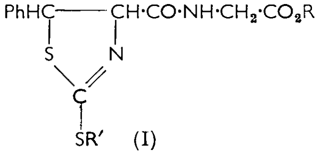
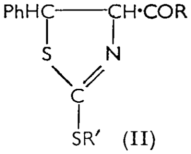
926. *Thiazolidines. Part II.*[1] *Some Reactions of 5-Phenyl-2-thiothiazolidine-4-carboxylic Acid.*

By D. O. Holland and P. Mamalis.

Like the α-form of 5-phenyl-2-thiothiazolidine-4-carbonylglycine (I; R = R′ = H),* *cis*-5-phenyl-2-thiothiazolidine-4-carboxylic acid (II; R = OH, R′ = H) and its derivatives have been inverted to the lower-melting *trans*-isomers by the action of alkali. The inference that the α-peptide has the *cis*- and the β-peptide the *trans*-configuration has been confirmed by synthesis of the latter from the *trans*-acid (II; R = OH, R′ = H) by way of the hydrazide (II; R = NH·NH$_2$, R′ = H). Attempts to use this route to the *cis*-peptide were unsuccessful.

It has been shown [1] that the higher-melting or α-isomer of 5-phenyl-2-thiothiazolidine-4-carbonylglycine (I; R = R′ = H) * can be converted into the lower-melting β-isomer by the action of alkali. It was of interest to correlate these by attempting their synthesis from the two isomeric 5-phenyl-2-thiothiazolidine-4-carboxylic acids (II; R = OH, R′ = H) of Chatterjee, Cook, Heilbron, and Levy.[2]


(I)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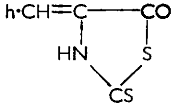
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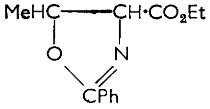
(IV)

The lower-melting (m. p. 175—176°) 5-phenyl-2-thiothiazolidine-4-carboxylic acid (II; R = OH, R′ = H) which Chatterjee *et al.*[2] designated the α-form has been shown by Sicher *et al.*[3] probably to possess the *trans*-configuration. It was readily obtained by the action of methanolic potassium hydroxide on 4-benzylidene-2-thiothiazolid-5-one [2] (III). Preparation of the *cis*-form, m. p. 235° (decomp.), from the same starting material by reaction with aqueous sodium carbonate [2] gave low and variable yields in our hands: at best 20% was produced, together with 50% of the *trans*-isomer, by heating the reactants on the steam-bath for 30—45 min. Longer heating gave a greater proportion of the *trans*-acid and after six hours only this form could be isolated. The inference that the higher-melting *cis*-form could be converted into the lower-melting *trans*-form was confirmed by heating a sample of the former in aqueous sodium carbonate or sodium hydroxide for several hours, complete conversion occurring. It seems likely from this that the higher-melting α-form and the lower-melting β-form of the peptide (I; R = R′ = H) and their derivatives possessed the *cis*- and the *trans*-configuration respectively and this was confirmed by the synthesis, described below, of the β-form of (I; R = R′ = H) from *trans*-5-phenyl-2-thiothiazolidine-4-carboxylic acid.

The *cis*- and the *trans*-methyl and -ethyl esters (II; R = OMe or OEt, R′ = H) on hydrolysis behaved similarly to the α- and β-peptide esters (I; R = Me or Et, R′ = H), giving the respective acids when acid was used but only the *trans*-acid with cold alkali. Attempts to hydrolyse the *trans*-methyl ester (II; R = OMe, R′ = H) with aqueous-ethanolic hydrochloric acid gave the ethyl ester, and the *trans*-acid could be esterified by heating it with methanol in the absence of catalyst.

Hydrolysis of the two isomeric 5-phenyl-2-thiothiazolidine-4-carboxyamides (II; R = NH$_2$, R′ = H), prepared by the action of one equivalent of cold aqueous ammonia on 4-benzylidene-2-thiothiazolid-5-one (III), as described by Chatterjee *et al.*,[2] fitted the same

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* See footnote on p. 4584.

[1] Part I, preceding paper.

