Importance of the C(3) Substituent of the Penam Derivative in Interconversion Reactions of Penam and Cepham Systems

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The azetidinone disulphide (1b), a structural analogue of Kamiya's disulphide (1a), has been synthesized. Some cyclization reactions of the disulphides (1) (Br_2 in CH_2Cl_2 and AcOAg in $ClCH_2CO_2H$–CH_2Cl_2) leading to penam and cepham derivatives through episulphonium ions (2), have been studied. The data obtained show that changing the substituent X in (1a) and (1b) brings about changes in the distribution of the positive charge in the intermediate episulphonium ions (2a) and (2b), and thus affects to some extent the regioselectivity of the episulphonium ring opening and the chemical behaviour of (1a) and (1b).

The interconversion reaction of thiazine and thiazolidine in β-lactam antibiotics is an interesting and potentially useful route to new penam and cepham derivatives, as well as simple cephalosporins. These interconversion reactions are usually assumed to proceed through the intermediate formation of episulphonium ions of type (2) (Scheme 1). The regiochemistry of the step following the formation of the intermediates (2), *i.e.* the cleavage of one of the C–S bonds of the three-membered ring, leads to penam [(3),(4)] or cepham [(5),(6)] reaction products.[1-4]

An episulphonium ion (a) (Figure) can be considered to be formally equivalent to the protonated heterocycles formed as intermediates in the ring-opening reactions in acid media of oxiranes (b) and other small-ring heterocycles such as (c). It is well known that the positive charge in these systems is localized on the heteroatom and on the adjacent carbon. The regioselectivity of the ring opening of these intermediates depends to a large extent on electronic effects (inductive or resonance), as well as on the steric effect of substituents on the heterocyclic ring and the reaction conditions.[5]

On the basis of such considerations, as a continuation of our studies on the interconversion reactions of penam and cepham systems,[2,3] we were interested in investigating the way in which different substituents on the intermediate episulphonium ion could modify the course of these reactions. We wanted in particular to find out what differences exist, if any, between the chemical behaviour of the intermediate (2a), and (2b) in which the CO_2R group has been substituted by a less electron-withdrawing group (*e.g.* a protected hydroxymethylenic group). This substitution should modify the charge distribution in the episulphonium ion, and therefore the regioselectivity of the ring opening and the product ratio.

Asymmetric azetidinone disulphides of type (1a) (Kamiya's disulphides),[6] available from penicillin sulphoxides, are useful and reliable sources of episulphonium ions of type (2a). We here report the study of some cyclization reactions of the disulphide (1b), a structural analogue of Kamiya's disulphide (1a) in which the CO_2R group present in the side chain of (6a) has been replaced by a CH_2OR group. The cyclization reactions of the disulphide (1b) were chosen for investigation because similar reactions of the unmodified Kamiya's disulphide (1a) have been examined previously and are known to proceed through episulphonium intermediates of type (2).[6,7] The disulphide (1b) was allowed to react with bromine in CH_2Cl_2 and with CH_3CO_2Ag in $ClCH_2CO_2H$–CH_2Cl_2, and the results obtained were compared with those found in the analogous reactions of Kamiya's disulphide (1a).

The *p*-nitrobenzoate (1b) was prepared in the following manner (Scheme 2): the phenoxyacetamidopencillin (7) was transformed into the corresponding mixed anhydride with

