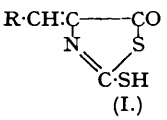
387. *Studies in the Azole Series. Part XXXII. Syntheses of Peptides of Substituted Cysteines.*

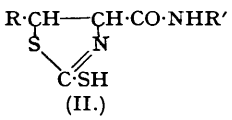
By A. H. Cook and J. R. A. Pollock.

2-Mercapto-4-arylidene- and -alkylidene-5-thiazolinones (I) react with amino-acids or derivatives thereof, to give 5-substituted 2-mercaptothiazoline-4-carboxylic acid peptides or their derivatives (VI). The peptide derivatives can be degraded in satisfactory yield to 5-substituted thiazolidine-4-carboxylic acid peptide derivatives, *e.g.*, (X), which can be split to give formaldehyde and peptides of substituted cysteines.

Amines have been shown (see Parts VII, XXIV, and XXXI, *J.*, 1948, 1337; 1949, 3007; 1950, 1892) to react with 2-mercapto-4-alkylidene- and -arylidene-5-thiazolinones (I) (2-thio-4-alkylidene- and -arylidene-5-thiazolidones) to afford 2-mercapto-5-alkyl- and -5-aryl-thiazoline-4-carboxyamides (II), which may be regarded as derivatives of substituted cysteine amides, to which they can in fact be degraded. The present paper deals with a similar sequence of reactions which follow the combination of amino-acids or their derivatives and the thiazolinones (I). The



(I.)



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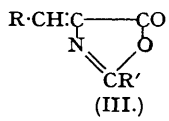
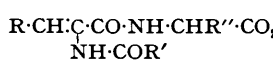


(III.)

primary reaction may be compared with that occurring between the azlactones (III) and amino-acids, which has been studied by Bergmann *et al.* (*Annalen*, 1926, **449**, 277; 1927, **458**, 40; *J. Biol. Chem.*, 1938, **124**, 321; 1939, **129**, 587), who have thus obtained the dehydropeptides (IV). In the case of the thiazolinones, the intermediate comparable with (IV) is the dithiocarbamic acid (V), which appears to cyclise to the 2-mercapto-thiazoline system as in (VI).



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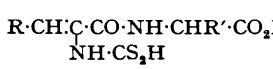

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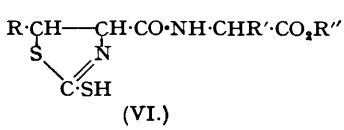
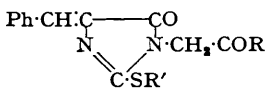


(VI.)

Glycine ethyl ester reacted smoothly with 2-mercapto-4-benzylidene-5-thiazolinone (I; R = Ph) to yield a mixture from which ethyl 2-mercapto-5-phenyl-Δ^2-thiazoline-4-carboxyamidoacetate (VI; R = Ph, R′ = H, R″ = Et) could be isolated, though in poor yield. Analogy with the reaction between (I; R = Ph) and methylamine (Part XXXI, *loc. cit.*)

suggested that ethyl 2-thio-5-benzylidenehydantoin-3-acetate (VII; R = OEt, R′ = H) might have arisen as a by-product from this reaction, and this compound was isolated from the methylated reaction mixture as its *S*-methyl derivative (VII; R = OEt, R′ = Me). This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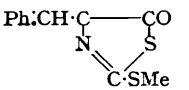
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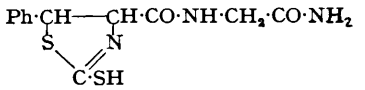
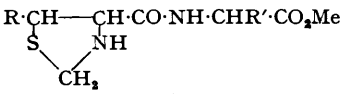

(IX.)

derivative was identical with a sample prepared by methylating the thiohydantoin prepared from 2-methylthio-4-benzylidene-5-thiazolinone (VIII) and glycine ester. The reaction between aminoacetamide and (I; R = Ph) took a similar course, the chief product being 2-thio-5-benzylidenehydantoin-3-acetamide (VII; R = NH_2, R′ = H), which was characterized as its *S*-methyl derivative, while 2-mercapto-5-phenylthiazoline-4-carboxyamidoacetamide (IX) was also produced, in small yield.

