ment of the drug molecule could occur, with a major contribution from hydrophobic bonding, at proximal sites with consequent steric blocking of the normal Ca^{2+} site either directly or perhaps following an induced receptor perturbation.

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π-Substituent Constants for the 2*H*-1,2,4-Benzothiadiazine 1,1-Dioxide System

John G. Topliss* and Milton D. Yudis

Departments of Medicinal and Physical Analytical Chemistry, Schering Corporation, Bloomfield, New Jersey 07003.
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Partition coefficients for a series of substituted 2*H*-1,2,4-benzothiadiazine 1,1-dioxides were measured in the system *n*-octanol-H_2O from which π values for a variety of substituents at different positions in the heterocyclic nucleus were calculated. There were marked variations in π for the same substituent depending on its position of attachment to the nucleus. Low values were obtained for the 3,5 and 8 positions due to the proximity of polar atoms. The additivity of π values in some polysubstituted compounds was examined.

In recent years the value of the substituent constant approach in structure-activity correlations has been amply demonstrated. It has been shown that π, a free energy related constant, derived from partition coefficient data, which relate to penetration and hydrophobic bonding effects, is particularly useful in such work.[1] The π value for a substituent X is defined by the relationship $\pi_X = \log P_X - \log P_H$, where P_H is the partition coefficient of the parent nucleus and P_X that of an X-substituted derivative.[2] As in the case of the analogous Hammet σ constants, π values are additive except where strong group interactions are present.

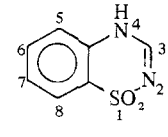
In connection with structure-activity correlations using the substituent constant approach in a series of 2*H*-1,2,4-benzothiadiazine 1,1-dioxide† antihypertensive agents,[3] we were faced with the problem of obtaining suitable π values for substituents in various positions in the nucleus. Previous work[4,5] on π values did not utilize heterocyclic systems as the parent molecule and did not appear therefore, to offer an adequate basis for selection in this case. Accordingly, it was necessary to obtain π values for substituents in the 2*H*-1,2,4-benzothiadiazine 1,1-dioxide series directly from partition coefficient measurements of the appropriate compounds.

Method. Partition coefficients, between *n*-octanol and water, of a series of substituted 2*H*-1,2,4-benzothiadiazine 1,1-dioxides were measured (Table I) from which π values for a variety of substituents at different positions in the nucleus were calculated (Table III) using the relationship $\pi_X = \log P_X - \log P_H$. In addition to the parent 2*H*-1,2,4-benzothiadiazine 1,1-dioxide (Table I, **1**), the 3-methyl, 6-chloro, 7-chloro, and 7-chloro-3-methyl compounds (Table I, **2**, **8**, **19**, and **20**) were required to provide reference values ($\log P_H$) for the determination of some π_X values. Where a π value for a substituent could be computed in more than one way from different reference compounds with comparable accuracy an averaged value was used. In these cases the individual values before averaging, were usually very similar. Reference (parent) compounds used in the determination of individual π values are noted in Table II.

†These compounds are designated 2*H* consistent with Chemical Abstracts practice although in solution they probably exist as the 4*H* tautomers and are depicted as such in structural formulas in this paper (see ref 5).

Results and Discussion

Large differences in π values for the same substituent at different positions in the nucleus were found. In the benzenoid portion of the nucleus (I) highest π values were observed for the 6 and 7 positions; these values were close to those reported by Fujita, *et al.*,[3] for the meta and para positions in the phenol system. There is a sharp drop in the π values at the 5 and 8 positions reflecting the proximity of the polar NH and SO_2 functions, respectively, with attendant possibilities for hydrogen bonding to water molecules. This drop is more pronounced, particularly at the 8 position, than that experienced in the change from the meta or para to the ortho position in the phenol system. A good illustration is afforded by comparing π values for the Cl function at the 5,6,7, and 8 positions in the benzothiadiazine system and the ortho, meta, and para positions in the phenol system (Chart I).



