Studies Related to Thietan-2-ones. Part 2.[1] Conversion of a Benzylpenicillin-derived Thietan-2-one into D- and L-2-Methylpenicillamines

Martine M. L. Crilley and Richard J. Stoodley*
Department of Organic Chemistry, The University, Newcastle upon Tyne NE1 7RU

(3*R*)- and (3*S*)-{(1*S*,5*R*)-3-Benzyl-7-oxo-4-oxa-2, 6-diazabicyclo[3.2.0]hept-2-en-6-yl}-3,4,4-trimethylthietan-2-ones (**8b**) and (**9b**) were isomerised to (3*R*)- and (3*S*)-3-(2-benzyloxazol-5-ylcarbonyl)amino-3,4,4-trimethylthietan-2-ones (**10**) and (**14**) by *m*-chlorobenzoic acid in methanol. Attempts to cleave the amide linkage of compound (**10**), by the action of phosphorus(v) chloride–methanol, were unrewarding.

In dichloromethane containing boron trifluoride, compound (**8b**) was converted into (3*R*)-3-(2-benzyl-5-oxo-2-oxazolin-4-ylidene)amino-3,4,4-trimethylthietan-2-one (**16**). Ozonolysis of the last-mentioned compound in dichloromethane at −78 °C and addition of ethanol yielded (3*R*)-3-(formyl)amino-3,4,4-trimethylthietan-2-one (**17**) and *N*-(ethoxycarbonyl)phenylacetamide (**22a**). Removal of the formyl group from compound (**17**) was achieved by the action of phosphorus(v) trichloride oxide–methanol to give, following addition of toluene-*p*-sulphonic acid, (3*R*)-3-amino-3,4,4-trimethylthietan-2-one toluene-*p*-sulphonate (**4c**). In boiling water, the thietanone (**4c**) underwent hydrolysis to give (2*S*)-2-amino-2,3-dimethyl-3-mercaptobutanoic acid toluene-*p*-sulphonate (D-2-methylpenicillamine toluene-*p*-sulphonate) (**27b**).

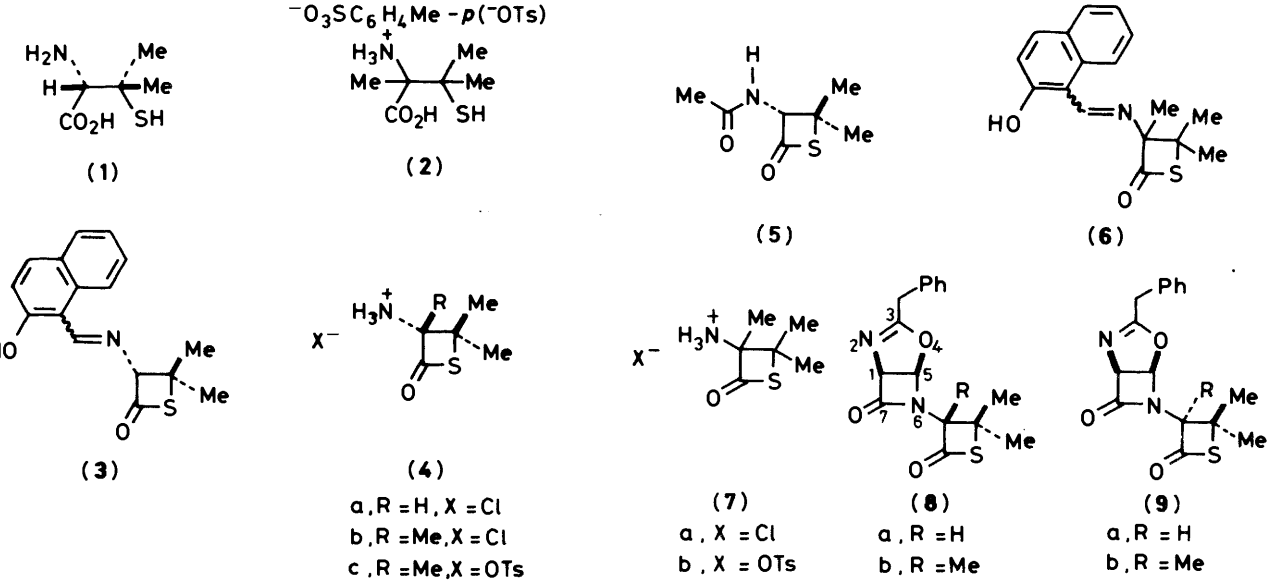
Using a similar reaction sequence, the thietanone (**9b**) was transformed into L-2-methylpenicillamine toluene-*p*-sulphonate (**28b**).

D-Penicillamine toluene-*p*-sulphonate (**27a**) underwent thiazolidine formation with formaldehyde [to give (4*S*)-5,5-dimethylthiazolidine-4-carboxylic acid toluene-*p*-sulphonate (**32a**)] more rapidly than did compound (**27b**).

(2*S*)-2-Amino-3-mercapto-3-methylbutanoic acid (D-penicillamine) (**1**) is an important chemotherapeutic agent.[2] Its powerful chelating properties form the basis of its application in the treatment of Wilson's disease (a disorder associated with ineffective excretion of copper) and of poisoning due to heavy metals such as lead and mercury. The amino acid is also of value in the long-term treatment of rheumatoid arthritis, although the mechanism whereby it exerts its beneficial effect is not understood.

As part of a programme aimed at deriving analogues of D-penicillamine and of extending the chemistry of thietan-2-ones (β-thiolactones), we recently described[1] the synthesis of (2*RS*)-2-amino-2,3-dimethyl-3-mercaptobutanoic acid toluene-*p*-sulphonate (DL-2-methylpenicillamine toluene-*p*-sulphonate) (**2**). A key intermediate in the synthesis was the Schiff base (**3**), obtained from the reaction of the salt (**4a**) with 2-hydroxy-1-naphthaldehyde and triethylamine. The salt (**4a**) was prepared from the thietanone (**5**)—itself available from the reaction of D-penicillamine (**1**) with acetic anhydride—by sequential treatment with phosphorus(v) chloride and methanol. Methylation of the imine (**3**), to give compound (**6**), was achieved by using iodomethane and sodium hydride. In the presence of dilute hydrochloric acid, the imine (**6**) was converted into the salt (**7a**) which underwent hydrolysis in boiling water to give, following addition of toluene-*p*-sulphonic acid, the salt (**2**).

