Each compound was tested on three different nerve–ganglion preparations and the effect of the highest concentration of each compound used on the preganglionic nerve action potential was measured.

Acknowledgment. We thank the SRC for the provision of the NMR service and the Pharmaceutical Society of Great Britain for the award of a research scholarship to C.F.C.S.

References and Notes

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Sulfamylurea Hypoglycemic Agents. 6. High-Potency Derivatives

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Synthetic methods for a series of novel sulfamylurea derivatives have been developed. The hypoglycemic activity of simple 1-piperidinosulfonylureas is greatly enhanced by attaching an acylaminoethyl function in the 4 position of the piperidine ring. Optimum activity is achieved when the acyl radical is 5-chloro-2-methoxybenzoyl, 2-methoxynicotinyl, 5-chloro-2-methoxynicotinyl, 1,2-dihydro-1-methyl-2-ketonicotinyl, 2,3-ethylenedioxybenzoyl, quinoline-8-carbonyl, or 6-chloroquinoline-8-carbonyl. Optimal substituents on the terminal urea nitrogen are cyclohexyl, bicycloheptenylmethyl, and in certain cases propyl, 7-oxabicycloheptanylmethyl, and adamantyl. One of these compounds (**81**, gliamilide) was found to be well tolerated in man and it displayed a very short plasma half-life.

Previous publications from these laboratories[1] have shown that sulfamylureas and sulfamylsemicarbazides, especially those which contain a piperidine ring, display hypoglycemic activity similar to the sulfonylureas chlorpropamide and tolbutamide. The dramatic potency enhancement achieved by attachment of an acylaminoalkyl chain to the benzene nucleus of tolbutamide[2] prompted us to investigate the effect of a similar structural modification in the sulfamylurea series.

Chemistry. The synthesis of the 4-(5-chloro-2-methoxybenzamidoalkyl)piperidinosulfonylureas was initially approached as outlined in Scheme I. The coupling products of 2-methoxy-5-chlorobenzoyl chloride and 4-(2-aminoethyl)pyridine or 4-aminomethylpyridine were reduced under carefully controlled conditions to avoid loss of the aromatic chlorine. The resulting piperidine derivatives were converted by heating with sulfamide in 1,2-dimethoxyethane[1a] to the corresponding sulfamide derivatives. Treatment of these as the sodium salts with isocyanates or 3-substituted 1,1-diphenylureas[1a] gave the sulfamylureas listed in Tables I and II.

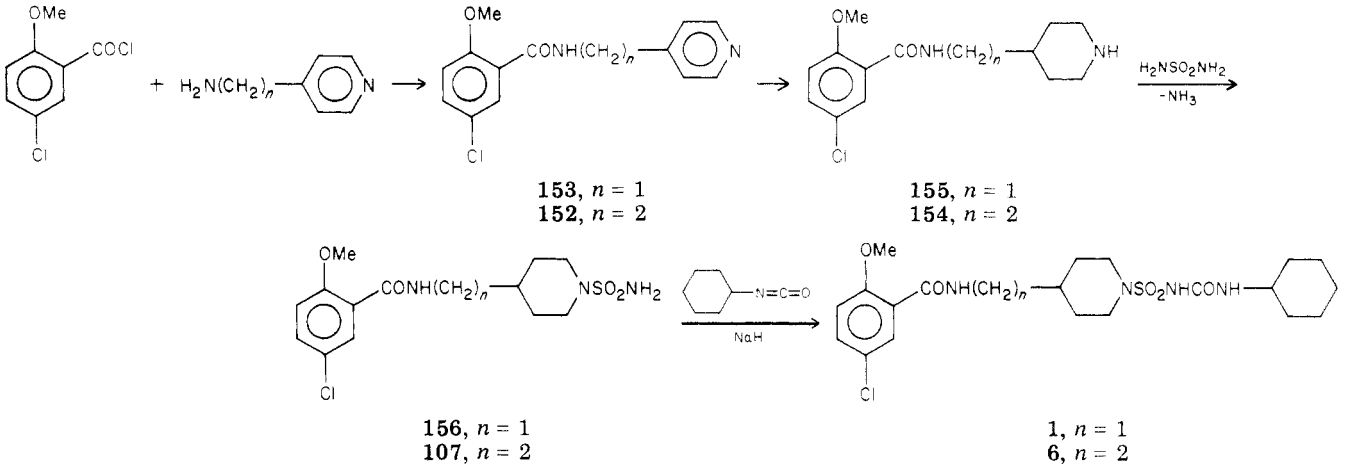
Subsequently, our interest shifted to the preparation of a wide variety of acylaminoethylpiperidinosulfonylureas and it became apparent that a versatile synthetic route to these compounds required 4-(2-aminoethyl)piperidinosulfonamide (**160**) as an intermediate. The most successful synthesis of **160** is depicted in Scheme II. Reaction of 4-(2-aminoethyl)pyridine with phthalic anhydride gave the phthalimide derivative **157** in excellent yield. Reduction of **157** to the piperidine derivative **158** was straightforward. After considerable experimentation pyridine was found to be the solvent of choice for converting **158** to the sulfonamide derivative **159**. Removal of the phthalimido group with anhydrous hydrazine followed by hydrochloric acid gave **160** in good overall yield.

Compound **160** was acylated using aqueous or nonaqueous acid chloride procedures, reactions with acid anhydrides, or EEDQ[3] couplings to afford the sulfonamide derivatives listed in Table VII. With a few exceptions (compounds **118** and **120**) no attempt was made to maximize yields.

Several procedures were investigated for the conversion of these sulfonamides to sulfamylureas. Reaction of a sulfonamide and an appropriate amine with carbonyldiimidazole, or reaction of a sulfonamide with ethyl chloroformate, forming a carbamate, followed by aminolysis (Scheme III) gave good yields of the desired products only in certain cases. However, two previously applied methods[1a] were found to be advantageous and generally applicable: conversion of the sulfonamides to the sodium salts with NaH in DMF, followed by reaction with an isocyanate or a 3-substituted 1,1-diphenylurea. The first method was used whenever the isocyanate of a desired amine was commercially available. Again, with the exception of compound **81**, no attempt was made to maximize yields.

Pharmacology. All compounds were tested in groups of five or six unanesthetized male rats of the Charles River strain (200–250 g), fasted 18–24 h prior to the experiment. The drugs were administered intraperitoneally at the doses indicated (5–25 mg/kg), and blood samples were taken from the tail vein prior to dosing and 1 h after drug administration. Blood glucose was determined using the ferricyanide reduction micromethod on a Technicon Autoanalyzer. Hypoglycemic activity is reported as percent drop in blood glucose at 1 h after dosing relative to a saline-treated control group. Statistical significance was ascertained by Student's t test.[4] Chlorpropamide is

Scheme I



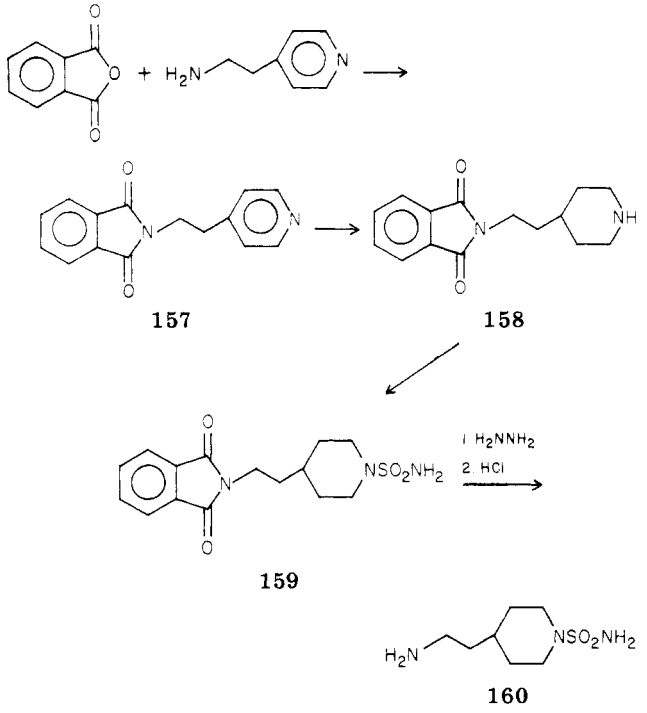
153, n = 1
152, n = 2

155, n = 1
154, n = 2

156, n = 1
107, n = 2

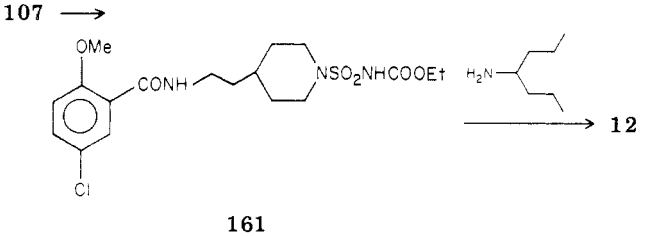
1, n = 1
6, n = 2

Scheme II



157 158 159 160

Scheme III



161

included in Table VI as a reference agent.

