The Chemistry of 4-Mercaptoazetidin-2-ones. Part 3.[1] Synthesis of 6-Phenoxyacetamido-2-alkylidenepenam-3-carboxylic Acids

By **Neal F. Osborne**, Beecham Pharmaceuticals Research Division, Brockham Park, Betchworth, Surrey RH3 7AJ

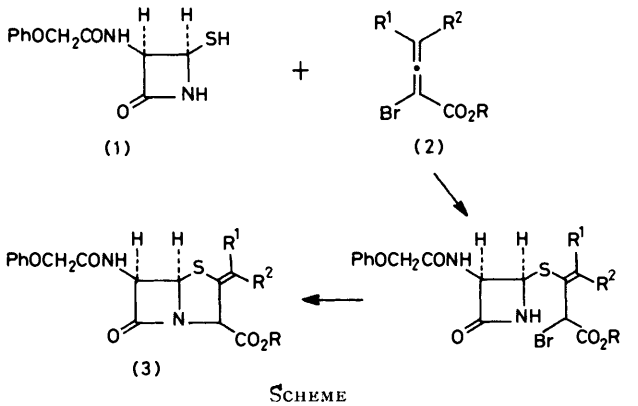
A general method for the preparation of α-bromoallenic esters (2) involving the reaction of an acid chloride with a carboxybromomethylenetriphenylphosphorane has been developed. Reaction of these esters with the 4-mercaptoazetidin-2-one (1) gave rise to the 2-alkylidenepenam esters (3). The title compounds, obtained by hydrogenolysis of the corresponding benzyl esters, showed only moderate antibacterial properties.

A RECENT publication from these laboratories [1] demonstrated the utility of the 4-mercaptoazetidin-2-one (1) in the synthesis of bicyclic azetidinones. As part of our continuing interest in the synthesis of novel bicyclic azetidinones we undertook the synthesis of a penam of the type (3) bearing an alkylidene function at the C-2 position. These compounds may be considered as 6-acylamino-1-thiadeoxa-analogues of the naturally occurring β-lactamase inhibitor clavulanic acid (4).[2]

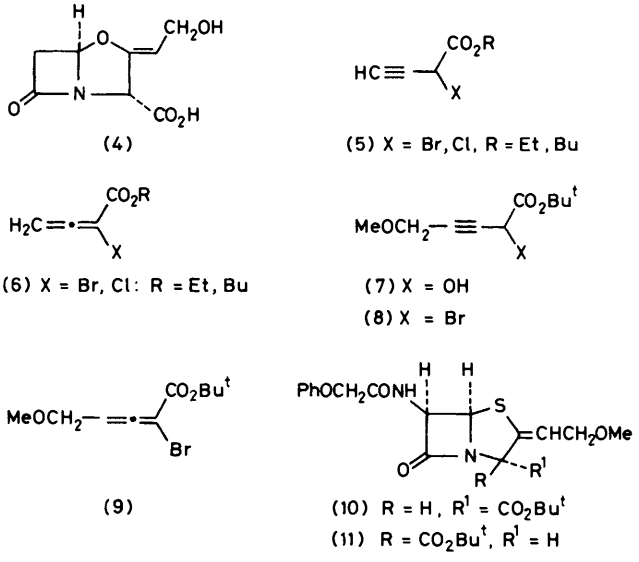
The strategy adopted was that shown in the Scheme, namely Michael addition of the thiol (1) to an α-bromoallenic ester (2) followed by intramolecular *N*-alkylation. A prerequisite for the proposed route was a synthesis of the α-bromoallenic esters (2), only few examples of which have appeared in the literature. Verny and Vessière [3] obtained the α-halogenoacetylenic esters (5) by the reaction of ethynylmagnesium bromide with a glyoxylic ester followed by halogenation and demonstrated that these esters underwent rearrangement to the α-halogenoallenic esters (6) in the presence of potassium carbonate. We initially adopted the same strategy, with experimental modifications, for the preparation of the more elaborate α-bromoallenic esters required for our synthesis.

