

SYNTHETIC STUDIES ON β -LACTAM ANTIBIOTICS II.[†]CONDENSATION OF β -LACTAMS WITH ACTIVE METHYLENE GROUPS

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Abstract — β -Lactams (3), (6), and (14) were not condensed with 2-methylthiazoline anion. 4-Acetoxy-2-azetidinone (5) reacted at the 4-position with diethyl bromomalonate, but in the case of diethyl malonate, N_1 - C_4 cleavage occurred after C_4 -condensation, and the product (16) was obtained.

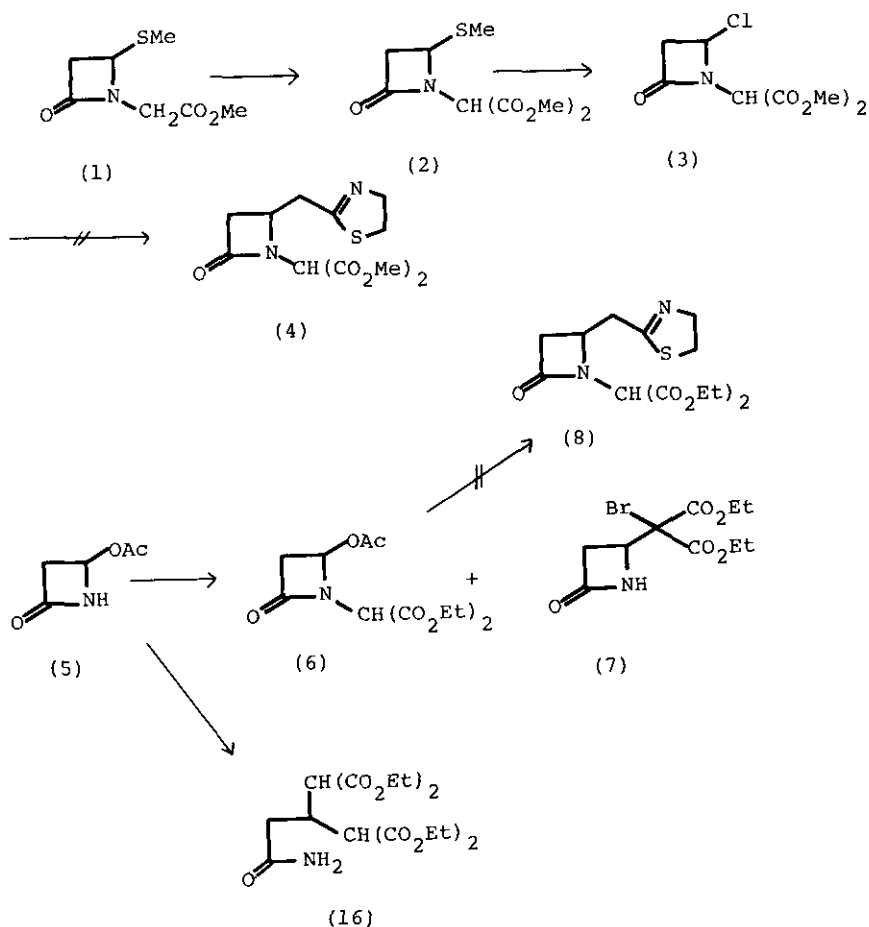
Recently several reports^{1,4} on carbapenem type antibiotics, which are strongly active against resistant bacteria or possess an inhibitory activity against β -lactamase have been published. Instead of a sulfur atom, the carbapenem system has a carbon atom adjacent to the 4-position of a β -lactam. Both carbapenem⁵ and carbapenam⁶ derivatives have been synthesized, but no synthetic method via C_4 -alkylation after β -lactam formation has been reported. Only a few studies^{7,8} have been described regarding C_4 -alkylation of β -lactams. Here we wish to report our studies on the C_4 -alkylation of β -lactams.

N-Methoxycarbonylmethyl-4-methylthio-2-azetidinone⁹ (1) in tetrahydrofuran was treated with methyl chloroformate in the presence of 2 equiv. of lithium diisopropylamide at -78°C for 1 hr to afford *N*-bis(methoxycarbonyl)methyl-4-methylthio-2-azetidinone (2) as an oil [i.r. (CHCl_3) 1770, 1750 cm^{-1} ; δ (CDCl_3) 2.11 (3H, s), 3.4 (1H, dd, $J = 2.5, 15$ Hz), 3.47 (1H, dd, $J = 5, 15$ Hz), 3.83 (6H, s), 5.4 (1H, s), 5.15 (1H, dd, $J = 2.5, 5$ Hz), m/e 247 (M^+)] in 61.3 % yield. The diester (2) was chlorinated with a slight excess of chlorine in methylene chloride at 78°C to give the unstable *N*-bis(methoxycarbonyl)methyl-4-chloro-2-azetidinone (3) as an oil [i.r. (CHCl_3) 1785, 1750 cm^{-1} ; δ (CDCl_3) 3.32 (1H, dd, $J = 2, 15$ Hz), 3.76 (1H, dd, $J = 4.5, 15$ Hz), 3.87 (6H, s), 5.12 (1H, s), 6.08 (1H, dd, $J = 2, 4.5$ Hz)] in

quantitative yield. After purification by Bio-Beads S-X3 column chromatography, chloroazetidinone (3) was treated with 2-methylthiazoline anion¹⁰, prepared from 2-methylthiazoline and n-butyllithium in tetrahydrofuran, to form none of the expected product (4). Only decomposition products were obtained.

