treated with 3 *N* MeOH-HCl (0.5 ml) to afford 30 (306 mg, 40%), mp 140.5–142.5°. *Anal.* ($C_{16}H_{21}NO_3 \cdot HCl$) C, H, N, Cl.

Acknowledgment. The authors wish to thank Miss Diane Miekle for chemical syntheses, Dr. R. C. Millonig and his associates for the biological data, Dr. A. I. Cohen and Dr. M. Puar for the nmr spectra, Dr. P. Funke for the mass spectra, and Mr. J. Alicino and his staff for microanalyses.

References

(1) (a) A. Burger, C. S. Davis, H. Greene, D. H. Tedeschi, and C. L. Zirkle, *J. Med. Chem.*, 4, 571 (1961); (b) C. L. Zirkle, C. Kaiser, D. H. Tedeschi, R. E. Tedeschi, and A. Burger, *ibid.*, 5, 1265 (1962); (c) R. A. Pages and A. Burger, *ibid.*, 9, 766 (1966).
(2) (a) S. S. Adams, E. E. Cliffe, B. Lessel, and J. S. Nicholsen, *J. Pharm. Sci.*, 56, 1686 (1967); (b) *Nature (London)*, 200, 271 (1963).
(3) E. D. Morgan, *Tetrahedron*, 23, 1735 (1967).
(4) (a) W. G. Close, *J. Amer. Chem. Soc.*, 79, 1455 (1957); (b) P. A. J. Janssen, Belgium Patent 577,977 (1959); *Chem. Abstr.*, 54, 4629 (1960); (c) P. A. J. Janssen, U. S. Patent 2,997,472 (1961); *Chem. Abstr.*, 56, 11,603 (1962).
(5) W. G. Kenyon, E. M. Kaiser, and C. R. Hauser, *J. Org. Chem.*, 30, 2937 (1965).
(6) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, 111, 544 (1962).

4- and 5-Aryl-1-naphthaleneacetic Acids as Antiinflammatory Agents

James S. Kaltenbronn

Chemistry Department, Research and Development Division, Parke, Davis and Company, Ann Arbor, Michigan 48106.
Received November 1, 1972

A series of 4- and 5-aryl-1-naphthaleneacetic acids has been prepared and its antiinflammatory activity investigated. Among its 29 members are several which are among the most potent compounds yet reported. As measured by the anti-uv-erythema test, the most potent compound is 4-phenyl-1-naphthaleneacetic acid (**8**) with a potency 62 times that of phenylbutazone. Measured by the cotton-pellet antigranulation test, the most potent compound is (+)-α-methyl-5-phenyl-1-naphthaleneacetic acid (**34**), whose potency is 46 times that of phenylbutazone.

Among the reports of compounds exhibiting antiinflammatory activity which have appeared in recent years,[1] a number describe compounds which belong to the general class of arylacetic acids. Our own research in this area has led to the synthesis of a series of 4- and 5-aryl-1-naphthaleneacetic acids which exhibit this activity. As measured by the anti-uv-erythema test,[2] the potency of several members is among the highest yet reported.[3]

Chemistry. The compounds were prepared according to Scheme I. When 4- or 5-methyl-1-tetralone (**1b,c**) was the starting point of the sequence, the side chain was eventually functionalized using NBS. When 1-tetralone (**1a**) was the starting point, a functionalized side chain was eventually added *via* the chloromethylation technique. Chloromethylation of 1-arylnaphthalenes containing aryl groups which are not highly activated leads to substitution in the 4 position of the naphthalene nucleus and thus can be used only to prepare 4-aryl-1-naphthaleneacetic acids. This technique was also necessary in those cases where the aryl group bore an alkyl substituent which would compete in the subsequent NBS reaction.

