925. *Thiazolidines. Part I. Some Reactions of 4-Benzylidene-2-thiothiazolid-5-one with Glycine Derivatives.*

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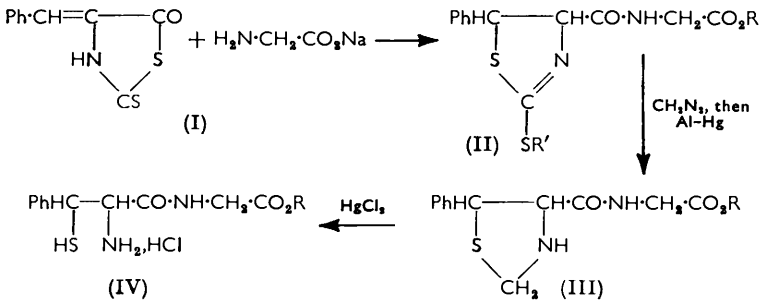
The higher-melting α-forms of 5-phenyl-2-thiothiazolidine-4-carbonylglycine (II; R = R′ = H) * and its derivatives undergo inversion in the presence of alkali to the lower-melting β-forms.

In a programme undertaken to prepare simple peptides of cysteine analogues the synthesis of β-phenylcysteinylglycine methyl ester hydrochloride (IV; R = Me) by Cook and Pollock's route [1] (I ⟶ IV) was examined. In contrast to their results we obtained two isomers of the thiazolidine ester (III; R = Me), m. p. 172—173° and 100—102° respectively, even when excess of the sodium salt of glycine was used in the first stage and the yields were very low. By treating the acid (II; R = R′ = H) * with alkali and methyl iodide



(which favour *S*-methylation [2]) instead of with dimethyl sulphate, we obtained 2-methylthio-5-phenylthiazoline-4-carbonylglycine (II; R = H, R′ = Me) crystalline rather than as an oil; esterification of this product with diazomethane also afforded a solid in contrast to the oil obtained by Cook and Pollock. Reduction of the resulting methylthiothiazoline ester with amalgamated aluminium gave 5-phenylthiazolidine-4-carbonylglycine methyl ester (III; R = Me), m. p. 104—105°, in 63% yield. This compound evidently corresponded to the β-form, m. p. 113—115°, described by Cook and Pollock. None of the α-form, m. p. 173°, was detected. It seems likely from these results that the low yields obtained in the original method arose, not only through the presence of α- and β-forms, but also because of the possibility of *N*-methylation in the reaction of the mercapto-acid (II; R = R′ = H) with diazomethane.

During the reaction of the sodium salt of glycine with 4-benzylidene-2-thiothiazolid-5-one (I) a considerable amount of hydrogen sulphide was evolved, indicating formation of the thiohydantoin (V; R = R′ = H), a reaction which Cook and Pollock considered took place only when a glycine ester was condensed with the thiazolidone. Isolation of the *S*-methylated thiohydantoin (V; R = H, R′ = Me) from the mother-liquors of the methylation of the acid (II; R = R′ = H) with methyl iodide and alkali, identical with the compound obtained by the direct *S*-methylation of the thiohydantoin (V; R = R′ = H), supported our view that the thiohydantoin was present as impurity in the original thiazolidine acid (II; R = R′ = H), m. p. 178—181°.

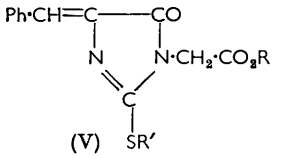
Hydrolysis of the β-form of the thiazolidine peptide ester (III; R = Me) with one equivalent of sodium hydroxide gave 5-phenylthiazolidinecarbonylglycine (III; R = H),

* The formulæ of thiothiazolidines [containing the –C(:S)–NH– grouping] are shown in this and the following four papers as mercaptothiazolines [containing the –C(SH)=N– grouping], so as to economise in structural formulæ, but the compounds are held to exist actually in the thiothiazolidine forms, at least in alcoholic solution (see p. 4591), and are named in the latter form.

