treated with 9 ml. of 30% hydrogen peroxide at 75–80° and allowed to cool to room temperature (2 hr.). The mixture was cooled and the crystalline precipitate collected, washed with water, and recrystallized from alcohol-water; yield, 12 g. (42%) of colorless needles.

5-Chloro-2,4-disulfamyl-6-iodoaniline[18] (No. 15, Table I). A solution of iodine monochloride (21.1 g., 0.13 mole) in concd. hydrochloric acid (50 ml.) was added dropwise over 30 min. to a solution of 5-chloro-2,4-disulfamylaniline (25.3 g., 0.089 mole) in concd. hydrochloric acid (350 ml.) maintained at 98°. After stirring at 98° for 24 hr., the mixture was cooled to 5° and the product collected on a sintered glass funnel, washed with water, and dried; yield, 27 g. (82%), m.p. 308–309° dec. (corr.). An analytical sample prepared by recrystallization from ethanol-water showed no change in melting point.

(18) We are indebted to Dr. E. J. Cragoe for this preparation.

WEST POINT, PA.

[CONTRIBUTION FROM THE MERCK SHARP AND DOHME RESEARCH LABORATORIES DIVISION OF MERCK AND COMPANY, INC.]

Diuretics: 1,2,4-Benzothiadiazine-1,1-dioxides

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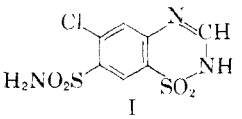
Ring closure of aniline-2,4-disulfonamides with acylating agents, aldehydes, or urea to give sulfamylbenzothiadiazine-1,1-dioxide derivatives is described. Sulfamylbenzothiadiazine-1,1-dioxides promote excretion of sodium chloride in animals and man and constitute a novel class of orally effective diuretic agents. Several aspects of the chemistry of this class of compounds are reported in detail.

6-Chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide[1] (I) is an orally effective diuretic and is

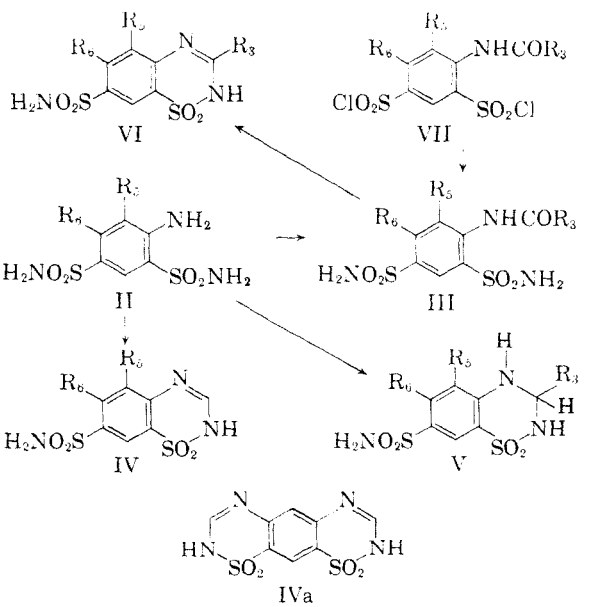


I

being employed currently in therapy for conditions associated with fluid and electrolyte retention such as congestive heart failure and hypertension. Preliminary communications have reported some of the chemistry and biological properties of this compound and some closely related derivatives.[2,3,4] The present paper reports on these more fully and describes the extension of this series of compounds.

1,2,4-Benzothiadiazine-1,1-dioxides as a class have been known since 1902[5–9] and a number of derivatives have been prepared from the appropriately substituted orthanilamide by the general procedures involving ring closure of the orthanilamide by reaction with acylating agents, aldehydes or urea. However, no compound of this class has been reported where a sulfamyl group is present. The only biologic property previously noted for any 1,2,4-benzothiadiazine-1,1-dioxide is the sweet taste of 3-oxodihydro-1,2,4-benzothiadiazine-1,1-dioxide.[6,7,9]

In our studies, compounds of greatest interest have the general structures IV, V and VI where a sulfamyl group occupies the 7 position. Benzothiadiazine-1,1-dioxides of types IV and VI and related isomers having the sulfamyl group in the 5 or 6 position as well as representative reference compounds lacking a sulfamyl group are recorded in Table I.



(1) The generic name of chlorothiazide has been given to this compound and Diuril is the trademark of Merck and Co., Inc., for chlorothiazide.

(2) F. C. Novello and J. M. Sprague, *J. Am. Chem. Soc.*, 79, 2028 (1957).

(3) F. C. Novello and J. M. Sprague, 132nd Meeting of the American Chemical Society, New York, N. Y., September 8–13, 1957; abstracts, pp. 32-40.

(4) J. M. Sprague, *Ann. N. Y. Acad. Sci.* 71, 328 (1958).

(5) Ekbom, *Bih. Svensk Vetenskakad Handl.*, 27, (II), 3 (1902).

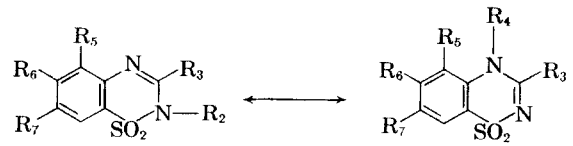
(6) E. Schrader, *J. prakt. Chem.* (2) 95, 392 (1917).

(7) D. V. Parke and R. T. Williams, *J. Chem. Soc.*, 1760 (1950).

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

(9) L. Raffa, *Farmaco (Pavia), Ed. sci.*, 9, 661 (1954); E. Grana and L. Lilla, *Ed. Sci.*, 12, 65 (1957).

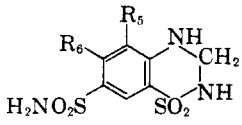
TABLE I.



No.	R_2	R_3	R_4	R_5	R_6	R_7	Recrystn. Solvent[a]	M.P.°	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	H	H	—	H	H	SO_2NH_2	A	319–320	$C_7H_7N_3O_4S_2$	32.18	32.19	2.70	2.94	16.08	15.91
2	H	H	—	H	F	SO_2NH_2	A	304–305	$C_7H_6FN_3O_4S_2$	30.10	30.14	2.17	2.50	15.05	14.88
3	H	H	—	H	Cl	SO_2NH_2	A	342.5–343	$C_7H_6ClN_3O_4S_2$	28.43	28.65	2.05	2.23	14.21	14.11
4	H	H	—	H	Br	SO_2NH_2	B	347–349	$C_7H_6BrN_3O_4S_2$	24.71	24.91	1.78	1.93	12.35	12.24
5	H	H	—	H	CF_3	SO_2NH_2	C	294–295	$C_8H_6F_3N_3O_4S_2$	29.18	28.95	1.84	2.24	12.76	12.80
6	H	H	—	H	CH_3	SO_2NH_2	D	344–345	$C_8H_9N_3O_4S_2$	34.90	35.05	3.30	3.32	15.26	15.17
7	H	H	—	H	OCH_3	SO_2NH_2	A	305–307	$C_8H_9N_3O_5S_2$	32.98	33.22	3.11	3.03	14.43	14.42
8	H	H	—	H	NO_2	SO_2NH_2	A	338–339	$C_7H_6N_4O_6S_2$	27.45	27.73	1.98	2.28	18.30	18.17
9[b]	H	H	—	H	NH_2	SO_2NH_2	A	323–324	$C_7H_8N_4O_4S_2$	30.43	30.62	2.92	3.16	20.28	20.16
10	CH_3	H	—	H	Cl	SO_2NH_2	E	217–220	$C_8H_8ClN_3O_4S_2$	31.02	30.98	2.60	2.74	13.57	13.41
11	H	CH_3	—	H	Cl	SO_2NH_2	F	332	$C_8H_8ClN_3O_4S_2$	31.02	31.27	2.60	2.53	13.57	13.50
12	H	*n*-C_3H_7	—	H	Cl	SO_2NH_2	A	305–307	$C_{10}H_{12}ClN_3O_4S_2$	35.55	35.89	3.58	3.56	12.44	12.43
13	H	*n*-C_5H_{11}	—	H	Cl	SO_2NH_2	A	269–270	$C_{12}H_{16}ClN_3O_4S_2$	39.39	39.21	4.41	4.70	11.30	11.33
14	H	$ClCH_2$	—	H	Cl	SO_2NH_2	A	323–326	$C_8H_7Cl_2N_3O_4S_2$	27.91	28.45	2.05	2.28	12.21	12.23
15	H	C_6H_5	—	H	Cl	SO_2NH_2	B	>350	$C_{13}H_{10}ClN_3O_4S_2$	41.99	42.64	2.71	2.93	11.30	11.36
16	H	*o*-ClC_6H_4	—	H	Cl	SO_2NH_2	A	>330	$C_{13}H_9Cl_2N_3O_4S_2$	38.43	38.62	2.23	2.39	10.34	10.33
17	H	*p*-ClC_6H_4	—	H	Cl	SO_2NH_2	A	>350	$C_{13}H_9Cl_2N_3O_4S_2$	38.43	38.76	2.23	2.36	10.34	10.35
18	—	H	CH_3	H	Cl	SO_2NH_2	G	325–326	$C_8H_8ClN_3O_4S_2$	31.02	31.24	2.60	2.72	13.57	13.49
19	—	H	Allyl	H	Cl	SO_2NH_2	A	257.5–258.5	$C_{10}H_{10}ClN_3O_4S_2$	35.77	35.79	3.00	3.08	12.51	12.48
20	—	CH_3	CH_3	H	H	SO_2NH_2	H	258–260	$C_9H_{11}N_3O_4S_2$	37.36	37.43	3.83	3.86	14.52	14.50
21	H	H	—	Cl	H	SO_2NH_2	A	276.5–277.5	$C_7H_6ClN_3O_4S_2$	28.43	28.64	2.05	2.25	14.21	14.11
22	H	H	—	Cl	Cl	SO_2NH_2	A	355–356	$C_7H_5Cl_2N_3O_4S_2$	25.46	25.88	1.53	1.61	12.72	12.74
23[c]	H	H	—	I	Cl	SO_2NH_2	B	376–377[d]	$C_7H_5ClIN_3O_4S_2$	19.94	20.40	1.20	1.24	9.97	9.85
24	CH_3	H	—	H	Cl	SO_2NHCH_3	F	219–221	$C_9H_{10}ClN_3O_4S_2$	33.38	33.69	3.11	3.25	12.98	13.01
25	*p*-ClC_6H_4	H	—	H	Cl	$SO_2NHC_6H_4Cl$-*p*	I	247–249	$C_{19}H_{12}Cl_3N_3O_4S_2$	44.15	44.17	2.34	2.55	8.13	8.11
26	H	H	—	H	Cl	$SO_2N(CH_3)_2$	A	265–267	$C_9H_{10}ClN_3O_4S_2$	33.39	33.09	3.11	3.15	12.98	12.85
27	H	H	—	SO_2NH_2	H	H	J	249–250	$C_7H_7N_3O_4S_2$	32.18	32.48	2.70	2.79	16.08	15.96
28	H	H	—	SO_2NH_2	H	Br	K	291–292	$C_7H_6BrN_3O_4S_2$	24.71	24.58	1.78	1.92	12.35	12.35
29	H	H	—	SO_2NH_2	H	SO_2NH_2	A	316–318	$C_7H_8N_4O_6S_3$	24.70	24.89	2.37	2.58	16.46	16.43
30	H	H	—	H	SO_2NH_2	H	A	309–312	$C_7H_7N_3O_4S_2$	32.18	32.44	2.70	2.75	16.08	16.08
31	H	H	—	H	SO_2NH_2	Cl	L	327–330	$C_7H_6ClN_3O_4S_2$	28.43	28.90	2.05	2.09	14.21	14.15
32	H	H	—	H	Cl	H	M	253–254	$C_7H_5ClN_2O_2S$	38.80	38.89	2.33	2.40	12.93	12.90
33	H	H	—	H	Cl	Cl	L	293–294	$C_7H_4Cl_2N_2O_2S$	33.48	33.73	1.61	1.53	11.16	11.15
34	H	H	—	H	Cl	CH_3	A	287–288	$C_8H_7ClN_2O_2S$	41.65	41.94	3.06	3.18	12.15	12.14
35	H	H	—	H	CH_3	Cl	I	260–261	$C_8H_7ClN_2O_2S$	41.65	41.80	3.06	3.17	12.15	12.07
36	H	H	—	H	Cl	CH_3SO_2	A	329–331	$C_8H_7ClN_2O_4S_2$	32.60	32.62	2.39	2.61	9.51	9.46
37[e]	CH_3	H	—	H	H	H	F	95–97	$C_6H_8N_2O_2S$	48.97	49.05	4.11	4.05	14.28	14.15

