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SYNTHESIS OF BICYCLIC γ-LACTAMS VIA OXAZOLIDINONES

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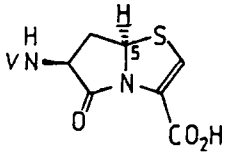
Abstract: Oxazolidinone aldehyde 10 reacts with L-cysteine methyl ester to produce N-hydroxymethyl bicyclic γ-lactam 11 in a double cyclisation reaction. With D-cysteine methyl ester, an epimeric mixture of N-hydroxymethyl bicyclic γ-lactams 12 is obtained. Bicyclic γ-lactams 3, 4 and 13 are easily prepared from 11 and 12.

We recently communicated the synthesis of a γ-lactam analogue 1 of the penems which showed weak but real antibacterial activities.[1] N-Benzyloxycarbonyl-L-aspartic semi-aldehyde benzyl ester (2) was reacted with cysteine methyl esters to obtain the bicyclic γ-lactams 3 (2R, 5S, 7S; from L-cysteine methyl ester) and 4 (2S, 5R, 7S; from D-cysteine methyl ester) in refluxing pyridine, both of which could be used as intermediates for the synthesis of 1. Equilibrating epimers of the intermediate thiazolidines 5 and 6 were initially formed respectively, and the preferential formation of 3 from 5 and 4 from 6 may be explained on steric grounds. In each case, the thiazolidine with a 2,5-trans relationship is better arranged for lactam formation than the epimer with 2,5-cis arrangement.



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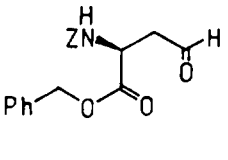

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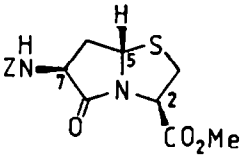

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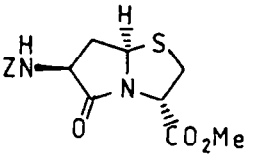

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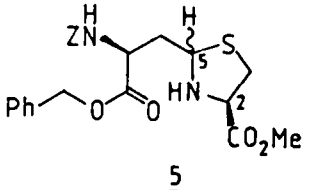

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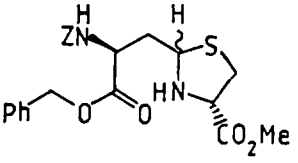

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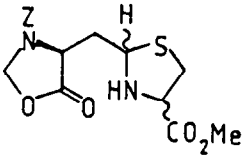

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V = $PhOCH_2CO$ Z = $PhCH_2OCO$

Since, in the corresponding β-lactam derivatives, it has been conclusively demonstrated that the absolute stereochemistry at C-5 shown in 1 is crucial in providing biological activity,[2] we

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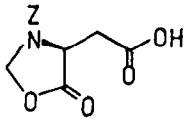
needed to devise ways to prepare epimers (at C-5) of 3 and 4 by reacting more reactive aspartic semi-aldehyde derivatives with cysteine methyl esters under milder conditions than previously used. If the rate of lactamisation was fast enough to compete with the rate of epimerisation at C-5 of thiazolidines, then it should be possible to obtain epimers of 3 and 4.

Oxazolidinones[3] have been previously used in the synthesis of N-alkyl amino acids via reductions[4] and for the protection of α-amino carboxyl groups during synthetic manipulations.[5] Facile formation of monocyclic lactams and lactones via intramolecular nucleophilic opening of oxazolidinone rings by amines and alcohols has been noted.[5a] It was hoped that thiazolidine-oxazolidinone intermediates of type 7 would be sufficiently reactive that formation of bicyclic γ-lactams could be achieved under very mild conditions.

Thus N-benzyloxycarbonyl-L-aspartic acid was reacted with paraformaldehyde to yield oxazolidinone acid 8. The corresponding acid chloride 9 was reduced with tributylstannane to yield oxazolidinone aldehyde 10.

Reaction of crude 10 with L-cysteine methyl ester in pyridine at room temperature yielded the N-hydroxymethyl bicyclic γ-lactam 11 via sequential double cyclisations. Removal of the one-carbon appendage was achieved in methanol containing solid sodium carbonate to produce 3. There was no sign of the presence of the sterically crowded (2R, 5R, 7S) epimer. This new route to 3 offers practical advantages over the reported scheme[1] as it proceeds in approximately the same yield without the need to purify intermediates.

