SYNTHESIS AND PROPERTIES OF 3-SUBSTITUTED 2H-1,2,4-BENZOTHIADIAZINE 1,1-DIOXIDES

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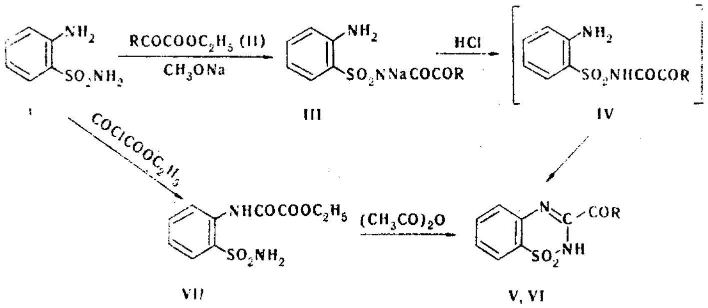
The ethyl ester and amides of 2H-1,2,4-benzothiadiazine-3-carboxylic acid 1,1-dioxide were obtained by reaction of 2-aminobenzenesulfonamide with diethyl oxalate or oxamic acid esters in the presence of sodium methoxide. The hydrolysis, amination, and hydrazinolysis of the ester were studied.

2H-1,2,4-Benzothiadiazine 1,1-dioxide derivatives are obtained by cyclization of N-acyl-2-aminobenzenesulfonamides [1] or by reaction of 2-aminobenzenesulfonamide with aldehydes [2].

To synthesize 2H-1,2,4-benzothiadiazine 1,1-dioxide derivatives we used the reaction of 2-aminobenzenesulfonamide (I) with diethyl oxalate or oxamic acid esters in the presence of sodium methoxide.



V $R = OC_2H_5$; VI $R = R'NH$

In contrast to its isomers [3], sulfonamide I does not react with diethyl oxalate when sodium methoxide is absent, even on prolonged heating; this is probably associated with the presence of a strong intramolecular hydrogen bond between the amino and sulfonamide groups [4].

When sodium methoxide is present, sulfonamide I is readily acylated by esters II to give sodium salts of esters or amides of 2-aminophenylsulfonyloxamic acids (III), which can be isolated. However, when hydrochloric acid is added to them they are cyclized to 2H-1,2,4-benzothiadiazine 1,1-dioxide derivatives (V, VI). We were unable to isolate intermediate IV. Cyclization also occurred during an attempt to diazotize salt III.

The structure of ester V was proved by alternative synthesis by cyclization of ethyl 2-aminosulfonyloxanilate (VII) [5] under the influence of acetic anhydride.

Ester V readily reacts with nucleophilic reagents. It is saponified by aqueous alkalis to give 2H-1,2,4-benzothiadiazine-3-carboxylic acid 1,1-dioxide (VIII). The latter is readily decarboxylated on heating to give 2H-1,2,4-benzothiadiazine 1,1-dioxide (IX), which was also synthesized from I and oxalic or formic acids. Acid VIII has two ionization constants [pK_a (COOH) = 7.66 and pK_a (SO_2NH) = 10.36] and reacts with CH_3ONa to give disodium salt X, aqueous solutions of which give crystalline precipitates with a number of cations (Ba^{2+}, Cu^{2+}, Mn^{2+}, Cd^{2+}, Sr^{2+}, Al^{3+}, Fe^{3+}, and Bi^{3+}).

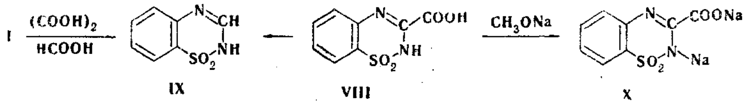


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TABLE 1. Substituted Amides of 2H-1,2,4-Benzothiadiazine-3-carboxylic Acid 1,1-Dioxide (VI)

