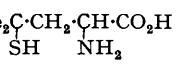
320. *Syntheses of Some Amino-acids, including Methionine.*

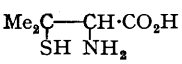
By J. R. Catch, A. H. Cook, A. R. Graham, and Sir Ian Heilbron.

Methyl-, ethyl-, and benzyl-thiol readily combined with acraldehyde in presence of organic bases to give β-methyl-, -ethyl-, and -benzyl-thiopropaldehydes, which were satisfactorily converted by the Strecker reaction into methionine, ethionine, and *S*-benzylhomocysteine respectively. Similar reactions employing benzylthiol with crotonaldehyde or β-methylcrotonaldehyde led to the corresponding α-amino-γ-benzylthio-acids of which the second was debenzylated to α-amino-γ-mercapto-γ-methyl-*n*-valeric acid. In accordance with this formulation, the acid did not behave like a substituted cysteine but gave thiazans (*i.e.*, 6-membered ring compounds) by condensation with carbonyl compounds. Some of the above amino-acids were also obtained by indirect hydrolysis of the corresponding nitriles *via* heterocyclic intermediates.

This work was carried out in connection with the synthesis of α-amino-γ-mercapto-γ-methyl-*n*-valeric acid (I). This acid is of interest in view of its relationship to penicillamine (II), a degradation product of the various naturally occurring penicillins, and therefore presents the possibility of obtaining analogues of the natural antibiotics.



(I.)



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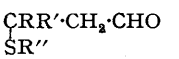


(III.)

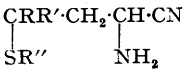
Compounds which might have provided the closest models for the synthesis of (I) were methionine and homocysteine. However the syntheses of these acids which have hitherto been considered most practicable would require, when applied to (I), intermediates of doubtful accessibility. An obvious route to methionine, the Strecker reaction applied to β-methylthiopropaldehyde (III; R, R′ = H; R″ = Me), has been explored by Barger and Coyne (*Biochem. J.*, 1928, **22**, 1420) and rejected as a useful method because of poor yields. Despite this circumstance it seemed worth while exploring the possibilities of working with the analogue (III; R, R′ = Me; R″ = H or other group).

The aldehyde (III; R, R′ = H; R″ = Me) has previously been obtained (Barger and Coyne, *loc. cit.*) from β-chloropropaldehyde diethylacetal *via* the β-methylthioacetal, but direct addition of thioacetic acid or thiols to αβ-unsaturated aldehydes offered an improved route. Kaneko and Mii (*J. Chem. Soc. Japan*, 1938, **59**, 1382; *C.A.*, 1939, **33**, 2106), and Rothstein (*J.*, 1940, 1560) have described the addition of methyl- and ethyl-thiol respectively to acraldehyde, but the conditions employed by the first-mentioned authors are obscure and the yield recorded for the second addition is poor. It has now been found that thioacetic acid readily adds to acraldehyde, crotonaldehyde, and β-methylcrotonaldehyde to give satisfactory yields of β-*acetylthio-propaldehyde*, -n-*butaldehyde*, and -iso*valeraldehyde* (III; R, R′ = H; R = H, R′ = Me; R, R′ = Me respectively, R″ = Ac); these formulations are based on analogy with additions of thiols (see below) where there can be no doubt of the direction of addition. Meanwhile, similar reactions with thiols were found to proceed equally readily, and closer attention was paid to them in view of the greater probability of cleaner transformations at later stages.

Methyl- and ethyl-thiols were found to react quickly with acraldehyde at 0° in presence of a catalytic quantity of a strong base such as triethylamine to give β-methylthio- and β-ethylthio-propaldehyde (III; R, R′ = H; R″ = Me, Et, respectively) in good yield. In similar fashion benzylthiol and the appropriate αβ-unsaturated aldehyde afforded β-*benzylthio-propaldehyde*, -n-*butaldehyde*, and -iso*valeraldehyde* (III; R, R′ = H; R = H, R′ = Me; R, R′ = Me respectively, R″ = CH_2Ph). All these aldehydes were characterised as their *dinitrophenylhydrazones*.