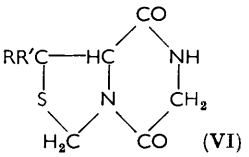
[1] Cook and Pollock, *J.*, 1950, 1898.
[2] Cf. Carrington and Waring, *J.*, 1950, 354.

m. p. *ca.* 80°, which when heated readily lost a molecule of water to give the dioxopiperazine (VI; R = H, R′ = Ph). Similar cyclisations have been reported [3] in the preparation of the dimethyl analogue (VI; R = R′ = Me). The dioxopiperazine was also obtained directly by heating the thiazolidine peptide ester (III; R = Me) with N-hydrochloric acid at 100°. Prolonged heating with 6N-hydrochloric acid gave 5-phenylthiazolidine-4-carboxylic acid hydrochloride.[4]

The reaction of glycine esters with 4-benzylidene-2-thiothiazolid-5-one has also been examined. Cook and Pollock,[1] using glycine ethyl ester, obtained a mixture of a thiothiazolidine ethyl ester (II; R = Et, R′ = H), m. p. 170°, and the crude thiohydantoin (V; R = Et, R′ = H), isolated as its *S*-methyl derivative. We, however, obtained,



(V)



(VI)

instead of the ester of m. p. 170°, a small quantity of an isomer, m. p. 230—231°, together with the pure thiohydantoin (V; R = Et, R′ = H). This ester on acid hydrolysis gave the isomeric acid (II; R = R′ = H), m. p. 224° (decomp.), but when alkali was used the acid (II; R = R′ = H) of m. p. 186—187° resulted, identical with that obtained from the sodium salt of glycine and 4-benzylidene-2-thiothiazolid-5-one. This compound also arose when the higher-melting acid was kept overnight in N-sodium hydroxide at room temperature.

Glycine methyl ester gave similar results. The higher-melting (m. p. 207—208°) 5-phenyl-2-thiothiazolidine-4-carbonylglycine methyl ester (II; R = Me, R′ = H) on alkaline hydrolysis gave the lower-melting thiazolidine acid (II; R = R′ = H) and on acid hydrolysis gave the isomer, m. p. 224° (decomp.). The ease of inversion of this form to the lower-melting isomer by mild treatment with alkali was further demonstrated when attempts were made to prepare its *S*-methyl derivative (II; R =H, R′ = Me) by reaction with methyl iodide and alkali; the product was identical with that derived from the isomer of m. p. 186—187°.

When 4-benzylidene-2-thiothiazolid-5-one was allowed to react with glycine ethyl ester hydrochloride in the presence of one equivalent of 2-aminopyridine [5] much hydrogen sulphide was evolved, the sole product isolated being the thiohydantoin (V; R = Et, R′ = H).

The results described here indicate that under weakly basic conditions the higher-melting peptide (II) can be formed, although the major products are thiohydantoins, while under more strongly alkaline conditions the lower-melting isomer is produced. Evidence to support this arises from the ease with which inversion to the lower-melting acid or its derivatives takes place in the presence of alkali. The latter compounds evidently correspond to the β-form of the ester (III; R = Me) described by Cook and Pollock, and the higher-melting isomers are related to the α-form.

Experimental

2-Methylthio-5-phenylthiazoline-4-carbonylglycine (β-*Form*).—A mixture of 5-phenyl-2-thiothiazolidine-4-carbonylglycine, m. p. 178—181° (20 g.) (prepared from 4-benzylidene-2-thiothiazolid-5-one and excess of the sodium salt of glycine essentially as described by Cook and Pollock [1]), and methyl iodide (8·5 ml.) in N-sodium hydroxide (135 ml.) was stirred for 1 hr. Next day it was acidified with hydrochloric acid, and the precipitated gum extracted with chloroform. The dried extract was concentrated to small volume and treated with light

[3] Neher, Spillmann, Werner, Wettstein, and Miescher, *Helv. Chim. Acta*, 1946, **29**, 1874; Süs, *Annalen*, 1948, **561**, 31; Süs and Rosenberger, *ibid.*, 1949, **564**, 54.
[4] Kashida and Yamanaka, *J. Pharm. Soc. Japan*, 1953, **73**, 953 (*Chem. Abs.*, 1954, **48**, 11,394).
[5] Cook, Hunter, and Pollock, *J.*, 1950, 1892.

petroleum (b. p. 80—100°), β-2-*methylthio*-5-*phenylthiazoline*-4-*carbonylglycine* (12·25 g.), m. p. 130—132°, slowly separating as needles. Recrystallised from aqueous methanol, this had m. p. 131—133° (Found: C, 50·3; H, 4·6; N, 9·0; S, 19·8. $C_{13}H_{14}O_3N_2S_2$ requires C, 50·3; H, 4·6; N, 9·0; S, 20·6%).

