Studies Related to Penicillins. Part XVI.[1] Preparation of Methyl 2-{(1*S*,5*R*)-3-Benzyl-7-oxo-4-oxa-2,6-diazabicyclo[3.2.0]hept-2-en-6-yl}-3-methylbut-2-enoate

By **Richard J. Stoodley** * and **Nigel S. Watson**, Department of Organic Chemistry, The University, Newcastle upon Tyne NE1 7RU

Acetoxymercury(II) (2*S*)-3-acetoxymercurio(II)thio-2-{(1*S*,5*R*)-3-benzyl-7-oxo-4-oxa-2,6-diazabicyclo[3.2.0]-hept-2-en-6-yl}-3-methylbutanoate (9) is converted by hydrogen sulphide into the mercaptobutanoic acid (11), which readily rearranges to a mixture of 2-(2-benzyloxazol-4-ylcarbonylamino)-3-mercapto-3-methylbutanoic acid (17), (3*S*)-2.3,4.7-tetrahydro-2,2-dimethyl-6-phenylacetamido-7-oxo-1.4-thiazepine-3-carboxylic acid (19). and (2*S*,5*S*,6*S*)-2-(1-mercapto-1-methylethyl)-6-phenylacetamido-4-oxa-1-azabicyclo[3.2.0]heptane-3.7-dione (21).

The mercaptobutanoate (10), derived from the acid (11) and diazomethane, reacts with mercury(II) acetate to to give dimethyl 3.3'-mercurio(II)dithiobis-[(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-methylbutanoate] (15). Diazomethane transforms the mercaptobutanoate (10) into the methylthio-butanoate (13). which is oxidised to a mixture of sulphoxides (14) by *m*-chloroperbenzoic acid. Compound (13) is also produced when the potassium salt of the acid (11) is treated with methyl iodide. In dimethyl sulphoxide the potassium salt of the acid (11) isomerises to the potassium salt of the thiazepine (20).

The title compound is produced when the mercaptobutanoate (10) is treated with methanolic sodium methoxide, when the bis(sulphide) (15) is treated with mercury(II) acetate. and when the sulphoxides (14) are heated in benzene.

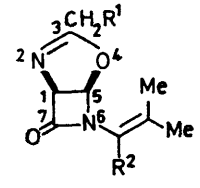
As part of a programme aimed at the synthesis of oxa-analogues of penicillins and cephalosporins, we have initiated a study of 4-oxa-2,6-diazabicyclo[3.2.0]hept-2-en-7-ones.† The first reported example of this class of compounds was the derivative (1), obtained originally from the reaction of methyl benzylpenicillinate (4) with

† The Editor regrets that this ring system was numbered incorrectly in ref. 1 and earlier papers.

[1] Part XV, D. F. Corbett and R. J. Stoodley, *J.C.S. Perkin I*, 1975, 432.

t-butyl hypochlorite;[2] subsequently the material was prepared from the ester (4) and iodobenzene dichloride[3] and from the chloride (7) and sodium hydrogen carbonate.[4] Treatment of the azetidinone (8) with either lead tetra-acetate or *N*-bromosuccinimide and of *p*-methoxybenzyl phenoxymethylpenicillinate (5) with t-butyl hypochlorite afforded the oxazoline (2).[5] In the foregoing examples the yields of the oxazolines were low (18% or less based upon the starting penicillin ester).

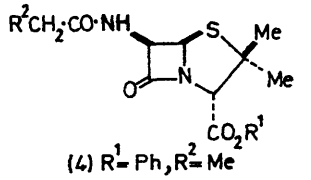
Recently it was shown that mercury(II) acetate in acetic acid converted penicillins, *e.g.* (6), into the mercury derivatives, *e.g.* (9), which were transformed into the oxazolines, *e.g.* (3), in the presence of dimethyl



(1) R^1 = Ph, R^2 = MeO_2C

(2) R^1 = PhO, R^2 = *p*-MeO·C_6H_4·CH_2·O_2C

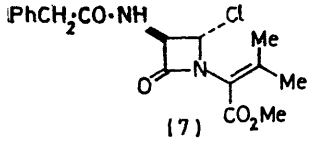
(3) R^1 = Ph, R^2 = H



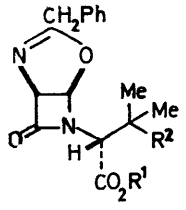
(4) R^1 = Ph, R^2 = Me

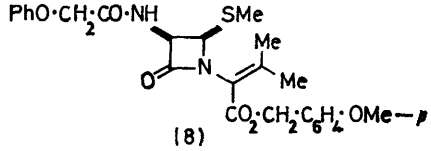
(5) R^1 = PhO, R^2 = *p*-MeO·C_6H_4·CH_2

(6) R^1 = Ph, R^2 = K



(7)





(8)

