929. *Thiazolidines. Part V.*[1] *Synthesis of β-Alkylcysteines.*

By F. P. Doyle, D. O. Holland, P. Mamalis, and A. Norman.

Synthesis of β-methyl-, β-*iso*propyl-, and ββ-dimethyl-cysteine from the appropriate 4-alkylidene-2-thiothiazolid-5-ones is described. Correlation of the β-methylcysteine (thiothreonine) produced by this route with the A-isomer prepared by Carter *et al.*[2] and also with threonine is suggested.

Synthesis of β-alkylcysteines from 2-alkyl-4-alkylidene- or 4-alkylidene-2-aryl-oxazolones has been often described [3] but little attention has been paid to the route [4] from 4-alkylidene-2-thiothiazolid-5-ones (I). In view of the ready availability of the starting material, 2-thiothiazolid-5-one,[5] we concentrated our attention on this route.

4-Ethylidene-2-thiothiazolid-5-one (I; R^1 = Me, R^2 = H) was converted into 5-methyl-2-thiothiazolidine-4-carboxylic acid (II; R^1 = Me, R^2 = R^3 = R^4 = H) * by methanolic

* See footnote on p. 4584.

[1] Parts I—IV, preceding papers.

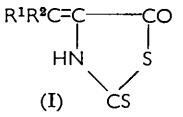
[2] Carter, Stevens, and Ney, *J. Biol. Chem.*, 1941, **139**, 247.

[3] (*a*) "Chemistry of Penicillin," Princeton Univ. Press, Princeton, 1949, pp. 465 *et seq.*; (*b*) Savard, Richardson, and Grant, *Canad. J. Res.*, 1946, **24**, *B*, 28; Neher, Spillmann, Werner, Wettstein, and Miescher, *Helv. Chim. Acta*, 1946, **29**, 1874; Tatsuoka, Miyamoto, Shiu, and Tamura, *J. Penicillin, Japan*, 1947, **1**, 382; Tatsuoko, Ueno, and Kinoshita, *J. Pharm. Soc. Japan*, 1949, **69**, 291.

[4] Cook, Hunter, and Pollock, *J.*, 1950, 1892.

[5] Cook, Heilbron, and Levy, *J.*, 1948, 201; Holland, B.P. 689,243/1951, 733,090/1953.

potassium hydroxide. The acid was characterised as its methyl ester (II; $R^1 = R^3 = Me$, $R^2 = R^4 = H$) which with hydrazine readily gave the hydrazide (IV) and not the triazine (V) which might have been expected from the analogous experiment in the 5-phenyl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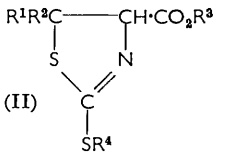
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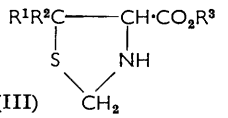
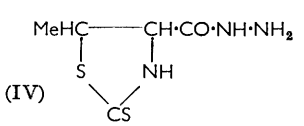

(III)

series.[1] The acid with methyl iodide and potassium carbonate in acetone gave the *S*-methyl derivative (II; $R^1 = R^4 = Me$, $R^2 = R^3 = H$) as an oil (characterised as the *S*-benzylthiuronium salt), which with diazomethane gave its methyl ester (II; $R^1 = R^3 = R^4 = Me$, $R^2 = H$), and this with aluminium amalgam gave methyl 5-methylthiazolidine-4-carboxylate (III; $R^1 = R^3 = Me$, $R^2 = H$) as an oil characterised as the hydrazide.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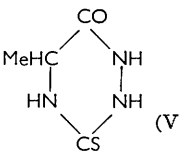
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The last-mentioned ester, when heated with methanolic mercuric chloride, gave methyl α-amino-β-mercaptopropionate hydrochloride (VI; $R^1 = R^3 = Me$, $R^2 = H$) by ring-fission and elimination of formaldehyde. Acid-hydrolysis of this ester gave α-amino-β-mercaptopropionic acid (β-methylcysteine, thiothreonine) hydrochloride (VI; $R^1 = Me$, $R^2 = R^3 = H$) also obtained directly, in the same isomeric form, by heating 5-methyl-2-thiothiazolidine-4-carboxylic acid (II; $R^1 = Me$, $R^2 = R^3 = R^4 = H$) with concentrated hydrochloric acid in a sealed tube.

Carter *et al.*[2] found that both diastereoisomeric forms of α-amino-β-mercaptopropionic acid (designated A and B) were formed when 4-ethylidene-2-phenyl-5-oxazolone [6] reacted with toluene-ω-thiol under alkaline conditions and the resulting *N*-benzoyl-*S*-benzyl derivatives (VII; $R^3 = H$, $R^1 = CH_2Ph$, $R^2 = Bz$) were hydrolysed and debenzylated. It was of interest to determine which of these two forms corresponded to the single form described in the above series of reactions, and also to correlate the isomers with the threonine or *allo*threonine structure (VIII; $R^1 = R^2 = H$).

Our ester (VI; $R^1 = R^3 = Me$, $R^2 = H$) with benzyl bromide and triethylamine gave an oily *S*-benzyl derivative (VII; $R^3 = Me$, $R^1 = CH_2Ph$, $R^2 = H$), whose hydrochloride, m. p. **131—132°**, appeared to be identical (m. p. and mixed m. p.) with methyl α-amino-β-benzylthiopropionate hydrochloride prepared by the action of methanolic hydrogen chloride on the *S*-benzylthiothreonine A of Carter *et al.*[2] The corresponding *S*-benzylthiothreonine B[2] gave a methyl ester hydrochloride, m. p. **171°**, under the same conditions. Benzoylation of the *S*-benzyl ester hydrochloride, m. p. **131—132°**, followed by hydrolysis with hydrochloric acid, gave a compound (VII; $R^1 = CH_2Ph$, $R^2 = Bz$, $R^3 = H$) identical (mixed m. p.) with *N*-benzoyl-*S*-benzylthiothreonine A [it was shown that benzoylation (Schotten–Baumann) did not cause inversion of either the A or the B form of *S*-benzylthiothreonine methyl ester]. As an alternative route to the same *N*-benzoyl-*S*-benzylthiothreonine, our ester (VI; $R^1 = R^3 = Me$, $R^2 = H$) was benzoylated under the same conditions to give the neutral methyl α-benzamido-β-benzoylthiopropionate as well as the expected alkali-soluble mono-*N*-benzoyl derivative (VII; $R^1 = H$, $R^2 = Bz$, $R^3 = Me$). The latter product, on cold alkaline hydrolysis followed by reaction with benzyl chloride and alkali, gave an *N*-benzoyl-*S*-benzylthiothreonine again identical with Carter's A derivative.

