Synthesis and Antiinflammatory and Analgesic Activity of 5-Aroyl-6-(methylthio)-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic Acids and 1-Methyl-4-(methylthio)-5-aroylpyrrole-2-acetic Acids[1]

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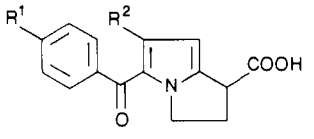
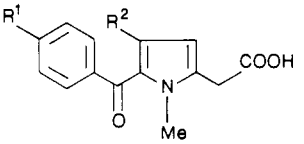
5-Aroyl-6-(methylthio)-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic acids and 1-methyl-4-(methylthio)-5-aroylpyrrole-2-acetic acids were synthesized and assayed as antiinflammatory and analgesic agents. The majority of these compounds exhibit a surprisingly low level of antiinflammatory activity (rat carrageenan paw) but have considerable potency as analgesics (mouse phenylquinone writhing). For example, the *p*-tolyl-substituted bicyclic and monocyclic compounds **44** and **58** are 301 and 66 times more potent than aspirin (mouse writhing) but only 3.4 and 1.5 times more potent than phenylbutazone in the antiinflammatory screen (rat paw).

The synthesis and pharmacological evaluation of various 6-substituted 5-aroyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]-pyrrole-1-carboxylic acids (I, $R^2 \neq H$) were recently reported.[2] Some members of this series of compounds were of comparable potency to ketorolac (I, R^1, R^2 = H) as analgesics (mouse phenylquinone writhing assay) and 2–3-fold more potent as antiinflammatory agents (carrageenan rat paw edema assay). Indeed, in both acute and chronic animal models of inflammation, several of the 6-methyl and 6-chloro compounds were of equivalent or greater potency than indomethacin. Inasmuch as the lipophilicity of a methylthio group ($\pi = 0.61$)[3] is quite similar to that of a methyl (0.56) or a chloro (0.71) moiety, it was of interest to examine the effect of this substituent on the activity of I (R^2 = MeS).[4] This paper describes the synthesis and pharmacological activity of such compounds as well as of the 4-(methylthio) derivatives of the monocyclic compounds II ($R^2 = CH_3S$) related to zomepirac (II, R^1 = Cl, $R^2 = CH_3$).[5] As measured by the mouse writhing assay, 5-(4-methylbenzoyl)-6-(methylthio)-1,2-dihydro-3*H*-pyrrolo [1,2-*a*]pyrrole-1-carboxylic acid (**44**) is approximately 300 times more potent than aspirin as an analgesic.



I



II

Chemistry. The carboxylic acids IV were prepared by the alkaline hydrolysis of the corresponding nitriles III or esters V which were synthesized by acylation of the bicyclic 6-(methylthio)pyrrolopyrrole derivatives **6** or **8** with the appropriate carboxylic acid chloride in an inert high-boiling solvent at reflux temperature in the absence of a catalyst[6] (Scheme I, Tables I and II). 6-(Methylthio)-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carbonitrile (**6**) and methyl 6-(methylthio)-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]-pyrrole-1-carboxylate (**8b**) were derived from the 5-(methylthio) compound **3**, which in turn was obtained from the known[7] bicyclic nitrile **1**. Thus, condensation of nitrile **1** with the *N*-chlorosuccinimide–dimethyl sulfide adduct, at −55 °C in dichloromethane solution, gave the sulfonium salt **2** which, on heating in toluene at reflux temperature, lost methyl chloride to give the low-melting methylthio compound **3** in 82% overall yield. This sulfide was oxidized with sodium periodate to the mixture of epimeric sulfoxides **4** which was rearranged[8] to the thermodynamically more stable sulfoxide mixture **5** with trifluoroacetic acid in dichloromethane solution. Reduction of **5** with the triphenylphosphine–iodine–sodium iodide system of Olah et al.[9] provided the 6-(methylthio) compound **6** isomeric with **3**.

To prepare the methyl ester **8b**, the nitrile **3** was hydrolyzed with potassium hydroxide in aqueous ethanol and the carboxylic acid **7a** thus produced was esterified with ethereal diazomethane. Trifluoroacetic acid induced isomerization[10] of **7b** gave the 6-(methylthio) compound **8b** in 60% overall yield from **3**.

The carboxylic acid congeners VII of zomepirac were obtained by potassium carbonate hydrolysis of the esters VI (Scheme II), which were synthesized by aroylation of ethyl 1-methyl-4-(methylthio)-pyrrole-2-carboxylate (**13**). The aroylation was carried out by heating a solution of **13** and the aroyl chloride in boiling xylene or by reaction of the Vilsmeier–Haack reagent, prepared from an *N*,*N*-dimethylarylcarboxamide and phosphorus oxychloride, with the ester **13** in boiling 1,2-dichloroethane solution. The ester **13** was synthesized from ethyl 1-methylpyrrole-2-carboxylate,[11] via intermediates **10–12**, in a manner entirely

[†] Institute of Organic Chemistry.
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[§] Institute of Biological Sciences.