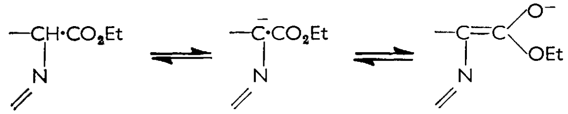
[2] Chatterjee, Cook, Heilbron, and Levy, *J.*, 1948, 1337.

pattern. The higher-melting isomer, m. p. 241—242° (decomp.), on acid hydrolysis afforded a convenient synthesis of *cis*-5-phenyl-2-thiothiazolidine-4-carboxylic acid, while the other isomer, m. p. 180—181°, gave the *trans*-acid. Both gave the *trans*-acid on treatment with cold N-sodium hydroxide. *cis*-5-Phenyl-2-thiothiazolidine-4-carboxylic acid itself was unaffected by cold alkali.

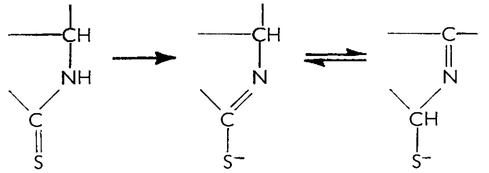
The action of aqueous ammonia on the *trans*-methyl ester (II; R = OMe, R′ = H) gave the *trans*-amide (II; R = NH_2, R′ = H), but from the *cis*-methyl ester a mixture was obtained from which only the *trans*-amide could be isolated pure.

In the analogous alkaline hydrolysis of the two forms of 5-methyl-2-phenyl-Δ^2-oxazoline ethyl ester (IV), Elliott[4] postulated that inversion is effected at the 4-carbon atom, by enolisation of the ethoxycarbonyl group before hydrolysis (scheme A).

(A)

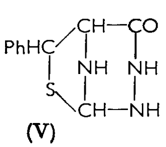


(B)

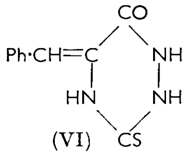


That inversion in the thiothiazolidines also took place at position 4 and not by opening of the ring between the sulphur atom and $C_{(5)}$ can be inferred from the fact that rearrangement of the thiazolidone (III) with either sodium carbonate or ammonia gave some of the *cis*-derivatives in the first place. The inversion therefore probably follows Elliott's mechanism. However, since the free *cis*-acid (II; R = OH, R′ = H) can be inverted with alkali, it is possible that inversion at $C_{(4)}$ can occur as shown in scheme B.

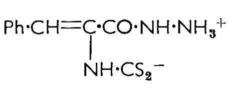
For the attempted synthesis of the two 5-phenyl-2-thiothiazolidine-4-carbonylglycines (I; R = R′ = H) from the corresponding 5-phenyl-2-thiothiazolidinecarboxylic acids the azide method was used. The action of excess of hydrazine hydrate on the *trans*-methyl ester (II; R = OMe, R′ = H) gave a yellow product $C_{10}H_9ON_3S_3$, m. p. 265° (decomp.), insoluble in dilute acid but soluble in alkali, instead of the expected hydrazide (II; R = $NH{\cdot}NH_2$, R′ = H). Two structures (V) and (VI) were considered for this compound, the first arising by ring-closure of the hydrazide (II; R = $NH{\cdot}NH_2$, R′ = H), and the second by rupture of the 1 : 5-bond and ring turning. Compound (VI) has been reported by Cook, Hunter, and Pollock[5] to be formed by the action of hydrazine hydrate on 4-benzylidene-2-thiothiazolid-5-one. We obtained, however, an unstable solid, probably the internal dithiocarbamic salt (VII) rather than the isomeric hydrazine salt (VIII) since it was colourless. This, when heated with water, lost hydrogen sulphide to yield the suspected triazine (VI) identical with the compound obtained from the ester (II; R = OMe, R′ = H) and hydrazine hydrate. Both gave the same methyl derivative, m. p. 163—164°,



(V)

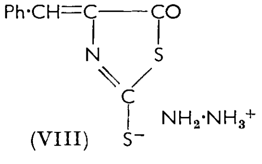


(VI)



$$\underset{\textstyle NH{\cdot}CS_2^-}{Ph{\cdot}CH{=}\underset{|}{C}{\cdot}CO{\cdot}NH{\cdot}NH_3^+}$$

(VII)



(VIII)

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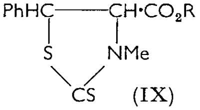
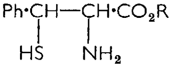
[3] Sicher, Svoboda, and Farkas, *Coll. Czech. Chem. Comm.*, 1955, **20**, 1439.
[4] Elliott, *J.*, 1949, 589.
[5] Cook, Hunter, and Pollock, *J.*, 1950, 1892.

