Antihypertensive Agents. II.[1] 3-Substituted 2H-1,2,4-Benzothiadiazine 1,1-Dioxides

JOHN G. TOPLISS, LEROY M. KONZELMAN, ELIZABETH P. SHAPIRO, NATHAN SPERBER, AND FRANKLIN E. ROTH

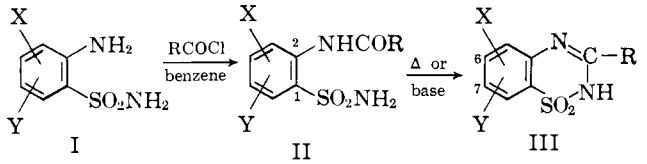
Chemical and Biological Research Divisions, Schering Corporation, Bloomfield, New Jersey

Received November 8, 1963

A series of 2H-1,2,4-benzothiadiazine 1,1-dioxides, embracing different types of 3-substituents and varying degree and type of substitution in the benzene portion of the nucleus, has been synthesized. The effect of structural changes on the antihypertensive activity of the compounds has been determined.

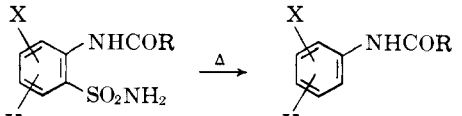
In part I[1] the synthesis and antihypertensive activity of the nondiuretic 7-chloro-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (diazoxide) and a number of related compounds was discussed. The effect on biological activity of changes in the single benzene ring substituent, N-alkylation, saturation of the 3,4 double bond and the chain length of the 3-substituent was examined. These studies have been extended and in this paper we discuss the variation of antihypertensive activity with different types of 3-substituents and the effect on activity of additional substitution in the benzene portion of the nucleus.[2]

With simple 3-substituents the 2H-1,2,4-benzothiadiazine 1,1-dioxides were usually synthesized by the condensation of a substituted *o*-aminobenzenesulfonamide (I) with the appropriate orthoester as described in part I.[1,3] However, for more complex 3-substituents a convenient synthesis of the benzothiadiazine (III) was the cyclization of the amide (II) under the influence of heat[4] or base.[5] Cyclization by fusion was the procedure generally employed and in most cases the yields



I II III

were satisfactory. A side reaction in the fusion method was found to be elimination of the sulfamoyl group to give amides of type IV.[6] The yield of the amide IV rises with increasing bulk of R and is approximately the same as that of the benzothiadiazine when R = CH(cyclohexyl)C_6H_5 and CH(cyclohexyl)$_2$. In a few instances the use of base in the cyclization step was investigated. It was found that the cyclization of the amide (II, X = 5-Cl, Y = H, R = $CH_2CH_2OCH_3$), which failed by the fusion method, proceeded in high yield with concentrated ammonium hydroxide solution at steam-bath temperature to give the benzothiadiazine III (X = 7-Cl, Y = H, R = $CH_2CH_2OCH_3$). Also, the action of 10% sodium hydroxide solution on the amide (II, X = 4-Cl, Y = 5-Cl, R = CH (cyclohexyl) C_6H_5) gave the corresponding benzothiadiazine in 88% yield compared to a 35% yield obtained with the fusion method.[6] In some cases it was possible to obtain the benzothiadiazine (III) directly from the acid(RCO_2H) and the substituted *o*-aminobenzenesulfonamide (I) by heating a mixture of the reactants at *ca.* 250°.[6]



II IV

The amides (II) were prepared by reaction of the appropriate acid chloride with the substituted *o*-aminobenzenesulfonamide (I) in refluxing benzene.[6] Those *o*-aminobenzenesulfonamides employed which were new were synthesized by standard methods.

Pharmacological Methods.[7]—The test procedure used was the same as that described in part I.[1] The activities of the compounds are given in Table I. Six categories of activity were established, defined as in Table II (dose, 20 mg./kg. i.v.).

Structure–Activity Relationships.—It is clear from an examination of the activities of the compounds listed in Table I that, in general terms, a substituent of the saturated hydrocarbon type at position 3 is superior to other types of substituents for high activity. In part I[1] the 3-methyl, ethyl, *n*-propyl, and hydrogen substituents were compared. The results of the present investigation show that in the unbranched series activity is reduced for the longest chain lengths (**16, 17**). Chain branching tends to increase activity, particularly branching in the α-position (**18, 19, 22, 26–28**), and a tertiary carbon atom at the α-position seems to be especially favorable (**21, 25**). Alkenes (**33–36, 54**) show the same or slightly less activity than their saturated counterparts. Modification of a saturated hydrocarbon 3-substituent by the introduction of oxygen, halogen, nitrogen, or sulfur in various ways (**37–48, 55**) results in a marked loss of activity. Aralkyl 3-substituents (**49–53**) are associated with compounds of moderate activity, although, if the substituent is considered to be derived from an alkyl group by substitu-

(1) J. G. Topliss, M. H. Sherlock, H. Reimann, L. M. Konzelman, E. P. Shapiro, B. W. Pettersen, H. Schneider, and N. Sperber, *J. Med. Chem.*, **6**, 122 (1963).

