C-2 and C-4 Reactions of Cephalosporanates and their (*S*)- and (*R*)-Oxides with Toluene-*p*-sulphonyl Azide, Acrylonitrile, and Ethyl Chloroformate [1]

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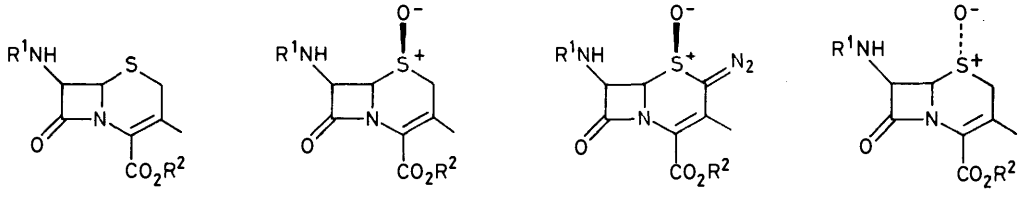
Comparative reactions of cephalosporanates and their (*S*)- and (*R*)-oxides were performed. Diazo-exchange leading to 2-diazoceph-3-ems was accomplished only with the (*S*)-oxide. The 2-diazoceph-3-ems reacted with halogens and pseudohalogens to give 2,2-disubstituted ceph-3-ems. Michael additions with acrylonitrile, were performed, the cephalosporanates giving mainly a 4β-(2-cyanoethyl)ceph-2-em. The (*S*)-oxides gave 2α-(2-cyanoethyl)ceph-3-em adducts, whereas the (*R*)-oxides gave the 4β-adducts. Ethyl chloroformate reacted in the presence of triethylamine only with the (*S*)-oxides, giving by a Pummerer rearrangement both 2α- and 2β-(ethyl carbonate)s.

SUBSTITUTION at C-2 and C-4 of the cephalosporanates is of considerable current interest. Aspects of these reactions including C-2 and C-4 alkylations have been reviewed.[2-4] More recent work relevant to the present studies includes the preparation of 2-, 4-, and 7-methylthio-derivatives from base-catalysed reactions of methanethiosulphonate and methanesulphenyl chloride.[5] Many related reactions have been described in recent patents.[6] New C-2 substitutions have also been reported by Spry,[7] in studies with 3-formylceph-2-ems. Functionalization at C-2 has also been achieved by addition of halogens and pseudohalogens across the double bond of ceph-2-ems, leading, for example, to 2,3-dibromocephems which could be converted into 2-methoxyceph-3-ems.[8] The importance of C-2 substitution of cephems is further illustrated by semi-syntheses of 2,2-dimethyl,[9] 2-alkylidene,[10,11] and 2-alkyl [11] analogues of the cephalosporanate antibiotics.

Base-catalysed reactions of cephalosporanates and their (*S*)- and (*R*)-oxides might be expected to afford products derived from anions at C-2, C-4, and C-7 (reactions at the C-3 methyl group are also theoretically possible). This paper describes exploratory studies of C-2 and C-4 anions derived from cephalosporanates (1) and (2), their (*S*)-oxides (3) and (4), and their (*R*)-oxides (7).

Diazo-exchange Reactions.—Activated methylene groups may be transformed into diazo-groups by base-catalysed diazo-exchange reactions.[12] Application of this reaction to the ceph-3-ems and their (*S*)- and (*R*)-oxides was therefore of interest because of the possibility of introducing a diazo-group at C-2 and its subsequent utilization [13,14] in a range of structural modifications. Precedent for the successful exploitation of diazo-groups at C-6 of the penams and C-7 of the cephems exists.[15]



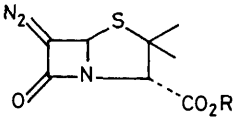
(1) $R^2 = CH_2CCl_3$ (2) $R^2 = Me$ (3) $R^2 = CH_2{\cdot}CCl_3$ (4) $R^2 = Me$ (5) $R^2 = CH_2{\cdot}CCl_3$ (6) $R^2 = Me$ (7) $R^2 = CH_2{\cdot}CCl_3$

$R' = PhO{\cdot}CH_2{\cdot}CO$

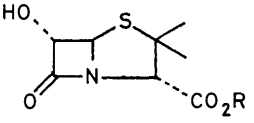
Attempts to effect a diazo-exchange reaction of trichloroethyl (1) or methyl cephalosporanate (2) with toluene-*p*-sulphonyl azide and triethylamine were complicated by the instability of the products. However, the trichloroethyl (*S*)-oxides (3) reacted readily and the 2-diazo-compound (5) was obtained in 70% yield as a yellow crystalline solid, following rapid, short-path pressurized chromatography. Similarly, the methyl cephalosporanate (4) was converted into (6) in 50%

[1] Preliminary communications, D. H. Bremner and M. M. Campbell, *J.C.S. Chem. Comm.*, 1976, 538; D. H. Bremner and M. M. Campbell, *Tetrahedron Letters*, 1976, 3205.
[2] A. K. Mukerjee and A. K. Singh, *Synthesis*, 1975, 547.
[3] R. J. Stoodley, *Tetrahedron*, 1975, **31**, 2321.
[4] P. G. Sammes, *Chem. Rev.*, 1976, **76**, 113.
[5] A. Yoshida, S. Oida, and E. Ohki, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 2507, 2518.
[6] See, for example, G.P. 2,337,445/1975; G.P. 2,453,601/1975; G.P. 2,455,358/1975; Jap. P. 75,108,284/1975.
[7] D. O. Spry, *J. Org. Chem.*, 1975, **40**, 2411.
[8] A. Balsamo, P. Crotti, B. Macchia, and F. Macchia, *J. Org. Chem.*, 1976, **41**, 2150.
[9] Swiss P. 556,875/1974.
[10] Swiss P. 561,727/1975.
[11] G.P. 2,461,932; G.P. 2,461,933/1975.
[12] M. Regitz, *Synthesis*, 1972, 351.
[13] H. Zollinger, 'Azo and Diazo Chemistry,' Interscience, New York, 1961.
[14] G. W. Cowell and A. Ledwith, *Quart. Rev.*, 1970, **24**, 119.
[15] (*a*) J. C. Sheehan, Y. S. Lo, J. Loliger, and C. C. Podewell, *J. Org. Chem.*, 1974, **39**, 1444; (*b*) D. Hauser and H. P. Sigg, *Helv. Chim. Acta*, 1967, **50**, 1327; (*c*) I. McMillan and R. J. Stoodley, *J. Chem. Soc.* (*C*), 1968, 2533; (*d*) J. P. Clayton, *ibid.*, 1969, 2123; (*e*) Y. S. Lo and J. C. Sheehan, *J. Amer. Chem. Soc.*, 1972, **94**, 8253; (*f*) L. D. Cama, W. J. Leanza, T. R. Beattie, and B. G. Christensen, *ibid.*, 1972, **94**, 1408; (*g*) D. M. Brunwin and G. Lowe, *J.C.S. Chem. Comm.*, 1972, 192.

yield although in this instance the product was not obtained analytically pure. The i.r. spectra of (5) and (6) showed the presence of β-lactam and diazo-groups. In the n.m.r. spectra the signals of the C-2 protons had disappeared, and those of H-6, H-7, and the C-3 methyl group were shifted to lower field. The u.v. spectra contained absorptions at 268 and 318 nm. No molecular ion appeared in the mass spectrum, but a peak at $M - 28$ corresponded to loss of nitrogen. The (*R*)-oxide (7) did not undergo diazo-exchange under similar reaction conditions, possibly because of steric inhibition of approach of the tosyl azide to the α-face.

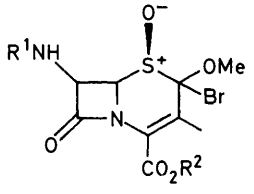


(8)

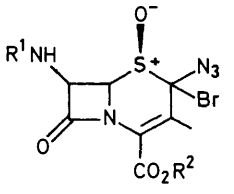


(9)

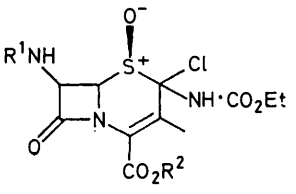
Exploratory reactions on the 2-diazo-(*S*)-1-oxide products afforded an insight into the reactivity of this diazo-absorption in the i.r. spectrum, and showed the ceph-3-em band at 269 nm in the u.v. spectrum. The n.m.r. spectrum contained a new methoxy-singlet, and the C-3 methyl signal was shifted upfield by 0.38 p.p.m. The spectroscopic data and elemental composition were in accord with a 2-bromo-3-methoxy-(*S*)-oxide structure (10). Similarly, compound (5) was transformed into (11). In each case, only one of the possible 2,2-disubstituted isomers was obtained, and if the mechanism involves initial addition of a positive bromine species followed by reaction with methanol from the less hindered α-face, 2β-bromo-2α-methoxy-stereochemistry can be envisaged. In the absence of the other isomers, or of an *X*-ray crystallographic structure determination, the stereochemistry at C-2 cannot be assigned. Bromine azide [17] also reacted with (6) giving only one of the 2-azido-2-bromo-isomers (12). Ethyl *N*-chlorocarbamate [18] also reacted with the 2-diazo-(*S*)-oxides, compound (5) for example giving the 2-ethoxyformamido-2-chloroceph-3-em (*S*)-oxide (13). Repeated chromatography failed to produce a pure sample of



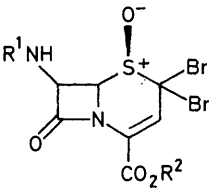
(10) R^2 = Me
(11) R^2 = $CH_2 \cdot CCl_3$



