11 and *p*H 1 identical to that of 6-chloro-4,5-diaminopyrimidine.

Anal. Calcd. for $C_4H_5N_4Cl$: C, 33.3; H, 3.46. Found: C, 33.7; H, 3.88.

6-Methylamino-9-(tetrahydro-2-furyl)purine. 6-Chloro-9-(tetrahydro-2-furyl)purine (I) (1.5 g.) was added to 75 ml. of 40% aqueous methylamine and the solution heated on a steam bath for 1 hr. The solution was then reduced to an oil under vacuum and the syrupy residue recrystallized from a mixture of petroleum ether (b.p. 60–110°) and ethyl acetate to yield 0.9 g. of white crystals, m.p. 103–104°.

Anal. Calcd. for $C_{10}H_{13}N_5O$: C, 54.8; H, 5.94. Found: C, 54.6; H, 5.79.

6-Cyano-9-(tetrahydro-2-furyl)purine. 6-Cyanopurine[10] (2.0 g.) was stirred in 75 ml. of ethyl acetate with *p*-toluenesulfonic acid (0.1 g.) present, while 1.0 g. of 2,3-dihydrofuran was added over a period of 30 min. at room temperature. After stirring for 2 hr. at 50° the solution was treated with charcoal and filtered. The filtrate was washed once with 50 ml. of saturated sodium carbonate and once with 75 ml. of water, then dried over anhydrous sodium sulfate. Upon removal of the ethyl acetate under reduced pressure, an oily residue remained which solidified upon standing. Recrystallization from a mixture of petroleum ether (b.p. 60–110°) and ethyl acetate yielded 1.3 g. of crystalline product. A second recrystallization from the same solvent mixture gave a product of m.p. 92–93°.

Anal. Calcd. for $C_{10}H_9N_5O$: C, 55.8; H, 4.18; N, 32.6. Found: C, 55.8; H, 4.50; N, 32.4.

Trimethyl[9-(tetrahydro-2-furyl)-6-purinyl]ammonium chloride. To a solution of 3 g. of anhydrous trimethylamine, dissolved in 30 ml. of anhydrous benzene, was carefully added a solution of 5.0 g. of 6-chloro-9-(tetrahydro-2-furyl)purine, dissolved in 50 ml. of anhydrous benzene. The solution was allowed to stand at room temperature for 30 min. Reaction took place almost immediately as evidenced by the formation of a white precipitate. This precipitate was removed by filtration and recrystallized from an absolute ethanol-ether mixture to yield 6.2 g., m.p. 148°.

Anal. Calcd. for $C_{12}H_{18}N_5OCl$: C, 50.8; H, 6.36. Found: C, 50.5; H, 6.54.

Acknowledgment. The authors are indebted to James J. Sims who prepared trimethyl[9-(tetrahydro-2-furyl)-6-purinyl]ammonium chloride (VII) for this study.

TEMPE, ARIZ.

[CONTRIBUTION FROM THE MEDICINAL CHEMICAL RESEARCH DEPARTMENT, SCHERING CORP.]

3-Substituted Dihydrobenzothiadiazine 1,1-Dioxides as Diuretic Agents[1]

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Received April 6, 1961

A series of 3-substituted 3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxides has been synthesized by the condensation of substituted orthanilamides with aldehydes and the compounds tested for their efficacy as diuretic agents. Some side products and unusual reactions which occurred in the application of the general synthetic method have been examined.

The discovery of chlorothiazide, 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide (I. Y = R = H, X = Cl), as an orally effective diuretic agent with a concomitant favorable effect on electrolyte excretion rates announced in 1957 by Novello and Sprague[2] has led to a major advance in diuretic therapy. We have been engaged in preparing other compounds of the 1,2,4-benzothiadiazine type with the object of finding new agents with superior diuretic properties. Saturation of the 3,4- double bond in I (Y = R = H, X = Cl) resulted in a compound with at least ten times the potency of chlorothiazide.[3] Our research has resulted in the synthesis of a series of 3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxides (II) with emphasis placed on substituents at position 3. Recently other reports of work in this area have appeared.[4]

From our studies, 6-chloro-3-dichloromethyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-di-

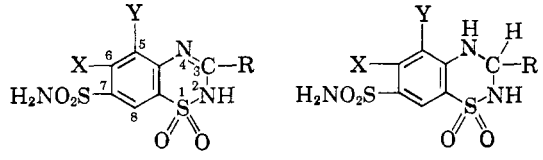
(1) Presented in part before the Division of Medicinal Chemistry, 136th Meeting of the American Chemical Society, Atlantic City, N. J., September 1959.

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

(3) While this work was in progress, G. de Stevens, L. H. Werner, A. Halamandaris, and S. Ricca, Jr., *Experientia*, **14**, 463 (1958) described the synthesis and diuretic activity of hydrochlorothiazide, 6-chloro-3,4-dihydro-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (II. Y = R = H; X = Cl).

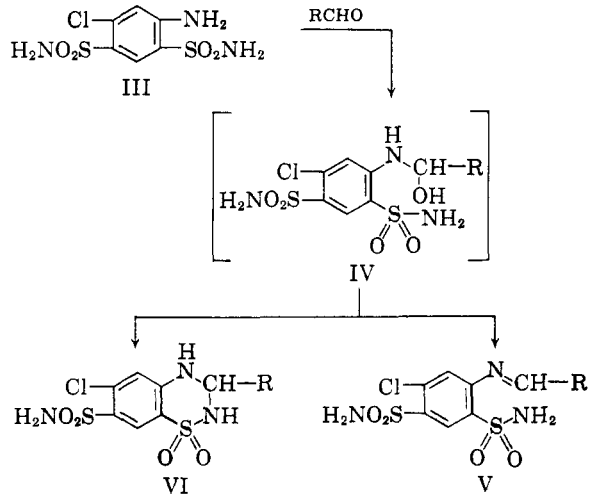
(4)(a) M. E. Goldberg and K. Hwang, Federation Meeting, Atlantic City, N. J., September 1959. (b) J. M. McManus, A. Scriabine, S. Y. Pan, W. M. McLamore, and G. D. Laubach, American Chemical Society Meeting, Atlantic City, N. J., September 1959. (c) R. M. Taylor and M. M. Winbury, *Pharmacologist*, **1**, 53, Fall 1959, No. 2; (d) C. T. Holdrege, R. B. Babel, and Lee C. Cheney, *J. Am. Chem. Soc.*, **81**, 4807 (1959). (e) W. J. Close, L. R. Swett, L. E. Brady, J. H. Short, and M. Vesusten, *J. Am. Chem. Soc.*, **82**, 1132 (1960). (f) J. H. Short and U. Biermacher, *J. Am. Chem. Soc.*, **82**, 1135 (1960). (g) L. H. Werner, A. Halamandaris, S. Ricca, Jr., L. Dorfman, and G. de Stevens, *J. Am. Chem. Soc.*, **82**, 1161 (1960). (h) H. L. Yale, K. Losee and J. Bernstein, *J. Am. Chem. Soc.*, **82**, 2042 (1960). (i) F. C. Novello, S. C. Bell, E. L. A. Abrams, C. Ziegler, and J. M. Sprague, *J. Org. Chem.*, **25**, 965 (1960). (j) F. C. Novello, S. C. Bell, E. L. A. Abrams, C. Ziegler and J. M. Sprague, *J. Org. Chem.*, **25**, 970 (1960). (k) C. Pelayo, J. Iriarte, and H. J. Ringold, *J. Org. Chem.*, **25**, 1067 (1960). (l) F. J. Lund and W. Kobinger, *Acta Pharmacol. Toxicol.*, **16**, 297 (1960).

oxide[5] was one of the compounds selected for clinical trial. Pharmacological[6] and clinical testing[7] have shown that this drug is approximately ten to fifteen times more potent than hydrochlorthiazide and possesses a more favorable electrolyte excretion pattern.



