Cyanoethylation of Aromatic Amides[1]

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Very little is known concerning the cyanoethylation of aromatic amides.[2] The one report indicates that benzamide is cyanoethylated to give *N*-β-cyanoethylbenzamide, m.p. 91–93°.[3] In our laboratory eleven different aromatic amides (Table I) were cyanoethylated in the presence of an excess of acrylonitrile and the products uniformly contained two cyanoethyl groups on the amide nitrogen, as shown by the following equation:

$$ArCONH_2 + CH_2{=}CHCN \longrightarrow ArCON(CH_2CH_2CN)_2$$

This was proved by analysis and by the fact that the *N,N*-di-β-cyanoethylbenzamide was identical to that produced by the reaction of benzoyl chloride on $HN(CH_2CH_2CN)_2$.[4]

EXPERIMENTAL[5]

The synthetic method given below is essentially the same for all the aromatic amides, and is based on a method by Galat.[6]

N,N,-Di-β-cyanoethylnicotinamide. In a three-neck 300-ml. flask equipped with a reflux condenser, a mechanical stirrer, and a separatory funnel, were placed 0.2 mole (24.4 g.) of nicotinamide and 100 ml. of acrylonitrile. This mixture was stirred, and cooled by means of an external cooling bath. Then 2.0 ml. of 40% benzyl trimethylammonium hydroxide (Triton B) was added, dropwise, over a 15-min. period.

After all the base had been added, the cooling bath was removed, and the mixture was allowed to gradually warm. The nicotinamide dissolved with the liberation of heat, which was controlled by external cooling. A precipitate formed, and stirring and cooling were continued for 10 min., and then the reaction mixture was neutralized with glacial acetic acid. The excess acrylonitrile was removed under reduced pressure.

After all the excess acrylonitrile had been removed, the yellow precipitate (33 g.) was separated by filtration. The product was crystallized repeatedly from hot water.

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TABLE I

N,N-Di-β-CYANOETHYL AMIDES

Starting Amide	Empirical Formula	M.P., °C.	Yield, %	% Nitrogen Calcd.	% Nitrogen Found
Benzamide	$C_{13}H_{13}N_3O$	110	77	18.48	18.41
Nicotinamide	$C_{12}H_{12}N_4O$	104	70	24.54	24.59
Isonicotinamide	$C_{12}H_{12}N_4O$	108	67	24.54	24.46
o-Toluamide	$C_{14}H_{16}N_3O$	83	62	17.42	17.42
p-Toluamide	$C_{14}H_{15}N_3O$	87	65	17.42	17.29
2-Furamide	$C_{11}H_{11}N_3O_2$	112	72	19.44	19.45
2-Naphthamide	$C_{17}H_{15}N_3O$	120	75	15.15	15.31
o-Chlorobenzamide	$C_{13}H_{12}ClN_3O$	83	70	16.06	16.28
3,4-Dichlorobenzamide	$C_{13}H_{11}Cl_2N_3O$	152	82	14.19	14.33
o-Iodobenzamide	$C_{13}H_{12}IN_3O$	99	66	11.92	12.17
m-Bromobenzamide	$C_{13}H_{12}BrN_3O$	83	62	13.73	13.73

(1) Taken from the M. S. thesis of Miss Romana Jonauskas.

(2) For leading reviews see (*a*) H. Bruson, *Org. Reactions*, Chapter 2 (1949) and (*b*) *The Chemistry of Acrylonitrile*, American Cyanamid Co. (1951), N. Y. 20, N. Y.

(3) I. G. Farbenind. A.G. Fr. Patent **877,120** (1942). When the reaction was run with essentially equimolar quantities of benzamide (2 moles) and acrylonitrile (2.26 moles) a 57% yield was obtained. No analytical figures were given. When the reaction was run between one mole of benzamide and 2.26 moles of acrylonitrile an oil was reported, and no physical constants nor analytical data were given.

