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Antiinflammatory Agents. 3.[1] Synthesis and Pharmacological Evaluation of 2-Amino-3-benzoylphenylacetic Acid and Analogues

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A series of substituted derivatives of 2-amino-3-benzoylphenylacetic acid (amfenac) has been synthesized and evaluated for antiinflammatory, analgesic, and cyclooxygenase inhibiting activity. Several derivatives including **157** (4′-chloro), **158** (4′-bromo), and **182** (5-chloro, 4′-bromo) were more potent than indomethacin in these assays.

Initial investigations[2] into the pharmacological activity of derivatives of 2-amino-3-benzoylphenylacetic acid (**1**, amfenac, Scheme I), a potent analgesic and nonsteroidal antiinflammatory drug,[3] suggested that the potency of **1** could be increased by the addition of certain substituents to the molecule. This article describes the results obtained from a comprehensive structure–activity study of analogues of **1**.

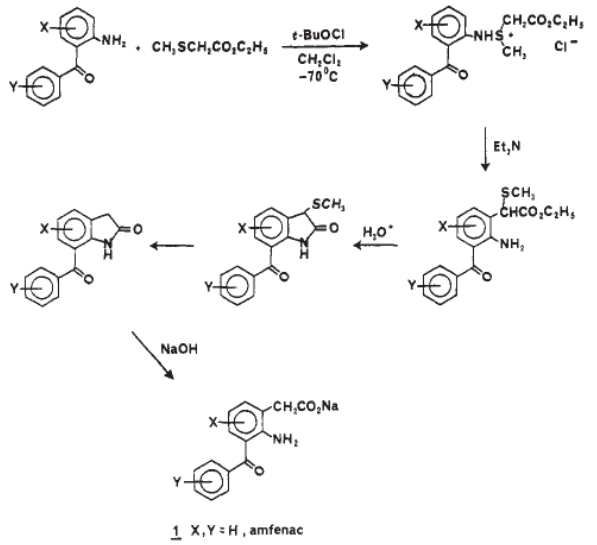
Chemistry. Substituted 7-benzoyloxindoles, precursors to the desired 2-amino-3-benzoylphenylacetic acids, were prepared by two general methods (Schemes I and IV). Gassman's[4] method for the synthesis of oxindoles, utilizing substituted 2-aminobenzophenones[5] (Table I) as starting material, gave the 3-(methylthio)oxindoles in good yields (Tables II, III) in a one-pot synthetic sequence. Removal of the 3-methylthio group with either Raney nickel or tin and hydrochloric acid gave the oxindoles (Scheme I). In cases where the electron-donating 5-methoxy substituent was required, a modification[6] of Gassman's original procedure was used due to the instability of the *N*-chloro-*p*-anisidine intermediate.

The reaction of 3-aminobenzophenone under the standard reaction conditions gave exclusively 4-benzoyl-3-(methylthio)oxindole (**13**) and none of the 6-benzoyl isomer (**17**). Strongly electron withdrawing groups direct attack to the more hindered ortho position.[7] The synthesis of **17** is described in Scheme II.

Scheme III depicts some miscellaneous synthetic reactions that gave specific 7-benzoyloxindole derivatives. The 4′-fluoro group of **48** could be displaced with sodium methoxide to give **35** or with sodium thiomethoxide to give **36**. The sulfoxide **37** and the sulfone **38** were prepared from **36** by using *m*-chloroperbenzoic acid. The oxindole **54** could be nitrated in concentrated sulfuric acid with potassium nitrate to yield **106**. The nitro group was reduced with iron and acetic acid to give the amine **107**.

