Chemistry of Cephems: C-4 Substitution and Sulphoxide De-oxygenation Reactions.[1]

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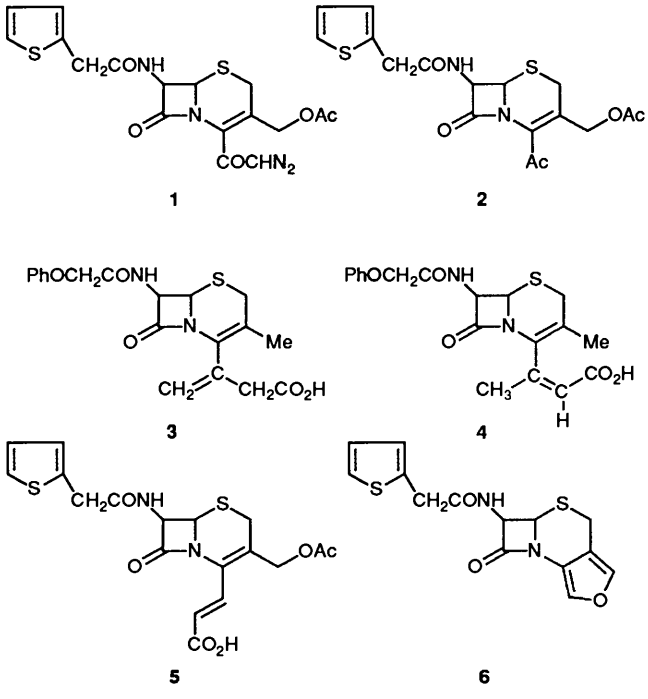
The anion derived from ceph-3-em esters adds readily to Michael acceptors to give C-4 disubstituted ceph-2-ems. Oxidation of a typical adduct, such as the 4-cyanoethyl-4-diphenylmethyl ester, followed by ester hydrolysis and decarboxylation, gives the 4-cyanoethylceph-3-em sulphoxide which is easily reduced to the sulphide. Furthermore, zinc–acetic acid in DMF (dimethylformamide) is found to be an effective, mild reagent for the de-oxygenation of ceph-2-em sulphoxides.

The majority of reported modifications at the C-4 position in ceph-3-ems have resulted from chemical manipulation of the carboxylic acid group. Thus, conversion of the acid functionality into the acid chloride and thence to the diazoketone **1** has proved[2] to be a fruitful source of polar groupings such as the methyl ketone **2**. A related methyl ketone has been further converted[3] *via* a Reformatsky reaction into derivatives such as **3** and **4** which have an additional double bond conjugated with the ceph-3-em double bond. Additionally, cephalosporin-4-aldehydes have been utilised[4] as precursors to vinylogue **5** and the tricyclic furocepham **6**.[5]

It is well known that cephalosporanic acids and ceph-3-em esters form equilibrium mixtures of the Δ^2 and Δ^3 isomers when treated with base.[6] The position of the equilibrium depends on the ester protecting group and the C-3′ substituent. As a direct consequence of this equilibrium it is possible to trap the developing carbanion by alkylation with a number of electrophiles. Yoshida *et al.*[7] used lithium diisopropylamide at −78 °C to remove a C-2 proton and then added a variety of electrophiles to produce C-4 disubstituted derivatives such as **7a**. With iodomethane, the 4-methylceph-2-em **7b** was found[8] to have the 4-methyl group β-oriented due to repulsion between the α-oriented nitrogen lone pair and the evolving C-4 carbanion. Similar results have been obtained using sodium hydride in DMF (dimethylformamide)[9] and potassium *tert*-butoxide in DMF–THF (tetrahydrofuran).[10] It has also been claimed[11] that the *N*-protected ceph-3-ems **8** can be alkylated to give **9** (R^2 = alkyl, CH_2CO_2H, carbalkoxy, halogenomethyl, benzyl or substituted benzyl) which have been transformed into 4-disubstituted ceph-2-em derivatives which show antibacterial activity. A limited number of routes to C-4 disubstituted cephems which do not involve base have been reported, for example, ethyl *N*-chloro-*N*-sodiocarbamate reacts[12] with ceph-3-em **10a** to give a 17% yield of ceph-2-em **7c**. More recently, Stoodley[13,14] has described a novel oxidative allylic rearrangement in which the sulphone **11** is transformed into the ceph-2-em **12** on reaction with 5% Pd/C.

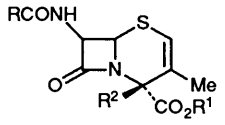
Since C-4 disubstituted ceph-2-ems are readily prepared[15] we believed that a de-esterification–decarboxylation sequence would constitute a novel approach to ceph-3-ems which possess a new functionality at the 4-position in place of the original carboxy grouping. During our study of these transformations we also discovered a surprisingly facile de-oxygenation of ceph-2-em sulphoxides.



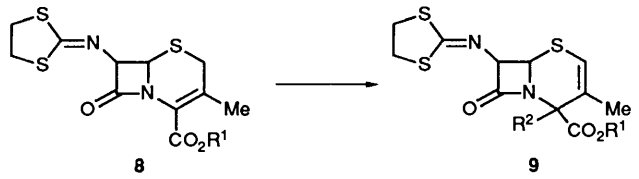
Results and Discussion

Michael Adducts.—The reaction of **10a** with acrylonitrile and dimethyl butynedioate has previously been described.[15] Under similar conditions, Michael reactions have been extended to the ceph-3-em esters **10b** and **10c**, and we report, additionally, that methyl vinyl ketone and methyl acrylate also add in an analogous manner. Thus, reaction of diphenylmethylceph-3-em **10b** and acrylonitrile in the presence of a catalytic amount of triethylamine afforded the adduct **13b** in 74% yield after chromatography. By analogy with previous work, the stereochemistry of the new functionality is assumed to be β. In this instance, there was no evidence of the C-4 α-isomer which had been isolated in the reaction involving the corresponding trichloroethyl ester.[15] Cephalosporanate **10c** also reacted smoothly to give adduct **15a** in 61% yield, and cephems **10a** and **10b** afforded high yields of adducts **13c** and **13d** on treatment with methyl vinyl ketone and triethylamine.

Attempts to add methyl acrylate to **10b** failed with triethylamine as base, but the desired reaction was achieved when Triton-B was utilised along with ethanol as an added proton source. It proved impossible to separate **13e** from unchanged starting material, so the reaction mixture was oxidised with *m*-chloroperoxybenzoic acid to give a mixture of sulphoxides from which **14e** was isolated in 53% yield. De-oxygenation of **14e** gave the expected sulphide **13e**. Diphenylmethylceph-3-em **10b** also reacted with dimethyl butynedioate in the presence of triethylamine to give the fumarate derivative **17b** in 40% yield.



7 **a**; R = Ph, R^1 = Me, R^2 = SMe
b; R = Ph, R^1 = Me, R^2 = Me
c; R = $PhOCH_2$, R^1 = CH_2CCl_3 R^2 = $NHCO_2Et$



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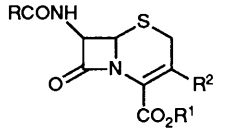
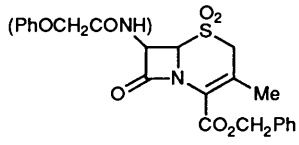


10 **a**; R = $PhOCH_2$, R^1 = CH_2CCl_3, R^2 = Me
b; R = $PhOCH_2$, R^1 = $CHPh_2$, R^2 = Me
c; R =  R^1 = CH_2CCl_3, R^2 = CH_2OAc



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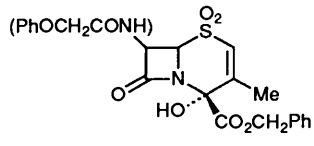

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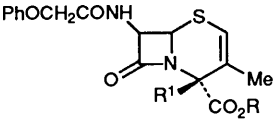

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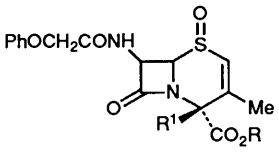

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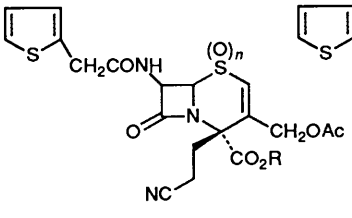
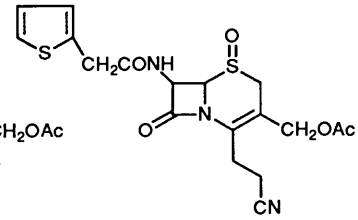
a; R = CH_2CCl_3, R^1 = CH_2CH_2CN
b; R = $CHPh_2$, R^1 = CH_2CH_2CN
c; R = CH_2CCl_3, R^1 = CH_2CH_2COMe
d; R = $CHPh_2$, R^1 = CH_2CH_2COMe
e; R = $CHPh_2$, R^1 = $CH_2CH_2CO_2Me$
f; R = H, R^1 = CH_2CH_2COMe
g; R = $CHPh_2$, R^1 = $CH_2CH_2CO_2H$
h; R = $CHPh_2$, R^1 = $CH(CO_2Me)CH_2CO_2Me$



15 **a**; R = CH_2CCl_3, n = 0
b; R = CH_2CCl_3, n = 1



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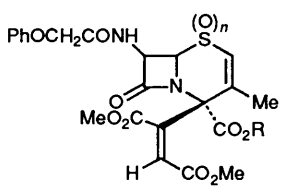
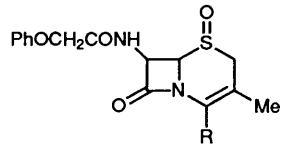
It was expected that an acid derivative such as **13g** might be readily prepared from these Michael adducts. Attempts to hydrolyse the methyl ester **13e** with dilute aqueous sodium hydroxide were not successful. Trichloroethyl acrylate was prepared but this ester could not be added to the cephem nucleus, whilst *p*-nitrobenzyl acrylate was de-esterified under the reaction conditions employed. An alternative route to **13g** was envisaged *via* oxidation of the aldehyde derived from addition of acrolein at C-4. However, no such adduct from acrolein and ceph-3-em **10a** or **10b** could be isolated and the only product obtained from the reaction was a polymer of acrolein.[16] Other possible Michael acceptors which failed to react under our conditions included dimethyl maleate and acryloyl chloride.

