indices are considerably higher than those of the analogous oxazolines. Their neutralization equivalents can be determined by dissolving in excess 0.1 *N* HCl and back-titrating with 0.1 *N* NaOH to a potentiometric end point.

4-Methyl-2-thiazoline-2-thiol (19).—The route used was described by Böse.[30] A solution of 22.8 g. (0.4 mole) of 2-methylaziridine (Chemirad Corp.) in ethyl alcohol was added slowly to a solution of 48 g. (0.62 mole) of CS_2 in 120 ml. of ethyl alcohol. The addition was made at such a rate that the exothermic reaction caused the CS_2 to reflux moderately; in runs involving ten times the amounts specified above this addition was completed in 1.5 hr. The reaction mixture was refluxed for an additional hour, excess CS_2 was distilled, and the residual alcohol solution was stored at 0° to yield 31 g. (58%) of crude product. Two recrystallizations from CH_2Cl_2–CCl_4 (1:4) gave 23 g. (44%), m.p. 98.5–99°, lit.[29] m.p. 99–99.5°. This compound and the analogous 5-methyl compound (**20**) are almost colorless, water-insoluble, weakly basic solids which do not reduce iodine. The 2-thione structure is preferred[20,21] on the basis of infrared spectra.

Aminoalkanethiols (Table III).—With the exception of **21**, which was prepared by the hydrolysis of a thiazoline thiol (see below), all compounds described in Table III were prepared by acid hydrolysis of the appropriate 2-thiazoline. In a typical procedure a solution of 15.8 g. (0.122 mole) of 5-ethyl-2-methyl-2-thiazoline in 100 ml. of 2.5 *N* HCl was refluxed under nitrogen for 17 hr., then evaporated to dryness under vacuum. The residue was recrystallized from acetonitrile, washed on the filter with ether, and dried *in vacuo* to give 16.2 g. (94%) of 1-amino-2-butanethiol hydrochloride, m.p. 159–160°.

2-Amino-1-propanethiol hydrochloride (**21**) was prepared by the hydrolysis of 4-methyl-2-thiazoline-2-thiol (**19**).[30] In a typical run a solution of 250 g. (1.88 moles) of the thiazolinethiol in 2500 ml. of 6 *N* HCl was refluxed for 140 hr. Iodimetric assay of aliquots had shown that at this time the hydrolysis to aminothiol was 95% complete. The analogous hydrolysis of 2-thiazoline-2-thiol[31] had required 336 hr. The product was isolated as described in the preceding paragraph.

During the recrystallization of 95% pure 2-amino-1-propanethiol hydrochloride obtained by the hydrolysis of 700 g. of 4-methyl-2-thiazoline-2-thiol, we isolated 10 g. of a substance, m.p. 208–211°, insoluble in boiling isopropyl alcohol, which proved to be **bis(2-amino-1-propyl) dithiolcarbonate dihydrochloride,** $(CH_3CHNH_2CH_2S)_2CO\cdot 2HCl$.

Anal. Calcd. for $C_7H_{18}Cl_2N_2OS_2$: C, 29.89; H, 6.45; Cl, 25.21; N, 9.96; S, 22.80; neut. equiv., 140. Found: C, 30.40; H, 6.68; Cl, 24.86; N, 9.89; S, 23.21; neut. equiv., 136.

As analogous intermediate had been isolated during the incomplete hydrolysis of 2-thiazoline-2-thiol.[31] When the substance was refluxed with 6 *N* HCl for 150 hr. it was converted to 2-amino-1-propanethiol hydrochloride.

All of the aminoalkanethiol hydrochlorides prepared by us were colorless crystalline solids. Some were quite hygroscopic, but all were reasonably resistant to oxidation by air and required no extraordinary precautions in handling and storage.

Acknowledgment.—We wish to thank Professor John C. Sheehan and Dr. David P. Jacobus for stimulating discussions during the course of this work.

(30) M. Böse, *Ber.*, **53** 2000 (1920).

(31) R. J. Gaul and W. J. Fremuth, *J. Org. Chem.*, **25**, 869 (1960).

Sulfamylurea Hypoglycemic Agents. I. Synthesis and Screening

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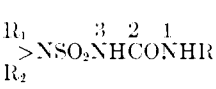
A number of sulfamylureas of general structure $R_1R_2NSO_2NHCONHR$ have been prepared and screened for hypoglycemic activity in the rat. The more promising variations in the R_1R_2N portion of the molecule were those derived from heterocyclic amines, especially piperidines and morpholines. In these series, activity was maximal when R was cyclohexyl, cycloheptyl, or bicycloalkyl. Several analogs, notably certain 4,4-disubstituted piperidine derivatives, were comparable in hypoglycemic potency to chlorpropamide. Structure–activity relationships are discussed, and a brief discussion is given of the use in synthetic planning of certain physical and chemical parameters that appear to be important determinants of drug dynamics in this class of compounds.

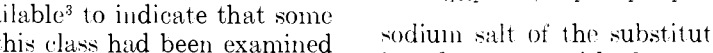
Previous publications from these laboratories[1] have indicated our interest in seeking more effective oral hypoglycemic agents; this interest has now led us to investigate the structural class of sulfamylureas (I).



I

Although clearly related to the well-studied sulfonylureas, very little was known about this class of compounds when we began our work; very few such compounds had been described chemically,[2] and only a general statement was available[3] to indicate that some members (I, R_1 = H) of this class had been examined and found to be inactive as hypoglycemic agents. While our work was in progress, however, some additional sulfamylureas were disclosed and stated to have hypoglycemic activity.[4] In this paper the synthesis and hypoglycemic screening of the more important groups of compounds that were investigated are reported, and structure–activity relationships are discussed. In paper II[5] a study of the drug dynamics of the more promising analogs is described.

Synthetic Methods.—The synthetic approach consisted essentially of the following. An amine was condensed with sulfamide to give a N-substituted or N,N-disubstituted sulfamide (Tables I and II)[6]; the



sodium salt of the substituted sulfamide was then allowed to react with the appropriate 3-substituted 1,1-diphenylurea (Table III) to produce a sulfamylurea and diphenylamine. This latter reaction was developed

(1) (a) W. M. McLamore, G. M. Fanelli, S. Y. P'an, and G. D. Laubach, *Ann. N. Y. Acad. Sci.*, **74**, 443 (1959); (b) G. F. Holland, D. A. Jaeger, R. L. Wagner, G. D. Laubach, W. M. McLamore, and S. Y. P'an, *J. Med. Pharm. Chem.*, **3**, 99 (1961); (c) G. F. Holland, *J. Org. Chem.*, **26**, 1662 (1961).

(2) S. Petersen, *Chem. Ber.*, **83**, 551 (1950).

(3) H. Ruschig, G. Korger, W. Aumüller, H. Wagner, and R. Weyer, *Arzneimittel-Forsch.*, **7A**, 453 (1958).

(4) Ciba, S. A., Belgian Patent 594,041 (1960); Ciba Ltd., British Patent 896,455; *Chem. Abstr.*, **57**, 1250*i* (1962).

(5) E. H. Wisenian, J. N. Pereira, K. F. Finger, and E. R. Pinson, Jr., *J. Med. Chem.*, **8**, 777 (1965).

(6) K. Hamann, German Patent 869,065 (1953); *Chem. Abstr.*, **48**, 1112*i* (1954).

TABLE I

SULFAMIDES

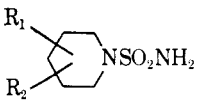
$$\begin{matrix} R_1 \\ >NSO_2NH_2 \\ R_2 \end{matrix}$$

No.	R_1	R_2	Yield, %	M.p., °C.	Crystn. solvent	Formula	Calcd., % C	H	N	Found, % C	H	N
1	CH_3	CH_3	76	97–98.5	*a*	$C_2H_8N_2O_2S$[b]	19.4	6.5	22.6	19.7	6.4	22.4
2	CH_3CH_2	CH_3CH_2	33	Oil		$C_4H_{12}N_2O_2S$[c]						
3	CH_3	$CH(CH_2)_4$	36	118–120	*d*	$C_7H_{26}N_2O_2S$	43.7	8.4	14.6	43.9	8.5	14.8
4	CH_3	α-Picolyl	54	106–107.5	*e*	$C_7H_{11}N_3O_2S$	41.8	5.5	20.9	41.3	5.2	20.6
5	CH_3	*p*-$ClC_6H_4CH_2$	19	129–131	*d*	$C_8H_{11}ClN_2O_2S$	40.9	4.7	11.9	40.9	4.7	11.8
6	H	$CH(CH_2)_5$	48	88.5–89.5	*f*	$C_6H_{13}O_2N_2S$[g]	40.7	7.4	15.8	40.7	7.8	15.6
7		$-(CH_2)_4-$	48	94–95	*f*	$C_4H_{10}N_2O_2S$	32.0	6.7	18.7	32.4	7.0	18.8
8		$-(CH_2)_6-$	43	66–67	*h*	$C_6H_{14}N_2O_2S$	40.4	7.9	15.7	40.4	7.6	15.7

[a] Acetone. [b] See ref. 2. [c] A. Vandi, T. Moeller, and L. F. Audrieth, *J. Org. Chem.*, **26,** 1136 (1961). [d] Toluene. [e] Ethanol. [f] Ether. [g] A. M. Pacquin, *Angew. Chem.*, **A60,** 316 (1948). [h] Water.

TABLE II

PIPERIDINE SULFAMIDES



No.	R_1	R_2	Yield, %	M.p., °C.	Crystn. solvent	Formula	Calcd., % C	H	N	Found, % C	H	N
1	H	H	66	119–120	*a*	$C_5H_{12}N_2O_2S$[b]	36.6	7.4	17.1	36.4	7.2	17.3
2	2-CH_3	H	5	60–61	*c*	$C_6H_{14}N_2O_2S$	40.4	7.9	15.7	40.6	7.8	15.9
3	3-CH_3	H	56	98–98.5	*c*	$C_6H_{14}N_2O_2S$	40.4	7.9	15.7	40.5	8.2	15.7
4	4-CH_3	H	52	127–128	*c*	$C_6H_{14}N_2O_2S$	40.4	7.9	15.7	40.5	7.9	15.6
5	4-C_2H_5	H	86	128–129	*d*	$C_7H_{16}N_2O_2S$	43.7	8.4	14.6	43.9	8.4	14.7
6	4-$CH_3(CH_2)_2$	H	87	128.5–129.5	*c*	$C_8H_{18}N_2O_2S$	46.6	8.8	13.6	46.6	8.7	13.6
7	3-CF_3	H	71	131–132.5	*c*	$C_6H_{11}F_3N_2O_2S$	31.0	4.8	12.1	31.1	5.0	11.8
8	4-CF_3	H	68	167–168	*c*	$C_6H_{11}F_3N_2O_2S$	31.0	4.8	12.1	30.7	4.6	12.1
9	4-OH	H	65	104.5–105.5	*e*	$C_5H_{12}N_2O_3S$	33.3	6.7	15.6	33.3	6.8	15.2
10	3-CH_3O	H	49	84–85	*c*	$C_6H_{14}N_2O_3S$	37.1	7.3	14.4	37.2	7.3	14.0
11	4-CH_3O	H	91	142–143	*f*	$C_6H_{14}N_2O_3S$	37.1	7.3	14.4	37.3	7.3	14.1
12	3-CH_3	5-CH_3	86	121–126	*d*	$C_7H_{16}N_2O_2S$	43.7	8.4	14.6	43.6	8.2	14.6
13	4-CH_3	4-CH_3	62	80.5–81.5	*d*	$C_7H_{16}N_2O_2S$	43.7	8.4	14.6	43.6	8.4	14.5
14	4-CH_3	4-C_2H_5	68	64.5–65	*d*	$C_8H_{18}N_2O_2S$	46.6	8.8	13.6	47.0	8.8	13.5
15	4-C_2H_5	4-C_2H_5	91	114.5–115.5	*d*	$C_9H_{20}N_2O_2S$	49.1	9.2	12.7	49.2	8.9	12.6
16	4,4-$(CH_2)_4$		92	105.5–106.5	*d*	$C_9H_{18}N_2O_2S$	49.5	8.3	12.8	49.6	8.2	13.2
17	4,4-$(CH_2)_5$		20	129.5–130.5	*c*	$C_{10}H_{20}N_2O_2S$	51.7	8.7	12.1	51.8	8.5	11.8
18	4-CH_3	4-CH_3O	67	145–145.5	*c*	$C_7H_{16}N_2O_3S$	40.4	7.7	13.5	40.7	7.8	13.4
19	4-CH_3	4-HO	41	118–120	*c*	$C_6H_{14}N_2O_3S$	37.1	7.3	14.4	36.9	7.1	14.6
20	4,4-$(CH_2)_3O$		77	136–137	*c*	$C_8H_{16}N_2O_3S$	43.6	7.3	12.7	43.6	7.7	12.6
21	4,4-$O(CH_2)_2O$		65	146–147	*g*	$C_7H_{14}N_2O_4S$	37.8	6.4	12.6	37.9	6.3	12.3
22	4,4-$OCH(CH_3)CH_2O$		67	134–136	*f*	$C_8H_{16}N_2O_4S$	40.7	6.8	11.9	40.9	6.9	11.6
23	4,4-$OCH_2C(CH_3)_2CH_2O$		60	133–135	*f*	$C_{10}H_{20}N_2O_4S$	45.4	7.6	10.6	45.2	7.7	10.5

