Studies Related to Thietan-2-ones. Part 1. Conversion of D-Penicillamine into DL-2-Methylpenicillamine using Thietan-2-one-based Chemistry

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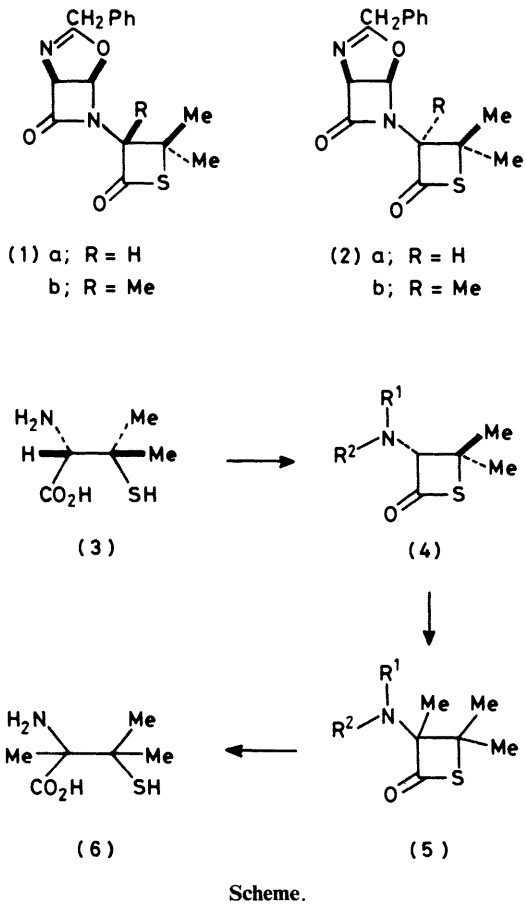
A series of *N*-substituted derivatives of (3*R*)-3-amino-4,4-dimethylthietan-2-one has been prepared from D-penicillamine (3). Attempts to effect the methylation at position 3 of the *N*-acetyl (7a), *N*,*N*-diacetyl (12), *N*-benzyloxycarbonyl (7b), or *N*-(*p*-nitrobenzylidene) derivative (15a) were unrewarding. Although the *N*-benzylidene and *N*-furfurylidene derivatives (15b) and (15c) were successfully methylated at position 3 by using iodomethane and potassium t-butoxide in tetrahydrofuran (THF), best results were achieved by treating the *N*-(2-hydroxy-1-naphthylmethylene) derivative (15d) with iodomethane and sodium hydride in *N*,*N*-dimethylformamide.

Cleavage of the imine linkage of the methylated derivatives of the thietanones (15c) and (15d), *i.e.* compounds (19b) and (19c), was effected by using, respectively, toluene-*p*-sulphonic acid in THF and dilute hydrochloric acid in acetone. The derived salts of (3*RS*)-3-amino-3,4,4-trimethylthietan-2-one, *i.e.* (21a) and (21b), underwent hydrolysis in boiling water to give the corresponding salts of DL-2-methylpenicillamine, *i.e.* (22a) and (22b).

As part of a programme aimed at extending the role of small-ring heterocycles in organic synthesis, we have developed an interest in the chemistry of thietan-2-ones (β-thiolactones). The ability of such heterocycles to participate in C–C bond-forming reactions was unknown until recently, when we showed that compounds (1a) and (2a) (which were equilibrated in the presence of triethylamine) underwent alkylations at position 3 of the thietanone ring.[1] For example, a 1 : 1 mixture of the derivatives (1b) and (2b) was produced when the thietanone (1a) or (1b) was treated in tetrahydrofuran (THF) with iodomethane and sodium hydride.

(*S*)-2-Amino-3-mercapto-3-methylbutanoic acid (D-penicillamine) (3) is an important chemotherapeutic agent.[2] Originally employed to promote the renal excretion of copper, the amino acid has subsequently been used to combat heavy-metal poisoning due to lead and mercury. The effectiveness of compound (3) in the above-mentioned contexts is associated with its powerful chelating properties. Recent interest in D-penicillamine has centred upon its value in the long-term treatment of rheumatoid arthritis. The mechanism whereby the amino acid exerts its beneficial effect is not understood. However, one hypothesis is that D-penicillamine inhibits the cross-linking of soluble collagen fibres to form insoluble precollagens. The cross-linking reaction is believed to involve the formation of imine bridges between aldehyde and amino functions; possibly, the amino acid prevents this reaction by reacting with the aldehyde moieties to give thiazolidines.[2]

On the basis of the Ingold–Thorpe effect,[3] it may be expected that thiazolidine formation between an aldehyde and 2-amino-3-mercapto-2,3-dimethylbutanoic acid (2-methylpenicillamine) (6) should occur more readily than with penicillamine. Accordingly, D-2-methylpenicillamine would be worth examining as an anti-arthritic agent. In this paper we describe the conversion of D-penicillamine (3) into DL-2-methylpenicillamine (6) using thietanone-based chemistry.

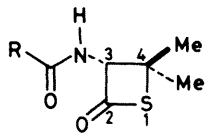


Scheme.

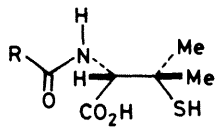
Results and Discussion

Our basic strategy for effecting the conversion of D-penicillamine (3) into DL-2-methylpenicillamine (6) is summarised in the Scheme. It was envisaged that the mercapto and carboxy groups of the product (6) would be produced by acidic hydrolysis of the thietanone ring of a precursor of type (5). Accordingly, an acid-labile amino-protecting group was required since, in principle, it would be removable in tandem with the hydrolytic ring opening. Clearly, in addition to permitting the formation of a thietanone precursor of type (4), the amino-protecting group had to be compatible with the methylation reaction.

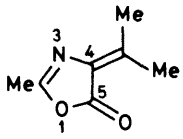
The thietanone (7a) was selected for an initial study. The compound had previously been described in racemic form by



(7) a; R = Me
b; R = $PhCH_2O$



(8) a; R = Me
b; R = $PhCH_2O$



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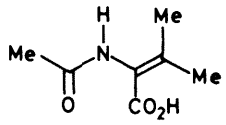

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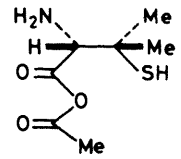

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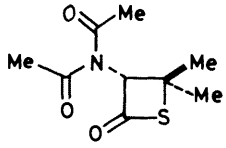
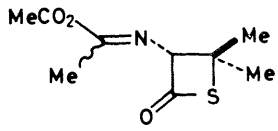
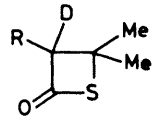


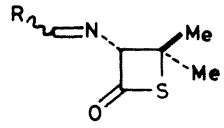
(12)



(13)



(14) a; R = Ac_2N
b; R = $PhCH_2OC(=O)NH$



(15) a; R = p-$NO_2C_6H_4$
b; R = Ph
c; R = 2-furyl
d; R = 2-hydroxy-1-naphthyl

Knunyants *et al.*,[4] who prepared it from the racemate of the penicillamine derivative (8a) by the action of triethylamine and isobutyl chloroformate.