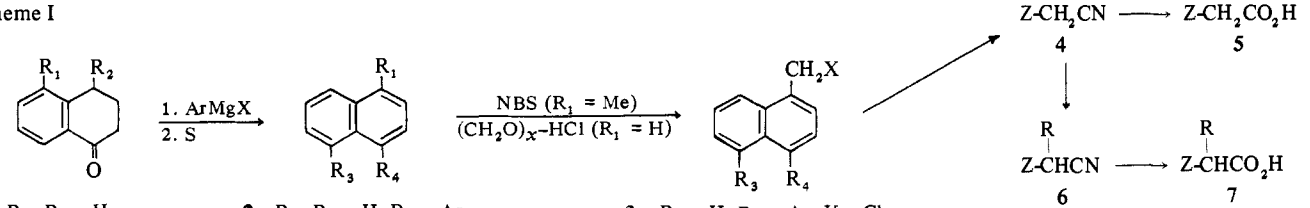
In those cases where the nitrile was to be alkylated, the nitrile was purified, either by recrystallization or by chromatography on neutral alumina. Since unalkylated material proved to be difficult to separate from monoalkylated products, the alkylation was carried out using a 15% excess of NaH, ensuring that no unalkylated material was present. Subsequent basic hydrolysis proceeded only as far as the amide stage with any dialkylated material, enabling an easy separation from monoalkylated acid. However, when the α-alkyl group became large, an acid hydrolysis became necessary (compounds **27** and **28**).

The position of chloromethylation was proven to be as depicted in Scheme I in two cases (compounds **8** and **13**). These compounds were prepared both by the chloromethylation procedure and by the NBS method starting from 4-methyl-1-tetralone (**1b**), a method which leads to an unambiguous structural assignment. The respective products obtained by both methods were identical. By analogy the other compounds prepared by the chloromethylation technique (compounds **17–19**) are presumed to have the 4-aryl-1-naphthaleneacetic acid structure.

In preparing the *o*-fluorophenyl derivatives from 1-bromo-2-fluorobenzene, it was necessary to use low-temperature lithium exchange to prevent extensive benzyne formation.[4,5]

Pharmacology. Compounds were screened for their ability to suppress the erythema developing in albino guinea pig skin 2 hr after a standard exposure to ultraviolet irradiation using Winder's modification[2] of Wilhelmi's method.[6] All agents were administered by gavage to depilated guinea pigs. Responses to treatment on an all-or-non basis were compared for test drug ($N = 5$) and the phenylbutazone reference dose ($N = 10$) or vehicle ($N = 10$). The significance of treatment contrasts was determined by reference to tables of ready-computed probabilities.[7] Com-

Scheme I



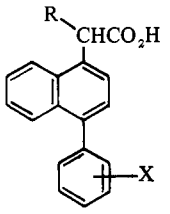
1a, R_1, R_2 = H
b, R_1 = H; R_2 = Me
c, R_1 = Me; R_2 = H

2a, R_1, R_3 = H; R_4 = Ar
b, R_1 = Me; R_3 = H; R_4 = Ar
c, R_1 = Me; R_3 = Ar; R_4 = H

3a, R_3 = H; R_4 = Ar; X = Cl
b, R_3 = H; R_4 = Ar; X = Br
c, R_3 = Ar; R_4 = H; X = Br

