cm.$^{-1}$ which are absent in 6-chloro-5,8-diacetoxyquinoline (XXI). There was no evidence of these bands in the spectrum of the above crude diacetyl derivative obtained from the hydrogen chloride addition product or of that of the second crop of crystals obtained on recrystallization.

COLLEGE PARK, MD.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

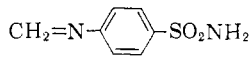
Dihydrobenzothiadiazine 1,1-Dioxides and their Diuretic Properties

BY L. H. WERNER, A. HALAMANDARIS, S. RICCA, JR., LOUIS DORFMAN AND GEORGE DESTEVENS

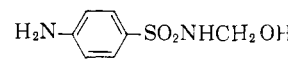
RECEIVED JUNE 12, 1959

A wide variety of 3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxides has been prepared by different methods. The nature of each of these reactions has been explored. The most promising procedure consists in condensing the appropriate *o*-aminobenzenesulfonamide with an aldehyde or acetal. Alkylation studies on 6-chloro-3,4-dihydro-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (VIIIa) have also led to some interesting products, the nature of which has been elucidated by chemical and physical means. The unique infrared absorption characteristics of this class of compounds have been studied. Some of these compounds were found to exhibit unusually high diuretic activity.

In the course of our studies on the chemotherapeutic properties of sulfonamides, it became of interest to determine the nature of the products derived from the condensation of sulfonamides with aldehydes. The literature[1] records that such condensations lead to resins or trimers. With regard to the *p*-aminobenzenesulfonamide–formaldehyde condensation, Wood and Battye[2] reported that products with the formulas I and II were obtained along with some polymer. A similar type of con-



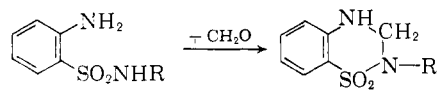
I



II

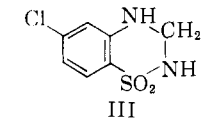
densation leading to a high molecular weight product has been suggested by Druey[3] for the reaction of formaldehyde with sulfathiazole.

However, it has been reported[4] that substituted *o*-aminobenzenesulfonamides react with formaldehyde in alkaline alcoholic solution to yield dihydrobenzothiadiazine 1,1-dioxides.



R = phenyl and substituted phenyl

We have carried out this reaction with unsubstituted *o*-aminobenzenesulfonamide[5] and various aldehydes in non-polar solvents with catalytic amounts of hydrogen chloride and have obtained analogous compounds. When the condensation was carried out with 2-amino-4-chlorobenzenesulfonamide and paraformaldehyde, the yield of 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide (III) dropped off markedly concomitant with the formation of an amorphous powder. It thus appeared that the polar chloro group on the



III

benzene ring modified the reactivity of the amino and sulfamyl functions. Since our interest in these heterocycles was influenced primarily by the inherent diuretic effect of disulfonamides and related substances,[6] we now turned our attention to the condensation of 6-substituted-4-amino-*m*-benzenedisulfonamides with various aldehydes. On the basis of previous experience, the possible formation of a polymer could not be discounted.

One of the first reactions explored was condensation of formaldehyde under acidic conditions with 4-amino-6-chloro-*m*-benzenedisulfonamide Va (see Scheme I). It was of interest to note that only cyclization had occurred to yield 6-chloro-3,4-dihydro-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (VIIIa). The structure of this compound was confirmed by sodium borohydride reduction of 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide (VI).[7]

A large number of dihydrobenzothiadiazine 1,1-dioxides was prepared and selected representative examples are given in Tables I, II and III.

The methylation and acetylation of 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide (VI) and of the corresponding dihydro compound VIIIa were studied and interesting differences in the reactivity of these two compounds were noticed.

The methylation of VIIIa with dimethyl sulfate yielded a monomethyl and dimethyl derivative. The latter was found to be identical with VIIIb which was obtained by condensing the N,N′-dimethyl-*m*-benzenedisulfonamide Vb with formaldehyde. Moreover, the infrared spectrum of this compound did not show NH_2 bands. Its diacetyl derivative XIb was devoid of NH bands (*vide infra*). However, the infrared spectrum of the monomethyl derivative *did* exhibit the bands characteristic of NH_2 absorption suggesting structures X or XIII. Nevertheless, the 7-methylsulfamyl derivative XVa could not be discounted

(1) A. Magnus-Levy, *Ber.*, **26**, 2148 (1893); E. Hug, *Bull. soc. chim.*, **5**, 1, 990 (1934); L. McMaster, THIS JOURNAL, **56**, 204 (1934); O. Albrecht, *Rev. gen. mat. plastiques*, **15**, 135 (1939); for a brief but concise review of this subject see also C. M. Suter, "The Organic Chemistry of Sulfur," J. Wiley and Sons, Inc., New York, N. Y., 1944, pp. 855–857.

(2) F. C. Wood and A. E. Battye, *J. Soc. Chem. Ind.*, **52**, 346 (1933).

(3) J. Druey, *Helv. Chim. Acta*, **31**, 179 (1948).

