Studies Related to Penicillins. Part 19.[1] Alkylations of (3*R*)-3-{(1*S*,5*R*)-3-Benzyl-7-oxo-4-oxa-2,6-diazabicyclo[3.2.0]hept-2-en-6-yl}-4,4-dimethylthietan-2-one [2]

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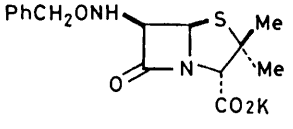
The title compound (7a) undergoes epimerisation at position 3 of the thietanone ring in the presence of triethylamine; the equilibrium ratio of the starting material and its epimer (9a) is *ca.* 1.5 : 1. Methylation of the compounds (7a) or (9a) also occurs at position 3 of the thietanone ring, in the presence of sodium hydride–methyl iodide; a *ca.* 1 : 1 mixture of the (3*R*)-3-methylthietanone (7b) and the (3*S*)-3-methylthietanone (9b) is produced when tetrahydrofuran is used as the solvent whereas a *ca.* 2.5 : 1 mixture of the compounds (7b) and (9b) is formed when *NN*-dimethylformamide is employed. With potassium t-butoxide-t-butyl bromoacetate in *NN*-dimethylformamide, the thietanone (7a) affords a *ca.* 6 : 1 mixture of the (3*R*)-3-t-butyloxycarbonylmethylthietanone (7c) and its (3*S*)-isomer (9c). Only the (3*R*)-3-allylthietanone (7d) is formed when the thietanone (7a) is treated with potassium t-butoxide–allyl iodide in *NN*-dimethylformamide.

Attempts to hydroxymethylate the thietanone (7a), by using potassium t-butoxide–formaldehyde, were thwarted by further reactions of the hydroxymethyl derivative (7e) or (9d), resulting in the formation of a mixture of 7-(α-mercapto-α-methylethyl)-3-phenylacetamido-1-aza-5,9-dioxabicyclo[5.3.0]dec-2-ene-4,8-dione (16a) and 11,11-dimethyl-5-phenylacetamido-3,9-dioxa-12-thia-7-azatricyclo[5.3.2.0^{1,7}]dodecane-4,10-dione (20).

RECENTLY it was shown that mercury(II) acetate in acetic acid converted penicillins, *e.g.* (1), into bis(mercury) salts, *e.g.* (2a), which afforded monomercury salts, *e.g.* (2b), when treated with pyridine.[3] The reactions of the derivatives (2a) or (2b) with hydrogen sulphide followed by diazomethane yielded initially the mercaptobutanoate (2c) and then the methylthiobutanoate (2d).[4]



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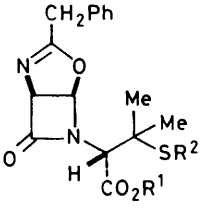

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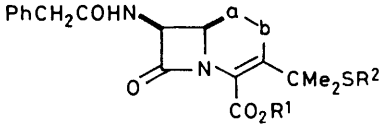


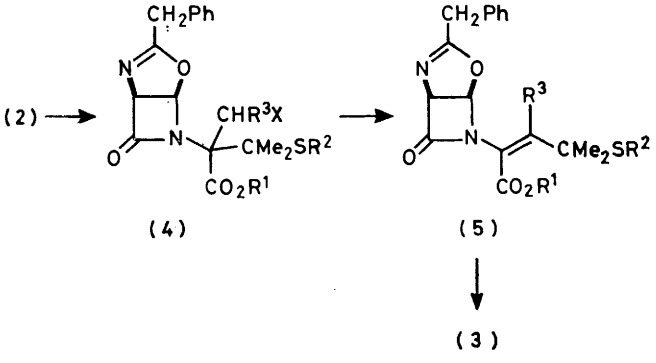
(3)

(a) $R^1 = R^2 = HgOAc$ (c) $R^1 = Me, R^2 = H$
(b) $R^1, R^2 = Hg$ (d) $R^1 = R^2 = Me$
(e) $R^1 = R^2 = H$

As part of a programme aimed at assessing the utility of oxazoline-azetidinones as precursors of β-lactam-antibiotic analogues, we have been interested in converting compounds of type (2) into cephalosporin analogues of type (3). In one approach to these target systems, which is outlined in Scheme 1, one is faced with three significant problems. First, the elaboration of the system (4; X = leaving group) requires the introduction of carbon *functionality* at position 2 of the butanoate group; β-elimination of the sulphur moiety may present a serious competing reaction. Second, the (4) ⟶ (5) transformation requires the specific migration of the methylethyl substituent and the generation of a β,β-disubstituted acrylate in which R^3 is *anti* with respect to the carboxylate moiety. Third, there is the problem of effecting the ring closure in a stereocontrolled manner.

In this paper, we address ourselves to the first objective. Although offering only a partial solution to the problem in hand, we believe that the methodology which has been developed will have a wider application.

In principle, compound (2d) possesses six sites at which alkylation may occur—the sulphur atom, position 2 of the butanoate moiety, the benzylic methylene group, the oxazoline-nitrogen atom, and the bridgehead-methine function adjacent to the β-lactam-carbonyl group.

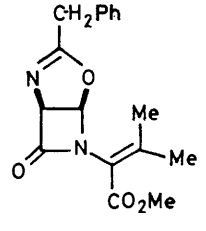


SCHEME 1

However, when treated with sodium hydride and methyl iodide in tetrahydrofuran, the methylthiobutanoate (2d) was cleanly converted into the but-2-enoate (6); evidently β-elimination of the sulphur moiety was the preferred reaction.