[a] Benzene. [b] See footnote *c*, Table I. [c] Ether. [d] Ether–petroleum ether (b.p. 39–45°). [e] Acetone. [f] Isopropyl alcohol. [g] Ethyl acetate.

$$R_1R_2NSO_2NH^-Na^+ + (C_6H_5)_2NCONHR \xrightarrow[2.\ H_3O^+]{1.\ \Delta,\ DMF} R_1R_2NSO_2NHCONHR + H_2N(C_6H_5)_2^+$$

in these laboratories and was previously utilized[1b,c] for the preparation of some sulfonylureas. The more conventional reaction of a sulfamide with an isocyanate[7] was employed to make some of the sulfamylureas, and these are indicated in the tables by footnotes. Details of representative procedures are given in the Experimental Section.

Since a number of secondary amines not previously described in the literature were prepared as intermediates, their syntheses will be discussed. Treatment of 3-hydroxy- or 4-hydroxy-*N*-acetylpiperidine with sodium hydride and methyl iodide gave the corresponding 3- or 4-methoxy derivatives; hydrolysis of these products furnished 3- or 4-methoxypiperidine, respectively. Each of the 4,4-dialkyl- and spiroalkylenepiperidines was prepared by lithium aluminum hydride reduction of the appropriately substituted glutarimide.

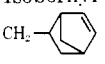
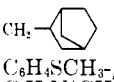
A number of amines were prepared from 1-benzyl-4-piperidone; Chart I illustrates the transformations involved. The adduct from 1-benzyl-4-piperidone and methyllithium was hydrogenolyzed to afford 4-hydroxy-4-methylpiperidine; methylation of the adduct prior to debenzylation gave 4-methoxy-4-methylpiperidine. The product of the reaction of 1-benzyl-4-piperidone with the lithium reagent from 3-bromo-1-(1,1-dimethylpropoxy)propane was treated with strong acid to effect dealkylation and concomitant cyclization; hydrogenolysis of the benzyl group afforded 1-oxa-8-aza-

(7) F. Kurzer, *J. Chem. Soc.*, 1258 (1961).

Table III

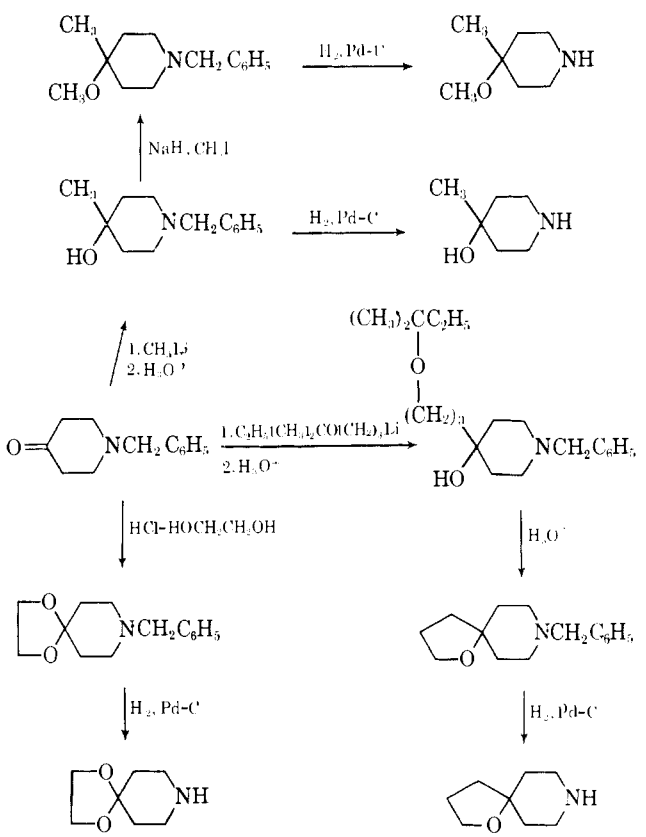
Diphenylurea Derivatives

$(C_6H_5)_2NCONHR$

No.	R	M.p., °C.	Crystn. solvent	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
1	$CH_2CF_2CF_3$	115–116	*a*	$C_{16}H_{13}F_5N_2O$	56.6	3.9	8.3	56.2	3.7	8.4
2	$CH[CH(CH_3)_2]_2$	77–77.5	*b*	$C_{20}H_{26}N_2O$	77.4	8.4	9.0	77.2	8.2	9.5
3	$C(CH_3)_2CH_2C(CH_3)_3$	63–65	*c*	$C_{21}H_{28}N_2O$	77.7	8.7	8.6	77.5	8.5	8.5
4	$CH(CH_2)_4$	131.5–133	*d*	$C_{18}H_{20}N_2O$	77.1	7.2	10.0	76.8	7.1	9.8
5	$CH(CH_2)_5$	187–188	*d*	$C_{19}H_{22}N_2O^e$	77.5	7.5	9.5	77.2	7.5	9.5
6	$CH(CH_2)_6$	143–144.5	*d*	$C_{26}H_{24}N_2O$	77.9	7.8	9.1	77.8	7.7	9.1
7	$CH(CH_2)_7$	113–113.5	*a*	$C_{21}H_{26}N_2O$	78.2	8.1	8.7	78.0	7.8	8.8
8	$(CH_3)C(CH_2)_5$	138.5–139.5	*a*	$C_{20}H_{24}N_2O$	77.9	7.8	9.1	77.6	7.7	9.2
9	Bornyl	91–92	*b*	$C_{23}H_{28}N_2O$	79.3	8.1	8.0	79.5	7.9	8.1
10	Isobornyl	98–99	*f*	$C_{23}H_{28}N_2O$	79.3	8.1	8.0	79.2	8.0	8.3
11	CH_2– 	125.5–126.5	*a*	$C_{21}H_{22}N_2O$	79.2	7.0	8.8	79.2	7.0	8.9
12	CH_2– 	120.5–122	*a*	$C_{21}H_{24}N_2O$	78.7	7.6	8.7	78.8	7.6	8.8
13	$C_6H_4SCH_3$-*p*	144–145	*d*	$C_{20}H_{18}N_2OS$	71.8	5.4	8.4	71.8	5.2	8.5
14	$C_6H_4N(CH_3)_2$-*p*	178–179	*g*	$C_{21}H_{21}N_3O$	76.1	6.4	12.7	75.9	6.5	12.3

[a] Ether. [b] Ether–pentane. [c] Ethanol–water. [d] Ethanol. [e] F. L. Scott and M. T. Scott, *J. Am. Chem. Soc.*, **79**, 6077 (1957). [f] Pentane. [g] Ethyl acetate–chloroform.

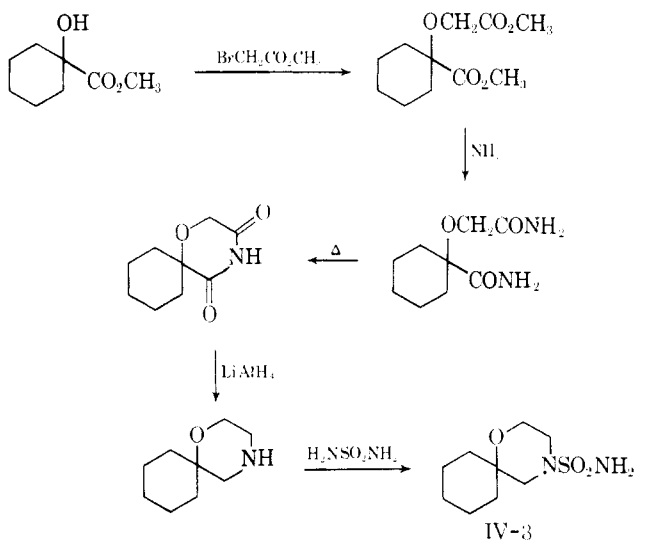
Chart I



spiro[4.5]decane (intermediate for II-20[8]). Ethylene glycol was condensed with 1-benzyl-4-piperidone to give 8-benzyl-1,4-dioxa-8-azaspiro[4.5]decane; hydrogenolysis of this product gave 1,4-dioxa-8-azaspiro[4.5]-decane, the precursor for II-21. Similar reaction sequences, with propylene glycol or 1,3-propanediol instead of ethylene glycol furnished, respectively, the amine precursors for II-22 and II-23.

Synthesis of 1-oxa-4-azaspiro[5.5]undecane (intermediate for IV-3) was effected by the following sequence of reactions (see Chart II). Methyl 1-hydroxycyclohexanecarboxylate was alkylated with methyl bromoacetate; the resulting diester was converted to the corresponding diamide; pyrolysis of the diamide afforded the expected imide, which was subsequently reduced with lithium aluminum hydride to give the desired spiromorpholine. The crude amine was not purified but was converted directly to the sulfamide IV-3.

Chart II

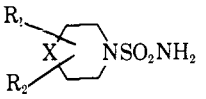


Several thiomorpholines were also made. Alkylation of 2-mercaptoethylamine with ethyl α-bromopropionate afforded the expected thioether; cyclization of this product gave 2-methyl-3-oxothiomorpholine,

(8) In designating a compound by this method, the Roman numeral corresponds to the table where the compound may be found, while the Arabic numeral indicates its position within that table.

