928. *Thiazolidines. Part IV.*[1] *Further Reactions of 2-Methylthio-5-phenylthiazoline-4-carboxylic Acid.*

By D. O. Holland and P. Mamalis.

cis- and *trans*-2-Oxo-5-phenylthiazolidine-4-carboxylic acid have been prepared from the corresponding 2-methylthio-acids by way of *erythro*- and *threo*-*S*-(methylthio-carbonyl)-β-phenylcysteine hydrochloride (II) and by the action of chloroacetic acid on the respective 2-methylthiothiazoline acids. The action of hydrogen peroxide on the *trans*-2-methylthiothiazoline acid gave (probably) 5-phenylthiazole-4-carboxylic acid, as well as the expected thiazolidone. This acid, together with phenylpyruvic acid, also arose by the action of alkali on the *trans*-2-methylthio-acid (I; R = Me, R′ = H). Methyl *cis*-2-oxo-5-phenylthiazolidine-4-carboxylate has been converted into the *trans*-acids.

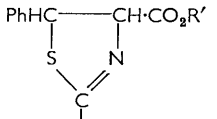
Whereas hydrolysis of methyl *cis*- and *trans*-5-phenyl-2-thiothiazolidine-4-carboxylate (I; R = H, R′ = Me) * with hydrochloric acid gives the respective acids which are therefore stable to this treatment (Part II of this series [1]), the corresponding 2-methylthiothiazoline esters and acids (I; R = Me, R′ = H; and R = R′ = Me) have now been found to yield the two diastereoisomeric *S*-(methylthio-carbonyl)-β-phenylcysteine hydrochlorides (II), as in the conversion of 2-benzylthiothiazoline-4-carboxylic acid into *S*-(benzylthio-carbonyl)cysteine hydrochloride (Crawhall and Elliott [2]). In accord with the suggestions of Sicher *et al.*[3] it is probable the amino-acids (II) arising from the *cis*- and the *trans*-thiazoline have the *erythro*- and the *threo*-configuration respectively.

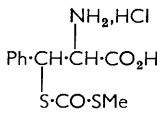
With aqueous-alcoholic sodium hydroxide at room temperature the two forms of the

* See footnote on p. 4584.

[1] Parts II and III, preceding papers.
[2] Crawhall and Elliott, *J.*, 1951, 2071.
[3] Sicher, Svoboda, and Farkas, *Coll. Czech. Chem. Comm.*, 1955, **20**, 1439.

amino-acid (II) likewise behaved similarly to *S*-(benzylthio-carbonyl)cysteine hydrochloride, to give two forms of 2-oxo-5-phenylthiazolidine-4-carboxylic acid (III; R = OH)


(I)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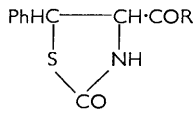
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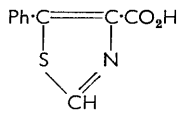
(IV)

The derived methyl esters of these two acids (III; R = OMe), on hydrolysis with hot dilute hydrochloric acid, reverted to the corresponding acids without inversion, but as in the case of the 2-thio-analogues (I; R = H, R′ = Me) [1] hydrolysis with cold aqueous-alcoholic sodium hydroxide caused inversion of the higher-melting to the lower-melting form.

That the higher- and the lower-melting form of the oxothiazolidine acid (III; R = OH) corresponded to the *cis*- and the *trans*-form respectively of the 2-methylthiothiazoline ester (I; R = R′ = Me) from which they were derived thus appeared likely and was confirmed by the preparation of the two oxothiazolidine acids by treatment of *cis*- and *trans*-5-phenyl-2-thiothiazolidine-4-carboxylic acid (I; R = R′ = H) with hot aqueous chloroacetic acid.[4] Similar treatment of *cis*-5-phenyl-2-thiothiazolidine-4-carboxyamide with chloroacetic acid likewise gave the corresponding *cis*-oxothiazolidine amide (III; R = NH_2), but the *trans*-amide yielded only the free acid (II; R = OH). However, the required product was obtained by the action of aqueous ammonia on the *trans*-ester (III; R = OMe) or of thionyl chloride on the oxothiazolidine acid followed by treatment of the gummy product with ammonia. The corresponding 2-thio-acid (I; R = R′ = H) gave only an intractable gum in this reaction.[1]