I II

Compounds of type II were prepared by condensation of a substituted orthanilamide such as III with the appropriate aldehyde or its acetal. Conditions for the reaction varied depending on the particular aldehyde involved. In some cases, notably the lower aliphatic aldehydes, refluxing III with a substantial excess of aldehyde in a suitable solvent such as acetonitrile was successful. In other cases the presence of an acid catalyst such as hydrogen chloride was necessary. With aromatic aldehydes, fusion of the two components at temperatures in the region of 200° often effected the desired conversion.



III IV VI V

It is of interest to note that in a number of instances, chiefly involving aromatic aldehydes, the anil (V) was obtained, the yield being dependent both on the reaction conditions and the structure of the aldehyde. The nature of the reaction product, anil or dihydrobenzothiadiazine, was determined from a study of its ultraviolet and infrared absorption spectra.

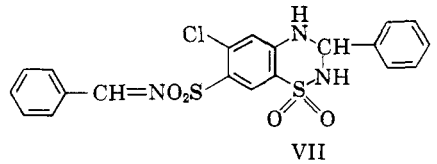
When R was ethoxymethyl, either the dihydrobenzothiadiazine (VI) or the anil (V) could be obtained. Condensation with ethoxyacetaldehyde diethyl acetal and hydrogen chloride in tetrahydrofuran at room temperature yielded the anil while reaction with the acetal in the presence of hydrogen chloride in ethanol at steam bath temperature gave the dihydrobenzothiadiazine.

When *p*-chlorobenzaldehyde was fused with III either the anil or the cyclized product was obtained under apparently identical conditions.

With 3,4,5-trimethoxybenzaldehyde only an anil [V. R = 3,4,5-$(CH_3O)_3C_6H_2$] was isolated from the reaction carried out using the fusion method. The cyclized compound [VI. R = 3,4,5-$(CH_3O)_3C_6H_2$] was prepared by condensation of the substituted orthanilamide (III) with 3,4,5-trimethoxybenzaldehyde in ethanol in the presence of hydrogen chloride. This compound was found to be unstable when heated with hydroxylic solvents in the absence of acid. On attempted recrystallization from methanol the compound gradually reverted to III. This behavior was not characteristic of other compounds bearing 3-aryl substituents.

ortho- and *para*-Carboxybenzaldehydes reacted differently when condensed with 5-chloro-2,4-disulfamylaniline (III) under the same conditions. On fusion at 200° with the *ortho*-carboxyaldehyde the anil (V. R = *o*-$COOHC_6H_4$) was obtained whereas the *para* isomer yielded the cyclized product (VI. R = *p*-$COOHC_6H_4$). Condensation of III with *o*-carboxybenzaldehyde in ethanol in the presence of hydrogen chloride also afforded the anil rather than the cyclized compound, whereas under these conditions the *para* isomer gave the cyclized product (VI. R = *p*-$COOHC_6H_4$) and the corresponding ethyl ester (VI. R = *p*-$CO_2C_2H_5$-C_6H_4). These results indicate that the orientation of the carboxyl group is of prime importance in determining the course of the reaction.

When the substituted orthanilamide (III) was heated with a large excess of benzaldehyde the condensation product was shown by its elemental analysis to have been formed from two molecules of benzaldehyde and one molecule of III. Since spectral evidence indicated the presence of the 3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxide system the product was assigned structure VII. This structure was supported by the observation that in its infrared spectrum a marked change in the asymmetric stretching SO_2 absorption was noted in contrast to the corresponding compound lacking



VII

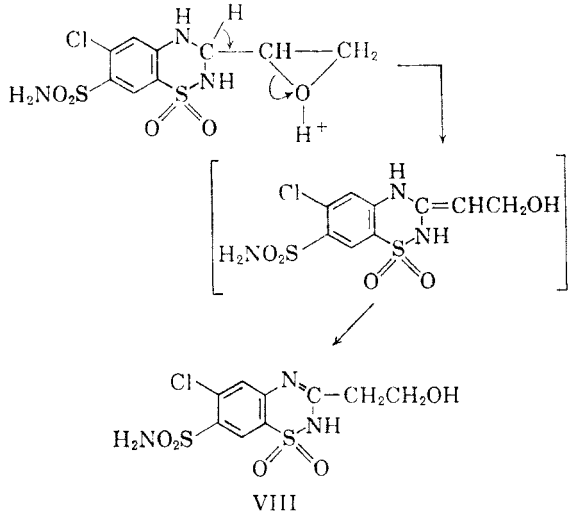
(5) (a) This compound has the generic name of trichlormethiazide and is marketed by Schering Corp. as Naqua. (b) M. H. Sherlock, N. Sperber, and J. Topliss, *Experientia*, **16**, 184 (1960). (c) G. de Stevens, L. H. Werner, W. E. Barrett, J. J. Chart, and A. H. Renzi, *Experientia*, **16**, 114 (1960).

(6)(a) R. M. Taylor, J. S. Mershon, and M. M. Winbury, *Federation Proc.*, **19**, 364 (March) 1960, Part 1. (b) R. M. Taylor and M. M. Winbury, *Nature*, **187**, 603 (1960).

(7) R. V. Ford, *Am. J. Cardiol.*, **5**, 407 (1960).

benzylidene substitution of the 7-sulfamyl group.

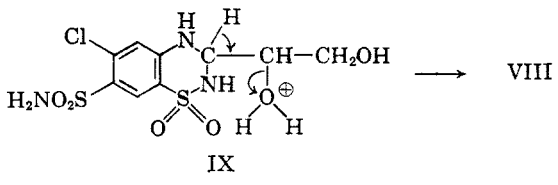
The condensation of glycidaldehyde with the substituted orthanilamide (III) in acetonitrile and in the absence of acid afforded the cyclized epoxyethyl compound (VI. R = CH—CH_2). However, when the reaction was carried out in ethanol in the presence of hydrogen chloride the product was 6-chloro-3-β-hydroxyethyl-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide (VIII). The latter compound was also formed when the 3-epoxyethyl-3,4-dihydrobenzothiadizine (VI. R = CH—CH_2) was treated with ethanolic hydrogen chloride. Thus the formation of VIII by condensation of glycidaldehyde with the substituted orthanilamide (III) in ethanolic hydrogen chloride probably takes place *via* the epoxyethyl compound as intermediate. The probable pathway for the conversion of the epoxyethyl compound into VIII is protonation of the epoxide oxygen followed by opening of the epoxide ring. Isomerization of the resulting



VIII

double bond into conjugation with the aromatic ring then would give 6-chloro-3-β-hydroxyethyl-7-sulfamyl-1,2,4-benzothiadiazine (VIII).

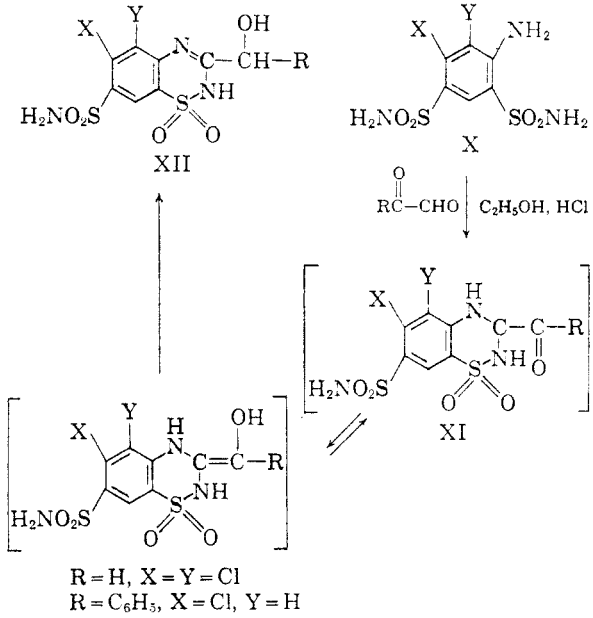
The condensation of dihydroxyacetone or glyceraldehyde under acidic conditions with III also yielded VIII as the only product. Since dihydroxyacetone and glyceraldehyde possess a common tautomeric enetriol it would seem probable that the 3-(α,β-dihydroxyethyl)dihydrobenzothiadiazine is the intermediate in both cases. The protonated form (IX) can eliminate water as indicated with



IX

subsequent isomerization of the resulting double bond furnishing VIII.