(4) A. N. Kost, *Uchenye Zapiski Moskov. Gosudarst. Univ. im. M. V. Lomonosova*, **No. 2**, 141 (1947), *Chem. Abstr.*, **47**, 9906 (1953). It is interesting to note that *N*-β-cyanoethylbenzamide was reported by Goldberg and Kelly, *J. Chem. Soc.*, 1369 (1947), to melt at 96–98°, when prepared by the reaction of benzoyl chloride and β-cyanoethylamine. It would appear that the compound reported in reference 3 was a mixture of mono- and dicyanoethylated products.

(5) Microanalyses by Micro-Tech Labs., Skokie, Ill.

(6) A. Galat, *J. Am. Chem. Soc.*, **67**, 1414 (1945).

Sulfonylureas and Related Compounds

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Attempts in this laboratory to prepare hypoglycemic compounds based upon the structure of *N*-sulfanilyl-*N'*-*n*-butylurea, also known as BZ-55 or Carbutamide, have led to a series of new and active compounds. Marshall and Sigal[1] have reported upon the variations in the arylsulfonylureas. This note reports the preparation of some alkylsulfonylureas, and other varied compounds based upon the parent structure. The pharmacology[2] of these compounds will be reported elsewhere in the near future.

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

(2) The pharmacological testing was performed under the direction of Dr. M. Root.

