492. *Studies in the Azole Series. Part XIX. Reactions with 2-Mercaptothiazol-5-one.*

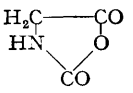
By J. D. Billimoria and A. H. Cook.

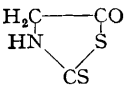
Anhydro-*N*-carboxyglycine (I) proved too labile for use in projected condensation reactions but its dithio-analogue (II) was readily converted into a variety of condensation products of type (III). Products (III) were converted into α-amino-acids either directly or through the analogue of (II) of general formula (V), the constitution of representatives of which were confirmed by their preparation from α-amino-acids.

Anhydro-*N*-carboxyglycine (I) (Leuchs, *Ber.*, 1906, **39**, 857; Go and Tani, *Bull. Chem. Soc. Japan*, 1939, **14**, 510) has been used in the preparation of polyglycine, whilst the analogous 2-mercaptothiazol-5-one [or a tautomeric form, 2-thiothiazolid-5-one] (II) (Cook, Heilbron, and Levy, *J.*, 1948, 201) is a useful intermediate in the preparation of simple peptides of known constitution (Sir Ian Heilbron, this vol., p. 2099). Compound (II) has also provided

* This is not an assumption of the *sense* of the moment but only that the moment acts in one or other sense in the direction of this line.

a route to an analogue of penicillamine (Billimoria, Cook, and Heilbron, this vol., p. 1437) and to α-amino-β-thiol-acids generally (unpublished work). The same compound (II) had virtually been condensed with benzaldehyde or with ethyl orthoformate in an acid medium (Cook, Heilbron, and Levy, *loc. cit.*) to give the products (III; R = H, R′ = Ph; R = H, R′ = OEt, respectively), thus demonstrating the presence of a reactive methylene group in (II). It seemed possible therefore that (II) and perhaps (I) might, with appropriate treatment, prove useful in the ways indicated below in the synthesis of higher amino-acids and near derivatives thereof, and the present paper described experiments to these ends.


(I.)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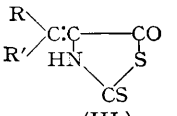
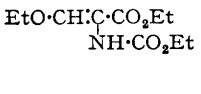

(III.)

It soon became apparent that the ring of (I) was too labile for the present purposes. Thus with alcoholic hydrogen chloride anhydrocarboxyglycine was quantitatively converted into glycine ethyl ester hydrochloride, and alcoholic sodium ethoxide opened the ring in a similar manner but with partial polymerisation. Again, on treatment with morpholine (I) afforded *glycine morpholide* which was further characterised as its *picrate*. Under similar conditions glycine ethyl ester reacted with (I) to give glycylglycine ethyl ester in poor yield, and it seemed unprofitable to attempt the preparation in this manner of other peptides in useful yield. The compound (I) failed to condense with benzaldehyde under a variety of conditions, though it reacted with ethyl orthoformate undergoing condensation and simultaneous ring-fission with the formation of an unsaturated compound, possibly (IV). Clearly the methylene group of (I) was not as reactive as was desired.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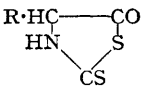
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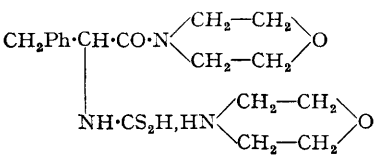
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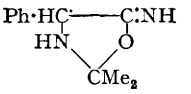
(VII.)

By contrast with (I), the 2-mercaptothiazol-5-one (II) was found to condense readily with a wide variety of aldehydes, ketones, or acetals or ketals thereof, in presence of a basic catalyst, to give compounds of the type (III). The 4-*ethylidene* (III; R = Me, R′ = H), *methylthioethylidene* (III; R = CH_2·SMe, R′ = H), n-*butylidene* (III; R = Pr^n, R′ = H), iso*butylidene* (III; R = Pr^i, R′ = H), *iso*propylidene (III; R = R′ = Me), benzylidene (III; R = Ph, R′ = H), and o- and p-*hydroxybenzylidene* (III; R = C_6H_4·OH, R′ = H) compounds were obtained.

Attempts to reduce representative compounds of those mentioned immediately above with reagents such as iron and hydrochloric acid, magnesium and alcohol, titanous chloride in acid solution, or calcium in acetic acid were unsuccessful. However, zinc dust in presence of acetic acid was more effective and the benzylidene compound was readily reduced in this manner to 2-*thio*-4-*benzylthiazolid*-5-*one* (V; R = CH_2Ph). The latter, the first analogue of the parent compound (II) to be described, was characterised by its reaction with morpholine to give the *morpholinium* salt of *N*-dithiocarboxy-β-phenylanaline morpholide (VI). On treatment with hydrochloric acid (VI) reverted to (V; R = CH_2Ph), just as carbamidomethyldithiocarbamates afforded (II) on acidification (cf. Cook, Heilbron, and Levy, *loc. cit.*). Finally, when (V; R = CH_2Ph) was treated with methanolic sodium methoxide, followed by methanolic hydrogen chloride, the hydrochloride of β-phenylalanine methyl ester was obtained. The series of reactions thus virtually provides a novel route to phenylalanine.

