# Total Synthesis of Analogues of the β-Lactam Antibiotics. Part 2.[1] Isopenam-3-carboxylates and their 2,2-Dioxides[2]

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t-Butyl hydroxy-(2-iodomethyl-4-oxoazetidin-1-yl)acetate (**10a**), as a 1 : 1 mixture of diastereoisomers, was transformed, by sequential reactions involving thionyl chloride–2,6-lutidine and hydrogen sulphide–triethylamine, into a 1 : 1.7 mixture of t-butyl isopenam-3-*exo*-carboxylate (**3b**) and its *endo*-diastereoisomer (**12a**). Using a similar reaction sequence, *p*-nitrobenzyl hydroxy-(2-iodomethyl-4-oxoazetidin-1-yl)acetate (**10b**), as a 1 : 1 mixture of diastereoisomers, was converted into a 1 : 1.5 mixture of *p*-nitrobenzyl isopenam-3-*exo*-carboxylate (**3d**) and its *endo*-diastereoisomer (**12b**). In the presence of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), the *endo*-compounds (**12a**) and (**12b**) underwent epimerisations to the *exo*-isomers (**3b**) and (**3d**).

Oxidation of the isopenams (**3b**), (**3d**), and (**12a**) with potassium permanganate gave the corresponding isopenam 2,2-dioxides, *i.e.* (**4b**), (**4c**), and (**22**). Epimerisation of the *endo*-compound (**22**) to its *exo*-diastereoisomer (**4b**) was effected by DBN.

Hydrogenolyses of the *p*-nitrobenzyl esters (**3d**) and (**4c**), over palladium and in the presence of sodium hydrogen carbonate, gave the sodium salts of isopenam-3-*exo*-carboxylic acid and 3-*exo*-carboxyisopenam 2,2-dioxide, *i.e.* (**3a**) and (**4a**), respectively. Although stable in aqueous solution, the sodium salts (**3a**) and (**4a**) were inactive as antibacterial agents. The sodium salt (**4a**), unlike its analogue sulbactam sodium salt (**21a**), was ineffective as a β-lactamase inhibitor.

When treated with trifluoroacetic acid, the isopenams (**3b**) and (**12a**) were converted respectively, into *trans*-(2-t-butoxycarbonyl-3-trifluoroacetylthiazolidin-4-yl)acetic acid (**13b**) and its *cis*-diastereoisomer (**14b**). Under similar conditions, the isopenam dioxides (**4b**) and (**22**) afforded *trans*-2-t-butoxycarbonyl-4-methonycarbonylmethyl-3-trifluoroacetylthiazolidine 1,1-dioxide (**13e**) and its *cis*-diastereoisomer (**14d**). Trifluoroacetolysis of sulbactam benzyl ester (**21b**) gave (2*R*,4*S*)-4-benzyloxycarbonyl-2-methoxycarbonylmethyl-5,5-dimethyl-3-trifluoroacetylthiazolidine 1,1-dioxide (**26b**).

The aforecited results suggest that 3,4-bond ruptures do not accompany β-lactam cleavages of compounds (**3b**), (**4b**), (**12a**), and (**22**) and that a 1,5-bond breakage is not associated with rupture of the β-lactam linkage of sulbactam benzyl ester (**21b**). The failure to observe such fragmentation processes is interpreted in terms of unfavourable stereoelectronic factors. *N*-Unsubstituted thiazolidine 1,1-dioxides, species with hitherto have never been isolated or detected, are implicated as intermediates in the trifluoroacetolyses of compounds (**4b**), (**21b**), and (**22**).

The lethal effect of the β-lactam antibiotics against bacteria is associated with a cleavage of the azetidinone linkage by an enzymic nucleophile.[3] In general, biologically active antibiotics of this genre incorporate chemically reactive β-lactam entities. Recently, we described[1] a synthesis of the racemate of the isoclavam (**1a**). It was hoped that this compound would possess a higher chemical reactivity (and, perhaps, some antibacterial activity) than the clavam (**2**) (which was biologically inactive). In the event, compound (**1a**) was too reactive chemically, undergoing substantial decomposition in deuterium oxide during 12 h. This reactivity precluded a meaningful assessment of its biological properties.

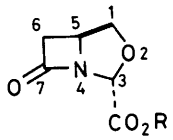
Because the C–S bond is significantly longer than the C–O bond (181 *vs.* 143 pm),[4] the isopenam (**3a**) is a less strained entity than the isoclavam (**1a**). The β-lactam linkage of the former compound is therefore expected to be less reactive than that of the latter. Furthermore, by oxidation of the sulphur atom, there is the prospect of augmenting the β-lactam reactivity. We now report on our studies which have resulted in the synthesis of the racemates of the isopenams (**3a**) and (**4a**).

## Results and Discussion

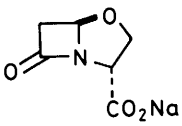
At the outset of our work, two syntheses of the isopenam ring system had been described. Bose and his co-workers had used an approach based upon the final construction of the 5,6- and 4,7-bond.[5] Thus the isopenam (**5a**) was prepared by treating the thiazoline (**6**) with azidoacetyl chloride and triethylamine; the procedure, however, was inapplicable to the synthesis of the isopenam (**5b**). The final construction of the 1,2- and 2,3-bond was the basis of the procedure developed by Huffman and his co-workers.[6] Thus treatment of the azetidinone (**7b**), generated *in situ* from the azetidinone (**7a**) by the action of thionyl chloride, with potassium thioacetate gave the thioester (**7c**) which was transformed into the isopenicillin (**8a**) (as a mixture of 3-epimers) in the presence of cyclohexylamine. We planned to generate isopenams of the type (**3**) by the Huffman strategy but hoped to effect transformations of the type (**9**)→(**3**) directly, by employing hydrogen sulphide under basic conditions.

Treatment of a solution of the azetidinone (**10a**)[1] (present as a 1 : 1 mixture of diastereoisomers) in tetrahydrofuran (THF) at −20 °C with 2,6-lutidine and thionyl chloride[7] gave the azetidinone (**9a**). In dichloromethane at 0 °C, the azetidinone (**9a**) reacted with hydrogen sulphide and triethylamine to give, following silica-gel chromatography, two products.

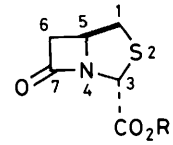
The first eluted material, isolated as a chromatographically homogeneous syrup in 32% yield, was considered to be the isopenam (**3b**) on the basis of its spectroscopic properties. In particular, it showed a strong i.r. absorption at 1 780 $cm^{-1}$ attributable to the β-lactam carbonyl group. In the 360 MHz $^1H$ n.m.r. spectrum ($CDCl_3$), the two one-proton double doublets at δ 2.72 (*J* 16 and 2.5 Hz) and δ 3.38 (*J* 16 and 5 Hz) and the one-proton singlet at δ 5.38 were clearly assignable to the 6-*endo*-, 6-*exo*-, and 3-proton, respectively; these values are close to those reported for the corresponding protons of the isoclavam (**1b**).[1] In addition to showing a molecular ion at *m/z* 229, corres-



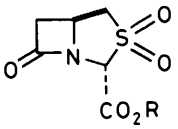
(1) a; R = Na
b; R = Bu$^t$



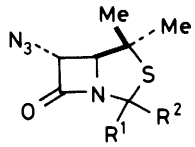
(2)



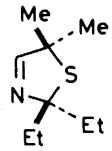
(3) a; R = Na
b; R = Bu$^t$
c; R = H
d; R = $CH_2C_6H_4NO_2$-*p*



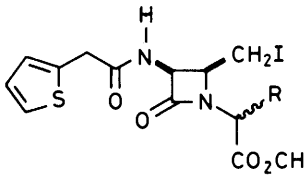
(4) a; R = Na
b; R = Bu$^t$
c; R = $CH_2C_6H_4NO_2$-*p*
d; R = $H{\cdot}H_2NC_6H_4Me$-*p*
e; R = $CH_2Ph$



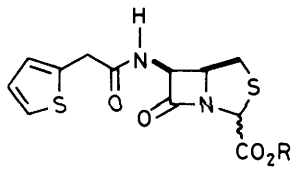
(5) a; $R^1 = R^2 = Et$
b; $R^1 = H$, $R^2 = CO_2Bu^t$



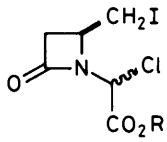
(6)



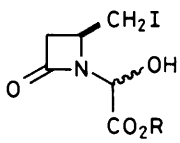
(7) a; R = OH
b; R = Cl
c; R = SC(=O)Me



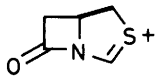
(8) a; R = $CH_2Ph$
b; R = Na



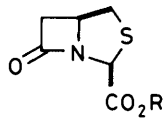
(9) a; R = Bu$^t$
b; R = $CH_2C_6H_4NO_2$-*p*



(10) a; R = Bu$^t$
b; R = $CH_2C_6H_4NO_2$-*p*



(11)



(12) a; R = Bu$^t$
b; R = $CH_2C_6H_4NO_2$-*p*

ponding to $C_{10}H_{15}NO_3S$ by accurate-mass measurement, the mass spectrum possessed a base peak at *m/z* 128, attributable to the ion (**11**).

