The Chemistry of 4-Mercaptoazetidin-2-ones. Part 2.[1] Synthesis of Bisnorpenicillins

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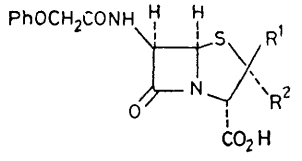
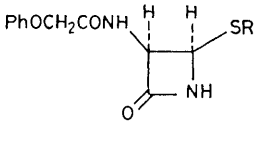
Reaction of the 4-mercaptoazetidinone (2) with benzyl 2-bromoacrylate gave the C-3-epimeric bisnorpenicillin esters (6b) and (7b). Standard procedures were used to convert the ester (6b) into bisnorpenicillin V (3) and bisnorampicillin (15). By contrast (2), with either (*E*)- or (*Z*)-benzyl 2-bromocrotonates, gave the penam esters (20) and (21) and not the expected benzyl esters of the norpenicillanic acids (16a) and (16b). This reaction was shown to proceed *via* the olefin (22).

SEVERAL analogues of penicillins in which the methyl groups at C-2 have been replaced by other groups have been reported. Total synthesis has been used to prepare analogues of penicillin V (1) in which either [2] or both [3] the methyl groups are replaced by hydrogen or in which both methyl groups are replaced by an ethyl group.[4] More recently [5,6] this approach has been used to prepare analogues in which the two methyl groups have been replaced by a spirocycloalkane ring. Other modifications have been achieved using a penicillin as starting material, the β-lactam ring being kept intact throughout. These include compounds in which either [7] or both [8] the methyl groups have been replaced by an acetoxymethyl function, the latter being obtained only as esters. Similarly, compounds in which a bromine or chlorine atom has been introduced into one of the methyl groups have only been obtained as esters,[9,10] which readily undergo ring expansion to 3-halocephams *via* an episulphonium intermediate.[9] A recent paper [11] described analogues in which one or both the methyl groups have been replaced by an alkoxycarbonyl or acetyl group although most of these were also obtained only as esters.

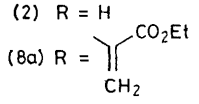


(1) $R^1 = R^2 = Me$

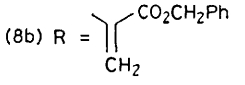
(3) $R^1 = R^2 = H$



(2) R = H



(8a) R = CH_2CO_2Et



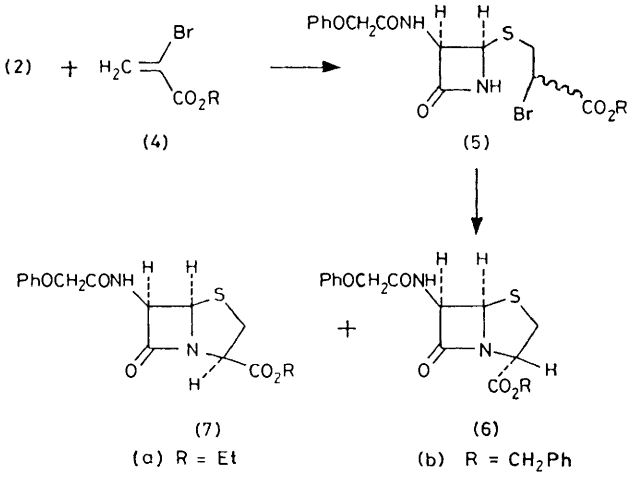
(8b) R = $CH_2CO_2CH_2Ph$

(16a) R^1 = Me, R^2 = H

(16b) R^1 = H R^2 = Me

The 4-mercaptoazetidin-2-one (2) [1] appeared to be an eminently suitable intermediate from which to construct bicyclic β-lactams. To this end the synthesis of bisnorpenicillin V (3) [3] by the route outlined in Scheme 1 was chosen as our first attempt. The 4-mercaptoazetidinone (2) has been shown to undergo a series of reactions preferentially at the sulphur atom.[1] It therefore seemed likely that Michael addition of the thiol (2) to an α-haloacrylic ester (4) followed by intramolecular *N*-alkylation would lead to the epimeric bisnorpenicillin V esters (6) and (7). Thus, a mixture of the 4-mercaptoazetidinone (2) and ethyl 2-bromoacrylate (4a) [12,†] was stirred in dry hexamethylphosphoramide (HMPT) at room temperature overnight in the hope of obtaining the bromo-compound (5a). Examination of the reaction mixture by t.l.c. revealed little or no reaction to have taken place. However, when the reaction was repeated with the careful addition of one equivalent of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) at 0 °C the bisnorpenicillanate (6a) was obtained in 20% yield. The C-3-epimeric bisnorpenicillanate (7a) was not isolated. A low yield of the intermediate bromide (5a) was obtained in this experiment, the n.m.r. spectrum of which indicated it was a mixture of stereoisomers. An interesting by-product, the olefin (8a) which is presumably formed *via* the episulphonium salt (9), was also isolated. When the reaction was repeated at room temperature an increase in the yield of the bisnorpenicillanate (6a) and the olefin (8a) was observed but none of the intermediate bromide (5a) was isolated.