When D-cysteine methyl ester was reacted with crude 10 under the same conditions, an epimeric mixture of the N-hydroxymethyl bicyclic γ-lactams 12 was obtained, which was converted to two major products 4 and 13 upon treatment with sodium carbonate in methanol. In this case, the random stereochemistry of the intermediate thiazolidine 7 was trapped as anticipated. The third stereoisomer 13 (2S, 5S, 7S) was unstable under methanol-sodium carbonate conditions and prolonged reaction times caused substantial formation of 3, presumably the most stable epimer.



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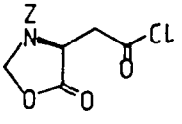

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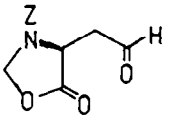

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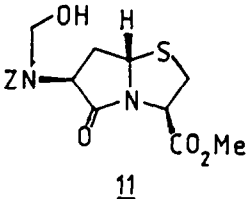

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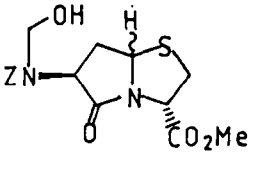

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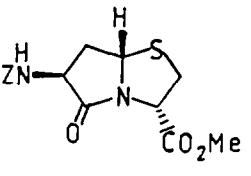

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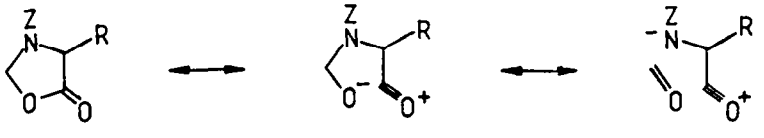
These results demonstrate the utility of the oxazolidinone derivatives of amino acids for protection and activation of α-carboxyl groups. The origin of this activation may result from contribution of the structures 14 and 15 for the ground state of such oxazolidinones.



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GENERAL EXPERIMENTAL

Melting points (m.p.) were determined on a Büchi 510 capillary apparatus and are uncorrected. Optical rotations were measured using a Perkin-Elmer 241 automatic polarimeter in a 10 cm cell. Infra red spectra (ν_{max}) were recorded in $CHCl_3$ solutions on Perkin-Elmer 681 spectrophotometer. Mass spectra (m/e) using desorption chemical ionisation (D.C.I.) or in beam electron impact (I.B.E.I.) techniques were recorded on V.G. Micromass 30F or ZAB 1F spectrometers. The m/e values are quoted with the relative abundunce (base ion = 100%). Proton magnetic resonance spectra (^1H NMR) were recorded at 300 MHz and 500 MHz on Bruker WH 300 and Bruker AM 500 spectrometers respectively. Chemical shifts (δ_H) are reported in ppm relative to the $CHCl_3$ peak at δ 7.27, with the notations giving the number of protons, the multiplicity of the signals, and the coupling constants (if applicable); spin multiplicity is given by s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Carbon magnetic resonance spectra (^{13}C NMR) were recorded at 62.5 MHz on a Bruker AM 250 spectrometer. Chemical shifts (δ_C) are quoted in ppm and are referenced to $CDCl_3$. Microanalyses were performed by the Dyson Perrins Laboratory staff. Flash column chromatography was performed with Merck 9385 silica gel.

(4S)-3-(Benzyloxycarbonyl)-4-(carboxymethyl)-5-oxooxazolidine (8)

N-Cbz-L-Aspartic acid (10.3 g) was suspended in 750 ml toluene and paraformaldehyde (7.3 g) and p-toluenesulphonic acid (770 mg) were added. The mixture was heated under reflux for 100 min with azeotropic removal of water. The reaction mixture was filtered through silica gel (100 g, Merck 7734). The toluene eluent contained very little product. The product was eluted with ether (2 l) and the ether solution was concentrated to give 11.7 g (> 95%) of oil : $[\alpha]_D^{\beta}$° = +143° (c = 1.40, $CHCl_3$); ν_{max} 1720, 1805 cm^{-1}; m/e (D.C.I., NH_3) 576 (12, $2M.NH_4^+$), 387 (27), 326 (22), 297 (100, $.MNH_4^+$), 236 (27); δ_H (300 MHz) 3.06-3.40 (2H, m, CH_2-CO_2H), 4.38 (1H, broad s, CH), 5.14-5.25 (2H, m, Ph-CH_2-O), 5.32-5.52 (2H, m, N-CH_2-O), 7.33-7.42 (5H, m, aromatic).

