In a previously reported series,[1] 4-amino-6-anilinopyrimidine (L-25043) was assigned a potency of 100% and used as a reference compound. In this report N-(4-amino-6-pyrimidyl)acetamide was used as the reference compound; it was twice as potent as L-25043, so all relative potency figures in this report can be referred to the previous report if multiplied by 2.

Effect of N-(4-Amino-6-pyrimidinyl)acetamide on Blood Pressure, Respiration and the Electrocardiogram.—The blood pressure, respiration and electrocardiogram were studied in two dogs anesthetized with sodium phenobarbital. Following 5 mg./kg. given by tube into the duodenum, there was no significant change in mean arterial pressure in one dog during a 1 hr. observation period. In the second dog this dose was followed by a gradual fall in blood pressure (48%) reaching a maximum in 40 min. The respiration and electrocardiogram were not altered. In this dog a second dose of 10 mg./kg. was administered 4 hr. after the original dose. This was followed by an increase in mean arterial pressure of 14% in 40 min. Respiration and the electrocardiogram were not altered. In spite of a fall in pressure after 5 mg./kg. in one dog, it appears this compound has very little effect on blood pressure, respiration and the electrocardiogram. Since the blood pressure in this same dog showed a slight increase in mean artery pressure, it indicates that depressor action following 5 mg./kg. was due to anesthesia.

Acknowledgments.—The toxicity and pathology results were obtained by Drs. R. C. Anderson, P. N. Harris and F. G. Henderson of this laboratory. The microanalyses were done by William Brown, Howard Hunter, George Maciak and Miss Gloria Beckman.

Antidiabetic Agents. N^4-Arylsulfonylsemicarbazides

JOHN B. WRIGHT AND ROBERT E. WILLETTE

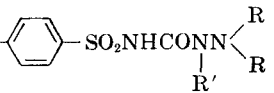
Research Laboratories of The Upjohn Company, Kalamazoo, Michigan

Received March 5, 1962

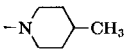
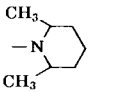
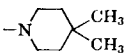
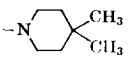
A series of N^4-arylsulfonylsemicarbazides (I, Table I) was prepared by reaction of arylsulfonylurethanes with suitably substituted hydrazines (II). The requisite hydrazines were prepared by reduction of nitrosamines (III) with lithium aluminum hydride. A number of the compounds prepared showed appreciable antidiabetic activity.

During the course of continuing work in these laboratories on antidiabetic compounds, we were interested in investigating arylsulfonylsemicarbazides of the general type I. Our initial experiments in this area produced compounds showing several times the blood sugar