(1) Contribution No. 718 from the Institute of Organic Chemistry.
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(3) Unger, S. H. *Drug Design* **1980**, *9*, 48.
(4) Muchowski, J. M.; Greenhouse, R. U.S. Patent 4,612,325 (1986).
(5) The synthesis of II (R^1 = Cl, $R^2 = CH_3S$) and several derivatives thereof was recently reported, but surprisingly, neither physical constants nor pharmacological activity were given for any of the compounds claimed. Doherty, J. P.; Chang, M. N.; Dorn, C. P. U.S. Patent 4,434,175 (1984).
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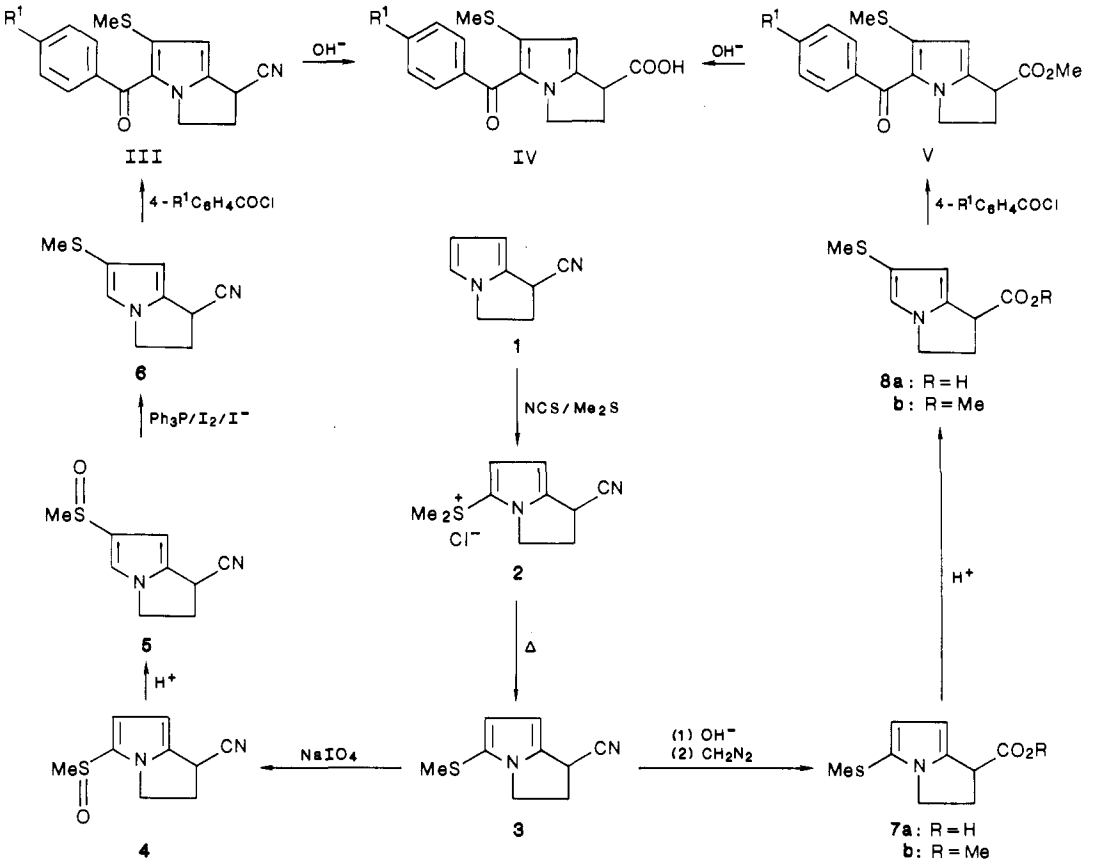
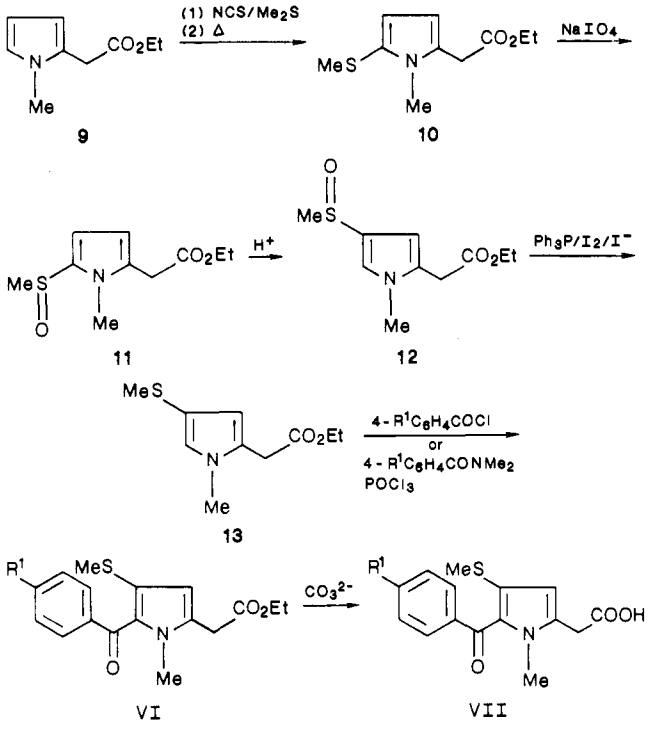
Scheme I



Scheme II



analogous to that described for the bicyclic nitrile **6**.

Discussion

The carboxylic acids listed in Table III were first screened for antiinflammatory and analgesic activity by using the carrageenan rat paw and mouse phenylquinone writhing assays.

Since it previously had been shown[2,12] that the most active compounds, as measured by the above-mentioned assays, were those in which the benzoyl group at C-5 was unsubstituted or bore a para substituent, no meta- or ortho-substituted benzoyl compounds were prepared in this study. The data in Table III show that the presence of the methylthio group at C-6 in the pyrrolopyrrole series of compounds caused a considerable diminution in both antiinflammatory and analgesic activity in comparison to other 6-substituted congeners (e.g., R^2 = Me, Et, Cl, Br).[2] The reduction in activity was, however, relatively greater in the rat paw assay than in the mouse writhing assay. Indeed, the *p*-tolyl compound **44** is a remarkably potent analgesic (301 times the potency of aspirin), as measured by the latter assay, with a very low level of antiinflammatory activity (3.4 times the potency of phenylbutazone; rat paw assay). This skewed biological activity spectrum is even more evident in the monocyclic series where several of the compounds (**56–58**, **60**) are equal to or greater in potency than zomepirac with only minimal activity in the carrageenan rat paw assay.

