SYNTHETIC STUDIES ON β-LACTAM ANTIBIOTICS. V[1]. STEREOSELECTIVE SYNTHESIS OF 1,9b-DIHYDRO-2H,4H-2-OXO-AZETO[1,2-C][1,3]BENZOXAZINE-4-CARBOXYLIC ACID DERIVATIVES

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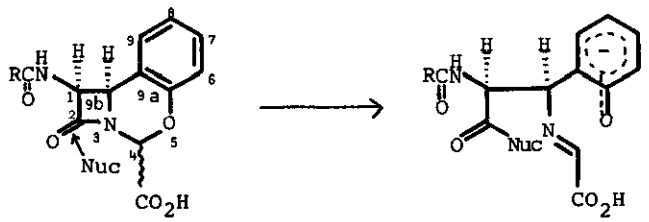
Abstract —— 2,2,2-Trichloroethyl 1-phthalimido-1,9b-dihydro-2H,4H-2-oxo-azeto[1,2-c][1,3]benzoxazine-4-carboxylate (11) was synthesised stereoselectively by cyclisation of 2,2,2-trichloroethyl 2-[cis-4-(2-hydroxyphenyl)-3-phthalimido-2-oxo-1-azetidinyl]-2-hydroxyacetate (8), which was prepared from N-(2-benzyloxybenzylidene)-2,4-dimethoxybenzylamine (4) by cycloaddition with ketene, followed by debenzylation and condensation with 2,2,2-trichloroethyl glyoxalate. The corresponding p-nitrobenzyl ester (12) which was obtained by a similar method, was converted to the free carboxylic acid (16).

In the preceding paper[1], we reported a synthesis of the 1,2-benzo-3-oxa-cepham derivatives, and compound (1) would form the stable anion (2) by ring opening of

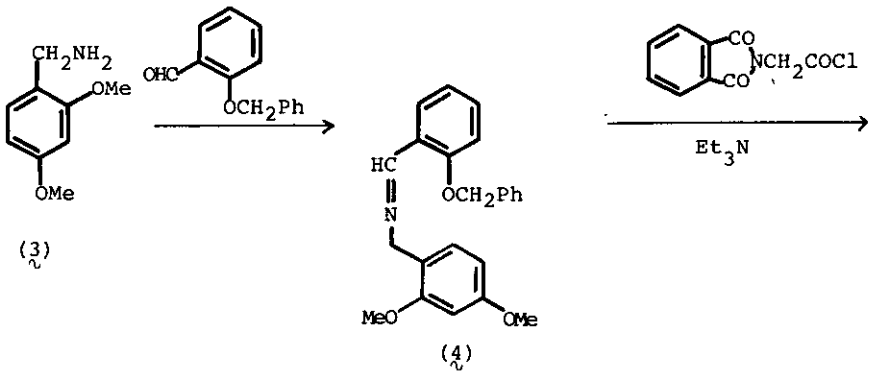
Scheme 1



(1) (2)

