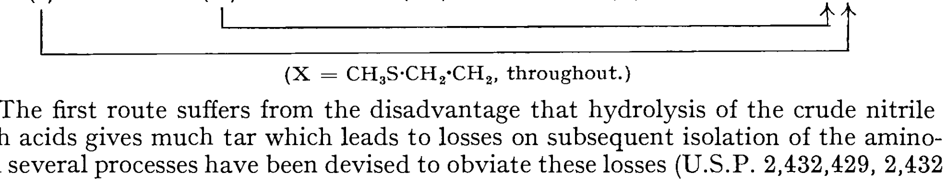
654. *Experiments in the Synthesis of Methionine.*

By D. O. Holland and J. H. C. Nayler.

The synthesis of methionine from β-methylthiopropaldehyde *via* α-amino-γ-methylthiobutyronitrile and *via* 5-2′-methylthioethylhydantoin has been examined, and the action of carbon dioxide on α-amino-γ-methylthiobutyronitrile studied.

Several satisfactory syntheses of DL-methionine from β-methylthiopropaldehyde (I) have recently been reported although the original attempts by Barger and Coyne (*Biochem. J.*, 1928, **22**, 1417) to use (I) in the Zelinsky modification of the Strecker reaction resulted in an overall yield of only 6%. Syntheses *via* the amino-nitrile (III) have been described by Catch, Cook, Graham, and Heilbron (*Nature*, 1947, **159**, 578; *J.*, 1947, 1609), Pierson, Giella, and Tishler (*J. Amer. Chem. Soc.*, 1948, **70**, 1450), and in U.S.PP. 2,485,236, 2,564,105, and B.P. 605,311; Gaudry and Nadeau (*Canadian J. Res.*, 1948, **26**, *B*, 226) and Pierson *et al.* (*loc. cit.*; cf. also B.P. 630,139) have used the Bucherer–Bergs method, *via* the hydantoin (IV).



(X = $CH_3S{\cdot}CH_2{\cdot}CH_2$, throughout.)

The first route suffers from the disadvantage that hydrolysis of the crude nitrile (III) with acids gives much tar which leads to losses on subsequent isolation of the amino-acid, and several processes have been devised to obviate these losses (U.S.P. 2,432,429, 2,432,478, 2,443,391, 2,504,425). The intermediate amino-nitrile was purified as its oxalate (Catch *et al., loc. cit.*), the hydrochloride being unsatisfactory (Barger and Coyne, *loc. cit.*). On hydrolysis with hydrochloric acid, however, only a 52% yield of methionine was obtained.

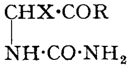
We have found the normal sulphate and the dihydrogen phosphate to be very suitable salts for the purification of the amino-nitrile, since they are formed in good yield and purity from ethyl alcohol. Subsequent acid hydrolysis did not produce tar, and methionine was readily isolated in a high state of purity and in very good yield. The precipitation of the sulphate also proved of value in assessing yields of the amino-nitrile.

Most previous workers have prepared the amino-nitrile (III) by reaction of the cyanohydrin (II) with ammonia. The only attempt to use the reaction of the aldehyde (I) with potassium cyanide and ammonium chloride in aqueous solution was by Barger and Coyne (*loc. cit.*) with very unsatisfactory results. We have found, however, that the latter method is entirely satisfactory if the reaction mixture is saturated with ammonia, the yield of amino-nitrile being about 90%. Subsequent acid hydrolysis gave methionine in 65% overall yield from the aldehyde. When ammonia was omitted the yield of amino-nitrile was only 14%.

