Oxidative Decarboxylation of Clavulanic Acid and Its 9-Methyl Ether

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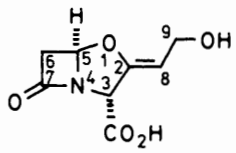
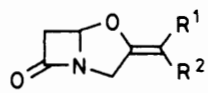
The carboxy group of clavulanic acid has been replaced by a methoxy group, an acetoxy group, and a *m*-chlorobenzoyloxy group using standard methods for oxidative decarboxylation (electrolysis, reaction with lead tetra-acetate, and decarboxylative rearrangement of a diacyl peroxide, respectively). In an unexpected reaction, 9-*O*-methylclavulanic acid (20) reacted with *p*-chlorophenylselenenyl bromide and base to give 3-(*p*-chlorophenylseleno)-2-(2-methoxyethylidene)clavam (21). Refluxing a solution of compound (21) in toluene gave 3-hydroxy-2-(2-methoxyethylidene)clavam and bis(*p*-chlorophenyl) diselenide, the overall result being the replacement of the carboxy group in the acid (20) by a hydroxy group. In chloroform, this 3-hydroxyclavam exists predominantly as the ring-opened aldehyde. Possible mechanisms for the formation of the seleno derivative (21) and its decomposition in refluxing toluene are discussed.

Clavulanic acid (1) is a naturally occurring, clinically useful β-lactamase inhibitor, which also possesses weak antibacterial activity.[1] Since its discovery, there has been much interest in preparing analogues and derivatives of this natural product in the hope of finding new compounds with enhanced biological activity. Thus, it has been shown that quite drastic changes can be made in the C-2 † alkylidene moiety while retaining useful levels of β-lactamase inhibition.[3] Also, it has been demonstrated that the C-3 carboxy group is not essential for activity,[4] and many compounds with the general structure (2) are able to inhibit a range of β-lactamase enzymes.[3b] We were interested, therefore, in the effect on biological activity of replacing the C-3 carboxy group in compound (1), and its derivatives, by groups other than hydrogen.‡ In order to prepare such compounds, in which the carboxy group has been replaced by an oxygen group, we have investigated methods for the oxidative decarboxylation of the acid (1).

Our first oxidative decarboxylation of the acid (1) was achieved by electrolysis of a solution of the acid and triethylamine in methanol using platinum electrodes. This was expected to result in the replacement of the carboxy group by a methoxy group, by analogy with the known [5] electrochemical reaction of α-acylamino acids in methanol. In practice, three products were obtained: the dihydro-oxazole (6) (9%), the expected methyl ether (7) (1.2%), and the known [1b] methyl ester (8) (0.5%). In addition to these products, which were isolated by chromatography, the reaction also produced a great deal of insoluble, polymeric material. Structures (6) and (7) were deduced from the spectroscopic properties of these compounds. The assigned double-bond geometries followed from a comparison of the chemical shifts of the vinyl protons [δ 5.05 § for compound (6) and δ 4.90 for compound (7)] with those of the corresponding protons in methyl clavulanate (δ 4.97) and methyl isoclavulanate [6] (δ 5.38). The configuration of the methoxy group in compound (7) is not known with certainty, but from the discussion given below on the probable mechanism of formation of this compound, the *S*-configuration would be suggested.



(1)



