Synthesis of Analogues of 6β-Bromopenicillanic Acid and Penicillanic Acid *S,S*-Dioxide. Part 1. Synthesis of 3α-Derivatives of 6β-Bromo-2,2-dimethylpenam and 2,2-Dimethylpenam *S,S*-Dioxide

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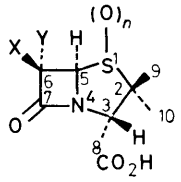
The synthesis of analogues of 6β-bromopenicillanic acid (**1**) and the sulphone of penicillanic acid (**2**), where the 3α-carboxyl group has been transformed into 3α-hydroxymethyl, fluoromethyl and cyano groups and the attempted transformation into a 3α-formyl group are described. These analogues showed no significant β-lactamase inhibitory activity against *B. cereus* β-lactamase I.

Although 6β-bromopenicillanic acid[1] (**1**) and penicillanic acid sulphone[2] (**2**) have been extensively studied as β-lactamase inhibitors and some aspects of the mechanism by which they operate have been elucidated,[3–5] there appear to have been no reports of carboxy group modification to give new and useful β-lactamase inhibitors. We therefore decided to synthesize



(**1**) X = Br, Y = H, *n* = 0
(**2**) X = Y = H, *n* = 2
(**3**) X = Y = Br, *n* = 0

analogues of (**1**) and (**2**) and determine their biological activity, in order to gain a better understanding of the functional groups essential for β-lactamase inhibitor activity.

We report herein the preparation of analogues of (**1**) and (**2**) in which the 3-carboxy group was replaced by a hydroxymethyl, fluoromethyl, and cyano groups and the attempted introduction of a formyl group.

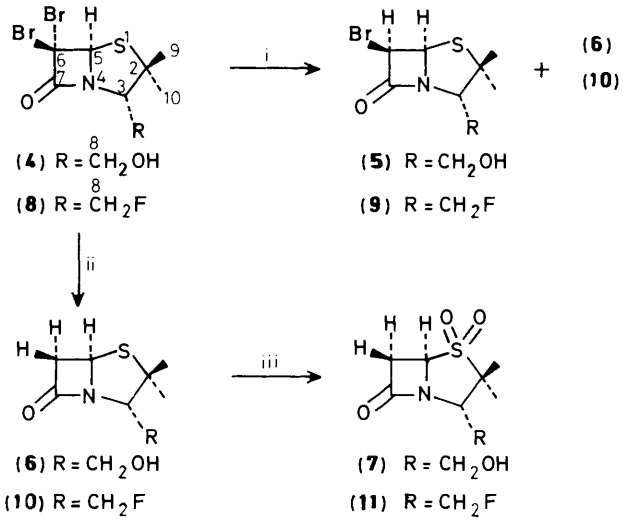
Our first target was the synthesis of 6β-bromo-3α-hydroxymethyl-2,2-dimethylpenam (**5**) and its corresponding *S,S*-dioxide (**7**) (see Scheme 1). 6,6-Dibromopenicillanic acid[2] (**3**) was reduced by borane–methyl sulphide complex (BH_3·Me_2S)[6] to give the alcohol (**4**) in a high yield (80%). Attempted reduction of the acid employing borane in tetrahydrofuran (BH_3·THF) under the same conditions led only to starting material, whilst use of chloromethylene(dimethyl)ammonium chloride and sodium borohydride[7] produced (**4**) in a rather low yield (30%).

Although the syntheses of 3α-hydroxymethylpenam derivatives have been reported,[8] our synthesis constitutes the first example of a direct reduction of a penicillanic acid derivative.

Reduction of compound (**4**) with 1 equiv. of tributyltin hydride in the presence of small amount of azoisobutyronitrile (AIBN) in ether at 10 °C gave the required 6β-bromo compound (**5**) in 45% yield after chromatographic purification. The stereochemistry at C-6 was assigned by ^{1}H n.m.r. spectroscopy on the basis of the 5-H, 6-H coupling constant, which was 4.0 Hz.[9]

Likewise, reduction with an excess of Bu_3SnH in the presence of AIBN,[10] after 24 h at room temperature in benzene gave 3α-hydroxymethyl-2,2-dimethylpenam (**6**) in 93% yield. Treatment of this alcohol with potassium hydrogen persulphate[11] (commercially sold as oxone)* furnished the sulphone (**7**).

