Total Synthesis of Analogues of the β-Lactam Antibiotics. Part 1. Isoclavam-3-carboxylates [1]

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4-Hydroxymethylazetidin-2-one (15a), prepared from 4-vinylazetidin-2-one (16) by reductive ozonolysis, was converted into 4-iodomethylazetidin-2-one (15c) by sequential reactions involving toluene-*p*-sulphonyl chloride and sodium iodide. Compound (15c) reacted with methyl glyoxylate hydrate in the presence of triethylamine to give methyl hydroxy-(2-iodomethyl-4-oxoazetidin-1-yl)acetate (13b) as a 1 : 1 mixture of diastereoisomers, which was transformed into methyl 7-oxo-3-oxa-1-azabicyclo[3.2.0]-heptane-2-carboxylate (12a), as a single *exo*-diastereoisomer, by the action of sodium hydride. The t-butyl, *p*-nitrobenzyl, and benzyl esters of 7-oxo-3-oxa-1-azabicyclo[3.2.0]heptane-2-*exo*-carboxylic acid, *i.e.* (12d—f), were similarly prepared.

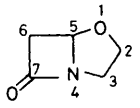
Brief treatment of the t-butyl ester (12d) with trifluoroacetic acid resulted in β-lactam cleavage to give (2-t-butoxycarbonyl-3-trifluoroacetyloxazolidin-4-yl)acetic acid (19c) which reacted further with trifluoroacetic acid to give (2-carboxy-3-trifluoroacetyloxazolidin-4-yl)acetic acid (19d). Hydrogenolysis of the benzyl ester (12f), in the presence of sodium hydrogen carbonate, afforded the sodium salt (12b) which underwent rapid β-lactam cleavage in aqueous solution.

The 7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane skeleton (1) (systematic numbering given), trivially referred to as 'clavam' [2,†] or 'oxapenam,' [3] is a structural feature of a growing number of antibiotics. Clavulanic acid (2a),[4] obtained from *Streptomyces clavuligerus*, is the parent and most important member; it is a potent irreversible inhibitor of several clinically important β-lactamases. 2-Hydroxymethylclavam (3a),[2] 2-formyloxymethylclavam (3b),[2] clavam-2-carboxylic acid (3c),[2] and 2-(3-alanyl)clavam (3d),[5] metabolites of the same micro-organism, are endowed with antifungal properties, as is 2-hydroxyethylclavam (4),[6] produced by *S. antibioticus*.

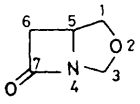
Inevitably, considerable effort has been devoted to the synthesis and biological evaluation of compounds incorporating the clavam nucleus.[7] With respect to structure–activity relationships, the following points can be made. Oxapenicillins, *e.g.* (5a), show a much lower order of antimicrobial activity than do the corresponding penicillins, *e.g.* (5b), possibly because of the inherent instability of the compounds.[8,9] Strong β-lactamase-inhibitory effects are retained in clavams of type (6).[10] Compounds lacking the exocyclic methylene group, *e.g.* (1) [11] and (7),[7] are usually inactive. However, some activity is retained in clavams of type (8; X = a heteroatom substituent) but not in their diastereoisomers (9; X = a heteroatom substituent).[11]

Our interest in compounds incorporating the isoclavam moiety (10) † stemmed from two considerations. First, such compounds had not previously been described and therefore a synthetic challenge was apparent. Secondly, there was the possibility that the β-lactam linkage of such compounds might be more reactive than that of clavams, *i.e.* the concerted fragmentation process (11) was stereoelectronically permissible (the cleavage of the β-lactam linkage by an enzymic nucleophile is implicated in the lethal action of the β-lactam antibiotics). We now report our studies which have resulted in the synthesis of isoclavam-3-carboxylates of type (12).

† The trivially named moieties clavam/isoclavam are numbered non-systematically as follows.



clavam



isoclavam

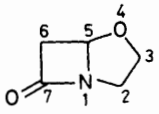
Results and Discussion

It was planned to generate isoclavams of type (12) by final closure of the 1,2-bond.† This approach defined azetidinones of type (13; X = a leaving group) as possible precursors. Hopefully, such precursors would be available from compounds of type (15; X = a leaving group) by an hydroxyalkylation reaction involving glyoxylic acid esters of type (14).[12]

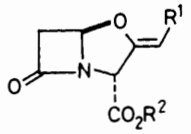
To test the feasibility of the approach, the tosyloxymethylacetidinone (15b) was selected for an initial study. Sequential treatment of the vinylazetidinone (16) [13] in methanol with ozone and sodium borohydride afforded the hydroxymethylazetidinone (15a) as a waxy brown solid (84% yield); an analytically pure sample was obtained by sublimation. The crude hydroxymethylazetidinone (15a) reacted with toluene-*p*-sulphonyl chloride in pyridine to give the crystalline tosyloxymethylazetidinone (15b) (50% yield after SiO_2 chromatography).

Triethylamine treatment [14] of a solution of the tosyloxazetidinone (15b) and methyl glyoxylate hydrate (14a) [15] in tetrahydrofuran (THF) gave the carbinolamide (13a), isolated as a syrup (57% yield after SiO_2 chromatography). Although apparently homogeneous (t.l.c. and n.m.r. spectroscopy), the carbinolamide (13a) was probably a mixture of diastereoisomers (*vide infra*). In the presence of sodium hydride in THF the carbinolamide underwent partial reaction to give a more mobile material which was isolated as a chromatographically homogeneous syrup in 15% yield following silica-gel chromatography. On the basis of its spectroscopic properties, the product was considered to be the isoclavam (12a) or (17). In particular, it possessed a strong i.r. absorption at 1 790 cm^{-1}, attributable to the β-lactam carbonyl group. Although the n.m.r. spectrum could not be fully interpreted, the two one-proton double doublets at δ 2.90 (*J* 16 and 2 Hz) and 3.50 (*J* 16 and 4 Hz) and the one-proton singlet at δ 5.55 were clearly assignable to the 6β-, 6α-, and 3-protons,‡ respectively. The presence of a base peak at *m/z* 112, corres-

‡ Non-systematic numbering.