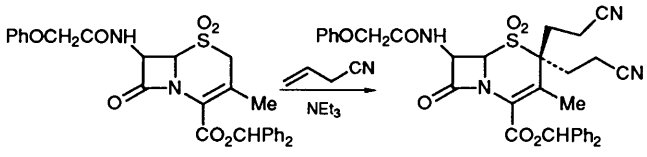


17 **a**; R = CH_2CCl_3, n = 0
b; R = $CHPh_2$, n = 0
c; R = CH_2CCl_3, n = 1
d; R = $CHPh_2$, n = 1

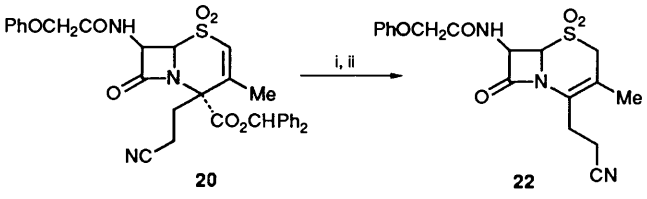


18 **a**; R = CH_2CH_2CN
b; R = CH_2CH_2COMe
c; R = $CH_2CH_2CO_2Me$
d; R = $C(CO_2Me)$=$CHCO_2Me$
e; R = $CH(CO_2Me)CH_2CO_2Me$

Earlier work[15] has examined Michael reactions under these conditions with ceph-3-em (*S*)- and (*R*)-sulphoxides, however ceph-3-em sulphones have not previously been examined. When the sulphone **19** was treated with acrylonitrile and triethylamine a high yield of β-lactam containing adduct was obtained which was not identical with the C-4 disubstituted sulphone **20**, prepared *via* oxidation of sulphoxide **14b**. In this instance, the Michael reaction occurs at the C-2 position to give **21**. Similar regiospecificity has been found with the ceph-3-em (*S*)-sulphoxides.



19 21



20 22

Reagents: Trifluoroacetic acid (TFA)–anisole, methylene dichloride; ii, NEt_3, ethyl acetate

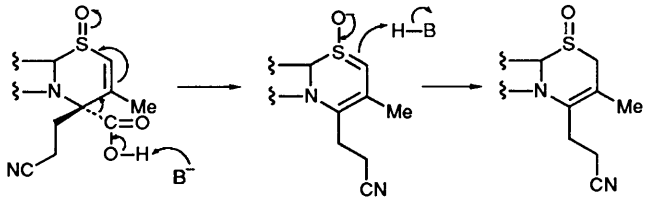
De-esterification and Decarboxylation.—It is well known[17] that in unsaturated sulphoxides, the double bond favours the β,γ-position rather than the α,β-position. This stability is utilised in the oxidative–reductive process for converting ceph-2-ems into ceph-3-ems.[18] We reasoned that, in the C-4 disubstituted cephem sulphoxides, decarboxylation of the corresponding carboxylic acid might be facilitated by utilising the enhanced thermodynamic stability of the β,γ-unsaturated sulphoxide.

Oxidation of the Michael adducts **13a–d**, **15a** and **17a,b** with *m*-chloroperoxybenzoic acid (CH_2Cl_2, 0 °C) gave high yields of the corresponding sulphoxides **14a–d**, **15b** and **17c,d**. Only one sulphoxide isomer, the stereochemistry of which is assumed to be (*S*), was obtained in each case.

Removal of the ester protecting group proceeded readily using trifluoroacetic acid–anisole[19] for the diphenylmethyl esters, and zinc–acetic acid in DMF for the trichloroethyl esters.[20] In some cases it was possible to isolate the carboxylic acid although these were thermally unstable and spontaneously decarboxylated when heated. In the majority of cases, however, the basic conditions employed in the work-up

facilitated decarboxylation. For example, sulphoxide **14d** on treatment with TFA (trifluoroacetic acid)–anisole provided, in 76% yield, the crystalline C-4 disubstituted carboxylic acid **14f** which melted with evolution of CO_2 at 110 °C. Attempts to recrystallise **14f** failed due to thermal decarboxylation, however it was conveniently transformed into the monosubstituted C-4 derivative **18b** by dissolution in acetone and stirring with a catalytic amount of triethylamine. On the other hand, the ketone **18b** was obtained directly from the sulphoxide **14c** by zinc–acetic acid treatment in DMF followed by hydrogen carbonate-induced decarboxylation during work-up. Other C-4 monosubstituted sulphoxides prepared by these methods include **16** and **18a,c**.

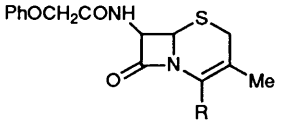
It was shown that the sulphoxide functionality was necessary for decarboxylation under mild base catalysis by the behaviour of the ester **13d** on reaction with TFA–anisole. De-esterification proceeded normally to give the acid **13f**, but no decarboxylation was observed under the conditions where the corresponding sulphoxide **14f** readily lost carbon dioxide. The enhanced thermodynamic stability of the ceph-3-em sulphoxide[17] is, therefore, suggested as the driving force for this decarboxylation, and delocalisation of the negative charge onto the sulphoxide oxygen might explain the reactivity of the sulphoxide compared to the sulphide[6] (Scheme 1).

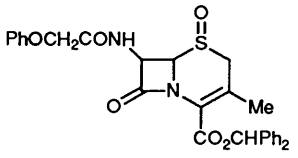


Scheme 1

Interestingly, the sulphone **20**, prepared by oxidation of the sulphoxide **14b** with an excess of *m*-chloroperoxybenzoic acid behaves in an identical manner to **14b** on de-esterification. Reaction with TFA–anisole gave the corresponding carboxylic acid which underwent decarboxylation on being stirred with triethylamine in ethyl acetate over several days. After work-up, a white crystalline solid (m.p. 154–157 °C) was obtained, in 82% yield, which possessed neither ester nor acid functionality in its IR spectrum. The ^1H NMR spectrum showed complete loss of the ester function and is, along with analytical data, consistent with structure **22**.

The sulphoxides **18a–c** were readily de-oxygenated to the corresponding sulphides **23a–c** using either phosphorus penta-





23 **a**; R = CH_2CH_2CN
b; R = CH_2CH_2COMe
c; R = $CH_2CH_2CO_2Me$
d; R = $C(CO_2Me)=CHCO_2Me$

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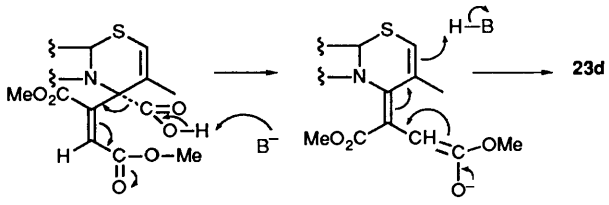
sulphide–pyridine[21] or potassium iodide–acetyl chloride.[22] Compound **23d** was prepared *via* de-esterification and decarboxylation of sulphide **17b**. Although this appears to be in conflict with the preceding discussion with regard to the decarboxylation of **13d**, we propose that the α,β-unsaturated ester functionality participates in this decarboxylation as shown in Scheme 2. These sulphides are all highly crystalline compounds which exhibit the expected spectroscopic and analytical data. The overall yield of **23a** from **10b** is 48%. None of these compounds showed any antibacterial or β-lactamase activity.



Scheme 2

Reaction with Zinc–Acetic Acid.—The normal method for removal of trichloroethyl ester protecting groups is to use zinc–acetic acid in DMF.[20] When the sulphoxide triester **17c** was stirred at ice temperature under these conditions, the expected unsaturated ceph-3-em ester sulphoxide **18d** was not produced. Instead, after neutralisation and work-up, a 79% yield of a white crystalline solid (m.p. 169–170 °C) was obtained which showed no signals in the ^1H NMR spectrum characteristic of an unsaturated system. Analytical figures indicated the addition of two hydrogens to the expected product formula, and consequently, suggest that the data is consistent with structure **18e**. Zinc–acetic acid is a well known reducing agent[23] and, in this instance, the α,β-unsaturated ester system is particularly susceptible to reduction. When the sulphide **17b** was treated in a similar manner, reduction of the fumaryl double bond also occurred readily and the saturated triester **13h** was obtained in 62% yield (m.p. 89–90 °C) indicating that the sulphoxide function is not necessary for this reduction.

