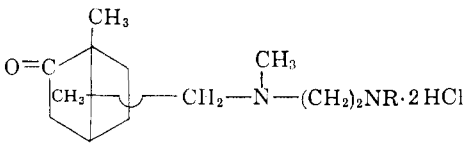
pharmacological activities such as toxicity, analgesia,[1] general CNS depressant and local anesthetic action in connection with cough depression resulting from stretch receptor anesthesia,[21] although it definitely increases antitussive activity. It appears that piperidino compounds depress predominantly the central respiratory mechanisms[22,23] and definitely inhibit the respiration of brain tissue slices in a glucose medium when tested by Warburg's manometric technique. More detailed mechanisms are now under investigation and will be reported in the near future.

TABLE X

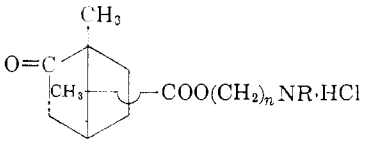
SERIES 5.[a] CAMPHOR DERIVATIVES. α-9-(N-*tert*-AMINOETHYL-N-METHYLAMINO)-CAMPHOR DIHYDROCHLORIDES

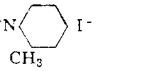


Compd.	NR	M.p., °C.	Antitussive activity: Animals used	Antitussive activity: AtD_{50} (mg./kg.) cat i.v.
LXIV	$N(C_2H_5)_2$	165	3	Ineffective at 20.0
LXV	Piperidino	220.4	5	10.7[b]

TABLE X (*continued*)

dl-tert-AMINOALKYL ISOKETOPINATE HYDROCHLORIDES



Compd.	n	NR	M.p., °C.	Antitussive activity: Animals used	Antitussive activity: AtD_{50} (mg./kg.) cat i.v.
LXVI	2	$N(CH_3)_2$	191	3	Ineffective at 20.0
LXVII	2	$N(CH_3)_3 \cdot I^-$	208	3	Ineffective at 20.0
LXVIII	2	Piperidino	247	20	5.2 (4.4–6.2)
LXIX	2		208	2	Ineffective at 20.0
LXX	3	$N(CH_3)_2$	162	2	Ineffective at 20.0
LXXI	3	$N(CH_3)_3 \cdot I^-$	181	2	Ineffective at 20.0
LXXII	3	Piperidino	203	20	10.5 (8.8–11.6)
LXXIII	3		190	2	Ineffective at 20.0
Control	Codeine phosphate		Dog: 3.76 (3.38–4.19)		Cat: 2.53 (2.24–2.86)

[a] Synthesized and supplied by Dr. M. Nakanishi.[18] [b] Minimal effective dose (MED).

(21) K. Bucher, *Schweiz. Med. Wochschr.*, **86**, 10 (1956); *Pharmacol. Rev.*, **10**, 43 (1958).

(22) Y. Kasé and T. Yuizono, *Nippon Yakugaku Zasshi*, **56**, 181 (1960).

(23) Y. Kasé, *Yakkyoku* (*J. Practical Pharmacy*) (Tokyo), **12**, 65 (1961).

Antihypertensive Agents. I. Non-diuretic 2H-1,2,4-Benzothiadiazine 1,1-Dioxides

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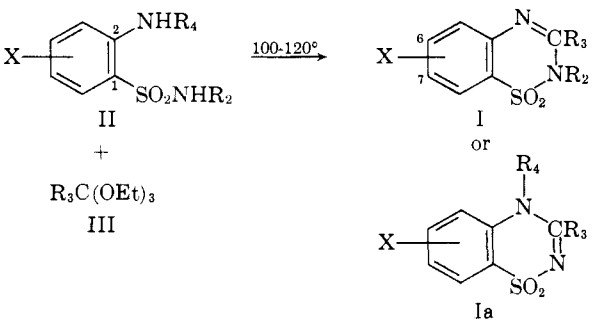
Certain substituted 2H-1,2,4-benzothiadiazine 1,1-dioxides have been synthesized which show antihypertensive but not diuretic activity. The effect on activity of some structural modifications in this series has been examined.

Sulfamoyl substituted 2H-1,2,4-benzothiadiazine 1,1-dioxides, including the 3,4-dihydro compounds, are a well known class of orally effective diuretic agents.[1] Many of them also show an antihypertensive effect and are used clinically in the treatment of mild hypertension.[2] Although the precise mechanism of this action is not known, it has generally been assumed to be related to the diuretic and natriuretic properties of the compounds.[3] However, it has been shown recently that the non-diuretic 7-chloro-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide[4] (I, X = 7-Cl, R_2 = H R_3, = CH_3) exerts a pronounced antihypertensive effect which is thought to be due to the direct action of the compound at the vascular level.[5] This paper reports the synthesis of I (X = 7-Cl, R_2 = H, R_3 = CH_3) and of related compounds as part of a study to determine the effect of certain structural modifications in this series on biological activity.

The synthesis of the 2H-1,2,4-benzothiadiazine 1,1-dioxides (I) was accomplished by the condensation of a substituted *o*-aminobenzenesulfonamide (II) with the appropriate orthoester (III).[6]



(1) For a recent review see E. Schlittler, G. deStevens, and L. Werner, *Angew. Chemie*, **74**, 317 (1962).

(2) A. Grollmann *Clin. Pharm. Therap.*, **1**, 735 (1960).

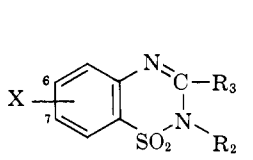
(3) F. A. Tapia, H. P. Dustan, R. E. Scheckloth, A. C. Corcoran, and I. H. Page, *Lancet*, **2**, 831 (1957); E. D. Freis, A. Wanko, I. M. Wilson, and A. E. Parrish, *Ann. N. Y. Acad. Sci.*, **7**, 450 (1958).