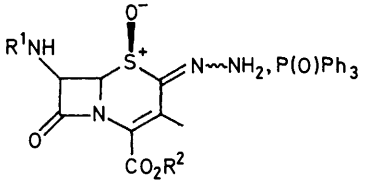
(12) R^2 = Me



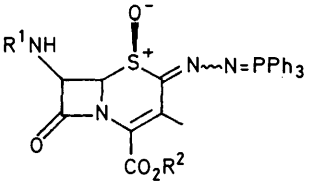
(13) R^2 = $CH_2 \cdot CCl_3$



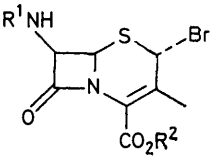
(14) R^2 = $CH_2 \cdot CCl_3$



(15) R^2 = Me



(16) R^2 = $CH_2 \cdot CCl_3$
R^1 = PhO · CH_2 · CO



(17) R^2 = $CH_2 \cdot CCl_3$

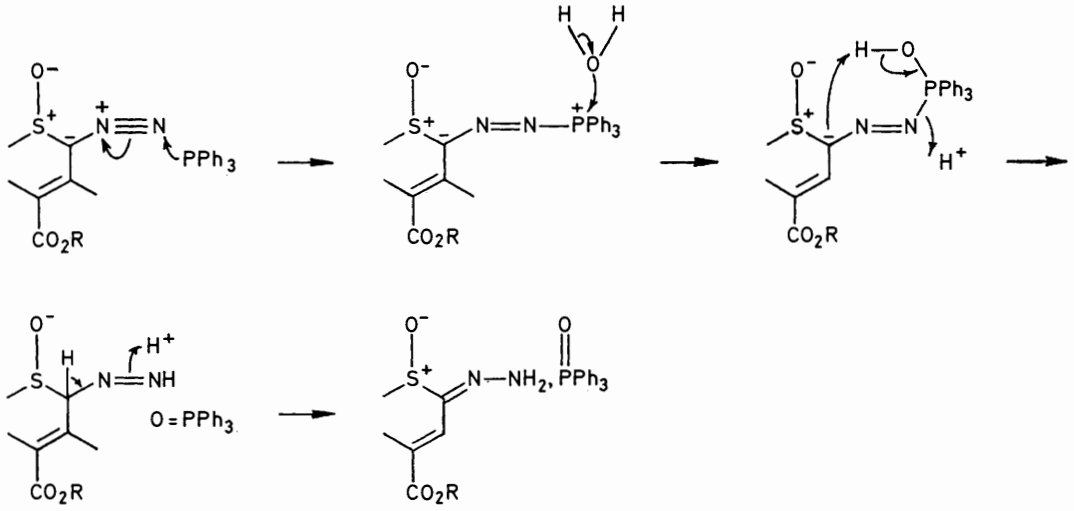
unusual functional group. For example, compound (6) was stable to aqueous perchloric acid, in contrast to 6-diazopenicillanates (8) which readily gave 6α-hydroxypenicillanates (9).[15a] In addition, (6) was stable to glacial acetic acid, and also to an excess of triethylamine. Treatment of (6) with zinc in glacial acetic acid gave a complex mixture of β-lactam-cleaved products. A range of successful reactions was, however, obtained with halogens and pseudohalogens.[16]

The 2-diazo-(*S*)-oxide (6) reacted with bromine in dry methanol, giving a less polar product which had lost the (13) because of on-column reactions, but the spectroscopic data paralleled those for compounds (10)—(12), and supported the suggested structure.

The 2-diazo-(*S*)-oxide (5) reacted readily with bromine in carbon tetrachloride, giving the 2,2-dibromo-product (14) as a crystalline solid. Deoxygenation of the sulphoxide group in (14) could not be effected with phosphorus tribromide under standard conditions.[19] Excess of reagent and more forcing conditions led to β-lactam cleavage. Spry [20] has noted difficulties in reducing 2-chloro-(*S*)-oxides.

[16] (*a*) C. Rappe, *Acta Chem. Scand.*, 1963, **17**, 2140; (*b*) H. Baganz and H.-J. May, *Chem. Ber.*, 1966, **99**, 3766; (*c*) F. Weygand, H.-J. Bestmann and H. Fritsche, *ibid.*, 1960, **93**, 2340.
[17] D. Van Ende and A. Krief, *Angew. Chem. Internat. Edn.*, 1974, **13**, 279.
[18] D. Saika and D. Swern, *J. Org. Chem.*, 1968, **33**, 4548.
[19] P. Claes, A. Vlietinck, E. Roets, H. Vanderhaeghe, and S. Toppet, *J.C.S. Perkin I*, 1973, 932.
[20] D. O. Spry, *Tetrahedron Letters*, 1972, 3717.

Diazo-alkanes react with phosphines forming phosphazenes.[13,14] In the presence of water hydrolysis may occur to form a hydrazone–triphenylphosphine oxide complex. For example, a 6-diazopenicillanate afforded a complex which was acylated to give the 6-acetylhydrazonopenicillanate.[15g] The 2-diazo-(*S*)-oxide (6) was therefore treated with triphenylphosphine–water, giving two less-polar products of closely similar retention characteristics which were isolated as a yellow crystalline mixture. Elemental analysis of the inseparable mixture of isomers indicated the formula $C_{35}H_{33}N_4O_7PS$. The *E*- and *Z*-isomers of (15) are suggested as probable structures, and a mechanistic sequence is proposed (Scheme 1). The trichloroethyl ester (5) also gave a mixture of geometrical isomers, but in this instance the analytical and spectroscopic data can be rationalized in terms of the (*E*)- and (*Z*)-phosphazenes (16) rather than a phosphine oxide complex. The course of reaction thus depends on the nature of the ester group in (5) and (6).



SCHEME 1

It had not proved practicable to synthesize a 2-diazocephem by diazo-exchange with compound (1), and as an alternative route the deoxygenation of (5) was briefly investigated. However the reaction of (5) with phosphorus tribromide led to a 2α-bromoceph-3-em (17) ($J_{2,7}$ 1 Hz). Although related α-chloro-sulphides are reactive and in some cases unstable,[20,21] this 2α-bromocephem is stable under ambient conditions.

Other aspects of the reactivity of the 2-diazo-(*S*)-oxides included a reluctance to undergo 1,3-cycloaddition reactions with dimethyl butynedioate. Under forcing conditions (benzene reflux) the β-lactam was cleaved. Initial attempts to effect thermal extrusion of nitrogen from (5) or (6) in refluxing toluene or at room temperature in the presence of copper salts led to β-lactam cleavage, as did photolysis.

Reactions with Michael Acceptors.—Although C-2 and C-4 anions have been used in alkylation reactions, no direct Michael reactions have been reported previously. With the objective of ascertaining relative reactivities at C-2, C-4, and C-7, the reactions of some cephalosporanates and their (*S*)- and (*R*)-oxides with Michael acceptors were investigated, employing triethylamine as base.

When the ceph-3-em (1) was stirred at room temperature in acrylonitrile containing triethylamine (conditions expected to cause equilibration of ceph-3-em with ceph-2-em *via* C-2 and C-4 anions[22]) the major product was the 4β-(2-cyanoethyl) derivative (18) and a minor product the 4α-(2-cyanoethyl) compound (19). Structure (18) was assigned by analogy with other alkylations which gave predominantly the 4β-isomers.[5,6] De-esterification of (18) with zinc–acetic acid in dimethylformamide gave the acid (20), which did not display significant antibiotic activity.

To assess the effects of C-3 methyl substituents, the diphenylmethyl ester of cephalothin (21) was treated with acrylonitrile–triethylamine, giving compound (22) and in low yield an isomer tentatively assigned structure (23).

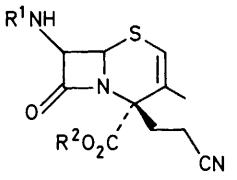
Treatment of compound (1) with methyl acrylate under similar conditions gave no reaction apart from equilibration with the ceph-2-em isomer. Dimethyl butynedioate reacted readily with (1) in the presence of triethylamine giving (24) as the only isolated product. Comparison of the chemical shift of the olefinic proton of the butenedioate group (δ 6.46) with those of dimethyl mesaconate (δ 6.69) and dimethyl citraconate (δ 5.75)[23] indicates the fumarate structure, but in the absence of the other isomer this assignment must be viewed with caution. The net anisotropic shielding effect of the adjacent cephem nucleus and the trichloroethyl ester group may significantly affect the chemical shift of the butenedioate proton. On treatment of (24) with

[21] U.S.P. 3,852,282/1974.

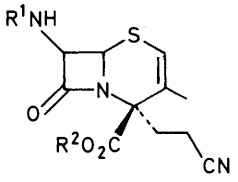
[22] R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnigno, W. B. Scanlon, and S. L. Andrews, *J. Amer. Chem. Soc.*, 1969, **91**, 1401.

[23] L. M. Jackman, 'Applications of Nuclear Magnetic Resonance in Organic Chemistry,' Pergamon, Oxford, 1959, p. 121.

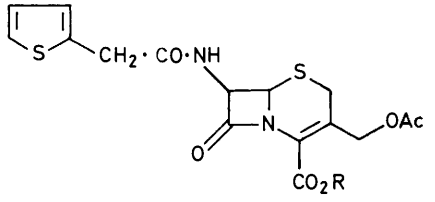
zinc–acetic acid in dimethylformamide the anticipated carboxylic acid was not obtained. Instead, four β-lactam products were formed which were then separated chromatographically into two pairs of isomers. The elemental composition of each pair of isomers



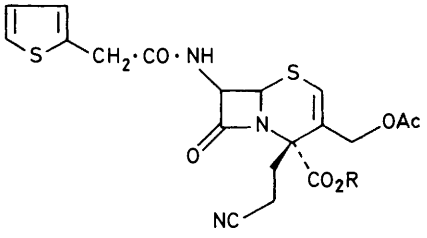
(18) $R^2 = CH_2 \cdot CCl_3$
(20) $R^2 = H$



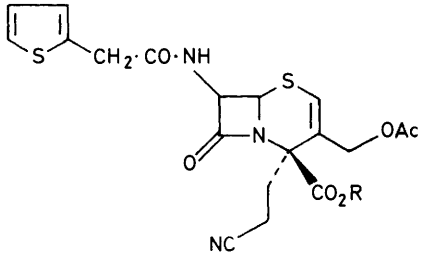
(19) $R^2 = CH_2 \cdot CCl_3$



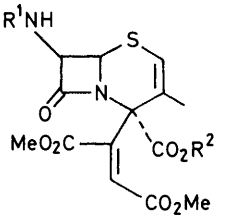
(21) $R = Ph_2CH$



(22) $R = Ph_2CH$

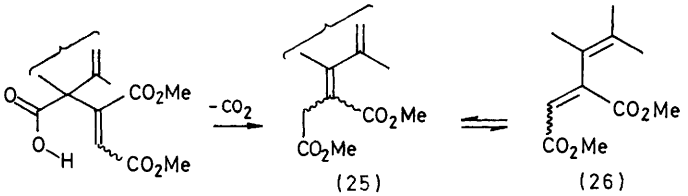


(23) $R = Ph_2CH$



(24) $R^2 = CH_2 \cdot CCl_3$
$R^1 = PhO \cdot CH_2 \cdot CO$

($C_{21}H_{22}N_2O_7S$), spectroscopic analysis, and mechanistic considerations (Scheme 2) suggest part structures (25) and (26).



