Studies related to Penicillins. Part 27.[1] A Strategy for the Conversion of 1,1-Dioxides of Penicillanates into 1,1-Dioxides of 3-Methylceph-3-em-4-carboxylates[2]

G. D. Sriyani Ananda and Richard J. Stoodley *,†
Department of Organic Chemistry, The University, Newcastle upon Tyne, NE1 7RU

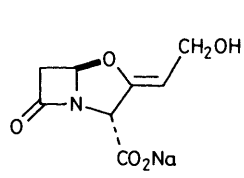
Methodology for the conversion of benzyl (3*S*,5*R*)-penicillanate 1,1-dioxide (**2b**) into (6*R*)-4-benzyloxycarbonyl-3-methylceph-3-em 1,1-dioxide (**3b**) has been devised. In the process, the 3,4-double bond of the product was constructed by a reductive carbonyl-carbonyl coupling reaction, induced by trimethyl phosphite, of benzyl 2-[(2*R*)-2-acetonylsulphonyl-4-oxoazetidin-1-yl]glyoxylate (**12a**). This compound was prepared from (2*R*)-1-(1-benzyloxycarbonyl-2-methylprop-1-enyl)-4-oxoazetidine-2-sulphinic acid (**13a**), obtained from the precursor (**2b**) by a β-elimination reaction, by an acetonylation–ozonolysis sequence.

By a similar route, benzyl (3*S*,5*R*,6*S*)-6-chloropenicillanate 1,1-dioxide (**2c**) was transformed into (6*R*,7*S*)-4-benzyloxycarbonyl-7-chloro-3-methylceph-3-em 1,1-dioxide (**3d**).

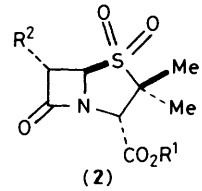
The reductive carbonyl–carbonyl coupling reaction was inapplicable to benzyl 2-[(2*R*,3*S*)-2-acetonylsulphonyl-4-oxo-3-phenoxyacetamidoazetidin-1-yl]glyoxylate (**12c**) [prepared from benzyl (3*S*,5*R*,6*R*)-6-phenoxyacetamidopenicillanate 1,1-dioxide (**17b**)]. However, it could be used to prepare (6*R*,7*R*)-4-diphenylmethoxycarbonyl-3-methyl-7-phenoxyacetamidoceph-3-em 1,1-dioxide (**8b**) from diphenylmethyl 2-[(2*R*,3*R*)-2-acetonylsulphonyl-4-oxo-3-phenoxyacetamidoazetidin-1-yl]glyoxylate (**19**) [obtained by ozonolysis of the cephem dioxide (**8b**)].

Many penicillins are hydrolysed by β-lactamases and they are, therefore, ineffective against bacteria that produce these enzymes. Sodium clavulanate (**1**)[3] and sulbactam sodium salt (**2a**)[4] are powerful β-lactamase inactivators which are capable of protecting penicillins from such enzymic destruction. In consequence, combinations of penicillins with compound (**1**) or (**2a**) can play a useful role in the treatment of infections caused by β-lactamase-producing bacteria.

As part of a programme aimed at defining the structural features of β-lactam derivatives that are necessary for β-lactamase inhibition, we became interested in the cephem dioxide (**3a**). Were it to act as a substrate for a β-lactamase, a species of type (**4**) would be generated which might isomerise to an intermediate of type (**5**). Analogous processes, leading to intermediates of types (**6**) and (**7**), are implicated in the inactivation of β-lactamases by compounds (**1**)[5] and (**2a**).[6] In this paper, we report on the synthesis of compound (**3a**), from sulbactam sodium salt (**2a**), and its biological evaluation. We also examine the scope of the cephem-ring-forming reaction that is involved.

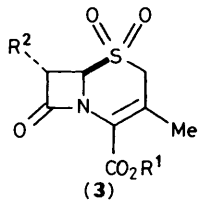


(**1**)



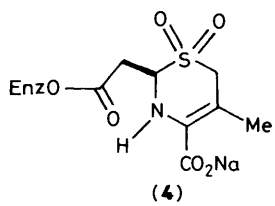
(**2**)

a; R^1 = Na, R^2 = H
b; R^1 = CH_2Ph, R^2 = H
c; R^1 = CH_2Ph, R^2 = Cl

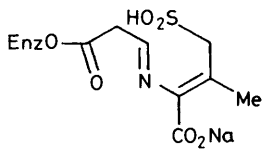


(**3**)

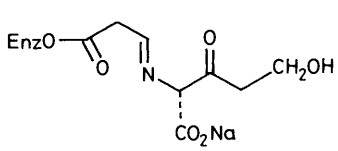
a; R^1 = Na, R^2 = H
b; R^1 = CH_2Ph, R^2 = H
c; R^1 = R^2 = H
d; R^1 = CH_2Ph, R^2 = Cl
e; R^1 = CH_2Ph, R^2 = $NHCOCH_2OPh$



(**4**)



(**5**)



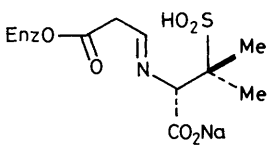
(**6**)

Results and Discussion

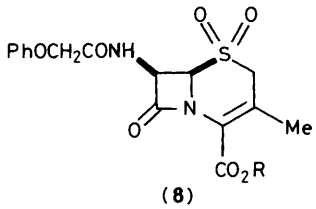
At the outset of our studies, a few acylamino substituted cephem dioxides had been described;[7,8] these compounds, *e.g.* (**8a**), were derived from the corresponding cephems, *e.g.* (**9a**), by oxidation with a peroxy acid. Although we were confident that a similar procedure would provide sulphones of type (**3**; R^2 = H) and that precursors of type (**10**; R^2 = H) would be accessible from penam oxides of type (**11**; R^2 = H) by a Morin-type ring expansion,[9] we elected to examine a new approach. Based upon the findings of the Schering,[10] Sankyo,[11] and Farmitalia-Carlo Erba groups,[12] we hoped that azetidinones of type (**12**; R^2 = H)

† *Present address:* Department of Chemistry, UMIST, P.O. Box 88, Manchester, M60 1QD

would undergo a reductive cyclisation in the presence of a trialkyl phosphite to give cephem dioxides of type (**3**; R^2 = H). We further envisaged that the required intermediates would be available from sulphinic acids of type (**13**; R^2 = H). In earlier work, we had shown that compounds of this type could be prepared by β-elimination reactions of penicillanate dioxides of type (**2**; R^2 = H).[13]

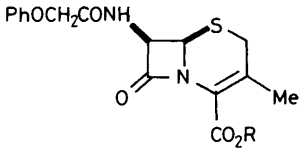


(**7**)



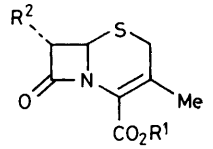
(**8**)

a; R = CH_2CCl_3
b; R = $CHPh_2$



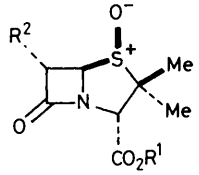
(**9**)

a; R = CH_2CCl_3
b; R = $CHPh_2$

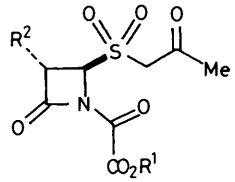


(**10**)

a; R^1 = Me, R^2 = H

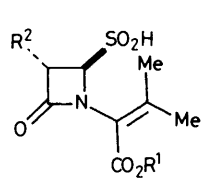


(**11**)



