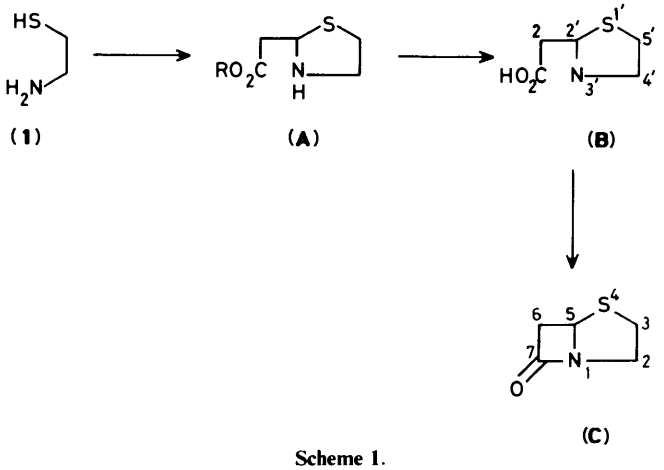
# Studies on Amino Acid Derivatives. Part 7.[1] General Method for the Synthesis of Penam and Cepham and Their Substituted Derivatives

**Takuo Chiba,* Jun-ichi Sakaki, Takumi Takahashi, Kumi Aoki, Akiko Kamiyama, Chikara Kaneko,* and (in part) Masayuki Sato**
*Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan*

Penam (7-oxo-4-thia-1-azabicyclo[3.2.0]heptane), a basic skeleton of penicillin-type β-lactams, has been synthesized as a stable compound from thiazolidinylacetic acid. The key step in this synthesis is the formation of the β-lactam ring by Mukaiyama-Ohno's procedure. Three methods are developed for the synthesis of thiazolidinylacetic acid from cysteamine by reactions with ethyl propiolate, ethyl ethoxycarbonylacetimidate, or t-butyl formylacetate. Using appropriate derivatives of the latter compounds, 5-, 6-, and 5,6-substituted derivatives of penam are also synthesized. The yields of the bicyclic β-lactams are shown to be strongly dependent upon the pattern of substituents on the thiazolidinylacetic acid. The synthesis of cephams using homocysteamine is also described.

Recently, we reported in a communication form [2,3] the synthesis of penam and its 6-methyl derivatives from corresponding thiazolidinylacetic acids. The key step in these syntheses was the formation of the β-lactam ring by using Mukaiyama-Ohno's procedure [$Ph_3P$–(2-PyS)$_2$/MeCN].* This paper is a full description of that work together with the synthesis of some new derivatives of penam and cepham, showing that this method has wide application in the synthesis of these bicyclic β-lactams.

Though our primary aim was the synthesis of penam itself (an unknown compound at that time), our final synthetic target was a chiral penam having a carboxy group at the 2-position, by using D-cysteine as the starting material. Thus, with cysteamine (**1**) as the starting material (which will be replaced by D-cysteine in our future study), we chose the route shown in Scheme 1




**Scheme 1.**

involving thiazolidinylacetic acid (**B**) or its ester (**A**) as the intermediates whose cyclization would entail N-1 to C-7 bond formation at the final stage. The route was essentially the same as that developed in the pioneering work of Sheehan in the syntheses of penicillins from D-penicillamine [7,8] and the success of the synthesis depended on β-lactam ring closure of thiazolidinylacetic acid or its ester. As expected, difficulty was encountered in cyclizing these compounds to bicyclic systems. However, while many methods had been applied without success either to the acid (**B**) (including the DCC method used in Sheehan's synthesis) or to the ester (**A**) to effect the β-lactam formation,† only the use of Mukaiyama-Ohno's method [4,5] to the acid (**B**) gave the desired β-lactam (**C**).

In this paper, we report our results in three parts: (i) synthesis of thiazolidinylacetic acid and its derivatives; (ii) cyclization of these acids to bicyclic β-lactams (penam and its 5- and/or 6-alkylated derivatives); and (iii) synthesis of cepham derivatives from homocysteamine by the same method.

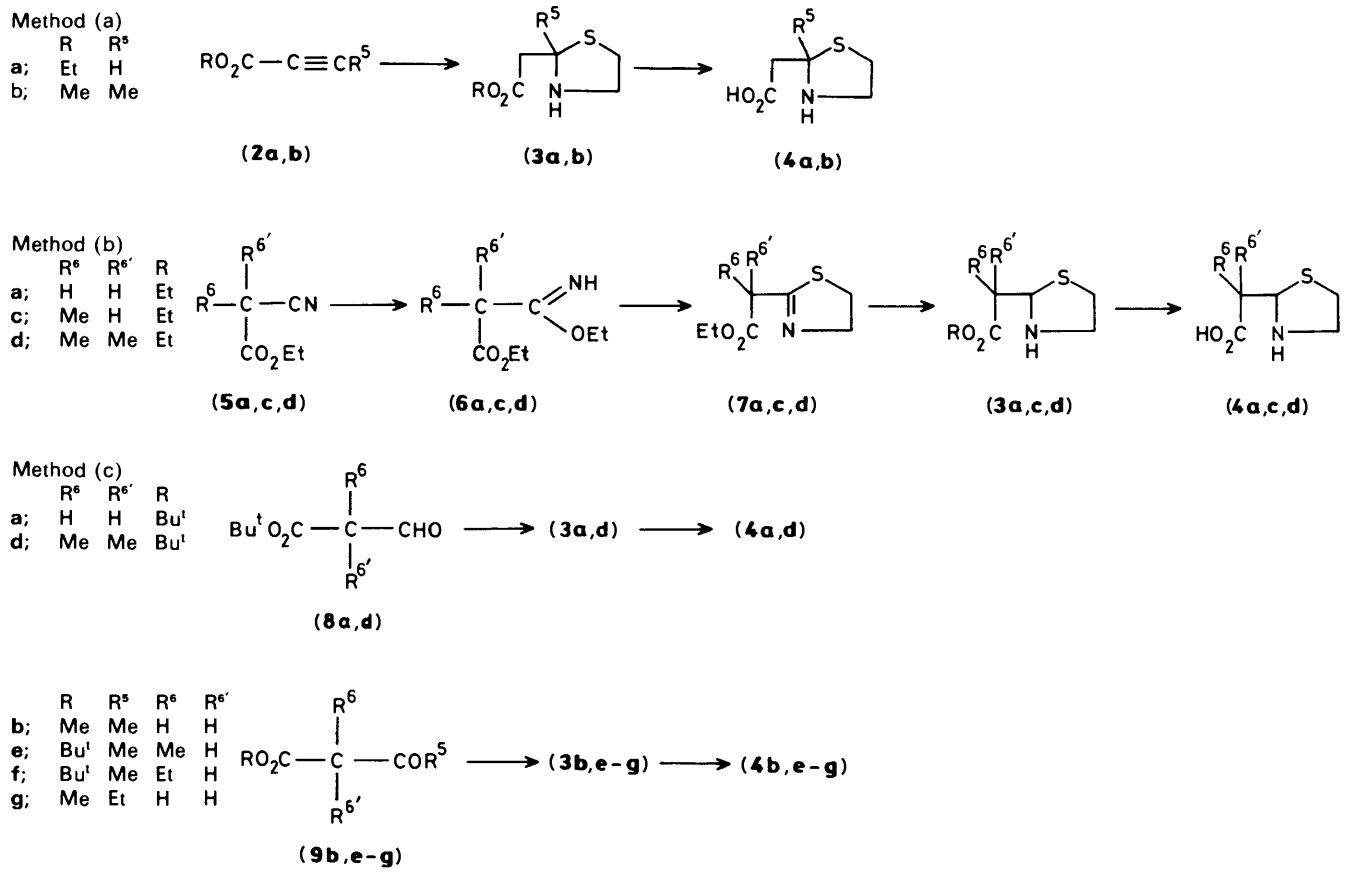
## Results and Discussion

*Synthesis of Thiazolidinylacetic Acid and its Derivatives.*— Three methods, (a), (b), and (c), were developed for the synthesis of thiazolidinylacetic acid from cysteamine (**1**) *via* the corresponding ester. Method (a) was the reaction of (**1**) with ethyl propiolate [2] and method (b) was the reduction of dihydrothiazolylacetate obtained from the reaction of (**1**) with ethyl ethoxycarbonylacetimidate.[3] A facile synthesis of t-butyl formylacetate (*vide infra*) provided another route, method (c), to thiazolidinylacetic acid.

