STUDIES ON SEMI-SYNTHETIC 7α-FORMAMIDOCEPHALOSPORINS

II. SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF SOME 7α-FORMAMIDOCEPH-3-EM-1-OXIDE AND 7α-FORMAMIDO-1-OXADETHIACEPH-3-EM DERIVATIVES

Sir:

A recent communication from these laboratories has described the potent antibacterial activity of selected C(7)α-formamido-7β-acyl-amino cephalosporins against a wide range of β-lactamase-producing Gram-positive and Gram-negative bacteria, including Pseudomonas aeruginosa. The effect on antimicrobial activity of modifying the dihydrothiazine ring sulfur was also of interest. For many years it was generally accepted that oxidation of cephalosporins to the corresponding sulfoxide or sulfone resulted in a considerable decrease in antibiotic potency, the R-oxide retaining more activity than the S-isomer which was more active than the sulfone. More recently, the S-oxides HR109 and CM 4087 have been disclosed as being more active than the parent sulfide against Enterobacteriaceae although activity against Gram-positive bacteria was diminished. On the other hand, replacement of sulfur by oxygen has often improved the antibacterial spectrum. We now report application of these chemical modifications to the C(7)α-formamidocephalosporin series to provide further novel, highly active, β-lactamase stable antimicrobial agents.

Direct oxidation of the cephalosporin (1a) with peracetic acid in methanol gave only a partially separable mixture of sulfoxides (1b and 1c); further reaction provided the sulfone (1d). In contrast, when the ester (1e) was similarly oxidised, the sulfoxides, 1f and 1g, were readily separated and deprotected with trifluoroacetic acid to afford 1b and 1c respectively; each in 30% overall yield. The stereochemical assignments were initially made on the basis of 1H NMR; the C(2)β-proton signal in the R-oxide (1e) (δ 4.09, d, J=18 Hz) was, as expected, considerably deshielded relative to the S-oxide (1b) (δ 3.63, d, J=19 Hz). Correlation was later made with unambiguously synthesised derivatives. A wide range of C(7)α-formamidocephalosporin sulfoxides were prepared and evaluated using these procedures, including the R-oxides (2b and 2d). Deacetylation of the latter with sodium sulfite at pH 8.5 gave the catecholic sulfone (2e).

The C(7)α-formamidooxacephalosporins, 5e and 6b were synthesised from the oxacephalosporin nucleus (3a), via the C(7)α-methylthio derivatives, 5a and 6a, respectively. A variation of the Merck procedure was employed to introduce the C(7)α-methylthio functionality. Thus, condensation of 3a with p-nitrobenzaldehyde in the presence of 4 Å molecular sieves afforded the Schiff base (3b). Conversion of 3b to 3c was achieved by reaction with anhydrous potassium carbonate in N,N-dimethylformamide at -20°C, followed by quenching the C(7)-carbanion with methyl methanethiosulfonate, addition taking place from the least hindered α-face. Use of stronger bases or higher temperatures produced J-3 to y-2 isomerisation. Cleavage of the imine (3c) with p-toluene sulfonic acid in ethyl acetate, followed by acylation of 3d11) with the acid chloride (4) gave the amide (5a).

The methylthio group in 5a was elaborated to a formamido moiety using a procedure developed in these laboratories. Accordingly, sequential oxidation of 5a to the sulfone (5b) with peracetic acid, followed by reaction with ammonia produced the amine (5c), contaminated with some C-7 epimer. Subsequent formylation gave the esters (5d) and C-7 epimeric (5d). Deprotection afforded the required derivative (5e), which possessed the expected chromophore in the UV spectrum (λmax 257 nm, ε 13,066) and β-lactam carbonyl stretching frequency in the IR (KBr) spectrum (1779 cm⁻¹). As in the sulfide counterpart (2a), in addition to the cis NHCHO rotamer at δ 8.1, the 1H NMR spectrum of 5e showed a small amount of trans NHCHO rotamer at δ 8.4. By the same reaction sequence, the nucleus (3d) was progressed via 6a to the diacetoxy derivative (6b).