The feasibility of the route to the bisnorpenicillanate nucleus having been demonstrated, attention was focused on the synthesis of a labile ester which would facilitate the preparation of the free acid (3). The benzyl ester was chosen for this purpose since it also allowed a direct comparison to be made with the work of Vanderhaeghe *et al.*[3] Thus, treatment of a mixture of the 4-mercaptoazetidinone (2) and benzyl 2-bromoacrylate (4b) with



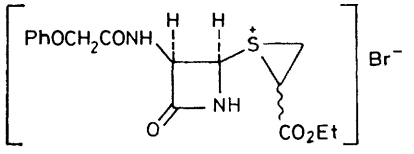
(4) (5) (7) (6)

(a) R = Et (b) R = CH_2Ph

SCHEME 1

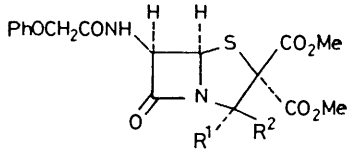
† B.p. 60—62 °C at 20 mmHg.

DBN at room temperature gave rise to the expected bisnorpenicillin ester (6b) in 20% yield, the spectral data of which were in good agreement with those in the literature.[3] The intermediate bromide (5b) and the olefin (8b) were also isolated. A range of bases including sodium hydride, 1,1,3,3-tetramethylguanidine, Triton B, and potassium carbonate were found to be effective in this reaction when either HMPT or dimethylformamide (DMF) was used as solvent. The use of potassium carbonate in DMF proved to be of particular interest.



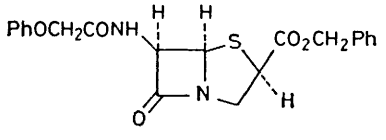
(9)

Examination of the reaction mixture by t.l.c. showed an initial rapid formation of the bromide (5b) which then cyclised slowly. The major product, isolated by chromatography, was found to be a mixture of the C-3-epimeric bisnorpenicillanates (6b) and (7b) from which the epimer (6b), having the natural penicillin stereochemistry at C-3, could be crystallised. Re-chromatography of the mother-liquors gave an impure sample of the epimeric bisnorpenicillanate (7b). The C-3 proton for the 3*R*-epimer (7b) was observed as a multiplet at δ 3.95—4.21 compared with a triplet at δ 5.10 for the 3*S*-epimer (6b). A similar relationship was observed for the epimeric penams (10) and (11).[11] The isolation of



(10) $R^1 = CO_2CH_2CCl_3$, $R^2 = H$

(11) $R^1 = H$, $R^2 = CO_2CH_2CCl_3$

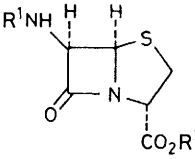


(12)

the 2-benzyloxycarbonylpenam (12) in this reaction was also of interest. It seems possible that this product was produced by an intramolecular Michael addition of the olefin (8b) which was not isolated from the reaction.

De-protection of the benzyl ester (6b) was achieved by hydrogenolysis over 10% palladium–charcoal catalyst in aqueous tetrahydrofuran to give the free acid (3) which was converted into its sodium salt using sodium 2-ethylhexanoate.

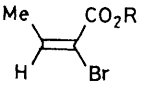
The phenoxyacetyl side-chain of the bisnorpenicillanate (6b) was removed by a method analogous to that used for benzylpenicillin.[13] The benzyl ester (6b) was treated successively with phosphorus pentachloride in methylene chloride containing *N*-methylmorpholine followed by methanol and water to give the 6-aminopenam benzyl ester (13), isolated as its toluene-*p*-sulphonic acid salt. Acylation of the 6-aminopenam benzyl ester (13) was



(13) $R^1 = H$, $R^2 = CH_2Ph$

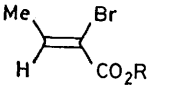
(14) $R^1 = D-PhCH(NHCO_2CH_2C_6H_4NO_2-(p))CO-$, $R^2 = CH_2Ph$

(15) $R^1 = D-PhCH(NH_2)CO-$, $R^2 = H$



(17a) R = H

(17b) R = CH_2Ph



(18a) R = H

(18b) R = CH_2Ph

effected using the mixed anhydride derived from *N*-(*p*-nitrobenzyloxycarbonyl)-D-α-phenylglycine and methyl chloroformate to give the *N*-protected bisnorampicillin ester (14). Hydrogenolysis of (14) gave bisnorampicillin (15), isolated as its *p*-toluidine salt, a fairly pure amorphous solid.

