AMINO ACIDS

III. CYCLIC GUANIDINO ACIDS AND THEIR DERIVATIVES[1]

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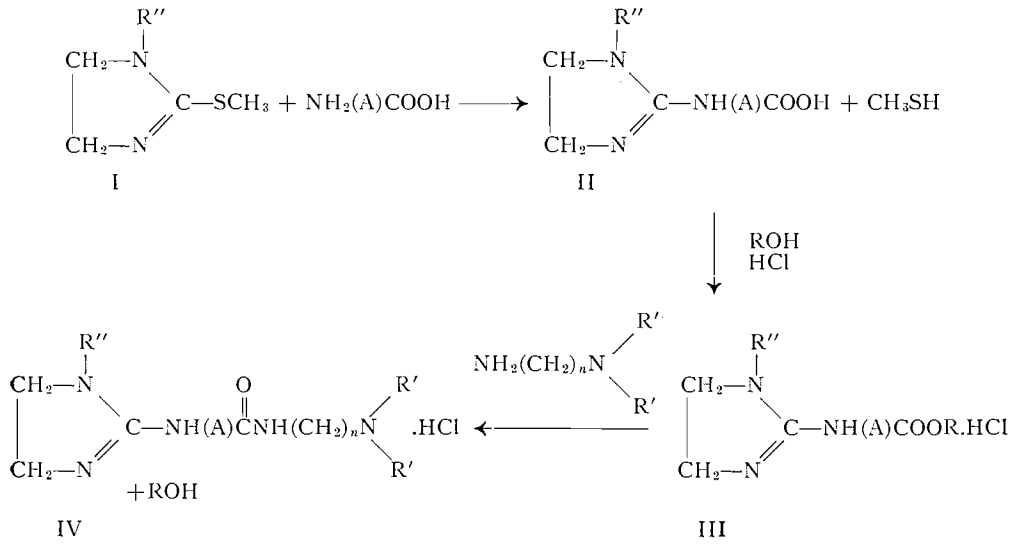
ABSTRACT

Several new cyclic guanidino acids have been prepared by the reaction of cyclic isothioureas with amino acids. The ethyl esters of some of these acids have been converted into dialkylaminoalkylamides by refluxing with dialkylaminoalkylamines in the presence of an inert solvent. A series of dialkylaminoethyl esters of the 2-(carboxyalkylamino)-2-imidazolines also have been prepared.

The reaction (3) of amino acids with cyclic isothioureas (I) provides a convenient method for the preparation of 2-(carboxyalkylamino)-2-imidazolines (II) (or the tautomeric 2-(carboxyalkylimino)-imidazolidines). These imidazoline derivatives are prepared most conveniently in the laboratory by refluxing the free base of a 2-methylmercapto-2-imidazoline and an amino acid in the presence on an inert solvent such as methanol or benzene. In this manner, the products have been obtained in yields as high as 96%.

Some difficulty has been experienced with the esterification of the 2-(carboxyalkylamino)-2-imidazolines (II). The yields of ester hydrochlorides (III) vary considerably although yields as high as 83% have been obtained. A



A = alkylene group R = alkyl or dialkylaminoethyl R′ = alkyl R″ = H or $-CH_2CH_2OH$

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number of dialkylaminoethyl esters of the 2-(carboxyalkylamino)-2-imidazolines also have been prepared. These are described fully in the Experimental section.

The ethyl esters of the 2-(carboxyalkylamino)-2-imidazolines are converted into the corresponding amides (IV) by refluxing with amines in the presence of inert solvents. The amides are very difficult to purify as free bases. They are generally waxy light brown solids, so their dipicrates have been prepared for identification.

EXPERIMENTAL[4]

γ-Aminobutyric Acid

A solution of 2-pyrrolidone[5] (212.5 gm., 2.50 mole) and anhydrous barium hydroxide (223.3 gm., 1.30 mole) in 1 liter of water was heated at 100°C. for two hours. The solution was cooled, a few drops of concentrated hydrochloric acid added, and the solution was neutralized with 2.3 *N* sulphuric acid (1129 cc.). The suspension was boiled for 30 min. and then allowed to stand overnight. The barium sulphate was filtered (with the aid of Celite) and the filtrate, on evaporation, gave 200 gm. (78%) of crude product. One crystallization from ethyl alcohol (2 liters) yielded 170 gm. (68%) of product melting at 198–198.5°C.