When the acrylonitrile adduct **14b** was subjected to zinc–acetic acid conditions, a remarkably facile de-oxygenation was observed. The ceph-2-em **14b** when stirred for 1 h at ice temperature, followed by neutralisation and work-up of the reaction mixture gave an 89% yield of the corresponding sulphide **13b**. This easy de-oxygenation of a ceph-2-em sulphoxide contrasts markedly with the relative difficulty observed in removal of oxygen from ceph-3-em sulphoxides which normally require activation prior to reduction.[18] We assume that, as compounds such as **14b** are locked in the ceph-2-em structure, electronic factors allow easy reduction of the Δ^2 compound compared to Δ^3 cephems.* No such reduction is observed when ceph-3-em sulphoxides **18b** and **24** are treated with zinc–acetic acid under identical conditions.

Further insights into the structural requirements of this de-oxygenation were obtained from the following reactions. The C-4 adduct sulphoxides **14d** and **14e** were readily de-oxygenated and reduced to the sulphides **13d** and **13e**, and the unsaturated ester sulphoxide **17d** was de-oxygenated to the sulphide **13h**. With trichloroethyl esters, there is the additional possibility of de-esterification. Thus, when the trichloroethyl ester sulphoxides **14a**, **14c** and **17c** are treated with zinc–acetic acid in DMF they are converted into the corresponding C-4 monosubstituted sulphoxides **18a**, **18b** and **18e** respectively, with compound **18e** also having the fumarate double bond reduced. No de-oxygenation is observed in these cases, indicating that de-esterification and decarboxylation occur first, resulting in the formation of a C-4 monosubstituted ceph-3-em which, now having a Δ^3 double bond, is not de-oxygenated with zinc–acetic acid.

* We thank a referee for drawing our attention to the use of zinc–acetic acid for the reduction of α,β-unsaturated sulphoxides to the corresponding sulphides: D. H. Hua, S. Venkataraman, R. O. Ostrander, G-Z. Sinai, P. J. McCann, M. J. Coulter and M. R. Xu, *J. Org. Chem.*, 1988, **53**, 507.

Conclusions

We have shown that the anion derived from ceph-3-ems, under very mild conditions, adds readily to several Michael acceptors to give C-4 disubstituted ceph-2-ems. Using an oxidation, de-esterification, decarboxylation and de-oxygenation sequence, novel C-4 monosubstituted ceph-3-ems have been prepared. Furthermore, we have found that zinc–acetic acid in DMF is an effective, mild reagent for de-oxygenation of ceph-2-em sulphoxides.

Experimental

M.p.s were determined using an Electrothermal melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1600 FT–IR or a Perkin-Elmer 457 grating spectrophotometer and UV spectra were obtained using a Beckman DU-68 or a Shimadzu UV-160 spectrophotometer. ^{1}H NMR spectra were recorded at 250 MHz on a Bruker WM250. All spectra were recorded in deuteriochloroform, except where otherwise stated, using tetramethylsilane as internal reference. *J* values are given in Hz. Mass spectra were measured on either a VG 7070 or VG ZAB spectrometer operating in the electron impact mode. Column chromatography was performed using pressurised short path columns with Kieselgel 60, particle size < 0.063 mm (Merck No. 7729). Reactions were monitored by thin layer chromatography on Merck DC-Alufoilien Kieselgel 60 F_{254} (Merck No. 5554) plates which were visualised under UV irradiation or with iodine vapour. Solvents were dried with anhydrous magnesium sulphate unless otherwise stated.

Penicillin V, used to synthesise trichloroethyl (6*R*,7*R*) 7β-phenoxyacetamidoceph-3-em-4-carboxylate, was kindly donated by Smithkline Beecham.

Diphenylmethyl (6R,7R)-4-(2′-*Cyanoethyl*)-3-*methyl*-7β-*phenoxyacetamidoceph*-2-*em*-4-*carboxylate* **13b**.—Diphenylmethyl (6*R*,7*R*)-3-methyl-7β-phenoxyacetamidoceph-3-em-4-carboxylate **10b** (3.0 g, 5.84 mmol) in acrylonitrile (30 cm^3) was stirred with triethylamine (0.5 cm^3) at room temperature for 20 h. Solvents were removed under reduced pressure, and the residue partitioned between ethyl acetate and 1 mol dm^{-3} HCl. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried and evaporated under reduced pressure. The resulting oil was chromatographed on silica gel using light petroleum–ethyl acetate as eluent to afford ceph-2-em **13b** as a colourless oil (2.45 g, 74%); $[\alpha]_D^{20}$ + 1130° (*c* 0.27 in $CHCl_3$) (Found: C, 67.55; H, 5.05; N, 7.3; S, 5.45. $C_{32}H_{29}N_3O_5S$ requires C, 67.72; H, 5.11; N, 7.41; S, 5.64%); λ_{max}(EtOH)/nm 257 (ε 5367); ν_{max}(film)/cm^{-1} 3345, 1773, 1739 and 1690; δ_H($CDCl_3$) 1.67 (3 H, d, *J* 1.2, 3-CH_3), 2.36–2.59 (3 H, m, CH_2CHCN), 3.14–3.27 (1 H, m, CHCN), 4.55 (2 H, s, OCH_2CON), 5.21 (1 H, d, *J* 4.4, 6-H), 5.48 (1 H, dd, *J* 4.4 and 8.8, 7-H), 6.31 (1 H, d, *J* 1.2, 2-H), 6.88–7.42 (16 H, m, $CHPh_2$ and PhO) and 7.53 (1 H, d, *J* 8.8, NH).

Trichloroethyl(6R,7R)-3-*Methyl*-4-(3′-*oxobutyl*)-7β-*phenoxyacetamidoceph*-2-*em*-4-*carboxylate* **13c**.—A solution of ceph-3-em **10a** (0.48 g, 1 mmol) in methyl vinyl ketone (10 cm^3) and triethylamine (0.5 cm^3) was stirred at room temperature for 18 h. Removal of solvents under reduced pressure afforded a brown semi-solid which was chromatographed on silica gel, with ethyl acetate–light petroleum (4:1) as eluent, to yield the ceph-2-em **13c** (0.28 g, 51%) as a white crystalline solid, m.p. 171–173 °C; $[\alpha]_D^{20}$ + 250° (*c* 1.0 in $CHCl_3$) (Found: C, 48.05; H, 4.2; N, 5.1; S, 5.8. $C_{22}H_{23}Cl_3N_2O_6S$ requires C, 48.15; H, 4.07; N, 4.99; S, 5.82%); λ_{max}/nm 259 (ε 5680); ν_{max}(KBr)/cm 3310, 1762, 1748, 1709 and 1691; δ_H($CDCl_3$) 1.85 (3 H, d, *J* 1.3, 3-CH_3), 2.18 (3 H, s, $COCH_3$), 2.35–2.95 (4 H, m, CH_2CH_2), 4.58 (2 H, s, OCH_2CON), 4.76 and 4.87 (2 H, ABq, *J* 12.0, $CO_2CH_2CCl_3$), 5.35 (1 H, d, *J* 4.5, 6-H), 5.58 (1 H, dd, *J* 4.5 and 8.8, 7-H), 6.20 (1 H, d, *J* 1.3, 2-H) and 6.92–7.40 (6 H, m, Ph and NH).

Diphenylmethyl (6R,7R)-3-*Methyl*-4-(3′-*oxobutyl*)-7β-*phenoxyacetamidoceph*-2-*em*-4-*carboxylate* **13d**.—A solution of ceph-3-em **10b** (1.08 g, 2 mmol) in methyl vinyl ketone (15 cm^3) and triethylamine (0.5 cm^3) was stirred for 24 h at room temperature. The reaction mixture was diluted with ethyl acetate and washed successively with 1 mol dm^{-3} HCl, saturated aqueous $NaHCO_3$ and brine, dried and evaporated under reduced pressure. The residue was chromatographed on silica gel with ethyl acetate–light petroleum as eluent to give the ceph-2-em **13d** (1.05 g, 90%); m.p. 108–110 °C; $[\alpha]_D^{20}$ + 262° (*c* 1.0 in $CHCl_3$) (Found: C, 67.8; H, 5.5; N, 4.8; S, 5.5. $C_{33}H_{32}N_2O_6S$ requires C, 67.42; H, 5.47; N, 4.79; S, 5.58); λ_{max}(EtOH)/nm 257 (ε 6050); ν_{max}(KBr)/cm^{-1} 1770, 1742, 1710 and 1690; δ_H($CDCl_3$) 1.75 (3 H, d, *J* 1.0, 3-CH_3), 2.09 (3 H, s, $COCH_3$), 2.32–2.93 (4 H, m, CH_2CH_2), 4.56 (2 H, s, OCH_2CON), 5.22 (1 H, d, *J* 4.5, 6-H), 5.49 (1 H, dd, *J* 4.5 and 8.8, 7-H), 6.11 (1 H, d, *J* 1.0, 2-H) and 6.88–7.55 (17 H, m, $CHPh_2$, PhO and NH).