When a solution of D-penicillamine (3) in pyridine at 0 °C was treated with acetic anhydride (3 mol equiv.), two neutral products were obtained. Initially, the compounds were separated by silica-gel chromatography. The more mobile product, isolated as a waxy solid in 22% yield, was considered to be the oxazol-5(4*H*)-one (9) (a compound first prepared during the collaborative penicillin programme[5]) on the basis of its spectroscopic properties. The less mobile material, obtained as needle-like crystals in 23% yield, was characterised as the thietanone (7a) by its analytical and spectroscopic properties. Subsequently, it was found that the latter compound was readily isolated by the addition of light petroleum to the crude neutral product. Following filtration and recrystallisation, the material was obtained in 31% yield.

The structures of the thietanone (7a) and the oxazolone (9) were substantiated by hydrolysis. Thus the former compound was converted into *N*-acetyl-D-penicillamine (8a)[6] when heated in dilute hydrochloric acid; the optical rotation of the hydrolysis product{$[\alpha]_D$ +18° (water–EtOH)} was identical with that recorded in the literature for compound (8a), suggesting that the thietanone (7a) was enantiomerically pure. *N*-Acetyldehydrovaline (10)[7] was isolated when the oxazolone (9) was heated in water.

Since the thietanone (7a) was not converted into the oxazolone (9) in the presence of pyridine and acetic anhydride, it seems likely that the anhydride (11) serves as a common precursor of the products (7a) and (9).

An attempt to effect the methylation of the thietanone (7a) at position 3, using iodomethane and sodium hydride in *N*,*N*-dimethylformamide (DMF), resulted in the isolation of the oxazolone (9) (77% yield after SiO_2 chromatography); evidently, the amide anion had been generated and its carbonyl group had attacked the thietanone linkage.

To avoid the aforementioned intramolecular reaction, attempts were made to protect the NH group of the secondary amide function. It has been reported[8] that isopropenyl acetate is a useful agent for effecting the *N*-acetylation of secondary amides. When heated in toluene containing isopropenyl acetate and a trace of toluene-*p*-sulphonic acid, the thietanone (7a) was converted into a crystalline acetylated material in 65% yield (after SiO_2 chromatography). That the product was the *N*-acetyl derivative (12), rather than the *O*-acetyl derivative (13), was suggested by ^1H n.m.r. spectroscopy, which showed the acetyl methyl-groups as a singlet at δ 2.45. The presence of two signals in the ^{13}C n.m.r. spectrum, at δ 172 and 187 p.p.m. (attributed to the amide- and thietanone-carbonyl groups, respectively), corroborated the former structure.

Although attempts to effect the methylation of the thietanone (12) were unrewarding, the acidic nature of its 3-hydrogen atom was readily demonstrated by a deuterium-exchange experiment. Thus, when treated with triethylamine in chloroform containing deuterium oxide, the thietanone (12) was converted (with racemisation) into the deuteriated derivative (14a).

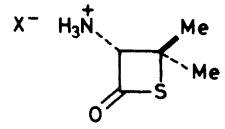
The thietanone (7b), a compound described in racemic form by Sheehan[9] and Field,[10] is less likely to undergo oxazol-5-(4*H*)-one formation than its relative (7a). Accordingly, an examination of its reactivity under methylation conditions was undertaken.

Sequential treatment of D-penicillamine (3) with benzyl chloroformate–sodium hydroxide and dicyclohexylcarbodiimide (DCC) gave, following silica-gel chromatography, the crystalline thietanone (7b) in 40% yield. It is noteworthy that Field and his co-workers[10] reported unsuccessful attempts to prepare the thietanone (7b) from *N*-benzyloxycarbonyl-D-penicillamine (8b).

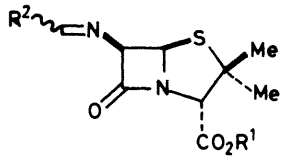
A complex mixture of products resulted when the thietanone (7b) was subjected to methylation conditions. Again, however, the material (7b) readily underwent exchange of its 3-hydrogen atom (with racemisation), to give compound (14b) when treated in chloroform with triethylamine and deuterium oxide.

In the light of the foregoing results it was decided to increase the acidity of the thietanone hydrogen atom in the hope of promoting the desired methylation. Since it is well established that Schiff's bases of 3-aminoazetidin-2-ones[11–13] and α-amino esters[14] undergo alkylation reactions under basic conditions, efforts were devoted to the synthesis of imines of type (15).

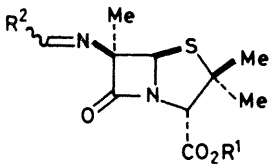
The conversion of the racemate of the thietanone (7b) into the racemate of the salt (16a) has been reported.[9,10] When a



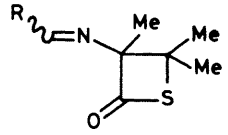
(16) a; X = Br
b; X = Cl
c; X = p-MeC$_6$H$_4$SO$_3$



(17) a; R^1 = PhCH$_2$, R^2 = p-NO$_2$C$_6$H$_4$
b; R^1 = Me, R^2 = Ph



(18) a; R^1 = PhCH$_2$, R^2 = p-NO$_2$C$_6$H$_4$
b; R^1 = Me, R^2 = Ph



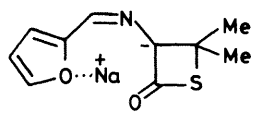
(19) a; R = Ph
b; R = 2-furyl
c; R = 2-hydroxy-1-naphthyl

solution of the thietanone (7b) in glacial acetic acid saturated with hydrogen bromide was left for 0.5 h and diethyl ether was added, the salt (16a) was obtained in 87% yield as a white solid. The salt (16a) reacted with acetic anhydride in pyridine to give the thietanone (7a) which possessed an optical rotation similar to the material obtained from D-penicillamine (3) and acetic anhydride in pyridine. This result indicated that the thietanones (7b) and (16a) were optically pure.

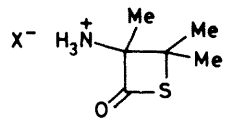
It was also possible to prepare the salt (16b) (53% yield) from the thietanone (7a) by treatment with phosphorus(v) chloride in dichloromethane followed by addition of methanol.[15] Again, no racemisation occurred during this reaction since the thietanone (7a), regenerated from the salt (16b) by the action of acetic anhydride in pyridine, showed an unchanged optical rotation.

The first Schiff's base of type (15) to be selected was the *p*-nitrobenzaldehyde derivative, (15a), since Firestone *et al.* had successfully converted compound (17a) into the methylated derivative (18a).[13] Treatment of the salt (16a) with *p*-nitrobenzaldehyde and triethylamine in dichloromethane afforded the imine (15a) in 95% yield as a slightly impure syrup; the material decomposed when subjected to silica-gel chromatography. That no racemisation had accompanied the Schiff's-base formation was shown by treating the imine (15a) with toluene-*p*-sulphonic acid monohydrate in THF. The derived crystalline salt (16c) reacted with acetic anhydride in pyridine to give the optically pure thietanone (7a). Unfortunately, attempts to effect the methylation of the Schiff's base (15a) led to complex mixtures of products.

