Studies Related to Penicillins. Part X.[1] Some Transformations of 4-Isopropylidene-3-oxo-7β-phenoxyacetamidocepham

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m-Chloroperbenzoic acid converts 4-isopropylidene-3-oxo-7β-phenoxyacetamidocepham (2) into a mixture of sulphoxides (10) and (11), which is then oxidised to the sulphone (3). 3-Hydroxy-4-isopropylidene-7β-phenoxyacetamidocepham (12), obtained by reduction of the cepham (2) with lithium hydridotri-t-butoxyaluminate, affords a single sulphoxide with sodium periodate. The cepham (2) is also converted into [(2*R*,3*R*)-1-(2-hydroxy-2-methylpropionyl)-4-oxo-3-phenoxyacetamidoazetidin-2-ylthio]acetic acid (7) by potassium permanganate and into 4″,4″-dimethyl-7′β-phenoxyacetamidodispiro[oxiran-2,3′-cepham-4′,3″-$\Delta^{1''}$-pyrazoline] (19) by diazomethane.

RECENTLY we reported on[2] the base-promoted ring enlargement of penicillanoylhalogenomethanes [*e.g.* (1)] to give cepham derivatives [*e.g.* (2)]. Our interest in the latter derivatives stems from the hope that they can be converted into cephalosporin and penicillin analogues. We now describe the results of some attempts to cleave the 4,5-bond of the cepham (2), with a view to preparing penicillin analogues.

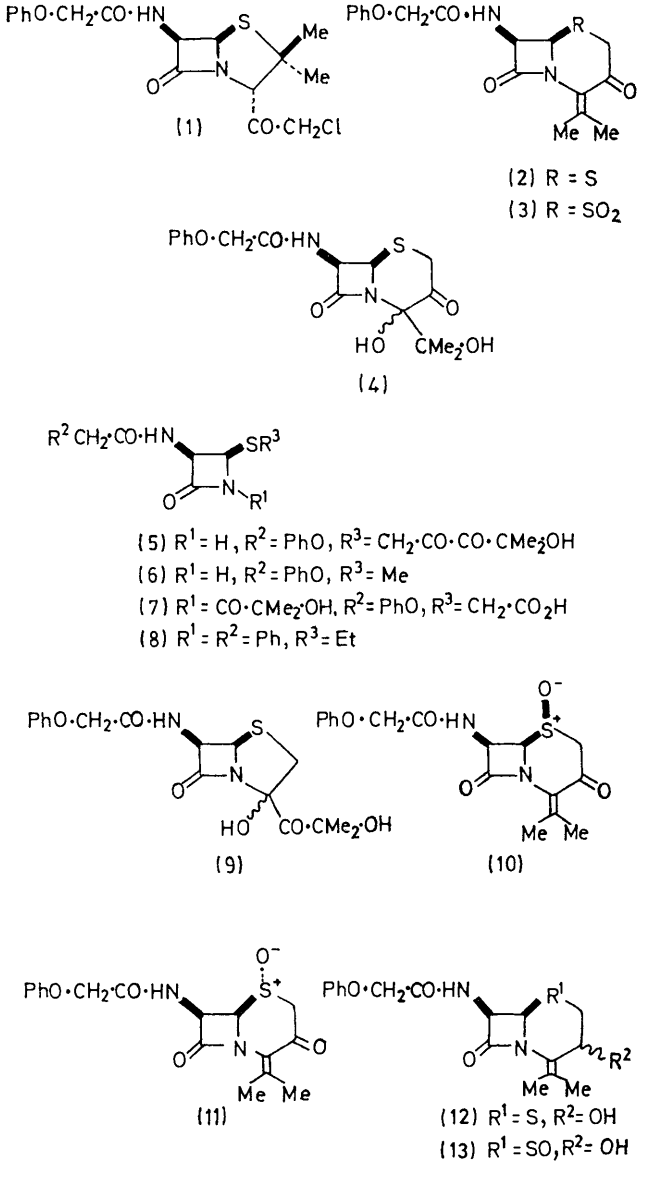
The initial objective was to transform the cepham (2) into the dihydroxy-ketone (4) and to equilibrate the latter with the hydroxy-diketone (5) and/or the carbinolamine (9).