In method (a), cysteamine hydrochloride (**1**)·HCl reacted with an equimolar amount of ethyl propiolate (**2a**) in the presence of triethylamine in ethanol to give ethyl thiazolidin-2-ylacetate (**3a**) in 65% yield. In method (b), the reaction of (**1**)·HCl with ethyl ethoxycarbonylacetimidate (**6a**), which was easily prepared from the reaction of ethyl cyanoacetate (**5a**) with an equimolar amount of ethanol in ether saturated with dry hydrogen chloride, gave ethyl 4,5-dihydrothiazol-2-ylacetate (**7a**) in 65% yield. Reduction of dihydrothiazolylacetate (**7a**) by sodium cyanoborohydride in methanol saturated with dry hydrogen chloride gave the acetate (**3a**; R = Et) in 65% yield. In method (c) t-butyl formylacetate (**8a**), which was obtained in 77% yield by heating formyl Meldrum's acid (5-formyl-2,2-dimethyl-1,3-dioxin-4,6-dione) in benzene in the presence of t-butyl alcohol,[9] reacted with (**1**) to give t-butyl thiazolidin-2-ylacetate (**3a**; R = Bu$^t$) in 88% yield. More conveniently, the same acetate (**3a**) was obtained in a comparable yield from formyl Meldrum's acid without isolation of t-butyl formyl-

* Though Mukaiyama's reagent, $PPh_3$–(2-PyS)$_2$, was originally used for peptide synthesis using $CH_2Cl_2$ or DMF as solvent,[4] Ohno *et al.* used this reagent for the formation of β-lactams from β-amino acids and found acetonitrile as a solvent of choice for this reaction.[5] However, its application to the synthesis of bicyclic β-lactam was only limited to some carbapenams.[6]

† The following β-lactam formation reactions were applied either to the acid (**B**) or the ester (**A**): (i) Grignard reagent addition to (**A**), (ii) dehydration of (**B**) by DCC or $PPh_3$–(2-PyS)$_2$–$CH_2Cl_2$ or DMF, (iii) cyclization of (**B**) by treatment with $SOCl_2$ followed by triethylamine.




**Scheme 2.**

acetate (see the Experimental section). Though the acetate (**3a**; R = Et) was hydrolysed with concentrated hydrochloric acid to afford thiazolidin-2-ylacetic acid hydrochloride (**4a**)·HCl in satisfactory yield (*ca.* 50%), the same acid was obtained in a much higher yield (82%) when the acetate (**3a**; R = Bu$^t$) was treated with dry hydrogen chloride in dichloromethane.

By the application of method (a), methyl 2-methylthiazolidin-2-ylacetate (**3b**; R = Me) was obtained from the reaction of (**1**) with methyl but-2-ynoate (**2b**) in 58% yield. By adaptation of method (b), ethyl 2-(4,5-dihydrothiazol-2-yl)propionate (**7c**) and ethyl 2-(4,5-dihydrothiazol-2-yl)isobutyrate (**7d**) were obtained from the reaction of (**1**) with ethyl 2-ethoxycarbonylpropionimidate (**6c**) or ethyl 2-ethoxycarbonylisobutyrimidate (**6d**), in 64% and 68% yields, respectively. These dihydrothiazole derivatives (**7c**) and (**7d**) were reduced by sodium cyanoborohydride under the same acidic conditions as in the conversion of (**7a**) to (**3a**) to give the corresponding substituted thiazolidinylacetates (**3c**) and (**3d**) in 54% and 46% yields, respectively. In method (c), methyl acetoacetate (**9b**) and methyl propionylacetate (**9g**) in place of the formylacetate (**8a**) reacted with cysteamine (**1**) to give methyl 2-methylthiazolidin-2-ylacetate (**3b**) and methyl 2-ethylthiazolidin-2-ylacetate (**3g**) in 85% and 70% yields, respectively. When 2-substituted t-butyl acetoacetates (**9e**) and (**9f**) were used in this reaction, the corresponding 2-substituted t-butyl 2-methylthiazolidin-2-ylacetates (**3e**) and (**3f**) were obtained in *ca.* 55% yield. Though all of these acetates (**3b**—**g**) were again hydrolysed to the corresponding acids (**4b**—**g**) in satisfactory yields by treatment with concentrated hydrochloric acid, t-butyl acetates (**3e**) and (**3f**) were especially prone to the deprotection and afforded the acids in higher yields under much milder acidic conditions (HCl–$CH_2Cl_2$, room temperature).

*Cyclization of Thiazolidinylacetic Acids to Bicyclic β-Lactams.*—Since attempted cyclization of thiazolidin-2-ylacetate (**3a**) using organometallic compounds such as methylmagnesium iodide,[10] triethylaluminium,[11] or butyllithium[12] had failed to give the desired cyclized product, we investigated the ring closure of free thiazolidin-2-ylacetic acid (**4a**) by conventional methods. Though DCC, chlorination by thionyl chloride followed by base, carbonyl di-imidazole, or even Mukaiyama's reagent[4] in dichloromethane was used for this reaction, none of the cyclized product was obtained. Only Mukaiyama-Ohno's method using triphenylphosphine and di-2-pyridyl disulphide in acetonitrile[5] (10mM solution) gave the desired penam (**10a**) in 8% yield. Dilution of a solution of (**4a**) in acetonitrile to 2mM in the above reaction resulted only in a slight increase of the yield (9%). The other products in these reactions were intractable oils with high polarity, whose i.r. spectra revealed only an amide carbonyl band (*ca.* 1 630 cm$^{-1}$). The structure of (**10a**) was confirmed by elemental analysis and spectral measurements. Although it has been reported that carbapenam (**11**), the carbocyclic analogue of penam, is unstable,[13] compound (**10a**) is stable and can be stored indefinitely. Similar treatment of the acid (**4b**) with Mukaiyama-Ohno's reagent gave 5-methylpenam (**10b**) in 30% yield.

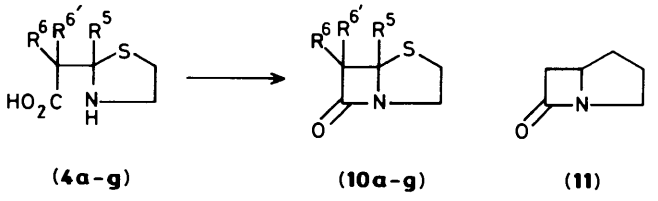
Substituted penams (**10c**—**g**) were also obtained from the corresponding thiazolidinylacetic acids and the yields obtained under a standard set of reaction conditions are summarized in the Table.

Although the acetic acid (**4c**) existed as a mixture of diastereoisomers (*ca.* 1:1 ratio), only a single 6-methylpenam (**10c**) was obtained. A small coupling constant (*J* 1.4 Hz) between 5-H and 6-H in (**10c**) indicates clearly the *trans*-relationship between these two protons. This fact indicates that

**Table.** Cyclization of thiazolidinylacetic acids (**4a**—**g**) to penams (**10a**—**g**) by Mukaiyama-Ohno's procedure

| Thiazolidinylacetic acids | | | | Penams | |
|---|---|---|---|---|---|
| Compd. | $R^5$ | $R^6$ | $R^{6'}$ | Compd. | Yield[a] (%) |
| (**4a**) | H | H | H | (**10a**) | 8[b] |
| (**4b**) | Me | H | H | (**10b**) | 30[c] |
| (**4c**) | H | Me | H | (**10c**) | 70[b] |
| (**4d**) | H | Me | Me | (**10d**) | 71[b] |
| (**4e**) | Me | Me | H | (**10e**) | 41[c] |
| (**4f**) | Me | Et | H | (**10f**) | 23[c] |
| (**4g**) | Et | H | H | (**10g**) | 21[c] |

[a] All reactions were carried out using 0.01 M solution of acids (**4**). [b] Yields from the acids (**4**). [c] The reactions were carried out from the esters (**3**) without isolation of the acids (**4**). Yields from the esters (**3**).