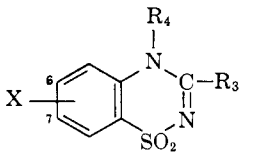
(4) Generic name, diazoxide.

(5) A. A. Rubin, F. E. Roth, M. M. Winbury, J. C. 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 (1961).

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

TABLE I[a]

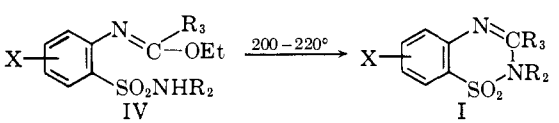




No.	X	R_2	R_3	R_4	M.p., °C.[b]	Recryst. solvent[c]	Formula	—Nitrogen, %— Calcd.	Found	—Chlorine, %— Calcd.	Found	—Sulfur, %— Calcd.	Found
1	7-Cl	H	CH_3		330–331	EtOH–H_2O	$C_8H_7ClN_2O_2S$	12.15	12.40	15.37	15.41		
2	6-Cl	H	CH_3		276–277	EtOH–Hex.	$C_8H_7ClN_2O_2S$	12.15	12.15			13.90	13.87
3	5-Cl	H	CH_3		278–280	Trit. ether	$C_8H_7ClN_2O_2S$	12.15	12.20	15.37	15.51		
4	8-Cl	H	CH_3		264–266	EtOH	$C_8H_7ClN_2O_2S$	12.15	12.07			13.90	13.86
5	7-Cl	H	H		246–247	EtOH–H_2O	$C_7H_5ClN_2O_2S$	12.94	12.68	16.37	15.92		
6	6-Cl	H	H		262–263[e]	95% EtOH	$C_7H_5ClN_2O_2S$					14.77	14.94
7	7-Cl	H	C_2H_5		267–269	EtOH–H_2O	$C_9H_9ClN_2O_2S$			14.49	14.55	13.10	13.29
8	6-Cl	H	C_2H_5		267–268	EtOH–H_2O	$C_9H_9ClN_2O_2S$	11.45	11.49	14.49	14.20		
9	6-Cl	H	n-C_3H_7		266–267	EtOH–H_2O	$C_{10}H_{11}ClN_2O_2S$			13.71	13.90	12.39	12.38
10[d]	H	H	CH_3				$C_8H_8N_2O_2S$						
11[d]	H	H	H				$C_7H_8N_2O_2S$						
12	7-Br	H	CH_3		333.5–336.5	MeOH	$C_8H_7BrN_2O_2S$			29.05[f]	28.52[f]	11.65	11.50
13	6-Br	H	CH_3		309–310	MeOH–Ac	$C_8H_7BrN_2O_2S$	10.19	10.08			11.65	11.69
14	6-CF_3	H	CH_3		325–326	MeOH–H_2O	$C_9H_7F_3N_2O_2S$	10.60	10.47			12.13	12.42
15	6-OCH_3	H	CH_3		253–255	MeOH–H_2O	$C_9H_{10}N_2O_3S$	12.38	12.91			14.17	13.95
16	6-CH_3	H	CH_3		250–252	MeOH	$C_9H_{10}N_2O_2S$	13.33	13.26			15.25	15.18
17[g]	6-NH_2	H	CH_3		290–292	MeOH–H_2O	$C_8H_9N_3O_2S$	19.89	19.99			15.18	15.20
18	6-$NHCOCH_3$	H	CH_3		337 dec.	MeOH–H_2O	$C_{10}H_{11}N_3O_3S$	16.62	16.77			12.67	12.70
19	7-NO_2	H	CH_3		154–156	MeOH	$C_9H_{11}N_3O_5S$[h]						
20[g]	7-NH_2	H	CH_3		>360	MeOH–H_2O	$C_8H_9N_3O_2S$	19.89	20.10			15.18	15.24
21[g]	7-$SO_2N(CH_3)_2$	H	CH_3		269–270	Ac–Hex	$C_{10}H_{13}N_3O_4S_2$	13.86	13.71				
22	6-CO_2H	H	CH_3		>360	Ac–H_2O	$C_9H_8N_2O_4S$	11.66	11.42			13.35	13.49
23[g]	6-CO_2CH_3	H	CH_3		273–275	MeOH	$C_{10}H_{10}N_2O_4S$	11.02	11.20			12.61	12.87
24	6-Cl	CH_3	CH_3		138–140	Bz–Hex	$C_9H_9ClN_2O_2S$	11.45	10.98			13.10	13.47
25	6-Cl	C_2H_5	CH_3		115–117	EtOH	$C_{10}H_{11}ClN_2O_2S$	10.83	10.66			12.39	12.81
26	6-Cl		CH_3	CH_3	248–249	Ac–H_2O	$C_9H_9ClN_2O_2S$	11.45	11.19	14.49	14.52		
27	6-Cl		H	CH_3	287–289	MeOH	$C_8H_7ClN_2O_2S$	12.15	12.49	15.37	15.41		
28	7-Cl		CH_3	CH_3	232–234	MeOH–H_2O	$C_9H_9ClN_2O_2S$	11.45	11.55	14.49	14.19		

[a] The structural assignments given to compounds reported in this table are fully supported by spectral data. [b] Melting points are uncorrected. [c] Ac for acetone, Bz for benzene and Hex for hexane. [d] D. O. Parke and R. T. Williams, *J. Chem. Soc.*, 1760 (1950). [e] J. H. Short and U. Biermacher, *J. Am. Chem. Soc.*, **82**, 1135 (1960), report m.p. 255–256°. [f] Bromine. [g] For the preparation of this compound see Experimental section. [h] Calcd. for CH_3OH of solvation: C, 39.55; H, 4.06. Found: C, 40.17; H, 4.35.