A few of the compounds which showed high activity in the mouse writhing assay were studied in chronic models of inflammation (Table IV). The weak antiinflammatory activity found for **44** in the rat paw assay was also reflected in both the cotton pellet granuloma and adjuvant-induced arthritis screens. Evaluation of this compound for gastrointestinal erosive activity in a 7-day assay in rats gave

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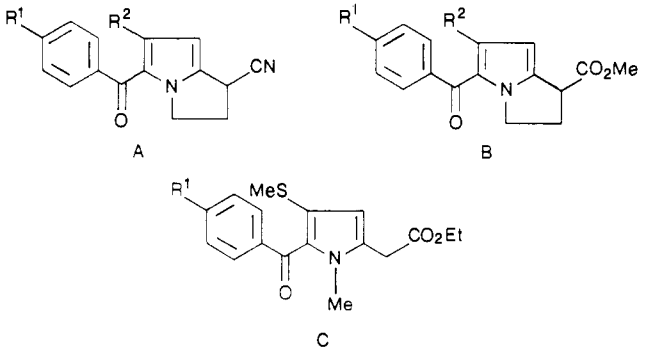
Table I. 6-Substituted 5-Aroyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic Esters and Nitriles and Ethyl 1-Methyl-4-(methylthio)-5-aroylpyrrole-2-acetates



no.	system	R^1	R^2	rctn time, h	% yield	mp, °C	recrystn solvent[a]	formula	anal.[b]
14	A	H	CH_3S	20	84	90–91	CH_2Cl_2–eth	$C_{16}H_{14}N_2OS$	*c*
15	A	F	CH_3S	8	82	127–127.5	CH_2Cl_2–eth	$C_{16}H_{13}FN_2OS$	C, H, N
16	A	Cl	CH_3S	8	82	160.5–161	CH_2Cl_2–eth	$C_{16}H_{13}ClN_2OS$	C, H, N
17	B	Br	CH_3S	22	26	136–137	MeOH	$C_{17}H_{16}BrNO_3S$	C, H, N, Br
18	B	Br	CH_3SO	1.5	99	170–171	MeOH	$C_{17}H_{16}BrNO_4S$	C, H, N, Br
19	B	Br	CH_3SO_2	1	84	153–154	CH_2Cl_2–MeOH	$C_{17}H_{16}BrNO_5S$	C, H, N, Br
20	B	CH_3	CH_3S	24	31	122–124	MeOH	$C_{18}H_{19}NO_3S$	C, H, N
21	B	CH_3CH_2	CH_3S	20	36	oil		$C_{19}H_{21}NO_3S$	C, H, N[d]
22	B	$CH_3CH_2CH_2$	CH_3S	48	33	oil		$C_{20}H_{23}NO_3S$	*e*
23	B	*c*-C_3H_5	CH_3S	36	35	94–95	EtOAc–hex	$C_{20}H_{21}NO_3S$	C, H, N
24	B	*c*-C_6H_{11}	CH_3S	72	15	oil		$C_{23}H_{27}NO_3S$	C, H, N
25	B	CH_2=CH	CH_3S	5	17	120–121	CH_2Cl_2–MeOH	$C_{19}H_{19}NO_3S$	C, H, N[f]
26	A	CH_3O	CH_3S	31	64	137.5–139	CH_2Cl_2–eth	$C_{17}H_{16}N_2O_2S$	*g*
27	B	CH_3CH_2O	CH_3S	48	23	oil		$C_{19}H_{21}NO_4S$	C, H, N
28	B	$(CH_3)_2CHO$	CH_3S	48	30	oil		$C_{20}H_{23}NO_4S$	C, H, N[h]
29	B	CH_3S	CH_3S	24	40	oil		$C_{18}H_{19}NO_3S_2$	C, H, N[i]
30	B	CF_3	CH_3S	3	38	90–92	CH_2Cl_2–MeOH	$C_{18}H_{16}F_3NO_3S$	C, H, N, F
31	C	H		30	87	88–89	CH_2Cl_2–hex	$C_{17}H_{19}NO_3S$	C, H, N
32	C	F		18	31	122	CH_2Cl_2–hex	$C_{17}H_{18}FNO_3S$	C, H, N
33	C	Cl		31	32	135	EtOAc	$C_{17}H_{18}ClNO_3S$	C, H, N
34	C	CH_3		23	28	91.5	hex	$C_{18}H_{21}NO_3S$	C, H, N
35	C	$CH_3CH_2CH_2$		20	44	oil		$C_{20}H_{25}NO_3S$	C, H, N
36	C	*c*-C_3H_5		20	33	106–109	acet–hex	$C_{20}H_{23}NO_3S$	C, H, N
37	C	CH_3CH_2O		34	32	111	CH_2Cl_2–hex	$C_{19}H_{23}NO_4S$	C, H

[a] hex = hexane; acet = acetone; eth = ether. [b] Elements shown analyzed correctly to within ±0.4% of the calculated values. [c] *m/e* 282.0822 (calcd for $C_{16}H_{14}N_2OS$: 282.0827). [d] Anal. Calcd for $C_{19}H_{21}NO_3S \cdot 0.5H_2O$. [e] MS M^+ 357. [f] Anal. Calcd for $C_{19}H_{19}NO_3S \cdot 0.2H_2O$. [g] *m/e* 312.0931 (calcd for $C_{17}H_{16}N_2O_2S$: 312.0933). [h] Anal. Calcd for $C_{20}H_{23}NO_4S \cdot 0.33H_2O$. [i] Anal. Calcd for $C_{18}H_{19}NO_3S_2 \cdot 0.33H_2O$.

a minimum effective dose causing erosion (MED) of 19 mg/kg per day. The therapeutic ratio for this compound was then calculated (MED divided by ED_{30} for the carrageenan rat paw assay) to be about 4. This figure must be viewed as a minimum value in view of the low activity measured in the rat paw screen. If the activity in the mouse writhing assay is taken to be predictive[13] of the analgesic potency in man, as is true for ketorolac (10 mg of oral ketorolac is equivalent to 10 mg of intramuscular morphine sulfate for the relief of moderate to severe postoperative pain[14]), then compound **44** should be ca. equipotent with ketorolac but with an improved safety margin. Similarly, the monocyclic compound **58** whould be more potent that zomepirac as an analgesic agent with a considerably greater therapeutic ratio.

Experimental Section

The animal assays referred to above were carried out as described below.