β-Methylthiopropaldehyde was converted by anhydrous hydrogen cyanide followed by ammonia into α-amino-γ-methylthio-*n*-butyronitrile (IV) (R, R′ = H, R″ = Me) which was more conveniently isolated as its *oxalate* than as its hydrochloride. In the same way the homologous nitrile (IV; R, R′ = H, R″ = Et) was obtained, also as its *oxalate*, and the

above-mentioned benzylthioaldehydes were similarly converted into the nitriles (IV; R″ = CH_2Ph; R, R′ = H; R = H, R′ = Me; R, R′ = Me), isolated as their *hydrochlorides*.



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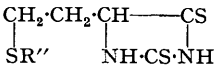

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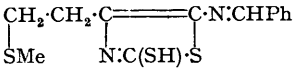
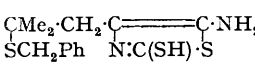


(VI.)

Facile hydrolysis of certain α-amino-nitriles has been effected (Cook, Heilbron, and Levy, in the press) by first allowing them to react with carbon disulphide and refluxing the resulting 5-amino-2-mercaptothiazoles with dilute mineral acids, and the behaviour of some of the present α-amino-nitriles under these conditions was therefore investigated. α-Amino-γ-methylthio-*n*-butyronitrile and carbon disulphide gave 5-β-*methylthioethyldithiohydantoin* (V) (R″ = Me) directly, though the anticipated 5-amino-2-mercapto-4-β-methylthioethylthiazole could be obtained as its *benzylidene* derivative (VI) by carrying out the condensation in presence of benzaldehyde (Cook, Heilbron, and Levy, *loc. cit.*). The nitrile (IV; R, R′ = H; R″ = Et) similarly afforded 5-*ethylthioethyldithiohydantoin* (V; R″ = Et). Hydrolysis of (V; R″ = Me) and of (VI) yielded methionine as was anticipated, but in these instances there was no advantage in proceeding *via* the heterocyclic compounds for methionine could be obtained in satisfactory yield by direct hydrolysis of the appropriate nitrile with boiling hydrochloric acid. It is noteworthy that by the steps outlined above methionine was obtained from acraldehyde in an overall yield of 29%, the process thus appearing much superior to earlier preparations. Ethionine was obtained similarly in equally satisfactory yield.

Two of the above α-aminobenzylthio-nitriles (IV; R″ = CH_2Ph; R = H, R′ = H or Me) were hydrolysed similarly without difficulty to give *s*-benzylhomocysteine and α-*amino*-γ-*benzylthio*-n-*valeric acid* respectively. The third α-aminobenzylthio-nitrile (IV) (R″ = CH_2Ph; R, R′ = Me) was however converted into the corresponding α-amino-acid only in poor yield by direct hydrolysis. It was fortunate that in this case reaction with carbon disulphide under selected conditions gave not a dithiohydantoin but 5-*amino*-2-*mercapto*-4-β-*benzylthio*isobutyl-*thiazole* (VII). Unlike the previous dithiohydantoins, compound (VII) was not only pseudoacidic but was also basic and condensed easily with glyoxal in the characteristic manner of 5-amino-



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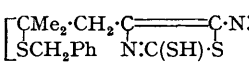
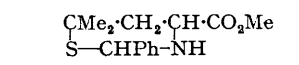


(VIII.)



(IX.)

2-mercaptothiazoles to give the *bisazomethine* derivative (VIII). The thiazole (VII) could be hydrolysed without difficulty and thus satisfactorily afforded α-*amino*-γ-*benzylthio*-γ-*methyl*-n-*valeric acid*. The benzyl group was removed from the latter compound by means of sodium in liquid ammonia to give α-*amino*-γ-*thiol*-γ-*methyl*-n-*valeric acid* (I).

The direction of addition of methyl- and ethyl-thiol to acraldehyde is clear from the eventual emergence of methionine and ethionine. That similar additions of benzylthiol take place in a comparable direction to that postulated above seems certain in that the amino-acid formulated as (I) failed to give the indigo-blue colour with ferric chloride which is characteristic of α-amino-β-thiol-acids such as cysteine and its homologues. The acid (I) still however condensed easily with carbonyl compounds, for example giving with benzaldehyde 4-*carbomethoxy*-6 : 6-*dimethyl*-2-*phenylthiazan* (IX) by simultaneous esterification.

It was at first thought that the amine corresponding to the amino-acid (I) might be more easily accessible and worthy of study. To this end β-benzylthio-*n*-butaldehyde and -β-methyl-*n*-butaldehyde were converted into their oximes which were reduced to γ-*benzylthio*-n-*butylamine* and -γ-*methyl*-n-*butylamine*. The preparation of the acid (I) however made the debenzylation of these amines less important and the pursuit of this part of the project was discontinued.