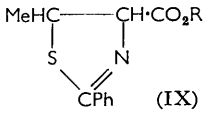
[6] Finar and Libman, *J.*, 1949, 2726.

By analogy with the work of Sicher *et al.*,[19] and with that reported in previous papers in this series,[1] it is considered likely that the stable form of 5-methyl-2-thiothiazolidine-4-carboxylic acid used in the above reaction has the *trans*-configuration and that subsequent

(VI) $R^1R^2C(SH)\cdot CH(NH_2)\cdot CO_2R^3$

(VII) $Me\cdot CH(SR^1)\cdot CH(NHR^2)\cdot CO_2R^3$

(VIII) $Me\cdot CH(OH)\cdot CH(NHR^1)\cdot CO_2R^2$



(IX)

reactions are unlikely to have affected the configuration of the derivatives. Since the thiothreonine prepared appears to be identical with the A isomer of Carter *et al.*, this implies that this isomer has the *threo*-configuration. Support for this was obtained when the hydrochloride of *allo*threonine methyl ester (VIII; $R^1 = H$, $R^2 = Me$) with thiobenzoylthioacetic acid in the presence of pyridine gave the thiobenzoyl derivative [8] (VIII; $R^1 = CSPh$, $R^2 = Me$). This was cyclised with cold thionyl chloride to give methyl 5-methyl-2-phenylthiazoline-4-carboxylate (IX; R = Me). By analogy with the observations of Fry [9] and of Attenburrow *et al.*,[10] it was assumed that the *trans*-form of the thiazoline (corresponding to the threonine configuration) was produced in this reaction, inversion occurring during the replacement of the β-hydroxy-group of *allo*threonine by the sulphur of the thiobenzoyl group. Hydrolysis of the ester (IX; R = Me) with hot hydrochloric acid gave a mercapto-amino-acid, m. p. 184—186° (decomp.), which was benzylated in liquid ammonia to give an *S*-benzyl(thiothreonine), m. p. 171—173°, from which was obtained an *N*-benzoyl derivative, m. p. 140—142° not depressed on admixture with Carter's A compound.

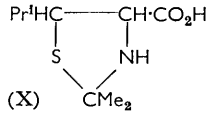
These findings are contrary to those reported recently, and some time after this work had been completed, by Arnstein [11] who suggests that it is Carter's B isomer which is identical with the thiothreonine prepared from *allo*threonine (and incidentally also from threonine) by the same route as ours.

4-*iso*Butylidene-2-thiothiazolid-5-one [12] (I; $R^1 = Pr^i$, $R^2 = H$) with methanolic potassium hydroxide gave the expected *trans*-5-*iso*propyl-2-thiothiazolidine-4-carboxylic acid (II; $R^1 = Pr^i$, $R^2 = R^3 = R^4 = H$). *S*-Methylation with methyl iodide in aqueous sodium hydroxide, followed by esterification and reduction as described previously, gave the thiazolidine ester (III; $R^1 = Pr^i$, $R^2 = H$, $R^3 = Me$). Ring-fission as before gave methyl α-amino-β-mercapto*iso*hexanoate (VI; $R^1 = Pr^i$, $R^2 = H$, $R^3 = Me$) as the hydrochloride which was hydrolysed by hydrochloric acid to *threo*-α-amino-β-mercapto*iso*hexanoic acid (β-*iso*propylcysteine) hydrochloride [3] (VI; $R^1 = Pr^i$, $R^2 = R^3 = H$). This product exhibited the usual colour reactions of the thiol group and readily gave an *iso*propylidene derivative (X) when warmed with acetone. As was observed with β-methylcysteine methyl ester, benzoylation of β-*iso*propylcysteine methyl ester under Schotten–Baumann conditions gave a neutral product, which was assumed to be the *NS*-dibenzoyl derivative, even with only one equivalent of benzoyl chloride.

In parallel experiments 5-*iso*propyl-2-thiothiazolidine-4-carboxylic acid (II; $R^1 = Pr^i$, $R^2 = R^3 = R^4 = H$) gave an oily methyl ester which was smoothly converted with aqueous ammonia into the amide (XI; R = H) identical with the material isolated from the reaction of 4-*iso*butylidene-2-thiothiazolid-5-one (I; $R^1 = Pr^i$, $R^2 = H$) with aqueous ammonia.[4,13] With methyl iodide and alkali the amide gave *trans*-2-methylthio-5-*iso*propylthiazolidine-4-carboxyamide (XI; R = Me) which, as in the case of the corresponding ester (II; $R^1 = Pr^i$, $R^2 = H$, $R^3 = R^4 = Me$), was reduced with aluminium amalgam to the thiazolidine amide (XII; R = H) also obtained directly from the ester (III; $R^1 = Pr^i$, $R^2 = H$,

[7] Sicher, Svoboda, and Farkas, *Coll. Czech. Chem. Comm.*, 1955, **20**, 1439.
[8] Cf. Crawhall and Elliott, *J.*, 1951, 2071.
[9] Fry, *J. Org. Chem.*, 1949, **14**, 887.
[10] Attenburrow, Elliott, and Penny, *J.*, 1948, 310.
[11] Arnstein, *Biochem. J.*, 1958, **68**, 333.
[12] Billimoria and Cook, *J.*, 1949, 2323.
[13] Doyle, Holland, and Nayler, *J.*, 1955, 2265.

R^3 = Me). Ring-fission of the amide with mercuric chloride in methanol proceeded normally, to give *threo*-α-amino-β-mercapto*iso*hexanamide (β-*iso*propylcysteine amide) hydrochloride which, like the corresponding acid hydrochloride, gave the *iso*propylidene derivative (XII; R = Me).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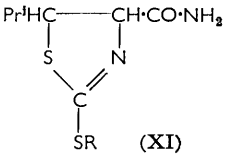
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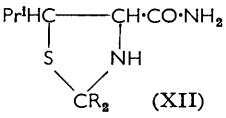
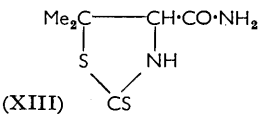

(XII)

2-Methylthio-5-*iso*propylthiazoline-4-carboxylic acid (II; R^1 = Pr^i, R^2 = R^3 = H, R^4 = Me), like the two forms of the 5-phenyl compound,[1] on successive treatment with thionyl chloride and ammonia gave a compound isomeric with the amide (XI; R = Me) described above. By analogy with the suggestion in Part III,[1] this isomer is believed to be 4-methyl-2-(methylthio-thiocarbonylamino)pent-2-enamide. An anilide prepared similarly is believed to have an analogous structure.

