281. *The Synthesis of Some α-Amino-acids.*

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Several α-amino-acids structurally related to the natural amino-acids have been synthesised.

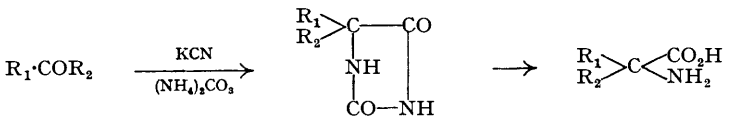
Several examples are known of compounds that inhibit the growth of micro-organisms by interfering with either the formation or the utilisation of amino-acids, the inhibitor usually being

structurally related to the amino-acid concerned. References to these will be found in the extensive review of metabolite antagonists by Roblin (*Chem. Reviews*, 1946, **38**, 255). Recent examples of such inhibitors include certain halogen derivatives of phenylalanine and tyrosine, which competitively inhibit the growth-promoting action of phenylalanine and tyrosine respectively for certain organisms (Mitchell and Niemann, *J. Amer. Chem. Soc.*, 1947, **69**, 1232) and thienylalanine (α-amino-β-2-thienylpropionic acid) which has been shown to inhibit the growth of certain yeasts and bacteria, the effect being reversed by phenylalanine (du Vigneaud *et al.*, *J. Biol. Chem.*, 1945, **159**, 385; 1946, **164**, 761; Beerstecher and Shive, *ibid.*, p. 53; 1947, **167**, 49, 527).

We have prepared a number of α-amino-acids related to various types of natural amino-acids in the hope that they might compete with the natural compounds and so act as growth inhibitors. Most of our compounds were aliphatic amino-acids differing from the natural products only in having longer carbon chains, but one new heterocyclic analogue of phenylalanine was also synthesised. Professor H. A. Krebs of the M.R.C. Unit for Research in Cell Metabolism is carrying out a biological examination of these compounds.

Straight chain α-amino-monocarboxylic acids were prepared by bromination of the fatty acid and treatment of the α-bromo-acid with aqueous ammonia. In the experimental section will be found details of the preparation of α-aminoundecoic acid (1-amino-*n*-decane-1-carboxylic acid), which has not previously been prepared by this method.

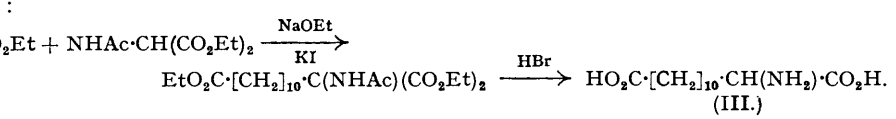
α-Aminodialkylacetic acids (II) were conveniently prepared from the appropriate ketone by treatment with potassium cyanide and ammonium carbonate (Henze and Speer, *J. Amer. Chem. Soc.*, 1942, **64**, 522) and hydrolysis of the 5 : 5-dialkylhydantoin (I) so formed.



(I.) (II.)

The lower hydantoins (I; $R_1 = Me$, $R_2 = Pr^n$; $R_1 = Me$, $R_2 = n\text{-}C_6H_{13}$; $R_1 = R_2 = Et$) were readily hydrolysed by boiling barium hydroxide solution, but those with larger substituents in the 5-position (I; $R_1 = Me$, $R_2 = n\text{-}C_9H_{19}$; $R_1 = Me$, $R_2 = n\text{-}C_{11}H_{23}$; $R_1 = R_2 = n\text{-}C_5H_{11}$; $R_1 = R_2 = n\text{-}C_7H_{15}$) were unaffected by this treatment; the amino-acids were obtained from these hydantoins by treatment with concentrated hydrochloric acid at 160—180° in a sealed tube.

α-Aminobrassylic acid (1-amino-*n*-undecane-1 : 11-dicarboxylic acid) (III) was prepared as shown below :

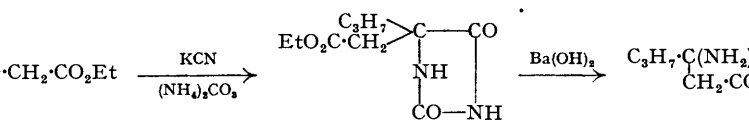


(III.)