TABLE I

$RSO_2NHCONHR'$

R	R'[a]	M.P., °C.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3	C_2H_5	170–171.5	$C_4H_{10}N_2O_3S$	28.92	6.07	16.86	28.92	6.02	16.65
CH_3	n-C_4H_9	106–107	$C_6H_{14}N_2O_3S$	37.11	7.27	14.43	37.02	7.40	14.67
CH_3	n-C_7H_{15}	123.5–124	$C_9H_{20}N_2O_3S$	45.75	8.53	11.86	46.01	8.50	11.76
n-C_3H_7	n-C_3H_7	125	$C_7H_{16}N_2O_3S$	40.38	7.75	13.46	40.32	7.91	13.59
n-C_3H_7	n-C_4H_9	114	$C_8H_{18}N_2O_3S$	43.25	7.99	12.30	43.45	8.20	12.49
n-C_3H_7	n-C_5H_{11}	105	$C_9H_{20}N_2O_3S$	45.98	8.49	11.84	46.19	8.47	12.04
n-C_3H_7	n-C_6H_{13}	97	$C_{10}H_{22}N_2O_3S$	47.97	8.86	11.19	48.35	9.09	11.37
n-C_4H_9	n-C_3H_7	43.0–43.5	$C_8H_{18}N_2O_3S$	43.22	8.16	12.60	43.25	7.99	12.30
n-C_4H_9	2-$CH_3OC_2H_5$	115–117	$C_8H_{18}N_2O_4S$			11.60			11.42
n-C_4H_9	n-C_4H_9	96–97	$C_9H_{20}N_2O_3S$	45.75	8.53	11.86	45.96	8.67	11.73
n-C_4H_9	i-C_4H_9	111–112	$C_9H_{20}N_2O_3S$	45.75	8.53	11.86	46.02	8.56	11.70
n-C_4H_9	2-C_4H_9	96–97	$C_9H_{20}N_2O_3S$	45.75	8.53	11.86	45.98	8.49	11.84
n-C_4H_9	t-C_4H_9	129–131	$C_9H_{20}N_2O_3S$			11.86			11.93
n-C_4H_9	1-HO-2-C_4H_8	Liquid	$C_9H_{20}N_2O_4S$			11.10			10.78
n-C_4H_9	$C_2H_5O_2CCH_2$[b]	109–110	$C_9H_{18}N_2O_5S$	40.59	6.81	10.51	40.91	6.81	11.28
n-C_4H_9	n-C_5H_{11}	91–92	$C_{10}H_{22}N_2O_3S$	47.97	8.86	11.19	48.26	9.07	11.10
n-C_4H_9	i-C_5H_{11}	76–77	$C_{10}H_{22}N_2O_3S$	47.97	8.86	11.19	48.27	8.75	10.82
n-C_4H_9	2-C_5H_{11}	87–89	$C_{10}H_{22}N_2O_3S$			11.19			11.14
n-C_4H_9	t-C_5H_{11}	82–84	$C_{10}H_{22}N_2O_3S$			11.19			11.51
n-C_4H_9	Cyclo-C_5H_9	131–132	$C_{10}H_{20}N_2O_3S$	48.39	8.12	11.28	48.60	8.55	11.47
n-C_4H_9	n-C_6H_{13}	91–93	$C_{11}H_{24}N_2O_3S$			10.59			10.40
n-C_4H_9	Cyclo-C_6H_{11}	139–140	$C_{11}H_{22}N_2O_3S$	50.38	8.45	10.65	50.55	8.65	10.43
n-C_4H_9	4-CH_3-2-C_5H_{10}	77–79	$C_{11}H_{24}N_2O_3S$			10.59			10.42
n-C_4H_9	n-C_7H_{15}	95–97	$C_{12}H_{26}N_2O_3S$			10.06			9.96
n-C_4H_9	2-C_7H_{15}	67–69	$C_{12}H_{26}N_2O_3S$			10.06			10.02
n-C_4H_9	3-C_7H_{15}	63–65	$C_{12}H_{26}N_2O_3S$			10.06			9.89
n-C_4H_9	p-$CH_3C_6H_4$[b]	118–120	$C_{12}H_{18}N_2O_3S$	53.32	6.71	10.37	53.54	6.79	10.64
n-C_4H_9	o-$CH_3OC_6H_4$[b]	164–165	$C_{12}H_{18}N_2O_4S$	50.30	6.33		50.48	6.53	
n-C_4H_9	p-$O_2NC_6H_4$[b]	184–185	$C_{11}H_{15}N_3O_5S$			13.33			13.40
i-C_4H_9	n-C_3H_7	142–144	$C_8H_{18}N_2O_3S$			21.61			12.91
i-C_4H_9	n-C_4H_9	107–109	$C_9H_{20}N_2O_3S$			11.86			12.15
i-C_4H_9	t-C_4H_9	133–135	$C_9H_{20}N_2O_3S$			11.86			11.89
CH_2=$C(CH_3)CH_2$—	n-C_3H_7	162–163	$C_8H_{16}N_2O_3S$	43.63	7.32		43.91	7.13	
CH_2=$C(CH_3)CH_2$—	n-C_4H_9	118–120	$C_9H_{18}N_2O_3S$			11.96			11.98