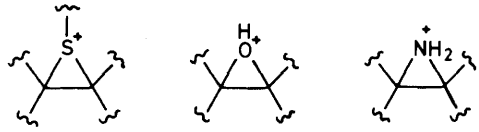
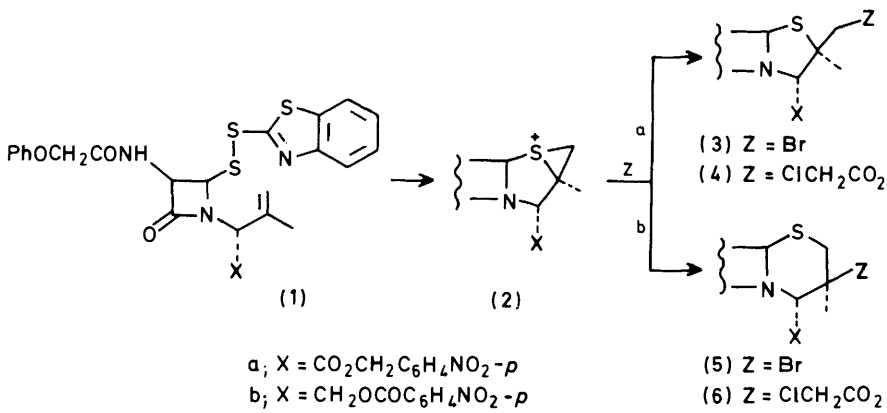
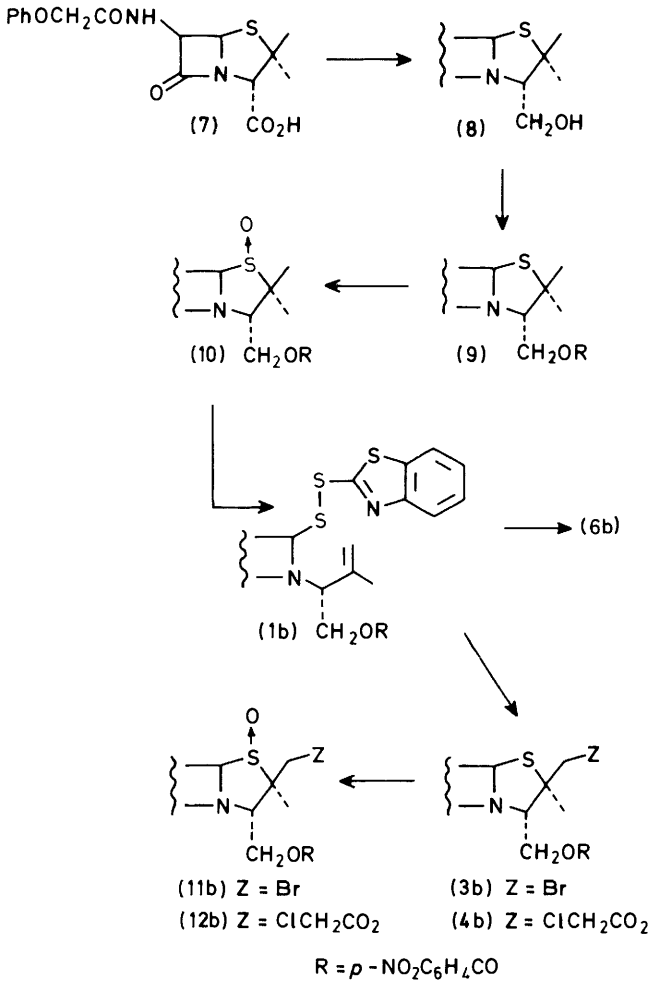


Figure.



Scheme 1.



Scheme 2.

ethyl chloroformate and then directly reduced with $NaBH_4$ to the 3α-hydroxymethylpenam derivative (8).[8] Reaction of compound (8) with *p*-nitrobenzoyl chloride afforded the ester (9)[8] which on oxidation with *m*-chloroperoxybenzoic acid gave the (*S*)-penam *S*-oxide (10). Reaction of the oxide (10) with 2-mercaptobenzothiazole, under the same conditions as those used by Kamiya,[6] afforded the required disulphide (1b).

The reaction of (1b) with bromine in CH_2Cl_2, analogously to (1a), afforded exclusively the 2β-bromomethylpenam derivative (3b). As in the case of (3a),[3] attempts to purify compound (3b) by chromatography led to its extensive rearrangement to the 3β-bromocepham (5b). Also, dissolution of (3b) in dimethylformamide (DMF) yielded the rearranged product (5b). However, oxidation of (3b) with *m*-chloroperoxybenzoic acid gave the corresponding stable (*S*)-penam *S*-oxide (11b) which can be isolated in a pure state. The reaction of the disulphide (1b) with silver acetate and monochloroacetic acid in CH_2Cl_2 followed a similar course to that of Kamiya's disulphide (1a), affording a mixture of the 2β-chloroacetoxymethylpenam (4b) and the 3β-chloroacetoxycepham (6b). However, the ratio of penam and cepham derivatives depends to some extent on the nature of the starting disulphide (6) (see Table 1). Oxidation with *m*-chloroperoxybenzoic acid of the penam compound (4b) yielded the (*S*)-penam *S*-oxide (12b). On the other hand, the same oxidation of the cepham derivatives (5b) and (6b) gave exclusively the (*R*)-isomers (13b) and (14b) (Scheme 3).[9]

