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

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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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After lyophyllization and drying *in vacuo* at room temperature, the polymer (50 mg) was analyzed for α,γ-diaminobutyric acid. The theoretical yield of the latter was obtained on hydrolysis of the polymer and amino acid analysis of the hydrolysate.

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Sulfamylsemicarbazide Hypoglycemic Agents. IV

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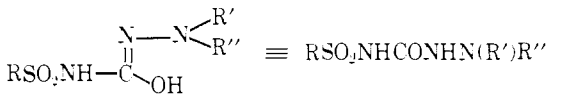
Early reports of the blood sugar lowering effects of certain sulfonamido-1,3,4-thiadiazoles,[1] and more recently of the corresponding oxadiazoles[2] suggested that amalgamation of portions of these heterocyclic structures into the urea portion of known hypoglycemic sulfonyl- and sulfamylureas[3] might lead to new and more useful agents for the treatment of diabetes.

The portion of the thia- and oxadiazoles which most readily appeared to lend itself to incorporation with the sulfonyl- and sulfamylurea structure was the N–C–N–N linkage (I). Such a combination would conceivably give rise to a sulfonylsemicarbazide (II).

I, X = O and S



II

Shortly after the work had commenced certain sulfonylsemicarbazides were disclosed in the literature to have hypoglycemic activity in man.[4,5] Additional research with these classes of compounds, therefore, was restricted to the sulfamylsemicarbazides.

The synthesis of these compounds was most conveniently effected by a variation of a method developed in our laboratories for the preparation of sulfonylureas.[6] Essentially, it consisted of the reaction of the sodium salt of an appropriately substituted sulfamide with a 4,4-diphenyl-1,1-tetrasubstituted semicarbazide in a highly polar solvent. The tetrasubstituted semicarbazides were most readily prepared from diphenylcarbamoyl chloride and the requisite hydrazine. The hydrazines were synthesized by reduction of the corresponding nitrosoamines. Preparation of the sulfamides and the amines from which they were derived, with a few exceptions, have been previously reported.[3]

Pharmacological Methods and Results.—All compounds were screened in groups of 8–10 rats of the Sprague–Dawley strain, fasted for 18 hr prior to the experiment. The rats were lightly anesthetized with pentobarbital (15 mg/kg ip), a blood sample was taken from the tail vein, and the compound was administered orally by stomach tube at a dose of 100 mg/kg. Additional blood samples were taken at 2, 4, and 6 hr after administration of drug. Blood glucose was determined with an Auto Analyzer according to the micromethod recommended by the manufacturer (Technicon Instruments Corp.). The maximum percentage decrease, with standard deviation, in blood sugar was calculated and is reported as hypoglycemic activities in the tables. Chlorpropamide was included in Table I as a standard hypoglycemic agent.

It can be seen that many compounds have hypoglycemic activity equal to the standard, chlorpropamide. In general, peak activity was attained when a 4,4-disubstituted piperidine moiety was employed in the sulfamyl portion of the structure, while poor activity was associated with the congeners in which the sulfamyl portion was derived from thiomorpholine. Both these structure–activity characteristics are also found in the sulfamylurea series.[3] Since it was also evident from the sulfamylurea study that a cycloalkyl group on the terminal nitrogen of the urea led to compounds with better hypoglycemic activity, this structural feature was incorporated by synthesis of a 1,1-disubstituted semicarbazide in which the substituents, taken together, formed a cyclic structure. When the sulfamyl portion of the compounds was kept the same, and only the size of the cyclic structure was varied, insignificant changes in hypoglycemic activity were seen.

Experimental Section[7]

1,1-Hexamethylene-4-(4,4-dimethyl-1-piperidinesulfamyl)-semicarbazide.—To 4.28 g (0.02 mole) of sodium salt of 1-sulfamyl-4,4-dimethylpiperidine suspended in 60 ml of dimethylformamide was added 8.6 g (0.028 mole) of 1,1-hexamethylene-4,4-diphenylsemicarbazide. The resulting mixture was heated on a steam bath for a total of 45 min; during this time the dissolution of the reactants was followed by the formation of a new precipitate. The mixture was cooled in an ice bath and was filtered. The collected sodium salt of the product was partially dissolved in 125 ml of water, and the pH was adjusted to 6.5–7.0 by the addition of dilute HCl. The desired product (3.7 g) was filtered, dried, and recrystallized from ether. The sulfamylsemicarbazides prepared by the diphenylsemicarbazide route were synthesized by a similar procedure in yields which varied between 50–70%. The sulfamylsemicarbazides and their physical properties are listed in Tables I and II.

1-Sulfamylpiperazine.—A mixture of 96.1 g (1.0 mole) of sulfamide and 89.6 g (1.04 moles) of piperazine in 200 ml of 1,2-dimethoxyethane was allowed to reflux on a steam bath overnight. The resulting mixture was cooled to room temperature and was filtered. The solids were suspended in 600 ml of water and maintained at steam-bath temperatures for 1 hr. The suspension (1,4-disulfamylpiperazine) was cooled and filtered. The filtrate was concentrated *in vacuo* to a small volume, and the precipitated solid was triturated with methanol. The desired product was filtered and recrystallized from methanol (53 g, mp

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(7) Boiling points are uncorrected. Melting points were determined on a Thomas–Hoover capillary melting point apparatus and are uncorrected. The analyses were carried out by the Physical Measurements Laboratory of Chas. Pfizer & Co., Inc.