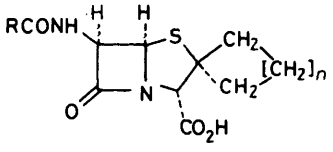
The Chemistry of 4-Mercaptoazetidin-2-ones. Part 4.[1] Synthesis of Cyclopropanespiro-2-bisnorpenicillanic Acids

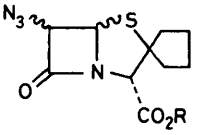
By Neal F. Osborne, Beecham Pharmaceuticals Research Division, Brockham Park, Betchworth, Surrey RH3 7AJ

Reaction of the 4-mercaptoazetidin-2-one (6) with benzyl 2-bromocyclopropylideneacetate (7) gave the C-3 epimeric cyclopropanespiro-2-bisnorpenicillanates (9) and (10). Standard procedures were used to convert the 3*S*-epimer into the ampicillin analogue (15). Hydrogenolysis of the esters (9) and (15) gave the cyclopropanespiro-2-bisnorpenicillanic acids (13) and (16) both of which had antibacterial properties similar to those of the corresponding penicillins.

THE synthesis of cycloalkanespiro-2-bisnorpenicillins has been the subject of several recent papers. Cycloaddition of azidoacetyl chloride to a suitably substituted thiazoline was used to prepare penicillins in which the methyl groups were replaced by spirocyclobutane (1) and spirocyclopentane (2) rings.[2] The same two ring systems together with the spirocyclohexane (3) homologue were synthesised by another group [3] using the classical Sheehan approach. More recently a third method,[4] involving the formation of the thiazolidine ring on a preformed azetidinone, has been used to prepare the cyclopentanespiro-2-penams (4). The present report describes the synthesis of representatives of an important member of this series having the cyclopropanespiro-2-penam ring system (5).



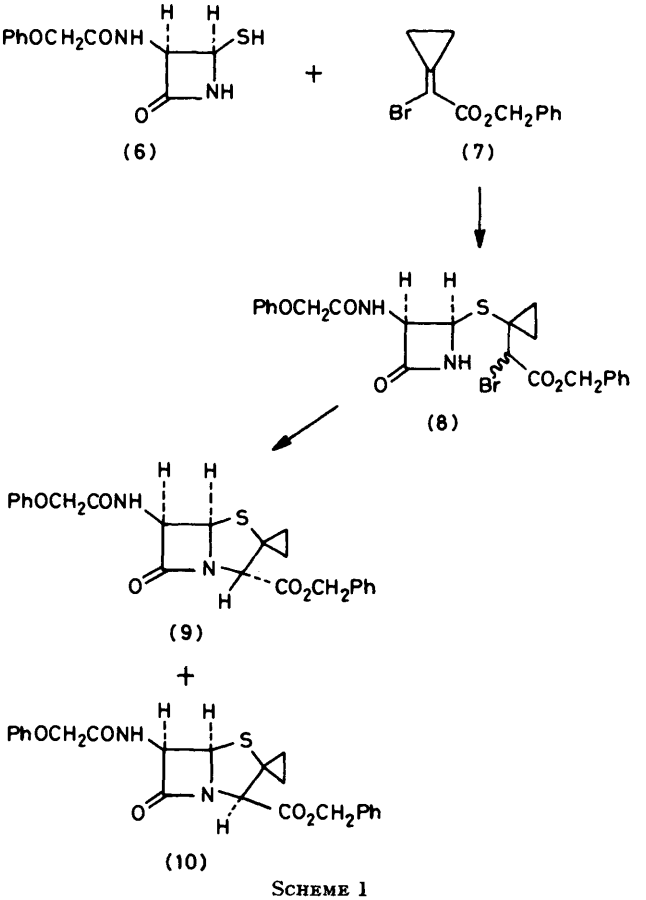
(1) *n* = 1
(2) *n* = 2
(3) *n* = 3
(5) *n* = 0



(4)

The method chosen was similar in concept to that successfully used in these laboratories for the synthesis of bisnorpenicillins [5] and 2-alkylidenepenams [1] and is shown in Scheme 1. By contrast with the aforementioned workers, who all used total synthesis, our approach was based on the previously described, penicillin-derived, 4-mercaptoazetidin-2-one (6). This method, particularly attractive since it required minimal handling of the sensitive cyclopropane ring, required a synthesis of the 2-bromocyclopropylideneacetic ester (7).