TABLE IV

MORPHOLINE-, THIOMORPHOLINE-, AND PIPERAZINESULFAMIDES

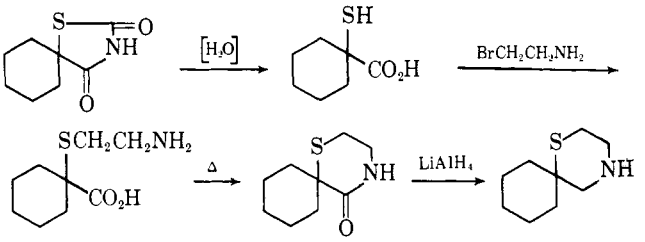


No.	R_1	R_2	X	Yield, %	M.p., °C.	Crystn. solvent	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
1	2-CH_3	H	O	85	94–95	*a*	$C_5H_{12}N_2O_3S$	33.3	6.7	15.6	33.4	6.7	15.3
2	2-CH_3	6-CH_3	O	49	133–134.5	*b*	$C_6H_{14}N_2O_3S$	37.1	7.3	14.4	37.0	7.2	14.4
3	2,2-$(CH_2)_5$		O	44	121–122	*c*	$C_9H_{18}N_2O_3S$	46.1	7.7	12.0	46.2	7.6	11.6
4	H	H	S	70	111.5–112.5	*d*	$C_4H_{10}N_2O_2S_2$	26.4	5.5	15.4	26.5	5.4	15.2
5	H	H	SO_2	70	201–202.5	*e*	$C_4H_{10}N_2O_4S_2$	22.4	4.7	13.1	22.5	4.7	13.2
6	2-CH_3	H	S	61	87.5–88.5	*a*	$C_5H_{12}N_2O_2S_2$	30.6	6.2	14.3	30.6	6.1	13.8
7	2-CH_3	2-CH_3	S	67	149–150	*f*	$C_6H_{14}N_2O_2S_2$	34.3	6.7	13.3	34.5	6.7	13.0
8	2-CH_3	2-CH_3	SO	85	196.5–197.5	*d*	$C_6H_{14}N_2O_3S_2$	31.8	6.2	12.4	31.7	5.9	12.4
9	2-CH_3	2-CH_3	SO_2	58	161–162	*e*	$C_6H_{14}N_2O_4S_2$	29.7	5.8	11.6	29.9	5.8	11.5
10	2,2-$(CH_2)_5$		S	53	129–130	*g*	$C_9H_{18}N_2O_2S_2$	43.2	7.3	11.2	43.1	7.1	11.0
11	2,2-$(CH_2)_5$		SO	97	211–212	*h*	$C_9H_{18}N_2O_3S_2$	40.6	6.8	10.5	40.6	6.7	10.4
12	2,2-$(CH_2)_5$		SO_2	74	197–199	*h*	$C_9H_{18}N_2O_4S_2$	38.3	6.4	9.9	38.4	6.3	9.8
13	4-C_2H_5	H	N	50	137–139	*b*	$C_6H_{15}N_3O_2S$	37.3	7.8	21.7	37.3	7.8	21.6

[a] Ether–petroleum ether (b.p. 39–45°). [b] Ethanol. [c] Chloroform–isopropyl ether. [d] Acetone. [e] Water. [f] Ether. [g] Chloroform–hexane. [h] Isopropyl alcohol.

which was reduced with lithium aluminum hydride to 2-methylthiomorpholine. In similar fashion, 2,2-dimethylthiomorpholine was prepared from 2-mercaptoethylamine and ethyl α-bromoisobutyrate. Synthesis of 1-thia-4-azaspiro[5.5]undecane was accomplished as illustrated in Chart III. Alkaline hydrolysis of 1-

CHART III



thia-3-azaspiro[4.5]decane-2,4-dione[9] gave 1-mercaptocyclohexanecarboxylic acid, which was alkylated with 2-bromoethylamine to provide 1-(2-aminoethylthio)-cyclohexanecarboxylic acid. The latter product was heated to 220° to give a lactam, which was reduced with lithium aluminum hydride to the desired spirothiomorpholine. Oxidation of the thiomorpholinesulfamides by conventional procedures gave the corresponding sulfoxides and sulfones listed in Table IV.

All the primary amines employed were known except 2,4-dimethyl-3-aminopentane and 2-aminomethylbicyclo[2.2.1]heptane; the former was prepared by hydride reduction of the known 2,4-dimethyl-3-pentanone oxime, and the latter by catalytic hydrogenation of commercially available 2-aminomethylbicyclo-[2.2.1]-5-heptene.

Pharmacological Methods.—All compounds were screened in groups of 8–10 male rats of the Sprague–Dawley strain, fasted for 18 hr. prior to the experiment. The rats were lightly anesthetized with pentobarbital (15 mg./kg. i.p.), 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 per cent decrease, with standard deviation, in blood sugar was calculated and reported as hypoglycemic activities in the tables. Chlorpropamide is included in Table V as a standard hypoglycemic agent.

Structure–Activity Relationships.—With one exception, all the sulfamylureas reported in this paper were prepared from N,N-disubstituted sulfamides; the exception, VI-8, had weak activity, in accord with a generalization in the literature[3] about hypoglycemic activity of this structure type. As implied by the generic structure I, the substituent at position 1 of all compounds reported here is derived from a primary amine[10]; the 1-substituent is uniformly referred to in the text and tables as the R substituent.

Initially, R substituents were chosen from those known to be compatible with good activity in the sulfonylurea series,[1,11] and emphasis was placed on variation of the sulfamide portion of the molecule. Sulfamylureas derived from nonheterocyclic secondary amines had, in general, minimal activity (Table VI), whereas a piperidinesulfamyl derivative (VI-14) proved to have very high activity. Activity appeared to be maximal at the six-membered piperidine ring, since the corresponding pyrrolidine (VI-12) and hexamethyleneimine (VI-16) derivatives were much less active. Accordingly, a number of piperidinesulfonylureas were prepared with variation of the R substituent (see Table V). From compounds VI-14 and V-3, it is evident that peak activity for this series requires cyclohexyl or cycloheptyl as the R substituent. This is true also in the morpholinesulfamyl series (Table VII) where greatest activity was observed in analogs with C_6–C_8 cycloalkyl or bicycloalkyl R substituents. In

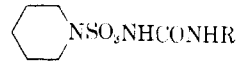
(9) E. R. H. Jones, F. A. Robinson, and M. N. Strachan, *J. Chem. Soc.*, 91 (1946).

(10) Compounds of the type $R_1R_2NSO_2NHCONR_3R_4$, in which R_1R_2N and NR_3R_4 are both derived from secondary amines, will be reported in a subsequent paper: J. W. McFarland, C. F. Gerber, and W. M. McLamore, *J. Med. Chem.*, **8**, 781 (1965).

(11) (a) F. J. Marshall, M. V. Sigal, Jr., H. R. Sullivan, C. Cesnik, and M. A. Root, *ibid.*, **6**, 60 (1963); (b) F. G. McMahon, H. L. Upjohn, O. S. Carpenter, J. B. Wright, H. L. Oster, and W. E. Dulin, *Current Therap. Res.*, **4**, 330 (1962).

Table V

Unsubstituted Piperidinesulfamylureas

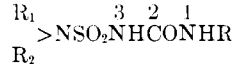


No.	R	M.p., °C.	Crystn. solvent	Formula	Calcd., % C	H	N	Found, % C	H	N	Hypoglycemic activity
1[a]	$(CH_2)_3CH_3$	98.5–100	*b*	$C_{10}H_{21}N_3O_3S$	45.6	8.0	16.0	45.6	8.0	15.9	20 ± 3.5
2	$CH(CH_2)_4$	135–135.5	*c*	$C_{11}H_{21}N_3O_3S$	48.0	7.7	15.3	48.2	7.6	14.9	22 ± 3.8
3	$CH(CH_2)_6$	108–109	*b*	$C_{13}H_{25}N_3O_3S$	51.5	8.3	13.8	51.4	8.1	13.8	41 ± 2.5
4	$CH(CH_2)_5$	105–105.5	*d*	$C_{14}H_{27}N_3O_3S$	53.0	8.6	13.2	53.0	8.6	13.2	22 ± 2.0
5	$C(CH_3)_2CH_2C(CH_3)_3$	130–131	*b*	$C_{14}H_{29}N_3O_3S$	52.6	9.2	13.2	52.6	8.9	13.0	2 ± 2.5
6	$(CH_3)C(CH_2)_5$	150–150.5	*b*	$C_{13}H_{25}N_3O_3S$	51.5	8.3	13.8	51.7	8.2	13.8	1 ± 2.7
7	$CH[CH(CH_3)_2]_2$	158–159	*c*	$C_{13}H_{27}N_3O_3S$	51.1	8.9	13.8	51.4	9.0	13.9	16 ± 2.7
8[a]	C_6H_4Cl-*p*	160–161	*b*	$C_{12}H_{16}N_3O_3S$	45.4	5.1	13.2	45.3	4.7	13.2	16 ± 4.6
9	$C_6H_4S(CH_3)$-*p*	139–140	*b*	$C_{13}H_{19}N_3O_3S$	47.2	6.1	12.7	47.1	6.0	12.7	21 ± 2.6
10	$C_6H_4N(CH_3)_2$-*p*	157–158	*b*	$C_{14}H_{22}N_4O_3S$	51.5	6.8	17.2	51.6	6.9	16.7	25 ± 1.7
	Chlorpropamide										35 ± 3.3

[a] Prepared by the isocyanate method. [b] Not recrystallized. [c] Ether. [d] Ether–pentane.

Table VI

Sulfamylureas



No.	R_1	R_2	R	M.p., °C.	Crystn. solvent	Formula	Calcd., % C	H	N	Found, % C	H	N	Hypoglycemic activity
1[a]	CH_3	CH_3	$(CH_2)_2CH_3$	138.5–139.5	*b*	$C_6H_{15}N_3O_3S$	34.4	7.2	20.1	34.2	7.2	20.1	13 ± 3.5
2	CH_3	CH_3	$C_6H_4N(CH_3)_2$-*p*	165–166.5	*b*	$C_{11}H_{18}N_4O_3S$	46.1	6.3	19.6	45.7	6.5	19.6	7 ± 1.4
3[a]	C_2H_5	C_2H_5	$(CH_2)_2CH_3$	89.5–90	*b*	$C_8H_{19}N_3O_3S$	40.5	8.1	17.7	40.1	7.8	17.6	15 ± 3.3
4	C_2H_5	C_2H_5	$C_6H_4N(CH_3)_2$-*p*	145–147	*b*	$C_{13}H_{22}N_4O_3S$	49.7	7.0	17.8	49.5	7.3	18.0	10 ± 3.3
5	C_2H_5	C_2H_5	$CH(CH_2)_5$	135–136	*b*	$C_{11}H_{23}N_3O_3S$	47.6	8.4	15.2	47.4	8.3	15.3	11 ± 2.0
6[a]	CH_3	$CH(CH_2)_5$	$(CH_2)_2CH_3$	118–119	*b*	$C_{11}H_{23}N_3O_3S$	47.6	8.4	15.2	47.6	8.3	15.1	18 ± 4.4
7	CH_3	$CH(CH_2)_5$	$CH(CH_2)_5$	122–123	*b*	$C_{14}H_{27}N_3O_3S$	53.0	8.6	13.2	53.1	8.4	13.0	27 ± 3.2
8	H	$CH(CH_2)_5$	$CH(CH_2)_5$	168–168.5	*c*	$C_{13}H_{25}N_3O_3S$	51.5	8.3	13.8	51.7	8.2	13.6	17 ± 2.6
9[a]	CH_3	*p*-$ClC_6H_4CH_2$	$(CH_2)_2CH_3$	118–119	*b*	$C_{12}H_{18}ClN_3O_3S$	45.1	5.7	13.1	45.1	5.6	12.9	11 ± 3.3
10[a]	CH_3	α-Picolyl	$(CH_2)_2CH_3$	115–116	*b*	$C_{11}H_{18}N_4O_3S$	46.1	6.3	19.6	46.6	6.1	19.4	1 ± 3.2
11[a]	$-(CH_2)_4-$		$(CH_2)_2CH_3$	148–149.5	*b*	$C_8H_{17}N_3O_3S$	40.8	7.3	17.9	41.1	7.1	17.8	13 ± 3.2
12	$-(CH_2)_4-$		$CH(CH_2)_5$	187.5–188	*c*	$C_{11}H_{21}N_3O_3S$	48.0	7.7	15.3	48.1	7.6	15.4	8 ± 3.2
13[a]	$-(CH_2)_5-$		$(CH_2)_2CH_3$	144–145	*b*	$C_9H_{19}N_3O_3S$	43.4	7.7	16.9	43.2	7.6	16.7	23 ± 1.8
14	$-(CH_2)_5-$		$CH(CH_2)_5$	135–136	*b*	$C_{12}H_{23}N_3O_3S$	49.8	8.0	14.5	49.6	8.1	14.6	41 ± 2.4
15[a]	$-(CH_2)_6-$		$(CH_2)_2CH_3$	120–121	*b*	$C_{10}H_{21}N_3O_3S$	45.6	8.0	16.0	45.8	8.3	15.7	1 ± 2.2
16	$-(CH_2)_6-$		$CH(CH_2)_5$	162–162.5	*b*	$C_{13}H_{25}N_3O_3S$	51.5	8.3	13.8	51.4	8.2	13.7	9 ± 3.8

