Total Synthesis of β-Lactamase Inhibitors based on the 4-Oxa-1-azabicyclo[3.2.0]heptan-7-one Ring System

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4-(2-Bromoethoxy)azetidin-2-one (4), 4-(1,3-dibromoisopropoxy)azetidin-2-one (5), 4-(1-benzyloxy-3-chloroisopropoxy)azetidin-2-one (6), 4-[(1-bromomethyl)prop-2-enoxy]azetidin-2-one (7), and 4-[3-bromo-1-(bromomethyl)propoxy]azetidin-2-one (8) have been synthesised and their use for the preparation of bicyclic β-lactam compounds has been investigated. On treatment with base, (4) gave 4-oxa-1-azabicyclo[3.2.0]heptan-7-one, (5) gave (3*RS*, 5*SR*)-3-(bromomethyl)-4-oxa-1-azabicyclo[3.2.0]heptan-7-one (9) and its (3*RS*, 5*RS*)-isomer (21), and (6) gave (3*RS*, 5*SR*)-3-(benzyloxymethyl)-4-oxa-1-azabicyclo[3.2.0]heptan-7-one (10) and its (3*RS*, 5*RS*)-isomer (22). Compound (7) did not undergo cyclisation; instead elimination occurred to give a conjugated diene, 4-(1-methylene-prop-2-enoxy)azetidin-2-one. Cyclisation of (8) gave not only the five-membered-ring compound but also the six-membered-ring compound, 4-(bromomethyl)-5-oxa-1-azabicyclo-[4.2.0]octan-8-one.

Compounds (9) and (21) reacted with a variety of nucleophilic reagents to give products derived by displacement of bromide. Catalytic hydrogenation of (10) removed the benzyl group to give the hydroxymethyl compound. Removal of the benzyl group from (22) under these conditions gave a hydroxymethyl compound which rearranged on silica gel to give 3,9-dioxa-7-azabicyclo[4.2.1]nonan-4-one.

Differences in the ^{1}H n.m.r. spectra of pairs of stereoisomers such as (9) and (21), and (10) and (22), are discussed. Relative stereochemistries have been deduced for two natural products previously isolated from *Streptomyces clavuligerus*. Compound (9) and some of its relatives have been found to be β-lactamase inhibitors.

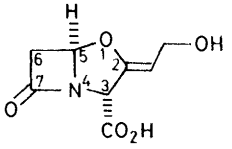
SINCE the isolation [1] and structural elucidation [2a] of the natural β-lactamase inhibitor clavulanic acid (1) † a number of syntheses of compounds containing the 7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane (clavam ‡) ring system have been reported.[3] We now wish to describe the preparation of some further novel compounds of this type, some of which have also been found to possess β-lactamase inhibitory activity. The compounds with which we were concerned were all unsubstituted at C-3 and were prepared by the extension of a general synthesis previously reported from these laboratories.[3a]

RESULTS AND DISCUSSION

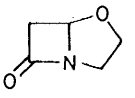
The simplest representative of this structural type, 4-oxa-1-azabicyclo[3.2.0]heptan-7-one (2) itself, was obtained from cyclisation of 4-(2-bromoethoxy)azetidin-2-one (4) using 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in ether. This cyclisation also proceeded readily when (4) was stirred overnight with anhydrous potassium carbonate in dimethylformamide (DMF). The alkoxyazetidinone (4) was prepared by condensation of 2-bromoethanol with 4-acetoxyazetidin-2-one (3) [4] in the presence of zinc acetate.

The alkoxyazetidinones (5)—(8) § were similarly prepared from acetoxyazetidinone (3) and the appropriate alcohols. When compound (5) was treated with potassium carbonate in DMF two isomeric clavams were produced. The major product (46% yield), as will be shown later, had the relative stereochemistry depicted in (9), whereas the minor product (11% yield) had structure (21). The chloroalkoxy-azetidinone (6) was also cyclised on treatment with potassium carbonate in DMF, but the reaction proceeded less readily than for (4) and (5). Again, two isomeric clavams were formed; the major isomer (10) was obtained in 14% yield and the minor isomer (22) in 8% yield.

When the alkoxyazetidinone (7) was treated with either DBU in ether or potassium carbonate in DMF there was no cyclisation to the 2-vinylclavams; ¶ instead,



(1)



(2)

the conjugated diene (25) was produced. Presumably the acidity of the allylic proton in (7) is such that the 1,2-elimination *via* (26) occurs to the complete exclusion of the internal nucleophilic displacement *via* (27).

The dibromoalkoxyazetidinone (8) could in principle undergo cyclisation to yield a five- or six-membered-ring. In practice, formation of the five-membered-ring was greatly preferred. Thus, cyclisation of (8) in the presence of potassium carbonate in DMF gave a pair of isomeric clavams (28) (inseparable by chromatography) in 36% yield and two isomeric 1-oxadethiacephams (29) in 3% yield.

Some of the clavams described so far have themselves been used to prepare further members of the series. In particular, the 2-(bromomethyl)clavam (9), from which

† Structure (1) denotes the optically active form; the remainder represent racemates.

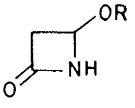
‡ The name clavam [2b] is used for the 4-oxa-1-azabicyclo-[3.2.0]heptan-7-one nucleus; the clavam ring system is numbered as shown in (1), by analogy with the numbering of the penam and cepham ring systems.

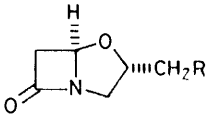
§ Compounds (6)—(8) were mixtures of diastereoisomers.

¶ The 2-vinylclavams were subsequently prepared by reaction of 2-(2-bromoethyl)clavam (28) with sodium *o*-nitrophenyl selenide and oxidation of the resulting selenide with hydrogen peroxide (see ref. 3*g*).