Since L-penicillamine is toxic,[2] it may be important to have D-2-methylpenicillamine for biological studies. In earlier work, we showed[3] that the thietanone (**8a**) (prepared from potassium



benzylpenicillinate) underwent methylation to give a mixture of the compounds (**8b**) and (**9b**). The last-mentioned compounds appeared to be useful precursors of D- and L-2-methylpenicillamines. In this paper, we describe the attainment of these *transformations*.

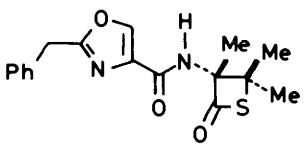
Results and Discussion

Previously, it was shown that the methylation of the thietanone (**8a**) with iodomethane was dependent upon the reaction conditions.[3] When a solution of the thietanone (**8a**) in tetrahydrofuran (THF) at 0 °C was treated with sodium hydride followed by iodomethane (method *A*), a *ca.* 1:1 mixture of the methylated derivatives (**8b**) and (**9b**) resulted; following silica-gel fractionation, the products were isolated in respective yields of 29 and 39%. A 2.5:1 mixture of compounds (**8b**) and (**9b**) was formed when a solution of the thietanone (**8b**) in *N,N*-dimethylformamide (DMF) at 0 °C was treated with iodomethane followed by sodium hydride (method *B*). In the present study, method *B* provided compounds (**8b**) and (**9b**) in isolated yields of 48 and 21% (after SiO_2 chromatography).

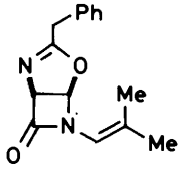
In principle, vigorous acidic hydrolysis of the thietanone (**8b**) would be expected to afford phenylacetic acid, D-2-methylpenicillamine, and either glycine and formic acid or aminoacetaldehyde and carbon dioxide. When a mixture of the thietanone (**8b**) and 6M-hydrochloric acid was heated under reflux for 15 h, a dark brown solution resulted. Extraction of the solution with chloroform and evaporation of the organic extract gave phenylacetic acid in 96% yield. The aqueous layer, which gave a strong thiol test, was expected to leave a syrupy product; on the basis of n.m.r. spectroscopy, it contained mainly a mixture of 2-methylpenicillamine and glycine hydrochlorides (ratio *ca.* 1:1) as well as unidentified materials.

Since attempts to isolate D-2-methylpenicillamine in a pure state from the aforementioned hydrolysate were unrewarding, attention was turned to the stepwise degradation of compound (**8b**). In particular, efforts were directed to the derivation of the salt (**4b**). It was hoped that, under acidic conditions, compound (**8b**) would isomerise to the oxazole (**10**), which would be convertible into the salt (**4b**) by the action of phosphorus(v) chloride and methanol.

In earlier work,[4] in which the reaction of the oxazoline (**11**) with 85% *m*-chloroperoxybenzoic acid was examined, it was shown that the oxazole (**12**) was formed when methanol was used as the solvent; subsequent studies revealed that the isomerisation was induced by *m*-chlorobenzoic acid, present in the peroxy acid. When treated with *m*-chlorobenzoic acid in methanol, the oxazoline (**8b**) was transformed into the oxazole (**10**), isolated as a syrup in 63% yield (after SiO_2 chromatography). Compound (**10**) was characterised by its spectroscopic properties. In particular, it possessed a u.v. absorption (EtOH) at 227 nm (ε 6 400); in the n.m.r. spectrum ($CDCl_3$), the oxazole hydrogen atom appeared as a sharp singlet at δ 8.08. These values are in agreement with those reported[5] for the related oxazole (**13**) [$\lambda_{max.}$(EtOH) 222 nm (ε 10 900) and δ($CDCl_3$) 8.04].



(**10**)

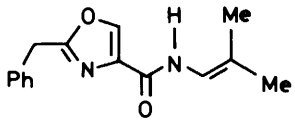


(**11**)

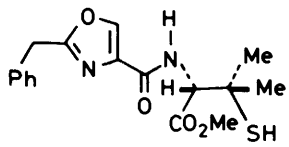
Under corresponding conditions, the oxazoline (**9b**) was converted into the oxazole (**14**), isolated as a syrup in 69% yield (after SiO_2 chromatography). The i.r. and n.m.r. spectroscopic properties of the sample were identical with those of the enantiomer (**10**); its optical rotation was equal in magnitude but opposite in sign to that of the enantiomer (**10**).

In one possible mechanism for the aforementioned isomerisations, the β-lactam nitrogen atom of the oxazoline, *e.g.* (**8b**), is protonated and a cationic intermediate, *e.g.* (**15**), is generated; a subsequent deprotonation then leads to the product *e.g.* (**10**).

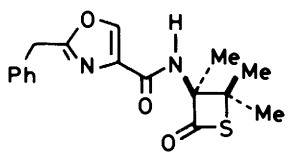
Under conditions in which the amide (**5**) reacted with phosphorus(v) chloride to give the salt (**4a**) (CH_2Cl_2 at room temperature for 5 min followed by additions of MeOH)[1] and more vigorous conditions (boiling CH_2Cl_2 or CCl_4 for 24 h followed by addition of MeOH), the oxazole (**10**) was recovered unchanged. Probably, the methyl group is mainly responsible for impeding imino-chloride formation.