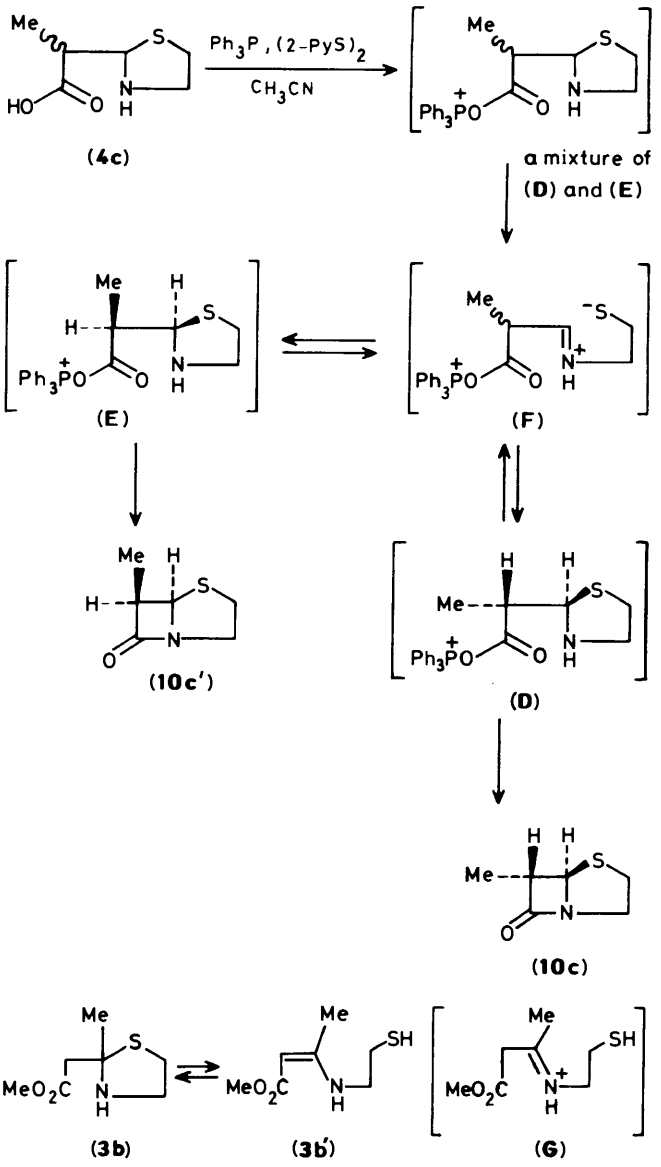



**Scheme 3.**

at least one diastereoisomer of (**4c**) cyclizes to (**10c**) with inversion of configuration at the 2-position of (**4c**). Methyl 2-methylthiazolidin-2-ylacetate (**3b**) exists in tautomeric equilibria with the corresponding β-aminocrotonate [(**3b'**) δ of Me = 1.96 and δ of 2-H = 4.50] in *ca.* 4:1 ratio, as judged from n.m.r. spectroscopy.* Thus, such equilibrium may also exist for the unsubstituted thiazolidinylacetic acid derivatives, although the corresponding β-aminoacrylates cannot be detected by n.m.r. spectroscopy. By assuming that the activated esters (**D**) and (**E**) may equilibrate *via* the iminium ion (**F**), the apparently exclusive formation of the *trans*-β-lactam (**10c**) from (**4c**) is explained by the equilibrium being displaced to (**D**) because (**D**) cyclizes much faster than (**E**). The large difference between the cyclization reactions of (**D**) ⟶ (**10c**) and (**E**) ⟶ (**10c'**) is due to the fact that the transition state of the former [which reflects stability of the product (**10c**)] is much more stable than that of the latter. This explanation is in good accordance with the cyclizations of (**4e**) and (**4f**) (both are again mixtures of diastereoisomers) to the corresponding β-lactams (**10e**) and (**10f**). In these cases, the products are mixtures of diastereoisomers, showing that the rate of cyclization of each isomer does not differ significantly due to the presence of the 2-substituent in each of the activated esters.

It is noteworthy that the presence of a methyl group on the acetic acid chain [e.g., (**4c**) and (**4d**)] remarkably enhances the yields of β-lactams (Table 1). Thus, although the yield of the penam itself (**10a**) was only 8%, the yields of (**10c**) and (**10d**) obtained under the same cyclization conditions were *ca.* 70%. A slight increase of the yield (30%) of (**10b**) indicates that the presence of methyl group at the 2-position in the thiazolidine ring may also facilitate the cyclization. All of these data suggest that the yields of β-lactams increase markedly as the number of substituents on the β-lactam ring being formed increases. The same phenomena were observed when β-amino acid esters were cyclized to monocyclic β-lactams using a Grignard reagent as the catalyst.[15]

* The same equilibration was also observed for ethyl (2-methylthiazolidin-2-ylacetate: see ref. 14.



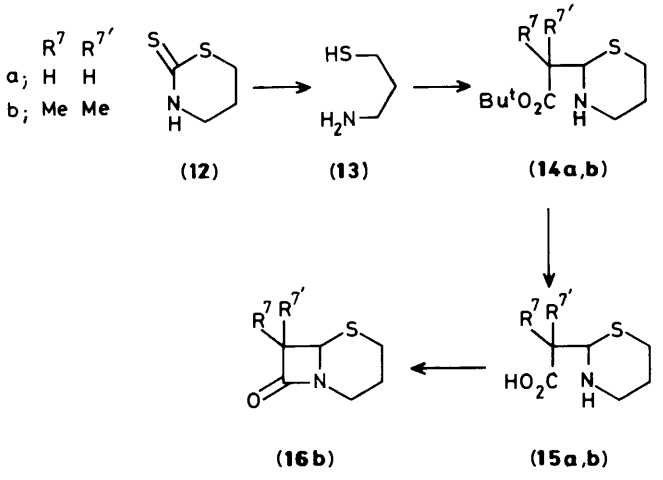

**Scheme 4.**

Although the reason is not clear at present, it is important to note for further use of the present method to the synthesis of related β-lactams that the presence of substituents on the thiazolidinylacetic acid greatly enhances the yield of β-lactams.

*Synthesis of Cepham Derivatives from Homocysteamine.*—Perhydro-1,3-thiazine-2-thione (**12**) was refluxed in 40% aqueous sodium hydroxide for 1 h and then acidified with concentrated hydrochloric acid to give homocysteamine hydrochloride (**13**-HCl)† in 95% yield. Reaction of the latter with t-butyl formylacetate (**8a**) in the presence of triethylamine gave t-butyl perhydro-1,3-thiazin-2-ylacetate (**14a**) in 85% yield. The latter was treated with concentrated hydrochloric acid to give the corresponding acid (**15a**). The latter failed to cyclize to cepham (**16a**)‡ even by Mukaiyama-Ohno's method.

† The same hydrolysis of (**12**) to (**13**) was originally attained under acidic conditions. However, heating under reflux in concentrated hydrochloric acid for a week was necessary for that reaction; see ref. 16.

‡ It has been reported that attempted cyclization of the ester (**14a**) to (**16a**) was unsuccessful; see ref. 17.




Scheme 5.