[a] A = alcohol-water, B = dimethylformamide-water, C = alcohol-hexane, D = acetic acid-water, E = dimethylformamide-ether, F = alcohol, G = acetone-alcohol, H = dimethylformamide-alcohol, I = acetonitrile, J = acetone-benzene, K = acetone, L = acetone-petroleum ether, M = butanone. [b] Prepared by hydrogenation of No. 8 in ethanol in presence of platinum oxide catalyst in 73% yield. [c] We are indebted to Dr. E. J. Cragoe for preparation of this compound. [d] Corrected melting point. [e] 2-Methylsulfamylaniline was prepared in 80% yield by hydrogenation of 2-methylsulfamylnitrobenzene in ethanol in presence of platinum oxide catalyst; m.p. 56–56.5°. *Anal.* Calcd. for $C_7H_{10}N_2O_2S$: C, 45.16; H, 5.41; N, 15.05. Found: C, 45.29; H, 5.42; N, 15.00.

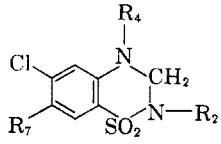
TABLE II



No.[a]	R_5	R_6	M.P.°	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1[b]	H	H	216–217	$C_7H_9N_3O_4S_2$	31.93	31.90	3.45	3.35	15.96	15.80
2	H	Cl	262–263	$C_7H_8ClN_3O_4S_2$	28.24	28.55	2.71	2.78	14.11	13.93
3	H	Br	287–288	$C_7H_8BrN_3O_4S_2$	24.56	24.86	2.36	2.50	12.27	12.27
4	H	CF_3	263–264	$C_8H_8F_3N_3O_4S_2$	29.00	29.22	2.43	2.67	12.68	12.52
5	H	CH_3	253–254	$C_8H_{11}N_3O_4S_2$	34.65	35.07	4.00	4.11	15.15	15.13
6	H	NO_2	263.5–264.5	$C_7H_8N_4O_6S_2$	27.27	27.61	2.62	2.96	18.17	17.80
7	Cl	Cl	288–289	$C_7H_7Cl_2N_3O_4S_2$	25.31	25.63	2.12	2.31	12.65	12.62

[a] Alcohol-water employed for recrystallization. [b] Prepared also by catalytic dehalogenation of No. 2, Table II, in dilute sodium hydroxide solution in presence of palladium-charcoal catalyst; 90% yield.

TABLE III



No.	R_2	R_4	R_7	M.P.°	Recrystn. Solvents[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	H	H	H	164–166	A	$C_7H_7ClN_2O_2S$	38.45	38.76	3.23	3.29	12.81	12.78
2	H	CH_3	SO_2NH_2	249–250	B	$C_8H_{10}ClN_3O_4S_2$	30.82	31.21	3.23	3.35	13.48	13.45
3	CH_3	H	SO_2NH_2	239–241	B	$C_8H_{10}ClN_3O_4S_2$	30.82	31.06	3.23	3.42	13.48	13.39
4	CH_3	H	SO_2NHCH_3	195–197	C	$C_9H_{12}ClN_3O_4S_2$	33.18	33.28	3.71	3.77	12.90	12.75
5	H	H	$SO_2N(CH_3)_2$	202–204	B	$C_9H_{12}ClN_3O_4S_2$	33.18	33.38	3.71	3.84	12.90	12.85
6	H	H	CH_3SO_2	248–249	B	$C_8H_9ClN_2O_4S_2$	32.38	32.63	3.06	3.10	9.44	9.41

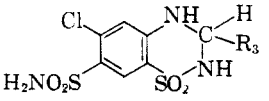
[a] A = toluene, B = alcohol-water, C = alcohol.

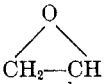
The preparation of sulfamylbenzothiadiazine-1,1-dioxides (VI) was generally accomplished by cyclization of 2,4-disulfamyl-*N*-acylanilines (III) in presence of base. Ammonium hydroxide was employed in most instances. For some ring closures, potassium fluoride in dimethylformamide proved more satisfactory. As either liquid ammonia or ammonium hydroxide were convenient for ring closure, the cyclized products (VI) were prepared directly from the *N*-acylaniline-2,4-disulfonyl chlorides (VII) in these media, thus accomplishing the formation of the disulfonamide (III) and the ring closure in one step. The required intermediates II, III and VII have been described.[10]

When formic acid was employed as the acylating agent in reactions with II, the formyl derivative III (R_3=H) was not obtained but only the corresponding cyclic product IV (VI. R_3=H) resulted. Any formyl derivative (III. R_3=H) apparently has only transitory existence. Ring closure of 5-amino-2,4-disulfamylaniline (II. R_6=NH_2, R_5=H) gave the tricyclic compound (IVa), benzo[1,2-e, 5,4-e']bis[1,2,4-thiadiazine-1,1-dioxide], which has a melting point above 500°. With compounds in which the sulfamyl group *ortho* to the amino group held a substituent (*e.g.*, methyl), formic acid proved less satisfactory for ring closure and in these instances (*e.g.*, 2-methylsulfamylaniline, 5-chloro-2-methylsulfamyl-4-sulfamylaniline, and 5-chloro-2,4-di(methylsulfamyl)-aniline) ethyl orthoformate was the reagent of choice.[8] This reagent also effected a smooth and rapid ring closure when the *ortho* sulfamyl group was unsubstituted. However, with reactants having a second unsubstituted sulfamyl group not amenable to cyclization, a further reaction occurred. Under conditions affecting ring formation, ethyl orthoformate reacted also with the unsubstituted sulfamyl group to yield ethoxymethylene derivatives of the type VIII. Where the cyclization reaction was rapid, the formation of appreciable amounts of VIII could be avoided by short reaction times; prolonged reaction led to VIII, exclusively. The same type of compounds (VIII) resulted from treatment of the sulfamylbenzothiadiazines I, IV, and VI with ethyl orthoformate. Similar reaction occurred between V and ethyl orthoformate. Mild alkaline hydrolysis removed the ethoxymethylene group to yield the desired products. Upon treatment with ammonia, VIII gave the formamidine IX.