The occurrence of a mixture of compounds in this way could be avoided, it was found, by using as ring-opening agent the amino-acid rather than amino-acid derivatives. When one equivalent each of the sodium salt of glycine and (I; R = Ph) were heated together in water, a material was obtained which appeared to consist of a mixture from which one of the two possible stereoisomeric forms of the acid (VI; R = Ph, R′ = H, R″ = H) was isolated. The presence of the second form was proved by degradation of the crude mixture by treatment of the oily methylation product with amalgamated aluminium. By this means methanethiol was eliminated (cf. Cook, Hunter, and Pollock, Part XXXI, *loc. cit.*) and the product was separable into the two stereoisomeric forms of methyl 5-phenylthiazolidine-4-carboxyamidoacetate (X; R = Ph, R′ = H). A better overall yield resulted from the use of a 50% excess of glycine sodium salt, an apparently pure intermediate (VI; R = Ph, R′ = H, R″ = H) being isolated which gave one form only of the thiazolidine (X; R = Ph, R′ = H). The acid (VI; R = Ph, R′ = H, R″ = H) was treated with ethanolic hydrogen chloride in an attempt to prepare the ethyl ester (VI; R = Ph, R′ = H, R″ = Et), one isomeride of which had already been isolated. However, the product had the empirical formula $C_{14}H_{16}O_4N_2S$ and it was perhaps ethyl 5-α-mercaptobenzylhydantoin-3-acetate (XI).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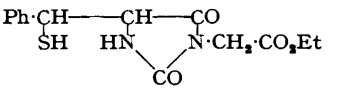
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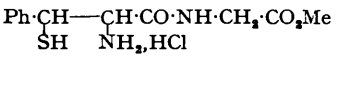
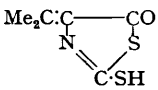

(XII.)

The thiazolidine (X; R = Ph, R′ = H) recalls the amide (II; R = Ph, R′ = H), which has been converted into β-phenylcysteineamide (Cook, Hunter, and Pollock, *loc cit.*); in the same manner, treatment of the new peptide with mercuric chloride caused fission of the thiazolidine ring, yielding formaldehyde and a mercaptide, which was decomposed to yield (*N*-α-amino-β-mercapto-β-phenylpropionyl)glycine methyl ester hydrochloride (XII) in good yield.

The stereoisomerism of the intermediate 2-mercapto-Δ^2-thiazolines and the corresponding thiazolidines complicates the extension of these reactions. The general reaction involving any α-amino-acid and any alkylidene- or arylidene-thiazolinone must lead to a 2-mercaptothiazoline (VI) containing 3 asymmetric carbon atoms, and thus capable of yielding four optically inactive forms. In a preliminary investigation we therefore used 2-mercapto-4-*iso*-propylidene-5-thiazolinone (XIII), the rearrangement products of which possessed only two asymmetric centres. 2-Mercapto-5 : 5-dimethylthiazoline-4-carboxyamidoacetic acid (XIV; R = H) was readily prepared by reaction of (XIII) with glycine. DL-Alanine rapidly gave a mixture of two compounds which were readily separated, although only one isomeride (XIV; R = Me) was obtained crystalline. Further simplification was achieved by use of an excess of the amino-acid sodium salt which favoured the production of one only of the isomers of (VI; R = Ph, R′ = H, R″ = H). When this method was applied to the reaction between (I; R = Ph) and DL-alanine, the product, presumably a mixture of the two acids (VI; R = Ph, R′ = Me, R″ = H), was an intractable gum. However, methylation gave an oily methyl derivative which, on reduction in the usual way, yielded a mixture of two isomeric esters (X; R = Ph, R′ = Me), both isolated in a crystalline condition.

In a further study, intermediates were used where the 5-position carried only one aliphatic substituent. A convenient starting material was 2-mercapto-4-*iso*butylidene-5-thiazolinone (I;

R = Pr^i) which reacted rapidly with the sodium salt of glycine: one isomeride only of 2-mercapto-5-*iso*propylthiazoline-4-carboxyamidoacetic acid (VI; R = Me_2CH, R′ = H,



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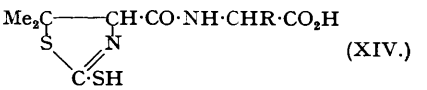

(XIV.)