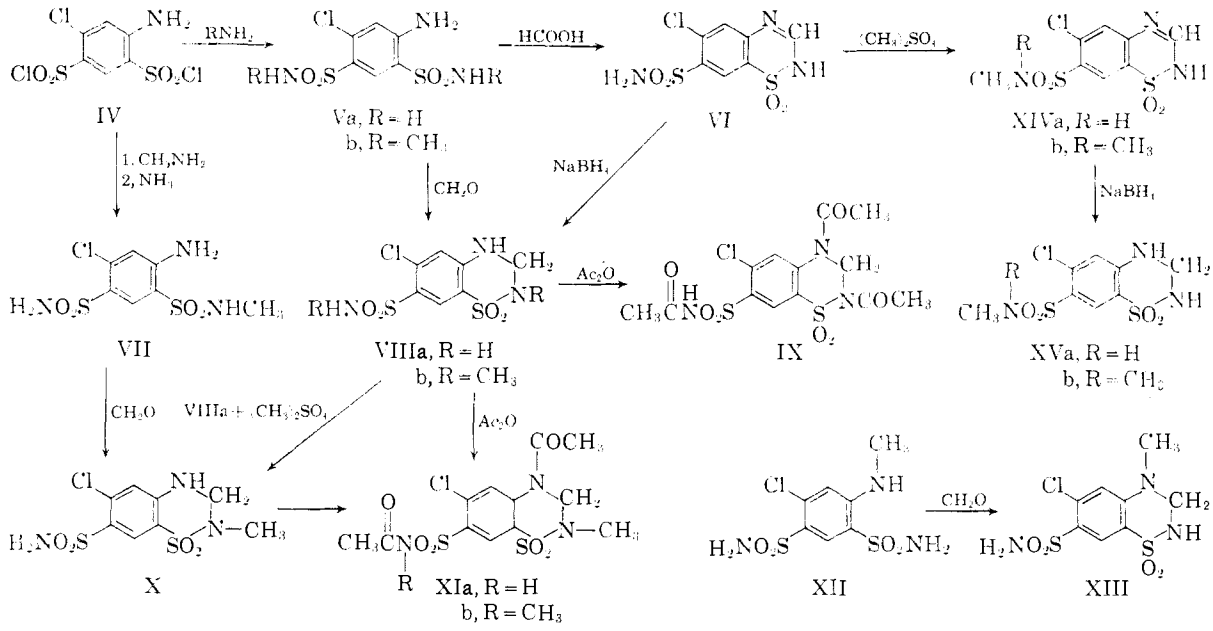
(4) J. H. Freeman and E. C. Wagner, *J. Org. Chem.*, **16**, 815 (1951).

(5) This compound was prepared according to the procedure outlined by H. E. Fierz-David, E. Schlittler and H. Waldman, *Helv. Chim. Acta*, **12**, 663 (1929).

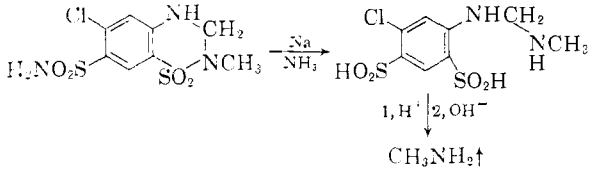
(6) J. M. Sprague, N. Y. Acad. Sci., Biol. Sect., November 8, 1957.

(7) F. C. Novello and J. M. Sprague, THIS JOURNAL, **79**, 2028 (1957).

SCHEME I



absolutely. The 4-methyl derivative XIII was synthesized from XII, but was not identical with the methylation product X. Compound X formed a diacetyl derivative XIa whose infrared spectrum showed one bonded NH band. The product resulting from the reductive cleavage of the two sulfonamide functions of X, using sodium in liquid ammonia,[8] was treated with dilute acid followed by alkali. The methylamine so liberated was identified by vapor phase chromatography and as its hydrochloride.[9] This could only have



arisen from the 2-methyl derivative X, whereas the 7-methylsulfamyl derivative would have liberated ammonia. Under identical reaction conditions compound Vb yielded only ammonia, nor was any cleavage found by subjecting X only to the hydrolytic steps of the degradation. Finally compound X was also obtained by treating the disulfonyl chloride IV first with 2 molar equivalents of methylamine, then with ammonia to give VII, followed by ring closure with formaldehyde.

The methylation of 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide (VI) with dimethyl sulfate also gave a monomethyl and a dimethyl derivative, XIVa and XIVb, respectively. Sodium borohydride reduction of these compounds yielded the corresponding monomethyldihydro derivative XVa and the dimethyldihydroderivative XVb. The methyl group in XVa must be attached to the 7-sulfamyl group since it is not identical with compounds X or XIII.

The 7-N-dimethylsulfamyl derivative XVb was formed only in very small quantities. Besides this formulation two other structures were possible; the 2-methyl-7-N-methylsulfamyl was ruled out since its reduction product was found to be different from VIIIb, and the 4-methyl-7-N-methylsulfamyl structure was eliminated on the basis of its typical 1,2,4-benzothiadiazine 1,1-dioxide type ultraviolet absorption spectrum.[10] Acetylation of the dihydrobenzothiadiazine 1,1-dioxide derivatives as well as the corresponding benzenedisulfonamides showed that all NH and NH_2 groups are acetylated readily (*e.g.*, IX, XIa,b), whereas under identical conditions the benzothiadiazine 1,1-dioxide VI failed to give an acetyl derivative. Thus the 3,4-double bond in VI influences the reactivity of the whole molecule markedly.

Spectral Properties.—Because of the insolubility of these compounds in the usual solvents all infrared curves were run as Nujol mulls. Although this led to some difficulties in the absolute interpretation of the NH absorption, the empirical relationships evolved were consistent enough to aid in the determination of structure of the methylation products.