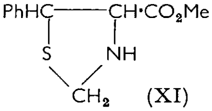
on reaction with methyl iodide and sodium hydroxide. The methyl derivative, m. p. 227° (decomp.), described by Cook *et al.*[5] was not obtained.

The required hydrazide (II; R = NH·NH$_2$, R′ = H) was eventually obtained with the triazine (VI) by slow addition of one equivalent of hydrazine hydrate to a methanolic solution of the methyl ester (II; R = OMe, R′ = H). It formed a crystalline hydrochloride and benzylidene derivative. None of the compound of m. p. 265° (decomp.) was produced when the hydrazide was heated with an excess of hydrazine hydrate, thus rendering the structure (V) unlikely.

The hydrazide on reaction with nitrous acid and then glycine ethyl ester gave an oily peptide ester which on hydrolysis with dilute acid or alkali gave β-5-phenyl-2-thiothiazolidine-4-carbonylglycine (I; R = R′ = H). It is evident that this peptide possesses the *trans*-configuration.


(IX)


$Ph\cdot CH(SH)\text{—}CH(NH_2)\cdot CO_2R$
(X)

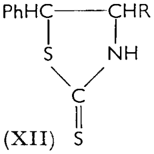

(XI)

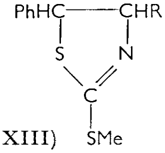
Attempts to prepare the *cis*-peptide (I; R = R′ = H) from methyl *cis*-5-phenyl-2-thiothiazolidine-4-carboxylate (II; R = OMe, R′ = H) by the above method were unsuccessful, a mixture being obtained from which only the suspected triazine (VI) was obtained pure. Attention was therefore directed to the possible synthesis of the 2-methylthio-5-phenylthiazoline-4-carbonylglycines (I; R = H, R′ = Me) by a similar procedure from the two forms of 2-methylthio-5-phenylthiazoline-4-carboxylic acid (II; R = OH, R′ = Me).

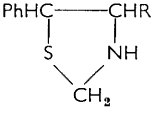
trans-5-Phenyl-2-thiothiazolidine-4-carboxylic acid (II; R = OH, R′ = H) with dimethyl sulphate and N-sodium hydroxide yielded an oil, possibly a mixture of the 3-methyl derivative (IX; R = H) with the required 2-methylthio-acid (cf. Carrington and Waring [6]). By the use of methyl iodide and two equivalents of N-sodium hydroxide, however, the methylthio-acid (II; R = OH, R′ = Me) was obtained crystalline. Kashida and Yamanaka [7] obtained a 66% yield of what was probably the same acid by methylation with diazomethane followed by alkaline hydrolysis of the crude methyl ester. Esterification of *trans*-2-methylthio-5-phenylthiazoline-4-carboxylic acid with diazomethane gave the ester

Cook, Hunter, and Pollock [5] for the preparation of phenylcysteine amide. Reduction of the methyl ester (II; R = OMe, R′ = Me) with amalgamated aluminium gave methyl 5-phenylthiazolidine-4-carboxylate (XI). Ring opening of the thiazolidine ester with mercuric chloride in aqueous methanol and decomposition of the resulting mercaptide with hydrogen sulphide gave a good yield of the hydrochloride of phenylcysteine methyl ester (X; R = Me) from which on hydrolysis with hydrochloric acid the amino-acid hydrochloride, m. p. 204° (decomp.), was obtained.

Examination of the ultraviolet absorption spectra of many of the compounds described in this and the preceding paper has shown that to a large extent the 2-thiothiazolidine derivatives exist in alcoholic solution in the form (XII). They exhibit almost identical absorption with a characteristic maximum at about 281 mμ, whereas stabilisation of the thiazoline structure by *S*-methylation (XIII) leads to the disappearance of the peak. Variation of the group R or stereochemical configuration appears to have little or no influence on the absorption. The absorption also disappears when the C=S group in the thiazolidines is replaced by methylene (XIV).