R″ = H) was obtained. This with methyl sulphate gave 2-methylthio-5-*iso*propylthiazoline-4-carboxyamidoacetic acid, which gave an oily ester. The ester, reduced with amalgamated aluminium, afforded methyl 5-*iso*propylthiazolidine-4-carboxyamidoacetate (X; R = Pr^i, R′ = H), in an overall yield of 21% from *iso*butyraldehyde.

Experimental.

Reaction between 2-Mercapto-4-benzylidene-5-thiazolinone and Glycine Ethyl Ester.—The thiazolinone (2·2 g.) was heated under reflux for 2 hours with glycine ethyl ester hydrochloride (1·5 g.) dissolved in a mixture of N-sodium hydroxide (10 c.c.) and methanol (20 c.c.). The solution was cooled to 0° and the crystalline material (0·7 g.; m. p. 135°) was washed with ether (10 c.c.): the residue (0·4 g.) had m. p. 170°. *Ethyl 2-mercapto-5-phenylthiazoline-4-carboxyamidoacetate* separated from a little methanol in colourless needles, m. p. 170° (Found: C, 51·3; H, 4·8. $C_{14}H_{16}O_3N_2S_2$ requires C, 51·8; H, 4·9%). In another experiment, the crude reaction product (1 g.; m. p. 135°) was dissolved in N-sodium hydroxide (5 c.c.), and crushed ice was added, followed by methyl sulphate (0·25 c.c.). A white solid (0·5 g.), m. p. 103°, separated after 5 minutes. Recrystallization from aqueous methanol gave *ethyl 2-methylthio-5-keto-4-benzylidene-4 : 5-dihydroglyoxaline-1-acetate* as colourless needles, m. p. 121° (Found: N, 9·2. $C_{15}H_{16}O_3N_2S$ requires N, 9·2%).

2-Mercapto-4-benzylidene-5-thiazolinone (4·4 g.) was dissolved in N-sodium hydroxide (20 c.c.), and methyl sulphate (2·5 g.) was added. The solution was shaken until separation of the 2-methylthio-derivative (4·0 g.) was complete. It recrystallized from methanol (50 c.c.) as long orange needles (2·8 g.), m. p. 124°. To a solution of this compound (1·2 g.) and glycine ethyl ester hydrochloride (0·8 g.) in methanol (50 c.c.) was added N-sodium hydroxide (5 c.c.), and the solution was heated under reflux for 1 hour, methanethiol being evolved. The solution was concentrated to 15 c.c. and cooled to 0° while *ethyl 2-mercapto-5-keto-4-benzylidene-4 : 5-dihydroglyoxaline-1-acetate* (0·8 g.), m. p. 160°, separated. The product was recrystallized from methanol, without change in m. p., as colourless needles (Found: C, 57·8; H, 4·9; N, 9·6. $C_{14}H_{14}O_3N_2S$ requires C, 57·9; H, 4·9; N, 9·7%). The thiohydantoin (0·5 g.) in N-sodium hydroxide (1·5 c.c.) with methyl sulphate (0·2 c.c.) gave the 2-methylthio-derivative which, recrystallized from aqueous methanol, had m. p. 121°, undepressed on admixture with the compound described above.

Reaction between 2-Mercapto-4-benzylidene-5-thiazolinone and Glycine.—(*a*) The thiazolinone (2·2 g.) was warmed with a solution of glycine (0·75 g.) in N-sodium hydroxide (10 c.c.) for 1 hour. A small quantity of unchanged thiazolinone (m. p. 211°) was removed, and the filtrate was acidified with concentrated hydrochloric acid, whereby an oil was precipitated which had partly crystallized after 24 hours at 0°. The oil was taken up in ethyl acetate (60 c.c.), and the solution dried and evaporated to 10 c.c. Slow addition of light petroleum (b. p. 60—80°) then precipitated gummy material and colourless crystals; the latter were removed, giving 0·3 g. of material having m. p. 176—182°. Recrystallized from ethyl acetate–light petroleum, *2-mercapto-5-phenylthiazoline-4-carboxyamidoacetic acid* separated as small colourless needles, m. p. 179° (Found: C, 48·3; H, 4·1; N, 9·4. $C_{12}H_{12}O_3N_2S_2$ requires C, 48·6; H, 4·1; N, 9·5%).