It was observed that where the benzene ring of the heterocycles was unsubstituted, the NH bands appeared at approximately 3360 and 3250 cm.$^{-1}$ with the latter band being the stronger. In one example (VIIIb) a single strong band was present at 3350 cm.$^{-1}$. From our experience with other structures containing a sulfonamide with a free NH_2 group, the strongest band appeared at approximately 3360 cm.$^{-1}$ with a weaker band at 3250 cm.$^{-1}$. Occasionally the free NH_2 band appears at 3485 cm.$^{-1}$. However, in no instance does a single strong NH band appear. With the aid of this empirical relationship it was always an

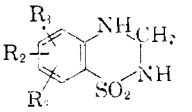
(8) V. du Vigneaud and O. K. Behrens, *J. Biol. Chem.*, **117**, 27 (1937).

(9) We wish to thank Dr. M. Kuehne of our laboratories for suggesting and carrying out this elegant proof of structure.

(10) A compound to be reported later which contains a methyl group at position 4 and the double bond at the 2,3-position has been synthesized and found to have quite a different ultraviolet absorption spectrum.

TABLE I

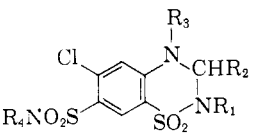
DERIVATIVES OF 3,4-DIHYDRO-1,2,4-BENZOTHIADIAZINE 1,1-DIOXIDE



No.	R_1 =	R_2 =	R_3 =	Formula	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	H	H	7-SO_2NH_2	$C_7H_9N_3O_4S_2$	208–211	31.93	31.81	3.45	3.45		
2	6-F	H	7-SO_2NH_2	$C_7H_8FN_3O_4S_2$	229–231					14.94	14.75
3	5-Cl	H	7-SO_2NH_2	$C_7H_8ClN_3O_4S_2$	216–217	28.24	28.49	2.70	2.85		
4	6-Cl	H	7-SO_2NH_2	$C_7H_8ClN_3O_4S_2$	273–275	28.24	28.49	2.70	2.72	14.11	13.94
5	5-SO_2NH_2	H	7-Cl	$C_7H_8ClN_3O_4S_2$	207–210	28.24	28.65	2.70	2.64		
6	5-CH_3	H	7-SO_2NH_2	$C_8H_{11}N_3O_4S_2$	232–235	34.64	34.01	3.99	4.03		
7	6-CH_3	H	7-SO_2NH_2	$C_8H_{11}N_3O_4S_2$	263–265	34.64	34.43	3.99	4.06		
8	6-OCH_3	H	7-SO_2NH_2	$C_8H_{11}N_3O_5S_2$	254–257	32.86	32.61	3.80	3.93		
9	6-CF_3	H	7-SO_2NH_2	$C_8H_8F_3N_3O_4S_2$	254–255					12.60	12.35
10	5-SO_2NH_2	H	7-SO_2NH_2	$C_7H_{10}N_4O_6S_3$	286–287	24.56	24.92	2.94	3.06		
11	5-CH_3	6-Cl	7-SO_2NH_2	$C_8H_{10}ClN_3O_4S_2$	307–309	30.82	31.16	3.23	3.53		

