from EtOH–H_2O gave 92.2 g of pure **35**, mp 120–121.5°, $[\alpha]^{25}D$ −89° (*c* 1.04, $CHCl_3$).

4-(*p*-Hydroxyphenyl)-1-naphthaleneacetic Acid (21). A solution of 4.4 g (0.015 mol) of 4-(*p*-methoxyphenyl)-1-naphthaleneacetic acid (**20**) in 50 ml of AcOH was treated with 25 ml of 47% HI and heated at reflux for 4 hr. After standing overnight, the product was filtered off. Recrystallization from EtOAc–cyclohexane gave pure **21**.

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Potent Antiinflammatory N-Heterocyclic 3-Carboxamides of 4-Hydroxy-2-methyl-2*H*-1,2-benzothiazine 1,1-Dioxide

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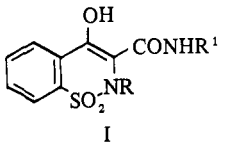
N-Heterocyclic 3-carboxamides of 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine 1,1-dioxide have been found to possess antiinflammatory activity in the carrageenan-induced rat paw edema test, with potencies up to three times that of indomethacin. Adrenalectomy does not affect the antiinflammatory test results. An internally hydrogen bonded enolate anion is suggested as a possible explanation for the greatly enhanced acidity of these enolic carboxamides. Selected potent analogs also exhibit extended plasma half-lives in four species of laboratory animals and 4-hydroxy-2-methyl-*N*-(2-thiazolyl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide, compound **1** (sudoxicam), is presently undergoing clinical trials.

A previous publication[1] from these laboratories reported the antiinflammatory activity of some *N*-aryl- and *N*-alkylcarboxamides I derived from 2-alkyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide. These compounds generally exhibited potencies one to two times that of phenylbutazone in suppressing carrageenan-induced edema in the rat paw[1] and pK_a values (measured in 2:1 dioxane–H_2O) in the range 6.4–8.6, depending on the substitution on the carboxamide function.[1] When a few N-heterocyclic carboxamide derivatives were made of this same ring system, two dramatic differences from the corresponding *N*-aryl carboxamides became apparent: (a) pK_a values were approximately 2–4 units lower and (b) the antiinflammatory potency was as much as seven times greater than the most active *N*-arylcarboxamides. This report deals with 26 N-heterocyclic carboxamides derived from 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide with special attention given to certain physical properties and biological activity of these compounds.



I

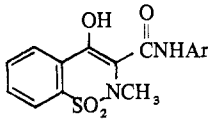
Since 2-methyl substitution (I, R = CH_3) had previously been found to produce optimal antiinflammatory activity,[1] the N-heterocyclic carboxamides were made from 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylic acid methyl ester 1,1-dioxide[1] using the appropriate amino heterocycles in refluxing xylene solution. This method is illustrated in the Experimental Section for compound **1** (I, R = CH_3; R^1 = 2-thiazolyl).[2] (For a preliminary communication on compound **1**, sudoxicam, see ref 2a.) After this work was completed, a U. S. patent[3a] and publication[3b] by Zinnes, *et al.*, appeared claiming related compounds (*e.g.*, I, R = CH_3; R^1 = 2-furyl) as weak or inactive antiinflammatory agents.†

The N-heterocyclic carboxamides described in the present study were generally more acidic than the *N*-aryl- and *N*-alkylcarboxamides derived from the same 1,2-benzothiazine system and previously reported.[1] Table I compares the acidities of various carboxamides of 4-hydroxy-1,2-benzothiazine 1,1-dioxide with the acidities of the amines from which they are derived. Acidity constants (pK_a) for the amines are literature values determined in H_2O; in our hands, most of these weakly basic amines failed to titrate to a discernible end point using HCl in 2:1 dioxane–H_2O.

