

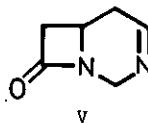
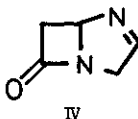
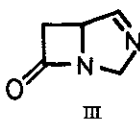
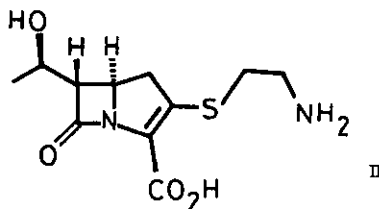
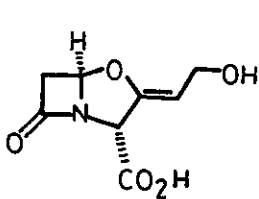
SYNTHESES OF AZAPENEM AND AZACEPHEM RING SYSTEM

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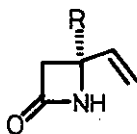
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Abstract — Novel β -lactam ring systems, 7-oxo-1,3-diazabicyclo [3.2.0] hept-3-ene(III), 7-oxo-1,4-diazabicyclo [3.2.0] hept-3-ene(IV), and 8-oxo-1,3-diazabicyclo [4.2.0] oct-3-ene(V) have been synthesized via cyclization of olefinic azide.

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 acid²(I) and thienamycin³(II) have spurred a chemist to create new type of β -lactam antibiotics. During a few years a series of new ring system was synthesized.⁴ However report concerning the syntheses of azapenem(IV) and isoazapenem(III) have been non existent.⁵ We report here the simple syntheses of precedently unknown title compounds via cyclization of olefinic azide.⁶

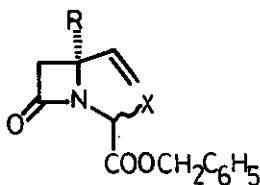


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1 R = CH₃

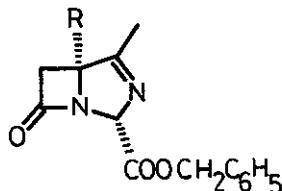
2 R = H



3 R = CH₃, X = OH 7 R = H, X = OH

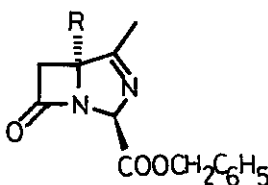
4 R = CH₃, X = Cl 8 R = H, X = Cl

5 R = CH₃, X = N₃ 9 R = H, X = N₃



6a R = CH₃

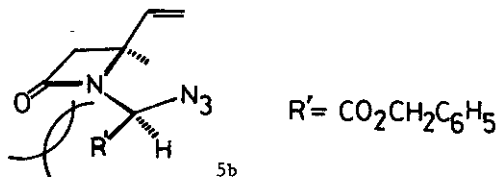
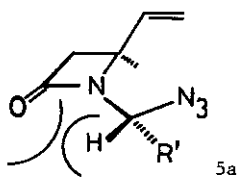
10a R = H



6b R = CH₃

10b R = H

Treatment of 4-methyl-4-vinylazetidinone (1) with benzyl glyoxylate (benzene reflux 6 h) gave (3). Chlorination of (3) with mesyl chloride (Et₃N, CH₂Cl₂, 0°, 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 reaction⁷ (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)¹¹: 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.



R' = CO₂CH₂C₆H₅

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-

The methodology was also applied to the synthesis of 1-azapenam. Treatment of 4-acetoxy-2-azetidione (16)¹⁰ with t-butanethiol in the presence of sodium methoxide gave (17), which was alkylated with allyl bromide (NaH, DMF, 0°, 65%) to (18). Bromination of (18) (1 eq. Br₂, CH₂Cl₂/glyme, -30°), followed by reaction with sodium azide (glyme/H₂O, -30-0°) afforded (19) in 56% yield after silica gel chromatography. Intramolecular cycloaddition (toluene reflux, 16 h) of (19) gave unstable (20) in 31% yield after rapid fractionation on silica gel. Compound (20)¹¹: IR (CHCl₃) 1775 (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-H_β), 3.53 (dd, J=3.0, 16.2, C₃-H_α), 3.57 (ddd, J=1.3, 6.0, 16.3, C₆-H_α), 4.42 (dd, J=3.0, 16.2, C₃-H_β), 5.35 (bs, C₅-H) ppm.¹²

ACKNOWLEDGEMENTS

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

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Received, 22nd May, 1981