Treatment of methyl prop-2-ynyl ether with an equivalent of n-butyl lithium followed by freshly distilled t-butyl glyoxylate gave the α-hydroxyacetylenic ester (7) which was converted into the α-bromoacetylenic ester (8) using carbon tetrabromide and triphenylphosphine. Rearrangement to the α-bromoallenic ester (9) was effected using aqueous potassium carbonate but with the concomitant appearance of a by-product. More satisfactory results were obtained using basic alumina when rearrangement to the desired ester (9) was observed in high yield.

Reaction of the 4-mercaptoazetidin-2-one (1) with the α-bromoallenic ester (9) in dimethylformamide (DMF) in the presence of potassium carbonate gave the two isomeric 2-methoxyethylidenepenam esters (10) and (11). The less polar isomer (10) was assigned the 3*S*-configuration by virtue of the downfield shift of the C-3 proton (5.38 p.p.m.) as compared with that of the more polar 3*R*-epimer (11) (4.61 p.p.m.); a similar relationship was observed in a series of penams bearing electron-withdrawing substituents in the 2-position.[4] Although the geometry of the methoxyethylidene substituent could not be assigned with certainty, it was felt that an alternative interpretation of the n.m.r. data in terms of two geometric isomers having the same C-3 stereochemistry could be ruled out on the basis of the magnitude of this difference in chemical shifts. The observed



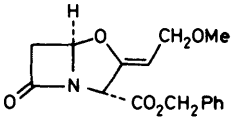
SCHEME



difference in chemical shifts for the C-3 protons of the methyl ethers of benzyl clavulanate (12) and benzylisoclavulanate (13) was only 0.13 p.p.m.† as compared with

† The C-3 protons of the methyl ethers of benzyl clavulanate and benzyl isoclavulanate appear at δ 5.08 and 5.21, I. Stirling, personal communication.

0.77 p.p.m. observed here. Removal of the t-butyl group using trifluoroacetic acid could not be accomplished without destruction of the β-lactam ring.



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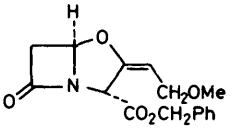

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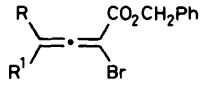
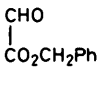


(14) R = CH_2OMe, R^1 = H
(19) R = CH_2OCH_2Ph, R^1 = H
(20) R = R^1 = Me
(21) R = Ph, R^1 = H



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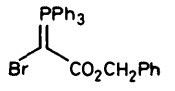

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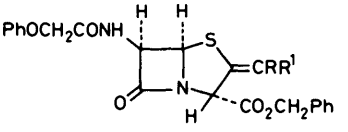
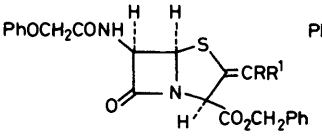
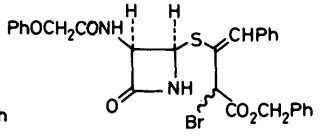


(17) R = H, R^1 = CH_2OMe
(22) R = H, R^1 = CH_2OCH_2Ph
(23) R = R^1 = Me
(26) R = H, R^1 = Ph



(18) R = H, R^1 = CH_2OMe
(24) R = R^1 = Me



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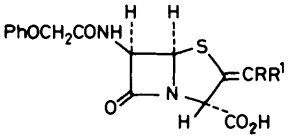
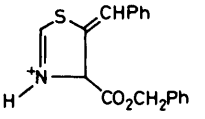


(27) R = H, R^1 = CH_2OMe
(28) R = H, R^1 = CH_2OCH_2Ph
(29) R = R^1 = Me
(30) R = H, R^1 = Ph



(31)

It seemed more likely that the desired C-3 free carboxylic acid would be accessible by hydrogenolysis of the corresponding benzyl ester. Accordingly, a synthesis of the required α-bromoallenic benzyl ester (14) was undertaken. Unfortunately, the previously described process involving the quenching of an acetylenic anion by a glyoxylic ester was unsuccessful in this case. The problem was associated with an inability to obtain a stable sample of the desired aldehydic-ester (15), distillation of benzyl glyoxylate monohydrate giving a product which rapidly underwent polymerisation. An alternative route, based on the work of Bestmann and Hartung [5] proved more satisfactory. Thus, reaction of benzyloxycarbonylbromomethylenetriphenylphosphorane (16) with 3-methoxypropionyl chloride [6] in dry tetrahydrofuran (THF) in the presence of an equivalent of triethylamine gave a good yield of benzyl 2-bromo-5-methoxypenta-2,3-dienoate (14). Treatment of the 4-mercaptoazetidin-2-one (1) with the α-bromoallenic ester (14) in the presence of potassium carbonate as previously described gave the two epimeric penam esters (17) and (18).