The intermediate acetamido-ester was not isolated, but hydrolysis with hydrobromic acid gave a rather poor yield of the desired amino-acid.

α-Amino-β-n-butyl- and *α-amino-β-n-octyl-succinic acid* were prepared in much the same way as α-aminobrassylic acid, ethyl α-bromohexoate and ethyl α-bromodecoate, respectively, being treated with ethyl sodioacetamidomalonate and the products hydrolysed with hydrobromic acid

α-Amino-α-propylsuccinic acid (V) was prepared by conversion of ethyl butyrylacetate into *ethyl 5-propylhydantoin-5-acetate* (IV) by treatment with potassium cyanide and ammonium carbonate, and barium hydroxide hydrolysis of the hydantoin.



(IV.) (V.)

For the synthesis of *α-amino-β-2-quinolylpropionic acid*, 5-(2′-quinolylmethylene)-2-thiohydantoin was prepared as described by Phillips (*J. Amer. Chem. Soc.*, 1945, **67**, 744). This compound proved to be rather resistant to desulphurisation with 50% aqueous chloroacetic acid, and the yield of 5-(*2′-quinolylmethylene*)*hydantoin* was low. Catalytic hydrogenation of the

hydantoin in the presence of Raney nickel gave 5-(2′-*quinolylmethyl*)*hydantoin*, which yielded the required amino-acid after hydrolysis with barium hydroxide.

Experimental.

α-Aminoundecoic Acid (1-*Amino*-n-*decane*-1-*carboxylic Acid*).—1-Bromo-*n*-decane-1-carboxylic acid (Pickard and Kenyon, *J.*, 1913, **103**, 1923) (27 g.) was treated with ammonia (*d* 0·88; 250 c.c.) at 55—60° in a closed vessel for 17 hours. After cooling, the solid was filtered off and washed with water and methanol till free from ammonium bromide. Crystallisation from 50% acetic acid gave colourless crystals, m. p. 258—259° (decomp.; sealed tube) (Found: C, 65·4; H, 11·3; N, 6·8. Calc. for $C_{11}H_{23}O_2N$: C, 65·6; H, 11·5; N, 7·0%). Yield 17·4 g.; 85%. (Albertson, *J. Amer. Chem. Soc.*, 1946, **68**, 450, gives m. p. 253°.)

Preparation of 5 : 5-*Dialkylhydantoins*.—The hydantoins were all made from the appropriate ketones by reaction with ammonium carbonate and potassium cyanide in aqueous alcoholic solution as described by Henze and Speer (*ibid.*, 1942, **64**, 522); the proportion of alcohol was increased for the less soluble ketones. The following compounds were prepared: 5-*methyl*-5-n-*nonylhydantoin*, m. p. 108—110° (from aqueous alcohol) (Found: C, 64·5; H, 9·8; N, 11·6. $C_{13}H_{24}O_2N_2$ requires C, 65·0; H, 10·1; N, 11·7%); 5-*methyl*-5-n-*undecylhydantoin*, m. p. 103—105° (from aqueous alcohol) (Found: C, 67·4; H, 10·5; N, 10·3. $C_{15}H_{28}O_2N_2$ requires C, 67·15; H, 10·5; N, 10·4%); 5 : 5-diethylhydantoin, m. p. 158—160° (from benzene; lit. m. p. 165°) (Found: C, 53·9; H, 7·6; N, 17·9. Calc. for $C_7H_{12}O_2N_2$: C, 53·9; H, 7·7; N, 17·95%); 5 : 5-*di*-n-*amylhydantoin*, m. p. 137—138° (from aqueous alcohol) (Found: C, 65·5; H, 10·2; N, 11·2. $C_{13}H_{24}O_2N_2$ requires C, 65·0; H, 10·1; N, 11·7%); 5 : 5-*di*-n-*heptylhydantoin*, m. p. 135—136° (from aqueous alcohol) (Found: C, 69·0; H, 10·9; N, 9·5. $C_{17}H_{32}O_2N_2$ requires C, 68·9; H, 10·8; N, 9·5%).

