3-Oxo-1,2-benzoisothiazoline-2-acetic Acid 1,1-Dioxide Derivatives. II. Reaction of Amides with Alkoxides (1)

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Reaction of some 3-oxo-1,2-benzoisothiazoline-2-acetamide 1,1-dioxides (**1a-f**) with alkaline alkoxides was carried out under various conditions. Under mild conditions, **1a-f** with sodium methoxide gave *o*-(*N*-carboxamidomethylsulfamyl)benzoic acid methyl esters (**2a-f**, R = CH_3). Compounds **1a** or **2a** reacted with sodium alkoxides under drastic conditions affording only ester **5**. Under the same conditions, **1b-d** or **2b-d** gave 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxides (**3b-d**), while **1e-f** or **2e-f** afforded the acid **6** in variable amounts, together with the expected benzothiazines **3e-f**. Isolation of ethyl ether as another product in the reaction of **1e-f** with sodium ethoxide supports the suggestion that the formation of **6** involves the *O*-alkyl fission on the alkyl carbon of the esters **2e-f**. An explanation of these results may be related to the acidic character of the amide hydrogen in compounds **2e-f**.

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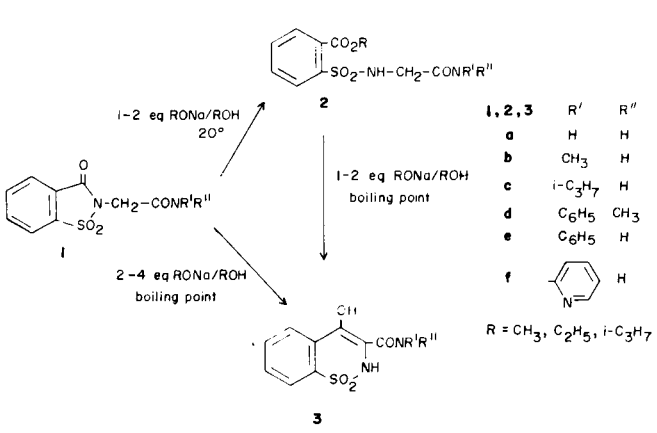
Certain 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxides (**3**) (most of them heterocyclic) with antiinflammatory activity were prepared by aminolysis of the corresponding esters (2-5) or by direct rearrangement of 3-oxo-1,2-benzoisothiazoline-2-acetamide 1,1-dioxides (saccharin-acetamides). In our knowledge, the latter reaction was described only in one patent using sodium methoxide in an inert solvent such as dimethylsulfoxide or dimethylformamide (**6**). Other synthetic methods were also reported (2,3,7,8).

In continuation of our study on saccharin-2-acetic acid derivatives (1), we wish to report the reaction of some 3-oxo-1,2-benzoisothiazoline-2-acetamide 1,1-dioxides (**1**) with sodium alkoxides in the corresponding alcohol under different conditions.

As previously stated with saccharin-2-acetic acid esters (1), compounds **1a-f**, reacted with 1-2 equivalents of sodium methoxide in absolute methanol under mild conditions affording *o*-(*N*-carboxamidomethylsulfamyl)benzoic acid methyl esters (**2a-f**, R = CH_3) (Scheme I). The structure assignments of compounds **2a-f** were based on microanalysis and spectroscopic properties (Table I).

SCHEME I



By treatment of compounds **1b-d** or **2b-d** (R = CH_3) with 2-4 equivalents of alkoxide in drastic conditions only 1,2-benzothiazines **3b-d** were obtained in variable amounts according to the alkoxide (Table II). In all cases the yields increase in the order methoxide < ethoxide < isopropoxide. Compounds **1a**, **e** and **f** show a different behaviour under the same conditions.

