The *picrate* crystallized from methanol-acetone in yellow flakes, m.p. 136–138°.

Anal. Calcd. for $C_{23}H_{30}N_4O_8$: C, 56.32; H, 6.17; N, 11.42. Found: C, 56.38; H, 6.06; N, 11.16.

1-Ethyl-7-methoxynaphthalene (VIII). An intimate mixture of 0.5 g. of IX and 0.5 g. of 5% palladium charcoal was immersed in an oil bath preheated to 250°. The temperature of the bath was raised to 290° during 30 min. where it was maintained for another 30 min. The cooled mixture was extracted with ether and the extracts were washed with dilute hydrochloric acid. Drying and evaporation of the ether left a residue which was evaporatively distilled at 120° (bath temperature)/0.1 mm. giving 0.15 g. (42%) of crude VIII,[13] 0.1 g. of which was converted to the picrate (0.1 g. of picric acid, 5 ml. of methanol); yield 90 mg., orange needles from aqueous methanol, m.p. 85–87°.

Anal. Calcd. for $C_{19}H_{17}N_3O_9$: C, 54.94; H, 4.13; N, 10.12. Found: C, 54.69; H, 4.28; N, 10.65.

BETHESDA 14, MD.

(13) The ultraviolet spectrum of this distillate in ethanol was consistent with the naphthalene structure.

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Diuretics. VI. 1,2,4-Benzothiadiazine 1,1-Dioxides Substituted at 2,3,4- and 7-*N*-Sulfamoyl Positions

CALVERT W. WHITEHEAD AND JOHN J. TRAVERSO

Received August 9, 1961

Fluorobenzenes were chlorosulfonated to yield 2,4-bischlorosulfonylfluorobenzenes. These were converted to 2,4-bissulfamoylanilines and in turn to 4-alkyl-, aralkyl-, and aryl-1,2,4-benzothiadiazine 1,1-dioxides and their 3,4-dihydro analogues. Other benzothiadiazine 1,1-dioxide derivatives having alkyl and aralkyl groups in the 2, 3, and 7-*N*-sulfamoyl positions were prepared. Comparisons made of these compounds revealed interesting differences in their physical properties and their biological activities.

During the investigation of 1,2,4-benzothiadiazine 1,1-dioxides it became apparent that closely related 2- and 4-alkyl derivatives had marked differences in both their physical and biological properties.[1] Because of these interesting differences the study was extended to benzothiadiazine 1,1-dioxides and 3,4-dihydro analogues having alkyl, aralkyl, and aryl groups in 2,3,4 and 7-*N*-sulfamoyl positions. This paper describes the syntheses of the appropriate compounds and results of the comparisons of their physical properties and of their saluretic activities.

The usual methods of preparing 1,2,4-benzothiadiazines have been to chlorosulfonate anilines and thereby obtain 2,4-bischlorosulfonylanilines.[1] These are converted to sulfamoylanilines and then cyclized by an acylating agent. We found, and it has also been recently reported,[2,3] that fluorobenzenes are easily chlorosulfonated and the resulting 2,4-bischlorosulfonylfluorobenzenes are readily converted to 2,4-bissulfamoylanilines. The latter are very excellent precursors for 4- and some 2-and 3-substituted 1,2,4-benzothiadiazine 1,1,-dioxides. Chlorosulfonation of 1-chloro-3-fluorobenzene and 1-fluoro-3-methylbenzene yielded 5-chloro-2,4-bis(chlorosulfonyl)fluorobenzene and 2,4-bis(chlorosulfonyl)-5-methylfluorobenzene, respectively. The sulfonylchlorides were treated with liquid ammonia and also with dilute aqueous ammonia to yield sulfonamides (I). Both alkyl- and arylamines reacted with the 2,4-bissulfamoylfluorobenzenes (I) by displacing the fluorine with formation of *N*-alkyl- and *N*-arylanilines (II). Displacement of the fluorine with the more basic methyl- and ethylamines (*pK* 10.62 and 10.63) occurred rapidly at room temperature while reactions with aniline (*pK* 4.7) required a higher temperature for reasonably rapid completion. Dilute aqueous ammonia solutions (*pK* 9.21) of I were concentrated by boiling without conversion to the 2,4-bis-sulfamoylanilines (II. R = H). We assume that, at least in the case with ammonia, the displacement is not entirely *pK* dependent.