When R_2 was other than hydrogen (R_4 = H), the reaction did not usually proceed directly to the benzothiadiazine (I) but gave the imino ether (IV).[7] Upon heating at 200–220°, the imino ether yielded the expected 2-substituted benzothiadiazine when R_2 was methyl or ethyl (I, R_3 = CH_3, X = 6-Cl). However, when R_2 was isopropyl, the group R_2 was eliminated in the cyclization step giving I (R_2 = H, R_3 = CH_3, X = 6-Cl).[8]



The use of the orthoester reaction for the preparation of 4-substituted benzothiadiazines proved satisfactory in the one case investigated (II, X = 5-Cl, R_2 = H, R_3 = CH_3, R_4 = CH_3) the reaction proceeding directly to the benzothiadiazine (Ia, X = 7-Cl, R_3 = R_4 = CH_3). The synthesis of 4-substituted benzothiadiazines was also accomplished by the alkylation of a benzothiadiazine in the presence of base. For example, I (X = 7-Cl R_2 = H, R_3 = CH_3), when treated with methyl iodide in the presence of sodium methoxide yielded an N-methyl derivative (Ia, X = 7-Cl, R_3 = R_4 = CH_3) identical with that synthesized by the unequivocal orthoester synthesis thus establishing the site of alkylation as position 4.[9] A number of substituted 2H-1,2,4-benzothiadiazine 1,1-dioxides synthesized according to the foregoing methods are listed in Table I.

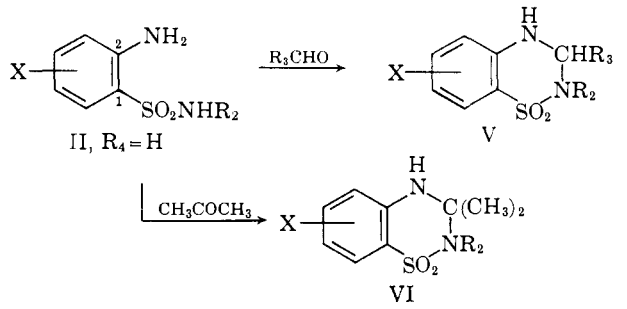
In order to determine the effect on antihypertensive activity of saturation of the 3,4-double bond in this series, a number of substituted 3,4-dihydro-2H-1,2,4-benzothiadazine 1,1-dioxides (V) were synthesized from the *o*-aminobenzenesulfonamide (II, R_4 = H) and an aldehyde R_3CHO.[6] The condensations, which involved low molecular weight aliphatic aldehydes, were carried out using a large excess of the aldehyde in acetonitrile as solvent in the absence of acid catalyst.[10] Some 3,3-disubstituted 3,4-dihydrobenzothiadiazines, VI (X = 8-Cl, R_2 = H), VI (X = 6-Cl, R_2 = H) and VI (X = 8-Cl, R_2 = CH_3) were synthesized by condensation of the appropriate *o*-aminobenzenesulfonamide with acetone. The position of the chlorine atom was found to have an important effect on the reactivity of the substituted *o*-aminobenzenesulfonamide in this reaction. Thus 2-amino-6-chlorobenzenesulfonamide (II, X = 6-Cl, R_2 = R_4 = H) and 2-amino-6-chloro-N-methylbenzenesulfonamide (II, X = 6-Cl, R_2 = CH_3, R_4 = H) upon warming with a large excess of acetone on the steam bath for 0.5 hr. gave VI (X = 8-Cl, R_2 = H) and VI (X = 8-Cl, R_2 = CH_3), respectively, in high yield. The condensation of 2-amino-4-chlorobenzenesulfonamide with acetone to give VI (X = 6-Cl, R_2 = H) required an additional 5 days of reaction time at room temperature. However, no reaction of 2-amino-5-chlorobenzenesulfonamide with acetone was observed either after warming on the steam bath, or after an additional 13 days of reaction time at room temperature.

(7) Not isolated in the pure state in all cases.

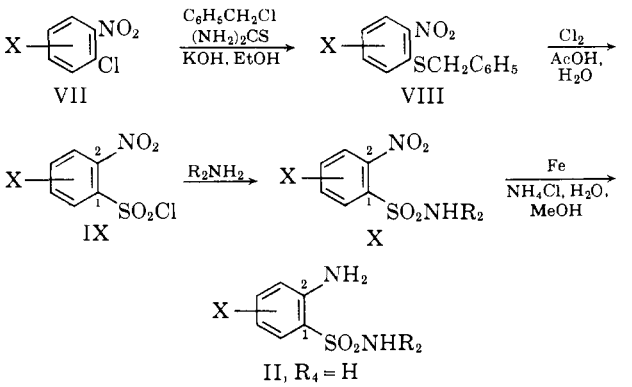
(8) This interesting reaction will be discussed in more detail in a forthcoming publication.

(9) Similar findings have been reported by A. Ekbom, *Bihang till Svenska Vet. Akad. Handl.*, **27**, II, No. 1, 3 (1902); *Beilstein*, **27**, 571; and F. C. Novello, S. C. Bell, E. L. A. Abrams, C. Ziegler, and J. M. Sprague, *J. Org. Chem.*, **25**, 970 (1960).

(10) J. G. Topliss, M. H. Sherlock, F. H. Clarke, M. C. Daly, B. W. Pettersen, J. Lipski, and N. Sperber, *J. Org. Chem.*, **26**, 3842 (1961).



The substituted 3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxides prepared according to the foregoing methods are listed in Table II.