The reaction of the available alcohol (**4**) with diethylaminosulphur trifluoride (DAST),[12,13] in dichloromethane at 25 °C gave 6,6-dibromo-3α-fluoromethyl-2,2-dimethylpenam (**8**) in 58% yield. Both ^{1}H and ^{13}C n.m.r. spectra confirm the location of the fluorine atom of (**8**). One of the methyl groups, presumably the α-oriented, is coupled to the fluorine ($^5J_{H,F}$ 1.6 Hz). This coupling could be explained as a 'direct' interaction between the fluorine nucleus and 10-Me hydrogens, because the substituents at C-3 and C-2 in the α-orientation can approach one another very closely.[14,†]



(**4**) R = CH_2OH (**5**) R = CH_2OH
(**8**) R = CH_2F (**9**) R = CH_2F
(**6**) R = CH_2OH (**7**) R = CH_2OH
(**10**) R = CH_2F (**11**) R = CH_2F

Scheme 1. *Reagents:* i, 1 equiv. of Bu_3SnH, AIBN; ii, excess of Bu_3SnH, AIBN; iii, SO_5HK

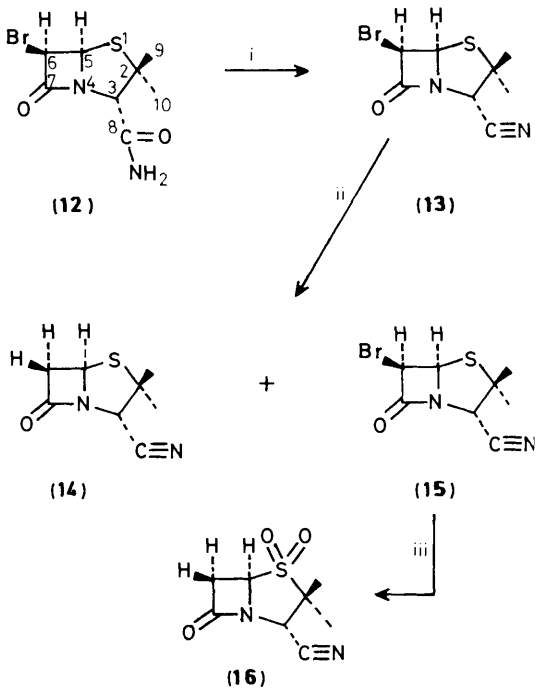
* Oxone contains 2 mol equiv. of $KHSO_5$, 1 mol equiv. of K_2SO_4, and 1 mol equiv. of $KHSO_4$, and was purchased from Aldrich Chemical Co.
† This behaviour was also observed in compounds (**9**), (**10**), and (**11**) (see Experimental section).

Reactions similar to those used in the preparation of compounds (**5**) and (**7**) provided 6β-bromo- and penam sulphone derivatives (**9**) and (**11**) (see Scheme 1).

Treatment of the alcohol (**4**) with toluene-*p*-sulphonyl chloride–pyridine gave its corresponding tosylate (79%). This failed to react with tetrabutylammonium fluoride (TBAF) on silica gel[15] at room temperature and in refluxing benzene gave an intractable mixture of products. The failure of this displacement reaction is presumably due to the fact that 'naked' fluoride is a hard nucleophile[16] and a rather strong base.

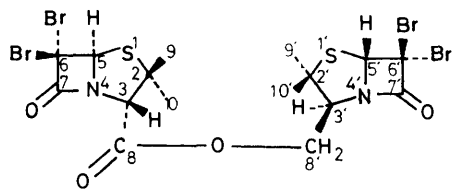
Although there is scant reference to the preparation of 3α-cyanopenam derivatives in the literature,[17,18] 6,6-dibromo-3α-cyano-2,2-dimethylpenam (**13**) was obtained in good yield (89%) by treatment of the amide (**12**) with chloromethylene(dimethyl)ammonium chloride in anhydrous acetonitrile.[19]

The nitrile (**13**), on treatment with 2 equiv. of Bu_3SnH and traces of AIBN in benzene at 15 °C, gave, after purification by column chromatography, 3α-cyano-2,2-dimethylpenam (**14**) (93%) and 6β-bromo-3α-cyano-2,2-dimethylpenam (**15**) (5%).* The β-configuration at C-6 was assigned to product (**15**) on the basis of its 5-H, 6-H coupling constant.[9] The conversion of the 3α-cyanopenam sulphide (**14**) into the corresponding sulphone (**16**) was readily achieved in 89% yield by the action of oxone in aqueous methanol (Scheme 2).



Scheme 2. *Reagents:* i, $HC(Cl)\overset{+}{N}Me_2Cl^-$–pyridine; ii, 2 equiv. of Bu_3SnH, AIBN, iii, SO_5HK

The next target was the synthesis of 3α-formyl-2,2-dimethylpenam derivatives. Attempts to oxidize the alcohol (**4**) to the corresponding aldehyde using pyridinium fluorochromate,[20] afforded the ester (**17**) (35%) as a crystalline product. Analogously, pyridinium chlorochromate (PCC),[21] pyridinium dichromate,[22] and potassium chromate–tetrabutylammonium hydrogen sulphate under phase-transfer conditions[23] also gave



(**17**)

(**17**) (*ca.* 30%), the structure of which was established by ^1H and ^{13}C n.m.r. spectroscopy and high and low mass spectrometry.