Structure–Activity Relationships. Initially, we investigated the effect of attaching the 5-chloro-2-methoxybenzamide function, which had been found to impart optimum activity in the sulfonylurea series,[2] to the 4 position of the piperidine ring of a sulfamylurea such as **106** (Table VI) with a one- or two-carbon alkyl chain (Tables I and II). It became apparent that this modification indeed led to a significant increase in hypoglycemic potency (compounds **1** and **6** vs. **106**). In general, compounds with the methylene bridge (Table I) appeared less potent than those with the ethylene bridge (Table II), and further structure–activity exploration was therefore carried out in the latter series. Inspection of Table II indicates that (apart from the sulfamylsemicarbazide **18**, which was not pursued further) optimal hypoglycemic activity was associated with the cyclohexyl (**6**), *endo*-bicycloheptenylmethyl (**7**), propyl (**8**), and *endo*-7-oxabicycloheptanylmethyl (**15**) substituents on the urea nitrogen, and these substituents were generally used in our subsequent exploration of a wide variety of acyl functions in the amide part of this sulfamylurea series. These results are summarized in Table III; hypoglycemic activity equivalent to that observed with the 5-chloro-2-methoxybenzoyl derivatives (Table II) was displayed by compounds containing the 2-methoxynicotinyl (**36**), 5-chloro-2-methoxynicotinyl (**48**), 1,2-dihydro-1-methyl-2-ketonicotinyl (**48**), quinoline-8-carbonyl (**70, 71**), 6-chloroquinoline-8-carbonyl (**72, 73**), and 2,3-ethylenedioxybenzoyl (**76**) radicals. Compounds **21, 27, 31, 37, 44, 51,** and **58** showed moderate activity. Compound **36** was elaborated by further modification of the urea nitrogen substituents; these derivatives are listed in Table IV. In this series potent hypoglycemic activity was associated with the cyclohexyl (**36**), *endo*-bicycloheptenylmethyl (**81**), *endo*-7-oxabicycloheptanylmethyl (**84**), and *endo*-bicycloheptanylmethyl (**86**) derivatives. By contrast, modification of **34** (Table V), undertaken because this compound offered the potential for extensive structural variations, did not lead to compounds with noteworthy activity.

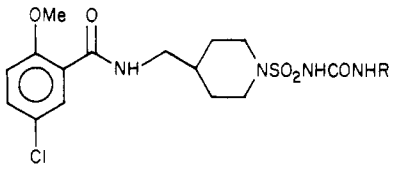
In summary, the following structure–activity rules emerged. Substitution of piperidinosulfonylureas with acylamidoethyl in the 4 position leads to enhanced potency. Optimal acyl substituents are 5-chloro-2-methoxybenzoyl, substituted nicotinyl, 2,3-ethylenedioxybenzoyl, and substituted quinoline-8-carbonyl radicals. Optimal substituents on the terminal urea nitrogen are generally cyclohexyl, bicycloheptenylmethyl, and in certain cases propyl, 7-oxabicycloheptanylmethyl, and adamantyl. In the bicycloheptenylmethyl and 7-oxabicycloheptanylmethyl derivatives, the endo isomers are without exception more potent than the corresponding exo isomers.

Compound **81** (gliamilide) was selected for clinical trials. It proved to be active and well tolerated in maturity-onset diabetic patients, with a short plasma half-life.[5]

Experimental Section

Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Analyses were carried out by the Physical Measurements Laboratory of Pfizer Inc. Where analyses are indicated only by symbols of the elements,

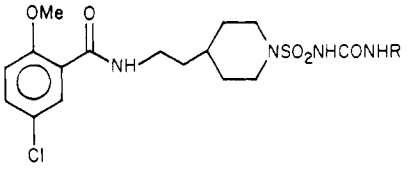
Table I

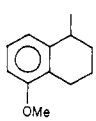


No.	R	Mp, °C	Formula[a]	Method[b]	Recrystn solvent	% yield	Hypoglycemic act.[c] at 5 mg/kg ip
1	c-C_6H_{11}	187-188	$C_{21}H_{31}ClN_4O_5S \cdot 0.25H_2O$	D	MeCN	63	20**
2		224-226 dec	$C_{23}H_{30}ClNaN_4O_5S$	E	MeCN-MeOH	53	15*
3	Pr	176-177	$C_{18}H_{27}ClN_4O_5S$	D	MeCN	86	NS
4	$(CH_2)_5CH_3$	158-159	$C_{21}H_{33}ClN_4O_5S$	D	MeCN	74	17**
5	4-$OMeC_6H_4$	157-158	$C_{22}H_{27}ClN_4O_6S$	D	MeCN	78	NS

[a] All compounds were analyzed for C, H, and N. [b] Method D = coupling of a sulfonamide with an isocyanate; see Experimental Section for preparation of compound **56**. Method E = coupling of a sulfonamide with a diphenylurea derivative; see Experimental Section for preparation of **81**. Method F = coupling of a sulfonamide and an amine with carbonyldiimidazole; see Experimental Section for preparation of compound **6**. Method G = reaction of a sulfonamide with ethyl chloroformate to form a carbamate followed by aminolysis; see Experimental Section for preparation of compounds **161** and **12**. Method H = hydrogenation of unsaturated sulfamylurea; see Experimental Section for preparation of compound **86**. [c] Percent drop in blood sugar in rats at 1 h after dosing relative to a saline-treated control group. The method is described in detail in the text. NS indicates not significant ($p > 0.05$); *** indicates $p < 0.001$; ** indicates $p < 0.01$; * indicates $p < 0.05$.

Table II



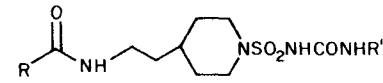
No.	R	Mp, °C	Formula[a]	Method[b]	Recrystn solvent	% yield	Hypoglycemic act.,[c] mg/kg ip 25	5	1
6	c-C_6H_{11}	149.5-151	$C_{22}H_{33}ClN_4O_5S$	F, D	MeCN	66		25***	39***
7		73-74.5	$C_{24}H_{33}ClN_4O_5S$	E	CH_2Cl_2-hexane	36		37***	27***
8	Pr	139-140	$C_{19}H_{29}ClN_4O_5S$	D	EtOAc	53	41***	11*	24***
9	$(CH_2)_5CH_3$	Oil	$C_{22}H_{35}ClN_4O_5S \cdot 0.5H_2O$	D		72		NS	
10	4-$OMeC_6H_4$	99-100 dec	$C_{23}H_{29}ClN_4O_6S \cdot 0.5H_2O$	D	CH_2Cl_2-hexane	68		27***	
11	2-$OMeC_6H_4$	111-113 dec	$C_{23}H_{29}ClN_4O_6S$	D	MeCN	76		NS	
12	$CH(Pr)_2$	99-102	$C_{23}H_{37}ClN_4O_5S \cdot 0.5CH_3COCH_3$	G	Me_2CO-H_2O	58		NS	
13	1-Adamantyl	130-133	$C_{27}H_{37}ClN_4O_5S$	D	Me_2CO	45		29***	
14		100-102	$C_{23}H_{36}ClN_5O_5S \cdot 0.5H_2O$	F	MeCN	16		NS	
15		125-126	$C_{23}H_{33}ClN_4O_6S$	E	MeCN	20		30***	
16		128	$C_{23}H_{33}ClN_4O_6S \cdot 0.5H_2O$	E	MeCN	9		27***	
17		117-120	$C_{27}H_{35}ClN_4O_6S \cdot 0.25H_2O$	E	MeCN-Et_2O	7		NS	
18	c-C_6H_{12}N-	114-116	$C_{22}H_{34}ClN_5O_5S$	F	MeCN	18		36***	

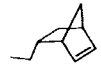
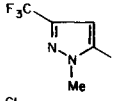
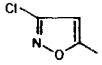
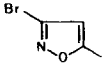
[a] All compounds were analyzed for C, H, and N. [b] See footnote *b* in Table I. [c] See footnote *c* in Table I.

analytical results obtained for these elements are within ±0.4% of the theoretical values.