These results parallel those of Gaudry (*Canadian J. Res.*, 1946, **24**, *B*, 301), who found that inclusion of ammonia in the Strecker reaction gave improved yields of α-amino*iso*valeronitrile from *iso*butaldehyde, and concluded that the reaction between the initial aldehyde or intermediate cyanohydrin and ammonia was an equilibrium, the presence of an excess of ammonia favouring amino-nitrile formation. It seems more probable, however, that the beneficial effect of the ammonia was to minimise the formation of the corresponding imino-dinitrile. The main product from the reaction of β-methylthiopropaldehyde with ammonium chloride and sodium cyanide, although insoluble in dilute hydrochloric acid, evidently contained only a little of the cyanohydrin (II) since it gave only a very small quantity of α-hydroxy-γ-methylthiobutyric acid on hydrolysis : it contained only a trace of unreacted aldehyde. Since the hydrochlorides of imino-dinitriles are known to be hydrolysed by water (Pinner and Lifschutz, *Ber.*, 1887, **20**, 2356) it appears likely that the bulk of the product was the dinitrile di-(1-cyano-3-methylthiopropyl)amine.

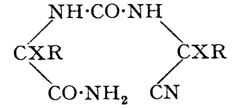
In the synthesis of methionine from β-methylthiopropaldehyde *via* 5-2′-methylthioethylhydantoin (IV) we obtained results similar to those recorded by Pierson *et al.* (*loc. cit.*), although reduction of the amount of sodium cyanide from 2·2 to 1·1 moles gave rather better yields. We could not confirm the presence of the hydantoic acid (VI; R = OH) reported by Pierson *et al.*, but isolated a small quantity of the corresponding amide (VI; R = NH_2), m. p. 173·5—174·5° (decomp.). Hill and Robson (*Biochem. J.*, 1936, **30**, 248) gave the m. p. of the acid (VI; R = OH) as 171—172°, but we find that this compound melts with decomposition at 138—139°.

Hydrolysis of 5-2′-methylthioethylhydantoin to methionine was effected in good yield by heating it under pressure with an aqueous suspension of lime. Contrary to the statement in U.S.P. 2,527,366, the product was practically as pure as that obtained when baryta was employed. Hydrolysis with lime under reflux, however, was very slow and even after 48 hours some of the acid (VI; R = OH) could be isolated.

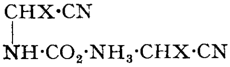


$$\begin{array}{l}\mathrm{CHX{\cdot}COR}\\ |\\ \mathrm{NH{\cdot}CO{\cdot}NH_2}\end{array}$$

(VI)



(VII)



$$\begin{array}{l}\mathrm{CHX{\cdot}CN}\\ |\\ \mathrm{NH{\cdot}CO_2{\cdot}NH_3{\cdot}CHX{\cdot}CN}\end{array}$$

(VIII)

$CO(NH{\cdot}CHX{\cdot}CO{\cdot}NH_2)_2$

(IX)

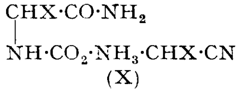
Bucherer and Steiner (*J. pr. Chem.*, 1934, **140**, 291) reported that when carbon dioxide was passed into an aqueous solution of α-amino*iso*butyronitrile or α-amino-α-methylbutyronitrile at room temperature the corresponding hydantoins separated rapidly in practically quantitative yield. When this reaction was applied to α-amino-γ-methylthiobutyronitrile, a solid, m. p. 161°, separated very slowly which was formulated as *N*-(1-carbamido-3-methylthiopropyl)-*N*′-(1-cyano-3-methylthiopropyl)urea (VII; R = H). Compounds possessing this suggested structure were obtained by Bucherer and Steiner when the amino-nitriles mentioned above were allowed to react with carbon dioxide in the absence of water (VII; X = R = Me and X = Et, R = Me, respectively), and Cook, Heilbron, and Levy (*J.*, 1947, 1598) have described the formation of a similar compound (VII; X = Ph, R = H) from α-aminobenzyl cyanide.

After 4 days the yield of the urea (VII; R = H) was only 23% and there were also isolated small quantities of methionine hydantoin and unchanged amino-nitrile; the remainder of the product appeared to be the corresponding imino-dinitrile. When the reaction was conducted at 50° for 4 hours, none of the urea was obtained, an 18% yield of methionine hydantoin being formed instead together with 16% of unchanged starting material. The main product, insoluble in dilute hydrochloric acid, again appeared to be the imino-dinitrile.

