STUDIES RELATED TO ß-LACTAM ANTIBIOTICS. PART 8. A FACILE ACID-CATALYZED RING TRANSFORMATION OF 1-DETHIA-1-OXA-5-EPI-ISOANHYDROPENICILLINS INTO OXAZOLINONES

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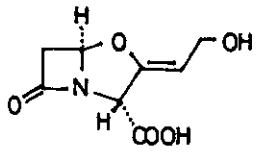
Abstract —— 1-Dethia-1-oxa-5-epiisoanhydropenicillin (2) undergoes with ease an acid-catalyzed ring transformation by virtue of the participation of an acylamino side chain to give oxazolinone derivative (4), as a mixture of geometrical isomers, under mild conditions in an excellent yield.

Since the isolation and structural elucidation of clavulanic acid (1),[1] a naturally occurring ß-lactamase inhibitor, a number of compounds containing the 4-oxa-1-azabicyclo[3.2.0]heptan-7-one (clavam) ring system have been synthesized.[2] A possible mode for the irreversible inactivation of ß-lactamase by clavulanic acid (1) has been also proposed on the basis of the biochemical experiments.[3] Our previous report [4] described a convenient method for the synthesis of 1-dethia-1-oxa-5-epiisoanhydropenicillin (2)(azetidinone-lactone) from penicillin G, involving an intramolecular ring transformation of the oxazolinoazetidinone (3). The molecule of (2) possesses the clavam ring system which functions significantly for the inactivation of ß-lactamase, although the functionality and stereochemistry of (2) are different from those of clavulanic acid (1).[5] We now report here a facile ring transformation of the azetidinone-lactone (2) into the oxazolinone ring system, involving an acid-catalyzed cleavage of the clavam ring. The present result accommodates to some extent the manner proposed in the enzymatic reaction of clavulanic acid (1).



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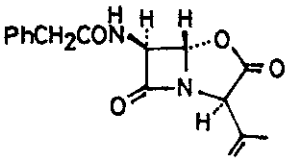

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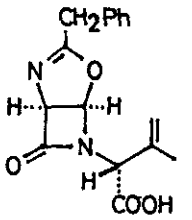

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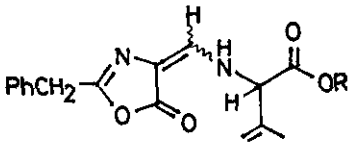

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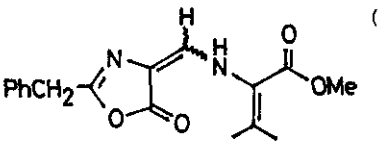


(5)

a : R= H

b : R= Me

Scheme 1

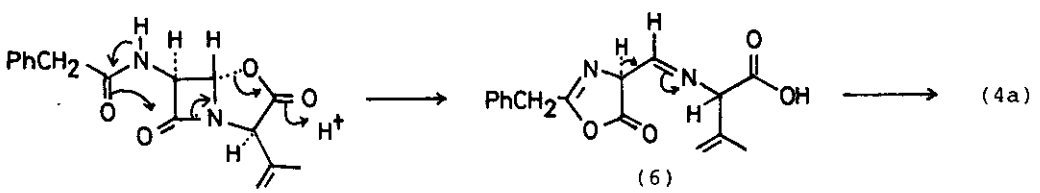
A solution of the azetidinone-lactone (2) in acetonitrile was stirred at room temperature for 0.5 hr in the presence of a catalytic amount of p-toluenesulfonic acid. After removal of the solvent under reduced pressure, the reaction mixture was chromatographed on silica gel to give 2-benzyl-4-(substituted aminomethylidene)oxazolin-5-one (4a), as an oily product, in 93 % yield. The structure of (4a) was supported by its microanalytical results and spectral data [mass m/e 300(M^+); ir (film) 3350(NH), 1750(C=O)cm^{-1}; uv (MeCN) 317(2×10^4)nm; nmr (DMSO-d_6, δ) 1.75(3H, broad s, =C-Me), 3.84(2H, s, benzyl protons), 5.06(2H, b, -C=CH_2), 4.89 and 5.65(each 1/2H, each d, J=each 8 Hz, -NH-CH-), 7.28(5H, s, aromatic protons), 7.08 and 7.62(each 1/2H, each d, J=8 Hz for δ7.08 and J=14 Hz for δ7.62, =CH-NH-)]. The nmr spectrum of (4a) showed two pairs of doublet signals (δ4.89 and 5.65, δ7.08 and 7.62) which were integrated as about 1/2 H, respectively. Addition of deuterium oxide collapsed the doublet signals at δ4.89, 5.65, 7.08, and 7.62 to singlets, respectively. The signals at δ7.62 and 7.08 can be assigned to the vinyl protons (=CH-NH-) of E- and Z-isomer, respectively, on the basis of the coupling constants between a vinyl proton and an amino proton (14 Hz and 8 Hz).[6,7] Thus, it was indicated that (4a) is a mixture of geometrical isomers (a E/Z ratio is ca. 1:1), which are difficult to separate. No formation of other products in this reaction was confirmed by tlc analysis and the nmr spectrum of the reaction mixture. Analogous results were also obtained by using boron trifluoride etherate or trifluoroacetic acid as an

acid catalyst.