The structure of the compound formulated as (V; R = CH_2Ph) was established by its synthesis from β-phenylalanine. The methyl ester of the amino-acid was converted into the amide and thence with carbon disulphide into a salt of the corresponding dithiocarbamic acid. On acidification of its solution the latter compound was converted into the compound obtained previously. This method of obtaining 2-thiothiazolid-5-ones seems to be of general applicability and was used to prepare the analogue (V; R = Ph).

α-Aminobenzyl cyanide condensed with acetone in presence of sodium methoxide to give 5-*imino*-4-*phenyl*-2 : 2-*dimethyloxazolidine* (VII) (cf. the similar behaviour of aminoacetonitrile;

Cook, Heilbron, and Levy, *loc. cit.*), which on treatment with water was converted into α-amino-phenylacetamide. The sodium *N*-dithiocarbamate derived from the latter yielded, on acidification, 2-*thio*-4-*phenylthiazolid*-5-*one* (V; R = Ph). The new compound behaved like its analogues, reacting with morpholine to give the *morpholinium* salt (cf. VI).

2-Thio-4-*p*-hydroxybenzylidene- and -4-*cyclo*hexylidene-thiazolid-5-one (Billimoria, Cook, and Heilbron, Part XVI, this vol., p. 1437) were also reduced by zinc dust in acetic acid to 2-*thio*-4-p-*hydroxybenzyl*- and -4-cyclo*hexyl-thiazolid*-5-*one*, respectively, but similar treatment of (III; R = CH_2·SMe, R′ = H) led to its losing the methylthio-group, and 2-*thio*-4-*ethylthiazolid*-5-*one* (V; R = Et) was obtained in small yield. This structure was certain because on treatment with ethanolic hydrogen chloride the ring was opened to afford ethyl α-aminobutyrate hydrochloride.

When representative 2-thio-4-alkylidene- and -arylidene-thiazolid-5-ones were reduced with red phosphorus and hydrogen iodide, simultaneously the ring was opened with loss of the elements of carbon disulphide to give α-amino-acids. β-Phenylalanine, tyrosine, valine, leucine, norleucine, and *cyclo*hexylglycine were so obtained in good yield, whilst even methionine was obtained in small quantity by reducing (III; R = CH_2·SMe, R′ = H). α-Aminobutyric acid prepared in this manner from (III; R = Me, R′ = H) was esterified to give ultimately the ester hydrochloride identical with that obtained from (V; R = Et) as described above. In view of the facility with which (II) may be condensed with carbonyl compounds, and the ease of reductive fission of the condensation products (III), these reactions appear to provide useful new routes to α-amino-acids.

Experimental.

Reactions of Anhydrocarboxyglycine.—This compound (Go and Tani, *Bull. Chem. Soc. Japan*, 1939, **14**, 510) did not melt at 100° as described but evolved carbon dioxide at that temperature and gave thus an amorphous infusible residue. It was more conveniently crystallised from anhydrous acetone and could be partly sublimed in a high vacuum to give colourless needles.

(*a*) The anhydride (0·5 g.) was kept in saturated alcoholic hydrogen chloride (10 c.c.) at 0°. After ½ hour the mixture was warmed until dissolution of the compound was complete. On cooling and addition of a little ether, glycine ethyl ester hydrochloride was obtained, having m. p. 144°, undepressed on admixture with an authentic specimen prepared from glycine.

(*b*) The anhydride (0·5 g.) was kept at 0° with ethanolic sodium ethoxide (10 c.c.) containing sodium (0·13 g.). A solid (polymeride?) which separated was removed. The filtrate was titrated with 5N-ethanolic hydrogen chloride, until just acid to phenolphthalein; the sodium chloride which separated was filtered off, and on addition of a little ether to the filtrate glycine ethyl ester hydrochloride was again obtained, having m. p. and mixed m. p. with an authentic specimen 144°.

(*c*) The anhydride (0·51 g.) was kept with water (20 c.c.) for 4 hours at 15°. The anhydride gradually dissolved, and a trace of precipitate was filtered off. The filtrate on evaporation *in vacuo* yielded glycine which was identified as its picrate.

(*d*) The anhydride (0·5 g.) was suspended in water (20 c.c.) at 40°. After some time, a precipitate was obtained which was insoluble in most organic solvents and resembled the compound described by Go and Tani (*loc. cit.*), namely a polyglycine.