Unlike the two β-alkylcysteines described above, α-amino-β-mercapto*iso*valeric acid (VI; R^1 = R^2 = Me, R^3 = H) (penicillamine) exists in only one optically inactive form. An attempt to prepare this compound by the reduction of 5 : 5-dimethyl-2-thiothiazolidine-4-carboxylic acid (II; R^1 = R^2 = Me, R^3 = R^4 = H) with aluminium and hydrochloric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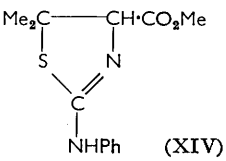

(XIV)

acid [14] was unsuccessful in our hands. The required thiothiazolidine (II; R^1 = R^2 = Me, R^3 = R^4 = H) was readily obtained from 4-*iso*propylidene-2-thiothiazolid-5-one (I; R^1 = R^2 = Me) by reaction with methanolic potassium hydroxide.[15] The non-acidic gummy by-product noted by Chatterjee *et al.* has now been shown to be the methyl ester (II; R^1 = R^2 = R^3 = Me, R^4 = H) identical with a sample prepared from penicillamine methyl ester and carbon disulphide.[16] It was readily converted into the amide (XIII) by aqueous ammonia.

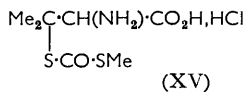
In view of our failure to reduce the thiazoline (II; R^1 = R^2 = Me, R^3 = R^4 = H) directly to penicillamine it was converted into the *S*-methyl derivative and its methyl ester as described earlier. The same ester was also obtained as an oil when methyl 5 : 5-dimethyl-2-thiothiazolidine-4-carboxylate [17] (II; R^1 = R^2 = R^3 = Me, R^4 = H) was allowed to react with diazomethane. It was identified as a picrate identical with that derived from an authentic specimen and gave the 2-anilino-compound (XIV) with warm aniline.

Reduction of the ester (II; R^1 = R^2 = R^3 = R^4 = Me) with aluminium amalgam gave the crystalline methyl 5 : 5-dimethylthiazolidine-4-carboxylate (III; R^1 = R^2 = R^3 = Me), m. p. 43—44°. Neher *et al.*[3b] describe this ester, prepared from the corresponding acid and diazomethane, as having m. p. 204—207° (decomp.). Its ring-fission with mercuric chloride, followed by acid-hydrolysis of the penicillamine ester, gave crude penicillamine (VI; R^1 = R^2 = Me, R^3 = H) as its hydrochloride characterised by conversion into its *iso*propylidene derivative.

With hot hydrochloric acid 5 : 5-dimethyl-2-methylthiothiazoline-4-carboxylic acid

[14] Ref. 3*a*, p. 467.
[15] Cf. Chatterjee, Cook, Heilbron, and Levy, *J.*, 1948, 1337.
[16] Cook, Elvidge, and Shaw, *J.*, 1949, 2367.
[17] Süs, *Annalen*, 1948, **561**, 31.

(II; $R^1 = R^2 = R^4 = Me$, $R^3 = H$) gave *S*-(methylthio-carbonyl)penicillamine hydrochloride (XV). On treatment with aqueous sodium hydroxide, the latter compound readily lost methanethiol, to give 5 : 5-dimethyl-2-oxothiazolidine-4-carboxylic acid (XVI) identical with the product obtained from the thiazoline ester (II; $R^1 = R^2 = R^3 = Me$, $R^4 = H$) and alkaline hydrogen peroxide.[16] The same compound was prepared in improved



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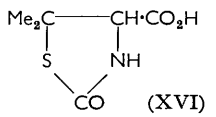

(XVI)

yield by treating the thiothiazolidine acid (II; $R^1 = R^2 = Me$, $R^3 = R^4 = H$) with aqueous chloroacetic acid. Crawhall and Elliott [8] found that 2-oxothiazolidine-4-carboxylic acid itself was cleaved to cysteine by hot hydrochloric acid, but we have found that the 5 : 5-dimethyl derivative, like the 5-phenyl compound,[1] resists such treatment.

Experimental

4-Alkylidene-2-thiothiazolid-5-ones.—4-Ethylidene-, 4-*iso*butylidene-, and 4-*iso*propylidene-2-thiothiazolid-5-ones were prepared as described by Billimoria and Cook.[12]

Reaction of 4-Alkylidene-2-thiothiazolid-5-ones with Potassium Hydroxide.[15]—The thiazolidone (0·1 mole) was added to a warm solution of potassium hydroxide (14·0 g.) in methanol (250 ml.) and left for 24 hr. at room temperature. The solution, after filtration, was evaporated *in vacuo* to a syrup which was dissolved in water (100 ml.) and acidified with hydrochloric acid. The resulting precipitate was collected and extracted with excess of aqueous sodium hydrogen carbonate solution, and the filtered extracts were acidified to give the 5-alkyl-2-thiothiazolidine-4-carboxylic acids shown in the Table.

5-Substituted 2-thiothiazolidine-4-carboxylic acids (II; $R^3 = R^4 = H$).

		Yield			Found (%)			Required (%)		
R^1	R^2	(%)	M. p.	Formula	C	H	N	C	H	N
Me	H	76	182—183° [a]	$C_5H_7O_2NS_2$	34·1	4·0	7·9	34·1	3·8	8·1
Pr^i	H	72	168—170 [b]	$C_7H_{11}O_2NS_2$	41·3	5·8	6·8	41·0	5·4	6·3
Me	Me	76	148 [c]	$C_6H_9O_2NS_2$	38·3	4·7	7·0	37·7	4·8	7·3

[a] Prisms from ethyl acetate–light petroleum. [b] Needles from water. [c] Needles from chloroform–light petroleum; Chatterjee *et al.*[15] give m. p. 145°.

Methyl 5-Methyl-2-thiothiazolidine-4-carboxylate.—5-Methyl 2-thiothiazolidine-4-carboxylic acid (5·0 g.), methanol (50 ml.), and concentrated sulphuric acid (6 drops) were refluxed together for 3 hr. The solution was concentrated and the residue stirred with aqueous methanol to give the *methyl ester* (4·7 g.) which recrystallised from aqueous methanol and then from ethyl acetate–light petroleum, to give prisms, m. p. 85—87° (Found: C, 37·2; H, 4·9; N, 7·5. $C_6H_9O_2NS_2$ requires C, 37·7; H, 4·8; N, 7·3%).