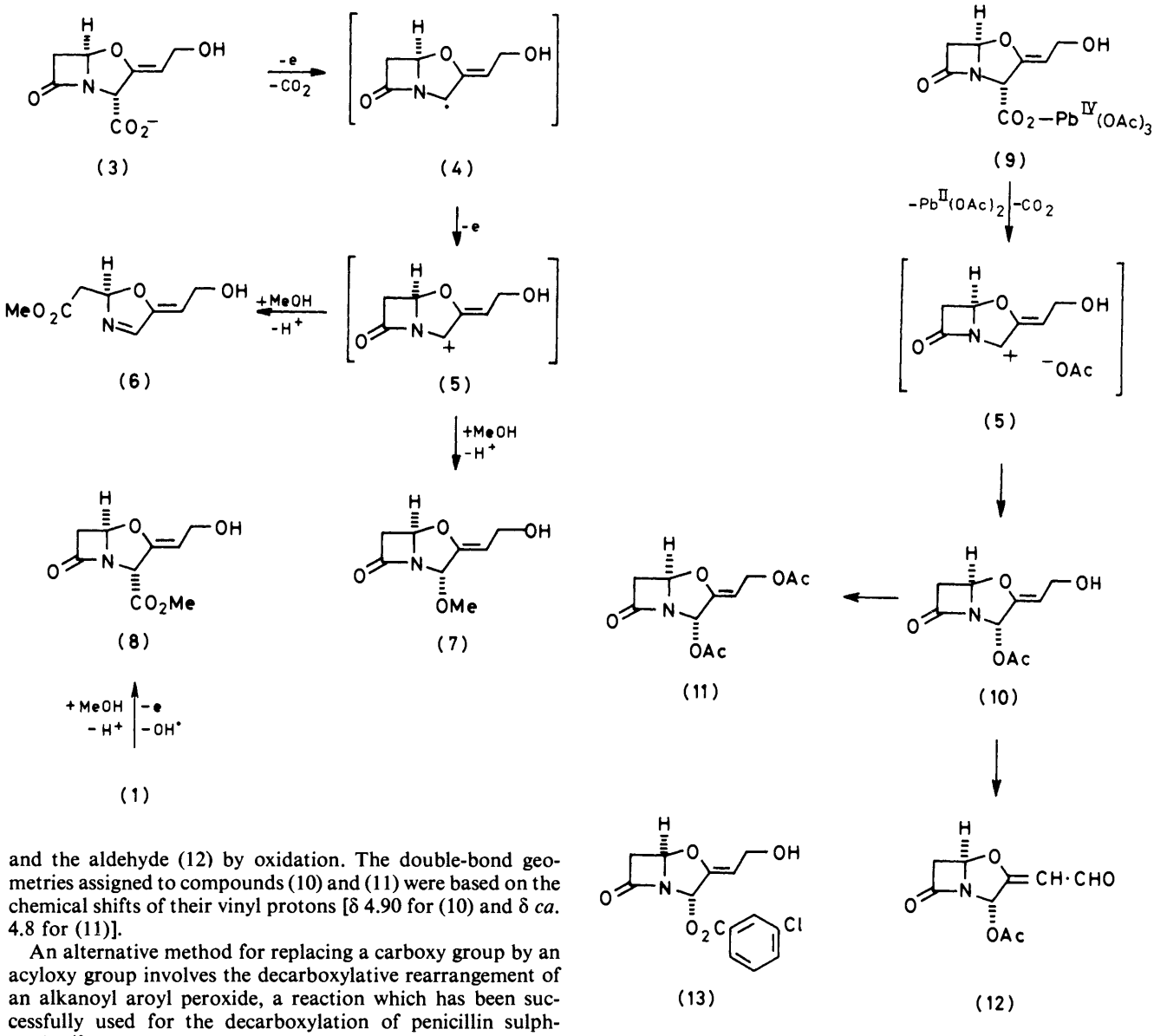
(2)*

* R^1 and R^2 = various (see refs. 3*b*, 4).

The formation of these products can be explained as follows. Discharge of the carboxylate anion (3) at the anode followed by decarboxylation would give the allylic radical (4). Further anodic oxidation [7] of this radical would then give a carbonium ion (5), which can react with methanol in two ways. Firstly, reaction at the β-lactam carbonyl gives rise to the dihydro-oxazole (6), and, on the basis of the relative product yields, this would appear to be the more favoured process. Secondly, reaction of methanol at C-3 yields the methyl ether (7). If it is assumed that addition of methanol occurs on the least hindered face of the carbonium ion (5), then the configuration of the resulting methoxy group will be as shown in structure (7). The formation of methyl esters during the electrolysis of carboxylic acids in methanol has been observed before.[8] In our case, anodic oxidation of the free acid (1) followed by loss of a hydroxy radical and reaction of methanol with the resulting acylium ion gives rise to methyl clavulanate (8).

We next investigated the reaction of clavulanic acid with lead tetra-acetate, a reagent which has been much used for the oxidative decarboxylation of carboxylic acids.[9] Thus, after heating a solution of the acid (1) and lead tetra-acetate in benzene and 1,2-dimethoxyethane at 70 °C for 20 min, three products were isolated by chromatography. These were the C-3 acetoxy compound (10) (8.5%), the diacetate (11) (1%), and, as a 2 : 1 mixture of geometric isomers, the aldehyde (12) (0.9%). The formation of this mixture of products is consistent with the known reactions of lead tetra-acetate.[9] Break-down of the lead(IV) carboxylate (9) would give the same carbonium ion (5) that was postulated in the electrolytic decarboxylation. Addition of an acetoxy anion (or acetic acid) to C-3 of this carbonium ion would give the acetoxy derivative (10), and if this occurred on the less hindered face of the carbonium ion (5), then the *S*-configuration would result at C-3. (Additional evidence for this configuration will be presented later.) Further reactions of lead tetra-acetate with the hydroxy group in compound (10) give rise to the diacetate (11) by acetylation,

† Non-systematic clavam numbering (ref. 2) is used throughout.
‡ Four such compounds have already been reported (ref. 4*b*): (*E*)- and (*Z*)-(2*S*,5*R*)-3-ethylidene-2-phenylthio-4-oxa-1-azabicyclo-[3.2.0]heptan-7-one, (*Z*)-(2*S*,5*R*)-3-(2-hydroxyethylidene)-2-phenylthio-4-oxa-1-azabicyclo[3.2.0]heptan-7-one, and (*Z*)-(2*S*,5*R*)-3-(2-acetoxyethylidene)-2-phenylthio-4-oxa-1-azabicyclo[3.2.0]heptan-7-one.
§ Chemical shifts are relative to internal $SiMe_4$ for solutions in $CDCl_3$.



and the aldehyde (12) by oxidation. The double-bond geometries assigned to compounds (10) and (11) were based on the chemical shifts of their vinyl protons [δ 4.90 for (10) and δ *ca.* 4.8 for (11)].

An alternative method for replacing a carboxy group by an acyloxy group involves the decarboxylative rearrangement of an alkanoyl aroyl peroxide, a reaction which has been successfully used for the decarboxylation of penicillin sulphoxides.[10] Clavulanic acid was therefore brought into reaction with *m*-chloroperoxybenzoic acid and dicyclohexylcarbodiimide to give the carboxy-inversion product (13) in 12% yield. As expected, the double-bond geometry was unchanged in this reaction (vinyl proton chemical shift at δ 4.97). Also, this type of decarboxylative rearrangement is known to proceed with retention of configuration at the alkyl centre,[11] and so the product (13) has the *S*-configuration at C-3.* One point of interest from this was that, since the stereochemistry for compound (13) is known, a comparison of the chemical shifts for the C-3 protons in compounds (13) (δ 6.65) and (10) (δ 6.42) provides some confirmation of the stereochemistry at C-3 in compounds (10), (11), and (12).†