Synthesis of the 4-(5-Chloro-2-methoxybenzamidoalkyl)piperidinosulfonylureas (Scheme I). 4-[2-(5-Chloro-2-methoxybenzamido)ethyl]pyridine (152). 5-Chloro-2-methoxybenzoic acid (4.0 g, 0.022 mol) was placed in benzene (50 ml), $SOCl_2$ (10.7 g, 0.09 mol) was added in one portion, and the solution was refluxed for 2 h. Evaporation in vacuo

Table III



No.	R	R′	Mp, °C	Formula[a]	Method[b]	Recrystn solvent	% yield	Hypoglycemic act.,[c] mg/kg ip 15	5	1
19	MeCO		141–142	$C_{18}H_{30}N_4O_4S$	E	EtOAc–hexane	40	25***	18**	
20	CF_3CO	c-C_6H_{11}	178–180	$C_{16}H_{27}F_3N_4O_4S$	D	EtOAc–hexane	50		13**	
21	CF_3CO		137–138	$C_{18}H_{27}F_3N_4O_4S$	E	EtOAc–hexane	12		22***	
22		Pr	138–140	$C_{17}H_{27}F_3N_6O_4S$	D	MeCN	71		11**	
23			89–92	$C_{19}H_{28}ClN_5O_6S \cdot H_2O$	E	MeCN	26	NS		
24			162–164	$C_{19}H_{28}BrN_5O_6S$	E	MeCN	39	NS	NS	
25			99–101	$C_{20}H_{29}N_5O_4S_2$	E	Et_2O–hexane	20	14**		
26			79–99	$C_{21}H_{31}N_5O_4S_2$	E	Et_2O–hexane	32	25***	11*	
27		c-C_6H_{11}	144–146	$C_{18}H_{29}N_5O_4S_2$	D	MeCN	10		23***	
28			186–189	$C_{20}H_{29}N_5O_4S_2$	E	MeCN	20	37***	NS	
29		Pr	157–159	$C_{15}H_{25}N_5O_4S_2$	D	MeCN	29		10**	
30			177–179	$C_{19}H_{29}N_5O_5S_2$	E	MeCN	44		NS	
31		c-C_6H_{11}	174–176	$C_{17}H_{28}N_6O_4S_2$	D	MeCN	39		19**	
32		Pr	148–149	$C_{14}H_{24}N_6O_4S_2$	D	MeCN	63		NS	
33			138–140	$C_{20}H_{30}N_6O_4S_2$	E	MeCN	47		NS	

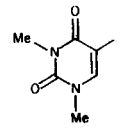
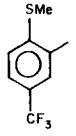
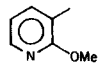
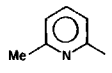
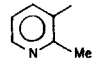
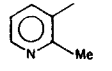
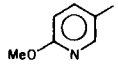
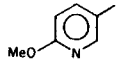
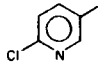
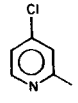
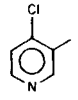
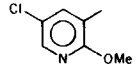
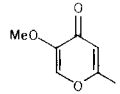
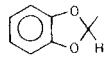
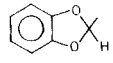
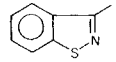
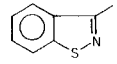
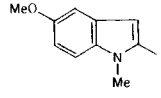
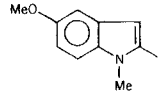
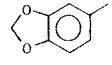
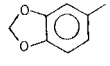
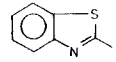
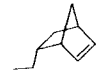
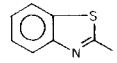
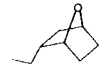
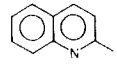
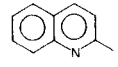
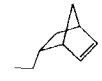
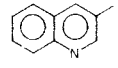
34		c-C_6H_{11}	207–209	$C_{21}H_{34}N_6O_6S \cdot 0.5H_2O$	D	MeCN	42	15**	NS	
35		c-C_6H_{11}	214–215	$C_{23}H_{33}F_3N_4O_4S_2 \cdot 0.5H_2O$	D	MeCN–$CHCl_3$	34	24***	NS	
36		c-C_6H_{11}	173–175	$C_{21}H_{33}N_5O_5S$	D	EtOH	43	35***	33***	22***
37			124–125	$C_{23}H_{33}N_5O_4S$	E	MeCN	17		20**	
38		c-C_6H_{11}	130–132	$C_{21}H_{33}N_5O_4S$	D	MeCN	68		16***	
39			128–130	$C_{23}H_{33}N_5O_4S \cdot 0.5H_2O$	E	MeCN	52		16**	
40			143–145	$C_{23}H_{33}N_5O_5S$	E	MeCN–Et_2O	40	32***	11*	
41			94–96	$C_{22}H_{33}N_5O_6S$	E	$CHCl_3$–hexane	20	NS	NS	
42			152–154	$C_{23}H_{33}N_5O_5S$	E	MeCN–Et_2O	66		14*	
43			151–152	$C_{22}H_{30}ClN_5O_4S \cdot 0.5H_2O$	E	$CHCl_3$–hexane	24		NS	
44			75–80	$C_{22}H_{30}ClN_5O_4S$	E	MeCN	87	46***	32***	16**
45			184–185	$C_{22}H_{30}ClN_5O_4S$	E	MeCN	43	NS		
46			165–166	$C_{22}H_{30}ClN_5O_4S$	E	MeCN–Et_2O	54	12**	NS	
47			120–124 dec	$C_{23}H_{32}ClN_5O_5S \cdot H_2O$	F	MeCN	4			20***[d]

Table III (*Continued*)

No.	R	R′	Mp, °C	Formula[a]	Method[b]	Recrystn solvent	% yield	Hypoglycemic act.,[c] mg/kg ip		
								15	5	1
48			161–163	$C_{23}H_{33}N_5O_5S$	E	EtOAc	22	40***		19*
49		c-C_6H_{11}	130–133	$C_{21}H_{32}N_4O_7S \cdot 0.25H_2O$	D	MeCN	5		NS	
50		c-C_6H_{11}	187–189	$C_{22}H_{32}N_4O_6S$	D	EtOH	54		8**	
51			143–146	$C_{23}H_{32}N_4O_7S$	E	MeCN	48	38***	15**	
52		c-C_6H_{11}	181–182	$C_{22}H_{31}N_5O_4S_2$	D	MeCN	72	17**	NS	
53		Pr	163–165	$C_{19}H_{27}N_5O_4S_2$	D	MeCN	62		NS	
54		c-C_6H_{11}	178–180	$C_{25}H_{39}N_5O_5S$	D	MeCN	38		NS	
55		Pr	183–185	$C_{22}H_{33}N_5O_5S$	D	MeCN	50		NS	
56		c-C_6H_{11}	195–197	$C_{22}H_{32}N_4O_6S$	D	MeCN	63	17**	NS	
57		Pr	188–190	$C_{19}H_{28}N_4O_6S$	D	MeCN	38		NS	
58			102–104	$C_{24}H_{31}N_5O_4S_2 \cdot 0.5H_2O$	E	MeCN	36	34***	24***	14**
59			95–97	$C_{23}H_{31}N_5O_5S_2 \cdot 0.5MeCN$	E	MeCN	40	30***		
60		c-C_6H_{11}	201–203	$C_{24}H_{33}N_5O_4S$	D	MeCN	48		11**	
61			165–167	$C_{26}H_{33}N_5O_4S$	E	MeCN	34		21***	
62		c-C_6H_{11}	198 dec	$C_{24}H_{33}N_5O_4S \cdot 0.25H_2O$	D	EtOH	59		NS	

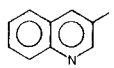
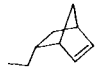
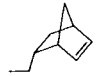
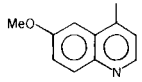
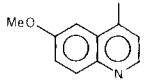
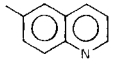
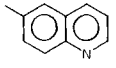
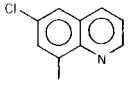
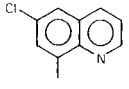
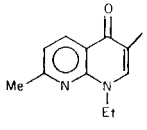
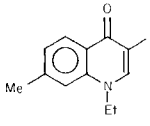
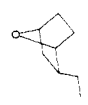
63			212–215	$C_{26}H_{33}N_5O_4S\cdot0.5H_2O$	E	EtOH–H_2O	44		NS	
64		c-C_6H_{11}	150–153	$C_{24}H_{33}N_5O_4S\cdot0.5H_2O$	D	EtOH–H_2O	56		16***	
65			148 dec	$C_{26}H_{33}N_5O_4S\cdot0.5H_2O$	E	EtOH–H_2O	49		NS	
66		c-C_6H_{11}	201–204	$C_{25}H_{35}N_5O_5S\cdot0.5H_2O$	D	EtOH	60		15**	
67			250–253 dec	$C_{27}H_{34}NaN_5O_5S$	E	MeCN	56		10*	NS
68		c-C_6H_{11}	191–193	$C_{24}H_{33}N_5O_4S\cdot0.5H_2O$	D	MeCN	36		NS	
69			140 dec	$C_{26}H_{33}N_5O_4S$	E	EtOAc	42		NS	
70		c-C_6H_{11}	177–179	$C_{24}H_{33}N_5O_4S$	D	MeCN	61		37***	29***
71			150 dec	$C_{26}H_{33}N_5O_4S\cdot0.5H_2O$	E	H_2O	47		34***	32***
72		c-C_6H_{11}	168–172	$C_{24}H_{32}ClN_5O_4S\cdot1.5H_2O$	D	MeCN	63		52***	17*[d]
73			146 dec	$C_{26}H_{31}ClNaN_5O_4S\cdot0.5H_2O$	E	MeCN	44		35***	16**[d]
74		c-C_6H_{11}	155 dec	$C_{26}H_{38}N_6O_5S\cdot0.5H_2O$	D	MeCN	68		NS	
75			145 dec	$C_{26}H_{38}N_6O_5S\cdot0.5H_2O$	E	MeCN	32		NS	
76		c-C_6H_{11}	189–191	$C_{23}H_{34}N_4O_6S$	D	MeCN	60	42***	34***	

Table III (*Continued*)

No.	R	R′	Mp, °C	Formula[a]	Method[b]	Recrystn solvent	% yield	Hypoglycemic act.,[c] mg/kg ip		
								15	5	1
77		Pr	159–161	$C_{20}H_{30}N_4O_6S$	D	MeCN	52	25**		
78			202–204	$C_{23}H_{34}N_4O_6S$	E	MeCN	56	40***	11*	
79			163–165	$C_{24}H_{34}N_4O_7S$	E	MeCN–C_6H_6	37	13**	15*	
80			196–198	$C_{24}H_{34}N_4O_7S$	E	MeCN	52		NS	

[a] All compounds were analyzed for C, H, and N. [b] See footnote *b* in Table I. [c] See footnote *c* in Table I. [d] Inactive at 0.5 mg/kg ip.

afforded the crude acid chloride as a waxy residue. This material was used directly without further purification. A solution of 4-(2-aminoethyl)pyridine[6] (740 mg, 6.1 mmol) in THF (50 ml) was treated with 5-chloro-2-methoxybenzoyl chloride (500 mg, 2.44 mmol) in THF (15 ml) and the mixture was stirred at room temperature for 3 h. After evaporation in vacuo, the oily residue was partitioned between CH_2Cl_2–H_2O (100 ml/100 ml) and the separated organic phase washed again with H_2O (50 ml), dried over $MgSO_4$, and filtered, and the filtrate was evaporated. The residue was recrystallized from benzene–heptane to yield 542 mg (77%) of **152**: mp 108–110°. Anal. ($C_{15}H_{15}ClN_2O_2$) C, H, N.