Condensation of a substituted orthanilamide (X) with glyoxal gave XII instead of the dihydrobenzothiadiazine (XI. R = H, X = Y = Cl). This was readily apparent on examination of the ultraviolet absorption spectrum which resembled that of chlorothiazide and the infrared spectrum which had a band attributable to a hydroxyl group but no carbonyl band. Phenylglyoxal gave a similar result affording XII. (R = C_6H_5, X = Cl, Y = H) rather than a 3-benzoyl-3,4-dihydrobenzothiadiazine. It is likely that the 3-substituted 3,4-dihydrobenzothiadiazine (XI) is first formed



followed by enolization of the carbonyl group and migration of the double bond to the 3,4-position. The powerful driving force influencing the migration of the double bond into the benzothiadiazine nucleus is evident from the case of phenylglyoxal where in order for this migration to take place conjugation of the double bond (or carbonyl) with the phenyl nucleus in the side chain is lost.

The condensation of α-chlorophenylacetaldehyde dimethyl acetal with III in the presence of ethanolic hydrogen chloride yielded the desired 3-α-chlorobenzyldihydrobenzothiadiazine. However, in an attempt to prepare the corresponding 3-α-bromobenzyl compound from α-bromophenylacetaldehyde dimethyl acetal under the same conditions, halogen interchange occurred and the product obtained was identical with VI (R = $CHClC_6H_5$).

Another route to the compounds under study involved the preparation of the 3-substituted benzothiadiazines followed by reduction with sodium borohydride to the corresponding, 3,4-dihydro derivatives.[3]

By application of the foregoing methods many 3-substituted dihydrobenzothiadiazine 1,1-dioxides were prepared and a representative number of these are listed in Table I.

In order to assess the effect on diuretic activity of additional substitution in position 5 of the benzothiadiazine nucleus some compounds of this type were prepared. The necessary substituted disulfamylanilines were synthesized from the appropriate 2,3-disubstituted aniline by chlorosulfonation followed by amination according to the method already described for certain monosubstituted anilines.[8]

Infrared absorption spectra.[9] The infrared absorption spectra which were obtained from Nujol mulls because of the poor solubility properties of the compounds were very useful in monitoring the reactions and in structural elucidation.

Some characteristic features of the infrared spectra of the substituted 2,4-disulfamylanilines (X) include a band at 2.95–3.15 μ attributed to the N—H stretching vibration of the sulfonamide (which appeared consistently at a higher wave length than that of the aromatic amine) and an intense band at 6.12 μ assigned to aromatic NH_2 deformation. A band at 7.5 μ was associated with the asymmetric S—O stretching vibration of the aromatic sulfonamide and was easily distinguished from the corresponding band of the aromatic sulfonyl chloride which appeared at a lower wave length. Bands due to the symmetric S—O stretching vibrations of the sulfonamide groups appeared in the vicinity of 8.6 μ.

The infrared absorption spectra of the cyclized dihydro compounds of structure II possess sharp bands in the vicinity of 6.20 μ which are easily distinguished from the bands due to the C=N stretching vibrations of the uncyclized anils of structure V. The latter have bands of medium to high intensity at 6.08 μ when R is alkyl or a broad summation absorption when R is aromatic. The C=N stretching absorption is also clearly evident in the spectra of 1,2,4-benzothiadiazine 1,1-dioxides of structure I.

Ultraviolet absorption spectra. The ultraviolet absorption spectra were routinely determined in methanol solution. They were found to be particularly useful in distinguishing 3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxides from the corresponding anils and also in identifying 1,2,4-benzothiadiazine 1,1-dioxides of the chlorothiazide type. 3,4 - Dihydro - 1,2,4 - benzothiadiazine - 1,1-dioxides were found to have three absorption bands at 223–228 mμ (ϵ 35,000–50,000), 266–275 mμ (ϵ 19,000–28,000) and 310–320 mμ (ϵ 2000–8000). The anil compounds differed in having only two major bands at 210–220 mμ (ϵ 30,000–50,000) and 250–300 mμ (ϵ 10,000–25,000) (broad). 1,2,4-Benzothiadiazines of the chlorothiazide type showed a strong absorption band at 223–227 mμ (ϵ 25,000–30,000) and a broad band in the 275–285 mμ region (ϵ 8000–12,000) with inflections at about 290 and 320 mμ.

Structure-activity relationships. Particularly interesting from an activity standpoint was the 3-haloalkyl series. The dihalomethyl compounds were found to be far more active than their mono- or trihalomethyl counterparts as determined by oral studies in rats and dogs. Thus the activities of the monochloromethyl, dichloromethyl[5] (compound 21), and trichloromethyl compounds were found to be approximately two, fifteen, and one-half times as active as hydrochlorothiazide, respectively. The 3-benzyl series also had high activity, compound 50 having five to ten times the activity of hydrochlorothiazide. With an aryl group at position 3 activity in most cases dropped below that of hydrochlorothiazide. A comparison of the effects of the chloro, bromo, fluoro, and trifluoromethyl substituents at position 6 indicated that generally the chloro compounds had the highest activity and the fluoro compounds the lowest. Additional substitution at position 5 produced unfavorable results. The activities of a number of 3-substituted chlorothiazides were compared with the corresponding 3,4-dihydro compounds. The latter were found to have about ten times the activity of the former. An exception appears to be the 3-benzylthiomethyl compounds in which saturation of the 3,4-double bond does not seem to appreciably change the activity.[4b]

Full details of the biological activities of these compounds will be published elsewhere.

EXPERIMENTAL

Intermediate acetals. The following acetals were prepared according to procedures found in the literature: the diethyl acetals of bromochloroacetaldehyde,[10] iodoacetaldehyde,[11] dibromoacetaldehyde,[12] α-bromoisovaleraldehyde,[13] α-bromopropionaldehyde,[14] α-bromo-α-methylbutyraldehyde,[15] phenylglyoxal,[16] methylthioacetaldehyde,[17] benzylthioacetaldehyde,[17] phenylthioacetaldehyde,[18] phenoxyacetaldehyde,[18] *p*-chloro-*p*-methyl- and *p*-methoxyphenyl

(8) F. C. Novello, U. S. Patent 2,809,194, Oct. 8, 1957.

(9) We are indebted to Mr. R. Wayne of the Physical and Analytical Chemical Research Department, Schering Corp., for the interpretation of the infrared absorption spectra.

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(12) F. Beyerstedt and S. M. McElvain, *J. Am. Chem. Soc.*, **59**, 2266 (1937).

(13) S. M. McElvain, R. L. Clarke, and G. D. Jones, *J. Am. Chem. Soc.*, **64**, 1966 (1942).

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(15) W. H. Hartung and H. Adkins, *J. Am. Chem. Soc.*, **49**, 2520 (1927).

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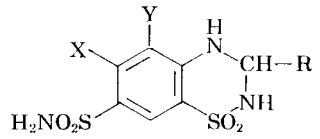
(17) G. Nadeau and R. Gaudry, *Can. J. Research*, **27B**, 421 (1949).

(18) W. Autenrieth, *Ber.*, **24**, 159 (1891).

