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A series of 4-hydroxy-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxides substituted on the sulfonamide nitrogen with ethoxycarbonylalkyl, cyanoalkyl and dialkylaminoalkyl groups was synthesized. Spectroscopic properties of the obtained products were analyzed. Findings from the pharmacological study of some of the compounds as antiinflammatory and analgesic agents are reported.

Introduction.

In the search for new non-steroidal antiinflammatory drugs during the 1970's, the striking properties of a series of 4-hydroxy-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxides ("oxicams") were described [1,2] and their pharmacological action attributed to the acidic features conferred by the presence of the enolic hydroxyl group. The literature describes the synthesis of a large number of these compounds with diverse structural variations. The most valuable modifications, carried out in order to enhance their pharmacological activity, include the introduction of substituents in the benzene nucleus [3-7], replacement of the latter by a heterocyclic ring [8,9] and variations in the amine of the carboxamide group [2,4,10-13]. In most of these cases the sulfonamide hydrogen is found to be substituted by alkyl or aralkyl groups, with

hardly any mention of 2-substituted compounds with functional alkyl groups. With the aim to develop novel non-steroidal antiinflammatory drugs, we synthesized a series of 2-dialkylaminoalkyl, alkoxycarbonylalkyl and cyanoalkylbenzothiazines **1** (Table I).

Synthesis and Spectral Properties of Compounds **1**.

The benzothiazine nucleus was generated in all cases by alkoxide induced rearrangement of saccharin-2-acetic esters or amides [14,15] (Scheme I). Compounds
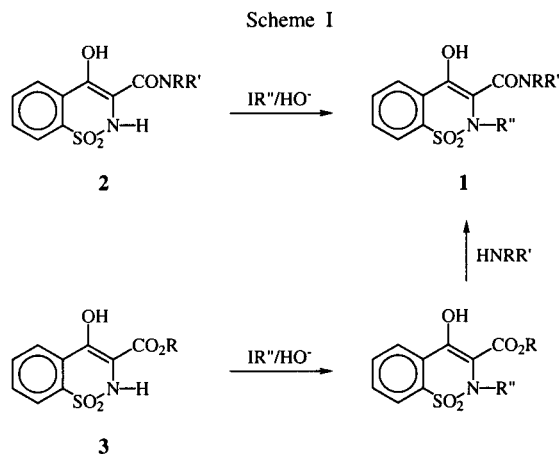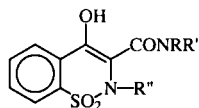
Scheme I

1a-l were mostly obtained by N-alkylation of the corresponding benzothiazine-3-carboxamide **2**, though in the case of the 2-pyridyl derivative **1l**, an analog of piroxicam (**1**, R = 2-pyridyl, R' = H, R" = CH₃), yields were hardly satisfactory [16]. N-Alkylation of the benzothiazine-3-carboxylic acid ethyl ester **3** and subsequent aminolysis failed to provide a general method. Attempts to obtain dialkylaminomethyl derivatives **1** (R" = CH₂NR₂) by the Mannich reaction proved unsuccessful [18].

Table I

2-Substituted 4-Hydroxy-2H-1,2-benzothiazine-3-carboxamide 1,1-Dioxides

Compound	R	R'	R"
1a	H	C₆H₅	CH₂CH₂N(CH₃)₂
1b	H	C₆H₅	CH₂CH₂N(CH₂CH₃)₂
1c	H	C₆H₅	CH₂CO₂CH₂CH₃
1d	H	C₆H₅	CH₂CH₂CO₂CH₂CH₃
1e	H	C₆H₅	CH₂CN
1f	CH₃	C₆H₅	CH₂CN
1g	H	C₆H₁₁	CH₂CH₂N(CH₃)₂
1h	H	C₆H₁₁	CH₂CH₂N(CH₂CH₃)₂
1i	H	C₆H₁₁	CH₂CN
1j	H	CH(CH₃)₂	CH₂CH₂N(CH₂CH₃)₂
1k	H	CH(CH₃)₂	CH₂CH₂N(CH₃)₂
1l	H	[2-pyridyl]	CH₂CH₂N(CH₃)₂

The structure of compounds **1** was confirmed by elemental analysis and spectroscopic methods. In ^{1}H nmr spectra (Table II) the enol hydroxyl signal is typically observed at *ca.* δ 12 ppm and in monosubstituted amides the carboxamide hydrogen appears at δ 8-11. In the aromatic region one proton is generally observed at low fields as a doublet which was assigned to the hydrogen adjacent to the sulfonamide group (Ha).

As a rule, ^{13}C nmr spectra show, for the benzothiazine nucleus, features similar to those observed in the 2-H analogs [21] (Table III). The most striking difference, attributable to the influence of the side chain in N-2, is manifested in the enolic carbon (C-7) which appears substantially unshielded (Δ δ *ca.* 8 ppm).