(1) **Inhibition of Carrageenan-Induced Edema.** This assay was conducted as described in recent publications from these laboratories.[15]

(2) **Inhibition of Cotton Pellet Granuloma.** This assay was carried out by a modification[16] of a procedure first described by Meier et al.[17]

(3) **Inhibition of Adjuvant-Induced Arthritis.** This assay was performed by using a modification[16] of a procedure of Pearson.[18]

(4) **Inhibition of Phenylquinone-Induced Writhing.** This assay was conducted as described by Rooks et al.[16]

(5) **Chronic Gastrointestinal Erosive Activity.** This assay was carried out as described in a previous publication in this series of compounds.[12]

Physical Constants. The melting points were determined in a Mel-Temp melting point apparatus and are corrected. The IR spectra were measured on a Perkin-Elmer Model 237 grating infrared spectrophotometer as solutions in chloroform unless specified otherwise. The UV spectra were recorded in methanol

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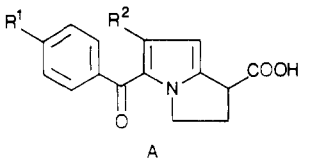
Table II. 6-Substituted 5-Aroyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic Acids and 1-Methyl-4-(methylthio)-5-aroylpyrrole-2-acetic Acids



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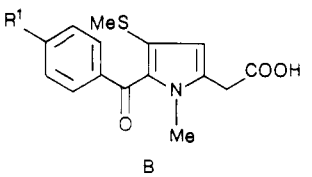

B

no.	system	R^1	R^2	hydrolysis method[a]	rctn time, h	% yield	mp, °C	recrystn solvent[b]	formula	anal.[c]
38	A	H	CH_3S	A	8	77	191–192	EtOAc	$C_{16}H_{15}NO_3S$	C, H, H
39	A	F	CH_3S	A	14.5	82	201–202	EtOAc	$C_{16}H_{14}FNO_3S$	C, H, N
40	A	Cl	CH_3S	A	5	81	200.5–201	EtOAc	$C_{16}H_{14}ClNO_3S$	C, H, N
41	A	Br	CH_3S	B	5	80	204–205	acet–eth	$C_{16}H_{14}BrNO_3S$	C, H, N, Br
42	A	Br	CH_3SO	B	13	64	226–227	MeOH	$C_{16}H_{14}BrNO_4S$	C, H, N
43	A	Br	CH_3SO_2	B	0.75	76	205–205.5	EtOAc–eth	$C_{16}H_{14}BrNO_5S$	C, H, N
44	A	CH_3	CH_3S	B	3	90	182–183	EtOAc–eth	$C_{17}H_{17}NO_3S$	C, H, N
45	A	CH_3CH_2	CH_3S	B	1	50	164–166	EtOAc–eth	$C_{18}H_{19}NO_3S$	C, H, N[d]
46	A	$CH_3CH_2CH_2$	CH_3S	B	2	86	160–161	EtOAc–eth	$C_{19}H_{21}NO_3S$	C, H, N
47	A	*c*-C_3H_5	CH_3S	B	1.5	86	186–187	EtOAc	$C_{19}H_{19}NO_3S$	C, H, N[e]
48	A	*c*-C_6H_{11}	CH_3S	B	2	69	175–176	EtOAc–eth	$C_{22}H_{25}NO_3S$	C, H, N
49	A	$CH_2{=}CH$	CH_3S	B	5	52	182–183	EtOAc	$C_{18}H_{17}NO_3S$	C, H, N[f]
50	A	CH_3O	CH_3S	B	8.5	78	197–198	EtOAc	$C_{17}H_{17}NO_4S$	C, H, N
51	A	CH_3CH_2O	CH_3S	B	18	84	167–168	EtOAc–eth	$C_{18}H_{19}NO_4S$	C, H, N
52	A	$(CH_3)_2CHO$	CH_3S	B	18	71	192–193	MeOH	$C_{19}H_{21}NO_4S$	C, H, N
53	A	CH_3S	CH_3S	B	1	50	185–187	EtOAc–eth	$C_{17}H_{17}NO_3S_2$	C, H, N
54	A	CF_3	CH_3S	B	2	58	210–211	EtOAc–eth	$C_{17}H_{14}F_3NO_3S$	C, H, N, F
55	B	H		B	0.75	93	134–135	CH_2Cl_2–hex	$C_{15}H_{15}NO_3S$	C, H, N
56	B	F		C	1	88	165	EtOAc	$C_{15}H_{14}FNO_3S$	C, H
57	B	Cl		C	1	85	167	MeOH	$C_{15}H_{14}ClNO_3S$	C, H, N
58	B	CH_3		C	1	82	147	CH_2Cl_2–hex	$C_{16}H_{17}NO_3S$	C, H, N
59	B	$CH_3CH_2CH_2$		C	0.5	80	122–124	acet–hex	$C_{18}H_{21}NO_3S$	C, H, N
60	B	*c*-C_3H_5		C	0.5	87	138–139	acet–hex	$C_{18}H_{19}NO_3S$	C, H, N
61	B	CH_3CH_2O		C	1	93	125–126	CH_2Cl_2–hex	$C_{17}H_{19}NO_4S$	C, H, N

[a] Hydrolysis methods: (A) NaOH/aqueous ethanol on nitriles; (B) NaOH/aqueous methanol on esters; (C) K_2CO_3/aqueous methanol on esters. [b] See Table I for key to abbreviations. [c] Elements shown analyzed to ±0.4% of the calculated values. [d] Anal. Calcd for $C_{18}H_{19}NO_3S{\cdot}0.33H_2O$. [e] Anal. Calcd for $C_{19}H_{19}NO_3S{\cdot}0.75H_2O$. [f] Anal. Calcd for $C_{18}H_{17}NO_3S{\cdot}0.24H_2O$.