4-*Benzylidene*-4 : 5-*dihydro*-2-*methylthio*-5-*oxoglyoxalin*-1-*ylacetic acid* separated in small amount on further concentration of the mother-liquors from the above preparation. It recrystallised from chloroform–methanol as needles, m. p. 203—205° (Found: C, 56·7; H, 4·5; N, 10·1. $C_{13}H_{12}O_3N_2S$ requires C, 56·6; H, 4·4; N, 10·1%).

2-*Methylthio*-5-*phenylthiazoline*-4-*carbonylglycine Methyl Ester* (β-*Form*).—This *ester* was obtained in 82% yield on esterifying a suspension of the acid (9 g.) in ether (50 ml.) with diazomethane in the usual way. It recrystallised from ether–light petroleum as needles, m. p. 80—81° (Found: C, 52·1; H, 5·0; N, 9·1. $C_{14}H_{16}O_3N_2S_2$ requires C, 51·9; H, 5·0; N, 8·7%).

5-*Phenylthiazolidine*-4-*carbonylglycine Methyl Ester* (β-*Form*).—A solution of 2-methylthio-5-phenylthiazoline-4-carbonylglycine methyl ester (3·5 g.) in methanol (70 ml.) was added to amalganated aluminium foil (2 g.). Next day methanol (70 ml.) was added, and the mixture boiled and filtered and the residue extracted with hot methanol (2 × 50 ml.). When the combined filtrate and extracts were concentrated to small volume the required product separated. Ether (20 ml.) was then added and the solid, m. p. 104—105° (1·9 g., 63%), removed. It recrystallised from aqueous alcohol with unchanged m. p. (Found: C, 55·6; H, 5·9; N, 9·9. Calc. for $C_{13}H_{16}O_3N_2S$: C, 55·8; H, 5·7; N, 10·0%).

This compound was obtained in 60% overall yield from 2-methylthio-5-phenylthiazoline-4-carbonylglycine by omitting the purification of the intermediate ester.

5-*Phenylthiazolidine*-4-*carbonylglycine* (β-*Form*).—The methyl ester (0·5 g.) was kept in N-sodium hydroxide (2 ml.) and 2 : 1 v/v aqueous alcohol (6 ml.) for 1 hr. at room temperature. The resulting clear solution was extracted with ether, the aqueous layer acidified to pH 4, and the product extracted with chloroform (4 × 50 ml.). The residual *acid* from the dried chloroform extract, recrystallised from ethyl acetate, had m. p. *ca.* 80° (decomp.). It was soluble in sodium hydrogen carbonate solution (Found: C, 53·9; H, 5·6; N, 10·5. $C_{12}H_{14}O_3N_2S$ requires C, 54·2; H, 5·3; N, 10·5%).

The *dioxopiperazine* (VIII; R = H, R′ = Ph) was obtained by heating this acid for 5 min. at 120—130°. The acid melted with decomposition and then resolidified. The solid recrystallised from alcohol as plates, m. p. 203—204° (Found: C, 58·1; H, 4·9; N, 10·9. $C_{12}H_{12}O_2N_2S$ requires C, 58·1; H, 4·8; N, 11·3%).