[a] Prepared by the isocyanate method. [b] Not recrystallized. [c] Ether.

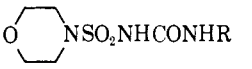
subsequent work, therefore, emphasis was placed on changes in the sulfamyl portion of the molecule, restricting, with a few exceptions, the R substituents to cyclohexyl and cycloheptyl.

Planning of further analogs was influenced not only by structure–activity relationships but also by the results of a concurrent study of acidity (pK_a), relative lipophilicity, and the drug dynamics (in the dog) of certain key analogs.[5] In brief, these studies suggested that: (1) the more acidic sulfamylreas have longer plasma half-lives, and (2) the more polar (less lipophilic) sulfamylureas are rapidly excreted by the kidney. Since all sulfamylureas studied exhibited shorter half-lives in the dog than chlorpropamide or tolbutamide, and since they are less acidic and more lipophilic than these standard sulfonylureas, it became an important goal of the synthetic program to provide compounds with increased acidity and without loss of lipophilicity, all within the scope of the structure–activity relationships. It was believed sulfamylureas having these properties would also be more rapidly and completely absorbed.

The outstanding hypoglycemic activity of VI-14 and V-3 prompted the preparation of a substantial series of mono- and disubstituted piperidinesulfamylureas. As can be seen from Table VIII, peak activity in the monosubstituted series was found in the 4-methylpiperidine, cycloheptyl analog, VIII-6. Similarly, 4,4-disubstituted analogs (Table IX), such as IX-3, IX-4, IX-10, and IX-17, had outstanding activity in our screen. However, the low solubility of IX-4 and especially of IX-10 led to poor oral absorption. Compound IX-17 was designed to overcome this problem. The spiroether function was expected to confer additional polarity and solubility on the molecule while maintaining the desirable 4,4-disubstitution. No absorption problem was observed with IX-17, which also proved to be one of the more active compounds

TABLE VII

MORPHOLINESULFAMYLUREAS

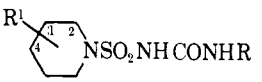


No.	R	M.p., °C.	Crystn. solvent	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N	Hypglycemic activity
1[a]	$(CH_2)_2CH_3$	101–102	*b*	$C_8H_{17}N_3O_4S$	38.2	6.8	16.7	38.7	6.8	16.9	4 ± 2.5
2	$CH(CH_2)_4$	138–138.5	*b*	$C_{10}H_{19}N_3O_4S$	43.3	6.9	15.2	43.3	6.8	15.1	29 ± 2.8
3	$CH(CH_2)_5$	125–126	*b*	$C_{11}H_{21}N_3O_4S$	45.3	7.3	14.4	45.1	7.2	14.6	25 ± 1.0
4	$CH(CH_2)_6$	107–108.5	*b*	$C_{12}H_{23}N_3O_4S$	47.2	7.6	13.8	47.4	7.7	13.8	30 ± 4.0
5	$CH(CH_2)_7$	112.5–114	*b*	$C_{13}H_{25}N_3O_4S$	48.9	7.9	13.2	48.7	7.8	13.0	32 ± 1.7
6	$(CH_3)C(CH_2)_5$	159–160	*b*	$C_{12}H_{23}N_3O_4S$	47.2	7.6	13.8	47.1	7.5	13.8	14 ± 1.4
7	Bornyl	181–182	*c*	$C_{15}H_{27}N_3O_4S$	52.2	7.9	12.2	52.1	7.7	12.1	22 ± 3.5
8	Isobornyl	167–168	*c*	$C_{15}H_{27}N_3O_4S$	52.2	7.9	12.2	52.2	7.8	12.0	27 ± 2.9
9		122.5–123.5	*c*	$C_{13}H_{20}N_3O_4S$	49.7	6.4	13.4	49.5	6.5	13.4	28 ± 3.6
10		134–135	*d*	$C_{13}H_{23}N_3O_4S$	49.2	7.3	13.2	49.4	7.3	13.0	21 ± 3.2
11	$CH[CH(CH_3)_2]_2$	135–136	*c*	$C_{12}H_{25}N_3O_4S$	46.9	8.2	13.7	47.3	8.0	13.7	20 ± 3.3

[a] Prepared by the isocyanate method. [b] Not recrystallized. [c] Ether. [d] Acetone–ether.

TABLE VIII

SUBSTITUTED PIPERIDINESULFAMYLUREAS



No.	R_1	R	M.p., °C.	Crystn. solvent	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N	Hypoglycemic activity
1	2-CH_3	$CH(CH_2)_5$	149–150	*a*	$C_{13}H_{25}N_3O_3S$	51.5	8.3	13.8	51.6	8.1	13.8	12 ± 2.2
2	2-CH_3	$CH(CH_2)_6$	146.5–147.5	*a*	$C_{14}H_{27}N_3O_3S$	53.0	8.6	13.2	53.1	8.5	13.4	12 ± 2.7
3	3-CH_3	$CH(CH_2)_5$	111–112	*b*	$C_{13}H_{25}N_3O_3S$	51.5	8.3	13.8	51.1	8.0	13.4	34 ± 2.0
4	3-CH_3	$CH(CH_2)_6$	106–107.5	*a*	$C_{14}H_{27}N_3O_3S$	53.0	8.6	13.2	52.9	8.4	13.0	27 + 2.5
5	4-CH_3	$CH(CH_2)_5$	132–133	*a*	$C_{13}H_{25}N_3O_3S$	51.5	8.3	13.8	51.5	8.2	13.7	22 ± 3.5
6	4-CH_3	$CH(CH_2)_6$	123.5–124.5	*a*	$C_{14}H_{27}N_3O_3S$	53.0	8.6	13.2	53.1	8.8	12.8	44 ± 2.4
7	3-CF_3	$CH(CH_2)_5$	130.5–131.5	*c*	$C_{13}H_{22}F_3N_3O_3S$	43.7	6.2	11.8	43.7	6.2	11.6	22 ± 2.4
8	4-CF_3	$CH(CH_2)_5$	181.5–182.5	*a*	$C_{13}H_{22}F_3N_3O_3S$	43.7	6.2	11.8	44.2	6.3	11.6	26 ± 2.8
9	4-C_2H_5	$CH(CH_2)_5$	156–156.5	*c*	$C_{19}H_{27}N_3O_3S$	53.0	8.6	13.2	53.2	8.5	13.3	24 ± 2.8
10	4-C_3H_7	$CH(CH_2)_5$	167–168	*a*	$C_{15}H_{29}N_3O_3S$	54.4	8.8	12.7	54.2	8.6	12.6	22 ± 2.7
11	3-OCH_3	$CH(CH_2)_5$	139–140	*d*	$C_{13}H_{25}N_3O_4S$	48.9	7.9	13.2	49.3	8.3	13.3	24 ± 2.5
12	4-OCH_3	$CH(CH_2)_6$	143–144	*d*	$C_{14}H_{27}N_3O_4S$	50.4	8.2	12.6	50.6	8.2	12.4	32 ± 2.5
13	4-OH	$CH(CH_2)_7$	150–151	*a*	$C_{14}H_{27}N_3O_4S$	50.4	8.2	12.6	50.4	8.1	12.7	11 ± 4.6
14[e]	Δ^3	$(CH_2)_2CH_3$	119.5–120.5	*a*	$C_9H_{17}N_3O_3S$	43.7	6.9	19.4	43.7	6.9	19.6	14 ± 1.4
15	Δ^3	$CH(CH_2)_6$	98–99	*a*	$C_{13}H_{23}N_3O_3S$	51.8	7.7	13.9	51.7	7.8	13.8	38 ± 3.5

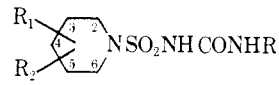
[a] Not recrystallized. [b] Hexane. [c] Ether–pentane. [d] Ether. [e] Prepared by the isocyanate method.

of this series. The chief shortcoming of compound IX-17 was its relatively short plasma half-life in the dog.[5] In accord with the considerations outlined above, more acidic analogs were therefore prepared. Since it is known[1b] that an R substituent which is electron withdrawing increases acidity in the sulfonylurea series, the pentafluoropropyl analog, IX-18, was prepared. This compound was indeed more acidic and had a longer half-life,[5] thus substantiating further the nexus between these two variables. The pentafluoro compound proved to be less active, although this decreased activity was anticipated from known structure–activity relationships. The spiroketal analog, IX-19, was also more acidic, and exhibited a longer half-life than IX-17,[5] but it too was somewhat less active. A possible acid stability problem was anticipated with the spiroketal, but there was no evidence of a major stability problem in oral administration to the rat or dog.

