117. *A New Synthesis of Cystine and Lanthionine.*

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The reaction of aqueous sodium sulphide and alcoholic sodium benzyl sulphide with diethyl α-acetamido-α-dimethylaminomethylmalonate methiodide yields products which on hydrolysis and decarboxylation give inactive lanthionine and inactive cystine respectively in good yield. An improved preparation of the methiodide is given, and a mechanism for the reaction is suggested.

It has been shown by Atkinson (*J.*, 1952, 3317) that diethyl α-dimethylaminomethyl-α-formamidomalonate methiodide reacts readily with hot aqueous sodium cyanide, to give diethyl α-cyanomethyl-α-formamidomalonate in good yield. Snyder and Speck (*J. Amer. Chem. Soc.*, 1939, **61**, 668, 2895) record that the following reaction takes place readily:

$$2Ph\cdot CH_2\cdot \overset{+}{N}Me_2Ph\}Cl^- + Na_2S \longrightarrow (Ph\cdot CH_2)_2S + 2NaCl + 2Ph\cdot NMe_2$$

It appeared of interest, therefore, to investigate the action of sodium sulphide on α-acetamido-α-dimethylaminomethylmalonate methiodide (I). In accordance with expectations, heating (I) with an excess of aqueous sodium sulphide yielded a product which on acid hydrolysis and decarboxylation gave inactive lanthionine in 57% yield. The reaction between (I) and excess of alcoholic potassium hydrogen sulphide, followed by hydrolysis and decarboxylation, did not, however, give cysteine, but only lanthionine. No reaction occurred when the non-quaternised base was used (cf. Snyder and Eliel, *J. Amer. Chem. Soc.*, 1948, **70**, 1703; Atkinson, *loc. cit.*).

Heating (I) with 2 mols. of sodium benzyl sulphide in ethyl alcohol for 130 hours, followed by acid hydrolysis and decarboxylation, gave *S*-benzyl-DL-cysteine in 68% yield. The latter compound was reduced with sodium in liquid ammonia and then oxidised, to give inactive cystine in 80% yield, this being a new and easy synthesis of the amino-acid. The above reactions provide a convenient method for the preparation of lanthionine and cystine having a radioactive β-carbon atom.

Since the formation of an ethylenic intermediate of (I) by elimination of amine is precluded, it is suggested that fission may occur through the agency of a proton donor by donation of an electron pair from the β-carbon atom to the nitrogen to form a highly reactive transient carbonium cation (II) (cf. Bauer, Cymerman, and Sheldon, *J.*, 1951, 3311),

$$(I)\quad (EtO_2C)_2C(NHAc)\cdot CH_2\cdot NMe_3^+\}I^- \qquad\qquad (EtO_2C)C(NHAc)\cdot CH_2^+\quad (II)$$

followed by rapid addition to the sulphide or HS anion. In the latter case it appears that the desired thiol intermediate reacts more readily with the carbonium cation than does the acid sulphide, thus affording the sulphide as an end-product (cf. Snyder and Speck, *loc. cit.*).

Experimental

M. p.s are uncorrected.

Diethyl α-Acetamido-α-dimethylaminomethylmalonate Methiodide.—33% Dimethylamine solution (68 c.c.) was treated at 0° with acetic acid (75 c.c.). Diethyl acetamidomalonate (108·5 g., 0·5 mole) and 40% formaldehyde solution (41 c.c.) were added, and after 30 minutes at room temperature the mixture was cooled to −10° and made alkaline by slow addition of 20% sodium hydroxide solution. The base was extracted with ether (300 c.c.), and the extract dried (Na_2SO_4) and concentrated to 150 c.c. Methyl iodide (80 g.) was added and the mixture heated at the b. p. for 5 hours and cooled overnight. Filtration and washing with ether gave the product (144 g., 69·3%) (Found: N, 6·8; I^-, 29·9. Calc. for $C_{13}H_{25}O_5N_2I$: N, 6·75; I, 30·5%).

Inactive Lanthionine.—The methiodide (20·8 g., 0·05 mole) and sodium sulphide nonahydrate (24 g., 0·1 mole) in water (100 c.c.) were heated on a steam-bath until evolution of trimethylamine had ceased (12 hr.). The solution was concentrated to dryness *in vacuo*, and the residue was dissolved in hydrochloric acid (100 c.c.) and heated for 6 hours. Evaporation to dryness *in vacuo* and neutralisation of the aqueous solution with ammonia gave the crude amino-acid, which after dissolution in hydrochloric acid and reprecipitation with ammonia, weighed 3·0 g.

(57%) (Found: N, 13·2; S, 15·4. Calc. for $C_6H_{12}O_4N_2S$: N, 13·5; S, 15·4%). Partition chromatography on paper, with phenol as solvent, gave identical R_F values (0·19) for the material and an authentic sample of lanthionine. A solution of the material in dilute ammonia, when evaporated slowly, afforded the characteristic six-sided plates having a triangular appearance noted by Horn, Jones, and Ringel (*J. Biol. Chem.*, 1941, **138**, 141). The dibenzoyl derivative had m. p. 204—205°.

The methiodide and an excess of alcoholic potassium hydrogen sulphide (Crawhall and Elliott, *J.*, 1951, 2074) were heated on a steam-bath for 12 hours. Evaporation to dryness, followed by acid hydrolysis and decarboxylation, gave lanthionine.

S-*Benzyl*-DL-*cysteine*.—The methiodide (20·8 g., 0·05 mole) and sodium benzyl sulphide (6 g.) in ethyl alcohol (100 c.c.) were heated on a steam-bath for 130 hours. The solution was evaporated to dryness, and the residue boiled for 6 hours with concentrated hydrochloric acid (100 c.c.) Crystals of the hydrochloride separated on cooling. A solution of this in hot dilute hydrochloric acid was treated with charcoal, filtered, and neutralised with ammonia while still hot. Cooling, filtration, washing with ice-cold water, and drying, gave the product (7·3 g., 69%) m. p. 215—216° (Found: N, 6·6; S, 14·9. Calc. for $C_{10}H_{13}O_2NS$: N, 6·65: S, 15·2%). The acetyl derivative had m.p. 157—158°.

Inactive Cystine.—S-Benzyl-DL-cysteine (10 g.) was debenzylated with sodium in liquid ammonia and oxidised by Wood and du Vigneaud's method (*J. Biol. Chem.*, 1939, **131**, 267) to give inactive cystine (4·5 g., 80%) (Found: N, 11·5. Calc. for $C_6H_{12}O_4N_2S_2$: N, 11·65%).

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