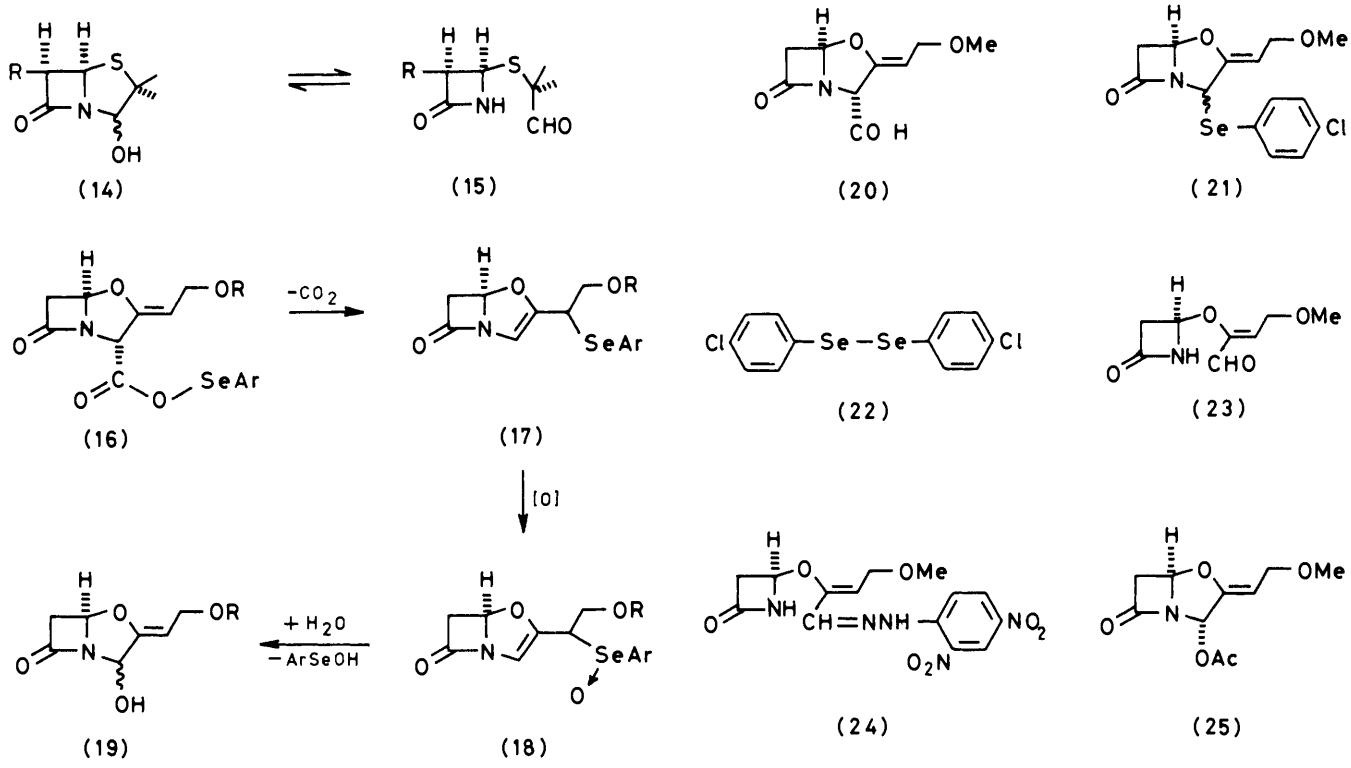
Having developed routes for replacing the carboxy group of clavulanic acid by an alkoxy or acyloxy group, we then turned our attention to its replacement by a hydroxy group. Such a transformation has been achieved for penicillins by way of the Curtius degradation,[13] and for penicillin *S*-oxides by way of the carboxy-inversion reaction.[10] The 3-hydroxypenam (14) is usually favoured over the ring-opened aldehyde (15) with which it is in equilibrium, and this is also the case in the penam *S*-oxide series. It would be interesting to see how the corresponding clavam derivatives compared.

A proposed route to the required 3-hydroxyclavam (19) is shown in Scheme 1. The initial steps rely on the fact that mixed selenenic anhydrides, RCO_2SeAr, add to olefins to give β-acyloxy selenides,[14] and from this we reasoned that the mixed selenenic anhydride (16) might react intramolecularly, with loss of carbon dioxide, to give the rearranged allylic selenide (17). The selenide (17) might then be converted into the desired 3-hydroxyclavam (19) by way of the selenoxide (18).[15]

In the event, reaction of 9-*O*-methylclavulanic acid (20) with *p*-chlorophenylselenenyl bromide in the presence of *N*-methylmorpholine gave neither the mixed selenenic anhydride (16; R = Me) nor the rearranged selenide (17; R = Me), but the C-3 seleno derivative (21) (55%). Structure (21) was established for this product on the basis of its spectral proper-

* This presumes that there has been no epimerisation at C-3 during the formation of compound (13). Previous experience with derivatives and analogues of compound (1) suggests that such an epimerisation would be unlikely (ref. 12).

† Clavams which are epimeric at C-3 are known to have significantly different chemical shifts for their C-3 protons (ref. 12).

