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

Tetsuji Kametani*, Shoji Hirata, Hideo Nemoto, Masataka Ihara, and Keiichiro Fukumoto
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

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.

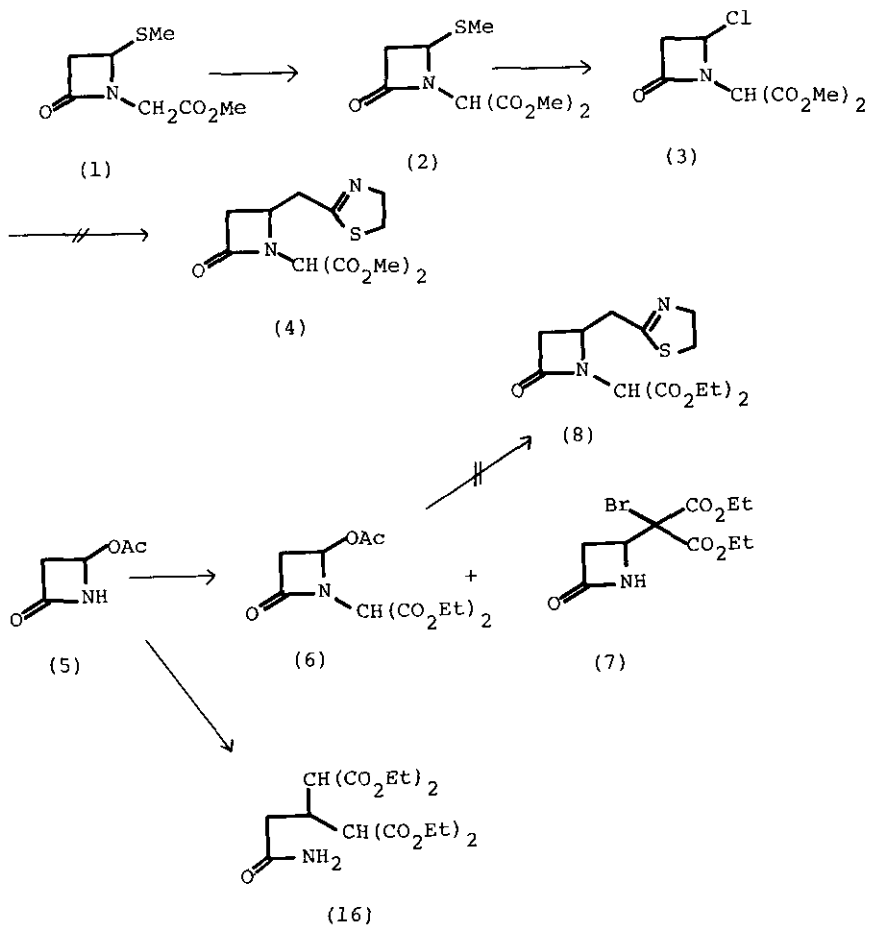
Recently several reports[1~4] on carbapenem type antibiotics, which are strongly active against resistant bacteria or possess an inhibitory activity against β-lactamase have been published. Instead of a sulfur atom, the carbapenem system has a carbon atom adjacent to the 4-position of a β-lactam. Both carbapenem[5] and carbapenam[6] 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-azetidinone[9] (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 anion[10], 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-azetidinone[11] (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-azetidinone[11] (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 (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.

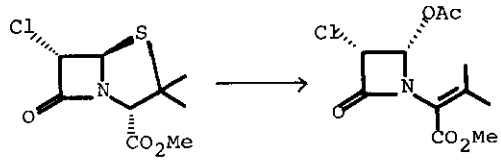
The reaction of 2-methylthiazoline with N-bis(ethoxycarbonyl)methyl-4α-acetoxy-3α-chloro-2-azetidinone (14) was then investigated. Methyl 6α-chloropenicillanate[12] (9) was refluxed with 2 equiv. of mercuric acetate in acetic acid[13] for 4 hr to give a separable mixture of 4α-acetoxy-3α-chloro-2-azetidinone (10) [i.r. ($CHCl_3$) 1785, 1755, 1720 cm^{-1}; δ ($CDCl_3$) 2.04, 2.18, 2.3, 3.83 (3H×4, each s), 5.13 (1H, d, J = 4 Hz), 6.05 (1H, d, J = 4 Hz)] and 4β-acetoxy-3α-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 7[14], at 0°C for 30 min to afford a mixture of unstable 4β-acetoxy-3α-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 (M^++2)] and 4β-acetoxy-3α-chloro-2-azetidinone (13) as stable colorless needles, m.p. 88 - 89°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 (M^++2)] in the ratio 3 : 2, in 50.0 % yield, which were separated by silica gel column chromatography. 4α-Acetoxy-3α-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(ethoxycarbonyl)methyl-4α-acetoxy-3α-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-butyllithium[10] in tetrahydrofuran at -78°C for 30 min to give colorless needles, m.p. 106 - 107°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]