Ester formation can be explained in terms of an unstable aldehyde reacting with unchanged alcohol (**4**) to give a hemiacetal which is then oxidized to the ester (**17**).[24] Even when a dilute chloroform solution of the alcohol (**4**) was slowly added to a boiling chloroform solution of PCC, the main product was again the ester (**17**). No aldehyde was detected in the plate (t.l.c.) by staining with 2,4-dinitrophenylhydrazine[25] or in the crude reaction mixture in $CDCl_3$ by ^1H n.m.r. spectroscopy.

In an attempt to overcome the acidic nature of chromium(VI) reagents,[20] and on the basis that 4-formylcephalosporins were obtained *via* Moffat oxidation of the corresponding 4-hydroxymethylcephalosporins,[26] we attempted to oxidize the alcohol (**4**) with dimethyl sulphoxide–oxalyl chloride[27] at both −60 and at 0 °C; in each case unchanged starting material was recovered. Dimethyl sulphoxide–sulphur trioxide–pyridine[28] also failed to react with (**4**).

In a final attempt to obtain the target compound by oxidation, we chose 'mild' oxidizing agents such as *N*-iodosuccinimide–tetrabutylammonium iodide[29] and *N*-chlorosuccinimide–dimethyl sulphide,[30] but they too failed to give the aldehyde, instead providing a mixture of (**17**) and starting alcohol (**4**) as the only identifiable products.

The reason for the failure of the alcohol (**4**) to undergo oxidation to the corresponding carbonyl compound is unclear to us and currently we are attempting to develop an efficient synthesis by a different route. Although the 3α-formylpenam system was synthesized some years ago *via* a three-step process[31] (thioacid formation/reduction of thioacid/imidazolidine hydrolysis), this procedure is unsuitable in the 6,6-dibromopenam series, since soft nucleophiles, such as sodium hydrogen sulphide are likely to displace[32] the 6-bromo substitute in the first step, and debromination to occur during the Raney nickel reduction.

The incubation of β-lactamase I from *Bacillus cereus* 569/H with 0.005 mM 6β-bromopenicillanic acid (**1**), almost completely inactivated the enzyme in less than 1 min. Compound (**9**), at a concentration 20 times higher, induced only a slow decay of the enzyme activity ($t_{0.5}$ = 17 min) whilst compound (**5**) failed to produce any significant irreversible inactivation.

Penicillanic acid sulphone (**2**), as an alternative substrate for β-lactamase[4b] inhibited instantaneously (60% at 0.15 mM) the hydrolysis of nitrocefin catalyzed by β-lactamase I. On the other hand, the incubation of β-lactamase I with 0.5 mM penicillanic acid sulphone induced an exponential and irreversible decay ($t_{0.5}$ = 11 min) of the enzyme activity. Neither instantaneous inhibition, nor time-dependent irreversible inactivation were produced by the structurally related compounds (**7**), (**11**), and (**16**).

In summary, we have described conditions for transformations of the 3-carboxy group and for the oxidation of sulphide to sulphone by reactions that are rapid, efficient, and selective.

We have found that replacement of the carboxy group in compounds (**1**) and (**2**) by hydroxymethyl, fluoromethyl, or cyano groups results in either a drastic decrease or a complete loss of the β-lactamase inhibitory activity of the parent

* This compound decomposes in the atmosphere in 20 min at 20 °C. For this reason the mass spectrum and the biological activity could not be determined.

compounds. Therefore, the presence of the carboxy group in compounds (**1**) and (**2**) is an essential requirement for their β-lactamase inhibitory properties. A similar result has already been found for the antibacterial activity of β-lactam antibiotics.[33]

Experimental

I.r. spectra were taken on a Beckman Acculab 8 Spectrometer. ^1H and ^{13}C N.m.r. spectra were taken on a Bruker WP 80 SY. Low resolution mass spectra (electron impact, 70 eV) were obtained with a Varian MAT 1125, CH7A. High resolution and fast atom bombardment (f.a.b.) mass spectra were obtained on a Kratos MS-30 spectrometer. F.a.b. mass spectra used glycerol as matrix. Samples on which exact masses were obtained exhibited no significant peaks at *m/z* values greater than that of the parent. Column chromatography was performed on silica gel 60 H, slurry packed, run under a low pressure of nitrogen. Preparative t.l.c. was carried out with silica gel GF_{254} (Type 60, Merck). The 6,6-dibromopenicillanic acid (**3**) was synthesized as reported in the literature.[2]

β-Lactamase I was purified as described by Davies *et al.*[34] from *Bacillus cereus* 569/H. The enzymatic activity was measured spectrophotometrically at 482 nm in 100 mM sodium phosphate (pH 7.0) at 30 °C using 0.1 mM nitrocefin[35] as substrate. For the study of irreversible inactivation, the enzyme was incubated in 100 mM sodium phosphate (pH 7.0) at 30 °C, in the presence of the inactivators, and aliquots were removed at different times, and diluted at least 100 times in the reaction medium for the enzyme-activity assay. The assay compounds were dissolved in dimethyl sulphoxide. Proper controls of enzyme activity and stability were run in the presence of the solvent (DMSO) (less than 2% v/v).

