Alkoxide-Induced Reactions of *N*-Substituted Saccharins. Synthesis of 1,2-Benzothiazocine 1,1-Dioxide and 2,3-Dihydropyrrolo[1,2-*b*]-[1,2]benzisothiazole 5,5-Dioxide Derivatives

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Received August 15, 1994

The reactions of saccharin derivatives **1** with sodium alkoxides were studied. Under mild conditions, compounds **1a-f** gave the corresponding open sulfonamides **5a-f**. Under drastic conditions, β-(saccharin-2)propionic acid derivatives **1a,b** reacted with sodium ethoxide affording saccharin and β-ethoxypropionic acid derivatives **4a,b**. γ-(Saccharin-2)butyric acid derivatives **1c,d** and γ-(saccharin-2)-butyrophenone **1f** reacted with sodium *t*-butoxide in dimethyl sulfoxide affording 5-substituted 6-hydroxy-3,4-dihydro-2*H*-1,2-benzothiazocine 1,1-dioxides **9**. From mother liquors, 1-substituted 2,3-dihydro-pyrrolo[1,2-*b*][1,2]benzisothiazole 5,5-dioxides **10** were isolated several hours later, though not detected immediately after completing the reaction. When the reactions were carried out in *t*-butyl alcohol, the yields of **9** diminished and those of **10** increased with product ratio inversion. Different experimental observations on the possible pathway generating **9** and **10** are discussed.

J. Heterocyclic Chem., **32**, 145 (1995).

Introduction.

The alkoxide-induced rearrangement of *N*-substituted 1,2-benzisothiazol-3-one 1,1-dioxides (*N*-substituted saccharins) is the method of choice for the preparation of 3-substituted 4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxides [1-5]. It has been amply demonstrated that such rearrangement takes place by initial ethanolysis of the amide affording open sulfonamides, followed by a Dieckmann cyclization [1,4,5] (Scheme I).

Here we present the results achieved on attempting to apply this reaction to prepare the seven and eight-membered benzothiazine homologues, that is 1,2-benzothiazepine and 1,2-benzothiazocine 1,1-dioxide derivatives **2** and **9**, starting from the corresponding *N*-substituted saccharins **1** (Table I). For this purpose, a series of derivatives of β-(saccharin-2)propionic acid **1a,b** and γ-(saccharin-2)butyric acid **1c-e**, as well as γ-(saccharin-2)butyrophenone (**1f**) were treated with alkoxides under different conditions.

Scheme I

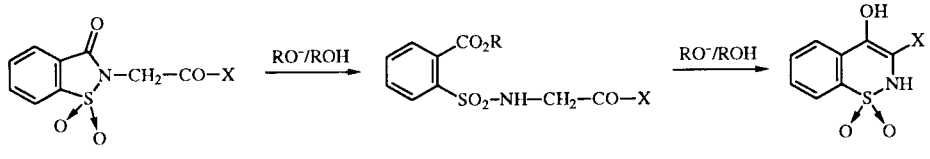
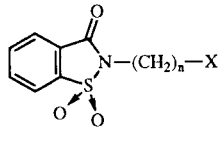


Table I

N-Substituted Saccharins



Compound	n	X
1a	2	CO_2Et
1b	2	CN
1c	3	CO_2CH_3
1d	3	$CO_2CH(CH_3)_2$
1e	3	CN
1f	3	$CO\text{-}C_6H_5$

Results and Discussion.

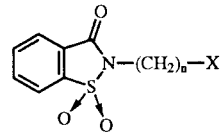
Compounds **1** were obtained in good yields from the saccharin sodium salt and the corresponding halogen derivative. Analytical and spectroscopic data are shown in Table II.

The reaction of compounds **1a,b** with hot sodium ethoxide followed an unexpected course: instead of providing the 1,2-benzothiazepine **2** after acid quenching of the reaction, saccharin (**3**) was obtained as the single product. From the mother liquors, ethyl β-ethoxypropionate (**4a**) and β-ethoxypropionitrile (**4b**) were isolated respectively (Scheme II). Employing sodium *t*-butoxide whether in *t*-butyl alcohol or in dimethyl sulfoxide (DMSO), C-N cleavage was again observed with the formation of saccharin in practically quantitative yields.

Although the appearance of products **3** and **4** might be interpreted as direct nucleophilic substitution, this explanation seems highly improbable, since no similar cases in α-(saccharin-2)acetic acid derivatives or in related com-

Table II

N-Substituted Saccharins **1a-f**



Compound No.	Mp (°C)	Recrystallization Solvent	Formula	Analyses Calcd./Found %C	%H	%N	%S	IR ν (cm^{-1})	δ (ppm)	^{1}H-NMR Multiplicity	Assignment
1a	95	methanol	$C_{12}H_{13}NO_5S$	50.88	4.59	4.95	11.31	2950 (CH)	8.20-7.70	m	aromatics
				51.00	4.48	5.05	11.50	1740 (CO)	4.18	c	OCH_2
								1725 (CO)	3.80	t	NCH_2
								1330 (SO_2)	2.40	t	CH_2-CO
								1190 (SO_2)	1.25	t	CH_3
1b	144	methanol	$C_{10}H_8N_2O_3S$	50.85	3.39	11.86	13.56	2920 (CH)	8.20-7.60	m	aromatics
				50.98	3.55	11.70	13.72	2250 (CN)	3.10	t	CH_2-N
								1740 (CO)	2.45	t	CH_2-CN
								1360 (SO_2)			
								1190 (SO_2)			
1c	85	ethanol	$C_{12}H_{13}NO_5S$	50.88	4.59	4.95	11.31	2900 (CH)	8.10-7.80	m	aromatics
				50.68	4.73	5.09	11.50	1730 (CO)	3.80	t	N-CH_2
								1720 (CO)	3.60	s	CH_3
								1320 (SO_2)	2.60-2.00	m	CH_2-CH_2-CO
								1180 (SO_2)			
1d	47	ethanol	$C_{14}H_{17}NO_5S$	54.02	5.47	4.50	10.29	2890 (CH)	8.30-7.90	m	aromatics
				54.25	5.63	4.36	10.48	1750 (CO)	5.10	m	CH
								1730 (CO)	3.90	t	N-CH_2
								1325 (SO_2)	2.6-2.1	m	CH_2-CH_2-CO
								1190 (SO_2)	1.30	d	CH_3
1e	103	ethanol	$C_{11}H_{10}N_2O_3S$	52.80	4.00	11.20	12.80	2900 (CH)	8.10-7.70	m	aromatics
				52.95	4.20	11.01	12.41	2300 (CN)	3.85	t	N-CH_2
								1750 (CO)	2.70-2.20	m	CH_2-CH_2-CN
								1350 (SO_2)			
								1200 (SO_2)			
1f	119	ethanol-water	$C_{17}H_{15}NO_4S$	62.00	4.56	4.25	9.73	2900 (CH)	8.10-7.70	m	C_6H_4 and C_6H_5 (2 *ortho* H)
				62.18	4.75	4.03	9.57	1720 (CO)			
								1700 (CO)	7.50-7.20	m	C_6H_5 (*para* and *meta* H)
								1330 (SO_2)			
								1195 (SO_2)	3.80	t	N-CH_2
									2.90	t	CH_2-CO
									2.20	m	CH_2-CH_2-CH_2