Compound	R′	mp, °C*	Empirical formula	N, %		IR spectra, ν, cm⁻¹				UV spectra		Yield, %†
				found	calc.	NH	CO	SO_2, *as*	SO_2, *s*	λ_{max}, nm	lg ε	
VIa	H	342 (dec.)	$C_3H_7N_3O_3S$	18,7	18,6	3470 3230	1735	1305	1170	288	3,75	81
VIb	CH_3	334—336	$C_9H_9N_3O_3S$	17,7	17,5	3385 3260	1705	1315	1170	288	3,74	76
VIc	C_3H_7	280—281	$C_{11}H_{13}N_3O_3S$	15,8	15,7	—	—	—	—	—	—	68
VId	C_4H_9	210—212	$C_{12}H_{15}N_3O_3S$	15,1	15,0	—	—	—	—	—	—	53
VIe	C_6H_{11}	266—268	$C_{14}H_{17}N_3O_3S$	13,7	13,7	—	—	—	—	262	4,58	49
VIf	*o*-$CH_3OC_6H_4$	304—305	$C_{15}H_{13}N_3O_4S$	12,7	12,7	—	—	—	—	—	—	57
VIg	*p*-$CH_3OC_6H_4$	287—289	$C_{15}H_{13}N_3O_4S$	12,8	12,7	—	—	—	—	—	—	63
VIh	*p*-$CH_3C_6H_4$	332—334	$C_{15}H_{13}N_3O_3S$	13,4	13,3	3375 3245	1700	1310	1180	302	3,91	50
VIi	*m*-$CH_3C_6H_4$	315—317	$C_{15}H_{13}N_3O_3S$	13,6	13,3	—	—	—	—	—	—	67
VIj	C_6H_5	316—317	$C_{14}H_{11}N_3O_3S$	14,0	14,0	3342 3250	1710	1310	1160	—	—	58
VIk	*m*-$CH_3OC_6H_4$	284—285	$C_{15}H_{13}N_3O_4S$	13,0	12,7	3340 3230	1716	1310	1160	297	4,50	74
VI*l*	*p*-ClC_6H_4	342—344	$C_{14}H_{10}ClN_3O_3S$	12,6	12,5	3335 3270	1718	1305	1160	—	—	48
VIm	*p*-BrC_6H_4	322—324	$C_{14}H_{10}BrN_3O_3S$	11,3	11,1	—	—	—	—	—	—	44
VIn	*m*-ClC_6H_4	316—318	$C_{14}H_{10}ClN_3O_3S$	12,7	12,5	3330 3220	1724	1315	1160	290	4,20	59
VIo	*m*-$NO_2C_6H_4$	330—331	$C_{14}H_{10}N_4O_5S$	16,5	16,2	—	—	—	—	—	—	71
VIp	*p*-$NO_2C_6H_4$	354—356	$C_{14}H_{10}N_4O_5S$	16,4	16,2	—	—	—	—	—	—	63

*All of the compounds were crystallized from aqueous DMF.
†According to method B, the yields of amides VIa-e with respect to method A are, respectively 85, 73, 56, 69, and 86%.

Amides VI are formed when ester V is heated with amines in dimethylformamide (DMF), and hydrazide XI is formed when V is heated with hydrazine hydrate. Hydrazide XI reacts with acyl halides and carbonyl compounds to give acylhydrazide XII (Table 2) and arylidenehydrazides XIII (Table 3), respectively.

Amides VI (Table 1) have acidic properties (pK_a 7.65-8.50) and are titrated as monobasic acids in DMF in the presence of thymolphthalein.

The IR spectra of V-VIII and XI-XIII contain characteristic bands of stretching vibrations of NH, CO, and SO_2 groups [6]. The ν_{NH} vibrations are characterized by one band at 3200-3500 cm⁻¹ for hydrazides XIII and by two bands in this region for amides VI and acylhydrazides XII.

EXPERIMENTAL METHOD

The IR spectra of dioxane solutions of the compounds (c $2 \cdot 10^{-3}$-$2 \cdot 10^{-5}$ M) were recorded with an SF-4 spectrometer. The IR spectra of KBr pellets of the compounds (0.5% of the compound) were recorded with a UR-20 spectrometer.

Ethyl 2-Aminophenylsulfonyloxamate Sodium Salt (III). This compound was obtained by the method in [7]. At the end of the reaction, the precipitated salt was removed by filtration and washed repeatedly with anhydrous methanol to give the product in 51% yield. Found: Na 7.9%. $C_{10}H_{11}N_2NaO_5S$. Calculated: Na 7.8%.