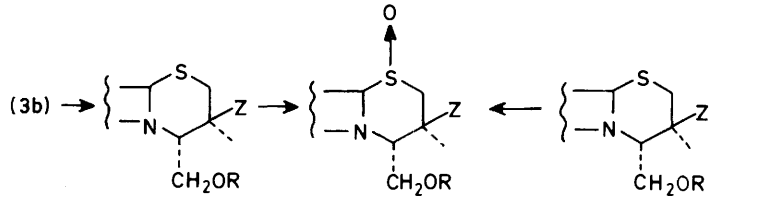
The structures of all the compounds have been confirmed by their ^1H n.m.r. spectra, and on the basis of the signals due to stretching of the β-lactam C=O in the i.r. In particular, the penam and cepham nature of (3b) and (4b), and (5b) and (6b), respectively, has been established on the basis of the geminal coupling constants of the methylene protons of the CH_2Z and SCH_2 groups;[10] the cepham derivatives (5b) and (6b) have higher values than the corresponding penam compounds (3b) and (4b). The configuration of the sulphoxide group was deduced from intermolecular hydrogen-bonding studies of the amide proton using $[^2H_6]$-Me_2SO (see Table 2).[2,11,12]

Little change in the shift for the amide proton of the penam derivatives (10), (11b), and (12b) was observed on passing from $CDCl_3$ to $[^2H_6]$-Me_2SO, which suggests the *S* configuration for the *S*-oxide; however, larger changes were obtained for the cepham compounds (13b) and (14b), indicating the *R* configuration for the same group.[2,11,12] The stereochemistry at the C(2) carbon of the penam derivatives (3b) and (4b), and at the C(3) carbon of the cepham derivatives (5b) and (6b), can be deduced by analogy with that found for the corresponding products obtained from the carboxy substituted azetidinone disulphide (6a).[3,6,7] The C(2) configuration of the penam compounds (3b) and (4b) has also been confirmed by comparison of their aromatic solvent-induced shifts (ASIS) with those of corresponding (*S*)-penam *S*-oxides (11b) and (12b) (see Table 3).[2,11,12] Unfortunately, this type of configurational study is not possible for the *R* configuration of the *S*-oxides (13b) and (14b) obtained from the cepham derivatives (5b) and (6b).[11]

The similarity in chemical behaviour of the disulphide (1b) and Kamiya's disulphide (1a) suggests that they react by similar mechanisms, *i.e. via* the analogous episulphonium intermediates (2). Unfortunately, the cyclization reactions induced by bromine of both the disulphides (1a) and (1b) occurs in a regiospecific fashion, affording exclusively penam compounds of type (3); this is because the strong nucleophile (Br^-) present in the reaction medium attacks exclusively the less hindered carbon (pathway a, Scheme 1) of the episulphonium ion (2). We are therefore unable to make any evaluation of the effect of the substituent X. On the other hand, the reactions of both the disulphides (1a) and (1b) with Ag^+ ions in the presence of $ClCH_2CO_2H$ are not regiospecific and show differences that, although not great, are significant. The yield of the Markovnikov type product (6) [*i.e.* the product arising by attack of the nucleophile on the tertiary carbon of (2)] increases from 43 to 55% when the substituent X is changed from CO_2R to CH_2OR; this is because CH_2OR is less electron withdrawing than CO_2R, leading to a relative increase in the stability of the partial positive charge on the episulphonium ion carbon next to the substituent. This could slightly favour attack of the nucleophile on this carbon (pathway b), thereby decreasing the ratio of (4) : (6), as observed. An alternative rationalization of the observed results could be based on differences in the steric hindrance of the two substituents in (2a) and (2b).