5-*Phenylthiazolidine*-4-*carboxylic Acid* (β-*Form*).—5-Phenylthiazolidine-4-carbonylglycine methyl ester (0·5 g.) was heated under reflux in 6N-hydrochloric acid (5 ml.) for 6 hr. and the resulting solution concentrated to small volume. β-5-Phenylthiazolidine-4-carboxylic acid hydrochloride (0·35 g.), m. p. 192—193°, separated. It recrystallised from alcohol–ether with unchanged m. p. [lit.,[4] m. p. 193° (decomp.)] (Found: C, 49·0; H, 5·5; Cl, 14·6. Calc. for $C_{10}H_{12}O_2NSCl$: C, 49·0; H, 4·9; Cl, 14·5%). When a solution of the hydrochloride in water was neutralised with N-sodium hydroxide β-5-phenylthiazolidine-4-carboxylic acid separated. Recrystallised from water, it had m. p. 214° (decomp.) [lit.,[4] m. p. 213° (decomp.)] (Found: N, 7·1. Calc. for $C_{10}H_{11}O_2NS$: N, 6·7%).

Reaction between 4-*Benzylidene*-2-*thiothiazolid*-5-*one and Glycine Ethyl Ester.*—(*a*) The thiazolidone (8·8 g.), glycine ethyl ester hydrochloride (6·0 g.), and N-sodium hydroxide (40 ml.) were heated under reflux in ethanol (80 ml.) for 2 hr. The resulting solution was kept at room temperature overnight and the white solid that separated was removed (0·98 g.; m. p. 220—222°). Recrystallisation from ethanol gave the α-*form* of 5-*phenyl*-2-*thiothiazolidine*-4-*carbonylglycine ethyl ester* as needles, m. p. 230—231° (Found: C, 51·8; H, 5·3; N, 9·0. $C_{14}H_{16}O_3N_2S_2$ requires C, 51·9; H, 5·0; N, 8·7%). The filtrate, on concentration, yielded ethyl 4-benzylidene-4 : 5-dihydro-2-mercapto-5-oxoglyoxalin-1-ylacetate as yellow platelets (5·4 g.), m. p. 158—160°, raised to m. p. 167—170° (lit., 160°) by recrystallisation from ethanol (Found: C, 57·6; H, 4·7; N, 9·8. Calc. for $C_{14}H_{14}O_3N_2S$: C, 57·9; H, 4·9; N, 9·7%). On reaction with dimethyl sulphate and sodium hydroxide, as described by Cook and Pollock, this compound gave the *S*-methyl derivative, m. p. 122° (Found: C, 59·3; H, 5·3; N, 8·9. Calc. for $C_{15}H_{16}O_3N_2S$: C, 59·3; H, 5·3; N, 9·2%).

(*b*) When the reaction between the thiazolidone (4·4 g.) and glycine ethyl ester hydrochloride (3 g.) in methanol (50 ml.) was effected in the presence of 2-aminopyridine (4·2 g.) under reflux for 5 hr. there was considerable evolution of hydrogen sulphide and when the solution

was cooled ethyl 4-benzylidene-4 : 5-dihydro-2-mercapto-5-oxoglyoxalin-1-ylacetate (1·4 g.) separated; it formed yellow needles (from methanol), m. p. and mixed m. p. 165—168° (Found: C, 57·5; H, 4·9; N, 10·1%).

Reaction between 4-Benzylidene-2-thiothiazolid-5-one and Glycine Methyl Ester.—The thiazolidone (2·2 g.) and glycine methyl ester hydrochloride (1·4 g.) were heated under reflux in N-sodium hydroxide (10 ml.) for 2 hr., then cooled to room temperature and kept overnight. The *α-form of 5p-henyl-2-thiothiazolidine-4-carbonylglycine methyl ester* (0·7 g.) separated as needles, m. p. 200—202°, raised to 207—208° by recrystallisation from methyl alcohol (Found: C, 50·6; H, 4·8; N, 8·8. $C_{13}H_{14}O_3N_2S_2$ requires C, 50·4; H, 4·6; N, 9·0%). From the concentrated filtrate *methyl 4-benzylidene-4 : 5-dihydro-2-mercapto-5-oxoglyoxalin-1-ylacetate* (0·45 g.) separated as yellow prisms, m. p. 160—161° (from methanol) (Found: C, 56·3; H, 4·7; N, 10·1. $C_{13}H_{12}O_3N_2S$ requires C, 56·6; H, 4·4; N, 10·1%).