Experimental.

Acraldehyde (5·6 g.; 6·7 c.c.) was cooled in ice, and thioacetic acid (7·6 g., 7·1 c.c.) was added. A brisk reaction took place and the product, after standing overnight, was distilled under reduced pressure. β-*Acetylthiopropaldehyde*, b. p. 92—93°/14 mm., $n_D^{18°}$ 1·4943, was obtained as a colourless liquid (68%) (Found : C, 45·9; H, 6·4; S, 23·0. $C_5H_8O_2S$ requires C, 45·4; H, 6·1; S, 24·2%). The *dinitrophenylhydrazone* recrystallised from ethanol in yellow needles, m. p. 127·5° (Found : C, 42·5; H, 4·2. $C_{11}H_{12}O_5N_4S$ requires C, 42·3; H, 3·9%). Crotonaldehyde (21 g.) and thioacetic acid (22·5 g.) reacted as above. β-*Acetylthio*-n-*butaldehyde* had b. p. 91—92°/11 mm., $n_D^{14°}$ 1·4882 (65%) (Found : C, 49·8; H, 7·2. $C_6H_{10}O_2S$ requires C, 49·3; H, 6·9%). The *dinitrophenylhydrazone* crystallised from ethanol in yellow hexagonal plates, m. p. 96° (Found : C, 44·4; H, 4·4. $C_{12}H_{14}O_5N_4S$ requires C, 44·2; H, 4·3%).

β-Methylcrotonaldehyde (8 g.) and thioacetic acid (8 g.) similarly gave β-acetylthio-β-methyl-*n*-butaldehyde, b. p. 110°/20 mm., $n_D^{20°}$ 1·4922 (33%). The *dinitrophenylhydrazone* crystallised from ethanol in yellow rhombic plates, m. p. 94° (Found : C, 45·6; H, 4·6. $C_{13}H_{16}O_5N_4S$ requires C, 45·9; H, 4·7%).

Methylthiol, generated from *S*-methyl*iso*thiourea sulphate (60 g.) and 5N-sodium hydroxide (100 c.c.) (*Org. Synth.*, Coll. Vol. II, 345), was passed in a slow stream of coal gas into acraldehyde (20 g.) containing triethylamine (2 drops) and cooled to 0°. The mixture was distilled and the fraction, b. p. 165—175°, collected (32 g.; 86%). Redistillation gave β-methylthiopropaldehyde, b. p. 166°/750 mm. (Barger and Coyne, *Biochem. J.*, 1928, **22**, 1420, give b. p. 60°/12 mm.), $n_D^{20°}$ 1·4824 (Found : C, 46·0; H, 7·5; S, 30·3. Calc. for C_4H_8OS : C, 46·1; H, 7·8; S, 30·8%). The *dinitrophenylhydrazone* crystallised from ethanol in yellowish-orange needles, m. p. 122—123° (Found : C, 42·5; H, 4·4. $C_{10}H_{12}O_4N_4S$ requires C, 42·2; H, 4·3%). Ethylthiol (12 g.) was added dropwise with stirring to a mixture of acraldehyde (10 g.) and triethylamine (5 drops) cooled to 0°. Distillation of the product gave β-ethylthiopropaldehyde, b. p. 180—190° (62%) which, on redistillation, had b. p. 185°/760 mm. (Rothstein, *J.*, 1940, 1560, gives b. p. 60°/10 mm.), $n_D^{20°}$ 1·4788 (Found : C, 50·4; H, 8·2; S, 27·4. Calc. for $C_5H_{10}OS$: C, 50·8; H, 8·5; S, 27·1%). The *dinitrophenylhydrazone* crystallised from 90% aqueous ethanol, in orange-red laths, m. p. 100° (Found : C, 44·6; H, 4·6; N, 18·4. $C_{11}H_{14}O_4N_4S$ requires C, 44·3; H, 4·7; N, 18·4%).