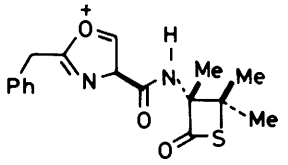
(**12**)



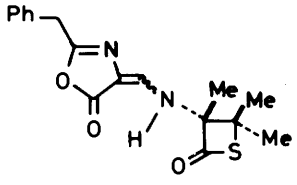
(**13**)



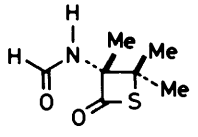
(**14**)



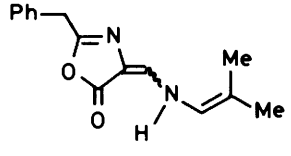
(**15**)



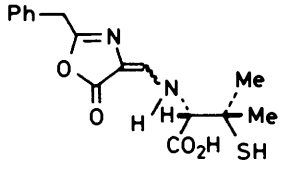
(**16**)



(**17**)



(**18**)

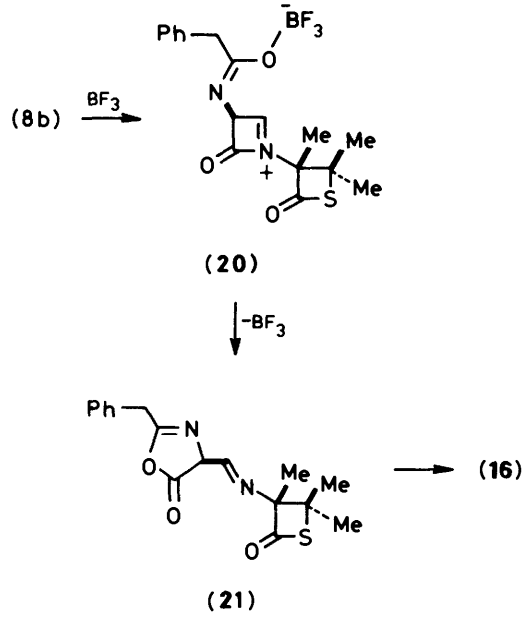


(**19**)

In principle, the oxazolinone (**16**) may be convertible into the salt (**4b**) by way of the formamide (**17**). Attempts were therefore made to isomerise the oxazoline (**8b**) to the oxazolinone (**16**), a possible precursor of the formamide (**17**).

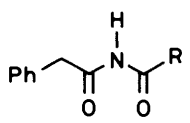
In previous work, it was reported that the oxazoline (**11**) was converted into the oxazolinone (**18**) by trifluoroacetic acid[6] or by boron trifluoride–diethyl ether.[7] In dichloromethane containing the latter reagent, the oxazoline (**8b**) was transformed into the oxazolinone (**16**), isolated as a syrup in 69% yield (after SiO_2 chromatography). The product showed strong u.v. absorption (EtOH) at 322 nm (ε 35 700), in agreement with that reported for benzylpenicillenic acid (**19**) [$\lambda_{max.}$(EtOH) 322 nm (ε 23 300)].[8]

Presumably, the aforementioned isomerisation occurs by the route outlined in Scheme 1, in which the Lewis acid induces the 4,5-bond rupture of the oxazoline (**8b**) to give the species (**20**), which affords the product (**16**) by way of the intermediate (**21**).



Scheme 1.

When a solution of the oxazolinone (**16**) in dichloromethane at −78 °C was treated with ozone followed by ethanol, two materials were isolated after silica-gel chromatography. The first-eluted material, isolated as a crystalline solid in 35% yield, was identified as the urethane (**22a**). The possible structure (**22b**) was eliminated by elemental analysis and by the presence of only two carbonyl absorptions [δ($CDCl_3$) 151.2 and 171.8] in the ^{13}C n.m.r. spectrum. The second eluted material (72% yield), which was also crystalline, was the desired formamide (**17**). Interestingly, if the ozonolysis mixture was allowed to warm to room temperature prior to the addition of ethanol, the crude product contained the formamide (**17**) but not the urethane (**22a**). Evidently, the precursor of the urethane (**22a**) is a thermally labile species.



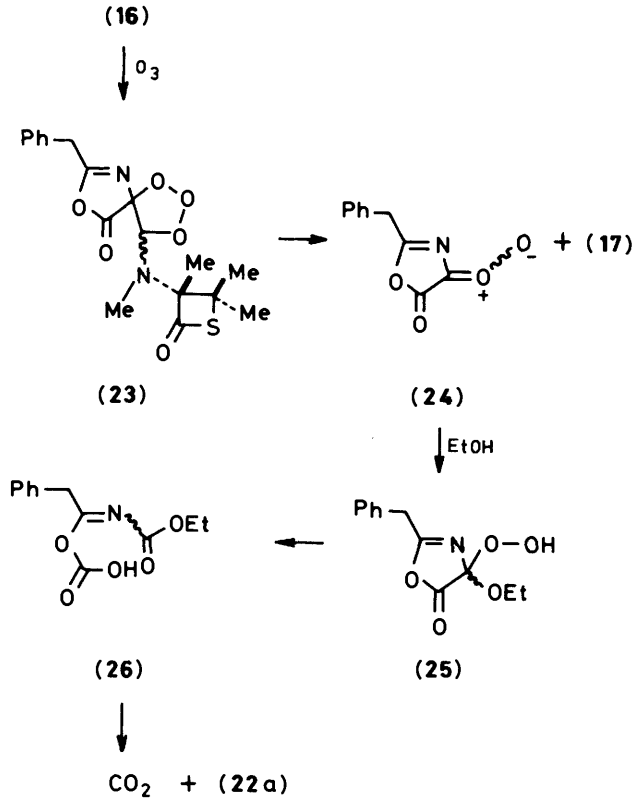
(**22**)

a, R = OEt

b, R = CO_2Et

A possible explanation for the outcome of the ozonolysis reaction is suggested in Scheme 2. Thus the primary ozonide (**23**) may decompose to the formamide (**17**) and the carbonyl oxide (**24**). At low temperatures, the last-mentioned species may be intercepted by ethanol to give the hydroperoxide (**25**) which may afford the urethane (**22a**) (and CO_2) by way of the carbonic acid (**26**).