the β-lactam system by nucleophiles. Recently, Huffman[2] suggested that activated β-lactams show enhanced antibiotic activities incomparison with ones which are more stable to this nucleophilic ring opening. Therefore, we have investigated a more effective synthesis of 1,2-benzo-3-oxacepham type compounds and now wish to report a stereoselective synthesis of 1,9b-dihydro-2H,4H-2-oxo-azeto[1,2-c][1,3]benzoxazine-4-carboxylates. 2,4-Dimethoxybenzylamine (3)[3,4], prepared in 87.9 % yield by a dissolving metal reduction of 2,4-dimethoxybenzaldoxime with nickel-aluminium alloy in sodium hydroxide solution, was cendensed with o-benzyloxybenzaldehyde in boiling benzene to give the imine (4), [ν (KBr) 1620 cm^{-1}; δ (CCl_4 + $CDCl_3$) 8.84 (1H, s, -CH=N-)], which was treated with phthaloylglycyl chloride and triethylamine in methylene chloride as usual to afford in 77 % overall yield the β-lactam (5) [mp 201 ∿ 204°C; m/e 548 (M^+); ν (KBr) 1775, 1748 and 1715 cm^{-1}]. The stereochemistry of the C_3 and C_4 positions was determined as cis by nmr spectral analysis (DMSO-d_6) which revealed C_3-H and C_4-H each as a doublet, with J = 5.6 Hz, at 5.56 and 5.14, respectively. Selective N-debenzylation was achieved by reaction of 5 with 1.6 molar equivalents of potassium persulphate[3] in aqueous acetonitrile in the presence of phosphate buffer at 80°C, giving the secondary amide (6) [mp 224 ∿ 226°C; ν (KBr) 3200, 1775, 1752, and 1715 cm^{-1}; δ ($CDCl_3$ + DMSO-d_6) 8.50 (1H, br s, NH) and 4.93 (2H, s, ArOCH_2Ph); m/e 398 (M^+)] in 74.3 % yield[5]. Hydrogenation[6] of 6 on 15 % palladium-charcoal in dioxane and methanol at room temperature and atmospheric pressure gave, in 83.9 % yield, the phenolic β-lactam (7) [mp 281 ∿ 284°C; ν (KBr) 3350, 1778, 1750 and 1710 cm^{-1}; δ ($CDCl_3$ + DMSO-d_6) 9.18 and 8.77 (each 1H, br s, OH and NH, exchangeable with D_2O); m/e 308 (M^+)], which was treated with 2,2,2-trichloroethyl glyoxalate[9] in toluene and dioxane in the presence of molecular sieve at 90 ∿ 100°C to afford a diastereoisomeric mixture [ratio 2.7 : 1 by nmr spectral analysis of the methylene protons at 5.01 and 4.67] of the N-hydroxyacetylated β-lactam (8) [mp 185 ∿ 188°C; ν (KBr) 3470, 3380, 1778, 1758, 1745 and 1713 cm^{-1}; δ ($CDCl_3$ + DMSO-d_6) 5.5 ∿ 5.85 (3H, C_3-H, C_4-H and >N-$\overset{CO}{C}H_2$-O)] in 78.7 % yield. This compound was also obtained by another route. Thus, reaction of 6 with 2,2,2-trichloroethyl glyoxalate as above yielded the 2-(2-oxo-azetidinyl)-2-hydroxyacetate (9), which on hydrogenolysis over 15 % palladium-charcoal gave 8 in 35.3 % yield, together with the phenolic β-lactam (7). The p-nitroacetate (10) was also obtained from 7 by reaction with p-nitrobenzyl glyoxalate[10] and molecular sieve in benzene and dioxane in 98.8 % yield.