SCHEME 2

When the (*S*)-oxide (4) was treated with acrylonitrile–triethylamine two products were separated with difficulty and assigned structures (27) and (28). The more polar product (28) showed coupling between H-2 and H-7 (1 Hz) indicating a 2β-proton and therefore 2α-(2-cyanoethyl) substitution. To overcome the severe separation problems the reaction was repeated and the crude (*S*)-oxide product mixture was deoxygenated. Three β-lactam products were then separated chromatographically in low yield, and identified as the 7α-phenoxyacetamidocephalosporanate (29),* the 2α-(2-cyanoethyl) product (30), and a final product which could not be obtained completely free from (30), tentatively assigned the 2,2-bis-(2-cyanoethyl) structure (31) on spectroscopic grounds.

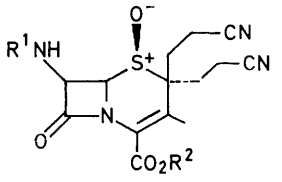
The (*S*)-oxide (3) was treated similarly; deoxygenation of the crude product and chromatography gave only the 2α-(2-cyanoethyl) product (32).† A comparison of the 2α-methyl- and 2β-methyl-cephems (34) and (36) and their (*S*)-oxides (35) and (37) [25] with the acrylonitrile adducts (28) and (30) obtained in this study further indicated that (28) and (30) possessed α-substituents (Table). When (32) was de-esterified the

* There is precedent for epimerization at C-7 of a cephalosporanate (*S*)-oxide with triethylamine.[24]

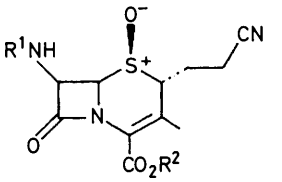
† In this instance coupling between H-2 and H-7 was not distinct.

[24] M. L. Sassiver and R. G. Shepherd, *Tetrahedron Letters*, 1969, 3993.

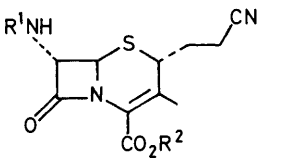
[25] 'Cephalosporins and Penicillins,' ed. E. H. Flynn, Academic Press, New York, 1972, p. 335.



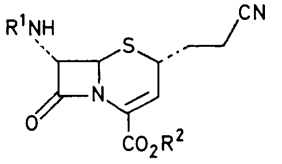
(27) R^2=Me



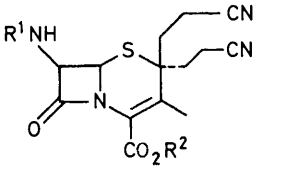
(28) R^2=Me



(29) R^2=Me



(30) R^2 = Me
(32) R^2 = $CH_2 \cdot CCl_3$
(33) R^2 = H

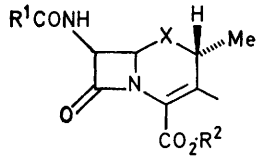


(31) R^2=Me

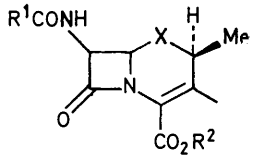
R^1 = $PhO \cdot CH_2 \cdot CO$

resultant acid (33) * could be methylated, forming the ester (30), verifying that the reaction of (3) with acrylonitrile had given a 2α-product.

Because the (*S*)-oxides (3) and (4) had not undergone complete reaction with acrylonitrile–triethylamine, certain other bases including 1,5-diazabicyclo[4.3.0]non-5-ene and pyridine were evaluated, but the former gave a complex mixture of products and the latter afforded little reaction. Under conditions in which acrylonitrile reacted, methyl methacrylate gave only trace products. The successful reactions of the (*S*)-oxides thus involved



(34) X = S
(35) X = S-O



(36) X = S
(37) X = S-O

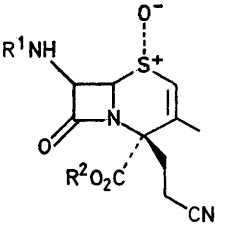
(34)	(36)	(30)
3.46	3.66	3.41
(35)	(37)	(28)
3.60	3.27	3.56

Comparative chemical shift data for H-2

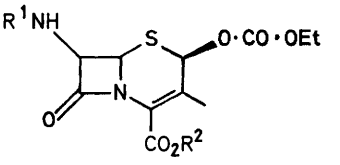
room temperature treatment with acrylonitrile–triethylamine, leading predominantly to 2α-substitution.

In an extension of the studies on cephalosporanate *S*-oxides the (*R*)-oxide (7) was investigated. With acrylonitrile–triethylamine the sole product was a 4-substituted cephem (38). The C-2 vinylic proton signal was readily assigned and the u.v. spectrum pointed to a ceph-2-em. On the basis of precedent, 4β-(2-cyanoethyl) stereochemistry is suggested. Previous work [5,6] has shown that methylsulphenylation and methylation give 4β-adducts, and it has been argued that the stereochemistry of the N-5 lone pair, which is α-oriented, controls such substitutions.

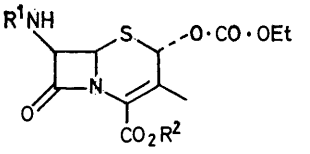
* This acid was not significantly active as an antibiotic.



(38) R^1 = $PhO \cdot CH_2 \cdot CO$,
R^2 = $CH_2 \cdot CCl_3$

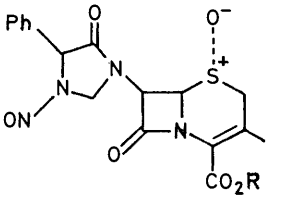


(39) R^2 = $CH_2 \cdot CCl_3$



(40) R^2 = $CH_2 \cdot CCl_3$

R^1 = $PhO \cdot CH_2 \cdot CO$

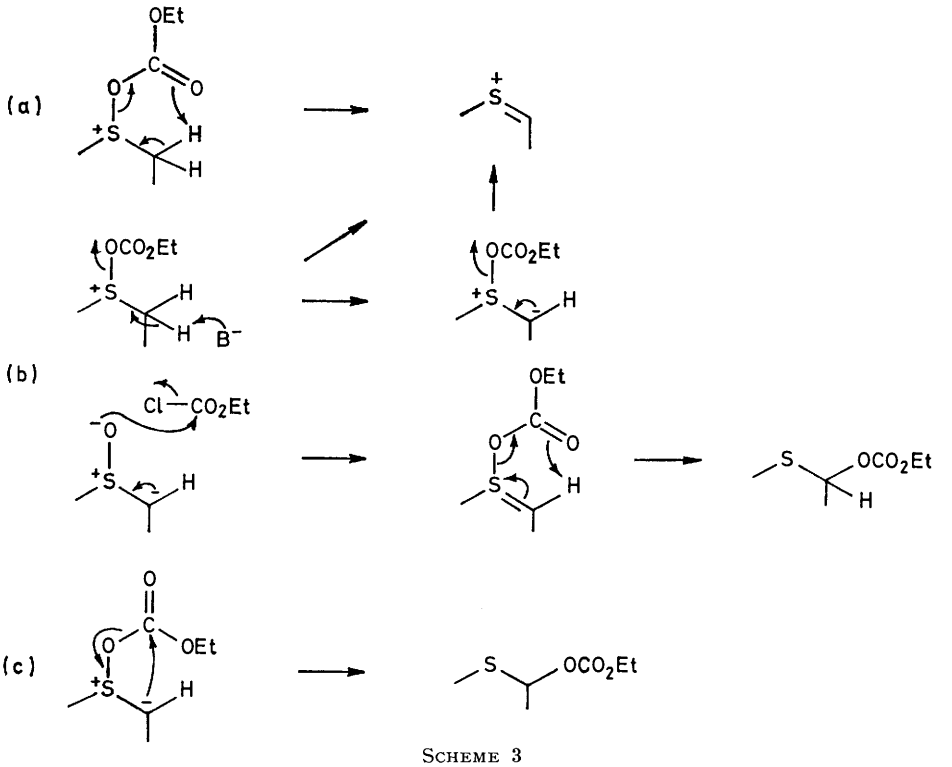


(41) R = $CH_2O \cdot COBu^t$

The reaction at C-4 in the (*R*)-oxides is therefore controlled in part by steric factors involving the 7β-side chain and the (*R*)-oxide (*i.e.* α-oxide) system, which inhibit reaction at H-2β and H-2α, respectively. Reaction is therefore preferred at C-4, and stereoselective attack at the β-face occurs because of the presence of the α-oriented N-5 lone pair and the α-oriented sulphoxide, and possibly also because of kinetic reactivity parameters. The (*R*)-oxide (7) gave only one of the C-4 isomers, whereas the sulphides (1) and (2) gave *both* 4α- and 4β-adducts, although the latter predominated.

ethyl chloroformate proceeded only in tetrahydrofuran, and not in methanol, acrylonitrile, or chloroform, or when base was absent. Under similar reaction conditions acetic anhydride, acetyl chloride, and trichloroethyl chloroformate either did not react or gave complex mixtures.

