Synthesis and Antiinflammatory and Analgesic Activity of 5-Aroyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic Acids and Related Compounds[1]

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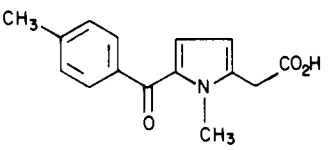
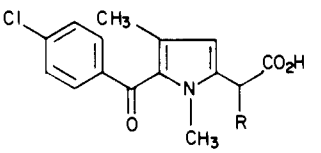
5-Acyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic acids and the homologous pyridine and azepine derivatives were synthesized and assayed for antiinflammatory and analgesic activity. 5-Benzoyl-1,2-dihydro-3*H*-pyrrolo-[1,2-*a*]pyrrole-1-carboxylic acid (**62**) and the corresponding *p*-methoxy compound **74** were selected for evaluation as analgesic agents in humans on the basis of their high potency in the mouse phenylquinone writhing assay as well as on their minimal liability to elicit gastrointestinal erosion in rats on chronic administration. Extensive quantitative structure–activity relationship (QSAR) studies of the benzoylpyrrolopyrrolecarboxylic acids have demonstrated that the analgesic (mouse writhing) and antiinflammatory (rat carrageenan paw) potencies of these compounds are satisfactorily correlated with the steric and hydrogen-bonding properties of the benzoyl substituent(s). The 4-vinylbenzoyl compound **95**, which was correctly predicted to be highly active in both assays on this basis, is undergoing advanced pharmacological evaluation in animals as a potential antiinflammatory agent.

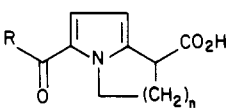
In the early part of the last decade, a wide ranging program was initiated in these laboratoires, the objective of which was to develop new high-potency nonsteroidal antiinflammatory agents that elicited fewer side effects than those in use (e.g., indomethacin). Tolmetin (I) and zomepirac (II) are two pyrroleacetic acid derivatives that now enjoy a modicum of success in the treatment of rheumatoid arthritis[2] and pain.[3] These compounds were chosen as one class of arylacetic acids, among others,[4-6] that was of interest as a starting point for structural modifications. In this connection, it was reported by Carson and Wong[7] that methylation of zomepirac in the acetic acid side chain, as in III, markedly increased the antiinflammatory potency as measured by the rat paw kaolin edema assay. It was therefore not illogical to expect that the rigid bicyclic framework that would result from the inclusion of the carbon atoms corresponding to the *N*- and *C*-methyl groups of III in a cyclic system (i.e., IV) might be associated with an increase in antiinflammatory potency. This paper describes the synthesis, pharmacological evaluation, and structure–activity relationships of various 5-acyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic acids (IV, n = 1) and the homologous six-membered (IV, n = 2) and seven-membered (IV, n = 3) analogues thereof.[8] Many members of the 5-benzoyl pyrrolopyrrole series of compounds show high antiinflammatory and/or analgesic activity in animal models. Two of these [**62** (assigned the generic name "ketorolac") and **74** (assigned the generic name "anirolac")][9,10] are currently undergoing clinical evaluation in man as analgesic agents,[11] and a third (**95**) is being subjected to advanced pharmacological study in various animal species.



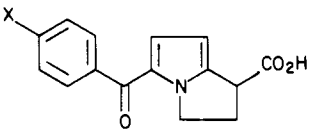
I



II, R = H
III, R = CH_3



IV



62, X = H
74, X = CH_3
95, X = CH_2=CH

Chemistry. With very few exceptions (see below), the carboxylic acids IV were prepared by alkaline hydrolysis of the corresponding esters VI or the nitriles VII (Scheme I, Tables I and II), which in turn were obtained by acylation of the appropriate parent bicyclic systems V and VII.[12] The acylation of the esters V was effected with either the Vilsmeier–Haack reagent derived from an *N,N*-dimethylcarboxamide and phosphorus oxychloride in boiling 1,2-dichloroethane[7] or with a carboxylic acid

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(1) Contribution No. 647 from the Syntex Institute of Organic Chemistry.
(2) Berkowitz, S. A.; Bernhard, G.; Bilka, P. J.; Marchesano, J. M.; Rosenthal, M.; Wortham. G. F. *Curr. Ther. Res.* **1974**, *16*, 442.
(3) "Zomepirac: A New Non-Narcotic Analgesic"; Proceedings of the Symposium on Zomepirac; Atlanta, GA, 1979: *J. Clin. Pharmacol.* **1980**, *20*, 213.
(4) Dunn, J. P.; Green, D. M.; Nelson, P. H.; Rooks, W. H.; Tomolonis, A.; Untch, K. G. *J. Med. Chem.* **1977**, *20*, 1557.
(5) Ackrell, J.; Antonio, Y.; Franco, F.; Landeros, R.; Leon, A.; Muchowski, J. M.; Maddox, M. L.; Nelson, P. H.; Rooks, W. H.; Roszkowski, A. P.; Wallach, M. B. *J. Med. Chem.* **1978**, *21*, 1035.
(6) Dunn, J. P.; Muchowski, J. M.; Nelson, P. H. *J. Med. Chem.* **1981**, *24*, 1097.
(7) Carson, J. R.; Wong, S. *J. Med. Chem.* **1973**, *16*, 172.
(8) Muchowski, J. M.; Kluge, A. F. *U.S. Patent* 4089969, 1978; U.S. Patent 4232038, 1980; *Chem. Abstr.* **1981**, *94*, 103156a. Muchowski, J. M.; Greenhouse, R. U.S. Patent 4347187, 1982.
(9) A detailed account of the animal pharmacology of 5-benzoyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic acid (**62**) has recently been published. Rooks, W. H.; Tomolonis, A. J.; Maloney, P. J.; Wallach, M. B.; Schuler, M. E. *Agents Actions* **1982**, *12*, 684.
(10) Syntheses different from those described herein have been reported for several of the 5-benzoylpyrrolopyrrolecarboxylic acids. Franco, F.; Greenhouse, R.; Muchowski, J. M. *J. Org. Chem.* **1982**, *47*, 1682.

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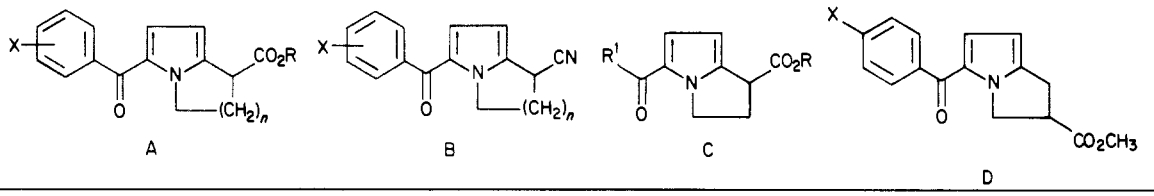
Table I. Acyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrolecarboxylic Esters and Nitriles and Homologous Pyridine and Azepine Analogues



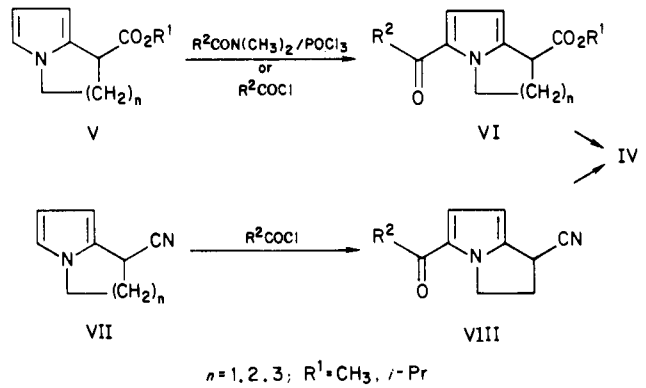
no.	system	X	*n*	R	R^1	acylation method[a]	rctn time, h	% yield	mp, °C	recrystn solvent[b]	emp formula	anal.[c]
1	A	H	1	*i*-Pr		A	24	85	oil	*d*	$C_{18}H_{19}NO_3$	*e*
2	A	2-CH_3	1	*i*-Pr		A	168	37	oil	*f*	$C_{19}H_{21}NO_3$	*g*
3	A	3-CH_3	1	*i*-Pr		A	78	90	oil	*h*	$C_{19}H_{21}NO_3$	*g*
4	A	4-CH_3	1	*i*-Pr		A	8	66	oil	*i*	$C_{19}H_{21}NO_3$	*g*
5	A	3-F	1	*i*-Pr		A	11	66	oil	*j*	$C_{18}H_{18}FNO_3$	*k*
6	A	4-F	1	*i*-Pr		A	34	98	72–72.5	CH_2Cl_2–hex	$C_{18}H_{18}FNO_3$	C, H, F
7	A	2-Cl	1	*i*-Pr		A	150	19	oil	*l*	$C_{18}H_{18}ClNO_3$	*m*
8	A	3-Cl	1	*i*-Pr		A	27	70	oil	*l*	$C_{18}H_{18}ClNO_3$	*m*
9	A	4-Cl	1	*i*-Pr		A	40–70	79–91	80.5–81	CH_2Cl_2–MeOH	$C_{18}H_{18}ClNO_3$	C, H, Cl, N
10	A	4-Br	1	CH_3		B	20	85	82–84	acet–hex	$C_{16}H_{14}BrNO_3$	C, H, Br, N
11	A	2-I	1	CH_3		B	1.5	79	174–175	acet–hex	$C_{16}H_{14}INO_3$	C, H, N
12	A	3-OCH_3	1	*i*-Pr		A	12	66	oil	*j*	$C_{19}H_{21}NO_4$	*n*
13	A	4-OCH_3	1	*i*-Pr		A	65	100	oil	*h*	$C_{19}H_{21}NO_4$	*n*
14	A	3-OEt	1	*i*-Pr		A	19	45	50–51	eth–hex	$C_{20}H_{23}NO_4$	C, H, N
15	A	4-OEt	1	*i*-Pr		A	22	52	94–95	CH_2Cl_2–MeOH	$C_{20}H_{23}NO_4$	C, H, N
16	A	4-O-*i*-Pr	1	*i*-Pr		A	24	93	oil	o	$C_{21}H_{25}NO_4$	*p*
17	A	4-$OCH_2CH{=}CH_2$	1	CH_3		B	72	67[q]	105–107	acet–hex	$C_{19}H_{19}NO_4$	C, H, N
18	A	4-$OCH_2C{\equiv}CH$	1	CH_3		B	50	58[r]	121–122	acet–hex	$C_{19}H_{17}NO_4$	C, H, N
19	B	2-CH_3CO_2	1			D	40	20	oil	*d*	$C_{17}H_{14}N_2O_3$	*s*
20	A	3-CH_3CO_2	1	CH_3		C	30	60–73	oil	*t*	$C_{18}H_{17}NO_5$	*m*
21	A	4-CH_3CO_2	1	CH_3		C	45	70[o]	90.5–91	CH_2Cl_2–MeOH	$C_{18}H_{17}NO_5$	C, H, N
22	A	4-CH_3S	1	CH_3		C	63	80[u]	77–78	CH_2Cl_2–eth	$C_{17}H_{17}NO_3S$	C, H, N
23	A	4-CH_3SO	1	CH_3		v	1	76[w]	113–114	CH_2Cl_2–eth	$C_{17}H_{17}NO_4S$	C, H, N
24	B	4-CH_3S	1			E	168	25[o]	113–113.5	CH_2Cl_2–eth	$C_{16}H_{14}N_2O_3S$	C, H, N
25	B	4-CH_3SO_2	1			*x*	1.5	94	183–184	CH_2Cl_2–eth	$C_{16}H_{14}N_2O_3S$	C, H, N
26	A	3-NO_2	1	CH_3		C	20	61–76[t]	124–125	CH_2Cl_2–MeOH	$C_{16}H_{14}N_2O_5$	C, H, N
27	A	4-NO_2	1	CH_3		C	68	51[y]	118–120	acet–hex	$C_{16}H_{14}N_2O_5$	C, H, N
28	A	3-NH_2	1	CH_3		*z*	0.5	96	78–79	MeOH–EtOAc	$C_{16}H_{16}N_2O_3$	C, H, N
29	A	3-*i*-C_3H_7CONH	1	CH_3		*b'*	0.5	40–46[o]	134–135	MeOH–H_2O	$C_{20}H_{22}N_2O_5$	C, H, N
30	A	4-NH_2	1	CH_3		*c'*	0.5	76	109–111	acet–hex	$C_{16}H_{16}N_2O_3$	C, H, N
31	A	4-N_3	1	CH_3		*b'*	0.5	70	90–92	CH_2Cl_2–MeOH	$C_{15}H_{12}N_4O_3$	C, H, N
32	A	3-CN	1	CH_3		C	23	70	101.5–102	CH_2Cl_2–eth	$C_{17}H_{14}N_2O_3$	C, H, N
33	A	4-CN	1	CH_3		C	15	59	112–113	CH_2Cl_2–ether	$C_{17}H_{14}N_2O_3$	C, H, N
34	A	3-CF_3	1	CH_3		C	41	98	oil	o	$C_{17}H_{14}F_3NO_3$	*d'*
35	A	4-CF_3	1	CH_3		B	1	74[e']	73–75	acet–hex	$C_{17}H_{14}F_3NO_3$	C, H, F, N
36	A	4-CH_3CO	1	CH_3		B	20	44[u]	114–116	acet–hex	$C_{18}H_{17}NO_4$	C, H, N
37	A	4-$CH_2{=}CH$	1	CH_3		B	6	36[f]	99–100	MeOH	$C_{18}H_{17}NO_3$	C, H, N
38	A	4-$CH{\equiv}C$	1	CH_3		B	12	45[f]	113–114	acet–hex	$C_{18}H_{15}NO_3$	C, H, N
39	A	2,6-F_2	1	CH_3		C	64	83[o']	84–84.5	CH_2Cl_2–eth	$C_{16}H_{13}F_2NO_3$	C, H, F, N
40	A	2,4-F_2	1	CH_3		C	67	82[g']	81–81.5	CH_2Cl_2–MeOH	$C_{16}H_{13}F_2NO_3$	C, H, F, N
41	A	2,4-Cl_2	1	CH_3		C	22	81	oil	*u*	$C_{16}H_{13}Cl_2NO_3$	*h'*
42	A	3,4-OCH_2O	1	CH_3		B	42	52[f]	98–100	acet–hex	$C_{17}H_{15}NO_5$	C, H, N
43	A	F_5	1	CH_3		B	1	93[i']	103–105	CH_2Cl_2–MeOH	$C_{16}H_{10}F_5NO_3$	C, H, F, N
44	A	4-C_6H_5	1	*i*-Pr		A	20	50[o]	121–123	CH_2Cl_2–hex	$C_{24}H_{23}NO_3$	C, H, N
45	C			*i*-Pr	β-napthyl	A	15	88	oil	o	$C_{22}H_{21}NO_3$	*j'*
46	C			*i*-Pr	cyclobutyl	A	5	88	54–55	eth–hex	$C_{16}H_{21}NO_3$	C, H, N
47	C			*i*-Pr	*tert*-butyl	A	96	25	oil	*d*	$C_{16}H_{23}NO_3$	*k'*
48	C			*i*-Pr	benzyl	A	5	70	oil	*o*	$C_{19}H_{21}NO_3$	*g*
49	D	H				C	24	89	oil	*l'*	$C_{16}H_{15}NO_3$	*m'*
50	D	Cl				C	40	86[l']	74.5–75.5	eth–EtOAc	$C_{16}H_{14}ClNO_3$	C, H, Cl, N
51	B	H	2			D	24	65[y]	100–102	acet–hex	$C_{16}H_{14}N_2O$	C, H, N
52	B	4-CH_3	2			D	48	25[n']	92–94	MeOH	$C_{17}H_{16}N_2O$	C, H, N
53	A	4-F	2	CH_3		C	20	52[o']	78–79	acet–hex	$C_{17}H_{16}FNO_3$	C, H, N
54	B	3-Cl	2			D	50	53[f']	113–115	acet–hex	$C_{16}H_{13}ClN_2O$	C, H, Cl, N
55	B	4-Cl	2			D	66	62[o']	102–104	MeOH	$C_{16}H_{13}ClN_2O$	C, H, Cl, N
56	B	4-CH_3O	2			D	48	26[n']	112–113	acet–hex	$C_{17}H_{16}N_2O_2$	C, H, N
57	B	4-CH_3S	2			D	24	24[n']	118–119	acet–hex	$C_{17}H_{16}N_2OS$	C, H, N
58	B	4-CH_3SO_2	2			*p'*	1	74	199–201	acet	$C_{17}H_{16}N_2O_3S$	C, H, N
59	A	H	3	CH_3		C	44	50[a']	98–99	acet–hex	$C_{18}H_{19}NO_3$	C, H, N
60	A	4-F	3	CH_3		C	24	68[q']	78–80	acet–hex	$C_{18}H_{18}FNO_3$	C, H, F, N
61	A	4-CH_3S	3	CH_3		A	68	57[q']	96–98	MeOH	$C_{19}H_{21}NO_3S$	C, H, N