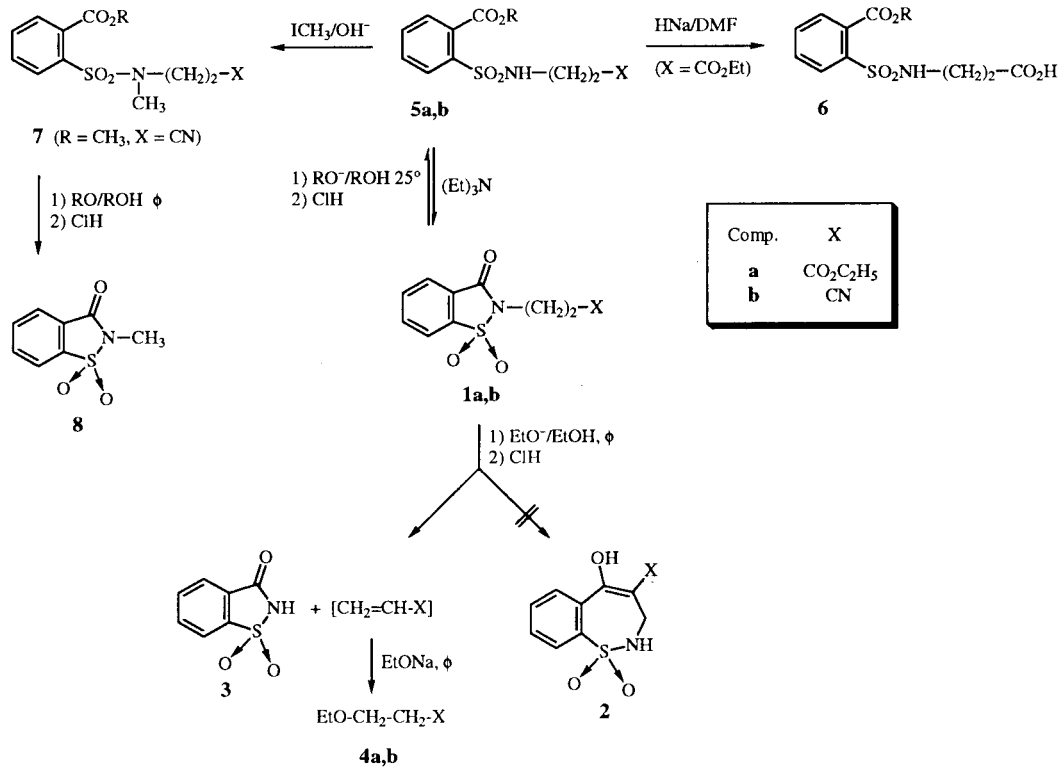
pounds have been reported [1-5]. In all likelihood the reaction proceeds *via* β-elimination followed by alkoxide addition to the α,β-unsaturated acid derivative obtained [6] (Scheme II).

In a further effort to obtain benzothiazepines **2**, ring closure of the open sulfonamide **5a** (R = C_2H_5) (Table III), readily prepared by reaction of **1a** with sodium ethoxide at room temperature, was attempted (Scheme II). With hot alkoxides, saccharin was again obtained, most likely through **5** ⇌ **1** equilibrium in alkoxide/alcohol medium [9]. With triethylamine, the saccharin derivative **1a** was regenerated, whereas with sodium hydride in dimethylformamide, among other unidentified products, *o*-[*N*-(2-carboxyethyl)sulfamyl]benzoic acid (**6**) was obtained [10]. In order to avoid saccharin ring regeneration, compound **5b** (R = CH_3) was transformed into the corresponding *N*-methyl derivative **7** and its cyclization attempted with alkoxides under drastic conditions. Results again proved unsuccessful as only moderate amounts of *N*-methylsaccharin (**8**) were isolated.

The reaction of saccharin derivatives **1c-f** with alkoxides [13] (Scheme III) is discussed below and summarized in Tables III and IV. At room temperature the reaction of compounds **1c,e,f** with sodium methoxide and **1d** with sodium isopropoxide, led to the expected open sulfonamides **5** (Table III) in good yields [15]. With sodium *t*-butoxide in *t*-butyl alcohol at 50° (the required temperature due to alkoxide insolubility) compounds **1** produced a complex mixture of products from which only small amounts of **5** (R = *t*-C_4H_9) were isolated.

The reactions of compounds **1c,d,f** with hot alkoxides (Table IV) followed a common behavior (Scheme III). Treatment with sodium *t*-butoxide in DMSO afforded immediately after acid quenching the expected 6-hydroxy-3,4-dihydro-2*H*-benzothiazocine 1,1-dioxides **9** (Table V). From mother liquors, 1-substituted 2,3-dihydropyrrolo[1,2-*b*][1,2]benzisothiazole 5,5-dioxides **10c,d,f** were obtained several hours later. When the reaction was carried out in *t*-butyl alcohol, the yields of **9** diminished and those of **10** increased, with product ratio