Scheme 2



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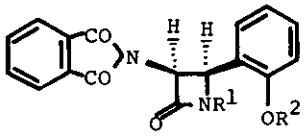
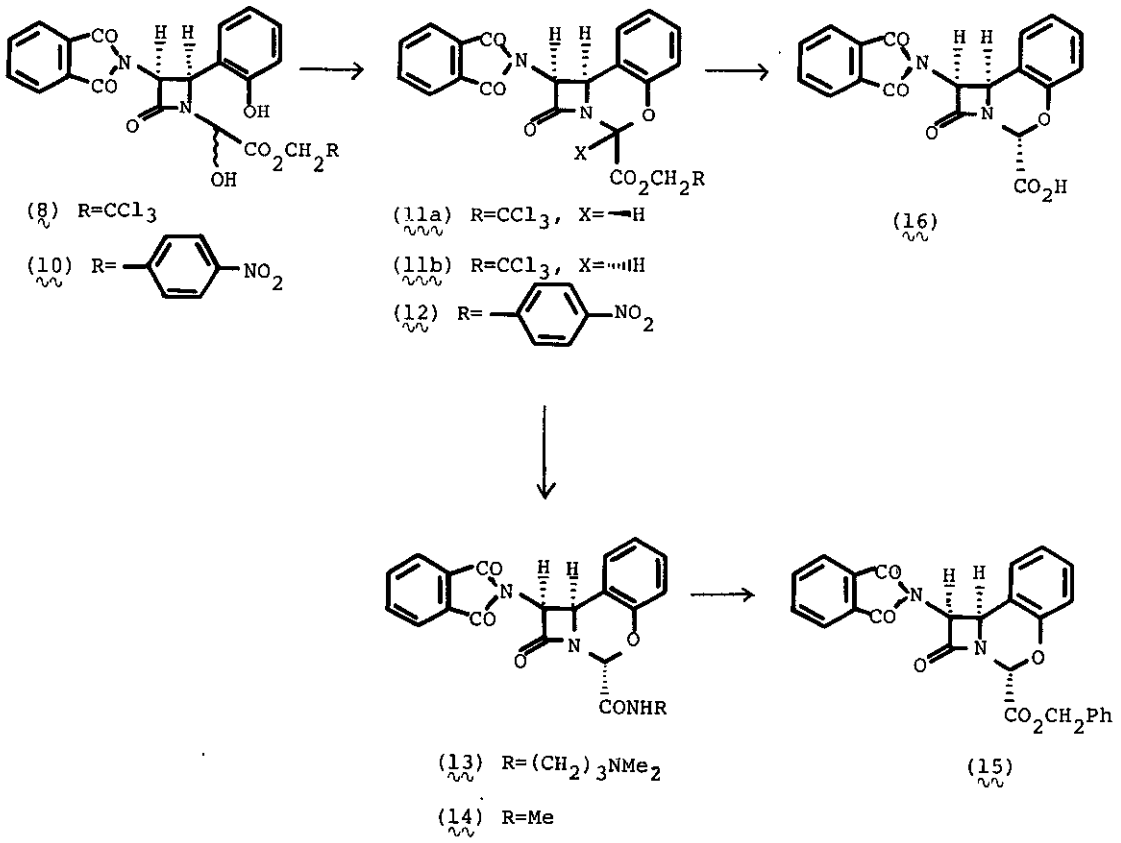


(5) R^1=2,4-$(MeO)_2C_6H_3CH_2$, R^2=CH_2Ph
(6) R^1=H, R^2=CH_2Ph
(7) R^1=R^2=H
(8) R^1=-$CHCO_2CH_2CCl_3$ (OH), R^2=H
(9) R^1=-$CHCO_2CH_2CCl_3$ (OH), R^2=CH_2Ph
(10) R^1=$CHCO_2CH_2$-(p-NO_2-C_6H_4) (OH), R^2=H

Treatment of (8) with phosphorous pentoxide in dioxane at 11 ∿ 13°C for 0.75 h gave in 78.8 % yield the (±)-1α,9bα-dihydro-2H,4βH-2-ozo-azeto[1,2-c][1,3]benzoxazine-4α-carboxylate (11a) [mp 218 ∿ 220°C; ν (KBr) 1792, 1767, 1755, and 1715 cm^{-1}; δ ($CDCl_3$) 6.37 (1H, s, C_4-H) 5.07 (1H, d, J = 5.0 Hz, C_{9b}-H), 5.90 (1H, d, J = 5.0 Hz, C_1-H) and 4.82 (2H, s, CH_2); m/e 495 (M^+)] in addition to a trace amount of the $C_{4\alpha}$-hydrogen isomer (11b) [mp 275 ∿ 276°C (decomp.); ν (KBr) 1785, 1770 and 1725 cm^{-1}; δ ($CDCl_3$ + DMSO-d_6) 4.95 and 5.25 (each 1H, d, J = 12 Hz, OCH_2), 5.28 (1H, d, J = 5.5 Hz, C_{9b}-H), 5.82 (1H, s, C_4-H) and 5.99 (1H, d, J = 5.5 Hz, C_1-H); m/e 495 (M^+)][11]. The stereochemistry of both products has been determined from their nmr spectra described above. Thus, the C_4-proton proton in (11a) resonated at lower field than those of (11b) due to the anisotropic effect of the benzene ring oriented in the same plane as the former isomer, and the methylene protons of the latter isomer have been appeared at lower field in a splitting pattern due to prevention of free