Table I reveals the following: (a) although the conjugate acid of aniline is a stronger acid (*i.e.*, aniline is a weaker base) than the conjugate acid of 2-aminothiazole, the carboxamide **1** is a much stronger acid (100 times) than the carboxanilide **27**; (b) although 2-aminopyrimidinium ion is a much stronger acid than 2-aminothiazolinium ion, the corresponding carboxamides **1** and **12** do not differ very much in acidity. Thus, the enhanced acidities of the carboxamides cannot be attributed solely to inductive effects of the N-heterocyclic

†The N-heterocyclic amides reported by Zinnes, *et al.*,[3b] were inactive or weakly active and might lead one to conclude that, contrary to our findings, heterocyclic amides of I are not very effective antiinflammatory agents. This conclusion, shown to be erroneous by the present report and from data in ref 2a and 2b, possibly was a result of Zinnes, *et al.*, reporting only on amides of I not previously revealed in ref 2a or 2b.

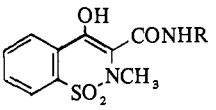
Table I. Comparison of Apparent pK_a of Carboxamides and Corresponding Amines



Carboxamides			$ArNH_3^+$ Amines	
Ar	Compd no.	pK_a[a]		pK_a[b] in H_2O
2-Thiazolyl	1	5.3	2-Aminothiazole	5.4
2-Benzothiazolyl	7	5.0	2-Aminobenzothiazole	4.5
2-Pyrimidinyl	12	5.4	2-Aminopyrimidine	3.5
2-Pyridyl	15	6.3	2-Aminopyridine	6.9
Phenyl[c]	27	7.3	Aniline	4.6
4-$CF_3C_6H_4$[c]	28	6.4	4-CF_3-aniline	2.6[d]

[a]Determined in 2:1 dioxane–H_2O using NaOH as titrant. [b]Values from A. Albert, R. Goldacre, and J. Phillips, *J. Chem. Soc.*, 2240 (1948); determined in H_2O using HCl as titrant. [c]See ref 1. [d]"Handbook of Organic Structural Analysis," Y. Yukawa, Ed., W. A. Benjamin, New York, N. Y., 1965, p 595.

Table II. N-Heterocyclic 3-Carboxamides of 4-Hydroxy-2-methyl-2*H*-1,2-benzothiazine 1,1-Dioxide[a]