Both olefins[3] and sulphides[4] are oxidised by *m*-chloroperbenzoic acid under mild conditions. In the hope of epoxidising the double bond, the cepham (2) was treated with this oxidant in dichloromethane. However, a mixture (*ca.* 2 : 1 by n.m.r. spectroscopy) of sulphoxides was produced; it was fractionated by silica gel chromatography to give the less-polar minor isomer (24%) and the major isomer (57%).

On the assumption that an intramolecular hydrogen bond between the amide hydrogen and the sulphinyl oxygen atom can only occur in the (*S*)-oxide and that such hydrogen bonding results in a downfield shift of the proton signal, the stereochemistry of the sulphoxides can be determined from the chemical shifts of the amide protons in deuteriochloroform and hexadeuteriodimethyl sulphoxide.[5] The results (Table) indicate that only the minor sulphoxide is intramolecularly hydrogen bonded. Furthermore, the amide proton of the major isomer experiences a larger downfield shift in hexadeuteriodimethyl sulphoxide than does that of the minor isomer, which reflects the greater ability of the former proton to be involved in hydrogen bonding with the solvent. Consequently, the minor isomer is considered to be the (*S*)-sulphoxide (10) and the major isomer the (*R*)-sulphoxide (11).

m-Chloroperbenzoic acid converted both sulphoxides into the sulphone (3) (96%), which was resistant to further oxidation. It is evident therefore that the sulphur atom of the cepham (2) is more readily oxidised by the peroxy-acid than the olefinic linkage.

Since the rate of epoxidation of an alkene is increased



[1] Part IX, R. J. Stoodley, and N. W. Whitehouse, *J.C.S. Perkin I*, 1973, 32.

[2] B. G. Ramsay and R. J. Stoodley, *Chem. Comm.*, 1970, 1517; *J. Chem. Soc.* (*C*), 1971, 3859, 3864.

[3] N. N. Schwartz and J. H. Blumbergs, *J. Org. Chem.*, 1964, **29**, 1976.

[4] R. Curci, A. Giovine, and G. Modena, *Tetrahedron*, 1966, **22**, 1235.

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

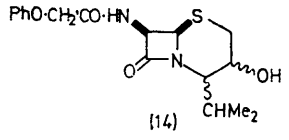
when it bears an electron-donating group and decreased by an electron-withdrawing substituent,[6] the above results suggest that the enone character of the double

Chemical shifts (τ) of the amide protons of 4-isopropylidene-3-oxo-7β-phenoxyacetamidocepham 1-oxides

Compound	$CDCl_3$	$(CD_3)_2SO$
(*S*)-Sulphoxide (10)	1·95	1·79
(*R*)-Sulphoxide (11)	2·17	0·69

bond of the cepham (2) outweighs the enamide character. In the hope that the reverse would be true in the case of the allylic alcohol (12), its reaction with *m*-chloroperbenzoic acid was investigated.

The allylic alcohol (12), contaminated with *ca.* 30% of the saturated alcohol (14), was initially obtained by reduction of the cepham (2) with sodium borohydride. Subsequently, however, it was prepared in an almost pure state by using lithium hydridotri-t-butoxyalumin-



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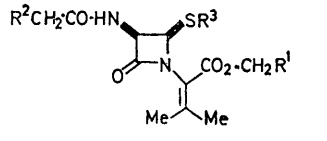
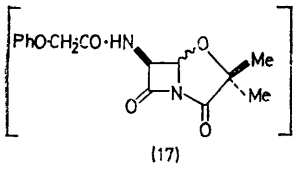


(15) $R^1 = C_6H_4 \cdot OMe\text{-}p$, $R^2 = PhO$, $R^3 = Me$
(16) $R^1 = CCl_3$, $R^2 = Ph$, $R^3 = Et$



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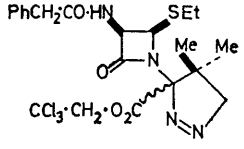

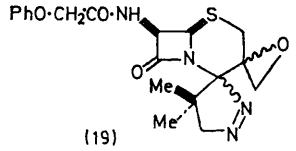

(19)

ate. When treated with *m*-chloroperbenzoic acid in dichloromethane, the allylic alcohol (12) was converted into a mixture of three products, which contained only vinylic methyl groups on the basis of n.m.r. spectroscopy. The mixture was not recovered from column chromatography on silica gel or alumina. Oxidation of the allylic alcohol (12) with sodium periodate afforded a single sulphoxide (13) (90%), which possessed a chromatographic mobility similar to that of one of the *m*-chloroperbenzoic acid oxidation products. The results suggest that the sulphur atom of the allylic alcohol is attacked by *m*-chloroperbenzoic acid in preference to the olefinic group.