The compound, m. p. 161°, gave no effervescence on treatment with acid, showing that it was not the isomeric carbamate (VIII), and when heated with water it was converted into the corresponding amide (IX). Hydrolysis with an aqueous suspension of lime under pressure gave a 58% yield of methionine.

Bucherer and Steiner suggested that formation of both hydantoin and urea (VII) arose from amino-nitriles *via* a common labile imino-oxazolidone of type (XI) which was produced *via* a carbamic acid. It was conjectured that the intermediate rearranged to the hydantoin in the presence of water, but in its absence reacted with another molecule of the amino-nitrile to yield (VII). The postulated intermediate is closely analogous to the 5-amino-2-mercaptothiazoles described by Cook, Heilbron, and Levy (*loc. cit.*) which were found to rearrange to the corresponding dithiohydantoins on treatment with bases (Cook, Heilbron, and Stern, *J.*, 1948, 2031).

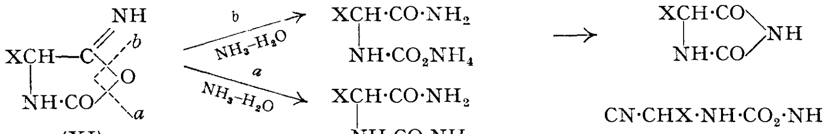
The failure of methionine nitrile to form substantial quantities of the hydantoin is probably due to its being too weak a base to effect the opening of the ring of the intermediate imino-oxazolidone (XI) to give the carbamate (X). In the same way the very slow formation of the urea (VII; R = H) is probably due to the very slight tendency of the amino-nitrile to form the initial carbamate (VIII).



$$\begin{array}{l}\mathrm{CHX{\cdot}CO{\cdot}NH_2}\\ |\\ \mathrm{NH{\cdot}CO_2{\cdot}NH_3{\cdot}CHX{\cdot}CN}\end{array}$$

(X)

The small amount of hydantoin isolated may have arisen through the presence of ammonia released by the slow breakdown of the amino-nitrile to the imino-dinitrile. The higher yield of the hydantoin from the reaction at higher temperatures supports this view, since amino-nitriles are known to yield imino-dinitriles and ammonia under these conditions. In this event it seems likely that ring fission of the hypothetical intermediate (XI) occurred at (*b*) rather than at (*a*) since the latter would be expected to yield the amide (VI; R = NH_2) under the mild conditions employed. It should be noted, however, that Slotta, Behnisch, and Szyszka (*Ber.*, 1934, **67**, 1529) have prepared hydantoins from α-amino-amides by heating them with ammonium carbonate, although the conditions used were far more drastic than those employed here.



(XI)

CN·CHX·NH·CO_2·$NHEt_3$ (XII)

From the above considerations it seemed likely that if a comparatively strong base were used in the reaction of the nitrile of methionine with carbon dioxide the formation of the urea (VII; R = H) would be avoided and the reaction would be much more rapid. By including 1 mol. of triethylamine in the reaction it was, indeed, found that good yields (90%) of the hydantoin could readily be obtained, the reaction being complete in about 30 minutes.

Attempts to obtain the initial carbamate (XII) by carrying out the reaction in dry benzene gave rise to a heavy oil which failed to yield a crystalline benzyl ester on reaction with benzyl bromide. When the oil reacted with carbon disulphide in alcoholic solution, however, carbon dioxide was evolved and the corresponding crystalline dithiocarbamate was obtained, identical with the product from the direct action of the nitrile of methionine with carbon disulphide in the presence of triethylamine. Since it has already been shown

(Holland, *J.*, 1950, 2134) that carbamates can be converted into the corresponding dithiocarbamates in this way, there is reasonable confirmation that the initial reaction product is the carbamate (XII).