Reaction of the β -lactam (6), where acetoxyl rather than chlorine would be better as a leaving group, was then examined. 4-Acetoxy-2-azetidinone¹¹ (5) was treated with diethyl bromomalonate and sodium hydride in tetrahydrofuran at -50°C for 1 hr to give N-bis(ethoxycarbonyl)methyl-4-acetoxy-2-azetidinone¹¹ (6) as an oil [i.r. (CHCl_3) 1785, 1740 (broad) cm^{-1} ; δ (CDCl_3), 1.3 (6H, t, $J = 7$ Hz), 2.08 (3H, s), 3.02 (1H, dd, $J = 2, 15$ Hz), 3.42 (1H, dd, $J = 4, 15$ Hz), 4.26 (2H, q, $J = 7$ Hz), 4.3 (2H, q, $J = 7$ Hz), 5.07 (1H, s), 6.35 (1H, dd, $J = 2, 4$ Hz), m/e 287 (M^+)] in 22.5 % yield, and 4-bis(ethoxycarbonyl)bromomethyl-2-azetidinone (7) as an oil [i.r. (CHCl_3), 3450, 1770, 1735 cm^{-1} , δ (CDCl_3), 1.33 (6H, t, $J = 7$ Hz), 3.05 - 3.2 (2H, m), 4.2 - 4.5 (1H, m), 4.43 (4H, q, $J = 7$ Hz), 6.65 (1H, broad s), m/e 307 (M^+), 309 ($\text{M}^+ + 2$)] in 35.3 % yield. The acetoxyazetidinone (6) was treated with 2-methylthiazoline anion, prepared from 2-methylthiazoline and n-butyllithium, in tetrahydrofuran to afford no alkylated product.

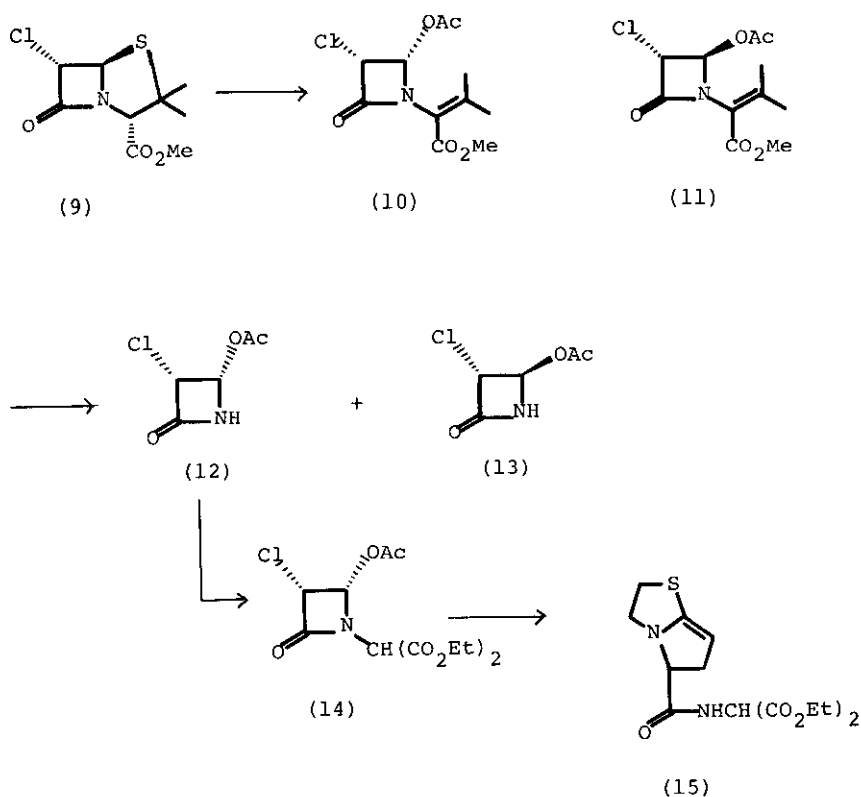
The reaction of 2-methylthiazoline with N-bis(ethoxycarbonyl)methyl-4 α -acetoxy-3 α -chloro-2-azetidinone (14) was then investigated. Methyl 6 α -chloropenicillanate¹² (9) was refluxed with 2 equiv. of mercuric acetate in acetic acid¹³ for 4 hr to give a separable mixture of 4 α -acetoxy-3 α -chloro-2-azetidinone (10) [i.r. (CHCl_3) 1785, 1755, 1720 cm^{-1} ; δ (CDCl_3) 2.04, 2.18, 2.3, 3.83 (3H \times 4, each s), 5.13 (1H, d, $J = 4$ Hz), 6.05 (1H, d, $J = 4$ Hz)] and 4 β -acetoxy-3 α -chloro-2-azetidinone (11) [i.r. (CHCl_3) 1785, 1755, 1720 cm^{-1} ; δ (CDCl_3) 1.98, 2.12, 2.28, 3.83 (each 3H, each s), 4.38 (1H, s), 6.18 (1H, s)] in the ratio 3 : 2, in 26.3 % yield. This mixture was oxidized with potassium permanganate in aqueous acetone, buffered at pH 7¹⁴, at 0°C for 30 min to afford a mixture of unstable 4 β -acetoxy-3 α -chloro-2-azetidinone (12) as an oil [i.r. (CHCl_3) 3450, 1805, 1750 cm^{-1} ; δ (CDCl_3) 2.22 (3H, s), 5.1 (1H, t, $J = 3.5$ Hz), 6.1 (1H, d, $J = 3.5$ Hz), 6.9 (1H, broad s), m/e 164 (M^+), 166 ($\text{M}^+ + 2$)] and 4 β -acetoxy-3 α -chloro-2-azetidinone (13) as stable colorless needles, m.p. 88 - 89 $^{\circ}\text{C}$ [i.r. (CHCl_3) 3440, 1795, 1740 cm^{-1} ; δ (CDCl_3) 2.18 (3H, s), 4.78 (1H, s), 5.78 (1H, s), 7.1 (1H, broad s), m/e 164 (M^+), 166 ($\text{M}^+ + 2$)] in the ratio 3 : 2, in 50.0 % yield, which were separated by silica gel column chromatography. 4 α -Acetoxy-3 α -chloro-2-azetidinone (12) was alkylated by treatment with diethyl bromomalonate and sodium hydride in tetrahydrofuran at -50°C for 1 hr to