Knowing that the presence of an alkyl group on the side chain greatly enhances the yield of the β-lactam in the penam series, we then examined the cyclization reaction of 2-perhydro-1,3-thiazin-2-ylisobutyric acid (**15b**). This acid was prepared from the reaction of homocysteamine hydrochloride (**13**-HCl) with t-butyl 2-formylisobutyrate (**8d**) [which is readily synthesized from the ester (**8a**)] in the presence of triethylamine, followed by the treatment with dry hydrogen chloride in methylene dichloride. The acid (**15b**) was then treated with Mukaiyama-Ohno's reagent to give the expected cepham (**16b**) in 39% yield. In this case, 2-isopropylperhydro-1,3-thiazine, which had obviously arisen by decarboxylation of (**15b**), was also obtained in a significant amount.

The synthesis of chiral penams using D-cysteine and D-penicillamine instead of cysteamine is now under investigation.

## Experimental

M.p.s were determined on a Yanaco micromelting point apparatus (MP-S2), and are uncorrected. I.r. spectra were recorded on a JASCO A-102 spectrophotometer. $^1$H N.m.r. spectra were recorded using tetramethylsilane as an internal standard on JEOL JNM PMX-60 and FX-100 spectrometers at 60 MHz and 100 MHz, respectively. Mass spectra were recorded on a Hitachi model M-52, and high-resolution mass spectra on a JEOL JMS-01SG-2 system. Wakogel (C-200) was employed for silica gel column chromatography. Merck Kieselgel 60F 254 was employed for t.l.c.

*Ethyl* 4,5-*Dihydrothiazol*-2-*ylacetate* (**7a**).—A solution of ethyl ethoxycarbonylacetimidate hydrochloride[18] (**6**)·HCl (3.91 g, 0.02 mol), cysteamine hydrochloride (**1**)·HCl (2.27 g, 0.02 mol), and triethylamine (2.02 g, 0.02 mol) in ethanol (40 ml) was heated at 80 °C for 2 h. The ethanol was evaporated under reduced pressure, 5% aqueous sodium hydrogencarbonate was added, and the mixture was extracted with methylene dichloride. The organic layer was dried ($Na_2SO_4$) and evaporated under reduced pressure and the residue was recrystallized from hexane to give (**7a**) (2.25 g, 65%), as colourless prisms, m.p. 57—59 °C (lit.,[19] 42—43 °C).

*Ethyl Thiazolidin*-2-*ylacetate* (**3a**; R = Et).—(a) *From ethyl propiolate.* Triethylamine (5.15 g, 0.05 mol) was added dropwise to an ice-cooled solution of ethyl propiolate (**2a**; R = Et) (5.0 g, 0.05 mol) and (**1**)·HCl (5.79 g, 0.05 mol) in ethanol (50 ml). After being stirred for 10 h at room temperature, the reaction mixture was evaporated under reduced pressure and the residue was chromatographed over silica gel using hexane–ethyl acetate (3:1) as eluant to give (**3a**; R = Et) (5.84 g, 65%) (Found: C, 48.0; H, 7.45; N, 7.7; S, 18.4. $C_7H_{13}NO_2S$ requires C, 48.0; H, 7.5; N, 8.0; S, 18.3%); $\nu_{max.}$($CHCl_3$) 3 320 and 1 730 cm$^{-1}$; δ($CDCl_3$) 1.27 (3 H, t, *J* 7.0 Hz, $OCH_2$*Me*), 1.97 (1 H, br s, NH), 2.78 (2 H, dd, *J* 1.4 and 6.4 Hz, 2 × 2-H), 2.84—3.53 (4 H, m, 2 × 4′-H and 2 × 5′-H), 4.16 (2 H, q, *J* 7.0 Hz, $OCH_2$Me), and 4.84 (1 H, t, *J* 6.4 Hz, 2′-H).

(b) *From ethyl* 4,5-*dihydrothiazol*-2-*ylacetate.* A 20% hydrogen chloride (2 g)–methanol (10 ml) solution was added to a solution of (**5a**) (170 mg, 1 mmol) in methanol (3 ml) until the solution was brought to about pH 4.0. Sodium cyanoborohydride[20] (63 mg, 1 mmol) in hydrogen chloride–methanol solution (0.3 ml) was added to this solution with ice-cooling to keep the pH in the range 3.0—4.0 after being stirred for 30 min, the reaction mixture was diluted with water (3 ml) and 5% aqueous sodium hydrogen carbonate (2 ml), and extracted with methylene dichloride (3 × 5 ml), the organic layer was dried and evaporated under reduced pressure and the residue was purified by silica gel column chromatography using hexane–ethyl acetate (3:1) as eluant to give (**3a**; R = Et) (114 mg, 65%).

*t-Butyl Thiazolidin*-2-*ylacetate* (**3a**; R = Bu$^t$).—(a) *From compounds* (**8a**) *and* (**1**)·HCl. A solution of t-butyl formylacetate (**8a**) (490 mg, 3.4 mmol), compound (**1**)·HCl (387 mg, 3.4 mmol), and triethylamine (344 mg, 3.4 mmol) in methanol (20 ml) was stirred for 20 h at room temperature. After evaporation of the solvent, the residue was chromatographed over silica gel using hexane–ethyl acetate (10:1) as eluant to give the product (**3a**) (0.5 g, 72%), as a colourless oil (Found: $M^+$, 203.0976. $C_9H_7NO_2SO_4$ requires *M*, 203.0979); $\nu_{max.}$($CHCl_3$) 3 320 and 1 725 cm$^{-1}$; δ($CDCl_3$) 1.46 (9 H, s, Bu$^t$), 1.79 (1 H, br s, NH), 2.71 (2 H, dd, *J* 3.1 and 7.4 Hz, 2 × 2-H), 2.81—3.55 (4 H, m, 2 × 4′-H and 2 × 5′-H), and 4.79 (1 H, t, *J* 7.4 Hz, 2′-H).

(b) *From compounds* (**8a**) *and* (**1**). A solution of (**8a**) (2.45 g, 17 mmol) and (**1**) (1.31 g, 17 mmol) in methanol (60 ml) was stirred for 20 h at room temperature. In a similar manner to that described above, the title compound (**3a**; R = Bu$^t$) (3.049 g, 88%) was obtained.

(c) *From formyl Meldrum's acid and* (**1**). A solution of formyl Meldrum's acid[21] (2.58 g, 15 mmol) and t-butyl alcohol in toluene (30 ml) was refluxed for 15 min. Cysteamine (**1**) (1.16 g, 15 mmol) was added and the mixture was stirred for 20 h at room temperature. After evaporation of the solvent, the residue was chromatographed over silica gel to give (**3a**; R = Bu$^t$) (2.71 g, 89%).

*Methyl* 2-*Methylthiazolidin*-2-*ylacetate* (**3b**).—(a) *From methyl but*-2-*ynoate.* A solution of methyl but-2-ynoate (**2b**; R = Me) (0.98 g, 0.01 mol), compound (**1**)·HCl (1.14 g, 0.01 mol), and triethylamine (1.01 g, 0.01 mmol) in methanol (30 ml) was stirred for 20 h at room temperature. The residue was purified by silica gel column chromatography [hexane–ethyl acetate (5:1)] to give the acetate (**3b**) (1.02 g, 58%) (Found: $M^+$, 175.0667. $C_7H_{13}NO_2S$ requires *M*, 175.0666); $\nu_{max.}$($CHCl_3$) 3 480 and 1 730 cm$^{-1}$; δ($CDCl_3$) 1.65 (3 H, s, 2′-Me), 2.49 (1 H, br s, NH), 2.86 (2 H, s, 2 × 2-H), 2.93—3.57 (4 H, m, 2 × 4′-H and 2 × 5′-H), and 3.71 (3 H, s, OMe).

(b) *From compound* (**9b**). The reaction of methyl acetoacetate (**9b**) (2.32 g, 0.02 mol) with compound (**1**)·HCl (2.27 g, 0.02 mol) in the presence of triethylamine (2.02 g, 0.02 mol) in methanol (30 ml) gave (**3b**) (2.98 g, 85%).