As indicated above, a second structural class that gave early promise of good activity was that derived from morpholinesulfamide. Moreover, such morpholine derivatives as VII-4 proved to be more acidic and to have superior plasma half-lives as compared to the piperidine analogs.[5] A fairly extensive exploration of

Table IX

Disubstituted Piperidinesulfamylureas



No.	R_1	R_2	R	M.p., °C.	Crystn. solvent	Formula	Calcd., % C	H	N	Found, % C	H	N	Hypoglycemic activity
1	3-CH_3	5-CH_3	$CH(CH_2)_5$	139.5–140	*a*	$C_{14}H_{27}N_3O_3S$	53.0	8.6	13.2	54.5	8.8	13.0	16 ± 2.0
2	4-CH_3	4-CH_3	$CH(CH_2)_4$	167–168	*b*	$C_{13}H_{25}N_3O_3S$	51.5	8.3	13.8	51.4	8.4	14.0	36 ± 2.5
3	4-CH_3	4-CH_3	$CH(CH_2)_5$	175–175.5	*a*	$C_{14}H_{27}N_3O_3S$	53.0	8.6	13.2	52.8	8.4	12.9	44 ± 2.7
4	4-CH_3	4-CH_3	$CH(CH_2)_6$	138–139	*b*	$C_{15}H_{29}N_3O_3S$	54.5	8.8	12.7	54.4	8.4	12.8	48 ± 2.7
5	4-CH_3	4-CH_3	$CH(CH_2)_7$	143–144	*c*	$C_{16}H_{31}N_3O_3S$	55.6	9.0	12.2	55.7	8.9	12.0	21 ± 1.7
6	4-CH_3	4-CH_3	$CH_2CF_2CF_3$	169–170	*a*	$C_{11}H_{18}F_5N_3O_3S$	36.0	4.9	11.4	35.8	4.7	11.3	25 ± 1.4
7	4-CH_3	4-C_2H_5	$CH(CH_2)_6$	174–175	*a*	$C_{15}H_{29}N_3O_3S$	54.4	8.8	12.7	54.7	8.7	12.4	34 ± 2.0
8	4-C_2H_5	4-C_2H_5	$CH(CH_2)_6$	138–139	*c*	$C_{17}H_{33}N_3O_3S$	56.8	9.2	11.7	56.8	9.0	11.7	29 ± 2.7
9	4,4-$(CH_2)_4$		$CH(CH_2)_5$	177–178	*b*	$C_{16}H_{29}N_3O_3S$	55.9	8.5	12.2	55.7	8.3	12.1	29 ± 3.8
10	4,4-$(CH_2)_4$		$CH(CH_2)_6$	154–155	*a*	$C_{17}H_{31}N_3O_3S$	57.1	8.7	11.8	57.0	8.6	11.9	43 ± 3.0
11	4,4-$(CH_2)_4$		$CH(CH_2)_7$	134–135	*a*	$C_{18}H_{33}N_3O_3S$	58.2	9.0	11.3	58.0	8.8	11.0	22 ± 3.9
12	4,4-$(CH_2)_5$		$CH(CH_2)_5$	204–205	*d*	$C_{17}H_{31}N_3O_3S$	57.1	8.7	11.8	57.1	8.6	11.7	9 ± 1.4
13	4,4-$(CH_2)_5$		$CH(CH_2)_6$	154–155	*b*	$C_{18}H_{33}N_3O_3S$	58.2	9.0	11.3	57.8	9.0	11.5	15 ± 2.2
14	4-OH	4-CH_3	$CH(CH_2)_5$	150–151	*a*	$C_{13}H_{25}N_3O_4S$	48.9	7.9	13.2	48.5	7.7	12.9	37 ± 4.3
15	4-OCH_3	4-CH_3	$CH(CH_2)_6$	132–132.5	*a*	$C_{15}H_{29}N_3O_4S$	51.8	8.4	12.1	51.6	8.4	12.0	30 ± 1.9
16	4-OH	4-C_6H_5	$CH(CH_2)_5$	183–184	*a*	$C_{18}H_{27}N_3O_4S$	56.7	7.1	11.0	56.7	7.1	10.9	15 ± 2.1
17	4,4-$O(CH_2)_3$		$CH(CH_2)_4$	182.5–183.5	*e*	$C_{15}H_{27}N_3O_4S$	52.2	7.9	12.2	52.5	7.8	12.2	38 ± 2.0
18	4,4-$O(CH_2)_3$		$CH_2CF_2CF_3$	170.5–171.5	*a*	$C_{12}H_{13}F_5N_3O_4S$	36.4	4.6	10.6	36.1	4.3	10.8	24 ± 2.7
19	4,4-$O(CH_2)O$		$CH(CH_2)_5$	173–174	*f*	$C_{14}H_{25}N_3O_5S$	48.3	7.2	12.1	48.6	7.3	12.1	36 ± 3.2
20	4,4-$OCH_2CH(CH_3)O$		CH_2–cyclohexyl	131–132	*g*	$C_{17}H_{29}N_3O_5S$	52.7	7.5	10.8	52.8	7.5	10.9	26 ± 2.0
21	4,4-$OCH_2C(CH_3)_2CH_2O$		$CH(CH_2)_5$	218–219	*h*	$C_{17}H_{31}N_3O_5S$	52.4	8.0	10.8	52.5	8.0	10.8	17 ± 2.3

[a] Ether. [b] Not recrystallized. [c] Ether–pentane. [d] Acetone. [e] Benzene–ether. [f] Ethyl acetate. [g] Acetonitrile. [h] Ethyl acetate–isopropyl alcohol.

morpholine derivatives was therefore undertaken as indicated in Tables VII and X. As stated previously, cycloalkyl and bicycloalkyl R substituents appeared to be optimal (Table VII), and emphasis was placed on variations in the morpholine portion (Table X). With the exception of the 2-methylmorpholine derivative X-3, which was the most active morpholine analog examined in our screen, there appeared to be no particular advantage in substitution of the morpholine ring. The spiro analogs X-7 and X-8, designed as more lipophilic members of the relatively acidic morpholine series, were particularly disappointing. Such thiomorpholines as X-9 and X-11 were comparable in activity to the corresponding morpholine analogs, but in the dog they were converted to the corresponding sulfoxides, which were rapidly excreted.[5] The high polarity of thiomorpholine sulfoxides and sulfones appeared to account for the short half-lives generally observed, presumably owing to rapid renal excretion. Even X-19, with the additional bulk of the spiro ring, was no exception.

Preliminary human pharmacology data indicate that several of these sulfamylureas (VII-4, VII-9, IX-4, IX-10, IX-17, and IX-19) have a blood sugar lowering effect in man.

Experimental Section[12]

1-(1-Piperidinesulfonyl)-3-cyclohexylurea.—To 3.7 g. (0.02 mole) of the sodium salt of 1-sulfamylpiperidine suspended in 40 ml. of dimethylformamide was added 6.17 g. (0.021 mole) of N,N-diphenyl-N'-cyclohexylurea. The resulting mixture was heated on a steam bath overnight. The solution was poured into 200 ml. of water and extracted with ether, and the aqueous layer was acidified with 6 *N* HCl. The solid which precipitated was filtered, washed with water, and dried *in vacuo* over P_2O_5.

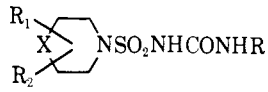
The sulfamylureas prepared by the diphenylurea route were synthesized by a similar procedure in which the yields varied from 50–75%. The sulfamylureas and their physical properties are listed in Tables V–X.

1-(1,1-Dioxo-2-methyl-4-thiomorpholinesulfonyl)-3-cycloheptylurea.—To a solution of 2.5 g. (0.008 mole) of 1-(2-methyl-4-thiomorpholinesulfonyl)-3-cycloheptylurea in 50 ml. of glacial acetic acid was added dropwise 2.5 g. of $KMnO_4$ dissolved in 125 ml. of water. The reaction mixture was cooled so that the temperature did not exceed 30°. When the reaction was complete, the excess permanganate was decomposed by the addition of a sodium bisulfite solution. The reaction mixture was cooled, and the precipitated solid was filtered, washed with water, and dried; yield 2.2 g. The physical and analytical data for this compound are listed in Table X.

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

TABLE X

MORPHOLINE-, THIOMORPHOLINE-, AND PIPERAZINESULFAMYLUREAS



No.	X	R_1	R_2	R	M.p., °C.	Crystn. solvent	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N	Hypoglycemic activity
1	O	2-CH_3	H	$CH(CH_2)_5$	154–155	*a*	$C_{12}H_{23}N_3O_4S$	47.2	7.6	13.8	47.1	7.8	13.7	24 ± 4.7
2	O	2-CH_3	H	$CH(CH_2)_6$	96.5–97	*a*	$C_{13}H_{25}N_3O_4S$	48.9	7.9	13.2	48.9	7.8	12.8	23 ± 2.5
3	O	2-CH_3	H	CH_2– 	115–116	*a*	$C_{14}H_{23}N_3O_4S$	51.0	7.0	12.8	51.2	7.0	12.7	47 ± 3.7
4	O	2-CH_3	H	$CH_2CF_2CF_3$	97.5–98.5	*a*	$C_9H_{14}F_5N_3O_4S$	30.4	4.0	11.8	30.4	3.9	11.6	16 ± 3.2
5	O	2-CH_3	6-CH_3	$CH(CH_2)_6$	170–171	*b*	$C_{14}H_{27}N_3O_4S$	50.4	8.2	12.6	50.3	8.1	12.5	11 ± 2.3
6	O	2-CH_3	6-CH_3	$CH_2CF_2CF_3$	157–158	*a*	$C_{10}H_{16}F_5N_3O_4S$	32.5	4.4	11.4	32.8	4.5	11.4	18 ± 2.5
7	O	2,2-$(CH_2)_5$		$CH(CH_2)_5$	132–133	*c*	$C_{16}H_{29}N_3O_4S$	53.4	8.1	11.7	53.6	8.3	11.3	13 ± 1.9
8	O	2,2-$(CH_2)_5$		$CH(CH_2)_6$	163–165	*d*	$C_{17}H_{31}N_3O_4S$	54.7	8.4	11.2	54.7	8.5	11.0	1 ± 2.5
9	S	H	H	$CH(CH_2)_6$	130–130.5	*e*	$C_{12}H_{23}N_3O_3S_2$	44.8	7.2	13.1	44.3	7.1	13.1	20 ± 2.8
10	SO_2	H	H	$CH(CH_2)_6$	84–86	*f*	$C_{12}H_{23}N_3O_5S_2$	40.8	6.6	11 9	40.4	6.7	11.9	11 ± 2.8
11	S	2-CH_3	H	$CH(CH_2)_6$	119–120	*e*	$C_{13}H_{25}N_3O_3S_2$	46.5	7.5	12.5	46.5	7.3	12.4	33 ± 3.0
12	SO_2	2-CH_3	H	$CH(CH_2)_6$	115–116	*f*	$C_{13}H_{25}N_3O_5S_2$	42.5	6.9	11.4	42.1	6.9	11.5	14 ± 3.0
13	S	2-CH_3	2-CH_3	$CH(CH_2)_6$	143–144	*a*	$C_{14}H_{27}N_3O_3S_2$	48.1	7.8	12.0	48.4	7.7	11.8	15 ± 3.0
14	SO	2-CH_3	2-CH_3	$CH(CH_2)_6$	140.5–141.5	*a*	$C_{14}H_{27}N_3O_4S_2$	46.0	7.4	11.5	45.6	7.2	11.5	27 ± 2.4
15	SO	2-CH_3	2-CH_3	$CH(CH_2)_5$	161.5–162.5	*b*	$C_{13}H_{25}N_3O_4S_2$	44.4	7.2	12.0	44.4	7.1	11.8	28 ± 1.6
16	SO_2	2-CH_3	2-CH_3	$CH(CH_2)_6$	169–170	*g*	$C_{14}H_{27}N_3O_5S_2$	44.1	7.1	11.0	44.3	7.3	10.6	27 ± 3.2
17	S	2,2-$(CH_2)_5$		$CH(CH_2)_6$	147–150	*h*	$C_{17}H_{31}N_3O_3S_2$	52.4	8.0	10.8	52.6	7.8	10.7	15 ± 1.6
18	SO	2,2-$(CH_2)_5$		$CH(CH_2)_6$	202–204	*i*	$C_{17}H_{31}N_3O_4S_2$	50.3	7.7	10.4	50.1	7.5	10.0	11 ± 3.2
19	SO_2	2,2-$(CH_2)_5$		$CH(CH_2)_6$	201–202	*i*	$C_{17}H_{31}N_3O_5S_2$	48.4	7.4	10.0	48.8	7.4	9.9	11 ± 1.1
20	C_2H_5N	H	H	$CH(CH_2)_5$	144–145	*a*	$C_{13}H_{26}N_4O_3S$	49.0	8.2	17.6	48.9	8.4	17.4	18 ± 3.0

[a] Ether. [b] Benzene. [c] Isopropyl ether. [d] Acetone–isopropyl ether. [e] Not recrystallized. [f] Water–ethanol. [g] Benzene–ether. [h] Benzene–isopropyl ether. [i] Isopropyl alcohol.