Table III. Antiinflammatory and Analgesic Activities of 5-(4-Substituted benzoyl)-6-(methylthio)-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic Acids and 1-Methyl-4-(methylthio)-5-(4-substituted benzoyl)pyrrole-2-acetic Acids

no.	rat paw assay, phenylbutazone = 1[a]	mouse writhing assay, aspirin = 1[b]
38	2.0 (0.9–7)[c]	78 (32–225)[c]
39	≤10 (18)[d]	60 (24)[e]
40	35 (24–52)	130 (24)
41	26 (7–83)	<9 (24)
42	0.5 (0.1–1.1)	<3 (16)
43	<1 (12)	*f*
44	3.4 (0.8–9)	301 (228–401)
45	16 (7–40)	70 (16)
46	2.5 (1.1–4.9)	7 (16)
47	13 (7–29)	25 (16)
48	<1 (12)	<3 (16)
49	16 (12)	38 (23–66)
50	<10 (18)	50 (24)
51	4 (2.3–7)	≤13 (16)
52	<1 (12)	1 (16)
53	10 (6–19)	50 (16)
54	15 (12)	50 (16)
55	1 (0.4–3.2)	≥11 (16)
56	0.5 (0.2–1.2)	37 (20–68)
57	1.5 (0.8–3.7)	56 (10–72.5)
58	1.5 (0.5–12.5)	66 (39–108)
59	0.2 (0.01–0.7)	5 (16)
60	10 (17)	30 (22–40)
61	3.6 (0.4–5.3)	6 (18)

[a] ED_{30} = 15 mg/kg. [b] ED_{50} = 70 mg/kg. [c] 95% confidence limits. [d] Number of mice. [e] Number of rats. [f] Not tested.

solution with a Perkin-Elmer Model 402 ultraviolet–visible spectrometer. The NMR spectra were measured with a Varian T-60, a Varian HA-100, or a Bruker WM 300 NMR spectrometer in $CDCl_3$ solutions. The chemical shifts are expressed in parts per million (δ) from internal Me_4Si. The low-resolution mass spectra were obtained with Atlas CH-4, Varian MAT CH-7, and AEI MS-9 spectrometers. The high-resolution mass spectra were measured with a Finnigan MAT 112S mass spectrometer. These compounds were of at least 95% purity as determined by TLC and NMR analysis. The reactions were followed by thin-layer chromatography (TLC) on silica gel plates.

Starting Materials. The acid chlorides were either commercially available or known and prepared from the carboxylic acids by literature procedures. The acid chlorides not described in the literature were synthesized from the known carboxylic acids in the manner described below.

***N*,*N*-Dimethyl-4-propylbenzamide (62).** A solution of 4-propylbenzoic acid (5.0 g, 31 mmol) in dry benzene (5 mL) containing thionyl chloride (16.6 g, 10 mL, 140 mmol) was heated at reflux temperature for 18 h. The solution was concentrated in vacuo, and benzene (200 mL) was added to the residue. The solution was cooled to 10 °C, and gaseous dimethylamine was bubbled in until the reaction was complete. A stream of nitrogen was then passed through the reaction mixture to eliminate the excess dimethylamine. The mixture was washed with water, the benzene solution was dried, and the solvent was removed in vacuo. The residue was passed through a column of neutral alumina (200 g, Fluka, Act II) using hexane–ethyl acetate (9:1) as the eluting solvent. The product (88% yield) was obtained as an oil: bp 135–136 °C/0.2 mmHg; UV 235 nm (ε 7590); IR 1618 cm^{-1}; NMR δ 0.91 (t, 3 H, *J* = 7 Hz), 1.60 (m, 2 H), 2.60 (m, 2 H), 3.00 (s, 6 H), 7.28 (m, 4 H); MS *m*/*e* 191.1307 (calcd for $C_{12}H_{17}NO$: 191.1310).

***N*,*N*-Dimethyl-4-cyclopropylbenzamide (63).** This compound was prepared in 90% yield as described above for **62**. It was an oil: bp 92–95 °C/0.2 mmHg; UV 250 nm (ε 8510); IR 1618 cm^{-1}; NMR δ 0.83 (m, 4 H), 1.90 (m, 1 H) 3.00 (s, 3 H), 7.06 (d, 2 H, *J* = 9 Hz), 7.33 (d, 2 H, *J* = 9 Hz); MS *m*/*e* 189.1149 (calcd for $C_{12}H_{15}NO$: 189.1154).

5-(Methylthio)-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carbonitrile (3). A solution of *N*-chlorosuccinimide (1.15 g) in

Table IV. Antiinflammatory Profile of Selected 5-(4-Substituted benzoyl)-6-(methylthio)-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic Acids and 1-Methyl-4-(methylthio)-5-(4-methylbenzoyl)pyrrole-2-acetic Acid

compd	rat paw, phenylbutazone = 1[a]	mouse writhing, aspirin = 1[a]	cotton pellet, indomethacin = 1[b]	adjuvant arthritis, naproxen = 1[c]	GI erosion, MED,[d] mg/kg per day	therapeutic ratio[e]
40	35	130			1.5 (15)[f]	3.5
44	3.4	301	0.2 (36)	0.2 (48)	19 (15)	4
58	1.5	66			>45	>4.5
zomepirac[g]	26 (13–62)[h]	36 (29–44)[h]			10	17
naproxen	11 (7–17)	7 (4–12)	0.2	1	30	22
indomethacin	16 (8–31)	≃60 (100)[i]	1	7		
ketorolac	55 (33–92)	347 (256–480)	0.5	2	5	18

[a] Data for compounds **40**, **44**, and **58** taken from Table III. ED_{30} of phenylbutazone = 15 mg/kg (rat paw). ED_{50} of aspirin = 70 mg/kg (mouse writhing). [b] ED_{50} = 3 mg/kg (2.0–4.6). [c] ED_{50} = 1.7 mg/kg (0.9–2.8). [d] Gastrointestinal erosion, 7-day chronic assay; minimum effective dose; see Experimental Section. [e] MED GI erosion/ED_{30} rat paw. [f] Number of rats. [g] Data for zomepirac and ketorolac taken from ref 12; data for naproxen and indomethacin taken from ref 19. [h] 95% confidence limits. [i] Number of mice.