6,6-*Dibromo*-3α-*hydroxymethyl*-2,2-*dimethylpenam* (**4**).—Borane–methyl sulphide complex (2M solution in THF; 1.2 ml, 2.4 mmol) was gradually added to a stirred solution of 6,6-dibromopenicillanic acid (**3**) (574 mg, 1.6 mmol) in dry THF (3.2 ml) over 20 min. The resulting solution was stirred at room temperature in an atmosphere of nitrogen for 40 h and then was cautiously decomposed by the addition of water (0.3 ml). The mixture was then concentrated to dryness and the solid residue was chromatographed, eluting with ethyl acetate–hexane (4:6), to give (**4**) (441 mg, 80%) as white crystals, m.p. 77—78 °C; $\nu_{max.}$(KBr) 3 280 (OH) and 1 795 cm^{-1} (β-lactam); δ_H(80 MHz; $CDCl_3$; standard Me_4Si) 1.47 (3 H, s, 10-Me), 1.56 (3 H, s, 9-Me), 1.82 (1 H, br s, OH), 3.73 (2 H, m, AB_2 system, *J* 7 Hz, 8-H), 4.03 (1 H, m, AB_2 system, *J* 7 Hz, 3-H), and 5.56 (1 H, s, 5-H); δ_C (20.15 MHz; $CDCl_3$; standard $CDCl_3$) 166.2 (C-7), 78.4 (C-5), 70.9 (C-3), 63.1 (C-2), 58.8 (C-6), 59.4 (C-8), 33.3 (C-9), and 24.2 (C-10); *m/z* 347 (3.7%), 345 (7), 343 (M^+, 3.5), 266 (43.2), 264 (44.1, M^+-Br), 261 (16), 259 (20.9), 257 (9.2), 114 (56.3), and 85 (100) (Found: M^+, 342.8892. Calc. for $C_8H_{11}Br_2NO_2S$: M^+, 342.8877).

6β-*Bromo*-3α-*hydroxymethyl*-2,2-*dimethylpenam* (**5**). A solution of tributyltin hydride (0.086 ml, 0.319 mmol) in anhydrous ether (1.0 ml) was added gradually over 2 h to a solution of (**4**) (100 mg, 0.29 mmol) and AIBN (4 mg) in anhydrous ether (5 ml) at 10 °C. The reaction was stirred at this temperature for 24 h after which the solvent was removed and the product pre-purified by flash chromatography; elution was with hexane to remove organotin impurities and then with methanol. The solvent was evaporated and the crude product was subjected to preparative t.l.c., eluting with benzene–acetonitrile (7:3). The major product was identified as (**5**) (35 mg, 45%), a crystalline solid, m.p. 172—174 °C (from $CHCl_3$–hexane); $\nu_{max.}$(KBr) 3 500 (OH) and 1 760 cm^{-1} (β-lactam); δ_H(80 MHz; $CDCl_3$; standard Me_4Si) 1.47 (3 H, s, 10-Me), 1.58 (3 H, s, 9-Me), 1.69 (1 H, br s, OH), 3.69 (2 H, m, AB_2 system, *J* 7 Hz, 8-H), 4.00 (1 H, m, AB_2 system, *J* 7 Hz, 3-H), 5.32 (1 H, d, *J* 6.4 Hz, 6-H), and 5.36 (1 H, d, *J* 6.4 Hz, 5-H); δ_C(20.15 MHz; $CDCl_3$; standard $CDCl_3$) 170.3 (C-7), 71.4 (C-3), 66.2 (C-5), 62.9 (C-2), 60.0 (C-8), 50.1 (C-6), 32.6 (C-9), and 24.8 (C-10); *m/z* 267 (2.6%), 265 (M^+, 2.7), 186 (100, M^+ − Br), 146 (40), 114 (59), and 85 (59) (Found: M^+, 264.9752. Calc. for $C_8H_{12}BrNO_2S$: M^+, 264.97721). The minor product was identified as 3α-hydroxymethyl-2,2-dimethylpenam (**6**) (19 mg, 35%), described below.

