Total Synthesis of Analogues of the β-Lactam Antibiotics. Part 5.[1] 3-Thiacepham-4-*exo*-carboxylates and their 1,1,3,3-Tetraoxides[2]†

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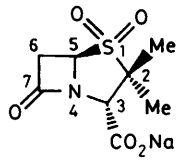
t-Butyl hydroxy{4-[(*Z*)-2-(methoxycarbonyl)vinylthio]-2-oxoazetidin-1-yl}acetate (**19a**) was transformed into t-butyl 2-*endo*-methoxycarbonylmethyl-3-thiacepham-4-*exo*-carboxylate (**20a**) by sequential reactions involving thionyl chloride, potassium thioacetate, and cyclohexylamine. Oxidation of compound (**20a**) with potassium permanganate gave the 1,1,3,3-tetraoxide (**23a**), the structure of which was established by X-ray crystallography. The exceptional acidity of the 2- and 4-hydrogen atoms of compound (**23a**) was revealed by their replacement with deuterium atoms in the presence of deuterium oxide and with methyl groups in the presence of diazomethane. Cleavage of the t-butyl ester function of the thiacepham tetraoxide (**23a**) was effected by trifluoroacetic acid but the resultant acid (**23b**) underwent a rapid decarboxylation in water to give 2-*endo*-methoxycarbonylmethyl-3-thiacepham 1,1,3,3-tetraoxide (**26a**).

Sulbactam sodium salt (**1**) is a powerful inactivator of a number of β-lactamases produced by pathogenic bacteria.[3] The inactivation process is believed to be associated with further reactions of a species of type (**2**; Nu = EnzO).[4] In earlier work, we described the preparation of the isopenam dioxide (**3a**).[5] We had hoped that the relocation of the sulphonyl group would increase the reactivity of the β-lactam linkage and permit the formation of a species of type (**4**; Nu = EnzO) which might lead to enzymic inactivation. In the event, compound (**3a**) failed to act as a β-lactamase inhibitor.

In principle, the bicyclic β-lactams (**1**) and (**3a**) may react with nucleophiles (NuH) to give species of types (**2**) and (**4**) by two pathways. Thus, intermediates of types (**5**) and (**6**) may undergo heterolytic fragmentations to give species of types (**2**) and (**4**) directly; alternatively, intermediates of types (**7**) and (**8**) may intervene. Our studies suggested[5] that the latter pathway was operative and, therefore, we proposed that the species (**2**; Nu = EnzO) arose from the intermediate (**7**; Nu = EnzO) by a rapid ring-opening reaction. Moreover, we pointed out[5] that β-lactam cleavages by heterolytic fragmentations are stereoelectronically unfavourable in bicyclic systems incorporating 5-membered rings because the bonds that are required to rupture cannot attain an antiperiplanar relationship [see (**9**) and (**10**) in which the bonds that have to be cleaved are emphasized by thick lines].

The geometric constraints to heterolytic fragmentations imposed by the fusion of β-lactams to 5-membered rings can be removed in their 6-membered counterparts, *cf.* (**11**), although boat-like geometries of the 6-membered rings must be invoked. In this paper, we describe the synthesis of the first examples of 3-thiacepham‡ 1,1,3,3-tetraoxides, conceived to incorporate the structural features of both compounds (**1**) and (**3a**).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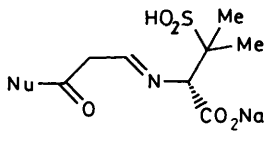
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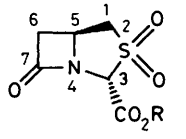
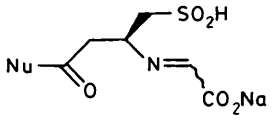

(3)
a; R = Na
b; R = Bu^t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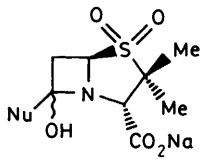
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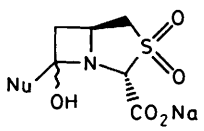
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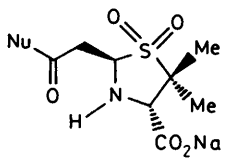
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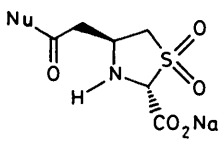
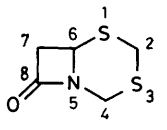
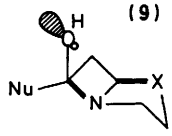

(8)

† Part of this work was carried out in the Department of Organic Chemistry, University of Newcastle upon Tyne.
‡ This trivial name refers to the the following ring system which is numbered as shown.



Results and Discussion

It was envisaged that thiacepham tetraoxides of type (**12**) would be available by oxidation of thiacephams of type (**13**) which, in turn, would be derivable from precursors of type (**14**). The last-cited species were expected to be accessible from chlorides of type (**15**) either by the Huffman procedure (sequential treatment with KSAc and cyclohexylamine)[6] or by our method (treatment with H_2S–Et_3N).[5] Since Woodward and his co-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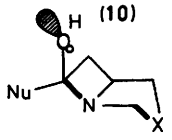
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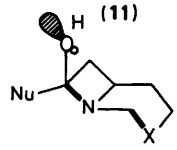
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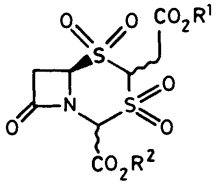
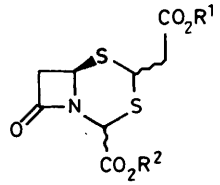
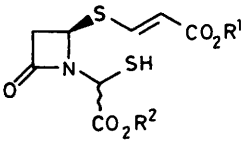

(12)
a; R^1 = Me, R^2 = Bu^t


(13)
a; R^1 = Me, R^2 = Bu^t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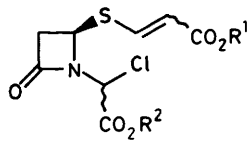
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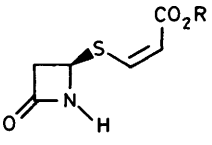
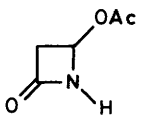

(16)
a; R = Me
b; R = H
c; R = CH_2OMe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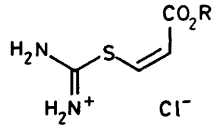
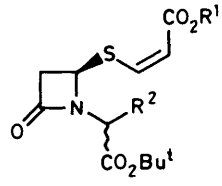

(18)
a; R = Me
b; R = H


(19)
a; R^1 = Me, R^2 = OH
b; R^1 = Me, R^2 = Cl
c; R^1 = Me, R^2 = SAc
d; R^1 = CH_2OMe, R^2 = OH
e; R^1 = CH_2OMe, R^2 = Cl
f; R^1 = CH_2OMe, R^2 = SAc

workers had described[7] a simple synthesis of compound (**16a**), it was selected as the starting material.

Compound (**16a**), prepared by reaction of the acetoxyazetidinone (**17**)[8] with the isothiouronium chloride (**18a**)[7] and sodium hydroxide, was obtained in 70% yield after silica-gel chromatography and crystallisation. It reacted with t-butyl dihydroxyacetate[9] and triethylamine in tetrahydrofuran (THF) to give the carbinolamide (**19a**) (80% yield after SiO_2 chromatography) as a syrupy 1:1 mixture of diastereoisomers. When subjected to the action of thionyl chloride and 2,6-dimethylpyridine in THF, compound (**19a**) was transformed into the chloride (**19b**) which reacted with potassium thioacetate in *N*,*N*-dimethylformamide (DMF) to give the thioacetate (**19c**) (72% yield after SiO_2 chromatography), isolated as a syrupy 1.5:1 mixture of diastereoisomers. In the presence of cyclohexylamine and dichloromethane, compound (**19c**) was converted into the thiacepham (**13a**) (63% yield after recrystallisation). The last-cited compound was also obtained [23% yield after SiO_2 chromatography based upon (**19a**)] from the reaction of the chloride (**19b**) with hydrogen sulphide and triethylamine in dichloromethane at 0 °C.

The constitution of the thiacepham (**13a**) followed from its analytical and spectroscopic properties. In particular, the 250 MHz ^{1}H NMR spectrum ($CDCl_3$) featured the β-lactam hydrogen atoms as three double doublets—at δ 2.94 (*J* 15 and 2 Hz) for 7-Hβ, at δ 3.52 (*J* 15 and 4 Hz) for 7-Hα, and at δ 5.42 (*J* 4 and 2 Hz) for 6-H; the 2-hydrogen atom appeared as a triplet (separation 6 Hz) at δ 4.99 and the 4-hydrogen atom as a singlet at δ 5.41.

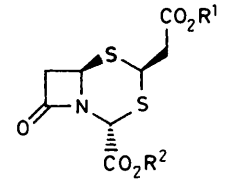
Although it was clear that the thiacepham (**13a**) had been isolated as a single diastereoisomer, its stereostructure was not unequivocal. That the cyclisation reaction had led to the thermodynamically preferred thiacepham was suggested by deuterium-exchange experiments; thus, treatment of the material with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in the presence of deuterium oxide resulted in the exchange of the hydrogen atom at position 4 and of the side-chain methylene protons. The *exo*-preference for an alkoxycarbonyl group in related bicyclic systems is well documented[10] and, therefore, the thiacepham was considered to possess the stereostructure (**20a**) or (**21**). However, nuclear Overhauser effect difference (NOED) spectroscopy suggested that the 2-, 4-, and 6-hydrogen atoms of the thiacepham were *syn*-disposed, *cf.* structure (**22a**); thus, irradiation of the 2-hydrogen atom apparently caused a 4% enhancement of the 4-hydrogen atom and a 3% enhancement of the 6-hydrogen atom (however, the signals for the 4- and 6-hydrogen atoms did overlap).