When **1a** is treated with sodium methoxide in methanol under drastic conditions, ammonia is rapidly evolved. After 10 minutes of reaction, 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylic acid methyl ester 1,1-dioxide (**5a**) was the sole product isolated (15%). The same result was obtained starting from the open sulfonamide **2a**. With sodium ethoxide in ethanol **1a** gave compound **5b** in 2-5% yield, whereas with sodium isopropoxide only traces of **5c** were detected. In all cases none of the expected 4-hydroxy-2*H*-1,2-benzothiazine-3-carboximide 1,1-dioxide **3a** was detected.

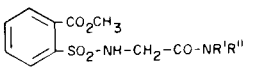
Reaction of **1a** with sodium methoxide was studied at different times. The first product isolated was **2a** (R = CH_3) which partially undergoes alcoholysis affording the diester **4** (R = CH_3). Longer reaction times resulted in the disappearance of **4** which was transformed in the benzothiazine **5a** (Scheme II) (9). The remainder of **2a** was transformed in water soluble products (10).

Some cases of alcoholysis of amides have been reported (11-14). It has been established that it decreases on increasing the basicity of the leaving group. According to this, alcoholysis of **2a** should not proceed. However, displacement of equilibrium is favored because ammonia is evolved (Scheme II) and high temperatures of reaction were used (12). The greater size of isopropoxide compared with that of methoxide would explain the lower alcoholysis.

In attempts to synthesize **3e-f**, the same procedure for the preparation of **3b-d** was tested. Surprisingly, **1e** was

Table I

o-(*N*-Carboxamidomethylsulfamyl)benzoic Acid Methyl Esters (**2a-f**)

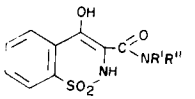


Compound No.	Yield (a) %	Mp (°C)	Recrystallization Solvent		Analyses %C	%H	%N	%S	p*K*a (b)	IR ν, cm^{-1}	Solvent	δ, ppm	^{1}H NMR Multiplicity	Assignment
											DMOS-d_6	7.7-8.2	(M)	(aromatics)
												7.46	(S) (c)	(NH)
2a	55	160	methanol	Calcd.	44.12	4.41	10.29	11.76		3400 (NH)		7.30	(bs) (c)	(NH_2)
				Found	44.05	4.60	10.18	11.52		3250 (NH)		3.96	(S)	(CH_3)
										1715 (CO)		3.62	(S)	(CH_2)
										1670 (CO)				
										1380 (SO_2)	chloroform	7.7-8.3	(M)	(aromatics)
										1160 (SO_2)		6.7-7.2	(bs) (c)	(2 NH)
2b	68	oil		Calcd.	46.15	4.90	9.79	11.19	18.0	3370 (NH) (d)		4.20	(S)	(CO_2CH_3)
				Found	46.30	4.98	9.62	11.32		3300 (NH)		3.8	(D) (e)	(CH_2)
										1720 (CO)		3.00	(D) (e)	($\rangle NCH_3$)
										1660 (CO)	chloroform	7.7-8.4	(M)	(aromatics)
										1160 (SO_2)		6.5-7.1	(bs) (c)	(2 NH)
2c	72	106	benzene	Calcd.	49.68	5.73	8.92	10.19	18.1	3300 (NH)		4.16	(S)	(CO_2CH_3)
				Found	49.95	5.90	9.10	10.30		1725 (CO)		*ca.* 4.16	(M) (f)	(CH)
										1650 (CO)		3.76	(D) (e)	(CH_2)
										1370 (SO_2)		1.30	(D)	($\rangle C(CH_3)_2$)
										1165 (SO_2)	chloroform	7.1-8.2	(M)	(aromatics)
												7.00	(T) (c)	(SO_2NH)
2d	59	135	ethanol	Calcd.	56.35	4.97	7.73	8.84		3250 (NH)		4.12	(S)	(CO_2CH_3)
				Found	56.17	5.10	7.87	8.70		1720 (CO)		3.75	(D) (e)	(CH_2)
										1660 (CO)		3.31	(S)	($\rangle NCH_3$)
										1375 (SO_2)	chloroform	8.55	(bs) (c)	(NH)
										1170 (SO_2)		7.3-8.4	(M)	(aromatics)
2e	70	105	methanol	Calcd.	55.17	4.60	8.04	9.20	17.9	3400 (NH)		7.03	(bs) (c)	(NH)
				Found	55.14	4.69	7.99	9.40	19.0	3330 (NH)		4.15	(S)	(CH_3)
										1705 (CO)		3.93	(D) (e)	(CH_2)
										1680 (CO)				
										1340 (SO_2)	DMSO-d_6	8.33	(D)	-C=N-CH=CH_2
										1160 (SO_2)		7.8-8.1	(M)	(aromatics
2f	65	150	methanol	Calcd.	51.58	4.30	12.03	9.17	17.5	3270 (NH)				+ NH)
				Found	51.72	4.50	11.92	9.31	18.9	1740 (CO)		*ca.* 3.90	(S)	(CH_3 + CH_3)
										1680 (CO)				
										1350 (SO_2)				
										1170 (SO_2)				