(9) R^1 = AcO·Hg, R^2 = AcO·Hg·S

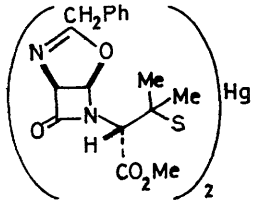
(10) R^1 = Me, R^2 = HS

(11) R^1 = H, R^2 = HS

(12) R^1 = K, R^2 = HS

(13) R^1 = Me, R^2 = MeS

(14) R^1 = Me, R^2 = MeSO



(15)

sulphoxide.[6] This procedure provided a convenient route to the oxazoline (3), enabling the derivative to be prepared from potassium benzylpenicillinate (6) in 23% yield. It was also reported that treatment of the salt (9) with diazomethane in dimethyl sulphoxide afforded an ester, formulated as the mercaptobutanoate (10), which was transformed into the oxazoline (1) by mercury(II) acetate in dimethyl sulphoxide.[6] By this method the potassium salt (6) was converted into the oxazoline in 23% yield.

A disadvantage of the last-described route was that the mercaptobutanoate (10) was contaminated with the methylpropenyl derivative (3). It was therefore necessary to purify the product by silica-gel chromatography prior to its conversion into the oxazoline (1). Since we required appreciable quantities of compound (1), we sought a more convenient method for its derivation. We now report the results of this study.

Neutralisation with diazomethane of the solution obtained by treating the salt (9) with hydrogen sulphide in dichloromethane gave a crystalline ester. Its n.m.r. spectrum differed from that of the ester derived from the reaction of the salt (9) with diazomethane in dimethyl sulphoxide; the former derivative showed signals at τ 8·84 and 8·68 for the *gem*-dimethyl group and 5·60 for the methine hydrogen atom adjacent to the methoxycarbonyl group, whereas the corresponding signals of the latter appeared at 8·62, 8·50, and 5·38.

Mercury(II) acetate (0·5 mol. equiv.) in chloroform converted the crystalline ester into a product which was identical (i.r., n.m.r., and mass spectroscopy) with that isolated from the salt (9) and diazomethane. When the product was treated with hydrogen sulphide the starting ester was recovered and mercury(II) sulphide was deposited. Consequently the material is reformulated as the mercury(II) bis(sulphide) (15) and the crystalline ester is considered to be the mercaptobutanoate (10).

Attempts to convert compound (10) into the oxazoline (1) with triethylamine and 1,5-diazabicyclo[4.3.0]non-5-ene were unsuccessful. However, the reaction was accomplished with methanolic sodium methoxide. Using this procedure potassium benzylpenicillinate (6) was converted into the oxazoline (1) in 42% yield.

When treated with mercury(II) acetate in chloroform, the mercaptobutanoate (10) was converted into the oxazoline (1) in high yield. By this method the oxazoline (1) was obtained from potassium benzylpenicillinate (6) in 50% yield.

The formation of the ester (10) indicated that the acid (11) was produced from the mercury salt (9) and hydrogen sulphide. Since compound (11) is an isomer of benzylpenicillin and it incorporates some of the features which are believed to be necessary for the biological effectiveness of the β-lactam antibiotics,[7] attempts were made to isolate the derivative. Evaporation of the solution obtained by treating the mercury salt (9) with hydrogen sulphide in dichloromethane,

[2] J. C. Sheehan in 'Molecular Modification in Drug Design,' A.C.S. Advances in Chemistry Series No. 45, Washington, D.C., 1964, p. 15.

[3] D. H. R. Barton, F. Comer, and P. G. Sammes, *J. Amer. Chem. Soc.*, 1969, **91**, 1529; D. H. R. Barton, F. Comer, D. G. T. Greig, P. G. Sammes, C. M. Cooper, G. Hewitt, and W. G. E. Underwood, *J. Chem. Soc.* (*C*), 1971, 3540.

[4] S. Wolfe, J.-B. Ducep, G. Kannengiesser, and W. S. Lee, *Canad. J. Chem.*, 1972, **50**, 2902.

[5] E. G. Brain, A. J. Eglington, J. H. C. Nayler, M. J. Pearson, and R. Southgate, *J.C.S. Chem. Comm.*, 1972, 229.

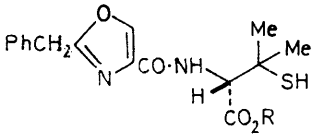
[6] R. J. Stoodley and N. R. Whitehouse, *J.C.S. Chem. Comm.*, 1973, 477; *J.C.S. Perkin I*, 1974, 181.

[7] M. Gorman and C. W. Ryan in 'Cephalosporins and Penicillins,' ed. E. H. Flynn, Academic Press, New York, 1972, p. 532; J. H. C. Nayler, *Adv. Drug Res.*, 1973, **7**, 1.

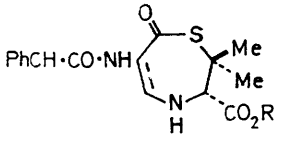
followed by partitioning of the product between sodium hydrogen carbonate solution and chloroform, afforded an acidic and a neutral fraction.