Oxidation of the thiacepham (**13a**) to the thiacepham tetraoxide (**12a**) (82% yield after recrystallisation) was achieved by using potassium permanganate in aqueous acetic acid. The β-lactam carbonyl group of compound (**12a**) absorbed in the IR region at a significantly higher wavenumber (1 805 cm^{-1}) than that of its precursor (**13a**) (1 765 cm^{-1}). In the 250 MHz ^{1}H NMR spectrum ($CDCl_3$), the 4-, 6-, and 7α-hydrogen atoms displayed chemical shifts which were very similar to those of their counterparts in the precursor (**13a**); however, the 2-hydrogen atom (δ *ca.* 5.45) and the 7β-hydrogen atom (δ 3.74) were notably deshielded compared with their counterparts in the precursor (**13a**).

An attempt was made to deduce the stereostructure of the thiacepham tetraoxide (**12a**) by NOED spectroscopy. Irradiation of the signal for the 2-hydrogen atom (which overlapped in part with that for the 6-hydrogen atom) caused a 1% enhancement of the signal for the 4-hydrogen atom. This result suggested that the 2- and 4-substituents were *syn*-disposed and was consistent with the stereostructure (**22b**) for the thiacepham tetraoxide.

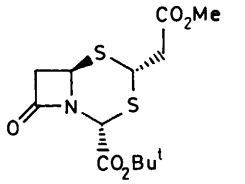
To unequivocally resolve the stereochemical issue, an X-ray analysis of the thiacepham tetraoxide (**12a**) was undertaken. The molecular structure (see Experimental section for crystal data and other information) is shown in the Figure together with its crystallographic numbering.* Refined atomic coordinates are include in Table 1 and selected bond lengths and bond angles are presented in Table 2. Clearly, the thiacepham tetraoxide possesses the stereostructure (**23a**), in which the six-membered ring adopts a chair-like geometry with an equatorial disposition of the methoxycarbonylmethyl group and an axial

* This numbering is based upon the systematic name for the compound, *i.e.* (2*RS*,4*RS*)-2-(t-butoxycarbonyl)-4-methoxycarbonylmethyl-8-oxo-3,5-dithia-1-azabicyclo[4.2.0]octane 3,3,5,5-tetraoxide.



(20)

a; R^1 = Me, R^2 = Bu^t
b; R^1 = Me, R^2 = H
c; R^1 = Me, R^2 = Na
d; R^1 = R^2 = Me
e; R^1 = Na, R^2 = Bu^t
f; R^1 = CH_2OMe, R^2 = Bu^t



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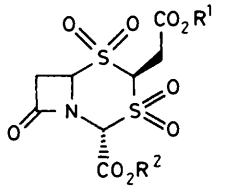
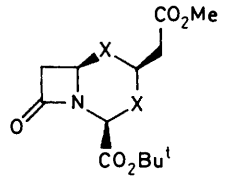


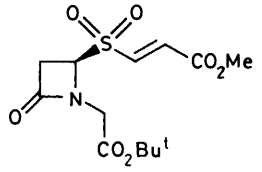
(23)

a; R^1 = Me, R^2 = Bu^t
b; R^1 = Me, R^2 = H
c; R^1 = Me, R^2 = Na
d; R^1 = R^2 = Me
e; R^1 = R^2 = Na
f; R^1 = CH_2OMe, R^2 = Bu^t
g; R^1 = R^2 = H

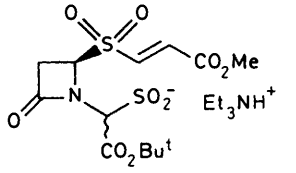


(22)

a; X = S
b; X = SO_2



(24)



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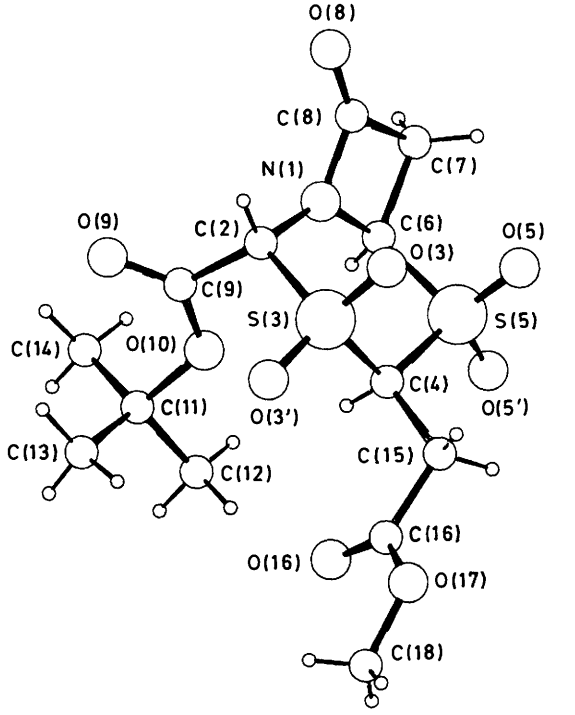


Figure. The molecular structure of compound (**23a**).

orientation of the t-butoxycarbonyl function. Presumably, therefore, the thiacepham precursor was the 2-*endo*-4-*exo*-stereoisomer (**20a**).

The high acidity of the 2- and 4-hydrogen atoms of compound (**23a**) was demonstrated by their exchange in the presence of deuterium oxide without the need of an added base. In fact, in the presence of triethylamine, the thiacepham tetraoxide (**23a**) was rapidly converted into the syrupy monocyclic azetidinone (**24**) (62% yield after SiO_2 chromatography), identified by its spectroscopic properties. In particular, the methylene hydrogen atoms of the t-butoxycarbonylmethyl group appeared as doublets (J 18 Hz) at δ 3.78 and 4.30 and the olefinic hydrogen atoms as doublets (J 15 Hz) at δ 6.87 and 7.40 ($CDCl_3$). Presumably, compound (**24**) arises by way of the sulphinate salt (**25**), formed from the thiacepham dioxide (**23a**) by a β-elimination reaction.

In the presence of trifluoroacetic acid, the t-butyl ester (**20a**) was transformed into the acid (**20b**) (79% yield after recrystallisation). The derived sodium salt (**20c**), which was stable in deuterium oxide over a period of 18 h, showed no antibacterial activity.

The acid (**23b**) was formed in a somewhat impure state by treatment of the ester (**23a**) with trifluoroacetic acid. It reacted with sodium hydrogen carbonate in aqueous ethanol to give a neutral product [19% yield after recrystallisation based on (**23a**)] which was formulated as the decarboxylated material (**26a**) on the basis of its elemental analysis and spectroscopic properties. In particular, the ^1H NMR spectrum (CD_3SOCD_3) featured doublets (J 14 Hz) at δ 4.86 and 5.77 attributed to the 4-methylene group. It was possible to isolate the sodium salt (**23c**) as an amorphous solid (ν_{max} 1 790, 1 740, and 1 650 cm^{-1}) by treating the crude acid (**23b**) with sodium 2-ethylhexanoate in a mixture of ethyl acetate, diethyl ether, and butan-1-ol; however, in the presence of water, it readily underwent decarboxylation to give compound (**26a**) [30% yield after recrystallisation based on (**23a**)].

The ease of decarboxylation of the thiacepham tetraoxide salt (**23c**) is of note. Previously, the isopenam dioxide salt (**3a**) was reported [5] to be stable in deuterium oxide over a period of 12 h.

In the expectation of generating the methyl ester (**23d**), the crude acid (**23b**) was treated with ethereal diazomethane. However, the product of the reaction, isolated in 54% yield after recrystallisation, was identified as compound (**27a**). Thus, the ^1H NMR spectrum ($CDCl_3$) incorporated two singlets at δ 2.19 and 2.30 attributed to the *C*-methyl groups and an AB quartet (J 14 Hz) at δ 3.24 for the methylene hydrogen atoms of the methoxycarbonylmethyl group. Compound (**27a**) was also obtained from the reaction of the thiacepham tetraoxide (**23d**) [prepared from the acid (**20b**) by way of the ester (**20d**)] with diazomethane.

The thiacepham tetraoxide (**23a**) reacted in an analogous manner with diazomethane to give the dimethyl derivative (**27b**) (60% yield after recrystallisation). That compounds (**27a, b**) possessed a common stereostructure was established by converting the latter material into the former by the action of trifluoroacetic acid followed by diazomethane. On the basis of chemical shift comparisons [the β-lactam hydrogen atoms of compounds (**23a**) and (**27b**) showed very similar δ values] and an NOED spectroscopic study [irradiation of the 2-Me group of compound (**27b**) caused only a 3% enhancement of one of the CH_2 protons of the CH_2CO_2Me group; irradiation of the 4-Me group caused no enhancements], the dimethyl derivatives were tentatively assigned the stereostructures (**28a,b**).