(a) Given yields were obtained with 2 equivalents of sodium alkoxide. With 1-1.5 equivalents, lower yields were observed. (b) p*K*a were determined in isopropanol as pointed out by Hine and Hine (22). (c) Exchangeable. (d) Ir was carried out in Nujol. (e) Upon deuteration the doublet collapsed into a singlet. (f) Overlap with CH_3.

Table II

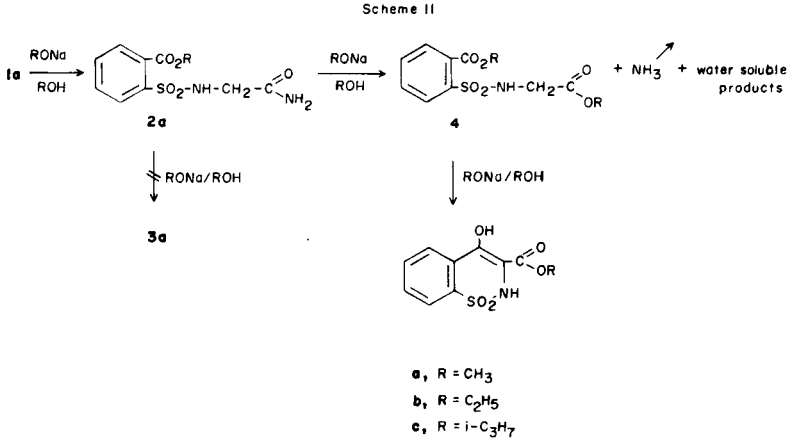
4-Hydroxy-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxides (**3b-f**)