I

Chart I. π Values for Chloro Substituents

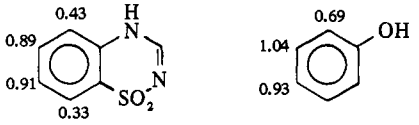
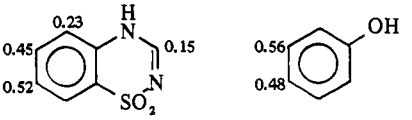


Chart II. π Values for Methyl Substituents



At the 3 position in the benzothiadiazine system there is a very marked effect from the two adjacent nitrogen atoms at positions 2 and 4. For the 3-methyl substituent the π value is 0.15 compared to 0.52 for the 7-methyl substituent and 0.52 for a normal aliphatic methyl group[4] (Chart II). Apparently, water aggregates clustering around the polar functions at the proximal 2 and 4 positions effectively negate most of the usual lipophilic contribution of a methyl group. The effect is restricted to groups or portions of groups immediately adjacent to the 3 position. Thus, the 3-ethyl substituent has a π value of 0.57, the 3-*n*-propyl group a π value of 1.03, and the 3-*n*-butyl group a π value

Table I. Logarithm of the Octanol-Water Partition Coefficients of Substituted 2*H*-1,2,4-Benzothiadiazine 1,1-Dioxides