TABLE I[cc]



No.	X	Y	R	Method	M.P.[a]	Recryst.[b] Solvent	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found	Sulfur, % Calcd.	Sulfur, % Found
1	Cl	H	H	c	269–270[d]	H_2O	$C_7H_8ClN_3O_4S_2$	14.11	13.93	11.91	12.04		
2	Cl	Cl	H	c	307–309[e]	H_2O	$C_7H_7Cl_2N_3O_4S_2$	12.64	12.69	21.34	20.90		
3	Cl	CH_3	H	c	302–303[f]	C_2H_5OH-H_2O	$C_8H_{10}ClN_3O_4S_2$	13.47	13.32	11.37	11.50		
4	Cl	H	CH_3	A	256[g]	EA-hex	$C_8H_{10}ClN_3O_4S_2$	13.47	13.25	11.37	11.27		
5	Cl	Cl	CH_3	A	268–269	EA-hex	$C_8H_9Cl_2N_3O_4S_2$	12.14	11.93	20.48	20.46		
6	Cl	H	C_2H_5	A	269–270[h]	THF-$CHCl_3$	$C_9H_{12}ClN_3O_4S_2$	12.89	12.41	10.88	11.26		
7	Cl	H	n-C_3H_7	B	247[i]	CH_3OH—$CHCl_3$	$C_{10}H_{14}ClN_3O_4S_2$	12.39	12.49	10.44	10.42		
8	Cl	H	i-C_3H_7	A	308–309[j]	CH_3CN	$C_{10}H_{14}ClN_3O_4S_2$	12.39	12.42	10.44	10.36		
9	Cl	H	n-C_4H_9	B	213[k]	CH_3OH—$CHCl_3$	$C_{11}H_{16}ClN_3O_4S_2$	11.88	11.75	10.02	10.03		
10	CF_3	H	n-C_4H_9	B	174–175[l]	EA-$CHCl_3$	$C_{12}H_{16}F_3N_3O_4S_2$	10.84	10.45			16.55	16.68
11	Cl	H	i-C_4H_9	B	228[m]	CH_3OH—$CHCl_3$	$C_{11}H_{16}ClN_3O_4S_2$	11.88	12.01	10.02	10.29		
12	Cl	H	t-C_4H_9	B	326–327	CH_3OH	$C_{11}H_{16}ClN_3O_4S_2$	11.72	12.00			18.15	18.46
13	Cl	H	n-C_5H_{11}	B	207–208	CH_3OH—$CHCl_3$	$C_{12}H_{18}ClN_3O_4S_2$	11.42	11.22	9.64	9.46		
14	Cl	H	n-C_6H_{13}	B	125	EA—$CHCl_3$	$C_{13}H_{20}ClN_3O_4S_2$	11.00	10.93	9.30	9.56		
15	Cl	H	CH_2Cl	C	239–240[n]	EA—hex	$C_8H_9Cl_2N_3O_4S_2$	12.14	12.05	20.48	20.45		
16	Cl	H	CH_2Br	C	216–217	EA-hex	$C_8H_9BrClN_3O_4S_2$	10.76	10.30				
17	Cl	H	CH_2I	C	214	EA-hex	$C_8H_9ClIN_3O_4S_2$	9.60	9.56			14.63	15.09
18	Cl	H	$CHBrCH_3$	C	252–253	EA-hex	$C_9H_{11}BrClN_3O_4S_2$	10.38	10.50			15.84	15.89
19	Cl	H	CHBr-i-C_3H_7	C	180	EA-hex	$C_{11}H_{15}BrClN_3O_4S_2$	9.70	9.69			14.79	14.78
20	Cl	H	$CBr(CH_3)C_2H_5$	C	188–189	EA-hex	$C_{11}H_{15}BrClN_3O_4S_2$	9.70	9.59			14.79	14.70
21	Cl	H	$CHCl_2$	B[c]	280–281	CH_3OH—$CHCl_3$	$C_8H_8Cl_3N_3O_4S_2$	11.22	11.04	27.96	27.85		
22	Br	H	$CHCl_2$	B	264–266	CH_3OH—$CHCl_3$	$C_8H_8BrCl_2N_3O_4S_2$	9.89	10.36			15.09	15.36
23	F	H	$CHCl_2$	B	266	CH_3OH—$CHCl_3$	$C_8H_8Cl_2FN_3O_4S_2$	11.54	11.54				
24	CF_3	H	$CHCl_2$	B	259–260	CH_3OH—$CHCl_3$	$C_9H_8Cl_2F_3N_3O_4S_2$	10.15	10.50				
25	Cl	H	CHClBr	C	256	EA-hex	$C_8H_8BrCl_2N_3O_4S_2$	9.90	9.98			15.05	15.01
26	Cl	H	$CHBr_2$	C	247	EA	$C_8H_8Br_2ClN_3O_4S_2$	8.96	8.79			13.62	13.46
27	Cl	H	CHF_2	B[c]	296–297	CH_3OH—$CHCl_3$	$C_8H_8ClF_2N_3O_4S_2$	12.09	12.11			18.44	18.31
28	Cl	H	CCl_2CH_3	B	285	Acet—$CHCl_3$	$C_8H_{10}Cl_3N_3O_4S_2$	10.64	11.19	26.96	26.49		
29	Cl	H	CCl_3	c	301–302[o]	CH_3OH—$CHCl_3$	$C_8H_7Cl_4N_3O_4S_2$	10.13	10.29	34.17	33.64		
30	Cl	Cl	CH_2OH	c	235	CH_3CN	$C_8H_9Cl_2N_3O_5S_2$	11.60	11.49				
31	Cl	H	CH_2CH_2OH	c	234–235	CH_3OH—$CHCl_3$	$C_9H_{12}ClN_3O_5S_2$	12.30	12.02	10.38	10.39		
32	Cl	H	$C(CH_3)_2CH_2OH$	B	250–251	CH_3OH	$C_{11}H_{16}ClN_3O_5S_2$	11.37	11.15			17.30	17.03
33	Cl	H	$CH_2OC_2H_5$	B	223	C_2H_5OH—$CHCl_3$	$C_{10}H_{14}ClN_3O_5S_2$	11.81	11.92	9.96	9.87		
34	Cl	H	CH_2COCH_3	C	210	C_2H_5OH—hex	$C_{10}H_{12}ClN_3O_5S_2$	11.86	11.58			18.12	18.08
35	Cl	H	CH——CH_2 \ / O	A	246[p]	CH_3CN	$C_9H_{10}ClN_3O_5S_2$	12.37	12.32	10.43	10.53		
36	Cl	H	CH_2SCH_3	B	216–217	EA—$CHCl_3$	$C_9H_{12}ClN_3O_4S_3$	11.74	11.70			26.88	26.90
37	Cl	H	$CH_2CO_2C_2H_5$	B	216–217	CH_3OH—$CHCl_3$	$C_{11}H_{14}ClN_3O_6S_2$	10.95	10.97	9.24	9.50		

TABLE I (*Continued*)

