# Syntheses based on 1,2-Secopenicillins. Part 5.[1] Penicillin Analogues with Electron-withdrawing 2-Substituents

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6-Acylaminopenam-3-carboxylic esters substituted at C-2 by one or two alkoxycarbonyl groups or by an acetyl group have been prepared from penicillins. The azetidinone ring remained intact throughout the reaction sequence, and the thiazolidine ring was completed by intramolecular alkylation at an activated methylene or methine group adjacent to the sulphur atom. Only in the case of the 2-alkoxycarbonylpenams could stable carboxylic acids be liberated from the esters.

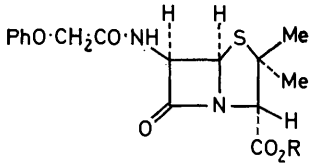
ONLY a few analogues of penicillins in which the methyl groups at C-2 are replaced by other substituents have been reported. Total synthesis has been used to prepare analogues of penicillin V (1) in which either [2] or both [3] of the methyl groups are replaced by hydrogen or in which both methyl groups are replaced by ethyl,[4] these changes having a slightly adverse effect on antibacterial activity. Other investigators have started from penicillin G (7) and modified one or both methyl groups while keeping the penam nucleus intact. Some antibacterial activity is retained when an acetoxy-substituent is introduced into either methyl group,[5] but compounds containing more than one acetoxy-group appear to have been obtained only as the methyl esters.[6] Bromomethyl and chloromethyl analogues of penicillin have likewise only been obtained as esters,[7,8] which in solution undergo spontaneous ring expansion to cephams by way of episulphonium intermediates.[7] Ring contraction of a cephalosporin has been used [9] to prepare the 2-ethoxycarbonyl penam (10). This compound lacks antibacterial activity,[9] but this may be due to the isopropenyl substituent at C-3 rather than to the unusual ethoxycarbonyl substituent at C-2.

We attempted to prepare penams which resembled compound (10) in carrying a strongly electron-withdrawing substituent at C-2, but differed from it in having only the normal carboxy-substituent at C-3. Suitable intermediates for this purpose appeared to be 1,2-secopenicillanates [*e.g.* (11)], which are readily derived [10] from 6-aminopenicillanic acid (8).

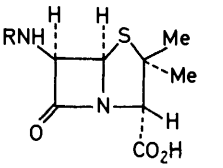
The secopenicillanate (11) was accordingly oxidised with potassium permanganate [11] to give the simple azetidinone (12). Condensation with t-butyl glyoxylate according to the general procedure of Scartazzini and his co-workers [12] gave the α-hydroxy-ester (13) as a mixture of epimers, and this with thionyl chloride [12] gave the mixed α-chloro-esters (14). We had hoped that the methylene group in (14) would be sufficiently reactive to permit intramolecular alkylation, but in the event

[1] Part 4, M. J. Pearson, *J.C.S. Perkin I*, 1977, 189.
[2] P. J. Claes, J. Hoogmartens, G. Janssen, and H. Vanderhaeghe, *European J. Medicin. Chem.*, 1975, **10**, 373.
[3] J. Hoogmartens, P. J. Claes, and H. Vanderhaeghe, *J. Medicin. Chem.*, 1974, **17**, 389.
[4] P. J. Claes and H. Vanderhaeghe, *European J. Medicin. Chem.*, 1976, **11**, 359.
[5] D. H. R. Barton, F. Comer, D. G. T. Greig, P. G. Sammes, C. M. Cooper, G. Hewitt, and W. G. E. Underwood, *J. Chem. Soc.* (*C*), 1971, 3540.
[6] D. O. Spry, *J.C.S. Chem. Comm.*, 1973, 259.
[7] T. Kamiya, T. Teraji, Y. Saito, M. Hashimoto, O. Nakaguchi, and T. Oku, *Tetrahedron Letters*, 1973, 3001.
[8] H. Tanida, T. Tsuji, T. Tsushima, H. Ishitobi, T. Irie, T. Yano, H. Mastsumura, and K. Tori, *Tetrahedron Letters*, 1975, 3303.
[9] M. Yoshimoto, S. Ishihara, E. Nakagama, and N. Soma, *Tetrahedron Letters*, 1972, 2923.
[10] E. G. Brain, I. McMillan, J. H. C. Nayler, R. Southgate, and P. Tolliday, *J.C.S. Perkin I*, 1975, 562.
[11] E. G. Brain, A. J. Eglington, J. H. C. Nayler, M. J. Pearson, and R. Southgate, *J.C.S. Perkin I*, 1976, 447.
[12] R. Scartazzini, H. Peter, H. Bickel, K. Heusler, and R. B. Woodward, *Helv. Chim. Acta*, 1972, **55**, 408; R. Scartazzini and H. Bickel, *ibid.*, p. 423.

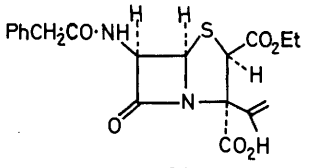
treatment with various bases failed to give a penam. The methylene group was therefore further activated by oxidising the sulphide (14) with *m*-chloroperbenzoic acid to give the sulphoxide (15). Treatment of the latter with potassium t-butoxide at −20 °C then gave two



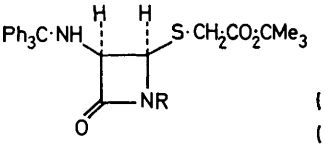
(1) R = H
(2) R = $CH_2CCl_3$
(3) R = $CH_2CH_2SMe$
(4) R = $CH_2CH_2\overset{+}{S}Me_2$ $I^-$
(5) R = $CH_2C_6H_4NO_2$ (*p*)
(6) R = $CH_2Ph$



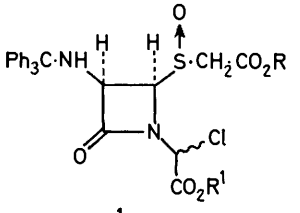
(7) R = $PhCH_2CO$
(8) R = H
(9) R = (D)PhCH($NH_2$)CO



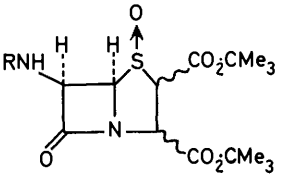
(10)



(11) R = $C(:CMe_2)\cdot CO_2CH_2Ph$
(12) R = H
(13) R = $CHOH\cdot CO_2CMe_3$
(14) R = $CHCl\cdot CO_2CMe_3$



(15) R = $R^1$ = $CMe_3$
(16) R = Me, $R^1$ = $CH_2C_6H_4NO_2$ (*p*)

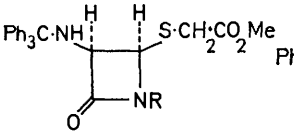


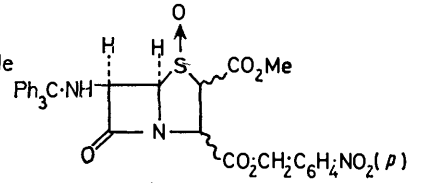
(17) R = $Ph_3C$
(18) R = $PhO\cdot CH_2CO$

separable isomeric penam *S*-oxides (17). Detritylation and acylation afforded two isomeric amides (18), but attempts to remove the t-butyl groups with trifluoroacetic acid resulted in destruction of the β-lactam.

It then occurred to us that the desired free carboxy-group at C-3 might be more readily generated from a *p*-nitrobenzyl ester, and a methoxycarbonyl group at C-2 might be more conducive to antibacterial activity than the bulky t-butoxycarbonyl group. We accordingly prepared the azetidinone (20) by way of the secopenicillanate (19), and treated it with *p*-nitrobenzyl glyoxylate to give the mixed epimers of the α-hydroxy-ester(21). Reaction with thionyl chloride then gave the mixed chlorides (22), which on oxidation afforded the mixed sulphoxides (16). Cyclisation with potassium t-butoxide gave the penam *S*-oxide (23) as a mixture of isomers, but subsequent reduction with phosphorus tribromide gave the sulphide apparently as the single isomer (24) (the spectroscopic evidence for this assignment will be discussed later). Detritylation with toluene-*p*-sulphonic acid gave the primary amine (25), which on acylation afforded the amides (26) and (27). Catalytic hydrogenation then gave the penicillin V analogue (28) and the ampicillin analogue (29), which showed antibacterial activity (Table 1) but were less active than penicillin V (1) or ampicillin (9).