The acidic material, which possessed no β-lactam carbonyl absorption in the i.r. region, was treated with diazomethane and the product was fractionated by silica-gel chromatography. The first-eluted constituent was formulated as the oxazole (16) on the basis of its spectroscopic properties. The more polar component was the known thiazepine (18).[8]

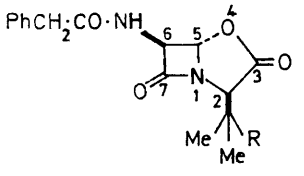
The neutral fraction was considered to be the azetidinone-lactone (21). Elemental analysis and mass spectroscopy established the molecular formula, $C_{16}H_{18}N_2O_4S$. I.r. spectroscopy suggested that the material contained a β-lactam ring (1785 cm^{-1}), a secondary amide linkage (1680 and 1515 cm^{-1}), and a thiol group (2580 cm^{-1}). The n.m.r. spectrum showed the β-lactam proton signals as a doublet (J 8 Hz) at τ 5·35 (which collapsed to a singlet after exchange of the amido proton) and as a singlet at 4·13. The failure



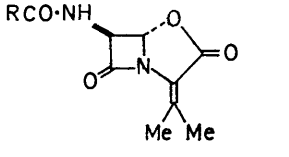
(16) R = Me
(17) R = H



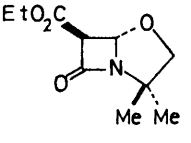
(18) R = Me
(19) R = H
(20) R = K



(21) R = HS
(22) R = MeS
(23) R = MeSO



(24) R = $PhCH_2O$
(25) R = $PhCH_2$



(26)

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 [9]). This result may reflect the increased electronegativity of oxygen compared with sulphur (J_{vic} decreases with an increase in the electronegativity of substituents [10]) and/or some distortion of the azetidinone ring.

Derivative (21) is a rare example of a fused azetidinone-oxazolidine. The oxa-anhydropenicillin (24) [4] and the oxa-penam (26) [11] have been reported. The β-lactam protons of the former resonate as a quartet at τ 4·98 (J 8 and 1·8 Hz) and a doublet at 4·14 (J 1·8 Hz) whereas those of the latter resonate as doublets at τ 6·29 and 4·69 (J 1 Hz).

Efforts were made to convert the thiol (21) into the oxa-anhydropenicillin (25). Attempts to eliminate hydrogen sulphide under basic conditions and in the presence of mercury(II) acetate were unsuccessful. When treated with diazomethane or methyl iodide, the thiol (21) was transformed into the methylthio-derivative (22). However, the crude mixture of sulphoxides (23), obtained by oxidation of compound (22) with *m*-chloroperbenzoic acid, afforded a complex array of products when heated in benzene or chloroform.

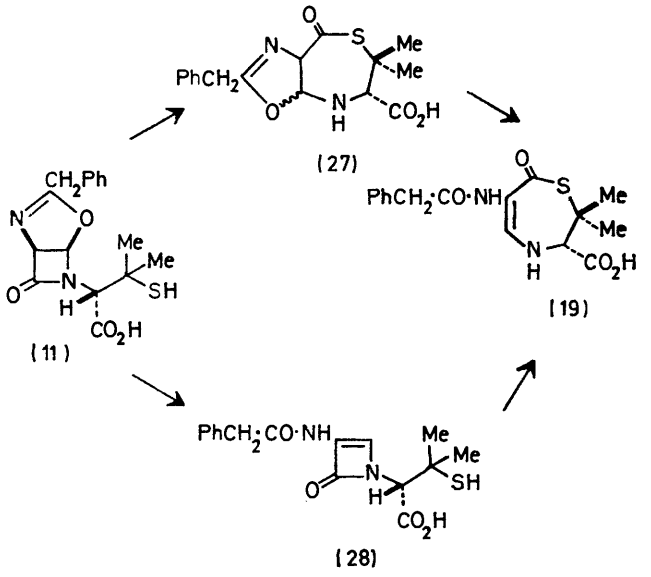
It is clear from the foregoing results that the acid (11) is a labile species and that it undergoes three types of reaction. The formation of the oxazole (17) probably involves initial protonolysis of the 5,6-bond followed by elimination of the 1-hydrogen atom. There is precedent for this behaviour in the chemistry of azetidinone-thiazolines.[12] The production of the thiazepine (19) may involve either rupture of the azetidinone linkage by the thiol group to give species (27) which then undergoes a β-elimination or the initial generation of the azetinone (28) (Scheme). Azetinones are likely intermediates in the base-induced rearrangement of penicillinates to thiazepines.[8,13] The formation of the azetidinone-lactone (21) probably involves the cleavage of the 4,5-bond by the carboxy-function with inversion of configuration at position 5. An intermolecular example of this reaction has been described recently.[6]

N.m.r. spectroscopy established that the solution obtained by treating the mercury salt (9) with hydrogen sulphide in deuteriochloroform initially contained the acid (11) as the major component. However, after 24 h the acid (11) was no longer detectable. Addition of potassium 2-ethylhexanoate to a freshly prepared solution of the acid (11) afforded the potassium salt (12), which crystallised in association with 1 mol. equiv. of potassium acetate.