TABLE II

DERIVATIVES OF 3,4-DIHYDRO-2H-1,2,4-BENZOTHIADIAZINE 1,1-DIOXIDE



No.	R_1	R_2	R_3	R_4	Formula	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
12	H	CH_3	H	H_2	$C_8H_{10}ClN_3O_4S_2$	256–258	30.82	30.66	3.23	3.11	13.5	13.8
13	H	*n*-C_3H_7	H	H_2	$C_{10}H_{14}ClN_3O_4S_2$	254–256	35.34	35.53	4.15	4.35		
14	H	*i*-C_3H_7	H	H_2	$C_{10}H_{14}ClN_3O_4S_2$	304–306	35.34	35.67	4.15	4.21		
15	H	*n*-C_4H_9	H	H_2	$C_{11}H_{16}ClN_3O_4S_2$	176–179	37.34	37.53	4.56	4.60		
16	H	*i*-C_4H_9	H	H_2	$C_{11}H_{16}ClN_3O_4S_2$	241–245	37.34	37.09	4.56	4.54		
17	H	$-CH_2Cl$	H	H_2	$C_9H_9Cl_2N_3O_4S_2$	235 dec.	27.74	27.69	2.62	2.90		
18	H	$-C_6H_5$	H	H_2	$C_{15}H_{12}ClN_3O_4S_2$	248–250	41.77	41.85	3.24	3.42		
19	H	$-CH_2C_6H_5$	H	H_2	$C_{14}H_{14}ClN_3O_4S_2$	247–250	43.35	43.88	3.64	3.86		
20	H	$CH_2CH_2C_6H_5$	H	H_2	$C_{15}H_{16}ClN_3O_4S_2$	174–175	44.82	44.83	4.01	4.13	10.45	10.42
21	H	2-Thienyl	H	H_2	$C_{11}H_{10}ClN_3O_4S_3$	222–225	34.77	35.14	2.65	2.69	11.06	11.17
22	H	2-Furyl	H	H_2	$C_{11}H_{10}ClN_3O_5S_2$	214–218	36.31	36.24	2.77	2.94		
23	H	4-Pyridyl	H	H_2	$C_{12}H_{11}ClN_4O_4S_2$	>310	38.45	39.04	2.96	2.81	14.95	14.48
24	CH_3	H	H	H_2	$C_8H_{10}ClN_3O_4S_2$	252–255	30.82	30.73	3.23	3.30		
25	H	H	CH_3	H_2	$C_8H_{10}ClN_3O_4S_2$	225–227	30.82	30.62	3.23	3.28		
26	H	H	H	H; CH_3	$C_8H_{10}ClN_3O_4S_2$	260–265	30.82	31.13	3.23	3.33		
27	C_2H_5	H	H	H_2	$C_9H_{12}ClN_3O_4S_2$	194–197	33.18	32.84	3.71	3.54		
28	CH_3	CH_3	H	H_2	$C_9H_{12}ClN_3O_4S_2$	274–276	33.18	33.03	3.71	3.44		
29	CH_3	H	H	H; CH_3	$C_9H_{12}ClN_3O_4S_2$	203–206	33.18	33.26	3.71	3.66		
30	C_2H_5	H	H	C_2H_5	$C_{11}H_{16}ClN_3O_4S_2$	163–166	37.34	37.76	4.56	4.98		
31	*n*-C_4H_9	H	H	H; *n*-C_4H_9	$C_{13}H_{24}ClN_3O_4S_2$	170–171	43.95	43.88	5.90	5.88		
32	CH_3	CH_3	H	H; CH_3	$C_{10}H_{14}ClN_3O_4S_2$	248–251	35.34	35.34	4.15	4.00		
33	H	H	H	$(CH_3)_2$	$C_9H_{12}ClN_3O_4S_2$	238–240	33.18	33.64	3.71	3.70		
34	CH_3CO	H	CH_3CO	H; CH_3CO	$C_{13}H_{14}ClN_3O_7S_2$	225–227	36.84	37.10	3.33	3.39		
35	CH_3	H	CH_3CO	H; CH_3CO	$C_{12}H_{14}ClN_3O_6S_2$	227–229	36.41	36.76	3.56	3.69		
36	H	H	H	CH_3; CH_3CO	$C_{10}H_{12}ClN_3O_5S_2$	211–214	33.95	34.15	3.42	3.14		
37	CH_3CO	H	H	CH_3; CH_3CO	$C_{12}H_{14}ClN_3O_6S_2$	167–170	36.41	36.20	3.56	3.70		
38	CH_3	H	CH_3CO	CH_3; CH_3CO	$C_{13}H_{13}ClN_3O_6S_2$	197–199	38.09	37.99	3.94	3.99		

easy matter to determine when the sulfonamide moiety was methylated.

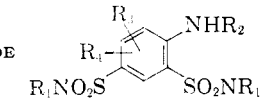
With regard to the acetylated derivatives of the 3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxide a strong band appears at approximately 1715 cm.$^{-1}$ for substitution at the 2- and 4-positions. For compounds IX and XIa the amide type grouping at position 4 exhibits an additional weaker band at 1735 and 1742 cm.$^{-1}$, respectively. When the 7-sulfamyl group is methylated, this band disappears and only that at 1715 cm.$^{-1}$ is present. The 7-N-acetylated derivatives have a band from 1680 to 1695 cm.$^{-1}$. No amide II band is observed for compounds IX and XIa.

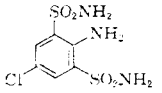
The 1,2,4-benzothiadiazine 1,1-dioxide type compounds such as VI always exhibit a strong band at approximately 1625 cm.$^{-1}$ which is due to the C=N group adjacent to an aromatic nucleus. In addition a strong band is present at 1600 cm.$^{-1}$ which is caused by the —NH deformation absorption superimposed on the —C=C— stretching vibrations of the aromatic system. The strength of the band must also be associated with the presence of electronegative groups on the aromatic moiety. On the other hand, the dihydro-1,2,4-benzothiadiazine 1,1-dioxides contain only one strong band at 1600 cm.$^{-1}$ as is expected. In the acetylated compounds this band now centers at 1590 cm.$^{-1}$ and is weak to medium strong which is more typical of aromaticity.

The two anti-symmetric SO_2 bands appear at approximately 1340 and 1325 cm.$^{-1}$ with the latter band sometimes appearing as an inflection and may be associated with the ring SO_2 group. The symmetric SO_2 band absorbs in the region of 1170 cm.$^{-1}$ and in the case of compounds

TABLE III

DERIVATIVES OF 4-AMINO-1,3-BENZENEDISULFONAMIDE



No.	R_1	R_2	R_3	R_4	Formula	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	H_2	H	H	6-F	$C_6H_8FN_3O_4S_2$	237–238					15.6	15.6
2	H_2	H	H	5-CH_3	$C_7H_{11}N_3O_4S_2$	271–275	31.7	31.8	4.2	4.4		
3	H_2	H	H	6-CF_3	$C_7H_8F_3N_3O_4S_2$	235–236	26.3	26.0	2.5	2.8	13.2	13.2
4	H_2	H	5-CH_3	6-Cl	$C_7H_{10}ClN_3O_4S_2$	308–310	28.1	27.8	3.4	3.3		
5	H_2	CH_3	H	6-Cl	$C_7H_{10}ClN_3O_4S_2$[a]	230–235	28.1	28.2	3.4	3.3		
6	H; CH_3	H	H	6-Cl	$C_8H_{12}ClN_3O_4S_2$[b]	186–190	30.6	30.4	3.8	3.8		
7	H; C_2H_5	H	H	6-Cl	$C_{10}H_{16}ClN_3O_4S_2$	196–198	35.1	35.6	4.7	5.0		
8	H; n-C_4H_9	H	H	6-Cl	$C_{14}H_{24}ClN_3O_4S_2$[b]	83–87	42.2	42.8	6.1	6.4		
9	H; CH_3CO	CH_3CO	H	6-Cl	$C_{12}H_{14}ClN_3O_7S_2$	248–250	35.0	35.1	3.4	3.7		
10	CH_3; CH_3CO	CH_3CO	H	6-Cl	$C_{14}H_{18}ClN_3O_7S_2$	194–196	38.2	38.4	4.1	4.1	9.6	9.5
11					$C_6H_8ClN_3O_4S_2$	232–235	25.2	25.0	2.8	2.9		

[a] Ref. 1; the compound was mentioned but not characterized (see C. M. Suter reference). [b] Ref. 17.