The second eluted material, isolated as needle-like crystals in 53% yield,* was identified as the isopenam (**12a**) on the basis of its analytical and spectroscopic properties. Its β-lactam carbonyl group absorbed at 1 760 cm$^{-1}$. In the 360 MHz $^1$H n.m.r. spectrum ($CDCl_3$), the 6-*endo*-proton appeared as a double doublet at δ 2.71 (*J* 16 and 2.5 Hz), the 6-*exo*-proton as a doublet of doublet doublets at δ 3.02 (*J* 16, 5, and 1.5 Hz), and the 3-proton as a doublet at δ 4.58 (*J* 1.5 Hz). It is well established, in related bicyclic systems, that the 3-*exo*-proton is shielded compared with its 3-*endo*-counterpart;[8,9] moreover, when long-range coupling is observed between the 3- and 6-*exo*-proton, the 3-proton is *exo*-orientated.[10] The mass spectrum of the isopenam (**12a**) featured as base peak at *m/z* 128, again attributable to the ion (**11**).

In deuteriochloroform containing 1,5-diazabicyclo[4.3.0]-non-5-ene (DBN), the isopenam (**12a**) was converted into the diastereoisomer (**3b**) in 95% yield. This result reinforced the stereochemical assignments of the isopenams (**3b**) and (**12a**), since the *exo*-orientation of the carboxylate moiety represents the thermodynamically preferred situation in related bicyclic systems.[9]

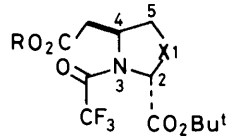
With a view to obtaining the acid (**3c**), and thence the sodium salt (**3a**) for biological evaluation, the behaviour of the isopenam (**3b**) towards trifluoroacetic acid was investigated. When trifluoroacetic acid (1 mol equiv.) was added to a deuteriochloroform solution of the isopenam (**3b**), an acidic material was formed. Following esterification with diazomethane and fractionation of the product by silica-gel chromatography, a homogeneous syrup was isolated in 58% yield. The material, of constitution $C_{13}H_{18}F_3NO_5S$ by high-resolution mass spectroscopy, was formulated as the thiazolidine (**13a**) on the basis of its spectroscopic properties. In particular, the compound showed a strong i.r. absorption at 1 695 cm$^{-1}$, attributable to the amide carbonyl group. 360 MHz $^1$H N.m.r. spectroscopy suggested that the thiazolidine (**13a**) was present in deuteriochloroform as a 1.5:1 mixture of rotamers, due to restricted rotation about the amide group; for example, there were two signals for the methoxy group [δ 3.69 (1.8 H) and δ 3.71 (1.2 H)] and for the 2-proton of the thiazolidine ring [δ 5.10 (0.4 H) and δ 5.22 (0.6 H)]. Evidently, the reaction of the isopenam (**4b**) with trifluoroacetic acid had led to the acid (**13b**).

When treated sequentially with trifluoroacetic acid and diazomethane, the isopenam (**12a**) was converted into a crystalline product (82% yield after $SiO_2$ chromatography), formulated as the thiazolidine (**14a**). 360 MHz $^1$H N.m.r. spectroscopy established that the compound was present in deuteriochloroform as a 2:1 mixture of rotamers; thus there were two signals for the methoxy group [δ 3.70 (2 H) and δ 3.71 (1 H)] and for the 2-proton of the thiazolidine ring [δ 5.38 (0.66 H) and δ 5.48 (0.33 H)]. Clearly, the acid (**14b**) was the product of the reaction of the isopenam (**12a**) with trifluoroacetic acid.

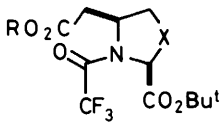
Presumably, the formation of the acids (**13b**) and (**14b**) involves attack of trifluoroacetic acid at the β-lactam carbonyl groups of the isopenams (**3b**) and (**12a**) to give the mixed anhydrides (**15a**) and (**16a**) as intermediates. Although an analogous reaction was observed with the isoclavam (**1b**) [to give the acid (**13c**)],[1] the present results argue against the involvement of the fragmentation processes (**17a**) and (**18a**); they also reveal that the mixed anhydrides (**15a**) and (**16a**) do not isomerise to the imine thiols (**19a**) and (**20a**).

If the fragmentation processes (**17a**) and (**18a**) were involved, two postulates would be necessary. First, the imine thiols (**19a**) and (**20a**) [the respective products of the processes (**17a**) and (**18a**)] must not interconvert. Second, the imine thiol (**19a**) must afford exclusively the thiazolidine (**13b**) whereas its counterpart (**20a**) must give rise only to the thiazolidine (**14b**). Whilst the

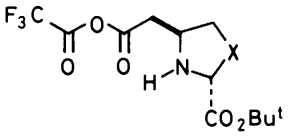
* The yield of this compound reported in the preliminary communication is incorrect.



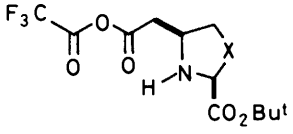
(13) a; R = Me, X = S
b; R = H, X = S
c; R = H, X = O
d; R = Me, X = S(=O)$_2$
e; R = H, X = S(=O)$_2$



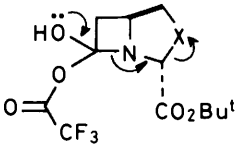
(14) a; R = Me, X = S
b; R = H, X = S
c; R = Me, X = S(=O)$_2$
d; R = H, X = S(=O)$_2$



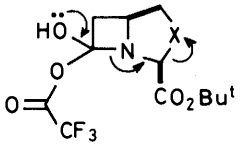
(15) a; X = S
b; X = S(=O)$_2$



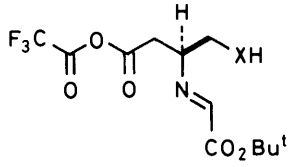
(16) a; X = S
b; X = S(=O)$_2$



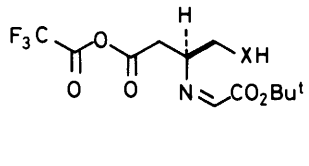
(17) a; X = S
b; X = S(=O)$_2$



(18) a; X = S
b; X = S(=O)$_2$



(19) a; X = S
b; X = S(=O)O



(20) a; X = S
b; X = S(=O)O

former postulate may not be unreasonable,[11] the latter requirement demands an exceptional role for the chiral centre in the species (**19a**) and (**20a**). Thus the chiral centre must ensure that the transition states leading from the imine thiols (**19a**) and (**20a**) to the respective thiazolidines (**13b**) and (**14b**) are substantially favoured over their diastereoisomeric counterparts [which would lead, respectively, to the thiazolidines (**14b**) and (**13b**)]. However, if the (**19a**)→(**13b**) transition state is adopted because steric interactions between the 2- and 4-substituent (thiazolidine numbering) are minimised, it is difficult to understand why the (**20a**)→(**13b**) transition state should not be favoured. Using similar arguments, isomerisation of the mixed anhydrides (**15a**) and (**16a**) to the imine thiols (**19a**) and (**20a**) can also be discounted.

The *p*-nitrobenzyl ester moiety is an effective precursor of the carboxylic acid group in sensitive β-lactam substrates; its hydrogenolysis in the presence of sodium hydrogen carbonate affords the sodium salt directly.[12] Accordingly, efforts were directed to the preparation of the isopenams (**3d**) and (**12b**).

Treatment of the hydroxyamide (**10b**)[1] (as a 1:1 mixture of diastereoisomers) with 2,6-lutidine and thionyl chloride afforded the chloride (**9b**), which was converted into the isopenams (**3d**) and (**12b**) by the action of hydrogen sulphide and triethylamine. The more mobile material, isolated as a chromatographically homogeneous syrup (20% yield after $SiO_2$ chromatography), was the isopenam (**3d**). The less mobile material, obtained as pale-yellow needles (30% yield after $SiO_2$ chromatography), was the isopenam (**12b**). In the presence of DBN, the last mentioned compound underwent epimerisation to give the isopenam (**3d**) in 96% yield.