6,6-*Dibromo*-3α-*fluoromethyl*-2,2-*dimethylpenam* (**8**).—A solution of (**4**) (1.0 g, 2.9 mmol) in anhydrous dichloromethane (8.0 ml) was added slowly to a solution of DAST (0.75 ml, 6 mmol) in anhydrous dichloromethane (3 ml) at −23 °C under nitrogen. The reaction mixture was stirred for 5 h at room temperature and then cooled to −10 °C, quenched with methanol (1 ml) and concentrated. Column chromatography of the residue with chloroform as eluant yielded (**8**) (0.58 g, 58%) as white crystals, m.p. 95—96 °C (from benzene–hexane); $\nu_{max.}$(KBr) 1 790 (β-lactam) and 1 010 cm^{-1} (C-F); δ_H(80 MHz; $CDCl_3$; standard Me_4Si) 1.53 (3 H, d, $J_{H,F}$ 1.6 Hz, 10-Me), 1.57 (3 H, s, 9-Me), 3.92—4.84 (3 H, m, $J_{H,F}$ 53 Hz, 8-H and 3-H), and 5.54 (1 H, s, 5-H); δ_C(20.15 MHz; $CDCl_3$; standard $CDCl_3$) 165.2 (C-7); 80.1 (d, $^1J_{C,F}$ 176 Hz, C-8), 78.8 (C-5), 66.9 (d, $^2J_{C,F}$ 21.2 Hz, C-3), 63.0 (C-2), 58.8 (C-6), 33.2 (C-9), and 24.4 (C-10); *m/z* 349 (7.4%), 347 (13.6), 345 (M^+, 7.1), 330 (1.5), 328 (3.4), 326 (2.2, M^+ − F), 268 (21.7), 266 (20.7, M^+ − Br), 261 (8.8), 259 (15.4), 257 (7.7), 220 (13), 218 (24.5), 216 (12.5), 114 (48.6), and 70 (100) (Found: M^+, 344.8807. Calc. for $C_8H_{10}Br_2FNOS_2$: M^+, 344.8834).

6β-*Bromo*-3α-*fluoromethyl*-2,2-*dimethylpenam* (**9**).—A solution of tributyltin hydride (0.086 ml, 0.319 mmol) in anhydrous ether (1.0 ml) was added dropwise to a solution of (**8**) (100 mg, 0.29 mmol) and AIBN (4 mg) in anhydrous ether (5 ml) at 0 °C over 2 h. After 3 h at this temperature, the solvent was evaporated. Work-up was similar to that described for compound (**5**), using benzene–acetonitrile (9.5:0.5) as eluant for preparative t.l.c. The major product was identified as (**9**) (39 mg, 50%), a crystalline solid, m.p. 79—81 °C; $\nu_{max.}$(KBr) 1 780 (β-lactam) and 1 000 cm^{-1} (C–F); δ_H(80 MHz; $CDCl_3$; standard Me_4Si) 1.54 (3 H, d, $J_{H,F}$ 1.6 Hz, 10-Me), 1.61 (3 H, s, 9-Me), 3.94—4.83 (3 H, m, $J_{H,F}$ 53 Hz, 8-H and 3-H), 5.3 (1 H, d, *J* 5.6 Hz, 6-H), and 5.35 (1 H, d, *J* 5.6 Hz, 5-H); δ_C(20.15 Hz; $CDCl_3$; standard $CDCl_3$) 169.3 (C-7), 80.5 (d, $^1J_{C,F}$ 176 Hz, C-8), 68.6 (C-5), 67.1 (d, $^2J_{C,F}$ 21.33 Hz, C-3), 62.9 (C-2), 50.1 (C-6), 32.5 (C-9), and 24.9 (C-10); *m/z* 269 (10.8%), 267 (M^+, 10.6), 188 (40, M^+ − Br), 148 (100), 114 (52), and 70 (56) (Found: M^+, 266.9696. Calc. for $C_8H_{11}BrFNOS$: M^+, 266.97286). The minor product was identified as 3α-fluoromethyl-2,2-dimethylpenam (**11**) (19 mg, 35%), described below.

6,6-*Dibromo*-3α-*carbamoyl*-2,2-*dimethylpenam* (**12**).—This compound was prepared according to a method described by Johnson[36] for benzylpenicillamide. It yielded (**12**) (75%), m.p. 143—145 °C; $\nu_{max.}$($CHCl_3$) 1 790 (β-lactam) and 1 650 cm^{-1} (amide); δ_H(80 MHz; $CDCl_3$; standard Me_4Si) 1.58 (3 H, s, 10-Me), 1.70 (3 H, s, 9-Me), 4.36 (1 H, s, 3-H), 5.68 (1 H, s, 5-H), 6.03 (1 H, br s, NH), and 6.30 (1 H, br s, NH); δ_C(20.15 MHz; $CDCl_3$; standard $CDCl_3$) 167.4 (C-8), 164.8 (C-7), 79.9 (C-5), 69.5 (C-3), 64.0 (C-2), 58.5 (C-6), 32.8 (C-9), and 25.4 (C-10) (Found: C, 26.95; H, 3.0; N, 7.55; Br, 44.30; S, 9.15. $C_8H_{10}Br_2N_2O_2S$ requires C, 26.84; H, 2.80; Br, 44.64; N, 7.82; S, 8.96%).

