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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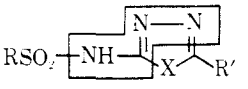
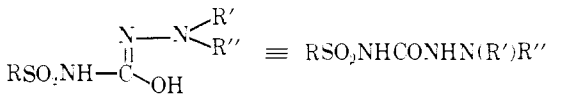
Early reports of the blood sugar lowering effects of certain sulfonamido-1,3,4-thiadiazoles,[1] and more recently of the corresponding oxadiazoles[2] suggested that amalgamation of portions of these heterocyclic structures into the urea portion of known hypoglycemic sulfonyl- and sulfamylureas[3] might 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 95.1 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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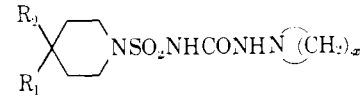
(7) Boiling points are uncorrected. Melting points were determined on a Thomas–Hoover capillary melting point apparatus and are uncorrected. The analyses were carried out by the Physical Measurements Laboratory of Chas. Pfizer & Co., Inc.

TABLE I

PIPERIDINESULFAMYLSEMICARBAZIDES



No.	R_1	R_2	x	Mp, °C	Crystn solvent[a]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Hypoglycemic activity[b]
1	H	H	5	131.5–132	E	$C_{11}H_{22}N_4O_3S$	45.4	7.6	19.3	45.5	7.5	19.5	14.8 ± 7.0
2	H	H	6	157.5 dec	E	$C_{12}H_{24}N_4O_3S$	47.4	8.0	18.4	47.6	7.9	18.1	11.1 ± 1.9
3	H	CH_3	5	162–162.5	A	$C_{12}H_{24}N_4O_3S$	47.4	8.0	18.4	47.9	8.0	18.6	26.1 ± 2.6
4	H	CH_3	6	148 dec	E	$C_{13}H_{26}N_4O_3S$	49.0	8.2	17.6	49.1	8.0	17.0	33.9 ± 1.5
5	CH_3	CH_3	5	153.5 dec	E	$C_{13}H_{26}N_4O_3S$	49.0	8.2	17.6	49.0	8.0	17.5	39.1 ± 2.8
6	CH_3	CH_3	6	146 dec	E	$C_{14}H_{28}N_4O_3S$	50.6	8.5	16.9	50.3	8.4	16.8	34.9 ± 3.3
7	CH_3	C_2H_5	6	135.5 dec	E	$C_{15}H_{30}N_4O_3S$	52.0	8.7	16.2	52.3	8.6	15.8	42.0 ± 3.3
8	C_2H_5	C_2H_5	6	139.5 dec	E	$C_{16}H_{32}N_4O_3S$	53.3	9.0	15.5	53.0	8.7	15.2	34.4 ± 2.8
9	$-(CH_2)_4-$		5	154.5–155	E–A	$C_{15}H_{28}N_4O_3S$	52.3	8.2	16.3	52.7	8.3	16.6	35.6 ± 2.4
10	$-(CH_2)_4-$		6	155 dec	E	$C_{16}H_{30}N_4O_3S$	53.6	8.4	15.6	53.7	8.5	15.3	30.8 ± 3.7
11	$-(CH_2)_5-$		6	152 dec	E	$C_{17}H_{32}N_4O_3S$	54.8	8.7	15.0	55.0	8.7	15.1	25.0 ± 3.7
12	CH_3O	H	6	132–133	E	$C_{13}H_{26}N_4O_4S$	46.7	7.8	16.8	46.8	7.8	16.5	24.8 ± 3.1
Chlorpropamide													35 ± 3.3

[a] E = ether, A = acetone. [b] Maximum per cent fall in blood sugar and standard error at 100 mg/kg.

TABLE II

MORPHOLINE-, THIOMORPHOLINE-, AND PIPERAZINESULFAMYLSEMICARBAZIDES

No.	Y	x	Mp, °C	Crystn solvent[a]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Hypoglycemic activity[b]
1	O	5	153–153.5	A	$C_{10}H_{20}N_4O_4S$	41.1	6.9	19.2	41.1	6.7	19.3	14.8 ± 2.9
2	O	6	154 dec.	*c*	$C_{11}H_{22}N_4O_4S$	43.1	7.2	18.3	43.1	7.1	18.6	22.5 ± 2.6
3	S	5	150.5–152	A	$C_{10}H_{20}N_4O_3S_2$	38.9	6.5	18.2	38.9	6.6	18.1	6.5 ± 1.7
4	CH_3CON	6	172 dec.	N	$C_{13}H_{25}N_5O_4S$	44.9	7.3	20.2	44.9	7.2	20.1	23.8 ± 3.5
5	$(CH_3)_2CHCON$	6	138 dec.	B	$C_{15}H_{29}N_5O_4S$	48.0	7.8	18.7	47.5	7.2	18.5	11.7 ± 3.7

[a] A = acetone, N = acetonitrile, B = benzene. [b] See footnote *b* of Table I. [c] Not recrystallized.

