SYNTHESIS OF 2H-1,2,4-BENZOTHIADIAZINE-3-CARBOXYLIC ACID 1,1-DIOXIDE DERIVATIVES FROM 2-SULFAMOYLOXANILIC ACID ESTERS*

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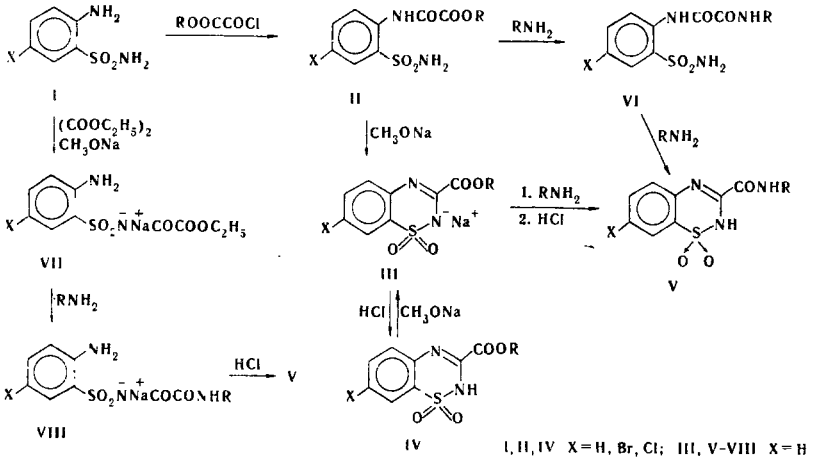
Esters and amides of 2H-1,2,4-benzothiadiazine-3-carboxylic acid 1,1-dioxide were synthesized from 2-sulfamoyloxanilic acid esters.

In a development of our research [2] we accomplished the synthesis of 2H-1,2,4-benzothiadiazine-3-carboxylic acid 1,1-dioxide derivatives from 2-sulfamoyloxanilic acid esters (II, Table 1). The latter were obtained by the action of ethoxalyl chloride on 2-sulfanilamide I in glacial acetic acid in the presence of triethylamine.

Under the influence of sodium methoxide, esters II undergo cyclization to give salts (III) of 2H-1,2,4-benzothiadiazine-3-carboxylic acid 1,1-dioxide esters, which were also obtained by the action of sodium methoxide on 2H-1,2,4-benzothiadiazine-3-carboxylic acid 1,1-dioxide esters (IV). Absorption bands of the stretching vibrations of CO, SO_2, and C–O–C groups are observed in the IR spectrum of salt III; the band of vibrations of the NH group is absent.

Esters IV (Table 2) were isolated by acidification of salts III. Their structure was confirmed by conversion of ester VIa to the known 2H-1,2,4-benzothiadiazine 1,1-dioxide [3] by brief heating with aqueous alkali.



2-Sulfamoyloxanilic acid amides (VI) are formed by treatment of esters II with amines at room temperature. These amides are converted to 2H-1,2,4-benzothiadiazine-3-carboxylic acid amide 1,1-dioxides (V, method B) on heating with amines in dimethylformamide (DMF) or in methanol in the presence of sodium methoxide. Salts III can also be used for the synthesis of amides V (method A, Table 3).

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TABLE 1. 2-Sulfamoyloxanilic Acid Esters (II)

Compound	R	X	mp, °C	Empirical formula	N, % found	N, % calc.	Yield, %
IIa	C_2H_5	H	183—184[2]	$C_{10}H_{12}N_2O_5S$	—	—	71
IIb	C_2H_5	Br	193—195	$C_{10}H_{11}BrN_2O_5S$	8,2	8,0	74
IIc	C_2H_5	Cl	191—192	$C_{10}H_{11}ClN_2O_5S$	9,1	9,1	69
IId	*iso*-C_3H_7	H	180—181	$C_{11}H_{14}N_2O_5S$	10,0	9,8	73

TABLE 2. 2H-1,2,4-Benzothiadiazine-3-carboxylic Acid 1,1-Dioxide Esters (IV)

Compound	R	X	mp, °C*	Empirical formula	N, % found	N, % calc.	Yield, %
IVa[2]	C_2H_5	H	255	$C_{10}H_{10}N_2O_4S$	—	—	83
IVb	C_2H_5	Br	246	$C_{10}H_9BrN_2O_4S$	8,2	8,4	81
IVc	C_2H_5	Cl	248	$C_{10}H_9ClN_2O_4S$	9,8	9,7	81
IVd	*iso*-C_3H_7	H	247	$C_{11}H_{12}N_2O_4S$	10,7	10,4	77

*With decomposition.