ε-Aminocaproic Acid

A solution of ε-caprolactam[6] (113 gm., 1.0 mole) and anhydrous barium hydroxide (95.0 gm., 0.55 mole) in 1500 cc. water was heated at 100°C. for two hours. The solution was cooled, a few drops of concentrated hydrochloric acid were added, and the solution was neutralized by dropwise addition of 3 *N* sulphuric acid (370 cc.). The suspension of barium sulphate was boiled for 10 min., and then allowed to settle overnight. The precipitate was removed by filtration and the filtrate was evaporated, yield 120 gm. (92%). This crude residue was crystallized from ethyl alcohol (1 liter) to give 100 gm. (76.5%) of material melting at 200–202°C.

2-(γ-Carboxypropylamino)-2-imidazoline

Method A

A solution of 2-methylmercapto-2-imidazolinium iodide (1) (244 gm., 1.0 mole), γ-aminobutyric acid (98.0 gm., 0.95 mole), and sodium hydroxide (80 gm., 2.0 mole) in 2 liters of water was allowed to stand at room temperature for three days. The evolved methyl mercaptan was absorbed in 20% sodium hydroxide solution. At the end of the reaction period, the solution was diluted to a volume of 6 liters with water and it was passed through a column of mixed-bed resin (2 liters of Amberlite IRA–400[7] activated resin and 2 liters of Amberlite IRC-50 resin[7]) at a rate of 20 cc. per min. The column was washed with water and the combined eluate and washings were evaporaed *in vacuo*. The semicrystalline residue weighed 130 gm. (80% yield). Crystallization from methanol (300 cc.) gave 100 gm. of white crystals melting at 185–224°C.

[4]*All melting points are uncorrected. Microanalyses by C. W. Beazley, Skokie, Illinois, and Drs. Weiler and Strauss, Oxford, England.*
[5]*General Aniline and Film Corp., New York, N.Y.*
[6]*Dupont Co. of Canada Limited, Montreal, Que.*
[7]*Rohm and Haas Company, Philadelphia, Penn., U.S.A.*

Another crystallization from methanol raised the melting point to a constant value of 224–225°C. Calc. for $C_7H_{13}N_3O_2$: C, 49.10; H, 7.65; N, 24.52%. Found: C, 48.78; H, 7.99; N, 24.75%. Its picrate, which was formed in aqueous solution, melted at 171–172°C. after crystallization from alcohol. Calc. for $C_{13}H_{16}N_6O_9$: C, 38.99; H, 4.03; N, 21.00%. Found: C, 38.79; H, 3.88; N, 21.18%.

Method B

A solution of 2-methylmercapto-2-imidazolinium iodide (122 gm., 0.5 mole) in 500 cc. of water was passed through a column of Amberlite IRA–400 resin (1 liter) at a rate of 7 cc. per min. and then the column was washed with 2 liters of water. γ-Aminobutyric acid (50.0 gm., 0.49 mole) was added to the total eluate and the solution was allowed to stand in the fume-hood at room temperature for 60 hr. An amorphous residue (79 gm., 95% yield)was obtained from evaporation of this solution *in vacuo*. One crystallization from methanol (200 cc.) gave pure 2-(γ-carboxypropylamino)-2-imidazoline (m.p. 224–225°C.). This product did not depress the melting point of a sample of the acid prepared by method A. The methanolic mother liquor on evaporation gave 12 gm. of oily residue. This oil has not been identified.

Method C

2-Methylmercapto-2-imidazolinium iodide (24.4 gm., 0.10 mole) was added to a solution of potassium hydroxide (11.4 gm., 0.20 mole) in 12 cc. of water. This solution was extracted with ether (4×50 cc.) and the ethereal solution was evaporated. Nine grams (77.5%) of the free base, 2-methylmercapto-2-imidazoline, was obtained. The 2-methylmercapto-2-imidazoline and γ-aminobutyric acid (7.5 gm., 0.073 mole) in methanol (100 cc.) were refluxed for two hours until the evolution of methylmercaptan had ceased. When the solution was concentrated *in vacuo*, 12 gm. (96% yield based on γ-aminobutyric acid) of 2-(γ-carboxypropylamino)-2-imidazoline (m.p. 223–225°C.) was obtained.

1-(β-Hydroxyethyl)-2-(γ-carboxypropylamino)-2-imidazoline

γ-Aminobutyric acid (64.3 gm., 0.62 mole), 1-(β-hydroxyethyl)-2-methylmercapto-2-imidazolinium iodide (4) (179.4 gm., 0.60 mole), and sodium hydroxide (25.0 gm., 0.62 mole) were dissolved in 3 liters of water and this solution was allowed to stand at room temperature for three days. After the reaction was complete, the solution was processed as described in method A above for 2-(γ-carboxypropyl)-2-imidazoline. The crude product (94 gm., 77% yield) was purified to constant melting point of 204.5–205.5°C. by crystallization from methanol, yield 36.0 gm. Calc. for $C_9H_{17}N_3O_3$: C, 50.22; H, 7.97; N, 19.53%. Found: C, 50.21; H, 8.12; N, 19.80%.