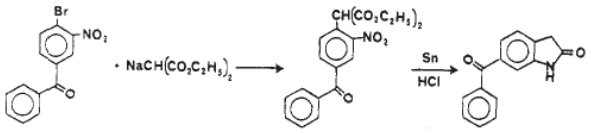
Derivatives containing bromine or iodine were sometimes difficult to prepare by the method outlined in Scheme I since these groups could be partially removed by the Raney nickel or the tin and hydrochloric acid that was used to remove the 3-methylthio group. These halogenated derivatives were conveniently prepared by a procedure described by Lo et al.[8] (Scheme IV). Thus,

Scheme I



1 X,Y = H, amfenac

Scheme II



20 **17**

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(1) For part 2 in this series, see: Walsh, D. A.; Shamblee, D. A.; Welstead, W. J., Jr.; Sancilio, L. F. *J. Med. Chem.* **1982**, *25*, 446–51.
(2) Welstead, W. J., Jr.; Moran, H. W.; Taylor, C. R., Jr.; Stauffer, H. F., Jr. "Abstracts of Papers", 170th National Meeting of the American Chemical Society, Chicago, IL, Aug 1975; American Chemical Society: Washington, DC, 1975; MEDI 16.
(3) Welstead, W. J., Jr.; Moran, H. W.; Stauffer, H. F.; Turnbull, L. B.; Sancilio, L. F. *J. Med. Chem.* **1979**, *22*, 1074–9.
(4) Gassman, P. G.; van Bergen, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 5508–17.
(5) Walsh, D. A. *Synthesis* **1980**, 677–88.

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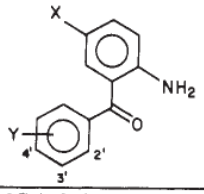
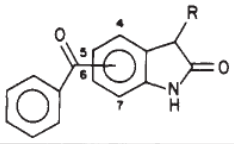
Table I. 2-Aminobenzophenones



no.	X	Y	mp, °C (solv[a])	method of prep[b]	% yield	formula
2	H	3′,4′-Cl_2	87–88 (w)	6.4	5	$C_{13}H_9Cl_2NO$
3	H	4′-C_6H_5	142–144 (z)	6.2	27	$C_{19}H_{15}NO$
4	OCH_3	4′-Cl	73–75.5 (x)	6.2	67	$C_{14}H_{12}ClNO_2$
5	OCH_3	4′-Br	68.5–70 (w)	6.2	85	$C_{14}H_{12}BrNO_2$
6	CH_3	4′-F	70–71.5 (w)	7.1	62	$C_{14}H_{12}FNO$
7	CH_3	4′-Br	105.5–107 (w)	7.1	13	$C_{14}H_{12}BrNO$
8	CH_3	2′,4′-Cl_2	69–71 (x)	7.1	78	$C_{14}H_{11}Cl_2NO$
9	F	4′-CH_3	113–114.5 (w)	7.1	29	$C_{14}H_{12}FNO$
10	F	4′-Br	96–97.5 (w)	7.1	39	$C_{13}H_9BrFNO$
11	F	2′,4′-Cl_2	60–62.5 (w)	7.1	42	$C_{13}H_8Cl_2FNO$
12	Cl	4′-Br	126–127.5 (y)	6.2	18	$C_{13}H_9BrClNO$

[a] w = cyclohexane, x = ligroin, y = 2-propanol, z = 95% ethanol. [b] Numbers refer to sections in ref 5 in which methods of preparation are described.

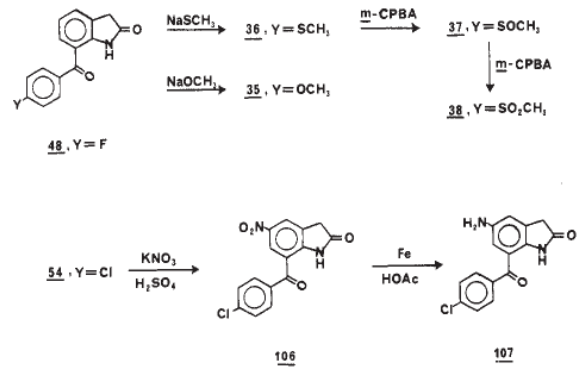
Table II. Benzoyloxindoles



no.	isomer	R	mp, °C (solv[a])	method of prep[b]	% yield	formula
13	4	SCH_3	235–237 (p)	A	62	$C_{16}H_{13}NO_2S$
14	4	H	210.5–216 (p)	C	76	$C_{15}H_{11}NO_2$
15	5	SCH_3	181–183 (q)	A	64	$C_{16}H_{13}NO_2S$
16	5	H	204–205 (p)	C	73	$C_{15}H_{11}NO_2$
17	6	H	209–211 (w)	F	80	$C_{15}H_{11}NO_2$
18	7	SCH_3	130 (x)	A	80	$C_{16}H_{13}NO_2S$
19	7	H	154 (y)	C	94	$C_{15}H_{11}NO_2$