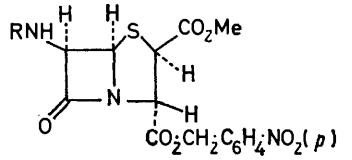
We also prepared penams with two identical alkoxycarbonyl groups at C-2, but this required a different approach since 1,2-secopenicillanates cannot normally be prepared from 6β-(triphenylmethylamino)penicillanates and secondary alkyl halides. Fortunately a



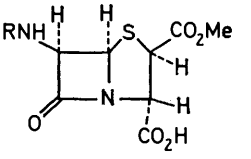


(19) R = $C(:CMe_2)\cdot CO_2CH_2Ph$
(20) R = H
(21) R = $CHOH\cdot CO_2CH_2C_6H_4NO_2$ (*p*)
(22) R = $CHCl\cdot CO_2CH_2C_6H_4NO_2$ (*p*)

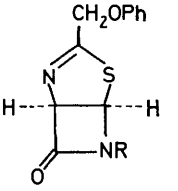
(23)



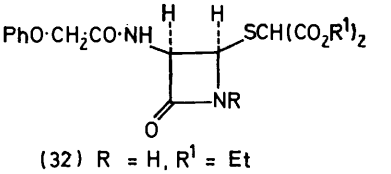
(24) R = $Ph_3C$
(25) R = H
(26) R = $PhO\cdot CH_2CO$
(27) R = (D)PhCH(NH·$CO_2CH_2C_6H_4NO_2$ (*p*))·CO



(28) R = $PhO\cdot CH_2CO$
(29) R = (D)PhCH($NH_2$)·CO



(30) R = $C(:CMe_2)\cdot CO_2CH_2CCl_3$
(31) R = H



(32) R = H, $R^1$ = Et
(33) R = $CHOH\cdot CO_2CMe_3$, $R^1$ = Et
(34) R = $CHCl\cdot CO_2CMe_3$, $R^1$ = Et
(35) R = H, $R^1$ = Me

suitable alternative route was available from the fused thiazoline–azetidinone (31), which is readily accessible from penicillin V trichloroethyl ester (2) in two steps [11,13] *via* the intermediate (30). Barton and his co-workers [14] showed that when an analogue of (31) derived from penicillin G was treated with certain alkyl halides in

[13] R. D. G. Cooper and F. L. José, *J. Amer. Chem. Soc.*, 1970, **92**, 2575.

[14] D. H. R. Barton, P. G. Sammes, G. Hewitt, B. E. Looker, and W. G. E. Underwood, B. Pat. 1368234/1974.

aqueous dimethylformamide containing urea and an antioxidant at 50 °C, *S*-alkylation occurred with hydrolytic opening of the thiazoline ring. By applying this procedure to diethyl bromomalonate and the thiazoline

C-3 epimers. In an attempt to prepare the free acid (37) the t-butyl ester (36) was treated with trifluoroacetic acid at room temperature, but rupture of the β-lactam ring was complete within 3 min.

TABLE 1

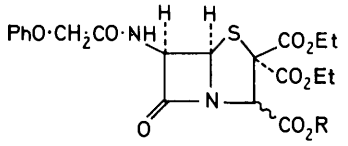
Antibacterial activity * of penams

| Bacterium | Penicillins (1) | (4) | (5) | (9) | New penams (28) | (29) | (43) | (53) |
|---|---|---|---|---|---|---|---|---|
| β-Haemolytic streptococcus | 0.012 | 0.02 | 0.5 | 0.06 | 5 | 4 | 500 | 62 |
| *Staphylococcus aureus* Oxford | 0.05 | 0.05 | 0.5 | 0.1 | 12.5 | 8 | >500 | 125 |
| *Staphylococcus aureus* Russell † | >500 | >500 | 250 | >250 | >500 | >250 | >500 | >250 |
| *Escherichia coli* | 125 | 500 | 500 | 5 | >500 | >250 | >500 | >250 |
| *Salmonella typhi* | 125 | 500 | 500 | 0.6 | >500 | >250 | >500 | >250 |

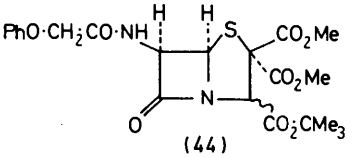
* The figures are the minimum inhibitory concentrations (μg ml$^{-1}$) required to inhibit bacterial growth after incubation on nutrient agar for 18 h. † Penicillinase-producing strain.

(31) we readily obtained the azetidinone (32), which on successive treatment with t-butyl glyoxylate and thionyl chloride gave the α-hydroxy-ester (33) and the α-chloro-ester (34), each as a mixture of epimers.

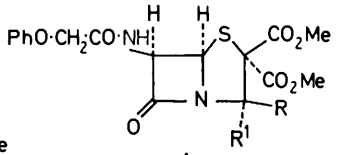
In this series conversion into a sulphoxide was not



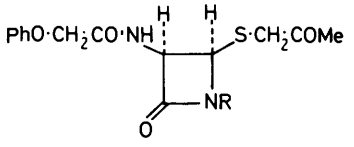
(36) R = $CMe_3$
(37) R = H
(38) R = $CH_2Ph$
(39) R = $CH_2C_6H_4NO_2(p)$
(40) R = $CH_2CCl_3$
(41) R = Me
(42) R = $CH_2CH_2SMe$
(43) R = $CH_2CH_2\overset{+}{S}Me_2$ $I^-$



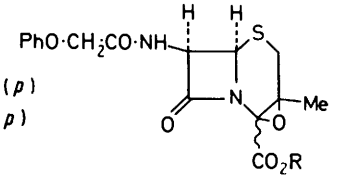
(44)



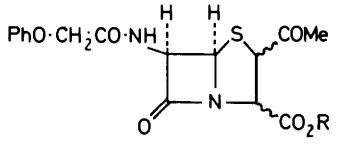
(45) R = H, $R^1$ = $CO_2CH_2CCl_3$
(46) R = $CO_2CH_2CCl_3$, $R^1$ = H



(47) R = H
(48) R = $CHCl\cdot CO_2CH_2CCl_3$
(49) R = $CHOH\cdot CO_2CH_2C_6H_4NO_2(p)$
(50) R = $CHCl\cdot CO_2CH_2C_6H_4NO_2(p)$



(51) R = $CH_2CCl_3$
(52) R = $CH_2C_6H_4NO_2(p)$



(53) R = $CH_2C_6H_4NO_2(p)$
(54) R = H

required since the malonate (34) underwent intramolecular alkylation when treated with potassium t-butoxide at −20 °C, the resulting penam (36) being a mixture of

Various other esters of the desired acid (37), all as mixtures of epimers, were then made from the azetidinone (32) and the appropriate glyoxylate in the hope of finding one from which the group R could be removed without disrupting the evidently very sensitive 2,2-bis(ethoxycarbonyl)penam nucleus. The benzyl (38) and *p*-nitrobenzyl (39) esters were readily prepared but hydrogenation failed to give the desired acid (37). The 2,2,2-trichloroethyl ester (40) was treated with zinc powder and aqueous 90% acetic acid at 0 °C, conditions which permitted the recovery of penicillin V (1) from its ester (2) in 75% yield, but the resulting crude acid proved devoid of antibacterial activity. Moreover it appeared to be a mixture, and esterification with diazomethane gave a further mixture of which no component corresponded (by chromatography) to a reference sample of the penam (41) prepared by the usual reaction sequence from the azetidinone (32) and methyl glyoxylate.

Finally the β-methylthioethyl ester (42) was prepared and treated with methyl iodide to give the crude sulphonium salt (43), but when this was treated in dry acetone at 0 °C with 1 equiv. of potassium t-butoxide for 5 min the β-lactam was lost. The corresponding penicillin V ester (4) afforded penicillin V potassium salt in 82% yield under the same conditions. Moreover, the ester (4) was so readily hydrolysed that, under normal conditions of antibacterial testing, it appeared to be almost as active as free penicillin V (1) (see Table 1). By contrast, the analogue (43) was devoid of antibacterial activity. Hence, although the acid (37) was not obtained, it seems reasonable to conclude that it is either antibacterially inactive or, more likely, so unstable as to be incapable of more than transitory existence.

Dimethyl bromomalonate was used to prepare the azetidinone (35), which on successive treatment with t-butyl glyoxylate, thionyl chloride, and potassium t-butoxide gave the 2,2-bis(methoxycarbonyl)penam (44). This was again a mixture of epimers, but its n.m.r. spectrum was simpler than that of the diethyl analogue (36) and permitted the conclusion that both epimers were present in approximately equal amounts. Finally the trichloroethyl ester was similarly prepared, and in this case it proved possible to separate the epimers [(45) and

(46)] by chromatography. The assignment of stereochemistry at C-3 will be discussed later.

Lastly we attempted the preparation of 2-acetylpenams. Reaction of the thiazoline–azetidinone (31) with bromoacetone gave the 4-(acetonylthio)azetidinone (47). Condensation with trichloroethyl glyoxylate, followed by reaction with thionyl chloride, then gave the mixed epimers of the α-chloro-ester (48). Treatment of this compound with potassium t-butoxide gave a complex mixture from which the only product isolated in pure form was not a penam but the 3,4-epoxycepham (51), clearly derived from the chloro-ketone (48) by an intramolecular Darzens reaction.

More success was achieved when the azetidinone (47) was condensed with *p*-nitrobenzyl glyoxylate, both epimers of the α-hydroxy-ester (49) being separated. The chloride (50) was prepared from the mixed epimers, and this time cyclisation with potassium t-butoxide gave both the epoxycepham (52) and a mixture of isomers of the penam (53). One isomer of the latter was separated in pure form by chromatography, but the substantial losses incurred suggested that these penams tended to decompose on silica gel. The products of the hydrogenolysis of (53) proved to be even more unstable, and no free acid (54) was isolated. Therefore, the *p*-nitrobenzyl ester (53) was itself subjected to antibacterial testing. It showed slight activity against Gram-positive bacteria (Table 1), but less than that of the corresponding ester (5) of penicillin V.