Preparation of α-Aminodialkylacetic Acids.—(a) *By barium hydroxide hydrolysis of* 5 : 5-*dialkylhydantoins*. The hydantoin was boiled under reflux for 48 hours with a 10% solution of barium hydroxide (3·5—4 mols.). The solution was boiled for a few minutes without a condenser to allow the last traces of ammonia to escape. Water was added and the mixture heated on the water-bath while carbon dioxide was passed in. When the liquid was no longer alkaline to litmus, the barium carbonate was filtered off and washed with hot water. The combined filtrate and washings were heated on the water-bath and treated with 2N-sulphuric acid till barium ions were just absent (sodium rhodizonate as external indicator). The solution was filtered and the amino-acid obtained by concentration of the filtrate.

The following amino-acids were prepared by this method: α-amino-α-methylvaleric acid (2-amino-*n*-pentane-2-carboxylic acid), m. p. 302—303° (decomp.) in a sealed tube, after crystallisation from aqueous acetone (Kurona, *J. Chem. Soc. Japan*, 1925, **45**, 239 gives m. p. 295°) (Found: C, 54·75; H, 9·7; N, 10·5. Calc. for $C_6H_{13}O_2N$: C, 54·9; H, 10·0; N, 10·7%); α-amino-α-methyloctoic acid (2-amino-*n*-octane-2-carboxylic acid), m. p. 315° (decomp.) in a sealed tube, after crystallisation from water (Gulewitsch and Wasmus, *Ber.*, 1906, **39**, 1181, report that this compound sublimes without melting) (Found: C, 62·2; H, 11·0; N, 8·0. Calc. for $C_9H_{19}O_2N$: C, 62·4; H, 11·1; N, 8·1%); α-amino-α-ethylbutyric acid (3-amino-*n*-pentane-3-carboxylic acid) crystallised from aqueous acetone, and sublimed on heating (cf. Steiger, *Org. Synth.*, 1942, **22**, 13) (Found: C, 54·8; H, 9·8; N, 11·3%).

(b) *By acid hydrolysis of* 5 : 5-*dialkylhydantoins*. The hydantoin was heated with 12 times its weight of concentrated hydrochloric acid in a sealed tube at 160—180° for 24 hours (40 hours in the case of 5-methyl-5-*n*-undecylhydantoin). The contents of the tube were diluted with sufficient water to dissolve the separated solid, filtered, and made alkaline with ammonia. The amino-acid was filtered off and crystallised from aqueous acetic acid.

The following amino-acids were prepared by this method: *α-amino-α-methylundecylic acid* (2-amino-*n*-undecane-2-carboxylic acid), m. p. 290° (decomp.) in a sealed tube (Found: C, 67·3; H, 11·7; N, 6·2. $C_{12}H_{25}O_2N$ requires C, 66·95; H, 11·7; N, 6·5%); *α-amino-α-methyltridecylic acid* (2-amino-*n*-tridecane-2-carboxylic acid), m. p. 276—279° (decomp.) in a sealed tube (Found: C, 69·3; H, 11·7; N, 5·8. $C_{14}H_{29}O_2N$ requires C, 69·1; H, 12·0; N, 5·8%); *α-amino*-α-n-*amyloenanthic acid* (6-amino-*n*-undecane-6-carboxylic acid), sublimed on heating (Found: C, 66·9; H, 11·6; N, 7·1. $C_{12}H_{25}O_2N$ requires C, 66·95; H, 11·7; N, 6·5%); *α-amino*-α-n-*heptylpelargonic acid*) (8-amino-*n*-pentadecane-8-carboxylic acid), m. p. 269—271° (decomp.) (Found: C, 70·9; H, 12·1; N 5·3. $C_{16}H_{33}O_2N$ requires C, 70·8; H, 12·2; N, 5·2%).