The use of the readily available cyclopropanone ethyl hemiacetal (11) as a convenient cyclopropanone synthon was demonstrated by its reaction with Grignard reagents [6] and it was hoped that this utility could be extended to a Wittig reaction. The hemiacetal (11) when heated with the bromomethylenetriphenylphosphorane (12) [1] in refluxing benzene containing a small quantity of benzoic acid gave the desired olefin (7) contaminated with benzyl bromoacetate (40—50%) and other minor impurities. Purification of the olefin (7) by vacuum distillation could not be achieved without considerable losses due to decomposition. It seemed likely that the impurity arose by reaction of the ylide (Scheme 2) with the ethanol generated in the process,

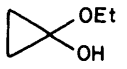


(6) (7) (8) (9) (10)

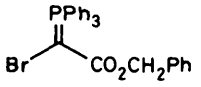
SCHEME 1

a fact borne out in a separate experiment in which the ylide was heated in benzene containing a little ethanol. The experiment was therefore repeated under conditions in which the ethanol produced was removed by azeotropic distillation in the hope of suppressing the competing reaction. The material obtained in this way contained only 10—20% of benzyl bromoacetate and proved to be of sufficient purity for further synthetic work.

Reaction of the 4-mercaptoazetidin-2-one (6) with the olefin (7) in dimethylformamide (DMF) in the presence of a catalytic amount of potassium carbonate gave an approximately 1 : 1 mixture of the stereoisomers of the

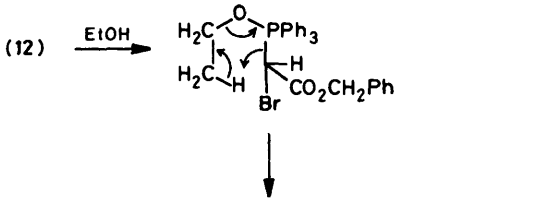


(11)



(12)

bromoester (8). Cyclisation of the bromoester (8) was achieved using potassium carbonate (10 equiv.) in hexamethylphosphoric triamide (HMPT) when the 3*S*-(9) and 3*R*-(10) penam esters were obtained in 25 and 3% yields respectively. Lower yields of cyclised products were obtained when other solvents (*e.g.* DMF) or other bases (*e.g.* potassium t-butoxide) were employed. More conveniently the process could be carried out as a one-pot reaction in HMPT when the penam esters (9) and (10) were obtained in 15 and 4% overall yields. The assignment of the C-3 stereochemistry was based on n.m.r. data. Thus the C-3 protons of the penam having the 3*S*-configuration (9) appeared at 4.28 p.p.m. compared with 3.58 p.p.m. for its 3*R*-epimer (10), a downfield shift of 0.70 p.p.m. which was in accord with previously examined penams.[1,5,7] Furthermore, a long-range coupling ($J \simeq 1$ Hz) was observed between 3-H and 6-H

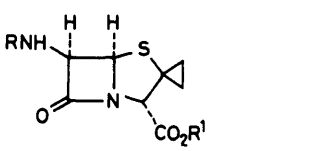


SCHEME 2

for 3*R*-epimer (10), a feature in common with a series of (3*R*)-2-alkylidenepenam esters.[1]

Catalytic hydrogenation of the penam ester (9) in aqueous tetrahydrofuran (THF) gave the free acid (13) which showed antibacterial properties (Table) comparable with those of penicillin V.

Encouraged by this result we undertook a preparation of the ampicillin analogue (16) in the hope of improving the activity against Gram-negative bacteria. Accordingly the penam ester (9) was treated with phosphorus pentachloride in methylene chloride containing *N*-methylmorpholine followed by methanol and water to give the amine (14) isolated as its toluene-*p*-sulphonic acid salt. Acylation of the amine (14) with D-phenylglycyl chloride hydrochloride in the presence of *N*,*N*-dimethylaniline gave the desired penam ester (15) which yielded the amino-acid (16) on hydrogenolysis.



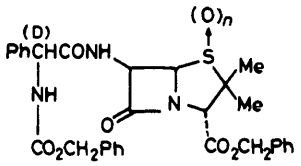
(13) R = $PhOCH_2CO$, R^1 = H

(14) R = H, R^1 = CH_2Ph

(15) R = (D) PhCHCO, R^1 = CH_2Ph (NH_2)

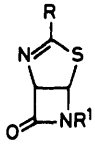
(16) R = (D) PhCHCO, R^1 = H (NH_2)

(24) R = (DL) PhCHCO, R^1 = CH_2Ph ($NHCO_2CH_2Ph$)



(17) *n* = 0

(18) *n* = 1



(19) R = (D) PhCH— ($NHCO_2CH_2Ph$)

R^1 = $C(:CMe_2)CO_2CH_2Ph$

(20) R = (L) PhCH— ($NHCO_2CH_2Ph$)

R^1 = $C(:CMe_2)CO_2CH_2Ph$

(21) R = (D) PhCH— ($NHCO_2CH_2Ph$)

R^1 = H

In general the spirocyclopropane analogue (16) had similar antibacterial activity (Table) to that of ampicillin against penicillin-sensitive Gram-positive and Gram-negative bacteria. However, the superior activity against *Staphylococcus aureus* Russell indicated that compound (16) was slightly more stable than ampicillin to the staphylococcal β-lactamase.