1-Sulfamylpiperidine.—A mixture of 105 g. (1.1 moles) of sulfamide and 85 g. (1.0 mole) of piperidine in 100 ml. of dimethoxyethane was heated under reflux on a steam bath overnight. The resulting solution was cooled in ice, and the precipitated product was filtered and dried. This general procedure was used for the preparation of all the sulfamides (Tables I and II).

4-Sulfamylthiomorpholine 1-oxides and 1,1-dioxides were prepared according to a general literature procedure[13] (Table VI).

Preparation of Sulfamide Sodium Salts.—To a solution of the sulfamide in methanol was added an equimolar amount of sodium methoxide in the same solvent. The resulting solution was concentrated to a small volume and the desired sodium salt was precipitated by the addition of diethyl ether.

N,N-Diphenyl-N′-cycloheptylurea.—To a mixture of 102 g. (0.44 mole) of diphenylcarbamyl chloride and 88.9 g. (0.88 mole) of triethylamine in 220 ml. of ethanol was added 50 g. (0.44 mole) of cycloheptylamine. The resulting solution was allowed to reflux at steam-bath temperatures overnight. Cooling the reaction mixture in a salt–ice bath precipitated the crude product which was filtered, washed with water, and dried. Recrystallization from ethanol gave 106 g. of the pure product. This procedure typifies that used in the synthesis of all the diphenylurea intermediates (Table III).

1-Acetyl-4-hydroxypiperidine.—To 50.5 g. (0.5 mole) of 4-hydroxypiperidine dissolved in 200 ml. of methylene chloride was added, with cooling and stirring, 54 g. (0.53 mole) of acetic anhydride over a period of 20 min. The solution was heated to reflux on the steam bath for a period of 2 hr. The solvent and acetic acid were removed under vacuum, and the residue was distilled to give the desired product, yield 68 g., b.p. 143–145° (0.01 mm.).

Anal. Calcd. for $C_7H_{13}NO_2$: C, 58.7; H, 9.2; N, 9.8. Found: C, 58.3; H, 9.2; N, 9.6.

1-Acetyl-4-methoxypiperidine.—1-Acetyl-4-hydroxypiperidine (15.7 g., 0.1 mole), dissolved in 55 ml. of dimethylformamide, was treated with 5.3 g. (0.11 mole) of a 50% sodium hydride suspension. The mixture was stirred for 20 min. and then treated with 17 g. (0.12 mole) of methyl iodide. The resulting solution was heated on a steam bath for 2 hr. Ether, 300 ml., was added to the cooled reaction mixture, and the precipitate of NaI was removed by filtration. The ether and dimethylformamide were removed *in vacuo*, and the residue was distilled; yield 13.5 g., b.p. 86° (0.05 mm.). Redistillation gave the pure product, yield 11.5 g., b.p. 76° (0.01 mm.).

Anal. Calcd. for $C_8H_{15}NO_2$: C, 61.1; H, 9.6; N, 8.9. Found: C, 60.5; H, 10.0; N, 9.1.

4-Methoxypiperidine.—A mixture of 11.5 g. (0.073 mole) of 1-acetyl-4-methoxypiperidine and 5.6 g. (0.14 mole) of NaOH in 45 ml. of water was heated under reflux overnight. The reaction mixture was cooled, saturated with Na_2CO_3, and extracted several times with ether. The ether extracts were combined and dried ($MgSO_4$), and the solvent was removed *in vacuo*. Distillation of the residual oil gave 6.2 g. of the product, b.p. 66° (10 mm.).

Anal. Calcd. for $C_6H_{13}NO$: C, 62.6; H, 11.4. Found: C, 62.1; H, 11.2.

The **hydrochloride** melted at 132–133°, lit.[14] m.p. 137.5–139.5°.

(13) M. M. Klenk, C. M. Suter, and S. Archer, *J. Am. Chem. Soc.*, **70**, 3848 (1948).

(14) R. R. Renshaw and R. C. Conn, *ibid.*, **60**, 745 (1938).

Anal. Calcd. for $C_6H_{13}NO\cdot HCl$: C, 47.5; H, 9.3; N, 9.2. Found: C, 47.6; H, 9.3; N, 8.9.

The **picrate** melted at 108–109°.

Anal. Calcd. for $C_6H_{13}NO\cdot C_6H_3N_3O_7$: C, 41.7; H, 5.0; N, 16.2. Found: C, 41.9; H, 4.9; N, 16.2.

1-Acetyl-3-hydroxypiperidine.—In a preparation analogous to that of 1-acetyl-4-hydroxypiperidine, 50.5 g. (0.5 mole) of 3-hydroxypiperidine and 54 g. (0.53 mole) of acetic anhydride in 200 ml. of methylene chloride gave 57.0 g. of 1-acetyl-3-hydroxypiperidine, b.p. 115° (1.0 mm.).

Anal. Calcd. for $C_7H_{13}NO_2$: C, 58.7; H, 9.2; N, 9.8. Found: C, 58.6; H, 8.8; N, 10.0.

1-Acetyl-3-methoxypiperidine.—By a methylation procedure similar to that used to prepare 1-acetyl-4-methoxypiperidine, 35.7 g. (0.25 mole) of 1-acetyl-3-hydroxypiperidine in 100 ml. of dimethylformamide was treated with 13.2 g. (0.28 mole) of 50% NaH and 39.0 g. (0.28 mole) of methyl iodide to give 26 g. of the product, b.p. 143–145° (23 mm.).

Anal. Calcd. for $C_8H_{15}NO_2$: C, 61.1; H, 9.6; N, 8.9. Found: C, 60.6; H, 9.4; N, 8.7.

3-Methoxypiperidine.—1-Acetyl-3-methoxypiperidine (26 g., 0.17 mole) and 12 g. (0.3 mole) of NaOH in 75 ml. of water were refluxed overnight. The reaction mixture was saturated with K_2CO_3 and extracted with ether. The ether extracts were dried, and the ether was removed *in vacuo*. Distillation of the residue gave 10 g. of the desired product, b.p. 24° (0.28 mm.), lit.[15] b.p. 159–160° (748 mm.).

Anal. Calcd. for $C_6H_{13}NO$: C, 62.6; H, 11.4; N, 12.2. Found: C, 62.1; H, 11.4; N, 12.3.

4,4-Dimethylpiperidine.—To a slurry of 22.8 g. (0.6 mole) of $LiAlH_4$ in 500 ml. of anhydrous ether under a nitrogen atmosphere was added over a 2-hr. period 28.2 g. (0.2 mole) of 3,3-dimethylglutarimide in 1200 ml. of ether. Stirring and cooling were maintained during the addition period. The reaction mixture was allowed to warm to room temperature and was then heated under reflux for 2.5 hr. The mixture was cooled and 65 ml. of ice water was added slowly. The ether layer was separated, and the aqueous phase was extracted with two 500-ml. portions of ether. All ether extracts were combined and dried ($MgSO_4$). Removal of the ether and distillation of the residue gave 7.5 g. of the product, b.p. 52–53° (22 mm.), lit. b.p. 135–138°,[16] 145–146°.[17]

Anal. Calcd. for $C_7H_{15}N$: C, 74.3; H, 13.4; N, 12.4. Found: C, 73.9; H, 12.8; N, 13.0.

4-Ethyl-4-methylpiperidine.—In an analogous manner 100 g. (0.65 mole) of 3-ethyl-3-methylglutarimide and 76 g. (2.0 moles) of $LiAlH_4$ gave 55.2 g. of the desired product, b.p. 69–70° (12 mm.).

The **hydrochloride** was recrystallized from ethanol, m.p. 228–229°.

Anal. Calcd. for $C_8H_{17}N\cdot HCl$: C, 58.7; H, 11.1; N, 8.6. Found: C, 58.8; H, 11.3; N, 8.8.

4,4-Diethylpiperidine.—By a similar method 50 g. (0.3 mole) of 3,3-diethylglutarimide[18] and 38 g. (1.0 mole) of $LiAlH_4$ gave 30.6 g. of the desired amine, b.p. 52–53° (2.0 mm.).

The **hydrochloride** was recrystallized from ethanol; m.p. 205–206°.

Anal. Calcd. for $C_9H_{19}NO\cdot HCl$: C, 60.8; H, 11.3; N, 7.9. Found: C, 60.9; H, 11.5; N, 7.9.

8-Azaspiro[4.5]decane.—3,3-Tetramethyleneglutarimide (50 g., 0.3 mole) was reduced in a similar manner to give 18 g. of the product, b.p. 40–41° (0.1 mm.).

Anal. Calcd. for $C_9H_{17}N$: C, 77.6; H, 12.3; N, 10.1. Found: C, 77.5; H, 12.2; N, 10.4.

3-Azaspiro[5.5]undecane.—In like manner 50 g. (0.28 mole) of 3,3-pentamethyleneglutarimide and 31.5 g. (0.83 mole) of $LiAlH_4$ in 4 l. of ether gave 36 g. of the product, m.p. 58–60°. This amine was used without further purification.

1-Benzyl-4-hydroxy-4-methylpiperidine.—To a solution of methyllithium prepared from 141.9 g. (1.0 mole) of methyl iodide and 13.9 g. (2.0 g.-atoms) of lithium wire in 1 l. of ether under a nitrogen atmosphere was added 94.5 g. (0.5 mole) of 1-benzyl-4-piperidone in 100 ml. of ether over a period of 2 hr. The reaction mixture was then heated under reflux for 1 hr. After cooling, 55 ml. of water was added dropwise. The ether layer was separated and dried ($MgSO_4$). The water layer was further extracted with four 200-ml. portions of ether, and the dried ether extracts were combined and concentrated to an oil. Distillation of the residual oil gave the product, yield 91.2 g., b.p. 118–121° (0.3 mm.), which crystallized on standing, m.p. 57–58°.

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.1; H, 9.3; N, 6.8. Found: C, 76.1; H, 9.3; N, 7.0.

The **picrate** melted at 127–128.5°.

Anal. Calcd. for $C_{13}H_{19}NO\cdot C_6H_3N_3O_7$: C, 52.5; H, 5.1; N, 12.9. Found: C, 52.6; H, 5.1; N, 13.0.

4-Hydroxy-4-methylpiperidine.—A mixture of 36 g. (0.165 mole) of 1-benzyl-4-hydroxy-4-methylpiperidine and 10 g. of 10% palladium on charcoal in 150 ml. of absolute ethanol was first treated with 10 ml. of 12 *N* HCl and was then shaken in an atmosphere of hydrogen at an initial pressure of 3.5 kg./cm.^{2} (50 p.s.i.). After 16 hr., the catalyst was filtered and the filtrate was concentrated to dryness. The residue was washed with acetone, dried, and then dusted into an excess of 50% aqueous KOH. The basic solution was extracted with ether, and all ether extracts were combined and dried (KOH). Removal of the ether and distillation of the residue gave 18 g. of the desired product, b.p. 115–117° (30 mm.).

