SYNTHESES OF AZAPENEM AND AZACEPHEM RING SYSTEM

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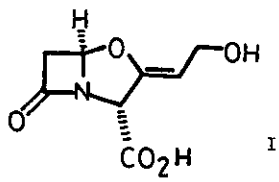
Abstract —— Novel β-lactam ring systems, 7-oxo-1,3-diazabicyclo [3.2.0] hept-3-ene(III), 7-oxo-1,4-diazabicyclo [3.2.0] hept-3-ene(IV), and 8-oxo-1, 3-diazabicyclo [4.2.0] oct-3-ene(V) have been synthesized via cyclization of olefinic azide.

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[2](I) and thienamycin[3](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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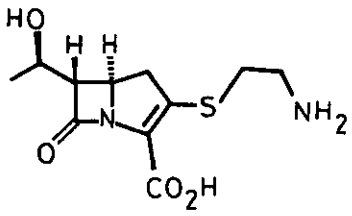

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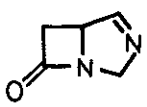

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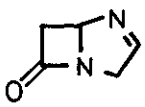

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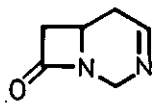

V

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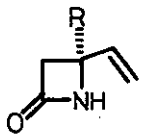
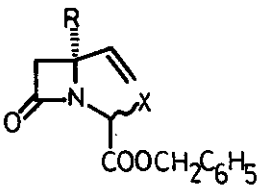




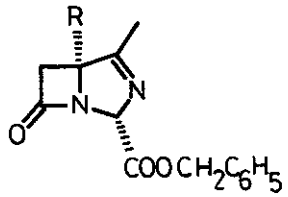
1 R = CH_3

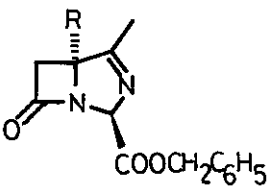
2 R = H

3 R = CH_3, X = OH 7 R = H, X = OH

4 R = CH_3, X = Cl 8 R = H, X = Cl

5 R = CH_3, X = N_3 9 R = H, X = N_3

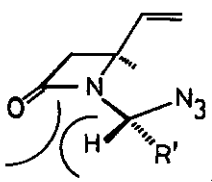




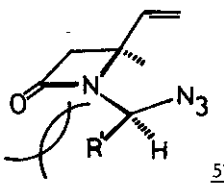
6a R = CH_3 6b R = CH_3

10a R = H 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 (Et_3N, CH_2Cl_2, 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 reaction[7] (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 ($CHCl_3$) 1780 (CO), 1755 (ester), 1625 (c=N) cm^{-1} ; nmr ($CDCl_3$) 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, C_3-H, 1H), 7.37 (s, 5H, Ar-H) ppm. Compound (6b) : mp 101-4°, ir ($CHCl_3$) 1780 (CO), 1755 (ester), 1630 (C=N), cm^{-1} ; nmr ($CDCl_3$) 1.54 (s, 3H), 2.20 (d, J=1.5, 3H), 3.15 (s, 2H), 5.27 (s, 3H, C_3-H + CH_2-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.



5a

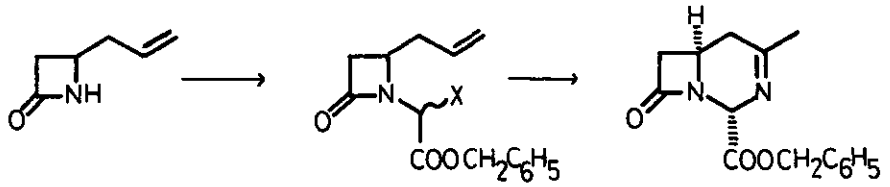


5b

R'= $CO_2CH_2C_6H_5$

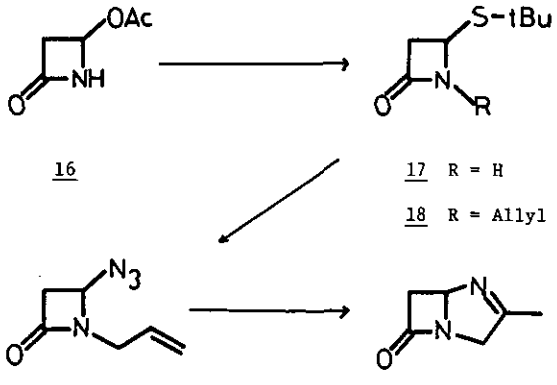
Compound (10) and (15a) were synthesized by the same manner. Compound (2) and (11) were converted to (9) via 2 - 7 - 8 - 9 and (14) via 11 - 12 - 13 - 14, respectively. Intramolecular cycloaddi-

tion (toluene reflux, 8 h) of (9) gave (9), (10a) and (10b) in 34%, 41% and 7% yield, respectively. Compound (10a)[8]: ir ($CHCl_3$) 1780 (CO), 1745 (ester), 1625 (C=N) cm^{-1}; nmr ($CDCl_3$) 2.22 (d, J=1, 3H), 2.95 (dd, J=3.2, 16, C_6-Hβ), 3.57 (dd, J=6.4, 16, C_6-Hα), 4.48 (bs, C_5-H), 5.29 (s, 2H), 6.05 (bs, C_3-H), 7.2-7.8 (m, 5H) ppm. Compound (10b)[8]: ir ($CHCl_3$) 1780 (CO), 1750 (ester), 1630 (C=N) cm^{-1}; nmr ($CDCl_3$) 2.22 (bs, 3H), 3.03 (dd, J=4.2, 16, C_6-Hβ), 3.50 (dd, J=6.0, 16, C_6-Hα), 4.32 (bs, C_5-H), 5.26 (s, CH_2+C_3-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)[8]: ir ($CHCl_3$) 1755 (CO + ester), 1655 (C=N) cm^{-1}; nmr ($CDCl_3$) 2.12 (d, J=1, C_2-CH_3), 2.0-3.6 (m, C_1-H + C_7-H), 3.7 (m, C_6-H), 5.21 (s, 2H), 5.77 (bs, C_4-H), 7.30 (s, 5H) ppm.



11 — 12 X = OH; 13 X = Cl; 14 X = N_3 — 15a

The stereochemistry of (6) and (10) was assigned as follows. The nmr chemical shift of C_3-H in the compound (6a) and (10a) are ca.0.5 ppm lower field than those in (6b) and (10b).[4c,9] 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]



16 — 17 R = H; 18 R = Allyl — 19 — 20

The methodology was also applied to the synthesis of 1-azapenem. Treatment of 4-acetoxy-2-azetidinone (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.Br_2, CH_2Cl_2/glyme, -30°), followed by reaction with sodium azide (glyme/H_2O, -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 ($CHCl_3$) 1775 (CO), 1635 (C=N) cm^{-1} ; nmr ($CDCl_3$) 2.13 (d, J=1.3, C_2-CH_3), 2.96 (dd, J=2.3, 16.3, C_6-Hβ), 3.53 (dd, J=3.0, 16.2, C_3-Hα), 3.57 (ddd, J=1.3, 6.0, 16.3, C_6-Hα), 4.42 (dd, J=3.0, 16.2, C_3-Hβ), 5.35 (bs, C_5-H) ppm.[12]

ACKNOWLEDGEMENTS

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References

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