The hydrogen atom of the β-thiolactone ring in compound (7a) is expected to be quite acidic. Moreover,

the tendency of this derivative to undergo β-elimination is expected to be markedly reduced since the derived carbanion, *e.g.* (8), possesses a near-orthogonal arrangement of the anionic centre and the C–S bond. Consequently, compound (7a) appeared to be a promising candidate for effecting the desired alkylation. Surprisingly, although it is established that thiol esters [5] and γ-thiolactones [6] undergo alkylation adjacent to the carbonyl group, the corresponding reaction of β-thiolactones does not appear to have been reported. In addition to facilitating the alkylation reaction, it was hoped that the presence of the β-thiolactone ring would



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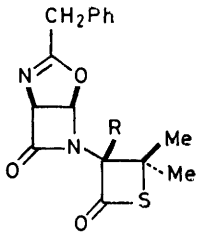

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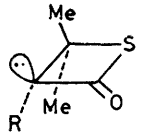


(8)

(a) R = H
(b) R = Me
(c) R = $CH_2CO_2Bu^t$
(d) R = $CH_2CH{:}CH_2$
(e) R = CH_2OH

also aid the (4) ⟶ (5) transformation. Thus the projected 1,2-shift should be promoted—by relief of ring strain—and the correct disposition of R^3 should be ensured.

It is well known that β-mercaptocarboxylic acids are converted into β-thiolactones by reaction with either dicyclohexylcarbodi-imide or triethylamine–ethyl chloroformate.[7] When treated with the former reagent, the acid (2e)—liberated *in situ* by passing hydrogen sulphide into a dichloromethane suspension of the salt (2a) or (2b)—was converted into the desired compound (7a), contaminated with some dicyclohexylurea. Although a pure product could be obtained by recrystallisation, subsequent experiments revealed that treatment of the monomercury salt (2b) with ethyl chloroformate in pyridine provided a better route to the thietanone (7a).

The acidic nature of its β-thiolactone-ring hydrogen atom was readily demonstrated by adding a drop of triethylamine to a deuteriochloroform solution of the derivative (7a); a *ca.* 1.5 : 1 mixture of the starting material and the epimer (9a) was rapidly produced. A similar mixture resulted when the pure epimer (9a) was treated under corresponding conditions, indicating that the reaction was at equilibrium.

When treated with sodium hydride and methyl iodide in tetrahydrofuran at 0 °C, the compound (7a) was converted into a *ca.* 1 : 1 mixture of two new materials which were separated by silica gel chromatography. Analytical and spectral considerations left little doubt that the products were the isomers (7b) and (9b). Tentatively, the more mobile isomer, $[\alpha]_D$ −60° ($CHCl_3$), is considered to be the derivative (7b) and the less mobile isomer, $[\alpha]_D$ +178° ($CHCl_3$), to be the derivative (9b). This stereochemical assignment is based upon the observation that compound (7a) possesses a greater chromatographic mobility than its epimer (9a) and that compound (7a) is laevorotatory {$[\alpha]_D$ −26° ($CHCl_3$)} whereas its epimer (9a) is dextrorotatory {$[\alpha]_D$ +121° ($CHCl_3$)}.

A *ca.* 1 : 1 mixture of the derivatives (7b) and *(9b) was* also produced when the compound (9a) was treated with sodium hydride and methyl iodide in tetrahydrofuran at 0 °C. This result implicates a common intermediate in the alkylation reactions and suggests that pyramidal carbanionic species, *e.g.* (8), if involved, undergo inversion more rapidly than methylation.

Solvent evidently plays an important role in determining the stereochemical outcome of the foregoing reactions. Thus when treated with sodium hydride in *NN*-dimethylformamide at 0 °C, compound (7a) was converted into a *ca.* 2.5 : 1 mixture of the derivatives (7b) and (9b).

With potassium t-butoxide and t-butyl bromoacetate in *NN*-dimethylformamide at −20 °C, compounds (7a) and (9a) afforded a *ca.* 6 : 1 mixture of the derivatives (7c) and (9c). Silica gel chromatography afforded a pure sample of the major isomer but the minor isomer could not be obtained free of impurities. On the basis of its greater chromatographic mobility and its laevorotation {$[\alpha]_D$ −60° ($CHCl_3$)}, the major isomer is considered to be the compound (7c).

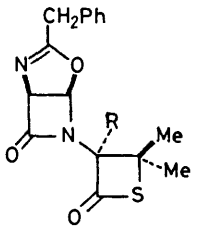
Allylation of compound (7a) was effected by using potassium t-butoxide and allyl iodide in *NN*-dimethylformamide at −20 °C. On the basis of t.l.c., the crude product appeared to be predominantly one compound; this was isolated in a pure state after silica gel chromatography. The material is considered to be the derivative (7d) since it possessed a negative optical rotation {$[\alpha]_D$ −70° ($CHCl_3$)}.

Having successfully achieved the alkylation of the β-thiolactone ring of compound (7a), attention was turned to its hydroxymethylation. In principle, the hoped-for product of this reaction, *i.e.* (7e) or (9d), should serve as a useful model compound for testing the feasibility of the planned ring expansion [to (10)].

Sequential treatment of compound (7a) in tetrahydrofuran at 0 °C with potassium t-butoxide and gaseous formaldehyde afforded two new materials, which were separated by silica gel chromatography.

The less mobile compound possessed the molecular formula $C_{18}H_{20}N_2O_5S$, on the basis of analytical evidence; evidently, it was derived by the addition of two molecules of formaldehyde to the starting molecule. That the aforementioned product incorporated the diaminoacrylate moiety (11) was strongly suggested by spectroscopic methods. Thus absorptions were present at 3 260, 1 690, 1 660, and 1 630 cm^{-1} in the i.r. region and at 286 nm (ε 11 000) in the u.v. region; the n.m.r. spectrum showed signals at δ 3.65 (2 H, s), 7.2 (6 H, s, 1 H exchanged with D_2O), and 7.91 (1 H, s). These

properties are in good agreement with those reported [8] for the diaminoacrylate moiety of compound (12) [$\nu_{max.}$ 3 320, 1 660 and 1 640 cm^{-1}; $\lambda_{max.}$ 285 nm (ε 29 850); δ 3.44 (PhCH_2·CO),* 7.32 (Ph), 8.13 (C=CH·N), and 9.22 (CO·NH·C)].