Clearly, in the afore-cited reactions, diazomethane initially acts as a base to give ion-pair intermediates, *e.g.* (**29**), which then react with loss of nitrogen. Seemingly, the methylations occur with retention of configuration.

It was of interest to compare the behaviour of the isopenam dioxides (**3b**) and (**30**) [5] towards diazomethane. Whereas the former material was unaffected by the reagent, the latter was

Table 1. Fractional atomic co-ordinates ($\times 10^4$) for compound (**23a**) with estimated standard deviations (esds) in parentheses.

Atom	*x/a*	*y/b*	*z/c*
N(1)	8 432(3)	125(2)	8 809(1)
C(2)	6 523(4)	1 173(3)	8 845(2)
S(3)	5 442(1)	878(1)	7 829(1)
O(3)	4 996(3)	−475(2)	7 941(2)
O(3′)	3 841(3)	2 086(2)	7 676(2)
C(4)	7 494(4)	763(3)	6 871(2)
S(5)	9 755(1)	−628(1)	6 991(0)
O(5)	9 250(3)	−1 953(2)	7 053(1)
O(5′)	11 350(3)	−415(2)	6 279(1)
C(6)	10 283(4)	−193(3)	8 111(2)
C(7)	11 130(4)	−1 485(3)	8 709(2)
C(8)	9 087(4)	−1 017(3)	9 360(2)
O(8)	8 273(3)	−1 386(2)	10 086(1)
C(9)	6 670(4)	2 680(3)	8 943(2)
O(9)	5 859(4)	3 368(2)	9 624(2)
O(10)	7 823(3)	3 031(2)	8 196(1)
C(11)	8 116(5)	4 498(3)	8 074(2)
C(12)	9 459(6)	4 378(4)	7 125(3)
C(13)	6 032(7)	5 509(4)	8 056(3)
C(14)	9 183(9)	4 797(5)	8 851(4)
C(15)	6 695(6)	622(3)	5 955(2)
C(16)	5 858(5)	2 053(3)	5 561(2)
O(16)	6 449(5)	3 063(3)	5 670(2)
O(17)	4 398(4)	2 027(2)	5 076(2)
C(18)	3 541(17)	3 311(7)	4 601(6)

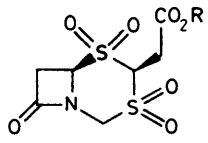
Table 2. Selected bond lengths (Å) and bond angles (°) for compound (**23a**) with esds in parentheses.

(*a*) Bond lengths

N(1)–C(2)	1.430(3)	N(1)–C(6)	1.456(3)
N(1)–C(8)	1.373(3)	C(2)–S(3)	1.817(3)
C(2)–C(9)	1.520(4)	S(3)–O(3)	1.430(2)
S(3)–O(3′)	1.420(2)	S(3)–C(4)	1.798(3)
C(4)–S(5)	1.805(3)	C(4)–C(15)	1.534(4)
S(5)–O(5)	1.425(2)	S(5)–O(5′)	1.426(2)
S(5)–C(6)	1.802(3)	C(6)–C(7)	1.547(4)
C(7)–C(8)	1.522(4)	C(8)–O(8)	1.196(3)
C(9)–O(9)	1.185(3)	C(9)–O(10)	1.322(3)
O(10)–C(11)	1.505(3)	C(11)–C(12)	1.512(4)
C(11)–C(13)	1.512(5)	C(11)–C(14)	1.509(5)
C(15)–C(16)	1.502(4)	C(16)–O(16)	1.187(3)
C(16)–O(17)	1.315(4)	O(17)–C(18)	1.446(5)

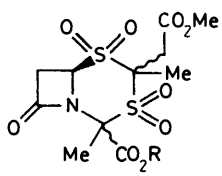
(*b*) Bond angles

C(2)–N(1)–C(6)	131.9(2)	C(2)–N(1)–C(8)	132.8(2)
C(6)–N(1)–C(8)	94.9(2)	N(1)–C(2)–S(3)	107.0(2)
N(1)–C(2)–C(9)	114.4(2)	S(3)–C(2)–C(9)	114.1(2)
C(2)–S(3)–O(3)	107.1(1)	C(2)–S(3)–O(3′)	109.8(1)
O(3)–S(3)–O(3′)	119.9(1)	C(2)–S(3)–C(4)	103.5(1)
O(3)–S(3)–C(4)	108.3(1)	O(3′)–S(3)–C(4)	107.1(1)
S(3)–C(4)–S(5)	113.8(1)	S(3)–C(4)–C(15)	108.3(2)
S(5)–C(4)–C(15)	111.9(2)	C(4)–S(5)–O(5)	109.5(1)
C(4)–S(5)–O(5′)	106.7(1)	O(5)–S(5)–O(5′)	119.8(1)
C(4)–S(5)–C(6)	101.4(1)	O(5)–S(5)–C(6)	109.3(1)
O(5′)–S(5)–C(6)	108.6(1)	N(1)–C(6)–S(5)	111.3(2)
N(1)–C(6)–C(7)	87.7(2)	S(5)–C(6)–C(7)	114.5(2)
C(6)–C(7)–C(8)	85.6(2)	N(1)–C(8)–C(7)	91.8(2)
N(1)–C(8)–O(8)	130.5(2)	C(7)–C(8)–O(8)	137.7(2)
C(2)–C(9)–O(9)	121.5(3)	C(2)–C(9)–O(10)	110.3(2)
O(9)–C(9)–O(10)	128.1(3)	C(9)–O(10)–C(11)	121.8(2)
O(10)–C(11)–C(12)	101.6(2)	O(10)–C(11)–C(13)	107.8(3)
O(12)–C(11)–C(13)	111.6(3)	O(10)–C(11)–C(14)	108.7(2)
C(12)–C(11)–C(14)	112.4(3)	C(13)–C(11)–C(14)	113.9(3)
C(4)–C(15)–C(16)	110.4(2)	C(15)–C(16)–O(16)	124.4(3)
C(15)–C(16)–O(17)	110.6(3)	O(16)–C(16)–O(17)	125.0(3)
C(16)–O(17)–C(18)	116.9(4)		



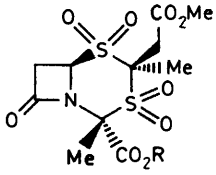
(**26**)

a; R = Me
b; R = H
c; R = Na



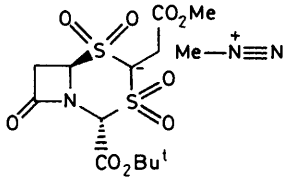
(**27**)

a; R = Me
b; R = Bu^t

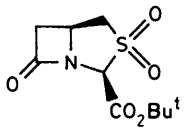


(**28**)

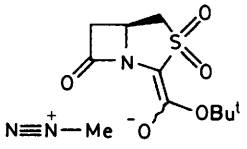
a; R = Me
b; R = Bu^t



(**29**)



(**30**)



(**31**)

converted exclusively into the former. Evidently, in this system, diazomethane acts only as a base to generate the ion-pair intermediate (**31**) which then collapses to give the thermodynamically favoured isopenam dioxide (**3b**) with the regeneration of diazomethane.

There are only a few examples of *C*-methylations with diazomethane in the literature. Thus, the reagent has been reported to convert 1,3,5-trithiane 1,1,3,3,5,5-hexaoxide into its 2,2,4,4,6,6-hexamethyl derivative,[11] dimethyl 2-(methoxycarbonyl)malonate into its 2-methyl derivative,[10] and acetylacetone into its 3-methyl derivative.[12]

The instability of the salt (**23c**) in water precluded its biological evaluation. In the hope that it would be less susceptible to decarboxylation, the disodium salt (**23e**) was sought. Since attempts to convert compound (**20a**) into the sodium salt (**20e**) by the action of sodium hydroxide in aqueous ethanol or sodium iodide in boiling pyridine were unproductive, it was decided to proceed by way of the methoxymethyl ester (**20f**).

When a solution of the isothiouronium chloride (**18b**) [prepared by the reaction of H_2NCSNH_2 with $HC{\equiv}C{-}CO_2H$ in MeOH–HCl] in ethanol was treated with sodium hydroxide followed by the acetoxyazetidinone (**17**), the acid (**16b**) was isolated in 29% yield after recrystallisation following an acidic work-up. The acid (**16b**) reacted with chloromethyl ether in the presence of triethylamine to give the syrupy methoxymethyl ester (**16c**) (90% yield after SiO_2 chromatography) which was transformed by way of the intermediates (**19d–f**) into the crystalline thiacepham (**20f**) in 25% overall yield.

Oxidation of the thiacepham (**20f**) to the thiacepham tetraoxide (**23f**) was achieved (88% yield after recrystallisation) by using potassium permanganate in aqueous acetic acid. Compound (**23f**) was converted into the diacid (**23g**), isolated as a crystalline hemihydrate in 73% yield, by the action of trifluoroacetic acid. The diacid (**23g**) reacted with diazo-

methane to give compound (**28a**) (29% yield after recrystallisation); in the presence of water, it underwent decarboxylation to give compound (**26b**) (66% yield after recrystallisation). The derived sodium salt (**26c**), which was stable in deuterium oxide over a period of 12 h, showed no antibacterial activity and it failed to act as an ampicillin synergist against β-lactamase-producing bacteria.