Compd no.	R	Yield, %	Mp, °C	Crystn solvent[b]	Formula[c]	pK_a[d]	Anti-inflammatory activity[e]
1	2-Thiazolyl	78	256 dec	X	$C_{13}H_{11}N_3O_4S_2$	5.3	6+[f]
2	4-Methyl-2-thiazolyl	72	252 dec	X	$C_{14}H_{13}N_3O_4S_2$	5.7	5+
3	4-Phenyl-2-thiazolyl	71	283 dec	X[g]	$C_{19}H_{15}N_3O_4S_2$		2+
4	4,5-Dimethyl-2-thiazolyl	87	234 dec	X	$C_{15}H_{15}N_3O_4S_2$	5.8	5+
5	1,2,4-Triazol-3-yl	40	275 dec	A	$C_{12}H_{11}N_5O_4S$		+
6	5-Phenyl-1,2,4-triazol-3-yl	72	277 dec	M	$C_{18}H_{15}N_5O_4S$		+
7	2-Benzothiazolyl	62	237 dec	M	$C_{17}H_{13}N_3O_4S_2$	5.0	5+
8	6-Methyl-2-benzothiazolyl	73	257 dec	M[g]	$C_{18}H_{15}N_3O_4S_2$		+
9	6-Bromo-2-benzothiazolyl	69	305 dec	X[g]	$C_{17}H_{13}BrN_3O_4S_2$		+
10	5-Methyl-1,3,4-thiadiazolyl	66	276 dec	M[g]	$C_{13}H_{12}N_4O_4S_2$	4.6	+
11	2-Pyrazinyl	27	258 dec	C	$C_{14}H_{12}N_4O_4S$	*h*	4+
12	2-Pyrimidinyl	20	135 dec	C	$C_{14}H_{12}N_4O_4S_2 \cdot 0.5CHCl_3$	5.4	+
13	6-Methoxy-3-pyridazinyl	43	237 dec	M	$C_{15}H_{14}N_4O_5S$	5.9	4+
14	1,2,4-Triazin-3-yl	18	201 dec	E[g]	$C_{13}H_{11}N_5O_4S$		2+
15	2-Pyridyl	45	198–200	M	$C_{15}H_{13}N_3O_4S$	6.3	5+
16	3-Hydroxy-2-pyridyl	37	265 dec	M	$C_{15}H_{13}N_3O_5S$		2+
17	5-Bromo-2-pyridyl	87	267 dec	X[g]	$C_{15}H_{12}BrN_3O_4S$	*h*	4+
18	5-Chloro-2-pyridyl	48	263 dec	B[g]	$C_{15}H_{12}ClN_3O_4S$		3+
19	3-Methyl-2-pyridyl	68	278 dec	X[g]	$C_{16}H_{15}N_3O_4S$	*h*	–
20	4-Methyl-2-pyridyl	79	245 dec	E[g]	$C_{16}H_{15}N_3O_4S$	6.6	3+
21	5-Methyl-2-pyridyl·HCl	49	236 dec	M–I[g]	$C_{16}H_{15}N_3O_4S \cdot HCl$	*h*	3+
22	6-Methyl-2-pyridyl	62	189–191	X	$C_{16}H_{15}N_3O_4S$	6.6	6+[f]
23	4,6-Dimethyl-2-pyridyl	28	198 dec	E[g]	$C_{17}H_{17}N_3O_4S$	6.7	+
24	3-Pyridyl·HCl	26	243 dec	M–I[g]	$C_{15}H_{14}N_3O_4S \cdot HCl$	6.3, 2.8	2+
25	4-Pyridyl·HCl	7	254 dec	M–HCl	$C_{15}H_{13}N_3O_4S \cdot HCl$	*h*	2+
26	2-Quinolyl	57	227 dec	X	$C_{19}H_{15}N_3O_4S$	*h*	+
27	Phenyl	*i*				7.3	4+
28	4-$CF_3C_6H_4$	*i*				6.4	–
	Indomethacin					7.0	5+
	Phenylbutazone					6.1	3+

[a]Except as noted, all compounds reported in this table were prepared by reaction of a heterocyclic amine with 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylic acid methyl ester 1,1-dioxide[1] as illustrated in the Experimental Section for 1. [b]X = xylene; A = acetic acid; M = methanol; C = chloroform; B = benzene; I = 2-propanol; E = ethanol. [c]Satisfactory analyses (C, H, N) were obtained for all of these compounds. [d]Titrated in 2:1 dioxane–H_2O with sodium hydroxide. A blank space indicates the pK_a values were not determined. [e]Antiinflammatory activity is reported as a mean inhibition of edema in the treated animals 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; 2+, drug given at 33 mg/kg; 3+, drug given at 10 mg/kg; 4+, drug given at 3.3 mg/kg; 5+, drug given at 1.0 mg/kg; 6+, drug given at 0.3 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. Compounds 1, 2, 15, and 22, chosen as representatives, all exhibited antiinflammatory activity (at 33 mg/kg) in adrenalectomized rats. [f]Dose–response comparisons of 1 and 22 with indomethacin in the rat foot edema test gave parallel straight lines indicating potencies of three times (ID_{50} = 3 mg/kg) and 1.8 times indomethacin, respectively. [g]Small amounts of unreacted heterocyclic amine were completely removed from the product by trituration successively with 3 *N* HCl and H_2O followed by recrystallization from the solvents indicated. [h]Insoluble in 2:1 dioxane–water. [i]See ref 1 for this compound.

ring. There must, however, be some contribution due to inductive effects since the 4-CF_3-carboxanilide **28** is a stronger acid than the carboxanilide **27**.