Although stable in the solid state, the potassium salt (12) decomposed in [$^2H_6$]dimethyl sulphoxide during

[8] O. K. J. Kovacs, B. Ekström, and B. Sjöberg, *Acta Chem. Scand.*, 1973, **27**, 677.
[9] E. J. Corey and A. M. Felix, *J. Amer. Chem. Soc.*, 1965, **87**, 2518; I. McMillan and R. J. Stoodley, *Tetrahedron Letters*, 1966, 1205.
[10] L. M. Jackman and S. Sternhell, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' Pergamon, Oxford, 1969, p. 283.
[11] B. T. Golding and D. R. Hall, *J.C.S. Chem. Comm.*, 1973, 293.
[12] R. D. G. Cooper and F. L. José, *J. Amer. Chem. Soc.*, 1970, **92**, 2575.
[13] O. K. L. Kovacs, B. Ekström, and B. Sjöberg, *Tetrahedron Letters*, 1970, 1863; S. Wolfe, W. S. Lee, and R. Misra, *Chem. Comm.*, 1970, 1067; J. R. Jackson and R. J. Stoodley, *ibid.*, p. 14; *J.C.S. Perkin I*, 1972, 1063; B. G. Ramsay and R. J. Stoodley, *Chem. Comm.*, 1971, 450; J. P. Clayton, R. Southgate, B. G. Ramsay, and R. J. Stoodley, *J. Chem. Soc.* (*C*), 1970, 2089; A. Vlietinck, E. Roets, P. Claes, and H. Vanderhaeghe, *Tetrahedron Letters*, 1972, 285; A. Vlietinck, E. Roets, P. Claes, G. Janssen, and H. Vanderhaeghe, *J.C.S. Perkin I*, 1973, 937.

6 h. Treatment of the product with methyl iodide yielded the thiazepine (18).



SCHEME

The potassium salt (12) was converted into the methylthio-butanoate (13) by methyl iodide in *NN*-dimethylformamide. Compound (13) was also produced when the mercaptobutanoate (10) was treated with diazomethane. Oxidation of derivative (13) with *m*-chloroperbenzoic acid gave a mixture of the sulphoxides (14), which could be separated by silica-gel chromatography. When heated in boiling benzene, the oxides (14) were readily transformed into the oxazoline (1). The thermal elimination of sulphenic acids from sulphoxides bearing a hydrogen atom at the β-carbon atom is a well-established reaction.[14] Although in principle either a hydrogen atom of the *gem*-dimethyl group or that adjacent to the methoxycarbonyl group of derivatives (14) could be involved in this sigmatropic process, only the latter shift was observed. It has recently been shown that, providing there are no undue transition-state constraints, the acidity of the migrating hydrogen atom determines the reaction outcome.[15] By the aforementioned sequence the oxazoline (1) was obtained in 62% yield from potassium benzylpenicillinate (6).

Compounds (12) and (21) showed no significant antimicrobial activity.

EXPERIMENTAL

For general experimental details see Part I.[16] Mercury was determined gravimetrically as mercury(II) sulphide.[17]

Methyl (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* (10).—Hydrogen sulphide was passed through a suspension of the mercury salt (9) [6] (18·0 g, 0·21 mol) in dichloromethane (50 ml) and the filtered solution was treated with diazomethane in ether until the yellow colour persisted. Evaporation left the *mercaptobutanoate* (10) (6·60 g, 90%), m.p. 115—117° (from $CHCl_3$–Et_2O), $[\alpha]_D$ +23° (0·12% in $CHCl_3$), $\nu_{max.}$ (KBr) 2540 (SH), 1765 (β-lactam C=O), 1730 (ester C=O), and 1645 cm^{-1} (C=N), τ ($CDCl_3$) 8·84 and 8·68 (each 3H, s, *gem*-Me_2), 8·1br (1H, s, SH), 6·30 (2H, s, CH_2·CO), 6·27 (3H, s, MeO_2C), 5·60 (1H, s, 2-H), 4·8br and 3·75 (each 1H, d, *J* 3·5 Hz, β-lactam H), and 2·72 (5H, m, aromatic H) (addition of D_2O caused the signal at τ 8·1 to disappear) (Found: C, 58·6; H, 5·8; N, 8·1%; M^+, 348·1136. $C_{17}H_{20}N_2O_4S$ requires C, 58·6; H, 5·6; N, 8·3%; *M*, 348·1144).