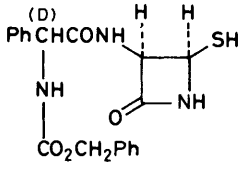
An alternative route to the ampicillin analogue (16) starting from a mercaptoazetidinone bearing the desired acylamino side-chain was also investigated. This route would be advantageous in that it circumvents the poor yielding stage in which the phenoxyacetyl group was removed [(9)→(14)]. Reaction of benzyl 6-amino-

Antibacterial activity *

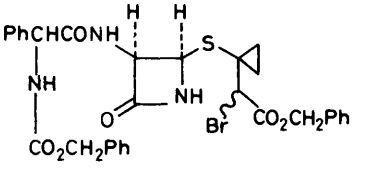
Bacterium	(13)	Penicillin V	(16)	Ampicillin
Escherichia coli NCTC 10418	500	125	10	2.5
Klebsiella aerogenes	>500	250	100	50
Proteus mirabilis	>500	125	5.0	1.0
Staphylococcus aureus Oxford	0.4	0.2	0.1	0.1
Staphylococcus aureus Russell †	>100	>100	25	125
Streptococcus faecalis	6.2	3.1	1.0	0.5
β-Haemolytic streptococcus	≤0.1	≤0.1	0.02	0.02

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

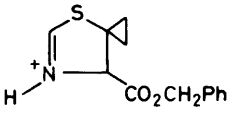
penicillanate with the mixed anhydride derived from *N*-benzyloxycarbonyl-D-α-phenylglycine and methyl chloroformate gave the penicillanate (17) which, on oxidation with *m*-chloroperbenzoic acid, gave the sulphoxide (18). The sulphoxide (18) when heated with trimethyl phosphite [8] in refluxing benzene (48 h) or refluxing toluene (2 h) followed by treatment with triethylamine at room temperature afforded the D-thiazoloazetidinone (19) (43%) and its L-epimer (20) (8%). Oxidative removal of the nitrogen substituent of (19) using potassium permanganate proceeded without side-chain epimerisation to give the D-thiazoloazetidinone (21), hydrolysis of which gave the 4-mercaptoazetidin-2-one (22). Base-



(22)



(23)



(25)

catalysed addition of the 4-mercaptoazetidin-2-one (22) to the olefin (7) gave the bromoester (23) which was cyclised to the penam (24). Unfortunately, it was evident from the complexity of the n.m.r. spectra that epimerisation of the phenylglycine side-chain had occurred during the last two stages of the synthesis.

To conclude, the replacement of the C-2 methyl groups in penicillins by a spirocyclopropane group had no marked effect on the antibacterial properties of the molecule. This result together with similar findings for other cycloalkanespirobisnorpenicillins [2,3] suggests a reasonable tolerance in terms of steric and ring strain requirements at the C-2 position for antibacterial activity in penicillins.

EXPERIMENTAL

General procedures were as in Part 1 [9] except where indicated otherwise. Accurate mass measurements of molecular ions were carried out on compounds shown to be homogeneous by t.l.c.

Benzyl 2-Bromocyclopropylideneacetate (7).—To a slowly distilling mixture of 1-ethoxycyclopropanol (11) (13.1 g) and benzoic acid (3.14 g) in dry benzene (500 ml) was added dropwise a solution of benzyloxycarbonylbromomethylenetriphenylphosphorane (12) (62.8 g) in dry benzene (600 ml) to maintain an approximately constant volume of reaction mixture. After the addition was complete (3.5 h) the mixture was cooled, evaporated, and the residual oil extracted with ethyl acetate–light petroleum (1 : 9; 4 × 300 ml). The combined extracts were concentrated and chromatographed to give an oil which partially crystallised (10.0 g). Examination of the product by n.m.r. spectroscopy revealed the presence of benzyl bromoacetate (10—20%) but this material proved to be of sufficient purity for further synthetic work. However, rapid distillation of the mixture gave pure benzyl 2-bromocyclopropylideneacetate (7), b.p. 115—120 °C (0.01 mmHg), $\nu_{max.}$ (CCl_4) 1.10—1.92 (4 H, m), 5.27 (2 H, s), and 7.39 (5 H, s).