*Stereochemistry at* C-3 *and* C-2.—In penicillins [*e.g.* (1)] having the C-3 and C-5 protons *trans*, the chemical shift of the C-3 proton is in the range δ 4.3—4.9.[15] When H-3 and H-5 are *cis* as in 5-*epi*-penicillins, this shift is 3.7—4.0.[16] Corresponding differences in chemical shifts have been noted in simple 4-carboxythiazolidines [17] and in the stereoisomers of synthetic 7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylates.[18] The chemical shift of the C-3 proton in penams is therefore considered to be indicative of the relative stereochemistry at C-3 and C-5. If both C-3 epimers are available that in which the C-3 proton signal appears at lower field should have the same relative stereochemistry as penicillins. On this basis the 3*S*-configuration is assigned to the ester (45) and the 3*R*-configuration to its epimer (46) (Table 2). In those 2,2-bisalkoxycarbonyl penams which were obtained only as mixtures of C-3 epimers the resonances of each C-3 proton could usually be distinguished in the spectrum of the mixture [*e.g.* (36), (41), and (44)], the signal for the 3*R*-epimer occurring at δ 4.40—4.57 and that for the 3*S*-epimer at δ 5.20—5.37. The downfield shift of the C-3 proton signal as compared with penicillins is attributed to shielding by the 2-alkoxycarbonyl substituents.

TABLE 2

$^1$H N.m.r. data * for penams

| Structure and stereochemistry | $\delta_{3-H}$ in normal spectrum | Shift (p.p.m.) and shift ratio (relative to 6-H) induced by 0.9 mol. equiv. Eu([$^2H_9$]fod)$_3$ | | | | | |
|---|---|---|---|---|---|---|---|
| | | $OCH_2CO$ | NH | 6-H | 5-H | 3-H | $CO_2CH_2R$ |
| (6) | 4.47 | 5.57 | 4.79 | 6.79 | 1.50 | 1.44 | 0.24 |
| 3*S*,5*R*,6*R* | | 0.82 | 0.71 | 1.00 | 0.22 | 0.21 | 0.04 |
| (45) | 5.37 | 7.28 | 5.74 | 8.46 | 1.54 | 1.24 | 0.14 |
| 3*S*,5*R*,6*R* | | 0.86 | 0.68 | 1.00 | 0.18 | 0.15 | 0.02 |
| (46) | 4.57 | 6.05 | 4.66 | 7.26 | 1.31 | 0.68 | 0.43 and 0.47 |
| 3*R*,5*R*,6*R* | | 0.83 | 0.64 | 1.00 | 0.18 | 0.09 | (ABq) |
| (26) | 5.33 | 7.43 | *ca.* 6 | 9.10 | 1.40 | 1.40 | 0.15 |
| 2*R*,3*S*,5*R*,6*R* | | 0.82 | 0.66 | 1.00 | 0.15 | 0.15 | 0.02 |

* Solvent $CDCl_3$; $Me_4Si$ as internal standard; Perkin-Elmer R32 spectrometer.

In the series with only one methoxycarbonyl group at C-2 only a single epimer was available after reduction of the sulphoxide (23). Since the C-3 proton in the ester (26) shows practically the same chemical shift as that in the ester (45), it too was assigned the 3*S*-configuration. Support for the view that ester (26) has the same stereochemistry as penicillins is provided by the finding that the derived acids (28) and (29) possess appreciable antibacterial activity against streptococci and a penicillin-sensitive staphylococcus but are inactive against a penicillinase-producing penicillin-resistant staphylococcus (Table 1).

Further evidence for these assignments was obtained from a comparison of the lanthanoid-induced shifts in the n.m.r. spectra of penicillin V benzyl ester (6) and the new penams (45), (46), and (26). All four compounds show similar dominant shifts (Table 2), which is indicative of the same substrate–complex geometry. The three compounds (6), (45), and (26) assigned the 3*S*-configuration show lanthanoid-induced downfield shifts in the range 1.24—1.44 p.p.m. for the C-3 proton and 0.14—0.24 p.p.m. for the C-3 ester methylene group. Such figures are typical of penicillin esters.[19] By contrast, in the 3*R*-epimer (46) the downfield shift of the C-3 proton signal is reduced to 0.68 p.p.m. and that of the ester methylene group increased (0.43 and 0.47 p.p.m.; AB quartet).

The C-2 configuration of the ester (26) was then deduced from the normal n.m.r. spectrum. The di-

[15] P. V. Demarco and R. Nagarajan, 'Cephalosporins and Penicillins,' ed. E. H. Flynn, Academic Press, New York and London, 1972, p. 340.

[16] R. Busson and H. Vanderhaeghe, *J. Org. Chem.*, 1976, **41**, 2561.

[17] I. McMillan and R. J. Stoodley, *Chem. Comm.*, 1968, 11.

[18] A. G. Brown, D. F. Corbett, and T. T. Howarth, *J.C.S. Chem. Comm.*, 1977, 359; R. G. Alexander and R. Southgate, *ibid.*, p. 405.

[19] R. G. Alexander, personal communication.

hedral angle between the C-2 and C-3 protons was considered to be *ca.* 90° since only slight coupling was observed between the signals. Molecular models indicate that only one conformation of the thiazolidine ring with the ester groups *trans* results in this arrangement, thus pointing to the 2*R*,3*S*-configuration (26). This assignment is supported by the observed chemical shift for the C-2 proton, which is virtually identical with that in the penam (10).[9]

## EXPERIMENTAL

General procedures were as in Part 1 [11] except where indicated otherwise.

*Esters of Penicillin V.*—Penicillin V potassium salt (3.88 g) and 2-methylthioethyl chloride (1.22 g) were stirred in dimethylformamide (20 ml) at 50 °C for 48 h. The mixture was cooled, diluted with ethyl acetate (100 ml), and washed with water (3 × 20 ml). The dried ($MgSO_4$) organic layer was evaporated to give a crude gum (2.74 g). Chromatography gave *2-methylthioethyl 6β-phenoxyacetamidopenicillanate* (3) (2.20 g) as a gum, $\nu_{max.}$ 1 790, 1 750, and 1 690 $cm^{-1}$; δ 1.48 (s) and 1.56 (s) (6 H, $CMe_2$), 2.09 (3 H, s, $SCH_3$), 2.69 (2 H, t, *J* 6 Hz, $CO_2{\cdot}CH_2{\cdot}CH_2{\cdot}SCH_3$), 4.20 (2 H, t, *J* 6 Hz, $CO_2{\cdot}CH_2{\cdot}CH_2{\cdot}SCH_3$), 4.34 (1 H, s, 3-H), 4.40 (2 H, s, $PhOCH_2$), 5.55—5.90 (2 H, m, 5- and 6-H), and 6.8—7.6 (6 H, m, aromatic + NH) (Found: $M^+$, 424.112 1. $C_{19}H_{24}N_2O_5S_2$ requires *M*, 424.112 7). A portion (1.40 g) was dissolved in methyl iodide (5 ml) and kept at room temperature for 3 days. The crystalline solid was filtered off, washed with ether, and dried to give the sulphonium iodide (4) (750 mg), m.p. 106—108°, $\nu_{max.}$ 3 380, 1 790, 1 755, and 1 690 $cm^{-1}$.

*De-esterification of Penicillin V Esters.*—(*a*) 2,2,2-Trichloroethyl 6β-phenoxyacetamidopenicillanate (2) [20] (500 mg) was dissolved in acetic acid (5 ml) and water (0.5 ml), cooled in an ice-bath, and treated with zinc powder (500 mg; previously washed with dilute hydrochloric acid, water, methanol, and ether). After stirring in the ice-bath for 30 min, the mixture was filtered and the residual zinc washed with a little aqueous acetic acid. The combined filtrates were evaporated and the residue was re-evaporated with dry toluene (2 ml). The resulting gum was stirred with a mixture of ethyl acetate (10 ml) and water (10 ml) and cooled in an ice-bath, and the pH was adjusted to 3 with N-hydrochloric acid. The organic layer was separated and the aqueous layer was re-extracted with ethyl acetate (10 ml). The combined organic layers were washed with water (4 × 5 ml), dried ($MgSO_4$), and evaporated to give penicillin V free acid (1) (273 mg) as an amorphous solid having spectral data identical with those of an authentic specimen.

(*b*) The sulphonium iodide (4) (57 mg) was dissolved in dry acetone (2 ml), cooled to 0 °C, and treated with potassium t-butoxide (0.11 ml of a 0.944M-solution in t-butyl alcohol) added dropwise in 1 min with stirring. After stirring at 0 °C for 5 min the mixture was filtered and the product washed with dry acetone and dried under vacuum to give penicillin V potassium salt as an amorphous solid (32 mg). The spectral data were in agreement with those of an authentic sample.

