SYNTHETIC STUDIES ON β-LACTAM ANTIBIOTICS. VI.[1] SYNTHESIS OF 7H-AZETO[1,2-a]THIENO[2,3-c]PYRIDINE DERIVATIVES

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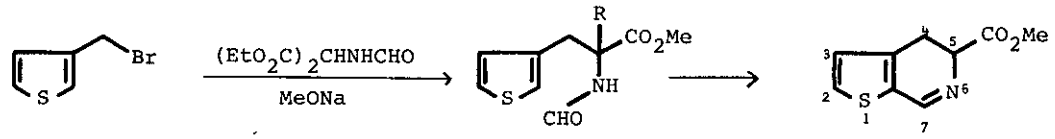
Abstract —— Methyl 4,5-dihydrothieno[2,3-c]pyridine-5-carboxylate (4) was converted into several 8-substituted 4,5,8,8a-tetrahydro-7-oxo-7H-azeto[1,2-a]thieno[2,3-c]pyridine-7-carboxylates (7 ∿ 10) by reaction with phthalimidoacetyl chloride and triethylamine, followed by hydrolysis and acylation.

Previously, we have reported the synthesis of 1,9b-dihydro-2H,4H-2-oxo-azeto[1,2-c]-[1,3]benzoxazines[1,2] in order to obtain new chemotherapeutics, as some modified cephalosporins and carbocyclic β-lactams showed effective antibacterial activities.[3∿6] In a continuation of these studies, we have investigated the preparation of a new type of tricyclic β-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[7] as follows. Condensation of 3-thenyl bromide (1)[8] with diethyl formamidomalonate[9] in boiling methanol in the presence of sodium methoxide for 3.5 h formed, in 64 % yield, the dimethyl ester (2)[10] [mp 165 ∿ 166°; ν (KBr) 3280, 1735, 1665 and 1645 cm^{-1}; δ ($CDCl_3$) 3.70 (2H, s, CH_2) and 3.80 (6H, s, 2xOMe)], which was subjected to demethoxycarbonylation[11] with sodium chloride in wet dimethyl sulphoxide at 170 ∿ 180° to give in 74 % yield the amido monoester (3) [mp 69 ∿ 71°; ν (KBr) 3200, 1730 and 1645 cm^{-1}; δ ($CDCl_3$) 3.18 (2H, d, J = 6, $ArCH_2CH$), 3.76 (3H, s, OMe) and 4.92 (1H, t, J = 6, $ArCH_2CH$)].

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 [δ ($CDCl_3$) 6.97 (1H, d, J = 4.8 Hz, C_2-H), 7.45 (1H, d, J = 4.8 Hz, C_3-H) and 8.33 (1H, d, J = 3 Hz, C_7-H)] revealed this cyclisation to have occurred at the α-position of the thiophene ring.[12,13]

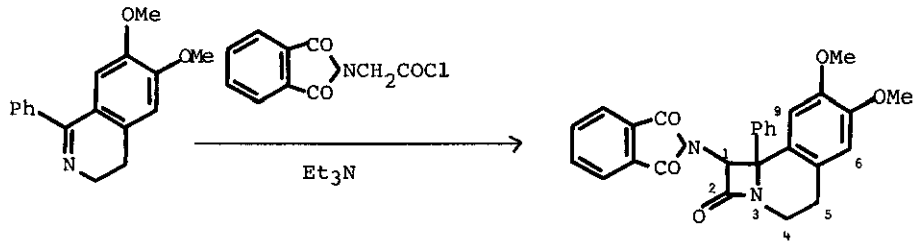
Scheme 1



1 2 R=CO_2Me 3 R=H 4

Prior to the β-lactam formation from (4), we investigated whether or not the imine system in a piperidine ring would react with ketene to form a β-lactam. Thus, 3,4-dihydro-6,7-dimethoxy-1-phenylisoquinoline (5)[14] was treated with phthalimidoacetyl chloride[15] in benzene in the presence of triethylamine by Bose's method[5] 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°; ν (KBr) 1780, 1775, and 1718 cm^{-1}; δ ($CDCl_3$) 2.60 ∿ 2.95 (2H, C_5-H_2), 3.75 ∿ 4.03 (2H, C_4-H_2), 3.90 (3H, s, OMe), 4.16 (3H, s, OMe), 5.53 (1H, s, C_1-H), 6.70 (1H, s, C_6-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.

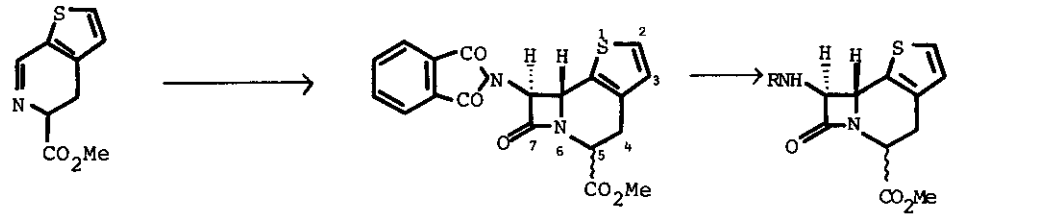
Scheme 2



5 6

The reaction of 4 with phthalimidoacetyl chloride preceeded in the presence of triethylamine in benzene at 0 ∿ 5° to afford, in 24 % yield, the β-lactam (7) [mp 165 ∿ 167°; ν (KBr) 1780, 1760, 1735 and 1715 cm^{-1}], whose nmr spectrum [δ ($CDCl_3$) 3.20 ∿ 3.45 (2H, C_4-H_2), 3.76 (3H, s, OMe), 5.08 (1H, t, J = 5.5 Hz, C_5-H), 5.21 and 5.29 (each 1H, d, J = 2.5 Hz, C_8-H and C_{8a}-H), 6.48 (1H, d, J = 5 Hz, C_3-H), 7.28 (1H, d, J = 5 Hz, C_2-H) and 7.65 ∿ 7.98 (4H, ArH)] indicated the stereochemical relationship between C_8-H and C_{8a}-H to be trans.[16] However, the relative configuration of the methoxycarbonyl group at the C_5-position could not be determined. Treatment of this phthalimido β-lactam (7) with dimethylaminopropylamine[17] in methanol and chloroform for 40 h at room temperature gave, in 87 % yield, the amino derivative of the β-lactam (8) [mp 109 ∿ 110°; ν (KBr) 3420, 1755 and 1735 cm^{-1} δ ($CDCl_3$) 1.85 (2H, s, NH_2), 3.10 ∿ 3.22 (2H, C_4-H_2), 3.72 (3H, s, OMe), 4.02 (1H, d, J = 2 Hz, C_{8a}-H), 4.68 (1H, d, J = 2 Hz, C_8-H), 4.92 (1H, d, J = 5.5 Hz, C_5-H), 6.80 (1H, d, J = 5 Hz, C_3-H) and 7.26 (1H, d, J = 5 Hz, C_2-H)] which was converted into the phenylacetamide (9) [mp 190 ∿ 193°; 54 % yield; ν (KBr) 3240, 1765, 1738 and 1655 cm^{-1}; δ ($CDCl_3$) 3.70 (2H, s, $PhCH_2CO$)] and the thienylacetamide derivative (10) [mp 176 ∿ 178°; 61 % yield; ν (KBr) 3230, 1775, 1738 and 1655 cm^{-1}; δ ($CDCl_3$) 3.90 (2H, s, CH_2CONH)] 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



4 7 8 R=H; 9 R=$COCH_2Ph$; 10 R=$COCH_2$-(thienyl)

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.

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