(2) A paper by B. A. Bierbaum, J. J. Traverso, and C. W. Whitehead, *ibid.*, **6**, 272 (1963), on hypotensive benzothiadiazines has recently appeared. These workers were apparently unaware of earlier publications on this subject, *viz.* A. A. Rubin, F. E. Roth, M. M. Winbury, J. G. Topliss, M. H. Sherlock, N. Sperber, and J. Black, *Science*, **133**, 2067 (1961); A. A. Rubin, F. E. Roth, and M. M. Winbury, *Nature*, **192**, 176 (1962).

(3) J. H. Freeman and E. C. Wagner, *J. Org. Chem.*, **16**, 815 (1951).

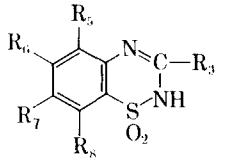
(4) A. Ekbom, *Bihang till Svenska Vet. Akad. Handl.*, **27** II, 3 (1902); *Beilstein*, **27**, 571.

(5) F. C. Novello, S. C. Bell, E. L. A. Abrams, C. Ziegler, and J. M. Sprague, *J. Org. Chem.*, **25**, 970 (1960).

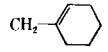
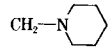
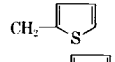
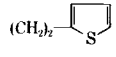
(6) J. G. Topliss, L. M. Konzelman, and E. P. Shapiro, *ibid.*, **28**, 2595, (1963).

(7) These studies were carried out by Drs. F. E. Roth, A. A. Rubin, and R. M. Taylor of the Department of General Pharmacology, Biological Research Division, Schering Corporation.

