Derivatives of 2-Methylenepenam: Analogues of Clavulanic Acid

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Some substituted 2-methylenepenams have been synthesised by ring closure of acetylenic azetidinone-thiols. Substituents on the methylene group include aryl, hydroxymethyl, and alkoxycarbonylvinyl.

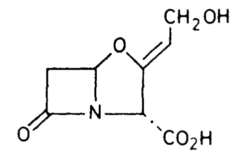
FOLLOWING the isolation and characterisation of clavulanic acid (1),[1] a naturally occurring β-lactam possessing high activity as a β-lactamase inhibitor, a number of analogues have been synthesised including some 1-thia-analogues.[2] 1-Oxa-derivatives lacking the carboxy-group at position 3 have been shown to retain potent inhibitory activity,[3] and this has led to interest in the 1-thia-analogues. The present work describes the synthesis of penams substituted with an exocyclic double bond at position 2 by means of the intramolecular addition of an azetidinone-4-thiol group to an activated triple bond.[4]

RESULTS AND DISCUSSION

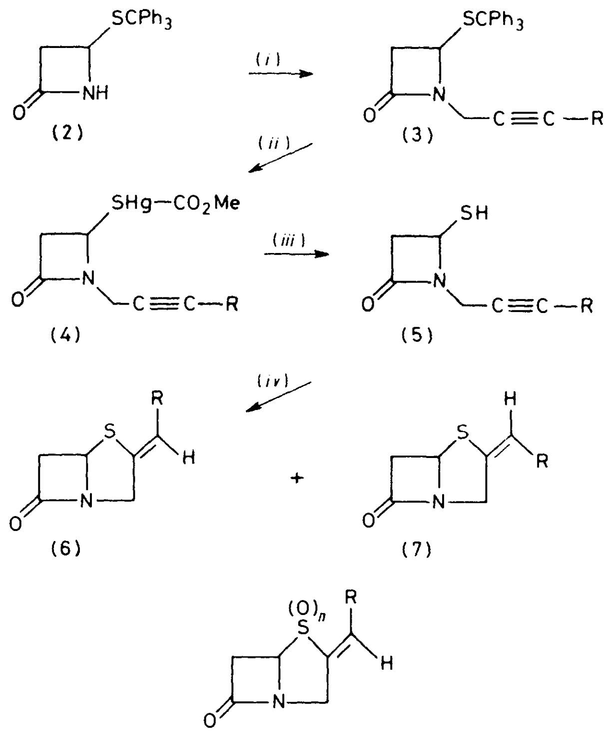
4-Tritylthioazetidin-2-one (2), obtained from 4-acetoxyazetidin-2-one and triphenylmethanethiol, was alkylated by 1-bromo-3-phenylprop-2-yne in the presence of potassium t-butoxide to give the *N*-phenylpropynyl compound (3a). The azetidinone (3a) was detritylated by the method of Lattrell[5] with methoxycarbonylmercury(II) acetate in dichloromethane–methanol solution to give 4-(methoxycarbonylmercuriothio)-1-(3-phenylprop-2-ynyl)azetidin-2-one (4a) in good yield. The unstable thiol (5a) was then rapidly formed on passing hydrogen sulphide through a dichloromethane solution of the mercury derivative (4a). Stirring the thiol (5a) in tetrahydrofuran with silica gel caused cyclisation to a mixture of the *E*- and *Z*-isomers of benzylidenepenam, (6a) and (7a). Crystallisation afforded the major isomer which was shown to have the *Z*-configuration (6a) by *X*-ray analysis.[6] A somewhat similar cyclisation of a mercaptoacetylene (9) to benzylidenetetrahydrothiophen (10) has been achieved by an irradiation method.[7]

The benzylidene compounds (6a) and (7a) showed no β-lactamase inhibition, nor did the *p*-methoxycarbonyl esters (6b) and (7b) prepared by similar routes. Attempts to introduce more hydrophilic character into these molecules by hydrolysis of the esters to the corresponding acids failed, resulting in destruction of the β-lactam nucleus.

The 2-hydroxyethylidene grouping characteristic of clavulanic acid would be introduced by cyclisation of 4-mercapto-1-(4-hydroxybut-2-ynyl)azetidin-2-one (5d). In this compound, however, activation of the triple bond was insufficient for cyclisation to occur. The problem was overcome by use of the acetylenic acetal (3e), obtained from 1-bromo-4,4-diethoxybut-2-yne and triphenylmethylthioazetidinone (2). After deprotection of the formyl group with trifluoroacetic acid, detritylation of the mercapto-group as previously described gave the unstable mercapto-aldehyde (5f) which, with silica gel, cyclised to the formylmethylenepenam (6f),



(1)



