Synthesis and Antiinflammatory Activity of Some 3-Carboxamides of 2-Alkyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-Dioxide

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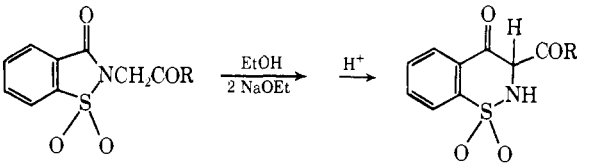
A number of 3-carboxamides of 2-alkyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxide were synthesized and their antiinflammatory activity was investigated. A procedure for isomerizing saccharin-2-acetic ester to 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylic ester 1,1-dioxide in DMSO is described. Reasons for the enhanced acidity observed for the 3-carboxamides as compared to the 3-carboxylic ester derivatives of this heterocyclic system are discussed. Most compounds were inhibitors of carrageenin-induced rat foot edema and some exceeded phenylbutazone in potency. Similar activity was also demonstrated in adrenalectomized rats. Of the 49 compounds tested, 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxanilide 1,1-dioxide proved most active with approximately twice the potency of phenylbutazone and an $ID_{50\%}$ of 37 mg/kg in the rat foot edema test.

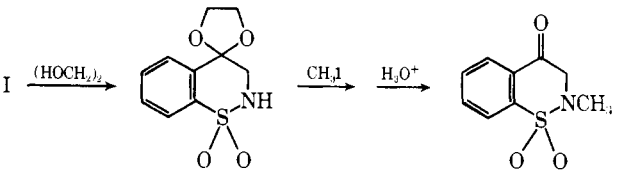
The search for more effective antiinflammatory agents has led medicinal chemists to explore a wide variety of chemical structures.[1,2] A majority of these compounds, especially those with proven clinical efficacy, are acidic, *i.e.*, carboxylic acids such as aspirin, indomethacin, and flufenamic acid, or β-diketones such as phenylbutazone. Some antiinflammatory agents have previously been found in these laboratories among acidic β-diketones, such as 2-aryl-1,3-indandiones[3] and certain β-keto amides such as 1,3-dioxoisoquinoline-4-carboxanilides[4a] and 3-oxo-1,2-benzothiazine-4-carboxamides.[4b] The pK_a's of these active classes of compounds were generally in the range of 4–6, when measured in 2:1 dioxane–H_2O. The 1,2-benzothiazin-4-(3*H*)-one 1,1-dioxide heterocyclic system has received little attention and, in view of the activity found for the aforementioned β-diketonic acids,[3,4] appeared attractive as a potential source of acidic, and possibly biologically active, compounds. This present paper reports the discovery of potent antiinflammatory activity for certain acidic β-keto carboxamides derived from this class of compounds.

Chemistry.—Comparatively little has been published on the 2*H*-1,2-benzothiazin-4(3*H*)-one 1,1-dioxide system.[5–10] Abe and coworkers[6] were the first to apply the principle of the Gabriel–Colman rearrangement of phthalimides[11a,b] to the rearrangement of *N*-phenacylsaccharin which gave 3-benzoyl-2*H*-1,2-benzothiazin-4(3*H*)-one 1,1-dioxide (Ia). Zinnes, *et al.*,[7]



Ia, R = C_6H_5
Ib, R = CH_3

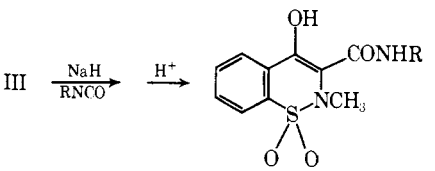
later applied these conditions to *N*-acetonylsaccharin; they obtained Ib which was then deacylated to II while undergoing conversion to an ethylene glycol ketal. After N-methylation and hydrolysis of the ketal II, the 1,2-benzothiazine III was obtained.[7] These same



II III

workers also reported the failure to condense III with esters such as EtOAc or dimethyl oxalate in the presence of base; they attributed this result to the rapid self-condensation of III. With AcCl, O-acetylation of III was observed.[7]

In our hands, III could be made to condense with aryl and alkyl isocyanates using NaH as base. However, because of the rapid self-condensation of III, the simultaneous addition of a combination of III and isocyanate to the hydride was found to be a practical technique. By this procedure, a number of previously unknown 3-carboxamides of 2-methyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxide (IV) were made (Table I). All of these amides were completely enolized as indicated by ir spectra (no C=O absorptions below 6.0 μ), positive $FeCl_3$ tests, and nmr spectra



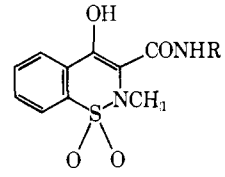
IV

(enol OH near −3τ). Variation in the substituent at the 2 position (see Table II) was achieved by alkyl-