It proved possible, using the appropriate acid chlorides, to prepare in good yield the α-bromoallenic esters (19)—(21) which showed differing behaviour when treated with the 4-mercaptoazetidin-2-one (1). The reaction with benzyl 5-benzyloxy-2-bromopenta-2,3-dienoate (19) in the presence of potassium carbonate as previously described gave the 3-*S*-2-benzyloxyethylidenepenam ester (22), none of the 3*R*-epimer being isolated. By contrast both the C-3 epimeric 2-isopropylidenepenams (23) and (24) were obtained, but only in very poor yield, from the reaction with benzyl 2-bromo-4-methylpenta-2,3-dienoate (20). A variety of reaction conditions and bases (potassium t-butoxide and 1,5-diazabicyclo[4.3.0]non-5-ene) were examined but the best yields, albeit low, were obtained using 1,1,3,3-tetramethylguanidine in DMF at 0 °C. Even these conditions failed in the reaction with benzyl 2-bromo-4-phenylbuta-2,3-dienoate (21), the mercaptoazetidinone (1) apparently being destroyed before it could add to the allene. The silica gel-catalysed Michael addition of the 4-mercaptoazetidin-2-one (1) to an acetylenic ester was reported in an earlier paper [7] and it seemed reasonable to suppose a similar effect would operate with an allenic ester. In the event, the reaction with the allenic ester (21) proceeded well in the presence of silica gel to give the intermediate bromoester (25) which was cyclised to a single 3*S*-epimer of the 2-benzylidenepenam ester (26) in low yield.

Examination of the n.m.r. spectra of these penams revealed an interesting long-range coupling effect. The penams having the 3*R*-configuration [(11), (18), and (24)] exhibited coupling between the 3-H and 6-H which was not observed in the 3*S*-epimers. This effect

Antibacterial activity *

Bacterium	(27)	(28)	(29)	(30)	Penicillin V
Staphylococcus aureus Oxford	0.5	0.5	25	50	0.05
Staphylococcus aureus Russell †		100	50	100	>500
β-Haemolytic streptococcus	0.2	0.2	100	50	0.01
Streptococcus faecalis	50	25	>100	>100	2.5
Escherichia coli	>100	>100	>100	100	125
Klebsiella aerogenes	>100	>100	>100	>100	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.

was most marked (J 1 Hz) in the case of the isopropylidenepenam ester (23) and was confirmed by a decoupling experiment.

Deprotection of the benzyl esters of the penams having the natural, 3*S*, penicillin stereochemistry [(17), (22), (23), and (26)] was achieved by hydrogenolysis over 10% palladium on charcoal catalyst in aqueous THF to give the corresponding carboxylic acids [(27), (28), (29), and (30)]. The antibacterial activity of these compounds along with that of penicillin V are shown in the Table. Although the compounds exhibited some antibacterial activity it was of a low order, none of the compounds being better than penicillin V. None of the compounds showed any significant β-lactamase inhibition properties.

EXPERIMENTAL

General procedures were as in Part 1 [7] except where indicated otherwise. Accurate mass measurements of molecular ions were carried out on compounds shown to be homogeneous by thin layer chromatography.

