Syntheses of β-Lactams by Ring Contraction of Isothiazolidinones

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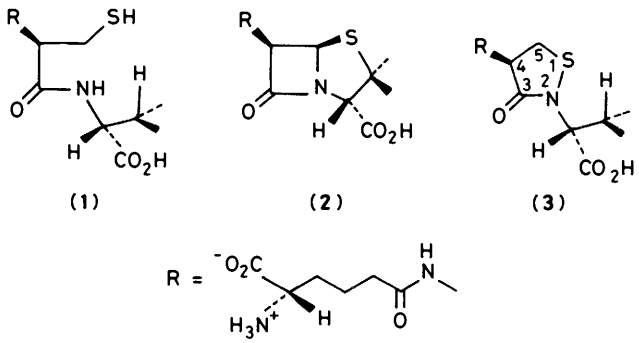
Several methods have been developed for the preparation of β-lactams from isothiazolidinones. Oxidation of 2-t-butyl-4,4-diphenyl- and 2,4,4-trimethyl-isothiazolidin-3-ones (**4a**) and (**4b**) with sulphuryl chloride afforded the 5-chloroisothiazolidinones (**5a**) and (**5b**), which were converted into 1-t-butyl-3,3-diphenyl- and 1,3,3-trimethyl-4-phenylthioazetidin-2-ones (**6a**) and (**6b**) by treatment with phenyl-lithium. Alternatively, reaction of the isothiazolidinones (**4a**) and (**4b**) with phenyl-lithium gave *N*-t-butyl-2,2-diphenyl- and *N*,2,2-trimethyl-3-phenylthiopropionamides (**12a**) and (**12b**), which were transformed into the β-lactams (**6a**) and (**6b**) by halogenation at C-3, followed by treatment with potassium amide. These are examples of methods used to prepare β-lactams from isothiazolidinones. The versatility of these reactions and their relevance to penicillin biosynthesis is discussed.

Studies of the biosynthesis of penicillins have shown that isopenicillin N (**2**) is derived from the tripeptide, [δ-(L-α-aminoadipoyl)]-L-cysteinyl-D-valine (**1**),[1]† but the mechanism of this conversion is unknown. On the basis of the facile *in vitro* oxidation of peptides to isothiazolidinones,[2,3] the isothiazolidinone (**3**) has been proposed as an intermediate in the *in vivo* transformation (**1**)→(**2**).[4] However, attempts to prepare β-lactams from isothiazolidinones, *in vitro*, as models for the conversion (**3**)→(**2**), have been unsuccessful.[4]

In this report full details are given of several preparations of β-lactams from isothiazolidinones.[5] The ease of transformation of isothiazolidinones into β-lactams gives credence to the proposed involvement of similar species in the *in vivo* conversion (**1**)→(**2**) in penicillin biosynthesis.



Results and Discussion

The isothiazolidinones (**4a**) and (**4b**) were chosen for initial studies because the substituents at C-4 limit possible side reactions involving that site. These compounds were prepared as shown in Scheme 1 *via* a procedure similar to that used by Baldwin *et al.*[4] in the preparation of compound (**4a**). The chlorides (**5a**) and (**5b**) were prepared from the isothiazolidinones (**4a**) and (**4b**) by treatment with sulphuryl chloride in carbon tetrachloride. They reacted with phenyl-lithium in ether at −78 °C to give the respective β-lactams (**6a**) and (**6b**) or, when scrupulously dry conditions were not maintained, mixtures of (**6a**) or (**6b**) and the corresponding chloroamide (**7a**) or (**7b**). When mixtures of compound (**5a**) or (**5b**) with 1.5 equivalents of water were treated with 1.5 equivalents of phenyl-lithium, the chloride (**7a**) or (**7b**) was produced in almost quantitative yield. Treatment of the chlorides (**7a**) and (**7b**) with potassium amide at −78 °C gave the corresponding β-lactams (**6a**) and (**6b**). The high yields of the products obtained in these reactions indicate that other modes of reaction are unimportant.