(1) W. C. Kuzell, *Annu. Rev. Pharmacol.*, **8**, 367 (1968).
(2) T. Y. Shen in "Topics in Medicinal Chemistry," Vol. 1, J. L. Rabinowitz and R. M. Meyerson, Ed., Wiley, New York, N. Y., 1967, pp 45–64.
(3) J. G. Lombardino and E. H. Wiseman, *J. Med. Chem.*, **11**, 342 (1968).
(4) (a) S. B. Kadin and E. H. Wiseman, *Nature (London)*, **222**, 275 (1969); (b) J. G. Lombardino and E. H. Wiseman, *J. Med. Chem.*, **14**, 973 (1971).
(5) J. von Braun, *Chem. Ber.*, **56**, 2332 (1923).
(6) K. Abe, S. Yamamoto, and K. Matsui, *Yakagaku Zasshi*, **76**, 1058 (1956); *Chem. Abstr.*, **51**, 3499 (1957).
(7) H. Zinnes, R. Comes, F. Zuleski, A. Caro, and J. Shavel, Jr., *J. Org. Chem.*, **30**, 2241 (1965).
(8) (a) H. Zinnes, R. Comes, and J. Shavel, Jr., *ibid.*, **31**, 162 (1966); (b) H. Zinnes, J. Shavel, and M. S. Sternberg, U. S. Patent 3,479,436 (Nov 1969); *Chem. Abstr.*, **72**, 55476b (1970); (c) J. Shavel, Jr., and H. Zinnes, U. S. Patent 3,408,347 (1968); *Chem. Abstr.*, **70**, 68387 (1969).
(9) (a) Netherlands Application 283,525 (Jan 1965); *Chem. Abstr.*, **62**, 16262 (1965); and U. S. Patent 3,284,450 (1966); *Chem. Abstr.*, **66**, 28789 (1967); (b) C. R. Rasmussen, U. S. Patent 3,476,749 (Nov 1969); *Chem. Abstr.*, **72**, 21727 (1970); (c) T. P. Pruss, *Toxicol. Appl. Pharmacol.*, **14**, 1 (1969).
(10) (a) H. Zinnes, R. A. Comes, and J. Shavel, Jr., *J. Med. Chem.*, **10**, 223 (1967); (b) H. Zinnes, R. A. Comes, and J. Shavel, Jr., *J. Heterocycl. Chem.*, **5**, 875 (1968).
(11) (a) W. J. Gensler, *Heterocycl. Compounds*, **4**, 378 (1952); (b) J. H. M. Hill, *J. Org. Chem.*, **30**, 620 (1965).

TABLE I

3-CARBOXAMIDES OF 4-HYDROXY-2-METHYL-2*H*-1,2-BENZOTHIAZINE 1,1-DIOXIDE[a]

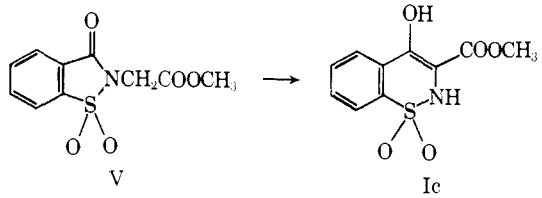


No.	R	Yield, %	Mp, °C	Crystn solvent[c]	Formula[d]
1	C_6H_5	48[b]	214–215	I	$C_{16}H_{14}N_2O_4S$
2	4-ClC_6H_4	43	230–232	E	$C_{16}H_{13}ClN_2O_4S$
3	2-$CH_3OC_6H_4$	17	179–181	I	$C_{17}H_{16}N_2O_5S$
4	2,5-$Cl_2C_6H_3$	14	223–225	E	$C_{16}H_{12}Cl_2N_2O_4S$
5	2-$CH_3OC_6H_4$	22	250–252	HAc	$C_{17}H_{16}N_2O_5S$
6	3-$CF_3C_6H_4$	29	199–201	I	$C_{17}H_{13}F_3N_2O_4S$
7	4-$CH_3C_6H_4$	26	237–239	I	$C_{17}H_{16}N_2O_4S$
8	3-ClC_6H_4	29	271–273 dec	HAc	$C_{16}H_{13}ClN_2O_4S$
9	3,4-$Cl_2C_6H_3$	17	282–284 dec	HAc	$C_{16}H_{12}Cl_2N_2O_4S$
10	2-ClC_6H_4	25	197–199	E	$C_{16}H_{13}ClN_2O_4S$
11	4-$NO_2C_6H_4$	10	282–284 dec	HAc	$C_{16}H_{13}N_3O_6S$
12	4-FC_6H_4	29	239–241	I	$C_{16}H_{13}FN_2O_4S$
13	1-Naphthyl	46	226–228	HAc	$C_{20}H_{16}N_2O_4S$
14	4-BrC_6H_4	38	234–236	E	$C_{16}H_{13}BrN_2O_4S$
15	3-$CH_3C_6H_4$	38	221–223	HAc	$C_{17}H_{16}N_2O_4S$
16	4-$EtOC_6H_4$	58	260–262	HAc	$C_{18}H_{16}N_2O_5S$
17	C_6H_{11}	42	178–179	HAc–W	$C_{16}H_{20}N_2O_4S$
18	Allyl[e]	25	128–129	E–W	$C_{13}H_{14}N_2O_4S$
19	*n*-C_4H_9	43	115–117	E–W	$C_{14}H_{18}N_2O_4S$
20	CH_3	15	180–182	W–E	$C_{11}H_{12}N_2O_4S$

