Studies Related to Penicillins. Part 17.[1] Reactions of (2*S*)-3-Mercapto-3-methyl-2-{(1*S*,5*R*)-7-oxo-4-oxa-2,6-diazabicyclo[3.2.0]hept-2-en-6-yl}-butanoates

By **Wasna Baker, Chandra M. Pant,** and **Richard J. Stoodley,*** Department of Organic Chemistry, The University, Newcastle upon Tyne NE1 7RU

Methyl (2*S*)-2-{(1*S*,5*R*)-3-benzyl-7-oxo-4-oxa-2,6-diazabicyclo[3.2.0]hept-2-en-6-yl}-3-mercapto-3-methylbutanoate (4a) reacts with toluene-*p*-sulphonic acid monohydrate to give (2*S*,3*S*)-1-[(1*S*)-2-mercapto-1-methoxycarbonyl-2-methylpropyl]-4-oxo-3-phenylacetamidoazetidin-2-yl 3-[(1*S*)-2-mercapto-1-methoxycarbonyl-2-methylpropyl]amino-2-phenylacetamidoacrylate (7). With anhydrous toluene-*p*-sulphonic acid, the mercaptobutanoate (4a) affords methyl 5,5-dimethyl-2-thiazoline-4-carboxylate (16).

The mercaptobutanoate (4a) is converted into a mixture of methyl benzylpenicillenate (18), methyl benzyl-5-*epi*-penicillinate (6a), and the thiazepinone (11a) with zinc acetate in boiling benzene. A corresponding reaction, to give the *epi*-penicillinate (6d) and the thiazepinone (11c), occurs with *p*-nitrobenzyl (2*S*)-3-mercapto-3-methyl-2-{(1*S*,5*R*)-7-oxo-3-phenoxymethyl-4-oxa-2,6-diazabicyclo[3.2.0]hept-2-en-6-yl}butanoate (20a). Hydrogenolysis of the derivative (6d) in the presence of sodium hydrogen carbonate yields sodium phenoxymethyl-5-*epi*-penicillinate (6e), which is devoid of antimicrobial activity.

Acetic acid reacts with the mercaptobutanoate (4a) to give methyl (2*S*)-[(2*S*,3*S*)-2-acetoxy-4-oxo-3-phenylacetamidoazetidin-1-yl]-3-mercapto-3-methylbutanoate (9a). Analogous reactions, affording the chloroazetidinone (9b) and the trifluoroacetoxyazetidinone (9c), occur with hydrogen chloride and trifluoroacetic acid.

The mercaptobutanoate (4a) is transformed into (2*S*,6*S*,7*S*)-2-methoxycarbonyl-3,3-dimethyl-8-oxo-7-phenylacetamido-5-oxa-4-thia-1-azabicyclo[4.2.0]octane 4-oxide (24a) by *m*-chloroperbenzoic acid. Hydrogenolysis of the 2-*p*-nitrobenzyloxycarbonyl analogue of (24a) in the presence of sodium hydrogen carbonate yields the salt (24c), which shows no significant biological activity.

As part of a programme aimed at the synthesis of penicillin analogues, we have initiated a study of 4-oxa-2,6-diazabicyclo[3.2.0]hept-2-en-7-ones. In the presence of Lewis acids and alcohols,[2] these compounds, *e.g.* (1), undergo 4,5-bond rupture to give *trans*-azetidinones, *e.g.* (2a). However, with Lewis acids and thiols,[3] mixtures of *trans*- and *cis*-azetidinones, *e.g.* (2b) and (3), are produced. The availability of the mercaptobutanoate (4a)[1] prompted us to explore the feasibility of effecting an intramolecular version of the foregoing reaction; it was hoped to derive the penicillinate (5) and/or the 5-*epi*-penicillinate (6a) in this manner. We now report the results of this study.

Previously, toluene-*p*-sulphonic acid monohydrate was found to be effective[3] in promoting the addition of

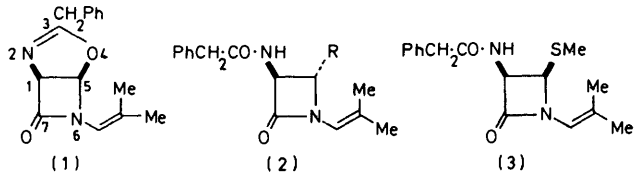
[1] Part 16, R. J. Stoodley and N. S. Watson, *J.C.S. Perkin I*, 1975, 883.

[2] D. F. Corbett and R. J. Stoodley, *J.C.S. Perkin I*, 1974, 185.

[3] D. F. Corbett and R. J. Stoodley, *J.C.S. Chem. Comm.*, 1974, 438; *J.C.S. Perkin I*, 1975, 432.

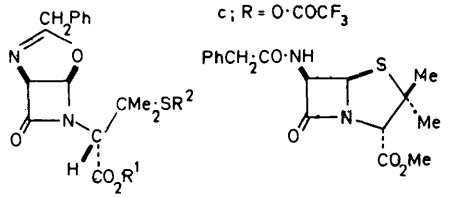
thiols to the oxazoline-azetidinone (1). However, when the mercaptobutanoate (4a) was treated with this reagent in acetone a product, $C_{34}H_{42}N_4O_9S_2$, formally derived from the starting material by dimerization and hydration, was obtained. Spectroscopic considerations suggested that the derivative possessed the structure (7). Thus i.r. spectroscopy revealed absorptions characteristic of secondary amide (3 370, 1 675, and 1 510 cm^{-1}), β-lactam (1 780 cm^{-1}), carboxylic ester (1 735 cm^{-1}), and C=C (1 605 cm^{-1}) moieties. The u.v. spectrum [$\lambda_{max.}$ (EtOH) 280 nm (ε 26 000)] was in accord with the presence of the aminoacrylate chromophore.[4] N.m.r. spectroscopy showed signals for *trans*-disposed β-lactam protons [5] at δ 4.80 and 6.55 (J 1.2 Hz); the former proton was further coupled (J 3.6 Hz) with the amido-proton of the phenylacetamido-group. The methine protons of the butanoate moieties resonated at δ 4.59 and 4.60, the latter signal appearing as a doublet (J 3.6 Hz), due to coupling with the adjacent amino-proton. The signal for the vinylic proton appeared as a doublet (J 4.4 Hz) at δ 6.83, due to coupling with the amino-proton.