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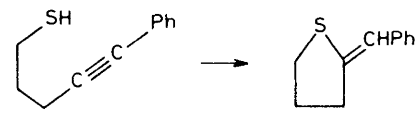
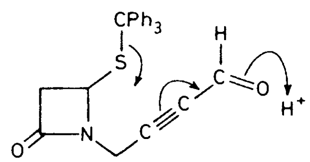
a; Ph	g; $CH=CHCO_2Me$-*trans*
b; $C_6H_4CO_2Me$-*p*	h; $CH=CHCO_2Me$-*cis*
c; $C_6H_4(CO_2CH_2C_6H_4OMe$-*p*)-*p*	i; $CH=CHCO_2CMe_3$-*trans*
d; CH_2OH	
e; $CH(OEt)_2$	
f; CHO	

SCHEME (*i*) DMF, $BrCH_2C{\equiv}CR$, $KOBu^t$; (*ii*) $Hg(CO_2Me)OAc$, DCM, MeOH; (*iii*) H_2S, DCM; (*iv*) SiO_2, THF obtained as a single isomer, which was tentatively assumed to have the same *Z*-configuration as the major isomer of the benzylidene compound (6a).

During the experiments to improve the de-acetalisation step it was noticed (by t.l.c.) that when a mixture of equal parts of wet tetrahydrofuran and trifluoroacetic acid was used the initial formation of the acetylenic aldehyde (3f) was followed by a slower direct conversion to the penam (6f). This must be a case of assisted detritylation involving an intermediate such as (11), since



(9) (10)



(11)

similar reaction conditions do not affect the triphenylmethylthio-compounds (3a) and (3d).

The unsaturated aldehyde (6f) was reduced by either lithium aluminium hydride or sodium borohydride to the alcohol (6d) having the desired hydroxy-ethylidene side-chain. The aldehyde (6f) also reacted with stabilised Wittig reagents such as alkoxycarbonylmethylenetriphenylphosphoranes to give the diene esters (6g) and (6i), although it was not possible to obtain the corresponding free acids either by mild hydrolysis of the methyl esters or by trifluoroacetic acid treatment of the t-butyl ester.

Oxidation of the penams (6a) and (6c) with 1.2 or 2.4 equivalents of *m*-chloroperbenzoic acid afforded the α- and β-isomers of the sulphoxides (8a; $n = 1$) and (8c; $n = 1$) or the sulphones (8a; $n = 2$) and (8c; $n = 2$), respectively.

Chemical shifts of C-5 and C-6 protons (δ)

Compound		C-5-H	C-6-H_2
Sulphides	(6a)	5.17	3.65, 3.10
	(7a)	5.07	3.65, 3.10
	(6c)	5.29	3.17, 3.71
	(7c)	5.04	3.17. 3.71
α-Sulphoxides	(8a; $n = 1$)	4.76	3.07, 3.64
	(8c; $n = 1$)	4.82	3.14, 3.70
β-Sulphoxides	(8a; $n = 1$)	4.56	3.36
	(8c; $n = 1$)	4.66	3.42
Sulphones	(8a; $n = 2$)	4.46	3.48
	(8c; $n = 2$)	4.45	3.51

The stereochemical assignments of the sulphoxides are tentatively made on the basis of ^{1}H n.m.r. spectra (see Table). In the β-isomers appearance of the C-6 protons as a doublet or broad singlet at δ *ca.* 3.5 and the C-5 proton as a triplet or broad singlet at δ *ca.* 4.6 instead of the usual ABX system indicates proximity of the sulphoxide oxygen. The same effect is observed in the sulphones (8a; $n = 2$) and (8c; $n = 2$).

No appreciable β-lactamase inhibitory activity was shown by any of the penams described, thus marking an important biological distinction between the oxygen and the sulphur ring systems.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. All i.r. spectra were recorded for solutions in chloroform. ^{1}H N.m.r. spectra were recorded in $CDCl_3$ with tetramethylsilane as internal standard with a Perkin-Elmer R32 90 MHz instrument or with a Varian 80 MHz spectrometer where indicated. Mass spectra were determined with a V.G. 70-70 spectrometer. Merck silica gel 60 was used for the cyclisations and for column chromatography, with ethyl acetate–light petroleum as eluant. Light petroleum refers to the fraction of b.p. 60—80 °C. Tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) were dried by distillation over sodium hydride immediately before use. Dimethylformamide (DMF) was dried over a molecular sieve, type 4A.