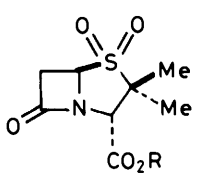
When hydrogenolysed over palladium in the presence of sodium hydrogen carbonate (1 mol equiv.), the isopenam (**3d**) was converted into the salt (**3a**), isolated as an off-white solid in 81% yield; under corresponding conditions, the isopenam (**12b**) afforded non-β-lactam products. The salt (**3a**), which showed a β-lactam carbonyl absorption at 1 750 $cm^{-1}$, was stable in deuterium oxide for 12 h according to n.m.r. spectroscopy. By contrast the salt (**1a**), which featured a β-lactam carbonyl absorption at 1 770 $cm^{-1}$, underwent *ca.* 80% decomposition in deuterium oxide within 12 h.[1]

In contrast to the isopencillin (**8b**) which, as a racemic mixture of 3-epimers, inhibited the growth of several bacteria including *Staphylococcus aureus*,[6] the isopenam (**3a**) showed no antibacterial activity against *Staphylococcus aureus* or *Salmonella typhi*. Clearly, the presence of a *cis*-orientated acylamino group at position 6 is necessary for the bioactivity of isopenam-3-carboxylic acid salts.

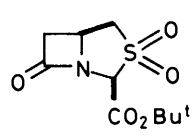
Attention was next turned to the synthesis of the isopenam dioxide (**4a**). It was expected that the β-lactam linkage of this compound would be more susceptible to nucleophilic attack than that of the isopenam (**3a**).

When oxidised with potassium permanganate in aqueous acetic acid, the isopenam (**3d**) was converted into the isopenam dioxide (**4c**) (55% yield after $SiO_2$ chromatography). Hydrogenolysis of the last cited compound, over palladium in the presence of sodium hydrogen carbonate, gave the salt (**4a**) as an off-white solid in 60% yield; when the hydrogenolysis was performed in the absence of sodium hydrogen carbonate, the salt (**4d**) was isolated as an amorphous solid in 76% yield. The salt (**4a**), which possessed a β-lactam carbonyl absorption at 1 775 $cm^{-1}$ and was unchanged in deuterium oxide during 12 h, was inactive against *Staphylococcus aureus* and *Salmonella typhi*.

Although devoid of useful antibacterial activity, sulbactam sodium salt (**21a**) synergises the effect of penicillins against β-lactamase-producing bacteria.[13] The synergy is due to the inactivation of the β-lactamase by the sulphone (**21a**), thereby preventing hydrolysis of the penicillin by the enzyme. Because of its structural resemblance to sulbactam sodium salt (**21a**), the isopenam dioxide (**4a**) was tested as a β-lactamase inhibitor. It had no effect upon the β-lactamase from *Pseudomonas aeruginosa*. Clearly, the location of the sulphonyl group at position 1 of compound (**21a**) is an essential requirement for its β-lactamase-inhibitory properties.



(21) a; R = Na
b; R = $CH_2Ph$



(22)

As already indicated, the reactions of the isopenams (**3b**) and (**12a**) with trifluoroacetic acid afforded the acids (**13b**) and (**14b**), respectively. In addition to excluding the fragmentation processes (**17a**) and (**18a**), the results established that the intermediates (**15a**) and (**16a**) underwent intramolecular acyl transfers to give the acids (**13b**) and (**14b**) faster than isomerisations to the imine thiols (**19a**) and (**20a**). Since sulphones are better leaving groups than sulphides[14] and, to our knowledge, *N*-unsubstituted thiazolidine dioxides have never been isolated or detected (presumably because of the ease

with which they undergo ring-chain tautomerisation), it was of interest to examine the behaviour of the isopenam dioxides (**4b**) and (**22**) towards trifluoroacetic acid.

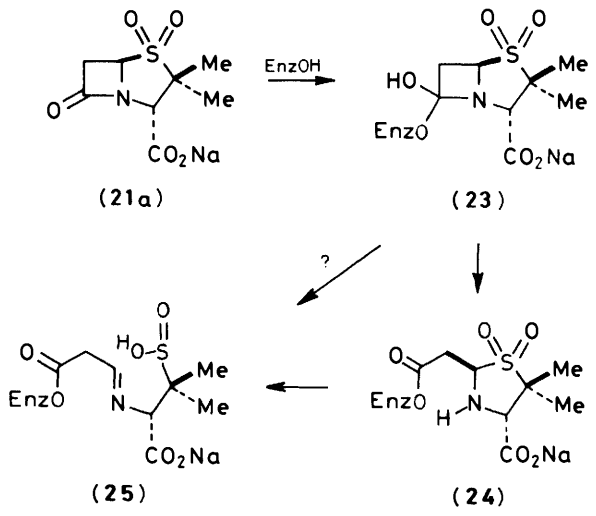
The isopenam dioxides (**4b**) and (**22**), isolated in respective yields of 64 and 50% after recrystallisation, were obtained from the isopenams (**3b**) and (**12a**) by oxidation with potassium permanganate.* In the 360 MHz $^1$H n.m.r. spectrum ($CDCl_3$) of the sulphone (**22**), the 3-proton showed long-range coupling (*J* 1.8 Hz) to the 5-*exo*-proton, in accord with its *exo*-orientation; furthermore, the proton was significantly shielded (δ 4.49) compared with that of its counterpart in compound (**4b**) (δ 5.13). When treated in deuteriochloroform with DBN, the isopenam dioxide (**22**) was isomerised to its diastereoisomer (**4b**) (90% yield), consolidating the stereochemical assignments.

By sequential reactions with trifluoroacetic acid and diazomethane, the isopenam dioxide (**4b**) was converted into a material (64% yield after recrystallisation), designated sample *A*, of constitution $C_{13}H_{18}F_3NO_7S$. A substance of identical constitution, referred to as sample *B*, was isolated (41% yield after recrystallisation) from the reaction of the thiazolidine (**13a**) with potassium permanganate. Although the samples differed in their m.p.s (118—120 °C for the former and 111—114 °C for the latter) and their solid-state i.r. spectra [$\nu_{max.}$(KBr) *inter alia* 1 745, 1 735, and 1 695 $cm^{-1}$ for the former and 1 725 $cm^{-1}$ for the latter], they were identical by 250 MHz $^1$H n.m.r. spectroscopy. In addition to corroborating the structure (**13d**), $^1$H n.m.r. spectroscopy indicated that the compound was present in deuteriochloroform as one major rotamer. Presumably, the different physical properties of the samples *A* and *B* are to be ascribed to dimorphic forms of the crystals. Indeed, in a repeat of the reaction of the isopenam dioxide (**4b**) with trifluoroacetic acid followed by diazomethane, a compound of m.p. 115—116 °C, designated sample *C*, was isolated (52% after recrystallisation). Its solid-state i.r. spectrum showed peaks which were present in each of the previous spectra, implying that sample *C* comprised a mixture of samples *A* and *B*. Finally, when sample *C* was subjected to recrystallisation and the solution seeded with sample *A*, the recovered material was identical with sample *A* in its m.p. and i.r. spectrum.

When allowed to react sequentially with trifluoroacetic acid and diazomethane, the isopenam dioxide (**22**) was converted into a material (62% yield after recrystallisation) of constitution $C_{13}H_{18}F_3NO_7S$. Although its m.p. was similar to that of sample *B* of compound (**13d**), its i.r. and 250 MHz $^1$H n.m.r. spectra were different. The material was found to be identical with that obtained (82% yield after recrystallisation) from the thiazolidine (**14a**) by the action of potassium permanganate, establishing that it possessed the structure (**14c**). On the basis of 250 MHz $^1$H n.m.r. spectroscopy, compound (**14c**) existed in deuteriochloroform as a 3.5:1 mixture of rotamers.

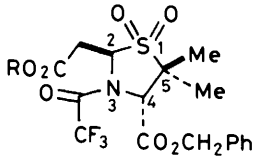
In the light of the foregoing results, it is clear that the acids (**13e**) and (**14d**) are the respective products of the reactions of the isopenam dioxides (**4b**) and (**22**) with trifluoroacetic acid. Evidently, the fragmentation processes (**17b**) and (**18b**) play no role in the reactions. Moreover, the intermediates (**15b**) and (**16b**), which are implicated, undergo intramolecular acyl transfers to give the acids (**13e**) and (**14d**) more rapidly than tautomerisation to the imine sulphinic acids (**19b**) and (**20b**).