dry dichloromethane (40 mL) was cooled, in a nitrogen atmosphere, to −10 °C (bath temperature), and a solution of dimethyl sulfide (1 mL) in anhydrous dichloromethane (10 mL) was added dropwise with stirring over a 10-min period. After a further 10 min at this temperature the bath temperature was lowered to −55 °C and a solution of 1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carbontrile (**1**, 1.08 g) in dry dichloromethane (10 mL) was added with stirring over a 10-min period. The cooling bath was removed, and when the reaction temperature reached ambient, the solvent was removed in vacuo. The residual solid sulfonium salt **2** was suspended in toluene (100 mL), and the stirred mixture was heated at reflux temperature for 5 min. The solvent was decanted from an insoluble tar, toluene (100 mL) was added thereto, and the mixture was heated at reflux temperature for 20 min. The toluene was decanted from the insoluble material, and the combined toluene phases were evaporated in vacuo. The residual oil was passed through a short column of silica gel using dichloromethane as the solvent. The nearly colorless oil **3** (1.20 g, 90%) obtained after evaporation of the solvent was sufficiently pure for use in the next reaction. An analytical specimen was obtained by HPLC purification (Microsorb column, 50 cm × $^3/_8$ in.) using hexane–ethyl acetate (85:15) as the eluting solvent at 1100 psig and a flow rate of 9.7 mL/min (Du Pont Model 841 high-pressure liquid chromatography unit). The sulfide **3** had a retention time of 13.5 min, and after removal of the solvent it crystallized. Crystallization of this material from ether–hexane gave a solid: mp 58–58.5 °C; UV 225, 249 nm (ε 6920, 7950); IR (KBr) 2220 cm^{-1}; NMR δ 2.38 (s, 3 H), 2.61–3.09 (m, 2 H), 3.81–4.43 (m, 3 H), 6.05 (d, 1 H, J = 3.5 Hz), 6.35 (d, 1 H, J = 3.5 Hz). Anal. ($C_9H_{10}N_2S$) C, H, N.

5-(Methylsulfinyl)-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carbonitrile (4). A solution of the sulfide **3** (1.20 g) in methanol (30 mL) was cooled to 0 °C, and sodium periodate (1.58 g) dissolved in water (30 mL) was added with stirring over a 20-min period. The cooling bath was then removed, and the reaction was stirred at room temperature for 3 h. The methanol was removed in vacuo, and the residue was extracted with dichloromethane. The aqueous phase was diluted with water, saturated with sodium chloride, and then extracted again with dichloromethane. The combined extracts were dried over sodium sulfate and evaporated in vacuo to give the sulfoxide **4** [1.27 g, 97% yield, two very closely running spots on TLC [ethyl acetate–triethylamine (95:5)]], which was pure enough to be used directly in the next step: NMR δ 2.38–3.17 (m, 2 H), 2.93 (s, 3 H), 3.94–4.57 (m, 3 H), 5.32 (m, 1 H), 6.58 (d, 1 H, J = 4 Hz), 6.60 (d, 1 H, J = 4 Hz); MS m/e 194.0515 (calcd for $C_9H_{10}N_2OS$: 194.0514).

6-(Methylsulfinyl)-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carbonitrile (5). A solution of the sulfoxide **4** (1.05 g) in dry dichloromethane (20 mL) containing trifluoroacetic acid (10 mL) was left at room temperature for 1 h 50 min. The solution was diluted with benzene (250 mL) and then evaporated in vacuo. The dark colored oil so obtained was applied to a short column of silica gel, and the column was eluted with dichloromethane (to remove nonpolar impurities), and then with ethyl acetate–triethylamine (95:5) to remove colored material. When the product began to come off the column, elution with ethyl acetate–triethylamine (9:1) completely removed the sulfoxide. The sulfoxide **5** (1.02 g, 97% yield) was obtained as an oil [two closely running spots on TLC [ethyl acetate–triethylamine (95:5)]]. It was used in the next step without further purification: NMR δ 2.81, 2.82 (singlets, 3 H), 2.83–3.05 (m, 2 H), 4.02–4.27 (m, 3 H), 6.42, 6.49 (triplets, 1 H, $J_{1,7}$ = 1.2 Hz, $J_{5,7}$ = 1.4 Hz), 7.10, 7.12 (doublets, 1 H, $J_{5,7}$ = 1.4 Hz); MS m/e 194.0513 (calcd for $C_9H_{10}N_2OS$: 194.0514).

6-(Methylthio)-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carbonitrile (6). The reduction of the sulfoxide **5** was carried out by the method of Olah et al.[8]

Powdered iodine (1 equiv) was added to a stirred solution of triphenylphosphine (1.15 equiv) in dry acetonitrile (10 mL/mmol of sulfoxide to be used) in a nitrogen atmosphere. The mixture was stirred until the iodine color was no longer present and a yellow colored suspension had formed. The sulfoxide **5** (1 equiv) in dry acetonitrile (2.5 mL/mmol of sulfoxide) was added in one portion. This was immediately followed by solid powdered sodium iodide (2 equiv). The mixture was stirred and rapidly changed to a dark color. TLC showed that the reaction was complete after 1 min. After being stirred for no more than 5 min, the solution was poured into a mixture of 5% sodium thiosulfate solution and ether. The mixture was shaken until the iodine color had disappeared, and the ether phase was separated and washed with a 5% sodium bicarbonate solution. The ether solution was dried over sodium sulfate and evaporated in vacuo. The crude material was passed through a short column of silica gel (30 g/g of crude product) using dichloromethane. The excess triphenylphosphine came off with the solvent front and was followed almost immediately by the product. The sulfide **6** was obtained as an oil, which was sufficiently pure to be used in the next step: NMR δ 2.34 (s, 3 H), 2.75–2.87 (m, 2 H), 3.94–4.18 (m, 3 H), 6.15 (t, 1 H, $J_{1,7}$ = 1.2 Hz, $J_{5,7}$ = 1.4 Hz), 6.71 (d, 1 H, $J_{5,7}$ = 1.4 Hz); MS m/e 178.0563 (calcd for $C_9H_{10}N_2S$: 178.0565).