Although attempts to convert the formamide (**17**) into the salt (**4b**) by the action of phosphorus(v) chloride in dichloromethane followed by addition of methanol were unsatisfactory, the reaction was achieved by using phosphorus(v)



Scheme 2.

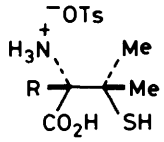
trichloride oxide in methanol.[9] Following addition of toluene-*p*-sulphonic acid and recrystallisation, the salt (**4c**) was isolated in 36% yield.

In boiling water, the salt (**4c**) underwent hydrolysis to give the penicillamine (**27b**) in 75% yield after recrystallisation. The sample, which gave a strong thiol test, possessed an n.m.r. spectrum identical with and an i.r. spectrum very similar to those of the racemate (**2**).[1] However, the material showed $[\alpha]_D$ +10° (H_2O).

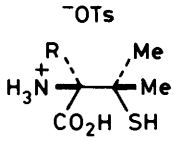
Having achieved the conversion of the thietanone (**8b**) into the salt (**27b**), it was considered appropriate to effect the corresponding transformation of the thietanone (**9b**) into the salt (**28b**).

Boron trifluoride–diethyl ether in dichloromethane effected the rearrangement of compound (**9b**) to the oxazolinone (**29**), isolated as a syrup in 76% yield (after SiO_2 chromatography). Ozonolysis of the oxazolinone (**29**) provided the crystalline formamide (**30**) (55% yield), which was transformed into the salt (**31**) (36% yield after recrystallisation) by treatment with phosphorus(v) trichloride oxide in methanol followed by toluene-*p*-sulphonic acid. The penicillamine (**28b**) (96% yield after recrystallisation) was obtained by hydrolysis of the salt (**31**). The spectroscopic properties of compounds (**29**)—(**31**) and (**28b**) were in excellent agreement with those of their enantiomers; the optical rotations were equal and opposite to those of their enantiomers.

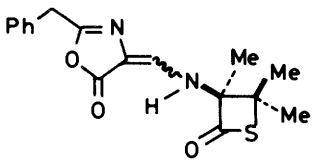
It has been suggested that D-penicillamine (**1**) exerts its beneficial effect against rheumatoid arthritis by inhibiting the cross linking of soluble collagen fibres to insoluble pre-collagens.[2] The cross linking reaction is believed to involve the formation of imine bridges between aldehyde and amino functions; possibly, the amino acid prevents this condensation by intercepting the aldehyde moieties to give thiazolidines. Earlier we speculated, on the basis of the Ingold-Thorpe effect,



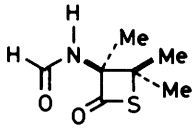
(27)
a, R = H
b, R = Me



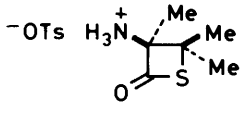
(28)
a, R = H
b, R = Me



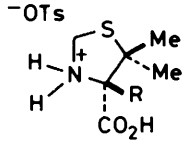
(29)



(30)



(31)



(32)
a, R = H
b, R = Me

that thiazolidine formation between an aldehyde and 2-methylpenicillamine should occur more readily than with penicillamine.[1] It was therefore hoped that 2-methylpenicillamine would act as an anti-arthritic agent.

On the basis of the foregoing considerations, it was of interest to compare the relative rates of thiazolidine formation of the salts (**27a**) and (**27b**) with an aldehyde. In preliminary experiments, it was established that the salts (**27a**) and (**27b**) reacted with formaldehyde to give the thiazolidines (**32a**)* and (**32b**). The former product was isolated in 66% yield after recrystallisation and the latter product as a gum in 98% yield. In a competition experiment, a 1:1 mixture of the salts (**27a**) and (**27b**) in deuterium oxide was treated with a deuterium oxide solution of formaldehyde. By n.m.r. spectroscopy, the salt (**27a**) was converted into the thiazolidine (**32a**) before any significant depletion of its relative (**27b**). Evidently, the salt (**27a**) is *more reactive* than its methylated counterpart (**27b**) towards formaldehyde.

The absolute stereochemistry of the salts (**27b**) and (**28b**) rests upon the assignment of the stereostructures (**8a**) and (**9b**) to their respective precursors. This assignment was based upon [3] a comparison of their optical rotations in chloroform solution {$[\alpha]_D$ −60° for (**8b**) and +178° for (**9b**)} with those of their non-methylated counterparts {$[\alpha]_D$ −26° for (**8a**) and +121° for (**9a**)}. During the course of this work, additional evidence in support of the assigned configuration has emerged. Thus the optical rotation of the presumed formamide (**17**) {$[\alpha]_D$ −197° ($CHCl_3$)} was in the same direction as that of the known acetamide (**5**)[1] {$[\alpha]_D$ −112° ($CHCl_3$)}. Similarly, the optical rotation of the presumed thiazolidine (**32b**) {$[\alpha]_D$ +60° (H_2O)} was very close to that of the thiazolidine (**32a**) {$[\alpha]_D$ +59° (H_2O)}.

* (4*S*)-5,5-Dimethylthiazolidine-4-carboxylic acid has been prepared previously.[10]

In summary, the methodology has been developed which enables the compounds (**8b**) and (**9b**) to be converted into the thietanones (**4c**) and (**31**). In addition to their intrinsic chemical interest, the thietanones (**4c**) and (**31**) serve as precursors of D- and L-2-methylpenicillamines (**27b**) and (**28b**). Clearly, the thietanone (**8a**) (which is derived from potassium benzylpenicillinate) can, in principle, be converted into a wide range of D-2-alkylpenicillamines, a hitherto unreported class of compounds of interest as potential anti-arthritic and chelating agents.

Experimental

Dry solvents, referred to in the ensuing experiments, were prepared as follows. DMF was distilled under reduced pressure from calcium hydride and stored over molecular sieves (Type 4A); dichloromethane was stored over calcium chloride flakes; methanol was treated with magnesium and iodine and distilled. Light petroleum refers to that fraction boiling in the range 40—60 °C. Sodium hydride (50% dispersion in mineral oil) was washed (3 ×) with sodium-dried light petroleum and stored *in vacuo* (over $CaCl_2$).