Z = the 4- or 5-aryl-1-naphthyl group
R = alkyl

Table I. 4-Aryl-1-naphthaleneacetic Acids



Compd no.	X	R	Relative potency[a] (95% confidence limits)	Mp,[b] °C	Recrystn solvent[c]	Formula	Analyses[d]
8	H	H	62 (45-90)	120.5-121.5	A	$C_{18}H_{14}O_2$	C, H
9	*o*-F	H	29 (16-45)	131-133[e]	C	$C_{22}H_{24}O_4NF$[e]	C, H, N
10	*m*-F	H	22 (12-63)	145.5-146.5	A	$C_{18}H_{13}FO_2$	C, H
11	*p*-F	H	3.3	162-163.5	A	$C_{18}H_{13}FO_2$	C, H
12	*o*-Cl	H	26 (17-43)	(171) 184.5-186[f]	A	$C_{18}H_{13}ClO_2$	C, H, Cl[g]
13	*m*-Cl	H	9.4 (4.9-21)	146-148	A	$C_{18}H_{13}ClO_2$	C, H, Cl
14	*m*-Br	H	0.8	162.5-163.5	A	$C_{18}H_{13}BrO_2$	C, H, Br[h]
15	*m*-CF_3	H	0.05	141.5-142.5	A	$C_{19}H_{13}F_3O_2$	C, H
16	*m*-OCH_3	H	0.4	116.5-118.5	A	$C_{19}H_{16}O_3$	C, H
17	*m*-CH_3	H	1.7	124-125.5	B	$C_{19}H_{16}O_2$	C, H
18	*m*-C_2H_5	H	0.2	110-111	A	$C_{20}H_{18}O_2$	C, H
19	*p*-CH_3	H	0.1	149-150.5	A	$C_{19}H_{16}O_2$	C, H
20	*p*-OCH_3	H	0.2	151-152	A	$C_{19}H_{16}O_3$	C, H
21	*p*-OH	H	0.2	250-254 eff	D	$C_{18}H_{14}O_3$	C, H[i]
22	2,3-di-Cl	H	1.7	154.5-157	A	$C_{18}H_{12}Cl_2O_2$	C, H, Cl
23	3,5-di-Cl	H	0.1	156-157	A	$C_{18}H_{12}Cl_2O_2$	C, H, Cl
24	H	CH_3	13 (6.4-29)	123-125	B	$C_{19}H_{16}O_2$	C, H
25	H	C_2H_5	9.3 (5.1-19)	143.5-144.5	B	$C_{20}H_{18}O_2$	C, H
26	H	*n*-C_3H_7	17 (8.7-49)	140-142	B	$C_{21}H_{20}O_2$	C, H
27	H	*n*-C_4H_9	1.7	133-133.5	B	$C_{22}H_{22}O_2$	C, H
28	H	*n*-C_5H_{11}	0.2	89-90	B	$C_{23}H_{24}O_2$	C, H

[a] Values are obtained from formal quantitative bioassays, except those for compounds **11**, **14-23**, **27**, and **28** which are preliminary screening estimates. Phenylbutazone = 1. [b] Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. [c] A = PhH-hexane; B = EtOH-H_2O; C = PhH; D = EtOAc-cyclohexane; E = acetone-hexane; F = acetonitrile. [d] Analyses of the elements indicated were within ±0.3% of the calculated values except where indicated. [e] Isolated as the diethanolamine salt. [f] Exhibits polymorphism at the melting point. [g] Calcd: C, 72.85; H, 4.42; Cl, 11.95. Found: C, 72.25; H, 4.55; Hal, 12.39. When preparing the Grignard from *o*-chlorobromobenzene, a small amount of the *o*-bromo Grignard forms, giving a small per cent of *o*-bromo derivative which is difficult to remove. The halogen determination was estimated to be Cl, 10.74; Br, 1.65. [h] Br: calcd, 23.43; found, 22.85. [i] H: calcd, 5.07; found, 5.40.

pounds significantly more active than vehicle ($0.05 > p$) were then tested at one-half the previous dose until a dose was reached where the response was significantly less than that of the reference level of phenylbutazone ($0.05 > p$).

Compounds considered suitable for further testing were then assessed by the anti-uv-erythema method in a formal quantitative bioassay employing overall randomization of treatment. Proportions of animals failing to develop erythema, as related to dosage, were subjected to standard probit analysis[8] with appropriate consideration of erythema failures with vehicle. This quantitative assay employed 40 animals per dose level of test compound, 40 animals per dose level of phenylbutazone, and 120 animals receiving vehicle.

Compounds of further interest were then subjected to the cotton-pellet granulation assay of Meier[9] as modified by Winder and coworkers.[10] This test normally employed 18 rats per dose level of test compound, 18 rats per dose level of phenylbutazone, and 54 rats receiving vehicle. Drug or vehicle was administered by gavage daily for 7 days. Complete analysis of variance provided the estimation of antigranulation potency relative to phenylbutazone and the 95% confidence limits of the potency estimate.

Discussion

From Tables I and II it can be seen that the most potent compounds with an unalkylated side chain are those with an unsubstituted phenyl ring (**8** and **29**). Fluorine with its small size can be present at any position in the phenyl ring and still maintain high potency (**9-11**, **30**, **31**). A large substituent in the meta or para position appears to have an unfavorable influence on potency.