Number	Compd	Formula	Anal.	Recryst solvent	Mp, °C	Method[a]	Log P [b]
1[c]	Parent nucleus	$C_7H_6N_2O_2S$					0.16
2[c]	3-CH_3	$C_8H_8N_2O_2S$					0.29
3[d]	5-Cl, 3-CH_3	$C_8H_7ClN_2O_2S$					0.72
4	5-Br, 7-Cl, 3-CH_3	$C_8H_6BrClN_2O_2S$	C, H, N	MeOH	284-285	A	1.65
5	7-Cl, 5-I, 3-CH_3	$C_8H_6ClIN_2O_2S$	C, H, N, S	MeOH	320-321	A	1.81
6	3,5-di-CH_3	$C_9H_{10}N_2O_2S$	C, H, N, S	MeOH-H_2O	274-275	E	0.52
7[e]	7-Cl, 3-CH_3, 5-NO_2	$C_8H_6ClN_3O_4S$					0.85
8[d]	6-Cl	$C_7H_5ClN_2O_2S$					1.01
9[d]	6-Cl, 3-CH_3	$C_8H_7ClN_2O_2S$					1.21
10[d]	6-Br, 3-CH_3	$C_8H_7BrN_2O_2S$					1.37
11[d]	3-CH_3, 6-CF_3	$C_9H_7F_3N_2O_2S$					1.59
12[d]	3,6-di-CH_3	$C_9H_{10}N_2O_2S$					0.74
13	6-CH_3CH_2, 3-CH_3	$C_{10}H_{12}N_2O_2S$	N, S	MeOH	236-237	A	1.25
14[d]	6-CH_3O, 3-CH_3	$C_9H_{10}N_2O_3S$					0.56
15	7-Cl, 3-CH_3, 6NO_2	$C_8H_6ClN_3O_4S$	Cl, S	MeOH-Me_2CO-H_2O	293-294	A	1.42
16	6-NH_2, 7-Cl, 3-CH_3	$C_8H_8ClN_3O_2S$	Cl, N[f]	MeOH-H_2O	329-330		0.63
17	6-NHAc, 7-Cl, 3-CH_3	$C_{10}H_{10}ClN_3O_3S$	Cl, N	MeOH-Me_2CO	325-326	E	0.53
18	7-F, 3-CH_3	$C_8H_7FN_2O_2S$	F, N	MeOH-H_2O	280-282	C	0.62
19[d]	7-Cl	$C_7H_5ClN_2O_2S$					1.07
20[d]	7-Cl, 3-CH_3	$C_8H_7ClN_2O_2S$					1.20
21[d]	7-Br, 3-CH_3	$C_8H_7BrN_2O_2S$					1.37
22	7-I, 3-CH_3	$C_8H_7IN_2O_2S$	I, S	MeOH-H_2O	331-332	C	1.61
23	3-CH_3, 7-CF_3	$C_9H_7F_3N_2O_2S$	N, S, F	MeOH	305-307	C	1.51
24	3,7-di-CH_3	$C_9H_{10}N_2O_2S$	C, H, N, S	Me_2CO	298-300	A	0.81
25[d]	3-CH_3, 7-NO_2	$C_8H_7N_3O_4S$					0.65
26[g]	6-Cl, 7-SO_2NH_2	$C_7H_6ClN_3O_4S_2$					−0.24
27[d]	7-$SO_2N(CH_3)_2$, 3-CH_3	$C_{10}H_{13}N_3O_4S_2$					0.32
28[d]	8-Cl, 3-CH_3	$C_8H_7ClN_2O_2S$					0.62
29[d]	6-Cl, 3-C_2H_5	$C_9H_9ClN_2O_2S$					1.61
30[d]	7-Cl, 3-C_2H_5	$C_9H_9ClN_2O_2S$					1.62
31[d]	6-Cl, 3-*n*-C_3H_7	$C_{10}H_{11}ClN_2O_2S$					2.04
32	6-Cl, 3-*i*-C_3H_7	$C_{10}H_{11}ClN_2O_2S$	Cl, N	EtOH-H_2O	285-287	A	2.00
33[h]	6-Cl, 3-cyclopropyl	$C_{10}H_9ClN_2O_2S$					1.98
34[h]	3-*n*-C_4H_9, 7-Cl	$C_{11}H_{13}ClN_2O_2S$					2.52
35[h]	3-*i*-C_4H_9, 6-Cl	$C_{11}H_{13}ClN_2O_2S$					2.35
36[h]	3-*sec*-C_4H_9, 7-Cl	$C_{11}H_{13}ClN_2O_2S$					2.47
37[h]	3-*tert*-C_4H_9, 7-Cl	$C_{11}H_{13}ClN_2O_2S$					2.40
38[h]	7-Cl, 3-cyclobutyl	$C_{11}H_{11}ClN_2O_2S$					2.24
39	3-$(C_2H_5)_2CH$	$C_{12}H_{16}N_2O_2S$	C, H, N, S	DMF-H_2O	>300	B	1.88
40[h]	7-Cl, 3-$(CH_3)_3CCH_2$	$C_{12}H_{15}ClN_2O_2S$					2.71
41	3-Cyclopentyl	$C_{12}H_{14}N_2O_2S$	N, S	MeOH-H_2O	227-229	B	1.83
42	3-Cyclohexyl	$C_{13}H_{16}N_2O_2S$	C, H, N, S	MeOH	280	B	2.20
43[h]	6-Cl, 3-CH_3CH=CH	$C_{10}H_9ClN_2O_2S$					1.96
44	3-Δ′-Cyclopentenyl	$C_{12}H_{12}N_2O_2S$	C, H, N, S	Me_2CO	>300	D	1.69
45	3-Δ^3-Cyclopentenyl	$C_{12}H_{12}N_2O_2S$	N, S	MeOH-H_2O	273-275	B	1.53
46	3-Δ^3-Cyclohexenyl	$C_{13}H_{14}N_2O_2S$	C, H, N, S	MeOH-H_2O	245-246	B	2.05
47	3-(5-Norbornen-2-yl)	$C_{14}H_{14}N_2O_2S$	C, H, N, S	MeOH-H_2O	255-256	B	2.06
48	3-C_6H_5	$C_{13}H_{10}N_2O_2S$	C, H, N, S	DMF-H_2O	307-308	B	1.78
49	3-$C_6H_5CH_2$	$C_{14}H_{12}N_2O_2S$	C, H, N, S	MeOH	227	B	1.89
50	3-(2-Thienyl)	$C_{11}H_8N_2O_2S_2$	C, H, N, S	MeOH	>310	D	1.68
51	3-(2-Furyl)	$C_{11}H_8N_2O_3S$	C, H, N	MeOH-H_2O	235	D	1.06
52[h]	6-Cl, 3-CH_2Cl	$C_8H_6Cl_2N_2O_2S$					1.68
53[h]	6-Cl, 3-$CHCl_2$	$C_8H_5Cl_3N_2O_2S$					1.81
54[h]	6-Cl, 3-CF_3	$C_8H_4ClF_3N_2O_2S$					1.65
55[i]	6-Cl, 3-NH_2	$C_7H_6ClN_3O_2S$					0.91
56[h]	6-Cl, 3-CH_3OCH_2	$C_9H_9ClN_2O_3S$					1.12
57	6-Cl, 3-$C_2H_5SCH_2$	$C_{10}H_{11}ClN_2O_2S$	N	EtOH-H_2O	179-181	E	2.26