Ozone was generated with a Wallace and Tieman ozonator operating at 150 V and a flow rate of 50 $dm^3\ h^{-1}$. For other instrumental and for chromatographic details, see Part 1.[1]

Reaction of the Thietanone (**8a**) *with Iodomethane–Sodium Hydride.*—To a stirred solution of the thietanone (**8a**) (7.90 g, 25 mmol), iodomethane (3.9 cm^3, 62.6 mmol), and dry DMF (50 cm^3) at 0 °C was added sodium hydride (0.600 g, 25 mmol). After 0.5 h, the mixture was diluted with ethyl acetate and washed with brine (3 ×). Evaporation of the dried ($MgSO_4$) organic layer and purification of the residue by silica-gel chromatography (light petroleum–EtOAc, gradient elution) gave three fractions.

On the basis of n.m.r. spectroscopic evidence the first fraction (3.96 g, 48%), isolated as a crystalline solid, was compound (**8b**). A sample, recrystallised from chloroform–diethyl ether, showed the following properties: m.p. 114—116 °C (lit.,[3] 113—115 °C); $[\alpha]_D$ −60° (1% in $CHCl_3$) [lit.,[3] −60° ($CHCl_3$)]; δ($CDCl_3$) 1.30, 1.63, and 1.68 (each 3 H, s, CMe_2 and CMe), 3.68 (2 H, s, $PhCH_2$), 5.12 and 5.95 (each 1 H, d, *J* 3 Hz, NCHCHO), and 7.25 (5 H, s, Ph).

The second fraction (2.12 g, 26%) was a mixture of compounds (**8b**) and (**9b**).

On the basis of n.m.r. spectroscopic evidence the third fraction (1.70 g, 21%), isolated as a crystalline solid, was compound (**9b**). A sample, recrystallised from chloroform–diethyl ether, showed the following properties: m.p. 130—132 °C (lit.,[3] 131—132 °C); $[\alpha]_D$ +176° (0.6% in $CHCl_3$) [lit.,[3] +178° ($CHCl_3$)]; δ($CDCl_3$) 1.26, 1.38, and 1.60 (each 3 H, s, CMe_2, and CMe), 3.66 (2 H, s, $PhCH_2$), 5.10 and 5.70 (each 1 H, d, *J* 3 Hz, NCHCHO), and 7.30 (5 H, s, Ph).

Reaction of the Thietanone (**8b**) *with Hydrochloric Acid.*—A mixture of the thietanone (**8b**) (0.330 g, 1 mmol) and 6M-hydrochloric acid (10 cm^3) was heated under reflux for 15 h. The dark brown solution was cooled and extracted with chloroform (3 ×). Evaporation of the dried ($MgSO_4$) organic layer left a crystalline solid (0.131 g, 96%), identified as phenylacetic acid by its m.p. [77—79 °C (from MeOH–H_2O)] and n.m.r. spectrum [δ($CDCl_3$) 3.65 (2 H, s, $PhCH_2$), 7.32 (5 H, s, Ph), and 9.5br (1 H, s, OH)]. The aqueous layer, which imparted a transient blue colouration to an aqueous solution of iron(III) chloride (penicillamine reacts analogously[11]), was evaporated to leave a brown syrup (0.266 g). On the basis of n.m.r. spectroscopic evidence, the syrup was predominantly a 1:1 mixture of glycine and 2-methylpenicillamine hydrochlor-

ides; δ(D_2O) *inter alia* 1.55 and 1.65 (6 and 3 H, each s, CMe_2 and CMe), and 3.88 (2 H, s, CH_2).

Reaction of the Oxazoline (**8b**) *with* m-*Chlorobenzoic Acid.*—To a stirred solution of the oxazoline (**8b**) (0.175 g, 0.53 mmol) in methanol (5 cm^3) was added *m*-chlorobenzoic acid (0.100 g, 0.64 mmol). After 5 h, the solution was evaporated and the residue partitioned between chloroform and aqueous sodium hydrogen carbonate. Evaporation of the dried ($MgSO_4$) organic layer and purification of the residue by silica-gel chromatography [light petroleum–EtOAc (2:1) as eluant] gave (3*R*)-3-(2-benzyloxazol-5-ylcarbonyl)amino-3,4,4-trimethylthietan-2-one (**10**) (0.100 g, 63%) as a chromatographically homogeneous syrup, which showed the following properties: $[\alpha]_D$ −91° (2.9% in $CHCl_3$); $\nu_{max.}$(film) *inter alia* 3 380 (NH), 1 740 (thietanone CO), and 1 650 cm^{-1} (amide CO); $\lambda_{max.}$(EtOH) 227 nm (ε 6 400); δ($CDCl_3$) 1.75, 1.78, and 1.83 (each 3 H, s, CMe_2 and CMe), 4.07 (2 H, s, PhCH_2), 7.25 (5 H, s, Ph), 7.75br (1 H, s, CONH), and 8.08 (1 H, s, OCHC) (addition of D_2O caused the signal at 7.75 to disappear); *m/z inter alia* 330 (M^+), 302 (M^+ − CO), and 91 ($C_7H_7^+$, base peak) (Found: M^+ − CO, *m/z* 302.1100. $C_{16}H_{18}N_2OS$ requires *m/z* 302.1089).

Reaction of the Oxazoline (**9b**) *with* m-*Chlorobenzoic Acid.*—To a stirred solution of the oxazoline (**9b**) (0.330 g, 1 mmol) in methanol (5 cm^3) was added *m*-chlorobenzoic acid (0.188 g, 1.2 mmol). After 7 h, the solvent was evaporated and the residue partitioned between chloroform and aqueous sodium hydrogen carbonate. Evaporation of the dried ($MgSO_4$) organic layer and purification of the residue by silica-gel chromatography [light petroleum–EtOAc (2:1) as eluant] gave (3S)-3-(2-*benzyloxazol*-5-*ylcarbonyl*)*amino*-3,4,4-*trimethylthietan*-2-*one* (**14**) (0.229 g, 69%) as a chromatographically homogeneous oil that showed the following properties: $[\alpha]_D$ +92° (1% in $CHCl_3$) (Found: M^+, *m/z* 330.1037. $C_{17}H_{18}N_2O_3S$ requires *M*, 330.1038). The i.r., n.m.r., and mass spectra of the sample were identical with those of the enantiomer (**10**).