N-Alkylsulfamoyl and *N*-benzylsulfamoylanilines were prepared by treating 5-chloro-2,4-bischlorosulfonylaniline with appropriate alkylamines or with benzylamine. A method described by Close and co-workers[4] was used to introduce a substituent only on the nitrogen of the sulfamoyl group *ortho* to the amino group. The products in the first case were 2,4-bis- *N*-alkylsulfamoyl-5-chloroanilines (VII. R and R_1 = alkyl), and 2,4-bis-*N*-benzylsulfamoyl-5-chloroanilines (VII. R and R_1 = benzyl). In the second case, 6-chloro-3,4-dihydro-3-keto-7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxide[4] was benzylated with benzyl bromide and sodium in *N*,*N*-dimethylformamide solution to yield 2 - benzyl - 6 - chloro - 3,4 - dihydro - 3 - keto-7-

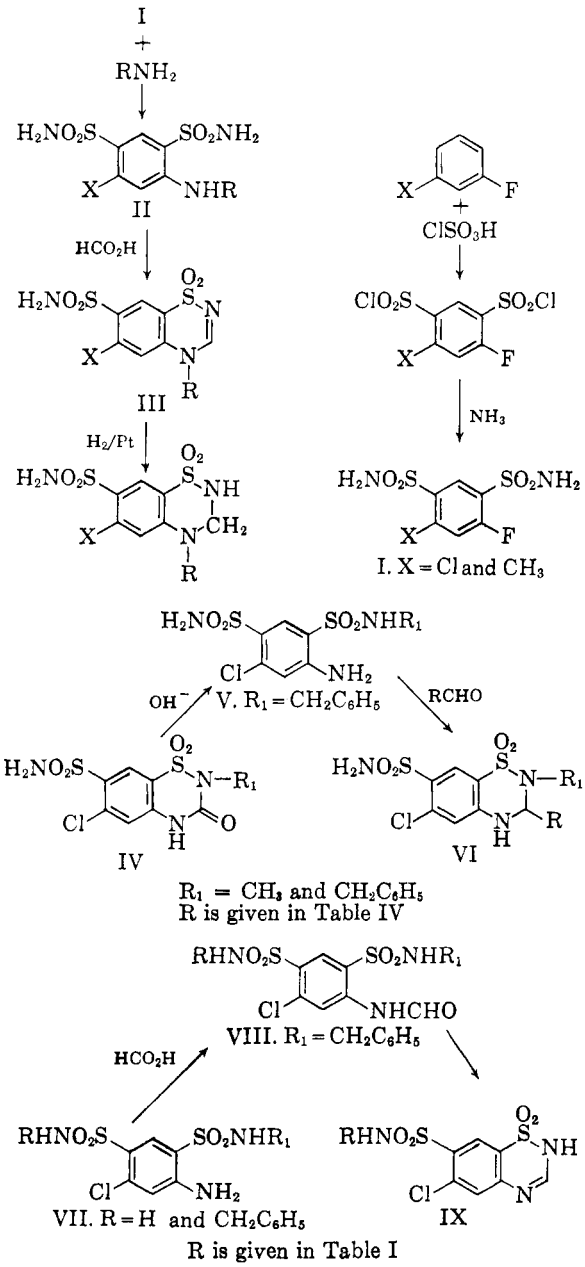
(1) F. C. Novello, S. C. Bell, E. L. A. Abrams, C. Ziegler, and J. M. Sprague, *J. Org. Chem.*, **25**, 970 (1960).

(2) B. G. Boggiano, S. Condon, M. T. Davies, G. B. Jackman, B. G. Overell, V. Petrow, O. Stephenson, and A. M. Wild, *J. Pharm. Pharmacol.*, **12**, 419 (1960).

(3) G. B. Jackman, V. Petrow, O. Stephenson, and A. M. Wild, *J. Pharm. Pharmacol.*, **12**, 648 (1960).

(4) W. L. Close, L. R. Swett, L. F. Brady, J. H. Short, and M. Vernsten, *J. Am. Chem. Soc.*, **82**, 1132 (1960).

sulfamoyl - 1,2,4 - benzothiadiazine 1,1 - dioxide (IV. $R_1 = CH_2C_6H_5$). Hydrolysis of this in sodium hydroxide gave 2-*N*-benzylsulfamoyl-5-chloro-4-sulfamoylaniline (V. $R_1 = CH_2C_6H_5$).



Cyclizations of the above *N*-substituted-2,4-bis-sulfamoylanilines were studied by treating them with substances that have been shown to cause cyclization[5,6] of the unsubstituted *o*-sulfamoylanilines. It was found that a substituent on the nitrogen of the amino group has an interesting effect upon these cyclization processes. For example, 2,4-bissulfamoyl-*N*-alkylanilines (II) were readily cyclized with formic acid, but cyclization did not occur with urea or acetaldehydes. Formic acid yielded 4-alkyl-7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxides (III). Acetaldehydes—*i.e.*, cyclohexyl- and cyclopentylacetaldehyde—in the presence of mineral acid yielded only unchanged starting material. Cyclizations with formaldehyde were not attempted because the desired 3,4-dihydro-4-substituted 7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxides were easily obtained by hydrogenating the unsaturated derivatives III. The facility with which the 4-substituted benzothiadiazine 1,1-dioxides are catalytically hydrogenated is contrasted by the inertness of 3-alkyl- or 3-aralkylbenzothiadiazine 1,1-dioxides toward hydrogenation.[7]