(*b*) 2-Mercapto-4-benzylidene-5-thiazolinone (11 g.) was dissolved by warming in a solution of glycine (5·7 g.) in water (20 c.c.) containing sodium hydroxide (3 g.). The solution was acidified at 0° with concentrated hydrochloric acid, and the precipitated oil was rubbed until solidification to a pale yellow powder (2·2 g.; m. p. 170°) was complete. Recrystallized from boiling water, *2-mercapto-5-phenylthiazoline-4-carboxyamidoacetic acid hemihydrate* (11·5 g., 77%) formed colourless thick rods having m. p. 170°. Further crystallization in the same way raised the m. p. to 186° (Found: C, 47·3; H, 4·3; N, 9·4. $C_{12}H_{12}O_3N_2S_2,\frac{1}{2}H_2O$ requires C, 47·2; H, 4·3; N, 9·2%).

Methyl 5-Phenylthiazolidine-4-carboxyamidoacetate.—(*a*) The crude peptide, as obtained in (*a*) above from 2-mercapto-4-benzylidene-5-thiazolinone (2·2 g.), was dissolved in ethyl acetate (30 c.c.), and the solution dried (Na_2SO_4). A solution of diazomethane (0·6 g.) in ether (20 c.c.) was added slowly, nitrogen being evolved. After 3 hours, the solvents were removed *in vacuo* to leave a mobile yellow oil. Clean aluminium foil (0·5 g.) was amalgamated in 3% aqueous mercuric chloride solution for 10 minutes and washed well with water and methanol. To it was added a solution of the yellow oil in methanol (20 c.c.); methanethiol was evolved. The solution was heated under reflux at the end of the reaction, and the alumina filtered off and extracted twice with hot methanol (20 c.c.). The combined filtrates were evaporated to leave a pale yellow oil, which was stirred with a mixture of ether (5 c.c.) and water (5 c.c.), whereupon crystallization commenced in the ethereal layer. The mixture was kept at 0° for 5 hours, colourless needles (0·7 g.), m. p. 126°, separating. The material was extracted with boiling ether (60 c.c.) (extract *A*). The residue (0·3 g.) of the *α-form* of *methyl 5-phenylthiazolidine-4-carboxyamidoacetate* formed colourless needles, m. p. 173°, from hot water (Found: C, 55·8; H, 5·8; N, 10·0. $C_{13}H_{16}O_3N_2S$ requires C, 55·7; H, 5·7; 10·0%). The compound gave a *picrate* which formed yellow prisms, m. p. 170°, from water (Found: N, 13·8. $C_{13}H_{16}O_3N_2S,C_6H_3O_7N_3$ requires N, 13·8%). The ether–water filtrate from the crystallization of the α-compound was separated, and the aqueous layer washed with ether. The ethereal extracts were combined with the extract *A*, dried, and evaporated to 5 c.c. Addition of light petroleum (b. p. 60—80°) caused the separation of rosettes of colourless needles (0·2 g.),

m. p 110—112°. These, the *β-form* of the peptide, separated from a little hot water as colourless needles, m. p. 115° (Found : C, 55·8; H, 5·7; N, 10·2%).

(*b*) The peptide hemihydrate (10 g.; m. p. 177°) was suspended in ether (50 c.c.) and treated with a solution of diazomethane (3 g.) in ether (100 c.c.); nitrogen was rapidly evolved. After 3 hours the solution was worked up to a yellow oil and reduced in methanol as recorded in (*a*). Evaporation gave a colourless oil which was stirred with ether (10 c.c.) and water (10 c.c.). After 24 hours at 0°, the above *β*-form (3·5 g., 40%) was filtered off. It had m. p. 112—113°, undepressed on admixture with previously prepared material.