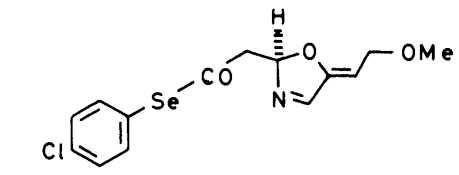


Scheme 1. Ar = 4-Chlorophenyl

ties; the compound is a single diastereoisomer with the configuration at C-3 unknown. More interestingly, refluxing a solution of compound (21) in toluene for 5 h gave, in addition to 73% recovered starting material, the diselenide (22) (14%) and the desired 3-hydroxyclavam (19; R = Me) (4.3%). The n.m.r. spectrum of this 3-hydroxyclavam in chloroform showed that it exists predominantly as the ring-opened aldehyde (23). The compound could be characterised in both its ring-opened and ring-closed forms: with 2,4-dinitrophenylhydrazine it gave the ring-opened hydrazone derivative (24) and with acetyl chloride and pyridine it formed the ring-closed acetate (25). Comparison of n.m.r. spectra showed that compound (25) has the same double bond geometry and the same configuration at C-3 as compounds (10) and (11).

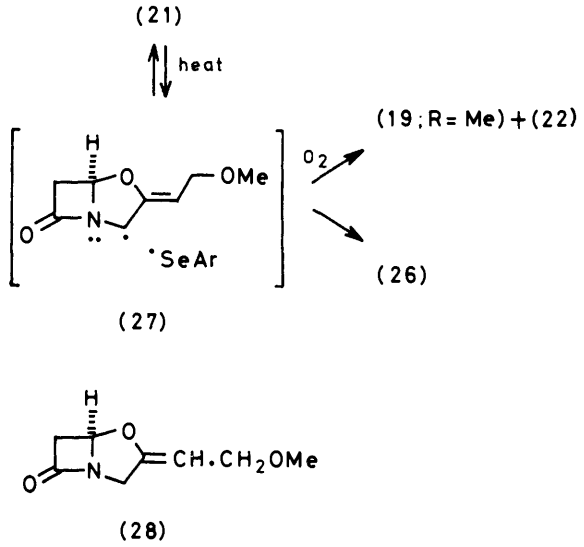
The rate of decomposition of selenide (21) was increased in the presence of the free-radical initiator α,α′-azobisisobutyronitrile. Thus, after refluxing a solution of compound (21) and free-radical initiator in toluene for 3 h all the starting material had been consumed and compound (19; R = Me) was isolated in 23% yield together with the diselenide (22) (98%). Atmospheric oxygen is obviously involved in this reaction. When a toluene solution of compound (21) was refluxed for 5 h under nitrogen, compound (19; R = Me) was not obtained. Instead, a new compound (26) (8%) was produced, together with the diselenide (22) (7%) and 81% recovered starting material. When the reaction was repeated in the presence of α,α′-azobisisobutyronitrile, the yields were increased to 50% for compound (26) and 35% for diselenide (22), with 7% of compound (21) being recovered.

The mechanism by which the selenide (21) is formed is not immediately obvious. One possibility is that the selenide (17; R = Me) is formed, as proposed in Scheme 1, and then undergoes a [1,3]-sigmatropic rearrangement to the selenide (21). However, to occur under the conditions of our reaction, this would have to be a very facile example of this type of rearrangement.[16] A more likely possibility is that the anhydride



Scheme 2.

(16; R = Me) is formed and loses carbon dioxide to give the selenide (21) directly. This decomposition could occur by way of a concerted 4-centre reaction, or in a step-wise fashion involving radical or ionic intermediates as shown in the generalised Scheme 2. (This has some similarities to the decomposition of diacyl peroxides.[17]) The subsequent reactions of compound (21) in refluxing toluene certainly would seem to involve free radicals. We propose that these reactions are initiated by the homolysis of the Se–C(3) bond to give the carbon radical (27). This radical could then react with oxygen



to give, eventually, the 3-hydroxyclavam (19; R = Me), while selenium radicals give the diselenide (22). In the absence of oxygen, carbon and selenium radicals can combine to give starting selenide (21) or the dihydro-oxazole (26). The formation of the oxazole (26) in this reaction is reminiscent of the formation of the oxazole (6) during the electrolysis of clavulanic acid in methanol.

We have also converted the acid (20) into the 3-hydroxyclavam (19; R = Me) by a two-step process involving decarboxylation and oxidation. The acid (20) was decarboxylated using mercury(II) acetate [4a] to give the clavam (28) as a 1 : 1 mixture of geometric isomers. This mixture of isomers was then subjected to allylic axidation, using selenium dioxide and t-butyl hydroperoxide,[18] to give, as a single geometric isomer, the 3-hydroxyclavam (19; R = Me) (30%). This product was identical in all respects with the 3-hydroxyclavam obtained from the oxidative decomposition of the selenide (21).

In conclusion, we have shown that clavulanic acid (and its derivatives) will quite readily undergo decarboxylation reactions which involve a C-3 radical or carbonium ion [*e.g.* (4), (5), and (27)]. Undoubtedly, this is largely due to the fact that a radical or carbonium ion is highly stabilised at this position by the adjacent double bond and tertiary lactam nitrogen. It is quite likely that the more unusual reactions described above, that is the formation and decomposition of the selenide (21) and the decarboxylation catalysed by mercury(II) acetate, are a consequence of this stabilisation in a decarboxylated C-3 radical or carbonium ion. Also, as was seen in some of the above work, reactions involving this type of intermediate are sometimes characterised not only by products derived from reaction at C-3, but also by dihydro-oxazole products resulting from reaction at the β-lactam carbonyl.

Some of the new compounds described in this paper, for example the 3-methoxy derivative (7) and the 3-acetoxy derivative (10), were found to be β-lactamase inhibitors.[19] However, none of these compounds was as active as clavulanic acid.