Knowles and his co-workers[15] have shown that the inactivation of the β-lactamase from *Escherichia coli* by sulbactam sodium salt (**21a**) is associated with further reactions of the species (**25**). By analogy with penicillinate substrates, the species (**25**) may be expected to arise from the precursor (**24**). However, since such an intermediate could not be detected; the possibility that the initially formed enzyme–substrate complex (**23**) underwent fragmentation to the species (**25**) was considered by the Harvard workers (Scheme).

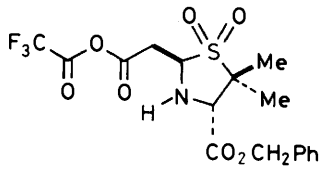



**Scheme.**

When sulbactam benzyl ester (**21b**), prepared (80% yield after $SiO_2$ chromatography) from the reaction of sulbactam sodium salt (**21a**) with benzyl bromide in *NN*-dimethylformamide (DMF), was treated sequentially with trifluoroacetic acid and diazomethane, a crystalline material (62% yield after $SiO_2$ chromatography) was produced. On the basis of its analytical and spectroscopic properties, the material was assigned the structure (**26a**). Its stereostructure was inferred by n.O.e.-difference spectroscopy (250 MHz; $CDCl_3$). Thus irradiation of the signal at δ 1.50, attributed to the 5α-methyl group, caused a ⩽1% enhancement of the singlet at δ 4.70, assigned to 4-H, a 0.5% enhancement of the double doublet centred at δ 5.25, due to the benzylic methylene group, and a 1% enhancement of the multiplet at δ 5.28—5.37, attributed to 2-H. Irradiation of the signal at δ 1.58, for the 5β-methyl group, increased the intensity of the 4-H signal by >2% and of those of the methylene protons of the 2-substituent (δ 2.83—2.97 and δ 3.33—3.44) by 2%. When 4-H was irradiated, the signal for the 5β-methyl group was enhanced by 1.7%.



(**26**) a; R = Me
b; R = H

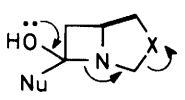


(**27**)

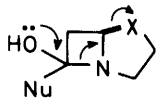
The formation of the thiazolidine dioxide (**26a**) means that the acid (**26b**) is the product of the reaction of sulbactam benzyl ester (**21b**) with trifluoroacetic acid. Clearly, the intermediate (**27**), formed by trifluoroacetolysis of the β-lactam linkage of compound (**21b**), is the precursor of the acid (**26b**).

The failure to observe processes of the types (**28**) and (**29**) has, we believe, a stereoelectronic basis. In heterolytic fragmentations, a partial requirement is that the bonds undergoing rupture must possess an antiperiplanar relationship;[16] this geometry is precluded in intermediates of the types (**30**) and (**31**)

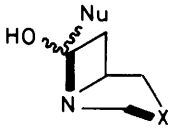
* In initial studies, a 1:1 mixture of the isopenams (**3b**) and (**12a**) was oxidised to the isopenam dioxide (**4b**) (59% yield after $SiO_2$ chromatography), implicating an epimerisation of the isopenam dioxide (**12a**) under the work-up conditions.



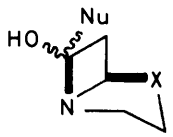
(28)



(29)



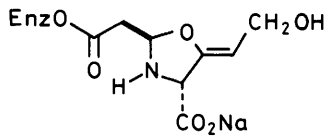
(30)



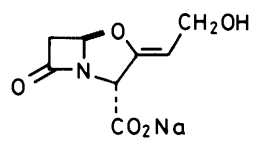
(31)

(where the bonds that have to be cleaved are emphasized by heavy lines).* In consequence, we infer that the species (**24**) is an obligatory intermediate in the reaction of sulbactam sodium salt (**21a**) with β-lactamases. Obviously, the aforecited stereoelectronic requirements cannot be realized in any species of the types (**30**) and (**31**) (where X = a heteroatomic substituent). Necessarily, therefore, the intermediate (**32**) (which has not been detected)[17] is implicated in the inactivation of β-lactamases by sodium clavulanate (**33**).

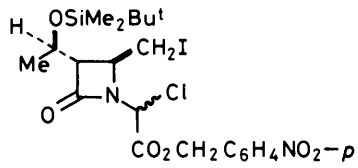
During the course of this work, there have been additional developments in the isopenam area. On the synthetic front, the procedure employed in the present investigation was used to convert the azetidinone (**34**) into the isopenam (**35**) (as a mixture of diastereoisomers).[18] A further method, based upon the final construction of the 1,2- and 2,3-bond, has also been reported.[19] It involved treating an azetidinone, *e.g.* (**36**), with potassium t-butoxide and sulphur to give an isopenam, *e.g.* (**37a**). The procedure appears to be a general one and was used to prepare the isopenams (**37b**), (**37c**), (**38a**), and (**38b**). Finally, a new strategy, involving final construction of the 1,2- and 3,4-bond,[20] was used to prepare the isopenam dioxide (**4e**). Thus the azetidinone (**39b**), obtained from the iodide (**39a**) and *p*-nitrobenzyl 2-mercaptoacetate, was converted *via* the sulphone (**39c**) into the diazo compound (**39d**). In the presence of rhodium(II) acetate the last cited material afforded the isopenam (**4e**).



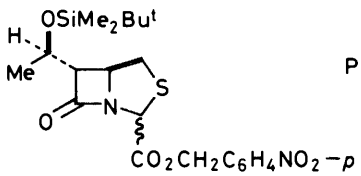
(32)



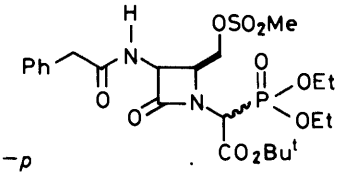
(33)



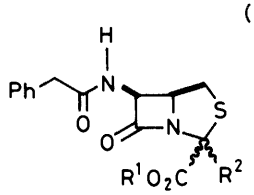
(34)



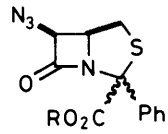
(35)



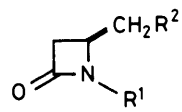
(36)



(37) a ; $R^1$ = Bu$^t$ , $R^2$ = P(=O)(OEt)$_2$
b ; $R^1$ = $CH_2Ph$ , $R^2$ = Ph
c ; R = Me , $R^2$ = 2 - furyl



(38) a ; R = $CH_2C_6H_4NO_2$-*p*
b ; R = Et



(39) a ; $R^1$ = $SiMe_2Bu^t$ , $R^2$ = I
b ; $R^1$ = $SiMe_2Bu^t$ , $R^2$ = $SCH_2CO_2CH_2Ph$
c ; $R^1$ = H , $R^2$ = $S(=O)_2CH_2CO_2CH_2Ph$
d ; $R^1$ = H , $R^2$ = $S(=O)_2C(N_2)CO_2CH_2Ph$

## Experimental

Dry solvents, referred to in the ensuing experiments, were prepared as follows: THF was dried over calcium hydride and, immediately prior to use, was distilled; DMF was distilled under reduced pressure from calcium hydride and stored over molecular sieves (Type 4A). Light petroleum refers to that fraction boiling in the range 40—60 °C. Ethereal diazomethane was prepared by adding a solution of 'Diazald' in diethyl ether to potassium hydroxide in aqueous ethanol.[21] For chromatographic and instrumental details, see Part 1.[1] High-field $^1H$ n.m.r. spectroscopy was performed at 250 MHz and 360 MHz using Bruker WH-250 and WH-360 spectrometers. Microanalyses were performed using a Carlo-Erba 1106 Elemental Analyser.

*Preparation of the Isopenams* (**3b**) *and* (**12a**).—To a cooled ($CCl_4$–solid $CO_2$) stirred solution of the hydroxyamide (**10a**) (1.00 g, 2.93 mmol) in dry THF (15 cm$^3$) were added 2,6-lutidine (0.345 g, 3.22 mmol) and thionyl chloride (0.698 g, 5.87 mmol). When the formation of the chloride (**9a**) was complete (t.l.c.), the mixture was filtered and the filtrate was evaporated. The resultant syrup was dissolved in dry dichloromethane (20 cm$^3$) and the ice-cooled solution was saturated with hydrogen sulphide. After 15 min, triethylamine (0.650 g, 6.42 mmol) was added. When the reaction was complete (t.l.c.), the solvent was evaporated off and the residue was partitioned between ethyl acetate and brine. Evaporation of the dried ($MgSO_4$) organic layer and subjection of the residue to silica-gel chromatography (light petroleum–EtOAc, gradient elution) gave two major fractions.