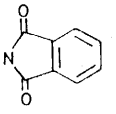
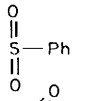
bromide was easily displaced by a variety of nucleophiles, provided a ready source of a group of closely related compounds. For example, sodium thiophenolate gave the thioether (11), with potassium iodide in DMF halide exchange occurred to give the (iodomethyl)-clavam (12), potassium phthalimide gave the phthalimido-derivative (13), sodium *p*-nitrophenolate gave the ether (14), and potassium *p*-nitrobenzoate and potassium formate gave the esters (15) and (16). Thioether derivatives provided further members by oxidation with *m*-chloroperbenzoic acid. Thus, (11) gave the crystalline sulphone (17) and two crystalline, isomeric sulphoxides (18) (separated by chromatography).

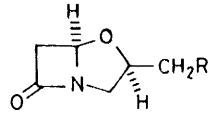
The *p*-nitrobenzoate (15) has been subjected to *X*-ray crystallography [5] and the results of this study established





(3) R = COMe
(4) R = CH_2CH_2Br
(5) R = $CH(CH_2Br)_2$
(6) R = $CH(CH_2Cl)CH_2OCH_2Ph$
(7) R = $CH(CH_2Br)CH{=}CH_2$
(8) R = $CH(CH_2Br)CH_2CH_2Br$

(9) R = Br
(10) R = OCH_2Ph
(11) R = SPh
(12) R = I
(13) R = 
(14) R = $OC_6H_4NO_2$-*p*
(15) R = $O_2CC_6H_4NO_2$-*p*
(16) R = OCHO
(17) R = 
(18) R = 
(19) R = OH
(20) R = OCONHPh

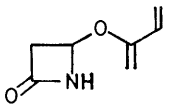


(21) R = Br
(22) R = OCH_2Ph
(23) R = OCHO
(24) R = OH

its stereochemistry as shown. From this, the stereochemistries of the bromides (9) and (21) and all compounds derived therefrom were readily deduced.

The (bromomethyl)clavam (21) appeared to be less reactive than its isomer (9). For example, when (9) was treated with potassium formate in DMF the formate (16) was obtained in 38% yield together with 16% recovered starting material, whereas (21), under exactly the same conditions, gave the formate (23) in 12% yield, with 55% recovery of starting material. Apparently the *endo*-bromomethyl group of (21) is less accessible to nucleophiles.

Hydrogenolysis of the (benzyloxymethyl)clavam (10) gave the alcohol (19), which was characterised by its spectroscopic properties, and by the formation of a crystalline carbamate (20) with phenyl isocyanate. When the isomeric (benzyloxymethyl)clavam (22) was subjected to catalytic hydrogenolysis it appeared, from t.l.c., that the alcohol (24) was being produced which, however, did not survive column chromatography on silica gel. The only product eluted from the column was the lactone (30), which appeared to have been formed from (24) during the chromatography. The same type of rearrangement has been reported [3k] for the analogous 3-methoxycarbonyl-derivative of (24). The fact that



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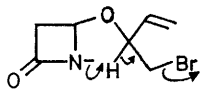

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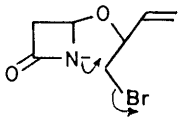

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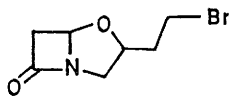

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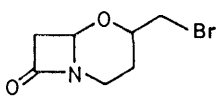

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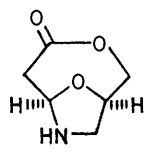

(30)

(24) undergoes this rearrangement, whereas its isomer (19) does not, is consistent with the assigned stereochemistries for the (benzyloxymethyl)clavams.

The clavams with the relative stereochemistry denoted by (9)—(20) had ^1H n.m.r. spectral properties which distinguished them from the stereoisomers (21)—(23). The most outstanding difference between the n.m.r. spectra of the isomers appears to be the chemical shift separation for the two C-3 protons. For clavams (9)—(20) the signals of the C-3 protons are separated by about 1.0—1.4 p.p.m. whereas the separations for the

^1H N.m.r. data (δ values at 60 MHz) for clavams in $CDCl_3$

Compound	2-H	3-H_2	5-H	6-H_2	C-2-CH_2X *
(9)	4.68	2.95, 4.17	5.52	2.88, 3.44	3.57
(10)	4.32	2.86, 3.85	5.35	2.70, 3.20	3.49
(16)	4.68	2.90, 4.10	5.48	2.88, 3.43	4.34
(21)	4.65	3.38, 3.78	5.36	2.93, 3.42	3.51
(22)	4.37	3.05, 3.50	5.20	2.73, 3.18	3.43
(23)	4.70	*ca.* 3.2, *ca.* 3.7	5.32	2.92, 3.27	4.38

* X = Br, OCH_2Ph, or OCHO.

isomeric clavams (21)—(23) are much less, *ca.* 0.4—0.5 p.p.m. Some representative n.m.r. data are summarised in the Table. It is also noted that for clavams (21)—(23) the C-5 proton resonates at *ca.* 0.15 p.p.m. to higher field than it does for the respective isomers (9), (10), and (16).

A recent report [2b] has described the isolation of optically active 2-(hydroxymethyl)clavam and 2-(formyloxymethyl)clavam from *Streptomyces clavuligerus*, but neither absolute nor relative stereochemistries were assigned to these compounds. Comparison of the reported n.m.r. spectral data for these natural products with those for our totally synthetic clavams showed that the natural compounds have the same relative stereochemistry as (16) and (19).