[6] D. Swern, *J. Amer. Chem. Soc.*, 1947, **69**, 1692.
[7] E. G. Brain, A. J. Eglington, J. H. C. Nayler, M. J. Pearson, and R. Southgate, *J.C.S. Chem. Comm.*, 1972, 229.
[8] H. B. Kagan, J.-J. Basselier and J.-L. Luche, *Tetrahedron Letters*, 1964, 941; K. D. Barrow and T. M. Spotswood, *ibid.*, 1965, 3325; J.-L. Luche, H. B. Kagan, R. Parthasarathy, G. Tsoucaris, C. De Rango, and C. Zelwer, *Tetrahedron*, 1968, **24**, 1275.

Potassium permanganate is a useful olefin oxidant and it has been successfully employed in the penicillin field [7] to convert, for example, the ester (15) into the azetidinone (6). In an attempt to prepare the dihydroxy-ketone (4), the cepham (2) was treated with this reagent in aqueous pyridine. An acidic product ($C_{17}H_{20}N_2O_7S$) was isolated in high yield. N.m.r. spectroscopy [$(CD_3)_3SO$] showed that the *gem*-dimethyl group (τ 8·6) was not attached to a double bond. Furthermore, the β-lactam protons, [τ 4·72(d) and 4·48(d) after deuterium exchange of the amide NH] possessed a larger coupling constant (6·5 Hz) than that of the cepham [2] (2) (4 Hz), implying that the azetidinone was monocyclic.[8] The acid did not show a molecular ion in the mass spectrum; however, it did possess a peak at *m/e* 304 ($C_{15}H_{16}N_2O_5$ by mass measurement), which is ascribable to the ion (17). The product is formulated as the acid (7).

The formation of the acid (7) by oxidation of the cepham (2) with potassium permanganate is in accord with an initial hydroxylation of the cepham double bond to give the dihydroxy-ketone (4), which then undergoes an oxidative 3,4-bond cleavage.

Attempts to oxidise the double bond of the cepham (2) by using osmium tetroxide,[7] alkaline hydrogen peroxide,[9] or iodine–silver(I) acetate [10] were unsuccessful.

Barton and his co-workers [11] have recently described a useful method for the removal of the *N*-substituent of the ester (16). Thus, the pyrazoline (18), derived from the reaction of the ester (16) with diazomethane, yielded the azetidinone (8) in the presence of potassium t-butoxide or zinc–acetic acid.

When treated with an excess of diazomethane, the cepham (2) was converted into a product (90%), which is considered to be the pyrazoline epoxide (19) on the basis of analytical and spectral evidence. Attempts to cleave the 4′,5′-bond of the derivative (19) by potassium t-butoxide and by zinc–acetic acid were unrewarding; a complex mixture of non-β-lactam-containing products was obtained in each case.

EXPERIMENTAL

For general experimental details see Part I.[12]

Reaction of 4-Isopropylidene-3-oxo-7β-phenoxyacetamidocepham (2) with m-*Chloroperbenzoic Acid.*—The cepham [2] (2) (0·208 g, 0·6 mmol) was dissolved in dry dichloromethane (5 ml) and treated with a solution of *m*-chloroperbenzoic acid (0·104 g, 0·6 mmol) in dry dichloromethane (5 ml). After 2 h the solution was diluted with chloroform, washed with sodium hydrogen carbonate solution followed by water, and dried ($MgSO_4$). Evaporation left a product (0·212 g), which contained two components (t.l.c.; *ca.* 2 : 1 by n.m.r. spectroscopy); the material was fractionated by silica gel chromatography ($CHCl_3$ as eluant).