4-(*Triphenylmethylthio*)*azetidin*-2-*one* (2).—To a suspension of 4-acetoxyazetidin-2-one (2.9 g) and triphenylmethanethiol (12.87 g) in methanol (80 ml) and dichloromethane (10 ml) at −30 °C was added dropwise a 1M solution of potassium t-butoxide in t-butyl alcohol (23.8 ml). The mixture was kept for 4 h at room temperature, most of the solvent was evaporated off, and the residue was dissolved in ethyl acetate. The solution was washed with water, dried ($MgSO_4$), concentrated, and the residue chromatographed. Finally the *product* (2) was crystallised from ethyl acetate–light petroleum to give white needles (5.45 g, 69%), m.p. 148—149 °C; $\nu_{max.}$ 3 370 and 1 765 cm^{-1}; δ 2.61 (1 H, dd, *J* 16, 2 Hz), 3.0 (1 H, ddd, *J* 16, 5, 2 Hz), 4.11 (1 H, dd, *J* 5, 2 Hz), 5.66 (1 H, br s), and 7.75 (15 H, m) (Found: C, 76.7; H, 5.8; N, 3.8; S, 9.5. $C_{22}H_{19}NOS$ requires C, 76.5; H, 5.5; N, 4.0; S, 9.5%).

Substitution at the 1-*Position of* 4-(*Triphenylmethylthio*)-*azetidin*-2-*one* (2). *General Method.*—To a 5% solution of the appropriate bromoacetylene (1 equiv.) in DMF was added 4-(triphenylmethylthio)azetidin-2-one (1 equiv.) followed at 0 °C by the dropwise addition of a 1M solution of potassium t-butoxide in t-butyl alcohol (1.1 equiv.) over 30 min. The mixture was diluted with ethyl acetate, washed with water, dried ($MgSO_4$), and evaporated. The residue was then chromatographed. In this way the following products were obtained from the quoted bromides.

1-Bromo-3-phenylprop-2-yne gave 1-(3-*phenylprop*-2-*ynyl*)-4-(*triphenylmethylthio*)*azetidin*-2-*one* (3a) (73%), m.p. 144—145 °C (from ethyl acetate–light petroleum); $\nu_{max.}$ 1 760 cm^{-1}; δ 2.59 (1 H, dd, *J* 14, 2 Hz), 2.88 (1 H, dd, *J* 14, 4 Hz), 3.87 and 4.42 (2 H, AB q, *J* 19 Hz), 4.54 (1 H, dd, *J* 4, 2 Hz), and 7.1—7.7 (20 H, m) (Found: C, 0.88; H, 5.8; N, 3.0; S, 7.2. $C_{31}H_{25}NOS$ requires C, 81.1; H, 5.5; N, 3.1; S, 7.0%).

From 1-bromo-3-(*p*-methoxycarbonylphenyl)prop-2-yne was obtained 1-[3-(p-*methoxycarbonylphenyl*)*prop*-2-*ynyl*]-4-(*triphenylmethylthio*)*azetidin*-2-*one* (3b) as white needles (78%), m.p. 55 °C (from ethyl acetate–light petroleum); $\nu_{max.}$ 1 755 and 1 725 cm^{-1}; δ 2.68 (1 H, dd, *J* 15, 3 Hz), 3.00 (1 H, dd, *J* 15, 4 Hz), 3.89 and 4.41 (2 H, AB q, *J* 18 Hz), 3.95 (3 H, s), 4.55 (1 H, dd, *J* 4, 3 Hz), and 7.2—8.1

(19 H, m) (Found: M^+, 517.175 7. $C_{33}H_{27}NO_3S$ requires M, 517.171 2).*

From 1-bromo-3-[*p*-(*p*-methoxybenzyloxycarbonyl)-phenyl]prop-2-yne was likewise obtained 1-{3-[p-(p-*methoxybenzyloxycarbonyl)phenyl*]*prop-2-ynyl*}-4-(*triphenylmethylthio)azetidin-2-one* (3c) as white needles (56%), m.p. 144—145 °C (from ethyl acetate–light petroleum); $\nu_{max.}$ 1 755 and 1 715 cm^{-1}; δ 2.66 (1 H, dd, *J* 15, 2 Hz), 2.90 (1 H, dd, *J* 15, 4 Hz), 3.76 (3 H, s), 3.84 and 4.29 (2 H, AB q, *J* 18 Hz), 4.42 (1 H, dd, *J* 4, 2 Hz), 5.24 (2 H, s), 6.84 (2 H, d, *J* 9 Hz), 7.07—7.46 (19 H, m), and 7.92 (2 H, d, *J* 8 Hz) (Found: C, 77.0; H, 5.6; N, 2.4; S, 5.1. $C_{40}H_{33}NO_4S$ requires C, 77.0; H, 5.3; N, 2.2; S, 5.1%).

