267. *Studies in the Azole Series. Part VII. A New Route to α-Amino-β-mercapto-acids.*

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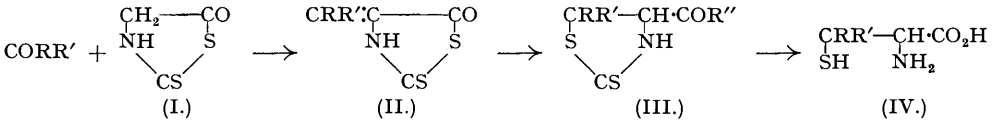
2-Thiothiazolone (I) has been condensed with benzaldehyde and with acetone under acid conditions. The resulting substituted 4-methylene-2-thiothiazolones (*e.g.*, II) undergo rearrangement in presence of bases to give 2-thiothiazolidone-4-carboxylic acid derivatives (*e.g.*, III). The latter have been smoothly hydrolysed to α-amino-β-mercapto-acids, β-phenylcysteine and penicillamine being prepared in this way in good yield. Cysteine was obtained by a modified procedure from 4-hydroxymethylene-2-thiothiazolone (II; R = H, R′ = OH).

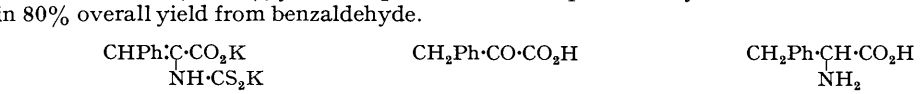
The synthesis of β-phenylcysteine (IV; R = H, R′ = Ph) from 2-ethylthio-4-benzylidenethiazolone (IX) has been described as an example of a general route to α-amino-β-mercapto-acids starting essentially from *N*-dithiocarbethoxyglycine (Cook, Harris, and Heilbron, this vol., p. 1060). The use of 2-thiothiazolone (I) (Cook, Heilbron, and Levy, this vol., p. 201) promised a more elegant means of access to the same acids, and this has now been realised. Three stages are involved starting from an aldehyde or ketone, the reactions having been demonstrated in model syntheses using benzaldehyde and acetone.



(I.) (II.) (III.) (IV.)

Benzaldehyde condenses smoothly with 2-thiothiazolone (I) in cold acetic acid solution containing hydrogen chloride to give 4-benzylidene-2-thiothiazolone (II; R = H, R′ = Ph) (Cook, Heilbron, and Levy, *loc. cit.*) in high yield. Attempts to effect the condensation in hot acetic anhydride resulted in acetylation of the thiazolone (cf. *idem, ibid.*), the resulting monoacetyl derivative failing to condense further with the aldehyde.

The compound (II; R = H, R′ = Ph) was markedly resistant to acid hydrolysis, being recovered unchanged after many hours' boiling with concentrated hydrochloric acid. With 1 equiv. of aqueous or alcoholic potassium hydroxide, it formed a moderately stable potassium salt (behaviour with sodium hydroxide was analogous), which could be ethylated to give 2-ethylthio-4-benzylidenethiazolone (IX); the latter was identical with the product of this designation obtained by Cook, Harris, and Heilbron (*loc. cit.*) and thus provides a link between the two series of experiments. With 2 equivs. of potassium hydroxide, however, the thiazolone ring of (II; R = H, R′ = Ph) was opened within about 30 secs., giving, it would appear, the dithiocarbamic salt (V). In aqueous media, hydrolysis of the latter to phenylpyruvic acid (VI) competed with cyclisation to 4-carboxy-5-phenyl-2-thiothiazolidone (III; R = H, R′ = Ph, R″ = OH) (Cook, Harris, and Heilbron, *loc. cit.*) of which only a poor yield was obtained. In methanol, on the other hand, the hydrolysis was effectively inhibited and (II; R = H, R′ = Ph) was quantitatively converted into (III; R = H, R′ = Ph, R″ = OH). As it has already been shown (Cook, Harris, and Heilbron, *loc. cit.*) that the thiothiazolidone (III; R = H, R′ = Ph, R″ = OH) can be hydrolysed with hydrochloric acid at 100° to give β-phenylcysteine (IV; R = H, R′ = Ph) in 90% yield, the present reactions provide a synthesis of the latter compound in 80% overall yield from benzaldehyde.

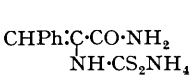


(V.) (VI.) (VII.)