Equally interesting effects caused by substituents on the sulfamoyl nitrogen *ortho* to the amino group were observed with 5-chloro-2,4-bis-*N*-alkylsulfamoylanilines and 5-chloro-2-*N*-benzylsulfamoylanilines. Formaldehyde, arylaldehydes, and cycloalkylacetaldehydes all reacted with 5-chloro-2-*N*-methylsulfamoyl-4-sulfamoylaniline and with 2-*N*-benzylsulfamoyl-5-chloro-4-sulfamoylaniline to yield cyclic 3,4-dihydrobenzothiadiazine 1,1-dioxides (VI. $R_1 = CH_3$ and $CH_2C_6H_5$). Urea did not react with 2,4-bis-*N*-alkylsulfamoylanilines (VII) at temperatures of 185–195°. The alkylsulfamoylanilines were recovered unchanged. Formic acid did, however, react with 2,4-bis-*N*-alkylsulfamoylanilines to give the corresponding 5-chloro-2,4-bis-*N*-alkylsulfamoylformanilides (VIII. R and R_1 = alkyl). In this case the *N*-alkyl substituent prevented the formanilide from cyclizing. When it was possible to remove a substituent from the *ortho* sulfamoyl group, the intermediate formanilide was allowed to cyclize. This was conveniently demonstrated by employing *N*-benzylsulfamoyl derivatives. Debenzylations occurred when both 2-*N*-benzylsulfamoyl-5-chloro-4-sulfamoylaniline and 5-chloro-2,4-bis-*N*-benzylsulfamoylaniline (VII. $R_1 = CH_2C_6H_5$) were heated in formic acid. The products were 6-chloro-7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxide (IX. R = H), and 6-chloro-7-*N*-benzylsulfamoyl-1,2,4-benzothiadiazine 1,1-dioxide (IX. R = $CH_2C_6H_5$), respectively. The structure of the 6-chloro-7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxide was confirmed by comparing it with an authentic sample. The position of the remaining benzyl group of IX was demonstrated by titrating it in 66% *N*,*N*-dimethylformamide. Two ionizable groups were observed with pK_a' of 6.8 and 12.9. The benzyl group cannot be on the nitrogen in the two position of the thiadiazine ring and must be on the seven sulfamoyl nitrogen.

The relative stabilities of the 2,3- and 4-alkyl-1,2,4-benzothiadiazine 1,1-dioxides toward hydrolysis were determined by titration with acid or base in *N*,*N*-dimethylformamide solution and by ultraviolet absorption spectra in neutral, acid, and basic

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

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

(7) C. W. Whitehead, J. J. Traverso, H. R. Sullivan, and F. J. Marshall, *J. Org. Chem.*, 26, 2814 (1961).

alcohol all at room temperature. When 4-alkyl- and 4-aryl-6-chloro-7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxides were titrated in 66% *N,N*-dimethylformamide, they exhibited two pK_a"s in the range of 10.3–11.5 and 12.5–13.3. As these compounds have only one ionizable group, the second equivalent of base is used in hydrolyzing open the ring. Hydrolysis of the ring occurred rapidly because the observed titration curve matched the standard curve. Furthermore, hydrolysis and ionization of the newly formed sulfonamide occur simultaneously. The ultraviolet absorption spectra of 4-benzyl-6-methyl-7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxide in neutral alcohol showed two maxima at 210 mμ and 284 mμ. The absorption curve and the compound were not altered when hydrochloric acid was added to give a pH of 2–3. Two new bands at 267 mμ and 318 mμ occurred when base was added. This new ultraviolet absorption curve is identical to that of 5-chloro-2,4-bissulfamoyl-*N*-benzylaniline. Addition of acid did not cause the new absorption curve to revert to the original shape. The 4-alkyl - 6 - chloro - 3,4 - dihydro - 7 - sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxides exhibited two pK_a"s at 11.3 and 13.3 in 66% *N,N*-dimethylformamide. Ultraviolet absorption curves of the 4-alkyl-3,4-dihydro derivatives show maxima at approximately 275 mμ and 316 mμ. These maxima were not shifted in either base or acid. It could not be determined from the titration or ultraviolet absorption curves whether hydrolysis of the 4-alkyl-3,4-dihydro derivatives occurred. This is because both their titration and ultraviolet absorption curves are almost identical to the corresponding curves for the hydrolyzed open ring compounds. A sample of 6-chloro-3,4-dihydro-4-ethyl-7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxide was not hydrolyzed in a solution of 5% sodium hydroxide at 50° after three hours. The unchanged compound was recovered when the solution was acidified. The 2-alkyl- and 2,3-dialkyl-6-chloro-3,4-dihydro-7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxides showed only one ionizable group in the range of pK_a' 11.85–11.90 in 66% *N,N*-dimethylformamide. This ionization is associated with the exocyclic sulfonamide. The titration curves were reversible indicating that hydrolysis does not occur under these conditions. As the pK_a' of the exocyclic sulfonamide is now established as 11.85–11.90, it becomes apparent that hydrolysis of the 4-alkyl-1,2,4-benzothiadiazine 1,1-dioxides occurs at a *p*H of 12.5–13.3.

