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

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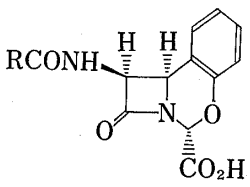
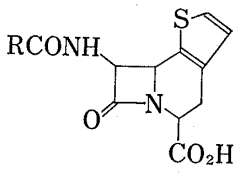
Cycloaddition of the 4,5-dihydrothieno[2,3-*c*]pyridine (**6**) and phthalimidoacetyl chloride gave a novel tricyclic β-lactam, methyl 4,5,8,8a-tetrahydro-7-oxo-8-phthalimido-7H-azeto[1,2-*a*]thieno[2,3-*c*]pyridine-5-carboxylate (**7**). On deprotection followed by acylation, this gave the 8-acylamino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




**1**

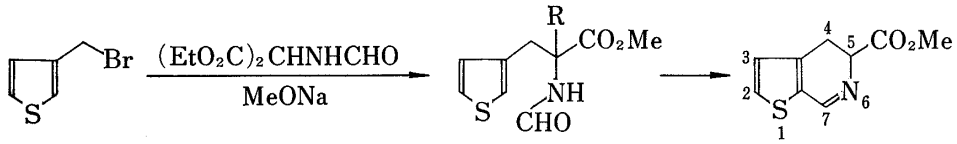



**2**

Chart 1

1) Part XIII: T. Kametani, T. Nagahara, Y. Suzuki, S. Yokohama, S.-P. Huang, and M. Ihara, *Heterocycles*, **14**, 403 (1980).
2) T. Kametani, K. Kigasawa, M. Hiiragi, K. Wakisaka, K. Tanigawa, and H. Sugi, *Heterocycles*, **12**, 741 (1979).
3) Location: *a*) *Aobayama, Sendai 980, Japan*; *b*) *Sakurashinmachi, Setagaya-ku, Tokyo 154, Japan.*
4) *a*) J.A. Webber, *Annual Reports in Medicinal Chemistry*, **12**, 105 (1977); *b*) M. Hashimoto and T. Kamiya, *The Japanese J. Antibiot.*, **30**, S-218 (1977).
5) *a*) B.G. Christensen and R.W. Ratcliffe, *Annual Reports in Medicinal Chemistry*, **11**, 271 (1976); *b*) A.K. Bose, S.G. Amin, J.C. Kapur, and M.S. Manhas, *J. Chem. Soc. Perkin I*, **1976**, 2193; *c*) J. Finkelstein, K.G. Holden, and C.D. Perchonock, *Tetrahedron Lett.*, **1978**, 1629.
6) F.A. Firestone, J.L. Fahey, N.S. Maciejewicz, G.S. Patel, and B.G. Christensen, *J. Medicin. Chem.*, **20**, 551 (1977).
7) T. Kametani, K. Kigasawa, M. Hiiragi, K. Wakisaka, H. Sugi, and K. Tanigawa, *Heterocycles*, **12**, 735, 795 (1979).

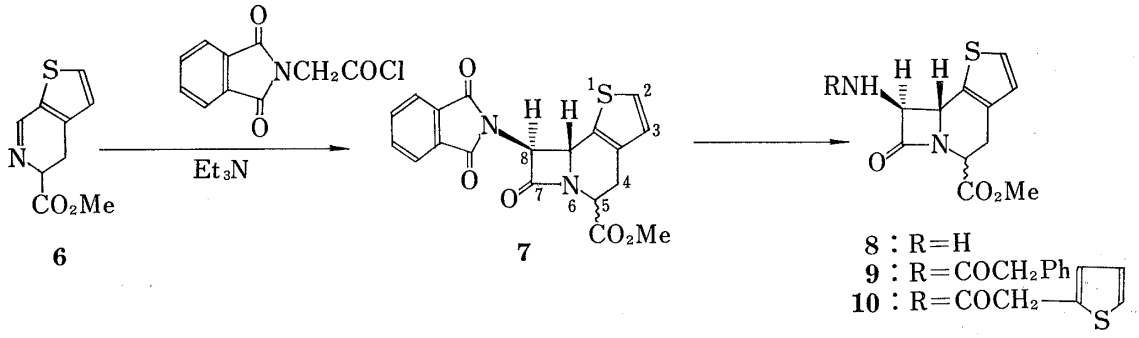
The important intermediate, 4,5-dihydrothieno[2,3-*c*]pyridine (**6**), was prepared by means of the Bischler-Napieralski reaction[8] as follows. Condensation of 3-thenyl bromide (**3**)[9] with diethyl formamidomalonate[10] in the presence of sodium methoxide, followed by demethoxycarbonylation of the 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 $\alpha$-position of the thiophene ring.[13,14]




**3** **4** : R=$CO_2Me$, **5** : R=H **6**

Chart 2

Since Bose and co-workers reported that imine group in a dihydropyridine ring reacted with a ketene to yield the $\beta$-lactam compound,[5b] cycloaddition of the above cyclic imine (**6**) with a ketene was examined. On treatment of **6** with phthalimidoacetyl chloride[15] in the presence of triethylamine, the $\beta$-lactam (**7**) was obtained in 24% yield. The coupling constant, $J$=2.5 Hz, between the protons at the $C_8$ 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 $C_5$-position could not be determined.




