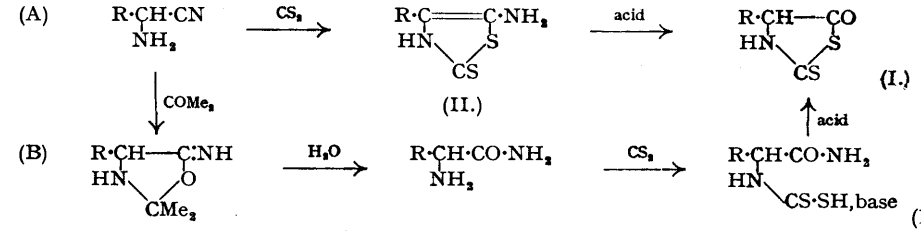
535. *Peptide Synthesis from Heterocyclic Intermediates. Part I. 2-Thio-5-thiazolidone Derivatives of Valine, Leucine, Norleucine, Methionine, L-Tyrosine, Glutamine, α-Aminoisobutyric Acid, and Aminomalonamide.*

By A. C. Davis and A. L. Levy.

The thiothiazolidones mentioned in the title are made by cyclisation of the dithiocarbamates of the appropriate α-amino-amides with aqueous mineral acid; the mechanism of this reaction is discussed. The valine derivative is better prepared by hydrolysis of the corresponding 5-amino-2-mercapto-thiazole. Representative members of this thiothiazolidone series have been found to racemise with great ease.

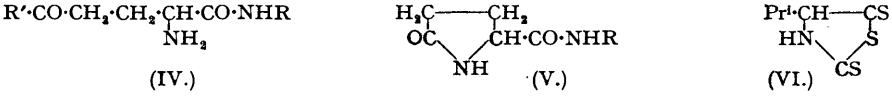
Cook, Heilbron, and Levy (*J.*, 1948, 201) prepared a 2-thio-5-thiazolidone (I; R = H) by routes (A) and (B), of which the latter, though longer, was more convenient preparatively. Billimoria and Cook (*J.*, 1949, 2323) introduced a third general route (C), namely, reduction with zinc and hot acetic acid of the corresponding 4-alkylidene- or 4-arylidene-thiazolones,

which were readily obtained by condensation of (I; R = H) with aldehydes or ketones. By this method they prepared 2-thio-5-thiazolidones (I; R = CH_2Ph, *p*-$OH{\cdot}C_6H_4{\cdot}CH_2$, *cyclo*hexyl, and Et) related to phenylalanine, tyrosine, *C-cyclo*hexylglycine, and α-aminobutyric



acid. The corresponding derivative of *C*-phenylglycine (I; R = Ph) was obtained by route (B). Cook and Levy (*J.*, 1950, 642) prepared the alanine thiothiazolidone (I; R = Me) by route (B), though route (A) was not successful in this case. A number of related *N*-methyl-2-thio-5-thiazolidones have also been made by appropriate modifications of all three routes (Fourneau and Vila, *Bull. Soc. chim.*, 1911, **9**, 985; Carrington, *J.*, 1948, 1619; Cook and Cox, *J.*, 1949, 2342). The finding that 2-thio-5-thiazolidone (I; R = H) could be used to effect a ready synthesis of glycyl-polypeptides (Cook and Levy, *J.*, 1950, 646), and that route (B) presented a method for the stepwise degradation of peptides (Levy, *J.*, 1950, 404), made it desirable to extend the available range of these compounds, and the present communication records the synthesis of eight new 2-thio-5-thiazolidones, related to both natural and artificial α-amino-acids. These compounds were briefly reported earlier (Levy, *loc. cit.*).

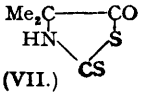
L-Tyrosine, L-leucine, and DL-methionine were converted by known methods into their methyl esters, and thence by reaction with ammonia into their amides. These were condensed with carbon disulphide, and the resulting dithiocarbamates (isolated in the case of L-tyrosine as a crystalline triethylamine salt) acidified with aqueous hydrochloric acid to yield 4-*p*-hydroxybenzyl- (I; R = *p*-$OH{\cdot}C_6H_4{\cdot}CH_2$), 4-*iso*butyl- (I; R = Bu^i), and 4-2′-methylthioethyl-2-thio-5-thiazolidine (I; R = $MeS{\cdot}CH_2{\cdot}CH_2$). In the case of tyrosine, the thiothiazolidone was optically active, but racemised during 2—3 hours in methanol solution. However, in the presence of 0·1 equivalent of hydrogen chloride, or in ethanol solution, it was considerably more stable, and little or no racemisation was apparent in ethyl acetate. In the presence of bases, optical rotation was rapidly lost, and although tyrosylglycylglycine ethyl ester hydrochloride was secured in 78% yield from glycylglycine ethyl ester by Cook and Levy's procedure (*loc. cit.*), it was found to be optically inactive. When freshly prepared, the crude leucine thiothiazolidone was also optically active, but it appeared to racemise with great ease, and only inactive material was recovered after crystallisation. These results are very similar to those obtained with simple oxazolones (" The Chemistry of Penicillin," Princeton Univ. Press, 1949, p. 742), though it is possible that by careful control of pH peptide syntheses may be effected without prohibitive racemisation.