It can be seen from Table 1 that although sulfones (1b and 1c) were equiactive as the parent sulfide (1a) against Escherichia coli, the sulf-
oxide configuration affected the potency against other organisms. The R-oxide (1c) was superior to the S-oxide (1b) and possessed activity of the same order, or slightly better than 1a against other Enterobacteriaceae and *P. aeruginosa*. Similarly, the sulfoxides (2b and 2e) exhibited potent activity against Gram-negative bacteria. However, *Staphylococcus aureus* was much less
Table 1. The relative antibacterial activity* of 7α-formamidoceph-3-em-1-oxide and 7α-formamido-1-oxadethiaceph-3-em derivatives.

<table>
<thead>
<tr>
<th>Organism</th>
<th>1a</th>
<th>1b</th>
<th>1c</th>
<th>1d</th>
<th>2a</th>
<th>2b</th>
<th>2c</th>
<th>2e</th>
<th>5e</th>
<th>6b</th>
<th>LMOX</th>
<th>CAZ</th>
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<tr>
<td><em>Escherichia coli</em> NCTC 10418</td>
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<td>0.12</td>
<td>0.25</td>
<td>2</td>
<td>0.06</td>
<td>0.06</td>
<td>≤0.03</td>
<td>≤0.03</td>
<td>0.12</td>
<td>≤0.03</td>
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<td>0.06</td>
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<tr>
<td>E. coli JT4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.25</td>
<td>0.12</td>
<td>0.25</td>
<td>2</td>
<td>0.12</td>
<td>0.12</td>
<td>≤0.03</td>
<td>≤0.03</td>
<td>0.12</td>
<td>≤0.03</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>E. coli JT425&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>8</td>
<td>0.5</td>
<td>0.25</td>
<td>≤0.03</td>
<td>≤0.03</td>
<td>0.12</td>
<td>0.12</td>
<td>1</td>
<td>2</td>
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<td><em>Enterobacter cloacae</em> N1</td>
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<td>2</td>
<td>0.25</td>
<td>8</td>
<td>1</td>
<td>1</td>
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<td>0.25</td>
<td>0.5</td>
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<td>≤0.03</td>
<td>≤0.03</td>
<td>0.12</td>
<td>0.06</td>
<td>0.25</td>
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<td>0.12</td>
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<td>Pseudomonas aeruginosa NCTC 1062</td>
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<td>128</td>
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<tr>
<td>P. aeruginosa Dalgleish&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>32</td>
<td>8</td>
<td>128</td>
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<td>8</td>
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<td>8</td>
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<tr>
<td>Staphylococcus aureus Oxford</td>
<td>8</td>
<td>32</td>
<td>16</td>
<td>32</td>
<td>4</td>
<td>32</td>
<td>16</td>
<td>64</td>
<td>4</td>
<td>16</td>
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<td>16</td>
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<tr>
<td>S. aureus Russell&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>32</td>
<td>32</td>
<td>32</td>
<td>4</td>
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<td>0.06</td>
<td>0.5</td>
<td>2</td>
<td>0.12</td>
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</table>

<sup>a</sup> MICs (µg/ml) determined by serial dilution in nutrient agar containing 5% defibrinated horse blood, inoculum 0.001 ml of an undiluted overnight broth culture.

<sup>b</sup> Plasmid-mediated β-lactamase-producing strain.

<sup>c</sup> Non-plasmid-mediated β-lactamase-producing strain.

LMOX: Latamoxef.

CAZ: Ceftazidime.
susceptible to the sulfoxides than to the parent sulfide. The sulfone (1d) was markedly less antibacterially active. The oxacephalosporins (5e and 6b) were very similar in antibacterial activity to their cephem counterparts (2a and 2c), although P. aeruginosa potency was reduced 2-4-fold. Even so, 6b was still similar in activity overall to ceftazidime and generally more active than latamoxef.

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References


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1 Diacetoxy accepted as an in vitro hydrolysable ester of the dihydroxy derivatives (G. Burton, personal communication).