*p-Nitrobenzyl Glyoxylate Monohydrate.*—Bis-*p*-nitrobenzyl tartrate (51.2 g) and lead tetra-acetate (61.0 g) were refluxed in dry benzene (500 ml) for 2 h. The mixture was cooled and filtered, and the filtrate was evaporated to give a gum which on trituration with water afforded *p*-nitrobenzyl glyoxylate monohydrate (39.1 g) as a white solid, m.p. 80—88°, $\nu_{max.}$ (Nujol) 3 400br, 1 740, 1 530, and 1 350 $cm^{-1}$; δ [$(CD_3)_2SO$] 3.33 (1 H, s, exch. $D_2O$), 5.10 (1 H, d, *J* 8 Hz, collapsing to a s with $D_2O$), 5.33 (2 H, s), 6.83 (1 H, d, *J* 8 Hz, exch. $D_2O$), 7.68 (2 H, d, *J* 9 Hz), and 8.28 (2 H, d, *J* 9 Hz).

*2-Methylthioethyl Glyoxylate Monohydrate.*—This was prepared using the general method of Jurczak and Zamojski.[21] 2-Methylthioethanol (18.4 g) and redistilled 2,6-dimethylpyridine (23.5 g) were dissolved in dry ether (200 ml), cooled to −10 °C, and treated dropwise in 1 h with a solution of bromoacetyl bromide (44.4 g) in dry ether (100 ml). The mixture was stirred at −10 °C for a further 1 h and filtered, and the filtrate was washed with dilute sodium hydrogen carbonate solution and water. The dried ($MgSO_4$) organic layer was evaporated to give crude 2-methylthioethyl bromoacetate as an oil (45.0 g), $\nu_{max.}$ (film) 1 740 $cm^{-1}$. The unstable crude ester (42.6 g) was immediately dissolved in acetonitrile (100 ml) and treated with a solution of silver nitrate (68.0 g) in acetonitrile (100 ml). The mixture was kept in the dark at room temperature for 18 h, then silver bromide was filtered off and washed with a little ethyl acetate. The combined filtrates were evaporated and the residue was shaken with ethyl acetate (200 ml) and water (100 ml). The organic layer was separated and the aqueous layer was re-extracted with ethyl acetate (50 ml). The combined organic layers were washed with water (3 × 50 ml), dried ($MgSO_4$), and evaporated to give crude 2-methylthioethoxycarbonylmethyl nitrate as an oil (8.4 g), $\nu_{max.}$ (film) 1 760, 1 660, and 1 290 $cm^{-1}$; δ 2.19 (3 H, s), 2.82 (2 H, t, *J* 7 Hz), 4.48 (2 H, t, *J* 7 Hz), and 5.08 (2 H, s).

Sodium acetate trihydrate (5.8 g) was added in portions during 15 min to a stirred solution of the crude nitrate ester (8.4 g) in dimethyl sulphoxide (50 ml). Stirring was continued until dissolution of the sodium acetate was complete (*ca.* 30 min). The mixture was poured into brine (500 ml) and extracted with ethyl acetate (4 × 100 ml). The combined organic layers were washed with sodium hydrogen carbonate solution and brine, dried ($MgSO_4$), and evaporated to give crude 2-methylthioethyl glyoxylate monohydrate as an oil (3.3 g), $\nu_{max.}$ (film) 3 400br and 1 750 $cm^{-1}$.

(3R,4R)-1-[*Hydroxy-(t-butoxycarbonyl)-methyl*]-4-(*t-butoxycarbonylmethylthio*)-3-(*triphenylmethylamino*)*azetidin-2-one* (13).—t-Butyl glyoxylate monohydrate (3.1 g) was refluxed in benzene (30 ml) for 0.5 h with provision for the removal of water. (3*R*,4*R*)-4-(t-Butoxycarbonylmethylthio)-3-triphenylmethylaminoazetidin-2-one (12) [11] (1.1 g) was added and refluxing continued for 10 h. The benzene solution was washed with water (×6), dried, and evaporated. The residual gum (2.0 g) was chromatographed to give the α-hydroxy-ester (13) (0.85 g) as a foam, $\nu_{max.}$ 3 450, 1 770, and 1 725br $cm^{-1}$; the n.m.r. spectrum (after $D_2O$ exchange) showed singlets at δ 5.18 and 5.24 for CH·OH of the two epimers.

(3R,4R)-1-[*Chloro-(t-butoxycarbonyl)methyl*]-4-(*t-butoxycarbonylmethylthio*)-3-(*triphenylmethylamino*)*azetidin-2-one* (14).—A solution of the α-hydroxy-ester (13) (0.55 g) in tetrahydrofuran–dioxan (1 : 1; 12 ml) was cooled to −10 °C and treated with 2,6-lutidine (0.31 g) followed dropwise by

[20] R. R. Chauvette, P. A. Pennington, C. W. Ryan, R. D. G. Cooper, F. L. José, I. G. Wright, E. M. Van Heyningen, and G. W. Huffman, *J. Org. Chem.*, 1971, **36**, 1259.

[21] J. Jurczak and A. Zamojski, *Roczniki Chem.*, 1970, **44**, 2275.

thionyl chloride (0.336 g) in dioxan (2 ml) over about 1 min. After 0.5 h at −10 °C the mixture was filtered and the filtrate evaporated to dryness. The residual gum was extracted with toluene (4 × 10 ml) and the extracts evaporated to give the α-chloro-ester (14) as an amorphous solid (0.536 g), $\nu_{max.}$ 1 780, 1 740, and 1 720 $cm^{-1}$; δ 5.86 (s) and 5.90 (s) for CHCl of the two epimers.

(3R,4R)-1-[*Chloro*-(*t-butoxycarbonyl*)*methyl*]-4-(*t-butoxycarbonylmethylsulphinyl*)-3-(*triphenylmethylamino*)*azetidin*-2-*one* (15).—The α-chloro-ester (14) (0.536 g) in chloroform (10 ml) was cooled (ice-bath) and treated with *m*-chloroperbenzoic acid (0.168 g) in chloroform added dropwise over a few min. After 0.5 h the solution was evaporated to dryness, and the residue was dissolved in ethyl acetate and washed with sodium hydrogen carbonate solution and then water. The dried organic layer was evaporated to give the sulphoxide (15) as a foam (0.54 g), $\nu_{max.}$ 1 790, 1 740, and 1 720 $cm^{-1}$; the n.m.r. spectrum showed that the product was a mixture of isomers, the CHCl signals appearing as sharp singlets between δ 6.00 and 6.07.

*t-Butyl* (5R,6R)-2-*t-Butoxycarbonyl*-6-(*triphenylmethylamino*)*penam*-3-*carboxylate* 1-*Oxide* (17).—The sulphoxide (15) (0.406 g) in dry tetrahydrofuran (5 ml) was cooled (−20 °C), potassium t-butoxide (0.53 ml of a 1.23M-solution in t-butyl alcohol) was added, and the mixture was left at −20 °C for 2 h, then diluted with ethyl acetate, and washed with water. The dried organic layer was evaporated and the residue chromatographed. Two separable isomers of the penam (17) were obtained: *major isomer* (94 mg), m.p. 164—165°, $\nu_{max.}$ 3 290, 1 790, and 1 730 $cm^{-1}$, δ 1.40 (9 H, s, $Bu^t$), 1.56 (9 H, s, $Bu^t$), 3.33—4.83 (5 H, m, 2-H, 3-H, 5-H, 6-H, and NH not readily exchangeable), and 7.0—7.8 (15 H, ArH) (Found: C, 67.9; H, 6.3; N, 4.1%; $M^+$, 602. $C_{34}H_{38}N_2O_6S$ requires C, 67.8; H, 6.4; N, 4.6%; *M*, 602); *minor isomer* (64 mg), $\nu_{max.}$ 3 290, 1 790, and 1 730 $cm^{-1}$; δ 1.50br (18 H, s, $Bu^t$), 3.23 (1 H, d, *J* 10 Hz, exchangeable with $D_2O$, NH), 4.13 (1 H, d, *J* 4 Hz, 5-H), 4.33 (1 H, d, *J* 2 Hz, 2-H), 4.86 (1 H, dd, *J* 10 and 4 Hz collapsing to d, *J* 4 Hz, on $D_2O$ exch., 6-H), 5.10 (1 H, d, *J* 2 Hz, 3-H), and 7.2—7.8 (15 H, ArH).