Dimethyl 3,3′-*Mercurio*(II)*dithiobis*-[(2S)-2-{(1S,5R)-3-*benzyl*-7-*oxo*-4-*oxa*-2,6-*diazabicyclo*[3.2.0]*hept*-2-*en*-6-*yl*}-3-*methylbutanoate*] (15).—Mercury(II) acetate (0·143 g, 0·45 mmol) was added to a solution of the thiol (10) (0·313 g, 0·90 mmol) in dichloromethane (5 ml). After 15 min the mixture was diluted with dichloromethane and washed with water. Evaporation of the dried ($MgSO_4$) organic layer left the *mercury*(II) *bis*(*sulphide*) (15) (0·400 g, 99%), m.p. 104—106°, $[\alpha]_D$ +38° (1·0% in $CHCl_3$), $\nu_{max.}$ (KBr) 1780 (β-lactam C=O), 1735 (ester C=O), and 1645 cm^{-1} (C=N), τ ($CDCl_3$) 8·63 and 8·50 (each 6H, s, 2 *gem*-Me_2), 6·30 (10H, s, 2 MeO and 2 CH_2·CO), 5·37 (2H, s, 2 × 2-H), 4·89 and 3·83 (each 2H, d, *J* 4 Hz, 2 β-lactam H), and 2·76 (10H, s, aromatic H) (Found: C, 45·2; H, 4·2; Hg, 21·2; N, 6·0. $C_{34}H_{38}HgN_4O_8S_2$ requires C, 45·5; H, 4·3; Hg, 22·4; N, 6·3%).

Reaction of the Mercury(II) *Bis*(*sulphide*) (15) *with Hydrogen Sulphide*.—A suspension of the mercury(II) bis(sulphide) (15) (0·150 g, 0·17 mmol) in dichloromethane (3 ml) was treated with hydrogen sulphide. Evaporation of the filtered solution left a residue (0·100 g, 96%) which was identical (t.l.c. and n.m.r. spectroscopy) with the thiol (10).

Reaction of the Mercury(II) *Bis*(*sulphide*) (15) *with Mercury*(II) *Acetate*.—A solution of the mercury(II) bis(sulphide) (15) (0·672 g, 0·75 mmol) in dichloromethane (10 ml) was treated with mercury(II) acetate (0·476 g, 1·5 mmol) for 18 h. The filtered solution was then treated with hydrogen sulphide and refiltered. After washing with water and drying ($MgSO_4$), the filtrate was evaporated to give a solid (0·350 g, 74%), m.p. 120—122° (from $CHCl_3$–Et_2O), identical (t.l.c. and n.m.r. spectroscopy) with the oxazoline (1).[3]

Reaction of the Thiol (10) *with Sodium Methoxide*.—A solution of the thiol (10) (0·140 g, 0·4 mmol) in methanol (5 ml) was treated with 0·1M-sodium methoxide (2·0 ml, 0·2 mmol) for 4 h. The solution was then diluted with chloroform, washed with water, and dried ($MgSO_4$). Evaporation gave a syrup which was fractionated by silica-gel chromatography ($CHCl_3$ as eluant) to give material (0·08 g, 63%) identical (t.l.c., i.r. and n.m.r. spectroscopy) with the oxazoline (1).[3]

(2S)-2-{(1S,5R)-3-*Benzyl*-7-*oxo*-4-*oxa*-2,6-*diazabicyclo*-[3.2.0]*hept*-2-*en*-6-*yl*}-3-*mercapto*-3-*methylbutanoic Acid* (11).—(*a*) Hydrogen sulphide was passed through a suspension of the salt (9) (4·25 g, 5·0 mmol) in deuteriochloroform (4 ml). The n.m.r. spectrum of the filtered solution showed signals at τ 8·87 and 8·67 (each 3H, s, *gem*-Me_2), 6·3br (2H,

[14] C. A. Kingsbury and D. J. Cram, *J. Amer. Chem. Soc.*, 1960, **82**, 1810.

[15] A. G. W. Baxter, J. Kitchin, R. J. Stoodley, and R. B. Wilkins, *J.C.S. Chem. Comm.*, 1973, 285; R. J. Stoodley and R. B. Wilkins, *J.C.S. Perkin I*, 1974, 1572.

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

[17] A. I. Vogel, 'A Textbook of Quantitative Inorganic Analysis Including Elementary Instrumental Analysis,' Longmans, London, 1962, p. 486.

s, CH_2Ph), 5·62 (1H, s, 2-H), 4·83 and 3·72 (each 1H, d, *J* 3·5 Hz, β-lactam H), and 2·78 (5H, s, aromatic H) for the acid (11) and signals at τ 7·94 and 0·54 for acetic acid. After 24 h the signals for the acid (11) were no longer detectable.