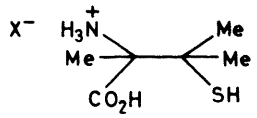
The conversion of the imine (17b) into the methylated derivative (18b) has been reported by Böhme *et al.*[12] The Schiff's base (15b) was prepared in 54% yield by treating the salt (16b) with benzaldehyde and triethylamine in dichloromethane. That the imine (15b) was enantiomerically pure was established by its conversion into the optically pure salt (16c).



(20)



(21) a; X = p-MeC$_6$H$_4$SO$_3$
b; X = Cl



(22) a; X = p-MeC$_6$H$_4$SO$_3$
b; X = Cl

When treated with iodomethane and potassium t-butoxide in THF at 0 °C the imine (15b) was transformed (with racemisation) into the methylated derivative (19a), isolated as an impure syrup in low yield after silica-gel chromatography.

In the hope that a further reduction of the acidity of the thietanone hydrogen atom would be advantageous, the preparation of the Schiff's base (15c) was undertaken. In this compound there is also the possibility that an ion-pair intermediate, *e.g.* (20), if it adopts the (*Z*)-geometry about the imine linkage, may benefit from a co-ordination of the furan oxygen atom with the metal. The Schiff's base (15c) was obtained as a syrup (59% yield after SiO_2 chromatography) by treating the salt (16b) with 2-furaldehyde and triethylamine in dichloromethane. Its enantiomeric purity was established by its transformation into the optically pure salt (16c). When treated with iodomethane and potassium t-butoxide in THF at 0 °C, the imine (15c) was converted (with racemisation) into the methylated imine (19b), albeit in low yield (22% after SiO_2 chromatography).

The imine (15d) was selected as a further candidate for examining the methylation reaction. Treatment of the salt (16b) with 2-hydroxynaphthalene-1-carbaldehyde and triethylamine in dichloromethane gave the Schiff's base (15d) as a crystalline yellow solid in 92% yield. Hydrolysis of the imine linkage of the aforementioned compound was effected by using dilute hydrochloric acid in acetone to give the optically pure salt (16b). When treated with iodomethane and sodium hydride in DMF at 0 °C, the imine (15d) was converted (with racemisation) into the methylated derivative (19c), isolated as a crystalline solid in 65% yield (after SiO_2 chromatography).

In the presence of toluene-*p*-sulphonic acid monohydrate in THF, the imine (19b) was converted into the crystalline salt (21a) in 40% yield. Dilute hydrochloric acid in acetone effected the hydrolysis of the imine (19c), giving the salt (21b) in 46% yield after recrystallisation.

Hydrolysis of the thietanone linkage of the salt (21a) was effected in boiling water to give crystalline DL-2-methylpenicillamine toluene-*p*-sulphonate (22a) in quantitative yield. Under similar conditions, the salt (21b) was converted into the syrupy hydrochloride, (22b), which was transformed into the crystalline toluene-*p*-sulphonate (22a) in 69% yield.

In summary, the foregoing results illustrate that the ability of *N*-substituted derivatives of 3-amino-4,4-dimethylthietan-2-ones to undergo methylation at position 3 is critically dependent upon the nature of the *N*-substituent; to date, the best results have been achieved by using the *N*-(2-hydroxy-1-naphthylmethylene) derivative (15d). The methodology has been used to effect the first synthesis of DL-2-methylpenicillamine (6), an analogue of the important chemotherapeutic agent D-penicillamine (3).

Experimental

Dry solvents, referred to in the ensuing experiments, were prepared as follows: pyridine was kept over potassium hydroxide, distilled, and stored over molecular sieves (Type 4A) dichloromethane was stored over calcium chloride flakes; THF was stored over calcium hydride and, immediately prior to use, distilled; DMF was distilled under reduced pressure from calcium hydride and stored over molecular sieves (Type 4A). Sodium hydride (50% dispersion in oil) was washed with sodium-dried light petroleum and dried (*in vacuo*) prior to use. Light petroleum refers to the fraction boiling in the range 40—60 °C.

T.l.c. was performed on Schleicher and Schull plastic sheets coated with silica gel (F1500 LS 254); the plates were initially examined under u.v. light and spots were then visualised with iodine vapour. Column chromatography was effected, under pressure, using Merck Kieselgel H (Type 60).

Evaporations were carried out using a Buchi rotary evaporator. M.p.s were determined using a Kofler hot-stage apparatus and were uncorrected. I.r. spectra were recorded using either a Hilger and Watts Infrascan or a Perkin-Elmer 457 spectrophotometer. A Unicam SP 800 spectrometer was employed to determine u.v. spectra. ^{1}H N.m.r. spectra were run using $SiMe_4$ or sodium 3-(trimethylsilyl)propane-1-sulphonate as internal standard; spectra were measured at 60 MHz using either a Varian EM 360 or a Hitachi Perkin-Elmer R 24B spectrometer. ^{13}C N.m.r. spectra were recorded at 22.6 MHz with a Brucker HX90E spectrometer. Mass spectra were determined using an A.E.I. MS9 instrument operating at 70 eV. Microanalyses were performed using either a Hewlett-Packard 185 CHN Analyser or a Carlo-Erba 1106 Elemental Analyser.

Reaction of D-*Penicillamine* (3) *with Acetic Anhydride*.—(*a*) A solution of D-penicillamine (3) (5.00 g, 33.6 mmol) in dry pyridine (50 cm^3) at 0 °C was treated with acetic anhydride (10.2 g, 100 mmol). After 48 h in the refrigerator the mixture was diluted with chloroform and washed with dilute hydrochloric acid. Evaporation of the dried ($MgSO_4$) organic layer left a residue which contained two components (t.l.c.), considered to be a mixture of the derivatives (7a) and (9) (n.m.r. spectroscopy). The components were separated by silica-gel chromatography [EtOAc–light petroleum (1 : 1) as eluant].

The first eluted material, isolated as a waxy solid (1.03 g, 22%), was considered to be 4-isopropylidene-2-methyloxazol-5(4*H*)-one (9),[5] $\nu_{max.}$ (KBr) *inter alia* 1 795 and 1 760 (C=O), and 1 680 and 1 620 cm^{-1} (C=N and C=C); $\lambda_{max.}$ (EtOH) 213 (ε 3 000) and 268 nm (4 700); δ ($CDCl_3$) 2.25, 2.30, and 2.37 (each 3 H, s, together Me_2C and MeC); *m*/*z inter alia* 139 (M^+) and 43 ($C_2H_3O^+$, base peak) (Found: M^+, 139.0630. Calc. for $C_7H_9NO_2$: *M*, 139.0633).