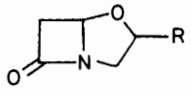


(1)



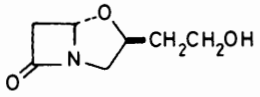
(2)

a; $R^1 = CH_2OH$, $R^2 = H$
b; $R^1 = Ph$, $R^2 = Me$
c; $R^1 = Ph$, $R^2 = Na$

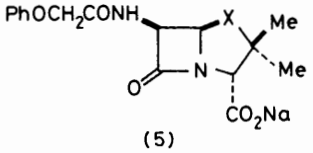


(3)

a; R = CH_2OH
b; R = CH_2OCHO
c; R = CO_2H
d; R $CH_2CH(NH_2)CO_2H$

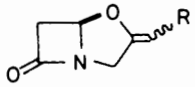


(4)

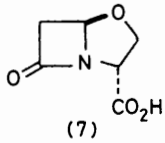


(5)

a; X = O
b; X = S



(6)



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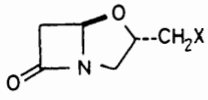
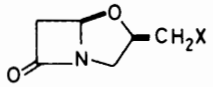
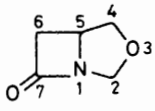


(8)



(9)



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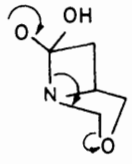
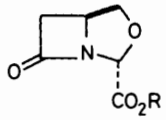
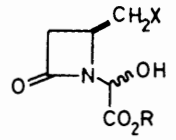


(11)



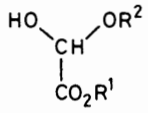
(12)

a; R = Me
b; R = Na
c; R = H
d; R = Bu^t
e; R = $CH_2C_6H_4NO_2$-*p*
f; R = CH_2Ph



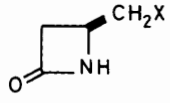
(13)

a; X = $OSO_2C_6H_4Me$-*p*, R = Me
b; X = I, R = Me
c; X = I, R = Bu^t
d; X = I, R = $CH_2C_6H_4NO_2$-*p*
e; X = I, R = CH_2Ph



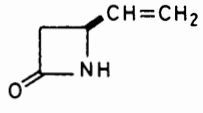
(14)

a; R^1 = Me, R^2 = H
b; R^1 = Bu^t, R^2 = H
c; R^1 = $CH_2C_6H_4NO_2$-*p*, R^2 = Et
d; R^1 = CH_2Ph, R^2 = H

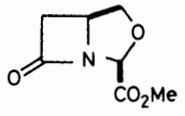


(15)

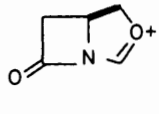
a; X = OH
b; X = $OSO_2C_6H_4Me$-*p*
c; X = I



(16)



(17)



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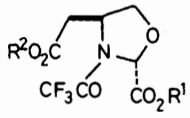
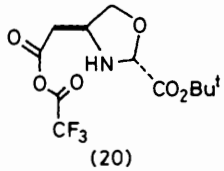


(19)

a; $R^1 = R^2$ = Me
b; R^1 = Bu^t, R^2 = Me
c; R^1 = Bu^t, R^2 = H
d; $R^1 = R^2$ = H



(20)

ponding to $C_5H_6NO_2$ by accurate mass measurement, was attributable to the ion (18).

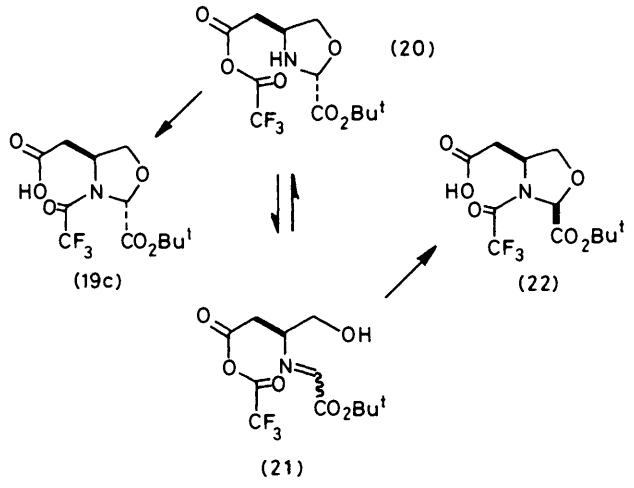
The poor yield of the isoclavam (12a) [or (17)] could be partly attributed to an incomplete reaction since *ca.* 45% of the starting carbinolamide (13a) was recovered. However, the moderate material balance (*ca.* 60%), coupled with the observation that the addition of more sodium hydride did not substantially improve the yield of the isoclavam, suggested that other reactions were competing. Accordingly, it was decided to examine the behaviour of the carbinolamide (13b).

In the presence of sodium iodide in refluxing acetone, the tosylmethylazetidinone (15b) was readily transformed into the crystalline iodomethylazetidinone (15c) (90% yield). Hydroxyalkylation of the iodomethylazetidinone (15c) with methyl glyoxylate hydrate (14a) gave the carbinolamide (13b) (66% yield after SiO_2 chromatography); n.m.r. spectroscopy clearly revealed that the material was a 1 : 1 mixture of diastereoisomers. Sodium hydride converted the carbinolamide (13b) into a syrupy material (58% yield after SiO_2 chromatography), identical with the isoclavam obtained from the carbinolamide (13a). The isolation of the isoclavam as a single diastereoisomer in 58% yield, starting from the carbinolamide (13b) as a 1 : 1 mixture of diastereoisomers, strongly suggests that the isoclavam possesses the stereostructure (12a). The *cis* arrangement of the 3-carboxylic acid moiety and the 5-hydrogen atom * represents the thermodynamically favoured situation in related systems.[16] Presumably, a mixture of the isoclavams (12a) and (17) is initially produced in the cyclisation reaction but, under the reaction conditions, the isoclavam (17) is isomerised to the isoclavam (12a).

In the hope of obtaining the salt (12b) for biological evaluation, the isoclavam (12a) was treated with sodium hydroxide (1 mol equiv.) in aqueous THF; only non-β-lactam products resulted. It is noteworthy that, under corresponding conditions, the clavam (2b) is reported to give the salt (2c).[17] Evidently, the β-lactam ring of the isoclavam (12a) is more susceptible to attack by sodium hydroxide than is that of the clavulanate (2b).