* Earlier, we (see ref. 1) and others (see refs. 6, 15, and 17) missed this point.

The first eluted fraction, identified as *t-butyl isopenam*-3-exo-*carboxylate* (**3b**), was isolated as a chromatographically homogeneous syrup (0.216 g, 32%) which showed the following properties: $\nu_{max.}$(film) *inter alia* 1 780 (β-lactam C=O) and 1 735 $cm^{-1}$ (ester C=O); $\lambda_{max.}$(EtOH) 215 (ε 1 000) and 250sh nm (200); δ (360 MHz; $CDCl_3$) 1.45 (9 H, s, $Bu^t$), 2.72 (1 H, dd, *J* 16 and 2.5 Hz, 6-*endo*-H), 3.00 (1 H, dd, *J* 11 and 4.5 Hz, 1-*endo*-H), 3.38 (1 H, dd, *J* 16 and 5 Hz, 6-*exo*-H), 3.44 (1 H, dd, *J* 11 and 7 Hz, 1-*exo*-H), 4.40—4.45 (1 H, m, 5-H), and 5.38 (1 H, s, 3-H); *m/z inter alia* 229 ($M^+$) and 128 ($C_5H_6NOS^+$, base peak) (Found: $M^+$, 229.0773. $C_{10}H_{15}NO_3S$ requires *M*, 229.0773).

The second eluted fraction, isolated as a crystalline solid (0.355 g, 53%), was *t-butyl isopenam*-3-endo-*carboxylate* (**12a**). A sample, recrystallised from chloroform–diethyl ether, showed the following properties: m.p. 67—68 °C; $\nu_{max.}$(KBr) *inter alia* 1 760 (β-lactam C=O) and 1 730 $cm^{-1}$ (ester C=O); $\lambda_{max.}$(EtOH) 215 (ε 2 050) and 253 nm (250); δ (360 MHz; $CDCl_3$) 1.49 (9 H, s, $Bu^t$), 2.71 (1 H, dd, *J* 16 and 2.5 Hz 6-*endo*-H), 3.01 (1 H, t, *J* 11 and 11 Hz, 1-H), 3.02 (1 H, ddd, *J* 16, 5, and 1.5 Hz, 6-*exo*-H), 3.08 (1 H, dd, *J* 11 and 5 Hz, 1-H), 4.09—4.15 (1 H, m, 5-H), and 4.58 (1 H, d, *J* 1.5 Hz, 3-H); *m/z inter alia* 229 ($M^+$) and 128 ($C_5H_6NOS^+$, base peak) (Found: C, 52.1; H, 6.6; N, 5.8. $C_{10}H_{15}NO_3S$ requires C, 52.4; H, 6.55; N, 6.10%).

*Epimerisation of the Isopenam* (**12a**).—To a solution of the isopenam (**12a**) (0.100 g, 0.44 mmol) in deuteriochloroform (0.5 $cm^3$) was added a small quantity of DBN. The reaction was monitored by n.m.r. spectroscopy and, when the starting material had disappeared, the solution was diluted with chlorofrom and with dil. hydrochloric acid. Evaporation of the dried ($MgSO_4$) organic layer left a syrup (0.095 g, 95%) that was identical with the isopenam (**3b**) by n.m.r. spectroscopy.

*Reaction of the Isopenam* (**3b**) *with Trifluoroacetic Acid Followed by Diazomethane.*—Trifluoroacetic acid (0.070 g, 0.61 mmol) was added to a solution of the isopenam (**3b**) (0.140 g, 0.61 mmol) in deuteriochloroform (1 $cm^3$). When the reaction was complete (n.m.r. spectroscopy), the solution was evaporated and the syrup treated with an excess of ethereal diazomethane. The residue, obtained after evaporation, was subjected to silica-gel chromatography [light petroleum–EtOAc (2:1) as eluant]. The derived *methyl* trans-(2-*t-butoxycarbonyl*-3-*trifluoroacetylthiazolidin*-4-*yl*)*acetate* (**13a**) (0.120 g, 58%), obtained as a chromatographically homogeneous syrup, possessed the following properties: $\nu_{max.}$(film) *inter alia* 1 735 (ester C=O) and 1 695 $cm^{-1}$ (amide C=O); $\lambda_{max.}$(EtOH) 214 nm (ε 4 900); δ (360 MHz; $CDCl_3$) 1.45 (9 H, s, $Bu^t$), 2.60 and 2.67 [0.4 and 0.6 H, br d (separation 17 Hz) and dd (*J* 16 and 10 Hz), C*H*H·$CO_2$Me], 2.91—3.11 (2 H, m, CH*H*·$CO_2$Me and 5-H), 3.46—3.59 (1 H, m, 5-H), 3.69 and 3.71 (1.8 and 1.2 H, each s, together OMe), 4.97—5.10 (1 H, m, 4-H), and 5.10 and 5.22 [0.4 and 0.6 H, s and d (*J* 1 Hz), together 2-H)]; *m/z inter alia* 357 ($M^+$) and 256 ($C_8H_9F_3NO_3S^+$, base peak) (Found: $M^+$, 357.0854. $C_{13}H_{18}F_3NO_5S$ requires *M*, 357.0858).

*Reaction of the Isopenam* (**12a**) *with Trifluoroacetic Acid Followed by Diazomethane.*—Trifluoroacetic acid (0.090 g, 0.79 mmol) was added to a solution of the isopenam (**12a**) (0.180 g, 0.79 mmol) in deuteriochloroform (1 $cm^3$). Work-up, when the reaction was complete (n.m.r. spectroscopy) (as described in the previous experiment), gave *methyl* cis-(2-*t-butoxycarbonyl*-3-*trifluoroacetylthiazolidin*-4-*yl*)*acetate* (**14a**) (0.230 g, 82%). The sample, recrystallised from diethyl ether–light petroleum, showed the following properties: m.p. 112—114 °C; $\nu_{max.}$(KBr) *inter alia* 1 730 (ester C=O) and 1 700 $cm^{-1}$ (amide C=O); $\lambda_{max.}$(EtOH) 220 nm (ε 2 900); δ (360 MHz; $CDCl_3$) 1.46 and 1.47 (6 and 3 H, each s, $Bu^t$), 2.72—2.83, 3.04—3.14, 3.29—3.39, [illegible] 1.33, 1, and 0.66 H, each m, together C*H*$CO_2$Me and 5-$H_2$), 3.70 and 3.71 (2 and 1 H, each s, together OMe), 4.79—4.82 and 4.94—5.05 (0.66 and 0.33 H, each m, 4-H), and 5.38 and 5.48 [0.66 and 0.33 H, d, (*J* 1.3 Hz) and s, together 2-H]; *m/z inter alia* 357 ($M^+$) and 256 ($C_8H_9F_3NO_3S^+$, base peak) (Found: C, 43.5; H, 5.05; N, 3.85%; $M^+$, 357.0880. $C_{13}H_{18}F_3NO_5S$ requires C, 43.6; H, 5.05; N, 3.90%; *M*, 257.0858).

*Preparation of the Isopenams* (**3d**) *and* (**12b**).—To a cooled ($CCl_4$–solid $CO_2$) stirred solution of the hydroxyamide (**10b**) (1.35 g, 3.21 mmol) in dry THF (15 $cm^3$) was added 2,6-lutidine (0.370 g, 3.46 mmol) and thionyl chloride (0.760 g, 6.39 mmol). When the formation of the chloride (**9b**) was complete (t.l.c.), the mixture was filtered and the filtrate was evaporated. The resultant syrup was dissolved in dry dichloromethane (20 $cm^3$) and the ice-cooled solution was saturated with hydrogen sulphide. After 15 min, triethylamine (0.322 g, 3.18 mmol) and anhydrous sodium carbonate (0.388 g, 3.19 mmol) were added and the mixture was stirred. Filtration and evaporation, when the reaction was complete (t.l.c.), left a residue which was partitioned between ethyl acetate and dil. hydrochloric acid. Evaporation of the dried ($MgSO_4$) organic layer and subjection of the residue to silica-gel chromatography [light petroleum–EtOAc (2:1) as eluant] gave two major fractions.