[a] Acylation methods: A, Vilsmeier–Haack reaction; B, acid chloride and methyl ester in boiling xylene; C, acid chloride and methyl ester in boiling toluene; D, acid chloride and nitrile in boiling xylene; E, acid chloride and nitrile in boiling toluene; see Experimental Section. [b] hex = hexane; acet = acetone; eth = ether. [c] Elements shown analysed correctly to within ±0.4% of the calculated values. [d] Purified by TLC; EtOAc–CH_2Cl_2 (3:97). [e] MS M^+ 297. [f] Purified by TLC; EtOAc–CH_2Cl_2 (2:98). [g] MS M^+ 311. [h] Purified by TLC; EtOAc–CH_2Cl_2 (1.5:98.5). [i] Purified by column chromatography on silica gel; EtOAc–hexane (1:3). [j] Purified by column chromatography on silica gel; EtOAc–hexane (6:94). [k] MS M^+ 315. [l] Purified by TLC;

Footnotes to Table I (Continued)

EtOAc–CH_2Cl_2 (2.5:97.5). [m] MS M^+ 333, 331. [n] MS M^+ 327. [o] Purified by column chromatography on silica gel; EtOAc–hexane (1:1). [p] MS M^+ 355. [q] Purified by column chromatography on Activity 11 neutral alumina; EtOAc–hexane (1:9). [r] Purified by column chromatography on Activity 11 neutral alumina; EtOAc–hexane (1:4). [s] MS M^+ 294. [t] Purified by TLC; EtOAc–hexane (3:7). [u] Purified by column chromatography on silica gel; EtOAc–hexane (2:3). [v] Peracid oxidation of **22**; see Experimental Section. [w] Purified by column chromatography on silica gel; EtOAc. [x] Peracid oxidation of **24**; see Experimental Section. [y] Purified by column chromatography on silica gel; CH_2Cl_2. [z] Catalytic hydrogenation of **26**; see Experimental Section. [a'] Purified by TLC; EtOAc–hexane (1:1). [b'] See Experimental Section. [c'] Catalytic hydrogenation of **27**; see Experimental Section. [d'] MS M^+ 337. [e'] Purified by column chromatography on Florisil; EtOAc–hexane (5:95). [f'] Purified by column chromatography on Activity 11 neutral alumina; EtOAc–hexane (5:95). [g'] Purified by column chromatography on silica gel; EtOAc–hexane (3:7). [h'] MS M^+ 339, 337. [i'] Purified by column chromatography on silica gel; EtOAc–hexane (5:95). [j'] MS M^+ 347. [k'] MS M^+ 277. [l'] Purified by TLC; EtOAc–hexane (1:4). [m'] MS M^+ 269. [n'] Purified by TLC; CH_2Cl_2. [o'] Purified by TLC; EtOAc–hexane (1:3). [p'] Peracid oxidation of **57**; see Experimental Section. [q'] Purified by column chromatography on silica gel; EtOAc–hexane (1:9).

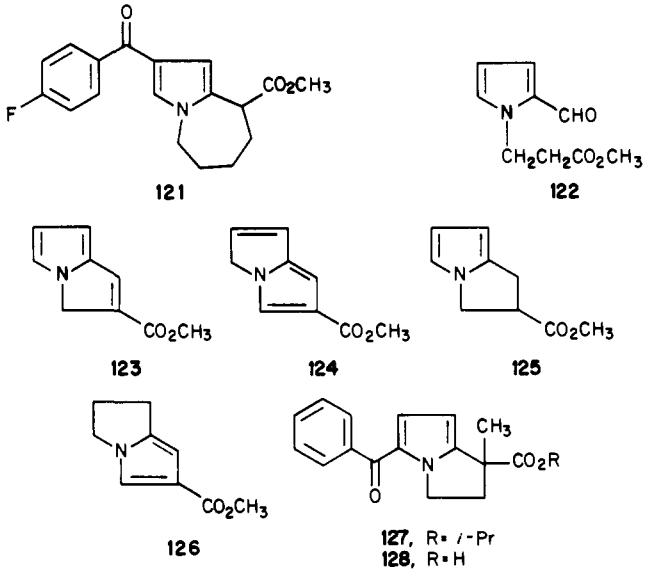
Scheme I



chloride in an inert high-boiling solvent at reflux temperature in the absence of a catalyst[13] (methods A–C, see Experimental Section). The latter technique was also utilized to acylate the nitriles VII (methods D and E). There are several noteworthy features of each acylation process. Thus, the Vilsmeier–Haack reaction was particularly efficient for the acylation of the esters V with nonhindered *N,N*-dimethylcarboxamides (Table I, method A). When moderately hindered amides were used, low product yields resulted even after exceedingly long reaction times (e.g., *N,N*-dimethyl-2-chlorobenzamide, 19% after 150 h; *N,N*-dimethylpivalamide, 25% after 96 h; Table I, **7** and **47**). With an even more sterically encumbered system, such as *N,N*-dimethyl-2,6-difluorobenzamide, acylation did not occur at all. Another problem was encountered when Vilsmeier–Haack acylations were effected on the pyrroloazepine system V ($n = 3$, $R^1 = CH_3$). The initially formed 3-acylated product underwent facile acid catalyzed rearrangement[14] to the more thermodynamically stable 2-acylated compound. Indeed, with *N,N*-dimethyl-4-fluorobenzamide, **121** was the only product isolated. In contrast to the Vilsmeier–Haack process, the noncatalyzed acylation with acid chlorides was generally applicable. The required products were usually obtained in good yields even with sterically hindered acid halides (e.g., compounds **39** and **41**; Table I) and acid-promoted acyl group migration was not a problem.

The use of the bicyclic systems V and VII was also associated with advantages and disadvantages. Thus, the esters V were readily acylated by either of the above processes, but, in general, these compounds required storage at 0 °C or less, in the absence of light and acids, if appreciable decomposition was to be avoided. While the bicyclic nitriles VII were stable solids, the rate of acylation thereof was considerably less than that observed for the esters. This rate retardation is consistent with the greater inductive effect of the nitrile moiety ($\sigma_m = 0.56$) vs. that of an alkoxycarbonyl group (e.g., $\sigma_m = 0.37$ for CO_2CH_3).[15]

Methyl 1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-2-carboxylate (**125**), the precursor of carboxylic acids **107** and **108**, isomeric with **62** and **70**, was prepared by catalytic reduction (Rh/Al_2O_3 or $Pd/CaCO_3$) of the mixture of **123** and **124** obtained from the sodium methoxide promoted cyclization of the aldehyde **122**.[16] The more polar, less abundant pyrrole **126** was separated from **125** by preparative TLC (see Experimental Section).



The 1-methyl analogue **128** of **62** was prepared by alkylation of the sodium salt of the ester **1** with methyl iodide and subsequent hydrolysis of the product thus obtained with potassium carbonate.

General Discussion

The antiinflammatory and analgesic activities of the compounds listed in Table III were first determined by using the carrageenan rat paw edema and mouse phenylquinone writhing assays, respectively (see Experimental Section). From these data it is obvious that particularly high analgesic and antiinflammatory activities reside in

(11) The initial results from clinical evaluation of **62** indicate that this compound (10 mg, oral) is equivalent to morphine sulfate (10 mg, intramuscular) for the relief of moderate to severe postoperative pain (Yee, J.; Brown, C. R.; Sevelius, H.; Wild, V. *Clin. Pharmacol. Ther.* 1984, *35*, 285) and is more efficacious than aspirin (650 mg, oral) in the aleviation of moderate or severe postpartum uterine cramps (Bloomfield, S. S.; Mitchell, J.; Cissell, G.; Barden, T. P. *Ibid.* 1984, *85*, 228).

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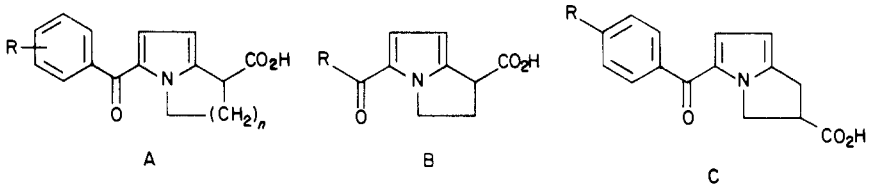
Table II. Acyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrolecarboxylic Acids and Homologous Pyridine and Azepine Analogues