1-[(2R,3R)-4-*Oxo*-3-*phenoxyacetamidoazetidin*-2-*ylthio*]-1-(1-*benzyloxycarbonyl*-1-*bromomethyl*)*cyclopropane* (8).—Finely powdered anhydrous potassium carbonate (87 mg) was added, portionwise during 5 min, to a stirred mixture of the 4-mercaptoazetidinone (6) (1.59 g) and benzyl 2-bromocyclopropylideneacetate (7) (1.69 g) in dry DMF (20 ml). After being stirred for a further 30 min at room temperature, the mixture was diluted with ethyl acetate (80 ml) and washed with brine (3 × 15 ml). The dried ($MgSO_4$) organic layer was evaporated and the residue chromatographed to give the bromoester (8) (1.70 g), a 1 : 1 mixture of stereoisomers, as an amorphous solid, $\nu_{max.}$ 3 430, 1 780, 1 740, and 1 690 cm^{-1}; δ(90 MHz) 1.04—1.30 (4 H, m), 4.19 (½ H, s), 4.24 (½ H, s), 4.44 (2 H, s), 4.87 (½ H, d, *J* 5 Hz), 5.08—5.19 (2½ H, m), 5.30—5.55 (1 H, m), 6.48br (1 H, s, exch. D_2O), 6.78—7.36 (11 H, m).

(3S,5R,6R) *and* (3R,5R,6R)-*Benzyl* 6-*Phenoxyacetamidocyclopropanespiro*-2-*bisnorpenicillanates* (9) *and* (10).—(*a*) A mixture of the bromoester (8) (2.0 g) and finely powdered anhydrous potassium carbonate (2.56 g) in dry HMPT (30 ml) was stirred at room temperature for 8 h. The mixture was diluted with ethyl acetate (150 ml) and washed with brine (3 × 40 ml). The dried ($MgSO_4$) organic layer was evaporated and the residue carefully chromatographed to give two products. The less polar product, the 3S-*epimer* (9) (427 mg) was obtained as a gum, $[\alpha]_D^{22}$ +74° (*c* 1 in $CHCl_3$); $\nu_{max.}$ 3 420, 1 795, 1 745, and 1 690 cm^{-1}; δ(90 MHz) 0.55—1.30 (4 H, m), 4.28 (1 H, s), 4.50 (2 H, s), 5.13 (2 H, s), 5.53 (1 H, d, *J* 4 Hz), 5.70 (1 H, dd, *J* 4 and 8 Hz), 6.76—7.36 (11 H, m); ^{13}C ($CDCl_3$) (80 MHz) fully proton decoupled spectrum had lines at the following p.p.m. downfield relative to $SiMe_4$ (multiplicity of off-resonance spectrum shown in brackets) 7.08 (t), 18.73 (t), 37.40 (s), 59.21 (d), 67.19 (d + t), 67.52 (t), 68.44 (d), 114.75 (d), 122.36 (d), 128.32 (d), 128.66 (d), 129.81 (d), 134.96 (s), 156.99 (s), 166.99 (s), 167.74 (s), and 173.83 (s) (Found: M^+, 438.1252. $C_{23}H_{22}N_2O_5S$ requires *M*, 438.1250). The more polar product, the 3R-*epimer* (10) (58 mg) was also obtained as a gum, $[\alpha]_D^{22}$ +147.5° (*c* 1 in $CHCl_3$); $\nu_{max.}$ 3 420, 1 795, 1 745, and 1 690 cm^{-1}; δ(90 MHz) 0.85—1.30 (4 H, m), 3.58 (1 H, d, *J* approximately 1 Hz), 4.47 (2 H, s), 5.15 (2 H, s), 5.33 (1 H, d, *J* 4 Hz), 5.59 (1 H, ddd, *J* 4, 9, and *ca.* 1 Hz), and 6.76—7.35 (11 H, m) (Found: M^+, 438.1233. $C_{23}H_{22}N_2O_5S$ requires *M*, 438.1250).

(*b*) Finely powdered anhydrous potassium carbonate (11.2 g) was added, portionwise during 30 min to a stirred mixture of the 4-mercaptoazetidinone (6) (4.10 g) and benzyl 2-cyclopropylideneacetate (7) (4.35 g) in dry HMPT (80 ml) at ice-bath temperature. After being stirred at room temperature for a further 40 h the mixture was worked up as before to give the 3*S*-epimer (9) (1.07 g) and the 3*R*-epimer (10) (0.26 g).