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; dichloromethane was stored over anhydrous calcium chloride. Light petroleum refers to that fraction boiling in the range 40–60 °C. Ethereal diazomethane[13] was generated by adding a solution of Diazald in diethyl ether to potassium hydroxide in aqueous ethanol at *ca.* 60 °C. For chromatographic and instrumental details, see Parts 1[14] and 2.[5]

Preparation of Methyl (Z)-3-(4-*Oxoazetidin*-2-*ylthio*)*propenoate* (**16a**).—The acetoxyazetidinone (**17**) (4.00 g, 31 mmol) was converted into the title compound (**16a**) by the method of Woodward.[7] The product (4.06 g, 70% after SiO_2 column chromatography), after recrystallisation from benzene, showed m.p. 92–93 °C (lit.,[7] 92–93 °C).

Preparation of t-Butyl Hydroxy{4-[(Z)-2-*methoxycarbonylvinylthio*]-2-*oxoazetidin*-1-*yl*}*acetate* (**19a**).—t-Butyl dihydroxyacetate[9] (1.60 g, 10.8 mmol) and triethylamine (0.96 cm^3, 7 mmol) were added to a stirred solution of the azetidinone (**16a**) (2.00 g, 10.7 mmol) in dry THF (20 cm^3). When the reaction was complete (TLC), the mixture was diluted with ethyl acetate and washed with brine. Evaporation of the dried ($MgSO_4$) organic phase and purification of the residue by silica-gel column chromatography (light petroleum–EtOAc; gradient elution) gave the title compound (**19a**) (2.72 g, 80%) as a syrupy 1:1 mixture of diastereoisomers; ν_{max}(film) 3 420 (OH), 1 770 (β-lactam C=O), 1 745 (ester C=O), and 1 700 cm^{-1} (conjugated ester C=O); λ_{max}(EtOH) 209 (ε 2 200) and 275 nm (10 500); δ(60 MHz; $CDCl_3$) 1.46 and 1.53 (each 4.5 H, s, Me_3C), 3.06 (1 H, dm, separation 16 Hz, COC*H*HCH), 3.56 (1 H, dd, *J* 16 and 5 Hz, COCH*H*CH), 3.74 and 3.76 (each 1.5 H, s, MeO), 4.3 (1 H, br s, HO), 4.90–5.20 and 5.43 (1.5 and 0.5 H, m and br s, $COCH_2CH$ and NC*H*OH), 6.02 and 6.04 (each 0.5 H, d, *J* 10 Hz, CH:C*H*CO_2), and 7.17 and 7.27 (each 0.5 H, d, *J* 10 Hz, C*H*:$CHCO_2$) (addition of D_2O caused the signal at δ 4.3 to disappear and those at δ 4.90–5.20 and 5.43 to sharpen); *m/z* (EI) 216 ($M^+ - C_5H_9O_2$), 200 ($M^+ - C_4H_5O_2S$), and 57 ($C_4H_9^+$, base peak) (Found: $M^+ - C_5H_9O_2$, 216.0315. $C_8H_{10}NO_4S$ requires *m/z* 216.0330).

Preparation of t-Butyl Acetylthio{4-(Z)-2-*methoxycarbonylvinylthio*]-2-*oxoazetidin*-1-*yl*}*acetate* (**19c**).—2,6-Dimethylpyridine (0.98 cm^3, 8.4 mmol) followed by thionyl chloride (1.12 cm^3, 15.3 mmol) were added to a stirred cooled (CCl_4–solid CO_2) solution of the carbinolamide (**19a**) (2.44 g, 7.7 mmol) in dry THF (15 cm^3). When the reaction was complete (TLC), the mixture was filtered and the filtrate was evaporated. The residual chloride (**19b**) was dissolved in dry DMF (10 cm^3) and potassium thioacetate (1.05 g, 0.92 mmol) was added to the stirred solution. After 1 h, the mixture was diluted with ethyl acetate and washed (× 3) with brine. Evaporation of the dried ($MgSO_4$) organic phase and purification of the residue by silica-gel column chromatography (light petroleum–EtOAc; gradient elution) gave the title compound (**19c**) (2.08 g, 72%) as a syrupy 1.5:1 mixture of diastereoisomers; ν_{max}(film) 1 775 (β-lactam C=O), 1 735 (ester C=O), and 1 700 cm^{-1} (unsaturated ester and thioester C=O); λ_{max}(EtOH) 210 (ε 5 600) and 274 nm (12 500); δ(60 MHz; $CDCl_3$) 1.41 (9 H, s, Me_3C), 2.36 and 2.38 (1.8 and 1.2 H, each s, MeCOS), 3.00 (1 H, dm, separation 16 Hz, COC*H*HCH), 3.53 (1 H, dd, *J* 16 and 5 Hz, COCH*H*CH), 3.71 and 3.73 (1.2 and 1.8 H, each s, MeO), 4.80–5.00 and 5.15–5.35 (0.4 and 0.6 H, each m, CH_2CHS), 5.80 and 5.84 (0.4 and 0.6 H, each s, NC*H*SCOMe), 6.00 (1 H, d, *J* 10 Hz, CH:C*H*CO_2), and 7.11 and 7.25 (0.4 and 0.6 H, each d, *J* 10 Hz, C*H*:$CHCO_2$); *m/z* (EI) 258 ($M^+ - C_4H_5O_2S$) and 57 ($C_4H_9^+$, base peak).

Preparation of t-Butyl 2-endo-*Methoxycarbonylmethyl*-3-*thiacepham*-4-exo-*carboxylate* (**20a**).—(*a*) Cyclohexylamine (0.76 cm^3, 6.6 mmol) was added to a stirred ice-cooled solution of the thioester (**19c**) (2.08 g, 5.54 mmol) in dichloromethane (15 cm^3). After 1 h, the mixture was allowed to warm to room temperature. When the reaction was complete (TLC), the mixture was diluted with ethyl acetate and washed with brine. Evaporation of the dried ($MgSO_4$) organic phase and crystallisation of the residue from ethanol gave the *title compound* (**20a**) (1.16 g, 63%), m.p. 124–128 °C; ν_{max}(KBr) 1 765 (β-lactam C=O) and 1 735 and 1 725 cm^{-1} (ester C=O); λ_{max}(EtOH) 216 nm (ε 3 500); δ(250 MHz; $CDCl_3$) 1.50 (9 H, s, Me_3C), 2.75 (2 H, d, separation 6 Hz, $CHCH_2CO_2Me$), 2.94 (1 H, dd, *J* 15 and 2 Hz, 7-Hβ), 3.52 (1 H, dd, *J* 15 and 4 Hz, 7-Hα), 3.72 (3 H, s, MeO), 4.99 (1 H, t, separation 6 Hz, 2-H), 5.41 (1 H, s, 4-H), and 5.42 (1 H, dd, *J* 4 and 2 Hz, 6-H) (in an NOED experiment, irradiation of the signal at δ 2.75 caused a 4% enhancement of the signal at δ 4.99; irradiation of the signal at δ 4.99 enhanced that at δ 2.75 by 4%, that at δ 5.41 by 3%, and that at δ 5.42 by 4%; irradiation of the signal at δ 5.42 caused 3% and 6% enhancements of the signals at δ 3.52 and 4.99); *m/z* (EI) 334 (M^+), 277 ($M^+ - C_4H_8$), 232 ($M^+ - C_5H_9O_2$), and 57 ($C_4H_9^+$, base peak) (Found: C, 46.9; H, 5.7; N, 4.3. $C_{13}H_{19}NO_5S_2$ requires C, 46.8; H, 5.75; N, 4.20%).

(*b*) 2,6-Dimethylpyridine (0.14 cm^3, 1.2 mmol) followed by thionyl chloride (0.28 cm^3, 2.2 mmol) were added to a stirred cooled (CCl_4–solid CO_2) solution of the carbinolamide (**19a**) (0.350 g, 1.1 mmol) in dry THF (5 cm^3). When the reaction was complete (TLC), the mixture was filtered and the filtrate evaporated. The residual chloride (**19b**) was dissolved in dry dichloromethane (5 cm^3) and the ice-cooled solution was saturated with hydrogen sulphide. After 30 min, triethylamine (0.31 cm^3, 2.2 mmol) was added to the mixture. When the reaction was complete (TLC), the solution was concentrated and the residue subjected to silica-gel column chromatography (light petroleum–EtOAc; gradient elution). The crystalline product (0.084 g, 23%) was identified as the thiacepham (**20a**) by ^1H NMR spectroscopy.

Deuterium Exchange of the Thiacepham (**20a**).—A few drops of DBN followed by a few drops of deuterium oxide were added to a solution of the thiacepham (**20a**) in deuteriochloroform. The mixture was shaken from time to time. When the signal at δ 5.41 in the ^1H NMR spectrum had disappeared, the mixture was diluted with ethyl acetate and washed with dilute hydrochloric acid. Evaporation of the dried ($MgSO_4$) organic layer gave the thiacepham (**20a**) deuteriated at position 4 and at the exocyclic methylene group; δ(60 MHz; $CDCl_3$) 1.51 (9 H, s, Me_3C), 2.94br (1 H, d, *J* 15 and 2 Hz, 7-Hβ), 3.53 (1 H, dd, *J* 15 and 4 Hz, 7-Hα), 8.73 (3 H, s, MeO), 5.00 (1 H, br s, 2-H), and 5.45 (1 H, dd, *J* 4 and 2 Hz, 6-H).

