182. *The Synthesis of α-Amino-acids. Part I.* dl-*Methionine.*

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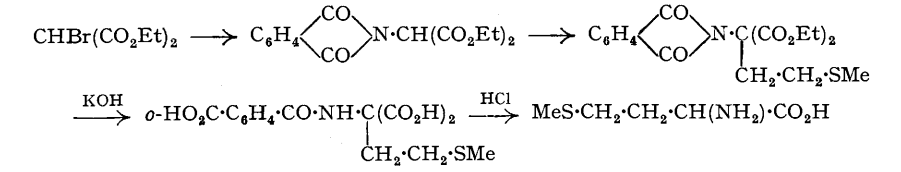
The preparation of *dl*-methionine has been investigated on the large laboratory scale, a modification of the published method starting from ethyl bromomalonate being used. The overall yield is approximately 40%.

Beattie and Marshall (*Nature*, 1944, **153**, 525) have indicated the value of methionine in the treatment of certain types of jaundice, and the synthesis of this compound on a comparatively large scale has been investigated. The following routes are described in the literature: (*a*) From β-chloropropaldehyde diethylacetal (Barger and Coyne, *Biochem. J.*, 1928, **22**, 1417); overall yield, 3%. (*b*) From methyl β-chloroethyl sulphide by a malonic ester synthesis (Windus and Marvel, *J. Amer. Chem. Soc.*, 1930, **52**, 2575); yield, 8%. (*c*) Condensation of methyl β-chloroethyl sulphide with ethyl phthalimidomalonate, hydrolysis, and decarboxylation (*Organic Syntheses*, Coll. Vol. II, 384); yield, 50%, calculated on methyl β-chloroethyl sulphide. (*d*) From α-benzamido-γ-butyrolactone *via* ethyl α-benzamido-γ-methylthiobutyrate (Hill and Robson, *Biochem. J.*, 1936, **30**, 248); yield, 3%. (*e*) From 3 : 6-bis-β-chloroethyl-2 : 5-diketopiperazine (Snyder and Cannon, *J. Amer. Chem. Soc.*, 1944, **66**, 511); yield, 60%.

Owing to either inaccessibility of starting materials or poor yields, methods (*a*), (*b*), (*d*) and (*e*) were considered unsuitable for large-scale operation and attention was concentrated on method (*c*), which involves the following stages:



The following are the most important modifications made in the method described in the literature: (1) Methyl β-hydroxyethyl sulphide is more conveniently obtained from monothioethylene glycol and methyl sulphate than from sodium methyl mercaptide and ethylene chlorohydrin.* (2) It is essential that methyl β-chloroethyl sulphide should not be distilled at pressures above 30 mm., otherwise decomposition occurs, giving rise to impurities in the methionine, which are difficult to remove (cf. Snyder, Howe, Cannon, and Nyman, *J. Amer. Chem. Soc.*, 1944, **66**, 511). (3) An 80% yield of ethyl phthalimidomalonate is obtained by heating together phthalimide, ethyl bromomalonate, and sodium carbonate in xylene. Agitation must be very efficient and the sodium carbonate must be finely divided. The condensation of ethyl bromomalonate with potassium phthalimide (isolated) cannot be carried out with safety on a large scale. (4) Isolation of ethyl sodium phthalimidomalonate is unnecessary. It can be formed in alcoholic solution with sodium ethoxide, and the condensation with methyl β-chloroethyl sulphide carried out in the same solution.

The following derivatives of *dl*-methionine have been prepared: (a) *ethyl* ester, b. p. 112°/2·5 mm.; (b) N-*cinnamoyl*, m. p. 162—164°; (c) 2 : 5-*dibromobenzenesulphonate*, m. p. 186°; (d) 3 : 4-*dichlorobenzenesulphonate*, m. p. 183°.

Experimental.

Ethyl Phthalimidomalonate.—A suspension of anhydrous sodium carbonate (1590 g.) and phthalimide (2940 g.; 20 mols.) in dry xylene (7 l.) was refluxed with vigorous stirring in a 20-litre three-necked flask, and ethyl bromomalonate (4780 g.; 20 mols.) added during ½—1 hr. After being heated and stirred for a further 4 hrs., the mixture was cooled to 35°, filtered, and the cake washed with xylene (1 l.). The combined washings and filtrate were evaporated to about two-thirds and treated with stirring at 30° with light petroleum (5 l., b. p. 40—60°). After cooling below 20°, the phthalimidomalonic ester was obtained as a pale brown, crystalline powder on filtration and washing with light petroleum. During recovery of the mixed solvents a further quantity of the product was obtained, raising the yield to approx. 80%.

Methyl β-Chloroethyl Sulphide.—A solution of monothioethylene glycol (780 g.; 10 mols.) in aqueous sodium hydroxide (450 g. in 3 l. of water) was treated gradually with methyl sulphate (945 c.c.) below 30° with stirring. After standing overnight, the solution was extracted with chloroform (4 × 1 l.), and solvent distilled from the extracts until the volume had been reduced to about 2 l. To the stirred solution, thionyl chloride (1200 g.), diluted with its own volume of chloroform, was added at such a rate as to keep the mixture refluxing gently. Stirring and refluxing were continued for a further 2 hrs., and the solution then cooled, washed successively with water, dilute sodium hydroxide solution, and water, and dried over calcium chloride. Removal of the solvent and distillation of the residue at 30 mm. gave the product as an oil, b. p. 58°. The yield varied from 70—90% depending on the quality of the monothioethylene glycol.

