

SYNTHETIC STUDIES ON  $\beta$ -LACTAM ANTIBIOTICS. VI.<sup>1</sup> SYNTHESIS OF  
 7H-AZETO[1,2-a]THIENO[2,3-c]PYRIDINE DERIVATIVES

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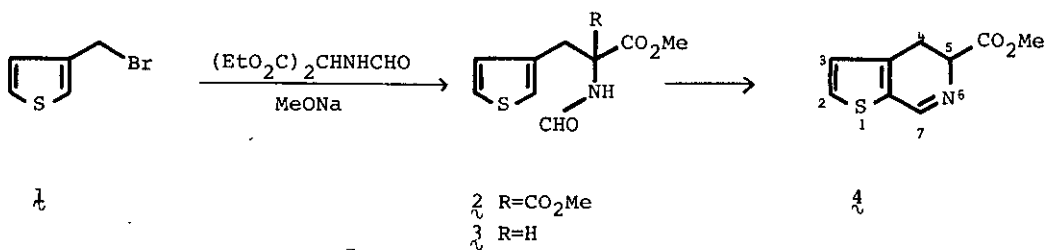
**Abstract** — Methyl 4,5-dihydrothieno[2,3-c]pyridine-5-carboxylate  
 (4) was converted into several 8-substituted 4,5,8,8a-tetrahydro-7-  
 oxo-7H-azeto[1,2-a]thieno[2,3-c]pyridine-7-carboxylates ( $\lambda \sim 10$ ) by  
 reaction with phthalimidoacetyl chloride and triethylamine,  
 followed by hydrolysis and acylation.

Previously, we have reported the synthesis of 1,9b-dihydro-2H,4H-2-oxo-azeto[1,2-c]-  
 [1,3]benzoxazines<sup>1,2</sup> in order to obtain new chemotherapeutics, as some modified  
 cephalosporins and carbocyclic  $\beta$ -lactams showed effective antibacterial activities.<sup>3-6</sup>  
 In a continuation of these studies, we have investigated the preparation of a new  
 type of tricyclic  $\beta$ -lactam and here wish to report the synthesis of 7H-azeto[1,2-a]-  
 thieno[2,3-c]pyridines.

The key intermediate, the 4,5-dihydrothieno[2,3-c]pyridine (4) was prepared by  
 application of the Bischler-Napieralski reaction<sup>7</sup> as follows. Condensation of 3-  
 thenyl bromide (1)<sup>8</sup> with diethyl formamidomalonate<sup>9</sup> in boiling methanol in the  
 presence of sodium methoxide for 3.5 h formed, in 64 % yield, the dimethyl ester  
 (2)<sup>10</sup> [mp 165 ~ 166°;  $\nu$  (KBr) 3280, 1735, 1665 and 1645  $\text{cm}^{-1}$ ;  $\delta$  ( $\text{CDCl}_3$ ) 3.70 (2H,  
 s,  $\text{CH}_2$ ) and 3.80 (6H, s, 2xOMe)], which was subjected to demethoxycarbonylation<sup>11</sup>  
 with sodium chloride in wet dimethyl sulphoxide at 170 ~ 180° to give in 74 % yield  
 the amido monoester (3)<sup>10</sup> [mp 69 ~ 71°;  $\nu$  (KBr) 3200, 1730 and 1645  $\text{cm}^{-1}$ ;  $\delta$  ( $\text{CDCl}_3$ )  
 3.18 (2H, d,  $\underline{J} = 6$ ,  $\text{ArCH}_2\text{CH}$ ), 3.76 (3H, s, OMe) and 4.92 (1H, t,  $\underline{J} = 6$ ,  $\text{ArCH}_2\text{CH}$ ).