(4S)-3-(Benzyloxycarbonyl)-4-(2-chloro-2-oxoethyl)-5-oxo-oxazolidine (9)

Crude oxazolidinone acid 8 (11.7 g) was heated under reflux in thionyl chloride (100 ml) for 20 min. The reaction mixture was concentrated to give 12.2 g (> 95%) of oil : $[\alpha]_D^{\beta}$° = +101° (c = 1.61, $CHCl_3$); ν_{max} 1720, 1780 (shoulder), 1805 cm^{-1}; δ_H (300 MHz) 3.54-3.94 (2H, m, CH_2COCl), 4.34 (1H, m, CH), 5.15-5.26 (2H, m, Ph-CH_2-O), 5.34-5.51 (2H, m, N-CH_2-O), 7.34-7.43 (5H, m, aromatic).

(4S)-3-(Benzyloxycarbonyl)-4-(2-oxoethyl)-5-oxo-oxazolidine (10)

Crude oxazolidinone acid chloride 9 (12.2 g) was dissolved in ethyl acetate (50 ml) and the solution was treated in an ice bath with dropwise addition of tributylstannane solution (12.0 g in 25 ml ethyl acetate) for 20 min. The reaction mixture was allowed to stand 20 hours at room temperature under argon atmosphere. After evaporation of ethyl acetate, the residue was partitioned between acetonitrile and petroleum ether. Acetonitrile solution (appr. 250 ml) was washed with petroleum ether (5 x 100 ml). Evaporation of acetonitrile yielded 10.6 g of crude oil: ν_{max} 1720, 1802 cm^{-1}. Proton magnetic resonance spectrum was complex suggesting presence of several products but clearly showed an aldehyde proton signal at δ 9.6 with integration corresponding to approximately 0.4 H compared to 5 H of aromatic proton signals.

On TLC (SiO_2, ether) several spots were seen, but column chromatographic separation (SiO_2, ether) did not yield any compound with an aldehyde signal in NMR. The crude product was therefore used without further purification in the next step. Reduction of 9 with lithium tri-t-butoxy-aluminium hydride failed to give any aldehyde.

(2R,5S,7S)-1-Aza-7-benzyloxycarbonyl(hydroxymethyl)amino-8-oxo-4-thiabicyclo[3.3.0]octane-2-carboxylic acid methyl ester (11)

Crude oxazolidinone aldehyde 10 (905 mg) and L-cysteine methyl ester hydrochloride (629 mg) were dissolved in anhydrous pyridine (9 ml) and stirred at room temperature for 72 hours. The crude product was partitioned in ether-water and the ether solution (100 ml) was washed with aqueous 2N hydrochloric acid and brine before drying over anhydrous sodium sulphate. Ether was evaporated to yield 938 mg of oil. The crude product was separated on a column (100 g SiO_2) using ether-ethyl acetate (2 : 1) mixture to yield 278 mg (21%) of 11 as colourless oil. Many peaks in 300 MHz NMR spectrum were broad and some peaks in ^{13}C NMR spectrum were broad and split indicating slow internal rotations. Mass spectrum was similar to that of 3. Selected physical properties of 11 : ν_{max} 1710 (broad), 3460, 3600 cm^{-1}; m/e (D.C.I., NH_3) 368 (25, MNH_4^+-CH_2O), 351 (33, $\overline{MH}^+$-CH_2O), 260 (100), 243 (36), 217 (16); δ_H (300 MHz) 2.62 (2H, m, 6-H_2), 3.36-3.54 (2H, m, 3-H_2), 3.79 (3H, s, OCH_3), 5.07 (1H, dd, J = 4.5 Hz, 9.0 Hz, 2-H), 4.5-5.3 (6H, m, Ph-CH_2-O, N-CH_2-OH, 7-H); 7.37 (5H, m, aromatic); δ_C (62.5 MHz) 28.3 and 29.1 (broad peaks, CH_2), 36.8 (CH_2), 52.9 (OCH_3), 58.2 (CH), 58.0 and 58.6 (broad peaks, CH), 63.9 (CH), 67.9 (CH_2), 71.9 and 72.6 (broad peaks, CH_2), 128.0, 128.2, 128.5, 135.7 (aromatic), 155.2 (CO), 170.0 (CO), 174.0 and 174.4 (broad peaks, CO).