The electron impact mass spectra of compounds **1** display the molecular ion peak with a relative abundance

Table II

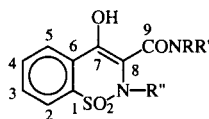2-Substituted 4-Hydroxy-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxides **1a-l**
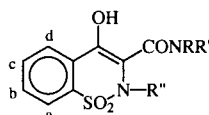
Compound No.	Yield (%) [a]	Mp (°C)	Formula	Analyses (Calcd./Found)			UV in 0.1N HCl λ max (nm) [b]	in 0.1N NaOH λ max (nm) [b]	δ (ppm)	^{1}H-NMR Multiplicity	Assignment
				%C	%H	%N					
1a	72	208-210 dec	$C_{19}H_{21}N_3O_4S$	58.90	5.46	10.85	238 and 313	262 and 360 [d]	12.50	s [e]	OH
	28 [c]			58.75	5.51	10.90			9.40	s [e]	NH
									7.90	d	Ha
									7.72-7.61	m	Hb-d
									7.50-7.20	m	C_6H_5
									3.30	t	SO_2NCH_2
									2.70	t	$CH_2N(CH_3)_2$
									1.80	s	CH_3
1b	75	210-212 dec	$C_{21}H_{25}N_3O_4S$	60.70	6.06	10.11	312	362 [d]	12.77	s [e]	OH
	25 [c]			60.86	6.15	9.98			11.40	s [e]	NH
									8.02	d	Ha
									7.85-7.65	m	Hb-d
									7.37-7.00	m	C_6H_5
									3.44	t	SO_2NCH_2
									3.40-3.50	m	$CH_2N(CH_2CH_3)_2$
									1.30	t	CH_3
1c	80	255	$C_{19}H_{18}N_2O_6S$	56.71	4.51	6.96	323 [d]	360	12.32	s [e]	OH
				56.90	4.58	6.88			10.80	s [e]	NH
									7.90	d	Ha
									7.69-7.60	m	Hb-d
									7.52-7.13	m	C_6H_5
									4.36	s	SO_2NCH_2
									3.95	c	CH_2CH_3
									1.1	t	CH_3
1d	68	168-170	$C_{20}H_{20}N_2O_6S$	57.68	4.84	6.73	325 [d]	363	12.10	s [e]	OH
				57.73	4.80	6.80			10.60	s [e]	NH
									7.95-7.59	m	Ha-d
									7.50-7.45	m	C_6H_5
									3.89	c	CH_2CH_3
									3.30	t	SO_2NCH_2
									2.70	t	$SO_2NCH_2CH_2$
									1.20	t	CH_3
1e	51	198	$C_{17}H_{13}N_3O_4S$	57.46	3.69	11.82	309 [d]	250 and 350	12.60	s [e]	OH
				57.51	3.65	11.90			10.75	s [e]	NH
									8.00-7.60	m	Ha-d
									7.50-7.00	m	C_6H_5
									4.57	s	CH_2
1f	55	175	$C_{18}H_{15}N_3O_4S$	58.52	4.09	11.38	322 [d]	350	12.50	s [e]	OH
				58.34	4.15	11.32			8.10-7.45	m	Ha-d
									7.50-6.90	m	C_6H_5

Table II

Compound No.	Yield (%) [a]	Mp (°C)	Formula	Analyses (Calcd./Found)			UV in 0.1N HCl λ max (nm) [b]	in 0.1N NaOH λ max (nm) [b]	^{1}H-NMR δ (ppm)	Multiplicity	Assignment
				%C	%H	%N					
1g	77	210	$C_{19}H_{27}N_3O_4S$	57.99	6.92	10.68	238 and 314	246 and 359 [d]	4.50	s	CH_2
									2.50	s	CH_3
				57.87	7.01	10.77			12.60	s [e]	OH
									10.75	s [e]	NH
									7.90	d	Ha
									7.60-7.40	m	Hb-d
									3.90	m	CH
									3.59	t	SO_2NCH_2
									3.08	t	$SO_2NCH_2CH_2$
									1.97	s	CH_3
									1.79-1.52	m	$(CH_2)_5$
1h	79	185-188	$C_{21}H_{31}N_3O_4S$	59.83	7.42	9.97	235 and 313	240 and 354 [d]	12.60	s [e]	OH
				59.70	7.50	9.88			10.75	s [e]	NH
									7.93	d	Ha
									7.71-7.64	m	Hb-d
									3.70	m	CH
									3.24	t	SO_2NCH_2
									3.10	t	$SO_2NCH_2CH_2$
									2.88	c	CH_2CH_3
									1.82-1.53	m	$(CH_2)_5$
									1.28	t	CH_3
1i	60	142	$C_{17}H_{19}N_3O_4S$	56.50	5.30	11.63	313 [d]	240 and 340	12.80	s [e]	OH
				56.31	5.38	11.68			10.52	s [e]	NH
									8.00-7.60	m	Ha-d
									4.00	m	CH
									3.40	s	CH_2CN
									1.85-1.00	m	$(CH_2)_5$
1j	70	200-1	$C_{18}H_{27}N_3O_4S$	56.67	7.13	11.01	238 and 312	238 and 340 [d]	10.80	s [e]	OH
				56.82	7.18	10.96			9.31	s [e]	NH
									7.97	d	Ha
									7.87-7.70	m	Hb-d
									4.05	m	CH
									3.17	t	SO_2NCH_2
									2.78-3.25	m	$CH_2N(CH_2CH_3)_2$
									1.20	d	$CH(CH_3)_2$
									1.12	t	CH_2CH_3
1k	68	245	$C_{16}H_{23}N_3O_4S$	54.37	6.56	11.89	240 and 312	240 and 340 [d]	11.80	s [e]	OH
				54.31	6.71	11.78			9.41	s [e]	NH
									7.94	d	Ha
									7.67-7.60	m	Hb-d
									4.0	m	CH
									3.17	t	SO_2NCH_2
									2.70	t	$SO_2NCH_2CH_2$
									1.75	s	$N-CH_3$
									1.20	d	$CH(CH_3)_2$
1l	18	250-260 dec	$C_{18}H_{20}N_4O_4S$	55.66	5.19	14.42	242 and 339	248 and 375 [d]	12.40	s [e]	OH
				55.49	5.26	14.48			8.40-7.30	m	aromatics + NH
									3.40	t	SO_2NCH_2
									2.80	t	$SO_2NCH_2CH_2$
									1.15	t	CH_3