To examine the feasibility of generating the isoclavam (12c) under acidic conditions, efforts were made to obtain the t-butyl ester (12d). The carbinolamide (13c), prepared by hydroxyalkylation of the iodomethylazetidinone (15c) with t-butyl glyoxylate hydrate (14b),[18] was isolated as a syrupy 1 : 1

* Non-systematic numbering.



Scheme

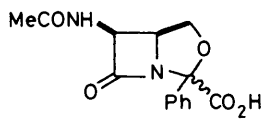
mixture of diastereoisomers (79% yield after SiO_2 chromatography). In the presence of sodium hydride the carbinolamide (13c) afforded the crystalline isoclavam (12d) in 59% yield, The spectroscopic properties of the isoclavam (12d) were in good agreement with those observed for the isoclavam (12a). Furthermore, by 220-MHz ^1H n.m.r. spectroscopy, it was possible to resolve the 1α- and 1β-protons * into two one-proton double doublets at δ 3.95 (*J* 8 and 5 Hz) and 4.50 (*J* 8 and 7 Hz). It is noteworthy that a methylene group adjacent to an oxygen atom in a five-membered ring typically shows a geminal coupling constant of *ca.* 8 Hz.[19]

The isoclavam (12d) was treated briefly (15 min) with trifluoroacetic acid and, following evaporation of the solution, the acidic product was esterified with diazomethane. The crystalline material which resulted (89% yield) was considered to be the dimethyl ester (19a), on the basis of its analytical and spectroscopic properties.

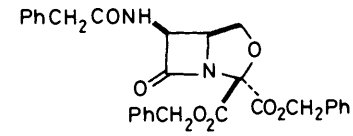
Whilst the isolation of the oxazolidine (19a) clearly revealed the lability of both the β-lactam ring and the t-butyl ester group towards trifluoroacetic acid, it gave no clue as to their relative labilities. Accordingly, the isoclavam (12d) was treated at 0 °C for *ca.* 0.5 min with trifluoroacetic acid. Work-up and treatment of the product with diazomethane gave the oxazolidine (19b) (71% yield after SiO_2 chromatography). Evidently, the β-lactam ring of the isoclavam (12d) is more reactive towards trifluoroacetic acid than is the t-butyl ester moiety.

Presumably, the formation of the acid (19c) is triggered by attack of trifluoroacetic acid on the β-lactam ring of the isoclavam (12d) to give the mixed anhydride (20) as a reaction intermediate. Analogous reactions have been observed in penicillin chemistry.[20]

As illustrated in the Scheme, the possibility exists that the intermediate (20) may afford, in addition to the oxazolidine (19c), the diastereoisomer (22) by way of the imine (21). In consequence, the oxazolidine (22) [or a mixture of the oxazolidines (19c) and (22)] represents an alternative possibility for the product of the reaction of the isoclavam (12d) with trifluoroacetic acid. In the n.m.r. spectra of the derived methyl esters, presumed to possess the structures (19a) and (19b), the 2-protons of the oxazolidine rings appeared as two half-proton singlets [δ 5.60 and 5.80br for (19a) and δ 5.30 and 5.50br for (19b)]. In principle, this result may be ascribed to the presence of two diastereoisomers or to a single diastereoisomer existing in solution as two rotameric forms due to restricted rotation about the amide bond. That the latter explanation was the correct one was indicated by variable-temperature n.m.r. spectroscopic studies involving the presumed oxazolidine (19a). At *ca.* 140 °C in [$^2H_6$]dimethyl sulphoxide the signals at δ 5.60 and 5.80 coalesced to a broad singlet at δ 5.70; the original spectrum was restored on cooling. In the light of the foregoing information it seems likely that the oxazolidines possess the stereostructures (19a) and (19b).



(23)



(24)

The *p*-nitrobenzyl ester moiety has proven to be a particularly effective protector of the carboxylic acid moiety in sensitive substrates; its hydrogenolytic removal in the presence of sodium hydrogen carbonate affords the sodium salt directly.[15] Accordingly, efforts were directed to the preparation of the isoclavam (12e). Treatment of the iodomethylazetidinone (15c) with *p*-nitrobenzyl ethoxyglycolate (14c)[15] afforded the carbinolamide (13d) as a syrupy 1 : 1 mixture of diastereoisomers (70% yield after SiO_2 chromatography). Disappointingly, the cyclisation reaction with sodium hydride to give the isoclavam (12e) was inefficient and somewhat capricious. Operating on a 0.6 mmol scale, the optimum yield of the isoclavam (12e) was 30%; cleavage of the ester function represented a competing reaction since *p*-nitrobenzyl alcohol was isolated in 50% yield. On occasions, particularly when the reaction was scaled up, very little of the isoclavam (12e) was isolated. Attempts to derive the salt (12b), by hydrogenolysis of the isoclavam (12e) in the presence of sodium hydrogen carbonate, afforded non-β-lactam products.

The problems associated with the aforementioned cyclisation were circumvented by the use of the carbinolamide (13e), prepared as a 1 : 1 mixture of diastereoisomers (93% yield after SiO_2 chromatography) from the iodomethylazetidinone (15c) and benzyl glyoxylate hydrate (14d) [prepared from D-tartaric acid by a route analogous to that used for the preparation of the glyoxylate (14a)[15]]. The isoclavam (12f) was isolated as a syrup (50% yield after SiO_2 chromatography). Furthermore, when hydrogenolysed over palladium in the presence of sodium hydrogen carbonate (1 mol equiv.), the salt (12b) was isolated as a foam (89% yield). The salt (12b) was characterised by its i.r. and n.m.r. spectral properties and by its conversion into the methyl ester (12a) (48% yield after SiO_2 chromatography) by the action of iodomethane in *NN*-dimethylformamide (DMF).

Although it showed no antibacterial activity and no β-lactamase-inhibitory properties, the salt (12b) underwent substantial decomposition in deuterium oxide solution (*ca.* 80% by n.m.r. spectroscopy) within 12 h. Presumably, the β-lactam linkage of the isoclavam (12b) is endowed with a high chemical reactivity, which probably precludes a meaningful evaluation of its biological properties. The ester (12d) showed no antifungal activity.