No.	X	Y	R	Method	M.P.[a]	Recryst.[b] Solvent	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found	Sulfur, % Calcd.	Sulfur, % Found
38	Cl	H	CH_2NH_2	B[c]	178–180	Acet-pent	$C_{11}H_{17}ClN_4O_5S_2$[q]	14.56	14.83			16.66	17.03
39	Cl	H	$CH_2NC_5H_{10}$[r]	B[c]	173–175	EA-hex	$C_{13}H_{19}ClN_4O_4S_2$	14.19	13.94				
40	Cl	H	C_6H_5	B	241–242[s]	Acet-pent	$C_{13}H_{12}ClN_3O_4S_2$	11.24	11.14			17.15	17.08
41	Cl	H	*p*-ClC_6H_4	D[c]	258–259[t]	CH_3OH—$CHCl_3$	$C_{13}H_{11}Cl_2N_3O_4S_2$	10.29	10.17	17.37	17.48		
42	Cl	H	*o*-ClC_6H_4	D	272–274	CH_3OH—$CHCl_3$	$C_{13}H_{11}Cl_2N_3O_4S_2$	10.29	10.38	17.37	16.83		
43	Cl	H	2,4$(CH_3O)_2C_6H_3$	D	211–212	CH_3OH	$C_{15}H_{16}ClN_3O_6S_2$	9.68	9.68			14.78	14.71
44	Cl	H	3,4,5$(CH_3O)_3C_6H_2$	B[c]	244–246	Acet-$CHCl_3$	$C_{16}H_{18}ClN_3O_7S_2$	9.06	9.22	7.64	7.74		
45	Cl	H	*p*-$C_2H_5O_2CC_6H_4$	B	255–256	CH_3OH	$C_{16}H_{16}ClN_3O_6S_2$	9.42	9.78	7.95	8.06		
46	Cl	H	*p*-$HO_2CC_6H_4$	D	289–290	THF-$CHCl_3$	$C_{14}H_{12}ClN_3O_6S_2$	10.06	9.93	8.49	8.71		
47	Cl	H	2-Furyl	B	190–195[u]	CH_3OH—$CHCl_3$	$C_{11}H_{10}ClN_3O_5S_2$	11.55	11.64				
48	Cl	H	2-Thienyl	D	211–213[v]	CH_3OH—$CHCl_3$	$C_{11}H_{10}ClN_3O_4S_3$	11.06	10.90			25.33	25.92
49	Cl	H	2-(5-Nitrofuryl)	B	239[w]	CH_3OH—$CHCl_3$	$C_{11}H_9ClN_4O_7S_2$	13.71	13.45	8.67	9.06		
50	Cl	H	$CH_2C_6H_5$	C	267–268[x]	CH_3OH	$C_{14}H_{14}ClN_3O_4S_2$	10.82	10.34			16.50	16.59
51	Br	H	$CH_2C_6H_5$	B	266	Acet-$CHCl_3$	$C_{14}H_{14}BrN_3O_4S_2$	9.72	9.88			14.84	14.69
52	CF_3	H	$CH_2C_6H_5$	B	228[y]	CH_3OH—$CHCl_3$	$C_{15}H_{14}F_3N_3O_4S_2$	9.97	10.12			15.22	15.44
53	Cl	H	*p*-$CH_3C_6H_4CH_2$	B	242–244	CH_3OH	$C_{15}H_{16}ClN_3O_4S_2$	10.08	10.47			15.36	15.86
54	Cl	H	*p*-*i*-$C_3H_7C_6H_4CH_2$	B	232–233	EA-hex	$C_{17}H_{20}ClN_3O_4S_2$	9.77	9.82			14.92	14.85
55	Cl	H	2,4,6$(CH_3)_3C_6H_2CH_2$	B	276–278	THF-$CHCl_3$	$C_{17}H_{20}ClN_3O_4S_2$	9.77	9.94			14.92	14.96
56	Cl	H	*p*-$ClC_6H_4CH_2$	B	245–246	CH_3OH-ether	$C_{14}H_{13}Cl_2N_3O_4S_2$	9.95	9.82			15.17	14.91
57	Cl	H	*p*-$CH_3OC_6H_4CH_2$	B	239–241	CH_3OH	$C_{15}H_{16}ClN_3O_5S_2$	10.06	10.00			15.35	15.44
58	Cl	H	3,4$(CH_3O)_2C_6H_3CH_2$	B	250–251	C_2H_5OH	$C_{16}H_{18}ClN_3O_6S_2$	9.38	9.30			14.32	14.43
59	Cl	H	$CHCH_3C_6H_5$	B	231–232	EA-hex	$C_{15}H_{16}ClN_3O_4S_2$	10.44	10.42			15.95	16.02
60	Cl	H	$CH_2CH_2C_6H_5$	B	230[z]	CH_3OH—$CHCl_3$	$C_{15}H_{16}ClN_3O_4S_2$	10.46	10.31	8.82	8.58		
61	CF_3	H	$CH_2CH_2C_6H_5$	B	234–236[aa]	EA-hex	$C_{16}H_{16}F_3N_3O_4S_2$	9.65	9.62			14.70	15.02
62	Cl	H	$(CH_2)_3C_6H_5$	B	214–215	CH_3OH—$CHCl_3$	$C_{16}H_{18}ClN_3O_4S_2$	10.10	10.35	8.53	7.97		
63	Cl	H	$CH_2OC_6H_5$	B	257	Acet-$CHCl_3$	$C_{14}H_{14}ClN_3O_5S_2$	10.40	10.42	8.78	8.80		
64	Cl	H	$CH_2SC_6H_5$	B	211–213	CH_3OH—$CHCl_3$	$C_{14}H_{14}ClN_3O_4S_3$	10.01	10.10			22.91	23.35
65	Cl	H	$CH_2SCH_2C_6H_5$	B	218–219	CH_3OH—$CHCl_3$	$C_{15}H_{16}ClN_3O_4S_3$	9.68	9.40			22.18	22.14
66	Cl	H	Δ^3-Cyclohexenyl	A	248–249	CH_3OH—$CHCl_3$	$C_{13}H_{16}ClN_3O_4S_2$	11.12	11.03	9.39	9.61		
67	Cl	H	C≡C—C_6H_5	C	238–239	C_2H_5OH-hex	$C_{15}H_{12}ClN_3O_4S_2$	10.56	10.52			16.12	16.11
68	Cl	H	$C_{10}H_{15}O_2$[bb]	B	245–247	CH_3OH-hex	$C_{17}H_{22}ClN_3O_6S_2$	9.06	9.13	7.64	7.90		

[a] All melting points are uncorrected; most of the compounds melted with decomposition. [b] EA = ethyl acetate; hex = hexane; Acet = acetone; pent = pentane; THF = tetrahydrofuran. [c] See Experimental section. [d] Ref. 3 reports m.p. 273–275°; Ref. 4e reports m.p. 270–272°. [e] Ref. 4f reports m.p. 302–303°. [f] Ref. 4g reports m.p. 307–309°; Ref. 4l reports m.p. 296.5–298°. [g] Ref. 4e reports m.p. 249–250°; Ref. 4g reports m.p. 256–258°; Ref. 4j reports m.p. 252–253°. [h] Ref. 4e reports m.p. 266–267°; Ref. 4j reports m.p. 265°. [i] Ref. 4g reports m.p. 254–256°; Ref. 4l reports m.p. 250–251°. [j] Ref. 4e reports m.p. 286–290°; Ref. 4g reports m.p. 304–306°. [k] Ref. 4g reports m.p. 176–179°; Ref. 4l reports m.p. 213–215°. [l] Ref. 4l reports m.p. 216–217.5°. [m] Ref. 4g reports m.p. 241–245°. [n] Ref. 4e reports m.p. 235–236°; Ref. 4g reports m.p. 235° d.; Ref. 4l reports m.p. 239.5–240°. [o] Ref. 4e reports m.p. 300–303°; Ref. 4j reports m.p. 287°. [p] Ref. 4j reports m.p. 233–235°. [q] Calculated for one mole of acetone of solvation. [r] Piperidino. [s] Ref. 4g reports m.p. 248–250°; Ref. 4l reports m.p. 238–240°. [t] Ref. 4j reports m.p. 250–251°. [u] Ref. 4g reports m.p. 214–218°. [v] Ref. 4g reports m.p. 222–225°. [w] Ref. 4j reports m.p. 239–240°. [x] Ref. 4g reports m.p. 247–250°; Ref. 4j reports m.p. 260–262°; Ref. 4l reports m.p. 249–250°. [y] Ref. 4d reports m.p. 221–223°; Ref. 4l reports m.p. 226–227°. [z] Ref. 4g reports m.p. 174–175°. [aa] Ref 4l reports m.p. 235–236°. [bb] 1-(2,5-*endo*-Methylene-3-ethoxycarbonylcyclohexyl). [cc] The structural assignments given to compounds reported in this table are fully supported by infrared and ultraviolet absorption spectral data.

acetaldehydes (from the appropriately substituted Grignard reagent and ethyl orthoformate),[19] and carbethoxyacetaldehyde[20]; the dimethylacetals of α-bromophenylacetaldehyde and α-chlorophenylacetaldehyde[21]; and the dipropyl acetal of α,α-dichloropropionaldehyde.[22]

Intermediate aldehydes. With the exception of *p*-isopropylphenyl- and 2,4,6-trimethylphenylacetaldehydes,[23] the requisite aldehydes were commercially available.