Experimental

M.p.s were determined with a Kofler hot-stage apparatus and are uncorrected. I.r. spectra for comparisons of compounds were taken on paraffin oil mulls on a Perkin-Elmer model 197 instrument and those for the determination of C=O stretching bands with a Perkin-Elmer model 257 double-beam grating spectrophotometer using a NaCl cell of 1-mm optical length in dried $CHCl_3$. ^1H N.m.r. spectra were detected with a Varian EM360 Å spectrometer in a *ca.* 10% solution of $CDCl_3$, in $[^2H_6]$-Me_2SO and in C_6D_6, or with a Varian CFT-20 instrument operating at 80 MHz in a *ca.* 1% solution of the same solvents, depending on the solubility of the compounds. Me_4Si was used as internal standard. The relative percentages



Scheme 3.

Table 1. Ratios of penam and cepham products obtained in the cyclization reactions of (1a) and (1b) with Br_2 and with silver ions in the presence of monochloroacetic acid

Compd	Reagent	Product ratios (%) (3)	(5)	(4)	(6)
(1a)	Br_2	100	0		
(1b)	Br_2	100	0		
(1a)	$Ag^+/ClCH_2CO_2H$			57	43
(1b)	$Ag^+/ClCH_2CO_2H$			45	55

Table 2. NH Proton shifts

Compd	δ($CDCl_3$)	δ([$^2H_6$]-Me_2SO)	Δ [a,b]
(10)	8.32	8.33	−0.01
(11b)	8.25	8.27	−0.02
(12b)	8.23	8.40	−0.17
(13b)	7.55	8.87	−1.32
(14b)	7.37	9.17	−1.80

[a] Δ = δ($CDCl_3$) − δ([$^2H_6$]-Me_2SO). [b] Negative values indicate deshielding effects.

Table 3. Benzene-induced shifts in $CDCl_3$ and C_6D_6 for compounds (3b), (4b), (11b), and (12b) [a]

Compound	Solvent	5-H	6-H	2α-Me
(3b)	$CDCl_3$	5.51	5.60	1.70
(3b)	C_6D_6	4.97	5.50	1.23
$\Delta_{(3b)}$ [b]		0.54	0.10	0.47
(11b)	$CDCl_3$	5.00	6.12	1.50
(11b)	C_6D_6	3.84	6.05	0.65
$\Delta_{(11b)}$ [b]		1.16	0.07	0.85
$\Delta_{(11b)}$	$-\Delta_{(3b)}$	0.62	−0.03	0.38
(4b)	$CDCl_3$	5.42	5.63	1.62
(4b)	C_6D_6	4.90	5.60	1.05
$\Delta_{(4b)}$ [b]		0.52	0.03	0.57
(12b)	$CDCl_3$	5.03	6.12	1.38
(12b)	C_6D_6	4.09	5.98	0.42
$\Delta_{(12b)}$ [b]		0.94	0.14	0.96
$\Delta_{(12b)}$	$-\Delta_{(4b)}$	0.42	0.11	0.39

[a] Positive values indicate shielding effects. [b] δ($CDCl_3$) − δ(C_6D_6).

of compounds (4a) and (6a), and (4b) and (6b), have been calculated on the basis of the integrals of the 2α-Me [for (4)] and 3α-Me [for (6)] singlets in the ^1H n.m.r. spectra of the crude reaction mixture. Preparative t.l.c. was carried out on 0.5-mm layer silica gel plates (Merck F_{254}) containing a fluorescent indicator; spots were detected under u.v. light (254 nm). Column chromatography was carried out with 70—230 mesh silica gel (Merck 60). Evaporations were carried out under reduced pressure (rotary evaporator), and magnesium sulphate was used as the drying agent. CH_2Cl_2, tetrahydrofuran (THF), and toluene were refluxed over P_2O_5, $LiAlH_4$, and Na, respectively, and then rectified. Dimethylformamide (DMF) was passed through an aluminium oxide (Activity I) column, degassed with N_2, and dried on molecular sieves.