Ammonolysis of dimethyl or diethyl glutamate produces almost exclusively pyrrolidone-5-carboxyamide (V; R = H), so alternative methods to glutamic amides (IV) were used. The L-α-anilide (IV; R = Ph, R′ = OH) was prepared enzymically by condensing *N*-carbobenzyloxy-L-glutamic acid with aniline in the presence of papain, and removing the protecting group by hydrogenation (Behrens and Bergmann, *J. Biol. Chem.*, 1939, **129**, 594). It was shaken with carbon disulphide and sodium carbonate solution but acidification did not yield the required thiothiazolidone. *N*-Carbobenzyloxy-L-glutamic acid α-anilide was therefore esterified with methanolic hydrogen chloride, but hydrogenation of the resulting γ-methyl *N*-carbobenzyloxy-L-glutamate α-anilide yielded only pyrrolidone-5-carboxyanilide (IV; R = Ph), despite the mild reaction conditions employed. Difficulties were also experienced in using L-*iso*glutamine (IV; R = H, R′ = OH), and the final successful approach utilised the hitherto unknown L-glutamamide (IV; R = H, R′ = NH_2), which was, however, not isolated. Catalytic hydrogenation of *N*-carbobenzyloxy-L-glutamamide (Fruton, *J. Biol. Chem.*,

1946, **165**, 333) was rendered difficult by its insolubility in common solvents, but debenzylation with sodium in liquid ammonia (Loring and Du Vigneaud, *J. Biol. Chem.*, 1935, **111**, 385) yielded crude glutamamide, which on treatment with carbon disulphide in methanol, followed by acidification, gave 4-2′-carbamylethyl-2-thio-5-thiazolidone (I; R = NH_2·CO·CH_2·CH_2) in poor yield. It proved to be optically inactive.

In the valine series, an entirely synthetic approach from *iso*butaldehyde was adopted; this was converted successively into the cyanohydrin and aminonitrile, which by route (B) was transformed through four stages into the required 4-*iso*propyl-2-thio-5-thiazolidone (I; R = Pr^i). The thiazolidone proved to be remarkably stable to acids, so that in this case route (A) became the procedure of choice, 5-amino-2-mercapto-4-*iso*propylthiazole (II; R = Pr^i) being deaminated to (I; R = Pr^i) in 66% yield when warmed with 3N-hydrochloric acid. In the course of attempts to obtain the sulphur analogue (VI) of (I) by treating (II) with hydrogen sulphide, 5-*iso*propyl-2 : 4-dithiohydantoin was obtained, and identified with the product of alkaline rearrangement of (II; R = Pr^i) (cf. Cook, Heilbron, and Levy, *J.*, 1947, 1598). The 2-thio-5-thiazolidones of glycine, alanine, methionine, and valine form a series showing increasing stability to hydrolysis. Thus (I; R = H) is hydrolysed rapidly by water at 70° (I; R = Me) in 1—2 minutes at 100°, and (I; R = MeS·CH_2·CH_2) in about 5 minutes at 100°; (I; R = Pr^i) is stable for a prolonged period to boiling water, and refluxing for about 5 minutes with concentrated hydrochloric acid is needed to cause complete breakdown.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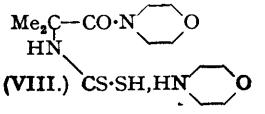
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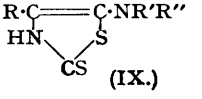
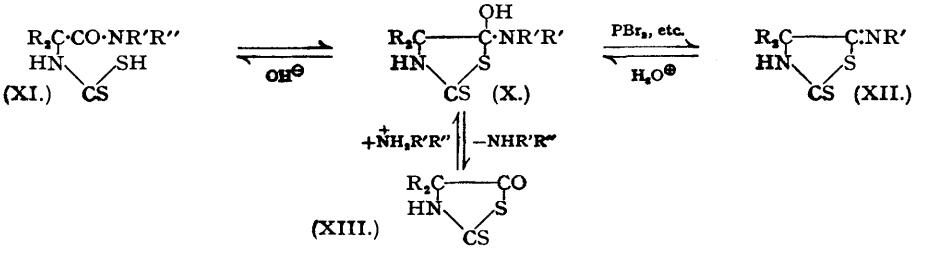

(IX.)