t-Butyl 2-Hydroxy-5-methoxypent-3-ynoate (7).—n-Butyllithium (8.2 ml of a 2.4M solution in n-hexane) was added dropwise in 5 min to a stirred solution of methyl prop-2-ynyl ether (1.4 g) in dry THF (20 ml) with cooling at −20 °C. After being stirred at −20 °C for a further 5 min the mixture was cooled to −70 °C and treated dropwise with a solution of freshly distilled t-butyl glyoxylate (2.6 g) in dry THF (10 ml) during 15 min. The mixture was stirred at −70 °C for a further 15 min and then treated with glacial acetic acid (1.8 ml). Stirring was continued for a further 10 min whilst the temperature of the mixture rose to −20 °C. The mixture was poured into brine and extracted with ethyl acetate (3 × 20 ml). The combined organic layers were washed with brine (2 × 20 ml), dried ($MgSO_4$), and evaporated to give a crude oil. Chromatography of the crude product gave the desired acetylenic alcohol (7) (1.04 g) as an oil, $\nu_{max.}$ (film) 3 450 and 1 740 cm^{-1}; $\delta(CCl_4)$ 1.55 (9 H, s), 3.38 (4 H, s overlying a broad signal, broad signal 1 H exch. D_2O), 4.15 (2 H, d, J 2 Hz), 4.69br (1 H, s, sharpens to t, J 2 Hz, on exch. D_2O).

t-Butyl 2-Bromo-5-methoxypent-3-ynoate (8).—Triphenylphosphine (288 mg) was added portionwise in 5 min to a stirred solution of the acetylenic alcohol (7) (200 mg) and freshly distilled carbon tetrabromide (365 mg) in dry benzene (5 ml), the temperature being maintained at *ca.* 20 °C by use of a water-bath. The reaction mixture was stirred at room temperature for 2 h. The benzene liquors were decanted and the residual gum was re-extracted with dry benzene (5 ml). The combined benzene extracts were evaporated and chromatographed to give the bromoacetylenic ester (8) (81 mg) as an oil, $\nu_{max.}$ 1 740 cm^{-1}; $\delta(CCl_4)$ 1.55 (9 H, s), 3.45 (3 H, s), 4.25 (2 H, d, J 2 Hz), and 4.82 (1 H, t, J 2 Hz).

t-Butyl 2-Bromo-5-methoxypenta-2,3-dienoate (9).—A mixture of the bromoacetylenic ester (8) (250 mg) and basic alumina (Brockmann Activity I) (500 mg) in chloroform (5 ml) was stirred at room temperature for 3 h. The alumina was filtered off and washed with a little chloroform. The combined filtrates were evaporated to give the bromoallenic ester (9) (230 mg) as an oil, $\nu_{max.}$ 1 960 and 1 720 cm^{-1}; $\delta(CCl_4)$ 1.49 (9 H, s), 3.41 (3 H, s), 4.17 (2 H, d, J 7 Hz), and 5.67 (1 H, t, J 7 Hz).

Benzyloxycarbonylbromomethylenetriphenylphosphorane (16).—A solution of bromine (14.3 g) in water (1 500 ml) was added dropwise to a stirred suspension of benzyloxycarbonylmethyltriphenylphosphonium bromide (prepared from benzyl bromoacetate and triphenylphosphine in refluxing benzene) (44.0 g) in water (800 ml). After the addition was complete the mixture was diluted with ethyl acetate (500 ml) and made alkaline with 40% sodium hydroxide solution. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 200 ml). The combined extracts were washed with water, dried ($MgSO_4$), and evaporated to give a gum which on trituration with ether, gave the *phosphorane* (16) (29.3 g) as an off-white solid, m.p. 127—128 °C, $\nu_{max.}$ 1 630 and 1 590sh cm^{-1} (Found: C, 67.0; H, 4.6; Br, 16.1; P, 6.3. $C_{27}H_{22}BrO_2P$ requires C, 66.3; H, 4.5; Br, 16.4; P, 6.3%).

Benzyl 2-Bromo-5-methoxypenta-2,3-dienoate (14).—A solution of 3-methoxypropionyl chloride (612 mg) in dry THF (10 ml) was added dropwise during 15 min to a stirred solution of benzyloxycarbonylbromomethylenetriphenylphosphorane (2.45 g) and triethylamine (505 mg) in dry THF (25 ml) at room temperature. The mixture was then stirred at room temperature for a further 15 min and filtered. The filtrate was evaporated to give a crude oil which was extracted with ethyl acetate–light petroleum (b.p. 60—80 °C) mixtures (2 : 8; 3 × 25 ml). The combined extracts were concentrated and chromatographed to give the desired *bromoallenic ester* (14) (1.08 g) as an oil, $\nu_{max.}$ (film) 1 960 and 1 730 cm^{-1}; $\delta(CCl_4)$ 3.05 (3 H, s), 3.85 (2 H, d, J 6 Hz), 5.00 (2 H, s), 5.60 (1 H, t, J 6 Hz), and 7.21 (5 H, s) (Found: MH^+, 297.0118. $C_{13}H_{14}BrO_3$ requires MH, 297.0127).