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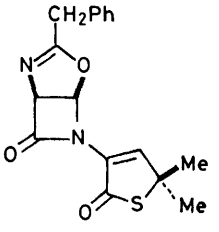
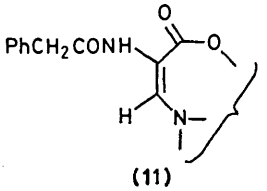


(10)

(a) R = H (c) $CH_2CO_2Bu^t$
(b) R = Me (d) R = CH_2OH



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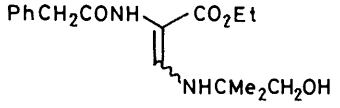

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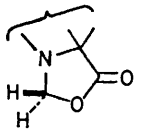

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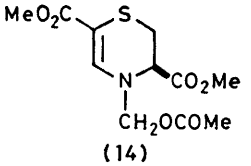

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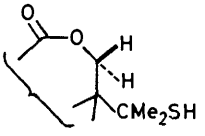

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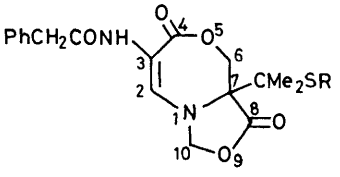
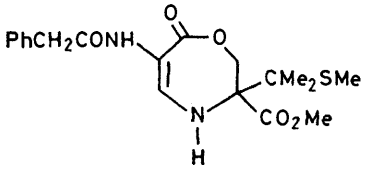


(16)
(a) R = H
(b) R = Me



(17)

The presence of the oxazolidinone moiety (13) in the product was also inferred on the basis of spectroscopic considerations. Thus the i.r. spectrum displayed an absorption at 1 780 cm^{-1}, a frequency characteristic of the oxazolidin-3-one carbonyl group.[9] The n.m.r. spectrum showed two one-proton doublets at δ 5.27 and 5.67 (J 4.4 Hz). Although the n.m.r. spectral characteristics of 2-unsubstituted N-acyloxazolidin-3-ones do not appear to have been reported, the acetoxymethylene group of compound (14) resonates [10] at δ 5.23. Furthermore, the 2-protons of 2-unsubstituted N-acyloxazolidines absorb in the δ 4.7—5.5 region and show a geminal coupling constant of 3—5 Hz.[11] The base peak in the mass spectrum at m/e 44 (CO_2^+) was also in accord with the presence of the oxazolidin-3-one ring.

The n.m.r. spectrum of the product also contained two three-proton singlets at δ 1.47 and 1.67, an exchangeable proton at δ 2.24, and an AB quartet centred at δ 4.52 (J 13 Hz). These signals were indicative of the presence of the moiety (15) in the product.

On the basis of the foregoing considerations, it is clear that the less mobile compound obtained from the reaction of formaldehyde and the thietanone (7a) is the oxazepinone-oxazolidinone (16a).

The presence of the mercapto-group in compound (16a) was confirmed by effecting its methylation with diazomethane. The n.m.r. spectrum of the product, *i.e.* (16b), was very similar to that of the precursor except that the one-proton signal at δ 2.24 was replaced by a three-proton singlet at δ 2.10.

The structure of the methylthio-derivative (16b) was also corroborated by ^{13}C n.m.r. spectroscopy. Thus by using noise- and off-resonance decoupling techniques, the compound was shown to possess three methyl groups (δ 12.7, 22.6, and 27.2), three methylene groups (δ 44.4, 67.2, and 84.9), two quaternary carbon atoms (δ 50.9 and 72.6), a phenyl group (δ 127.5, 129.0, 129.4, and 134.4), and three carbonyl groups (δ 166.4, 168.5, and 170.2); in addition, the presence of a disubstituted vinylic carbon atom (δ 101.7) and a monosubstituted vinylic carbon atom (δ 138.7) was indicated.

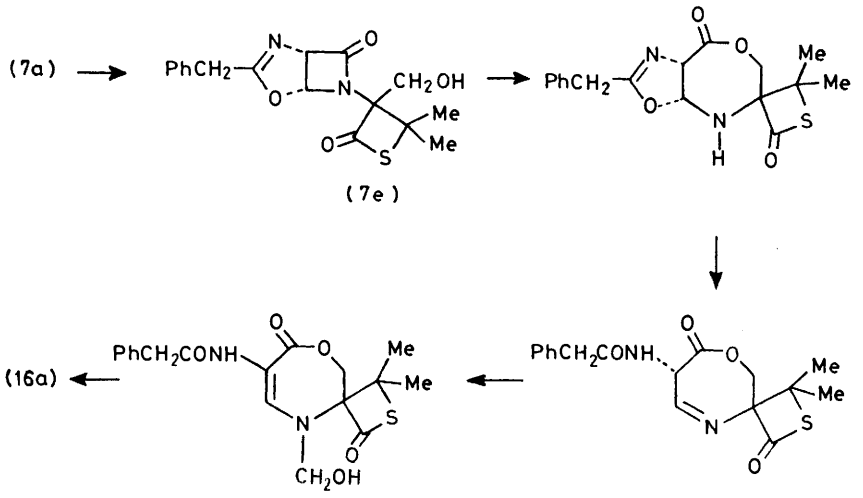
In further support of its assigned structure, compound (16b) reacted with basic methanol to give the oxazepinone (17).

A pathway which accounts for the formation of the oxazepinone-oxazolidinone (16a) is suggested in Scheme 2.

The more mobile compound obtained from the reaction of the thietanone (7a) with formaldehyde was an isomer of the oxazepinone-oxazolidinone (16a). The presence of the moiety (18) in the product was suggested on the basis of spectroscopic evidence. Thus the i.r. spectrum possessed an absorption at 1 790 cm^{-1}. Furthermore, the n.m.r. spectrum contained two three-proton singlets at δ 1.50 and 1.73 due to the isopropylidene group, a two-proton AB quartet centred at δ 4.48 (J 13 Hz) attributable to the acyloxymethylene moiety, and a pair of one-proton doublets at δ 4.78 and 5.19 (J 3.5 Hz) ascribable to the oxazolidinone-ring protons. The shielding of the last-mentioned protons compared with the corresponding protons of compound (16a) implied that the nitrogen atom of the moiety (18) was not attached to a conjugating group. Finally, the mass spectrum showed a base peak at m/e 44 (CO_2^+).