Preparation of 4-exo-(*t-Butoxycarbonyl*)-2-endo-*methoxycarbonylmethyl*-3-*thiacepham* 1,1,3,3-*Tetraoxide* (**23a**).—Potassium permanganate (1.05 g, 6.65 mmol) dissolved in water (10 cm^3) was added in drops to a stirred solution of the

thiacepham (**20a**) (0.500 g, 1.5 mmol) in glacial acetic acid (10 cm^3) with ice cooling. After 1 h, the mixture was decolourised by the addition of 30% aqueous hydrogen peroxide and partitioned between ethyl acetate and brine. Evaporation of the dried ($MgSO_4$) organic phase and recrystallisation of the residue from ethanol gave the *title compound* (**23a**) (0.490 g, 82%), m.p. 138–139 °C; ν_{max}(KBr) 1 805 (β-lactam C=O), and 1 755 and 1 740 cm^{-1} (ester C=O); λ_{max}(EtOH) 209 nm (ε 2 100); δ(250 MHz; $CDCl_3$) 1.56 (9 H, s, Me_3C), 3.20 and 3.30 (each 1 H, d, *J* 16 and 7 Hz, $CHCH_2CO_2$), 3.58 (1 H, *J* 16 and 5 Hz, 7-Hα), 3.74 (1 H, dd, *J* 16 and 2 Hz, 7-Hβ), 3.79 (3 H, , MeO), 5.42–5.47 (2 H, m, 2- and 6-H), and 5.54 (1 H, s, 4-H) (in an NOED experiment, irradiation of the signal at δ 5.45 caused a 1% enhancement of the signal at δ 5.54; no signal enhancements were observed when the signal at δ 5.54 was irradiated); *m/z* (EI) 324 ($M^+ - C_3H_5O_2$) and 296 ($M^+ - C_5H_9O_2$) (Found: C, 39.3; H, 4.8; N, 3.6. $C_{13}H_{19}NO_9S_2$ requires C, 39.3; H, 4.8; N, 3.5%).

Crystal data. $C_{13}H_{19}NO_9S_2$, *M*, 397.43. Triclinic, *a* = 6.839(3), *b* = 9.811(3), *c* = 14.446(4) Å, α = 88.08(2), β = 80.69(3), γ = 74.89(3)°, *U* = 932(1) $Å^3$ (by least-squares refinement on setting angles of 25 accurately centred reflections $5.6 \leqslant \theta \leqslant 8.7°$), λ = 0.71069 Å, space group $P\bar{1}$ (No. 2), *Z* = 2, D_c = 1.43 g cm^{-3}, *F*(000) = 416. Crystal dimensions: 0.1 × 0.2 × 0.3 mm, μ(Mo-K_α) = 0.28 mm^{-1}.

Data collection and processing. An Enraf-Nonius CAD4 diffractometer was employed using graphite-monochromated Mo-K_α radiation in ω/20 scan mode with ω scan width = 0.70 + 0.35tan θ and ω scan speed in the range 1–5° min^{-1} depending on the intensity gathered in a pre-scan; 2 976 reflections were measured ($0 \leqslant \theta \leqslant 24°$, $0 \leqslant h \leqslant 7$, $-11 \leqslant k \leqslant 11$, $-16 \leqslant l \leqslant 16$) yielding 2 278 unique structure factors [R_{int} = 0.010, $F \geqslant 3\sigma(F)$]. There was no significant drift in intensity standards (−10 − 5, −2 − 2 − 4, −11 − 3) measured repeatedly at 2.5 hourly intervals. Lorenz and polarisation corrections were applied but absorption effects were ignored.

Structure analysis and refinement. Direct methods (MULTAN-80[15]) were used to locate non-hydrogen atoms and difference Fourier maps, produced during the course of full matrix least-squares refinement (SHELX-76[16]), were employed to locate the hydrogen atoms. A final *R* value of 0.038 was obtained {R_w = 0.040, $w = 1.813/[\sigma^2(|F_o|) + 0.0003\ F_o^2]$, $\sigma|F_o|$ from counting statistics} with non-hydrogen atoms anisotropic and hydrogen atoms isotropic. The maximum shift/esd on the final cycle was 0.069[H(18B), *y*]. Fluctuations in the final difference Fourier map were in the range 0.22–0.27 e $Å^{-3}$. Neutral atom scattering factors were obtained from 'International Tables for X-Ray Crystallography';[17] computations were carried out on the Amdahl 5830 computer of the University of Manchester Regional Computing Centre. Complete listings of the bond lengths and angles, the hydrogen atom co-ordinates, and thermal parameters are available on request from the Cambridge Crystallographic Data Centre.*

Deuterium Exchange of the Thiacepham Tetraoxide (**23a**).—Deuterium oxide (3 drops) was added to a solution of the thiacepham dioxide (**23a**) in deuteriochloroform. After 2 h, ^1H NMR spectroscopy indicated that deuterium exchange had occurred at the 2- and 4-positions; δ(60 MHz) 1.60 (9 H, s, Me_3C), 3.20 (2 H, s, $CDCH_2CO_2$), 3.60–3.80 (2 H, m, 7-H_2), 3.82 (3 H, s, MeO), and 5.45 (1 H, dd, *J* 4 and 3 Hz, 6-H).

Preparation of t-Butyl {4-[(E)-*Methoxycarbonylvinylsulphonyl*]-2-*oxoazetidin*-1-*yl*}*acetate* (**24**).—Triethylamine (0.021 cm^3, 0.151 mmol) was added to a solution of the thiacepham tetraoxide (**23a**) (0.050 g, 0.126 mmol) in dry dichloromethane (3 cm^3). After 30 min, the mixture was concentrated and the residue subjected to silica-gel column chromatography (light petroleum–EtOAc; gradient elution) to give the title compound (**24**) (0.026 g, 62%) as a syrup; ν_{max}(film) 1 785 (β-lactam C=O) and 1 735 cm^{-1} (ester C=O); λ_{max}(EtOH) 213 (ε 6 400); δ(60 MHz; $CDCl_3$) 1.40 (9 H, s, Me_3C), 3.10 (1 H, dd, *J* 16 and 3 Hz, 7-Hβ), 3.40 (1 H, dd, *J* 16 and 5 Hz, 7-Hα), 3.78 and 4.30 (each 1 H, d, *J* 18 Hz, NCH_2CO_2), 4.87 (3 H, s, OMe), 5.03 (1 H, dd, *J* 5 and 3 Hz, $COCH_2CH$), 6.97 (1 H, d, *J* 15 Hz, $CH{:}CHCO_2$), and 7.40 (1 H, d, *J* 15 Hz, $CH{:}CHCO_2$); *m/z* (EI) 232 ($M^+ - C_5H_9O_2$) and 57 ($C_4H_9^+$, base peak) (Found: $M^+ - C_5H_9O_2$, 232.0288. $C_8H_{10}NO_5S$ requires *m/z* 232.0280).

Preparation of 2-endo-*Methoxycarbonylmethyl*-3-*thiacepham*-4-exo-*carboxylic Acid* (**20b**) *and its Sodium Salt* (**20c**).—Trifluoroacetic acid (1 cm^3) was added to a solution of the t-butyl ester (**20a**) (0.200 g, 0.60 mmol) in dry dichloromethane (2 cm^3). After 12 h, the mixture was concentrated and the residue recrystallised from ethanol to give the *title acid* (**20b**) (0.131 g, 71%), m.p. 152–154 °C; ν_{max}(KBr) 1 720br (β-lactam, ester, and carboxylic acid C=O); λ_{max} 214 nm (ε 4 300); δ(60 MHz; $CDCl_3$ containing CD_3COCD_3) 2.80 (2 H, d, separation 7 Hz, $CHCH_2CO_2$), 2.93 (1 H, dd, *J* 16 and 2 Hz, $COCHHCH$), 3.63 (1 H, dd, *J* 16 and 4 Hz, $COCHHCH$), 3.73 (3 H, s, MeO), 5.00 (1 H, t, separation 7 Hz, 2-H), 5.43 (1 H, dd, *J* 4 and 2 Hz, 6-H), 5.56 (1 H, s, 4-H), and 7.15br (1 H, s, CO_2H) (addition of D_2O caused the signal at δ 7.16 to disappear); *m/z* (EI) 277 (M^+), 232 ($M^+ - CHO_2$), and 204 ($M^+ - C_3H_5O_2$) (Found: C, 38.7; H, 3.8; N, 5.0. $C_9H_{11}NO_5S$ requires C, 39.0; H, 4.00; N, 5.05%).