α-Aminobrassylic Acid (1-*Amino*-n-*undecane*-1 : 11-*dicarboxylic Acid*).—Ethyl acetamidomalonate (21·7 g.) was added to a solution of sodium ethoxide, prepared from sodium (2·3 g.) and anhydrous alcohol (150 c.c.). The solution was boiled under reflux while ethyl 10-bromo-*n*-decane-1-carboxylate (29·3 g.) was added slowly. Since the reaction appeared to be very slow, potassium iodide (0·4 g.) was added and the mixture was refluxed for 24 hours in all. Most of the alcohol was distilled off, the residue poured into water, and the oil extracted with ether. The extract was dried ($MgSO_4$) and the ether removed, leaving a yellow oil (33 g.). In order to characterise the oil, a portion was hydrolysed with alcoholic sodium hydroxide, giving a rather poor yield of *α-acetamidobrassylic acid*, m. p. 116—118° (Found: C, 59·8; H, 9·0; N, 4·1. $C_{15}H_{27}O_5N$ requires C, 59·8; H, 9·0; N, 4·65%).

The crude 1-acetamido-*n*-undecane-1 : 1 : 11-tricarboxylic ester (21·5 g.) was boiled under reflux for 8 hours with hydrobromic acid (46—48%; 107 c.c.). On cooling and leaving overnight, a solid separated, which was filtered off, stirred with water, and filtered off again. The solid was washed repeatedly with methanol and crystallised from dilute acetic acid. *α-Aminobrassylic acid* melted at 217—219° (decomp.) (Found: C, 60·2; H, 9·8; N, 5·0. $C_{13}H_{25}O_4N$ requires C, 60·2; H, 9·7; N, 5·4%). Yield 8·5 g.; 50% based on ethyl acetamidomalonate.

α-Amino-β-n-*butylsuccinic Acid*.—Ethyl acetamidomalonate (10·9 g.) was added to a solution of sodium ethoxide, prepared from sodium (1·15 g.) and dry ethyl alcohol (75 c.c.), and the solution was boiled under reflux while ethyl α-bromohexoate (11·2 g.) was added gradually. When the addition was complete, the mixture was boiled for a further 6 hours. Most of the alcohol was distilled off, water was

added, and the oil was extracted with ether. The extract was dried (Na_2SO_4) and the solvent removed, leaving a pale yellow oil (14 g.)

The oil (13 g.) was boiled under reflux for 8 hours with hydrobromic acid (46—48%; 65 c.c.). The solution was evaporated under reduced pressure from a bath at 60—70°, and the residual syrup was dissolved in ethyl alcohol (100 c.c.). Aniline was added till no further precipitation occurred. After standing in the refrigerator for some time, the solid was filtered off and washed with alcohol. After crystallisation from water, the *amino-acid* melted at 215° (decomp.) (Found: C, 50·3; H, 7·6; N, 7·5. $C_8H_{15}O_4N$ requires C, 50·8; H, 8·0; N, 7·4%). Yield 3·6 g.; 41% based on ethyl acetamidomalonate.

α-Amino-β-n-octylsuccinic Acid.—Ethyl acetamidomalonate (10·9 g.) was brought into reaction with ethyl α-bromodecoate (14·0 g.) as in the preceding experiment, but, in this case, with the addition of potassium iodide (0·5 g.). The crude ethyl α-acetamido-α-carbethoxy-β-*n*-octylsuccinate (18·0 g.) was hydrolysed with hydrobromic acid (46—48%; 90 c.c.), and the product isolated as above, giving the *amino-acid*, m. p. 209—210° after crystallisation from aqueous acetic acid (Found: C, 58·9; H, 9·5; N, 5·4. $C_{12}H_{23}O_4N$ requires C, 58·75; H, 9·45; N, 5·7%). Yield 4·7 g.; 38% based on ethyl acetamidomalonate.

Ethyl 5-Propylhydantoin-5-acetate.—Butyryl chloride was brought into reaction with the sodium derivative of ethyl acetoacetate as described by Bouveault and Bongert (*Bull. Soc. chim.*, 1902, **27**, 1046, 1088) and the mixture of *C*- and *O*-butyryl derivatives so obtained was dissolved in ether and treated with ammonia gas (cf. Blaise and Luttringer, *ibid.*, 1905, **33**, 1101) to give ethyl butyrylacetate in 41% yield.