The dithiocarbamate was somewhat unstable, becoming brown with the release of triethylamine. A solution in hot water gave rise to a solid, m. p. 222° (decomp.), which appeared to be the expected 5-2′-methylthioethyl-2 : 4-dithiohydantoin described by Catch *et al.* (*loc. cit.*). These workers gave m. p. 212° (decomp.) but we have found that the m. p. (196°) of the initial product obtained by their method is only slowly raised on repeated recrystallisation, indicating a mixture of the dithiohydantoin and the isomeric 5-amino-2-mercapto-4-2′-methylthioethylthiazole. A similar crude product was also obtained from the mother-liquors of the product, m. p. 222° (decomp.), described above. When these crude products were refluxed with aqueous ammonia the dithiohydantoin, m. p. 222° (decomp.), was readily isolated.

An attempt to apply the reaction with carbon dioxide in the presence of triethylamine to the crude mixture obtained from β-methylthiopropaldehyde, ammonium chloride, sodium cyanide, and ammonia (excess of which was removed after amino-nitrile formation) in aqueous alcohol gave only a small amount of the urea (VII; R = H) together with triethylamine hydrochloride. This puzzling result was traced to a reaction analogous to the Solvay process for the manufacture of sodium carbonate, triethylamine taking the place of ammonia, for when carbon dioxide was passed into an aqueous-alcoholic solution of sodium chloride and triethylamine, substantial quantities of sodium hydrogen carbonate were precipitated and triethylamine hydrochloride was isolated from the mother-liquors. Triethylamine is thus removed from the reaction and the nitrile of methionine then yields only (VII; R = H). By carrying out the preparation of the nitrile of methionine in industrial spirit and filtering off the sodium chloride, conversion into the hydantoin proceeded in 85% yield.

The effect of triethylamine on the preparation of the hydantoin corresponding to methionine from the nitrile indicated that it might prove of value in the Bucherer–Bergs method, and this was, in fact, found to be so. By use of 1·1 mol. of triethylamine in the reaction and by reducing the ammonium carbonate to 2·2 mol., 90—95% yields of the hydantoin corresponding to methionine were easily obtained on keeping the reaction mixture for 18 hours at room temperature, or by boiling it for 15 minutes. Reduction of the amount of triethylamine in the reaction led to decreased yields, and attempts to replace the base partly or wholly by ammonia were also unsatisfactory. By the use of this method overall yields of pure methionine of 79% from β-methylthiopropaldehyde were obtained, the intermediate hydantoin not being isolated.

EXPERIMENTAL

(M. p.s are uncorrected.)

Although the m. p. of an amino-acid is not always held to be a satisfactory criterion of purity, we have found that with methionine it can be used as a reliable guide provided a control specimen of pure material is examined at the same time under identical conditions; *e.g.*, a sample behaving in the same way as the control specimen on heating showed 99·3% of methionine in the formaldehyde titration, while a less pure specimen melting with decomposition some 6—7° lower than the control had an estimated purity of 94·6%.

α-Amino-γ-methylthiobutyronitrile.—To a mixture of ammonium chloride (59 g.), sodium cyanide (53 g.), concentrated aqueous ammonia (350 ml.), and alcohol (200 ml.) saturated with ammonia, β-methylthiopropaldehyde (52 g.) was added dropwise with stirring during 30 minutes, the temperature being kept at 15—20°. After being stirred overnight, the mixture was concentrated under reduced pressure to about 300 ml. The upper oily layer that had appeared was separated, and the residual aqueous layer extracted with ether (4 × 75 ml.). After the combined oil and extracts had been dried and the solvent removed, finally under reduced pressure, the amino-nitrile remained as a mobile orange-red oil (62·1 g.; 95·5%).

Conversion of the amino-nitrile into its *sulphate* was carried out by adding dropwise the calculated quantity of sulphuric acid (8·4 ml.) to a cooled and stirred solution of the amino-nitrile (41·1 g.) in absolute alcohol (200 ml.). The salt (36·9 g.) separated at once as a cream-coloured powder, m.p. 175° (decomp.) after being washed with alcohol and ether. Addition of a little sulphuric acid to the filtrate yielded a further 3·2 g. of sulphate, m. p. 174° (decomp.) (total yield 70·9%). Amino-nitrile regenerated from the sulphate gave a 75% yield of the salt in this way. Any considerable excess of sulphuric acid must be avoided since this causes redissolution of the sulphate. The salt was purified by dissolution in the minimum volume of cold water and addition of alcohol and separated as micro-crystals, m. p. 176° (decomp.) (Found: C, 33·2; H, 6·5; N, 15·4; S, 25·6. $C_{10}H_{20}N_4S_2,H_2SO_4$ requires C, 33·5; H, 6·2; N, 15·6; S, 26·8%).