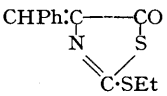
When the above rearrangement was conducted in sodium carbonate solution, an *isomeride* of (III; R = H, R′ = Ph, R″ = OH) was obtained, and this compound also appeared in smaller amounts when aqueous sodium hydroxide was used. This is almost certainly the second

possible stereoisomeric form of (III; R = H, R′ = Ph, R″ = OH), obtained by *cis*- or *trans*-addition to the double bond, and has been termed the β-form, that first described, from (IX), being the α-form. Under the vigorous hydrolytic conditions employed the difference was not preserved, and both the α- and the β-form gave the same β-phenylcysteine.

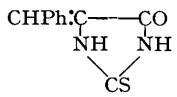
2-Thiothiazolone could also be utilised in a more orthodox fashion to give α-amino-acids, for phenylalanine (VII) was formed when an aqueous solution of (IV; R = H, R′ = Ph) was shaken with Raney nickel catalyst.



(VIII.)



(IX.)



(X.)

A rearrangement similar to that described above was demonstrated with aqueous ammonia, rapid ring opening giving, it is believed, the compound (VIII) which reverted to (II; R = H, R′ = Ph) if the solution were immediately acidified [cf. the preparation of the thiazolone (I) from dithiocarbamates derived from aminoacetamide; Cook, Heilbron, and Levy, *loc. cit.*]. On standing, however, *cis*- and *trans*-addition to the double bond occurred, giving both the α- and the β-form of *5-phenyl-2-thiothiazolidone-4-carboxyamide* (III; R = H, R′ = Ph, R″ = NH_2). The *S*-ethyl derivative (IX), on the other hand, reacted in a different manner with ammonia, losing ethanethiol to give 5-benzylidene-2-thiohydantoin (X).

Most of the above reactions were repeated in principle with acetone. The initial condensation proceeded in only 20% yield in presence of hydrogen chloride but was increased to 60% by refluxing an acetone solution of 2-thiothiazolone containing phosphoric oxide. Methanolic potassium hydroxide transformed (II; R = R′ = Me) into (III; R = R′ = Me, R″ = OH) which was hydrolysed by hydrochloric acid to penicillamine (IV; R = R′ = Me) (cf. Cook, Heilbron, and Shaw, C.P.S. 311).

The parent compound of this amino-acid series, cysteine, was obtained by a modified route. 4-Ethoxymethylene-2-thiothiazolone (Cook, Heilbron, and Levy, *loc. cit.*) was rapidly hydrolysed by cold sodium hydroxide to *4-hydroxymethylene-2-thiothiazolone* (II; R = H, R′ = OH), which underwent simultaneous reduction and rearrangement when treated with sodium amalgam, giving *2-thiothiazolidone-4-carboxylic acid* (III; R = R′ = H, R″ = OH), which upon treatment with aluminium and mineral acid gave cysteine (IV; R = R′ = H).

Experimental.

4-Benzylidene-2-thiothiazolone (II; R = H, R′ = Ph).—2-Thiothiazolone (24 g.) and benzaldehyde (50 g.) were warmed with acetic acid (250 c.c.) until dissolved, and the cold solution treated with dry hydrogen chloride for 30 minutes. 4-Benzylidene-2-thiothiazolone (35 g., 88%) separated in yellow needles, m. p. 211°, on standing overnight, identical with the compound described earlier (Cook, Heilbron, and Levy, *loc. cit.*).

2-Ethylthio-4-benzylidenethiazolone (IX).—The above benzylidene compound (1·0 g.) was dissolved in just sufficient N-sodium hydroxide to give a clear red solution, and shaken with ethyl iodide (0·8 g.) in ether (3·0 c.c.) for 5 hours. 2-Ethylthio-4-benzylidenethiazolone (1·0 g.) separated, and was recrystallised from aqueous acetone, having m. p. 64—65°, undepressed on admixture with an authentic sample (Cook, Harris, and Heilbron, *loc. cit.*).

Action of Aqueous Sodium Hydroxide on (II; R = H, R′ = Ph).—The benzylidenethiazolone (4·0 g.) was mixed with 2N-sodium hydroxide (40 c.c.), the red colour fading after 0·5 min. After standing for 15 hrs. at room temperature, the pale yellow solution was cooled to 0° and acidified with 2N-hydrochloric acid; the gum crystallised fairly rapidly on trituration (yield, 1·6 g.). On standing overnight, the filtrate deposited phenylpyruvic acid (0·75 g.; 30%), m. p. 154—155°, which was identified with an authentic sample (*Org., Synth.*, **19**, 77). The above crystalline material was extracted with ether (25 c.c.) and washed with a further quantity (2 × 10 c.c.), the β-form of 5-phenyl-2-thiothiazolidone-4-carboxylic acid (see below) (0·72 g.; 16%), m. p. 208° (decomp.), remaining. The m. p. was raised to 225° after one crystallisation from methanol–water. The ethereal filtrate was evaporated to small bulk and diluted with ethylene dichloride to give the α-form of the above acid (see below) (0·35 g.; 8%), m. p. 173°.