*t-Butyl* 6β-(*Phenoxyacetamido*)-2-*t-butoxycarbonylpenam*-3-*carboxylate* 1-*Oxide* (18).—The penam *S*-oxide (17), (major isomer) (0.1 g) in methylene chloride was treated with toluene-*p*-sulphonic acid monohydrate (38 mg) dissolved in the minimum volume of methanol. After 5.5 h at room temperature the solution was evaporated to dryness and the residue was dissolved in fresh methylene chloride, cooled (−15 °C), and treated with triethylamine (0.07 ml) followed by phenoxyacetyl chloride (34 mg). After 15 min at −15 °C the solution was washed with water, dried, and evaporated, and the residue chromatographed to give one isomer of the *amide* (18) (54 mg), m.p. 191—193°, $\nu_{max.}$ 1 802, 1 740—1 720br, and 1 690 $cm^{-1}$; δ 1.47 (9 H, s, $Bu^t$), 1.55 (9 H, s, $Bu^t$), 4.53 (2 H, s, covering further 1 H signal, $CH_2$, 2-H), 4.80 (1 H, d, *J* 5 Hz, 5-H), 4.76—4.86 (1 H, m, 3-H), 6.09 (1 H, dd, *J* 10 and 5 Hz, 6-H with further fine splitting resulting from long-range coupling to 3-H), 6.80—7.50 (5 H, Ar), and 8.26 (1 H, d, *J* 10 Hz, NH) (Found: $M^+$, 494.170 2. $C_{23}H_{30}N_2O_8S$ requires *M*, 494.172 3). Similarly the sulphoxide (17) (minor isomer) (0.2 g) was detritylated with toluene-*p*-sulphonic acid (76 mg) and the resulting primary amine treated with triethylamine (0.14 ml) and phenoxyacetyl chloride (68 mg); chromatography gave a second *isomer* of the amide (18) (57 mg), $\nu_{max.}$ 1 810, 1 740br, and 1 700 $cm^{-1}$; δ 1.50 (18 H, s, $Bu^t$), 4.53 (2 H, partially covering 1 H signal, $CH_2$, 2-H), 5.00 (1 H, d, *J* 5 Hz, 5-H), 5.33 (1 H, d, *J* 2 Hz, 3-H), 5.81 (1 H, dd, *J* 9 and 5 Hz, 6-H), 6.76—7.49 (5 H, ArH), and 7.96 (1 H, d, *J* 9 Hz, NH) (Found: $M^+$, 494.174 9. $C_{23}H_{30}N_2O_8S$ requires *M*, 494.172 3).

(3R,4R)-1-(1-*Benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-(*methoxycarbonylmethylthio*)-3-(*triphenylmethylamino*)*azetidin*-2-*one* (19).—Benzyl 6β-(triphenylmethylamino)penicillanate (3.23 g) and methyl bromoacetate (0.91 g) in tetrahydrofuran (60 ml) was stirred under nitrogen. Potassium 2,6-di-t-butylphenoxide (1.5 equiv. prepared from 2,6-di-t-butylphenol and potassium hydride) in tetrahydrofuran was added over 15 min. After stirring overnight, ethyl acetate was added and the solution was washed with brine, dried, and evaporated. On trituration with ether unchanged penicillanate solidified and was removed (1.65 g). Chromatography of the ether-soluble fraction gave the azetidinone (19) (0.8 g), m.p. 120—121° (lit.,[22] 120—121°).

(3R,4R)-4-(*Methoxycarbonylmethylthio*)-3-(*triphenylmethylamino*)*azetidin*-2-*one* (20).—The azetidin-2-one (19) (2.48 g) in pyridine (24 ml) and water (1.2 ml) was cooled to −5 °C. Solid potassium permanganate (0.948 g) was added and the mixture left stirring for 1 h (0 °C). Work-up as for the corresponding t-butyl ester [11] gave starting material (19) (0.61 g) and the *azetidinone* (20) as an amorphous solid (0.65 g), $\nu_{max.}$ 1 775 and 1 738 $cm^{-1}$; δ 2.88 and 3.18 (2 H, ABq, *J* 15 Hz, covering exchangeable NH signal), 3.67 (3 H, s), 4.52 (2 H, s, β-lactam protons), 6.60br (1 H, s, exch., $D_2O$), and 7.10—7.64 (15 H, ArH) (Found: $M^+$, 432.150 8. $C_{25}H_{24}N_2O_5S$ requires *M*, 432.150 8).

(3R,4R)-1-(1-*Hydroxy*-1-p-*nitrobenzyloxycarbonylmethyl*)-4-(*methoxycarbonylmethylthio*)-3-(*triphenylmethylamino*)-*azetidin*-2-*one* (21).—*p*-Nitrobenzyl glyoxylate (0.34 g) and the azetidin-2-one (20) (0.435 g) were refluxed in benzene (40 ml) for 7 h, then the solution was cooled, washed, dried, and evaporated. Chromatography gave the α-hydroxy-ester (21) (0.595 g), $\nu_{max.}$ ($CHCl_3$) 1 760br, 1 522, and 1 350 $cm^{-1}$. The n.m.r. spectrum showed singlets (after $D_2O$ exchange) at δ 5.53 and 5.57 for C*H*OH of the two isomers.

(3R,4R)-1-(1-*Chloro*-1-p-*nitrobenzyloxycarbonylmethyl*)-4-(*methoxycarbonylmethylthio*)-3-(*triphenylmethylamino*)-*azetidin*-2-*one* (22).—The α-hydroxy-ester (21) (6.6 g) in tetrahydrofuran (200 ml) was treated with 2,6-lutidine (1.79 ml) and thionyl chloride (1.12 ml) at −20 °C to give the chloride (22) (6.1 g), $\nu_{max.}$ 1 778, 1 765, 1 740, 1 522, and 1 350 $cm^{-1}$; δ 6.15 (s) and 6.20 (s) (1 H, CHCl).

(3R,4R)-1-(1-*Chloro*-1-p-*nitrobenzyloxycarbonylmethyl*)-4-(*methoxycarbonylmethylsulphinyl*)-3-(*triphenylmethylamino*)*azetidin*-2-*one* (16).—The chloride (22) (5.74 g) in chloroform (100 ml) was cooled (−4 °C) and treated with *m*-chloroperbenzoic acid (1.76 g) in chloroform (20 ml) as described for the analogue (15). The isomeric mixture of sulphoxides (16) (5.57 g) showed $\nu_{max.}$ 1 792, 1 750br, 1 525, and 1 352 $cm^{-1}$. The n.m.r. spectrum showed singlets at δ 6.27 and 6.30 (CHCl).

p-*Nitrobenzyl* (2R,3S,5R,6R)-2-*Methoxycarbonyl*-6-(*phenoxyacetamido*)*penam*-3-*carboxylate*.—The sulphoxide (16) (4.88 g) in dry tetrahydrofuran (200 ml) under nitrogen was cooled (−20 °C). Potassium t-butoxide (8 ml of a 0.178M-solution in t-butyl alcohol) was added dropwise with stirring over 2 h. The mixture was evaporated and the residue was dissolved in ethyl acetate and washed with brine. Evaporation of the dried organic layer gave the

[22] M. A. Harris, I. McMillan, J. H. C. Nayler, N. F. Osborne, M. J. Pearson, and R. Southgate, *J.C.S. Perkin I*, 1976, 1612.

penam 1-oxide (23) as a solid (4.8 g), which was taken up in dimethylformamide (50 ml) and cooled (ice-bath). Phosphorus tribromide (2.5 ml) was added, and the mixture was stirred for 15 min in the cold, then poured into aqueous sodium hydrogen carbonate solution, and extracted with ethyl acetate (×3). After washing with 0.1N-hydrochloric acid and water, the dried ethyl acetate layer was evaporated and the residual orange foam chromatographed to give the penam (24) (0.35 g), $\nu_{max.}$ 1 790, 1 740, 1 522, and 1 350 $cm^{-1}$; δ 3.58 (1 H, d, *J* 12 Hz exch. $D_2O$, NH), 3.68 (3 H, s, OMe), 4.31 (1 H, d, *J* 4 Hz, 5-H), 4.45 (1 H, d, *J ca.* 1 Hz, 2-H), 4.67 (1 H, dd, *J* 12 and 4 Hz, collapsing to d, *J* 4 Hz, on $D_2O$ exch., 6-H), 5.27 (2 H, s), 5.33 (1 H, d, *J ca.* 1 Hz, 3-H), and 7.18—8.45 (19 H, ArH).

The penam (24) (0.3 g) in acetone (2 ml) at −10 °C was treated with toluene-*p*-sulphonic acid (102 mg) in the minimum of acetone. After 5 h at 0 °C, the precipitated toluene-*p*-sulphonic acid salt of the 6-aminopenam (25) (156 mg) was collected; m.p. 152—158° (decomp.), $\nu_{max.}$ (mull) 1 790, 1 750, 1 725, 1 522, and 1 350 $cm^{-1}$. Concentration of the mother liquors and ether washings gave a further crop (76 mg) of the salt. This salt (100 mg) in methylene chloride (5 ml) was cooled (−10 °C) and treated with triethylamine (40 mg) and phenoxyacetyl chloride (34 mg). After 20 min at −10 °C the solution was washed with brine, dried, and evaporated to dryness. Chromatography of the residue gave p-*nitrobenzyl* (2R,3S,5R,6R)-2-*methoxycarbonyl*-6-(*phenoxyacetamido*)*penam*-3-*carboxylate* (26) (78 mg), $\nu_{max.}$ 1 782, 1 755, 1 742, 1 690, 1 525, and 1 355 $cm^{-1}$, δ 3.75 (3 H, s, OMe), 4.57 (2 H, s, $CH_2$, covering 1 H signal, 2-H), 5.33 (2 H, s, $CH_2$ covering 1 H signal, 3-H) (separation of signals with shift reagent revealed very slight coupling between 2- and 3-H), 5.51 (1 H, d, *J* 4 Hz, 5-H), 5.89 (1 H, dd, *J* 10 and 4 Hz, 6-H), 6.90—8.50 (10 H, ArH, NH), δ [$(CD_3)_2CO$] 3.83 (3 H, s, OMe), 4.68 (2 H, s, $CH_2$), 4.88 (1 H, s, 2-H), 5.22 (2 H, s, $CH_2$), 5.67 (1 H, s, 3-H), 5.71 (1 H, d, *J* 4 Hz, 5-H), 5.93 (1 H, dd, *J* 10 and 4 Hz, 6-H), and 7.08—8.50 (10 H, ArH, NH) (Found: $M^+$, 515.099 1. $C_{23}H_{21}N_3O_9S$ requires *M*, 515.099 8.