VIIIb and XIVa it is split into two bands 25 cm.$^{-1}$ apart. In the 1,2,4-benzothiadiazine 1,1-dioxides an additional medium to strong band appears at 1120 cm.$^{-1}$ which is probably characteristic of the SO_2 moiety in the ring. For the acetylated compounds outlined in Scheme I strong bands appear at 1350 and 1380 cm.$^{-1}$ and at 1130 and 1170 cm.$^{-1}$. In each region the latter band is the stronger. The acetyl group appears to exert a hypsochromic effect. It must be kept in mind that the 1380 cm.$^{-1}$ band is also composed of methyl deformation frequency bands and a C–N stretching vibration of variable strength appears at 1350–1300 cm.$^{-1}$.[11] This band is weak to medium in the parent methylated compounds. The S–N frequency[12] has been tentatively assigned to a strong band at 1070–1100 cm.$^{-1}$ In our series a weak to strong band appeared at 1050 to 1087 cm.$^{-1}$, thus casting some doubt to this assignment.

Pharmacology.—The compounds reported herein were tested by our Biological Division. Several have shown excellent diuretic and saluretic effects in experimental animals.[13] One of these compounds 6 - chloro - 3,4 - dihydro - 7 - sulfamyl - 2H - 1,2,4-benzothiadiazine 1,1-dioxide (VIIIa)[14] has undergone extensive clinical trials and the high diuretic potency and low toxicity has been substantiated in man.

Acknowledgments.—The authors are grateful to Dr. E. Schlittler for his interest and encouragement throughout this investigation. We also wish to thank Mr. Erno Mohacsi and Miss Patricia Wenk for their technical assistance, Mr. George Robertson and Miss Patricia Gallant for the microanalyses and Miss Natalie Cahoon, Mrs. Violet Loire and Mr. Herbert Behrens for the spectral data.

Experimental

All melting points in the tables and in the Experimental section are uncorrected.

Preparation of Disulfonamide Intermediates.—The *o*-aminobenzenedisulfonamides were prepared by chlorosulfonation of the corresponding aniline derivatives according to the method outlined by Lustig and Katscher[15] for 2-amino-5-methyl-1,3-benzenedisulfonamide and 2-amino-1,-3,5-benzenetrisulfonamide.

Novello[16] has reported 4-amino-*m*-benzenedisulfonamide, 4-methylamino-6-chloro-*m*-benzenedisulfonamide and the 6-fluoro-, 6-chloro-, 5-chloro, 6-methyl and 6-methoxy derivatives of 4-amino-*m*-benzenedisulfonamides. More recently, Logemann, *et al.*,[17] have mentioned 4-amino-6-chloro-*N*,*N*′-dimethyl- and *N*,*N*′-dibutyl-*m*-benzenedisulfonamide without characterizing these compounds. In Table III are presented the physical data of the new *o*-amino-*m*-benzenedisulfonamides used as intermediates in the preparation of the dihydrobenzothiadiazine 1,1-dioxides.

An Example of the Method for Preparing the Disulfonamides. 6-Fluoro-4-amino-*m*-benzenedisulfonamide.—*m*-Fluoroaniline (11.1 g., 0.1 mole) was added dropwise with stirring to 100 ml. of chlorosulfonic acid in a 1-liter round-bottom, 3-necked flask cooled in an ice-bath. The addition was complete in 20 minutes. Sodium chloride (85 g.) was added over a one-hour period with stirring. The mixture was then heated at 150° in an oil-bath for 4 hours. The flask was cooled thoroughly in an ice-bath and the contents treated with 300 ml. of cold water. The product was extracted with ether, the extract washed with water and dried over sodium sulfate. After removal of the ether on the steam-bath a light brown oil (26 g.) remained which resisted crystallization. This oil was chilled to 0° and treated slowly with 42 ml. of 28% ammonium hydroxide. The mixture was heated on the steam-bath for one hour and then chilled. The gray powder was collected and recrystallized from boiling water, to give white needles, m.p. 237–238°. The other compounds presented in Table III were prepared in the same manner.

General Method for the Preparation of Dihydrobenzothiadiazine 1,1-Dioxides.—This method is illustrated for the preparation of **3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide**. A mixture of 5.7 g. (0.03 mole) of *o*-aminobenzenesulfonamide, 1.0 g. of paraformaldehyde, 0.5 ml. of ethyl acetate containing 20% hydrogen chloride and 50 ml. of dimethyl carbitol was heated on the steam-bath for one hour after which the clear solution was evaporated to one-third

(11) J. J. Bellamy, "The Infrared Spectra of Complex Molecules," J. Wiley and Sons, Inc., New York, N. Y., 1958, 2nd Edition, p. 19, 249.