Cook, Harris, and Heilbron [5] reported that a 2-oxo-5-phenylthiazolidine-4-carboxylic acid was formed through the 2-ethylthiothiazoline acid (I; R = Et, R′ = H) when 4-benzylidene-2-ethylthiothiazol-5-one was heated with aqueous-alcoholic sodium hydroxide. The m. p. of their product was, however, different from that of either the *cis*- or the *trans*-oxothiazolidine acids described above, and using 4-benzylidene-2-methylthiothiazol-5-one [1] we obtained *trans*-5-phenyl-2-thiothiazolidine-4-carboxylic acid (I; R = R′ = H). Further, when 2-methylthio-5-phenylthiazoline-4-carboxylic acid (*trans*-form used) is heated under reflux with N-sodium hydroxide, ammonia and methanethiol are evolved to yield, after acidification, a product giving analytical figures for 5-phenylthiazole-4-carboxylic acid (IV) together with phenylpyruvic acid.

Cook, Harris, Pollock, and Swan [6] obtained a compound, m. p. 225° (decomp.), considered to be 5-phenylthiazole-4-carboxylic acid hydrochloride, by heating triethylammonium 5-phenyl-2-thiothiazolidine-4-thiocarboxylate with concentrated hydrochloric acid. The suspected 5-phenylthiazole-4-carboxylic acid obtained by us, however, could not be converted into a hydrochloride.

Conversion of 5-substituted 2-thiothiazolidine-4-carboxylic acids and esters into their corresponding 2-oxo-analogues by alkaline hydrogen peroxide has been reported by Cook *et al.*[6,7] and by Kashida and Yamanaka.[8] In our hands good yields of the required 2-oxo-5-phenylthiazolidine-4-carboxylic acid were sometimes obtained in this way, but on other occasions considerable quantities of 5-phenylthiazole-4-carboxylic acid were also isolated. When alkaline potassium permanganate was used instead of hydrogen peroxide, only the thiazole was obtained. The corresponding 2-oxo-5-phenylthiazolidine-4-carboxylic acid was unaffected by this treatment, so it was not an intermediate in the conversion.

[4] Cf. Johnson and O'Brien, *J. Biol. Chem.*, 1912, **12**, 205.
[5] Cook, Harris, and Heilbron, *J.*, 1948, 1060.
[6] Cook, Harris, Pollock, and Swan, *J.*, 1950, 1947.
[7] Cook, Elvidge, and Shaw, *J.*, 1949, 2367.
[8] Kashida and Yamanaka, *J. Pharm. Soc. Japan*, 1953, **73**, 953 (*Chem. Abs.*, 1954, **48**, 11394).

Experimental

S-(*Methylthio-carbonyl*)-β-*phenylcysteine.*—*trans*-2-Methylthio-5-phenylthiazoline-4-carboxylic acid (1·25 g.) was heated with concentrated hydrochloric acid (10 ml.) and water (10 ml.) under reflux for 1 hr. threo-S-(*Methylthio-carbonyl*)-β-*phenylcysteine hydrochloride* (1·35 g.) separated. It formed colourless needles, m. p. 183—184° (decomp.), from alcohol–light petroleum (Found: C, 43·0; H, 5·0; N, 4·2; S, 21·5; Cl, 11·0. $C_{11}H_{14}O_3NS_2Cl$ requires C, 43·0; H, 4·6; N, 4·6; S, 20·8; Cl, 11·5%).

The same product was obtained when the corresponding thiazoline methyl ester was heated with aqueous hydrochloric acid.

When a solution of the hydrochloride in aqueous sodium hydrogen carbonate was carefully neutralised with dilute hydrochloric acid the free *amino-acid* separated, which was obtained as colourless needles, m. p. 164—168° (decomp.), from aqueous alcohol (Found: C, 49·3; H, 5·0; N, 5·7; S, 23·2. $C_{11}H_{13}O_3NS_2$ requires C, 48·8; H, 4·8; N, 5·2; S, 23·6%). The product gave a positive ninhydrin test for an α-amino-acid but a negative result in the nitroprusside and the iodine–sodium azide test for thiol groups.

trans-2-*Oxo*-5-*phenylthiazolidine*-4-*carboxylic Acid.*—(a) *From the* threo-S-(*methylthio-carbonyl*)-β-*phenylcysteine hydrochloride.* A suspension of the acid hydrochloride (1·0 g.) in alcohol (30 ml.) was treated with N-sodium hydroxide (10 ml.), a clear solution being formed. After 2 hr. the mixture was neutralised with N-hydrochloric acid and concentrated to small volume; *trans*-2-oxo-5-phenylthiazolidine-4-carboxylic acid separated as plates, m. p. 192—194° (decomp.), unchanged on recrystallisation from hot water [lit.,[8] m. p. 193—195° (decomp.)] (Found: C, 54·0; H, 4·1; N, 6·0. Calc. for $C_{10}H_9O_3NS$: C, 53·8; H, 4·1; N, 6·3%). The S-*benzylthiuronium salt* prepared in the usual way was obtained as colourless needles, m. p. 130—132° (after drying at 78°/3 mm.), from aqueous methanol (Found: C, 54·7; H, 5·6; N, 10·4. $C_{18}H_{19}O_3N_3S_2,CH_3{\cdot}OH$ requires C, 54·2; H, 5·5; N, 10·0%).