(2R,3S,5R,6R)-2-*Methoxycarbonyl*-6-(*phenoxyacetamido*)-*penam*-3-*carboxylic Acid* (28).—The ester (26) (78 mg) in tetrahydrofuran (15 ml) was hydrogenated at room temperature and atmospheric pressure for 1.5 h over 10% palladium–carbon (150 mg). The solution was filtered through kieselguhr and evaporated to dryness to give the *p*-toluidine salt of the acid (28) (75 mg), $\nu_{max.}$ 1 798, 1 738, and 1 690 $cm^{-1}$.

(2R,3S,5R,6R)-2-*Methoxycarbonyl*-6-[(R)-α-*phenylglycylamino*]*penam*-3-*carboxylic Acid* (29).—Methyl chloroformate (20 mg) in tetrahydrofuran (5 ml) was cooled (−10 °C). A solution of *N*-*p*-nitrobenzyloxycarbonyl-(*R*)-phenylglycine (69 mg), triethylamine (22 mg) and dimethylbenzylamine (1 drop) in tetrahydrofuran (5 ml) was added. After stirring in the cold for 20 min the free base (25) (80 mg; from toluene-*p*-sulphonic acid salt by partition between ethyl acetate and sodium hydrogen carbonate) in tetrahydrofuran (5 ml) was added, and stirring continued in the cold (−10 °C) for a further 20 min. The mixture was filtered, the filtrate evaporated to dryness, and the residue chromatographed to give the protected penam (27) (50 mg), $\nu_{max.}$ 1 300, 1 735br, 1 692, 1 525, and 1 355 $cm^{-1}$; δ 3.80 (3 H, s), 4.50 (1 H, s), 4.75 (1 H, s), 5.19—5.47 (6 H, overlapping signals), 5.80 (1 H, dd, *J* 10 and 4 Hz), 6.40 (1 H, d, *J* 6 Hz), and 7.31—8.46 (14 H, m). Hydrogenolysis of (27) (42 mg) as for the phenoxyacetamido-derivative gave the ampicillin analogue (29) as a solid *p*-toluidine salt (26 mg), $\nu_{max.}$ (KBr) 1 780, 1 722, and 1 680 $cm^{-1}$.

(3R,4R)-4-(*Bisethoxycarbonylmethylthio*)-3-*phenoxyacetamidoazetidin*-2-*one* (32).—(1*R*,5*R*)-3-Phenoxymethyl-4-thia-2,6-diazabicyclo[3.2.0]hept-2-en-7-one (31) [11] (200 mg) was dissolved in a mixture of dimethylformamide (2 ml) and water (0.05 ml) and treated with urea (600 mg), 2,6-di-t-butyl-4-methylphenol (10 mg), and diethyl bromomalonate (820 mg). The mixture was heated at 50 °C under nitrogen for 12 h, cooled, diluted with ethyl acetate, and washed with water. The dried ($MgSO_4$) organic layer was evaporated to give a crude oil (830 mg) which on chromatography gave the *azetidinone* (32) (87 mg), m.p. 85—87° (from ether); $\nu_{max.}$ 1 775, 1 725, and 1 685 $cm^{-1}$; δ 1.29 (6 H, t, *J* 7 Hz), 4.00—4.50 (5 H, m), 4.60 (2 H, s), 5.40 (1 H, d, *J* 5 Hz), 5.65 (1 H, dd, *J* 5 and 9 Hz), 6.8—7.6 (6 H, m, 1 H exch. $D_2O$), and 7.85 (1 H, d, *J* 9 Hz) (Found: C, 52.6; H, 5.5; N, 6.6%; $M^+$, 410.114 1. $C_{18}H_{22}N_2O_7S$ requires C, 52.7; H, 5.4; N, 6.8%; *M*, 410.114 8).

(3R,4R)-4-(*Bisethoxycarbonylmethylthio*)-1-[*hydroxy*-(*t-butoxycarbonyl*)*methyl*]-3-*phenoxyacetamidoazetidin*-2-*one* (33).—The azetidinone (32) (82 mg) and t-butyl glyoxylate monohydrate (296 mg) in dry benzene (3 ml) were refluxed under nitrogen with provision for the removal of water. After 1 h the mixture was cooled, diluted with benzene (5 ml), and washed with water (5 × 5 ml). The dried ($MgSO_4$) organic layer was evaporated to give the α-hydroxy-ester (33) (82 mg), a mixture of epimers, as an amorphous solid, $\nu_{max.}$ 1 775, 1 730, and 1 685 $cm^{-1}$; δ 1.00—1.70 (s and 2 overlapping t), 4.0—5.0br (1 H, s, exch. $D_2O$), 4.05—4.45 (5 H, s and 2 overlapping q), 4.59 (2 H, s), 5.30—5.75 (3 H, m), and 6.85—7.80 (6 H, m).

(3R,4R)-4-(*bisethoxycarbonylmethylthio*)-1-[*chloro*-(*t-butoxycarbonyl*)*methyl*]-3-*phenoxyacetamidoazetidin*-2-*one* (34).—A solution of the α-hydroxy-ester (33) (54 mg) in a mixture of dry tetrahydrofuran (1 ml) and dry dioxan (1 ml) was cooled to −10 °C and treated with dry 2,6-dimethylpyridine (32 mg) followed by thionyl chloride (36 mg). The mixture was stirred at 0 to −5 °C for a further 15 min and filtered. The filtrate was evaporated to give the α-chloro-ester (34) (54 mg) as an amorphous solid, $\nu_{max.}$ 1 785, 1 735, and 1 690 $cm^{-1}$.

(5R,6R)-*t-Butyl* 2,2-*Bisethoxycarbonyl*-6-*phenoxyacetamidopenam*-3-*carboxylate* (36).—The α-chloro-ester (34) (135 mg) was dissolved in dry tetrahydrofuran (2 ml), cooled to −20 °C, and treated dropwise with a solution of potassium t-butoxide in t-butyl alcohol (1 equiv.; 0.21 ml of a 1.01M-solution). After stirring at −20 °C for 30 min the mixture was diluted with ethyl acetate and washed with brine. The dried ($MgSO_4$) organic layer was evaporated and chromatography of the residual gum (126 mg) gave the penam (36) (54 mg), a mixture of C-3 epimers, as an amorphous solid, $\nu_{max.}$ 3 380, 1 800, 1 735, and 1 685 $cm^{-1}$; δ 1.29 (t, *J* 7 Hz) and 1.33 (t, *J* 7 Hz) (6 H, $CO_2{\cdot}CH_2{\cdot}CH_3$), 1.50 (s) and 1.55 (s) (9 H, $Bu^t$), 4.28 (q, *J* 7 Hz) and 4.34 (q, *J* 7 Hz) (4 H, $CO_2{\cdot}CH_2{\cdot}CH_3$), 4.45 (s) and 5.20 (s) (1 H, 3-H), 4.60 (2 H, s, $PhOCH_2$), 5.45–5.93 (2 H, m, 5- and 6-H), 6.9—7.6 (5 H, m, aromatic), and 7.96 (d, *J* 10 Hz) and 8.12 (d, *J* 10 Hz) (1 H, NH) (Found: $M^+$, 522.167 4. $C_{24}H_{30}N_2O_9S$ requires *M*, 522.167 2).

The following penam esters, all as mixtures of C-3 epimers, were similarly prepared from the appropriate glyoxylates: (a) (5R,6R)-*benzyl* 2,2-*bisethoxycarbonyl*-6-*phenoxyacetamidopenam*-3-*carboxylate* (38) (25%), a gum, $\nu_{max.}$ 3 360, 1 800, 1 740, and 1 685 $cm^{-1}$, δ 5.24 (s) and 5.32 (s) (2 H, $CH_2Ph$)