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

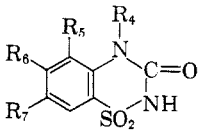
TABLE IV



No.	R_3	M.P.°	Recrystn. Solvent[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	CH_3	252–253	A	$C_8H_{10}ClN_3O_4S_2$	30.82	30.94	3.23	3.23	13.48	13.33
2	C_2H_5	265	A	$C_9H_{12}ClN_3O_4S_2$	33.17	33.40	3.71	3.79	12.90	12.75
3	Cl_3C	287	B	$C_8H_7Cl_4N_3O_4S_2$	23.15	23.56	1.70	1.93	10.12	10.13
4	$HOCH_2$	225–226	C	$C_8H_{10}ClN_3O_5S_2$	29.31	29.59	3.08	3.25	12.82	12.72
5		233–235	C	$C_9H_{10}ClN_3O_5S_2$	31.81	32.03	2.97	3.24	12.37	12.18
6	$(CH_2)_5$[b]	259–260	D	$C_{12}H_{16}ClN_3O_4S_2$	39.39	39.70	4.41	4.60	11.49	11.35
7	$C_6H_5CH_2$	260–262	A	$C_{14}H_{14}ClN_3O_4S_2$	43.35	43.43	3.64	3.96	10.83	10.70
8	p-ClC_6H_4	250–251	A	$C_{13}H_{11}Cl_2N_3O_4S_2$	38.24	38.48	2.72	2.95	10.29	10.26
9	p-$NO_2C_6H_4$	268–269	E	$C_{13}H_{11}ClN_4O_6S_2$	37.28	37.47	2.65	3.14	13.38	13.18
10	2-Pyridyl	260	F	$C_{12}H_{11}ClN_4O_4S_2$	38.45	38.87	2.95	3.05	14.95	14.91
11	5-Nitro-2-furyl	239–240	E	$C_{11}H_9ClN_4O_7S_2$	32.32	32.89	2.22	2.38	13.70	13.01

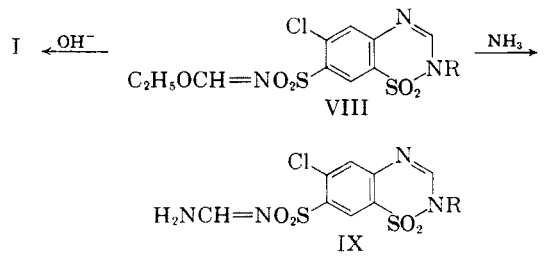
[a] A = acetic acid-water, B = ethylene glycol monomethyl ether-water, C = acetone-water, D = dimethylformamide-water, E = acetone-ether, F = acetonitrile. [b] R_3 and H replaced by this group.

TABLE V



No.[a]	R_4	R_5	R_6	R_7	M.P.°	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	H	H	Cl	SO_2NH_2	313	$C_7H_6ClN_3O_5S_2$	26.97	27.29	1.94	2.10	13.48	13.44
2	H	Cl	H	SO_2NH_2	314–315	$C_7H_6ClN_3O_5S_2$	26.97	27.09	1.94	2.20	13.48	13.48
3	H	H	SO_2NH_2	Cl	323–324	$C_7H_6ClN_3O_5S_2$	26.97	27.23	1.94	2.06	13.48	13.47
4	H	H	Br	SO_2NH_2	323–324	$C_7H_6BrN_3O_5S_2$	23.60	23.76	1.70	1.97	11.80	11.83
5	H	H	CH_3	SO_2NH_2	307–308	$C_8H_9N_3O_5S_2$	32.98	32.98	3.11	3.29	14.42	14.37
6	H	H	CH_3O	SO_2NH_2	291–293	$C_8H_9N_3O_6S_2$	31.27	31.32	2.95	3.10	13.67	13.66
7	H	H	NO_2	SO_2NH_2	>350	$C_7H_6N_4O_7S_2$	26.08	26.47	1.88	2.14	17.38	17.99
8	CH_3	H	Cl	SO_2NH_2	315	$C_8H_8ClN_3O_5S_2$	29.49	29.58	2.48	2.59	12.90	12.87

[a] Alcohol-water employed for recrystallization.



VIII

IX

Preparation of dihydrobenzothiadiazine-1,1-dioxides (V) was accomplished by ring closure of representative 2,4-disulfamylanilines with appropriate aldehydes in the presence of catalytic amounts of acid or base. In Tables II and III are listed compounds prepared by ring closure of various 2,4-disulfamylanilines with formaldehyde. From this series a second clinically useful diuretic agent has resulted—6-chloro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide,[11–13] the dihydro derivative of I (V. R_6=Cl, R_3=R_5=H). Derivatives of V (R_6=Cl, R_5=H) prepared by ring closure of 5-chloro-2,4-disulfamylaniline with various aldehydes are listed in Table IV. Chloral underwent reaction with 5-chloro-2,4-disulfamylaniline in either of two ways. In the absence of acid or base and in dimethylformamide solution, the product was 6-chloro-7-sulfamyl-3-trichloromethyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide (V. R_3=CCl_3, R_6=Cl, R_5=H), the expected product from such an aldehyde. However, under the general procedure employing a basic catalyst, chloral behaved as a formylating agent and the product was 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-di-

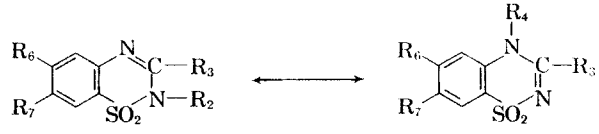
(11) This compound has been given the generic name of hydrochlorothiazide; HydroDIURIL is the trademark of Merck and Co., Inc. for hydrochlorothiazide.

(12) Preparation of this compound has been reported by G. de Stevens, L. H. Werner, A. Halamandaris, and S. Ricca, Jr., *Experientia* **14**, 463 (1958).

(13) Preparation of 6-trifluoromethyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide has been reported by C. T. Holdrege, R. B. Babel, and L. C. Cheney, *J. Am. Chem. Soc.*, **81**, 4807 (1959).

TABLE VI

ULTRAVIOLET ABSORPTION SPECTRA OF 1,2,4-BENZOTHIADIAZINE-1,1-DIOXIDES[a]

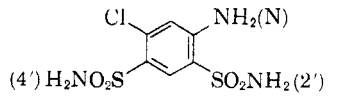


	R_2	R_3	R_4	R_6	R_7	Solvent[b]	λ_{max}, mμ	$\epsilon \times 10^{-3}$	λ_{max}, mμ	$\epsilon \times 10^{-3}$	λ_{max}[f], mμ	$\epsilon \times 10^{-3}$
1	H	H	—	H	H	A[c]			267–269	8.12		
						B			277	9.47	298–300	4.45
2	H	H	—	Cl	H	A	221–222	30.5	266–269	7.37		
3	H	H	—	H	SO_2NH_2	A			277–278	11.6		
4[e]	H	H	—	Cl	SO_2NH_2	A	226	30.0	280	11.1		
						B	224–226	22.8	291–293	13.1		
5	H	CH_3	—	Cl	SO_2NH_2	A	225–226	30.8	275–277	11.8		
							228.5–229	30.3				
						B	224–227	23.1	289–292	11.7		
6	H	H	—	F_3C	SO_2NH_2	A			278–279	11.0		
		4-Substituted Series										
7	—	CH_3	CH_3	H	H	A			266–268	8.37		
8	—	CH_3	CH_3	H	SO_2NH_2	A			277.5	12.6		
9[g]	—	H	CH_3	Cl	SO_2NH_2	A	228–229	27.9	284	11.3		
10	—	H	allyl	Cl	SO_2NH_2	A	228.5	28.0	283–285	11.2		
						B[d]	229	35.8	269.5	17.7	319–322	4.77
		2-Substituted Series										
11	CH_3	H	—	H	H	A			262–264	7.94	296–298.5	5.35
12	CH_3	H	—	Cl	SO_2NH_2	A	228–230	26.4	283–286	10.3	302–305	8.83
						C	228–229	24.5	282–286	9.81	305–307	8.88
13	CH_3	H	—	Cl	SO_2NH_2	A	227–228	26.1	288–289	10.6	308–310	9.52
		3,4-Dihydro Series (cf. V)										
14	H	H	H	Cl	SO_2NH_2	A	226	36.7	269–271	19.8	315–318	3.10
15	CH_3	H	H	Cl	SO_2NH_2	A	225	36.5	267–269	19.5	312–316	3.14
16	H	H	CH_3	Cl	SO_2NH_2	A	228	34.5	276	21.9	322–325	3.72
17	H	$HOCH_2$	H	Cl	SO_2NH_2	A	226	39.7	268–270	20.8	310–315	3.13
18	H	$C_6H_5CH_2$	H	Cl	SO_2NH_2	A	226.5	42.4	270–271	23.5	314–316	3.05
19	H	*p*-$NO_2C_6H_4$	H	Cl	SO_2NH_2	A	225	39.7	271	35.1	307–313[j]	3.83
20	H	Cl_3C	H	Cl	SO_2NH_2	A	225	43.0	264–266	19.3	302–308	2.75
21	H	=O	H	Cl	SO_2NH_2	A	223–224	48.4	259–260	16.1		
22	6-Chloro-3,3-pentamethylene-7-sulfamyl					A	226–227.5	33.8	272–273.5	21.8	315–321	2.73

[a] Determined with Cary Recording Spectrophotometer, Model 11. [b] A = ethanol, B = 0.1*N* aqueous sodium hydroxide, C = acetonitrile. [c] D. V. Parke and R. T. Williams, ref. 7 found λ_{max} 207, 269 mμ, $\epsilon \times 10^{-3}$ 13.4, 7.6 respectively. [d] Gives ring-opened compound, see Table VII. [e] The spectra in ethanol of the derivatives bearing an acetyl, butyryl, or ethoxymethylene group on the 7-sulfamyl were identical with the unsubstituted compound recorded here. [f] The spectra of compounds 2–10 inclusive in ethanol showed pronounced shoulders in the region 290–310 mμ. [g] Prepared either by methylation of chlorothiazide (I) or by the ring closure synthesis starting with *m*-chloro-*N*-methylaniline. [j] Shoulder.