[a] Prepd from the appropriate isocyanate and 2-methyl-2*H*-1,2-benzothiazin-4(3*H*)-one, 1,1-dioxide as illustrated in the Experimental Section for **1**. [b] Yields of 56% of **1** were obtd by reaction of 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylic acid methyl ester 1,1-dioxide (VI) with $PhNH_2$ by the method illustrated for **22**. [c] I, *i*-PrOH; E, EtOH; HAc, AcOH; W, H_2O. [d] Analyses for C, H, N detd for each compd. [e] Neut equiv 298 (calcd 294), pK_a = 8.4 in 2:1 dioxane–H_2O.

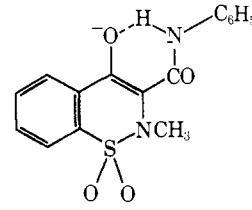
ating II with either allyl bromide or benzyl bromide followed by reaction with an isocyanate. At a later stage, catalytic debenzylation of some 2-benzyl derivatives of IV produced 2-H analogs of IV (**36–38**, Table II).

After antiinflammatory activity was demonstrated for the first compounds of type IV prepared by the above route, a more versatile approach for preparing analogs of IV was sought. To avoid the need for preparing various isocyanates, it was felt that I, R = OCH_3 (Ic), if it could be made, should react with amines to provide examples of IV. By analogy to the work of Abe[6] on *N*-phenylacylsaccharin, rearrangement in basic media of 3-oxo-1,2-benzoisothiazoline-2-acetic acid methyl ester (V) was expected to produce Ic. NaOMe was used in a variety of solvents in an effort to maximize yields of this rearrangement and it was



V Ic

eventually found that the best results were obtained in DMSO. N-Alkylation of Ic followed by reaction with amines under forcing conditions then provided the desired structural variations of IV (Table II). No useful yields of products could be realized by reaction of Ic itself with amines in a variety of solvents, even at temperatures above 150°. Even after N-alkylation of Ic, heating of the resulting ester with an amine to 130° for 18 hr in DMF or xylene was required to produce optimum yields of amides of type IV. Titration of 2-methyl-Ic (VI) indicated a pK_a of 8.4 (in 2:1 dioxane–H_2O) while a similar titration of IV, R = C_6H_5 (**1**), indicated a pK_a of 7.3. By analogy with the observations of Kadin and Wiseman[4] for some 1,3-dioxoisoquinoline-4-carboxanilides, the enhanced acidity in the carboxanilide **1** compared to the ester VI may be explained by invoking stabilization of the enolate anion (**1a**) through H bonding to the carboxanilide proton. Enhanced stabilization of anion **1a** favors its formation by ionization of a proton from **1**. Support



Ia

for this suggestion comes from the titration of N-methylated **1** (**45**), where the carboxanilide proton is absent, which indicated a pK_a of 9.8.

Pharmacology.—Antiinflammatory activity was assessed as inhibition of edema formation in the hind paw of the rat (Charles River Strain, average weight 170 g) in response to a subplantar injection of carrageenin. The experimental procedure followed that of Winter, *et al.*[12,13] Edema formation was measured 3 hr after oral administration of test drug (in aq soln) and 2 hr after carrageenin injection. Response of drug-treated animals (6 rats/group) was compared with that of animals receiving vehicle alone and animals receiving aspirin (100 mg/kg).

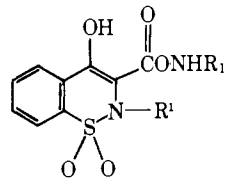
Superior antiinflammatory activity (Table III) was observed with 2-Me substitution of carboxamides of 4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxide (*e.g.*, **1–32**) compared with any other 2-substituents, *i.e.*, benzyl (**33–35**), allyl (**39, 40**), Et (**41, 42**), or Pr (**43, 44**). The 2-H analogs (**36, 37, 38**) were also somewhat less active than the corresponding 2-Me compounds. The presence of carboxanilides at the 3 position produced more active compounds than substitution by *N*-alkylcarboxamides (**46–49**) at the same position. One sample of a tertiary carboxanilide (**45**) was found to be only weakly active as compared with the corresponding secondary carboxanilide **1**. Of those carboxanilides with 2-Me substitution, the anilide without Ph ring substitution (**1**) was the most potent except for the *m*-chloroanilide **8**. Generally, meta-substituted anilides (**6, 8, 15, 24, 26**) were more potent than their corresponding para-substituted isomers (**23, 2, 7, 14**). Ortho-substitution gave variable results, with 2 compounds proving to be quite active (**3, 30**) while one (**10**) was only weakly active. It is difficult to rationalize the pattern of structure–activity relationships within the carboxanilides of 2-methyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxide (**1–32**). Neither acidities, partition coefficients, electronic, nor spatial factors can

(12) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol.*, **111**, 544 (1962).