The second eluted material, isolated as a crystalline solid (1.34 g, 23%), was (3R)-3-*acetamido*-4,4-*dimethylthietan*-2-*one* (7a), m.p. 158—160 °C (from EtOH); $[\alpha]_D$ −112° (1% in $CHCl_3$); $\nu_{max.}$ (KBr) *inter alia* 3 460 and 3 260 (NH), 1 755 (thietanone C=O), and 1 655 cm^{-1} (amide C=O); $\lambda_{max.}$ (EtOH) 237 nm (ε 1 790); δ($CDCl_3$) 1.63 and 1.85 (each 3 H, s, together Me_2C), 2.05 (3 H, s, MeC=O), 5.70 (1 H, d, *J* 8 Hz, 3-H), and 6.80 (1 H, br s, NH) (addition of D_2O caused the signal at δ 6.80 to disappear and that at δ 5.70 to collapse to a s); *m*/*z inter alia* 174 (MH^+) and 43 ($C_2H_3O^+$, base peak) (Found: C, 48.5; H, 6.45; N, 8.15. $C_7H_{11}NO_2S$ requires C, 48.55; H, 6.35; N, 8.10%).

(*b*) Acetic anhydride (24.5 g, 0.24 mol) was added during 1 h to a stirred solution of D-penicillamine (3) (15.0 g, 0.1 mol) in dry pyridine (65 cm^3) at 0 °C. The mixture was then allowed to warm to room temperature and, after 15 h, it was partitioned between chloroform and dilute hydrochloric acid. The organic phase was freed of pyridine by being washed several times with dilute hydrochloric acid and was then dried ($MgSO_4$) and evaporated. Addition of light petroleum to the residue induced crystallisation of the thietanone (7a). The sample (5.33 g, 31% after recrystallisation from EtOH) was identical (n.m.r. spectroscopy) with that obtained from the aforementioned reaction.

Hydrolysis of the Thietanone (7a).—A mixture of the thietanone (7a) (0.346 g, 2 mmol) and water (5 cm^3) containing a few drops of 1M-hydrochloric acid was heated under reflux for 3 h. Evaporation and recrystallisation of the product from water gave *N*-acetyl-D-penicillamine (8a)[6] (0.240 g, 63%), m.p. 188—190 °C (lit.,[6] 189—190 °C); $[\alpha]_D$ +18° (1.2% in 50% water–EtOH) [lit.,[6] +18° (water–EtOH)]; $\nu_{max.}$ (KBr) *inter alia* 3 380 (NH), 1 705 (acid C=O), and 1 620 cm^{-1} (amide C=O); δ (D_2O containing $NaHCO_3$) 1.40 and 1.48 (each 3 H, s, together Me_2C), 2.08 (3 H, s, MeC=O), and 4.24 (1 H, s, CHC=O); *m*/*z inter alia* 173 ($M^+ - H_2O$) and 75 ($C_3H_7S^+$, base peak).

Hydrolysis of the Oxazolone (9).—A mixture of the oxazolone (9) (0.139 g, 1 mmol) and water (5 cm^3) was heated under reflux for 10 min. As the mixture was cooled *N*-acetyldehydrovaline (10)[7] (0.062 g, 39%) crystallised out, m.p. 201—203 °C (lit.,[7] *ca.* 200 °C); $\nu_{max.}$ (KBr) *inter alia* 3 330 (NH), 1 700 (unsaturated acid C=O), 1 655 (amide C=O), and 1 620 cm^{-1} (C=C); $\lambda_{max.}$ (EtOH) 225br nm (ε 6 900); δ (D_2O) 1.85, 2.00, and 2.02 (each 3 H, s, together Me_2C and MeC=O); *m*/*z inter alia* 158 (MH^+) and 115 ($M^+ - C_2H_2O$, base peak) (Found: C, 53.7; H, 7.0; N, 8.9. Calc. for $C_7H_{11}NO_3$: C, 53.50; H, 7.00: N, 8.90%).

Reaction of the Thietanone (7a) *with Iodomethane*.—To a stirred solution of the thietanone (7a) (0.173 g, 1 mmol) in dry DMF (4 cm^3) at 0 °C was added iodomethane (0.355 g, 2.5 mmol) followed by sodium hydride (0.024 g, 1 mmol). After 45 min the mixture was diluted with ethyl acetate and washed with brine. Evaporation of the dried ($MgSO_4$) organic layer and purification of the product by silica-gel chromatography (light petroleum as eluant) gave the oxazolone (9)[5] (0.107 g, 77%) (identical by i.r., n.m.r., and mass spectroscopy with the sample prepared previously).

Reaction of the Thietanone (7a) *with Isopropenyl Acetate*.—A mixture of the thietanone (7a) (0.346 g, 2 mmol), isopropenyl acetate (0.601 g, 6 mmol), and a trace of toluene-*p*-sulphonic acid in toluene (5 cm^3) was heated under reflux for 8 h. The cooled mixture was diluted with dichloromethane and washed with aqueous sodium hydrogen carbonate. Evaporation of the dried ($MgSO_4$) organic layer and purification of the residue by silica-gel chromatography [EtOAc–light petroleum (1 : 2) as eluant] gave 3-*diacetylamino*-4,4-*dimethylthietan*-2-*one* (12) (0.280 g, 65%) as needles, m.p. 108—110 °C (from EtOH); $[\alpha]_D$ −49° (1% in $CHCl_3$); $\nu_{max.}$ (KBr) *inter alia* 1780sh, 1 765 (thietanone C=O), and 1 725 and 1 690 cm^{-1} (imide* C=O); $\lambda_{max.}$ (EtOH) 214 nm (ε 2 700); δ_H ($CDCl_3$) 1.72 and 1.88 (each 3 H, s, together Me_2C), 2.45 (6 H, s, 2 × MeC=O), and 5.42 (1 H, s, 3-H); δ_C ($CDCl_3$) 24.6, 26.4, and 32.4 (3 × CH_3), 49.1 (CMe_2), 80.3 (NCH), 172 (NC=O), and 187 p.p.m. (SC=O); *m*/*z inter alia* 215 (M^+), 187 (M^+−CO), 173 (M^+−C_2H_2O), and 43 (C_2H_3O, base peak) (Found: C, 50.05; H, 6.0; N, 6.45. $C_9H_{13}NO_3S$ requires C, 50.25; H, 6.05; N, 6.50%).

* Strictly speaking, a secondary amide.

Reaction of the Thietanone (12) *with Triethylamine–Deuterium Oxide*.—A solution of the thietanone (12) (0.215 g, 1 mmol) in chloroform (2 cm^3) was treated with deuterium oxide (0.5 cm^3) and triethylamine (0.2 cm^3). After 4 h the mixture was diluted with chloroform and washed with dilute hydrochloric acid. Evaporation of the dried ($MgSO_4$) organic layer gave (3RS)-3-*diacetylamino*-4,4-*dimethyl*[3-^{2}H]*thietan*-2-*one* (14a) (0.180 g, 83%) as a white solid, m.p. 169—171 °C (decomp.) (from EtOH); $[\alpha]_D$ 0° (1% in EtOH); $\nu_{max.}$ (KBr) *inter alia* 1 785sh, 1 755 (thietanone C=O), and 1 725 and 1 690 cm^{-1} (imide*C=O); $\lambda_{max.}$ (EtOH) 215 nm (ε 3 300); δ($CDCl_3$) 1.70 and 1.87 (each 3 H, s, together Me_2C) and 2.47 (6 H, s, 2 × MeC=O); *m/z inter alia* 188 ($M^+ - CO$), 174 ($M^+ - C_2H_2O$), and 43 ($C_2H_3O^+$, base peak) (Found: C, 50.25; H, 6.05; N, 6.5. $C_9H_{12}DNO_3S$ requires C, 50.00; H, 6.00; N, 6.50%).

