zation constant for compounds in this series, which would strike a balance between metabolic stability and renal elimination.

Attempts to attain this balance in this sulfamylurea series met with varied results. The longest plasma half-lives were seen in the compounds in the morpholine series; I (pK_a = 5.6) exhibited a plasma half-life in the dog of 10–14 hr., and approximately 30% of the drug was recovered unchanged in the urine after intravenous administration. Substitution in the morpholine ring had little effect on pK_a (II), but attempts to increase the acidity of compounds in this series by introduction of a pentafluoropropyl group in the place of a cycloalkyl group were successful.[17] The expected resistance to metabolism was obtained, but the increase in ionization constant (III and IV, pK_a = 4.8) was such that these compounds, being extensively ionized in tubular urine, were probably poorly reabsorbed and consequently rapidly excreted. Plasma drug half-life decreased to 1–2 hr. and about 60% of the drug was recovered unchanged in the urine.

Compounds in the piperidine series were of higher pK_a than their morpholine analogs, and, as was expected, proved to be relatively vulnerable to metabolism. VI (pK_a = 6.2) had a plasma half-life of 3–4 hr. and was extensively metabolized, less than 25% being recovered unchanged in the urine. The same extensive metabolism was seen in VIII (pK_a = 6.4, plasma half-life 2.5–3.5 hr.) and IX (pK_a = 6.4, plasma half-life 2–3 hr.). In this series also, an increase in acid strength was obtained by the introduction of the pentafluoropropylamine moiety.[17] Thus the analog of VI, VII (pK_a = 5.6), showed an increase in plasma half-life to 7–9 hr. This compound was more resistant to metabolism than VI, a reflection of increased acidity. Similar success was obtained with the pentafluoropropyl analog of VIII, X (pK_a = 5.4). This compound had a half-life in the dog of 6–9 hr., which appeared, from the urinary recovery of unchanged drug, to result from its comparative resistance to metabolism.

The broad generalizations concerning the effects of physical properties on physiological dynamics that have emerged from the study of this series of compounds are all consistent with well-established concepts of drug dynamics. Rate of oral absorption, related to rate of solution, is as much a function of the surface area of the compound presented for solution as it is of the absolute solubility. It appears that in a series such as the sulfamylureas, which in general have high lipid–water partition ratios, small changes in lipophilicity are without significance in control of physiological disposition. Increase in acidity confers resistance to metabolism. Since chemical hydrolysis is known[18] to occur by a mechanism facilitated by low degree of ionization (high pK_a), it is possible that the enzymatic process of metabolism is subject to similar control. Thus, relatively high acidity can lead to an extended drug plasma half-life. However, if the acidity of the compound becomes too high, the extent of ionization in tubular urine will be increased, and facile renal excretion will occur, presumably because tubular reabsorption is hindered.

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Sulfamylurea Hypoglycemic Agents. III. Tetrasubstituted Sulfamylureas and N-Sulfamylcarbamates

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Two new series of hypoglycemic agents have been synthesized: (1) tetrasubstituted sulfamylureas of the general formula $R_1R_2NSO_2NHCONR_3R_4$ (II) in which both R_1R_2N and NR_3R_4 are derived from secondary amines, and (2) sulfamylcarbamates $R_1R_2NSO_2NHCO_2R_5$ in which R_5 is cycloalkyl. Generally, the hypoglycemic activities of these compounds are somewhat less than those of previously described sulfamylureas represented by $R_1R_2NSO_2NHCONHR$ (I) in which NHR is derived from a primary amine. A simple method for the preparation of sulfonyl isocyanates is also described.

Earlier papers in this series[1,2] described the synthesis, hypoglycemic action, and drug dynamic properties of trisubstituted sulfamylureas of the general formula $R_1R_2NSO_2NHCONHR$ (I) wherein NHR is derived from various primary amines. These studies suggested that of two closely related sulfamylureas the more acidic analog will exhibit the longer half-life. Since longer half-lives were desirable in this series, efforts were made to increase the acidity of sulfamylureas.