Attempted de-esterification of (39) with zinc–acetic acid–dimethylformamide led to complex mixtures, probably because of attack by zinc on the carbonyl oxygen of the trichloroethyl ester group as proposed for related reactions.[5]



SCHEME 3

Pummerer Reactions.—Under the reaction conditions employed for the diazo-exchange and the Michael reactions (*i.e.* triethylamine catalysis) the ceph-3-em (1) did not react with ethyl chloroformate. However, the (*S*)-oxide (3) reacted with reagents in excess to give the Pummerer rearrangement products, *i.e.* the 2β-ethylcarbonate (39) and its 2α-isomer (40) in 68 and 4% yield, respectively. No 2-ethoxycarbonylceph-3-em resulting from direct alkylation at C-2 was detected. N.m.r. spectra (^1H and ^{13}C) were in accord with the proposed structures. The 2-proton in (39) resonated at higher field whereas the C-3 methyl signal was at lower field than in the case of (40). The minor product (40) exhibited five-bond coupling [20] (1 Hz) between H-2 and H-7. Furthermore, the chemical shift of H-2 in (40) was similar to that of the known [26] 2α-acetoxy-derivative. Possible mechanisms [27] for the formation of one or both products are depicted in Scheme 3. The reaction with

When the (*R*)-oxide (7) or a mixture of (3) and (7) was treated with ethyl chloroformate–triethylamine, the (*R*)-oxide did not react. In addition, the (*R*)-oxide (41) was unreactive. It appears that the α-oxide stereochemistry in the (*R*)-oxides inhibits attack from the α-face, the 7β-amide inhibits attack from the β-face, and formation of an intermediate such as a sulphurane is disfavoured.

Conclusions.—In three classes of reaction, (a) diazo-exchange, (b) Michael alkylation, and (c) Pummerer rearrangement, significant differences in reactivity were observed for the cephalosporanates and their (*S*)- and (*R*)-oxides. These studies extend and complement the work of others on the reactions at C-2 and C-4 of the cephalosporanates; in particular, the use of (*S*)- and (*R*)-oxides in regiospecific and stereoselective functionalization has been demonstrated.

[26] R. D. G. Cooper, P. V. Demarco, C. F. Murphy, and L. A. Spangle, *J. Chem. Soc.* (*C*), 1970, 340.

[27] C. R. Johnson and W. G. Phillips, *J. Amer. Chem. Soc.*, 1969, **91**, 682; M. Kise and S. Oae, *Bull. Chem. Soc. Japan*, 1970, **43**, 1421.

EXPERIMENTAL

General details are as reported previously.[28]

2,2,2-Trichloroethyl (1S)-2-*Diazo*-3-*methyl*-7β-*phenoxyacetamidoceph*-3-*em*-4-*carboxylate* 1-*Oxide* (5).—To the sulphoxide (3) (1 g, 2.02 mmol) in acetonitrile (60 ml) at 0 °C were added toluene-*p*-sulphonyl azide (2 g, 10.2 mmol) and triethylamine (0.41 g, 4.05 mmol). The mixture was stirred for 20 min and then poured into water and extracted with ethyl acetate. The organic phase was washed with 2N-hydrochloric acid, water, aqueous sodium hydrogen carbonate, and water, and dried ($MgSO_4$). Evaporation *in vacuo* yielded a red oil which was chromatographed to give *compound* (5) as the only β-lactam product (0.74 g, 70%), a yellow-orange crystalline solid. Recrystallised from light petroleum–ethyl acetate this had m.p. 89—90° (decomp.), $[\alpha]_D^{21}$ +7° (*c* 1.00 in chloroform), $\lambda_{max.}$ 268 (ε 5 500) and 318 nm (10 200), $\nu_{max.}$ (KBr) 3 360 (NH), 2 070 (diazo str.), 1 770 (β-lactam C=O), 1 720 (ester C=O), and 1 690 cm^{-1} (amide C=O), δ ($CDCl_3$) 2.36 (3 H, s, Me), 4.54 (2 H, s, PhOCH_2), 4.72 (1 H, d, *J* 5 Hz, 6-H), 4.93 (2 H, s, CH_2 of ester), 6.22 (1 H, dd, *J* 11 and 5 Hz, 7-H), 6.70—7.50 (5 H, m, Ph), and 7.91 (1 H, d, *J* 11 Hz, NH) (Found: C, 41.6; H, 3.0; N, 10.5; Cl, 20.2; S, 6.2. $C_{18}H_{15}Cl_3N_4O_6S$ requires C, 41.4; H, 2.9; N, 10.7; Cl, 20.4; S, 6.1%).

Methyl (1S)-2-*Diazo*-3-*methyl*-7β-*phenoxyacetamidoceph*-3-*em*-4-*carboxylate* 1-*Oxide* (6).—The sulphoxide (4) (2 g, 5.3 mmol) was stirred for 4.5 h in acetonitrile (150 ml) at 0 °C with toluene-*p*-sulphonyl azide (5.2 g, 26.4 mmol) and triethylamine (1.07 g, 10.6 mmol). The mixture was poured into water and extracted with ethyl acetate. The organic phase was washed with 2N-hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate solution, and water and dried ($MgSO_4$). Evaporation afforded a deep red oil. Chromatography gave compound (6) as the only β-lactam product (1.1 g, 50%), $\lambda_{max.}$ 270 (ε 10 200) and 316 nm (16 000), $\nu_{max.}$ (film) 3 300 (NH), 2 060 (diazo), 1 775 (β-lactam C=O), 1 720 (ester C=O), and 1 690 cm^{-1} (amide C=O), δ ($CDCl_3$) 2.30 (3 H, s, Me), 3.85 (3 H, s, OMe), 4.55 (2 H, s, CH_2), 4.65 (1 H, d, *J* 5 Hz, 6-H), 6.20 (1 H, dd, *J* 11 and 5 Hz, 7-H), 6.80—7.50 (5 H, m, Ph), and 7.90 (1 H, d, *J* 11 Hz, NH). This compound was chromatographically unstable and could not be obtained analytically pure. Spectroscopic data quoted are for material slightly impure according to t.l.c.

2,2,2-Trichloroethyl (1S)-2-*Bromo*-2-*methoxy*-3-*methyl*-7β-*phenoxyacetamidoceph*-3-*em*-4-*carboxylate* 1-*Oxide* (11).—The diazo-sulphoxide (5) (0.3 g, 0.58 mmol) in methanol (35 ml) was stirred with *N*-bromosuccinimide (0.095 g, 0.53 mmol) at room temperature for 1.5 h. The methanol was removed *in vacuo* and replaced by ethyl acetate; the solution was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo* to yield a yellow-orange oil. Chromatography afforded the *bromo-ester* (11) as an oil (0.08 g, 23%), $[\alpha]_D^{22}$ −33° (*c* 1.69 in chloroform), $\lambda_{max.}$ 268 nm (ε 6 800), $\nu_{max.}$ (film) 3 350 (NH), 1 790 (β-lactam C=O), 1 755 (ester C=O), and 1 690 cm^{-1} (amide C=O), δ ($CDCl_3$) 2.11 (3 H, s, Me), 3.55 (3 H, s, OMe), 4.56 (2 H, s, PhOCH_2), 4.58 and 5.19 (2 H, ABq, *J* 12 Hz, CH_2 of ester), 4.89 (1 H, d, *J* 5 Hz, 6-H), 6.25 (1 H, dd, *J* 11 and 5 Hz, 7-H), 6.80—7.55 (5 H, m, Ph), and 8.22 (1 H, d, *J* 11 Hz, NH) (Found: M^+, 601.9058. $C_{19}H_{18}{}^{79}Br^{35}Cl_3N_2O_7S$ requires *M*, 601.9084).

Methyl (1S)-2-*Bromo*-2-*methoxy*-3-*methyl*-7β-*phenoxyacetamidoceph*-3-*em*-4-*carboxylate* 1-*Oxide* (10).—The diazo-sulphoxide (6) (0.1 g, 0.19 mmol) in dry methanol (10 ml) was stirred at room temperature with *N*-bromosuccinimide (0.67 g, 0.38 mmol) for 1.5 h. The mixture was poured into ethyl acetate and then washed with water, dried ($MgSO_4$) and evaporated *in vacuo*. Chromatography gave the product (10) as an oil (0.06 g, 50%), $[\alpha]_D^{23}$ −32° (*c* 1.00 in chloroform), $\lambda_{max.}$ 269 nm (ε 2 100), $\nu_{max.}$ (film) 3 250 (NH), 1 780 (β-lactam C=O), 1 755 (ester C=O), and 1 690 cm^{-1} (amide C=O), δ ($CDCl_3$) 2.05 (3 H, s, Me), 3.50 (3 H, s, OMe), 3.88 (3 H, s, OMe of ester), 4.58 (2 H, s, CH_2), 4.85 (1 H, d, *J* 5 Hz, 6-H), 6.25 (1 H, dd, *J* 10 and 5 Hz, 7-H), 6.80—7.50 (5 H, m, Ph), and 8.25 (1 H, d, *J* 10 Hz, NH) (Found: M^+, 486.0080. $C_{18}H_{19}{}^{79}BrN_2O_7S$ requires *M*, 486.0097).

Methyl (1S)-2-*Azido*-2-*bromo*-3-*methyl*-7β-*phenoxyacetamidoceph*-3-*em*-4-*carboxylate* 1-*Oxide* (12).—The diazo-sulphoxide (6) (0.25 g, 0.62 mmol) in 1,2-dimethoxyethane (20 ml) was stirred at −5 °C with sodium azide (0.2 g, 3.6 mmol) and water (5 ml). To this solution was added *N*-bromosuccinimide (0.84 g, 4.7 mmol) in portions until effervescence had ceased. After 30 min the solution was diluted with ethyl acetate, washed with brine, dried ($MgSO_4$), and evaporated *in vacuo* to yield an oil. Chromatography gave the *bromo-ester* (12) as the only isolable β-lactam product, an oil (0.065 g, 22%), $[\alpha]_D^{23}$ +5° (*c* 0.84 in chloroform), $\lambda_{max.}$ 270 nm (ε 3 000), $\nu_{max.}$ (film) 3 300 (NH), 2 120 (azide), 1 780 (β-lactam C=O), 1 750 (ester C=O), and 1 680 cm^{-1} (amide C=O), δ ($CDCl_3$) 2.02 (3 H, s, Me), 3.97 (3 H, s, OMe), 4.58 (2 H, s, PhOCH_2), 5.04 (1 H, d, *J* 5 Hz, 6-H), 6.18 (1 H, dd, *J* 11 and 5 Hz, 7-H), 6.70—7.60 (5 H, m, Ph), and 8.30 (1 H, d, *J* 11 Hz, NH) [Found: $M^+ - (H_2O + N_2)$, 450.9846. $C_{17}H_{14}{}^{79}BrN_3O_5S$ requires 450.9839].