The same general method, using 4-bromobut-2-yn-1-ol [8] and 4-bromo-1,1-diethoxybut-2-yne [9] gave the corresponding 1-(4-hydroxybut-2-ynyl)- (3d) and 1-(4,4-diethoxybut-2-ynyl)- (3e) azetidinones as viscous oils characterised only by n.m.r. and i.r. spectra: (3d) (48%); $\nu_{max.}$ 3 600—3 100 and 1 755 cm^{-1}; δ 2.60 (1 H, dd, *J* 16, 3 Hz) and 2.99 (1 H, dd, *J* 16, 5 Hz), 3.05 (1 H, br s exchangeable with D_2O), 3.60 and 4.15 (2 H, centres of AB q, *J* 15 Hz), 4.23 (2 H, br s sharpens to s with D_2O), 4.46 (1 H, dd, *J* 5, 3 Hz), and 7.2—7.6 (15 H, m). Compound (3e) (62%); $\nu_{max.}$ 1 760 cm^{-1}; δ 1.2 (6 H, br t, *J* 5 Hz), 2.58 (1 H, dd, *J* 14, 2 Hz), 2.88 (1 H, dd, *J* 14, 4 Hz), 3.76 (4 H, q, *J* 5 Hz), 3.71 and 4.20 (2 H, centres of AB q, *J* 18 Hz), 4.62 (1 H, dd, *J* 4, 2 Hz), 5.3 (1 H, s), and 7.3—7.7 (15 H, m).

Detritylation with Methoxycarbonylmercury(II) *Acetate. General Method*.—The triphenylmethylazetidinone was treated with 1 equivalent of methoxycarbonylmercury(II) acetate in dry methanol–dichloromethane (4 : 1) for 3 h at room temperature. The product was isolated by evaporation and chromatography. The following products were thus obtained.

The N-*phenylpropynyl compound* (4a) as fine white crystals (56%), m.p. 106 °C (from ethyl acetate); $\nu_{max.}$ 1 760 and 1 690 cm^{-1}; δ 2.90 (1 H, dd, *J* 14, 2 Hz), 3.52 (s, Me) and 3.54 (dd, *J* 14, 5Hz) (together 4 H), 4.13 and 4.60 (2 H, centres of AB q *J* 18 Hz), and 5.4 (1 H, dd, *J* 5, 2 Hz) (Found: C, 35.3; H, 2.7; N, 2.9. $C_{14}H_{13}HgNO_3S$ requires C, 35.3; H, 2.7; N, 2.9%).

The N-{3-[p-(p-*methoxybenzyloxycarbonyl)phenyl*]*propynyl*} *compound* (4c) (74%) as white platelets, m.p. 143—144 °C (from ethyl acetate–light petroleum); $\nu_{max.}$ 1 755, 1 710, and 1 690 cm^{-1}; δ 2.84 (1 H, dd, *J* 15, 2 Hz), 3.43 (3 H, s), 3.51 (1 H, dd, *J* 15, 5 Hz), 3.77 (3 H, s), 4.07 and 4.49 (2 H, centres of AB q *J* 18 Hz), 5.23 (2 H, s), 5.20—5.33 (1 H, m), 6.84 (2 H, d, *J* 9 Hz), 7.31 (2 H, d, *J* 9 Hz), 7.40 (2 H, d, *J* 8 Hz), and 7.92 (2 H, d, *J* 8 Hz) (Found: C. 43.2; H, 3.3; N, 2.2. $C_{23}H_{21}HgNO_6S$ requires: C, 43.2; H, 3.3; N, 2.2%). The other mercury compounds (4b) (68%), (4d) (63%), and (4e) (68%) were obtained as amorphous solids characterised only by i.r. and n.m.r. spectra: compound (4b); $\nu_{max.}$ 1 755, 1 725, and 1 690 cm^{-1}: δ 2.89 (1 H, ddd, *J* 16, 3, 1 Hz), 3.30 (1 H, ddd, *J* 16, 4, 2 Hz), 3.54 (3 H, s), 3.92 (3 H, s), 4.14 and 4.62 (2 H, centres of AB q, *J* 18 Hz), 5.39 (1 H, dd, *J* 4, 3 Hz), 7.52 (2 H, d, *J* 8 Hz), and 8.05 (2 H, d, *J* 8 Hz): compound (4d); $\nu_{max.}$ 3 400 (br), 1 755, and 1 675 cm^{-1}: δ 2.92 (1 H, dd, *J* 16, 2 Hz), 3.35 (1 H, br s exchangeable with D_2O), 3.60 (1 H, dd, *J* 16, 5 Hz), 3.80 (3 H, s), 4.34, (2 H, br, s, sharpens with D_2O), 4.35 and 4.75 (2 H, centres of Ab q, *J* 20 Hz), and 5.44 (1 H, dd. *J* 5, 2 Hz): compound (4e); $\nu_{max.}$ 1 760 and 1 685 cm^{-1}: δ 1.27 (6 H, t, *J* 7 Hz), 2.9 (1 H, dd, *J* 14, 2 Hz), 3.75 (s), 3.4—4.1 (m), 3.95 and 4.4 (centres of AB q, *J* 18 Hz) (together 10 H), 5.3 (s) and 5.33 (dd, *J* 5, 2 Hz) (together 2 H).