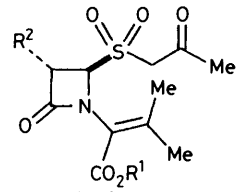
(**12**)

a; R^1 = CH_2Ph, R^2 = H
b; R^1 = CH_2Ph, R^2 = Cl
c; R^1 = CH_2Ph, R^2 = $NHCOCH_2OPh$



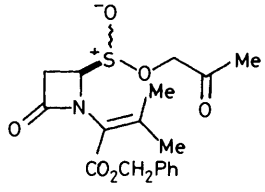
(**13**)

a; R^1 = CH_2Ph, R^2 = H
b; R^1 = CH_2Ph, R^2 = Cl
c; R^1 = Me, R^2 = $NHCOCH_2OPh$
d; R^1 = CH_2Ph, R^2 = $NHCOCH_2OPh$

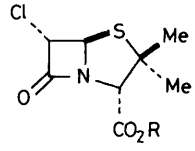


(**14**)

a; R^1 = CH_2Ph, R^2 = H
b; R^1 = CH_2Ph, R^2 = Cl
c; R^1 = CH_2Ph, R^2 = $NHCOCH_2OPh$

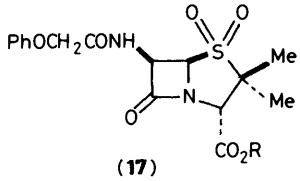


(**15**)



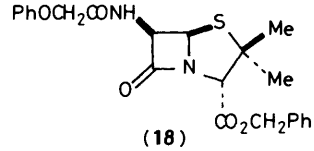
(**16**)

a; R = CH_2Ph
b; R = H



(**17**)

a; R = Me
b; R = CH_2Ph



(**18**)

When treated with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in dichloromethane followed by an acidic work-up, sulbactam benzyl ester (**2b**)[14] was converted into the sulphinic acid (**13a**) in 90% yield. This compound, after transformation into its sodium salt, reacted in acetone with chloroacetone and a trace of sodium iodide to give the sulphone (**14a**) (80% yield after SiO_2 chromatography) as a syrup. That the aforecited reaction had led to the sulphone (**14a**) rather than the sulphinate (**15**) was suggested by the spectroscopic properties of the product. Thus it showed a strong i.r. absorption at 1 330 cm^{-1}, attributed to the symmetrical stretch of a sulphone group.[15] Moreover, ^1H n.m.r. spectroscopy established that the material, which incorporated an AB quartet (*J* 14 Hz) centred at δ 3.80 for the methylene protons of the acetonyl group, was a single entity [a diastereoisomeric mixture would have been expected for the sulphinate (**15**)]. Finally, the rapid deuterium exchange of the methylene protons of the acetonyl group, which occurred when deuterium oxide was added to a deuteriochloroform solution of the sample, left little doubt that the sulphone formulation (**14a**) was the correct one.

Ozonolysis of the butenoate (**14a**) in dichloromethane at −78 °C provided the oxamide (**12a**) as a slightly impure foam. The i.r. spectrum of the latter compound featured a strong absorption at 1 830 cm^{-1}, characteristic of a β-lactam moiety bearing an *N*-acyl function.[16] When heated in toluene with trimethyl phosphite at *ca.* 90 °C, the oxamide (**12a**) was transformed into the cephem dioxide (**3b**) [84% yield after SiO_2 chromatography based on (**14a**)] isolated as a crystalline solid. The structure of the cephem dioxide (**3b**) followed from its elemental composition and its spectroscopic properties. In particular, the material showed a strong i.r. absorption at 1 795 cm^{-1} for the β-lactam moiety, a u.v. absorption at 260 nm (ε 10 300) for the cephalosporanate chromophore,[17] and ^1H n.m.r. absorptions at δ 3.66 and 3.86 (each 1 H, d, *J* 18 Hz) for the hydrogen atoms of the 2-methylene group.

Careful hydrogenolysis of the benzyl ester (**3b**) over 10% palladium-carbon in ethyl acetate provided the acid (**3c**) (30% yield after recrystallisation). This compound, which gradually decomposed at ambient temperature, was transformed into the sodium salt (**3a**) by the action of either sodium hydrogen carbonate in aqueous ethanol or sodium 2-ethylhexanoate in diethyl ether. The salt (**3a**) was characterised by its spectroscopic properties. It featured a strong i.r. absorption at 1 770 cm^{-1} for the β-lactam moiety, a u.v. absorption at 248 nm (ε 7 800) for the cephalosporanate chromophore, and ^1H n.m.r. absorptions at δ 3.89 and 4.21 (each 1 H, d, *J* 18 Hz) (which disappeared when $NaHCO_3$ was added to a D_2O solution of the sample) for the hydrogen atoms of the 2-methylene group.

The salt (**3a**), which was unchanged according to ^1H n.m.r. spectroscopy when left in deuterium oxide over a period of 24 h, did not act as an ampicillin synergist against β-lactamase-

producing bacteria. It also failed to inhibit the growth of a range of Gram-positive and Gram-negative bacteria.

The aforecited synthesis of the cephem dioxide (**3b**) is of interest in two respects. First, the sequence provides a novel process for the transformation of 1,1-dioxides of penicillanates into 1,1-dioxides of 3-methylceph-3-em-4-carboxylates. Secondly, the demonstration that the (**12a**) → (**3b**) transformation can be induced by trimethyl phosphite is noteworthy in that a six-membered ring is constructed in the reductive coupling reaction. Previously, trialkyl phosphites have been shown to be useful reagents for effecting related reductive coupling reactions leading to penems and carbapenems.[10-12]

It was of interest to examine whether the aforementioned process was applicable to 6-substituted penicillanate 1,1-dioxides. Thus the syrupy chloropenicillanate (**16a**), prepared (69% yield after SiO_2 chromatography) by treating the acid (**16b**)[18] with sodium hydrogen carbonate followed by benzyl bromide. reacted with potassium permanganate in aqueous acetic acid to give the crystalline dioxide (**2c**) (43% yield after SiO_2 chromatography). Treatment of the latter compound with DBN followed by an acidic work-up provided the sulphinic acid (**13b**) (48% yield) as a crystalline solid. The acid (**13b**), after transformation into its sodium salt, reacted in acetone with chloroacetone and a trace of sodium iodide to afford the syrupy sulphone (**14b**) (66% yield after SiO_2 chromatography). The ^1H n.m.r. spectrum of compound (**14b**) featured an AB quartet (J 15 Hz) centred at δ 3.97 for the methylene hydrogen atoms of the acetonyl group.

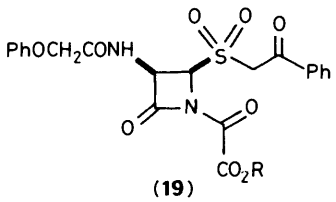
Ozonolysis of the butenoate (**14b**) provided the oxamide (**12b**), showing a strong i.r. absorption at 1 830 cm^{-1}, which reacted with trimethyl phosphite in hot toluene to yield the cephem dioxide (**3d**) (21% yield after SiO_2 chromatography). As well as being analytically characterised, the latter compound showed a strong i.r. absorption at 1 790 cm^{-1} for the β-lactam moiety, a u.v. absorption at 265 nm (ε 11 000) for the cephalosporanate chromophore, and ^1H n.m.r. absorptions at δ 3.70 and 3.90 (each 1 H, d, J 18 Hz) for the hydrogen atoms of the 2-methylene group.

The possibility of preparing the phenoxyacetamidocephem dioxide (**3e**) was next investigated. In earlier work, we had shown that the sulphone (**17a**) reacted with DBN to give, after an acidic work-up, the azetidinone (**13c**) in which the phenoxyacetamido moiety had undergone epimerisation.[13] Consequently, it was envisaged that the sulphone (**3e**) would be accessible from the penicillanate 1,1-dioxide (**17b**) by way of the sulphinic acid (**13d**).