(*e*) The anhydride (0·5 g.), dissolved in ethyl acetate, was treated at 40° with a number of bases in equivalent amounts. Ethylamine, aniline, benzylamine, *p*-toluidine, and triethylamine were used. In each case a polymeric product was obtained which could not be crystallised from organic solvents.

Glycine Morpholide.—Anhydrocarboxyglycine (5 g.) was dissolved in acetone (150 c.c.), the solution cooled to 0°, and morpholine (6 g.), dissolved in acetone (30 c.c.) and pre-cooled to 0°, was added. After 20 minutes at 0° the solution was kept overnight at room temperature. It was finally heated under reflux for a few minutes, a trace of precipitated polymeride filtered off, the filtrate concentrated *in vacuo*, and the residual oil distilled at 0·5 mm. whereupon partial decomposition occurred and a fraction, b. p. 120—130° (2·5 g.), was collected. On refractionation, *glycine morpholide* (2 g.) was obtained as a pale yellow oil, b. p. 128—130°/0·5 mm. (Found: C, 50·55; H, 8·4; N, 19·0. $C_6H_{12}O_2N_2$ requires C, 50·05; H, 8·35; N, 19·45%). The compound was characterised by the preparation, in ethyl acetate, of the *picrate*, which crystallised from alcohol in pale yellow needles, m. p. 222—224° (decomp.) (Found: C, 38·5; H, 4·05. $C_{12}H_{15}O_9N_5$ requires C, 38·6; H, 4·0%).

Glycylglycine Ethyl Ester.—Anhydrocarboxyglycine (5 g.) was dissolved in acetone (150 c.c.) and cooled to 0°. Glycine ethyl ester (7 g.), also dissolved in acetone (20 c.c.) and cooled to 0°, was added dropwise to the solution of the anhydride with stirring. The mixture was kept for ½ hour at 0° and overnight at room temperature and finally heated under reflux for a few minutes. A trace of precipitated polymeride was filtered off, the solvent removed *in vacuo*, and the residual oil distilled at 100° in a high vacuum. Considerable decomposition occurred, and the colourless viscous distillate solidified with some difficulty. On recrystallisation from alcohol–ethyl acetate, colourless needles (Found: N, 17·55. Calc. for $C_6H_{12}O_3N_2$: N, 17·5%), m. p. 85°, undepressed on admixture with authentic glycylglycine ethyl ester, were obtained. The m. p. of its hydrochloride was not depressed by glycylglycine ethyl ester hydrochloride.

Condensation of Anhydrocarboxyglycine with Ethyl Orthoformate.—The anhydride (5 g.), ethyl orthoformate (18 c.c.), and acetic anhydride (15 c.c.) were heated on the water-bath for 1 hour with occasional stirring, until a clear solution was obtained. A trace of amorphous matter which soon separated was rejected and the filtrate was concentrated *in vacuo* to give a crystalline mass contaminated with a syrupy mother-liquor. This was treated with light petroleum (200 c.c.) and chloroform

(10 c.c.), whereupon the crystals dissolved and the syrup deposited a dark amorphous powder which was rejected. The filtrate, when kept at 0° for some hours, deposited long colourless needles (1·25 g.). On recrystallisation from benzene–light petroleum, colourless plates of (?) *ethyl α-carbethoxyamino-β-ethoxyacrylate*, m. p. 92°, were obtained (Found : C, 51·0; H, 7·2. $C_{10}H_{17}O_5N$ requires C, 51·0; H, 7·6%). The compound was very unstable and decomposed within a day even under nitrogen.

2-*Thio*-4-*ethylidenethiazolid*-5-*one*.—(*a*) 2-Mercaptothiazol-5-one (Cook, Heilbron, and Levy, *loc. cit.*) (4 g.) was dissolved in warm ethyl acetate (75 c.c.), and a large excess of freshly distilled acetaldehyde (12 c.c.) was added. Piperidine (2 drops) was added and the solution kept at room temperature for several days. A crop of large straw-coloured plates which separated was filtered off and further crops were obtained by concentrating the mother-liquor. The combined yield (3 g.) of the *ethylidene* compound recrystallised from glacial acetic acid in straw-coloured plates, m. p. 195—196° (Found : C, 38·0; H, 3·4; S, 40·4. $C_5H_5ONS_2$ requires C, 37·8; H, 3·2; S, 40·3%).

(*b*) 2-Mercaptothiazol-5-one (5 g.) was dissolved in boiling glacial acetic acid (50 c.c.), and acetaldehyde diethyl acetal (6 g.) was added, followed by morpholine (2 drops). After 12 hours the crystals were filtered off, and a further two crops (total yield, 5 g.) obtained from the filtrate by successive dilutions with water. The compound was recrystallised from glacial acetic acid and was identical with the previous preparation (*a*).