Several modifications of the sulfonylurea structure can be made which will lower the pK_a. For example 1-butyl-1-methyl-3-(*p*-tolylsulfonyl)urea is about 2.5 times more acidic than its parent, 1-butyl-3-(*p*-tolylsulfonyl)urea (tolbutamide)[3] (see Table I). Reasoning that secondary amine derivatives might in general be more acidic than comparable primary amine derivatives, we undertook to synthesize tetrasubstituted sulfamylureas represented by $R_1R_2NSO_2NHCONR_3R_4$ (II) in which R_1R_2N is derived from piperidine or 4,4-dimethylpiperidine, and NR_3R_4 is derived from diverse secondary amines. A small series of N-sulfamyl-

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Table I

ASO_2NHCOB

A	Primary amine derivatives B	pK_a[a]	Secondary amine derivatives B	pK_a
p-Tolyl	Butylamino	6.1	Butylmethylamino	6.0
Piperidino	Cyclohexylamino	8.1	Cyclohexylmethylamino	7.8
Piperidino	Cycloheptylamino	8.1	1-Hexahydroazepinyl	7.8

[a] The pK_a values of the *p*-toluenesulfonylureas are data from Morozowich[3] and were determined in 50% aqueous ethanol. The other pK_a values are data from E. H. Wiseman of these laboratories (personal communication) and were determined in 50% aqueous dioxane.

Table II

ASO_2NCO

A	Reaction time, hr.	B.p., °C. (mm.)	Yield, %	Infrared, μ[a]
Phenyl	6	85–86 (0.6)	15	4.50[b]
p-Tolyl	8	106–107 (0.6)[c]	29	4.52[b]
Piperidino	1	70–71 (0.35)	34	4.47[d]
4,4-Dimethylpiperidino	1	95–98 (0.35)	26	...
Morpholino	1	...	0	...

[a] Only the characteristic absorption of the isocyanate group is given. [b] 5% in CH_2Cl_2. [c] Lit. b.p. 90–93° (0.05 mm.),[6] 90–92° (0.5 mm.).[3] [d] Film.

carbamates of the type $R_1R_2NSO_2NHCO_2R_5$, where R_5 is cycloalkyl, was also made in order to investigate the blood sugar lowering activity of this class. It has been reported that N-sulfonylcarbamates are hypoglycemic.[4]

A special case of type II sulfamylureas is that in which NR_3R_4 is the same as R_1R_2N. To investigate this series, chlorosulfonyl isocyanate was prepared by the method of Graf[5] and was subsequently treated with various secondary amines. Only with piperidine was a product of the desired type obtained, and then only in poor yield. The reaction of chlorosulfonyl isocyanate with other secondary amines proved to be too unreliable for further studies.

For compounds in which NR_3R_4 is not identical with R_1R_2N, as well as for compounds in which it is the same, sulfamyl isocyanates appeared to be ideal intermediates. Preliminary attempts to make these highly reactive intermediates by the action of phosgene on N,N-disubstituted sulfamides[6] failed to yield the desired products. Recently Speziale and Smith[7] reported a remarkably simple process for making acyl isocyanates by reaction of oxalyl chloride with carboxamides. This report prompted us to try the analogous

$$RCONH_2 + (COCl)_2 \longrightarrow RCONCO + CO + 2HCl$$

reaction of piperidine-1-sulfonamide.[8] Under conditions nearly identical with those given by Speziale and Smith,[7] the reaction furnished piperidine-1-sulfonyl isocyanate in 19% yield. Catalysis by benzoyl peroxide led to a slight improvement in yield (24%), but even better results were obtained when a trace of boron trifluoride was employed (34% yield). Similarly, 4,4-dimethylpiperidine-1-sulfonamide, *p*-toluenesulfonamide, and benzenesulfonamide were each treated with oxalyl chloride in the presence of trace amounts of boron trifluoride to give the corresponding sulfonyl isocyanate (Table II). However, morpholine-1-sulfonamide did not give detectable amounts of the sulfonyl isocyanate.[9] In each reaction (except that with morpholine-1-sulfonamide) the corresponding N,N′-bis(sulfonyl)-oxamide (Table III) was obtained as a by-product. In contrast to these findings, Speziale and Smith[7] reported only negligible amounts of bisacylureas as by-products of their reactions.