The acid (**20b**) (0.057 g, 0.20 mmol) was added to a stirred solution of sodium hydrogen carbonate (0.017 g, 0.20 mmol) in water (2 cm^3). After 15 min, the solvent was evaporated off and the residue dried (*in vacuo* over $CaCl_2$). The resultant sodium salt (**20c**) showed δ(60 MHz; D_2O) 3.00 (2 H, d, separation 7 Hz, $CHCH_2CO_2$), 3.10 (1 H, d, *J* 15 and 2 Hz, 7-Hβ), 3.55 (1 H, dd, *J* 15 and 4 Hz, 7-Hα), 3.80 (3 H, s, MeO), 4.85 (1 H, t, separation 7 Hz, 2-H), 5.45 (1 H, dd, *J* 4 and 2 Hz, 6-H), and 5.57 (1 H, s, 4-H). The spectrum was unchanged after 18 h.

Reaction of the t-Butyl Ester (**23a**) *with Trifluoroacetic Acid followed by Sodium Hydrogen Carbonate.*—Trifluoroacetic acid (1.5 cm^3) was added to a solution of the t-butyl ester (**23a**) (0.141 g, 0.35 mmol) in dry dichloromethane (9 cm^3). After 1 h, the mixture was concentrated and the resultant foam was dissolved in ethanol (3 cm^3) and treated with a solution of sodium hydrogen carbonate (0.026 g, 0.31 mmol) in water (3 cm^3). The precipitate, which formed, was filtered off and recrystallised from acetone–light petroleum to give 2-endo-*methoxycarbonylmethyl*-3-*thiacepham* 1,1,3,3-*tetraoxide* (**26a**) (0.020 g, 19%), m.p. 197–199 °C; ν_{max}(KBr) 1 790 (β-lactam C=O), and 1 745 and 1 730 cm^{-1} (ester C=O); λ_{max}(EtOH) 207 nm (ε 1 800); δ(360 MHz; CD_3SOCD_3) 3.11 (1 H, dd, *J* 17 and 6 Hz, $CHCHHCO$), 3.19 (1 H, dd, *J* 17 and 6 Hz, $CHCHHCO$), 3.39 (1 H, dd, *J* 16 and 2 Hz, 7-Hβ), 3.73 (1 H, dd, *J* 16 and 4 Hz, 7-Hα), 4.86 and 5.77 (each, 1 H, d, *J* 16 Hz, 4-H_2), 5.28 (1 H, dd, *J* 4 and 2 Hz, 6-H), and 6.05 (1 H, t, separation 6 Hz, 2-H); *m/z* (EI) 266 ($M^+ - CH_3O$) (Found: C, 32.1; H, 3.5; N, 4.7. $C_8H_{11}NO_7S_2$ requires C, 32.3; H, 3.75; N, 4.7%).

Reaction of the t-Butyl Ester (**23a**) *with Trifluoroacetic Acid followed by Sodium* 2-*Ethylhexanoate.*—The t-butyl ester (**23a**) (0.060 g, 0.15 mmol) was treated with trifluoroacetic acid as

* See instructions for Authors (1990), *J. Chem. Soc., Perkin Trans. 1*, 1990, Issue 1.

described in the previous experiment. The crude acid (**23b**) was dissolved in ethyl acetate (2 cm^3) and a solution of sodium 2-ethylhexanoate in a mixture of butan-1-ol and diethyl ether was added until no further precipitation occurred. The filtered material was considered to be the sodium salt (**23c**) on the basis of IR spectroscopy; ν_{max}(KBr) 1 790 (β-lactam C=O), 1 740 (ester C=O), and 1 650 cm^{-1} (carboxylate C=O).

Recrystallisation of the salt (**23c**) from water gave the decarboxylated material (**26a**) (0.015 g, 33%), m.p. 199 °C, identified by IR spectroscopy.

Reaction of the t-Butyl Ester (**23a**) *with Trifluoroacetic Acid followed by Diazomethane.*—The t-butyl ester (**23a**) (0.056 g, 0.14 mmol) was converted into the crude acid (**23b**) as described previously. Ethereal diazomethane was added to an ice-cooled solution of the acid (**23b**) in ethyl acetate (2 cm^3). After 15 min, the mixture was concentrated and the residue recrystallised from ethanol to give 4-endo-*methyl*-2-exo-*methyl*-4-exo-*methoxycarbonyl*-2-endo-*methoxycarbonylmethyl*-3-*thiacepham* 1,1,3,3-*tetraoxide* (**28a**) (0.029 g, 54%), m.p. 153–155 °C; ν_{max}(KBr) 1 800 (β-lactam C=O) and 1 735 cm^{-1} (ester C=O); λ_{max}(EtOH) 212 nm (ε 2 300); δ(250 MHz; $CDCl_3$) 2.19 and 2.30 (each 3 H, s, 2- and 4-Me), 3.24 (2 H, AB q, *J* 14 Hz, separation of inner lines 4 Hz, CH_2CO_2), 3.57 (1 H, dd, *J* 16 and 5 Hz, 7-Hα), 3.75 and 3.97 (each 3 H, s, 2 × MeO), 3.75 (1 H, dd, *J* 16 and 2 Hz, 7-Hβ), and 5.57 (1 H, dd, *J* 5 and 2 Hz, 6-H); *m/z* (EI) 382 (M^+), 350, and 59 ($C_2H_3O_2^+$, base peak) (Found: C, 37.9; H, 4.5; N, 3.5. $C_{12}H_{17}NO_9S_2$ requires C, 37.6; H, 4.45; N, 3.65%).

Preparation of 4-exo-*Methoxycarbonyl*-2-endo-*methoxycarbonylmethyl*-3-*thiacepham* (**20d**).—Ethereal diazomethane was added to an ice-cooled solution of the acid (**20b**) (0.100 g, 0.36 mmol) in dry dichloromethane (3 cm^3) until a yellow colour persisted. After 15 min, the mixture was concentrated and the residue recrystallised from ethanol–light petroleum to give the *title compound* (**20d**) (0.078 g, 74%), m.p. 93 °C; ν_{max}(KBr) 1 760 (β-lactam C=O) and 1 735 cm^{-1} (ester C=O); λ_{max}(EtOH) 213 nm (ε 4 500); δ(60 MHz; $CDCl_3$) 2.71 (2 H, d, separation 7 Hz, $CHCH_2CO_2$), 2.86 (1 H, dd, *J* 16 and 2 Hz, 7-Hβ), 3.50 (1 H, dd, *J* 16 and 4 Hz, 7-Hα), 3.67 and 3.76 (each 3 H, s, 2 × MeO), 4.86 (1 H, t, separation 7 Hz, 2-H), 5.30 (1 H, dd, *J* 4 and 2 Hz, 6-H), and 5.46 (1 H, s, 4-H); *m/z* (EI) 291 (M^+), 232 ($M^+ - C_2H_3O_2$), and 218 ($M^+ - C_3H_5O$) (Found: C, 41.3; H, 4.3; N, 4.7. $C_{10}H_{13}NO_5S_2$ requires C, 41.2; H, 4.5; N, 4.8%).

Preparation of 4-exo-*Methoxycarbonyl*-2-endo-*methoxycarbonylmethyl*-3-*thiacepham* 1,1,3,3-*Tetraoxide* (*23d*).—Potassium permanganate (0.205 g, 1.3 mmol) dissolved in water (5 cm^3) was added in drops to a stirred solution of the thiacepham (**20d**) (0.086 g, 0.295 mmol) in glacial acetic acid (5 cm^3) with ice cooling. After 1 h, the mixture was decolourised by the addition of 30% aqueous hydrogen peroxide and partitioned between ethyl acetate and brine. Evaporation of the dried ($MgSO_4$) organic layer and purification of the residue by silica-gel column chromatography (light petroleum–EtOAc; gradient elution) gave the title compound (**23d**) (0.035 g, 33%) as a chromatographically homogenous foam; ν_{max}(KBr) 1 805 (β-lactam C=O) and 1 740 cm^{-1} (ester C=O); λ_{max}(EtOH) 209 nm (ε 2 000); δ(60 MHz; $CDCl_3$) 3.18 (2 H, d, *J* 5 Hz, $CHCH_2CO_2$), 3.50–3.80 (2 H, m, 7-H_2), 3.70 and 3.86 (each 3 H, s, 2 × MeO), 5.16–5.50 (2 H, m, 2- and 6-H), and 5.63 (1 H, s, 4-H); *m/z* (EI) 356 (MH^+) and 324 ($M^+ - CH_3O$) (Found: $M^+ - CH_3O$, 323.9862. $C_9H_{10}NO_8S_2$ requires *M*, 323.9848).

Reaction of the Thiacepham (**23d**) *with Diazomethane.*—Ethereal diazomethane was added to an ice-cooled solution of the thiacepham (**23d**) (0.035 g, 0.099 mmol) in dry dichloromethane (2 cm^3) until a yellow colour persisted. After 15 min, the mixture was concentrated and the residue recrystallised from ethanol to give the dimethyl derivative (**28a**) (0.022 g, 58%), m.p. 152–155 °C, identified by IR spectroscopy.