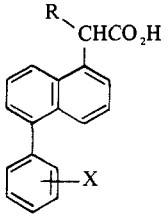
When the side chain is substituted with alkyl groups through butyl, good potency is maintained (**24-27**, **30**, **33**, **36**) in the anti-uv-erythema test; however, these compounds are less potent than the unsubstituted ones. With α-pentyl (**28**) the potency falls below that of phenylbutazone. Resolution of α-methyl-5-phenyl-1-naphthaleneacetic acid (**33**) showed that most of the antiinflammatory activity resided in the dextro rotating enantiomer **34**.

Table III compares the relative potencies of several compounds in the anti-uv-erythema test (in guinea pigs) and the cotton-pellet antigranulation test (in rats). It can be seen that in several cases a dramatic fall in potency accompanies the species change in test animal. This fall off in potency is circumvented by α substitution, especially in the *dl* (**33**) and *d*-α-methyl-5-phenyl-1-naphthaleneacetic acid (**34**) cases.

Experimental Section

Aryldihydronaphthalene. To a Grignard solution prepared from 24.5 g (1.02 g-atoms) of Mg and 1.02 mol of the substituted bromobenzene in 400 ml of Et_2O was added dropwise a solution of 0.973 mol of the tetralone (**1**) in 400 ml of Et_2O. After refluxing for 2 hr, the solution was decomposed with dilute HCl and worked up in the usual fashion. The crude product was then taken up in 300 ml of Ac_2O and heated at reflux for 1 hr. The Ac_2O was removed under reduced pressure; the residue was taken up in Et_2O and washed several times with saturated $NaHCO_3$. Concentration of the Et_2O solution left the crude dihydronaphthalene.

Table II. 5-Aryl-1-naphthaleneacetic Acids



Compd no.	X	R	Relative potency[a] (95% confidence limits)	Mp, °C[b]	Recrystn solvent[c]	Formula	Analyses[d]
29	H	H	43 (26-68)	180-182	A	$C_{18}H_{14}O_2$	C, H
30	*o*-F	CH_3	9.6 (5.3-23)	178.5-180.5[e]	C	$C_{23}H_{26}O_4NF$[e]	C, H, N
31	*m*-F	H	20 (12-34)	127.5-128.5	A	$C_{18}H_{13}FO_2$	C, H, F
32	*o*-Cl	H	15 (9.4-23)	203-205	F	$C_{18}H_{13}ClO_2$	C, H, Cl[f]
33	H	CH_3	12 (7.4-21)	137.5-138	B	$C_{19}H_{16}O_2$	C, H
34	H	*d*-CH_3	30 (15-90)	121-122	B	$C_{19}H_{16}O_2$	C, H
35	H	*l*-CH_3	1.3 (0.75-2.1)	120-121.5	B	$C_{19}H_{16}O_2$	C, H
36	H	C_2H_5	9.0 (5.4-16)	173-175	B	$C_{20}H_{18}O_2$	C, H

[a-e]See footnotes in Table I. [f]Calcd Cl, 11.95; found Hal, 12.89. Estimate Cl 9.75, Br 3.14. See footnote *g*, Table I.

Table III. Potency Comparisons by Test Method

Compd	Anti-uv-erythema[a]	Antigranulation[b] (95% confidence limits)
8	62	0.6 (0.24-1.2)
24	13	2 (0.24-4.3)
29	43	3.9 (2.0-7.7)
31	20	≤1
33	12	18 (11-36)
34	30	46 (26-115)
35	1.3	0.58 (0.32-0.93)
36	9	1.8 (0.0003-7.7)

[a]In guinea pigs. Values repeated from Tables I and II. [b]Values are obtained from formal comparative bioassays in rats utilizing the cotton-pellet antigranulation test. Phenylbutazone = 1.

If ir evidence showed the presence of starting tetralone, the oil was taken up in 500 ml of absolute EtOH and 60 ml of AcOH, and 60 g of Girard's T reagent was added. After refluxing for 0.5 hr, 500 ml of ethylene glycol was added and the EtOH removed under reduced pressure. The ethylene glycol solution was extracted twice with Et_2O and the Et_2O was washed with saturated $NaHCO_3$. Concentration of the Et_2O solution left the crude dihydronaphthalene.