[a] See Experimental Section. [b] For method of determination see Experimental Section. [c] Parke and Williams.[15] [d] Ref 7. [e] Raffa, *et al.*[16] [f] Cl: calcd, 14.43; found, 13.44. N: calcd, 17.10; found, 15.68. [g] Novello and Sprague.[17] [h] Ref 8. [i] Topliss and Konzelman.[18]

Table II. π-Substituent Constants for the 2*H*-1,2,4-Benzothiadiazine 1,1-Dioxide Systems

Substituent	π	Reference compd[a]	Substituent	π	Reference compd[a]
H	0.00		3-*n*-C_3H_7	1.03	C
5-Cl	0.43	B	3-*i*-C_3H_7	0.99	C
5-Br	0.45	E	3-Cyclopropyl	0.97	C
5-I	0.61	E	3-*n*-C_4H_9	1.45	D
5-CH_3	0.23	B	3-*i*-C_4H_9	1.34	C
5-NO_2	−0.35	E	3-*sec*-C_4H_9	1.40	D
6-Cl	0.89	A, B	3-*tert*-C_4H_9	1.33	D
6-Br	1.08	B	3-Cyclobutyl	1.26	D
6-CF_3	1.30	B	3-$(C_2H_5)_2CH$	1.72	A
6-CH_3	0.45	B	3-$(CH_3)_3CCH_2$	1.64	D
6-CH_3CH_2	0.96	B	3-Cyclopentyl	1.67	A
6-OCH_3	0.27	B	3-Cyclohexyl	2.04	A
6-NO_2	0.22	E	3-CH_3-CH=CH	0.95	C
6-NH_2	−0.57	E	3-Δ^1-Cyclopentenyl	1.53	A
6-NHAc	−0.67	E	3-Δ^3-Cyclopentenyl	1.37	A
7-F	0.33	B	3-Δ^3-Cyclohexenyl	1.89	A
7-Cl	0.91	A, B	3-(5-Norbornen-2-yl)	1.90	A
7-Br	1.08	B	3-C_6H_5	1.62	A
7-I	1.32	B	3-$C_6H_5CH_2$	1.73	A
7-CF_3	1.22	B	3-(2-Thienyl)	1.52	A
7-CH_3	0.52	B	3-(2-Furyl)	0.90	A
7-NO_2	0.36	B	3-CH_2Cl	0.67	C
7-SO_2NH_2	−1.25	C	3-$CHCl_2$	0.80	C
7-$SO_2N(CH_3)_2$	0.03	B	3-CF_3	0.64	C
8-Cl	0.35	B	3-NH_2	−0.16	C
3-CH_3	0.15	A, C, D	3-CH_3OCH_2	0.11	C
3-C_2H_5	0.57	C, D	3-$C_2H_5SCH_2$	1.25	C

[a] A = Table I, **1**; B = Table I, **2**; C = Table I, **8**; D = Table I, **19**; E = Table I, **20**.

of 1.45, reflecting successive incremental π values of 0.42, 0.46, and 0.42, respectively, for each CH_2 group added to the 3-methyl substituent.