Following our preliminary communication of the work discussed in this paper, Hakimelahi and Just reported the preparation of the iso-oxapenicillins (23) and (24), by a 2,3-bond-forming * strategy.[21]

* Non-systematic numbering.

Experimental *

THF was dried over calcium hydride and, immediately prior to use, was distilled. Sodium hydride (60% dispersion in mineral oil) was washed (3×) with sodium-dried light petroleum (b.p. 40—60 °C) and stored *in vacuo* (over $CaCl_2$). Pyridine was dried over potassium hydroxide, and was then distilled and stored over molecular sieves (Type 4A). Ethereal diazomethane was prepared by adding an ethereal solution of 'diazald' to aqueous potassium hydroxide.[22] Ozone was generated using a Wallace and Tieman ozonator. All other solvents and chemicals were used as purchased.

T.l.c. was performed on Scheicher and Schull plastic sheets coated with silica gel (F 1500 LS254); the plates were initially examined under u.v. light and spots were then visualised with either iodine vapour or an aqueous potassium permanganate spray. Column chromatography was effected, under pressure, using Merck Kieselgel H (Type 60).

Evaporations were carried out at *ca.* 40 °C using a Buchi rotary evaporator. M.p.s were determined using a Kofler hot-stage apparatus and were uncorrected. I.r. spectra were recorded using a Hilger and Watts Infrascan machine. A Uniscan SP 800 spectrometer was employed to determine u.v. spectra. ^{1}H N.m.r. spectra were run using $SiMe_4$ or sodium 3-(trimethylsilyl)propane-1-sulphonate as internal standard; spectra were measured at 60 MHz using a Varian EM 360 spectrometer, or at 90 MHz using a Bruker Spectrospin spectrometer. Mass spectra were determined using an A.E.I. MS9 spectrometer operating at 70 eV. Microanalyses were performed using a Hewlett-Packard 185 CHN Analyser.

Reaction of the Vinylazetidinone (16) *with Ozone–Sodium Borohydride.*—A solution of the vinylazetidinone (16) (2.00 g, 20.6 mmol) in methanol (50 cm^3) at −78 °C was saturated with ozone. After the removal of excess of ozone by flushing the solution with nitrogen, sodium borohydride (2.00 g, 52.9 mmol) was added in portions during 0.5 h and the mixture was allowed to warm to room temperature. After complete dissolution of the sodium borohydride and when effervescence had subsided, Amberlite IR 120 (H^+) ion-exchange resin was added to the solution until a pH of 5—6 was attained. The methanolic solution was decanted and the resin was washed with methanol (3 × 50 cm^3). Evaporation of the combined washings gave a residue which was dissolved in methanol (100 cm^3) and the solution was filtered and re-evaporated; this operation was repeated twice more. Benzene was added to the residue and the solution was evaporated; the product was dried (*in vacuo*, P_2O_5) and the derived *4-hydroxymethylazetidin-2-one* (15a) was isolated as a waxy brown solid (1.75 g, 84%). A sample, purified by sublimation, showed m.p. 60—66 °C; $\nu_{max.}$ (KBr) *inter alia* 3 400br (NH and OH) and 1 740br cm^{-1} (β-lactam C=O); δ (D_2O) 2.70 (1 H, dd, *J* 16 and 2 Hz, 3-H), 3.07 (1 H, dd, *J* 16 and 4 Hz, 3-H) and 3.50—3.90 (total 3 H, m, 4-H and C*H*$_2$OH) [irradiation at δ 3.75 caused the signals at δ 2.70 and 3.07 to collapse to doublets (each *J* 16 Hz)]; *m/z inter alia* 102 (*M*H$^+$) and 28 (CO^+, base peak) (Found: C, 47.6; H, 7.1; N, 13.8. $C_4H_7NO_2$ requires C, 47.5; H, 6.95; N, 13.9%).

Reaction of the Hydroxymethylazetidinone (15a) *with Toluene-p-sulphonyl Chloride.*—Toluene-*p*-sulphonyl chloride (3.40 g, 17.8 mmol) was added to a stirred solution of the crude hydroxymethylazetidinone (15a) (1.70 g, 16.8 mmol) in dry pyridine (50 cm^3) at −30 °C. After 1 h the mixture was allowed to warm to 0 °C. Chloroform was added after a further 1 h and the mixture was washed with dilute hydrochloric acid. Evaporation of the dried ($MgSO_4$) organic layer left a dark red oil which was purified by silica-gel chromatography (EtOAc as eluant) to give *4-(p-tolylsulphonyloxymethyl)-azetidin-2-one* (15b) (2.15 g, 50%) as a cream-coloured solid. A sample, recrystallised from ethyl acetate–light petroleum, was obtained as white needles, m.p. 102—103 °C; $\nu_{max.}$ (KBr) *inter alia* 3 420 and 3 240 (NH) and 1 775sh and 1 760 cm^{-1} (β-lactam C=O); $\lambda_{max.}$ (EtOH) 221sh (ε 7 300), 231 (8 700), 263 (820) and 274 nm (730); δ ($CDCl_3$) 2.45 (3 H, s, Me), 2.45—3.35 (2 H, m, 3-H_2), 3.75—4.35 (total 3 H, m, 4-H and CH_2O), 6.5br (1 H, s, NH), and 7.35 and 7.85 (each 2 H, d, *J* 8 Hz, together C_6H_4) [addition of D_2O caused the signal at δ 6.5 to disappear and that at 2.45—3.35 to collapse to a double doublet (*J* 15 and 2 Hz) at δ 2.63 and a double doublet (*J* 15 and 4 Hz) at δ 3.10]; *m/z inter alia* 255 (*M*$^+$) and 91 ($C_7H_7^+$, base peak) (Found: C, 52.1; H, 5.2; N, 5.55%; *M*$^+$, 255.0580. $C_{11}H_{13}NO_4S$ requires C, 51.8; H, 5.10; N, 5.50%; *M*, 255.0565).