The antibacterial activity of the salts of bisnorpenicillin V (3) and bisnorampicillin (15) are shown in the Table. Both compounds were less active than their

Antibacterial activity *

Bacterium	(3)	Penicillin V	(15)	Ampicillin
Staphylococcus aureus Oxford	0.5	0.05	0.5	0.1
Staphylococcus aureus Russell †	>500	>500	>100	>100
β-Haemolytic *streptococcus*	0.25	0.01	0.25	0.02
Streptococcus faecalis	50	2.5	25	0.5
Escherichia coli	>500	125	10	5
Salmonella typhi	>500	125	10	0.5
Shigella sonnei	>500	125	10	5
Klebsiella aerogenes	>500	250	10	50
Proteus mirabilis	250	50	10	2.5

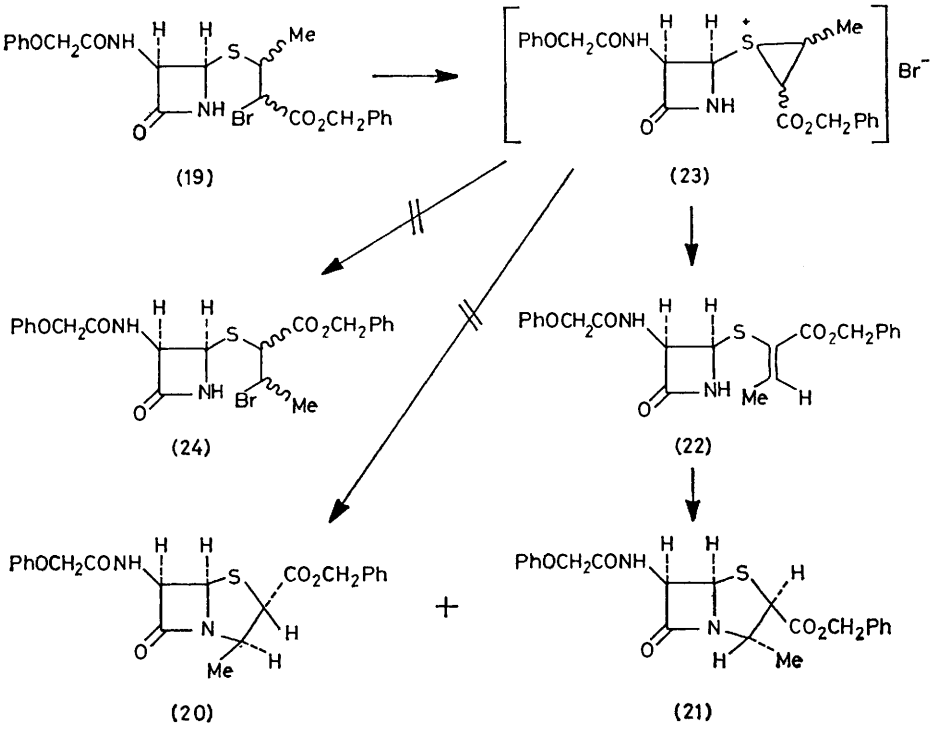
* The figures are the minimum inhibitory concentrations (μg ml^{-1}) required to inhibit bacterial growth after incubation on nutrient agar for 18 h. † Penicillinase-producing strain.

corresponding natural penicillin analogues with the exception that compound (15) showed slightly better activity than ampicillin against *Klebsiella aerogenes*.

In an effort to widen the scope of the approach to bicyclic β-lactams exemplified above, a synthesis of the norpenicillins [2] (16a) and (16b) was attempted. Thus, reaction of the 4-mercaptoazetidinone (2) with (*Z*)-benzyl 2-bromocrotonate (18b) and potassium carbonate in

DMF at −50 °C gave a product presumed to be a mixture of isomers of the bromide (19). When this product was subjected to further treatment with potassium carbonate in HMPT two isomeric penam esters were obtained which were not the expected benzyl esters [2] of the norpenicillanic acids (16a) and (16b). Also obtained was the olefin (22), a single isomer, assigned the *Z*-configuration by virtue of the very low-field vinylic proton revealed (20) and (21) do not appear consistent with the experimental observations.

