 48.70; H, 4.83; N, 5.16. Found: C, 48.50; H, 4.81; N, 5.23.

Methyl 2-Formamido-3-(3-thienyl)propionate (5)—A mixture of the diester (4) (4.4 g, 0.016 mol), sodium chloride (0.9 g, 0.016 mol), water (0.6 ml, 0.032 mol) and dimethyl sulfoxide (30 ml) was heated at 170–180° for 2.5 hr. After cooling, the reaction mixture was poured into ice-water and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel using chloroform as an eluent to yield 5 (2.55 g, 74%) as prisms, mp 69–71° (from diethyl ether-*n*-hexane). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3200 (NH), 1730 (C=O) and 1645 (NHCO). NMR (CDCl_3) δ : 3.18 (2H, d, $J=6$ Hz, CHCH_2), 3.76 (3H, s, OMe), 4.92 (1H, t, $J=6$ Hz, CHCH_2), 6.20 br (1H, s, NH), 6.85 (1H, dd, $J=1.5, 4.8$ Hz, 4'-H), 6.95–7.10 (1H, m, 2'-H), 7.28 (1H, dd, $J=3, 4.8$ Hz, 5'-H) and 8.18 (1H, s, CHO). Anal. Calcd for $\text{C}_9\text{H}_{11}\text{NO}_3$: C, 50.68; H, 5.20; N, 6.57. Found: C, 50.56; H, 5.16; N, 6.57.

Methyl 4,5-Dihydrothieno[2,3-*c*]pyridine-5-carboxylate (6)—A mixture of the amide (5) (2 g), chloroform (50 ml) and phosphorus pentachloride (7.8 g) was stirred at 5–15° for 3 hr. The mixture was poured into ice-water and the aqueous layer separated. This extract was made basic with ammonia and extracted with dichloromethane. The organic layer was dried (Na_2SO_4) and concentrated below 30° to afford 6 (1.3 g, 71%) as an unstable oil, NMR (CDCl_3) δ : 2.96 (1H, dd, $J=16, 14$ Hz, 4-H), 3.20 (1H, dd, $J=16, 8$ Hz, 4-H), 3.85 (3H, s, OMe), 4.40 (1H, ddd, $J=3, 8, 14$ Hz, 5-H), 6.97 (1H, d, $J=4.8$ Hz, 3-H), 7.45 (1H, d, $J=4.8$ Hz, 2-H) and 8.33 (1H, d, $J=3$ Hz, 7-H).

Methyl 4,5,8,8a-Tetrahydro-7-oxo-8-phthalimido-7H-azeto[1,2-*a*]thieno[2,3-*c*]pyridine-5-carboxylate (7)—Phthalimidoacetyl chloride¹⁵⁾ (450 mg) in benzene (15 ml) was added to a stirred mixture of the thienopyridine (6) (400 mg), triethylamine (300 mg) and benzene (30 ml) at 0–5° during 2 hr under nitrogen. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with chloroform gave the β -lactam (7) (190 mg, 24.2%) as prisms (from methanol), mp 165–167°, IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1780, 1760, 1730 and 1715 (C=O). NMR (CDCl_3) δ : 3.20–3.45 (2H, m, 4- H_2), 3.76 (3H, s, OMe), 5.08 (1H, t, $J=5.5$ Hz, 5-H), 5.21 and 5.29 (each 1H, each d, $J=2.5$ Hz, 8 and 8a-H), 6.84 (1H, d, $J=5$ Hz, 3-H), 7.28 (1H, d, $J=5$ Hz, 2-H) and 7.65–7.98 (4H, m, $4 \times \text{ArH}$). Anal. Calcd for $\text{C}_{19}\text{H}_{14}\text{N}_2\text{O}_5$: C, 59.68; H, 3.69; N, 7.32. Found: C, 59.42; H, 3.77; N, 7.29%.