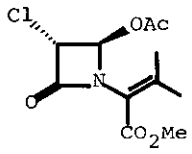
Condensation at the C_4-position of the β-lactams(3,6,14) with 2-methylthiazoline did not proceed, but 4-acetoxy-2-azetidinone (5) reacted easily at such position

with diethyl bromomalonate. On this finding the reaction of 4-acetoxy-2-azetidinon (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.

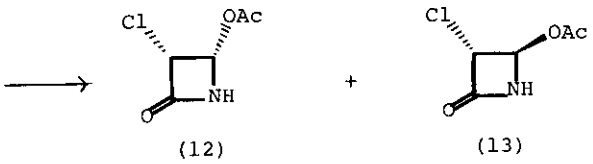


(9)

(10)

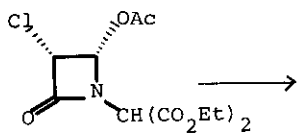


(11)

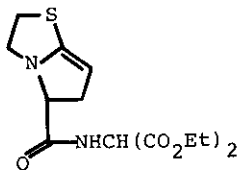


(12)

(13)



(14)



(15)

References

[†]Part I, T. Kametani, S. Yokohama, Y. Shiratori, S. Aihara, and K. Fukumoto, Heterocycles, 1979, 12, 405.

1. G. Albers-Schönberg, B. H. Arison, O. D. Hensens, J. Hirshfield, K. Hoogsteen, E. A. Kaczka, R. E. Rhodes, J. S. Kahan, F. M. Kahan, R. W. Ratcliffe, E. Walton, L. J. Ruswinkle, R. B. Morin, and B. G. Christensen, J. Amer. Chem. Soc., 1978,

100, 6491.

2. A. G. Brown, D. F. Corbett, A. J. Eglington, and T. T. Howarth, J. C. S. Chem. Commun., 1977, 523.

3. D. F. Corbett, A. J. Eglington, and T. T. Howarth, J. C. S. Chem. Commun., 1977, 953.

4. K. Okamura, S. Hirata, Y. Okumura, Y. Fukagawa, Y. Shimauchi, K. Kouno, T. Ishikura, and J. Lein, J. Antibiotics, 1978, 31, 480.

5. D. B. R. Johnston, S. M. Schmitt, F. A. Bouffard, and B. G. Christensen, J. Amer. Chem. Soc., 1978, 100, 313.

6. G. Lowe and D. D. Ridley, J. C. S. Chem. Commun., 1973, 328.

7. I. Ernest, Tetrahydron, 1977, 33, 547.

8. M. D. Bachi, O. Goldberg, and A. Gross, Tetrahedron Letters, 1978, 4167.

9. P. H. Bentley, G. Brooks, M. L. Gilpin, and E. Hunt, J. C. S. Chem. Commun., 1977, 905.

10. A. I. Meyers and J. L. Durandetta, J. Org. Chem., 1975, 40, 2021.

11. K. Clauss, D. Grimm, and G. Prossel, Annalen, 1974, 539.

12. I. McMillan and R. J. Stoodley, J. Chem. Soc. (C), 1968, 2533.

13. R. J. Stoodley and N. R. Whitehous, J. C. S. Perkin I, 1973, 32.

14. E. G. Brain, A. J. Eglington, J. H. C. Nayler, M. J. Pearson, and R. Southgate, J. C. S. Perkin I, 1976, 447.

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

Received, 29th January, 1979