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[1] has described the potent antibacterial activity of selected C(7)α-formamido-7β-acylamino 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[2] which was more active than the sulfone. More recently, the *S*-oxides HR109[3] and CM 40874[4] 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[5]. 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[6] (**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**)[6] 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 ^{1}H NMR; the C(2)β-proton signal in the *R*-oxide (**1c**) (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)[7]. Correlation was later made with unambiguously synthesised derivatives[8]. 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 sulfoxide (**2e**).

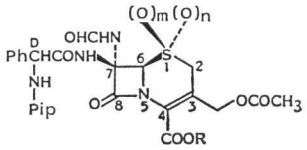
The C(7)α-formamidooxacephalosporins, **5e** and **6b** were synthesised from the oxacephalosporin nucleus (**3a**)[9], *via* the C(7)α-methylthio derivatives, **5a** and **6a**, respectively. A variation of the Merck procedure[10] was employed to introduce the C(7)α-methylthio functionality. Thus, condensation 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 Δ-3 to Δ-2 isomerisation. Cleavage of the imine (**3c**) with *p*-toluene sulfonic acid in ethyl acetate, followed by acylation of **3d**[11] with the acid chloride (**4**)[6] gave the amide (**5a**).

The methylthio group in **5a** was elaborated to a formamido moiety using a procedure developed in these laboratories[12]. Accordingly, sequential oxidation of **5a** to the sulfoxide (**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 ($\lambda_{max}^{H_2O}$ 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**)[6], in addition to the *cis* NHC*H*O rotamer at δ 8.1, the ^{1}H NMR spectrum of **5e** showed a small amount of *trans* NHC*H*O rotamer at δ 8.4. By the same reaction sequence, the nucleus (**3d**) was progressed *via* **6a** to the diacetoxy derivative (**6b**).

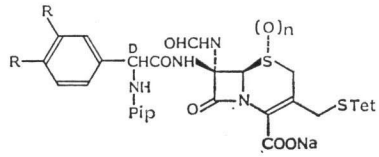
It can be seen from Table 1 that although sulfoxides (**1b** and **1c**) were equiactive as the parent sulfide (**1a**) against *Escherichia coli*, the sulf-

† All acids were isolated and purified as sodium salts by Diaion HP-20SS chromatography.

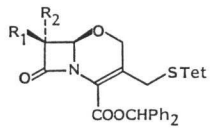
†† Satisfactory spectroscopic data and mass spectrometric analyses (FAB) were obtained for new compounds.



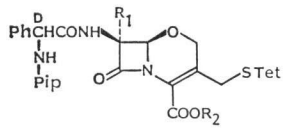
1a R = H m = n = 0
1b R = Na m = 1 n = 0
1c R = Na m = 0 n = 1
1d R = Na m = n = 1
1e R = ^{t}Bu m = n = 0
1f R = ^{t}Bu m = 1 n = 0
1g R = ^{t}Bu m = 0 n = 1



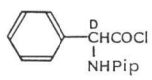
2a R = H n = 0
2b R = H n = 1
2c R = OH n = 0
2d R = $OCOCH_3$ n = 1
2e R = OH n = 1



3a R_1 = H R_2 = NH_2
3b R_1 = H R_2 = N=CHPh(*p*-NO_2)
3c R_1 = N=CHPh(*p*-NO_2) R_2 = SCH_3
3d R_1 = NH_2 R_2 = SCH_3



5a R_1 = SCH_3 R_2 = $CHPh_2$
5b R_1 = S(O)CH_3 R_2 = $CHPh_2$
5c R_1 = NH_2 R_2 = $CHPh_2$
5d R_1 = NHCHO R_2 = $CHPh_2$
5e R_1 = NHCHO R_2 = Na



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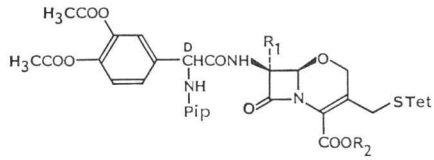
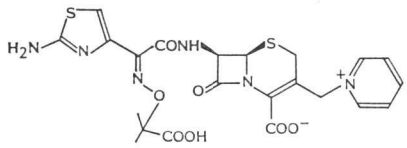
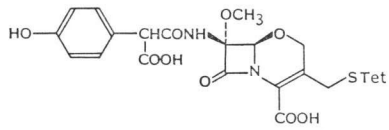


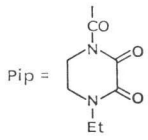
6a R_1 = SCH_3 R_2 = $CHPh_2$
6b R_1 = NHCHO R_2 = Na

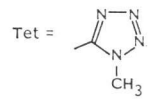


Ceftazidime (CAZ)



Latamoxef (LMOX)





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[a] of 7α-formamidoceph-3-em-1-oxide and 7α-formamido-1-oxadethiaceph-3-em derivatives.

Organism	1a	1b	1c	1d	2a	2b	2c	2e	5e	6b	LMOX	CAZ
Escherichia coli NCTC 10418	0.12	0.12	0.25	2	0.06	0.06	≤0.03	≤0.03	0.12	≤0.03	0.12	0.06
E. coli JT4[b]	0.25	0.12	0.25	2	0.12	0.12	≤0.03	≤0.03	0.12	≤0.03	0.25	0.25
E. coli JT425[c]	0.5	0.5	0.5	8	0.5	0.25	≤0.03	≤0.03	0.12	0.12	1	2
Enterobacter cloacae N1	1	2	0.25	8	1	1	0.12	0.25	0.5	0.25	0.12	0.25
Klebsiella aerogenes A	0.12	1	0.12	8	0.12	0.06	≤0.03	≤0.03	0.12	0.06	0.25	0.25
Proteus mirabilis C977	0.5	1	0.25	8	0.5	0.5	0.12	0.25	0.5	0.5	0.25	0.12
Serratia marcescens US32	1	4	0.25	16	0.25	0.5	0.12	0.25	0.25	0.5	0.5	0.5
Pseudomonas aeruginosa NCTC 10662	8	64	8	128	4	8	0.25	0.5	16	1	8	1
P. aeruginosa Dalgleish[b]	4	32	8	128	4	8	0.25	0.5	8	0.5	8	0.5
Staphylococcus aureus Oxford	8	32	16	32	4	32	16	64	4	16	16	8
S. aureus Russell[b]	8	32	32	32	4	32	16	64	8	16	16	16
Streptococcus pyogenes CN10	1	1	0.5	4	0.12	2	0.5	2	0.06	0.5	2	0.12

[a] 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.

[b] Plasmid-mediated β-lactamase-producing strain.

[c] 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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† Diacetoxy accepted as an *in vitro* hydrolysable ester of the dihydroxy derivatives (G. BURTON, personal communication).