The reaction sequence most frequently used for the preparation of the substituted *o*-aminobenzenesulfonamides (II, R_4 = H) required as intermediates is illustrated. The compounds prepared in this reaction sequence corresponding to VIII, X and II (R_4 = H) are listed in Tables III, IV and V, respectively. In general the sulfonyl chloride (IX) was not isolated in pure form but was utilized in the crude state for the next stage in the sequence. In the attempted conversion of IX to X (X = 4-CF_3, R_2 = CH_3), the use of excess of liquid methylamine gave 2-nitro-4-trifluoromethyl-*N*-methylaniline, rather than the expected compound X (X = 4-CF_3, R_2 = CH_3). The substituent at position 1 in this case is apparently sufficiently activated by the nitro group in the *ortho* position and the trifluoromethyl group in the *para* position that it can be displaced by a strong base (methylamine). It may be noted that when a weaker base, ammonia, is substituted for methylamine in this reaction, the product is X (X = 4-CF_3, R_2 = H).

An alternative route for the preparation of II (X = 5-Cl, R_2 = R_4 = H) and for the synthesis of I (X = 7-Cl, R_2 = H, R_3 = CH_3) is shown in the reaction scheme.

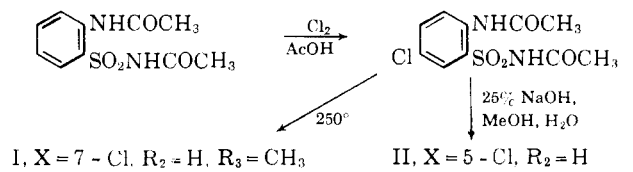
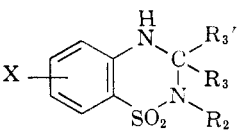


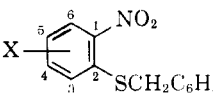
TABLE II[a]



No.	X	R_2	R_3	R_3'	M.p., °C.[b]	Recryst. solvent[c]	Formula	Nitrogen % Calcd.	Nitrogen % Found	Chlorine % Calcd.	Chlorine % Found	Sulfur % Calcd.	Sulfur % Found
29	7-Cl	H	CH_3	H	213–214	EtOH	$C_9H_9ClN_2O_2S$	12.04	12.15	15.24	15.22	13.78	13.51
30	7-Cl	H	H	H	197–199	EtOH–H_2O	$C_7H_7ClN_2O_2S$	12.81	12.61	16.22	16.01		
31	7-Cl	H	C_2H_5	H	183–184	MeOH–$CHCl_3$	$C_9H_{11}ClN_2O_2S$	11.36	11.53	14.37	14.46	13.00	13.20
32	6-Cl	H	*n*-C_3H_7	H	191–193	EtOH-$CHCl_3$	$C_{10}H_{13}ClN_2O_2S$			13.60	13.24	12.30	12.65
33	6-Cl	H	CH_3	CH_3	188–191	Ac-Hex	$C_9H_{11}ClN_2O_2S$	11.36	11.06	14.37	14.33	13.00	13.23
34	8-Cl	H	CH_3	CH_3	241–244	Ac-Hex	$C_9H_{11}ClN_2O_2S$	11.36	11.11	14.37	14.55	13.00	13.23
35	8-Cl	CH_3	CH_3	CH_3	190–193	Ac-Hex	$C_{10}H_{13}ClN_2O_2S$	10.77	10.54	13.60	13.31	12.30	12.27

[a] The structural assignments given to compounds reported in this table are fully supported by spectral data. [b] Melting points are uncorrected. [c] Ac for acetone and Hex for hexane.

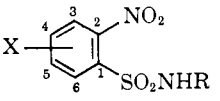
TABLE III



No.	X	M.p., °C.[a]	Recryst. solvent[b]	Formula	Nitrogen % Calcd.	Nitrogen % Found	Chlorine % Calcd.	Chlorine % Found	Sulfur % Calcd.	Sulfur % Found
33	4-Cl	132–134	95% EtOH	$C_{13}H_{10}ClNO_2S$	5.01	5.03				
34	5-Cl	134–135	95% EtOH	$C_{13}H_{10}ClNO_2S$			12.67	12.45	11.46	11.42
35	6-Cl	65–66	EtOH–H_2O	$C_{13}H_{10}ClNO_2S$	5.01	5.22	12.67	12.73	11.46	11.59
36[c]	3-Cl			$C_{13}H_{10}ClNO_2S$						
37[c]	5-Br			$C_{13}H_{10}BrNO_2S$						
38	5-CF_3	135–137	Bz–Hex	$C_{14}H_{10}F_3NO_2S$	4.48	4.92			10.22	10.62
39	5-OCH_3	109–110	Bz–Hex	$C_{14}H_{13}NO_3S$	5.08	5.14			11.65	11.95
40	5-CH_3	96–98	Bz–Hex	$C_{14}H_{13}NO_2S$	5.40	5.45			12.39	11.82
41[d]	5-NO_2			$C_{13}H_{10}N_2O_4S$						
42	5-NH_2	122–123.5	Bz–Hex	$C_{13}H_{12}N_2O_2S$	10.76	10.24			12.32	12.13
43	5-$NHCOCH_3$	176.5–178	EtOH	$C_{15}H_{14}N_2O_3S$	9.27	9.29			10.61	10.67
44	5-CO_2H	215–217	EtOH	$C_{14}H_{11}NO_4S$		[e]			11.08	11.11

[a] Melting points are uncorrected. [b] Bz for benzene and Hex for hexane. [c] R. Specklin and J. Meybeck, *Bull. soc. chim. France*, **18**, 621 (1951). [d] R. W. Bost, J. O. Turner, and R. D. Norton, *J. Am. Chem. Soc.*, **54**, 1985 (1932). [e] Calcd.: C, 58.11; H, 3.83. Found: C, 57.86; H, 3.88.