TABLE VII

ULTRAVIOLET ABSORPTION SPECTRA OF 5-CHLORO-2,4-DISULFAMYLANILINE AND RELATED COMPOUNDS

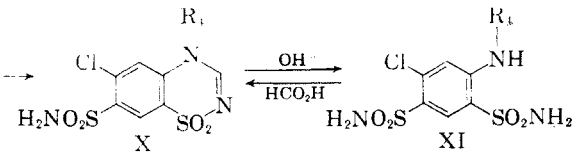


		Solvent[a]	λ_{max}, mμ	$\epsilon \times 10^{-3}$	λ_{max}, mμ	$\epsilon \times 10^{-3}$	λ_{max}, mμ	$\epsilon \times 10^{-3}$
1	5-Chloro-2,4-disulfamylaniline	A	223–224	41.8	265–266	18.6	312–314	3.87
		B	222–223	32.2	262	14.8	305–309	3.11
2	*N*-Methyl[b]	A	225–227	38.2	269–271	20.3	317–322	4.49
3	*N*-Acetyl	A	226–228	37.0	261–263	18.4		
4	*N*-Butyryl[c]	A	227–228	38.3	261–265	19.8		
5	*N*-Acetyl-2′,4′-tetramethyl	A	231–234	26.6	267–270	17.1		
6	2′-Methyl	A	224–225	38.6	264–265	18.2	309–312	3.85
7	2′,4′-Tetramethyl	A	227.5	29.4	271.5	19.2	316–319	4.20
8	2′,4′-Bis(pentamethylene)	A	228	28.0	272	19.0	317–320	4.29
9	*N*-Allyl-2′-formyl	A	229	36.9	269–270	17.6	321–327	4.49
		B[d]	229	35.8	269.5	17.7	319–322	4.77
10	*N*-Formyl-2′,4′-dimethyl	A	230.5	33.1	266–268	18.4		
11	*N*-Methyl-2′-acetyl-5-deschloro	A	215–217	24.2	267–269	19.5	323–328	4.47
12	2-(*N*-Methyl-*N*-formylsulfamyl)aniline	A			246–247	12.3	284.5–286.5	3.33

[a] A = ethanol, B = 0.1*N* aqueous sodium hydroxide. [b] The *N*-allyl analog gave identical values. [c] The chloroacetyl analog had the same spectra as the acetyl and butyryl derivatives. [d] 4-Allyl-6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide in 0.1*N* sodium hydroxide.

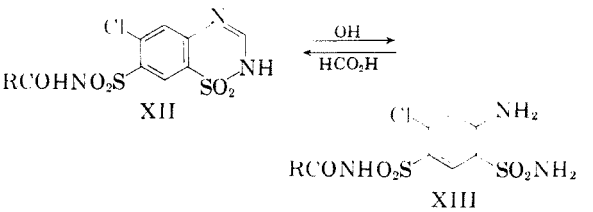
oxide (I). This property of chloral has been employed for preparation of *N*-formylamines.[14] Further ramifications in the dihydrobenzothiadiazine-1,1-dioxide series included preparation of 3-oxodihydro-1,2,4-benzothiadiazine-1,1-dioxides (Table V) by fusion of the disulfamylanilines with urea.

Using 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (I, chlorothiazide) and certain of its derivatives as illustrative examples of the series, several aspects of the chemistry of this type of structure were investigated.



Alkylation of I with methyl sulfate or with allyl bromide in aqueous or alcoholic alkali yielded the 4-methyl and 4-allyl derivatives (X) respectively. The position of the entering group was established by hydrolysis of X (R_4=CH_3) to XI (R_4=CH_3) and by ring closure of XI (R_4=CH_3) prepared from *N*-methyl-*m*-chloroaniline. The ultraviolet spectra of these substances and of pertinent reference compounds (Tables VI and VII) also support the 4 position of the alkyl group in X.

Acylation with either acetic or butyric anhydride in pyridine at room temperature yielded the 7-acylsulfamyl derivative XII (R=CH_3, C_3H_7) which exhibits two acid dissociations, pK'_a 3.7 and pK'_a 7.2, consistent with this structure. Con-



trolled alkaline hydrolysis of XII (R=CH_3) gave XIII which upon treatment with formic acid was recyclized to XII.

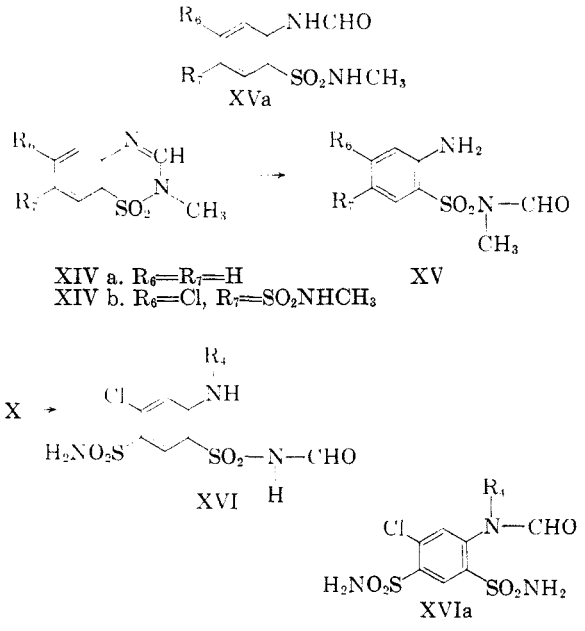
The benzothiadiazine-1,1-dioxides (IV, VI) are readily cleaved by hot aqueous alkali to yield as final products the disulfamylaniline II. This reaction, which has been established chemically and spectrophotometrically, is the basis of an analytical method[15] for the determination of I in biological specimens through the quantitative diazo color reaction of 5-chloro-2,4-disulfamylaniline (II) (R_6=Cl, R_5=H). In 1.0*N* sodium hydroxide ring opening was complete in thirty minutes at steam-bath temperature but required 26–48 hours at room temperature. In 0.1*N* sodium hydroxide with heating the reaction was complete in three hours but at room temperature it was not complete in 168 hours. In acid media the heterocyclic ring proved more stable; I in hydrochloric acid-acetic acid at the boiling point for one hour was recovered essentially unchanged.

The presence of an alkyl substituent on either nitrogen atom in positions 2 or 4 greatly increased lability of the heterocyclic ring to hydrolytic cleavage. The 2-methyl derivatives (XIV) underwent ring fission upon recrystallization from hot

(14) F. F. Blicke and C. J. Lu, *J. Am. Chem. Soc.*, **74**, 3933 (1952).

(15) J. E. Baer, L. Leidy, A. V. Brooks, and K. H. Beyer, *J. Pharmacol. Exp. Therap.*, **125**, 295 (1959).

aqueous ethanol. Two structures, XV and XVa, are possible for these products. Comparative ultraviolet spectral data (Table VII) indicate that the product (Table VII, No. 12) isolated from XIVa has structure XV, whereas the product (Table VII, No. 10) from XIVb is probably XVa as its spectrum resembles that of the 2,4-disulfamyl-*N*-acylanilines. The 4-substituted derivatives, X, underwent analogous cleavage. Mild treatment of the allyl compound (X, R_4=allyl) with aqueous alkali yielded XVI. The formation of XVI rather than XVIa is supported as follows. The ultraviolet absorption spectra (Table VII) of XVI differ from those of the disulfamyl-*N*-acylanilines (Table VII) by the presence of a distinct band of low intensity in the 300–325 mμ region. XVI (R_4=allyl) titrates as a dibasic acid, pK'_a 2.9, 10.1, consistent with the presence of the strongly acidic —SO_2NHCHO group. Acid titration of an alkaline solution of both the 4-methyl and 4-allyl compounds (X, R_4=CH_3 and allyl) reveals two acidic dissociations for each compound, pK'_a 2.8, 10.0 and 3.0, 10.2 respectively, consistent with ring opening to give XVI.



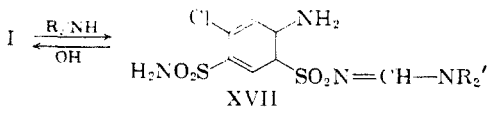
XIV a. R_6=R_7=H
XIV b. R_6=Cl, R_7=SO_2NHCH_3

XV

XVI

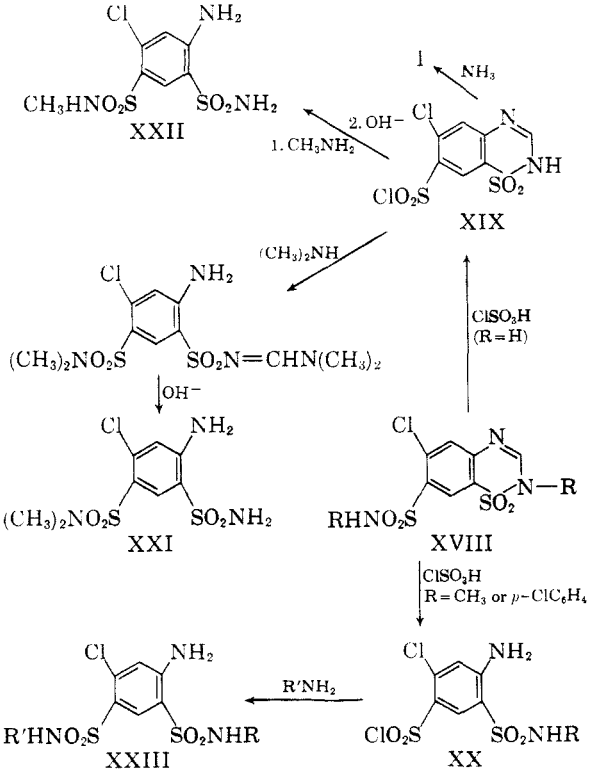
XVIa

On reaction with anhydrous dimethylamine or piperidine, I underwent ring opening to give the substituted formamidine derivative, XVII (R'_2N=$(CH_3)_2N$ or $C_5H_{10}N$). Primary amines gave only mixtures of products that were not further characterized and no ring opening occurred with anhydrous liquid ammonia. The products, XVII, are stable to boiling water but reform the benzothiadiazine with loss of the secondary amine upon mild treatment with aqueous alkali.