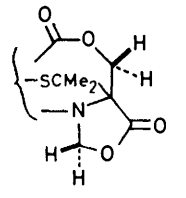
Spectroscopic considerations also indicated that the aforementioned product incorporated the moiety (19). I.r. spectroscopy revealed the presence of an amide

* This absorption was erroneously assigned to the hydroxymethylene group in the publication.



SCHEME 2

function (3 460 and 1 645 cm^{-1}) and an ester-like carbonyl group (1 740 cm^{-1}). The n.m.r. spectrum displayed singlets at δ 3.60 (2 H) find 7.30 (5 H), attributable to the benzyl group, and one-proton signals at δ 4.86 (d, *J* 2 Hz), 4.97 (dd, *J* 2 and 6 Hz), and 6.73 (d, *J* 6 Hz); after addition of deuterium oxide to the solution, the signal at δ 6.73 disappeared and that at 4.97 collapsed to a doublet (*J* 2 Hz).



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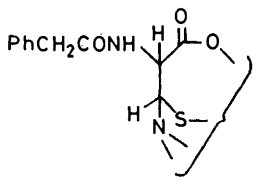

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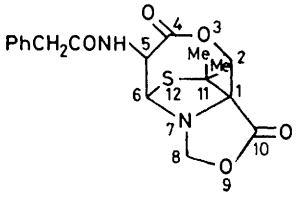

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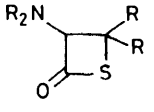

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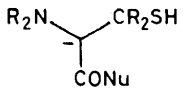

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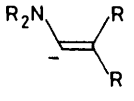

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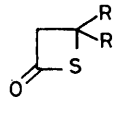

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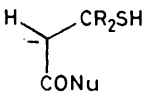

(25)

(26)

On the basis of the foregoing evidence, the more mobile compound obtained from the reaction of the thietanone (7a) and formaldehyde is considered to possess the structure (20).*

Clearly, compound (20) is derived from the oxazepinone-oxazolidinone (16a) by an intramolecular conjugate addition of the thiolate moiety to the acrylate function. The inter-relationship between the compounds (16a) and (20) was firmly established when it was shown that the former material was converted into the latter in the presence of triethylamine.

Potentially, the demonstration that position 3 of the thietan-2-one ring can be alkylated has important applications in synthesis. Thus it is well known that β-thiolactones react readily with nucleophilic reagents, always with cleavage of the S–CO bond; there are also reports of the derivatives undergoing thermal cycloreversion to alkenes and carbonyl sulphide.[7] In principle, therefore, β-thiolactones of type (21) may be regarded as equivalents of the carbanions (22) and (23); similarly, β-thiolactones of type (24) should serve as equivalents of the species (25) and (26).

EXPERIMENTAL

Prior to use, tetrahydrofuran was dried over calcium hydride and freshly distilled, potassium t-butoxide was freshly sublimed, and sodium hydride (50% oil dispersion) was washed with sodium-dried light petroleum (b.p. 40—60 °C); *NN*-dimethylformamide, after a preliminary drying by azeotropic distillation with benzene, was distilled *in vacuo* and stored over molecular sieves (BDH, Type 4A). All other solvents and chemicals were used as purchased.

Column chromatography was effected, under pressure, using Merck Kieselgel H (Typ 60). T.l.c. was performed on either Gelman Instrument Company glass-fibre sheets impregnated with polysilicic acid gel (ITLC™ SA) or Schlei-

* The presence of a weak u.v. absorption at 285 nm (ε 3 200) suggested that this compound, in dilute ethanolic solution, was in equilibrium with the oxazepinone-oxazolidinone (16a).

cher and Schüll plastic sheets coated with silica gel (F1500 LS 254); the former were developed with iodine vapour and the latter with an aqueous potassium permanganate spray.

Evaporations were carried out at *ca.* 40 °C using a Buchi rotary evaporator. Melting points were determined using a Kofler hot-stage apparatus. A Bendix-Ericson automatic polarimeter was used to measure optical rotations. I.r. spectra were measured using a Hilger and Watts Infrascan. A Unicam SP800 spectrometer was employed to determine u.v. spectra. N.m.r. spectra refer to tetramethylsilane as the internal standard; ^{1}H spectra were measured at 60 MHz using a Varian EM 360 spectrometer and ^{13}C Fourier-transform spectra were recorded at 22.6 MHz with a Brucker HX90E spectrometer. Mass spectra were determined using an A.E.I. MS9 spectrometer operating at 70 eV. Microanalyses were performed using a Hewlett Packard 185 CHN Analyser.

Reaction of the Butanoate (2d) *with Sodium Hydride–Methyl Iodide.*—Sodium hydride (0.036 g, 1.5 mmol) was added to a stirred solution of the butanoate (2d) [4] (0.181 g, 0.5 mmol) in tetrahydrofuran at 0 °C and after 0.5 min an excess of methyl iodide was added. The mixture was diluted with dichloromethane and washed with 0.1M-hydrochloric acid. Evaporation of the dried ($MgSO_4$) organic layer left a residue (0.110 g) which was identical (t.l.c. and n.m.r. spectroscopy) with the butenoate (6).[4]