α-Amino-γ-methylthiobutyronitrile dihydrogen phosphate separated slowly from a solution of the base in alcohol on addition of phosphoric acid as a white granular powder, m. p. 114—118°. Recrystallised from alcohol, it separated as a white powder with unchanged m. p. (Found: C, 26·2; H, 5·9; N, 12·2. $C_5H_{10}N_2S,H_3PO_4$ requires C, 26·3; H, 5·7; N, 12·3%).

S-*Benzyl*iso*thiuronium α-Hydroxy-γ-methylthiobutyrate.*—α-Hydroxy-γ-methylthiobutyronitrile [prepared from β-methylthiopropaldehyde by the method of Pierson *et al.* (*loc. cit.*)] (5 g.) was heated on the steam-bath with hydrochloric acid (5 ml.) and water (10 ml.) for 80 minutes. The resulting solution was cooled and adjusted to pH 7 with sodium hydrogen carbonate, and the small amount of oil that separated was extracted into ether. To the residual aqueous solution there was added a solution of *S*-benzyl*iso*thiuronium chloride (2 g.) in hot alcohol, and the *α-hydroxy-γ-methylthiobutyrate* (4·4 g.), m. p. 156°, separated as needles; recrystallised from water, it had m. p. 157° (Found: C, 49·2; H, 6·7; N, 9·0. $C_{13}H_{20}O_3N_2S_2$ requires C, 49·3; H, 6·4; N, 8·9%).

5-2′-*Methylthioethylhydantoin.*—(*a*) A mixture of sodium cyanide (16·2 g.), ammonium carbonate (99·0 g.), and β-methylthiopropaldehyde (30 ml.) in 50% aqueous alcohol (780 ml.) was heated for 12 hours at 50—55°. The resulting pale yellow solution was concentrated under reduced pressure to *ca.* 100 ml. and stored at 0°, yielding crude hydantoin (24·5 g.). The mother-liquors (pH 9·2) were then acidified carefully at room temperature with concentrated hydrochloric acid (27 ml.) to pH 1 to avoid ring closure of any hydantoic acid that might have been present. There was considerable effervescence as more 5-2′-methylthioethylhydantoin (22·7 g.) separated (total yield 90%). This material was quite suitable for hydrolysis to methionine. It was purified by recrystallisation from water (charcoal), separating as a white crystalline powder, m. p. 108° (lit., m. p. 103—105°) (Found: C, 41·2; H, 5·9; N, 15·7. Calc. for $C_6H_{10}O_2N_2S$: C, 41·4; H, 5·8; N, 16·1%).

(*b*) A mixture of sodium cyanide (16·2 g.), ammonium carbonate (63·6 g.), β-methylthiopropaldehyde (30 ml.), and triethylamine (45·6 ml.) in 50% aqueous alcohol (300 ml.) was kept at room temperature for 24 hours. The resulting pale yellow solution was worked up as described above to yield 89% of crude methionine hydantoin.

(*c*) Carbon dioxide was passed for 1 hour through a solution of α-amino-γ-methylthiobutyronitrile (10·9 g.) and triethylamine (11·6 ml.) in 50% aqueous alcohol (50 ml.). Next morning the mixture was concentrated under reduced pressure to about one-half of its original volume, whereupon the crude hydantoin (10·8 g.) separated. From the mother-liquors after further concentration more hydantoin (2·32 g.) separated on acidification (total yield 89·5%).