XVII

The well-known conversion of a sulfamyl group to the sulfonyl chloride by the action of chlorosulfonic acid has proved useful in the benzothiadiazine-1,1-dioxide series. In this manner, the 7-sulfamyl group was converted to the sulfonyl chloride without attack upon the sulfamyl group that is a part of the thiadiazine ring. However, the nature of the final sulfonyl chloride that was obtained after treatment of the chlorosulfonic acid reaction mixture with ice and water varied with the substituent on the nitrogen in the 2 position. When this position was unsubstituted (XVIII, R=H), the heterocyclic ring remained intact and the sulfonyl chloride, XIX, was obtained (96%). As pointed out previously, a substituent in the 2 position labilizes the ring toward hydrolytic cleavage. Where R = CH_3 or *p*-ClC_6H_4, the product of the chlorosulfonic acid reaction was the corresponding 2-substituted-sulfamyl-5-chloroaniline-4-sulfonyl chloride XX (60%) resulting from such ring opening. The sulfonyl chlorides, XIX and XX, reacted with ammonia or various amines, as expected from the properties discussed above, and provided satisfactory routes to several derivatives of 2,4-disulfamylaniline (XXI, XXII, XXIII) variously substituted in the sulfamyl groups as shown in the following series of reactions. Acylation and cyclization of these compounds led to further examples of the benzothiadiazine-1,1-dioxide series.



XXII

XIX

XXI

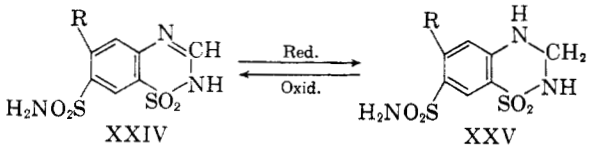
XVIII

XXIII

XX

The interconversion of benzothiadiazine-1,1-dioxides and dihydrobenzothiadiazine-1,1-dioxides was accomplished with representatives of each series. Catalytic hydrogenation of XXIV (R=Cl)

using ruthenium on charcoal catalyst gave the dihydro compound XXV (R=Cl) in 83% yield. Sodium borohydride reduction of XXIV (R=Cl) to XXV (R=Cl) has been reported.[12] Conversely, permanganate oxidation of XXV (R=Cl, CH_3) yielded the corresponding dehydrogenated compound XXIV (R=Cl, CH_3) in good yield.



XXIV XXV

The structure of the thiadiazine ring of 1,2,4-benzothiadiazine-1,1-dioxides has not been studied in detail or extensively. It is undoubtedly a tautomeric system (A⇌B). The double bond may occupy either the 2,3 or the 3,4 positions and the anion would be expected to be a resonance hybrid. A comparison (Table VI) of the ultraviolet spectra of the parent compound, 1,2,4-benzothiadiazine-1,1-dioxide and several of its derivatives, including I and related compounds having the nitrogen atoms in positions 2 and 4 unsubstituted, with the spectra of derivatives where the double bond is fixed in the 2,3 or 3,4 locations by appropriate substitution at positions 2 or 4 permits some tentative conclusions. These comparative data indicate that in ethanol solutions the benzothiadiazine-1,1-dioxides (A⇌B) that are unsubstituted on either nitrogen exist predominantly in the form B with the double bond at the 2,3 position. In aqueous alkali, however, there is a shift toward the spectra of form A in ethanol where the double bond is at the 3,4 position.

A B

In ethanol solution, the spectra of compounds having the unsubstituted nitrogen bear a close resemblance to the spectra of those compounds which have the double bond fixed in the 2,3 position. They show absorption maxima of similar intensity in the region 265–280 mμ. The presence of chlorine (but not of trifluoromethyl) in the benzenoid ring at position 6 produces a strong band at 220–230 mμ. Most of the compounds have a detectable shoulder at 290–310 mμ. In aqueous sodium hydroxide solution, the spectra of the 2 and 4 unsubstituted compounds show a shift of the 265–280 mμ band to higher wave lengths by 8–17 mμ; the 220–230 mμ band, if present, is unaffected and the shoulder at 290–310 mμ becomes more pronounced. In the 2-methyl derivatives which have the double bond fixed at the 3,4-position, a distinct band now appears at 295–310 mμ where only a shoulder exists in the other compounds.

The spectra of the dihydro derivatives (V) have three distinct maxima of decreasing intensity at 224–226 mμ, 264–273 mμ and 302–325 mμ (Table VI) comparable to the spectra of the aniline-2,4-disulfonamides (Table VII). The 3-*p*-nitrophenyl and 3-oxo derivatives present exceptions. In the spectra of the *p*-nitrophenyl compound (Table VI, No. 19), the maximum at 307–313 mμ appears only as a shoulder. The spectra of the 3-oxo derivatives, *e.g.*, 6-chloro-7-sulfamyl-3-oxo-dihydrobenzothiadiazine-1,1-dioxide (Table VI, No. 21), resemble closely the disulfamyl-*N*-acylanilines (Table VII). For spectral comparison, two anils of 2,4-bis(dimethylsulfamyl)-5-chloroaniline were prepared from *p*-nitrobenzaldehyde and phenylacetaldehyde. These compounds cannot undergo cyclization to the dihydrobenzothiadiazine system and exhibit spectra markedly different from the analogous cyclic structures (Table VI), thus lending further support to the heterocyclic structure for V.

A tabular summary of the comparative activity of many of these compounds on electrolyte excretion in the dog following oral and intravenous administration has been presented previously.[4,16] A sulfamyl group is essential for any degree of activity; benzothiadiazine-1,1-dioxides without this group are inactive. High activity is obtained when this group is in the 7 position—that is, when it is in the *meta* relation to the sulfamyl that is part of the thiadiazine ring. For maximum activity an augmenting group must also be present in the benzene ring. This is most striking when such a group is in the 6 position adjacent to the sulfamyl group. Chlorine, bromine, trifluoromethyl, and nitro groups in this position yield highly active compounds. Methyl, fluorine, methoxy, and amino are less effective as augmenting substituents. Conversion of chlorothiazide (I) to the dihydro derivative (V. R_6=Cl, R_3=R_5=H) results in a ten-fold increase in potency. Oxygen at the 3-position depresses activity. In both the dihydro and 3-oxodihydro series the influence of substituents parallels that observed in the benzothiadiazine-1,1-dioxides.

Compounds with an alkyl group in the 3 position retain a high order of activity but the 3-phenyl derivatives are less effective. Substitution on either nitrogen atom in positions 2 and 4 gives compounds with lower activities. The order of activity of compounds substituted (alkyl or acyl) on the 7-sulfamyl group is consistent with the assumption that the substituent is removed metabolically. That metabolic removal of such groups from substituted sulfonamides can occur has been clearly demonstrated in the acetazolamide series.[17] Replacement of the

(16) We are indebted to Drs. John E. Baer and Karl H. Beyer and their associates for the biological data that are summarized here.

(17) T. H. Maren, *J. Pharmacol. Exp. Therap.*, 117, 385 (1956).

7-sulfamyl group by a methylsulfonyl group produces little change in many of the chemical and physical properties and some of the biological properties of the original sulfonamide. However, the methylsulfonyl analogs are exceedingly weak carbonic anhydrase inhibitors and do not promote electrolyte excretion in the dog.

EXPERIMENTAL[18,19]

The following procedure is illustrative of the formic acid ring closure of aniline-2,4-disulfonamides to benzothiadiazine-1,1-dioxides listed in Table I and not described elsewhere in the Experimental. The yield is typical.

6-Chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (No. 3, Table I). A solution of 5-chloro-2,4-disulfamylaniline (5.7 g., 0.02 mole) in 75 ml. of 98–100% formic acid was heated under reflux for 24 hr. After cooling, water (100 ml.) was added and the product collected, washed with water, and recrystallized. Colorless needles were obtained in 90% yield.

Benzo[1,2-e,5,4-e']bis[1,2,4-thiadiazine-1,1-dioxide]. A solution of 5-amino-2,4-disulfamylaniline (1.3 g., 0.005 mole) in 98–100% formic acid (20 ml.) was heated under reflux for 2.5 hr. and cooled. Recrystallization of the precipitate, 1.14 g. (82%), from dimethylformamide-water afforded pale yellow needles, m.p. >500°.

Anal. Calcd. for $C_8H_6N_4O_4S_2$: C, 33.56; H, 2.11; N, 19.57. Found: C, 34.03; H, 2.37; N, 19.55.

2-Methyl-1,2,4-benzothiadiazine-1,1-dioxide (No. 37, Table I). Following the procedure of Freeman and Wagner,[8] a mixture of 2 g. of 2-methylsulfamylaniline and 5 ml. of ethyl orthoformate was heated in an open flask at 125–135° for 30 min., concentrated to dryness *in vacuo* and the residue recrystallized from ethanol; yield, 1.6 g. (76%) of colorless needles.

Recrystallization of *2-methyl-1,2,4-benzothiadiazine-1,1-dioxide* from hot (50%) aqueous ethanol gave *2-(N-formyl-N-methylsulfamyl)aniline;* colorless needles, m.p. 116–118°.

Anal. Calcd. for $C_8H_{10}N_2O_3S$: C, 44.86; H, 4.71; N, 13.08. Found: C, 45.04; H, 4.57; N, 13.14.

Ring closure of 5-chloro-2,4-dimethylsulfamylaniline was carried out in like manner to give *6-chloro-2-methyl-7-methylsulfamyl-1,2,4-benzothiadiazine-1,1-dioxide* (No. 24, Table I). When this compound was recrystallized from hot aqueous ethanol, 5-chloro-2,4-di(methylsulfamyl)-*N*-formylaniline was obtained; colorless plates, m.p. 192–195°.