(XII)


(XIII)


(XIV)

EXPERIMENTAL

cis-5-*Phenyl-2-thiothiazolidine-4-carboxylic Acid*.—To a hot solution of sodium carbonate (75 g.) in water (600 ml.) 4-benzylidene-2-thiothiazolid-5-one [2] (30 g.) was added with stirring and the mixture was heated on a steam-bath for 45 min. The hot solution was filtered from a little insoluble material and carefully acidified with hydrochloric acid. The solid that separated was removed, washed with water, and dried. Recrystallising the solid from methanol gave the *cis*-acid (7·9 g.) as needles, m. p. 230—234° (decomp.), raised to 235° (decomp.) on recrystallisation from aqueous methanol (Found: C, 50·0; H, 3·8; N, 5·8. Calc. for $C_{10}H_9O_2NS_2$: C, 50·2; H, 3·8; N, 5·9%). From the methanolic filtrate on dilution with much water about 20 g. of solid were deposited. This was removed and treated with a solution of sodium hydrogen carbonate. The insoluble residue (5·1 g.), m. p. 100—101°, on recrystallisation from chloroform–light petroleum was obtained as needles, m. p. 105—106°, undepressed on admixture with methyl *trans*-5-phenyl-2-thiothiazolidine-4-carboxylate described below. This compound was apparently formed by esterification of the *trans*-acid during the crystallisation of the *cis*-acid from methanol. From the sodium hydrogen carbonate extract the *trans*-acid (14·8 g.) was obtained on acidification.

Inversion of cis- *to* trans-5-*Phenyl-2-thiothiazolidine-4-carboxylic Acid*.—The *cis*-acid (0·5 g.) was heated on a steam-bath for 5 hr. in a solution of sodium carbonate (2 g.) in water (40 ml.). The mixture was then cooled and acidified, the *trans*-acid (0·36 g.) separating. On recrystallisation from aqueous acetic acid it was obtained as needles, m. p. and mixed m. p. 175—176°.

Methyl trans-5-*Phenyl-2-thiothiazolidine-4-carboxylate*.—The *trans*-acid (0·5 g.) in methanol (5 ml.) was saturated with hydrogen chloride, and the mixture kept at 0° overnight. The solution was then concentrated to small volume and diluted with water, the *methyl ester* separating as colourless leaflets (0·37 g.), m. p. 105—106°, not raised when recrystallised from aqueous methanol (Found: C, 52·2; H, 4·6; N, 5·6. $C_{11}H_{11}O_2NS$ requires C, 52·2; H, 4·4; N, 5·5%). The same compound was obtained when concentrated sulphuric acid (3 drops) was used instead of hydrogen chloride. The methyl ester also arose when the *trans*-acid (2·0 g.) was refluxed in methanol (20 ml.) for 0·5 hr. After evaporation of the solution to dryness, the residue was extracted with a solution of sodium hydrogen carbonate to leave the ester (0·8 g.), m. p. and mixed m. p. 101—102°.

The methyl ester also arose on transesterification from the ethyl ester (1·0 g.) in methyl alcohol (15 ml.) overnight in the presence of a trace of sodium methoxide. The resulting solution was neutralised with dilute hydrochloric acid and concentrated to about 5 ml., the methyl ester (0·55 g.) separating. Its m. p. (104—105° after recrystallisation from aqueous methanol) was not depressed on admixture with a pure specimen, but depressed on admixture with the ethyl ester.

Ethyl trans-*5-Phenyl-2-thiothiazolidine-4-carboxylate.*—Esterification of the *trans*-acid (1·0 g. in ethanol (15 ml.) as above gave the *ethyl ester* as leaflets (1·05 g.). It was obtained as needles, m. p. 112·5°, after shrinking from 99°, on recrystallisation from aqueous ethanol (Found: C, 53·5; H, 5·0; N, 4·9. $C_{12}H_{13}O_2NS_2$ requires C, 54·0; H, 4·9; N, 5·2%). The ethyl ester was also obtained by heating the methyl ester (1·0 g.) in ethanol (20 ml.) for 1 hr. on a steam-bath in the presence of dissolved sodium (*ca.* 0·05 g.). When the solution was concentrated and acidified with dilute hydrochloric acid leaflets (0·6 g.) separated, m. p. 105—107°, undepressed on admixture with the ethyl ester, but markedly depressed on admixture with the (*d* 0·88; 2 ml.) for 15 hr. and the resulting solution was diluted with water (10 ml.) and neutralised with hydrochloric acid the *trans*-amide (0·15 g.) separated; it had m. p. 172—173°, raised to 181—182° on recrystallisation from aqueous methanol. The same amide (0·19 g.) also arose from the *trans*-methyl ester (0·20 g.). Both samples failed to depress the m. p. of the lower-melting amide described above.