Scheme II



Scheme III

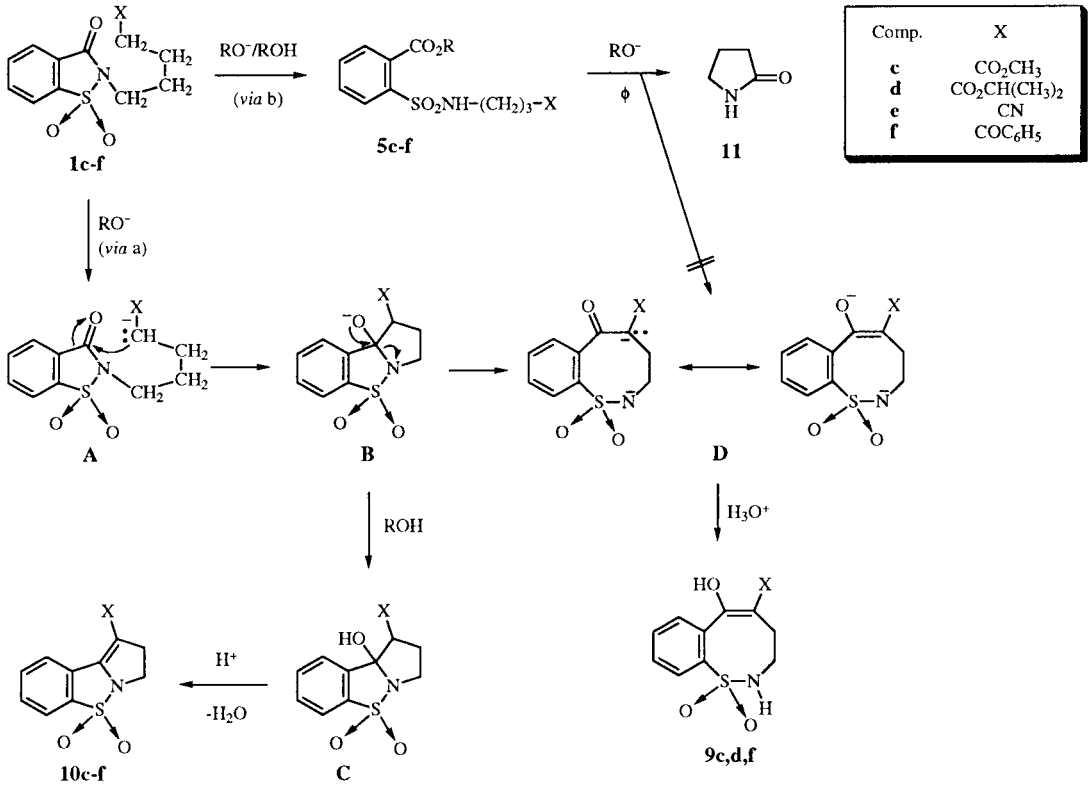
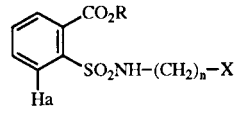


Table III

N-Substituted *o*-Sulfamylbenzoic Acid Alkyl Esters **5a-f**



Compound No.	Starting Materials	[RONa]	Conditions Temp (°C)	Yield (%)	Formula	Analyses (Calcd./Found) %C	%H	%N	%S	IR ν (cm^{-1})	^{1}H-NMR δ (ppm)	Multiplicity	Assignment
5a (R = C_2H_5)	**1a** + C_2H_5ONa	1.6 *M*	25	70	$C_{14}H_{19}NO_6S$	51.06	5.77	4.25	9.72	3380 (NH)	8.30-8.10	m	Ha
						51.20	5.89	4.35	9.90	2950 (CH)	8.00-7.65	m	aromatics
										1750 (CO)	6.50	t [a]	NH
										1330 (SO_2)	4.60	c	OCH_2
										1180 (SO_2)	4.15	c	OCH_2
											3.10	c [b]	NCH_2
											2.45	t	CH_2-CO
											1.60	t	CH_3
											1.35	t	CH_3
5b (R = CH_3)	**1b** + CH_3ONa	1.6 *M*	25	65	$C_{11}H_{12}N_2O_4S$	49.25	4.48	10.45	11.94	3390 (NH)	8.20-8.00	m	Ha
						49.02	4.26	10.64	11.75	2900 (CH)	7.90-7.40	m	aromatics
										2300 (CN)	6.40	t [a]	NH
										1730 (CO)	3.90	s	CH_3
										1350 (SO_2)	3.0	c [b]	N-CH_2
										1200 (SO_2)	2.50	t	CH_2-CN
5c (R = CH_3)	**1c** + CH_3ONa	1.6 *M*	25	86	$C_{13}H_{17}NO_6S$	49.52	5.39	4.44	10.16	3330 (NH)	8.20-8.00	m	Ha
						49.30	5.62	4.21	10.39	2900 (CH)	8.00-7.40	m	aromatics
										1750 (CO)	6.10	bs [a]	NH
										1720 (CO)	4.00	s	CH_3
										1350 (SO_2)	3.75	s	CH_3
										1180 (SO_2)	3.10	c [b]	N-CH_2
											2.40	t	CH_2-CO
											1.80	q	CH_2-CH_2-CH_2
5c (R = *t*-C_4H_9)	**1c** + *t*-C_4H_9ONa	0.8 *M*	50	10	$C_{16}H_{23}NO_6S$	53.78	6.44	3.92	8.96	3280 (NH)	8.20-7.50	m	aromatics
			[c]	[d]		53.82	6.69	4.07	8.73	2940 (CH)	6.20	bs [a]	NH
										1730 (CO)	3.90	s	CH_3O
										1710 (CO)	3.20	c [b]	N-CH_2
										1340 (SO_2)	2.50	t	CH_2-CO
										1190 (SO_2)	1.80	q	CH_2-CH_2-CH_2
											1.60	s	C-CH_3
5d (R = *i*-C_3H_7)	**1d** + *i*-C_3H_7ONa	0.8 *M*	25	45	$C_{17}H_{25}NO_6S$	43.68	5.35	3.00	6.85	3300 (NH)	8.07-8.00	m	Ha
						43.45	5.58	3.20	6.62	2950 (CH)	7.80-7.52	m	aromatics
										1740 (CO)	6.00	t [a]	NH
										1720 (CO)	5.25	m	CH
										1350 (SO_2)	4.95	m	CH
										1180 (SO_2)	3.00	c [b]	N-CH_2
											2.30	t	CH_2-CO
											1.80	t	CH_2-CH_2-CH_2
											1.40	d	CH_3
											1.15	d	CH_3
5e (R = CH_3)	**1e** + CH_3ONa	1.6 *M*	25	70	$C_{12}H_{14}N_2O_4S$	51.06	4.96	9.93	11.35	3350 (NH)	8.20-8.00	m	Ha
						49.94	5.15	9.78	11.56	2950 (CH)	8.00-7.55	m	aromatics
										2300 (CN)	6.25	t [a]	NH
										1740 (CO)	3.90	s	CH_3
										1350 (SO_2)	3.10	c [b]	N-CH_2
										1180 (SO_2)	2.50	t	CH_2-CN
											1.90	q	CH_2-CH_2-CH_2
5e (R = t-C_4H_9)	**1e** + *t*-C_4H_9ONa	0.8 *M*	50	7	$C_{15}H_{20}N_2O_4S$	55.56	6.17	8.64	9.88	3330 (NH)	8.10-8.00	m	Ha
			[c]	[e]		55.30	6.40	8.45	9.65	2960 (CH)	7.70-7.50	m	aromatics
										2300 (CN)	6.15	t [a]	NH
										1750 (CO)	3.10	c [b]	N-CH_2
										1190 (SO_2)	2.50	t	CH_2-CN
											2.00	q	CH_2-CH_2-CH_2
											1.70	s	CH_3
5f (R = CH_3)	**1f** + CH_3ONa	0.8 *M*	30	65	$C_{18}H_{19}NO_5S$	59.83	5.26	3.88	8.86	3340 (NH)	8.10-7.60	m	Ha and C_6H_5
						59.95	5.40	3.70	8.95	2950 (CH)			(2 *ortho* H)
										1750 (CO)	7.50-7.30	m	aromatics
										1690 (CO)	6.10	t [a]	NH
										1350 (SO_2)	4.00	s	OCH_3
										1190 (SO_2)	3.20-2.80	m	CH_2-CH_2-CH_2
											1.90	q	CH_2-CH_2-CH_2