(b) *From* trans-5-*phenyl*-2-*thiothiazolidine*-4-*carboxylic acid.* The acid (2 g.) and chloroacetic acid (4 g.) were heated in water (20 ml.) under reflux for 2 hr. After several days at room temperature the precipitate (1·4 g.) was removed and recrystallised from water, as needles, m. p. and mixed m. p. 194—195° (decomp.).

Methyl trans-2-*oxo*-5-*phenylthiazolidine*-4-*carboxylate* was obtained by refluxing the acid (2·0 g.; prepared by method (b) with methyl alcohol (30 ml.) and concentrated sulphuric acid (0·5 ml.) for 2 hr., as needles, m. p. 93—94° (from aqueous methanol) (Found: C, 55·5; H, 4·9; N, 5·6. $C_{11}H_{11}O_3NS$ requires C, 55·8; H, 4·7; N, 5·9%). It was also obtained from the acid prepared by the former method described above by treatment with diazomethane in ethyl acetate, as prisms (from ethyl acetate–light petroleum), m. p. and mixed m. p. 94—95°.

Hydrolysis of Methyl trans-2-*Oxo*-5-*phenylthiazolidine*-4-*carboxylate.*—(a) *With acid.* When the ester (1·0 g.) was heated under reflux for 1 hr. in concentrated hydrochloric acid (5 ml.) and water (7 ml.) the *trans*-acid (0·9 g.), m. p. 192—194° (decomp.), was obtained on cooling of the solution. It did not depress the m. p. of an authentic specimen.

(b) *With alkali.* Similarly the *trans*-acid (0·4 g.), m. p. 192—193° (decomp.), was obtained when the ester (0·5 g.) was kept in a mixture of methyl alcohol (3 ml.) and N-sodium hydroxide (3 ml.) at room temperature for 16 hr. It separated as prisms when the solution was acidified with N-hydrochloric acid.

cis-2-*Oxo*-5-*phenylthiazolidine*-4-*carboxylic Acid.*—(a) *Via* erythro-S-(*methylthio-carbonyl*)-β-*phenylcysteine hydrochloride. cis*-2-Methylthio-5-phenylthiazoline-4-carboxylic acid (2 g.) was heated under reflux in 6N-hydrochloric acid (30 ml.) for 1 hr. erythro-S-(*Methylthio-carbonyl*)-β-*phenylcysteine hydrochloride* (1·75 g.) that separated was removed after cooling. It had m. p. 179—180° (decomp.), raised to 185—186° (decomp.) on recrystallisation from alcohol–ether (Found: C, 43·0; H, 5·3; N, 4·6. $C_{11}H_{14}O_3NS_2Cl$ requires C, 43·0; H, 4·6; N, 4·6%). It depressed slightly the m. p. of the *threo*-amino-acid hydrochloride on admixture. To a suspension of this compound in alcohol (50 ml.) N-sodium hydroxide (30 ml.) was added. Next day a trace of insoluble material was removed, and the solution concentrated *in vacuo* to small volume and acidified with concentrated hydrochloric acid, cis-2-*oxo*-5-*phenylthiazolidine*-4-*carboxylic acid* separating as cream-coloured leaflets (1·05 g.), m. p. 219—220° (decomp.), not depressed on admixture with a sample prepared by the method described below. The S-*benzylthiuronium salt* was obtained as colourless needles (from methanol), m. p. 242—244° (decomp.) (Found: C, 55·6; H, 5·1; N, 10·7. $C_{18}H_{19}O_3N_3S_2$ requires C, 55·6; H, 4·9; N, 10·8%).

(b) *From* cis-5-*phenyl*-2-*thiothiazolidine*-4-*carboxylic acid.* The acid (1 g.) was allowed to react with chloroacetic acid (2 g.) under essentially the same conditions as the *trans*-isomer. The product, m. p. 218° (decomp.), recrystallised from aqueous acetic acid as prismatic needles, m. p. 225—226° (decomp.) (Found: C, 53·9; H, 4·5; N, 6·1%).