Hydrolysis of cis-*5-Phenyl-2-thiothiazolidine-4-carboxyamide*.—(a) *With acid.* The amide (0·5 g.) was heated under reflux for 15 hr. in a mixture of dioxan (4 ml.), water (3 ml.), and concentrated hydrochloric acid (4 ml.). The solid that separated from the cooled solution was removed and extracted with sodium hydrogen carbonate solution, and the extract was clarified with charcoal. On acidification the extract yielded the *cis*-acid (0·25 g.), m. p. and mixed m. p. 231—233°.

(b) *With alkali.* When the amide (0·5 g.) was kept in N-sodium hydroxide (5 ml.) at room temperature for 2 days a clear yellow solution was obtained from which a pale yellow solid separated on acidification with N-hydrochloric acid (5 ml.). Extraction of the solid with sodium hydrogen carbonate solution left about 0·04 g. of solid, m. p. 173—175°, not depressed on admixture with the *trans*-amide. From the extract on acidification *trans*-5-phenyl-2-thiothiazolidine-4-carboxylic acid (0·29 g.) separated as needles, m. p. and mixed m. p. 175—176°.

Hydrolysis of trans-*5-Phenyl-2-thiothiazolidine-4-carboxyamide*.—Acid or alkali under conditions similar to those used for the *cis*-isomer gave the *trans*-acid, m. p. 175—176°.

5-Benzylidenehexahydro-6-oxo-3-thio-1 : 2 : 4-triazine (VI).—(a) *Action of hydrazine hydrate on 4-benzylidene-2-thiothiazolid-5-one* (cf. Cook, Hunter, and Pollock [5]). A mixture of the thiazolidone (4·5 g.) and 90% hydrazine hydrate (6 ml.) in methanol (30 ml.) was kept at room temperature for 48 hr. The colourless solid (3·3 g.) that separated was removed and washed with methanol. It had m. p. 182—184° (decomp.) after gradually softening and becoming red from 132°. When this product [which is perhaps (VII)] was dissolved in hot water, hydrogen sulphide was evolved and the triazine separated as pale yellow needles, m. p. 244—246° (decomp.) (3·0 g.) raised to 263—265° (decomp.) on recrystallisation from acetic acid (Found: C, 54·7; H, 4·3; N, 19·3. Calc. for $C_{10}H_9ON_2S$: C, 54·8; H, 4·2; N, 19·2%) [lit., m. p. 251° (decomp.)].

(b) *Action of hydrazine hydrate on methyl* trans-*5-phenyl-2-thiothiazolidine-4-carboxylate.* A mixture of the ester (1 g.) and 90% hydrazine hydrate (1 ml.) was kept overnight at room temperature, then diluted with water (15 ml.) and warmed to 40°; the triazine (0·55 g.), m. p. 261° (decomp.), separated. The m. p., raised to 265° (decomp.) on recrystallisation from acetic acid, was not depressed on admixture with the previous sample.

The products formed by both methods gave the same methylated *derivative* when a sample (1·05 g.) suspended in N-sodium hydroxide (7 ml.) was shaken with methyl iodide (0·5 ml.). The derivative (0·7 g.) formed yellow needles, m. p. 164—165°, from methanol (Found: C, 57·1; H, 4·5; N, 18·3; S, 13·7. $C_{11}H_{11}ON_3S$ requires C, 56·7; H, 4·8; N, 18·0; S, 13·7%).