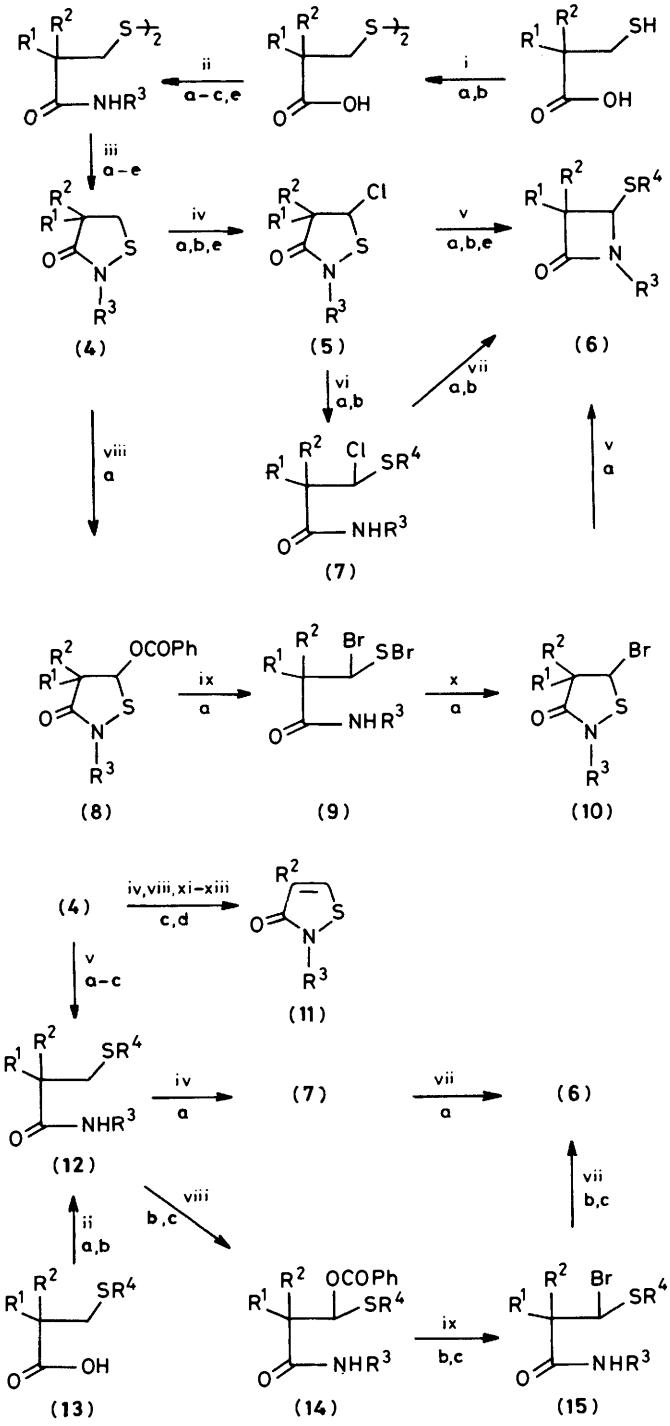
The reaction of the isothiazolidinones (**5a**) and (**5b**) with phenyl-lithium is thought to occur as shown in Scheme 2. Under moist conditions protonation of the intermediate amide anions competes with cyclisation. From the controlled experiment with 1.5 substrate-equivalents of water, it is clear that phenyl-lithium reacts with the isothiazolidinones (**5a**) and (**5b**) faster than it reacts with water, but cyclisation of the intermediate anions is slower than their reaction with water. The high reactivity of isothiazolidinones accounts for the anomalous formation of strained four-membered ring β-lactams by ring contraction of five-membered ring isothiazolidinones.

The ring contraction of isothiazolidinones to β-lactams occurs equally well with displacement of bromide as of chloride. The bromide (**10a**), synthesised from the isothiazolidinone (**4a**), *via* the benzoate (**8a**) and the sulphenyl bromide (**9a**),[4] also reacted with phenyl-lithium to give the β-lactam (**6a**).

An alternative preparation of the β-lactams (**6a**) and (**6b**) was accomplished by ring opening of the isothiazolidinones (**4a**) and (**4b**) prior to halogenation, with subsequent cyclisation. Treatment of the isothiazolidinones (**4a**) and (**4b**) with phenyl-lithium afforded the corresponding amides (**12a**) and (**12b**), identical with samples prepared from the respective carboxylic acids (**13a**) and (**13b**). The synthesis of the β-lactam (**6b**) from the amide (**12b**) *via* the benzoate (**14b**) and the bromide (**15b**) has already been reported.[6] The amide (**12a**) did not react with t-butyl perbenzoate under the conditions used to produce (**14b**), even with 10 molar equivalents of perester, indicating the greater steric hindrance towards hydrogen atom abstraction from the diphenyl-substituted amide (**12a**) than from the dimethyl-substituted analogue (**12b**). However, treatment of compound (**12a**) with sulphuryl chloride afforded the chloride (**7a**), a precursor of the β-lactam (**6a**) (see above).

To extend the examination of the versatility of these reactions, the reactions of the isothiazolidinone (**4c**) with no substituents at C-4 were investigated. This compound was prepared from 3,3′-dithiodipropionic acid using the same method as that used to prepare compounds (**4a**) and (**4b**) (Scheme 1). Treatment of compound (**4c**) with sulphuryl chloride, *N*-chlorosuccinimide, chlorine, t-butyl perbenzoate, or bromine, failed to yield any C-5 substituted isothiazolidinone (**5c**), (**8c**), or (**10c**), thus preventing further elaboration to the β-lactam (**6c**). In each reaction the dihydroisothiazolone (**11c**) was produced. The β-lactam (**6c**) was synthesised from the

† δ-(α-Aminoadipoyl) = 5-amino-5-carboxypentanoyl.

