at 3 atm for 16 hr. Filtration and evaporation of the filtrate to dryness under vacuum yielded a yellow oil. This was treated with 80 mg of picric acid in the minimum of boiling $CHCl_3$. On cooling and addition of a few drops of *n*-hexane, 155 mg (91%) of dark red crystals were obtained; mp 110–112° dec. Three crystallizations of the picrate from $CHCl_3$ containing a few drops of *n*-hexane gave pure VII, mp 114–114.5° dec.

Anal. Calcd for $C_{19}H_{18}N_4O_{11}$: C, 47.70; H, 3.79; N, 11.71. Found: C, 47.64; H, 3.99; N, 11.72.

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Heterocyclic Amines. III. 3-Dimethylaminofuran[1]

JOHN D. PRUGH[2] AND WALTER C. MCCARTHY

College of Pharmacy, University of Washington, Seattle, Washington 98105

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3-Dimethylaminofuran has been prepared from 3-furoyl azide by rearrangement to the urethan, methylation, and reduction, a route analogous to that recently reported for the synthesis of 3-dimethylaminothiophene.[3] The free base, isolated by preparative gas chromatography, was stable under vacuum or inert atmosphere, but it polymerized very rapidly in contact with the air. The amine readily reacted with methyl iodide to produce the quaternary salt, a white crystalline compound stable in air.

Pharmacology.[4]—3-Furyltrimethylammonium iodide, administered intravenously in a dose of 100 mg/kg, was fatal to two mice. The next lower dose, 31.6 mg/kg, was not lethal but produced ptosis, decreased activity, and irregular respiratory movements. A dose of 1 mg/kg administered quickly intravenously to a rat induced a biphasic vasomotor response of small magnitude; a similar response followed slow injection of 5 mg/kg. After this latter dose, epinephrine elicited a vasodepressor response, the pressor effect of norepinephrine was reduced, and the fall in blood pressure evoked by acetylcholine was markedly enhanced and prolonged.

For comparison, 3-thienyltrimethylammonium iodide[3] administered intravenously in doses of 100, 31.6, and 10 mg/kg to groups of two mice produced respectively 2, 1, and 0 fatalities. Ptosis, decreased locomotor activity, ataxia, and respiratory irregularities were observed in the survivors. In the rat, an intravenous dose of 0.5 mg/kg evoked a transient hypotensive response, and a dose of 5 mg/kg increased the magnitude and duration of the depressor response evoked by acetylcholine. In a cat, an intravenous dose of 1 mg/kg elicited a sharp, brief fall in blood pressure, but did not modify responses to epinephrine, norepinephrine, acetylcholine, or histamine. A dose of 4.7 mg/kg administered slowly intravenously to a cat caused complete respiratory arrest, a slight depressor response followed quickly by a marked rise in blood pressure, and copious salvation. Death ensued within a few minutes; marked fasciculations were evident for several minutes after death.

Phenyltrimethylammonium iodide was lethal to mice intravenously at doses of 10 mg/kg and higher. Increased locomotor activity and hypersensitivity to sound were observed at a dose of 1 mg/kg; ptosis and hyperpnea were noted after 3.16 mg/kg.

Experimental Section

3-Furoyl Azide.[5]—From 10.5 g (0.081 mole) of 3-furoyl chloride[6] in cold acetone and excess aqueous sodium azide, worked up as reported for the thiophene compound,[3] there was obtained 9.3 g (84%) of crude oily azide. Some crystallization occurred while evaporating the ether solution, but these crystals melted below room temperature.