*Ethyl* 2-(4,5-*Dihydrothiazol*-2-*yl*)*propionate* (**7c**).—A solution of ethyl 2-ethoxycarbonylpropionimidate hydrochloride (**6c**)·HCl[22] (1.0 g, 4.8 mmol), compound (**1**)·HCl (542 mg, 4.8 mmol), and triethylamine (482 mg, 4.8 mmol) in ethanol (20 ml) was refluxed for 4 h. The mixture was evaporated under reduced

pressure, sodium hydrogencarbonate solution added to the residue, and the mixture extracted with methylene dichloride. The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure and the residue was chromatographed over silica gel using hexane–ethyl acetate (4:1) as eluant to give (**7c**) (573 mg, 64%). This compound existed as a tautomeric mixture (*ca.* 1:1) of (**7c**) [(Found: $M^+$, 187.0670. $C_8H_{13}NSO_2$ requires $M$, 187.0666); $\nu_{max.}$($CHCl_3$) 1 730 and 1 620 $cm^{-1}$; δ($CDCl_3$) 1.25 (3 H, t, *J* 7.0 Hz, $OCH_2$*Me*), 1.43 (3 H, d, *J* 7.0 Hz, Me), 2.97—4.43 (7 H, m, $OCH_2$Me, 2 × 4′-H, 2 × 5′-H, and 2-H)] and 2-(1-ethoxycarbonylethylidene)thiazolidine (**7c′**); $\nu_{max.}$($CHCl_3$) 3 300 and 1 640 $cm^{-1}$; δ($CDCl_3$) 1.25 (3 H, t, *J* 7.0 Hz, $OCH_2$*Me*), 1.80 (3 H, s, Me), 2.97—4.43 (6 H, m, OC*H*Me, 2 × 4′-H and 2 × 5′-H), and 7.97—8.43 (1 H, br, NH).

*Ethyl* 2-(4,5-*Dihydrothiazol*-2-*yl*)*isobutyrate* (**7d**).—A solution of ethyl 2-ethoxycarbonylisobutyrimidate hydrochloride (**6d**)·HCl (1.73 g, 7.7 mmol), compound (**1**)·HCl (0.88 g, 7.7 mmol), and triethylamine (0.78 g, 7.7 mmol) in ethanol (20 ml) was refluxed for 6 h. In a procedure similar to that described for (**7c**), (**7d**) (0.92 g, 68%) was obtained from purification by silica gel column chromatography [hexane–ethyl acetate (4:1)] as a colourless oil (Found: $M^+$, 201.0816. $C_9H_{15}NO_2S$ requires $M$, 201.0823); $\nu_{max.}$($CHCl_3$) 1 725 $cm^{-1}$; δ($CDCl_3$) 1.27 (3 H, t, *J* 7.0 Hz, $OCH_2$*Me*), 1.50 (6 H, s, 2 × Me), 3.28 (2 H, t, *J* 8.0 Hz, 2 × 5′-H), 4.20 (2 H, q, *J* 7.0 Hz, $OCH_2$Me), and 4.25 (2 H, t, *J* 8.0 Hz, 2 × 4′-H).

*Ethyl* 2-*Thiazolidin*-2-*ylpropionate* (**3c**).—In a procedure similar to that described for the synthesis of (**3a**) from (**7a**), (**7c**) was reduced by sodium cyanoborohydride (32 mg, 0.5 mmol) in 20% hydrogen chloride–methanol. Purification by silica gel column chromatography [hexane–ethyl acetate (4:1)] gave (**3c**) (55 mg, 54%) as a mixture of diastereoisomers (Found: $M^+$, 189.0830. $C_8H_{15}NO_2S$ requires $M$, 189.0823); $\nu_{max.}$($CHCl_3$) 3 300 and 1 720 $cm^{-1}$; δ($CDCl_3$) 1.30 (3 H, t, *J* 7.0 Hz, $OCH_2$*Me*), 1.31 (3/2 H, d, *J* 7.0 Hz, Me), 1.34 (3/2 H, d, *J* 7.0 Hz, Me), 2.13 (1 H, br s, NH), 2.40—3.60 (5 H, m, 2 × 4′-H, 2 × 5′-H, and 2-H), 4.17 (2 H, q, *J* 7.0 Hz, $OCH_2$Me), 4.62 (1/2 H, d, *J* 9.0 Hz, 2′-H), and 4.65 (1/2 H, d, *J* 7.0 Hz, 2′-H).

*Ethyl* 2-*Thiazolidin*-2-*ylisobutyrate* (**3d**; R = Et).—Compound (**7d**) (1.0 g, 5 mmol) was similarly reduced by sodium cyanoborohydride (313 mg, 5 mmol) in 20% hydrogen chloride–methanol solution. Purification by column chromatography [hexane–ethyl acetate (5:1)] gave (**3d**) (466 mg, 46%), as a colourless oil (Found: $M^+$. 203.0964. $C_9H_{17}NSO_2$ requires $M$, 203.0979); $\nu_{max.}$($CHCl_3$) 3 300 and 1 715 $cm^{-1}$; δ($CDCl_3$) 1.27 (3 H, t, *J* 7.0 Hz, $OCH_2$*Me*), 1.28 (3 H, s, Me), 1.33 (3 H, s, Me), 2.43 (1 H, br s, NH), 2.53—3.70 (4 H, m, 2 × 4′-H and 2 × 5′-H), 4.15 (2 H, q, *J* 7.0 Hz, $OCH_2$Me), and 4.60 (1 H, s, 2′-H) together with (**7d**) (189 mg, 19%).

*t-Butyl* 2-*Thiazolidin*-2-*ylisobutyrate* (**3d**; R = Bu$^t$).—A solution of (**8d**) (172 mg, 1 mmol), (**1**)·HCl (113 mg, 1 mmol), and triethylamine (101 mg, 1 mmol) in methanol (10 ml) was stirred for 8 h at room temperature. After evaporation of the solvent, the residue was purified by silica gel column chromatography to give (**3d**) (196 mg, 85%), as an oil (Found: $M^+$, 231.1292. $C_{11}H_{21}NO_2S$ requires $M$, 231.1292); $\nu_{max.}$($CHCl_3$) 3 300 and 1 718 $cm^{-1}$; δ($CDCl_3$) 1.27 (3 H, s, Me), 1.34 (3 H, s, Me), 1.47 (9 H, s, Bu$^t$), 2.40 (1 H, br s, NH), 2.50—3.13 (3 H, m, 4′-$H_\alpha$ and 2 × 5′-H), 3.30—3.93 (1 H, m, 4′-$H_\beta$), and 4.60 (1 H, s, 2′-H).

*t-Butyl* 2-(2-*Methylthiazolidin*-2-*yl*)*propionate* (**3e**).—Cysteamine (**1**) (0.89 g, 11.6 mmol) and toluene-*p*-sulphonic acid (0.23 g, 1.2 mmol) was added to a solution of t-butyl 2-methylacetoacetate (**9e**) (2.0 g, 11.6 mmol) in methanol (50 ml). The reaction mixture was deaerated with argon and then with this as an atmosphere was stirred for 15 h at room temperature. The residue upon work-up was purified by silica gel column chromatography [hexane–ethyl acetate (10:1)] to give (**3e**) (1.44 g, 54%) (Found: $M^+$, 231.1274. $C_{11}H_{21}NO_2S$ requires $M$, 231.1292; Found: $M^+ - Me_2C{=}CH_2$, 175.0689. $C_7H_{13}NO_2S$ requires 175.0666); $\nu_{max.}$($CHCl_3$) 3 310 and 1 715 $cm^{-1}$; δ($CDCl_3$) 1.26 (3 H × 1/4, d, *J* 7.2 Hz, 2-Me), 1.29 (3 H × 3/4, d, *J* 7.2 Hz, 2-Me), 1.46 (9 H × 3/4, s, Bu$^t$), 1.47 (9 H × 1/4, s, Bu$^t$), 1.55 (3 H × 3/4, s, 2′-Me), 1.61 (3 H × 1/4, s, 2′-Me), 2.64—3.63 (5 H, m, 2 × 4′-H, 2 × 5′-H, and 2-H), and 2.70 (1 H, br s, NH).