(3S,5R,6R)-6-*Phenoxyacetamidocyclopropanespiro*-2-*bisnorpenicillanic Acid* (13).—The penam ester (9) (200 mg) was dissolved in a mixture of THF (16 ml) and water (4 ml) and was hydrogenated over 10% palladium–charcoal (200 mg) at s.t.p. for 15 min. The mixture was filtered through a bed of Kieselguhr, the residual catalyst being washed with a little THF. The combined filtrates were evaporated to low volume and diluted with ethyl acetate (10 ml). The pH

of the vigorously stirred, cooled (ice-bath) mixture was adjusted to 7.0 using saturated aqueous $NaHCO_3$. The aqueous layer was separated and the organic layer was re-extracted with water (5 ml). The combined aqueous layers were washed with ethyl acetate (5 ml). The aqueous layer was covered with ethyl acetate (10 ml) and the pH of the vigorously stirred, cooled (ice-bath), mixture was adjusted to 3.0 using N-hydrochloric acid. The organic layer was separated and the aqueous layer re-extracted with ethyl acetate (2 × 5 ml). The combined organic layers were washed with brine (3 × 5 ml), dried ($MgSO_4$), and evaporated to give the free acid (13) (50 mg), a hydrate, as an amorphous solid; $[\alpha]_D^{22}$ +68.6° (*c* 1 in $CHCl_3$); $\nu_{max.}$ 3 600—2 300, 1 795, 1 735, and 1 690 cm^{-1}; δ(90 MHz) 0.5—1.5 (4 H, m), 4.29 (1 H, s), 4.52 (2 H, s), 5.55 (1 H, d, *J* 4 Hz), 5.71 (1 H, dd, *J* 4 and 8 Hz), 6.31br (2 H, s, exch. D_2O), and 6.75—7.40 (6 H, m).

(3S,5R,5R)-*Benzyl* 6-*Aminocyclopropanespiro*-2-*bisnorpenicillanate* (14).—A solution of phosphorus pentachloride (125 mg) in dry methylene chloride (2 ml) was added dropwise during 3 min to a stirred mixture of the penam ester (9) (219 mg) and *N*-methylmorpholine (101 mg) in dry methylene chloride (5 ml) at −25 °C. The mixture was stirred for a further 30 min during which the temperature was allowed to reach 0 °C. The mixture was re-cooled to −25 °C and treated with *N*-methylmorpholine (101 mg) followed by dropwise addition of dry methanol (2 ml). After being stirred at 0—5 °C for a further 1.5 h the mixture was poured into ice–water (10 ml) and stirred at pH 2 for 10 min with cooling at 0—5 °C. The pH of the mixture was adjusted to 6.0 using dilute aqueous NH_4OH and the organic layer was separated. The aqueous layer was re-extracted with methylene chloride (2 × 3 ml). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (3 ml) and brine (3 × 5 ml). The dried ($MgSO_4$) organic layer was evaporated to give a crude gum which was immediately redissolved in acetone (1 ml) and treated with a solution of toluene-*p*-sulphonic acid monohydrate (95 mg) in acetone (0.5 ml). The resulting mixture was diluted with ether to give the toluene-*p*-sulphonic acid salt of (14) (33 mg) as an amorphous solid, $[\alpha]_D^{22}$ +47.4° (*c* 0.5 in CH_3OH); $\nu_{max.}$ (Nujol) 1 785 and 1 730 cm^{-1}; δ(90 MHz) (CD_3OD) 0.85—1.30 (4 H, m), 2.32 (3 H, s), 4.54 (1 H, s), 4.73 (s, hydrated NH_3^+), 5.04 (1 H, d, *J* 4 Hz), 5.17 (2 H, s), 5.58 (1 H, d, *J* 4 Hz), 7.15 (2 H, d, *J* 8 Hz), 7.30 (5 H, s), 7.64 (2 H, d, *J* 8 Hz). The toluene-*p*-sulphonic acid salt of (14) (15 mg) was shaken with ethyl acetate (2 ml) and saturated aqueous $NaHCO_3$ (0.5 ml). The organic layer was separated and aqueous layer re-extracted with ethyl acetate (2 × 1 ml). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated to give the free 6-aminopenam ester (14) (9 mg), $\nu_{max.}$ 3 400br, 1 780, and 1 740 cm^{-1}; δ(90 MHz) 0.75—1.36 (4 H, m), 1.94br (2 H, s) 4.27 (1 H, s), 4.56 (1 H, d, *J* 4 Hz), 5.13 (2 H, s), 5.49 (1 H, d, *J* 4 Hz), and 7.28 (5 H, s).