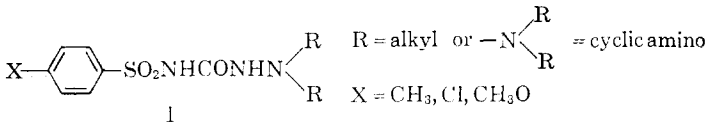
TABLE I: N^4-ARYLSULFONYLSEMICARBAZIDES



X	R′	R	Yield, %	M.p., °C.	Formula	Calcd., % C	H	N	S	Found, % C	H	N	S	Anti-diabetic activity (tolbutamide = 1)[a]
CH_3	H	$-N(CH_3)_2$	75	183–186[b]	$C_{10}H_{15}N_3O_3S$	46.68	5.88	16.33	12.46	47.03	6.01	16.27	12.37	1
CH_3	H	$-N(C_2H_5)_2$	34	150–152[c]	$C_{12}H_{19}N_3O_3S$	50.50	6.71	14.72	11.24	50.17	6.72	14.73	11.49	0.25
CH_3	H		33	189–191[c]	$C_{12}H_{17}N_3O_3S$	50.86	6.05	14.83	11.32	51.55	6.22	14.28	11.43	4
Cl	H		60	200.5–201.5[c]	$C_{11}H_{14}N_3O_3S$	43.49	4.64	13.83	10.56	43.68	4.72	13.91	10.13	1
CH_3	H		86	205–208[c]	$C_{13}H_{19}N_3O_3S$	52.51	6.44	14.13	10.78	52.76	6.41	13.93	10.94	2
CH_3	H		91	203–205[c]	$C_{12}H_{17}N_3O_4S$	48.15	5.73	14.04	10.71	47.78	5.35	14.24	10.74	0.5–1
Cl	H		67	170° dec.[d]	$C_{12}H_{17}ClN_4O_3S$	43.31	5.15	16.84	9.63	42.97	5.19	17.17	9.87	<0.2
CH_3	H		45	179–181[c]	$C_{13}H_{17}N_3O_3S$	52.86	5.80	14.23	10.85	52.76	5.54	14.16	10.82	5
CH_3	H		51	173.5–174.5[c]	$C_{14}H_{21}N_3O_3S$	54.00	6.80	13.49	10.30	54.56	6.96	13.21	11.02	0.25
CH_3	H		91	179–180[c]	$C_{14}H_{21}N_3O_3S$	54.00	6.80	13.49	10.30	54.27	7.18	13.07	10.39	0.5
CH_3	H		86	188–189[f]	$C_{14}H_{21}N_3O_3S$	54.00	6.80	13.49	10.30	53.90	6.69	13.34	10.33	4-6

Cl	H		60	222 dec.[g]	$C_{13}H_{18}ClN_3O_3S$[h]	47.06	5.47	12.66	9.66	47.38	5.37	12.75	9.85	1
CH_3	H		89	191–192[c]	$C_{15}H_{23}N_3O_3S$	55.36	7.12	12.91	9.85	55.60	6.95	12.80	9.91	<0.25
CH_3	H		67	165–167[i]	$C_{15}H_{23}N_3O_3S$	55.36	7.12	12.91	9.85	55.29	7.10	12.52	9.69	8
Cl	H		59	220 dec.[g]	$C_{14}H_{20}ClN_3O_3S$[j]	48.62	5.83	12.15	9.27	48.79	5.85	11.45	9.60	2
CH_3	H		54	170–173	$C_{14}H_{21}N_3O_3S$	54.00	6.80	13.49	10.30	54.04	6.83	13.35	10.55	6
Cl	H		66	197–198.5[k]	$C_{13}H_{18}ClN_3O_3S$[l]	47.06	5.47	12.66	9.66	46.95	5.36	12.57	9.73	2–4
Br	H		36	205–206.5[k]	$C_{13}H_{18}BrN_3O_3S$	41.50	4.82	11.17	8.52	41.88	4.83	11.03	8.51	0.5–0.75
CH_3O	H		24	169–170.5[c]	$C_{14}H_{21}N_3O_4S$	51.36	6.47	12.83	9.79	51.44	6.44	12.45	9.73	4–5
CH_3	CH_3		56	172–173.5[c]	$C_{15}H_{23}N_3O_3S$	55.36	7.12	12.91	9.85	55.59	7.34	12.61	9.75	<0.125
Cl	CH_3		72	188–189[c]	$C_{14}H_{20}ClN_3O_3S$	48.62	5.83	12.15	9.27	48.75	5.78	11.98	9.42	<0.125
CH_3	H		16	146–147[m]	$C_{15}H_{23}N_3O_3S$	55.36	7.12	12.91	9.85	55.73	7.03	12.78	9.90	1

[a] These experiments were carried out on intact rats. The compounds were administered orally. [b] Recrystallization from ethyl acetate. [c] Recrystallized from ethanol. [d] The material was not recrystallized but was triturated with boiling acetone. Calcd.: Cl, 10.65. Found: Cl, 10.50. [e] Recrystallized from 1:1 ethanol–ethyl acetate. [f] Recrystallized from methanol. [g] Recrystallized from dioxane. [h] Calcd.: Cl, 10.68. Found: Cl, 10.51. [i] Recrystallized from ethanol containing 5% methanol. [j] Calcd.: Cl, 10.25. Found: Cl, 9.80. [k] Recrystallized from butanone-2. [l] Calcd.: Cl, 10.65. Found: Cl, 10.50 [m] Recrystallized from 50% ethanol.