2-C_4H_9	n-C_4H_9	106–107	$C_9H_{20}N_2O_3S$	45.75	8.53	11.86	45.86	8.55	11.82
i-C_4H_9	i-C_5H_{11}	101–103	$C_{10}H_{22}N_2O_3S$			11.19			10.92
i-C_4H_9	3-$CH_3OC_3H_6$	82–83	$C_9H_{20}N_2O_4S$			11.10			10.96
n-C_5H_{11}	n-C_3H_7	89–90	$C_9H_{20}N_2O_3S$	45.75	8.53	11.86	46.10	8.54	11.66
n-C_5H_{11}	CH≡C—CH_2—	143–145	$C_9H_{16}N_2O_3S$			12.00			12.01
n-C_5H_{11}	n-C_4H_9	98–99	$C_{10}H_{22}N_2O_3S$	47.97	8.86	11.19	47.89	8.61	11.35
n-C_5H_{11}	2-C_4H_9	115–117	$C_{10}H_{22}N_2O_3S$			11.19			11.10
n-C_5H_{11}	i-C_4H_9	106–108	$C_{10}H_{22}N_2O_3S$			11.19			11.18
n-C_5H_{11}	t-C_4H_9	94–96	$C_{10}H_{22}N_2O_3S$			11.19			11.09
n-C_5H_{11}	n-C_5H_{11}	88–89	$C_{11}H_{24}N_2O_3S$	49.99	9.15		50.04	9.25	
n-C_5H_{11}	i-C_5H_{11}	89–90	$C_{11}H_{24}N_2O_3S$	49.99	9.15	10.60	50.28	8.95	10.89
n-C_5H_{11}	$C_6H_5CH_2$—	161–162	$C_{13}H_{20}N_2O_3S$			9.85			9.61
i-C_5H_{11}	n-C_3H_7	148–149	$C_9H_{20}N_2O_3S$	45.75	8.53	11.86	45.86	8.48	11.65
i-C_5H_{11}	i-C_3H_7	106–107	$C_9H_{20}N_2O_3S$	45.75	8.53	11.86	45.88	8.61	11.65
i-C_5H_{11}	n-C_4H_9	113–114	$C_{10}H_{22}N_2O_3S$	47.97	8.86	11.19	47.94	8.86	11.00
i-C_5H_{11}	i-C_4H_9	159–160	$C_{10}H_{22}N_2O_3S$			11.19			11.23
i-C_5H_{11}	2-C_4H_9	117–119	$C_{10}H_{22}N_2O_3S$			11.19			11.03
i-C_5H_{11}	3-$CH_3OC_3H_6$	101–102	$C_{10}H_{22}N_2O_4S$			10.53			10.34
i-C_5H_{11}	1-Cl-2-C_4H_9	162–164	$C_{10}H_{21}ClN_2O_3S$	42.18	7.43	9.84	42.21	7.35	9.95
i-C_5H_{11}	n-C_5H_{11}	84–85	$C_{11}H_{24}N_2O_3S$	49.99	9.15	10.60	50.16	9.49	10.89
i-C_5H_{11}	i-C_5H_{11}	79–81	$C_{11}H_{24}N_2O_3S$	49.99	9.15	10.60	50.36	9.21	10.34
i-C_5H_{11}	2-C_5H_{11}	108–109	$C_{11}H_{24}N_2O_3S$	49.99	9.15	10.60	49.84	9.29	10.76
Cyclo-C_5H_9	n-C_3H_7	146–148	$C_9H_{18}N_2O_3S$	46.14	7.75		46.66	7.67	
Cyclo-C_5H_9	3-$CH_3OC_3H_7$	128–129	$C_{10}H_{20}N_2O_4S$	47.46	7.97	10.06	47.97	8.16	9.84
Cyclo-C_5H_9	n-C_4H_9	154–155	$C_{10}H_{20}N_2O_3S$	48.37	8.12		48.33	8.24	
Cyclo-C_5H_9	i-C_5H_{11}	139.5–140.5	$C_{11}H_{22}N_2O_3S$	50.37	8.45		50.47	8.37	
n-C_6H_{13}	3-$CH_3OC_3H_6$	71–73	$C_{10}H_{22}N_2O_4S$			10.52			10.66
Cyclo-C_6H_{11}	C_2H_5	145–146	$C_9H_{18}N_2O_3S$	46.14	7.75		46.01	7.61	
Cyclo-C_6H_{11}	n-C_3H_7	155.0–156.5	$C_{10}H_{20}N_2O_3S$	48.37	8.12		48.32	8.34	
Cyclo-C_6H_{11}	i-C_3H_7	151–152	$C_{10}H_{20}N_2O_3S$	48.37	8.12		48.50	8.35	
Cyclo-C_6H_{11}	n-C_4H_9	133–134	$C_{11}H_{22}N_2O_3S$	50.37	8.45		50.19	8.45	
Cyclo-C_6H_{11}	i-C_5H_{11}	121–123	$C_{12}H_{24}N_2O_3S$	52.16	8.75	10.14	52.36	8.93	10.00
Cyclo-C_6H_{11}	Cyclo-C_6H_{11}	145–147	$C_{13}H_{26}N_2O_3S$	54.15	8.39	9.72	54.29	8.65	9.50
n-C_8H_{17}	H	142–143	$C_9H_{20}N_2O_3S$	45.75	8.53	11.86	45.76	8.79	11.65