Benzene solutions of the sulfonyl isocyanates were treated with appropriate secondary amines to give sulfamylureas of type II (see Table IV). Similarly, addition of appropriate alcohols to these sulfonyl isocyanates gave sulfamylcarbamates (see Table V). Besides these compounds, the arylsulfonyl derivatives **1** (tolbutamide) and **11** were also prepared. As indicated in Table I, sulfamylureas of type II do indeed show an increased acidity over those of I. Unfortunately these pK_a data cannot be correlated with the plasma half-life in this series owing to the fact that a sufficiently sensitive assay for type II compounds has not yet been developed.

Table III

$(R_1SO_2NHCO-)_2$

R_1	M.p., °C. dec.	Recrystn. solvent	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Phenyl	266[a]	MeOH	$C_{14}H_{12}N_2O_6S_2$	45.64	45.69	3.29	3.38	7.61	7.60
p-Tolyl	287	MeOH	$C_{16}H_{16}N_2O_6S_2$	48.47	48.54	4.07	4.23	7.07	6.83
Piperidino	212	MeCN	$C_{12}H_{22}N_4O_6S_2$	37.68	37.82	5.80	5.67	14.65	14.48
4,4-Dimethylpiperidino	212	MeCN	$C_{16}H_{30}N_4O_6S_2$	43.82	43.77	6.90	6.76	12.78	12.56

[a] R. Adams and W. Reifschneider [*J. Am. Chem. Soc.*, **78**, 3825 (1956)] report m.p. 256° dec.; M. V. Charaute [*Rec. trav. chim.*, **32**, 94 (1913)] reports m.p. 256° dec.

Hypoglycemic activities were determined in rats as previously described.[1] Results for compounds under present consideration are reported in the last columns of Tables IV and V. Generally, a sulfamylurea of type II is somewhat less active than a comparable derivative of type I having the same number of carbon atoms and similar structural features. Activities of the sulfamylcarbamates vary from quite low to a level comparable to that of tolbutamide.

Experimental Section

All boiling points are uncorrected. Melting points were determined on a Fisher-Johns melting point apparatus and are corrected. Sulfonamides and amines not commercially available were prepared by previously described methods. Analyses were made by the Physical Measurements Laboratory of Chas. Pfizer & Co.

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(9) A referee of this paper has suggested that the morpholine ring system would be unstable to the conditions of anhydrous HCl and heat.