Oxidation of the benzyl phenoxyacetamidopenicillanate (**18**)[19] with potassium permanganate in aqueous acetic acid provided the crystalline sulphone (**17b**) (78% yield) which was transformed into the syrupy sulphinic acid (**13d**) (*ca.* 81% yield) by the action of DBN followed by an acidic work-up. The acid (**13d**), after transformation into its sodium salt, reacted with chloroacetone to afford the acetonyl derivative (**14c**) (38% yield after SiO_2 chromatography) as a foam. The acetonyl methylene hydrogen atoms of compound (**14c**) appeared as two one-proton doublets (J 15 Hz) at δ 3.98 and *ca.* 4.35.

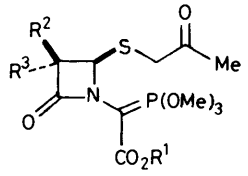
Although ozonolysis of the butenoate (**14c**) proceeded in the desired manner to give the oxamide (**12c**), characterised by the presence of a strong β-lactam carbonyl absorption at 1 830 cm^{-1}, the reductive coupling conditions [$P(OMe)_3$ in PhMe at *ca.* 90 °C] led to non-β-lactam products. Evidently, the *trans*-orientated phenoxyacetamido group had caused the oxamide (**12c**) and/or the cephem dioxide (**3e**) to undergo other reactions.

To determine whether the geometry of the phenoxyacetamido group was influential on the reaction outcome, an oxamide of type (**19**) was sought. Thus oxidation of the cephem (**9b**) with



(**19**)

a; $R^1 = CHPh_2$



(**20**)

a; $R^1 = CH_2Ph$, $R^2 = R^3 = H$
b; $R^1 = CH_2Ph$, $R^2 = H$, $R^3 = Cl$
c; $R^1 = CHPh_2$, $R^2 = NHCOCH_2OPh$, $R^3 = H$
d; $R^1 = CH_2Ph$, $R^2 = H$, $R^3 = NHCOCH_2OPh$

hydrogen peroxide–formic acid[8] provided the cephem dioxide (**8b**) (93% yield) as a crystalline solid. Ozonolysis of the latter compound gave the oxamide (**19a**), which featured a strong i.r. absorption at 1 830 cm^{-1}. Although isolated as a slightly impure syrup, the oxamide (**19a**) was free of the cephem dioxide (**8b**) according to t.l.c. and ^1H n.m.r. spectroscopy. It reacted with trimethyl phosphite in toluene at *ca.* 90 °C to give compound (**8b**) (30% yield after SiO_2 chromatography). Evidently, the reductive coupling reaction can tolerate a phenoxyacetamido function when it is *cis*-orientated.

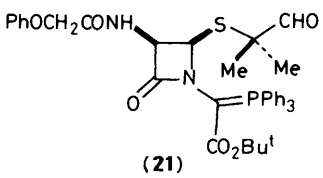
In summary, trimethyl phosphite is capable of effecting the reductive coupling of compounds (**12a,b**) and (**19a**) to the corresponding cephem dioxides (**3b,d**) and (**8b**). On the basis of previous proposals,[10-12] we infer that the products arise by intramolecular Wittig reactions of the species (**20a—c**). Analogous phosphoranes, *e.g.* (**21**), are well-established precursors of cephems, *e.g.* (**22**).[20]

The failure to isolate the cephem (**3e**) from the reaction of compound (**12c**) with trimethyl phosphite is of note. Previously, we reported that thermolysis of the phosphorane (**23a**) led to the thiazole (**24**) and probably the oxazolinone (**25**)[21] whereas the penem (**26b**) was isolated from the corresponding reaction of the phosphorane (**23b**).[22] We suggested that the penem (**26a**) was formed but that it was converted into the products (**24**) and (**25**) under the conditions of the reaction. Possibly, therefore, the species (**20d**) gives rise to the cephem (**3e**) which is converted into non-β-lactam products under the thermolysis conditions.

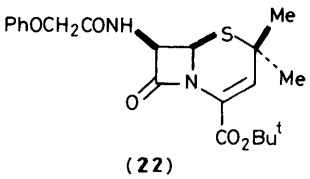
Experimental

Dry solvents, referred to in the ensuing experiments, were prepared as follows: dichloromethane was distilled from calcium chloride: DMF was stored over 4 Å molecular sieves. Light petroleum refers to that fraction boiling in the range 40—60 °C. 300 MHz ^1H N.m.r. spectra were measured on a Bruker WM-300 WB spectrometer. Ozone was generated with a Wallace and Tieman ozonator operating at 150 V and a flow rate of 50 $dm^3\ h^{-1}$. For chromatographic and other instrumental details, see Part 20.[23]

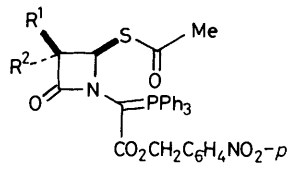
Preparation of (2R)-1-(1-*Benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-*oxoazetidine*-2-*sulphinic Acid* (**13a**) *and its Sodium*



(21)



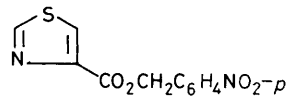
(22)



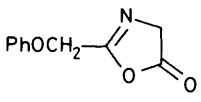
(23)

a; R^1 = H, R^2 = $NHCOCH_2OPh$

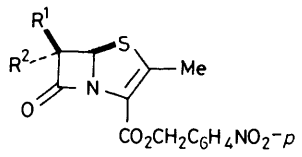
b; R^1 = $NHCOCH_2OPh$, R^2 = H



(24)



(25)



(26)

a; R^1 = H, R^2 = $NHCOCH_2OPh$

b; R^1 = $NHCOCH_2OPh$, R^2 = H

Salt.—A 30% solution of DBN in dichloromethane was added in drops to a stirred solution of the penam dioxide (**2b**)[14] (3.66 g, 11.3 mmol) in dry dichloromethane (20 cm^3) until the reaction was complete (t.l.c.). The mixture was then diluted with dichloromethane, washed with dilute hydrochloric acid, and extracted with aqueous sodium hydrogen carbonate. Acidification of the aqueous extract with dilute hydrochloric acid was followed by its extraction with dichloromethane. Evaporation of the dried ($MgSO_4$) organic layer left the *title acid* (**13a**) (3.29 g, 90% yield) as a pale-yellow syrup with the following properties: $[\alpha]_D$ −13° (1% in $CHCl_3$); $\nu_{max.}$(film) *inter alia* 1 775 (β-lactam C=O), 1 720 (unsaturated ester C=O), and 1 635 cm^{-1} (C=C); $\lambda_{max.}$(EtOH) 212 (ε 15 000) and 225sh nm (10 600); δ (60 MHz, $CDCl_3$) 1.99 and 2.18 (each 3 H, s, together CMe_2), 3.15 br (2 H, d, separation 3 Hz, $COCH_2CH$), 4.64 (1 H, t, separation 3 Hz, CH_2CH), 5.20 (2 H, s, OCH_2Ph), 7.30 (5 H, s, Ph), and 8.9 br (1 H, s, SO_2H) (addition of D_2O caused the signal at δ 8.9 to disappear); *m/z* (e.i.) *inter alia* 258 ($M^+ - HO_2S$) and 91 ($C_7H_7^+$, base peak).