The aminoacrylate (8a) and the acetoxyazetidinone (9a) are expected to be reliable spectroscopic models for the two units of the dimer (7). The former derivative,



(1) (2) (3)

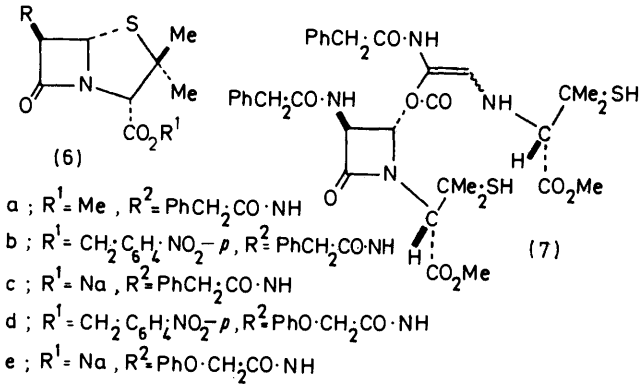
a; R = OMe
b; R = SMe
c; R = O·COCF$_3$



(4) (5)

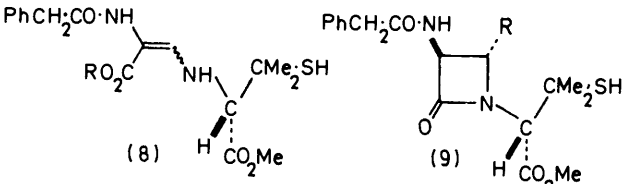
a; R^1 = Me, R^2 = H
b; R^1 = K, $MeCO_2K$, R^2 = H
c; R^1 = R^2 = $CH_2C_6H_4NO_2$-*p*
d; R^1 = R^2 = Hg
e; R^1 = $CH_2C_6H_4NO_2$-*p*, R^2 = H
f; R^1 = R^2 = H
g; R^1 = Me, R^2 = OH
h; R^1 = Me, R^2 = O_2H
i; R^1 = $CH_2C_6H_4NO_2$-*p*, R^2 = O_2H

although not isolable, was described in the early penicillin literature; [6] it was prepared in ethanolic solution by treating dimethyl benzylpenicilloate (10a) with mercury(II) chloride in the presence of benzylamine and was characterised by $\lambda_{max.}$ 280 nm (ε 17 300). The compound



(6) (7)

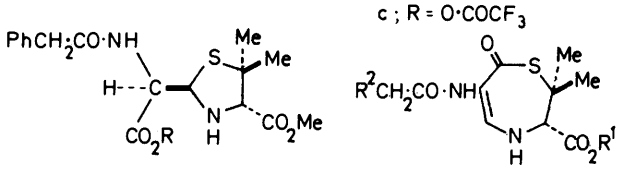
a; R^1 = Me, R^2 = $PhCH_2CO·NH$
b; R^1 = $CH_2C_6H_4NO_2$-*p*, R^2 = $PhCH_2CO·NH$
c; R^1 = Na, R^2 = $PhCH_2CO·NH$
d; R^1 = $CH_2C_6H_4NO_2$-*p*, R^2 = $PhO·CH_2CO·NH$
e; R^1 = Na, R^2 = $PhO·CH_2CO·NH$



(8) (9)

a; R = Me
b; R = H

a; R = OAc
b; R = Cl
c; R = O·COCF$_3$



(10) (11)

a; R = Me
b; R = H

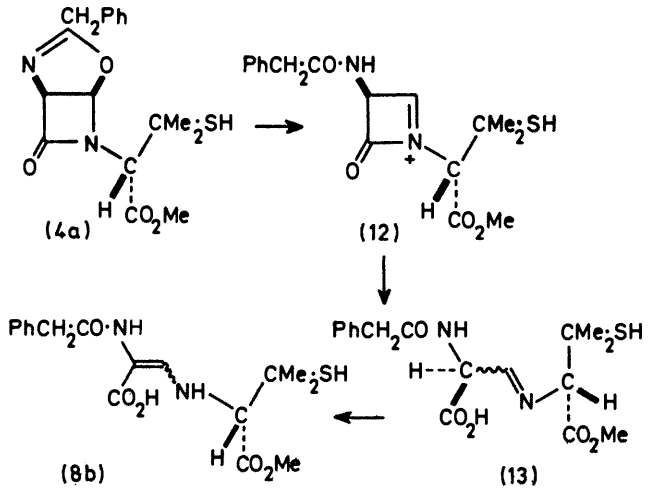
a; R^1 = Me, R^2 = Ph
b; R^1 = $CH_2C_6H_4NO_2$-*p*, R^2 = Ph
c; R^1 = $CH_2C_6H_4NO_2$-*p*, R^2 = PhO

(9a) was readily obtained by treating the mercaptobutanoate (4a) with glacial acetic acid for 18 h; the reaction was much slower than that involving the isobutenyl derivative (1).[2] The n.m.r. spectroscopic properties of the acetoxyazetidinone (9a) were similar to those of the azetidinone unit of the dimer; in particular, the β-lactam protons resonated at δ 4.40 and 6.60 (J 1 Hz), the former signal being further coupled (J 8 Hz) with the amido-proton of the phenylacetamido-group, and the methine proton of the butanoate moiety resonated at δ 4.47. The acetoxyazetidinone (9a) was an unstable compound which rearranged to the known thiazepinone (11a) [7] either when chromatographed on silica gel or when left at ambient temperature for several days.

The dimer (7) is possibly derived from the reaction of the mercaptobutanoate (4a) with the acrylic acid (8b).

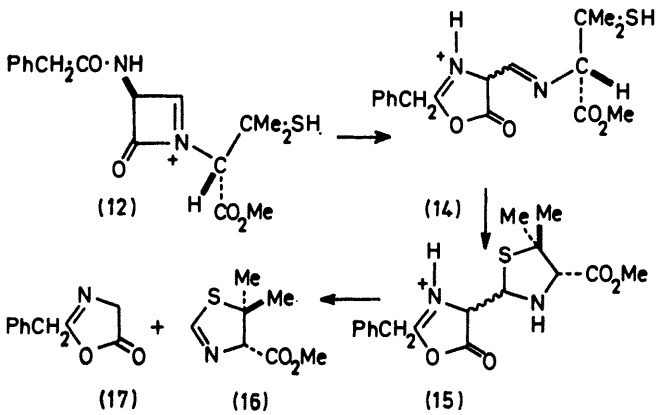
[4] D. L. Ostercamp, *J. Org. Chem.*, 1970, **35**, 1632.
[5] H. B. Kagan, J. J. Basselier, and J. L. Luche, *Tetrahedron Letters*, 1964, 941; K. D. Barrow and T. M. Spotswood, *ibid.*, 1965, 3325.
[6] H. T. Clarke, J. R. Johnson, and R. Robinson, 'The Chemistry of Penicillin,' Princeton University Press, Princeton, New Jersey, 1949, pp. 204 and 427—428.
[7] O. K. J. Kovacs, B. Ekström, and B. Sjöberg, *Acta Chem. Scand.*, 1973. **27**, 677.

A likely sequence for the conversion (4a) ⟶ (8b) is summarised in Scheme 1. It is suggested that the reaction is triggered by rupture of the 4,5-bond to give the azetinium cation (12), which then undergoes hydrolysis to the imine (13); tautomerisation of the imine (13) may then afford the acrylic acid (8b). An alternative pathway, involving the reaction of the carboxylic acid (10b) or (13) with the oxazoline-azetidinone (4a), followed by tautomerisation, also accounts for the formation of the dimer (7).