Diphenylmethyl (1S,6R,7R)-4-(2′-*Methoxycarbonylethyl*)-3-*methyl*-7β-*phenoxyacetamidoceph*-2-*em*-4-*carboxylate* 1-*Oxide* **14e**.—A solution of the ceph-3-em **10b** (5.0 g, 9.73 mmol) in methyl acrylate (40 cm^3), ethanol (8 cm^3) and Triton-B (40% w/v solution in MeOH; 5 drops) was stirred at room temperature for 24 h. The reaction mixture was diluted with ethyl acetate and washed with 1 mol dm^{-3} HCl, saturated aqueous $NaHCO_3$ and brine, dried and evaporated under reduced pressure to give a yellow oil. The oil was dissolved in CH_2Cl_2 (50 cm^3) and stirred at 0 °C with *m*-CPBA (*m*-chloroperoxybenzoic acid) (80% pure, 2.0 g; 10 mmol) for 30 min. The reaction mixture was filtered and the filtrate washed with 10% w/v aqueous $Na_2S_2O_5$, saturated aqueous $NaHCO_3$ and brine, dried and evaporated under reduced pressure to give the sulphoxide **14e** as a pale yellow solid after recrystallisation from ethyl acetate–light petroleum (3.17 g, 53%); m.p. 154–157 °C; $[\alpha]_D^{20}$ + 181 ° (*c* 1.0 in $CHCl_3$) (Found: C, 64.4; H, 5.1; N, 4.4; S, 4.85. $C_{33}H_{32}N_2O_8S$ requires C, 64.3; H, 5.2; N, 4.55; S, 5.2%); λ_{max}(EtOH)/nm 258 (ε 4980); ν_{max}(KBr)/cm^{-1} 3372, 1779, 1738 and 1690; δ_H($CDCl_3$) 1.81 (3 H, d, *J* 1.2, 3-CH_3), 2.23–3.31 (4 H, m, CH_2CH_2), 3.66 (3 H, s, CO_2CH_3), 4.54 (3 H, m, OCH_2CON and 6-H), 5.85 (1 H, dd, *J* 4.7 and 10.5, 7-H), 6.77 (1 H, d, *J* 1.2, 2-H), 6.91–7.43 (16 H, m, $CHPh_2$ and PhO) and 8.17 (1 H, d, *J* 10.5, NH). Also isolated was diphenylmethyl (1S,6R,7R) 3-methyl-7β-phenoxyacetamidoceph-3-em-4-carboxylate 1-oxide **24** as a white crystalline solid (0.25 g, 5%).

Diphenylmethyl (6*R*,7*R*)-4-(4′-*Methoxycarbonylethyl*)-3-*methyl*-7β-*phenoxyacetamidoceph*-2-*em*-4-*carboxylate* **13e**.—A solution of the sulphoxide **14e** (0.18 g, 0.29 mmol) in a mixture of DMF and glacial acetic acid (25:7.5 v/v; 10 cm^3) was stirred with powdered zinc (0.5 g) at room temperature for 6 h. The suspension was filtered through Celite and the filtrate partitioned between ethyl acetate and saturated aqueous $NaHCO_3$. The organic phase was washed with brine, dried and evaporated under reduced pressure to afford the crude product. Chromatography on silica gel, eluting with light petroleum–ethyl acetate, gave the *title compound* as a white foam (0.14 g, 80%); $[\alpha]_D^{20}$ + 152° (*c* 1.0 in $CHCl_3$) (Found: C, 65.8; H, 5.4; N, 4.5; S, 5.25. $C_{33}H_{32}N_2O_7S$ requires C, 66.0; H, 5.3; N, 4.7; S, 5.3%); λ_{max}(EtOH)/nm 261 (*e* 4810); ν_{max}(KBr)/cm^{-1} 1773, 1736 and 1686; δ_H($CDCl_3$) 1.72 (3 H, d, *J* 0.9, 3-CH_3), 2.05–3.08 (4 H, m, CH_2CH_2), 3.67 (3 H, s, CO_2CH_3), 4.55 (2 H, s, OCH_2CON), 5.19 (1 H, d, *J* 4.4, 6-H), 5.49 (1 H, dd, *J* 4.4 and 8.9, 7-H), 6.17 (1 H, d, *J* 0.9, 2-H) and 6.88–7.40 (17 H, m, $CHPh_2$, PhO and NH).

Trichloroethyl (6R,7R)-3-*Acetoxymethyl*-4-(2′-*cyanoethyl*)-

7β-(2-*thienylacetamido*)-*ceph*-2-*em*-4-*carboxylate* **15a**.—A solution of the ceph-3-em **10c** (7.72 g, 14.6 mmol) in acrylonitrile (50 cm^3) was stirred with triethylamine (2 cm^3) at room temperature for 24 h. Solvents were removed under reduced pressure and the residue partitioned between ethyl acetate and water. The organic layer was washed with 1 mol dm^{-3} HCl, saturated aqueous $NaHCO_3$ and brine, dried and evaporated under reduced pressure. The resultant oil was chromatographed on silica gel, eluting with light petroleum–ethyl acetate to afford the *title compound* **15a** as a colourless oil (5.2g, 61%); $[\alpha]_D^{20}$ + 244° (*c* 1.0 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2250, 1780, 1755 and 1692; $\delta_H(CDCl_3)$ 2.08 (3 H, s, $OCOCH_3$), 2.45–2.68 (3 H, m, CH_2CHCN), 3.13–3.30 (1 H, m, CHCN), 3.83 (2 H, s, CH_2CON), 4.56 and 4.68 (2 H, ABq, *J* 13.2, CH_2OAc), 4.72 and 4.91 (2 H, ABq, *J* 11.8, CO_2CH_2), 5.31 (1 H, d, *J* 4.4, 6-H), 5.44 (1 H, dd, *J* 4.4 and 8.3, 7-H), 6.84 (1 H, d, *J* 8.3, NH), 6.85 (1 H, s, 2-H), 6.94–7.04 (2 H, m, 2-thienyl Hs) and 7.27 (1 H, m, 2-thienyl H) (Found: M^+ 578.9845. $C_{21}H_{20}Cl_3N_3O_6S_2$ *m*, requires 578.9859).

Diphenylmethyl (6R,7R)-4-[1′,2′-*Bis*(*methoxycarbonyl*)*vinyl*]-3-*methyl*-7β-*phenoxyacetamidoceph*-2-*em*-4-*carboxylate* **17b**.—To a solution of the ceph-3-em **10b** (5.14 g, 10 mmol) in acetonitrile (100 cm^3) at −15 °C was added dimethyl butynedioate (3.12 g, 22 mmol) and triethylamine (1 cm^3), and the reaction mixture was stirred for 30 min. It was then warmed to room temperature and evaporated under reduced pressure. The residue was dissolved in ethyl acetate and the solution was washed successively with 1 mol dm^{-3} HCl, saturated aqueous $NaHCO_3$ and brine, dried and evaporated under reduced pressure. The resultant dark red oil was chromatographed on silica gel using light petroleum–ethyl acetate (3:1 to 1:1) as eluent to afford the triester **17b** as a white crystalline solid (2.7 g, 40%); m.p. 123–125 °C; $[\alpha]_D^{20}$ + 368° (*c* 1.0 in $CHCl_3$) (Found: C, 63.9; H, 4.9; N, 4.3; S, 4.8. $C_{35}H_{32}N_2O_9S$ requires C, 64.0; H, 4.9; N, 4.3; S, 4.9%); λ_{max}(EtOH)/nm 254 (ε 7903); ν_{max}(KBr)/cm^{-1} 3210, 1775, 1735, 1715 and 1670; $\delta_H(CDCl_3)$ 1.73 (3 H, d, *J* 1.0, 3-CH_3), 3.39 (3 H, s, CO_2CH_3), 3.83 (3 H, s, CO_2CH_3), 4.54 (2 H, s, OCH_2CON), 5.42 (1 H, d, *J* 4.4, 6-H), 5.63 (1 H, dd, *J* 4.4 and 9.1, 7-H), 6.33 (1 H, d, *J* 1.0, 2-H), 6.35 (1 H, s, $CHCO_2CH_3$) and 6.85–7.50 (17 H, m, $CHPh_2$, PhO and NH).

Trichloroethyl (1S,6R,7R)-3-*Methyl*-4β-(2′-*cyanoethyl*)-7β-*phenoxyacetamidoceph*-2-*em*-4-*carboxylate* 1-*Oxide* **14a**.—A solution of sulphide **13a** (1.10 g, 2.04 mmol) in dichloromethane (80 cm^3) was stirred at 0 °C with *m*-CPBA (0.45 g, 80% pure, hence 2.1 mmol) for 40 min. The reaction mixture was then washed with 10% w/v aqueous $Na_2S_2O_5$ solution, saturated aqueous $NaHCO_3$ solution and brine, dried and the solvent evaporated under reduced pressure to give a pale yellow solid. Recrystallisation from ethyl acetate–light petroleum gave the *title compound* **14a** as white crystals (0.50 g, 44%); m.p. 147–148 °C; $[\alpha]_D^{20}$ + 78° (*c* 1.0 in $CHCl_3$); (Found: C, 45.9; H, 3.6; N, 7.6; Cl, 19.2; S, 5.8. $C_{21}H_{20}N_3Cl_3O_6S$ requires C, 45.9; H, 3.65; N, 7.7; Cl, 19.4; S, 5.6%); λ_{max}(EtOH)/nm 259 (ε 3815); ν_{max}(KBr)/cm^{-1} 3320, 2247, 1778, 1755 and 1688; $\delta_H(CDCl_3)$ 2.06 (3 H, d, *J* 1.3, 3-CH_3), 2.58–2.78 (3 H, m, CH_2CHCN), 3.31–3.41 (1 H, m, CHCN), 4.54 and 4.58 (2 H, ABq, *J* 15.2, CH_2CON), 4.75 and 4.94 (2 H, ABq, *J* 11.9, CH_2CCl_3), 4.78 (1 H, d, *J* 4.7, 6-H), 6.01 (1 H, dd, *J* 4.7 and 10.5, 7-H), 6.94–7.35 (6 H, m, PhO and 2-H) and 8.09 (1 H, d, *J* 10.5, NH).