[a] Exchangeable. [b] Upon deuteration the quartet collapsed into a singlet. [c] Required temperature due to the alkoxide insolubility. [d] Immediately after the acid quenching of the reaction, traces of **9c** were detected. After 36 hours, 4% of compound **10c** was obtained. [e] The crude product showed at least two spots by tlc. After 6 days, 6% of compound **10e** was obtained.

Table IV

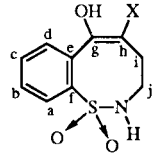
Reaction of Compounds **1c-f** with Alkoxides Under Drastic Conditions

Starting Materials	Conditions [RONa]	Solvent	Temp (°C)	Time (min)	Reaction Products (Yields, %)					
1c + CH_3ONa	3.2 *M*	methanol	100	30	**9c** (3)	**10c** (10)	[a]	**11**	(15)	
1c + *t*-C_4H_9ONa	1.68 *M*	*t*-butyl alcohol	110	30	**9c** (10)	**10c** (38)	[a]			
1c + *t*-C_4H_9ONa	2.6 *M*	DMSO	60	25	**9c** (40)	**10c** (10)	[a]			
1d + *t*-C_4H_9ONa	1.68 *M*	*t*-butyl alcohol	110	30	**9d** [b]	**10d** (56)	[a]			
1d + *t*-C_4H_9ONa	2.6 *M*	DMSO	60	25	**9d** (47)	**10d** (14)	[a]			
1e + *t*-C_4H_9ONa	1.68 *M*	*t*-butyl alcohol	110	30		**10e** (35)	[c]			
1e + *t*-C_4H_9ONa	2.6 *M*	DMSO	60	20		**10e** (5)	[c]	**12**	(30)	
1f + t-C_4H_9ONa	1.68 *M*	*t*-butyl alcohol	110	30	**9f** [b]	**10f** (43)	[d]			
1f + t-C_4H_9ONa	2.6 *M*	DMSO	60	30	**9f** (68)	**10f** (7)	[d]			

[a] The compound was obtained 18 hours after the end of the reaction. [b] Small amounts were detected by tlc. [c] The compound was obtained 3 days after the end of the reaction. [d] The compound was obtained 10 hours after the end of the reaction.

Table V

5-Substituted 6-Hydroxy-3,4-dihydro-2*H*-1,2-benzothiazocine 1,1-Dioxides **9c,d,f**