[a] Prepared from the corresponding 4-hydroxy-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide **2**. [b] Only bands above 230 nm were considered. [c] Prepared from 4-hydroxy-2H-1,2-benzothiazine-3-carboxylic acid ethyl ester 1,1-dioxide **3**. [d] The spectrum is very similar in alcoholic solution. Observed difference ± 5 nm. [e] Exchangeable.

Table III

^{13} C NMR Chemical Shifts (in ppm) of Compounds 1a-k [a]

Compound	C-1	C-2 and C-5	C-3 and C-4	C-6	C-7 and C-9	C-8	R and R'	R"
1a	139.2	128.0, 122.5	135.0, 133.1	130.1	168.2, 167.2	105.5	140.2 (C-1) 128.5 (C-3) 123.4 (C-4) 119.5 (C-2)	55.0, 50.0 (CH$_2$-CH$_2$) 41.4 (CH$_3$)
1b	136.0	127.5, 122.5	136.2, 132.5	130.6	168.0, 167.1	107.7	140.5 (C-1) 129.3 (C-3) 123.2 (C-4) 119.6 (C-2)	53.8, 51.8 (CH$_2$-CH$_2$) 47.7 (N-CH$_2$-CH$_3$) 9.3 (CH$_3$)
1c	138.5	127.0, 123.4	134.7, 132.0	129.0	168.5, 167.6 166.3 [b]	105.5	139.9 (C-1) 129.7 (C-3) 123.0 (C-4) 120.1 (C-2)	168.5, 167.6 or 166.3 (CO) 61.7 (CH$_2$-CH$_3$) 52.0 (CH$_2$-CO) 14.0 (CH$_3$)
1d	138.2	127.7, 123.2	135.1, 132.8	130.8	168.0, 167.3 166.5 [b]	107.5	140.9 (C-1) 128.7 (C-3) 123.6 (C-4) 119.1 (C-2)	168.0, 167.3 or 166.5 (CO) 61.6 (O-CH$_2$-CH$_2$) 44.8, 39.4 (CH$_2$-CH$_2$) [c] 14.6 (CH$_3$)
1e	136.7	126.5, 122.4	135.2, 133.5	129.5	166.6, 159.2	107.8	140.1 (C-1) 129.1 (C-3) 124.0 (C-4) 118.8 (C-2)	114.1 (CN) 38.0 (CH$_2$)
1f	136.9	127.4, 123.6	136.0, 133.1	130.2	168.8, 166.9	107.2	139.8 (C-1) 129.0 (C-3) 123.5 (C-4) 118.9 (C-2) 36.6 (CH$_3$)	114.0 (CN) 38.2 (CH$_2$)
1g	136.2	127.4, 122.6	135.6, 132.7	130.0	170.1, 168.5	105.0	48.0 (C-1) 32.6 (C-2) 25.0, 24.2 (C-3 and C-4)	54.8, 51.1 (CH$_2$-CH$_2$) 42.3 (CH$_3$)
1h	136.8	127.5, 122.9	136.0, 132.8	130.1	168.5, 165.6	107.0	48.5 (C-1) 33.2 (C-2) 25.5, 24.5 (C-3 and C-4)	53.5, 52.4 (CH$_2$-CH$_2$) 47.1 (N-CH$_2$-CH$_3$) 9.3 (CH$_3$)
1i	136.0	126.6, 123.9	133.9, 132.7	130.9	169.3, 166.8	106.8	48.6 (C-1) 32.2 (C-2) 25.2, 24.8 (C-3 and C-4)	114.2 (CN) 39.3 (CH$_2$) [c]
1j	136.2	127.1, 122.3	135.8, 132.4	129.7	168.4, 166.0	106.4	48.0 (CH) 23.2 (CH$_3$-CH)	53.2, 52.0 (CH$_2$-CH$_2$) 47.0 (N-CH$_2$-CH$_3$) 8.8 (N-CH$_2$-CH$_3$)
1k	138.1	127.0, 123.2	135.2, 132.8	130.6	168.4, 166.1	107.0	48.2 (CH) 22.8 (CH$_3$-CH)	54.8, 50.0 (CH$_2$-CH$_2$) 41.8 (CH$_3$)