Reaction of the Diazo-sulphoxide (6) *with Ethyl* N-*Chlorocarbamate*.—The sulphoxide (6) (0.2 g, 0.38 mmol) in acetonitrile (10 ml) was treated with the carbamate (0.05 g, 0.40 mmol) at room temperature. No reaction was observed after 2 h. The mixture was heated to 50 °C for 1 h; t.l.c. then indicated that no starting material remained. The solution was diluted with ethyl acetate and the organic phase was washed with aqueous sodium disulphite, sodium hydrogen hydrogen carbonate, 0.5M-sodium hydroxide, and water, dried ($MgSO_4$), and evaporated *in vacuo* to yield a dark yellow oil. Chromatography afforded methyl (1S)-2-chloro-2-ethoxyformamido-3-methyl-7β-phenoxyacetamidoceph-3-em-4-carboxylate 1-oxide (13) (0.06 g, 25%) as an oil, $\nu_{max.}$ (film) 3 480 and 3 370 (NH), 1 810 (β-lactam C=O), 1 750 (ester C=O), 1 720 (carbamate C=O), and 1 695 cm^{-1} (amide C=O), δ ($CDCl_3$) 1.25 (3 H, t, 7 Hz, CH_2CH_3), 2.37 (3 H, s, Me), 4.10 (2 H, q, 7 Hz, $CH_2{\cdot}CH_3$), 4.60 (2 H, s, CH_2), 5.30 (1 H, d, *J* 5 Hz, 6-H), 6.26 (1 H, dd, *J* 10 and 5 Hz, 7-H), 6.80—7.45 (6 H, m, Ph and NH of carbamate), and 7.80 (1 H, d, *J* 10 Hz, NH). This material was not obtained homogeneous even after repeated chromatography.

Reaction of the Diazo-sulphoxide (5) *with Bromine*.—The diazo-sulphoxide (5) (0.25 g, 0.48 mmol) in carbon tetrachloride (15 ml) was treated dropwise with bromine in carbon tetrachloride until t.l.c. indicated complete removal of starting material. The mixture was washed with sodium hydrogen carbonate solution and brine, dried ($MgSO_4$), and evaporated to dryness to give a yellow oil. Column chromatography yielded *2,2,2-trichloroethyl* (1S)-2,2-*dibromo*-3-*methyl*-7β-*phenoxyacetamidoceph*-3-*em*-4-*carboxylate* 1-*oxide*

[28] M. M. Campbell, G. Johnson, A. F. Cameron, and I. R. Cameron, *J.C.S. Perkin I*, 1975, 1208.

(14) as a crystalline solid (0.21 g, 68%). Recrystallisation from light petroleum–ethyl acetate gave material with m.p. 134—136°, $[\alpha]_D^{23}$ −169° (*c* 0.77 in chloroform), $\lambda_{max.}$ 275 nm (ε 1 200), $\nu_{max.}$ (KBr) 3 350 (NH), 1 780 (β-lactam C=O), 1 740 (ester C=O), and 1 695 cm^{-1} (amide C=O), δ ($CDCl_3$) 2.45 (3 H, s, Me), 4.60 (2 H, s, CH_2), 4.95 (2 H, s, CH_2 of ester), 5.58 (1 H, d, *J* 5 Hz, 6-H), 6.33 (1 H, dd, *J* 11 and 5 Hz, 7-H), 6.90—7.60 (5 H, m, Ph), and 7.84 (1 H, d, *J* 11 Hz, NH) (Found: C, 33.2; H, 2.4; N, 4.4; S, 4.9. $C_{18}H_{15}Cl_3Br_2N_2O_6S$ requires C, 33.1; H, 2.3; N, 4.3; S, 5.0%).

Reaction of Methyl (1S)-2-*Diazo*-3-*methyl*-7β-*phenoxyacetamidoceph*-3-*em*-4-*carboxylate* 1-*Oxide* (6) *with Triphenylphosphine*.—The diazo-sulphoxide (6) (0.18 g, 0.45 mmol) was stirred at room temperature in wet tetrahydrofuran with triphenylphosphine (0.235 g, 0.90 mmol) for 4 h. The mixture was poured into water and extracted with ethyl acetate. The organic phase was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo* to give a dark yellow oil. Chromatography yielded methyl (1*S*)-2-hydrazono-3-methyl-7β-phenoxyacetamidoceph-3-em-4-carboxylate 1-oxide–triphenylphosphine oxide complex (15) (0.195 g, 73%) as a yellow crystalline solid, m.p. 124—127° (decomp.). This material ran as an inseparable double spot on t.l.c.; $\nu_{max.}$ (KBr) (mixture) 3 400 (NH), 1 780 (β-lactam C=O), 1 755 (ester C=O), and 1 685 cm^{-1} (amide C=O), δ ($CDCl_3$) (mixture) 2.20br (3 H, s, Me), 2.75br (2 H, s, NH_2 exch.), 3.82 (3 H, 2 × s, OMe), 4.53 (3 H, m, CH_2 and 5-H), 6.13 (1 H, 2 × dd, *J* 11 and 5 Hz, 7-H), 6.80—7.85 (20 H, m, Ph), and 8.16 (1 H, s, exch., *J* 11 Hz, NH) (Found: C, 61.6; H, 4.9; N, 8.4; S, 4.9. $C_{35}H_{33}N_4O_7PS$ requires C, 61.5; H, 4.8; N, 8.2; S, 4.7%).

Reaction of the Diazo-sulphoxide (5) *with Triphenylphosphine*.—To the diazo-sulphoxide (5) (0.22 g, 0.42 mmol) in tetrahydrofuran (30 ml) and water (0.5 ml) was added triphenylphosphine (0.23 g, 0.88 mmol). The mixture was stirred at room temperature for 3 h, then poured into water and extracted with ethyl acetate. The organic phase was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*. The resulting yellow oil was chromatographed on silica gel to give as the only product 2,2,2-trichloroethyl (1*S*)-3-methyl-7β-phenoxyacetamido-2-triphenylphosphoranylidenehydrazonoceph-3-em-4-carboxylate 1-oxide (16) (0.31 g, 91%) as a yellow crystalline solid which appeared on t.l.c. as a double spot, m.p. 180—182°, $\nu_{max.}$ (KBr) 3 370 (NH), 1 785 (β-lactam C=O), 1 740 (ester C=O), and 1 705 cm^{-1} (amide C=O), δ ($CDCl_3$) 2.32 (3 H, s, Me), 4.72 (2 H, s, CH_2), 4.76 (1 H, d, *J* 5 Hz, 6-H), 4.98 and 5.18 (2 H, ABq, *J* 12 Hz, CH_2 of ester), 6.36 (1 H, dd, *J* 11 and 5 Hz, 7-H), 7.0—8.04 (20 H, m, Ph), and 8.46 (1 H, d, *J* 11 Hz, NH) (Found: C, 55.3; H, 3.8; N, 6.9; Cl, 13.6; S, 5.6. $C_{36}H_{30}Cl_3N_4O_6PS$ requires C, 55.1; H, 3.8; N, 7.1; Cl, 13.6; S, 5.1%).

Deoxygenation of the Diazo-sulphoxide (5).—The diazo-sulphoxide (5) (0.3 g, 0.58 mmol) in dry dimethylformamide (10 ml) was stirred with phosphorus tribromide (0.2 ml, 23 mmol) at ice temperature for 10 min. The mixture was poured into ice cold sodium hydrogen carbonate solution and extracted with ethyl acetate. The extract was washed with more sodium hydrogen carbonate solution and brine, dried, and evaporated *in vacuo* to yield a red oil. Chromatography on silica gave 2,2,2-*trichloroethyl* 2-*bromo*-3-*methyl*-7β-*phenoxyacetamidoceph*-3-*em*-4-*carboxylate* (17) as an oil (0.13 g, 41%), $[\alpha]_D^{22}$ +179° (*c* 1.67 in chloroform), $\lambda_{max.}$ 268 nm (ε 5 300), $\nu_{max.}$ (film) 3 310 (NH), 1 780 (β-lactam C=O), 1 750 (ester C=O), and 1 685 cm^{-1} (amide C=O), δ ($CDCl_3$) 2.10 (3 H, s, Me), 4.60 (2 H, s, CH_2), 4.73 and 4.95 (2 H, ABq, *J* 12 Hz, CH_2 of ester), 5.04 (1 H, d, *J* 1 Hz, 2-H), 5.54 (1 H, d, *J* 5 Hz, 6-H), 5.73 (1 H, ddd, *J* 11, 5, and 1 Hz, 7-H), and 6.88—7.55 (6 H, m, Ph and NH) (Found: M^+, 555.9041. $C_{18}H_{16}{}^{35}Cl_3{}^{79}BrN_2O_5S$ requires *M*, 555.9030).

Reaction of 2,2,2-*Trichloroethyl* 7β-*Phenoxyacetamidoceph*-3-*em*-4-*carboxylate* (1) *with Acrylonitrile*.—The ester (1) (0.3 g, 0.63 mmol) in acrylonitrile (20 ml) was stirred at room temperature for 5 h with triethylamine (0.5 ml). The mixture was poured into 0.05N-hydrochloric acid and extracted with ethyl acetate. The organic phase was washed with sodium carbonate solution and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The resulting oil was chromatographed to yield as the major product 2,2,2-*trichloroethyl* 4β-(2-*cyanoethyl*)-3-*methyl*-7β-*phenoxyacetamidoceph*-2-*em*-4-*carboxylate* (18) (0.25 g, 75%) as an oil, $[\alpha]_D^{23}$ (*c* 1.33 in chloroform), $\lambda_{max.}$ 258 nm (ε 4 900), $\nu_{max.}$ (film) 3 340 (NH), 2 240 (nitrile), 1 780 (β-lactam C=O), 1 760 (ester C=O), and 1 695 cm^{-1} (amide C=O), δ ($CDCl_3$) 1.85 (3 H, d, *J* 1 Hz, Me), 2.30—3.45 (4 H, m, $CH_2{\cdot}CH_2{\cdot}CN$), 4.55 (2 H, s, CH_2), 4.72 and 4.98 (2 H, ABq, *J* 12 Hz, CH_2 of ester), 5.37 (1 H, d, *J* 4 Hz, 6-H), 5.61 (1 H, dd, *J* 10 and 4 Hz, 7-H), 6.40 (1 H, q, *J* 1 Hz, 2-H), 6.85—7.50 (5 H, m, Ph), and 7.70 (1 H, d, *J* 10 Hz, NH) (Found: M^+, 531.0197. $C_{21}H_{20}{}^{35}Cl_3N_3O_5$ requires *M*, 531.0190).