Compound No.	Starting Materials	[RONa]	Time (minutes)	Yield (a) %	Mp (°C)	Recrystallization Solvent	Previous Reference		Analyses %C	%H	%N	%S	IR ν, cm^{-1}	^{1}H NMR Solvent	δ, ppm	Multiplicity	Asisgnment
3b	**1b** + CH_3ONa	3.1 *M*	5	3 (b)	235	methanol		Calcd.	47.24	3.94	11.01	12.60	3400 (NH)	DMSO-d_6	14.30	(bs) (c)	(OH)
	1b + C_2H_5ONa	3.1 *M*	5	39				Found	47.15	4.01	11.21	12.38	1620 (CO)		9.33	(bs) (c)	(NH)
	1b + *i*-C_3H_7ONa	2.5 *M*	5	50									1320 (SO_2)		8.45	(bs) (c)	(NH)
													1180 (SO_2)		7.7-8.1	(M)	(aromatics)
															2.82	(D) (d)	(CH_3)
3c	**1c** + CH_3ONa	3.1 *M*	5	8	197	benzene		Calcd.	51.06	4.96	9.93	11.35	3340 (NH)	chloroform	13.66	(bs) (c)	(OH)
	1c + C_2H_5ONa	3.1 *M*	5	28				Found	51.30	5.06	10.15	11.20	1624 (CO)		7.4-8.0	(M)	(aromatics)
	1c + *i*-C_3H_7ONa	2.5 *M*	5	85									(1330 (SO_2)		6.42	(bs) (c)	(NH)
													1180 (SO_2)		6.00	(bs) (c)	(NH)
															4.00	(M)	(CH)
															1.06	(D)	(CH_3)
3d	**1d** + CH_3ONa	3.1 *M*	10	25	148	methanol	(6)						3220 (NH)	DMSO-d_6	12.80	(S) (c)	(OH)
	1d + C_2H_5ONa	3.1 *M*	10	38									1605 (CO)		9.15	(bs) (c)	(NH)
	1d + *i*-C_3H_7ONa	2.5 *M*	10	73									1340 (SO_2)		7.7-8.0	(M)	(aromatics)
													1180 (SO_2)		7.44	(S)	(C_6H_5)
															3.43	(S)	(CH_3)
3e	**1e** + CH_3ONa	3.1 *M*	30	10 (e)	265 (f)	methanol	(2, 3, 6)						3350 (NH)	DMSO-d_6	10.20	(S) (c)	(OH)
	1e + C_2H_5ONa	3.1 *M*	30	40 (g)									1620 (CO)		7.1-8.2	(M)	(aromatics
	1e + *i*-C_3H_7ONa	2 *M*	30	60 (h)									1320 (SO_2)				+ NH)
													1180 (SO_2)				
3f	**1f** + CH_3ONa	3.1 *M*	40	0									3100 (NH)	DMSO-d_6	8.45	(D)	=N-CH-
	1f + C_2H_5ONa	3.1 *M*	40	5 (i)	215 (24)	acetic acid	(6)						1650 (CO)		7.2-8.1	(M)	(aromatics
	1f + *i*-C_3H_7ONa	2.5 *M*	40	25 (j)									1335 (SO_2)				+ NH)
													1180 (SO_2)				

(a) Given yields were obtained with 4 equivalents of RONa. (b) Traces of **5a** were detected. (c) Exchangeable. (d) Upon deuteration collapsed into a singlet. (e) 18% of **6a** was also obtained. (f) Lit 261-268° (3) and 270° (6). (g) 10% of **6a** was also obtained. (h) 7% of **6a** was also obtained. (i) 38% of **6b** was also obtained. (j) 40% of **6b** was also obtained.

Scheme II



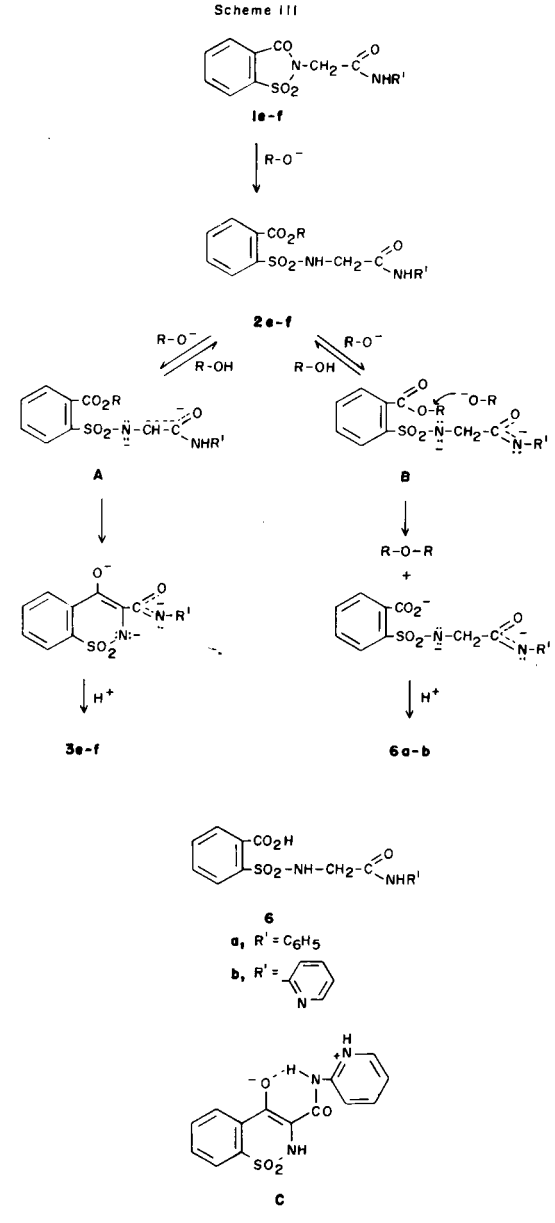
a, R = CH_3
b, R = C_2H_5
c, R = i-C_3H_7