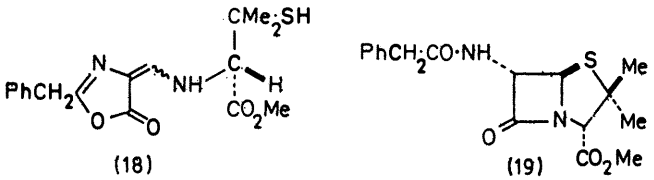
SCHEME 1

In order to preclude the formation of the dimer (7), the mercaptobutanoate (4a) was treated with anhydrous toluene-*p*-sulphonic acid in dry benzene. However, on the basis of n.m.r. spectroscopy, the major neutral product was the thiazoline (16).[8] A possible pathway for the formation of this compound is suggested in Scheme 2. The azetinium cation (12) is considered to rearrange to the protonated oxazolinone-thiazolidine (15) by way of the oxazolinium ion (14); fragmentation of the species (15) may then afford the thiazoline (16) and the oxazolinone (17). The species (15) is implicated as an intermediate in the trifluoroacetic acid-induced degradation of methyl benzylpenicillinate (5) to the thiazoline (16).[8]



SCHEME 2

When heated with zinc acetate dihydrate in benzene, the mercaptobutanoate (4a) was converted into three major new products which were separated by silica gel chromatography. The first-eluted compound was indistinguishable from methyl benzylpenicillenate (18), prepared by the literature method.[9] The second-eluted material {m.p. 136 °C, $[\alpha]_D$ −154° ($CHCl_3$)} was considered to be the 5-*epi*-penicillinate (6a); it differed from the 6-*epi*-penicillinate (19)[10] {m.p. 116 °C, $[\alpha]_D$ +119° ($CHCl_3$)} and n.m.r. spectroscopy confirmed that its β-lactam protons were *trans*-oriented. The 3-proton of the derivative (6a) as significantly shielded (δ 3.75 in $CDCl_3$) as compared with those of methyl benzylpenicillinate (5a) (δ 4.37) and methyl benzyl-6-*epi*-penicillinate (19) (δ 4.44).[11] This effect, originally noted with monocyclic thiazolidines,[12] has been observed by other workers,[13,14] and shown to be of value in diagnosing the configuration of penicillinates and related molecules. The third-eluted substance was identical with the thiazepinone (11a).



The azetinium cation (12) is a possible intermediate in the foregoing reaction, undergoing ring relocations to give the oxazolinone (18) and the thiazepinone (11a) and a ring construction to afford the 5-*epi*-penicillinate (6a). Control experiments established that the derivatives (5) and (6a) were stable under the reaction conditions, indicating that the 5-*epi*-penicillinate was formed in a kinetically controlled process.

In order to prepare a salt of benzyl-5-*epi*-penicillinic acid for biological evaluation, attention was turned to the derivation of the *p*-nitrobenzyl ester (6b); it was hoped that hydrogenolysis of this derivative in the presence of sodium hydrogen carbonate would yield the sodium salt (6c).

Treatment of the potassium salt (4b)[1] with *p*-nitrobenzyl bromide (1 mol. equiv.) in *NN*-dimethylformamide afforded only the bis-*p*-nitrobenzyl derivative (4c). However, sequential reactions of the mercury salt (4d)[15] with hydrogen sulphide and *p*-nitrophenyldiazo-

[8] M. R. Bell, J. A. Carlson, and R. Oesterlin, *J. Amer. Chem. Soc.*, 1970, **92**, 2177; *J. Org. Chem.*, 1972, **37**, 2733.
[9] Ref. 6, pp. 163—164.
[10] D. A. Johnson and D. Mania, *Tetrahedron Letters*, 1969, 267.
[11] A. Vlietinck, E. Roets, P. Claes, G. Janssen, and H. Vanderhaeghe, *J.C.S. Perkin I*, 1973, 937.
[12] I. McMillan and R. J. Stoodley, *Chem. Comm.*, 1968, 11.
[13] R. Busson and H. Vanderhaeghe, *J. Org. Chem.*, 1976, **41**, 2561.
[14] A. G. Brown, D. F. Corbett, and T. T. Howarth, *J.C.S. Chem. Comm.*, 1977, 359.
[15] R. J. Stoodley and N. R. Whitehouse, *J.C.S. Perkin I*, 1974, 181.

methane [16] did yield the desired ester (4e). When heated in boiling benzene containing zinc acetate, the derivative (4e) was converted into two major new products, which were separated by silica gel chromatography. The less polar component was the 5-*epi*-penicillinate (6b) and the more polar material the thiazepinone (11b). Attempts to derive the salt (6c), by hydrogenolysis of the ester (6b) over palladium–carbon, were unrewarding; non-β-lactam products were formed.

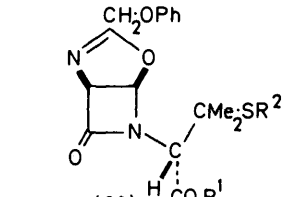
To extend the scope of the foregoing procedure as a route to 5-*epi*-penicillin esters and in the hope of deriving a 5-*epi*-penicillin salt for bioassay, efforts were made to prepare the mercaptobutanoate (20a). Treatment of the mercury salt (20b) [15] with hydrogen sulphide followed by *p*-nitrophenyldiazomethane afforded the desired material. When heated with zinc acetate in boiling benzene, the derivative (20a) was transformed into two major new products, which were separated by silica gel chromatography. The first-eluted material was the 5-*epi*-penicillinate (6d) and the second-eluted compound the thiazepinone (11c). Hydrogenolysis of the ester (6d) over palladium–carbon in aqueous ethanol containing sodium hydrogen carbonate afforded the salt (6e) as an amorphous solid. The salt (6e), which was reconverted into the ester (6d) when treated with *p*-nitrobenzyl bromide in *NN*-dimethylformamide, did not inhibit bacterial growth at concentrations of 500 μg cm^{-3}.

After the aforementioned work was complete, Busson and Vanderhaeghe [13] described the preparation of derivatives of benzyl-5-*epi*-penicillin by another route. The Belgian workers also found that the sodium salt (6c) possessed no significant antimicrobial activity.

Our efforts to construct penicillinates from the chloroazetidinone (9b) and the trifluoroacetoxyazetidinone (9c), by using tin(II) chloride and silver(I) salts, were unrewarding. The derivatives (9b) and (9c) were readily prepared from the oxazoline-azetidinone (4a) by reactions with hydrogen chloride in dry ether and with trifluoroacetic acid in chloroform. In contrast with the trifluoroacetate (2c), which spontaneously rearranged to the oxazolinone (21),[2] the derivative (9c) was isolable.

Parallel with our studies to effect the conversion of the mercaptobutanoate (4a) into penicillinates, attempts were made to bring about the reaction under oxidative conditions. Previously it was shown [1] that the acid (4f) spontaneously isomerised to the oxazolidinone-azetidinone (22). It was therefore hoped that the sulphenic acid (4g) or the sulphinic acid (4h) would react in a corresponding manner to give the sulphoxide (23a) or the sulphone (23b).