α-Amino*iso*butyronitrile did not undergo satisfactory condensation with acetone in the presence of sodium methoxide, but the amide sulphate was readily secured by mixing the aminonitrile with concentrated sulphuric acid, and pouring the whole into ethanol (cf. Cook and Cox, *J.*, 1949, 2334). The remaining stages of route (B) then proceeded normally, giving 4 : 4-dimethyl-2-thio-5-thiazolidone (VII) in 86% yield. With morpholine in acetone, this afforded morpholinium 2-formomorpholidyl-2-propyldithiocarbamate (VIII) in the usual way, morpholinium dithiocarbamate being obtained under slightly more vigorous conditions. It had hitherto been supposed (A. L. Levy, Ph.D. Thesis, London, 1947) that the mechanism of the remarkable fission of the peptide linkage by NH·CS·SH in compounds such as (III) involved a momentary cyclisation to the 5-amino- or 5-imino-thiazole derivatives (IX) or (XII), followed at once by hydrolysis to the 2-thio-5-thiazolidones. This suggestion arose from the evidence presented by Cook, Heilbron, and Levy (*loc. cit.*) that the *S*-benzyl ester of (III; R = H) was quantitatively transformed into the *S*-benzyl derivative of (II; R = H) with phosphorus tribromide, and that (II; R = H) was hydrolysed by acids to (I; R = H). It also seemed to account for the fact that (I; R = H) was obtained from (III) under hydrolysing conditions, but not by the action of anhydrous acids. It was of particular interest, therefore, to find that the morpholine derivative (VIII), in which such a mechanism could not operate, was readily recyclised to (VII) in 93% yield with dilute mineral acid.

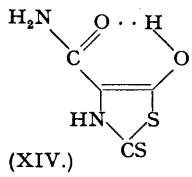

(XI.) (X.) (XII.) (XIII.)

It would appear, then, that fission of the peptide linkage must take place *via* the ortho-acid derivative (X), which can be represented as the common intermediate in all the above-mentioned transformations: (*a*) α-amino-amide dithiocarbamate ⟶ 2-thio-5-thiazolidone; (XI) ⟶ (X) ⟶ (XIII) under acid conditions; (*b*) 2-thio-5-thiazolidone + amine ⟶ α-amino-amide dithiocarbamate; (XIII) ⟶ (X) ⟶ (XI) under basic conditions; (*c*) α-

thioacylamino-amide ⟶ 5-aminothiazole; (XI) ⟶ (X) ⟶ (XII) under dehydrating conditions; (*d*) 5-aminothiazole ⟶ thiazol-5-one; (XII) ⟶ (X) ⟶ (XIII) with aqueous acid. This series is analogous to the " ester " or " amide " fission of imino-ethers with acids or bases. It is interesting that Hanby, Whaley, and Watson (*Proc. Roy. Soc.*, 1949, *A*, **199**, 499) have suggested the intervention of an intermediate similar to (X), to account for the kinetics of polymerisation of *N*-carboxysarcosine anhydride. The driving force of the reaction (X) ⟶ (XIII) must arise in part from the aromaticity of the thiazolone ring, since the dithiocarbamate of β-alanine amide did not cyclise to a thiazine derivative on acidification.

For preparations in the norleucine series, *n*-hexanoic acid was a convenient starting material. Bromination by the Hell–Volhard–Zelinsky method yielded the known 2-bromo-*n*-hexanoyl bromide, which gave DL-norleucine amide directly by the action of methanolic ammonia. This afforded a crystalline dithiocarbamate salt with carbon disulphide, which cyclised to 4-*n*-butyl-2-thio-5-thiazolidone (I; R = Me·[CH_2]$_3$) in 78% overall yield on acidification in water.

4-Carbamyl-2-thio-5-thiazolidone (I; R = CO·NH_2) was obtained by route (B) in 90% yield from aminomalonamide, either by shaking the amide in aqueous sodium carbonate with carbon disulphide, or, better, by conversion into the crystalline dithiocarbamate by heating a suspension of the highly insoluble amide in pyridine with carbon disulphide under reflux. It was rather less stable than the other thiothiazolidones which have been made, decomposing gradually on storage and losing carbon disulphide and carbon dioxide with effervescence when boiled with water. An interesting possibility arises with (I; R = CO·NH_2), in that the products of reaction with bases (III; R = CO·NR′R″) can cyclise in two ways with acids, eliminating either ammonia or the base, and it was hoped that such experiments would indicate the relative efficiency of different amines in promoting ring closure. In fact, (I; R = CO·NH_2) yielded crystalline derivatives on treatment with aniline, benzylamine, and morpholine, and all of these gave back (I; R = CO·NH_2) on acidification. Analysis showed, however, that the morpholine adduct contained only one molecule of the base, and was presumably, therefore, a morpholine salt. A similar result has been noted in the case of 4-carbethoxy-2-phenyl-5-oxazolone, which gives a salt with benzylamine, converted into the normal benzylamide by heating it in xylene (*op. cit.*, p. 787). This behaviour can probably be ascribed to hydrogen-bond formation, as shown in (XIV), a view which receives strong support from the fact that (I; R = CO·NH_2), and its morpholine salt, give an intense indigo-blue colour with ferric chloride. A similar tendency may well account for the rather exceptional properties of the 5-amino-4-carbethoxyazoles, encountered by Cook, Heilbron, *et al.* (*locc. cit.*).