(*b*) Hydrogen sulphide was passed through a suspension of the salt (9) (18·0 g, 21 mmol) in dichloromethane (50 ml). The solution was filtered and treated with 3M-potassium 2-ethylhexanoate in butan-1-ol (25 ml, 75 mmol). Addition of ether induced the crystallisation of *potassium* (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* (12) (5·0 g, 50%), $[\alpha]_D$ −11° (0·7% in EtOH), $\nu_{max.}$ (KBr) 2540 (SH), 1755 (β-lactam C=O), 1645 (C=N), and 1605 cm^{-1} (CO_2^-), τ [$(CD_3)_2SO$] 9·01 and 8·80 (each 3H, s, *gem*-Me_2), 8·27 (3H, s, $MeCO_2K$), 6·37 (2H, s, CH_2Ph), 6·14 (1H, s, 2-H), 4·96 and 3·63 (each 1H, d, *J* 3·5 Hz, β-lactam H), and 2·78 (5H, s, aromatic H) (Found: C, 46·0; H, 4·3; N, 5·7. $C_{16}H_{17}N_2O_4S,CH_3CO_2K$ requires C, 46·0; H, 4·3; N, 6·0%).

Decomposition of the Acid (11).—Hydrogen sulphide was passed through a solution of the salt (9) (8·5 g, 10 mmol) in dichloromethane (25 ml). The filtered solution was evaporated and the residue was partitioned between chloroform and sodium hydrogen carbonate solution. The aqueous layer was acidified with dilute hydrochloric acid and extracted (twice) with chloroform. Evaporation of the dried ($MgSO_4$) organic layer left a residue which was treated with diazomethane in ether. The product was fractionated by silica-gel chromatography ($CHCl_3$ as eluant).

The first-eluted material (0·170 g, 5%), recovered as a chromatographically homogeneous syrup, was *methyl* 2-(2-*benzyloxazol*-4-*ylcarbonylamino*)-3-*mercapto*-3-*methylbutanoate* (16), $[\alpha]_D$ −8° (0·4% in $CHCl_3$), $\nu_{max.}$ (film) 3400 (NH), 1740 (ester C=O), 1675 (amide C=O), 1600, and 1505 cm^{-1} (amide II), $\lambda_{max.}$ (EtOH) 222 nm (ε 10,900), τ ($CDCl_3$) 8·58 and 8·47 (each 3H, s, *gem*-Me_2), 7·9br (1H, s, SH), 6·27 (3H, s, MeO), 5·90 (2H, s, CH_2Ph), 5·26 (1H, d, *J* 9·5 Hz, 2-H), 2·74 (5H, s, aromatic H), 2·3br (1H, d, *J* 9·5 Hz, NH), and 1·96 (1H, s, oxazole H) (addition of D_2O caused the signals at τ 7·9 and 2·3 to disappear and that at 5·26 to collapse to a singlet) (Found: M^+, 348·1120. $C_{17}H_{20}N_2O_4S$ requires *M*, 348·1144).

The second-eluted component (0·180 g, 5%), m.p. 149—150° (from MeOH), $[\alpha]_D$ −180° (0·2% in $CHCl_3$), was identical (t.l.c., n.m.r., i.r., and mass spectroscopy) with methyl (3*S*)-2,3,4,7-tetrahydro-2,2-dimethyl-6-phenylacetamido-7-oxo-1,4-thiazepine-3-carboxylate (18) prepared by the literature procedure [8] (Found: M^+, 348·1149. Calc. for $C_{17}H_{20}N_2O_4S$: *M*, 348·1144).

Evaporation of the chloroform solution left (2S,5S,6S)-2-(1-*mercapto*-1-*methylethyl*)-6-*phenylacetamido*-4-*oxa*-1-*azabicyclo*[3.2.0]*heptane*-3,7-*dione* (21), (1·15 g, 35%), m.p. 145—148° [from $CHCl_3$–light petroleum (b.p. 30—40°)], $[\alpha]_D$ −39° (0·15% in $CHCl_3$), $\nu_{max.}$ (KBr) 3430 (NH), 2580 (SH), 1785br (β-lactam and lactone C=O), 1680 (amide C=O), and 1515 cm^{-1} (amide II), τ ($CDCl_3$) 8·50 and 8·45 (each 3H, s, *gem*-Me_2), 7·95 (1H, s, SH), 6·36 (2H, s, CH_2·CO), 5·85 (1H, s, 2-H), 5·35 (1H, d, *J* 9 Hz, 6-H), 4·13 (1H, s, 5-H), 3·5br (1H, d, *J* 8 Hz, NH), and 2·60 (5H, s, aromatic H) (addition of D_2O caused the signals at τ 7·95 and 3·5 to disappear and that at 5·35 to collapse to a singlet) (Found: C, 57·4; H, 5·4; N, 8·3%; M^+, 334. $C_{16}H_{18}N_2O_4S$ requires C, 57·5; H, 5·4; N, 8·4%; *M*, 334).