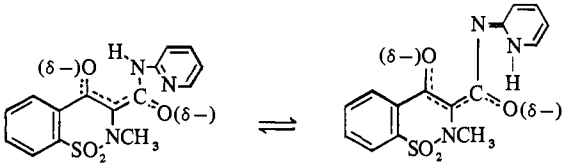
To explain an acidity enhancing effect observed earlier for carboxanilides in this series, a contribution from a structure such as A [illustrated for the *N*-(2-pyridyl)carboxamide] to stabilization of the enolate anion has previously been postulated.[1] The suggestion has also been made[2] that, in addition

Table III. Physiochemical Properties and Plasma Half-Lives of Selected N-Heterocyclic Carboxamides of 4-Hydroxy-2-methyl-2*H*-1,2-benzothiazine 1,1-Dioxide

Compd no.	Partition coefficient[a]	pK_a[b]	Plasma half-life, hr			
			Rabbit	Dog	Rat	Monkey
1	0.5	5.3	3.5	60.0	13.0	8.0
2	1.3	5.7	4.0	42.0	5.4	
4	4.8	5.8	2.8	53.0	3.7	
15	1.8	6.3	4.5	37.0	5.8	
22	4.0	6.6	1.3	12.0	3.6	6.0
Indomethacin	0.3	7.0		0.3[c]	4.0[c]	0.3[c]

[a]Determined by equilibrating at 25°; solutions of drug in pH 7.4 buffer with an equal volume of octanol. [b]Determined in 2:1 dioxane-H_2O using NaOH as titrant. [c]H. B. Hucker, A. G. Zacchei, S. V. Cox, D. A. Brodie, and N. H. R. Cantwell, *J. Pharmacol. Exp. Ther.*, 153, 237 (1966).

to A, some contributions from the tautomeric structure B may further stabilize the enolate anion in the present series of N-heterocyclic carboxamides. Such stabilization of the enolate ion would result in an increased acidity for the conjugate acid. Table II presents additional pK_a values as well as other physical data on carboxamides prepared in this work.



A B

Discussion

Table II summarizes the antiinflammatory activity and acidity constants for the title compounds. Compounds **1**, **2**, **4**, **7**, **15**, and **22** displayed antiinflammatory activity equal to or greater than that of indomethacin. Acidities of active analogs ranged from pK_a = 4.6 (compound **10**) to 6.7 (compound **23**). However, the carboxanilide **28**, despite a pK_a of 6.4, was not very active suggesting that some properties other than pK_a, and as yet unknown, are necessary for antiinflammatory activity in these compounds. The antiinflammatory activity is not mediated through activation of the adrenals; compounds **1**, **2**, **15**, and **22**, chosen as representatives, all retained antiedema activity when tested in adrenalectomized animals.

The more potent antiinflammatory compounds in this study also possessed extended half-lives in laboratory animals (Table III). Of the analogs studied in this series, compound **1** (sudoxicam), which displays antiinflammatory activity in many models of inflammation,[4] is three times more potent than indomethacin in a dose-response comparison in the rat paw edema test and has the longest plasma half-life in almost all species studied. Compound **1** was also well tolerated in laboratory animals in extended safety evaluation studies and is presently under clinical investigation.

Experimental Section‡

Pharmacology. Antiinflammatory activity was assessed by inhibition of edema formation in the hind paw of the rat (Charles River Strain, six rats per group, average weight 170 g) in response to a subplantar injection of carrageenan. The experimental procedure followed that of Winter, *et al.*[5] Edema formation was measured 3 hr after oral administration of test drug (in weakly basic NaOH solution), and the response of drug-treated animals was compared with that of animals receiving vehicle alone and animals receiving aspirin (100 mg/kg).

Bilateral adrenalectomy was performed through a retroperitoneal incision, while the rats were maintained 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 postoperatively.