TABLE I



No.	R_3[a]	R_5	R_6	R_7	R_8	Method of prepn.	M.p., °C.	Recrystn.[a] solvent	Empirical formula	% Chlorine Calcd.	% Chlorine Found	% Nitrogen Calcd.	% Nitrogen Found	% Sulfur Calcd.	% Sulfur Found	Activity
1[b,c]	CH_3	H	H	Cl	H											++++
2	CH_3	H	Cl	Cl	H	A	324–325[d]	EtOH–H_2O	$C_8H_6Cl_2N_2O_2S$	26.75	26.55	10.57	10.97			++++
3	CH_3	H	Cl	H	Cl	A	>360[e]	EtOH–H_2O	$C_8H_6Cl_2N_2O_2S$					12.10	12.27	++
4	CH_3	Cl	H	Cl	H	A	283–285	MeOH–H_2O	$C_8H_6Cl_2N_2O_2S$			10.57	10.80			+
5	CH_3	H	H	Cl	Cl	A	328–330	MeOH	$C_8H_6Cl_2N_2O_2S$	26.75	26.69	10.57	10.52			++
6	CH_3	H	Br	Br	H	A	337–338	Acet.–H_2O	$C_8H_6Br_2N_2O_2S$			7.91	7.95	9.05	9.27	++++
7	CH_3	H	CF_3	Cl	H	A	298–305	EtOH–H_2O	$C_9H_6ClF_3N_2O_2S$	19.08[f]	19.48[f]	9.38	9.42			++++
8	CH_3	H	Cl	Cl	Cl	A	>360	MeOH–Acet.	$C_8H_5Cl_3N_2O_2S$	35.51	35.45	9.35	9.44			+++
9	CH_3	H	Cl	CH_3	H	A	301–302[g]	Acet.	$C_9H_9ClN_2O_2S$			11.45	11.25	13.10	12.90	+++++
10	CH_3	H	CH_3	Cl	H	A	333–335	Acet.	$C_9H_9ClN_2O_2S$			11.45	11.72	13.10	13.51	++++
11	CH_3	H	Cl	SO_2CH_3	H	A	297–300	MeOH	$C_9H_9ClN_2O_4S_2$	*h*	*h*	9.07	9.22			–
12	CH_3	H	SO_2NH_2	Cl	H	E	>360	MeOH–H_2O	$C_8H_8ClN_3O_4S_2$	11.45	11.49	13.57	13.47	20.70	21.05	–
13	CH_3	H	OCH_3	Cl	H	E	338–340	MeOH–H_2O	$C_9H_9ClN_2O_3S$	13.60	13.59			12.29	12.07	+++
14	$(CH_2)_3CH_3$	H	H	Cl	H	B	213–214	EtOH–H_2O	$C_{11}H_{13}ClN_2O_2S$	13.00	13.35	10.27	10.23	11.75	11.73	++
15	$(CH_2)_4CH_3$	H	H	Cl	H	B	209–210	EtOH–H_2O	$C_{12}H_{15}ClN_2O_2S$	12.37	12.05			11.18	11.25	++++
16	$(CH_2)_5CH_3$	H	Cl	H	H	B	246–248	EtOH–H_2O	$C_{13}H_{17}ClN_2O_2S$	11.79	12.22	9.31	9.11			++
17	$(CH_2)_6CH_3$	H	Cl	H	H	B	241–242	EtOH–H_2O	$C_{14}H_{19}ClN_2O_2S$	11.26	11.66	8.90	8.87			++
18	*i*-C_3H_7	H	H	Cl	H	B	256–257	EtOH–H_2O	$C_{10}H_{13}ClN_2O_2S$	13.71	13.77	10.83	10.91			+++
19	*sec*-C_3H_9	H	H	Cl	H	B	218–219	MeOH–H_2O	$C_{11}H_{15}ClN_2O_2S$	13.00	13.35	10.27	10.34			+++
20	*i*-C_4H_9	H	Cl	H	H	B	275–278	MeOH–H_2O	$C_{11}H_{15}ClN_2O_2S$			10.27	10.59	11.75	11.96	+++
21	*t*-C_4H_9	H	H	Cl	H	B	292–293	EtOH–H_2O	$C_{11}H_{15}ClN_2O_2S$			10.27	10.11	11.44	11.68	++++
22	$CH(C_2H_5)_2$	H	H	Cl	H	B	185–186	MeOH–H_2O	$C_{12}H_{15}ClN_2O_2S$	12.37	12.33	9.77	9.82			++++
23	$CH(CH_3)CH(CH_3)_2$	H	Cl	Cl	H	B, C	252–254	MeOH–H_2O	$C_{12}H_{14}Cl_2N_2O_2S$	22.08	22.31	8.72	8.83			+++
24	$CH_2C(CH_3)_2CH_3$	H	H	Cl	H	B	285–286	EtOH–H_2O	$C_{12}H_{15}ClN_2O_2S$	12.36	12.30			11.18	11.34	+++
25	$C(CH_3)_2C_2H_5$	H	H	Cl	H	B	212–214	EtOH–H_2O	$C_{12}H_{15}ClN_2O_2S$	12.36	12.05			11.18	11.17	++++
26	C_3H_5	H	H	Cl	H	B	286–288	MeOH	$C_{10}H_9ClN_2O_2S$	13.81	13.75	10.92	11.31			++++
27	C_4H_7	H	H	Cl	H	B	299–301	MeOH	$C_{11}H_{11}ClN_2O_2S$	13.10	13.54	10.35	10.46			+++
28	C_5H_9	H	Cl	H	H	B	312–314	MeOH	$C_{12}H_{13}ClN_2O_2S$			9.84	10.03	11.26	10.76	++++
29	C_6H_{11}	H	Cl	H	H	B	319–320	MeOH–Acet.	$C_{13}H_{15}ClN_2O_2S$	11.86	12.26	9.38	9.37			++
30	$CH_2C_6H_5$	H	H	Cl	H	B	274–275	MeOH	$C_{13}H_{13}ClN_2O_2S$	11.86	12.09	9.38	9.58			++
31	$CH_2C_6H_5$	H	C	Cl	H	B	303–314	MeOH–Acet.	$C_{14}H_{16}Cl_2N_2O_2S$	20.45	20.29	8.07	8.19			++
32[h]	$CH(C_6H_{11})_2$	H	Cl	Cl	H				$C_{26}H_{35}Cl_2N_2O_2S$							+++
33	$CH=CH-CH_3$	H	Cl	H	H	B	310–313	MeOH	$C_{10}H_9ClN_2O_2S$	13.81	13.81	10.92	10.80	12.49	12.52	++
34		H	H	Cl	H	B	242–246	MeOH	$C_{13}H_{13}ClN_2O_2S$	11.94	11.92			10.80	11.10	++