(*c*) The peptide hemihydrate (m. p. 177°; 10·5 g.) in water (20 c.c.) containing sodium hydroxide (2·8 g.) was shaken for 30 minutes with methyl sulphate (3·3 c.c.), giving a clear solution which was acidified cautiously with hydrochloric acid. The precipitated oil was extracted with ethyl acetate (300 c.c.) and the aqueous layer extracted similarly (2 × 50 c.c.). The combined extracts were dried and evaporated to 100 c.c. Attempts to obtain crystalline material from the solution failed. The solution was treated with diazomethane (1·5 g.) in ether (50 c.c.). After 0·5 hour the solution was evaporated, to give a clear yellow oil which was reduced as described in (*a*). The product, worked up as described in (*b*), yielded the *β*-form (4·1 g., 46%), m. p. 113—115°.

Treatment of 2-Mercapto-5-phenylthiazoline-4-carboxyamidoacetic Acid with Ethanolic Hydrogen Chloride.—The thiazoline (1 g.) was kept in saturated ethanolic hydrogen chloride (5 c.c.) at 0° for 3 days, after which the crystalline material (0·3 g.), m. p. 105—108°, was removed. *Ethyl 4-α-mercaptobenzylhydantoin-1-acetate* (?) separated as colourless shining plates, m. p. 114°, from aqueous ethanol (Found : C, 55·5; H, 5·1; N, 9·1. $C_{14}H_{16}O_4N_2S$ requires C, 54·9; H, 5·3; N, 9·2%). The compound gave no colour with aqueous or ethanolic ferric chloride, or with sodium nitroprusside reagent.

1-Amino-2-mercapto-2-γ-phenylpropionylglycine Methyl Ester Hydrochloride.—The *β*-form of the above ester (3·8 g.) was dissolved in hot water (1 l.), and a solution of mercuric chloride in water (500 c.c.) at 60° was rapidly introduced, the solution becoming turbid and formaldehyde being evolved. After 3 hours the curd was filtered off, washed with water, and dried in air at 40° (9·5 g.). The mercaptide (2 g.) was finely powdered and suspended in ethanol, which was then saturated with hydrogen sulphide with vigorous stirring. Mercuric sulphide was removed. A small part of the filtrate, after being boiled to expel hydrogen sulphide, was neutralized with sodium hydrogen carbonate and treated with ethanolic ferric chloride, which produced an intense Prussian-blue colour. The bulk of the solution was evaporated to dryness, giving a pale yellow gum which crystallized on repeated trituration with small quantities of dry ether. After reduction to a fine powder, the material was removed and, while still covered with ether, was transferred to a desiccator and dried over concentrated sulphuric acid *in vacuo*. *1-Amino-2-mercapto-2-phenylpropionylglycine ethyl ester hydrochloride* (0·4 g., 29%) was thus obtained as a colourless hygroscopic hemihydrate, m. p. 90—91° (decomp.) (Found : C, 45·9; H, 6·0; N, 9·0. $C_{12}H_{16}O_3N_2S,HCl,\frac{1}{2}H_2O$ requires C, 45·9; H, 5·8; N, 8·9%).

Reactions with 2-Mercapto-4-isopropylidene-5-thiazolinone.—(a) *With glycine.* The thiazolinone (1·7 g.) was suspended in a solution of glycine (0·75 g.) in N-sodium hydroxide (10 c.c.) and heated on the steam bath until a clear solution was obtained. After acidification at 0° with hydrochloric acid, the clear solution was extracted with ethyl acetate (3 × 10 c.c.). The combined extracts were dried and evaporated to 5 c.c. Light petroleum (b. p. 60—80°) was added to precipitate a sticky mass which broke up to give a pale yellow powder (1·7 g.), m. p. 190°. *2-Mercapto-5 : 5-dimethylthiazoline-4-carboxyamidoacetic acid* recrystallized from ethyl acetate–light petroleum (b. p. 40—60°) as minute colourless needles, m. p. 193° (Found : C, 38·9; H, 4·8; N, 11·2. $C_6H_{12}O_3N_2S_2$ requires C, 38·7; H, 4·9; N, 11·3%).