[a] Assignments were made on the basis of literature data, attached proton test and fully coupled ^{13}C NMR spectra. [b] Ester carbonyl is included. [c] Overlapped with dimethyl-d$_6$ sulfoxide.

lower than 15% throughout. The main fragment ions as well as their relative intensities are given in Table IV.

Bearing in mind the ions observed in each case and literature data for related compounds [22,23], we propose the fragmentation routes indicated in Scheme II. It may be observed that fragmentation can take place with charge retention in the N-2 side chain (Route *a*), in the benzothiazine nucleus (Route *b*) or in the carboxamide moiety (Route *c*), depending on the nature of the substituents in positions 2 and 3. In the case of the dialkylaminoalkyl derivatives, regardless of the nature of the carboxamide function, the major fragmentation occurs along route *a*,

Table IV

Select Fragments in the Electron Impact Mass Spectra of Compounds **1a-l**

[m/z (% relative abundance)] [a]

m/z	1a	1b	1c	1d	1e	1f	1g	1h	1i	1j	1k	1l
M+•	387 (5.4)	415 (3.7)	402 (13.1)	416 (15.0)	355 (14.9)	369 (8.2)	393 (3.4)	421 (2.3)	361 (5.1)	381 (3.4)	353 (3.6)	388 (2.4)
[RR'NCO]+	120 (1.4)	120 (-)	120 (6.2)	120 (9.1)	120 (9.2)	134 (9.9)	126 (-)	126 (-)	126 (7.6)	86 (100)	86 (1.0)	121 (-)
[RR'NH]+•	93 (13.9)	93 (7.4)	93 (100) [c]	93 (100)	93 (100)	107 (100)	99 (2.2)	99 (11.6)	99 (5.6)[e]	59 (-)	59 (-)	94 (2.4)
169	-	-	2.8	13.5	7.5	-	-	-	20.6	-	-	1.3
117	1.0	-	5.2	4.0	-	13.2	-	-	10.3	-	1.5	-
105	5.7	3.2	31.4	30.0	88.6	28.7	-	2.7	72.9	3.2	5.2	4.0
104	4.9	1.0	15.8	52.6	10.8	12.7	3.8	1.8	32.1	2.6	4.4	3.3
86	1.4	100	4.2	-	-	-	1.5	100	4.4	100	1.0	3.5
77	8.2	5.8	29.0	59.1	41.6	57.5	-	1.6	24.7	2.6	8.3	3.5
76	3.2	2.4	10.0	53.6	13.2	25.2	-	-	38.8	1.6	6.1	2.9
66	1.7	-	1.0	10.6	5.0	3.3	-	-	-	-	-	-
65	2.4	1.3	7.9	17.9	14.0	9.5	-	2.5	-	-	-	-
58	100	9.2	2.7	2.1	1.0	-	100	7.6	4.4	11.4	100	100
51	2.7	1.9	7.9	14.8	14.0	31.6	-	-	8.7	-	4.4	-
50	1.2	-	3.6	12.8	6.8	18.1	-	-	14.6	-	3.8	-
Other ions [b]	-	-	329 (10.0) 265 (13.9) 172 (23.3) 159 (12.4) 132 (10.4)	371 (10.1) 297 (59.7) 251 (84.6) 187 (20.3) 159 (16.8) 145 (19.1) 131 (28.3) 119 (28.8) 82 (19.7)	213 (29.0) 147 (13.5)	91 (16.7) 81 (15.3) 44 (46.0) 41 (10.5)[d]	71 (26.8)	87 (12.3)	198 (52.5) 150 (24.0) 98 (24.5) 93 (22.1) 83 (91.7) 67 (18.9) 56 (31.3) 55 (100)[f] 43 (27.5) 41 (76.3)[g]	99 (11.1) 43 (10.1)	71 (22.0) 69 (13.6) 44 (50.1) 43 (51.0) 42 (36.1)	-