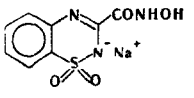
TABLE 3. Amides (V) of 2H-1,2,4-Benzothiadiazine-3-carboxylic Acid 1,1-Dioxide

Compound	R	mp, °C*	Empirical formula	N, % found	N, % calc.	Yield, % A	Yield, % B	Yield, % C
Va	H	342 (dec.) [2]	$C_8H_7N_3O_3S$	—	—	71	—	—
Vb	CH_3	334—336[2]	$C_9H_9N_3O_3S$	—	—	84	—	92
Vc	*iso*-C_4H_9	233—234	$C_{12}H_{15}N_3O_3S$	15,0	14,9	75	—	67
Vd	C_6H_{11}	262—263[2]	$C_{14}H_{18}N_3O_3S$	—	—	—	—	74
Ve	$C_6H_5CH_2$	243—245	$C_{15}H_{13}N_3O_3S$	13,5	13,3	77	77	88

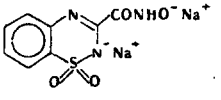
*Aqueous DMF was used as the crystallization solvent.

In contrast to ester II, ethyl 1-aminophenylsulfonyloxamate is not cyclized in the presence of sodium methoxide. However, acidification of the resulting salt VII* or of salt VIII, obtained by treatment of salt VII with amines, leads to ester IV [2] and amides V (method C), respectively. Amides V can be synthesized in one step by this method starting from sulfonamide I and diethyl oxalate without isolation of the intermediates.

The ionization constants were determined for 2H-1,2,4-benzothiadiazine-3-carbohydroxamic acid 1,1-dioxide (V, R = OH), and the mono-(IXa) and disubstituted (IXb) sodium salts were obtained.



IX a



IX b

Compounds IXa, b form precipitates with metal cations (Co^{2+}, Ni^{2+}, Cd^{2+}, Zn^{2+}, Pd^{2+}, Hg^{2+}, Mn^{2+}, Sn^{2+}, Al^{3+}, Bi^{3+}, and Sn^{4+}) and also give specific reactions for the CONHOH group with Fe^{3+} (red coloration) and Cu^{2+} (green precipitate). In contrast to IXa, IXb gives precipitates with Ba^{2+}, Sr^{2+}, and Th^{4+} cations.

EXPERIMENTAL

The IR spectra of the compounds were recorded with a UR-20 spectrometer. The ionization constants in 60% dioxane were determined with a pH-340 apparatus at 20°.

Ethyl 2-Sulfamoyl-4-bromooxanilate (IIb). A 0.2-mole sample of triethylamine and 0.1 mole of ethoxalyl chloride were added to a solution of 0.1 mole of 2-amino-5-bromobenzenesulfonamide (I) in 30 ml of glacial

*IR spectrum of salt VII, ν, cm^{-1}: 3480, 3390 (NH), 1750, 1700 (CO), 1375 (SO_2,as), 1245 (C–O–C, as), 1190 (C–O–C, s), 1140 (SO_2, s).

acetic acid, and the mixture was allowed to stand for 1 h. It was then diluted with 100 ml of water and acidified with HCl solution (1 : 1), and the resulting precipitate was removed by filtration and crystallized from aqueous ethanol. Compounds IIa, c, d were similarly obtained.

Sodium Salt (III) of Ethyl 2H-1,2,4-Benzothiadiazine-3-carboxylate 1,1-Dioxide. A) A suspension of 0.01 mole of ester IIa in 10 ml of methanol was added to sodium methoxide obtained from 0.01 g-atom of sodium in 10 ml of methanol. After ester IIa dissolved, the salt began to precipitate. It was removed by filtration and washed with methanol to give III in 65% yield.

