Cyclic Sulphamidite Analogues of Penicillanic Acid

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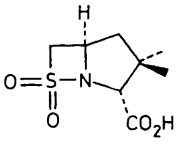
Diastereoisomeric analogues of penicillanic acid have been synthesised in which the β-lactam ring is replaced with the 2-oxo-1,2,3-oxathiazolidine (cyclic sulphamidite) ring; ring fusion greatly increases the chemical reactivity of the 2-oxo-1,2,3-oxathiazolidine ring to nucleophilic attack.

Over the last few years considerable interest has been shown in the possibility of replacing the β-lactam ring in the β-lactam antibiotics by some other functionality in the hope of developing new families of antibacterial agents which are not susceptible to β-lactamases or are inhibitors of them.[1] Since simple alkyl and aryl sulphonyl fluorides are potent irreversible inhibitors of the serine proteases[2] but are not inhibitors of the serine dependent β-lactamases, it seemed likely that this is due to the greater specificity of the latter enzymes. The β-sultam analogue (**1**) of penicillanic acid (**2**, R = H), however, is not an effective antibiotic.[3] Since penicillanic acid (**2**, R = H) itself is not an antibiotic this is perhaps not surprising. However, we considered that even if an appropriate acyl amino group was attached to give analogues of 6-acylaminopenicillanic acid (**2**, R = R'CONH), the presence of one of the two exocyclic oxygen atoms on sulphur would probably sterically preclude the β-sultam (**1**) and the cyclic sulphamidate (**3**) from binding effectively to the enzyme active site. For this reason cyclic sulphamidites were considered to be more promising target molecules, and it was encouraging to note that the cyclic sulphamidites (**4**) and (**5**) are effective inhibitors of the growth of *Staphylococcus aureus, Escherichia coli, etc.*[4] Surprisingly, the only bicyclic sulphamidites reported in the literature are substituted bicyclic 2-oxo-1,2,3-oxathiazolidines (**6**), but no information was available concerning their chemical reactivity.[5] In view of this the diastereoisomeric bicyclic sulphamidites (**7**) and (**8**) were made our initial target molecules. Conversion of these to the bicyclic sulphamidate (**3**) could be achieved, if desired, by oxidation with ruthenium tetroxide.[6]



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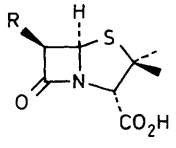

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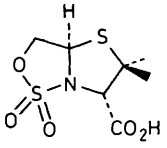

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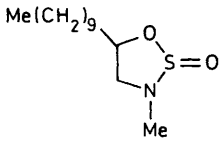

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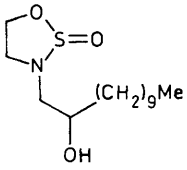

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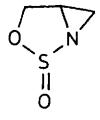

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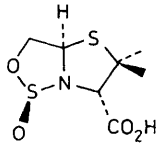

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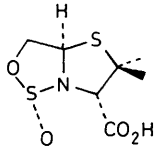
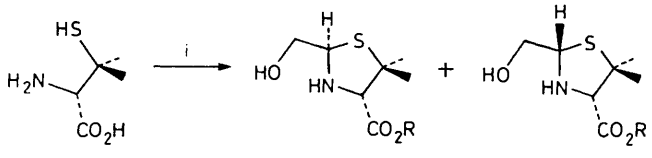
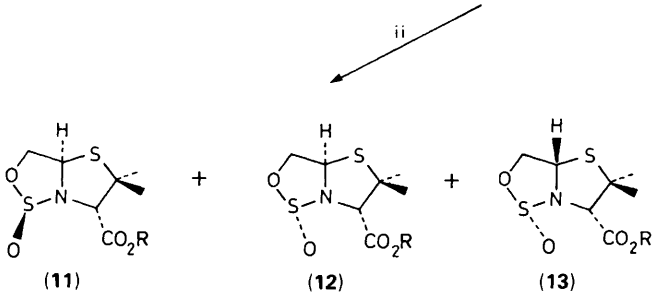


(8)