TABLE I (*Continued*)

R	R'[a]	M.P., °C.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
n-C_8H_{17}	n-C_4H_9	74–75	$C_{13}H_{28}N_2O_3S$	53.40	9.65	9.58	53.80	9.86	9.53
n-$C_{10}H_{21}$	CH_3	103.5–104.5	$C_{12}H_{26}N_2O_3S$	51.78	9.42		52.13	9.69	
n-$C_{10}H_{21}$	C_2H_5	87–89	$C_{13}H_{28}N_2O_3S$	53.40	9.65		53.61	9.73	
n-$C_{10}H_{21}$	n-C_4H_9	90–92	$C_{15}H_{32}N_2O_3S$	56.22	10.07		56.13	10.01	
$C_6H_5CH_2$	n-C_3H_7	203–205	$C_{11}H_{16}N_2O_3S$	51.56	6.29		51.81	6.33	
$C_6H_5CH_2$	n-C_4H_9	161.0–161.5	$C_{12}H_{18}N_2O_3S$	53.32	6.71		53.29	6.87	
2-Thienyl	n-C_3H_7	141–143	$C_8H_{12}N_2O_3S_2$	38.69	4.87		38.69	4.79	
2-Thienyl	n-C_4H_9	151–152	$C_9H_{14}N_2O_3S_2$	41.22	5.38	10.68	41.24	5.54	10.29

[a] All compounds were made by procedure 1 except as noted. [b] Made by procedure 2.

TABLE II

$RSO_2NHCOOR'$

R	R'	M.P., °C.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3	C_2H_5	Oil	$C_4H_9NO_4S$	28.75	5.43	8.38	28.72	5.28	8.46
n-C_4H_9	C_2H_5	Oil	$C_7H_{15}NO_4S$	40.19	7.23	6.70	40.30	7.25	6.65
n-C_4H_9	n-C_3H_7	Oil[a]	$C_8H_{16}NO_4SNa$	39.18	6.58	5.71	39.18	6.67	5.64
n-C_4H_9	n-C_4H_9	46–48	$C_9H_{19}NO_4S$			5.90			6.08
n-C_4H_9	n-C_5H_{11}	Oil[a]	$C_{10}H_{20}NO_4SNa$			5.13			5.10
n-C_4H_9	n-C_6H_{13}	Oil[a]	$C_{11}H_{22}NO_4SNa$	45.98	7.72	4.87	45.75	7.86	5.02
n-C_5H_{11}	C_2H_5	Oil	$C_8H_{17}NO_4S$			6.28			6.35
n-C_5H_{11}	n-C_4H_9	Oil	$C_{10}H_{21}NO_4S$			5.57			5.63
n-C_5H_{11}	i-C_4H_9	73–75	$C_{10}H_{21}NO_4S$			5.57			5.42
Cyclo-C_5H_9	C_2H_5	Oil[b]	$C_8H_{15}NO_4S$	43.42	6.83		43.29	6.92	
n-C_6H_{13}	C_2H_5	Oil	$C_9H_{19}NO_4S$			5.90			5.74
Cyclo-C_6H_{11}	C_2H_5	81–83	$C_9H_{17}NO_4S$			5.96			6.22
n-$C_{10}H_{21}$	C_2H_5	46–48	$C_{13}H_{27}NO_4S$	53.21	9.27		53.35	9.31	
$C_6H_5CH_2$	C_2H_5	101–103	$C_{10}H_{13}NO_4S$			5.76			5.69
2-Thienyl	C_2H_5	80–81	$C_7H_9NO_4S_2$	35.75	3.86	5.96	35.98	3.64	5.89

[a] Analyses were made on the crystalline sodium salts which were purified by recrystallization from ethanol-acetone. [b] n_D^{25} 1.4795.