Action of Methanolic Potash on (II; R = H, R′ = Ph).—The benzylidenethiazolone (2·2 g.) and potassium hydroxide (1·12 g.; 2 equivs.) were dissolved in methanol (10 c.c.), and the solution kept overnight. The solvent was evaporated in a vacuum, and the syrup dissolved in water (5 c.c.) and acidified with concentrated hydrochloric acid to give the α-form of 5-phenyl-2-thiothiazolidone-4-carboxylic acid (III; R = H, R′ = Ph, R″ = OH) (2·4 g.; 100%), m. p. 166—168°, raised to 175—176° by one crystallisation from toluene–acetic acid. The compound also crystallised well from ethylene dichloride in glistening laths, m. p. 175—176°, undepressed on admixture with an authentic sample (Cook, Harris, and Heilbron, *loc. cit.*).

Action of Aqueous Sodium Carbonate on (II; R = H, R′ = Ph).—The benzylidenethiazolone (1·0 g.) was kept with 2N-sodium carbonate (20 c.c.) for 6 days; acidification then gave the β-form of *5-phenyl-2-thiothiazolidone-4-carboxylic acid* (III; R = H, R′ = Ph, R″ = OH) (0·85 g.) which was recrystallised

from a small volume of ethanol to form long colourless needles, m. p. 225° (decomp.) (Found : C, 49·9; H, 3·7; N, 5·5. $C_{10}H_9O_2NS_2$ requires C, 50·2; H, 3·8; N, 5·8%). It was soluble in alcohols and acetone, in hot acetic acid and ethyl acetate, and sparingly soluble in ether, chloroform, and benzene.

The above thiazolidone (2·1 g.) was heated with concentrated hydrochloric acid (25 c.c.) in a sealed tube at 135° for 36 hours. The resulting pale brown solution was shaken with a little charcoal, whereupon the filtrate deposited β-phenylcysteine (IV; R = H, R′ = Ph) hydrochloride (0·25 g.), m. p. 202° (decomp.) after drying over phosphoric oxide in a vacuum.

Desulphurisation of β-Phenylcysteine.—β-Phenylcysteine hydrochloride (0·71 g.) was suspended in water (10 c.c.), and neutralised with 2N-sodium hydroxide (3·0 c.c.). Raney nickel (5 c.c. of ethanolic suspension) was added, and the mixture shaken for 36 hours at room temperature (after 5 mins. the solution gave a negative thiol test with ferric chloride). The nickel was removed, and the filtrate concentrated to 2—3 c.c.; acidification with acetic acid then caused separation of β-phenylalanine (0·2 g.), m. p. 263° (decomp.), characterised as its benzoyl derivative, m. p. 188°.

Action of Aqueous Ammonia on (II; R = H, R′ = Ph).—The benzylidenethiazolone (1·5 g.) was suspended in water (10 c.c.), and dissolved by addition of ammonia (*d* 0·880). After 1 hr. a copious crystalline precipitate (1·15 g.) separated and was extracted with several portions of hot ether; *β-5-phenyl-2-thiothiazolidone-4-carboxyamide* (III; R = H, R′ = Ph, R″ = NH_2) remained, and recrystallised from ethanol in platelets, m. p. 229—230° (decomp.) (Found : C, 50·5; H, 4·2; N, 11·5. $C_{10}H_{10}ON_2S_2$ requires C, 50·4; H, 4·2; N, 11·8%). The ethereal extracts yielded the corresponding *α-form*, which crystallised from ethylene dichloride in needles, m. p. 178° (Found : C, 49·8, 51·1; H, 4·4, 4·2; N, 11·7%).

When (II; R = H, R′ = Ph) (0·6 g.) was dissolved in ammonia (*d* 0·880) (3·0 c.c.), the colour rapidly faded and immediate acidification gave back the starting material. Longer standing gave a 70% yield of the above α-amide, when the ammonia was removed in a vacuum.

Action of Ammonia on (IX).—The 2-ethylthiothiazolone (1·0 g.) in ether (10 c.c.) was treated with dry ammonia for 3 hrs.; ethanethiol was liberated, and 5-benzylidene-2-thiohydantoin (X) (0·7 g.), m. p. 266—267° (decomp.), produced and identified with an authentic sample (Wheeler, Nicolet, and Johnson, *Amer. Chem. J.*, 1911, **46**, 468).