(3S,5R,6R)-*Benzyl* 6-D-α-*Aminophenylacetamidocyclopropanespiro*-2-*bisnorpenicillanate* (15).—D-Phenylglycyl chloride hydrochloride (63 mg) was added portionwise during 5 min to a stirred, ice-bath cooled, mixture of the 6-aminopenam ester (14) (78 mg) and *N*,*N*-dimethylaniline (37 mg) in methylene chloride (2 ml). After 20 min at ice-bath temperature the stirred mixture was allowed to reach room temperature during a further 20 min. The mixture was diluted with ethyl acetate (5 ml) and washed with saturated $NaHCO_3$ solution and brine. The dried ($MgSO_4$) organic layer was evaporated and the residue chromatographed to give the desired penam ester (15) (53 mg) as an amorphous solid, $[\alpha]_D^{20}$ +57.3° (*c* 1 in $CHCl_3$); $\nu_{max.}$ 3 400, 3 350, 1 790, 1 740, and 1 680 cm^{-1}; δ 0.72—1.30 (4 H, m), 1.98br (2 H, s, exch. D_2O), 4.42 (1 H, s), 4.62 (1 H, s), 5.25 (2 H, s) 5.53—5.90 (2 H, m, collapsing to 5.57 and 5.70 each d, *J* 4 Hz on exch. D_2O), 7.44 (10 H, s), and 8.07 (1 H, d, *J* 8 Hz exch. D_2O) (Found: M^+, *m/e* 437; $[M - 189]^+$, *m/e* 248 corresponding to the ion (25)].

(3S,5R,6R)-6-D-α-*Aminophenylacetamidocyclopropanespiro*-2-*bisnorpenicillanic Acid* (16).—The penam ester (15) (130 mg) dissolved in a mixture of THF (8 ml) and water (2 ml) was hydrogenated over pre-hydrogenated 10% palladium–charcoal (130 mg) at s.t.p. for 40 min. The mixture was evaporated to low volume, diluted with water (5 ml), cooled in an ice-bath, and the pH adjusted to 2.0 using N-hydrochloric acid. After being stirred for 5 min at ice-bath temperature the mixture was filtered through a bed of Kieselguhr. The pH of the stirred, ice-bath cooled, filtrate was adjusted to 5.0 using dilute aqueous $NaHCO_3$ and the mixture extracted with ethyl acetate (2 ml). The aqueous phase was evaporated and the residue triturated with ether to give the amino-acid (16) (53 mg), containing sodium chloride as impurity, as an amorphous solid, $\nu_{max.}$ (KBr) 3 650—2 500, 1 780, 1 760 slight shoulder, 1 675, 1 600br, 1 525br cm^{-1}.

(3S,5R,6R)-*Benzyl* 6-(D-α-*Benzyloxycarbonylaminophenylacetamido*)*penicillanate* (17).—A solution containing *N*-benzyloxycarbonyl-D-α-phenylglycine (3.14 g), triethylamine (1.11 g), and *N*,*N*-dimethylbenzylamine (1 drop) in dry THF (10 ml) was added dropwise during 10 min to a stirred solution of methyl chloroformate (1.04 g) in dry THF (20 ml) at −10 °C. After being stirred at −10 °C for a further 25 min a solution of benzyl 6-aminopenicillanate (3.06 g) in dry THF (10 ml) was added dropwise during 10 min. The mixture was stirred at −10 °C for a further 2 h, filtered, and the filtrate evaporated. The residue was dissolved in ethyl acetate (50 ml) and washed with saturated aqueous $NaHCO_3$ and brine. The dried ($MgSO_4$) organic layer was evaporated and the residue chromatographed to give the *penam ester* (17) (4.53 g) as an amorphous solid, $[\alpha]_D^{23}$ +95.2° (*c* 1 in $CHCl_3$); $\nu_{max.}$ 3 430, 1 790, 1 730br, and 1 695 cm^{-1}; δ 1.28 (3 H, s), 1.37 (3 H, s), 4.40 (1 H, s), 5.04 (2 H, s), 5.12 (2 H, s), 5.30—5.67 (3 H, m), 6.29 (1 H, d, *J* 7 Hz), and 7.27br (16 H, s) (Found: M^+, 573.1981. $C_{31}H_{31}N_3O_6S$ requires *M*, 573.1933).