The following bromoallenic esters were similarly prepared from the appropriate acid chloride, the reaction times and temperatures being given in brackets: (*a*) benzyl 5-benzyloxy-2-bromopenta-2,3-dieneoate (19) (90%) (15 min at room temperature) an oil, $\nu_{max.}$ (film) 1 960 and 1 730 cm^{-1}; $\delta(CCl_4)$ 4.02 (2 H, d, J 6 Hz), 4.35 (2 H, s), 5.08 (2 H, s), 5.70 (1 H, t, J 6 Hz), and 7.30 (10 H, s); (*b*) *benzyl 2-bromo-4-methylpenta-2,3-dienoate* (20) (50%) (4 h at 50 °C) an oil, $\nu_{max.}$ (film) 1 950 and 1 730 cm^{-1}; $\delta(CCl_4)$ 1.80 (6 H, s), 5.17 (2 H, s), and 7.32 (5 H, s) (Found: M^+, 280.0126. $C_{13}H_{13}BrO_2$ requires M, 280.0099); *benzyl 2-bromo-4-phenylbuta-2,3-dienoate* (21) (73%) (15 min at 0 °C) an oil, $\nu_{max.}$ (film) 1 940 and 1 730 cm^{-1}; $\delta(CCl_4)$ 5.02 (2 H, s), 6.48 (1 H, s), and 7.19 (10 H, s) (Found: M^+, 328.0091. $C_{17}H_{13}BrO_2$ requires M, 328.0098).

Reaction of the 4-Mercaptoazetidinone (1) *with Bromoallenic Esters.*—(a) *t-Butyl 2-bromo-5-methoxypenta-2,3-dienoate* (9). A stirred solution containing the 4-mercaptoazetidinone (1) (200 mg) and the bromoallenic ester (9) (230 mg) in dry DMF (2 ml) was treated, portionwise during 10 min at room temperature, with finely powdered anhydrous potassium carbonate (55 mg). The mixture was stirred at room temperature for a further 20 h, diluted with ethyl acetate (20 ml), and washed with brine (3 × 5 ml). The dried ($MgSO_4$) organic layer was evaporated and the crude product chromatographed to give two products. The less polar product (3S,5R,6R)-*t-butyl 2-(2-methoxyethylidene)-6-phenoxyacetamidopenam-3-carboxylate* (10) (57 mg) was obtained as a gum, $[\alpha]_D^{22}$ +63.4° (*c* 1 in $CHCl_3$); $\nu_{max.}$ 3 400, 1 795, 1 735, 1 690, and 1 640sh cm^{-1}; δ(90 MHz) 1.47 (9 H, s), 3.30 (3 H, s), 3.60—4.21 (2 H, m), 4.52 (2 H, s), 5.38 (1 H, slightly broadened s), 5.59 (1 H, d, J 4 Hz), 5.68—5.90 (2 H, m), and 6.8—7.5 (6 H, m) (Found: M^+, 434.1516.

$C_{21}H_{26}N_2O_6S$ requires *M*, 434.1511). The more polar product (3R,5R,6R)-*t-butyl* 2(2-*methoxyethylidene*)-6-*phenoxyacetamidopenam*-3-*carboxylate* (11) (56 mg) was also obtained as a gum, $[\alpha]_D^{22}$ +213.8° (*c* 1 in $CHCl_3$); $\nu_{max.}$ 3 400, 1 795, 1 735, 1 690, and 1 640sh cm^{-1}; δ(90 MHz) 1.50 (9 H, s), 3.30 (3 H, s), 3.65—4.15 (2 H, m), 4.53 (s) and 4.61 (slightly broadened s) (together 3 H), 5.30 (1 H, d, *J* 4 Hz), 5.62 (1 H, slightly broadened dd, *J* 4 and 9 Hz), 5.94 (1 H, dt, *J* 2 and 7 Hz), and 6.85—7.40 (6 H, m) (Found: M^+, 434.1507. $C_{21}H_{26}N_2O_6S$ requires *M*, 434.1511).