γ-Methylthio-α-ureidobutyramide (VI; R = NH_2).—The final liquors from the above preparation (*a*) of methionine hydantoin were concentrated *in vacuo* nearly to dryness and the residual yellow gum was extracted with absolute alcohol from the sodium chloride. After removal of the solvent the gum was dried *in vacuo* (NaOH) and then heated with a little ethyl acetate. When this was kept at 0° a small quantity (0·37 g.) of the *amide* separated as a white powder, which was filtered off and washed with a little ethyl acetate; it had m. p. 164—166° (decomp.). The residue from the mother-liquors when boiled with a little water gave on refrigeration a second crop (0·55 g.) of the amide, needles, m. p. 168—169° (decomp.). The combined solids, recrystallised from 80% alcohol, had m. p. 173·5—174·5° (decomp.) (Found: C, 37·8; H, 6·6; N, 22·4. $C_6H_{13}O_2N_3S$ requires C, 37·7; H, 6·8; N, 22·0%).

γ-Methylthio-α-ureidobutyric Acid (VI; R = OH).—Methionine (2 g.) and sodium cyanate (1·1 g.) were heated in water (25 ml.) on a steam-bath for 15 minutes. After cooling to room temperature the mixture was acidified with hydrochloric acid to about pH 3 and solid began to separate after a few minutes. After concentration of the reaction mixture under reduced pressure to about 10 ml. and refrigeration overnight, the precipitated hydantoic acid was filtered off and washed with a little water; it had m. p. 132—135° (decomp.). On recrystallisation from water it separated as needles, m. p. 138—139° (decomp.) (Found: C, 37·6; H, 6·8; N, 14·5. Calc. for $C_6H_{12}O_3N_2S$: C, 37·5; H, 6·3; N, 14·6%).

N-(1-*Carbamido*-3-*methylthiopropyl*)-N′-(1-*cyano*-3-*methylthiopropyl*)*urea* (VII; R = H).—Carbon dioxide was passed in a slow stream through a solution of α-amino-γ-methylthiobutyronitrile (2·87 g.) in a mixture of alcohol (20 ml.) and water (15 ml.). The *urea* began to separate after 19 hours and was collected after a further 31 hours (0·41 g.; m. p. 161°). The passage of carbon dioxide through the mother-liquors was continued for a further 2 days and more product (0·36 g.), m. p. 155°, separated. The combined solids were recrystallised from alcohol, the urea separating as white microcrystals, m. p. 161° (Found: C, 43·8; H, 6·7; N, 18·0. $C_{11}H_{20}O_2N_4S_2$ requires C, 43·4; H, 6·6; N, 18·4%).

The final mother-liquors were acidified with dilute hydrochloric acid and thoroughly extracted with ether. Evaporation of the dried ether extracts left a yellow gum (1·51 g.) which partly crystallised on storage, and when rubbed with benzene gave 5-2′-methylthioethylhydantoin (0·22 g.). The residual oil gave a considerable blue precipitate when heated with aqueous sodium hydroxide and ferrous sulphate followed by the addition of ferric chloride and hydrochloric acid, but on hydrolysis with hydrochloric acid the oil failed to yield α-hydroxy-γ-methylthiobutyric acid and was therefore probably largely di-(1-cyano-3-methylthiopropyl)amine.

The acidified aqueous layer after extraction with ether was basified and re-extracted with ether, giving unchanged α-amino-γ-methylthiobutyronitrile (0·3 g.), characterised as its sulphate.

NN′-*Di*-(1-*carbamido*-3-*methylthiopropyl*)*urea*.—The urea (VII; R = H) (2·5 g.) in water (100 ml.) was heated on the steam-bath for 30 minutes, and the resulting solution concentrated *in vacuo* to leave a sticky solid. This yielded the *amide* (0·42 g.) on dissolving it in hot alcohol and cooling the solution. Recrystallisation from this solvent gave the amide as tiny needles, m. p. 216° (decomp.) (Found: C, 41·2; H, 7·4; N, 17·2. $C_{11}H_{22}O_3N_4S_2$ requires C, 41·0; H, 6·9; N, 17·4%).