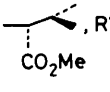


a; $R^1 = R^2 = R^4 = Ph$, $R^3 = Bu^t$

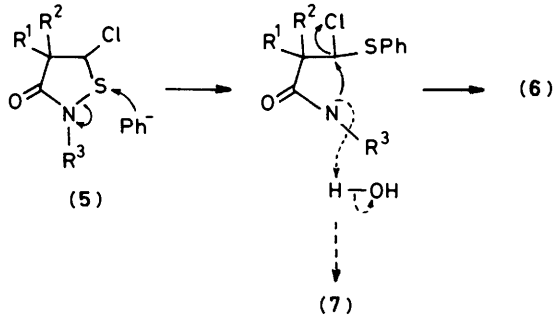
b; $R^1 = R^2 = R^3 = Me$, $R^4 = Ph$

c; $R^1 = R^2 = H$, $R^3 = Me$, $R^4 = Ph$

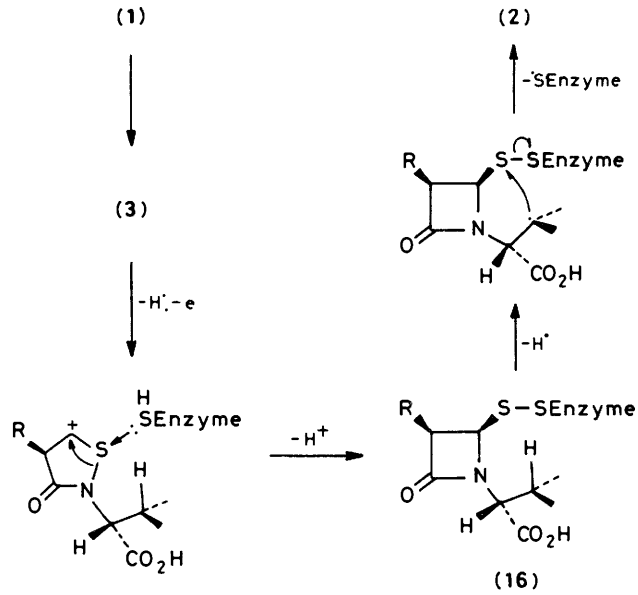
d; $R^1 = H$, $R^2 =$ —$NHCO_2CH_2Ph$, $R^3 =$ 

e; $R^1 = R^2 = Ph$, $R^3 =$  , $R^4 = Me$ 

Scheme 1. *Reagents:* i, I_2; ii, (*a*) $SOCl_2$, (*b*) R^3NH_2, Et_3N; iii, Br_2, pyridine; iv, SO_2Cl_2 v, R^4Li; vi, R^4Li, H_2O; vii, KNH_2; viii, $Bu^tOOCOPh$; ix, HBr; x, NaOH; xi, *N*-chlorosuccinimide; xii, Cl_2; xiii, Br_2



Scheme 2.



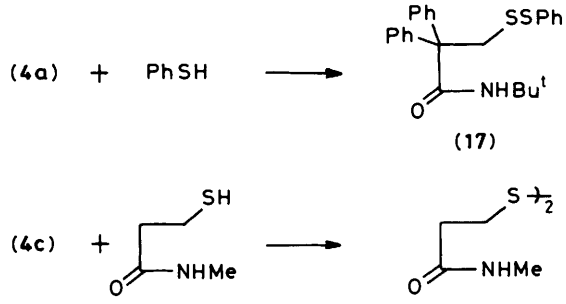
Scheme 3.

isothiazolidinone (**4c**) by the alternative method. Thus, treatment of compound (**4c**) with phenyl-lithium gave the amide (**12c**), from which the synthesis of the β-lactam (**6c**), *via* (**14c**) and (**15c**), has already been reported.[6]

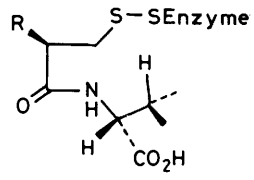
The isothiazolidinone (**4d**) was synthesised[3] since it closely resembles the isothiazolidinone (**3**). Treatment of compound (**4d**) with sulphuryl chloride, *N*-chlorosuccinimide, chlorine, bromine, or t-butyl perbenzoate, gave the dihydroisothiazolone (**11d**). The production of the dihydroisothiazolones (**11c**) and (**11d**) in these reactions of the isothiazolidinones (**4c**) and (**4d**) indicates that for isothiazolidinones not disubstituted at C-4, deprotonation and elimination is a very facile process. The C-5 substituted isothiazolidinones (**5d**), (**8d**), and (**10d**), were not detected in the reactions of compound (**4d**).