6,6-*Dibromo*-3α-*cyano*-2,2-*dimethylpenam* (**13**).—Oxalyl chloride (2.01 ml, 23 mmol) was added to a solution of dimethylformamide (1.95 ml, 26 mmol) in anhydrous aceto-

nitrile (30 ml) at 0 °C. A white precipitate was formed immediately and was accompanied by gas evolution. When it was over, a solution of amide (**12**) (7.0 g, 19.5 mmol) in anhydrous acetonitrile (5 ml) was added. When the mixture became homogeneous, pyridine (3.8 ml, 47 mmol) was added. After 30 min at room temperature the reaction was complete. The solvent was evaporated and the oily residue was chromatographed with ethyl acetate–hexane (1:4) as eluant to give (**13**) (6.56 g, 89%), m.p. 118—120 °C (decomp.); $\nu_{max.}$(CHCl$_3$) 2 135 (cyano) and 1 805 cm^{-1} (β-lactam); δ_H(80 MHz; CDCl$_3$; standard Me$_4$Si) 1.60 (3 H, s, 10-Me), 1.73 (3 H, s, 9-Me), 4.79 (1 H, s, 3-H), and 5.74 (1 H, s, 5-H); δ_C(20.15 MHz; CDCl$_3$; standard CDCl$_3$) 163.5 (C-7), 112.9 (C-8), 79.4 (C-5), 63.8 (C-2), 59.5 (C-3), 57.7 (C-6), 31.5 (C-9), and 26.2 (C-10); *m/z* 342 (9.5%), 340 (18.5), 338 (M^+, 9), 327 (2.7), 325 (5.3), 323 (2.9, $M^+ - CH_3$), 261 (23), 259 (42), 257 (20), 202 (48), 200 (100), 198 (51), and 82 (36) (Found: M^+, 337.8769. Calc. for $C_8H_8Br_2N_2OS$: M^+, 337.87238).

General Procedure for Total Dehalogenation.—Tributyltin hydride (2.2 mmol) was added to a solution of the substrate (1 mmol) and AIBN (4 mg) in anhydrous benzene (7 ml), at room temperature. The reaction mixture was stirred for 20 h and then the solvent was removed. The product was purified by flash chromatography; elution was with hexane to remove organotin impurities and then with methanol. Using this general procedure, the following compounds were prepared.

3α-*Hydroxymethyl*-2,2-*dimethylpenam* (**6**) (93%) a colourless oil, $\nu_{max.}$(film) 3 400 (OH) and 1 770 cm^{-1} (β-lactam); δ_H(80 MHz; CDCl$_3$; standard Me$_4$Si) 1.46 (3 H, s, 10-Me), 1.55 (3 H, s, 9-Me), 2.65 (1 H, br s, OH), 3.05 (1 H, dd, ABX system, J_{gem} 16.0, J_{vic} 1.95 Hz, 6β-H), 3.54 (1 H, dd, ABX system, J_{gem} 16.0, J_{vic} 4.1 Hz, 6α-H), 3.62 (2 H, m, AB$_2$ system, *J* 7 Hz, 8-H), 3.94 (1 H, m, AB$_2$ system, *J* 7 Hz, 3-H), and 5.09 (1 H, dd, ABX system, J_{vic} 4.9 and 1.95 Hz, 5-H); δ_C(20.15 MHz; CDCl$_3$; standard CDCl$_3$) 174.2 (C-7), 70.3 (C-3), 63.6 (C-2), 59.9 (C-8), 58.5 (C-5), 46.6 (C-6), 32.4 (C-9), and 24.7 (C-10).

3α-*Fluoromethyl*-2,2-*dimethylpenam* (**10**) (90%) a colourless oil, $\nu_{max.}$(film) 1 780 (β-lactam) and 1 025 cm^{-1} (CF); δ_H(80 MHz; CDCl$_3$; standard Me$_4$Si) 1.53 (3 H, d, $J_{H,F}$ 1.6 Hz, 10-Me), 1.58 (3 H, s, 9-Me), 3.05 (1 H, dd, ABX system, J_{gem} 16.0, J_{vic} 1.95 Hz, 6β-H), 3.54 (1 H, dd, ABX system, J_{gem} 16.0, J_{vic} 4.1 Hz, 6α-H), 3.88—4.80 (3 H, m, $J_{H,F}$ 54 Hz, 8-H and 3-H), and 5.07 (1 H, dd, ABX system, J_{vic} 4.1 and 1.95 Hz, 5-H); δ_C(20.15 MHz; CDCl$_3$; standard CDCl$_3$) 173.2 (C-7), 81.0 (d, $^1J_{C,F}$ 173 Hz, C-8), 67.2 (d, $^2J_{C,F}$ 20 Hz, C-3), 63.9 (C-2), 59.2 (C-5), 46.9 (C-6), 32.2 (C-9), and 25.2 (C-10).