Reaction of the Oxazoline (**8b**) *with Boron Trifluoride.*—Boron trifluoride–diethyl ether (1.36 cm^3, 15 mmol) was added to a stirred solution of the oxazoline (**8b**) (1.98 g, 6 mmol) in dichloromethane (35 cm^3). After 12 h, the solution was washed with aqueous sodium hydrogen carbonate. Evaporation of the dried ($MgSO_4$) organic layer and purification of the product by silica-gel chromatography [light petroleum–EtOAc (3:1) as eluant] gave (3*R*)-3-(2-benzyl-5-oxo-2-oxazolin-4-ylidene)-amino-3,4,4-trimethylthietan-2-one (**16**) (1.36 g, 69%) as a chromatographically homogeneous syrup, which showed the following properties: $[\alpha]_D$ −25° (1.6% in $CHCl_3$); $\nu_{max.}$(film) *inter alia* 3 300 (NH), 1 740 (thietanone CO), and 1 660 cm^{-1} (oxazolinone CO); $\lambda_{max.}$(EtOH) 210 (ε 19 900) and 322 nm (35 700); δ($CDCl_3$) 1.65, 1.67, and 1.70 (each 3 H, s, CMe_2 and CMe), 3.80 (2 H, s, PhCH_2), and 7.30br (7 H, s, Ph and C=CHNH); *m/z inter alia* 330 (M^+), 302 (M^+ − CO), and 91 ($C_7H_7^+$, base peak) (Found: M^+ − CO, *m/z* 302.1116. $C_{16}H_{18}N_2O_2S$ requires *m/z* 302.1089).

Reaction of the Oxazolinone (**16**) *with Ozone.*—A cooled (Me_2CO–solid CO_2) solution of the oxazolinone (**16**) (1.36 g, 4.12 mmol) in dichloromethane (30 cm^3) was saturated with ozone. After flushing with oxygen, ethanol (2 cm^3) was added and the solution allowed to warm to room temperature. Evaporation and purification of the residue by silica-gel chromatography [light petroleum–EtOAc (5:1) as eluant] gave two fractions.

The first-eluted fraction (0.299 g, 35%), isolated as a crystalline solid, was (N-*ethoxycarbonyl*)*phenylacetamide* (**22a**). The sample, recrystallised from chloroform–light petroleum, possessed the following properties: m.p. 109—110 °C; $\nu_{max.}$(KBr) *inter alia* 3 420 (NH), and 1 755, and 1 685 cm^{-1} (imide CO); $\lambda_{max.}$(EtOH) 217 nm (ε 1 200); δ_H($CDCl_3$) 1.24 (3 H, t, *J* 7 Hz, CH_2Me), 3.97 (2 H, s, PhCH_2), 4.14 (2 H, q, *J* 7 Hz, OCH_2Me), 7.14 (5 H, s, Ph), and 7.53br (1 H, s, CONH) (addition of D_2O caused the signal at 7.53 to disappear); δ_C($CDCl_3$) 13.5 (CH_3), 42.1 (PhCH_2), 61.7 (OCH_2), 126.6, 128, 128.9, and 133.1 (C_6H_5), 151.2 (CONH), and 171.8 (COO); *m/z inter alia* 207 (M^+) and 117 (base peak) (Found: C, 63.5; H, 6.15; N, 6.8%; M^+, 207.0907. $C_{11}H_{13}NO_3$ requires C, 63.75; H, 6.30; N, 6.75%; *M*, 207.0895).

The second-eluted fraction (0.514 g, 72%), isolated as a crystalline solid, was (3*R*)-3-(*formyl*)*amino*-3,4,4-*trimethylthietan*-2-*one* (**17**). The sample, recrystallised from chloroform–light petroleum, showed the following properties: m.p. 94—96 °C; $[\alpha]_D$ −197° (0.8% in $CHCl_3$); $\nu_{max.}$(KBr) *inter alia* 3 320 (NH), 1 745 (thietanone CO), and 1 670 cm^{-1} (amide CO); $\lambda_{max.}$(EtOH) 215 (ε 7 200) and 235sh nm (2 500); δ($CDCl_3$) 1.75br (9 H, s, CMe_2 and CMe), 6.75 (1 H, s, CONH), and 8.07 (1 H, s, CHO) (addition of D_2O caused the signal at 6.78 to disappear); *m/z inter alia* 173 (M^+), 145 (*M* − CO), and 75 (base peak) (Found: C, 48.65; H, 6.35; N, 8.15. $C_7H_{11}NO_2S$ requires C, 48.55; H, 6.35; N, 8.10%).

Preparation of the Aminothietanone Salt (**4c**).—Phosphorus(v) trichloride oxide (0.20 cm^3, 2.15 mmol) was added to a stirred solution of the formamide (**17**) (0.169 g, 0.98 mmol) in dry methanol (3 cm^3). After 4 h, the solvent was evaporated and the residue partitioned between ethyl acetate and water. Toluene-*p*-sulphonic acid monohydrate (0.199 g, 1.05 mmol) was added to the aqueous layer which was evaporated. Recrystallisation of the residue from methanol–diethyl ether gave (3R)-3-*amino*-3,4,4-*trimethylthietan*-2-*one toluene*-p-*sulphonate* (**4c**) (0.112 g, 36%) which showed the following properties: m.p. 202—203 °C; $[\alpha]_D$ −12° (0.7% in EtOH); $\nu_{max.}$(KBr) *inter alia* 1 760 and 1 740 cm^{-1} (thietanone CO); $\lambda_{max.}$(EtOH) 221 (ε 6 500) and 240sh nm (1 550); δ(D_2O) 1.74 and 1.86 (6 and 3 H, s, CMe_2 and CMe), 2.39 (3 H, s, C_6H_4Me), and 7.27 and 7.55 (each 2 H, d, *J* 8 Hz, C_6H_4); *m/z inter alia* 172 ($C_7H_8O_3S^+$) and 117 ($C_5H_{11}NS^+$, base peak) (Found: C, 48.95; H, 5.9; N, 4.35. $C_{13}H_{19}NO_4S$ requires C, 49.20; H, 6.00; N, 4.40%). The n.m.r. spectrum of the sample was identical with that recorded for the racemate (**7b**).[1]