Anal. Calcd. for $C_9H_{12}ClN_3O_5S_2$: C, 31.63; H, 3.54; N, 12.29. Found: C, 31.99; H, 3.68; N, 12.29.

6-Chloro-7-ethoxymethylenesulfamyl-1,2,4-benzothiadiazine-1,1-dioxide. A suspension of 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (15 g., 0.05 mole) in 100 ml. of ethyl orthoformate was heated under reflux with stirring for 24 hr. Upon cooling to room temperature, the product was collected and washed with alcohol; yield, 15.4 g. (87%), m.p. 207–210° with softening at 195°. A sample recrystallized from acetonitrile-ether melted at 195–196° with resolidification and remelting at 210–211°.

Anal. Calcd. for $C_{10}H_{10}ClN_3O_5S_2$: C, 34.14; H, 2.87; N, 11.94; OC_2H_5, 12.81. Found: C, 34.35; H, 2.95; N, 11.96; OC_2H_5, 12.70.

6-Chloro-7-ethoxymethylenesulfamyl-2-methyl-1,2,4-benzothiadiazine-1,1-dioxide was prepared according to the above procedure from 6-chloro-2-methyl-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide and ethyl orthoformate, m.p. 155–157°.

Anal. Calcd. for $C_{11}H_{12}ClN_3O_5S_2$: C, 36.11; H, 3.31; N, 11.49; OC_2H_5, 12.32. Found: C, 35.48; H, 3.68; N, 11.35; OC_2H_5, 12.94.

6-Chloro-7-ethoxymethylenesulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide was prepared in like manner from 6-chloro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide and ethyl orthoformate, m.p. 222–230° eff.

Anal. Calcd. for $C_{10}H_{12}ClN_3O_5S_2$: C, 34.94; H, 3.42; N, 11.88. Found: C, 34.67; H, 3.60; N, 11.82.

7-Aminomethylenesulfamyl-6-chloro-1,2,4-benzothiadiazine-1,1-dioxide. Ammonia was passed into a suspension of 6-chloro-7-ethoxymethylenesulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (6.5 g., 0.0185 mole) in 50 ml. of anhydrous alcohol for 30 min. Complete solution occurred within a few minutes with subsequent separation of product; yield, 3.6 g. (60%), m.p. 308–310°. Recrystallization from alcohol raised the melting point to 309–311°.

Anal. Calcd. for $C_8H_7ClN_4O_4S_2$: C, 29.77; H, 2.19; N, 17.36. Found: C, 29.89; H, 2.52; N, 17.04.

7-Aminomethylenesulfamyl-6-chloro-2-methyl-1,2,4-benzothiadiazine-1,1-dioxide was prepared from 6-chloro-7-ethoxymethylenesulfamyl-2-methyl-1,2,4-benzothiadiazine-1,1-dioxide according to the above procedure, m.p. 233–234°.

6-Chloro-3-methyl-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (No. 11, Table I). 5-Chloroacetanilide-2,4-disulfonyl chloride (4.4 g.) was added portionwise to 50 ml. of 10% alcoholic ammonia. After the initial reaction had subsided, the solution was evaporated to dryness on the steam bath and the residue recrystallized from aqueous ethanol.

In like manner, using concd. ammonium hydroxide in place of alcoholic ammonia, *6-chloro-3-n-propyl-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide* (No. 12, Table I) and *3-n-amyl-6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide* (No. 13, Table I) were prepared from the corresponding *N*-acylanilinedisulfonyl chlorides.

3-Chloromethyl-6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (No. 14, Table I). A solution of 5-chloro-2,4-disulfamyl-*N*-(chloroacetyl)aniline (7.2 g.) in dimethylformamide (30 ml.) was heated on the steam bath with stirring with 2.3 g. of anhydrous potassium fluoride for 1.5 hr., cooled, and diluted with water; yield, 5.5 g. (80%).

6-Chloro-3-phenyl-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (No. 15, Table I). *Method A.* 5-Chloroaniline-2,4-disulfonyl chloride (8.4 g.) was dissolved in 13 ml. of benzoyl chloride by warming briefly on the steam bath and allowed to stand at room temperature overnight. 5-Chloro-*N*-benzoylaniline-2,4-disulfonyl chloride (10.9 g.) was collected, washed with benzene, added to 50 ml. of concd. ammonium hydroxide, and heated on the steam bath for 2 hr. Recrystallization of the precipitate from dimethylformamide-water gave 2.7 g. of 6-chloro-3-phenyl-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide as colorless needles.

Acidification of the ammoniacal filtrate and recrystallization of the precipitate from aqueous ethanol gave 5-chloro-2,4-disulfamyl-*N*-benzoylaniline.[10]

Method B. A solution of 1 g. of 5-chloro-2,4-disulfamyl-*N*-benzoylaniline[10] in 25 ml. of concd. ammonium hydroxide was allowed to stand at room temperature for 48 hr. and concentrated to dryness *in vacuo*. The residue was washed with water and afforded 84% yield of product identical with that prepared by Method A.

In like manner, ring closure of 5-chloro-2,4-disulfamyl-*N*-*p*-chlorobenzoylaniline gave *3-(p-chlorophenyl)-6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide* (No. 17, Table I) in 85% yield.

3-(o-Chlorophenyl)-6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (No. 16, Table I) was prepared in 56% yield from 5-chloro-2,4-disulfamyl-N-o-chlorobenzoylaniline according to the procedure described for compound No. 14.

General procedure for 3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxides (Tables II and III). *Method A. Base catalyzed ring closure.* A solution of 0.02 mole of the orthanilamide compound and 0.025 mole of 37% formaldehyde in 50 ml. of 90% ethanol-water containing 300 mg. of sodium hy-

(18) Melting points are uncorrected. Data shown in the tables are not reproduced in the Experimental.

(19) We are indebted to Mr. K. B. Streeter and Mr. Y. C. Lee and their associates for analytical and spectral data and pK'_a determinations.

droxide was heated on the steam bath for 2 hr. and acidified. This mixture was cooled and the product collected, washed with water, dried, and recrystallized; yield, 80%.

Method B. Acid catalyzed ring closure. A suspension of 0.02 mole of the orthanilamide compound and 0.04 mole of paraformaldehyde in 60 ml. of ethanol and 60 ml. of 6.0*N* hydrochloric acid was heated on the steam bath. Complete solution occurred with subsequent separation of product. Reaction was complete in 1 hr.; average yield, 85–90%.

Compounds listed in Table IV were prepared by ring closure of 5-chloro-2,4-disulfamylaniline with the appropriate aldehyde. Acid cyclization was employed for compounds No. 1, 2, 9 and base cyclization for the remainder.

6-Chloro-7-sulfamyl-3-trichloromethyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide (No. 3, Table IV). A solution of 11.4 g. (0.04 mole) of 5-chloro-2,4-disulfamylaniline in 20 ml. of dimethylformamide and 17.6 g. (0.12 mole) of chloral was heated on the steam bath for 24 hr. Water (100 ml.) was added and the semisolid reprecipitated from dilute ammonium hydroxide; yield, 14.5 g. (87.5%) of colorless needles, m.p. 278–279°.

When this reaction was carried out in 60 ml. of dimethylformamide in the presence of 4.6 g. (0.08 mole) of anhydrous potassium fluoride for 3 hr. on the steam bath, *6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide* was obtained in 76% yield; m.p. 330°, mixed melting point with chlorothiazide was not depressed, $\lambda_{max}^{C_2H_5OH}$ 225 and 279–280 mμ, ε 29,592 and 11,465.

6-Chloro-7-sulfamyl-3,3-pentamethylene-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide (No. 6, Table IV). A solution of 5.7 g. (0.02 mole) of 5-chloro-2,4-disulfamylaniline and 5.9 g. (0.06 mole) of cyclohexanone in 30 ml. of dimethylformamide was heated with stirring with 2.3 g. (0.04 mole) of anhydrous potassium fluoride on the steam bath for 2 hr. and diluted with 100 ml. of water; yield, 4.7 g. (57%), m.p. 259–261°.

6-Chloro-3-oxo-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide (No. 1, Table V). The following procedure is illustrative of the method[7] employed for preparation of compounds in Table V. Compounds were recrystallized from aqueous ethanol and obtained in yields of 35–73%.

An intimate mixture of 5-chloro-2,4-disulfamylaniline (8.4 g., 0.03 mole) and urea (3.5 g., 0.06 mole) was heated in an oil bath at 200° for 45–60 min. The mixture liquified with evolution of ammonia and solidified after 30 min. The solid was cooled, dissolved in water, filtered, and acidified. Recrystallization from aqueous alcohol afforded colorless plates.

6-Chloro-4-methyl-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (No. 18, Table I). *Method A. Methylation of 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide.* A filtered solution of 5.9 g. (0.02 mole) of 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide in 25 ml. of water containing 0.88 g. (0.022 mole) of sodium hydroxide was shaken with 3.0 g. (0.024 mole) of methyl sulfate in a stoppered flask at room temperature for 10 min. The precipitate was collected, washed with water, alcohol, and dried; yield, 2.8 g. (45%), m.p. 308°. Admixture of analytical specimen (m.p. 325–326°) and product obtained by Method B showed no depression in melting point.

A sample when heated on the steam bath with 10% sodium hydroxide for 2.5 hr. gave 5-chloro-2,4-disulfamyl-*N*-methylaniline[10]; no depression in mixed melting point.