3α-*Cyano*-2,2-*dimethylpenam* (**14**).—A solution of tributyltin hydride (0.77 ml, 2.9 mmol) and AIBN (4 mg) in anhydrous benzene (1.0 ml) was added to a solution of (**13**) (500 mg, 1.45 mmol) in anhydrous benzene (3.0 ml) at 15 °C. The reaction was stirred at this temperature for 24 h after which the solvent was removed and the product purified by column chromatography; elution was with hexane to remove organotin impurities and then with ethyl acetate–hexane (1:9). The major product was identified as (**14**) (250 mg, 93%), a white crystalline solid, m.p. 80—81 °C; $\nu_{max.}$(CHCl$_3$) 2 130 (CN) and 17 85 cm^{-1} (β-lactam); δ_H(80 MHz; CDCl$_3$ standard Me$_4$Si) 1.60 (3 H, s, 10-Me), 1.74 (3 H, s, 9-Me), 3.08 (1 H, dd, ABX system, J_{gem} 16.0, J_{vic} 1.6 Hz, 6β-H), 3.60 (1 H, dd, ABX system, J_{gem} 16.0, J_{vic} 4.16 Hz, 6α-H), 4.66 (1 H, s, 3-H), and 5.23 (1 H, dd, ABX system, J_{vic} 4.16 (and 1.6 Hz, 5-H); δ_C(20.15 MHz; CDCl$_3$; standard CDCl$_3$) 171.1 (C-7), 114.1 (C-8), 64.0 (C-2), 60.0 (C-5), 59.4 (C-3), 47.1 (C-6), 30.3 (C-9), and 26.5 (C-10). The minor product was identified as 6β-bromo-3α-cyano-2,2-dimethylpenam (**15**) (20 mg, 5%), an oil; $\nu_{max.}$(CHCl$_3$) 2 130 (cyano) and 1 800 cm^{-1} (β-lactam); δ_H(80 MHz; CDCl$_3$; standard Me$_4$Si) 1.63 (3 H, s, 10-Me), 1.74 (3 H, s, 9-Me), 4.73 (1 H, s, 3-H), 5.37 (1 H, d, *J* 4.0 Hz, 6-H), and 5.55 (1 H, d, *J* 4.0 Hz, 5-H); δ_C(20.15 MHz; CDCl$_3$; standard CDCl$_3$) 167.7 (C-7), 113.7 (C-8), 67.5 (C-5), 63.6 (C-2), 60.5 (C-3), 49.9 (C-6), 30.7 (C-9), and 26.8 (C-10).

General Procedure for Oxidation from Sulphide to Sulphone.—The substrate (0.535 mmol) was dissolved in methanol (2.2 ml) and the solution cooled to 0 °C. To this was added a solution of oxone (containing 1.6 mmol of KHSO$_5$) in water (2.2 ml). The resulting slurry was stirred for 24 h at room temperature after which methanol was removed under reduced pressure, ethyl acetate (3 ml) added to the residue and the layers separated. The aqueous layer was extracted with ethyl acetate (2 × 3 ml). The combined organic layers were washed with brine (2 × 2 ml), dried (Na$_2$SO$_4$), and concentrated. Compounds prepared by this method were as follows.

3α-*Hydroxymethyl*-2,2-*dimethylpenam* S,S-*dioxide* (**7**) (70%), a crystalline solid, m.p. 105—107 °C; $\nu_{max.}$(KBr) 3 510 (OH), 1 770 (β-lactam), 1 340, and 1 145 cm^{-1} (SO$_2$); δ_H(80 MHz; CDCl$_3$; standard Me$_4$Si) 1.48 and 1.50 (each 3 H, s, 2 × Me), 2.26 (1 H, br s, OH), 3.43 (2 H, d, *J* 3.2 Hz, 6-H), 3.72 (2 H, m, AB$_2$ system, *J* 7 Hz, 8-H), 3.85 (1 H, m, AB$_2$ system, *J* 7 Hz, 3-H), and 4.49 (1 H, t, *J* 3.2 Hz, 5-H); δ_C(20.15 MHz; CDCl$_3$; standard CDCl$_3$) 172.4 (C-7), 63.2 (C-3), 62.9 (C-2), 61.4 (C-8), 60.7 (C-5), 38.0 (C-6), and 18.9 (C-9 and C-10); f.a.b. m.s. (glycerol) *m/z* 220 (40%, MH^+) and 202 (26, $MH^+ - 18$); e.i. m.s. *m/z* 155 (5.9%, $M^+ - SO_2$), 149 (26), 86 (14), 85 (68), and 71 (100)* (Found: $M^+ - SO_2$, 155.0941. Calc. for $C_8H_{13}NO_2$: $M^+ - SO_2$, 155.09462).