Anal. Calcd. for $C_6H_{13}NO$: C, 62.6; H, 11.4; N, 12.2. Found: C, 62.4; H, 11.2; N, 11.6.

1-Benzyl-4-methoxy-4-methylpiperidine.—To 60 g. (0.3 mole) of 1-benzyl-4-hydroxy-4-methylpiperidine in 150 ml. of dimethylformamide was added 17.2 g. (0.36 mole) of a 50% NaH suspension. The reaction mixture was stirred for 1 hr. followed by the dropwise addition of 47.0 g. (0.033 mole) of methyl iodide over a period of 2 hr. The resulting mixture was allowed to stir at room temperature for 3 hr. and at steam-bath temperature for 1 hr. Ether (250 ml.) was added to the cooled reaction mixture and the resulting precipitate was filtered. The ether and dimethylformamide were removed under vacuum, and the residue was distilled to give the product, yield 43.0 g., b.p. 84° (0.01 mm.).

Anal. Calcd. for $C_{14}H_{21}NO$: C, 76.7; H, 9.7; N, 6.4. Found: C, 76.5; H, 9.7; N, 6.8.

The **picrate** was recrystallized from isopropyl alcohol; m.p. 126–127°.

Anal. Calcd. for $C_{14}H_{21}NO\cdot C_6H_3N_3O_7$: C, 53.6; H, 5.4; N, 12.5. Found: C, 53.7; H, 5.1; N, 12.8.

The **hydrochloride** was recrystallized from ethyl acetate; m.p. 194–195°.

Anal. Calcd. for $C_{14}H_{21}NO\cdot HCl$: C, 65.7; H, 8.7; N, 5.5. Found: C, 65.5; H, 8.5; N, 5.5.

4-Methoxy-4-methylpiperidine.—A solution of 65.7 g. (0.3 mole) of 1-benzyl-4-methoxy-4-methylpiperidine in 300 ml. of ethanol was shaken with 20 g. of 15% palladium on charcoal overnight in a hydrogen atmosphere at an initial pressure of 3.5 kg./cm.^{2} (50 p.s.i.). The catalyst was filtered and the ethanol was removed *in vacuo*. Distillation of the residue gave 22.9 g. of product, b.p. 95–110° (10 mm.); 13.2 g. of recovered starting material was obtained as a higher boiling fraction.

The **hydrochloride** melted at 178–179°.

Anal. Calcd. for $C_7H_{15}NO\cdot HCl$: C, 50.8; H, 9.7; N, 8.5. Found: C, 50.5; H, 9.6; N, 8.4.

1-Benzyl-4-hydroxy-4-(3-amyloxypropyl)piperidine.—To a solution of 3-amyloxypropyllithium, prepared from 105 g. (0.5 mole) of 3-bromo-1-(1,1-dimethylpropoxy)propane[19] and 6.94 g. (1.0 g.-atom) of lithium wire in 600 ml. of ether, was added 63 g. (0.33 mole) of 1-benzyl-4-piperidone in 100 ml. of ether over a period of 2 hr. The reaction mixture was allowed to stir at room temperature overnight and was then refluxed for 1 hr. Water (26 ml.) was added to the cooled mixture. The ether layer was separated and dried ($MgSO_4$). The insoluble materials at the ether–water interface were dissolved in 300 ml. of water and extracted further with five 100-ml. portions of ether. The combined ether layers were dried and concentrated to an oil. Distillation of the residue gave the desired product, yield 89.2 g., b.p. 180–188° (0.2 mm.)

The **hydrochloride** melted at 181–182°.

Anal. Calcd. for $C_{20}H_{33}NO_2\cdot HCl$: C, 67.5; H, 9.6; N, 3.9. Found: C, 67.4; H, 9.7; N, 3.9.

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8-Benzyl-1-oxa-8-azaspiro[4.5]decane.—A mixture of 6.1 g. (0.02 mole) of 1-benzyl-4-hydroxy-4-(3-*t*-amyloxypropyl)piperidine and 4.56 g. (0.024 mole) of *p*-toluenesulfonic acid monohydrate in 35 ml. of xylene was heated at reflux overnight with removal of the water formed by a Dean–Stark trap. A solid was collected by filtration and dissolved in water. The aqueous solution was made strongly basic by addition of 10% NaOH solution and was then extracted with ether. The ether extract was dried and concentrated to an oil. Distillation of the residue gave 3.6 g. of product, b.p. 108–110° (0.04 mm.).

Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.8; H, 9.2; N, 6.1. Found: C, 77.6; H, 9.1; N, 6.1.

The **picrate** was recrystallized from ethanol; m.p. 130–131°.

Anal. Calcd. for $C_{15}H_{21}NO \cdot C_6H_3N_3O_7$: C, 54.8; H, 5.3; N, 12.2. Found: C, 54.9; H, 5.2; N, 12.2.

1-Oxa-8-azaspiro[4.5]decane.—A mixture of 23.1 g. (0.1 mole) of 8-benzyl-1-oxa-8-azaspiro[4.5]decane and 10 g. of 10% palladium on charcoal in 200 ml. of absolute ethanol was shaken in an atmosphere of hydrogen overnight at an initial pressure of 3.15 kg./cm.^{2} (45 p.s.i.). The catalyst was filtered and the ethanol was removed by distillation at atmospheric pressure. The residual oil was distilled to give 11.0 g. of the desired product, b.p. 95–96° (15 mm.).

Anal. Calcd. for $C_8H_{15}NO$: C, 68.0; H, 10.7; N, 9.9. Found: C, 67.6; H, 10.6; N, 9.6.

The **picrate** was recrystallized from ethanol; m.p. 178–180°.

Anal. Calcd. for $C_8H_{15}NO \cdot C_6H_3N_3O_7$: C, 45.4; H, 4.9; N, 15.1. Found: C, 45.4; H, 4.9; N, 15.4.

The **hydrochloride** was recrystallized from ethanol; m.p. 170–171°.

Anal. Calcd. for $C_8H_{15}NO \cdot HCl$: C, 54.1; H, 9.1; N, 7.9. Found: C, 54.1; H, 9.0; N, 7.9.

8-Benzyl-1,4-dioxa-8-azaspiro[4.5]decane Hydrochloride.—A solution of 37.9 g. (0.20 mole) of freshly distilled 1-benzyl-4-piperidone and 18.6 g. (0.3 mole) of ethylene glycol in 500 ml. of chloroform was saturated with HCl gas at room temperature. A Hercules-type moisture trap was fitted to the flask, and the solution was heated under reflux until no more water collected in the trap. The solvent was removed *in vacuo*, and the residue was recrystallized from a mixture of methanol–isopropyl ether; yield 47.4 g., m.p. 253–258°.

Anal. Calcd. for $C_{14}H_{19}NO_2 \cdot HCl$: C, 62.3; H, 7.5; N, 5.2. Found: C, 62.3; N, 7.5; N, 4.7.

8-Benzyl-1,4-dioxa-2-methyl-8-azaspiro[4.5]decane hydrochloride was prepared in an analogous manner starting with 37.9 g. (0.20 mole) of 1-benzyl-4-piperidone and 21.6 g. (0.30 mole) of 1,2-propanediol. The resulting ketal was recrystallized from a mixture of isopropyl alcohol and isopropyl ether; yield 34.5 g., m.p. 187–189°.

Anal. Calcd. for $C_{15}H_{21}NO_2 \cdot HCl$: C, 63.5; H, 7.8; N, 4.9. Found: C, 63.6; H, 7.7; N, 5.3.

9-Benzyl-1,5-dioxa-3,3-dimethyl-9-azaspiro[5.5]undecane Hydrochloride.—By a similar procedure 37.9 g. (0.2 mole) of 1-benzyl-4-piperidone and 31.2 g. (0.3 mole) of 2,2-dimethylpropylene glycol gave 49.1 g. of the spiroketal after recrystallization from a mixture of methanol and diethyl ether; m.p. 246–248°.

Anal. Calcd. for $C_{17}H_{25}NO \cdot HCl$: C, 65.6; H, 8.4; N, 4.5. Found: C, 65.6; H, 8.2; N, 4.8.

1,4-Dioxa-8-azaspiro[4.5]decane.—A solution of 26.9 g. (0.1 mole) of 8-benzyl-1,4-dioxa-8-azaspiro[4.5]decane hydrochloride in 150 ml. of water was shaken with 5.0 g. of 5% palladium on charcoal in an atmosphere of hydrogen at an initial pressure of 3.5 kg./cm.^{2} (50 p.s.i.) until the theoretical amount of hydrogen was absorbed. The mixture was filtered, and the filtrate was made basic by the addition of concentrated KOH. The aqueous solution was then extracted three times with 50-ml. portions of methylene chloride. The combined extracts were dried (Na_2SO_4), filtered, and evaporated to yield a clear oil. The oil was distilled to give 5.2 g. of pure product, b.p. 91° (12 mm.). This compound has since been prepared by Stach, *et al.*,[20] b.p. 108–110° (26 mm.).

Anal. Calcd. for $C_7H_{13}NO_2$: C, 58.7; H, 9.2; N, 9.8. Found: C, 58.6; H, 9.0; N, 9.7.

1,4-Dioxa-2-methyl-8-azaspiro[4.5]decane.—A mixture of 28.3 g. (0.1 mole) of 8-benzyl-1,4-dioxa-2-methyl-8-azaspiro[4.5]-decane hydrochloride, 150 ml. of methanol, and 5.0 g. of 5% palladium on charcoal was shaken in an atmosphere of hydrogen at an initial pressure of 3.5 kg./cm.^{2} (50 p.s.i.). When the theoretical amount of hydrogen had been absorbed, the catalyst was filtered, and the filtrate was evaporated to dryness. The residue was recrystallized from isopropyl alcohol–isopropyl ether to give 20.1 g. of the hydrochloride salt. The salt was treated with aqueous KOH to liberate the free base, which was used immediately.

The **hydrochloride** melted at 172–173°.

Anal. Calcd. for $C_8H_{15}NO_2 \cdot HCl$; C, 49.6; H, 8.3; N, 7.2. Found: C, 49.6; H, 8.2; N, 7.2.

1,5-Dioxa-3,3-dimethyl-9-azaspiro[5.5]undecane.—Similarly 31.2 g. (0.1 mole) of 9-benzyl-1,4-dioxa-3,3-dimethyl-9-azaspiro-[5.5]undecane hydrochloride was debenzylated to give 19.0 g. of the expected secondary amine hydrochloride. The free base was generated by treatment of the salt with aqueous KOH.

The **hydrochloride** was recrystallized from isopropyl alcohol; m.p. 238–241°.

Anal. Calcd. for $C_{10}H_{19}NO_2 \cdot HCl$: C, 54.2; H, 9.1; N, 6.3. Found: C, 54.3; H, 9.0; N, 6.3.

Methyl 1-Methoxycarbonylmethoxycyclohexanecarboxylate.—Under an atmosphere of nitrogen, a solution of 144 g. (0.91 mole) of methyl 1-hydroxycyclohexanecarboxylate[21] in 250 ml. of dry dimethylformamide was treated portionwise with 45.5 g. (0.91 mole) of 50% NaH in mineral oil. After the addition of sodium hydride was complete, 133 g. (0.91 mole) of methyl bromoacetate was added dropwise with stirring and cooling. The reaction mixture was then heated on a steam bath for 30 min. The mixture was cooled and filtered, and the filtrate was evaporated under reduced pressure to yield an oil. Fractional distillation afforded starting ester, 35.4 g., b.p. 44–48° (0.15 mm.), and product, 67.3 g., b.p. 93–96° (0.15 mm.).