(13) C. A. Winter, E. A. Risley, and G. W. Nuss, *J. Pharmacol. Exp. Ther.*, **141**, 369 (1963).

TABLE II

3-CARBOXAMIDES OF 4-HYDROXY-2-ALKYL-2*H*-1,2-BENZOTHIAZINE 1,1-DIOXIDE[a]



No.	R	R^1	Yield, %	Mp, °C	Crystn solvent[b]	Formula[c]
21	2,4-$Cl_2C_6H_3$	CH_3	17	258–259	HAc	$C_{16}H_{12}Cl_2N_2O_4S$
22	2,4-$(CH_3O)_2C_6H_3$	CH_3	52	193–195	HAc	$C_{18}H_{18}N_2O_6S$
23	4-$CF_3C_6H_4$[d]	CH_3	42	248–250	I	$C_{17}H_{13}F_3N_2O_4S$
24	3-BrC_6H_4	CH_3	43	273–274	HAc	$C_{16}H_{13}BrN_2O_4S$
25	5-Cl-2-$CH_3OC_6H_3$	CH_3	32	256–257	HAc	$C_{17}H_{15}ClN_2O_5S$
26	3-FC_6H_4	CH_3	52	248–250	HAc	$C_{16}H_{43}FN_2O_4S$
27	4-HOC_6H_4[d]	CH_3	12	286 dec	E-W	$C_{16}H_1N_2O_{15}S$
28	2,5-$F_2C_6H_3$	CH_3	36	205–206	HAc	$C_{16}H_{12}F_2N_2O_4S$
29	2,4-$F_2C_6H_3$	CH_3	47	211–212	E	$C_{16}H_{12}F_2N_2O_4S$
30	2-FC_6H_4	CH_3	54	183–184	E	$C_{16}H_{13}FN_2O_4S$
31	5-F-2-$CH_3C_6H_3$	CH_3	57	166–168	I	$C_{17}H_{15}FN_2O_4S$
32	3-$NO_2C_6H_4$	CH_3	41	281–282	HAc	$C_{16}H_{13}N_3O_6S$
33	C_6H_5[e]	$CH_2C_6H_5$	27	215–217	E	$C_{22}H_{18}N_2O_4S$
34	3-ClC_6H_4[e]	$CH_2C_6H_5$	29	247–249	E	$C_{22}H_{17}ClN_2O_4S$
35	3-Cl-4-$CH_3C_6H_3$	$CH_2C_6H_5$	48	233–235	A	$C_{23}H_{19}ClN_2O_4S$
36	C_6H_5[f]	H	72	253 dec	Et	$C_{15}H_{12}N_2O_4S$[g]
37	3-ClC_6H_4[f]	H	64	218 dec	E	$C_{15}H_{11}ClN_2O_4S$
38	3-Cl-4-$CH_3C_6H_3$[f]	H	34	254 dec	E	$C_{16}H_{13}ClN_2O_4S$
39	C_6H_5[h]	$CH_2CH{=}CH_2$	15	161–163	E	$C_{18}H_{16}N_2O_4S$
40	3-ClC_6H_4[h]	$CH_2CH{=}CH_2$	6	229–230	E	$C_{18}H_{15}ClN_2O_4S$
41	C_6H_5	CH_2CH_3	21	200–202	HAc	$C_{17}H_{16}N_2O_4S$
42	3-ClC_6H_4	CH_2CH_3	24	247–279	HAc	$C_{17}H_{15}ClN_2O_4S$
43	C_6H_5	$CH_2CH_2CH_3$	42	187–189	HAc	$C_{18}H_{18}N_2O_4S$
44	3-ClC_6H_4	$CH_2CH_2CH_3$	43	213–216	HAc	$C_{18}H_{17}ClN_2O_4S$
45	C_6H_5, CH_3[i,j]	CH_3	40	162–165	E	$C_{17}H_{16}N_2O_4S$
46	Cyclooctyl[j]	CH_3	53	193–195	HAc	$C_{18}H_{24}N_2O_4S$
47	$C_6H_5CH_2$[j,l]	CH_3	49	193–195	HAc	$C_{17}H_{16}N_2O_4S$
48	1-Piperidino[j]	CH_3	33	209–213		$C_{15}H_{19}N_3O_4S$
49	$C_6H_5CH_2CH_2$[j,k]	CH_3	42	124–126	HAc	$C_{18}H_{18}N_2O_4S$