1-(β-Hydroxyethyl)-2-(ε-carboxypentylamino)-2-imidazoline

1-(β-Hydroxyethyl)-2-methylmercapto-2-imidazolinium iodide (115.2 gm., 0.40 mole) in 62 cc. of absolute ethanol was added to a 2.42 *N* absolute ethanolic potassium hydroxide solution at 0°C. Ether (680 cc.) was added and the precipitated potassium iodide (65.3 gm., 98.2% yield) was removed by filtration. ε-Aminocaproic acid (46 gm., 0.35 mole) was added to the filtrate and the ether was removed by distillation. The residual alcoholic solution was refluxed for six hours until the evolution of methylmercaptan ceased. The alcoholic

solution on cooling gave 66.2 gm. (78%) of crude product which melted at 188–195°C. Crystallization from methanol (6 cc. per gm.) raised the melting point to a constant value of 209–210°C. Calc. for $C_{11}H_{21}N_3O_3$: C, 54.20; H, 8.70; N, 17.28%. Found: C, 54.25; H, 8.76; N, 16.80%.

2-(γ-Carbethoxypropylamino)-2-imidazoline

A solution of 2-(γ-carboxypropylamino)-2-imidazoline (17.1 gm., 0.1 mole) in ethanol (150 cc.) containing 0.3 mole of hydrogen chloride was refluxed for two hours. Benzene (50 cc.) was added and the refluxing was continued another hour. The benzene was distilled from the solution to remove water as the benzene–water–alcohol azeotrope. This procedure was repeated twice more and then the solution was taken to dryness, yield 21.0 gm. (89.5%). A sample of this product in aqueous solution was converted into its picrate. Its melting point was raised from 104–108°C. to 114–115°C. by three crystallizations from 50% aqueous ethanol. Calc. for $C_{15}H_{20}N_6O_9$: C, 42.02; H, 4.71; N, 19.62%. Found: C, 42.19; H, 4.65; N, 19.9%.

2-(N-γ-Dimethylaminopropyl-γ-carbamylpropylamino)-2-imidazoline

The above-described 2-(γ-carbethoxypropylamino)-2-imidazolinium chloride (20.5 gm., 0.087 mole) and γ-dimethylaminopropylamine (10.4 gm., 0.1 mole) were dissolved in absolute ethanol (200 cc.) and this solution was refluxed for four hours. Then the solution was evaporated to dryness and the residue was dissolved in 300 cc. of water. This aqueous solution was passed through a column of activated Amberlite IRA-400 resin (400 cc.) and the column was washed with water (1 liter). On evaporation the eluate gave 5.5 gm. (24.7%) of a brown gummy solid. This solid, its mono- and its di-hydrochlorides, could not be purified by crystallization. Its picrate formed from aqueous solution melted at 155–155.5°C. Calc. for $C_{24}H_{31}N_{11}O_{15}$: C, 40.38; H, 4.38; N, 21.6%. Found: C, 40.37; H, 4.56; N, 21.82%.

β-Diethylaminoethylamine

N,N-Diethyl ethylenediamine (b.p. 146–150°C. at 760 mm.; $n_D^{25} = 1.4345$) was obtained in 41% yield by the method of Braz and Skorodumov (2). This reaction also gave a 21.8% yield of N,N-diethyl-N′-(2-aminoethyl) ethylenediamine ($n_D^{27} = 1.4572$) as well as higher addition products.

2-(N-β-Diethylaminoethyl-γ-carbamylpropylamino)-2-imidazoline

A solution of 2-(β-carbethoxyethylamino)-2-imidazolinium chloride (7.34 gm., 0.029 mole) and β-diethylaminoethylamine (3.4 gm., 0.029 mole) in 60 cc. of absolute ethanol was refluxed for four hours. After evaporation, this solution gave 9.0 gm. (95%) of amorphous material. The residue was dissolved in methanol (100 cc.) and the methanolic solution was passed through a column of Amberlite IRA-400 resin (150 cc.). After the column was washed with methanol (450 cc.), the total eluate was evaporated. The oily residue weighed 3.2 gm. (35.6%). It could be crystallized from ethyl acetate (8 cc.) to give a gummy reddish solid. A picrate formed from this solid melted at 135–135.5°C. Calc. for $C_{25}H_{33}N_{11}O_{15}$: C, 41.26; H, 4.57; N, 21.2%. Found: C, 41.11; H, 4.36; N, 21.28%.

