Hypoglycemic Activity in Relation to Chemical Structure of Potential Oral Antidiabetic Substances. I. 1-Sulfonyl-3-alkylureas

BERNT HÖKFELT

Department of Physiology, Karolinska Institutet, Stockholm, Sweden

AND ÅKE JÖNSSON

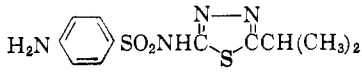
Department of Organic Chemistry, Kungl. Tekniska Högskolan, Stockholm, and Research Laboratories, AB Astra, Södertälje, Sweden

Received June 22, 1961

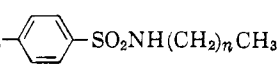
As part of an investigation aiming at the elucidation of structure-activity relationships in oral antidiabetic compounds a number of 1-sulfonyl-3-alkylureas have been prepared. The syntheses and the results of preliminary testing of the compounds are described.

During the clinical trial of a new chemotherapeutic agent 2-*p*-aminobenzensulfonamido-5-isopropyl-1,3,4-thiadiazole (I), Janbon and co-workers[1] in 1942 observed that this chemical caused a marked fall of blood sugar in non-diabetic human beings. Further research showed that sulfanilamide derivatives such as other sulfanilamido-thiadiazoles[2–4] and also 1-*p*-amidobenzenesulfonyl-3-*n*-butyl-urea (carbutamide; Nadisan®; "Bz-55"; II) exerted hypoglycemic effects not only in normal humans but also in patients with certain types of diabetes mellitus. Thus II was introduced as an oral antidiabetic drug.

After the present investigation had begun, several non-sulfanilamide drugs, *e.g.*, 1-*p*-methylbenzenesulfonyl-3-*n*-butylurea (tolbutamide; "D-860," III) and 1-*p*-chlorobenzenesulfonyl-3-*n*-propylurea (chlor-



I



II, R = NH_2, n = 3
III, R = CH_3, n = 3
IV, R = Cl, n = 2

(1) M. Janbon, P. Lazerges, and J. H. Metropolitanski, *Montpellier méd.*, **21–22**, 489 (1942).
(2) D. Bovet and P. Dubost, *Compt. rend. soc. biol.*, **138**, 764 (1944).
(3) A. Loubatières, *ibid.*, **138**, 830 (1944).
(4) K. K. Chen, R. C. Anderson, and N. Maze, *Proc. Soc. Exp. Biol. Med.*, **63**, 483 (1946).

propamide; IV) were also introduced as orally active hypoglycemic agents.

The present studies, carried out in 1956 and 1957, were to find relationships between the hypoglycemic activity and changes in the chemical structure of various compounds related to known antidiabetic drugs. This paper reports on the synthesis and the activity of a number of sulfonylurea derivatives of the general structure $RSO_2NHCONHR'$ in which changes have been made in group R and, to a lesser extent, group R', whereas further compounds in which alterations have been made in the interjacent part of the molecule will be discussed in paper II. While the experiments were in progress data have been presented on the synthesis of a great number of substituted sulfonylureas.[5-9]

Evaluation of the Hypoglycemic Effect.—All assays were carried out on rabbits (2.0 to 2.5 kg.) that had been starved for 15 to 24 hr. prior to the start of the experiment. All compounds were administered orally by stomach tube either suspended in water containing 0.1% Tween 80 and 1% low viscosity CMC or as sodium salts dissolved in water. Using the Hagedorn and Jensen procedure blood sugar was followed at hourly intervals for at least 8 hr. after the administration; blood samples were taken from the marginal ear-vein. As a rule each substance was tested in a dose of 0.5 and 1.0 g./kg. given to no less than three animals in each series. For comparison and as a reference standard tolbutamide was given simultaneously to three animals. As the number of animals used to test most of the compounds was limited, no statistical evaluation of the values obtained for the hypoglycemic activity of the respective compounds has been applied. In the Tables the hypoglycemic potency has been graded from + to +++, referring to the lowest blood sugar value registered within 8 hr. after the administration of the substance; ++ corresponds to the hypoglycemic effect obtained after the same dose of tolbutamide. Compounds less potent than tolbutamide but still definitely active have been designated by + and those definitely

(5) See *e.g.* German Patent applications F18136, 18339, 18648, 18659 IVb/12o and 1,003,716; 1,024,074, 1,028,114, 1,032,734, 1,034,618 and 1,036,218.