3α-Hydroxymethyl-2,2-dimethyl-6β-phenoxyacetamidopenam (8).—A stirred solution of penicillin V (7) (5.0 g, 14.3 mmol) in anhydrous THF (40 ml) was cooled to −10 °C and then treated dropwise with, successively, Et_3N (1.45 g, 14.3 mmol) and with a solution of ethyl chloroformate (1.55 g, 14.3 mmol) in anhydrous THF (10 ml). After the resulting mixture had been stirred for 2 h at −10 °C, $NaBH_4$ (1.08 g, 28.6 mmol) was added in small portions during 2 min. The reaction mixture was then stirred for 30 min at room temperature, diluted with H_2O (70 ml), and extracted with CH_2Cl_2. Evaporation of the washed (H_2O) and filtered organic solvent afforded an oily residue (4.0 g) which was chromatographed through a 3 × 30-cm column of silica gel (150 g), eluting with toluene–ethyl acetate (3 : 7) and collecting 15 ml fractions. Fractions 17—27 yielded a solid which on crystallization from acetone–hexane gave the penam (8) (1.5 g, 31%), m.p. 128—130 °C (lit.,[8] m.p. 130—131 °C); $\nu_{max.}$ 1 787 cm^{-1} (β-lactam C=O); δ 1.48 (6 H, s, Me), 3.45—4.10 (3 H, br, $CHCH_2$), 4.55 (2 H, s, CH_2CO), 5.37 (1 H, d, *J* 4.0 Hz, CHS), and 5.64 (1 H, q, *J* 4.0 and 9.2 Hz, NHC*H*).

2,2-Dimethyl-3α-(p-nitrobenzoyloxymethyl)-6β-phenoxyacetamidopenam (9).—A stirred solution of compound (8) (1.0 g, 2.97 mmol) in anhydrous THF (10 ml) was treated dropwise at 0 °C with a solution of *p*-nitrobenzoyl chloride (1.65 g, 8.9 mmol) in anhydrous benzene–pyridine (15 : 1; 15 ml). The stirred suspension was allowed to warm to room temperature during 15 h, poured into water, and extracted with ethyl acetate. The organic layer was washed with 2N-phosphoric acid, aqueous $NaHCO_3$ (5%), and water before being dried and evaporated. The resulting residue was chromatographed through a 3 × 17-cm column of silica gel (85 g) eluting with 7 : 2 : 1 toluene–CH_2Cl_2–acetone and collecting 15-ml fractions. Fractions 9—13 gave the penam (9) (0.9 g, 62%) as a vitreous product (lit.,[8] m.p. 60—65 °C): $\nu_{max.}$ 1 778 cm^{-1} (β-lactam C=O); δ 1.57 (6 H, s, Me), 4.38 (3 H, br, $CHCH_2$), 4.53 (2 H, s, CH_2CO), 5.42 (1 H, d, *J* 4.0 Hz, CHS), and 5.67 (1 H, q, *J* 4.0 and 8.6 Hz, NHC*H*).

(S)-2,2-Dimethyl-3α-(p-nitrobenzoyloxymethyl)-6β-phenoxyacetamidopenam S-Oxide (10).—A stirred solution of (9) (1.09 g, 2.2 mmol) in CH_2Cl_2 (70 ml) was cooled to 0 °C and

treated with a solution of 90% *m*-chloroperoxybenzoic acid (0.42 g, 2.2 mmol) in CH_2Cl_2 (90 ml). The resulting solution was stirred for 1 h at the same temperature, washed (10% aqueous $NaHCO_3$ and H_2O), filtered and evaporated to dryness to give an oily residue (1.0 g), which was crystallized from $CHCl_3$–hexane to yield the *penam* S-*oxide* (10) (0.6 g, 54%); m.p. 153—156 °C; $\nu_{max.}$ 1 783 cm^{-1} (β-lactam C=O); δ 1.33 (3 H, s, Me), 1.66 (3 H, s, Me), 4.42 (3 H, br, $CHCH_2$), 4.53 (2 H, s, CH_2CO), 4.99 (1 H, d, *J* 4.8 Hz, CHS), and 6.06 (1 H, q, *J* 4.8 and 10.8 Hz, NHC*H*) (Found: C, 54.8; H, 4.5; N, 8.2. $C_{23}H_{23}N_3O_8S$ requires C, 55.08; H, 4.62; N, 8.38%).