[9] H. O. House and R. L. Wasson, *J. Amer. Chem. Soc.*, 1957, **79**, 1488; L. F. Fieser, *J. Biol. Chem.*, 1940, **133**, 391.
[10] C. Prévost, *Compt. rend.*, 1933, **196**, 1129; **197**, 166; R. B. Woodward and F. V. Brutcher, *J. Amer. Chem. Soc.*, 1958, **80**, 209.
[11] D. H. R. Barton, D. G. T. Greig, P. G. Sammes, and M. V. Taylor, *Chem. Comm.*, 1971, 845.
[12] I. McMillan and R. J. Stoodley, *J. Chem. Soc.* (*C*), 1968, 2533.

The first-eluted constituent (0·052 g, 24%) was (1S)-4-*isopropylidene*-3-*oxo*-7β-*phenoxyacetamidocepham* 1-*oxide* (10), m.p. 242—244° (from ethanol), $[\alpha]_D$ +30° (0·5% in $CHCl_3$), $\nu_{max.}$ (KBr) 3380 (NH), 1775 (β-lactam C=O), 1695 (unsat. C=O and amide C=O), 1620, and 1600 (C=C) cm^{-1}, $\lambda_{max.}$ 217 (ε 13,200), 262sh (6600), 268 (7900), 274 (8100), and 278sh nm (7000), τ ($CDCl_3$) 7·90 and 7·71 (each 3H, s, *gem*-Me_2), 6·22 (2H, ABq, *J* 17 Hz, 2-H_2), 5·38 (2H, s, CH_2·O), 4·96 (1H, d, *J* 4 Hz, 6-H), 3·89 (1H, dd, *J* 10, *J'* 4 Hz, 7-H), 3·07—2·45 (5H, m, aromatic), and 1·95br (1H, d, *J* 10 Hz, NH) [addition of D_2O caused the signal at τ 1·95 to disappear and that at 3·89 to collapse to a doublet (*J* 4 Hz)] (Found: C, 56·4; H, 4·9; N, 8·1%; M^+, 362. $C_{17}H_{18}N_2O_5S$ requires C, 56·4; H, 5·0; N, 7·7%; *M*, 362).

The major constituent (0·103 g, 57%) was (1R)-4-*isopropylidene*-3-*oxo*-7β-*phenoxyacetamidocepham* 1-*oxide* (11), m.p. 206—208° (from ethyl acetate), $[\alpha]_D$ +228° (0·5% in $CHCl_3$), $\nu_{max.}$ (KBr) 3500 and 3380 (NH), 1745 (β-lactam C=O), 1700 (unsat. C=O), 1670 (amide C=O), 1635, and 1605 (C=C) cm^{-1}, $\lambda_{max.}$ 221 (ε 13,800), 261 (6700), 268 (7700), 275 (8200), and 282sh nm (7000), τ ($CDCl_3$) 8·0 and 7·73 (each 3H, s, *gem*-Me_2), 5·84 (2H, ABq, *J* 15 Hz, 2-H_2), 5·42 (2H, s, CH_2·O), 5·28 (1H, d, *J* 5·5 Hz, 6-H), 4·83 (1H, dd, *J* 6·5, *J'* 5·5 Hz, 7-H), 3·11—2·41 (5H, m, aromatic), and 2·17br (1H, d, *J* 6·5 Hz, NH) [addition of D_2O caused the signal at τ 2·17 to disappear and that at 4·83 to collapse to a doublet (*J* 5·5 Hz)] (Found: C, 56·1; H, 4·9; N, 7·7%; M^+, 362).