To acraldehyde (5·6 g.; 6·7 c.c.) cooled in ice, benzylthiol (12·4 g.) was added, followed by a droplet of piperidine. Heat was evolved. After 15 minutes at 0° and 1 hour at room temperature, ether was added and the solution washed with dilute hydrochloric acid and water, dried, evaporated, and distilled. *β-Benzylthiopropaldehyde* was obtained as a colourless oil, b. p. 158°/12 mm., $n_D^{15°}$ 1·5650 (15 g.; 83%) (Found : C, 66·65; H, 6·90; S, 18·0. $C_{10}H_{12}OS$ requires C, 66·65; H, 6·90; S, 17·8%). The *dinitrophenylhydrazone* crystallised from ethanol in yellow needles, m. p. 112·5° (Found : C, 53·5; H, 4·7. $C_{16}H_{16}O_4N_4S$ requires C, 53·3; H, 4·5%). Crotonaldehyde (28 g.; 32·8 c.c.) and benzylthiol (50 c.c.) were mixed at 0°, a droplet of piperidine was added, and the mixture was kept at room temperature for 3 hours and heated on the steam-bath for 1 hour. The product was isolated as above. *β-Benzylthio*-n-*butaldehyde* (68 g.; 87%) had b. p. 156—157°/10 mm., $n_D^{20°}$ 1·5523 (Found : C, 68·2; H, 7·4; S, 16·9. $C_{11}H_{14}OS$ requires C, 68·0; H, 7·3; S, 16·5%). The *dinitrophenylhydrazone* crystallised from ethanol in small yellow leaflets, m. p. 69° (Found : C, 54·2; H, 4·9. $C_{17}H_{18}O_4N_4S$ requires C, 54·5; H, 4·8%).

Benzylthiol (7·5 c.c.) containing piperidine (5 drops) was added to freshly prepared β-methylcrotonaldehyde (5 g.) and the mixture heated on the steam-bath for 3 hours. *β-Benzylthioisovaleraldehyde* was isolated as above (7 g.; 56%), b. p. 109—110°/0·1 mm., 172°/15 mm., $n_D^{15°}$ 1·5484 (Found : C, 69·2; H, 7·6; S, 15·9. $C_{12}H_{16}OS$ requires C, 69·2; H, 7·7; S, 15·4%). The *dinitrophenylhydrazone* crystallised from ethanol in needles, m. p. 113° (Found : C, 55·7; H, 5·1. $C_{18}H_{20}O_4N_4S$ requires C, 55·6; H, 5·2%).

A mixture of β-benzylthiopropaldehyde (1·12 g.) and hydrogen cyanide (1 c.c.) at 0° was treated with a droplet of piperidine. After 0·5 hour at room temperature a small excess of ethereal hydrogen chloride was added and the excess of hydrogen cyanide removed under reduced pressure. After addition of 10% alcoholic ammonia (3 c.c.), the solution was sealed, left overnight, heated at 100° for 0·5 hour, concentrated under reduced pressure, taken up in ether, and filtered. Addition of ethereal hydrogen chloride precipitated an oil which readily crystallised (820 mg.; 55%). Recrystallisation from ethanol–ether gave *α-amino-γ-benzylthio*-n-*butyronitrile hydrochloride* in rosettes of hair-like needles, m. p. 134—135° (Found : C, 54·45; H, 6·4. $C_{11}H_{15}N_2ClS$ requires C, 54·4; H, 6·2%). β-Benzylthio-*n*-butaldehyde (10 g.), hydrogen cyanide (10 c.c.), and potassium cyanide (100 mg.) were mixed. A violent reaction ensued and the mixture was then treated as above with 10% alcoholic ammonia (5 c.c.) and left overnight. *α-Amino-γ-benzylthio*-n-*valeronitrile hydrochloride* crystallised (9 g.; 68%) and after recrystallisation from ethanol–ether formed slender needles, m. p. 159° (decomp.) (Found : C, 55·7; H, 6·7; N, 11·0; S, 12·5. $C_{12}H_{17}N_2ClS$ requires C, 56·1; H, 6·7; N, 10·9; S, 12·5%). β-Benzylthio*iso*-valeraldehyde (2·9 g.) and hydrogen cyanide (1 c.c.) were treated as above. *α-Amino-γ-benzylthio-γ-methyl*-n-*valeronitrile hydrochloride* recrystallised from ethanol–ether in triangular plates, m. p. 156—157° (1·0 g.; 27%) (Found : C, 57·4; H, 7·3; N, 9·9. $C_{13}H_{19}N_2ClS$ requires C, 57·6; H, 7·1; N, 10·35%).