Experimental

M.p.s were determined using a Kofler hot-stage apparatus. Except where stated otherwise, i.r. spectra and specific rotations were recorded for solutions in chloroform, u.v. spectra were recorded for solutions in ethanol, and ^{1}H n.m.r. spectra were recorded at 90 MHz for solutions in $CDCl_3$ with $SiMe_4$ as internal standard. Mass spectra were determined using either an A.E.I. MS9 instrument or a V.G. Micromass 70-70F instrument. Merck silica gel 60 was used for t.l.c. and for column chromatography, with ethyl acetate–light petroleum (b.p. 60—80 °C) mixtures as eluant. Solutions were dried using magnesium sulphate and solvents were removed by evaporation under reduced pressure using a rotary evaporator with the bath temperature below 30 °C.

Electrolysis of Clavulanic Acid (1) *and Triethylamine in Methanol.*—Clavulanic acid (1) (900 mg) and triethylamine (200 mg) were dissolved in methanol (15 ml). The solution was stirred at −30 °C (bath temperature) while being electrolysed using a pair of platinum-foil electrodes (1.8 × 0.9 cm) placed 1 mm apart and passing a current of 200—250 mA for 50 min. The mixture was diluted with benzene (50 ml) and filtered. The solvent was removed from the filtrate and the resulting dark coloured gum was chromatographed to give, in order of elution, (Z)-(3S,5R)-2-(2-*hydroxyethylidene*)-3-*methoxyclavam* (7) as a colourless oil (10 mg), methyl clavulanate (8) as a colourless oil (5 mg), and (Z)-(2R)-5-(2-*hydroxyethylidene*)-2-*methoxycarbonylmethyl*-2,5-*dihydro-oxazole* (6) as a colourless gum (75 mg). The clavam (7) had $[\alpha]_D^{22}$ +45.5° (*c* 0.75); $\nu_{max.}$ 3 550, 3 370, 1 800, and 1 698 cm^{-1}; δ 1.55br (1 H, exchanges with D_2O), 2.96 (1 H, d, *J* 16 Hz), 3.35 (1 H, dd, *J* 16, 2 Hz), 3.38 (3 H, s), 4.20 (2 H, d, *J* 6 Hz), 4.89 (1 H, t, *J* 6 Hz), 5.27 (1 H, s), and 5.53 (1 H, d, *J* 2 Hz); *m/z* 185 (M^+, 6%), 168 (2), 153 (7), 102 (17), 87 (53), 86 (25), 85 (18), 72 (100), and 69 (72) (Found: M^+, 185.0672. $C_8H_{11}NO_4$ requires *M*, 185.0688). The oxazole (6) had $[\alpha]_D^{22}$ −116.5° (*c* 1); $\lambda_{max.}$ 271 nm (ε 12 000); $\nu_{max.}$ 3 500, 3 330, 1 735, 1 675, 1 620, and 1 585 cm^{-1}; δ 2.50br (1 H, exchanges with D_2O), 2.57 (1 H, dd, *J* 15, 6 Hz), 2.85 (1 H, dd, *J* 15, 5 Hz), 3.69 (3 H, s), 4.23 (2 H, dd, *J* 6.5, 1 Hz), 5.05 (1 H, t, *J* 6.5, 1.5 Hz), 6.33 (1 H, m), and 7.52 (1 H, d, *J* 2 Hz); double-resonance experiments showed that the proton at δ 6.33 was coupled to the protons at δ 2.57 (*J* 6 Hz), 2.85 (*J* 5 Hz), 4.23 (*J* 1 Hz), 5.05 (*J* 1.5 Hz), and 7.52 (*J* 2 Hz); *m/z* 185 (M^+, 16%), 168 (100), 167 (20), 155 (22), 125 (19), 113 (52), 108 (30), 101 (35), 85 (53), and 70 (30) (Found: C, 51.3; H, 6.1; N, 7.2%; M^+, 185.0687. $C_8H_{11}NO_4$ requires C, 51.9; H, 6.0; N, 7.55%; *M*, 185.0688).

Reaction of Clavulanic Acid (1) *with Lead Tetra-acetate.*—Clavulanic acid (1) (1.7 g) was dissolved in dry 1,2-dimethoxyethane (10 ml) and the solution was diluted with dry benzene (20 ml). The solution was stirred under dry nitrogen while dry lead tetra-acetate (3.7 g) was added in one portion. The mixture was then stirred at 70 °C (bath temperature) under dry nitrogen for 20 min. The mixture was cooled, diluted with ethyl acetate (100 ml), and filtered. The filtrate was washed with saturated sodium hydrogen carbonate (30 ml) and saturated brine (30 ml). The solution was dried, the solvent was removed, and the resulting residue was chromatographed to give, in order of elution, (Z)-(3S,5R)-3-*acetoxy*-2-(2-*acetoxyethylidene*)*clavam* (11) as a colourless gum (20 mg), (*E*)- and (*Z*)-(3*S*,5*R*)-3-acetoxy-2-formylmethyleneclavam (12) as a colourless gum (17 mg), and (Z)-(3S,5R)-3-*acetoxy*-2-(2-*hydroxyethylidene*)*clavam* (10) as a colourless gum (145 mg). The diacetate (11) had $[\alpha]_D^{22}$ +102.1° (*c* 1.0); $\nu_{max.}$ 1 805, 1 740br, and 1700sh cm^{-1}; δ 2.01 (3 H, s), 2.04 (3 H, s), 3.04 (1 H, d, *J* 16 Hz), 3.42 (1 H, dd, *J* 16, 2 Hz), 4.55—4.95 (3 H, complex m), 5.65 (1 H, d, *J* 2 Hz), and 6.45 (1 H, s); *m/z* 255 (M^+, 2%), 213 (12), 199 (10), 171 (4), 154 (100), 153 (65), 125 (20), 99 (32), 71 (40), and 55 (48) (Found: M^+, 255.0734. $C_{11}H_{13}NO_6$ requires *M*, 255.0743). The aldehyde (12) was obtained as a 2 : 1 mixture of geometric isomers, and had $[\alpha]_D^{22}$ +95.6° (*c* 1.0); $\lambda_{max.}$ 254 nm (ε 14 300); $\nu_{max.}$ 2 800, 1 807, 1 750, 1 675, and 1 663 cm^{-1}; δ 2.07 (3 H, s), 3.0—3.65 (2 H, complex m), 5.32 (1 H, d, *J* 7 Hz), 5.90 (1 H, d, *J* 2 Hz), 6.44 (1 H, s), 9.53 (0.35 H, d, *J* 7 Hz), and 9.85 (0.65 H, d, *J* 7 Hz);

