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REACTIVITY OF PEPTIDE HYDROXAMATES A MODEL FOR THE BIOSYNTHESIS OF β-LACTAM ANTIBIOTICS

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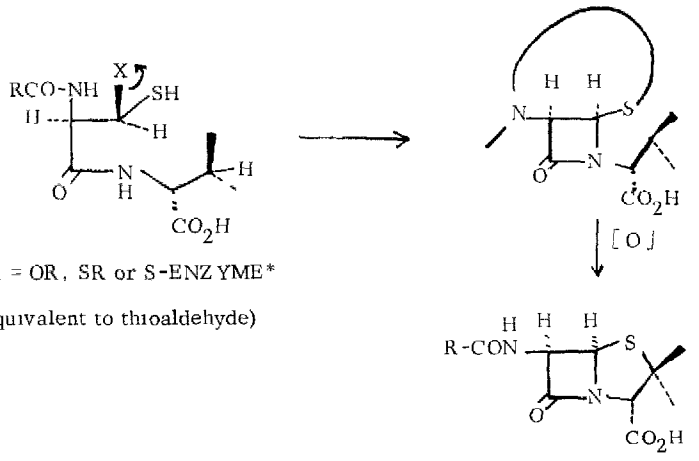
Strong circumstantial evidence[1,2] has implicated the Arnstein tripeptide" δ-(L-α-aminoadipyl)-L-cysteinyl-D-valine[3] as a linear precursor of the β-lactam antibiotics, penicillin and cephalosporin C, while recent chiral labelling studies[4-6] have placed severe restrictions on any proposed mechanism for the biochemical oxidation of such a tripeptide to the penam or cepham nucleus One such proposal which still satisfies the requirement for retention of the α-S and β-pro R protons of cysteine[4] and the α-hydrogen at the (D)-valyl position of the tripeptide[6] is the nucleophilic attack of amide nitrogen on the sp^2 carbon of a thioaldehyde[7] or its sp^3 receptor equivalent, a β-substituted cysteine (as shown in Scheme 1) for which

Scheme 1

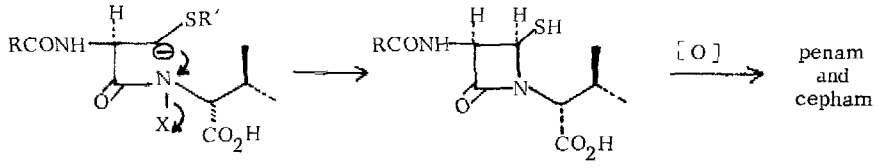


X = OR, SR or S-ENZYME*

(*equivalent to thioaldehyde)

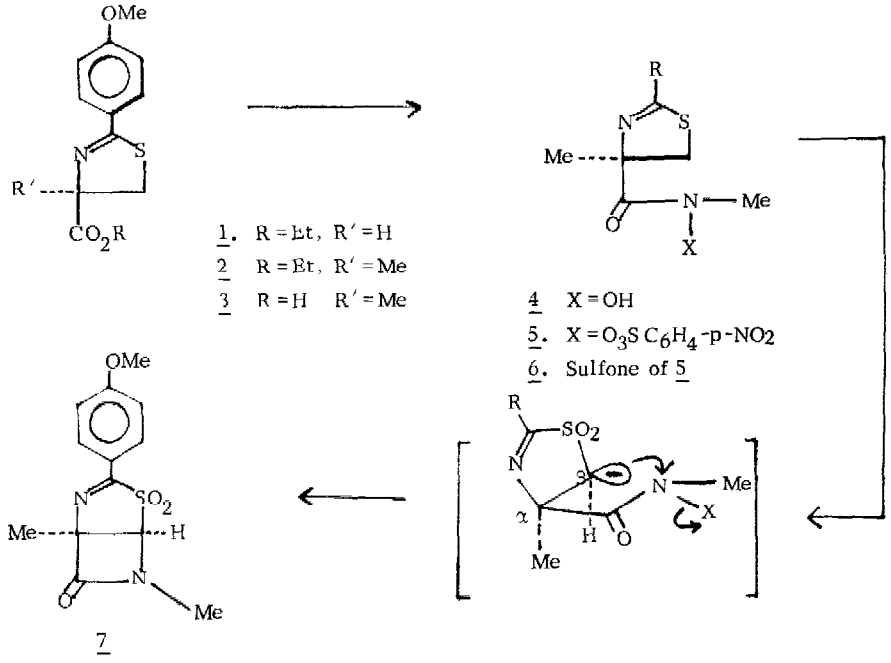
some interesting biogenetic models have recently been provided (Scheme 1, X = Br or Cl, SH replaced by a thiazolidine ring)[8] Another proposal which, perhaps for lack of analogy, has received little attention, concerns oxidation at amide nitrogen followed by nucleophilic displacement by an anion generated at the β-carbon of the cysteine segment[9] (Scheme 2) Prompted by the natural occurrence of oxidized peptides

Scheme 2



in the form of hydroxamic acids we have modified the above postulate to examine for the first time the nucleophilic displacement chemistry of hydroxamic esters by anions derived from sulfones and sulfoxides and herein report the successful cyclization of a peptide hydroxamate to a thiosubstituted β-lactam ring in a model reaction which also mimics the observed stereochemical fate of β-protons of cysteine in the biosynthesis of β-lactam antibiotics (See Scheme 3).

Scheme 3



The thiazoline 1, readily prepared from cysteine, was methylated (KOtBu/MeI) to 2, hydrolyzed to 3 and condensed (acid chloride method) with methyl hydroxylamine in CH_2Cl_2 to give, in 55% overall yield, the hydroxamic acid 4 [amorphous solid, positive $FeCl_3$ test, ir ($CHCl_3$) 1720 cm^{-1}, nmr ($CDCl_3$) δ 1.68 (s, 3H), 3.36 (s, 3H), 3 28 (d, J=11 hz, 1H), 3 89 (s, 3H), 4 24 (d, J=11 hz, 1H), 6.95 and 7 76 (each d, 2H)] Treatment of 4 with p-nitrobenzenesulfonyl chloride and Et_3N in CH_2Cl_2 gave 5 in 90% yield. The corresponding sulfone 6 [amorphous, ir ($CHCl_3$) 1700 cm^{-1}, nmr ($CDCl_3$) δ 1 7 (s, 3H), 2.97 (d, J=14 5 hz, 1H), 3 8 (d, J=14 5 hz, 1H), 3 97 (s, 6H), 7.0-8.4 (8H), ms 497 (M^+)] was readily formed upon oxidation of 5 with 2 equiv m-chloroperbenzoic acid in CH_2Cl_2

When 6 was treated with 1 1 equiv KOtBu in dry THF (overnight, -78° → rt), the crystalline β-lactam 7 (mp 135-137°) was obtained in ca 50% yield after silica gel chromatography The structural assignment is based on the following spectroscopic data ir ($CHCl_3$) 1784 cm^{-1}, nmr ($CDCl_3$) δ 1.88 (s, 3H), 3 1 (s, 3H), 3.9 (s, 3H), 4.32 (s, 1H), 7 0-8 1 (each d, 2H). High resolution ms. Observed m/e 294.06749, calcd for $C_{13}H_{14}N_2O_4S$ m/e 294 06749 The possibility that hydroxamates might be involved as biosynthetic intermediates of the β-lactam antibiotics and further obvious extension of this scheme are being explored.

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