163–165°). The analytical sample was recrystallized once again; mp 168–170°.

Anal. Calcd for $C_4H_{11}N_3O_2S$: C, 29.1; H, 6.7; N, 25.4. Found: C, 29.4; H, 6.7; N, 24.9.

1-Sulfamyl-4-acetylpiperazine.—To a suspension of 16.5 g (0.1 mole) of 1-sulfamylpiperazine in 230 ml of methylene chloride was added slowly 11.2 g (0.11 mole) of acetic anhydride. The resulting mixture was refluxed for 2 hr, and was then cooled and filtered, to yield 20 g, mp 177–179°. The product was further purified by recrystallization from ethanol; mp 179–181°.

Anal. Calcd for $C_6H_{13}N_3O_3S$: C, 34.8; H, 6.3; N, 20.3. Found: C, 34.4; H, 6.1; N, 20.3.

1-Sulfamyl-4-isobutyroylpiperazine.—By a similar procedure, 12.7 g (0.077 mole) of 1-sulfamylpiperazine and 11.0 g (0.07 mole) of isobutyric anhydride in 100 ml of CH_2Cl_2 gave 11.7 g of the desired product, mp 179–181°.

Anal. Calcd for $C_8H_{17}N_3O_3S$: C, 40.8; H, 7.3; N, 17.9. Found: C, 40.6; H, 7.1; N, 17.9.

1,1-Pentamethylene-4,4-diphenylsemicarbazide.—To a solution of 171 g (0.75 mole) of diphenylcarbamoyl chloride in 300 ml of dimethoxyethane was added 153 g (1.51 moles) of 1-aminopiperidine. The addition was made dropwise, with cooling, over a period of 2–3 hr. The mixture of product and hydrazine hydrochloride was filtered and suspended in 1500 ml of water. Filtration of the aqueous suspension, followed by drying of the filtered solids afforded 186 g of crude product, mp 154–158°. Two recrystallizations from acetone gave 142 g of pure product, mp 167.5–169°. Concentration of the aqueous filtrate gave 97.8 g of recovered 1-aminopiperidine as the hydrochloride salt.

Anal. Calcd for $C_{18}H_{21}N_3O$: C, 73.2; H, 7.2; N, 14.2. Found: C, 73.0; H, 7.2; N, 14.1.

1,1-Hexamethylene-4,4-diphenylsemicarbazide.—In an analogous manner 91 g (0.39 mole) of diphenylcarbamoyl chloride and 90 g (0.78 mole) of 1-aminohomopiperidine in 150 ml of dimethoxyethane gave 80.6 g of the desired product, mp 107.5–108.5°, and 55 g of recovered 1-aminohomopiperidine as the hydrochloride salt.

Anal. Calcd for $C_{19}H_{23}N_3O$: C, 73.8; H, 7.5; N, 13.6. Found: C, 73.8; H, 7.4; N, 13.8.

1-Aminopiperidine.—1-Nitrosopiperidine (44 g, 0.386 mole) was reduced with zinc dust and acetic acid[8] to give 36.5 g of the pure product, bp 41–44° (12 mm), lit.[9] bp 146° (728 mm).

Anal. Calcd for $C_5H_{12}N_2$: C, 60.1; H, 12.1; N, 28.0. Found: C, 59.7; H, 11.8; N, 27.9.

1-Aminohomopiperidine.—By a similar procedure 180 g (1.4 moles) of 1-nitrosohomopiperidine gave 86.8 g of the desired hydrazine, bp 86–86.5° (25 mm).

Anal. Calcd for $C_6H_{14}N_2$: C, 63.1; H, 12.4; N, 24.5. Found: C, 62.9; H, 12.0; N, 24.9.

1-Nitrosohomopiperidine.—To 79.5 g (0.8 mole) of hexamethylenimine was added, with cooling, 80 ml of 12 *N* HCl. The viscous liquid was warmed to 70°, and 69 g (1.0 mole) of $NaNO_2$ in 160 ml of water was added. During the addition, which required 1 hr, the product separated as an oil on the surface. After an additional 2 hr of stirring at 70°, the product was extracted with ether. The ether layer was dried, and the ether was removed *in vacuo* leaving an oil. Distillation of the residual oil gave 72.7 g of the desired product, bp 83–86° (2.0 mm).

Anal. Calcd for $C_6H_{12}N_2O$: C, 56.2; H, 9.4; N, 21.9. Found: C, 56.4; H, 9.6; N, 21.8.

Acknowledgments.—The authors are indebted to Messrs. Harold Ramus, Andrew Popson, and Frederic Smith for their technical assistance.

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