The endocyclic sulfonamide of 6-chloro-3,4-dihydro - 3 - keto - 7 - sulfamoyl - 1,2,4, - benzothiadiazine 1,1-dioxide has a pK_a' of less than 3 in 66% *N,N*-dimethylformamide and the exocyclic sulfonamide a value of 11.6. The pK_a' values for 2-benzyl-6-chloro-3-keto-7-sulfamoyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxide (IV. R_1 = $CH_2C_6H_5$) were found to be 8.35 and 12.2. The value 8.35 is similar to the value 8.7 observed for the enolic group of barbituric acid and suggests an enolic character for the 3-keto group of IV. Further evidence of this enolization was a low intense carbonyl infrared absorption at 5.77 μ and a broad absorption band at 3.1–3.4 μ. The latter indicates the bonded nature of the enolic hydrogen.

The infrared absorption of all the 1,2,4-benzothiadiazine 1,1-dioxides[8] showed characteristic NH absorption at 2.9–3.1 μ and two bands for the SO_2 groups that are split at 7.5 μ and 8.6 μ. The 3,4-dihydro derivatives including those substituted at positions 2,3, and 4 show a characteristic strong and sharp infrared absorption band at 6.2 μ. This 6.2 band was used to help identify and confirm the 3,4-dihydro structures.

The results obtained in this laboratory show that alkyl, aralkyl, or aryl substituents attached to the 4 position of 6-chloro-7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxide result in a nulification of the saluretic activity when the dose is in the range of 0.5–5.0 mg. per kg. This loss of activity may be a result of *in vivo* hydrolysis of the heterocyclic ring. An alkyl substituent in the same position of 6 - chloro - 3,4 - dihydro - 7 - sulfamoyl - 1,2,4 - benzothiadiazine 1,1-dioxide also causes almost complete diminution of saluretic activity. These latter dihydro derivatives, however, were found to be stable to hydrolysis. 2-Benzyl-6-chloro-3,4-dihydrosulfamoyl-1,2,4-benzothiadiazine 1,1-dioxide is approximately five times more active than 6-chloro-3,4 - dihydro - 6 - sulfamoyl - 1,2,4 - benzothiadiazine. When a cyclopentylmethyl or phenyl group is added to the 3 position of the 2-benzyl-3,4-dihydro compound, the activity is considerably decreased. Saluretic activies of 6-chloro-3-cyclopentylmethyl - 3,4 - dihydro - 2 - methyl - 7 - sulfamoyl - 1,2,4 - benzothiadiazine 1,1 - dioxide and 6-chloro-3,4-dihydro-2-methyl-3-(5-norbornen-2-yl)-7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxide are 25 times that of 6-chloro-3,4-dihydro-7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxide.

EXPERIMENTAL

5-Chloro-2,4-bis(chlorosulfonyl)fluorobenzene. One kilogram of chlorosulfonic acid was placed in a three-necked flask fitted with a stirrer and a large bore rubber tube. The rubber tube was attached to the top of a column packed with porcelain chips. The escaping hydrochloric acid gas was dissolved in water flowing over the porcelain chips. One hundred grams of 1-chloro-3-fluorobenzene was added dropwise to the stirred chlorosulfonic acid. The mixture was heated gradually and 400 g. of sodium chloride was added portionwise by means of a powder-addition flask. By the time the sodium chloride had been added the temperature was about 120°. Heating was continued until the temperature reached 160° and maintained for 4 hr. The mixture became thick and the stirring was stopped. Contents of the flask were added to crushed ice and the resulting solid collected on

(8) See also L. H. Werner, A. Halamandaris, S. Ricca, Jr., L. Dorfman, and G. D. Stevens, *J. Am. Chem. Soc.*, **82**, 1161 (1960).

a filter funnel. After the product was washed several times with water, it was dissolved into ether. The ether solution was washed four times with cold water then dried over magnesium sulfate. Evaporation of the ether yielded 130 g. (52%) of product which melted at 105–107° when recrystallized from a mixture of ether and petroleum ether.

Anal. Calcd. for $C_6H_2Cl_3FO_4S_2$: C, 22.05; H, 0.62. Found: C, 22.58; H, 0.92.

2,4-Bis(chlorosulfonyl)-5-methylfluorobenzene was prepared from 1-fluoro-3-methylbenzene in the same manner described above for the preparation of 5-chloro-2,4-bis-(chlorosulfonyl)fluorobenzene. The yield of 2,4-bis(chlorosulfonyl)-5-methylfluorobenzene was 139 g. (50%), m.p. 97°.