(XIV.)

All the thiothiazolidones here mentioned have been characterised as anhydrides by reaction with hydroxylamine, the resulting hydroxamic acid giving an intense brown colour with ferric chloride (cf. *op. cit.*, p. 1029).

Experimental.

L-4-p-*Hydroxybenzyl-2-thio-5-thiazolidone.* (This and the succeeding preparation were carried out by R. Sayers and L. Steensgaard.)—L-Tyrosine amide (Königs and Mylo, *Ber.*, 1908, **41**, 4441) (1·0 g.) in ethanol (16 c.c.) was treated with carbon disulphide (2·0 c.c.) and triethylamine (2·0 c.c.), and the resulting crystalline triethylamine salt of L-tyrosine amide dithiocarbamate (1·9 g., 96%), $[\alpha]_D^{23}$ +43·0° ±0·4° (*c*, 3·4 in water), was filtered off after 2 hours at room temperature. The salt in water (40 c.c.) was treated with 4N-hydrochloric acid; on seeding, almost colourless L-4-p-*hydroxybenzyl-2-thio-5-thiazolidone* (1·1 g., 93%) separated; recrystallised from ethyl acetate–light petroleum (b. p. 60—80°), it had m. p. 154° (Found: C, 50·5; H, 3·85; N, 5·9; S, 26·6. $C_{10}H_9O_2NS_2$ requires C, 50·2; H, 3·8; N, 5·85; S, 26·8%), $[\alpha]_D^{22}$ +174° (*c*, 2·4 in methanol). The thiazolidone (0·72 g.) and glycylglycine ethyl ester hydrochloride (0·59 g.) were shaken with ethanol (10 c.c.) containing triethylamine (0·83 c.c.), and after 10 minutes 2 equivs. of hydrogen chloride in ethanol, followed by a little ether, were added to precipitate the peptide (0·85 g., 78%), m. p. 209—210° (decomp.). DL-*Tyrosylglycylglycine ethyl ester hydrochloride*, recrystallised from methanol–ether, had m. p. 212° (decomp.) (Found: C, 49·65; H, 5·6; N, 11·2. $C_{15}H_{22}O_5N_3Cl$ requires C, 50·0; H, 6·1; N, 11·7%); it gave a single spot (R_F 0·76) on a butanol–acetic acid paper chromatogram and gave rise to tyrosine and glycine (1 : 2) on hydrolysis.

4-iso*Butyl-2-thio-5-thiazolidone.*—L-Leucine amide, prepared by Yang and Rising's method (*J. Amer. Chem. Soc.*, 1931, **53**, 3183), had m. p. 101—102°, $[\alpha]_D^{23}$ −34·8° (*c*, 1·27 in chloroform). The amide (0·25 g.) in ethanol (4 c.c.) was kept with triethylamine (0·5 c.c.) and carbon disulphide (0·5 c.c.) for 1 hour at room temperature, and poured into 6N-hydrochloric acid (20 c.c.). The thiazolidone was extracted with chloroform (4 × 10 c.c.), and the lævorotatory extract (α −1·07°, l = 1) was dried and evaporated in a vacuum to give a very pale yellow solid, m. p. 89—90°. 4-iso*Butyl-2-thio-5-thiazolidone* crystallised from light petroleum (b. p. 60—80°) in almost colourless needles, m. p. 94° (Found: C, 44·6; H, 5·9. $C_7H_{11}ONS_2$ requires C, 44·4; H, 5·9%). The colour could be completely removed by adsorption on alumina from benzene solution. The recrystallised material was optically inactive.

4-2′-*Methylthioethyl*-2-*thio*-5-*thiazolidone*.—DL-Methionine amide (1·68 g.) (Jones, *J. Amer. Chem. Soc.*, 1949, **71**, 79) in ethanol (20 c.c.) at 0° was treated with carbon disulphide (1 c.c.). After 1 hour at 0°, the solution was evaporated in a vacuum at 25°. Addition of ice-cold concentrated hydrochloric acid (10 c.c.) to a solution of the residue in water (7·5 c.c.) at 0° gave an oil which soon crystallised (0·92 g., 95%). After recrystallisation from *cyclo*hexane the 2-*thio*-5-*thiazolidone* formed colourless needles, m. p. 97° (Found: N, 6·7. $C_6H_9ONS_3$ requires N, 6·8%).

4-2′-*Carbamylethyl*-2-*thio*-5-*thiazolidone and Related Compounds*.—L-Glutamic acid α-anilide (Behrens and Bergmann, *loc. cit.*) (300 mg.) was shaken overnight in 2N-aqueous sodium carbonate (2 c.c.) with carbon disulphide (0·5 c.c.). Extraction with ethyl acetate after acidification with mineral acid yielded only an unidentified gummy solid (20 mg.).