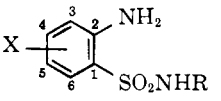
TABLE IV



No.	X	R	M.p., °C.[a]	Recryst. solvent[b]	Formula	Nitrogen % Calcd.	Nitrogen % Found	Chlorine % Calcd.	Chlorine % Found	Sulfur % Calcd.	Sulfur % Found
45	5-Cl	H	159–160	MeOH	$C_6H_5ClN_2O_4S$	11.84	11.71			13.55	13.61
46[c]	4-Cl	H			$C_6H_5ClN_2O_4S$						
47	3-Cl	H	171–173	MeOH–H_2O	$C_6H_5ClN_2O_4S$	11.84	12.15	14.98	14.93	13.55	13.91
48	6-Cl	H	145–145.5	H_2O	$C_6H_5ClN_2O_4S$	11.84	12.03	14.98	14.60	13.55	13.71
49	4-Br	H	176–177	MeOH–H_2O	$C_6H_5BrN_2O_4S$	9.97	9.78			11.40	11.49
50	4-CF_3	H	168–170.5[d]	EtOH–H_2O	$C_7H_5F_3N_2O_4S$						
51	4-OCH_3	H	142–144	MeOH–H_2O	$C_7H_8N_2O_5S$	12.10	11.92			13.81	13.97
52	4-CH_3	H	170–172	MeOH–H_2O	$C_7H_8N_2O_4S$	12.96	12.73				
53	4-$NHCOCH_3$	H	250–251	EtOH–H_2O	$C_8H_9N_3O_5S$	16.23	16.34			12.38	12.67
54	4-CO_2H	H	260–261	H_2O	$C_7H_6N_2O_6S$	11.38	11.12			13.02	13.06
55	4-Cl	CH_3	123–124	H_2O	$C_7H_7ClN_2O_4S$	11.18	11.56			12.78	12.89
56	6-Cl	CH_3	132–133	MeOH–H_2O	$C_7H_7ClN_2O_4S$	11.18	11.37	14.14	14.14	12.78	12.93
57	4-Cl	C_2H_5	85.5–87	Bz–Hex	$C_8H_9ClN_2O_4S$	10.59	10.39			12.12	12.28
58	4-Cl	i-C_3H_7	127–128	EtOH–H_2O	$C_9H_{11}ClN_2O_4S$	10.05	10.00			11.50	11.87

[a] Melting points are uncorrected. [b] Bz for benzene and Hex for hexane. [c] E. Riesz, A. Lorenz, Ch. Myschalow, and O. Strakosch, *Monatsh.*, **50**, 263 (1928). [d] Ref. 16 reports m.p. 165–167°.

TABLE V



No.	X	R	M.p., °C.[a]	Recryst. solvent[b]	Formula	Nitrogen % Calcd.	Nitrogen % Found	Chlorine % Calcd.	Chlorine % Found	Sulfur % Calcd.	Sulfur % Found
59	5-Cl	H	152–153	EtOH–H_2O	$C_6H_7ClN_2O_2S$	13.56	13.27	17.15	17.22		
60	4-Cl	H	145–146[c]	EtOH–H_2O	$C_6H_7ClN_2O_2S$						
61	3-Cl	H	153–154	MeOH–H_2O	$C_6H_7ClN_2O_2S$	13.56	13.78	17.15	17.11	15.51	15.58
62	6-Cl	H	139–140	H_2O	$C_6H_7ClN_2O_2S$	13.56	13.41			15.51	15.61
63	4-Br	H	140–141	MeOH–H_2O	$C_6H_7BrN_2O_2S$	11.16	11.33			12.76	12.64
64[d]	5-Br	H			$C_6H_7BrN_2O_2S$						
65	4-CF_3	H	143–145[e]	MeOH–H_2O	$C_7H_7F_3N_2O_2S$						
66	4-OCH_3	H	143–144	MeOH–H_2O	$C_7H_{10}N_2O_3S$	13.86	13.77			15.87	15.75
67	4-CH_3	H	124–126	MeOH–H_2O	$C_7H_{10}N_2O_2S$	15.05	15.18			17.22	17.48
68	4-$NHCOCH_3$	H	216–216.5	EtOH	$C_8H_{11}N_3O_3S$					13.98	14.29
69[f]	5-NO_2	H			$C_6H_7N_3O_4S$						
70	4-CO_2H	H	277–278	H_2O	$C_7H_8N_2O_4S$	12.96	12.79			14.83	14.63
71	4-Cl	CH_3	112–114	H_2O	$C_7H_9ClN_2O_2S$	12.71	12.48			14.53	14.37
72	6-Cl	CH_3	92–95	MeOH–H_2O	$C_7H_9ClN_2O_2S$	12.71	12.52	16.07	16.08	14.53	14.12
73	4-Cl	C_2H_5	67–68	Bz–Hex	$C_8H_{11}ClN_2O_2S$	11.94	11.91				
74	4-Cl	i-C_3H_7	112–113	EtOH–H_2O	$C_9H_{13}ClN_2O_2S$	11.26	11.16			12.89	12.87

[a] Melting points are uncorrected. [b] Bz for benzene and Hex for hexane. [c] J. H. Short and U. Biermacher, *J. Am. Chem. Soc.*, **82** 1135 (1960), report m.p. 144–146°. [d] D. O. Parke and R. T. Williams, *J. Chem. Soc.*, 1760 (1950). [e] Ref. 16 reports m.p. 143–146°. [f] A. R. Goldfarb and B. Berk, *J. Am. Chem. Soc.*, **65**, 738 (1943).