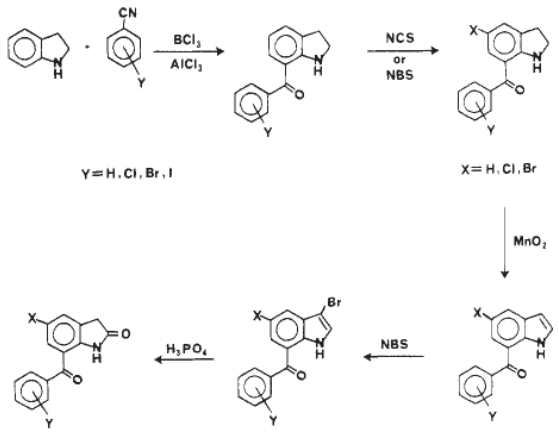
[a] p = methanol, q = 2-propanol, w = nitromethane, x = toluene, y = ethanol. [b] Letters refer to methods of preparation described in the Experimental Section■

Scheme III



indoline was benzoylated exclusively in the 7-position under Friedel–Crafts conditions by a modification of the method of Sugasawa et al.[9] The 7-benzoylindoline de-

Scheme IV



rivative was halogenated in the 5-position with either *N*-bromosuccinimide or *N*-chlorosuccinimide (Table IV). Liquid bromine was also used to introduce a bromine in the 5-position. Oxidation with activated manganese dioxide gave the substituted indole. Indoles with no halogen in the 5-position were halogenated in the 3-position with

(6) Gassman, P. G.; van Bergen, T. J.; Gruetzmacher, G. *J. Am. Chem. Soc.* **1973**, *95*, 6508–9.
(7) Gassman, P. G.; Cue, B. W., Jr.; Luh, T. Y. "Abstracts of Papers", 169th National Meeting of the American Chemical Society, Philadelphia, PA, April 1975; American Chemical Society: Washington, DC, 1975; ORGN 54.
(8) Lo, Y. S.; Walsh, D. A.; Welstead, W. J., Jr.; Mays R. P.; Rose, E. K.; Causey, D. H.; Duncan, R. L. *J. Heterocycl. Chem.* **1980**, *17*, 1663–4.
(9) Sugasawa, T.; Toyoda, T.; Adachi, M.; Sasakwa, K. *J. Am. Chem. Soc.* **1978**, *100*, 4842–52.

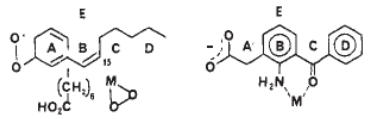


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Figure 1.

either *N*-bromosuccinimide or *N*-chlorosuccinimide; however, indoles bearing a halogen in the 5-position would only undergo reaction with *N*-bromosuccinimide (Table V). The 3-haloindoles were hydrolyzed to oxindoles with phosphoric acid in either 2-methoxyethanol or acetic acid.

The substituted oxindoles were hydrolyzed to the aminobenzoylphenylacetic acid sodium salts (Tables VI and VII) most conveniently with 3 N sodium hydroxide at reflux overnight (Scheme I). In one instance, the 4′-fluoro group of **97** was converted to a phenolic hydroxyl (**184**) under the reaction conditions.

Oxindoles **37** (4′-$SOCH_3$), **38** (4′-SO_2CH_3), **106** (5-NO_2), and **107** (5-NH_2) decomposed under basic hydrolysis conditions.