TABLE III[a]

$RSO_2NHCONR'R$

R	R'	R''	M.P., °C.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
n-C_4H_9	CH_3	CH_3	Oil	$C_7H_{16}N_2O_3S$			13.46			13.53
n-C_4H_9	C_2H_5	C_2H_5	Oil	$C_9H_{20}N_2O_3S$	45.75	8.53		45.74	8.67	
n-C_4H_9	Morpholinyl		95	$C_9H_{18}N_2O_4S$	43.19	7.25		42.84	7.58	
n-C_4H_9	Piperidyl		37–38	$C_{10}H_{20}N_2O_3S$	48.37	8.12	11.28	48.27	8.39	11.09
n-C_4H_9	Pyrrolidyl		125	$C_9H_{18}N_2O_3S$	46.14	7.75	11.96	46.03	7.47	12.10

[a] Compounds were prepared by procedure 1 for Table I.

Replacement of the aryl group of the parent compound with an alkyl radical has resulted in the alkylsulfonylureas listed in Table I. The intermediate carbamates were all prepared by a general method[3] and many were not characterized due to the difficulty encountered in distillation. The carbamates characterized or analyzed are listed in Table II.

To complete this series several *bis* compounds were prepared: 1,6-bis(sulfonamido)hexane; 1,6-bis(*N*-carbethoxysulfonamido)hexane; 1,6-bis-(*N*-*n*-propylcarbamoylsulfonamido)hexane; 1,6-bis(*N*-isoamylcarbamoylsulfonamido)hexane; 1,6-bis(*n*-amylsulfonylureido)hexane; *N*,*N'*-bis(isoamylsulfonyl)urea. Secondary amines were also used in the reaction with the sulfonylcarbamates leading to a series of *N*,*N'*-disubstituted *n*-butylsulfonylureas as listed in Table III.

Variations in the basic sulfonylurea structure by replacement of each of the nitrogen moieties in turn by methylene gave the new compounds listed in Tables IV and V.

EXPERIMENTAL[4]

Preparation of the alkylsulfonylureas in Table I. Procedure 1.[3a] One molar part of the sulfonamide[5] was dissolved in

(3) (a) Haack, E. and Hagedorn, A., private communication. (b) J. R. Geigy A.-G., British Patent **538,884**, Aug. 20, 1941.

(4) The melting points are uncorrected.

(5) All sulfonamides were known compounds and were commercially available or prepared by literature methods.

TABLE IV

RSO_2NHCOR'

R	R'	M.P., °C.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
n-C_4H_9	n-C_4H_9	61–62[a]	$C_9H_{19}NO_3S$			6.33			6.07
i-C_5H_{11}	n-C_3H_7	35–36[b]	$C_9H_{19}NO_3S$			6.33			6.08
p-$CH_3C_6H_4$	n-C_5H_{11}	63–65[c]	$C_{13}H_{19}NO_3S$	57.96	7.11	5.20	58.05	7.30	5.49

[a] B.p. 204–206° at 10 mm. Hg. [b] B.p. 200–201° at 10 mm. Hg. [c] Recrystallized from isopropyl ether–petroleum ether 60–90°.

TABLE V

RSO_2CH_2CONHR'

R	R'	M.P., °C.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
C_6H_5	n-C_4H_9	112–113	$C_{12}H_{17}NO_3S$	56.44	6.71	5.49	56.61	6.89	5.20
p-$CH_3C_6H_4$	n-C_3H_7	117–118	$C_{12}H_{17}NO_3S$	56.44	6.71	5.49	56.29	6.79	5.26
p-$CH_3C_6H_4$	n-C_4H_9	103–104	$C_{13}H_{19}NO_3S$	57.96	7.11		57.72	7.12	

about 10 molar parts of dry acetone and 1.2 molar parts of anhydrous finely divided potassium carbonate were added. With refluxing and stirring 1.2 molar parts of alkyl chlorocarbonate were added dropwise over a period of 1–2 hr. The mixture was then refluxed for 15 hr. with stirring, cooled, and filtered. The solid was dissolved in a minimum of water and acidified with concentrated hydrochloric acid. Ether extraction of the freed carbamate from the aqueous solution of salts and vacuum removal of the ether gave a 60–80% yield of the corresponding carbamate. Most of these compounds were viscous oils, which decomposed upon attempted distillation, and were used without further purification. A few representative samples of these carbamates are in Table II.