found to react with sodium methoxide in absolute methanol affording 18% of *o*-(*N*-phenylcarboxamidomethylsulfamyl)benzoic acid (**6a**) and only 10% of the expected **3e**. In the same conditions **1e** with sodium ethoxide gave 40% of **3e** and 10% of **6a**, whereas with sodium isopropoxide 60% of **3e** and 6-8% of **6a** were obtained. Compound **1f** behaves similarly; sodium isopropoxide gave 25% of **3f** and 40% of *o*-[*N*-(2-pyridyl)carboxamidomethylsulfamyl]benzoic acid (**6b**), whereas with sodium methoxide only **6b** was obtained.

It was demonstrated that the open sulfonamides **2e-f** are intermediates in the formation of **6a-b** and **3e-f**. The formation of **6** probably involves the *O*-alkyl fission in compounds **2e-f**, and is simply a special case of SN_2 reaction on the alkyl carbon of an ester (15-18). This is in accord with the attainment of ethyl ether as another product of the reaction of **1e-f** with sodium ethoxide (Scheme III). An explanation for these experimental results is found if it is considered that, as in benzoisothiazoline-2-acetic acid esters (1), rearrangement takes place affording the open sulfonamides **2e-f** followed by a Dieckmann cyclization. The acidic character of the amide hydrogen in compounds **2e-f** (19) would result in a less probable formation of the carbanion A necessary for the cyclization. Product distribution therefore, is presumably a consequence of the position of the equilibrium between the anions A and B, and the relative rates to undergo transformation in **3** or **6** respectively (Scheme III). Higher basic alkoxides, such as sodium isopropoxide allow more efficient attack on the methylene hydrogen than sodium methoxide and hence increase the yield of **3e-f**.

Nmr and ir spectra, and the positive ferric chloride test for **3b-e** support the enolic form of these benzothiazines. Instead, no enol OH was observed in compound **3f**. The keto form was also discarded as indicated by ir spectrum (no C=O absorption over 1660 cm^{-1}) and nmr spectrum (no >CH-CO-) (20). These results would be consistent with

Scheme III



a hydrogen bond-stabilized dipolar ion C which is similar to that suggested by Lombardino to explain the enhanced acidity of some benzothiazine-3-carboxamides (2,21).

EXPERIMENTAL

Melting points were taken on a Büchi capillary apparatus and are uncorrected. Ir spectra were recorded on a Perkin Elmer 700 A spectrometer using potassium bromide pellets unless stated otherwise. The ^{1}H nmr spectra were obtained on a Perkin Elmer R 12 (60 MHz) instrument with tetramethylsilane as internal reference. Chemical shifts are reported in parts per million (δ) and signals are quoted as: S (singlet), D (doublet), T (triplet), M (multiplet) and bs (broad signal). The presence of exchangeable protons was confirmed by use of deuterium oxide. Analytical tlc was carried out on 10 × 20 cm glass plates coated with Merck Silica Gel $HF_{254+366}$ using benzene-methanol (9:1) as solvent. Preparative thin layer separations (plc) were performed on Silica Gel HF_{254} on 40 × 20 × 0.15 cm layers. The gc analysis were performed on a 2 m × 1/8 inch column packed with 3% SE-30 on Chromosorb P. Reagents, solvents and starting materials were purchased from standard sources and purified according to literature procedures.