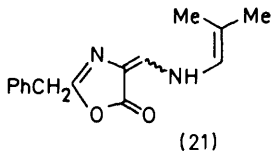
When treated with *m*-chloroperbenzoic acid in dichloromethane, the mercaptobutanoate (4a) was transformed into one major neutral product, $C_{17}H_{20}N_2O_6S$ (elemental analysis and mass spectrometry). Although this formula is that expected for the sulphone (23b), spectroscopic data were not in accord with this structure. Thus the i.r. spectrum contained no strong absorption at 1 310—1 340 cm^{-1}, a region where the symmetrical S=O stretching vibration of sulphones typically appears.[17] N.m.r. spectroscopy left little doubt that the material was the oxathiazine-azetidinone (24a); in particular, the β-lactam proton signals appeared as a doublet (*J* 8 Hz)



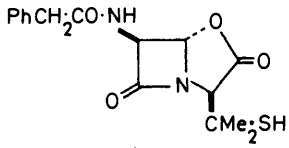
(20)

a; $R^1 = CH_2C_6H_4NO_2$-*p*, $R^2 = H$

b; $R^1 = R^2 = Hg$



(21)



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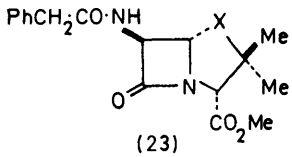
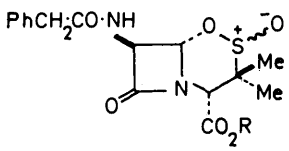


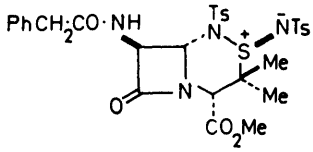
(23)

a; X = SO

b; X = SO_2



(24)



(25)

a; R = Me

b; R = $CH_2C_6H_4NO_2$-*p*

c; R = Na

at δ 4.98 (which collapsed to a singlet after exchange of the amido-proton) and as a singlet at 5.50. The failure to detect coupling between *trans*-disposed azetidinone protons is unusual (a coupling constant of 1.5—2.0 Hz is typically observed in penam derivatives [18]) but has been noted previously [1] with the oxazolidine-azetidinone (22).

Application of the foregoing oxidation to the *p*-nitrobenzyl ester (4e) afforded the oxathiazine-azetidinone (24b), which underwent hydrogenolysis over palladium–charcoal in the presence of sodium hydrogen carbonate. The derived salt (24c), which was converted into the ester (24a) when treated with methyl iodide in *NN*-dimethylformamide, displayed no appreciable antimicrobial activity.

The conversion of the thiols (4a) and (4e) into the oxathiazine-azetidinones (24a) and (24b) almost certainly involves the sulphinic acids (4h) and (4i). Evidently the 4,5-bond of the derivatives (4h) and (4i) is cleaved by an oxygen atom of the sulphinic acid moiety with an inversion of configuration at position 5.

[16] W. Jugelt and L. Berseck, *Tetrahedron*, 1970, **26**, 5581.

[17] A. D. Cross, 'An Introduction to Practical Infra-red Spectroscopy,' Butterworths, London, 1964, p. 78.

[18] E. J. Corey and A. M. Felix, *J. Amer. Chem. Soc.*, 1965, **87**, 2518; I. McMillan and R. J. Stoodley, *Tetrahedron Letters*, 1966, 1205.

The oxathiazine-azetidinones, *e.g.* (24a), are closely related to the thiadiazine-azetidinones, *e.g.* (25), compounds isolated by Campbell and his co-workers [19] from the reactions of penicillin esters with chloramine T.

EXPERIMENTAL

For general experimental details see Part I.[20] 60 MHz N.m.r. spectra were recorded with a Varian EM-360 spectrometer.

Reaction of the Mercaptobutanoate (4a) *with Toluene-p-sulphonic Acid Monohydrate.*—A solution of the mercaptobutanoate (4a) [1] (0.208 g, 0.6 mmol) in acetone (10 cm^3) was treated with toluene-*p*-sulphonic acid monohydrate (0.114 g, 0.6 mmol). After 15 min the mixture was diluted with dichloromethane, washed with sodium hydrogen carbonate solution followed by water, and dried ($MgSO_4$). Evaporation and addition of ether to the residue gave (2S,3S)-1-[(1S)-2-*mercapto*-1-*methoxycarbonyl*-2-*methylpropyl*]-4-*oxo*-3-*phenylacetamidoazetidin*-2-*yl* 3-[(1S)-2-*mercapto*-1-*methoxycarbonyl*-2-*methylpropyl*]*amino*-2-*phenylacetamidoacrylate* (7) (0.096 g, 45%), m.p. 176—178 °C (from EtOH), $[\alpha]_D$ +10° (0.4% in $CHCl_3$), $\nu_{max.}$ (KBr) 3 370 and 3 240 (N–H), 1 780 (azetidinone C=O), 1 735 (ester C=O), 1 675 (amide C=O), 1 605 (C=C), and 1 510 cm^{-1} (amide II), $\lambda_{max.}$ (EtOH) 213 (ε 21 800) and 280 nm (26 000), δ (220 MHz; $CDCl_3$) 1.30 and 1.46 (each 6 H, s, 2 × *gem*-Me_2), 1.95 and 1.99 (each 1 H, s, 2 × SH), 3.67 and 3.73 (each 2 H, s, 2 × PhCH_2), 3.71 and 3.76 (each 3 H, s, 2 × CO_2Me), 4.59 (1 H, s, N·CH·CO_2), 4.60 (1 H, d, *J* 3.6 Hz, NH·C*H*·CO_2), 4.80 (1 H, dd, *J* 3.6 and 1.2 Hz, β-lactam H), 5.87 (1 H, dd, *J* 3.6 and 4.4 Hz, N*H*·CH·CO_2), 6.41 (1 H, s, NH), 6.43 (1 H, d, *J* 3.6 Hz, NH), 6.55 (1 H, d, *J* 1.2 Hz, β-lactam H), 6.83 (1 H, d, *J* 4.4 Hz, vinylic H), and 7.2—7.3 (10 H, m, 2 × Ph) [addition of D_2O caused the signals at 1.95, 1.99, 5.87, 6.41, and 6.43 to disappear, those at 4.6 and 6.83 to collapse to s, and that at 4.8 to collapse to a d (*J* 1.2 Hz)], *m/e* 91 (base peak, $C_7H_7^+$) (Found: C, 57.6; H, 6.1; N, 7.6%; M^+, 714.237 5. $C_{34}H_{42}N_4O_9S$ requires C, 57.2; H, 5.9; N, 7.8%; *M*, 714.239 3).

Reaction of the Mercaptobutanoate (4a) *with Acetic Acid.*—The mercaptobutanoate (4a) (0.104 g, 0.3 mmol) was dissolved in glacial acetic acid (1 cm^3). After 18 h the mixture was diluted with water and extracted with chloroform. Evaporation of the water-washed and dried ($MgSO_4$) organic layer gave *methyl* (2S)-[(2S,3S)-2-*acetoxy*-4-*oxo*-3-*phenylacetamidoazetidin*-1-*yl*]-3-*mercapto*-3-*methylbutanoate* (9a) (0.082 g, 67%), as a chromatographically homogeneous pale yellow foam, $\nu_{max.}$ (film) 3 340 (N–H), 1 780 (β-lactam C=O), 1 745 (ester C=O), 1 675 (amide C=O), and 1 515 cm^{-1} (amide II), $\lambda_{max.}$ (EtOH) 213 nm (ε 8 600), δ ($CDCl_3$) 1.57 (6 H, s, *gem*-Me_2), 2.06 (3 H, s, O·COMe), 2.61 (1 H, s, SH), 3.61 (2 H, s, PhCH_2), 3.77 (3 H, s, CO_2Me), 4.40 (1 H, d, *J* 8 Hz, β-lactam H), 4.47 (1 H, s, N·CH·CO_2), 6.37 (1 H, d, *J* 8 Hz, NH), 6.60 (1 H, s, β-lactam H), and 7.33 (5 H, s, Ph) (addition of D_2O caused the signals at 2.61 and 6.37 to disappear and that at 4.40 to collapse to s), *m/e* 91 (base peak, $C_7H_7^+$) (Found: M^+, 408.136 1. $C_{19}H_{24}N_2O_6S$ requires *M*, 408.135 5).