N-Carbobenzyloxy-L-glutamic acid α-anilide (Behrens and Bergmann, *loc. cit.*) (5 g.) in dry methanol (250 c.c.) at room temperature was treated with saturated methanolic hydrogen chloride (2·5 c.c.). After 12 hours the crystalline product was collected, and a further quantity obtained by concentration of the filtrate in a vacuum; the combined products were dissolved in chloroform and precipitated with light petroleum to yield *γ-methyl* N-*carbobenzyloxy*-L-*glutamate* α-*anilide* (4·9 g., 94%), which crystallised from ethanol in colourless needles, m. p. 152° (Found: C, 65·1; H, 6·05; N, 7·6. $C_{20}H_{22}O_5N_2$ requires C, 64·85; H, 6·0; N, 7·6%). On hydrogenation over 5% palladium–charcoal in ethyl acetate containing 1 equivalent of acetic acid, the substance (3·6 g.) took up the theoretical volume of hydrogen; evaporation at a low temperature in a vacuum gave an oil which did not react with carbon disulphide in ethanol, but on being kept overnight in that solvent (10 c.c.) deposited crystalline pyrrolid-2-one-5-carboxyanilide (1 g.), m. p. 186—187° (Found: C, 64·7; H, 5·9; N, 13·9. Calc. for $C_{11}H_{12}O_2N_2$: C, 64·8; H, 5·9; N, 13·7%).

N-Carbobenzyloxy-L-glutamamide was obtained by Fruton (*loc. cit.*) by esterification of L-glutamic acid and then carbobenzyloxylation, to give the oily dimethyl *N*-carbobenzyloxy-L-glutamate, which was converted directly into the amide. In the present instance, *N*-carbobenzyloxy-L-glutamic acid (15 g.) in dry methanol (500 c.c.) was treated with hydrogen chloride in a rapid stream for 1 hour, with ice-cooling. After 24 hours at room temperature, the solution was evaporated in a vacuum to a syrup, which was taken up in chloroform (80 c.c.), washed with dilute hydrochloric acid, and with aqueous sodium hydrogen carbonate until neutral, dried, and re-evaporated to give the dimethyl ester as an oil (14 g.). On treatment with methanolic ammonia according to Fruton (*loc. cit.*), the diamide (10·5 g.; 67% from *N*-carbobenzyloxy-L-glutamic acid) separated gradually during 3 days. The substance did not absorb hydrogen in suspension in aqueous acetic acid in presence of a palladium catalyst, but a solution of the amide (4 g.) in liquid ammonia (400 c.c.) took up *ca.* 4 atoms (1·24 g.) of sodium before appearance of a permanent blue colour. Acidification with ammonium iodide (7·8 g.) and evaporation gave a hygroscopic solid which could not be cleanly separated to give the desired L-glutamamide; it was therefore extracted twice with cold ethanol (30 c.c., 20 c.c.) to remove sodium iodide, and the hygroscopic residue dissolved in the minimum of methanol and kept overnight at 0° with excess of carbon disulphide. Evaporation in a vacuum gave a solid residue, which was treated, in water (5 c.c.) at 0°, with concentrated hydrochloric acid (5 c.c.). Extraction with ethyl acetate (3 × 15 c.c.) and evaporation of the dried extracts in a vacuum gave a semi-solid residue; on precipitation from ethyl acetate with light petroleum, the 4-2′-*carbamylethyl*-2-*thio*-5-*thiazolidone* (25 mg.) formed lightly-coloured needles, m. p. 143—145°. The compound imparted blue or green colours to organic solvents, from which it could not be satisfactorily crystallised; on a micro-scale it was observed to crystallise well from water, but crystallisation of a larger sample failed owing to gross decomposition (Found, on unrecrystallised material: N, 14·3. $C_6H_8O_2N_2S_2$ requires N, 13·7%). The thiothiazolidone was optically inactive; kept in acetone with morpholine overnight, it yielded colourless needles of the morpholine derivative, m. p. 224°.

L-Glutamic acid (10 g.) was converted into the dimethyl ester hydrochloride by Fruton's method (*loc. cit.*); the free base was liberated by neutralisation in methanol with sodium methoxide, and added to saturated methanolic ammonia (400 c.c.) at 0°. After 7 days at room temperature, 2N-ethanolic hydrogen chloride (30 c.c.) was added, and excess of ammonia and methanol removed in a vacuum. The residue was treated with methanol (50 c.c.) and carbon disulphide (10 c.c.), neutralised with sodium methoxide, and kept overnight at 0°. After evaporation in a vacuum, the semi-solid residue, in the minimum of water, was acidified with concentrated hydrochloric acid. By extraction with ethyl acetate as in the preceding experiment, the product was obtained as a crystalline solid (0·25 g.); recrystallisation from acetic acid gave very pale yellow needles, m. p. 145—147°, strongly depressed by admixture with the above glutamine 2-thiothiazolidone. Analysis confirmed that the compounds were different, suggesting rather the *glutamic acid* derivative (Found: C, 32·0; H, 3·5; N, 6·7. $C_6H_7O_3NS_2$ requires C, 35·1; H, 3·4; N, 6·8. $C_6H_8O_2N_2S_2$ requires N, 13·7%).