I

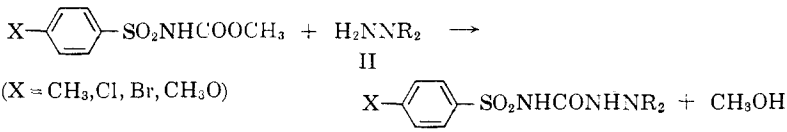
lowering activity of tolbutamide when measured in intact or adrenalectomized rats. Accordingly, a detailed study was made of the structure-activity relationship in compounds of this general class. The compounds prepared and the preliminary results of the testing of these compounds in rats are listed in Table I.

Biological Testing and Results.—The compounds listed in Table I were tested in intact male Sprague Dowley rats following overnight fast. At the time of treatment with the test compound the rats were injected subcutaneously with 100 mg. of glucose. The blood sugar lowering ability was compared with that for tolbutamide. Potency estimates were made by determining, from the dose response curves, doses of compounds which produce comparable blood sugar lowering.[1]

From the preliminary activity data presented in Table I several tentative conclusions can be drawn with regard to the relationship between structure and activity in this series. First, it appears that cyclic amino derivatives (*i.e.*, NR_2 = cycloalkylamine) in general appear to be the most active derivatives, especially those containing pyrrolidino, piperidino or hexamethyleneimino rings or homologs of these. Second, it appears that methyl substitution on the N^2 nitrogen eliminates activity. Third, where the tertiary amine function NR^2 of the molecule possesses any appreciable steric hindrance relative to the urea nitrogen, the activity is less.

Clinical and biological studies on one of these compounds (Table I, $NR_2 = -N(CH_2)_6$, R′ = H) were reported recently.[2,3]

Chemistry.—The compounds listed in Table I were all prepared by



treatment of arylsulfonylurethanes with hydrazines, according to the

(1) We are indebted to Dr. William E. Dulin, Mrs. Fredricka Schmidt and co-workers of these laboratories for the biological results reported here.

(2) W. E. Dulin, H. Oster and F. G. McMahon, *Proc. Exptl. Biol. Med.*, **107**, 245 (1961).

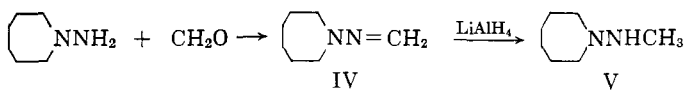
(3) W. Abelove, Fourth Congress of the International Diabetes Association, Geneva, Switzerland, July 10–14 (1961).

general method of Marshall and Sigal[4] for preparing sulfonylureas. The requisite hydrazines (II) were prepared by lithium aluminum hydride reduction of the corresponding nitrosamines (III) in ether solution.

$$R_2NH + HONO \rightarrow \underset{\text{III}}{R_2NNO} \xrightarrow{LiAlH_4} \underset{\text{II}}{R_2NNH_2}$$

In most cases the hydrazines were characterized by conversion to their hydrochlorides. Those hydrazines and nitrosamines previously not reported in the literature are listed in Tables II and III, respectively.

The one trisubstituted hydrazine (V) listed in Table II [R′ = CH_3, R = $-\overline{N(CH_2)_6}$] was prepared by treatment of the disubstituted hydrazine, 1-aminohexamethyleneimine, with formaldehyde solution to give 1,1-hexamethylene-2-methylenehydrazine (IV), and reduction of this with lithium aluminum hydride, according to the general method of Class, *et al.*[5]



Since all of the final compounds of this series contain a basic nitrogen function one would expect them to possess greater solubility at lower pH's. Experiments carried out in these laboratories[6] indicate that at least one of these compounds, namely, 1,1-hexamethylene-4-*p*-tolylsulfonylsemicarbazide, is in fact much more soluble at stomach pH's than sulfonylureas such as tolbutamide. This may account, at least in part, for the greater activity of some of these compounds.[7]

Experimental[8,9]

1-Nitrosohexamethyleneimine. General Procedure for the Preparation of Nitrosamines.—A solution of 89.5 g. (0.9 mole) of freshly distilled hexamethylene-

(4) F. J. Marshall and M. V. Sigal, Jr., *J. Org. Chem.*, **23**, 927 (1958).