The following general methods were employed in the condensation of the substituted orthanilamide (III) with various aldehydes. The yields varied from 30–90% and optimum conditions were not determined.

Method A. The substituted orthanilamide (III) (0.01 mole) and the aldehyde component (0.20 mole) were refluxed for 12 hr. in acetonitrile (25–50 ml.). The solvent and excess of aldehyde were then removed by evaporation on the steam bath and the residue crystallized.

Method B. A solution of the orthanilamide (III) and two molar equivalents of the aldehyde (or its acetal) in ethanolic hydrogen chloride was refluxed (1–2 hr.), concentrated, diluted with chloroform, and again concentrated until solid just began to separate. The mixture was cooled and the product collected, washed with chloroform, and purified by recrystallization.

Method C. A solution of 5 g. of III, the acetal (15–30 ml.) and enough 18% ethanolic hydrogen chloride to render the reaction mixture acidic was heated at 110–150° with stirring for 30–60 min. allowing the alcohol formed to distill. The reaction mixture was cooled and the solid product filtered and washed with ether. In instances where the product did not crystallize from the reaction mixture the excess solvent was evaporated and the residue triturated with ether.

Method D. A mixture of the substituted orthanilamide (III) and the aldehyde (1.1 equivalents) was heated at *ca.* 200° for 1 hr. After cooling, the resultant crude product was purified by recrystallization from a suitable solvent.

6-Chloro-3,4-dihydro-7-sulfamyl-1,2,4-benzothiadiazine 1,1 dioxide. Aqueous (36–38%) formaldehyde solution (1.2 g.) was added to a solution of 5-chloro-2,4-disulfamylaniline (2.94 g.) in methanol (5 ml.) and the mixture refluxed for 1 hr. The methanol was removed by evaporation on the steam bath, the sticky residue was then dissolved in boiling water (150 ml.), cooled, and the crystalline product collected 2.05 g., m.p. 269–270°. Concentration of the filtrate under vacuum at room temperature afforded a further 0.55 g. of product, m.p. 266.5–267.5°. λ_{max} 222 mμ (ε 37,800), 269 mμ (ε 19,100), 315 mμ (ε 7800).

Essentially the same procedure was employed in the preparation of 5,6-dichloro-3,4-dihydro-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide (reaction time 4 hr.) and 6-chloro-3,4-dihydro-5-methyl-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide.

6-Chloro-3-dichloromethyl-3,4-dihydro-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide. A mixture of 5-chloro-2,4-disulfamylaniline (2.5 g.), dichloroacetal (3.0 g.), 18% ethanolic hydrogen chloride (25 ml.), and water (0.25 ml.) was heated under reflux with stirring. In *ca.* 4 hr. complete solution of the reactants was effected and after one further hour under reflux the alcohol was allowed to evaporate until the internal temperature reached 100°. The reaction mixture was cooled, twice its volume of chloroform added and the solution refrigerated overnight. The crude product which separated was collected by filtration and recrystallized from methanol-chloroform (charcoal), (2 g.) m.p. 280–281° dec.[24]

6-Chloro-3-difluoromethyl-3,4-dihydro-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide. Difluoroacetaldehyde. A mixture of difluoroacetic acid (17.9 g.) and benzotrichloride (31 ml.), to which a small crystal of granular zinc chloride had been added, was heated cautiously to reflux until hydrogen chloride evolution had ceased and the mixture was homogeneous. The difluoroacetyl chloride was then distilled through a short column and condensed in a Dry Ice–acetone bath. The condensate was dissolved in anhydrous ether and the solution cooled and treated with an excess of anhydrous dimethylamine. After filtration and evaporation, the residue was distilled to give difluoro-*N,N*-dimethylacetamide (15.6 g.), b.p. 101–102°/12.0 mm.

Anal. Calcd. for $C_4H_7F_2NO$: C, 39.03; H, 5.73. Found: C, 38.78; H, 5.66.

A solution of lithium diethoxyaluminohydride[25] (prepared from 0.63 g. of lithium aluminum hydride) in anhydrous ether (30 ml.) was added over a 15-min. interval to a stirred, ice-cooled solution of difluoro-*N,N*-dimethylacetamide (3.1 g.) in 150 ml. of anhydrous ether, and stirring continued overnight at room temperature. Following the addition of a saturated aqueous solution of sodium sulfate (5 ml.) and then of anhydrous sodium sulfate (70 g.), the reaction mixture was filtered, the solids washed well with anhydrous ether and the ethereal filtrate containing the difluoroacetaldehyde used in the next step.

To the ethereal solution containing difluoroacetaldehyde was added a 4% solution of ethanolic hydrogen chloride (25 ml.), the solution decanted from a small volume of a second layer and most of the ether removed by distillation through a column of glass helices. The remaining solution was treated with 5-chloro-2,4-disulfamylaniline (1.0 g.) and the reaction carried out according to Method C to give 0.83 g. of product, m.p. 297–298° dec. Recrystallization from methanol-chloroform did not raise the melting point.

6-Chloro-3,4-dihydro-3-piperidinomethyl-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide. The crude hydrochloride (2.2 g.) prepared according to Method C was dissolved in hot dilute acetic acid (100 ml., *ca.* 0.002*M*), the solution filtered, cooled, and brought to *p*H 8.0 with dilute aqueous potassium hydroxide. Cooling in ice gave colorless crystals (1.1 g.), m.p. 160–163° dec. Recrystallization from ethyl acetate-cyclohexane gave the free base, m.p. 173–175° dec.

When the free base was recrystallized from acetone-pentane a solvate was obtained containing one mole of acetone of crystallization. (The infrared spectrum showed carbonyl absorption at 5.84 μ.)

Anal. Calcd. for $C_{13}H_{19}ClN_4O_4S_2 \cdot C_3H_6O$: N, 12.37. Found: N, 12.34.

3-Aminomethyl-3,4-dihydro-6-chloro-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide. The crude hydrochloride prepared according to Method B was dissolved in hot water and the solution cooled. After the addition of one equivalent of aqueous potassium hydroxide the solution was treated quickly with charcoal without heating and then allowed to stand in an ice bath until colorless crystals of the free base separated. The product was collected and recrystallized from acetone-pentane to give the acetone solvate, m.p. 177.5–178° dec.

(19) G. Bryant Bachman, *Org. Syntheses*, Coll. Vol. II, 323 (1943).

(20) F. Straus and W. Voss, *Ber.*, 59, 1681 (1926).

(21) P. Z. Bedoukian, *J. Am. Chem. Soc.*, 66, 1325 (1944).

(22) L. Moelants, *Bull. Soc. Chim. Belg.*, 52, 53 (1943).

(23) P. Chuit and J. Bolle, *Bull. Soc. Chim.*, 35, 200 (1924).

(24) de Stevens *et al.* (ref. 5c) report a m.p. of 248–250° dec. Two polymorphic modifications have been obtained by us but both have a m.p. of 280–281° dec. We have recrystallized a sample of our product, m.p. 280–281° dec., from the solvent mixture (methanol:acetone:water 1:1:1) employed by de Stevens *et al.*, and have obtained material, m.p. 248–250° dec. which, however, can be shown by infrared spectroscopy and paper chromatographic analysis to contain 10–20% of 5-chloro-2,4-disulfamylaniline. The latter compound can be shown to be absent from the sample, m.p. 280–281° and is presumably formed during crystallization from methanol:acetone:water by hydrolysis.

(25) H. C. Brown and A. Tsukamoto, *J. Am. Chem. Soc.*, 81, 502 (1959).