Reaction of the Tosyloxymethylazetidinone (15b) *with Methyl Glyoxylate Hydrate* (14a).—To a stirred solution of the tosyloxymethylazetidinone (15b) (0.800 g, 3.14 mmol) in dry THF (15 cm^3) was added methyl glyoxylate hydrate (14a) (0.840 g, 7.9 mmol) followed by triethylamine (0.320 g, 3.17 mmol). After being stirred for 16 h the solution was evaporated to dryness and the residue was dissolved in ethyl acetate. The solution was washed with brine (2×) and was dried ($MgSO_4$) and evaporated to dryness. Purification of the product by silica-gel chromatography [EtOAc–light petroleum (1 : 1) as eluant] afforded methyl hydroxy-[2-oxo-4-(*p*-tolylsulphonyloxymethyl)azetidin-1-yl]acetate (13a) (0.610 g, 57%) as a chromatographically homogeneous syrup; $\nu_{max.}$ (film) *inter alia* 3 440 (OH), 1 770 (β-lactam C=O), and 1 750 cm^{-1} (ester C=O); $\lambda_{max.}$ (EtOH) 220sh (ε 9 700), 230 (11 300), 263 (1 000), and 274 nm (860); δ ($CDCl_3$) 2.50 (3 H, s, CMe), 2.50—3.35 (2 H, m, $COCH_2$), 3.85 (3 H, s, OMe), 3.95—4.25 (total 3 H, m, $CHCH_2O$), 4.65br (1 H, s, OH), 5.43 [1 H, d, *J* 6 Hz, C*H*(OH)], and 7.35 and 7.80 (each 2 H, s, together C_6H_4) (addition of D_2O caused the signal at δ 4.65 to disappear and that at δ 5.43 to collapse to a singlet); *m/z inter alia* 326 (*M*$^+$ − OH) and 91 ($C_7H_7^+$, base peak) [Found: (*M*$^+$ − OH), 326.0690. Calc. for $C_{14}N_{16}NO_6S$: *m/z* 326.0698].

Reaction of the Azetidinone (13a) *with Sodium Hydride.*—Sodium hydride (0.027 g, 1.13 mmol) was added to a stirred solution of the azetidinone (13a) (0.320 g, 0.93 mmol) in dry THF (15 cm^3) at 0 °C. After 0.5 h the mixture was allowed to warm to room temperature. After being kept for 23 h, the mixture was treated with glacial acetic acid (0.070 g, 1.17 mmol) and was then diluted with ethyl acetate. After being washed with water, the organic phase was dried ($MgSO_4$) and evaporated to dryness to leave a pale-yellow syrup containing two components (t.l.c.). These were separated by silica-gel chromatography [EtOAc–light petroleum (1 : 1) as eluant].

The first eluted material, isolated as a syrup (0.016 g, 15%), was methyl 7-oxo-3-oxa-1-azabicyclo[3.2.0]heptane-2-*exo*-carboxylate (12a); $\nu_{max.}$ (film) *inter alia* 1 790 (β-lactam C=O) and 1 745 cm^{-1} (ester C=O); δ ($CDCl_3$) 2.90 (1 H, dd, *J* 16 and 2 Hz, 6-H), 3.50 (1 H, dd, *J* 16 and 4 Hz, 6-H), 3.65 (3 H, s, OMe), 3.65—4.60 (total 3 H, m, 4-H_2 and 5-H), and 5.55 (1 H, s, 2-H); *m/z inter alia* 143 (*M*$^+$ − CO) and 112 (*M*$^+$ − $C_2H_3O_2$, base peak) [Found: (*M*$^+$ − $C_2H_3O_2$), 112.0409. Calc. for $C_5H_6NO_2$: *m/z*, 112.0399].

The second eluted material (0.144 g, 45%) was identical with the starting azetidinone (13a) (t.l.c. and n.m.r. spectroscopy).

Reaction of the Tosyloxymethylazetidinone (15b) *with Sodium Iodide.*—A mixture of the tosylmethylazetidinone (15b) (2.00 g, 7.8 mmol), sodium iodide (7.45 g, 50 mmol), and acetone (75 cm^3) was heated under reflux for 6 h. Evaporation of the

* Systematic numbering used throughout this section.

solvent under reduced pressure left a residue which was partitioned between ethyl acetate and water. The organic phase was dried ($MgSO_4$) and evaporated to dryness. Purification of the product by silica-gel chromatography (EtOAc as eluant) gave *4-iodomethylazetidin-2-one* (15c) (1.49 g, 90%) as a pale-yellow solid. A sample, recrystallised from diethyl ether, showed m.p. 105—107 °C; $\nu_{max.}$ (KBr) *inter alia* 3 330 (NH), and 1 755 and 1 725 cm^{-1} (β-lactam C=O); δ ($CDCl_3$) 2.65 (1 H, ddd, *J* 15, 2, and 1.5 Hz, 3-H), 3.15 (1 H, ddd, *J* 16, 4, and 2 Hz, 3-H), 3.30 (2 H, d, separation 7 Hz, CH_2I), 3.75—4.05 (1 H, m, 4-H), and 6.50br (1 H, s, NH) [addition of D_2O caused the signal at δ 6.50 to disappear, that at δ 2.65 to collapse to a double doublet (*J* 16 and 2 Hz), and that at δ 3.15 to collapse to a double doublet (*J* 16 and 4 Hz)]; *m/z* 211 (M^+) and 168 ($M^+ - C_2H_3O$, base peak) (Found: C, 23.1; H, 2.90; N, 6.60. C_4H_6INO requires C, 22.8; H, 2.85; N, 6.65%).