A B C

no.	system	R	*n*	hydrol method[a]	rctn time, h	% yield	mp, °C	recryst solvent[b]	emp formula	anal.[c]
62	A	H	1	A	0.5	64	160–161	EtOAc–eth	$C_{15}H_{13}NO_3$	C, H, N
63	A	2-CH_3	1	A	0.4	95	161–163[d]	CH_2Cl_2–eth[d]	$C_{28}H_{38}N_2O_3$[d]	C, H, N[d]
64	A	3-CH_3	1	A	0.5	95	144–145	CH_2Cl_2–eth	$C_{16}H_{15}NO_3$	C, H, N
65	A	4-CH_3	1	A	0.5	95	182–183	EtOAc–hex	$C_{16}H_{15}NO_3$	C, H, N
66	A	3-F	1	A	1	85	150–152	EtOAc–hex	$C_{15}H_{12}FNO_3$	C, H, N
67	A	4-F	1	A	0.33	63	179.5–180.5	EtOAc–CH_2Cl_2–eth	$C_{15}H_{12}FNO_3$	C, H, N
68	A	2-Cl	1	A	0.33	85	173–175[d]	CH_2Cl_2–eth[d]	$C_{27}H_{35}ClN_2O_3$[d,e]	C, H, N[d,e]
69	A	3-Cl	1	A	0.5	52	180–181	EtOAc–eth	$C_{15}H_{12}ClNO_3$	C, H, Cl, N
70	A	4-Cl	1	A	0.33	61	201.5–202.5	EtOAc–eth	$C_{15}H_{12}ClNO_3$	C, H, N
71	A	4-Br	1	A	0.5	50	180–182	acet–hex	$C_{15}H_{12}BrNO_3$	C, H, Br, N
72	A	2-I	1	A	1.5	79	174–175	acet–hex	$C_{15}H_{12}INO_3$	C, H, N
73	A	3-OCH_3	1	A	1	61	168–170	EtOAc–hex	$C_{16}H_{15}NO_4$	C, H, N
74	A	4-OCH_3	1	A	0.33	85	187–187.5	MeOH–CH_2Cl_2–eth	$C_{16}H_{15}NO_4$	C, H, N
75	A	3-OC_2H_5	1	A	0.25	79	155–156	EtOAc–eth	$C_{17}H_{17}NO_4$	C, H, N
76	A	4-OC_2H_5	1	A	0.5	76	169.5–170	EtOAc–eth	$C_{17}H_{17}NO_4$	C, H, N
77	A	4-O-*i*-Pr	1	A	0.25	59	157–158	EtOAc–eth	$C_{18}H_{19}NO_4$	C, H, N
78	A	4-$OCH_2CH{=}CH_2$	1	A	0.5	90	112–113	acet–hex	$C_{18}H_{17}NO_4$	C, H, N
79	A	4-$OCH_2C{\equiv}CH$	1	A	0.5	79	185–187	EtOAc	$C_{18}H_{15}NO_4$	C, H, N
80	A	2-OH	1	B	18	40	160–161	EtOAc–eth	$C_{15}H_{13}NO_4$	C, H, N
81	A	3-OH	1	C	3	49	190–191	EtOAc–eth	$C_{15}H_{13}NO_4$	C, H, N
82	A	4-OH	1	C	1.5	47	191–192	MeOH–EtOAc–eth	$C_{15}H_{13}NO_4$	C, H, N
83	A	4-CH_3S	1	A	0.25	70	156–157	EtOAc–eth	$C_{16}H_{15}NO_3S$	C, H, N
84	A	4-$SOCH_3$	1	A	0.25	71	214–214.5	MeOH	$C_{16}H_{15}NO_4S$	C, H, N
85	A	4-SO_2CH_3	1	B	6	35	211–212	EtOAc–eth	$C_{16}H_{15}NO_5S$	C, H, N[f]
86	A	3-NO_2	1	C	3	39	221–222	EtOAc–CH_2Cl_2	$C_{15}H_{12}N_2O_5$	C, H, N
87	A	4-NO_2	1	D	20	100	189–191	acet–C_6H_6	$C_{15}H_{12}N_2O_5$	C, H, N
88	A	3-$NHCOCH(CH_3)_2$	1	C	1	51	187–188	EtOAc–eth	$C_{19}H_{20}N_2O_4$	C, H, N[g]
89	A	4-N_3	1	C	2	54	167–169	EtOAc–hex	$C_{15}H_{12}N_4O_3$	C, H, N
90	A	3-CN	1	C	1.5	77	193–194	MeOH–EtOAc	$C_{16}H_{12}N_2O_3$	C, H, N[h,i]
91	A	4-CN	1	C	1.5	54	198.5–199.5	MeOH	$C_{16}H_{12}N_2O_3$	C, H, N
92	A	3-CF_3	1	A	0.25	50	185–186	EtOAc–hex	$C_{16}H_{12}F_3NO_3$	C, H, F, N
93	A	4-CF_3	1	A	0.5	80	187–188	acet–hex	$C_{16}H_{12}F_3NO_3$	C, H, F, N
94	A	4-$COCH_3$	1	A	1	72	155–156	acet–hex	$C_{17}H_{15}NO_4$	C, H, N
95	A	4-$CH{=}CH_2$	1	E	5	88	155–157	acet–hex	$C_{17}H_{15}NO_3$	C, H, N
96	A	4-$C{\equiv}CH$	1	E	2	93	161–162	acet	$C_{17}H_{13}NO_3$[j]	C, H, N[j]
97	A	2,6-F_2	1	A	0.25	71	165–166.5	EtOAc–eth–hex	$C_{15}H_{11}F_2NO_3$	C, H, F, N
98	A	2,4-F_2	1	C	1.5	53	154–155	EtOAc–eth	$C_{15}H_{11}F_2NO_3$	C, H, F, N
99	A	2,4-Cl_2	1	A	0.25	39	150–151	EtOAc–eth	$C_{15}H_{11}Cl_2NO_3$	C, H, Cl, N
100	A	3,4-OCH_2O	1	A	0.5	98	166–168	EtOAc–hex	$C_{16}H_{13}NO_5$	C, H, N
101	A	F_5	1	F	48	80	128–130	eth–hex	$C_{15}H_8F_5NO_3$	C, H, F, N[b]
102	A	4-C_6H_5	1	A	0.25	64	202.5–203.5	EtOAc–eth	$C_{21}H_{17}NO_3$	C, H, N
103	B	β-naphthyl	1	A	0.25	80	179–180	EtOAc	$C_{19}H_{15}NO_3$	C, H, N
104	B	cyclobutyl	1	A	0.4	78	152–153	CH_2Cl_2–eth–hex	$C_{13}H_{15}NO_3$	C, H, N
105	B	*tert*-butyl	1	A	0.6	71	175–175.5	CH_2Cl_2–hex	$C_{13}H_{17}NO_3$	C, H, N
106	B	benzyl	1	A	0.25	66	142–144	EtOAc–eth	$C_{16}H_{15}NO_3$	C, H, N[l]
107	C	H		C	0.5	99	125.5–126.5	hex	$C_{15}H_{13}NO_3$	C, H, N
108	C	Cl		C	0.5	90	171.5–172.5	EtOAc	$C_{15}H_{12}ClNO_3$	C, H, Cl, N
109	A	H	2	G	3	62	168–169	EtOAc–eth	$C_{16}H_{15}NO_3$	C, H, N
110	A	4-CH_3	2	G	1	46	146–147	acet–hex	$C_{17}H_{17}NO_3$	C, H, N
111	A	4-F	2	A	2	70	161–162	acet	$C_{16}H_{14}FNO_3$	C, H, F, N
112	A	3-Cl	2	B	10	61	145–147	EtOAc	$C_{16}H_{14}ClNO_3$	C, H, Cl, N
113	A	4-Cl	2	G	2	54	153–155	EtOAc–hex	$C_{16}H_{14}ClNO_3$[m]	C, H, N[m]
114	A	4-OCH_3	2	G	1	61	156–157	acet–hex	$C_{17}H_{17}NO_4$	C, H, N
115	A	4-SCH_3	2	G	2.5	55	174–175	CH_2Cl_2–MeOH	$C_{17}H_{17}NO_3S$	C, H, N
116	A	4-$SOCH_3$	2	k	18	60	201–202	CH_2Cl_2–MeOH	$C_{17}H_{17}NO_4S$	C, H, N
117	A	4-SO_2CH_3	2	G	2.5	35	179–180	acet–eth	$C_{17}H_{17}NO_5S$	C, H, N
118	A	H	3	A	2	73	163–165	EtOAc–Hex	$C_{17}H_{17}NO_3$	C, H, N
119	A	4-F	3	A	1	80	142–144	acet–hex	$C_{17}H_{16}FNO_3$	C, H, F, N
120	A	4-SCH_3	3	A	1	60	165–167	acet–hex	$C_{18}H_{19}NO_3S$	C, H, N

[a] Hydrolysis methods: A, K_2CO_3/aqueous methanol on esters; B, KOH/aqueous ethanol on nitriles; C, KOH/aqueous methanol on esters; D, DBN/THF; E, NaOH/aqueous methanol on esters; F, TsOH/HCOOH; G, KOH/aqueous ethylene glycol on nitriles. [b] See Table I for key to abbreviations. [c] Elements shown analyzed correctly to within ±0.4% of the calculated values except where indicated otherwise. [d] Refers to dicyclohexylammonium salt. [e] Anal. Calcd for $C_{27}H_{35}ClN_2O_3 \cdot 0.25H_2O$. [f] Calcd C, 57.64; found C, 56.39. [g] Calcd C, 67.03; N, 8.23; found C, 66.40; N, 7.77. [h] Calcd C, 68.56; N, 10.00; found C, 67.01; N, 8.85. [i] *m/e* 280.0841 (calcd for $C_{16}H_{12}N_2O_3$: 280.0848). [j] Anal. Calcd for $C_{17}H_{13}NO_3 \cdot 0.1H_2O$. [k] Calcd F, 27.51; found F, 26.96. [l] Calcd C, 71.36; found C, 70.86. [m] Anal. Calcd for $C_{16}H_{14}ClNO_3 \cdot 0.25H_2O$.

Table III. Historical Antiinflammatory and Analgesic Activities of Acyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrolecarboxylic Acids and Homologous Pyridine and Azepine Analogues

no.	rat paw assay, phenylbutazone = 1[a]	mouse writhing assay, aspirin = 1[b]	no.	rat paw assay phenylbutazone = 1	mouse writhing assay, aspirin = 1
62	36 (89)[c]	350 (152)[d]	**92**	≤1 (28)	<10 (16)
63[e]	~1.5 (12)	35 (40)	**93**	<10 (12)	100 (24)
64	≤0.4 (24)	~7 (40)	**94**	15 (30)	160 (24)
65	~55 (48)	200 (48)	**95**	160 (30)	330 (48)
66	6 (30)	~20 (24)	**96**	17 (12)	23 (40)
67	35 (71)	~200 (56)	**97**	~4 (18)	~45 (40)
68[c]	~4 (12)	35 (24)	**98**	~14 (71)	120 (42)
69	≤4 (17)	~20 (24)	**99**	~10 (12)	35 (40)
70	17 (18)	85 (48)	**100**	<10 (12)	0.6 (16)
71	25 (12)	13 (16)	**101**	<3 (12)	<0.25 (12)
72	1.5 (12)	<1 (16)	**102**	<1 (12)	<0.2 (8)
73	<1 (18)	~4 (16)	**103**	5 (30)	~5 (16)
74	43 (36)	130 (24)	**104**	~1.5 (12)	30 (24)
75	<1 (18)	≤1 (16)	**105**	1 (12)	~10 (16)
76	55 (30)	35 (24)	**106**	3 (12)	≤14 (16)
77	<1 (12)	0.8 (24)	**107**	<1 (12)	~4 (16)
78	<10 (12)	2 (32)	**108**	≤0.3 (12)	<10 (16)
79	<10 (12)	2 (16)	**109**	<1 (12)	9 (48)
80	~4 (12)	~100 (72)	**110**	<1 (23)	<0.5 (8)
81	<1 (12)	<0.7 (8)	**111**	<1 (12)	<10 (16)
82	<10 (12)	<3 (16)	**112**	~8 (24)	~9 (32)
83	40 (36)	150 (32)	**113**	≤0.6 (12)	<1 (16)
84	~10 (42)	~3 (16)	**114**	1.6 (12)	1.5 (16)
85	<0.5 (24)	≤0.6 (16)	**115**	~1 (12)	3 (16)
86	<1 (12)	<1 (8)	**116**	<0.2 (12)	~0.5 (8)
87	<2 (12)	~14 (16)	**117**	3 (12)	<1 (8)
88	<2 (12)	<0.5 (16)	**118**	~0.4 (12)	~3 (16)
89	5 (30)	35 (48)	**119**	<1 (12)	<1.3 (16)
90	<5 (12)	≤2.5 (16)	**120**	<0.2 (12)	~6 (16)
91	<1 (24)	6 (24)	**128**	~7 (12)	<6 (16)

[a] ED_{30} = 15 mg/kg. [b] ED_{50} = 70 mg/kg. [c] Number of rats. [d] Number of mice. [e] Tested as dicyclohexylammonium salt.

the 1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic acids bearing an aroyl group at the 5-position. Alteration of this basic structure was invariably associated with a major reduction in potency in both test systems. Thus, the 5-cyclobutylcarbonyl (**104**), 5-*tert*-butylcarbonyl (**105**), and 5-phenylacetyl (**106**) derivatives were weakly active in the rat paw assay (1–3 times phenylbutazone) and showed only modest activity, at best, in the mouse writhing assay (10–30 times aspirin), even though the log *P* values (Table V) of these substances differ only slightly from that of the highly active 5-benzoyl compound (**62**). Furthermore, translocation of the carboxyl group from C-1 to C-2, as in compounds **107–109**, virtually abolished antiinflammatory activity and greatly attenuated the analgesic activity. Similar results were observed when the size of the saturated ring of the pyrrolopyrrole moeity was increased by one or two carbon atoms as found in the 3-aroyltetrahydropyrrolo[1,2-*a*]pyridinecarboxylic acids and the 2-aroyltetrahydro-9*H*-pyrrolo[1,2-*a*]azepinecarboxylic acids **109–117** and **118–120**, respectively. This latter observation implies that the region of the cyclooxygenase[17] receptor site[18-20] occupied by the methyl group of arylpropionic acid antiinflammatory agents is sensitive to steric bulk. The low degree of activity observed for the α-methyl compound **128** is also explicable as an exacerbation of a sterically demanding situation in the region of the carboxyl group.[18]

A detailed study of quantitative structure–activity relationships (QSARs) for the 5-aroyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic acids (see next section) for both assays has revealed that the potencies are correlated neither with log *P* nor with the electronic substituent constants (e.g., *fF*, *rR*).[21] The near constancy of the pK_a values measured for the carboxylic acids (Table V) as well as the virtual invariance of ν ($CHCl_3$) of the ester carbonyl (1738 ± 4 cm^{-1}) and the NMR chemical shift of H-1 (δ 4.04 ± 0.05) for a series of 20 meta and para-substituted 5-aroyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic acid esters (Table XI) are at least consistent with minimal electronic effects on the biological activity. Both the analgesic and antiinflammatory activities are, however, acceptably correlated with precise steric and hydrogen-bonding properties of the substituents (eq 1–7, 10; Tables VI, VII, IX). Thus the ortho position is only moderately tolerant of bulky substituents [e.g., **80** (OH), **97** (2,6-F_2), Table III], whereas the meta position cannot tolerate such groups [**88** ($NHCOCHMe_2$)] and the para position has specific shape requirements. Hydrogen bond acceptor substituents have a deleterious effect on the activities at either the meta or the para position. On the above basis, the 4-vinylbenzoyl compound **95** was predicted to be highly active and this prediction was subsequently confirmed when the compound was synthesized and subjected to the biological assays.