5-Methyl-2-thiothiazolidine-4-carboxyhydrazide.—The above methyl ester (1·0 g.) was left with methanol (10·0 ml.) and 90% hydrazine hydrate (0·4 ml.) for 24 hr. Concentration and addition of water gave the hydrazide which separated from aqueous methanol as prisms (0·6 g.), m. p. 172° (decomp.) (Found: C, 31·7; H, 4·8; N, 22·5. $C_5H_9ON_3S_2$ requires C, 31·4; H, 4·8; N, 22·0%).

5-isoPropyl-2-thiothiazolidine-4-carboxyamide.—5-*iso*Propyl-2-thiothiazolidine-4-carboxylic acid (10 g.), methanol (100 ml.), and sulphuric acid (0·5 ml.) were refluxed for 3 hr., then evaporated to small volume. The residue was dissolved in chloroform, washed with sodium hydrogen carbonate solution, dried, and recovered as an amber oil. This ester (2 g.) and ammonium hydroxide (15 ml.; *d* 0·88) were mixed and methanol was added until a one-phase solution was present. After 24 hr. this was evaporated to leave the *amide* (1·8 g.) which crystallised from aqueous methanol as needles, m. p. 152—153°, identical (mixed m. p.) with a sample prepared by the reaction of 4-*iso*butylidene-2-thiothiazolid-5-one with ammonia [4, 13] (Found: C, 41·3; H, 5·0; N, 13·9. Calc. for $C_7H_{12}ON_2S_2$: C, 41·2; H, 6·0; N, 13·7%).

Methyl 5 : 5-Dimethyl-2-thiothiazolidine-4-carboxylate.—The residue insoluble in sodium

hydrogen carbonate from the reaction of 4-*iso*propylidene-2-thiothiazolid-5-one with potassium hydroxide crystallised from aqueous methanol, to give methyl 2-thio-5 : 5-dimethylthiazolidine-4-carboxylate, m. p. 106—107°, identical with a sample prepared by Cook, Elvidge, and Shaw's method [16] (Found: C, 41·1; H, 5·8; N, 6·8. Calc. for $C_7H_{11}O_2NS_2$: C, 41·0; H, 5·4; N, 6·8%).

5 : 5-*Dimethyl*-2-*thiothiazolidine*-3-*carboxyamide*.—The preceding methyl ester (1·0 g.) was left in aqueous ammonia (10 ml.; *d* 0·88) at room temperature for 24 hr. Evaporation gave a buff solid (0·5 g.) which crystallised from water to give the amide as needles, m. p. 175—177°, identical with a sample prepared by the method of Doyle *et al.*[13] (Found: C, 37·9; H, 5·4; N, 15·1. Calc. for $C_6H_{10}ON_2S_2$: C, 37·8; H, 5·3; H, 14·7%).

5-*Methyl*-2-*methylthiothiazoline*-4-*carboxylic Acid*.—5-Methyl-2-thiothiazolidine-4-carboxylic acid (5·0 g.), acetone (100 ml.), and potassium carbonate (10 g.) were refluxed with methyl iodide (20 ml.) for 2 hr. The solid was separated and the filtrate concentrated to yield the *S*-methyl-acid as an oil (5·0 g.). The S-*benzylthiuronium salt* formed needles (from dioxan), m. p. 149—150° (Found: C, 46·9; H, 5·7; N, 11·7. $C_{14}H_{19}O_2N_3S_3$ requires C, 47·0; H, 5·4; N, 11·8%).

2-*Methylthio*-5-iso*propylthiazoline*-4-*carboxylic Acid*.—5-*iso*Propyl-2-thiothiazolidine-4-carboxylic acid (8·7 g.) in aqueous N-sodium hydroxide (100 ml.) was stirred with methyl iodide (4 ml.) for 24 hr. at room temperature. The solution, after concentration, was acidified with concentrated hydrochloric acid, and the oil extracted with chloroform. Evaporation of the dried extract and recrystallisation of the residue (4·2 g.) from chloroform–light petroleum gave the *acid* as prisms, m. p. 74—75° (Found: C, 43·7; H, 6·5; N, 6·9. $C_8H_{13}O_2NS_2$ requires C, 43·7; H, 6·0; N, 6·4%) [S-*benzylthiuronium salt*, m. p. 148—149°, needles from aqueous alcohol (Found: C, 49·6; H, 5·8; N, 11·1; S, 25·2. $C_{16}H_{23}O_2N_3S_3$ requires C, 49·7; H, 6·0; N, 11·3; S, 24·9%)].

2-*Methylthio*-5-iso*propylthiazoline*-4-*carboxyamide*.—This was prepared similarly from 5-*iso*propyl-2-thiothiazolidine-4-carboxyamide (1 g.) and methyl iodide (0·5 ml.) in N-sodium hydroxide (5·5 ml.). The *methylthio-amide* crystallised from aqueous methanol as needles, m. p. 127—128° (Found: C, 44·1; H, 7·0; N, 13·2. $C_8H_{14}ON_2S_2$ requires C, 44·0; H, 6·5; N, 12·8%).

Reaction of 2-*Methylthio*-5-iso*propylthiazoline*-4-*carboxylic Acid with Thionyl Chloride*.—The acid hydrochloride (3·0 g.), thionyl chloride (5 ml.), and dry chloroform (15 ml.) were refluxed for 0·75 hr. to give a clear solution which was left for 24 hr., then evaporated to a syrup. After double evaporation with dry benzene the presumed " acid chloride " tended to crystallise. It was dissolved in dry benzene (15 ml.) and this solution (7·5 ml.) was shaken with aqueous ammonia (4 ml.; *d* 0·88) for 24 hr. The resulting solution was diluted with chloroform and acidified with dilute hydrochloric acid, and the organic layer separated. This was washed with dilute sodium hydrogen carbonate solution and water, and then dried ($MgSO_4$). Concentration and addition of light petroleum gave 4-*methyl*-2-(*methylthio-thiocarbonylamino*)*pent*-2-*enamide* as cream-coloured needles, m. p. 90—91° (from light petroleum) (Found: C, 44·8; H, 6·1; N, 12·5. $C_8H_{14}ON_2S_2$ requires C, 44·1; H, 6·5; N, 12·8%).