The first eluted fraction, identified as p-*nitrobenzyl isopenam*-3-exo-*carboxylate* (**3d**), was isolated as a chromatographically homogeneous syrup (0.196 g, 20%) which showed the following properties: $\nu_{max.}$(film) *inter alia* 1 775 (β-lactam C=O) and 1 750 $cm^{-1}$ (ester C=O); $\lambda_{max.}$(EtOH) 212 (ε 4 400) and 265 nm (5 900); δ (60 MHz; $CDCl_3$) 2.80 (1 H, dd, *J* 17 and 3 Hz, 6-*endo*-H), 2.90—3.60 (3 H, m, 6-*exo*-H and 1-$H_2$), 4.30—4.53 (1 H, m, 5-H), 5.22 (2 H, s, $CO_2CH_2$), 5.58 (1 H, s, 3-H), and 7.45 and 8.18 (each 2 H, d, *J* 8 Hz, together $C_5H_4$); *m/z inter alia* 308 ($M^+$) and 128 ($C_5H_6NOS^+$, base peak) (Found: $M^+$, 308.0489. $C_{13}H_{12}N_2O_5S$ requires *M*, 308.0467).

The second eluted fraction, isolated as a crystalline solid (0.295 g, 30%), was p-*nitrobenzyl isopenam*-3-endo-*carboxylate* (**12b**). A sample, recrystallised from chloroform–diethyl ether, showed the following properties: m.p. 108—110 °C; $\nu_{max.}$(KBr) *inter alia* 1 770 and 1 765 (β-lactam C=O) and 1 735 $cm^{-1}$ (ester C=O); $\lambda_{max.}$(EtOH) 210 (4 400) and 265 nm (4 000); δ (60 MHz; $CDCl_3$) 2.75 (1 H, dd, *J* 16 and 3 Hz, 6-*endo*-H), 2.95—3.30 (3 H, m, 6-*exo*-H and 1-$H_2$), 4.00—4.30 (1 H, m, 5-H), 4.74 (1 H, s, 3-H), 5.25 (2 H, s, $CO_2CH_2$), and 7.47 and 8.15 (each 2 H, s, *J* 8 Hz, together $C_6H_4$); *m/z inter alia* 308 ($M^+$) and 128 ($C_5H_6NOS^+$, base peak) (Found: C, 50.7; H, 3.75; N, 9.25%; $M^+$, 308.0473. $C_{13}H_{12}N_2O_5S$ requires C, 50.6; H, 3.90; N, 9.10%; *M*, 308.0467).

*Epimerisation of the Isopenam* (**12b**).—To a solution of the isopenam (**12b**) (0.135 g, 0.44 mmol) in deuteriochloroform (1 $cm^3$) was added a small quantity of DBN. The reaction was monitored by n.m.r. spectroscopy and, when the starting material had disappeared, the solution was diluted with chloroform and washed with dil. hydrochloric acid. Evaporation of the dried ($MgSO_4$) organic layer left a syrup (0.130 g, 96%) that was identical with the isopenam (**3d**) by n.m.r. spectroscopy.

*Hydrogenolysis of the* p-*Nitrobenzyl Ester* (**3d**).—To a solution of sodium hydrogen carbonate (0.055 g, 0.65 mmol) in water (1 $cm^3$) was added a solution of the *p*-nitrobenzyl ester (**3d**) (0.200 g, 0.65 mol) in ethyl acetate (16 $cm^3$) and ethanol (3 $cm^3$) followed by 10% palladium–charcoal (0.400 g, 2 mass equiv.). The mixture was stirred under hydrogen and, when the gas uptake had ceased, was filtered through 'Hyflo'. Evaporation of the filtrate left a residue which was partitioned between dichloromethane and water. The aqueous layer was evaporated to leave an off-white solid (0.103 g, 81%) that was predominantly sodium isopenam-3-*exo*-carboxylate (**3a**). The

sample showed the following properties: $\nu_{max.}$(KBr) *inter alia* 1 750 (β-lactam C=O) and 1 640 $cm^{-1}$ (carboxylate C=O); δ (60 MHz; $D_2O$; external $Me_4Si$) 2.70 (1 H, dd, *J* 16 and 2 Hz, 6-*endo*-H), 2.83 (1 H, dd, *J* 11 and 8 Hz, 1-H), 3.20 (1 H, dd, *J* 16 and 5 Hz, 6-*exo*-H), 3.22 (1 H, dd, *J* 11 and 6 Hz, 1-H), 4.05—4.35 (1 H, m, 5-H), and 5.25 (1 H, s, 3-H) (the spectrum was unchanged during 12 h).

*Oxidation of the Isopenam* (**3d**) *with Potassium Permanganate.*—To a stirred solution of the isopenam (**3d**) (1.00 g, 3.25 mmol) in 4:1 acetic acid–water (25 $cm^3$) was added, during 0.5 h, a solution of potassium permanganate (0.770 g, 4.87 mmol) in water (10 $cm^3$). After a further 1 h, aqueous 30% hydrogen peroxide was added to discharge the colour and the solution was diluted with water and extracted with dichloromethane. The organic layer was washed with aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated. Purification of the resultant syrup by silica-gel chromatography [light petroleum–EtOAc (2:1) as eluant] gave 3-exo-*p-nitrobenzyloxycarbonylisopenam* 2,2-*dioxide* (**4c**) (0.607 g, 55%) as an amorphous solid which showed the following properties: $\nu_{max.}$(film) *inter alia* 1 780 (β-lactam C=O) and 1 745 $cm^{-1}$ (ester C=O); $\lambda_{max.}$(EtOH) 210 (ε 2 000) and 265 nm (2 100); δ (60 MHz; $CDCl_3$) 3.16 (1 H, dd, *J* 17 and 2.5 Hz, 6-*endo*-H), 3.18 (1 H, dd, *J* 13 and 6 Hz, 1-H), 3.57 (1 H, dd, *J* 13 and 7 Hz, 1-H), 3.70 (1 H, dd, *J* 17 and 5.5 Hz, 6-*exo*-H), 4.10—4.35 (1 H, m, 3-H), 5.32 (2 H, s, $CO_2CH_2$), 5.38 (1 H, s, 3-H), and 7.48 and 8.18 (each 2 H, d, *J* 8 Hz, together $C_6H_4$); *m/z inter alia* 276 ($M^+ - O_2S$) and 69 (base peak) (Found: C, 45.8; H, 3.5; H, 8.3. $C_{13}H_{12}N_2O_7S$ requires C, 45.9; H, 3.50; N, 8.25%).

*Hydrogenolysis of the Isopenam Dioxide* (**4c**).—(*a*) To a solution of the isopenam dioxide (**4c**) (0.600 g, 1.76 mmol) in ethyl acetate (160 $cm^3$) and ethanol (30 $cm^3$) was added a solution of sodium hydrogen carbonate (0.148 g, 1.76 mmol) in water (10 $cm^3$) followed by 10% palladium–charcoal (1.20 g, 2 mass equiv.). The mixture was stirred under hydrogen and, when the gas uptake had ceased, was filtered through 'Hyflo'. Evaporation of the filtrate left a residue that was partitioned between dichloromethane and water. The aqueous layer was evaporated to leave an off-white solid (0.240 g, 60%) that was predominantly the sodium salt of 3-*exo*-carboxyisopenam 2,2-dioxide, (**4a**). The sample showed the following properties: $\nu_{max.}$(KBr) *inter alia* 1 775 (β-lactam C=O) and 1 635 $cm^{-1}$ (carboxylate C=O); δ (60 MHz; $D_2O$; external $Me_4Si$) 3.00 (1 H, dd, *J* 17 and 2.5 Hz, 6-*endo*-H), 3.20 (1 H, dd, *J* 13 and 8 Hz, 1-H), 3.48 (1 H, dd, *J* 17 and 4 Hz, 6-*exo*-H), 3.50 (1 H, dd, *J* 13 and 6 Hz, 1-H), 3.95—4.25 (1 H, m, 5-H), and 5.15 (1 H, s, 3-H) (the spectrum was unchanged during 12 h).

(*b*) To a solution of the isopenam dioxide (**4c**) (0.200 g, 0.59 mmol) in ethyl acetate (10 $cm^3$) was added 10% palladium–charcoal (0.300 g, 1.5 mass equiv.). The mixture was stirred under hydrogen and, when the gas uptake had ceased, was filtered through 'Hyflo'. Evaporation left the *p*-toluidine salt of 3-*exo*-carboxyisopenam 2,2-dioxide, (**4d**) (0.140 g, 76%) as a pale-yellow amorphous solid with the following properties: $\nu_{max.}$(film) *inter alia* 1 775 (β-lactam C=O) and 1 640 $cm^{-1}$ (carboxylate C=O); δ (60 MHz; $D_2O$; external $Me_4Si$) 2.20 (3 H, s, *Me*$C_6H_4$), 3.05 (1 H, dd, *J* 17 and 3 Hz, 6-*endo*-H), 3.25 (1 H, dd, *J* 14 and 8 Hz, 1-H), 3.63 (1 H, dd, *J* 14 and 7 Hz, 1-H), 3.66 (1 H, dd, *J* 17 and 6 Hz, 6-*exo*-H), 4.00—4.35 (1 H, m, 5-H), 5.20 (1 H, s, 3-H), and 7.20 (5 H, s, Ph).