B) A 0.01-mole sample of sodium methoxide in 10 ml of methanol was added to 0.01 mole of ester IVa in 10 ml of methanol, and the precipitated salt was removed by filtration and washed with methanol to give III in 73% yield. Found: N 9.8%. $C_{10}H_9N_2NaO_4S$. Calculated: N 9.5%. IR spectrum ν, cm^{-1}: 1740 (CO), 1350 (SO_2, as), 1240 (C–O–C, as), 1180 (C–O–C, s) 1150 (SO_2, s).

Ethyl 2H-1,2,4-Benzothiadiazine-3-carboxylate 1,1-Dioxide (IVa). A 0.01-mole sample of sodium methoxide in 10 ml of methanol and a small amount of phenolphthalein were added to a suspension of 0.01 mole of ester IIa in 10 ml of methanol. After a few minutes, the ester dissolved and the crimson coloration vanished. The solution was diluted with 20 ml of water and acidified with dilute HCl (1 : 1). The precipitate was removed by filtration. IR spectrum, ν, cm^{-1}: 3250 (NH), 1780 (CO), 1360 (SO_2, as), 1240 (C–O–C, as), 1190 (C–O–C, s), 1145 (SO_2, s). Esters IVb-d were similarly obtained. All of the compound were crystallized from aqueous DMF.

2-Sulfamoyloxanilic Acid Benzylamide (VIa). A 0.01-mole sample of benzylamine was added to a solution of 5 mmole of ester IIa in 7 ml of DMF, and the mixture was allowed to stand at room temperature for 10 h. Water (10 ml) was added, the mixture was acidified with dilute HCl (1 : 1), and the precipitate was removed by filtration to give VIa, with mp 165-166° (from aqueous DMF), in 71.6% yield. Found: N 12.9%. $C_{15}H_{15}N_3O_4S$. Calculated: N 12.6%.

2-Sulfamoyloxanilohydroxamic acid (VIb), with mp 180° (dec., from water), was similarly obtained in 74.5% yield. Found: N 16.4%. $C_8H_9N_3O_5S$. Calculated: N 16.2%.

2H-1,2,3-Benzothiadiazine-3-carboxylic Acid Benzylamide 1,1-Dioxide (Ve). A) A solution of 3 mmole of sodium methoxide in 5 ml of methanol and a few crystals of phenolphthalein were added to a suspension of 3 mmole of ester IIa in 5 ml of methanol. After ester IIa dissolved and the crimson coloration vanished, 3 mmole of benzylamine was added, and the mixture was allowed to stand for 12 h. It was then diluted with 20 ml of water and acidified to pH 2-3 with dilute HCl (1 : 1), and the precipitated Ve was removed by filtration. Compounds Va-c were similarly obtained.

B) A few drops of benzylamine (or a solution in methanol containing sodium methoxide and phenolphthalein) were added to a solution of 1 mmole of benzylamide VIa in 5 ml of DMF, and the mixture was heated for 1 h. It was then diluted with 20 ml of water and worked up as in the preceding experiment.

C) A 0.01-mole sample of sulfonamide I(X = H), a small amount of phenolphthalein, and 0.01 mole of diethyl oxalate were added to 0.01 mole of sodium methoxide in 10 ml of methanol, and the mixture was heated until the crimson coloration vanished, after which 0.01 mole of benzylamine was added, and the mixture was allowed to stand for 12 h. It was then acidified with dilute HCl (1 : 1) to isolate amide Ve. Compounds Vb-d were similarly obtained.

2H-1,2,4-Benzothiadiazine-3-carbohydroxamic Acid 1,1-Dioxide (V, R = OH). This compound, with mp 230° (dec., from aqueous DMF), was obtained in 78.8% yield by the action of hydroxylamine on ester IVa by the method in [2]. Found: N 17.5%. $C_8H_7N_3O_4S$. Calculated: N 17.4% pKa_1 (SO_2NH) 7.54 and pKa_2 (NHOH) 10.40.

Salt IXa was obtained by neutralization (with respect to phenolphthalein) of an aqueous alcohol solution of acid V (R = OH); salt IXb was obtained by mixing methanol solutions of acid V (R = OH) and sodium methoxide. Found: N 14.9%. $C_8H_5N_3Na_2O_4S$. Calculated: N 14.7%.

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3. Beilstein, 27, 570 (1937).