The " acid chloride " (7·5 ml. of the solution in benzene) and aniline (3 ml.) were left for 24 hr., diluted with chloroform, and washed with dilute hydrochloric acid, dilute sodium hydrogen carbonate solution, and water. The organic extracts were dried and concentrated with light petroleum to give the analogous *anilide* as needles, m. p. 97—98° (Found: C, 57·4; H, 5·8; N, 9·6. $C_{14}H_{18}ON_2S_2$ requires C, 57·2; H, 6·2; N, 9·5%).

5 : 5-*Dimethyl*-2-*methylthiothiazoline*-4-*carboxylic Acid*.—This *acid* was prepared from 5 : 5-dimethyl-2-thiothiazolidine-4-carboxylic acid (12 g.) and methyl iodide (6 ml.) in N-sodium hydroxide (120 ml.) as prisms (9·1 g.), m. p. 126° (from ethyl acetate) (Found: C, 40·6; H, 5·0; N, 6·8. $C_7H_{11}O_2NS_2$ requires C, 40·8; H, 5·4; N, 6·8%). The *sodium salt* was only moderately water-soluble and was isolated directly from the reaction mixture. It crystallised from ethanol as needles, m. p. >280° (Found: C, 36·6; H, 4·4; N, 6·7. $C_7H_{10}O_2NS_2Na$ requires C, 37·0; H, 4·3; N, 6·2%).

Methyl 5-*Methyl*-2-*methylthiothiazoline*-4-*carboxylate*.—An excess of ethereal diazomethane was added to crude 5-methyl-2-methylthiothiazoline-4-carboxylic acid (5·0 g.) in ether (100 ml.). After 24 hr. the ether was evaporated and the residue distilled to give the *methyl ester* (4·5 g.), b. p. 93—95°/0·3 mm., n_D^{18} 1·5485 (Found: C, 41·0; H, 5·8; N, 7·0. $C_7H_{11}O_2NS_2$ requires C, 41·0; H, 5·4; N, 6·8%).

Methyl 2-*Methylthio*-5-iso*propylthiazoline*-4-*carboxylate*.—This *ester* (15·0 g.), b. p. 118—

120°/1·5 mm., was prepared similarly from 2-methylthio-5-*iso*propylthiazoline-4-carboxylic acid (15·8 g.) (Found: C, 46·9; H, 6·9; N, 6·1; S, 27·7. $C_9H_{15}O_2NS_2$ requires C, 46·4; H, 6·5; N, 6·0; S, 27·5%).

Methyl 5 : 5-*Dimethyl-2-methylthiothiazoline-4-carboxylate.*—(1) This *ester*, prepared as above from 5 : 5-dimethyl-2-methylthiothiazoline-4-carboxylic acid (14 g.), had b. p. 82—83°/0·15 mm. (14·7 g.) (Found: C, 44·1; H, 5·3; N, 6·4. $C_8H_{13}O_2NS_2$ requires C, 43·8; H, 6·0; N, 6·4%). Its *picrate* formed needles, m. p. 107—108°, from aqueous ethanol (Found: C, 37·5; H, 3·9; N, 13·0. $C_{14}H_{16}O_9N_4S_2$ requires C, 37·4; H, 3·6; N, 12·5%). (2) Excess of ethereal diazomethane was added to a suspension of methyl 5 : 5-dimethyl-2-thiothiazolidine-4-carboxylate (0·5 g.) in ether (10 ml.). After 24 hr. evaporation gave the ester whose picrate had m. p. and mixed m. p. 107—108° (Found: C, 37·7; H, 3·6; N, 12·7%).

Methyl 2-*Anilino*-5 : 5-*dimethylthiazoline-4-carboxylate.*—Methyl 5 : 5-dimethyl-2-methylthiothiazoline-4-carboxylate (2·2 g.) and aniline (0·95 g.) were heated at 95° for 6 hr. and unchanged reactants were removed *in vacuo*. The residue, recrystallised from ethanol, gave the *anilino-derivative* (0·6 g.) as needles, m. p. 160—161° (Found: C, 59·6; H, 6·0; N, 10·6. $C_{13}H_{16}O_2N_2S$ requires C, 59·1; H, 6·1; N, 10·6%).

5-*Methylthiazolidine-4-carboxylic Acid and its Derivatives.*—Methyl 2-methylthiothiazoline-4-carboxylate (10·0 g.) in methanol (300 ml.) was added to amalgamated aluminium foil (7·0 g.). After 24 hr. the solids were extracted with hot methanol (3 × 300 ml.), the combined filtrates evaporated, and the residual oil distilled *in vacuo*, to give *methyl* 5-*methylthiazolidine-4-carboxylate* (4·4 g.), b. p. 66—67°/0·5 mm., n_D^{20} 1·5050 (Found: C, 44·7; H, 7·0; N, 9·0. $C_6H_{11}O_2NS$ requires C, 44·7; H, 6·9; N, 8·7%). Alcoholic hydrazine hydrate gave the *hydrazide*, m. p. 111—113° (Found: C, 37·2; H, 6·7; N, 26·3. $C_5H_{11}ON_3S$ requires C, 37·2; H, 6·8; N, 26·0%).

Methyl 5-iso*Propylthiazolidine-4-carboxylate.*—This *ester* (4·8 g.) was prepared similarly from methyl 2-methylthio-5-*iso*propylthiazoline-4-carboxylate (10 g.) as a pale yellow oil, b. p. 67—68°/0·5 mm. (Found: C, 50·8; H, 8·0; N, 7·6. $C_8H_{15}O_2NS$ requires C, 51·0; H, 8·0; N, 7·4%) [*hydrochloride*, needles (from methanol–ether), m. p. 133—134° (Found: C, 42·7; H, 7·3; N, 6·5; Cl, 15·8. $C_8H_{16}O_2NSCl$ requires C, 42·7; H, 7·2; N, 6·2; Cl, 15·7%)].

5-iso*Propylthiazolidine-4-carboxyamide.*—(1) 2-Methylthio-5-*iso*propylthiazoline-4-carboxyamide (20 g.) was similarly reduced to 5-*iso*propylthiazolidine-4-carboxyamide, needles (10 g.), 126—127° (from aqueous methanol) (Found: C, 48·3; H, 8·2; N, 16·2. $C_7H_{14}ON_2S$ requires C, 48·4; H, 8·1; N, 16·1%).

(2) Methyl 5-*iso*propylthiazolidine-4-carboxylate (0·45 g.), ammonia (5 ml.; *d* 0·88) and methanol (4 ml.) were left for 24 hr. at room temperature. Evaporation gave a solid amide (0·35 g.) which, crystallised from aqueous methanol, had m. p. and mixed m. p. 126°.