No.	R_2[a]	R_6	R_8	R_7	R_8	Method of prepn.	M.p., °C.	Recrystn.[a] solvent	Empirica formula	—% Chlorine— Calcd.	Found	—% Nitrogen— Calcd.	Found	—% Sulfur— Calcd.	Found	Activity
35		H	Cl	Cl	H	B	298–300	MeOH	$C_{13}H_{12}Cl_2N_2O_2S$	21.41	21.66	8.50	8.70			++
36		H	Cl	Cl	H	B	274–275	MeOH–Acet.	$C_{14}H_{14}Cl_2N_2O_2S$	20.54	20.11	8.12	8.20	9.29	9.35	±
37	CH_2Cl	H	H	Cl	H	A	272–274[j]	EtOH–H_2O	$C_8H_6Cl_2N_2O_2S$	26.75	26.97			12.09	12.22	+
38	$CHCl_2$	H	Cl	H	H	B	272–274	MeOH–H_2O	$C_8H_5Cl_3N_2O_2S$			9.35	9.42	10.70	10.66	−
39	CF_3	H	Cl	H	H	B	319	EtOH–H_2O	$C_8H_4ClF_3N_2O_2S$	12.46	12.15	9.85	10.03			−
40	CH_2OCH_3	H	Cl	H	H	B	254–256	MeOH–H_2O	$C_9H_9ClN_2O_3S$	13.60	13.41					+++
41	$(CH_2)_2OCH_3$	H	H	Cl	H	C	148–150	MeOH–H_2O	$C_{10}H_{11}ClN_2O_3S$	12.91	12.71	10.20	10.12			+
42	$(CH_2)_2OH$	H	H	Cl	H	E	224–226	EtOH–H_2O	$C_9H_9ClN_2O_3S$	13.60	13.47	10.75	10.84			±
43		H	H	Cl	H	E	178–180	EtOH–H_2O	$C_{13}H_{16}ClN_3O_2S$	11.30	11.19	13.30	13.13			−
44[k]	$(CH_2)_2CO_2CH_3$	H	H	Cl	H	B	194–196	MeOH–H_2O	$C_{11}H_{11}ClN_2O_4S$			9.26	9.61	10.59	10.83	−
45	$(CH_2)_2CO_2H$	H	H	Cl	H	B	231–235	MeOH–Acet.–H_2O	$C_{10}H_9ClN_2O_4S$	12.28	11.84	9.71	9.85	11.10	10.85	−
46	$CH_2SCH_2CO_2CH_3$	H	Cl	H	H	B	129–130	$CHCl_3$–CCl_4	$C_{11}H_{11}ClN_2O_4S$					19.15	18.73	+
47	$CH_2SCH_2CONH_2$	H	Cl	H	H	E	222–223	MeOH–H_2O	$C_{10}H_{10}ClN_3O_3S_2$	13.14	13.00	11.09	11.04			−
48	$CH_2SCH_2CO_2H$	H	Cl	H	H	E	205–206.5	MeOH–H_2O	$C_{10}H_9ClN_2O_4S_2$	8.74	8.72			19.99	20.13	−
49	$CH_2C_6H_5$	H	Cl	H	H	B	300–301	MeOH	$C_{14}H_{11}ClN_2O_2S$	11.56	11.77	9.13	9.03			++
50	p-$CH_3OC_6H_4CH_2$	H	Cl	H	H	D	286–287	EtOH–H_2O	$C_{15}H_{13}ClN_2O_3S$	10.53	10.46	8.32	8.24			±
51	p-$ClC_6H_4CH_2$	H	Cl	H	H	D	314–316	EtOH–H_2O	$C_{14}H_{10}Cl_2N_2O_2S$	20.78	20.52	8.21	7.92			+
52	$CH(CH_3)C_6H_5$	H	Cl	H	H	B	300–303	Acet.	$C_{15}H_{13}ClN_2O_2S$	11.06	11.43	8.74	8.71			+++
53	$(CH_2)_2C_6H_5$	H	Cl	H	H	B	288–289	EtOH–H_2O	$C_{15}H_{13}ClN_2O_2S$	11.06	11.26	8.74	8.96			++
54	$CH{=}CH{-}C_6H_5$	H	Cl	H	H	B	>360	DMF–H_2O	$C_{15}H_{11}ClN_2O_2S$	11.02	11.04	8.79	9.06			++
55	$CH_2OC_6H_5$	H	Cl	Cl	H	D	308–310	DMF–H_2O	$C_{14}H_{10}Cl_2N_2O_3S$	19.85	19.61	8.98	9.13			−
56[i]	$CH(C_6H_{11})C_6H_5$	H	Cl	Cl	H	B, C			$C_{20}H_{20}Cl_2N_2O_2S$							+
57[i]	$CH(C_6H_5)_2$	H	Cl	Cl	H	B			$C_{20}H_{14}Cl_2N_2O_2S$							+
58	C_6H_5	H	Cl	H	H	B	>360	DMF–H_2O	$C_{13}H_9ClN_2O_2S$	12.12	12.15	9.58	9.55			−
59	p-ClC_6H_4	H	Cl	H	H	B	>360	EtOH	$C_{13}H_8ClN_2O_2S$	21.60	21.51	8.54	8.51			±
60	2[l]-furyl	H	Cl	H	H	B	>360	MeOEtOH	$C_{11}H_7ClN_2O_3S$	12.54	12.48	9.91	9.53			±
61	2[l]-thienyl	H	Cl	H	H	B	>360	MeOEtOH	$C_{11}H_7ClN_2O_2S$	11.87	12.03			21.46	21.40	+
62	2[l]-C_5H_4N	H	H	Cl	H	E	355–357	EtOH–H_2O	$C_{12}H_8ClN_3O_2S$	12.07	12.02	14.31	14.54			±
63		H	Cl	H	H	B	280–282	EtOH–H_2O	$C_{12}H_{19}ClN_2O_3S$	11.33	11.59	8.97	9.39			++
64		H	Cl	H	H	B	273–276	EtOH–H_2O	$C_{13}H_{11}ClN_2O_2S_2$	10.85	10.85			19.17	19.45	+