Reaction of D-*Penicillamine* (3) *with Benzyl Chloroformate followed by DCC*.—To a stirred solution of D-penicillamine (3) (7.50 g, 50 mmol) in 1M-sodium hydroxide (50 cm^3, 50 mmol) at 0 °C, solutions of benzyl chloroformate (9.00 g, 52.8 mmol) in dioxane (25 cm^3) and 1M-sodium hydroxide (50 cm^3, 50 mmol) were added simultaneously during 15 min. After 3 h the mixture was diluted with water and washed with diethyl ether. The aqueous layer was then acidified with dilute hydrochloric acid and extracted with diethyl ether (3×). Evaporation of the dried ($MgSO_4$) extracts left *N*-benzyloxycarbonyl-D-penicillamine (8b) as a yellow syrup, δ($CDCl_3$) 1.35 and 1.48 (each 3 H, s, together Me_2C), 1.93 (1 H, s, SH), 4.37 (1 H, d, *J* 10 Hz, CHC=O), 5.10 (2 H, s, PhCH_2O), 5.69 (1 H, br d, *J* 10 Hz, NH), 7.27 (5 H, s, Ph), and 9.47 (1 H, s, CO_2H). The product (8b) was dissolved in dichloromethane (100 cm^3) and DCC (7.70 g, 37.3 mmol) was added to the solution at 0 °C. After 1 h the mixture was filtered and the filtrate was evaporated. Purification of the residue by silica-gel chromatography [EtOAc–light petroleum (1 : 9) as eluant] and recrystallisation (from Et_2O–light petroleum) of the purified product gave (3R)-3-*benzyloxycarbonylamino*-4,4-*dimethylthietan*-2-*one* (7b) [5.00 g, 40% based upon (3)], m.p. 58—60 °C (from Et_2O–light petroleum); $[\alpha]_D$ −22° (0.75% in EtOH); $\nu_{max.}$ (KBr) *inter alia* 3 400 and 3 340 (NH), 1 745 (thietanone C=O), and 1 695 cm^{-1} (urethane C=O); $\lambda_{max.}$ (EtOH) 213 (ε 8 600) and 237sh nm (1 900); δ($CDCl_3$) 1.62 and 1.80 (each 3 H, s, together Me_2C), 5.10 (2 H, s, PhCH_2O), 5.42 (1 H, d, *J* 9 Hz, 3-H), 5.75 (1 H, br d, *J* 9 Hz, NH), and 7.30 (5 H, s, Ph) (addition of D_2O caused the signal at δ 5.42 to collapse to a s and that at δ 5.75 to disappear); *m/z inter alia* 265 (M^+) and 91 ($C_7H_7^+$, base peak) (Found: C, 58.9; H, 5.75; N, 5.45%; M^+, 265.0797. $C_{13}H_{15}NO_3S$ requires C, 58.85; H, 5.65; N, 5.30%; *M*, 265.0773).

Reaction of the Thietanone (7b) *with Triethylamine–Deuterium Oxide*.—A mixture of the thietanone (7b) (0.400 g, 1 mmol), chloroform (5 cm^3), triethylamine (0.8 cm^3), and deuterium oxide (1 cm^3) was stirred for 2 d. The mixture was diluted with chloroform and washed with dilute hydrochloric acid. Evaporation of the dried ($MgSO_4$) organic layer and recrystallisation of the product (from CCl_4) gave (3RS)-3-*benzyloxycarbonylamino*-4,4-*dimethyl*[3^2-H]*thietan*-2-*one* (14b) (0.264 g, 66%), m.p. 83—84 °C; $[\alpha]_D$ 0° (1% in $CHCl_3$); $\nu_{max.}$ (KBr) *inter alia* 3 320 (NH), 1 755 (thietanone (C=O), and 1 685 cm^{-1} (urethane C=O); $\lambda_{max.}$ (EtOH) 215 (ε 7 700) and 235 nm (1 800); δ($CDCl_3$) 1.62 and 1.78 (each 3 H, s, together Me_2C), 5.05 (2 H, s, PhCH_2O), 5.35 (1 H, br s, NH), and 7.30 (5 H, s, Ph) (addition of D_2O caused the signal at δ 5.35 to disappear); *m/z inter alia* 266 (M^+) and 91 ($C_7H_7^+$, base peak) (Found: C, 58.75; H, 5.25; N, 5.35. $C_{13}H_{14}DNO_3S$ requires C, 58.65; H, 5.65; N, 5.25%).

Reaction of the Thietanone (7b) *with Hydrogen Bromide*.—To a stirred solution of acetic acid saturated with hydrogen bromide (8 cm^3) was added the thietanone (7b) (0.530 g, 2 mmol). After 0.5 h the solution was diluted with dry diethyl ether until a turbidity developed. Whilst the mixture was allowed to stand (3R)-3-*amino*-4,4-*dimethylthietan*-2-*one hydrobromide* (16a) (0.367 g, 87%) precipitated out, m.p. 72—74 °C (from Et_2O); $[\alpha]_D$ +11° (1% in EtOH); $\nu_{max.}$ (KBr) *inter alia* 1 760 cm^{-1} (thietanone C=O); $\lambda_{max.}$ (EtOH) 216 (ε 2 300) and 236 nm (2 000); δ(D_2O) 1.85 (6 H, s, Me_2C) and 5.10 (1 H, s, 3-H); *m/z inter alia* 103 ($C_4H_9NS^+$, base peak) (Found: C, 28.2; H, 4.5; N, 6.85. $C_5H_{10}BrNOS$ requires C, 28.30; H, 4.70; N, 6.60%).

Reaction of the Thietanone (7a) *with Phosphorus*(v) *Chloride followed by Methanol*.—To a stirred solution of the thietanone (7a) (1.04 g, 6 mmol) in dry dichloromethane (10 cm^3) was added phosphorus(v) chloride (1.60 g, 7.2 mmol) followed, after 5 min, by methanol (3 cm^3, dropwise). After 10 min the mixture was evaporated and the residue was treated with diethyl ether. Filtration gave (3R)-3-*amino*-4,4-*dimethylthietan*-2-*one hydrochloride* (16b) (0.532, 53%), m.p. 160—163 °C (decomp.); $[\alpha]_D$ +13° (1% in EtOH); $\nu_{max.}$ (KBr) *inter alia* 1 755 cm^{-1} (thietanone C=O); $\lambda_{max.}$ (EtOH) 213 (ε 3 400) and 237 nm (1 800); δ(D_2O) 1.84 (6 H, s, Me_2C) and 5.16 (1 H, s, 3-H); *m/z inter alia* 103 ($C_4H_9NS^+$, base peak) (Found: C, 35.65; H, 5.75; N, 8.45. $C_5H_{10}ClNOS$ requires C, 35.80; H, 5.95; N, 8.35%).