(6) E. Haack, *Arzneimittel-Forsch.*, **8**, 444 (1958).

(7) H. Ruschig, G. Karger, W. Aumüller, H. Wagner, R. Weyer, A. Bämler, and J. Scholz, *Arzneimittel-Forsch.*, **8**, 448 (1958).

(8) D. R. Cassady, C. Ainsworth, N. R. Easton, M. Livezey, M. V. Sigal, Jr., and E. Van Heyningen, *J. Org. Chem.*, **23**, 923 (1958).

(9) F. J. Marshall and M. V. Sigal, Jr., *ibid.*, **23**, 926 (1958).

more active, by +++. When the effect is being reported as zero either no hypoglycemia was found or hyperglycemic response was evoked by the compound.

Results and Discussion.—The direct comparison of the hypoglycemic effect of the substances is made rather difficult by the fact that not only the maximal decrease of the blood sugar level produced by a standard amount of compound, but also the dose-response and the time-response curves vary from compound to compound. A rough classification of the compounds has, however, been attempted and included in the Tables. It is quite obvious from these results that the hypoglycemic activity of the sulfonylureas is influenced by the nature of both the R and R′ radicals.

(a) Structure of Group R′.—Preliminary experiments in which the R′ radical was changed (ethyl, propyl, butyl, etc.) indicated that although a wide variety of such radicals gave active compounds the *n*-butyl group probably was the most favorable one. Branching of the carbon chain as in iso- and especially *tert*-butyl derivatives considerably reduced the activity. In order to limit the number of variables we therefore concentrated our interest on 3-*n*-butylurea derivatives. A more comprehensive study of the importance of the nature of group R′ has been published recently by Ruschig, *et al.*[7]

(b) Structure of Group R.—The only hypoglycemic sulfonylurea derivative described at the beginning of our investigations was 1-*p*-aminobenzenesulfonyl-3-*n*-butylurea. The first object was therefore to investigate whether the *p*-amino group was an essential structural feature. The fairly high activity found in 1-phenyl-3-*n*-butylurea immediately proved that this was not the case. The activity of this "parent" compound could be increased by the introduction of one amino, dimethylamino, methyl, isopropyl, methoxy, ethoxy, nitro, fluoro, chloro or bromo substituent. Our experience with 1-*p*-nitrobenzenesulfonyl-3-*n*-butylurea is not in agreement with the claim[7] that nitro derivatives should be inactive. On the other hand, one *tert*-butyl, diethylamino, isobutoxy, or iodo group reduced or abolished the activity. The position of the substituent does not appear to be too important, although the *para* position seems to be the most favorable. It is difficult to find any common chemical feature which distinguishes those substituents that increase the activity from those which decrease it. The latter, however, appear to be more "bulky." It is therefore felt that the differences may be

of a physical rather than a chemical nature. Probably this is also true for group R′, whereas the interjacent part of the molecule may have more specific chemical functions.

The effect of introducing more than one substituent was not studied systematically, but the only compound of this kind tested, 1-(2,4,6-trimethylbenzenesulfonyl)-3-*n*-butylurea, was almost inactive.

The activity of carbutamide was destroyed entirely by acetylation of the amino group and also the *m*-acetamido isomer was inactive. On the other hand the acetyl derivative of 1-*p*-ethylaminobenzenesulfonyl-3-*n*-butylurea was quite active. This different behavior possibly may be due to differences in resorption as it has been shown recently[10] that the inactivity of acetylated carbutamide when administered orally is due to its very low resorption; the compound is active when injected intravenously. The behavior of acetyl-carbutamide also illustrates the difficulties encountered when structure-activity discussions, based on results obtained in complex tests such as the one used in the present investigation, are attempted.

Substituting the naphthyl for the phenyl nucleus yielded active compounds, but the two substances with heterocyclic ring systems, 1-(β-pyridinesulfonyl)-3-*n*-butylurea and 1-[5-(2-acetamido-1,3,4-thiadiazole)-sulfonyl]-3-*n*-butylurea, were inactive.