rotation by the bulky cisorientated aromatic ring and phthalimido residue than those of (11a). The cyclisation product (11a) was converted into the corresponding amides (13 and 14) by reaction with N,N-dimethyl-1,3-propanediamine and methylamine respectively, and the latter compound (14) was transformed into the benzyl ester (15) [mp 182 ∿ 184°C; ν (KBr) 1775, 1765, 1730 and 1710 cm^{-1}; δ ($CDCl_3$) 4.88 (1H, d, J = 5.4 Hz, C_{9b}-H), 5.17 (2H, s, CH_2), 5.76 (1H, d, J = 5.4 Hz, C_1-H), 6.18 (1H, s, C_4-H) and 7.25 (5H, s, ArH) in 12.5 % yield by treatment with phosphorous pentachloride in pyridine at 50 ∿ 60°C, followed by reaction with benzyl alcohol at -10°C and then water[12].

Scheme 3



In an attempt to get the free carboxylic acid (16), the trichloroethyl ester (11b) was treated with zinc powder, but the reaction was unsuccessful. However, the p-nitrobenzyl ester (10) was converted into the cyclisation product (12) [mp 174 ∿ 177°C; ν (KBr) 1780, 1765, 1740 and 1715 cm^{-1}; δ ($CDCl_3$ + DMSO-d_6) 5.33 (2H, s, OCH_2)

and 6.30 (1H, s, C_9-H)] with phosphorous pentoxide at 15°C, which was subjected to hydrogenolysis with 15 % palladium-charcoal in dioxane as usual to give quantitatively the expected carboxylic acid (16) [mp 198 ∿ 202°C (decomp.); ν (KBr) 1775, 1765 and 1715 cm^{-1}; δ ($CDCl_3$ + DMSO-d_6) 4.86 (1H, d, J = 5.4 Hz, C_{9b}-H), 5.83 (1H, d, J = 5.4 Hz, C_1-H) and 6.11 (1H, s, C_4-H).

Thus, we have achieved a stereoselective synthesis of (±)-1α,9bα-dihydro-2H,4H-2-oxoazeto[1,2-c][1,3]benzoxazine-4α-carboxylic acid which is expected to have antibiotic activity[2].

ACKNOWLEDGEMENT

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4. F. Weygand, W. Steglich, J. Bjarnason, R. Akhtar, and N. Chytil, Chem. Ber., 1968, 101, 3623.
5. On reaction of 5 with 3 molar equivalents of $K_2S_2O_8$, cis-4-(2-benzyloxyphenyl)-1-(2,4-dimethoxybenzoyl)-4-phthalimido-azetidin-2-one was formed in 20.9 % yield in addition to the expected N-debenzylation product (6) (32.5 %).
6. Hydrogenation of cis-4-(2-benzyloxyphenyl)-3-phenoxyacetamido-azetidin-2-one, prepared from 6 by dephthaloylation[7] and acylation with phenoxyacetyl chloride, by the same method gave 3-phenoxyacetamidocoumarin [mp 169 ∿ 171°C; ν (KBr) 3360, 1715 and 1680 cm^{-1}; δ ($CDCl_3$) 9.22 (1H, br s, NH), 8.69 (1H, s, C_4-H) and 4.63 (2H, s, CH_2); m/e 295 (M^+)][8].

7. Fujisawa Yakuhin, Japan Kokai Patent, 65,263 (1977).

8. Similar reaction has been reported by Bose; M. S. Manhas, S. G. Amin, and A. K. Bose, Heterocycles, 1976, 5, 669.

9. R. B. Woodward, U. S. Patent, 3,468,933 (1969).

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11. Higher reaction temperature of this reaction or application of other acidic catalysts such as $BF_3 \cdot Et_2O$ or p-TsOH has effected the ratio of products. This phenomenon will be reported in a full paper.

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