Similarly, **4-(5-chloro-2-methoxybenzamidomethyl)pyridine (153)** was prepared by treating 5-chloro-2-methoxybenzoyl chloride (10.25 g, 0.05 mol) with 4-picolylamine (11.0 g, 0.11 mol). After the standard work-up, the crude product was dissolved in EtOAc (100 ml) and treated with anhydrous HCl gas to give after filtration and recrystallization from MeOH–EtOAc 11.82 g (75.4%) of **153** as the HCl salt: mp 219–221°. Anal. ($C_{14}H_{13}ClN_2O_2$·HCl) C, H, N.

4-[2-(5-Chloro-2-methoxybenzamido)ethyl]piperidine (154). A solution of **152** (4.0 g, 0.014 mol) in glacial AcOH (100 ml) was hydrogenated in a Parr shaker at 50 psi over PtO_2 (400 mg) for 5 h at room temperature. The catalyst was removed by filtration and the filtrate concentrated to dryness in vacuo. The residual viscous yellow oil was dissolved in 50 ml of H_2O, layered with CH_2Cl_2 (100 ml), and treated with 4 N NaOH until the aqueous layer was strongly basic (pH 12). The layers were separated and the H_2O layer was extracted with 2 × 150 ml of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and filtered, and the filtrate was evaporated to dryness to give 3.94 g of oily product. After treatment with HCl gas in EtOAc and recrystallization from EtOH–EtOAc 4.16 g (91%) of **154** as the HCl salt, mp 181–183°, was obtained. Anal. ($C_{15}H_{21}ClN_2O_2$·HCl) C, H, N.

Similarly, **4-(5-chloro-2-methoxybenzamidomethyl)piperidine (155)** was obtained by hydrogenation of **153**·HCl (6.0 g, 0.019 mol) over PtO_2 (600 mg) in glacial AcOH (50 ml) to give 5.73 g (89%) of **155** as the HCl salt: mp 192–194° (EtOH–EtOAc). Anal. ($C_{14}H_{19}ClN_2O_2$·HCl) C, H, N.

4-[2-(5-Chloro-2-methoxybenzamido)ethyl]piperidinosulfonamide (107). A mixture of **154** as the free base (116 g, 0.39 mol), sulfamide (46.6 g, 0.485 mol), and 1,2-dimethoxyethane (2 l.) was refluxed overnight and the solvent then removed in vacuo. The resulting tan solid was triturated with 2 N HCl (1 l.) and then filtered to afford 97 g of crude product. Recrystallization from MeCN gave 82.5 g (57%) of **107**: mp 155–157.5°.

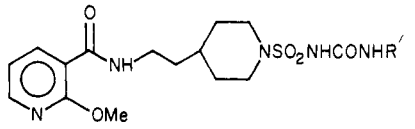
Similarly, **4-(5-chloro-2-methoxybenzamidomethyl)piperidinosulfonamide (156)** was prepared from **155** (1.41 g, 5 mmol) and sulfamide (520 mg, 6 mmol) in 1,2-dimethoxyethane (20 ml) to give after recrystallization from EtOH–H_2O (1:1) 986 mg (54%) of product: mp 172–174°. Anal. ($C_{14}H_{20}ClN_3O_4S$) C, H, N.

Synthesis of Compound 160 (Scheme II). 4-(2-Phthalimidoethyl)pyridine (157). 4-(2-Aminoethyl)pyridine (122.1 g, 1.0 mol) in 250 ml of xylene was added dropwise, with rapid stirring, to a solution of phthalic anhydride (148.1 g, 1.0 mol) in xylene (1 l.) containing 13 ml of NEt_3. The reaction was slightly exothermic and a heavy orange-yellow gum precipitated from the reaction mixture toward the end of the addition. The reaction mixture was then refluxed until the elimination of H_2O had been completed (2 h). At the end of this reflux period the reaction mixture was a homogeneous yellow liquid which was decanted, while hot, into a 2-l. Erlenmeyer flask. Cooling afforded 209 g (83%) of product: mp 155–557°. Anal. ($C_{15}H_{12}N_2O_2$) C, H, N.

4-(2-Phthalimidoethyl)piperidine (158). A 15-gal autoclave was charged with **157** (1800 g, 7.13 mol), anhydrous MeOH (10.62 gal) saturated with anhydrous HCl, and PtO_2 catalyst (72.2 g). The autoclave was held at 50° under 200 psi of H_2 until 95% of the theoretical H_2 uptake had occurred ($4^1/_3$ h). The reaction mixture was cooled to 24°, vented, and purged with N_2. The catalyst was removed by filtration and the filtrate concentrated to a final volume of 3 l. The precipitated product was removed by filtration, washed with 2-propanol, and air-dried to give 1070 g (51%) of a white crystalline solid: mp 235–242°. Recrystallization from EtOH–Et_2O gave pure **158** as the HCl salt: mp 240–242°. Anal. ($C_{15}H_{18}N_2O_2$·HCl) C, H, N.

4-(2-Phthalimidoethyl)piperidinosulfonamide (159). A 12-l. flask was charged with **158** hydrochloride (1700 g, 5.69 mol),

Table IV



No.	R′	Mp, °C	Formula[a]	Method[b]	Recrystn solvent	% yield	Hypoglycemic act.,[c] mg/kg ip 5	1
36	c-C_6H_{11}	173–175	$C_{21}H_{33}N_5O_5S$	D	EtOH	43	33***	22***
81		90–92	$C_{23}H_{33}N_5O_5S$	E	MeCN	64	32***	25***
82		104–105	$C_{23}H_{33}N_5O_5S \cdot 0.25H_2O$	E	MeCN-Et_2O	30	20**	NS
83	Pr	141–143	$C_{18}H_{29}N_5O_5S$	D	Me_2CO	36	NS	
84		109–110	$C_{22}H_{33}N_5O_6S$	E	MeCN-hexane	57	34***	NS
85		105–110	$C_{22}H_{33}N_5O_6S$	E	MeCN	74	14*	
86		105–108	$C_{23}H_{35}N_5O_5S$	H	MeCN	56	35***	NS
87		111.5–112.5	$C_{20}H_{31}N_5O_6S$	E	MeCN-Et_2O	66	16***	
88		152–153	$C_{21}H_{33}N_5O_6S$	E	MeCN	41	12*	
89	$-(CH_2)_2OEt$	138–140	$C_{19}H_{31}N_5O_6S$	E	MeCN	46	7*	
90	1-Adamantyl	171–173	$C_{25}H_{37}N_5O_5S$	D	MeCN	33	25***	12**

[a] All compounds were analyzed for C, H, and N. [b] See footnote *b* in Table I. [c] See footnote *c* in Table I.

sulfamide (552 g, 5.69 mol), and pyridine (5.8 l.). The mixture was stirred and refluxed for 24 h and then cooled to room temperature. After pouring into an ice–water mixture (36 l.) and stirring for 30 min, the precipitate was filtered and washed with 0.1 N HCl (5 l.), H_2O (15 l.), and finally with cold EtOH (3 l.) to give 1326 g (71%) of product: mp 195–197°. Recrystallization from EtOH gave pure **159**: mp 202–203°. Anal. ($C_{15}H_{19}N_3O_3S$) C, H, N.

4-(2-Aminoethyl)piperidinosulfonamide (160). A suspension of **159** (28.4 g, 0.084 mol), anhydrous hydrazine (2.7 g, 0.084 mol), and MeOH (250 ml) was refluxed for 90 min and then most of the MeOH was distilled off to give a homogeneous yellow solution. Concentrated HCl (350 ml) was added and the reaction mixture refluxed an additional 3 h and then cooled to room temperature. After filtration the filtrate was evaporated to dryness to give a white solid, which was triturated with hot acetone, filtered, and dried to afford 18.5 g (91%) of white crystals: mp 188–192°. Recrystallization from EtOH gave the analytical sample of **160** as the HCl salt: mp 195–197°. Anal. ($C_7H_{17}N_3O_2S \cdot HCl$) C, H, N.