*t-Butyl* 2-(2-*Methylthiazolidin*-2-*yl*)*butyrate* (**3f**).—In a procedure similar to that described for (**3b**), the reaction of t-butyl 2-ethylacetoacetate (**9f**) (2.5 g, 13.4 mmol) with (**1**) (1.03 g, 13.4 mmol) and toluene-*p*-sulphonic acid (0.25 g, 1.3 mmol) in methanol (60 ml) gave product (**3f**) (1.84 g, 56%) (Found: $M^+$, 245.1460. $C_{12}H_{23}NO_2S$ requires $M$, 245.1448; Found: $M^+ - Me_2C{=}CH_2$, 189.0819. $C_8H_{15}NO_2S$ requires $M$, 189.0823); $\nu_{max.}$($CHCl_3$) 3 300 and 1 710 $cm^{-1}$; δ($CDCl_3$) 0.93 (3 H, t, *J* 7.2 Hz, $CH_2$*Me*), 1.47 (9 H, s, Bu$^t$), 1.59 (3 H, s, 2′-Me), 1.64—1.84 (2 H, m, $CH_2$Me), 2.40—3.62 (5 H, m, 2 × 4′-H, 2 × 5′-H, and 2-H), and 2.58 (1 H, br s, NH).

*Methyl* 2-*Ethylthiazolidin*-2-*ylacetate* (**3g**).—In a procedure similar to that described for the synthesis of (**3b**), reaction of methyl propionylacetate (**9g**) (2.60 g, 0.02 mol) with (**1**)·HCl (2.27 g, 0.02 mol) and triethylamine (2.02 g, 0.02 mol) gave (**3g**) (2.65 g, 70%), as a colourless oil (Found: $M^+$, 189.0855. $C_8H_{15}NO_2S$ requires $M$, 189.0823; Found: $M^+ - C_2H_5$, 160.0407. $C_6H_{16}NO_2S$ requires $M$, 160.0432); $\nu_{max.}$($CHCl_3$) 3 340 and 1 730 $cm^{-1}$; δ($CDCl_3$) 0.99 (3 H, t, *J* 7.2 Hz, $CH_2$*Me*), 1.92 (2 H, q, *J* 7.2 Hz, $CH_2$Me), 2.63 (1 H, br s, NH), 2.77—3.53 (4 H, m, 2 × 4′-H and 2 × 5′-H), 2.83 (2 H, s, 2 × 2-H), and 3.71 (3 H, s, OMe).

*Thiazolidin*-2-*ylacetic Acid Hydrochloride* (**4a**)·HCl.—(a) A solution of (**3a**; R = Et) (5.26 g, 0.03 mol) in concentrated hydrochloric acid (150 ml) was stirred for 1 h at room temperature. Water (50 ml) was added to this solution which was then stirred for 15 h at room temperature. After this it was evaporated under reduced pressure and the residual solid recrystallized from ethanol–ether to give (**4**)·HCl (2.59 g, 47%), as colourless needles, m.p. 103—105 °C (Found: C, 32.85; H, 5.55; Cl, 19.3; N, 7.55; S, 17.35. $C_5H_9NO_2S$·HCl requires C, 32.7; H, 5.5; Cl, 19.3; N, 7.65; S, 17.45%); $\nu_{max.}$(KBr) 2 770—2 260 and 1 715 $cm^{-1}$; δ[$(CD_3)_2SO$] 2.95—3.78 (6 H, m, 2 × 4′-H, 2 × 5′-H, and 2 × 2-H), 4.93 (1 H, dd, *J* 6.0 and 8.4 Hz, 2′-H), and 8.80—11.25 (3 H, br, OH and $NH_2$).

(b) Dry hydrogen chloride was bubbled into a solution of compound (**3a**; R = Bu$^t$) (0.46 g, 2.26 mmol) in $CH_2Cl_2$ (50 ml) with ice-cooling until the solution was saturated with HCl. It was then left for 3 h at room temperature to give (**4a**)·HCl (327 mg, 79%).

2-(*Thiazolidin*-2-*yl*)*propionic Acid Hydrochloride* (**4c**)·HCl.—Compound (**3c**) (600 mg, 3.2 mmol) was hydrolysed with cold concentrated hydrochloric acid (7.0 ml) for 2 h to give (**4c**)·HCl (281 mg, 45%), as a mixture of diastereoisomers; $\nu_{max.}$(Nujol) 3 600—2 200 and 1 710 $cm^{-1}$; δ[$(CD_3)_2SO$] 1.25 (3/2 H, d, *J* 8.0 Hz, Me), 1.35 (3/2 H, d, *J* 8.0 Hz, Me), 2.90—3.83 (5 H, m, 2 × 4′-H, 2 × 5′-H, and 2-H), 4.68 (1/2 H, d, *J* 9.0 Hz, 2′-H), and 4.90 (1/2 H, d, *J* 8.0 Hz, 2′-H).

2-*Thiazolidin*-2-*ylisobutyric Acid Hydrochloride* (**4d**)·HCl.—(*a*) A solution of the ester (**3d**) (200 mg, 0.99 mmol) was

hydrolysed with concentrated hydrochloric acid (3.5 ml) at 70 °C for 4 h to give (**4d**)·HCl (198 mg, 95%), m.p. 120—121 °C; $\nu_{max.}$(Nujol) 3 600—2 000 and 1 705 $cm^{-1}$; δ($CD_3OD$) 1.35 (3 H, s, Me), 1.40 (3 H, s, Me), 3.05—3.92 (4 H, m, 2 × 4′-H and 2 × 5′-H), and 4.97 (1 H, s, 2′-H).

(*b*) Treatment of (**3d**; R = Bu$^t$) (115 mg, 0.5 mmol) with dry hydrogen chloride–$CH_2Cl_2$ (20 ml) gave (**4d**)·HCl (87 mg, 82%).

4-*Thia*-1-*azabicyclo*[3.2.0]*heptan*-7-*one* (**10a**).—Triphenylphosphine (0.31 g, 1.2 mmol), di-2-pyridyl disulphide (0.26 g, 1.2 mmol), and triethylamine (0.11 g, 1.1 mmol) were added to a 2mM solution of (**4a**) (0.18 g, 1.0 mmol) in acetonitrile (500 ml) with ice-cooling. After being stirred for 3 h at room temperature, the reaction mixture was evaporated under reduced pressure and the residue was purified by silica gel column chromatography [hexane–ethyl acetate (10:1)] to yield (**10a**) (11.2 mg, 9%), as a colourless oil (Found: $M^+$, 129.0272. $C_5H_7NOS$ requires *M*, 129.0248; Found: $M^+ - CO$, 101.0284. $C_4H_7NS$ requires *M*, 101.0299; Found: $M^+ - CH_2{=}C{=}O$, 87.0177. $C_3H_5NS$ requires *M*, 87.0142); $\nu_{max.}$($CHCl_3$) 1 770 $cm^{-1}$; δ($CDCl_3$) 2.69—3.35 (3 H, m, 2 × 3-H and 2-$H_\alpha$), 3.50 (1 H, dd, *J* 2.0 and 16.0 Hz, 6-$H_\alpha$), 3.95 (1 H, ddd, *J* 1.0, 4.0, and 16.0 Hz, 6-$H_\beta$), 4.15 (1 H, ddd, *J* 4.0, 6.0, and 11.5 Hz, 2-$H_\beta$), and 4.92 (1 H, dd, *J* 2.0 and 4.0 Hz, 5-H).