3α-*Fluoromethyl*-2,2-*dimethylpenam* S,S-*dioxide* (**11**) (78%), white crystals, m.p. 133—135 °C; $\nu_{max.}$(KBr) 1 770 (β-lactam), 1 015 (C-F), and 1 310 and 1 130 cm^{-1} (SO$_2$); δ_H(80 MHz; CDCl$_3$; standard Me$_4$Si) 1.51 (3 H, s, 9-Me), 1.52 (3 H, d, $J_{H,F}$ 1.6 Hz, 10-Me), 3.44 (2 H, d, *J* 3.2 Hz, 6-H), 3.94—4.84 (3 H, m, $J_{H,F}$ 54 Hz, 8-H and 3-H), and 4.47 (1 H, t, *J* 3.2 Hz, 5-H); δ_C(20.15 MHz; CDCl$_3$; standard CDCl$_3$) 171.6 (C-7), 80.6 (d, $^1J_{C,F}$ 176 Hz, C-8), 62.5 (d, $^3J_{C,F}$ 5.6 Hz, C-2), 60.8 (C-5), 60.4 (d, $^2J_{C,F}$ 23Hz, C-3), 38.4 (C-6), 19.2 (C-9),† and 19.0 (C-10);† f.a.b. m.s.(glycerol) *m/z* 222 (12%, MH^+); e.i. m.s. *m/z* 157 (16%, $M^+ - SO_2$), 114 (8), 96 (11), 88 (40), 87 (14), 73 (80), and 70 (100)* (Found: $M^+ - SO_2$, 157.0883. Calc. for $C_8H_{12}NOF$: $M^+ - SO_2$, 157.09028).

3α-*Cyano*-2,2-*dimethylpenam* S,S-*dioxide* (**16**) (89%), white crystals, m.p. 108—109 °C; $\nu_{max.}$(KBr) 2 240 (cyano), 1 790 (β-lactam), and 1 330 and 1 170 cm^{-1} (SO$_2$); δ_H(80 MHz; CDCl$_3$; standard Me$_4$Si) 1.53 (3 H, s, 10-Me), 1.65 (3 H, s, 9-Me), 3.39 (2 H, d, *J* 3.2 Hz, 6-H), 4.69 (1 H, s, 3-H), and 4.99 (1 H, t, *J* 3.2 Hz, 5-H); δ_C (20.15; CDCl$_3$; standard CDCl$_3$) 170.2 (C-7), 114.1 (C-8), 73.1 (C-2), 71.6 (C-3), 55.5 (C-5), 36.6 (C-6), 19.3 (C-9),‡ and 18.6 (C-10);‡ f.a.b. m.s. (glycerol) *m/z* 215 (6.1%, MH^+), 214 (6.7, M^+), 213 (28, $M - H^+$), and 199 (100, $M^+ - 15$); e.i. m.s. *m/z* 150 (2.6%, $M^+ - SO_2$), 108 (14), 91 (31), 81 (100), and 80 (28) (Found: $M^+ - SO_2$, 150.0761. Calc. for $C_8H_{10}N_2O$: $M^+ - SO_2$, 150.07931).

Dimeric Ester (**17**).—A solution of compound (**4**) (80 mg, 0.23 mmol) in dichloromethane (0.5 ml) was added gradually to a suspension of pyridinium fluorochromate (70 mg, 0.35 mmol) in dichloromethane (1.0 ml) at room temperature with vigorous stirring which was continued for 6 h. Dry ether (3 ml) was added to the resultant mixture, and the mixture was filtered and washed with ether. The filtrate was evaporated to give a solid residue, which was chromatographed with chloroform–ether

* These figures were taken from the high resolution mass spectra (70 eV). The low resolution mass spectra at 20 eV shows the same fragmentation pattern.

†, ‡, §, ¶, ||, #, and ** assignments could be reversed.

(9:1) as eluant to yield (**17**) (34 mg, 49%) as white crystals, m.p. 167—169 °C (from ethyl acetate–hexane); $\nu_{max.}$(KBr) 1 795 (β-lactam) and 1 770 cm^{-1} (ester); δ_H(80 MHz; CD_3CN; standard Me_4Si) 1.53 (3 H, s, Me), 1.55 (3 H, s, Me), 1.57 (3 H, s, Me), 1.65 (3 H, s, Me), 4.33 (3H, s, 8′-H and 3′-H), 4.73 (1 H, s, 3-H), and 5.77 and 5.95 (each 1 H, s, 5-H and 5′-H); δ_C(20.15 MHz; CD_3CN: standard CD_3CN) 167.6 (C-8), 166.4 (C-7′),§ 165.7 (C-7),§ 80.4 (C-5), 78.6 (C-5′), 69.7 (C-3′), 66.3 (C-3), 64.5 (C-2),¶ 63.3 (C-2′),¶ 62.0 (C-8′), 59.0 (C-6′),‖ 58.2 (C-6),‖ 32.9 (C-9),# 32.5 (C-9′),# 25.3 (C-10),** and 23.5 (C-10′);** *m/z* 690 (6.9%), 688 (22.8), 686 (31.6), 684 (20.8), 682 (M^+, 5.2), 609 (6), 607 (18.2), 605 (18.5), 603 (6.4, M^+ − Br), 316 (2.2), 314 (4.4), 312 (2.3), 261 (16), 259 (30), 257 (14.5), and 114 (100) (Found: M^+, 681.74040. Calc. for $C_{16}H_{18}Br_4N_2O_4S_2$: M^+, 681.74418).

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