[a] Ions with m/z <40 are not recorded. [b] Peaks greater than 10% are included. [c] Hrms: m/z 93.0584. Calcd. for C_6H_7N: 93.0579. [d] Hrms: m/z 41.0270. Calcd. for C_2H_3N: 41.0266. [e] Hrms: m/z 99.1044. Calcd. for $C_6H_{13}N$: 99.1048. [f] Hrms: m/z 55.0554. Calcd. for C_4H_7: 55.0548. [g] Hrms: m/z 41.0397. Calcd. for C_3H_5: 41.0391.

with charge retention in the amine moiety, originating base peaks of m/z 58 (dimethylaminoalkyl derivatives **1a,g,k,l**) and m/z 86 (diethylaminoalkyl derivatives **1b,h,j**). In alkoxycarbonylalkyl **1c,d** and cyanoalkyl derivatives

Scheme II
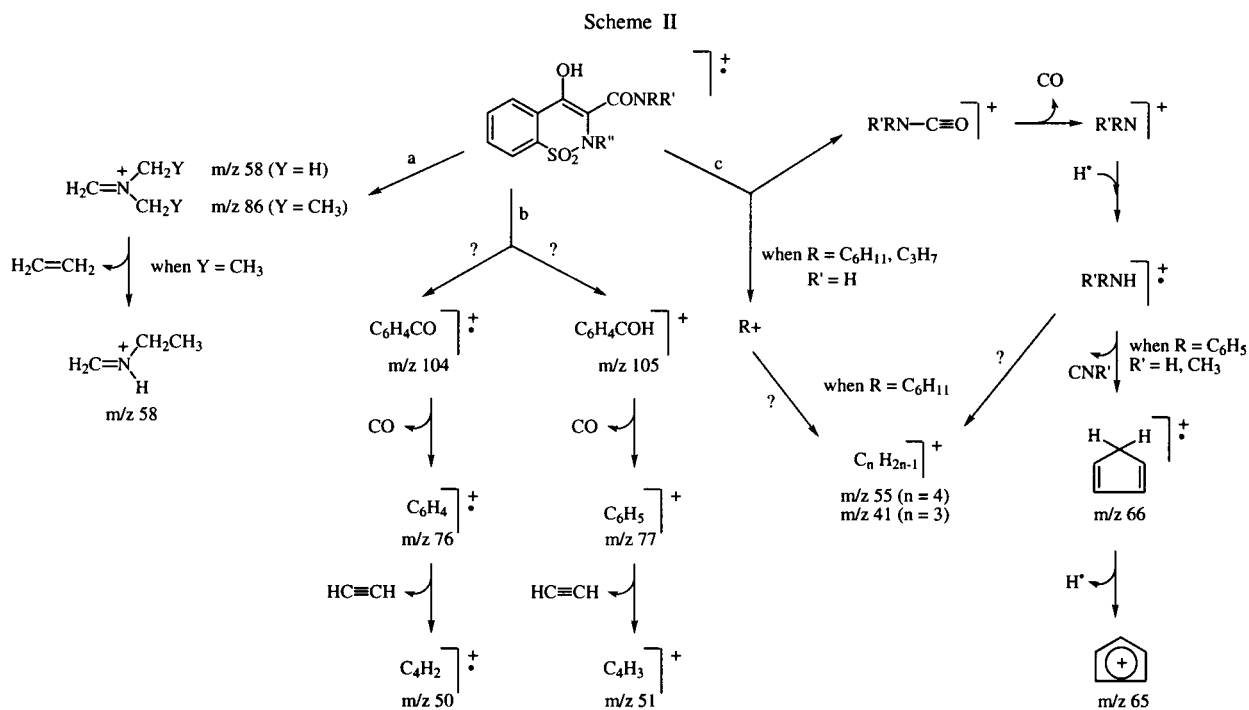
1e,f,i, the base peak results from cleavage with charge retention in the carboxamide moiety (Route *c*), corresponding to [HNRR']$^{+\bullet}$ ions in compounds **1c-f**. Thus, like in other simple anilides, the base peak of compounds **1c-e** is the m/z 93 fragment containing the elemental aniline composition (experimental exact mass 93.0584, calculated 93.0579) also accompanied by peaks of m/z 65 and 66 attributable to the cyclopentadienyl cation and its precursor [24]. The amine could originate from the stabilized [RR'NCO]$^+$ ion, resulting in turn from α-carbonyl cleavage, which is detected in variable proportions.

In the *N*-cyclohexyl derivative **1i** the base peak m/z 55 (experimental exact mass 55.0554, calculated 55.0548) corresponds to the ion [C$_4$H$_7$]$^+$. This peak and that of m/z 41 (experimental exact mass 41.0397, calculated 41.0391) belong to the homologous series of unsaturated [C$_n$H$_{2n-1}$]$^+$ ions and originate quite reasonably from the abundant cyclohexyl ion (m/z 83, 91.7%) or from that of m/z 99 ([C$_6$H$_{13}$N]$^{+\bullet}$, experimental exact mass 99.1044, calculated 99.1048). The latter ion may correspond to the cyclohexylamine or more likely to the [H$_2$N=CH-(CH$_2$)$_4$-CH$_2$]$^{+\bullet}$ ion derived from the *N*-cyclohexylcarboxamide function as a result of double α- and C-N cleavage with hydrogen rearrangement [24].