The C-4 disubstituted analogue of compound (**4d**), the isothiazolidinone (**4e**), was synthesised as shown in Scheme 1. Treatment of this compound with sulphuryl chloride gave the chloride (**5e**). Subsequent reaction with methyl-lithium afforded a mixture of the diastereoisomers of the β-lactam (**6e**). Thus rearrangement of oxidised isothiazolidinones to β-lactams can be promoted by methyl-lithium or phenyl-lithium, and occurs for a variety of *N*-substituted isothiazolidinones.

The reactions shown in Scheme 1 establish that β-lactams can be prepared from isothiazolidinones. *In vitro*, isothiazolidinones have been oxidised at C-5, and subsequently undergo nucleophile-promoted rearrangement to β-lactams. A similar mechanism could be involved in the *in vivo* transformation



Scheme 4.



(18)

(1)→(2) (Scheme 3). The idea that the nucleophile promoting the biological rearrangement could be a thiol residue of the penicillin synthetase enzyme is particularly appealing, as the formation of the disulphide (**16**) is fundamental to the mechanism proposed for the formation of the thiazolidine ring in (**2**).[6,7] This hypothesis is supported by *in vitro* experiments with model compounds. Thus, thiophenol reacted spontaneously with compound (**4a**) at room temperature to give the disulphide (**17**) and *N*-methyl-3-mercaptopropionamide reacted with compound (**4c**) to give *N,N'*-dimethyl-3,3'-dithiodipropionamide (Scheme 4). The mechanism shown in Scheme 3 is consistent with the results of all labelling and other biosynthetic studies[8,9] and accounts for the crucial role of the thiol group in compound (**1**) in binding the substrate to the enzyme during penicillin biosynthesis.[9]

The formation of disulphides by the reaction of isothiazolidinones with thiols provides *in vitro* models for the formation of the disulphide (**18**) from compound (**1**), *via* (**3**). An alternative mechanism proposed for the formation of the β-lactam ring in compound (**2**),[6,10] proceeding *via* the disulphide (**18**), did not rationalise the formation of (**18**) from (**1**).

Experimental

M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. I.r. spectra as liquid films, unless otherwise stated, were recorded on a Shimadzu IR-27G spectrometer. ^{1}H N.m.r. spectra were recorded in carbon tetrachloride using Me_4Si as internal standard, unless otherwise stated, on a Varian T60 spectrometer. Mass spectra were recorded on an AEI MS902 spectrometer and a Hewlett Packard 5982A spectrometer. Microanalyses were performed by the microanalytical laboratory, University of Otago. All solvents were purified and dried by standard methods. Ether refers to diethyl ether and light petroleum to the fraction with b.p. 50—70 °C.

2,2,2',2'-Tetraphenyl-3,3'-dithiodipropionic Acid.—Iodine (2.55 g, 10 mmol) was added in small portions to a mixture of 2,2-diphenyl-3-mercaptopropionic acid[11] (5.2 g, 20 mmol), sodium hydroxide (0.8 g, 20 mmol), and potassium iodide (0.1 g, 0.6 mmol) in methanol (100 ml). After 15 min, sodium sulphite was added to decolourise the solution and the solvent was removed under reduced pressure. The residue was extracted with ethyl acetate and the extracts were evaporated to give crude 2,2,2',2'-tetraphenyl-3,3'-dithiodipropionic acid (4.9 g, 94%) as a white solid, m.p. 120—124 °C (lit.,[4] 125—128 °C).

2,2,2',2'-Tetramethyl-3,3'-dithiodipropionic Acid.—This compound was prepared from 2,2-dimethyl-3-mercaptopropionic acid[12] by treatment with iodine as described above. The crude product recrystallised from aqueous ethanol as white plates of the dithiodicarboxylic acid in 72% yield, m.p. 144—147 °C (lit.,[13] 145—146 °C).