(12) J. N. Baxter, J. Cymerman-Craig and J. B. Willis, *J. Chem. Soc.*, 671 (1955).

(13) A. A. Renzi, J. J. Chart and R. Gaunt, *Toxicol. Appl. Pharmacol.*, 1, 406 (1959); W. E. Barrett, R. A. Rutledge, H. Sheppard and A. J. Plummer, *ibid.*, 1, 333 (1959).

(14) G. deStevens, L. H. Werner, A. Halamandaris and S. Ricca, Jr., *Experientia*, **14**, 463, 1958; this compound has been assigned the generic name hydrochlorothiazide and the CIBA Tradename Esidrix.

(15) O. Lustig and E. Katscher, *Monatsh.*, **48**, 87 (1927).

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

(17) W. Logemann, P. N. Giraldi and M. A. Parenti, *Nature*, **182**, 1510 (1958).

its volume at the water-pump. This solution, on cooling to room temperature, was added with vigorous stirring to 200 ml. of water resulting in a fine pinkish precipitate which was collected and recrystallized from water using Norite; yield of pure product, m.p. 166–167°, 65%.

Anal. Calcd. for $C_7H_8N_2O_2S$: C, 45.64; H, 4.37; N, 15.21. Found: C, 45.82; H, 4.37; N, 14.90.

3,4-Dihydro-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide, m.p. 218–219°, was prepared in 90% yield.

Anal. Calcd. for $C_8H_{10}N_2O_2S$: C, 48.48; H, 5.09; N, 14.14. Found: C, 48.53; H, 5.20; N, 13.90.

A 10% yield of 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide, m.p. 170°, was obtained on condensing 2-amino-4-chlorobenzenesulfonamide[6] with paraformaldehyde.

Anal. Calcd. for $C_7H_7ClN_2O_2S$: C, 38.45; H, 3.23; N, 12.81. Found: C, 38.40; H, 3.12; N, 12.63.

6-Chloro-3,4-dihydro-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide, m.p. 202–204°, was obtained in 42% yield.

Anal. Calcd. for $C_8H_9ClN_2O_2S$: N, 12.04. Found: N, 11.92.

6-Chloro-3,4-dihydro-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-Dioxide (VIIIa).—A mixture of 5.8 g. (0.02 mole) of 4-amino-6-chloro-*m*-benzenedisulfonamide (Va), 0.66 g. of paraformaldehyde, 1.0 ml. of ethyl acetate solution containing 109.5 g. of hydrogen chloride per liter and 50 ml. of dimethyl carbitol was heated at 90° for one hour. The solution was then concentrated to one-third its volume under reduced pressure, diluted with 200 ml. of water and then allowed to stand at room temperature for 2 hours. The resulting crystals were filtered off and recrystallized from water; yield of pure product, m.p. 273–275°, was 75% of theoretical.

6-Chloro-3-methyl-7-sulfamyl-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-Dioxide.—A mixture of 5.8 g. (0.02 mole) of Va, 2.36 g. (0.02 mole) of diethyl acetal, 1.0 ml. of ethyl acetate solution saturated with hydrogen chloride and 50 ml. of dimethyl carbitol was heated at 90° for one hour. The work-up of the solution as described above gave an 80% yield of product, m.p. 256–258°. When acetaldehyde (0.8 g.) was condensed with Va (5.8 g.) under the same reaction conditions a comparable yield of product was obtained. All the cyclization reactions were carried out in the above-described manner with an aldehyde or an acetal as the condensing agent.

Reduction of 6-Chloro-7-sulfamyl-1,2,4-benzothiadiazine 1,1-Dioxide (VI).—6-Chloro-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide (0.75 g.) was dissolved in 10 ml. of water by adding 35 drops of 2 *N* aqueous solution of sodium hydroxide. To the clear solution there was added 0.2 g. of sodium borohydride and the reaction mixture was allowed to stand at room temperature for 5 hours, after which it was filtered and the filtrate was adjusted to *p*H 7–7.5. A crystalline precipitate was obtained which was filtered off, washed with a small amount of water and recrystallized from boiling water, m.p. 268–272°. The mixed melting point with a sample of 6-chloro-7-sulfamyl-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide (VIIIa) obtained by condensing 4-amino-6-chloro-*m*-benzene-disulfonamide with paraformaldehyde showed no depression. The infrared spectra of the two samples were superimposable.

Methylation Experiments.—Methylation of 6-chloro-3,4-dihydro-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide (VIIIa), 6-chloro-3,4-dihydro-3-methyl-7-sulfamyl-1,2,4-benzothiazine 1,1-dioxide and 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide (VI): To a solution of 12.7 g. (0.042 mole) of 6-chloro-3,4-dihydro-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (VIIIa) in a mixture of 55 ml. of N sodium hydroxide and 200 ml. of water, 7.0 g. (0.055 mole) of dimethyl sulfate was added at 10°, with stirring. Stirring was continued for one hour at 10° followed by one hour at 25°. The reaction product had separated from the solution and was filtered off. Fractional recrystallization from aqueous alcohol (1:1 mixture) gave two products. The less soluble product was identified as 6-chloro-3,4-dihydro-2-methyl-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide (X), m.p. 252–255° (Table II, 24). The mother liquors yielded the 6-chloro-3,4-dihydro-2-methyl-7-N-methylsulfamyl-1,2,4-benzothiadiazine 1,1-dioxide (VIIIb), m.p. 203–206° (Table II, 29).