When subjected to silica gel chromatography, the acetoxyazetidinone (9a) was converted into a compound (80%), m.p. 149—150 °C (from MeOH), identical (i.r. and n.m.r. spectroscopy) with the thiazepinone (11a).[7]

Reaction of the Mercaptobutanoate (4a) *with Anhydrous Toluene-p-sulphonic Acid.*—The mercaptobutanoate (4a) (0.174 g, 0.5 mmol), dissolved in dry benzene (3 cm^3), was treated with a benzene solution of toluene-*p*-sulphonic acid [*ca.* 5 cm^3 of a stock solution prepared by refluxing toluene-*p*-sulphonic acid monohydrate (0.190 g) in dry benzene (10 cm^3) and removing the water using a Dean–Stark trap]. After 0.5 h the resultant yellow solution was diluted with benzene and washed with sodium hydrogen carbonate solution followed by water. Evaporation of the dried ($MgSO_4$) organic layer left a residue which contained predominantly the thiazoline (16) [8] on the basis of n.m.r. spectroscopy.

Reaction of the Mercaptobutanoate (4a) *with Zinc Acetate.*—The mercaptobutanoate (4a) (1.00 g, 2.87 mmol) was heated in benzene (200 cm^3) containing zinc acetate dihydrate (0.30 g, 1.4 mmol). After 3 h the mixture was washed with sodium hydrogen carbonate solution followed by water, dried ($MgSO_4$), and evaporated. The product was fractionated by silica gel chromatography [C_6H_6–Et_2O (1 : 1) as eluant].

The first-eluted material (0.150 g, 15%), $[\alpha]_D$ +30° (0.94% in $CHCl_3$), isolated as a chromatographically homogeneous syrup, was identical (i.r., u.v., and n.m.r., and mass spectra) with methyl benzylpenicillenate (18).[9]

The second-eluted material (0.200 g, 20%) was methyl benzyl-5-*epi*-penicillinate (6a), m.p. 136 °C (from $CHCl_3$–Et_2O), $[\alpha]_D$ −154° (1.0% in $CHCl_3$), $\nu_{max.}$ (KBr) 3 300 (N–H), 1 780 (β-lactam C=O), 1 740 (ester C=O), 1 655 (amide C=O), and 1 530 cm^{-1} (amide II), $\lambda_{max.}$ (EtOH) 208 nm (ε 6 300), δ ($CDCl_3$) 1.40 and 1.60 (each 3 H, s, *gem*-Me_2), 3.60 (2 H, s, PhCH_2), 3.75 (4 H, s, CO_2Me and N·CH·CO_2), 4.90 (1 H, dd, *J* 2.0 and 7.5 Hz, β-lactam H), 5.15 (1 H, d, *J* 2.0 Hz, β-lactam H), 6.9br (1 H, d, NH), and 7.3 (5 H, s, Ph) [addition of D_2O caused the signal at 6.9 to disappear and that at 4.90 to collapse to a d (*J* 2.0 Hz)], *m/e* 348 (M^+) and 91 (base peak, $C_7H_7^+$) (Found: C, 59.0; H, 5.9; N, 8.1%; M^+, 348.115 3. $C_{17}N_{20}N_2O_4S$ requires C, 58.8; H, 5.7; N, 8.0%; *M*, 348.114 4),

The third-eluted material (0.50 g, 50%) was identical (n.m.r., i.r., and mass spectroscopy) with the thiazepinone (11a).

Reaction of the Potassium Salt (4b) *with* p-*Nitrobenzyl Bromide.*—The potassium salt (4b) [1] (0.510 g, 1.1 mmol) was treated with *p*-nitrobenzyl bromide (0.286 g, 1.3 mmol) in *NN*-dimethylformamide (10 cm^3). After 2.5 h the mixture was diluted with chloroform and washed (2 ×) with sodium hydrogen carbonate solution followed by water. Evaporation of the dried ($MgSO_4$) organic layer gave a product which was fractionated by silica gel chromatography (C_6H_6–Et_2O as eluant).

The first-eluted material (0.057 g, 36%) was *p*-nitrobenzyl acetate.

The second-eluted material (0.048 g, 37%) was *p*-nitrobenzyl (2*S*)-2-{(1*S*,5*R*)-3-benzyl-7-ozo-4-oxa-2,6-diazabicyclo[3.2.0]hept-2-en-6-yl}-3-methyl-3-(*p*-nitrobenzylthio)butanoate (4c), $[\alpha]_D$ +20° (1.0% in $CHCl_3$), $\nu_{max.}$ (film) 1 770 (β-lactam C=O), 1 735 (ester C=O), 1 650 (C=N), and 1 605 cm^{-1}, $\lambda_{max.}$ (EtOH) 212 (ε 26 900), 244sh (11 900), 249sh (15 700), 255 (19 900), 261 (21 100), and 269sh nm (19 600), δ($CDCl_3$) 1.16 and 1.33 (each 3 H, s, *gem*-Me_2), 3.66 (3 H, s, PhCH_2), 3.81 (2 H, s, S·CH_2), 4.65 (1 H, s,

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[20] I. McMillan and R. J. Stoodley, *J. Chem. Soc.* (*C*), 1968, 2533.

N·CH·CO_2), 5.22 (1 H, d, *J* 3.6 Hz, β-lactam H), 5.30 (2 H, s, CO_2CH_2), 6.25 (1 H, d, *J* 3.6 Hz, β-lactam H), 7.25 (5 H, s, Ph), and 7.2—8.3 (8 H, m, 2 × C_6H_4·NO_2), *m/e* 435 (M^+ − HS·CH_2·C_6H_4·NO_2) and 91 (base peak, $C_7H_7^+$).

Preparation of p-*Nitrobenzyl* (2S)-2-{(1S,5R)-3-*Benzyl*-7-*oxo*-4-*oxa*-2,6-*diazabicyclo*[3.2.0]*hept*-2-*en*-6-*yl*}-3-*mercapto*-3-*methylbutanoate* (4e).—A suspension of the mercury salt (4d) [15] (1.00 g, 1.88 mmol) in dichloromethane (10 cm^3) was treated with hydrogen sulphide. The mixture was filtered, treated with ethereal *p*-nitrophenyldiazomethane,[16] and evaporated. Silica gel chromatography afforded the *p-nitrobenzyl ester* (4e) (0.528 g, 62%), m.p. 128—130 °C (from $CHCl_3$–Et_2O), $[\alpha]_D$ +5° (0.87% in $CHCl_3$), $\nu_{max.}$ (KBr) 2 590 (S–H), 1 765 (β-lactam C=O), 1 730 (ester C=O), and 1 650 cm^{-1} (C=N), $\lambda_{max.}$ (EtOH) 208 (ε 13 700) and 262 nm (8 200), δ($CDCl_3$) 1.16 and 1.32 (each 3 H, s, *gem*-Me_2), 2.08 (1 H, s, SH), 3.78 (2 H, s, PhCH_2), 4.56 (1 H, s, N·CH·CO_2), 5.24 (1 H, d, *J* 3.6 Hz, β-lactam H), 5.32 (2 H, s, CO_2·CH_2), 6.30 (1 H, d, *J* 3.6 Hz, β-lactam H), 7.33 (5 H, s, Ph), and 7.60 and 8.30 (each 2 H, *J* 8 Hz, C_6H_4·NO_2) (irradiation at 5.24 caused the d at 6.30 to collapse to s and *vice versa*; addition of D_2O caused the signal at 2.08 to disappear), *m/e* 469 (M^+) and 91 (case peak, $C_7H_7^+$) (Found: C, 59.1; H, 4.9; N, 8.9. $C_{23}H_{23}N_3O_6S$ requires C, 58.8; H, 4.9; N, 8.9%).