That an aromatic ring system is, however, by no means a necessary requirement for hypoglycemic activity in urea derivatives is shown clearly by the fact that not only 1-ω-arylalkyl derivatives (in which series even mono-substitution of the phenyl nucleus always reduced activity), *e.g.*, 1-benzyl-and 1-phenethylsulfonyl-3-alkylureas, but also purely aliphatic and alicyclic sulfonylureas can be highly active. This supports the assumption that the function of the group R is to provide the molecule with certain favorable physical properties rather than with groups entering into any specific chemical reaction.

Experimental

Several methods for the synthesis of sulfonylureas have been described, mainly in patent literature, and recently reviewed by Kurzer.[11] In the present investigation three methods have been used: (a) addition of a sulfonamide to an alkyl isocyanate, (b) aminolysis of a sulfonylurethan and (c) addition of an amine to a sulfonyl isocyanate. In respect to manageability and to yields obtained,

(10) N. Quattrini, A. Brancaccio, G. Jacono, and N. Lioia, *Clin. terap.*, **13**, 152 (1957); *Chem. Abstr.*, **52**, 12227 (1958).

(11) F. Kurzer, *Chem. Revs.*, **50**, 1 (1952).

the first mentioned method was much superior and it was used in the majority of the preparations. Typical examples of the methods are given below. Ethanol and methanol were found to be suitable solvents for crystallization. Melting points and analytical data of the compounds are given in Tables I and II. The melting points are corrected.

Most of the sulfonamides have been described in the literature. With two exceptions all were prepared from the appropriate sulfonyl chloride and aqueous ammonia. *o*-Diethylamino- and *m*-dimethylaminobenzenesulfonamide were obtained by the alkylation of orthanilamide and metanilamide with ethyl iodide, and methyl iodide, respectively, a method originally used by Ekbom[12] for the methylation of orthanilamide.

The alkyl- and arylalkylsulfonyl chlorides were obtained by chlorination of the appropriate isothiuronium salts according to the general method of Johnson and Sprague.[13] Although it has been reported[14] that explosive by-products may be formed in this reaction if the chlorination is extended over several hours, it seems to be safe when applied to most isothiuronium salts as the reaction mostly can be completed in less than 1 hr.

This method gave satisfactory yields of sulfonyl chlorides from all isothiuronium salts used with the exception of *o*- and *p*-benzylisothiuronium chloride. In these cases the chlorination apparently proceeded normally, but the sulfonyl chlorides formed decomposed into the corresponding chlorobenzyl chloride and sulfur dioxide even on standing at room temperature. When, however, the crude sulfonyl chlorides were treated with ammonia immediately after the chlorination the sulfonamides could be obtained in good yields. This tendency to decompose with evolution of sulfur dioxide was not observed with the other sulfonyl chlorides.

Method a

1-*p*-(*N*-Acetyl-*N*-ethylamino)-benzenesulfonyl-3-*n*-butylurea. — *p*-(*N*-Acetyl-*N*-ethylamino)-benzenesulfonamide (48.4 g.; 0.2 mole), *n*-butyl isocyanate (25 g., 0.25 mole) and triethylamine (10 ml.) were intimately mixed and heated at 85–95° for 10 to 15 hr. (When aliphatic sulfonamides were used the reaction time could be shortened to 4 to 6 hr.) The mixture was poured into water (500 ml.) containing acetic acid (25 ml.) and agitated until crystallization started. The solid product was filtered off and crystallized from dilute ethanol. Deacetylation was effected by refluxing the compound (25 g.) with 15% aqueous sodium hydroxide (150 ml.) for 3 hr.

1-*p*-*n*-Butylcarbamoyloxybenzenesulfonyl-3-*n*-butylurea was similarly prepared from *p*-hydroxybenzenesulfonamide using a molar ratio sulfonamide to isocyanate of 1:3.

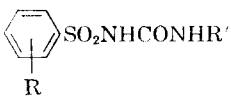
Method b

1-*n*-Hexanesulfonyl-3-isobutylurea.—Ethyl chloroformate (65 g., 0.6 mole)

(12) A. Ekbom, *Bihang till Kungl. Vetenskapsakademiens Handlingar*, **27**, II, No. 1 (1902).
(13) T. B. Johnson and J. M. Sprague, *J. Am. Chem. Soc.*, **58**, 1348 (1936).
(14) K. Folkers, A. Russel, and R. W. Bost, *ibid.*, **63**, 3530 (1941).