(17) Several of the highly active compounds described herein are, like the common nonsteroidal antiinflammatory agents, potent inhibitors of prostaglandin biosynthesis. Thus, compounds **62** and **70** were 2.8- and 1.7-fold more potent than indomethacin (IC_{50} = 7.3 ± 3.5 × 10^{-7} M) with regard to the inhibition of the prostaglandin synthetase of bovine seminal vessicles (Tomlinson, R. V.; Ringold, H. J.; Qureshi, M. C.; Forchielli, E. *Biochem. Biophys. Res. Commun.* **1972**, *46*, 552). In addition, **62** and **70** were 5.8 and 1.8 times as potent as indomethacin (IC_{50} = 11.0 ± 5.5 × 10^{-7} M) for the inhibition of human platelet microsomal prostaglandin synthetase (Hammerström, S.; Falardeau, P. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 3691. Flower, R. J.; Cheung, H. S.; Cushman, D. W. *Prostaglandins* **1973**, *4*, 325).

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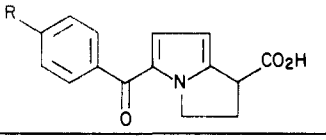
Table IV. Antiinflammatory Profile of 5-Aroyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic Acids



compound no.	R	antiinflammatory assays: rat paw, phenylbutazone = 1	mouse writhing, aspirin = 1	cotton pellet, indomethacin = 1[a]	adjuvant arthritis, naproxen = 1[b]	gastrointestinal erosion[c]: MED,[d] mg/kg per day	gastrointestinal erosion[c]: ED_{50}, mg/kg per day	therapeutic ratio[e]
62	H	55 (33–92)[f]	347 (256–480)[f]	0.5 (357)[g]	2 (216)[g]	5 (230)[g]	13	18
65	CH_3	39 (21–73)	165 (101–264)	<0.3 (54)	0.6 (36)	3 (15)	15	8
67	F	61 (17–214)	183 (117–310)	1–2 (63)	1–3 (120)	5 (30)	13	20
70	Cl	21 (9–60)	83 (53–135)	1–3 (36)	4 (36)	3 (45)	6	4
74	CH_3O	83 (30–414)	117 (57–246)	0.6 (99)	<0.3 (72)	7 (56)	22	39
95	CH_2=CH	127 (78–240)	~200 (48)[h]	1.0 (54)	7 (72)	1 (30)	3	8
zomepirac		26 (13–62)	36 (29–44)			10		17
naproxen		11 (7–17)[i]	7 (4–12)[i]	0.2	1	30	40	22
indomethacin		16 (18–31)[i]	~60 (100)[h,i]	1	7			

[a] ED_{30} = 3 mg/kg (2.0–4.6). [b] ED_{50} = 1.7 mg/kg (0.9–2.8). [c] Seven-day chronic assay; see Experimental Section. [d] Minimum effective dose; see Experimental Section. [e] MED GI erosion/ED_{30} rat paw. [f] 95% confidence limits. [g] Number of rats. [h] Number of mice. [i] Data taken from ref 35.

The compounds that showed high potencies in the acute screens, referred to above, were then selected for study in the cotton pellet granuloma and adjuvant arthritis assays that are chronic models of inflammation. The data obtained for several of the more interesting agents are shown in Table IV. All of these compounds have considerable activity, but the 4-vinylbenzoyl compound **95** is the most potent, being equiactive with indomethacin in both assays. In addition, these compounds were evaluated for gastrointestinal erosive activity by using a 7-day assay in rats (see Experimental Section). The minimum (MED) and median effective erosion doses are also given in Table IV. The therapeutic ratio was calculated for the compounds by dividing the minimum effective dose causing gastrointestinal erosion by the ED_{30} for the carrageenan rat paw assay. The benzoyl compound **62** thus had a therapeutic ratio (Table IV) of 18. On the basis of particularly favorable therapeutic ratios as well as the results of acute and chronic toxicity studies in animals, the benzoyl and 4-methoxybenzoyl compounds **62** and **74** were selected for clinical evaluation as analgesic agents. The 4-vinylbenzoyl compound **95**, which was the most active agent in the acute and chronic models of inflammation, is currently undergoing extensive pharmacological evaluation in animals. The gastrointestinal erosion liability of this compound, though somewhat higher than other members of this series, is nevertheless considered to be within acceptable limits.

QSAR of the Pyrrolopyrrole Derivatives. In the initial phases of the program a correlation of the phenylquinone writhing (QW) assay for 12 para substituents was obtained (eq 1). The parameters investigated were

$$\log A_{qw} = \underset{(5.71)}{-4.45} - \underset{(0.76)}{0.73}D^4_{ha} + \underset{(5.35)}{6.50}B^4_3 - \underset{(1.21)}{1.55}(B^4_3)^2 \quad (1)$$

$n = 12$, $s = 0.55$, $r = 0.832$, $F_{3,8} = 6.00$, sd/sdm = 20%

$(B^4_3)_0 = 2.09$ (1.52–2.37); jackknifed $(B^4_3)_0 =$ 2.18 (1.77–2.60)

log *P*, $(\log P)^2$, D^4_{ha}, MR^4, *fF*, *rR*, and the five Verloop steric constants and the squares thereof. $D^4_{ha} = 1$ for hydrogen bond acceptor substituents, MR^4 is the molar refractivity, *fF* and *rR* are the corrected[20] Wellcome field and resonance constants, and L^4 and B^4_{1-4} are the Verloop[22] steric constants (the 4 refers to the para position). Figures in parentheses are 95% confidence levels, n = number of points, s = standard deviation, r = correlation coefficient, F = overall F test for significance of regression, and sd/sdm = s/standard deviation of data (a rough measure of the precision of the regression compared to the range in the data). All terms are significant at ≥95% confidence level unless otherwise noted (in this case D^4_{ha} is significant at the 90% confidence level).

As can be seen from Table VI, there are no significant deviations and an analysis of the residuals shows them to be evenly distributed with no obvious trends. However, in the B^4_3 terms are highly correlated due to the small range in B^4_3. This can be reduced by subtracting the mean of the B^4_3 values (2.02) and recalculating $(B^4_3)^2$ values. Since the mean is close to the optimum B^4_3 found in eq 1, the linear term is no longer significant in eq 2. The cross-correlation

$$\log \bar{A}_{qw} = \underset{(0.43)}{0.36} - \underset{(0.72)}{0.71}\bar{D}^4_{ha} - \underset{(1.01)}{1.40}(\bar{B}^4_3)^2 \quad (2)$$

$n = 12$, $s = 0.53$, $r = 0.823$, $F_{2,9} = 9.45$, sd/sdm = 19%

between B^4_3 terms drops from $r = 0.991$ to 0.505, but eq 2 also has one less term. The D^4_{ha} is significant at 90% CL.

Since eq 2 does not significantly differ from eq 1, we examined a list of Verloop's steric constants for $6.5B^4_3 - 1.55(B^4_3)^2 > 0$ and with $D_{ha} = 0$. The 4-CH=CH_2 substituent was at the top of this list and, when synthesized, **95** turned out to be a very active compound at 330 times aspirin in QW and 160 times phenylbutazone in the rat carrageenan paw antiinflammatory assay (CP). That there are subtle steric differences in the receptor[17] can be seen by comparison with **96**, the 4-C≡CH analogue, which is only 23 or 17 times the standards, despite very similar log *P* values.

The calculated potencies in QW from eq 1 for 4-CH=CH_2 **95** is 224 and for 4-C≡CH **96** is 96. Both calculated values are quite within the standard deviation limit of the eq 1 and 2. The 4-CH=CH_2 is correctly predicted on steric and hydrogen-bonding properties alone; thus, it is not likely that there are chemical interactions of the vinyl group with the receptor despite the fact that the 4-CH=CH_2 moiety would occupy a position equivalent to the Δ_{14} of arachidonic acid in the receptor site models of Gund and Shen or Salvetti et al.[20,23]

(22) Verloop, A.; Hoogenstraaten, W.; Tipker, J. *Drug Design* **1976**, *7*, 165.

(23) Salvetti, F.; Buttinoni, A.; Ceserani, R.; Tosi, C. *Eur. J. Med. Chem.* **1981**, *16*, 81.

Table V. log P and pK_a Values Determined by Reverse-Phase HPLC[a]

no.	log P	pK_a	n[c]	r[c]	no.	log P	pK_a	n[c]	r[c]
62	2.72[c] ± 0.02	3.49 ± 0.02 (3.54)[b]	10	0.986	**93**	3.71			
63	2.90[c] ± 0.02	3.44 ± 0.03	11	0.975	**94**	2.27			
64	3.23[c] ± 0.01	3.44 ± 0.02	10	0.991	**95**	3.47			
65	3.24[c] ± 0.01	3.44 ± 0.02	10	0.993	**96**	3.33			
66	2.90[c] ± 0.02	3.46 ± 0.03	9	0.976	**97**	2.47			
67	2.82[c] ± 0.02	3.51 ± 0.03	11	0.979	**98**	2.59			
68	2.71[c] ± 0.02	4.33 ± 0.04	10	0.955	**99**	3.56			
69	3.48[c] ± 0.03	3.44 ± 0.04	9	0.968	**100**	3.61			
70	3.49[c] ± 0.02	3.40 ± 0.03	10	0.975	**101**	3.24			
71	3.60				**102**	4.27			
72	2.98				**103**	3.97[c] ± 0.01	3.44 ± 0.01	4	1.00
73	2.74				**104**	2.41[c] ± 0.02	3.54 ± 0.05	12	0.938
74	2.81[c] ± 0.02	3.55 ± 0.04 (3.69)[d]	10	0.967	**105**	2.60[c] ± 0.02	3.57 ± 0.09	10	0.967
75	3.31[c] ± 0.02	3.46 ± 0.03	9	0.984	**106**	2.52			
76	3.30[c] ± 0.02	3.46 ± 0.03	9	0.983	**107**	2.57			
77	3.38[c] ± 0.01	3.43 ± 0.02	12	0.992	**108**	3.45			
78	3.48				**109**	...			
79	3.63				**110**	3.35			
80	2.94				**111**	2.94			
81	2.18				**112**	2.61			
82	2.17				**113**	3.60			
83	3.68				**114**	2.90			
84	1.08				**115**	3.54			
85	1.41				**116**	1.41			
86	2.47				**117**	1.53			
87	2.48				**118**	3.17			
88	2.57				**119**	3.32			
89	1.15				**120**	3.92			
90	2.14								
91	2.21								
92	3.69								

[a] Log P determined by correction of log D at pH 2.2 (μ = 0.01) determined on C-18 Corasil, unless otherwise noted. [b] Spectrophotometric (μ = 0.10); RP-HPLC at μ = 0.10 is 3.52. [c] Determined from log D data at several pH values by curve fitting,[32] μ = 0.01. Standard deviations are indicated. n = number of individual injections, r = correlation coefficient of fit. [d] Spectrophotometric (μ = 0.03), 25 °C.