trans-*5-Phenyl-2-thiothiazolidine-4-carboxyhydrazide*.—To a solution of methyl *trans*-5-phenyl-2-thiothiazolidine-4-carboxylate (10 g.) in methanol (50 ml.) at 25°, 95% hydrazine hydrate (2·1 ml.) was added. Next day the colourless needles (7·0 g.) m. p. 189—191° (decomp.), that had separated were removed, washed with hot methanol, and dissolved in warm 2N-hydrochloric acid. The acid solution was filtered from a little insoluble material and cooled; trans-*5-phenyl-2-thiothiazolidine-4-carboxyhydrazide hydrochloride* which was precipitated, formed colourless needles, m. p. 206—207° (decomp.), from dilute hydrochloric acid (Found: C, 41·8; H, 4·4; N, 14·6. $C_{10}H_{12}ON_3S_2Cl$ requires C, 41·5; H, 4·2; N, 14·5%). When a solution of the hydrochloride was basified with sodium hydrogen carbonate trans-*5-phenyl-2-thiothiazolidine-4-carboxyhydrazide* was deposited. It was obtained as prisms, m. p. 195—196° (decomp.), on recrystallisation from ethanol (Found: C, 47·4; H, 4·5; N, 16·5. $C_{10}H_{11}ON_3S_2$ requires C, 47·4; H, 4·4; N, 16·6%).

The hydrazide (0·2 g.) in boiling alcohol (20 ml.) with benzaldehyde (0·15 ml.) gave the *benzylidene derivative* (0·22 g.), prisms, m. p. 225—226° (decomp.) (from ethanol) (Found: C, 60·0; H, 4·6; N, 12·4. $C_{17}H_{15}ON_3S_2$ requires C, 59·9; H, 4·4; N, 12·3%).

Diluting the filtrate of the original reaction product with water afforded the triazine (*ca.* 0·7 g.), m. p. and mixed m. p. 258—260° (decomp.).

trans-*5-Phenyl-2-thiothiazolidine-4-carbonylglycine*.—Powdered *trans*-5-phenyl-2-thiothiazolidine-4-carboxyhydrazide hydrochloride (2·8 g.) was suspended in a mixture of water (25 ml.), N-hydrochloric acid (5 ml.), and chloroform (20 ml.) at 0°, and sodium nitrite (0·8 g.) in a little water was added slowly with stirring. When the solid had dissolved the chloroform layer was separated, washed with water, and dried ($MgSO_4$). To this extract glycine ethyl ester (1·35 g.) in chloroform (10 ml.) was added. After the mixture had been kept overnight at 0° the solvent was removed to leave an orange-red gum which was stirred for 3 hr. with N-sodium hydroxide (15 ml.). The resulting solution was then extracted with chloroform, and the aqueous layer acidified, to yield an oil which solidified when scratched (0·85 g.). Purified by dissolution in sodium hydrogen carbonate and re-acidification, it had m. p. 180—184° (decomp.) raised to 185—186° (decomp.) on recrystallisation from water. The product gave no depression on admixture with authentic *trans*-5-phenyl-2-thiothiazolidine-4-carbonylglycine (preceding paper) and gave the same *S*-benzylthiuronium salt, m. p. 183—184° (from alcohol) (Found: C, 51·8; H, 5·1; N, 12·2; S, 20·6. Calc. for $C_{20}H_{22}O_3N_4S_3$: C, 52·0; H, 4·8; N, 12·1; S, 20·8%).

The same product was obtained when the crude reaction mixture was hydrolysed for 1 hr. by a refluxing mixture of concentrated hydrochloric acid (4 ml.), water (20 ml.), and dioxan (10 ml.)

trans-2-*Methylthio*-5-*phenylthiazoline*-4-*carbonylglycine*.—A solution of the above acid (0·3 g.) in N-sodium hydroxide (2·2 ml.) was treated with methyl iodide (0·2 ml.) and shaken for 3 hr. The gum that was precipitated on neutralisation with dilute hydrochloric acid was dissolved in chloroform, and the dried solution was concentrated to small volume and diluted with a little light petroleum. The 2-methylthio-derivative which separated formed needles, m. p. and mixed m. p. 130—132°, on recrystallisation from chloroform–light petroleum.