Spectral Data.[11]—The infrared absorption spectra were determined from Nujol mulls. Some characteristic features of the infrared spectra of the substituted 2H-1,2,4-benzothiadiazine 1,1-dioxides (I) synthesized were noted. Among these were three closely positioned bands (medium-weak) attributable to N–H stretching at 3.04–3.08, 3.13–3.18 and 3.20–3.25 μ of diminishing relative intensity with increasing wave length, a medium to strong band at 6.14–6.20 μ due to C=N stretching vibrations, a strong band at 7.70–7.85 μ resulting from asymmetric S–O stretching vibrations and a strong band at 8.6–8.7 μ associated with symmetric S–O stretching vibrations. The 3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxides prepared showed medium-strong bands at 2.95–2.99 μ (N–H stretching of aromatic amine) and 3.08–3.13 μ (N–H stretching of sulfonamide). Also evident was a medium band at 6.20–6.25 μ due to N–H deformation absorption and strong bands at 7.60–7.65 and 8.65–8.70 μ associated with asymmetric and symmetric S–O stretching, respectively. The imino ethers (IV) exhibited a strong band at 5.95–6.05 μ (C=N stretching).

The ultraviolet absorption spectra were determined in methanol solution. The 2H-1,2,4-benzothiadiazine 1,1-dioxides exhibited characteristic absorption maxima at 215–220 mμ (ϵ 14,000–20,000) and 267–272 mμ (ϵ 8,000–12,000). 3,4-Dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxides showed absorption maxima at 214–220 mμ (ϵ 25,000–35,000), 253–256 mμ (ϵ 11,000–16,000) and 315–325 mμ (ϵ 1,500–3,500).

Pharmacological Methods.[12]—Mongrel dogs of both sexes were anesthetized with vinbarbital (50 mg./kg.,

(11) We are indebted to Mr. R. Wayne for discussions in connection with the interpretation of the infrared absorption spectra.

(12) 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.

i.v.) and blood pressure responses were recorded from the femoral artery with an Anderson glass membrane manometer. Respiration was measured with an Anderson respirometer and heart rate monitored continuously with a Waters cardiotachometer. Drugs were injected into a cannulated femoral vein as aqueous solutions of their sodium salts where possible, otherwise as solutions in aqueous dimethyl acetamide. The initial test dose was generally 10 mg./kg. Where little or no response was observed, higher doses of the compound, up to 40 mg./kg. were administered. For potent compounds further experiments were carried out with doses as low as 0.25 mg./kg. The effects of the compounds on pressor responses to norepinephrine, epinephrine and bilateral carotid occlusion were also noted. In estimating the relative efficacies of the compounds as antihypertensive agents, due weight was given to duration of action in addition to the magnitude of the pressure drop. The diuretic activity of the compounds was determined by oral administration to saline loaded rats using a modification of the Lipschitz procedure.

Structure–Activity Relationships.—2H-1,2,4-Benzothiadiazine 1,1-dioxide (11) showed a detectable but very weak antihypertensive activity. Considerable enhancement of activity was achieved by the introduction of a chlorine substituent (5, 6). Activity was further increased when a methyl group was present at position 3 (1, 2). The most advantageous position for the chlorine atom was found to be at 7 or 6 (1, 2). Activity was noticeably reduced with chlorine at position 8 (4) and scarcely apparent when the chlorine was moved to position 5 (3). Some slight increase in activity was noted with substitution of ethyl for methyl at position 3 (7, 8), but this diminished again with extension of the chain to *n*-propyl (9). With bromine or trifluoromethyl in place of chlorine (12, 13, 14) activity was little changed. Most of the activity was retained with the nitro group at position 7 (19) but was diminished if the ring substituent was methyl or methoxyl (15, 16). In the case of a number of other substituents the molecule was rendered essentially inactive (17, 18, 20, 21, 22, 23). The introduction of alkyl substituents at positions 2 or 4 (24–28) resulted in a reduction of antihypertensive activity. 3,4-Dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxides (29–32) were much less active than the corresponding compounds with a double bond at position 3,4. 3,3-Disubstituted 3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxides (33–35) were found to be essentially devoid of antihypertensive activity. None of the compounds (Tables I and II) tested showed significant diuretic activity; some exhibited antidiuretic properties.

Experimental

2H-1,2,4-Benzothiadiazine 1,1-dioxides.—The substituted *o*-aminobenzenesulfonamide was heated with the appropriate orthoester (*ca.* 3 pts. by weight) for 1–2 hr. at 100–120° in an open vessel. The cooled reaction mixture was diluted with dry ether and the product collected by filtration. Yields ranged from 30–80%.

6-Amino-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide.—A solution of 6-acetamido-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (Table I) (8.0 g.), ethanol (160 ml.) and concd. hydrochloric acid (16 ml.) was refluxed for 1 hr. The solution was cooled and the colorless solid (6.3 g.) which separated, filtered off. On recrystallization from methanol-water, product (4.8 g.) was obtained, m.p. 290–292° (Table I).

7-Amino-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide.—To a stirred refluxing solution of 3-methyl-7-nitro-2H-1,2,4-benzothiadiazine 1,1-dioxide (Table I) (6.0 g.), ammonium chloride (8.75 g.) in methanol (100 ml.) and water (50 ml.), iron filings (8.75 g.) was added, portionwise, over 1 hr. After an additional reflux period of 1.5 hr., the reaction mixture was filtered, the filtered cake washed well with boiling water and the combined filtrates cooled. There was obtained colorless crystals (3.0 g.) m.p. > 360°. The analytical sample was recrystallized from methanol–water, m.p. > 360° (Table I).