Methyl 5 : 5-*Dimethylthiazolidine-4-carboxylate.*—Methyl 5 : 5-dimethyl-2-methylthiothiazoline-4-carboxylate (21·5 g.) was similarly reduced to the *thiazolidine* (12·1 g.), b. p. 70—75°/0·2 mm., prisms, m. p. 43—44° (from light petroleum) (Found: C, 47·9; H, 7·2; N, 8·2. $C_7H_{13}O_2NS$ requires C, 47·9; H, 7·5; N, 8·0%).

β-*Methylcysteine* (*Thiothreonine*) *Methyl Ester Hydrochloride.*—Methyl 5-methylthiazolidine-4- carboxylate (2·0 g.) and 10% methanolic mercuric chloride (50 ml.) were heated under reflux for 2 hr. The cooled suspension of mercuric salts was treated with hydrogen sulphide for 1 hr., then filtered, and evaporated. The residue gave *thiothreonine methyl ester hydrochloride*, m. p. 138—139° (from propan-2-ol), giving an intense violet colour with sodium nitroprusside (Found: C, 32·5; H, 6·3; N, 7·4; S, 16·9. $C_5H_{12}O_2NSCl$ requires C, 32·4; H, 6·5; N, 7·5; S, 17·3%).

Thiothreonine Hydrochloride.—(1) The foregoing ester (1·0 g.) was refluxed with 5N-hydrochloric acid (15 ml.) for 2·5 hr. Evaporation and drying *in vacuo* over potassium hydroxide gave *thiothreonine hydrochloride* as needles, m. p. 184—185° (from methanol–ether) (Found: C, 28·2; H, 5·9; N, 8·5. $C_4H_{10}O_2NSCl$ requires C, 28·0; H, 5·9; N, 8·2%).

(2) 5-Methyl-2-thiothiazolidine-4-carboxylic acid (5·0 g.) and concentrated hydrochloric acid (40 ml.) were heated in a sealed tube at 110—120° for 60 hr., then evaporated, leaving thiothreonine hydrochloride (1·8 g.), needles, m. p. and mixed m. p. 184—185° (from methanol–ether).

S-*Benzylthiothreonine Methyl Ester Hydrochloride.*—Triethylamine (9·0 ml.) and then benzyl bromide (2·6 ml.) were added with shaking to thiothreonine methyl ester hydrochloride (3·7 g.) suspended in dry chloroform (15 ml.). After 1 hr. the mixture was concentrated, basified with 4N-sodium hydroxide, and extracted with ether. Evaporation of the extracts afforded an oil, converted by ethereal hydrogen chloride into crystalline S-*benzylthiothreonine methyl ester hydrochloride* (3·5 g.), m. p. 129—130°. Crystallisation from propan-2-ol gave

needles, m. p. 131—132° (Found: C, 51·8; H, 6·7; N, 5·1. $C_{12}H_{18}O_2NSCl$ requires C, 52·2; H, 6·6; N, 5·1%).

N-*Benzoyl*-S-*benzylthiothreonine Methyl Ester*.—*S*-Benzylthiothreonine methyl ester hydrochloride (1·4 g.) was shaken with N-sodium hydroxide (10·0 ml.) and benzoyl chloride (0·58 ml.) for 20 min. The insoluble product (1·65 g.) gave N-*benzoyl*-S-*benzylthiothreonine methyl ester* as needles, m. p. 88—89°, from ethyl acetate–light petroleum (Found: C, 66·7; H, 6·5; N, 4·4. $C_{19}H_{21}O_3NS$ requires C, 66·6; H, 6·2; N, 4·1%).

Benzoylation of Thiothreonine Methyl Ester Hydrochloride.—The ester hydrochloride (1·9 g.) was shaken with N-sodium hydroxide (32 ml.) and benzoyl chloride (2·0 ml.) for 5 min. The oil which separated was extracted with ether, and the extracts were evaporated. Crystallisation of the residue from ether–light petroleum (b. p. 40—60°) gave NS-*dibenzoylthiothreonine methyl ester* (1·45 g.), m. p. 89—90° (Found: C, 63·9; H, 5·4; N, 3·9; S, 9·4. $C_{19}H_{19}O_4NS$ requires C, 63·9; H, 5·4; N, 3·9; S, 9·0%). The aqueous layer was acidified and extracted with chloroform, to give N-*benzoylthiothreonine methyl ester* a sneedles, m. p. 84—85° (from ether–light petroleum) (Found: C, 56·8; H, 5·9; N, 5·3. $C_{12}H_{15}O_3NS$ requires C, 57·0; H, 6·0; N, 5·5%).

The *N*-benzoyl ester (1 g.) was left in N-sodium hydroxide (10 ml.) overnight. Acidification gave N-*benzoylthiothreonine* as needles (from aqueous alcohol), m. p. 149—150° (Found: C, 54·9; H, 5·3; N, 6·3. $C_{11}H_{13}O_3NS$ requires C, 55·3; H, 5·5; N, 5·9%).

N-*Benzoyl*-S-*benzyl*(*thiothreonine*).—(1) *N*-Benzoyl-*S*-benzylthiothreonine methyl ester (1·5 g.) was heated with concentrated hydrochloric acid (7·5 ml.), water (15 ml.), and acetic acid (25 ml.) for 30 min. under reflux. Water (5 ml.) was added and after 24 hr. the product was collected (1·05 g.); m. p. 142—144°. *N*-Benzoyl-*S*-benzylthiothreonine separated from benzene as plates, m. p. 142—143°, not depressed on admixture with a specimen prepared according to Carter *et al.*[1] (see below) (Found: C, 65·5; H, 6·0; N, 4·5. Calc. for $C_{18}H_{19}O_3NS$: C, 65·6; H, 5·8; N, 4·2%). The phenethylamine salt formed needles, m. p. and mixed m. p. 165—167° from ethyl acetate–ethanol (Found: C, 68·9; H, 6·8; N, 6·0. Calc. for $C_{26}H_{30}O_3N_2S$: C, 69·3; H, 6·7; N, 6·2%).

(2) *N*-Benzoylthiothreonine (2·4 g.) was stirred with N-sodium hydroxide (23 ml.) and benzyl chloride (1·3 g.) for 2 hr. The mixture was extracted once with ether, and the aqueous layer acidified with hydrochloric acid, to give a solid which on crystallisation from benzene furnished *N*-benzoyl-*S*-benzylthiothreonine (2·5 g.), m. p. 140—143°, not depressed on admixture with an authentic specimen of the A-series (see below).