De-esterification of the Ceph-2-em (18).—The ester (18) (0.25 g, 0.47 mmol) in dimethylformamide–glacial acetic acid (30 ml; 25 : 7.5 v/v) was stirred at 0 °C with zinc (0.5 g) for 2 h. The zinc was filtered off and the solution was extracted with ethyl acetate. The ethyl acetate was extracted with aqueous sodium carbonate, which was then acidified with 2N-hydrochloric acid and re-extracted with fresh ethyl acetate. The organic solvent was removed *in vacuo* to yield an oil containing traces of acetic acid. Azeotropic removal of acetic acid with carbon tetrachloride afforded 4β-(2-*cyanoethyl*)-7β-*phenoxyacetamidoceph*-2-*em*-4-*carboxylic acid* (20) (0.11 g, 59%) as a white solid, m.p. 212—214°, $[\alpha]_D^{22}$ +315° (*c* 0.4 in acetone), $\lambda_{max.}$ 257 nm (ε 5 200), $\nu_{max.}$ (KBr) 3 330 (NH), 3 020—2 400br (OH), 2 240 (nitrile), 1 770 (β-lactam C=O), 1 745 (acid C=O), and 1 655 cm^{-1} (amide C=O), δ [$(CD_3)_2SO$] 1.85 (3 H, d, *J* 1 Hz, Me), 2.0—3.40 (4 H, m, CH_2CH_2CN), 4.60 (2 H, s, CH_2), 5.31 (1 H, d, *J* 4 Hz, 6-H), 5.50 (1 H, dd, *J* 10 and 4 Hz, 7-H), 6.34 (1 H, q, *J* 1 Hz, 2-H), 6.80—7.50 (5 H, m, Ph), and 8.25 (1 H, d, *J* 10 Hz, NH) (Found: $M^+ - CO_2$, 357.1151. $C_{17}H_{19}N_3O$ requires 357.1147).

Reaction of Diphenylmethyl 3-*Acetoxymethyl*-7β-(2-*thienylacetamido*)*ceph*-3-*em*-4-*carboxylate* (21) *with Acrylonitrile*.—The ester (21) (0.40 g, 0.71 mmol) in acrylonitrile (20 ml) was stirred at room temperature with triethylamine (1.0 ml). After 18 h t.l.c. showed the presence of a product of almost the same R_F value as starting material. The reaction mixture was diluted with ethyl acetate and the organic phase was washed with 2N-hydrochloric acid, water, sodium hydrogen carbonate, brine, dried ($MgSO_4$), and evaporated *in vacuo* to give an oil. Chromatography afforded *diphenylmethyl* 3-*acetoxymethyl*-4β-(2-*cyanoethyl*)-7β-(2-*thienylacetamido*)*ceph*-2-*em*-4-*carboxylate* (22) as an oil (0.38 g, 87%), $[\alpha]_D^{23}$ +230° (*c* 1.52 in chloroform), $\lambda_{max.}$ 255 nm (ε 5 800), $\nu_{max.}$ (film) 3 300 (NH), 2 250 (nitrile), 1 780 (β-lactam C=O), 1 745 (ester C=O), and 1 685 cm^{-1} (amide C=O), δ ($CDCl_3$) 1.80 (3 H, s, Me), 2.20—3.45 (4 H, m, CH_2CH_2CN), 3.80 (2 H, s, CH_2 side chain), 4.56 (2 H, s,

CH_2OCOMe), 5.16 (1 H, d, *J* 5 Hz, 6-H), 5.34 (1 H, dd, *J* 10 and 5 Hz, 7-H), 6.82 (1 H, s, 2-H), 6.80—7.31 (5 H, m, thiophen, CH, and NH), and 7.37 (10 H, s, 2 × Ph) (Found: C, 62.3; H, 4.9; N, 6.6; S, 10.2. $C_{32}H_{29}N_3O_6S_2$ requires C, 62.5; H, 4.7; N, 6.8; S, 10.4%).

Also isolated, in low yield (0.025 g, 6%), was a slightly more polar compound tentatively identified as diphenylmethyl 3-acetoxymethyl-4-(2-cyanoethyl)-7β-(2-thienylacetamido)ceph-2-em-4β-carboxylate (23), $\nu_{max.}$ (film) 3 280 (NH), 2 240 (nitrile), 1 765 (β-lactam C=O), 1 735 (ester C=O), and 1 670 cm^{-1} (amide C=O), δ ($CDCl_3$) 1.93 (3 H, s, Me), 2.10—3.40 (4 H, m, CH_2CH_2CN), 3.80 (2 H, s, CH_2 of side chain), 4.45 (2 H, s, CH_2·OCOMe), 5.12 (1 H, d, *J* 5 Hz, 6-H), 5.50 (1 H, dd, *J* 9 and 5 Hz, 7-H), 6.70—7.15 (6 H, m, thiophen, NH, CH, and 2-H), and 7.40 (10 H, s, 2 × Ph), M^+ 615 ($C_{32}H_{29}N_3O_6S$).

Reaction of the Ester (1) *with Dimethyl Butynedioate.*—To the ester (1) (1.5 g, 3.1 mmol) in acetonitrile (60 ml) at −24 °C were added dimethyl butynedioate (1.0 g, 7.0 mmol) and triethylamine (0.35, 3.5 mmol). The mixture was stirred at −24 °C for 10 min and then allowed to warm to room temperature over 0.5 h. The solvent was removed *in vacuo* and the residue was dissolved in ethyl acetate; the solution was washed with 2N-hydrochloric acid, water, aqueous sodium hydrogen carbonate, and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The resulting oil was chromatographed on silica to yield 2,2,2-*trichloroethyl* 4β-(1,2-*bismethoxycarbonylvinyl*)-7β-*phenoxyacetamidoceph*-2-*em*-4α-*carboxylate* (24) (1.4 g, 74%) as a white crystalline solid, m.p. 143—144°, $[\alpha]_D^{22}$ 355° (*c* 0.85 in chloroform), $\lambda_{max.}$ 258 nm (ε 7 200), $\nu_{max.}$ (KBr) 3 300 (NH), 1 790 (β-lactam C=O), 1 760 (ester C=O), 1 735 (ester C=O), and 1 690 cm^{-1} (amide C=O), δ ($CDCl_3$) 1.90 (3 H, d, *J* 1 Hz, Me), 3.77 (3 H, s, OMe), 3.82 (3 H, s, OMe), 4.53 (2 H, s, CH_2), 4.80 (2 H, s, CH_2 of ester), 5.48 (1 H, d, *J* 4 Hz, 6-H), 5.70 (1 H, dd, *J* 9 and 4 Hz, 7-H), 6.46 (2 H, m, 2-H and HC=C), and 6.85—7.60 (6 H, m, Ph and NH) (Found: C, 46.4; H, 3.8; Cl, 16.7; S, 5.2. $C_{24}H_{23}Cl_3N_2O_9S$ requires C, 46.3; H, 3.7; Cl, 17.1; S, 5.2%).

Reaction of Methyl (1S)-3-*Methyl*-7β-*phenoxyacetamidoceph*-3-*em*-4-*carboxylate* 1-*Oxide* (4) *with Acrylonitrile.*—The sulphoxide (4) (1 g, 2.6 mmol) was stirred at room temperature in acrylonitrile (50 ml) containing triethylamine (2 ml). After 2 h t.l.c. indicated a build-up of a slightly less polar material. After 18 h at room temperature the solvent was removed at reduced pressure. A white solid which crystallised out was identified as (4) (0.25 g, 25%). The remaining material was taken up in ethyl acetate and washed with 2N-hydrochloric acid, sodium hydrogen carbonate solution, and brine, dried ($MgSO_4$), and evaporated *in vacuo* to yield a brown oil. All attempts to separate this mixture by column chromatography failed. However preparative t.l.c. yielded as the least polar material *methyl* (1S)-2,2-*bis*-(2-*cyanoethyl*)-3-*methyl*-7β-*phenoxyacetamidoceph*-3-*em*-4-*carboxylate* 1-*oxide* (27) (0.04 g, 20%) as an amorphous solid, $[\alpha]_D^{22}$ +13° (*c* 0.98 in chloroform), $\lambda_{max.}$ 268 nm (ε 14 000), $\nu_{max.}$ (film) 3 360 (NH), 2 240 (nitrile), 1 780 (β-lactam C=O), 1 720 (ester C=O), and 1 680 cm^{-1} (amide C=O), δ ($CDCl_3$) 1.15—3.1 (8 H, m, 2 × CH_2CH_2CN), 2.08 (3 H, s, Me), 3.91 (3 H, s, OMe), 4.59 (2 H, s, CH_2), 4.76 (1 H, d, *J* 5 Hz, 6-H), 6.22 (1 H, dd, *J* 11 and 5 Hz, 7-H), 6.85—7.66 (5 H, m, Ph), and 7.85 (1 H, d, *J* 11 Hz, NH) (Found: $M^+ - H_2O$, 466.1302. $C_{23}H_{22}N_4O_5S$ requires 466.1311).