Methyl N-(3-Furyl)carbamate.—Crude 3-furoyl azide (9.3 g, 0.068 mole) refluxed with 100 ml of absolute methanol for 12 hr; subsequent evaporation of the solvent gave 9.3 g of crude product, mp 76–83°. This crude material was satisfactory for methylation and the compound could be more readily purified at the next step. Recrystallization from ligroin gave 4.4 g (46%) of purified product, mp 81–83°, which upon vacuum sublimation gave white crystals: mp 82–83°; nmr spectrum[7] in $CDCl_3$, δ = 3.74 (s, CH_3, 3 H), 6.36 (q, 4-H of ring, 1 H), 7.24 (t, 5-H of ring, 1 H), 7.49 (broad s, NH,[8] 1 H), 7.74 (broad s, 2-H of ring, 1 H) ppm; J_{24} = 0.9 cps, J_{25} = 1.9 cps, J_{45} = 1.9 cps.

Anal.[9] Calcd for $C_6H_7NO_3$: C, 51.06; H, 5.00; N, 9.93; O, 34.01. Found: C, 51.02; H, 4.93; N, 9.92; O, 33.96.

Methyl N-Methyl-N-(3-furyl)carbamate.—Crude methyl N-(3-furyl)carbamate (14.1 g, 0.1 mole), 1 l. of anhydrous xylene, 32 ml (0.5 mole) of methyl iodide, and 45.8 g (1.0 mole) of a 52.5% dispersion of NaH in mineral oil were refluxed under nitrogen for 12 hr, with agitation by means of a Vibro Mixer.[10] The precipitated NaI and excess NaH were removed by filtration, and the xylene was evaporated under reduced pressure. The residue was chromatographed on 450 g of Merck alumina. The mineral oil from the NaH dispersion was removed by washing with petroleum ether. The methylated carbamate product was eluted with 4 l. of benzene. (Unmethylated starting material remained on the column and could be subsequently eluted with ether.) Evaporation of the benzene eluates gave an oil which distilled at 50–56° (0.2 mm) in a yield of 13.4 g (86%). An analytical sample was redistilled at 42° (0.06 mm): nmr spectrum in $CDCl_3$, δ = 3.26 (s, NCH_3, 3 H), 3.80 (s, OCH_3, 3 H), 6.60 (m, 4-H of ring, 1 H), 7.30 (t, 5-H of ring, 1 H), 7.55 (broad s, 2-H of ring, 1 H) ppm; J_{25} = 1.7 cps, J_{45} = 1.7 cps.

Anal. Calcd for $C_7H_9NO_3$: C, 54.19; H, 5.85; N, 9.03; O, 30.94. Found: C, 54.34, 54.32; H, 5.93, 5.77; N, 9.10, 9.12; O, 30.81, 31.02.

3-Dimethylaminofuran.—Methyl N-methyl-N-(3-furyl)carbamate (5 g, 0.032 mole), dissolved in 50 ml of anhydrous tetrahydrofuran was added to a solution of 2.4 g (0.064 mole) of $LiAlH_4$ in 100 ml of anhydrous tetrahydrofuran. The mixture was refluxed under dry nitrogen for 70 hr, cooled to room temperature, 5 ml of water was added with vigorous stirring, followed by the addition of 2 mg of hydroquinone. The solid was removed by

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(2) Fellow of the American Foundation for Pharmaceutical Education and Josiah Kirby Lilly Memorial Fellow for 1962–1964.

(3) J. B. Sullivan and W. C. McCarthy, *J. Org. Chem.*, **30**, 662 (1965).

(4) We wish to acknowledge our indebtedness to Dr. Winnie Teeters, of Hazleton Laboratories, Inc., Falls Church, Va, who performed the pharmacological tests reported here.

(5) Prepared without isolation by a different method and utilized for subsequent syntheses by R. R. Burtner, *J. Am. Chem Soc.*, **56**, 666 (1934).

(6) (a) H. Gilman and R. R. Burtner, *ibid.*, **55**, 2903 (1933). (b) The 3-furoic acid was prepared according to S. Gronowitz and G. Sorlin, *Arkiv Kemi*, **19**, 515 (1962).

(7) Nmr spectra were taken at 60 Mc and reported as δ values in ppm from tetramethylsilane (internal reference). Coupling constants are reported in cps ±0.2.