Preparation of Sulfonamides (Table VII). 4-(2-Acetamidoethyl)piperidinosulfonamide (108). A THF (50 ml) solution of **160** hydrochloride (4.2 g, 0.017 mol) and NEt_3 (3.5 g, 0.035 mol) was treated dropwise with Ac_2O (1.77 g, 0.017 mol) at 0 °C. The reaction mixture was stirred at room temperature overnight and then evaporated to dryness to give a tacky solid, which was triturated with 1 N HCl (50 ml), washed well with H_2O, and finally recrystallized from EtOH to afford 2.21 g (51%) of **108** as white needles: mp 204–205°.

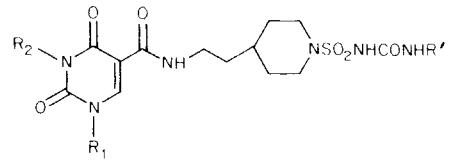
4-(2-Trifluoroacetamidoethyl)piperidinosulfonamide (109). A THF (100 ml) solution of **160** hydrochloride (10.0 g, 0.041 mol) and NEt_3 (8.08 g, 0.08 mol) was treated dropwise with trifluoroacetic anhydride (8.64 g, 0.041 mol) at 0 °C. The reaction mixture was stirred for 36 h at room temperature and then evaporated to dryness in vacuo. The residue was dissolved in EtOAc (250 ml) and washed twice with H_2O (100 ml). The organic layer was dried over $MgSO_4$, filtered, and evaporated. Recrystallization of the residue from EtOAc–hexane gave 7.96 g (64%) of **109**: mp 165–167°.

General Method A. The preparation of sulfonamides by the aqueous acid chloride coupling procedure is exemplified by the synthesis of **4-[2-(2-methoxynicotinamido)ethyl]piperidinosulfonamide (120).** A solution of 2-methoxynicotinyl chloride (286.5 g, 1.67 mol), prepared from nicotinic acid as described above for 2-methoxy-5-chlorobenzoyl chloride, in $CHCl_3$ (2 l.) and a solution of Na_2CO_3 (530 g, 5 mol) in H_2O (2.25 l.) were added simultaneously at a rate of 25 ml/min, with vigorous stirring, to a solution of **160**·HCl (407 g, 1.67 mol) and Na_2CO_3 (177 g, 1.67 mol) in H_2O (2.75 l.). After the addition was complete, the reaction mixture was allowed to stir at room temperature for 90 min. The precipitated solids were removed by filtration and washed twice with acetone (500 ml). The crude product was recrystallized from hot MeCN to give 409 g (71%) of pure product, mp 182–183°.

General Method B. The preparation of sulfonamides by the nonaqueous acid chloride coupling procedure is exemplified by the synthesis of **4-[2-(1,3-dimethyl-1,2,3,4-tetrahydropyrimidine-2,4-dione-5-carboxamido)ethyl]piperidinosulfonamide (118).** A suspension of 1,3-dimethyl-1,2,3,4-tetrahydropyrimidine-2,4-dione-5-carboxylic acid (9.2 g, 0.05 mol) in CCl_4 (50 ml) and $SOCl_2$ (70 ml) was heated on a steam bath for 45 min. The resulting solution was evaporated to dryness and residual $SOCl_2$ removed by azeotroping twice with benzene (100 ml). The white crystalline residue was suspended in THF (50 ml) and added to a mixture of **160**·HCl (12.1 g, 0.05 mol) and NEt_3 (10.2 g, 0.10 mol) in THF (100 ml). The mixture was stirred overnight at room temperature, the solids were filtered and digested in H_2O (200 ml), and the insoluble product was removed by filtration. Recrystallization from MeCN gave 17 g (94%) of product: mp 200–201°.

General Method C. The preparation of sulfonamides by the EEDQ coupling procedure[3] is exemplified by the synthesis of **4-[2-(1,3-benzodioxol-2-ylcarboxamido)ethyl]piperidino-**

Table V



No.	R′	R_1	R_2	Mp, °C	Formula[a]	Method[b]	Recrystn solvent	% yield	Hypoglycemic act.,[c] mg/kg ip 15	5	1
34	c-C_6H_{11}	Me	Me	207–209	$C_{21}H_{34}N_6O_6S·0.5H_2O$	D	MeCN	42	15**	NS	
91		Me	Me	216–217	$C_{23}H_{34}N_6O_6S$	E	MeCN	73	32***	23***	12*
92	Pr	Me	Me	216–218	$C_{18}H_{30}N_6O_6S$	D	MeCN	57	NS		
93		Me	Me	217–218	$C_{22}H_{34}N_6O_7S$	E	MeCN	19	NS	NS	
94		Me	Me	187–188	$C_{22}H_{34}N_6O_7S·0.25H_2O$	E	MeCN–Et_2O	49		NS	
95		Me	Me	214–215	$C_{23}H_{36}N_6O_6S·0.5H_2O$	H	MeCN	84		22***	
96		Me	Me	190–193.5	$C_{20}H_{32}N_6O_7S$	E	MeCN	72		NS	
97		Me	Me	193–195	$C_{21}H_{34}N_6O_7S·0.5H_2O$	E	MeCN	57		NS	
98	$(CH_2)_2OEt$	Me	Me	144.5 dec	$C_{19}H_{32}N_6O_7S$	E	EtOH	48		NS	
99	1-Adamantyl	Me	Me	224–226	$C_{25}H_{38}N_6O_6S·H_2O$	D	MeCN	38		27***	
100		Pr	Et	143 dec	$C_{26}H_{40}NaN_6O_6S·2H_2O$	E	$CHCl_3$–EtOAc	40		19***	
101		Bu	Bu	108–109	$C_{29}H_{47}N_6O_6S$	E	MeCN–Et_2O	25		12*	
102		$C_6H_5CH_2$	Bu	149–151	$C_{32}H_{44}N_6O_6S$	E	C_6H_6–cyclohexane	50		NS	
103		3-$F_3CC_6H_4CH_2$	Bu	119–121	$C_{33}H_{43}F_3N_6O_6S$	E	C_6H_6–cyclohexane	28		NS	
104		3-$ClC_6H_4CH_2$	Bu	172–173	$C_{32}H_{43}ClN_6O_6S$	E	MeCN	37		NS	
105		2-$ClC_6H_4CH_2$	Bu	159–161	$C_{32}H_{43}ClN_6O_6S$	E	MeCN	42		NS	

[a] All compounds were analyzed for C, H, and N. [b] See footnote *b* in Table I. [c] See footnote *c* in Table I.

Table VI

Ref drugs	Dose, mg/kg ip	Hypoglycemic act.[a]
Chlorpropamide	50	46***
	15	18***
	5	10*
106,[b]	100	34***
c-C_5H_{10}N-SO_2NHCONH-c-C_6H_{11}	15	19***

[a] See footnote *c* in Table I. [b] See ref 1a.

sulfonamide (132). Benzo-1,3-dioxol-2-ylcarboxylic acid (1.0 g, 0.006 mol), **160**·HCl (1.46 g, 0.006 mol), NEt_3 (606 mg, 0.006 mol), and ethyl 1,2-dihydro-2-ethoxy-1-quinolinecarboxylate (EEDQ)[3] were combined in THF (50 ml) and the white suspension was stirred at room temperature for 24 h. The solvent was then removed in vacuo to give a tacky white solid which was slurried in 100 ml of 1 N HCl. The product was removed by filtration and recrystallized from MeCN to give 1.79 g (84%) of product: mp 190–192°.

Preparation of Sulfamylureas (Tables I–V). General Method D. The preparation of sulfamylureas by the coupling of a sulfonamide with an isocyanate is exemplified by the synthesis of **1-cyclohexyl-3-[4-[2-(1,3-benzodiox-5-ylcarboxamido)-ethyl]piperidinosulfonyl]urea (56). 4-[2-(1,3-Benzodiox-5-ylcarboxamido)ethyl]piperidinosulfonamide (135,** 300 mg, 0.85 mmol) was suspended in dry DMF (5 ml), cyclohexyl isocyanate (319 mg, 2.55 mmol) in toluene was added in one portion, and to this suspension was added 100 mg (2.5 mmol) of 57% NaH. The reaction mixture was stirred at room temperature for 18 h and then poured into 100 ml of Et_2O. The precipitate was filtered, suspended in $CHCl_3$ (100 ml), and washed with 1 N HCl (two 50-ml portions). The $CHCl_3$ solution was dried over $MgSO_4$, filtered, and concentrated to dryness in vacuo affording a white solid. This material was recrystallized from MeCN to give 260 mg (63%) of product: mp 195–197°.