Anal. Calcd. for $C_7H_5Cl_2FO_4S_2$: C, 27.43; H, 1.64. Found: C, 27.55; H, 1.72.

5-Chloro-2,4-bis(sulfamoyl)fluorobenzene. One hundred grams of 5-chloro-2,4-bis(chlorosulfonyl)fluorobenzene was added portionwise to a large excess of liquid ammonia in an open beaker. The sulfonyl chloride dissolved and the excess liquid ammonia was allowed to evaporate. The solid product was recrystallized from dilute alcohol, yield 90%, m.p. 223–224°.

Anal. Calcd. for $C_6H_6ClFN_2O_4S_2$: C, 25.02; H, 2.03; N, 9.73. Found: C, 25.42; H, 1.99; N, 9.52.

5-Methyl-2,4-bis(sulfamoyl)fluorobenzene. One hundred grams of 2,4-bis(chlorosulfonyl)-5-methylfluorobenzene was treated with liquid ammonia to give a 90% yield of the *bis*-sulfonamide, m.p. 210°.

Anal. Calcd. for $C_7H_9FN_2O_4S_2$: N, 10.44. Found: 10.34.

5-Chloro-2,4-bis(sulfamoyl)anilines and 5-methyl-2,4-bis-(sulfamoyl)anilines (Table I). A solution of 28.8 g. (0.1 mole) of 5-chloro-2,4-bis(sulfamoyl)fluorobenzene or 26.8 g. (0.1 mole) of 5-methyl-2,4-bis(sulfamoyl)fluorobenzene, 15 g. (0.15 mole) of triethylamine, and 0.1 mole of the appropriate primary amine was dissolved in dilute alcohol and warmed on the steam bath. After 1–2 hr. the solution was concentrated under reduced pressure, diluted with water, and neutralized with dilute hydrochloride acid. The products crystallized from solution and were further purified by recrystallization from dilute alcohol.

6-Chloro-4-substituted 7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxides and 6-methyl-4-substituted 7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxides (Table II). Ten grams of the *N*-alkyl- or *N*-aryl-5-chloro or 5-methyl-2,4-bis(sulfamoyl)-aniline was dissolved in 50–75 ml. of hot formic acid and boiled under reflux for 4 hr. The hot solution was concentrated under reduced pressure and diluted with water. The solid product was collected and washed with water until it was free of acid. Recrystallization was from dilute alcohol or from a mixture of alcohol, water, and *N,N*-dimethylformamide.

6-Chloro-3,4-dihydro-4-substituted 7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxides and 3,4-dihydro-6-methyl-4-substituted 7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxides (Table III). Five grams of the 6-chloro- or 6-methyl-7-sulfamoyl-4-substituted 1,2,4-benzothiadiazine 1,1-dioxide was dissolved in hot ethyl alcohol and reduced over platinum catalyst with hydrogen at 1000 lb. pressure and at 80°. The catalyst was separated by filtration. The filtrate was concentrated to yield the product which was recrystallized from dilute alcohol.

6-Chloro-3,4-dihydro-2-methyl-3-substituted 7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxides (Table IV). To a warm solution of 3 g. (0.01 mole) of 5-chloro-2-*N*-methylsulfamoyl-4-sulfamoylaniline[4] in 40 ml. of a 50% mixture of ethanol and 6 *N* hydrochloric acid was added 0.01 mole of the aldehyde. The product separated after standing at room temperature. It was collected on a filter funnel, washed several times with water, and recrystallized from dilute alcohol.

2-Benzyl-6-chloro-3-keto-7-sulfamoyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxide. Four-tenths mole (124.4 g.) of 6 - chloro - 3,4 - dihydro - 3 - keto - 7 - sulfamoyl - 1,2,4-benzothiadiazine 1,1-dioxide[4] was dissolved in 150 ml. of *N,N*-dimethylformamide. To this was added 9.6 g. (0.4 mole) of sodium hydride. After the sodium hydride had dissolved, 50.4 g. (0.4 mole) of benzylchloride was added and the solution heated to 70° for 1 hr. The cooled mixture was poured into 4 l. of water and the product separated. It was recrystallized from water, yield 20 g. (25%), m.p. 243°.

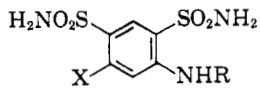
The above alkylation was repeated, only 0.4 mole of benzyl bromide was used in place of benzyl chloride, and the reaction heated for 12 hr. at 70°. The yield was 84%, m.p. 243°.

Anal. Calcd. for $C_{14}H_{12}ClN_3O_5S_2$: C, 41.84; H, 3.01, N, 10.45. Found: C, 41.93; H, 2.96; N, 10.41.