(8) Identified by deuteration in heavy water plus deuteriomethanol.

(9) Elemental analyses by A. Bernhardt, Mülheim (Ruhr), Germany.

(10) In similar runs with conventional stirring, yields of only about 20% were obtained, apparently because the sodium salt of the urethan formed a coating on the NaH particles.

filtration and the filtrate was stored at 0° under nitrogen. After evaporating part of the solvent under reduced pressure, the pure amine was isolated by preparative-scale gas chromatography on a 5-ft Carbowax column at 100°; nmr spectrum in CCl_4, δ = 2.59 (s, CH_3, 6 H), 6.03 (q, 2-H of ring, 1 H), 6.74 (q, 4-H of ring, 1 H), 7.15 (t, 5-H of ring, 1 H) ppm; J_{24} = 1.1 cps, J_{25} = 1.8 cps, J_{45} = 1.8 cps.

Anal. Calcd for C_6H_9NO: C, 64.84; H, 8.16; N, 12.60; O, 14.40. Found: C, 64.72, 64.64; H, 8.09, 8.03; N, 12.56, 12.57; O, 14.61, 14.52.

3-Furyltrimethylammonium Iodide.—The amine was added to excess methyl iodide at 0° and the salt was recrystallized from anhydrous ethanol. No satisfactory melting point could be obtained; it started to turn brown at 160°, with progressive decomposition above that temperature until a black mass was obtained at 190°.

Anal. Calcd for $C_7H_{12}INO$: C, 33.22; H, 4.78. Found: C, 33.24, 33.09; H, 4.70, 4.78.

Poly-L-α,γ-diaminobutyric Acid Hydrochloride

MARGARET J. FRIDECKY AND WILLIAM H. MCGREGOR

Union Carbide Research Institute, P. O. Box 278, Tarrytown, New York

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The biocidal properties of polylysine and polyornithine[1] has prompted us to prepare a polymer of the next lower homolog. A crude poly-α,γ-diaminobutyric acid had been prepared by Schmidt degradation of polyglutamic acid[2] but the preparation of this polymer by polymerization of N^{α}-carbobenzoxy-L-α,γ-diaminobutyric N-carboxyanhydride has not been reported.[3] The action of phosphorus pentachloride on $N^{\alpha,\gamma}$-dicarbobenzoxydiaminobutyric acid yielded 1-carbobenzoxy-3-carbobenzoxyaminopyrrolid-2-one and not the expected N-carboxyanhydride.[4] More recently,[5] N^{γ}-tosyl-L-α,γ-diaminobutyric acid was phosgenated and then treated with hydrochloric acid resulting in a sequence of ring closure, opening, decarboxylation, and ring closure. The presumed intermediate, an N-carboxyanhydride (NCA), was neither isolated or characterized but the results suggested the NCA could be prepared in this manner. The polymer was then synthesized by methods already described for polylysine[6] except for minor details.

The polymer was an effective inhibitor of the growth of *Alternaria* species at levels of 0.5% (by weight) and caused lysis of *Paramecium caudatum* at levels equivalent to polylysine and polyornithine (see Table I). The polymer was not attacked by trypsin or pepsin under the usual conditions.

Experimental Section

Melting points are uncorrected. Elementary analyses were performed by Schwarzkopf Microanalytical Laboratory. Amino acid analysis was performed by Analytica Corp.

TABLE I

ACTIVITY AGAINST *Paramecium caudatum*

Prepn	DP[a]	Survival of paramecium[b] — Concn of prepn 10^{-5} M	10^{-4} M	10^{-3} M
Poly-L-lysine	5–10	>3000	>3000	...
Poly-L-lysine	25	10–12	3–5	<3
Poly-L-ornithine	25	13–17	5–7	<5
Poly-L-α,γ-diaminobutyric acid	50	12–14	6–8	<6
Streptomycin		>3000	500	75

[a] Degree of polymerization. [b] Time required for complete lysis in seconds.