(b) *Benzyl* 2-*bromo*-5-*methoxypenta*-2,3-*dieneoate* (14). A stirred solution containing the 4-mercaptoazetidinone (1) (504 mg) and the bromoallenic ester (14) (643 mg) in dry DMF (4 ml) was treated, portionwise during 10 min at room temperature, with finely powdered anhydrous potassium carbonate (138 mg). The mixture was stirred at room temperature for a further 16 h and worked up as in example (a) to give two products. The less polar product (3S,5R,6R)-*benzyl* 2-(2-*methoxyethylidene*)-6-*phenoxyacetamidopenam*-3-*carboxylate* (17) (130 mg) was obtained as a gum, $[\alpha]_D^{22}$ +120° (*c* 1 in $CHCl_3$); $\nu_{max.}$ 3 450, 1 795, 1 740, 1 685, and 1 635sh cm^{-1}; δ(90 MHz) 3.15 (3 H, s), 3.77 (1 H, dd, *J* 6 and 13 Hz), 3.98 (1 H, dd, *J* 7 and 13 Hz), 4.46 (2 H, s), 5.11 (2 H, s), 5.45—5.85 (4 H, m), and 6.7—7.5 (11 H, m) (Found: M^+, 468.1357. $C_{24}H_{24}N_2O_6S$ requires *M*, 468.1355). The more polar product (3R,5R,6R)-*benzyl* 2-(2-*methoxyethylidene*)-6-*phenoxyacetamidopenam*-3-*carboxylate* (18) (79 mg) was also obtained as a gum, $[\alpha]_D^{22}$ +198° (*c* 1 in $CHCl_3$); $\nu_{max.}$ 3 450, 1 795, 1 745, 1 690, and 1 640sh cm^{-1}; δ(90 MHz) 3.10 (3 H, s), 3.67 (1 H, dd, *J* 6 and 14 Hz), 3.84 (1 H, dd, *J* 6 and 14 Hz), 4.46 (2 H, s), 4.73 (1 H, br s), 5.17 (2 H, s), 5.24 (1 H, d, *J* 4 Hz), 5.62 (1 H, ddd, *J* 4, 9 and *ca.* 1 Hz), 5.82 (1 H, ddd, *J* 2, 6 and 6 Hz), and 6.75—7.4 (11 H, m). Irradiation of either the ddd signal at 5.62 or that at 5.82 resulted in a sharpening of the broad singlet at 4.73 p.p.m. Irradiation of the broad singlet at 4.73 p.p.m. caused the ddd signal at 5.82 p.p.m. to collapse to a dd, *J* 6 and 6 Hz. The expected collapse of the ddd at 5.62 could not be observed clearly due to proximity of the irradiating and observing frequencies (Found: M^+, 468.1347. $C_{24}H_{24}N_2O_6S$ requires *M*, 468.1355).

(c) *Benzyl* 5-*benzyloxy*-2-*bromopenta*-2,3-*dienoate* (19). A stirred solution containing the 4-mercaptoazetidinone (1) (2.07 g) and the bromoallenic ester (19) (3.37 g) in dry DMF (20 ml) was treated, portionwise during 15 min at room temperature, with finely powdered anhydrous potassium carbonate (565 mg). After being stirred for a further 18 h, the mixture was worked up as in example (a) to give (3S,5R,6R)-*benzyl* 2-(2-*benzyloxycthylidene*)-6-*phenoxyacetamidopenam*-3-*carboxylate* (22) (880 mg) as a gum, $[\alpha]_D^{22}$ +105° (*c* 1 in $CHCl_3$); $\nu_{max.}$ 3 380, 1 795, 1 745, 1 690, and 1 640 cm^{-1}; δ(90 MHz) 3.90 (1 H, dd, *J* 6 and 13 Hz), 4.11 (1 H, dd, *J* 7 and 13 Hz), 4.37 (2 H, s), 4.50 (2 H, s), 5.10 (2 H, s), 5.49 (1 H, d, *J* 1 Hz), 5.54 (1 H, d, *J* 4 Hz), 5.70—5.90 (2 H, m), and 6.80—7.50 (16 H, m). Irradiation at 4.01 p.p.m. caused a simplification of the multiplet at 5.7—5.9 p.p.m. while irradiation of the latter caused the two double doublets at 3.90 and 4.11 to collapse to an AB quartet (*J* 13 Hz) (Found: M^+, 544.1678. $C_{30}H_{28}N_2O_6S$ requires *M*, 544.1670).