Results and Discussion

Table VI lists the acute antiinflammatory activity for **1** and several positional isomers. Only **1** possesses activity at 4.0 mg/kg, a dose at which indomethacin is also active. In recent years, there have been various models proposed that describe the binding of a nonsteroidal antiinflammatory drug (NSAID) to the cyclooxygenase enzyme. Many of these models have been reviewed by Bekemeier et al.[10] and they agree with the view[11] that the inhibition of prostaglandin formation by NSAIDs is due to their interaction with cyclooxygenase and is responsible for their therapeutic utility. One such model was described by Appleton and Brown[12] and is illustrated in Figure 1. These investigators concluded that the carboxyl group of a NSAID competes with the peroxy group of the precursor peroxy radical of the cyclic endoperoxide (PGG_2) for the same site. In addition, substituents that could occupy a position that is equivalent to carbon atom 15 of the peroxy radical and could chelate to the oxygen-orienting site on the enzyme would be favorable to binding. The fit of **1** in this receptor is excellent. Isomers **138**, **139**, and **140** do not have the benzoyl group ortho to the amino group and the possibility of a bidentate chelation with a metal is lost. Isomer **141**,[13] while possessing the ortho arrangement of the benzoyl and amino groups, does not have the amino group in a favorable position for chelation.

Derivatives of **1** were tested for their acute antiinflammatory activity and for their ability to inhibit cyclooxygenase obtained from bovine seminal vesicles (Table VII). Addition of a substituent to the ring of **1** containing the amino group (**142** to **148**) decreased antiinflammatory potency with the 5-Cl (**148**) group being the least detrimental. Taylor and Salata[14] have reported that for the tolmetin (1-methyl-5-*p*-toluoylpyrrole-2-acetic acid) series, substitution of a methyl group ortho to the benzoyl substituent increases the inhibition of prostaglandin E_2 synthesis. However, in this series **143** was devoid of antiinflammatory activity of 100 mg/kg in vivo and did not inhibit cyclooxygenase at 1 mM.

Substitution of a group in the benzoyl ring (**149**–**164**) of **1** had a pronounced effect on both the in vitro and in vivo potency. In general, the most potent compounds contained a halogen in the 4′-position with I ~ Br > Cl ~ 2′,4′-Cl_2 ~ 2′-Cl, 4′-Br > F ~ SCH_3 > H > CH_3 ~ CF_3 > OCH_3 ~ C_6H_5. Derivatives containing a substituent in the 3′-position (**156** and **163**) were less active than **1** in both test systems.

Compounds that were equipotent to **1** in the acute antiinflammatory test system were then screened in a battery of test systems to determine antiinflammatory activity in a chronic model, analgesic activity, and gastrointestinal irritation liability. Table VIII lists the potency of compounds in relation to that of indomethacin, which has been assigned a potency of 1. Analgesic activity in the acetylcholine-induced abdominal constriction model in mice was determined twice for each compound: once at a pretreatment time of 20 min that gave an indication of onset of action and once at a 5-h pretreatment time that gave an indication of duration of action.

Several compounds listed in Table VIII were very potent antiinflammatory and analgesic agents. It is interesting to note that compounds containing a metabolically labile group such as methyl (**170**, **171**, and **180**) and methylthio (**173** and **179**) were relatively less potent in the chronic model of inflammation and in the analgesia model (5-h pretreatment), suggesting that these compounds were rapidly degraded. Compound **173** was the most potent cyclooxygenase-inhibiting compound tested (Table VII), but its relative potency in the antiinflammatory assay was not retained in vivo.

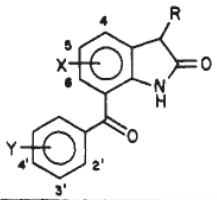
Compounds that contain a halogen substituent in each ring of **1** are among the most potent prostaglandin synthetase inhibiting compounds reported to date and are very potent in both pharmacological models of inflammation. In order to assess the relative gastrointestinal irritation liabilities of these compounds, therapeutic indexes were computed and are listed in Table IX. The acute therapeutic index is defined as the potency (relative to indomethacin) in the pleural effusion assay/potency (relative to indomethacin) in the gastric toxicity assay, and the chronic therapeutic index is defined as the potency (relative to indomethacin) in the adjuvant-induced arthritis assay/potency (relative to indomethacin) in the intestinal toxicity assay. Several compounds have therapeutic indexes greater than that of indomethacin. As a result, compounds **157**, **158**, and **182** are being developed as analgesic and antiinflammatory agents.