TABLE I

1-BENZENESULFONYL-3-ALKYLUREAS



No.	R	R′	Activity[a]	Method of prepn.	M.p., °C.	Formula	Analyses: Calcd., % C	H	N	Found, % C	H	N
1	H	*n*-C_4H_9	+(+)	A	132.5–134	$C_{11}H_{16}N_2O_3S$	51.6	6.29	10.9	51.8	6.31	10.9
2	*p*-CH_3 (tolbutamide)	*n*-C_4H_9	++	A	134–135.5	$C_{12}H_{18}N_2O_3S$	53.3	6.71	10.4	53.4	6.69	10.3
3	*m*-CH_3	*n*-C_4H_9	+++	A	105–106	$C_{12}H_{18}N_2O_3S$	53.3	6.71	10.4	53.3	6.92	10.4
4	*o*-CH_3	*n*-C_4H_9	++	A	162–163	$C_{12}H_{18}N_2O_3S$	53.3	6.71	10.4	53.5	6.66	10.3
5	*p*-iso-C_3H_7	*n*-C_4H_9	++	A	135.5–136.5	$C_{14}H_{22}N_2O_3S$	56.4	7.43	9.39	56.7	7.36	9.25
6	*p*-*tert*-C_4H_9	*n*-C_4H_9	0(+)[b]	A	181.5–183	$C_{15}H_{24}N_2O_3S$	57.7	7.74	8.97	57.5	7.80	8.94
7	*p*-NH_2	*n*-C_4H_9	+++		Carbutamide							
8	*p*-C_2H_5NH	*n*-C_4H_9	++	..	148–150	$C_{13}H_{21}N_3O_3S$	52.2	7.07	14.0	52.7	7.32	13.9
9	*p*-$(CH_3)_2N$	*n*-C_4H_9	++	A	157–158	$C_{13}H_{21}N_3O_3S$	52.2	7.07	14.0	52.9	7.17	13.8
10	*m*-$(CH_3)_2N$	*n*-C_6H_{13}	++	A	158–159	$C_{14}H_{23}N_3O_3S$	53.6	7.40	13.4	53.7	7.22	13.5
11	*o*-$(CH_3)_2N$	*n*-C_4H_9	++(+)[b]	A	151–152	$C_{13}H_{21}N_3O_3S$	52.2	7.07	14.0	52.2	7.17	14.0
12	*p*-$(C_2H_5)_2N$	*n*-C_4H_9	+	A	176–178	$C_{15}H_{25}N_3O_3S$	55.0	7.70	12.8	55.3	7.76	12.6
13	*o*-$(C_2H_5)_2N$	*n*-C_4H_9	+	A	140–141.5	$C_{15}H_{25}N_3O_3S$	55.0	7.70	12.8	54.7	7.68	12.6
14	*p*-CH_3CONH	*n*-C_4H_9	0	A	194–196	$C_{13}H_{19}N_3O_4S$	49.8	6.11	13.4	50.2	6.39	13.3
15	*m*-CH_3CONH	*n*-C_4H_9	0	A	164–165.5	$C_{13}H_{19}N_3O_4S$	49.8	6.11	13.4	50.1	6.39	13.1
16	*p*-$CH_3CON(C_2H_5)$	*n*-C_4H_9	++	A	183–185	$C_{15}H_{23}N_3O_4S$	52.8	6.79	12.3	52.7	6.86	12.3
17	*p*-NO_2	*n*-C_4H_9	++(+)	A	160–162.5	$C_{11}H_{16}N_3O_5S$	43.8	5.02	13.9	43.9	5.11	13.7
18	*p*-CH_3O	*n*-C_4H_9	+++	A	119.5–121	$C_{12}H_{18}N_2O_4S$	50.3	6.34	9.78	50.6	6.48	9.42
19	*m*-CH_3O	*n*-C_4H_9	++	A	136–137	$C_{12}H_{18}N_2O_4S$	50.3	6.34	9.78	50.3	6.55	9.43
20	*o*-CH_3O	*n*-C_4H_9	+++	A	118.5–150	$C_{12}H_{18}N_2O_4S$	50.3	6.34	9.78	50.1	6.17	9.98
21	*p*-C_2H_5O	*n*-C_4H_9	++	A	159–160	$C_{13}H_{20}N_2O_4S$	52.0	6.71	9.33	51.8	6.61	9.35
22	*p*-iso-C_4H_9O	*n*-C_4H_9	+	A	150–151	$C_{15}H_{24}N_2O_4S$	54.8	7.37	8.53	54.6	7.52	8.37