2-*Thio*-4-2′-*methylthioethylidenethiazolid*-5-*one* (III; R = CH_2·SMe, R′ = H).—2-Mercaptothiazol-5-one (4 g.) was dissolved in boiling glacial acetic acid (50 c.c.), and methyl 2 : 2-diethoxyethyl sulphide (5·2 g.) was added, followed by piperidine (2 drops). After several hours the condensation product (5·5 g.) separated as pale orange-yellow plates. A small amount (0·2 g.) was obtained on dilution of the mother-liquor with water. The *compound* crystallised from acetic acid in pale yellow plates, m. p. 158° (Found : C, 35·6; H, 3·7; N, 6·8. $C_6H_7ONS_3$ requires C, 35·1; H, 3·4; N, 6·8%).

2-*Thio*-4-n-*butylidenethiazolid*-5-*one*.—2-Mercaptothiazol-5-one (25 g.) was dissolved in boiling glacial acetic acid (250 c.c.), and an excess of *n*-butyraldehyde (40 c.c.) was added, followed by piperidine (2 drops). After 24 hours a crystalline crop (14 g.) was collected, and dilution of the filtrate with water yielded a further crop (10 g.) of the condensation *product* which crystallised as pale yellow needles, m. p. 133°, from acetic acid (Found : C, 44·9; H, 4·8; N, 7·2. $C_7H_9ONS_2$ requires C, 44·9; H, 4·8; N, 7·4%).

2-*Thio*-4-iso*butylidenethiazolid*-5-*one*.—This was prepared similarly from 2-mercaptothiazol-5-one (1 g.), glacial acetic acid (10 c.c.), an excess of *iso*butyraldehyde (2 g.), and piperidine (1 drop). After being kept for 12 hours the solution was filtered from a trace of dark crystalline deposit, and the filtrate diluted with water to give pale brown plates (1·3 g.), m. p. 122°. The 2-*mercapto*-4-iso-*butylidenethiazol*-5-*one* was recrystallised from aqueous acetic acid without further elevation of m. p. (Found : C, 44·8; H, 5·1; S, 34·4%).

2-*Thio*-4-iso*propylidenethiazolid*-5-*one* —(*a*) 2-Mercaptothiazol-5-one (10 g.) was dissolved in boiling glacial acetic acid, and the solution cooled to 50°. Dry acetone (20 c.c.) was added, a small precipitate filtered off, and the filtrate set aside for 12 hours at room temperature and then diluted with water, whereupon the *iso*propylidene compound was obtained (3 g.).

(*b*) 2-Mercaptothiazol-5-one (5 g.) was dissolved in warm dry acetone (100 c.c.), and morpholine (1 drop) added. The solution was treated with morpholine (1 drop) each day for 6 days, after which the solution contained no unchanged 2-mercaptothiazol-5-one (the thiazole in dilute aqueous sodium hydrogen carbonate, when treated with aqueous iodine–potassium iodide gives a deep purple colour). The solution was diluted with water, giving pale yellow needles, m. p. 211° (4·5 g., 77%), of the condensation product (Found : C, 41·5; H, 4·4; N, 8·0. Calc. for $C_6H_7ONS_2$ C, 41·6; H, 4·1; N, 8·1%). This compound had previously been prepared in 20% yield (Cook, Heilbron, and Levy, *loc. cit.*) by condensing the 2-mercaptothiazol-5-one with acetone in the presence of hydrogen chloride.

2-*Thio*-4-*benzylidenethiazolid*-5-*one*.—2-Mercaptothiazol-5-one (20 g.) was dissolved in boiling glacial acetic acid (200 c.c.), benzaldehyde (21 g.) was added, and the solution treated with piperidine (3 drops). After 15 minutes at room temperature the solution set to a solid mass of yellow crystals. After 12 hours, the crystals were filtered off and a second crop was obtained by concentration of the mother-liquor. A combined crop (31 g., 98%) of the condensation product, m. p. 212—214°, was obtained and no elevation of m. p. was observed on recrystallisation from glacial acetic acid. When melted in admixture with an authentic specimen of 2-thio-4-benzylidenethiazolid-5-one (Cook, Heilbron, and Levy *loc. cit.*) no depression was observed. The condensation was successfully repeated, with theoretical yield, when the piperidine was replaced by primary, secondary, or tertiary bases in catalytic amounts. Thus, aniline, methylaniline, morpholine, diethylamine, dimethylamine, triethylamine, and pyridine were found to be equally effective in the condensation. A small amount of anhydrous sodium acetate was also found to be effective in this condensation.