Benzoylation of S-*Benzylthiothreonine A and B*.—The method of Carter *et al.*[2] was used to prepare reference samples of *N*-benzoyl-*S*-benzylthiothreonine A, m. p. 142—143° (lit., m. p. 143—145°) and B, m. p. 183—185° (lit., m.p. 177—182°).

Esterification of S-*Benzylthiothreonine A and B*.—Dry hydrogen chloride was passed into a suspension of *S*-benzylthiothreonine A (11·5 g.) in dry methanol (160 ml.) for 1·5 hr. without external cooling. After 24 hr. the methanol was evaporated, to give the *methyl ester hydrochloride A* (10·8 g.), m. p. 130—131°, needles from ethanol–ether (Found: C, 52·3; H, 6·6; N, 5·2. $C_{12}H_{18}O_2NSCl$ requires C, 52·3; H, 6·6; N, 5·1%). S-*Benzylthiothreonine methyl ester hydrochloride B* was similarly prepared as needles, m. p. 171° (Found: C, 52·6; H, 6·8; N, 5·4%).

N-*Thiobenzoyl*-DL-allo*threonine and its Methyl Ester*.—DL-*allo*Threonine methyl ester hydrochloride (4·05 g.) in pyridine (25 ml.) was treated with triethylamine (13·7 ml.), followed by thiobenzoylthioacetic acid (6·7 g.) in pyridine (30·5 ml.). After 24 hr. the addition of cold dilute sulphuric acid gave an oil which was extracted into ether, washed with aqueous sodium hydrogen carbonate, and dried. Evaporation left an oil which crystallised from ether–light petroleum to give the N-*thiobenzoyl*-DL-allo*threonine methyl ester* as pale yellow prisms (3·7 g. 48%), m. p. 66—67° (Found: C, 56·6; H, 6·4; N, 5·7. $C_{12}H_{15}O_3NS$ requires C, 57·0; H, 6·0; N, 5·5%).

The ester (0·5 g.) was dissolved in methyl alcohol (5·0 ml.), and N-sodium hydroxide (2·5 ml.) added. After 24 hr. N-hydrochloric acid (2·5 ml.) was added and the product extracted into ethyl acetate. Concentration and addition of light petroleum (b. p. 60—80°) gave cream-coloured prisms, m. p. 137—138° (decomp.), of N-*thiobenzoyl*-DL-allo*threonine* (Found: C, 55·7; H, 6·0; N, 6·0. $C_{11}H_{13}O_3NS$ requires C, 55·3; H, 5·5; N, 5·9%).

Methyl trans-5-*Methyl*-2-*phenylthiazoline*-4-*carboxylate Hydrochloride*.—*N*-Thiobenzoyl-DL-*allo*threonine methyl ester (4·2 g.) was added in portions with shaking to thionyl chloride (10 ml.)

at 0°. After 30 min. the excess of thionyl chloride was removed under reduced pressure and the residue re-evaporated with dry chloroform. The buff solid obtained crystallised from chloroform–light petroleum (b. p. 60—80°), to give the *thiazoline ester hydrochloride* as needles (2·4 g., 53%), m. p. 165—167° softening at 160° (Found: C, 53·0; H, 5·1; N, 5·6. $C_{12}H_{14}O_2NSCl$ requires C, 52·9; H, 5·2; N, 5·2%). The *picrate* separated from water containing a little alcohol as yellow prisms, m. p. 183—184° (decomp.) (Found: C, 46·5; H, 3·7; N, 12·5. $C_{18}H_{16}O_9N_4S$ requires C, 46·6; H, 3·5; N, 12·1%).

trans-N-*Benzoyl*-S-*benzylthiothreonine and its Identity with the A-Series.*—Methyl *trans*-5-methyl-2-phenylthiazoline-4-carboxylate hydrochloride (4·2 g.) and 3N-hydrochloric acid (100 ml.) were refluxed for 4 hr. under nitrogen, the benzoic acid which crystallised on cooling was extracted into ether, and the aqueous layer evaporated to a gum which was repeatedly evaporated with dry benzene under nitrogen. The gum, suspended in chloroform (30 ml.), was treated with triethylamine (2·0 ml.), giving crude thiothreonine (1·35 g. 63%), m. p. 184—186° (decomp.), which gave a strong violet colour with sodium nitroprusside reagent.

The crude thiothreonine (0·95 g.) in liquid ammonia (50 ml.) was treated with sodium until a permanent deep blue colour was obtained which was then removed with a trace of solid ammonium chloride. Benzyl chloride (0·85 ml.) was added and the ammonia allowed to evaporate overnight, to give a solid which was suspended in hot water (10 ml.) and brought to pH 6 with 3N-hydrochloric acid. The *S*-benzylthiothreonine (1·25 g. 80%), m. p. 171—173°, was collected and washed with water. It gave no reaction for a free thiol group.

The foregoing product (1·2 g.), dissolved in N-sodium hydroxide (12·0 ml.), was shaken with benzoyl chloride (0·7 ml.) for 15 min. Acidification gave a cream-coloured solid (1·6 g., 91%) which was extracted with light petroleum (2 × 10 ml.). The residue crystallised from aqueous methyl alcohol to give needles of the A-series product, m. p. 140—142°, not depressed on admixture with the product described by Carter *et al.*[2] (see above.).

β-iso*Propylcysteine Methyl Ester Hydrochloride.*—Methyl 5-*iso*propylthiazolidine-4-carboxylate (10·5 g.) and mercuric chloride (35 g.) reacted in methanol (120 ml.) as described above for the 5-methyl analogue, to give β-iso*propylcysteine methyl ester hydrochloride* (10·1 g.) as needles, m. p. 169—170° (decomp.) (from methanol–ether) (Found: C, 39·3; H, 7·4; N, 6·8; S, 15·0. $C_{17}H_{16}O_2NSCl$ requires C, 39·3; H, 7·6; N, 6·6; S, 15·0%).

NS-*Dibenzoyl*-β-iso*propylcysteine Methyl Ester.*—The above ester hydrochloride (2·1 g.) was shaken with N-sodium hydroxide (32 ml.) and benzoyl chloride (2 ml.), the gum which separated was extracted with chloroform, and the extracts were washed with water and dried. Evaporation of the chloroform gave an oil which crystallised under light petroleum. Recrystallisation from ethanol–light petroleum gave the NS-*dibenzoyl derivative* (1·0 g.) as needles, m. p. 96—97° (Found: C, 65·2; H, 6·4; N, 3·6; S, 8·3. $C_{21}H_{23}O_4NS$ requires C, 65·5; H, 6·0; N, 3·6; S, 8·4%). The same product was formed even if only half the quantity of benzoyl chloride was used.