4-*Benzothiazol-2-yldithio*-1-[2-*methyl*-1-(p-*nitrobenzoyloxymethyl*)*prop*-2-*enyl*]-3-*phenoxyacetamidoazetidin*-2-*one* (1b).—A solution of (10) (0.78 g, 1.56 mmol) and 2-mercaptobenzothiazole (0.28 g, 1.67 mmol) in toluene (60 ml) was refluxed for 2 h. After being cooled, the solution was evaporated to dryness to yield an oily residue which was chromatographed through a 2.5 × 15-cm column of silica gel (40 g) eluting with toluene–ethyl acetate (8 : 2) and collecting 15-ml fractions. Fractions 10—15 yielded the *azetidinone* (1b) (0.84 g, 83%) as an oil; δ 1.35 (3 H, s, Me), 4.53 (2 H, s, CH_2CO), 5.20 (1 H, d, *J* 4.8 Hz, CHS), and 5.38 (1 H, q, *J* 4.8 and 8.4 Hz, NHC*H*) (Found: C, 55.6; H, 4.2; N, 8.3. $C_{30}H_{26}N_4O_7S_3$ requires C, 55.37; H, 4.03; N, 8.61%).

Reaction of the Azetidinone (1b) *with Bromine in Anhydrous* CH_2Cl_2.—A stirred solution of (1b) (0.1 g, 0.15 mmol) in anhydrous CH_2Cl_2 (15 ml) was treated dropwise with a solution of Br_2 (0.012 g, 0.075 mmol) in the same solvent (1 ml) at −35 °C. When the addition was complete, the reaction mixture was left at the same temperature for 10 min and then washed with H_2O, and evaporated to yield a semi-solid residue (0.09 g) consisting exclusively of 2β-*bromomethyl*-2α-*methyl*-3α-(p-*nitrobenzoyloxymethyl*)-6β-*phenoxyacetamidopenam* (3b) (^1H n.m.r.), together with 2-benzothiazolyl disulphide: $\nu_{max.}$ ($CHCl_3$) 1 786 cm^{-1} (β-lactam CO); δ 1.70 (3 H, s, Me), 3.33 and 3.52 (2 H, d, *J* 11.0 Hz, CH_2Br), 5.48 (1 H, d, *J* 4.2 Hz, CHS), and 5.60 (1 H, q, *J* 4.2 and 8.6 Hz, NHC*H*).

Attempts to purify (3b) by preparative t.l.c. eluting with toluene–ethyl acetate (7 : 3), led to recovery of the 3β-*bromo*-3α-*methyl*-4α-(p-*nitrobenzoyloxymethyl*)-7β-*phenoxyacetamidocepham* (5b); m.p. 153—155 °C (ethyl acetate); $\nu_{max.}$ ($CHCl_3$) 1 774 cm^{-1} (β-lactam C=O); δ 2.05 (3 H, s, Me), 2.99 and 3.33 (2 H, d, *J* 14.8 Hz, SCH_2), 5.13 (1 H, d, *J* 4.4 Hz, CHS), and 5.59 (1 H, q, *J* 4.4 and 9.4 Hz, NHC*H*) (Found: C, 48.95; H, 4.3; Br, 14.3; N, 7.1. $C_{23}H_{22}BrN_3O_7S$ requires C, 48.94; H, 3.93; Br, 14.16; N, 7.44%).

Compound (5b) was also obtained by dissolving the penam (3b) in anhydrous DMF and allowing the solution to stand for 48 h at room temperature.