We now turn to the correlation of the full set of pyrrolopyrroles in the QW assay. The variables are the same as discussed for eq 1, in that terms are added for each position, except for the electronic terms. An extensive set of steric parameters is justified by the previous experience with respect to the shape of the receptor.[20,23]

Equations were first developed for each position of substitution independently. The general procedure was to use a simple stepwise regression to reduce the number of variables to be examined by all-regressions. The best of the all-regressions (those with about five data points per variable) were examined in detail, including simple and multiple colinearities[21,24] and residuals. The ratio of about five data points per variable stems from consideration of F levels and not from the Topliss criterion,[25] which we feel is, in fact, unworkable because it raises the logical dilemma of not investigating sufficient parameters because one is fearful of "chance" correlations. The only solution to this logical fallacy is to be cautious in the interpretation of the results, especially, to predict new compounds and to assure that the equations are consistent with all available knowledge.[21,26] The B_3^4 terms are correlated with r^2 = 98%.

para

$$\log A_{qw} = \underset{(3.52)}{-1.76} - \underset{(1.76)}{2.40fF} + \underset{(3.56)}{5.28B_3^4} - \underset{(0.04)}{0.07(L^4)^2} - \underset{(0.80)}{1.29(B_3^4)^2} \quad (3)$$

n = 21, s = 0.61, r = 0.847, $F_{4,16}$ = 10.13, sd/sdm= 13%

$(B_3^4)_0$ = 2.04 (1.60–2.27); jackknifed 2.01 (1.66–2.37)

The sd/sdm ratio is about the order of experimental error for this assay. The "jackknifed" optimal value is calculated according to Dietrich et al.[27] Compound **82** deviated by 2.6 standard deviations and, when omitted, the statistics improved to n = 20, s = 0.43, r = 0.926, $F_{4,15}$ = 22.65, sd/sdm = 9.7% with $(B_3^4)_0$ = 1.92 (1.46–2.13), jackknifed 1.88 (1.57–2.19). Equations 4 and 5 describe the para, meta, ortho, disubstituted (omitting **82** and **103**) meta and ortho subsets and eq 6 the total set, including the four disubstituted compounds but with the outliers **82** and **103** omitted. Equation 6 can be compared to eq 7, which was

meta

$$\log A_{qw} = \underset{(0.46)}{1.04} - \underset{(0.60)}{1.05D_h^3} \quad (4)$$

n = 10, s = 0.40, r = 0.819, $F_{1,8}$ = 16.32, sd/sdm = 20%

ortho

$$\log A_{qw} = \underset{(0.66)}{2.65} - \underset{(0.08)}{0.21MR^2} \quad (5)$$

n = 4, s = 0.16, r = 0.992, $F_{1,2}$ = 122.0, sd/sdm = 9%

$$\log A_{qw} = \underset{(1.72)}{-1.28} + \underset{(1.94)}{4.34B_3^4} - \underset{(0.03)}{0.05(L^4)^2} - \underset{(0.47)}{1.15(B_3^4)^2} - \underset{(0.60)}{1.58D_{ha}^3} - \underset{(0.08)}{0.11MR^2} \quad (6)$$

n = 37, s = 0.55, r = 0.851, $F_{5,31}$ = 16.26, sd/sdm = 9%

obtained by a stepwise regression (BMDP2R) with F_{enter} = 3.0, F_{remove} = 2.9, and tolerance = 0.10 using all of the data and all of the parameters as input. In this case, we have subtracted the mean for each parameter from each

(24) Farrar, D. E.; Glauber, R. R. *Rev. Econ. Stat.* **1969**, *49*, 92.
(25) Topliss, J. G.; Costello, R. J. *J. Med. Chem.* **1972**, *15*, 1066.
(26) Unger, S. H.; Hansch, C. *J. Med. Chem.* **1973**, *16*, 745.
(27) Dietrich, S. W.; Dreyer, W. D.; Hansch, C.; Bentley, D. L. *J. Med. Chem.* **1980**, *23*, 1201.

Table VI. Historical Correlation of log A_{qw} (Equation 1)

no.	X	log A_{qw}[a]	calcd	Δ	sdu	D^4_{ha}	B^4_3
65	Me	2.30	2.28	0.02	0.03	0	1.9
67	F	2.30	1.49	0.81	1.49	0	1.35
70	Cl	1.93	2.21	−0.28	−0.51	0	1.8
74	OMe	2.11	1.56	0.55	1.02	1	1.9
76	OEt	1.54	1.56	−0.02	−0.02	1	1.9
77	i-OPr	−0.10	−0.16	0.06	0.12	1	3.16
82	OH	0.18	0.76	−0.58	−1.07	1	1.35
83	SMe	2.18	2.28	−0.10	−0.20	0	1.9
87	NO_2	1.15	1.42	−0.27	−0.51	1	2.44
89	N_3	1.54	1.99	−0.45	−0.81	0	2.57
91	CN	0.78	1.24	−0.46	−0.84	1	1.6
94	COMe	2.20	1.50	0.70	1.29	1	2.36

[a] Log activity relative to aspirin in phenylquinone mouse writhing assay, Table 3. For activities reported as $\sim x$ or $\leq x$, x was taken; for $<x$, $x/2$ was taken.

Table VII. Data and Residuals for Equation 7: Analgetic Activity

no.	log $\bar{A}_{qw}$[a]	calcd	Δ	sdu	$\bar{D}^3_{ha}$	$\bar{D}^4_{ha}$	$\bar{B}^3_3$	$(\bar{L}^2)^2$	$(\bar{L}^4)^2$	$(\bar{B}^4_3)^2$
62	1.47	0.68	0.79	1.47	−0.1538	−0.2564	−0.2533	0.04093	1.36	0.4188
63	0.47	0.44	0.03	0.05	−0.1538	−0.2564	−0.2533	0.5442	1.36	0.4188
64	−0.23	−0.03	−0.20	−0.37	−0.1538	−0.2564	0.6467	0.04093	1.36	0.4188
65	1.22	1.10	0.12	0.23	−0.1538	−0.2564	−0.2533	0.04093	0.05115	0.06392
66	0.22	0.40	−0.18	−0.33	−0.1538	−0.2564	0.09667	0.04093	1.36	0.4188
67	1.22	1.05	0.18	0.33	−0.1538	−0.2564	−0.2533	0.04093	0.332	0.08832
68	0.47	−0.05	0.51	0.96	−0.1538	−0.2564	−0.2533	1.582	1.36	0.4188
69	0.22	0.04	0.18	0.33	−0.1538	−0.2564	0.5467	0.04093	1.36	0.4188
70	0.85	1.12	−0.27	−0.51	−0.1538	−0.2564	−0.2533	0.04093	0.08635	0.02335
71	0.03	1.04	−1.01	−1.88	−0.1538	−0.2564	−0.2533	0.04093	0.3646	0.0917
72	−1.38	−1.13	−0.25	−0.47	−0.1538	−0.2564	−0.2533	3.872	1.36	0.4188
73	−0.48	−1.12	0.65	1.21	0.8462	−0.2564	0.6467	0.04093	1.36	0.4188
74	1.04	0.37	0.67	1.25	−0.1538	0.7436	−0.2533	0.04093	0.5683	0.06392
75	−1.08	−1.12	0.05	0.08	0.8462	−0.2564	0.6467	0.04093	1.36	0.4188
76	0.47	0.07	0.40	0.75	−0.1538	0.7436	−0.2533	0.04093	2.869	0.06392
77	−1.17	−1.38	0.20	0.38	−0.1538	0.7436	−0.2533	0.04093	1.86	2.289
79	−0.78	−1.03	0.25	0.46	−0.1538	0.7436	−0.2533	0.04093	11.25	0.06392
80	0.90	0.59	0.31	0.58	−0.1538	−0.2564	−0.2533	0.2282	1.36	0.4188
81	−1.23	−0.69	−0.55	−1.02	0.8462	−0.2564	0.09667	0.04093	1.36	0.4188
82	−0.90	0.39	−1.29	−2.41	−0.1538	0.7436	−0.2533	0.04093	0.2363	0.08832
83	1.10	0.96	0.14	0.26	−0.1538	−0.2564	−0.2533	0.04093	1.153	0.06392
84	−0.60	−0.77	0.17	0.31	−0.1538	0.7436	−0.2533	0.04093	0.6462	1.646
85	−1.30	−0.43	−0.67	−1.63	−0.1538	0.7436	−0.2533	0.04093	1.308	1.046
86	−1.38	−1.55	0.17	0.32	0.8462	−0.2564	1.187	0.04093	1.36	0.4188
87	0.07	0.03	0.03	0.06	−0.1538	0.7436	−0.2533	0.04093	0.04573	0.6286
88	−1.68	−1.15	−0.53	−0.98	0.8462	−0.2564	0.6867	0.04093	1.36	0.4188
89	0.47	0.30	0.17	0.32	−0.1538	−0.2564	−0.2533	0.04093	1.943	0.8516
90	−0.68	−0.69	0.21	0.38	0.8462	−0.2564	0.3467	0.04093	1.36	0.4188
91	−0.30	0.35	−0.65	−1.21	−0.1538	0.7436	−0.2533	0.04093	1.008	0.002226
92	−0.38	−0.46	0.08	0.16	−0.1538	−0.2564	1.187	0.04093	1.36	0.4188
93	0.92	0.71	0.22	0.40	−0.1538	−0.2564	−0.2533	0.04093	0.005453	0.6286
94	1.13	0.03	1.09	2.04	−0.1538	0.7436	−0.2533	0.04093	0.6953	0.5081
95	1.43	0.92	0.52	0.96	−0.1538	−0.2564	−0.2533	0.04093	1.132	0.1245
96	0.28	0.88	−0.60	−1.12	−0.1538	−0.2564	−0.2533	0.04093	2.056	0.002226
97	0.58	0.63	0.05	−0.10	−0.1538	−0.2564	−0.2533	0.1503	1.36	0.4188
98	1.00	0.99	0.01	0.01	−0.1538	−0.2564	−0.2533	0.1503	0.332	0.08832
99	0.47	0.40	0.07	0.13	−0.1538	−0.2564	−0.2533	1.582	0.08635	0.02335
102	−2.08	−1.58	−0.50	−0.93	−0.1538	−0.2564	−0.2533	0.04093	9.326	2.14
103	−0.38	−0.11	−0.27	−0.50	−0.1538	−0.2564	1.007	0.04093	0.005453	0.3755

[a] Mean = 1.08.

parameter, before taking the squares, in order to reduce colinearities. Compounds **82** and **94** are greater than 2 standard deviations and removing these gives an improvement in $r = 0.93$ and $s = 0.37$. However, additional multicolinearities are introduced compared to eq 7, which

$$\log \bar{A}_{qw} = \underset{(0.26)}{0.63} - \underset{(0.60)}{1.09}\bar{D}^3_{ha} - \underset{(0.45)}{0.67}\bar{D}^4_{ha} - \underset{(0.50)}{0.79}\bar{B}^3_3 - \underset{(0.27)}{0.47}(\bar{L}^2)^2 - \underset{(0.09)}{0.13}(\bar{L}^4)^2 - \underset{(0.36)}{0.70}(\bar{B}^4_3)^2 \quad (7)$$

$n = 39$, $s = 0.54$, $r = 0.860$, $F_{6,32} = 15.14$, sd/sdm = 9%

contains only one statistically significant colinearity, viz., that between $\bar{D}^3_{ha}$ and $\bar{B}^3_3$ of 33%. Furthermore, the regression coefficients are stable to a ridge trace,[28] which indicates that the colinearities are not severe. The log $\bar{A}_{qw}$ activities, residuals, and variables are given in Table VII. The residuals show no trends nor do the probability plots show deviations.[33]

Since the square terms have been corrected for the mean, the optimal values are the means themselves. Thus, $(L^2)_o = 2.26$ $(L^4)_o = 3.23$, and $(B^4_3)_o = 1.65$. It is possible, of course, that linear terms could be introduced with more compounds in the equation, but these do not appear to be justified with $n = 39$ compounds.

The ortho position can tolerate some bulk (eq 7) but probably not a great deal (eq 5 and 6). The meta position can tolerate neither hydrogen bond acceptor substituents

(28) Hoerl, A. E.; Kennard, R. W. *Technometrics* **1970**, *12*, 65.

Table VIII. Correlation of A_{qw} by A_{cp} (Equation 9)

no.	A_{qw}	calcd	Δ	sdu	no.	A_{qw}	calcd	Δ	sdu
62	350.00	105.93	244.07	4.08	**83**	150.00	115.10	34.90	0.58
63	35.00	26.78	8.22	0.14	**84**	3.02	46.28	−43.26	−0.72
64	7.00	24.26	−17.26	−0.29	**85**	0.60	23.91	−23.31	−0.39
65	200.00	149.52	50.48	0.84	**86**	0.50	24.49	−23.99	−0.40
66	20.00	37.10	−17.10	−0.29	**87**	14.00	25.63	−11.63	−0.19
67	200.00	103.63	96.37	1.61	**88**	0.25	25.63	−25.38	−0.42
68	35.00	32.52	2.48	0.04	**89**	35.00	34.81	0.19	0.00
69	20.00	32.52	−12.52	−0.21	**90**	2.50	29.08	−26.58	−0.44
70	85.00	62.34	22.66	0.38	**91**	6.00	24.49	−18.49	−0.31
71	12.88	80.97	−68.08	−1.14	**92**	5.00	25.63	−20.63	−0.35
72	0.50	26.78	−26.28	−0.44	**93**	100.00	34.84	65.16	1.09
73	4.00	24.49	−20.49	−0.34	**94**	160.00	57.75	102.25	1.71
74	130.00	121.99	8.01	0.13	**95**	323.59	386.93	−63.34	−1.06
75	1.00	24.49	−23.49	−0.39	**96**	22.91	62.30	−39.39	−0.66
76	35.00	149.52	−114.52	−1.92	**97**	45.00	32.52	12.48	0.21
77	0.80	24.49	−23.69	−0.40	**98**	120.00	55.46	64.54	1.08
79	2.00	34.84	−32.84	−0.55	**99**	35.00	46.28	−11.28	−0.19
80	95.50	32.47	63.03	1.05	**102**	0.10	24.49	−24.39	−0.41
81	0.70	24.49	−23.79	−0.40	**103**	5.00	34.81	−29.81	−0.50
82	1.50	34.81	−33.31	−0.56					