(5) J. B. Class, J. G. Aston and T. S. Oakwood, *J. Am. Chem. Soc.*, **75**, 2937 (1953).

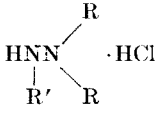
(6) These experiments were carried out by Dr. Arlington Forist and Mr. Leo Humphrey of these laboratories. These authors will report a detailed description of these experiments elsewhere.

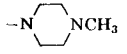
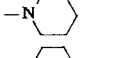
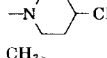
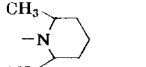
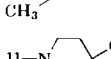
(7) Before completion of this work one of the compounds that we prepared (I, X = CH_2; $-NR_2$ = piperidyl) was reported by F. Haack [*Arzneimittelforschung*, **8**, 447 (1958)]. No mention was made of biological activity nor the method of synthesis.

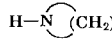
(8) All melting points and boiling points are uncorrected for stem exposure.

(9) We are indebted to Mr. William A. Struck and co-workers of these laboratories for the microanalytical data reported and to Mr. Marvin F. Grostic and Dr. Robert Rinehart for spectral studies. We are indebted especially to Mr. Albert Lallinger for a great amount of technical assistance and to Dr. Richard V. Heinzelman for helpful discussions.

TABLE II

SUBSTITUTED HYDRAZINE HYDROCHLORIDES 

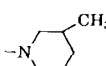
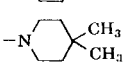
R′		Yield, %[a]	B.p.,[a] °C.	mm.	M.p.,[b] °C.	Formula	Calcd., % C	H	Cl	N	Found, % C	H	Cl	N
H		40	58–60	55	117–119[c]	$C_4H_{10}N_2 \cdot HCl$	39.19	9.05	28.92	...	38.99	8.71	29.13	...
H		42	171–174	..	215 dec.[d]	$C_6H_{13}N_3 \cdot 2HCl$	31.92	8.04	37.70	22.34	31.72	8.13	38.16	22.57
H		38	92	28	154–155[e]	$C_6H_{10}N_2 \cdot HCl$	44.61	8.24	26.34	20.82	44.83	8.50	26.57	20.92
H		53	66–68	32	120–122[f]	$C_6H_{14}N_2 \cdot HCl$	47.83	10.04	23.53	18.60	47.86	9.68	23.66	18.60
H		67	60–63	21	...	$C_6H_{14}N_2$	63.11	12.36	...	24.53	63.24	12.47	...	24.33
H		66	60–63	21	172–173.5[c]	$C_6H_{14}N_2 \cdot HCl$	47.83	10.04	23.53	18.60	48.03	9.77	23.34	18.85
H		87	65–66	22	165–167[c]	$C_7H_{16}N_2 \cdot HCl$	51.05	10.41	21.53	17.01	50.96	10.43	21.21	17.20
H		81	168–176	..	192–194[g]	$C_7H_{16}N_2 \cdot HCl$	51.05	10.41	21.53	17.01	51.34	10.25	21.56	16.95
H		88	67	14	...	$C_6H_{14}N_2$	63.11	12.36	...	24.53	63.06	12.07	...	24.55

CH_3		89	67	14	...	$C_7H_{16}N_2$	65.57	12.58	...	21.85	65.63	12.34	...	21.95
H		69	77–78	18	90–95[h]	$C_7H_{16}N_2 \cdot HCl$[i]	51.05	10.41	21.53	17.01	51.40	10.22	21.30	16.90

[a] B.p. of free base. [b] M.p. of the hydrochloride. [c] Recrystallized from 2-propanol. [d] Recrystallized from a methanol–ethanol mixture. [e] Recrystallized from absolute ethanol. [f] Recrystallized from benzene–abs. ethanol. [g] Recrystallized from ethyl acetate–2-propanol. [h] Recrystallized from ethyl acetate–ethanol. [i] The free base has been reported previously by R. Takamoto [*J. Pharm. Soc. Japan.*, **48**, 686 (1928); *Chem. Abstr.*, **23**, 387[8] (1929)].