Since it was possible to measure with reasonable accuracy the partition coefficients of a number of benzothiadiazines with multiple substituents we were able to check empirically the additivity of π values for polysubstituted compounds. Table III lists 11 such compounds whose experimental log *P* values have accuracy limits ranging from ±0.01 for compounds with lower partition coefficients to ±0.05 for compounds with higher partition coefficients. Although there are no sizable deviations from additivity in this series there does appear to be some tendency for experimental values to slightly exceed calculated values.

Experimental Section‡

Partition Coefficients. These were detd in the system *n*-octanol–water and defined as the ratio of the solute concn in the organic phase to the solute concn in the aqueous phase. In the few cases where there was a significant effect due to the acidity of the compd, the partition coefficient was calcd as $P = (C_{octanol}/C_{H_2O})\cdot(1 - \alpha)$ where α is the degree of dissocn.

The *n*-octanol (Mathieson, Coleman and Bell, mp 16–17°) was washed thoroughly with distd water before use in the distribution studies. Only a trace of C_6H_6 (<0.1 mg/ml) and no acidic components (<0.1 mole % octanoic acid) were detected by uv spectral analysis and acid titer, respectively, in either the washed or untreated octanol. A weighed quantity of solute, usually from 10 to 20 mg, was dissolved in 50 ml of *n*-octanol, previously satd with water, with gentle warming (to 65°) if required. The octanol soln was then shaken thoroughly with a known volume of distd water (50–200 ml) previously satd with octanol and the two-phase system was equilibriated in a separatory funnel overnight at const temp (24 ± 1°). The concn of the benzothiadiazine in each of the phases was detd by uv spectral analysis using a Cary Model 14 spectrophotometer. Appropriate dilns with MeOH were made for spectral analysis as required from middle portions of each of the phases and run against a blank soln of the same solvent composition. Absorbance was measured in the range 0.2–1.0. Reference absorptivity data were obtained in MeOH soln and in MeOH–H_2O soln for comparison with the octanol and aqueous phases, respectively. In most cases duplicate detns were made and the reported constants are the average of these results.

Material balances were calcd based on the total quantity of solute found in the sum of the two phases and compared with the initial quantity of solute added. The average recovery for the entire set of detns was 98.8%. If the recovery was less than 95% or more than 103% the detn was repeated. In a few cases in which limited solubility was encountered, a modified dissolution procedure was used. Either the solute was dissolved in the aqueous phase or a satd octanol soln was prepd, dild with addnl octanol, and then equilibrated with water. The concn of the satd soln was detd by uv analysis of an aliquot taken from it.

Preparation of Compounds. 2*H*-1,2,4-Benzothiadiazine 1,1-Dioxides (see Tables I and III). A. Condensation of a substituted *o*-aminobenzenesulfonamide with the appropriate ortho ester[6] gave the appropriate compd.

B. Base-catalyzed cyclization of a substituted *o*-(acylamino)-benzenesulfonamide with conc NH_4OH soln[7] gave the appropriate compd.

C. To a stirred soln of a substituted aniline (1 mole) in *o*-dichlorobenzene (10 ml/g), concd H_2SO_4 (1.1 moles) was added dropwise over a period of 10 min. The reaction mixt was refluxed for 1.5 hr during which time *ca.* 0.25 of the solvent was removed *via* a Dean–Stark separator. After cooling the resulting sulfonic acid was collected by filtration, washed with $CHCl_3$, dried, mixed with anhyd NaAc (1.01 mole ratio based on actual yield of sulfonic acid), and refluxed in Ac_2O (2 ml/g of sulfonic acid) for 2 hr. The cooled reaction mixt was poured into a large vol of cold dry Et_2O and stored in the refrigerator overnight. The solid product (*o*-acetamidobenzenesulfonic acid Na salt) was pulverized to a fine powder and added portionwise to a stirred suspension of PCl_5 (2 mole ratio) in CH_2Cl_2 (3 ml/g of Na salt) at 30–40°. After 2 hr the reaction mixture was poured onto ice and stirred for 20 min. The organic layer was sepd, the aqueous layer extd with CH_2Cl_2, and the combined exts washed with a small vol of water. The CH_2Cl_2 soln was mixed with an equal vol of concd NH_4OH soln, heated on the steam bath until the vol had been reduced *ca.* 75%, and then cooled. The resulting benzothiadiazine was filtered off, washed with water, dried, and recrystd.