(3S,5R,6R)-*Benzyl* 6-(D-α-*Benzyloxycarbonylaminophenylacetamido*)*penicillanate* 1-*Oxide* (18).—A solution of *m*-chloroperbenzoic acid (760 mg) in chloroform (10 ml) was added dropwise during 15 min to a stirred, ice-bath cooled solution of the penam ester (17) (2.29 g) in chloroform (25 ml). After being stirred at ice-bath temperature for a further 20 min the mixture was diluted with chloroform (30 ml) and washed with saturated aqueous $NaHCO_3$ and brine. The dried ($MgSO_4$) organic layer was evaporated and the residue crystallised from ethyl acetate–light petroleum (b.p. 60—80 °C) to give the *sulphoxide* (18) (1.63 g) as a microcrystalline solid, m.p. 155—156 °C, $[\alpha]_D^{23}$ +96.6° (*c* 1 in $CHCl_3$); $\nu_{max.}$ 3 430, 3 370, 1 805, 1 750, 1 725, and 1 695 cm^{-1}; δ 0.95 (3 H, s), 1.56 (3 H, s), 4.63 (1 H, s), 4.83 (1 H, d, *J* 4 Hz), 5.08 (2 H, s), 5.12—5.30 (3 H, m), 5.92 (1 H, dd, *J* 4 and 10 Hz), 6.12 (1 H, d, *J* 6 Hz), 7.31br (15 H, s), and 7.67 (1 H, d, *J* 10 Hz) (Found: C, 63.2; H, 5.5; N, 7.1; S, 5.5. $C_{31}H_{31}N_3O_7S$ requires C, 63.2; H, 5.3; N, 7.1; S, 5.4%).

(1R,5R)-3-D-[(1-*Benzyloxycarbonylamino*-1-*phenyl*)-*methyl*]-6-[(2-*methyl*-1-*benzyloxycarbonyl*)*prop*-1-*enyl*]-4-*thia*-2,6-*diazabicyclo*[3.2.0]*hept*-2-*en*-7-*one* (19).—A mixture of the sulphoxide (18) (5.89 g) and trimethyl phosphite (3.5 ml) were refluxed in dry toluene (50 ml) under argon for 2 h. The reaction mixture was cooled to room temperature and treated with triethylamine (1.11 g). After 2 h at room temperature the mixture was evaporated and the gum obtained by trituration of the residue with light petroleum (b.p. 60—80 °C) was chromatographed to give the D-thiazoloazetidinone (19) (2.36 g) as an amorphous solid, $[\alpha]_D^{23}$ −69.2° (*c* 1 in $CHCl_3$); $\nu_{max.}$ 3 430, 1 770, 1 720, 1 660, and 1 615 cm^{-1}; δ 1.76 (3 H, s), 2.23 (3 H, s), 5.06 and 5.30 (2 H, ABq, *J* 12 Hz), 5.11 (2 H, s), 5.52 (1 H, d, *J* 6 Hz), 5.75 (1 H, d, *J* 4 Hz), 5.94 (1 H, d, *J* 4 Hz), 6.29 (1 H, d, *J* 6 Hz), and 7.37 (15 H, s). Also obtained was the less polar L-thiazoloazetidinone (20) (0.45 g) as an amorphous solid, $[\alpha]_D^{22}$ −6.4° (*c* 1 in $CHCl_3$); $\nu_{max.}$ 3 430, 1 770, 1 720, and 1 615 cm^{-1}; δ 1.27 (3 H, s), 2.04 (3 H, s), 4.97 and 5.21 (2 H, ABq, *J* 12 Hz), 5.00 (2 H, s), 5.49br (1 H, d, *J* 8 Hz), 5.75 (1 H, d, *J* 4 Hz), 5.88 (1 H, dd, *J* 4 and 1 Hz), 6.44 (1 H, d, *J* 8 Hz), and 7.27 (15 H, s).

(1R,5R)-3-D-[(1-*Benzyloxycarbonylamino*-1-*phenyl*)-*methyl*]-4-*thia*-2,6-*diazabicyclo*[3.2.0]*hept*-2-*en*-7-*one* (21).—Finely powdered potassium permanganate (0.96 g) was added portionwise during 5 min to a stirred ice-bath cooled, solution of D-thiazoloazetidinone (19) (2.25 g) in a mixture of DMF (20 ml), water (2 ml), and pyridine (1 ml). After being stirred for a further 15 min at ice-bath temperature the mixture was diluted with ethyl acetate (200 ml) and brine (100 ml) and treated with sulphur dioxide until clear. The organic layer was separated and the aqueous layer re-extracted with ethyl acetate (25 ml). The combined organic layers were washed with aqueous $NaHCO_3$ and brine. The dried ($MgSO_4$) organic layer was evaporated and the residue chromatographed to give the desired *thiazoloazetidinone* (21) (804 mg), a crystalline solid, m.p. 96—99 °C (ethanol–water); $[\alpha]_D^{22}$ −39.6° (*c* 1 in $CHCl_3$); $\nu_{max.}$ 3 410, 1 790, 1 720, and 1 615 cm^{-1}; δ 5.08 (2 H, s), 5.34 (1 H, d, *J* 4 Hz), 5.54 (1 H, d, *J* 7 Hz), 5.81—5.98 (1 H, m, collapsing to 5.90, d, *J* 4 Hz on exch. D_2O), 6.50 (1 H, d, *J* 7 Hz), 7.15 (1 H, d, *J* 2 Hz, readily exch. D_2O), and 7.33 (10 H, s) (Found: C, 61.6; H, 4.9; N, 11.3; S, 8.8. $C_{19}H_{17}N_3O_3S$ requires C, 62.1; H, 4.6; N, 11.5; S, 8.7%).