Reaction of Compound (1a) *with Bromine in Anhydrous* CH_2Cl_2.—Reaction of (1a) [6] in CH_2Cl_2 with Br_2 in CH_2Cl_2, as described above for the analogous reaction of (1b), yielded exclusively the p-*nitrobenzyl* 2β-*bromomethyl*-2α-*methyl*-6β-*phenoxyacetamidopenam*-3α-*carboxylate* (3a) [3] (^1H n.m.r.) together with 2-benzothiazolyl disulphide.

Reaction of Compound (1b) *with Silver Acetate and Monochloroacetic Acid in Anhydrous* CH_2Cl_2.—A mixture of (1b) (0.2 g, 0.3 mmol), AgOAc (0.1 g, 0.6 mmol), and $ClCH_2CO_2H$ (1.2 g, 13 mmol) in anhydrous CH_2Cl_2 (45 ml) was stirred for 4 h at room temperature. The reaction mixture was filtered and the organic phase was washed [aqueous $NaHCO_3$ (5%), and brine], dried and evaporated to yield an oily residue (0.14 g) consisting of 2β-*chloroacetoxymethyl*-2α-*methyl*-3α-(p-*nitrobenzoyloxymethyl*)-6β-*phenoxyacetamidopenam* (4b) and 3β-*chloroacetoxy*-3α-*methyl*-4α-(p-*nitrobenzoyloxymethyl*)-7β-*phenoxyacetamidocepham* (6b) in the ratio 45 : 55 (^1H n.m.r.). The crude oil was subjected to preparative t.l.c. eluting with toluene–ethyl acetate (7 : 3) and the two bands obtained were extracted with $CHCl_3$. Extraction of the upper band of the chromatogram gave the *penam* (4b) (0.048 g) as an oil; $\nu_{max.}$ ($CHCl_3$) 1 786 cm^{-1} (β-lactam C=O); δ 1.62 (3 H, s, Me), 3.90 and 4.43 (2 H, d, *J* 11.8 Hz, $SCCH_2CO$), 4.07 (2 H, s, CH_2Cl), 5.42 (1 H, d, *J* 4.0 Hz, CHS), and 5.63 (1 H, q, *J* 4.0 and 9.0 Hz, NHC*H*) (Found: C, 52.3; H, 4.3; Cl, 6.5; N, 7.0. $C_{25}H_{24}ClN_3O_9S$ requires C, 51.95; H, 4.18; Cl, 6.13; N, 7.27%).

Extraction of the lower band of the chromatogram gave an oil consisting of the *cepham* (6b) (0.055 g); $\nu_{max.}$ ($CHCl_3$) 1 776 cm^{-1} (β-lactam C=O); δ 1.70 (3 H, s, Me), 3.17 and 3.60 (2 H, d, *J* 14.4 Hz, SCH_2), 4.00 (2 H, s, CH_2Cl), 5.13 (1 H, d, *J* 4.4 Hz, CHS), and 5.57 (1 H, q, *J* 4.4 and 9.4 Hz, NHC*H*) (Found: C, 51.65; H, 4.2; Cl, 6.4; N, 7.0. $C_{25}H_{24}ClN_3O_9S$ requires C, 51.95; H, 4.18; Cl, 6.13; N, 7.27%).

The 45 : 55 mixture of (4b) and (6b) was stable under the reaction conditions.

Reaction of Compound (1a) *with Silver Acetate and Monochloroacetic Acid in Anhydrous* CH_2Cl_2.—Reaction of (1a) [6] with AgOAc and $ClCH_2CO_2H$ in CH_2Cl_2 as described above for the analogous reaction of (1b), yielded a residue consisting of p-*nitrobenzyl* 2β-*chloroacetoxymethyl*-2α-*methyl*-6β-*phenoxyacetamidopenam*-3α-*carboxylate* (4a) [7] and p-*nitrobenzyl* 3β-*chloroacetoxy*-3α-*methyl*-7β-*phenoxyacetamidocepham*-4α-*carboxylate* (6a) in the ratio of 57 : 43 (^1H n.m.r.). This reaction was previously reported,[7] but the ratio of (4a) and (6a) in the crude reaction mixture was not given. Products (4a) and (6a) were stable under the reaction conditions.