(2R,5S,7S)-1-Aza-7-benzyloxycarbonylamino-8-oxo-4-thiabicyclo[3.3.0]octane-2-carboxylic acid methyl ester (3)

Crude N-hydroxymethyl bicyclic γ-lactam 11 (7.66 g) was dissolved in anhydrous methanol (200 ml) containing solid sodium carbonate (1.5 g) and the suspension was stirred 50 min at room temperature. The reaction mixture was poured into 500 ml of half-saturated solution of ammonium chloride and the mixture was extracted with ether (3 x 200 ml). The ether solution was washed with brine, dried over anhydrous sodium sulphate, and concentrated to give 5.38 g of crude product. Flash column chromatographic separation (200 g SiO_2) using ether-ethyl acetate (3 : 1) mixture yielded 1.70 g of 3 : total yield of 3 from N-Cbz-L-aspartic acid in five steps was approximately 13% : m.p. 109-110° (from ether); $[\alpha]_D^{\beta}$° = -199° (c = 0.67, $CHCl_3$); ν_{max} 1715 cm^{-1}; m/e (D.C.I.,

NH_3) 368 (50, MNH_4^+), 351 (92, MH^+), 260 (100), 243 (48), 217 (22); δ_H (300 MHz) 2.40-2.50 (1H, m, 6-βH), 2.70-2.78 (1H, m, 6-αH), 3.40 (1H, dd, J = 4.5 Hz, 11.5 Hz, 3-βH), 3.50 (1H, dd, J = 8.5 Hz, 11.5 Hz, 3-αH), 3.79 (3H, s, OCH_3) 4.42-4.50 (1H, m, 7-H), 5.06 (1H, dd, J = 4.5 Hz, 8.5 Hz, 2-H), 5.14 (2H, s, Ph-CH_2-O), 5.18 (1H, d, J = 6.5 Hz, 5-H), 5.28 (1H, broad, s, NH), 7.32-7.39 (5H, m, aromatic); δ_C (62.5 MHz) 29.9 (CH_2), 36.9 (CH_2), 52.1 (CH), 52.8 (OCH_3), 58.4 (CH), 63.8 (CH), 67.1 (CH_2), 128.05, 128.11, 128.4, 136.0 (aromatic), 156.0 (CO), 170.0 (CO), 174.7 (CO); [Found C, 54.66%; H, 5.21%, N, 7.87%. $C_{16}H_{18}N_2O_5S$ requires C, 54.86%; H, 5.18%; N, 8.00%]. The relative stereochemistry was determined by nuclear Overhauser enhancement difference spectroscopy (N.O.E.D.S, 500 MHz, CD_3CN-D_2O, 45°), selected details : irradiation of 6-βH showed a 15% enhancement of 5-H; irradiation of 6-αH showed a 20% enhancement of 7-H; irradiation of 3-βH showed a 3% enhancement of 5-H; irradiation of 3-αH showed a 16% enhancement of 2-H.

A small amount of a by-product was isolated (< 1%), which had identical NMR spectrum as that of 4 but with the opposite sign of rotation; $[\alpha]_D^{25}$ = -82° (c = 1.16, $CHCl_3$). It may arise from partial racemisations of the C-7 and C-2 centres during the course of reaction, most probably at the thiazolidine stage.

Conversion of 11 to 3 could also be achieved in boiling pyridine or in boiling benzene using catalytic amount of p-toluenesulphonic acid. The corresponding methyl ether was formed in methanol-p-toluenesulphonic acid.

Reaction of 10 with D-cysteine methyl ester

Crude oxazolidinone aldehyde 10 (939 mg) and D-cysteine methyl ester hydrochloride (612 mg) were dissolved in anhydrous pyridine (20 ml) and stirred at room temperature for 64 hours. Work-up in ether-water (as in the work-up of 11) yielded 840 mg of crude oil. Flash column chromatography (200 g SiO_2) using ether-ethyl acetate (3 : 2) produced 251 mg (19%) of 12 as colourless oil. Broad peaks in 300 MHz proton NMR and 62.5 MHz ^{13}C NMR spectra indicated the presence of stereoisomers and slow internal rotations : m/e (D.C.I., NH_3) 368 (20, MNH_4^+ - CH_2O), 351 (84, MH^+ - CH_2O), 260 (100), 243 (87), 217 (42).

A purified sample of 12 (125 mg) was dissolved in anhydrous methanol (12 ml) containing solid sodium carbonate (620 mg) and the suspension was stirred for 1 hour at room temperature. Work-up in ether-aqueous ammonium chloride solution (as in the work-up of 3) yielded 111 mg of crude products. Flash column chromatography (50 g SiO_2) using ether-ethyl acetate (3 : 1) mixture yielded 11 mg (10%) of 3, 42 mg (36%) of 4, and 33 mg (29%) of 13.