3-Oxo-1,2-benzoisothiazoline-2-acetamide 1,1-Dioxides (**1a-e**). General Procedure.

A mixture of 0.12 mole of benzoisothiazolin-3-one 1,1-dioxide sodium salt, 0.08 mole of the corresponding 2-chloroacetamide and 15 ml of *N,N*-dimethylformamide was heated at 120° for 6 hours. The reaction mixture was poured into ice-water and the resulting solid was filtered, washed with water, dried and recrystallized from ethanol.

Compounds **1d** and **1e** were described by Zinnes, *et al.*, (6).

Compound **1a**.

This compound was obtained in 65% yield, had mp 210°; ir: 3405 (N-H), 3200 (N-H), 1742 (C=O), 1690 (C=O), 1340 (SO_2) and 1188 cm^{-1} (SO_2).

Anal. Calcd. for $C_9H_8N_2O_4S$: C, 45.00; H, 3.33; N, 11.67; S, 13.33. Found: C, 44.95; H, 3.50; N, 11.82; S, 13.15.

Compound **1b**.

This compound was obtained in 62% yield, had mp 208°; ir: 3270 (N-H), 1740 (C=O), 1650 (C=O), 1320 (SO_2) and 1180 cm^{-1} (SO_2).

Anal. Calcd. for $C_{10}H_{10}N_2O_4S$: C, 47.24; H, 3.94; N, 11.02; S, 12.60. Found: C, 47.20; H, 4.07; N, 11.10; S, 12.38.

Compound **1c**.

This compound was obtained in 85% yield, had mp 167°; ir: 3300 (N-H), 2990 (C-H), 1740 (C=O), 1660 (C=O), 1340 (SO_2) and 1195 cm^{-1} (SO_2).

Anal. Calcd. for $C_{12}H_{14}N_2O_4S$: C, 51.06; H, 4.96; N, 9.93; S, 11.35. Found: C, 51.15; H, 5.01; N, 9.82; S, 11.20.

3-Oxo-1,2-benzoisothiazoline-2-[*N*-(2-pyridyl)]acetamide 1,1-Dioxide (**1f**).

To a suspension of saccharin-2-acetic acid (15 g) in chloroform (90 ml) and *N,N*-dimethylformamide (1.2 ml) heated in a water bath (60°), thionyl chloride (9 ml) in chloroform (30 ml) was added. After 12 hours at room temperature, the solvent was evaporated and the residue was treated with chloroform (20 ml) and concentrated under reduced pressure. The crude product was suspended in chloroform (100 ml) and added with stirring to a solution of 2-aminopyridine (11.28 g) in chloroform (50 ml). After 1 hour of stirring the reaction mixture was allowed to stand for 12 hours and heated in a water bath for 1 hour. After removal of solvent *in vacuo*, the oily residue was washed with water and the resulting gummy solid was taken up in methanol. Scratching gave a solid which was recrystallized from methanol affording **1f** (65% yield), mp 179-181°. Structure was confirmed by comparison with an authentic sample (6), ir and ^{1}H nmr spectra.

o-(*N*-Carboxamidomethylsulfamyl)benzoic Acid Methyl Esters (**2a-f**, R = CH_3). General Procedure.

A solution of sodium methoxide was prepared from 0.46 g of sodium (0.02 mole) in 12 ml of absolute methanol. 3-Oxo-1,2-benzoisothiazoline-2-acetamide 1,1-dioxide (0.01 mole) (**1a-f**) was added at room temperature, all at once as the powder. After 3 minutes the reaction was quenched by pouring into concentrated hydrochloric acid-ice, except compound **2f**, which was poured in acetic acid. Compounds **2a,c-f** were collected, washed with water and recrystallized. Compound **2b** is an oil which was extracted three times with chloroform. After washing with water, the organic solution was dried, concentrated *in vacuo* and purified by plc (benzene-methanol 9:1). Yields, melting points, recrystallization solvents, elemental analysis and spectroscopic data of the compounds are given in Table I.

4-Hydroxy-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxides (**3b-d**).