Method B. A solution of 5-chloro-2,4-disulfamyl-*N*-methylaniline (5 g.) in 98–100% formic acid (70 ml.) was heated under reflux for 24 hr. and cooled to room temperature; yield, 4.7 g. (90.5%), m.p. 325–327°.

4-Allyl-6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (No. 19, Table I). 6-Chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (32.2 g., 0.11 mole) was added portionwise with stirring to a cold solution of 2.5 g. (0.11 mole) of sodium dissolved in 200 ml. of ethanol. Allyl bromide (16.3 g., 0.135 mole) was added and the solution heated on the steam bath for 24 hr. with the intermittent addition of 4.0 g. of allyl bromide after 6 hr. of heating. The mixture was cooled, filtered, and the precipitate washed with water, alcohol, and dried; yield, 27.2 g., m.p. 244–246°, cloudy melt. Repeated extraction of this material with acetone (1 l. total) at room temperature afforded 11.9 g. of starting material (insoluble fraction) and 12.5 g. of 4-allyl-6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (soluble fraction), m.p. 243–245°. Final purification was accomplished by recrystallization from aqueous ethanol.

A sample (1.0 g.) of 4-allyl-6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide in 20 ml. of 10% aqueous sodium hydroxide was heated on the steam bath for 2 hr., cooled, and acidified. Recrystallization of the precipitate from water gave *5-chloro-2,4-disulfamyl-N-allylaniline*; yield, 0.5 g. of colorless needles, m.p. 181–183°; negative test[20] for diazotizable amine.

Anal. Calcd. for $C_9H_{12}ClN_3O_4S_2$: C, 33.18; H, 3.71; N, 12.90. Found: C, 32.92; H, 3.71; N, 12.90.

5-Chloro-2-formylsulfamyl-4-sulfamyl-N-allylaniline. A solution of 1.0 g. of 4-allyl-6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide in 70 ml. of water and 9 ml. of 1.0*N* sodium hydroxide was allowed to stand at room temperature for 30 min., cooled in an ice bath, and acidified with dilute hydrochloric acid. The precipitate was collected, washed with water, and dried in a vacuum desiccator over sulfuric acid. Recrystallization from chloroform-acetone yielded 0.4 g. of colorless needles, m.p. 142.5–143.5°, with effervescence; readily soluble in bicarbonate solution.

Anal. Calcd. for $C_{10}H_{12}ClN_3O_5S_2$: C, 33.94; H, 3.42; N, 11.88. Found: C, 33.72; H, 3.52; N, 11.40.

Recrystallization of a sample from water yielded a bicarbonate insoluble product which gave no depression in melting point upon admixture with *5-chloro-2,4-disulfamyl-N-allylaniline.*

3,4-Dimethyl-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (No. 20, Table I). A solution of 3,4-dimethyl-1,2,4-benzothiadiazine-1,1-dioxide[5] (11.4 g., 0.054 mole) in 35 ml. of chlorosulfonic acid was heated in an oil bath at 150–160° for 2.5 hr., cooled, and poured onto ice. The precipitate was collected and added to 50 ml. of concd. ammonium hydroxide. After brief standing (30–60 min.), the product was collected and recrystallized from dimethylformamide-water.

Reprecipitation of a sample from dilute sodium hydroxide gave 2-acetylsulfamyl-4-sulfamyl-*N*-methylaniline, colorless needles from acetone-petroleum ether, m.p. 208–210°.

Anal. Calcd. for $C_9H_{13}N_3O_5S_2$: C, 35.17; H, 4.26; N, 13.67. Found: C, 35.27; H, 4.27; N, 13.68.

7-Acetylsulfamyl-6-chloro-1,2,4-benzothiadiazine-1,1-dioxide. Acetic anhydride (25 ml.) was added to a suspension of 8.9 g. (0.03 mole) of 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide in 75 ml. of pyridine at room temperature. Complete solution occurred within 20 min. and was followed by gradual separation of colorless needles. After standing at room temperature overnight, the product was collected, washed with alcohol, and dried; yield, 7.7 g., m.p. 314°. Recrystallization from either acetone-alcohol or alcohol-water gave colorless needles, soluble in bicarbonate solution; melting point, dependent on rate of heating, 299° (rapid heating), 289° (slow heating); pK'_a 3.7, 7.2.[21]

Anal. Calcd. for $C_9H_8ClN_3O_5S_2$: C, 32.00; H, 2.39; N, 12.44. Found: C, 32.20; H, 2.56; N, 12.36.

A solution of 7-acetylsulfamyl-6-chloro-1,2,4-benzothiadiazine-1,1-dioxide (2 g.) in 10 ml. of 10% aqueous sodium hydroxide when heated on the steam bath for 15 min., cooled, and acidified gave *4-acetylsulfamyl-5-chloro-2-sulfamylaniline;* colorless plates from acetone-alcohol, m.p. 221°; positive test for diazotizable amine.

Anal. Calcd. for $C_8H_{10}ClN_3O_5S_2$: C, 29.31; H, 3.08; N, 12.82. Found: C, 29.54; H, 3.20; N, 12.73.

(20) A. C. Bratton and E. K. Marshall, Jr., *J. Biol. Chem.*, **128**, 537 (1939).

(21) pK'_a values were determined according to the method described by T. V. Parke and W. W. Davis, *Anal. Chem.* **26**, 642 (1954).

Cyclization of 4-acetylsulfamyl-5-chloro-2-sulfamylaniline with formic acid in the usual manner gave 7-acetylsulfamyl-6-chloro-1,2,4-benzothiadiazine-1,1-dioxide; no depression in mixed melting point.

7-Butyrylsulfamyl-6-chloro-1,2,4-benzothiadiazine-1,1-dioxide. Butyric anhydride (25 ml.) was added to a suspension of 8.9 g. (0.03 mole) of 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide in 75 ml. of pyridine at room temperature. Complete solution occurred in 4 hr. After standing at room temperature overnight, the solution was poured into 200 ml. of ice water and acidified with concd. hydrochloric acid. The solid was collected, washed with water, and recrystallized from alcohol-water; yield, 8.1 g. (74%), colorless needles, soluble in bicarbonate solution, m.p. 286°.

Anal. Calcd. for $C_{11}H_{12}ClN_3O_5S_2$: C, 36.11; H, 3.31; N, 11.49. Found: C, 36.31; H, 3.38; N, 11.47.

5-Chloro-2-dimethylaminomethylenesulfamyl-4-sulfamylaniline. 6-Chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (10 g., 0.034 mole) was added to 50 ml. of anhydrous dimethylamine and allowed to stand at room temperature until all the amine had evaporated (2 hr.). The residue was dissolved in 50 ml. of 50% aqueous ethanol and then acidified with dilute hydrochloric acid. Recrystallization of the precipitate from ethanol-water (9:1) gave 5.8 g. (50%) of product, m.p. 208–210°.

Anal. Calcd. for $C_9H_{13}ClN_4O_4S_2$: C, 31.71; H, 3.84; N, 16.44. Found: C, 32.10; H, 3.86; N, 16.35.

5-Chloro-2-piperidinomethylenesulfamyl-4-sulfamylaniline. A mixture of 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (10 g., 0.034 mole) and piperidine (13.6 g., 0.16 mole) was heated on the steam bath for 1 hr., diluted with water, and acidified with dilute hydrochloric acid. The resinous product was dissolved in dilute sodium hydroxide and the solution washed with ether and then acidified. The initial precipitate (4.3 g.) was starting material. Upon prolonged standing, the filtrate yielded 3.8 g. (30%) of product, m.p. 208–210°, which was purified by recrystallization from aqueous alcohol, m.p. 210–212°.

Anal. Calcd. for $C_{12}H_{17}ClN_4O_4S_2$: C, 37.84; H, 4.50; N, 14.71. Found: C, 37.96; H, 4.58; N, 14.69.

6-Chloro-1,2,4-benzothiadiazine-1,1-dioxide-7-sulfonyl chloride. 6-Chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (29.6 g., 0.1 mole) was added in portions to chlorosulfonic acid (150 ml.) and heated on the steam bath for 2 hr. Upon cooling to room temperature, the reaction mixture was poured onto crushed ice. The precipitate was collected on the filter, washed by suspension in 2 l. of ice water, filtered, and air-dried; yield, 30.3 g. (96%), m.p. 250–253°. A sample (10 g.) purified by reprecipitation from acetone (200 ml.) with hexane melted at 259–261°.

Anal. Calcd. for $C_7H_4Cl_2N_2O_4S_2$: C, 26.67; H, 1.28; N, 8.89. Found: C, 26.98; H, 1.43; N, 8.83.

5-Chloro-2-methylsulfamylaniline-4-sulfonyl chloride. 6-Chloro-2-methyl-7-methylsulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (68.3 g., 0.21 mole) was added in portions to 200 ml. of chlorosulfonic acid and heated on the steam bath for 5 hr. Upon cooling, the solution was poured onto crushed ice and the precipitate collected on the filter, washed with water, and dried. Recrystallization from acetone-benzene gave 60 g. (90%) of product, m.p. 150°, with effervescence. Repeated recrystallization from acetone-benzene raised the m.p. to 158°, with effervescence.

Anal. Calcd. for $C_7H_5Cl_2N_2O_4S_2$: C, 26.34; H, 2.53; N, 8.78. Found: C, 26.99; H, 2.64; N, 8.72.

5-Chloro-2-methylsulfamyl-4-sulfamylaniline. 5-Chloro-2-methylsulfamylaniline-4-sulfonyl chloride (43.2 g., 0.135 mole) was added portionwise to 250 ml. of concd. ammonium hydroxide and heated on the steam bath for 1 hr. Upon concentration *in vacuo*, the product was collected and recrystallized from water; yield, 17.9 g. (45%). The compound was obtained in two crystalline modifications; m.p.'s 168–170° and 188–190°. A mixture of both melted at 188–190°.