Table IX. Data and Residuals for Equation 10: Antiinflammatory Activity

no.	log $\bar{A}_{cp}$[a]	calcd	Δ	sdu	$\bar{D}^4_{ha}$	$\bar{B}^3_4$	$\bar{B}^4_4$	$(\bar{B}_3{}^4)^2$
62	0.93	−0.04	0.97	1.98	−0.2564	−0.389	−0.092	0.4188
63	−0.45	−0.04	−0.41	−0.83	−0.2564	−0.389	−0.092	0.4188
64	−1.03	−0.45	−0.58	−1.17	−0.2564	0.651	−0.092	0.4188
65	1.11	0.67	0.44	0.89	−0.2564	−0.389	0.12	0.06392
66	0.15	−0.18	0.33	0.67	−0.2564	−0.03897	−0.92	0.4188
67	0.92	0.38	0.54	1.09	−0.2564	−0.389	−0.57	0.08832
68	−0.03	−0.04	0.02	0.03	−0.2564	−0.389	−0.92	0.4188
69	−0.03	−0.36	0.33	0.67	−0.2564	0.411	−0.92	0.4188
70	0.60	0.61	−0.01	−0.02	−0.2564	−0.389	−0.12	0.02335
71	0.77	0.61	0.16	0.32	−0.2564	−0.389	0.03	0.0917
72	−0.45	−0.04	−0.41	−0.83	−0.2564	−0.389	−0.92	0.4188
73	−0.93	−0.78	−0.15	−0.31	−0.2564	1.481	−0.92	0.4188
74	1.00	0.46	0.54	1.11	0.7436	−0.389	0.95	0.06392
75	−0.93	−0.97	0.04	0.08	−0.2564	1.971	−0.92	0.4188
76	1.11	0.65	0.46	0.93	0.7436	−0.389	1.44	0.06392
77	−0.93	−1.15	0.23	0.46	0.7436	−0.389	1.69	2.289
79	0.07	0.48	−0.41	−0.84	0.7436	−0.389	1.01	0.06392
80	−0.03	−0.04	0.01	0.03	−0.2564	−0.389	−0.92	0.4188
81	−0.93	−0.41	−0.52	−1.06	−0.2564	0.541	−0.92	0.4188
82	0.07	0.07	0.00	0.00	0.7436	−0.389	0.01	0.08832
83	0.07	1.16	−0.18	−0.37	−0.2564	−0.389	1.34	0.06392
84	0.37	−0.70	1.07	2.19	0.7436	−0.389	1.44	1.646
85	−1.23	−0.27	−0.96	−1.96	0.7436	−0.389	1.23	1.046
86	−0.93	−0.61	−0.32	−0.66	−0.2564	1.051	−0.92	0.4188
87	−0.63	−0.19	−0.43	−0.89	0.7436	−0.389	0.52	0.6286
88	−0.63	−1.07	0.44	0.89	−0.2564	2.221	−0.92	0.4188
89	0.07	0.84	−0.77	−1.58	−0.2564	−0.389	2.26	0.8516
90	−0.23	−0.28	0.05	0.10	−0.2564	0.211	−0.92	0.4188
91	−0.93	0.01	−0.94	−1.92	0.7436	−0.389	−0.32	0.002226
92	−0.63	−0.66	0.05	0.09	−0.2564	1.221	−0.92	0.4188
93	0.07	0.41	−0.34	−0.70	−0.2564	−0.389	0.69	0.6286
94	0.55	0.10	0.44	0.91	0.7436	−0.389	1.01	0.5081
95	1.57	1.04	0.54	1.09	−0.2564	−0.369	1.17	0.1245
96	0.60	0.55	0.05	0.10	−0.2564	−0.389	−0.32	0.002226
97	−0.03	−0.04	0.02	0.03	−0.2564	−0.389	−0.92	0.4188
98	0.52	0.38	0.14	0.28	−0.2564	−0.389	−0.57	0.08832
99	0.37	0.61	−0.24	−0.49	−0.2564	−0.389	−0.12	0.02335
102	−0.93	−0.69	−0.24	−0.50	−0.2564	−0.389	1.19	2.14
103	0.07	0.00	0.07	0.15	−0.2564	1.171	0.64	0.3755

[a] Mean = 0.63.

(eq 4, 6, 7) nor bulky substituents (eq 7). The para position cannot tolerate hydrogen bond acceptor substituents (eq 3 (since substituents are largely alkyls) and eq 7) in addition to the specific steric requirements mentioned above. In general, the agreement between these five equations is quite good, and the equations are all within the expected level of experimental error, about 10%.

Turning now to the antiinflammatory activity, log A_{cp}, we have noted previously[21] that there is a significant linear trend between log A_{qw} and log A_{cp}, with $r \simeq 0.8$ for two different series of acidic nonsteroidal antiinflammatory agents, the pyrrolopyrroles and the benzothiepins. In the case of the larger set of data presented here, with a greater range of activity, we observe again a significant correlation (eq 8). However, compound **62** is no longer an outlier

$$\log A_{qw} = \underset{(0.26)}{0.44} + \underset{(0.27)}{1.01} \log A_{cp} \qquad (8)$$

$n = 39$, $s = 0.61$, $r = 0.780$, $F_{1,37} = 57.53$, sd/sdm = 10%

Table X. Selected IR and NMR Spectroscopic Properties of Some Meta- and Para-Substituted 5-Benzoyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic Acids

compound no.	X	R	IR ($CHCl_3$), $\nu(CO_2R)$, cm^{-1}	NMR ($CHCl_3$), $\delta(H_1)$
1	H	*i*-Pr	1735	3.97
3	3-CH_3	*i*-Pr	1735	3.92
8	3-Cl	*i*-Pr	1735	3.93
9	4-Cl	*i*-Pr		3.92
10	4-Br	CH_3	1742	4.06
13	4-OCH_3	*i*-Pr	1730	3.93
16	4-O-*i*-Pr	*i*-Pr	1730	3.97
17	4-$OCH_2C{=}CH$	CH_3	1735	4.06
18	4-$OCH_2C{\equiv}CH$	CH_3	1733	4.06
20	3-CH_3CO_2	CH_3	1740	4.07
26	3-NO_2	CH_3		4.10
27	4-NO_2	CH_3	1740	4.10
28	3-NH_2	CH_3	1740	4.03
29	3-*i*-C_3H_7CONH	CH_3	1740	4.03
30	4-NH_2	CH_3	1740	4.03
31	4-N_3	CH_3	1735	4.10
34	3-CF_3	CH_3	1745	4.05
35	4-CF_3	CH_3	1745	~4.1
36	4-CH_3CO	CH_3	1742	4.05
37	4-$CH{=}CH_2$	CH_3	1739	~4.1
38	4-$C{\equiv}CH$	CH_3	1742	4.13
42	3,4-OCH_2O	CH_3	1745	4.13

compared to the original study.[21] In fact, there are no outliers in the log correlation (eq 8). If one correlates the actual potencies, however (eq 9), compound **62** deviates by over 4 standard deviations. Data is given in Table X.

$$A_{qw} = \underset{(22.06)}{23.34} + \underset{(0.70)}{2.29}A_{cp} \quad (9)$$

$n = 39$, $s = 59.77$, $r = 0.739$, $F_{1,37} = 44.61$, sd/sdm = 11%

Compound **62** is predicted to be 106 times aspirin from eq 9 but is found to be 350 times aspirin. These differences might, of course, be due to unusual metabolic differences between the mouse (QW) and rat (CP); however, it is interesting that **62** is significantly better analgesic than an antiinflammatory agent in humans.[11]

Equation 10 was obtained using BMDP2R with $F_{enter} = 4.0$, $F_{remove} = 3.9$, and tolerance 0.1. Lower limits of $F_{enter} = 3.0$ and $F_{remove} = 2.9$ gave one additional term but two additional outliers greater than 2 standard deviations (**62** and **91**) over that of eq 10 (**84** only outlier) were obtained, and so this equation was deemed unacceptable. Unfor-

$$\log \bar{A}_{cp} = \underset{(0.22)}{0.39} - \underset{(0.44)}{0.54}\bar{D}^4_{ha} - \underset{(0.25)}{0.39}\bar{B}^3_4 + \underset{(0.22)}{0.40}\bar{B}^4_4 - \underset{(0.34)}{0.86}(\bar{B}^4_3)^2 \quad (10)$$

$n = 39$, $s = 0.49$, $r = 0.782$, $F_{4,34} = 13.4$, sd/sdm = 11%

tunately, there are a number of statistically significant, but small magnitude, multicolinearities: $\bar{B}^4_3$ is correlated with $\bar{D}^4_{ha}$ (29%), $\bar{B}^3_4$ (18%), and $(\bar{B}^4_4)^2$ (15%). The ridge trace is flat, however, so that these do not appear to have any practical consequence. Compound **84** deviates by 2.2 standard deviations. Various other methods (stepwise regression with RSWAp, all-regressions with Mallow's C_p criterion, weighted least squares with various weights, etc.[33,34]), all failed to give any better results. Data residuals are given in Table IX. Comparisons with eq 7 for the analgetic assay shows that the $(\bar{B}^4_3)^2$ and $\bar{D}^4_{ha}$ terms have been selected for the analgetic assay and that the $(\bar{B}^4_3)$ and $\bar{D}^4_{ha}$ terms have been selected for both bioassays and both have negative steric requirements in the meta position. Because of the experimental error in the data, highly detailed comparisons between the two equations (7 and 10) are probably not warranted with the present in vivo data sets.

Although it has been proposed that B_2 and B_3 contribute little information and should be ignored[22] in the case of eq 7 and 10, it is quite apparent that B_3 cannot be substituted for other Verloop parameters in the present case. This may arise because the vinyl is coplanar with the phenyl ring and if the phenyl ring lies in a flat, sterically constrained hydrophobic region, the B^4_1 and B^4_2 parameters would correspond to the dimensions perpendicular to this plane (the shallow dimension of the plane). B^4_3 would then correspond to the projected dimensions along the geminal hydrogen and B^4_4 to the projected dimension along the methylene. L^4 and B^4_3 are constrained, while larger B_4 can be tolerated (in the CP assay, at least).

The deleterious effect of hydrogen bond acceptor substituents at both the meta and para positions may be due to several possibilities. The polar substituents may destroy the alignment of the drug in the receptor by preferentially binding to a nearby hydrogen-bond donor (e.g., tyrosine) which might be located nearer the para than meta position. The D_{ha} term may be an approximation for localized hydrophilic effect, although when we derived π values for each position of substitution from our measured log P, we found no terms entering the equations.

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.[4-6]

(2) **Inhibition of Cotton Pellet Granuloma.** This assay was effected according to a modification[29] of a procedure originally described by Meier et al.[30]

(3) **Inhibition of Adjuvant-Induced Arthritis.** This assay was carried out by a modification[29] of the procedure first described by Pearson.[31]

(4) **Inhibition of Phenylquinone-Induced Writhing.** This assay was conducted as described by Rooks et al.[29]

(5) **Chronic Gastrointestinal Erosive Activity.** This assay was effected as described by Rooks et al.[9,29] Thus, male rats weighing 190–220 g (Cox/SD obtained from Laboratory Supply Co., Indianapolis, IN) were acclimated for ca. 1 week. The animals (groups of five rats per dose) were given the test material po daily in phosphate-buffered saline (1 mL/100 g of body weight) for 7 consecutive days. One day after the last dose, the rats were sacrificed. Body weights were obtained on the first day of dosing and at sacrifice. Food, but not water, was removed from the cages in the last day of dosing. At necrospy, the stomach and small intestine were removed from each rat and examined blindly for lesions, which were scored as follows:

focal		diffuse
0	no gastric changes	
1	minimal, rare	2
3	slight, low, few	4
5	moderate, medium, several	6
7	marked, severe, many	8

In addition, a score of 10 was assigned to those rats that died during the test from complications due to gastrointestinal erosion. The scores for each rat ranged from 0 to 10; the scores for each dosage group ranged from 0 to 50. Arbitrarily, the dose giving

(29) Rooks, W. H.; Tomolonis, A. J.; Maloney, P. J.; Roszkowski, A.; Wallach, M. B. *Agents Actions* **1980**, *10*, 266.
(30) Meier, R.; Schuler, W.; Desaulles, P. *Experientia* **1950**, *6*, 469.
(31) Pearson, C. M. *Proc. Soc. Exp. Biol. Med.* **1959**, *91*, 95.
(32) Unger, S. H.; Feuerman, T. F. *J. Chromatogr.* **1979**, *176*, 426.

a score of 5 (1/rat) was assigned as the minimum effective dose and that dose giving a score of 25 (5/rat) was the median effective erosive dose.

Statistical work was performed either with use of APL language programs written by the author[21] or with BMDP statistical package[33] or SAS package[34] on the Syntex IBM 3081. Various types of weighted and unweighted multiple linear regression models, several different stepwise and leaps and bounds models, and ridge models were investigated (see text).

Determination of log *P* and pK_a Values. The procedure of Unger and Feuerman was used[21,32] except that a HP 3390A integrator was used for accurate determination of retention times. Experimental conditions are given in Table V, where n = number of individual injections. For other compounds, log D was determined at pH 2.2 and corrected to log P by addition of 0.02 constant based on a constant pK_1 = 3.48 and log P = log D + log $(1 + 10^{pH-pK_a})$.

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. The UV spectra were recorded in methanol solution with a Perkin-Elmer Model 402 ultraviolet–visible spectrometer. The NMR spectra were measured with a Varian T-60 or a Varian HA-100 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 recorded on a Varian MAT 311A mass spectrometer.

The elemental analyses of the new compounds described in the Experimental Section were within ±0.4% of the calculated values.

Starting Materials. All of the *N,N*-dimethylcarboxamides, except those described below, were known compounds prepared by literature procedures. Most of 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 lterature were synthesized from the known carboxylic acids in the manner described below.