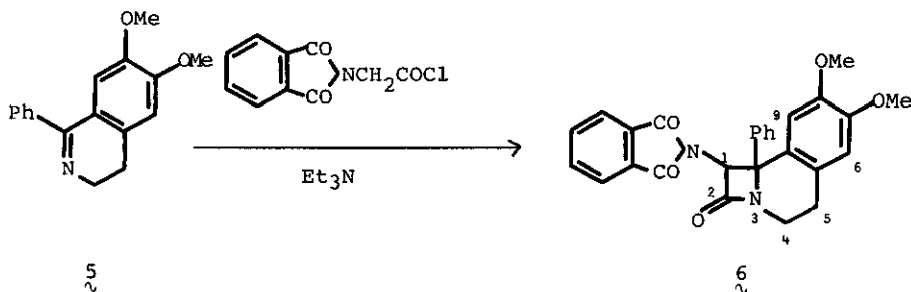
The Bischler-Napieralski cyclisation of **3** was achieved with phosphorous pentachloride in dry chloroform at 5 ~ 15° for 3 h to afford the 4,5-dihydrothieno[2,3-*c*]pyridine (**4**) as an unstable oil in 71 % yield, whose nmr spectral data [ $\delta$  (CDCl<sub>3</sub>) 6.97 (1H, d,  $J$  = 4.8 Hz, C<sub>2</sub>-H), 7.45 (1H, d,  $J$  = 4.8 Hz, C<sub>3</sub>-H) and 8.33 (1H, d,  $J$  = 3 Hz, C<sub>7</sub>-H)] revealed this cyclisation to have occurred at the  $\alpha$ -position of the thiophene ring.<sup>12,13</sup>

Scheme 1



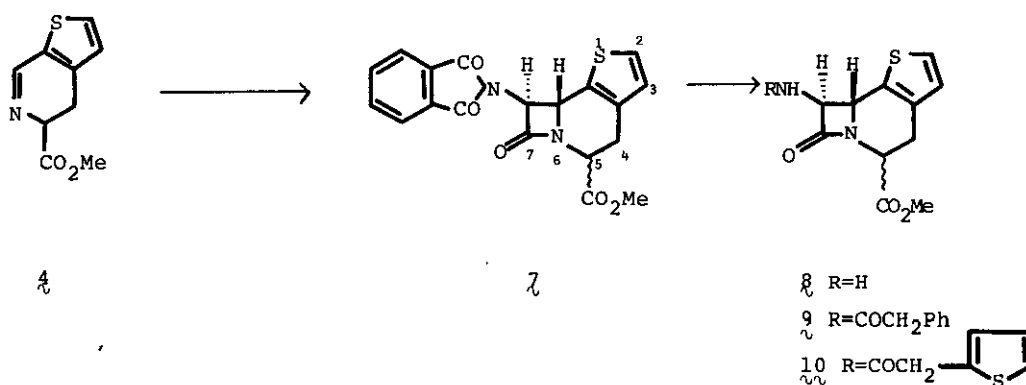
Prior to the  $\beta$ -lactam formation from (**4**), we investigated whether or not the imine system in a piperidine ring would react with ketene to form a  $\beta$ -lactam. Thus, 3,4-dihydro-6,7-dimethoxy-1-phenylisoquinoline (**5**)<sup>14</sup> was treated with phthalimidoacetyl chloride<sup>15</sup> in benzene in the presence of triethylamine by Bose's method<sup>5</sup> to give the expected 1,4,5,9b-tetrahydro-7,8-dimethoxy-9b-phenyl-1-phthalimido-2H-azeto-[2,1-*a*]isoquinolin-2-one (**6**) [mp 272 ~ 274°;  $\nu$  (KBr) 1780, 1775, and 1718 cm<sup>-1</sup>;  $\delta$  (CDCl<sub>3</sub>) 2.60 ~ 2.95 (2H, C<sub>5</sub>-H<sub>2</sub>), 3.75 ~ 4.03 (2H, C<sub>4</sub>-H<sub>2</sub>), 3.90 (3H, s, OMe), 4.16 (3H, s, OMe), 5.53 (1H, s, C<sub>1</sub>-H), 6.70 (1H, s, C<sub>6</sub>-H), and 7.05 ~ 7.80 (10H, ArH)] in 76 % yield. On the basis of this finding, the cycloaddition reaction of the cyclic imine **4** was examined as follows.