Experimental Section

Pharmacology. A. Antiinflammation. 1. Acute antiinflammatory activity was determined in the Evans blue–carrageenan-induced pleural effusion model by a modification of the method of Sancilio and Fishman.[15] Each compound was administered orally at doses of 100 and 4.0 mg/kg to six fasted rats, and the 5-h effusive response to the intrapleural injection of 5 mL of 0.075% Evans blue–0.5% carrageenan type 7 at 37 °C was measured. Indomethacin at 4.0 mg/kg orally was used for comparison. The data were reported as a percentage decrease in the average volume of pleural fluid from that of the control group. Compounds that were approximately equipotent to **1** were further tested in a battery of pharmacological test systems to determine antiinflammatory potency, analgesic potency, and relative gastrointestinal irritation liability compared with indomethacin

(10) Bekemeier, H.; Böhm, R.; Hagen, V.; Hannig, E.; Henkel, H. J.; Hirschelmann, R.; Wenzel, U. In "Trends in Inflammation Research, 2", Agents and Actions Supplement; Bekemeier, H., Hirschelmann, R., Eds.; Birkhaüser Verlag: Basel, 1982; Vol. 10, pp 17–34.
(11) Vane, J. R. *Agents Actions* **1978**, *8*, 430.
(12) Appleton, R. A.; Brown, K. *Prostaglandins* **1979**, *18*, 29–33.
(13) Bays, D. E.; Foster, R. V.; U.S. Patent 3 828 093, 1974.
(14) Taylor, R. J., Jr.; Salata, J. J. *Biochem. Pharmacol.* **1976**, *25*, 2479–84.
(15) Sancilio, L. F.; Fishman, A. *Toxicol. Appl. Pharmacol.* **1973**, 26, 575–84.