D. Fusion of a substituted *o*-aminobenzenesulfonamide and an acid RCO_2H[8] gave the appropriate compd.

E. See individual descriptions which follow.

3,5-Dimethyl-2*H*-1,2,4-benzothiadiazine 1,1-Dioxide (Table I,

‡Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

Table III. Calculated and Observed Octanol-Water Partition Coefficients of Polysubstituted 2*H*-1,2,4-Benzothiadiazine 1,1-Dioxides

Number	Compd	Formula	Anal.	Recryst solvent	Mp, °C	Method[a]	Log P_{obsd}[b]	Log P_{calcd}	Δ log P
1[c]	6,7-Di-Cl, 3-CH_3	$C_8H_6Cl_2N_2O_2S$					1.96	1.92	0.04
2[c]	7,8-Di-Cl, 3-CH_3	$C_8H_6Cl_2N_2O_2S$					1.50	1.37	0.13
3[c]	6,8-Di-Cl, 3-CH_3	$C_8H_6Cl_2N_2O_2S$					1.54	1.34	0.20
4[c]	5,7-Di-Cl, 3-CH_3	$C_8H_6Cl_2N_2O_2S$					1.52	1.47	0.05
5[c]	7-Cl, 3-CH_3, 6-CF_3	$C_9H_6F_3ClN_2O_2S$					2.34	2.24	0.10
6[c]	7-Cl, 6-CH_3O, 3-CH_3	$C_9H_9ClN_2O_3S$					1.30	1.31	−0.01
7	7-Cl, 3-CH_3, 6-NO_2	$C_8H_6ClN_3O_4S$	Cl, S	MeOH-H_2O	293–294	A	1.47	1.28	0.19
8	7-Cl,3,5-di-CH_3	$C_9H_9ClN_2O_2S$	N, S	MeOH-H_2O	319–320	C	1.44	1.29	0.15
9	6,8-Di-Cl, 3-CH_2CH_3	$C_9H_8Cl_2N_2O_2S$	N, S	MeOH-Me_2CO	335–336	A	1.94	1.81	0.13
10	6-Cl, 3-*i*-C_3H_7, 7-CH_3	$C_{11}H_{13}ClN_2O_2S$		MeOH-H_2O	207–209	B	2.42	2.40	0.02
11[c]	3-CH_3,6,7,8-trichloro	$C_8H_5Cl_3N_2O_2S$					2.26	2.25	0.01

[a] See Experimental Section. [b] For method of determination see Experimental Section. [c] Ref 8.

3). 7-Chloro-3,5-dimethyl-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (Table III, 8) (1.3 g) was dissolved in 5% NaOH soln and hydrogenated over a 5% Pd/C catalyst (1.3 g) at room temp and atmospheric pressure. The catalyst was removed by filtration, the soln acidified, and the solid product collected, dried, and recrystd.

6-Amino-7-chloro-3-methyl-2*H*-1,2,4-benzothiadiazine 1,1-Dioxide (Table I, 16). 7-Chloro-3-methyl-6-nitro-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (Table III, 7) was reduced with Fe filings in a medium consisting of NH_4Cl-H_2O-MeOH according to a literature procedure.[9]

6-Acetamido-7-chloro-3-methyl-2*H*-1,2,4-benzothiadiazine 1,1-Dioxide (Table I, 17). Compd **16**, Table I (1.0 g), was heated on the steam bath with Ac_2O (7 ml) for 45 min, and the reaction mixt was refrigerated overnight. The solid product was filtered off and recrystd.