It is of particular interest to note the profound effect that the presence of a methyl group has had on the course of the reactions described here. The rearrangement leading to the olefin (22) and subsequently the penam esters (20) and (21), the major products in the attempted synthesis of the norpenicillin nucleus, was only observed



SCHEME 2

in a decoupling experiment. The two penam esters were assigned the structures (20) and (21) based on both mechanistic and spectroscopic considerations. Thus, the same three products were obtained when the process was repeated using (*E*)-benzyl 2-bromocrotonate (17b) suggesting a common intermediate. The identity of this intermediate was revealed when brief treatment of the bromide (19) with potassium carbonate in HMPT resulted in a partial conversion into the olefin (22), presumably by a β-elimination of the episulphonium ion (23). An intramolecular Michael addition of the olefin (22) would then lead exclusively to the penam esters (20) and (21), a fact borne out by experiment. The stereochemistry at the C-2 and C-3 positions of structures (20) and (21) was deduced from the observed coupling constants in their n.m.r. spectra. Assuming that the thiazolidine ring conformation is the same as that in natural penicillins, the dihedral angles between the C-2 and C-3 protons for the structures (20) and (21) are approximately 160 and 90° which is consistent with the observed $J_{2,3}$ values of 7 and 0 Hz respectively. The other two possible mechanisms (Scheme 2) which can be written to account for the formation of the penam esters as a competing reaction in the synthesis of the bisnorpenicillin nucleus. This may reflect a partial stabilisation of the episulphonium ion (23) by the inductive effect of the methyl group as compared with the ion (9).

EXPERIMENTAL

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

Reaction of the 4-Mercaptoazetidinone (2) *with Ethyl 2-Bromoacrylate.*—A solution of DBN (248 mg) in dry HMPT (1 ml) was added dropwise over 10 min to a stirred solution of the 4-mercaptoazetidinone (2) (504 mg) [1] and ethyl 2-bromoacrylate (4a) (394 mg) [12] in dry HMPT (5 ml) at 0 °C. The mixture was stirred at 0 °C for a further 15 min, diluted with ethyl acetate (30 ml), and washed with brine. The dried ($MgSO_4$) organic layer was evaporated and the residue was chromatographed to give three compounds. The least polar product was (3S,5R,6R)-*ethyl 6-phenoxyacetamidobisnorpenicillanate* (6a) (140 mg), m.p. 101—103 °C (needles from ethyl acetate–light petroleum), $\nu_{max.}$ 3 400, 1 790, 1 740, and 1 690 cm^{-1}; δ 1.35 (3 H, t, *J* 7 Hz), 3.56 (2 H, d, *J* 5 Hz), 4.35 (2 H, q, *J* 7 Hz), 4.65 (2 H, s), 5.09 (1 H, t, *J* 5 Hz), 5.50 (1 H, d, *J* 4.5 Hz), 5.88 (1 H, dd, *J* 4.5 and 9 Hz), and 6.93—7.67 (6 H, m) (Found: M^+, 350.0907. $C_{16}H_{18}N_2O_5S$ requires *M*, 350.0936). The

second most polar product the intermediate bromide (5a) (63 mg), a mixture of stereoisomers, was obtained as an amorphous solid, $\nu_{max.}$ 3 400, 1 780, 1 735, and 1 690 cm^{-1}; δ 1.27 (3 H, t, *J* 7 Hz), 2.72—3.50 (2 H, m), 4.00—4.43 (3 H, m), 4.58 (2 H, s), 5.06 and 5.09 (1 H, 2 overlapping d, both *J* 4 Hz), 5.55 (1 H, broadened dd, *J* 4 and 9 Hz), 6.8—7.5 (6 H, m), and 7.70 (1 H, d, *J* 9 Hz). The most polar product, the olefin (8a) (29 mg) was also obtained as an amorphous solid, $\nu_{max.}$ 3 400, 3 300, 1 780, and 1 690br cm^{-1}; δ 1.29 (3 H, t, *J* 7 Hz), 4.22 (2 H, q, *J* 7 Hz), 4.55 (2 H, s), 5.16 (1 H, d, *J* 4 Hz), 5.73 (1 H, dd, *J* 4 and 9 Hz), 5.76 (1 H, s), 6.45 (1 H, s), 6.8—7.5 (6 H, m), and 7.72 (1 H, d, *J* 9 Hz).

In a further experiment the 4-mercaptoazetidinone (2) (126 mg) and ethyl 2-bromoacrylate (4a) (98 mg) were treated with DBN (62 mg) in dry HMPT at room temperature. Chromatography of the crude product afforded the bisnorpenicillin ester (6a) (51 mg) and the olefin (8a) (56 mg).

Benzyl 2-Bromoacrylate (4b).—2-Bromoacrylic acid [14] (14.0 g) and benzyl bromide (11 ml) were dissolved in DMF (100 ml) and treated with anhydrous potassium carbonate (6.4 g) portionwise with stirring at room temperature. The mixture was stirred at room temperature for a further 24 h, diluted with ethyl acetate (300 ml), and washed successively with water, saturated $NaHCO_3$ solution, and water. Distillation of the dried ($MgSO_4$) organic layer under reduced pressure of nitrogen gave benzyl 2-bromoacrylate (4b) (10.8 g) as a colourless oil, b.p. 108—110 °C at 1 mmHg, $\nu_{max.}$ (film) 1 720 and 1 605 cm^{-1}. This oil rapidly became yellow and polymerised in a few hours even on storage at 5 °C. Stabilisation of the product was achieved by addition of a little hydroquinone to both distillation pot and receiver flask. The distilled product was immediately dissolved in dry benzene to give a solution which could be stored under nitrogen at 5 °C for many weeks.