Hydrolysis of the Thietanone (**4c**).—A solution of the thietanone (**4c**) (0.100 g, 0.32 mmol) in water (5 cm^3) was heated under reflux for 1.5 h. Evaporation and recrystallisation of the residue from methanol–diethyl ether gave (2S)-2-*amino*-2,3-*dimethyl*-3-*mercaptobutanoic acid toluene*-p-*sulphonate* (**27b**) (0.079 g, 75%); m.p. 188—191 °C; $[\alpha]_D$ +10° (1% in H_2O); $\nu_{max.}$(KBr) *inter alia* 1 715 cm^{-1} (acid CO); $\lambda_{max.}$(EtOH) 224 nm (ε 10 050); δ(D_2O) 1.58 and 1.66 (6 H and 3 H, each s, CMe_2 and CMe), 2.43 (3 H, s, C_6H_4Me), and 7.39 and 7.73 (each 2 H, d, *J* 8 Hz, C_6H_4); *m/z inter alia* 172 ($C_7H_8O_3^+$) and 89 (base peak) (Found: C, 46.7; H, 6.2; N, 4.0. $C_{13}H_{21}NO_5S_2$ requires C, 46.55; H, 6.25; N, 4.15%). The material (which imparted a transient blue colouration to a solution of $FeCl_3$ in H_2O [11]) was identical (n.m.r. spectroscopy) with that of the racemate (**2**).[1]

Reaction of the Oxazoline (**9b**) *with Boron Trifluoride.*—Boron trifluoride–diethyl ether (0.829 cm^3, 6.74 mmol) was added to a stirred solution of the oxazoline (**9b**) (0.890 g, 2.7 mmol) in dichloromethane (15 cm^3). After 48 h, the solution was washed with aqueous sodium hydrogen carbonate. Evaporation of the dried ($MgSO_4$) organic layer and purification of the residue by silica-gel chromatography [light petroleum–EtOAc (3:1) as eluant] gave (3S)-3-(2-benzyl-5-oxo-2-oxazolin-4-ylidene)amino-3,4,4-trimethylthietan-2-one (**29**)

(0.690 g, 76%) as a chromatographically homogeneous syrup, which showed the following properties: $[\alpha]_D$ +25° (1.2% in $CHCl_3$); $\lambda_{max.}$(EtOH) 210 (ε 20 600) and 322 nm (36 000) (Found: $M^+ - CO$, m/z 302.1089. $C_{16}H_{18}N_2O_2S$ requires m/z 302.1089). The sample was shown to be identical, on the basis of its i.r., n.m.r., and mass spectra, with the oxazolinone (**16**).

Reaction of the Oxazolinone (**29**) *with Ozone.*—A cooled (Me_2CO–solid CO_2) solution of the oxazolinone (**29**) (0.690 g, 2.09 mmol) in dichloromethane (15 cm^3) was saturated with ozone. After flushing with oxygen, ethanol (2 cm^3) was added and the solution allowed to warm to room temperature. Evaporation and purification of the residue by silica-gel chromatography [light petroleum–EtOAc (5:1) as eluant] gave two fractions.

On the basis of n.m.r. spectroscopic evidence the first-eluted fraction (0.169 g, 39%) was shown to be the phenylacetamide (**22a**).

The second-eluted fraction was (3S)-3-(*formyl*)*amino*-3,4,4-*trimethylthietan*-2-*one* (**30**). The sample (0.199 g, 55%), obtained after recrystallisation from chloroform–light petroleum, showed the following properties: m.p. 85—88 °C; $[\alpha]_D$ +197° (0.6% in $CHCl_3$); $\lambda_{max.}$(EtOH) 215 (ε 5 700) and 236sh nm (2 200) (Found: C, 48.5; H, 6.25; N, 8.0%; M^+, 173.0523. $C_7H_{11}NO_2S$ requires C, 48.55; H, 6.35; N, 8.10%; M, 273.1510). The compound was identical (i.r. and n.m.r. spectroscopy) with the thietanone (**17**).

Preparation of the Aminothietanone Salt (**31**).—Phosphorus(v) trichloride oxide (0.19 cm^3, 2.04 mmol) was added to a stirred solution of the formamide (**30**) (0.168 g, 0.97 mmol) in dry methanol (5 cm^3). After 4 h, the solvent was evaporated and the residue partitioned between chloroform and water. Toluene-*p*-sulphonic acid monohydrate (0.190 g, 1 mmol) was added to the aqueous layer which was evaporated. Recrystallisation of the residue from methanol–diethyl ether gave (3S)-3-*amino*-3,4,4-*trimethylthietan*-2-*one toluene*-p-*sulphonate* (**31**) (0.100 g, 36%), which showed the following properties: m.p. 200—201 °C (decomp.); $[\alpha]_D$ +12° (0.8% in EtOH); $\lambda_{max.}$(EtOH) 224 (ε 8 400) and 236 nm (1 800) (Found: C, 48.9; H, 6.0; N, 4.4. $C_{13}H_{19}NO_4S_2$ requires C, 49.20; H, 6.0; N, 4.40%). The material was identical (i.r. and n.m.r. spectroscopy) with the thietanone (**4c**).