2-*Thio*-4-p-*hydroxybenzylidenethiazolid*-5-*one*.—2-Mercaptothiazol-5-one (10 g.) was dissolved in boiling glacial acetic acid (100 c.c.), and *p*-hydroxybenzaldehyde (11 g.) was added, followed by piperidine (3 drops). After 12 hours, the crystals were filtered off, and the product was recrystallised from glacial acetic acid in yellow needles, m. p. 199—200° (Found : C, 50·8; H, 3·2. $C_{10}H_7O_2NS_2$ requires C, 50·6; H, 3·0%). Prolonged boiling of the above compound with glacial acetic acid converted it into its geometric isomer, obtained as orange-red needles, m. p. 219—221°. This latter form could also be prepared by dissolving 2-mercaptothiazol-5-one (10 g.) and *p*-hydroxybenzaldehyde (11 g.) in glacial acetic acid (100 c.c.) and saturating the solution with gaseous hydrogen chloride at 0°. On recrystallisation from boiling glacial acetic acid, orange-red needles (6 g.), m. p. 219—221°, were obtained (Found : C, 50·4; H, 3·1; N, 5·8. $C_{10}H_7O_2NS_2$ requires C, 50·6; H, 3·0; N, 5·9%).

2-*Thio*-4-o-*hydroxybenzylidenethiazolid*-5-*one*.—2-Mercaptothiazol-5-one (5 g.) was dissolved in boiling glacial acetic acid (50 c.c.) and *o*-hydroxybenzaldehyde (5 g.) added, followed by piperidine (2 drops). The yellow crystals were filtered off and further crops were obtained by diluting the mother-liquor with water. The product (7·2 g.) was recrystallised from aqueous acid in orange-yellow needles, m. p. 164° (Found : C, 50·4; H, 3·1; N, 5·8. $C_{10}H_7O_2NS_2$ requires C, 50·6; H, 3·0; N, 5·9%).

Reduction of 2-*Thio*-4-*benzylidenethiazolid*-5-*one*.—(*a*) This compound (25 g.) was dissolved in glacial

acetic acid (1 l.), and concentrated hydrochloric acid (0·5 c.c.) was added. Zinc dust (40 g.) was added in 10-g. portions. After 0·5 hour the solution was decolorised and was filtered from the excess of zinc dust. The filtrate was evaporated to dryness *in vacuo*, and the *2-thio-4-benzylthiazolid-5-one* was obtained as a pale yellow crust. The solid was digested with aqueous hydrochloric acid (1 : 1) and filtered, the filtrate containing the last traces of zinc being rejected. The residue (23·5 g.), m. p. 152—153°, was purified by rapid dissolution in cold 2N-sodium hydroxide, followed by acidification and cooling, whereupon pale-yellow to almost colourless matted needles of the benzylthiazol-5-one, m. p. 157—160°, separated. The material could be recrystallised only with great loss, by slow separation from benzene–light petroleum. A portion recrystallised in this manner gave the pure *compound* in almost colourless needles, m. p. 159—160° (Found: C, 53·5; H, 4·1; N, 6·1. $C_{10}H_9ONS_2$ requires C, 53·8; H, 4·1; N, 6·3%).

(*b*) 2-Thio-4-benzylidenethiazolid-5-one (10 g.) was dissolved in warm dioxan (25 c.c.), and zinc dust (15 g.) was added. Glacial acetic acid (10 c.c.) was added and the solution gently heated until the yellow colour was discharged. The excess of zinc dust was filtered off and the filtrate on dilution with water and cooling to 0° slowly deposited 2-mercapto-4-benzylthiazol-5-one as a micro-crystalline powder (7·5 g.), m. p. 157—160°, recrystallised as described in the previous experiment.

The above compound (1·8 g.) was triturated with morpholine (1·69 g.) dissolved in dry acetone (4 c.c.). An exothermic reaction was observed, followed by sudden crystallisation. The product (3·2 g.) was filtered off and a portion (0·5 g.) was added to hot acetone (5 c.c.) and dissolved by the addition of water (3 drops). On cooling, rectangular plates of the *morpholinium* salt of *N*-dithiocarboxy-β-phenylalanine morpholide, m. p. 150°, were obtained (Found: C, 54·3; H, 6·6; N, 10·6; S, 16·3. $C_{18}H_{27}O_3N_3S_2$ requires C, 54·4; H, 6·8; N, 10·6; S, 15·9%). This salt (0·5 g.) when treated with 2N-hydrochloric acid was reconverted into 2-mercapto-4-benzylthiazol-5-one, m. p. 159—160°, undepressed when melted in admixture with the previously prepared compound.

The above benzylthiazol-5-one (5 g.) was suspended in methanol (20 c.c.), and a solution of sodium (1·2 g.) in methanol (20 c.c.) was run in, whereupon the compound dissolved completely. The solution was kept at room temperature for 10 minutes, and the excess of alkali removed by adding to it a small excess of 5N-methanolic hydrogen chloride (using phenolphthalein as indicator). Sodium chloride was filtered off and the filtrate evaporated to dryness. The residual oil, when rubbed with ether, set to a crystalline mass. The crystals were dissolved in chloroform, the solution treated with charcoal. The filtrate on dilution with ether, followed by cooling, deposited β-phenylalanine methyl ester hydrochloride as colourless needles (2·5 g.), m. p. 156—158°, undepressed on admixture with the authentic compound.