A solution of the freshly prepared sulphinic acid (**13a**) (3.00 g, 9.3 mmol) in acetone (25 cm^3) was treated with a solution of sodium hydrogen carbonate (0.781 g, 9.3 mmol) in water (25 cm^3). Evaporation, addition of ethanol to the residue, and re-evaporation (repeated 2 ×) left the sodium salt of the acid (**13a**) which, after drying (*in vacuo*, $CaCl_2$), was obtained as a white powder [3.19 g, 87% yield based upon (**2b**)] with the following properties: δ (60 MHz, D_2O) 1.85 and 2.00 (each 3 H, s, together CMe_2), 2.95 (2 H, d, separation 4 Hz, $COCH_2CH$), 3.92 (1 H, t, separation 4 Hz, CH_2CH), 5.00 (2 H, s, $PhCH_2O$), and 7.15 (5 H, s, Ph).

Preparation of Benzyl 2-[(2*R*)-2-*Acetonylsulphonyl*-4-*oxoazetidin*-1-*yl*]-3-*methylbut*-2-*enoate* (**14a**).—90% Chloroacetone (0.088 cm^3, 0.995 mmol) and a trace of sodium iodide were added to a stirred solution of the sodium salt of compound (**13a**) (0.253 g, 0.732 mmol) in acetone (10 cm^3). After 19 h, the mixture was diluted with ethyl acetate and washed sequentially with aqueous sodium thiosulphate, brine, and water. Evaporation of the dried ($MgSO_4$) organic layer and purification of the resultant syrup by silica-gel column chromatography (light petroleum–EtOAc, gradient elution) gave the *title compound* (**14a**) (0.223 g, 80% yield) as a chromatographically homogeneous syrup with the following properties: $[\alpha]_D$ −53° (0.6% in $CHCl_3$); $\nu_{max.}$(film) *inter alia* 1 780 (β-lactam C=O), 1 720 (ketone and unsaturated ester C=O), 1 630 (C=C), and 1 330 cm^{-1} (symmetric SO_2); $\lambda_{max.}$ (EtOH) 217 (ε 9 800) and 228sh nm (9 000); δ (60 MHz, $CDCl_3$) 2.02, 2.21, and 2.28 (each 3 H, s, together CMe_2 and COMe), 3.10—3.30 (2 H, m, $COCH_2CH$), 3.80 (2 H, centre of ABq, *J* 14 Hz, separation of inner lines 8 Hz, SO_2CH_2CO), 5.05—5.15 (3 H, m, OCH_2Ph and CH_2CHSO_2), and 7.21 (5 H, s, Ph) (addition of D_2O caused the AB q centred at δ 3.80 to disappear over 12 h); *m/z* (c.i.) *inter alia* 379 (M^+) and 91 ($C_7H_7^+$, base peak) (Found: M^+, 379.1107. $C_{18}H_{21}NO_6S$ requires *M*, 379.1090).

Preparation of (6R)-4-*Benzyloxycarbonyl*-3-*methylceph*-3-*em* 1,1-*Dioxide* (**3b**).—A cooled (Me_2CO–solid CO_2) solution of the butenoate (**14a**) (0.171 g, 0.451 mmol) in dry dichloromethane (20 cm^3) was saturated with ozone. The solution was then aerated to remove excess of ozone and, after warming to room temperature, concentrated to leave benzyl 2-[(2*R*)-2-acetonylsulphonyl-4-oxoazetidin-1-yl]glyoxylate (**12a**) as a slightly impure foam with the following properties: $[\alpha]_D$ −78° (1.3% in EtOH); $\nu_{max.}$(film) *inter alia* 1 830 (β-lactam C=O), 1 750 (ester C=O), and 1 715 cm^{-1} (imide and ketone C=O); $\lambda_{max.}$(EtOH) 218 (ε 8 700), 257 (2 800), 263 (2 700), and 268 nm (2 800); δ (60 MHz, $CDCl_3$) *inter alia* 2.25 (3 H, s, COMe), 3.48 (2 H, d, separation 5 Hz, $COCH_2CH$), 4.33 (2 H, centre of AB q, *J* 15 Hz, separation of inner lines 3 Hz, SO_2CH_2CO), 5.21 (2 H, s, OCH_2Ph), 5.52 (1 H, t, separation 5 Hz, CH_2CHSO_2), and 7.20 (5 H, s, Ph); *m/z* (e.i.) *inter alia* 325 ($M^+ - CO$), 289 ($M^+ - O_2S$), and 91 ($C_7H_7^+$, base peak). The oxamide (**12a**) decomposed when subjected to silica-gel chromatography.

A solution of the oxamide (**12a**) [derived from the butenoate (**14a**) (0.417 g, 1.1 mmol)] in toluene (20 cm^3) containing trimethyl phosphite (0.28 cm^3, 2.29 mmol) was heated at *ca.* 90 °C for 2.5 h. The mixture was then diluted with dichloromethane and washed with water. Evaporation of the dried ($MgSO_4$) organic layer and purification of the residue by silica-gel column chromatography (light petroleum–EtOAc, gradient elution) gave the *title compound* (**3b**) (0.296 g, 84% yield). The sample, after recrystallisation from dichloromethane–light petroleum, showed the following properties: m.p. 113—115 °C; $[\alpha]_D$ −11° (1% in EtOH); $\nu_{max.}$(KBr) *inter alia* 1 795 (β-lactam C=O), 1 720 (ester C=O), and 1 635 cm^{-1} (C=C); $\lambda_{max.}$(EtOH) 214 (ε 8 700) and 260 nm (10 300); δ (300 MHz, $CDCl_3$) 2.07 (3 H, s, 3-Me), 3.47 (1 H, dd, *J* 16 and 5 Hz, 7α-H), 3.57 (1 H, dd, *J* 16 and 2 Hz, 7β-H), 3.66 and 3.86 (each 1 H, d, *J* 18 Hz, together 2-H_2), 4.69—4.72 (1 H, m, 6-H), 5.28 (2 H, centre of AB q, *J* 12 Hz, separation of inner lines 5 Hz, OCH_2Ph), and 7.35—7.41 (5 H, m, Ph); *m/z* (e.i.) 321 (M^+) and 91 ($C_7H_7^+$, base peak) (Found: C, 56.3; H, 4.6; N, 4.3%; M^+, 321.0664. $C_{15}H_{15}NO_5S$ requires C, 56.05; H, 4.70; N, 4.35%; *M*, 321.0671).

Preparation of 4-*Carboxy*-3-*methylceph*-3-*em* 1,1-*Dioxide* (**3c**).—A stirred solution of the benzyl ester (**3b**) (0.050 g, 0.156 mmol) in ethyl acetate (10 cm^3) containing 10% palladium–carbon (0.10 g, 2 mass equiv.) was saturated with hydrogen. When the reaction was complete (t.l.c.), the mixture was filtered through 'Hyflo' and the filtrate concentrated. Recrystallisation of the resultant solid from acetone–light petroleum afforded the

title compound (**3c**) (0.011 g, 30% yield) with the following properties: m.p. 141—144 °C; $[\alpha]_D$ +78° (0.9% in EtOH); $\nu_{max.}$(KBr) *inter alia* 3 430br (OH), 1 750 (β-lactam C=O), 1 715 (unsaturated acid C=O), and 1 655 cm^{-1} (C=C); $\lambda_{max.}$(EtOH) 212 (ε 3 300) and 256 nm (7 850); δ (300 MHz, CD_3COCD_3) 3.31 (3 H, s, 3-Me), 3.37 (1 H, dd, *J* 16 and 2.5 Hz, 7β-H), 3.45 (1 H, dd, *J* 16 and 5 Hz, 7α-H), 3.58 and 4.15 (each 1 H, d, *J* 17 Hz, together 2-H_2), 5.01—5.03 (1 H, m, 6-H), and 6.5br (1 H, s, CO_2H); *m/z* (e.i.) *inter alia* 187 ($M^+ - CO_2$) (Found: $M^+ - CO_2$, 187.0322. $C_7H_9NO_3S$ requires *M*, 187.0303). The sample was unstable at ambient temperature.