[a] Acet. for acetone, D.M.F. for dimethylformamide and MeOEtOH for 2-methoxyethanol, C_3H_5 = cyclopropyl, C_4H_7 = cyclobutyl, C_5H_9 = cyclopentyl, C_6H_{11} = cyclohexyl. [b] See ref 1. [c] In comparison chlorothiazide showed no activity at doses as high as 40 mg.kg. i. v. [d] B. A. Bierbaum, J. J. Traverso, and C. W. Whitehead, *J. Med. Chem.*, **6**, 272 (1963), report m.p. 322°. [e] Lit.[d] m.p. 370°. [f] Fluorine. [g] Bierbaum, *et. al.*, ref. *d* report m.p. 304°. [h] *Anal.* Calcd.: C, 35.06; H, 2.93. Found: C, 35.29; H, 2.99. [i] See ref. 6. [j] L. Raffa and A. Monzani, *Farmaco* (Pavia) *Ed. Sci.*, **17**, 244 (1962), report m.p. 265–266°. See also E. Grana, L. Lilla and L. Raffa, *ibid.*, **17**, 974 (1962). [k] The cyclization was carried out on the corresponding carboxylic acid intermediate and the crude product was esterified by boiling with methanol.

TABLE II

Symbol	Description
−	No action
±	Equivocal action (very slight if anything)
+	Slight decrease in blood pressure, transient. Mean blood pressure lowered by 10–20 mm. with return to base level in 0.5 hr. or less.
++	Moderate decrease in blood pressure, transient. Mean blood pressure lowered by 20–40 mm. with return to base level in 0.5 hr. to 1 hr.
+++	Slight to moderate decrease in blood pressure, prolonged. Mean blood pressure lowered by 20–40 mm. for longer than 1 hr.
++++	Marked decrease in blood pressure, prolonged. Mean blood pressure lowered by 40–60 mm. for longer than 1 hr. Also similar quantitative effects may be achieved at doses of 10 mg./kg., or less, in most cases.

tion of an aryl moiety for a hydrogen atom, this substitution results in a loss of activity. Attachment of an aryl group or a heterocyclic moiety directly at the 3-position (**58–62**) produces compounds of negligible activity.

With regard to benzene ring substitution it has already been established (part I[1]) that a single halogen substituent at position 6 or 7 exerts a highly favorable effect on activity. In the present series the effect of additional halogen substitution is considered and the most favorable type of disubstitution is clearly 6,7 (**2–5**). As with the monohalogen-substituted compounds, substitution of bromine for chlorine does not change the activity significantly (**6**). Other benzene ring substituent combinations associated with compounds of high activity are 6-trifluoromethyl-7-chloro (**7**), 6-chloro-7-methyl (**9**), 6-methyl-7-chloro (**10**), and 6-methoxy-7-chloro (**13**). The presence of the sulfamoyl (**12**) or methylsulfonyl (**11**) substituents appears to inactivate the molecule, since even with an accompanying 6- (or 7-) chloro substituent there is no detectable activity. None of the compounds tested show significant diuretic activity; some exhibit antidiuretic properties.

Experimental

2H-1,2,4-Benzothiadiazine 1,1-Dioxides (see Table I).

A.—Condensation of a substituted *o*-aminobenzenesulfonamide with the appropriate orthoester.[1]

B.—Fusion of a substituted o-(acylamino)benzenesulfonamide.[6]

C.—Base catalyzed cyclization of a substituted o-(acylamino)-benzenesulfonamide. (a) With sodium hydroxide solution.[6] (b) With concentrated ammonium hydroxide solution. The requisite intermediate (II) was heated on the steam bath for 1–2 hr. with 28% ammonium hydroxide solution (*ca.* 30 ml./g. of compound). The reaction mixture was chilled and acidified and the crude product washed with water and recrystallized.

D.—Fusion of a substituted *o*-aminobenzenesulfonamide and an acid RCO_2H.[6]

E.—See individual descriptions which follow.

7-Chloro-3-methyl-2H-1,2,4-benzothiadiazine-6-sulfonamide 1,1-Dioxide.—5-Amino-2-chlorobenzenesulfonic acid was chlorosulfonated[8] and the resulting 2-amino-5-chloro-*p*-benzenedisulfonyl chloride purified by recrystallization from chloroform–hexane. The analytical sample melted at 169–170°.

Anal. Calcd. for $C_6H_4Cl_2NO_4S_2$: Cl, 32.77; S, 19.75. Found: Cl, 32.43; S, 19.55.

(8) F. C. Novello, S. C. Bell, E. L. A. Abrams, C. Ziegler, and J. M. Sprague, *J. Org. Chem.*, **25**, 965 (1960).

A solution of 2-amino-5-chloro-*p*-benzenedisulfonyl chloride (30.0 g.) and acetic anhydride (20.0 g.) was kept at room temperature for 16 hr. The solution was concentrated to 100 ml. whereupon addition of hexane and chilling gave crude 2-acetamido-5-chloro-*p*-benzenedisulfonyl chloride (34.0 g.). Recrystallization from benzene–hexane (an oil was removed by decantation) gave 22.6 g., m.p. 132–135°. An analytical sample prepared by further recrystallization from the same solvent system had m.p. 133–136°.