Reaction of (1S)-4-*Isopropylidene*-3-*oxo*-7β-*phenoxyacetamidocepham* 1-*Oxide* (10) *and its* (1R)-*Isomer* (11) *with* m-*Chloroperbenzoic Acid*.—A mixture of the sulphoxides (10) and (11) (0·212 g, 0·59 mmol), prepared as above, was dissolved in dry dichloromethane (10 ml) and a solution of *m*-chloroperbenzoic acid (0·312 g, 1·8 mmol) in dry dichloromethane (10 ml) was added. The mixture was heated under reflux for 24 h, diluted with chloroform, washed with sodium hydrogen carbonate solution followed by water, and dried ($MgSO_4$). Evaporation gave 4-*isopropylidene*-3-*oxo*-7β-*phenylacetamidocepham* 1,1-*dioxide* (3) (0·212 g, 96%), which crystallised on addition of ethanol; m.p. 126—128° (from ethanol), $[\alpha]_D$ +48° (0·1% in $CHCl_3$), $\nu_{max.}$ (KBr) 3390 (NH), 1790 (β-lactam C=O), 1690 (unsat. C=O and amide C=O), and 1605 (C=C) cm^{-1}, $\lambda_{max.}$ 216 (ε 9100), 262sh (4200), 268 (5300), and 274 nm (5300), τ ($CDCl_3$) 7·92 and 7·79 (each 3H, s, *gem*-Me_2), 5·70 (2H, ABq, *J* 16 Hz, 2-H_2), 5·38 (2H, s, CH_2·O), 4·92 (1H, d, *J* 5 Hz, 6-H), 4·03 (1H, dd, *J* 9, *J'* 5 Hz, 7-H), 3·08—2·49 (5H, m, aromatic), and 1·92br (1H, d, *J* 9 Hz, NH) [addition of D_2O caused the signal at τ 1·92 to disappear and that at 4·03 to collapse to a doublet (*J* 5 Hz)] (Found: C, 54·1; H, 4·8; N, 7·3%; M^+, 378. $C_{17}H_{18}N_2O_6S$ requires C, 54·0; H, 4·8; N, 7·4%; *M*, 378).

Reaction of 4-*Isopropylidene*-3-*oxo*-7β-*phenylacetamidocepham* (2) *with Metal Hydrides*.—(*a*) Lithium hydridotri-t-butoxyaluminate [13] (0·228 g, 0·8 mmol) was added to a solution of the cepham [2] (2) (0·156 g, 0·45 mmol) in dry tetrahydrofuran (5 ml). After 4 h the solution was diluted with chloroform, washed with dilute hydrochloric acid followed by water, and dried ($MgSO_4$). Evaporation left 3-*hydroxy*-4-*isopropylidene*-7β-*phenoxyacetamidocepham* (12) (0·155 g, 97%) as a chromatographically homogeneous syrup, $[\alpha]_D$ +144° (0·1% in $CHCl_3$), $\nu_{max.}$ (film) 3380 (NH and OH), 1755 (β-lactam C=O), 1675 (amide C=O), and 1605 (C=C) cm^{-1}, $\lambda_{max.}$ 223 (ε 23,400), 261 (5400), 268 (5600), and 275 nm (4400), τ ($CDCl_3$) 8·22 and 8·14 (each 3H, s, *gem*-Me_2), 7·50—6·88 (3H, m, 2-H_2 and OH), 5·34 (2H, s, CH_2·O), 5·22 (1H, m, 3-H), 4·96 (1H, d, *J* 4 Hz, 6-H), 4·56 (1H, dd, *J* 8·5, *J'* 4 Hz, 7-H), and 3·17—2·45 (6H, m, aromatic and NH) [addition of D_2O caused the multiplet at τ 7·50—6·88 to sharpen to two double doublets (*J* 14·4, *J'* 3·6, *J''* 2 Hz)] (Found: M^+ 348·1127. $C_{17}H_{20}N_2O_4S$ requires *M*, 348·1144).

(*b*) Sodium borohydride (0·015 g, 0·4 mmol) was added to a solution of the cepham (2) (0·104 g, 0·3 mmol) in dioxan (5 ml). After 2 h the mixture was diluted with chloroform, washed with dilute hydrochloric acid followed by water, and dried ($MgSO_4$). Evaporation left a product (0·095 g), which possessed a chromatographic mobility similar to that of the alcohol (12). N.m.r. spectroscopy indicated that the material was a mixture (*ca.* 7 : 3) of the alcohol (12) (major component) and 3-hydroxy-4-isopropyl-7β-phenoxyacetamidocepham (14) [τ ($CDCl_3$) 9·07 and 8·96 (each, 3H, d, *J* 6·5 Hz, *gem*-Me_2); the remaining signals coincided with those of the allylic alcohol (12)]. The mass spectrum contained peaks at *m/e* 348 and 350.