TABLE IV

$R_1SO_2NHCOR_2$

Compd.	R_1	R_2	M.p., °C.	Recrystn. solvent[a]	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Hypoglycemic activity[b]
1	*p*-Tolyl	Butylamino	126–127[c]	CH_2Cl_2–IPE	72	$C_{12}H_{18}N_2O_3S$	...	...	...	...	...	...	35 ± 5.1
2	Piperidino	Piperidino	135–137	PhH–hex	22	$C_{11}H_{21}N_3O_3S$	47.98	48.06	7.69	7.62	15.26	15.25	19 ± 4.0
3	Piperidino	1-Hexahydroazepinyl	139–141	PhH	55	$C_{12}H_{23}N_3O_3S$	49.81	50.18	8.01	7.78	14.52	14.53	27 ± 2.3
4	Piperidino	1-Octahydroazocinyl	146–148	IPA–IPE	42	$C_{13}H_{25}N_3O_3S$	51.46	51.51	8.31	8.23	13.85	13.60	19 ± 3.2
5	Piperidino	4,4-Dimethylpiperidino	138–139	PhH–hex	69	$C_{13}H_{25}N_3O_3S$	51.46	51.73	8.31	8.25	13.85	13.57	13 ± 4.0
6	Piperidino	Cyclohexylmethylamino	116–117	PhH–IPE	38	$C_{13}H_{25}N_3O_3S$	51.46	51.79	8.31	8.04	13.85	13.25	2 ± 3.7
7	Piperidino	3-Aza-3-bicyclo[3.2.2]-nonyl	189–190	PhH	27	$C_{14}H_{25}N_3O_3S$	53.31	53.53	7.99	7.98	13.32	12.93	22 ± 3.2
8	Piperidino	2-Tetrahydro-1,2-oxazinyl	123–124	PhH–hex	53	$C_{10}H_{19}N_3O_4S$	43.30	43.63	6.91	6.88	15.15	14.63	10 ± 3.5
9	4,4-Dimethylpiperidino	2-Tetrahydro-1,2-oxazinyl	129–131	PhH–hex	43	$C_{12}H_{23}N_3O_4S$	47.19	47.44	7.59	7.45	13.76	13.61	22 ± 1.9
10	4,4-Dimethylpiperidino	Morpholino	160–162[d] (170–172)	PhH–hex	31	$C_{12}H_{23}N_3O_4S$	47.19	47.25	7.59	7.38	13.76	13.38	19 ± 6.7

[a] CH_2Cl_2 = methylene chloride, hex = hexane, IPA = isopropyl alcohol, IPE = isopropyl ether, MeOH = methanol, PhH = benzene. [b] Maximum per cent fall in blood sugar ± standard error. [c] M.m.p. (with authentic tolbutamide) 129–132°. [d] After standing a few weeks at room temperature, the melting point changes from an initial 160–162° to 170–172°, indicating dimorphism.

TABLE V

$R_1SO_2NHCO_2R_3$

Compd.	R_1	R_3	M.p., °C.	Recrystn. solvent[a]	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Hypoglycemic activity[b]
11	Phenyl	*trans*-4-*t*-Butylcyclohexyl	165–166	IPA–IPE	32	$C_{17}H_{25}NO_4S$	60.15	59.98	7.42	7.51	4.13	4.11	24 ± 3.0
12	Piperidino	Cyclohexyl	84–85	Hex	19	$C_{12}H_{22}N_2O_4S$	49.63	49.22	7.64	7.39	9.65	9.62	0 ± 4.9
13	Piperidino	*trans*-4-*t*-Butylcyclohexyl	108–109	Hex	43	$C_{16}H_{30}N_2O_4S$	55.46	55.37	8.73	8.56	8.09	8.10	35 ± 2.5
14	Piperidino	Cholesteryl	148–149	MeOH–acet	21	$C_{33}H_{56}N_2O_4S$	68.70	68.88	9.79	9.80	4.86	4.64	7 ± 3.2
15	4,4-Dimethylpiperidino	Cyclohexyl	72–73	Hex	22	$C_{14}H_{26}N_2O_4S$	52.80	52.70	8.23	8.39	8.80	8.01	30 ± 2.8

[a] IPA = isopropyl alcohol, IPE = isopropyl ether, Hex = hexane, acet = acetone. [b] Maximum per cent fall in blood sugar ± standard error.

Sulfonyl Isocyanates from Sulfonamides.—A three-neck round-bottom flask was flushed with nitrogen and was charged with a mixture of 0.1 mole of a suitable sulfonamide, 0.5 ml. of boron trifluoride etherate, and 150 ml. of 1,2-dichloroethane. A gas outlet adapter at the top of the reflux condenser leading to a trap partially filled with water prevented excessive amounts of HCl from escaping into the hood. With efficient stirring, 14.0 g. (9.4 ml., 0.11 mole) of oxalyl chloride was added to the mixture dropwise. Evolution of gases began immediately, and, after the addition of oxalyl chloride was complete, the mixture was heated under reflux with stirring from 1–8 hr. After the reaction mixture cooled to room temperature, the mixture was treated with Supercel and filtered through a sintered-glass funnel to give a clear red-brown solution. The solvent was removed from the filtrate by distillation at atmospheric pressure, and the residue was then distilled at reduced pressure to give the desired sulfonyl isocyanate as a clear colorless oil. For examples of products obtained by this method see Table II.