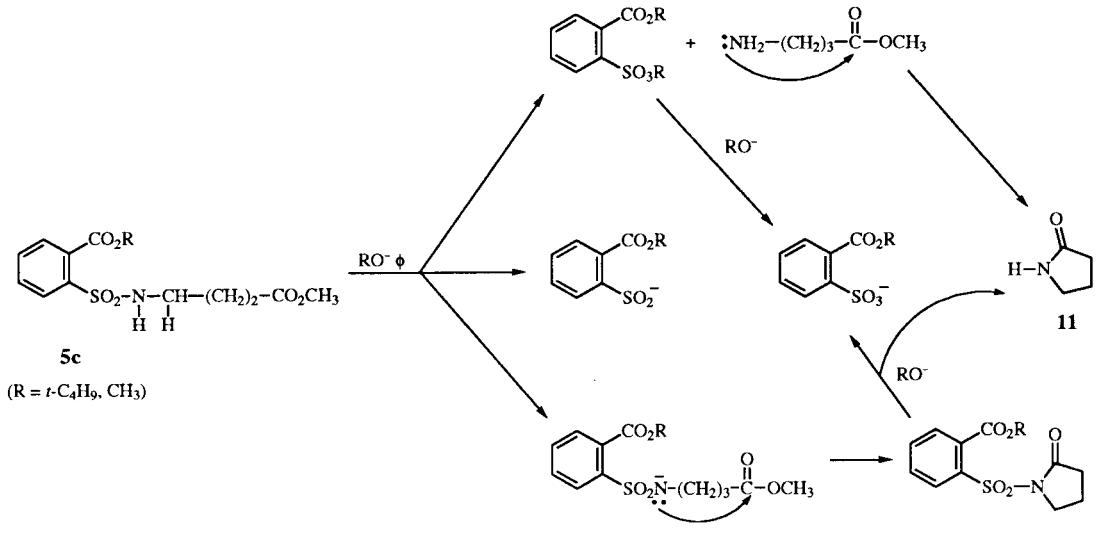


9c,d,f

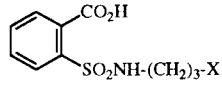
Compound No.	Mp (°C)	Formula	Analyses Calcd./Found %C	%H	%N	%S	Mass M⁺ (%)	IR ν (cm^{-1})	^{1}H-NMR δ (ppm)	Multiplicity	Assignment	^{13}C-NMR [a] δ (ppm)	Assignment [b]
9c	93	$C_{12}H_{13}NO_5S$	50.88	4.59	4.95	11.31	283	3280 (NH)	12.80	s [c]	OH	171.9 and 168.7	C g and CO
			50.70	4.72	4.72	11.54	(15.5)	2978 (CH)	8.1-8.0	m	Ha	142.3	C f
								2950 (CH)	7.9-7.5	m	aromatics	133.0-131.9	C a-d
								1660 (CO)	4.75	t [c]	NH	131.9 and 129.6	
								1600 (C=C)	3.90	s	CH_3	127.5	C e
								1450 (aromatic)	3.45-3.3	m	CH_2j	101.3	C h
								1382 (SO_2)	2.8-2.6	m	CH_2i	52.3	CH_3
								1163 (SO_2)				42.0	CH_2 j
												25.5	CH_2 i
9d	95	$C_{14}H_{17}NO_5S$	54.02	5.47	4.50	10.29	311	3260 (NH)	13.0	s [c]	OH	171.1 and 168.8	C g and CO
			54.33	5.58	4.30	10.41	(64.2)	2900 (CH)	8.1-7.9	m	Ha	131.4, 131.3,	C a-d
								1660 (CO)	7.7-7.4	m	aromatics	130.2 and 129.5	
								1340 (SO_2)	5.05	m	CH	142.2	C f
								1190 (SO_2)	4.60	t [c]	NH	127.3	C e
									3.4-3.2	m	CH_2j	101.3	C h
									2.5-2.3	m	CH_2i	68.5	CH
									1.10	d	CH_3	42.2	CH_2 j
												25.6	CH_2 i
												21.5	CH_3
9f	122	$C_{17}H_{15}NO_4S$	62.00	4.56	4.25	9.73	329	3280 (NH)	16.50	s [c]	OH	197.2	CO
			62.24	4.75	4.01	9.50	(20.3)	1680 (CO)	8.10-7.65	m	H a and C_6H_5	169.3	C g
								1650 (CO)			(2 *ortho* H)	139.6 and 137.3	C f and C-CO
								1350 (SO_2)	7.60-7.15	m	aromatics	133.5, 133.0,	aromatics
								1170 (SO_2)	4.60	t [c]	NH	131.2, 129.4,	
									3.80-2.60	m	CH_2-CH_2	129.2, 129.1,	
												128.8 and 128.4	
												128.2	C e
												100.3	C h
												42.7	CH_2 j
												31.5	CH_2 i

[a] Spectra of compounds **9c** and **9f** were performed in dimethyl sulfoxide-d_6. [b] Assignments were made on the basis of literature data, attached proton test (APT) and fully coupled ^{13}C-nmr spectra. [c] Exchangeable.

Scheme IV



inversion (Table IV). When sodium methoxide was employed to induce rearrangement, **9** and **10** yields dropped drastically and considerable amounts of pyrrolidone (**11**) were obtained. Compound **1e** showed a rather different behavior. Employing sodium *t*-butoxide in DMSO, the reaction gave the acid **12** as the main product. With sodium *t*-butoxide in *t*-butyl alcohol, compound **10e** was obtained in the usual yields after several days.



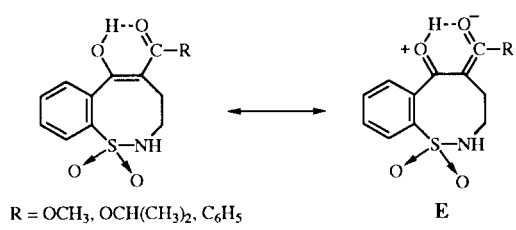
12 (X = CN)
13 (X = CO_2H)

Experimental observations indicating a likely pathway generating **9**, **10** and **11** include: (a) in contrast with the behavior observed in the preparation of 1,2-benzothiazines [1,4,5] (Scheme I), open sulfonamides **5** are not intermediates in the rearrangement **1**→**9**, as demonstrated by the observation that treatment of **5c** (R = *t*-C_4H_9 or CH_3) with hot sodium *t*-butoxide in DMSO did not produce **9c**, but instead a mixture of water-soluble products [16] from which pyrrolidone (**11**) may be isolated (Scheme IV) [18]; (b) tricyclic compounds **10** were not detected immediately after acid quenching of the reaction and isolation of **9**, indicating that its formation is due to a change taking place after acidification; and (c) the course of the reaction varied remarkably, both as regards the alkoxide employed (whether primary or tertiary) and according to the protic or aprotic nature of the solvent.

The foregoing findings led us to propose a mechanism explaining the formation of compounds **9** and **10** through a common anionic intermediate, as well as the presence of pyrrolidone when sodium methoxide is used (Scheme III). Due to its strongly basic character and great volume which hinders carboxamide alcoholysis, the reaction with *t*-butoxide would presumably lead almost exclusively to the formation of the carbanion **A** (*via* **a**). Nucleophilic attack of this carbanion on the saccharin carbonyl group would then generate a new five-membered ring with the formation of the tertiary alkoxide **B**. As a result of proton exchange in *t*-butyl alcohol, the main product would therefore be the alcohol **C**, which explains why compounds **10** are not detected immediately after reaction completion, since they would arise from slow dehydration of such an alcohol after acid quenching. On the other hand, in the aprotic solvent DMSO, benzothiazocines **9** would appear as the main product through the formation of the stabilized enolate ion **D**. This interpretation is supported by the fact that the reaction of compound **1c** with strongly basic sodium hydride in dimethylformamide gives **9c** and **10c** though in poor yields. Side reactions promoted by the hydride may account for such yields.