[a] All compds, except as noted, were prepd from combination of the appropriate amine and corresponding 2-substituted-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylic acid methyl ester 1,1-dioxide in DMF as illustrated in the Experimental Section for **22**, **35**, and **42**. [b] HAc, AcOH; I, *i*-PrOH; E, EtOH; W, H_2O; A, MeCN; Et, Et_2O. [c] Analyses detd for C, H, N for each compd. [d] For **23**, neut equiv 392 (calc 398), pK_a = 6.4; for **27** neut equiv 347 (calc 346), pK_a = 7.4, both in 2:1 dioxane-H_2O. [e] Prepd from 2-benzyl-2*H*-1,2-benzothiazin-4(3*H*)-one 1,1-dioxide and the corresponding aryl isocyanate by a procedure similar to that used to prep **1**. [f] Prepd by catalytic debenzylation of the appropriate 2-benzyl analog (**34**, **35**, or **36**) as exemplified in the Experimental Section for **37**. [g] No combustion anal. data are available for this compd but a mass spectral analysis showed a parent ion at mass 316 (calcd 316) and major ions at mass 252, 159, 147, 119, 105, 104, 94, 93, 77, 76. [h] Prepd from 2-allyl-2*H*-1,2-benzothiazin-4(3*H*)-one 1,1-dioxide and an aryl isocyanate as illustrated for **39**. [i] A tertiary carboxamide prepd from *N*-methylaniline as illustrated in the Experimental Section. [j] Prepd from 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylic acid methyl ester 1,1-dioxide (VI) and the corresponding amine in xylene as illustrated for **45**. [k] Required only 4-hr reflux in xylene. [l] Neut equiv 344 (calcd 344), pK_a = 8.6 in 2:1 dioxane-H_2O.

explain the variations in activity seen between isomers such as **6** and **23**, or **2** and **8**, or **7** and **15**.

The antiinflammatory activity of the clinically useful drugs indomethacin and phenylbutazone has been shown not to depend on activation of the adrenal gland.[13,14] In our studies, the antiedema activity of the more potent representatives of the carboxanilides was examined in adrenalectomized rats. Bilateral adrenalectomy was performed through a retroperitoneal incision, while the rats were under light Et_2O anesthesia. Animals were maintained on a normal diet with 0.9% saline in place of drinking water, and were used 5–7 days after the operation. The antiedema activity of **1**, **3**, and **8** was essentially the same in intact or adrenalectomized rats. Thus, like indomethacin and phenylbutazone, the antiinflammatory activity of these agents is not mediated through adrenal stimulation.

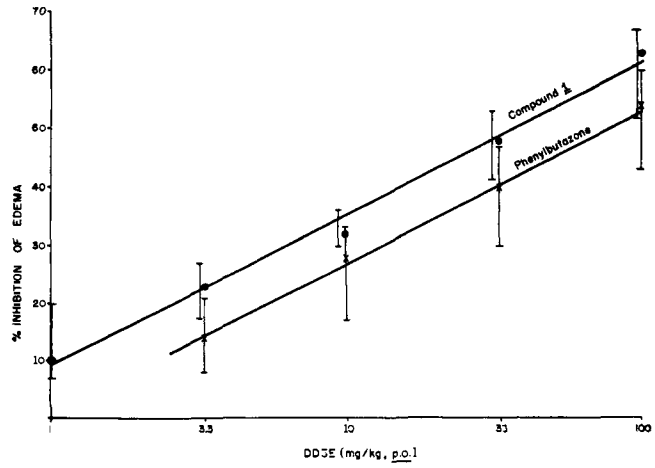


Figure 1.—Dose-response comparison of **1** with phenylbutazone in the rat foot edema test (6 animals per point).

(14) R. Domenjoz, *Ann. N. Y. Acad. Sci.*, **86**, 263 (1960).

TABLE III

ANTIINFLAMMATORY ACTIVITY OF *N*-SUBSTITUTED-2-ALKYL-4-HYDROXY-2*H*-1,2-BENZOTHIAZINE-3-CARBOXAMIDE 1,1-DIOXIDES

No.	Activity[a]	No.	Activity
1	++++[b]	26	++
2	++	27	−
3	+++[b]	28	++
4	+	29	++
5	++	30	+++
6	+++	31	++
7	+	32	++
8	++++[b]	33	++
9	+	34	−
10	+	35	−
11	−	36	++
12	++	37	++
13	++	38	++
14	−	39	*c*
15	+++	40	*c*
16	−	41	+
17	*c*	42	−
18	++	43	+
19	+	44	−
20	−	45	+
21	−	46	−
22	−	47	−
23	−	48	−
24	++	49	−
25	++	Phenylbutazone	+++

[a] Antiinflammatory activity is reported as a mean inhibition of edema in the treated animals (6 rats/group) within the range of 0.5–1.5 times that of the mean inhibition of concurrently treated animals receiving aspirin (100 mg/kg po); +, drug given at 100 mg/kg; ++, drug given at 33 mg/kg; +++, drug given at 10 mg/kg; ++++, drug given at 3.3 mg/kg po. Compounds with antiinflammatory activity (at 100 mg/kg) of less than 0.5 times aspirin are reported as −; these compounds, however, still exhibit low levels of inhibition of edema in this test. [b] Similar results were obtained with these compounds in both adrenalectomized and nonadrenalectomized rats dosed at 33 mg/kg po. [c] Inactive at 33 mg/kg but not tested at 100 mg/kg.