(Found: $M^+$, 556.152 4. $C_{27}H_{28}N_2O_9S$ requires $M$, 556.151 5); (b) (5R,6R)-p-*nitrobenzyl* 2,2-*bisethoxycarbonyl*-6-*phenoxyacetamidopenam*-3-*carboxylate* (39) (50%), an amorphous solid, $\nu_{max.}$ 3 400, 1 800, 1 750sh, 1 740, and 1 690 $cm^{-1}$; δ 5.34 (s) and 5.42 (s) (2 H, $CH_2C_6H_4NO_2$) (Found: $M^+$, 601.141 7, $C_{27}H_{27}N_3O_{11}S$ requires $M$, 601.136 6); (c) (5R,6R)-2,2,2-*trichloroethyl* 2,2-*bisethoxycarbonyl*-6-*phenoxyacetamidopenam*-3-*carboxylate* (40) (63%), an amorphous solid, $\nu_{max.}$ 3 360, 1 800, 1 765, 1 735, and 1 685 $cm^{-1}$ (Found: $M^+$, 596.013 9. $C_{22}H_{23}Cl_3N_2O_9S$ requires $M$, 596.018 9); (d) (5R,6R)-*methyl* 2,2-*bisethoxycarbonyl*-6-*phenoxyacetamidopenam*-3-*carboxylate* (41) (34%), an amorphous solid, $\nu_{max.}$ 3 400, 1 805, 1 750sh, 1 740, and 1 690 $cm^{-1}$; δ 1.29 (t, $J$ 7 Hz) and 1.32 (t, $J$ 7 Hz) (6 H, $CO_2{\cdot}CH_2{\cdot}CH_3$), 3.81 (s) and 3.89 (s) (3 H, $CO_2CH_3$), 4.28 (q, $J$ 7 Hz) and 4.32 (q, $J$ 7 Hz) (4 H, $CO_2{\cdot}CH_2{\cdot}CH_3$), 4.53 (s) and 5.33 (s) (1 H, 3-H), 4.60 (2 H, s, $PhOCH_2$), 5.48—5.94 (2 H, m, 5- and 6-H), 6.9—7.6 (5 H, m, aromatic), and 7.99 (d, $J$ 10 Hz) and 8.17 (d, $J$ 10 Hz) (1 H, NH) (Found: $M^+$, 480.122 5. $C_{21}H_{24}N_2O_9S$ requires $M$, 480.120 2); (e) (5R,6R)-2-*methylthioethyl* 2,2-*bisethoxycarbonyl*-6-*phenoxyacetamidopenam*-3-*carboxylate* (42) (50%), a gum, $\nu_{max.}$ 3 380, 1 800, 1 740, and 1 690 $cm^{-1}$; δ 1.31 (t, $J$ 7 Hz) and 1.35 (t, $J$ 7 Hz) (6 H, $CO_2{\cdot}CH_2{\cdot}CH_3$), 2.20 (3 H, s, $SCH_3$), 2.65—3.00 (2 H, m, $CO_2{\cdot}CH_2{\cdot}CH_2{\cdot}SCH_3$), 4.1—4.7 (8½ H, m, $PhOCH_2$, $CO_2{\cdot}CH_2{\cdot}CH_2{\cdot}SCH_3$, $CO_2{\cdot}CH_2{\cdot}CH_3$, and 3-H), 5.39 (½ H, s, 3-H), 5.52—6.04 (2 H, m, 5- and 6-H), 6.9—7.6 (5 H, m, aromatic), and 8.08 (d, $J$ 10 Hz) and 8.25 (d, $J$ 10 Hz) (1 H, NH) (Found: $M^+$, 540.126 2. $C_{23}H_{28}N_2O_9S_2$ requires $M$, 540.123 6). The methylthioethyl ester (42) (120 mg) was dissolved in methyl iodide (1 ml) and kept at room temperature for 40 h. The methyl iodide was decanted and the residual gum was triturated with dry ether to give the crude sulphonium iodide (43) (85 mg) as a yellow amorphous solid, $\nu_{max.}$ 1 795, 1 740br, and 1 690 $cm^{-1}$.

(3R,4R)-4-(*Bismethoxycarbonylmethylthio*)-3-*phenoxyacetamidoazetidin*-2-*one* (35).—The thiazoline (31) (2.0 g) was dissolved in dimethylformamide (20 ml) and water (0.5 ml) and treated with urea (6.0 g), 2,6-di-t-butyl-4-methylphenol (100 mg), and dimethyl bromomalonate (7.2 g) under the conditions described for the preparation of the diethyl analogue (32). The *azetidinone* (35) (554 mg) crystallised from ethyl acetate–light petroleum; m.p. 106—108°, $\nu_{max.}$ 3 430, 1 785, 1 755, 1 740, and 1 690 $cm^{-1}$; δ 3.79 (6 H, s), 4.30 (1 H, s), 4.58 (2 H, s), 5.36 (1 H, d, $J$ 5 Hz), 5.60 (1 H, dd, $J$ 5 and 9 Hz), and 6.8—7.8 (7 H, m) (Found: C, 50.3; H, 4.8; N, 7.3%; $M^+$, 382.085 9. $C_{16}H_{18}N_2O_7S$ requires C, 50.2; H, 4.7; N, 7.3%; $M$, 382.083 5).

(5R,6R)-*t-Butyl* 2,2-*Bismethoxycarbonyl*-6-*phenoxyacetamidopenam*-3-*carboxylate* (44).—Treatment of the azetidinone (35) (190 mg) with t-butyl glyoxylate followed by thionyl chloride–2,6-dimethylpyridine and finally potassium t-butoxide as for the preparation of the penam (36) gave, after chromatography, the penam ester (44) (70 mg), a mixture of C-3 epimers, as a gum, $\nu_{max.}$ 3 400, 1 800, 1 740, and 1 690 $cm^{-1}$; δ 1.45 (s) and 1.50 (s) (9 H, $Bu^t$), 3.65—3.95 (6 H, m, $CO_2{\cdot}CH_3$), 4.40 (½ H, s, 3-H), 4.54 (2 H, s, $PhOCH_2$), 5.20 (½ H, s, 3-H), 5.35—5.90 (2 H, m, 5- and 6-H), and 6.8—7.5 (6 H, m, aromatic +NH) (Found: $M^+$, 494.135 9. $C_{22}H_{26}N_2O_9S$ requires $M$, 494.135 9).

(5R,6R)-2,2,2-*Trichloroethyl* 2,2-*Bismethoxycarbonyl*-6-*phenoxyacetamidopenam*-3-*carboxylate* (45) *and* (46).—Similar treatment of the azetidinone (35) (530 mg) with 2,2,2-trichloroethyl glyoxylate, thionyl chloride–2,6-dimethylpyridine, and finally potassium t-butoxide gave the penam ester as a mixture of C-3 epimers. Careful chromatography gave the 3*S*-epimer (45) (100 mg), the 3*R*-epimer (46) (164 mg), and a mixture of both epimers (37 mg). The 3S-*epimer* (45) had $\nu_{max.}$ 3 400, 1 810, 1 770, 1 745, and 1 690 $cm^{-1}$; δ 3.76 (6 H, s, $CO_2CH_3$), 4.52 (2 H, s, $PhOCH_2$), 4.72 (2 H, s, $CO_2{\cdot}CH_2{\cdot}CCl_3$), 5.37 (1 H, s, 3-H), 5.65 (1 H, d, $J$ 4 Hz, 5-H), 5.78 (1 H, dd, $J$ 4 and 9 Hz, 6-H), 6.83—7.36 (5 H, m, aromatic), and 7.86 (1 H, d, $J$ 9 Hz, NH) (Found: $M^+$, 567.989 4. $C_{20}H_{19}Cl_3N_2O_9S$ requires $M$, 567.987 7). The 3R-*epimer* (46) had $\nu_{max.}$ 3 400, 1 810, 1 770, 1 750, 1 740, and 1 690 $cm^{-1}$; δ 3.75 (6 H, s, $CO_2CH_3$), 4.50 (2 H, s, $PhOCH_2$), 4.57 (1 H, s, 3-H), 4.65 and 4.96 (2 H, ABq, $J$ 13 Hz, $CO_2{\cdot}CH_2CCl_3$), 5.48 (1 H, d, $J$ 4 Hz, 5-H), 5.74 (1 H, dd, $J$ 4 and 9 Hz, 6-H), 6.75—7.36 (5 H, m, aromatic), and 8.00 (1 H, d, $J$ 9 Hz, NH) (Found: $M^+$, 567.988 4. $C_{20}H_{19}Cl_3N_2O_9S$ requires $M$, 567.987 7).

(3R,4R)-4-*Acetonylthio*-3-*phenoxyacetamidoazetidin*-2-*one* (47).—The thiazoline (31) (1.0 g) and bromoacetone (1.5 ml) were mixed in *NN*-dimethylformamide (10 ml) containing water (0.25 ml), urea (3.0 g), and 2,6-di-t-butyl-4-methylphenol (50 mg), then heated at 50 °C for 5 h. Ethyl acetate was added and the mixture was washed with water (3 ×), then with brine, and dried ($MgSO_4$) and evaporated to leave an oil.

This was chromatographed rapidly on silica gel, eluting with ethyl acetate, to give the *azetidinone* (47) (433 mg, 33%), which formed plates (from ethyl acetate), m.p. 109—110°, $\nu_{max.}$ ($CH_2Cl_2$) 3 400, 1 785, and 1 690br $cm^{-1}$; δ ($CDCl_3$) 2.18 (3 H, s), 3.32 (2 H, s), 4.55 (2 H, s), 4.96 (1 H, d, $J$ 5 Hz), 5.55 (1 H, dd, $J$ 5 and 10 Hz), 6.8—7.5 (6 H, m; 5 H, m, after $D_2O$ exch.), and 7.80 (1 H, d, $J$ 10 Hz) (Found: C, 54.3; H, 4.9; N, 9.0; S, 10.5%; $M^+$, 308.083 24. $C_{14}H_{16}N_2O_4S$ requires C, 54.5; H, 5.2; N, 9.1; S, 10.4%; $M$, 308.083 07).