2-N-Benzylsulfamoyl-5-chloro-4-sulfamoylaniline. Eighteen grams of 2-benzyl-6-chloro-3-keto-7-sulfamoyl-3,4-dihydro-

TABLE I

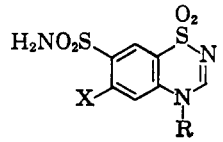
5-CHLORO- AND 5-METHYL-2,4-BIS(SULFAMOYL)ANILINES



R	X	Formula	Yield, %	M.P.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3	Cl	$C_7H_{10}ClN_3O_4S_2$	70	249			14.01			14.09
C_2H_5	Cl	$C_8H_{12}ClN_3O_4S_2$	70	165			13.31			13.07
$(CH_2)_2OCH_3$	Cl	$C_9H_{14}ClN_3O_5S_2$	51	165			12.26			11.88
n-C_3H_7	Cl	$C_9H_{14}ClN_3O_4S_2$	50	188	33.05	4.31	12.85	33.26	4.62	12.71
C_6H_5	Cl	$C_{12}H_{12}ClN_3O_4S_2$	40	230–240			11.62			11.73
C_6H_{11}	Cl	$C_{12}H_{18}ClN_3O_4S_2$	64	214	39.30	4.94	11.45	39.61	5.05	11.02
$C_6H_5CH_2$	Cl	$C_{13}H_{14}ClN_3O_4S_2$	50	200	41.70	3.76	11.20	42.07	3.82	11.03
CH_3	CH_3	$C_8H_{13}N_3O_4S_2$	31	243	34.46	4.71	15.05	34.87	5.02	14.99
C_2H_5	CH_3	$C_9H_{15}N_3O_4S_2$	20	170	36.90	5.16	14.35	36.80	5.30	14.12
$(CH_2)_2OH$	CH_3	$C_9H_{15}N_3O_5S_2$	51	205	34.00	4.90	13.60	34.89	5.45	13.34
$(CH_2)_2OCH_3$	CH_3	$C_{10}H_{17}N_3O_5S_2$	35	147			12.99			13.05
C_6H_5	CH_3	$C_{13}H_{15}N_3O_4S_2$	73	178	45.70	4.43	12.32	45.57	4.56	12.31
C_6H_{11}	CH_3	$C_{13}H_{21}N_3O_4S_2$	55	208			12.09			12.01
$C_6H_5CH_2$	CH_3	$C_{14}H_{17}N_3O_4S_2$	30	198	47.30	4.82	11.82	47.24	4.91	11.76
$(CH_2)_2OC_6H_5$	CH_3	$C_{15}H_{19}N_3O_5S_2$	70	192	46.74	4.97	10.90	46.75	4.69	10.63

TABLE II

4-SUBSTITUTED 1,2,4-BENZOTHIADIAZINE 1,1-DIOXIDES

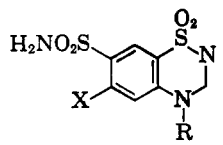


R	X	Formula	Yield, %	M.P.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3	Cl	$C_8H_8ClN_3O_4S_2$	65	280	31.01	2.60	13.51	31.41	2.39	13.21
C_2H_5	Cl	$C_9H_{10}ClN_3O_4S_2$	75	260	33.40	3.12	12.98	33.51	3.18	12.62
n-C_3H_7	Cl	$C_{10}H_{12}ClN_3O_4S_2$	57	252	35.55	18.98[a]	12.44	35.49	19.00[a]	12.43
$CH_3O(CH_2)_2$	Cl	$C_{10}H_{12}ClN_3O_5S_2$	78	280	33.92	3.41	11.89	34.35	3.70	11.82
C_6H_5	Cl	$C_{13}H_{10}ClN_3O_4S_2$	57	244	42.80	17.28[a]	11.32	42.74	16.93[a]	11.09
C_6H_{11}	Cl	$C_{13}H_{16}ClN_3O_4S_2$	60	250		16.63[a]			16.66[a]	
$C_6H_5CH_2$	Cl	$C_{14}H_{12}ClN_3O_4S_2$	54	272	43.60	3.11	10.92	43.58	3.39	10.69
CH_3	CH_3	$C_9H_{11}N_3O_4S_2$	50	310	37.36	3.83	14.52	37.70	3.86	14.32
$HO(CH_2)_2$	CH_3	$C_{10}H_{13}N_3O_5S_2$	60	264	37.67	4.12	13.18	37.62	4.17	12.58
$HCO_2(CH_2)_2$	CH_3	$C_{11}H_{13}N_3O_6S_2$	58	272	38.08	3.77	12.13	37.85	3.94	11.95
C_6H_5	CH_3	$C_{14}H_{13}N_3O_4S_2$	40	195	47.95	3.73	11.97	48.64	4.12	11.96
C_6H_{11}	CH_3	$C_{14}H_{19}N_3O_4S_2$	50	261	47.10	5.32	11.76	47.00	4.99	11.37
$C_6H_5CH_2$	CH_3	$C_{15}H_{15}N_3O_4S_2$	51	250	49.30	4.14	11.50	49.28	4.37	11.54
$C_6H_5O(CH_2)_2$	CH_3	$C_{16}H_{17}N_3O_5S_2$	55	262	48.70	4.34	10.55	48.57	4.51	10.51
$C_6H_5(CH_2)_2$	CH_3	$C_{16}H_{17}N_3O_4S_2$	73	222	50.60	4.52	11.08	50.66	4.65	10.82

[a] Values for sulfur.