Anal. Calcd. for $C_8H_6Cl_2NO_5S_2$: Cl, 29.01; S, 17.49. Found: Cl, 29.31; S, 17.44.

2-Acetamido-5-chloro-*p*-benzenedisulfonyl chloride (34.0 g.) was added in small portions with cooling to 28% ammonium hydroxide solution (300 ml.) and the resultant solution kept at room temperature for 16 hr. The solution was concentrated on a steam bath until ammonia was no longer evolved, treated with charcoal, acidified with concentrated hydrochloric acid, and allowed to cool slowly. Filtration after *ca.* 1 hr. gave 7-chloro-3-methyl-2H-1,2,4-benzothiadiazine-6-sulfonamide 1,1-dioxide (2.9 g.), m.p. >360°. An analytical sample was obtained by recrystallization from methanol–water, m.p. >360° (see Table I, **12**). The results obtained in this later step were erratic.

7-Chloro-6-methoxy-3-methyl-2H-1,2,4-benzothiadiazine 1,1-Dioxide.—Acetic anhydride (6.3 g.) was added slowly to a solution of 2-amino-4-methoxybenzenesulfonamide[1] (5.0 g.) in pyridine (25 ml.) and the reaction mixture heated for 1 hr. at 50–75°. Most of the pyridine was evaporated at room temperature, the residue triturated with 10% hydrochloric acid, and the resulting solid collected by filtration, washed with water, and air-dried to give 2-acetylsulfamoyl-5-methoxyacetanilide (6.15 g.), m.p. 200–202°. A sample was recrystallized from methanol, m.p. 203.5–205°, unchanged on further recrystallization from the same solvent; λ_{max}^{Nujol} 5.82 (s) and 5.95 μ (vs).

Anal. Calcd. for $C_{11}H_{14}N_2O_6S$: S, 11.86. Found: S, 11.82.

2-Acetylsulfamoyl-5-methoxyacetanilide (1.0 g.) was added, portionwise, with swirling to a solution of chlorine in glacial acetic acid (15.8 g. of solution containing 0.31 g. of chlorine). Some heat was generated and the temperature rose to *ca.* 40°. At the end of the addition the yellow color had almost disappeared and the reaction mixture was homogeneous. The reaction mixture was warmed on a steam bath for 5 min., diluted with an equal volume of water, and allowed to cool to room temperature. The white crystalline solid which separated was collected by filtration and air-dried to give crude 2-acetylsulfamoyl-4-chloro-5-methoxyacetanilide (0.5 g.), m.p. 212–214°. The analytical sample, m.p. 237–238°, was obtained by recrystallization (3 times) from methanol.

Anal. Calcd. for $C_{11}H_{13}ClN_2O_6S$: Cl, 11.63; S, 10.52. Found: Cl, 11.71; S, 10.62.

2-Acetylsulfamoyl-4-chloro-5-methoxyacetanilide (2.3 g.) was heated at 250–260° (bath temp.) for 5 min. The residue was dissolved in methanol–acetone–water (charcoal) and the solution concentrated and cooled. Two recrystallizations from methanol–water gave the analytical sample (0.6 g.), m.p. 338–340° (see Table I, **13**).

7-Chloro-3-(2-hydroxyethyl)-2H-1,2,4-benzothiadiazine 1,1-Dioxide.—A solution of 2-amino-5-chlorobenzenesulfonamide[1] (6.0 g.), glycidaldehyde (4.2 g.), ethanol (180 ml.), 15% ethanolic hydrogen chloride (12 ml.), and water (12 drops) was refluxed for 19 hr. The solution was decanted from a small amount of insoluble white material and concentrated. On dilution with water, a solid and a gum formed. The gum was removed and the solid was filtered and dried to give crude product (3.9 g., m.p. 205–211°). The filtrate was concentrated to give additional crude product (1.1 g.), m.p. 225–229°. Both crops of crude material were combined and recrystallized 3 times from ethanol–water to give product (1.4 g.), m.p. 218–220°. The analytical sample melted at 224–226° (see Table I, **42**); λ_{max}^{Nujol} 2.95 (sh), 3.10 (s), and 6.22 (s); λ_{max}^{Meoh} 269 mμ (ε 10,700). The infrared and ultraviolet spectra of the product support its formulation as given rather than as a 3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide.[1]

7-Chloro-3-piperidinomethyl-2H-1,2,4-benzothiadiazine 1,1-Dioxide.—Piperidine (2.1 g.) in ethanol (10 ml.) was added to a solution of 7-chloro-3-chloromethyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (3.0 g.) in ethanol (200 ml.) and the resultant solution refluxed for 16 hr. The reaction mixture was treated with charcoal, evaporated to dryness at room temperature, and the yellow residue triturated with cold water (10 ml.), collected, and dried to give crude product (3.3 g.), m.p. 165–172°. This was

recrystallized from ethanol–water to give a product (2.3 g.), m.p. 178–180°, unchanged on further recrystallization from the same solvent system (see Table I, **43**).