5-*Methyl*-4-*thia*-1-*azabicyclo*[3.2.0]*heptan*-7-*one* (**10b**).—The ester (**3b**) (584 mg, 3.33 mmol) was hydrolysed with concentrated hydrochloric acid (10 ml) and the reaction mixture was evaporated under reduced pressure below 20 °C. The residue was dissolved in 0.01M acetonitrile (330 ml) and treated with triphenylphosphine (1.05 g, 3.99 mmol), di-2-pyridyl disulphide (881 mg, 3.99 mmol), and triethylamine (370 mg, 3.67 mmol) to give (**10b**) (144 mg, 30%), as colourless oil (Found: $M^+$, 143.0384. $C_6H_9NOS$ requires *M*, 143.0404; Found: $M^+ - CO$, 115.0443. $C_5H_9NS$ requires *M*, 115.0455; Found: $M^+ - CH_2{=}C{=}O$, 101.0308. $C_4H_7NS$ requires *M*, 101.0299); $\nu_{max.}$($CHCl_3$) 1 765 $cm^{-1}$; δ($CDCl_3$) 1.78 (3 H, s, Me), 2.84—3.40 (3 H, m, 2 × 3-H and 2-$H_\alpha$), 3.26 (2 H, s, 2 × 6-H), and 4.13 (1 H, ddd, *J* 3.8, 5.8, and 11.4 Hz, 2-$H_\beta$).

6-*Methyl*-4-*thia*-1-*azabicyclo*[3.2.0]*heptan*-7-*one* (**10c**).—In a procedure similar to that described for the synthesis of (**10a**), the reaction of (**4c**)·HCl (150 mg, 0.76 mmol) with triphenylphosphine (240 mg, 0.92 mmol), di-2-pyridyl disulphide (202 mg, 0.92 mmol), and triethylamine (77 mg, 0.76 mmol) in acetonitrile (75 ml) gave (**10c**) (76 mg, 70%) (Found: $M^+$, 143.0411. $C_6H_9NOS$ requires *M*, 143.0404; Found: $M^+ - C_3H_4O$, 87.0151. $C_3H_5NS$ requires *M*, 87.0142); $\nu_{max.}$($CHCl_3$) 1 760 $cm^{-1}$; δ($CDCl_3$) 1.42 (3 H, d, *J* 7.5 Hz, Me), 2.65—3.30 (4 H, m, 3-$H_\alpha$, 2 × 3-H and 6-H), 4.15 (1 H, ddd, *J* 3.5, 5.5, and 10.5 Hz, 2-$H_\beta$), and 4.62 (1 H, d, *J* 1.4 Hz, 5-H).

6,6-*Dimethyl*-4-*thia*-1-*azabicyclo*[3.2.0]*heptan*-7-*one* (**10d**).—In a procedure similar to that described for the synthesis of (**10a**), the reaction of (**4d**)·HCl (100 mg, 0.47 mmol) with triphenylphosphine (149 mg, 0.59 mmol), di-2-pyridyl disulphide (130 mg, 0.59 mmol), and triethylamine (48 mg, 0.47 mmol) in acetonitrile (50 ml) gave (**10d**) (52 mg, 71%), m.p. 34 °C (Found: $M^+$,157.0563. $C_7H_{11}NOS$ requires *M*, 157.0561); $\nu_{max.}$($CHCl_3$) 1 755 $cm^{-1}$; δ($CCl_4$) 1.15 (3 H, s, Me), 1.45 (3 H, s, Me), 2.45—3.15 (3 H, m, 2-$H_\alpha$ and 2 × 3-H), 3.90—4.30 (1 H, m, 2-$H_\beta$), and 4.70 (1 H, s, 5-H).

5,6-*Dimethyl*-4-*thia*-1-*azabicyclo*[3.2.0]*heptan*-7-*one* (**10e**).—The ester (**3e**) (367 mg, 1.59 mmol) was treated with dry hydrogen chloride in methylene dichloride (20 ml) for 1 h at room temperature. The mixture was then evaporated, and the residue was dissolved in 1mM acetonitrile (159 ml) and treated with triphenylphosphine (502 mg, 1.91 mmol), di-2-pyridyl disulphide (421 mg, 1.91 mmol), and triethylamine (177 mg, 1.75 mmol) to give (**10e**) (104 mg, 41%), as a colourless oil (Found: $M^+$, 157.0560. $C_7H_{11}NOS$ requires *M*, 157.0561; Found: $M^+ - CO$, 129.0596. $C_6H_{11}NS$ requires *M*, 129.0612); $\nu_{max.}$($CHCl_3$) 1 760 $cm^{-1}$; δ($CDCl_3$) 1.24 (3 H × 1/3, d, *J* 7.2 Hz, 6-Me), 1.29 (3 H × 2/3, d, *J* 7.2 Hz, 6-Me), 1.65 (3 H × 2/3, s, 5-Me), 1.76 (3 H × 1/3, s, 5-Me), 2.79—3.56 (4 H, m, 2 × 3-H, 2-$H_\alpha$, and 6-H), and 3.88—4.21 (1 H, m, 2-$H_\beta$).

6-*Ethyl*-5-*methyl*-4-*thia*-1-*azabicyclo*[3.2.0]*heptan*-7-*one* (**10f**).—In a procedure similar to that described for (**10e**), (**3f**) (200 mg, 0.82 mmol) was first treated with dry hydrogen chloride in methylene dichloride (20 ml); the product was cyclized by triphenylphosphine (257 mg, 0.98 mmol), di-2-pyridyl disulphide (215 mg, 0.98 mmol), and triethylamine (91 mg, 0.90 mmol) in 1mM acetonitrile (90 ml) to give (**10f**) (32 mg, 23%), as a colourless oil (Found: $M^+$, 171.0722. $C_8H_{13}NOS$ requires *M*, 171.0717; Found: $M^+ - CO$, 143.0727. $C_7H_{13}NS$ requires 143.0768); $\nu_{max.}$($CHCl_3$) 1 760 $cm^{-1}$; δ($CDCl_3$) 0.99 (3 H × 1/5, t, *J* 7.2 Hz, $CH_2$*Me*), 1.06 (3 H × 4/5, t, *J* 7.2 Hz, $CH_2$*Me*), 1.67 (3 H × 4/5, s, Me), 1.77 (3 H × 1/5, s, Me), 1.52—1.93 (2 H, m, $CH_2$Me), 2.79—3.39 (4 H, m, 2 × 3-H, 2-$H_\alpha$, and 6-H), and 3.94—4.22 (1 H, m, 2-$H_\beta$).

5-*Ethyl*-4-*thia*-1-*azabicyclo*[3.2.0]*heptan*-7-*one* (**10g**).—In a procedure similar to that described for the synthesis of (**10b**), after hydrolysis of (**3g**) (500 mg, 2.64 mmol) by concentrated hydrochloric acid (10 ml), treatment of the crude acid (**4g**)·HCl with triphenylphosphine (832 mg, 3.17 mmol), di-2-pyridyl disulphide (698 mg, 3.17 mmol), and triethylamine (291 mg, 2.88 mmol) in 1mM acetonitrile (264 ml) gave (**10g**) (87.2 mg, 21%), as a colourless oil (Found: $M^+$, 157.0547. $C_7H_{11}NOS$ requires *M*, 157.0561; Found: $M^+ - CO$, 129.0567. $C_6H_{11}NS$ requires *M*, 129.0621; Found: $M^+ - CH_2{=}C{=}O$, 115.0436. $C_5H_9NS$ requires *M*, 115.0455); $\nu_{max.}$($CHCl_3$) 1 765 $cm^{-1}$; δ($CDCl_3$) 1.05 (3 H, t, *J* 7.2 Hz, $CH_2$*Me*), 1.99 (2 H, q, *J* 7.2 Hz, $CH_2$Me), 2.80—3.52 (3 H, m, 2 × 3-H and 2-$H_\alpha$), 3.19 (2 H, s, 2 × 6-H), and 4.14 (1 H, ddd, *J* 3.2, 5.6, and 11.2 Hz, 2-$H_\beta$).

*Homocysteamine Hydrochloride* (**13**)·HCl.—Perhydro-1,3-thiazine-2-thione[23] (**12**) (1.33 g, 10 mmol) dissolved in 40% aqueous NaOH (15 ml) was refluxed for 1 h after which it was acidified with concentrated hydrochloric acid and evaporated under reduced pressure. The residual mass was recrystallized from ethanol to give (**13**)·HCl (1.2 g, 95%), as colourless crystals, m.p. 69 °C (lit.,[16] 69 °C).