m/z 181 (17%), 169 ($C_7H_7NO_4$, 60), 154 (40), 113 (50), and 71 (100). The acetate (10) had $[\alpha]_D^{22}$ +145.8° (*c* 0.64); $\nu_{max.}$ 3 500, 3 320, 1 803, 1 750, and 1 698 cm^{-1}; δ 1.90 (1 H, s, exchanges with D_2O), 2.03 (3 H, s), 3.00 (1 H, d, *J* 16 Hz), 3.41 (2 H, dd, *J* 16, 2 Hz), 4.18 (2 H, d, *J* 7 Hz), 4.90 (1 H, t, *J* 7 Hz), 5.63 (1 H, d, *J* 2 Hz), and 6.42 (1 H, s); *m/z* 171 (37%), 154 (33), 153 (16), 112 (28), 111 (20), and 109 (100) (Found: C, 50.7; H, 5.6; N, 6.4. $C_9H_{11}NO_5$ requires C, 50.7; H, 5.2; N, 6.55%).

Reaction of Clavulanic Acid (1) *with Dicyclohexylcarbodi-imide and* m-*Chloroperoxybenzoic Acid.*—Clavulanic acid (350 mg) in dry 1,2-dimethoxyethane–dichloromethane (1 : 1; 10 ml) was treated with *m*-chloroperoxybenzoic acid (380 mg) and dicyclohexylcarbodi-imide (400 mg). The mixture was stirred with exclusion of moisture for 3 h at 0 °C and then for 15 h at room temperature. The mixture was diluted with ethyl acetate (50 ml) and filtered. The filtrate was washed with saturated sodium hydrogen carbonate (30 ml) and saturated brine (30 ml). The solution was dried, the solvent was removed, and the resulting residue was chromatographed to give (*Z*)-(3*S*,5*R*)-2-(2-hydroxyethylidene)-3-(*m*-chlorobenzoyloxy)clavam (13) as a colourless gum (60 mg); $[\alpha]_D^{22}$ +88.8° (*c* 1.0); $\nu_{max.}$ 3 320, 1 805, 1 730, and 1 700 cm^{-1}; δ 2.28br (1 H, exchanges with D_2O), 3.10 (1 H, d, *J* 16 Hz), 3.48 (1 H, dd, *J* 16, 2 Hz), 4.26 (2 H, d, *J* 7 Hz), 4.97 (1 H, t, *J* 7 Hz), 5.75 (1 H, d, *J* 2 Hz), 6.65 (1 H, s), 7.25—7.60 (2 H, m), and 7.80—8.00 (2 H, m). The n.m.r. spectrum also showed signals for small amounts of impurity in this product. Since these were not removed on repeated chromatography, the product was characterised by conversion into its phenylacetate derivative.

The clavam (13) (40 mg) in dry diethyl ether (3 ml) was treated with phenylacetyl chloride (60 mg) and dry pyridine (30 mg) at 0 °C. The mixture was kept at 0 °C for 17 h and was then diluted with ethyl acetate (50 ml). The solution was washed with 1M-HCl (10 ml), 1M-sodium hydrogen carbonate (20 ml), and saturated brine (10 ml). The solution was dried, the solvent was removed, and the resulting residue was chromatographed to give (Z)-(3S,5R)-3-(m-*chlorobenzoyloxy*)-2-(2-*phenylacetoxyethylidene*)*clavam* as a colourless gum (50 mg) which appeared to be homogeneous by t.l.c. and n.m.r.; $[\alpha]_D^{23}$ +59.4° (*c* 1.0); $\nu_{max.}$ 1 805, 1 730, and 1 700sh cm^{-1}; δ 3.00 (1 H, d, *J* 16 Hz), 3.38 (1 H, dd, *J* 16, 2 Hz), 3.55 (2 H, s), 4.60—5.00 (3 H, complex m), 5.70 (1 H, d, *J* 2 Hz), 6.62 (1 H, s), and 7.10—7.95 (9 H, complex m); *m/z* 429 (M^+, 0.4%), 427 (M^+, 1.2), 311 (2), 309 (6), 229 (9), 139 (100), and 91 (55) (Found: M^+, 427.0800. $C_{22}H_{18}{}^{35}ClNO_6$ requires 427.0823).