β-iso*Propylcysteine Amide Hydrochloride.*—5-*iso*Propylthiazolidine-4-carboxyamide (5 g.), mercuric chloride (25 g.), and methanol (300 ml.) were treated as described above for the analogous acid, to give β-iso*propylcysteine amide hydrochloride* (1·5 g.), m. p. 179—181° (decomp.) (Found: C, 36·5; H, 7·4; N, 14·1. $C_6H_{15}ON_2SCl$ requires C, 36·2; H, 7·6; N, 14·0%).

2 : 2-*Dimethyl*-5-iso*propylthiazolidine*-4-*carboxyamide Hydrochloride.*—β-*iso*Propylcysteine amide hydrochloride (1·0 g.), methanol (10 ml.) and acetone (10 ml.) were heated at 100° for 10 min. Concentration and addition of acetone gave the *thiazolidine hydrochloride* (0·8 g.), needles, m. p. 199—200° (decomp.) (from methanol–acetone) (Found: C, 45·5; H, 7·8; N, 11·9. $C_9H_{19}ON_2SCl$ requires C, 45·2; H, 8·0; N, 11·7%).

β-iso*Propylcysteine Hydrochloride.*—β-*iso*Propylcysteine methyl ester hydrochloride (1·5 g.), concentrated hydrochloric acid (7 ml.), and water (20 ml.) were refluxed for 3 hr. under carbon dioxide. Evaporation under reduced pressure gave an oil which was evaporated twice with alcohol and dry benzene; it then crystallised. Recrystallisation from dry alcohol–chloroform–light petroleum gave β-iso*propylcysteine hydrochloride hydrate* as needles, m. p. 142—144° (softening at *ca.* 90°) (Found: C, 33·7; H, 7·7; S, 14·9. $C_6H_{14}O_2NSCl,H_2O$ requires C, 33·0; H, 7·4; S, 14·7%). Drying for 14 hr. at 78°/15 mm. gave the anhydrous form, m. p. 180—182° (lit.,[3] m. p. 197—199°) (Found: C, 35·4; H, 7·4; N, 6·7. Calc. for $C_6H_{14}O_2NSCl$: C, 36·0; H, 7·1; N, 7·0%).

2 : 2-*Dimethyl*-5-iso*propylthiazolidine*-4-*carboxylic Acid Hydrochloride.*—β-*iso*Propylcysteine hydrochloride (0·45 g.) was refluxed in acetone (20 ml.) until dissolved, and the solution cooled,

the product then separating (0·4 g.). Filtration followed by crystallisation from acetone–alcohol gave the *thiazolidine* as needles, m. p. 202—204° (decomp.) (Found: C, 45·3; H, 7·6; S, 13·5. $C_9H_{18}O_2NSCl$ requires C, 45·0; H, 7·6; S, 13·3%).

ββ-*Dimethylcysteine Methyl Ester Hydrochloride.*—Methyl 5 : 5-dimethylthiazolidine-4-carboxylate (15 g.) and mercuric chloride (15 g.) were allowed to react in methanol (150 ml.) as described above for the 5-methyl analogue, to give ββ-dimethylcysteine methyl ester hydrochloride as needles (8·0 g), m. p. 169—171° (lit., m. p. 173—175°) (from methanol–ether) (Found: C, 36·6; H, 7·2; N, 7·4. Calc. for $C_6H_{14}O_2NSCl$: C, 36·1; H, 7·1; N, 7·0%).

2 : 2 : 5 : 5-*Tetramethylthiazolidine-4-carboxylic Acid.*—ββ-Dimethylcysteine methyl ester hydrochloride (4·3 g.) was refluxed with 5N-hydrochloric acid (60 ml.) under nitrogen for 3 hr. and the solution evaporated to a colourless gum. After re-evaporation twice with dry benzene the crude ββ-dimethylcysteine hydrochloride (4·5 g.) was refluxed in acetone (100 ml.) for 0·5 hr. and cooled, to give the thiazolidine hydrochloride (3 g.), m. p. 208—209° (decomp.) (lit., m. p. 191—194°), needles (from acetone–alcohol) (Found: C, 42·2; H, 7·3; N, 6·2; Cl, 15·7. Calc. for $C_8H_{16}O_2NSCl$: C, 42·6; H, 7·2; N, 6·2; Cl, 15·7%).

S-*Methylthiocarbonylpenicillamine Hydrochloride.*—5 : 5-Dimethyl-2-methylthiothiazoline-4-carboxylic acid (3 g.), concentrated hydrochloric acid (10 ml.), and water (10 ml.) were refluxed for 3 hr. under carbon dioxide. Evaporation gave a syrup which solidified under ethanol, was filtered off, and crystallised from ethanol to give S-*methylthiocarbonylpenicillamine hydrochloride* (2·0 g.), m. p. 186—187° (decomp.) (Found: C, 32·9; H, 5·3; N, 5·8; Cl, 13·8. $C_7H_{14}O_3NS_2Cl$ requires C, 32·3; H, 5·4; N, 5·4; Cl, 13·7%).

5 : 5-*Dimethyl-2-oxothiazolidine-4-carboxylic Acid.*—(1) *S*-Methylthiocarbonylpenicillamine hydrochloride (0·26 g.) in aqueous N-sodium hydroxide (3 ml.) was left at room temperature for 3 hr., then neutralised with N-hydrochloric acid (3 ml.). After concentration the colourless precipitate was separated and crystallised from water to give the thiazolidone as needles, m. p. 180—181°, identical (mixed m. p.) with that prepared by Cook, Elvidge, and Shaw's method [16] (Found: C, 40·9; H, 5·2; N, 8·1. Calc. for $C_6H_9O_3NS$: C, 41·1; H, 5·2; N, 8·0%)

(2) 5 : 5-Dimethyl-2-thiothiazolidine-4-carboxylic acid (2 g.) and chloroacetic acid (4 g.) in water (20 ml.) were refluxed for 4 hr. After 24 hr. at room temperature the solution was concentrated *in vacuo* and the precipitate separated. Crystallisation from water gave the thiazolidone as needles, m. p. and mixed m. p. 182—183°.

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