2,2,2-*Trichloroethyl* (6R,7R)-3,4-*Epoxy*-3-*methyl*-7-*phenoxyacetamidocepham*-4-*carboxylate* (51).—The 4-acetonylthioazetidinone (47) (784 mg) was added to a suspension of 2,2,2-trichloroethyl glyoxylate monohydrate (286 mg) in benzene (40 ml), which had previously been heated under reflux in a Dean–Stark apparatus. The mixture was heated under reflux for 3½ h, cooled, and washed with water (5 ×). After drying ($MgSO_4$) the benzene layer was evaporated to leave the crude α-hydroxy-ester as a crisp foam (1.75 g), $\nu_{max.}$ ($CHCl_3$) 3 400, 1 780, and 1 695 $cm^{-1}$; δ [$(CD_3)_2SO$] 2.17 (3 H, s), 4.04 (1 H, d, $J$ 7 Hz), 4.65 (2 H, s), 4.8—5.5 (4 H, m), 5.60 (1 H, d, $J$ 7 Hz, s on $D_2O$ exch.), 6.7—7.6 (5 H, m), and 9.1 (d, $J$ 7 Hz, slowly exch. $D_2O$). The crude hydroxy-ester was taken up in tetrahydrofuran (30 ml) and cooled to −40 °C; 2,6-dimethylpyridine (410 mg) in tetrahydrofuran (5 ml) was added, followed dropwise by thionyl chloride (455 mg) in tetrahydrofuran (8 ml). The mixture was stirred in the cold for 2 h, then allowed to warm to room temperature, and the amine hydrochloride was filtered off. The filtrate was evaporated, then the residue was treated with toluene and evaporation repeated (3 ×) to leave the crude chloride (48) as a gum (1.67 g), $\nu_{max.}$ ($CHCl_3$) 3 400, 1 790, and 1 695 $cm^{-1}$; δ 6.32 (s) and 6.36 (s) (CHCl in each epimer). The crude chloride (48) was taken up in dry tetrahydrofuran (50 ml), cooled to −20 to −30 °C, and treated with 0.944M-potassium t-butoxide in t-butyl alcohol (2.66 ml). The mixture was stirred for 1½ h, then allowed to warm to room temperature, and ethyl acetate and brine were added. The layers were separated and the ethyl acetate layer was dried ($MgSO_4$) and evaporated to leave a gum (1.14 g). Chromatography on silica gel

(20 g), eluting with ethyl acetate–light petroleum mixtures (gradient elution from 3 : 7 to 10 : 0) gave the 3,4-*epoxycepham* (51) [70 mg, 6% overall yield from (47)], m.p. 144—147° (from ether), $\nu_{max.}$ ($CHCl_3$) 3 430, 1 805, 1 780sh, and 1 695 $cm^{-1}$; δ ($CDCl_3$) 1.62 (3 H, s), 3.09 and 3.42 (2 H, ABq, *J* 15 Hz), 4.58 (2 H, s), 4.97 (3 H, s, superimposed on d?), 5.87 (1 H, dd, *J* 4 and 10 Hz), and 6.8—7.7 (6 H, m) (Found: $M^+$, 493.984 6. $C_{18}H_{17}Cl_3N_2O_6$ requires *M*, 493.987 3). Earlier and later chromatographic fractions contained mixtures of β-lactam-containing compounds which were not characterised.

p-*Nitrobenzyl* 2-[(3R,4R)-4-*Acetonylthio*-2-*oxo*-3-*phenoxyacetamidoazetidin*-1-*yl*]-2-*hydroxyacetate* (49).—*p*-Nitrobenzyl glyoxylate monohydrate (14.2 g) was dissolved in hot ethyl acetate (250 ml) and the ethyl acetate–water azeotrope was distilled off, with addition of more ethyl acetate at the same rate as the azeotrope distilled over. When 200 ml of distillate had been collected the azetidinone (47) (6.43 g) was added. A further 250 ml of distillate was collected and then the mixture was heated under reflux for 4 h. The mixture was cooled, the ethyl acetate removed on a rotary evaporator, and the residue chromatographed on silica gel, eluting with ethyl acetate–light petroleum mixtures (1 : 1, then 7 : 3, then 10 : 0). This resulted in the isolation of two epimeric α-hydroxy-esters (49). The first *epimer* to be eluted was recrystallised from ethyl acetate–light petroleum; m.p. 144—145°, $\nu_{max.}$ (KBr) 1 760, 1 740sh, 1 705, 1 670, 1 520, and 1 345 $cm^{-1}$; δ [$(CD_3)_2SO$] 2.17 (3 H, s), 3.67 (2 H, s), 4.68 (2 H, s), 5.0—5.6 (5 H, m), 6.7—7.5 (5 H, m), 7.75 (2 H, d, *J* 9 Hz), 8.32 (2 H, d, *J* 9 Hz), and 9.06 (1 H, exch. $D_2O$, d, *J* 8 Hz) (Found: C, 53.4; H, 4.5; N, 8.1; S, 6.2. $C_{23}H_{23}N_3O_9S$ requires C, 53.4; H, 4.5; N, 8.1; S, 6.2%). The second epimer to be eluted was a gum, $\nu_{max.}$ ($CH_2Cl_2$) 1 780, 1 755, and 1 690 $cm^{-1}$; δ 2.17 (3 H, s), 3.35 (2 H, s), 4.57 (2 H, s), 4.9br (1 H, s, exch. $D_2O$), 5.0—5.6 (6 H, m), 5.65 (1 H, s), and 6.7—8.4 (10 H, m).

p-*Nitrobenzyl* 2-[(3R,4R)-4-*Acetonylthio*-2-*oxo*-3-*phenoxyacetamidoazetidin*-1-*yl*]-2-*chloroacetate* (50).—The hydroxy-ester (49) (mixed epimers) (7.66 g) was taken up in tetrahydrofuran (160 ml), cooled to −50 °C, and treated with 2,6-dimethylpyridine (2.29 g). Thionyl chloride (2.5 g) in tetrahydrofuran (15 ml) was then added dropwise and the mixture was stirred in the cold for 1 h, then allowed to warm to room temperature over 1 h and filtered. Evaporation of the filtrate gave the crude chloride (50) as a gum, $\nu_{max.}$ 1 795, 1 760sh, and 1 690 $cm^{-1}$.

*Cyclisation of the Chloride* (50).—The crude product from the foregoing reaction was taken up in tetrahydrofuran (200 ml), cooled to −40 °C, and treated dropwise with 0.944M-potassium t-butoxide in t-butyl alcohol (15.1 ml). After stirring in the cold for 30 min a further portion (1.0 ml) of the butoxide solution was added, and the mixture stirred for a further 10 min. Ethyl acetate and brine were added and the mixture was allowed to warm to room temperature. The ethyl acetate layer was separated and dried ($MgSO_4$), then evaporated to leave a gum (8.3 g). This was chromatographed on silica gel (300 g), eluting with ethyl acetate–light petroleum mixtures followed by chloroform to give mixtures of penams, and also some fractions containing the 3,4-epoxycepham (52). Trituration of the residue (1.17 g) from evaporation of these fractions with ethyl acetate gave the 3,4-epoxycepham (52) (210 mg). Recrystallisation from ethyl acetate–acetone–light petroleum gave p-*nitrobenzyl* (6R,7R)-3,4-*epoxy*-3-*methyl*-7-*phenoxyacetamidocepham*-4-*carboxylate* (52), m.p. 199—204°, $\nu_{max.}$ ($CHCl_3$) 3 420, 1 800, 1 755, 1 695, 1 525, and 1 350 $cm^{-1}$; δ [wet $(CD_3)_2SO$] 1.43 (3 H, s), 3.28 and 3.59 (2 H, ABq, *J* 16 Hz), 4.61 (2 H, s), 5.13 (1 H, d, *J* 15 Hz), 5.47 (2 H, s), 5.71 (1 H, d, *J* 5 Hz), 6.7—7.5 (5 H, m), 7.67 (2 H, d, *J* 9 Hz), and 8.27 (2 H, d, *J* 9 Hz) (Found: $M^+$, 499.104 6. $C_{23}H_{21}N_3O_8S$ requires *M*, 499.104 9). Repeated chromatography of the fractions containing the penam mixtures on silica gel eventually yielded one stereoisomer of *p-nitrobenzyl* (5R,6R)-2-*acetyl*-6-*phenoxyacetamidopenam*-3-*carboxylate* (53) in a pure state as a non-crystalline solid (90 mg), $\nu_{max.}$ ($CHCl_3$) 3 420, 1 800, 1 750, 1 720, 1 690, 1 520, and 1 350 $cm^{-1}$; δ ($CDCl_3$) 2.34 (3 H, s, $CH_3CO$), 4.57—4.66 (s, superimposed on d, $OCH_2CO$, 3- or 2-H), 4.82 (d, *J* 7 Hz, 2- or 3-H) (total integral δ 4.3—4.9 4 H), 5.33 (3 H, s, with shoulder at δ 5.38, $OCH_2Ar$, 5-H), 5.71 (1 H, dd, *J* 4 and 9 Hz, 6-H), 6.7—7.7 (8 H, m, 7 ArH, NH), and 8.24 (2 H, d, *J* 10 Hz). Other isomers were obtained as mixtures, and repeated chromatography of these only resulted in substantial losses of material, without effecting any separation.

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