Preparation of 2-Thio-4-benzylthiazolid-5-one from β-Phenylalanine.—β-Phenylalanine (5 g.) was esterified by suspending it in methanol (25 c.c.) and heating the mixture under reflux with a current of gaseous hydrogen chloride passing through it for 0·5 hour. The solution was then evaporated to dryness *in vacuo*, and the β-phenylalanine methyl ester hydrochloride (5·6 g.), m. p. 154—155°, obtained as colourless needles was used without further purification. The ester hydrochloride (5 g.) was dissolved in chloroform (100 c.c.) and was titrated against 20% aqueous sodium hydroxide (phenolphthalein). The chloroform layer was separated and the aqueous solution extracted twice with chloroform (25-c.c. portions). The chloroform extracts were dried ($MgSO_4$), the solvent was distilled off *in vacuo*, and the residual oil (2 g.) was kept with liquid ammonia (100 c.c.) in a sealed vessel for 30 hours. On evaporation of the ammonia, a white crystalline residue was obtained which was dissolved in hot chloroform and filtered from a little residual solid. The filtrate, diluted with light petroleum, gave colourless prisms of β-phenylalanine amide (85%), m. p. 139—140°. The above amide (0·5 g.) was dissolved in a minimum of ethanol at room temperature with just sufficient water to give a clear solution, and an excess of carbon disulphide (1 g.) was added. The clear solution was set aside for 0·5 hour at room temperature and then acidified with concentrated hydrochloric acid (10 c.c.), and the excess of carbon disulphide removed *in vacuo*. On dilution with water (10 c.c.) and cooling in ice 2-mercapto-4-benzylthiazol-5-one separated in colourless needles, m. p. 159—160°, undepressed on admixture with the compound prepared by the reduction of 2-mercapto-5-benzylidenethiazol-5-one (Found: C, 53·5; H, 4·1; N, 6·1. Calc. for $C_{10}H_9ONS_2$: C, 53·6; H, 4·1; N, 6·3%).

5-Imino-4-phenyl-2 : 2-dimethyloxazolidine.—α-Aminobenzyl cyanide (20 g.) was dissolved in cold acetone (300 c.c.), and sodium methoxide obtained from sodium (0·8 g.) in methanol (5 c.c.) was added. After some time, an exothermic reaction was observed, and the mixture was cooled in ice and kept overnight at 0°. The *oxazolidine* (23 g.) which separated was recrystallised from dry acetone in colourless needles, m. p. 142—144° (Found: C, 69·9; H, 7·4; N, 15·2. $C_{11}H_{14}ON_2$ requires C, 69·5; H, 7·4; N, 14·7%).

The above oxazolidine (15 g.) was heated under reflux with water (40 c.c.). On cooling, the solution set to a solid mass of crystals, which were filtered off, and the α-aminophenylacetamide (13 g.) was recrystallised from water; m. p. 132—133°.

The above amide (20 g.) was dissolved in hot dry ethanol (50 c.c.), and an excess of carbon disulphide (40 c.c.) was added. The solution was kept at room temperature for 1 hour and finally boiled under reflux for 15 minutes. The excess of carbon disulphide was removed *in vacuo*, and the solution poured on crushed ice and hydrochloric acid. The crystalline precipitate so obtained was filtered off after 1 hour at 0°. On recrystallisation from aqueous ethanol containing a trace of dilute aqueous hydrochloric acid, 2-mercapto-4-phenylthiazol-5-one (12 g.) was obtained in pale yellow prismatic needles, m. p. 155—156° (decomp.) (Found: C, 51·8; H, 3·5; N, 6·9; S, 30·2. $C_9H_7ONS_2$ requires C, 51·7; H, 3·4; N, 6·7; S, 30·7%).

The above phenylthiazol-5-one was triturated with acetone (5 c.c.) containing morpholine (1·90 g.). The compound immediately dissolved, giving a yellow solution which soon became dark. After some minutes the colour again rapidly faded and the crystalline deposit of the morpholinium salt (4·4 g.) was obtained. The *morpholinium* salt of *N*-dithiocarboxyphenylglycine morpholide (cf. VI) was recrystallised from dry acetone (as described for the previous morpholinium salt) in colourless prisms, m. p. 140—141° (Found: C, 53·6; H, 6·5; N, 11·0; S, 16·4. $C_{17}H_{25}O_3N_3S_2$ requires C, 53·3; H, 6·6; N, 11·0; S, 16·7%).

The above morpholinium salt (0·5 g.), dissolved in a little water, was treated with 15% hydrochloric acid, whereupon a precipitate was obtained which, after recrystallisation from aqueous ethanol containing a few drops of hydrochloric acid, was identified with the previously prepared 2-mercapto-4-phenylthiazol-5-one, m. p. and mixed m. p. 155—156°.