Reaction of the 4-Mercaptoazetidinone (2) *with Benzyl 2-Bromoacrylate.*—(a) *Using DBN.* A solution of DBN (248 mg) in dry HMPT (5 ml) was added dropwise over 30 min at room temperature to a stirred solution of the 4-mercaptoazetidinone (2) (504 mg) and benzyl 2-bromoacrylate (4b) (530 mg) in dry HMPT (5 ml). The mixture was stirred at room temperature for a further 15 min, diluted with ethyl acetate (50 ml), and washed with brine. The dried ($MgSO_4$) organic layer was evaporated and the residue was chromatographed to give three compounds. The least polar (3*S*,5*R*,6*R*)-benzyl 6-phenoxyacetamidobisnorpenicillanate (6b) (161 mg) was obtained as a solid, m.p. 115—116 °C (needles from ethyl acetate–light petroleum) (lit.,[3] 113—114 °C). The second most polar product, the intermediate bromide (5b) (90 mg), a mixture of stereoisomers, was obtained as an amorphous solid, $\nu_{max.}$ 3 400, 1 780, 1 735, and 1 690 cm^{-1}; δ 2.80—3.55 (2 H, m), 4.20—4.44 (1 H, m), 4.60 (2 H, s), 5.04 and 5.08 (1 H, 2d, both *J* 4 Hz), 5.27 (2 H, s), 5.41—5.73 (1 H, m), and 6.9—7.9 (12 H, m). The most polar product, the olefin (8b) (202 mg) was also obtained as an amorphous solid, $\nu_{max.}$ 3 400, 1 780, and 1 690br cm^{-1}; δ 5.79 and 6.52 (both s, $=CH_2$).

(b) *Using anhydrous potassium carbonate.* Finely powdered anhydrous potassium carbonate (580 mg) was added portionwise during 30 min to a stirred mixture of the 4-mercaptoazetidinone (2) (2.12 g) and benzyl 2-bromoacrylate (4b) (4.20 g of a 53% w/w solution in dry benzene) in dry DMF (40 ml) with cooling in an ice-bath. The mixture was stirred at room temperature for 20 h, diluted with ethyl acetate (250 ml), and washed with brine. The dried ($MgSO_4$) organic layer was evaporated and the residual gum was chromatographed to give two fractions. The first fraction, a gummy solid, on trituration with ether afforded (3*S*,5*R*,6*R*)-benzyl 6-phenoxyacetamidobisnorpenicillanate (6b) (920 mg) as a microcrystalline solid, m.p. 114—115 °C. Re-chromatography of the ethereal liquors gave a gum (350 mg), the main component of which was the (3*R*,5*R*,6*R*)-epimer (7b), $\nu_{max.}$ 3 380, 1 795, 1 745, and 1 690 cm^{-1}; δ 3.05—3.70 (2 H, m), 3.95—4.21 (1 H, m), 4.57 (2 H, s), 5.20—5.34 (3 H, m), 5.72 (1 H, dd, *J* 4 and 9 Hz), 6.8—7.5 (10 H, m), and 7.72 (1 H, d, *J* 9 Hz). The second fraction afforded (2R,5R,6R)-*benzyl 6-phenoxyacetamidopenam-2-carboxylate* (12) (137 mg) as an amorphous solid, $\nu_{max.}$ 3 350, 1 790, 1 730, and 1 685 cm^{-1}; δ 3.15 (1 H, dd, *J* 7 and 14 Hz), 4.20 (1 H, d, *J* 7 Hz), 4.51 (1 H, d, *J* 14 Hz), 4.60 (2 H, s), 5.20 (2 H, s), 5.49 (1 H, d, *J* 4 Hz), 5.89 (1 H, dd, *J* 4 and 10 Hz), 6.9—7.5 (10 H, m), and 8.42 (1 H, d, *J* 10 Hz) (Found: M^+, 412.1086. $C_{21}H_{20}N_2O_5S$ requires *M*, 412.1093).