Methylation of the oxazolinone (4a) obtained above with diazomethane gave the corresponding methyl ester (4b) as a mixture of E,Z-isomer almost quantitatively [mass m/e 314(M^+); ir (film) 3350(NH), 1750(C=O)cm^{-1}; uv (MeCN) 317(2×10^4)nm; nmr (DMSO-d_6, δ) 1.76(3H, broad s, =C-Me), 3.70(3H, s, COOMe), 3.85(2H, s, benzyl protons), 5.05(2H, b, -C=CH_2), 4.91 and 5.67(each 1/2H, each d, J=each 8 Hz, -NH-CH-), 7.28(5H, s, aromatic protons), 7.08 and 7.62(each 1/2H, each d, J=8 Hz for δ7.08 and J=14 Hz for δ7.62, =CH-NH-), 8.70(1H, m, deuterium exchangeable NH)]. Treatment of the methyl ester (4b) with triethylamine caused isopropenyl-isopropylidene isomerization of the N-side chain to give the oxazolinone (5) as a mixture of E,Z-isomer (a E/Z ratio is ca. 1:1 by nmr)[8] [nmr ($CDCl_3$, δ) 1.92(3H, s, =C-Me), 2.16(3H, s, =C-Me), 3.75(3H, s, COOMe), 3.81(2H, s, benzyl protons), 6.98 and 7.30(each 1/2H, each d, J=each 14 Hz, =CH-NH), 7.30(5H, s, aromatic protons), 8.53(1H, broad d, J=14 Hz, deuterium exchangeable NH)].

As mentioned above, the azetidinone-lactone (2) was converted with ease into the oxazolinone (4a) in the presence of various acid catalysts under mild conditions. Since the reaction proceeded rapidly, attempts to confirm the presence of any possible intermediates in the reaction by uv and nmr spectroscopy were unsuccessful. Analogous acid-catalyzed ring transformations leading to the oxazolinone ring system have been already observed in the cases of 3-phenylacetamido-4-trifluoroacetoxyazetidin-2-ones[9,10] or anhydropenicillins.[11]

We propose the reaction sequence for the present ring transformation as depicted in Scheme 2.



Scheme 2

The reaction could be initiated by protonation at the carbonyl group of the lactone ring. The concurrent participation of the acylamino side chain causes the cleavage of the lactone ring and the ß-lactam ring to give an oxazolinone inter-

mediate (6). Subsequent prototropy of (6) results in the formation of the oxazolinone (4a) as a final product.

The present results provide a further example in the ring transformation of the ß-lactam derivatives into the oxazolinones which proceeds in a manner closely related to the enzymatic degradation of clavulanic acid (1) by ß-lactamase.

REFERENCES AND FOOTNOTES

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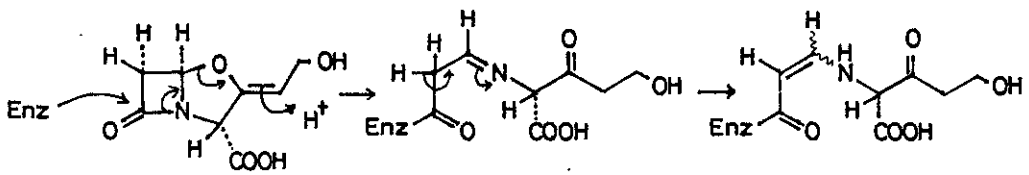
3 One of degradative patterns of clavulanic acid (1) by ß-lactamase is outlined as shown below. cf. R. L. Charnas, J. Fisher, and J. R. Knowles, Biochemistry, 1978, 17, 2185.



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5 No inhibition of azetidinone-lactone (2) against ß-lactamase was observed in bioassay.

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8 Young et al.[9] have suggested that the acid catalyzed ring transformation of 4-trifluoroacetoxyazetidinones gives only the E-isomer in (5) on the basis of nmr spectroscopy. Our oxazolinone (5), however, showed identical spectral data with the compound prepared according to their procedure.

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