(b) *With* DL-*alanine.* To a solution of DL-alanine (4·2 g.) and potassium hydroxide (2·6 g.) in water (20 c.c.) was added 2-mercapto-4-*iso*propylidene-5-thiazolinone (5·4 g.); reaction was rapid and a clear solution obtained after warming for 10 minutes. Acidification at 0° gave a clear solution which was extracted with ethyl acetate (2 × 30 c.c.). The extracts were dried, concentrated to 20 c.c., and cooled to 0°, whereupon *α-(2-mercapto-5 : 5-dimethylthiazoline-4-carboxyamido)propionic acid* (2·3 g., 33%), m. p. 196°, separated. When recrystallized from a little ethyl acetate, the peptide separated as colourless thick needles, m. p. 208° (Found : C, 41·3; H, 5·5; N, 10·5. $C_9H_{14}O_3N_2S_2$ requires C, 41·2; H, 5·4; N, 10·7%). The ethyl acetate filtrates were evaporated to leave a sticky gum, which did not crystallize.

Reaction between 2-Mercapto-4-benzylidene-5-thiazolinone and DL-*Alanine.*—A suspension of the thiazolinone (11 g.) in a solution of alanine (6·8 g.) in N-potassium hydroxide (75 c.c.) was warmed, the thiazolinone rapidly dissolving. The clear liquid was heated on the steam bath for 1 hour, cooled, and acidified with concentrated hydrochloric acid, whereby a brown oil was precipitated. This was dissolved in ethyl acetate (40 c.c.), the aqueous layer was extracted with ethyl acetate (2 × 30 c.c.), and the combined extracts were dried and evaporated to 20 c.c. Diazomethane (4 g.) in ether (100 c.c.) was slowly added and the solution kept at room temperature overnight. Solvents were evaporated and the remaining pale yellow oil was dissolved in methanol (200 c.c.) and added to amalgamated aluminium foil (6 g.). Methanethiol was evolved. When reduction was complete, the methanolic solution was boiled and filtered hot, and the alumina twice extracted with boiling methanol (200 c.c.). The combined filtrates were evaporated to a colourless oil, which was stirred with water (30 c.c.) and ether (20 c.c.). After 16 hours at 0°, the mixture was filtered (*A*). The product (4 g.), m. p. 90—120°, was dried *in vacuo* and extracted with boiling ether (150 c.c.) (*B*), a residue of colourless needles (1 g.), m. p. 130—150°, remaining. When recrystallized from water, the *α-form* of *methyl α-(5-phenylthiazolidine-4-carboxyamido)propionate* formed colourless needles, m. p. 166° (Found : C, 56·7; H, 6·2; N, 9·8. $C_{14}H_{18}O_3N_2S$ requires C, 57·1; H, 6·2; N, 9·5%). The ethereal filtrate *B*, kept at 0° overnight, yielded a further crop of the impure *α*-form (0·2 g.), m. p. 145—153° (filtrate *C*). The ethereal layer from *A* was combined with *C*, and the whole dried, evaporated to 20 c.c., and diluted with light petroleum (b. p. 40—60°; 200 c.c.), whereafter the *β-form* of the thiazolidine-peptide separated (2·8 g.; m. p. 110—114°). Recrystallized from water, this formed colourless fine needles, m. p. 118° (Found : C, 57·3; H, 6·2; N, 9·6%). A mixture with the *α*-form had m. p. 94—97°. Evaporation of the ether–light petroleum filtrate left a further crop of crude *β*-form (0·9 g.), m. p. 105—107°, giving a total yield of 4·9 g. (33%, based on the original thiazolinone).

Reaction between 2-Mercapto-4-isobutylidene-5-thiazolinone and Glycine.—A solution prepared by stirring the thiazolinone into a hot solution of glycine (5·7 g.) and sodium hydroxide (3·0 g.) in water (50 c.c.) was heated on the steam-bath for 0·5 hour. The solution was acidified at 0° with concentrated hydrochloric acid, a mobile oil separating which when kept at 0° overnight solidified to a crystalline mass, m. p. 40°. *2-Mercapto-5-isopropylthiazoline-4-carboxyamidoacetic acid sesquihydrate* formed colourless plates, m. p. 42°, from a little warm water (Found : C, 37·3; H, 6·1; N, 9·5. $C_9H_{14}O_3N_2S_2,1{\cdot}5H_2O$ requires C, 37·3; H, 5·9; N, 9·7%).