2,2,2',2'-Tetraphenyl-N,N'-di-t-butyl-3,3'-dithiodipropionamide.—A mixture of 2,2,2',2'-tetraphenyl-3,3'-dithiodipropionic acid (4.6 g, 9 mmol) and thionyl chloride (6.0 g, 51 mmol) in dry benzene (50 ml) was heated under reflux for 4 h. The mixture was concentrated under reduced pressure and the residue was dissolved in dry dichloromethane, then added dropwise with stirring to an ice-cooled solution of t-butylamine (4.0 g, 55 mmol) and triethylamine (5.0 g, 49 mmol) in dichloromethane (50 ml). After 2 h at room temperature the mixture was repeatedly washed with water, then dried ($MgSO_4$) and concentrated to give crude 2,2,2',2'-tetraphenyl-*N,N'*-di-t-butyl-3,3'-dithiodipropionamide (4.7 g, 84%) as a glass with spectral properties consistent with those previously reported.[4]

N,N',2,2,2',2'-Hexamethyl-3,3'-dithiodipropionamide.—The crude acid chloride prepared from 2,2,2',2'-tetramethyl-3,3'-dithiodipropionic acid (5.3 g, 20 mmol) by treatment with thionyl chloride as described above, was dissolved in dry dichloromethane (20 ml) then added dropwise with stirring to an ice-cooled mixture of dichloromethane (50 ml) and 25% aqueous methylamine (50 ml). After 2 h at room temperature the dichloromethane layer was separated, repeatedly washed with water, then dried ($MgSO_4$) and concentrated to give crude *N,N',2,2,2',2'*-hexamethyl-3,3'-dithiodipropionamide (4.8 g, 82%) as an oil, δ($CDCl_3$) 6.3 (2 H, br), 3.05 (4 H, s), 2.82 (6 H, d, *J* 5 Hz), and 1.27 (12 H, s); $\nu_{max.}$ 3 350, 1 634, and 1 541 cm^{-1}; *m/z* 292 (M^+, 5%) and 146 (100).

N,N'-Dimethyl-3,3'-dithiodipropionamide.—Treatment of 3,3'-dithiodipropionic acid (Aldrich) with thionyl chloride and, subsequently, with methylamine as described above gave, after recrystallisation from aqueous ethanol, the required amide in 69% yield, m.p. 104—106 °C (lit.,[14] 105—108 °C).

N,N,'-Bis(1-methoxycarbonyl-2-methylpropyl)-2,2,2',2'-tetraphenyl-3,3'-dithiodipropionamide.—The crude acid chloride prepared from 2,2,2',2'-tetraphenyl-3,3'-dithiodipropionic acid (4.6 g, 9 mmol) by treatment with thionyl chloride as described above, was dissolved in dry dichloromethane (20 ml) then added dropwise with stirring to an ice-cooled solution of L-valine methyl ester hydrochloride (5.0 g, 30 mmol) and triethylamine (7.5 g, 75 mmol) in dichloromethane (50 ml). After 2 h at room temperature the mixture was washed repeatedly with water, then dried ($MgSO_4$) and concentrated to give the crude amide (4.8 g, 72%) as a glass, δ($CDCl_3$) 7.3—7.0 (20 H, m), 5.9 (2 H, br d, *J* 9 Hz), 4.45 (2 H, dd, *J* 4 and 9 Hz), 3.68 (4 H, s), 3.64 (6 H, s), 2.0 (2 H, m), 0.70 (6 H, d, *J* 7 Hz) and 0.60 (6 H, d, *J* 7 Hz); $\nu_{max.}$ 3 480, 1 726, 1 656, and 1 479 cm^{-1}; *m/z* 370 (M^+/2, 2%) and 180 (100); *m/z* (C.I.; isobutane) 741 (MH^+).

4,4-Diphenyl-2-t-butylisothiazolidin-3-one (**4a**).—A solution of 2,2,2',2'-tetraphenyl-*N,N'*-di-t-butyl-3,3'-dithiodipropionamide (4.7 g, 7.5 mmol) and pyridine (1.2 g, 15 mmol) in dichloromethane (100 ml) under N_2, cooled to −78 °C, was treated dropwise with a solution of bromine (1.2 g, 7.5 mmol) in dichloromethane (10 ml). After 15 min the mixture

was warmed to room temperature, concentrated, and the residue chromatographed on silica. Elution with chloroform afforded the isothiazolidinone (**4a**), which recrystallised from light petroleum as needles (3.3 g, 70%), m.p. 88—90 °C (lit.,[4] 89—90 °C).

2,4,4-*Trimethylisothiazolidin*-3-*one* (**4b**).—Treatment of *N,N'*,2,2,2',2'-hexamethyl-3,3'-dithiodipropionamide with bromine as described above afforded the isothiazolidinone (**4b**) as an oil in 57% yield, b.p. 120—130 °C at 0.8 mmHg (GKR); δ 3.27 (2 H, s), 2.85 (3 H, s), and 1.24 (6 H, s); $\nu_{max.}$ 1 652 cm^{-1}; *m/z* 145 (M^+, 78%), 56 (65), and 55 (100); *m/z* 145.0558 (M^+) [Calc. for $C_6H_{11}NOS$ (M^+) *m/z* 145.0561]. This compound was too hygroscopic for satisfactory microanalysis.