Drug plasma half-life in laboratory animals was determined after intravenous administration of drug solution (10 mg/kg). In the rat, the drug was injected into the tail vein; groups of three animals were sacrificed at each of six time intervals. The drug was injected into the cephalic vein of each of five dogs and five monkeys and the marginal ear vein of each of three rabbits. Blood samples for analysis of drug concentrations were drawn from the abdominal aorta of rats maintained under pentobarbital anesthesia, from the jugular vein of dogs and monkeys, and from the marginal ear vein of rabbits. Plasma samples were stored at 4° until assayed. A specific modification of a common assay procedure was developed for each compound. In outline, the sample (2 ml) was acidified with 1 *N* HCl (0.5 ml) and extracted by shaking with the appropriate solvent. The layers were separated by centrifugation, and an aliquot of the organic layer was extracted with pH 9.0 $NaHCO_3$–Na_2CO_3 (0.1 *M*) buffer (5 ml). The optical density of the aqueous phase was determined at the appropriate wavelengths in a Beckman Model DU spectrophotometer. The assay for each compound was calibrated by carrying samples of known concentration through the entire assay. The solvents and absorbance wavelengths for each compound are shown in Table IV.

Table IV. Assay Procedures for N-Heterocyclic Carboxamides of 4-Hydroxy-2-methyl-2*H*-1,2-benzothiazine 1,1-Dioxide in Biological Fluids

Compd	Extraction solvent		Aliquot, ml	Absorbance maxima, mμ
	Identity	Vol, ml		
1	Ethylene dichloride	10	8	270, 360
2	Ethylene dichloride	10	8	270, 360
4	Ethylene dichloride	10	8	270, 360
15	Ethylene dichloride	10	8	250, 350
22	*n*-Heptane[a]	5	4	290, 355

[a]Containing 1.5% (v/v) isoamyl alcohol.

Chemistry. Heterocyclic amines were purchased from the Aldrich Chemical Co. and used as received. All of the carboxamides in Table II were prepared by combining the appropriate ester and a heterocyclic amine according to the procedure illustrated below for **1**.

N-(2-Thiazolyl)-4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxide (1). A suspension of 2.0 g (0.0075 mol) of 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylic acid methyl ester 1,1-dioxide[1] and 0.90 g (0.009 mol) of 2-aminothiazole in 200 ml of dry xylene was flushed thoroughly with a stream of N_2. At reflux, the yellow solution was periodically reduced in volume and solvent replaced as needed. Refluxing overnight was followed by slow distillation to a final volume of 75 ml. Cooling and filtration gave 1.8 g (78%) of **1**, mp 248° dec. Recrystallization from either xylene or DMA–MeOH gave analytically pure material, mp 256° dec.

‡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 at 25°. 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, analytical results obtained for those elements were within ±0.4% of the theoretical values. A Varian A-60 spectrometer (Me_4Si) was used to measure nmr spectra and mass spectra were determined on a Hitachi Perkin-Elmer Model RMU-6E.

See Table II for analytical data. Ir (KBr) indicated the enol form: 3.2–3.6 (broad), 6.10, 6.20, 6.35, 6.50, 7.35, 8.44 μ; nmr (DMSO-d_6) τ 7.12 (s, 3, NCH_3), 2.80 and 2.40 (d, J = 4.5 cps, 1 each, thiazole protons), 1.9–2.2 (m, 4, aromatic protons), a broad, weak peak from −2.0 to −0.6 (2, the enol OH and the NH, exchanges D_2O); mass spectrum parent ion m/e 337 (calcd 337) with major ions of m/e 273, 173, 174, 145, 144, 117, 104, and 100. A sample of 1 gave a deep red-brown color with 5% $FeCl_3$ reagent. A very stable hemichloroform solvate of 1 was isolated when chloroform was used on one occasion to recrystallize 1. Infrared spectra obtained on all compounds in Table II indicated the enol form in every case. All of the compounds gave a deep red color with dilute $FeCl_3$ solution.