β-Benzylthio-*n*-butaldehyde (15 g.), potassium acetate (15 g.), hydroxylamine hydrochloride (5·5 g.), and ethanol (100 c.c.) were refluxed for 30 minutes, left over-night, and the oxime precipitated by adding water. A portion of the oily oxime (5 g.) in moist ether (150 c.c.) was reduced by refluxing with amalgamated aluminium (4 g.) overnight. The solution was filtered and the alumina washed with further ether. The filtrate was washed, dried, concentrated, and distilled. The fraction, b. p. 85—95°/0·1 mm., was redistilled to give *γ-benzylthio*-n-*butylamine* as a colourless oil (2 g.), b. p. 90—92°/0·1 mm., $n_D^{20°}$ 1·5545 (Found : C, 67·3; H, 9·0; N, 7·2. $C_{11}H_{17}NS$ requires C, 67·6; H, 8·8; N, 7·2%). The *hydrochloride*, prepared with ethereal hydrogen chloride, recrystallised from ethanol–ether in rhombic plates, m. p. 123° (Found : C, 57·1; H, 7·9; N, 6·4. $C_{11}H_{18}NClS$ requires C, 57·0; H, 7·9; N, 6·0%).

β-Benzylthio-β-methyl-*n*-butaldehyde (5 g.), potassium acetate (5 g.), hydroxylamine hydrochloride (2 g.), and ethanol (40 c.c.) were treated as before and the product reduced with aluminium amalgam (4 g.). The fraction, b. p. 160—165°/15 mm., was redistilled to give *γ-benzylthio-γ-methyl*-n-*butylamine* as a colourless oil (25%), b. p. 102—104°/0·1 mm., $n_D^{20°}$ 1·5521 (Found : C, 69·0; H, 8·7; N, 6·1. $C_{12}H_{19}NS$ requires C, 68·8; H, 9·2; N, 6·7). The *hydrochloride* recrystallised from ethanol–ether, m. p. 157° (Found : C, 58·7; H, 8·0; N, 5·8. $C_{12}H_{20}NClS$ requires C, 58·6; H, 8·2; N, 5·7%).

β-Methylthiopropaldehyde (6·3 g.), anhydrous hydrogen cyanide (5 c.c.), and potassium cyanide (100 mg.) were mixed; a vigorous reaction took place. The excess of hydrogen cyanide was removed under reduced pressure and the residue sealed up with 10% ethanolic ammonia (40 c.c.), heated to 80° for two hours, and left overnight. Ethanol and ammonia were removed under reduced pressure, water and chloroform were added, and the basic fraction was isolated in the chloroform. After removal of the solvent, the residue was taken up in ethanol and ethanolic anhydrous oxalic acid was added. A white solid was precipitated (6·9 g.; 65%). Recrystallisation from ethanol gave *α-amino-γ-methylthio*-n-*butyronitrile oxalate* in colourless laths, m. p. 200° (decomp.) (Found : C, 41·3; N, 6·5; N, 15·3. $C_5H_{10}N_2S,\frac{1}{2}C_2H_2O_4$ requires C, 41·1; H, 6·3; N, 16·0%). β-Ethylthiopropaldehyde (10 g.), hydrogen cyanide (10 c.c.), and potassium cyanide (*ca.* 100 mg.) were treated as above. *α-Amino-γ-ethylthio-*

n-*butyronitrile oxalate* recrystallised from ethanol in colourless laths, m. p. 230° (decomp.) (3·5 g.) (Found : C, 42·2; H, 7·1; N, 14·5. $C_6H_{12}N_2S,\frac{1}{2}C_2H_2O_4,\frac{1}{2}H_2O$ requires C, 42·4; H, 7·1; N, 14·1%).