7-Chlorosulfonyl-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide.—3-Methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (Table I) (20.0 g.) was refluxed in chlorosulfonic acid (150 ml.) for 18 hr. The cooled reaction mixture was poured onto ice and the precipitated product collected by filtration, washed with water and air dried: crude yield 20.0 g. Recrystallization was effected from acetone–petroleum ether affording 11.0 g. of product, m.p. 338–340°. Further recrystallization from the same solvent mixture raised the melting point to 342–345°.

Anal. Calcd. for $C_8H_7ClN_2O_4S_2$: N, 9.51; S, 21.76. Found: N, 9.58; S, 21.99.

7-Dimethylsulfamoyl-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide.—7-Chlorosulfonyl-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (10.0 g.) was added portionwise to liquid dimethylamine (200 ml.). The excess of dimethylamine was evaporated, the residue dissolved in water, and the solution neutralized and allowed to stand at room temperature for several hours. The precipitated solid was collected by filtration, washed with water, air dried and recrystallized from acetone–hexane yielding product (5.0 g.), m.p. 269–270° (Table I).

6-Carbomethoxy-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide.—A solution of 6-carboxy-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (Table I) (1.0 g.) in methanol (50 ml.) containing concd. sulfuric acid (1 ml.) was refluxed for 5 hr., concentrated to *ca.* 10 ml. and chilled. Filtration gave crude product (1.0 g.) m.p. 269–273°. Recrystallization from methanol yielded 0.9 g., m.p. 272–274°. Another recrystallization from the same solvent gave the analytical sample, m.p. 273–275° (Table I).

4-Chloro-2-(1-ethoxyethylideneamino)-N-methylbenzenesulfonamide.—A mixture of 2-amino-4-chloro-N-methylbenzenesulfonamide (1.4 g.) and ethyl orthoacetate (10 ml.) was heated slowly with stirring to 145° in an open vessel. The reaction mixture was cooled, diluted with hexane and the solid which crystallized, collected: yield 1.2 g., m.p. 116–120°. Recrystallization from hexane gave a colorless solid, m.p. 121–123°.

Anal. Calcd. for $C_{11}H_{15}ClN_2O_3S$: C, 45.44; H, 5.20; N, 9.64; S, 11.03. Found: C, 45.64; H, 5.38; N, 10.19; S, 11.13.

6-Chloro-2,3-dimethyl-2H-1,2,4-benzothiadiazine 1,1-dioxide.—4-Chloro-2-(1-ethoxyethylideneamino)-N-methylbenzenesulfonamide[18] (2.8 g.) was heated gradually to 250° in an open vessel. The liquid solidified on cooling and on trituration with ether yielded 1.3 g. of a tan solid, m.p. 136–139°. On recrystallization from benzene–hexane the melting point was raised to 138–140° (Table I).

7-Chloro-3,4-dimethyl-4H-1,2,4-benzothiadiazine 1,1-dioxide.—Methyl iodide (4.65 g.) was added to a solution of 7-chloro-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (Table I) (5.0 g.) in ethanolic sodium ethoxide (prepared from sodium (0.625 g.) and ethanol, 125 ml.) and the mixture refluxed for 3.5 hr. On standing a solid separated which was collected by filtration, washed with water and air dried; yield, 1.1 g., m.p. 220–223°. Recrystallization from methanol–water afforded 0.95 g. of product, m.p. 232–234° (Table I).

3,4-Dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxides. (a) **3-Substituted Compounds.**—The substituted *o*-aminobenzenesulfonamide (0.01 mole) was refluxed in acetonitrile (25–50 ml.) with the appropriate aldehyde (0.10 mole) of 12–16 hr. The solvent and excess of aldehyde then were removed by evaporation on the steam bath and the residue crystallized.

(b) **3,3-Dimethyl Compounds.**—The substituted 2-aminobenzenesulfonamide (0.01 mole) was dissolved in acetone (50 ml.) and the solution warmed on the steam bath for 0.5 hr. Hexane was added and the solution concentrated and cooled to give the crystalline product. In the case of compound 33 an additional 5 days of reaction time at room temperature was required for formation of the product.

[18] Purification of the ethoxyethylideneamino compound is usually unnecessary prior to its use in this step. The corresponding N-ethyl- and N-isopropylbenzenesulfonamides were used without purification.

2-Benzylthionitrobenzenes.—These were prepared from *o*-chloronitrobenzenes by the procedure of Baker *et al.*[14]; see also Riegel, *et al.*,[15] Yields were usually in the range 60–90%.

The crude product obtained from 2,6-dichloronitrobenzene (12.0 g.) by this procedure was washed with cold ethanol, triturated with water and dried to give bright yellow crystals, 2.7 g., m.p. 82–84°. A sample was recrystallized from hexane to give pure 2,6-bis-benzylthionitrobenzene, m.p. 85–86°.

Anal. Calcd. for $C_{20}H_{17}NO_2S_2$: C, 65.47; H, 4.66; N, 3.81; S, 17.49. Found: C, 65.51; H, 4.95; N, 3.43; S, 17.62.

The mother liquor containing the ethanol wash was poured into ice-water and the mixture extracted with ether. The dried extracts were concentrated and chromatographed on Florisil (580 g.) packed in hexane. Elution with hexane gave some early fractions of colorless crystals and oils which contained some starting material and were not further investigated. Further elution with hexane gave a series of fractions containing the desired 6-chloro-2-benzylthionitrobenzene. These were combined and crystallized from ether–hexane to give material (4.2 g.), m.p. 65–67° and a second crop (0.2 g.), m.p. 57–63°. The analytical sample was crystallized from aqueous ethanol (Table III). Elution with 1% ether in hexane gave some additional bis-benzylthio compound, m.p. 82–85°, while increasing percentages of ether yielded more polar, colored materials which were not further investigated.

