SYNTHESES OF AZAPENEM AND AZACEPHEM RING SYSTEM

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Abstract — Novel β-lactam ring systems, 7-oxo-1,3-diazabicyclo [3.2.0] hept-3-ene(III), 7-oxo-1,4-diazabicyclo [3.2.0] hept-3-ene(IV), and 8-oxo-1,3-diazabicyclo [4.2.0] oct-3-ene(V) have been synthesized via cyclization of olefinic azide.

The chemical modification of β-lactam antibiotics is important research to improve its biological activities and therapeutic effects. Especially the nucleus modification is of considerable interest because they would change intrinsic nature of β-lactam antibiotics and confer new activities. Recent discoveries of novel β-lactam antibiotics, clavulanic acid(II) and thienamycin(III) have spurred a chemist to create new type of β-lactam antibiotics. During a few years a series of new ring system was synthesized. However report concerning the syntheses of azapenem(IV) and isoazapenem(III) have been non existent. We report here the simple syntheses of precedently unknown title compounds via cyclization of olefinic azide.

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Treatment of 4-methyl-4-vinylazetidinone (1) with benzyl glyoxylate (benzene reflux 6 h) gave (2). Chlorination of (2) with mesyl chloride (Et3N, CH2Cl2, 0 °C, 15 min.) and subsequent treatment of the resulting (4) with sodium azide (glyme and water, 0°, 15 min.) produced after purification by silica gel chromatography the azide (5) in 55% yield from (1) as a mixture of diastereomer.

Cycloaddition reaction (toluene reflux, 8 h) of azide (5), followed by silica gel chromatography afforded one of the isomer (5), (6a) and (6b) in 15%, 34% and 17% yield, respectively. Compound (6a): mp 81-2°, ir (CHCl3) 1780 (CO), 1755 (ester), 1625 (C=N), cm⁻¹; nmr (CDCl3) 1.63 (s, 3H), 2.20 (d, J=1.5, 3H), 3.15 (s, 2H), 5.20 (s, 2H), 5.97 (q, J=1.5, C3-H, 1H), 7.37 (s, 5H, Ar-H) ppm.

Compound (6b): mp 101-4°, ir (CHCl3) 1780 (CO), 1755 (ester), 1630 (C=N), cm⁻¹; nmr (CDCl3) 1.54 (s, 3H), 2.20 (d, J=1.5, 3H), 3.15 (s, 2H), 5.27 (s, 3H, C3-H + CH2-O), 7.2-7.7 (m, 5H) ppm. When the recovered (5) was refluxed in toluene for 16 h, compound (6b) was isolated as a major product. The relatively facile cyclization of (5) to (6a) compared with to (6b) could be explained in terms of the steric hindrance between carbonyl in β-lactam and R' as shown in the following figure.

Compound (10) and (15a) were synthesized by the same manner. Compound (2) and (11) were converted to (9) via 2 - 7 - 8 - 9 and (14) via 11 - 12 - 13 - 14, respectively. Intramolecular cycloaddi-
tion (toluene reflux, 8 h) of (9) gave (9), (10a) and (10b) in 34%, 41% and 7% yield, respectively. Compound (10a): \text{ir (CHCl}_3\text{) 1780 (CO), 1745 (ester), 1625 (C=N) cm}^{-1}; \text{nmr (CDCl}_3\text{) 2.22 (d, J=1, 3H), 2.95 (dd, J=3.2, 16, C6-Hg), 3.57 (dd, J=6.4, 16, C6-Hg), 4.48 (bs, C5-H), 5.29 (s, 2H), 6.05 (bs, C3-H), 7.2-7.8 (m, 5H) ppm. Compound (10b): \text{ir (CHCl}_3\text{) 1780 (CO), 1750 (ester), 1630 (C=N) cm}^{-1}; \text{nmr (CDCl}_3\text{) 2.22 (bs, 3H), 3.03 (dd, J=4.2, 16, C6-Hg), 3.50 (dd, J=6.0, 16, C6-Hg), 4.32 (bs, C5-H), 5.26 (s, CH2+C2-H), 7.12-7.70 (5H) ppm. Thermolysis (toluene reflux 8 h) of (14) gave (14) and (15a) in 23% and 31% yield, respectively. Compound (15a): \text{ir (CHCl}_3\text{) 1755 (CO + ester), 1655 (C=N) cm}^{-1}; \text{nmr (CDCl}_3\text{) 2.12 (d, J=1, C2-CH3), 2.0-3.6 (m, C1-H + C7-H), 3.7 (m, C6-H), 5.21 (s, 2H), 5.77 (bs, C4-H), 7.30 (s, 5H) ppm.}

\[ \begin{align*}
11 & \rightarrow \\
12 & \quad X = \text{OH} \\
13 & \quad X = \text{Cl} \\
14 & \quad X = \text{N}_3
\end{align*} \]

The stereochemistry of (6) and (10) was assigned as follows. The nmr chemical shift of C3-H in the compound (6a) and (10a) are ca.0.5 ppm lower field than those in (6b) and (10b). Furthermore compound (6b) was entirely converted to its isomer (6a) by catalytic amount of 1,5-diazabicyclo [4.3.0] non-5-ene.4c,9a

\[ \begin{align*}
16 & \rightarrow \\
17 & \quad R = \text{H} \\
18 & \quad R = \text{Allyl} \\
19 & \rightarrow \\
20 & \quad R = \text{H}
\end{align*} \]
The methodology was also applied to the synthesis of 1-azapenem. Treatment of 4-acetoxy-2-azetidinone (16) with t-butanol in the presence of sodium methoxide gave (17), which was alkylated with allyl bromide (NaH, DMF, 0 °C, 65%) to (18). Bromination of (18) (1 eq. Br2, CH2Cl2/glyme, -30 °C), followed by reaction with sodium azide (glyme/H2O, -30 °C) afforded (19) in 56% yield after silica gel chromatography. Intramolecular cycladdition (toluene reflux, 16 h) of (19) gave unstable (20) in 31% yield after rapid fractionation on silica gel. Compound (20); ir (CHCl3) 1715 (CO), 1635 (C=N) cm⁻¹; nmr (CDCl3) 2.13 (d, J=1.3, C2-CH3), 2.96 (dd, J=2.3, 16.3, C6-Hg), 3.53 (dd, J=3.0, 16.2, C3-Hg), 4.42 (dd, J=3.0, 16.2, C3-Hg), 5.35 (bs, Cg-H) ppm.

ACKNOWLEDGMENTS

The author thanks Professor M. Schlosser of this institute of Lausanne University for encouragement and support of this work.

References

5. Recently syntheses of Iso-azapenem\(^4\)e and 3-aza-cephalosporin\(^4\)e have been published.
8. Numberings of the system are employed as in penicillin and cephalosporin.
11. Satisfactory microanalysis was obtained for compound 6a.  Compound 10, 15, and 20 were not stable enough to obtain satisfactory microanalysis.
12. Recently Canadian group\(^13\) has reported the synthesis of the same ring system.

Received, 22nd May, 1981