Anal. Calcd. for $C_{11}H_{18}O_5$: C, 57.4; H, 7.9. Found: C, 57.0; H, 7.6.

1-Carbamoylmethoxycyclohexanecarboxamide.—A solution of 64.6 g. (0.28 mole) of methyl 1-methoxycarbonylmethoxycyclohexanecarboxylate in 600 ml. of methanol was cooled in an ice bath and saturated with NH_3. The reaction flask was loosely stoppered and stored for 3 days at room temperature. A small amount of crystalline material precipitated and was filtered; 2.0 g., m.p. >300° dec.; this proved to be piperazine-2,5-dione. The filtrate was concentrated to 300 ml. to give, on cooling, 24.2 g. of the desired product, m.p. 176–181°. The analytical sample was recrystallized from acetonitrile; m.p. 176–178°.

Anal. Calcd. for $C_9H_{16}N_2O_3$: C, 54.0; H, 8.1; N, 14.0. Found: C, 53.9; H, 7.9; N, 14.5.

1-Oxa-4-azaspiro[5.5]undecane-3,5-dione.—A 500-ml. erlenmeyer flask containing 29.6 g. (0.148 mole) of 1-carbamoylmethoxycyclohexanecarboxamide was heated at 200–205° for 6 hr., during which time the evolution of NH_3 was noted. The contents of the flask, upon cooling to room temperature, were taken up in a mixture of methanol and water (1:3), treated with Darco, and filtered hot. The filtrate on cooling yielded colorless needles of the product, yield 17.9 g., m.p. 122–124°. A small sample of this material was recrystallized for analysis; m.p. 123–124°.

Anal. Calcd. for $C_9H_{13}NO_3$: C, 59.0; H, 7.2; N, 7.7. Found: C, 58.8; H, 7.3; N, 7.6.

1-Oxa-4-azaspiro[5.5]undecane.—With mechanical stirring and cooling, and under a nitrogen atmosphere, a suspension of 4.93 g. (0.130 mole) of $LiAlH_4$ in 50 ml. of dry tetrahydrofuran was treated dropwise with a solution of 12.0 g. (0.065 mole) of 1-oxa-4-azaspiro[5.5]undecane-3,5-dione in 100 ml. of dry tetrahydrofuran. On completion of the addition, the reaction mixture was stirred overnight at room temperature. About 15 ml. of acetic acid was added cautiously to the reaction mixture with cooling and stirring, followed by addition of 50 ml. of water. The solid materials were filtered, and the cake was washed with tetrahydrofuran and then water. The filtrate was evaporated under reduced pressure, and the oily residue (13 g.) was stirred with a mixture of 1 *N* KOH and isopropyl ether. The aqueous phase was washed once with isopropyl ether. The combined organic layers were dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give crude 1-oxa-4-azaspiro[5.5]undecane, 5.6 g. This crude amine was not purified further but was converted directly to the sulfamide by a procedure outlined previously.

2-Methylthiomorpholine.—To a suspension of 2.26 g. (0.02 mole) of β-mercaptoethylamine hydrochloride in 150 ml. of cold ethanol was added 2.64 g. (0.04 mole) of KOH. To this

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(21) P. J. Tarbouriech, *Compt. rend.*, **149**, 604 (1910); *Chem. Abstr.*, **4**, 583 (1910).

cooled mixture was then added 3.64 g. (0.02 mole) of ethyl α-bromopropionate in 20 ml. of ethanol. The reaction mixture was allowed to warm to room temperature and was heated to reflux for 3 hr. The mixture was then cooled and filtered, and the filtrate was evaporated to dryness. The residue was taken up in chloroform and dried (Na_2SO_4). Removal of chloroform gave 1.7 g. of 3-oxo-2-methylthiomorpholine, m.p. 82–82.5°.

To 11.4 g. (0.03 mole) of $LiAlH_4$ suspended in 250 ml. of cold ether was added 20.7 g. (0.157 mole) of 3-oxo-2-methylthiomorpholine in 1 l. of ether at such a rate as to maintain a gentle ether reflux (3–4 hr.). The reaction mixture was further heated under reflux for 2 hr., cooled, and treated dropwise with 33 ml. of ice water. The ether layer was separated, dried (KOH), and concentrated *in vacuo*. The residual oil was distilled to give 13 g. of the desired product, b.p. 55° (4 mm.), lit.[22] b.p. 163°.

Anal. Calcd. for $C_5H_{11}NS$: C, 51.2; H, 9.5; N, 12.0. Found: 50.9; H, 9.5; N, 11.8.

2,2-Dimethylthiomorpholine.—In a similar manner 113 g. (1.0 mole) of mercaptoethylamine hydrochloride, 112 g. (2.0 mole) of KOH, and 195 g. (1.0 mole) of ethyl α-bromoisobutyrate in 450 ml. of ethanol gave 61 g. of 3-oxo-2,2-dimethylthiomorpholine, m.p. 108.5–110°.

By the same reduction procedure, 61 g. (0.4 mole) of 3-oxo-2,2-dimethylthiomorpholine and 30.3 g. (0.8 mole) of $LiAlH_4$ in 700 ml. of ether gave 43.5 g. of the product, b.p. 66° (12 mm.).

Anal. Calcd. for $C_6H_{13}NS$: C, 54.9; H, 10.0; N, 10.7. Found: C, 54.8; H, 9.8; N, 10.5.

1-Mercaptocyclohexanecarboxylic Acid.—Under a nitrogen atmosphere, a solution of 14.0 g. (0.0076 mole) of 1-thia-3-azaspiro[4.5]decane-2,4-dione[9] and 15 g. of NaOH in 100 ml. of water was heated under reflux for 48 hr. The solution was cooled, a small amount of precipitated material was filtered, and the filtrate was washed twice with diethyl ether. The aqueous solution was adjusted to pH 1 with 12 *N* HCl and was again extracted with ether. This ether extract was then extracted three times with 100-ml. portions of saturated $NaHCO_3$ solution. The combined bicarbonate extracts were adjusted to pH 1, and 150 ml. of ether was added to the flask. The mixture was stirred overnight. The ether phase was then separated, dried, and evaporated to give 10.0 g. of the product, $n^{25}D$ 1.5130. This product would not crystallize, and distillation was not attempted.

1-(2-Aminoethylmercapto)cyclohexanecarboxylic Acid.—A flask, flushed with nitrogen, was charged with a solution of 45.2 g. (0.282 mole) of 1-mercaptocyclohexanecarboxylic acid in 100 ml. of 10% NaOH. To the stirred, ice-cooled solution was added dropwise over a 30-min. period 57.8 g. (0.282 mole) of 2-bromoethylamine hydrobromide in 202 ml. of 10% NaOH solution. The reaction solution was allowed to warm to room temperature and was then adjusted to pH 5 by addition of acetic acid. The resulting precipitate was filtered and washed with hot methanol to give crude product, 28.0 g., m.p. 247–249°. An analytical sample was prepared by sublimation at 0.1 mm. (bath temperatures 240°), m.p. 244–245°.

Anal. Calcd. for $C_9N_{17}NO_2S$: C, 53.2; H, 8.4; N, 6.9. Found: C, 53.3; H, 8.2; N, 6.6.

1-Thia-4-azaspiro[5.5]undecan-5-one.—Under a nitrogen atmosphere and without solvent, 5.0 g. (0.0246 mole) of 1-(2-aminoethylmercapto)cyclohexanecarboxylic acid was heated at 220° for 75 min. during which time water vapor evolved. After cooling, the contents of the flask were taken up in hot 1,2-dimethoxyethane. The solution was filtered and allowed to cool. The precipitated solid was filtered, yield 2.05 g., m.p. 184–185°. A second crop of 0.16 g., m.p. 183–184°, was obtained by concentration of the dimethoxyethane filtrate.

Anal. Calcd. for $C_9N_{15}NOS$: C, 58.3; H, 8.2; N, 7.6. Found: C, 58.1; H, 8.1; N, 7.2.

1-Thia-4-azaspiro[5.5]undecane. A predried three-neck 1000-ml. round-bottom flask was flushed with nitrogen and charged with 6.45 g. (0.170 mole) of $LiAlH_4$ and 100 ml. of dry tetrahydrofuran. During all operations in the reaction flask vigorous stirring was maintained. The mixture was heated under reflux for 30 min. and was then cooled in an ice bath. A solution of 20.0 g. (0.108 mole) of 1-thia-4-azaspiro[5.5]undecan-5-one in 300 ml. of dry warm dioxane was added dropwise over a period of 6 hr. to the cooled reaction mixture. During the addition, the dioxane solution was warmed by means of a heat lamp to prevent the solute from crystallizing. After the addition was complete, the mixture was allowed to warm to room temperature and was stirred overnight. The mixture was then treated with 40 ml. of glacial acetic acid and then with 200 ml. of water. Insoluble solids were filtered, and the filtrate was evaporated under reduced pressure to yield 28 g. of a gum. The gum was stirred in a mixture of 1 *N* KOH and isopropyl ether until all the gum was in solution. The ether phase was separated, washed twice with 1 *N* KOH and three times with water. The organic phase was dried, filtered, and evaporated to give 14.0 g. of an oil, which was fractionally distilled to give the product, 11.7 g., b.p. 141–142.5° (22 mm.).

Anal. Calcd. for $C_9H_{17}NS$: C, 63.1; H, 10.0; N, 8.2. Found: C, 63.2; H, 9.9; N, 8.0.

2,4-Dimethyl-3-amylamine.—2,4-Dimethyl-3-pentanone oxime[23] (65 g., 0.5 mole) in 150 ml. of dry ether was added dropwise under a nitrogen atmosphere to a suspension of 70 g. (1.83 moles) of $LiAlH_4$ in 1500 ml. of ether. The reaction mixture was allowed to stand at room temperature overnight. Excess hydride was hydrolyzed by the cautious, dropwise addition of 200 ml. of cold water. The ether layer was separated, and the aqueous phase was extracted with five 200-ml. portions of ether. Combined ether extracts were dried (KOH), and the ether was removed *in vacuo*. Distillation of the residue gave 38.7 g. of the product, b.p. 36–38° (22 mm.).

The **hydrochloride** was recrystallized from a large volume of ether; m.p. 193–194°.

Anal. Calcd. for $C_7N_{17}N\cdot HCl$: C, 55.4; H, 12.0; N, 9.2. Found: C, 55.2; H, 12.0; N, 9.4.

2-Aminomethylbicyclo[2.2.1]heptane.—A solution of 48.7 g. (0.3 mole) of 2-aminomethylbicyclo[2.2.1]-5-heptene hydrochloride in 100 ml. of absolute ethanol was shaken with 3.0 g. of platinum oxide in an atmosphere of hydrogen at an initial pressure of 3.5 kg./cm.^{2} (50 p.s.i.). After 2 hr., the uptake of hydrogen was complete, and the catalyst was filtered. Concentration of the resulting filtrate gave 39.1 g. of the desired product as the hydrochloride, m.p. >320°.

Anal. Calcd. for $C_8N_{14}N\cdot HCl$: C, 59.4; H, 10.0; N, 8.7. Found: C, 59.9; H, 10.1; N, 8.6.

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