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Effects of a Series of New Synthetic High Polymers on Cancer Metastases†

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Sixteen new synthetic high polymers were studied for a possible effect on the dissemination of cancer cells from Sarcoma 180 implanted intracerebrally (ic). The efficacy in reducing the formation of lung metastases form Lewis lung carcinoma implanted intramuscularly (im) and of lymphnodal metastases from Ehrlich carcinoma implanted intratibially (it) was also determined after treatment with the polymeric substances. Some compounds tested showed almost the same activity, in the same experimental conditions, of several well-known antitumor agents, such as, for instance, cyclophosphamide and Triton WR 1339. The structure of most of the polymers is such that they may show simultaneously both cationic and tensioactive properties. The structure–activity relationship is discussed and a suggestion is made concerning the properties of polymers which should be taken into account when designing new macromolecular drugs with a potential antimetastatic activity.

A considerable amount of information is available concerning the importance of the cell membrane in affecting the various aspects of cancer cell kinetics, such as motility, invasion of normal tissue, vascular and lymphatic dissemination, and metastases formation.[1-4] Consequently, any possible physicochemical and biochemical interaction of the cancer cell membrane with foreign compounds may be regarded as a possible method for controlling cancer growth and dissemination. To this end high polymers may prove to be of particular interest. Polyfunctional polymers, in fact, are expected to have a stronger overall power of interaction with the cell membrane than small molecules of similar structure. This power of interaction may be due to a synergistic effect of many functional groups, either of the same kind or chemically different, attached to the same macromolecular backbone. Recent results from this[5,6] and other laboratories[7-9] seem to be encouraging in pursuing this approach. Several high polymers were tested in the present study for their possible effect on cancer dissemination and metastases.

Chemistry. The polymers tested, which are listed in the Table I, have cationic properties and most of them contain both hydrophilic and lipophilic groups. They may be grouped into three classes: G_1–G_{12} are poly(amide amine) polymers; G_{13} and G_{14} are acrylamide-type polymers; and finally G_{15} and G_{16} are *N*-oxide polymers.

The poly(amide amine) polymers were prepared by hydrogen-transfer polyaddition of suitable primary or secondary amines to a bisacrylamide. In this kind of polyaddition, linear polymers can be obtained with primary monoamines or secondary bisamines. This reaction was extensively studied during a research on the synthesis of *tert*-amino polymers,[10] and it was found to proceed very smoothly, in aqueous or alcoholic solution, without catalysts, according to the general eq 1 and 2.

$$x\mathrm{CH_2{=}CHC(O)NR^1R^2NC(O)CH{=}CH_2} + x\mathrm{HNR^3R^4NH} \rightarrow \left[\mathrm{-CH_2CH_2C(O)NR^1R^2NC(O)CH_2CH_2NR^3R^4N-}\right]_x \quad (1)$$

$$x\mathrm{CH_2{=}CHC(O)NR^1R^2NC(O)CH{=}CH_2} + x\mathrm{H_2NR^3} \rightarrow \left[\mathrm{CH_2CH_2C(O)NR^1R^2NC(O)CH_2CH_2NR^3N-}\right]_x \quad (2)$$

In the resulting polymers, amide and amine bonds regularly alternate along the main chain. In a previous investigation[10-12] it was found that the reactivity of the amines toward polyaddition of bisacrylamides is mainly dependent from the steric hindrance on the α carbon, provided their basicity is not too different.

On this ground, the reactivities of the amines employed in the synthesis of the poly(amide amines) listed in the Table I cannot be expected to be very different. Hence, in the case of copolymeric products, such as are the polymers G_1 and G_{12}, no rule may be expected to exist in the distribution of the different amine units among themselves, possibly with the only exception of G_4. In all cases, however, amide and amine

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