Reaction of 9-O-*Methylclavulanic Acid* (20) *with* p-*Chlorophenylselenenyl Bromide.*—9-*O*-Methylclavulanic acid (2.3 g) in dichloromethane (100 ml) was stirred at −30 °C under nitrogen while *N*-methylmorpholine (1.19 ml) was added. A solution of *p*-chlorophenylselenenyl bromide [prepared [20] from bis(*p*-chlorophenyl) diselenide (2.06 g)] in dichloromethane (20 ml) was then added dropwise during 10 min. The mixture was warmed to −10 °C and stirred for a further 1.5 h. The solution was washed with 0.1M-HCl and 1M-sodium hydrogen carbonate. The solution was dried, the solvent was removed, and the resulting residue was chromatographed to give (Z)-(5R)-3-(p-*chlorophenylseleno*)-2-(2-*methoxyethylidene*)-*clavam* (21) * as a pale yellow oil (2.4 g); $[\alpha]_D^{20}$ +9.5° (*c* 1.1); $\lambda_{max.}$ 233 nm (ε 16 220); δ 2.97 (1 H, d, *J* 17 Hz), 3.2—3.5 (4 H, m, including s at δ 3.28), 3.99 (2 H, d, *J* 7 Hz), 4.77br (1 H, t, *J* 7 Hz), 5.42 (1 H, d, *J* 2.5 Hz), 5.98br (1 H, s), 7.26 (2 H, d, *J* 8.5 Hz), and 7.54 (2 H, d, *J* 8.5 Hz); δ(^{13}C) (62.9 MHz; $CDCl_3$) 45.64 (C-6), 57.06 (C-3), 57.66 (OMe), 66.30 (OCH_2), 86.05 (C-5), 97.79 (=CH−), 126.24 (Ar), 129.37 (Ar), 135.00 (Ar), 135.98 (Ar), 156.07 (C-2), and 173.63 (C-7); *m/z* 361 (M^+, 1%), 359 (M^+, 3), 330 (0.2), 328 (0.6), 194 (1), 193 (3), 192 (3), 191 (10), 168 (20), 126 (100), 96 (20), 68 (80), and 54 (40) (Found: M^+, 358.9822. $C_{14}H_{14}{}^{35}ClNO_3Se$ requires 358.9827). The compound appeared to be unstable when stored neat. It could be kept for up to a month in dilute solution in ethyl acetate at 5 °C.

Reactions of the Selenide (21) *in Refluxing Toluene.*—(a) The selenide (21) (150 mg) was dissolved in dry toluene (7.5 ml) and the solution was refluxed while air was continuously bubbled through the solution. Some solvent was lost by evaporation during this process, and this was periodically replaced by fresh solvent to maintain the initial volume. After 5 h, the solvent was removed and the resulting residue was chromatographed to give, in order of elution, bis(*p*-chlorophenyl) diselenide (22) (10 mg), the selenide (21) (110 mg), and (Z)-(5R)-3-*hydroxy*-2-(2-*methoxyethylidene*)*clavam* (19; R = Me) * as a colourless gum (3 mg).

(b) This was carried out as in (a), but α,α′-azobisisobutyronitrile (15 mg) was added to the solution and the reaction mixture was irradiated using a 150-W tungsten lamp. The reaction was stopped after 3 h, and chromatography gave bis(*p*-chlorophenyl) diselenide (22) (70 mg) and the hydroxyclavam (19; R = Me) (16 mg). The hydroxyclavam (19; R = Me) had $[\alpha]_D^{20}$ −0.5° (*c* 1.1); $\lambda_{max.}$ 243 nm (ε 5 770); $\nu_{max.}$ 3 420, 1 785, 1 690, and 1 645 cm^{-1}; the n.m.r. spectrum showed that this compound existed as a 6 : 1 mixture of ring-opened (major) tautomer (23) and ring-closed (minor) tautomer (19; R = Me); δ (250 MHz) 2.99 (1 H, major tautomer, dd, *J* 15, 1.5 Hz), 3.24 (1 H, major tautomer ddd, *J* 15, 4, 2.5 Hz), 3.34 (3 H minor tautomer, s), 3.40 (3 H, major tautomer, s), 4.06 (2 H minor tautomer, d, *J* 7.5 Hz), 4.27 (2 H major tautomer, d, *J* 6 Hz), 4.93 (1 H minor tautomer, t, *J* 7.5 Hz), 5.54 (1 H major tautomer, dd, *J* 4, 1.5 Hz), 5.63 (1 H minor tautomer, d, *J* 2.5 Hz), 6.10 (1 H major tautomer, t, *J* 6 Hz), 6.63br (1 H major tautomer, s), and 9.26 (1 H major tautomer, s); *m/z* (NH_3 CI) 203 ($[M + NH_4]^+$, 100%), 186 ($[M + H]^+$, 15), 171 (20), 154 (25), 134 (40), 87 (45), 84 (30), and 70 (50).

(c) This was carried out as in (a), but dry nitrogen was bubbled through the solution instead of air. Chromatography gave, in order of elution, bis(*p*-chlorophenyl) diselenide (22) (5 mg), selenide (21) (121 mg), and (Z)-(2R)-2-(p-*chlorophenylselenocarbonylmethyl*)-5-(2-*methoxyethylidene*)-2,5-*dihydrooxazole* (26) as a pale yellow oil (11 mg).