5-(Methylthio)-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic Acid (7a) and Methyl 5-(Methylthio)-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylate (7b). A solution of the nitrile **3** (53 g, 0.3 mol) in 1:1 aqueous ethanol (1 L) containing potassium hydroxide (53 g, 85%; 0.8 mol) was heated at reflux temperature for 8 h. The ethanol was removed in vacuo, and the residue was extracted with ether. The aqueous alkaline phase was acidified to pH 3 with 10% hydrochloric acid, the product was extracted into ethyl acetate, and the extract was washed with water, dried over sodium sulfate, and evaporated in vacuo. A portion of the residual carboxylic acid was dissolved in dichloromethane, and a slight excess of dicyclohexylamine was added thereto. The solvent was removed in vacuo, and the residue on crystallization from acetone–hexane gave the pure salt: mp 118–120 °C. Anal. ($C_{21}H_{34}N_2O_2S$) C, H.

The crude carboxylic acid from above was dissolved in ether and an excess of ethereal diazomethane was added. When the reaction was completed, the solvent was removed in vacuo to give the ester **7b** (80% yield) as an oil: UV 222, 252 nm (ε 6170, 7240); IR 1742 cm^{-1}; NMR δ 2.28 (s, 3 H), 2.83 (m, 2 H), 3.80 (s, 3 H), 4.10 (m, 3 H), 6.00 (d, 1 H, J = 4 Hz), 6.36 (d, 1 H, J = 4 Hz); MS m/e 211 (M^+).

Methyl 6-(Methylthio)-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylate (8b) and 6-(Methylthio)-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic Acid (8a). A solution of the ester **7b** (3.00 g) in dichloromethane (30 mL) and trifluoroacetic anhydride (28 mL) was stirred at ambient temperature for 0.5 h. Excess saturated aqueous sodium bicarbonate solution

was added, and the organic phase was separated, dried over sodium sulfate, and evaporated in vacuo. The residue was taken up in dichloromethane and passed over a short column of neutral alumina (Fluka, Act II, 30 g). Removal of the solvent in vacuo gave the crude acid **8b** (2.25 g, 75% yield) as an oil: UV 222 sh, 288 nm (ϵ 5500, 1380); IR 1739 cm^{-1}; NMR δ 2.23 (s, 3 H), 2.63 (m, 2 H), 3.63 (s, 3 H), 4.00 (m, 3 H), 5.90 (s, 1 H), 6.53 (s, 1 H); MS *m/e* 211 (M^+).

A solution of sodium hydroxide (0.5 g, 12.5 mmol) in water (15 mL) was added at 0 °C to a solution of the ester **8b** (1.00 g, 4.74 mmol) in methanol (30 mL). The stirred solution was left to reach room temperature, and after a further 0.5 h the methanol was removed in vacuo. The aqueous phase was cooled to 0 °C and made acidic with 10% hydrochloric acid, and the product was extracted into ethyl acetate. The extract was washed with water, dried, and evaporated in vacuo. The crude material was converted into the dicyclohexylammonium salt as described for **7a**. The pure salt was obtained by crystallization from ethyl acetate–ether: mp 126–128 °C.

Ethyl 1-Methyl-5-(methylthio)pyrrole-2-acetate (10). Dimethyl sulfide (7.94 g, 9.45 mL, 0.125 mol) was added to a stirred solution of *N*-chlorosuccinimide (8.4 g, 0.063 mol) in dry dichloromethane (150 mL) during a 10-min period (argon atmosphere). After a further 15 min, the stirred suspension was cooled to −55 °C and a solution of ethyl 1-methylpyrrole-2-acetate (10.0 g, 0.060 mol) in dichloromethane (40 mL) was added thereto. The reaction temperature was left to reach ambient during a 2-h period, and then the solvent was removed in vacuo. Dry toluene (400 mL) was added to the residue, and the mixture was heated at reflux temperature for 10 min. The toluene was removed in vacuo, the residue was dissolved in ether, and the solution was washed with water and dried. Removal of the solvent in vacuo gave an oily mixture which was subjected to purification by column chromatography on silica gel using hexane–ethyl acetate (96:4) to elute the product **10** (6.10 g, 48%). This material, an oil, was not stable at room temperature. It could be stored in the refrigerator for some time if a few drops of triethylamine was added: IR 1736 cm^{-1}; NMR δ 1.24 (t, 3 H, J = 7.3 Hz), 2.22 (s, 3 H), 3.51 (s, 2 H), 3.63 (s, 3 H), 4.18 (q, 2 H, J = 7.3 Hz), 6.21 (q, 2 H, J = 3.7 Hz); MS *m/e* 213.0826 (calcd for $C_{10}H_{15}NO_2S$: 213.0824).

Ethyl 1-Methyl-5-(methylsulfinyl)pyrrole-2-acetate (11). This compound was prepared in the same manner as described for **4** except that the reaction time was 18 h and the product was purified by column chromatography on silica gel using ethyl acetate–triethylamine (95:5) as the eluting solvent. The sulfoxide **11** was obtained as a solid (76%) which had mp 99–101 °C after crystallization from dichloromethane–hexane: IR 1739 cm^{-1}; NMR δ 1.30 (t, 3 H, J = 7.2 Hz), 2.99 (s, 3 H), 3.69 (s, 2 H), 3.87 (s, 3 H), 4.14 (q, 2 H, J = 7.2 Hz), 6.42 (q, 2 H, J = 4.0 Hz). Anal. ($C_{10}H_{15}NO_3S$) C, H, N.

Ethyl 1-Methyl-4-(methylsulfinyl)pyrrole-2-acetate (12). This compound was prepared in the same manner as described for **5**. It was obtained as a solid in 87% yield after crystallization from ether–hexane: mp 92–93 °C; IR 1743 cm^{-1}; NMR δ 1.29 (t, 3 H, J = 7.6 Hz), 2.84 (s, 3 H), 3.69 (s, 3 H), 3.78 (s, 2 H), 4.32 (q, 2 H, J = 7.6 Hz), 6.48 (d, 1 H, J = 1.7 Hz), 7.11 (d, 2 H, J = 1.7 Hz). Anal. ($C_{10}H_{15}NO_3S$) C, H, N, S.