Methyl 5-isoPropylthiazolidine-4-carboxyamidoacetate.—The above sesquihydrate (10 g.) was dissolved in water (30 c.c.) containing sodium hydroxide (2·9 g.), and methyl sulphate (4·9 g.) was added. After 0·5 hour's shaking, a clear solution was obtained, which was acidified with hydrochloric acid. The supernatant liquid was decanted and extracted with ethyl acetate (2 × 100 c.c.), and the extract dried, evaporated to 20 c.c. and diluted with light petroleum (b. p. 40—60°), to give *2-methylthio-5-isopropylthiazoline-4-carboxyamidoacetic acid* (3·2 g.), m. p. 50°. The residual oily precipitate crystallized on trituration under water; recrystallization from ethyl acetate–light petroleum (b. p. 40—60°) gave a further 2·7 g., m. p. 50°, of the 2-methylthio-derivative (total yield : 5·9 g., 62%) (Found : C, 43·0; H, 5·7; N, 10·2. $C_{10}H_{16}O_3N_2S_2$ requires C, 43·1; H, 5·8; N, 10·1%). The 2-methylthio-derivative (3 g.) was suspended in ether (10 c.c.), and methylated with diazomethane (0·7 g.) in ether (50 c.c.). After 5 minutes the solution was evaporated to a colourless oil, which was reduced in ethanol (50 c.c.) with amalgamated aluminium foil (2 g.). The reaction mixture was filtered hot, and the alumina extracted with boiling ethanol (2 × 50 c.c.). Evaporation of the filtrates gave a colourless oil which was taken up in ether (20 c.c.) and kept at 0° for 16 hours, while *methyl 5-isopropylthiazolidine-4-carboxyamidoacetate* (0·8 g.), m. p. 84°, separated. The ethereal filtrate was largely diluted with light petroleum (b. p. 40—60°), giving rosettes of colourless needles, m. p. and mixed m. p. 80—82°. The peptide crystallized from a little hot water in colourless needles having m. p. 85° (Found : C, 49·0; H, 7·3; N, 11·5. $C_{10}H_{18}O_3N_2S$ requires C, 48·8; H, 7·4; N, 11·5%).

Reaction between 2-Mercapto-4-benzylidene-5-thiazolinone and Aminoacetamide.—A suspension of the thiazolinone (4·4 g.) in methanol (100 c.c.) containing N-sodium hydroxide (20 c.c.) and aminoacetamide hydrochloride (2·3 g.) was heated under reflux for 1 hour, diluted with water (200 c.c.), and cooled. The pale yellow solid product (2 g.), m. p. 220°, was recrystallized from the minimum quantity of hot glacial acetic acid, whereupon *2-thio-4-benzylidenehydantoin-1-acetamide* (1·3 g.), m. p. 257°, separated. For analysis, a small quantity was recrystallized from much hot water, forming long pale yellow needles, m. p. 257° (Found : C, 55·4; H, 4·3; N, 16·0. $C_{12}H_{11}O_2N_3S$ requires C, 55·2; H, 4·3; N, 16·1%).

The amide (1 g.) treated in a solution of potassium hydroxide (0·19 g.) in water (10 c.c.) with methyl sulphate (0·3 c.c.) gave a rapidly-crystallizing oil. *2-Methylthio-5-keto-4-benzylidene-4 : 5-dihydroglyoxaline-1-acetamide* (0·7 g.) was filtered off. It separated from aqueous methanol as pale yellow rhombohedra, m. p. 154° (Found : C, 56·9; H, 5·2; N, 15·3. $C_{13}H_{13}O_2N_3S$ requires C, 56·7; H, 5·5; N, 15·2%).

The acetic acid solution from crystallization of the thiohydantoin was largely diluted with water, whereby further material (0·5 g.) m. p. 190—195°, was precipitated. This was recrystallized from hot water, giving *2-mercapto-5-phenylthiazoline-4-carboxyamidoacetamide* as colourless rods, m. p. 200° (Found : N, 14·1. $C_{12}H_{13}O_2N_3S_2$ requires N, 14·2%).

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IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
S. KENSINGTON, LONDON, S.W.7.

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