Preparation of 4-exo-(*t-Butoxycarbonyl*)-2-endo-*methyl*-4-exo-*methyl*-2-endo-*methoxycarbonyl*-3-*thiacepham* 1,1,3,3-*Tetraoxide* (**28b**).—Ethereal diazomethane was added to an ice-cooled solution of the thiacepham tetraoxide (**23a**) (0.050 g, 0.126 mmol) in dry dichloromethane (2 cm^3) until a yellow colour persisted. After 15 min, the mixture was concentrated and the residue recrystallised from ethanol to give the *title compound* (**28b**) (0.032 g, 60%), m.p. 131–132 °C; ν_{max}(KBr) 1 790 (β-lactam C=O), and 1 745 and 1 715 cm^{-1} (ester C=O); λ_{max}(EtOH) 208 (ε 2 400); δ(250 MHz; $CDCl_3$) 1.56 (9 H, s, Me_3C), 2.20 and 2.23 (each 3 H, s, 2- and 4-Me), 3.23 and 3.43 (each 1 H, d, *J* 16 Hz, CH_2CO_2), 3.57 (1 H, dd, *J* 16 and 5 Hz, 7-Hα), 3.73 (1 H, dd, *J* 16 and 2 Hz, 7-Hβ), 3.77 (3 H, s, MeO), and 5.50 (1 H, dd, *J* 5 and 2 Hz, 6-H) (in an NOED experiment, irradiation of the signal at δ 2.20 caused a 3% enhancement of the d at δ 3.23; irradiation of the signal at δ 2.23 caused no enhancements); *m/z* (EI) 426 (MH^+), 324 ($M^+ - C_5H_9O_2$), and 57 ($C_4H_9^+$, base peak) (Found: C, 42.0; H, 5.3; N, 3.4. $C_{15}H_{23}NO_9S_2$ requires C, 42.35; H, 5.45; N, 3.3%).

Reaction of the t-Butyl Ester (**28b**) *with Trifluoroacetic Acid followed by Diazomethane.*—Trifluoroacetic acid (1 cm^3) was added to a solution of the t-butyl ester (**28b**) (0.040 g, 0.094 mmol) in dry dichloromethane (2 cm^3). After 12 h, the mixture was concentrated and the residue was dissolved in dichloromethane (2 cm^3). Ethereal diazomethane was added to the ice-cooled solution until a yellow colour persisted. After 15 min, the mixture was concentrated and the residue recrystallised from ethanol. The product (0.020 g, 56%), m.p. 152–154 °C, was identified as the methyl ester (**28a**) by IR spectroscopy.

Reaction of the Isopenam Dioxide (**30**) *with Diazomethane.*—A solution of the isopenam dioxide (**30**) (0.050 g) in ice-cold dichloromethane (3 cm^3) was treated with an excess of ethereal diazomethane. The mixture was left in the refrigerator overnight and then concentrated to leave the isopenam dioxide (**3b**) identified by 60 MHz ^1H NMR spectroscopy.

Preparation of 4-[(Z)-2-*Carboxyvinylthio*]*azetidin*-2-*one* (**16b**).—A solution of propiolic acid (6.2 cm^3, 101 mmol) in methanol (20 cm^3) was added to a stirred solution of thiourea (7.60 g, 99.8 mmol) in 2M hydrochloric acid (40 cm^3) at a rate sufficient to maintain a temperature of *ca.* 50 °C. When the addition was complete, the solution was left for 1 h and then concentrated to leave the crude isothiouronium chloride (**18b**).

Sodium hydroxide (2.79 g, 69.8 mmol) in water (30 cm^3) was added to a stirred ice-cooled solution of the crude isothiouronium chloride (**18b**) (4.24 g, 23.2 mmol) in ethanol 30 cm^3) followed, after 15 min, by a solution of the acetoxyazetidinone (**17**) (3.00 g, 23.2 mmol) in ethanol (30 cm^3). After 1 h, the bulk of the ethanol was evaporated off and the concentrate was partitioned between ethyl acetate and dilute hydrochloric acid. Evaporation of the dried ($MgSO_4$) organic phase and recrystallisation of the residue from ethanol–light petroleum gave the *title compound* (**16b**) (1.16 g, 29%), m.p. 153–156 °C; ν_{max}(KBr) 1 725br (β-lactam C=O) and 1 665 cm^{-1} (unsaturated carboxylic acid C=O); λ_{max}(EtOH) 213 (ε 7 900) and 272 nm (15 000); δ(60 MHz; D_2O containing Na_2CO_3) 2.91 (1 H, dd, *J* 16 and 2 Hz, 3-Hβ), 3.45 (1 H, dd, *J* 16 and 5 Hz, 3-Hα), 4.95 (1 H, dd, *J* 5 and 2 Hz, 4-H), 5.82 (1 H, d, *J* 10 Hz, SCH:C*H*), and 6.85 (1 H, d, *J* 10 Hz, SC*H*:CH);

m/z (EI) 173 (M^+), 104 ($C_3H_4O_2S^+$), and 42 ($C_2H_2O^+$, base peak) (Found: C, 41.7; H, 4.0; N, 8.0. $C_6H_7NO_3S$ requires C, 41.6; H, 4.05; N, 8.1%).

Preparation of Methoxymethyl (Z)-3-[4-*Oxoazetidin*-2-*ylthio*]*propenoate* (**16c**).—Triethylamine (0.24 cm^3, 1.72 mmol) was added to a stirred suspension of the acid (**16b**) (0.300 g, 1.73 mmol) in dry dichloromethane (15 cm^3). The resulting solution was then treated with chloromethyl methyl ether (0.13 cm^3, 1.7 mmol). When the reaction was complete (TLC), the solvent was removed by evaporation and the residue was purified by silica-gel column chromatography (light petroleum–EtOAc; gradient elution) to give the title ester (**16c**) (0.338 g, 90%) as a chromatographically homogeneous syrup; ν_{max}(film) 1 760br (β-lactam C=O) and 1 700 cm^{-1} (unsaturated ester C=O); λ_{max}(EtOH) 206 (ε 5 600) and 280 nm (13 700); δ(60 MHz; $CDCl_3$) 3.06 (1 H, br d, separation 16 Hz, COC*H*HCH), 3.50 (3 H, s, MeO), 3.56 (1 H, br d, separation 16 Hz, COCH*H*CH), 4.90–5.05 (1 H, m, $COCH_2CH$), 5.30 (2 H, s, OCH_2O), 6.03 (1 H, d, *J* 10 Hz, SCH:C*H*), 7.00 (1 H, br s, CONH), and 7.28 (1 H, d, *J* 10 Hz, SC*H*:CH) [addition of D_2O caused the signal at δ 7.00 to disappear, that at δ 3.06 to collapse to a dd (*J* 16 and 2 Hz), that at δ 3.56 to collapse to a dd (*J* 16 and 5 Hz), and that at δ 4.90–5.05 to collapse to a dd (*J* 5 and 2 Hz)]; *m/z* (EI) 172 ($M^+ - C_2H_5O_2$), 114 ($M^+ - C_5H_8O_3$), and 45 ($C_2H_5O^+$, base peak).

Preparation of t-Butyl Hydroxyl{4-[(Z)-*methoxymethoxycarbonylvinylthio*]-2-*oxoazetidin*-1-*yl*}*acetate* (**19d**).—t-Butyl dihydroxyacetate[9] (0.215 g, 1.45 mmol) followed by triethylamine (0.15 cm^3, 1.08 mmol) were added to a stirred solution of the azetidinone (**16c**) (0.338 g, 1.56 mmol) in dry THF (15 cm^3). When the reaction was complete (TLC), the solution was diluted with ethyl acetate and washed with brine. Evaporation of the dried ($MgSO_4$) organic phase and purification of the residue by silica-gel column chromatography (light petroleum–EtOAc; gradient elution) gave the title compound (**19d**) (0.519 g, 96%) as a syrup; ν_{max}(film) 3 440 (OH), 1 775 (β-lactam C=O), 1 740 (ester C=O), and 1 705 cm^{-1} (unsaturated ester C=O); λ_{max}(EtOH) 207 (ε 13 500) and 281 nm (9 600); δ(60 MHz; $CDCl_3$) 1.50 (9 H, s, Me_3C), 2.75–3.22 (2 H, m, $COCH_2CH$), 3.42 (3 H, s, MeO), 4.27 (1 H, br s, OH), 4.55–5.45 (4 H, m, $COCH_2CH$, OCH_2O, and NC*H*OH), 5.94 (1 H, d, *J* 10 Hz, SCH:C*H*), and 7.34 (1 H, d, *J* 10 Hz, SC*H*:CH) (addition of D_2O caused the signal at δ 4.27 to disappear); *m/z* (EI) 320 ($M^+ - CO$) and 45 ($C_2H_5O^+$, base peak).