Reaction of the Iodomethylazetidinone (15c) *with Methyl Glyoxylate Hydrate* (14a).—Methyl glyoxylate hydrate (14a) (0.890 g, 8.4 mmol) and triethylamine (0.121 g, 1.2 mmol) were added to a solution of the iodomethylazetidinone (15c) (0.250 g, 1.2 mmol) in dry THF (15 cm^3). The solution was kept for 12 h and was then evaporated to dryness to leave a pale-yellow oil which was dissolved in ethyl acetate. The solution was washed in turn with dilute hydrochloric acid and brine (2×) and the organic phase was dried ($MgSO_4$) and evaporated to dryness. Purification of the product by silica-gel chromatography [EtOAc–light petroleum (1 : 2) as eluant] gave methyl hydroxy-(2-iodomethyl-4-oxoazetidin-1-yl)acetate (13b) (0.233 g, 66%) as a syrupy 1 : 1 mixture of diastereoisomers; $\nu_{max.}$ (film) *inter alia* 3 400br (OH) and 1 750 cm^{-1} (β-lactam and ester C=O); δ ($CDCl_3$) 2.75 (1 H, dd, *J* 16 and 2 Hz, COC*H*H-CH), 3.00—4.20 (total 4 H, m, CH*HCHCH*$_2$I), 3.85 (3 H, s, OMe), 5.00—5.20 (1 H, m, OH), and 5.45—5.60 [1 H, m, C*H*(OH)] [addition of D_2O caused the signal at δ 5.00—5.20 to disappear and that at δ 5.45—5.60 to sharpen to two singlets (each 0.5 H) at δ 5.48 and 5.53]; *m/z inter alia* 240 ($M^+ - C_2H_3O_2$, base peak) [Found: ($M^+ - C_2H_3O_2$), 239.9550. Calc. for $C_5H_7INO_2$: *m/z*, 239.9524].

Reaction of the Azetidinone (13b) *with Sodium Hydride.*—Sodium hydride (0.020 g, 0.83 mmol) was added to a stirred solution of the azetidinone (13b) (0.230 g, 0.77 mmol) in dry THF (12 cm^3) at 0 °C. After 0.5 h the mixture was allowed to warm to room temperature and was kept for 2 h. Glacial acetic acid (0.05 g, 0.85 mmol) was then added to the mixture which was then diluted with ethyl acetate and washed with brine (2×). The dried ($MgSO_4$) organic phase was evaporated to dryness and the product was purified by silica-gel chromatography [EtOAc–light petroleum (1 : 2) as eluant] to give a material (0.076 g, 58%) that was identical (i.r. and n.m.r. spectroscopy) with the isoclavam (12a).

Reaction of the Iodomethylazetidinone (15c) *with t-Butyl Glyoxylate Hydrate* (14b).—t-Butyl glyoxylate hydrate (14b) [18] (1.00 g, 6.8 mmol) and triethylamine (0.240 g, 2.4 mmol) were added to a stirred solution of the iodomethylazetidinone (15c) (0.500 g, 2.4 mmol) in dry THF (14 cm^3). After 15 h the solvent was evaporated off under reduced pressure and the residue was partitioned between ethyl acetate and brine. The organic phase was dried ($MgSO_4$) and evaporated to dryness. Purification of the product by silica-gel chromatography [EtOAc–light petroleum (1 : 1) as eluant] gave t-butyl hydroxy-(2-iodomethyl-4-oxoazetidin-1-yl)acetate (13c) (0.640 g, 79%) as a syrupy 1 : 1 mixture of diastereoisomers; $\nu_{max.}$ (film) *inter alia* 3 400 br (OH), 1 760 (β-lactam C=O), and 1 740 cm^{-1} (ester C=O); δ ($CDCl_3$) 1.50 (9 H, s, CMe_3), 2.60—4.20 [total 6 H, m, CH_2-$CHCH_2$ and CH(O*H*)], and 5.25 and 5.32 [each 0.5 H, s, together C*H*(OH)] (addition of D_2O caused the signal centred at δ 4.00 to decrease in intensity); *m/z inter alia* 324 ($M^+ - OH$) and 240 ($M^+ - C_5H_9O_2$, base peak) [Found: ($M^+ - C_5H_9O_2$), 239.9546. Calc. for $C_5H_7INO_2$: *m/z*, 239.9523].

Reaction of the Azetidinone (13c) *with Sodium Hydride.*—Sodium hydride (0.057 g, 2.4 mmol) was added to a stirred solution of the azetidinone (13c) (0.650 g, 1.9 mmol) in dry THF (30 cm^3) at 0 °C. After 0.5 h the mixture was warmed to room temperature and was kept for 6 h. Glacial acetic acid (0.144 g, 2.4 mmol) was then added to the mixture which was then diluted with ethyl acetate. The organic phase, after being washed with brine, was dried ($MgSO_4$) and evaporated to dryness. Purification of the product by silica-gel chromatography [EtOAc–light petroleum (1 : 1) as eluant] gave crystalline *t-butyl 7-oxo-3-oxa-1-azabicyclo*[3.2.0]*heptane-2-exo-carboxylate* (12d) (0.240 g, 59%). A sample, recrystallised from light petroleum, was obtained as needles, m.p. 63—65 °C; $\nu_{max.}$ (KBr) *inter alia* 1 790 (β-lactam C=O) and 1 745 cm^{-1} (ester C=O); δ (220 MHz; $CDCl_3$) 1.50 (9 H, s, CMe_3), 2.90 (1 H, dd, *J* 16 and 2.5 Hz, 6-H), 3.50 (1 H, dd, *J* 16 and 5 Hz, 6-H), 3.95 (1 H, dd, *J* 8 and 5 Hz, 4-H), 4.20—4.30 (1 H, m, 5-H), 4.50 (1 H, dd, *J* 8 and 7 Hz, 4-H), and 5.50 (1 H, s, 2-H); *m/z inter alia* 170 ($M^+ - C_2H_3O$) and 112 ($M^+ - C_5H_9O_2$, base peak) (Found: C, 56.4; H, 7.10; N, 6.60. $C_{10}H_{15}NO_4$ requires C, 56.3; H, 7.10; N, 6.55%).