Formation and Cyclisation of 4-Mercaptoazetidinones. General Method.—A slow stream of hydrogen sulphide was passed at room temperature for 10 min through 3% dichloromethane solutions of the (methoxycarbonylmercuriothio)azetidinones described above. The black precipitate was filtered off, and the filtrate was evaporated leaving the mercaptoazetidinones as unstable yellow gums which were used with further purification. A typical product (5a) (75%) had $\nu_{max.}$ 1 760 cm^{-1}; δ 2.17 (1 H, d, *J* 9 Hz, SH), 2.88 (1 H, dd, *J* 15, 2 Hz), 3.57 (1 H, dd, *J* 15, 4 Hz), 4.00 and 4.58 (2 H, AB q, *J* 18 Hz), 4.98 (1 H, ddd, *J* 9, 4, 2 Hz), and 7.3—7.7 (5 H, m). The mercaptoazetidinone (3% solution in tetrahydrofuran) was stirred with three times its own weight of silica gel for 2 h. The products were isolated by column chromatography and recrystallisation. The yield of mixed *E*- and *Z*-isomers from (methoxycarbonylmercuriothio)azetidinone is quoted, followed by the data for the major isomer isolated by crystallisation.

2-*Benzylidenepenam* (6a) and (7a), 41%, a mixture of *Z*- and *E*-isomers (*ca*. 4 : 1 ratio). The Z-*isomer* (6a) had m.p. 114.5—115.5 °C (from ethyl acetate); $\nu_{max.}$ 1 780 and 1 620(w) cm^{-1}; δ (80 MHz) 3.1 (1 H, dd, *J* 17, 1.5 Hz, C-6-H *trans*), 3.63 (ddd, *J* 17, 4, 1 Hz, C-6-H *cis*) and 3.75 (dd, *J* 14, 1 Hz, C-3-H) (together 2 H), 4.79 (1 H, dd, *J* 14, 1.5 Hz, C-3-H), 5.17 (1 H, dd, *J* 4, 1.5 Hz, C-5-H), 6.4 (1 H, d, *J* 1 Hz, vinyl C-H), and 7.5—7.7 (5 H, m, aromatic) (Found: C, 66.5; H, 4.9; N, 6.2; S, 14.5. $C_{12}H_{11}NOS$ requires C, 66.4; H, 5.0; N, 6.5; S, 14.8%). The minor E-*isomer* (7a) was not obtained pure but showed characteristic n.m.r. frequencies in the mixture at 5.07 (dd, *J* 4, 1.5 Hz) and 6.5 (d, *J* 1 Hz).

2-(p-*Methoxycarbonylbenzylidene)penam* (6b) and (7b) (13%, *ca*. 5 : 2 ratio). The major *Z-isomer* (6b) had m.p. 82—84 °C (from ethyl acetate–light petroleum); $\nu_{max.}$ 1 760, 1 725, and 1 610 cm^{-1}; δ (80 MHz) 3.13 (1 H, dd, *J* 16, 1 Hz), 3.64 (1 H, ddd, *J* 16, 4, 1 Hz), 3.80 (1 H, d, *J* 15 Hz), 3.86 (3 H, s), 4.83 (1 H, dd, *J* 15, 1 Hz), 5.23 (1 H, dd, *J* 4, 1 Hz), 6.43 (1 H, d, *J* 1 Hz), 7.33 (2 H, d, *J* 8 Hz), and 7.94 (2 H, d, *J* 8 Hz) (Found: C, 61.3; H, 4.8; N, 4.9. $C_{14}H_{13}NO_3S$ requires C, 61.1; H, 4.8; N, 5.1%) (Found: M^+, 275.062 5. $C_{14}H_{13}NO_3S$ requires *M*, 275.061 6). The minor E-*isomer* (6b) showed signals at 5.13 (dd, *J* 4, 1 Hz) and 6.55 (d, *J* 1 Hz). Attempted hydrolysis of (6b) (0.25M methanolic NaOH, 20 °C, 10 min) resulted in destruction of the β-lactam ring (i.r.).