Preparation of t-Butyl Acetylthio{4-[(Z)-*methoxycarbonylvinylthio*]-2-*oxoazetidin*-1-*yl*}-*acetate* (**19f**).—2,6-Dimethylpyridine (0.26 cm^3, 2.3 mmol) followed by thionyl chloride (0.33 cm^3, 4.5 mmol) were added to a stirred cooled (CCl_4–solid CO_2) solution of the azetidinone (**19d**) (0.519 g, 1.49 mmol) in dry THF (15 cm^3). When the reaction was complete (TLC), the mixture was filtered and the filtrate evaporated. The residual chloride (**19e**) was dissolved in dry DMF (15 cm^3) and potassium thioacetate (0.205 g, 1.80 mmol) was added to the stirred solution. After 1 h, the mixture was diluted with ethyl acetate and washed (× 3) with brine. Evaporation of the dried ($MgSO_4$) organic phase and purification of the residue by silica-gel column chromatography (light petroleum–EtOAc; gradient elution) gave the *title compound* (**19f**) (0.298 g, 49%) as a syrupy 1:1 mixture of diastereoisomers; ν_{max}(film) 1 775 (β-lactam C=O), 1 735 (ester C=O), and 1 700 cm^{-1} (unsaturated ester C=O); λ_{max}(EtOH) 210 (ε 15 400), 221sh (13 800), and 276 nm (16 600); δ(60 MHz; $CDCl_3$) 1.45 (9 H, s, Me_3C), 2.38 and 2.40 (each 1.5 H, s, MeCOS), 3.00 (1 H, dm, separation 15 Hz, COC*H*HCH), 3.48 (3 H, s, MeO), 3.50 (1 H, dm, separation 15 Hz, COCH*H*CH), 3.91 and 4.22 (each 0.5 H, dd, *J* 5 and 2 Hz, $COCH_2CH$), 5.27 and 5.29 (each 1 H, s, OCH_2O), 5.80 and 5.82 (each 0.5 H, s, NC*H*SCOMe), 5.99 (1 H, d, *J* 10 Hz, SCH:C*H*), and 7.18 and 7.30 (each 0.5 H, d, *J* 10 Hz, SC*H*:CH); *m/z* (EI) 405 (M^+) and 57 ($C_4H_9^+$, base peak) (Found: M^+, 405.0948. $C_{16}H_{23}NO_7S_2$ requires *M*, 405.0916).

Preparation of t-Butyl 2-endo-*Methoxymethoxycarbonylmethyl*-3-*thiacepham*-4-exo-*carboxylate* (**20f**).—Cyclohexylamine (0.18 cm^3, 1.57 mmol) was added to a stirred ice-cooled solution of the thioester (**19f**) (0.267 g, 0.66 mmol) in dry dichloromethane (10 cm^3). When the reaction was complete (TLC), the mixture was diluted with ethyl acetate and washed with brine. Evaporation of the dried ($MgSO_4$) organic phase and purification of the residue by silica-gel chromatography (light petroleum–EtOAc; gradient elution) gave the *title compound* (**20f**). After recrystallisation from diethyl ether–light petroleum, the sample (0.129 g, 54%) showed m.p. 81 °C; ν_{max}(KBr) 1 760 (β-lactam C=O), and 1 740 and 1 720 cm^{-1} (ester C=O); λ_{max}(EtOH) 215 nm (ε 4 700); δ(360 MHz; $CDCl_3$) 1.50 (9 H, s, Me_3C), 2.78 (2 H, d, separation 7 Hz, $CHCH_2CO_2$), 2.95 (1 H, dd, *J* 15 and 2 Hz, 7-Hβ), 3.48 (3 H, s, MeO), 3.53 (1 H, dd, *J* 15 and 4 Hz, 7-Hα), 5.00 (1 H, t, separation 7 Hz, 2-H), 5.27 (2 H, AB q, *J* 6 Hz, separation of inner lines 2 Hz, OCH_2O), 5.41 (1 H, s, 4-H), and 5.42 (1 H, dd, *J* 4 and 2 Hz, 6-H); *m/z* (EI) 363 (M^+), 307 ($M^+ - C_4H_8$), 262 ($M^+ - C_5H_9O_2$), and 57 ($C_7H_7^+$, base peak) (Found: C, 46.3; H, 5.7; N, 3.8%; M^+, 363.0794. $C_{14}H_{21}NO_6S_2$ requires C, 46.25; H, 5.85; N, 3.85%; M^+, 363.0810).

Preparation of 4-exo-(*t-Butoxycarbonyl*)-2-endo-*methoxymethoxycarbonylmethyl*-3-*thiacepham* 1,1,3,3-*Tetraoxide* (**23f**).—Potassium permanganate (0.069 g, 0.437 mmol) dissolved in water (3 cm^3) was added to a stirred solution of the thiacepham (**20f**) (0.050 g, 0.138 mmol) in glacial acetic acid (3 cm^3) with ice cooling. After 1 h, the mixture was decolourised y the addition of 30% aqueous hydrogen peroxide and partitioned between ethyl acetate and aqueous sodium hydrogen carbonate. After washing with brine, the organic layer was dried ($MgSO_4$) and concentrated. Recrystallisation of the residue from ethanol gave the *title compound* (**23f**) (0.052 g, 88%), m.p. 132–134 °C; ν_{max}(KBr) 1 800 (β-lactam C=O) and 1 755 cm^{-1} (ester C=O); λ_{max}(EtOH) 213 nm (ε 2 300); δ(60 MHz; $CDCl_3$) 1.56 (9 H, s, Me_3C), 3.25 (2 H, d, separation 6 Hz, $CHCH_2CO_2$), 3.45 (3 H, s, MeO), 3.55–3.75 (2 H, m, 7-H_2), 5.26 (2 H, s, OCH_2O), 5.30–5.50 (2 H, m, 2-and 6-H), and 5.53 (1 H, s, 4-H); *m/z* (EI) 372 ($M^+ - C_4H_8$), 128, and 57 ($C_4H_9^+$, base peak) (Found: C, 39.2; H, 4.8; N, 3.2. $C_{14}H_{21}NO_{10}S_2$ requires C, 39.35; H, 4.95; N, 3.3%).

Reaction of the Thiacepham Tetraoxide (**23f**) *with Trifluoroacetic Acid followed by Diazomethane.*—Trifluoroacetic acid (0.5 cm^3) was added to a solution of compound (**23f**) (0.070 g, 0.164 mmol) in deuteriochloroform (1 cm^3). The progress of the reaction was monitored by ^1H NMR spectroscopy and, when the mixture was left overnight, a crystalline material had separated out. This was collected by filtration and identified as 4-exo-*carboxy*-2-endo-*carboxymethyl*-3-*thiacepham* 1,1,3,3-*tetraoxide hemihydrate* (**23g**) (0.040 g, 73%), m.p. 184–186 °C; ν_{max}(KBr) 3 400 (OH), 1 795 (β-lactam C=O), and 1 740 and 1 720 cm^{-1} (carboxylic acid C=O); λ_{max}(EtOH) 209 nm (ε 2 000); δ(60 MHz; CD_3COCD_3) 3.27 (2 H, d, separation 7 Hz, $CHCH_2CO_2$), 3.60 (1 H, dd, *J* 16 and 2 Hz, 7-Hβ), 3.85 (1 H, dd, *J* 16 and 4 Hz, 7-Hα), 5.50–5.70 (2 H, m, 2- and 6-H), 6.15 (1 H, s, 4-H), and 7.10 (3 H, br s, 0.5 H_2O and 2 × CO_2H) (Found: C, 28.6; H, 2.9; N, 4.5. $C_8H_9NO_9S_2 \cdot 0.5H_2O$ requires C, 28.6; H, 3.0; N, 4.15%).

Ethereal diazomethane was added to an ice-cooled

suspension of the diacid (**23g**) (0.015 g, 0.045 mmol) in dry dichloromethane (1 cm^3) until a yellow colour persisted. After 15 min, when a solution had resulted, the mixture was concentrated. Recrystallisation of the residue from ethanol gave a material (0.005 g, 29%), m.p. 151–153 °C, that was identified as compound (**28a**) by IR spectroscopy.

Preparation of 2-endo-*Carboxymethyl*-3-*thiacepham* 1,1,3,3-*Tetraoxide* (**26b**) *and Its Sodium Salt* (**26c**).—Water (3 drops) was added to a solution of the diacid (**23g**) (0.027 g, 0.080 mmol) in deuterioacetone (0.5 cm^3); gas evolution was noted. Evaporation and crystallisation of the residue from ethanol gave the *title acid* (**26b**) (0.015 g, 66%), m.p. 196–197 °C; ν_{max}(KBr) 1 775 (β-lactam C=O), and 1 740 and 1 710 cm^{-1} (carboxylic acid C=O); λ_{max}(EtOH) 206 nm (ε 700); δ(60 MHz; CD_3COCD_3) 3.15 (2 H, d, separation 7 Hz, $CHCH_2CO_2$), 3.25–3.90 (2 H, m, 7-H_2), 4.90 (1 H, d, *J* 16 Hz, 4-H), and 5.0–6.0 (4 H, m, 2-, 4-, and 6-H, and CO_2H) [addition of D_2O caused the signal at δ 3.15 to appear as a s and that at δ 5.0–6.0 to collapse to a d (1 H, *J* 16 Hz) at δ 5.45 and a m (1 H) at δ 5.35–5.50]; *m/z* (EI) 147 ($M^+ - C_3H_6O_4S$) and 44 (CO_2^+, base peak) (Found: C, 29.3; H, 3.1; N, 4.8. $C_7H_9NO_7S_2$ requires C, 29.7; H, 3.2; N, 4.95%).

The acid (**26b**) (0.017 g, 0.060 mmol) was added to a solution of sodium hydrogen carbonate (0.005 g, 0.060 mmol) in water (1 cm^3); dissolution occurred with evolution of carbon dioxide. Evaporation left a white solid which was dried (*in vacuo* over $CaCl_2$) and identified as the sodium salt (**26c**) by IR spectroscopy; ν_{max}(KBr) 1 810 (β-lactam C=O) and 1 615 cm^{-1} (carboxylate C=O). The IR spectrum was unchanged when the sample was left in water for 12 h.

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