Reaction of the Isoclavam (12d) *with Trifluoroacetic Acid followed by Diazomethane.*—(*a*) A solution of the isoclavam (12d) (0.040 g, 0.19 mmol) in trifluoroacetic acid (0.6 cm^3) was kept for 15 min and was then diluted with benzene and evaporated to dryness. The residue was dissolved in benzene, the solution was filtered, and the filtrate was evaporated to dryness; this operation was repeated twice more. An ethereal solution of diazomethane was added to the final residue until a yellow colour persisted. Evaporation of the solution left a solid which was recrystallised from light petroleum to give *methyl (2-methoxycarbonyl-3-trifluoroacetyloxazolidin-4-yl)acetate* (19a) (0.050 g, 89%) as needles, m.p. 48—50 °C; $\nu_{max.}$ (KBr) *inter alia* 1 755 and 1 730 (ester C=O) and 1 707 cm^{-1} (amide C=O); δ ($CDCl_3$) 2.55—3.00 [2 H, s, C(=O)CH_2], 3.80 and 3.90 (each 3 H, s, together 2 × OMe), 4.00—4.90 (total 3 H, m, $CHCH_2O$), and 5.60 and 5.80br (each 0.5 H, s, together NCHO) [temperature-dependent studies (90 MHz; CD_3SOCD_3) showed that at 140 °C the signals at δ 5.60 and 5.80 coalesced to a broad singlet at 5.70]; *m/z inter alia* 268 ($M^+ - CH_3O$), 240 ($M^+ - C_2H_3O_2$), and 99 ($C_2F_3O^+$, base peak) (Found: C, 40.5; H, 4.05; N, 4.75. $C_{10}H_{12}F_3NO_6$ requires C, 40.15; H, 4.00; N, 4.70%).

(*b*) A solution of the isoclavam (12d) (0.030 g, 0.14 mmol) in trifluoroacetic acid (0.4 cm^3) at 0 °C was kept for 0.5 min and was then diluted with benzene and the mixture was evaporated to dryness. Work-up as described in (*a*) above, treatment of the residue with diazomethane, and purification of the product by silica-gel chromatography [EtOAc–light petroleum (1 : 1) as eluant] gave methyl (2-t-butoxycarbonyl-3-trifluoroacetyl-oxazolidin-4-yl)acetate (19b) (0.034 g, 71%) as a waxy solid; $\nu_{max.}$ (KBr) *inter alia* 1 760 and 1.735 (ester C=O) and 1 700 cm^{-1} (amide C=O); δ ($CDCl_3$) 1.48 (9 H, s, CMe_3), 2.55—3.00 [2 H, m, C(=O)CH_2], 3.66 (3 H, s, OMe), 4.10—4.85 (total 3 H, m, $CHCH_2O$), and 5.30 and 5.50br (each 0.5 H, s, together NCHO); *m/z inter alia* 310 ($M^+ - CH_3O$), 240 ($M^+ - C_5H_3O_2$), and 212 ($C_7H_9F_3O_3^+$, base peak) [Found: ($M^+ - C_5H_3O_2$), 240.1601. Calc. for $C_8H_9F_3NO_4^+$: *m/z* 240.1604].

Reaction of the Iodomethylazetidinone (15c) *with* p-*Nitrobenzyl Ethoxyglycolate* (14c).—*p*-Nitrobenzyl ethoxyglycolate (14c) (0.250 g, 0.98 mmol) and triethylamine (0.120 g 1.2 mmol) were added to a stirred solution of the iodomethylazetidinone (15c) (0.250 g, 1.2 mmol) in dry THF (15 cm^3). The mixture was stirred for 12 h and was then evaporated to dryness; the residue was partitioned between ethyl acetate and brine. The dried ($MgSO_4$) organic phase was evaporated to dryness. Purification of the product by silica-gel chromatography [EtOAc–light petroleum (1 : 3) as eluant] gave *p*-nitrobenzyl hydroxy-(2-iodomethyl-4-oxoazetidin-1-yl)-acetate (13d) (0.350 g, 70%) as a syrupy 1 : 1 mixture of diastereoisomers; $\nu_{max.}$ (film) *inter alia* 3 400br (OH) and 1 750br cm^{-1} (β-lactam and ester C=O); $\lambda_{max.}$ (EtOH) 214 (ε 27 500) and 265 nm (35 600); δ ($CDCl_3$) 2.75 (1 H, dd, *J* 16 and 3 Hz, COC*H*HCH), 3.17 (1 H, dd, *J* 16 and 5 Hz, COCH*H*CH), 3.20—4.20 (total 3 H, m, $CHCH_2I$), 5.30br (1 H, s, OH), 5.40 (2 H, s, $CH_2C_6H_4$), 5.60br [1 H, s, C*H*(OH)], and 7.50 and 8.20 (each 2 H, d, *J* 8 Hz, together C_6H_4) [addition of D_2O caused the signal at δ 5.30 to disappear and that at δ 5.60 to sharpen to two singlets at δ 5.58 and 5.61 (each 0.5 H)]; *m/z inter alia* 403 ($M^+ - OH$) and 136 ($C_7H_6NO_2^+$, base peak) [Found: ($M^+ - C_8H_6NO_4$), 239.9544. Calc. for $C_5H_7INO_2$: *m/z* 239.9523].

Reaction of the Azetidinone (13d) *with Sodium Hydride.*—Sodium hydride (0.018 g, 0.75 mmol) was added to a stirred solution of the azetidinone (13d) (0.250 g, 0.6 mmol) in dry THF (10 cm^3) at 0 °C. The mixture was stirred at 0 °C for 0.5 h and was then allowed to warm to room temperature and was kept for 4 h. Glacial acetic acid (0.050 g, 0.8 mmol) was added to the mixture which was then diluted with ethyl acetate. The organic phase, after being washed with brine, was dried ($MgSO_4$) and evaporated to dryness. Purification of the product by silica-gel chromatography [EtOAc–light petroleum (1 : 3) as eluant] gave two fractions.

The first eluted material, isolated as a syrup (0.052 g, 30%), was *p*-nitrobenzyl 7-oxo-3-oxa-1-azabicyclo[3.2.0]heptane-2-*exo*-carboxylate (12e); $\nu_{max.}$ (film) *inter alia* 1 790 (β-lactam C=O) and 1 750 cm^{-1} (ester C=O); $\lambda_{max.}$ (EtOH) 214 (ε 25 500) and 265 nm (34 500); δ ($CDCl_3$) 3.00 (1 H, dd, *J* 16 and 2 Hz, 6-H), 3.60 (1 H, dd, *J* 16 and 4 Hz, 6-H), 3.90—4.70 (total 3 H, m, 4-H_2 and 5-H), 5.30 (2 H, s, $CH_2C_6H_4$), 5.70 (1 H, s, 2-H), and 7.80 and 8.30 (each 2 H, d, *J* 8 Hz, together C_6H_4); *m/z inter alia* 293 (MH^+) and 112 ($M^+ - C_8H_6NO_4$, base peak) [Found: ($M^+ - C_8H_6NO_4$), 112.0391. Calc. for $C_5H_6NO_2$: *m/z* 112.0399].