The clavams (9)—(20) are inhibitors [6] of the β-lactamase produced by *Staphylococcus aureus* Russell. Moreover, some of these compounds are able to synergistically enhance the antibacterial activity of ampicillin against such β-lactamase producing *Staphylococci*.[7] For example, when the sulphone (17) was combined with ampicillin at a level of 20 μg ml^{-1} it reduced the minimum inhibitory concentration of ampicillin from 500 to 1.25 μg ml^{-1} against a β-lactamase-producing strain of *Staphylococcus aureus*. The clavams (21)—(23) and clavam (2) were not β-lactamase inhibitors.

EXPERIMENTAL

M.p.s were determined using a Kofler hot-stage apparatus. I.r. spectra were recorded for solutions in chloroform, ^{1}H n.m.r. spectra were recorded at 60 MHz for solutions in $CDCl_3$ with tetramethylsilane as internal standard, and mass spectra were determined using an A.E.I. MS9 instrument. Merck silica gel 60 was used for column chromatography with ethyl acetate–light petroleum mixtures as eluant. Light petroleum refers to the fraction with b.p. 60—80 °C. Ether is diethyl ether. Solutions were dried with magnesium sulphate, and solvents were removed by evaporation under reduced pressure using a rotary evaporator with bath temperature below 30° C. All compounds were racemic.

4-(2-*Bromoethoxy*)*azetidin*-2-*one* (4).—4-Acetoxyazetidin-2-one [4] (3) (10 g) and 2-bromoethanol (10 g) were dissolved in dry benzene (150 ml) and finely powdered zinc acetate dihydrate (9 g) was added. The mixture was stirred and refluxed with azeotropic removal of water for 24 h. The mixture was cooled, diluted with ethyl acetate (200 ml), and washed twice with saturated sodium hydrogencarbonate solution and three times with water. The solution was dried and the solvent removed to yield a yellow oil (4.54 g) which was chromatographed to give the azetidin-2-one (4) as a pale yellow gum (2.6 g); $\nu_{max.}$ 3 390, 3 230, and 1 780 cm^{-1}; δ 3.10 (2 H, m), 3.60 (2 H, m), 3.95 (2 H, m), 5.27 (1 H, dd, *J* 3 and 2 Hz), and 7.60 (1 H, br s); *m/e* 196 (M^+ + H, 0.1%), 194 (M^+ + H, 0.1), 167 (3), 165 (3), 144 (5), 142 (32), 140 (27), 109 (80), 107 (82), and 43 (100) (Found: M^+ + H, 193.981 7. $C_5H_9{}^{79}BrNO_2$ requires *M*, 193.981 9).

4-*Oxa*-1-*azabicyclo*[3.2.0]*heptan*-7-*one* (2).—1,5-Diazabicyclo[5.4.0]undec-5-ene (1.8 g) was added dropwise to a stirred solution of the azetidin-2-one (4) (1.5 g) in ether (15 ml). The mixture was stirred for 18 h and was then concentrated to 5 ml. The concentrated solution was chromatographed to give *clavam* (2) as a colourless oil (270 mg); $\nu_{max.}$ 1 785 cm^{-1}; δ 2.84 (1 H, d, *J* 17 Hz), 2.9—3.6 (2 H, m), 3.7—4.4 (3 H, m), and 5.25 (1 H, d, *J* 2 Hz) (Found: M^+, 113.047 64. $C_5H_7NO_2$ requires *M*, 113.047 67).

4-(1,3-*Dibromoisopropoxy*)*azetidin*-2-*one* (5).—1,3-Dibromopropan-2-ol [8] (6.8 g) and 4-acetoxyazetidin-2-one (3) (6.0 g) were dissolved in dry benzene (100 ml). Finely powdered zinc acetate dihydrate (3.0 g) was added and the mixture was stirred and refluxed, with azeotropic removal of water, for 48 h. More 4-acetoxyazetidin-2-one (2.0 g) and zinc acetate dihydrate (1.0 g) were added, and refluxing was continued for a further 48 h. The mixture was cooled and filtered, and the solid was washed with ethyl acetate. The combined filtrate and washings were washed with saturated sodium hydrogencarbonate solution and water. The solution was dried and the solvent removed to yield a yellow gum (6.9 g), which was chromatographed to give the *azetidin*-2-*one* (5) as colourless prisms (3.9 g), m.p. 80—80.5 °C (ether–pentane); $\nu_{max.}$ 3 390, 3 220, and 1 780 cm^{-1}; δ 3.15 (2 H, m), 3.62 (4 H, d, *J* 5 Hz), 3.98 (1 H, m), 5.38 (1 H, dd, *J* 3 and 2 Hz), and 7.43 (1 H, br s) (Found: C, 25.3; H, 3.0; N, 4.5. $C_6H_9Br_2NO_2$ requires C, 25.11; H, 3.16; N, 4.88%).

4-(1-*Benzyloxy*-3-*chloroisopropoxy*)*azetidin*-2-*one* (6).—1-Benzyloxy-3-chloropropan-2-ol [9] (10.0 g) was converted into the title compound (6) using the process described for the preparation of (5). The azetidin-2-ones (6) were obtained as a pale yellow gum (7.9 g); $\nu_{max.}$ 3 380, 3 200, and 1 775 cm^{-1}; δ 2.7—3.3 (2 H, m), 3.5—4.0 (5 H, m), 4.49 (2 H, s), 5.17 (1 H, m), 7.00 (1 H, br s), and 7.30 (5 H, s).