Diphenylmethyl (1S,6R,7R)-4-(2′-*Cyanoethyl*)-3-*methyl*-7β-*phenoxyacetamidoceph*-2-*em*-4-*carboxylate* 1-*Oxide* **14b**.—A solution of ceph-2-em **13b** (1.14 g, 2 mmol) in CH_2Cl_2 (40 cm^3) was stirred at 0 °C with *m*-CPBA (80%; 0.4 g, 2 mmol) for 40 min. The resulting solution was washed with 10% w/v aqueous $Na_2S_2O_5$, saturated aqueous $NaHCO_3$ and brine, dried and evaporated under reduced pressure to yield a pale yellow oil which was chromatographed on silica gel with light petroleum–ethyl acetate (1:1 to 1:2) to give the *title compound* **14b** as a white crystalline solid (0.89 g, 76%); m.p. 160–162 °C; $[\alpha]_D^{20}$ + 198° (*c* 1.0 in $CHCl_3$) (Found: C, 66.2; H, 4.9; N, 7.1; S, 5.5. $C_{32}H_{29}N_3O_6S$ requires C, 65.9; H, 5.0; N, 7.2; S, 5.5%); ν_{max}(EtOH)/nm 256 (ε 2300); ν_{max}(KBr)/cm^{-1} 3370, 2244, 1781, 1740 and 1684; $\delta_H(CDCl_3)$ 1.83 (3 H, d, *J* 1.4, 3-CH_3), 2.49–2.79 (3 H, m, CH_2CHCN), 3.29–3.41 (1 H, m, CHCN), 4.55 (2 H, s, OCH_2CON), 4.59 (1 H, d, *J* 4.6, 6-H), 5.87 (1 H, dd, *J* 4.6 and 10.5, 7-H), 6.89 (1 H, d, *J* 1.4, 2-H), 6.93–7.43 (16 H, m, $CHPh_2$ and PhO) and 8.08 (1 H, d, *J* 10.5, NH).

Diphenylmethyl (6R,7R)-4-(2′-*Cyanoethyl*)-3-*methyl*-7β-*phenoxyacetamidoceph*-2-*em*-4-*carboxylate* 1,1-*Dioxide* **20**.—The sulphoxide **14b** (0.08 g, 0.14 mmol) in CH_2Cl_2 (10 cm^3) was stirred at 0 °C with *m*-CPBA (80%; 0.03, 0.14 mmol) for 30 min. The reaction mixture was partitioned between CH_2Cl_2 and 10% w/v aqueous $Na_2S_2O_5$, and the organic phase washed with saturated aqueous $NaHCO_3$ and brine, dried and evaporated under reduced pressure to yield a colourless oil. Crystallisation of the oil from ethyl acetate–light petroleum yielded the *title compound* **20** as a white amorphous powder (0.07 g, 85%); m.p. 145–147 °C; $[\alpha]_D^{20}$ + 105° (*c* 1.0 in $CHCl_3$) (Found: C, 63.85; H, 4.7; N, 6.95; S, 5.0. $C_{32}H_{29}N_3O_7S$ requires C, 64.1; H, 4.8; N, 7.0; S, 5.3%); λ_{max}(EtOH)/nm 268 (ε 1560); ν_{max}(KBr)/cm^{-1} 3391, 2247, 1782, 1735 and 1688; $\delta_H(CDCl_3)$ 1.80 (3 H, d, *J* 1.4, 3-CH_3), 2.33 (1 H, m, CH), 2.60 (2 H, m, CH_2), 3.30 (1 H, m, CH), 4.52 and 4.59 (2 H, ABq, *J* 15.2, OCH_2CON), 4.80 (1 H, d, *J* 4.7, 6-H), 5.93 (1 H, dd, *J* 4.7 and 10.7, 7-H), 6.53 (1 H, d, *J* 1.4, 2-H), 6.88–7.48 (16 H, m, $CHPh_2$ and PhO) and 8.07 (1 H, d, *J* 10.7, NH).

Diphenylmethyl (6R,7R)-2,2-*Bis*(2′-*cyanoethyl*)-3-*methyl*-7β-*phenoxyacetamidoceph*-3-*em*-4-*carboxylate* 1,1-*Dioxide* **21**.—The sulphone **19** (0.55 g, 1.0 mmol) in acrylonitrile (20 cm^3) was stirred at room temperature with triethylamine (0.1 cm^3) for 20 h. The solution was diluted with ethyl acetate and washed with 1 mol dm^{-3} HCl, saturated aqueous $NaHCO_3$ and brine, dried and evaporated under reduced pressure. Column chromatography afforded the *title compound* **21** as a white foam (0.35 g, 54%) (Found: C, 64.3; H, 5.1; N, 8.5; S, 4.9. $C_{35}H_{32}N_4O_7S$ requires C, 64.3; H, 4.9, N, 8.6; S, 4.9%); λ_{max}(EtOH)/nm 264 (ε 1821); ν_{max}(KBr)/cm^{-1} 3403, 2250, 1790, 1744 and 1702; $\delta_H(CDCl_3)$ 1.83 (3 H, s, 3-CH_3), 2.47–3.31 (8 H, m, 2 × CH_2CH_2CN), 4.53 (2 H, s, CH_2CON), 4.76 (1 H, d, *J* 4.6, 6-H), 5.90 (1 H, dd, *J* 4.6 and 10.6, 7-H), 6.92–7.42 (16 H, m, PhO and $CHPh_2$) and 7.98 (1 H, d, *J* 10.6, NH).

Trichloroethyl (1S,6R,7R)-3-*Methyl*-4-(3′-*oxobutyl*)-7β-*phenoxyacetamidoceph*-2-*em*-4-*carboxylate* 1-*Oxide* **14c**.—A solution of the ceph-2-em **13c** (1.0 g, 1.82 mmol) in CH_2Cl_2 (30 cm^3) was stirred with *m*-CPBA (80%; 0.36 g, 1.85 mmol) at 0 °C for 30 min. The solution was washed with 10% w/v aqueous $Na_2S_2O_5$, saturated aqueous $NaHCO_3$ and brine, dried and evaporated under reduced pressure. The residue was chromatographed on silica gel with light petroleum–ethyl acetate (3:1 to 2:3) as eluent to afford the *title compound* **14c** as a colourless oil (0.86 g, 85%); $[\alpha]_D^{20}$ + 159° (*c* 1.0 in $CHCl_3$) (Found: C, 46.8; H, 4.0; N, 4.6; S, 5.85. $C_{22}H_{23}Cl_3N_2O_7S$ requires C, 46.7; H, 4.1; N, 5.0; S, 5.7%); λ_{max}(EtOH)/nm 267 (ε 2037); $\nu_{max}(CHCl_3)/cm^{-1}$ 3373, 1780, 1705 and 1690; $\delta_H(CDCl_3)$ 2.00 (3 H, d, *J* 1.3, 3-CH_3), 2.17 (3 H, s, $COCH_3$), 2.80 (4 H, m, CH_2CH_2), 4.54 and 4.61 (2 H, ABq, *J* 15.1 , OCH_2CON), 4.74 and 4.92 (2 H, ABq, *J* 9.8, $CO_2CH_2CCl_3$), 4.747 (1 H, d, *J* 4.7, 6-H), 6.00 (1 H, dd, *J* 4.7 and 10.5, 7-H), 6.80 (1 H, d, *J* 1.3, 2-H), 6.94–7.40 (5 H, m, PhO) and 8.23 (1 H, d, *J* 10.5, NH).

Diphenylmethyl (1S,6R,7R)-3-*Methyl*-4-(3′-*oxobutyl*)-7β-*phenoxyacetamidoceph*-2-*em*-4-*carboxylate* 1-*Oxide* **14d**.—A solution of the sulphide **13d** (2.08 g, 3.56 mmol) in CH_2Cl_2 (80 cm^3) was stirred with *m*-CPBA (80%; 0.77 g, 3.55 mmol) for 1 h at 0 °C. The solution was washed with 10% w/v aqueous $Na_2S_2O_5$, saturated aqueous $NaHCO_3$ and brine, dried and evaporated under reduced pressure. Crystallisation of the crude solid from CH_2Cl_2–light petroleum afforded the *title compound* **14d** as a white amorphous powder (1.66 g, 85%); m.p. 175–177 °C; $[\alpha]_D^{20}$ + 172° (*c* 1.0 in $CHCl_3$) (Found: C, 66.0; H, 5.4; N, 4.9; S, 5.2. $C_{33}H_{32}N_2O_7S$ requires C, 66.0; H, 5.3; N, 4.7; S, 5.3%); λ_{max}(EtOH)/nm 255 (ε 6430); ν_{max}(KBr)/cm^{-1} 3300, 1770, 1730, 1700 and 1680; δ_H($CDCl_3$) 1.80 (3 H, d, *J* 0.9, 3-CH_3), 2.14 (3 H, s, $COCH_3$), 2.49–3.10 (4 H, m, CH_2CH_2), 4.52 (3 H, d and s, *J* 4.8, 6-H and OCH_2CON), 5.84 (1 H, dd, *J* 4.8 and 10.6, 7-H), 6.71 (1 H, d, *J* 0.9, 2-H), 6.91–7.42 (16 H, m, $CHPh_2$ and PhO) and 8.21 (1 H, d, *J* 10.6, NH).