(S)-2β-*Methyl-substituted Penam* S-*Oxide Derivatives* (11b) *and* (12b).—A solution of the penam derivative [(3b) or (4b)] (0.25 mmol) in anhydrous CH_2Cl_2 (6 ml) was treated, as described for the preparation of (10), with a solution of 90% *m*-chloroperoxybenzoic acid (0.048 g, 0.25 mmol) in anhydrous CH_2Cl_2 (4 ml), yielding a crude oily residue consisting almost exclusively of the corresponding *S*-oxide [(11b) or (12b)] (^1H n.m.r.). The crude product was subjected to preparative t.l.c. using the proper solvent mixture [ethyl acetate–toluene (1 : 1) for (11b) and CH_2Cl_2–acetone (9 : 1) for (12b)] as eluant. Extraction with CH_2Cl_2 of the top band of the chroatogram gave the *S*-oxide derivative [(11b) or (12b), respectively].

Compound (11b) (45%); $\nu_{max.}$ ($CHCl_3$) 1 803 cm^{-1} (β-lactam C=O); δ 1.48 (3 H, s, Me), 3.68 and 4.08 (2 H, d, *J* 11.2 Hz, CH_2Br), 4.98 (1 H, d, *J* 4.8 Hz, CHS), and 6.08 (1 H, q, *J* 4.8 and 10.4 Hz, NHC*H*) (Found: C, 47.9; H, 4.1; Br, 14.0; N, 7.0. $C_{23}H_{22}BrN_3O_8S$ requires C, 47.59; H, 3.82; Br, 13.77; N, 7.24%).

Compound (12b)·$CHCl_3$ (50%); m.p. 99—101 °C ($CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 1 798 cm^{-1} (β-lactam C=O); δ 1.38 (3 H, s, Me), 4.17 (2 H, s, $SCCH_2O$), 5.03 (1 H, d, *J* 4.4 Hz, CHS), and 6.12 (1 H, q, *J* 4.4 and 10.0 Hz, NHC*H*) (Found: C, 44.0; H, 3.45; Cl, 19.8; N, 5.7. $C_{26}H_{25}Cl_4N_3O_{10}S$ requires C, 43.78; H, 3.53; Cl, 19.88; N, 5.89%).

(R)-3β-*Substituted Cepham* S-*Oxide Derivatives* (13b) *and* (14b).—A solution of the cepham derivative [(5b) or (6b)] (0.20 mmol) in anhydrous CH_2Cl_2 (6 ml) was treated, as described for the preparation of (10), with a solution of 90% *m*-chloroperoxybenzoic acid (0.038 g, 0.20 mmol) in anhydrous CH_2Cl_2 (4 ml), yielding a solid residue which on crystallization

from $CHCl_3$ gave the pure *S*-oxide derivative [(13b) or (14b), respectively].

Compound (13b) (75%); m.p. 177—179 °C; $\nu_{max.}$ ($CHCl_3$) 1 782 cm^{-1} (β-lactam C=O); δ 2.08 (3 H, s, Me), 3.40 and 3.93 (2 H, d, *J* 14.0 Hz, SCH_2), 4.83 (1 H, d, *J* 4.4 Hz, CHS), and 5.56 (1 H, q, *J* 4.4 and 10.0 Hz, NHC*H*) (Found: C, 47.6; H, 3.95; Br, 14.0; N, 7.5. $C_{23}H_{22}BrN_3O_8S$ requires C, 47.59; H, 3.82; Br, 13.77; N, 7.24%).

Compound (14b) (60%); m.p. 211—212 °C; $\nu_{max.}$ ($CHCl_3$) 1 782 cm^{-1} (β-lactam C=O); δ 1.80 (3 H, s, Me), 3.11 and 4.20 (2 H, d, *J* 13.7 Hz, SCH_2), 4.73 (1 H, d, *J* 4.0 Hz, CHS), and 5.42 (1 H, q, *J* 4.0 and 8.5 Hz, NHC*H*) (Found: C, 50.55; H, 4.2; Cl, 6.15; N, 6.9. $C_{25}H_{24}ClN_3O_{10}S$ requires C, 50.55; H, 4.07; Cl, 5.97; N, 7.07%).

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