Methylation of 6-chloro-3,4-dihydro-3-methyl-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (Table II, 12) under identical conditions gave 6-chloro-3,4-dihydro-2,3-dimethyl-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide, m.p. 274–276° (Table II, 28), and the corresponding 2,3-dimethyl-7-N-methyl derivative (Table II, 32) m.p. 248–251°.

A solution of 18 g. (0.061 mole) of 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide, 66 ml. of *N* sodium hydroxide and 240 ml. of water was allowed to react with 8.4 g. (0.067 mole) of dimethyl sulfate as above. The reaction product was recrystallized by dissolving in the minimum amount of dimethylformamide and adding this solution to a sixfold volume of boiling water. The first crop gave 6-chloro-7-N-methylsulfamyl-1,2,4-benzothiadiazine 1,1-dioxide (XIVa), m.p. 337–340°.

Anal. Calcd. for $C_8H_8ClN_3O_4S_2$: C, 31.01; H, 2.60. Found: C, 30.87; H, 2.44.

The mother liquors yielded a second crop which on further recrystallization melted at 295–297° (XIVb) and was identified as 6-chloro-7-N-dimethylsulfamyl-1,2,4-benzothiadiazine 1,1-dioxide.

Anal. Calcd. for $C_9H_{10}ClN_3O_4S_2$: C, 33.38; H, 3.11. Found: C, 33.31; H, 3.18.

4-Amino-6-chloro-1,3-N,N′-dialkyl benzenedisulfonamide.—These compounds (Table III, 6,7,8) were prepared by treating the 4-amino-6-chloro-1,3-benzenedisulfonylchloride (0.01 mole) with a 25–50% aqueous solution of the amine (0.12 mole) at 25° for 30 minutes and completing the reaction by warming on the steam-bath for 15 minutes. The crystalline reaction product was recrystallized from aqueous alcohol (1:1 mixture).

4-Amino-6-chloro-3-N-methylsulfamyl-benzenesulfonamide.—A solution of 17.7 g. (0.05 mole) of 4-amino-6-chloro-1,3-benzenedisulfonyl chloride in 250 ml. of chloroform was stirred with 12.5 ml. (0.1 mole) of a 25% aqueous solution of methylamine at 25° for 1.5 hours. A substance (2.3 g.) had crystallized and was filtered off. It was identified by mixed melting point as 4-amino-6-chloro-1,3-N,N′-dimethylbenzenedisulfonamide. The filtrate was concentrated *in vacuo* and gave 5.5 g. of 4-amino-6-chloro-3-N-methylsulfamyl chloride which after recrystallization from a mixture of ethyl acetate and hexane melted at 158–162°.

Anal. Calcd. for $C_7H_8Cl_2N_2O_4S_2$: C, 26.34; H, 2.33. Found: C, 26.82; H, 2.56.

Reaction of 3.6 g. of the above product with 25 ml. of liquid ammonia gave 2.8 g. of VII. After recrystallization from aqueous alcohol (1:1 mixture) the compound melted at 175–180°.

Anal. Calcd. for $C_7H_{10}ClN_3O_4S_2$: C, 28.04; H, 3.36. Found: C, 27.92; H, 3.47.

This substance was condensed with paraformaldehyde in the usual manner and the product isolated was found to be identical in all respects with X.

General procedure for acetylations (Table II, 34, 35, 36, 37, 38; and Table III, 9 and 10).—The acetylated products were obtained by refluxing 1 g. of the compound with 5 ml. of acetic anhydride for one hour. The reaction mixture was concentrated *in vacuo* and the residue recrystallized from aqueous alcohol. In the case of compound 37, Table II, 1 g. of material was refluxed for 4 hours with 7.5 ml. of acetic anhydride as this compound was more resistant to acetylation.

Reductive Cleavage of 6-Chloro-3,4-dihydro-2-methyl-7-sulfamyl-1,2,4-benzothiadiazine 1,1-Dioxide (X).—To a stirred solution of 1 g. (0.0032 mole) of X in 400 ml. of liquid ammonia was added 0.50 g. (0.022 mole) of sodium in small pieces. The blue coloration which persisted after most of the sodium had been added was destroyed after 15 minutes by addition of 1.5 ml. of ethanol. The ammonia was evaporated spontaneously, the flask then swept out by a stream of nitrogen and finally warmed at 60° for 2 hours at 0.01 mm.; 200 ml. of dry benzene was added and distilled off in two successive portions. Passing a stream of nitrogen through the reaction mixture after the second addition of benzene and subsequently through a 3% hydrochloric acid trap showed that no further trace of ammonia could be swept out.

The reduction product was then dissolved in 30 ml. of 10% hydrochloric acid, the clear solution refluxed for 2 hours, cooled and made strongly basic by addition of a 40% aqueous sodium hydroxide solution. A stream of nitrogen was

passed through the reaction mixture and then through 3% hydrochloric acid for 15 hours. The acid solution was evaporated to dryness *in vacuo* and the white, crystalline residue identified as a mixture of methylamine hydrochloride, m.p. 225°, and ammonium chloride, no m.p. to 300°, by recrystallization from methanol-ether and by vapor phase chromatography. For the latter a Perkin–Elmer model 154 Vapor Fractometer with a 1-m. triethanolamine impregnated Celite column was used at 79°. The mixture of amines was introduced in methanol solution after liberation from their hydrochlorides by addition of methanolic potassium hydroxide. Four sharp maxima were obtained corresponding to control peaks obtained for ammonia, methylamine, methanol and water. The area under the ammonia peak was smaller than that from methylamine.