*t-Butyl Perhydro*-1,3-*thiazin*-2-*ylacetate* (**14a**).—A mixture of (**13**)·HCl (245 mg, 2 mmol), t-butyl formylacetate (**8a**) (288 mg, 2 mmol), and triethylamine (202 mg, 2 mmol) in methanol (20 ml) was stirred for 3 h at room temperature. The residue obtained by evaporation of methanol was separated by silica gel column chromatography to give (**14a**) (347 mg, 80%), as an oil (Found: $M^+$, 217.1139. $C_{10}H_{19}NO_2S$ requires *M*, 217.1135); $\nu_{max.}$($CHCl_3$) 3 350 and 1 737 $cm^{-1}$; δ($CDCl$)$_3$ 1.43 (9 H, s, Bu$^t$), 1.30—1.87 (2 H, m, 2 × 5′-H), 1.68 (1 H, br s, NH), 2.65 (2 H, d, *J* 6 Hz, 2 × 2-H), 2.70—3.65 (4 H, m, 2 × 4′-H and 2 × 6′-H), and 4.50 (1 H, t, *J* 6 Hz, 2′-H).

*Perhydro*-1,3-*thiazin*-2-*ylacetic Acid Hydrochloride* (**15a**)·HCl.—The ester (**14a**) (217 mg, 1 mmol) was dissolved in concentrated hydrochloric acid (5 ml) and left at room temperature overnight. The reaction mixture was evaporated under reduced pressure and the residue triturated with ether, and recrystallized from EtOH–ether to give (**15a**)·HCl (148 mg, 75%), m.p. 195—197 °C (Found: C, 36.65; H, 6.15; Cl, 18.0; N, 7.2; S, 16.1. $C_6H_{11}NO_2S$·HCl requires C, 36.45; H, 6.1; Cl,

17.95; N, 7.1; S, 16.2%); $\nu_{max.}$(KBr) 2 780—2 400 and 1 720 $cm^{-1}$; δ($CD_3OD$) 1.60—2.50 (2 H, m, 2 × 5′-H), 2.50—3.85 (4 H, m, 2 × 4′-H and 2 × 6′-H), 2.97 (2 H, d, *J* 6 Hz, 2 × 2-H), and 4.77 (1 H, t, *J* 6 Hz, 2′-H).

*t-Butyl 2-Formylisobutyrate* (**8d**).—(a) t-Butyl formylacetate (**8a**) (5.76 g, 40 mmol) was added to a solution of sodium methoxide (2.02 g) in methanol (80 ml) and iodomethane (22.4 g, 160 mmol) was added. The solution was stirred for 2 h at room temperature after which it was evaporated under reduced pressure. Water and ether were added to the residue, and the organic layer was separated, dried and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using hexane–ether (20:1) as eluant to give (**8d**) (2.62 g, 38%), b.p. 78 °C (17 mmHg); $\nu_{max.}$($CHCl_3$) 1 740 and 1 720 $cm^{-1}$; δ($CCl_4$) 1.27 (6 H, s, 2 × Me), 1.47 (9 H, s, $Bu^t$), and 9.55 (1 H, s, CHO); *m/z* 172 ($M^+$); semicarbazone of (**8d**): needles (EtOAc), m.p. 158—159 °C (Found: C, 52.15; H, 8.65; N, 18.3. $C_{10}H_{19}N_3O_3$ requires C, 52.3; H, 8.35; N, 18.35%).

(b) A solution of formyl Meldrum's acid (8.6 g, 50 mmol) and t-butyl alcohol (4.56 g, 60 mmol) in benzene (100 ml) was heated under reflux for 90 min, after which the benzene was evaporated off under reduced pressure. The crude t-butyl formylacetate was added to sodium methoxide (0.1 mol)–methanol (80 ml). Iodomethane (28 g, 0.2 mol) was added to the mixture which after being stirred for 3 h at room temperature, was evaporated under reduced pressure. The residue was purified by a procedure similar to that described above to give (**8d**) (3.2 g, 37%), b.p. 70—71 °C (16 mmHg).

*t-Butyl 2-Perhydro-1,3-thiazin-2-ylisobutyrate* (**14b**).—A mixture of (**13**)·HCl (255 mg, 2 mmol), (**8d**) (344 mg, 2 mmol), triethylamine (202 mg, 2 mmol), and methanol (20 ml) was stirred for 4 h at room temperature after which it was evaporated under reduced pressure. The residue was chromatographed over silica gel using hexane–EtOAc (10:1) as eluant to give (**14b**) (405 mg, 82%), as a colourless oil (Found: $M^+$, 245.1548. $C_{12}H_{23}O_2NS$ requires *M*, 245.1553); $\nu_{max.}$($CHCl_3$) 3 320 and 1 720 $cm^{-1}$; δ($CDCl_3$) 1.20 (6 H, s, 2 × Me), 1.45 (9 H, s, $Bu^t$), 1.50—1.80 (2 H, m, 2 × 5′-H), 2.57—3.56 (5 H, m, 2 × 4′-H, 2 × 6′-H, and NH), and 4.24 (1 H, s, 2′-H).

*2-Perhydro-1,3-thiazin-2-ylisobutyric Acid Hydrochloride* (**15b**)·HCl.—The ester (**14b**) (245 mg, 1 mmol) was treated with concentrated hydrochloric acid (5 ml) for 2 h at room temperature to give (**15b**)·HCl (168 mg, 75%), m.p. 199—200 °C (decomp.) (Found: C, 42.7; H, 7.2; Cl, 15.75; N, 6.3; S, 14.05. $C_8H_{15}NO_2S$·HCl requires C, 42.55; H, 7.15; Cl, 15.7; N, 6.2; S, 14.2%); $\nu_{max.}$(KBr) 2 780—2 460 and 1 730 $cm^{-1}$; δ($CD_3OD$) 1.35 (6 H, s, 2 × Me), 1.70—2.50 (2 H, m, 2 × 5′-H), 2.60—3.10 (2 H, m, 2 × 6′-H), 3.10—3.70 (2 H, m, 2 × 4′-H), and 4.75 (1 H, s, 2′-H).

*7,7-Dimethyl-5-thia-1-azabicyclo*[4.2.0]*octan-8-one* (**16b**).—A suspension of (**15b**)·HCl (112 mg, 0.5 mmol), triphenylphosphine (44 mg, 0.55 mmol), and triethylamine (55 mg, 0.55 mmol) in acetonitrile (50 ml) was stirred for 0.5 h. After addition of di-2-pyridyl disulphide (121 mg, 0.55 mmol), the reaction mixture was stirred for a further 2 h at room temperature. The residue obtained by evaporation of the solvent was chromatographed over silica gel using hexane–EtOAc (10:1) as eluant to give (**16b**) (33 mg, 39%) (Found: $M^+$, 171.0722. $C_8H_{13}NOS$ requires *M*, 171.0717); $\nu_{max.}$($CHCl_3$) 1 740 $cm^{-1}$; δ($CDCl_3$) 1.30 (3 H, s, Me), 1.36 (3 H, s, Me), 1.50—2.10 (2 H, m, 2 × 3-H), 2.50—3.10 (3 H, m, 2 × 4-H and $2H_\alpha$), 3.80—4.20 (1 H, m, 2-$H_\beta$), and 4.47 (1 H, s, 6-H). Further elution gave 2-isopropylperhydro-1,3-thiazine (17 mg, 23%); *m/z* 145 ($M^+$); $\nu_{max.}$($CHCl_3$) 3 320 $cm^{-1}$; δ($CDCl_3$) 1.00 (6 H, d, *J* 6 Hz, 2 × Me), 1.40—2.01 (3 H, m, 2 × 5′-H and 2-H), 2.60—3.70 (5 H, m, 2 × 4′-H, 2 × 6′-H, and NH), and 3.92 (1 H, d, *J* 5 Hz, 2′-H).

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