A. From 3-Oxo-1,2-benzoisothiazoline-2-acetamide 1,1-Dioxides (**1b-d**).

A solution of sodium alkoxide was prepared from 0.92 g of sodium (0.04 mole) in the corresponding absolute alcohol. The solution was refluxed in an oil bath (140°) and 0.01 mole of 3-oxo-1,2-benzoisothiazoline-2-acetamide 1,1-dioxides (**1b-d**) was added all at once as the powder. When the reaction was completed, the orange slurry was poured into ice-concentrated hydrochloric acid. The solid was filtered off, washed with water and recrystallized affording compounds **3b-d**. Details of reaction (time, alkoxide concentration), melting points, recrystallization solvents, elemental analysis and spectroscopic data of the compounds are given in Table II.

B. From *o*-(*N*-Carboxamidomethylsulfamyl)benzoic Acid Methyl Esters (**2b-d**, R = CH_3).

The reaction was carried out in the same manner as above, but using 0.46 g of sodium (0.02 mole) in the appropriate volume of the alcohol.

Attempted Synthesis of 4-Hydroxy-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxide (**3a**).

When reaction of **1a** with sodium methoxide was carried out under the same drastic conditions as **1b-d**, ammonia is evolved. After 10 minutes, the reaction was quenched by pouring into concentrated hydrochloric acid-ice. The white precipitate was filtered off, washed with water and dried to give 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylic acid methyl ester 1,1-dioxide (**5a**) (15% yield). Structure was confirmed by elemental analysis, spectroscopic properties and by comparison with an authentic sample (1), mp and mixed mp 171°.

Following the reaction at different times by tlc, after 1 minute only **2a** (R = CH_3) was observed. After 2 minutes a mixture of **2a** and *o*-(*N*-carboxymethylsulfamyl)benzoic acid dimethyl ester (**4**, R = CH_3) (1) was obtained. After 4 minutes **4** as the major product and traces of **5a** were observed. By carrying out the reaction for 10 minutes, only **5a** was isolated. No traces of **3a** (23) were detected.

Compound **2a** reacted with 2 equivalents of sodium methoxide under the same conditions as above affording only **5a** (12% yield).

Reaction of **1a** with sodium ethoxide under drastic conditions afforded only **5b** (1) (2-5% yield), whereas with sodium isopropoxide only traces of **5c** (1) were obtained.

Reaction of **1e** and **2e** with Sodium Alkoxides Under Drastic Conditions.

The reaction was carried out in the same manner as for compounds **1b-d** and **2b-d**. The solid was triturated with saturated sodium bicarbonate solution and filtered off affording **3e** (Table II). The alkaline solution was acidified with hydrochloric acid and the precipitate was filtered off, washed with water and dried to give *o*-(*N*-phenylcarboxamidomethylsulfamyl)benzoic acid (**6a**) (18%, 10% and 7% yield from reaction of **1e** with sodium methoxide, ethoxide or isopropoxide, respectively), mp 175° (methanol) ir: 3350 (N-H), 3270 (N-H), 1710 (C=O), 1666 (C=O), 1342 (SO_2) and 1170 cm^{-1} (SO_2); ^{1}H nmr (DMSO-d_6): δ 9.87 (S, 1, exchangeable, CO_2H), 6.83-8.08 (M, 11, aromatics and NH) and 3.76 (S, 2, CH_2).

Anal. Calcd. for $C_{15}H_{14}N_2O_5S$: C, 53.89; H, 4.19; N, 8.38; S, 9.58. Found: C, 53.73; H, 4.37; N, 8.49; S, 9.83.

Reaction of **1e** with sodium methoxide was studied at different times by tlc. Reaction for 1 minute afforded only **2e** (R = CH_3) in good yields. After 3 minutes low yields of **6a** and considerable amounts of **2e** were obtained. By carrying out the reaction for 12 minutes, traces of **3e**, considerable amounts of **6a** and lower yields of **2e** appear. After 30 minutes the reaction was completed (yield, 18% of **6a** and 10% of **3e**).