The next compound, obtained as an amorphous solid, was identified as *methyl* (1S)-2α-(2-*cyanoethyl*)-3-*methyl*-7β-*phenoxyacetamidoceph*-3-*em*-4-*carboxylate* 1-*oxide* (28) (0.03 g, 16%), $[\alpha]_D^{22}$ +13° (*c* 1.3 in chloroform), $\lambda_{max.}$ 268 nm (ε 4 900), $\nu_{max.}$ (film) 3 360 (NH), 2 240 (nitrile), 1 780 (β-lactam C=O), 1 720 (ester C=O), and 1 685 cm^{-1} (amide C=O), δ ($CDCl_3$) 2.04 (2 H, m, CH_2CH_2CN), 2.16 (3 H, s, Me), 2.57 (2 H, m, CH_2CH_2CN), 3.56 (1 H, ddd, *J* 9, 4, and 1 Hz, 2-H), 4.50 (1 H, d, *J* 5 Hz, 6-H), 4.52 (2 H, s, CH_2), 6.09 (1 H, ddd, *J* 11, 5, and 1 Hz, 7-H), 6.80—7.36 (5 H, m, Ph), and 7.78 (1 H, d, *J* 11 Hz, NH) (Found: C, 55.8; H, 4.7; N, 9.5; S, 7.3. $C_{20}H_{21}N_3O_6S$ requires C, 55.7; H, 4.9; N, 9.7; S, 7.4%).

In order to overcome the separation difficulties, the sulphoxide (4) (1 g, 2.6 mmol) was treated as described above to yield a mixture of sulphoxide products. This mixture in dimethylformamide was treated with phosphorus tribromide (0.7 ml) for 20 min at ice temperature. The mixture was poured into ice cold sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic phase was washed with sodium hydrogen carbonate solution and brine, dried ($MgSO_4$), and evaporated *in vacuo*. Column chromatography yielded first the sulphide (2) (0.12 g).

The next material eluted was identified as *methyl* 2α-(2-*cyanoethyl*)-3-*methyl*-7α-*phenoxyacetamidoceph*-3-*em*-4-*carboxylate* (29) (0.03 g, 3%), m.p. 209—210°, $[\alpha]_D^{22}$ +143° (*c* 0.88 in chloroform), $\lambda_{max.}$ 265 nm (ε 13 000), $\nu_{max.}$ (KBr) 3 360 (NH), 2 240 (nitrile), 1 780 (β-lactam C=O), 1 720 (ester C=O), and 1 675 cm^{-1} (amide C=O), δ [$(CD_3)_2SO$] 1.94 (3 H, s, Me), 2.0—2.60 (4 H, m, CH_2CH_2CN), 3.44 (1 H, m, 2-H), 3.76 (3 H, s, OMe), 4.54 (2 H, s, CH_2), 4.90 (1 H, d, *J* 2 Hz, 6-H), 4.94 (1 H, dd, *J* 7 and 2 Hz, 7-H), 6.80—7.40 (5 H, m, Ph), and 9.10 (1 H, d, *J* 7 Hz, NH) (Found: C, 57.7; H, 5.1; N, 10.0; S, 7.9. $C_{20}H_{21}N_3O_5S$ requires C, 57.8; H, 5.1; N, 10.1; S, 7.7%).

Further elution yielded *methyl* 2α-(2-*cyanoethyl*)-3-*methyl*-7β-*phenoxyacetamidoceph*-3-*em*-4-*carboxylate* (30) (0.15 g, 13%) as an amorphous solid, $[\alpha]_D^{22}$ +100° (*c* 1.31 in chloroform), $\lambda_{max.}$ 266 nm (ε 11 000), $\nu_{max.}$ (film) 3 310 (NH), 2 240 (nitrile), 1 780 (β-lactam C=O), 1 730 (ester C=O), and 1 690 cm^{-1} (amide C=O), δ ($CDCl_3$) 1.70—2.35 (4 H, m, CH_2CH_2CN), 2.20 (3 H, s, Me), 3.41 (1 H, ddd, *J* 12, 3, and 1 Hz, 2-H), 3.84 (3 H, s, OMe), 4.58 (2 H, s, CH_2), 4.98 (1 H, d, *J* 5 Hz, 6-H), 5.90 (1 H, ddd, *J* 10, 5, and 1 Hz, 7-H), and 6.81—7.55 (6 H, m, Ph and NH) (Found: M^+, 415.1212. $C_{20}H_{21}N_3O_5S$ requires *M*, 415.1202).

Final elution yielded a compound (0.06 g) contaminated with (30), tentatively identified as methyl 2,2-bis-(2-cyanoethyl)-3-methyl-7β-phenoxyacetamidoceph-3-em-4-carboxylate (31), $\nu_{max.}$ (film) 3 300 (NH), 2 240 (nitrile), 1 775 (β-lactam C=O), 1 730 (ester C=O), and 1 685 cm^{-1} (amide C=O), δ ($CDCl_3$) (by subtraction) 1.90—2.85 (8 H, m, CH_2CH_2CN), 3.88 (3 H, s, OMe), 4.77 (2 H, s, CH_2), 5.00 (1 H, d, *J* 5 Hz, 6-H), 5.80 (1 H, dd, *J* 9 and 5 Hz, 7-H), 6.80—7.65 (5 H, m, Ph), and 7.92 (1 H, d, *J* 9 Hz, NH), M^+ 468 ($C_{23}H_{24}N_4O_5S$).

Reaction of 2,2,2-*Trichloroethyl* (1S)-3-*Methyl*-7β-*phenoxyacetamidoceph*-3-*em*-4-*carboxylate* 1-*Oxide* (3) *with Acrylonitrile.*—The oxide (3) (0.25 g, 0.5 mmol) in acrylonitrile (15 ml) was stirred at room temperature with triethylamine (0.5 ml) for 18 h. The acrylonitrile was removed *in vacuo* and the residue was taken up in ethyl acetate and washed with 2N-hydrochloric acid, water, sodium hydrogen carbonate solution, and water, dried ($MgSO_4$), and evaporated *in vacuo*. Preparative t.l.c. yielded 2,2,2-*trichloroethyl* (1S)-2-(2-*cyanoethyl*)-3-*methyl*-7β-*phenoxyacetamido*-

ceph-3-*em*-4-*carboxylate* 1-*oxide* as an amorphous solid (0.05 g, 24%), $[\alpha]_D^{22}$ +50° (*c* 1.00 in chloroform), $\lambda_{max.}$ 267 nm (ε 10 000), $\nu_{max.}$ (film) 3 380 (NH), 2 240 (nitrile), 1 800 (β-lactam C=O), 1 750 (ester C=O), and 1 700 cm^{-1} (amide C=O), δ ($CDCl_3$) 1.85—2.80 (4 H, m, CH_2CH_2CN), 2.34 (3 H, s, Me), 3.70 (1 H, m, 2-H), 4.53 (2 H, s, CH_2), 4.57 (1 H, d, *J* 5 Hz, 6-H), 4.82 and 5.04 (2 H, ABq, *J* 12 Hz, CH_2 of ester), 6.14 (1 H, ddd, *J* 11, 5, and 1 Hz, 7-H), 6.72—7.40 (5 H, m, Ph), and 7.82 (1 H, d, *J* 11 Hz, NH) (Found: C, 45.9; H, 3.8; Cl, 19.1; N, 7.5; S, 5.7. $C_{21}H_{20}Cl_3N_3O_6S$ requires C, 45.9; H, 3.6; Cl, 19.4; N, 7.7; S, 5.8%).

Also obtained was compound (3) (0.12 g, 60%).

2,2,2-*Trichloroethyl* 2-(2-*Cyanoethyl*)-3-*methyl*-7β-*phenoxyacetamidoceph*-3-*em*-4-*carboxylate* (32).—To the sulphoxide (3) (0.75 g, 1.5 mmol) in acrylonitrile (40 ml) at room temperature was added triethylamine (1.5 ml). The mixture was stirred for 18 h and the solvent was then removed *in vacuo*. The residue dissolved in ethyl acetate was washed with 2N-hydrochloric acid, water, sodium hydrogen carbonate, and water, dried ($MgSO_4$), and evaporated *in vacuo* to yield a yellow oil. This oil was dissolved in dimethylformamide (20 ml) and treated at 0 °C with phosphorus tribromide (0.8 ml) for 20 min. The mixture was poured into ice-cold sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic phase was washed with sodium hydrogen carbonate solution and water, dried ($MgSO_4$), and evaporated *in vacuo* to give an oil which was chromatographed on silica to yield compound (1) (0.47 g, 63%) and 2,2,2-*trichloroethyl* 2α-(2-*cyanoethyl*)-3-*methyl*-7β-*phenoxyacetamidoceph*-3-*em*-4-*carboxylate* (32), an amorphous solid (0.2 g, 25%), $[\alpha]_D^{22}$ +97° (*c* 1.08 in chloroform), $\lambda_{max.}$ 267 nm (ε 11 400), $\nu_{max.}$ (film) 3 300 (NH), 2 240 (nitrile), 1 790 (β-lactam C=O), 1 750 (ester C=O), and 1 690 cm^{-1} (amide C=O), δ ($CDCl_3$) 1.50—2.0 (2 H, m, CH_2CH_2CN), 2.30 (3 H, s, Me), 2.60—2.88 (2 H, m, CH_2CH_2CN), 3.50 (1 H, dd, *J* 9 and 2 Hz, 2-H), 4.69 (2 H, s, CH_2), 4.88 and 5.10 (2 H, ABq, *J* 12 Hz, CH_2 of ester), 5.06 (1 H, d, *J* 5 Hz, 6-H), 6.10 (1 H, dd, *J* 10 and 5 Hz, 7-H), and 7.0—7.64 (6 H, m, Ph and NH) (Found: M^+, 531.0814. $C_{21}H_{20}{}^{35}Cl_3N_3O_5S$ requires *M*, 531.0190).