Preparation and Deuterium Exchange of the Sodium Salt of 4-*Carboxy*-3-*methylceph*-3-*em* 1,1-*Dioxide* (**3a**).—(*a*) A solution of the freshly prepared acid (**3c**) (0.026 g, 0.112 mmol) in ethanol (1 cm^3) was stirred with a solution of sodium hydrogen carbonate (0.009 g, 0.107 mmol) in water (1 cm^3) for 10 min. Evaporation left a crystalline solid which was dried (*in vacuo*, $CaCl_2$). The resultant title salt (**3a**) possessed the following properties: m.p. 147—150 °C (decomp.); $[\alpha]_D$ +30° (0.2% in EtOH); $\nu_{max.}$(KBr) *inter alia* 1 770 (β-lactam) C=O) and 1 610 cm^{-1} (carboxylate C=O); $\lambda_{max.}$(EtOH) 212 (ε 4 100) and 248 nm (7 800); δ (300 MHz, D_2O) 1.88 (3 H, s, 3-Me), 3.52 (1 H, dd, *J* 16 and 2 Hz, 7β-H), 3.58 (1 H, dd, *J* 16 and 5 Hz, 7α-H), 3.89 and 4.21 (each 1 H, d, *J* 18 Hz, together 2-H_2), and 5.18—5.20 (1 H, m, 6-H). The ^{1}H n.m.r. spectrum was unchanged over a period of 24 h.

(*b*) A solution of sodium 2-ethylhexanoate in a mixture of butan-1-ol and diethyl ether was added in drops to a solution of the acid (**3c**) (0.020 g, 0.087 mmol) in acetone (1 cm^3) until no further precipitation occurred. The resultant white solid (0.012 g, 55% yield), which was collected by centrifugation and dried (*in vacuo*, $CaCl_2$), was identical (^{1}H n.m.r. spectroscopy) with the salt (**3a**).

(*c*) When a small quantity of sodium hydrogen carbonate was added to a solution of the salt (**3a**) in deuterium oxide, the one-proton doublets at δ 3.89 and 4.21 disappeared; the remainder of the spectrum was unaltered.

Preparation of Benzyl (3S,5R,6S)-6-*Chloropenicillanate* (**16a**).—A solution of sodium hydrogen carbonate (2.87 g, 34.2 mmol) in water (80 cm^3) was added to a stirred solution of the acid (**16b**)[18] (7.99 g, 34.2 mmol) in ethanol (80 cm^3). After 0.5 h, the solvent was evaporated (with several additions of EtOH) and the residue was dried (*in vacuo*, $CaCl_2$). The material was stirred with dry DMF (80 cm^3) and benzyl bromide (4.1 cm^3, 34.4 mmol) was added. The mixture was stirred overnight and then partitioned between ethyl acetate and water. After being washed with water (2 ×), the organic phase was dried ($MgSO_4$) and concentrated. Purification of the residue by silica-gel column chromatography [light petroleum—EtOAc (9:1) as eluant] gave the *title compound* (**16a**) (7.68 g, 69% yield) as a chromatographically homogeneous syrup with the following properties: $[\alpha]_D$ +163° (0.4% in EtOH); $\nu_{max.}$(film) *inter alia* 1 790 (β-lactam C=O) and 1 750 cm^{-1} (ester C=O); $\lambda_{max.}$(EtOH) 210 (ε 14 800), 251 (870), 257 (760), 263 (540), and 268 nm (435); δ (60 MHz, $CDCl_3$) 1.39 and 1.55 (each 3 H, s, together 2-Me_2), 4.54 (1 H, s, 3-H), 4.72 and 5.30 (each 1 H, d, *J* 2 Hz, together 5- and 6-H), 5.15 (2 H, s, OCH_2Ph), and 7.30 (5 H, s, Ph); *m/z* (e.i.) *inter alia* 327 and 325 (together M^+), 250, and 91 ($C_7H_7^+$, base peak) (Found: M^+, 325.0584. $C_{15}H_{16}{}^{35}ClNO_3S$ requires *M*, 325.0540).

Preparation of Benzyl (3S,5R,6S)-6-*Chloropenicillanate* 1,1-*Dioxide* (**2c**).—Potassium permanganate (13.2 g, 83.3 mmol) in water (120 cm^3) was added in drops over 2.5 h to a stirred ice-cooled solution of the penicillanate (**16a**) (10.5 g, 32.2 mmol) in acetic acid–water (4:1; 600 cm^3). After a further 1 h, the purple colour was discharged by the addition of 10% aqueous hydrogen peroxide and the mixture was extracted with dichloromethane. The organic layer was washed with water and aqueous sodium hydrogen carbonate before being dried ($MgSO_4$) and concentrated. Purification of the residue by silica-gel chromatography (light petroleum–EtOAc, gradient elution) gave the *title compound* (**2c**) (5.00 g, 43% yield). The sample, after recrystallisation from dichloromethane–diethyl ether, possessed the following properties: m.p. 81—84 °C; $[\alpha]_D$ +156° (0.6% in EtOH); $\nu_{max.}$(KBr) *inter alia* 1 810 (β-lactam C=O), 1 770sh and 1 760 cm^{-1} (together ester C=O); $\lambda_{max.}$(EtOH) 210 (ε 9 800), 250 (660), 257 (530), 262 (400), and 268 nm (270); δ (60 MHz, $CDCl_3$) 1.26 and 1.52 (each 3 H, s, together 2-Me_2), 4.45 (1 H, s, 3-H), 4.65 and 5.15 (each 1 H, d, *J* 2 Hz, together 5- and 6-H), 5.20 (2 H, centre of AB q, *J* 12 Hz, separation of inner lines 2 Hz, OCH_2Ph), and 7.32 (5 H, s, Ph); *m/z* (e.i.) *inter alia* 190 and 91 ($C_7H_7^+$, base peak) (Found: C, 50.4; H, 4.5; N, 3.9. $C_{15}H_{16}ClNO_5S$ requires C, 50.35; H, 4.50; N, 3.90%).

Preparation of Benzyl 2-[(3S,4R)-3-*Chloro*-2-*oxo*-4-*sulphinoazetidin*-1-*yl*]-2-*methylbut*-2-*enoate* (**13b**).—A 30% solution of DBN in deuteriochloroform was added in drops to a solution of the penam dioxide (**2c**) (1.27 g, 3.55 mmol) in deuteriochloroform (5 cm^3) until the reaction was complete (^{1}H n.m.r. spectroscopy). The mixture was then diluted with dichloromethane and washed with dilute hydrochloric acid. The water layer, obtained on extracting the mixture with aqueous sodium hydrogen carbonate, was acidified with dilute hydrochloric acid and re-extracted with ethyl acetate. Evaporation of the dried ($MgSO_4$) organic phase left the *title compound* (**13b**) (0.610 g, 48% yield) as a crystalline solid. The sample, after recrystallisation from dichloromethane–diethyl ether, possessed the following properties: m.p. 97—101 °C; $[\alpha]_D$ −19° (0.6% in EtOH); $\nu_{max.}$(KBr) *inter alia* 1 790 (β-lactam C=O), 1 730 (ester C=O), and 1 640 cm^{-1} (C=C); $\lambda_{max.}$(EtOH) 212 (ε 19 100) and 223sh nm (15 500); δ (60 MHz, $CDCl_3$) 1.99 and 2.22 (each 3 H, s, together CMe_2), 4.75 and 4.98 (each 1 H, d, *J* 2 Hz, together 2 × β-lactam-H), 5.22 (2 H, s, OCH_2Ph), and 7.33 (5 H, s, Ph); *m/z* (e.i.) *inter alia* 294 and 292 (together $M^+ - HO_2S$) and 91 ($C_7H_7^+$, base peak) (Found: C, 49.9; H, 4.3; N, 3.8. $C_{15}H_{16}ClNO_5S$ requires C, 50.35; H, 4.50; N, 3.90%).