In the *N*-isopropylamide **1j**, the base peak (m/z 86) could be attributed to the ion [CONHC$_3$H$_7$]$^+$ resulting from α-carbonyl cleavage, or alternatively to the one originating from fragmentation of the N-2 side chain (Route *a*). The low intensity of such ion in compound **1k** supports the second option. Characteristically, these amides

present a fragment at m/z 43 attributed to the stabilized isopropyl ion.

Charge retention in the benzothiazine nucleus (Route *b*), which would lead to m/z 104 and 105 ion (and of derived ions at m/z 76, 77, 50 and 51), failed to predominate in dialkylaminoalkyl derivatives **1a,b,g,h,j-l**, unlike the behavior of 2-unsubstituted benzothiazines [22], where the m/z 105 ion mostly presents high relative abundance, proving base peak in some cases. Instead, in compounds **1c,d,e,f,i**, the presence of such ion is observed with relative abundance greater than 28%. In these cases molecular degradation apparently does not start with the elimination of sulfur dioxide or with the cleavage of the carboxamide originating an acylium ion, since neither [M-SO$_2$]$^{+\bullet}$, nor [M-NRR']$^+$ fragments are detected. In alkoxycarbonyl derivatives degradation may start with ester or amide fragmentation. Thus for example, compound **1d** can undergo elimination of C$_2$H$_5$O$^\bullet$ or phenyl isocyanate, giving the two important peaks at m/z 371 and 297 respectively. Subsequent fragmentation give rise peaks at m/z 251, 187, 159, 145 and 131. The loss of CNH from the last peak could originate the m/z 104 ion (Scheme III). Likewise, compound **1c** shows m/z 329, 265 and 172 fragments resulting from successive loss of C$_2$H$_5$O$^\bullet$ and carbon monoxide, sulfur dioxide and aniline.

Other ions resulting from heterocyclic nucleus degradation and described for benzothiazine-3-carboxamides [22], especially m/z 169 (A) and 117 (B) ions, fail to appear regularly. Interestingly, this latter ion attributed by Mihalic [23] to loss of the carboxamide and sulfon-

Scheme III

m/z 169

A

m/z 117

B
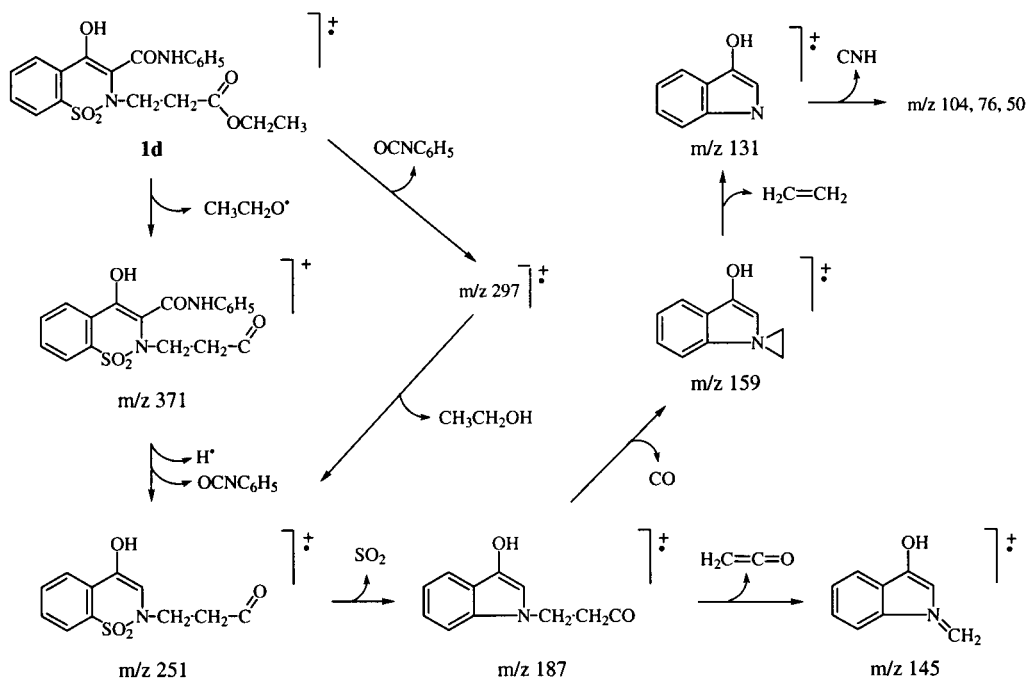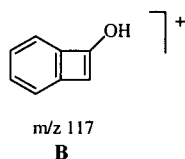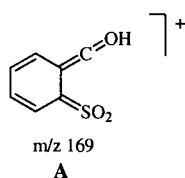
amide function, and which seemed characteristic of 2-methyl derivatives, also appears in some of the analyzed compounds.