Reaction of the Salts (16a), (16b), *and* (16c) *with Acetic Anhydride and Pyridine*.—(*a*) A solution of the salt (16a) (0.128 g, 0.6 mmol) in dry pyridine (2 cm^3) was treated with acetic anhydride (0.154 g, 1.5 mmol). After 12 h the mixture was diluted with chloroform and washed with dilute hydrochloric acid. Evaporation of the dried ($MgSO_4$) organic layer and purification of the product by silica-gel chromatography [EtOAc–light petroleum (1 : 1) as eluant] gave the thietanone (7a) (0.054 g, 52%) (n.m.r. spectroscopy), m.p. 159—160 °C (from EtOH); $[\alpha]_D$ −115° (1.4% in $CHCl_3$).

(*b*) A solution of the salt (16b) (0.168 g, 1 mmol) in dry pyridine (5 cm^3) was treated with acetic anhydride (0.265 g, 25 mmol). Work-up after 12 h as described in the foregoing experiment gave the thietanone (7a) (0.113 g, 65%) (n.m.r. spectroscopy), m.p. 159—160 °C (from EtOH); $[\alpha]_D$ −113° (0.9% in $CHCl_3$).

(*c*) A solution of the salt (16c) (0.056 g, 0.18 mmol) in dry pyridine (1 cm^3) was treated with acetic anhydride (0.047 g, 0.46 mmol). Work-up after 12 h as described in (*a*) and recrystallisation of the product from ethanol gave the thietanone (7a) (0.024 g, 75%) (n.m.r. spectroscopy), m.p. 157—159 °C; $[\alpha]_D$ −112° (1.2% in $CHCl_3$).

Reaction of the Thietanone (16a) *with* p-*Nitrobenzaldehyde*.—To a stirred suspension of the thietanone (16a) (0.212 g, 0.1 mmol) in dichloromethane (10 cm^3) was added *p*-nitrobenzaldehyde (0.151 g, 0.1 mmol) followed by triethylamine (0.101 g, 0.1 mmol). After 3 h the mixture was diluted with dichloromethane and washed with water (2×). Evaporation of the dried ($MgSO_4$) organic layer left (3R)-4,4-*dimethyl*-3-(*p*-*nitrobenzylideneamino*)*thietan*-2-*one* (15a) (0.250 g, 95%) as a pale yellow syrup, $[\alpha]_D$ +173° (1.2% in EtOH); $\nu_{max.}$ (film) *inter alia* 1 745 (thietanone C=O) and 1 640 cm^{-1} (C=N); $\lambda_{max.}$ (EtOH) 215 (ε 17 000) and 281 nm (20 800); δ($CDCl_3$) 1.85 and 1.88 (each 3 H, s, together Me_2C), 5.25 (1 H, d, *J* 2 Hz, 3-H), 7.92 and 8.25 (each 2 H, d, *J* 8 Hz, together C_6H_4)

* Strictly speaking, a secondary amide.

and 8.63 (1 H, d, *J* 2 Hz, CH=N) (irradiation at δ 5.25 caused the d at δ 8.63 to collapse to s and *vice versa*); *m/z inter alia* 264 (M^+), 236 ($M^+ - CO$), and 204 ($M^+ - COS$, base peak) (Found: *M*, 264.0565. $C_{12}H_{12}N_2O_3S$ requires *M*, 264.0569).

Reaction of the Thietanone (15a) *with Toluene*-p-*sulphonic Acid.*—To a stirred solution of the thietanone (15a) (0.130 g, 0.49 mmol) in dry THF (5 cm³) was added toluene-*p*-sulphonic acid monohydrate (0.104 g, 0.55 mmol). After 3 h the precipitated (3R)-3-*amino*-4,4-*dimethylthietan*-2-*one toluene*-p-*sulphonate* (16c) (0.079 g, 53%) was collected by filtration. The sample, recrystallised from diethyl ether, had m.p. 180—181 °C, $[\alpha]_D$ +13° (0.8% in EtOH); $\nu_{max.}$ (KBr) *inter alia* 1 765 cm^{-1} (thietanone C=O); $\lambda_{max.}$ (EtOH) 228 (ε 13 600) and 239 nm (2 700); δ (D_2O) 1 84 and 1.85 (each 3 H, s, together Me_2C), 2.39 (3 H, s, MeC_6H_4), 5.20 (1 H, s, 3-H), and 7.35 and 7.69 (each 2 H, d, *J* 8 Hz, together C_6H_4); *m/z inter alia* 172 ($C_7H_8O_3S^+$), 107 ($C_7H_7O^+$), 103 ($C_4H_9NS^+$), and 91 ($C_7H_7^+$, base peak) (Found: C, 47.6; H, 5.65; N, 4.5; S, 21.0 $C_{12}H_{17}NO_4S_2$ requires C, 47 50; H, 5.60; N, 4.60; S, 21.10%).

Reaction of the Thietanone (16b) *with Benzaldehyde.*—To a stirred solution of the thietanone (16b) (0.168 g, 1 mmol) in dichloromethane (6 cm³) was added benzaldehyde (0.096 g, 0.9 mmol) followed by triethylamine (0.101 g, 1 mmol). After 12 h the solution was diluted with dichloromethane and washed in turn with water and aqueous sodium metabisulphite (sodium pyrosulphite). Evaporation of the dried ($MgSO_4$) organic layer left (3*R*)-3-benzylideneamino-4,4-dimethylthietan-2-one (15b) (0.118 g, 54%) as a pale yellow syrup; $[\alpha]_D$ +207° (0.2% in $CHCl_3$); $\nu_{max.}$ (film) *inter alia* 1 750 (thietanone C=O) and 1 635 cm^{-1} (C=N); $\lambda_{max.}$ (EtOH) 212 (ε 18 600) and 253 nm (14 000); δ ($CDCl_3$) 1.83 and 1.86 (each 3 H, s, together Me_2C), 5.12 (1 H ,d, *J* 2 Hz, 3-H), 7.27—7.41 (3 H, m, C_6H_3), 7.60—7.77 (2 H, m, C_6H_2), and 8.30 (1 H, d, *J* 2 Hz, CH=N); *m/z inter alia* 191 ($M^+ - CO$, base peak) [Found: ($M^+ - CO$), 191.0779. $C_{11}H_{13}NS$ requires *m/z* 191.0769].

Reaction of the Thietanone (15b) *with Toluene*-p-*sulphonic Acid.*—To a stirred solution of the thietanone (15b) (0.130 g, 0.59 mmol) in dry THF (5 cm³) was added toluene-*p*-sulphonic acid monohydrate (0.112 g, 0.59 mmol). After 24 h the precipitate (0.079 g, 43%) [shown to be the salt (16c) by n.m.r. spectroscopy] was collected by filtration. The sample, after recrystallisation from diethyl ether, showed m.p. 180—182 °C and $[\alpha]_D$ +13° (0.8% in EtOH).