TABLE I (*Continued*)

No.	R	R′	Activity[a]	Method of prepn.	M.p., °C.	Formula	Analyses Calcd., % C	H	N	Found, % C	H	N
23	*p*-F	*n*-C_4H_9	++	A	106–107.5	$C_{11}H_{15}FN_2O_3S$	48.2	5.51	10.2	48.6	5.33	10.2
24	*p*-Cl	iso-C_4H_9	+(+)	C	175–176.5	$C_{11}H_{15}ClN_2O_3S$	45.4	5.20	9.64	46.0	5.26	9.42
25	*p*-Cl	*tert*-C_4H_9	(+)	C	158–159.5	$C_{11}H_{15}ClN_2O_3S$	45.4	5.20	9.64	45.1	5.22	9.59
26	*m*-Cl	*n*-C_4H_9	+(+)	A	106–108	$C_{11}H_{15}ClN_2O_3S$	45.4	5.20	9.64	45.3	5.05	9.62
27	*p*-Br	*n*-C_4H_9	+++	A	127–128.5	$C_{11}H_{15}BrN_2O_3S$	39.4	4.51	8.36	39.7	4.48	8.22
28	*p*-I	*n*-C_4H_9	+	A	151.5–153.5	$C_{11}H_{15}IN_2O_3S$	34.6	3.96	7.33	35.1	3.99	7.21
29	*p*-*n*-C_4H_9NHCOO—	*n*-C_4H_9	++	A[c]	147–149.5	$C_{16}H_{25}N_3O_5S$	51.7	6.79	11.3	51.3	7.04	10.9

[a] See text. [b] Only tested at 1 g./kg. level. Result obscured by toxic effects. [c] From sulfanilamide (1 mole) and *n*-butyl isocyanate (3 moles).

TABLE II

FURTHER 1-SULFONYL-3-ALKYLUREA DERIVATIVES, $RSO_2NHCONHR'$

No.	R	R′	Activity[a]	Method of prepn.	M.p., °C.	Formula	Analyses Calcd., % C	H	N	Found, % C	H	N
30	2,4,6-$(CH_3)_3$-C_6H_2	*n*-C_4H_9	+	A	158–160	$C_{14}H_{22}N_2O_3S$	56.4	7.43	9.39	56.2	7.61	9.14
31	α-Naphthyl	*n*-C_4H_9	+	A	166.5–167.5	$C_{15}H_{18}N_2O_3S$	58.8	5.92	9.14	58.9	6.12	9.18
32	β-Naphthyl	*n*-C_4H_9	++	A	152.5–154	$C_{15}H_{18}N_2O_3S$	58.8	5.92	9.14	59.2	6.23	9.20
33	β-Pyridyl	*n*-C_4H_9	0	A[b]	105–107	$C_{10}H_{15}N_3O_3S$	46.7	5.88	16.3	46.8	6.04	16.0
	K-salt	*n*-C_4H_9	..	..	208–210	$C_{10}H_{14}KN_3O_3S$	40.7	4.78	14.2	40.5	4.92	14.1
34	5-(2-Acetamido-1,3,4-thiadiazolyl)-	*n*-C_4H_9	0	A	210–211	$C_9H_{15}N_5O_4S_2$	33.6	4.71	21.8	33.7	4.78	21.6
35	Cyclohexyl	*n*-C_4H_9	+++	A	128–129	$C_{11}H_{22}N_2O_3S$	50.4	8.45	10.7	49.7	8.13	10.4
36	*n*-C_3H_7	*n*-C_4H_9	+(+)	A	112–113.5	$C_8H_{18}N_2O_3S$	43.2	8.16	12.6	43.2	8.07	12.3
37	*n*-C_4H_9	*n*-C_4H_9	++(+)	A	103.5–104.5	$C_9H_{20}N_2O_3S$	45.7	8.53	11.8	46.2	8.40	11.5
38	*sec*-C_4H_9	*n*-C_4H_9	+(+)	A	110–111	$C_9H_{20}N_2O_3S$	45.7	8.53	11.8	46.2	8.73	11.6
39	iso-C_5H_{11}	*n*-C_4H_9	+(+)	A	120.5–121.5	$C_{10}H_{22}N_2O_3S$	48.0	8.86	11.2	48.2	8.92	10.7
40	*n*-C_6H_{13}	*n*-C_3H_7	(+)	B	95–96	$C_{10}H_{22}N_2O_3S$	48.0	8.86	11.2	48.8	8.91	10.9
41	*n*-C_6H_{13}	*n*-C_4H_9	++(+)	A	102–103	$C_{11}H_{24}N_2O_3S$	50.0	9.15	10.6	50.0	9.19	10.5