6-Chloro-3,4-dihydro-7-sulfamyl-3-trichloromethyl-1,2,4-benzothiadiazine 1,1-dioxide. 5-Chloro-2,4-disulfamylaniline (5 g.), chloral (25 ml.), and concd. sulfuric acid (5 drops) were heated together under reflux with stirring for 2 hr. The cooled reaction mixture was diluted with chloroform and the crude product collected by filtration and crystallized from methanol affording 2.8 g. of product, m.p. 294–295° dec. Recrystallization from methanol-chloroform afforded 6-chloro-3,4-dihydro-7-sulfamyl-3-trichloromethyl-1,2,4-benzothiadiazine 1,1-dioxide, m.p. 301–302° dec.

5-Chloro-2,4-disulfamyl-1-(2'-ethoxyethylideneamino)benzene. A mixture of 5-chloro-2,4-disulfamylaniline(5.0 g.), ethoxyacetal (25 ml.), tetrahydrofuran (100 ml.), and 18% ethanolic hydrogen chloride (1 ml.) was kept at room temperature for 12 hr. The reaction mixture was poured into hexane and the precipitated product collected by filtration and air dried (5.81 g.). Crystallization from tetrahydrofuran furnished 1.73 g., m.p. 321°. Further recrystallization from the same solvent afforded 0.77 g. of pure product, m.p. 350°. λ_{max} 221 mμ (ε 31,800); 255 mμ (ε 9300); shoulder 294 mμ. (ε 2320). λ_{max} 6.06 μ (strong), attributable to —C=N—.

Anal. Calcd. for $C_{10}H_{14}ClN_3O_6S_2$: N, 11.81; Cl, 9.96. Found: N, 11.84; Cl, 9.83.

Reaction of 5-chloro-2,4-disulfamylaniline with p-chlorobenzaldehyde. An intimate mixture of 5-chloro-2,4-disulfamylaniline (2.0 g., 0.007 mole) and *p*-chlorobenzaldehyde (1.98 g., 0.014 mole) was heated in an oil bath at 230–240° (bath temperature) for 0.5 hr. Upon cooling, the crude product was crystallized from methanol-chloroform. Either of two products could be obtained from the reaction, compound (A) m.p. 257–258° and compound (B) m.p. 360°. In any given run one of the two products seemed always to predominate. The factors controlling these results were not elucidated.

Compound A. λ_{max} 225 mμ (ε 48,700); 272 mμ (ε 24,800); 316 mμ (ε 3900).

Anal. Calcd. for $C_{13}H_{11}Cl_2N_3O_4S_2$: N, 10.29; Cl, 17.37. Found: N, 10.17, Cl, 17.48.

Compound B. λ_{max} 213 mμ (ε 39,800); shoulder 230 mμ (ε 24,500); 263 mμ (ε 23,100); 340 mμ (ε 4200).

Anal. Calcd. for $C_{13}H_{11}Cl_2N_3O_4S_2$: N, 10.29; Cl, 17.37. Found: N, 10.59; Cl, 17.34.

On the basis of these data compound A was assigned the structure 6-chloro-3-(*p*-chlorophenyl)-3,4-dihydro-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide and compound B the structure 5-chloro-1-(*p*-chlorobenzylideneamino)-2,4-disulfamylbenzene. Both structures were also supported by infrared evidence.

Reaction of 5-chloro-2,4-disulfamylaniline with 3,4,5-trimethoxybenzaldehyde. (a) An intimate mixture of 5-chloro-2,4-disulfamylaniline (5.0 g., 0.0175 mole) and 3,4,5-trimethoxybenzaldehyde (5.15 g., 0.0262 mole) was heated in an oil bath at 220–225° (bath temperature) for 0.5 hr. After cooling, the reaction product was boiled with methanol (1 l.) and the insoluble material removed by filtration. The filtrate was treated with charcoal, concentrated and cooled, affording 5-chloro-2,4-disulfamyl-1-(3',4',5'-trimethoxybenzylideneamino)benzene (1.75 g.), m.p. 300° (sintering at 238°). Recrystallization from methanol and then from acetonitrile did not change the melting point. λ_{max} 218 mμ (ε 50,800); 300 mμ (ε 22,500).

Anal. Calcd. for $C_{16}H_{18}ClN_3O_7S_2$: N, 9.05; Cl, 7.64. Found: N, 8.85; Cl, 7.50.

(b) A mixture of 5-chloro-2,4-disulfamylaniline (4.0 g., 0.014 mole), 3,4,5-trimethoxybenzaldehyde (5.48 g., 0.028 mole) and 2% ethanolic hydrogen chloride (40 ml.) was heated on the steam bath. Solution occurred within 15 min. and the reaction mixture was heated for 45 min. longer and then cooled. On standing overnight at room temperature crystals formed which were collected by filtration and dried, 4.8 g., m.p. 247–249°. Recrystallization from acetone-chloroform gave 6-chloro-3,4-dihydro-7-sulfamyl-3-(3',4',5'-trimethoxyphenyl)-1,2,4-benzothiadiazine 1,1-dioxide, m.p. 244–246°. λ_{max} 224 mμ (ε 49,200); 272 mμ (ε 28,000); 315 mμ (ε 3200). On attempted crystallization of the product from methanol-chloroform, a high yield of 5-chloro-2,4-disulfamylaniline was obtained.

5-Chloro-(2'-carboxybenzylideneamino)-2,4-disulfamylbenzene. (a) A mixture of 5-chloro-2,4-disulfamylaniline (1.0 g., 0.0035 mole) and *o*-carboxybenzaldehyde (0.68 g., 0.0047 mole) was fused in an oil bath at a bath temperature of 200–205° for 1 hr. The residue was crystallized from acetonitrile-tetrahydrofuran and then tetrahydrofuran-chloroform affording 5-chloro-1-(2'-carboxybenzylideneamino)-2,4-disulfamylbenzene (0.6 g.), m.p. 354°. λ_{max} 222 mμ (ε 30,300); 286 mμ (ε 20,200); inflections at 300 mμ (ε 15,200) and 307 mμ (ε 11,400).

Anal. Calcd. for $C_{14}H_{12}ClN_3O_6S_2$: N, 10.06; Cl, 8.49. Found: N, 10.04; Cl, 8.55.

(b) 5-Chloro-2,4-disulfamylaniline (1.0 g., 0.0035 mole), *o*-carboxybenzaldehyde (0.68 g., 0.0047 mole), and 2% ethanolic hydrogen chloride (10 ml.) were warmed on the steam bath for 1 hr. The crystalline product was collected by filtration of the warm reaction mixture, 1.35 g., m.p. 356–357° dec., shown to be identical with the product obtained in (a) bb the usual criteria.

7-Benzylidenesulfamyl-6-chloro-3,4-dihydro-3-phenyl-1,2,4-benzothiadiazine 1,1-dioxide. 5-Chloro-2,4-disulfamylaniline (5 g.) was heated with benzaldehyde (15 ml.) until the distillate was clear and its boiling point the same as that of benzaldehyde. At this point the reaction mixture was allowed to cool and the residue triturated with chloroform-cyclohexane affording crude product (7.6 g.). Crystallization from tetrahydrofuran-cyclohexane and then from acetone-pentane furnished 7-benzylidenesulfamyl-6-chloro-3,4-dihydro-3-phenyl-1,2,4-benzothiadiazine 1,1-dioxide, m.p. 241–242°. λ_{max} 222 mμ (ε 39,200); 273 mμ (ε 25,200); shoulder 308 mμ (ε 7100).

Anal. Calcd. for $C_{20}H_{16}ClN_3O_4S_2$: C, 52.00; H, 3.49; N, 9.10. Found: C, 52.06; H, 3.64; N, 9.27.