The synthetic route used for the cyclic sulphamidites (**7**) and (**8**) is outlined in Scheme 1. Condensation of D-(−)-penicillamine with a concentrated solution (0.5 M) of glycolaldehyde (as its cyclic dimer) in hot aqueous methanol resulted in the deposition of a crystalline product of high purity in 68% yield. The ^{1}H NMR spectrum, however, showed it to be a mixture of the diastereoisomers (**9**, R = H) and (**10**, R = H) in the ratio of 4:1. Nuclear Overhauser enhancement (NOE) experiments using the H-3 proton as reference showed that the major isomer was the desired (5*R*,3*S*)-diastereoisomer (**9**, R = H). Attempts to form the bicyclic sulphamidites from these diastereoisomers without protecting the carboxylic acid group failed. The carboxylic acids were protected, therefore, as their benzyl esters by treating the caesium salts of the mixture of acids (**9**, R = H) and (**10**, R = H) with benzyl bromide in dimethylformamide (DMF). The product was a mixture of the diastereoisomeric benzyl esters (73%) (**9**, R = CH_2Ph) and (**10**, R = CH_2Ph) in approximately the same ratio as the acids. The major isomer was shown to be the (5*R*,3*S*)-diastereoisomer (**9**, R = CH_2Ph) by an NOE experiment. Reaction of the mixture of diastereoisomeric benzyl esters with thionyl



(9) (10)



(11) (12) (13)

Scheme 1. *Reagents*: i, (a) $HOCH_2CHO$; (b) Cs_2CO_3, $PhCH_2Br$, in DMF, or $Me_3SiCH_2CH_2Br$, 1,8-diazabicyclo[5.4.0]undec-7-ene in MeCN; ii, $SOCl_2$, C_5H_5N in C_6H_6.

chloride by the method of Deyrup and Moyer[7] gave three bicyclic sulphamidites, which were separated and assigned by ^{1}H NMR spectroscopy the structures (**11**, R = CH_2Ph) (19%), (**12**, R = CH_2Ph) (25%), and (**13**, R = CH_2Ph) (10%). No evidence for the fourth possible stereoisomer could be found. The two (5*R*,3*S*)-sulphamidites (**11**, R = CH_2Ph) and (**12**, R = CH_2Ph) could not be crystallised; by contrast the (5*S*,3*S*)-sulphamidite (**13**, R = CH_2Ph) crystallised readily (m.p. 146—148 °C). The stereochemistry of the diastereoisomers was readily assigned because of the strong diamagnetic anisotropy associated with the S=O bond.[8] Acyclic sulphamidites have $\nu_{max.}$ for the S=O stretching frequency between 1155 and 1164 cm^{-1} in their infrared spectra.[9] The bicyclic sulphamidites (**11**, R = CH_2Ph), (**12**, R = CH_2Ph), and (**13**, R = CH_2Ph) have $\nu_{max.}$ of 1170, 1165, and 1170 cm^{-1} ($CHCl_3$), respectively. These higher values may be associated with the strain caused by ring fusion but the frequency shift is only slight. All attempts to remove the benzyl protecting group of these diastereoisomeric sulphamidites by catalytic hydrogenolysis failed and consequently another protecting group was sought. Several others were investigated but only the 2-(trimethylsilyl)ethyl ester proved satisfactory.[10] The mixture of diastereoisomeric esters (**9**, R = $Me_3SiCH_2CH_2$–) and (**10**, R = $Me_3SiCH_2CH_2$–) on treatment with thionyl chloride again gave three diastereoisomeric cyclic sulphamidites which after separation were identified by ^{1}H NMR spectroscopy as (**11**, R = $Me_3SiCH_2CH_2$–), (**12**, R = $Me_3SiCH_2CH_2$–), and (**13**, R = $Me_3SiCH_2CH_2$–). Deprotection of these bicyclic sulphamidite trimethylsilylethyl esters with tetrabutylammonium fluoride (1 equiv.) in DMF was complete in 20 min, to give the two target bicyclic sulphamidites (**7**) and (**8**), as well as (**13**, R = H) quantitatively, as their tetrabutylammonium salts. In each case the ^{1}H NMR spectrum demonstrated the cyclic sulphamidite to be unaffected by the deprotection conditions.

The stability of the tetrabutylammonium salts of the cyclic sulphamidites (**7**) and (**8**), and (**13**, R = H) in aqueous solution was investigated. Dissolution of the samples in D_2O resulted in rapid effervescence (of SO_2) and a lowering of the pD from 7.0 to 4.5. The ^{1}H NMR spectrum indicated that hydrolysis to (**9**, R = H) or (**10**, R = H) was complete before the spectrum could be obtained (about 1 min.) Since monocyclic sulphamidites are stable in neutral aqueous solution (although hydrolysed in acidic or basic media),[11] it is evident that ring fusion greatly increases the reactivity. It is clear, however, that if such molecules are to be useful antibacterial agents their reactivity must be modulated.

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