3-*Methylthio*-1-*phthalamidopropane*-1 : 1-*dicarboxylic Acid.*—A solution of sodium (144 g.) in absolute alcohol (2·25 l.) was added during a few minutes with stirring to a warm solution of ethyl phthalimidomalonate (1900 g.; 6·2 mols.) in absolute alcohol (2 l.) in a 20-litre flask. The solution was then refluxed with stirring while methyl β-chloroethyl sulphide (690 g.; 6·2 mols.) was added during 1½ hrs. The mixture was refluxed for a further 3 hrs. and cooled, and water (13 l.) added, stirring being continued for a further ½ hr. The oily layer was then separated, dissolved in alcohol (2·25 l.), and refluxed with stirring for 3 hrs. after addition of 30% aqueous potassium hydroxide (6·25 l.). After cooling, ice (7 kg.) was added, and the solution made acid to Congo-red with concentrated hydrochloric acid (2·6—3 l.), the temperature not being allowed to exceed 3°. The solution was run into a mixture of concentrated hydrochloric acid (2·5 l.) and water (10 l.) and maintained below 5° overnight; the product was then collected and air-dried. The yield was 75—80%, the product containing less than 2% of potassium chloride.

dl-*Methionine.*—The tricarboxylic acid (1·6 kg.) was added to a mixture of concentrated hydrochloric acid (4 l.) and water (4 l.) in a 20-litre flask and carefully heated with stirring. Decarboxylation proceeded smoothly and was completed by boiling for 2 hrs. On cooling, phthalic acid separated; it was removed and washed with a little cold water. The

* The authors are indebted to Mr. L. J. Lermit for this information.

combined aqueous liquor was evaporated to dryness under reduced pressure, and the residue dissolved in hot water (0·6 l.), poured into a mixture of pyridine (1·25 l.) and alcohol (6·25 l.), and allowed to crystallise. The crude material was recrystallised (charcoal) from water (6 l.), giving pure *dl*-methionine (390 g.); a further quantity (approx. 85 g.) remained in the mother-liquor and was obtained on concentration, the total yield therefore being 64%. The product crystallised in small plates and was free from potassium chloride and " bimethionine " (Snyder, Howe, Cannon, and Nyman, *loc. cit.*) (Found : S, 21·3; N, 9·3. Calc. for $C_5H_{11}O_2NS$: S, 21·5; N, 9·4%). It formed an N-*cinnamoyl* derivative crystallising from aqueous alcohol in plates, m. p. 162—164° (Found : S, 11·2; N, 4·8. $C_{14}H_{17}O_3N$ requires S, 11·5; N, 5·0%).

dl-*Methionine Ethyl Ester.*—A suspension of methionine (25 g.) in absolute alcohol (150 c.c.) was saturated at 0° with hydrogen chloride and then refluxed for 1 hr. The solvent was removed in a vacuum, and the residue treated with saturated aqueous potassium carbonate and extracted with ether. The ethereal solution was dried over anhydrous sodium sulphate, the solvent removed, and the residue distilled, giving an 88% yield of the *ethyl* ester as a viscous oil, b. p. 112°/2·5 mm., $d_4^{20°}$ 1·0670, $n_D^{20°}$ 1·4819 (Found : N, 7·9. $C_7H_{15}O_2NS$ requires N, 7·9%).

dl-*Methionine* 2 : 5-*Dibromobenzenesulphonate.*—Methionine (3 g.) was added to a solution of 2 : 5-dibromobenzenesulphonic acid (7 g.) in water (20 c.c.), and the mixture warmed until a clear solution was obtained. After standing overnight at 0°, *methionine* 2 : 5-*dibromobenzenesulphonate* separated in fine needles, which were collected and washed twice with ice-water. Yield, 83%. M. p. 186°, not raised by recrystallisation from water (Found : N, 3·0; S, 14·2; Br, 34·7. $C_{11}H_{15}O_5NS_2Br_2$ requires N, 3·0; S, 13·8; Br, 34·4%). The corresponding 3 : 4-*dichlorobenzenesulphonate*, prepared in 80% yield in the same way, was obtained as a micro-crystalline powder, m. p. 183° (Found : N, 3·7; S, 17·1; Cl, 18·7. $C_{11}H_{15}O_5NS_2Cl_2$ requires N, 3·7; S, 17·0; Cl, 18·9%).

The authors wish to thank Messrs. R. E. Dewhirst, J. F. Jackson, A. Nightingale, and C. Powney for assistance and the Director General of Scientific Research and Development, Ministry of Supply, for permission to publish this work.

RESEARCH ESTABLISHMENT, SUTTON OAK. [*Received, August* 31*st,* 1944.]