(3R,4R)-3-D-α-*Benzyloxycarbonylaminophenylacetamido*-4-*mercaptoazetidin*-2-*one* (22).—A solution of the thiazoloazetidinone (21) (1.50 g) in 70% aqueous acetic acid (30 ml) was stirred at room temperature for 24 h. The product which had precipitated was filtered off, washed with dry ether, and dried *in vacuo* to give the mercaptoazetidinone (22) (320 mg) a monohydrate, as an amorphous solid, $\nu_{max.}$ (Nujol) 3 300br, 2 550w, 1 770sh, 1 750, 1 715, 1 690, 1 665, and 1 655 cm^{-1} (Found: C, 57.2; H, 4.9; N, 10.3. $C_{19}H_{19}N_3O_4S.1H_2O$ requires C, 56.5; H, 5.2; N, 10.4%). Evaporation of the filtrate and trituration of the residue with dry ether gave a second crop of the 4-mercaptoazetidinone (22) (793 mg) as an amorphous solid.

(3S,5R,6R)-*Benzyl* 6-DL-α-*Benzyloxycarbonylamino-phenylacetamidocyclopropanespiro*-2-*bisnorpenicillanate* (24).—A mixture of the 4-mercaptoazetidinone (22) (800 mg) and benzyl 2-bromocyclopropylideneacetate (7) (610 mg) was stirred with finely powdered anhydrous potassium carbonate (72 mg) in dry HMPT (8 ml) at room temperature for 30 min. The mixture was diluted with ethyl acetate (10 ml) and washed with brine (3 × 2 ml). The dried ($MgSO_4$) organic layer was evaporated and the residue chromatographed to give the bromoester (23) (404 mg) as an amorphous solid, $\nu_{max.}$ 3 430, 3 300, 1 780, 1 730, and 1 690 cm^{-1}. The bromoester was redissolved in dry HMPT (2 ml) and stirred with finely powdered anhydrous potassium carbonate (423 mg) at room temperature for 20 h. The mixture was diluted with ethyl acetate (50 ml) and washed with brine. The dried ($MgSO_4$) organic layer was evaporated and chromatographed to give the penam ester (24) (115 mg) as an amorphous solid, $[\alpha]_D^{25}$ +69.8° (*c* 1 in $CHCl_3$) $\nu_{max.}$ 3 430, 3 330sh, 1 795, 1 730br, and 1 690 cm^{-1}; δ(90 MHz) 0.72—1.30 (4 H, m), 4.20 (1 H, s), 5.01 (1 H, s), 5.10 (2 H, s), 5.20—5.61 (3 H, m), 4.91—6.11 (1 H, m), 6.52—6.72br (1 H, m), and 7.25 (15 H, s).

The author thanks Mr. M. J. Basker for the determination of antibacterial activities.

[1/1525 *Received*, 1*st October*, 1981]

REFERENCES

[1] Part 3, preceding paper.
[2] P. J. Claes, G. Janssen, and H. Vanderhaeghe, *Eur. J. Med. Chem.*, 1977, **12**, 521.
[3] J. Leclercq, E. Cossement, R. Boydens, L. A. M. Rodriguez, L. Brouwers, F. Laverleye, and W. Libert, *J. Chem. Soc., Chem. Commun.*, 1978, 46.
[4] M. D. Bachi, S. Sasson, and J. Vaya, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2228.
[5] N. F. Osborne, *J. Chem. Soc., Perkin Trans. 1*, 1980, 150.
[6] J. Salaün, *J. Org. Chem.*, 1976, **41**, 1237.
[7] E. G. Brain, A. J. Eglington, J. H. C. Nayler, N. F. Osborne, R. Southgate, and P. Tolliday, *J. Chem. Soc., Perkin Trans. 1*, 1977, 2479.
[8] R. D. G. Cooper and F. L. José, *J. Am. Chem. Soc.*, 1970, **92**, 2575.
[9] N. F. Osborne, *J. Chem. Soc., Perkin Trans. 1*, 1980, 146.