Reaction of 3-*Hydroxy*-4-*isopropylidene*-7β-*phenoxyacetamidocepham* (12) *with* m-*Chloroperbenzoic Acid*.—*m*-Chloroperbenzoic acid (0·026 g, 0·15 mmol), dissolved in dry dichloromethane (2 ml), was added dropwise to a cooled (acetone–solid carbon dioxide), stirred solution of the allylic alcohol (12) (0·052 g, 0·15 mmol) in dry dichloromethane (2 ml). After 20 min the solution was diluted with chloroform, washed with sodium hydrogen carbonate solution and water, and dried ($MgSO_4$). Evaporation left a syrup (0·05 g), which contained three components (t.l.c.) [$\nu_{max.}$ (film) 1775 cm^{-1} (β-lactam C=O), τ ($CDCl_3$) 8·12 (s, *gem*-Me_2)]. Attempts to fractionate the product by silica gel or alumina chromatography were unsuccessful.

Reaction of 3-*Hydroxy*-4-*isopropylidene*-7β-*phenoxyacetamidocepham* (12) *with Sodium Periodate*.—Sodium periodate (0·076 g, 0·36 mmol) in water (1 ml) was added to a stirred solution of the alcohol (12) (0·082 g, 0·24 mmol) in methanol (3 ml). After 16 h the mixture was diluted with water and extracted with chloroform. The dried ($MgSO_4$) organic layer was concentrated to a syrup which was triturated with light petroleum to give 3-*hydroxy*-4-*isopropylidene*-7β-*phenoxyacetamidocepham* 1-*oxide* (13) (90%), m.p. 174—176° (from chloroform–light petroleum), $[\alpha]_D$ +89° (0·1% in $CHCl_3$), $\nu_{max.}$ (KBr) 3460 and 3370 (OH and NH), 1745 (β-lactam C=O), 1690 (amide C=O), and 1600 (C=C) cm^{-1}, $\lambda_{max.}$ 219 (ε 13,000), 238sh (6500), 262sh (2400), 269 (2000), and 276 nm (1500), τ ($CDCl_3$) 8·12 and 8·08 (each 3H, s, *gem*-Me_2), 7·16—6·34 (3H, m, 2-H_2 and OH), 5·45 (2H, s, CH_2·O), 5·09 (1H, d, *J* 4·5 Hz, 6-H), 4·89 (1H, m, 3-H), 3·98 (1H, dd, *J* 10, *J'* 4·5 Hz, 7-H), 3·12—2·50 (5H, m, aromatic), and 1·60br (1H, d, *J* 10 Hz, NH) [addition of D_2O caused the multiplet at 7·16—6·34 to sharpen to two double doublets (*J* 14·4, *J'* 7, *J''* 3·6 Hz)] (Found: C, 55·8; H, 5·5; N, 8·0%; M^+, 364. $C_{17}H_{20}N_2O_5S$ requires C, 56·0; H, 5·5; N, 7·7%; *M*, 364).

Reaction of 4-*Isopropylidene*-3-*oxo*-7β-*phenoxyacetamidocepham* (2) *with Potassium Permanganate*.—Potassium permanganate (0·712 g, 4·5 mmol), dissolved in 50% aqueous acetone (100 ml), was added dropwise to an ice-cooled, stirred solution of the cepham [2] (2) (1·04 g, 3 mmol) in 50% aqueous acetone (100 ml) containing pyridine (1·208 g, 1·5 mmol). After 1 h the mixture was treated with sulphur dioxide and extracted (twice) with chloroform. The

[13] H. C. Brown and F. R. McFarlin, *J. Amer. Chem. Soc.*, 1958, **80**, 5372.