De-esterification of the Ceph-3-*em* (32).—The ester (32) (0.066 g, 0.12 mmol) in dimethylformamide–acetic acid (4 ml; 25 : 7.5) was stirred with zinc (0.2 g) for 1.5 h at ice temperature. The zinc was filtered off and the solution diluted with ethyl acetate. The organic phase was washed with water and extracted with sodium hydrogen carbonate solution. This aqueous solution was acidified with 2N-hydrochloric acid (to pH 2) and then extracted with fresh ethyl acetate. After washing with brine and drying ($MgSO_4$) the organic solvent was removed *in vacuo* to yield a clear oil contaminated with acetic acid. The acetic acid was removed by dissolving the oil in carbon tetrachloride and again evaporating *in vacuo* to afford 2α-(2-*cyanoethyl*)-3-*methyl*-7β-*phenoxyacetamidoceph*-3-*em*-4-*carboxylic acid* (33) as an amorphous solid (0.045 g, 85%), $[\alpha]_D^{23}$ +124° (*c* 0.5 in chloroform), $\lambda_{max.}$ 266 nm (ε 4 100), $\nu_{max.}$ (film) 3 300—2 300 (NH and OH), 2 240 (nitrile), 1 770 (β-lactam C=O), 1 720 (acid C=O), and 1 680 cm^{-1} (amide C=O), δ ($CDCl_3$) 1.5—2.0 (2 H, m, CH_2CH_2CN), 2.18 (3 H, s, Me), 2.40—2.80 (2 H, m, CH_2CH_2CN), 3.34 (1 H, dd, *J* 12 and 3 Hz, 2-H), 4.60 (2 H, s, CH_2), 5.00 (1 H, d, *J* 5 Hz, 6-H), 5.94 (1 H, dd, *J* 10 and 5 Hz, 7-H), 6.80—7.66 (6 H, m, Ph and NH), 7.95br (1 H, s, CO_2H, exch.) (Found: $M^+ - H_2O$, 383.0948. $C_{19}H_{17}N_3O_4S$ requires 383.0940).

Correlation of Compounds (33) *and* (30).—The acid (33) (0.05 g, 0.12 mmol) in methanol was treated with an excess of ethereal diazomethane until the yellow colouration just persisted. The excess of diazomethane was destroyed with a few drops of 2N-acetic acid. The solvent was removed *in vacuo* to yield an oil which was taken up in ethyl acetate; the solution was washed with sodium hydrogen carbonate solution and water, dried, and again evaporated *in vacuo* to give (30) as an amorphous solid (0.045 g, 88%), identical with that prepared previously.

Reaction of 2,2,2-*Trichloroethyl* (1R)-3-*Methyl*-7β-*phenoxyacetamidoceph*-3-*em*-4-*carboxylate* 1-*Oxide* (7) *with Acrylonitrile*.—To the oxide (7) (0.184 g, 0.37 mmol) in acrylonitrile (20 ml) at room temperature was added triethylamine (0.038 g, 0.38 mmol). The mixture was stirred for 2 h, after which t.l.c. showed complete conversion into a less polar product. The mixture was poured into 0.50N-hydrochloric acid and extracted with ethyl acetate. The organic phase was washed with sodium hydrogen carbonate solution and brine, dried ($MgSO_4$), and evaporated *in vacuo* to yield a yellow oil. Column chromatography yielded 2,2,2-*trichloroethyl* (1R)-4β-(2-*cyanoethyl*)-3-*methyl*-7β-*phenoxyacetamidoceph*-2-*em*-4α-*carboxylate* 1-*oxide* (38) (0.2 g, 99%) as an oil, $[\alpha]_D^{22}$ +67° in chloroform), $\lambda_{max.}$ 263 nm (ε 2 400), $\nu_{max.}$ (film) 3 300 (NH) (nitrile), 1 785 (β-lactam C=O), 1 760 (ester C=O), and 1 685 cm^{-1} (amide C=O), δ ($CDCl_3$) 1.94 (3 H, d, *J* 1 Hz, Me), 2.25—3.31 (4 H, m, CH_2CH_2CN), 4.51 (2 H, s, CH_2), 4.64 and 5.03 (2 H, ABq, *J* 12 Hz, CH_2 of ester), 4.81 (1 H, d, *J* 4 Hz, 6-H), 5.28 (1 H, dd, *J* 9 and 4 Hz, 7-H), 6.45 (1 H, q, *J* 1 Hz, 2-H), 6.85—7.47 (5 H, m, Ph), and 7.96 (1 H, d, *J* 9 Hz, N-H) (Found: C, 46.0; H, 3.9; Cl, 19.5; N, 7.5; S, 5.7. $C_{21}H_{20}Cl_3N_3O_6S$ requires C, 45.9; H, 3.7; Cl, 19.4; N, 7.7; S, 5.8%).

Deoxygenation of the Sulphoxide (38).—The sulphoxide (38) (0.13 g, 0.29 mmol) in dimethylformamide (10 ml) was stirred at 0 °C with phosphorus tribromide (0.1 ml) for 35 min. The mixture was poured into sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic phase was washed with sodium hydrogen carbonate solution and brine, dried ($MgSO_4$), and evaporated *in vacuo* to yield a clear yellow oil (0.11 g, 88%). T.l.c. and i.r., and n.m.r. spectra showed this to be identical with compound (18) (see above).

Reaction of the Sulphoxide (3) *with Ethyl Chloroformate*.—The ester sulphoxide (3) (1 g, 0.21 mmol) in dry tetrahydrofuran (50 ml) was treated with ethyl chloroformate (0.72 g, 0.66 mmol) at room temperature. To the stirred mixture was added dropwise triethylamine (0.67 g, 0.66 mmol) in tetrahydrofuran (10 ml). After 2 h at room temperature the mixture was poured into water and extracted with ethyl acetate. The organic phase was washed with 2N-hydrochloric acid, water, sodium hydrogen carbonate solution, and water, dried ($MgSO_4$), and evaporated *in vacuo* to give an oil. Chromatography afforded 2,2,2-*trichloroethyl* 2β-(*ethoxycarbonyloxy*)-3-*methyl*-7β-*phenoxyacetamidoceph*-3-*em*-4-*carboxylate* (39) as an oil (0.75 g, 68%), $[\alpha]_D^{22}$ +126° (*c* 1.1 in chloroform), $\lambda_{max.}$ 268 nm (ε 5 700), $\nu_{max.}$ (film) 3 400 (NH), 1 790 (β-lactam C=O), 1 750 (ester C=O), 1 740 (carbonate C=O), and 1 690 cm^{-1} (amide C=O), δ_H ($CDCl_3$) 1.20 (3 H, t, *J* 7 Hz, CH_2CH_3), 2.54 (3 H, s, Me), 4.24 (2 H, q, *J* 7 Hz, CH_2CH_3), 4.66 (2 H, s, CH_2), 4.88 and 5.04 (2 H, ABq, *J* 12 Hz, CH_2 of ester), 5.40 (1 H, d, *J* 5 Hz, 6-H), 5.96 (1 H, dd, *J* 10 and 5 Hz, 7-H), 6.00 (1 H, s, 2-H), 7.00—7.60 (5 H, m, Ph), and 7.50 (1 H, d, *J* 10 Hz,

NH), δ_C 14.03 (24-C), 19.59 (21-C), 60.54 (6-C), 62.25 (7-C), 65.58 (23-C), 67.64 (11-C), 74.97 (19-C), 77.89 (13-C), 94.35 (20-C), 115.13 (14- and 16-C), 122.43 (15-C), 124.51 (4-C), 129.70 (13- and 17-C), 151.40 (18-C), 153.42 (12-C), 157.36 (22-C), 160.66 (8-C), 166.65 (4-C), and 168.56 (10-C) (Found: C, 44.6; H, 3.9; Cl, 19.1; N, 4.9; S, 5.9. $C_{21}H_{21}Cl_3N_2O_8S$ requires C, 44.4; H, 3.7; Cl, 18.8; N, 4.9; S, 5.6%).

Also eluted was 2,2,2-*trichloroethyl* 2α-(*ethoxycarbonyloxy*)-3-*methyl*-7β-*phenoxyacetamidoceph*-3-*em*-4-*carboxylate* (40) as a crystalline solid (0.04 g, 4%), m.p. 209—210°, $[\alpha]_D^{23}$ +74° (*c* 0.78 in chloroform), $\lambda_{max.}$ 267 nm (ε 3 700), $\nu_{max.}$ (KBr) 3 310 (NH), 1 802 (β-lactam C=O), 1 755 (ester C=O), 1 740 (carbonate C=O), and 1 680 cm^{-1} (amide C=O), δ ($CDCl_3$ 1.38 (3 H, t, *J* 7 Hz, CH_2CH_3), 2.24 (3 H, s, Me), 4.39 (2 H, q, *J* 7 Hz, CH_2CH_3), 4.66 (2 H, s, CH_2), 4.94 and 5.18 (2 H, ABq, *J* 12 Hz, CH_2 of ester), 5.35 (1 H, d, *J* 5 Hz, 6-H), 6.14 (1 H, ddd, *J* 11, 5, and 1 Hz, 7-H), 6.33 (1 H, d, *J* 1 Hz, 2-H), and 7.00—7.68 (6 H, m, Ph and NH) (Found: C, 44.3; H, 3.7; Cl, 19.0; N, 5.1; S, 5.9. $C_{21}H_{21}Cl_3N_2O_8S$ requires C, 44.4; H, 3.7; Cl, 18.8; N, 4.9; S, 5.6%).

De-esterification of the Ester (40) *with Zinc*.—The ester (0.5 g, 0.88 mmol) in dimethylformamide–glacial acetic acid (20 ml; 25 : 7.5 v/v) was stirred at 0 °C with zinc (0.5 g) for 10 min. The zinc was filtered off and the solution extracted with ethyl acetate. The organic phase was then extracted with sodium hydrogen carbonate solution. This solution was re-acidified with 2N-hydrochloric acid and extracted with fresh ethyl acetate. Evaporation of the organic phase *in vacuo* yielded an oil (0.2 g), which was very complex (t.l.c.). This reaction was not pursued further.

Attempts at decarboxylation at the 2-position utilising (*a*) lithium iodide–monohydrate in dimethylformamide and (*b*) 1 equiv. of dilute sodium hydroxide solution in pyridine–acetonitrile both produced complex mixtures from which no homogeneous β-lactam product was obtained.

Attempted Reaction of 2,2,2-*Trichloroethyl* (1R)-3-*Methyl* 7β-*phenoxyacetamidoceph*-3-*em*-4-*carboxylate* 1-*Oxide* (7) *with Ethyl Chloroformate*.—The sulphoxide (7) (0.15 g, 0.3 mmol) in dry tetrahydrofuran (10 ml) was treated with ethyl chloroformate (0.11 g, 1 mmol) and triethylamine (0.1 g, 1 mmol). After 3 h there was no trace of reaction (t.l.c.).

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