Preparation of (3R)-3-{(1S,5R)-3-*Benzyl*-7-*oxo*-4-*oxa*-2,6-*diazabicyclo*[3.2.0]*hept*-2-*en*-6-*yl*}-4,4-*dimethylthietan*-2-*one* (7a).—(*a*) Potassium benzylpenicillinate (1) (14.88 g, 0.04 mol) was added in one portion to a stirred solution of mercury(II) acetate (25.48 g, 0.08 mol) in glacial acetic acid (400 cm^3). After a few min the mixture was diluted with acetone and filtered and the insoluble material was washed well with acetone followed by ether. The air-dried solid, which was the dimercury salt (2a), was suspended in dichloromethane (100 cm^3) and the mixture, after cooling to −10 °C, was saturated with hydrogen sulphide. The mixture was filtered and the filtrate was treated with dicyclohexylcarbodi-imide (4.12 g, 0.04 mol) dissolved in a small volume of dichloromethane. After 1 h the precipitated dicyclohexylurea was removed by filtration and the filtrate was washed with water, dried ($MgSO_4$), and evaporated. Methanol was added to the residue and the mixture was filtered. The dried solid (2.48 g, 20%) was predominantly (n.m.r. spectroscopy) the *thietanone* (7a). Recrystallisation of the material from chloroform–ether afforded an analytically pure sample; m.p. 129—131 °C; $[\alpha]_D$ −26° (1.05% in $CHCl_3$); $\nu_{max.}$ (KBr) 1 775 (azetidinone C=O), 1 760 (thietanone C=O), and 1 645 cm^{-1} (C=N); $\lambda_{max.}$ (EtOH) 214 nm (ε 8 700); δ($CDCl_3$) 1.21 and 1.65 (each 3 H, s, CMe_2), 3.70 (2 H, s, PhCH_2·CO), 5.20 and 5.50 (each 1 H, d, *J* 3.5 Hz, CO·CH·CH·N), 5.25 (1 H, s, CO·CH·N), and 7.30 (5 H, s, Ph); *m/e* 317 (MH^+) and 159 (base peak, $C_{10}H_9NO^+$) (Found: C, 60.4; H, 5.3; N, 8.85. $C_{16}H_{16}N_2O_3S$ requires C, 60.75; H, 5.07; N, 8.86%).

(*b*) Potassium benzylpenicillinate (1) (14.88 g, 0.04 mol) was converted, by the above-described method, into the dimercury salt (2a) which was dissolved in pyridine (150 cm^3) with vigorous stirring. Within a few minutes the monomercury salt (2b) was precipitated; this was filtered off, washed with methanol, and dried. The material was suspended in dichloromethane (100 cm^3) and the mixture was saturated with hydrogen sulphide and filtered. The filtrate was treated with dicyclohexylcarbodi-imide (4.12 g, 0.04 mol) as described in procedure (*a*). Work-up after 1 h as before yielded a material which was predominantly (n.m.r. spectroscopy) the thietanone (7a) (2.40 g, 19%).

(*c*) Potassium benzylpenicillinate (1) (14.88 g, 0.04 mol) was converted into the monomercury salt (2b) by the method described in procedure (*b*). A stirred suspension of the material in pyridine (120 cm^3) at 0 °C was treated dropwise with ethyl chloroformate (8.68 g, 0.08 mmol). After 10 min the mixture was diluted with dichloromethane and washed well with 1M-hydrochloric acid followed by water. Evaporation of the dried ($MgSO_4$) organic layer left a residue which was suspended in ether and filtered. The dried solid (3.50 g, 28%) was identical (n.m.r. spectroscopy) with the thietanone (7a).

Preparation of (3S)-3-{(1S,5R)-3-*Benzyl*-7-*oxo*-4-*oxa*-2,6-*diazabicyclo*[3.2.0]*hept*-2-*en*-6-*yl*}-4,4-*dimethylthietan*-2-*one* (9a).—A solution of the thietanone (7a) (0.512 g) in dichloromethane (10 cm^3) was treated with triethylamine (0.25 cm^3). After 30 min the mixture was washed with 1M-hydrochloric acid followed by water. Evaporation of the dried ($MgSO_4$) organic layer left a crystalline residue which was a *ca.* 1.5 : 1 mixture (n.m.r. spectroscopy) of the starting material and a new compound. The mixture was fractionated by silica gel chromatography [C_6H_6–Et_2O (9 : 1) as eluant].

The first-eluted material (0.215 g, 42%) was identical (t.l.c. and n.m.r. spectroscopy) with the starting thietanone (7a).

The second-eluted material (0.163 g, 32%) was the *thietanone* (9a); m.p. 159—162 °C (from MeOH); $[\alpha]_D$ +121° (1.5% in $CHCl_3$); $\nu_{max.}$ (KBr) 1 780 (azetidinone C=O), 1 760 (thietanone C=O), and 1 645 cm^{-1} (C=N); $\lambda_{max.}$ (EtOH) 213 nm (ε 11 300); δ($CDCl_3$) 1.38 and 1.57 (each 3 H, s, CMe_2), 3.76 (2 H, s, PhCH_2·CO), 4.88 (1 H, s, CO·C*H*·N), 5.27 and 5.82 (each 1 H, d, *J* 3.3 Hz, CO·CH·CH·N), and 7.40 (5 H, s, Ph); *m/e* 317 (MH^+) and 159 (base peak, $C_{10}H_9NO^+$) (Found: C, 60.35; H, 5.0; N, 8.9. $C_{16}H_{16}N_2O_3S$ requires C, 60.75; H, 5.07; N, 8.86%).

Equilibration of the Thietanones (7a) *and* (9a).—(*a*) A solution of the thietanone (7a) (0.050 g) in deuteriochloroform (0.5 cm^3) was treated with 1 drop of triethylamine and the reaction was monitored by n.m.r. spectroscopy. A *ca.* 1.5 : 1 mixture of the starting material and the thietanone (9a) was rapidly produced.

(*b*) The foregoing reaction was repeated using the thietanone (9a) as the starting material. A *ca.* 1 : 1.5 mixture of the derivatives (9a) and (7a) was rapidly formed.

Preparation of (3R)-3-{(1S,5R)-3-*Benzyl*-7-*oxo*-4-*oxa*-2,6-*diazabicyclo*[3.2.0]*hept*-2-*en*-6-*yl*}-3,4,4-*trimethylthietan*-2-*one* (7b) *and the* (3S)-*Isomer* (9b).—(*a*) A stirred solution of the thietanone (7a) (0.948 g, 3 mmol) in tetrahydrofuran (10 cm^3) was treated at 0 °C with sodium hydride (0.120 g, 5 mmol) followed, after 5 min, by an excess of methyl iodide. The mixture was left at 0 °C for 0.75 h, diluted with chloroform, and washed with brine. Evaporation of the dried ($MgSO_4$) organic layer left a residue which was predominantly a *ca.* 1 : 1 mixture of the thietanones (7b) and (9b) (n.m.r. spectroscopy). The mixture was fractionated by silica gel chromatography [light petroleum (b.p. 60—80 °C)–EtOAc as eluant].