trans-2-*Methylthio*-5-*phenylthiazoline*-4-*carboxylic Acid*.—To a solution of *trans*-5-phenyl-2-thiothiazolidine-4-carboxylic acid (26 g.) in N-sodium hydroxide (230 ml.), methyl iodide (18·3 ml.) was added, and the mixture stirred for 2 hr. The resulting solution was acidified with dilute hydrochloric acid, and the precipitated gum extracted into chloroform. After being washed and dried, the extract was concentrated to small volume and treated with light petroleum; *trans*-2-methylthio-5-phenylthiazoline-4-carboxylic acid (22·5 g.) separated as prisms, m. p. 104—105°, not raised on recrystallisation from chloroform–light petroleum (Found: C, 52·1; H, 4·6; N, 5·7; S, 25·8. Calc. for $C_{11}H_{11}O_2NS_2$: C, 52·3; H, 4·4; N, 5·5; S, 25·3%) (Kashida and Yamanaka [7] give m. p. 104—105°). This compound depressed the m. p. of the isomeric methyl *trans*-5-phenyl-2-thiothiazolidine-4-carboxylate (m. p. 105—106°) on admixture and gave an S-*benzylthiuronium salt*, needles (from aqueous methanol), m. p. 158—159° (decomp.) (Found: C, 54·3; H, 5·3; N, 9·9. $C_{19}H_{21}O_2N_3S_3$ requires C, 54·5; H, 5·0; N, 10·0%). trans-2-*Methylthio*-5-*phenylthiazoline*-4-*carboxylic acid hydrochloride* (1·3 g.), formed when a solution of the acid (1·25 g.) in dry chloroform (15 ml.) was treated with dry hydrogen chloride, was obtained as platelets, m. p. 166—167°, on recrystallisation from alcohol–ether (Found: C, 45·3; H, 4·3; N, 5·0; Cl, 12·3. $C_{11}H_{12}O_2NS_2Cl$ requires C, 45·6; H, 4·2; N, 4·8; Cl, 12·3%). When the hydrochloride was shaken with water it became gummy and reverted to the free acid which was obtained solid by extraction into chloroform and precipitation with light petroleum.

Methyl trans-2-*methylthio*-5-*phenylthiazoline*-4-*carboxylate* was obtained as a pale yellow oil (8·3 g.), b. p. 136°/0·2 mm., when the above acid (9 g.) was esterified with diazomethane in ether (Found: C, 53·7; H, 5·2; N, 5·5. $C_{12}H_{13}O_2NS_2$ requires C, 54·0; H, 4·9; N, 5·2%).

trans-2-*Methylthio*-5-*phenylthiazoline*-4-*carboxhydrazide*.—*trans*-2-Methylthio-5-phenylthiazoline-4-carboxylic acid (10 g.) was esterified in ether with diazomethane, and the resulting oil dissolved in methanol (50 ml.) and treated with 95% hydrazine hydrate (4·5 ml.). When next day the solution was diluted with water the required hydrazide separated, on scratching, as needles (8·45 g.), m. p. 95—97°, raised to 99—100° on recrystallisation from aqueous methanol (Found: C, 49·9; H, 5·2; N, 15·8. $C_{11}H_{13}ON_3S_2$ requires C, 49·5; H, 4·9; N, 15·7%). The p-*nitrobenzylidene derivative* prepared in methyl alcohol was obtained as yellow prisms, m. p. 194°, from ethyl cellosolve–methanol (Found: C, 54·2; H, 3·7; N, 13·9. $C_{18}H_{16}O_3N_4S_2$ requires C, 54·0; H, 4·0; N, 14·0%).

trans-2-*Methylthio*-5-*phenylthiazoline*-4-*carbonylglycine Methyl Ester*.—A solution of the above hydrazide (1·35 g.) in N-hydrochloric acid (7·5 ml.) was stirred with chloroform (10 ml.) in an ice-bath while sodium nitrite (0·4 g.) in a little water was slowly added. The chloroform layer was then separated, washed with a little water, dried ($MgSO_4$), and treated with a solution of glycine methyl ester in chloroform prepared from the hydrochloride (1·5 g.). After being kept overnight the mixture was washed with a little water, dried, and evaporated. A solution of the resulting oil in ether gave, on scratching, *trans*-2-methylthio-5-phenylthiazoline-4-carbonylglycine methyl ester (0·35 g.), m. p. and mixed m. p. 80—81°.

cis-2-*Methylthio-5-phenylthiazoline-4-carboxylic Acid.*—A stirred solution of *cis*-5-phenyl-2-thiothiazolidine-4-carboxylic acid (6 g.) in N-sodium hydroxide (53 ml.) was treated with methyl iodide (4·3 ml.). After 2 hr. chloroform (50 ml.) and concentrated hydrochloric acid (5 ml.) were added, and the mixture was stirred for a further 10 min. After being washed and dried the chloroform layer was concentrated to small volume and diluted with a little light petroleum; cis-2-*methylthio-5-phenylthiazoline-4-carboxylic acid* (3·1 g.) separated as needles, m. p. 137—138°, not raised on recrystallisation from chloroform–light petroleum (Found: C, 51·9; H, 4·3; N, 5·8%).