4-iso*Propyl*-2-*thio*-5-*thiazolidone*.—The starting material, α-amino*iso*valeronitrile, has been prepared by the action of hydrogen cyanide on the *iso*butaldehyde–ammonia complex (Lipp, *Annalen*, 1880, **205**, 9), but for the present work, it was conveniently prepared by ammonolysis in methanol of the aldehyde cyanohydrin. Since it largely decomposed, without yielding any pure fraction, on distillation in a vacuum, the crude material was employed for the following experiments:

(*a*) α-Amino*iso*valeronitrile (5 g.) and acetone (10 c.c.) (dried over K_2CO_3) were treated with concentrated methanolic sodium methoxide until solid methoxide separated, and left for 7 days at room temperature. The solvent was removed in a vacuum and the residue was treated for 10 minutes with water (10 c.c.) at 60°, and then re-evaporated in a vacuum. The crude valine amide was dissolved in dry ethyl acetate (20 c.c.) and carbon disulphide (5 g.) was added; the semi-solid dithiocarbamate salt separated almost immediately. After 2 hours, all volatile material was removed in a vacuum, and the residue, in water (20 c.c.) at 0°, was acidified with concentrated hydrochloric acid (10 c.c.). Colourless

needles (0·5 g., 11% overall) of 4-iso*propyl*-2-*thio*-5-*thiazolidone*, m. p. 88°, separated at once, and were recrystallised from *cyclo*hexane, the m. p. rising to 101° (Found: C, 41·6; H, 5·4; N, 8·3. $C_6H_9ONS_2$ requires C, 41·1; H, 5·2; N, 8·0%).

(*b*) The amino-nitrile (50 g.) in chloroform (50 c.c.) was treated with carbon disulphide (40 g.), external cooling for 30 minutes being necessary to moderate the reaction. 5-*Amino*-2-*mercapto*-4-iso*propylthiazole* separated in two crops (total yield 48 g., 55%) during 12 hours, in large yellow tablets, m. p. 135—136° (rapid heating), and was recrystallised from chloroform–light petroleum; it had m. p. 141—142° (Found: N, 15·7. $C_6H_{10}N_2S_2$ requires N, 16·1%), and was readily oxidised to a brown pigment in air. The fact that this was the highest yield of the thiazole obtained confirms Lipp's observation (*loc. cit.*) of the spontaneous decomposition of valine nitrile; after 3 weeks at 0°, the latter did not yield any product on treatment with carbon disulphide.

5-Amino-2-mercapto-4-*iso*propylthiazole (10 g.) was powdered finely and shaken with concentrated hydrochloric acid (50 c.c.) until completely replaced by a colourless crystalline precipitate (this deliquescent material, m. p. 143°, contained chlorine, and was probably the thiazole hydrochloride). Water (150 c.c.) was added, and the temperature raised slowly to 60°; after 2 minutes, the crystalline product began to separate, and after 10 minutes, the solution was cooled and kept at 0° for 15 minutes; the thiothiazolidone, which formed large, yellow-tinted needles (6·7 g., 66%), was collected. On recrystallisation from *cyclo*hexane, it formed yellow needles, m. p. 101°, from which the colour could be removed by sublimation at 60° in high vacuum, after which the m. p. was 101—102°.

An attempt to prepare a 2 : 5-dithiothiazolidone, by hydrolysis of the above 5-aminothiazole in cold dilute acid containing hydrogen sulphide, was unsuccessful, the 2-thio-5-thiazolidone being produced. A saturated solution of the thiazole in ethyl acetate was treated with hydrogen sulphide to saturation, and kept for 0° for 4 hours; the yellow crystalline material which was deposited was not a product of reaction with hydrogen sulphide, but proved to be identical with the corresponding dithiohydantoin, prepared as follows (cf. Cook, Heilbron, and Levy, *J.*, 1947, 1598). 5-Amino-2-mercapto-4-*iso*propylthiazole (2 g.) was kept overnight in 10% aqueous sodium hydroxide (20 c.c.) and acidified with hydrochloric acid. The separated 5-iso*propyl*-2: 4-*dithiohydantoin* (1·6 g., 80%) crystallised from ethyl acetate as yellow prisms, m. p. 232° after darkening and sintering at 200° (Found: C, 42·0; H, 5·9; N, 15·9. $C_6H_{10}N_2S_2$ requires C, 41·4; H, 5·8; N, 16·1%).