The physical properties of 3 isolated from this reaction were identical as those of the sample isolated from reactions with L-cysteine methyl ester except for lower specific rotation $[\alpha]_D^{25}$ = -163° (c = 0.54, $CHCl_3$). This suggested the formation of 3 predominantly by epimerization of 13 (after bicyclic ring formation).

Physical properties of 4 as colourless oil : $[\alpha]_D^{25}$ = +170° (c = 1.82, $CHCl_3$); ν_{max} 1715 cm^{-1}; m/e (I.B.E.I.) 350 (10, M^+), 259 (22), 156 (20), 91 (100), 86 (25); δ_H (300 MHz) 2.01-2.11 (1H, m, 6-βH), 3.15-3.24 (1H, m, 6-αH), 3.32-3.41 (2H, m, 3-H_2), 3.78 (3H, s, OCH_3), 4.64-4.72 (1H, m, 7-H), 5.09-5.19 (4H, m, Ph-CH_2-O, 2-H, 5-H), 5.43 (1H, m, NH), 7.32-7.38 (5H, m, aromatic); δ_C (62.5 MHz) 35.0 (CH_2), 38.5 (CH_2), 52.9 (OCH_3), 54.6 (CH), 57.7 (CH), 61.7 (CH), 67.1 (CH_2), 128.1, 128.2, 128.5, 136.0 (aromatic), 155.9 (CO), 169.4 (CO), 171.1 (CO); [Found C, 54.71%; H, 5.38%; N, 8.04%. $C_{16}H_{18}N_2O_5S$ requires C, 54.86%; H, 5.18%; N, 8.00%]. The relative stereochemistry was determined by N.O.E.D.S. (500 MHz, CD_3CN, 80°), selected details: irradiation of 6-βH showed no enhancement of 5-H; irradiation of 5-H showed a 5% enhancement of 6-αH and a 3% enhancement of 3-αH; irradiation of 6-αH showed a 8% enhancement of 7-H.

Physical properties of 13 as colourless oil; $[\alpha]_D^{25}$ = -4.7° (c = 1.57, $CHCl_3$); m/e (I.B.E.I.) 350 (10, M^+), 259 (42), 156 (23), 91 (100), 86 (23); δ_H (300 MHz) 2.43-2.52 (1H, m, 6-βH), 2.61-2.69 (1H, m, 6-αH), 3.37-3.60 (2H, broad m, 3-H_2), 3.81 (3H, s, OCH_3), 4.32-4.38 (2H, m, 2-H, 7-H), 5.08 and 5.14 (2H, ABq, J = 12 Hz, Ph-CH_2-O), 5.29 (1H, broad s, 5-H), 5.43 (1H, broad s, NH), 7.34-7.37 (5H, m, aromatic). The relative configuration was established by N.O.E.D.S. (500 MHz, CD_3CN, 80°), selected details: irradiation of 6-αH showed a 7% enhancement of 7-H; irradiation of 6-βH showed a 7% enhancementof 5-H; irradiation of 3-βH showed a 4% enhancement of 2-H and a 1.5% enhancement of 5-H.

Purified samples of 13 yielded approximately 1 : 1 mixture of 3 and 13 after stirring 1 hour at room temperature in methanol-sodium carbonate.

Acknowledgements: The Authors wish to thank Dr. A.E. Derome for assistance in taking NOE difference spectra. Technical services of the Dyson Perrins Laboratory and helpful discussions from Mr. C. Lowe, Dr. C.J. Schofield and Dr. R.M. Adlington are gratefully acknowledged. E.L. wishes to thank Ministry of Education, Republic of Korea, for a Scholarship Grant.

References

1. J.E. Baldwin, C. Lowe, C.J. Schofield, E. Lee, Tetrahedron Lett., 1986, 27, 3461.

2. R.B. Woodward, Phil.Trans.R.Soc.Lond.B., 1980, 289, 239.

3. D. Ben-Ishai, J.Am.Chem.Soc., 1957, 79, 5736.

4. R.M. Freidinger, J.S. Hinkle, D.S. Perlow, B.H. Arison, J.Org.Chem., 1983, 48, 77.

5. (a) B.H. Lee, M.J. Miller, Tetrahedron Lett., 1984, 25, 927.
(b) S. Hanessian, S.P. Sahoo, Tetrahedron Lett., 1984, 25, 1425.