Reaction of the Mercaptobutanoate (4e) *with Zinc Acetate.*—The mercaptobutanoate (4e) (2.70 g, 5.35 mmol) was heated in boiling benzene (1 dm^3) containing zinc acetate dihydrate (0.63 g, 2.87 mmol). Work-up as before gave a product which was fractionated by silica gel chromatography [C_6H_6–Et_2O (1 : 1) as eluant].

The first-eluted material, isolated as a chromatographically homogeneous syrup, was *p*-nitrobenzyl benzyl-5-*epi*-penicillinate (6b) (0.81 g, 30%), $[\alpha]_D$ −95° (0.8% in $CHCl_3$), $\nu_{max.}$ (film) 3 300 (N–H), 1 780 (β-lactam C=O), 1 745 (ester C=O), 1 680 (amide C=O), and 1 540 cm^{-1} (amide II), $\lambda_{max.}$ (EtOH) (ε 15 500) and 263 nm (8 700), δ ($CDCl_3$) 1.40 and 1.64 (each 3 H, s, *gem*-Me_2), 3.69 (2 H, s, PhCH_2), 3.90 (1 H, s, N·CH·CO_2), 4.88 (1 H, dd, *J* 2.0 and 7.6 Hz, β-lactam H), 5.18 (1 H, d, *J* 2.0 Hz, β-lactam H), 5.34 (2 H, s, CO_2·CH_2), 6.6br (1 H, d, *J* 7.6 Hz, NH), 7.35 (5 H, s, Ph), and 7.61 and 8.23 (each 2 H, d, *J* 8 Hz, C_6H_4·NO_2), *m/e* 435 (M^+ − H_2S) and 91 (base peak, $C_7H_7^+$).

The second-eluted material (1.62 g, 60%) was p-*nitrobenzyl* (3S)-2,3,4,7-*tetrahydro*-2,2-*dimethyl*-7-*oxo*-6-*phenylacetamido*-1,4-*thiazepine*-3-*carboxylate* (11b), m.p. 104—106 °C (from $CHCl_3$–Et_2O), $[\alpha]_D$ −170° (0.8% in $CHCl_3$), $\nu_{max.}$ (KBr) 3 300br (N–H), 1 740 (ester C=O), 1 640 (amide C=O), 1 570, and 1 530 cm^{-1}, $\lambda_{max.}$ (EtOH) 211 (ε 15 800), 260 (14 200), and 316 nm (8 500), δ($CDCl_3$) 1.40 and 1.49 (each 3 H, d, *gem*-Me_2), 3.65 (2 H, s, PhCH_2), 4.10 (1 H, d, *J* 5.6 Hz, NH·C*H*·CO_2), 5.28 (2 H, s, CO_2·CH_2), 6.6br (2 H, 2 × NH), 7.37 (5 H, s, Ph), 7.57 and 8.28 (each 2 H, d, *J* 8 Hz, C_6H_4·NO_2), and 7.98 (1 H, d, *J* 8.0 Hz, vinylic H) (addition of D_2O caused the signal at 6.6 to disappear and those at 4.10 and 4.98 to collapse to s), *m/e* 435 (M^+ − H_2S) and 91 (base peak, $C_7H_7^+$) (Found: C, 58.9; H, 4.9; N, 8.9. $C_{23}H_{23}N_3O_6S$ requires C, 58.8; H, 4.9; N, 9.0%).

Preparation of p-*Nitrobenzyl* (2S)-3-*Mercapto*-3-*methyl*-2-{(1S,5R)-7-*oxo*-3-*phenoxymethyl*-4-*oxa*-2,6-*diazabicyclo*-[3.2.0]*hept*-2-*en*-6-*yl*}*butanoate* (20a).—Hydrogen sulphide was passed through a suspension of the mercury salt (20b) [15] (2.00 g, 3.51 mmol) in dichloromethane (20 cm^3) and the mixture was filtered. The filtrate was treated with *p*-nitrophenyldiazomethane in ether, evaporated, and fractionated by silica gel chromatography [C_6H_6–Et_2O (7 : 3) as eluant] to give the p-*nitrobenzyl ester* (20a) (1.05 g, 62%), m.p. 102 °C (from $CHCl_3$–Et_2O), $[\alpha]_D$ −8° (0.88% in $CHCl_3$), $\nu_{max.}$ (KBr) 2 560 (S–H), 1 765 (β-lactam C=O), 1 725 (ester C=O), 1 660 (C=N), and 1 600 cm^{-1}, $\lambda_{max.}$ (EtOH) 210 (ε 17 000), 264 (12 500), 268 (12 500), and 275sh nm (10 900), δ($CDCl_3$) 1.5br (6 H, s, *gem*-Me_2), 2.36 (1 H, s, SH), 4.63 (1 H, s, N·CH·CO_2), 4.82 (2 H, s, PhO·CH_2), 5.34 (1 H, d, *J* 3.6 Hz, β-lactam H), 5.36 (2 H, s, CO_2·CH_2), 6.48 (1 H, d, *J* 3.6 Hz, β-lactam H), 7.0—7.54 (5 H, m, Ph), and 7.70 and 8.40 (each 2 H, d, *J* 8 Hz, C_6H_4·NO_2) (addition of D_2O caused the signal at 2.36 to disappear; irradiation at 5.34 caused the signal at 6.48 to collapse to s), *m/e* 485 (M^+) and 114 (base peak) (Found: C, 56.6; H, 4.8; N, 8.8%; M^+, 485.129 7. $C_{23}H_{23}N_3O_7S$ requires C, 56.9; H, 4.7; N, 8.6%; *M*, 485.125 7).

Reaction of the Mercaptobutanoate (20a) *with Zinc Acetate.*—The mercaptobutanoate (20a) (1.70 g, 3.5 mmol) was heated in benzene (600 cm^3) containing zinc acetate dihydrate (0.385 g, 1.75 mmol). Work-up after 3 h gave a mixture which was fractionated by silica gel chromatography [C_6H_6–Et_2O (9 : 1) as eluant].