Bisnorpenicillin V (3).—The benzyl ester (6b) (500 mg) was dissolved in a mixture of tetrahydrofuran (16 ml) and water (4 ml) and was hydrogenated over 10% palladium–charcoal (500 mg) at S.T.P. for 2 h. The mixture was filtered through a bed of Kieselghur, the residual catalyst being washed with a little tetrahydrofuran. The combined filtrates were evaporated to low volume and diluted with ethyl acetate (20 ml) and water (20 ml). The pH of the vigorously stirred, cooled (ice-bath), mixture was adjusted to 7.0 with saturated $NaHCO_3$ solution. The aqueous layer was separated and the organic layer was re-extracted with water (10 ml). The combined aqueous layers were washed with ethyl acetate (5 ml). The aqueous layer was covered with ethyl acetate (20 ml) and the pH of the vigorously stirred, cooled (ice-bath), mixture was adjusted to 2.0 using N-HCl. The organic layer was separated and the aqueous layer was re-extracted with ethyl acetate (2 × 5 ml). The combined organic layers were washed with brine (2 × 10 ml), dried ($MgSO_4$), and evaporated to give the free acid (3) (266 mg) as an amorphous solid, $\nu_{max.}$ 3 600—2 300, 1 790, 1 735, and 1 690 cm^{-1}.

The free acid (3) (266 mg) was dissolved in ethyl acetate (1 ml) and was treated with a 2N-solution of sodium 2-ethyl hexanoate in methyl isobutyl ketone (0.41 ml). The mixture was diluted with dry ether and the precipitate was filtered off, washed with dry ether, and dried under vacuum to give the sodium salt of (3) (231 mg) as an amorphous solid, $[\alpha]_D^{21}$ +192° (*c* 1 in water), $\nu_{max.}$ (KBr) 3 400 broad, 1 770, 1 675, and 1 600 cm^{-1}; δ (90 MHz) (D_2O) 3.22 (1 H, dd, *J* 11 and 6 Hz), 3.38 (1 H, dd, *J* 11 and 4 Hz), 4.80 (1 H, dd, *J* 4 and 6 Hz), 5.27 (1 H, d, *J* 4 Hz), 5.39 (1 H, d, *J* 4 Hz), and 6.8—7.5 (5 H, m).

(3S,5R,6R)-*Benzyl 6-Aminobisnorpenicillanate* (13).—A solution of phosphorus pentachloride (250 mg) in dry methylene chloride (5 ml) was added dropwise over 5 min to a stirred mixture of the benzyl ester (6b) (412 mg) and *N*-methylmorpholine (0.22 ml) in dry methylene chloride (10 ml) at −25 °C. The mixture was stirred for 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 (0.22 ml) followed by the dropwise addition of dry methanol (5 ml). After stirring at ice-bath temperature for a further 2.5 h the mixture was poured into ice–water (20 ml) and stirred at pH 2 for 20 min with cooling at 0—5 °C. The pH of the mixture was adjusted

to 6.0 using dilute NH_4OH solution and the organic layer separated. The aqueous layer was re-extracted with methylene chloride. The combined organic layers were washed with saturated $NaHCO_3$ solution (5 ml) and brine (3 × 10 ml). The dried ($MgSO_4$) organic layer was evaporated to give a crude gum which was immediately dissolved in acetone (2 ml) and treated with a solution of toluene-*p*-sulphonic acid monohydrate (190 mg) in acetone (1 ml). The resulting mixture was diluted with ether to give the toluene-*p*-sulphonic acid salt of (13) (110 mg) as a microcrystalline solid, m.p. 163—165 °C (decomp.) [lit.,[3] 169—170 °C (decomp.)]. The toluene-*p*-sulphonic acid salt of (13) was shaken with ethyl acetate–$NaHCO_3$ solution, the organic layer being washed with brine, dried ($MgSO_4$), and evaporated to give the free 6-aminopenam ester (13) (89%) as a gum, $\nu_{max.}$ 1 790 and 1 745 cm^{-1}.

(3S,5R,6R)-*Benzyl* 6-(N-p-*Nitrobenzyloxycarbonyl*-D-α-*aminophenylacetamido*)*bisnorpenicillanate* (14).—A solution containing *N*-(*p*-nitrobenzyloxycarbonyl)-D-α-phenylglycine (182 mg), dry triethylamine (55 mg), and *NN*-dimethylbenzylamine (1 drop) in dry tetrahydrofuran (5 ml) was added dropwise over 5 min to a stirred solution of methyl chloroformate (52 mg) in dry tetrahydrofuran (5 ml) at −10 °C. After stirring at −10 °C for a further 25 min a solution of the 6-aminopenam ester (13) (139 mg) in dry tetrahydrofuran (3 ml) was added dropwise over 5 min. The mixture was stirred at −10 °C for a further 2 h, filtered, and the filtrate evaporated. The residual gum was dissolved in ethyl acetate (20 ml) and washed with saturated $NaHCO_3$ solution and water. The dried ($MgSO_4$) organic layer was evaporated and the residue chromatographed to give the *penam ester* (14) (130 mg), m.p. 145—146 °C [needles from ethyl acetate–light petroleum (b.p. 60—80 °C)], $[\alpha]_D^{22}$ +81.6° (*c* 1 in $CHCl_3$); $\nu_{max.}$ 3 420, 1 795, 1 735, and 1 695 cm^{-1}; δ (90 MHz) 3.21—3.38 (2 H, m), 4.83—5.00 (1 H, m), 5.10—5.34 (6 H, m), 5.60 (1 H, dd, *J* 4 and 9 Hz, collapses to a d, *J* 4 Hz, on D_2O exch.), 6.18 (1 H, d, *J* 7 Hz, exch. D_2O), 6.58 (1 H, d, *J* 9 Hz, exch. D_2O), 7.21—7.54 (12 H, m), and 8.16 (2 H, d, *J* 8 Hz) (Found: C, 58.6; H, 4.5; N, 9.6; S, 5.5. $C_{29}H_{26}N_4O_8S$ requires C, 59.0; H, 4.4; N, 9.5; S, 5.4%).