Dose–response regression lines for the antiedema activity of **1** and phenylbutazone were parallel (Figure 1) and indicated that the potency of **1** was 2.1 times that of phenylbutazone with an ID_{50} for **1** of 37 mg/kg. Compd **1** has an extended plasma half-life in the rat (6 hr), monkey (4.5 hr), dog (30 hr), and man (21 hr); in man, the major metabolite is the 4′-OH compound **27**.[15]

Experimental Section[16]

All of the required aryl isocyanates and substituted anilines were commercially available and were used as received.

4-Hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxanilide 1,1-Dioxide (1).—In a 3-necked flask under dry N_2, 0.58 g (0.012 mole) of 50% NaH in mineral oil was triturated with dry hexane. After decanting the hexane and adding 15 ml of dry DMF, a soln consisting of 2.5 g (0.012 mole) of 2-methyl-2*H*-1,2-benzothiazin-4(3*H*)-one 1,1-dioxide[7] (III) and 1.44 g (0.012 mole) of phenyl isocyanate in 20 ml of DMF was added very slowly. After complete addn and 15 min of stirring at room temp, the red soln was poured into 100 ml of cold 3 *N* HCl to produce a pale yellow solid. Filtration and recrystn from *i*-PrOH gave 1.9 g (48%) of 1: mp 213–215°; ir (KBr) indicated the enol form, 2.95 (NH), 6.08, 6.21, 6.46 μ; nmr ($DCCl_3$) τ −3.44 (s, 1, exchanges in D_2O, enol OH), 1.67 (broad, 1, NH, exchanges in D_2O), 1.82–3.0 (m, 9, arom protons), 7.13 (s, 3, NCH_3); titration (2:1 dioxane–H_2O) with 0.5 *N* NaOH gave neut equiv 325 (calcd 330) and pK_a = 7.3. A test sample in MeOH gave a dark red color when a $FeCl_3$ soln was added. Analytical data are included in Table I.

2′,4′-Dimethoxy-4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxanilide 1,1-Dioxide (22).—A combination of 4.3 g (0.016 mole) of 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylic acid methyl ester 1,1-dioxide (VI), 4.9 g (0.032 mole) of 2,4-dimethoxyaniline, 100 ml of dry DMF, and a few mg of *p*-TsOH was placed under N_2 and heated at 130° for 18 hr. On pouring into 500 ml of 3 *N* HCl, a brown ppt was formed which was recrystd from HOAc: yield 3.2 g (52%) of **22**; mp 193–195° (see Table II).

2-Benzyl-3′-chloro-4′-methyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxanilide 1,1-Dioxide (35).—Heating 7.0 g (0.020 mole) of 2-benzyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylic acid methyl ester 1,1-dioxide, 5.7 g (0.040 mole) of 3-chloro-4-methylaniline, and a few mg of *p*-TsOH in 100 ml of dry DMF at 130° for 18 hr gave a deep red soln. After pouring into 500 ml of 3 *N* HCl the resulting yellow solid was recrystd from MeCN to yield 4.4 g (48%) of **35**, mp 233–235° (see Table II).

3′-Chloro-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxanilide 1,1-Dioxide (37).—A suspension of 1.5 g (0.003 mole) of **34** and 1.0 g of 10% Pd/C in 200 ml of 2:1 $CHCl_3$–MeOH was shaken under 2.8 kg/cm^2 of hydrogen. After 2 hr an additional 1 g of Pd was added, and shaking was continued for another 2 hr. Filtration and evapn of the filtrate gave 0.77 g (64%) of **37**, mp 218°. A test sample gave a deep red-brown color in MeOH when some 5% $FeCl_3$ was added (see Table II).

2-Allyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxanilide 1,1-Dioxide (39).—After washing 0.96 g (0.020 mole) of 50% NaH in mineral oil with dry hexane, and decanting the hexane, 15 ml of dry DMF was added. To the resulting gray suspension was added a soln of 4.1 g (0.018 mole) of 2-allyl-2*H*-1,2-benzothiazin-4(3*H*)-one 1,1-dioxide and 2.4 g (0.020 mole) of phenyl isocyanate in 40 ml of DMF. After stirring for 20 min at room temp, the red-brown soln was poured into 160 ml of 3 *N* HCl from which a solid slowly crystd. Filtration and recrystn from EtOH gave 0.90 g (15%) of **39**, mp 161–163° (see Table II).