TABLE III

3,4-DIHYDRO-4-SUBSTITUTED 1,2,4-BENZOTHIADIAZINE 1,1-DIOXIDES



R	X	Formula	Yield, %	M.P.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3	Cl	$C_8H_{10}ClN_3O_4S_2$	60	245	30.97	3.21		31.03	3.21	
C_2H_5	Cl	$C_9H_{12}ClN_3O_4S_2$	70	205	33.21	3.72		33.18	3.80	
$H_3CO(CH_2)_2$	Cl	$C_{10}H_{14}ClN_3O_5S_2$	50	232	33.85	3.69	11.84	33.92	3.70	11.85
C_6H_{11}	Cl	$C_{13}H_{18}ClN_3O_4S_2$	70	215	41.10	4.78		40.78	5.00	
CH_3	CH_3	$C_9H_{13}N_3O_4S_2$	92	245	37.10	4.50	14.42	37.30	4.62	14.39
$C_6H_5CH_2$	Cl	$C_{14}H_{14}ClN_3O_4S_2$	70	192			10.87			10.51
$C_6H_5(CH_2)_2$	CH_3	$C_{16}H_{19}N_3O_4S_2$	81	198	50.40	5.03	11.02	50.81	4.99	10.58
$C_6H_5O(CH_2)_2$	CH_3	$C_{16}H_{19}N_3O_5S_2$	80	200	48.40	4.83	10.60	48.31	4.77	10.57

1,2,4-benzothiadiazine 1,1-dioxide was boiled under reflux in 200 ml. of 20% sodium hydroxide solution for 8 hr. The cooled solution was filtered and acidified with concentrated hydrochloric acid. The product was collected and recrystallized from dilute alcohol, yield 10 g. (64%), m.p. 155°.

Anal. Calcd. for $C_{13}H_{14}ClN_3O_4S_2$: C, 41.60; H, 3.76; N, 11.20. Found: C, 41.82; H, 3.72; N, 11.03.

6-Chloro-2-benzyl-3,4-dihydro-7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxide (Table IV). To a stirred solution containing 2 g. of 2-*N*-benzylsulfamoyl-5-chloro-4-sulfamoylaniline in 250 ml. of hot water was added dropwise 1.5 g. of 37% formalin. The solution was boiled under reflux for 1.5 hr. The product separated after the solution was cooled. It was collected and recrystallized from dilute alcohol and then from alcohol.

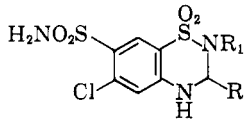
6-Chloro-2-benzyl-3,4-dihydro-3-substituted 7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxides (Table IV). A solution containing 2 g. of 2-*N*-benzylsulfamoyl-5-chloro-4-sulfamoylaniline and an equal molar quantity of the appropriate aldehyde in a mixture of 10 ml. of 6*N* hydrochloric acid and 10 ml. of ethyl alcohol was allowed to stand at room temperature for 2–3 hr. Water was added to cause complete separation of the product. The solid was collected, washed with water, and recrystallized from dilute alcohol.

6-Chloro-7-N-benzylsulfamoyl-1,2,4-benzothiadiazine 1,1-dioxide. To 21.4 g. or 0.2 mole of benzylamine and 20.2 g. or 0.02 mole of triethylamine in 200 ml. of dioxane was added 26 g. of 5-chloro-2,4-bischlorosulfonylaniline in 150 ml. of dioxane. The dioxane solution was diluted with water and concentrated under reduced pressure. The resulting solid was recrystallized from alcohol to yield 14 g. of 5-chloro-2,4-bis-*N*-benzylsulfamoylaniline, m.p. 160°.

The above product was dissolved in 50 ml. of 98% formic acid and boiled under reflux for 6 hr. The formic acid was distilled under reduced pressure and the 6-chloro-7-*N*-benzylsulfamoyl-1,2-4-benzothiadiazine 1,1-dioxide separated from solution. It was recrystallized from dilute alcohol, m.p. 268–270°, yield 7 g. (9%).