Preparation of Benzyl 2-[(2R,3S)-2-*Acetonylsulphonyl*-3-*chloro*-4-*oxoazetidin*-1-*yl*]-2-*methylbut*-2-*enoate* (**14b**).—The sulphinic acid (**13b**) (0.231 g, 0.646 mmol) was added to a stirred solution of sodium hydrogen carbonate (0.054 g, 0.646 mmol) in water (10 cm^3). After 0.5 h, the solvent was evaporated (with frequent additions of EtOH) and the residue was dried (*in vacuo*, $CaCl_2$). The material was stirred in acetone (10 cm^3) with 90% chloroacetone (0.08 cm^3, 0.9 mmol) and a trace of sodium iodide for 24 h. The mixture was then diluted with ethyl acetate and washed sequentially with aqueous sodium thiosulphate, brine, and water. Evaporation of the dried ($MgSO_4$) organic layer and purification of the residue by silica-gel column chromatography (light petroleum–EtOAc, gradient elution) gave the *title compound* (**14b**) (0.176 g, 66% yield), as a chromatographically homogeneous syrup with the following properties: $[\alpha]_D$ −53° (0.4% in EtOH); $\nu_{max.}$(film) *inter alia* 1 800 (β-lactam C=O), 1 725 (ester C=O), and 1 630 cm^{-1} (C=C); $\lambda_{max.}$(EtOH) 209 (ε 9 000) and 222sh nm (5 800); δ (60 MHz, $CDCl_3$) 2.11, 2.35, and 2.39 (each 3 H, s, together 2-Me_2 and COMe), 3.97 (2 H, d, centre of AB q, *J* 15 Hz, separation of inner lines 7 Hz, SO_2CH_2CO), 5.16 (1 H, d, *J* 2 Hz, 5- or 6-H), 5.3 br (3 H, s, 6- or 5-H and OCH_2Ph), and 7.44 (5 H, s, Ph); *m/z* (e.i.) *inter alia* 310 and 308 (together $M^+ - C_3H_5O_2S$), 294 and 292 (together $M^+ - C_3H_5O_3S$), and 91 ($C_7H_7^+$, base peak).

Preparation of (6R,7S)-4-*Benzyloxycarbonyl*-7-*chloro*-3-*methylceph*-3-*em* 1,1-*Dioxide* (**3d**).—A cooled (Me_2CO–solid CO_2) solution of the butenoate (**14b**) (0.320 g, 0.773 mmol) in dry dichloromethane (60 cm^3) was saturated with ozone. After removal of excess of ozone, the mixture was concentrated to leave benzyl 2-[(3*S*,2*R*)-2-acetonylsulphonyl-3-chloro-4-oxoazetidin-1-yl]glyoxylate (**12b**) as an impure syrup with the following properties: $\nu_{max.}$(film) *inter alia* 1 830 (β-lactam C=O), 1 760sh (imide and ester C=O), and 1 720 cm^{-1} (ketone C=O); δ (60 MHz, $CDCl_3$) *inter alia* 2.25 (3 H, s, COMe), 4.4br (2 H, s, SO_2CH_2CO), 5.21—5.37 (3 H, m, OCH_2Ph and β-lactam-H), 5.69 (1 H, d, *J* 2 Hz, β-lactam-H), and 7.31 (5 H, s, Ph).

A solution of the crude oxamide (**12b**) [derived from the butenoate (**14b**) (0.166 g, 0.40 mmol)] in toluene (10 cm^3) was heated at *ca.* 90 °C with trimethyl phosphite (0.10 cm^3, 0.85 mmol) for 3 h. The mixture, after being washed with water, was concentrated and the residue purified by silica-gel column chromatography [light petroleum–EtOAc (4:1) as eluant] to yield the *title compound* (**3d**) (0.030 g, 21% yield) as a crystalline solid. The sample, after recrystallisation from dichloromethane–diethyl ether, possessed the following properties: m.p. 141—143 °C; $[\alpha]_D$ +21° (0.4% in EtOH); $\nu_{max.}$(KBr) *inter alia* 1 790 (β-lactam C=O), 1 720 (unsaturated ester C=O), and 1 630 cm^{-1} (C=C); $\lambda_{max.}$(EtOH) 208 (ε 15 400) and 265 nm (11 000); δ (300 MHz, $CDCl_3$) 2.10 (3 H, s, 3-Me), 3.70 and 3.90 (each 1 H, d, *J* 18 Hz, together 2-H_2), 4.7 br and 5.29br (each 1 H, s, together 5- and 6-H), 5.31 (2 H, centre of AB q, *J* 12 Hz, separation of inner lines 16 Hz, OCH_2Ph), 5.31 (2 H, centre of AB q, *J* 12 Hz, separation of inner lines 16 Hz, OCH_2Ph), and 7.35—7.42 (5 H, m, Ph); *m/z* (e.i.) *inter alia* 357 and 355 (together M^+) and 91 ($C_7H_7^+$, base peak) (Found: C, 50.5; H, 3.9; N, 3.9. $C_{15}H_{14}ClNO_5S$ requires C, 50.60; H, 3.95; N, 3.95%).

Preparation of Benzyl (3S,5R,6R)-6-*Phenoxyacetamidopenicillanate* 1,1-*Dioxide* (**17b**).—Potassium permanganate (1.50 g, 9.49 mmol) in water (15 cm^3) was added in drops over 2.5 h to a stirred ice-cooled solution of the penicillanate (**18**)[19] (1.61 g, 3.65 mmol) dissolved in acetic acid–water (4:1; 65 cm^3). After a further 1 h, the purple colour was discharged by the addition of 10% aqueous hydrogen peroxide and the mixture was extracted with dichloromethane. The organic extract was washed with aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and concentrated to leave the *title compound* (**17b**) (1.35 g, 78% yield). After recrystallisation from dichloromethane–light petroleum, the sample displayed the following properties: m.p. 126—127 °C; $[\alpha]_D$ +66° [0.9% in EtOH–$CHCl_3$ (3:1)]; $\nu_{max.}$(KBr) *inter alia* 3 420 (NH), 1 820 (β-lactam C=O), 1 760 (ester C=O), and 1 690 cm^{-1} (amide C=O); $\lambda_{max.}$ (0.2% $CHCl_3$ in EtOH) 262 (ε 1 500), 268 (1 900), and 275 nm (1 600); δ (60 MHz, $CDCl_3$) 1.23 and 1.52 (each 3 H, s, together 2-Me_2), 4.43 (2 H, s, $PhOCH_2$), 4.64 (1 H, d, *J* 5 Hz, 5-H), 5.10 (2 H, centre of ABq, *J* 12 Hz, separation of inner lines 2 Hz, OCH_2Ph), 5.99 (1 H, dd, *J* 10 and 5 Hz, 6-H), 6.62—7.15 (10 H, m, 2 × Ph), and 7.9br (1 H, d, *J* 10 Hz, CONH); *m/z inter alia* 316, 302, 247, 233, 219, and 91 ($C_7H_7^+$, base peak) (Found: C, 58.5; H, 5.1, N, 5.9. $C_{23}H_{24}N_2O_4S$ requires C, 58.45; H, 5.10; N, 5.95%).