Bisnorampicillin (15).—The penam ester (14) (150 mg) was dissolved in a mixture of tetrahydrofuran (9 ml) and water (1 ml) and was hydrogenated over 10% palladium–charcoal (150 mg) for 2 h at S.T.P. The mixture was filtered through a bed of Kieselghur and the residue was washed with a little tetrahydrofuran. The combined filtrates were evaporated and the residual gum was re-evaporated from dry benzene (4 × 3 ml). The residual solid was triturated with dry ether and dried *in vacuo* to give bisnorampicillin (15) (100 mg) as a solid *p*-toluidine salt, $\nu_{max.}$ (KBr) 3 400br, 1 775, 1 680, and 1 610 cm^{-1}.

2-*Bromocrotonic Acid*.—The method of Cromwell and Pelletier [15] was used to prepare a 4 : 1 mixture of the *E*- and *Z*-isomers (17a) and (18a) as a low melting solid in 91% yield, δ (CCl_4) 2.00—2.26 (3 H, 2 overlapping d), 7.13 (0.8 H, q, *J* 8 Hz), 7.72 (0.2 H, q, *J* 7 Hz), and 12.77 (1 H, s, exch. D_2O).

Re-examination of this material after storage in a refrigerator at 4 °C for 14 months revealed that isomerisation had taken place resulting in a 1 : 4 mixture of the *E*- and *Z*-isomers (17a) and (18a) as indicated by comparison of the two quartets at δ 7.13 and 7.72 respectively.

(E)-*Benzyl* 2-*Bromocrotonate* (17b).—A mixture of the freshly prepared 2-bromocrotonic acid [4 : 1 mixture of (17a) and (18a); 6.60 g], benzyl bromide (7.52 g), and anhydrous potassium carbonate (2.76 g) was stirred in dry DMF (60 ml) at room temperature for 16 h. The mixture was diluted with ethyl acetate (200 ml) and washed with brine. The dried ($MgSO_4$) organic layer was evaporated and the residual oil distilled to give the essentially pure *E*-isomer (17b) (4.89 g), b.p. 154—160 °C (20 mm), $\nu_{max.}$ (film) 1 720, 1 630, and 1 620 cm^{-1}; δ (CCl_4) 2.02 (3 H, d, *J* 7 Hz), 5.20 (2 H, s), 6.74 (1 H, q, *J* 7 Hz), and 7.37 (5 H, s).

(Z)-*Benzyl* 2-*Bromocrotonate* (18b).—A mixture of the stored 2-bromocrotonic acid [1 : 4 mixture of (17a) and (18a); 3.30 g], benzyl bromide (3.76 g), and anhydrous potassium carbonate (1.38 g) was stirred in dry DMF (30 ml) at room temperature for 16 h. The mixture was worked up as in the previous example to give the *Z*-isomer (18b) (2.55 g), b.p. 158—162 °C at 20 mmHg, $\nu_{max.}$ (film) 1 725 and 1 630 cm^{-1}; δ (CCl_4) 1.91 (3 H, d, *J* 7 Hz), 5.25 (2 H, s), and 7.20—7.58 (6 H, m).

Reaction of the 4-*Mercaptoazetidinone* (2) *with* (Z)-*Benzyl* 2-*Bromocrotonate* (18b).—A mixture of the 4-mercaptoazetidinone (2) (1.65 g), (*Z*)-benzyl 2-bromocrotonate (18b) (1.84 g), and finely powdered anhydrous potassium carbonate (90 mg) was stirred in dry DMF (20 ml) at −50 °C for 1.5 h. The mixture was diluted with ethyl acetate and washed with brine. The dried ($MgSO_4$) organic layer was evaporated and the residue chromatographed to give the product, presumably the bromide (19) (1.23 g), a mixture of stereoisomers, as an amorphous solid, $\nu_{max.}$ 3 420, 1 785, 1 735, and 1 690 cm^{-1}.