1-*Bromobut*-3-*en*-2-*ol*.—Butadiene was passed into a stirred, ice-cooled solution of *N*-bromoacetamide (5.0 g) in water (15 ml) until the mixture no longer gave a positive reaction in the starch–iodide test. The solution was saturated with sodium bromide, extracted three times with ether, and the combined extracts dried and the ether removed by distillation. The residue was distilled to give 1-bromobut-3-en-2-ol as a colourless oil (3.6 g), b.p. 70—74 °C at 16 mmHg; [10] δ 2.90 (1 H, br s, exchanges with D_2O), 3.3—3.8 (2 H, AB of ABX), 4.48 (1 H, m), 5.2—6.3 (3 H, vinyl group).

4-[1-*Bromomethyl*)*prop*-2-*enoxy*]*azetidin*-2-*one* (7).—Finely powdered zinc acetate dihydrate (2.2 g) was suspended in dry benzene (50 ml) and the mixture was refluxed with azeotropic removal of water until no more water could be removed. 4-Acetoxyazetidin-2-one (3) (3.0 g) and 1-bromobut-3-en-2-ol (3.3 g) were added and the mixture was stirred and refluxed for 24 h. More 4-acetoxyazetidin-2-one (1.0 g) was added and refluxing was continued for a further 24 h. The mixture was cooled and filtered and the solid was washed well with ethyl acetate. The combined filtrate and washings were washed with saturated sodium hydrogencarbonate solution and water, dried, and the solvent removed to give a yellow oil (4.7 g) which was chromatographed to give the azetidin-2-ones (7) as a colourless gum (3.0 g); $\nu_{max.}$ 3 380, 3 210, and 1 780 cm^{-1}; δ 3.05 (2 H, m), 3.45 (2 H, d, *J* 6 Hz), 4.19 (1 H, q, *J* 6 Hz), 5.2—6.2 (4 H, complex), and 7.30 (1 H, br s).

4-[3-*Bromo*-1-(*bromomethyl*)*propoxy*]*azetidin*-2-*one* (8).—1,4-Dibromobutan-2-ol (12.0 g) was converted into the title compound (8) using the process described for the preparation of (5). The azetidin-2-ones (8) were obtained as a pale yellow oil (8.75 g); $\nu_{max.}$ 3 320, 3 200, and 1 780 cm^{-1}; δ 2.15 (2 H, m), 2.7—3.1 (2 H, m), 3.42 (2 H, d, *J* 5 Hz), 3.4—3.6 (2 H, m), 3.82 (1 H, quintet, *J* 5 Hz), 5.25 (1 H, m), and 7.15 (1 H, br s); *m/e* 304 (M^+, 0.4%), 302 (M^+, 0.8), 300 (M^+, 0.4), 260 (5), 258 (10), 256 (5), 217 (44), 215 (100), 213 (50), 139 (11), 137 (11), 135 (65), 133 (65), 109 (22), 107 (22), and 70 (70) (Found: M^+, 299.923 20. $C_7H_{12}{}^{79}Br_2NO_2$ requires *M*, 299.923 58).

(2RS, 5SR)-2-(*Bromomethyl*)*clavam* (9) *and* (2RS, 5RS)-2-(*Bromomethyl*)*clavam* (21).—The azetidin-2-one (5) (750 mg) was dissolved in dry DMF (5 ml) and anhydrous potassium carbonate (900 mg) was added to the stirred solution. The mixture was stirred for 24 h, then diluted with ethyl acetate (50 ml), washed three times with water, dried, and the solvent removed to give a colourless gum. The gum was chromatographed to give (2*RS*, 5*SR*)-2-(bromomethyl)clavam (9) as a colourless gum (250 mg); $\nu_{max.}$ 1 790 cm^{-1}; δ 2.88 (1 H, d, *J* 17 Hz), 2.95 (1 H, partly overlapped, dd, *J* 11.5 and 6 Hz), 3.44 (1 H, partly overlapped, dd, *J* 17 and 2.5 Hz), 3.57 (2 H, d, *J* 6 Hz), 4.17 (1 H, dd, *J* 11.5 and 6 Hz), 4.68 (1 H, quintet, *J* 6 Hz), and 5.52 (1 H, d, *J* 2.5 Hz); *m/e* 179 ($C_5H_8{}^{81}BrNO$, 24%), 177 ($C_5H_8{}^{79}BrNO$, 27%), 166 (9), 164 (10), 98 (100), and 70 (22): and (2RS, 5RS)-2-(*bromomethyl*)*clavam* (21) as colourless prisms (60 mg), m.p. 49—50 °C (ether–pentane); $\nu_{max.}$ 1 790 cm^{-1}; δ 2.93 (1 H, d, *J* 17 Hz), 3.38 (1 H, partly overlapped m), 3.42 (1 H, partly overlapped, dd, *J* 17 and 2.5 Hz), 3.51 (2 H, d, *J* 6 Hz), 3.78 (1 H, dd, *J* 11.5 and 6 Hz), 4.65 (1 H, quintet, *J* 6 Hz), and 5.36 (1 H, d, *J* 2.5 Hz); *m/e* 179 ($C_5H_8{}^{81}BrNO$, 38%), 177 ($C_5H_8{}^{79}BrNO$, 32%), 166 (22), 164 (34), 98 (100), and 70 (40) (Found: C, 35.1; H, 4.0; N, 6.8. $C_6H_8BrNO_2$ requires C, 35.0; H, 3.9; N, 6.8%).