Table III. Substituted 7-Benzoyloxindoles



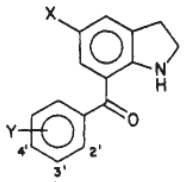
no.	X	Y	R	mp, °C (solv[a])	method of prep[b]	% yield	formula
21	5-OCH_3	H	SCH_3	138–142 (kl)	B	19	$C_{17}H_{15}NO_3S$
22	5-OCH_3	H	H	149–152 (m)	C	29	$C_{16}H_{13}NO_3$
23	4-CH_3	H	SCH_3	122–124 (n)	A	85	$C_{17}H_{15}NO_2S$
24	4-CH_3	H	H	177–180 (n)	C	96	$C_{16}H_{13}NO_2$
25	5-CH_3	H	SCH_3	185–187 (o)	A	74	$C_{17}H_{15}NO_2S$
26	5-CH_3	H	H	152–153.5 (n)	C	84	$C_{16}H_{13}NO_2$
27	6-CH_3	H	SCH_3	162–164 (n)	A	80	$C_{17}H_{15}NO_2S$
28	6-CH_3	H	H	176–177 (n)	C	95	$C_{16}H_{13}NO_2$
29	5-F	H	SCH_3	157–158 (l)	A	66	$C_{16}H_{12}FNO_2S$
30	5-F	H	H	159.5–166.5 (l)	C	82	$C_{15}H_{10}FNO_2$
31	5-Cl	H	SCH_3	213–214 (p)	A	47	$C_{16}H_{12}ClNO_2S$
32	5-Cl	H	H	184–185 (lq)	D	25	$C_{15}H_{10}ClNO_2$
33	6-Cl	H	SCH_3	158.5–160.5 (n)	A	67	$C_{16}H_{12}ClNO_2S$
34	6-Cl	H	H	206–209 (n)	C	80	$C_{15}H_{10}ClNO_2$
35	H	4′-OCH_3	H	146–147 (l)	G	51	$C_{16}H_{13}NO_3$
36	H	4′-SCH_3	H	167–169 (r)	H	70	$C_{16}H_{13}NO_2S$
37	H	4′-$SOCH_3$	H	199–201 (n)	I	92	$C_{16}H_{13}NO_3S$
38	H	4′-SO_2CH_3	H	254–258 (l)	J	89	$C_{16}H_{13}NO_4S$
39	H	4′-CF_3	SCH_3	194–197 (n)	A	56	$C_{17}H_{12}F_3NO_2S$
40	H	4′-CF_3	H	220–223 (l)	C	80	$C_{16}H_{10}F_3NO_2$
41	H	2′-CH_3	SCH_3	131–132 (n)	A	61	$C_{17}H_{15}NO_2S$
42	H	2′-CH_3	H	146–148 (n)	C	83	$C_{16}H_{13}NO_2$
43	H	4′-CH_3	SCH_3	162–163 (l)	A	77	$C_{17}H_{15}NO_2S$
44	H	4′-CH_3	H	171–173 (l)	C	92	$C_{16}H_{13}NO_2$
45	H	2′-F	SCH_3	147–148.5 (kl)	A	55	$C_{16}H_{12}FNO_2S$
46	H	2′-F	H	209–210 (l)	D	60	$C_{15}H_{10}FNO_2$
47	H	4′-F	SCH_3	165–167 (s)	A	53	$C_{16}H_{12}FNO_2S$
48	H	4′-F	H	185–187 (n)	D	72	$C_{15}H_{10}FNO_2$
49	H	2′-Cl	SCH_3	142–144 (l)	A	55	$C_{16}H_{12}ClNO_2S$
50	H	2′-Cl	H	170–172 (l)	D	79	$C_{15}H_{10}ClNO_2$
51	H	3′-Cl	SCH_3	177–177.5 (l)	A	85	$C_{16}H_{12}ClNO_2S$
52	H	3′-Cl	H	178–180 (l)	C	83	$C_{15}H_{10}ClNO_2$
53	H	4′-Cl	SCH_3	186–188 (q)	A	33	$C_{16}H_{12}ClNO_2S$
54	H	4′-Cl	H	177 (q)	C	93	$C_{15}H_{10}ClNO_2$
55	H	4′-Br	SCH_3	202–205 (nt)	A	58	$C_{16}H_{12}BrNO_2S$
56	H	4′-Br	H	196–198 (o)	T	61	$C_{15}H_{10}BrNO_2$
57	H	4′-I	H	213–214 (t)	T	68	$C_{15}H_{10}INO_2$
58	H	4′-C_6H_5	SCH_3	149–150 (nr)	A	66	$C_{22}H_{17}NO_2S$
59	H	4′-C_6H_5	H	212–215 (nt)	C	93	$C_{21}H_{15}NO_2$
60	H	2′,4′-$(CH_3)_2$	SCH_3	149–150.5 (n)	A	75	$C_{18}H_{17}NO_2S$
61	H	2′,4′-$(CH_3)_2$	H	176–177.5 (n)	C	70	$C_{17}H_{15}NO_2$
62	H	2′,4′-Cl_2	SCH_3	202–204 (o)	A	57	$C_{16}H_{11}Cl_2NO_2S$
63	H	2′,4-Cl_2	H	251–256 (nt)	C	83	$C_{15}H_9Cl_2NO_2$
64	H	3′,4′-Cl_2	SCH_3	178–181	A	48	$C_{16}H_{11}Cl_2NO_2S$
65	H	3′,4′-Cl_2	H	191.5–193 (n)	C	73	$C_{15}H_9Cl_2NO_2$
66	H	2′-Cl, 4′-Br	H	271–274 (w)	T	55	$C_{15}H_9BrClNO_2$
67	5-OCH_3	4′-Cl	SCH_3	142–144.5 (n)	B	74	$C_{17}H_{14}ClNO_3S$
68	5-OCH_3	4′-Cl	H	174.5–176 (n)	C	90	$C_{16}H_{12}ClNO_3$
69	5-OCH_3	4′-Br	SCH_3	158.5–160 (nr)	B	66	$C_{17}H_{14}BrNO_3$
70	5-OCH_3	4′-Br	H	180.5–182 (lt)	C	79	$C_{16}H_{16}BrNO_3$
71	5-CH_3	4′-SCH_3	H	176–177.5 (kl)	H	92	$C_{17}H_{15}NO_2S$
72	5-CH_3	4′-CH_3	SCH_3	160–161 (m)	A	53	$C_{18}H_{17}NO_2$
73	5-CH_3	4′-CH_3	H	148.5–150 (kl)	C	83	$C_{17}H_{15}NO_2$
74	5-CH_3	4′-F	SCH_3	171–172.5 (m)	A	79	$C_{17}H_{14}FNO_2S$
75	5-CH_3	4′-F	H	204–206.5 (kl)	C	91	$C_{16}H_{12}FNO_2$
76	5-CH_3	4′-Cl	SCH_3	182.5–184 (l)	A	72	$C_{17}H_{14}ClNO_2S$
77	5-CH_3	4′-Cl	H	167–171 (kl)	C	79	$C_{16}H_{12}ClNO_2$
78	5-CH_3	4′-Br	SCH_3	187–189	A	71	$C_{17}H_{14}BrNO_2S$
79	5-CH_3	4′-Br	H	179–181.5 (n)	C	70	$C_{16}H_{12}BrNO_2$
80	5-CH_3	2′,4′-Cl_2	SCH_3	216–217 (kl)	A	53	$C_{17}H_{13}Cl_2NO_2S$
81	5-CH_3	2′,4′-Cl_2	H	211–213	C	85	$C_{16}H_{11}Cl_2NO_2$
82	5-F	4′-SCH_3	H	178–180 (n)	H	60	$C_{16}H_{12}FNO_2S$
83	5-F	4′-CH_3	SCH_3	176–178 (n)	A	66	$C_{17}H_{14}FNO_2S$
84	5-F	4′-CH_3	H	189.5–191.5 (n)	C	86	$C_{16}H_{12}FNO_2$
85	5-F	4′-F	SCH_3	171–172.5 (m)	A	45	$C_{16}H_{11}F_2NO_2S$
86	5-F	4′-F	H	195–196.5 (m)	C	64	$C_{15}H_9F_2NO_2$
87	5-F	4′-Cl	SCH_3	177–185	A	80	$C_{16}H_{11}ClFNO_2S$