Methyl cis-2-*methylthio-5-phenylthiazoline-4-carboxylate* was obtained as colourless needles (from ether–light petroleum), m. p. 82—83°, when the *cis*-acid was esterified with diazomethane in the usual way (Found: C, 54·1; H, 5·5; N, 5·5%).

Reaction of Methyl cis-2-*Methylthio-5-phenylthiazoline-4-carboxylate with Hydrazine Hydrate.*—The ester (0·5 g.) in methanol (10 ml.) was treated with 90% hydrazine hydrate (1 ml.). When next day the solution was diluted with water, needles, m. p. 97—98°, of the *trans*-hydrazide separated. The m. p. was not depressed on admixture with a sample prepared from the *trans*-ester.

Reaction of cis-5-*Phenyl-2-thiothiazolidine-4-carboxylic Acid with Diazomethane.*—A suspension of the acid (1·5 g.) in ether was treated with an excess of diazomethane. Next day the crystals that had separated were removed (0·45 g.), to give needles, m. p. 125—125·5°, on recrystallisation from ether–methanol. The product was probably *methyl* cis-3-*methyl-5-phenyl-2-thiothiazolidine-4-carboxylate* (Found: C, 54·0; H, 4·5; N, 4·9%), $\lambda_{max.}$ (in EtOH) 275 mμ (ε 19310). From the original ether filtrate there was obtained on concentration methyl *cis*-2-methylthio-5-phenylthiazoline-4-carboxylate (0·58 g.), m. p. and mixed m. p. 80—81°.

Methyl trans-5-*Phenylthiazolidine-4-carboxylate.*—A solution in methanol (250 ml.) of the oily ester derived from *trans*-2-methylthio-5-phenylthiazoline-4-carboxylic acid (13 g.) and diazomethane was added to amalgamated aluminium (8 g.) at room temperature. After 3 days the alumina that had formed was removed and extracted with hot methanol in several portions (250 ml. total). The extracts were combined with the original reaction solution, and the whole was concentrated *in vacuo*, to leave methyl *trans*-5-phenylthiazolidine-4-carboxylate as a pale yellow oil which crystallised (scratching) (5·4 g.); m. p. 76—77°, unchanged on recrystallisation from methanol–ether (whence it was obtained as needles) (lit.,[7] m. p. 73°) (Found: C, 59·4; H, 5·9; N, 6·3. Calc. for $C_{11}H_{13}O_2NS$: C, 59·2; H, 5·9; N, 6·3%).

threo-*Phenylcysteine Methyl Ester Hydrochloride.*—A solution of methyl *trans*-5-phenylthiazolidine-4-carboxylate (2 g.) in boiling ethanol (20 ml.) was diluted with water (200 ml.) at 80°, and the mixture immediately treated with a solution of mercuric chloride (2·5 g.) in hot water (100 ml.). After the mixture had cooled to room temperature the white solid that had been precipitated was filtered off, washed with water, and dried (4·5 g.). It was then suspended in ethanol and decomposed with hydrogen sulphide. After removal of the mercuric sulphide the solution was evaporated to dryness, to leave *threo*-phenylcysteine methyl ester hydrochloride (2·2 g.), m. p. 174—176° (decomp.), raised to 184—185° (decomp.) on recrystallisation from alcohol–ether (Found: C, 48·6; H, 6·0; N, 5·7. Calc. for $C_{10}H_{14}O_2NSCl$: C, 48·5; H, 5·7; N, 5·7%).

threo-*Phenylcysteine Hydrochloride.*—The above methyl ester hydrochloride (1·14 g.) was heated under reflux with concentrated hydrochloric acid (2·5 ml.) and water (2·5 ml.) for 0·5 hr. On cooling, the *threo*-amino-acid hydrochloride slowly separated as leaflets (0·73 g.), m. p. 205—207° (decomp.), not raised on recrystallisation from propan-2-ol–ether (Found: C, 46·9; H, 5·5; N, 5·6; Cl, 15·2. Calc. for $C_9H_{12}O_2NSCl$: C, 46·3; H, 5·2; N, 6·0; Cl, 15·2%).

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