TABLE IV

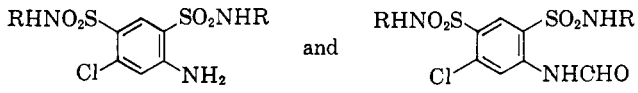
3,4-DIHYDRO-2,3-DISUBSTITUTED 1,2,4-BENZOTHIADIAZINE 1,1-DIOXIDES



R	R_1	Formula	Yield, %	M.P.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Furfuryl	CH_3	$C_{12}H_{12}ClN_3O_5S_2$	70	240			11.10			10.97
Cyclopentylmethyl	CH_3	$C_{14}H_{20}ClN_3O_4S_2$	75	235	42.70	5.12	10.68	42.99	5.21	10.56
6-Methyl-3-cyclohexenyl	CH_3	$C_{15}H_{19}ClN_3O_4S_2$	71	234	44.51	4.93	10.35	44.40	4.92	10.34
5-Norbornen-2-yl	CH_3	$C_{15}H_{18}ClN_3O_4S_2$	50	260	44.62	4.48	10.39	44.69	4.54	10.17
3-Methylcyclopentylmethyl	CH_3	$C_{15}H_{22}ClN_3O_4S_2$	80	235	44.18	5.42	10.28	44.17	5.32	10.22
Cyclohexylmethyl	CH_3	$C_{15}H_{22}ClN_3O_4S_2$	68	282	44.18	5.42	10.28	44.32	5.29	10.46
3-Methyl-5-norbornen-2-yl	CH_3	$C_{16}H_{20}ClN_3O_4S_2$	50	246	45.80	4.82	10.05	45.60	4.89	10.32
Cycloheptylmethyl	CH_3	$C_{16}H_{24}ClN_3O_4S_2$	75	275	45.40	5.73	9.92	45.18	6.09	9.72
Hydrogen	$C_6H_5CH_2$	$C_{14}H_{14}ClN_3O_4S_2$	50	226	43.40	3.66	10.84	43.48	3.74	10.68
Phenyl	$C_6H_5CH_2$	$C_{20}H_{18}ClN_3O_4S_2$	78	233			9.09			9.03
Cyclopentylmethyl	$C_6H_5CH_2$	$C_{20}H_{24}ClN_3O_4S_2$	75	210	50.90	5.09	8.96	50.42	5.07	8.90

TABLE V

5-CHLORO-2,4-BIS-*N*-ALKYLSULFAMOYLANILINES AND -FORMANILIDES



R	Formula	Yield, %	M.P.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
C_2H_5	$C_{10}H_{16}ClN_3O_4S_2$	67	184	35.28	4.73	12.32	35.68	4.76	11.81
CH_2=$CHCH_2$	$C_{12}H_{16}ClN_3O_4S_2$	42	130	39.50	4.12	11.50	39.80	4.55	11.41
n-C_3H_7	$C_{12}H_{20}ClN_3O_4S_2$	63	120	39.10	5.42	11.37	39.38	5.26	11.12
C_2H_5	$C_{11}H_{16}ClN_3O_5S_2$	50	152	35.77	4.37	11.41	35.89	4.40	11.58
CH_2=$CHCH_2$	$C_{12}H_{16}ClN_3O_5S_2$	49	140	39.63	4.10	10.68	39.95	4.25	10.70
n-C_3H_7	$C_{12}H_{20}ClN_3O_5S_2$	49	152	39.35	5.04	10.58	39.69	4.51	10.68

Anal. Calcd. for $C_{14}H_{12}ClN_3O_4S_2$: N, 10.89; S, 16.63. Found: N, 10.65; S, 16.74.

6-Chloro-7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxide from 2-N-benzylsulfamoyl-5-chloro-4-sulfamoylaniline. A solution of 0.2 g. of 2-*N*-benzylsulfamoyl-5-chloro-4-sulfamoylaniline in 5 ml. of 98% formic acid was boiled under reflux for 1 hr. The solution was cooled and the product crystallized, yield 0.1 g. (73%), m.p. 342–343° (reported 342.5–343°).[9]

5-Chloro-2,4-bis-N-alkylsulfamoylanilines and 5-chloro-2,4-bis-N-alkylsulfamoylformanilides (Table IV). One-tenth mole of the appropriate alkylamine in dioxane solution was treated with 5-chloro-2,4-bischlorosulfonylaniline to yield 5-chloro-2,4-bis-*N*-alkylsulfamoylanilines after the procedure of the Schotten-Baumann reaction.

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

Eight grams of the 5-chloro-2,4-bis-*N*-alkylsulfamoylaniline was boiled in 50 ml. of 98% formic acid for 3–4 hr. The formic acid solution was concentrated under reduced pressure and the solid residue recrystallized from ethyl acetate.

Acknowledgment. The authors thank W. L. Brown, H. L. Hunter, G. Maciak, A. C. Brown, and R. L. Simon for the microanalyses and D. Woolf and L. Howard for the physical chemical measurements.

The saluretic activities were determined by R. H. Tust of these laboratories.

INDIANAPOLIS 6, IND.