(*o*-Fluorophenyl)dihydronaphthalene. To 500 ml of Et_2O under N_2 was added 215 ml (0.358 mol) of *n*-BuLi (15% in heptane, Foote Mineral Co.) and the solution was cooled to −75°. To this was added dropwise 62.6 g (0.358 mol) of 1-bromo-2-fluorobenzene, keeping the temperature at −75°. This was followed immediately by 0.358 mol of the tetralone 1 keeping the temperature at −75°. After an additional 15 min at −75°, the mixture was allowed to warm to room temperature overnight. Work-up as in the previous example gave the crude dihydronaphthalene.

Arylnaphthalene (2). A mixture of 0.78 mol of the dihydronaphthalene with 25.6 g (0.8 g-atom) of sulfur was heated at 203-216° for 1 hr. The mixture was then diluted with C_6H_6 and passed through a column of Woelm basic alumina. The residue from removal of the C_6H_6 was purified by distillation or recrystallization.

1-(Bromomethyl)arylnaphthalene (3b,c). A solution of 0.557 mol of **2b,c** was dissolved in 1 l. of CCl_4 and 100 g (0.56 mol) of NBS added together with 0.7 g of dibenzoyl peroxide. The mixture was heated at reflux while irradiating with a floodlight for 6-15 hr. The succinimide was then filtered off and the filtrate extracted twice with 5% NaOH and then with H_2O. Concentration of the crude CCl_4 solution left the crude **3b,c**.

1-(Chloromethyl)-4-arylnaphthalene (3a). A mixture of 0.8 mol of **2a**, 44.5 g (1.48 mol) of paraformaldehyde, 165 ml of AcOH, 185 ml of concentrated HCl, and 89 ml of H_3PO_4 was heated at 89° with stirring for 20 hr. An additional 25 ml of concentrated HCl was added after 4 hr. The mixture was poured into H_2O and extracted with $CHCl_3$. Work-up in the usual manner gave crude **3a** which was purified by distillation or recrystallization.

Aryl-1-naphthaleneacetonitrile (4). A solution of 0.488 mol of **3** in 350 ml of Me_2CO and 350 ml of EtOH was treated with 24.5 g (0.5 mol) of NaCN in 175 ml of H_2O and heated at reflux 4 hr. Work-up in the usual manner left crude **4**.

Crude **4** was used in the hydrolysis step. If it was to be used in α-alkylation experiments, it was purified by recrystallization or by chromatography on neutral alumina followed by recrystallization.

Aryl-1-naphthaleneacetic Acid (5). A solution of 0.49 mol of **4** in 800 ml of EtOH was treated with 100 g (1.78 mol) of KOH in 200 ml of H_2O and heated at reflux overnight. The solvent was removed under reduced pressure and the residue taken up in H_2O and washed with Et_2O. Acidification with dilute HCl gave the crude **5**. It could be purified by recrystallization or by chromatography on silica gel followed by recrystallization.

α-Alkylaryl-1-naphthaleneacetonitrile (6). A suspension of 1.1 g (0.0237 mol, a 15% excess) of NaH–mineral oil (51.6%) in 10 ml of DMSO under N_2 was treated dropwise with a solution of 0.0206 mol of **4** in 15 ml of DMSO and stirred at room temperature for 4 hr. The alkyl halide (0.05 mol) was then added with cooling to keep the temperature at 25°. After stirring for 2 hr, an additional 2 ml of alkyl halide was added and the solution allowed to stir overnight. The reaction mixture was decomposed with dilute AcOH and extracted twice with Et_2O. After washing with saturated $NaHCO_3$, the Et_2O solution was processed in the usual manner to give crude **6**.

α-Alkylaryl-1-naphthaleneacetic Acid (7). Basic Hydrolysis. The same procedure was followed as for the unalkylated nitrile **4**. Work-up separates neutral dialkylated amide from monoalkylated acid.

α-Alkylaryl-1-naphthaleneacetic Acid (7). Acid Hydrolysis (Compounds 27 and 28). A solution of 20 ml of AcOH, 8 ml of H_2SO_4, and 8 ml of H_2O was treated with 0.013 mol of **6** and heated at reflux for 5 hr. The mixture was poured into H_2O and extracted with Et_2O, and the Et_2O extracted twice with 2.5% NaOH. Acidification with dilute HCl gave the crude **7** which was purified by recrystallization.