(2S,5S,6S)-2-(1-*Methyl*-1-*methylthioethyl*)-6-*phenylacetamido*-4-*oxa*-1-*azabicyclo*[3.2.0]*heptane*-3,7-*dione* (22).—(*a*) A solution of the thiol (21) (0·127 g, 0·38 mmol) in *NN*-dimethylformamide (2 ml) was treated with methyl iodide (0·2 ml) for 5 h. The mixture was diluted with ether, washed with water (twice), and dried ($MgSO_4$). Evaporation left a residue which was fractionated by silica-gel chromatography ($CHCl_3$ as eluant) to give the *methylthio-derivative* (22) (0·065 g, 49%), m.p. 119—121° (from $CHCl_3$–Et_2O), $[\alpha]_D$ −104° (0·46% in $CHCl_3$), $\nu_{max.}$ (KBr) 3420 (NH), 1795br (β-lactam and lactone C=O), 1675 (amide C=O), and 1520 cm^{-1} (amide II), $\lambda_{max.}$ (EtOH) 212 nm (ε 7400), τ ($CDCl_3$) 8·56 (6H, s, *gem*-Me_2), 7·87 (3H, s, MeS), 6·40 (2H, s, CH_2Ph), 5·93 (1H, s, 2-H), 5·45 (1H, d, *J* 7·5 Hz, 6-H), 4·28 (1H, s, 5-H), 3·6br (1H, d, *J* 7·5 Hz, NH), and 2·74 (5H, s, aromatic H) (addition of D_2O caused the signal at τ 5·45 to collapse to a singlet and that at 3·6 to disappear) (Found: C, 58·7; H, 6·1; N, 8·1%; M^+, 348. $C_{17}H_{20}N_2O_4S$ requires C, 58·6; H, 5·8; N, 8·1%; *M*, 348).

(*b*) A solution of the thiol (21) (0·050 g, 0·15 mmol) in dichloromethane (2 ml) was treated with diazomethane in ether. Evaporation after 12 h and purification of the product by silica-gel chromatography ($CHCl_3$ as eluant) gave a substance (0·016 g, 30%), m.p. 119—120° (from $CHCl_3$–Et_2O), identical (t.l.c. and n.m.r. spectroscopy) with the methylthio-derivative (22).

Reaction of the Methylthio-derivative (22) *with* m-*Chloroperbenzoic Acid.*—*m*-Chloroperbenzoic acid (0·034 g, 0·2 mmol) was added to a solution of the methylthio-derivative (22) (0·070 g, 0·2 mmol) in dichloromethane (5 ml). After 20 min the solution was diluted with chloroform, washed with sodium hydrogen carbonate solution followed by water, and dried ($MgSO_4$). Evaporation gave a residue (0·06 g) which contained several components (t.l.c.), $\nu_{max.}$ (film) 3340 (NH), 1795br (β-lactam and lactone C=O), 1670br (amide C=O), and 1520br cm^{-1} (amide II). N.m.r. spectroscopy suggested that the major component was a mixture (*ca.* 1 : 1) of (2*S*,5*S*,6*S*)-2-(1-methyl-1-methylthioethyl)-6-phenylacetamido-4-oxa-1-azabicyclo[3.2.0]heptane-3,7-dione 4-oxides (23), τ ($CDCl_3$) *inter alia* 8·69 and 8·60 (each 6H, s, 2 *gem*-Me_2), 7·54 and 7·49 (each 3H, s, 2 MeS), 6·46 (4H, s, 2 CH_2·CO), 5·8br (2H, s, 2 × 2-H), 5·40 (2H, d, *J* 6·5 Hz, 2 × 6-H), 4·30 (2H, s, 2 × 5-H), and 2·81 (10H, s, aromatic H).

Conversion of the Potassium Salt (12) *into the Thiazepine* (18).—A solution of the potassium salt (12) (0·104 g, 0·28 mmol) in [$^2H_6$]dimethyl sulphoxide (0·6 ml) was monitored by n.m.r. spectroscopy. After 6 h the signals of the starting material had been replaced by those of potassium (3*S*)-2,3,4,7-tetrahydro-2,2-dimethyl-6-phenylacetamido-7-oxo-1,4-thiazepine-3-carboxylate (20), τ *inter alia* 8·6br (6H, s, *gem*-Me_2), 6·51 (2H, s, CH_2·CO), 6·3br (1H, s, 3-H), 2·7br (6H, s, aromatic H and NH), and 1·3br (1H, s, 5-H).