One molar part of the crude carbamate was dissolved in an excess of the appropriate amine forming a salt and the excess amine removed *in vacuo*. The residue was then pyrolyzed *in vacuo* at 128–130° for 2–3 hr. or until bubbling had ceased. The product was crystallized and then recrystallized from aqueous ethanol. Yield of the sulfonylurea was about 60%, ranging from 37% to 94% in some cases.

Procedure 2. One molar equivalent of the sulfonamide was treated with the appropriate isocyanate in nitrobenzene.[6]

Preparation of the acylsulfonamides in Table IV. The compounds were prepared in the same manner as the carbamates of Procedure 1 above. After reflux the acetone was removed *in vacuo* and the residue was dissolved in a minimum of water. Acidification of the resulting solution with hydrochloric acid precipitated the new compound. Recrystallization was from aqueous methanol. These new compounds are listed in Table IV.

Preparation of the α-arylsulfonyl-N-alkylacetamides. The *N*-alkyl-α-chloroacetamide[7] (0.1 mole) and sodium aryl sulfinate (0.11 mole) were refluxed in 60 ml. of anhydrous ethanol for 16 hr. The reaction mixture was then diluted with 60 ml. of boiling water and the product allowed to crystallize slowly from the mixture. The product was recrystallized from 50% aqueous ethanol. Yields were approximately 60%.

Preparation of the "bis" compounds. The following compounds were prepared by Procedure 1 for the alkylsulfonylureas: Starting sulfonamide, 1,6-bis(sulfonamido)hexane, m.p. 173–174°, yield 67% from 1,6-dibromohexane.[8] (*Anal.* Calcd. for $C_8H_{16}N_2O_4S_2$: C, 29.49; H, 6.60; N, 11.47. Found: C, 29.43; H, 6.66; N, 11.11). 1,6-bis(*N*-carbethoxysulfonamido)hexane, m.p. 84–85°, yield 73%. (*Anal.* Calcd. for $C_{12}H_{24}N_2O_8S_2$: C, 37.11; H, 6.23; N, 7.21. Found: C, 37.15; H, 6.24; N, 7.34). 1,6-bis(*N*-*n*-propylcarbamoylsulfonamido)hexane, m.p. 200–201°, yield 85%. (*Anal.* Calcd. for $C_{14}H_{30}N_4O_6S_2$: C, 40.57; H, 7.30; N, 13.52. Found: C, 40.73; H, 7.16; N, 13.33). 1,6-bis(*N*-isoamylcarbamoylsulfonamido)hexane, m.p. 194–195°, yield 94% (*Anal.* Calcd. for $C_{18}H_{38}N_4O_6S_2$: C, 45.76; H, 8.50; N, 11.88. Found: C, 45.90; H, 8.34; N, 11.73). 1,6-bis(*n*-amylsulfonylureido)hexane, m.p. 174–175°, yield 84% (*Anal.* Calcd. for $C_{18}H_{38}N_4O_6S_2$: C, 45.76; H, 8.50; N, 11.18. Found: C, 45.94; H, 8.53; N, 10.86).

Preparation of N,N'-bis(isoamylsulfonyl)urea. Ten grams (0.67 mole) of isoamylsulfonamide was dissolved in an excess of 10% sodium hydroxide. Phosgene was added slowly until a sample of the solution was acid to litmus paper. The product was extracted with benzene, the solvent removed *in vacuo* and the product (10 g., 91%) distilled (b.p. 138–140° at 1.5 mm. Hg).

Anal. Calcd. for $C_{11}H_{24}N_2O_5S_2$: C, 40.22; H, 8.36; N, 8.52. Found: C, 39.97; H, 8.46; N, 8.61.

Upon standing the liquid crystallized to a waxy solid melting at 35–36°.

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(8) Prepared by methods of T. B. Johnson, U. S. Patent **2,146,744**, Feb. 14, 1939. Treatment of the resulting sulfonylchloride with anhydrous ammonia led directly to the bis-sulfonamide.