Cyanomethyl derivatives **1e,f,i** present no characteristic peak of diagnostic value, in agreement with the features of the nitriles that frequently undergo rearrangement reactions. Neither do they present the typical ions $[M-1]^+$, $[M+1]^+$ or $[CH_2CN]^+$ (m/z 40). The m/z 41 fragment that appears in compound **1i** fails to correspond to the ion $[CH_2=C=NH]^{+\bullet}$ (C_2H_3N) that could be originated in the cyanomethyl side chain. Instead, as already stated, this peak was assigned to an isobaric fragment, $[C_3H_5]^+$, originating from N-cyclohexylcarboxamide moiety. On the other hand, the ion at m/z 41 that appears in compound **1f**, though it corresponds to the formula C_2H_3N (experimental exact mass 41.0270, calculated 41.0266), can hardly arise from the nitrile function but is rather related to the N-methylcarboxanilide moiety, since it is also a major peak in 2,N-dimethyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxanilide 1,1-dioxide [25].

The uv spectra of compounds **1c-f,i** are similar in acid medium and in methanol, showing a strong bathochromic effect in alkaline medium consistent with the formation of the enolate ion. On the other hand, in dialkylaminoalkyl derivatives **1a,b,g,h,j-l** the similarity is found between spectra in alcoholic and basic media, with a hypsochromic effect upon acidifying. This indicates the predominance of zwitterion structures for such compounds in alcoholic solution.

Due to the fact that the acidic properties of these carboxamides are closely related to their potential antiinflammatory activity [2,11], the acidity constants of compounds tested pharmacologically were determined by means of uv spectrometry measuring the extinction coefficient of the partial and totally ionized acid (Table V). Data obtained confirm that the nature of the amide is the main factor that conditions the acidity of these compounds, the N-arylcarboxamides proving more acidic than the N-alkyl derivatives [1]. Instead, the nature of the substituents on the sulfonamide nitrogen fails to modify pK_a values appreciably.

These compounds were found to be stable in dilute aqueous solutions. No decomposition was observed at pH 4-8 [26].

Pharmacological Properties.

Table V presents the results obtained in the abdominal constriction test (writhing test) with some of compounds **1**. The greatest analgesic activity was achieved with carboxanilide derivatives **1b-e**. Within this series, compounds bearing an ethoxycarbonylalkyl group, **1c,d**, proved to be roughly three times more active than 2-dialkylaminoalkyl or cyanomethyl derivatives **1b** and **1e**. Nevertheless, in all cases the ID_{50} was less than that of the 2-methyl analog **1m**, suggesting that the presence of a functional group on the alkyl substituent enhances analgesic activity. N-Cyclohexyl and N-isopropylcarboxamides **1g,k** presented a marked decrease in activity.

Table V

Analgesic Activity of Compounds 1 (Writhing Test)

Compound	ID 50 mg/kg [a]	pK_a [b]
1b	20.20 (18.00-22.40)	6.23
1c	6.07 (5.12-8.02)	6.42
1d	7.24 (6.35-8.26)	6.46
1e	17.50 (15.90-19.25)	6.55
1j	>50	6.92
1k	>50	6.97
1m [c]	27.50 (23.91-31.62)	6.70
piroxicam	0.76 (0.31-1.87)	

[a] Values in parentheses are the 95% confidence limits. [b] In water, spectrophotometric method. [c] 2-Methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxanilide 1,1-dioxide [1].

Table VI

Antiinflammatory Activity of Compounds 1 on Carrageenan Induced Paw Edema in Rat

Compound	Edema Volume (ml)	% Inhibition [a]
Control	1.19 ± 0.14	-
1b	0.28 ± 0.10 [b]	76.47
1c	0.22 ± 0.06 [b]	81.51
1d	0.21 ± 0.08 [b]	82.36
1e	0.27 ± 0.13 [b]	77.31
1j	0.55 ± 0.23 [c]	54.54
1k	0.49 ± 0.14 [c]	53.78
1m [d]	0.21 ± 0.04 [b]	82.36
piroxicam	0.17 ± 0.04 [b]	85.71

[a] Values are mean ± Standard Error of Mean (n = 5). [b] p < 0.01 compared with control values. [c] p < 0.05 compared with control values. [d] 2-Methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxanilide 1,1-dioxide [1].

The results of the antiinflammatory activity test are listed in Table VI. Again, the most active compounds proved to be the 3-carboxanilides, especially **1c,d**, with inhibition percentages similar to those obtained with compounds **1m** and piroxicam taken as references. As in the previous assay, compounds **1g,k** presented lower antiinflammatory activity, confirming the relationship between activity and acidity.