4-Benzylthio-3-nitroaniline.—To a mixture of benzyl mercaptan (6.2 g.) and water (20 ml.) was added sodium carbonate and a solution of 4-chloro-3-nitroaniline in ethanol (40 ml.). The mixture was stirred and refluxed for 5 hr., diluted with water and the red solid filtered off and washed with hexane. Recrystallization from benzene–hexane afforded a bright red solid (4.6 g.), m.p. 84–96°. Two additional recrystallizations from benzene–hexane gave product (2.0 g.), m.p. 119–120°. The analytical sample melted at 122–123.5° (Table III).

4-Benzylthio-3-nitroacetanilide.—A solution of 4-benzylthio-3-nitroaniline (1.3 g.), benzene (2 ml.) and acetic anhydride (0.5 g.) was refluxed for 10 min. On cooling, orange crystals (1.1 g.), m.p. 177–179° separated. Two polymorphic forms (confirmed by solution infrared spectra) could be isolated on crystallization from ethanol: one (yellow needles), m.p. 176°, 185–187° and the other (bright orange crystals), m.p. 176.5–178° (Table III).

2-Nitrobenzenesulfonamides.—The 2-benzylthionitrobenzenes were oxidatively cleaved with chlorine in aqueous acetic acid to give the sulfonyl chlorides, which then were treated with ammonia or an amine essentially according to the procedure of Baker, *et al.*[14] Yields (40–70%, using procedure modifications) were improved by the addition of a small volume of chloroform in the separation of the sulfonyl chloride from the aqueous phase, by keeping the sulfonyl chloride solution below 5° prior to its use in the next stage, and by the use of liquid ammonia and liquid amines.

Cleavage of 2-benzylthio-5-trifluoromethylnitrobenzene (Table III) (27.0 g.) and treatment of the product with liquid methylamine (150 ml.) afforded a solid product (14.7 g.), m.p. 74–77°. A sample recrystallized from ethanol–water melted at 76–78° and did not depress the melting point of an authentic sample of 2-methylamino-5-trifluoromethylnitrobenzene (see next paragraph).

2-Methylamino-5-trifluoromethylnitrobenzene.—2-Nitro-4-trifluoromethylchlorobenzene (10.0 g.) was added to liquid methylamine (150 ml.) and the excess of methylamine allowed to evaporate overnight. The residual orange solid was triturated with water and collected by filtration giving product (8.4 g.), m.p. 71–75°. After several recrystallizations from ethanol–water, an analytical sample was obtained, m.p. 76–78°.

Anal. Calcd. for $C_8H_7F_3N_2O_2$: C, 43.64; H, 3.20; N, 12.73. Found: C, 44.03; H, 3.38; N, 12.84.

2-Aminobenzenesulfonamides.—These were prepared from the 2-nitrobenzenesulfonamides by reduction with iron and ammonium chloride solution according to the procedure of Holdrege, *et al.*,[16] Yields were 70–90%.

5-Chloro-2-methylaminobenzenesulfonamide.—2,5-Dichlorobenzenesulfonamide (5.0 g.) and 40% aq. methylamine solution (100 ml.) were heated in an autoclave for 5 hr. at 200°. The solvent was evaporated, water added, the crude solid product collected by filtration, washed with water and air dried affording a reddish solid (3.1 g.). Crystallization of the crude product from methanol–water furnished a faintly yellowish crystalline solid, m.p. 140–145°. Recrystallization from the same solvent system gave product (1.2 g.), m.p. 147–149°. This was repeated to give an analytical sample, m.p. 148.5–150°.

Anal. Calcd. for $C_7H_9N_2SO_2Cl$: N, 12.70; Cl, 16.06. Found: N, 12.56; Cl, 15.95.

2-Acetylsulfamoyl-4-chloroacetanilide.—To 2-acetylsulfamoylacetanilide[17] (30.0 g.) in glacial acetic acid (200 ml.) was added a solution of chlorine (16.0 g.) in glacial acetic acid (250 ml.) and the reaction mixture allowed to stand at room temperature for 16 hr. The solid which separated was collected by filtration, washed with water and air dried, affording crystalline product (13.5 g.), m.p. 215–220°. Concentration of the filtrate yielded a second crop of product (1.35 g.), m.p. 215–220°. The two crops were combined and recrystallized from 80% ethanol giving product (10.8 g.), m.p. 230–231°. Further recrystallization from the same solvent system gave an analytical sample, m.p. 232–233°.

Anal. Calcd. for $C_{10}H_{11}ClN_2O_3S$: Cl, 12.20. Found: Cl, 12.06.

2-Amino-5-chlorobenzenesulfonamide.—2-Acetylsulfamoyl-4-chloroacetanilide (26.0 g.) and sodium hydroxide (36.0 g.) were refluxed in a mixture of water (60 ml.) and methanol (60 ml.) for 72 hr. The cooled reaction mixture was diluted with water (300 ml.) and then acidified with concd. hydrochloric acid. After cooling, filtration gave product (14.9 g.), m.p. 148–150°. Recrystallization from ethanol–water raised the melting point to 152–153° (Table V).

7-Chloro-3-methyl-2H-1,2,4-benzothiadiazine 1,1-Dioxide.—2-Acetylsulfamoyl-4-chloroacetanilide (19.0 g.) was heated at 280–290° (bath temperature) for 10 min. The residue was recrystallized from ethanol–water giving product (9.0 g.), m.p. 320–322°. Two more recrystallizations from the same solvent system raised the melting point to 330–331° (Table I).

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(16) C. T. Holdrege, R. R. Babel, and L. C. Cheney, *ibid.*, **81**, 4807 (1959).

(17) J. G. Topliss, *J. Org. Chem.*, **27**, 654 (1962).