Ethyl-2-Aminosulfonyloxanilate (VII). A 0.011-mole sample of ethoxalyl chloride was added to a solution of 0.01 mole of sulfonamide I in 15 ml of pyridine, and the mixture was allowed to stand for 1 h. It was then diluted with water and acidified with HCl (1 : 1), and the resulting precipitate was removed by filtration, washed with water, and dried to give a product with mp 183-184° (from aqueous ethanol) in 53% yield. Found: N 10.4%. $C_{10}H_{12}N_2O_5S$. Calculated: N 10.3%. IR spectrum, ν, cm⁻¹: 3320, 3225 (NH), 1715 (CO), 1340 (SO_2, as), and 1165 (SO_2, s). UV spectrum, λ_{max}, nm (log ε): 292 (3.90).

Ethyl 2H-1,2,4-Benzothiadiazine-3-carboxylate 1,1-Dioxide (V).* A) This compound, with mp 265-266° (from aqueous DMF), was obtained in 84% yield by the method in [7].

B) A mixture of 0.01 mole of ester VII and 5 ml of acetic anhydride was heated for 3 h, after which it was cooled, diluted with water, and worked up to give a product with mp 265-266° (from aqueous DMF)

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*Obtained with the participation of I. I. Bondarchuk.

TABLE 2. Acylhydrazides of 2H-1,2,4-Benzothiadiazine-3-carboxylic Acid 1,1-Dioxide (XII)

Compound	Acyl	mp, °C*	Empirical formula	N, %		IR spectra, ν, cm⁻¹				UV spectra		Yield, %
				found	calc.	NH	CO	SO₂, as	SO₂, s	λ_max, nm	lg ε	
XII a	COC_6H_5	324†	$C_{15}H_{12}N_4O_4S$	16,5	16,3	—	—	—	—	—	—	63
XII b	$COC_6H_4NO_2$-*p*	328†	$C_{15}H_{11}N_5O_6S$	18,2	18,0	—	—	—	—	—	—	44
XII c	$SO_2C_6H_5$	256—259	$C_{14}H_{12}N_4O_5S_2$	14,9	14,7	3250	1725	1305	1175	288	3,87	59
XII d	$SO_2C_6H_4NO_2$-*p*	276—278	$C_{14}H_{11}N_5O_7S_2$	16,7	16,5	3245	1730	1300	1180	270	4,18	62
XII e	$SO_2C_6H_4Cl$-*p*	258—259	$C_{14}H_{11}ClN_4O_5S_2$	13,6	13,5	3260	1725	1304	1176	290	3,85	51
XII f	$SO_2C_6H_4Br$-*p*	258—260	$C_{14}H_{11}BrN_4O_5S_2$	12,5	12,2	3250	1720	1305	1175	290	3,87	73
XII g	$SO_2C_6H_4OCH_3$-*p*	277—280	$C_{15}H_{14}N_4O_6S_2$	13,9	13,7	3250 3190	1730	1320	1160	241 288	4,26 3,47	48
XII h	$SO_2C_6H_4CH_3$-*p*	272—273	$C_{15}H_{14}N_4O_5S_2$	14,1	14,2	—	—	—	—	—	—	54
XII i	$SO_2C_6H_4SO_2NH_2$-*p*	290—294	$C_{14}H_{13}N_5O_7S_3$	15,3	15,2	3229 3340	1734	1300	1180	—	—	78
XIIj	$SO_2C_6H_4SO_2NH_2$-*m*	270—274	$C_{14}H_{13}N_5O_7S_3$	15,5	15,2	3235 3050	1720	1310	1185	286	3,88	80

*All of the compounds were crystallized from aqueous DMF.

† With decomposition.