extracts were washed with water, dried ($MgSO_4$), and evaporated to afford [(2R,3R)-1-(2-*hydroxy*-2-*methylpropionyl*)-4-*oxo*-3-*phenoxyacetamidoazetidin*-2-*ylthio*]*acetic acid* (7) (1·148 g, 96%), m.p. 139—141° (from ethyl acetate–light petroleum), $[\alpha]_D$ −24° (0·1% in EtOH), $\nu_{max.}$ (KBr) 3435 (OH), 3385 (NH), 1790 (β-lactam C=O), 1700 (CO_2H), and 1675 (amide C=O), $\lambda_{max.}$ 219 (ε 13,600), 264 (1700), 270 (1900), and 276 nm (1600), τ [$(CD_3)_2SO$] 8·60 (6H, s, *gem*-Me_2), 6·38 (2H, ABq, *J* 16 Hz, CH_2·S) 5·41 (2H, s, CH_2·O) 4·72 (1H, dd, *J*, *J′* 6·5 Hz, 3-H), 4·48 (1H, d, *J* 6·5 Hz, 4-H), 3·11—2·56 (5H, m, aromatic), and 0·92br (1H, d, *J* 6·5 Hz, NH) [addition of D_2O caused the signal at τ 0·92 to disappear and that at 4·72 to collapse to a doublet (*J* 6·5 Hz)] (Found: C, 51·8; H, 4·8; N, 7·0%. $C_{17}H_{20}N_2O_7S$ requires C, 51·5; H, 5·1; N, 7·1%). The mass spectrum, which did not show a molecular ion, contained a peak at *m/e* 304·1021 ($C_{15}H_{16}N_2O_5S$ requires 304·1059).

Reaction of 4-*Isopropylidene*-3-*oxo*-7β-*phenoxyacetamidocepham* (2) *with Osmium Tetroxide.*—Osmium tetroxide (0·038 g, 0·15 mmol) and pyridine (0·06 g, 0·75 mmol) were added to a stirred solution of the cepham [2] (2) (0·052 g, 0·15 mmol) in benzene (15 ml). A black precipitate was slowly deposited and after 24 h the mixture was diluted with ethyl acetate, saturated with hydrogen sulphide, and filtered. Evaporation left a syrup (0·03 g), which was found to be a complex mixture by n.m.r. spectroscopy. An attempt to fractionate the product by silica gel chromatography was unsuccessful.

Reaction of 4-*Isopropylidene*-3-*oxo*-7β-*phenoxyacetamidocepham* (2) *with Hydrogen Peroxide.*—(*a*) To a stirred solution of the cepham [2] (2) (0·052 g, 0·15 mmol) in methanol (5 ml) was added a solution of 30% hydrogen peroxide (0·05 ml, 0·45 mmol) in 0·075N-sodium hydroxide (1 ml, 0·075 mmol). After 10 min the deep-red solution was diluted with chloroform and washed with dilute hydrochloric acid followed by water. The dried ($MgSO_4$) organic layer was evaporated to leave a syrup (0·05 g), which contained a complex mixture of non-β-lactam-containing products (n.m.r. spectroscopy) and was not further investigated.

(*b*) A solution of 30% hydrogen peroxide (0·025 ml, 0·22 mmol) in water (1 ml) containing sodium carbonate (0·005 g, 0·03 mmol) was added to a solution of the cepham [2] (2) (0·052 g, 0·15 mmol) in ethanol (5 ml). After 30 min the deep-red solution was diluted with chloroform and washed with dilute hydrochloric acid followed by water. The dried ($MgSO_4$) organic layer was evaporated to a syrup (0·05 g), which contained the cepham and its 7-epimer (*ca.* 2 : 1) on the basis of n.m.r. spectroscopy, τ [$CDCl_3$; 7-epimer of the cepham (2)] 7·85 and 7·68 (each 3H, s, *gem*-Me_2), 6·79 (2H, ABq, *J* 14 Hz, CH_2·S), 5·48 (2H, s, CH_2·O), 5·23 (1H, dd, *J* 7·5, *J′* 2 Hz, 7-H), 4·92 (1H, d, *J* 2 Hz, 6-H), and 3·18—2·55 (6H, m, aromatic and NH). An attempt to fractionate the mixture by silica gel chromatography was unsuccessful.

Reaction of 4-*Isopropylidene*-3-*oxo*-7β-*phenoxyacetamidocepham* (2) *with Iodine and Silver Acetate.*—(*a*) The cepham [2] (2) (0·052 g, 0·15 mmol) in dry benzene (5 ml) was added to a mixture of iodine (0·02 g, 0·15 mmol) and silver acetate (0·05 g, 0·3 mmol) in dry benzene (10 ml). The mixture was refluxed for 5 h, diluted with chloroform, and washed with sodium hydrogen carbonate solution followed by water. The dried ($MgSO_4$) organic layer was evaporated to leave the cepham (2) (0·05 g, 96%).