*Reduction of 2-Thio-*4-p-*hydroxybenzylidenethiazolid-5-one.*—This compound (5 g.) was dissolved in glacial acetic acid (150 c.c.) and reduced in the usual manner with zinc dust (7 g.). After removal of the excess of zinc dust, the filtrate on cooling deposited some crystals of zinc acetate which were filtered off and rejected. The filtrate was diluted with light petroleum (b.p. 60—80°) and kept at 0°, whereupon colourless needles (1 g.) slowly crystallised. The 2-*thio*-4-p-*hydroxybenzylthiazolid-5-one* recrystallised from glacial acetic acid–light petroleum in colourless needles, m. p. 162—164° (Found: C, 49·8; H, 4·0; N, 6·0; S, 26·2. $C_{10}H_9O_2NS_2$ requires C, 50·2; H, 3·8; N, 5·9; S, 26·8%).

The filtrate was evaporated to dryness, and the residual tar subjected to chromatography in ethyl acetate on an alumina column. The main fraction of the eluent, when diluted with light petroleum, deposited a further crop of crystals (1·5 g.) which were recrystallised in the above manner.

*Reduction of 2-Thio-*4-cyclo*hexylidenethiazolid-5-one.*—The compound (2 g.) was dissolved in acetic acid (25 c.c.) and reduced as described in the previous experiment with zinc dust (5 g.). 2-*Thio*-4-cyclo*hexylthiazolid-5-one* (0·25 g.) separated from aqueous acetic acid in pale yellow needles, m. p. 185—186° (Found: N, 6·1; S, 29·8. $C_9H_{13}ONS_2$ requires N, 6·5; S, 29·8%).

*Reduction of 2-Thio-*4-*methylthioethylidenethiazolid-5-one.*—(*a*) The compound (3 g.), dissolved in acetic acid (15 c.c.), was reduced in the usual manner with zinc dust (4 g.). Methanethiol was evolved and, after removing the solvent *in vacuo*, the residual gum was sublimed in a high vacuum at 85—90°, whereafter pale yellow plates (0·5 g.) were collected. 2-*Thio*-4-*ethylthiazolid-5-one* (0·5 g.) was recrystallised from ether after a second sublimation and then had m. p. 79—80° (Found: C, 38·15; H, 4·75; N, 8·7. $C_5H_7ONS_2$ requires C, 37·3; H, 4·55; N, 8·7%).

(*b*) The above reduced compound (0·2 g.) was dissolved in ethanol (2 c.c.), and 5N-ethanolic hydrogen chloride (5 c.c.) added. The solution was boiled under reflux for 10 minutes, the solvent evaporated *in vacuo*, and the residual oil crystallised by rubbing with ether. Recrystallisation from ethanol–ether yielded silky colourless needles of ethyl (±)-α-aminobutyrate hydrochloride, m. p. 129—131° (lit., m. p. 130—131°) (Found: N, 7·8. $C_6H_{13}O_2N$,HCl requires N, 8·3%).

*Preparation of α-Amino-*n-*butyric Acid from 2-Thio-*4-*ethylidenethiazolid-5-one.*—The thiothiazolidone (4 g.) was dissolved in boiling acetic acid (30 c.c.), and red phosphorus (6 g.) added, followed by 40% aqueous hydrogen iodide (12 c.c.). The mixture was then boiled under reflux for 4 hours. The solution was filtered and the filtrate diluted with a little water. A trace of unchanged material was rejected and the filtrate evaporated to dryness *in vacuo*. The residual oil was dissolved in aqueous ethanol (25 c.c.) and filtered through charcoal. The filtrate was cooled to 0°, and pyridine (5 c.c.) added. After the mixture had been kept overnight at 0° the microcrystalline amino-acid (2 g.) was filtered off and sublimed at 170° in a high vacuum. *α-Amino-*n-*butyric acid* recrystallised from aqueous ethanol in small colourless plates, m. p. 300° (Found: C, 46·6; H, 8·6; N, 13·55. $C_4H_9O_2N$ requires C, 46·6; H, 8·7; N, 13·6%).

The above acid was esterified with ethanolic hydrogen chloride and ethyl α-amino-*n*-butyrate hydrochloride crystallised from ethanol in colourless needles, m. p. 129—30°, undepressed on admixture with the ester hydrochloride previously obtained by the degradation of 2-mercapto-4-ethylthiazol-5-one.