Reaction of the Thietanone (15b) *with Iodomethane.*—To a stirred solution of the thietanone (15b) (0.148 g, 0.68 mmol) and iodomethane (0.274 g, 1.93 mmol) in dry THF at 0 °C was added potassium t-butoxide (0.174 g, 1.55 mmol). After 1 h the mixture was diluted with ethyl acetate and washed with brine. Evaporation of the dried ($MgSO_4$) organic layer and subjection of the product to silica-gel chromatography [light petroleum as eluant] gave a syrup (0.038 g) which contained *ca.* 50% of (3*RS*)-3-benzylideneamino-3,4,4-trimethylthietan-2-one (19a) by n.m.r. spectroscopy; $[\alpha]_D$ 0° (1.7% in $CHCl_3$); $\nu_{max.}$ (film) *inter alia* 1 770sh and 1 730 (thietanone C=O) and 1 640 cm^{-1} (C=N); δ($CDCl_3$) *inter alia* 1.55, 1.65, and 1.80 (each s, together Me_2C and MeC), 7.10—7.85 (m, C_6H_5), and 8.50 (s, CH=N); *m/z inter alia* 233 (M^+) and 205 ($M^+ - CO$) (Found: M^+, 233.0892. $C_{13}H_{15}NOS$ requires *M*, 233.0874).

Reaction of the Thietanone (16b) *with* 2-*Furaldehyde.*—To a stirred suspension of the thietanone (16b) (1.68 g, 10 mmol) in dichloromethane (20 cm³) was added freshly distilled 2-furaldehyde (0.864 g, 9 mmol) followed by triethylamine (1.01 g, 10 mmol) After 12 h the solution was diluted with dichloromethane and washed in turn with water and aqueous sodium metabisulphite. Evaporation of the dried ($MgSO_4$) organic layer gave (3*R*)-3-furfurylideneamino-4,4-dimethylthietan-2-one (15c) (1.23 g, 59%) as a chromatographically homogeneous pale yellow syrup; $[\alpha]_D$ +72° (1% in $CHCl_3$); $\nu_{max.}$ (film) *inter alia* 1 745 (thietanone C=O) and 1 640 cm^{-1} (C=N); $\lambda_{max.}$ (EtOH) 220 (ε 7 400) and 274 nm (16 100); δ($CDCl_3$) 1.72 and 1.80 (each 3 H, s, together Me_2C), 5.13 (1 H, d, *J* 2 Hz, 3-H), 6.35—6.45 (1 H, m, OCH=C*H*CH), 6.84 (1 H, d, *J* 4 Hz, OCH=CHC*H*), 7.50 (1 H, br s, OC*H*=CH), and 8.20 (1 H, d, *J* 2 Hz, CH=N); *m/z inter alia* 181 ($M^+ - CO$) and 149 ($M^+ - COS$, base peak) [Found: ($M^+ - CO$), 181.0563. $C_9H_{11}NOS$ requires *m/z*, 181.0561].

Reaction of the Thietanone (15c) *with Toluene*-p-*sulphonic Acid.*—To a stirred solution of the thietanone (15c) (0.125 g, 0.6 mmol) in dry THF (5 cm³) was added toluene-*p*-sulphonic acid monohydrate (0.114 g, 0.6 mmol). After 30 min the precipitate (0.112 g, 62%) [shown to be the salt (16c) by n.m.r. spectroscopy] was collected by filtration. The sample, recrystallised from diethyl ether, showed m.p. 180—181 °C and $[\alpha]_D$ +13° (1% in EtOH).

Reaction of the Thietanone (15c) *with Iodomethane.*—To a stirred solution of the thietanone (15c) (0.627 g, 3 mmol) in dry THF (15 cm³) at 0 °C was added iodomethane (1.06 g, 7.5 mmol) followed by potassium t-butoxide (0.672 g, 6 mmol). After 1 h the mixture was diluted with ethyl acetate and washed with brine. Evaporation of the dried ($MgSO_4$) organic layer and purification of the product by silica-gel chromatography [EtOAc–light petroleum (1 : 2) as eluant] gave (3*RS*)-3-furfurylideneamino-3,4,4-trimethylthietan-2-one (19b) (0.145 g, 22%) as a chromatographically homogeneous yellow syrup, $[\alpha]_D$ 0° (0.3% in $CHCl_3$); $\nu_{max.}$ (film) *inter alia* 1 770sh and 1 730 (thietanone C=O) and 1 640 cm^{-1} (C=N); $\lambda_{max.}$ (EtOH) 223 (ε 9 000) and 273 nm (11 000); δ($CDCl_3$) 1.65, 1.70, and 1.76 (each 3 H, s, together Me_2C and MeC), 6.45—6.55 (1 H, m, OCH=C*H*CH), 6.80 (1 H, d, *J* 3 Hz, OCH=CHC*H*), 7.50 (1 H, br s, OC*H*=CHCH), and 8.20 (1 H, s, CH=N); *m/z inter alia* 195 ($M^+ - CO$) and 121 ($M^+ - C_4H_6OS$, base peak) [Found: ($M^+ - CO$), 195.0737. $C_{10}H_{13}NOS$ requires *m/z* 195.0718).

Reaction of the Thietanone (16a) *with* 2-*Hydroxynaphthalene*-1-*carbaldehyde.*—To a stirred suspension of the thietanone (16a) (2.12 g, 10 mmol) in dichloromethane (50 cm³) was added 2-hydroxynaphthalene-1-carbaldehyde (1.63 g, 9.5 mmol) followed by triethylamine (1.01 g, 10 mmol). After 18 h the solution was washed in turn with water and aqueous sodium metabisulphite. Evaporation of the dried ($MgSO_4$) organic layer gave (3R)-3-(2-*hydroxy*-1-*naphthylmethyleneamino*)-*thietan*-2-*one* (15d) (2.63 g, 92%) as a yellow solid. A sample, obtained as yellow needles after recrystallisation from methanol, had m.p. 115—116 °C, $[\alpha]_D$ +343° (0.75% in $CHCl_3$); $\nu_{max.}$ (KBr) *inter alia* 1 740 (thietanone C=O) and 1 625 cm^{-1} (C=N); $\lambda_{max.}$ (EtOH) 229 (ε 54 300), 305 (10 900), 317 (12 000), and 352 nm (8 000); δ($CDCl_3$) 1.85 (6 H, s, Me_2C), 5.17 (1 H, s, 3-H), 6.90—8.00 (6 H, m, $C_{10}H_6$), 9.12 (1 H, s, CH=N), and 14.2 (1 H, br s, OH) (addition of D_2O caused the signal at δ 14.2 to disappear); *m/z inter alia* 285 (M^+) and 182 (base peak) (Found: C, 67.2; H, 5.25; N, 5.0%; M^+, 285.0852. $C_{16}H_{15}NO_2S$ requires C, 67.35; H, 5.25; N, 4.90%; *M*, 285.0824).

Reaction of the Thietanone (15d) *with Hydrochloric Acid.*—A solution of the thietanone (15d) (0.143 g, 0.5 mmol) in acetone (6 cm³) was treated with 1M-hydrochloric acid (8

cm^3). After 2 h the mixture was diluted with chloroform. Evaporation of the dried ($MgSO_4$) organic layer gave 2-hydroxynaphthalene-1-carbaldehyde (0.078 g, 90%) (n.m.r. spectroscopy). Evaporation of the aqueous layer and recrystallisation of the residue from methanol–diethyl ether gave the thietanone (16b) (0.071 g, 84%) (n.m.r. spectroscopy), m.p. 160—162 °C; $[\alpha]_D$ +14° (0.4% in EtOH).