The second eluted material (0.046 g, 50%) was identical (n.m.r. and mass spectroscopy) with *p*-nitrobenzyl alcohol.

Reaction of the Iodomethylazetidinone (15c) *with Benzyl Glyoxylate Hydrate* (14d).—Benzyl glyoxylate hydrate (14d) (2.92 g, 16 mmol) and triethylamine (1.20 g, 11.9 mmol) were added to a stirred solution of the iodomethylazetidinone (15c) (2.50 g, 11.8 mmol) in dry THF (200 cm^3). The solution was kept for 24 h and was then evaporated to give a residue which was partitioned between ethyl acetate and brine. The dried ($MgSO_4$) organic layer was evaporated to dryness and the crude material was purified by silica-gel chromatography [EtOAc–light petroleum (1 : 1) as eluant] to give benzyl hydroxy-(2-iodomethyl-4-oxoazetidin-1-yl)acetate (13e) (4.12 g, 93%), as a pale-yellow, syrupy 1 : 1 mixture of diastereoisomers; $\nu_{max.}$ (film) *inter alia* 3 430 (OH) and 1 750 cm^{-1} (β-lactam and ester C=O); $\lambda_{max.}$ (EtOH) 219 (ε 2 300), 230sh (890), 253 (430), 259 (390), 264 (350), and 269 nm (270); δ ($CDCl_3$) 2.67 (1 H, dd, *J* 16 and 3 Hz, COC*H*HCH), 2.85—4.10 (total 5 H, m, CH*H*C*H*CH_2I and OH), 5.20 (2 H, s, CH_2Ph), 5.40 and 5.50 [each 0.5 H, s, together C*H*(OH)], and 7.30 (5 H, s, Ph); *m/z inter alia* 376 (MH^+), 358 ($M^+ - OH$), and 240 ($M^+ - C_8H_7O_2$, base peak) [Found: ($M^+ - C_8H_7O_2$), 239.9541. Calc. for $C_5H_7INO_2$: *m/z* 239.9523].

Reaction of the Azetidinone (13e) *with Sodium Hydride.*—Sodium hydride (0.400 g, 16.7 mmol) was added to a stirred solution of the azetidinone (13e) (4.12 g, 11 mmol) in dry THF (150 cm^3). After the mixture had been stirred for 20 min glacial acetic acid (0.990 g, 16.5 mmol) was added and the mixture was then diluted with ethyl acetate. The organic phase, after being washed with brine, was dried ($MgSO_4$) and evaporated to dryness. Purification of the product by silica-gel chromatography [EtOAc–light petroleum (1 : 4) as eluant] gave benzyl 7-oxo-3-oxa-1-azabicyclo[3.2.0]heptane-2-*exo*-carboxylate (12f) (1.36 g, 50%) as a syrup; $\nu_{max.}$ (film) *inter alia* 1 790 (β-lactam C=O) and 1 745 cm^{-1} (ester C=O); $\lambda_{max.}$ (EtOH) 219 (2 200), 229sh (960), 253 (430), 259 (430), 264 (350), and 269 nm (290); δ ($CDCl_3$) 2.85 (1 H, dd, *J* 16 and 2 Hz, 6-H), 3.45 (1 H, dd, *J* 16 and 5 Hz, 6-H), 3.70—4.55 (total 3 H, m, 4-H_2 and 5-H), 5.15 (2 H, s, CH_2Ph), 5.60 (1 H, s, 2-H), and 7.30 (5 H, s, Ph); *m/z inter alia* 112 ($M^+ - C_8H_7O_2$, base peak) and 91 ($C_7H_7^+$) [Found: ($M^+ - C_8H_7O_2$), 112.0399. Calc. for $C_5H_6NO_2$: *m/z*, 112.0399].

Reaction of the Isoclavam (12f) *with Hydrogen–Palladium.*—To a solution of the isoclavam (12f) (0.070 g, 0.28 mmol) in a 1 : 1 mixture of ethyl acetate and ethanol (2 cm^3) was added an aqueous solution of sodium hydrogen carbonate (0.023 g, 0.28 mmol; 1 cm^3). The mixture was then added to a stirred suspension of 5% palladium–charcoal (0.140 g) in ethanol (3 cm^3) which had previously been activated in a hydrogen atmosphere. After being stirred for 10 min under hydrogen the mixture was filtered through Celite. Evaporation of the filtrate under reduced pressure left a foam which was dissolved in water. The aqueous solution, after being washed with ethyl acetate, was evaporated to dryness with frequent additions of ethanol. The resultant foam (0.040 g, 89%) was considered to be sodium 7-oxo-3-oxa-1-azabicyclo[3.2.0]heptane-2-*exo*-carboxylate (12b); $\nu_{max.}$ (film) *inter alia* 1 770 (β-lactam C=O) and 1 620 cm^{-1} (carboxylate C=O); δ (D_2O) 2.70 (1 H, dd, *J* 16 and 2 Hz, 6-H), 3.10—4.20 (total 3 H, m, 4-H_2 and 5- and 6-H), and 5.20 (1 H, s, 2-H).

Reaction of the Salt (12b) *with Iodomethane.*—Iodomethane (0.068 g, 0.48 mmol) was added to a stirred solution of salt (12b) (0.022 g, 0.21 mmol) in DMF (2 cm^3). After being stirred for 24 h the mixture was diluted with ethyl acetate and was washed with brine (4×). Evaporation to dryness of the dried ($MgSO_4$) organic phase and purification of the residue by silica-gel chromatography [EtOAc–light petroleum (1 : 1) as eluant] gave a syrup (0.010 g, 48%) that was identical (n.m.r. spectroscopy) with the isoclavam (12a).

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