(2RS, 5SR)-2-(*Benzyloxymethyl*)*clavam* (10) *and* (2RS, 5RS)-2-(*Benzyloxymethyl*)*clavam* (22).—The azetidin-2-one (6) (2.2 g) was dissolved in dry DMF (25 ml) and anhydrous potassium carbonate (1.2 g) and potassium iodide (0.12 g) were added to the solution. The mixture was stirred at 60—70 °C (bath temperature) for 20 h. The mixture was cooled, diluted with ethyl acetate (200 ml), washed with water (3 × 50 ml), dried, and the solvent removed to yield a yellow gum (1.1 g), which was chromatographed to give (2RS, 5SR)-2-(*benzyloxymethyl*)*clavam* (10) as a colourless oil (270 mg); $\nu_{max.}$ 1 785 cm^{-1}; δ 2.70 (1 H, d, *J* 16 Hz), 2.86 (1 H, dd, *J* 11 and 6 Hz), 3.20 (1 H, dd, *J* 16 and 6 Hz), 3.49 (2 H, d, *J* 4 Hz), 3.85 (1 H, dd, *J* 11 and 6.5 Hz), 4.1—4.55 (1 H, overlapped m), 4.45 (2 H, s), 5.35 (1 H, d, *J* 2 Hz), and 7.32 (5 H, s); *m/e* 233 (M^+, 5%), 205 (25), 132 (8), 112 (16), and 91 (100) (Found: M^+, 233.105 15. $C_{13}H_{15}NO_3$ requires *M*, 233.105 86): and (2RS, 5RS)-2-(*benzyloxymethyl*)*clavam* (22) as a colourless oil (150 mg); $\nu_{max.}$ 1 785 cm^{-1}; δ 2.73 (1 H, d, *J* 17 Hz), 2.9—3.2 (1 H, overlapped m), 3.18 (1 H, dd, *J* 17 and 2.5 Hz), 3.43 (2 H, d, *J* 4.5 Hz), 3.35—3.65 (1 H, overlapped m), 4.20—4.55 (1 H, overlapped m), 4.46 (2 H, s), 5.20 (1 H, d, *J* 2.5 Hz), and 7.32 (5 H, s); *m/e* 233 (M^+, 5%), 205 (20), 132 (5), 112 (15), and 91 (100) (Found: M^+, 233.104 93. $C_{13}H_{15}NO_3$ requires *M*, 233.105 86).

(2RS, 5SR)-2-[(*Phenylthio*)*methyl*]*clavam* (11).—2-(Bromomethyl)clavam (9) (210 mg) in dry DMF (2 ml) was added dropwise to a stirred solution of sodium thiophenolate [from thiophenol (130 mg) and 50% sodium hydride (55 mg)] in dry DMF (5 ml). The mixture was stirred for 16 h and was then diluted with ethyl acetate (50 ml). The solution was washed three times with water, dried, the solvent removed, and the resulting colourless oil chromatographed to give the [(*phenylthio*)*methyl*]*clavam* (11) as a colourless gum (205 mg); $\nu_{max.}$ 1 785 cm^{-1}; δ 2.80 (1 H, partly overlapped, dd, *J* 11 and 6 Hz), 2.84 (1 H, d, *J* 17 Hz), 3.13 (2 H, partly overlapped, d, *J* 6 Hz), 3.32 (1 H, partly overlapped, dd, *J* 17 and 2.5 Hz), 4.10 (1 H, dd, *J* 11 and 6 Hz), 4.52 (1 H, quintet, *J* 6 Hz), 5.43 (1 H, d, *J* 2.5 Hz), and 7.48 (5 H, m); *m/e* 235 (M^+, 100%), 192 (30), and 123 (71) (Found: M^+, 235.065 51. $C_{12}H_{13}NO_2S$ requires *M*, 235.066 69).

(2RS, 5SR)-2-(*Iodomethyl*)*clavam* (12).—2-(Bromomethyl)-clavam (9) (70 mg) and potassium iodide (600 mg) were dissolved in dry DMF (2 ml) and the solution was kept at room temperature for 5 days. The solution was diluted with ethyl acetate, washed three times with water, dried and the solvent removed to give a gum which was chromatographed to give the (*iodomethyl*)*clavam* (12) as a pale yellow gum (50 mg); $\nu_{max.}$ 1 790 cm^{-1}; δ 2.83 (1 H, partly overlapped; dd, *J* 11.5 and 6 Hz), 2.90 (1 H, d, *J* 17 Hz), 3.35 (2 H, partly overlapped, d, *J* 6 Hz), 3.42 (1 H, partly overlapped, dd, *J* 17 and 2.5 Hz), 4.18 (1 H, dd, *J* 11.5 and 6 Hz), 4.60 (1 H, quintet, *J* 6 Hz), and 5.54 (1 H, d, *J* 2.5 Hz); *m/e* 253 (M^+, 3%), 225 (100), 212 (30), 211 (40), 210 (15), 126 (75), and 98 (70) (Found: M^+, 252.959 82. $C_6H_8INO_2$ requires *M*, 252.960 16).

(2RS, 5SR)-2-(*Phthalimidomethyl*)*clavam* (13).—2-(Bromomethyl)clavam (9) (50 mg) and potassium phthalimide (50 mg) were dissolved in dry DMF (1 ml). The solution was stirred for 18 h, more potassium phthalimide (50 mg) was added, and stirring was continued for a further 24 h. The mixture was diluted with ethyl acetate, washed three times with water, dried, the solvent removed, and the resulting gum chromatographed to give the (*phthalimidomethyl*)*clavam* (13) as colourless needles (28 mg), m.p. 137—138 °C (ethyl acetate–light petroleum); $\nu_{max.}$ 1 785 and 1 720 cm^{-1}; δ 2.82 (1 H, d, *J* 17 Hz), 2.88 (1 H, partly overlapped, dd, *J* 12 and 6 Hz), 3.38 (1 H, dd, *J* 17 and 2.5 Hz), 3.84 (2 H, d, *J* 6 Hz), 4.06 (1 H, partly overlapped, dd, *J* 12 and 6 Hz), 4.76 (1 H, quintet, *J* 6 Hz), 5.51 (1 H, d, *J* 2.5 Hz), and 7.95 (4 H, m) (Found: C, 61.85; H, 4.7; N, 10.05. $C_{14}H_{12}N_2O_4$ requires C, 61.75; H, 4.45; N, 10.3%).