provide N-bis(ethoxycarbonylmethyl)methyl-4 α -acetoxy-3 α -chloro-2-azetidinone (14) as an oil [i.r. (CHCl_3) 1800, 1755 (broad) cm^{-1} ; δ (CDCl_3) 1.3 (6H, t, $J = 7$ Hz), 2.14 (3H, s), 4.92 (2H, q, $J = 7$ Hz), 4.32 (2H, q, $J = 7$ Hz), 5.1 (1H, s), 5.16 (1H, d, $J = 4$ Hz), 6.58 (1H, d, $J = 4$ Hz), m/e 312 (M^+), 314 ($M^+ + 2$)] in 32.5 % yield, which was treated with 5 molar equiv. of 2-methylthiazoline and 5 molar equiv. of *n*-butyllithium¹⁰ in tetrahydrofuran at -78°C for 30 min to give colorless needles, m.p. $106 - 107^\circ\text{C}$, in 54.2 % yield [i.r. (CHCl_3) 3450, 1758, 1740, 1680, 1625 cm^{-1} ; δ (CDCl_3) 1.33 (6H, t, $J = 7$ Hz), 2.8 - 3.05 (2H, m), 3.35 (2H, t, $J = 8.5$ Hz), 4.1 - 4.85 (8H, m), 5.2 (1H, d, $J = 7$ Hz), 7.86 (1H, broad s), m/e 328 (M^+), 327 ($M^+ - 1$), 326 ($M^+ - 2$)]. The spectral data indicated this product not to be the expected one and structure (15) is tentatively assigned.¹⁵

Condensation at the C_4 -position of the β -lactams(3,6,14) with 2-methylthiazoline did not proceed, but 4-acetoxy-2-azetidinone (5) reacted easily at such position

with diethyl bromomalonate. On this finding the reaction of 4-acetoxy-2-azetidinone (5) with diethyl malonate was investigated as follows. 4-Acetoxy-2-azetidinone (5) was treated with diethyl malonate and sodium hydride in tetrahydrofuran of -50°C for 1 hr and afforded only the cleaved product (16) as an oil [i.r. (CHCl_3) 3530, 3440, 1720, 1680 cm^{-1} ; δ (CDCl_3) 1.3 (12H, t, $J = 7$ Hz), 2.72 (2H, d, $J = 6$ Hz), 3.5 (1H, quintet, $J = 6$ Hz), 3.95 (2H, d, $J = 6$ Hz), 4.32 (8H, q, $J = 7$ Hz), 6.1 (2H, broad s)] in 48.0 % yield. This result showed that condensation of the β -lactam C_4 -position had occurred, but that the N_1 - C_4 bond was readily cleaved when an active methine group is adjacent to this position.



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15. Using 2 molar equivs. of 2-methylthiazoline and n-butyllithium, (15) was not obtained.

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