Trichloroethyl (1S,6R,7R)-3-*Acetoxymethyl*-4-(2′-*cyanoethyl*)-7β-(2-*thienylacetamido*)*ceph*-2-*em*-4-*carboxylate* 1-*Oxide* **15b**.—The cephalosporanate **15a** (2.0 g, 3.45 mmol) in CH_2Cl_2 (100 cm^3) was stirred at 0 °C with *m*-CPBA (80%; 0.75 g, 3.5 mmol) for 30 min. The solution was washed with 10% w/v aqueous $Na_2S_2O_5$, saturated aqueous $NaHCO_3$ and brine, dried and evaporated under reduced pressure. Chromatography of the crude product on silica gel using ethyl acetate–light petroleum (1:3 to 5:3) as eluent afforded the *title compound* **15b** (1.85 g, 90%) as a yellow oil; $[\alpha]_D^{20}$ + 156° (*c* 1.0 in $CHCl_3$) (Found: C, 42.55; H, 3.5; Cl, 17.6; N, 6.8; S, 10.9. $C_{26}H_{20}Cl_3N_3O_7S_2$ requires C, 42.35; H, 3.35; Cl, 17.9; N, 7.0; S, 10.7%); λ_{max}(EtOH)/nm 235 (ε 8162); ν_{max}($CHCl_3$)/cm^{-1} 3368, 2250, 1781, 1756 and 1683; δ_H($CDCl_3$) 2.13 (3 H, s, $OCOCH_3$), 2.43–2.78 (3 H, m, CH_2CHCN), 3.28–3.46 (1 H, m, CHCN), 3.85 (2 H, s, CH_2CON), 4.70 and 4.96 (2 H, ABq, *J* 11.8, $CO_2CH_2CCl_3$), 4.75 (3 H, d and s, *J* 4.6, 6-H and CH_2OCO), 5.99 (1 H, dd, *J* 4.6 and 10.2, 7-H), 6.93–7.07 (3 H, m, NH and 2-thienyl protons), 7.22 (1 H, s, 2-H) and 7.30 (1 H, m, thienyl-H).

Trichloroethyl (1S,6R,7R)-4β-[1′,2′-*Bis*(*methoxycarbonyl*)-*vinyl*]-3-*methyl*-7β-*phenoxyacetamidoceph*-2-*em*-4-*carboxylate* 1-*Oxide* **17c**.—A solution of ceph-2-em **17a** (2.40 g, 3.86 mmol) in dichloromethane (50 cm^3) was stirred with *m*-CPBA (80% 0.83; 3.9 mmol) for 30 min. The reaction mixture was then washed with 10% w/v aqueous $Na_2S_2O_5$, saturated aqueous $NaHCO_3$ and brine, dried and evaporated under reduced pressure to give, after chromatography, a colourless oil (1.92 g, 78%); λ_{max}(EtOH)/nm 261 (ε 2500); ν_{max}($CHCl_3$)/cm^{-1} 3378, 1789, 1761, 1727 and 1690; δ_H($CDCl_3$) 2.14 (3 H, d, *J* 1.3, 3-CH_3), 3.80 (3 H, s, CO_2CH_3), 3.84 (3 H, s, CO_2CH_3), 4.53 and 4.57 (2 H, ABq, *J* 15.0, CH_2CON), 4.74 and 4.92 (2 H, ABq, *J* 11.9, CH_2CCl_3), 4.87 (1 H, d, *J* 4.7, 6-H), 6.04 (1 H, dd, *J* 4.7 and 10.5, 7-H), 6.70 (1 H, s, $CHCO_2CH_3$), 6.96 (1 H, d, *J* 1.3, 2-H), 6.98–7.35 (5 H, m, PhO) and 8.14 (1 H, d, *J* 10.5, NH).

The sulphoxide **17d** was prepared as a mixture of sulphoxide isomers which could not be separated by extensive column chromatography. Spectroscopic data indicated that the structure was as assigned and the compound was used in reactions without further purification.

(1S,6R,7R)-3-*Methyl*-4-(3′-*oxobutyl*)-7β-*phenoxyacetamidoceph*-2-*em*-4-*carboxylic Acid* 1-*Oxide* **14f**.—A solution of the ester **14d** (0.85 g, 1.42 mmol) in anisole (1.2 cm^3) and trifluoroacetic acid (3.6 cm^3) was stirred at room temperature for 10 min. Solvents were removed under reduced pressure, and the residue partitioned between ethyl acetate and dilute aqueous $NaHCO_3$. The aqueous fraction was further extracted with ethyl acetate and then partitioned between ethyl acetate and 1 mol dm^{-3} HCl. The organic layer was washed with brine, dried and evaporated under reduced pressure to give the acid **14f** as a white amorphous powder (0.47 g, 76%); m.p. 110 °C decomp.

(1S,6R,7R)-3-*Methyl*-4-(3′-*oxobutyl*)-7β-*phenoxyacetamidoceph*-3-*em* 1-*Oxide* **18b**.—Triethylamine (4 drops) was added to a solution of the acid **14f** (0.32 g, 0.74 mmol) in acetone (20 cm^3) and the mixture stirred for 20 h to give a flocculent white precipitate. This was filtered off and recrystallised from refluxing acetone to afford the *title compound* **18b** (0.25 g, 87%); m.p. > 310 °C; $[\alpha]_D^{20}$ − 4.1° (*c* 1.0 in $CHCl_3$) (Found: C, 58.7; H, 5.6; N, 7.1; S, 8.2. $C_{19}H_{22}N_2O_5S$ requires C, 58.5; H, 5.6; N, 7.2; S, 8.2%); λ_{max}(EtOH)/nm 251 (ε 8300); ν_{max}(KBr_3)/cm^{-1} 3351, 1761, 1703 and 1689; δ_H($CDCl_3$) 1.85 (3 H, s, 3-CH_3), 2.18 (3 H, s, $COCH_3$), 2.68–3.03 (4 H, m, CH_2CH_2), 3.15 and 3.43 (2 H, ABq, *J* 18.0, 2-H), 4.41 (1 H, dd, *J* 4.6 and 1.2, 6-H), 4.58 (2 H, s, OCH_2CON), 6.01 (1 H, dd, *J* 4.6 and 10.4, 7-H), 6.92–7.35 (5 H, m, PhO) and 7.96 (1 H, d, *J* 10.4, NH).

Compound **18b** was also obtained upon de-esterification of **14c**. The ester **14c** (0.85 g, 1.77 mmol) in a mixture of DMF (10 cm^3) and glacial acetic acid (3 cm^3) was stirred with powdered zinc (1.3 g) at room temperature for 1 h. The reaction mixture was filtered through Celite and the filtrate partitioned between ethyl acetate and saturated aqueous $NaHCO_3$. A white solid appeared at the interface of the two layers and this was filtered off and allowed to dry. The solid was recrystallised from ethyl acetate to afford **18b** as a flocculent white solid (0.25 g, 36%), which was identical (m.p., IR, NMR, MS) to the previously prepared sample. No further **18b** could be isolated from either the organic or aqueous phases.

(1S,6R,7R)-3-*Acetoxymethyl*-4-(2′-*cyanoethyl*)-7β-(2-*thienylacetamido*)*ceph*-3-*em* 1-*Oxide* **16a**.—The ceph-2-em **15b** (1.2 g, 2 mmol) in a mixture of DMF (20 cm^3) and glacial acetic acid (6 cm^3) was stirred at room temperature with powdered zinc (2.5 g) for 4 h. The mixture was filtered through Celite, and the filtrate partitioned between ethyl acetate and water. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried and evaporated under reduced pressure to give an amorphous white solid. This was recrystallised from ethyl acetate–acetone to afford *title compound* **16a** as white needles (0.70 g, 83%); m.p. 183–186 °C; $[\alpha]_D^{20}$ + 5.9° (*c* 1.0 in $CHCl_3$) (Found: C, 51.4; H, 4.6; N, 9.9; S, 15.2. $C_{18}H_{19}N_3O_5S_2$ requires C, 51.3; H, 4.5; N, 10.0; S, 15.2%); λ_{max}(EtOH)/nm 239 (ε 14 200); ν_{max}(KBr)/cm^{-1} 3284, 2248, 1771, 1734 and 1678; δ_H($CDCl_3$) 2.06 (3 H, s, $COCH_3$), 2.62–2.82 (2 H, m, CH_2), 2.94–3.08 (1 H, m, CHCN), 3.18–3.33 (1 H, m, CHCN), 3.21 and 3.69 (2 H, ABq, *J* 17.7, 2-H), 3.85 (2 H, s, CH_2CON), 4.47 (1 H, dd, *J* 1.2 and 4.8, 6-H), 4.58 and 4.77 (2 H, ABq, *J* 12.8, CH_2OAc), 6.00 (1 H, dd, *J* 4.8 and 10.1, 7-H), 6.90 (1 H, d, *J* 10.1, NH), 6.95–7.02 (2 H, m, 2-thienyl protons) and 7.27 (1 H, m, 2-thienyl proton).