Preparation of Benzyl 2-[(3S,4R)-2-*Oxo*-3-*phenoxyacetamido*-4-*sulphinoazetidin*-1-*yl*]-2-*methylbut*-2-*enoate* (**13d**).—A 30% solution of DBN in deuteriochloroform was added in drops to a solution of the sulphone (**17b**) (1.29 g, 2.73 mmol) in deuteriochloroform (5 cm^3). When the reaction was complete (^1H n.m.r. spectroscopy), the mixture was diluted with dichloromethane and washed with dilute hydrochloric acid. The water layer, obtained on extracting the mixture with aqueous sodium hydrogen carbonate, was acidified with dilute hydrochloric acid and re-extracted with ethyl acetate. Evaporation of the dried ($MgSO_4$) organic phase left the title compound (**13d**) (1.04 g, *ca.* 81% yield) as a slightly impure syrup with the following properties: $\nu_{max.}$(film) *inter alia* 3 300br (OH), 1 775 (β-lactam C=O), 1 720sh (unsaturated ester C=O), and 1 695br cm^{-1} (amide C=O); δ (60 MHz, $CDCl_3$) *inter alia* 1.98 and 2.18 (each 3 H, s, together CMe_2), 4.38 (2 H, s, CH_2OPh), 4.61 (1 H, d, *J* 2 Hz, β-lactam-H), 5.04—5.15 (3 H, m, β-lactam-H and OCH_2Ph), 6.63—7.08 (10 H, m, 2 × Ph), 7.7br (1 H, s, SO_2H), and 7.8br (1 H, d, *J* 5 Hz, CONH); *m/z* (e.i.) 440 and 438 (together $M^+ - H_2O_2$), 424 and 422, and 331.

Preparation of Benzyl 2-[(2R,3R)-2-*Acetonylsulphonyl*-4-*oxo*-3-*phenoxyacetamidoazetidin*-1-*yl*]-2-*methylbut*-2-*enoate* (**14c**).—A solution of the sulphinic acid (**13d**) (0.122 g, 0.258 mmol) in ethanol (2 cm^3) was added to a stirred solution of sodium hydrogen carbonate (0.022 g, 0.261 mmol) in water (2 cm^3). After 0.5 h, the solvent was evaporated (with frequent addition of EtOH) and the residue dried (*in vacuo*, $CaCl_2$). The material was then stirred in acetone (5 cm^3) with 90% chloroacetone (0.04 cm^3, 0.45 mmol) and a trace of potassium iodide for 18 h. The mixture was diluted with ethyl acetate and washed sequentially with aqueous sodium thiosulphate, brine, and water. Evaporation of the dried ($MgSO_4$) organic layer and purification of the residue by silica-gel chromatography (light petroleum–EtOAc, gradient elution) gave the *title compound* (**14c**) (0.052 g, 38% yield) as a chromatographically homogeneous foam with the following properties: $[\alpha]_D$ +9° (0.8% in EtOH); $\nu_{max.}$(film) *inter alia* 3 400 (NH), 1 785 (β-lactam C=O), 1 720 (unsaturated ester C=O), and 1 690 cm^{-1} (ketone and amide C=O); δ (60 MHz, $CDCl_3$) 1.99, 2.15, and 2.18 (each 3-H, s, together CMe_2 and COMe), 3.98 (1 H, d, *J* 15 Hz, SO_2CHHCO), 4.29—4.52 (3 H, m, CH_2OPh and SO_2CHHCO), 5.02—5.32 (4 H, m, OCH_2Ph and 2 × β-lactam-H), 6.61—7.36 (10 H, m, 2 × Ph), and 7.7br (1 H, d, *J* 10 Hz, CONH); *m/z* (e.i.) *inter alia* 407 ($M^+ - C_3H_5O_3S$) and 91 ($C_7H_7^+$, base peak) (Found: $M^+ - C_3H_5O_3S$, 407.1630. $C_{23}H_{23}N_2O_5$ requires *M*, 407.1607).

Reaction of the Butenoate (**14c**) *with Ozone*.—A cooled (Me_2CO–solid CO_2) solution of the butenoate (**14c**) (0.090 g, 0.179 mmol) in dry dichloromethane (15 cm^3) was saturated with ozone. After aeration to remove excess of ozone, the mixture was treated with a few drops of dimethyl sulphide and then allowed to warm to room temperature. The mixture was washed with water, dried ($MgSO_4$), and concentrated to leave benzyl 2-[(2*R*,3*S*)-2-acetonylsulphonyl-4-oxo-3-phenoxyacetamidoazetidin-1-yl]glyoxylate (**12c**) (0.070 g) as a somewhat impure syrup with the following properties: $\nu_{max.}$(film) *inter alia* 1 830 cm^{-1} (β-lactam C=O); δ (60 MHz, $CDCl_3$) *inter alia* 2.23 (s, COMe), 4.34 (apparent d, separation 4 Hz, SO_2CH_2CO), 4.43 (s, $PhOCH_2$), 5.10 (dd, *J* 7 and 3 Hz, NHC*H*CH), 5.20 (s, OCH_2Ph), 5.76 (d, *J* 3 Hz, CHC*H*SO_2), and 6.70—7.20 (m, 2 × Ph), and 7.5br (d, *J* 7 Hz, CONH).

Preparation of (6R,7R)-4-*Diphenylmethoxycarbonyl*-3-*methyl*-7-*phenoxyacetamidoceph*-3-*em* 1,1-*Dioxide* (**8b**).—A mixture of 30% aqueous hydrogen peroxide (0.37 cm^3, 3.62 mmol) and formic acid (0.47 cm^3, 12.5 mmol) was added slowly to a stirred solution of the cephem (**9b**) (0.785 g, 1.53 mmol) in dichloromethane (25 cm^3). After 44 h, the mixture was washed successively with water, aqueous sodium hydrogen carbonate, and brine. Evaporation of the dried ($MgSO_4$) organic layer gave the *title compound* (**8b**) (0.776 g, 93% yield). The sample, after recrystallisation from dichloromethane–light petroleum, possessed the following properties: m.p. 184—187 °C; $[\alpha]_D$ −55° [0.4% in EtOH—$CHCl_3$ (1:1)]; $\nu_{max.}$(KBr) *inter alia* 3 420 (NH), 1 790 (β-lactam C=O), and 1 730, 1 720, 1 710, and 1 690 cm^{-1} (together ester and imide C=O); $\lambda_{max.}$ [EtOH—$CHCl_3$

(1:1)] 263 (ε 9 400), 268sh (9 200), and 275sh nm (7 000); δ (60 MHz, $CDCl_3$) 1.98 (3 H, s, 3-Me), 3.55—3.65 (2 H, m, 2-H_2), 4.39 (2 H, s, PhOCH_2), 4.15 (1 H, d, *J* 5 Hz, 6-H), 5.92 (1 H, dd, *J* 10 and 5 Hz, 7-H), 6.62—7.72 (16 H, m, Ph and $CHPh_2$), and 7.75br (1 H, d, *J* 10 Hz, CONH); *m/z inter alia* 167 ($C_{13}H_{11}^+$, base peak) (Found: C, 64.1; H, 4.7; N, 5.2. $C_{29}H_{26}N_2O_7S$ requires C, 63.70; H, 4.80; N, 5.15%).