Methyl cis-2-*oxo*-5-*phenylthiazolidine*-4-*carboxylate* was obtained as needles, m. p. 162—163°, from ethyl acetate–light petroleum when the acid prepared by either of the above described methods was esterified with diazomethane in ethyl acetate. The samples did not depress each other's m. p. (Found: C, 55·5; H, 4·7; N, 5·4%).

Hydrolysis of Methyl cis-2-*Oxo*-5-*phenylthiazolidine*-4-*carboxylate.*—(a) *With acid.* When the ester (0·4 g.) was heated under reflux with concentrated hydrochloric acid (2·5 ml.) and water (3·0 ml.) for 30 min. the *cis*-acid (0·35 g.) was obtained as needles, m. p. 220—222° (decomp.).

(b) *With alkali.* The ester (0·25 g.) in methyl alcohol (2 ml.) was hydrolysed with N-sodium hydroxide (2 ml.) at room temperature overnight. After acidification with N-hydrochloric acid (2 ml.) and concentration *trans*-2-oxo-5-phenylthiazolidine-4-carboxylic acid separated as needles, m. p. and mixed m. p. 190—192° (decomp.).

cis-2-*Oxo*-5-*phenylthiazolidine*-4-*carboxyamide.*—A mixture of *cis*-5-phenyl-2-thiothiazolidine-4-carboxyamide (5·0 g.), chloroacetic acid (10·0 g.), and water (50 ml.) was heated under reflux for 4 hr. cis-2-*Oxo*-5-*phenylthiazolidine*-4-*carboxyamide* (2·75 g.) was obtained as prisms, m. p. 210—212° (decomp.), raised to 219—221° (decomp.) on recrystallisation from aqueous acetic acid (Found: C, 53·6; H, 4·5; N, 12·6. $C_{10}H_{10}O_2N_2S$ requires C, 54·1; H, 4·6; N, 12·6%). The product depressed the m. p. of the corresponding *cis*-acid.

trans-2-*Oxo*-5-*phenylthiazolidine*-4-*carboxyamide.*—(a) *From methyl* trans-2-*oxo*-5-*phenylthiazolidine*-4-*carboxylate.* The required amide (0·65 g.), m. p. 192—193°, slowly separated when a mixture of the ester (1 g.), ammonia (*d* 0·88; 10 ml.), and methanol (5 ml.) was warmed on a steam-bath.

(b) *From* trans-2-*oxo*-5-*phenylthiazolidine*-4-*carboxylic acid.* The acid (1·0 g.) was heated under reflux with thionyl chloride (2 ml.) in chloroform (5 ml.) until dissolution was complete. The mixture was then concentrated *in vacuo* and the residue treated with ammonia (*d* 0·88; 5 ml.). The amide (0·9 g.) which separated was obtained as needles (from aqueous methanol), m. p. and mixed m. p. 192—193° (Found: C, 54·6; H, 4·4; N, 12·6%).

Reaction of 4-*Benzylidene*-2-*methylthiothiazol*-5-*one with Sodium Hydroxide.*—The thiazolone (1·0 g.) was heated under reflux for 2 hr. in N-sodium hydroxide (5 ml.) and alcohol (4 ml.). A little solid gradually separated and there was an odour of methanethiol. After the solution had been cooled, water (30 ml.) was added and the whole extracted with ether. The aqueous layer was then acidified with dilute hydrochloric acid and extracted with chloroform. After being washed and dried the extract was concentrated under reduced pressure to small volume and treated with light petroleum, a solid (0·35 g.), m. p. 156—160°, separating. This was dissolved in sodium hydrogen carbonate solution and treated with *S*-benzylthiuronium bromide to give the S-*benzylthiuronium salt* of *trans*-5-phenyl-2-thiothiazolidine-4-carboxylic acid, needles (from aqueous alcohol), m. p. 152—153°, alone and when mixed with a specimen prepared from the authentic acid [1] (Found: C, 53·5; H, 4·8; N, 10·3. $C_{18}H_{19}O_2N_3S_3$ requires C, 53·3; H, 4·7; N, 10·4%).

