Triaminoguanidinium 5-Nitroaminotetrazole from Aminoguanidinium 5-Nitroaminotetrazole

To a solution of aminoguanidinium 5-nitroaminotetrazole (2.04 g, 0.01 mole) in water (50 ml), anhydrous hydrazine (95%, 0.6 g, 0.02 mole) was added. The mixture was heated under reflux in a water bath for 2 h, partially evaporated, cooled, and filtered. The solid obtained melted at 184–186 °C. A mixed melting point with authentic triaminoguanidinium 5-nitroaminotetrazole was not depressed.

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SYNTHESIS OF α-ALKYL-SUBSTITUTED AMINO ACIDS AND DERIVATIVES

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The interesting biological properties of some α-substituted amino acids (1–5) made their preparation and pharmacological study of interest to us. We describe two such preparations starting from the available ketones.

α-(2-Furyl)-alanine was prepared from 2-furyl methyl ketone via the corresponding hydantoin 5-(2′-furyl)-5-methylhydantoin.* This new amino acid is an isomer of β-(2-furyl) alanine, β-(3-furyl) alanine, and β-(2-furyl)-β-alanine, all of which have been previously reported (8–10). The amino acid was characterized by its N-phenylcarbamyl derivative which was converted to the 3-phenylhydantoin by treatment with boiling glacial acetic acid. Although stable toward alkali each of these three compounds were decomposed by mineral acids, owing presumably to the lability of the furan nucleus. This instability resulted in the failure of the attempted cyclization of the N-phenylcarbamyl derivative to the 3-phenylhydantoin by hydrochloric acid.

α-Ethylserine has been prepared previously from 2-amino-2-hydroxymethyl-1-butanol (11, 12), from α-aminobutyric acid by the action of formaldehyde (13), and by a long route from ethyl α-acetylbutyrate (14). We report the convenient synthesis of this amino acid from 1-acetoxy-2-butanone via the hydantoin in an overall yield of 38%. α-Ethylserine was characterized by its cupric salt. Probably because of its high solubility, the hydantoin could not be isolated as an intermediate but was obtained from the pure amino acid. Reaction of α-ethylserine with phenyl isocyanate yielded N-phenylcarbamyl-α-ethylserine which in turn was cyclized to 3-phenyl-5-ethyl-5-hydroxymethylhydantoin.

Biological Evaluation

The amino acids and their carbamyl derivatives were nontoxic to rats on intraperitoneal injection and had no effect on Walker-cancer bearing rats. The amino acids had no effect on growth curves when fed to rats at a 1% concentration in the diet. The hydantoins (as their sodium salts) had no visible effects on metrazole-induced epileptic fits in rats.

**This hydantoin has been previously reported in two patents (6, 7).*

EXPERIMENTAL

5-(2'-Furyl)-5-methylhydantoin

The use of ammonium chloride with potassium cyanide in this preparation is a departure from the patent procedures (6, 7). To a stirred solution of 13.75 g of 2-furyl methyl ketone and 10 g of ammonium chloride in 200 ml of ethanol–water (1:1) was added a solution of 12.2 g of potassium cyanide in 20 ml of water; this was stirred at room temperature for 3 h. Then a mixture of 48 g of ammonium carbonate and 100 ml of water was added during 1 h; the resulting mixture was stirred overnight at 50–70°. Excess ammonium carbonate was decomposed by heating and the solution was concentrated *in vacuo* until a precipitate began to form. The cooled solution afforded 17 g (75%) of white crystals, m.p. 178–180° (lit. (6) 176–178°).

Anal. Calcd. for $C_8H_8N_2O_3$: N, 15.55. Found: N, 15.63.

α-(2-Furyl) Alanine

A mixture of 7 g of 5-(2'-furyl)-5-methylhydantoin and 14.2 g of barium hydroxide in 150 ml water was boiled under reflux in a stainless steel flask overnight. Addition of 2.4 ml of concentrated sulfuric acid precipitated barium sulfate which was removed by filtration. The filtrate was concentrated to a yellow gum, which crystallized after trituration with acetone. A 4.9 g yield (82%) of white solid melting at 194–200° was obtained; the crystals began to darken and decompose slowly at 174°. The amino acid gave the usual purple color with ninhydrin. A circular paper chromatogram developed in pyridine–water (4:1) gave an R_f of 0.71 for the compound.

Anal. Calcd. for $C_7H_9NO_3$: N, 9.14. Found: N, 9.15.

N-Phenylcarbamyl-α-(2-furyl) Alanine

α-(2-Furyl) alanine (1.55 g, 0.01 mole) in an equivalent of 4% sodium hydroxide was shaken for 1/2 h with a slight excess of phenyl isocyanate (1.55 g, 0.014 mole). The reaction mixture was filtered, the filtrate acidified with concentrated hydrochloric acid, and the white precipitate collected and washed with water. Crystallization from ethanol–water afforded 1.55 g (57%) of pure product, m.p. 159–161°; neutralization equivalent, found 276 (calcd. 274).

Anal. Calcd. for $C_{14}H_{14}N_2O_4$: N, 10.21. Found: N, 10.26.