6-Chloro-3-ethylthiomethyl-2*H*-1,2,4-benzothiadiazine 1,1-Dioxide (Table I, 57). To a stirred suspension of 6-chloro-3-chloromethyl-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (Table I, **52**) (6.0 g) in MeOH (75 ml) containing EtSH (6.0 g) and cooled to 5° was added a soln of KOH (6.0 g) in EtOH (100 ml). The solvent was evapd, and the residue was dissolved in ice water and acidified with concd HCl. The resulting crude product was collected by filtration, washed with water, dried, and recrystd affording pure product (4.7 g).

***o*-(Acylamino)benzenesulfonamides.** These were prepd[8] by reaction of the appropriate acid chloride with the substituted *o*-aminobenzenesulfonamide in refluxing THF containing a small amt of pyridine (Table I, **39, 41, 42, 45–49**), or refluxing benzene (Table III, **10**), or refluxing xylene (Table III, **11**). Reaction time was 3–4 hr. The compds were utilized in the cyclization step without purification.

***o*-Aminobenzenesulfonamides.** The following were prepd according to procedures in the literature: 2-amino-3-bromo-5-chlorobenzenesulfonamide,[10] 2-amino-4-chlorobenzenesulfonamide,[11] 2-aminobenzenesulfonamide,[12] 2-amino-4,6-dichlorobenzenesulfonamide,[10] 2-amino-4-chloro-5-methylbenzenesulfonamide,[13] and 2-amino-4-chloro-3,5-dibromobenzenesulfonamide.[10]

2-Amino-5-chloro-3-iodobenzenesulfonamide. A soln of ICl (1.67 g) in AcOH (5 ml) was added slowly to a soln of 2-amino-5-chlorobenzenesulfonamide[6] (2.0 g) in DMF (15 ml) at room temp. The reaction mixt was allowed to stand overnight and then poured into water (100 ml). The solid which pptd was filtered off, washed with water, and crystd from MeOH, mp 184–185°. *Anal.* ($C_6H_6ClIN_2O_2S$) C, H, N, S.

2-Amino-4-ethylbenzenesulfonamide. 2-Chloro-5-ethylnitrobenzene[14] was converted into 2-amino-4-ethylbenzenesulfonamide according to a general route previously described.[6] The crude product was utilized directly in the prepn of compd **13**, Table I.

2-Amino-5-chloro-4-nitrobenzenesulfonamide. 4-Chloro-3-nitroaniline (17.2 g) was added, portionwise, to a soln of PCl_5 (37.5 g) in $ClSO_3H$ (65 ml) at a temp of 15–20°. The reaction mixt was heated at 90° for 15 min and then at 115–120° for 45 min, cooled, and poured onto ice. The product was extd with Et_2O, the soln dried over Na_2SO_4, and NH_3 bubbled in to the saturation point. After decanting from solid material the Et_2O was evapd and the residue crystd from EtOH-H_2O. The resulting material was dissolved in dil NaOH and filtered, and the filtrate acidified. The pptd solid was filtered off, washed with water, dried, and crystd from EtOH, mp 238–240°. *Anal.* ($C_6H_6ClN_3O_4S$) N, S.

2-Amino-5-methylbenzenesulfonamide. 2-Amino-4-chloro-5-methylbenzenesulfonamide[12] (10 g) was dissolved in 10% NaOH soln (200 ml) and hydrogenated over 5% Pd/C (1 g) at 50° in a Parr apparatus overnight. The catalyst was filtered off, the filtrate acidified with HCl, and the pptd solid collected by filtration, washed with water, and air-dried. The resulting solid was then extd with hot Et_2O and filtered, and the exts were evapd to dryness. The residue consisted of crude product, 5.5 g, mp 114–118°, which was converted to the benzothiadiazine (Table I, **24**) without further purification.

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