Table III (Continued)

no.	X	Y	R	mp, °C (solv[a])	method of prep[b]	% yield	formula
88	5-F	4′-Cl	H	187–189 (r)	C	84	$C_{15}H_9ClFNO_2$
89	5-F	4′-Br	SCH_3	197–198 (rt)	A	52	$C_{16}H_{11}BrFNO_2S$
90	5-F	4′-Br	H	196–197 (nt)	C	60	$C_{15}H_9BrFNO_2$
91	5-F	2′,4′-Cl_2	SCH_3	198–200	A	44	$C_{16}H_{10}Cl_2FNO_2S$
92	5-F	2′,4′-Cl_2	H	207–208	C	83	$C_{15}H_8Cl_2FNO_2$
93	5-Cl	4′-SCH_3	H	179–181 (m)	H	68	$C_{16}H_{12}ClNO_2S$
94	5-Cl	4′-CH_3	SCH_3	187–189 (m)	A	43	$C_{17}H_{14}ClNO_2S$
95	5-Cl	4′-CH_3	H	152–155 (x)	C	74	$C_{16}H_{12}ClNO_2$
96	5-Cl	4′-F	SCH_3	202–204 (m)	A	43	$C_{16}H_{11}ClFNO_2S$
97	5-Cl	4′-F	H	222–225 (x)	C	64	$C_{15}H_9ClFNO_2$
98	5-Cl	4′-Cl	SCH_3	199–202 (ny)	A	35	$C_{16}H_{11}Cl_2NO_2S$
99	5-Cl	4′-Cl	H	196–201	C	80	$C_{15}H_9Cl_2NO_2$
100	5-Cl	4′-Br	SCH_3	208–211 (m)	A	46	$C_{16}H_{11}BrClNO_2S$
101	5-Cl	4′-Br	H	213–214 (r)	T	43	$C_{15}H_9BrClNO_2$
102	5-Cl	4′-I	H	218–221 (r)	T	48	$C_{15}H_9ClINO$
103	5-Cl	2′-Cl, 4′-Br	H	255–258 (ry)	T	33	$C_{15}H_9BrCl_2NO_2$
104	5-Br	4′-Cl	H	206–209 (r)	T	35	$C_{15}H_9BrClNO_2$
105	5-Br	4′-Br	H	206–207 (r)	T	41	$C_{15}H_9Br_2NO_2$
106	5-NO_2	4′-Cl	H	253–259 (mz)	K	75	$C_{15}H_9ClN_2O_4$
107	5-NH_2	4′-Cl	H	236–239 (mt)	L	32	$C_{15}H_{11}ClN_2O_2$

[a] k = water, l = ethanol, m = ethyl acetate, n = 2-propanol, o = acetonitrile, p = methylene chloride, q = toluene, r = benzene, s = methanol, t = tetrahydrofuran, w = 2-methoxyethanol, x = acetone, y = pyridine, z = dimethylformamide. [b] Letters refer to methods of preparation described in the Experimental Section.