Ethyl 1-Methyl-4-(methylthio)pyrrole-2-acetate (13). This compound was prepared in the same manner as described for **6** except that the product was purified by column chromatography on silica gel using hexane–ethyl acetate (1:4) as the eluting solvent. The product (86% yield) was obtained as an oil: IR 1735 cm^{-1}; NMR δ 1.29 (t, 3 H, J = 7.2 Hz), 2.34 (s, 3 H), 3.59 (s, 5 H), 4.21 (q, 2 H, J = 7.2 Hz), 6.14 (d, 1 H, J = 2.0 Hz), 6.68 (d, 1 H, J = 2.0 Hz); MS *m/e* 213.0822 (calcd for $C_{10}H_{15}NO_2S$: 213.0824).

Acylation of 6, 8b, and 13. Method A. Noncatalyzed Acylation of Bicyclic Nitrile 6 and Monocyclic Ester 13 with Acid Chlorides in Boiling Xylene. A solution of **6** or **8b** (10 mmol) i anhydrous xylene (30–65 mL) containing the appropriate acid chloride (20–50 mmol) was heated at reflux temperature for the time specified in Table I.

For the synthesis of the nitriles **14–16** and **26**, the solvent was removed in vacuo, methanol (40–65 mL) was added to esterify the excess acyl halide, and the mixture was then evaporated in vacuo. The residue was mixed with neutral alumina (35–50 g, Fluka, Act II) and placed on top of a column of the same stationary phase (85–130 g). For compound **14**, the column was eluted with hexane (to remove the benzoic acid methyl ester derivative), ethyl acetate–hexane (1:99, then 2:98), and dichloromethane (product). Compounds **15** and **16** were purified by use of hexane, ethyl acetate–hexane (1:99; 2:98; 3:97), and dichloromethane. For **26**, the column was eluted with hexane, ethyl acetate–hexane (2:98; 3:97; 4:96), and dichloromethane. The product obtained in this way was purified once more by column chromatography on alumina (130 g) using the following solvent systems as eluents: dichloromethane–hexane (1:1, then 3:1), dichloromethane, and ether (product).

For the synthesis of the esters **31–34** and **37**, the product mixture obtained after removal of the solvent was mixed with water and the mixture was extracted into ethyl acetate. The extract was washed with 10% sodium bicarbonate solution, dried, and evaporated in vacuo. The residue was subjected to column chromatography on silica gel, and the product was eluted with the mixture of hexane–ethyl acetate indicated: **31**, **33** (4:1); **32**, **34** (85:15); **37** (7:3).

The chromatographically pure solid products were recrystallized from the solvent system indicated in Table II and characterized fully by elemental analyses and spectroscopically. In general, oily products were only characterized spectroscopically.

Method B. Noncatalyzed Acylation of Bicyclic Ester 8b with Acid Chlorides in Boiling Toluene. A solution of the ester **8b** (10 mmol) and the acid chloride (20–30 mmol) in dry toluene (120 mL) was heated at reflux temperature for the period of time indicated in Table I. The solvent was removed, and the residue was subjected to column chromatography on Act II neutral alumina (10 g/g of crude product). The column was eluted with hexane–ethyl acetate (95:5, then 90:10).

Method C. Vilsmeier–Haack Reactions. A solution of the amide (26 mmol) in dry 1,2-dichloroethane (55 mL) containing phosphorus oxychloride (23 mmol) was heated at reflux temperature for 3 h. After the reaction mixture was cooled to room temperature, a solution of the ester **13** (10 mmol) in 1,2-dichloroethane (15 mL) was added and reflux was reinitiated and maintained for 20 h. The reaction mixture was cooled to room temperature, and a solution of sodium acetate (32 g) in water (110 mL) was added cautiously. The mixture was heated at reflux for 2 h and cooled, and the organic phase was separated and combined with a dichloromethane extract of the aqueous phase. The combined organic phases were washed with water, dried, and evaporated in vacuo. The residue was passed over a column of neutral alumina using hexane–ethyl acetate (92.5:7.5) as the eluting solvent, and then the product was purified further by preparative TLC on silica gel using hexane–ethyl acetate as the developing solvent [**35** (75:25); **36** (70:30)].

Synthesis of the Carboxylic Acids (Table II) by Hydrolysis of the Nitriles or the Esters. Method A. Hydrolysis of the Nitriles with Sodium Hydroxide in Aqueous Ethanol. A solution of the nitrile (10 mmol) in ethanol (30 mL) and water (10 mL) containing sodium hydroxide (40–47 mmol) was heated at reflux temperature for the time indicated in Table II. The ethanol was removed in vacuo, water was added to the residue, and the solution was extracted with ether. The aqueous phase was made acidic with 1 N hydrochloric acid, and the product was extracted into ethyl acetate. The extract was dried and evaporated in vacuo to give a solid which was crystallized from the solvent system indicated in Table II.

Method B. Saponification of the Esters with Sodium Hydroxide in Aqueous Methanol. A solution of the ester (10 mmol) in methanol (60 mL) and water (60 mL) containing sodium hydroxide (20–50 mmol) was stirred at room temperature for the time period specified in Table II. The reaction was worked up as in method A.

Method C. Hydrolysis of the Esters with Potassium Carbonate in Aqueous Methanol. A solution of the ester (10 mmol) in methanol (75–200 mL) and water (40–100 mL) containing potassium carbonate (20 mmol) was heated at reflux temperature for 1 h, and the methanol was then removed in vacuo. The aqueous phase was extracted with ethyl acetate and then made acidic, at 0 °C, with 20% hydrochloric acid. The solid product was collected by filtration, washed with water, and dried in vacuo. It was further purified by crystallization from the appropriate solvent system (Table II).