2-*Methylisothiazolidin*-3-*one* (**4c**).—Treatment of *N,N'*-dimethyl-3,3'-dithiodipropionamide with bromine as described above afforded the isothiazolidinone (**4c**) as an oil in 47% yield, b.p. 80—85 °C at 0.8 mmHg (lit.,[15] 46—47 °C at 0.05 mmHg).

4-*Benzyloxyformamido*-2-(1-*methoxycarbonyl*-2-*methylpropyl*)*isothiazolidin*-3-*one* (**4d**).—Treatment of benzyloxycarbonylcystinylvaline methyl ester[3] with bromine as described above afforded the isothiazolidinone (**4d**), recrystallised from light petroleum in 38% yield, m.p. 61—63 °C (lit.,[3] 65 °C).

2-(1-*Methoxycarbonyl*-2-*methylpropyl*)-4,4-*diphenylisothiazolidin*-3-*one* (**4e**).—Treatment of *N,N'*-bis(1-methoxycarbonyl-2-methylpropyl)-2,2,2',2'-tetraphenyl-3,3'-dithiodipropionamide with bromine as described above afforded the isothiazolidinone as an oil in 24% yield, b.p. 60—80 °C at 0.1 mmHg (GKR); δ 7.3 (10 H, m), 4.74 (1 H, d, *J* 8 Hz), 4.04 (2 H, s), 3.72 (3 H, s), 2.3 (1 H, m), 1.02 (3 H, d, *J* 7 Hz), and 0.92 (3 H, d, *J* 7 Hz); $\nu_{max.}$ 1 741 and 1 675 cm^{-1}; *m/z* 369 (M^+, 100%), 310 (94), and 254 (57); *m/z* 369.1390 (M^+) [Calc. for $C_{21}H_{23}NO_3S$ (M^+) *m/z* 369.1399].

5-*Chloro*-4,4-*diphenyl*-2-*t*-*butylisothiazolidin*-3-*one* (**5a**).—Sulphuryl chloride (1.35 g, 10 mmol) in carbon tetrachloride (10 ml) was added dropwise at room temperature to a stirred solution of the isothiazolidinone (**4a**) (3.1 g, 10 mmol) in carbon tetrachloride (50 ml). The resultant mixture was treated with $MgSO_4$, then filtered and concentrated to give white crystals of the crude chloride (**5a**) (2.45 g, 71%), m.p. 92—94 °C (decomp.); δ 7.5—7.0 (10 H, m), 6.18 (1 H, s), and 1.49 (9 H, s).

5-*Chloro*-2,4,4-*trimethylisothiazolidin*-3-*one* (**5b**).—Treatment of the isothiazolidinone (**4b**) with sulphuryl chloride as described above gave the crude chloride (**5b**) as an oil in 80% yield, δ 5.46 (1 H, s), 3.00 (3 H, s), and 1.37 (6 H, s).

5-*Chloro*-2-(1-*methoxycarbonyl*-2-*methylpropyl*)-4,4-*diphenylisothiazolidin*-3-*one* (**5e**).—Treatment of the isothiazolidinone (**4e**) with sulphuryl chloride as described above gave the crude chloride (**5e**) as an oil in 65% yield, δ 7.6—7.1 (10 H, m), 6.38 (1 H, s), 4.83 (1 H, d, *J* 8 Hz), 3.56 (3 H, s), 2.3 (1 H, m), and 1.02 (6 H, d, *J* 6 Hz).

3,3-*Diphenyl*-4-*phenylthio*-1-*t*-*butylazetidin*-2-*one* (**6a**).—A solution of the chloride (**5a**) (0.34 g, 1 mmol) in ether (20 ml) under N_2, cooled to −78 °C, was treated with *ca.* 1.6M-phenyl-lithium (0.7 ml, 1.1 mmol). After 30 min the mixture was warmed to room temperature and treated with water. The ether layer was separated, dried ($MgSO_4$) and concentrated. Distillation of the residue afforded the β-lactam (**6a**) (0.335 g, 86%) as a colourless oil, b.p. 120—130 °C at 1.0 mmHg (GKR), δ 7.3—6.9 (15 H, m), 5.53 (1 H, s), and 1.42 (9 H, s); $\nu_{max.}$ 1 752 cm^{-1}, *m/z* 387 (M^+, 14%), 288 (30), 278 (40), and 194 (100), *m/z* 387.1646 (M^+) [Calc. for $C_{25}H_{25}NOS$ (M^+) *m/z* 387.1657] (Found: C, 77.3; H, 6.7; N, 3.4. Calc. for $C_{25}H_{25}NOS$: C, 77.48; H, 6.50; N, 3.61%).