Triethylammonium 1-*Cyano*-3-*methylthiopropyldithiocarbamate*.—Carbon dioxide was passed through a solution of the nitrile of methionine (1·28 g.) and triethylamine (1·4 ml.) in absolute alcohol (5 ml.) at 0° for 20 minutes. Carbon disulphide (1 ml.) was then added, and the mixture kept at room temperature. The solution rapidly became bright yellow, and a steady stream of carbon dioxide was evolved during 50 minutes. On the addition of dry ether (30 ml.) an oil separated which gradually solidified when scratched. This was filtered off and washed with ether to give the required *dithiocarbamate* (1·17 g.) as a white powder, m. p. 134° (decomp.), which rapidly turned pale yellow in air. It was purified by solution in absolute alcohol (35 ml.) and precipitation with dry ether (100 ml.); m. p. 136° (decomp.) (Found: C, 46·6; H, 8·5; N, 13·5; S, 31·8. $C_{12}H_{25}N_3S_3$ requires C, 46·9; H, 8·2; N, 13·7; S, 31·3%).

The same compound was obtained in 65% yield when carbon disulphide (2 ml.) was added to a solution of the amino-nitrile (2·44 g.) and triethylamine (2·6 ml.) in alcohol (5 ml.) at 0°, and the mixture kept for 20 minutes then diluted with ether.

5-2′-*Methylthioethyl*-2 : 4-*dithiohydantoin*.—A solution of the dithiocarbamate (1 g.) in water (10 ml.) was heated on the steam-bath; triethylamine was evolved and yellow crystals of the dithiohydantoin gradually separated. After 5 hours the solid (0·40 g.) was removed, m. p. 219° (decomp.), after shrinking and darkening from 200°. Recrystallisation from alcohol raised the m. p. to 222° (decomp.) (Found: C, 35·1; H, 4·6; N, 13·6. Calc. for $C_6H_{10}N_2S_3$: C, 34·9; H, 4·9; N, 13·6%).

Methionine.—(a) *Hydrolysis of methionine nitrile with hydrochloric acid.* The amino-nitrile (5·38 g.), regenerated from the normal sulphate, was heated under reflux with concentrated hydrochloric acid (10 ml.) for 2 hours, and the dark reaction mixture then concentrated under reduced pressure to a gum. Excess of acid was removed by two evaporations with water under reduced pressure, and the final residue was dissolved in a little water and neutralised with triethylamine. An excess of triethylamine (8 ml.) was added, and the mixture warmed and then concentrated under reduced pressure virtually to dryness. The residue was boiled with alcohol to remove the triethylamine hydrochloride, and the residual methionine washed with alcohol till free from chloride. The product (5·55 g., 90·7%) was obtained as light brown platelets, m. p. 250° (decomp.) after softening from 247° [control, m. p. 252° (decomp.)]. The amino-acid was readily purified by treating an aqueous solution with charcoal and precipitating the amino-acid with alcohol.

(b) *Hydrolysis of methionine nitrile with sulphuric and phosphoric acids.* Methionine nitrile dihydrogen phosphate (6·0 g.) was refluxed for 1·5 hours with concentrated sulphuric acid (4·5 g.) and water (4·5 ml.), and the product cooled, diluted with water (7 ml.), and neutralised with ammonia (*d* 0·88). The solid that separated was filtered off and washed with water to yield methionine (3·36 g., 85·7%), m. p. 250° (decomp.) after softening from 248° [control, m. p. 258° (decomp.)], which contained not more than a trace of sulphate. A further 0·5 g. of methionine of similar purity was obtained from the mother-liquors.

(c) *From* β-*methylthiopropaldehyde* via *methionine nitrile.* To a mixture of ammonium chloride (29·5 g.), sodium cyanide (26·5 g.), water (350 ml.), and alcohol (200 ml.) saturated with ammonia at about 15°, β-methylthiopropaldehyde (50 ml.) was added dropwise during 30 minutes with stirring, the temperature being kept at 4—8° but then being allowed to rise to about 17° during 16 hours. The mixture was concentrated under reduced pressure, the internal temperature being kept as low as possible, till an oil began to separate. Concentrated hydrochloric acid (50 ml.) was then added, and the whole concentrated under reduced pressure to a gum. More hydrochloric acid (210 ml.) was added, and the mixture refluxed for 1·5 hours. The dark hydrolysate was freed from excess of acid in the usual way and the final black gum was dissolved in hot water (75 ml.) and treated with charcoal (15 g.), and the resulting orange solution boiled with sodium hydroxide solution (200 ml.; 40%) till ammonia ceased to be evolved. The solution was then filtered through a bed of kieselguhr to remove a little tar and adjusted to pH 6 with concentrated hydrochloric acid (76 ml.). After refrigeration, the precipitated methionine was filtered off, slurried with water (50 ml.), refiltered, washed with a little water, and dried at 100° [35·3 g.; m. p. 253—254° (decomp.)] [control, m. p. 255° (decomp.)].