TABLE III

NITROSOAMINES, R_2NNO

NR_2	Yield, %	B.p., °C.	mm.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
	92	101	17	$C_5H_8N_2O$	53.56	7.19	24.99	53.37	7.49	24.68
	89	111–112	21	$C_6H_{12}N_2O$	56.22	9.44	21.86	56.46	9.32	21.74
	66	..[a]	..[a]	$C_7H_{14}N_2O$	59.12	9.92	19.70	58.89	9.85	19.40
	85	136–138	34	$C_6H_{12}N_2O$	56.22	9.44	21.86	56.72	9.51	21.91

[a] This compound was a solid, melting at 69–70° after recrystallization from 50% ethanol.

imine[10] in 75 ml. of concd. HCl and 36 ml. of water was warmed to 70° and made acidic to test paper by the addition of 2 *N* HCl. To the solution was added with stirring a solution of 67 g. (0.97 mole) of sodium nitrite in 95 ml. of water. Stirring was continued for 2 hr. maintaining the temperature at 70°. The mixture was allowed to cool and extracted with ether. The ethereal extracts were dried over anhydrous magnesium sulfate, the ether removed by distillation and the residue distilled *in vacuo*.

1-Aminohexamethyleneimine. General Procedure for the Preparation of Disubstituted Hydrazines.—A solution of 43.4 g. (0.38 mole) of 1-nitrosohexamethyleneimine in 100 ml. of anhydrous ether was added to a refluxing and stirred solution of 28.9 g. (0.76 mole) of lithium aluminum hydride in 750 ml. of anhydrous ether at a rate determined by the reflux rate.[11] After refluxing for 2 hr. the reaction mixture was decomposed by the successive addition of 30.4 ml. of water, 22.8 ml. of 20% NaOH solution and 106 ml. of water. The inorganic precipitate was removed by filtration and washed well with ether. The ethereal filtrate was dried over anhydrous magnesium sulfate, the ether removed, and the residue distilled *in vacuo*.

***1,1*-Hexamethylene-4-*p*-tolylsulfonylsemicarbazide. General Procedure for the Preparation of N⁴-Arylsulfonylsemicarbazides.**—A mixture of 30 g. (0.131 mole) of *p*-toluenesulfomethylurethane and 16.4 g. (0.144 mole) of 1-aminohexamethyleneimine was heated in an oil bath at 130° for 2 hr. in a flask fitted with a condenser placed downward for distillation. During this time the methanol formed was allowed to distil. Vacuum (*ca.* 25 mm.) was then applied for 2 hr., maintaining the same oil bath temperature. The residue was allowed to cool and was purified by recrystallization.

1-Methylaminohexamethyleneimine.—The general procedure used was that of Class, *et al.*[5] To 22.84 g. (0.2 mole) of 1-aminohexamethyleneimine was added with stirring 21.10 g. (0.26 mole) of a 37% aqueous formaldehyde solution, keeping the temperature at 25–30°. The reaction mixture was stirred for an additional 45 min. The oil was separated and the aqueous layer extracted with ether. The combined oil and ether extracts were dried over calcium hydride, the ether was removed and the residue distilled *in vacuo* from calcium hydride through a distilling column. There was obtained 16.93 g. of a colorless liquid boiling at 80–81° (20 mm.). A solution of the methylenehexamethyleneimine obtained above in 25 ml. of anhydrous ether was added dropwise to a slurry of 1.9 g. (0.05 mole) of lithium aluminum hydride in 100 ml. of anhydrous ether. The reaction mixture was stirred and heated under reflux for 1 hr. and to the mixture cooled in an ice bath was added in succession 2 ml. of water, 1.5 ml. of a 20% NaOH solution, and 7 ml. of water. The inorganic precipitate was removed by filtration and washed with ether. The ethereal extracts were dried over anhydrous magnesium sulfate, the ether removed and the residue distilled *in vacuo*.

(10) Obtained from E. I. du Pont de Nemours and Co., Inc.

(11) The initial reaction in several cases was rather violent and not more than about 10% of the nitroso ethereal solution should be added until the reaction commences.