The first-eluted compound (0.283 g, 29%) was the *thietanone* (7b); m.p. 113—115 °C (from Et_2O–light petroleum); $[\alpha]_D$ −60° (0.75% in $CHCl_3$); $\nu_{max.}$ (KBr) 1 775 (azetidinone C=O), 1 740 (thietanone C=O), and 1 645 cm^{-1} (C=N); $\lambda_{max.}$ (EtOH) 218 nm (ε 7 700); δ($CDCl_3$) 1.32, 1.68, and 1.75 (each 3 H, s, CMe_2 and CMe), 3.82 (2 H, s,

PhCH_2·CO), 5.19 and 6.05 (each 1 H, d, *J* 3.3 Hz, CO·CH·CH·N), and 7.45 (5 H, s, Ph); *m/e* 331 (MH^+) and 159 (base peak, $C_{10}H_9NO^+$) (Found: C, 61.8; H, 5.25; N, 8.6%; MH^+, 331.112 3. $C_{17}H_{18}N_2O_3S$ requires C, 61.80; H, 5.49; N, 8.48%; *M*H, 331.111 6).

The second-eluted compound (0.385 g, 39%) was the *thietanone* (9b); m.p. 131—132 °C (from $CHCl_3$–Et_2O); $[\alpha]_D$ +178° (0.5% in $CHCl_3$); $\nu_{max.}$ (KBr) 1 765 (azetidinone C=O), 1 745 (thietanone C=O), and 1 645 cm^{-1} (C=N); $\lambda_{max.}$ (EtOH) 217 nm (ε 7 200); δ($CDCl_3$) 1.27, 1.39, and 1.61 (each 3 H, s, CMe_2 and CMe), 3.82 (2 H, s, PhCH_2·CO), 5.20 and 5.82 (each 1 H, d, *J* 3.3 Hz, CO·CH·CH·N), and 7.45 (5 H, s, Ph); *m/e* 331 (MH^+) and 159 (base peak, $C_{10}H_9NO^+$) (Found: C, 61.5; H, 5.35; N, 8.45%; MH^+, 331.112 0. $C_{17}H_{18}N_2O_3S$ requires C, 61.80; H, 5.49; N, 8.48%; *M*H, 331.111 6).

(*b*) Sodium hydride (0.024 g, 1 mmol) was added to a stirred solution of the thietanone (7a) (0.105 g, 0.33 mmol) and methyl iodide (0.5 cm^3) in *NN*-dimethylformamide at 0 °C. After 0.5 h the mixture was diluted with chloroform and washed (×3) with water. Evaporation of the dried ($MgSO_4$) organic layer gave a residue (0.070 g) which was a *ca.* 2.5 : 1 mixture of the thietanones (7b) and (9b) (n.m.r. spectroscopy).

(*c*) Procedure (*a*) was repeated using the thietanone (9a) (0.105 g, 0.33 mmol) as the starting material. Work-up afforded a residue (0.085 g) which was a *ca.* 1 : 1 mixture of the derivatives (7b) and (9b) (n.m.r. spectroscopy).

Preparation of (3R)-3-{(1S,5R)-3-*Benzyl*-7-*oxo*-4-*oxa*-2,6-*diazabicyclo*[3.2.0]*hept*-2-*en*-6-*yl*}-3-*t*-*butyloxycarbonylmethyl*-4,4-*dimethylthietan*-2-*one* (7c) *and its* (3S)-*Isomer* (9c).—(*a*) A stirred solution of the thietanone (7a) (0.316 g, 1 mmol) in *NN*-dimethylformamide (2 cm^3) at −20 °C was treated with potassium t-butoxide (0.134 g, 1.1 mmol) followed, after 0.5 min, by an excess of t-butyl bromoacetate. After 0.75 h acetic acid was added to the mixture which was diluted with chloroform and washed (×2) with brine. Evaporation of the dried ($MgSO_4$) organic layer left a residue which was predominantly a *ca.* 6 : 1 mixture of the derivatives (7c) and (9c) (n.m.r. spectroscopy). The mixture was fractionated by silica gel chromatography [light petroleum (b.p. 40—60 °C)–EtOAc as eluant].

The first-eluted compound (0.172 g, 40%) was the *thietanone* (7c); m.p. 125—126 °C [from Et_2O–light petroleum (b.p. 40—60 °C)], $[\alpha]_D$ −60° (1.3% in $CHCl_3$); $\nu_{max.}$ (KBr) 1 765 (azetidinone C=O), 1 740 (thietanone C=O), 1 725 (ester C=O), and 1 645 cm^{-1} (C=N); $\lambda_{max.}$ (EtOH) 214 nm (ε 13 300); δ($CDCl_3$) 1.25 and 1.60 (each 3 H, s, CMe_2), 1.45 (9 H, s, CMe_3), 3.00 (2 H, ABq, *J* 15 Hz, separation of inner lines 14 Hz, C·CH_2·CO), 3.67 (2 H, s, PhCH_2·C), 5.13 and 6.00 (each 1 H, d, *J* 3.4 Hz, CO·CH·CH·N), and 7.27 (5 H, s, Ph); *m/e* 431 (MH^+) and 57 (base peak $C_4H_9^+$) (Found: C, 61.05; H, 6.1; N, 6.45. $C_{22}H_{26}N_2O_5S$ requires C, 61.40; H, 6.05; N, 6.51%).

The second-eluted compound (0.045 g) was not obtained in a pure state. However, on the basis of n.m.r. spectroscopy, it was considered to be predominantly the thietanone (9c); δ(CCl_4) *inter alia* 1.30 and 1.40 (each 3 H, s, CMe_2), 1.47 (9 H, s, CMe_3), 2.85 (2 H, ABq, *J* 15 Hz, separation of inner lines 4 Hz, C·CH_2·CO), 3.67 (2 H, s, PhCH_2·C), 5.10 and 6.15 (each 1 H, d, *J* 3.4 Hz, CO·CH·CH·N), and 7.33 (5 H, s, Ph).