*Oxidation of the Isopenam* (**3b**) *with Potassium Permanganate.*—To a stirred ice-cooled solution of the isopenam (**3b**) (0.216 g, 0.94 mmol) in glacial acetic acid (5 $cm^3$) was added, during 15 min, potassium permanganate (0.326 g, 2.08 mmol) in water (5 $cm^3$). After 1 h, the mixture was decolourised with 30% aqueous hydrogen peroxide, diluted with ethyl acetate, and washed with water. The organic layer was washed with dil. aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated. Recrystallisation of the residue from ethanol–light petroleum gave 3-exo-*t-butoxycarbonylisopenam* 2,2-*dioxide* (**4b**) (0.155 g, 64%) which showed the following properties: m.p. 120—122 °C; $\nu_{max.}$(KBr) *inter alia* 1 780 and 1 765 (β-lactam C=O) and 1 735 $cm^{-1}$ (ester C=O); $\lambda_{max.}$(EtOH) 211 (ε 2 050) and 244sh nm (1 100); δ (60 MHz; $CDCl_3$) 1.50 (9 H, s, $Bu^t$), 2.95—3.80 (4 H, m, 1- and 6-$H_2$), 4.05—4.45 (1 H, m, 5-H), and 5.13 (1 H, s, 3-H); *m/z inter alia* 246 ($M^+ - CH_3$) and 57 ($C_4H_9^+$, base peak) (Found: C, 46.1; H, 5.8; N, 5.4. $C_{10}H_{15}NO_5S$ requires C, 46.0; H, 5.75; N, 5.35%).

*Oxidation of the Isopenam* (**12a**) *with Potassium Permanganate.*—To a stirred ice-cooled solution of the isopenam (**12a**) (0.150 g, 0.66 mmol) in glacial acetic acid (5 $cm^3$) was added, during 15 min, potassium permanganate (0.228 g, 1.44 mmol) dissolved in water (5 $cm^3$). Work-up after 1 h, as described in the foregoing experiment, gave 3-endo-*t-butoxycarbonylisopenam* 2,2-*dioxide* (**22**). The sample (0.058 g, 50%), obtained after recrystallisation from ethanol–light petroleum, possessed the following properties: m.p. 144—145 °C; $\nu_{max.}$(KBr) *inter alia* 1 775 (β-lactam C=O) and 1 720 $cm^{-1}$ (ester C=O); $\lambda_{max.}$(EtOH) 210 (ε 1 450) and 223sh nm (700); δ (360 MHz; $CDCl_3$) 1.53 (9 H, s, $Bu^t$), 3.13 (1 H, dd, *J* 16 and 2.7 Hz, 6-*endo*-H), 3.17 (1 H, dd, *J* 12 and 11 Hz, 1-H), 3.51 (1 H, dd, *J* 12 and 5 Hz, 1-H), 3.51 (1 H, ddd, *J* 16, 5, and 1.8 Hz, 6-*exo*-H), 4.07—4.14 (1 H, m, 5-H), and 4.49 (1 H, d, *J* 1.8 Hz, 3-H); *m/z inter alia* 246 ($M^+ - CH_3$) and 57 ($C_4H_9^+$, base peak) (Found: C, 46.1; H, 5.7; N, 5.3. $C_{10}H_{15}NO_5S$ requires C, 46.0; H, 5.75; N, 5.35%).

*Epimerisation of the Isopenam Dioxide* (**22**).—To a solution of the isopenam dioxide (**22**) (0.050 g, 0.19 mmol) in deuteriochloroform (0.5 $cm^3$) was added a small quantity of DBN. The reaction was monitored by n.m.r. spectroscopy and, when the starting material had disappeared, the solution was diluted with chloroform and washed with dil. hydrochloric acid. Evaporation of the dried ($MgSO_4$) organic layer left a residue (0.045 g, 90%) that was identical with the isopenam dioxide (**4b**) by n.m.r. spectroscopy.

*Reaction of the Isopenam Dioxide* (**4b**) *with Trifluoroacetic Acid Followed by Diazomethane.*—(*a*) To a solution of the isopenam dioxide (**4b**) (0.100 g, 0.38 mmol) in deuteriochloroform (1 $cm^3$) was added trifluoroacetic acid (0.043 g, 0.38 mmol). The reaction was monitored by n.m.r. spectroscopy and, when complete, the solvent was evaporated off and the syrup was treated with an excess of ethereal diazomethane. Recrystallisation of the residue, obtained on evaporation, from diethyl ether–light petroleum gave trans-2-*t-butoxycarbonyl*-4-*methoxycarbonylmethyl*-3-*trifluoroacetylthiazolidine* 1,1-*dioxide* (**13d**) (0.095 g, 64%). The material, designated sample *A*, possessed the following properties: m.p. 118—120 °C; $\nu_{max.}$(KBr) *inter alia* 1 745 and 1 735 (ester C=O) and 1 695 $cm^{-1}$ (amide C=O); δ (250 MHz; $CDCl_3$) 1.54 (9 H, s, $Bu^t$), 2.97, (1 H, dd, *J* 17 and 12.5 Hz, C*H*H·$CO_2$Me), 3.17 (1 H, dd, *J* 17 and 3.5 Hz, CH*H*·$CO_2$Me), 3.52—3.68 (2 H, m, 5-$H_2$), 3.74 (3 H, s, OMe), and 5.05—5.17 (2 H, m, 4- and 2-H); *m/z inter alia* 389 ($M^+$) and 57 ($C_4H_9^+$, base peak) (Found: C, 40.1; H, 4.5; N, 3.6%; $M^+$, 389.0757. $C_{13}H_{18}F_3NO_7S$ requires C, 40.1; H, 4.65; N, 3.60%; *M*, 389.0756).

(*b*) The aforementioned experiment was repeated with the isopenam dioxide (**4b**) (0.040 g, 0.15 mmol). Work-up and recrystallisation of the product as before gave sample *C* of the thiazolidine dioxide (**13d**) (0.031 g, 52%), m.p. 115—116 °C; $\nu_{max.}$(KBr) *inter alia* 1 745sh, 1 735, 1 725, and 1 695 $cm^{-1}$

When sample *C* of the thiazolidine dioxide (**13d**) was

dissolved in ethanol–light petroleum and the saturated solution seeded with sample *A* of the thiazolidine dioxide (**13d**), the crystalline material which was isolated was identical (m.p. and i.r. spectroscopy) with sample *A* of the thiazolidine dioxide (**13d**).

*Reaction of the Isopenam Dioxide* (**22**) *with Trifluoroacetic Acid Followed by Diazomethane.*—The aforementioned reaction was repeated using the isopenam dioxide (**22**) (0.100 g, 0.38 mmol). Work-up and recrystallisation as before gave cis-2-*t*-*butoxycarbonyl*-4-*methoxycarbonylmethyl*-3-*trifluoroacetylthiazolidine* 1,1-*dioxide* (**14c**) (0.092 g, 62%), m.p. 111—113 °C; $\nu_{max.}$(KBr) *inter alia* 1 745 (ester C=O) and 1 720 $cm^{-1}$ (amide C=O); δ (250 MHz; $CDCl_3$) 1.54 and 1.56 (7 and 2 H, each s, together Bu$^t$), 3.01 (1 H, dd, *J* 17 and 11 Hz, C*H*H·$CO_2$Me), 3.31—3.40 (2 H, m CH*H*·$CO_2$Me and 5-H), 3.72 and 3.74 (2.33 and 0.66 H, each s, together $CO_2$Me), 3.84 (1 H, ddd, *J* 14, 8, and 1 Hz, 5-H), 5.01—5.12 (1 H, m, 4-H), and 5.16 and 5.35 [0.78 and 0.22 H, t (*J* 1 Hz) and s, together 2-H]; *m/z inter alia* 373 ($M^+$ − O) and 57 ($C_4H_9^+$, base peak) (Found: C, 39.9; H, 4.5; N, 3.45. $C_{13}H_{18}F_3NO_7S$ requires C, 40.1; H, 4.65; N, 3.60%).