3′-Chloro-2-ethyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxanilide 1,1-Dioxide (42).—A soln of 2.5 g (0.009 mole) of 2-ethyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylic acid methyl ester 1,1-dioxide and 2.3 g (0.018 mole) of *m*-chloroaniline in 25 ml of DMF was placed under N_2 and heated at 130° for 20 hr. After pouring into 200 ml of 6 *N* HCl, filtration and recrystn from HOAc gave 0.810 g (24%) of **42**, mp 247–249° (see Table II).

4-Hydroxy-2*H*-1,2-benzothiazine-3-carboxylic Acid Methyl Ester 1,1-Dioxide (Ic).—To a suspension of 4.2 g (0.078 mole) of $NaOCH_3$ in 40 ml of dry DMSO was added 10 g (0.039 mole) of 3-oxo-1,2-benzoisothiazoline-2-acetic acid methyl ester 1,1-dioxide[17] in 1 portion with rapid stirring. Color changes from yellow to orange to red were seen as the temp was maintd near 30° by periodic immersions in an ice–water bath. After 4 min, the deep red soln was poured into 100 ml of 3 *N* HCl and extd 3 times with $CHCl_3$. After drying ($CaSO_4$) and evapn, the residue was recrystd from EtOH to give the desired ester: 3.8 g (38%); mp 168–171°. A second recrystn (EtOH) gave mp 172.5–173.5°. A sample in MeOH soln gave a wine-red color with 5% $FeCl_3$: ir (KBr) indicated the enol form, 3.09 (NH), 6.01, 6.20, 6.40 μ; mass spectrum showed a parent peak at mass 255 while titration in 2:1 dioxane–H_2O indicated neut equiv 255 (calcd 255) and pK_a = 7.9; nmr (Cl_3COCD_3) τ −1.64 (s, 1, exchanges in D_2O, enol OH), 1.4 (broad, 1, NH, exchanges in D_2O), 1.8–2.3 (m, 4, aromatic protons), 6.09 (s, 3, OCH_3). *Anal.* ($C_{10}H_9NO_5S$) C, H, N.

These reaction condns were found to be quite critical. Variable yields were obtd in DMF as solvent while MeOH as solvent failed to produce any detectable product. On scale-up to a 9.7-mole scale the following modifications were found to be practical:

(15) J. Chiaini, E. H. Wiseman, and J. G. Lombardino, *J. Med. Chem.*, **14**, 1175 (1971).

(16) Melting points were determined in a Thomas-Hoover capillary melting point apparatus using a calibrated thermometer and are uncorrected. Potentiometric titrations were carried out in 2:1 dioxane–H_2O (v/v) solvent using a Beckman Model G pH meter and standard 0.5 *N* NaOH; the apparent pK_a values correspond to the pH values at the half-neutralization point in these titrations. Ir spectra were determined in KBr pellets. Analyses were carried out by the Physical Measurements Laboratory of Pfizer, Inc. Where analyses are indicated only by symbols of the elements, anal. results obtained for those elements were within ±0.4% of the theoretical values. A Varian A-60 spectrometer was used to measure nmr spectra (Me_4Si), and mass spectra were determined on a Hitachi Perkin-Elmer Model RMU-6E.

(17) H. Eckenroth and G. Koerppen, *Chem. Ber.*, **30**, 1265 (1897).

to the starting ester in DMSO, a slurry of $NaOCH_3$ in DMSO was added with stirring over a 1-hr period while maintaining the temp below 30°. After complete addn and 15 min of addl stirring, acidification (excess 3 *N* HCl), filtration, and recrystn (IPO) gave a 59% yield of the desired ester Ic.

2-Methyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylic Acid Methyl Ester 1,1-Dioxide (VI).—A yellow soln resulted from a combination of 2.95 g (0.012 mole) of 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylic acid methyl ester 1,1-dioxide, 2.4 ml of MeI, 11 ml of H_2O, 40 ml of EtOH, and 12 ml of 1 *N* NaOH. After standing at room temp for 18 hr the resulting heavy yellow ppt was filtered, washed with H_2O, and dried to give 2.4 g (78%) of VI, mp 162–165°. A sample in MeOH soln gave a wine-red color with 5% $FeCl_3$. Titration in 2:1 dioxane–H_2O indicated neut equiv 266 (calcd 269) and pK_a = 8.4; nmr ($DCCl_3$) τ −2.04 (s, 1, exchanges with D_2O, enol OH), 1.8–2.4 (m, 4, arom protons), 6.05 (s, 3, OCH_3), 7.06 (s, 3, NCH_3). *Anal.* ($C_{11}H_{11}NO_5S$) C, H, N.

By an analogous alkylating procedure using either EtI, PrI, allyl bromide, or benzyl bromide the corresponding 2-alkyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylic acid methyl ester 1,1-dioxides were made (see Table IV).