1,3,3-*Trimethyl*-4-*phenylthioazetidin*-2-*one* (**6b**).—Treatment of the chloride (**5b**) with phenyl-lithium under anhydrous conditions as described above afforded the β-lactam (**6b**) in 89% yield, b.p. 70—80 °C at 1.0 mmHg (GKR), with spectral properties consistent with those previously reported.[6]

1-(1-*Methoxycarbonyl*-2-*methylpropyl*)-4-*methylthio*-3,3-*diphenylazetidin*-2-*one* (**6e**).—Treatment of the chloride (**5e**) with methyl-lithium as described above for the reactions of the chlorides (**5a**) and (**5b**) with phenyl-lithium afforded an oil which crystallised from ethyl acetate–light petroleum as flakes of the β-lactam (**6e**) in 39% yield, m.p. 81—88 °C (lit.[16] 75—87 °C). The diastereoisomers were in the ratio *ca.* 2:1 (^1H n.m.r.)[16]

3-*Chloro*-2,2-*diphenyl*-3-*phenylthio*-N-*t*-*butylpropionamide* (**7a**).—A solution of the chloride (**5a**) (0.34 g, 1 mmol) in ether (20 ml) and water (27 mg, 1.5 mmol) under N_2, cooled at −78 °C, was treated with *ca.* 1.6M-phenyl-lithium (0.95 ml, 1.5 mmol). After 30 min the mixture was warmed to room temperature and treated with water. The ether layer was separated, dried ($MgSO_4$), and concentrated to give the crude chloride (**7a**) as an oil (0.37 g, 88%), δ 7.6—6.9 (15 H, m), 6.22 (1 H, s), 5.3 (1 H,br), and 1.22 (9 H, s).

3-*Chloro*-N,2,2-*trimethyl*-3-*phenylthiopropionamide* (**7b**).—Treatment of the chloride (**5b**) with phenyl-lithium in moist ether as described above gave the chloride (**7b**) as an oil in 84% yield, δ 7.5—7.1 (5 H, m), 6.0 (1 H, br), 5.67 (1 H, s), 2.60 (3 H, d, *J* 5 Hz), and 1.42 (6 H, s).

Reaction of the Chloride (**7a**) *with Potassium Amide.*—The chloride (**7a**) (0.34 g, 0.8 mmol) was dissolved in dichloromethane (10 ml) and cooled to −78 °C, then added dropwise to a solution of potassium amide at −78 °C which had been prepared from ammonia (50 ml), potassium (40 mg, 1 mmol), and ferric nitrate (*ca.* 2 mg). After 30 min at −78 °C ammonia was removed under reduced pressure, dichloromethane (25 ml) and water (25 ml) were added, the organic layer was separated, washed with water, dried ($MgSO_4$) and concentrated, and the residue was distilled to give the β-lactam (**6a**) (0.26 g, 82%), identical in all respects with the sample obtained as described above.

Reaction of the Chloride (**7b**) *with Potassium Amide.*—Treatment of the chloride (**7b**) with potassium amide as described above afforded the β-lactam (**6b**) in 89% yield, identical in all respects with the sample obtained as described above.

Reaction of the Bromide (**10a**) *with Phenyl-lithium.*—Treatment of the bromide (**10a**)[4] with phenyl-lithium under anhydrous conditions as described above afforded the β-lactam (**6a**) in 64% yield, identical in all respects with the sample obtained as described above.

Reactions of the Isothiazolidinones (**4c**) *and* (**4d**) *with Sulphuryl Chloride, Chlorine, Bromine, and* N-*Chlorosuccinimide.*—A solution of the isothiazolidinone (**4c**) or (**4d**) (1 mmol) in carbon tetrachloride (20 ml) was treated at room temperature with sulphuryl chloride, chlorine, bromine, or *N*-chlorosuccinimide (1 mmol), either neat or as a solution in carbon tetrachloride. Analysis by t.l.c. and ^1H n.m.r. spectroscopy indicated virtually complete reaction of the isothiazolinones (**4c**) and (**4d**) and formation of the

corresponding dihydroisothiazolones (**11c**) and (**4d**),[3,14] but not of the respective isothiazolidinones (**5c**) and (**5d**) or (**10c**) and (**10d**). Reactions in other solvents and at lower temperatures produced similar results.

Reactions of the Isothiazolidinones (**4c**) *and* (**4d**) *with t-Butyl Perbenzoate.*—A mixture of the isothiazolidinone (**4c**) or (**4d**) (1 mmol), t-butyl perbenzoate (0.1 g, 2 mmol), and cuprous chloride (*ca.* 5 mg) in benzene (10 ml) under nitrogen, was heated under reflux for 4 h, then cooled. Analysis by t.l.c. and ^{1}H n.m.r. spectroscopy indicated incomplete reaction of the isothiazolidinones (**4c**) and (**4d**) and formation of the corresponding dihydroisothiazolones (**11c**) and (**11d**),[3,14] but not of the isothiazolidinones (**8c**) and (**8d**).

