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THE SYNTHESIS OF POTENTIAL γ-LACTAM ANTIBIOTICS CONTAINING A CYCLOSERINE NUCLEUS

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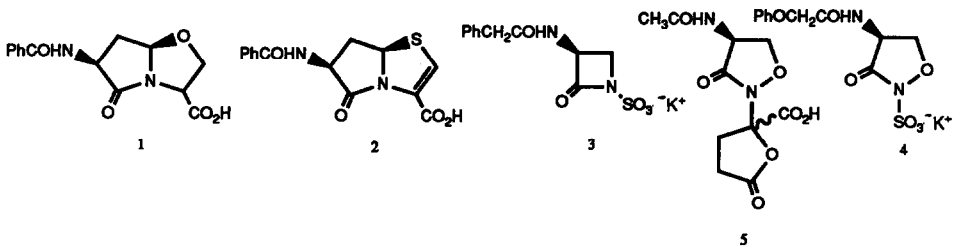
Summary: The synthesis of N-derivatised cycloserine derivatives, one of which possesses antibacterial activity is described.

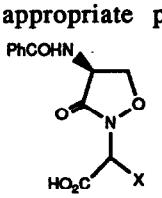
Recent reports by both ourselves and others have described the synthesis of bicyclic γ-lactam analogues of the penams and penems, such as (1)[1] and (2)[2], some of which possess antibacterial activity. Since certain monocyclic β-lactams, such as SQ 26, 324 (3)[3], in which the acylating potential of the lactam ring is increased by electron withdrawing substituents on nitrogen[4], are potent anibacterial agents, we have prepared activated monocyclic γ-lactams. The N-sulphonyl-L-cycloserine compound (4), however, was shown by us not to be an antibiotic against a panel of organisms[5] and similar results were obtained for γ-lactam analogues of the oxamazins[6]. The isolation of a new antibiotic, Lactivicin (5), which contained a cycloserine ring was thus of considerable interest to us. It was isolated from culture filtrates of *Empedobacter lactagenus* YK-258 and *Lysobacter albus* YK-422 and shown to bind to penicillin binding proteins, indicating a similar mode of action to the beta-lactam antibiotics.[7] In this report we describe the synthesis and biological activity of other functionalised cycloserine derivatives, one of which possessed antibacterial activity.



Initially, derivative (6) was chosen as a target for synthesis, since we envisaged that cleavage of the lactam ring would result in elimination of the leaving group (X) by the nitrogen lone pair, in a similar manner to that proposed for Lactivicin itself[7]. Thus, treatment of phenoxyacetyl cycloserine (7)[5] with LDA (THF, -78° to 6°C, 1,5h) followed by isolation of the lithium salt and alkylation with allyl 2-chloro-2-ethoxyacetate (DMF, -10° to 20°C, 16h) gave the epimeric ethers (8) [54% from (7)].[8] Removal of the allyl protecting group [$Pd(PPh_3)_4$, PPh_3, potassium 2-ethyl hexanoate][9] gave the desired diastereomers (10a,b) in a 1:1 ratio which were separated by reverse phase h.p.l.c. Neither (10a) nor (10b)

displayed activity against *Escherichia coli* X580 or *Staphylococcus aureus* N.C.T.C. 6571 at concentrations up to $1mgml^{-1}$.

In addition the synthesis of enamine (11) was carried out. Here, we anticipated that delocalisation of the nitrogen lone pair through the olefin might activate the lactam, as well as providing a pathway for the flow of electrons upon acylation of the appropriate penicillin binding proteins.



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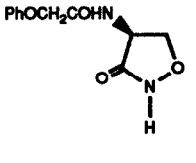

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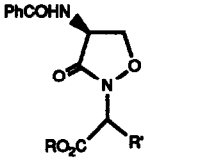
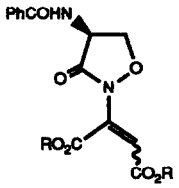


8a,b, R = $CH_2CH{=}CH_2$, R' = OEt
9a,b R = $CH_2CH{=}CH_2$, R' = X
10a,b R = K, R' = OEt



11, R = H
12, R = ^{t}-Bu
13, R = NH_4^+

Reaction of phenoxyacetyl cycloserine (7)[5] with LDA, and isolation of the lithium salt, as previously described, followed by reaction with di^t-butyl acetylene dicarboxylate (DMF, -50°C, 3h) and quenching with acetic acid gave the diester (12) as a single, as yet unassigned, diastereomer [60% from (7)]. Treatment with trifluoroacetic acid in the presence of anisole (0°C, toluene) gave the diacid (11) which was purified by h.p.l.c. to give the diammonium salt (13), which displayed low activity against both *E. coli* X580 and *S. aureus* N.C.T.C. 6571.

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