4-Chloro-2-(α-chloroacetamido)benzenesulfonamide.—A solution of 2-amino-4-chlorobenzenesulfonamide (10.0 g.) and chloroacetyl chloride (13.65 g.) in benzene (150 ml.) was refluxed with stirring for 4 hr. The reaction mixture was cooled, the solid material filtered, washed with benzene, and dried to give product (12 g.), m.p. 172–173°. The analytical sample, m.p. 173–174°, was obtained by recrystallization from methanol–chloroform.

Anal. Calcd. for $C_8H_8Cl_2N_2O_3S$: Cl, 25.03; N, 9.90. Found: Cl, 25.48; N, 9.95.

2-{α-[(Carbomethoxymethyl)thio]acetamido}-4-chlorobenzenesulfonamide.—Methyl mercaptoacetate (38.5 g.) was added to a solution of sodium hydroxide (14.5 g.) in methanol (650 ml.) and the resulting solution added to a solution of 4-chloro-2-(α-chloroacetamido)benzenesulfonamide (94.0 g.) in methanol (650 ml.). The reaction mixture was heated on a steam bath for 1 hr. and then concentrated by evaporation of methanol in an air current at room temperature. During this process a solid crystallized. Water was added, the solid collected by filtration, washed with water, and dried to give the product (99.2 g.), m.p. 127–130°. A second crop (7.0 g., m.p. 127–129°) was obtained on concentration of the filtrate. The two crops were combined and recrystallized from methanol yielding 80.0 g., m.p. 133–135°. The analytical sample, m.p. 134.5–135.5°, was obtained by recrystallization from the same solvent.

Anal. Calcd. for $C_{11}H_{13}ClN_2S_2O_5$: Cl, 10.05; N, 7.94. Found: Cl, 10.39; N, 7.88.

3-{[(Carbamoylmethyl)thio]methyl}-6-chloro-2H-1,2,4-benzothiadiazine 1,1-Dioxide.—3-{[(Carbomethoxymethyl)thio]methyl}-6-chloro-2H-1,2,4-benzothiadiazine 1,1-dioxide (Table I, **46**) (1.0 g.) was heated on the steam bath with 28% ammonium hydroxide solution (10 ml.) for 6 hr. during which time three 5-ml. portions of additional 28% ammonium hydroxide solution was added periodically. White crystals which separated from the cooled reaction mixture were collected by filtration, washed with water, and air-dried; yield, 0.65 g., m.p. 219–222°. Recrystallization from methanol–water gave 0.43 g. of product, m.p. 222–223° (Table I, **47**).

3-{[(Carboxymethyl)thio]methyl}-6-chloro-2H-1,2,4-benzothiadiazine 1,1-Dioxide.—3-{[(Carbomethoxymethyl)thio]methyl}-6-chloro-2H-1,2,4-benzothiadiazine 1,1-dioxide (Table I, **46**) (1.0 g.) was heated on a steam bath for 0.5 hr. with 10% sodium hydroxide solution (10 ml.). The reaction mixture was cooled, acidified with concentrated hydrochloric acid, and cooled again. The resulting white precipitate was collected by filtration, washed with water, and dried; yield, 0.6 g.; m.p. 170–177°. Recrystallization from methanol–water gave 0.35 g. of product m.p. 200–202°. Further recrystallization from methanol–water gave the analytical sample, m.p. 205–206.5° (Table I, **48**).

7-Chloro-3-(3-pyridyl)-2H-1,2,4-benzothiadiazine 1,1-Dioxide.—A mixture of 2-amino-5-chlorobenzenesulfonamide (2.0 g.) and nicotinoyl chloride hydrochloride (5.2 g.) was heated at 200–210° for 1.5 hr. Hot water (300 ml.) was added and the crude product collected by filtration and dried; yield, 2.1 g., m.p. 352–354° dec. Neutralization of the filtrate with 5% sodium bicarbonate solution did not yield any additional product. Recrystallization from 2-methoxyethanol (charcoal) afforded 1.3 g. of product, m.p. 355–357° dec. (Table I, **62**).

***o*-(Acylamino)benzenesulfonamides.**—These were prepared by reaction of the appropriate acid chloride with the substituted *o*-aminobenzenesulfonamide in refluxing benzene[6] and utilized in the cyclization step without purification.