4-Benzylidene-4 : 5-dihydro-2-mercapto-5-oxoglyoxalin-1-ylacetic Acid.—Ethyl 4-benzylidene-4 : 5-dihydro-2-mercapto-5-oxoglyoxalin-1-ylacetate (1 g.) in N-sodium hydroxide (12 ml.) was heated on a steam-bath for 20 min. The resulting red solution was filtered from a little insoluble material and acidified with hydrochloric acid; *4-benzylidene-4 : 5-dihydro-2-mercapto-5-oxoglyoxalin-1-ylacetic acid* (0·7 g.) which separated recrystallised from ethanol as yellow needles, m. p. 257° after softening from 252° (Found: C, 55·1; H, 3·7; N, 10·8. $C_{12}H_{10}O_3N_2S$ requires C, 55·1; H, 3·9; N, 10·7%). Hydrolysis of the methyl ester in the same way also yielded the 2-mercapto-acid, m. p. and mixed m. p. 240—242° (Found: C, 55·0; H, 3·9; N, 11·1%).

Treatment of a solution of the mercapto-acid (0·6 g.) in N-sodium hydroxide (5 ml.) with methyl iodide yielded, after acidification of the mixture with acetic acid, the 2-methylthio-derivative, m. p. 208—209°, not depressed when mixed with the product described above arising from *S*-methylation of crude (m. p. 178—181°) 5-phenyl-2-thiothiazolidine-4-carbonylglycine.

Hydrolysis of α-5-Phenyl-2-thiothiazolidine-4-carbonylglycine Ethyl Ester.—(a) *With acid.* The ester (1·0 g.) was heated under reflux for 1 hr. in concentrated hydrochloric acid (4 ml.), water (20 ml.), and dioxan (10 ml.). When the resulting solution was cooled and diluted with water the *α-form of 5-phenyl-2-thiothiazolidine-4-carbonylglycine* separated as needles, m. p. 223—224° (0·7 g.), not raised on recrystallisation from aqueous alcohol (Found: C, 49·1; H, 4·1; N, 9·1. $C_{12}H_{12}O_3N_2S_2$ requires C, 48·7; H, 4·1; N, 9·4%).

(b) *With alkali.* The ester (0·4 g.) in N-sodium hydroxide (5 ml.) was kept overnight and the resulting solution acidified with N-hydrochloric acid. An oil separated which solidified on warming (m. p. 183—184°). Recrystallisation from aqueous alcohol gave needles of the β-form of 5-phenyl-2-thiothiazolidine-4-carbonylglycine, m. p. 186—187°, not depressed on admixture with the crude acid of m. p. 178—181° obtained by Cook and Pollock's method (Found: C, 48·2; H, 4·1; N, 9·5; S, 21·6%). Each gave an *S-benzylthiuronium salt*, m. p. 185—186° (decomp.) not depressed when mixed (the m. p. depends on the rate of heating) (Found: C, 52·0; H, 4·9; N, 12·2; S, 20·4. $C_{20}H_{22}O_3N_4S_3$ requires C, 52·0; H, 4·8; N, 12·1; S, 20·8%).

Inversion of α-5-Phenyl-2-thiothiazolidine-4-carbonylglycine into the β-Form.—The α-acid (0·05 g.) was kept overnight in N-sodium hydroxide (1 ml.), and the solution acidified. The β-acid which separated, on crystallisation from water, formed needles (0·03 g.), m. p. and mixed m. p. 183—185°.

S-Methylation of α-5-Phenyl-2-thiothiazolidine-4-carbonylglycine.—A solution of the α-acid (0·25 g.) in N-sodium hydroxide (2 ml.) was treated with methyl iodide (0·1 ml.). The mixture was kept overnight and, after acidification with dilute hydrochloric acid, extracted with chloroform. After being washed and dried, the extract was concentrated to small volume and diluted with light petroleum; the β-form of 2-methylthio-5-phenylthiazoline-4-carbonylglycine (0·1 g.) slowly separated. After recrystallisation from aqueous methanol it had m. p. and mixed m. p. 129—131°.

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