6-Chloro-3-β-hydroxyethyl-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide. (a) 5-Chloro-2,4-disulfamylaniline (5.0 g., 0.0175 mole), glycidaldehyde (3.78 g., 0.0525 mole), and 50 ml. of 20% ethanolic hydrogen chloride were heated on the steam bath, complete solution being effected in 5–10 min. The reaction mixture was refluxed gently for an additional 20 min. when a solid separated. Cooling followed by filtration afforded 5.62 g. of crude product m.p. 312–314° dec. Recrystallization from ethanol afforded 6-chloro-3-β-hydroxyethyl-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide (3.17 g.) m.p. 320–321 dec. λ_{max} 225 mμ (ε 30,800); 278 mμ (ε 11,500); shoulder 303 mμ (ε 3500); 321 mμ (ε 1500).

Anal. Calcd. for $C_9H_{10}ClN_3O_5S_2$: N, 12.37; Cl, 10.43. Found: N, 12.31; Cl, 10.56.

(b) 6-Chloro-3-epoxyethyl-3,4-dihydro-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide (0.5 g.) was heated on the steam bath in 20% ethanolic hydrogen chloride for 15 min. The reaction mixture was then cooled and the solid product collected by filtration, 0.42 g., m.p. 326–327° dec. Recrystallization from ethanol afforded 6-chloro-3-β-hydroxyethyl-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide, m.p. 327–328° dec. as shown by standard criteria.

(c) A mixture of 5-chloro-2,4-disulfamylaniline (10 g.) and dihydroxyacetone (15 g.) was suspended in ethanol (50 ml.) and 18% ethanolic hydrogen chloride (50 ml.) and allowed to reflux for 6 hr. The resulting suspension was cooled, triturated with ether and the solid filtered, yield 12 g., m.p. 230° dec. After recrystallization from ethanol the colorless solid melted at 327–328° and did not depress the melting point of the previously prepared compound.

(d) A mixture of 5-chloro-2,4-disulfamylaniline (2.8 g.), glyceraldehyde (1.0 g.), absolute ethanol (18 ml.), and 30% ethanolic hydrogen chloride (12 ml.) was refluxed for 15 min. On cooling, 1.6 g. of a colorless solid separated, which melted at 325° dec. On admixture with a sample prepared from dihydroxyacetone there was no melting point depression and the infrared spectra of the two products were identical.

6-Chloro-3-(α-hydroxybenzyl)-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide. 5-Chloro-2,4-disulfamylaniline (4.5 g.), phenylglyoxal diethyl acetal (9.0 g.), and 8% ethanolic hydrogen chloride (70 ml.) were heated on the steam bath for 2 hr. Chloroform (100 ml.) was then added and the solution chilled. The solid which separated was collected by filtration; 2.8 g., m.p. 276–277° dec. Recrystallization from methanol-water gave 6-chloro-3-(α-hydroxybenzyl)-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide (2.42 g.), m.p. 282–283° dec. λ_{max} 224 mμ (ε 30,700); 278 mμ (ε 12,700).

Anal. Calcd. for $C_{14}H_{12}ClN_3O_5S_2$: N, 10.44; Cl, 8.83. Found: N, 10.44; Cl, 8.67.

5,6-Dichloro-3-hydroxymethyl-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide. 2,3-Dichloro-4,6-disulfamylaniline (10 g.) was dissolved in 95% ethanol (800 ml.) and refluxed overnight with 30% aqueous glyoxal (23 g.). The solvent was evaporated on a steam bath leaving a gummy residue which was dissolved in a water-alcohol mixture affording after concentration and cooling, a product (5.7 g.), m.p. 267–269° dec. Recrystallization from acetone furnished 5,6-dichloro-3-hydroxymethyl-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide (2.95 g.) m.p. 278–280° dec. λ_{max} 231 mμ (ε 30,000); 278 mμ (ε 10,500).

Anal. Calcd. for $C_8H_7Cl_2N_3O_5S_2$: N, 11.66; Cl, 19.68. Found: N, 11.43; Cl, 19.56.

6-Chloro-3,4-dihydro-3-β-hydroxyethyl-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide. Sodium borohydride (5.90 g.) was added to a solution of 6-chloro-3-β-hydroxyethyl-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide (5.90 g.) dissolved in tetrahydrofuran (250 ml.) and the mixture refluxed for 21 hr. The solvent was evaporated on the steam bath, the residue chilled in an ice bath and then acidified to *p*H 5 with 5% hydrochloric acid. The gum which first separated solidified when the mixture was allowed to warm to room temperature. The solid product was collected by filtration (4.69 g.), m.p. *ca.* 150° dec. Crystallization from methanol-chloroform afforded 6-chloro-3,4-dihydro-3-β-hydroxyethyl-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide (1.72 g.), m.p. 234° dec. λ_{max} 226 mμ (ε 36,700); 271 mμ (ε 20,200); 316 mμ (ε 3000).

An analogous procedure was used for the preparation of 5,6-dichloro-3,4-dihydro-3-hydroxymethyl-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide.

6-Chloro-3-α-chlorobenzyl-3,4-dihydro-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide. (a) A mixture of 5-chloro-2,4-disulfamylaniline (2 g.), α-chlorophenylacetaldehyde dimethyl acetal[19] (2.8 g.), absolute ethanol (100 ml.), 23% ethanolic hydrogen chloride (40 ml.), and 3 drops of water was refluxed for 1 hr. The excess ethanol was distilled and the residue triturated with hexane to give 3.7 g. of a tacky solid. After two recrystallizations from ethyl acetate-hexane the solid melted at 182–184° dec. and after drying under high vacuum melted at 198–205° dec. The infrared spectrum showed a strong carbonyl absorption due to solvation with ethyl acetate.

Anal. Calcd. for $C_{14}H_{13}Cl_2N_3O_4S_2 \cdot {}^1/_2\ CH_3COOC_2H_5$: C, 41.20; H, 3.68; Cl, 15.21; N, 9.01; Found: C, 41.54; H, 3.76; Cl, 15.30; N, 9.30.

(b) A mixture of 5-chloro-2,4-disulfamylaniline (2 g.), α-bromophenylacetaldehyde dimethyl acetal (3.4 g.), absolute ethanol (100 ml.), 23% ethanolic hydrogen chloride (40 ml.), and 3 drops of water was treated in the same manner as above. There was obtained 1.4 g. of a solid melting at 184–185.5° dec. which did not depress the melting point of the sample prepared in (a). The infrared spectra of the materials obtained in (a) and (b) were identical.

Anal. Calcd. for $C_{14}H_{13}Cl_2N_3O_4S_2 \cdot {}^1/_2\ CH_3COOC_2H_5$: Cl, 15.21; N, 9.01; S, 13.75. Found: Cl, 15.28; N, 8.92; S, 13.91.

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[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Thyroxine Analogs. I. Methylated Thyroformic Acids

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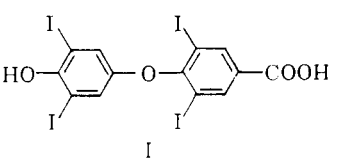
The preparations of several thyroformic acids variously substituted with methyl groups in the 3,5,3′,5′- positions are reported. The unusual debromination of 4-(4′-methoxy-3′,5′-dimethylphenoxy)-3,5-dimethylphenylbromide (XIII) and decarboxylation of the carboxylic acid (XIV) derived from bromide (XIII) were observed in 57% hydriodic acid in glacial acetic acid.

A greater separation of the hypocholesterolemic and metabolic effects was observed in the thyroxine analog, tetraiodothyroformic acid I, than in thyroxine, itself.[1] The effect of replacing the iodines of compound I with other groups was therefore investigated. The syntheses of compounds in which methyl group(s) or hydrogen(s) replace iodine(s) are reported in this paper.[2]



I

The general method used for preparing three methylated thyroformic acids is shown in Fig. 1.

(1) M. M. Best, C. H. Duncan, and E. Van Heyningen, *Endocrinology*, **60**, 161 (1957).

(2) The pharmacological results obtained with these compounds will be reported elsewhere.