Owing to the extreme reactivity of the sulfonyl isocyanates, elemental analyses of these compounds were not obtained; however, that these products are indeed sulfonyl isocyanates is shown by their characteristic infrared spectra.

Isolation of N,N'-Bis(sulfonyl)oxamides.—The mixtures of Supercel and crystalline by-products from the above procedures were each slurried in a hot solvent of recrystallization and filtered. Upon cooling, colorless crystals of the N,N'-bis(sulfonyl)oxamide formed. In each case the product was characterized by its melting point and infrared spectrum and was analyzed. For examples of compounds isolated by this process see Table III. No attempt was made to recover quantitatively these and other possible by-products.

Sulfonylureas from Sulfonyl Isocyanates.—A round-bottom flask was charged with a solution of 0.01 mole of the appropriate sulfonyl isocyanate in 10 ml. of dry benzene. With cooling in an ice bath and stirring, the solution in the flask was treated slowly with a solution of 0.01 mole of the appropriate amine in 10 ml. of dry benzene. After the addition was complete the reaction mixture was allowed to warm to room temperature; the volatile components were then evaporated under reduced pressure to give (usually) an oil. The oil was taken up in methylene chloride and washed successively with 1 *N* HCl and water. The organic phase was then dried (Na_2SO_4), filtered, and evaporated. The residue was recrystallized to give the product as colorless crystals. For examples of products obtained by this procedure see Table IV.

N-Sulfonylcarbamate Esters.—The procedure was essentially the same as that above except that 0.01 mole of the appropriate alcohol was substituted for the amine, and the wash with 1 *N* HCl was omitted. See Table V for N-sulfamylcarbamates made by this method.

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Sulfanilamido-*s*-triazines. I. Synthesis of 2-Sulfanilamido-4,6-diethyl-*s*-triazine and Related Compounds

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A series of 2-sulfanilamido-4,6-disubstituted *s*-triazines was prepared by nucleophilic displacement of methoxy groups from 2-methoxy-4,6-disubstituted *s*-triazines with sulfanilamide anion. 2-Sulfanilamido-4,6-diethoxy-*s*-triazine was only obtainable by acid-catalyzed nucleophilic substitution of 2-sulfanilamido-4,6-dimethoxy-*s*-triazine. 2-Sulfanilamido-4,6-diethyl-*s*-triazine has high antibacterial activity, good aqueous solubility, and other properties suitable to its use as a medicinal agent.

Previous attempts to prepare sulfanilamido-*s*-triazine *via* sulfonylation of 2-amino-*s*-triazine have been unsuccessful,[2,3] although one derivative, 2-sulfanilamido-4,6-diamino-*s*-triazine, has been obtained[2] by such a reaction. Although the latter had no antibacterial activity,[4] it was not considered to be a satisfactory criterion of activity of the triazine series.[4] In this relatively unexplored class of sulfanilamido heterocycle, the solubility desired in a sulfanilamide drug was expected on the basis of the high aqueous solubility of *s*-triazine[5] and various substituted *s*-triazines[6,7] and of 2-sulfanilamido-4,6-diamino-*s*-triazine.[2,8] No alkyl derivatives of 2-sulfanilamido-*s*-triazine have been reported and, in considering their possible synthesis at the initiation of this work, our attention was directed to methoxytriazines for two reasons. Preparation of 2-sulfanilamido-4,6-dimethoxy-*s*-triazine from trimethyl cyanurate had been reported,[9] and direct ring syntheses of 2-methoxy-4,6-dialkyl-*s*-triazines[10] and of 2-methoxy-*s*-triazine[11] had just been developed in our laboratories.

2-Sulfanilamido-*s*-triazine (IV) and its 4,6-dimethoxy (IX) and 4,6-dimethyl (V) derivatives were prepared

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