The first-eluted material (0.51 g, 30%) was p-*nitrobenzyl phenoxymethyl*-5-epi-*penicillinate* (6d), m.p. 112—113 °C (from $CHCl_3$–Et_2O), $[\alpha]_D$ −100° (1.0% in $CHCl_3$), $\nu_{max.}$ (KBr) 3 420 (N–H), 1 795 (β-lactam C=O), 1 750 (ester C=O), 1 675 (amide C=O), 1 600, and 1 530 cm^{-1} (amide II), $\lambda_{max.}$ (EtOH) 210 (ε 17 000), 264 (10 400), 268 (10 700), and 275sh nm (8 700), δ($CDCl_3$) 1.41 and 1.65 (each 3 H, s, *gem*-Me_2), 3.98 (1 H, s, N·CH·CO_2), 4.58 (2 H, s, PhO·CH_2), 5.13 (1 H, dd, *J* 2.2 and 8.0 Hz, β-lactam H), 5.30 (1 H, d, *J* 2.2 Hz, β-lactam H), 5.40 (2 H, s, CO_2·CH_2), 7.0 (1 H, d, *J* 8.0 Hz, NH), 7.20—7.60 (5 H, m, Ph), and 7.68 and 8.36 (each 2 H, d, *J* Hz, C_6H_4·NO_2) [addition of D_2O caused the signal at 7.0 to disappear and that at 5.13 to collapse to d (*J* 2.2 Hz)], *m/e* 294 (M^+ − PhO·CH_2·CO·NH·CH:CO), and 114 (base peak) (Found: C, 56.8; H, 4.5; N, 8.8. $C_{23}H_{23}N_3O_7S$ requires C, 56.9; H, 4.7; N, 8.7%).

The second-eluted material (1.02 g, 60%) was p-*nitrobenzyl* (3S)-2,3,4,7-*tetrahydro*-2,2-*dimethyl*-7-*oxo*-6-*phenoxyacetamido*-1,4-*thiazepine*-3-*carboxylate* (11c), m.p. 106—108 °C (from $CHCl_3$–Et_2O), $[\alpha]_D$ −120° (0.78% in $CHCl_3$), $\nu_{max.}$ (KBr) 3 400br (N–H), 1 735 (ester C=O), 1 660, and 1 640br cm^{-1} (amide C=O), $\lambda_{max.}$ (EtOH) 206 (ε 14 600), 262 (11 200), and 315 nm (4 900), δ($CDCl_3$) 1.45 and 1.52 (each 3 H, s, *gem*-Me_2), 4.43 (1 H, d, *J* 6 Hz, NH·C*H*·CO_2), 4.60 (2 H, s, PhO·CH_2), 5.34 (2 H, s, CO_2·CH_2), 6.9—7.5 (6 H, m, Ph and NH), 7.62 and 8.34 (each 2 H, d, *J* 8 Hz, C_6H_4·NO_2), 8.15 (1 H, d, *J* 9 Hz, vinylic H), and 8.60 (1 H, s, NH) (addition of D_2O caused the signal at 8.60 to disappear and those at 4.43 and 8.15 to collapse to s), *m/e* 485 (M^+) and 107 (base peak, PhO·CH_2^+) (Found: C, 56.6; H, 4.9; N, 8.9. $C_{23}H_{23}N_3O_7S$ requires C, 56.9; H, 4.7; N, 8.7%).

Hydrogenolysis of the p-*Nitrobenzyl Ester* (6d).—The *p*-nitrobenzyl ester (6d) (0.213 g, 0.44 mmol) was hydrogenolysed over 10% palladium–charcoal (0.2 g) in aqueous 80% ethanol (75 cm^3) containing sodium hydrogen carbonate (0.037 g, 0.44 mmol). After 30 min the mixture was filtered and evaporated and the residue washed with ether. The product (0.009 g, 58%) was sodium phenoxymethyl-5-*epi*-penicillinate (6e), $\nu_{max.}$ (KBr) 3 400br (N–H), 1 765 (β-lactam C=O), 1 670 (amide C=O), and 1 620 cm^{-1} (CO_2^-), δ(D_2O) 1.45 and 1.63 (each 3 H, s, *gem*-Me_2), 3.80 (1 H, s, N·CH·CO_2), 5.29 (1 H, s, *J* 2.4 Hz, β-lactam H), and 6.9—

7.5 (5 H, m, Ph) (the signals due to PhO·CH_2 and the second β-lactam H were obscured by the HOD signal at 4.7).

Reaction of the Sodium Salt (6e) *with* p-*Nitrobenzyl Bromide*.—The sodium salt (6e) (0.100 g, 0.26 mmol) was treated with *p*-nitrobenzyl bromide (0.056 g, 0.26 mmol) in *NN*-dimethylformamide (2 cm³). After 12 h the mixture was diluted with ether and washed (3 ×) with water. Evaporation of the dried ($MgSO_4$) organic layer and purification of the product by silica gel chromatography [C_6H_6–Et_2O (1 : 1) as eluant] gave a material (0.080 g, 62%) identical (t.l.c. and n.m.r. and mass spectroscopy) with *p*-nitrobenzyl phenoxymethyl-5-*epi*-penicillinate (6d).

Reaction of the Mercaptobutanoate (4a) *with Hydrogen Chloride*.—A suspension of the mercaptobutanoate (4a) (0.100 g, 0.29 mmol) in dry ether (5 cm³) was treated with ethereal hydrogen chloride. After 10 min the solution was diluted with ether and washed with sodium hydrogen carbonate solution followed by water. Evaporation of the dried ($MgSO_4$) organic layer left methyl (2*S*)-2-[(2*S*,3*R*)-2-chloro-4-oxo-3-phenylacetamidoazetidin-1-yl]-3-mercapto-3-methylbutanoate (9b) (0.093 g, 81%), as a chromatographically homogeneous foam, $[\alpha]_D$ +30° (0.67% in $CHCl_3$), $\nu_{max.}$ (film) 3 380br (N–H), 1 785 (β-lactam C=O), 1 740 (ester C=O), 1 660br (amide C=O), and 1 520br cm⁻¹ (amide II), $\lambda_{max.}$ (EtOH) 208 nm (ε 7 900), δ($CDCl_3$) 1.56 (6 H, s, *gem*-Me_2), 3.00 (1 H, s, SH), 3.63 (2 H, s, PhCH_2), 3.73 (3 H, s, CO_2Me), 4.45 (1 H, s, N·CH·CO_2), 4.59 (1 H, dd, *J* 2 and 6 Hz, β-lactam H), 6.20 (1 H, d, *J* 2 Hz, β-lactam H), 6.8br (1 H, d, *J* 6 Hz, NH), and 7.4 (5 H, s, Ph) [addition of D_2O caused the signals at 3.00 and 6.8 to disappear and that at 4.59 to collapse to d (*J* 2 Hz)], *m/e* 348 (M^+ — HCl) and 91 (base peak, $C_7H_7^+$).