In contrast with *t*-butoxide, methoxide would seem to act mainly as a nucleophilic reagent inducing alcoholysis of the carboxamide function rendering open sulfonamides **5** (*via* **b**, Scheme III) and giving rise to pyrrolidone and other water-soluble products, most likely sulfonates and sulfinates [16], probably through the pathways indicated

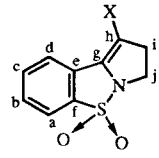
Scheme V



R = OCH_3, $OCH(CH_3)_2$, C_6H_5 **E**

Table VI

1-Substituted 2,3-Dihydropyrrolo[1,2-*b*][1,2]benzisothiazole 5,5-Dioxides **10c-f**



Compound No.	Mp (°C)	Formula	Analyses Calcd./Found %C	%H	%N	%S	Mass M+ (%)	IR ν (cm^{-1})	^{1}H-NMR δ (ppm)	Multiplicity	Assignment	^{13}C-NMR [a] δ (ppm)	Assignment [b]
10c	176	$C_{12}H_{11}NO_4S$	54.34	4.15	5.28	12.07	265	1700 (CO)	8.9-8.7	m	Hd	163.9	CO
			54.56	4.32	5.03	12.32	(100)	1630 (C=C)	7.8-7.5	m	aromatics	146.0	C g
								1300 (SO_2)	3.85	s	CH_3	139.2	C f
								1160 (SO_2)	*ca.* 3.80	[c]	CH_2 j	133.9 and 132.9	C b,c
									3.20	t [d]	CH_2 i	127.8 and 122.0	C a,d
												124.0	C e
												107.3	C h
												51.6	CH_3
												40.6 and 33.3	C i,j
10d	127	$C_{14}H_{15}NO_4S$	57.34	5.12	4.78	10.92	293	1710 (CO)	8.9-8.6	m	Hd	163.8	CO
			57.48	5.30	4.88	10.70	(87)	1620 (C=C)	8.2-7.8	m	aromatics	146.9	C g
								1290 (SO_2)	5.00	m	CH	139.6	C f
								1190 (SO_2)	3.65	t [d]	CH_2 j	133.4 and 132.0	C b,c
									3.15	t [d]	CH_2 i	128.6 and 121.7	C a,d
									1.22	d	CH_3	125.2	C e
												108.1	C h
												68.3	CH
												41.8 and 33.8	C i,j
												22.0	CH_3
10e	210	$C_{11}H_8N_2O_2S$	56.89	3.45	12.07	13.79	232	2200 (CN)	8.2-7.7	m	aromatics		
			56.70	3.65	12.09	13.62	(100)	1600 (C=C)	3.80	t [d]	CH_2 j	150.1	C g
								1300 (SO_2)	3.25	t [d]	CH_2 i	138.9	C f
								1180 (SO_2)				134.5 and 133.5	C b,c
												123.8 and 122.5	C a,d
												123.5	C e
												115.0	CN
												83.1	C h
												43.2 and 33.7	C i,j
10f	144	$C_{17}H_{13}NO_3S$	65.59	4.18	4.50	10.29	311	1690 (CO)	8.0-7.0	m	aromatics	191.5	CO
			65.72	4.32	4.35	10.20	(56.7)	1620 (C=C)	3.8-3.5	m	CH_2 j	146.1	C g
								1294 (SO_2)	3.4-3.0	m	CH_2 i	139.2 and 139.2	C f and phenyl (quaternary carbon)
								1200 (SO_2)				133.9, 133.1 and 132.4	C b,c and phenyl (*para* carbon)
												128.7, 128.1, 127.2 and 122.4	C a,d and phenyl (*ortho* and *meta* carbon)
												124.4	C e
												115.7	C h
												42.3 and 35.6	C i,j

[a] Spectra of compounds **10c,e,f** were performed in dimethyl sulfoxide-d_6. [b] Assignments were made on the basis of literature data, attached proton test (APT) and fully coupled ^{13}C-nmr spectra. [c] Signal overlapped with that of the methyl. [d] Each peak of the triplet shows additional splitting.

for compound **5c** (Scheme IV).

Spectroscopic properties (Table V) and the positive ferric chloride test support the enolic structure for compounds **9c,d,f**. In agreement, ^{1}H nmr spectra show the enol hydroxyl signal at δ 12-16.5, the sulfonamide hydrogen as a triplet at δ 4.6 and the presence of two asymmetric multiplets between 2.5-3.5 ppm for methylene hydrogens. Characteristically, ^{13}C nmr spectra exhibit two signals at δ *ca.* 160-170 and 100 ppm which were assigned to benzothiazocine nucleus carbons 6 (enolic, C_g) and 5 (olefinic, C_h), respectively. The ir spectrum for the carbonyl stretching zone shows a single intense band at considerably lower frequencies. In the 3000-3300 cm^{-1} range, there is a strong band assigned to NH stretching, whereas the band corresponding to the enolic OH, whether free or associated by intermolecular hydrogen band, is absent. This finding agrees with a conjugated chelate structure, having a substantial contribution from the polar **E** along with the normal covalent structure (Scheme V). Compounds with these features, exhibit broad weak OH absorption bands extending from 3500 to 2500 cm^{-1} [19-21], which in our case appeared masked by the bands corresponding to NH and CH stretching.

Lastly, ^{1}H nmr spectra of compounds **10** invariably

show the CH_2-CH_2 signal as a symmetric multiplet typical of an AA'BB' system. Besides, each methylene appears as a unsymmetric multiplet. Typically, esters **10c,d** present an aromatic hydrogen at remarkably low fields reaching δ 8.9. Deshielding is much higher than that observed in related compounds (1,2-benzothiazine 1,1-dioxides and open sulfonamides **5**) for hydrogens located *ortho* to the sulfonamide function [4,5]. Observation of the molecular model discloses the proximity of the ester group to the hydrogen **d** (Table VI) probably within the deshielding carbonyl zone, so that the least shielded signal was assigned to that hydrogen. The ^{13}C nmr data support the proposed structure. Quaternary C-g appears at *ca.* 145-150 ppm while C-e resonances are quite sensitive to substitution and appear between 83 and 108 ppm. The ir spectra show a strong C=C stretching band which agree with aryl conjugation [22].

EXPERIMENTAL

Melting points were taken on a Büchi capillary apparatus and are uncorrected. The ir spectra were recorded on a Beckman 180A spectrometer. Samples were run as potassium bromide pellets for solids and films for oils. The nmr spectra were recorded on a Varian FT-80A spectrometer. Deuteriochloroform was used as solvent, unless noted otherwise. Chemical shifts are quoted in parts per million (δ) downfield from an internal TMS reference. The presence of exchangeable protons was confirmed by use of deuterium oxide. Proton signals are quoted as: s (singlet), d (doublet), t (triplet), c (quartet), q (quintuplet), m (multiplet) and bs (broad signal). The ^{13}C nmr spectra were recorded at normal probe temperature (30°) using a decoupling power of 6W, pulse angles of 45°, a spectral width of 5000 Hz, an 8K data table, a 2s pulse repetition rate at *ca.* 0.7 Hz of line broadening due to exponential weighting of the free induction decay (FID). Mass spectra were recorded on a MS Shimadzu QP-1000 instrument at 20 eV. Analytical tlc was carried out on aluminium sheets Silica Gel 60 F_{254}. Column chromatography was carried out on Silica Gel G (70-325 mesh). Reagents, solvent and starting materials were purchased from standard sources and purified according to literature procedures.