**6** **7** **8** : R=H, **9** : R=$COCH_2Ph$, **10** : R=$COCH_2$—(thienyl)

Chart 3

8) W.M. Whaley and T.R. Govindachari, *Org. Reactions*, **6**, 74 (1951).
9) E. Campaigne and W.M. Lesuer, *J. Am. Chem. Soc.*, **70**, 1555 (1948).
10) A. Galat, *J. Am. Chem. Soc.*, **69**, 965 (1947).
11) Transesterification occurred in this reaction; *c.f.* S.G. Cohen and A. Schneider, *J. Am. Chem. Soc.*, **63**, 3382 (1941).
12) A.P. Krapcho and A.J. Lovey, *Tetrahedron Lett.*, **1973**, 957; A.P. Krapcho, E.G.E. Jahngen, and A.J. Lovey, *Tetrahedron Lett.*, **1974**, 1091.
13) R.V. Davies, B. Iddon, T. McC. Paterson, M.W. Pickering, H. Suschitzky, and M.W. Gittos, *J. Chem. Soc. Perkin I*, **1976**, 138.
14) J.W. Emsley, J. Feeney, and L.H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Pergamon Press Ltd., London, 1966, p. 789.
15) J.C. Sheehan and V.S. Frank, *J. Am. Chem. Soc.*, **71**, 1856 (1949).
16) I. McMillan and R.J. Stoodley, *Tetrahedron Lett.*, **1966**, 1205.

Treatment of the β-lactam (**7**) with dimethylaminopropylamine[17] 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-Thenylformamidomalonate (4)**——A mixture of 3-thenyl bromide (**3**)[9] (8.8 g), diethyl formamidomalonate[10] (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 $\nu_{max}^{KBr}$ $cm^{-1}$: 3280 (NH), 1735 (C=O), 1665 (C=O) and 1645 (N–CHO). NMR ($CDCl_3$) $\delta$: 3.70 (3H, s, $CH_2$), 3.80 (6H, s, 2×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 $C_{11}H_{13}NO_5S$: 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 $\nu_{max}^{KBr}$ $cm^{-1}$: 3200 (NH), 1730 (C=O) and 1645 (NHCO). NMR ($CDCl_3$) $\delta$: 3.18 (2H, d, $J$=6 Hz, $CHC\underline{H}_2$), 3.76 (3H, s, OMe), 4.92 (1H, t, $J$=6 Hz, $C\underline{H}CH_2$), 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 $C_9H_{11}NO_3S$: 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 ($CDCl_3$) $\delta$: 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 chloride[15] (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 $\nu_{max}^{KBr}$ $cm^{-1}$: 1780, 1760, 1730 and 1715 (C=O). NMR ($CDCl_3$) $\delta$: 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×ArH). *Anal.* Calcd for $C_{19}H_{14}N_2O_5S$: 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), dimethylaminopropylamine[17] (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 $\nu_{max}^{KBr}$ $cm^{-1}$: 3420 ($NH_2$), 1755 and 1735 (C=O). NMR ($CDCl_3$) $\delta$: 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 $C_{11}H_{12}N_2O_3S$: 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 $\nu_{max}^{KBr}$ $cm^{-1}$: 3240 (NH), 1765, 1738 (C=O) and 1655 (N–CO). NMR ($CDCl_3$) $\delta$: 3.13—3.35 (2H, m, 4-$H_2$), 3.70 (2H,

17) T. Kamiya, M. Hashimoto, O. Nakaguchi, and T. Oku, *Tetrahedron*, **35**, 323 (1979).

s, $CH_2CO$), 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, $6\times$ArH). *Anal.* Calcd for $C_{19}H_{18}N_2O_4S$: 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 $\beta$-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 $\nu_{max}^{KBr}$ $cm^{-1}$: 3230 (NH), 1775, 1738 (C=O) and 1655 $cm^{-1}$ (N–CO). NMR ($CDCl_3$) $\delta$: 3.10—3.35 (2H, m, 4-$H_2$), 3.71 (3H, s, OMe), 3.90 (2H, s, $CH_2CO$), 4.68—5.00 (3H, m, 5, 8 and 8a-H) and 6.75—7.40 (5H, m, $5\times$ArH). *Anal.* Calcd for $C_{17}H_{16}N_2O_4S$: C, 54.24; H, 4.21; N, 7.44. Found: C, 53.79; H, 4.08; N, 7.25.

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