(*b*) Silver acetate (0·056 g, 0·34 mmol) and iodine (0·02 g, 0·15 mmol) were added to a solution of the cepham (2) (0·052 g, 0·15 mmol) in glacial acetic acid. After 30 min, when the iodine colour had disappeared, 10% aqueous acetic acid (0·027 ml) was added and the solution was heated at 90° for 5 h, treated with an excess of sodium chloride, filtered, and diluted with chloroform. The organic layer was washed with sodium hydrogen carbonate solution followed by water and dried ($MgSO_4$). Evaporation left the cepham (2) (0·05 g, 96%).

Reaction of 4-*Isopropylidene*-3-*oxo*-7β-*phenoxyacetamidocepham* (2) *with Diazomethane.*—A solution of the cepham [2] (1·04 g, 3 mmol) in chloroform (10 ml) was treated with an excess of diazomethane in ether for 12 h. Evaporation left a syrup (1·15 g), which was fractionated by silica gel chromatography ($CHCl_3$ as eluant) to give 4″,4″-*dimethyl*-7′β-*phenoxyacetamidodispiro*[*oxiran*-2,3′-*cepham*-4′,3″-Δ¹″-*pyrazoline*] (19) (0·92 g, 90%), m.p. 172—174° (from ethanol), $[\alpha]_D$ +12° (0·1% in $CHCl_3$), $\nu_{max.}$ (KBr) 3480 (NH), 1770 (β-lactam C=O), and 1675 (amide C=O) cm^{-1}, $\lambda_{max.}$ 212 (ε 10,600), 263 (900), 270 (1300), and 277 nm (1100), τ ($CDCl_3$) 9·05 and 8·58 (each 3H, s, *gem*-Me_2), 7·76 (1H, d, *J* 14 Hz, 2-H), 6·25 (1H, dd, *J* 14, *J′* 2 Hz, 2-H), 7·52 (1H, d, *J* 4 Hz, epoxide CH), 6·93 (1H, dd, *J* 4, *J′* 2 Hz, epoxide CH), 5·61 (2H, ABq, *J* 17·5 Hz, CH_2·N), 5·36 (2H, s, CH_2·O), 4·73 (1H, d, *J* 5 Hz, 6′-H), 4·27 (1H, dd, *J* 9, *J′* 5 Hz, 7′-H), 3·04—2·43 (5H, m, aromatic), and 2·18br (1H, d, *J* 9 Hz, NH) [addition of D_2O caused the signal at τ 2·18 to disappear and that at 4·27 to collapse to a doublet (*J* 5 Hz)] (Found: C, 57·0; H, 5·7; N, 13·6%; M^+, 402·1354. $C_{19}H_{22}N_4O_4S$ requires C, 56·7; H, 5·5; N, 13·9; *M*, 402·1362).

Reaction of 4″,4″-*Dimethyl*-7′β-*phenoxyacetamidodispiro*-[*oxiran*-2,3′-*cepham*-4′,3″-Δ¹″-*pyrazoline*] (19) *with Zinc–Acetic Acid.*—Zinc dust (0·013 g, 0·2 mmol) was added to a stirred solution of the pyrazoline (19) (0·04 g, 0·1 mmol) in 95% aqueous acetic acid (5 ml). After 30 min the mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with sodium hydrogen carbonate solution followed by water, dried ($MgSO_4$), and evaporated. The product (0·02 g) was found to be a complex mixture by t.l.c. and n.m.r. spectroscopy and was not further investigated.

Reaction of 4″,4″-*Dimethyl*-7β-*phenoxyacetamododispiro*-[*oxiran*-2,3′-*cepham*-4′,3″-Δ¹″-*pyrazoline*] (19) *with Potassium t-Butoxide.*—Potassium t-butoxide (0·011 g, 0·1 mmol) was added to a solution of the pyrazoline (19) (0·04 g, 0·1 mmol) in dry t-butyl alcohol. After 30 min the solution was diluted with chloroform, washed with dilute hydrochloric acid and water, dried ($MgSO_4$), and evaporated. The product (0·02 g) was found to be a complex mixture by t.l.c. and n.m.r. spectroscopy and was not further investigated.

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