(2RS, 5SR)-2-(p-*Nitrophenoxymethyl*)*clavam* (14).—2-(Bromomethyl)clavam (9) (50 mg) in DMF (1 ml) was added to a solution of sodium *p*-nitrophenolate (40 mg) in dry DMF (2 ml), and the solution was stirred at room temperature for 20 h. More sodium *p*-nitrophenolate (50 mg) was added and stirring was continued at 60—70 °C (bath temperature) for 17 h. The mixture was diluted with ethyl acetate, washed three times with water, dried, the solvent removed, and the resulting yellow gum chromatographed to give the (*p-nitrophenoxymethyl*)*clavam* (14) as a colourless gum (12 mg); $\nu_{max.}$ 1 780, 1 610, 1 595, 1 515, 1 500, and 1 345 cm^{-1}; δ 2.95 (1 H, d, *J* 17 Hz), 3.08 (1 H, partly overlapped, dd, *J* 12 and 6 Hz), 3.48 (1 H, dd, *J* 17 and 2 Hz), 4.20 (1 H, partly overlapped, dd, *J* 12 and 6 Hz), 4.27 (2 H, partly overlapped, d, *J* 5 Hz), 4.85 (1 H, m), 5.60 (1 H, d, *J* 2 Hz), 7.22 (2 H, d, *J* 8 Hz), and 8.48 (2 H, d, *J* 8 Hz); *m/e* 264 (M^+, 15%), 236 (100), 222 (33), 181 (70), 169 (55), 152 (61), and 149 (100) (Found, M^+: 264.074 7. $C_{12}H_{12}N_2O_5$ requires *M*, 264.074 7).

(2RS, 5SR)-2-(p-*Nitrobenzoyloxymethyl*)*clavam* (15).—*p*-Nitrobenzoic acid (160 mg) and potassium carbonate (65 mg) were mixed together in hexamethylphosphoramide (2 ml). 2-(Bromomethyl)clavam (9) (50 mg) and potassium iodide (5 mg) were added to the solution, which was stirred for 66 h. The mixture was diluted with ethyl acetate, washed three times with water, dried, the solvent removed, and the resulting yellow gum chromatographed to give the p-*nitrobenzoate* (15) as colourless prisms (45 mg), m.p. 113—114 °C (ether); $\nu_{max.}$ 1 780, 1 720, 1 525, and 1 340 cm^{-1}; δ 2.80 (1 H, d, *J* 16 Hz), 2.88 (1 H, partly overlapped, dd, *J* 11 and 5.5 Hz), 3.32 (1 H, dd, *J* 16 and 2 Hz), 4.00 (1 H, dd,

J 11 and 6 Hz), 4.35 (2 H, d, *J* 4 Hz), 4.60 (1 H, partly overlapped, m), 5.43 (1 H, d, *J* 2 Hz), and 8.20 (4 H, s); *m/e* 264 (M^+ − CO, 12%), 251 (5), 249 (5), 204 (4), and 150 (100) (Found: C, 53.65; H, 4.4; N, 9.3. $C_{13}H_{12}N_2O_6$ requires C, 53.45; H, 4.15; N, 9.6%).

(2RS, 5SR)-2-(*Formyloxymethyl*)*clavam* (16).—2-(Bromomethyl)clavam (9) (80 mg) and sodium formate (130 mg) were dissolved in dry DMF (1 ml) and the solution was stirred at 70 °C (bath temperature) for 3 days. The mixture was diluted with ethyl acetate, washed three times with water, dried, the solvent removed, and the resulting gum chromatographed to give 2-(bromomethyl)clavam (9) (13 mg) and the formate (16) as a colourless gum (25 mg); $\nu_{max.}$ 1 790 and 1 735 cm^{-1}; δ 2.88 (1 H, d, *J* 17 Hz), 2.90 (1 H, partly overlapped, dd, *J* 11 and 6 Hz), 3.43 (1 H, dd, *J* 17 and 2 Hz), 4.10 (1 H, dd, *J* 11 and 6.5 Hz), 4.34 (2 H, d, *J* 4.5 Hz), 4.68 (1 H, m), 5.48 (1 H, d, *J* 2 Hz), and 8.30 (1 H, s); *m/e* 172 (M^+ + H, 3%), 143 (76), 130 (37), 112 (25), 82 (28), 70 (70), 55 (60), and 42 (100) (Found: M^+ + H, 172.060 6. $C_7H_{10}NO_4$ requires 172.060 9).