Hydrolysis of the Thietanone (**31**).—A solution of the thietanone (**31**) (0.065 g, 0.21 mmol) in water (2 cm^3) was heated under reflux for 1 h. Evaporation and recrystallisation of the residue from methanol–diethyl ether gave (2R)-2-*amino*-2,3-*dimethyl*-3-*mercaptobutanoic acid toluene*-p-*sulphonate* (**28b**) (0.066 g, 96%), which showed the following properties: m.p. 182—183 °C; $[\alpha]_D$ −10° (1% in H_2O); $\lambda_{max.}$(EtOH) 223 nm (ε 7 100) (Found: C, 46.35; H, 6.2; N, 4.1. $C_{13}H_{21}NO_5S_2$ requires C, 46.55; H, 6.25; N, 4.15%). The material (which imparted a transient blue colouration to a solution of $FeCl_3$ in H_2O) was identical (i.r. and n.m.r. spectroscopy) with the salt (**27b**).

Reaction of the Salts (**27a**) *and* (**27b**) *with Formaldehyde.*—(*a*) To a solution of the salt (**27a**) (0.321 g, 1 mmol) in water (5 cm^3) was added 37% aqueous formaldehyde (0.8 cm^3). Evaporation after 1 h, addition of methanol, filtration, and evaporation of the filtrate gave (4S)-5,5-*dimethylthiazolidine*-4-*carboxylic acid toluene*-p-*sulphonate* (**32a**). The sample (0.221 g, 66%), recrystallised from methanol–diethyl ether, showed the following properties: m.p. 197—199 °C; $[\alpha]_D$ +59° (0.9% in H_2O); $\nu_{max.}$(KBr) *inter alia* 1 745 cm^{-1} (acid CO); $\lambda_{max.}$(EtOH) 223 (ε 8 800), 227sh (7 300), 255 (370), 261 (370), and 268 nm (250); δ(D_2O) 1.45 and 1.65 (each 3 H, s, CMe_2), 2.35 (3 H, s, MeC_6H_4), 4.20 (1 H, s, 4-H), 4.45 (2 H, s, 2-H_2), and 7.30 and 7.60 (each 2 H, d, J 8 Hz, C_6H_4) (Found: C, 46.8; H, 5.7; N, 4.15. $C_{13}H_{19}NO_5S_2$ requires C, 46.85; H, 5.70; N, 4.20%).

(*b*) To a solution of the salt (**27b**) (0.080 g, 0.24 mmol) in water (1 cm^3) was added 37% aqueous formaldehyde (0.2 cm^3). Evaporation after 12 h (with re-evaporations and additions of C_6H_6 and CCl_4) gave (4*S*)-4,5,5-trimethylthiazolidine-4-carboxylic acid toluene-*p*-sulphonate (**32b**) (0.081 g, 98%) as a gum which showed the following properties: $[\alpha]_D$ +60° (2% in H_2O); $\nu_{max.}$(film) *inter alia* 1 735 cm^{-1} (acid CO); $\lambda_{max.}$(EtOH) 226 (ε 4 400), 256 (380), 261 (380), and 268 nm (270); δ(D_2O) 1.46, 1.51, and 1.68 (each 3 H, s, CMe_2 and CMe), 2.34 (3 H, s, MeC_6H_4), 4.38 and 4.44 (each 1 H, d, J 10 Hz, 2-H_2), and 7.24 and 7.58 (each 2 H, d, J 8 Hz, C_6H_4).

(*c*) To a solution of the salts (**27a**) (0.032 g, 0.1 mmol) and (**27b**) (0.034 g, 0.1 mmol) in deuterium oxide (0.5 cm^3) was added 1 drop of solution of formaldehyde in deuterium oxide [prepared by passing gaseous formaldehyde[12] into D_2O]. The reaction was monitored by n.m.r. spectroscopy and, within 1 h, the salt (**27a**) had disappeared, the thiazolidine (**32a**) had appeared, and the salt (**27b**) was still present.

Acknowledgements

We thank the S.E.R.C. for a CASE studentship (with Glaxo Group Research Ltd. to M. M. L. C.). We are also grateful to Drs. J. Elks, G. H. Phillips, and S. M. Roberts for their interest, Dr. M. N. S. Hill for recording the ^{13}C n.m.r. spectrum, Messrs. P. Kelly and S. Addison for measuring the mass spectra, and Mr. D. Dunbar for determining the i.r. spectra and microanalyses.

References

1 Part 1, S. M. R. Al-Zaidi, M. M. L. Crilley, and R. J. Stoodley, *J. Chem. Soc., Perkin Trans 1*, 1983, 2259.
2 W. M. Weigert, H. Offermanns, and P. Scherberich, *Angew. Chem., Int. Ed. Engl.*, 1975, **14**, 330.
3 S. D. Carter and R. J. Stoodley, *J. Chem. Soc., Chem. Commun.*, 1977, 92; S. D. Carter, A. C. Kaura, and R. J. Stoodley, *J. Chem. Soc., Perkin Trans. 1*, 1980, 388.
4 D. F. Corbett and R. J. Stoodley, unpublished work.
5 R. J. Stoodley and N. S. Watson, *J. Chem. Soc., Perkin Trans. 1*, 1975, 883.
6 D. F. Corbett and R. J. Stoodley, *J. Chem. Soc., Perkin Trans. 1*, 1974, 185.
7 D. F. Corbett and R. J. Stoodley, *J. Chem. Soc., Perkin Trans. 1*, 1975, 432.
8 E. S. Wagner, W. W. Davis, and M. Gorman, *J. Med Chem.*, 1969, **12**, 483.
9 B. R. Cowley, D. C. Humber, B. Loundon, A. G. Long, and A. L. Lynd, *Tetrahedron*, 1983, **39**, 461.
10 'The Chemistry of Penicillin,' eds. H. T. Clarke, J. R. Johnson, and R. Robinson, Princeton University Press, N. J., 1949, p. 958.
11 Ref. 10, p. 26.
12 G. Stork and J. d'Angelo, *J. Am. Chem. Soc.*, 1974, **96**, 7114.

Received 30*th September* 1983; *Paper* 3/1721