Reaction of the Isothiazolidinone (**4a**) *with Phenyl-lithium.*—Treatment of the isothiazolidinone (**4a**) with phenyl-lithium under anhydrous conditions as described above gave 2,2-diphenyl-3-phenylthio-*N*-t-butylpropionamide (**12a**), which recrystallised from light petroleum as needles in 82% yield, m.p. 80—81 °C, δ 7.4—6.9 (15 H, m), 5.3 (1 H, br), 3.83 (2 H, s), and 1.25 (9 H, s); $\nu_{max.}$(Nujol) 3 425 and 1 668 cm^{-1}; *m/z* 389 (M^+, 43%), 280 (9), 266 (10), and 180 (100); *m/z* 389.1777 (M^+) [Calc. for $C_{25}H_{27}NOS$ (M^+) *m/z* 389.1813] (Found: C, 76.95; H, 6.9; N, 3.6. Calc. for $C_{25}H_{27}NOS$: C, 77.08; H, 6.99; N, 3.60%).

Reaction of the Isothiazolidinone (**4b**) *with Phenyl-lithium.*—Treatment of the isothiazolidinone (**4b**) with phenyl-lithium under anhydrous conditions as described above afforded *N*,2,2-trimethyl-3-phenylthiopropionamide (**12b**), which recrystallised from ethyl acetate–light petroleum as needles in 92% yield, m.p. 60—61 °C (lit.,[6] 61.5—62.0 °C), identical with a sample synthesised from 2,2-dimethyl-3-phenylthiopropionic acid (**13b**).[6]

Reaction of the Isothiazolidinone (**4c**) *with Phenyl-lithium.*—Treatment of the isothiazolidinone (**4c**) with phenyl-lithium under anhydrous conditions as described above afforded *N*-methyl-3-phenylthiopropionamide (**12c**), which recrystallised from ethyl acetate–light petroleum as needles in 83% yield, m.p. 90—92 °C (lit.,[6] 89—91 °C).

2,2-*Diphenyl*-3-*phenylthio*-N-*t-butylpropionamide* (**12a**).—Treatment of 2,2-diphenyl-3-phenylthiopropionic acid (**13a**)[11] with thionyl chloride and, subsequently, with t-butylamine as described above afforded the amide (**12a**) in 90% yield, identical in all respects with the sample obtained as described above.

Attempted Reaction of the Amide (**12a**) *with t-Butyl Perbenzoate.*—A mixture of the amide (0.2 g, 0.5 mmol), t-butyl perbenzoate (0.26 g, 5 mmol), and cuprous chloride (*ca.* 5 mg) in benzene (20 ml) under nitrogen, was heated under reflux for 12 h, then cooled. Analysis by t.l.c. and ^{1}H n.m.r. spectroscopy indicated no reaction of the amide (**12a**), but >95% decomposition of t-butyl perbenzoate.

Reaction of the Amide (**12a**) *with Sulphuryl Chloride.*—Treatment of the amide (**12a**) with sulphuryl chloride as described above afforded the chloride (**7a**) in 60% yield, identical in all respects with the sample obtained as described above.

2,2-*Diphenyl*-3-*phenyldithio*-N-*t-butylpropionamide* (**17**).—A mixture of the isothiazolidinone (**4a**) (0.31 g, 1 mmol) and thiophenol (0.11 g, 1 mmol) in carbon tetrachloride (10 ml) was stirred at room temperature for 4 h, then concentrated under reduced pressure. The residue crystallised from light petroleum–dichloromethane to give the disulphide (**17**) (0.38 g, 89%) as a powder, m.p. 96—98 °C; δ($CDCl_3$) 7.4—7.1 (15 H, m), 5.3 (1 H, br), 3.90 (2 H, s), and 1.25 (9 H, s); $\nu_{max.}$ 3 440, 1 670, 1 509, and 1 451 cm^{-1}; *m/z* 421 (M^+, 9%), 312 (26), 280 (24), 194 (57), and 180 (100); *m/z* 421.1542 (M^+) [Calc. for $C_{25}H_{27}NOS_2$ (M^+) *m/z* 421.1534].

Reaction of the Isothiazolidinone (**4c**) *with* 3-*Mercapto*-N-*methylpropionamide.*—A mixture of the isothiazolidinone (**4c**) (0.12 g, 1 mmol) and 3-mercapto-*N*-methylpropionamide[17] (0.12 g, 1 mmol) in chloroform was stirred at room temperature for 24 h, then concentrated under reduced pressure. The residue recrystallised from ethyl acetate–light petroleum to give *N,N'*-dimethyl-3,3'-dithiodipropionamide (0.19 g, 81%), identical in all respects with the sample obtained as described above.

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