(2RS, 5SR)-2-(*Phenylsulphonylmethyl*)*clavam* (17) and (2RS, 5SR)-2-(*phenylsulphinylmethyl*)*clavam* (18).—2-[(Phenylthio)methyl]clavam (11) (200 mg) in dry methylene dichloride (5 ml) was stirred and ice-cooled while *m*-chloroperbenzoic acid (90% pure; 200 mg) in dry methylene dichloride (2 ml) was added dropwise. The solution was stirred and ice-cooled for 30 min and was then diluted with ethyl acetate (50 ml). The solution was washed with saturated sodium hydrogencarbonate solution, water, and saturated brine, dried, the solvent removed, and the residue chromatographed to give, in order of elution; the *sulphone* (17) as colourless needles (80 mg), m.p. 153—154 °C (ethyl acetate); $\nu_{max.}$ 1 785 and 1 150 cm^{-1}; δ 2.81 (1 H, partly overlapped, dd, *J* 12 and 6.5 Hz), 2.86 (1 H, d, *J* 17 Hz), 3.15—3.85 (3 H, complex), 4.21 (1 H, dd, *J* 12 and 6.5 Hz), 4.72 (1 H, quintet, *J* 6.5 Hz), 5.40 (1 H, d, *J* 2 Hz), and 7.70—8.25 (5 H, m) (Found: C, 53.75; H, 5.0; N, 5.2. $C_{12}H_{13}NO_4S$ requires: C, 53.9; H, 4.9; N, 5.25%), the less polar *sulphoxide* (18) as fine colourless needles (50 mg), m.p. 148—148.5 °C (ethyl acetate); $\nu_{max.}$ 1 790 and 1 040 cm^{-1}; δ 2.55—3.10 (4 H, complex), 3.45 (1 H, dd, *J* 16 and 2 Hz), 4.12 (1 H, dd, *J* 12 and 6.5 Hz), 4.89 (1 H, quintet, *J* 6.5 Hz), 5.52 (1 H, d, *J* 2 Hz), and 7.76 (5 H, m) (Found: C, 57.4; H, 5.5; N, 5.4. $C_{12}H_{13}NO_3S$ requires C, 57.35; H, 5.2; N, 5.6%): and the more polar *sulphoxide* (18) as colourless prisms (50 mg), m.p. 115—115.5 °C (ethyl acetate–light petroleum); $\nu_{max.}$ 1 785 and 1 040 cm^{-1}; δ 2.7—3.6 (5 H, complex), 4.12 (1 H, dd, *J* 11 and 6 Hz), 4.45 (1 H, quintet, *J* 6 Hz), 5.50 (1 H, d, *J* 2 Hz), and 7.70 (5 H, m) (Found: C, 57.2; H, 5.35; N, 5.3. $C_{12}H_{13}NO_3S$ requires: C, 57.35; H, 5.2; N, 5.6%).

(2RS, 5SR)-2-(*Hydroxymethyl*)*clavam* (19).—2-(Benzyloxymethyl)clavam (10) (120 mg) in 95% ethanol (10 ml) was shaken with 10% palladium–charcoal (80 mg) under hydrogen (1 atm) at room temperature for 6 h. The catalyst was removed by filtration and washed with ethanol. The solvent was removed from the filtrate and the resulting gum was chromatographed to give the alcohol (19) as a colourless oil (12 mg); $\nu_{max.}$ 3 380 and 1 785 cm^{-1}; δ 2.05 (1 H, br s, exchanges with D_2O), 2.81 (1 H, d, *J* 16 Hz), 2.88 (1 H, dd, *J* 11 and 6.5 Hz), 3.29 (1 H, dd, *J* 16 and 2 Hz), 3.45—3.85 (2 H, m), 3.92 (1 H, dd, *J* 11 and 7 Hz), 4.40 (1 H, m), and 5.33 (1 H, d, *J* 2 Hz).

(2RS, 5SR)-2-(N-*Phenylcarbamoyloxymethyl*)*clavam* (20).—2-(Hydroxymethyl)clavam (19) (12 mg), phenyl isocyanate (15 mg), and pyridine (2 mg) were dissolved in 1,2-dimethoxyethane (0.5 ml). The solution was kept at room temperature for 3 days and was then diluted with ethyl acetate (20 ml), washed with water, and dried. The solvent was removed and the resulting residue was chromatographed to give the *urethane* (20) as colourless prisms (15 mg), m.p. 104—105 °C (ether–pentane); $\nu_{max.}$ 3 350, 3 170, 1 780, 1 735, 1 600, and 1 520 cm^{-1}; δ 2.75 (1 H, d, *J* 16 Hz), 2.78 (1 H, partly overlapped, dd, *J* 11 and 6 Hz), 3.27 (1 H, dd, *J* 16 and 2 Hz), 3.95 (1 H, dd, *J* 11 and 6 Hz), 4.19 (2 H, d, *J* 4.5 Hz), 4.45 (1 H, m), 5.43 (1 H, d, *J* 2 Hz), 6.90 (1 H, br s), and 7.2—7.5 (5 H, m); *m/e* 262 (M^+, 10%), 220 (14), 162 (12), 119 (100), and 93 (15) (Found: M^+, 262.095 03. $C_{13}H_{14}N_2O_4$ requires *M*, 262.095 35) (Found: C, 59.55; H, 5.5; N, 10.35. $C_{13}H_{14}N_2O_4$ requires C, 59.55; H, 5.4; N, 10.7).

(2RS, 5RS)-2-(*Formyloxymethyl*)*clavam* (23).—2-(Bromomethyl)clavam (21) (130 mg) and sodium formate (200 mg) were dissolved in dry DMF (1.5 ml) and the solution was stirred at 70 °C (bath temperature) for 3 days. The mixture was diluted with ethyl acetate, washed three times with water, dried, the solvent removed, and the resulting gum chromatographed to give 2-(bromomethyl)clavam (21) (72 mg) and the formate (23) as a colourless gum (13 mg), $\nu_{max.}$ 1 790 and 1 735 cm^{-1}; δ 2.92 (1 H, d, *J* 17 Hz), 3.0—3.4 (2 H, complex), 3.65 (1 H, dd, *J* 11 and 6 Hz), 4.38 (2 H, d, *J* 4.5 Hz), 4.70 (1 H, m), 5.32 (1 H, d, *J* 2 Hz), and 8.27 (1 H, s); *m/e* 172 (M^+ + H, 2%), 143 (85), 130 (40), 112 (17), 98 (25), 82 (30), 70 (72), 55 (53), and 42 (100) (Found: M^+ + H, 172.060 7. $C_7H_{10}NO_4$ requires 172.060 9).