5-Amino-2-mercapto-4-*iso*propylthiazole, when heated beyond its m. p., resolidified and remelted at 230°, suggesting that the dithiohydantoin was formed also by thermal rearrangement; in an attempt to isolate it by this method, the thiazole (2 g.) was heated for 5 minutes at 175—180°. Treatment of the crude solid with ethanol left a light yellow powder (0·95 g.), m. p. 240° (decomp.), which recrystallised from acetic acid in yellow plates, m. p. 246° (decomp.). Analytical results showed that the product was stoicheiometrically an addition *compound* of the desired dithiohydantoin and the corresponding 2-thio-5-thiazolidone, but it was not further studied (Found: C, 41·7; H, 5·8; N, 11·7. $C_{12}H_{19}ON_3S_4$ requires C, 41·3; H, 5·45; N, 12·0%).

4 : 4-*Dimethyl*-2-*thio*-5-*thiazolidone*.—α-Amino*iso*butyronitrile (15 g.) was added dropwise to well-stirred sulphuric acid (30 c.c.) containing water (3 c.c.), cooled in ice. The resulting syrup was warmed on the steam-bath to dissolve a small quantity of crystalline material, and run into ethanol (200 c.c.) with efficient stirring and ice-cooling; after being kept overnight, the colourless granular precipitate (25·5 g.) (presumably α-amino*iso*butyramide hydrogen sulphate; cf. Cook and Cox, *loc. cit.*) was collected and washed well with ethanol. This material (23 g.) was suspended in ethanol (100 c.c.) and treated with 2N-methanolic sodium methoxide with vigorous stirring to feeble alkalinity to phenolphthalein. After removal of the sodium sulphate and washing with methanol, evaporation of the filtrate and washings in a vacuum left colourless crystalline α-amino*iso*butyramide (10·5 g., 64% overall). It was purified by sublimation in a high vacuum, leaving only a trace of residue; the m. p. was then 125—126°.

The resublimed amino-amide (1 g.) was dissolved in dried ethyl acetate (10 c.c.) under reflux, carbon disulphide (2 c.c.) added, and heating continued for 2 minutes. On cooling to 0°, the precipitated dithiocarbamate salt solidified, and a further quantity separated during 2 hours at 0°; the colourless salt (1·4 g.), m. p. 110° (indefinite), was collected and washed with ethyl acetate and light petroleum. It was hygroscopic, and decomposed on storage. The salt (1·1 g.) in water (10 c.c.) at 0° was acidified with concentrated hydrochloric acid (2 c.c.), to give crystalline 4 : 4-*dimethyl*-2-*thio*-5-*thiazolidone* (0·45 g., 86% from the dithiocarbamate), m. p. 130—132°; on crystallisation from benzene–light petroleum (1 : 1), the compound formed thick, colourless, rectangular tablets, m. p. 132° (Found: C, 37·5; H, 4·5; N, 8·7. $C_5H_7ONS_2$ requires C, 37·3; H, 4·4; N, 8·7%).

Action of Morpholine on 4 : 4-*Dimethyl*-2-*thio*-5-*thiazolidone*.—The compound (0·2 g.) in warm dry ethyl acetate (10 c.c.) was treated with morpholine (0·5 g.). After reaction had proceeded for 5 minutes at *ca.* 70°, crystallisation was induced by scratching the flask; on slow cooling, a mass of colourless prisms (0·5 g.) was produced. The *morpholinium* 2-*formomorpholidyl*-2-*propyldithiocarbamate* had m. p. 128—129° (foaming) (Found: C, 46·4; H, 7·1; N, 12·4. $C_{13}H_{25}O_3N_3S_2$ requires C, 46·5; H, 7·5; N, 12·5%). On attempted recrystallisation of this salt, decomposition occurred; it was complete after 15 minutes' refluxing in ethyl acetate–methanol (1 : 1), the precipitated crystals, which sublimed at 180°, proving to be morpholinium morpholinedithiocarbamate (Found: C, 42·9; H, 7·4; N, 10·9. Calc. for $C_9H_{18}O_2N_2S_2$: C, 43·2; H, 7·2; N, 11·2%). The original morpholine salt (200 mg.) in water (1 c.c.) was acidified with dilute hydrochloric acid to give the thiothiazolidone (90 mg., 93%), m. p. 129—130° undepressed by admixture with the original sample.