N-Substituted 1,2-Benzisothiazol-3-one 1,1-Dioxides **1a-f**. (*N*-Substituted Saccharins). General Procedure.

A mixture of 0.12 mole of 1,2-benzoisothiazol-3-one 1,1-dioxide sodium salt, 0.08 mole of the corresponding halogen derivative and 15 ml of dimethylformamide was heated at 120° for 2 hours. The reaction mixture was poured into ice-water and the resulting solid was filtered, washed with water and recrystallized from the appropriate solvent. Melting points, recrystallization solvents, elemental analyses and spectroscopic data are given in Table II.

N-Substituted *o*-Sulfamylbenzoic Acid Alkyl Esters **5a-f**. General Procedure.

A solution of sodium alkoxide was prepared from 0.46 g of sodium (0.02 mole) in the corresponding absolute alcohol. The solution was heated at the appropriate temperature and 0.01 mole of the *N*-substituted saccharin (**1a-f**) was added all at once as the powder. After 3 minutes, the reaction was quenched by pouring into concentrated hydrochloric acid-ice. The resulting suspension was extracted three times with chloroform. After washing with water, the organic solution was dried, concentrated *in vacuo* and purified by column chromatography (chloroform-methanol, 9.5:0.5 as the elution solvent) affording compounds **5a-f**. Details of the reaction (starting materials, temperature, alkoxide concentration, yields), analyses and spectroscopic data of the compounds are given in Table III.

Reaction of **1d** with sodium methoxide at 25°, following the procedure indicated above, provided **5c** as the sole product.

Reaction of Compounds **1a,b** with Sodium Alkoxides Under Drastic Conditions.

A solution of sodium ethoxide was prepared from 2.76 g of sodium (0.12 mole) in 30 ml of absolute ethanol. The solution was refluxed in an oil bath and 0.03 mole of compound **1a** was added all at once as the powder. A few minutes later, the slurry was poured into concentrated hydrochloric acid-ice and the solid was filtered affording saccharin (**3**) (50%) as the sole product, mp and mixed mp with an authentic sample 229°. The remaining solution was extracted three times with chloroform. The organic layer was extracted with 10% sodium hydroxide, washed with water, dried and concentrated. Distillation of the residue under diminished pressure afforded a fraction boiling at 59-62°/20 mm which was identified as β-ethoxypropionic acid ethyl ester (**4a**) by comparison of spectroscopic properties with that of an authentic sample [7]; ms: m/z 146 (M^+); ir: ν 3100, 1750, 1530, 1450, 1324 and 1155 cm^{-1}; ^1H nmr: δ 4.20 (c, 2H, CH_2-O-CO), 3.70 (t, 2H, CH_2-O-C_2H_5), 3.50 (c, 2H, CH_3-CH_2-OCH_2), 2.55 (t, 2H, CH_2-CO) and 1.3-1.0 (m, 6H, CH_3).

Reaction of compound **1b** with sodium ethoxide under the same conditions as above, gave saccharin (**3**) (55%) and β-ethoxypropionitrile (**4b**), bp 77-80°/25 mm, which was identified by comparison with an authentic sample [8]; ms: m/z 99 (M^+); ir: ν 3100, 2260, 1405 and 1100 cm^{-1}; ^1H nmr: δ 3.70-3.40 (m, 4H, CH_2-O-CH_2), 2.70 (t, CH_2-CN) and 1.05 (s, 3H, CH_3).

When reactions were performed with sodium *t*-butoxide in *t*-butyl alcohol (110°) or DMSO (60°), only saccharin (**3**) was isolated.

Attempted Synthesis of the Benzothiazepine **2** (X = $CO_2C_2H_5$) by Ring Closure of **5a** (R = C_2H_5).

A. With Sodium Alkoxides Under Drastic Conditions.

The reaction was performed in the same manner as for compounds **1a,b** with similar results.

B. With Triethylamine.

A mixture of **5a** (0.001 mole), triethylamine (1 ml) and ethanol (10 ml) was refluxed for 9 hours. The solution was concentrated *in vacuo* and the residue treated with 10% hydrochloric acid affording compound **1a** (90%).

C. With Sodium Hydride.

To a slurry of a 50% mineral oil dispersion of sodium hydride (0.02 mole of sodium hydride) in dimethylformamide (5 ml), 0.01 mole of **5a** was added all at once as the powder. The reaction mixture was stirred at room temperature and monitored by tlc (benzene-methanol, 9:1). When **5a** was no longer detectable (*ca.* 30 minutes), the mixture was carefully poured into

hydrochloric acid-ice and extracted with chloroform. The organic layer was washed, dried and concentrated *in vacuo*. The residue was purified by column chromatography (chloroform-2-propanol, 9:1). Removal solvent of the main fraction furnished *o*-[*N*-(2-carboxyethyl)sulfamyl]benzoic acid **6** (30%), mp 175° (ethyl acetate); ms: m/z 273 (M^+); ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 8.00-7.62 (m, 4H, aromatics), 7.60-6.80 (bs, 3H, exchangeable, CO_2H + NH), 3.15 (c, 2H, upon deuteration collapsed into a triplet, NH-CH_2) and 2.36 (t, 2H, CH_2-CO_2H).

Anal. Calcd. for $C_{10}H_{11}NO_6S$: C, 43.95; H, 4.03; N, 5.13; S, 11.72. Found: C, 43.78; H, 4.25; N, 4.99; S, 11.58.

o-[*N*-(2-Cyanoethyl)-*N*-methylsulfamyl]benzoic Acid Methyl Ester **7**.