Reaction of trans-2-*Methylthio*-5-*phenylthiazoline*-4-*carboxylic Acid with Alkali.*—The acid (10 g.) was heated under reflux for 5 hr. in N-sodium hydroxide (110 ml.). An odour of thiol and ammonia became apparent. The resulting yellow solution was acidified hot with concentrated hydrochloric acid, a white solid (7·0 g.), m. p. 170—175° (decomp.), separating. This was removed and dissolved in aqueous sodium hydrogen carbonate and the solution filtered, then heated and acidified, to yield crude 5-*phenylthiazole*-4-*carboxylic acid* (6·0 g.), m. p. 182—183° (decomp.), raised to 193—194° (decomp.) on recrystallisation (needles) from alcohol (Found: C, 58·7; H, 3·6; N, 6·5; S, 15·4. $C_{10}H_7O_2NS$ requires C, 58·6; H, 3·4; N, 6·8; S, 15·6%).

Concentrating the original acid filtrate to about 50 ml. under reduced pressure gave a solid (0·9 g.), m. p. 127—142° (decomp.), which on recrystallisation from water yielded phenylpyruvic acid as prisms, m. p. 142—145° (decomp.) (Found: C, 65·7; H, 5·1. Calc. for $C_9H_8O_3$: C, 65·9; H, 4·9%).

Methyl 5-*phenylthiazole*-4-*carboxylate* was obtained from the acid by use of diazomethane or methyl alcohol containing a trace of sulphuric acid, as needles (from aqueous methanol), m. p. 100—101° (Found: C, 60·2; H, 4·1; N, 6·1; S, 14·6. $C_{11}H_9O_2NS$ requires C, 60·3; H, 4·1; N, 6·4; S, 14·6%).

5-Phenylthiazole-4-carboxyhydrazide was obtained by heating the above methyl ester with hydrazine hydrate in methanol, as needles (from methanol), m. p. 183—184° (Found: C, 55·0; H, 4·5; N, 19·1. $C_{10}H_9ON_3S$ requires C, 54·8; H, 4·1; N, 19·2%).

Action of Hydrogen Peroxide on trans-*5-Phenyl-2-thiothiazolidine-4-carboxylic Acid.*—A solution of the acid (2·0 g.) in 10% sodium hydroxide solution (10 ml.) was treated portionwise with hydrogen peroxide (3 ml.; 30-volume), the mixture being kept at room temperature by cooling. The resulting pale yellow solution, on acidification, yielded a white solid (1·2 g.) which recrystallised from aqueous ethanol as platelets, m. p. 190—192° (decomp.) after softening from 180°. Although it caused a slight depression in the m. p. of *trans*-2-oxo-5-phenylthiazolidine-4-carboxylic acid it gave correct analyses for this compound (cf. Kashida and Yamanaka [8]) (Found: C, 54·4; H, 4·2; N, 6·3%).

When the acid (4·0 g.) in 10% sodium hydroxide solution (20 ml.) was treated portionwise with hydrogen peroxide (8 ml.; 100-volume) without cooling, the product (2·7 g.) obtained on acidification next day had m. p. 164—166° (decomp.) which was not raised on recrystallisation from aqueous ethanol. When a solution of it (0·5 g.) in a little methanol was diluted with water, however, a white solid (0·25 g.) was obtained, having m. p. 170—178° (decomp.), which on recrystallisation from aqueous methanol gave colourless needles (0·15 g.), m. p. 191—192° (decomp.). This depressed the m. p. of *trans*-2-oxo-5-phenylthiazolidine-4-carboxylic acid to 160—166° (decomp.) but did not depress the m. p. of 5-phenylthiazole-4-carboxylic acid. From the mother-liquors there was obtained a solid (0·2 g.), m. p. 162—178° (decomp.), which after recrystallisation from aqueous methanol yielded colourless needles, m. p. 188—191° (decomp.) undepressed on admixture with *trans*-2-oxo-5-phenylthiazolidine-4-carboxylic acid. It depressed the m. p. of the thiazole acid.

When a mixture of the two acids (0·3 g. of each) was crystallised from aqueous ethanol, needles, m. p. 163—166° (decomp.), were obtained.

Action of Potassium Permanganate on trans-*5-Phenyl-2-thiothiazolidine-4-carboxylic Acid.*—A solution of the acid (2·5 g.) in water (15 ml.) containing sodium hydroxide (1·5 g.) was treated portionwise with potassium permanganate (4·5 g.) at 30°. After 1 hr. the mixture was filtered through kieselguhr, and the filtrate brought to pH 4 with concentrated hydrochloric acid, affording 5-phenylthiazole-4-carboxylic acid (1·8 g.), m. p. 185—187° (decomp.) raised to 191—192° (decomp.) on recrystallisation from aqueous acetic acid (Found: C, 58·3; H, 3·4; N, 6·4%).

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