Methyl iodide (0·2 ml) was added to the mixture which, after 20 min, was diluted with ether. The organic layer was washed (twice) with water, dried ($MgSO_4$), and evaporated. Fractionation of the residue by silica-gel chromatography ($CHCl_3$ as eluant) gave a solid (0·045 g, 46%), m.p. 149—150° (from MeOH), identical (t.l.c., i.r. and n.m.r. spectroscopy) with the thiazepine (18).[8]

Methyl (2S)-2-{(1S,5R)-3-*Benzyl*-7-*oxo*-4-*oxa*-2,6-*diazabicyclo*[3.2.0]*hept*-2-*en*-6-*yl*}-3-*methyl*-3-*methylthiobutanoate* (13).—(*a*) Methyl iodide (1 ml) was added to a stirred solution of the potassium salt (12) (1·1 g, 2·96 mmol) in

NN-dimethylformamide (2 ml). After 20 min the mixture was diluted with ether and washed (twice) with water. Evaporation of the dried ($MgSO_4$) organic layer gave the *methylthio-butanoate* (13), m.p. 97—99° (from $CHCl_3$–light petroleum), $[\alpha]_D$ +8° (0·24% in $CHCl_3$), $\nu_{max.}$ (KBr) 1775 (β-lactam C=O), 1730 (ester C=O), and 1640 cm^{-1} (C=N), $\lambda_{max.}$ (EtOH) 209 nm (ε 12,400), τ ($CDCl_3$) 8·92 and 8·81 (each 3H, s, *gem*-Me_2), 8·03 (3H, s, MeS), 6·32 (5H, s, CH_2Ph and MeO_2C), 5·61 (1H, s, 2-H), 4·90 and 3·87 (each 1H, d, *J* 3·5 Hz, β-lactam H), and 2·77 (5H, s, aromatic H) (Found: M^+, 362·1336. $C_{18}H_{22}N_2O_4S$ requires *M*, 362·1300).

(*b*) Diazomethane in ether was added to the thiol (10) (0·104 g, 0·3 mmol). Evaporation of the solution after 18 h left a residue (0·105 g, 98%), m.p. 97—99° (from $CHCl_3$–light petroleum), identical (t.l.c., i.r. and n.m.r. spectroscopy) with the methylthio-butanoate (13).

Oxidation of the Methylthio-butanoate (13) *with* m-*Chloroperbenzoic Acid.*—*m*-Chloroperbenzoic acid (0·315 g, 1·8 mmol) was added to a solution of the methylthio-butanoate (13) (0·650 g, 1·8 mmol) in dichloromethane (10 ml). After 30 min the solution was diluted with chloroform and washed with sodium hydrogen carbonate solution followed by water. Evaporation of the dried ($MgSO_4$) organic layer gave a product which contained two components (3 : 2 by n.m.r. spectroscopy). The mixture was fractionated by silica-gel chromatography [C_6H_6–Et_2O (4 : 1) as eluant].

The first-eluted material (0·270 g, 40%) was 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-methyl-3-methylsulphinylbutanoate (14) $[\alpha]_D$ +7° (1·0% in $CHCl_3$), $\nu_{max.}$ (film) 1780 (β-lactam C=O), 1745 (ester C=O), and 1650 cm^{-1} (C=N), $\lambda_{max.}$ (EtOH) 211 nm (ε 10,000), τ ($CDCl_3$) 8·87 and 8·81 (each 3H, s, *gem*-Me_2), 7·67 (3H, s, MeSO), 6·3br (5H, s, CH_2Ph and MeO_2C), 5·50 (1H, s, 2-H), 4·84 and 3·72 (each 1H, d, *J* 3·5 Hz, β-lactam H), and 2·74 (5H, s, aromatic H). Although the sample did not show a molecular ion in the mass spectrum, it possessed a strong peak at *m/e* 314 and a metastable ion at *m/e* 260·8 (*i.e.* M^+ − MeSOH); the spectrum was significantly different from that of the oxazoline (1).

The second-eluted derivative (0·160 g, 24%) was the isomeric sulphoxide (14), $[\alpha]_D$ +18° (0·3% in $CHCl_3$), $\nu_{max.}$ (film) 1780 (β-lactam C=O), 1740 (ester C=O), and 1650 cm^{-1} (C=N), $\lambda_{max.}$ (EtOH) 212 nm (ε 10,000), τ ($CDCl_3$) 9·06 and 8·75 (each 3H, s, *gem*-Me_2), 7·70 (3H, s, MeSO), 6·33 (5H, s, CH_2Ph and MeO_2C), 5·88 (1H, s, 2-H), 4·83 and 3·82 (each 1H, d, *J* 3 Hz, β-lactam H), and 2·77 (5H, s, aromatic H). The mass spectrum was identical with that of the less polar sulphoxide.

Pyrolysis of the Sulphoxides (14).—A mixture (3 : 2) of the sulphoxides (14) (0·760 g, 2·0 mmol) was heated in boiling benzene (100 ml) for 0·5 h. Evaporation and purification of the product by silica-gel chromatography ($CHCl_3$ as eluant) gave material (0·570 g, 91%), m.p. 120—122° (from $CHCl_3$–Et_2O), identical (t.l.c., i.r. and n.m.r. spectroscopy) with the oxazoline (1).

We thank Dr. N. R. Whitehouse for preliminary experiments, the Beecham Research Laboratories for gifts of penicillins and for the antibacterial testing of compounds (12) and (21), and the S.R.C. for financial support.

[4/2178 *Received*, 22*nd October*, 1974]