2-[p-(p-*Methoxybenzyloxycarbonyl)benzylidene*]*penam* (6c) and (7c) (40%, *ca*. 3 : 1 ratio). The major *Z-isomer* (6c), white needles, had m.p. 144—145 °C (from ethyl acetate–light petroleum); $\nu_{max.}$ 1 780 and 1 710 cm^{-1}; δ (80 MHz) 3.17 (1 H, dd, *J* 16, 2 Hz), 3.71 (1 H, ddd, *J* 16, 4, 1 Hz), 3.81 (3 H, s), 3.84 (1 H, dd, *J* 15, 2 Hz), 4.88 (1 H, dd, *J* 15, 1 Hz), 5.29 (s overlaying dd, *J* 4, 2 Hz) (together 3 H), 6.49 (1 H, br s), 6.90 (2 H, d, *J* 9 Hz), 7.38 (2 H, d, *J* 9 Hz), 7.41 (2 H, d, *J* 8 Hz), and 8.04 (2 H, d, *J* 8 Hz) (Found: C, 66.2; H, 5.2; N, 3.6; S, 8.3. $C_{21}H_{19}NO_4S$ requires C, 66.1; H, 5.0; N, 3.7; S, 8.4%). The minor E-*isomer* showed signals at δ 5.04 (dd, *J* 4, 2 Hz) and 6.57 (br s). Attempted demethoxybenzylation of (6c) [trifluoroacetic acid (TFA), toluene, 0 °C, 90 min] resulted in destruction of the β-lactam ring.

2-*Formylmethylenepenam* (6f).—*Method A*. 1-(4,4-Diethoxybut-2-ynyl)-4-(triphenylmethylthio)azetidin-2-one (3e) (910 mg) in acetone (15 ml) was treated at room temperature with trifluoroacetic acid (5 ml) for 1.5 h. The

* Consistent analytical figures for this compound were not obtained from the sample available.

product was isolated by diluting with ethyl acetate, washing with aqueous sodium hydrogencarbonate solution, and chromatography to give the aldehyde (3f) as a gum (270 mg, 35%); $\nu_{max.}$ 1 760 and 1 675 cm^{-1}; δ 2.8 (1 H, dd, *J* 14, 2 Hz), 3.1 (1 H, dd, *J* 14, 4 Hz), 3.65 and 4.17 (2 H, AB q, *J* 19 Hz), 4.44 (1 H, dd, *J* 4, 2 Hz), 7.1—7.5 (15 H, m), and 9.1 (1 H, s). Treatment of this product (100 mg) with methoxycarbonylmercury(II) acetate in the usual way gave the unstable mercuriothio-compound (4f) which was not isolated but, after evaporation and redissolving in methylene chloride, was treated with hydrogen sulphide. The filtered solution was evaporated and the residue was redissolved in DMF (20 ml) and stirred overnight with silica gel (0.4 g). The filtered reaction mixture was poured into ethyl acetate, washed with dilute aqueous citric acid, dried ($MgSO_4$), and evaporated. Chromatography afforded the *aldehyde* (6f) (6 mg, 15%), identical (t.l.c., i.r., n.m.r.) with the product of method B.

Method B. The acetal (3e) (1.64 g) in tetrahydrofuran–water (10 : 1) (80 ml) was treated with trifluoroacetic acid (80 ml) at room temperature for 2.5 h. The mixture was then diluted with water (600 ml) and neutralised with solid sodium hydrogencarbonate. Extraction with ethyl acetate and evaporation of the dried ($MgSO_4$) extract gave a residue which was chromatographed to yield 2-formylmethylenepenam (6f) (234 mg, 38%) as pale fawn needles, m.p. 120—122 °C (from benzene); $\nu_{max.}$ 3 000, 2 840, 2 750, 1 785, and 1 665 cm^{-1}; δ 3.16 (1 H, dd, *J* 17, 2 Hz), 3.69 (ddd, *J* 17, 4, 2 Hz) and 3.71 (dd, *J* 17, 2 Hz) (together 2 H), 4.89 (1 H, dd, *J* 17, 2 Hz), 5.18 (1 H, dd, *J* 4, 2 Hz), 6.32 (1 H, dd, *J* 3, 2 Hz), and 9.67 (1 H, d, *J* 3 Hz) (Found: C, 49.6; H, 4.3; N, 8.2. $C_7H_7NO_2S$ requires C, 49.7; H, 4.1; N, 8.3%) (Found: M^+ −CO, 141.024 6. C_6H_7NOS requires *m/e*, 141.024 5).

2-(2-*Hydroxyethylidene*)*penam* (6d).—To a solution of formylmethylenepenam (6f) (50 mg) in isopropyl alcohol–tetrahydrofuran (1 : 2) (5 ml) was added sodium borohydride (0.7 ml) (1%) in wet isopropyl alcohol until t.l.c. showed no aldehyde remaining. Chromatographic isolation of the product eluting with ethyl acetate–light petroleum (4 : 1) gave a colourless viscous *oil* (30 mg, 60%); $\nu_{max.}$ 3 600, 3 400 (br), 1 780, and 1 640(w) cm^{-1}; δ 2.21 (1 H, br s, exchangeable with D_2O), 3.04 (1 H, dd, *J* 15, 2, C-6-H *trans*), 3.55 (2 H, 2 overlapping dd, *J* 15, 4 Hz and *J* 15, 2 Hz, C-6-H *cis*, and C-3-H), 4.10 (2 H, d, *J* 6 Hz, CH_2O), 4.58 (1 H, d, *J* 15 Hz, C-3-H), 5.07 (1 H, dd, *J* 4, 2 Hz, C-5-H), and 5.58 (1 H, t, *J* 6 Hz, vinyl C-H) (Found: M^+, 171.034 7. $C_7H_9NO_2S$ requires *M*, 171.035 4).