General Method E. The preparation of sulfamylureas by the coupling of a sulfonamide with a diphenylurea derivative is exemplified by the synthesis of **1-(bicyclo[2.2.1]hept-5-en-2-yl-*endo*-methyl)-3-[4-[2-(2-methoxynicotinamido)ethyl]-piperidinosulfonyl]urea (81).** A solution of 1,1-diphenyl-3-(bicyclo[2.2.1]hept-5-en-2-yl-*endo*-methyl)urea (380 g, 1.19 mol) and 4-[2-(2-methoxynicotinoamido)ethyl]piperidinosulfonamide (**120,** 407 g, 1.19 mol) in 3 l. of dry DMF was treated with 51 g (1.19 mol) of 56% NaH in one portion. The reaction mixture was heated to 65°, at which point it became exothermic, reaching a temperature of 70°. After 20 min a homogeneous solution resulted which was poured into 2 vol of Et_2O and extracted with 1 vol of H_2O. The aqueous layer was washed once more with 1 vol of Et_2O, acidified with 6 N HCl, and extracted with 1 l. of EtOAc. The EtOAc layer was decolorized with charcoal, dried over $MgSO_4$, and evaporated to a viscous oil which was dissolved in 1 l. in MeCN, filtered hot, allowed to cool to room temperature, and diluted with 2 l. of Et_2O. A pale yellow precipitate formed which was filtered to give 375 g (64%) of product: mp 90–92°.

General Method F. The preparation of sulfamylureas by the coupling of a sulfonamide to an amine with carbonyldiimidazole is exemplified by the synthesis of **1-cyclohexyl-3-[4-[2-(5-chloro-2-methoxybenzoyl)ethyl]piperidinosulfonyl]urea (6).** Cyclohexylamine (0.297 g, 3 mmol) was added dropwise to a solution of 0.487 g (3 mmol) of 1,1'-carbonyldiimidazole in 10 ml of dry THF. After stirring at room temperature for 1 h, this mixture was added to a solution of 1.19 g (3 mmol) of the sodium salt of **107** in 20 ml of THF. After refluxing for 4 h, the mixture was evaporated in vacuo. The residue was dissolved in H_2O and washed with Et_2O, and the aqueous layer was acidified. The precipitate was collected and recrystallized from MeCN to give 0.9 g (60%) of **6**: mp 148–150°.

General Method G. The preparation of sulfamylureas by the coupling of a sulfonamide with ethyl chloroformate, followed by aminolysis of the carbamate, is exemplified by the synthesis of **ethyl *N*-[4-[2-(2-methoxy-5-chlorobenzamido)ethyl]piperidinosulfonyl]carbamate (161)** and **1-(4-heptyl)-3-[4-[2-(2-methoxy-5-chlorobenzamido)ethyl]piperidinosulfonyl]urea (12). 107** (10.5 g, 0.028 mol), ethyl chloroformate (3.78 g, 0.035 mol), and anhydrous K_2CO_3 (6.71 g, 0.049 mol) were combined in acetone (250 ml) and the resulting white suspension was refluxed for 18 h. At this point the reaction mixture was concentrated in vacuo to afford a white solid, which was suspended in H_2O and washed three times with 200-ml portions of EtOAc. The basic, aqueous layer was filtered, acidified with 6 N HCl, and extracted three times with 250-ml portions of $CHCl_3$. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to give 8.5 g (68%) of **161**, mp 160–163°, after recrystallization from EtOH. Anal. ($C_{18}H_{26}ClN_3O_6S$) C, H, N. **161** (2.24 g, 0.005 mol) and 4-aminoheptane (1.2 g, 0.0104 mol) were placed in dry dioxane (50 ml) and the resulting white suspension was refluxed for 18 h. At this point the reaction mixture was evaporated to dryness in vacuo to afford a viscous tan oil which was suspended in 6 N HCl (100 ml) and extracted twice with 250-ml portions of $CHCl_3$. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to give a soft tan solid. Recrystallization from acetone–H_2O (1:1) gave 1.5 g (58%) of **12**: mp 99–102° dec.

General Method H. The preparation of sulfamylureas by hydrogenation of olefinic precursors is exemplified by the synthesis of **1-(bicyclo[2.2.1]heptan-2-yl-*endo*-methyl)-3-[4-[2-(2-methoxynicotinamido)ethyl]piperidinosulfonyl]urea (86).** 81 (983 mg, 0.002 mol), dissolved in THF (50 ml), was treated with 50 mg of 5% Pd/C and hydrogenated on a Parr shaker at 50 psi for 2 h. The catalyst was removed by filtration and the filtrate concentrated in vacuo. The residue was recrystallized from MeCN to afford 550 mg (56%) of **86**: mp 105–108°.

Preparation of Amines and Activated Amines. Isocyanates. All isocyanates used were commercially available with the exception of adamantyl isocyanate which was prepared by the literature procedure.[7]

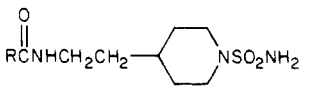
Diphenylurea Derivatives. The activation of amines by formation of their diphenylurea derivative is exemplified by the synthesis of **1,1-diphenyl-3-(bicyclo[2.2.1]hept-5-en-2-yl-*endo*-methyl)urea (162).** A 500-ml, three-necked flask was charged with *endo*-2-aminomethylbicyclo[2.2.1]hept-5-ene[8] (14.6 g, 0.12 mol) and NEt_3 (18.0 g, 0.18 mol) in 100 ml of THF. With ice cooling and rapid stirring diphenylcarbamoyl chloride (27.4 g, 0.12 mol) in THF (100 ml) was added dropwise. After the addition had been completed, the reaction mixture was stirred at room temperature for 1 h and then evaporated in vacuo. The resulting solid was suspended in 1 N HCl (250 ml) and extracted three times with 200-ml portions of $CHCl_3$. The combined organic layers were dried, filtered, and evaporated to give a viscous oil which crystallized when triturated with hexane. Recrystallization from Et_2O–hexane gave 29.2 g (77%) of **162**: mp 129–130°. Anal. ($C_{21}H_{22}N_2O$) C, H, N.

Similarly were prepared **1,1-diphenyl-3-(tetrahydrofuryl-2-methyl)urea (163)** (from tetrahydrofurfurylamine) [mp 99–101° (cyclohexane). Anal. ($C_{18}H_{20}N_2O_2$) C, H, N], **1,1-diphenyl-3-(tetrahydro-2-pyranylmethyl)urea (164)** (from 2-aminomethyltetrahydropyran) [mp 96–97° (cyclohexane). Anal. ($C_{19}H_{22}N_2O_2$) C, H, N], **1,1-diphenyl-3-(2-ethoxyethyl)urea (165)** (from 2-ethoxyethylamine) [mp 86–88° (Et_2O). Anal. ($C_{17}H_{20}N_2O_2$) C, H, N], **1,1-diphenyl-3-(*endo*-7-oxabicyclo-[2.2.1]hept-2-ylmethyl)urea (166)** (from *endo*-7-oxabicyclo-[2.2.1]hept-2-ylmethylamine, vide infra) [mp 109–111° (Et_2O). Anal. ($C_{20}H_{22}N_2O_2$) C, H, N], **1,1-diphenyl-3-(*exo*-7-oxabicyclo[2.2.1]hept-2-ylmethyl)urea (167)** (from *exo*-7-oxabicyclo[2.2.1]hept-2-ylmethylamine, vide infra) [mp 128–130° (Et_2O). Anal. ($C_{20}H_{22}N_2O_2$) C, H, N], and **1,1-diphenyl-3-(bicyclo[2.2.1]hept-5-en-2-yl-*exo*-methyl)urea (168)** (from *exo*-2-aminomethylbicyclo[2.2.1]hept-5-ene[8]) [mp 108–110° (Et_2O–hexane). Anal. ($C_{21}H_{22}N_2O$) C, H, N].

Amines. All amines used in this paper, with the exception of the two whose synthesis is described below, were either commercially available or prepared by literature procedures.

Preparation of *exo*- and *endo*-7-Oxabicyclo[2.2.1]hept-2-ylmethylamine. A 3-l. flask was charged with acrylonitrile (212 g, 4.0 mol), furan (272 g, 4.0 mol), and hydroquinone (50 mg) in benzene (1 l.). $TiCl_4$ (55 ml, 0.5 mol) in benzene (500 ml) was added, with vigorous stirring, at such a rate that the temperature did not exceed 35 °C. The resulting mixture was then stirred at room temperature for a period of 5 days at which point it was

Table VII



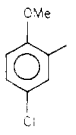
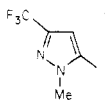
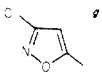
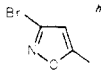
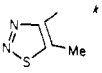
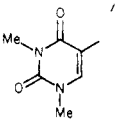
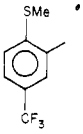
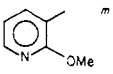
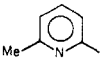
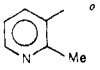
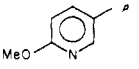
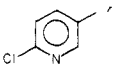
No.	R[a]	Mp, °C	Formula[b]	Method[c]	Recrystn solvent	% yield
107		155-157.5	$C_{15}H_{22}ClN_3O_4S$	*e*	MeCN	43
108	Me	204-205	$C_9H_{19}N_3O_3S$	*e*	EtOH	51
109	CF_3	165-167	$C_9H_{16}F_3N_3O_3S$	*e*	EtOAc-hexane	64
110		143-144	$C_{13}H_{20}F_3N_5O_3S$	B	C_6H_6	28
111		208-210	$C_{11}H_{17}ClN_4O_4S$	C	MeCN	48
112		214-216	$C_{11}H_{17}BrN_4O_4S$	C	MeCN	60
113		201-202	$C_{11}H_{18}N_4O_3S_2$	B	MeCN	58
114		200-201	$C_{12}H_{20}N_4O_3S_2$	B	MeCN	70
115		192-193	$C_{11}H_{18}N_4O_3S_2$	C	MeCN	41
116		211-212	$C_{10}H_{17}N_5O_3S_2$	C	MeCN	36
117		186-187.5	$C_{11}H_{19}N_5O_3S_2$	B	MeCN	41
118		200-201	$C_{14}H_{23}N_5O_5S$	B	MeCN	44
119		200-202	$C_{16}H_{12}F_3N_3O_3S_2$	C	MeCN	72
120		180-181	$C_{15}H_{17}N_3O_4S$	A	MeCN	85
121		188-190	$C_{14}H_{22}N_4O_3S$	A	MeCN	74
122		205-207	$C_{14}H_{22}N_4O_3S$	C	MeCN	64
123		204-205	$C_{14}H_{22}N_4O_4S$	C	MeCN	25
124		206-208	$C_{14}H_{22}N_4O_4S$	A	MeCN	66
125		214-215	$C_{13}H_{19}ClN_4O_3S$	A	MeCN	76
126		182-184	$C_{13}H_{19}ClN_4O_3S$	B	MeCN	36