α-Amino-γ-methylthio-*n*-butyronitrile, from the oxalate (2·5 g.), was refluxed with concentrated hydrochloric acid (10 c.c.) for 1½ hours. The solution was evaporated to dryness under reduced pressure, basified with concentrated aqueous ammonia, and re-evaporated. The residue was dissolved in warm water (20 c.c.), charcoaled, and diluted with ethanol (50 c.c.). Methionine crystallised in glistening plates (1·1 g., 52%), and after recrystallisation from water–ethanol had m. p. 276° (decomp.) (Found : C, 40·3; H, 7·5; N, 9·4. Calc. for $C_5H_{11}O_2NS$: C, 40·3; H, 7·4; N, 9·4%). α-Amino-γ-ethylthio-*n*-butyronitrile oxalate (1 g.) was refluxed with concentrated hydrochloric acid (5 c.c.) for 2 hours and evaporated to dryness under reduced pressure. The residue was basified with concentrated aqueous ammonia, re-evaporated, dissolved in the minimum quantity of boiling water, and left to crystallise. Ethionine crystallised (400 mg., 46%), and recrystallised from water–ethanol in colourless plates, m. p. 265° (decomp.) (Found : C, 44·4; H, 8·1; N, 8·9. Calc. for $C_6H_{13}O_2NS$: C, 44·2; H, 8·0; N, 8·6%).

α-Amino-γ-methylthio-*n*-butyronitrile oxalate (1 g.) was converted into the free base and extracted into chloroform. The solution was concentrated and the residue refluxed in 50% ethanolic carbon disulphide (5 c.c.) for 2 hours. Concentration of the solution and addition of ether left a yellow solid (47%). Recrystallisation from acetone–water gave 5-*β-methylthioethyldithiohydantoin* in sheaves of yellow hair-like needles, m. p. 212° (decomp.) (Found : C, 34·3; H, 4·4; N, 13·8; S, 47·8. $C_6H_{10}N_2S_3$ requires C, 34·9; H, 4·9; N, 13·6; S, 46·5%). The compound was soluble in aqueous sodium hydroxide, but the resulting solution failed to give a coloration with aqueous glyoxal. Repetition of the above reaction in the presence of benzaldehyde (0·5 c.c.) gave 5-*benzylideneamino-2-mercapto-4-β-methylthioethylthiazole* (95 mg.) which recrystallised from ethanol in yellow needles, m. p. 200° (decomp.) (Found : C, 53·2; H, 5·0; N, 9·8. $C_{13}H_{14}N_2S_3$ requires C, 53·0; H, 4·8; N, 9·5%). It gave a red coloration on warming with alkali and glyoxal. α-Amino-γ-ethylthio-*n*-butyronitrile, from the oxalate (1 g.), was refluxed with 50% ethanolic carbon disulphide (5 c.c.) and treated as above. 5-*β-Ethylthioethyldithiohydantoin* (40%) recrystallised from ethanol in fine yellow hairs, m. p. 196—197° (decomp.) (Found : C, 37·2; H, 5·2; N, 12·4. $C_7H_{12}N_2S_3$ requires C, 38·2; H, 5·5; N, 12·7%).

5-β-Methylthioethyldithiohydantoin (430 mg.) was refluxed with a 1 : 1 mixture of acetic and concentrated hydrochloric acids (10 c.c.) for two hours and the solution was concentrated under reduced pressure. The solution was made alkaline with ammonia and again evaporated under reduced pressure, taken up in water (5 c.c.), filtered, and diluted with ethanol (15 c.c.). Methionine separated in glistening plates, m. p. 270° (decomp.) (75 mg., 25%), on standing overnight. A similar hydrolysis of 5-benzylideneamino-2-mercapto-4-β-methylthioethylthiazole (190 mg.) gave methionine in plates, m. p. 271° (decomp.) (25 mg.; 25%).