Reaction of the Mercaptobutanoate (4a) *with Trifluoroacetic Acid*.—A solution of the mercaptobutanoate (4a) (0.104 g, 0.30 mmol) in chloroform (5 cm³) was treated with a few drops of trifluoroacetic acid in chloroform. After 5 min the mixture was diluted with chloroform and washed with sodium hydrogen carbonate solution followed by water. Evaporation of the dried ($MgSO_4$) organic layer left *methyl* (2S)-2-[(2S,3S)-4-*oxo*-3-*phenylacetamido*-2-*trifluoroacetoxyazetidin*-1-*yl*]-3-*mercapto*-3-*methylbutanoate* (9c) (0.101 g, 73%), m.p. 112—113 °C (from $CHCl_3$–Et_2O), $[\alpha]_D$ −11° (0.5% in $CHCl_3$), $\nu_{max.}$ (KBr) 3 440br and 3 280 (N–H), 1 785 (β-lactam and trifluoroacetyl C=O), 1 745 (ester C=O), 1 665 (amide C=O), and 1 535 cm⁻¹ (amide II), δ($CDCl_3$) 1.5br (6 H, s, *gem*-Me_2), 2.60 (1 H, s, SH), 3.55 (2 H, s, PhCH_2), 3.61 (3 H, s, CO_2Me), 4.24 (1 H, d, *J* 8 Hz, β-lactam H), 4.38 (1 H, s, N·CH·CO_2), 5.84 (1 H, d, *J* 8 Hz, NH), 6.88 (1 H, s, β-lactam H), and 7.14 (5 H, s, Ph) (addition of D_2O caused the signals at 2.60 and 5.84 to disappear and that at 4.24 to collapse to s), *m/e* 348 (M^+ — CF_3CO_2H) and 159 and 160 (base peaks) (Found: C, 49.4; H, 4.5; N, 6.0. $C_{19}H_{21}F_3N_2O_6S$ requires C, 49.5; H, 4.5; N, 6.1%).

Reaction of the Mercaptobutanoate (4a) *with* m-*Chloroperbenzoic Acid* (with N. S. Watson).—85% *m*-Chloroperbenzoic acid (0.144 g, 0.71 mmol) was added to a stirred solution of the mercaptobutanoate (4a) (0.104 g, 0.3 mmol) in dichloromethane (5 cm³). After 2 h the mixture was diluted with dichloromethane, washed with sodium hydrogen carbonate solution followed by water, and dried ($MgSO_4$). Evaporation left (2S,6S,7S)-2-*methoxycarbonyl*-3,3-*dimethyl*-8-*oxo*-7-*phenylacetamido*-5-*oxa*-4-*thia*-1-*azabicyclo*[4.2.0]-*octane* 4-*oxide* (24a) (0.029 g, 21%), m.p. 76—78 °C (from Me_2SO–H_2O), $[\alpha]_D$ −2° (0.7% in $CHCl_3$), $\nu_{max.}$ (KBr) 3 560, 3 400, and 3 320 (N–H), 1 775 (β-plactam C=O), 1 750 (ester C=O), 1 655 (amide C=O), 1 575, and 1 540 cm⁻¹ (amide II), $\lambda_{max.}$ (EtOH) 210 nm (ε 9 400), δ($CDCl_3$) 1.26 and 1.44 (each 3 H, s, *gem*-Me_2), 3.55 (2 H, s, PhCH_2), 3.76 (3 H, s, CO_2Me), 4.56 (1 H, s, N·CH·CO_2), 4.98 (1 H, d, *J* 8 Hz, β-lactam H), 5.50 (1 H, s, β-lactam H), 6.27 (1 H, d, *J* 8 Hz, NH), and 7.22 (5 H, s, Ph) (addition of D_2O caused the signal at 6.27 to disappear and that at 4.98 to collapse to s), *m/e* 380 (M^+) and 91 (base peak, $C_7H_7^+$) (Found: C, 45.0; H, 6.0; N, 4.3. $C_{17}N_{20}N_2O_6S$ requires C, 44.9; H, 5.9; N, 4.4%).

Reaction of the Mercaptobutanoate (4e) *with* m-*Chloroperbenzoic Acid*.—The mercaptobutanoate (4e) (1.20 g, 2.56 mmol) was treated with 85% *m*-chloroperbenzoic acid (1.04 g, 5.12 mmol) in dichloromethane (15 cm³). Work-up after 30 min and purification of the product by silica gel chromatography [C_6H_6–Et_2O (1 : 1) as eluant] gave (2S,6S,7S)-3,3-*dimethyl*-2-p-*nitrobenzyloxycarbonyl*-8-*oxo*-7-*phenylacetamido*-5-*oxa*-4-*thia*-1-*azabicyclo*[4.2.0]*octane* 4-*oxide* (24b) (0.551 g, 43%), as a chromatographically homogeneous foam, $[\alpha]_D$ −40° (0.65% in $CHCl_3$), $\nu_{max.}$ (film) 3 250 (N–H), 1 780 (β-lactam C=O), 1 750 (ester C=O), 1 665 (amide C=O), 1 610, and 1 540 cm⁻¹ (amide II), $\lambda_{max.}$ (EtOH) 210 (ε 21 900) and 265 nm (11 300), δ($CDCl_3$) 1.24 and 1.48 (each 3 H, s, *gem*-Me_2), 3.63 (2 H, s, PhCH_2), 4.83 (1 H, s, N·CH·CO_2), 4.90 (1 H, d, *J* 6.0 Hz, β-lactam H), 5.34 (2 H, s, CO_2·CH_2), 5.78 (1 H, s, β-lactam H), 6.80 (1 H, d, *J* 6.0 Hz, NH), 7.49 (5 H, s, Ph), and 7.68 and 8.30 (each 2 H, d, *J* 8 Hz, C_6H_4·NO_2) (addition of D_2O caused the signal at 6.80 to disappear and that at 4.90 to collapse to s), *m/e* 435 (M^+ — H_2O_2S) and 91 (base peak, $C_7H_7^+$) (Found: C, 55.4; H, 4.6; N, 8.1. $C_{23}H_{23}N_3O_8S$ requires C, 55.1; H, 4.6; N, 8.4%).

Hydrogenolysis of the p-*Nitrobenzyl Ester* (24b).—The *p*-nitrobenzyl ester (24b) (0.100 g, 0.2 mmol) was hydrogenolysed over 10% palladium–charcoal in aqueous 80% ethanol (15 cm³) containing sodium hydrogen carbonate (0.017 g, 0.2 mmol). After 30 min the mixture was filtered and evaporated and the residue washed with ether. The product (0.070 g, 90%) was the sodium salt of (2*S*,6*S*,7*S*)-2-carboxy-3,3-dimethyl-8-oxo-7-phenylacetamido-5-oxa-4-thia-1-azabicyclo[4.2.0]octane 4-oxide (24c), $\nu_{max.}$ 3 300br (N–H), 1 770 (β-lactam C=O), 1 680 (amide C=O), 1 640, 1 620 (CO_2^-), and 1 530 cm⁻¹ (amide II), δ(D_2O) 1.13 and 1.30 (each 3 H, s, *gem*-Me_2), 3.63 (2 H, s, PhCH_2), 4.95 and 5.68 (each 1 H, s, 2 × β-lactam H), and 7.30 (5 H, s, Ph) (the N·CH·CO_2 signal was obscured by the HOD signal at 4.7).

Reaction of the Sodium Salt (24c) *with Methyl Iodide*.—The sodium salt (24c) (0.100 g, 0.28 mmol) was treated with methyl iodide (0.038 g, 0.28 mmol) in *NN*-dimethylformamide (2 cm³). After 12 h the mixture was diluted with ether and washed (3 ×) with water. Evaporation of the dried ($MgSO_4$) organic layer and purification of the product by silica gel chromatography [C_6H_6–Et_2O (1 : 1) as eluant] gave a material (0.046 g, 47%) identical (t.l.c. and n.m.r. and mass spectroscopy) with the derivative (24a).

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