Table VII (*Continued*)

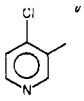
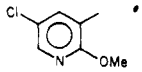
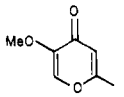
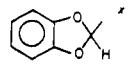
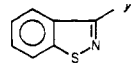
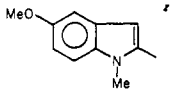
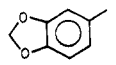
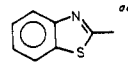
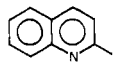
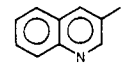
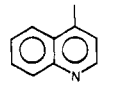
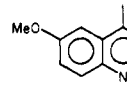
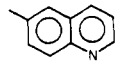
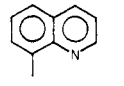
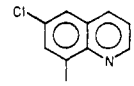
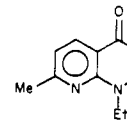
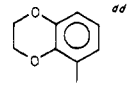
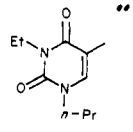
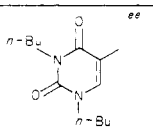
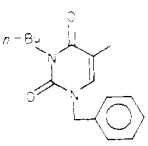
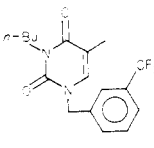
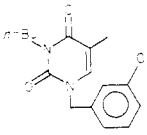
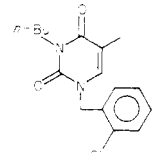
No.	R[a]	Mp, °C	Formula[b]	Method[c]	Recrystn solvent	% yield
127		167-168	$C_{13}H_{19}ClN_4O_3S$	A	MeCN	40
128		216-217	$C_{13}H_{19}ClN_4O_3S$	A	MeCN	59
129		189-190	$C_{14}H_{21}ClN_4O_4S$	A	MeCN	75
130		204-206	$C_{14}H_{22}N_4O_4S$	A	MeCN-Et_2O	25
131		201-202	$C_{14}H_{21}N_3O_6S$	C	MeCN	47
132		190-192	$C_{15}H_{21}N_3O_5S$	C	MeCN	84
133		197-198	$C_{15}H_{20}N_4O_3S_2$	C	MeCN	47
134		230-233	$C_{18}H_{26}N_4O_4S$	C	MeCN	78
135		226-228	$C_{15}H_{21}N_3O_5S$	B	MeCN	47
136		203-205	$C_{15}H_{20}N_4O_3S_2$	C	C_6H_6	64
137		194-196	$C_{17}H_{22}N_4O_3S$	C	MeCN	63
138		219-221	$C_{17}H_{22}N_4O_3S$	C	DMF-H_2O	58
139		215-217	$C_{17}H_{22}N_4O_3S$	C	MeCN	67
140		221-223	$C_{18}H_{24}N_4O_4S$	C	DMF-H_2O	66
141		214-216	$C_{17}H_{22}N_4O_3S$	C	DMF-H_2O	71
142		205-207	$C_{17}H_{22}N_4O_3S \cdot 0.5H_2O$	C	MeOH	54
143		224-226	$C_{17}H_{21}ClN_4O_3S$	C	DMF-H_2O	75
144		233-234	$C_{19}H_{27}N_5O_4S$	C	*i*-PrOH	41
145		175-177	$C_{16}H_{23}N_3O_5S \cdot 0.5$-MeCN	C	MeCN	55
146		164-165	$C_{17}H_{29}N_5O_5S$	B	MeCN	47

Table VII (*Continued*)

No.	R[a]	Mp, °C	Formula[b]	Method[c]	Recrystn solvent	% yield
147	 [ee]	148-149	$C_{20}H_{35}N_5O_5S$	B	MeCN	50
148	 [ee]	189-190	$C_{23}H_{33}N_5O_5S$	B	CH_3CN	50
149	 [ee]	175-176	$C_{24}H_{32}F_3N_5O_5S$	B	CH_3CN	44
150	 [ee]	197-200	$C_{23}H_{32}ClN_5O_5S$	B	CH_3CN	74
151	 [ee]	178-179	$C_{23}H_{32}ClN_5O_5S$	B	CH_3CN	54

[a] Footnotes in this column denote the reference used to prepare the acid starting materials; no footnote indicates that the acid was commercially available. [b] See footnote *a* of Table I. [c] Method A = aqueous coupling of acid chloride; see Experimental Section for preparation of compound **120**. Method B = nonaqueous coupling of acid chlorides; see Experimental Section for preparation of compound **118**. Method C = EEDQ coupling of acid to **160**; see Experimental Section for preparation of compound **132**. [d] A. S. Hussey and J. J. Wilk, *J. Am. Chem. Soc.*, **72**, 830 (1950). [e] See Experimental Section. [f] 3-Carbomethoxy-5-trifluoromethylpyrazole was prepared by the literature procedure: B. L. Dyatkin and E. P. Mochalina, *Izv. Akad. Nauk. SSR, Ser. Khim.*, 1225 (1964); *Chem. Abstr.*, **61**, 11881*f* (1964). This material was then alkylated with MeI in the standard manner (NaH-THF) to give an *N*-methyl analogue, which was hydrolyzed to the acid and used without further purification. The placement of the methyl group in the 2 position of the pyrazole ring is a tentative assignment. [g] P. Bravo, G. Gaudiano, A. Quilico, and A. Ricca, *Gazz. Chim. Ital.*, **91**, 97 (1961). [h] J. R. Geigy, Netherlands Patents 6 607 677 and 6 607 413 (1966); *Chem. Abstr.*, **66**, P 95029r (1967). [i] A. Adams and R. Slack, *J. Chem. Soc.*, 3061 (1959). [j] J. D'Amico and T. Bartram, *J. Org. Chem.*, **25**, 1336 (1960). [k] R. Micetich, R. Raap, J. Howard, and I. Pushkas, *J. Med. Chem.*, **15**, 333 (1972). [l] C. W. Whitehead, *J. Am. Chem. Soc.*, **74**, 4267 (1952). [m] K. Shimizu, J. Sakamoto, and S. Fukushima, *Yakugaku Zasshi*, **87**, 672 (1967); *Chem. Abstr.*, **68**, 12876g (1968). [n] G. Black, E. Deep, and B. B. Corson, *J. Org. Chem.*, **14**, 14 (1949). [o] P. Baumgarten and A. Dorrow, *Chem. Ber.*, **72**, 563 (1939). [p] H. Meyer, *Monatsh. Chem.*, **28**, 47 (1907). [q] W. C. J. Ross, *J. Chem. Soc.*, 1816 (1966). [r] W. Herz and D. R. K. Murtig, *J. Org. Chem.*, **26**, 122 (1961). [s] H. S. Mosher and M. Look, *ibid.*, **20**, 283 (1953). [t] G. M. Badger and R. P. Rao, *Aust. J. Chem.*, **18**, 1267 (1965). [u] E. C. Taylor and A. J. Crovetti, *J. Org. Chem.*, **19**, 1633 (1954). [v] D. Späth and G. Koller, *Chem. Ber.*, **56**, 880 (1923). [w] T. Yabuta, *J. Chem. Soc.*, **125**, 583 (1924). [x] W. G. Christiansen and M. A. Dolliver, *J. Am. Chem. Soc.*, **66**, 312 (1944). [y] R. Stolle, *Chem. Ber.*, **58**, 2095 (1925). [z] S. Ghosal, *Indian J. Chem.*, **5**, 650 (1967). [aa] H. Gilman and J. A. Beel, *J. Am. Chem. Soc.*, **71**, 2328 (1949). [bb] A. Lachowicz and T. Mazonski, *Rocz. Chem.*, **40**, 609 (1966); *Chem. Abstr.*, **65**, 3831*a* (1966). [cc] G. Lesher, E. Froelich, M. Gruett, J. H. Bailey, and R. P. Brundage, *J. Med. Pharm. Chem.*, **5**, 1063 (1962). [dd] R. C. Fuson, R. Gaertner, and D. H. Chadwich, *J. Org. Chem.*, **13**, 494 (1948). [ee] These acids were all prepared by alkylation of the known 3-ethyl- or 3-*n*-butyl-5-carbethoxyuracil followed by hydrolysis to the free acid. This work was completely analogous to numerous examples reported in the literature (see footnote *l* in this table).

treated with 0.5 N HCl (500 ml). The layers were separated and the aqueous layer was extracted with benzene (500 ml). The combined benzene layers were washed with water (500 ml), dried over $MgSO_4$, filtered, and evaporated in vacuo to give 156.3 g of crude 7-oxabicyclo[2.2.1]hept-5-en-2-ylnitrile as a mixture of exo and endo isomers. The above crude mixture was then hydrogenated in acetone (1 l.) at 50 psi, using 2 g of Pd on $BaSO_4$ as catalyst. After the calculated amount of H_2 had been taken up, the catalyst was removed by filtration and the filtrate concentrated under reduced pressure to give a yellow liquid, which was fractionally distilled to give 66.73 g (13.6%) of pure *endo*-7-oxabicyclo[2.2.1]hept-2-ylnitrile (**169**) [bp 45° (0.1 mm). Anal. (C_7H_9NO) C, H, N], 45.6 g (9.3%) of pure *exo*-7-oxabicyclo[2.2.1]hept-2-ylnitrile (**170**) [bp 48° (0.02 mm). Anal. (C_7H_9NO) C, H, N], and 17.8 g (3.6%) of an exo–endo mixture.