Isolation of ethyl ether was carried out after reaction of **1e** with sodium ethoxide was completed. The reflux condenser was replaced by a fractionating column connected to a condenser for downard distillation. The oil bath was heated until distillation began. A liquid (0.5 ml) was collected which was shown by gas chromatography to be a mixture of ethanol and ethyl ether (4:1).

Reaction of **1f** and **2f** with Sodium Alkoxides under Drastic Conditions.

A solution of sodium isopropoxide was prepared from 0.92 g of sodium (0.04 mole) in absolute 2-propanol. The solution was heated at 140° (oil bath) and 0.01 mole of **1f** was added all at once as the powder. After 40 minutes the reaction was quenched by pouring into acetic acid-ice. The solid was collected, washed with water and dried (yield, 2.5 g). In order to purify the crude product, an aliquot (50 mg) was boiled with 2-propanol for 10 minutes. The hot suspension was filtered affording 43 mg of a solid which showed two spots by tlc. Separation of the two products was accomplished by plc using benzene-methanol (9:1) as solvent. Thus, two main bands were separated and eluted with dioxane. The slower moving band afforded *o*-[*N*-(2-pyridyl)carboxamidomethylsulfamyl]benzoic acid **6b** (27 mg); mp 215° (acetic acid); ir: 3230 (N-H), 1700 (C=O), 1350 (SO_2) and 1170 cm^{-1} (SO_2); ^1H nmr (DMSO-d_6): δ 10.30 (bs, 1, exchangeable, CO_2H), 8.25 (D, 1, aromatic -N=C(-)-H), 6.82-8.05 (M, 10, aromatics and NH) and 3.83 (S, 1, CH_2).

Anal. Calcd. for $C_{14}H_{13}N_3O_5S$: C, 50.15; H, 3.88; N, 12.54; S, 9.55. Found: C, 50.28; H, 4.01; N, 12.60; S, 9.72.

The second band afforded **3f** (16 mg) (Table II) (24).

Reaction of **1f** with sodium ethoxide under the same drastic conditions afforded a mixture of **6b** (38% yield) and **3f** (5% yield). Ethyl ether as another product of this reaction was isolated in the same manner as in the reaction of **1e** with sodium ethoxide.

Reaction of **1f** with sodium methoxide under the same conditions afforded only **6b**.

Similar results were obtained starting from **2f**.

4-Hydroxy-2-methyl-*N*-(2-pyridyl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxide (**7**).

To a solution of **3f** (0.250 g) in a mixture of water (1 ml), methanol (2 ml) and 0.94*N* sodium hydroxide (0.86 ml) was added dimethyl sulfate (0.085 ml). The reaction mixture was stirred at room temperature while maintaining *p*H by addition of some drops of sodium hydroxide. When *p*H remained alkaline the mixture was allowed to stand for 10 minutes and filtered off. The solution was acidified with acetic acid and diluted with water. The resulting precipitate was collected, dried and recrystallized from methanol affording **7** (210 mg). Structure was confirmed by comparison with an authentic sample (21), mp and mixed mp 200°.

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(9) These results are in agreement with those observed in rearrangement of saccharin-acetic esters in which transesterifications also took place in the open sulfonamides (1).

(10) No explanation was found about the failure of **2a** to cyclize.

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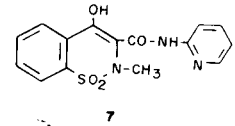
(19) In compounds **2e-f**, two acidic hydrogens (CH_2 and CO-NH) were detected at pK_a range between 17 and 19, whereas in compounds **2b-c** only one acidic hydrogen (p$K_a \cong$ 18) was detected (Table I).

(20) The 2-methyl derivative of **3f** (**7**) shows the same spectroscopic properties.



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(24) The compound has lower mp than that described in literature. Structure was demonstrated by elemental analysis, spectroscopic properties and by transformation in the 2-methyl derivative **7**.