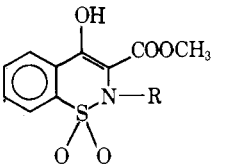
2-Benzyl- and 2-Allyl-2*H*-1,2-benzothiazin-4(3*H*)-one 1,1-Dioxides.—The 2-step procedure employed for prepg these compds is essentially the same as that reported by Zinnes,[8] *et al.*, for the 2-Me analog. Alkylation of 2*H*-1,2-benzothiazin-4(3*H*)-one 1,1-dioxide ethylene ketal[8] (II) with benzyl bromide gave a 75% yield of **2-benzyl-2*H*-1,2-benzothiazin-4(3*H*)-one 1,1-dioxide ethylene ketal**, mp 83–86°. *Anal.* ($C_{17}H_{17}NO_4S$) C, H, N. Hydrolysis[8] of this ketal gave 88% yield of **2-benzyl-2*H*-1,2-benzothiazine-4(3*H*)-one 1,1-dioxide**, mp 123–126°. *Anal.* ($C_{15}H_{13}NO_3S$) C, H, N.

Alkylation of 2*H*-1,2-benzothiazin-4(3*H*)-one 1,1-dioxide ethylene ketal[8] (II) with allyl bromide gave a 88% yield of **2-allyl-2*H*-1,2-benzothiazin-4(3*H*)-one 1,1-dioxide ethyl eneketal**, mp 75–77°. *Anal.* ($C_{13}H_{15}NO_4S$) C, H, N. Hydrolysis[8] of this ketal gave a 78% yield of **2-allyl-2*H*-1,2-benzothiazin-4(3*H*)-one 1,1-dioxide** as a viscous liquid which was purified by column chromatog (silica gel G, E. Merck, A. G., eluted with $CHCl_3$). A sample was vacuum distd for analysis. *Anal.* ($C_{11}H_{11}NO_3S$) C, H, N.

2,*N*-Dimethyl-4-hydroxy-2*H*-1,2-benzothiazin-3-carboxanilide 1,1-Dioxide (45).—A yellow soln of 4.0 g (0.015 mole) of VI and 1.8 g (0.017 mole) of *N*-methylaniline in 300 ml of xylene was placed under N_2 and refluxed for 22 hr. Distn of solvent to a final vol of 30 ml and cooling gave a yellow solid which, after recrystn from EtOH yielded 2.1 g (40%) of **45**: mp 162–165°; a $FeCl_3$ test was positive (red); ir (enol form) 6.0, 6.20, 6.26 μ; titration in 2:1 dioxane–H_2O indicated neut equiv 354 (calcd 344) and pK_a = 9.8; nmr (DMSO-d_6) τ 1.92–2.31 (m, 4, aromatic protons), 2.64 (s, 5, C_6H_5), 6.65 [s, 3 $CH_3(C_6H_5)N$], 7.60 (s, 3, the 2-CH_3).

TABLE IV

2-ALKYL-4-HYDROXY-2*H*-1,2-BENZOTHIAZINE-3-CARBOXYLIC ACID METHYL ESTER 1,1-DIOXIDES



R	Yield, %	Mp, °C	Crystn solvent[a]	Formula[b]
Et	35	97–100	E–W	$C_{12}H_{13}NO_5S \cdot 0.5H_2O$
Pr	21	125–127	E–W	$C_{13}H_{15}NO_5S \cdot 0.5H_2O$
$CH_2CH{=}CH_2$	62	97–100	E–W	$C_{13}H_{13}NO_5S$
$CH_2C_6H_5$	64	157–159	E	$C_{17}H_{15}NO_5S$

[a] See footnote *c* of Table I. [b] Satisfactory analyses for C, H, N were obtained for all of these compds.

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Excretion and Metabolism of a Nonsteroidal Antiinflammatory Agent, 4-Hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxanilide 1,1-Dioxide, in Rat, Dog, Monkey, and Man

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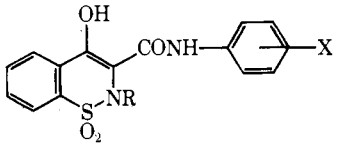
The nonsteroidal antiinflammatory agent, 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxanilide 1,1-dioxide has a plasma half-life of 6 hr in the rat, 30 hr in the dog, 4.5 hr in the monkey, and 21 hr in man. The principle metabolite in man, monkey, and rat, formed by hydroxylation of the carboxanilide moiety, is excreted in the urine as an acid-labile conjugate. The dog eliminates the drug in the urine mainly as a water-soluble conjugate of the parent drug.

4-Hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxanilide 1,1-dioxide (I) is a member of a series of potent antiinflammatory 1,2-benzothiazine-3-carboxanilides.[1] This paper is an account of pharmacokinetic and metabolic studies with I in man, monkey, dog, and rat.



I, R = CH_3; X = H
II, R = CH_3; X = OH
III, R = [^{14}C]CH_3; X = OH
IV, R = H; X = H

Experimental Section

Pharmacokinetic and metabolism studies were carried out in male albino rats (Charles River), mongrel dogs, and rhesus monkeys, maintained in metabolism cages with free access to

(1) J. G. Lombardino, E. H. Wiseman, and W. M. McLamore, *J. Med. Chem.*, **14**, 1171 (1971).