TABLE II (*Continued*)

No.	R	R′	Activity[a]	Method of prepn.	M.p., °C.	Formula	Analyses: Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
42	n-C_6H_{13}	iso-C_4H_9	(+)	B	127–128	$C_{11}H_{24}N_2O_3S$	50.0	9.15	10.6	50.1	9.12	10.4
43	n-C_6H_{13}	*sec*-C_4H_9	++	B	92–93	$C_{11}H_{24}N_2O_3S$	50.0	9.15	10.6	50.2	9.22	10.4
44	n-C_6H_{13}	*tert*-C_4H_9	−	C	95–96	$C_{11}H_{24}N_2O_3S$	50.0	9.15	10.6	50.5	9.36	10.5
45	n-C_7H_{15}	n-C_3H_7	+	B	95–101	$C_{11}H_{24}N_2O_3S$	50.0	9.15	10.6	49.7	9.06	10.5
46	n-C_7H_{15}	n-C_4H_9	+(+)	B	88–92	$C_{12}H_{26}N_2O_3S$	51.8	9.41	10.1	52.1	9.41	9.71
47	n-C_7H_{15}	n-C_8H_{17}	(+)	B	82–100	$C_{16}H_{34}N_2O_3S$	57.4	10.2	8.37	57.5	10.3	8.35
48	n-C_8H_{17}	C_2H_5	0	B	86.5–87	$C_{11}H_{24}N_2O_3S$	50.0	9.15	10.6	50.4	8.87	10.6
49	n-C_8H_{17}	n-C_3H_7	0	B	89–95	$C_{12}H_{26}N_2O_3S$	51.8	9.41	10.1	52.0	9.20	9.92
50	n-C_8H_{17}	n-C_4H_9	++	A	81–88	$C_{13}H_{28}N_2O_3S$	53.4	9.65	9.58	53.6	9.65	9.32
51	$C_6H_5CH_2$	n-C_4H_9	++	A	162–164	$C_{12}H_{18}N_2O_3S$	53.3	6.71	10.4	53.5	6.85	10.2
52	p-$NO_2C_6H_4CH_2$	n-C_4H_9	+	A	196–197	$C_{12}H_{17}N_3O_5S$	45.7	5.43	13.2	45.5	5.61	13.0
53	p-$ClC_6H_4CH_2$	n-C_4H_9	(+)	A	181.5–183	$C_{12}H_{17}ClN_2O_3S$	47.3	5.62	9.18	47.9	5.86	9.20
54	m-$ClC_6H_4CH_2$	n-C_4H_9	+	A	171–172	$C_{12}H_{17}ClN_2O_3S$	47.3	5.62	9.18	47.0	5.82	9.02
55	o-$ClC_6H_4CH_2$	n-C_4H_9	0	A	162.5–163.5	$C_{12}H_{17}ClN_2O_3S$	47.3	5.62	9.18	47.0	5.63	8.97
56	2,4-$Cl_2C_6H_4CH_2$	n-C_4H_9	0	A	187–189	$C_{12}H_{16}Cl_2N_2O_3S$	42.5	4.75	8.25	42.8	5.06	8.36
57	p-$BrC_6H_4CH_2$	n-C_4H_9		A	186–187	$C_{12}H_{17}BrN_2O_3S$	41.3	4.80	8.02	41.7	5.14	7.74
58	p-$CH_3C_6H_4CH_2$	n-C_4H_9	+(+)	A	180.5–182.5	$C_{14}H_{20}N_2O_3S$	54.9	7.08	9.85	54.9	7.11	9.77
59	3,5-$(CH_3)_2C_6H_4CH_2$	n-C_4H_9	0	A	181–183	$C_{14}H_{22}N_2O_3S$	56.4	7.43	9.34	56.2	7.32	9.21
60	$C_6H_5CH_2CH_2$	n-C_4H_9	++(+)	A	166.5–168	$C_{13}H_{20}N_2O_3S$	54.9	7.09	9.85	54.6	7.22	9.99
61	$C_6H_5CH_2CH_2$	n-C_5H_{11}		A	139.5–140.5	$C_{14}H_{22}N_2O_3S$	56.4	7.43	9.39	56.4	7.37	9.49
62	$C_6H_5CH_2CH_2CH_2$	n-C_4H_9	++(+)	A	124–125.5	$C_{14}H_{22}N_2O_3S$	56.4	7.43	9.39	56.5	7.48	9.41