The keto-ester was converted into *ethyl 5-propylhydantoin-5-acetate* by the general method of Henze and Speer (*loc. cit.*). The hydantoin, obtained in 59% yield, melted at 156° after crystallisation from water (Found: C, 53·1; H, 7·1; N, 12·7. $C_{10}H_{16}O_4N_2$ requires C, 52·6; H, 7·1; N, 12·3%).

α-Amino-α-propylsuccinic Acid.—The above hydantoin (5·4 g.) was boiled under reflux for 24 hours with a solution of crystalline barium hydroxide (35 g.) in water (205 c.c.). The product was worked up in the usual way, the *amino-acid* being crystallised from water. The anhydrous compound, which was hygroscopic, melted at 211—213° (decomp.) (Found: C, 47·4; H, 8·0; N, 7·8. $C_7H_{13}O_4N$ requires C, 48·0; H, 7·5; N, 8·0%). Yield 2·0 g.; 48%.

5-(2′-*Quinolylmethylene*)*hydantoin.*—5-(2′-Quinolylmethylene)-2-thiohydantoin (Phillips, *loc. cit.*) (4·8 g.) and 50% aqueous chloroacetic acid (48 c.c.) were heated on the water-bath for 6 hours. Filtration of the mixture gave 2·0 g. of unchanged starting material. The filtrate was diluted with a large volume of water and allowed to stand in the refrigerator. The solid was filtered off, and a further quantity was obtained by basifying the filtrate with 2N-ammonia, and again leaving in the refrigerator. On crystallisation from aqueous alcohol or, better, from glacial acetic acid, it gave yellow crystals, m. p. 266—268° (decomp.) (Found: C, 64·8; H, 3·9; N, 17·1. $C_{13}H_9O_2N_3$ requires C, 65·3; H, 3·8; N, 17·6%). Yield 1·1 g.; 42% based on unrecovered 5-(2′-quinolylmethylene)-2-thiohydantoin.

5-(2′-*Quinolylmethyl*)*hydantoin.*—5-(2′-Quinolylmethylene)hydantoin (1·5 g.) was suspended in N-sodium hydroxide solution (15 c.c.), and the mixture was shaken in hydrogen in the presence of Raney nickel. When only a small quantity of hydrogen had been absorbed, the mixture became very viscous, and hydrogenation ceased. Ethyl alcohol (distilled over Raney nickel; 15 c.c.) and more catalyst were added; the hydrogenation then proceeded to completion. The catalyst was filtered off, and the filtrate diluted with water, just acidified with acetic acid, made slightly alkaline with ammonia, and evaporated to small bulk. On standing, a solid (0·75 g.; 50% yield) separated, m. p. 173—175°. No more solid was obtained by further concentration and addition of ammonia to restore the solution to alkalinity. Crystallisation of a portion of the solid from water gave the *hydantoin* in fine needles, m. p. 177—179° (Found: C, 64·7; H, 4·75; N, 17·3. $C_{13}H_{11}O_2N_3$ requires C, 64·7; H, 4·6; N, 17·4%).

α-Amino-β-2-quinolylpropionic Acid.—5-(2′-Quinolylmethyl)hydantoin (0·6 g.) was boiled under reflux for 24 hours with a solution of barium hydroxide (crystalline; 3·0 g.) in water (18 c.c.). The mixture was worked up in the usual way. Evaporation of the aqueous solution of the *amino-acid* left a white solid, which was crystallised from a mixture of 80% ethyl alcohol and *iso*propyl ether. The amino-acid separated in small, slightly coloured needles, m. p. 167—168° (decomp.). A ninhydrin test was strongly positive (Found: C, 62·4; H, 5·8; N, 12·3. $C_{12}H_{12}O_2N_2,H_2O$ requires C, 61·5; H, 6·0; N, 12·0%).

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