2-(N-γ-Dimethylaminopropylcarbamylmethylamino)-2-imidazoline (VI)

2-(Carbethoxymethylamino)-Δ^2-1,3-diazacyclopentene hydrochloride (3) (4.23 gm., 0.02 mole) and 2.08 gm. (0.02 mole) of N,N-dimethylaminopropylamine were refluxed in the presence of 40 cc. of absolute ethanol for four hours. On cooling in the refrigerator, a white solid separated, yield 0.658 gm. (22.5%). This solid melted at 280°C. with decomposition. It was identified as the free acid 2-(carboxymethylamino)-Δ^2-1,3-diazacyclopentene, by a comparison of their infrared absorption spectra. The ethanolic filtrate from the free acid was taken to dryness *in vacuo*. The residue was a viscous oil, which crystallized on standing, yield 4.09 gm. (74.8% as the monohydrochloride). A small sample of this solid was precipitated as its picrate from its aqueous solution. Two crystallizations from water raised the melting point from 167°C. to 189.5–191°C. Anal. Calc. for dipicrate $C_{22}H_{27}N_{11}O_{15}$: C, 38.52; H, 3.97; N, 22.48%. Found: C, 38.11; H, 4.14; N, 22.25%.

Dimethylaminoethyl Ester of 2-(ε-Carboxypentylamino)-2-imidazolinium Chloride Monopicrate

2-(ε-Carboxypentylamino)-2-imidazoline (3) (9.9 gm., 0.05 mole) and dimethylaminoethanol (4.5 gm., 0.05 mole) were suspended in 150 cc. of toluene and heated at 140°C. for 10 hr. During the heating period dry hydrogen chloride was bubbled through the solution and toluene was distilled over slowly. Fresh toluene was added at intervals as required. On cooling, the toluene was decanted and the oily residue was converted into its picrate in aqueous solution, yield 17 gm. (63.5%). The melting point of this picrate was raised from 183–185°C. to 186–187.5°C. by one crystallization from ethanol. Calc. for $C_{19}H_{30}ClN_7O_9$: C, 42.65; H, 5.63; Cl, 6.62; N, 18.30%. Found: C, 43.02; H, 5.57; Cl, 6.75; N, 18.28%.

Dimethylaminoethyl Ester of 2-(γ-Carboxypropylamino)-2-imidazolinium Chloride Monopicrate

The dimethylaminoethyl ester of 2-(γ-carboxypropylamino)-2-imidazoline chloride monopicrate (m.p. 183–185°C.) was prepared in 46.3% yield by the above procedure. One crystallization from acetonitrile raised the melting point to a constant value of 188–189°C. Calc. for $C_{17}H_{26}ClN_7O_9$: C, 40.25; H, 5.16; Cl, 6.98; N, 19.35%. Found: C, 40.44; H, 5.15; Cl, 6.73; N, 19.25%.

Dimethylaminoethyl Ester of 2-(Carboxymethylamino)-2-imidazoline Dipicrate

The above esterification procedure gave the dipicrate of the dimethylaminoethyl ester of 2-(carboxymethylamino)-2-imidazoline (m.p. 152–156°C.) in 48.0% yield. Two crystallizations from acetonitrile raised the melting point to 161.5–165.5°C. Calc. for $C_{21}H_{24}N_{10}O_{16}$: C, 37.55; H, 3.37; N, 20.85%. Found: C, 37.85; H, 3.46; N, 20.57%.

In a similar manner the following dialkylaminoalkyl esters of 2-(ε-carboxypentylamino)-2-imidazoline were prepared.

Diisopropylaminoethyl Ester of 2-(ε-Carboxypentylamino)-2-imidazoline Dipicrate

M.p. 127–130°C.; yield 86.6%. Calc. for $C_{29}H_{40}N_{10}O_{16}$: C, 44.35; H, 5.14; N, 17.85%. Found: C, 44.76; H, 5.08; N, 17.78%.

Diethylaminoethyl Ester of 2-(ε-Carboxypentylamino)-2-imidazoline Dipicrate

M.p. 120–123°C.; yield 68.8%. Calc. for $C_{27}H_{36}N_{10}O_{16}$: C, 42.85; H, 4.79; N, 18.51%. Found: C, 43.15; H, 4.51; N, 18.49%.

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