Methyl 8-Amino-4,5,8,8a-tetrahydro-7-oxo-7H-azeto[1,2-*a*]thieno[2,3-*c*]pyridine-5-carboxylate (8)—A mixture of the β -lactam (7) (180 mg), dimethylaminopropylamine¹⁷⁾ (100 mg), chloroform (4 ml) and methanol (6 ml) was stirred at room temperature for 4 hr. The mixture was concentrated and the residue chromatographed on silica gel. Elution with chloroform-methanol (99:1 v/v) afforded 8 (95 mg, 87%) as prisms (from diethyl ether), mp 109–110°, IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3420 (NH_2), 1755 and 1735 (C=O). NMR (CDCl_3) δ : 1.85 (2H, s, NH_2), 3.10–3.22 (2H, m, 4- H_2), 3.72 (3H, s, OMe), 4.02 (1H, d, $J=2$ Hz, 8a-H), 4.68 (1H, d, $J=2$ Hz, 8-H), 4.92 (1H, t, $J=5.5$ Hz, 5-H), 6.80 (1H, d, $J=5$ Hz, 3-H) and 7.26 (1H, d, $J=5$ Hz, 2-H). Anal. Calcd for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_3$: C, 52.36; H, 4.79; N, 11.10. Found: C, 52.58; H, 4.71; N, 11.18.

Methyl 4,5,8,8a-Tetrahydro-7-oxo-8-phenylacetamido-7H-azeto[1,2-*a*]thieno[2,3-*c*]pyridine-5-carboxylate (9)—Phenylacetyl chloride (70 mg) in dichloromethane (5 ml) was added to a stirred mixture of the β -lactam (8) (50 mg), dichloromethane (5 ml) and aqueous 4% sodium hydroxide (5 ml) at 0° during 15 min. The mixture was stirred at room temperature for 1 hr and the organic layer was separated. This extract was washed with water, dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel using chloroform as an eluent to yield 9 (40 mg, 54%) as needles, mp 190–193° (from methanol), IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3240 (NH), 1765, 1738 (C=O) and 1655 (N-CO). NMR (CDCl_3) δ : 3.13–3.35 (2H, m, 4- H_2), 3.70 (2H,

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s, CH₂CO), 3.73 (3H, s, OMe), 4.65—5.05 (3H, m, 5, 8 and 8a-H), 6.60 br (1H, s, NH), 6.83 (1H, d, *J*=5 Hz, 3-H) and 7.25—7.50 (6H, m, 6 × ArH). *Anal.* Calcd for C₁₉H₁₈N₂O₄S: C, 61.61; H, 4.89; N, 7.56. Found: C, 61.54; H, 4.72; N, 7.48.

Methyl 4,5,8,8a-Tetrahydro-7-oxo-8-(2-thienylacetamido)-7H-azeto[1,2-*a*]thieno[2,3-*c*]pyridine-5-carboxylate (10)—A mixture of the β-lactam (8) (55 mg), thiophene-2-acetic acid (40 mg), dichloromethane (10 ml) and dicyclohexylcarbodiimide (50 mg) was stirred at room temperature for 1 hr. The mixture was filtered and the filtrate was concentrated. The residue was chromatographed on silica gel. Elution with chloroform afforded 10 (50 mg, 61%) as prisms (from methanol), mp 176—178°, IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3230 (NH), 1775, 1738 (C=O) and 1655 cm⁻¹ (N—CO). NMR (CDCl₃) δ : 3.10—3.35 (2H, m, 4-H₂), 3.71 (3H, s, OMe), 3.90 (2H, s, CH₂CO), 4.68—5.00 (3H, m, 5, 8 and 8a-H) and 6.75—7.40 (5H, m, 5 × ArH). *Anal.* Calcd for C₁₇H₁₆N₂O₄S: C, 54.24; H, 4.21; N, 7.44. Found: C, 53.79; H, 4.08; N, 7.25.

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