(d) This was carried out as in (c), but α,α′-azobisisobutyronitrile (15 mg), was added to the solution and the reaction mixture was irradiated using a 150-W tungsten lamp. Chromatography gave bis(*p*-chlorophenyl) diselenide (22) (25 mg), the selenide (21) (10 mg), and the oxazole (26) as a pale yellow oil (66 mg). The oxazole (26) had $[\alpha]_D^{20}$ −39.0° (*c* 1.0); $\lambda_{max.}$ 229 (ε 16 200), and 268 nm (12 000); $\nu_{max.}$ 1 720, 1 680, and 1 585 cm^{-1}; δ 2.8—3.5 (5 H, m, including s at δ 3.31), 4.07 (2 H, dd, *J* 7.5, 1.5 Hz), 5.04 (1 H, td, *J* 7.5, 1.5 Hz), 6.2—6.5 (1 H, m), and 7.2—7.8 (5 H, m); *m/z* 361 (M^+, 2%), 359 (M^+, 5), 330 (1), 328 (3), 194 (10), 193 (18), 192 (26), 191 (50), 168 (30), 156 (30), 126 (100), 112 (50), 68 (70), and 45 (70) (Found: M^+, 358.9835). $C_{14}H_{14}{}^{35}ClNO_3Se$ requires 358.9827). On storage, the oxazole appeared to be unstable, even at −20 °C.

2-(2-*Oxoazetidin*-4-*yloxy*)-1-(2,4-*dinitrophenylhydrazono*)-4-*methoxy*-(Z)-*but*-2-*ene* (24).†—The hydroxyclavam (19; R = Me) (80 mg) and 2,4-dinitrophenylhydrazine (54 mg) were dissolved in dry *N*,*N*-dimethylformamide (2 ml). Toluene-4-sulphonic acid monohydrate (5 mg) was added and the mixture was stirred for 5 h. The mixture was diluted with ethyl

* A single isomer with the stereochemistry at C-3 unknown.

† A single isomer with double bond geometries unknown.

acetate (15 ml), washed with 1M-sodium hydrogen carbonate (10 ml) and water (2 × 10 ml), dried, and filtered. The filtrate was refrigerated (4 °C) for 18 h and then the crystals of the *hydrazone* (24) * were collected by filtration, washed with ethyl acetate, and dried *in vacuo*. The hydrazone (24) was thus obtained as orange needles, m.p. 180—185 °C; $[\alpha]_D^{20}$ +27° (*c* 1.1, dimethyl sulphoxide); $\lambda_{max.}$ 256 (ε 12 780), 285infl. (7 160), and 369 nm (24 600); $\nu_{max.}$ (Nujol) 3 340, 3 280, 1 790, 1 755, 1 620, 1 600, and 1 585 cm^{-1}; δ ([$^2H_6$]dimethyl sulphoxide) 2.89 (1 H, d, *J* 15 Hz), 3.1—3.4 (4 H, m, including s at δ 3.23), 4.14 (2 H, d, *J* 7.5 Hz), 5.6—5.9 (2 H, m), 7.83 (1 H, d, *J* 11 Hz), 8.21 (1 H, s), 8.36 (1 H, dd, *J* 11, 2.5 Hz), 8.73br (1 H, s, exchanges with D_2O), 8.81 (1 H, d, *J* 2.5 Hz), and 11.49br (1 H, s, exchanges with D_2O) (Found: C, 46.0; H, 4.1; N, 19.1. $C_{14}H_{15}N_5O_7$ requires C, 46.0; H, 4.1; N, 19.2%).

(Z)-(3S,5R)-3-*Acetoxy*-2-(2-*methoxyethylidene*)*clavam* (25). —A solution of the hydroxyclavam (19; R = Me) (110 mg) in dichloromethane (1 ml) was stirred and cooled in an ice-bath while a solution of pyridine (0.048 ml) in dichloromethane (1 ml) was added followed by a solution of acetyl chloride (0.043 ml) in dichloromethane (1 ml). The mixture was stirred for 15 min, diluted with dichloromethane (10 ml), washed with water (5 ml), and dried. The solvent was removed and the residue was chromatographed to give the *clavam* (25) as a colourless gum (22 mg); $[\alpha]_D^{20}$ +132° (*c* 1.2); $\nu_{max.}$ 1 810, 1 750, and 1 700 cm^{-1}; δ 2.07 (3 H, s), 3.03br, (1 H, d, on irradiation at δ 5.67 this becomes a sharp d, *J* 17 Hz), 3.25—3.55 (4 H, m, including s at δ 3.29), 4.01 (2 H, d, *J* 7.5 Hz), 4.87br (1 H, t, on irradiation at δ 6.49 this becomes a sharp t, *J* 7.5 Hz), 5.67br (1 H, d, *J* 3 Hz), and 6.49br (1 H, s); *m/z* (NH_3 Cl) 245 ([*M* + NH_4]$^+$, 15%), 228 ([*M* + H]$^+$, 20), 217 (5), 200 (5), 186 (50), 168 (40), 154 (100), 126 (35), and 110 (30) (Found: C, 52.7; H, 5.9; N, 6.1. $C_{10}H_{13}NO_5$ requires C, 52.9; H, 5.7; N, 6.2%).

Oxidation of (5R)-2-(2-*Methoxyethylidene*)*clavam* (28) *with Selenium Dioxide*.—(5*R*)-2-(2-Methoxyethylidene)clavam [4a] (28) (a 1 : 1 mixture of geometric isomers) (850 mg) was dissolved in dichloromethane (60 ml) and the solution was treated with selenium dioxide (550 mg) and t-butyl hydroperoxide (1.3 ml; containing 30% t-butyl alcohol). The mixture was refluxed for 2.5 h. The mixture was cooled, washed with saturated sodium hydrogen carbonate (50 ml), and the aqueous wash was extracted with dichloromethane (3 × 30 ml). All the dichloromethane solutions were combined and dried. The solvent was removed and the residue was chromatographed to give the 3-hydroxyclavam (19; R = Me) as a colourless gum (280 mg). This product was identical in all respects with the 3-hydroxyclavam from the decomposition of the selenide (21) in refluxing toluene.

* A single isomer with double bond geometries unknown.

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