N^{γ}-Carbobenzoxy-L-α,γ-diaminobutyric Acid.—L-α,γ-Diaminobutyric acid dihydrochloride (1.9 g) was dissolved in 15 ml of boiling water and 2 g of basic copper carbonate added with stirring over a period of 10 min. The excess copper carbonate was removed and washed with 5 ml of hot water on the filter. The blue filtrate was cooled in an ice bath, 5 ml of 2 *N* NaOH was added, and with rapid stirring, 2 ml of carbobenzoxy chloride and 5 ml of 2 *N* NaOH were added simultaneously over a period of 1 hr. The light blue product formed was filtered, washed with water, acetone, and ether yielding 2.2 g (70%) of the carbobenzoxyamino acid copper chelate, mp 231–233° dec. The free acid was obtained by bubbling H_2S through a stirred suspension of the Cu salt in 50 ml of water for 30 min. The mixture was heated to boiling and filtered hot. The filtrate yielded on cooling 0.9 g of N^{γ}-carbobenzoxy-α,γ-diaminobutyric acid, mp 240–242° dec, lit.[7] mp 238° dec.

N^{γ}-Carbobenzoxy-L-α,γ-diaminobutyric Acid NCA.—Phosgene was bubbled for 30 min through a suspension of N^{γ}-carbobenzoxy-L-α,γ-diaminobutyric acid (1.1 g) in 60 ml of purified dioxane, during which solution occurred. Nitrogen was bubbled through the solution for 3 hr to remove excess phosgene. The solution was evaporated to 10 ml under reduced pressure to remove last traces of phosgene and 20 ml of ethyl acetate was added. The solution was filtered and hexane was added to the cloud point. After several hours at −20° a small amount of yellow oil had settled on the bottom of the flask, so the supernatant was decanted and hexane was added to the latter to the cloud point. After remaining at −20° overnight the crystals were collected and washed with hexane; yield 0.71 g, mp 54–59° (effervescing at 67°). An additional 100 mg of product was obtained from the mother liquor by addition of more hexane. For analysis the product was recrystallized from ethyl acetate and hexane and dried (NaOH, paraffin) *in vacuo* at −20° for several days. There was no change in the melting point after recrystallization.

Anal. Calcd for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.72; N, 10.07. Found: C, 56.04; H, 5.94; N, 10.17.

Poly-N^{γ}-Carbobenzoxy-L-α,γ-diaminobutyric Acid.—N^{γ}-Carbobenzoxy-L-α,γ-diaminobutyric acid NCA (500 mg) was dissolved in 5 ml of redistilled dimethylformamide, and 0.035 ml of a 10% (v/v) solution of diethylamine in dimethylformamide was added as initiator. Polymerization was allowed to proceed at room temperature for 2 days when 10 ml of water was added. The polymer was filtered, washed with water, and dried (NaOH) *in vacuo* giving 355 mg of a white solid. Titration of the amino end groups of this polymer with $HClO_4$ in glacial acetic acid indicated that the preparation had a DP of 50.

Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.52; H, 6.02; N, 11.96. Found: C, 61.24; H, 6.48; N, 11.60.

Poly-L-α,γ-diaminobutyric Acid Hydrochloride.—Poly-N^{γ}-carbobenzoxy-L-α,γ-diaminobutyric acid (100 mg) was suspended in 35 ml of dioxane–chloroform (2:5, v/v) and anhydrous HCl was bubbled through the mixture for 20 min at room temperature during which time the polymer dissolved.[6] Anhydrous HBr was then passed through the solution for 0.75 hr precipitating the mixed salt of the decarbobenzoxylated polymer. Nitrogen was bubbled through the mixture to remove the excess acid and the polymer was washed three times in the centrifuge with ethanol–ether (1:1, v/v). The product was dried *in vacuo* (NaOH) at room temperature giving 65 mg of a white solid, which was dialyzed against frequent changes of 0.01 *M* HCl for 5 days at 4° and for 2 days against distilled water at 4°.

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