***N,N*-Dimethyl-4-ethoxybenzamide (129).** Thionyl chloride (4.76 g, 40 mmol) was added to a solution of 4-ethoxybenzoic acid (3.67 g, 22 mmol) in anhydrous benzene (10 mL) and the solution thus obtained was heated at reflux temperature for 11 h. The solvent and excess thionyl chloride were removed in vacuo, and the residual oil was distilled, bp 124 °C (5 mm), to give the acid chloride (3.88 g, 95%), which was used immediately for the synthesis of the amide. Thus the acid chloride was dissolved in dry benzene (300 mL), the solution was cooled to 5 °C, and gaseous dimethylamine was bubbled into the solution until basic vapors were detected (moist litmus paper) issuing from the apparatus. Water was added to the mixture, and the organic phase was separated and washed successively with 10% hydrochloric acid, saturated sodium bicarbonate solution, and saturated sodium chloride solution. The benzene solution was dried and evaporated in vacuo. The residual solid was crystallized from dichloromethane–hexane to give the amide (3.82 g, 94%), which had a melting point of 52.5–53.5 °C after a further crystallization from ethane–hexane. Anal. ($C_{11}H_{15}NO_2$) C, H, N.

***N,N*-Dimethyl-4-isopropoxybenzamide (130).** This compound was prepared in the same manner as described above for the 4-ethoxy derivative 129. After crystallization from dichloromethane–hexane, it had a melting point of s 60–61 °C. Anal. ($C_{12}H_{17}NO_2$) C, H, N.

Acylation of the Bicyclic Esters V and the Nitriles VII. Method A. Vilsmeier–Haack Reactions. A solution of the appropriate *N,N*-dimethyl amide (10 mmol) and phosphorus oxychloride (10 mmol) in anhydrous 1,2-dichloroethane (1–7.5 mL/mmol amide) was heated at reflux temperature in a nitrogen atmosphere for 1 h. A solution of the bicyclic ester (5–9 mmol, but usually 5 mmol) in the same solvent (volume equal to that used above) was added and heating at reflux was maintained for the time indicated in Table I. The solution was cooled to room temperature, a solution of sodium acetate (50 mmol) in water (20 mL) was added cautiously, and the mixture was heated at reflux temperature for 1 h. The organic phase was separated, washed with saturated sodium chloride solution, and dried over sodium sulfate. The solvent was evaporated in vacuo and the residue was purified by the method indicated in Table I. If the ester was an oil, it was characterized by its spectroscopic properties only; e.g., compound 1 had UV 245, 311 nm (ϵ 7230, 17 800); IR 1735, 1620 cm^{-1}; NMR δ 1.24 (d, 6 H, J = 6 Hz), 2.50–3.13 (m, 2 H), 3.97 (dd, 1 H, $J_{1,2}$ = 6 Hz, $J_{1,2'}$ = 8 Hz), 4.18–4.70 (m, 2 H), 5.00 (septet, 1 H, J = 6 Hz), 6.00 (d, 1 H, $J_{6,7}$ = 4 Hz), 6.68 (d, 1 H, $J_{6,7}$ = 4 Hz).

Crystalline esters were characterized by elemental analysis as well as by the full range of spectroscopic properties.

Method B. Noncatalyzed Acylation of Bicyclic Esters V with Acid Chlorides in Boiling Xylene. A solution of the bicyclic ester (10 mmol) and the acid chloride (17–33 mmol) in anhydrous xylene (2–12 mL/mmol of ester) was heated at reflux temperature for the length of time indicated in Table I. The solvent was removed in vacuo and the residue was purified by the technique(s) indicated in Table I.

Method C. Noncatalyzed Acylation of Esters V with Acid Chlorides in Boiling Toluene. A solution of the ester V (10 mmol) and the acid chloride (18–33 mmol) was heated in toluene (4–25 mL/mmol of ester) at reflux temperature for the time period indicated in Table I. The reaction mixture was worked up by methods analogous to those described in method B.

Method D. Acylation of Nitriles VII with Acid Chlorides in Boiling Xylene. A solution of the nitrile VII (10 mmol) and the appropriate acid chloride (14–44 mmol) in anhydrous xylene (2–11 mL/mmol of nitrile) was heated at reflux temperature for the time indicated in Table I and the mixture was then worked up as described above.

Method E. Synthesis of 1-Cyano-5-[4-(methylthio)benzoyl]-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole (24). A solution of 4-(methylthio)benzoyl chloride (20 mmol) and the nitrile VII (n = 1) (10 mmol) in anhydrous toluene (50 mL) was heated at reflux temperature in a nitrogen atmosphere for 168 h. The solution was washed successively with saturated sodium bicarbonate solution and with saturated salt solution and then it was dried over sodium sulfate and evaporated in vacuo. The residue was purified as indicated in Table I.

Methyl 5-[4-(Methylsulfonyl)benzoyl]-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylate (23). A solution of *m*-chloroperbenzoic acid (0.703 g) in chloroform (20 mL) was added, over a 10-min period, to a stirred and cooled (0 °C) solution of the sulfide 22 (1.18 g) in the same solvent. The mixture was stirred for 1 h at 0 °C and then it was washed successively with saturated solutions of sodium bicarbonate and sodium chloride. The organic phase was dried over sodium sulfate, the solvent was removed in vacuo, and the residue was purified as indicated in Table I.

1-Cyano-5-[4-(methylsulfonyl)benzoyl]-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole (25). The oxidation of 24 was carried out in a manner similar to that described for the synthesis of the sulfoxide 23 except that a slight excess of *m*-chloroperbenzoic acid (2.24 mol/mol of sulfide) was added in two portions (75% initially, 25% after 1 h) and the reaction time was 1.5 h.

Methyl 5-(3-Aminobenzoyl)- and 5-(4-Aminobenzoyl)-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylate (28 and 30, Respectively). A solution of the nitro compound in methanol (50 mL/g of nitro compound) containing suspended 5% palladium on carbon catalyst (0.15 g/g of nitro compound) was hydrogenated at room temperature and a hydrogen pressure of 40 psig for 0.5 h. The mixture was filtered through Celite, the solvent was removed in vacuo, and the residue was crystallized from an appropriate solvent (Table I).

Methyl 5-(3-Isobutyramidobenzoyl)-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylate (29). Isobutyryl chloride (0.337 g, 3.16 mmol) was added to a solution of the amine 28 (0.900 g, 3.15 mmol) in anhydrous toluene (140 mL). After 0.5 h the solvent was removed in vacuo and the residue was purified as indicated in Table I.

(33) "Biomedical Computer Programs, P-Series"; Dixon, W. D., Brown, M. B., Ed.; University of California Press: Los Angeles, 1977.
(34) "SAS User's Guide: Statistics, 1982 Edition"; SAS Institute Inc., Cary, NC, 1982.
(35) Roszkowski, A. P.; Rooks, W. H.; Tomolonis, A. J.; Miller, L. M. *J. Pharmacol. Exp. Ther.* **1971**, *179*, 114.

Methyl 5-(4-Azidobenzoyl)-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylate (31). A solution of sodium nitrite (0.076 g, 1.1 mmol) in water (2 mL) was added to a stirred solution of the amine **30** (0.284 g, 1 mmol) in a mixture of concentrated hydrochloric acid (2 mL) and water (3 mL) maintained at −10 °C. After 0.5 h at this temperature, a solution of sodium azide (0.072 g, 1.1 mmol) in water (2 mL) was added and the solution was stirred at −10 to 0 °C for 1 h. The product was extracted into ethyl acetate, and the extract was washed with water, dried, and evaporated in vacuo. The residue was crystallized from acetone–hexane.

3-[4-(Methylsulfonyl)benzoyl]-8-cyano-5,6,7,8-tetrahydropyrrolo[1,2-*a*]pyridine (58). The synthesis of this compound was effected in the same manner as described for **23** except that 2.6 mol of *m*-chloroperbenzoic acid/mol of the sulfide **57** was used.

Synthesis of the Carboxylic Acids (Table II) by Hydrolysis of the Corresponding Esters or Nitriles. Method A. Hydrolysis of the Esters with Potassium Carbonate in Aqueous Methanol. A solution of the ester (10 mmol) in methanol (60 mL) containing water (15 mL) and potassium carbonate (20 mmol) was heated at reflux temperature in a nitrogen atmosphere for the time specified in Table II. The methanol was removed in vacuo, and the residue was diluted with water and extracted with ethyl acetate. The aqueous phase was made acidic with oxalic acid and then saturated with sodium chloride. The product was extracted into ethyl acetate, and the extract was dried and evaporated in vacuo. The residue, if solid, was crystallized from a suitable solvent (see Table II). If the carboxylic acid did not crystallize, it was dissolved in a suitable solvent (e.g., dichloromethane) and a slight excess of dicyclohexylamine was added. The solvent was removed in vacuo and the residue was crystallized from the solvent indicated in Table II.

Method B. Hydrolysis of Nitriles with Potassium Hydroxide in Aqueous Ethanol. A solution of the nitrile (10 mmol), in ethanol (70–250 mL) and water (15–35 mL), containing 85% potassium hydroxide (22.5–62.5 mmol), was heated at reflux temperature for the time specified in Table II. The ethanol was removed in vacuo, and the residue was diluted with water and extracted with ethyl acetate. The aqueous phase was made acidic with dilute hydrochloric acid and the product was extracted into ethyl acetate. The extract was dried over sodium sulfate and evaporated in vacuo. The residue was crystallized from the solvent system specified in Table II.

Method C. Hydrolysis of Esters with Potassium Hydroxide in Aqueous Methanol. A solution of the ester (10 mmol) in methanol (60–100 mL) and water (15–100 mL) containing 85% potassium hydroxide (17–20 mmol) was heated at reflux temperature for the period of time indicated in Table II. The reaction was worked up as described in method A.

Method D. Synthesis of 5-(4-Nitrobenzoyl)-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic Acid (87) by Hydrolysis of Ester 27 with 1,5-Diazabicyclo[3.4.0]non-5-ene (DBN). A solution of ester **27** (1.50 g, 4.7 mmol) in tetrahydrofuran (10 mL) containing water (5 mL) and DBN (0.198 g, 1.6 mmol) was stirred at room temperature for 20 h. The solution was poured into dilute hydrochloric acid and extracted with ethyl acetate. The extract was washed with water, dried, and evaporated in vacuo. Crystallization of the residue from ethyl acetate–hexane gave the required acid (0.48 g, 100% yield based on DBN).

Method E. Hydrolysis of Esters with Sodium Hydroxide in Aqueous Methanol. A solution of the ester (10 mmol) in 50% aqueous methanol (40–120 mL) containing sodium hydroxide (16–20 mmol) was stirred at room temperature for the time indicated in Table II. The reaction mixture was worked up as described in method B.

Method F. Synthesis of 5-(Pentafluorobenzoyl)-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic Acid (101) by Hydrolysis of Ester 43 with *p*-Toluenesulfonic Acid in Formic Acid. A solution of ester **43** (1.50 g, 41 mmol) in 97% formic acid (10 mL) containing *p*-toluenesulfonic acid hydrate (0.80 g) was left at room temperature for 48 h. The solution was poured into water and extracted in ethyl acetate. The extract was washed with saturated salt solution, dried, and evaporated in vacuo. The residue was crystallized from ether–hexane.

Method G. Hydrolysis of Nitriles with Potassium Hydroxide in Aqueous Ethylene Glycol. A solution of the nitrile (10 mmol) in 10% aqueous ethylene glycol (35–45 mL) containing 85% potassium hydroxide (52–65 mmol) was heated in an oil bath at 110–120 °C for the time specified in Table II. The solution was poured into water and extracted with ether. The aqueous phase was cooled to 0 °C and made acidic (pH 4) with concentrated hydrochloric acid. The product was extracted into ethyl acetate and then processed in the usual way.

3-[4-(Methylsulfinyl)benzoyl]-5,6,7,8-tetrahydropyrrolo-[1,2-*a*]pyridine-1-carboxylic Acid (116). Sodium periodate (0.200 g, 0.93 mmol) was added to a stirred solution of the methylthio compound **57** (0.150 g, 0.47 mmol) in methanol (5 mL) and tetrahydrofuran (92 mL). After 18 h the mixture was poured into water, and the precipitated solid was collected by filtration, washed with water, and dried. Crystallization of this material from dichloromethane–hexane gave the product in 60% yield.

Methyl 2-(4-Fluorobenzoyl)-5,6,7,8-tetrahydro-9*H*-pyrrolo[1,2-*a*]azepine-9-carboxylate (121). This compound was prepared by the Vilsmeier–Haack reaction from V (n = 3, R^1 = CH_3) and *N,N*-dimethyl-4-fluorobenzamide following method A. The reaction time was 20 h. The crude product was purified by TLC silica gel, using hexane–ethyl acetate (3:2) as the developing solvent. The oil (37% yield) thus obtained had UV 202, 265, 295 nm (ϵ 15900, 11000; 7410); IR 1739, 1634 cm^{-1}; NMR δ 1.83–2.33 (m, 6 H), 3.76 (s, 3 H), 4.03 (m, 3 H), 6.43 (d, 2 H, J = 2.0 Hz), 7.08 (m, 3 H), 7.82 (dd, 2 H, $J_{3'F}$ = 5.0 Hz, $J_{2'3'}$ = 9 Hz). Anal. ($C_{18}H_{18}FNO_3$) C, H, F, N.