β-Phenylalanine.—2-Thio-4-benzylidenethiazolid-5-one (3 g.) was suspended in glacial acetic acid (20 c.c.), and red phosphorus (4 g.) added, followed by 40% aqueous hydrogen iodide (10 c.c.). The whole was then heated under reflux for 1·5 hours. The solution was filtered and the filtrate diluted with water. A trace of gummy material was rejected, the filtrate evaporated to dryness *in vacuo*, and the residue dissolved in hot water (20 c.c.) and filtered through charcoal. The filtrate was concentrated to 15 c.c., and pyridine (10 c.c.) added. After 12 hours at 0° the silky plates deposited were recrystallised from aqueous ethanol, β-phenyl-α-alanine (70%) being obtained in large colourless plates, m. p. 282—284° (decomp.). The amino-acid was converted by methanolic hydrogen chloride into β-phenylalanine methyl ester hydrochloride, m. p. 156—158°, undepressed on admixture with an authentic specimen.

(±)-*Tyrosine.*—Thio-4-*p*-hydroxybenzylidenethiazolid-5-one (3 g.), suspended in glacial acetic acid, was similarly subjected to reductive hydrolysis with red phosphorus (4 g.) and 40% aqueous hydrogen iodide (10 g.). The (±)-tyrosine was obtained from boiling water as colourless needles (1·7 g.), m. p. 290—295° (sealed tube), and characterised as the ethyl ester hydrochloride which formed colourless needles, m. p. 166°, undepressed on admixture with a specimen prepared from authentic (±)-tyrosine.

(±)-*Valine.*—Thio-4-*iso*propylidenethiazolid-5-one (3 g.), dissolved in hot acetic acid (20 c.c.), was reduced in the above manner with red phosphorus (5 g.) and 40% aqueous hydrogen iodide (10 g.); (±)-valine (1·6 g.) separated from aqueous ethanol in colourless plates, m. p. 298° (sealed tube). The compound was characterised by the preparation of its ethyl ester hydrochloride which formed hygroscopic crystals, m. p. 73—76° (lit., m. p. 76°). The free ester was obtained from the above compound and characterised as its picrate which formed microcrystals (from aqueous ethanol), m. p. 138—139°, undepressed on admixture with an authentic specimen.

(±)-*Norleucine.*—2-Thio-4-*n*-butylidenethiazolid-5-one (5 g.), dissolved in hot acetic acid (25 c.c.), was reduced in the usual manner with red phosphorus (5 g.) and aqueous hydrogen iodide (10 c.c.); (±)-norleucine (2 g.) separated in colourless needles from aqueous ethanol and sublimed without melting, above 300° (Found: C, 54·9; H, 10·1; N, 10·5. Calc. for $C_6H_{13}O_2N$: C, 54·9; H, 10·0; N, 10·7%).

(±)-*Leucine.*—2-Thio-4-*iso*butylidenethiazolid-5-one (2·4 g.) in hot acetic acid (20 c.c.) was also reduced in the above manner, whereupon (±)-leucine (1·3 g.) separated from hot water in thin lustrous plates, m. p. 293—295° (sealed tube). The amino-acid (0·25 g.) in aqueous 2N-sodium hydroxide (5 c.c.) was treated with 3 : 5-dinitrobenzoyl chloride (0·3 g.). After being shaken for 10 minutes, the solution was acidified and the precipitated (±)-3 : 5-dinitrobenzoyl-leucine separated from aqueous ethanol in pale yellow needles, m. p. 187—189° (Found: N, 13·05. Calc. for $C_{13}H_{15}O_7N_3$: N, 12·9%).

(±)-*Methionine.*—2-Thio-4-methylthioethylidenethiazolid-5-one (2 g.) in acetic acid (25 c.c.) was

heated under reflux with red phosphorus (4 g.) and 40% aqueous hydrogen iodide for 30 minutes. Some methanethiol was evolved. The solution was filtered and the filtrate evaporated to dryness *in vacuo*. The residual oil was dissolved in water (10 c.c.), and the unchanged material rejected. The filtrate was again concentrated to dryness *in vacuo*, and the residue dissolved in aqueous ethanol (15 c.c.), treated with charcoal and cooled to 0°, and pyridine (5 c.c.) was added. After some hours the (±)-methionine (0·3 g.) was collected and recrystallised from aqueous ethanol in colourless needles, m. p. 275—280° (sealed tube), undepressed by admixture with authentic (±)-methionine.

The above acid, dissolved in aqueous sodium hydroxide, was benzoylated to give (±)-*N*-benzoylmethionine, crystallising from aqueous ethanol in colourless needles, m. p. 143—144°, undepressed by admixture with the compound prepared from authentic (±)-methionine.

(±)-cyclo*Hexylglycine*.—2-Thio-4-*cyclo*hexylidenethiazolid-5-one (2·2 g.) was similarly converted into (±)-*cyclo*hexylglycine (1·3 g.). The amino-acid was almost insoluble in hot water and was conveniently crystallised from hot acetic acid in colourless needles, m. p. 296—297°. The picrate separated from acetic acid in small crystals, m. p. 186—187° (cf. Zelinsky and Studnikoff, Ber., 1906, **39**, 1723).

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