TABLE 3. Alkyl (aryl-, heteryl-)idenehydrazides of 2H-1,2,4-Benzothiadiazine-3-carboxylic Acid 1,1-Dioxide (XIII)

Compound	R group	mp (dec.), °C*	Empirical formula	N, %		IR spectra, ν, cm⁻¹				UV spectra		Yield, %
				found	calc.	NH	CO	SO₂, as	SO₂, s	λ_max, nm	lg ε	
XIIIa	Isopropylidene	294—296	$C_{11}H_{12}N_4O_3S$	20,2	20,0	—	—	—	—	—	—	48
XIIIb	Benzylidene	340—342	$C_{15}H_{12}N_4O_3S$	17,2	17,1	3215	1710	1310	1165	305	4,17	45
XIIIc	Vanillylidene	322—324	$C_{16}H_{14}N_4O_5S$	15,1	15,0	—	—	—	—	—	—	75
XIIId	Furfurylidene	338—340	$C_{13}H_{10}N_4O_4S$	17,8	17,6	3205	1705	1310	1170	320	4,17	50
XIIIe	o-Nitrofurfurylidene	334—336	$C_{13}H_9N_5O_6S$	19,4	19,3	3215	1715	1310	1170	359	3,96	58
XIIIf	1-Methylindolin-2-on-3-idene	352—354	$C_{17}H_{13}N_5O_4S$	18,5	18,3	3225	1710	1330	1185	278 329	4,10 4,15	74

*Compound XIIIe was crystallized from DMF—methanol, and the remaining compounds were crystallized from aqueous DMF.

in 32% yield. Found: N 10.1%. $C_{10}H_{10}N_2O_4S$. Calculated: N 10.0%. IR spectrum, λ, nm (log ε): 248 (3.27) and 295 (3.30). No melting-point depression was observed for a mixture of samples of the compounds obtained by methods A and B.

N-Cyclohexyl-2H-1,2,4-benzothiadiazine-3-carboxamide 1,1-Dioxide (VIe). A) A 0.02-mole sample of cyclohexylamine was added to a solution of 0.01 mole of ester V in 20 ml of DMF, and the mixture was allowed to stand for 12 h. It was then diluted with water and acidified with HCl (1 : 1). The resulting precipitate was removed by filtration, washed with water, and dried. Compounds VIa-d (Table 1) were similarly obtained.

B) Amide VIe was obtained by the method in [7] from 0.01 mole of sodium in 50 ml of anhydrous methanol, 0.01 mole of sulfonamide I, and 0.01 mole of ethyl cyclohexyloxamate. Compounds VIa-d, f-p were similarly obtained.

No melting-point depressions were observed for mixtures of the substances obtained by methods A and B.

2H-1,2,4-Benzothiadiazine-3-carboxylic Acid Hydrazide 1,1-Dioxide (XI). A 0.02-mole sample of hydrazine hydrate was added to a solution of 0.01 mole of ester V in 50 ml of ethanol, and the mixture was allowed to stand at room temperature for 12 h. It was then diluted with water and acidified to pH 5 with HCl (1 : 1). The resulting precipitate was removed by filtration to give a product with mp 312° (dec., from aqueous DMF) in 95% yield. Found: N 23.5%. $C_8H_8N_4O_3S$. Calculated: N 23.3%. IR spectrum, ν, cm^{-1}: 3330 (NH), 1720 (CO), 1300 (SO_2, as), and 1190 (SO_2, c). UV spectrum, λ_{max}, nm (log ε): 292 (3.86).

2H-1,2,4-Benzothiadiazine-3-carboxylic Acid p-Bromophenylsulfonylhydrazide 1,1-Dioxide (XIIf). A 0.01-mole sample of p-bromobenzenesulfonyl chloride was added to a solution of 0.01 mole of hydrazide XI in 10 ml of dry pyridine, after which the mixture was heated for 1 h. It was then diluted with water and acidified. Compounds XIIa-e, g-j were similarly obtained.

2H-1,2,4-Benzothiadiazine-3-carboxylic Acid Benzylidenehydrazide 1,1-Dioxide (XIIIe). A mixture of 0.01 mole of hydrazide XI and 0.01 mole of benzaldehyde in 10 ml of DMF was heated for 30 min, after which it was cooled and poured into water. The resulting precipitate was removed by filtration, washed with water. and dried. Compounds XIIIa, c-f were similarly obtained.

2H-1,2,4-Benzothiadiazine-3-carboxylic Acid 1,1-Dioxide (VIII). A 0.01-mole sample of ester V was dissolved in 10 ml of 5% NaOH solution, and the mixture was allowed to stand at room temperature for 10 min. It was then acidified with HCl (1 : 1), and the resulting precipitate was removed by filtration and washed successively with water and alcohol to give a product with mp 285°(dec.) in 48% yield. Found: N 12.6%. $C_8H_6N_2O_4S$. Calculated: N 12.3%. IR spectrum, ν, cm^{-1}: 3250 (NH), 1770, 1690 (CO), 1300 (SO_2, as), and 1160 (SO_2, s).