The filtrate and washings were acidified with hydrochloric acid (10 ml.) and evaporated to dryness under reduced pressure. The residue was extracted twice with hot absolute alcohol (100 + 50 ml.), and the combined extracts were adjusted to pH 6 with triethylamine and refrigerated to give a second crop of methionine (12·6 g.), m. p. 250° (decomp.).

(d) *From β-methylthiopropaldehyde* via *methionine hydantoin.* To a mixture of sodium cyanide (16·2 g.) and ammonium carbonate (63·6 g.) in 50% aqueous alcohol (300 ml.), triethylamine (45·6 ml.) was added with stirring followed by β-methylthiopropaldehyde (30 ml.). The temperature of the mixture rose by 6—7° and remained thus for about 10 minutes and then slowly fell to room temperature. After 1 hour's stirring the mixture was kept overnight and the resulting pale yellow product was then diluted with alcohol (150 ml.); after about 15 minutes, the precipitated sodium carbonate was removed and washed with alcohol.

To the aqueous alcoholic filtrate, water (665 ml.) and barium hydroxide (200 g.) were added, and the mixture was boiled to remove the alcohol and triethylamine, then heated under reflux for 36 hours. The hydrolysate was filtered, the solid residue extracted with boiling water (300 ml.) and then washed with hot water (150 ml.), and the combined filtrate and extracts treated with ammonium carbonate (23 g.). After the mixture had been boiled for a few minutes, the precipitated barium carbonate was removed and washed with a little hot water, and the liquor then evaporated to dryness under reduced pressure. The residue was slurried with hot absolute alcohol, the mixture cooled and filtered, and the methionine washed with alcohol and ether (yield 33·8 g.). The alkaline mother-liquors, on treatment with acetic acid (to pH 6), yielded more methionine (3·1 g.) (total yield, 82·6%). The combined crops were recrystallised from water to yield pure methionine (34·0 g.), m. p. 260° (decomp.) [control, 260° (decomp.)]. From the mother-liquors there was obtained somewhat less pure methionine (1·3 g.), m. p. 246° (decomp.) [control, m. p. 249° (decomp.)].

(e) *Hydrolysis of methionine hydantoin with lime.* A mixture of 5-2′-methylthioethylhydantoin (7 g.) and calcium hydroxide (10·0 g.) in water (30 ml.) was heated in an autoclave for 4 hours at 150°. The product was worked up essentially as described under (d) to yield practically pure methionine (4·55 g.; 76%), m. p. 270° (decomp.) [control, m. p. 272° (decomp.)].

When the hydantoin (10 g.) was refluxed with calcium hydroxide (20 g.) and water (200 ml.) for 48 hours, 5·68 g. (66·3%) of methionine were obtained. The residual gum from this preparation was dissolved in a little hot water, and the solution cooled and adjusted to pH 1; some γ-methylthio-α-ureidobutyric acid (0·85 g.) separated on refrigeration; it had m. p. 134—136° (decomp.), not depressed on admixture with the compound prepared from methionine and sodium cyanate.

(f) *Hydrolysis of the urea* (VII; R = H) *with lime.* A mixture of the urea (1 g.), calcium hydroxide (2 g.), and water (20 ml.) was heated in a sealed tube at 150° for 6 hours. The product when worked up as described under (e) gave methionine (0·57 g.).

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Beecham Research Laboratories Ltd.,
Betchworth, Surrey.

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