(1S,6R,7R)-4-(2′-*Cyanoethyl*)-3-*methyl*-7β-*phenoxyacetamidoceph*-3-*em* 1-*Oxide* **18a**.—The ester **14b** (1.17 g, 2 mmol), CH_2Cl_2 (50 cm^3), anisole (0.5 cm^3) and trifluoroacetic acid (5 cm^3) were stirred at 0 °C for 30 min. after which the mixture was concentrated under reduced pressure. The resulting oil was redissolved in CH_2Cl_2 (25 cm^3) and stirred with triethylamine (3 drops) overnight. Removal of solvents under reduced pressure followed by recrystallisation from refluxing acetone afforded the *title compound* **18a** as a white crystalline solid (0.6 g, 80%); m.p. 205–208 °C; $[\alpha]_D^{20}$ + 10.2° (*c* 1.0 in $CHCl_3$) (Found: C, 57.85; H, 5.3; N, 11.3; S, 8.3. $C_{18}H_{19}N_3O_4S$ requires C, 57.9; H, 5.1; N, 11.3; S, 8.6%); λ_{max}(EtOH)/nm 250 (ε 9052); ν_{max}(KBr)/cm^{-1} 3345, 2244, 1765 and 1685;

δ_H($CDCl_3$ + CD_3OD) 1.91 (3 H, s, 3-CH_3), 2.68–2.83 (2 H, m, CH_2), 2.90–2.98 (1 H, m, CHCN), 3.17–3.25 (1 H, m, CHCN), 3.31 and 3.52 (2 H, ABq, *J* 18.3, 2-H), 4.57 (1 H, d, *J* 4.6, 6-H), 4.59 (2 H, s, OCH_2CON), 6.02 (1 H, d, *J* 4.6, 7-H) and 6.94–7.33 (5 H, m, PhO) {NH proton exchanged with CD_3OD).

(1S,6R,7R)-4-(2′-*Methoxycarbonylethyl*)-3-*methyl*-7β-*phenoxyacetamidoceph*-3-*em* 1-*Oxide* **18c**.—The ester **14e** (0.15 g, 0.24 mmol), anisole (1.2 cm^3) and trifluoroacetic acid (4 cm^3) were stirred at room temperature for 15 min after which the mixture was concentrated under reduced pressure. The resulting foam was dissolved in CH_2Cl_2 (20 cm^3) and stirred with triethylamine (3 drops) overnight. The mixture was then evaporated under reduced pressure and the residue recrystallised from refluxing acetone to give the *title compound* **18c** as a white amorphous powder (0.80 g, 82%); m.p. 162–164 °C; $[\alpha]_D^{20}$ +27° (*c* 0.5 in $CHCl_3$) (Found: C, 56.0; H, 5.2; N, 6.9; S, 7.8. $C_{19}H_{22}N_2O_6S$ requires C, 56.2; H, 5.4; N, 6.9; S, 7.9%); λ_{max}(EtOH)/nm 250 (ε 7135); ν_{max}(KBr)/cm^{-1} 3351, 1762, 1728 and 1686; δ_H($CDCl_3$) 1.86 (3 H, s, 3-CH_3), 2.62–3.09 (4 H, m, CH_2CH_2), 3.16 and 3.44 (2 H, ABq, *J* 17.8, 2-H), 3.68 (3 H, s, CO_2CH_3), 4.42 (1 H, d, *J* 4.6, 6-H), 4.58 (2 H, s, OCH_2CON), 6.02 (1 H, dd, *J* 4.6 and 10.4, 7-H), 6.93–7.34 (5 H, m, PhO) and 7.96 (1 H, d, *J* 10.4, NH).

(1S,6R,7R)-4-[1′,2′-*Bis*(*methoxycarbonyl*)*ethyl*]-3-*methyl*-7β-*phenoxyacetamidoceph*-3-*em*-1-*Oxide* **18e**.—To a stirred solution of the unsaturated triester **17c** (0.8 g, 1.25 mmol) in DMF (12 cm^3) and glacial acetic acid (5 cm^3) was added powdered zinc (1.2 g). Stirring was continued for 3 h after which the reaction mixture was filtered through Celite, and partitioned between ethyl acetate and water. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried and evaporated under reduced pressure to give a colourless oil. The oil was dissolved in ethyl acetate and stirred with triethylamine (3 drops) overnight. Evaporation of the mixture under reduced pressure followed by recrystallisation of the residue from CH_2Cl_2–light petroleum afforded the *title compound* **18e** as white needles (0.22 g, 38%); m.p. 169–170 °C; $[\alpha]_D^{20}$ + 62° (*c* 1.0 in $CHCl_3$) (Found: C, 54.1; H, 4.9; N, 5.9; S, 6.6. $C_{21}H_{24}N_2O_8S$ requires C, 54.3; H, 5.2; N, 6.0; S, 6.9%); λ_{max}(EtOH)/nm 251 (ε 8850); ν_{max}(KBr)/cm^{-1} 3450–3200, 1771, 1728 and 1693; δ_H($CDCl_3$) 1.91 (3 H, s, 3-CH_3), 2.78 (1 H, dd, *J* 17.1 and 7.5, CH), 3.25 (1 H, dd, *J* 17.1 and 7.2, CH), 3.30 and 3.51 (2 H, ABq, *J* 18.0, 2-H), 3.71 (3 H, s, CO_2CH_3), 3.72 (3 H, s, CO_2CH_3), 4.36 (1 H, dd, *J* 7.5 and 7.2, CH), 4.42 (1 H, dd, *J* 4.2 and 1.2, 6-H), 4.57 (2 H, s, OCH_2CON), 6.01 (1 H, dd, *J* 4.7 and 10.4, 7-H), 6.95–7.30 (5 H, m, PhO) and 7.94 (1 H, d, *J* 10.4, NH).

(6R,7R)-3-*Methyl*-4-(3′-*oxobutyl*)-7β-*phenoxyacetamidoceph*-2-*em*-4-*carboxylic Acid* **13f**.—A solution of the ester **13d** (0.85 g, 1.45 mmol) in anisole (1.2 cm^3) and trifluoroacetic acid (3.6 cm^3) was stirred at room temperature for 15 min, and then evaporated under reduced pressure. The residue was partitioned between ethyl acetate and dilute aqueous $NaHCO_3$. The aqueous portion was further extracted with ethyl acetate and then partitioned between dilute HCl and ethyl acetate. The organic phase was washed with brine, dried and evaporated under reduced pressure to yield the *title compound* **13f** as a white foam (0.52 g, 87%); m.p. 170–171 °C; $[\alpha]_D^{20}$ + 316° (*c* 1.0 in $CHCl_3$) (Found: C, 57.3; H, 5.3; N, 6.5; S, 7.6. $C_{20}H_{22}N_2O_6$ requires C, 57.4; H, 5.3; N, 6.7; S, 7.7%); λ_{max}(EtOH)/nm 254 (ε 5093); ν_{max}($CHCl_3$)/cm^{-1} 3700–3000, 1760, 1720 and 1680. δ_H([$^2H_6$]-DMSO) 1.70 (3 H, d, *J* 1.2, 3-CH_3), 2.10 (3 H, s, $COCH_3$), 2.18–2.35 and 2.52–2.72 (4 H, m, CH_2CH_2), 4.51 and 4.62 (2 H, ABq, *J* 15.0, OCH_2CON), 5.10 (1 H, d, *J* 4.3, 6-H), 5.29 (1 H, dd, *J* 4.3 and 7.6, 7-H), 6.38 (1 H, d, *J* 1.2, 2-H), 6.92–7.35 (5 H, m, PhO) and 9.12 (1 H, d, *J* 7.6, NH).

(6R,7R)-4-(2′-*Cyanoethyl*)-3-*methyl*-7β-*phenoxyacetamidoceph*-3-*em* 1,1-*Dioxide* **22**.—A solution of the ester **20** (0.3 g, 0.5 mmol) in CH_2Cl_2 (20 cm^3) was stirred at 0 °C with anisole (0.2 cm^3) and trifluoroacetic acid (1.5 cm^3) for 30 min after which it was evaporated under reduced pressure. The resulting oil was redissolved in ethyl acetate and the solution stirred overnight with triethylamine (5 drops). It was then partitioned between ethyl acetate and dilute HCl, and the organic phase washed with brine, dried and evaporated under reduced pressure to give the *title compound* **22** as a white powder (0.16 g, 82%); m.p. 155–157 °C; $[\alpha]_D^{20}$ + 56° (*c* 1.0 in $CHCl_3$) (Found: C, 55.3; H, 4.8; N, 10.6; S, 8.0. $C_{18}H_{19}N_3O_5S$ requires C, 55.5; H, 4.9; N, 10.8; S, 8.2%); λ_{max}(EtOH)/nm 245 (ε 8715); ν_{max}(KBr)/cm^{-1} 3325, 2250, 1777 and 1693. δ_H($CDCl_3$) 1.85 (3 H, s, 3-CH_3), 2.69 (2 H, m, CH_2), 2.77 (1 H, m, CHCN), 3.07 (1 H, m, CHCN), 3.45 and 3.90 (2 H, ABq, *J* 18.0, 2-H), 4.57 and 4.61 (2 H, ABq, *J* 15.4, CH_2CON), 4.84 (1 H, d, *J* 4.7, 6-H), 6.14 (1 H, dd, *J* 4.7 and 10.6, 7-H), 6.92–7.29 (5 H, m, PhO) and 7.98 (1 H, d, *J* 10.6, NH).