***o*-Aminobenzenesulfonamides.**—The following were prepared according to procedures in the literature: 2-amino-4-chlorobenzenesulfonamide,[3] 2-amino-5-chlorobenzenesulfonamide,[1] 2-amino-4,5-dichlorobenzenesulfonamide,[9] 2-amino-4,6-dichlorobenzenesulfonamide,[9] 2-amino-4-chloro-5-methylbenzenesulfonamide,[8] 2-amino-5-chloro-4-methylbenzenesulfonamide,[8] and 2-amino-4-chloro-5-methylsulfonylbenzenesulfonamide.[9]

2-Amino-3,5-dichlorobenzenesulfonamide.—2,4-Dichloroaniline (10.0 g.) was dissolved, with stirring, in chlorosulfonic acid (60 ml.) and the resultant solution heated for 4 hr. at 135° (bath temperature). The solution was poured into ice–water and a dark blue semisolid which separated was filtered, washed with water, and dissolved in liquid ammonia. The excess of ammonia was evaporated, water was added to the dark blue residue, and the crude product was collected by filtration, dissolved in aqueous alcohol (charcoal), and the solution concentrated and allowed to cool. A dark blue solid which separated first was removed by filtration. The filtrate was concentrated and cooled to give a gray-green solid (2.0 g.), m.p. 140–149°, which was recrystallized from acetone–water (charcoal) affording a product (1.2 g.), m.p. 155–156°, unchanged after further recrystallization from the same solvent system.

Anal. Calcd. for $C_6H_6Cl_2N_2O_2S$: Cl, 29.42; S, 13.29. Found: Cl, 29.64; S, 13.21.

2-Amino-5,6-dichlorobenzenesulfonamide.—The preparation of this compound was carried out according to the general procedure previously described.[7] 2,3,4-Trichloronitrobenzene[10] was converted by the action of benzyl chloride and thiourea in the presence of base to 2-benzylthio-3,4-dichloronitrobenzene, which, after purification by chromatography on alumina, melted at 80–83°. The benzylthio compound was cleaved oxidatively with chlorine in aqueous acetic acid and the resulting sulfonyl chloride treated with liquid ammonia affording 5,6-dichloro-2-nitrobenzenesulfonamide, m.p. 163.5–164.5°, which was reduced with iron filings in an aqueous methanolic ammonium chloride solution to give 2-amino-5,6-dichlorobenzenesulfonamide, m.p. 187–189° (methanol–water).

Anal. Calcd. for $C_6H_6Cl_2N_2O_2S$: Cl, 29.42; S, 13.29. Found: Cl, 29.47; S, 13.66.

2-Amino-5-chloro-4-trifluoromethylbenzenesulfonamide.—To 5-amino-2-chlorobenzotrifluoride (20.0 g.) in *o*-dichlorobenzene (100 ml.), chlorosulfonic acid (27.0 g.) was added dropwise, with stirring. After the addition was complete, the mixture was heated at 160° for 4 hr., then cooled and filtered. The solid obtained was washed with ether to give crude sulfonic acid (23.1 g.). The latter was heated with chlorosulfonic acid (50 ml.) at 100–130° (bath temperature) for 2 hr. The reaction mixture was poured onto ice and the precipitated solid filtered, washed with water, and dissolved in liquid ammonia (300 ml.). The excess of ammonia was allowed to evaporate and water was added to the residue. The resulting solid was collected by filtration, washed with water, and dried to give a crude product (5.5 g.), m.p. 168–171°. Recrystallization from methanol–water gave the product (4.1 g.), m.p. 168–171°.

Anal. Calcd. for $C_7H_6ClF_3N_2O_2S$: C, 30.61; H, 2.20; N, 10.20. Found: C, 31.03; H, 2.23; N, 10.41.

2-Amino-4,5-dibromobenzenesulfonamide.—This compound was obtained in poor yield from 3,4-dibromoaniline by following the procedure described by Short and Biermacher[9] for the preparation of the corresponding dichloro compound. The analytical sample, m.p. 178–180°, was obtained by recrystallization from chloroform.

Anal. Calcd. for $C_6H_6Br_2N_2O_2S$: N, 8.49; S, 9.41. Found: N, 8.06; S, 9.26.

2-Amino-4,5,6-trichlorobenzenesulfonamide.—A mixture of 3,4,5-trichloroaniline[11] (24.0 g.) and chlorosulfonic acid (200 ml.) was heated at 120° for 6 hr. The cooled reaction mixture was poured onto ice and the precipitated solid filtered and added to liquid ammonia (150 ml.). The excess ammonia was allowed to evaporate and dilute hydrochloric acid added to the residue. The resulting solid was filtered, washed with water, and crystallized from methanol to give the product (12.0 g.), m.p. 175–179°. An analytical sample, m.p. 179–181°, was obtained on further recrystallization from methanol.

Anal. Calcd. for $C_6H_5Cl_3N_2O_2S$: Cl, 38.60; N, 10.17; S, 11.63. Found: Cl, 38.45; N, 9.95; S, 11.54.

Acknowledgments.—The authors are indebted to Dr. J. Sanguigni and Mr. W. Boraczek for the synthesis of certain of the compounds described, to Mr. I. Berger for the preparation of some of the intermediates, and to Mr. E. Conner for the microanalyses.

(9) J. H. Short and U. Biermacher, *J. Am. Chem. Soc.*, **82**, 1135 (1960).

(10) F. Beilstein and A. Kurbatow, *Ann.*, **192**, 228 (1878).

(11) R. G. Shepherd, *J. Org. Chem.*, **12**, 275 (1947).