[a] See text. [b] Best purified *via* its potassium salt, which could be crystallized from ethanol.

was added with stirring to a refluxing mixture of *n*-hexanesulfonamide (63 g., 0.5 mole), acetone (400 ml.) and anhydrous potassium carbonate (85 g.). Heating and stirring was continued for a further 2 hr. Most of the acetone was distilled off on a water bath, and the residue in the flask poured into water and acidified with dilute hydrochloric acid. An oil separated, which was taken up in ether, washed with water and dried (Na_2SO_4). The ether was distilled off on the water bath, the last traces being removed under reduced pressure, yielding *n*-hexansulfonylurethan (91 g.) as a light yellow oil, which was used for aminolysis without further purification.

The crude sulfonylurethan (24 g., 0.1 mole), isobutylamine (14.6 g., 0.2 mole) and anhydrous diethoxyethane (75 ml.) were refluxed for 15 hr. and poured into water (300 ml.) containing acetic acid (20 ml.). The oil which separated was taken up in ether, washed with water, and extracted with 5% sodium carbonate solution. Acidification of this extract yielded crystalline 1-*n*-hexansulfonyl-3-isobutylurea, which was purified by crystallization from aqueous methanol.

Method c

1-*p*-Chlorobenzenesulfonyl-3-isobutylurea.—A mixture of *p*-chlorobenzenesulfonyl chloride (32 g., 0.15 mole), silver cyanate (30 g., 0.20 mole) and anhydrous nitrobenzene (100 ml.) was stirred at 160–170° for 1.5 hr. After cooling the solid material was removed by filtration and washed on the filter with a little nitrobenzene. Isobutylamine (14.6 g., 0.20 mole) was added to the filtrate drop by drop at 10–15° with stirring. After complete addition the mixture was heated at 90–95° for 1 hr., diluted with chloroform (200 ml.) and repeatedly extracted with 5% sodium carbonate solution. Acidification of the extracts precipitated a solid which was purified by crystallization from methanol.

***m*-Dimethylaminobenzenesulfonamide.**—Metanilamide (25 g.), methyl iodide (40 g.), and absolute methanol (50 ml.) were heated in a stainless steel autoclave at 100° for 4 hr. The methanol and excess methyl iodide were distilled off and the sticky oil dissolved in *N* sodium hydroxide and filtered. Acidification with acetic acid precipitated a solid which after crystallization from water had m.p. 184–185.5°.

Anal. Calcd. for $C_8H_{12}N_2O_2S$: N, 14.0. Found: N, 13.9.

***o*-Diethylaminobenzenesulfonamide** was obtained similarly from orthanilamide (25 g.), ethyl iodide (45 g.) and absolute ethanol (50 ml.); m.p. 108–109°; yield, 21 g.

Anal. Calcd. for $C_{10}H_{16}N_2O_2S$: N, 12.3. Found: N, 12.4.

Acknowledgment.—The authors are indebted to Messrs. Jan Gyllander and Lembit Mikiver for skillful assistance in the synthetic work. Microanalyses were by Dr. Alfred Bernhardt, Microanalytical Laboratory, Mühlheim, Germany.