(d) *Benzyl* 2-*bromo*-4-*methylpenta*-2,3-*dieneoate* (20). To a stirred solution containing the 4-mercaptoazetidinone (1) (252 mg) and the bromoallenic ester (20) (309 mg) in dry DMF (2 ml) was added, dropwise during 10 min with cooling at 0 °C, a solution containing 1,1,3,3-tetramethylguanidine (115 mg) in dry DMF (1 ml). The mixture was stirred at 0 °C for a further 1 h and worked up as in example (a) to give two products. The less polar product, (3S,5R,6R)-*benzyl* 6-*phenoxyacetamido*-2-*isopropylidenepenam*-3-*carboxylate* (23) (22 mg) as a solid, m.p. 105—106 °C (needles from ethyl acetate–light petroleum), $[\alpha]_D^{22}$ +111.4° (*c* 1 in $CHCl_3$); $\nu_{max.}$ 3 380, 1 795, 1 745 and 1 690 cm^{-1}; δ(90 MHz) 1.70 and 1.75 (6 H, each s), 4.45 (2 H, s), 5.22 (2 H, s), 5.48 (1 H, s), 5.69 (1 H, d, *J* 4 Hz), 5.89 (1 H, dd, *J* 4 and 10 Hz), and 6.9—7.6 (11 H, m) (Found: C, 63.5; H, 5.3; N, 6.2; S, 7.4%; M^+, 452.1399. $C_{24}H_{24}N_2O_5S$ requires C, 63.7; H, 5.3; N, 6,2; S, 7.1%; *M*, 452.1406). The more polar product (3R,5R,6R)-*benzyl* 6-*phenoxyacetamido*-2-*isopropylidenepenam*-3-*carboxylate* (24) (24 mg) was obtained as a gum, $\nu_{max.}$ 3 380, 1 795, 1 745, and 1 690 cm^{-1}; δ(90 MHz) 1.61 (3 H, s), 1.81 (3 H, s), 4.48 (2 H, s), 4.61br (1 H, s), 5.05—5.15 (3 H, m), 5.60 (1 H, ddd, *J* 1, 4 and 9 Hz), and 6.7—7.5 (11 H, m). Irradiation of the broadened singlet at 4.61 p.p.m. caused the ddd at 5.60 to collapse to a dd, *J* 4 and 9 Hz (Found: M^+, 452.1400. $C_{24}H_{24}N_2O_5S$ requires 452.1406).

(e) *Benzyl* 5-*bromo*-4-*phenylbuta*-2 3-*dienoate* (21). The 4-mercaptoazetidinone (1) (4.85 g) was added portionwise during 10 min to a stirred mixture of bromoallenic ester (21) (6.33 g) and silica gel (100 g; Merck Kieselgel type 60) in dry DMF (125 ml) and dry THF (125 ml) at room temperature. After being stirred at room temperature for a further 30 min the mixture was filtered and the residue washed with ethyl acetate (250 ml). The combined filtrates were washed with brine, dried ($MgSO_4$), evaporated, and chromatographed to give the bromoester (25) (3.17 g) as an amorphous solid, $\nu_{max.}$ 1 780, 1 740sh, and 1 690 cm^{-1}; δ 4.60 (2 H, s), 5.2—5.4 (3 H, m), 5.57—5.87 (2 H, m), 6.9—7.5 (17 H, m), and 7.83 (1 H, d, *J* 9 Hz). The bromoester (25) (2.97 g) was stirred with finely powdered anhydrous potassium carbonate (353 mg) in dry DMF (30 ml) at room temperature for 7 h. Work-up as for example (a) afforded (3S,5R,6R)-*benzyl* 2-*benzylidene*-6-*phenoxacetamidopenam*-3-*carboxylate* (26) (168 mg) as an amorphous solid, $[\alpha]_D^{22}$ +112.4° (*c* 1 in $CHCl_3$); $\nu_{max.}$ 3 400, 1 795, 1 740, and 1 690 cm^{-1}; δ(90 MHz) 4.50 (2 H, s), 5.07 (2 H, s), 5.50 (1 H, d, *J* 4 Hz)' 5.64 (1 H, d, *J* 1½ Hz), 5.76 (1 H, dd, *J* 4 and 9 Hz), and 6.6—7.4 (17 H, m) [Found: $(M - 191)^+$, 309.0816 corresponding to the ion (31). $C_{18}H_{15}NO_3S$ requires 309.0823].