4-n-*Butyl*-2-*thio*-5-*thiazolidone*.—2-Bromo-*n*-hexanoyl bromide (45 g.) (Auwers and Wegener, *J. pr. Chem.*, 1923, **106**, 226) was added cautiously with ice-cooling to saturated methanolic ammonia (500 c.c.). The solution was heated in an autoclave for 24 hours at 70°, and evaporated to dryness in

a vacuum; the residue was suspended in ethanol, and methanolic sodium methoxide was added until the solution was just alkaline to phenolphthalein. The solvents were removed in a vacuum and the dry residue was extracted with hot chloroform (3 × 25 c.c.); on evaporation of the chloroform, the crude amino-amide (20 g.) formed a pasty solid. By sublimation in high vacuum, DL-norleucine amide was obtained as a hard colourless mass (16·1 g., 71%), m. p. 88—90°. It crystallised from *cyclo*hexane in felted, colourless, hygroscopic needles, m. p. 91°, of the *hemihydrate* (Found: N, 20·7. $C_6H_{14}ON_2,\frac{1}{2}H_2O$ requires N, 20·1%). The compound was soluble in water, ethanol, acetone, and chloroform, sparingly soluble in ethyl acetate and benzene, and almost insoluble in ether and light petroleum. It was characterised as the *hydrochloride*, which crystallised in colourless, felted needles, m. p. 228—229°, from methanol–acetone (Found: N, 16·5. $C_6H_{15}ON_2Cl$ requires N, 16·8%).

The amino-amide (12 g.) in dried ethyl acetate (200 c.c.) was treated with carbon disulphide (8 g.); after 1 hour at 0°, the precipitated dithiocarbamate salt (14 g., 90%) was collected, dried in a vacuum, and dissolved in water (300 c.c.) at 0°. Acidification with concentrated hydrochloric acid (25 c.c.) gave 4-n-*butyl*-2-*thio*-5-*thiazolidone* (6·8 g., 86%), m. p. 65°; on sublimation in high vacuum a trace of colouring matter was removed, and subsequent crystallisation from *cyclo*hexane gave colourless hexagonal prisms, m. p. 73—74° (Found: N, 7·4. $C_7H_{11}ONS_2$ requires N, 7·4%).

4-*Carbamyl*-2-*thio*-5-*thiazolidone*.—Aminomalonic ester was prepared from ethyl malonate according to Bentley (Ph.D. Thesis, London, 1945; cf. Cerchez, *Bull. Soc. chim.*, 1930, **47**, 1287) and converted by treatment with aqueous ammonia into the diamide (Piloty and Neresheimer, *Ber.*, 1906, **39**, 514). For conversion into the thiothiazolidone two methods were used. (*a*) Aminomalonamide (5·9 g.), 2N-sodium carbonate (25 c.c., 1 equiv.), and carbon disulphide (5 c.c.) were shaken together at room temperature until all the amide was dissolved (3 days). On acidification with hydrochloric acid, hydrogen sulphide was evolved, and 4-*carbamyl*-2-*thio*-5-*thiazolidone* (1·5 g., 17%) was precipitated as a pale yellow, microcrystalline powder, which gave colourless needles, m. p. 190° (decomp.), after several recrystallisations from acetic acid, although prolonged boiling caused decomposition (Found: C, 27·7; H, 2·55; N, 15·8. $C_4H_4O_2N_2S_2$ requires C, 27·3; H, 2·3; N, 15·9%). The thiothiazolidone was sparingly soluble in the cold in methanol, ethanol, and acetic acid, and insoluble in other common organic solvents and in water. With ferric chloride in aqueous ethanol it gave an intense indigo-blue colour, becoming purple on dilution. When dissolved in hot water, it lost carbon disulphide and carbon dioxide with effervescence, leaving a solution of glycine amide (the presence also of glycine was shown by paper chromatography). (*b*) Aminomalonamide (5 g.) was powdered finely and suspended in pyridine under reflux. Carbon disulphide (10 c.c.) was added cautiously, and refluxing was continued for 5 minutes (longer heating caused loss of hydrogen sulphide, with formation of a water-insoluble, sulphur-containing product, not further examined). On cooling, the colourless crystalline dithiocarbamate salt (3·6 g.) separated, and a further quantity remained on evaporation of the pyridine mother-liquor in a vacuum. The combined crops were dissolved in water (25 c.c.) at 0°, and acidified with ice-cold concentrated hydrochloric acid (10 c.c.) to yield the colourless crystalline thiothiazolidone (3·4 g.; 90% from aminomalonamide), m. p. 189° (decomp.).

Action of Bases on 4-*Carbamyl*-2-*thio*-5-*thiazolidone*.—Compounds with bases were readily produced by addition of the base (1—2 mols.) to the thiothiazolidone (saturated solution) in methanol, followed by dilution with ether. They formed colourless prisms, m. p. (aniline) 128—129° (decomp.), (benzylamine) 138—139° (decomp.), (morpholine) 181° (decomp.). The last *compound* crystallised from methanol in colourless rectangular tablets, m. p. 181° (Found: C, 37·0; H, 4·7; N, 15·9. $C_4H_4O_2N_2S_2,C_4H_9ON$ requires C, 36·5; H, 5·0; N, 15·95%). All the compounds were readily soluble in water, acidification yielding a crystalline precipitate, m. p. 190° (decomp.) undepressed on admixture with the thiothiazolidone. They also gave the same intense blue colour with ferric chloride as the parent compound.

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