5-iso*Propylidene-2-thiothiazolone*.—2-Thiothiazolone (2·0 g.) in acetone (30 c.c.) was cooled to 0° and saturated with a stream of dry hydrogen chloride (30 mins.). Plates of the starting material separated, which redissolved as the mixture was allowed to regain room temperature. After standing overnight, 4-iso*propylidene-2-thiothiazolone* (II; R = R′ = Me) (0·6 g.) separated, and recrystallised from ethanol in pale yellow blades, m. p. 211° (Found : C, 41·5; H, 4·4; N, 8·0. $C_6H_7ONS_2$ requires C, 41·6; H, 4·1; N, 8·1%). The acetone filtrate deposited a water-soluble hydrochloride, which crystallised from acetic acid in long colourless needles, m. p. 177° (Found : C, 22·0; H, 5·8; N, 12·5%).

2-Thiothiazolone (2·2 g.) in dry acetone (15 c.c.) containing phosphoric oxide (2·2 g.) was heated under reflux for 24 hours. The crude *iso*propylidenethiazolone (1·7 g.), which separated on cooling, was best crystallised from acetic acid, then having m. p. 211°.

Action of Methanolic Potash on (II; R = R′ = Me).—The *iso*propylidenethiazolone (1·1 g.) and potassium hydroxide (0·7 g.; 2 equivs.) were dissolved in methanol (15 c.c.), and set aside overnight. The solvent was evaporated, and the residue treated with dilute hydrochloric acid, some gum, insoluble in sodium bicarbonate, being precipitated. On standing, the solution deposited 5 : 5-dimethyl-2-thiothiazolidone-4-carboxylic acid (III; R = R′ = Me, R″ = OH) (0·4 g.) in colourless prismatic needles, m. p. 145°, identified with an authentic specimen prepared from penicillamine and carbon disulphide.

4-Hydroxymethylene-2-thiothiazolone (II; R = H, R′ = OH).—4-Ethoxymethylene-2-thiothiazolone (5·0 g.) was dissolved in 10% sodium hydroxide (25 c.c.) and acidified immediately with concentrated hydrochloric acid to give *4-hydroxymethylene-2-thiothiazolone* (4·0 g.), m. p. 200° (decomp.), which was purified by repeated precipitation from alkali with acid (Found : C, 29·8; H, 2·0; N, 8·3. $C_4H_3O_2NS_2$ requires C, 29·8; H, 1·9; N, 8·7%). The compound was soluble in sodium hydrogen carbonate solution, and gave a blue colour with ferric chloride in aqueous-ethanolic solution.

2-Thiothiazolidone-4-carboxylic acid (III; R = R′ = H, R″ = OH).—The above hydroxymethylene compound (2·0 g.) in 10% sodium hydroxide (5 c.c.) was treated with 3% sodium amalgam (8·0 g.) during one hour. The solution was acidified with hydrochloric acid, and extracted with ether to yield, on evaporation, *2-thiothiazolidone-4-carboxylic acid* (0·5 g.), which crystallised from ether–light petroleum in colourless needles, m. p. 161° (decomp.) (Found : C, 29·4; H, 2·7; N, 8·85; *M*, by titration, 163·7. $C_4H_5O_2NS_2$ requires C, 29·4; H, 3·0; N, 8·6%; *M*, 163). The compound was soluble in water and common polar solvents, but insoluble in hydrocarbons.

Cysteine.—The above acid (4·2 g.) was refluxed under nitrogen with 2N-hydrochloric acid (50 c.c.) for 0·5 hr., and aluminium foil (2·0 g.) and 2N-hydrochloric acid (30 c.c.) were then added to the cooled solution. The mixture was heated at 80° for 0·5 hr. and then at 100° for 0·5 hr.; the aluminium dissolved and hydrogen sulphide was evolved. Saturated mercuric chloride (10 c.c.) was added, and the resulting white precipitate decomposed with hydrogen sulphide in dilute hydrochloric acid suspension. The mercuric sulphide was removed, and the filtrate evaporated under reduced pressure in a nitrogen atmosphere to give a gum. Rubbing with ether gave crude cysteine hydrochloride (0·11 g.), which recrystallised from 20% hydrochloric acid in prisms which softened at 100° and melted indefinitely above 180° (Found, in a sample dried in a vacuum for 1 hr.: C, 20·7; H, 5·3; N, 8·4. Calc. for $C_3H_8O_2NClS,H_2O$: C, 20·5; H, 5·3; N, 8·0%). The compound gave a deep blue colour with ferric chloride and a violet colour with alkaline sodium nitroprusside.

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