The bromide (19) (900 mg) and finely powdered anhydrous potassium carbonate (122 mg) were stirred in dry HMPT (20 ml) at room temperature for 48 h. The mixture was diluted with ethyl acetate (100 ml) and washed with brine. The dried ($MgSO_4$) organic layer was evaporated and the residue chromatographed to give three products. The least polar product (2S,3R,5R,6R)-*benzyl* 3-*methyl*-6-*phenoxyacetamidopenam*-2-*carboxylate* (20) (88 mg) was obtained as a gum, $\nu_{max.}$ 3 420, 1 790, 1 740, and 1 690 cm^{-1}; δ (90 MHz) 1.69 (3 H, d, *J* 7 Hz), 3.60—3.90 (1 H, m), 3.99 (1 H, d, *J* 7 Hz), 4.49 (2 H, s), 5.15 (2 H, s), 5.23 (1 H, d, *J* 4 Hz), 5.49 (1 H, dd, *J* 4 and 9 Hz), and 6.80—7.40 (11 H, m) (Found: M^+, 426.1243. $C_{22}H_{22}N_2O_5S$ requires *M*, 426.1249). The second most polar product (2R,3S,5R,6R)-*benzyl* 3-*methyl*-6-*phenoxyacetamidopenam*-2-*carboxylate* (21) (264 mg) was obtained as a gum, $\nu_{max.}$ 3 370, 1 790, 1 730, and 1 680 cm^{-1}; δ (90 MHz) 1.24 (3 H, d, *J* 6 Hz), 3.84 (1 H, s), 4.50 (2 H, s), 4.69 (1 H, q, *J* 6 Hz), 5.08 (2 H, s), 5.35 (1 H, d, *J* 4 Hz), 5.72 (1 H, dd, *J* 4 and 9 Hz), 6.8—7.4 (10 H, m), and 8.23 (1 H, d, *J* 9 Hz) (Found: M^+, 426.1246. $C_{22}H_{22}N_2O_5S$ requires *M*, 426.1249). The most polar product, the olefin (22) (131 mg) was obtained as an amorphous solid, $\nu_{max.}$ 3 430, 1 785, and 1 700 cm^{-1}; δ (80 MHz) 1.95 (3 H, d, *J* 7 Hz), 4.54 (2 H, s), 5.00 (1 H, d, *J* 5 Hz), 5.17 (2 H, s), 5.50 (1 H, dd, *J* 5 and 9 Hz), 6.75—7.50 (12 H, m), and 7.61 (1 H, d, *J* 9 Hz). Irradiation at 588 Hz resulted in a collapse of the doublet at δ 1.95.

Reaction of the 4-*Mercaptoazetidinone* (2) *with* (E)-*Benzyl* 2-*Bromocrotonate* (17b).—A mixture of the 4-mercaptoazetidinone (2) (2.52 g), (*E*)-benzyl 2-bromocrotonate (17b) (2.80 g), and finely powdered anhydrous potassium carbonate (118 mg) was stirred in dry DMF (40 ml) at −50 °C for 1.5 h. The mixture was worked up as for the *Z*-isomer to give the product, presumably the bromide (19) (2.45 g), a mixture of stereoisomers, as an amorphous solid, $\nu_{max.}$ 3 420, 1 785, 1 735, and 1 690 cm^{-1}.

The bromide (19) (1.52 g) and finely powdered anhydrous potassium carbonate (207 mg) were stirred in dry HMPT (30 ml) at room temperature for 24 h. Work-up as for the experiment using the *Z*-isomer gave the penam esters (20) (86 mg) and (21) (224 mg) together with the olefin (22) (385 mg).

Conversion of the Bromide (19) *into the Olefin* (22).—The bromide (19) (100 mg) and finely powdered anhydrous potassium carbonate (14 mg) were stirred in dry HMPT (1 ml) at room temperature for 1 h. The mixture was diluted with ethyl acetate (10 ml) and washed with brine. The dried ($MgSO_4$) organic layer was evaporated and chromatographed to give an amorphous solid (79 mg). The n.m.r. spectrum of this material revealed a mixture (*ca.* 1 : 1) of unchanged bromide (19) and olefin (22).

Cyclisation of the Olefin (22).—A mixture of the olefin (22) (350 mg) and finely powdered anhydrous potassium carbonate (11 mg) were stirred in dry HMPT (5 ml) at room temperature for 24 h. The mixture was diluted with ethyl acetate (25 ml) and washed with brine. The dried ($MgSO_4$) organic layer was evaporated and the residue chromatographed to give the penam esters (20) (30 mg) and (21) (66 mg) as gums.

[9/190 *Received, 7th February,* 1979]

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