On the basis of the results achieved, it may be concluded that the presence of functional alkyl groups at the 2 position increases the antinociceptive effect in the case of rapid onset pain, as evidenced by the writhing test without modifying, comparatively to their 2-methyl analog, the slow initiation response as shown by the carrageenan test.

EXPERIMENTAL

Melting points were taking on a Büchi capillary apparatus and are uncorrected. The ¹H nmr spectra were recorded on a Bruker MSL 300 Hz. Chemical shifts are quoted in parts per million (δ) downfield from an internal tetramethylsilane 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) and m (multiplet). Mass spectra were performed on a MS Shimadzu QP-1000 instrument at 70 eV. High resolution mass spectra (hrms) were taken on a ZAB-SEQ4F mass spectrometer. Analytical tlc was carried out on aluminium sheets Silica Gel 60 F_{254}. Preparative thin layer separations were carried out by centrifugally accelerated, radial chromatography using Chromatotron model 8924. The rotors were coated with Silica Gel 60 PF_{254} and the layer thickness was 2 mm. Reagents, solvents and starting materials were purchased from standard sources and purified according to literature procedures.

Alkylation of 4-Hydroxy-2H-1,2-benzothiazine-3-carboxamide 1,1-Dioxides **2**.

General Procedure.

To a solution of the corresponding carboxamide **2** [15] (0.012 mole) in ethanol (40 ml), water (11 ml) and sodium hydroxide (0.012 mole) was added the corresponding substituted alkyl chloride or bromide (0.04 mole). The reaction mixture was stirred at room temperature and monitored by tlc (benzene-methanol, 9:1). When the reaction was completed, the resulting solid was filtered, washed with water, air dried and triturated several times with hot methanol (3 ml) affording compounds **1a-k**.

In the case of compound **1l** the reaction mixture showed several spots by tlc. Separation of the product was achieved by centrifugal tlc by a solvent system selected after trial on a qualitative tlc plate. The reaction mixture in chloroform-methanol (50:50) was applied, the rotor dried and then eluted with chloroform and increasing percentages of methanol. The second moving band eluted afforded compound **1l**.

Melting points, elemental analysis, yields and spectroscopic data of the compounds are given in tables II, III and IV.

Synthesis of **1a,b** by Alkylation and Aminolysis of 4-Hydroxy-2H-1,2-benzothiazine-3-carboxylic acid Methyl Ester 1,1-Dioxide **3**.

N-Alkylation of compound **3** [14] was carried out in the same manner as described above using dimethyl or diethylaminoethyl chloride. A suspension of the crude product in dry toluene (100 ml), aniline (0.02 mole) and p-toluenesulphonic acid (0.001 mole) was refluxed for 12 hours. Refluxing was followed by slow distillation to a final volume of 50 ml. The mixture was cooled at room temperature and the resulting solid was collected, washed with cyclohexane and purified as above.

Attempted Synthesis of 2-Diethylaminomethyl-N-methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxanilide 1,1-Dioxide (Mannich Reaction).

A mixture of **2** (R = C_6H_5, R' = CH_3) (0.03 mole), absolute ethanol (30 ml), 37% formaldehyde solution (0.04 mole) and diethylamine (0.03 mole) was refluxed with stirring. Following the reaction at different times by tlc only starting material was detected after 12 hours.

pKa Determinations.

The pKa values for compounds listed in Table V were determined by uv spectrophotometry [28] in water. Compounds were found to be stable in diluted aqueous solutions. The uv spectra of 10^{-4}-10^{-5} M solutions remain unchanged after 7 days at pH 4-8.

Analgesic Activity.

For measuring antinociceptive activity the writhing test was employed [29]. The test compound or vehicle (2% carboxymethylcelulose) were administered intraperitoneally, and 10 minutes later 0.6% acetic acid solution (10 ml/kg intraperitoneally) was injected. The number of writhes induced in each mouse was observed for a 5 minute period starting 5 minutes after injection of acetic acid. Piroxicam was used as reference drug. The analgesic activity was expresed in terms of the dose of compound that reduce control responses by 50% (ID50) [30].

Antinflammatory Activity.

Antiinflammatory activity was assessed by inhibition of edema formation in the hind paw of the rat in response to a subplantar injection of carrageenan [31]. The test compound (30 mg/kg) or vehicle (2% carboxymethylcelulose) was administered intraperitoneally 30 minutes before carrageenan injection. Piroxicam was used as reference drug. Paw edema was measured 3 hours after using a plethismometer. Differences in volume displacement were recorded and percentage edema inhibition was calculated.

Statistical Analysis.

The results are presented as mean ± Standard Error of Mean and statistical significance between groups was analyzed by means of analysis of variance followed by Dunnett's multiple comparison test. P values less than 0.05 were considered as indicative of significance. Antinociceptive potency was assesed in terms of the dose inhibiting the pain response by 50% (ID 50%), with its 95% confidence intervals as determined by the Litchfield and Wilcoxon method [30].

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