*Oxidation of the Thiazolidine* (**13a**) *with Potassium Permanganate.*—To a stirred ice-cooled solution of the thiazolidine (**13a**) (0.016 g, 0.045 mmol) in glacial acetic acid (2 $cm^3$) was added, in drops, a solution of potassium permanganate (0.016 g, 0.10 mmol) in water (2 $cm^3$). After 1 h, the mixture was decolourised with 30% aqueous hydrogen peroxide and diluted with ethyl acetate and aqueous sodium hydrogen carbonate. Evaporation of the dried ($MgSO_4$) organic layer and recrystallisation of the solid from ethanol–light petroleum gave a material (0.007 g, 41%) that was identical (250 MHz $^1$H n.m.r. spectroscopy) with the thiazolidine dioxide (**13d**) obtained from the isopenam dioxide (**4b**). The material, designated sample *B*, possessed the following properties: m.p. 111—114 °C; $\nu_{max.}$(KBr) *inter alia* 1 725 $cm^{-1}$ (amide and ester C=O).

*Oxidation of the Thiazolidine* (**14a**) *with Potassium Permanganate.*—The aforementioned experiment was repeated with the thiazolidine (**14a**) (0.039 g, 0.11 mmol). Work-up as before and recrystallisation of the product from ethanol–light petroleum gave a material (0.035 g, 82%), m.p. 113—114 °C, that was identical (i.r. and 250 MHz $^1$H n.m.r. spectroscopy) with the thiazolidine dioxide (**14c**) obtained from the isopenam dioxide (**22**).

*Reaction of Sulbactam Sodium Salt* (**21a**) *with Benzyl Bromide.*—To a stirred suspension of sulbactam sodium salt (**21a**) (0.271 g, 1.06 mmol) in dry DMF (5 $cm^3$) was added benzyl bromide (0.181 g, 1.06 mmol). After 12 h, the solution was diluted with ethyl acetate and washed in turn with water (3 ×) and saturated brine. Evaporation of the dried ($MgSO_4$) organic layer and purification of the product by silica-gel chromatography (EtOAc–light petroleum, gradient elution) gave benzyl penicillanate 1,1-dioxide (**21b**) (0.275 g, 80%) as a syrup. The material showed the following properties: $[\alpha]_D$ +171° (0.5% in $CHCl_3$); $\nu_{max.}$(film) *inter alia* 1 795 (β-lactam C=O) and 1 755 $cm^{-1}$ (ester C=O); $\lambda_{max.}$(EtOH) 215 nm (ε 4 900); δ (60 MHz; $CDCl_3$) 1.28 and 1.55 (each 3 H, s, together $CMe_2$), 3.50 (2 H, d, separation 3 Hz, 6-$H_2$), 4.43 (1 H, s, 3-H), 4.63 (1 H, t, separation 3 Hz, 5-H), 5.20 and 5.35 (each 1 H, d, *J* 12 Hz, together O$CH_2$Ph), and 7.40 (5 H, s, Ph); *m/z inter alia* 257 ($M^+$ − $H_2O_2S$) and 91 ($C_7H_7^+$, base peak).

*Reaction of Sulbactam Benzyl Ester* (**21b**) *with Trifluoroacetic Acid Followed by Diazomethane.*—To a solution of sulbactam benzyl ester (**21b**) (0.070 g, 0.22 mmol) in deuteriochloroform (1 $cm^3$) was added trifluoroacetic acid (0.25 $cm^3$). When the reaction was complete (n.m.r. spectroscopy), the solvent was evaporated off and the residue was dissolved in dichloromethane (1 $cm^3$). Treatment of the solution, at 0 °C, with an excess of ethereal diazomethane was followed by evaporation. Purification of the residue by silica-gel chromatography (EtOAc–light petroleum, gradient elution) gave (2R,4S)-4-*benzyloxycarbonyl*-2-*methoxycarbonylmethyl*-5,5-*dimethyl*-3-*trifluoroacetylthiazolidine* 1,1-*dioxide* (**26a**) (0.061 g, 62%). The sample, recrystallised from ethanol–light petroleum, showed the following properties: m.p. 116—117 °C; $[\alpha]_D$ −14° (0.9% in $CHCl_3$); $\nu_{max.}$(KBr) *inter alia* 1 750 and 1 735 (ester C=O) and 1 715 $cm^{-1}$ (amide C=O); δ (250 MHz; $CDCl_3$) 1.50 and 1.58 (each 3 H, s, together $CMe_2$), 2.83—2.97 and 3.33—3.44 (each 1 H, m, together $CH_2CO_2$Me), 3.78 (3 H, s, OMe), 4.70 (1 H, s, 4-H), 5.23 and 5.27 (each 1 H, d, *J* 11 Hz, together O$CH_2$Ph), 5.28—5.37 (1 H, m, 2-H), and 7.35—7.40 (5 H, m, Ph); *m/z inter alia* 451 ($M^+$) and 91 ($C_7H_7^+$, base peak) (Found: C, 47.9; H, 4.35; N, 3.05. $C_{18}H_{20}F_3NO_7S$ requires C, 47.9; H, 4.45; N, 3.10%).

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## References

1 Part 1, J. Brennan, G. Richardson, and R. J. Stoodley, *J. Chem. Soc., Perkin Trans. 1*, 1983, 649.
2 Preliminary communications, C. M. Pant and R. J. Stoodley, *J. Chem. Soc., Chem Commun.*, 1980, 928; P. H. Crackett, C. M. Pant, and R. J. Stoodley, *ibid.*, 1983, 1284; P. H. Crackett and R. J. Stoodley, *Tetrahedron Lett.*, 1984, **25**, 1295.
3 M. Gorman and C. W. Ryan, in 'Cephalosporins and Penicillins: Chemistry and Biology,' ed. E. H. Flynn, Academic Press, ch. 12.
4 'Handbook of Chemistry and Physics,' ed. R. C. Weast, Chemical Rubber Publishing Co., Ohio, 1975, 56th edn., F-212.
5 A. K. Bose, G. Spiegelman, and M. S. Manhas, *J. Chem. Soc. C*, 1971, 188.
6 W. F. Huffman, R. F. Hall, J. A. Grant, and K. G. Holden, *J. Med. Chem.*, 1978, **21**, 413.
7 R. Scartazzini, H. Peter, H. Bickel, K. Heusler, and R. B. Woodward, *Helv. Chim. Acta*, 1972, **55**, 408.
8 R. Busson and H. Vanderhaeghe, *J. Org. Chem.*, 1976, **41**, 2561; W. Baker, C. M. Pant, and R. J. Stoodley, *J. Chem. Soc., Perkin Trans. 1*, 1978, 668.
9 A. G. Brown, D. F. Corbett, and T. T. Haworth, *J. Chem. Soc., Chem. Commun.*, 1977, 359; P. H. Bentley and E. Hunt, *ibid.*, 1978, 518.
10 N. F. Osborne, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1429 and 1435; M. D. Bachi, R. Breiman, and H. Meshulan, *J. Org. Chem.*, 1983, **48**, 1439.
11 H.-O. Kalinowski and H. Kessler, *Top. Stereochem.*, 1973, **7**, 295.
12 I. Ernest, J. Gosteli, C. W. Greengrass, W. Holick, D. E. Jackman, H. R. Pfaendler, and R. B. Woodward, *J. Am. Chem. Soc.*, 1978, **100**, 8214.
13 A. R. English, J. A. Retsema, A. E. Girard, J. E. Lynch, and W. E. Barth, *Antimicrob. Agents Chemother.*, 1978, **14**, 414.
14 T. J. Wallace, J. E. Hoffmann, and A. Schriesheim, *J. Am. Chem. Soc.*, 1963, **85**, 2739.
15 D. G. Brenner, J. R. Knowles, and G. Rihs, *Biochemistry*, 1981, **20**, 3680; C. Kemal and J. R. Knowles, *ibid.*, p. 3688.
16 C. A. Grob, *Angew. Chem. Int. Edn. Engl.*, 1969, **8**, 535.

17 R. L. Charnas and J. R. Knowles, *Biochemistry*, 1981, **20**, 3214.
18 K. Hirai, Y. Iwano, and K. Fujimoto, *Tetrahedron Lett.*, 1982, **23**, 4025.
19 G. H. Hakimelahi and G. Just, *Tetrahedron Lett.*, 1980, **21**, 2119; *Helv. Chim. Acta*, 1982, **65**, 1359; G. H. Hakimelahi and A. Ugolini, *Tetrahedron Lett.*, 1982, **23**, 913.
20 J. Brennan and I. L. Pinto, *Tetrahedron Lett.*, 1983, **24**, 4731.
21 A. I. Vogel, 'Practical Organic Chemistry,' Longman, London, 1979, 3rd edn., p. 771.

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