2H-1,2,4-Benzothiadiazine-3-carboxylic Acid 1,1-Dioxide Disodium Salt (X). A solution of 0.01 mole of acid VIII in 50 ml of DMF was mixed with a solution of sodium methoxide (0.02 g-atom of sodium in 20 ml of alcohol), and the resulting precipitate was removed by filtration, washed with anhydrous methanol, and dried to give the product in 69% yield. Found: Na 17.3%. $C_8H_4N_2Na_2O_4S$. Calculated: Na 17.0%.

2H-1,2,4-Benzothiadiazine 1,1-Dioxide (IX). A) A 0.01-mole sample of acid VIII was heated in water for 5 min, after which the mixture was cooled, and the precipitate was removed by filtration to give IX in 40% yield.

B) A 0.01-mole sample of sulfonamide I was heated with 0.08 mole of formic acid, after which the mixture was cooled, and the precipitate was removed by filtration and dried to give IX in 68% yield.

C) A mixture of 0.01 mole of sulfonamide I, 0.01 mole of ethyl formate, and 0.01 mole of sodium methoxide was heated for 10 h, after which the mixture was worked up as in the method in [7] to give IX in 18% yield.

D) A 0.01-mole sample of sulfonamide I was heated in 15 ml of DMF with 3 g of anhydrous oxalic acid for 1 h, after which the mixture was cooled, diluted with water, and worked up to give IX with mp 221-222° (from water) [8] in 58% yield. IR spectrum, ν, cm^{-1}: 3275 (NH), 1380, 1290 (SO_2, as), and 1160 (SO_2, s). UV spectrum, λ_{max}, nm (log ε): 264 (4.12). No melting-point depressions were observed for mixtures of the compounds obtained by the various methods.

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RESEARCH ON TWO-RING 1-AZA COMPOUNDS

XIII.* SYNTHESIS OF 3(5)-HYDROXYMETHYLPYRROLIZIDINES BY CATALYTIC HYDROGENATION OF 5-HYDROXYMETHYL-1,2-DIHYDROPYRROLIZINES. DETERMINATION OF THE CONFIGURATIONS OF THE REACTION PRODUCTS

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5-Hydroxymethyl-1,2-dihydropyrrolizines were catalytically hydrogenated to 3(5)-hydroxymethylpyrrolizidines, and the ratios of the isomers in the products of the reaction, which proceeds stereoselectively, were determined. The configuration of the diastereomers was established on the basis of the results of catalytic isomerization, a study of the chromatographic behavior of the isomers on a polar stationary phase, and a discussion of the isomeric composition of the hydrogenation products in the light of the general principles of the stereochemistry of catalytic hydrogenation. trans- and cis-3,8-H-3-Hydroxymethylpyrrolizidine and trans-3,8-H-3-methyl-trans-5,8-H-5-hydroxymethylpyrrolizidine were isolated from the mixtures of isomers. The existence of an intramolecular hydrogen bond in trans-3,8-H-3-hydroxymethyl- and trans-3,8-H-3-methyl-trans-5,8-H-5-hydroxymethylpyrrolizidine was shown by IR spectroscopy.

Up until now, very little study has been devoted to 3(5)-hydroxymethylpyrrolizidines. The simplest route to these compounds is catalytic hydrogenation of 5-hydroxymethyl-1,2-dihydropyrrolizidines [2, 3].

The hydrogenation of 5-hydroxymethyl-1,2-dihydropyrrolizine (I) and its 2- and 3-methyl-substituted derivatives (II, III) is examined in the present paper.

Hydroxymethylpyrrolizidines were obtained in 50-70% yields by hydrogenation of I-III on a 5% Rh/Al_2O_3 catalyst from Engelhard Industries, Baker Platinum Division, or one prepared by means of the method in [4, 5] at room temperature in methanol at 90-150°C (Raney nickel caused hydrogenolysis of the C−O bond, whereas a mixed Rh−Pt catalyst or 5% Rh/C from the above company were ineffective at 20-100°).

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*See [1] for communication XII.

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