(*b*) A solution of the thietanone (9a) (0.158 g, 0.5 mmol) was treated with potassium t-butoxide and t-butyl bromoacetate as described in procedure (*b*). Work-up afforded a product which was a *ca.* 6 : 1 mixture of the thietanones (7c) and (9c) (n.m.r. spectroscopy).

Preparation of (3R)-3-*Allyl*-3-{(1S,5R)-3-*benzyl*-7-*oxo*-4-*oxa*-2,6-*diazabicyclo*[3.2.0]*hept*-2-*en*-6-*yl*}-4,4-*dimethylthietan*-2-*one* (7d).—A stirred solution of the thietanone (7a) (0.316 g, 1 mmol) in *NN*-dimethylformamide (5 cm^3) at −20 °C was treated with potassium t-butoxide (0.112 g, 1 mmol) followed by allyl iodide (0.5 cm^3). After 1 h the mixture was allowed to warm to room temperature, diluted with chloroform, and washed with brine. Evaporation of the dried ($MgSO_4$) organic layer and purification of the product by silica gel chromatography (C_6H_6–Et_2O as eluant) gave the *thietanone* (7d) (0.163 g, 46%); m.p. 59 °C (from $CHCl_3$); $[\alpha]_D$ −70° (1.0% in $CHCl_3$); $\nu_{max.}$ (KBr) 1 775 (azetidinone C=O), 1 740 (thietanone C=O), and 1 650 cm^{-1} (C=N), $\lambda_{max.}$ (EtOH) 224 nm (ε 4 800); δ($CDCl_3$) 1.21 and 1.63 (each 3 H, s, CMe_2), 2.6—3.2 (2 H, m, C·CH_2·CH), 3.70 (2 H, s, PhCH_2·C), 4.92—5.15 (2 H, m, CH:C*H*H and CO·CH·C*H*·N), 5.26br (1 H, s, CH:CH*H*), 5.5—5.8 (1 H, m, CH_2·C*H*:CH_2), 5.98 (1 H, d, *J* 3.5 Hz, CO·C*H*·CH·N), and 7.27 (5 H, s, Ph) (irradiation at 2.95 caused the m at 5.5—5.8 to simplify, irradiation at 5.65 caused the m at 2.6—3.2 to simplify); *m/e* 356 (M^+) and 328 (M^+ − CO, base peak) (Found: C, 63.75; H, 5.4; N, 7.7. $C_{19}H_{20}N_2O_3S$ requires C, 64.03; H, 5.66; N, 7.86%).

Reaction of the Thietanone (7a) *with Formaldehyde.**—Potassium t-butoxide (0.056 g, 0.5 mmol) was added to a stirred solution of the thietanone (7a) (0.158 g, 0.5 mmol) in tetrahydrofuran (25 cm^3) at 0 °C. After 2 min a stream of gaseous formaldehyde [12] was passed through the solution for 5 min. The mixture was stirred at 0 °C for a further 10 min, diluted with chloroform, and washed with brine. Evaporation of the dried ($MgSO_4$) organic layer left a crude product which contained two new components (t.l.c.). The product was fractionated by silica gel chromatography (C_6H_6–Et_2O as eluant).

The first-eluted compound was 11,11-*dimethyl*-5-*phenylacetamido*-3,9-*dioxa*-12-*thia*-7-*azatricyclo*[5.3.2.$0^{1,7}$]*dodecane*-4,10-*dione* (20) (0.019 g, 10%); m.p. 78 °C (from $CHCl_3$–Et_2O); $[\alpha]_D$ −35° (1.4% in EtOH); $\nu_{max.}$ (KBr) 3 460br (N–H), 1 790 (oxazolidinone C=O), 1 740 (ester C=O), and 1 645 cm^{-1} (amide C=O); $\lambda_{max.}$ (EtOH) 211 (ε 10 000) and 285 nm (3 200); δ($CDCl_3$) 1.50 and 1.73 (each 3 H, s, CMe_2), 3.60 (2 H, s, PhCH_2·CO), 4.48 (2 H, ABq, *J* 13 Hz, separation of inner lines 16 Hz, C·CH_2·O), 4.78 and 5.19 (each 1 H, d, *J* 3.5 Hz, N·CH_2·O), 4.86 (1 H, d, *J* 2.0 Hz, CH·C*H*·S), 4.97 (1 H, dd, *J* 2.0 and 6.0 Hz, NH·C*H*·CH), 6.73br (1 H, d, *J* 6.0 Hz, CO·N*H*·CH), and 7.30 (5 H, s, Ph) [addition of D_2O caused the signal at 6.73 to disappear and that at 4.97 to collapse to a d (*J* 2.0 Hz)]; *m/e* 376 (M^+) and 44 (CO_2^+, base peak) (Found: C, 57.05; H, 5.4; N, 7.1%; M^+, 376.108 9. $C_{18}H_{20}N_2O_2S$ requires C, 57.43; H, 5.36; N, 7.44%; *M*, 376.109 3).

The second-eluted material was 7-(α-*mercapto*-α-*methylethyl*)-3-*phenylacetamido*-1-*aza*-5,9-*dioxabicyclo*[5.3.0]*dec*-2-*ene*-4,8-*dione* (16a) (0.038 g, 20%); m.p. 125—127 °C (from $CHCl_3$–Et_2O); $[\alpha]_D$ +63° (2.0% in EtOH); $\nu_{max.}$ (KBr) 3 320 (N–H), 1 780 (oxazolidinone C=O), and 1 700—1 630br cm^{-1} (thiol ester and amide C=O and C=C); $\lambda_{max.}$

* This reaction was somewhat capricious, particularly when conducted on a larger scale than that quoted. In general, compound (16a) was the major product, although, on occasions, compound (20) predominated; the total yield of the products (after isolation by silica gel chromatography) was also variable (25—50%).