Anal. Calcd. for $C_7H_{10}ClN_3O_4S_2$: C, 28.05; H, 3.36; N, 14.02. Found: C, 28.19; H, 3.41; N, 13.95.

5-Chloro-4-methylsulfamyl-2-sulfamylaniline. 6-Chloro-1,2,-4-benzothiadiazine-1,1-dioxide-7-sulfonyl chloride (10 g., 0.031 mole) was added to 30 ml. of anhydrous methylamine and allowed to stand at room temperature until excess methylamine had evaporated. The residue was dissolved in 200 ml. of 5% sodium hydroxide, heated on the steam bath for 2 hr. and acidified. Recrystallization of the precipitate from water gave 6.4 g. of product, m.p. 181–183°.

Anal. Calcd. for $C_7H_{10}ClN_3O_4S_2$: C, 28.05; H, 3.36; N, 14.02. Found: C, 28.22; H, 3.54; N, 14.05.

5-Chloro-2-dimethylaminomethylenesulfamyl-4-dimethylsulfamylaniline. 6-Chloro-1,2,4-benzothiadiazine-1,1-dioxide-7-sulfonyl chloride (30 g., 0.095 mole) was added to 150 ml. of anhydrous dimethylamine and allowed to stand at room temperature until excess amine had evaporated. Recrystallization of the residue from alcohol yielded 22.8 g. (64%) of product, m.p. 195–197°.

Anal. Calcd. for $C_{11}H_{17}ClN_4O_4S_2$: C, 35.81; H, 4.65; N, 15.19. Found: C, 35.81; H, 4.72; N, 15.10.

5-Chloro-4-dimethylsulfamyl-2-sulfamylaniline. A suspension of 5-chloro-2-dimethylaminomethylenesulfamyl-4-dimethylsulfamylaniline (6.7 g., 0.018 mole) in 20 ml. of 10% sodium hydroxide was heated on the steam bath for 1 hr., cooled, and acidified with dilute hydrochloric acid. Recrystallization of the precipitate from aqueous alcohol gave 4.0 g. (71%) of product, m.p. 158–160°.

Anal. Calcd. for $C_8H_{12}ClN_3O_4S_2$: C, 30.62; H, 3.86; N, 13.39. Found: C, 30.75; H, 3.93; N, 13.41.

Catalytic hydrogenation[22] *of 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide* (3.0 g.) was performed in methanol (100 ml.) in the presence of 5% ruthenium on charcoal catalyst (1.0 g.) at room temperature and at an initial hydrogen pressure of 39 lb./sq. in. Upon completion of reduction (10 hr.), the mixture was heated to boiling, filtered, and concentrated. An 83% yield of product was obtained which showed no depression in melting point upon admixture with a sample of 6-chloro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide prepared from 5-chloro-2,4-disulfamylaniline and formaldehyde.

Oxidation of 6-chloro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide to 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide. Potassium permanganate (3.75 g.) was added portionwise, with stirring, over 10 min. to a solution of 8.9 g. (0.03 mole) of 6-chloro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide in 150 ml. of water and 10 ml. of 20% sodium hydroxide. The solution was stirred at room temperature for 15 min. and warmed on the steam bath for 5 min. Excess permanganate was destroyed by addition of 2–3 ml. of ethanol. Upon filtration, acidification of the filtrate afforded 7.4 g. (84%) of product, m.p. 337°; mixed melting point with 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine was not depressed.

In like manner oxidation of *6-methyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide* gave *6-methyl-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide* in comparable yield, m.p. 345°; no depression in mixed melting point with material prepared by formic acid ring closure of 5-methyl-2,4-disulfamylaniline.

5-Chloro-2,4-bis(dimethylsulfamyl)-N-(2-phenylethylidene)-aniline. A mixture of 3.4 g. (0.01 mole) of 5-chloro-2,4-bis-(dimethylsulfamyl)aniline and 10 g. (0.04 mole) of 50% phenylacetaldehyde in alcohol was heated at 150° for 30 min. in an open flask. Complete solution occurred as alcohol distilled from the reaction mixture. Upon cooling, the residue was triturated with acetonitrile and the solid collected on the filter; yield, 2.4 g. (55%), m.p. 193–196°. Recrystallization from acetonitrile raised the melting point to 203–205°, $\lambda_{max}^{C_2H_5OH}$ 226–228 and 337–340 mμ, ε 27,351 and 36,106.

(22) We are indebted to Dr. W. H. Jones for this experiment.

Anal. Calcd. for $C_{18}H_{22}ClN_3O_4S_2$: C, 48.69; H, 5.00; N, 9.46. Found: C, 48.95; H, 4.98; N, 9.70.

5-Chloro-2,4-bis(dimethylsulfamyl)-N-(p-nitrobenzylidene)-aniline. A mixture of 3.4 g. of 5-chloro-2,4-bis(dimethylsulfamyl)aniline, 3.0 g. of *p*-nitrobenzaldehyde, and 60 ml. of toluene was heated under reflux with a water separator for 20 hr. Upon cooling, the crystalline solid was collected, triturated with 200 ml. of boiling alcohol, and recrystallized from acetonitrile; yield, 3.6 g. (76%), m.p. 221–223°, $\lambda_{max}^{C_2H_5OH}$ 276–281 mμ, ε 25,270.

Anal. Calcd. for $C_{17}H_{19}ClN_4O_6S_2$: C, 42.99; H, 4.03; N, 11.80. Found: C, 43.03; H, 4.26; N, 11.72.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ANDHRA UNIVERSITY]

New Alkaloids from *Tiliacora racemosa* (Colebr.). III.[1,2a] Constitution[2b] of Tiliacorine and Tiliarine

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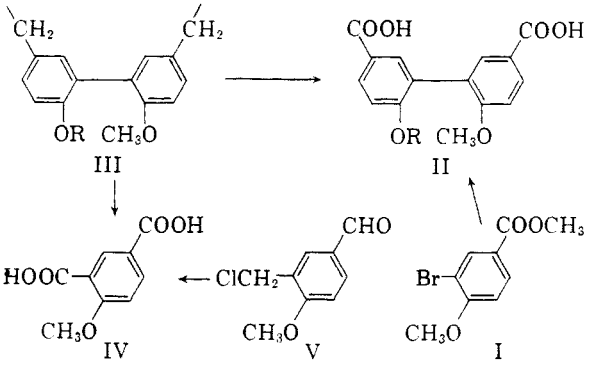
Permanganate oxidation of *O*-methyltiliacorine and *O,N*-dimethyltiliarine gives rise to 2,2′-dimethoxydiphenyl-5,5′-dicarboxylic acid. Tiliacorine and tiliarine yield, on the other hand, 4-methoxyisophthalic acid and no diphenyldicarboxylic acid. It is, therefore, felt that the free hydroxyl is present in the 2-position of the diphenyl system. This was confirmed by the oxidation of *O*-ethyl ethers of the two alkaloids, which yielded 2′-ethoxy-2-methoxy-diphenyl-5,5′-dicarboxylic acid. On this basis, a structure is suggested for tiliacorine which is derived from two coclaurine units and contains a dibenzo-*p*-dioxin system as in menisarine but with a 2′-hydroxy-2-methoxydiphenyl system in place of 2-methoxydiphenyl oxide group. Tiliacorine and tiliarine are thus the only two bisbenzyl isoquinoline alkaloids isolated from nature with 11,11′-diphenyl link.

In parts I[1] and II[2] of this series, tiliacorine and tiliarine were assigned the molecular formulas $C_{32}H_{23}O_3(OH)(2\text{-}OCH_3)(2\text{-}NCH_3)$ and $C_{32}H_{23}O_3$-$(OH)(2\text{-}OCH_3)(1\text{-}NCH_3, 1\text{-}NH)$ respectively. The hydroxyl is phenolic in character, and may be in a sterically hindered position as it resisted methylation with diazomethane. Both alkaloids exhibit a prominent blue color with sulfur-nitric acid reagent[3] indicating a dibenzo-*p*-dioxin system in the molecule. Furthermore, a study of their ultraviolet absorption spectra[2] suggested a close resemblance with trilobine or menisarine.

Confirmation of the above formulas was sought by a study of the permanganate oxidation of these two alkaloids and their *O*-methyl derivatives. *O*-Methyltiliacorine and *O,N*-dimethyltiliarine furnished the same carboxylic acid (m.p. 338–340°; dimethyl ester 171–173°) during oxidation with 2% permanganate at laboratory temperature. Analysis indicated a dicarboxylic acid with two methoxyls in it and it was identified as 2,2′-dimethoxydiphenyl-5,5′-dicarboxylic acid (II. R = CH_3) by direct comparison with a synthetic sample obtained by Ullmann's reaction with methyl-3-bromo-4-methoxybenzoate[4] (I).



The oxidation of these alkaloids to diphenyl-5-5′-dicarboxylic acid (II. R = CH_3) is a very significant feature. Diphenyldicarboxylic acids were previously isolated from cocculidine[5] from *Cocculus luarifolius D.C.*, lycorenine[6] from *Lycoris radiata* Herb., Sinomenine[7] from *Sinomenium acutum* and acetyl thebaol[8] after a series of degradative reactions involving Hofmann degradation. These diphenyldicarboxylic acids possess at least one carboxyl group in one of the *ortho* positions of the diphenyl system.

The isolation of the diphenylcarboxylic acid (II. R = CH_3) is thus very significant and indicates

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(2) (b) A recent publication on the same topic by Anjaneyulu *et. al.* (*Chem. & Ind.*, June 6, p. 702, 1959) has prompted us to publish this paper. The information included in this paper has been delayed in publication as the investigation formed part of the D.Sc. thesis of one of us (K. V. J.) which is under preparation.

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