Wittig Reactions of 2-*Formylmethylenepenam*.—The aldehyde (6f) (100 mg) was refluxed for 12 h in benzene (100 ml) with (methoxycarbonylmethylene)triphenylphosphorane (200 mg) to give a mixture of two products which were separated by chromatography, eluting with ethyl acetate–light petroleum (2 : 3). The *major* product, assigned the *trans* structure (6g) (105 mg, 79%), was obtained as white needles, m.p. 155—156 °C (from ethyl acetate–light petroleum); $\nu_{max.}$ 1 790 and 1 710 cm^{-1}; δ 3.1 (1 H, dd, *J* 15, 1 Hz), 3.6 (dd, *J* 15, 1 Hz), 3.62 (dd, *J* 15, 1 Hz), 3.67 (s) (three signals together 5 H), 4.68 (1 H, d, *J* 15 Hz), 5.17 (1 H, dd, *J* 4, 1 Hz), 5.74 (1 H, d, *J* 15 Hz, vinyl C-H *trans*), 6.04 (1 H, d, *J* 11 Hz), and 7.20 (1 H, dd, *J* 15, 11 Hz) (Found: C, 53.3; H, 5.0; N, 6.2; S, 14.1. $C_{10}H_{11}NO_3S$ requires C, 53.3; H, 4.9; N, 6.2; S, 14.2%). A slightly less polar chromatographic fraction yielded the cis-*isomer* (6h) (28 mg, 21%) as white needles, m.p. 120—123 °C (from ethyl acetate–light petroleum); $\nu_{max.}$ 1 780, 1 710, and 1 610 cm^{-1}; δ 3.12 (1 H, dd, *J* 15, 1 Hz), 3.57 (d, *J* 15 Hz), 3.67 (s), 3.67 (dd, *J* 15, 4 Hz) (total 5 H), 4.75 (1 H, d, *J* 15 Hz), 5.17 (1 H, dd, *J* 4, 1 Hz), 5.61 (1 H, d, *J* 11 Hz, vinyl C-H *cis*), 6.51 (1 H, t, *J* 11 Hz), and 7.25 (1 H, d, *J* 11 Hz) (Found: C, 53.6; H, 4.9; N, 6.2; S, 14.0. $C_{10}H_{11}NO_3S$ requires C, 53.3; H, 4.9; N, 6.2; S, 14.2%) (Found: M^+, 225.048 2. $C_{10}H_{11}NO_3S$ requires *M*, 225.045 9).

In a similar way, using (t-butoxycarbonylmethylene)triphenylphosphorane, was obtained only the trans-*t-butyl ester* (6i) (74%) as a colourless gum; $\nu_{max.}$ 1 785, 1 690, and 1 610 cm^{-1}; δ 1.50 (9 H, s), 3.14 (1 H, dd, *J* 17, 1 Hz), 4.10 (br d, *J* 17 Hz) and 4.16 (d, *J* 17 Hz) (together 2 H), 4.72 (1 H, d *J* 17 Hz), 5.20 (1 H, br s), 5.70 (1 H, d, *J* 16 Hz, vinyl C-H *trans*), 6.05 (1 H, d, *J* 11 Hz), and 7.15 (1 H, dd, *J* 16 Hz) (Found: M^+, 267.094 8. $C_{13}H_{17}NO_3S$ requires *M*, 267.092 9). Treatment with TFA caused loss of the β-lactam.