Table IV. 7-Benzoylindoline Derivatives



no.	X	Y	mp, °C (solv[a])	method of prep[b]	% yield	formula
108	H	4′-Cl	107–108 (w)	M	91	$C_{15}H_{12}ClNO$
109	H	4′-Br	128–129 (x)	M	76	$C_{15}H_{12}BrNO$
110	H	4′-I	149–150 (y)	M	85	$C_{15}H_{12}INO$
111	H	2′-Cl, 4′-Br	120–121 (x)	M	55	$C_{15}H_{11}BrClNO$
112	Cl	4′-Cl	146–148 (y)	N	45	$C_{15}H_{11}Cl_2NO$
113	Cl	4′-Br	168–169 (z)	N	67	$C_{15}H_{11}BrClNO$
114	Cl	4′-I	175 (z)	N	54	$C_{15}H_{11}ClINO$
115	Cl	2′-Cl, 4′-Br	113–118 (x)	N	68	$C_{15}H_{10}BrCl_2NO$
116	Br	4′-Cl	157–159 (z)	P	49	$C_{15}H_{11}BrClNO$
117	Br	4′-Br	167.5–168 (z)	O	89	$C_{15}H_{11}Br_2NO$

[a] w = petroleum ether, x = 2-propanol, y = absolute ethanol, z = ethyl acetate. [b] Letters refer to methods of preparation described in the Experimental Section.

(Table VIII). Potencies relative to indomethacin were determined by regression analysis.

2. Chronic antiinflammatory activity was determined in the adjuvant-induced arthritic rat model of Walz et al.[16] using a therapeutic rather than a prophylactic dosing regimen as described by Sancilio et al.[17]

B. Analgesia. Oral analgesic activity was determined in mice by the acetylcholine-induced abdominal constriction assay.[17] Acetylcholine bromide was administered intraperitoneally 20 min or 5 h following oral administration of the test compound. Zompirac was used as a standard.

C. Gastrointestinal Liability. 1. Acute Gastric Toxicity (Single Oral Dose). Male fasted rats weighing between 150 and 200 g were randomly divided into groups of seven. The compounds were dissolved or suspended in 0.5% Tween 80 and administered by gavage (10 mL/kg). Six hours later, the animals were killed with chloroform or carbon dioxide. The stomachs were removed, washed, and examined for the presence of erosions. On a blind basis, the degree of damage was scored according to the following system: 1, one to three erosions <3 mm in diameter; 2, many small erosions; 3, two to three erosions greater than 3 mm in diameter or 4–5 mm in length; and 4, four or more large erosions.

2. Chronic Intestinal Toxicity (Multiple Oral Doses). Male and female Sprague–Dawley rats, weighing between 160 and 200 g, were randomly divided into groups of eight. Excluding the weekend, compounds were orally administered on a daily basis for 11 days. Twenty-four hours after the last dose, the rats were killed with chloroform or carbon dioxide and the intestines were examined for the presence of ulcers. The severity of the lesions was scored in increments of 10, from 0 for no damage to +40 for maximum damage, plus 10 for perforations and/or adhesions, and an additional 10 if the animal died. Growth of the animals was also monitored during the course of the experiment.

D. Prostaglandin Synthetase Inhibition. The polarographic method used for the determination of the inhibition of cyclooxygenase obtained from bovine seminal vesicles has been described in detail.[1]

General Procedures. Melting points were determined in open capillary tubes in a Thomas-Hoover melting point apparatus and are uncorrected; ^1H NMR spectra were obtained in $CDCl_3$ or Me_2SO-d_6 with Me_4Si as internal standard or in D_2O with sodium

(16) Walz, D. T.; Di Martino, M. J.; Misher, A. *J. Pharmacol. Exp. Ther.* **1971**, *178*, 223–31.
(17) Sancilio, L. F.; Reese, D. L.; Cheung, S.; Alphin, R. S. *Agents Actions* **1977**, *7*, 133–44.

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