(EtOH) 214 (ε 8 100) and 286 nm (11 000); δ((CDCl$_3$) 1.47 and 1.67 (each 3 H, s, CMe$_2$), 2.24 (1 H, s, SH), 3.65 (2 H, s, PhC*H*$_2$·CO), 4.52 (2 H, ABq, *J* 13 Hz, separation of inner lines 18 Hz, O·CH$_2$·C), 5.27 and 5.67 (each 1 H, d, *J* 4.4 Hz, N·CH$_2$·O), 7.2br (6 H, s, Ph and CO·N*H*·C), and 7.91 (1 H, s, N·CH:C) (addition of D$_2$O caused the signal at 2.24 to disappear and the integral for that at 7.2 to reduce to 5 H); *m/e* 332 (M^+ − CO$_2$) and 44 (CO_2^+, base peak) (Found: C 57.1; H 5.35; N, 7.3. $C_{18}H_{20}N_2O_5S$ requires C, 57.43; H, 5.36; N, 7.44%).

Reaction of the Dione (16a) *with Diazomethane.*—A sample of the crude dione (16a) (0.113 g) was treated overnight with an excess of diazomethane in ether. Evaporation and purification of the product by silica gel chromatography afforded 7-(α-*methyl*-α-*methylthioethyl*)-3-*phenylacetamido*-5,9-*dioxa*-1-*azabicyclo*[5.3.0]*dec*-2-*ene*-4,8-*dione* (16b) (0.064 g, 50%) as a chromatographically homogeneous gum; ν$_{max.}$ (film) 1 785 (oxazolidinone C=O), 1 710. 1 690, 1 675 and 1 665 (vinylogous urethane and amide C=O), and 1 630 cm^{-1} (C=C); λ$_{max.}$ (EtOH) 208 (ε 9 000) and 285 nm (6 700); δ(CDCl$_3$) 1.40 and 1.63 (each 3 H, s, CMe$_2$), 2.10 (3 H, s, SMe), 3.62 (2 H, s, PhC*H*$_2$·CO), 4.47 (2 H, ABq, *J* 14 Hz, separation of inner lines 20 Hz, O·CH$_2$·C), 5.29 and 5.75 (each 1 H, d, *J* 4.3 Hz, O·CH$_2$·N), 7.1br (1 H, s, CO·NH·C), 7.30 (5 H, s, Ph), and 8.02 (1 H, s, N·CH:C) (addition of D$_2$O caused the signal at 7.1 to disappear); δ(CDCl$_3$; proton-decoupled spectrum; multiplicity deduced from an off-resonance decoupled spectrum) 12.7 (q, SMe), 22.6 and 27.2 (each q, CMe$_2$), 44.4 (t, PhCH$_2$·CO), 50.9 (s, C·*C*·SMe), 67.2 (t, O·*C*H$_2$·C), 72.6 (s, N·*C*·CMe$_2$), 84.9 (t, N·*C*H$_2$·O), 101.7 (s, NH·*C*:CH), 127.5 (s, *para*-phenyl C), 129.0 and 129.4 (each s, *ortho*- and *meta*-phenyl C), 134.4 (s, 1-phenyl C), 138.7 (d. N·*C*H:C), and 166.4, 168.5, and 170.2 (each s, 2 O·*C*O·C and CH$_2$·*C*O·NH); *m/e* 390 (M^+) and 89 ($C_4H_9S^+$, base peak) (Found: M^+, 390.124 7. $C_{19}H_{22}N_2O_5S$ requires *M*, 390.124 9).

Reaction of the Dione (16b) *with Potassium Methoxide.*—A solution of the dione (16b) (0.130 g, 0.33 mmol) in methanol (2 cm^3) was treated with a solution of potassium t-butoxide (0.035 g) in methanol (1 cm^3). After 15 min the mixture was diluted with chloroform and washed with water. Evaporation of the dried organic layer and purification of the product by silica gel chromatography afforded *methyl* 2,3,4,7-*tetrahydro*-3-(α-*methyl*-α-*methylthioethyl*)-7-*oxo*-1,4-*oxazepine*-3-*carboxylate* (17) (0.091 g, 70%), as a chromatographically homogeneous gum; ν$_{max.}$ (film) 3 300 (N–H), 1 730 (ester C=O), 1 680 (sh) and 1 650 (vinylogous urethane and amide C=O), and 1 630 cm^{-1} (C=C); λ$_{max.}$ (EtOH) 209 (13 500) and 285 nm (15 200); δ(CDCl$_3$) 1.35 and 1.62 (each 3 H, s, CMe$_2$), 2.07 (3 H, s, SMe), 3.70 (2 H, s, PhC*H*$_2$·CO), 3.87 (3 H, s, CO$_2$Me), 4.7br (2 H, s, O·CH$_2$·C), 6.7br (1 H, d, *J* 8.5 Hz, C·N*H*·CH), 7.1br (1 H, s, CO·NH·C), 7.40 (5 H, s, Ph), and 7.83 (1 H, d, *J* 8.5 Hz, NH·C*H*:C) (irradiation at 6.7 caused the d at 7.83 to collapse to a s and *vice versa*, addition of D$_2$O caused the signals at 6.7 and 7.1 to disappear and that at 7.83 to collapse to a s); *m/e* 392 (M^+) and 89 ($C_4H_9S^+$, base peak) (Found: M^+, 392.140 7. $C_{19}H_{24}N_2O_5S$ requires *M*, 392.140 6).

Reaction of the Dione (16a) *with Triethylamine.*—A solution of the dione (16a) (0.025 g) in deuteriochloroform (0.5 cm^3) was treated with a drop of triethylamine and the reaction was monitored by n.m.r. spectroscopy. The disappearance of the thiol (16a) was accompanied by the formation of compound (20). When the reaction was complete, the mixture was diluted with chloroform and washed with dilute hydrochloric acid followed by water. Evaporation of the dried (MgSO$_4$) organic layer afforded a material which was identical (t.l.c. and n.m.r. spectroscopy) with the tricyclododecanedione (20).

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