Control Experiments.—(a) The above procedure was repeated with 1 g. (0.0032 mole) of 4-amino-6-chloro-N,N'-dimethyl-*m*-benzenedisulfonamide (Vb). Only a small amount of ammonium chloride was isolated in this case. No trace of methylamine could be detected by vapor phase chromatography.

(b) A suspension of 0.50 g. (0.0016 mole) of X was refluxed for 2 hours in 60 ml. of 10% hydrochloric acid, cooled and made strongly basic with saturated sodium hydroxide solution. A stream of nitrogen was passed through the solution and through a trap of 3% hydrochloric acid for 15 hours. Evaporation of the acid to dryness did not leave any residue.

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[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORY, A. H. ROBINS CO., INC.]

5-Aryloxymethyl-2-oxazolidinones

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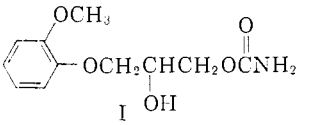
When (a) 3-(*o*-methoxyphenoxy)-1,2-propanediol (II) is fused at 180–200° with two molar equivalents of urea or when (b) 2-hydroxy-3-(*o*-methoxyphenoxy)-propyl carbamate (I) and one molar equivalent of urea are similarly fused, the major product is 5-(*o*-methoxyphenoxymethyl)-2-oxazolidinone (IIIa). A sequence of reactions by which the oxazolidinone ring is formed under these conditions has been investigated and these reactions are discussed. Following method (a) twenty-five 5-aryloxymethyl-2-oxazolidinones, in which the substitution in the aryl nucleus is alkyl, alkyloxy and/or halogen, have been prepared for pharmacological testing. A total of nineteen corresponding N-substituted-5-aryloxymethyl-2-oxazolidinones, prepared by condensation of 1-amino-3-aryloxy-2-propanols with ethyl carbonate or phosgene, are also reported.

In an effort to develop other processes of preparing the skeletal muscle relaxant 2-hydroxy-3-(*o*-methoxyphenoxy)-propyl carbamate (I)[1] the reaction between 3-(*o*-methoxyphenoxy)-1,2-propanediol (II) and urea was studied. Instead of yielding the desired carbamate, the fusion of these



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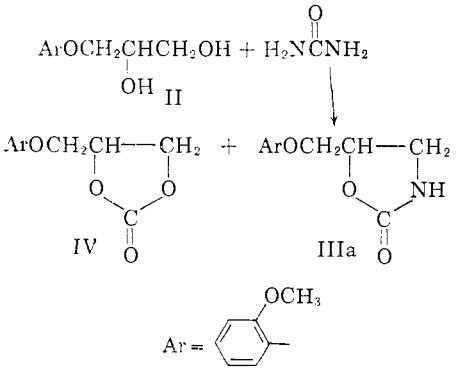
materials at 180–200° gave 5-(*o*-methoxyphenoxymethyl)-2-oxazolidinone (IIIa) as the major isolable product as well as minor amounts of the cyclic carbonate of II (IV) which has been reported previously.[2]



While the present investigation was in progress, the same reaction was reported to have occurred between mephenesin and urea.[3] The reaction has been extended to other α-aryl ethers of glycerol and found to be a general one. The resulting 5-aryloxymethyl-2-oxazolidinones possess several interesting pharmacological activities. They are generally antagonists of strychnine convulsions in rats and have consequently been investigated for use as skeletal muscle relaxants and for related pharmacological indications.

These compounds have also been prepared by the fusion of 1-chloro-3-aryloxy-2-propanol or 3-aryloxy-1,2-epoxypropane with urea, and by the reaction of 3-aryloxy-1,2-epoxypropane with urethan or acidified sodium cyanate.[3]

A recent patent[4] reported the preparation of IIIa by the reaction of urethan and 3-(*o*-methoxyphenoxy)-1,2-propanediol (II), but the structure was reported with the *o*-methoxyphenoxymethyl group located at position 4 of the oxazolidinone ring. Repetition of this work has shown that the product is identical to IIIa prepared by the glycol–urea fusion.

In order to locate unequivocally the aryloxymethyl group of the compound IIIa at position 5 (rather than 4) of the oxazolidinone ring, it was subjected to basic hydrolysis which gave the expected 1-amino-3-(*o*-methoxyphenoxy)-2-propanol (V). Lithium aluminum hydride reduction of IIIa produced the corresponding N-methylamino alcohol VI. The identical amino alcohols were synthesized by condensation of 1-chloro-3-(*o*-methoxyphenoxy)-2-propanol (VII) with ammonia or methylamine, respectively. The corresponding oxazolidinones IIIa and IIIb were obtained again when V and VI were treated with phosgene or diethyl carbonate.

The mechanism by which the 5-aryloxymethyl-2-oxazolidinones are formed in the fusion of an α-

(1) R. S. Murphey, U. S. Patent 2,770,649 (1956); generic name, methocarbamol.

(2) M. M. Baizer, J. R. Clark and J. Swidinsky, THIS JOURNAL, **79**, 1595 (1957).

(3) Y. M. Beasley, V. Petrow, O. Stephenson and A. S. Thomas, *J. Pharm. and Pharmacol.*, **9**, 10 (1957).

(4) Belgian Patent 570,147 (1958).