Methyl 1,2-Dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-2-carboxylate (125). A mixture of compounds **123** and **124** (6.60 g, 40.5 mmol)[16] in ethanol (150 mL), containing 5% rhodium on alumina catalyst (0.800 g), was hydrogenated at room temperature and atmospheric pressure until the theoretical amount of hydrogen was absorbed. The mixture was filtered, the filtrate was evaporated in vacuo, and the residue was subjected to preparative TLC on silica, using hexane–ethyl acetate (9:1) as the developing solvent. The more polar compound **126** (1.77 g 26%) was discarded and the less polar material **125** (2.95 g, 44%) was crystallized from hexane–ether to give a solid: mp 44–45 °C; UV 213 nm (ϵ 6460); IR 1730 cm^{-1}; NMR δ 3.10 (d, 2 H, J = 8 Hz), 3.72 (s, 3 H), 3.72 (m, 1 H), 4.20 (d, 2 H, J = 8 Hz), 5.77 (dd, 1 H, $J_{6,7}$ = 4 Hz, $J_{5,7}$ = 0.8 Hz), 6.18 (dd, 1 H, $J_{6,7}$ = 4 Hz, $J_{5,6}$ = 2.5 Hz), 6.53 (dd, 1 H, $J_{5,6}$ = 2.5 Hz, $J_{5,7}$ = 0.8 Hz). Anal. ($C_9H_{11}NO_2$) C, H, N.

When the hydrogenation was carried out with 5% palladium on calcium carbonate catalyst, **125** and **126** were obtained in 68% and 14% yields, respectively.

1-Methyl-5-benzoyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]-pyrrole-1-carboxylic Acid (128). A solution of the ester 1 (2.50 g, 8.4 mmol) in dry dimethoxyethane (10 mL) was added to a stirred suspension of sodium hydride (prepared from a 50% dispersion (0.450 g, 9.4 mmol) in mineral oil by washing with hexane) in anhydrous dimethoxyethane (90 mL). After 0.5 h the solution was cooled to 0 °C and methyl iodide (5.92 g, 41.8 mmol) was added rapidly. The cooling bath was removed and after 2 h at room temperature the solution was poured into a saturated sodium bicarbonate solution. The product was extracted into ether, and the extract was dried and evaporated in vacuo. The residue was purified by column chromatography on silica gel (100 g), using hexane ethyl acetate (9:1) to elute the product (2.10 g, 80% yield), which was an oil; UV 210, 247, 313 nm (ϵ 7760, 7420, 18200); IR 1730, 1615 cm^{-1}; MS, m/e 311 (M^+). This ester **127** was not characterized further but was hydrolyzed to the carboxylic acid **128** by using method C (3-h reaction time). This substance, obtained in 81% yield, had a melting point of 124–125 °C after crystallization from pentane–dichloromethane. Anal. ($C_{16}H_{15}NO_3$) C, H.

Registry No. 1, 66635-74-3; **2**, 66635-75-4; **3**, 66635-76-5; **4**, 66635-72-1; **5**, 96326-91-9; **6**, 66635-82-3; **7**, 66635-79-8; **8**, 66635-80-1; **9**, 66635-81-2; **10**, 96326-92-0; 11, 96326-93-1; **12**, 96326-94-2; **13**, 66635-77-6; **14**, 96326-95-3; **15**, 66635-78-7; **16**, 96326-96-4; **17**, 96326-97-5; **18**, 96326-98-6; **19**, 96326-99-7; **20**, 96327-00-3; **21**, 96327-01-4; **22**, 76786-66-8; **23**, 76786-73-7; **24**, 76786-76-0; **25**, 96327-02-5; **26**, 96327-03-6; **27**, 96327-04-7; **28**, 96327-05-8; **29**, 96327-06-9; **30**, 96327-07-0; **31**, 96327-08-1; **32**,

96327-09-2; **33**, 96327-10-5; **34**, 96327-11-6; **35**, 96327-12-7; **36**, 96327-13-8; **37**, 96327-14-9; **38**, 96327-15-0; **39**, 96348-37-7; **40**, 96327-16-1; **41**, 96327-17-2; **42**, 96327-18-3; **43**, 96327-19-4; **44**, 96327-20-7; **45**, 96327-21-8; **46**, 96327-22-9; **47**, 96327-23-0; **48**, 96327-24-1; **49**, 96327-25-2; **50**, 96327-26-3; **51**, 88777-62-2; **52**, 96327-27-4; **53**, 88777-68-8; **54**, 96327-28-5; **55**, 96327-29-6; **56**, 96348-38-8; **57**, 88777-70-2; **58**, 88777-71-3; **59**, 88777-64-4; **60**, 96327-30-9; **61**, 96327-31-0; **62**, 66635-83-4; **63**, 66635-84-5; **64**, 96327-32-1; **65**, 66635-73-2; **66**, 96327-33-2; **67**, 66635-90-3; **68**, 66635-87-8; **69**, 66635-88-9; **70**, 66635-89-0; **71**, 96327-34-3; **72**, 96327-35-4; **73**, 96327-36-5; **74**, 66635-85-6; **75**, 96327-37-6; **76**, 66635-86-7; **77**, 96327-38-7; **78**, 96327-39-8; **79**, 96327-40-1; **80**, 96327-41-2; **81**, 96327-42-3; **82**, 96327-43-4; **83**, 76786-67-9; **84**, 76786-74-8; **85**, 96327-44-5; **86**, 96327-45-6; **87**, 96327-46-7; **88**, 96327-47-8; **89**, 96327-48-9; **90**, 96327-49-0; **91**, 96327-50-3; **92**, 96327-51-4; **93**, 96327-52-5; **94**, 96327-53-6; **95**, 96327-54-7; **96**, 96327-55-8; **97**, 96327-56-9; **98**, 96327-57-0; **99**, 96327-58-1; **100**, 96327-59-2; **101**, 96327-60-5; **102**, 96327-61-6; **103**, 96327-62-7; **104**, 96327-63-8; **105**, 96327-64-9; **106**, 96327-65-0; **107**, 96327-66-1; **108**, 96327-67-2; **109**, 88777-63-3; **110**, 88777-65-5; **111**, 88777-59-7; **112**, 96327-68-3; **113**, 88777-67-7; **114**, 88777-66-6; **115**, 88777-73-5; **116**, 88777-74-6; **117**, 88777-72-4; **118**, 88777-69-9; **119**, 96327-69-4; **120**, 96327-70-7; **121**, 96327-71-8; **123**, 61338-78-1; **124**, 20929-02-6; **125**, 96327-72-9; **126**, 63486-71-5; **127**, 96327-73-0; **128**, 96327-74-1; **129**, 90526-03-7; **130**, 96327-75-2; V (R = *i*-Pr; *n* = 1), 66635-71-0; V (R = Me; *n* = 1), 76786-65-7; V (R = Me; *n* = 2), 83820-86-4; V (R = Me; *n* = 3), 83820-99-9; VII (*n* = 1), 76786-72-6; VII (*n* = 2), 83820-96-6; $PhCONMe_2$, 611-74-5; $2\text{-}CH_3C_6H_4CONMe_2$, 6639-19-6; $3\text{-}CH_3C_6H_4CONMe_2$, 6935-65-5; $4\text{-}CH_3C_6H_4CONMe_2$, 14062-78-3; $3\text{-}FC_6H_4CONMe_2$, 33322-64-4; $4\text{-}FC_6H_4CONMe_2$, 24167-56-4; $2\text{-}ClC_6H_4CONMe_2$, 6526-67-6; $3\text{-}ClC_6H_4CONMe_2$, 24167-52-0; $4\text{-}ClC_6H_4CONMe_2$, 14062-80-7; $3\text{-}CH_3OC_6H_4CONMe_2$, 7290-99-5; $4\text{-}CH_3OC_6H_4CONMe_2$, 7291-00-1; $3\text{-}EtOC_6H_4CONMe_2$, 96327-76-3; $4\text{-}PcC_6H_4CONMe_2$, 33322-67-7; $4\text{-}CH_3SC_6H_4CONMe_2$, 25771-25-9; $4\text{-}BrC_6H_4COCl$, 586-75-4; $2\text{-}IC_6H_4COCl$, 609-67-6; $4\text{-}CH_2{=}CHCH_2OC_6H_4COCl$, 36844-51-6; $4\text{-}CH{\equiv}CCH_2OC_6H_4COCl$, 96327-77-4; $4\text{-}CF_3C_6H_4COCl$, 329-15-7; $4\text{-}CH_3COC_6H_4COCl$, 31076-84-3; $4\text{-}CH_2{=}CHC_6H_4COCl$, 1565-41-9; $4\text{-}CH{\equiv}CC_6H_4COCl$, 62480-31-3; $3,4\text{-}OCH_2OC_6H_3COCl$, 25054-53-9; C_6F_5COCl, 2251-50-5; $3\text{-}CH_3CO_2C_6H_4COCl$, 16446-73-4; $4\text{-}CH_3CO_2C_6H_4COCl$, 27914-73-4; $4\text{-}CH_3SC_6H_4COCl$, 1442-06-4; $3\text{-}NO_2C_6H_4COCl$, 121-90-4; $4\text{-}NO_2C_6H_4COCl$, 122-04-3; $3\text{-}CNC_6H_4COCl$, 1711-11-1; $4\text{-}CNC_6H_4COCl$, 6068-72-0; $3\text{-}CF_3C_6H_4COCl$, 2251-65-2; $2,6\text{-}F_2C_6H_3COCl$, 18063-02-0; $2,4\text{-}F_2C_6H_3COCl$, 72482-64-5; $2,4\text{-}Cl_2C_6H_3COCl$, 89-75-8; $4\text{-}FC_6H_4COCl$, 403-43-0; PhCOCl, 98-88-4; $2\text{-}CH_3CO_2C_6H_4COCl$, 5538-51-2; $4\text{-}CH_3C_6H_4COCl$, 874-60-2; $3\text{-}ClC_6H_4COCl$, 618-46-2; $4\text{-}ClC_6H_4COCl$, 122-01-0; $4\text{-}CH_3OC_6H_4COCl$, 100-07-2; $RCONMe_2$ (R = β-napthyl), 13577-85-0; $RCONMe_2$ (R = cyclobutyl), 57056-80-1; $RCONMe_2$ (R = *tert*-butyl), 24331-71-3; $PhCH_2CONMe_2$, 18925-69-4; **63**·$(c\text{-}C_6H_{11})_2NH$, 96632-90-5; **68**·$(c\text{-}C_6H_{11})NH$, 96632-91-6.

Novel Dopamine Receptor Agonists and Antagonists with Preferential Action on Autoreceptors

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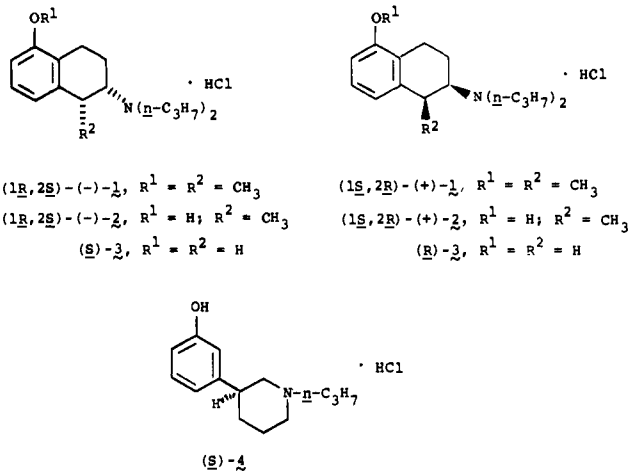
The enantiomers of *cis*-5-hydroxy-1-methyl-2-(di-*n*-propylamino)tetralin (**2**) and its methyl ether (**1**) have been synthesized. The compounds were tested for central dopamine (DA) receptor activity, by using biochemical and behavioral tests in rats. The (1*R*,2*S*)-(−) enantiomers of **1** and **2** are characterized as centrally acting DA-receptor agonists while the corresponding (1*S*,2*R*)-(+) enantiomers are characterized as centrally acting DA-receptor antagonists. Compounds (+)-**1** and (+)-**2** differ from classical neuroleptics in being able to increase DA synthesis rate in a wide dose range without reducing locomotor activity, suggesting a pronounced selectivity for DA autoreceptors. Also the (−) enantiomers seem to act preferentially on DA autoreceptors.

Recently, racemic *cis*-5-hydroxy-1-methyl-2-(di-*n*-propylamino)tetralin ((±)-**2**)[1] was classified as a centrally acting dopamine (DA) autoreceptor agonist without apparent postsynaptic DA stimulatory effects. This profile is similar to that of racemic 3-(3-hydroxyphenyl)-*N*-*n*-propylpiperidine (3-PPP, (±)-**4**).[2] We now report that the (1*R*,2*S*)-(−) enantiomers of **2** and its methyl ether (**1**) appear to be centrally acting DA-receptor agonists while the corresponding (1*S*,2*R*)-(+) enantiomers are characterized as DA-receptor antagonists. The four enantiomers investigated seem to exhibit a pronounced selectivity for DA autoreceptors, which makes them interesting as pharmacological tools and as potentially useful therapeutic agents.[3]

Chemistry. The preparation of the enantiomers of **1** and **2** is outlined in Scheme I. The enantiomers of **6** were synthesized from 5-methoxy-1-methyl-2-tetralone (**5**)[1] by use of a slightly modified literature procedure.[4] Thus, compound **5** was reacted with (*R*)-1-phenylethylamine and the resulting imine was hydrogenated (Pd/C) to afford



(+)-**6**. The use of (*S*)-1-phenylethylamine in the above reaction sequence gave (−)-**6**. This asymmetric reaction

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(1) Hacksell, U.; Johansson, A. M.; Arvidsson, L.-E.; Nilsson, J. L. G.; Hjorth, S.; Carlsson, A.; Wikström, H.; Sanchez, D.; Lindberg, P. *J. Med. Chem.* 1984, *27*, 1003.

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