3-Phenyl-5-(2'-furyl)-5-methylhydantoin

A solution of 6 g of N-phenylcarbamyl-α-(2-furyl) alanine in 50 ml glacial acetic acid was refluxed for 10 min then quickly cooled; if heating is continued for a longer period of time some darkening of the solution occurs probably due to decomposition of the furan ring. Excess water was added; the precipitate was filtered and recrystallized from ethanol–water. Yields in the range of 27 to 36% of a product melting at 170–172° were obtained. Cyclization had taken place because the product is now neutral in alcohol solution to bromothymol blue, whereas the starting material requires 1 equivalent of base for neutrality.

Anal. Calcd. for $C_{14}H_{12}N_2O_3$: N, 10.93. Found: N, 10.67.

α-Ethylserine and Its Copper Salt

Potassium cyanide (65 g, 1 mole) was added, with stirring, to a solution of 1-acetoxy-2-butanone (87 g, 0.67 mole) and ammonium chloride (53.5 g, 1 mole) in a 1:1 ethanol–water mixture (600 ml). The resulting mixture was stirred at room temperature for 3 h; then ammonium carbonate (300 g) was added and the mixture was stirred overnight at 50–70°. Residual ammonium carbonate was decomposed by refluxing 3 h, following which the solution was concentrated *in vacuo* to a brown oil; this was triturated with hot acetone and filtered, the filtrate being subsequently concentrated again. The residue, presumably a hydantoin, consisted of 152.8 g of a brown oil. Numerous attempts to crystallize it failed, so 87.6 g of it was hydrolyzed; this was added to a solution of 165.8 g of barium hydroxide in 500 ml of water and the solution was refluxed overnight in a steel vessel. Excess ammonium carbonate was added; the solution was refluxed 3 h and filtered, and concentrated to an oil *in vacuo*. This was subsequently dissolved in 171 ml of water and divided into two parts: 57 ml to make the copper salt, and 114 ml to isolate the free amino acid.

The 114 ml of solution above were added to 700 ml of acetone and allowed to crystallize slowly. The large white crystals were filtered and recrystallized from ethanol–water to yield 12 g (38%) of α-ethylserine melting at 257–259°. In electrophoresis using a buffer of pH 8.6, the product remained at the point of origin. A circular paper chromatogram employing pyridine–water (4:1) as solvent gave an R_f of 0.63 for the amino acid.

Anal. Calcd. for $C_5H_{11}NO_3$: N, 10.52. Found: N, 10.75.

The remaining 57 ml of the above solution was boiled for 15 min with excess cupric carbonate, then filtered. The copper salt was precipitated by the addition of acetone–ethanol and an 8.5 g yield (41%) was obtained. The compound does not melt below 300°; it turns from blue to brown gradually upon heating at about 194°. The product was dried at 100° for 2 h, then analyzed.

Anal. Calcd. for $C_{10}H_{20}N_2O_6Cu$: N, 8.55. Found: N, 8.75.

5-Ethyl-5-hydroxymethylhydantoin

A solution of α-ethylserine (2 g, 0.015 mole) and potassium cyanate (1.22 g, 0.015 mole) in 14 ml of water was stirred at 60–70° for 2 h. Then 14 ml of concentrated hydrochloric acid was added and the solution was

refluxed for 1 h, following which the solvent was removed by vacuum leaving a clear oily residue. This was triturated with hot alcohol; the inorganic salts were filtered and the filtrate again concentrated to an oil which crystallized on standing. An 800 mg yield (34%) of the hydantoin melting at 165–168° was obtained.

Anal. Calcd. for $C_6H_{10}N_2O_3$: N, 17.71. Found: N, 17.23.

N-Phenylcarbamyl-α-ethylserine

α-Ethylserine (1 g, 0.00752 mole) was dissolved in an equivalent of 10% aqueous sodium hydroxide (3 ml) and about 20 ml of water. To this was added a slight excess of phenyl isocyanate (1.07 g, 0.01 mole). The mixture was shaken vigorously for 1/2 h and then filtered. Acidification of the filtrate with concentrated hydrochloric acid precipitated a white solid which was filtered, washed with water, recrystallized from ethanol–water, and dried. A 1.3 g (69%) yield of pure material melting at 150–152° was obtained. The compound is acidic and requires 1 mole of sodium hydroxide for neutralization; neutralization equivalent, found 264 (calcd. 252).

Anal. Calcd. for $C_{12}H_{16}N_2O_4$: N, 11.11. Found: N, 10.64.

3-Phenyl-5-ethyl-5-hydroxymethylhydantoin

A solution of 350 mg of N-phenylcarbamyl-α-ethylserine in 20 ml of 6 *N* hydrochloric acid was refluxed 1 h, then concentrated *in vacuo* until a precipitate began to form. A small amount of water (10 ml) was added; the mixture was cooled and filtered, and the precipitate was dried. A 220 mg yield (68%) of a product melting at 155–156° was obtained. Cyclization had occurred because the product is now neutral.

Anal. Calcd. for $C_{12}H_{14}N_2O_3$: N, 11.96. Found: N, 11.62.

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STUDIES OF SODIUM CUPRATE(III) STABILITY

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We have recently completed a study of the stability of sodium dioxocuprate(III) in various alkali bases at several different base strengths. In no case did we find that the salt was stable in solution and, in fact, the half-life of the CuO_2^- ion was estimated to be only 25 s. Thus, it appears that tervalent copper can be present in aqueous solution only in the presence of large stabilizing anions such as periodate or tellurate (1–3) or in the presence of large concentrations of hypobromite (4).

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