α-Amino-γ-benzylthio-*n*-butyronitrile hydrochloride (860 mg.) and 47% aqueous hydrobromic acid (17·5 c.c.) were heated to 100° for 3½ hours with frequent shaking, and the solution evaporated under reduced pressure. The residue was taken up in water, charcoaled, and neutralised with 2N-ammonia. A flocculent precipitate of *S*-benzylhomocysteine (α-amino-γ-benzylthio-*n*-butyric acid) was obtained (450 mg.; 60%), m. p. 190—191°. The m. p. was undepressed on admixture with authentic material. α-Amino-γ-benzylthio-*n*-valeronitrile hydrochloride (257 mg.) and concentrated hydrochloric acid (3 c.c.) were heated in a sealed tube at 100° for 16 hours. The product was worked up as above. *α-Amino-γ-benzylthio*-n-*valeric acid* (110 mg.) recrystallised from 50% methanol in small plates, m. p. 215—216° (decomp.) (Found : C, 60·0; H, 7·4; N, 5·5. $C_{12}H_{17}O_2NS$ requires C, 60·2; H, 7·15; N, 5·9%). α-Amino-γ-benzylthio-γ-methyl-*n*-valeronitrile hydrochloride (3·8 g.) was added to aqueous sodium hydrogen carbonate, the free base was extracted into ether, the extract was dried and then concentrated under reduced pressure, and the residual oil was refluxed with 50% ethanol–carbon disulphide (20 c.c.) for 3 hours. After concentration under reduced pressure, the solid was filtered off and washed with a little cold ethanol. Further product was obtained by treating the mother liquors with ether (3·1 g.; 70%). *5-Amino-2-mercapto-4-β-benzylthio*isobutylthiazole recrystallised from ethanol–water in pale yellow rhombic plates, m. p. 237° (Found : C, 53·9; H, 5·5; N, 9·2; S, 30·5. $C_{14}H_{18}N_2S_3$ requires C, 54·2; H, 5·8; N, 9·0; S, 31·0%). Addition of 50% aqueous glyoxal to a solution of the thiazole in 2N-sodium hydroxide gave a red coloration, and after acidification, the *bisazomethine* derivative was precipitated; it recrystallised from pyridine–water in fine red hairs, m. p. 238° [Found : C, 56·3; H, 5·6; N, 9·0. $(C_{15}H_{17}N_2S_3)_2$ requires C, 56·1; H, 5·4; N, 8·7%]. The thiazole (5 g.) was refluxed in 50% acetic acid–concentrated hydrochloric acid (40 c.c.) for 2 hours, the solution concentrated under reduced pressure, and the residue taken up in water, filtered, and neutralised with 2N-ammonia. *α-Amino-γ-benzylthio-γ-methyl*-n-*valeric acid* separated as a flocculent buff precipitate which recrystallised from hot water in colourless plates, m. p. 178° (2·4 g.; 59%) (Found : C, 61·2; H, 7·4; N, 5·6. $C_{13}H_{19}O_2NS$ requires C, 61·6; H, 7·6; N, 5·5%). The product gave a strong ninhydrin reaction.

The preceding *S*-benzyl compound (2·4 g.) in liquid ammonia (40 c.c.) was stirred and reduced with sodium (*ca.* 0·6 g.) added in small pieces until a permanent blue colour was obtained. Ammonium chloride (2 g.) was added and the solution evaporated to dryness and evacuated on a water pump to remove remaining traces of ammonia. Ethereal hydrogen chloride was added, the solution was filtered, and the residue thoroughly extracted with ethanol. The extract was concentrated under reduced pressure, the residue extracted with chloroform, and the extract reconcentrated. The residual oil solidified under dry ether (1·4 g.; 73%). Recrystallisation from ethanol–ether gave micro-prisms of *α-amino-γ-mercapto-γ-methyl*-n-*valeric acid*, m. p. 219° (decomp.) (Found : C, 39·4; H, 6·8; N, 7·3; Cl, 18·4; S, 16·6. $C_6H_{14}O_2NClS$ requires C, 36·07; H, 7·0; N, 7·0; Cl, 17·8; S, 16·0%). The product gave a strong transient purple colour with alkaline nitroprusside, a weak red-brown ferric chloride colour after addition of aqueous sodium hydrogen carbonate, and a deep red-brown coloration with ninhydrin reagent.

α-Amino-γ-benzylthio-γ-methyl-*n*-valeronitrile (1 g.) was refluxed with 50% acetic acid–concentrated hydrochloric acid (10 c.c.) for 2 hours. The solution was concentrated under reduced pressure, and the residue dissolved in water, filtered, and neutralised with 2N-ammonia. The crystalline solid which separated was α-amino-γ-benzylthio-γ-methyl-*n*-valeric acid, m. p. 175° (110 mg. or 12%).

α-Amino-γ-mercapto-γ-methyl-*n*-valeric acid as its hydrochloride (250 mg.), benzaldehyde (1 c.c.), and methanolic hydrogen chloride (2 c.c.) were heated on the steam-bath for 15 minutes, cooled, and the product was extracted with ether. The residual solid was dissolved in water and the solution neutralised with 2N-ammonia. The oil which separated crystallised on scratching and was recrystallised from aqueous ethanol to give needles of *4-carbomethoxy-2-phenyl-6 : 6-dimethylthiazan*, m. p. 105° (Found : C, 63·4; H, 7·2; N, 5·3. $C_{14}H_{19}O_2NS$ requires C, 63·35; H, 7·2; N, 5·3%).

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