Scheme 2



The reaction of **4** with phthalimidoacetyl chloride preceded in the presence of triethylamine in benzene at  $0 \sim 5^\circ$  to afford, in 24 % yield, the  $\beta$ -lactam (**7**) [mp  $165 \sim 167^\circ$ ;  $\nu$  (KBr) 1780, 1760, 1735 and  $1715 \text{ cm}^{-1}$ ], whose nmr spectrum [ $\delta$  ( $\text{CDCl}_3$ ) 3.20  $\sim$  3.45 (2H,  $\text{C}_4\text{-H}_2$ ), 3.76 (3H, s, OMe), 5.08 (1H, t,  $\underline{J} = 5.5 \text{ Hz}$ ,  $\text{C}_5\text{-H}$ ), 5.21 and 5.29 (each 1H, d,  $\underline{J} = 2.5 \text{ Hz}$ ,  $\text{C}_8\text{-H}$  and  $\text{C}_{8a}\text{-H}$ ), 6.48 (1H, d,  $\underline{J} = 5 \text{ Hz}$ ,  $\text{C}_3\text{-H}$ ), 7.28 (1H, d,  $\underline{J} = 5 \text{ Hz}$ ,  $\text{C}_2\text{-H}$ ) and 7.65  $\sim$  7.98 (4H, ArH)] indicated the stereochemical relationship between  $\text{C}_8\text{-H}$  and  $\text{C}_{8a}\text{-H}$  to be trans.<sup>16</sup> However, the relative configuration of the methoxycarbonyl group at the  $\text{C}_5$ -position could not be determined. Treatment of this phthalimido  $\beta$ -lactam (**7**) with dimethylaminopropylamine<sup>17</sup> in methanol and chloroform for 40 h at room temperature gave, in 87 % yield, the amino derivative of the  $\beta$ -lactam (**8**) [mp  $109 \sim 110^\circ$ ;  $\nu$  (KBr) 3420, 1755 and  $1735 \text{ cm}^{-1}$   $\delta$  ( $\text{CDCl}_3$ ) 1.85 (2H, s,  $\text{NH}_2$ ), 3.10  $\sim$  3.22 (2H,  $\text{C}_4\text{-H}_2$ ), 3.72 (3H, s, OMe), 4.02 (1H, d,  $\underline{J} = 2 \text{ Hz}$ ,  $\text{C}_{8a}\text{-H}$ ), 4.68 (1H, d,  $\underline{J} = 2 \text{ Hz}$ ,  $\text{C}_8\text{-H}$ ), 4.92 (1H, d,  $\underline{J} = 5.5 \text{ Hz}$ ,  $\text{C}_5\text{-H}$ ), 6.80 (1H, d,  $\underline{J} = 5 \text{ Hz}$ ,  $\text{C}_3\text{-H}$ ) and 7.26 (1H, d,  $\underline{J} = 5 \text{ Hz}$ ,  $\text{C}_2\text{-H}$ )] which was converted into the phenylacetamide (**9**) [mp  $190 \sim 193^\circ$ ; 54 % yield;  $\nu$  (KBr) 3240, 1765, 1738 and  $1655 \text{ cm}^{-1}$ ;  $\delta$  ( $\text{CDCl}_3$ ) 3.70 (2H, s,  $\text{PhCH}_2\text{CO}$ )] and the thienylacetamide derivative (**10**) [mp  $176 \sim 178^\circ$ ; 61 % yield;  $\nu$  (KBr) 3230, 1775, 1738 and  $1655 \text{ cm}^{-1}$ ;  $\delta$  ( $\text{CDCl}_3$ ) 3.90 (2H, s,  $\text{CH}_2\text{CONH}$ )] by reaction with phenylacetyl chloride in the presence of **4** & sodium hydroxide in methylene chloride, and thiophene-2-carboxylic acid in methylene chloride in the presence of *N,N*-dicyclohexylcarbodiimide, respectively.

Scheme 3



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

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