***d*-α-Methyl-5-phenyl-1 naphthaleneacetic Acid (34).** A solution of 68.4 g (0.248 mol) of α-methyl-5 phenyl-1-naphthaleneacetic acid (**33**) in 600 ml of warm EtOAc was treated with 30.0 g (0.248 mol) of *l*-α-methylbenzylamine in 60 ml of EtOAc and 50 ml of MeOH. The solution was thoroughly mixed and after seeding and scratching to induce crystallization left standing for 2 days at 2° (All salt recrystallizations were left for 2 days at 2° and were occasionally swirled.) Three recrystallizations from EtOAc–MeOH (6:4) gave 37.3 g of the amine salt. The salt was suspended in Et_2O and washed twice with 5% HCl and then H_2O. Work-up in the usual manner gave the crude **34** as an oil. Recrystallization from EtOH–H_2O (1:1) gave 24.1 g of a white solid, mp 121-122°, $[\alpha]^{25}D$ +84.5° (*c* 1.1, $CHCl_3$).

***l*-α-Methyl-5-phenyl-1-naphthaleneacetic Acid (35).** A solution of 200 g (0.725 mol) of enriched *l*-acid, $[\alpha]^{25}D$ −75°, from the *d*-isomer resolution in 7 l. of EtOAc was treated with a solution of 87.5 g (0.725 mol) of *d*-α-methylbenzylamine in 4 l. of MeOH, swirled, and seeded. After standing for 2 days at 2° the salt was collected and the acid regenerated in the usual way. Recrystallization

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**.

Acknowledgments. We thank Tae O. Rhee, Margaret Devenish, and Mary Ann Dickinson for able technical assistance and Dr. C. V. Winder, Joan Wax, and associates of these laboratories for the antiinflammatory testing. We extend our gratitude to Dr. J. M. Vandenbelt and associates for the spectral determinations and to Mr. C. E. Childs and coworkers for the microanalyses. Thanks are also due Dr. Frank Short for helpful discussions during the progress of this work.

References

(1) P. F. Juby and T. W. Hudyma, *Annu. Rep. Med. Chem.*, 7, 208 (1972), and previous papers in this series.
(2) C. V. Winder, J. Wax, V. Burr, M. Been, and C. E. Rosiere, *Arch. Int. Pharmacodyn. Ther.*, 116, 261 (1958).
(3) J. S. Kaltenbronn, U. S. Patent 3,468,939 (1969).
(4) H. Gilman and R. D. Gorsich, *J. Amer. Chem. Soc.*, 77, 3919 (1955).
(5) H. Gilman and R. D. Gorisch, *ibid.*, 78, 2217 (1956).
(6) G. Wilhelmi, *Schweiz. Med. Wochenschr.*, 79, 577 (1949).
(7) D. J. Finney, R. Latscha, B. M. Bennett, and P. Hsu, "Tables for Testing Significance in a 2 × 2 Contingency Table," Cambridge University Press, New York, N. Y., 1963.
(8) D. J. Finney, "Probit Analysis," 2nd ed, Cambridge University Press, New York, N. Y., 1952.
(9) R. Meier, W. Schuler, and P. Desaulles, *Experientia*, 6, 469 (1950).
(10) C. V. Winder, J. Wax, L. Scotti, R. A. Scherrer, E. M. Jones, and F. W. Short, *J. Pharmacol. Exp. Ther.*, 138, 405 (1962).

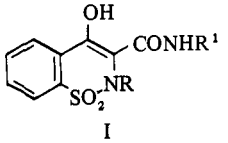
Potent Antiinflammatory N-Heterocyclic 3-Carboxamides of 4-Hydroxy-2-methyl-2*H*-1,2-benzothiazine 1,1-Dioxide

Joseph G. Lombardino,* Edward H. Wiseman, and Josephine Chiaini

Pfizer Central Research, Pfizer, Inc., Groton, Connecticut 06340. *Received August 11, 1972*

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.