Reaction of the Thietanone (15d) *with Iodomethane.*—To a stirred solution of the thietanone (15d) (1.43 g, 5 mmol) in dry DMF (50 cm^3) at 0 °C was added iodomethane (1.78 g, 12.5 mmol) followed by sodium hydride (0.120 g, 5 mmol). After 1 h the mixture was diluted with ethyl acetate and washed with brine. Evaporation of the dried ($MgSO_4$) organic layer and purification of the product by silica-gel chromatography (light petroleum as eluant) gave (3RS)-3-(2-*hydroxy*-1-*naphthylmethyleneamino*)-3,4,4-*trimethylthietan*-2-*one* (19c) (0.977 g, 65%) as orange needles, m.p. 82—83 °C; $[\alpha]_D$ 0° (0.5% in $CHCl_3$); $\nu_{max.}$ (KBr) *inter alia* 3 420br (OH), 1 770(w), and 1 730 (thietanone C=O), and 1 625 cm^{-1} (C=N); $\lambda_{max.}$ (EtOH) 228 (ε 59 800), 315 (10 900), and 350 nm (6 800); δ($CDCl_3$) 1.65 and 1.67 (3 H and 6 H, respectively, each s, together CMe_2 and CMe), 6.90—8.00 (6 H, m, $C_{10}H_6$), 9.42 (1 H, s, CH=N), and 14.2 (1 H, br s, OH) (addition of D_2O caused the signal at δ 14.2 to disappear); *m/z inter alia* 299 (M^+) and 196 (base peak) (Found: C, 68.3; H, 5.6; N, 4.6%; M^+, 299.0990. $C_{17}H_{17}NO_2S$ requires C, 68.20; H, 5.70: N, 4.70%; M^+, 299.0980).

Reaction of the Thietanone (19b) *with Toluene*-p-*sulphonic Acid.*—To a solution of the thietanone (19b) (0.794 g, 3.56 mmol) in dry THF (30 cm^3) was added toluene-*p*-sulphonic acid monohydrate (0.744 g, 3.9 mmol). After 1 h the precipitate of (3RS)-3-*amino*-3,4,4-*trimethylthietan*-2-*one toluene*-p-*sulphonate* (21a) (0.449 g, 40%) was filtered off, m.p. 194—195 °C (from MeOH–Et_2O); $[\alpha]_D$ 0° (0.5% in EtOH); $\nu_{max.}$ (KBr) *inter alia* 3 440 (NH) and 1 770 and 1 740 cm^{-1} (thietanone C=O); $\lambda_{max.}$ (EtOH) 229 (ε 5 800) and 232sh nm (2 800); δ(D_2O) 1.74 and 1.86 (6 H and 3 H, respectively, each s, together Me_2C and MeC), 2.39 (3 H, s, MeC_6H_4), and 7.33 and 7.68 (each 2 H, d, *J* 7 Hz, together C_6H_4); *m/z inter alia* 172 ($C_7H_8O_3S^+$), 155 ($C_7H_7O_2S^+$), 117 ($C_5H_{11}NS^+$), and 42 (base peak) (Found: C, 48.95; H, 6.0; N, 4.4. $C_{13}H_{19}NO_4S_2$ requires C, 49.20; H, 6.00; N, 4.40%).

Reaction of the Thietanone (19c) *with Hydrochloric Acid.*—To a stirred solution of the thietanone (19c) (0.654 g, 2.2 mmol) in acetone (20 cm^3) was added 1M-hydrochloric acid (25 cm^3). After 1 h the mixture was concentrated (to remove the acetone) and extracted with chloroform. Evaporation of the dried ($MgSO_4$) organic layer gave 2-hydroxynaphthalene-1-carbaldehyde (0.350 g, 93%) (n.m.r. spectroscopy). Evaporation of the aqueous layer and crystallisation of the residue from methanol–diethyl ether gave (3RS)-3-*amino*-3,4,4-*trimethylthietan*-2-*one hydrochloride* (21b) (0.182 g, 46%), m.p. 165—166 °C; $[\alpha]_D$ 0° (0.5% in EtOH); $\nu_{max.}$ (KBr) *inter alia* 1 765 and 1 740 cm^{-1} (thietanone C=O); $\lambda_{max.}$ (EtOH) 221 (ε 2 180), 235 (2 300), and 280 nm (260); δ(D_2O) 1.77 (br s) and 1.87 (s) (6 H and 3 H, respectively, together Me_2C and MeC); *m/z inter alia* 117 ($C_5H_{11}NS^+$, base peak) (Found: C, 39.3; H, 6.45; N, 7.65. $C_6H_{12}ClNOS$ requires C, 39.65; H, 6.60; N, 7.70%).

Hydrolysis of the Thietanones (21a) *and* (21b).—(*a*) A solution of the thietanone (21a) (0.317 g, 1 mmol) in water (8 cm^3) was heated under reflux for 1 h. Evaporation gave (2-RS)-2-*amino*-3-*mercapto*-2,3-*dimethylbutanoic acid toluene*-p-*sulphonate* (2-*methylpenicillamine toluene*-p-*sulphonate*) (22a) (0.335 g, 100%). A sample, recrystallised from aqueous acetone, had m.p. 192—193 °C; $\nu_{max.}$ (KBr) *inter alia* 3 420 (NH) and 1 715 cm^{-1} (acid C=O); $\lambda_{max.}$ (EtOH) 225 (ε 5 000), 257 (170), and 262 nm (170); δ(D_2O) 1.55 and 1.60 (6 H and 3 H, respectively, each s, together Me_2C and MeC), 2.37 (3 H, s, $MeC_6H)_4$, and 7.38 and 7.73 (each 2 H, d, *J* 8 Hz, together C_6H_4); *m/z inter alia* 172 ($C_7H_8O_3S^+$) and 107 ($C_7H_7O^+$, base peak) (Found: C, 46.25; H, 6.4; N, 4.25. $C_{13}H_{21}NO_5S_2$ requires C, 46.55; H, 6.25; N, 4.20%).

(*b*) A solution of the thietanone (21b) (0.163 g, 0.9 mmol) in water (2 cm^3) was heated under reflux. Evaporation after 1 h left (2*RS*)-2-amino-3-mercapto-2,3-dimethylbutanoic acid hydrochloride (2-methylpenicillamine hydrochloride) (22b) as a syrup. The syrup was dissolved in THF (4 cm^3) and to the solution was added toluene-*p*-sulphonic acid monohydrate (0.169 g, 0 89 mmol) Evaporation after 15 min and recrystallisation of the residue from methanol–diethyl ether gave DL-2-methylpenicillamine hydrogen toluene-*p*-sulphonate (22a) (0.209 g, 69%) (identical by i.r., n.m.r., and mass spectroscopy with the sample prepared above), m.p. 190—192 °C.

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