4-(1-*Methyleneprop*-2-*enoxy*)*azetidin*-2-*one* (25).—Compound (7) (500 mg) in dry ether (5 ml) was stirred while 1,5-diazabicyclo[5.4.0]undec-5-ene (400 mg) was added in one portion. The mixture was stirred for 5 h and was then passed through a short column of silica gel (10 g) eluting with ethyl acetate–light petroleum (1 : 1). Evaporation of solvent from the eluant gave a colourless gum (340 mg) which was purified further by chromatography to give the *diene* (25) as colourless prisms (115 mg), m.p. 75—76 °C (ether–pentane); $\lambda_{max.}$ (ethanol) 228 nm (ε 12 900); $\nu_{max.}$ 3 380, 3 200, 1 780, 1 640, and 1 590 cm^{-1}; δ 2.9—3.6 (2 H, AB part of ABX), 4.24 (1 H, br s), 4.38 (1 H, d, *J* 2 Hz), 5.29 (1 H, br d, *J* 11 Hz), 5.60 (1 H, partly overlapped, m), 5.72 (1 H, partly overlapped, dd, *J* 17 and 2 Hz), 6.33 (1 H, dd, *J* 17 and 11 Hz), and 7.72 (1 H, br s, exchanges with D_2O) (Found: C, 60.2; H, 6.6; N, 10.0. $C_7H_9NO_2$ requires: C, 60.4; H, 6.5; N, 10.05%).

2-(2-*Bromoethyl*)*clavam* (28) and 2-(*Bromomethyl*)-1-*oxadethiacepham* (29).—Compound (8) (4.0 g) in dry DMF (20 ml) was treated with anhydrous potassium carbonate (4.0 g) and the mixture was stirred for 40 h. Ethyl acetate (200 ml) was added and the mixture was washed three times with water, dried, the solvent removed, and the resulting gum chromatographed to give, in order of elution: 2-(2-Bromoethyl)clavams (28) (a 2 : 1 mixture of stereoisomers) as a colourless gum (1.06 g); $\nu_{max.}$ 1 785 cm^{-1}; δ 1.90—2.25 (2 H, m), 2.4—3.5 (*ca.* 5 H, complex), 3.91 (0.65 H, dd, *J* 11 and 6 Hz), 4.35 (1 H, m), 5.09 (0.35 H, d, *J* 2 Hz), and 5.28 (0.65 H, d, *J* 2 Hz): one stereoisomer of the 2-(*bromomethyl*)*oxacepham* (29) as a colourless gum (60 mg); $\nu_{max.}$ 1 760 cm^{-1}; δ 1.90 (2 H, m), 2.72 (1 H, d, *J* 15 Hz), 3.13 (1 H, part overlapped, dd, *J* 15 and 4 Hz), 3.2—3.9 (4 H, complex), 4.10 (1 H, m), and 5.08 (1 H, d, *J* 4 Hz); *m/e* 222 (M^+ + H, 1.3%), 221 (M^+, 3.8), 220 (M^+ + H, 1.4),

219 (M^+, 3.9), 193 (29), 191 (30), 178 (22), 176 (18), 140 (11), 135 (16), 133 (16), 126 (20), 112 (100), 98 (32), and 84 (53) (Found: M^+, 218.989 56. $C_7H_{10}{}^{79}BrNO_2$ requires M, 218.989 54); and the other stereoisomer of the 2-(*bromomethyl*)*oxacepham* (29) as a colourless gum (35 mg); $\nu_{max.}$ 1 760 cm^{-1}; δ 1.75 (2 H, m), 2.78 (1 H, d, *J* 15 Hz), 2.9—4.0 (6 H, complex), and 4.86 (1 H, d, *J* 4 Hz); *m/e* 222 (M^+ + H, 2%), 221 (M^+, 8), 220 (M^+ + H, 2), 219 (M^+, 8), 193 (28), 191 (29), 178 (38), 176 (36), 140 (7), 135 (23), 133 (23), 126 (7), 112 (100), 98 (32), 96 (30), and 84 (50) (Found: M^+, 218.989 34. $C_7H_{10}{}^{79}BrNO_2$ requires *M*, 218.989 54).

3,9-*Dioxa*-7-*azabicyclo*[4.2.1]*nonan*-4-*one* (30).—The (benzyloxymethyl)clavam (22) (200 mg) in tetrahydrofuran–ethanol (9 : 1) (20 ml) was shaken with 10% palladium–charcoal (200 mg) under hydrogen (1 atm) for 3 h. The catalyst was removed by filtration and was washed with tetrahydrofuran. The solvent was removed and the resulting gum was chromatographed to give the clavam (22) (100 mg) and, on eluting with ethyl acetate, the *lactone* (30) as a colourless gum (15 mg), $\nu_{max.}$ 3 470, 3 380, 1 730, and 1 625 cm^{-1}; δ (90 MHz; assignments confirmed by double-resonance experiments) 2.38 (1 H, br s, NH), 2.92 (2 H, m, 5-H_2), 3.28 (2 H, m, 8-H_2), 4.16 (1 H, dd, *J* 14 and 4 Hz, 2-H), 4.48 (1 H, d, *J* 14 Hz, 2-H), 4.64 (1 H, partly overlapped, m, 1-H), and 5.15 (1 H, dd, *J* 4 and 2 Hz, 6-H); *m/e* 143 (M^+, 38%), 101 (41), 100 (30), 82 (50), 70 (62), and 56 (100) (Found: M^+, 143.059 0. $C_6H_9NO_3$ requires *M*, 143.059 7).

We thank Dr. J. H. C. Nayler for his interest in this work, and Mr. J. W. Newman for skilful technical assistance.

[9/1889 *Received*, 28*th November*, 1979]

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