Reaction of the Cephem Dioxide (**8b**) *with Ozone followed by Trimethyl phosphite.*—A cooled (Me_2CO–solid CO_2) solution of the cephem dioxide (**8b**) (0.100 g, 0.183 mmol) in dry dichloromethane (15 cm^3) was saturated with ozone. After aeration to remove excess of ozone, the mixture was treated with a few drops of dimethyl sulphide and then allowed to warm to room temperature. The mixture was washed with water before being dried ($MgSO_4$) and concentrated to leave diphenylmethyl 2-[(2*R*,3*R*)-2-acetonylsulphonyl-4-oxo-3-phenoxyacetamido-azetidin-1-yl]glyoxylate (**19a**) as a slightly impure syrup with the following properties: $\nu_{max.}$(film) *inter alia* 1 830 (β-lactam C=O), 1 750sh (ester C=O), and 1 710br cm^{-1} (imide, ketone, and amide C=O); δ (60 MHz, $CDCl_3$) *inter alia* 2.15 (3 H, s, COMe), 4.17 (2 H, d, separation 2 Hz, SO_2CH_2CO), 4.4br (2 H, s, CH_2OPh), 5.75 (1 H, d, *J* 5 Hz, β-lactam-H), 6.15 (1 H, dd, *J* 8 and 5 Hz, β-lactam-H), 6.70—7.40 (16 H, m, Ph and $CHPh_2$), and 7.75br (1 H, d, *J* 10 Hz, CONH); *m/z* (e.i.) *inter alia* 386, 358, and 167 ($C_{13}H_{11}^+$, base peak).

A solution of the crude oxamide (**19a**) [derived from the cephem dioxide (**8b**) (0.100 g, 0.183 mmol)] in toluene (10 cm^3) was heated at *ca.* 90 °C with trimethyl phosphite (0.04 cm^3, 0.366 mmol) for 3 h. After being washed with water, the mixture was concentrated and the residue purified by silica-gel column chromatography [light petroleum–EtOAc (1:1) as eluant] to give a crystalline solid (0.030 g, 30% yield) that was identical to the cephem dioxide (**8b**) (^{1}H n.m.r. spectroscopy). After recrystallisation from dichloromethane–light petroleum, the sample showed the following properties: m.p. 184—188 °C; $[\alpha]_D$ −50° [0.5% in EtOH–$CHCl_3$ (1:1)].

Acknowledgements

We thank the Association of Commonwealth Universities for a studentship (to G. D. S. A.), Messrs. P. Kelly and S. Addison for the mass spectral determinations, Mr. D. Dunbar for recording the i.r. spectra and for the elemental analyses, and Dr. M. N. S. Hill for the 300 MHz ^{1}H n.m.r. spectral measurements. Acknowledgements are also due to Pfizer Central Research for a gift of sulbactam sodium salt (**2a**) and for the biological evaluation of the cephem dioxide (**3a**) and to Glaxo Group Research for a gift of the cephem (**9b**).

References

1 Part 26, A. C. Kaura and R. J. Stoodley, *J. Chem. Soc., Perkin Trans. 1*, 1988, 2813.
2 Preliminary communication, G. D. S. Ananda and R. J. Stoodley, *Tetrahedron Lett.*, 1985, **26**, 497.
3 T. T. Haworth, A. G. Brown, and T. J. King, *J. Chem. Soc., Chem. Commun.*, 1976, 266.
4 A. R. English, J. A. Retsema, A. E. Girard, J. E. Lynch, and W. E. Barth, *Antimicrob. Agents Chemother.*, 1978, **14**, 414.
5 R. L. Charnas, J. Fischer, and J. R. Knowles, *Biochemistry*, 1978, **17**, 2185; R. L. Charnas and J. R. Knowles, *ibid.*, 1981, **20**, 3214; C. Reading and P. Hepburn, *Biochem. J.*, 1979, **179**, 67.
6 D. G. Brenner, J. R. Knowles, and G. Rihs, *Biochemistry*, 1981, **20**, 3680; C. Kemal and J. R. Knowles, *ibid.*, p. 3688.
7 D. O. Spry, *Tetrahedron Lett.*, 1973, 165; W. Dürckheimer, N. Klesel, M. Limbert, E. Schrinner, K. Seeger, and H. Seliger in 'Recent Advances in the Chemistry of β-Lactam Antibiotics,' ed. G. I. Gregory, Special Publication, No. 38, The Chemical Society, London, 1981, p. 46; J. Cs. Jászberényi, I. Petrikovics, E. T. Gunda, and S. Hosztafi, *Acta. Chim. Acad. Sci. Hung.*, 1982, **110**, 81.
8 R. G. Micetich, R. Singh, and S. N. Maiti, *Heterocycles*, 1984, **22**, 531.
9 R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Am. Chem. Soc.*, 1963, **85**, 1896; *ibid.*, 1969, **91**, 1401.
10 H. Afonso, F. Hon, J. Weinstein, A. K. Ganguly, and A. T. McPhail, *J. Am. Chem. Soc.*, 1982, **104**, 6138.
11 A. Yoshida, T. Hayashi, N. Takeda, S. Oida, and E. Ohki, *Chem. Pharm. Bull.*, 1983, **31**, 768; A. Yoshida, Y. Tajima, N. Takeda, and S. Oida, *Tetrahedron Lett.*, 1984, **25**, 2793.
12 C. Battistini, C. Scarafile, M. Foglio, and C. Franceschi, *Tetrahedron Lett.*, 1984, **25**, 2395; E. Perrone, M. Alpegiani, A. Bedeschi, F. Giudici, and G. Franceschi, *ibid.*, p. 2399.
13 C. M. Pant, J. Steele, and R. J. Stoodley, *J. Chem. Soc., Perkin Trans. 1*, 1982, 595.
14 P. H. Crackett, C. M. Pant, and R. J. Stoodley, *J. Chem. Soc., Perkin Trans. 1*, 1984, 2785.
15 A. D. Cross, 'An Introduction to Practical Infra-Red Spectroscopy,' Butterworths, London, 1964, 2nd Edn., p. 78.
16 R. D. G. Cooper and F. L. José, *J. Am. Chem. Soc.*, 1972, **94**, 1021.
17 P. V. Demarco and R. Nagarajan in 'Cephalosporins and Penicillins: Chemistry and Biology,' ed. E. H. Flynn, Academic Press, London, 1972, pp. 360—366.
18 G. Cignarella, G. Pifferi, and E. Testa, *J. Org. Chem.*, 1962, **27**, 2668; I. McMillan and R. J. Stoodley, *J. Chem. Soc. C*, 1968, 2533.
19 A. W. Chow, N. M. Hall, and J. R. E. Hoover, *J. Org. Chem.*, 1962, **27**, 1381.
20 R. Scartazzini, H. Peter, H. Bickel, K. Heusler, and R. B. Woodward, *Helv. Chim. Acta*, 1972, **55**, 408; R. Scartazzini and H. Bickel, *ibid.*, p. 423; D. Borman, *Liebigs Annal.*, 1974, 1391; J. H. C. Nayler, N. F. Osborne, M. J. Pearson, and R. Southgate, *J. Chem. Soc., Perkin Trans. 1*, 1976, 1615; I. Ernest, *Helv. Chim. Acta*, 1979, **62**, 2681 and 1980, **63**, 201; I. Ernest, A. J. Main, and R. B. Woodward, *ibid.*, 1981, **64**, 1303; D. Hagiwara, M. Aratani, K. Hemmi, and M. Hashimoto, *Tetrahedron*, 1981, **37**, 703.
21 J. R. Irving, E. Perrone, and R. J. Stoodley, *Tetrahedron Lett.*, 1983, **24**, 2501.
22 R. B. Woodward in 'Recent Advances in the Chemistry of β-Lactam Antibiotics,' ed. J. Elks, Special Publication No. 28, The Chemical Society, London, 1978, p. 167; I. Ernest, J. Gosteli, C. W. Greengrass, W. Holick, D. E. Jackman, H. R. Pfaendler, and R. B. Woodward, *J. Am. Chem. Soc.*, 1978, **100**, 8214.
23 R. Sharma and R. J. Stoodley, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2001.

Received 5th April 1988; *Paper* 8/01325J