Preparation of Penam Free Acids.—(3S,5R,6R)-2-(2-*Methoxyethylidene*)-6-*phenoxyacetamidopenam*-3-*carboxylic acid* (27). The penam ester (17) (300 mg) was dissolved in a mixture of THF (8 ml) and water (2 ml) and hydrogenated over 10% palladium–charcoal catalyst (300 mg) at s.t.p. for 30 min. The mixture was filtered through a bed of Kieselguhr and the residue washed with a little THF. The combined filtrate were evaporated to low volume and diluted with ethyl acetate (10 ml) and water (10 ml). The pH of the vigorously stirred, ice-bath cooled, mixture was adjusted to 7 using saturated aqueous sodium hydrogencarbonate. The aqueous layer was separated and the organic layer was extracted with water (10 ml). The combined aqueous layers were washed with ethyl acetate (5 ml). The pH of a vigorously stirred, ice-bath cooled, mixture of the aqueous layer and ethyl acetate (10 ml) was adjusted to 2.0 using N-hydrochloric acid. The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 × 5 ml). The combined organic layers

were washed with brine (2 × 5 ml), dried ($MgSO_4$), and evaporated to give the desired acid (27) (112 mg), a hydrate, as an amorphous solid, $[\alpha]_D^{22}$ +122 (*c* 1 in $CHCl_3$); $\nu_{max.}$ 3 440, 3 600—2 300br, 1 795, 1 735, and 1 690 cm^{-1}; δ(90 MHz) 3.37 (3 H, s) 4.08 (2 H, d, *J* 6 Hz), 4.51 (2 H, s), 5.50—5.86 (4 H, m), and 6.8—7.6 (9 H, m, 3 H readily exch. D_2O).

Similarly prepared were the following penam acids: (a) (3S,5R,6R)-2-(2-benzyloxyethylidene)-6-phenoxyacetamidopenam-3-carboxylic acid (28) (31% an amorphous solid, $[\alpha]_D^{22}$ +131° (*c* 1 in $CHCl_3$); $\nu_{max.}$ 3 380, 3 500—2 300, 1 795, 1 735, 1 690 cm^{-1}; δ 4.10 (2 H, d, *J* 6 Hz), 4.44 and 4.48 (4 H, each s), 5.55—6.05 (4 H, m), 6.80—7.60 (11 H, m), and 9.40 (1 H, s, exch. D_2O).

(b) (3S,5R,6R)-6-phenoxyacetamido-2-isopropylidenepenam-3-carboxylic acid (29) (38%) an amorphous solid, $[\alpha]_D^{22}$ +88.4° (*c* 1 in $CHCl_3$); $\nu_{max.}$ 3 380, 3 500—2 300br, 1 795, 1 730, and 1 690 cm^{-1}; δ 1.73 (3 H, s), 1.84 (3 H, s), 4.45 (2 H, s), 5.44 (1 H, s), 5.65 (1 H, d, *J* 5 Hz), 5.85 (1 H, dd, *J* 5 and 9 Hz), 6.8—7.6 (6 H, m), and 9.50 (1 H, s, exch. D_2O).

(c) (3S,5R,6R)-2-benzylidene-6-phenoxyacetamidopenam-3-carboxylic acid (30) (14%) a hydrate as an amorphous solid, $[\alpha]_D^{22}$ +130.6° (*c* 1 in $CHCl_3$); $\nu_{max.}$ 3 400, 3 500—2 400br, 1 795, 1 730, and 1 690 cm^{-1}; δ 4.66 (2 H, s), 5.55—6.05 (3 H, m), 6.8—7.7 (12 H, m), and 8.25br (2 H, s, exch. D_2O).

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