2-*Benzylidenepenam Sulphoxides and Sulphone*.—*Z*-2-Benzylidenepenam (6a) (200 mg) in dichloromethane (10 ml) was treated at 0 °C with *m*-chloroperbenzoic acid (190 mg, 1.2 equiv.) for 15 min. The solution was washed with aqueous sodium hydrogencarbonate solution, dried ($MgSO_4$), evaporated, and the residue chromatographed to give two fractions. The less polar fraction, a white solid, was the β-sulphoxide (8a; $n = 1$) (β-isomer) (30 mg, 14%); $\nu_{max.}$ 1 785 and 1 010 cm^{-1}; δ 3.36 (2 H, br s), 3.75 (1 H, dd, *J* 17, 1 Hz), 4.56 (1 H, m), 4.85 (1 H, dd, *J* 17, 2 Hz), and 7.0—7.6 (m, 6 H) (Found: M^+, 233.052 9. $C_{12}H_{11}NO_2S$ requires *M*, 233.050 9). The more polar fraction was the α-sulphoxide (8a; $n = 1$) (α-isomer), a white solid (70 mg, 35%); $\nu_{max.}$ 1 790 and 1 010 cm^{-1}; δ 3.07 (1 H, dd, *J* 16, 3 Hz), 3.64 (1 H, dd, *J* 16, 5 Hz), 4.14 and 4.68 (AB q, *J* 14 Hz), 4.76 (m) (together 3 H), and 7.1—7.7 (6 H, m) (Found: M^+, 233.051 3. $C_{12}H_{11}NO_2S$ requires *M*, 233.050 9).

When the reaction was carried out at room temperature overnight using 2.4 equiv. of *m*-chloroperbenzoic acid the *product*, isolated as above, was the sulphone (8a; $n = 2$) (60%) as a white amorphous solid; $\nu_{max.}$ 1 790, 1 320, and 1 130 cm^{-1}; δ 3.48 (2 H, d, *J* 3 Hz), 4.0 (1 H, dd, *J* 16, 2 Hz), 4.46 (1 H, t, *J* 3 Hz), 4.78 (1 H, dd, *J* 16, 2 Hz), 7.01 (1 H, t, *J* 2 Hz), and 7.2—7.7 (5 H, m) (Found: M^+, 249.046 2. $C_{12}H_{11}NO_3S$ requires *M*, 249.041 4).

2-[p-(p-*Methoxybenzyloxycarbonyl*)*benzylidene*]*penam Sulphoxides and Sulphone*.—Oxidation of the substituted benzylidenepenam (6c) by the above methods gave the following products: (8c; $n = 1$) (α-sulphoxide), m.p. 158—160 °C (from ethyl acetate–light petroleum); $\lambda_{max.}$ (EtOH) 274 nm (ε 25 200); $\nu_{max.}$ 1 790, 1 710, and 1 610 cm^{-1}; δ 3.14 (1 H, dd, *J* 16, 2 Hz), 3.70 (1 H, dd, *J* 16, 4 Hz), 3.8 (3 H, s), 4.18 (1 H, d, with fine coupling, *J* 14 Hz), 4.75 (1 H, d, with fine coupling, *J* 14 Hz), 4.82 (1 H, dd, *J* 4, 2 Hz), 6.89 (2 H, d, *J* 8 Hz), 7.29 (1 H, br s), 7.37 (2 H, d, *J* 8 Hz), 7.70 (2 H, d, *J* 8 Hz), and 8.12 (2 H, d, *J* 8 Hz) (Found: M^+, 397.098 5. $C_{21}H_{19}NO_5S$ requires *M*, 397.098 2): (8c; $n = 1$) (β-sulphoxide), m.p. 145 °C (from ethyl acetate–light petroleum); $\lambda_{max.}$ (EtOH) 272 nm (ε 26 600); $\nu_{max.}$ 1 780, 1 710, and 1 610 cm^{-1}; δ 3.42 (2 H, distorted d, *J* 2 Hz), 3.80 (3 H, s), 3.83 (1 H, d with fine coupling, *J* 14 Hz), 4.66 (1 H, distorted t, *J* 2 Hz), 4.91 (1 H, dd, *J* 14, 2 Hz), 5.30 (2 H, s), 6.88 (2 H, d, *J* 8 Hz), 7.15 (1 H, br s), 7.37 (2 H, d, *J* 8 Hz), 7.71 (2 H, d, *J* 8 Hz), and 8.09 (2 H, d, *J* 8 Hz) (Found: M^+, 397.098 7. $C_{21}H_{19}NO_5S$ requires *M*, 397.098 2): (8c; $n = 2$) (*sulphone*), needles, m.p. 137—138 °C (from ethyl acetate–light petroleum);

$\nu_{max.}$ 1 790, 1 710, and 1 610 cm^{-1}; δ 3.51 (2 H, d, *J* 3 Hz), 3.82 (3 H, s), 4.02 (1 H, dd, *J* 15, 2 Hz), 4.45 (1 H, t, *J* 3 Hz), 4.80 (1 H, dd, *J* 15, 3 Hz), 5.28 (2 H, s), 6.88 (2 H, d, *J* 8 Hz), 7.00 (1 H, br s), 7.34 (2 H, d, *J* 8 Hz), 7.60 (2 H, d, *J* 8 Hz), and 8.08 (2 H, d, *J* 8 Hz) (Found: M^+, 413.093 6. $C_{21}H_{19}NO_6S$ requires *M*, 413.093 2).

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