A well-stirred solution of **169** (54.3 g, 0.44 mol) in MeOH (500 ml) was treated with a methanolic slurry of Raney nickel (24 ml), followed by the dropwise addition of $NaBH_4$ (33.2 g, 0.88 mol) dissolved in 4 N NaOH (110 ml),[9] keeping the temperature of the reaction mixture below 50°. After the addition was complete, the mixture was stirred at room temperature for about 20 min at which point no further gas evolution could be detected. The reaction mixture was then filtered and concentrated in vacuo to give a yellow oil, which was suspended in 1 N NaOH (500 ml) and extracted three times with $CHCl_3$ (500 ml). The $CHCl_3$ extracts were combined, dried over $MgSO_4$, evaporated to an oil, and distilled under reduced pressure to give 55.5 g (100%) of *endo*-7-oxabicyclo[2.2.1]-hept-2-ylmethylamine: bp 90° (10 mm). This material was converted directly to its diphenylurea derivative **166** (vide supra). Similarly, **170** was converted to *exo*-7-oxabicyclo[2.2.1]hept-2-ylmethylamine, bp 90° (10 mm), and characterized as its diphenylurea derivative **167**.

Preparation of Novel Acids. 2-Thiomethyl-5-trifluoromethylbenzoic Acid (171). MeSH was bubbled into a mixture of DMF (75 ml) and 5 N aqueous NaOH (20 ml, 0.1 mol) until the weight of the solution had increased by 6.3 g (ca. 0.13 mol

of MeSH, a 30% excess). 4-Chloro-3-cyanobenzyl trifluoride (20.5 g, 0.1 mol) was then added in one portion and the reaction mixture became slightly exothermic. After stirring for a few minutes, a solid started to precipitate from the reaction mixture and stirring was continued for 2 h. After filtration, the filtrate was diluted with H_2O (500 ml) and extracted with Et_2O. This Et_2O extract was washed with H_2O (100 ml), dried over Na_2SO_4, and evaporated in vacuo to give 15.2 g (70%) of crude 4-thiomethyl-3-cyanobenzyl trifluoride as a gummy white solid. This material (15.2 g, 0.07 mol) was dissolved in EtOH (150 ml) and 20% NaOH (200 ml) and heated at 90° for 18 h. At this point the mixture was cooled and acidified with 12 N HCl and the white solids which precipitated were removed by filtration and washed well with H_2O to give 16.4 g (99%) of **171**: a white solid; mp 198–200°. A small sample was sublimed (125°, 0.02 mm) to give the analytical sample: mp 198.5–200°. Anal. ($C_9H_7F_3O_2S$) C, H.

5-Chloro-2-methoxynicotinic Acid (172). Chlorine gas was bubbled into a stirred suspension of 2-methoxynicotinic acid (10.0 g, 0.065 mol) in H_2O (750 ml) for 30 min at room temperature. The precipitated crystals were collected and dried to give 10.19 g (84%) of **172**: mp 149–150°. Anal. ($C_7H_6ClNO_3$) C, H, N.

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References and Notes

(1) (a) J. M. McManus, J. W. McFarland, C. F. Gerber, W. M. McLamore, and G. D. Laubach, *J. Med. Chem.*, **8**, 766 (1965); (b) J. W. McFarland, C. F. Gerber, and W. M. McLamore, *ibid.*, **8**, 781 (1965); (c) J. M. McManus and C. F. Gerber, *ibid.*, **9**, 256 (1966); (d) J. M. McManus, *ibid.*, **9**, 967 (1966).
(2) W. Aumüller, A. Bänder, R. Heerdt, K. Muth, W. Pfaff, F. H. Schmidt, H. Weber, and R. Weyer, *Arzneim.-Forsch.*, **16**, 1640 (1966).
(3) B. Belleau and G. Malek, *J. Am. Chem. Soc.*, **90**, 1651 (1968).
(4) W. J. Dixon and F. J. Massey, "Introduction to Statistical Analysis", McGraw-Hill, New York, N.Y., 1969, pp 114–123.
(5) J. R. Ryan, F. G. McMahon, and A. K. Jain, *Clin. Pharmacol. Ther.*, **17**, 243 (1975).
(6) L. E. Brady, M. Freifelder, and G. R. Stone, *J. Org. Chem.*, **26**, 4758 (1961).
(7) H. Stetter, J. Mayer, M. Schwarz, and K. Wulff, *Chem. Ber.*, **93**, 226 (1960).
(8) (a) K. Alder, K. Heimbach, and R. Reubke, *Chem. Ber.*, **91**, 1516 (1958); (b) P. Wilder and D. B. Knight, *J. Org. Chem.*, **30**, 3078 (1965).
(9) R. A. Egli, *Helv. Chim. Acta*, **53**, 47 (1970).

Synthesis and Biological Evaluation of Substituted 2,2'-Oxybis(propionic acid) Derivatives and Related Compounds

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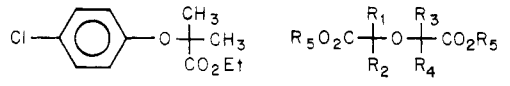
A series of 2,2'-oxybis(propionic acid) derivatives was prepared and their hypolipidemic activity measured. The lipid lowering activity of various 2,2,5,5-tetrasubstituted furan derivatives was also measured. No significant hypolipidemic activity was observed.

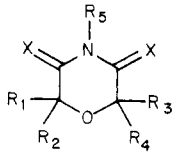
An enormous research effort has been directed at understanding and attacking atherosclerosis and coronary artery disease. Both abnormal serum lipoprotein metabolism[1] and abnormal arterial wall lipid metabolism[2] have been implicated. Whereas it has not been established that lowering serum lipoprotein concentration decreases the rate of deposition of lipid in arterial walls, the elevated serum lipid level associated with abnormal lipoprotein metabolism has been designated as a major risk factor in the atherosclerotic heart disease.[3] That coronary heart disease and cerebral vascular accident are the single largest cause of death in this country has stimulated efforts to discover agents which reduce circulatory lipid levels.

A large number of aryl- and aryloxy-substituted alkylcarboxylic acids have been reported to possess hypolipidemic activity.[4] Among these, clofibrate (A) has been the major drug available for treatment of these hyperlipidemias. The disadvantages of low potency[5] as well as its lack of effectiveness toward type II hyperlipoproteinemia[6] have led to a concentrated search for superior hypolipidemic agents among compounds containing the structural elements of clofibrate.[7]



A

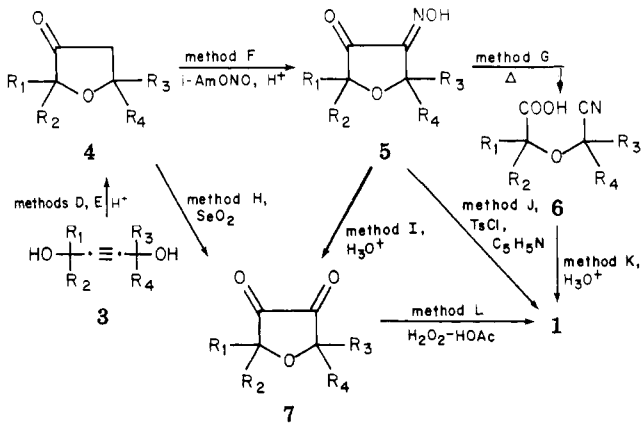
1



2

In this regard, a synthetic program directed toward 2,2'-oxybis(propionic acid) derivatives of type **1**, morpholines of structure **2**, and related compounds was initiated.

Scheme I



Chemistry. The synthetic pathways used to prepare the 2,2'-oxybis(propionic acid) derivatives **1** are displayed in Scheme I. Of the reported[8-11] conversions of furandiones **7** or furandione monooximes **5** (Table III) into 2,2'-oxybis(propionic acid) derivatives of formula **1** (Table I), oxidative cleavage[8] of α-dione **7** proved the most general pathway. In several cases (**1b,d,f**) purification of the diacid