To a solution of sodium (0.08 mole) in dry methanol (20 ml), compound **1b** (0.01 mole) was added all at once as the powder. The mixture was stirred and dimethylsulfate (0.03 mole) was added dropwise, the temperature being kept at 40° by cooling. The reaction mixture was stirred at room temperature for 2 hours, poured into ice-water and extracted with methylene chloride. After washing with water, the organic solution was dried, evaporated and the residue triturated with cyclohexane affording **7** (55%), mp 65° (benzene); ms: m/z 282 (M^+); ^{1}H-nmr: δ 8.10-7.70 (m, 4H, aromatics), 4.20 (s, 3H, CH_3-O), 3.15 (t, 2H, N-CH_2), 2.70 (s, 3H, N-CH_3) and 2.30 (t, 2H, CH_2-CN).

Anal. Calcd. for $C_{12}H_{14}N_2O_4S$: C, 51.06; H, 4.96; N, 9.93; S, 11.35. Found: C, 50.90; H, 5.15; N, 9.89; S, 11.18.

Attempted cyclization of compound **7** by reaction with sodium alkoxides in the same conditions as for compound **5a** afforded only *N*-methylsaccharin (**8**). Structure was confirmed by comparison with an authentic sample prepared from sodium saccharin and methyl iodide, mp and mixed mp 132°.

Reaction of Compounds **1c-f** Under Drastic Conditions.

A with Sodium *t*-Butoxide.

Sodium *t*-butoxide (0.04 mole) in DMSO or *t*-butyl alcohol was heated at the appropriate temperature and 0.01 mole of the saccharin derivative **1c-f** was added all at once as the powder. After the end of the reaction, the slurry was poured into concentrated hydrochloric acid-ice. In the case of the reactions involving compounds **1c,d,f**, the resulting solid was filtered, washed with water and air dried affording compounds **9c,d,f**. Compound **1e** gave an emulsion which was extracted with chloroform affording *o*-[*N*-(3-cyanopropyl)sulfamyl]benzoic acid (**12**). From the mother liquors of the reactions, compounds **10c-f** were obtained after 10 hours to 3 days. Details of the reactions (starting materials, alkoxide concentration, temperature, reaction products and yields) are given in Table IV.

Compounds **9c,d,f** were purified by column chromatography (benzene-methanol 9:1). Recrystallization from organic solvents or water resulted in partial decomposition. Melting points, analyses and spectroscopic data are given in Table V.

Compounds **10c-f** were purified by recrystallization from ethanol. Melting points, analyses and spectroscopic data are given in Table VI.

Compound **12** (oil) was purified by column chromatography (benzene-methanol 9:1) (35%); ms: m/z 268 (M^+); ir: ν 3500-3200, 3000, 2200, 1710, 1440, 1320, 1170 and 960 cm^{-1}; ^{13}C-nmr: δ 168.9 (CO_2H), 137.5, 132.1, 131.0, 130.8, 130.3 and 127.7 (aromatics), 118.7 (CN), 41.2 (NH-CH_2), 25.0 (CH_2-CH_2-CH_2) and 13.5 (CH_2-CN); ^{1}H nmr: δ 9.8 (bs, 1H, exchangeable, CO_2H), 8.1-7.6 (m, 4H, aromatics), 6.5 (t, 1H, exchangeable, NH), 3.05 (c, 2H, NH-CH_2), 2.40 (t, 2H, CH_2-CN) and 1.70 (q, 2H, CH_2-CH_2-CH_2).

Anal. Calcd. for $C_{11}H_{12}N_2O_4S$: C, 49.25; H, 4.48; N, 10.45; S, 11.94. Found: C, 49.10; H, 4.64; N, 10.31; S, 11.78.

B. With Sodium Methoxide.

The reaction was performed as above but using 0.12 mole of sodium methoxide and 0.03 mole of **1c**, affording poor yields of **9c** and **10c** (Table IV). After isolation of **10c**, the acidic liquor was extracted with chloroform and the organic layer was washed, dried and concentrated *in vacuo*. Distillation of the oily residue, under diminished pressure, afforded a fraction boiling at 125-128°/10 mm which was identified as pyrrolidone (**11**) by comparison of spectroscopic properties with that of an authentic sample; ir 3250, 2980, 1680, 1460, 1280, 1065 and 995 cm^{-1}; ^{1}H-nmr: δ 7.50 (bs, 1H, exchangeable, NH), 3.40 (t, 2H, N-CH_2) and 2.50-1.9 (m, 4H, CH_2-CH_2-CO).

C. With Sodium Hydride.

Reaction of compound **1c** (0.01 mole) with sodium hydride (0.02 mole) in dimethylformamide was performed following the procedure indicated for compounds **5a,b** affording a complex mixture of products from which compounds **9c** (9%) and **10c** (4%) were isolated.

Attempted Synthesis of **9c** from **5c** (R = CH_3, *t*-C_4H_9).

The reaction of **5c** (R = CH_3, *t*-C_4H_9) with sodium *t*-butoxide in DMSO, under the same conditions as for compounds **1c-f**, afforded only a mixture of water-soluble products from which pyrrolidone (**11**) (30%) was isolated. No traces of **9c** and **10c** were detected.

Attempts to cyclize **5c** with triethylamine or sodium hydride were performed following the same procedures as for compound **5a** affording **1c** (85%) and *o*-[*N*-3-carboxypropyl)sulfamyl]benzoic acid (**13**) (35%), respectively.

Compound **13** had mp 150° (benzene); ms: m/z 287 (M^+); ^{1}H-nmr: δ 9.10 (bs, 2H, exchangeable, CO_2H), 8.05-7.75 (m, 4H, aromatics), 7.15 (bs, 1H, exchangeable, NH), 2.90 (c, 2H, upon deuteration collapsed into a triplet, N-CH_2), 2.20 (t, 2H, CH_2-CO) and 1.75 (q, 2H, CH_2-CH_2-CH_2).

Anal. Calcd. for $C_{11}H_{13}NO_6S$: C, 45.99; H, 4.53; N, 4.88; S, 11.15. Found: C, 45.80; H, 4.70; N, 4.75; S, 11.01.

Acknowledgements.

Financial support of this investigation was given by the Consejo Nacional de Investigaciones Científicas y Técnicas and Universidad de Buenos Aires.

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formed when products are highly stabilized due to the presence of conjugate double bonds is widely recognized. Besides, the formation of compounds **4** is not unexpected since primary alcohols of low molecular weight readily add to acrylic esters and nitriles [7,8].

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