(6R,7R)-4-(2′-*Cyanoethyl*)-3-*methyl*-7β-*phenoxyacetamidoceph*-3-*em* **23a**.—The sulphoxide **18a** (0.37 g, 1.0 mmol) was stirred at ice temperature in DMF (10 cm^3). Potassium iodide (0.66 g, 4.0 mmol) and acetyl chloride (0.31 g, 4.0 mmol) were added and stirring was continued for 1.5 h. The reaction mixture was poured into ethyl acetate and washed with brine, 10% w/v aqueous $Na_2S_2O_5$, saturated aqueous $NaHCO_3$ and brine. The ethyl acetate phase was dried and the solvent evaporated under reduced pressure to afford the *title compound* as a crystalline solid (0.27 g, 75%); m.p. 168–170 °C; $[\alpha]_D^{20}$ + 78° (*c* 1.0 in $CHCl_3$) (Found C, 60.8; H, 5.7; N, 11.3; S, 8.6. $C_{18}H_{19}N_3O_3S$ requires C, 60.5; H, 5.3; N, 11.8; S, 9.0%); λ_{max}(EtOH)/nm 260 (ε 6060); ν_{max}(KBr)/cm^{-1} 3275, 2247, 1759 and 1680; δ_H($CDCl_3$) 1.87 (3 H, s, CH_3), 2.60–2.83 (3 H, m, CH_2CHCN), 3.06 (1 H, m, CHCN), 3.05 and 3.55 (2 H, ABq, *J* 17.4, 2-H), 4.57 (2 H, s, CH_2O), 5.0 (1 H, d, *J* 4.8, 6-H), 5.8 (1 H, dd, *J* 10.3 and 4.8, 7-H) and 6.92–7.45 (6 H, m, NH and PhO).

(6R,7R)-3-*Methyl*-4-(3′-*oxobutyl*)-7β-*phenoxyacetamidoceph*-3-*em* **23b**.—To a solution of the sulphoxide **18b** (0.20 g, 0.51 mmol) in CH_2Cl_2 (20 cm^3) and pyridine (0.16 g, 2.06 mmol) was added P_2S_5 (0.06 g, 0.26 mmol) and the suspension stirred at room temperature for 2 h. It was then filtered and partitioned between CH_2Cl_2 and water. The organic phase was washed with 1 mol dm^{-3} HCl and brine, dried and evaporated under reduced pressure. Chromatography of the resulting oil on silica gel using ethyl acetate–light petroleum (1:1 to 5:1) as eluent afforded the sulphide **23b** as a white amorphous powder (0.14 g, 73%); m.p. 160–162 °C; $[\alpha]_D^{20}$ − 17° (*c* 1.0 in $CHCl_3$) (Found: C, 60.6; H, 5.6; N, 7.5; S, 8.4. $C_{19}H_{22}N_2O_4S$ requires C, 61.0; H, 5.9; N, 7.5; S, 8.6%); ν_{max}(KBr)/cm^{-1} 3250, 1760, 1700 and 1670. δ_H($CDCl_3$) 1.80 (3 H, s, 3-CH_3), 2.17 (3 H, s, $COCH_3$), 2.64–2.87 (4 H, m, CH_2CH_2), 2.98 and 3.47 (2 H, ABq, *J* 17.3, 2-H), 4.57 (2 H, s, OCH_2CON), 4.94 (1 H, d, *J* 4.8, 6-H), 5.77 (1 H, dd, *J* 4.8 and 10.5, 7-H) and 6.92–7.36 (6 H, m, PhO and NH).

(6R,7R)-4-(2′-*Methoxycarbonylethyl*)-3-*methyl*-7β-*phenoxyacetamidoceph*-3-*em* **23c**.—A solution of the sulphoxide **18c** (0.33 g, 0.8 mmol) in CH_2Cl_2 (20 cm^3) containing pyridine (0.25 g, 3.2 mmol) was stirred with P_2S_5 (0.09 g, 0.4 mmol) at room temperature for 2 h. The reaction mixture was filtered and partitioned between CH_2Cl_2 and water. The organic phase was washed with 1 mol dm^{-3} HCl and brine, dried and evaporated under reduced pressure. Recrystallisation of the crude product from CH_2Cl_2–light petroleum afforded the sulphide **23c** as a white powder (0.19 g, 60%); m.p. 147–148 °C; $[\alpha]_D^{20}$ + 88°

(*c* 0.5 in $CHCl_3$) (Found: C, 58.5; H, 5.4; N, 7.0; S, 8.3. $C_{19}H_{22}N_2O_5S$ requires C, 58.5; H, 5.6; N, 7.2; S, 8.2%); ν_{max}(KBr)/cm^{-1} 3287, 1791, 1727 and 1691; δ_H($CDCl_3$) 1.80 (3 H, s, 3-CH_3), 2.55–2.88 (4 H, m, CH_2CH_2), 2.98 and 3.47 (2 H, ABq, *J* 17.3, 2-H), 3.67 (3 H, s, CO_2CH_3), 4.56 (2 H, s, OCH_2CON), 4.95 (1 H, d, *J* 4.8, 6-H), 5.77 (1 H, dd, *J* 4.8 and 9.5, 7-H) and 6.90–7.36 (6 H, m, PhO and NH).

(6R,7R)-4-[1′,2′-*Bis*(*methoxycarbonyl*)*vinyl*]-3-*methyl*-7β-*phenoxyacetamidoceph*-3-*em* **23d**.—The triester **17b** (0.5 g, 0.76 mmol) was stirred at room temperature in anisole (2.5 cm^3) and TFA (1.76 cm^3) for 1 h. after which the mixture was evaporated under reduced pressure to give a yellow oil. This was dissolved in MDC (methylene dichloride) and treated with NEt_3 (3 drops) for a further hour. The solution was then diluted with MDC and washed with dil HCl, saturated aqueous $NaHCO_3$ and brine, dried and evaporated under reduced pressure to give a solid which was recrystallised from EtOAc–light petroleum to afford white crystals (0.25 g, 84%); m.p. 146–148 °C; $[\alpha]_D^{20}$ + 68.9° (*c* 1.0 in $CHCl_3$) (Found: C, 56.4; H, 4.8; N, 6.1; S, 7.1. $C_{21}H_{22}N_2O_7S$ requires C, 56.5; H, 4.9; N, 6.3; S, 7.2%); λ_{max}(EtOH)/nm 259 (ε 9800); ν_{max}(KBr)/cm^{-1} 3278, 1767, 1731 and 1668; δ_H($CDCl_3$) 1.96 (3 H, d, *J* 0.8, 3-CH_3), 3.32 and 3.77 (2 H, ABq, *J* 17.5, 2-H), 3.72 (3 H, s, CO_2CH_3), 3.80 (3 H, s, CO_2CH_3), 4.55 (2 H, s, OCH_2), 5.21 (1 H, d, *J* 4.5, 6-H), 5.81 (1 H, ddd, *J* 9.1 and 4.5, 7-H), 6.61 (1 H, s, =CH) and 6.90–7.45 (6 H, m, Ph and NH).

Diphenylmethyl (6R,7R)-4-[1′,2′-*Bis*(*methoxycarbonyl*)*ethyl*]-3-*methyl*-7β-*phenoxyacetamidoceph*-2-*em*-4-*carboxylate* **13h**.—A solution of the triester **17d** (1.0 g, 1.5 mmol) in DMF (12 cm^3) and glacial acetic acid (4 cm^3) was stirred with powdered zinc (1.5 g) for 1 h at room temperature. The reaction mixture was filtered through Celite and the filtrate partitioned between ethyl acetate and water. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried and evaporated under reduced pressure to give a white foam. Crystallisation of this from CH_2Cl_2–ether afforded the *title compound* **13h** as white crystals (0.45 g, 46%); m.p. 89–98 °C; $[\alpha]_D^{20}$ + 296° (*c* 1.0 in $CHCl_3$) (Found: C, 63.6; H, 5.1; N, 4.2; S, 4.5. $C_{35}H_{34}N_2O_9S$ requires C, 63.8; H, 5.2; N, 4.25; S, 4.9%); λ_{max}(EtOH)/nm 257 (ε 5660); ν_{max}(KBr)/cm^{-1} 3413, 1773, 1740 and 1692; δ_H($CDCl_3$) 1.78 (3 H, d, *J* 1.0, 3-CH_3), 2.25 (1 H, dd, *J* 17.0 and 1.6, $CH_2CO_2CH_3$), 3.02 (1 H, dd, *J* 17.0 and 9.4, $CH_2CO_2CH_3$), 3.45 (3 H, s, CO_2CH_3), 3.75 (3 H, s, CO_2CH_3), 4.38 (1 H, dd, *J* 9.4 and 1.6, $CHCO_2CH_3$), 4.54 (2 H, s, OCH_2CON), 5.51 (1 H, d, *J* 4.6, 6-H), 5.57 (1 H, dd, *J* 9.1 and 4.6, 7-H), 6.20 (1 H, d, *J* 1.0, 2-H) and 6.90–7.42 (17 H, m, $CHPh_2$, PhO and NH).

Diphenylmethyl(6R,7R)-4-(2′-*Cyanoethyl*)-3-*methyl*-7β-*phenoxyacetamidoceph*-2-*em*-4-*carboxylate* **13b** via *De-oxygenation of the Sulphoxide* **14b**.—A solution of the sulphoxide ester **14b** (0.22 g, 0.38 mmol) in DMF–glacial acetic acid (10 cm^3 of a 25:7.5 v/v mixture) was stirred with powdered zinc (1.5 g) at room temperature for 4 h. The reaction mixture was filtered through Celite and the filtrate partitioned between ethyl acetate and water. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried and evaporated under reduced pressure to give **13b** as a white foam (0.19 g, 89%) which was identical (TLC, NMR, MS) with an authentic sample.

In an analogous manner, the sulphides **13d**, **13e** and **13h** were prepared from the corresponding sulphoxides **14d**, **14e** and **17d**. All compounds exhibited spectroscopic data which were identical with authentic samples of the respective sulphide.

Acknowledgements

We thank SmithKline Beecham for financial support. We also thank Dr. Irene Francois and Mr. Clive Branch for their interest and their very helpful comments.

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Paper 0/04910G
Received 31*st October* 1990
Accepted 3*rd January* 1991